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An Entry into Hexahydro-2*H*-thieno[2,3-*c*]pyrrole 1,1-Dioxide Derivatives

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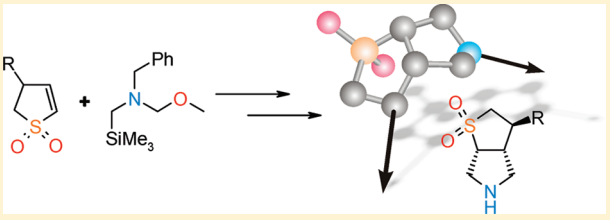
Supporting Information

ABSTRACT: Hexahydro-2*H*-thieno[2,3-*c*]pyrrole is proposed as a low molecular weight polar scaffold to construct compound libraries used in the search for new drugs. Practical syntheses of derivatives of this bicyclic scaffold were developed, based on [3 + 2] cycloaddition of the ylide generated from *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)-methyl)methanamine and 4-substituted 2,3-dihydrothiophene 1,1-dioxides. All of the 3-substituted hexahydro-2*H*-thieno[2,3-*c*]pyrrole 1,1-dioxide derivatives were obtained as single diastereomers. Conformational properties of the hexahydro-2*H*-thieno[2,3-*c*]pyrrole 1,1-dioxide derivatives were explored using X-ray diffraction studies. The potential of the scaffold to generate libraries of 3D-shaped molecules was demonstrated.



INTRODUCTION

Aromatic heterocyclic compounds have always been a major source of building blocks used in drug design. There are at least two reasons behind this: the heteroatoms and the aromatic π-system ensure binding of heterocyclic molecules to biological targets, whereas the ring systems provide conformationally restricted templates, or scaffolds, for constructing the molecules of potential drug candidates. A variety of synthetic methods have been developed for the synthesis of numerous aromatic heterocycles during the more than one-hundred year history of chemistry of heterocyclic compounds. However, aromatic heterocycles are flattened; therefore, libraries of their derivatives cannot be sufficiently structurally diverse. Structural diversity is a very important requirement for the compounds used in the search for new drugs;[1,2] therefore, the latest tendencies in drug design demonstrated attempts to move away from this "flattened" part of chemical space by increasing saturation and introducing chirality into the scaffolds.[2] Implementation of these principles leads to saturated heterocyclic compounds as preferred template structures.

The simplest saturated heterocycles are rather flexible, whereas conformational restriction is considered as one of the essential properties of drug molecules.[3] Bicyclic scaffolds are more beneficial in this respect due to their inherent conformational restrictions. For example, bicyclic pyrrolidine derivatives were widely used in drug design: antibacterials Moxifloxacin and Trovafloxacin,[4] antipsychotic Asenapine,[5] or antidiabetic Mitiglinide[6] can be mentioned as examples (Figure 1). However, a drawback of the saturated bicyclic scaffolds is their enhanced lipophilicity which imposes serious limitations on further optimization of the potential drug molecules.[7] In a search for new saturated hydrophilic scaffolds, we turned our attention to bicyclic sulfones. The sulfone moiety, in addition to the decrease of the lipophilicity, can be involved in the interaction of the molecules with biological targets. We were encouraged by the fact that several compounds possessing a cyclic sulfone moiety have reached preclinical or clinical trials: antiglaucoma agent Dorzolamide,[8] antitrypanosomal drug Nifurtimox,[9] and compounds with antiviral[10] or antipsychotic[11] activity (Figure 2). We would like to highlight the latter example (compound **1**), which is particularly relevant to the concept we pursue in this work: the nonplanar, bicyclic saturated scaffold of **1** features the sulfone moiety and the functional groups positioned properly in space to interact with the biological target, metabotropic glutamate receptors.

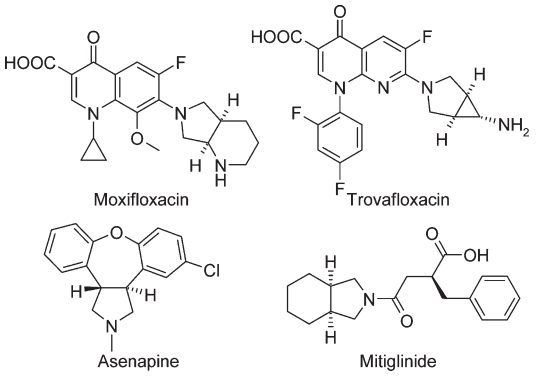


Figure 1. Fused pyrrolidine derivatives — marketed drugs.

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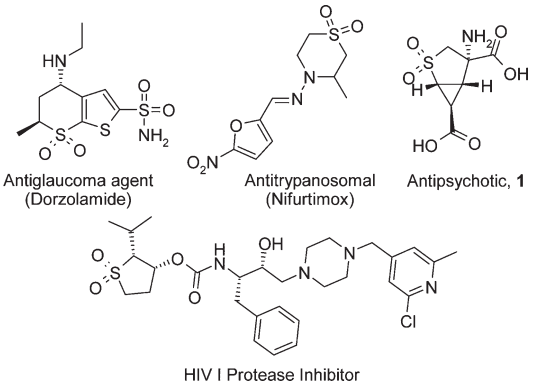
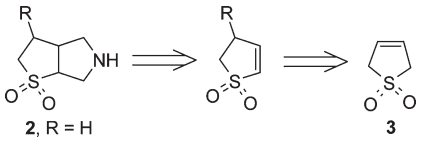
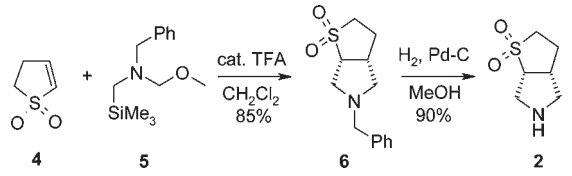


Figure 2. Biologically active cyclic sulfones.

Scheme 1. Retrosynthetic Analysis of Hexahydro-2*H*-thieno[2,3-*c*]pyrrole 1,1-Dioxide Scaffold



Scheme 2[a]



[a] Relative configurations are shown.

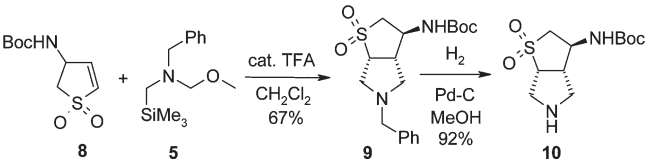
In this work, we report on an approach to the synthesis of the previously unknown saturated heterocyclic system — hexahydro-2*H*-thieno[2,3-*c*]pyrrole 1,1-dioxide **2** — a combination of pyrrolidine and sulfolane rings. We demonstrated that libraries of functionalized derivatives of **2** are easy to obtain and studied their essentialy nonflattened, three-dimensional structure. Calculated values of some physicochemical properties of **2** (*i.e.*, molecular weight 161.2, cLog *P* −1.25, TPSA 54.6 Å^2)[12] suggest the use of the derivatives of this scaffold in medicinal chemistry as building blocks for drug design.

RESULTS AND DISCUSSION

Synthesis. Our approach to the synthesis of **2** and its derivatives involved construction of a pyrrolidine ring *via* [3 + 2] cycloaddition reaction[13] to 2,3-dihydrothiophene 1,1-dioxide derivatives. The latter can be obtained from readily available sulfolene **3** by the methods reported in the literature (Scheme 1).[14−17] The presence of an electron-withdrawing sulfone moiety was expected to activate the double bond in the dipolarophiles toward the cycloaddition. It should be noted, however, that only a few reports on the analogous transformations involving vinyl sulfones were found in the literature to date.[18]

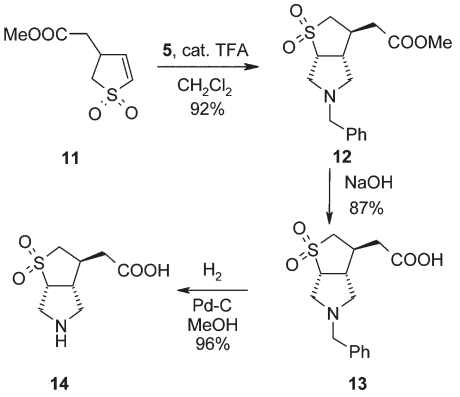
Reaction of the parent 2,3-dihydrothiophene 1,1-dioxide **4**[14] with the ylide generated from *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine **5** proceeded smoothly to give the benzyl derivative **6** in 85% yield (Scheme 2). It should be noted that using a 2-fold excess of **5** significantly improved the yield of the reaction. Deprotection of **6** gave the parent bicyclic compound, hexahydro-2*H*-thieno[2,3-*c*]pyrrole 1,1-dioxide **2**, which was isolated as the hydrochloride.

Scheme 3[a]



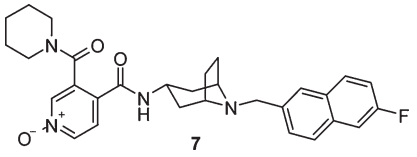
[a] Relative configurations are shown.

Scheme 4[a]



[a] Relative configurations are shown.

It would be of interest to obtain functionalized derivatives of **2** which could be used for constructing libraries of substituted analogues. Such libraries are often used in the search for lead compounds in medicinal chemistry and to fine-tune the biological activity of a lead. We refer here to a relevant successful example **7**,[19] taken randomly from the recent literature, where the authors modified the substituents around a bicyclic diamine scaffold and found a novel antagonist of a CC chemokine receptor CCR3 with reduced human cytochrome P450 2D6 inhibitory activity.



To synthesize functionalized analogs of **2**, we have tested derivatives of **4** in the reaction with the compound **5**. Using the *N*-Boc-protected amino derivative **8**[16] as the starting material, compound **9** was obtained as a single diastereomer in 67% yield (Scheme 3). It is interesting to note that the nonprotected (1,1-dioxido-2,3-dihydro-3-thienyl)amine did not undergo reaction with **5** under identical conditions. Debenzylation of **9** allowed selectively monoprotected diamine **10** to be obtained.

Amino ester **12** was obtained in 92% yield as a single diastereomer in the reaction between another derivative of **4**, compound **11**,[15] and the ylide generated from **5** (Scheme 4). Compound **12** was transformed into **13** upon alkaline hydrolysis. Finally, deprotection of **13** gave the amino acid **14**.

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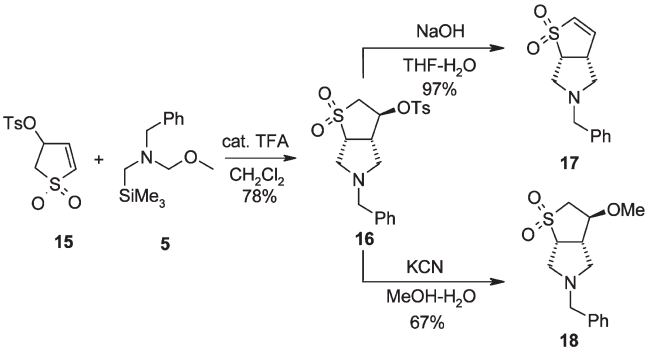
Scheme 5[a]



[a] Relative configurations are shown.

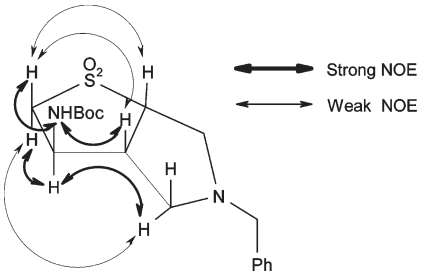


Figure 3. Significant correlations observed in the NOESY spectra of **9**.

The reaction of tosylate **15**[17] and **5** gave compound **16** as a single diastereomer in 78% yield (Scheme 5), which also can be used as an intermediate in syntheses of derivatives of **2**. Direct nucleophilic displacement of the OTs group in **16** was however accompanied by the elimination reaction, resulting in the formation of α,β-unsaturated sulfone **17**. In particular, compound **17** was obtained in almost quantitative yield by treatment of **9** with sodium hydroxide in aqueous THF. Reaction of **16** and potassium cyanide in aqueous methanol resulted in the formation of compound **18** instead of the expected nitrile. As the configuration at the electrophilic center was retained during the formation of **18**, we believe that **17** might be involved in this reaction as an intermediate.

To establish the relative stereochemistry of the obtained hexahydro-2*H*-thieno[2,3-*c*]pyrrole 1,1-dioxide derivatives, NOESY experiments and X-ray diffraction studies were performed. In particular, correlations observed in the NOESY spectrum of **9** were evident for the expected *cis*-fusion of the five-membered rings and for the *trans*-disposition of the Boc-amino substituent and the pyrrolidine ring (Figure 3). The *trans*-configuration was also confirmed by X-ray diffraction studies of **10**, **12**, **16**, and **18** (Figure 4).

Molecular Structure. Although compounds **10**, **12**, **16**, and **18** have the same relative configuration, their conformations observed in crystals are quite different (Figure 4; the atom numbering in Figure 4 will be used throughout this section). The five-membered rings adopt the envelope conformation in compounds **10**, **12**, and **16** with deviation of the C2 and N1 atoms from the mean plane of the remaining atoms of

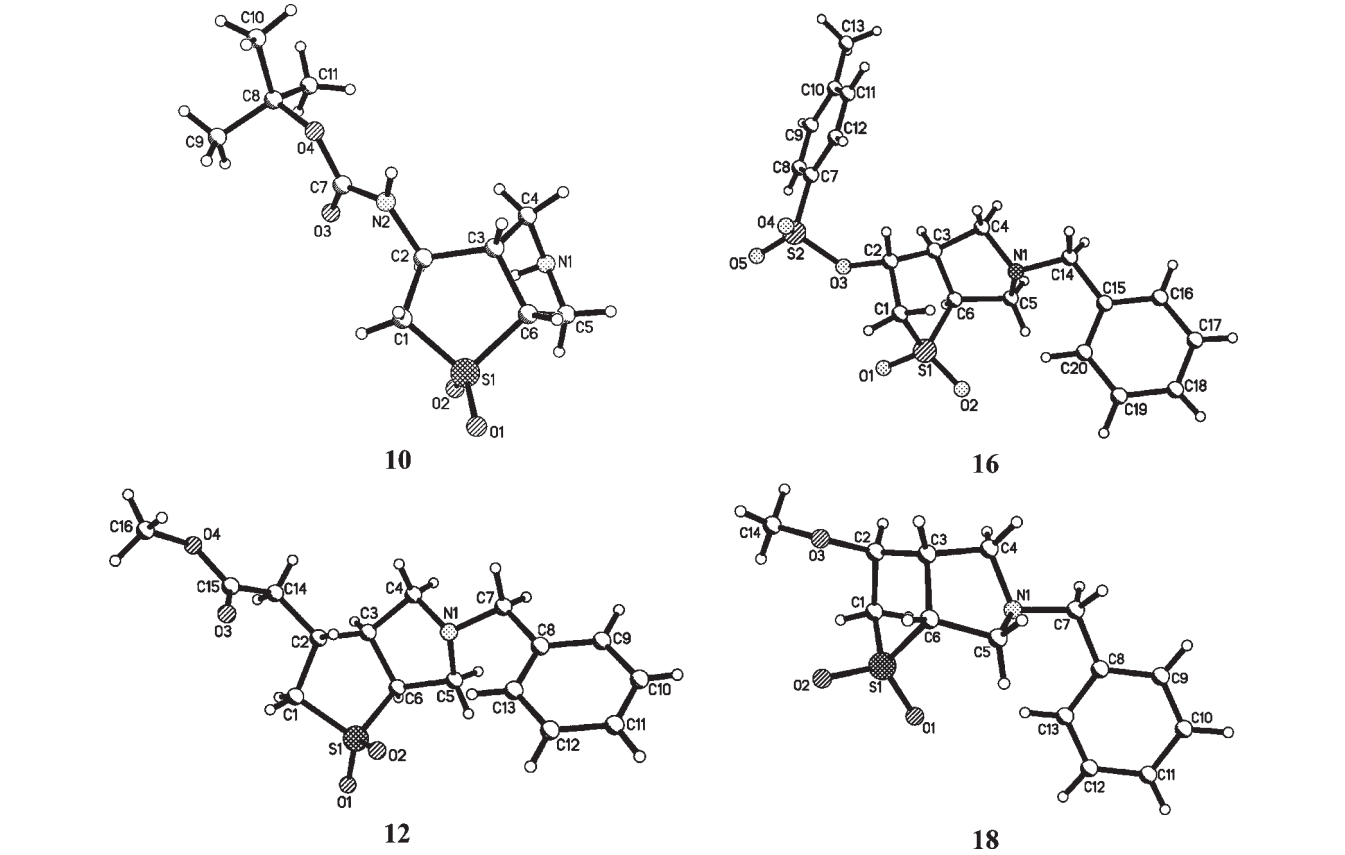


Figure 4. Molecular structures of **10**, **12**, **16**, and **18**.

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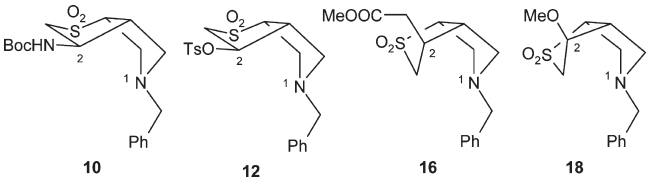

Figure 5. Conformations of **10**, **12**, **16**, and **18** observed in crystals (schematic representation).

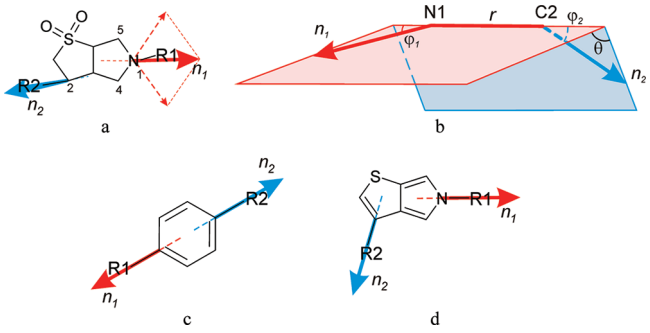

Figure 6. (a) Definition of vectors $\boldsymbol{n_1}$, $\boldsymbol{n_2}$ (scaffold **2** is given as an example); (b) definition of geometric parameters r, φ_1, φ_2, and θ; (c) vectors $\boldsymbol{n_1}$, $\boldsymbol{n_2}$ shown for benzene scaffold; (d) vectors $\boldsymbol{n_1}$, $\boldsymbol{n_2}$ shown for 2*H*-thieno[2,3-*c*]pyrrole scaffold.

corresponding rings. However, the directions of these deviations are different (Figure 5). The C2 and N1 atoms deviate correspondingly to the *exo* and *endo* directions with respect to the thienopyrrole bicycle in molecules of **10** and **12**, leading to a chairlike shape of the bicyclic fragment. In the case of **16**, both the C2 and N1 atoms deviate to the *endo* direction, which causes a boat-like shape of the bicyclic fragment. Five-membered rings in **18** adopt a twist conformation; in this case, the bicyclic scaffold also has a boat-like shape. These differences lead to the pseudoequatorial orientation of the substituent at the C-3 atom in the molecules of **10** and **12** and the pseudoaxial orientation for **16** and **18**.

All these differences indicate that the structure of the hexahydro-2*H*-thieno[2,3-*c*]pyrrole 1,1-dioxide core depends significantly on the nature of the substituent at C2. In particular, the conformations observed in the solid state are more or less similar for compounds **10** and **12** and different for **16** and **18**.

An important aspect of the conformational preferences of the hexahydro-2*H*-thieno[2,3-*c*]pyrrole 1,1-dioxide derivatives is their deviation from the "flattened" structure. Recently, we have proposed quantitative geometric parameters to estimate this property of molecular scaffolds.[20] In essence, a scaffold can be characterized by the relative spatial orientation of the substituents attached to the variation points. The role of the scaffold itself is reduced to providing this relative orientation. Hence only those parts of the molecule which are the most significant to interactions with potential biological targets are considered, an idea which has been embodied in the pharmacophore concept.[21]

In the case of scaffold **2**, the substituents attached to the variation points of the scaffold can be simulated by two vectors, $\boldsymbol{n_1}$ and $\boldsymbol{n_2}$ (Figure 6a).[22] The attachment points N1 and C2 can be regarded as the starting points of $\boldsymbol{n_1}$ and $\boldsymbol{n_2}$, respectively. To define the direction of $\boldsymbol{n_2}$, the **C2R2** vector can be used, whereas, for $\boldsymbol{n_1}$, the normalized sum of the vectors **C4N1** and **C5N1** is more convenient, as the nitrogen atom N1 is configurationally

Table 1. Values of the Parameters r, φ_1, φ_2, and θ Obtained from the X-ray Diffraction Data on Hexahydro-2*H*-thieno-[2,3-*c*]pyrrole 1,1-Dioxide Derivatives

Entry No.	Compound	r, Å	φ_1, deg	φ_2, deg	θ, deg
1	**10**	3.248	54.2	126.7	101.5
2	**12**	3.115	62.8	131.9	93.4
3	**16**	3.263	58.1	146.5	30.3
4	**18**	3.363	54.0	140.6	26.7

unstable. The relative orientation of these vectors can be described by four parameters: the distance r between the atoms N1 and C2, the plane angles φ_1 (between vectors $\boldsymbol{n_1}$ and **C2N1**) and φ_2 (between $\boldsymbol{n_2}$ and **N1C2**), and the dihedral angle θ defined by vectors $\boldsymbol{n_1}$, **N1C2**, and $\boldsymbol{n_2}$ (Figure 6b).

If this approach is applied to a "linear" 1,4-disubstituted benzene scaffold (Figure 6c), the following values of the angles are obtained: $\varphi_1 = \varphi_2 = 0°$ (θ is undefined). For 2,6-disubstituted derivatives of 2*H*-thieno[2,3-*c*]pyrrole — a "flattened" aromatic analogue of **2** (Figure 6d) — φ_1 and φ_2 are nonzero, whereas $\theta = 0°$. These examples show that the values of φ_1 and φ_2 close to 0° are characteristic of the "linear" relative disposition of the substituents attached to the scaffold, whereas θ values close to 0° (or 180°) correspond to the "flattened" structures.

The values of the above-defined geometric parameters for compounds **10**, **12**, **16**, and **18**, calculated from the X-ray diffraction data, are given in Table 1. As follows from these data, there is a significant difference in the values of θ observed for the compounds **10** and **12** (101.5° and 93.4°) and **16** and **18** (26.7° and 30.3°, respectively). Nevertheless, all these values are far from 0° or 180° characteristic of the "flattened" cores. The values of φ_1 and φ_2 angles which are far from 0° also demonstrate the three-dimensional nature of the hexahydro-2*H*-thieno [2,3-*c*]pyrrole 1,1-dioxide core.

CONCLUSIONS

A diastereoselective approach to 6-substituted hexahydro-2*H*-thieno[2,3-*c*]pyrrole 1,1-dioxide derivatives was developed. The method relied on [3 + 2] cycloaddition of the ylide generated from *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl)methanamine and 4-substituted 2,3-dihydrothiophene 1,1-dioxides and allowed the title compounds to be obtained in 67−92% yields. The structure of the 2,6-disubstituted hexahydro-2*H*-thieno[2,3-*c*]pyrrole 1,1-dioxide core depends significantly on the substituents attached to the scaffold; it opens an access to "nonflattened", three-dimensionally shaped derivatives. Favorable conformational and predicted physicochemical properties of the hexahydro-2*H*-thieno[2,3-*c*]pyrrole 1,1-dioxide core allowed us to assume that derivatives of this previously unknown scaffold could be promising building blocks for use in medicinal chemistry.

EXPERIMENTAL SECTION

General. Solvents were purified according to the standard procedures. Compounds **4**[14] and **15**,[17] (1,1-dioxido-2,3-dihydro-3-thienyl) amine,[16] and 1,1-dioxido-2,3-dihydro-3-thienylacetic acid[15] were prepared using the procedures reported in the literature. Melting points were measured on an automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using silica gel (230−400 mesh) as the stationary phase. ^{1}H, ^{13}C NMR and all 2D NMR spectra were recorded

at 499.9 or 400.4 MHz for protons and 124.9 or 100.4 MHz for carbon-13. Chemical shifts are reported in ppm downfield from TMS (^{1}H, ^{13}C) as an internal standard. ^{1}H−^{1}H COSY, HSQC/HETCOR, and HMBC experiments were used to establish atom connectivities for compounds **9** and **18**. MS analyses were done on an LCMS instrument with chemical ionization (CI) or a GCMS instrument with electron impact ionization (EI).

5-Benzylhexahydro-2*H*-thieno[2,3-*c*]pyrrole 1,1-Dioxide (6). *N*-(Methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine **5** (20 g, 0.085 mol, 2 equiv) was added to a solution of sulfolene **4**[14] (5 g, 0.042 mol, 1 equiv) in CH_2Cl_2 (75 mL) at 0 °C under an argon atmosphere. To the obtained mixture, 1 M CF_3COOH in CH_2Cl_2 (8 mL, 8 mmol) was added dropwise upon stirring. The resulting mixture was warmed to room temperature and then stirred for 12 h (monitored by TLC). The reaction mixture was evaporated *in vacuo*, and the residue was purified by column chromatography (EtOAc−hexanes−Et_3N (5:5:1) as an eluent) to give **6** (9.1 g, 85%) as a yellowish oil. ^{1}H NMR ($CDCl_3$), δ: 2.00 (1H, m), 2.33 (1H, m), 2.50 (2H, m), 2.69 (1H, d, J = 9.3 Hz), 3.02 (1H, m), 3.11 (2H, m), 3.33 (1H, t, J = 7.8 Hz), 3.49 (1H, m), 3.51 (1H, m), 3.70 (1H, d, J = 13.2 Hz), 7.25−7.35 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$), δ: 27.4, 39.4, 50.0, 56.0, 58.9, 60.9, 61.5, 127.2, 128.40, 128.43, 138.2. MS (CI, m/z): 252 (MH^+), 91 ($C_7H_7^+$). Anal. Calcd for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82; N, 5.57; S, 12.76. Found: C, 62.20; H, 6.98; N, 5.64; S, 12.68.

Hexahydro-2*H*-thieno[2,3-*c*]pyrrole 1,1-Dioxide (2), Hydrochloride. Compound **6** (5.1 g, 0.02 mol) was added to a suspension of 10% Pd−C (0.75 g) in anhydrous methanol (250 mL). This mixture was hydrogenated at 20 atm and rt for 10 h. The catalyst was filtered off through a pad of Celite, which was then washed with anhydrous methanol (200 mL). The solvent was evaporated under reduced pressure to afford the product **2** as a yellow oil. Crude **2** was dissolved in 0.5 N aq. HCl (50 mL), treated with charcoal, and filtered. The filtrate was evaporated to dryness to give 3.5 g (90%) of **2**·HCl as a white solid. Mp > 200 °C. ^{1}H NMR (DMSO-d^6), δ: 1.99 (1H, m), 2.21 (1H, m), 3.12 (1H, m), 3.26 (1H, m), 3.37 (3H, m), 3.53 (1H, m), 3.60 (1H, t, J = 9.5 Hz), 3.79 (1H, m), 9.93 (2H, br s). ^{13}C NMR ($CDCl_3$), δ: 23.9, 40.6, 45.4, 49.6, 49.9, 60.6. MS (CI, m/z): 162 (MH^+). Anal. Calcd for $C_6H_{12}ClNO_2S$: C, 36.46; H, 6.12; Cl, 17.93; N, 7.09; S, 16.22. Found: C, 36.57; H, 6.23; Cl, 18.08; N, 7.01; S, 16.37.

***tert*-Butyl (1,1-Dioxido-2,3-dihydro-3-thienyl)carbamate (8).** A solution of Boc_2O (33 g, 0.15 mol) in CH_2Cl_2 (150 mL) was added dropwise to a stirred mixture of (1,1-dioxido-2,3-dihydro-3-thienyl)amine[16] (20 g, 0.15 mol) and Et_3N (20 g, 0.15 mol) in CH_2Cl_2 (200 mL) at room temperature over 30 min. After the addition was complete, the reaction mixture was stirred at room temperature for 5 h and then washed with H_2O (2 × 50 mL), 1 N aq. HCl (2 × 50 mL), H_2O (2 × 50 mL), saturated aq. $NaHCO_3$ (2 × 75 mL), and brine (2 × 50 mL). After drying over $MgSO_4$, the solvent was evaporated under reduced pressure to give the *N*-Boc protected amine **8** (33 g, 0.142 mol, 95% yield) as a white solid. Mp 150 °C. ^{1}H NMR ($CDCl_3$), δ: 1.47 (9H, s, $(CH_3)_3$), 3.12 (1H, d, J = 17.0 Hz), 3.63 (1H, q, J = 7.5 Hz), 4.97 (1H, s), 5.14 (1H, s), 6.69 (1H, m), 6.75 (1H, m). ^{13}C NMR ($CDCl_3$), δ: 28.3, 49.2, 55.1, 81.2, 134.0, 138.8, 154.6. MS (EI, m/z): 218 ($M^+ - CH_3$), 177 ($M^+ - C_4H_8$), 57 ($C(CH_3)_3^+$). Anal. Calcd for $C_9H_{15}NO_4S$: C, 46.34; H, 6.48; N, 6.00; S, 13.75. Found: C, 46.25; H, 6.53; N, 6.07; S, 13.54.

***tert*-Butyl *rel*-[(3*S*,3a*S*,6a*R*)-5-Benzyl-1,1-dioxidohexahydro-2*H*-thieno[2,3-*c*]pyrrol-3-yl]carbamate (9).** Compound **9** was prepared from **8** in 67% yield as a white solid following the procedure described above for the synthesis of **6**. Mp 150 °C (dec). ^{1}H NMR (DMSO-d^6), δ: 1.39 (9H, s, $C(CH_3)_3$), 2.28 (1H, m, 4-C*H*H), 2.33 (1H, m, 6-C*H*H), 2.81 (1H, d, J = 9.0 Hz, 4-CH*H*), 2.97 (1H, m, 3a-C*H*), 3.11 (1H, dd, J = 12.8 and 9.0 Hz, 2-C*H*H), 3.26 (1H, d, J = 10.5 Hz, 6-CH*H*), 3.34 (1H, m, 2-CH*H*), 3.56 (1H, d, J = 13.6 Hz, C*H*HC_6H_5), 3.68 (1H, d, J = 13.6 Hz, CH*H*C_6H_5), 3.77 (1H, m, 6a-C*H*), 4.06 (1H, m, 3-C*H*), 7.11 (1H, d, J = 6.9 Hz, N*H*), 7.23−7.27 (1H, m, 4-CH of C_6H_5), 7.30−7.34 (4H, m, C_6H_5). ^{13}C NMR (DMSO-d^6), δ: 28.6 ($C(CH_3)_3$), 47.9 (3a-CH), 51.2 (3-CH), 53.2 (6-CH_2), 55.2 (2-CH_2), 57.3 (4-CH_2), 58.0 ($CH_2C_6H_5$), 63.0 (6a-CH), 79.0 ($CH(CH_3)_3$), 127.3 (C_6H_5), 128.6 (C_6H_5), 128.7 (C_6H_5), 139.0 (1-*C* of C_6H_5), 155.3 (*C*=O). MS (CI, m/z): 367 (MH^+), 311 ($MH^+ - C_4H_8$), 268. Anal. Calcd for $C_{18}H_{26}N_2O_4S$: C, 58.99; H, 7.15; N, 7.64; S, 8.75. Found: C, 59.08; H, 7.31; N, 7.44; S, 8.65.

***tert*-Butyl *rel*-[(3*S*,3a*S*,6a*R*)-1,1-Dioxidohexahydro-2*H*-thieno[2,3-*c*]pyrrol-3-yl]carbamate (10).** Compound **10** (isolated as a free base) was prepared from **9** in 92% yield as a white solid following the procedure described above for the synthesis of **2**. Mp 150 °C (dec). ^{1}H NMR (DMSO-d^6), δ: 1.40 (9H, s), 2.52 (1H, m), 2.65 (1H, m), 2.81 (2H, m), 2.96 (1H, m), 3.06 (1H, t, J = 11.2 Hz), 3.36 (2H, m), 3.71 (1H, t, J = 8.4 Hz), 3.83 (1H, m), 7.18 (1H, d, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$), δ: 28.6, 47.8, 50.4, 50.7, 51.7, 55.8, 65.0, 79.0, 155.4. MS (CI, m/z): 277 (MH^+), 221 ($MH^+ - C_4H_8$). Anal. Calcd for $C_{11}H_{20}N_2O_4S$: C, 47.81; H, 7.29; N, 10.14; S, 11.60. Found: C, 47.97; H, 7.01; N, 10.01; S, 11.21.

Methyl (1,1-Dioxido-2,3-dihydro-3-thienyl)acetate (11). To a vigorously stirred solution of 1,1-dioxido-2,3-dihydro-3-thienylacetic acid[15] (20 g, 0.113 mol) in absolute methanol (200 mL) $SOCl_2$ (14 g, 0.118 mol) was added dropwise. The resulting mixture was refluxed for 1 h. After cooling, the solvent was evaporated under reduced pressure. The residue was diluted with CH_2Cl_2 (250 mL), washed with H_2O (2 × 50 mL) and saturated aq. $NaHCO_3$ (2 × 75 mL), then dried over $MgSO_4$, and evaporated to dryness. The product (19 g, 88%) was obtained as a white solid. Mp 45−47 °C. ^{1}H NMR ($CDCl_3$), δ: 2.59 (1H, dd, J = 16.8 and 8.4 Hz), 2.68 (1H, dd, J = 16.8 and 6.1 Hz), 2.98 (1H, dd, J = 13.7 and 3.8 Hz), 3.49 (1H, m), 3.57 (1H, br s), 3.72 (3H, s), 6.67 (1H, dd, J = 6.6 and 1.7 Hz), 6.73 (1H, dd, J = 6.6 and 2.7 Hz). ^{13}C NMR ($CDCl_3$), δ: 35.7, 37.8, 52.2, 53.6, 132.5, 141.6, 170.8. MS (EI, m/z): 190 (M^+). Anal. Calcd for $C_7H_{10}O_4S$: C, 44.20; H, 5.30; S, 16.86. Found: C, 44.12; H, 5.22; S, 16.92.

Methyl *rel*-[(3*S*,3a*R*,6a*R*)-5-Benzyl-1,1-dioxidohexahydro-2*H*-thieno[2,3-*c*]pyrrol-3-yl]acetate (12). Compound **12** was prepared from **11** in 92% yield as a white solid following the procedure described above for the synthesis of **6**. Mp 99−102 °C. ^{1}H NMR ($CDCl_3$), δ: 2.44−2.51 (2H, m), 2.59−2.64 (1H, m), 2.67−2.73 (2H, m), 2.77 (1H, d, J = 9.5 Hz), 2.78−2.83 (1H, m), 2.99 (1H, dd, J = 13.2 and 5.4 Hz), 3.41 (1H, ddd, J = 13.2 Hz, 6.6 and 2.0 Hz), 3.51−3.57 (3H, m), 3.69 (3H, s), 3.69−3.73 (1H, m), 7.26−7.35 (5H, m). ^{13}C NMR ($CDCl_3$), δ: 36.5, 38.0, 46.4, 51.9, 54.5, 55.4, 58.7, 59.7, 62.1, 127.3, 128.4, 128.4, 138.0, 171.8. MS (CI, m/z): 324 (MH^+). Anal. Calcd $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.54; N, 4.33; S, 9.91. Found: C, 59.58; H, 6.63; N, 4.21; S, 9.79.

***rel*-[(3*S*,3a*R*,6a*R*)-5-Benzyl-1,1-dioxidohexahydro-2*H*-thieno-[2,3-*c*]pyrrol-3-yl]acetic Acid (13).** A solution of sodium hydroxide (0.62 g, 0.015 mol) in water (25 mL) was added dropwise to a stirred solution of the methyl ester **12** (5 g, 0.015 mol) in a mixture of methanol (150 mL) and water (50 mL) at 5 °C over 15 min. When the addition was complete, the mixture was stirred for 7 h. After evaporation of methanol under reduced pressure, the remaining aqueous phase was washed with ethyl acetate (3 × 50 mL). The aqueous phase was then cooled to 5 °C and acidified by the addition of 6 N HCl upon stirring to adjust to pH = 3. Then the solution was carefully diluted with saturated aq. NH_4OH (100 mL). The aqueous phase was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness under reduced pressure to give 4.1 g (87%) of the acid **13** as a white solid. Mp 148−150 °C. ^{1}H NMR (D_2O), δ: 2.38 (2H, m), 2.56 (1H, m), 3.21 (2H, t, J = 11.5 Hz), 3.52 (3H, m), 3.66 (1H, m), 3.87 (1H, d, J = 13.0 Hz), 4.17 (1H, m, C*H*SO_2), 4.34 (1H, d, J = 13.0 Hz), 4.43 (1H, d, J = 13.0 Hz), 7.45 (5H, s). ^{13}C NMR (D_2O), δ: 35.5, 40.4, 45.2, 51.4, 55.6, 57.0,

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58.4, 60.4, 129.5, 129.6, 130.4, 130.8, 178.5. MS (CI, *m*/*z*): 310 (MH^+). Anal. Calcd for $C_{15}H_{19}NO_4S$: C, 58.23; H, 6.19; N, 4.53; S, 10.36. Found: C, 58.14; H, 6.25; N, 4.42; S, 9.99.

***rel*-[(3*S*,3a*R*,6a*R*)-1,1-Dioxidohexahydro-2*H*-thieno[2,3-*c*]pyrrol-3-yl]acetic Acid (14), Hydrochloride.** Compound **14** (isolated as hydrochloride) was prepared from **13** in 96% yield as a white solid following the procedure described above for the synthesis of **2**. Mp 122−124 °C. ^{1}H NMR (D_2O), δ: 2.62 (2H, m), 2.75 (1H, m), 3.27 (2H, m), 3.47 (2H, m), 3.64 (2H, m), 3.94 (1H, dd, J = 13.6 and 3.0 Hz), 4.21 (1H, m). ^{13}C NMR (D_2O), δ: 34.3, 36.9, 44.5, 45.5, 49.5, 55.0, 60.8, 175.0. MS (CI, *m*/*z*): 220 (MH^+). Anal. Calcd for $C_8H_{14}ClNO_4S$: C, 37.58; H, 5.52; Cl, 13.86; N, 5.48; S, 12.54. Found: C, 37.45; H, 5.12; Cl, 13.48; N, 5.61; S, 12.31.

***rel*-(3*S*,3a*S*,6a*R*)-5-Benzyl-1,1-dioxidohexahydro-2*H*-thieno-[2,3-*c*]pyrrol-3-yl 4-Methylbenzenesulfonate (16).** Compound **16** was prepared from **15**[18] in 78% yield as a light yellow solid following the procedure described above for the synthesis of **6**. Mp 132−135 °C. ^{1}H NMR ($CDCl_3$), δ: 2.41 (2H, m), 2.46 (3H, s), 2.73 (1H, d, J = 9.6 Hz), 3.26 (3H, m), 3.59 (2H, m), 3.59 (1H, t, J = 8.1 Hz), 3.67 (1H, d, J = 13.2 Hz), 5.01 (1H, m), 7.36−7.24 (7H, m), 7.81 (2H, d, J = 8.1 Hz). ^{13}C NMR ($CDCl_3$), δ: 21.7, 48.2, 54.7, 55.3, 57.4, 58.2, 62.0, 78.4, 127.4, 127.9, 128.4, 128.5, 130.1, 133.1, 137.5, 145.6. MS (CI, *m*/*z*): 422 (MH^+), 250. Anal. Calcd for $C_{20}H_{23}NO_5S_2$: C, 56.99; H, 5.50; N, 3.32; S, 15.21. Found: C, 57.37; H, 5.26; N, 3.32; S, 14.93.

5-Benzyl-4,5,6,6a-tetrahydro-3a*H*-thieno[2,3-*c*]pyrrole 1,1-Dioxide (17). A solution of NaOH (0.8 g, 0.02 mol) in H_2O (25 mL) was added dropwise to a stirred solution of tosylate **16** (8.4 g, 0.02 mol) in THF (50 mL) at 0 °C over 15 min. After the addition was complete, the reaction mixture was stirred at rt for 5 h. The reaction mixture was then extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated to give the sulphone **17** (4.9 g, 97%). Mp 71−73 °C. ^{1}H NMR ($CDCl_3$), δ: 2.49 (1H, t, J = 8.1 Hz), 2.55 (1H, t, J = 8.8 Hz), 2.84 (1H, d, J = 8.8 Hz), 3.52−3.62 (3H, m), 3.69 (2H, s), 6.59 (1H, m), 6.70 (1H, d, J = 6.1 Hz), 7.26−7.33 (5H, m). ^{13}C NMR ($CDCl_3$), δ: 45.7, 54.2, 57.1, 58.2, 59.9, 127.3, 128.4, 128.5, 132.4, 137.6, 140.7. MS (CI, *m*/*z*): 250 (MH^+). Anal. Calcd for $C_{13}H_{15}NO_2S$: C, 62.62; H, 6.06; N, 5.62; S, 12.86. Found: C, 62.50; H, 6.15; N, 5.42; S, 12.97.

***rel*-(3*S*,3a*S*,6a*R*)-5-Benzyl-3-methoxyhexahydro-2*H*-thieno-[2,3-*c*]pyrrole 1,1-Dioxide (18).** A solution of tosylate **16** (2.2 g, 5.2 mmol) in MeOH (15 mL) was added dropwise to a stirred solution of KCN (0.390 g, 6.24 mmol) in MeOH (7.5 mL) and H_2O (7.5 mL) at 0 °C over 10 min. After the addition was complete, the reaction mixture was stirred at rt for 3 h. This solution was then diluted with H_2O (100 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic phases were dried over $MgSO_4$ and evaporated to dryness under reduced pressure to give 1.95 g (67%) of **16** as a yellow solid. Mp 84−87 °C. ^{1}H NMR ($CDCl_3$), δ: 2.47 (2H, m, 4-C*H*H and 6-C*H*H), 2.78 (1H, d, J = 9.5 Hz, 4-CH*H*), 3.14 (1H, m, 3a-C*H*), 3.28 (2H, m, 2-CH_2), 3.38 (3H, s, OCH_3), 3.56 (2H, m, C*H*HC_6H_5 and 6-CH*H*), 3.60 (1H, m, 6a-C*H*), 3.73 (1H, d, J = 13.5 Hz, C*H*HC_6H_5), 3.89 (1H, m, 3-C*H*), 7.27−7.35 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$), δ: 47.8 (3a-CH), 54.4 (2-CH_2), 54.9 (6-CH_2), 57.4 (OCH_3), 57.8 (4-CH_2), 58.6 ($CH_2C_6H_5$), 62.3 (6a-CH), 80.6 (3-CH), 127.3 (C_6H_5), 128.4 (C_6H_5), 128.4 (C_6H_5), 138.0 (1-C of C_6H_5). MS (CI, *m*/*z*): 282 (MH^+). Anal. Calcd for $C_{14}H_{19}NO_3S$: C, 59.76; H, 6.81; N, 4.98; S, 11.40. Found: C, 60.01; H, 6.82; N, 4.65; S, 11.92.

X-ray Diffraction Studies of 10, 12, 16, and 18. The crystals for X-ray diffraction studies were obtained by slow crystallization from methanol.

X-ray diffraction studies were performed on an automatic diffractometer (graphite monochromated Mo K_α radiation, CCD detector, ω-scanning). The structure was solved by a direct method using the SHELXTL package.[23] The restraints were applied to the lengths of C−C bonds in the *tert*-butyl substituents (1.54(1) Å) for the structure **10**.

Table 2. Crystallographic Data and Experimental Parameters for 10, 12, 16, and 18 (at 20 °C)

Parameter	10	12	16	18
Unit cell dimensions				
a, Å	20.080(5)	27.707(1)	7.944(1)	6.6298(2)
b, Å	5.978(1)	5.8066(2)	10.654(2)	7.9932(2)
c, Å	12.389(2)	21.0351(8)	13.268(2)	26.5748(8)
α, deg	–	–	107.76(1)	–
β, deg	104.40(2)	103.144(4)	107.42(2)	92.578(3)
γ, deg	–	–	90.00(2)	–
V, Å^3	1440.4(6)	3295.5(2)	1015.2(3)	1406.86(7)
F(000)	592	1376	444	600
Crystal system	Monoclinic	Monoclinic	Triclinic	Monoclinic
Space group	$P2_1/c$	$C2/c$	$P\bar{1}$	$P2_1/n$
Z	4	8	2	4
μ, mm^{-1}	0.233	0.213	0.294	0.234
d_{calc}, g/cm^3	1.274	1.304	1.379	1.328
$2\theta_{max}$, deg	50	60	55	60
Measured reflections	10 006	18 279	8225	13 044
Independent reflections	2531	4792	4678	4086
R_{int}	0.050	0.025	0.016	0.020
Reflections with $F > 4\sigma(F)$	1795	3869	4568	3229
Parameters				
R_1	0.069	0.039	0.036	0.035
wR_2	0.198	0.111	0.097	0.101
S	1.061	1.047	0.997	1.045
CCDC number	822804	822801	822802	822803

Positions of hydrogen atoms were located from electron density difference maps and refined within isotropic approximation (**10**, **16**, and **18**), or using a riding model with $U_{iso} = nU_{eq}$ (n = 1.5 for methyl groups and 1.2 for other hydrogen atoms) (**8**). The crystallographic data and experimental parameters are listed in Table 2. Final atomic coordinates, geometrical parameters, and crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, 11 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk). The deposition numbers are given in Table 2.

■ ASSOCIATED CONTENT

Supporting Information. Copies of NMR spectra and crystallographic information files. This material is available free of charge via the Internet at http://pubs.acs.org.

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