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A Radical Cascade Cyclization To Prepare Dihydrothiophenes Induced by Thiyl Radicals as Sulfur Biradical Equivalents

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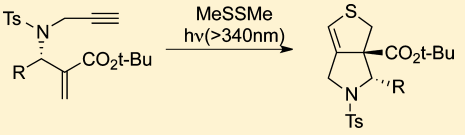
Supporting Information

ABSTRACT: Bicyclic dihydrothiophenes are readily prepared by a radical cascade cyclization reaction triggered by the addition of a thiyl radical under thermal or photoirradiation conditions. The translocated radical attacks the sulfur atom in the initial radical donor unit in an S_Hi manner. Sufficient stereoselectivity is achieved when a large excess of disulfide is used for the reaction under photoirradiation conditions. The reaction in the absence of solvents provides vinylsulfides instead of dihydrothiophenes. Thus, the sulfur atom in the thiyl radical serves as a sulfur biradical synthetic equivalent.



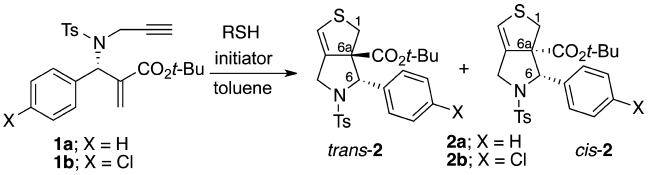
INTRODUCTION

Radical cyclization is recognized as a useful organic reaction for producing cyclic compounds.[1] Activated radicals that promote cyclization reactions are generated by many methods.[2] For example, the abstraction of halogens or halogen equivalents by tin radicals, the addition of a radical to α,β-unsaturated alkenes, and the homolytic fragmentation of carbon−heteroatom or heteroatom−heteroatom bonds are used frequently. The addition of thiyl radicals to carbon−carbon double bonds is a well-known reaction that gives the corresponding conjugate adducts in quantitative yields. Recently, we discovered an interesting radical cyclization reaction in which a tin radical adds to an α,β-unsaturated ester followed by cyclization with a terminal alkyne to generate a vinyl radical, which then attacks the tin atom in an S_Hi manner to give a bicyclic stannolane in good yields.[3] This transformation is the first example of a highly efficient S_Hi reaction on a tetraalkyltin unit.[4] The S_Hi reaction of sulfur atoms has been previously reported and used for the preparation of benzothiophene derivatives. This method has also been used for the generation of other carbon- or heteroatom-centered radicals.[5] We were interested in the potential of thiyl radicals to undergo such an S_Hi reaction during an addition−cyclization radical cascade. Herein, we report a novel radical cascade−S_Hi reaction using thiyl radicals that provides stereoselective preparation of bicyclic dihydrothiophenes, which are of interest as partial structures of new drug candidates.[6]

RESULTS AND DISCUSSION

We first examined octanethiol as the thiyl radical donor. Treatment of chiral enyne compound **1a**, which was prepared by N-propargylation of optically active α-methylene-β-(*N*-tosyl)amine,[7] with octanethiol in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) at 110 °C resulted in the smooth disappearance of **1a**. The reaction was carried out at a concentration of 10^{-2} M, and the results are summarized in Table 1.

Table 1. Synthesis of Pyrrolidinostannolane 2



entry	X	R (equiv)	initiator	temp (°C)	**2**; yield (%)[a]	trans/cis[b]
1	H	C_8H_{17} (1.2)	AIBN	110	**2a**; 45	66/34
2	Cl	C_8H_{17} (1.2)	AIBN	110	**2b**; 57	55/45
3	H	C_8H_{17} (1.2)	V70	25	**2a**; 0	
4	H	C_8H_{17} (10)	Et_3B/O_2	25	**2a**; 0	
5	H	C_8H_{17} (5)	AIBN	110	**2a**; 62	62/38
6	H	C_8H_{17} (10)	AIBN	110	**2a**; 49	55/45
7	H	*i*-Pr (10)	AIBN	85	**2a**; 66	58/42
8	H	*t*-Bu (10)	AIBN	85	**2a**; 53	58/42
9	H	allyl (10)	AIBN	110	**2a**; 0	
10	H	Bn (10)	AIBN	110	**2a**; 95	60/40

[a]Isolated yields. [b]Determined by HPLC analysis.

A typical workup and chromatographic purification provided the desired bicyclic dihydrothiophene **2a** in 45% yield (entry 1). Compound **2a** comprised two diastereomers in a 66:34 ratio, which were separated by careful flash column chromatography. Both compounds (major **2a** and minor **2a**)

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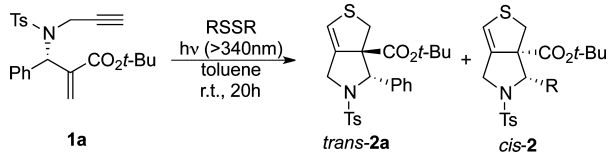
were crystallized, and their X-ray crystallographic analyses unambiguously indicated that major **2a** was *trans*-**2a** and minor **2a** was *cis*-**2a**.[8] The NMR spectra of these compounds also supported the structural assignment because the ^{1}H signals for the *tert*-butyl ester group at C6a in *cis*-**2a** and the CH_2S group at C1 in *trans*-**2a** exhibited an upfield shift owing to the presence of the aromatic ring at the C6 position. Use of the *p*-chloro derivative **1b** also gave a similar result (entry 2). The initiators 2,2'-azobis(4-methoxy-2.4-dimethyl valeronitrile) (V70) and Et_3B/O_2 were employed in an attempt to carry out the reaction at room temperature; however, no desired product was obtained (entries 3 and 4). When a large excess (10 equiv) of octanethiol was used, the yield of **2a** increased to 49%, although the stereoselectivity did not improve (entry 6). Different thiols were also examined, but the yield of **2a** was nearly the same, and the stereoselectivity ranged from approximately 1:1 to 2:1 (entries 7 and 8). Allylmercaptan did not give any desired product (entry 9). The use of benzylmercaptan increased the yield of **2a** to 95%, but the stereoselectivity was unchanged (entry 10).

We next examined disulfides as the radical promoter of cyclization. The results are summarized in Table 2.

Table 2. Synthesis of Pyrrolidinodihydrothiophene 2 in the Presence of RSSR



1a *trans*-**2a** *cis*-**2**

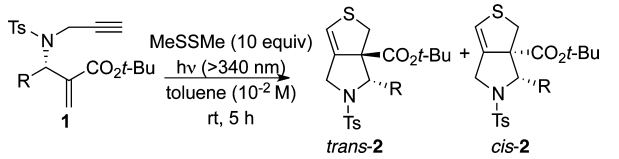
entry	R (equiv)	time (h)	**2a**; yield (%)[a]	trans/cis[c]	recovery of **1a** (%)[a]
1	Pr (10)	20	27[b]	83/17	65[b]
2	*i*-Pr (10)	20	19[b]	66/34	45[b]
3	*t*-Bu (10)	20	15[b]	77/23	16[b]
4	allyl (10)	20	0		0
5	Bn (10)	20	31[b]	85/15	67[b]
6	Me (2)	5	0		
7	Me (5)	5	63	62/38	0
8	Me (10)	5	72	83/17	0
9	Me (20)	5	78	90/10	0

[a]Isolated yields. [b]LC yields. [c]Determined by HPLC analyses.

This reaction was carried out under photoirradiation conditions; a UV lamp was used with a Pyrex filter to produce light with wavelengths greater than approximately 340 nm. The reaction slowly progressed in the presence of an excess amount of PrSSPr, and the desired product **2a** was isolated in 27% yield along with recovered **1a** in 65% yield after 20 h of reaction time (entry 1). The reaction seemed to stop at this stage. The use of other alkyl disulfides, such as *i*-PrSS*i*-Pr, *t*-BuSS*t*-Bu, and BnSSBn, did not improve the yield (entries 2, 3, and 5), while diallyl disulfides afforded a complex mixture (entry 4). On the other hand, MeSSMe dramatically improved the yield of **2a**, although a large excess of this disulfide was required. For example, 5 equiv of MeSSMe provided **2a** in 63% (entry 7) yield. The diastereomeric ratio of **2a** was determined to be 62:38 by HPLC analysis. The ratio was improved with 10 equiv of MeSSMe, and **2a** was isolated in 72% yield with an 83:17 diastereomeric ratio (entry 8). Twenty equivalents of MeSSMe provided the best result; the diastereoselectivity was enhanced to 90:10 (entry 9).

Using the optimized conditions for the formation of bicyclic pyrrolidinodihydrothiophene **2**, the generality of the reaction was then examined using various types of enynes **1**. The results are summarized in Table 3.

Table 3. Preparation of Pyrrolidinodihydrothiophenes 2



1 *trans*-**2** *cis*-**2**

entry	R	**2**; yield (%)[a]	trans/cis[b]	*trans* **2** ee[c]
1	2-MeC_6H_4	**2b**; 64	90/10	91
2	3-MeC_6H_4	**2c**; 71	74/26	98
3	4-MeC_6H_4	**2d**; 96	81/19	91
4	4-MeOC_6H_4	**2e**; 76	87/13	97
5	4-ClC_6H_4	**2f**; 43	83/17	93
6	4-FC_6H_4	**2g**; 63	86/14	95
7	2-furyl	**2h**; 62	80/20	90
8	2-nephthyl	**2i**; 76	78/22	93
9	3-MeOC_6H_4	**2j**; 49	77/23	94
10	Pr	**2k**; 29	50/50	not determined

[a]Isolated yield. [b]Determined by HPLC. [c]Determined by HPLC using a ChiralPak ID column.

The radical cascade reaction occurred smoothly under photoirradiation conditions in the presence of 10 equiv of MeSSMe. For example, treatment of **1b** with MeSSMe resulted in the smooth formation of **2b** in 64% yield. HPLC analysis revealed that the trans/cis ratio of **2b** was 90:10, respectively. The enantiomeric excess (ee) of *trans*-**2b** was determined by chiral HPLC analysis, which showed that compound **2b** was obtained in 91% ee. The ee of the starting material was 93%; thus, the reaction progressed with almost no loss of optical purity (entry 1). Most of the starting materials that possessed an aromatic group as the R substituent underwent smooth transformation to compound **2** in good yields, and the trans isomer of **2** was formed preferentially (entries 2−9). On the other hand, the reaction of aliphatic derivatives such as **1k** was sluggish, and the formation of **2k** occurred only in 29% yield in an approximate 1:1 mixture of the two diastereomers (entry 10). These trends were also observed in the formation of stannolopyrroles via a radical cascade process.[3]

To explore the reaction pathway, the reaction of **1a** was next examined without solvent. Treatment of a mixture of **1a** and dimethyldisulfide under UV irradiation conditions led to the formation of a diastereomeric mixture of monocyclic compound **3** in 27% yield (Scheme 1).

Formation of **2a** was not observed under these conditions. The two diastereomers of **3** were separated by careful flash chromatography. These compounds were monocyclic compounds that contained two methylthio groups. Nuclear Overhauser effect (NOE) and high-resolution mass spectrometry (HRMS) analyses supported the assignment of the structures as *trans*-**3a** and *cis*-**3a**. Thus, the structures of these compounds were confirmed by ^{1}H NMR analysis where upfield shifts were observed for the *tert*-butyl ester in *cis*-**3a** and the CH_2SMe group in *trans*-**3a**. As mentioned previously, similar upfield shifts were observed in *trans*-**2a** and *cis*-**2a**. The alkene

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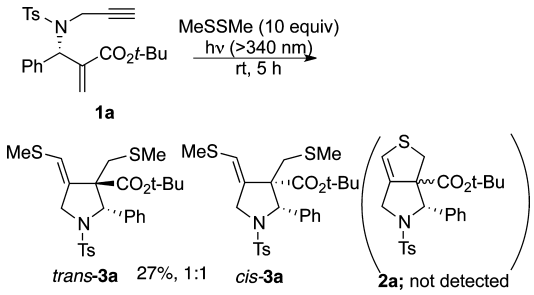
Scheme 1. Reaction of 1a without Solvent



configuration was determined by NOE analysis; a signal enhancement of approximately 14% was observed for the CH_2SMe group in *cis*-**3a** when the MeSCH= proton was irradiated.

These results clearly support the reaction pathway shown in Scheme 2. Thus, the thiyl radical, which is generated from either a thiol under thermal conditions or a disulfide under photoirradiation conditions, attacks the α,β-unsaturated ester unit in **1** to give the α-carbonyl radical **A**, which then undergoes 5-exo-dig mode radical cyclization to give vinyl radical **B**. This vinyl radical **B** is a highly reactive radical that attacks the sulfur atom in an S_Hi manner to give bicyclic adduct **2**. During the process, it appears that two pathways are possible: one is a direct S_Hi process, and the other is a stepwise S_Hi process that passes through intermediate **C**. Although the latter mechanism may explain some of the results, such as why a large excess of disulfide is required, it is less likely because the transformation from intermediate **C** to **2** requires an intermolecular S_H2 reaction on a carbon atom, which is regarded as a very rare and difficult reaction pathway.[9] Calculation of the structure of intermediate **C** was then attempted, but it was found that intermediate **C** has no stable structure. Any initial structure for intermediate **C** yields the optimized structure for intermediate **B** and compound **2**.[10] Thus, the presence of intermediate **C** is unlikely, and it is believed that the S_Hi process directly progresses from **B** to **2**. If the reaction is performed without solvent under photoirradiation conditions, a large excess amount of dimethyldisulfide exists that serves as a trapping agent for the vinylic radical **B**, resulting in the formation of compounds *trans*-**3a** and *cis*-**3a**. Thus, we conclude that the S_Hi process from **B** is not very rapid and progresses with a reaction rate comparable to that of intermolecular trapping by disulfide when the reaction is performed under high concentration conditions.

In conclusion, we have successfully converted chiral enynes **1**, which are readily available asymmetric Aza–Morita–Baylis–Hillman adducts,[7] to bicyclic pyrolidinodihydrothiophenes **2** in good yields. A thiyl radical serves as a sulfur biradical equivalent in this reaction and provides dihydrothiophenes in a one-step reaction via an addition–cyclization–substitution radical cascade. The stereoselectivity is improved when a large excess of disulfide is used in the reaction with photoirradiation initiation. This transformation occurs via a highly cumulated radical cascade process and is a potentially useful reaction for the preparation of thiazabicyclic compounds.

EXPERIMENTAL SECTION

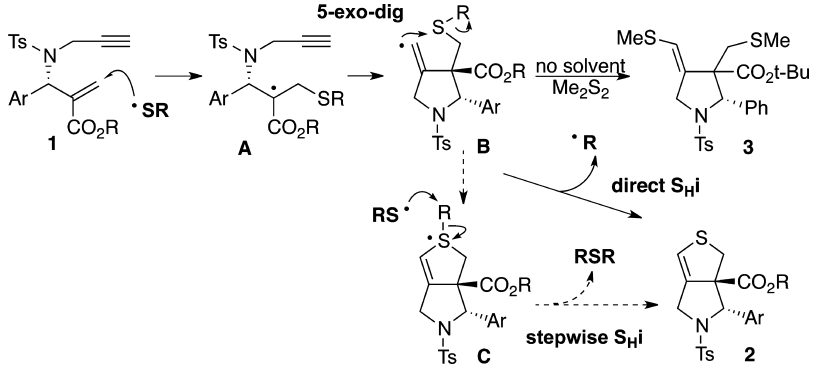
Preparation of (6*S*)-*tert*-Butyl 6-Phenyl-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole-6a-carboxylate (2a): Use of 5 equiv of Octanethiol (Table 1, Entry 6). A solution of **1a** (1.2795 g, 3.01 mmol), octanethiol (5.3 mL, 30.4 mmol), and AIBN (0.1202 g, 0.73 mmol) in toluene (300 mL) was heated at 110 °C for 20 h under nitrogen atmosphere. The reaction mixture was cooled and concentrated in vacuo. The residue was purified through flash chromatography (silica gel/hexane–EtOAc 20:1 then 5:1 v/v) to give *trans*-**2a** in 27% yield (0.3701 g, 0.81 mmol) and *cis*-**2a** in 22% yield (0.3030 g, 0.66 mmol).

Preparation of (6*S*)-*tert*-Butyl 6-Phenyl-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole-6a-carboxylate (2a): Use of 10 equiv of Dimethyldisulfide under Photoirradiation Conditions (Table 2, Entry 8). A Pyrex flask (100 mL) was charged with a solution of **1a** (211.8 mg, 0.50 mmol) and dimethyldisulfide (0.45 mL, 5.06 mmol) in toluene (50 mL), and the reaction solution was irradiated by a mercury lamp at ambient temperature under nitrogen atmosphere for 8 h. The reaction mixture was concentrated, and the residue was purified through flash chromatography (silica gel/hexane–EtOAc = 20:1 then 5:1) to give *trans*-**2a** in 60% yield (135.7 mg, 0.30 mmol) and *cis*-**2a** in 12% yield (27.3 mg, 0.060 mmol).

(6*S*,6a*S*)-*tert*-Butyl 6-Phenyl-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole-6a-carboxylate (*trans* 2a). White solid, mp 117.0–118.0 °C; $[\alpha]_D$ + 60.8 (c 0.87, $CHCl_3$). The enantiomeric purity was determined by HPLC analysis (230 nm, 40 °C) to be 97% ee, t_R 21.9 min (major), t_R 28.0 min (minor) [Column ID 0.46 cm × 25 cm, hexane–*i*-PrOH = 95:5, 1.00 mL/min]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 8.3 Hz, 2H), 7.34–7.19 (m, 3H), 7.11 (d, J = 7.9 Hz, 2H), 6.98 (br, 2H), 6.08 (s, 1H), 5.11 (s, 1H), 4.21 (dd, J = 12.6, 2.2 Hz, 1H), 4.10 (d, J = 1.2 Hz, 1H), 3.10 (d, J = 11.8 Hz, 1H), 2.60 (d, J = 11.8 Hz, 1H), 2.34 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 143.3, 138.6, 136.0, 133.8 (2C), 129.4 (2C), 128.8 (2C), 128.1, 127.3 (2C), 126.6, 120.9, 82.9, 73.2, 67.8, 47.7, 37.8, 27.8 (3C), 21.6; IR (neat) ν 1720, 1343, 1161, 1143, 1093, 912, 812 cm^{-1}; HRMS (ESI TOF M + Na) m/z 480.1283. Calcd for $C_{24}H_{27}NO_4S_2Na$ m/z 480.1279.

(6*S*,6a*R*)-*tert*-Butyl 6-Phenyl-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole-6a-carboxylate (*cis*-2a). White solid, mp

Scheme 2. Plausible Reaction Pathway



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71.0−72.0 °C; $[\alpha]_D$ + 133.5 (c 0.31, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 7.29−7.21 (m, 5H), 5.78 (s, 1H), 4.68 (s, 1H), 4.42 (dd, J = 14.2, 2.1 Hz, 1H), 4.28 (dd, J = 14.2, 0.9 Hz, 1H), 3.83 (d, J = 10.8 Hz, 1H), 3.25 (d, J = 10.9 Hz, 1H), 2.44 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 144.2, 137.5, 135.7, 134.1, 129.8 (2C), 128.2 (2C), 128.0, 127.8 (2C), 126.9 (2C), 119.1, 82.6, 75.2, 72.2, 50.1, 43.2, 27.5 (3C), 21.7; IR (neat) ν 1724, 1350, 1161, 1089 cm^{-1}; HRMS (ESI TOF M + Na) m/z 480.1291. Calcd for $C_{24}H_{27}NO_4S_2Na$ m/z 480.1279.

Preparation of (6*S*)-*tert*-Butyl 6-(*o*-Tolyl)-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole-6a-carboxylate (2b). A Pyrex flask (30 mL) was charged with a solution of **1b** (90.0 mg, 0.20 mmol) and dimethyldisulfide (0.17 mL, 1.91 mmol) in toluene (20 mL), and the reaction solution was irradiated by a mercury lamp at ambient temperature under nitrogen atmosphere for 5 h. The reaction mixture was concentrated, and the residue was purified through flash chromatography (silica gel/hexane−EtOAc = 20:1 then 5:1) to give **2b** in 64% yield (60.7 mg, 0.13 mmol); *trans*-**2b**/*cis*-**2b** was 90:10.

(6*S*,6a*S*)-*tert*-Butyl 6-(*o*-Tolyl)-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole-6a-carboxylate (*trans*-2b). White solid, mp 72.0−73.0 °C; $[\alpha]_D$ + 80.2 (c 0.88, $CHCl_3$). The enantiomeric purity was determined by HPLC analysis (230 nm, 40 °C) to be 91% ee, t_R 16.2 min (major), t_R 18.6 min (minor) [Column ID 0.46 cm × 25 cm, hexane−*i*-PrOH = 95:5, 1.00 mL/min]. ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, J = 8.3 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 7.13−7.10 (m, 2H), 7.03−6.98 (m, 1H), 6.78 (d, J = 7.6 Hz, 1H), 6.07 (s, 1H), 5.43 (s, 1H), 4.26 (dd, J = 12.6, 2.3 Hz, 1H), 4.12 (dd, J = 12.6, 1.2 Hz, 1H), 3.15 (d, J = 11.6 Hz, 1H), 2.58 (d, J = 11.6 Hz, 1H), 2.36 (s, 3H), 2.32 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 143.3, 136.8, 136.2, 135.1, 133.9, 130.4, 129.5 (2C), 127.8, 127.4 (2C), 127.2, 126.6, 121.0, 82.9, 73.0, 64.1, 47.6, 37.2, 27.8 (3C), 21.4, 19.4; IR (neat) ν 1716, 1340, 1162, 1145, 1094, 906 cm^{-1}; HRMS (ESI TOF M + Na) m/z 494.1426. Calcd for $C_{25}H_{29}NO_4S_2Na$ m/z 494.1436.

(6*S*,6a*R*)-*tert*-Butyl 6-(*o*-Tolyl)-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole-6a-carboxylate (*cis*-2b). Colorless oil; $[\alpha]_D$ + 120.0 (c 0.12, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, J = 8.2 Hz, 2H), 7.46 (dd, J = 7.5, 1.7 Hz, 1H), 7.29 (d, J = 8.0 Hz, 2H), 7.19−7.04 (m, 3H), 5.83 (s, 1H), 4.96 (s, 1H), 4.43 (d, J = 13.0 Hz, 1H), 4.40 (d, J = 14.2 Hz, 1H), 3.81 (d, J = 10.6 Hz, 1H), 3.22 (d, J = 10.6 Hz, 1H), 2.44 (s, 3H), 2.28 (s, 3H), 1.02 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 144.1, 137.5, 136.5, 135.1, 135.0, 130.1, 129.8 (2C), 128.2, 127.8, 127.6 (2C), 126.0, 118.6, 82.5, 74.9, 68.6, 50.2, 44.9, 27.4 (3C), 21.7, 19.9; IR (neat) ν 1751, 1303, 1288, 1246, 1163, 912 cm^{-1}; HRMS (ESI TOF M + Na) m/z 494.1433. Calcd for $C_{25}H_{29}NO_4S_2Na$ m/z 494.1436.

Preparation of (6*S*)-*tert*-Butyl 6-(*m*-Tolyl)-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole-6a-carboxylate (2c). A Pyrex flask (30 mL) was charged with a solution of **1c** (83.8 mg, 0.19 mmol) and dimethyldisulfide (0.20 mL, 2.25 mmol) in toluene (20 mL), and the reaction solution was irradiated by a mercury lamp at ambient temperature under nitrogen atmosphere for 5 h. The reaction mixture was concentrated, and the residue was purified through flash chromatography (silica gel/hexane−EtOAc = 20:1 then 5:1) to give **2c** in 71% yield (63.8 mg, 0.14 mmol); *trans*-**2c**/*cis*-**2c** was 74:26.

(6*S*,6a*S*)-*tert*-Butyl 6-(*m*-Tolyl)-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole-6a-carboxylate (*trans*-2c). White solid, mp 119.0−120.0 °C; $[\alpha]_D$ + 66.7 (c 1.02, $CHCl_3$). The enantiomeric purity was determined by HPLC analysis (230 nm, 30 °C) to be 98% ee, t_R 19.3 min (major), t_R 27.2 min (minor) [Column ID 0.46 cm × 25 cm, hexane−*i*-PrOH = 95:5, 1.00 mL/min]. ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 7.11−7.15 (br, 1 H), 7.02 (d, J = 7.5 Hz, 1H), 6.83−6.61 (br, 2H), 6.07 (s, 1H), 5.08 (s, 1H), 4.22 (dd, J = 12.6, 2.3 Hz, 1H), 4.08 (dd, J = 12.6, 1.1 Hz, 1H), 3.10 (d, J = 11.7 Hz, 1H), 2.61 (d, J = 11.7 Hz, 1H), 2.34 (s, 3H), 2.26−2.15 (br, 3H), 1.44 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 143.2, 138.4, 138.3, 136.1, 133.9, 129.3 (2C), 128.9 (2C), 128.7, 128.0, 127.3, 124.5, 120.8, 82.9, 73.1, 67.8, 47.7, 37.9, 27.8 (3C), 21.5; IR (neat) ν 1719, 1341, 1159, 1144, 1094, 812 cm^{-1}; HRMS (ESI TOF M + Na) m/z 494.1441. Calcd for $C_{25}H_{29}NO_4S_2Na$ m/z 494.1436.

(6*S*,6a*R*)-*tert*-Butyl 6-(*m*-Tolyl)-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole-6a-carboxylate (*cis*-2c). Colorless oil; $[\alpha]_D$ + 264.4 (c 0.09, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 7.15 (t, J = 7.6 Hz, 1H), 7.09−7.01 (m, 3H), 5.79 (s, 1H), 4.66 (s, 1H), 4.42 (dd, J = 14.1, 2.1 Hz, 1H), 4.31 (d, J = 14.8 Hz, 1H), 3.81 (d, J = 10.8 Hz, 1H), 3.26 (d, J = 10.9 Hz, 1H), 2.44 (s, 3H), 2.27 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 144.0, 137.5, 137.2, 135.8, 134.5, 129.7 (2C), 128.7, 128.1, 127.8 (2C), 127.6, 124.1, 119.0, 82.4, 75.2, 72.3, 50.1, 43.2, 27.5 (3C), 21.7, 21.5; IR (neat) ν 1722, 1350, 1163, 912 cm^{-1}; HRMS (ESI TOF M + Na) m/z 494.1426. Calcd for $C_{25}H_{29}NO_4S_2Na$ m/z 494.1436.

Preparation of (6*S*)-*tert*-Butyl 6-(*p*-Tolyl)-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole-6a-carboxylate (2d). A Pyrex flask (30 mL) was charged with a solution of **1d** (87.0 mg, 0.20 mmol) and dimethyldisulfide (0.19 mL, 2.14 mmol) in toluene (20 mL), and the reaction solution was irradiated by a mercury lamp at ambient temperature under nitrogen atmosphere for 5 h. The reaction mixture was concentrated, and the residue was purified through flash chromatography (silica gel/hexane−EtOAc = 20:1 then 5:1) to give **2d** in 96% yield (89.2 mg, 0.19 mmol); *trans*-**2d**/*cis*-**2d** was 81:19.

(6*S*,6a*S*)-*tert*-Butyl 6-(*p*-Tolyl)-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole-6a-carboxylate (*trans*-2d). White solid, mp 93.0−94.0 °C; $[\alpha]_D$ + 58.2 (c 0.91, $CHCl_3$). The enantiomeric purity was determined by HPLC analysis (230 nm, 40 °C) to be 91% ee, t_R 19.5 min (major), t_R 24.5 min (minor) [Column ID 0.46 cm × 25 cm, hexane−*i*-PrOH = 95/5, 1.00 mL/min]. ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 8.3 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 7.6 Hz, 2H), 6.87 (d, J = 7.0 Hz, 2H), 6.07 (s, 1H), 5.07 (s, 1H), 4.18 (dd, J = 12.6, 2.2 Hz, 1H), 4.08 (dd, J = 12.5, 1.2 Hz, 1H), 3.08 (d, J = 11.7 Hz, 1H), 2.63 (d, J = 11.8 Hz, 1H), 2.34 (s, 3H), 2.30 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 143.2, 137.9, 136.0, 135.6, 133.9, 129.5 (2C), 129.4 (2C), 127.3 (2C), 127.3 (2C), 120.8, 82.8, 73.2, 67.6, 47.7, 37.9, 27.8 (3C), 21.6, 21.3; IR (neat) ν 1718, 1342, 161, 1143, 1094, 912 cm^{-1}; HRMS (ESI TOF M + Na) m/z 494.1433. Calcd for $C_{25}H_{29}NO_4S_2Na$ m/z 494.1436.

(6*S*,6a*R*)-*tert*-Butyl 6-(*p*-Tolyl)-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole-6a-carboxylate (*cis*-2d). Colorless oil; $[\alpha]_D$ + 123.8 (c 0.24, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 7.2 Hz, 2H), 7.08 (d, J = 8.1 Hz, 2H), 5.77 (s, 1H), 4.60 (s, 1H), 4.42 (dd, J = 14.2, 2.1 Hz, 1H), 4.25 (dd, J = 14.2, 0.9 Hz, 1H), 3.80 (d, J = 10.8 Hz, 1H), 3.23 (d, J = 10.9 Hz, 1H), 2.44 (s, 3H), 2.30 (s, 3H), 1.12 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 144.1, 137.6, 135.7, 134.3, 134.1, 129.8 (2C), 128.8 (2C), 127.8 (2C), 126.9 (2C), 118.9, 82.5, 75.2, 72.2, 50.2, 43.1, 27.6 (3C), 21.7, 21.2; IR (neat) ν 1722, 1350, 1163, 912 cm^{-1}; HRMS (ESI TOF M + Na) m/z 494.1435. Calcd for $C_{25}H_{29}NO_4S_2Na$ m/z 494.1436.

Preparation of (6*S*)-*tert*-Butyl 6-(*p*-Methoxyphenyl)-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole-6a-carboxylate (2e). A Pyrex flask (30 mL) was charged with a solution of **1e** (93.7 mg, 0.21 mmol) and dimethyldisulfide (0.18 mL, 2.03 mmol) in toluene (20 mL), and the reaction solution was irradiated by a mercury lamp at ambient temperature under nitrogen atmosphere for 5 h. The reaction mixture was concentrated, and the residue was purified through flash chromatography (silica gel/hexane−EtOAc = 20:1 then 5:1) to give **2e** in 76% yield (77.9 mg, 0.16 mmol); *trans*-**2e**/*cis*-**2e** was 87:13.

(6*S*,6a*S*)-*tert*-Butyl 6-(*p*-Methoxyphenyl)-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno-[3,4-*c*]pyrrole-6a-carboxylate (*trans*-2e). Colorless oil; $[\alpha]_D$ + 34.0 (c 0.96, $CHCl_3$). The enantiomeric purity was determined by HPLC analysis (230 nm, 30 °C) to be 97% ee, t_R 21.9 min (major), t_R 28.4 min (minor) [Column ID 0.46 cm × 25 cm, hexane−*i*-PrOH = 95:5, 1.00 mL/min]. ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 8.3 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 7.5 Hz, 2H), 6.75 (d, J = 8.6 Hz, 2H), 6.07 (s, 1H), 5.08 (s, 1H), 4.19 (dd, J = 12.6, 2.2 Hz, 1H), 4.06 (dd, J = 12.5, 1.2 Hz, 1H), 3.77 (s, 3H), 3.10 (d, J = 11.8 Hz, 1H), 2.66 (d, J = 11.8 Hz, 1H), 2.34 (s, 3H), 1.43

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(s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 159.4, 143.2, 136.2, 133.9, 130.7, 129.4 (2C), 128.6, 127.3 (2C), 120.8, 114.1 (2C), 82.9, 73.3, 67.4, 55.4, 47.6, 37.7, 27.9 (3C), 27.8, 21.5; IR (neat) ν 1719, 1512, 1367, 1341, 1247, 1161, 1143, 1033, 839, 750 cm^{-1}; HRMS (ESI TOF M + Na) m/z 510.1385. Calcd for $C_{25}H_{29}NO_5S_2Na$ m/z 510.1385.

(6*S*,6a*R*)-*tert*-Butyl 6-(*p*-Methoxyphenyl)-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno-[3,4-*c*]pyrrole-6a-carboxylate (*cis*-2e). Colorless oil; $[\alpha]_D$ + 48.9 (c 0.36, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (dd, J = 8.1, 1.1 Hz, 2H), 7.30 (d, J = 7.8 Hz, 2H), 7.22 (d, J = 7.7 Hz, 2H), 6.80 (dd, J = 8.9, 1.3 Hz, 2H), 5.78 (s, 1H), 4.58 (s, 1H), 4.42 (d, J = 14.2 Hz, 1H), 4.26 (d, J = 14.1 Hz, 1H), 3.77 (s, 3H), 3.23 (d, J = 10.9 Hz, 1H), 2.44 (s, 3H), 1.14 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 159.4, 144.1, 135.7, 134.1, 129.8 (2C), 129.3, 128.2 (2C), 127.8 (2C), 118.9, 113.6 (2C), 82.6, 75.3, 72.0, 55.4, 50.2, 43.0, 27.6 (3C), 21.7; IR (neat) ν 1719, 1514, 1249, 1163, 912 cm^{-1}; HRMS (ESI TOF M + Na) m/z 510.1385. Calcd for $C_{25}H_{29}NO_5S_2Na$ m/z 510.1385.

Preparation of (6*S*)-*tert*-Butyl 6-(*p*-Chlorophenyl)-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole-6a-carboxylate (2f). A Pyrex flask (30 mL) was charged with a solution of **1f** (96.2 mg, 0.21 mmol) and dimethyldisulfide (0.17 mL, 1.91 mmol) in toluene (20 mL), and the reaction solution was irradiated by a mercury lamp at ambient temperature under nitrogen atmosphere for 5 h. The reaction mixture was concentrated, and the residue was purified through flash chromatography (silica gel/hexane−EtOAc = 20:1 then 5:1) to give **2f** in 76% yield (44.0 mg, 0.089 mmol); *trans*-**2f**/*cis*-**2f** was 83:17.

(6*S*,6a*S*)-*tert*-Butyl 6-(*p*-Chlorophenyl)-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno-[3,4-*c*]pyrrole-6a-carboxylate (*trans*-2f). Colorless oil; $[\alpha]_D$ + 38.7 (c 0.69, $CHCl_3$). The enantiomeric purity was determined by HPLC analysis (230 nm, 30 °C) to be 93% ee, t_R 19.1 min (major), t_R 24.1 min (minor) [Column ID 0.46 cm × 25 cm, hexane−*i*-PrOH = 95:5, 1.00 mL/min]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 7.3 Hz, 2H), 7.16 (d, J = 7.8 Hz, 2H), 6.94 (d, J = 7.8 Hz, 2H), 6.10 (dd, J = 2.1, 1.2 Hz, 1H), 5.08 (s, 1H), 4.17 (dd, J = 12.5, 2.2 Hz, 1H), 4.09 (dd, J = 12.5, 1.2 Hz, 1H), 3.10 (d, J = 11.8 Hz, 1H), 2.60 (d, J = 11.8 Hz, 1H), 2.37 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 143.6, 137.3, 135.8, 134.1, 133.3, 129.5 (2C), 129.0 (2C), 128.8, 127.3 (2C), 121.4 (2C), 83.1, 73.1, 67.1, 47.6, 37.8, 27.8 (3C), 21.5; IR (neat) ν 1742, 1370, 1350, 1228, 1163, 1091, 840 cm^{-1}; HRMS (ESI TOF M + Na) m/z 514.0903. Calcd for $C_{24}H_{26}ClNO_4S_2Na$ m/z 514.0890.

(6*S*,6a*R*)-*tert*-Butyl 6-(*p*-Chlorophenyl)-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno-[3,4-*c*]pyrrole-6a-carboxylate (*cis*-2f). Colorless oil; $[\alpha]_D$ + 96.6 (c 0.41, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 7.25 (s, 4H), 5.80 (s, 1H), 4.61 (s, 1H), 4.41 (dd, J = 14.2, 2.1 Hz, 1H), 4.26 (dd, J = 14.2, 1.1 Hz, 1H), 3.80 (d, J = 10.8 Hz, 1H), 3.23 (d, J = 10.9 Hz, 1H), 2.45 (s, 3H), 1.13 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0, 144.4, 136.1, 135.3, 133.9, 133.8, 129.9 (2C), 128.4, 128.3 (2C), 127.8 (2C), 119.3 (2C), 82.9, 75.2, 71.6, 50.1, 43.0, 27.6 (3C), 21.7; IR (neat) ν 1722, 1491, 1346, 1163, 1089 cm^{-1}; HRMS (ESI TOF M + Na) m/z 514.0901. Calcd for $C_{24}H_{26}ClNO_4S_2Na$ m/z 514.0890.

Preparation of (6*S*)-*tert*-Butyl 6-(*p*-Fluorophenyl)-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole-6a-carboxylate (2g). A Pyrex flask (100 mL) was charged with a solution of **1g** (271.0 mg, 0.61 mmol) and dimethyldisulfide (0.54 mL, 6.08 mmol) in toluene (60 mL), and the reaction solution was irradiated by a mercury lamp at ambient temperature under nitrogen atmosphere for 5 h. The reaction mixture was concentrated, and the residue was purified through flash chromatography (silica gel/hexane-EtOAc = 20:1 then 5:1) to give **2g** in 63% yield (182.1 mg, 0.38 mmol). *trans*-**2g**/*cis*-**2g** was 86:14.

(6*S*,6a*S*)-*tert*-Butyl 6-(*p*-Fluorophenyl)-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno-[3,4-*c*]pyrrole-6a-carboxylate (*trans*-2g). White solid, mp 62.0−63.0 °C; $[\alpha]_D$ + 51.5 (c 0.84, $CHCl_3$). The enantiomeric purity was determined by HPLC analysis (230 nm, 30 °C) to be 95% ee, t_R 19.9 min (major), t_R 25.9 min (minor) [Column ID 0.46 cm × 25 cm, hexane−*i*-PrOH = 95:5, 1.00 mL/min]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 8.2 Hz, 2H), 7.15 (dd, J = 7.9, 0.6 Hz, 2H), 7.04−6.85 (m, 4H), 6.10 (s, 1H), 5.10 (s, 1H), 4.18 (dd, J = 12.5, 2.3 Hz, 1H), 4.09 (dd, J = 12.5, 1.2 Hz, 1H), 3.10 (d, J = 11.8 Hz, 1H), 2.59 (d, J = 11.8 Hz, 1H), 2.36 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 162.5 (d, J = 247.2 Hz), 143.5, 135.8, 134.6 (d, J = 3.3 Hz), 133.4, 129.5 (2C), 129.1 (2C, d, J = 8.2 Hz), 127.3 (2C), 121.3, 115.8 (2C, d, J = 21.6 Hz), 83.1, 73.1, 67.0, 47.6, 37.8, 27.8 (3C), 21.6; IR (neat) ν 1718, 1508, 1341, 1225, 1155, 1093, 842 cm^{-1}; HRMS (ESI TOF M + Na) m/z 498.1184. Calcd for $C_{24}H_{26}FNO_4S_2Na$ m/z 498.1185.

(6*S*,6a*R*)-*tert*-Butyl 6-(*p*-Fluorophenyl)-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno-[3,4-*c*]pyrrole-6a-carboxylate (*cis*-2g). Colorless oil; $[\alpha]_D$ + 82.4 (c 0.52, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 7.30−7.26 (m, 2H), 7.00−6.95 (m, 2H), 5.80 (s, 1H), 4.62 (s, 1H), 4.42 (dd, J = 14.1, 2.1 Hz, 1H), 4.27 (dd, J = 14.2, 1.1 Hz, 1H), 3.80 (d, J = 10.8 Hz, 1H), 3.23 (d, J = 10.8 Hz, 1H), 2.45 (s, 3H), 1.13 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 162.5 (d, J = 246.5 Hz), 144.3, 135.4, 134.0, 133.2 (d, J = 3.0 Hz), 129.9 (2C), 128.7 (2C, d, J = 8.0 Hz), 127.8 (2C), 119.2, 115.1 (2C, d, J = 21.7 Hz), 82.8, 75.2, 71.6, 50.1, 43.0, 27.6 (3C), 21.7; IR (neat) ν 1722, 1508, 1350, 1161, 1089 cm^{-1}; HRMS (ESI TOF M + Na) m/z 498.1179. Calcd for $C_{24}H_{26}FNO_4S_2Na$ m/z 498.1185.

Preparation of 6-(2-Furyl)-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole-6a-carboxylate (2h). A Pyrex flask (100 mL) was charged with a solution of **1i** (250.1 mg, 0.60 mmol) and dimethyldisulfide (0.54 mL, 6.08 mmol) in toluene (60 mL), and the reaction solution was irradiated by a mercury lamp at ambient temperature under nitrogen atmosphere for 5 h. The reaction mixture was concentrated, and the residue was purified through flash chromatography (silica gel/hexane−EtOAc = 15:1 then 3:1) to give **2h** in 62% yield (166.8 mg, 0.37 mmol); *trans*-**2h**/*cis*-**2h** was 80:20.

(6*S*,6a*S*)-*tert*-Butyl 6-(2-Furyl)-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole-6a-carboxylate (*trans*-2h). Yellow oil; $[\alpha]_D$ + 22.8 (c 0.49, $CHCl_3$); The enantiomeric purity was determined by HPLC analysis (230 nm, 40 °C) to be 90% ee, t_R 17.1 min (major), t_R 26.7 min (minor) [Column ID 0.46 cm × 25 cm, hexane−*i*-PrOH = 95:5, 1.00 mL/min]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 8.3 Hz, 2H), 7.13−7.12 (m, 1H), 7.12 (d, J = 7.3 Hz, 2H), 6.25−6.22 (m, 2H), 6.02 (s, 1H), 5.23 (s, 1H), 4.18 (dd, J = 12.5, 2.2 Hz, 1H), 3.93 (dd, J = 12.5, 1.3 Hz, 1H), 3.26 (d, J = 11.7 Hz, 1H), 2.65 (d, J = 11.7 Hz, 1H), 2.35 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 150.8, 143.2, 143.0, 136.0, 134.4, 129.4 (2C), 127.0 (2C), 119.8, 110.3 (2C), 83.2, 72.9, 61.3, 46.8, 36.9, 27.9 (3C), 21.4; IR (neat) ν 1718, 1344, 1276, 1247, 1159, 1094, 813 cm^{-1}; HRMS (ESI TOF M + Na) m/z 470.1068. Calcd for $C_{22}H_{25}NO_5S_2Na$ m/z 470.1072.

(6*S*,6a*R*)-*tert*-Butyl 6-(2-Furyl)-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole-6a-carboxylate (*cis*-2h). Yellow oil; $[\alpha]_D$ + 16.2 (c 0.30, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.22 − 7.21 (m, 1H), 6.33 (d, J = 3.3 Hz, 1H), 6.28 (dd, J = 3.2, 1.8 Hz, 1H), 5.84 (s, 1H), 4.61 (s, 1H), 4.35 (dd, J = 13.8, 2.1 Hz, 1H), 3.79 (d, J = 11.1 Hz, 1H), 3.23 (d, J = 11.2 Hz, 1H), 2.43 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4, 149.8, 143.9, 142.3 (2C), 134.8, 129.7 (2C), 127.7 (2C), 119.4, 110.6, 109.3, 82.6, 73.9, 65.9, 49.6, 42.4, 27.7 (3C), 21.7; IR (neat) ν 1719, 1344, 1276, 1159, 1093 cm^{-1}; HRMS (ESI TOF M + Na) m/z 470.1068. Calcd for $C_{22}H_{25}NO_5S_2Na$ m/z 470.1072.

Preparation of (6*S*)-*tert*-Butyl 6-(2-Naphthyl)-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole-6a-carboxylate (2i). A Pyrex flask (30 mL) was charged with a solution of **1i** (77.7 mg, 0.16 mmol) and dimethyldisulfide (0.18 mL, 2.02 mmol) in toluene (20 mL), and the reaction solution was irradiated by a mercury lamp at ambient temperature under nitrogen atmosphere for 5 h. The reaction mixture was concentrated, and the residue was purified through flash chromatography (silica gel/hexane−EtOAc = 15:1 then 5:1) to give **2i** in 76% yield (62.1 mg, 0.13 mmol); *trans*-**2i**/*cis*-**2i** was 78:22.

(6*S*,6a*S*)-*tert*-Butyl 6-(2-Naphthyl)-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole-6a-carboxylate (*trans*-2i). White solid, mp 94.0−95.0 °C; $[\alpha]_D$ + 40.4 (c 0.88, $CHCl_3$). The enantiomeric purity was determined by HPLC analysis (230 nm, 30 °C) to be 93% ee, t_R 30.8 min (major), t_R 38.0 min (minor) [Column

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ID 0.46 cm × 25 cm, hexane−*i*-PrOH = 95:5, 1.00 mL/min]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (dd, J = 6.1, 3.2 Hz, 1H), 7.69 (d, J = 7.4 Hz, 2H), 7.47 (dd, J = 6.1, 3.1 Hz, 3H), 7.41 (d, J = 7.8 Hz, 2H), 7.05 (br, 1H), 6.99 (d, J = 8.1 Hz, 2H), 6.12 (s, 1H), 5.30 (s, 1H), 4.30 (dd, J = 12.6, 1.9 Hz, 1H), 4.20 (d, J = 12.7 Hz, 1H), 3.14 (d, J = 11.8 Hz, 1H), 2.63 (d, J = 11.8 Hz, 1H), 2.25 (s, 3H), 1.48 (d, J = 0.7 Hz, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 143.3, 136.0, 135.8, 133.9, 133.2, 133.0, 129.4 (2C), 128.7, 128.2, 127.7, 127.3 (2C), 126.8, 126.5, 126.4, 124.9, 121.0, 83.1, 73.2, 68.0, 47.9, 37.9, 27.9 (3C), 21.5; IR (neat) ν 1718, 1340, 1273, 1161, 1093, 910 cm^{-1}; HRMS (ESI TOF M + Na) m/z 530.1431. Calcd for $C_{28}H_{29}NO_4S_2Na$ m/z 530.1436.

(6*S*,6a*R*)-*tert*-Butyl 6-(2-Naphthyl)-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole-6a-carboxylate (*cis*-2i). White solid, mp 92.0−93.0 °C; $[\alpha]_D$ + 108.5 (c 0.39, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80−7.70 (m, 4H), 7.63 (d, J = 8.2 Hz, 2H), 7.47−7.41 (m, 2H), 7.39−7.33 (m, 1H), 7.26 (d, J = 8.0 Hz, 2H), 5.84 (d, J = 0.7 Hz, 1H), 4.85 (s, 1H), 4.50 (dd, J = 14.1, 2.1 Hz, 1H), 4.38 (d, J = 14.1 Hz, 1H), 3.87 (d, J = 10.8 Hz, 1H), 3.37 (d, J = 10.9 Hz, 1H), 2.41 (s, 3H), 0.96 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 144.2, 135.7, 134.7, 134.4, 133.2, 133.0, 129.8 (2C), 128.1, 127.9, 127.8 (2C), 127.7, 126.2, 126.1, 126.0, 124.9, 119.1, 82.6, 75.4, 72.5, 50.2, 43.2, 27.5 (3C), 21.7; IR (neat) ν 1751, 1340, 1163, 912 cm^{-1}; HRMS (ESI TOF M + Na) m/z 530.1428. Calcd for $C_{28}H_{29}NO_4S_2Na$ m/z 530.1436.

Preparation of (6*S*)-*tert*-Butyl 6-(*m*-Methoxyphenyl)-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole-6a-carboxylate (2j). A Pyrex flask (30 mL) was charged with a solution of **1j** (83.9 mg, 0.18 mmol) and dimethyldisulfide (0.20 mL, 2.25 mmol) in toluene (20 mL), and the reaction solution was irradiated by a mercury lamp at ambient temperature under nitrogen atmosphere for 5 h. The reaction mixture was concentrated, and the residue was purified through flash chromatography (silica gel/hexane−EtOAc = 15:1 then 5:1) to give **2j** in 49% yield (44.5 mg, 0.09 mmol); *trans*-**2j**/*cis*-**2j** was 77:23.

(6*S*,6a*S*)-*tert*-Butyl 6-(*m*-Methoxyphenyl)-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno-[3,4-*c*]pyrrole-6a-carboxylate (*trans*-2j). Colorless oil; $[\alpha]_D$ + 47.3 (c 0.63, $CHCl_3$). The enantiomeric purity was determined by HPLC analysis (230 nm, 40 °C) to be 94% ee, t_R 35.8 min (major), t_R 53.8 min (minor) [Column ID 0.46 cm × 25 cm, hexane−*i*-PrOH = 95:5, 1.00 mL/min]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 8.2 Hz, 2H), 7.15 (t, J = 8.2 Hz, 1H), 7.12 (d, J = 8.2 Hz, 2H), 6.76 (dd, J = 8.2, 2.5 Hz, 1H), 6.62−6.54 (br, 1H), 6.48−6.39 (br, 1H), 6.07 (s, 1H), 5.08 (s, 1H), 4.21 (dd, J = 12.6, 2.2 Hz, 1H), 4.07 (d, J = 12.7 Hz, 1H), 3.73−3.64 (br, 3H), 3.12 (d, J = 11.7 Hz, 1H), 2.64 (d, J = 11.7 Hz, 1H), 2.35 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 159.4, 143.2, 136.2, 133.9, 130.7, 129.4 (2C), 128.6, 127.3 (2C), 120.8, 114.1 (2C), 82.9, 73.3, 67.4, 55.4, 47.6, 37.7, 27.9 (3C), 27.8, 21.5; IR (neat) ν 1718, 1601, 1489, 1340, 1284, 1161, 1093, 1039, 914, 842 cm^{-1}; HRMS (ESI TOF M + Na) m/z 510.1385. Calcd for $C_{25}H_{29}NO_5S_2Na$ m/z 510.1385.

(6*S*,6a*R*)-*tert*-Butyl 6-(*m*-Methoxyphenyl)-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno-[3,4-*c*]pyrrole-6a-carboxylate (*cis*-2j). Colorless oil; $[\alpha]_D$ + 110.5 (c 0.19, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.19 (t, J = 7.9 Hz, 1H), 6.89−6.82 (br, 2H), 6.77 (dd, J = 8.1, 2.6 Hz, 1H), 5.78 (s, 1H), 4.65 (s, 1H), 4.41 (d, J = 14.1, 1H), 4.29 (d, J = 14.2, 1H), 3.82 (d, J = 10.8 Hz, 1H), 3.76 (s, 3H), 3.25 (d, J = 10.9 Hz, 1H), 2.44 (s, 3H), 1.11 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 159.4, 144.2, 138.9, 135.7, 134.3, 129.8 (2C), 129.2, 127.8 (2C), 119.3, 119.0, 113.3, 113.0, 82.5, 75.2, 72.1, 55.3, 50.1, 43.2, 27.5 (3C), 21.7; IR (neat) ν 1742, 1587, 1350, 1163, 912 cm^{-1}; HRMS (ESI TOF M + Na) m/z 510.1391. Calcd for $C_{25}H_{29}NO_5S_2Na$ m/z 510.1385.

Preparation of (6*S*)-*tert*-Butyl 6-Propyl-5-tosyl-4,5,6,6a-tetrahydro-1*H*-thieno[3,4-*c*]pyrrole-6a-carboxylate (2k). A Pyrex flask (30 mL) was charged with a solution of **1k** (117.6 mg, 0.30 mmol) and dimethyldisulfide (0.30 mL, 3.38 mmol) in toluene (30 mL), and the reaction solution was irradiated by a mercury lamp at ambient temperature under nitrogen atmosphere for 5 h. The reaction mixture was concentrated, and the residue was purified through flash chromatography (silica gel/hexane−EtOAc = 15:1 then 5:1) to give **2k** in 29% yield (36.5 mg, 0.09 mmol) as an inseparable diastereomeric mixture. The diastereomeric ratio was about 1:1.

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 5.0 Hz, 2H for one isomer), 7.68 (d, J = 5.0 Hz, 2H for another isomer), 7.32 (dd, J = 8.5, 0.5 Hz, 2H for one isomer), 7.28 (d, J = 8.0 Hz, 2H for another isomer), 5.99 (s, 1H for one isomer), 5.72 (s, 1H for one isomer), 4.21 (dd, J = 14.1, 2.1 Hz, 1H for one isomer), 4.05 (dd, J = 14.1, 1.1 Hz, 1H for one isomer), 4.00−3.95 (m, 1H for one isomer), 3.93 (dd, J = 12.9, 2.3 Hz, 1H for another isomer), 3.88 (dd, J = 12.9, 1.4 Hz, 1H for another isomer), 3.74 (d, J = 11.0 Hz, 1H for one isomer), 3.45 (d, J = 11.6 Hz, 1H for another isomer), 3.37 (dd, J = 9.9, 3.3 Hz, 1H for one isomer), 3.35 (dd, J = 7.9, 6.2 Hz, 1H for another isomer), 3.05 (d, J = 11.1 Hz, 1H for another isomer), 2.44 (s, 3H for one isomer), 2.40 (s, 3H for another isomer), 1.47 (s, 9H for one isomer), 1.77−1.19 (m, 4H for both isomers), 1.29 (s, 9H for another isomer), 0.90 (t, J = 7.7 Hz, 3H for one isomer), 0.88 (t, J = 7.4 Hz, 3H for another isomer); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 169.2, 143.9, 143.5, 136.0, 135.9, 135.2, 134.9, 130.0, 129.9, 129.8 (2C for one isomer), 129.7, 127.8, 127.6 (2C for one isomer), 127.5 (2C for another isomer), 127.1, 119.1, 118.2, 82.9, 82.5, 72.7, 71.7, 69.4, 63.6, 49.8, 46.9, 42.6, 37.5, 35.7, 34.5, 28.0 (3C for one isomer), 27.7 (3C for another isomer), 21.7, 21.6, 19.3, 18.3, 14.2, 14.0; HRMS (ESI TOF M + Na) m/z 446.1428. Calcd for $C_{21}H_{29}NO_4S_2Na$ m/z 446.1436.

Preparation of (2*S*,*Z*)-*tert*-Butyl 3-((Methylthio)methyl)-4-((methylthio)-methylene)-2-phenyl-1-tosylpyrrolidine-3-carboxylate (3): (Scheme 1). In a Pyrex flask (20 mL), compound **1a** (45.0 mg, 0.11 mmol) was dissolved in dimethyldisulfide (0.1 mL, 1.13 mmol), and the reaction solution was irradiated by a mercury lamp at ambient temperature under nitrogen atmosphere for 5 h. The reaction mixture was concentrated under reduced pressure, and the yellow residue was purified through flash chromatography (silica gel/hexane−EtOAc = 8:1 then 5:1) to give **3** in 27% yield (15.0 mg, 0.03 mmol). Compounds **3a** and **3b** were separated by careful chromatography followed by recycle GPC separation. The diastereomeric ratio of **3a** and **3b** was approximately 1:1.

(2*S*,3*S*,*Z*)-*tert*-Butyl 3-((Methylthio)methyl)-4-((methylthio)-methylene)-2-phenyl-1-tosylpyrrolidine-3-carboxylate (3a). Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, J = 8.2 Hz, 2H), 7.20 (t, J = 7.6 Hz, 1H), 7.17−7.10 (br, 2H), 7.01 (d, J = 8.4 Hz, 2H), 6.90−7.05 (br, 2H), 6.11 (t, J = 2.0 Hz, 1H), 5.50 (s, 1H), 4.07 (s, 2H), 2.66 (d, J = 12.5 Hz, 1H), 2.33 (s, 3H), 2.31 (s, 3H), 2.11 (d, J = 12.4 Hz, 1H), 1.86 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 142.7, 137.7, 136.3, 133.4, 129.2, 129.1 (2C), 128.2 (2C), 128.0 (2C), 127.2 (2C), 123.8, 82.9, 68.9, 63.4, 50.2, 37.4, 27.9 (3C), 21.5, 18.1, 17.7; HRMS (ESI TOF M + Na) m/z 542.1462. Calcd for $C_{26}H_{33}NO_4S_3Na$ m/z 542.1469.

(2*S*,3*R*,*Z*)-*tert*-Butyl 3-((Methylthio)methyl)-4-((methylthio)-methylene)-2-phenyl-1-tosylpyrrolidine-3-carboxylate (3b). Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, J = 8.1 Hz, 2H), 7.17−7.14 (m, 1H), 7.10 (t, J = 7.6 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 7.3 Hz, 2H), 6.70 (t, J = 2.2 Hz, 1H), 4.89 (s, 1H), 4.10 (dd, J = 14.4, 2.6 Hz, 1H), 4.02 (dd, J = 14.4, 2.1 Hz, 1H), 3.26 (d, J = 13.3 Hz, 1H), 2.76 (d, J = 13.2 Hz, 1H), 2.41 (d, J = 0.4 Hz, 3H), 2.31 (s, 3H), 2.08 (d, J = 0.5 Hz, 3H), 1.00 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0, 143.0, 142.4, 138.0, 129.2 (2C), 128.4 (2C), 128.2 (2C), 128.1, 127.2 (2C), 126.8, 126.4, 81.9, 72.0, 62.8, 50.0, 44.0, 27.4 (3C), 21.5, 18.0, 17.6; HRMS (ESI TOF M + Na) m/z 542.1456. Calcd for $C_{26}H_{33}NO_4S_3Na$ m/z 542.1469.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Compound characterization data and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(8) Crystallographic data (excluding structure factors) for the structures *cis* **2a** and *trans* **2a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 931892 and 931893, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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(10) Geometry optimizations were carried out using the B3PW91/6-311G(d), B3LYP-D/6-311G(d), and MP2/6-31G(d) methods. Initial structure for intermediate **C** gave compound **2** (by B3LYP-D/6-311G(d)) or intermediate **B** (by B3PW91/6-311G(d) or MP2/6-31G(d)) through optimization. All these calculations were performed with the Gaussian 09 program package.