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Synthesis of Thieno[3,2-*e*][1,4]diazepin-2-ones: Application of an Uncatalysed Pictet–Spengler Reaction

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A series of 5-substituted thieno[3,2-*e*][1,4]diazepin-2-ones was synthesized in four steps from methyl 3-aminothiophene-2-carboxylate. After the coupling of 3-aminothiophene with α-amino acids, the key final step that involves an uncatalysed Pictet–Spengler reaction allowed the cyclization of the seven-membered diazepinone ring. The reaction was first optimized and then exemplified in three different series (phenylalanine, alanine and proline) that led to 24 target diazepinones, which includes 19 optically pure diastereomers.

Introduction

The concept of privileged structure, which is defined as "a single molecular framework able to provide ligands for diverse receptors",[1] has emerged as a powerful approach to increase the chances of discovering lead compounds. The diazepine scaffold is one of the classical examples of privileged structures, which has proved its effectiveness in a number of pharmaceutical drugs and still continues to attract much interest today in medicinal chemistry.[2] Aryldiazepine ring systems achieved popularity first in the 1960s with diazepam as the first orally active anxiolytic by interaction with GABA receptors. This template was further shown to interact with high affinity with multiple receptor types and has also been used in the design of some enzyme inhibitors.[3–6]

Since the discovery of benzodiazepines as central nervous system depressants, many synthetic derivatives that display a wide range of therapeutic applications in antithrombotic,[7] antibiotic,[8] and antitumor[9,10] areas, have been extensively developed. Much attention has been paid to the replacement of the fused benzene ring by a heterocyclic structure such as pyrazole,[11,12] imidazole,[13] pyrrole,[14–16] and indole.[17,18] Recently, we focused our efforts on the development of a new azaheterocycle-fused [1,3]diazepine scaffold and successfully reported on the synthesis of the first series of imidazopyridine-fused [1,3]diazepinones.[19,20] We also investigated the thiophene isoster (namely thieno-[1,4]diazepine) scaffold. Indeed, this scaffold has shown interesting properties over the past years. As an example, Clotiazepam (Figure 1) is a thienodiazepine marketed drug with anxiolytic, anticonvulsant, sedative and muscle relaxant properties.[21,22] Tricyclic structures derived from the latter have been further described and include Etizolam (Figure 1).[23] Their notable activities, and the opportunity to introduce new diversity, led us to develop new methodolo-

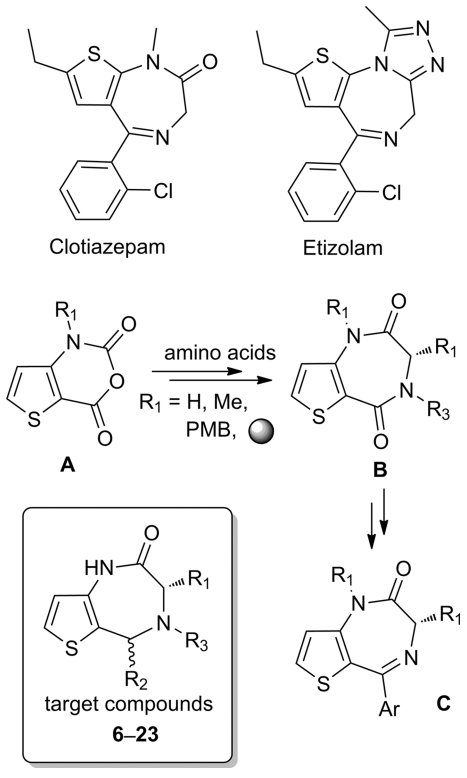

Figure 1. Representative thienodiazepines and target compounds.

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gies to afford functionalized thienodiazepines as promising structures for medicinal chemistry research.

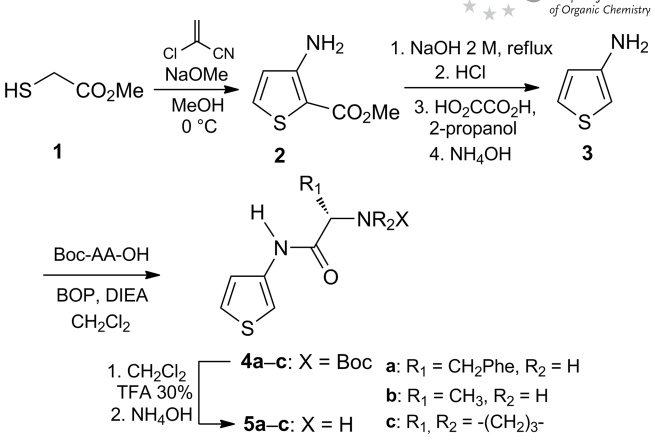
Because most synthetic routes described in the literature refer to a [2,3]-type fusion between thiophene and seven-membered heterocycles,[24,25] access to isomeric [3,2]-type fusion appears more intricate. In this context, we have recently described a general synthetic protocol to generate new thieno[3,2-*e*][1,4]diazepin-2,5-diones **B** by regioselective ring opening of 2-thiaisatoic anhydride **A** by α-amino acids, followed by intramolecular cyclocondensation reaction.[26] This methodology was further extended to the solid phase by using *N*-alkylated α-amino acids that led to *C*3,*N*4-substituted thieno[3,2-*e*][1,4]diazepin-2,5-diones **B** (Figure 1).[27] More recently, diversity was introduced by *N*-substituted thienodiazepinedione ring opening with a series of organomagnesium bromides and subsequent cyclization to afford 5-arylthienodiazepin-2-one **C** analogues (Figure 1).[28]

In our on-going interest in the development of focused heterocyclic libraries and to enlarge the chemical diversity of thienodiazepine scaffold, we present herein a new efficient synthesis of 5-substituted thieno[3,2-*e*][1,4]diazepin-2-ones **6**–**23** (Figure 1) by means of an uncatalysed Pictet–Spengler reaction as the key step. This reaction, commonly used in the synthesis of many isoquinoline and β-carboline alkaloids,[29,30] has already been applied to thiophene.[31–34] Moreover, few examples of the seven-membered diazepine ring closure have been described with electron-rich (hetero)cycles such as pyrrole[15,35] and imidazole.[36]

Results and Discussion

To access the target thieno[3,2-*e*][1,4]diazepin-2-ones, we envisioned a strategy by which the Pictet–Spengler cyclization key reaction step consists of a condensation reaction of N^1-3-thienylaminoamides **5a**–**5c** with various aromatic and aliphatic aldehydes. These amides were achieved by coupling 3-aminothiophene **3** with *tert*-butoxycarbonyl (Boc)-amino acids, followed by a subsequent removal of the Boc protecting group under acidic conditions. According to the literature, compound **2** was generated by reacting methylthioglycolate **1** with 2-chloroacrylonitrile in the presence of sodium methoxide in MeOH (Scheme 1).[37] The ester function of **2** was then hydrolysed in a solution of sodium hydroxide (2 M) in methanol at reflux temperatures as described by Florence et al.[38] Treatment with neat HCl allowed the precipitation and isolation of the resulting unstable amino acid derivative that was immediately decarboxylated by using oxalic acid in 2-propanol at reflux temperatures to yield the oxalate salt. This intermediate salt was treated with an aqueous solution of ammonia (28%) to afford 3-aminothiophene (**3**) in 69% overall yield from **2**.

Protected N^1-3-thienylaminoamides **4a**–**4c** were isolated in 74–85% yields after acylation of 3-aminothiophene **3** with *N*-Boc-amino acids (Phe, Ala and Pro) in the presence of (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) and *N*,*N*-diisopropylethylamine (DIEA) in CH_2Cl_2. Removal of the Boc protecting group with trifluoroacetic acid (TFA; 30%) in CH_2Cl_2 followed by basic treatment with NH_4OH yielded N^1-3-thienylaminoamides **5a**–**5c** that were used in the Pictet–Spengler reaction without further purification.

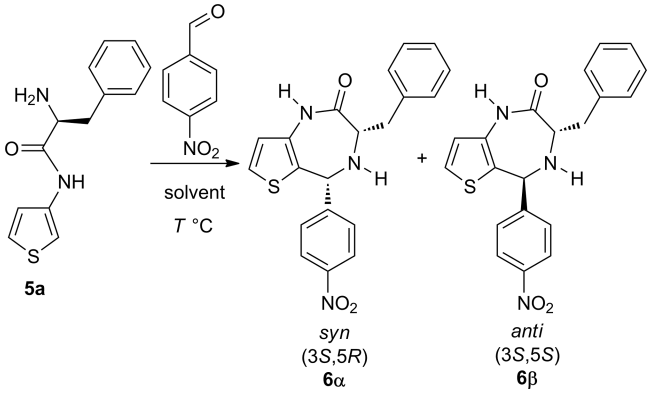


Scheme 1. Synthesis of N^1-3-thienylaminoamides **5a**–**5c**.

With these intermediates in hand, we were able to investigate their reactivity towards the intramolecular Pictet–Spengler cyclization reaction. To explore the formation of the thieno[3,2-*e*][1,4]diazepin-2-one scaffold and the possibility of introducing diversity at position 5 of the ring, N^1-3-thienylaminoamide **5a** (from the phenylalanine series) was treated with *p*-nitrobenzaldehyde (1 equiv.) under various experimental conditions (Table 1). Initially, a screen for solvent performance was undertaken with chloroform, THF, 1,4-dioxane, *n*-butanol and toluene, at different temperatures (25 °C and reflux). The reaction time was limited to 12 h when no conversion was observed. Reactions were monitored by TLC with silica gel (CH_2Cl_2/EtOAc, 9:1, v/v) and diazepinones were isolated as pure diastereomers **6α** (with a *syn* configuration) and **6β** (with an *anti* configuration) by flash chromatography with silica gel (CH_2Cl_2 to CH_2Cl_2/EtOAc, 95:5, v/v). Absolute configurations were ascertained by NOESY experiments (see Supporting information). The (3*S*,5*R*) and (3*S*,5*S*) relative stereochemistry was assigned based on the observed nuclear Overhauser effect between the resonances of the H_3 and H_5 protons of the diazepine ring. These experiments showed no reaction when performed at room temperature, whereas at reflux temperatures, the results indicated toluene at 110 °C as the best solvent, a yield of 49% was obtained after 6 h (Table 1, Entry 10). The same results were obtained with *n*-butanol but only after 12 h (Table 1, Entry 8). With this model, the ratio of diastereomers **6α/6β** did not seem to be dependent on the nature of the solvent or on the temperature and remained close to 1:1 after isolation of the compounds. Optimum conditions were obtained with freshly distilled toluene in the presence of 4 Å molecular sieves under N_2 atmosphere (Table 1, Entry 11), which suggests that the imine intermediate formed during the reaction might be sensitive to hydrolysis. Under these conditions, the yield was increased to 72% and the reaction time was optimized to 3 h.

To further improve the yield, classical acidic catalysis was evaluated. Indeed, Lubell et al. reported that TFA was able to catalyse the Pictet–Spengler cyclization reaction on the pyrrole.[15,16] In the case of thiophene, degradation was observed with a Brønsted acid, such as TFA (Table 1, Entry 12), or with a Lewis acid, such as $TiCl_4$ (Table 1, Entry 13). Therefore, uncatalysed conditions in anhydrous toluene at 110 °C were selected to perform all the Pictet–Spengler reactions described in this report. With these optimized conditions in hand, we investigated the reactivity of three different series (phenylalanine, alanine and proline) towards several aromatic and aliphatic aldehydes that offered a wide diversity of substituents.

Table 1. Optimization of the Pictet–Spengler reaction.[a]

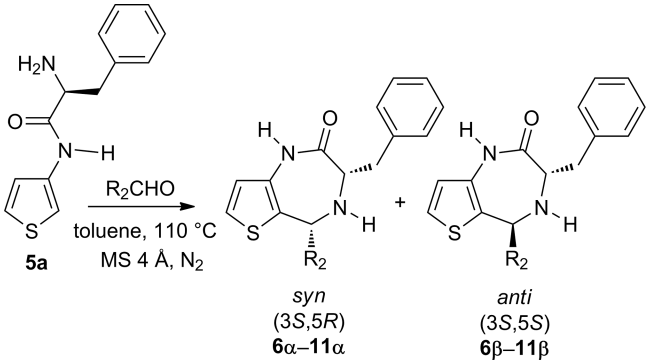


Entry	Solvent	*T* [°C]	Time [h]	Yield [%][e]	α/β ratio[f]
1	chloroform	25	12	0	–
2	chloroform	62	12	0	–
3	THF	25	12	0	–
4	THF	66	12	0	–
5	1,4-dioxane	25	12	0	–
6	1,4-dioxane	101	12	0	–
7	*n*-butanol	25	12	0	–
8	*n*-butanol	118	12	50	45:55
9	toluene	25	12	0	–
10	toluene	110	6	49	45:55
11	anhydr. toluene[b]	110	3	72	47:53
12	anhydr. toluene[b,c]	110	12	0	–
13	anhydr. toluene[b,d]	110	12	0	–

[a] Reaction was performed with: **5a** (100 mg) and *p*-nitrobenzaldehyde (1 equiv.) in solvent (5 mL). [b] Molecular sieves (4 Å) under N_2. [c] TFA (0.5 equiv.). [d] $TiCl_4$ (0.1 equiv.). [e] Overall yields after flash chromatography in normal phase. [f] Determined from isolated yields.

We exemplified the reaction in the phenylalanine series by reacting amine **5a** with several aromatic and aliphatic aldehydes (Table 2). In all cases, both diastereomers α and β were isolated by flash chromatography with silica gel (CH_2Cl_2/EtOAc) and their absolute configuration was ascertained by NOESY experiments (see Supporting information). As shown, ring closure, accomplished by the Pictet–Spengler condensation reaction with aromatic aldehydes with electron-withdrawing substituents, such as *p*-nitrobenzaldehyde, yielded thieno[3,2-*e*][1,4]diazepin-2-one in good overall yield, although no diastereoselectivity was observed (Table 2, compound **6**). Aldehydes with moderately electron-withdrawing substituents, such as *p*-bromobenzaldehyde and benzaldehyde, gave slightly lower overall yields 58–69% (Table 2, compounds **7** and **8**, respectively); no influence on the diastereoselectivity was observed, and the ratio of diastereomers α/β remained 1:1. However, a decrease in the overall yield was observed with aromatic electron-donor *p*-anisaldehyde (49% overall yield; Table 2, compound **9**). These results suggest that the aldehyde's electron properties influence imine stabilization. Indeed, the imine intermediate was less reactive to nucleophilic attack by thiophene when electron-donor aldehydes were used.[39] The Pictet–Spengler condensation reaction with aliphatic aldehyde 3-methylbutyraldehyde gave **10** in 75% overall yield, whereas with cyclohexylaldehyde, only diastereomer **11β** was isolated in 34% yield (Table 2). In this case, purification by flash chromatography did not allow the isolation of diastereomer **11α**. With 3-methylbutyraldehyde *syn* stereoselectivity was observed with a α/β ratio close to 2:1.

Table 2. Pictet–Spengler cyclization reaction with the phenylalanine series.[a]



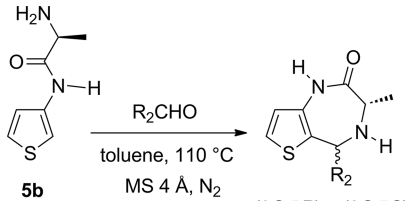
	R^2	α [%][b]	β [%][b]	Overall yield [%]	α/β ratio[c]
6	*p*-$O_2NC_6H_4$	34	38	72	47:53
7	*p*-BrC_6H_4	29	29	58	50:50
8	C_6H_5	34	35	69	49:51
9	*p*-$MeOC_6H_4$	25	24	49	51:49
10	$CH_2CH(CH_3)_2$	50	25	75	67:33
11	C_6H_{11}	0	34	34	0:100

[a] Reaction was performed with **5a** (100 mg) and aldehyde (1 equiv.) in freshly distilled toluene (5 mL) in the presence of 4 Å molecular sieves and was stirred at reflux temperatures for 3 h under N_2. [b] Isolated yields after flash chromatography in normal phase. [c] Determined from isolated yields.

In the alanine series, amine **5b** was treated with the same aromatic and aliphatic aldehydes, as in the phenylalanine series. Results are reported in Table 3. Although the overall yields were slightly better in most cases, diastereomers with aromatic substituents were not isolated as optically pure compounds because efficient separation conditions could not be found either with reverse phase HPLC or normal phase flash chromatography. Only compounds **16** and **17** with aliphatic substituents, were isolated as optically pure 3*S*,5*S* diastereomers (diastereomers 3*S*,5*R* could not be isolated in pure form). In both cases, the difference between the retention factors of the two diastereomers allowed their separation by flash chromatography on silica gel (CH_2Cl_2/

EtOAc). It is noticeable that with electron-donor *p*-anisaldehyde (Table 3, compound **15**), no yield was determined because a pure mixture of the two diastereomers could not be isolated. Problems not only occurred during the purification process but the compound was also unstable if the mixture was left at room temperature in $CDCl_3$.

Table 3. Pictet–Spengler cyclization reaction with the alanine series.[a]

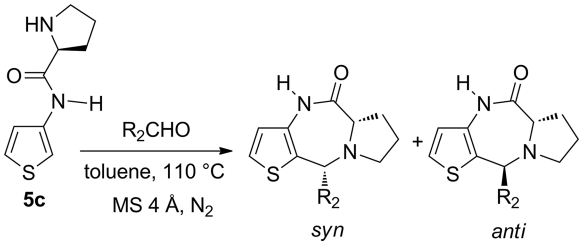


	R^2	Yield [%][b]
12	*p*-$O_2NC_6H_4$	88
13	*p*-BrC_6H_4	61
14	C_6H_5	36
15	*p*-$MeOC_6H_4$	n.d.[c]
16	$CH_2CH(CH_3)_2$	58[d]
17	C_6H_{11}	58[d]

[a] Reaction was performed with **5b** (100 mg) and aldehyde (1 equiv.) in freshly distilled toluene (5 mL) in the presence of molecular sieves (4 Å) and was stirred at reflux temperatures for 3 h under N_2. [b] Isolated yields after flash chromatography in normal phase; n.d.: not determined. [c] Not determined owing to low product stability. [d] Diastereomer 3*S*,5*S* optically pure.

In the proline series, amine **5c** was reacted with the same aldehydes used in the previous series. Results are reported in Table 4 and show the best overall yields either with aromatic (73–82%) or aliphatic aldehydes (70–92%). This fact is in agreement with the idea that the tetraalkylated iminium intermediate must be more reactive to the thiophene's nucleophilic attack as a result of exacerbated electrophilicity. All diastereomers were isolated as optically pure compounds and their configuration was ascertained by NOESY experiments (see Supporting information). Interestingly, it appears that when the C3- and C5-positions of the diazepine ring are conformationally constrained by the proline residue, *anti* stereoselectivity is observed because all the major diastereomers are of 3*S*,5*S* configuration. Indeed, when benzaldehyde (**20**), *p*-anisaldehyde (**21**), 3-methylbutyraldehyde (**22**) and cyclohexylaldehyde (**23**) are used in the Pictet–Spengler cyclization reaction, the 3*S*,5*R* configuration is not observed.

Table 4. Pictet–Spengler cyclization reaction with the proline series.[a]



	R^2	α [%][b]	β [%][b]	Overall yield [%]	α/β ratio[c]
18	*p*-$O_2NC_6H_4$	20	62	82	24:76
19	*p*-BrC_6H_4	16	62	78	30:70
20	C_6H_5	–	78	78	0:100
21	*p*-$MeOC_6H_4$	–	73	73	0:100
22	$CH_2CH(CH_3)_2$	–	70	70	0:100
23	C_6H_{11}	–	92	92	0:100

[a] Reaction was performed with **5c** (100 mg) and aldehyde (1 equiv.) in freshly distilled toluene (5 mL) in the presence of 4 Å molecular sieves and was stirred at reflux temperatures for 3 h under N_2. [b] Isolated yields after flash chromatography in normal phase. [c] Determined from isolated yields.

Conclusions

We have developed a practical sequence for the synthesis of original thieno[3,2-*e*][1,4]diazepin-2-ones that enables the introduction of a wide diversity of substituents. The key step was an uncatalysed Pictet–Spengler reaction that allows the intramolecular cyclization of the seven-membered diazepine ring. The reaction was exemplified in three different series (phenylalanine, alanine and proline series) by using several aromatic and aliphatic aldehydes. The resulting diastereomers were usually easily isolated as optically pure in the phenylalanine and proline series and more importantly, *anti* stereoselectivity was observed when the C3- and C5-positions of the diazepine ring were conformationally constrained by the proline residue. In light of the hopeful biological activities of diazepinone derivatives, this new thiophene-fused [3,2]diazepinone scaffold is promising for the development of biologically active compounds.

Experimental Section

General Methods: All reactions were performed in flame-dried glassware with magnetic stirring under an inert atmosphere (nitrogen). Toluene for reactions was distilled in the presence of sodium as a drying agent and transferred under nitrogen. Reagents were used as received. TLC was performed with Merck silica Gel 60 F254 plates. Visualization was accomplished by irradiation with a UV lamp, and then by staining with a ninhydrin solution in MeOH. Purification by flash column chromatography was performed with Biotage SP1 pre-packed columns filled with silica gel and monitored by UV detection at 254 and 280 nm. The ^1H and ^{13}C NMR spectroscopic data were recorded with a Bruker spectrometer at 300 and 75 MHz, respectively. Chemical shifts are reported [s (singlet), d (doublet), dd (doublet of doublets), t (triplet), td (triplet of doublets), q (quartet), m (multiplet)] relative to the solvent peak [δH = 7.26 ppm and δC = 77.16 ppm for $CHCl_3$, δH = 2.50 ppm and δC = 39.52 ppm for dimethyl sulfoxide (DMSO)]. Mass spectrum analyses were recorded with a Quatromicro (Micromass, Manchester, U.K.) triple-quadrupole mass spectrometer fitted with an electrospray interface. HRMS analyses were performed by the Laboratoire de Mesures Physiques, University of Montpellier.

General Procedure for the Synthesis of Aminoamides 4a–4c: To an ice-cold solution of compound **3** (1 g, 10.10 mmol) in CH_2Cl_2

(50 mL) were added Boc-AA-OH (11.11 mmol, 1.1 equiv.) and BOP (4.9 g, 11.11 mmol, 1.1 equiv.). The pH was adjusted to 8–9 by adding DIEA (5 mL, 30.30 mmol, 3 equiv.). The solution was stirred for 4 h at room temp. The solvent was then removed in vacuo and the residue was dissolved in EtOAc (100 mL). The solution was washed with a saturated sodium hydrogen carbonate solution (2× 100 mL) and brine (1× 100 mL). The organic layer was dried with Na_2SO_4, filtered, and the solvent was evaporated in vacuo. The residue was purified by flash chromatography with silica gel (CH_2Cl_2/EtOAc).

***N*-(*tert*-Butoxycarbonyl)-*N*-3-thienylphenylalaninamide (4a):** White solid, 74% (2.59 g), m.p. 154.1–154.9 °C. $[\alpha]_D^{29}$ = –12.7 (*c* = 1.0, MeOH). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 1.31 (s, 9 H), 2.78–2.86 (m, 1 H), 2.94–3.00 (m, 1 H), 4.23–4.31 (m, 1 H), 7.09–7.32 (m, 7 H), 7.45 (dd, *J* = 3.3, *J* = 5.1 Hz, 1 H), 7.54 (d, *J* = 3.3 Hz, 1 H), 10.45 (s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 28.18 (3 C), 37.46, 56.27, 78.10, 108.76, 121.43, 124.76, 126.30, 128.09 (2 C), 128.21, 129.22, 136.60, 138.06, 155.42, 169.91 ppm. LC–MS (ESI$^+$) *m*/*z* = 347.2 [M + H]$^+$.

***N*-(*tert*-Butoxycarbonyl)-*N*-3-thienylalaninamide (4b):** White solid, 78% (2.13 g), m.p. 187.3–187.8 °C. $[\alpha]_D^{29}$ = –56.9 (*c* = 1.0, MeOH). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 1.23 (d, *J* = 6.9 Hz, 3 H), 1.38 (s, 9 H), 4.05–4.09 (m, 1 H), 7.01 (d, *J* = 6.9 Hz, 1 H), 7.10 (dd, *J* = 1.2, *J* = 5.1 Hz, 1 H), 7.43 (dd, *J* = 3.3, *J* = 5.1 Hz, 1 H), 7.51 (dd, *J* = 1.2, *J* = 3.3 Hz, 1 H), 10.27 (s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 18.00, 28.15 (3 C), 50.03, 77.99, 108.44, 121.37, 124.56, 136.67, 155.10, 170.83 ppm. LC–MS (ESI$^+$): *m*/*z* = 293.2 [M + Na]$^+$.

***N*-(*tert*-Butoxycarbonyl)-*N*-3-thienylprolinamide (4c):** White solid, 85% (2.54 g), m.p. 210.8–212.9 °C. $[\alpha]_D^{29}$ = –77.4 (*c* = 1.0, MeOH); two conformers detected by NMR spectroscopy in [D$_6$]DMSO. ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 1.26 (s, 6 H), 1.40 (s, 3 H); 1.76–1.91 (m, 3 H), 2.14–2.22 (m, 1 H), 3.30–3.46 (m, 2 H), 4.12–4.22 (m, 1 H), 7.11 (m, 1 H), 7.42 (m, 1 H), 7.51 (m, 1 H), 10.29 (s, 0.6 H), 10.31 (s, 0.4 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 23.30/23.90 (1 C), 27.87–28.11 (3 C), 30.14/30.96 (1 C), 46.47/46.68 (1 C), 59.64/60.07 (1 C), 78.45/78.60 (1 C), 108.44, 121.26, 124.52, 136.71, 153.12/153.56 (1 C), 170.14/170.53 (1 C) ppm. LC–MS (ESI$^+$): *m*/*z* = 319.2 [M + Na]$^+$.

General Procedure for the Isolation of Deprotected Amino Amides 5a–5c: Trifluoroacetic acid (3 mL) was carefully added to a solution of **4a**–**4c** (500 mg) in CH_2Cl_2 (7 mL). The reaction mixture was stirred for 1.5 h at room temp. Trifluoroacetic acid and CH_2Cl_2 were then removed in vacuo and the crude mixture was dissolved in water (10 mL). The pH of the solution was adjusted to 8–9 by adding 28% aqueous ammonia and the solution was extracted with CH_2Cl_2 (2× 20 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and evaporated in vacuo to afford **5a**–**5c** (95–98%) as yellow waxes, which were used in the next reaction step without further purification.

General Procedure for the Synthesis of Thieno[3,2-*e*][1,4]diazepin-2-ones 6–23: To a solution of **5a**–**5c** (100 mg) in freshly distilled toluene (5 mL) kept under nitrogen were added molecular sieves 4 Å and the appropriate aldehyde (1 equiv.). The reaction mixture was stirred at 110 °C for 3 h under nitrogen. After the starting material was totally consumed (the reaction was monitored by TLC with CH_2Cl_2/EtOAc, 9:1 v/v), the reaction mixture was cooled to room temperature and the molecular sieves were filtered off. The solvent was removed in vacuo and the resulting mixture of two diastereomers was purified by flash chromatography (CH_2Cl_2/EtOAc) that, in some cases, allowed separation of diastereomers **α** and **β**.

(3*S*,5*R*)-3-Benzyl-5-(4-nitrophenyl)-1,3,4,5-tetrahydro-2*H*-thieno-[3,2-*e*][1,4]diazepin-2-one (6α): Orange wax, 34% (52.4 mg). $[\alpha]_D^{29}$ = –104.4 (*c* = 1.0, MeOH). ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 1.98 (s, 1 H), 3.07 (dd, *J* = 5.1, *J* = 13.8 Hz, 1 H), 3.31 (dd, *J* = 5.1, *J* = 13.8 Hz, 1 H), 4.00–4.03 (m, 1 H), 5.81 (s, 1 H), 6.94–7.02 (m, 4 H), 7.10–7.28 (m, 6 H), 7.99 (d, *J* = 8.4 Hz, 2 H) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 36.79, 60.55, 76.06, 112.32, 120.83, 124.18, 125.01, 127.21 (2 C), 127.65 (2 C), 128.95, 129.88 (3 C), 134.37, 136.11, 146.15, 148.22, 172.73 ppm. LC–MS (ESI$^+$): *m*/*z* = 380.1 [M + H]$^+$. HRMS: calcd. for $C_{20}H_{18}N_3O_3S$ 380.1069 [M + H]$^+$; found 380.1070.

(3*S*,5*S*)-3-Benzyl-5-(4-nitrophenyl)-1,3,4,5-tetrahydro-2*H*-thieno-[3,2-*e*][1,4]diazepin-2-one (6β): Orange wax, 38% (58.5 mg). $[\alpha]_D^{29}$ = –24.7 (*c* = 1.0, MeOH). ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 2.52 (s, 1 H), 3.11 (dd, *J* = 6.6, *J* = 14.1 Hz, 1 H), 3.16 (dd, *J* = 4.5, *J* = 14.1 Hz, 1 H), 3.99 (dd, *J* = 4.5, *J* = 6.6 Hz, 1 H), 5.68 (s, 1 H), 7.07–7.27 (m, 8 H), 7.40 (d, *J* = 8.7 Hz, 2 H), 8.13 (d, *J* = 8.7 Hz, 2 H) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 37.32, 59.26, 75.77, 111.51, 120.44, 124.31, 125.32, 127.05, 127.32 (3 C), 128.71 (3 C), 129.59, 134.63, 136.48, 146.23, 148.09, 172.55 ppm. LC–MS (ESI$^+$): *m*/*z* = 380.1 [M + H]$^+$. HRMS: calcd. for $C_{20}H_{18}N_3O_3S$ 380.1069 [M + H]$^+$; found 380.1071.

(3*S*,5*R*)-3-Benzyl-5-(4-bromophenyl)-1,3,4,5-tetrahydro-2*H*-thieno-[3,2-*e*][1,4]diazepin-2-one (7α): Pale yellow solid, 29% (48.6 mg), m.p. 112.0–114.1 °C. $[\alpha]_D^{29}$ = –122.3 (*c* = 1.0, MeOH). ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 1.94 (s, 1 H), 3.10 (dd, *J* = 4.5, *J* = 14.1 Hz, 1 H), 3.32 (dd, *J* = 5.4, *J* = 14.1 Hz, 1 H), 3.94–3.97 (m, 1 H), 5.64 (s, 1 H), 6.65–6.70 (m, 2 H), 6.99–7.11 (m, 3 H), 7.19–7.30 (m, 7 H) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 36.68, 60.72, 76.84, 112.21, 121.13, 123.41, 124.69, 127.25, 128.38, 129.08 (3 C), 129.94 (3 C), 132.31, 134.86, 136.27, 138.28, 173.17 ppm. LC–MS (ESI$^+$): *m*/*z* = 413.0 and 415.0 [M + H]$^+$. HRMS: calcd. for $C_{20}H_{18}BrN_2OS$ 413.0323 [M + H]$^+$; found 413.0322.

(3*S*,5*S*)-3-Benzyl-5-(4-bromophenyl)-1,3,4,5-tetrahydro-2*H*-thieno-[3,2-*e*][1,4]diazepin-2-one (7β): Pale yellow solid, 29% (48.7 mg), m.p. 127.8–129.0 °C. $[\alpha]_D^{29}$ = –28.1 (*c* = 1.0, MeOH). ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 2.30 (s, 1 H), 3.06 (dd, *J* = 6.6, *J* = 13.8 Hz, 1 H), 3.18 (dd, *J* = 4.5, *J* = 13.8 Hz, 1 H), 4.03 (dd, *J* = 4.5, *J* = 6.6 Hz, 1 H), 5.53 (s, 1 H), 7.09–7.17 (m, 5 H), 7.19–7.28 (m, 5 H), 7.44 (m, 2 H) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 37.65, 59.37, 76.30, 111.41, 120.67, 122.99, 124.87, 126.90, 127.85 (2 C), 128.60 (2 C), 129.60, 132.29 (3 C), 134.86, 136.90, 138.34, 172.64 ppm. LC–MS (ESI$^+$): *m*/*z* = 413.0 and 415.0 [M + H]$^+$. HRMS: calcd. for $C_{20}H_{18}BrN_2OS$ 413.0323 [M + H]$^+$; found 413.0325.

(3*S*,5*R*)-3-Benzyl-5-phenyl-1,3,4,5-tetrahydro-2*H*-thieno[3,2-*e*][1,4]-diazepin-2-one (8α): Pale yellow solid, 34% (46.2 mg), m.p. 123.1–126.1 °C. $[\alpha]_D^{29}$ = –118.4 (*c* = 1.0, MeOH). ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 1.92 (s, 1 H), 3.16 (dd, *J* = 4.8, *J* = 14.1 Hz, 1 H), 3.32 (dd, *J* = 5.4, *J* = 14.1 Hz, 1 H), 3.97 (dd, *J* = 4.8, *J* = 5.4 Hz, 1 H), 5.39 (s, 1 H), 6.87–6.90 (m, 2 H), 7.02–7.12 (m, 3 H), 7.16–7.17 (m, 8 H) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 36.82, 60.86, 77.61, 112.02, 121.26, 124.37, 126.68 (2 C), 127.14, 129.00 (2 C), 129.16, 129.22, 129.35, 129.87 (2 C), 135.23, 136.46, 139.24, 173.38 ppm. LC–MS (ESI$^+$): *m*/*z* = 335.2 [M + H]$^+$. HRMS: calcd. for $C_{20}H_{19}N_2OS$ 335.1218 [M + H]$^+$; found 335.1219.

(3*S*,5*S*)-3-Benzyl-5-phenyl-1,3,4,5-tetrahydro-2*H*-thieno[3,2-*e*][1,4]-diazepin-2-one (8β): Yellow solid, 35% (47.5 mg), m.p. 110.2–118.8 °C (degradation). $[\alpha]_D^{29}$ = –44.2 (*c* = 1.0, MeOH). ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 2.27 (s, 1 H), 3.06 (dd, *J* = 7.2, *J* = 14.1 Hz, 1 H), 3.20 (dd, *J* = 4.5, *J* = 14.1 Hz, 1 H), 4.08 (dd, *J* = 4.5, *J* = 7.2 Hz, 1 H), 5.58 (s, 1 H), 7.12–7.17 (m, 3 H), 7.20–7.33 (m, 10 H) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 38.15, 59.68, 77.19,

111.50, 121.02, 124.71, 126.22, 126.94, 128.69 (2 C), 129.18, 129.32 (3 C), 129.80 (2 C), 135.33, 137.43, 139.61, 172.89 ppm. LC–MS (ESI^+): m/z = 335.2 $[M + H]^+$. HRMS: calcd. for $C_{20}H_{19}N_2OS$ 335.1218 $[M + H]^+$; found 335.1217.

(3*S*,5*R*)-3-Benzyl-5-(4-methoxyphenyl)-1,3,4,5-tetrahydro-2*H*-thieno[3,2-*e*][1,4]diazepin-2-one (9α): Pale yellow wax, 25% (37.0 mg). $[\alpha]_D^{29}$ = –121.3 (c = 1.0, MeOH). ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.89 (s, 1 H), 3.14 (dd, J = 4.5, J = 13.8 Hz, 1 H), 3.32 (dd, J = 5.4, J = 14.1 Hz, 1 H), 3.72 (s, 3 H), 3.95 (m, 1 H), 5.64 (s, 1 H), 6.68–6.79 (m, 4 H), 7.09–7.12 (m, 3 H), 7.22–7.29 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 36.59, 55.18, 60.64, 77.14, 111.98, 114.38 (2 C), 121.24, 124.14, 127.00, 127.86 (2 C), 128.88, 129.77 (2 C), 131.08, 135.14, 136.36, 160.17, 162.41, 173.22 ppm. LC–MS (ESI^+): m/z = 365.2 $[M + H]^+$. HRMS: calcd. for $C_{21}H_{21}N_2O_2S$ 365.1324 $[M + H]^+$; found 365.1323.

(3*S*,5*S*)-3-Benzyl-5-(4-methoxyphenyl)-1,3,4,5-tetrahydro-2*H*-thieno[3,2-*e*][1,4]diazepin-2-one (9β): Pale yellow wax, 24% (35.5 mg). $[\alpha]_D^{29}$ = –70.7 (c = 1.0, MeOH). ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.19 (s, 1 H), 3.04 (dd, J = 7.2, J = 13.8 Hz, 1 H), 3.18 (dd, J = 4.2, J = 13.8 Hz, 1 H), 3.74 (s, 3 H), 4.08 (dd, J = 4.2, J = 7.2 Hz, 1 H), 5.53 (s, 1 H), 6.81–6.84 (d, J = 8.7 Hz, 2 H), 7.10–7.28 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 38.04, 55.24, 59.61, 76.74, 111.44, 114.48 (2 C), 120.95, 124.43, 126.72, 127.39 (2 C), 128.48 (2 C), 129.62, 131.50, 135.16, 137.34, 160.04, 162.42, 172.76 ppm. LC–MS (ESI^+): m/z = 365.2 $[M + H]^+$. HRMS: calcd. for $C_{21}H_{21}N_2O_2S$ 365.1324 $[M + H]^+$; found 365.1324.

(3*S*,5*R*)-3-Benzyl-5-isobutyl-1,3,4,5-tetrahydro-2*H*-thieno[3,2-*e*][1,4]diazepin-2-one (10α): Pale yellow solid, 50% (64.0 mg), m.p. 66.7–67.4 °C. $[\alpha]_D^{29}$ = –122.2 (c = 1.0, MeOH). ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.90 (d, J = 6.3 Hz, 3 H), 0.92 (d, J = 6.6 Hz, 3 H), 1.36–1.54 (m, 2 H), 1.81 (m, 1 H), 2.08 (s, 1 H), 3.13 (d, J = 5.1 Hz, 2 H), 3.93 (t, J = 5.1 Hz, 1 H), 4.67 (dd, J = 3.0, J = 9.9 Hz, 1 H), 7.15–7.30 (m, 8 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.48, 23.79, 24.71, 36.81, 42.09, 59.63, 73.76, 111.68, 120.97, 125.09, 126.92, 126.97, 128.70, 129.83 (2 C), 135.11, 136.90, 172.65 ppm. LC–MS (ESI^+): m/z = 315.2 $[M + H]^+$. HRMS: calcd. for $C_{18}H_{23}N_2OS$ 315.1531 $[M + H]^+$; found 315.1531.

(3*S*,5*S*)-3-Benzyl-5-isobutyl-1,3,4,5-tetrahydro-2*H*-thieno[3,2-*e*][1,4]diazepin-2-one (10β): Pale yellow wax, 25% (32.0 mg). $[\alpha]_D^{29}$ = –74.8 (c = 1.0, MeOH). ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.80–0.90 (m, 7 H), 1.55–1.64 (m, 1 H), 1.66–1.74 (m, 1 H), 1.89 (m, 1 H), 3.09 (dd, J = 6.9, J = 14.1 Hz, 1 H), 3.18 (dd, J = 4.5, J = 14.1 Hz, 1 H), 3.86 (dd, J = 4.5, J = 6.9 Hz, 1 H), 4.91 (dd, J = 2.1, J = 9.6 Hz, 1 H), 7.11 (d, J = 5.4 Hz, 1 H), 7.20–7.32 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.74, 23.92, 24.09, 38.14, 43.99, 60.89, 73.35, 113.74, 122.02, 125.02, 126.94, 128.68 (3 C), 129.75, 134.97, 137.40, 172.89 ppm. LC–MS (ESI^+): m/z = 315.2 $[M + H]^+$. HRMS: calcd. for $C_{18}H_{23}N_2OS$ 315.1531 $[M + H]^+$; found 315.1532.

(3*S*,5*S*)-3-Benzyl-5-cyclohexyl-1,3,4,5-tetrahydro-2*H*-thieno[3,2-*e*][1,4]diazepin-2-one (11β): White solid, 34% (47.0 mg), m.p. 109.9–112.5 °C. $[\alpha]_D^{29}$ = –93.2 (c = 1.0, MeOH). ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.01–1.27 (m, 5 H), 1.47 (m, 2 H), 1.59–1.74 (m, 4 H), 2.05 (s, 1 H), 3.03 (dd, J = 6.3, J = 14.1 Hz, 1 H), 3.62 (dd, J = 4.5, J = 14.1 Hz, 1 H), 3.92–3.96 (m, 1 H), 4.63 (d, J = 1.8 Hz, 1 H), 7.13 (d, J = 5.1 Hz, 1 H), 7.21–7.30 (m, 6 H), 7.33 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.86, 25.71, 26.25, 26.28, 29.07, 38.05, 41.23, 61, 78.79, 113.10, 121.58, 124.93 (2 C), 126.87 (2 C), 128.72, 129.65, 134.92, 136.97, 172.79 ppm. LC–MS (ESI^+): m/z = 341.2 $[M + H]^+$. HRMS: calcd. for $C_{20}H_{25}N_2OS$ 341.1688 $[M + H]^+$; found 341.1689.

3-Methyl-5-(4-nitrophenyl)-1,3,4,5-tetrahydro-2*H*-thieno[3,2-*e*][1,4]-diazepin-2-one (12): Yellow wax, 88% (156.8 mg); two diastereomers detected by NMR in $CDCl_3$. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.36–1.41 (m, 3 H), 2.24 (s, 1 H), 3.63–3.73 (m, 1 H), 5.89 (s, 0.4 H), 5.93 (s, 0.6 H), 6.99–7.02 (m, 1 H), 7.09–7.20 (m, 2 H), 7.40–7.50 (m, 2 H), 8.14 (d, J = 9.0 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.04–18.13 (1 C), 54.06–55.74 (1 C), 75.52–76.06 (1 C), 110.94 (1 C), 112.20 (1 C), 120.28–120.93 (1 C), 124.38–124.47 (2 C), 125.18–125.49 (1 C), 127.44–127.93 (2 C), 135.11 (1 C), 146.25–146.47 (1 C), 174.06 (1 C) ppm. LC–MS (ESI^+): m/z = 304.1 $[M + H]^+$. HRMS: calcd. for $C_{14}H_{14}N_3O_3S$ 304.0756 $[M + H]^+$; found 304.0755.

3-Methyl-5-(4-bromophenyl)-1,3,4,5-tetrahydro-2*H*-thieno[3,2-*e*]-[1,4]diazepin-2-one (13): Uncoloured wax, 61% (120.8 mg); two diastereomers detected by NMR in $CDCl_3$. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.45 (d, J = 6.6 Hz, 2 H), 1.51 (d, J = 6.6 Hz, 1 H), 2.20 (s, 1 H), 3.72–3.85 (m, 1 H), 5.82 (s, 0.4 H), 5.89 (s, 0.6 H), 7.12–7.14 (m, 1 H), 7.17–7.30 (m, 4 H), 7.51–7.55 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.39–17.89 (1 C), 54.08–55.89 (1 C), 76.08–76.74 (1 C), 110.95–110.97 (1 C), 120.59–121.09 (1 C), 121.35 (1 C), 124.77–125.10 (1 C), 128.02–128.47 (2 C), 132.48–132.62 (2 C) 135.36 (1 C), 138.35–138.42 (1 C), 161.26 (1 C) ppm. LC–MS (ESI^+): m/z = 337.0 and 339.0 $[M + H]^+$. HRMS: calcd. for $C_{14}H_{14}N_2OSBr$ 337.0010 $[M + H]^+$; found 337.0009.

3-Methyl-5-phenyl-1,3,4,5-tetrahydro-2*H*-thieno[3,2-*e*][1,4]diazepin-2-one (14): Pale yellow wax, 36% (54.6 mg); two diastereomers detected by NMR in $CDCl_3$. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.42 (d, J = 6.8 Hz, 1.8 H), 1.48 (d, J = 6.8 Hz, 1.2 H), 2.12 (s, 1 H), 3.71 (q, J = 6.8 Hz, 0.4 H), 3.83 (q, J = 6.8 Hz, 0.6 H), 5.80 (s, 0.4 H), 5.89 (s, 0.6 H), 7.09–7.26 (m, 4 H), 7.30–7.37 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 17.54–17.75 (1 C), 54.10–55.98 (1 C), 76.71 (1 C), 110.82–111.70 (1 C), 120.72–121.13 (1 C), 124.45–124.79 (1 C), 126.19–126.67 (2 C), 129.16–129.36 (1 C), 129.44–129.56 (2 C), 135.39–135.52 (1 C), 139.26 (1 C), 174.36–175.01 (1 C) ppm. LC–MS (ESI^+): m/z = 259.1 $[M + H]^+$. HRMS: calcd. for $C_{14}H_{15}N_2OS$ 259.0905 $[M + H]^+$; found 259.0905.

(3*S*,5*S*)-3-Methyl-5-isobutyl-1,3,4,5-tetrahydro-2*H*-thieno[3,2-*e*][1,4]diazepin-2-one (16): Pale yellow wax, 58% (81.2 mg). $[\alpha]_D^{29}$ = –47.6 (c = 1.0, MeOH). ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.89 (d, J = 6.6 Hz, 3 H), 0.94 (d, J = 6.6 Hz, 3 H), 1.33 (d, J = 6.9 Hz, 3 H), 1.44–1.49 (m, 2 H), 1.80–1.89 (m, 1 H), 1.99 (m, 1 H), 3.63 (q, J = 6.9 Hz, 1 H), 4.89–4.93 (m, 1 H), 7.23–7.24 (m, 2 H), 7.30 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 16.80, 21.45, 23.73, 24.90, 41.58, 54.32, 73.46, 110.58, 120.40, 125.10, 135.26, 173.77 ppm. LC–MS (ESI^+): m/z = 239.2 $[M + H]^+$. HRMS: calcd. for $C_{12}H_{19}N_2OS$ 239.1218 $[M + H]^+$; found 239.1219.

(3*S*,5*S*)-3-Methyl-5-cyclohexyl-1,3,4,5-tetrahydro-2*H*-thieno[3,2-*e*][1,4]diazepin-2-one (17): Pale yellow wax, 58% (90.0 mg). $[\alpha]_D^{29}$ = –42.4 (c = 1.0, MeOH). ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.95–1.26 (m, 5 H), 1.31 (d, J = 6.9 Hz, 3 H), 1.47–1.73 (m, 6 H), 1.97 (s, 1 H), 3.63 (q, J = 6.9 Hz, 1 H), 4.81 (d, J = 2.7 Hz, 1 H), 7.17–7.25 (m, 2 H), 7.35 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.21, 25.12, 25.80, 26.30, 26.36, 29.38, 41.32, 56.06, 78.63, 112.31, 121.34, 125.00, 135.16, 174.17 ppm. LC–MS (ESI^+): m/z = 265.1 $[M + H]^+$. HRMS: calcd. for $C_{14}H_{21}N_2OS$ 265.1375 $[M + H]^+$; found 265.1375.

(3*S*,5*R*)-10-(4-Nitrophenyl)-4,5a,6,7,8,10-hexahydro-5*H*-pyrrolo-[1,2-*a*]thieno[3,2-*e*][1,4]diazepin-2-one (18α): Pale orange wax, 20% (33.6 mg). $[\alpha]_D^{29}$ = +30.9 (c = 1.0, MeOH). ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.62–1.70 (m, 2 H), 2.05–2.22 (m, 3 H), 2.26–2.37 (m, 1 H), 3.94 (dd, J = 5.1, J = 8.7 Hz, 1 H), 6.22 (s, 1 H), 6.92–6.96 (m, 2 H), 7.07–7.10 (m, 1 H), 7.42 (d, J = 8.4 Hz, 2 H), 8.11

(t, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.94, 26.95, 49.25, 65.33, 78.73, 111.98, 121.01, 123.74 (*3 C*), 124.79, 129.08, 135.03, 141.74, 148.11, 175.43 ppm. LC–MS (ESI$^+$): m/z = 330.1 [M + H]$^+$. HRMS: calcd. for $C_{16}H_{16}N_3O_3S$ 330.0912 [M + H]$^+$; found 330.0915.

(3*S*,5*S*)-10-(4-Nitrophenyl)-4,5a,6,7,8,10-hexahydro-5*H*-pyrrolo-[1,2-*a*]thieno[3,2-*e*][1,4]diazepin-2-one (18β): Pale orange wax, 62% (104.0 mg). $[\alpha]_D^{29}$ = +8.8 (c = 1.0, MeOH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.83–1.92 (m, 2 H), 2.14–2.21 (m, 2 H), 2.90 (td, J = 8.7 Hz, 1 H), 3.41–3.47 (m, 1 H), 3.91 (t, J = 6.6 Hz, 1 H), 5.66 (s, 1 H), 7.17–7.24 (m, 3 H), 7.44 (d, J = 8.7 Hz, 2 H), 8.18 (t, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.88, 27.44, 56.40, 63.70, 82.66, 111.10, 120.28, 124.26 (2 C), 125.37, 127.05 (2 C), 135.23, 146.30, 147.97, 173.56 ppm. LC–MS (ESI$^+$): m/z = 330.1 [M + H]$^+$. HRMS: calcd. for $C_{16}H_{16}N_3O_3S$ 330.0912 [M + H]$^+$; found 330.0914.

(3*S*,5*R*)-10-(4-Bromophenyl)-4,5a,6,7,8,10-hexahydro-5*H*-pyrrolo-[1,2-*a*]thieno[3,2-*e*][1,4]diazepin-2-one (19α): Pale yellow wax, 16% (29.6 mg). $[\alpha]_D^{29}$ = –4.2 (c = 1.0, MeOH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.60–1.68 (m, 2 H), 2.08–2.24 (m, 3 H), 2.31–2.40 (m, 1 H), 3.92 (dd, J = 5.1, J = 9.0 Hz, 1 H), 6.08 (s, 1 H), 6.92–6.98 (m, 2 H), 7.05–7.10 (m, 3 H), 7.40 (d, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 25.01, 27.20, 49.22, 65.38, 79.28, 111.88, 121.22, 123.13, 124.47, 129.74 (2 C), 131.91 (2 C), 133.71, 135.33, 175.63 ppm. LC–MS (ESI$^+$): m/z = 363.1 and 365.1 [M + H]$^+$. HRMS: calcd. for $C_{16}H_{16}N_2OSBr$ 363.0167 [M + H]$^+$; found 363.0166.

(3*S*,5*S*)-10-(4-Bromophenyl)-4,5a,6,7,8,10-hexahydro-5*H*-pyrrolo-[1,2-*a*]thieno[3,2-*e*][1,4]diazepin-2-one (19β): Pale yellow wax, 62% (114.7 mg). $[\alpha]_D^{29}$ = +16.0 (c = 1.0, MeOH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.78–1.88 (m, 2 H), 2.11–2.18 (m, 2 H), 2.81 (td, J = 8.1, J = 9.0 Hz, 1 H), 3.36–3.43 (m, 1 H), 3.92 (t, J = 6.6 Hz, 1 H), 6.23 (s, 1 H), 7.13 (d, J = 8.4 Hz, 2 H), 7.17–7.21 (m, 3 H), 7.45 (d, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.73, 27.33, 56.18, 63.64, 83.05, 109.56, 110.92, 120.50, 122.57, 124.98, 127.66 (2 C), 132.18, 135.51, 138.34, 173.78 ppm. LC–MS (ESI$^+$): m/z = 363.1 and 365.1 [M + H]$^+$. HRMS: calcd. for $C_{16}H_{16}N_2OSBr$ 363.0167 [M + H]$^+$; found 363.0168.

(3*S*,5*S*)-10-Phenyl-4,5a,6,7,8,10-hexahydro-5*H*-pyrrolo[1,2-*a*]thieno-[3,2-*e*][1,4]diazepin-2-one (20β): White powder, 78% (113.0 mg), m.p. 147.9–150.1 °C. $[\alpha]_D^{29}$ = +27.9 (c = 1.0, MeOH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.83–1.89 (m, 2 H), 2.13–2.20 (m, 2 H), 2.82 (td, J = 8.1 Hz, 1 H), 3.42 (m, 1 H), 3.98 (t, J = 6.6 Hz, 1 H), 5.57 (s, 1 H), 7.13–7.36 (m, 8 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.90, 27.38, 56.32, 63.77, 83.82, 110.85, 120.74, 124.82, 125.94 (2 C), 128.70, 129.18, 132.69, 135.86, 139.25, 173.97 ppm. LC–MS (ESI$^+$): m/z = 285.1 [M + H]$^+$. HRMS: calcd. for $C_{16}H_{17}N_2OS$ 285.1062 [M + H]$^+$; found 285.1062.

(3*S*,5*S*)-10-(4-Methoxyphenyl)-4,5a,6,7,8,10-hexahydro-5*H*-pyrrolo-[1,2-*a*]thieno[3,2-*e*][1,4]diazepin-2-one (21β): Uncoloured wax, 73% (117.0 mg). $[\alpha]_D^{29}$ = +33.3 (c = 1.0, MeOH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.76–1.85 (m, 2 H), 2.09–2.16 (m, 2 H), 2.77 (td, J = 8.1, J = 9 Hz, 1 H), 3.33–3.39 (m, 1 H), 3.71 (s, 3 H), 3.94 (t, J = 6.6 Hz, 1 H), 5.51 (s, 1 H), 6.83 (d, J = 8.7 Hz, 2 H), 7.10–7.23 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.79, 27.29, 55.24, 56.00, 63.67, 83.33, 110.76 (2 C), 114.45, 120.71, 124.62, 127.12 (2 C), 131.39, 135.84, 159.73, 173.81 ppm. LC–MS (ESI$^+$): m/z = 315.1 [M + H]$^+$. HRMS: calcd. for $C_{17}H_{19}N_2O_2S$ 315.1167 [M + H]$^+$; found 315.1168.

(3*S*,5*S*)-10-Isobutyl-4,5a,6,7,8,10-hexahydro-5*H*-pyrrolo[1,2-*a*]-thieno[3,2-*e*][1,4]diazepin-2-one (22β): White powder, 70% (179.0 mg). 59.0–59.7 °C. $[\alpha]_D^{29}$ = –55.7 (c = 1.0, MeOH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.89 (d, J = 6.6 Hz, 3 H), 0.96 (d, J = 6.6 Hz, 3 H), 1.38–1.54 (m, 2 H), 1.69–1.81 (m, 2 H), 1.86–2.52 (m, 3 H), 2.56 (td, J = 7.2, J = 9.0 Hz, 1 H), 3.15–3.22 (m, 1 H), 3.86 (dd, J = 4.2, J = 9.0 Hz, 1 H), 4.62 (dd, J = 3, J = 9.3 Hz, 1 H), 7.20–7.27 (m, 2 H), 7.34 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.45, 23.56, 24.73, 24.90, 27.19, 42.87, 55.87, 63.98, 80.89, 110.38, 120.34, 124.88, 135.64, 173.34 ppm. LC–MS (ESI$^+$): m/z = 265.1 [M + H]$^+$. HRMS: calcd. for $C_{14}H_{21}N_2OS$ 265.1375 [M + H]$^+$; found 265.1375.

(3*S*,5*S*)-10-Cyclohexyl-4,5a,6,7,8,10-hexahydro-5*H*-pyrrolo[1,2-*a*]-thieno[3,2-*e*][1,4]diazepin-2-one (23β): White powder, 92% (258.0 mg). 168.5–169.8 °C. $[\alpha]_D^{29}$ = –63.2 (c = 1.0, MeOH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.99–1.24 (m, 4 H), 1.39–1.79 (m, 9 H), 1.91–2.02 (m, 1 H), 2.10–2.22 (m, 1 H), 2.67 (td, J = 6.6, J = 8.7 Hz, 1 H), 3.22–3.29 (m, 1 H), 3.88 (dd, J = 4.8, J = 8.7 Hz, 1 H), 4.50 (dd, J = 2.4 Hz, 1 H), 7.24–7.30 (m, 2 H), 7.43 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 25.07, 25.27, 25.63, 26.06, 26.18, 28.66, 28.92, 41.43, 58.12, 65.77, 87.24, 112.12, 121.67, 124.67, 135.29, 173.63 ppm. LC–MS (ESI$^+$): m/z = 291.1 [M + H]$^+$. HRMS: calcd. for $C_{16}H_{23}N_2OS$ 291.1531 [M + H]$^+$; found 291.1532.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of intermediates and final compounds, and NOESY experiment of diastereomers **10α**, **10β**, **18α** and **18β**.

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