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Organocatalyzed Highly Diastereo- and Enantioselective Tandem Sulfa-Michael–Mannich Reaction of 2-Mercaptoquinoline-3-carbaldimines with Maleimides

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A highly diastereo- and enantioselective organocatalyzed domino sulfa-Michael–Mannich reaction of 2-mercaptoquinoline-3-carbaldimines with maleimides has been developed. This approach provides a convenient and efficient access to multifuntionalized tetracyclic quinoline derivatives with three contiguous stereocenters in high yield with excellent stereoselectivity (up to >99:1 dr and >99% *ee*).

Introduction

Chiral polycyclic quinolines are ubiquitous and important ring systems found in many bioactive alkaloids and pharmaceuticals.[1] Consequently, the development of efficient synthetic methodologies, which allow for the rapid construction of intricate polycyclic quinolines scaffold containing multiple stereogenic centers, is of considerable significance and remains a preeminent goal in current synthetic chemistry. Compared with traditional stepwise chemical processes, tandem reactions have proven to be extremely useful in achieving these goals owing to their high reaction efficiency, atom economy, and operational simplicity.[2] Recently, we reported an elegant approach to the highly functionalized dihydro-2*H*-thiopyrano[2,3-b]quinolines with excellent diastereo- and enantioselectivity through an organocatalyzed cascade Michael–Henry reaction.[3] Subsequently, we also uncovered a diarylprolinol silyl ether catalyzed tandem Michael–aldol reaction of α,β-unsaturated aldehydes with 2-mercaptoquinoline-3-carbaldehydes to deliver 2*H*-thiopyrano[2,3-b]quinoline derivatives.[4] It should be noted that chiral succinimides, found in numerous biologically interesting natural products and pharmaceuticals, are often used as pharmacophores in drug discovery.[5,6] The incorporation of this important pharmacophores into biologically interesting quinoline architectures is of considerable significance from the standpoint of the medicinal and organic chemistry. Among the different methodologies available for the synthesis of synthetically and biologically interesting chiral α-substituted succinimides, the most straightforward one is the asymmetric conjugate addition of nucleophile to maleimides, especially using chiral organocatalysts.[7,8] On the basis of these previous reports and our experience in organocatalysis,[9] we envisioned achieving easy access to tetracyclic 1,3-dioxo-1,2,3,3a,11,11a-hexahydropyrrolo[3′,4′:5,6]thiopyrano[2,3-b]quinolines through an unprecedented tandem sulfa-Michael–Mannich reaction between 2-mercaptoquinoline-3-carbaldimines and maleimides.

Results and Discussion

To explore the proposed catalytic tandem sulfa-Michael–Mannich reaction process, a model reaction between 2-mercaptoquinoline-3-carbaldimine **1a** (2,4,6-trimethylphenylsulfonyl was chosen as the N-protecting group because the introduction of this group can efficiently improve the solubility of the Michael–Mannich product in common solvents, which is very important for the following NMR and HPLC analysis of the products) and *N*-phenyl maleimide **2a** was performed in dichloromethane at 20 °C in the presence of a chiral bifunctional organocatalyst (Figure 1). Molecular sieves (4 Å) were added as water scavengers to prevent decomposition of the aldimine. The results are collected in Table 1.

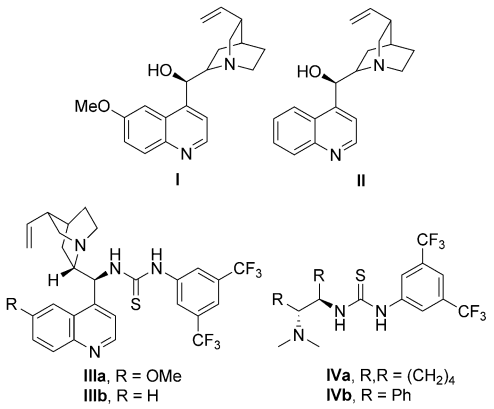

Figure 1. Catalyst candidates.

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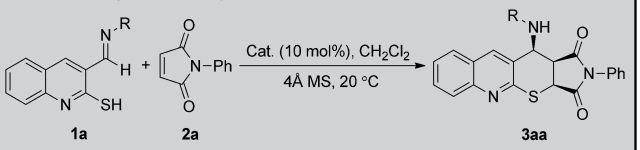
Table 1. Catalyst screening.[a]



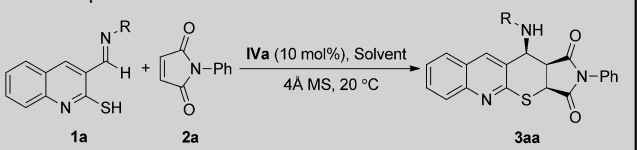
Entry	Catalyst	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**I**	2	94	23
2	**II**	3	93	−15
3	**IIIa**	8	90	−83
4	**IIIb**	24	80	−85
5	**IVa**	4	93	87
6	**IVb**	24	87	84

[a] All reactions were performed by using **1a** (0.2 mmol), **2a** (0.4 mmol), and 4 Å molecular sieve (50 mg) in CH_2Cl_2 (1.0 mL) at 20 °C in the presence of the catalyst (10 mol%). [b] Isolated yield. [c] In all cases, >99:1 *dr* was observed. Enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase.

Under the catalysis of bifunctional *Cinchona* alkaloids **I** and **II**, the tandem sulfa-Michael–Mannich reaction took place smoothly to generate the desired polycyclic quinoline **3aa** in good yields and excellent diastereoselectivities (in all cases, >99:1 *dr* was observed), but with unsatisfactory enantioselectivities (Table 1, entries 1 and 2). To further improve the enantioselectivity of this cascade process, we shifted our focus to some most commonly used tertiary amine–thiourea catalysts,[10] which have been proven to be a good type of hydrogen bond donor catalysts and can activate maleimide through hydrogen bond interaction.[8d,g,i,11] To our delight, amine–thiourea catalysts **III** and **IV** exhibited much better chiral induction ability, but the catalytic efficacy varied greatly depending on the organocatalyst employed (entries 3–6). Among them, Takemoto's catalyst **IVa** exhibited the most promising results in terms of *ee* value and catalytic efficacy (entry 5). This prompted us to select this catalyst for further optimization of the reaction conditions (Table 2).

Solvent evaluation indicated that the reaction medium has a remarkable influence on the reaction (Table 2, entries 1–8). In all the examples, although the diastereoselectivity was excellent, the enantioselectivity was highly dependent on the solvent employed. Generally, good *ee* values were observed by performing the reaction in chlorohydrocarbons, such as methylene chloride, chloroform, 1,2-dichloroethane, and 1,1,2,2-tetrachloroethane (entries 1–4, 84–87%). The enantioselectivity was sharply decreased when ethyl acetate, toluene, or acetonitrile was used as the solvent. Methylene chloride was the best solvent giving the highest *ee* of 87% among all the tested solvents. Moreover, decreasing the reaction temperature had a significant positive effect on the enantioselectivity of the reaction (entries 1, 10–11). Further improvement of the *ee* value to 97% could be achieved by lowering the reaction temperature to −40 °C at the expense of reaction time (entry 11). It was gratifying that an obvious acceleration of reaction rate and almost perfect stereocontrol was achieved by adjusting the catalyst loading from 10 mol% to 20 mol% (entry 12).

Table 2. Optimization of the reaction conditions.[a]



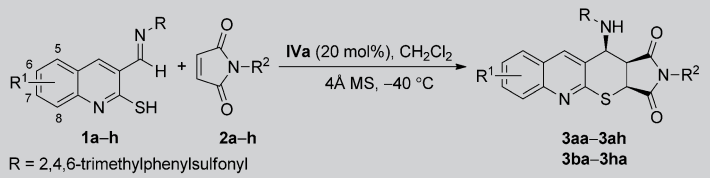
Entry	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1	CH_2Cl_2	4	93	87
2	$CHCl_3$	10	90	84
3	$ClCH_2CH_2Cl$	4	91	84
4	$Cl_2CHCHCl_2$	2	92	86
5	$PhCH_3$	10	80	40
6	ethyl acetate	24	78	33
7	Et_2O	24	73	75
8	CH_3CN	5	95	16
9[d]	CH_2Cl_2	10	93	91
10[e]	CH_2Cl_2	18	91	95
11[f]	CH_2Cl_2	48	79	97
12[g]	CH_2Cl_2	12	90	>99

[a] Unless otherwise specified, all reactions were performed by using **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst **IVa** (0.02 mmol, 10 mol%), and 4 Å molecular sieve (50 mg) in solvent (1.0 mL) at 20 °C. [b] Isolated yield. [c] In all cases, >99:1 dr was observed. Enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase. [d] Reaction was performed at 0 °C. [e] Reaction was conducted at −20 °C. [f] Reaction was run at −40 °C. [g] Reaction was performed at −40 °C with a 20 mol% catalyst loading.

Under the optimized reaction conditions (Table 2, entry 12), we next examined the scope and limitation of the **IVa**-promoted tandem sulfa-Michael–Mannich reactions, and the results are summarized in Table 3. For the aromatic maleimides, it appeared that the position and the electronic property of the substituents on the aromatic rings have a very limited impact on the enantioselectivities. The reactions of maleimides with electron-neutral, -donating and -withdrawing groups with 2-mercaptoquinoline-3-carbaldimine **1a** all proceeded smoothly to give structurally diverse succinimides **3** with uniformly high levels of enantioselectivity (entries 1–6, 98–>99% *ee*). The reaction was also applicable to less reactive aliphatic maleimides albeit with a slight decreased *ee* values (entries 7 and 8, 90% and 91% *ee*, respectively). To further expand the scope of this methodology, we subsequently investigated the tandem Michael–Mannich reactions with various 2-mercaptoquinoline-3-carbaldimines and *N*-phenyl maleimide **2a** (entries 9–15). In addition, the reaction appeared quite general with respect to other 2-mercaptoquinoline-3-carbaldimines bearing either an electron-donating or electron-withdrawing substituent in the quinoline ring. In all cases, the reactions ran efficiently to give the desired adducts in high yields and with excellent diastereo- and enantioselectivities.

To determine the relative and absolute configurations of the products from the asymmetric tandem Michael–Mannich process, a single crystal of compound **3ae** was obtained and the stereoconfiguration was unambiguously assigned as (3a*S*,11*S*,11a*S*) by X-ray diffraction analysis (Figure 2).[12] The absolute configurations of other products can therefore be determined by analogy.

Table 3. Substrate scope of **IVa**-catalyzed asymmetric domino Michael–Mannich reaction between **1** and **2**.[a]



Entry	**3** (R^1, R^2)	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**3aa** (H, Ph)	12	90	>99
2	**3ab** (H, 4-MeC_6H_4)	12	93	98
3	**3ac** (H, 4-MeOC_6H_4)	12	94	99
4	**3ad** (H, 4-BrC_6H_4)	12	93	99
5	**3ae** (H, 4-ClC_6H_4)	12	95	98
6	**3af** (H, 3-ClC_6H_4)	12	89	99
7	**3ag** (H, Et)	48	85	90
8	**3ah** (H, Bu)	48	93	91
9	**3ba** (6-Me, Ph)	12	92	98
10	**3ca** (7-Me, Ph)	12	94	99
11	**3da** (6-MeO, Ph)	12	90	98
12	**3ea** (7-MeO, Ph)	12	89	97
13	**3fa** (6-Et, Ph)	12	95	98
14	**3ga** (6-Bu, Ph)	12	87	96
15	**3ha** (7-Cl, Ph)	12	88	90

[a] All reactions were performed by using **1** (0.2 mmol), **2** (0.4 mmol), catalyst **IVa** (0.04 mmol, 20 mol%), and 4 Å molecular sieve (50 mg) and in CH_2Cl_2 (1.0 mL) at −40 °C. [b] Isolated yield. [c] In all cases, >99:1 *dr* was observed. Enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase.

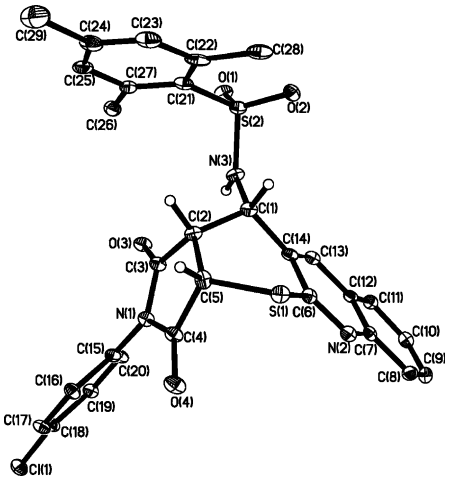


Figure 2. X-ray structure of compound (3a*S*,11*S*,11a*S*)-**3ae**, most of the hydrogen atoms have been omitted for clarity.

A transition state model that accounts for the stereochemical outcome is shown in Figure 3. In this model, the acidic protons of the thiourea moiety activate the maleimide through hydrogen bond interaction. The tertiary amine functionality of the catalyst deprotonates and activates the mercapto group to attack the maleimide from the *si*-face. This forms an enolate intermediate, which is involved in the successively nucleophilic attack of the carbon of the imine from the *si*-face to afford the observed products.

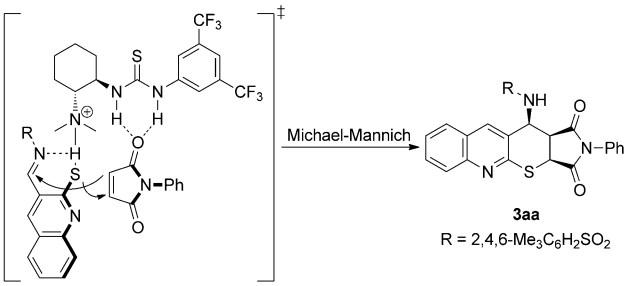


Figure 3. Proposed mechanism.

Conclusions

In conclusion, we have developed an efficient organocatalytic tandem sulfa-Michael–Mannich process for the stereocontrolled synthesis of multifunctionalized tetracyclic quinolines. Under the catalysis of a chiral bifunctional tertiary amine–thiourea catalyst, a broad range of 2-mercaptoquinoline-3-carbaldimines and maleimides can be tolerated well in this process, generating the desired tetracyclic quinoline derivatives with three contiguous stereocenters in high yields with excellent diastereo- (>99:1 dr) and enantioselectivities (90–>99% *ee*).

Experimental Section

General procedure for the preparation of 2-mercaptoquinoline-3-carbaldimines 1

To a solution of 2,4,6-trimethylbenzenesulfonamide and catalytic amount of 4-methylbenzenesulfonic acid (5%) in anhydrous toluene was added 2-mercaptoquinoline-3-carbaldehyde (1 equiv.) in one portion at RT. The resulting mixture was heated to reflux for 8 h, the water generated in the reaction was removed with a Dean–Stark apparatus. After cooling to RT, aqueous sodium hydrogencarbonate was added and the red precipitate was collected by filtration. The crude product was used directly without further purification. The structure of carbaldimine **1a** was confirmed by NMR and HRMS analysis.

N-(2,4,6-trimethylbenzenesulfonyl)-2-mercaptoquinoline-3-carbaldimine (**1a**): red solid, 73% yield, m.p. 184–186 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 14.09 (s, 1H), 9.79 (s, 1H), 8.59 (s, 1H), 7.97 (s, 1H), 7.71(s, 1H), 7.61 (s, 1H), 7.35 (s, 1H), 7.08 (s, 2H), 2.58 (s, 6H), 2.25 ppm (s, 3H); ^{13}C NMR (100.6 MHz, [D_6]DMSO): δ = 180.8, 168.1, 143.6, 141.2, 139.6, 138.0, 134.6, 131.9, 131.1, 130.5, 129.9, 125.0, 121.7, 116.3, 22.5, 20.5 ppm; HRMS (ESI) *m/z* calcd. for $C_{19}H_{18}N_2NaO_2S_2$ [*M*+Na]$^+$: 393.0702; found: 393.0705.

Typical procedure for thiourea–tertiary amine IVa-catalyzed asymmetric domino sulfa-Michael–Mannich reactions

To a stirred solution of catalyst **IVa** (20 mol%) in methylene chloride (1 mL) at −40 °C were added 2-mercaptoquinoline-3-carbaldi-

mines (1.0 equiv., 0.2 mmol) and maleimides (2.0 equiv., 0.4 mmol). After the reaction was completed (monitored by TLC), the reaction mixture was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel (200–300 mesh, petroleum ether (PE)/EtOAc = 8/1 to 5/1) to afford the desired 1,3-dioxo-1,2,3,3a,11,11a-hexahydropyrrolo[3′,4′:5,6]thiopyrano[2,3-b]quinolines as white solid. The title compounds were fully characterized by ^{1}H, ^{13}C NMR spectroscopy, HRMS and specific rotation data.

(3a*S*,11*S*,11a*S*)-1,3-Dioxo-2-phenyl-11-(2,4,6-trimethylbenzene-sulfonamido)-1,2,3,3a,11,11a-hexahydropyrrolo[3′,4′:5,6]thio-pyrano-[2,3-b]quinoline (**3 aa**): White solid, m.p. 188–190 °C, 90% yield, $[\alpha]_D^{25} = +65.0$ ($c = 1.0$, CH_2Cl_2), > 99% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.16$ (br. s, 1H), 8.02 (d, $J = 8.4$ Hz, 1H), 7.72 (t, $J = 7.6$ Hz, 2H), 7.54 (t, $J = 7.6$ Hz, 1H), 7.26 (br. s, 3H), 6.98 (s, 2H), 6.82 (br. s, 3H), 4.97 (dd, $J = 9.6$, 4.8 Hz, 1H), 4.38 (d, $J = 9.6$ Hz, 1H), 3.76 (dd, $J =$ 9.6, 4.8 Hz, 1H), 2.72 (s, 6H), 2.28 ppm (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 175.3$, 173.6, 152.8, 147.7, 142.9, 138.9, 134.4, 133.6, 132.3, 130.7, 130.4, 129.3, 129.1, 128.5, 128.1, 127.3, 126.9, 125.9, 52.7, 45.7, 42.1, 23.1, 20.9 ppm; HRMS (ESI) *m/z* calcd. for $C_{29}H_{24}N_3O_4S_2$ $[M-H]^-$: 542.1213; found: 542.1217; HPLC analysis (Chiralpak OD-H column, hexane/2-propanol/triethylamine (TEA) = 60:40:0.1, flow rate = 0.8 mL min^{-1}, wavelength = 230 nm): retention time (T_R) = 28.62 (major) and 57.06 min (minor).

(3a*S*,11*S*,11a*S*)-1,3-Dioxo-2-(4-methylphenyl)-11-(2,4,6-trimethyl-benzenesulfonamido)-1,2,3,3a,11,11a-hexahydropyrrolo[3′,4′:5,6]thio-pyrano[2,3-b]quinoline (**3 ab**): White solid, m.p. 166–168 °C, 93% yield, $[\alpha]_D^{25} = +93.2$ ($c = 1.0$, CH_2Cl_2), 98% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.15$ (br. s, 1H), 8.02 (d, $J = 8.8$ Hz, 1H), 7.72 (t, $J =$ 8.0 Hz, 2H), 7.53 (t, $J = 7.6$ Hz, 1H), 7.04 (d, $J = 7.6$ Hz, 2H), 6.98 (s, 2H), 6.87 (d, $J = 6.4$ Hz, 1H), 6.67 (d, $J = 6.8$ Hz, 2H), 4.96 (dd, $J =$ 9.6, 4.8 Hz, 1H), 4.36 (d, $J = 9.6$ Hz, 1H), 3.74 (dd, $J = 9.6$, 4.8 Hz, 1H), 2.72 (s, 6H), 2.28 (s, 3H), 2.24 ppm (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 175.4$, 173.7, 152.9, 147.7, 142.8, 139.3, 138.8, 134.4, 133.6, 132.3, 130.6, 129.7, 129.4, 128.4, 128.1, 127.7, 127.2, 126.9, 125.7, 52.5, 45.6, 42.3, 23.1, 21.0, 20.9 ppm; HRMS (ESI) *m/z* calcd. for $C_{30}H_{26}N_3O_4S_2$ $[M-H]^-$: 556.1370; found: 556.1368; HPLC analysis (Chiralpak OD-H column, hexane/2-propanol/TEA = 60:40:0.1, flow rate = 0.8 mL min^{-1}, wavelength = 230 nm): $T_R = 28.40$ (major) and 48.13 min (minor).

(3a*S*,11*S*,11a*S*)-1,3-Dioxo-2-(4-methoxyphenyl)-11-(2,4,6-trimethyl-benzenesulfonamido)-1,2,3,3a,11,11a-hexahydropyrrolo-[3′,4′:5,6]thiopyrano[2,3-b]quinoline (**3 ac**): White solid, m.p. 160–162 °C, 94% yield, $[\alpha]_D^{25} = +96.2$ ($c = 1.0$, CH_2Cl_2), 99% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.15$ (br. s, 1H), 8.01 (d, $J = 8.4$ Hz, 1H), 7.72 (t, $J = 7.6$ Hz, 2H), 7.53 (t, $J = 7.6$ Hz, 1H), 6.97 (s, 2H), 6.87 (br. s, 1H), 6.73 (br. s, 4H), 4.95 (dd, $J = 8.8$, 4.0 Hz, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 3.73 (dd, $J = 9.2$, 4.8 Hz, 1H), 3.69 (s, 3H), 2.71 (s, 6H), 2.28 ppm (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 175.6$, 173.8, 159.7, 152.9, 147.7, 142.8, 138.9, 134.4, 133.6, 132.3, 130.6, 129.4, 128.4, 128.1, 127.2, 127.1, 126.9, 122.9, 114.4, 55.4, 52.7, 45.6, 42.0, 23.0, 20.9 ppm; HRMS (ESI) *m/z* calcd. for $C_{30}H_{26}N_3O_5S_2$ $[M-H]^-$: 572.1319; found: 572.1313; HPLC analysis (Chiralpak OD-H column, hexane/2-propanol/TEA = 60:40:0.1, flow rate = 0.8 mL min^{-1}, wavelength = 230 nm): $T_R = 39.20$ (major) and 71.28 min (minor).

(3a*S*,11*S*,11a*S*)-2-(4-Bromophenyl)-1,3-dioxo-11-(2,4,6-trimethylben-zenesulfonamido)-1,2,3,3a,11,11a-hexahydropyrrolo-[3′,4′:5,6]thiopyrano[2,3-b]quinoline (**3 ad**): White solid, m.p. 164–166 °C, 93% yield, $[\alpha]_D^{25} = +67.4$ ($c = 1.0$, CH_2Cl_2), 99% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.12$ (br. s, 1H), 8.01 (d, $J = 8.4$ Hz, 1H), 7.70–7.75 (m, 3H), 7.55 (t, $J = 7.6$ Hz, 1H), 7.39 (d, $J = 8.4$ Hz, 2H), 6.97 (s, 2H), 6.75 (br. s, 3H), 4.97 (dd, $J = 9.6$, 4.4 Hz, 1H), 4.40 (d, $J = 9.2$ Hz, 1H), 3.78 (dd, $J = 9.6$, 4.4 Hz, 1H), 2.71 (s, 6H), 2.28 ppm (s, 3H); ^{13}C NMR (100.6 MHz, CDCl3): $\delta = 175.0$, 173.2, 152.7, 147.8, 143.0, 138.9, 134.3, 133.6, 132.3, 130.8, 129.4, 129.2, 128.5, 128.1, 127.4, 127.3, 126.9, 123.1, 52.7, 45.8, 42.1, 23.0, 20.9 ppm; HRMS (ESI) *m/z* calcd. for $C_{29}H_{23}BrN_3O_4S_2$ $[M-H]^-$: 620.0319; found: 620.0316; HPLC analysis (Chiralpak OD-H column, hexane/2-propanol/TEA = 60:40:0.1, flow rate = 0.8 mL min^{-1}, wavelength = 230 nm): $T_R =$ 39.55 (major) and 81.35 min (minor).

(3a*S*,11*S*,11a*S*)-2-(4-Chlorophenyl)-1,3-dioxo-11-(2,4,6-trimethyl-benzenesulfonamido)-1,2,3,3a,11,11a-hexahydropyrrolo[3′,4′:5,6]thio-pyrano[2,3-b]quinoline (**3 ae**): White solid, m.p. 154–156 °C, 95% yield, $[\alpha]_D^{25} = +75.3$ ($c = 1.0$, CH_2Cl_2), 98% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.13$ (s, 1H), 8.02 (d, $J = 8.4$ Hz, 1H), 7.73 (t, $J = 8.0$ Hz, 2H), 7.55 (t, $J = 7.6$ Hz, 1H), 7.23 (d, $J = 8.8$ Hz, 2H), 6.98 (s, 2H), 6.75–81 (m, 3H), 4.97 (dd, $J = 9.6$, 4.4 Hz, 1H), 4.40 (d, $J = 9.2$ Hz, 1H), 3.77 (dd, $J = 9.6$, 4.4 Hz, 1H), 2.71 (s, 6H), 2.29 ppm (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 175.0$, 173.3, 152.7, 147.7, 143.0, 138.9, 135.0, 134.3, 133.6, 132.3, 130.8, 129.3, 128.8, 128.5, 128.1, 127.3, 127.1, 126.9, 52.7, 45.8, 42.0, 23.1, 21.0 ppm; HRMS (ESI) *m/z* calcd. for $C_{29}H_{23}ClN_3O_4S_2$ $[M-H]^-$: 576.0824; found: 576.0826; HPLC analysis (Chiralpak OD-H column, hexane/2-propanol/TEA = 60:40:0.1, flow rate = 0.8 mL min^{-1}, wavelength = 230 nm): $T_R =$ 36.04 (major) and 71.62 min (minor).

(3a*S*,11*S*,11a*S*)-2-(3-Chlorophenyl)-1,3-dioxo-11-(2,4,6-trimethyl-benzenesulfonamido)-1,2,3,3a,11,11a-hexahydropyrrolo[3′,4′:5,6]thio-pyrano[2,3-b]quinoline (**3 af**): White solid, m.p. 193–195 °C, 89% yield, $[\alpha]_D^{25} = +88.8$ ($c = 1.0$, CH_2Cl_2), 99% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.14$ (br. s, 1H), 8.02 (d, $J = 8.4$ Hz, 1H), 7.73 (d, $J =$ 7.6 Hz, 2H), 7.55 (t, $J = 7.6$ Hz, 1H), 7.24 (s, 1H), 7.19 (t, $J = 7.6$ Hz, 1H), 6.98 (s, 2H), 6.91 (s, 1H), 6.76 (br. s, 2H), 4.98 (dd, $J = 9.6$, 4.4 Hz,1H), 4.41 (d, $J = 9.2$ Hz, 1H), 3.78 (dd, $J = 9.6$, 4.4 Hz, 1H), 2.71 (s, 6H), 2.29 ppm (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta =$ 174.9, 173.2, 152.7, 147.8, 143.0, 138.9, 134.7, 134.3, 133.7, 132.4, 132.4, 131.4, 130.8, 130.1, 129.3, 128.5, 128.1, 127.4, 127.0, 126.1, 124.1, 52.6, 45.8, 42.0, 23.1, 21.0 ppm; HRMS (ESI) *m/z* calcd. for $C_{29}H_{23}ClN_3O_4S_2$ $[M-H]^-$: 576.0824; found: 576.0820; HPLC analysis (Chiralpak OD-H column, hexane/2-propanol/TEA = 60:40:0.1, flow rate = 0.8 mL min^{-1}, wavelength = 230 nm): $T_R = 24.42$ (major) and 50.37 min (minor).

(3a*S*,11*S*,11a*S*)-1,3-Dioxo-2-ethyl-11-(2,4,6-trimethylbenzene-sulfon-amido)-1,2,3,3a,11,11a-hexahydropyrrolo[3′,4′:5,6]thiopyrano-[2,3-b]quinoline (**3 ag**): White solid, m.p. 168–170 °C, 85% yield, $[\alpha]_D^{25} =$ −12.0 ($c = 1.0$, CH_2Cl_2), 90% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.17$ (s, 1H), 7.98 (d, $J = 8.4$ Hz, 1H), 7.73 (d, $J = 8.4$ Hz, 1H), 7.70 (t, $J =$ 7.6 Hz, 1H), 7.53 (t, $J = 7.6$ Hz, 1H), 6.97 (s, 2H), 6.89 (d, $J = 8.4$ Hz, 1H), 4.85 (dd, $J = 9.6$, 4.8 Hz, 1H), 4.18 (d, $J = 9.6$ Hz, 1H), 3.53 (dd, $J = 10.0$, 5.2 Hz, 1H), 3.26 (q, $J = 6.8$ Hz, 2H), 2.71 (s, 6H), 2.28 (s, 3H), 0.67 ppm (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta =$ 175.9, 174.2, 152.9, 147.6, 142.8, 138.9, 134.4, 133.5, 132.3, 130.5, 129.5, 128.4, 128.0, 127.2, 126.9, 52.5, 45.4, 41.9, 34.3, 23.0, 20.9, 12.5 ppm; HRMS (ESI) *m/z* calcd. for $C_{25}H_{24}N_3O_4S_2$ $[M-H]^-$: 494.1213; found: 494.1216; HPLC analysis (Chiralpak OD-H column, hexane/2-propanol/TEA = 85:15:0.1, flow rate = 0.8 mL min^{-1}, wavelength = 230 nm): $T_R = 77.22$ (minor) and 85.67 min (major).

(3a*S*,11*S*,11a*S*)-2-Butyl-1,3-dioxo-11-(2,4,6-trimethylbenzene-sulfon-amido)-1,2,3,3a,11,11a-hexahydropyrrolo[3′,4′:5,6]thiopyrano-[2,3-b]quinoline (**3 ah**): White solid, m.p. 171–173 °C, 93% yield, $[\alpha]_D^{25} =$ −12.2 ($c = 1.0$, CH_2Cl_2), 91% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.20$ (br. s, 1H), 7.99 (d, $J = 8.4$ Hz, 1H), 7.75 (d, $J = 8.0$ Hz, 1H), 7.69 (t, $J = 7.6$ Hz, 1H), 7.53 (t, $J = 7.6$ Hz, 1H), 6.98 (s, 2H), 6.91 (d, $J =$

9.2 Hz, 1H), 4.85 (dd, J=9.6, 5.2 Hz, 1H), 4.16 (d, J=10.0 Hz, 1H), 3.51 (dd, J=10.0, 5.2 Hz, 1H), 3.24 (t, J=6.8 Hz, 2H), 2.72 (s, 6H), 2.28 (s, 3H), 0.92–1.02 (m, 2H), 0.30–0.35 (m, 2H), 0.20 ppm (t, J=6.8 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=176.2, 174.5, 152.8, 147.7, 142.8, 138.9, 134.4, 133.4, 132.3, 130.5, 129.8, 128.5, 127.9, 127.2, 127.0, 52.5, 45.3, 42.0, 39.1, 28.9, 23.0, 20.9, 19.0, 12.8 ppm; HRMS (ESI) m/z calcd. for $C_{27}H_{29}N_3NaO_4S_2$ $[M+Na]^+$: 546.1492; found: 546.1495; HPLC analysis (Chiralpak OD-H column, hexane/2-propanol/TEA=85:15:0.1, flow rate=0.8 mL min^{-1}, wavelength=230 nm): T_R=46.97 (major) and 62.78 min (minor).

(3a*S*,11*S*,11a*S*)-1,3-Dioxo-8-methyl-2-phenyl-11-(2,4,6-trimethyl-benzenesulfonamido)-1,2,3,3a,11,11a-hexahydropyrrolo[3′,4′:5,6]thiopyrano[2,3-b]quinoline (**3 ba**): White solid, m.p. 193–195 °C, 92% yield, $[\alpha]_D^{25}$=+82.6 (c=1.0, CH_2Cl_2), 98% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.04 (br. s, 1H), 7.91 (d, J=8.8 Hz, 1H), 7.55 (dd, J=8.4, 1.2 Hz, 1H), 7.46 (s, 1H), 7.25–7.26 (m, 3H), 6.98 (s, 2H), 6.81 (br. s, 3H), 4.96 (dd, J=9.6, 4.8 Hz, 1H), 4.37 (d, J=9.6 Hz, 1H), 3.76 (dd, J=9.6, 4.8 Hz, 1H), 2.71 (s, 6H), 2.52 (s, 3H), 2.29 ppm (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=175.3, 173.6, 151.6, 146.3, 142.8, 138.9, 137.4, 134.4, 133.0, 132.9, 132.3, 130.4, 129.3, 129.1, 129.1, 128.1, 127.0, 126.9, 125.9, 52.7, 45.8, 42.1, 23.0, 21.6, 20.9 ppm; HRMS (ESI) m/z calcd. for $C_{30}H_{26}N_3O_4S_2$ $[M-H]^-$: 556.1370; found: 556.1369; HPLC analysis (Chiralpak OD-H column, hexane/2-propanol/TEA=60:40:0.1, flow rate=0.8 mL min^{-1}, wavelength=230 nm): T_R=32.48 (major) and 52.90 min (minor).

(3a*S*,11*S*,11a*S*)-1,3-Dioxo-7-methyl-2-phenyl-11-(2,4,6-trimethyl-benzenesulfonamido)-1,2,3,3a,11,11a-hexahydropyrrolo[3′,4′:5,6]thiopyrano[2,3-b]quinoline (**3 ca**): White solid, m.p. 151–153 °C, 94% yield, $[\alpha]_D^{25}$=+56.8 (c=1.0, CH_2Cl_2), 99% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.09 (s, 1H), 7.79 (s, 1H), 7.60 (d, J=8.4 Hz, 1H), 7.37 (dd, J=8.4, 1.2 Hz, 1H), 7.26–7.28 (m, 3H), 6.98 (s, 2H), 6.82 (br. s, 3H), 4.95 (dd, J=9.6, 4.8 Hz, 1H), 4.35 (d, J=10.0 Hz, 1H), 3.72 (dd, J=10.0, 4.8 Hz, 1H), 2.71 (s, 6H), 2.54 (s, 3H), 2.29 ppm (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=175.4, 173.6, 152.6, 148.0, 142.8, 141.3, 138.9, 134.4, 133.3, 132.3, 130.4, 129.5, 129.3, 129.1, 127.7, 127.5, 126.4, 125.9, 125.0, 52.7, 45.7, 42.1, 23.1, 21.9, 21.0 ppm; HRMS (ESI) m/z calcd. for $C_{30}H_{26}N_3O_4S_2$ $[M-H]^-$: 556.1370; found: 556.1372; HPLC analysis (Chiralpak OD-H column, hexane/2-propanol/TEA=60:40:0.1, flow rate=0.8 mL min^{-1}, wavelength=230 nm): T_R=25.44 (major) and 52.43 min (minor).

(3a*S*,11*S*,11a*S*)-1,3-Dioxo-8-methoxy-2-phenyl-11-(2,4,6-trimethyl-benzenesulfonamido)-1,2,3,3a,11,11a-hexahydropyrrolo-[3′,4′:5,6]thiopyrano[2,3-b]quinoline (**3 da**): White solid, m.p. 194–196 °C, 90% yield, $[\alpha]_D^{25}$=+127.5 (c=1.0, CH_2Cl_2), 98% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (br. s, 1H), 7.91 (d, J=9.2 Hz, 1H), 7.36 (dd, J=9.2, 2.4 Hz, 1H), 7.26 (s, 3H), 7.00 (s, 3H), 6.85 (d, J=7.2 Hz, 1H), 6.78 (s, 2H), 4.93 (dd, J=9.6, 4.8 Hz, 1H), 4.34 (d, J=9.2 Hz, 1H), 3.91 (s, 3H), 3.70 (dd, J=9.6, 4.8 Hz, 1H), 2.73 (s, 6H), 2.30 ppm (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=175.4, 173.7, 158.3, 149.4, 144.0, 142.8, 138.9, 134.5, 132.4, 132.3, 130.4, 129.9, 129.1, 128.3, 125.9, 123.4, 105.5, 55.6, 52.7, 45.7, 42.2, 23.0, 20.9 ppm; HRMS (ESI) m/z calcd. for $C_{30}H_{26}N_3O_5S_2$ $[M-H]^-$: 572.1319; found: 572.1318; HPLC analysis (Chiralpak OD-H column, hexane/2-propanol/TEA=60:40:0.1, flow rate=0.8 mL min^{-1}, wavelength=230 nm): T_R=32.65 (major) and 53.89 min (minor).

(3a*S*,11*S*,11a*S*)-1,3-Dioxo-7-methoxy-2-phenyl-11-(2,4,6-trimethyl-benzenesulfonamido)-1,2,3,3a,11,11a-hexahydropyrrolo-[3′,4′:5,6]thiopyrano[2,3-b]quinoline (**3 ea**): White solid, m.p. 218–220 °C, 89% yield, $[\alpha]_D^{25}$=+1.29 (c=1.0, CH_2Cl_2), 97% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.04 (br. s, 1H), 7.57 (d, J=8.8 Hz, 1H), 7.32 (s, 1H), 7.26 (s, 3H), 7.18 (d, J=8.4 Hz, 1H), 6.97 (s, 2H), 6.82 (s, 3H), 4.93 (dd, J=9.2, 4.0 Hz, 1H), 4.36 (d, J=8.8 Hz, 1H), 3.92 (s, 3H), 3.73 (dd, J=8.8, 4.0 Hz, 1H), 2.71 (s, 6H), 2.28 ppm (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=175.4, 173.6, 161.6, 153.0, 149.5, 142.8, 138.9, 134.4, 133.1, 132.3, 130.5, 129.1, 129.0, 126.9, 125.9, 122.1, 120.5, 106.4, 55.6, 52.6, 45.9, 42.1, 23.0, 20.9 ppm; HRMS (ESI) m/z calcd. for $C_{30}H_{26}N_3O_5S_2$ $[M-H]^-$: 572.1319; found: 572.1313; HPLC analysis (Chiralpak OD-H column, hexane/2-propanol/TEA=60:40:0.1, flow rate=0.8 mL min^{-1}, wavelength=230 nm): T_R=31.44 (major) and 53.93 min (minor).

(3a*S*,11*S*,11a*S*)-1,3-Dioxo-8-ethyl-2-phenyl-11-(2,4,6-trimethyl-benzenesulfonamido)-1,2,3,3a,11,11a-hexahydropyrrolo[3′,4′:5,6]thiopyrano[2,3-b]quinoline (**3 fa**): White solid, m.p. 160–162 °C, 95% yield, $[\alpha]_D^{25}$=+103.8 (c=1.0, CH_2Cl_2), 98% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.08 (br. s, 1H), 7.94 (d, J=8.8 Hz, 1H), 7.59 (dd, J=8.8, 1.6 Hz, 1H), 7.48 (s, 1H), 7.25–7.26 (m, 3H), 6.99 (s, 2H), 6.83 (br. s, 3H), 4.97 (dd, J=9.6, 4.4 Hz, 1H), 4.39 (d, J=9.2 Hz, 1H), 3.77 (dd, J=9.6, 4.8 Hz, 1H), 2.82 (q, J=7.6 Hz, 2H), 2.73 (s, 6H), 2.29 (s, 3H), 1.33 ppm (t, J=7.6 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=175.4, 173.7, 151.6, 146.5, 143.5, 142.8, 138.9, 134.4, 133.1, 132.3, 131.9, 130.4, 129.3, 129.0, 128.2, 127.0, 126.4, 125.9, 125.6„ 52.7, 45.8, 42.1, 28.8, 23.0, 20.9, 15.1 ppm; HRMS (ESI) m/z calcd. for $C_{31}H_{29}N_3NaO_4S_2$ $[M+Na]^+$: 594.1492; found: 594.1496; HPLC analysis (Chiralpak OD-H column, hexane/2-propanol/TEA=60:40:0.1, flow rate=0.8 mL min^{-1}, wavelength=230 nm): T_R=21.69 (major) and 35.74 min (minor).

(3a*S*,11*S*,11a*S*)-8-Butyl-1,3-dioxo-2-phenyl-11-(2,4,6-trimethyl-benzenesulfonamido)-1,2,3,3a,11,11a-hexahydropyrrolo[3′,4′:5,6]thiopyrano[2,3-b]quinoline (**3 ga**): White solid, m.p. 149–151 °C, 87% yield, $[\alpha]_D^{25}$=+68.3 (c=1.0, CH_2Cl_2), 96% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.09 (s, 1H), 7.94 (d, J=8.8 Hz, 1H), 7.57 (dd, J=8.4, 1.6 Hz, 1H), 7.48 (s, 1H), 7.26–7.28 (m, 3H), 6.99 (s, 2H), 6.82 (br. s, 3H), 4.96 (dd, J=9.6, 4.8 Hz, 1H), 4.36 (d, J=9.6 Hz, 1H), 3.74 (dd, J=9.6, 4.8 Hz, 1H), 2.78 (t, J=7.6 Hz, 2H), 2.72 (s, 6H), 2.30 (s, 3H), 1.68 (quin, J=7.6 Hz, 2H), 1.39 (sex, J=7.6 Hz, 2H), 0.96 ppm (t, J=7.6 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=175.3, 173.6, 151.5, 146.5, 142.8, 142.4, 138.9, 134.5, 133.2, 132.3, 130.4, 129.3, 129.1, 128.1, 127.1, 126.3, 126.0, 52.7, 45.7, 42.1, 35.6, 33.2, 23.1, 22.3, 21.0, 13.9 ppm; HRMS (ESI) m/z calcd. for $C_{33}H_{32}N_3NaO_4S_2$ $[M+Na]^+$: 622.1805; found: 622.1807; HPLC analysis (Chiralpak OD-H column, hexane/2-propanol/TEA=60:40:0.1, flow rate=0.8 mL min^{-1}, wavelength=230 nm): T_R=21.56 (major) and 33.37 min (minor).

(3a*S*,11*S*,11a*S*)-7-Chloro-1,3-dioxo-2-phenyl-11-(2,4,6-trimethyl-benzenesulfonamido)-1,2,3,3a,11,11a-hexahydropyrrolo[3′,4′:5,6]thiopyrano[2,3-b]quinoline (**3 ha**): White solid, m.p. 150–152 °C, 88% yield, $[\alpha]_D^{25}$=+24.5 (c=1.0, CH_2Cl_2), 90% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.15 (br. s, 1H), 8.00 (d, J=1.2 Hz, 1H), 7.66 (d, J=8.8 Hz, 1H), 7.49 (dd, J=8.4, 1.6 Hz, 1H), 7.26–7.28 (m, 3H), 6.99 (s, 2H), 6.82 (br. s, 3H), 4.93 (dd, J=9.6, 4.8 Hz, 1H), 4.37 (d, J=9.6 Hz, 1H), 3.74 (dd, J=10.0, 4.8 Hz, 1H), 2.71 (s, 6H), 2.30 ppm (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=175.3, 173.4, 154.4, 147.9, 143.0, 138.9, 136.6, 134.4, 133.4, 132.3, 130.3, 129.7, 129.3, 129.2, 128.3, 127.5, 125.9, 125.3, 52.6, 45.5, 42.0, 23.0, 21.0 ppm; HRMS (ESI) m/z calcd. for $C_{29}H_{23}ClN_3O_4S_2$ $[M-H]^-$: 576.0824; found: 576.0829; HPLC analysis (Chiralpak OD-H column, hexane/2-propanol/TEA=60:40:0.1, flow rate=0.8 mL min^{-1}, wavelength=230 nm): T_R=27.50 (major) and 45.94 min (minor).

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