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A cinchona alkaloid catalyzed enantioselective sulfa-Michael/aldol cascade reaction of isoindigos: construction of chiral bispirooxindole tetrahydrothiophenes with vicinal quaternary spirocenters†

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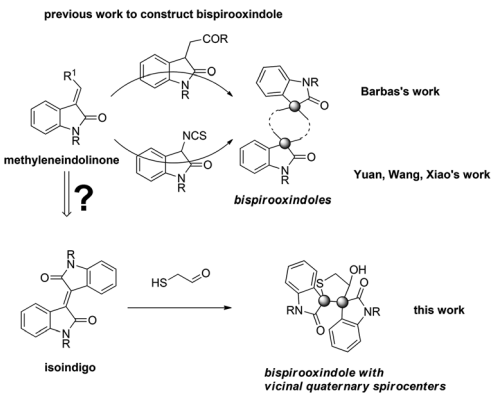
A cinchona alkaloid catalyzed diastereoselective and enantioselective sulfa-Michael/aldol cascade reaction between 1,4-dithiane-2,5-diol and isoindigos has been successfully developed to afford the highly congested bispirooxindole tetrahydrothiophenes with vicinal quaternary spirocenters in high yields (up to 91%), excellent diastereoselectivities (up to >20 : 1 dr), and good enantioselectivities (up to 98% ee). Some synthetic transformations of the reaction products were also studied.

Introduction

A spirocyclic-oxindole scaffold is a privileged heterocyclic structure frequently found in a wide range of natural products.[1] Accordingly, remarkable advances have been made for the stereoselective syntheses of the spirocyclic-oxindole skeletons.[2,3] However, most of the synthetic targets are restricted to mono-spirooxindoles, and the catalytic enantioselective approaches toward the bispirooxindoles are limited, probably because of the challenges associated with the construction of the structurally more constrained bispirooxindole moieties and at least two quaternary spirocenters. Bispirooxindoles, fusing two oxindole rings into one cyclic molecule, may exhibit enhanced bioactivities compared to those of mono-spirooxindoles.[4] Therefore, the development of new approaches to obtain bispirooxindoles is highly appealing. So far, only a few methods,[5] mainly confined to the Michael cascade reaction between 3-substituted oxindoles and methyleneindolinones, for the catalytic enantioselective construction of bispirooxindoles have been reported. Typically, the Barbas group[5a] has pioneered an organocatalytic asymmetric domino Michael/aldol reaction between 3-substituted oxindoles and methyleneindolinones that afforded complex bispirooxindoles. More recently, isothiocyanato oxindoles[5c–g] were used in the Michael/cyclization sequence to prepare synthetically valuable bispirooxindole scaffolds (Scheme 1). Nevertheless, efficient catalytic enantioselective methods to access chiral bispirooxindoles with two vicinal quaternary spirocenters still remain rare.[6,7]

On the other hand, isoindigo, an isomer of the well-known dye indigo, has recently attracted considerable attention as an electron-deficient building block for conjugated polymers.[8] However, a survey of the literature found that there was no report on organocatalytic asymmetric Michael cascade reac-



Scheme 1 Our strategy using isoindigo to construct structurally more rigid bispirooxindoles with two contiguous quaternary spirocenters.

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tions of isoindigo.[9] Several challenges arise when isoindigo is used as a Michael acceptor. One of the difficulties is its low reactivity due to steric congestion that is encountered in the carbon–carbon/carbon–heteroatom bond formation of nucleophilic addition with isoindigo. It is also difficult to achieve high levels of enantiotopic face selectivity because of relatively similar steric environments between the nonhydrogen substituents. Nevertheless, a successful organocatalytic asymmetric Michael/cascade reaction of isoindigo would present another method for the construction of a family of chiral bispirooxindoles with vicinal quaternary stereocenters (Scheme 1). Moreover, the tetrahydrothiophene structure embedded in the target bispirooxindole is unique and has gained much attention due to its diverse applications in chemistry and biology.[10] Commercially available 1,4-dithiane-2,5-diol (the dimer of mercaptoacetaldehyde) is usually used to construct tetrahydrothiophene derivatives.[11] Based on our previous related work in chiral spirooxindole syntheses,[12] we anticipated that the reaction of 1,4-dithiane-2,5-diol with isoindigo may be a straightforward way to construct oxindole-based bispirocyclic tetrahydrothiophenes through a Michael/aldol cascade reaction. Herein, we wish to report the first organocatalytic enantioselective Michael/aldol cascade reaction between 1,4-dithiane-2,5-diol and isoindigo with a commercially available cinchona alkaloid as a catalyst. This reaction readily afforded a family of enantioselective oxindole-based bispirocyclic tetrahydrothiophenes bearing highly congested contiguous quaternary stereocenters in up to 91% yield, >20 : 1 dr, and 98% ee.

Results and discussion

The initial investigation began with the model reaction between 1,4-dithiane-2,5-diol **1** and 1,1′-dimethyl isoindigo **2a** using 10 mol% quinine as the catalyst in $CHCl_3$ at 30 °C (Fig. 1). The sulfa-Michael/aldol cascade reaction proceeded smoothly and afforded the desirable product **3a** in 65% yield, with 72 : 28 dr and 66% ee (Table 1, entry 1). Other cinchona bases were also tested. Among the catalysts, quinidine gave the best enantioselectivity with moderate yield and diastereoselectivity (79% yield, 77 : 23 dr, 73% ee, Table 1, entry 2). Other bifunctional thiourea and squaramide catalysts were also screened. All the catalysts gave poor enantioselectivities compared to quinidine (Table 1, entries 5–8 *vs.* entry 2).

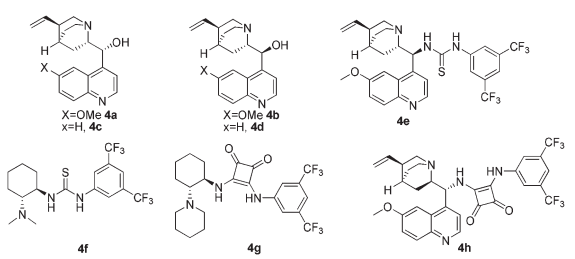
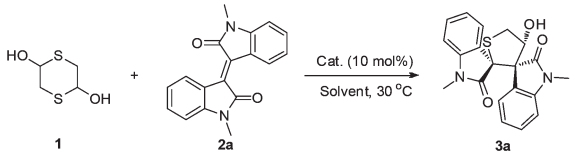


Fig. 1 Bifunctional chiral catalysts.

Table 1 Optimization of the reaction[a]



Entry	Cat.	Solvent	Time (h)	Yield[b] (%)	dr[c] (%)	ee[d] (%)
1	**4a**	$CHCl_3$	4	65	72 : 28	66[j]
2	**4b**	$CHCl_3$	2	79	77 : 23	73
3	**4c**	$CHCl_3$	2	77	57 : 43	70[j]
4	**4d**	$CHCl_3$	4	59	53 : 47	54
5	**4e**	$CHCl_3$	4	56	73 : 27	12
6	**4f**	$CHCl_3$	3	59	70 : 30	50
7	**4g**	$CHCl_3$	14	58	55 : 45	10
8	**4h**	$CHCl_3$	38	55	53 : 47	62[j]
9	**4b**	PhCN	6	59	85 : 15	2
10	**4b**	DMF	2	44	83 : 17	9
11	**4b**	CCl_4	12	75	86 : 14	78
12	**4b**	DCM	2	82	72 : 28	66
13	**4b**	THF	6	48	68 : 32	46
14	**4b**	$PhCH_3$	6	69	85 : 15	65
15	**4b**	Mesitylene	6	74	80 : 20	78
16[e]	**4b**	Mesitylene	72	45	81 : 19	73
17[f]	**4b**	Mesitylene	1	82	70 : 30	56
18[g]	**4b**	Mesitylene	5	82	84 : 16	80
19[g,h]	**4b**	Mesitylene	5	90	80 : 20	86
20[g,h,i]	**4b**	Mesitylene	5	90	82 : 18	86

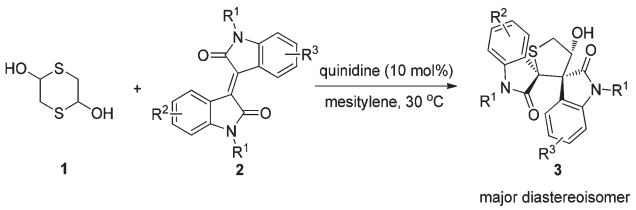
[a] Unless otherwise specified, the reaction was performed on a scale of 0.06 mmol **1** and 0.1 mmol **2a** in a 1 mL solvent at 30 °C. [b] Isolated yield. [c] Determined by isolated yield of two diastereoisomers. [d] Enantiomeric excess of the major diastereoisomer determined by chiral HPLC analysis. [e] The reaction was performed at 0 °C. [f] The reaction was performed at 50 °C. [g] 2 mL mesitylene was added. [h] The reaction was conducted with 0.1 mmol of **1**. [i] 50 mg $MgSO_4$ was added. [j] Contrary configuration.

Further screening of the solvents showed that less polar solvents such as toluene, mesitylene, and tetrachloromethane gave better enantioselectivities (65–78% ee, Table 1, entries 11, 14 and 15). However, strong polar solvents gave disappointing enantioselectivities (Table 1, entries 9 and 10). Of the screened solvents, mesitylene gave the best enantioselectivity (Table 1, entry 15) and was chosen for further investigations. Lowering the reaction temperature to 0 °C led to a slight decrease of enantioselectivity, yet a longer reaction time was required (Table 1, entry 16). When the reaction was conducted at an elevated temperature (50 °C), the enantioselectivity decreased dramatically (Table 1, entry 17). When 2 mL mesitylene was used, 84 : 16 dr and 80% ee were obtained (Table 1, entry 18). The increase of 1,4-dithiane-2,5-diol loading improved the enantioselectivity from 80% ee to 86% ee (Table 1, entry 19 *vs.* entry 18). Adding 50 mg $MgSO_4$ could slightly improve the diastereoselectivity of the reaction (Table 1, entry 20 *vs.* entry 19). Further screening of catalyst loading, additives did not give better results (see ESI†). Based on the comprehensive considerations of reaction time, yield, diastereoselectivity and enantioselectivity, the optimal reaction conditions were estab-

lished as: 0.1 mmol **1**, 0.1 mmol **2a** with 10 mol% of quinidine, 50 mg $MgSO_4$ in 2 mL mesitylene at 30 °C.

Under the optimized reaction conditions, the substrate scope of isoindigos was further evaluated. The substituents on the nitrogen atom were firstly examined. All substituted isoindigos bearing different alkyl groups worked well with excellent yields, diastereoselectivities and moderate to good enantioselectivities (78–91% yields, 82 : 18–>20 : 1 dr, 69–87% ee, Table 2, entries 1–6, 8, 10). It was found that the bulky alkyl substituents on the nitrogen atom to some extent favoured the diastereoselectivity (Table 2, entries 2–6, 8, 10 *vs.* entry 1). In particular for **2c**, only one diastereoisomer was obtained (>20 : 1 dr, Table 2, entry 3). When cinchonine was used as the catalyst, the reaction gave excellent diastereoselectivities and enantioselectivities (96 : 4 dr, 90% ee, 97 : 3 dr, 90% ee, Table 2, entries 7 and 9). Additionally, isoindigos with different substitutions at C5–C7 positions reacted smoothly with 1,4-dithiane-2,5-diol, affording the desired products in 71–90% yield (Table 2, entries 11–18, 29–31). However, we found that a halogen atom on the isoindigo aromatic ring has slight negative effects on the diastereoselectivity and enantioselectivity, and 1,1′-dipropyl-7,7′-difluoro-isoindigo **2l** gave a mixture of almost equal quantities of two diastereoisomers, with 68% and 32% ee respectively (Table 2, entry 14). Electron-rich isoindigos **2i** and **2n** gave good to excellent enantioselectivities (82% and 98% ee respectively, Table 2, entries 11 and 16). Generally, C6 substituted isoindigos gave better enantioselectivity than C5 substituted isoindigos (Table 2, entry 13 *vs.* 12, entry 18 *vs.* 17). *N*-Unprotected isoindigo **2q** gave no corresponding product after 72 hours, prob-

Table 2 Substrate scope of the sulfa-Michael/aldol cascade reaction[a]



Entry	2	R^1	R^2	R^3	Time (h)	3	Yield[b] (%)	dr[c]	ee[d] (%)
1	**2a**	Me	H	H	5	**3a**	90	82 : 18	86
2	**2b**	Et	H	H	5	**3b**	90	93 : 7	86
3	**2c**	*n*-Pr	H	H	3	**3c**	81	>20 : 1	87
4	**2d**	Allyl	H	H	3	**3d**	86	94 : 6	83
5	**2e**	i-Pr	H	H	3	**3e**	91	95 : 5	86
6	**2f**	*n*-Bu	H	H	3	**3f**	91	94 : 6	87
7[e]	**2f**	*n*-Bu	H	H	3	**3f**	78	96 : 4	90
8	**2g**	*n*-Octyl	H	H	3	**3g**	91	96 : 4	87
9[e]	**2g**	*n*-Octyl	H	H	3	**3g**	85	97 : 3	90
10	**2h**	Bn	H	H	3	**3h**	85	>20 : 1	69
11	**2i**	*n*-Pr	5-Me	5′-Me	5	**3i**	77	94 : 6	82
12	**2j**	*n*-Pr	5-Br	5′-Br	5	**3j**	81	90 : 10	67
13	**2k**	*n*-Pr	6-Br	6′-Br	5	**3k**	77	85 : 15	75
14	**2l**	*n*-Pr	7-F	7′-F	5	**3l**	90	50 : 50	68/32
15	**2m**	*n*-Pr	5-F	5′-F	5	**3m**	90	81 : 19	75
16	**2n**	*n*-Pr	5-OMe	5′-OMe	5	**3n**	79	62 : 38	98
17	**2o**	*n*-Pr	5-Cl	5′-Cl	5	**3o**	76	83 : 17	69
18	**2p**	*n*-Pr	6-Cl	6′-Cl	5	**3p**	71	>20 : 1	82
19[f]	**2q**	H	H	H	—	—	—	—	—
20[g]	**2r**	*n*-Pr	5-Cl	H	—	—	—	—	—
21[g]	**2s**	*n*-Pr	6-Cl	H	—	—	—	—	—
22[h]	**2a**	Me	H	H	5	***ent*-3a**	75	85 : 15	87
23[h]	**2b**	Et	H	H	5	***ent*-3b**	80	88 : 12	84
24[h]	**2c**	*n*-Pr	H	H	3	***ent*-3c**	76	90 : 10	85
25[h]	**2d**	Allyl	H	H	3	***ent*-3d**	83	89 : 11	81
26[h]	**2e**	i-Pr	H	H	3	***ent*-3e**	75	91 : 9	81
27[h]	**2f**	*n*-Bu	H	H	3	***ent*-3f**	74	91 : 9	86
28[h]	**2g**	*n*-Octyl	H	H	3	***ent*-3g**	80	93 : 7	88
29[h]	**2i**	*n*-Pr	5-Me	5′-Me	5	***ent*-3i**	70	86 : 14	80
30[h]	**2m**	*n*-Pr	5-F	5′-F	5	***ent*-3m**	82	78 : 22	71
31[h]	**2p**	*n*-Pr	6-Cl	6′-Cl	5	***ent*-3p**	82	>20 : 1	82

[a] Unless otherwise specified, the reaction was performed on a scale of 0.1 mmol **1** and 0.1 mmol **2a**, quinidine (10 mol%), 50 mg $MgSO_4$, in 2 mL mesitylene at 30 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Enantiomeric excess of the major diastereoisomer determined by chiral HPLC analysis [e] The reaction was conducted with 10 mol% of cinchonine. [f] No reaction after 72 hours. [g] Complex products. [h] The reaction was conducted with 10 mol% of quinine.

ably due to its poor solubility in mesitylene. The scope of the cascade reactions with unsymmetrical isoindigos was also examined (Table 2, entries 19 and 20). However, unsymmetrical isoindigos gave complex products, probably due to the poor regioselectivity of the nucleophilic addition of mercaptoacetaldehyde to isoindigo. It is worth noting that the configuration of the enantiomers of the bispirooxindole tetrahydrothiophenes could be correspondingly obtained by switching the catalyst from quinidine to quinine. Under similar reaction conditions, quinine gave the chiral bispirooxindole tetrahydrothiophenes with good yields, diastereoselectivities and enantioselectivities (70–83% yields, 78 : 22→20 : 1 dr, 71–88% ee, Table 2, entries 22–31).

To determine the relative and absolute configurations of the asymmetric sulfa-Michael/aldol addition products, a single crystal of compound **3k** was obtained and the structure was confirmed by X-ray diffraction analysis. As shown in Fig. 2, compound **3k** contains a (C11*R*,C12*R*,C14*S*) configuration.[13] Accordingly, the configurations of the other products in this work were tentatively assigned by assuming that a similar catalytic mechanism was followed.

According to the above data and a previously reported dual activation model,[14] we tentatively propose a working model as shown in Fig. 3. The OH moiety of the catalyst activates the isoindigo *via* hydrogen bonding interactions. On the other hand, the tertiary amine of the catalyst would provide suitable basicity to enhance the nucleophilicity of the mercaptoacetaldehyde. The well-defined orientation facilitates the *Si* attack on the activated isoindigo. A subsequent intramolecular aldol reaction through the attack from the *Re* face of the aldehyde will create the corresponding product with (C11*R*,C12*R*,C14*S*) configuration (Fig. 3).

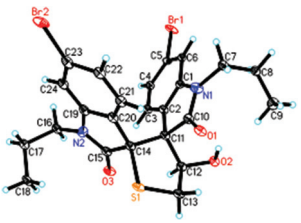


Fig. 2 X-ray structure of compound **3k**.

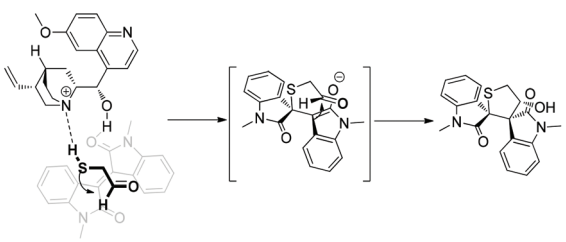
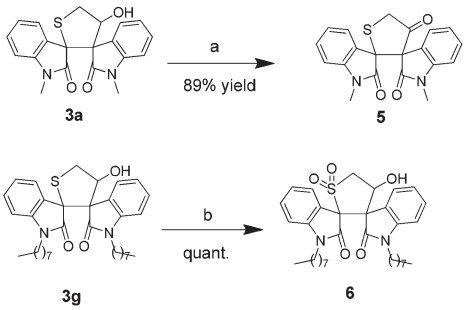


Fig. 3 A proposed working model for the sulfa-Michael/aldol cascade reaction between 1,4-dithiane-2,5-diol and isoindigo.



Scheme 2 Synthetic applications of our approach. Reaction conditions: (a) 3.0 eq. PCC, DCM, rt, overnight; (b) 3.0 eq. *m*-CPBA, DCM, rt, overnight.

Some synthetic selective oxidations of the multifunctional products were also studied using different oxidants. Treatment of **3a** with PCC in CH_2Cl_2 readily accomplished a selective oxidation of the alcohol **3a** to the corresponding ketone **5** in 89% yield, while *m*-CPBA selectively oxidized the sulfur group of **3g** to sulfone **6** with quantitative yield (Scheme 2).

Conclusions

In summary, we have firstly developed a novel and simple organocatalytic thiol initiated Michael/aldol cascade reaction between a variety of isoindigos and 1,4-dithiane-2,5-diol. The protocol, efficiently catalyzed by the commercially available quinidine, has been successfully used to construct highly functionalized bispirooxindoles bearing tetrahydrothiophene motifs by generating vicinal quaternary stereocenters in excellent yields (up to 91%), diastereoselectivities (up to >20 : 1 dr) and good enantioselectivities (up to 98% ee). Further investigation is under way to explore the reaction mechanism and expand the scope and application of this efficient cascade reaction.

General methods

A commercial grade solvent was dried and purified by standard procedures as specified in W. L. F. Armarego and D. D. Perrin, *Purification of Laboratory Chemicals*, Butterworth Heinemann, 4th edn, 1997. NMR spectra were recorded with tetramethylsilane as the internal standard. ^{1}H NMR spectra were recorded at 300 MHz, and ^{13}C NMR spectra were recorded at 75 MHz (Bruker Avance). ^{1}H NMR chemical shifts (δ) were reported in ppm relative to tetramethylsilane (TMS) with the solvent signal as the internal standard ($CDCl_3$ at 7.26 ppm, $(CD_3)_2SO$ at 2.50 ppm). ^{13}C NMR chemical shifts are reported in ppm from tetramethylsilane (TMS) with solvent resonance as the internal standard ($CDCl_3$ at 77.00 ppm, $(CD_3)_2SO$ at 39.52 ppm). Data are given as: s (singlet), d (doublet), t (triplet), q (quartet), dd (double of doublet) or m (multiplets), coupling constants (Hz) and integration. Flash column chromatography was carried out using silica gel eluting with ethyl

acetate and petroleum ether. High resolution mass spectra were obtained using a Q-TOF-Premier mass spectrometer. Reactions were monitored by TLC and visualized with ultraviolet light. Enantiomeric excess was determined by HPLC analysis on Chiralpak AD-H or IC columns. Optical rotations are reported as follows: $[\alpha]_D^{25}$ (*C* in g per 100 mL, $CHCl_3$).

General procedure for sulfa-Michael/aldol cascade reaction

To a stirred solution of quinidine (10 mol%), 1,1′-dimethyl isoindigo **2a** (0.10 mmol), and $MgSO_4$ (50 mg) in mesitylene (2.0 mL) at 30 °C was added 1,4-dithiane-2,5-diol **1** (0.1 mmol). The resulting reaction mixture was kept under vigorous stirring until the consumption of **2a** (monitored by TLC analysis). After completion of the reaction, the reaction solution was concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel to afford pure products **3a**.

(3*R*,4*R*,5*S*)-1′-Methyl-spiro[4.3′]oxindole-spiro[5.3″]1″-methyl-oxindole-tetrahydrothiophen-3-ol (3a). White solid, mp: 173–174 °C; 90% yield, $[\alpha]_D^{25}$ = +164.6 (*c* = 0.36, $CHCl_3$); (dr = 82 : 18, 86% ee for the major diastereomer). HPLC conditions: ee was determined by HPLC analysis (Chiralcel AD-H, hexane/i-PrOH = 80/20, 1.0 mL min^{-1}, 254 nm). Retention time: t_{minor} = 22.56 min, t_{major} = 25.94 min; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.48 (d, *J* = 8 Hz, 1H), 7.44 (d, *J* = 8 Hz, 1H), 7.12–7.20 (m, 2H), 6.94 (t, *J* = 8 Hz, 2H), 6.59 (d, *J* = 8 Hz, 1H), 6.53 (d, *J* = 8 Hz, 1H), 5.76–5.83 (m, 1H), 3.97 (t, *J* = 9 Hz, 1H), 3.58–3.64 (m, 1H), 3.10 (s, 3H), 3.06 (s, 3H), 2.12 (d, *J* = 7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 177.6, 172.7, 144.5, 143.2, 129.7, 129.3, 125.6, 124.9, 124.3, 123.9, 122.9, 122.5, 107.9, 76.7, 64.4, 60.1, 34.3, 26.3, 25.8. HRMS-ESI (*m*/*z*): Calcd for $C_{22}H_{22}N_2O_3S$, $[M + H]^+$: 367.11109, found: 367.11079.

(3*R*,4*R*,5*S*)-1′-Methyl-spiro[4.3′]oxindole-spiro[5.3″]1″-methyl-oxindole-tetrahydrothiophen-3-ol (ent-3a). White solid, mp: 178–180 °C; 75% yield, $[\alpha]_D^{25}$ = −147 (*c* = 0.27, $CHCl_3$); (dr = 75 : 25, 85% ee for the major diastereomer). HPLC conditions: ee was determined by HPLC analysis (Chiralcel AD-H, hexane/i-PrOH = 80/20, 1.0 mL min^{-1}, 254 nm). Retention time: t_{major} = 23.77 min, t_{minor} = 26.87 min.

(3*R*,4*R*,5*S*)-1′-Ethyl-spiro[4.3′]oxindole-spiro[5.3″]1″-ethyl-oxindole-tetrahydrothiophen-3-ol (3b). White solid, mp: 162–163 °C; 90% yield, $[\alpha]_D^{25}$ = +177.8 (*c* = 0.49, $CHCl_3$); (dr = 93 : 7, 86% ee for the major diastereomer). HPLC conditions: ee was determined by HPLC analysis (Chiralcel AD-H, hexane/i-PrOH = 80/20, 1.0 mL min^{-1}, 254 nm). Retention time: t_{minor} = 14.53 min, t_{major} = 27.53 min; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.55 (d, *J* = 8 Hz, 1H), 7.48 (d, *J* = 8 Hz, 1H), 7.14 (q, *J* = 8 Hz, 2H), 6.92 (t, *J* = 8 Hz, 2H), 6.61 (d, *J* = 8 Hz, 1H), 6.55 (d, *J* = 8 Hz, 1H), 5.74–5.79 (m, 1H), 3.97 (t, *J* = 9 Hz, 1H), 3.76–3.87 (m, 2H), 3.46–3.54 (m, 3H), 2.26 (d, *J* = 7 Hz, 1H), 1.08 (t, *J* = 7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 177.3, 172.4, 143.7, 142.3, 129.6, 129.3, 126.4, 125.2, 124.9, 124.1, 122.6, 122.2, 108.1, 108.0, 77.0, 64.0, 59.7, 34.9, 34.4, 34.1, 12.5, 12.4. HRMS-ESI (*m*/*z*): Calcd for $C_{22}H_{22}N_2O_3S$, $[M + H]^+$: 395.14239, found: 395.14269.

(3*R*,4*R*,5*S*)-1′-Ethyl-spiro[4.3′]oxindole-spiro[5.3″]1″-ethyl-oxindole-tetrahydrothiophen-3-ol (ent-3b). White solid, mp: 160–161 °C; 80% yield, $[\alpha]_D^{25}$ = −168 (*c* = 0.29, $CHCl_3$); (dr = 88 : 12, 84% ee for the major diastereomer). HPLC conditions: ee was determined by HPLC analysis (Chiralcel AD-H, hexane/i-PrOH = 80/20, 1.0 mL min^{-1}, 254 nm). Retention time: t_{major} = 14.86 min, t_{minor} = 28.13 min.

(3*R*,4*R*,5*S*)-1′-Propyl-spiro[4.3′]oxindole-spiro[5.3″]1″-propyl-oxindole-tetrahydrothiophen-3-ol (3c). White solid, mp: 125–127 °C; 81% yield, $[\alpha]_D^{25}$ = +126.4 (*c* = 0.41, $CHCl_3$); (dr > 20 : 1, 87% ee). HPLC conditions: ee was determined by HPLC analysis (Chiralcel AD-H, hexane/i-PrOH = 80/20, 1.0 mL min^{-1}, 254 nm). Retention time: t_{minor} = 9.89 min, t_{major} = 16.58 min; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.54 (d, *J* = 8 Hz, 1H), 7.47 (d, *J* = 8 Hz, 1H), 7.11 (m, 2H), 6.90 (t, *J* = 8 Hz, 2H), 6.61 (d, *J* = 8 Hz, 1H), 6.54 (d, *J* = 8 Hz, 1H), 5.74–5.80 (m, 1H), 3.94 (t, *J* = 9 Hz, 1H), 3.56–3.67 (m, 3H), 3.40–3.47 (m, 2H), 2.38 (bs, 1H), 1.48–1.61 (m, 4H), 0.84 (t, *J* = 7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 177.7, 172.7, 144.4, 142.9, 129.6, 129.3, 126.49, 125.2, 125.0, 124.1, 122.7, 122.3, 108.2, 76.6, 64.1, 59.8, 42.0, 41.6, 34.1, 20.8, 20.7, 11.5, 11.4. HRMS-ESI (*m*/*z*): Calcd for $C_{24}H_{26}N_2O_3S$, $[M + H]^+$: 423.17369, found: 423.17365.

(3*R*,4*R*,5*S*)-1′-Propyl-spiro[4.3′]oxindole-spiro[5.3″]1″-propyl-oxindole-tetrahydrothiophen-3-ol (ent-3c). White solid, mp: 130–132 °C; 76% yield, $[\alpha]_D^{25}$ = −112.5 (*c* = 0.50, $CHCl_3$); (dr = 90 : 10, 85% ee for the major diastereomer). HPLC conditions: ee was determined by HPLC analysis (Chiralcel AD-H, hexane/i-PrOH = 80/20, 1.0 mL min^{-1}, 254 nm). Retention time: t_{major} = 10.13 min, t_{minor} = 17.13 min.

(3*R*,4*R*,5*S*)-1′-Allyl-spiro[4.3′]oxindole-spiro[5.3″]1″-allyl-oxindole-tetrahydrothiophen-3-ol (3d). White solid, mp: 152–153 °C; 86% yield, $[\alpha]_D^{25}$ = +143.9 (*c* = 0.41, $CHCl_3$); (dr = 94 : 6, 83% ee for the major diastereomer). HPLC conditions: ee was determined by HPLC analysis (Chiralcel AD-H, hexane/i-PrOH = 80/20, 1.0 mL min^{-1}, 254 nm). Retention time: t_{minor} = 11.69 min, t_{major} = 24.04 min; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.53 (dd, J_1 = 8 Hz, J_2 = 1 Hz, 1H), 7.46 (d, J_1 = 8 Hz, J_2 = 1 Hz, 1H), 7.08–7.15 (m, 2H), 6.89–6.94 (m, 2H), 6.59 (d, *J* = 8 Hz, 1H), 6.53 (d, *J* = 8 Hz, 1H), 5.76–5.83 (m, 1H), 5.54–5.68 (m, 2H), 5.05–5.08 (m, 2H), 4.84–4.96 (m, 2H), 4.39–4.49 (m, 2H), 4.08–4.15 (m, 1H), 3.95–4.07 (m, 2H), 3.55–3.61 (m, 1H), 2.20–2.21 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 177.5, 172.5, 143.9, 142.6, 130.7, 129.6, 129.3, 126.4, 125.0, 124.0, 123.0, 122.6, 117.7, 117.6, 109.0, 108.9, 77.2, 64.3, 59.9, 42.6, 42.1, 34.2. HRMS-ESI (*m*/*z*): Calcd for $C_{24}H_{22}N_2O_3S$, $[M + H]^+$: 419.14239, found: 419.14162.

(3*R*,4*R*,5*S*)-1′-Allyl-spiro[4.3′]oxindole-spiro[5.3″]1″-allyl-oxindole-tetrahydrothiophen-3-ol (ent-3d). White solid, mp: 151–153 °C; 83% yield, $[\alpha]_D^{25}$ = −122.5 (*c* = 0.45, $CHCl_3$); (dr = 89 : 11, 81% ee for the major diastereomer). HPLC conditions: ee was determined by HPLC analysis (Chiralcel AD-H, hexane/i-PrOH = 80/20, 1.0 mL min^{-1}, 254 nm). Retention time: t_{major} = 11.69 min, t_{minor} = 24.04 min.

(3*R*,4*R*,5*S*)-1′-Isopropyl-spiro[4.3′]oxindole-spiro[5.3″]1″-isopropyl-oxindole-tetrahydrothiophen-3-ol (3e). White solid, mp: 150–152 °C; 91% yield, $[\alpha]_D^{25}$ = +99.3 (*c* = 0.45, $CHCl_3$); (dr = 95 : 5, 86% ee for the major diastereomer). HPLC con-

ditions: ee was determined by HPLC analysis (Chiralcel AD-H, hexane/i-PrOH = 90/10, 1.0 mL min^{-1}, 254 nm). Retention time: t_{minor} = 23.73 min, t_{major} = 80.10 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.56 (d, J = 8 Hz, 1H), 7.50 (d, J = 8 Hz, 1H), 7.11 (m, 2H), 6.89 (m, 2H), 6.76 (d, J = 8 Hz, 1H), 6.70 (d, J = 8 Hz, 1H), 5.75–5.77 (m, 1H), 4.49–4.62 (m, 2H), 3.95 (t, J = 9 Hz, 1H), 3.59 (d, J = 9 Hz, 1H), 2.11 (d, J = 7 Hz, 1H), 1.36–1.41 (m, 6H), 1.22–1.26 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 177.3, 172.5, 143.3, 141.9, 139.4, 129.1, 126.5, 125.3, 125.1, 124.3, 122.2, 121.9, 109.9, 109.6, 77.0, 63.9, 59.9, 44.1, 43.7, 34.3, 19.3, 19.1, 19.1, 19.0. HRMS-ESI (m/z): Calcd for $C_{24}H_{26}N_2O_3S$, $[M + H]^+$: 423.17369, found: 423.17323.

(3*R*,4*R*,5*S*)-1′-Isopropyl-spiro[4.3′]oxindole-spiro[5.3″]1″-isopropyl-oxindole-tetrahydrothiophen-3-ol (ent-3e). White solid, mp: 149–150 °C; 75% yield, $[\alpha]_D^{25}$ = −97 (c = 0.28, $CHCl_3$); (dr = 91 : 9, 81% ee for the major diastereomer). HPLC conditions: ee was determined by HPLC analysis (Chiralcel AD-H, hexane/i-PrOH = 90/10, 1.0 mL min^{-1}, 254 nm). Retention time: t_{major} = 23.75 min, t_{minor} = 77.92 min.

(3*R*,4*R*,5*S*)-1′-Butyl-spiro[4.3′]oxindole-spiro[5.3″]1″-butyl-oxindole-tetrahydrothiophen-3-ol (3f). White solid, mp: 126–127 °C; 91% yield, $[\alpha]_D^{25}$ = +169.0 (c = 0.86, $CHCl_3$); (dr = 94 : 6, 87% ee for the major diastereomer). HPLC conditions: ee was determined by HPLC analysis (Chiralcel AD-H, hexane/i-PrOH = 80/20, 1.0 mL min^{-1}, 254 nm). Retention time: t_{minor} = 9.21 min, t_{major} = 20.91 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.54 (dd, J_1 = 8 Hz, J_2 = 1 Hz, 1H), 7.48 (dd, J_1 = 8 Hz, J_2 = 1 Hz, 1H), 7.09–7.18 (m, 2H), 6.90 (t, J = 8 Hz, 2H), 6.60 (d, J = 8 Hz, 1H), 6.54 (d, J = 8 Hz, 1H), 5.74–5.81 (m, 1H), 3.95 (t, J = 8 Hz, 1H), 3.41–3.75 (m, 5H), 2.40 (d, J = 7 Hz, 1H), 1.45–1.53 (m, 4H), 1.18–1.31 (m, 4H), 0.92 (t, J = 7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 177.6, 172.7, 144.3, 142.9, 129.5, 129.2, 126.4, 125.3, 125.0, 124.2, 122.6, 122.2, 108.2, 77.2, 64.0, 59.7, 40.2, 39.7, 34.1, 29.4, 29.4, 20.1, 13.6. HRMS-ESI (m/z): Calcd for $C_{26}H_{30}N_2O_3S$, $[M + H]^+$: 451.20499, found: 451.20541.

(3*R*,4*R*,5*S*)-1′-Butyl-spiro[4.3′]oxindole-spiro[5.3″]1″-butyl-oxindole-tetrahydrothiophen-3-ol (ent-3f). White solid, mp: 127–128 °C; 78% yield, $[\alpha]_D^{25}$ = −159.7 (c = 0.42, $CHCl_3$); (dr = 91 : 9, 86% ee for the major diastereomer). HPLC conditions: ee was determined by HPLC analysis (Chiralcel AD-H, hexane/i-PrOH = 80/20, 1.0 mL min^{-1}, 254 nm). Retention time: t_{major} = 9.36 min, t_{minor} = 21.78 min.

(3*R*,4*R*,5*S*)-1′-Octyl-spiro[4.3′]oxindole-spiro[5.3″]1″-octyl-oxindole-tetrahydrothiophen-3-ol (3g). White solid, mp: 169–170 °C; 91% yield, $[\alpha]_D^{25}$ = +62.8 (c = 0.42, $CHCl_3$); (dr = 96 : 4, 87% ee for the major diastereomer). HPLC conditions: ee was determined by HPLC analysis (Chiralcel AD-H, hexane/i-PrOH = 80/20, 1.0 mL min^{-1}, 254 nm). Retention time: t_{minor} = 6.41 min, t_{major} = 12.34 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.53 (d, J = 8 Hz, 1H), 7.48 (d, J = 8 Hz, 1H), 7.10–7.18 (m, 2H), 6.90 (t, J = 8 Hz, 2H), 6.61 (d, J = 8 Hz, 1H), 6.57 (d, J = 8 Hz, 1H), 5.73–5.81 (m, 1H), 3.95 (t, J = 9 Hz, 1H), 3.49–3.71 (m, 3H), 3.41–3.49 (m, 2H), 2.21 (d, J = 7 Hz, 1H), 1.49–1.50 (m, 4H), 1.24–1.25 (m, 20H), 0.87 (t, J = 6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 177.6, 172.6, 144.3, 142.9, 129.6, 129.2, 126.4, 125.3, 125.0, 124.2, 122.6, 122.2, 108.2, 77.3, 64.0, 59.7, 40.4, 40.0, 34.1, 31.7, 29.2, 29.2, 29.1, 29.0, 27.4, 27.3, 26.9, 26.9, 22.6, 14.0. HRMS-ESI (m/z): Calcd for $C_{34}H_{46}N_2O_3S$, $[M + H]^+$: 563.33019, found: 563.32868.

(3*R*,4*R*,5*S*)-1′-Octyl-spiro[4.3′]oxindole-spiro[5.3″]1″-octyl-oxindole-tetrahydrothiophen-3-ol (ent-3g). White solid, mp: 167–169 °C; 80% yield, $[\alpha]_D^{25}$ = −154.3 (c = 0.65, $CHCl_3$); (dr = 93 : 7, 88% ee for the major diastereomer). HPLC conditions: ee was determined by HPLC analysis (Chiralcel AD-H, hexane/i-PrOH = 80/20, 1.0 mL min^{-1}, 254 nm). Retention time: t_{major} = 6.47 min, t_{minor} = 12.69 min.

(3*R*,4*R*,5*S*)-1′-Benzyl-spiro[4.3′]oxindole-spiro[5.3″]1″-benzyl-oxindole-tetrahydrothiophen-3-ol (3h). White solid, mp: 174–175 °C; 85% yield, $[\alpha]_D^{25}$ = +112.7 (c = 0.61, $CHCl_3$); (dr = 84 : 16, 99% ee for the major diastereomer). HPLC conditions: ee was determined by HPLC analysis (Chiralcel AD-H, hexane/i-PrOH = 50/50, 0.6 mL min^{-1}, 254 nm). Retention time: t_{minor} = 15.44 min, t_{major} = 56.70 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.47–7.48 (m, 2H), 7.20–7.22 (m, 6H), 7.00–7.09 (m, 6H), 6.81–6.82 (m, 2H), 6.50–6.51 (m, 2H), 5.86–5.87 (m, 1H), 4.87–4.99 (m, 3H), 4.71–4.88 (m, 1H), 4.04 (d, J = 8 Hz, 1H), 3.61 (t, J = 8 Hz, 1H), 2.31 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 178.0, 172.9, 144.0, 142.6, 135.1, 134.9, 129.6, 129.3, 128.7, 128.6, 127.5, 127.4, 127.1, 127.0, 126.6, 125.3, 124.2, 123.3, 122.8, 109.2, 109.1, 77.7, 64.3, 59.9, 44.1, 43.6, 34.1. HRMS-ESI (m/z): Calcd for $C_{32}H_{26}N_2O_3S$, $[M + H]^+$: 519.17369, found: 519.17267.

(3*R*,4*R*,5*S*)-1′-Propyl-5′-methyl-spiro[4.3′]oxindole-spiro[5.3″]-1″-propyl-5″-methyl-oxindole-tetrahydrothiophen-3-ol (3i). White solid, mp: 154–155 °C; 77% yield, $[\alpha]_D^{25}$ = +53.6 (c = 0.47, $CHCl_3$); (dr = 94 : 6, 82% ee for the major diastereomer). HPLC conditions: ee was determined by HPLC analysis (Chiralcel AD-H, hexane/i-PrOH = 90/10, 1.0 mL min^{-1}, 254 nm). Retention time: t_{minor} = 18.91 min, t_{major} = 20.39 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.37 (s, 1H), 7.36 (s, 1H), 6.90–6.97 (m, 2H), 6.51 (d, J = 8 Hz, 1H), 6.45 (d, J = 8 Hz, 1H), 5.73–5.78 (m, 1H), 3.95 (t, J = 9 Hz, 1H), 3.62–3.74 (m, 2H), 3.58–3.60 (m, 1H), 3.35–3.40 (m, 2H), 2.23 (s, 3H), 2.22 (s, 3H), 2.00 (bs, 1H), 1.50–1.64 (m, 4H), 0.85 (t, J = 7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 177.6, 172.7, 142.0, 140.7, 132.2, 131.7, 129.9, 129.5, 127.1, 125.8, 125.1, 124.1, 107.9, 77.2, 64.1, 59.9, 42.0, 41.6, 34.2, 21.0, 20.9, 20.8, 11.4, 11.3. HRMS-ESI (m/z): Calcd for $C_{24}H_{24}Br_2N_2O_3S$, $[M + H]^+$: 451.20499, found: 451.20491.

(3*R*,4*R*,5*S*)-1′-Propyl-5′-methyl-spiro[4.3′]oxindole-spiro[5.3″]-1″-propyl-5″-methyl-oxindole-tetrahydrothiophen-3-ol (ent-3i). White solid, mp: 153–154 °C; 70% yield, $[\alpha]_D^{25}$ = −72 (c = 0.23, $CHCl_3$); (dr = 86 : 14, 80% ee for the major diastereomer). HPLC conditions: ee was determined by HPLC analysis (Chiralcel AD-H, hexane/i-PrOH = 90/10, 1.0 mL min^{-1}, 254 nm). Retention time: t_{major} = 19.01 min, t_{minor} = 20.55 min.

(3*R*,4*R*,5*S*)-1′-Propyl-5′-bromo-spiro[4.3′]oxindole-spiro[5.3″]-1″-propyl-5″-bromo-oxindoletetrahydrothiophen-3-ol (3j). White solid, mp: 175–177 °C; 81% yield, $[\alpha]_D^{25}$ = −39.4 (c = 0.56, $CHCl_3$); (dr = 90 : 10, 67% ee for the major diastereomer). HPLC conditions: ee was determined by HPLC analysis (Chiralcel AD-H, hexane/i-PrOH = 80/20, 1.0 mL min^{-1}, 254 nm).

Retention time: t_{major} = 11.26 min, t_{minor} = 27.13 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.64 (d, J = 2 Hz, 1H), 7.57 (d, J = 2 Hz, 1H), 7.26–7.32 (m, 2H), 6.53 (d, J = 8 Hz, 1H), 6.48 (d, J = 8 Hz, 1H), 5.69–5.77 (m, 1H), 3.96 (t, J = 9 Hz, 1H), 3.74–3.82 (m, 2H), 3.57–3.60 (m, 1H), 3.34–3.39 (m, 2H), 2.15 (d, J = 7 Hz, 1H), 1.55–1.60 (m, 4H), 0.85 (t, J = 7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 177.0, 172.0, 143.5, 142.1, 132.7, 132.3, 129.4, 128.1, 127.0, 125.9, 115.6, 115.2, 109.8, 109.7, 77.1, 64.0, 59.8, 42.2, 41.8, 34.1, 20.9, 11.4, 11.3. HRMS-ESI (m/z): Calcd for $C_{24}H_{24}Br_2N_2O_3S$, $[M + H]^+$: 578.99471, found: 578.99355.

(3*R*,4*R*,5*S*)-1′-Propyl-6′-bromo-spiro[4.3′]oxindole-spiro[5.3″]-1″-propyl-6″-bromo-oxindole-tetrahydrothiophen-3-ol (3k). White solid, mp: 180–181 °C; 77% yield, $[\alpha]_D^{25}$ = +51.8 (c = 0.50, $CHCl_3$); (dr = 85 : 15, 75% ee for the major diastereomer). HPLC conditions: ee was determined by HPLC analysis (Chiralcel AD-H, hexane/i-PrOH = 80/20, 1.0 mL min^{-1}, 254 nm). Retention time: t_{minor} = 7.50 min, t_{major} = 8.64 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.37 (d, J = 8 Hz, 1H), 7.30 (d, J = 8 Hz, 1H), 7.04 (dd, J_1 = 8 Hz, J_2 = 1 Hz, 1H), 6.78 (d, J = 1 Hz, 1H), 6.73 (d, J = 1 Hz, 1H), 5.68–5.72 (m, 1H), 3.93 (t, J = 9 Hz, 1H), 3.44–3.62 (m, 5H), 2.01–2.02 (m, 1H), 1.51–1.60 (m, 4H), 0.88 (t, J = 7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 177.4, 172.4, 145.7, 144.2, 127.6, 126.3, 125.7, 125.2, 124.0, 123.7, 123.4, 122.9, 111.8, 63.7, 59.8, 42.1, 41.7, 34.0, 29.6, 20.6, 11.4, 11.3. HRMS-ESI (m/z): Calcd for $C_{24}H_{24}Br_2N_2O_3S$, $[M + H]^+$: 578.99471, found: 578.99445.

(3*R*,4*R*,5*S*)-1′-Propyl-7′-fluoro-spiro[4.3′]oxindole-spiro[5.3″]-1″-propyl-7″-fluoro-oxindole-tetrahydrothiophen-3-ol (3l). White solid, mp: 135–136 °C; 90% yield, $[\alpha]_D^{25}$ = +75.5 (c = 0.37, $CHCl_3$); (dr = 50 : 50, 68% ee for the major diastereomer). HPLC conditions: ee was determined by HPLC analysis (Chiralcel AD-H, hexane/i-PrOH = 80/20, 1.0 mL min^{-1}, 254 nm). Retention time: t_{minor} = 6.34 min, t_{major} = 11.09 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.33–7.36 (m, 1H), 7.27–7.30 (m, 1H), 6.85–6.97 (m, 4H), 5.72–5.80 (m, 1H), 3.93 (t, J = 9 Hz, 1H), 3.64–3.76 (m, 4H), 3.55–3.59 (m, 1H), 2.14–2.17 (m, 1H), 1.49–1.65 (m, 4H), 0.87 (t, J = 7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 177.3, 172.1, 148.4 (J = 242 Hz), 148.3 (J = 243 Hz), 131.1 (J = 8 Hz), 129.6 (J = 9 Hz), 127.8 (J = 3 Hz), 127.0 (J = 3 Hz), 123.4 (J = 6 Hz), 123.0 (J = 6 Hz), 122.3 (J = 4 Hz), 120.8 (J = 3 Hz), 118.1 (J = 20 Hz), 117.9 (J = 20 Hz), 77.3, 64.4, 59.9, 44.0 (J = 5 Hz), 43.5 (J = 5 Hz), 34.1, 22.1 (J = 3 Hz), 22.0 (J = 3 Hz), 11.1, 11.0. HRMS-ESI (m/z): Calcd for $C_{24}H_{24}F_2N_2O_3S$, $[M + H]^+$: 459.15485, found: 459.15548.

(3*R*,4*R*,5*S*)-1′-Propyl-5′-fluoro-spiro[4.3′]oxindole-spiro[5.3″]-1″-propyl-5″-fluoro-oxindole-tetrahydrothiophen-3-ol (3m). White solid, mp: 121–122 °C; 90% yield, $[\alpha]_D^{25}$ = +82.5 (c = 0.54, $CHCl_3$); (dr = 81 : 19, 75% ee for the major diastereomer). HPLC conditions: ee was determined by HPLC analysis (Chiralcel AD-H, hexane/i-PrOH = 80/20, 1.0 mL min^{-1}, 254 nm). Retention time: t_{minor} = 21.27 min, t_{major} = 11.17 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.33 (dd, J_1 = 8 Hz, J_2 = 2 Hz, 1H), 7.23–7.27 (m, 1H), 6.83–6.88 (m, 2H), 6.57–6.58 (m, 1H), 6.50–6.52 (m, 1H), 5.40–5.46 (m, 1H), 3.96 (t, J = 9 Hz, 1H), 3.70–3.72 (m, 2H), 3.54–3.57 (m, 1H), 3.40–3.41 (m, 2H), 2.40–2.50 (bs, 1H), 1.51–1.59 (m, 4H), 0.84 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 177.3, 172.3, 160.6 (J = 241 Hz), 160.4 (J = 239 Hz), 140.3 (J = 2 Hz), 138.8 (J = 2 Hz), 126.8 (J = 8 Hz), 125.7 (J = 8 Hz), 116.3 (J = 23 Hz), 115.7 (J = 23 Hz), 114.7 (J = 26 Hz), 113.5 (J = 26 Hz), 108.9 (J = 16 Hz), 117.9 (J = 20 Hz), 77.3, 64.2, 59.5, 42.1, 41.7, 34.1, 20.6, 22.3, 11.3, 11.2. HRMS-ESI (m/z): Calcd for $C_{24}H_{24}F_2N_2O_3S$, $[M + H]^+$: 459.15485, found: 459.15548.

(3*S*,4*S*,5*R*)-1′-Propyl-5′-fluoro-spiro[4.3′]oxindole-spiro[5.3″]-1″-propyl-5″-fluoro-oxindole-tetrahydrothiophen-3-ol (ent-3m). White solid, mp: 121–122 °C; 82% yield, $[\alpha]_D^{25}$ = −79.5 (c = 0.46, $CHCl_3$); (dr = 78 : 22, 71% ee for the major diastereomer). HPLC conditions: ee was determined by HPLC analysis (Chiralcel AD-H, hexane/i-PrOH = 80/20, 1.0 mL min^{-1}, 254 nm). Retention time: t_{minor} = 11.17 min, t_{major} = 22.32 min.

(3*R*,4*R*,5*S*)-1′-Propyl-5′-methoxy-spiro[4.3′]oxindole-spiro[5.3″]-1″-propyl-5″-methoxy-oxindole tetrahydrothiophen-3-ol (3n). White solid, mp: 165–167 °C; 79% yield, $[\alpha]_D^{25}$ = +139.4 (c = 0.60, $CHCl_3$); (dr = 62 : 38, 98% ee for the major diastereomer). HPLC conditions: ee was determined by HPLC analysis (Chiralcel AD-H, hexane/i-PrOH = 80/20, 1.0 mL min^{-1}, 254 nm). Retention time: t_{major} = 11.44 min, t_{minor} = 23.25 min; ^{1}H NMR (300 MHz, DMSO) δ (ppm): 7.03–7.04 (m, 1H), 6.93–6.94 (m, 1H), 6.72–6.73 (m, 4H), 5.60–5.62 (m, 1H), 5.46–5.49 (m, 1H), 3.77–3.78 (m, 1H), 3.63 (s, 6H), 3.54–3.61 (m, 2H), 3.43–3.44 (m, 2H), 3.23–3.24 (m, 1H), 1.40–1.48 (m, 4H), 0.70 (t, J = 7 Hz, 6H); ^{13}C NMR (75 MHz, DMSO) δ (ppm): 176.5, 171.8, 155.2, 154.7, 1337.6, 1336.0, 126.5, 125.7, 114.0, 113.0, 112.6, 112.5, 109.2, 108.5, 76.2, 63.5, 58.9, 55.4, 55.3, 41.1, 40.6, 33.6, 20.4, 20.3, 11.1, 11.0. HRMS-ESI (m/z): Calcd for $C_{26}H_{30}N_2O_5S$, $[M + H]^+$: 483.19471, found: 483.19355.

(3*R*,4*R*,5*S*)-1′-Propyl-5′-chloro-spiro[4.3′]oxindole-spiro[5.3″]-1″-propyl-5″-chloro-oxindole tetrahydrothiophen-3-ol (3o). White solid, mp: 171–172 °C; 76% yield, $[\alpha]_D^{25}$ = +99.4 (c = 0.66, $CHCl_3$); (dr = 83 : 17, 69% ee for the major diastereomer). HPLC conditions: ee was determined by HPLC analysis (Chiralcel AD-H, hexane/i-PrOH = 80/20, 1.0 mL min^{-1}, 254 nm). Retention time: t_{major} = 10.25 min, t_{minor} = 23.88 min; ^{1}H NMR (300 MHz, DMSO) δ (ppm): 7.37–7.38 (m, 1H), 7.26–7.29 (m, 3H), 6.92–6.95 (m, 2H), 5.82–5.84 (m, 1H), 5.47–5.49 (m, 1H), 3.80–3.84 (m, 1H), 3.70–3.77 (m, 2H), 3.40–3.44 (m, 2H), 3.31–3.34 (m, 1H), 1.44–1.19 (m, 4H), 0.70 (t, J = 7 Hz, 6H); ^{13}C NMR (75 MHz, DMSO) δ (ppm): 176.4, 171.7, 143.3, 141.8, 129.7, 129.0, 127.0, 126.7, 126.0, 125.8, 124.7, 110.6, 110.0, 76.2, 63.3, 58.2, 41.4, 40.8, 33.4, 20.5, 20.4, 10.9, 10.8. HRMS-ESI (m/z): Calcd for $C_{24}H_{24}Cl_2N_2O_3S$, $[M + H]^+$: 491.09575, found: 491.09677.

(3*R*,4*R*,5*S*)-1′-Propyl-6′-chloro-spiro[4.3′]oxindole-spiro[5.3″]-1″-propyl-6″-chloro-oxindole-tetrahydrothiophen-3-ol (3p). White solid, mp: 170–171 °C; 71% yield, $[\alpha]_D^{25}$ = +72.9 (c = 0.40, $CHCl_3$); (dr > 20 : 1, 82% ee). HPLC conditions: ee was determined by HPLC analysis (Chiralcel OD-H, hexane/i-PrOH = 90/10, 1.0 mL min^{-1}, 254 nm). Retention time: t_{minor} = 8.46 min, t_{major} = 12.32 min; ^{1}H NMR (300 MHz, DMSO) δ (ppm) 7.37 (d, J = 8 Hz, 1H), 7.26 (d, J = 8 Hz, 1H), 7.00–7.05 (m, 4H),

5.75–5.77 (m, 1H), 5.44–5.51 (m, 1H), 3.74–3.80 (m, 1H), 3.47–3.62 (m, 4H), 3.27–3.30 (m, 1H), 1.42–1.49 (m, 4H), 0.75 (t, J = 7 Hz, 6H); ^{13}C NMR (75 MHz, DMSO) δ (ppm): 176.8, 172.1, 145.8, 144.2, 134.5, 133.9, 127.1, 125.9, 123.8, 122.9, 122.3, 121.5, 109.4, 108.8, 76.0, 63.0, 58.1, 41.3, 40.8, 33.4, 20.3, 20.2, 11.1, 11.0. HRMS-ESI (m/z): Calcd for $C_{24}H_{24}Cl_2N_2O_3S$, $[M + H]^+$: 491.09571, found: 491.09657.

(3*S*,4*S*,5*R*)-1′-Propyl-6′-chloro-spiro[4.3′]oxindole-spiro[5.3″]-1″-propyl-6″-chloro-oxindole-tetrahydrothiophen-3-ol (ent-3p). White solid, mp: 167–168 °C; 82% yield, $[\alpha]_D^{25}$ = −79.9 (c = 0.36, $CHCl_3$); (dr > 20 : 1, 82% ee). HPLC conditions: ee was determined by HPLC analysis (Chiralcel OD-H, hexane/i-PrOH = 90/10, 1.0 mL min^{-1}, 254 nm). Retention time: t_{minor} = 8.57 min, t_{major} = 12.23 min.

1′-Methyl-spiro[4.3′]oxindole-spiro[5.3″]1″-methyl-oxindole-tetrahydrothiophen-3-one (5). White solid, mp: 163–164 °C; 89% yield, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.42 (d, J = 8 Hz, 1H), 7.20–7.26 (m, 3H), 6.97–7.00 (m, 2H), 6.64 (d, J = 8 Hz, 1H), 4.01–4.24 (m, 2H), 3.14 (s, 3H), 3.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 202.8, 176.6, 168.9, 144.4, 143.8, 130.4, 129.9, 126.4, 125.2, 123.3, 123.3, 123.2, 122.9, 108.6, 108.3, 72.1, 58.2, 38.8, 26.4, 26.2. HRMS-ESI (m/z): Calcd for $C_{20}H_{16}N_2O_3S$, $[M + H]^+$: 365.09544, found: 365.09604.

1′-Octyl-spiro[4.3′]oxindole-spiro[5.3″]1″-octyl-oxindole-3-hydroxy-tetrahydrothiophen1,1-dioxide (6). White solid, mp: 190–191 °C; Quant. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.55 (d, J = 7 Hz, 1H), 7.43 (d, J = 7 Hz, 1H), 7.23–7.26 (m, 1H), 7.19–7.23 (m, 1H), 6.96–7.00 (m, 1H), 6.91–6.96 (m, 1H), 6.67 (t, J = 8 Hz, 2H), 5.64–5.66 (m, 1H), 4.33–4.38 (m, 1H), 4.10–4.17 (m, 1H), 3.67–3.75 (m, 2H), 3.50–3.58 (m, 2H), 2.29–2.39 (bs, 1H), 1.54–1.58 (m, 4H), 1.24–1.28 (m, 20H), 0.86–0.94 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 173.0, 172.1, 144.6, 143.9, 130.5, 129.5, 128.3, 124.9, 124.5, 123.1, 122.6, 118.8, 108.6, 108.6, 74.4, 62.8, 58.5, 40.3, 31.8, 29.2, 29.2, 29.1, 29.1, 27.4, 27.3, 26.9, 26.8, 22.6, 14.1. HRMS-ESI (m/z): Calcd for $C_{34}H_{46}N_2O_5S$, $[M + H]^+$: 595.32002, found: 595.31809.

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