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Diastereoselective Synthesis of Biheterocyclic Tetrahydrothiophene Derivatives via Base-Catalyzed Cascade Michael-Aldol [3 + 2] Annulation of 1,4-Dithiane-2,5-diol with Maleimides

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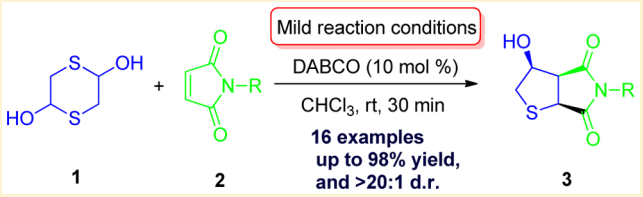
Supporting Information

ABSTRACT: A highly diastereoselective intermolecular [3 + 2] annulation of 1,4-dithiane-2,5-diol to maleimides has been developed by using DABCO as a catalyst, which provides a series of highly functionalized biheterocyclic tetrahydrothiophene derivatives containing tetrahydrothiophene and pyrolidine backbones in excellent yields and diastereoselectivities (up to 98% yield and >20:1 d.r.). The cascade Michael-aldol reaction is capable of tolerating organic solvents as well as water.



Thiophene derivatives are privileged structural units that are frequently encountered in many biologically active natural and synthetic compounds[1] as well as in materials.[2] In particular, some tetrahydrothiophene derivative backbones have attracted a great deal of attention, as they contain two biological, pharmaceutical, and agrochemical characteristics of both sulfur-containing compounds and biheterocycles (Figure 1).[3] Therefore, the development of highly efficient synthetic methods to access these biheterocyclic compounds is particularly appealing.

Commercially available 1,4-dithiane-2,5-diol (the dimer of mercaptoacetaldehyde) has been employed as an efficient substrate for the construction of tetrahydrothiophene derivatives via catalytic [3 + 2] annulation strategies.[4] Recently, 1,4-dithiane-2,5-diol has proved to be an attractive synthon for synthesizing a spiro heterocyclic compound and several methods for the synthesis of this structural unit have been reported by S. Vivek Kumar et al.,[5] J.-J. Liang et al.,[6] and S.-W. Duanet al.,[7] and diversely spiro heterocyclic tetrahydrothiophene derivatives can be simply synthesized in good yields and diastereomeric ratio values.

However, compared to the catalytic formation of spiroheterocycles, the biheterocyclic tetrahydrothiophenes have been much less studied. Furthermore, the reaction of 1,4-dithiane-2,5-diol with maleimides has not yet been established, and we believe this represents a considerable challenge. However, the development of efficient methodologies that enable cheaper, simpler, and more concise approaches to access molecular complexity with exquisite levels of stereocontrol remains a preeminent goal in modern organic chemistry. Herein, we introduce a base-catalyzed strategy as a new and convenient platform for the design of intermolecular [3 + 2] annulation processes. In this context, we report an unprecedented DABCO-catalyzed [3 + 2] annulation of 1,4-dithiane-2,5-diol with maleimides to afford highly functionalized bicyclic compounds containing tetrahydrothiophene and pyrolidine backbones under mild reaction conditions with high efficiency.

We initiated our studies by evaluating the reaction between 1,4-dithiane-2,5-diol **1** and *N*-benzyl maleimide **2a** by base-catalysts in dichloromethane at room temperature. We found that this reaction proceeded quickly with 10 mol % Et_3N and afforded the respective annulation products in 59% isolated yield and more than 20:1 diastereoselectivity within 40 min (Table 1, entry 1). Although high yields (up to 70% and 77%) were attained with the catalysts DBU and DIPEA, the diastereoselectivities were consistently poor (19:1 and 16:1) within 60 min (Table 1, entries 2 and 3). DABCO was found to be the most suitable catalyst for this reaction (Table 1, entry 4). Gratifyingly, a great improvement was observed by changing solvents, and the best yield (97%) and diastereoselectivity (>20:1) were obtained for product **3a** when $CHCl_3$ was used as a solvent (Table 1, entries 6−14). Surprisingly and remarkably, this reaction could also be performed in water with good yield (62%) and excellent diastereoselectivities (>20:1) within 30 min (Table 1, entry 15). In addition, when the catalyst loading was reduced to 5 or 1 mol %, respectively, no significant change in diastereoselectivities (>20:1) but poor yields (66%) were obtained (Table 1, entries 16 and 17).

Next, the substrate scope of the reaction under the optimized conditions was summarized in Table 2. In general, all the reactions proceeded well to complete in less than 30 min to give the corresponding products in high yields and diaster-

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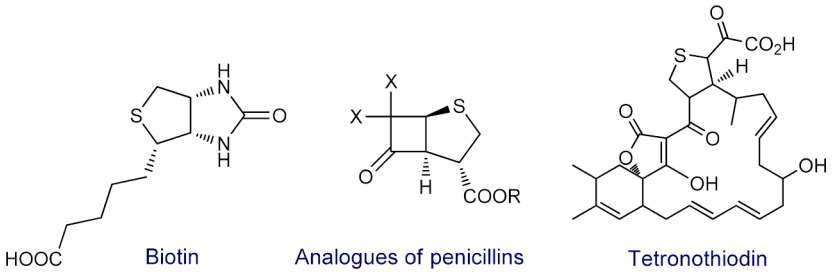
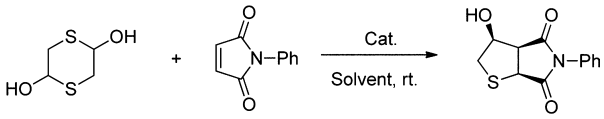


Figure 1. Structures of bioactive bicyclic tetrahydrothiophenes.

Table 1. Optimization of the Reaction Conditions[a]

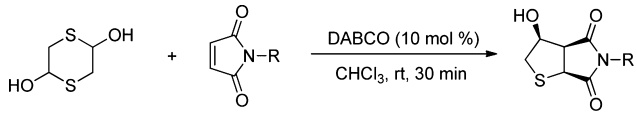


1 2a 3a

entry	cat.	x (mol %)	solvent	time (min)	yield (%)[b]	d.r.[c]
1	Et_3N	10	CH_2Cl_2	40	59	>20:1
2	DBU	10	CH_2Cl_2	60	70	19:1
3	DIPEA	10	CH_2Cl_2	60	77	16:1
4	DABCO	10	CH_2Cl_2	30	79	>20:1
5	Na_2CO_3	10	CH_2Cl_2		0	
6	**DABCO**	**10**	**$CHCl_3$**	**30**	**97**	**>20:1**
7	DABCO	10	THF	30	76	14:1
8	DABCO	10	PhMe	30	54	17:1
9	DABCO	10	MTBE	30	37	15:1
10	DABCO	10	MeOH	30	32	4:1
11	DABCO	10	EtOAc	30	86	16:1
12	DABCO	10	$Cl(CH_2)_2Cl$	30	53	17:1
13	DABCO	10	acetone	30	35	4:1
14	DABCO	10	CH_3CN	30	44	4:1
15	DABCO	10	H_2O	30	62	>20:1
16	DABCO	5	$CHCl_3$	120	66	>20:1
17	DABCO	1	$CHCl_3$	180	66	>20:1

[a]Reaction conditions: unless specified, a mixture of **1** (0.24 mmol), **2a** (0.4 mmol), and a catalyst (*x* mol %) in a solvent (1.5 mL) was stirred at rt. [b]Isolated yields. [c]Determined by ^1H NMR, and the configuration was assigned by comparison of X-ray crystal data of **3m**, **5a**, and **5b**.

Table 2. Scope of N-Substituted Maleimides[a]



1 2 3

entry	R (2)	product (3)	yield[b]	d.r.[c]
1	Ph (**2a**)	**3a**	97	>20:1
2	4-MePh (**2b**)	**3b**	55	>20:1
3	4-MeOPh (**2c**)	**3c**	62	>20:1
4	4-FPh (**2d**)	**3d**	98	>20:1
5	4-ClPh (**2e**)	**3e**	98	>20:1
6	4-BrPh (**2f**)	**3f**	92	>20:1
7	4-NO_2Ph (**2g**)	**3g**	89	>20:1
8	3-ClPh (**2h**)	**3h**	97	>20:1
9	2-ClPh (**2i**)	**3i**	<5	
10	1-Naphthyl (**2j**)	**3j**	97	17:1
11	H (**2k**)	**3k**		
12	Boc (**2l**)	**3l**	61	>20:1
13	Me (**2m**)	**3m**	72	4:1
14	Et (**2n**)	**3n**	96	>20:1
15	Bn (**2o**)	**3o**	96	>20:1
16	Hex (**2p**)	**3p**	67	>20:1

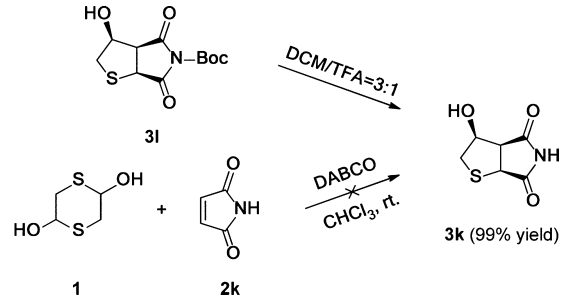
[a]Reaction conditions: unless specified, a mixture of **1** (0.24 mmol), **2** (0.4 mmol), and DABCO (0.024 mmol) in $CHCl_3$ (1.5 mL) was stirred for 30 min at rt. [b]Isolated yields. [c]Determined by ^1H NMR, and the configuration was assigned by comparison of X-ray crystal data of **3m**, **5a**, and **5b**.

eoselecttivities. Nonsubstituted or electron-withdrawing substituents at the *para*- or *meta*-position on the aromatic ring as well as 1-naphthyl in maleimide diversifications were tolerated, affording the desired products in excellent yields and diastereoselectivities (Table 2, entries 1, 4−8 and 10). The substrates with electron-donating substituents at *para*-position afforded the diastereoselectivities at the same levels albeit with moderate yields. (Table 2, entries 2 and 3). However, the substrates with *ortho*-substituent on aryl ring led to almost no product (Table 2, entries 9). Maleimide **2l** bearing an *N*-Boc group also proceeded with low yield, while when employing maleimide **2k** without protecting groups, no reaction occurred (Table 2, entries 11−12). It is noteworthy that the reactions of aliphatic-substituted maleimides **2n** and **2o** could proceed smoothly under standard conditions, giving the desired products in 96% yields with >20:1 d.r., whereas the yield was remarkably decreased for **2m** and **2p** (Table 2, entries 13−16). The absolute configuration of the products obtained through the Michael-aldol cascade process was determined by an X-ray analysis of compound **3m**[8] (see Supporting Information).

We also explored to remove the Boc group of product **3l**. Under the acidic condition, the reaction gave the *N*-unprotected product **3k** in high yield. Moreover, the NH of the unprotected compound **3k** can be easily further modified (Scheme 1).

We further extended the scope of the reaction, and 1,3-diphenylmaleimide proved to be amenable to this catalytic method, which gave the respective annulation products with

Scheme 1. Removal of the Boc Group in Compound 3l



3l 1 2k

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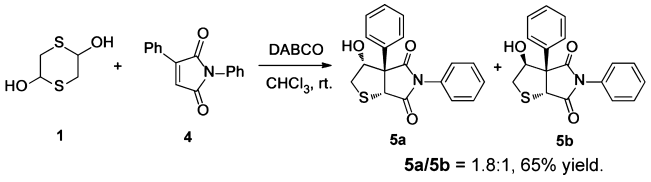
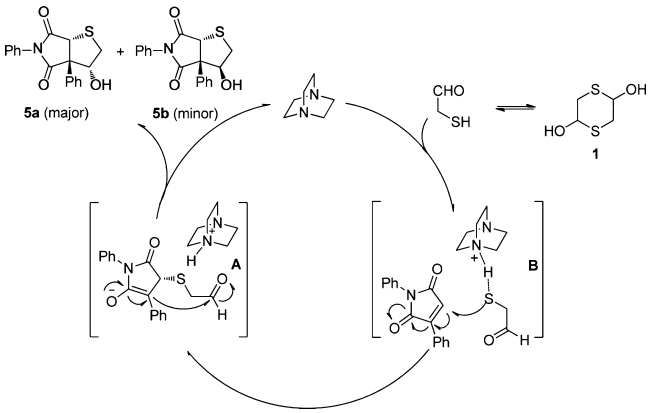
good yields. The absolute configuration of biheterocyclic tetrahydrothiophene derivatives were unambiguously confirmed by the X-ray crystallographic analysis, as shown in Supporting Information, and it is composed of (C8*R*, C9*R*, and C11*R*) configuration for **5a** and (C8*R*, C9*R*, and C11*S*) configuration for **5b**[9] (Scheme 2).

Scheme 2. Synthesis of 3-Hydroxy-3a,5-diphenyldihydro-2*H*-thieno[2,3-*c*]pyrrole-4,6(5*H*,6a*H*)-dione



On the basis of the experimental results described above, a plausible catalytic cycle of the current cascade reaction is outlined in Scheme 3. The mercaptoacetaldehyde that is

Scheme 3. Proposed Mechanism of the Michael-Aldol Reaction



generated from 1,4-dithiane-2,5-diol under equilibrium conditions could be activated by the tertiary amine of DABCO to form intermediate **B**. It undergoes the intermolecular sulfa-Michael addition to provide intermediate **A**. Subsequent intramolecular aldol reaction through nucleophilic attack of in situ enolate to the aldehyde moiety in excellent diastereoselective fashion, then followed by the regeneration of the DABCO provides the biheterocyclic tetrahydrothiophene compounds. The absolute configuration of the major product was determined as (C8*R*, C9*R*, and C11*R*) by using the X-ray crystallographic analysis of **5a**.

In summary, We have disclosed an unprecedented DABCO-catalyzed [3 + 2] Michael-aldol annulation of 1,4-dithiane-2,5-diol with maleimides to afford highly functionalized bicyclic compounds containing tetrahydrothiophene and pyrolidine backbones with high efficiency. The construction proceeds under mild conditions, providing a range of compounds in excellent yields and diastereoselectivities (up to 98% yield and >20:1 d.r.). In particular, the procedure is capable of tolerating a relatively wide range of solvents, especially in water. We consider that the utility of biheterocyclic tetrahydrothiophene derivatives may exhibit promising applications in drug discovery or chemical biology. The biological evaluation of these products is currently underway by our group.

EXPERIMENTAL SECTION

General Methods. Unless stated otherwise, all reactions were carried out in flame-dried glassware. All solvents were purified and dried according to standard methods prior to use. Reactions were monitored by thin layer chromatography (TLC), and column chromatography purifications were carried out using silica gel. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded using $(CD_3)_2SO$, $(CD_3)_2CO$, or $CDCl_3$ assolvents and TMS as an internal standard. The peak patterns of ^{1}H NMR are indicated as follows: s, singlet; d, doublet; t, triplet; dd, doublet of doublet; and m, multiplet. The coupling constants, *J*, are reported in hertz (Hz). Data for ^{19}F NMR and ^{13}C NMR are reported in terms of chemical shift and multiplicity. HRMS were performed on a Q-tof mass instrument (ESI). 1,4-Dithiane-2,5-diol **1**, all reagents, and catalysts were obtained from commercial sources and were used without further purification. All reactions were conducted in a closed system and were monitored by TLC. N-Substituted maleimides **2**[10] and 1,3-diphenylmaleimide **4**[11] were prepared according to the literature method or a similar method.

General Procedure for the Synthesis of 3a−3h, 3j−3p, 5a, and 5b. An ordinary vial equipped with a magnetic stirring bar was charged with 1,4-dithiane-2,5-diol **1** (0.24 mmol) and maleimides **2** (0.4 mmol) in $CHCl_3$ (1.5 mL), and then DABCO (4.5 mg, 10 mol %) was added. The stirring was maintained at room temperature for 30 min. The reaction mixture was directly charged onto silica gel and purified through flash chromatography (CH_2Cl_2/EtOAc = 4:1) to furnish the corresponding products **3**.

*(3S,3aS,6aS)-3-Hydroxy-5-phenyldihydro-2H-thieno[2,3-c]-pyrrole-4,6(5H,6aH)-dione (**3a**).* Yield 97% (97 mg); white solid; d.r. > 20:1. ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ (ppm) 7.51- 7.39 (m, 3H), 7.22 (d, *J* = 7.2 Hz, 2H), 5.66 (d, *J* = 3.9 Hz, 1H), 4.78 (s, 1H), 4.60 (d, *J* = 8.7 Hz, 1H), 3.65 (dd, *J* = 8.9, 5.3 Hz, 1H), 3.21 (dd, *J* = 11.6, 2.9 Hz, 1H), 2.93 (dd, *J* = 11.7, 1.8 Hz, 1H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$): δ (ppm) 176.14, 173.68, 132.92, 129.36, 128.80, 127.47, 74.65, 55.34, 48.62, 42.94. ESI-HRMS: calcd. for $C_{12}H_{11}NO_3S + H^+$ 250.0532; found, 250.0538.

*(3S,3aS,6aS)-3-Hydroxy-5-(p-tolyl)dihydro-2H-thieno[2,3-c]-pyrrole-4,6(5H,6aH)-dione (**3b**).* Yield 55% (58 mg); white solid; d.r. > 20:1. ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ (ppm) 7.25 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 8.3 Hz, 2H), 4.78−4.69 (m, 1H), 4.19 (d, *J* = 8.3 Hz, 1H), 3.84 (d, *J* = 7.5 Hz, 1H), 3.53 (dd, *J* = 8.2, 6.5 Hz, 1H), 3.11 (dd, *J* = 11.7, 4.4 Hz, 1H), 2.83 (dd, *J* = 11.8, 6.6 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$): δ (ppm) 175.5, 175.1, 139.2, 129.9, 128.7, 126.3, 76.0, 51.1, 45.4, 39.2, 21.3. ESI-HRMS: calcd. for $C_{13}H_{13}NO_3S + H^+$ 264.0689; found, 264.0691.

*(3S,3aS,6aS)-3-Hydroxy-5-(4-methoxyphenyl)dihydro-2H-thieno-[2,3-c]pyrrole-4,6(5H,6aH)-dione (**3c**).* Yield 62% (69 mg); white solid; d.r. > 20:1. ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ (ppm) 7.20 (d, *J* = 8.9 Hz, 2H), 7.00 (d, *J* = 8.9 Hz, 2H), 4.94−4.92 (m, 1H), 4.66 (s, 1H), 4.53 (d, *J* = 8.9 Hz, 1H), 3.82 (s, 3H), 3.72 (dd, *J* = 8.9, 5.6 Hz, 1H), 3.29 (dd, *J* = 11.7, 3.4 Hz, 1H), 3.00 (dd, *J* = 11.7, 3.4 Hz, 1H). ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ (ppm) 176.4, 174.4, 160.3, 129.1, 126.4, 114.8, 76.1, 55.8, 55.0, 48.5, 42.5. ESI-HRMS: calcd. for $C_{13}H_{13}NO_4S + Na^+$ 302.0457; found, 302.0465.

*(3S,3aS,6aS)-5-(4-Fluorophenyl)-3-hydroxydihydro-2H-thieno-[2,3-c]pyrrole-4,6(5H,6aH)-dione (**3d**).* Yield 98% (105 mg); white solid; d.r. > 20:1. ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ (ppm) 7.36−7.24 (m, 4H), 5.69 (d, *J* = 4.0 Hz, 1H), 4.78 (s, 1H), 4.58 (d, *J* = 8.9 Hz, 1H), 3.66 (dd, *J* = 8.9, 5.2 Hz, 1H), 3.21 (dd, *J* = 11.6, 2.9 Hz, 1H), 2.93 (dd, *J* = 11.6, 2.1 Hz, 1H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$): δ (ppm) 176.1, 173.7, 161.9 (J_{C-F} = 243.8HZ), 129.6 (J_{C-F} = 9HZ), 129.1 (J_{C-F} = 3HZ), 116.3 (J_{C-F} = 22.5HZ), 74.7, 55.3, 48.6, 42.9. ^{19}F NMR (282 MHz, $(CD_3)_2SO$) δ (ppm) −112.97. ESI-HRMS: calcd. for $C_{12}H_{10}FNO_3S + Na^+$ 290.0258; found, 290.0261.

*(3S,3aS,6aS)-5-(4-Chlorophenyl)-3-hydroxydihydro-2H-thieno-[2,3-c]pyrrole-4,6(5H,6aH)-dione (**3e**).* Yield 98% (111 mg); white solid; d.r. > 20:1. ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ (ppm) 7.63 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 8.6 Hz, 2H), 5.74 (d, *J* = 3.0 Hz, 1H), 4.83 (s, 1H), 4.65 (d, *J* = 8.9 Hz, 1H), 3.72 (dd, *J* = 8.9, 5.2 Hz, 1H), 3.27 (dd, *J* = 11.6, 2.8 Hz, 1H), 2.98 (dd, *J* = 11.6, 1.9 Hz, 1H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$): δ (ppm) 175.5, 173.0, 132.8, 131.2, 129.0,

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128.7, 74.2, 54.2, 54.9, 48.1, 42.4. ESI-HRMS: calcd. for $C_{12}H_{11}ClNO_3S + H^+$ 284.0143; found, 284.0152.

*(3S,3aS,6aS)-5-(4-Bromophenyl)-3-hydroxydihydro-2H-thieno-[2,3-c]pyrrole-4,6(5H,6aH)-dione (**3f**).* Yield 92% (120 mg); white solid; d.r. > 20:1. ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ (ppm) 7.70 (d, J = 8.7 Hz, 2H), 7.19 (d, J = 8.7 Hz, 2H), 5.68 (d, J = 3.9 Hz, 1H), 4.79−4.75 (m, 1H), 4.58 (d, J = 8.9 Hz, 1H), 3.66 (dd, J = 8.9, 5.1 Hz, 1H), 3.21 (dd, J = 11.6, 3.0 Hz, 1H), 2.92 (dd, J = 11.6, 2.2 Hz, 1H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$): δ (ppm) 175.9, 173.5, 132.4, 132.1, 129.5, 121.8, 74.7, 55.4, 48.6, 42.9. ESI-HRMS: calcd. for $C_{12}H_{11}BrNO_3S + H^+$ 327.9638; found, 327.9641.

*(3S,3aS,6aS)-3-Hydroxy-5-(4-nitrophenyl)dihydro-2H-thieno[2,3-c]pyrrole-4,6(5H,6aH)-dione (**3g**).* Yield 89% (105 mg); white solid; d.r. > 20:1. ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ (ppm) 8.37 (d, J = 8.9 Hz, 2H), 7.56 (d, J = 8.9 Hz, 2H), 5.74 (d, J = 2.9 Hz, 1H), 4.80 (s, 1H), 4.63 (d, J = 9.0 Hz, 1H), 3.71 (dd, J = 8.9, 5.2 Hz, 1H), 3.23 (dd, J = 11.6, 2.8 Hz, 1H), 2.94 (dd, J = 11.6, 1.9 Hz, 1H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$): δ (ppm) 175.7, 173.2, 147.0, 138.3, 128.2, 124.8, 74.8, 55.5, 48.7, 43.0. ESI-HRMS: calcd. for $C_{12}H_{10}N_2O_5S + Na^+$ 317.0203; found, 317.0202.

*(3S,3aS,6aS)-5-(3-Chlorophenyl)-3-hydroxydihydro-2H-thieno-[2,3-c]pyrrole-4,6(5H,6aH)-dione (**3h**).* Yield 97% (110 mg); white solid; d.r. > 20:1. ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ (ppm) 7.44−7.39 (m, 2H), 7.36- 7.35 (m, 1H), 7.26−7.22 (m, 1H), 4.88−4.79 (m,1H), 4.27 (d, J = 8.2 Hz, 1H), 3.66 (dd, J = 8.1, 6.6 Hz, 1H), 3.51 (d, J = 8.8 Hz, 1H), 3.23 (dd, J = 11.8, 4.7 Hz, 1H), 2.91 (dd, J = 11.8, 7.5 Hz, 1H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$): δ (ppm) 174.6, 134.8, 132.2, 130.3, 129.3, 126.6, 124.6, 76.2, 50.7, 44.9, 38.8. ESI-HRMS: calcd. for $C_{12}H_{10}ClNO_3S + Na^+$ 305.9962; found, 305.9972.

*(3S,3aS,6aS)-3-Hydroxy-5-(naphthalen-1-yl)dihydro-2H-thieno-[2,3-c]pyrrole-4,6(5H,6aH)-dione (**3j**).* Yield 97% (116 mg); white solid; d.r. = 17:1. ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ (ppm) 8.08−7.86 (m, 3H), 7.65−7.29 (m, 4H), 6.04−5.80 (m, 1H), 4.92−4.71 (m, 2H),3.83−3.77 (m, 1H), 3.34−3.26 (m, 1H), 3.02 (t, J = 11.0 Hz, 1H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$): δ (ppm) 176.7, 173.9, 134.1, 130.2, 130.1, 129.8, 128.5, 127.2, 127.1, 127.0, 126.0, 123.8, 74.1, 56.2, 49.2, 43.7. ESI-HRMS: calcd. for $C_{16}H_{13}NO_3S + H^+$ 300.0689; found, 300.0695.

*(3S,3aS,6aS)-3-Hydroxydihydro-2H-thieno[2,3-c]pyrrole-4,6-(5H,6aH)-dione (**3k**).* Yield 82% (60 mg); yellow solid; d.r. > 20:1. ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ (ppm) 7.66 (s, 1H), 7.33 (s, 1H), 5.30 (s, 1H), 3.92 (s, 1H), 3.27 (dd, J = 11.2, 1.9 Hz, 1H), 3.08 (dd, J = 8.4, 2.7 Hz, 2H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$): δ (ppm) 173.1, 169.5, 81.9, 57.6, 43.9, 37.0. ESI-HRMS: calcd. for $C_6H_7NO_3S + Na^+$ 196.0039; found, 196.0043.

*(3S,3aS,6aS)-tert-Butyl 3-hydroxy-4,6-dioxotetrahydro-2H-thieno[2,3-c]pyrrole-5(3H)-carboxylate (**3l**).* Yield 61% (67 mg); white solid; d.r. > 20:1. ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ (ppm) 8.20 (s, 1H), 5.26 (s, 1H), 3.76 (d, J = 5.9 Hz, 2H), 3.42−3.37 (m, 1H), 3.17 (d, J = 11.0 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$): δ (ppm) 172.1, 169.8, 150.8, 83.8, 80.5, 58.4, 43.9, 36.9, 27.9. ESI-HRMS: calcd. for $C_{11}H_{15}NO_5S + Na^+$ 296.0563; found, 296.0564.

*(3S,3aS,6aS)-3-Hydroxy-5-methyldihydro-2H-thieno[2,3-c]-pyrrole-4,6(5H,6aH)-dione (**3m**).* Yield 72% (54 mg); white solid; d.r. = 4:1. ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ (ppm) 4.74−4.66 (m, 1H), 4.11 (d, J = 8.2 Hz, 1H), 3.90 (d, J = 7.5 Hz, 1H), 3.51−3.46 (m, 1H), 3.09 (dd, J = 11.7, 4.5 Hz, 1H), 2.95 (s, 3H), 2.75 (dd, J = 11.7, 7.0 Hz, 1H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$): δ (ppm) 176.5, 175.8, 75.6, 50.8, 45.3, 38.9, 25.2. ESI-HRMS: calcd. for $C_7H_9NO_3S + Na^+$ 210.0195; found, 210.0196.

*(3S,3aS,6aS)-5-Ethyl-3-hydroxydihydro-2H-thieno[2,3-c]pyrrole-4,6(5H,6aH)-dione (**3n**).* Yield 96% (77 mg); white solid; d.r. > 20:1. ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ (ppm) 4.85−4.78 (m, 1H), 4.47 (d, J = 5.3 Hz, 1H), 4.35 (d, J = 8.7 Hz, 1H), 3.61 (dd, J = 8.7, 5.9 Hz, 1H), 3.46 (dt, J = 14.1, 6.9 Hz, 2H), 3.22 (dd, J = 11.7, 3.6 Hz, 1H), 2.88 (dd, J = 11.7, 4.2 Hz, 1H), 1.09 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ (ppm) 176.8, 175.0, 75.8, 54.2, 48.0, 41.9, 34.2, 13.1. ESI-HRMS: calcd. for $C_8H_{11}NO_3S + H^+$ 202.0532; found, 202.0535.

*(3S,3aS,6aS)-5-Benzyl-3-hydroxydihydro-2H-thieno[2,3-c]-pyrrole-4,6(5H,6aH)-dione (**3o**).* Yield 96% (101 mg); white solid; d.r. > 20:1. ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ (ppm) 7.21−7.09 (m, 5H), 4.68 (dd, J = 8.8, 4.3 Hz, 1H), 4.47 (d, J = 7.8 Hz, 2H), 4.41 (d, J = 4.2 Hz, 1H), 4.24 (d, J = 8.7 Hz, 1H), 3.50 (dd, J = 8.7, 5.9 Hz, 1H), 3.05 (dd, J = 11.7, 3.6 Hz, 1H), 2.72 (dd, J = 11.7, 4.2 Hz, 1H). ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ (ppm) 177.0, 175.1, 137.2, 129.3, 128.7, 128.3, 75.8, 54.5, 48.1, 42.8, 42.2. ESI-HRMS: calcd. for $C_{13}H_{13}NO_3S + H^+$ 264.0689; found, 264.0695.

*(3S,3aS,6aS)-5-Cyclohexyl-3-hydroxydihydro-2H-thieno[2,3-c]-pyrrole-4,6(5H,6aH)-dione (**3p**).* Yield 67% (68 mg); white solid; d.r. > 20:1. ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ (ppm) 4.82−4.76 (m, 1H), 4.45 (d, J = 5.6 Hz, 1H), 4.28 (d, J = 8.7 Hz, 1H), 3.3.93−3.82 (m,1H), 3.53 (dd, J = 8.7, 5.9 Hz, 1H), 3.22−3.17 (m, 1H), 2.85 (dd, J = 11.6, 4.4 Hz, 1H), 2.16−2.03 (m, 2H), 1.81−1.77 (m, 2H), 1.66−1.55 (m, 3H), 1.38−1.21 (m, 3H). ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ (ppm) 177.0, 175.3, 76.0, 53.6, 52.3, 47.7, 41.5, 29.6, 29.4, 26.5, 26.0. ESI-HRMS: calcd. for $C_{12}H_{17}NO_3S + H^+$ 256.1002; found, 256.1005.

*(3R,3aR,6aR)-3-Hydroxy-3a,5-diphenyldihydro-2H-thieno[2,3-c]-pyrrole-4,6(5H,6aH)-dione (**5a**).* Yield 42% (55 mg); brown solid. ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ (ppm) 7.77 (d, J = 7.5 Hz, 2H), 7.52−7.36 (m, 6H), 7.28 (d, J = 7.3 Hz, 2H), 6.31 (d, J = 2.3 Hz, 1H), 5.13 (s, 1H), 4.76 (s, 1H), 2.91 (s, 2H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$): δ (ppm) 174.9, 174.4, 135.7, 133.1, 129.4, 129.0, 129.0, 128.5, 127.7, 127.5, 82.4, 68.0, 52.4. ESI-HRMS: calcd. for $C_{18}H_{15}NO_3S + H^+$ 326.0845; found, 326.0849.

*(3S,3aR,6aR)-3-Hydroxy-3a,5-diphenyldihydro-2H-thieno[2,3-c]-pyrrole-4,6(5H,6aH)-dione (**5b**).* Yield 23% (30 mg); brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.60−7.56 (m, 2H), 7.48−7.37 (m, 6H), 7.25−7.20 (m, 2H), 5.20 (s, 1H), 4.60 (s, 1H), 3.33 (dd, J = 12.8, 3.2 Hz, 1H), 3.14 (dd, J = 12.8, 1.4 Hz, 1H), 1.17 (d, J = 6.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 175.7, 174.8, 133.0, 131.3, 129.4, 129.3, 129.0, 127.5, 126.5, 126.2, 79.0, 69.4, 50.3, 39.4. ESI-HRMS: calcd. for $C_{18}H_{15}NO_3S + H^+$ 326.0845; found, 326.0848.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray crystallographic data for **3m**, **5a**, and **5b** (CIF), and ^{1}H, ^{13}C, and ^{19}F NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00897.

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Notes

The authors declare no competing financial interest.

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(9) CCDC 1400568 **5a** and CCDC 1053203 **5b** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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