

Facile Construction of Structurally Diverse Thiazolidinedione-Derived Compounds via Divergent Stereoselective Cascade Organocatalysis and Their Biological Exploratory Studies

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S Supporting Information

ABSTRACT: In this article, we present a new approach by merging two powerful synthetic tactics, divergent synthesis and cascade organocatalysis, to create a divergent cascade organocatalysis strategy for the facile construction of new "privileged" substructure-based DOS (pDOS) library. As demonstrated, notably 5 distinct molecular architectures are produced facilely from readily available simple synthons thiazolidinedione and its analogues and α,β -unsaturated aldehydes in 1–3 steps with the powerful strategy. The beauty of the chemistry is highlighted by the efficient formation of structurally new and



diverse products from structurally close reactants under the similar reaction conditions. Notably, structurally diverse spirothiazolidinediones and -rhodanines are produced from organocatalytic enantioselective 3-component Michael–Michael–aldol cascade reactions of respective thiazolidinediones and rhodanines with enals. Nevertheless, under the similar reaction conditions, reactions of isorhodanine via a Michael–cyclization cascade lead to structurally different fused thiopyranoid scaffolds. This strategy significantly minimizes time- and cost-consuming synthetic works. Furthermore, these molecules possess high structural complexity and functional, stereochemical, and skeletal diversity with similarity to natural scaffolds. In the preliminary biological studies of these molecules, compounds **4f**, **8a**, and **10a** exhibit inhibitory activity against the human breast cancer cells, while compounds **8a**, **9a**, and **9b** display good antifungal activities against *Candida albicans* and *Cryptococcus neoformans*. Notably, their structures are different from clinically used triazole antifungal drugs. Therefore, they could serve as good lead compounds for the development of new generation of antifungal agents.

KEYWORDS: divergent cascade organocatalysis, thiazolidinedione derivatives, structural diversity, anticancer, antifungal

■ INTRODUCTION

The diversification of "privileged" structures¹ using diversityoriented synthesis (DOS),² defined as rational DOS or privileged substructure-based DOS (pDOS) strategy,^{2c,3} has proven to be a fruitful tool to rapidly discover biologically active lead compounds.⁴ However, one of the important challenges in the construction of pDOS libraries is to identify or develop efficient synthetic methods to creatively and facilely construct diverse molecular architectures embedded with privileged substructures.⁵

Organocatalytic cascade reactions have been demonstrated as powerful tools for the facile assembly of diverse and complex frameworks in "one-pot" operations with high enantio- and diastereoselectivity.⁶ Moreover, these processes have been utilized in target-oriented synthesis.⁷ Nevertheless, their applications in DOS is limited.^{8,9} Driven by our research interest in DOS and drug discovery, we recently have initiated a program aimed at incorporating cascade organocatalysis into DOS.¹⁰ A new divergent organocatalytic cascade approach was introduced into DOS¹¹ by merging two powerful synthetic strategies, divergent synthesis and cascade catalysis.¹² In divergent synthesis, the power of the strategy is fueled by the use of similar reactants under the same reaction conditions or the different reactants under the same/similar reaction conditions to generate different products. It is expected that incorporation of organocatalytic enantioselective cascade reactions into the strategy allows for the generation of compounds with functional, stereochemical, and skeletal diversity. Therefore, this new strategy could significantly save cost and improve synthetic efficiency. Moreover, the use of

Received: February 18, 2013 Revised: April 15, 2013 such an approach to building privileged substructure derived libraries with structural diversity can delivers drug like molecules and thereby offers the great possibility of identifying novel modulators for biological targets.

For the construction of pDOS libraries, it is crucial to identify a privileged substructure with the potential for synthetic transformations toward novel skeletons via the proposed divergent organocatalytic cascade approach (DOCA). It is recognized that heterocyclic thiazolidinedione, rhodanine and isorhodanine moieties units are featured in a number of molecules displaying a broad spectrum of biological activities, including antitumor, antibacterial, antiviral effect, etc. (Figure 1).¹³ In particular, thiazolidinediones represent an



Figure 1. Representative structures of pharmaceutically relevant thiazolidinedione or rhodanine derivatives.

important class of antidiabetic agents, such as rosiglitazone, troglitazone, and epalrestat (Figure 1).¹⁴ In the construction of the privileged substructure based libraries using the DOCA, the reactants should be simple and readily available or easily prepared. Furthermore, they should be able to participate in organocatalytic cascade reactions in a divergent fashion. This is a formidable challenging task. To our knowledge, thiazolidinedione-based diversity oriented synthesis and the constitution of their corresponding DOS libraries with skeletal and stereochemical diversity is a largely untapped field.

Herein, we wish to report the results of the investigation of the divergent, organocatalytic, enantioselective, cascade reactions between thiazolidinedione analogues and α , β -unsaturated aldehydes to yield diverse polyheterocyclic scaffolds with excellent stereoselectivity and to illustrate their efficiency in the generation of structural complexity and diversity of libraries (Scheme 1). Remarkably, by manipulation of the functional group reactivities in thiazolidinedione and rhodanine, and isorhodanine, respective organocatalytic enantioselective 3Scheme 1. Construction of Functional, Stereochemical, and Skeletal Diversified Thiazolidinedione-Derived Library via Divergent Organocatalytic Cascades



component Michael–Michael–aldol and Michael–cyclization cascades with enals proceeds to give spiro-thiazolidinedione and -rhodanine frameworks and fused thiopyranoids, respectively, in a divergent manner.

RESULTS AND DISCUSSION

Organocatalytic Enantioselective 3-Component Michael-Michael-Aldol Cascade Reaction of Thiazolidinedione with Enals: One-Pot Synthesis of Chiral Spirothiazolidinediones. Inspired by impressive organocatalytic asymmetric Michael-Michael-aldol cascade reaction in the synthesis of spiro-oxindoles,¹⁵ we envisioned that such a process could be applied in reaction of thiazolidinedione (3)with enal 2 in a 3-component reaction (Table 1). Double Michael reaction of thiazolidinedione (3) with enal 2 (2 equiv) produces an adduct, which undergoes a subsequent intramolecular aldol reaction, leading to a spiro-thiazolidinedione 4. To probe the feasibility, we initiated the study by reaction of thiazolidinedione (3) with trans-cinnamaldehyde (2a) catalyzed by 1a (20 mol %)¹⁶ at rt (Table 1). To our delight, by performing the reaction in CH₂Cl₂, we were able to isolate desired product 4a in 87% yield with excellent enantioselectivity and moderate diastereoselectivity (entry 1). The yield was dropped when 10 mol % 1a was used (entry 2). Lower diastereoselectivity was observed in other solvents (entries 2-8) and additives (entries 9-12) screened. Then catalysts 1b-d were examined (entries 13-15). Improved diastereoselectivity, but with lower yields, was obtained when a larger side chain moiety was introduced (1b, dr, 9:1, yield, 59%; 1c, dr, 10:1, yield, 46%). Enhancing reaction concentration by using 1b led to a better yield (entries 16-17). Finally, the optimal reaction condition was established in the presence of catalyst 1b without an acid additive (entry 16) in terms of yield, diastereoselectivity, and enantioselectivity. It should be noted that our study is inconsistent with the previous report, in which, no desired product was obtained without acid as additive.^{15b,c} The absolute configuration was determined by X-ray crystal structure analysis

 Table 1. Exploration and Optimization of Organocatalytic

 Michael-Michael-Aldol Cascade Reaction of

 Thiazolidinedione 3a with *trans*-Cinnamaldehyde 2a^a



^{*a*}Reaction conditions were as follows: **2a** (0.9 mmol), **3a** (0.3 mmol), and catalyst **1** (0.06 mmol) in solvent (3 mL) at rt to give **4a**. ^{*b*}Isolated yields. ^{*c*}Determined by ¹H NMR analysis. ^{*d*}Determined by chiral HPLC (see the Supporting Information). ^{*e*}cat (10 mol %) was used. ^{*f*}Not determined. ^{*g*}BA, benzoic acid; PNBA, *p*-nitrobenzoic acid. ^{*h*}Reaction was conducted with a concentration of 0.3 M. ^{*i*}Reaction was conducted with a concentration of 0.6 M.

of the product (4a) as (5S,6R,10S),¹⁷ when S-chiral secondary amine (1b) was used as catalyst (Figure 2).



Figure 2. X-ray crystal structure of compound 4a.

With the optimal reaction conditions in hand, the scope of the reaction of thiazolidinedione with α,β -unsaturated aldehydes **2** was explored next. As summarized in Table 2, excellent diastereo and enantioselectivities were obtained for enals bearing *p*-substituted aromatics and heterocyclics (entries 2–8). The diastereocontrol was less satisfying for substrates with o-substituted aryl groups (entries 9 and 10) although Table 2. Substrate Scope in the Organocatalytic Cascade Reaction of Thiazolidinedione 3a with α,β -Unsaturated Aldehydes 2^{*a*}

	R ¹ 0 +	O HN O 3a	1b [(20 mol%) DCM, rt HN		
entry	\mathbb{R}^1	<i>t</i> (h)	4	yield ^{b} (%)	dr ^c	ee^d (%)
1	C ₆ H ₅	36	4a	73	8.4:1	>99
2	p-BrC ₅ H ₄	36	4b	83	6.6:1	>99
3	<i>p</i> -MeOC ₅ H ₄	24	4c	75	7.3:1	>99
4	<i>p</i> -Me ₂ NC ₅ H ₄	24	4d	89	>30:1	>99
5	$p-NO_2C_5H_4$	36	4e	64	12.4:1	>99
6	2-furyl	24	4f	90	22.3:1	>99
7	2-thienyl	24	4g	98	8.9:1	>99
8	2-naphthyl	36	4h	86	8.4:1	>99
9	$o-NO_2C_5H_4$	36	4i	80	2.4:1	>99
10	o-MeOC ₅ H ₄	36	4j	79	3:1	>99
11	<i>n</i> -propyl	5	4k	trace	nd ^e	nd ^e
7				-	1	h- 1 1

^{*a*}Unless otherwise specified, see the Experimental Section. ^{*b*}Isolated yields. ^{*c*}Determined by ¹HNMR analysis. ^{*d*}The *ee* value of major diastereomer, determined by chiral HPLC (see the Supporting Information). ^{*e*}Not determined.

outstanding *ee* values were retained. Moreover, no spirothiazolidinedione product was detected for alkyl-substituted enals (entry 11). Notably, the process proceeded smoothly at a larger scale (1.5 mmol) with the similar results when **4f** was used an example. When *N*-benzyl-thiazolidinedione was reacted with compound **2a**, no desired product was obtained (data not shown), even with a base (e.g., DBU, K_2CO_3) as additive. It is suggested that thiazolidinedione can convert to an aromatic system to activate the methylene, whereas it is difficult for Nsubstituted thiazolidinedione to conduct this tautomerization (Scheme 2).





Organocatalytic Enantioselective Michael-Michael-Aldol Cascade Reaction of Rhodanine with Enals: One-Pot Synthesis of Chiral Spiro-rhodanines. Having developed a powerful 1b-catalyzed Michael-Michael-aldol cascade reaction with thiazolidinediones, we questioned whether this strategy could be extended to rhodanines. New chiral spiro-rhodanines would be produced. To our delight, under the same reaction conditions, the cascade reactions between rhodanines and α , β -unsaturated aldehydes proceeded in even shorter reaction times (1-8 h) with good diastereoselectivity (3.9:1 to >30:1) and excellent enantioselectivities (>99% ee for all cases) despite relatively low yields (35-95%) (Table 3). The steric demand in rhodanine led to better diastereoselectivity (entries 1-10). In addition to aromatic enals, linear alkyl, furan and ester substituted enals can be tolerated (entries 11-16). Notably, as compared with the aryl-substituted enals, better drs were observed for these Table 3. Scope for the Reactions between Rhodanine and Its Derivatives 5 and α_{β} -Unsaturated Aldehydes 2^{*a*}

F	$R^{4} \sim 0 + \frac{R^{4} \sim 0}{N}$	O D	20 mol%) CM, rt	R ⁴ · S ↓ N ~		D
entry	R^1/R^4	<i>t</i> (h)	6	yield ^b (%)	dr ^c	ee^d (%)
1	C ₆ H ₅ /H	8	6a	96	3.9:1	>99
2	<i>n</i> -propyl/H	1.5	6b	56	7.5:1	>99
3	C ₆ H ₅ /Me	6	6c	88	3.7:1	>99
4	C_6H_5/n -butyl	6	6d	60	8.6:1	>99
5	C ₆ H ₅ /allyl	6	6e	57	4.7:1	>99
6	C ₆ H ₅ /Bn	6	6f	63	5.7:1	>99
7	$C_6H_5/p-NO_2C_6H_4CH_2$	6	6g	70	5.6:1	>99
8	C_6H_5/o - $FC_6H_4CH_2$	6	6h	61	7.8:1	>99
9	$\mathrm{C_6H_5}/m\text{-}\mathrm{ClC_6H_4CH_2}$	6	6i	60	8.5:1	>99
10	C ₆ H ₅ /naphthalen-2- methyl	6	6j	73	9.4:1	>99
11	2-furyl/Bn	6	6k	68	11:1	>99
12	CO ₂ Et/Bn	1	61	95	>30:1	>99
13^e	CO ₂ Et/Bn	2	61	80	>30:1	>99
14	methyl/Bn	1	6m	44	>30:1	>99
15	<i>n</i> -propyl/Bn	1	6n	67	>30:1	>99
16	<i>n</i> -hexyl/Bn	1	60	72	>30:1	>99

^aUnless otherwise specified, see the Experimental Section. ^bProduct isolated. ^cDetermined by ¹HNMR analysis. ^dThe ee value of the major diastereomer, determined by chiral HPLC (see Supporting Information). ^eAt 1.6 mmol scale.

enals. Again, the reaction proceeded smoothly at a larger scale as well (1.6 mmol) with 21 (entry 13).

Organocatalytic Enantioselective Michael-Cyclization Cascade Reaction of Isorhodanine with Enals: One-Pot Synthesis of Fused Thiopyranoids. Having demonstrated the high efficiency in the synthesis of structurally diverse spiro-thiazolidinediones using the divergent organocatalytic Michael-Michael-aldol cascade reactions with thiazolidinediones and rhodanines, we further explored the strategy for isorhodanine 7 (Table 4). Unexpectedly, under the similar reaction conditions, reactions of isorhodanine with enals underwent a Michael-cyclization cascade. A new structurally different fused thiopyranoid scaffold 8 with good enantioselectivity and stereoselectivity was constructed instead. It is noted that the reactions with isorhodanine were somewhat complicated. Only a small amount of desired product was observed under the reaction conditions (data not shown). Therefore, we took effort to further optimize the reaction conditions. Better ee values (up to 89%) were obtained when more bulky catalyst 1e was used in toluene (entries 1-5). Lowering the temperature to -20 °C did not improve the stereoselectivity of the reaction but led to a lower yield (entries 3 and 5). It is noteworthy that the product can be purified through a simple washing and filtrating process due to the bad solubility of 8a in hexane (see Experimental Section). The process served as a general approach to the thiopyranoids 8 under the optimized reactions. Generally good yields and enantioselectivities were attained with various enals bearing electron-neutral (entry 3), -withdrawing (entries 8 and 9), and -donating (entry 10) substituents. Furthermore, heterocyclic substituted enals were able to participate in the process. The steric effect is also limited (entry 10). A single crystal of the product (8a) obtained for X-ray crystallographic analysis allowed to determine its absolute configuration with (5S,7S) (Figure 3).¹⁸

Synthetic Elaboration of Chiral Spiro-thiazolidinediones and -rhodanines and Fused Thiopyranoids: Facile Construction of Natural-Product-like Complex Molecular Architectures through Simple Operation. We have shown the divergent organocatalytic cascade strategy as a powerful approach to construct structurally diverse, chiral privileged substructures from simple achiral substances in onepot operation. The resulting products have complex structures containing multiple stereogenic centers and functionalities. They are expected to serve as good starting point for further synthetic elaboration to assemble more complex natural product-like molecules. Here we chose the products 4f, 6l, and 8a as examples to produce new scaffolds with higher structural complexity and diversity (Scheme 3). Notably,

Table 4. Scope for the Reactions between Isorhodanine and α_{β} -Unsaturated Aldehydes^a

		R ¹ ~~2	0 + HN 2 7	$\rightarrow \frac{H}{rt}$	"► HN	аран аран аран		
entry	cat.	\mathbb{R}^1	solvent	<i>t</i> (h)	8	yield ^{b} (%)	dr^c	ee^d (%)
1	1a	C ₆ H ₅	toluene	10	8a	87	5.6:1	55
2	1b	C ₆ H ₅	toluene	10	8a	84	3.0:1	79
3	1e	C ₆ H ₅	toluene	10	8a	82	5.5:1	89
4	1e	C ₆ H ₅	DCM	10	8a	54	5.5:1	79
5	$1e^e$	C ₆ H ₅	toluene	16	8a	50	5.3:1	90
6	1e	2-furyl	toluene	10	8b	87	5.5:1	56
7	1e	2-thienyl	toluene	10	8c	90	4.5:1	78
8	1e	$p-NO_2C_6H_4$	toluene	10	8d	56	5.4:1	79
9	1e	p-BrC ₆ H ₄	toluene	10	8e	87	4.3:1	89
10	1e	o-MeOC ₆ H ₄	toluene	10	8f	66	5.9:1	73

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^aUnless otherwise specified, see Experimental Section. ^bIsolated yields. ^cDetermined by ¹HNMR analysis. ^dThe *ee* value of the major diastereomer, determined by chiral-phase HPLC analysis of hydroxyl TBS-derived product (with TBSCl/imidazole/DMF) of 8 (see the Supporting Information). ^eThe reaction was conducted at −20 °C.



Figure 3. X-ray crystal structure of compound 8a.

straightforward reactions involving only 1-2 steps enabled to create polyheterocyclic structures.

Scheme 3. Generation of Diverse and Complex Ring Systems from the Products of Divergent Organocatalytic Cascade Reactions



In the light of the pyran moiety being widely distributed in natural and biological active compounds,¹⁹ L-proline catalyzed 3,3'-dipolar cycloaddition reactions of **4f** with 1,3-dicarbonyls were developed to form pyran and 2*H*-pyran rings (Scheme 3).²⁰ Fused pyrans **9a** and **b** incorporated into spiro-thiazolidinedione and spiro-rhodanine frameworks were successfully installed in high yields and with good enantiose-lectivity (*ee* up to >99%) and moderate diastereoselectivity (4:1 dr). It is noted that the fused thiopyranecycle and thiazolidine

scaffolds are also reported to possess anticancer activity.²¹ The hetero-Diels–Alder cycloaddition of **61** to ethylvinylether (EVE) was carried out to create a new framework **10a** in excellent yield (99%) and stereoselectivity. Further treatment with morpholine and *o*-aminobenzoic acid gave new polyheterocyclic ring systems **10b**²² and **10c**.²³ The absolute configurations of new scaffolds **9a** and **10a** were further assigned to be (5aS,5'S,7S,9S) and (3S,4aS,5'S,6S,8S) according to NOESY and ¹H NMR spectra (see Supporting Information) (Figure 4) on the basis of X-ray crystallographic



Figure 4. NOESY effects of compound 10a and 9a.

analysis of 8a. Finally, new functionalities 11a and 11b were constructed by the simple Witting reactions of 8a with high enantioselectivity (up to 99% *ee*).

Screening of the pDOS Library for Biological Studies. With the methodologies for the synthesis of spirothiazolidinedione, spiro-rhodanine and fused thiopyranoid libraries were completed, these compounds were screened for their antitumor and antifungal activities. In probe of anticancer properties, their inhibitory activity against three human cancer cell-lines, A549 (lung cancer), ZR-75-30 (breast cancer), and HCT116 (colon cancer), were determined using MTT assay.²⁴ As shown in Table 5, several compounds **4f**, **8a**, and **10a** showed inhibitory

 Table 5. In Vitro Antitumor Activities of Thiazolidinedione-Derived Compounds

entry	compounds	ZR-75-30 $(IC_{50} \mu M)^{a}$	$(IC_{50} \mu M)^{b}$	HCT116 (IC ₅₀ μM) ^c
1	4f	77.4	>100	>100
2	$ent-4f^d$	22.0	>100	>100
3	8a	19.1	>100	>100
4	9a	40.1	>100	>100
5	9b	>100	>100	>100
6	10a	14.7	>100	94.5
7	10b	>100	>100	>100
8	10c	>100	>100	>100
9	irinotecan	10.7	53.5	17.3

^aZR-75-30: Breast cancer cells. ^bA549: Lung cancer cell. ^cHCT116: Colon cancer cell. ^dGenerated with R-1b as catalyst.

activity against the ZR-75-30 cancer cell line. Among them, compound **10a** showed the best activity with an IC₅₀ value of 14.7 μ M, which can be used as a lead for the development of new antitumor agents.

Moreover, the compounds were assayed for their antifungal activities.²⁵ In vitro antifungal activity of each compound was expressed as the minimal inhibitory concentration (MIC) that achieved 80% inhibition of the tested fungi (Table 6). The results revealed that compounds **9a**, **9b**, and **8a** showed inhibitory activities against *Candida albicans* and *Cryptococcus neoformans*, which are leading causes of life-threatening fungal infections. Moreover, compounds **11a** and **11b** were only active against *Cryptococcus neoformans*. The most active antifungal

Table 6. Antifungal in Vitro Activities of Thiazolidinedione-Derived Compounds (MIC, μ g/mL)

entry	compounds	Candida albicans ^a	Cryptococcus neoformans ^b
1	4f	>64	>64
2	ent-4 f ^c	>64	>64
3	61	>64	>64
4	8a	64	32
5	9a	16	8
6	9b	32	32
7	10a	>64	>64
8	10b	>64	>64
9	10c	>64	>64
10	trans-11a	>64	8
11	cis-11a	>64	64
12	11b	>64	64
13	fluconazole	2	2

^{*a*}Strain number: SC5314. ^{*b*}Strain number: 32609. ^{*c*}Generated with *R*-1b as catalyst.

compound is 9a and its structure is completely different from traditional antifungal drugs, which provides a novel scaffold for further antifungal drug discovery. Interestingly, 9a and 9b displayed inhibitory activity against pathogenic fungi, while 4f and 10a showed better activity against human cancer cell line. These results show the importance of core skeletons embedded with privileged thiazolone motif.

CONCLUSION

In conclusion, motivated by the broadly application of pDOS in generating biologically active molecules and the lack of efficient synthetic methods to facilely assemble structurally diverse complex molecular architectures, we have developed a new powerful divergent organocatalytic cascade reactions of thiazolidinedione analogies to $\alpha_{j}\beta$ -unsaturated aldehydes to generate diverse scaffolds with high stereoselectivity and synthetic efficiency. As demonstrated in this study, the power of the divergent organocatalytic cascade strategies has been fueled by its high synthetic efficiency to create functional, stereochemical and skeletal diversified thiazolidinedionederived privileged substructure library compounds. The collection of these natural product-like polyheterocycles has been subjected to antifungal and antitumor bioassays to generate new promising leads for further development. In particular, compounds 8a, 9a, and 9b exhibit strong antifungal activities against Candida albicans and Cryptococcus neoformans, while their structures are different from triazole antifungal drugs. Therefore, they could serve as good lead compounds for the development of new generation antifungal agents. Furthermore, the application of the synthetic strategy in the construction of new pDOS libraries is being actively pursued in our laboratories.

EXPERIMENTAL PROCEDURES

General Procedure for Reactions of 2 with 3 (Table 2, 4a as Example). The catalyst 1b (22.0 mg, 0.06 mmol, 0.2 equiv) was added to a solution of α,β -unsaturated aldehyde 2a (120.0 mg, 0.9 mmol, 3 equiv) and thiazolidinedione 3 (35.0 mg, 0.3 mmol, 1 equiv) in DCM (1 mL). The resulted solution was stirred for 36 h at room temperature. After evaporation of the solvent, the product was purified though column chromatography over silica gel with hexane/EtOAc (10:1– 8:1) as the eluent to yield 4a (79.6 mg, 73% yield) as white solid. The pure product is used to determine *ee* by chiral HPLC analysis and for structural characterization (see Supporting Information for detail).

General Procedure for Reactions of 2 with 5 (Table 3, 6a as Example). The catalyst 1b (17.0 mg, 0.05 mmol, 0.2 equiv) was added to a solution of α , β -unsaturated aldehyde 2a (100 mg, 0.8 mmol, 3 equiv) and rhodanine 5a (35 mg, 0.3 mmol, 1 equiv) in DCM (1 mL). The resulted solution was stirred for 8 h at room temperature. After evaporation of the solvent, the product was purified though column chromatography over silica gel with hexane/EtOAc (10:1–8:1) as the eluent to yield 6a (94.0 mg, 95% yield) as white solid. The pure product is used to determine *ee* by chiral HPLC analysis and for structural characterization (see Supporting Information for detail).

General Procedure for Reactions of 2 with 7 (Table 4, 8a as Example). The catalyst 1e (22.0 mg, 0.04 mmol, 0.1 equiv) was added to a solution of α , β -unsaturated aldehyde 2a (74.0 mg, 0.6 mmol, 1.5 equiv) and isorhodanine 7 (50.0 mg, 0.4 mmol, 1 equiv) in toluene (1 mL). The mixture was stirred for 10h, then the resulting thick solution was diluted with hexane (10 mL), and stirred for another 30 min at room temperature, filtrated and washed with hexane to give the desired product 8a (82.0 mg, 82% yield) as white solid. The pure product is used for characterization (see Supporting Information for detail). It was further converted to more stable hydroxyl TBS-derived product to determine the corresponding *ee* value.

(5aS,5'S,7S,9S)-7,9-Di(furan-2-yl)-3-methyl-6,7-dihydro-1*H*-spiro[pyrano[4,3-*b*]chromene-8,5'-thiazolidine]-1,2',4'(5*aH*,9*H*)-trione (9a). A solution of 4f (50.0 mg, 0.15 mmol, 1.0 equiv), 4-hydroxy-6-methyl-2-pyrone (190.0 mg, 0.15 mmol, 1.0 equiv), and L-proline (86.0 mg, 0.075 mmol, 0.5 equiv) in 5 mL of ethyl acetate was heated at 70 °C under an argon atmosphere for 24 h. The mixture was cooled to room temperature, diluted with 50 mL of ethyl acetate, washed twice with 30 mL of brine, dried (Na₂SO4), filtered, and concentrated. Column chromatography on silica gel of the crude product using a gradient mixture of ethyl acetate/hexane (1:5–1:3) as eluent gave 59.0 mg (87% yield) of 9a.

¹H NMR (600 MHz, CDCl₃) δ = 8.06 (br s, 1H), 7.37–7.38 (m, 1H), 7.32–7.33 (m, 1H), 6.38–6.39 (m, 1H), 6.32–6.33 (m, 2H), 6.29 (d, *J* = 3.3 Hz, 1H), 6.25 (d, *J* = 3.3 Hz, 1H), 5.76 (s, 1H), 5.66 (dd, *J* = 5.8, 11.2 Hz, 1H), 4.26 (s, 1H), 4.00 (dd, *J* = 4.1, 13.7 Hz, 1H), 3.15 (q, *J* = 12.8 Hz, 1H), 2.45 (dt, *J* = 4.3, 12.9 Hz, 1H), 2.20 (s, 3H); ¹³CNMR (150 MHz, CDCl₃) δ =173.1, 168.6, 164.0, 163.0, 162.4, 152.5, 151.7, 142.7, 142.5, 126.1, 114.8, 111.0, 110.7, 109.6, 109.5, 97.8, 97.6, 75.5, 66.2, 50.0, 41.2, 34.6, 20.3; HRMS (ESI) calcd for C₂₃H₁₇NO₇S (M + H⁺) 452.0804, found 452.0792; HPLC (Chiralpak OD, 0.46 cm I.D. × 10 cm L × 5 um, ethanol/hexane =20/80, 35 °C, flow rate 1.0 mL/min, λ = 230 nm) $t_{major} = 6.4 \min, t_{minor} = 10.5 \min, ee > 99\%; [α]_D^{25} = 47.2 (c = 0.2 in EtOAc).$

(1'S,2'S,3'S,4a'S)-1',3'-Di(furan-2-yl)-4',4a',6',7'-tetrahydrospiro[thiazolidine-5,2'-xanthene]-2,4,8'(1'H,3'H,5'H)-trione (9b). A solution of 4g (50.0 mg, 0.15 mmol, 1 equiv), 1,3-dimedone (320.0 mg, 0.30 mmol, 2 equiv), and L-proline (170.0 mg, 0.15 mmol, 1 equiv) in 5 mL of ethyl acetate was heated at 70 °C under an argon atmosphere for 12 h. The mixture was cooled to room temperature, diluted with 50 mL of ethyl acetate, washed twice with 30 mL of brine, dried (Na₂SO₄), filtered, and concentrated. Column chroma-

tography on silica gel of the crude product using a gradient mixture of ethyl acetate/hexane (1:5-1:3) as eluent gave 57.0 mg (88% yield) of **9b**.

¹H NMR (600 MHz, CDCl₃) δ = 8.42 (br s, 1H), 7.34–7.36 (m, 1H), 7.30–7.31 (m, 1H), 6.35–6.36 (m, 2H), 6.31 (dd, *J* = 1.9, 3.2 Hz, 1H), 6.25 (d, *J* = 3.2 Hz, 1H), 6.23 (d, *J* = 3.3 Hz, 1H), 5.57 (ddd, *J* = 1.7, 5.9, 11.1 Hz, 1H), 4.22 (s, 1H), 3.97 (dd, *J* = 4.0, 13.7 Hz, 1H), 3.11 (q, *J* = 12.8 Hz, 1H), 2.33–2.45 (m, 5H), 1.92–1.99 (m, 2H); ¹³C NMR (150 MHz, CDCl₃) δ = 195.0, 174.6, 172.8, 168.6, 153.0, 151.9, 142.5, 142.4, 124.0, 114.5, 111.0, 110.7, 110.2, 109.4, 109.0, 75.4, 66.3, 50.0, 41.2, 36.3, 34.6, 29.8, 28.2; HRMS (ESI) calcd for C₂₃H₁₉NO₆S (M + H⁺) 438.1011, found 438.1003; HPLC (Chiralpak OD, Φ 0.46 × 25 cm, ethanol/hexane = 20/80, 35 °C, flow rate 1.0 mL/min, λ = 230 nm): t_{major} = 3.5 min, t_{minor} = 8.5 min, *ee* > 99%; $[\alpha]_D^{25}$ = -21.9 (*c* = 0.2 in EtOAc).

(35,4a5,5'5,65,85)-Diethyl-2'-(benzylthio)-3-ethoxy-4'-oxo-3,4,4a,5,6,8-hexahydro-4'H-spiro[isochromene-7,5'-thiazole]-6,8-dicarboxylate (10a). To a solution of 61 (50.0 mg, 0.11 mmol) in ethyl vinyl ether (2 mL) was added Yb(fod)₃ (10 mg, 20% w/w). The mixture was stirred three days under argon and after this time ethyl vinyl ether was evaporated under reduced pressure. Flash chromatography on silica gel (ethyl acetate/hexanes =15:1-10:1) afforded 58.0 mg (99% yield) of pure 10a as amorphous solid.

¹H NMR (600 MHz, CDCl₃) $\delta = 7.30-7.39$ (m, 5H), 6.12 (t, J = 1.5 Hz, 1H), 4.98 (dd, J = 2.6, 4.8 Hz, 1H), 4.60–4.62 (m, 3H), 4.13–4.16 (m, 4H), 3.80 (dq, J = 7.2, 9.6 Hz, 1H), 3.51 (dq, J = 7.2, 9.6 Hz, 1H), 3.03–3.10 (m, 1H), 2.87 (dd, J = 2.0, 4.7 Hz, 1H), 2.14 (ddd, J = 2.4, 7.7, 13.6 Hz, 1H), 2.02 (dt, J = 5.2, 14.1 Hz, 1H), 1.96 (ddd, J = 1.8, 5.5, 14.1 Hz, 1H), 1.61 (dt, J = 4.7, 14.0 Hz, 1H), 1.29 (t, J = 7.2 Hz, 3H), 1.20–1.25 (m, 6H); ¹³C NMR (150 MHz, CDCl₃) $\delta = 199.1$, 188.1, 171.4, 169.4, 136.8, 134.7, 129.4, 129.0, 128.3, 113.1, 97.1, 73.3, 64.1, 61.5, 61.4, 50.2, 47.7, 38.3, 34.7, 33.1, 27.2, 15.4, 14.2, 14.1; HRMS (ESI) calcd for C₂₆H₃₁NO₇S₂ (M + H⁺) 534.2620, found 534.2628; HPLC (Chiralpak AD, Φ 0.46 × 25 cm, 25 °C, ethanol/hexane = 20/80, flow rate 1.0 mL/min, $\lambda = 254$ nm) $t_{minor} = 14.7$ min, $t_{major} = 22.3$ min, ee > 99%; $[\alpha]_D^{25} = -97.3$ (c = 3.1 in EtOAc).

(35,4*a*5,5′5,65,85)-Diethyl-3-ethoxy-2′-morpholino-4′oxo-3,4,4*a*,5,6,8-hexahydro-4′*H*-spiro[isochromene-7,5′-thiazole]-6,8-dicarboxylate (10b). A solution of 10a (30.0 mg, 0.056 mmol, 1.0 equiv) and morpholine (24.0 mg, 0.28 mmol, 5.0 equiv) in acetonitrile (5 mL) was heated to 55 °C for 1 h, then cooled to room temperature, concentrated to give the crude product. It was purified through column chromatography on silica gel (ethyl acetate/hexanes = 5:1– 1:1), 23.5 mg (84% yield) of pure 10b was obtained as amorphous solid.

¹H NMR (600 MHz, CDCl₃) δ = 6.09 (s, 1H), 4.95–4.98 (m, 1H), 4.60 (s, 1H), 4.11–4.21 (m, 4H), 3.97–4.00 (m, 2H), 3.73–3.87 (m, 5H), 3.46–3.58 (m, 3H), 3.07–3.15 (m, 1H), 2.86 (d, *J* = 4.8 Hz, 1H), 2.15 (dd, *J* = 8.0, 13.6 Hz, 1H), 2.00 (dd, *J* = 5.2, 14.0 Hz, 1H), 1.92 (dt, *J* = 5.1, 13.4 Hz, 1H), 1.58 (dt *J* = 5.7, 13.4 Hz, 1H), 1.25–1.29 (m, 6H), 1.23 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ = 187.6, 179.3, 171.9, 169.7, 136.6, 113.5, 97.5, 73.8, 66.5, 66.2, 64.2, 61.2, 61.1, 50.9, 48.7, 48.2, 46.7, 35.0, 34.0, 27.4, 15.4, 14.2; HRMS (ESI) calcd for C₂₃H₃₂N₂O₈S (M + H⁺) 497.1958, found 497.1959; HPLC (Chiralpak AD, Φ 0.46 × 25 cm, 25 °C, ethanol/hexane =20/80, flow rate 1.0 mL/min, λ = 230 nm):

 $t_{\text{major}} = 8.7 \text{ min}, t_{\text{minor}} = 29.7 \text{ min}, ee > 99\%; [\alpha]_{D}^{25} = -53.7 (c = 1.2 \text{ in EtOAc}).$

(2'S,3S,4aS,6S,8S)-Diethyl-3-ethoxy-7'-methoxy-3',5'dioxo-3,3',4,4a,5,5',6,8-octahydrospiro[isochromene-7,2'-thiazolo[2,3-b]quinazoline]-6,8-dicarboxylate (10c). A solution of 10a (25.0 mg, 0.047 mmol, 1.0 equiv) and 2amino-5-methoxybenzoic acid (15.0 mg, 0.094 mmol, 2.0 equiv) in glacial acetic acid (2 mL) was heated to gentle reflux for 2.5 h, then cooled to room temperature. The pH was adjusted to 7 with saturated NaHCO₃ (aq), extracted with ethyl acetate (20 mL × 3), dried over Na₂SO₄, concentrated to give the crude product. It was purified through column chromatography on silica gel (ethyl acetate/hexanes =10:1–8:1), 17.0 mg (65% yield) of pure 10c was obtained as amorphous solid.

¹H NMR (600 MHz, CDCl₃) δ = 7.67 (d, J = 3.0 Hz, 1H), 7.48 (d, J = 8.9 Hz, 1H), 7.31 (dd, J = 3.0, 8.8 Hz, 1H), 6.20 (s, 1H), 5.05 (t, J = 3.0 Hz, 1H), 4.75 (s, 1H), 4.10–4.27 (m, 4H), 3.90 (s, 3H), 3.84 (dq, J = 7.3, 9.5 Hz, 1H), 3.54 (dq, J = 7.2)9.3 Hz, 1H), 3.03-3.09 (m, 1H), 3.00-3.03 (m, 1H), 2.29 (dt, *J* = 5.5, 14.1 Hz, 1H), 2.16 (ddd, *J* = 2.3, 7.7, 14.2 Hz, 1H), 1.92 (dd, J = 4.7, 14.0 Hz, 1H), 1.71 (dt, J = 3.6, 14.1 Hz, 1H),1.27-1.31 (m, 6H), 1.20 (t, J = 7.2 Hz, 3H); ${}^{13}C$ NMR (15025) MHz, CDCl₃) δ = 171.6, 171.3, 169.5, 158.5, 158.4, 152.5, 141.6, 138.1, 127.9, 125.4, 120.8, 111.1, 108.4, 96.8, 64.2, 63.8, 61.9, 61.9, 56.0, 50.8, 48.6, 32.8, 32.3, 29.8, 26.8, 15.5, 14.1; HRMS (ESI) calcd for $C_{27}H_{30}N_2O_9S$ (M + H⁺) 559.1750, found 559.1757; HPLC (Chiralpak AD, Φ 0.46 × 25 cm, 25 °C, ethanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): $t_{\text{minor}} = 11.0 \text{ min}, t_{\text{major}} = 16.5 \text{ min}, ee > 99\%; [\alpha]_{D}^{25} =$ -120.0 (c = 0.3 in EtOAc).

(75)-5-(2-Oxo-2-phenylethyl)-7-phenyl-3,5,6,7-tetrahydro-2*H*-thiopyrano[2,3-*d*]thiazol-2-one (11b). 8a (50.0 mg, 0.19 mmol, 1.0 equiv) and 1-phenyl-2-(triphenylphosphoranylidene) ethanone (140.0 mg, 0.38 mmol, 2.0 equiv) were dissolved into DCM (5 mL). The resulting mixture was stirred for 12 h at room temperature. After that time, the insoluble solid was removing through filtrating, and the organic phase was concentrated to give the crude product. It was purified through column chromatography on silica gel (ethyl acetate/ hexanes =10:1-5:1), 59.5 mg (85% yield) of pure 11b (trans/ cis = 1:1) was obtained as white solid. Two diastereoisomers were separated through further careful column chromatography on silica gel.

11b (*trans*): ¹H NMR (600 MHz, CDCl₃) δ = 8.93 (br s, 1H), 7.93 (d, *J* = 7.3 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.23 (d, *J* = 7.4 Hz, 2H), 4.01–4.05 (m, 1H), 3.93 (dd, *J* = 5.8, 7.5 Hz, 1H), 3.52 (dd, *J* = 8.3, 17.6 Hz, 1H), 3.31 (dd, *J* = 5.4, 17.5 Hz, 1H), 2.34–2.42 (m, 2H); ¹³C NMR (150 MHz, CDCl₃) δ = 196.6, 173.2, 142.5, 136.4, 133.8, 129.0, 128.9, 128.2, 128.0, 127.7, 120.1, 107.4, 43.2, 39.1, 38.7, 35.0; HRMS (ESI) calcd for C₂₀H₁₇NO₂S₂ (M + H⁺) 368.0774, found 368.0782; HPLC (Chiralpak AD, Φ 0.46 × 25 cm, 25 °C, *i*propanol/hexane = 30/70, flow rate 0.8 mL/min, λ = 230 nm) t_{major} = 13.7 min, t_{minor} = 20.9 min, *ee* > 99%; $[\alpha]_D^{25}$ = 88.1 (*c* = 0.4 in EtOAc).

11b (*cis*): ¹H NMR (600 MHz, CDCl₃) δ = 9.00 (br s, 1H), 7.90 (d, *J* = 7.4 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.27 (t, *J* = 7.4 Hz, 1H), 7.24 (d, *J* = 7.4 Hz, 2H), 4.17–4.23 (m, 1H), 4.03 (dd, *J* = 5.5, 10.8 Hz, 1H), 3.29 (dd, *J* = 7.8, 17.5 Hz, 1H), 3.23 (dd, *J* = 5.8, 17.5 Hz, 1H), 2.60 (ddd, *J* = 1.9, 5.5, 13.7 Hz, 1H), 2.05 (dt, *J* = 11.0, 13.6 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃) δ = 196.2, 173.3, 142.5, 136.3, 133.9, 129.0, 128.2, 128.0, 127.7, 119.8, 109.8, 43.2, 42.2, 41.7, 38.1; HRMS (ESI) calcd for $C_{20}H_{17}NO_2S_2$ (M + H⁺) 368.0779, found 368.0772; HPLC (Chiralpak AD, Φ 0.46 × 25 cm, 25 °C, *i*-propanol/hexane = 30:70, flow rate 0.8 mL/min, λ = 230 nm) t_{major} = 17.5 min, t_{minor} = 42.0 min, ee > 99%; $[\alpha]_D^{25}$ =15 (e = 0.4 in CHCl₃).

Ethyl-2-((75)-2-oxo-7-phenyl-3,5,6,7-tetrahydro-2*H*-thiopyrano[2,3-*d*]thiazol-5-yl)acetate (11a). To a solution of 8a (50.0 mg, 0.19 mmol, 1.0 equiv) in DCM (5 mL), 1-phenyl-2-(triphenylphosphoranylidene)ethanone (130.0 mg, 0.38 mmol, 2.0 equiv) was added, the resulting mixture was stirred, and the solution was gradually clear (12h), concentrated to give the crude product. It was purified through column chromatography on silica gel (ethyl acetate/hexanes = 10:1-5:1), 35.6 mg (56% yield) of pure 11a (trans/cis = 1:1) was obtained as white solid.

Compounds 11a (trans and cis). ¹H NMR (600 MHz, $CDCl_3$) $\delta = 9.53$ (br s, 1H), 9.49 (brs 1H), 7.20-7.36 (m, 10H), 4.11-4.18 (m, 4H), 3.96 (dd, J = 5.4, 11.1 Hz, 1H), 3.93–3.98 (m, 1H), 3.90 (dd, J = 5.7, 7.0 Hz, 1H), 3.74–3.79 (m, 1H), 2.76 (dd, J = 8.2, 16.0 Hz, 1H), 2.68 (dd, J = 8.2, 16.0 Hz, 1H), 2.60 (d, J = 7.1 Hz, 2H), 2.53 (ddd, J = 1.9, 5.5, 13.9 Hz, 1H), 2.26–2.35 (m, 2H), 2.00 (dt, J = 11.2, 13.7 Hz, 1H), 1.26 (t, J = 7.1 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H); ¹³C NMR $(150 \text{ MHz}, \text{CDCl}_3) \delta = 173.8, 173.7, 170.4, 170.2, 142.6, 142.4,$ 129.0, 128.0, 127.9, 127.8, 127.6, 120.0, 119.9, 109.8, 107.4, 61.3, 61.2, 42.4, 41.6, 39.4, 38.9, 38.9, 38.5, 35.7, 14.3, 14.2; HRMS (ESI) calcd for $C_{16}H_{17}NO_3S_2$ (M + H⁺) 336.0728 found 336.0730; HPLC (Chiralpak OZ, 0.46 cm I.D. × 25 cm $L \times 5$ mm, ethanol/hexane =20/80, 35 °C, flow rate 0.8 mL/ min, $\lambda = 230$ nm) $t_{1\text{minor}} = 11.1$ min, $t_{1\text{major}} = 12.9 \text{ min}/t_{2\text{minor}} =$ 17.6 min, $t_{2\text{major}} = 19.0$ min, ee = 89%/88%; $[\alpha]_{\text{D}}^{25} = 4.3$ (c = 2.2in EtOAc).

In Vitro Antitumor Activity Assay. Cells were plated in 96-well microtiter plates at a density of 5×10^3 /well and incubated in a humidified atmosphere with 5% CO₂ at 37 °C for 24 h. Test compounds were added onto triplicate wells with different concentrations and 0.1% DMSO for control. After they had been incubated for 72 h, 20 μ L of MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] solution (5 mg/mL) was added to each well and the plate was incubated for an additional 4 h. The formazan was dissolved in 100 μ L of DMSO. The absorbance (OD) was read on a WellscanMK-2 microplate reader (Labsystems) at 570 nm. The concentration causing 50% inhibition of cell growth (IC₅₀) was determined by the Logit method. Irinotecan, a clinically available antitumor agent, was used as the positive control. All experiments were performed three times.

In Vitro Antifungal Activity Assay. In vitro antifungal activity was measured by means of the minimal inhibitory concentrations (MIC) using the serial dilution method in 96-well microtest plates. Test fungal strains were obtained from the ATCC (American type culture collection). Fluconazole was used as a positive control. The MIC determination was performed according to the National Committee for Clinical Laboratory Standards (NCCLS) recommendations with RPMI 1640 (Cell culture from Sigma) buffered with 0.165MMOPS buffer [(3-*N*-morpholino)propanesulfonic acid, Sigma] as the test medium. The MIC value was defined as the lowest concentration of test compounds that resulted in a culture with turbidity less than or equal to 80% inhibition when compared with the growth of the control. Test compounds were dissolved in DMSO serially diluted in growth medium. The fungal strains

were incubated at 35 °C, and the growth MIC was determined at 24 h for *Candida albicans* and at 72 h for *Cryptococcus. neoformans.*

ASSOCIATED CONTENT

S Supporting Information

Experimental procedures and ¹H and ¹³C NMR, chiral HPLC analysis data for products 4, 6, 8, 9, and 10 and X-ray data (CIF files) of 4a and 8a. The antitumor inhibitory curve of compound 10a. This material is available free of charge via the Internet at http://pubs.acs.org.

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Funding

Financial support of this research by the National Natural Science Foundation of China (Grant 81222044, C.-Q.S.), the 863 Hi-Tech Program of China (Grant 2012AA020302, C.-Q.S.), Shanghai Rising-Star Program (grant 12QH1402600, C.-Q.S.), the National Science Foundation (CHE-1057569, W. W.), and East China University of Science & Technology (W.W.) is gratefully acknowledged.

Notes

The authors declare no competing financial interest.

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