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Note

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Direct Asymmetric Vinylogous Mannich Reaction of 3,4-dihalofuran-2(5H)-one with Aldimine Catalyzed by Quinine

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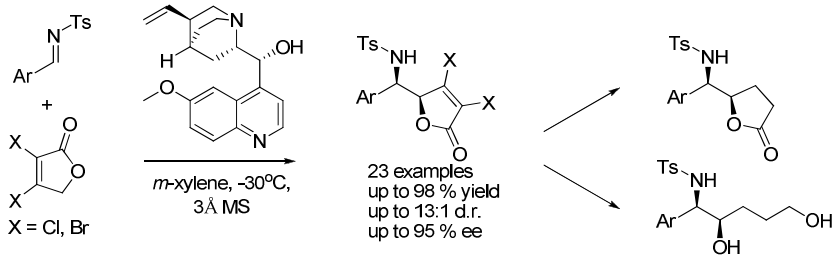


The direct asymmetric vinylogous Mannich reaction of 3,4-dihalofuran-2(5H)-one with aldimine catalyzed by quinine was firstly reported and γ-butenolides have been obtained in excellent yield (up to 98%) and enantioselectivities (up to 95% ee). The synthetic applications of this protocol are demonstrated in the preparations of γ-substituted amino butyrolactones and vicinal amino alcohols.

Mannich reaction is an important and effective carbon-carbon bond formation reaction for β-amino functional moieties.[1] Particularly, the vinylogous Mannich reaction，a vinyl insertion Mannich reaction, generates a new C-C bond and leads to the formation of δ-amino α,β-unsaturated carbonyl compounds

which are widely existed in natural compound skeletons.[2] The donors of which mainly include acyclic silyl dienolate,[3] 2-silyloxyfurans,[4] dicyanoalkylidenes,[5] and γ-butyrolactams.[6] Typically, the utilization of 2-silyloxyfuran as the nucleophile for vinylogous Mannich reaction catalyzed by transition metal catalysts[4a-h] and chiral phosphoric acids[4i-j] has been well documented. However, the direct asymmetric vinylogous Mannich reaction of 2-(5H)furanone derivatives has not drawn enough attentions until Shibasaki's group reported the first direct asymmetric Mannich-type reactions of γ-butenolides catalyzed by a chiral lanthanumpyridine bisoxazolinecomplex.[7] To the best of our knowledge, the small molecular catalytic direct asymmetric Mannich reaction of furanones has not been reported, partially because of the relative lower activities of furanones. In 2010, Terada[8] reported the first asymmetric direct vinylogous aldol reaction of 3,4-dihalofuran-2(5H)-one with aldehydes catalyzed by chiral guanidines, in which 3,4-dihalofuran-2(5H)-one showed extremely high reactivity. Based on those backgrounds, we envisioned that the asymmetric direct vinylogous Mannich reaction of 3,4-dihalofuran-2(5H)-one with imines may be realized by an organocatalyst and afforded the chiral 3,4-dihalofuran-2(5H)-one motifs with multifunctional groups and can be used as versatile building blocks after successive transformations.[9]

Cinchona alkaloids are widely used chiral organic catalysts for asymmetric synthesis.[10] In our previous work,[11] we have successfully applied their derivatives in some asymmetric catalyses. Inspired by those achievements, we recognized that the tertiary amine group would activate the 3,4-dihalofuran-2(5H)-one and the hydroxyl group would activate the imine through hydrogen bondings. Thus the synergistic interactions would ensure high stereoselectivity in this transformation, affording the corresponding optically active products via a postulated transition state (TS) as shown in Figure 1. As a part of our continuing interests in asymmetric syntheses,[12] herein, we wish to report the first asymmetric direct vinylogous Mannich reaction of 3,4-dihalofuran-2(5H)-one with aldimine catalyzed by quinine.

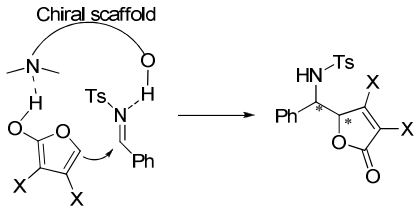
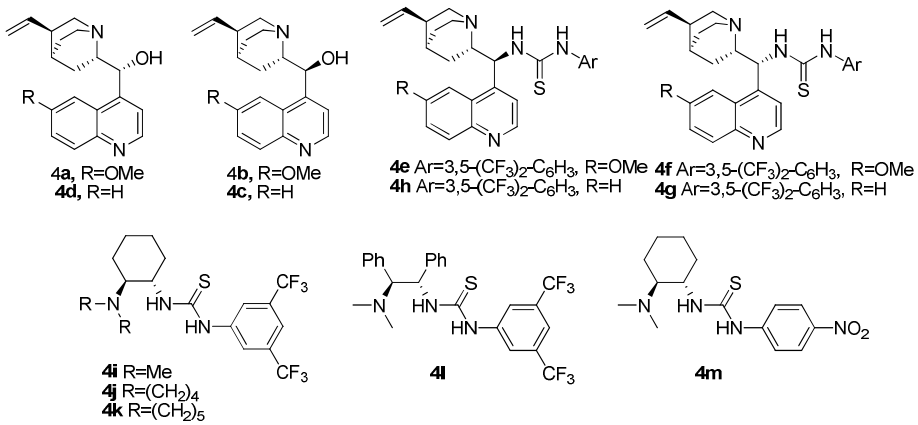


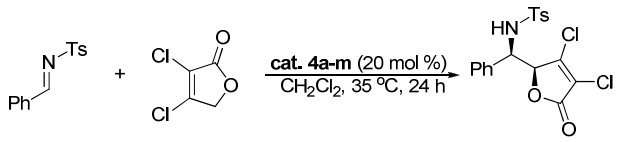
Figure 1. Proposed transition state

To devise a model reaction, imine **1a** and 3,4-dichlorofuran-2(5H)-one **2a** were selected as reactants to screen the asymmetric reaction conditions and the results were summarized in Table 1. The reaction was performed smoothly in CH_2Cl_2 with 20 mol % catalyst **4a** at 35 ^oC and afforded excellent yield and moderate enantioselectivitiy (91% yield, 41% ee; Table 1, entry 1). While other cinchona alkaloids **4b-4d** gave relative lower yields and enantioselectivities (76%-85% yield, 6%-24% ee, Table 1, entries 2-4). To further improve the results, a series of bifunctional tertiary amine-thiourea catalysts **4e-m** were also evaluated, and the products were obtained in poor ee values (6%-23% ee, Table 1, entries 5-13). Based on the screenings of catalysts, catalyst **4a**, with 91% yield, 41% ee and a diastereomeric ratio (dr) of 1.2:1 was selected for further optimization (Table 1, entry 1).



Scheme 1. catalysts **4a**–**m** investigated.

Table 1. Screenings of catalyst for the vinylogous Mannich reaction of **2a** with **1a**[a]



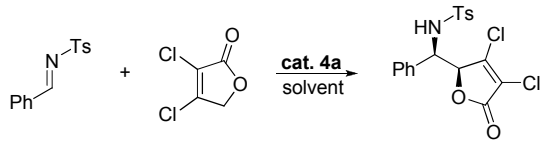
1a **2a** **3a**

entry	catalyst	yield[b] (%)	dr[c] (%)	ee[d] (%)
1	**4a**	91	1.2:1	41/40
2	**4b**	85	1.2:1	-24/-27
3	**4c**	85	1.5:1	-6/-10
4	**4d**	76	1.2:1	19/24
5	**4e**	77	1.3:1	-9/-2
6	**4f**	71	1.2:1	7/-4
7	**4g**	61	1.2:1	8/-8
8	**4h**	74	1.3:1	-23/-13
9	**4i**	76	1.7:1	-23/-10
10	**4j**	66	1.9:1	-12/-8
11	**4k**	32	2.9:1	-13/-20
12	**4l**	73	1.3:1	-13/-2
13	**4m**	68	1.2:1	-6/-9

[a] Reactions were performed with 0.1 mmol of **1a**, 0.2 mmol of **2a** in 1 mL of dichloromethane at 35 °C for 24h. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Enantiomeric excess determined by chiral HPLC.

With 20 mol % **4a** as the catalyst, solvents, temperature and additives were screened, and the results were listed in Table 2. Solvents dramatically affected the ee values (Table 2, entries 1-7). Aprotic solvents, such as toluene, mesitylene, *m*-xylene and tetrahydrofuran resulted in higher enantioselectivities than protonic solvent (Table 2, entries 1-6 vs entry 7). Relative strong polar solvents led to lower ee values (Table 2, entries 4-7). In the presence of 3Å MS, *m*-xylene afforded 63% ee (Table 2, entry 10). Lowering the temperature to -30 °C resulted in an increase of enantioselectivity (77% ee, Table 2, entry 14). When 10 mol% of **4a** used, the ee value slightly raised to 81% in 95% yield (Table 2, entry 16). The concentration of the substrates was also screened and **3a** was obtained in 85% ee and 85% yield in 2 mL *m*-xylene (Table 2, entry 19). Based on the above results, 0.1 mmol **1a** and 0.2 mmol **2a** in 2 mL *m*-xylene with 10 mol % catalyst **4a** at -30 °C were established as optimal reaction conditions.

Table 2. Screening of optimal reaction conditions for the vinylogous Mannich reaction of **1a** with **2a**[a]



1a 2a 3a

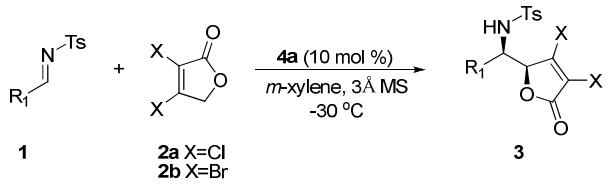
entry	solvent	t	T (^{o}C)	yield[b] (%)	dr[c] (%)	ee[d] (%)
1	toluene	24h	35	71	1.2:1	47
2	mesitylene	24h	35	75	1:1	44
3	*m*-xylene	24h	35	67	1.2:1	44
4	1,2-dichloroethane	24h	35	71	1.3:1	33
5	tetrahydrofuran	24h	35	76	1.4:1	27
6	acetonitrile	24h	35	73	2.2:1	11
7	methanol	24h	35	91	3:1	2
8[e]	toluene	24h	35	99	1.2:1	53
9[e]	mesitylene	24h	35	82	1.8:1	54
10[e]	*m*-xylene	24h	35	72	1.3:1	63
11[e]	*m*-xylene	69h	0	99	2.2:1	64
12[e]	*m*-xylene	52h	-10	99	2.3:1	68
13[e]	*m*-xylene	71h	-20	98	2.4:1	74
14[e]	*m*-xylene	76h	-30	99	2.0:1	77
15[e, f]	*m*-xylene	71h	-30	94	1.9:1	82
16[e, g]	*m*-xylene	71h	-30	95	3.2:1	81
17[e, h]	*m*-xylene	71h	-30	71	4.9:1	84
18[e, g, i]	*m*-xylene	144h	-30	88	6.0:1	84
19[e, g, j]	*m*-xylene	168h	-30	85	6.5:1	85

[a] Reactions were performed with 0.1 mmol of **1a**, 0.2 mmol of **2a,** 20 mol % **4a** in 1 mL solvent. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Enantiomeric excess of the major diastereoisomer determined by chiral HPLC. [e] 30 mg 3ÅMS was added. [f] with 15 mol % **4a**. [g] with 10 mol % **4a**. [h] with 5 mol % **4a**. [i] The reaction was carried out in 1.5 mL *m*-xylene. [j] The reaction was carried out in 2.0 mL *m*-xylene.

Under the optimized reaction conditions, the substrate scope of the reaction was further explored to test the generality of this protocol (Table 3). A series of aldimines derived from aromatic aldehydes bearing electron-withdrawing and electron-donating groups were selected and gave the adducts in moderate to high yields (37%-98%), moderate diastereoselectivities (3:1-13:1), and excellent ee (up to 95% ee). Aldimines with ortho-substitutents afforded slightly higher enantioselectivities than their para-substituted counterparts (Table 3, entries 4-6 vs 8-10). When meta-chloride substituted aldimine used, no product was detected (Table 3, entry 13). 4-OMe aromatic aldimine gave moderate yield and the highest enantioselectivity (54% yield, 95% ee; Table 3, entry 2). The optimized protocol was also expanded to 3,4-dibromofuran-2(5H)-one

2b, and moderate to good yields and excellent enantioselectivities were obtained (41%-95% yield, 84%-94% ee, Table 3, entries 14-24).

Table 3. Direct Catalytic Asymmetric vinylogous Mannich Reactions of Imines **1** and γ-Dihalobutenolides **2**[a]



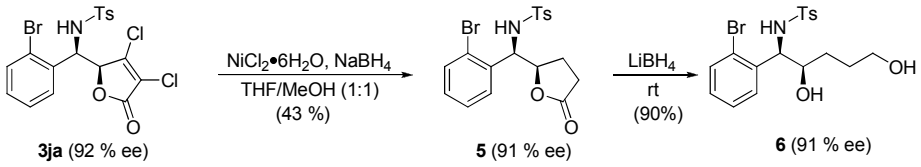
1 **2a** X=Cl **2b** X=Br **3**

entry	R_1	**1**	**2**	**3**	t	yield[b] (%)	dr	ee[e] (%)
1	Ph	**1a**	**2a**	**3aa**	7d	85	6.5:1[c]	85
2	4-MeO-Ph	**1b**	**2a**	**3ba**	7d	54	4:1[c]	95
3	4-Me-Ph	**1c**	**2a**	**3ca**	7d	89	4:1[d]	80
4	4-Br-Ph	**1d**	**2a**	**3da**	7d	66	6:1[d]	86
5	4-Cl-Ph	**1e**	**2a**	**3ea**	7d	81	7:1[d]	84
6	4-F-Ph	**1f**	**2a**	**3fa**	11d	60	13:1[d]	86
7	4-NO_2-Ph	**1g**	**2a**	**3ga**	7d	37	7:1[c]	88
8	2-F-Ph	**1h**	**2a**	**3ha**	10d	86	5:1[d]	90
9	2-Cl-Ph	**1i**	**2a**	**3ia**	8d	86	8:1[d]	91
10	2-Br-Ph	**1j**	**2a**	**3ja**	7d	98	12:1[d]	92
11	2-naphthyl	**1k**	**2a**	**3ka**	7d	95	10:1[d]	84
12	3-Me-Ph	**1l**	**2a**	**3la**	7d	95	4:1[d]	85
13	3-Cl-Ph	**1m**	**2a**	**3ma**	7d	nd	-	-
14	Ph	**1a**	**2b**	**3ab**	11d	80	3:1[d]	89
15	4-MeO-Ph	**1b**	**2b**	**3bb**	13d	44	6:1[c]	90
16	4-Me-Ph	**1c**	**2b**	**3cb**	11d	55	5:1[d]	86
17	4-Br-Ph	**1d**	**2b**	**3db**	10d	41	3:1[d]	88
18	4-Cl-Ph	**1e**	**2b**	**3eb**	10d	41	7:1[d]	88
19	4-F-Ph	**1f**	**2b**	**3fb**	10d	51	4:1[d]	94
20	2-F-Ph	**1g**	**2b**	**3gb**	8d	90	4:1[d]	91
21	2-Cl-Ph	**1h**	**2b**	**3hb**	7d	90	4:1[d]	94
22	2-Br-Ph	**1i**	**2b**	**3ib**	8d	94	10:1[d]	93
23	2-naphthyl	**1j**	**2b**	**3jb**	11d	95	11:1[d]	88
24	3-Me-Ph	**1k**	**2b**	**3kb**	11d	76	4:1[d]	84

[a] Reactions performed with 0.1 mmol of **1**, 0.2 mmol of **2**, **4a** (10 mol %), 3Å MS (30 mg) in 2.0 mL *m*-xylene at -30 °C for 7-13 days. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Determined by isolated yield of two diastereoisomers. [e] Enantiomeric excess of the major diastereoisomer determined by chiral HPLC.

Vinylogous Mannich products **3**, with multiple functional groups and potential chiral centers, may be easily transformed to γ-butyrolactones[13] which were the core structure of sapinofuranones.[14] Importantly, γ-butyrolactone derivatives could be readily converted to vicinal amino alcohols,[15] important pharmaceutical

skeletons widely exist in protease inhibitors such as ritonavir[16a] and swainsonine.[16b] Typically as shown in Scheme 2, reduction and dehalogation of **3ja** afforded the chiral γ-butyrolactone **5**. After further reduction of **5** with $LiBH_4$ at room temperature, vicinal amino alcohol **6** was obtained in almost unchanged ee value (Scheme 2). The absolute configuration was determined by an X-ray analysis of the single crystal of **6**, which was assigned as (C7R, C8R)(see supporting information).



Scheme 2. Preparation of chiral γ-substituted butyrolactone **5** and vicinal amino alcohol **6**

In summary, we have developed a direct vinylogous Mannich reaction of aldimines with 3,4-dihalofuran-2(5H)-one catalyzed by quinine. A series of γ-butenolides derivatives were obtained in good yields (up to 98% yield) and enantioselectivities (up to 95% ee), which were easily transformed to some chiral pharmaceutical intermediates γ-butyrolactones and vicinal amino alcohols.

Experimental Section

General Procedure for Vinylogous Mannich Reaction

Catalyst **4a** (10 mol %), 3Å MS (30 mg) and imine **1** (0.1 mmol) were dissolved in 2mL *m*-xylene at -30 ^{o}C for 0.5h. Substrate **2** (0.2 mmol) was added to the solution and stirred for 7-13d. The reaction was monitored by TLC analysis. The reaction mixture was directly subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate) to furnish the corresponding products **3**.

N-((R)-((S)-3,4-dichloro-5-oxo-2,5-dihydrofuran-2-yl)(phenyl)methyl)-4-methylbenzenesulfonamide ***(3aa)***

White solid, mp 148-149 ^{o}C; $[\alpha]_D^{20}$=-85 (c 0.1, CH_2Cl_2), yield 85 %; 6.5:1 dr, Enantiomeric excess: 85 %, determined by HPLC (Chiralcel AY-H column, hexane/ethanol /TFA= 55/45/0.1%, flow rate 0.7 mL/min,

UV detection at 220 nm), t_R (major) = 14.1 min, t_R (minor) = 24.4 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.2 Hz, 2H), 7.24-7.15 (m,5H), 7.10 (d, *J* = 8.0 Hz, 2H), 5.54 (d, *J* = 10.0 Hz, 1H), 5.09 (d, *J* = 1.6 Hz, 1H), 4.97 (dd, *J* = 10.0 Hz, 1.5 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR(75 MHz, $CDCl_3$) δ 164.9, 149.8, 143.6, 136.9, 135.9, 129.5, 129.4, 128.9, 128.6, 126.9, 122.8, 84.4, 56.6, 21.4; HRMS (ESI) Calcd. for $C_{18}H_{15}C_{l2}NNaO_4S$ $[M+Na]^+$: 433.9985; Found: 433.9991; IR (KBr) ν_{max}/cm^{-1}: 3295, 2923, 1769, 1627, 1337, 1239, 1162, 701.

*N-((R)-((S)-3,4-dichloro-5-oxo-2,5-dihydrofuran-2-yl)(4-methoxyphenyl)methyl)-4-methylbenzenesulfona mide (**3ba**)* White solid, $[\alpha]_D^{20}$=-76 (c 0.1, CH_2Cl_2), yield 54 %; 4:1 dr, Enantiomeric excess: 95 %, determined by HPLC (Chiralcel OD-H column, hexane/*i*-propanol = 90/10, flow rate 1 mL/min, UV detection at 220 nm), t_R (minor) = 26.1 min, t_R (major) = 39.9 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.2 Hz, 2H), 7.11-7.07 (m, 4H), 6.73 (d, *J* = 8.7 Hz, 2H), 5.59 (d, *J* = 9.8 Hz, 1H), 5.08 (d, *J* = 1.7 Hz, 1H), 4.91 (dd, *J* = 9.7Hz, 1.3Hz, 1H), 3.75 (s, 3H), 2.33 (s, 3H); ^{13}C MR (75 MHz, $CDCl_3$) δ 165.9, 160.7, 150.8, 149.6, 144.5, 138.0, 130.5, 129.3, 128.0, 124.3, 115.2, 85.5, 57.2, 56.2, 22.4; HRMS (EI) Calcd. for $C_{19}H_{17}NO_5SCl_2$ $[M]^+$: 441.0205; Found: 441.0247; IR (KBr) ν_{max}/cm^{-1}: 3296, 2936, 1778, 1629, 1334, 1257, 1161, 734.

*N-((R)-((S)-3,4-dichloro-5-oxo-2,5-dihydrofuran-2-yl)(p-tolyl)methyl)-4-methylbenzenesulfonamide (**3ca**)* White solid, mp 163-164 °C; $[\alpha]_D^{20}$=-160 (c 0.2, CH_2Cl_2), yield 89 %; 4:1 dr, Enantiomeric excess: 80 %, determined by HPLC (Chiralcel AY-H column, hexane/ethanol/TFA = 55/45/0.1%, flow rate 0.7 mL/min, UV detection at 220 nm), t_R (minor) = 20.5 min, t_R (major) = 14.7 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.2 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.06-7.00 (m, 4H), 5.47 (d, *J* = 9.7 Hz, 1H), 5.08 (d, *J* = 1.7 Hz, 1H), 4.92 (d, *J* = 10.0 Hz), 2.34 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 149.8, 143.5, 138.6, 136.9, 132.7, 129.5, 129.4, 127.0, 126.8, 122.7, 84.4, 56.4, 21.4; HRMS (EI) Calcd. for

$C_{19}H_{17}NO_4SCl_2$ $[M]^+$: 425.0255; Found: 425.0246; IR (KBr) ν_{max}/cm^{-1}: 3316, 2967, 1770, 1622, 1324, 1247, 1160, 706.

N-((R)-(4-bromophenyl)((S)-3.4-dichloro-5-oxo-2,5-dihydrofuran-2-yl)methyl)-4-methylbenzenesulfonamide ***(3da)*** White solid, mp 186-187 °C; $[\alpha]_D^{20}$=-98 (c 0.1, CH_2Cl_2), yield 66 %; 6:1 dr, Enantiomeric excess: 86 %, determined by HPLC (Chiralcel OD-H column, hexane/*i*-propanol = 90/10, flow rate 1 mL/min, UV detection at 220 nm), t_R (minor) = 11.0 min, t_R (major) = 21.2 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.12-7.03 (m, 4H), 6.82 (d, *J* = 10.3 Hz, 1H), 5.04 (d, *J* = 1.1 Hz, 1H), 4.94 (d, *J* = 10.3 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 149.7, 143.8, 136.7, 134.6, 131.9, 129.7, 129.5, 128.7, 126.9, 122.7, 84.3, 56.1, 21.4; HRMS (ESI) Calcd. for $C_{18}H_{18}BrCl_2N_2O_4S$ $[M+NH_4]^+$: 506.9542; Found: 506.9539; IR (KBr) ν_{max}/cm^{-1}: 3316, 2968, 1770, 1621, 1326, 1247, 1163, 722.

N-((R)-(4-chlorophenyl)((S)-3,4-dichloro-5-oxo-2,5-dihydrofuran-2-yl)methyl)-4-methylbenzenesulfonamide ***(3ea)*** White solid, mp 182-183 °C; $[\alpha]_D^{20}$=-105 (c 0.1, CH_2Cl_2), yield 81 %; 7:1 dr, Enantiomeric excess: 84 %, determined by HPLC (Chiralcel OD-H column, hexane/*i*-propanol = 80/20, flow rate 1 mL/min, UV detection at 220 nm), t_R (minor) = 10.3 min, t_R (major) = 19.8 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.2 Hz, 2H), 7.18-7.07 (m, 6H), 5.87 (d, *J* = 10.2 Hz, 1H), 5.04 (d, *J* = 1.4 Hz, 1H) 4.95 (d, *J* = 10.2 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 149.6, 143.7, 136.8, 134.6, 134.1, 129.4, 128.9, 128.4, 126.8, 122.8, 84.3, 56.0, 21.3; HRMS (EI) Calcd. for $C_{18}H_{14}NO_4SCl_3$ $[M]^+$: 444.9709; Found: 444.9721; IR (KBr) ν_{max}/cm^{-1}: 3265, 2924, 1760, 1628, 1340, 1243, 1159, 742.

N-((R)-((S)-3,4-dichloro-5-oxo-2,5-dihydrofuran-2-yl)(4-fluorophenyl)methyl)-4-methylbenzenesulfonamide ***(3fa)*** White solid, mp 138-139 °C; $[\alpha]_D^{20}$=-84 (c 0.1, CH_2Cl_2), yield 60 %; 13:1 dr, Enantiomeric excess: 86 %, determined by HPLC (Chiralcel OD-H column, hexane/ethanol = 85/15, flow rate 1 mL/min, UV detection at 220 nm), t_R (minor) = 13.0 min, t_R (major) = 23.2 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, *J*

= 8.2 Hz, 2H), 7.19-7.14(m, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.91-6.86 (m, 2H), 5.87 (d, *J* = 10.2 Hz, 1H), 5.05 (d, *J* = 1.6 Hz, 1H), 4.97 (d, *J* = 10.2 Hz, 1H), 2.35 (s, 3H); 13 C NMR (75 MHz, DCl_3) δ 165.1, 160.9 ($J_{C\text{-}F}$ = 247.0 Hz), 149.8, 136.9, 131.7, 129.4, 129.0 ($J_{C\text{-}F}$ = 8.3 Hz), 128.8, 126.9, 122.7, 115.9 ($J_{C\text{-}F}$ = 21.6 Hz), 84.5, 56.0, 21.4; HRMS (ESI) Calcd. for $C_{18}H_{14}Cl_2FNNaO_4S$ $[M+Na]^+$: 451.9897; Found: 451.9902; IR (KBr) ν_{max}/cm^{-1}: 3298, 2959, 1766, 1631, 1338, 1230, 1158, 686.

N-((R)-((S)-3,4-dichloro-5-oxo-2,5-dihydrofuran-2-yl)(4-nitrophenyl)methyl)-4-methylbenzenesulfonamide ***(3ga)*** Light yellow solid, yield 37 %; 7:1 dr, Enantiomeric excess: 88 %, determined by HPLC (Chiralcel OD-H column, hexane/*i*-propanol = 80/20, flow rate 1 mL/min, UV detection at 220 nm), t_R (minor) = 25.4 min, t_R (major) = 58.9 min. ^{1}H NMR (300 MHz, DMSO) δ 8.95 (d, *J* = 10.1 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.6 Hz, 1H), 7.47 (m, 2H), 7.13 (m, 1H), 5.60 (d, J = 2.4 Hz, 1H), 5.19 (dd, J = 10.2Hz, 2.1 Hz, 1H), 5.09 (m, 1H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 164.4, 147.0, 143.7, 142.6, 141.4, 137.7, 129.2, 126.3, 125.5, 122.8, 84.0, 57.1, 20.8; HRMS (ESI) Calcd. for $C_{18}H_{14}Cl_2N_2NaO_6S$ $[M+Na]^+$: 478.9842; Found: 478.9837; IR (KBr) ν_{max}/cm^{-1}: 3404, 2859, 1789, 1635, 1336, 1233, 1159, 756.

N-((3,4-dichloro-5-oxo-2,5-dihydrofuran-2-yl)(2-fluorophenyl)methyl)-4-methylbenzenesulfonamide ***(3ha)*** White solid, mp 150-151 ^{o}C; $[\alpha]_D^{20}$=-96 (c 0.1, CH_2Cl_2), yield 86 %; 5:1 dr, Enantiomeric excess: 90 %, determined by HPLC (Chiralcel OD-H column, hexane/*i*-propanol = 85/15, flow rate 1 mL/min, UV detection at 220 nm), t_R (minor) = 13.2 min, t_R (major) =14.1 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.7 Hz, 2H), 7.22-7.18 (m, 2H), 7.08 (d, *J* = 8.1 Hz, 2H), 6.98-6.90 (m, 2H), 5.96 (br, 1H), 5.38 (d, *J* = 10.7 Hz, 1H), 5.04 (d, *J* = 1.6 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 157.6 ($J_{C\text{-}F}$ =244.5 Hz), 149.8, 143.6, 136.7, 130.3 ($J_{C\text{-}F}$ = 8.3 Hz), 129.4, 128.3, 126.9, 126.4, 124.7, 122.9, 115.6 ($J_{C\text{-}F}$ = 21.5 Hz), 84.0, 50.3, 21.3; HRMS (ESI) Calcd. for $C_{18}H_{14}Cl_2FNNaO_4S$ $[M+Na]^+$: 451.9897; Found: 451.9897; IR (KBr) ν_{max}/cm^{-1}: 3295, 2925, 1782, 1631, 1343, 1242, 1165, 740.

N-((2-chlorophenyl)(3,4-dichloro-5-oxo-2,5-dihydrofuran-2-yl)methyl)-4-methylbenzenesulfonamide ***(3ia)***

White solid, mp 170-171 °C; $[\alpha]_D^{20}$=-96 (c 0.1, CH_2Cl_2), yield 86 %; 8:1 dr, Enantiomeric excess: 91 %, determined by HPLC (Chiralcel OD-H column, hexane/*i*-propanol = 90/10, flow rate 1 mL/min, UV detection at 220 nm), t_R (minor) = 17.6 min, t_R (major) =20.6 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.3 Hz, 2H), 7.29-7.28 (m, 1H), 7.21-7.15 (m, 2H), 7.10-7.02 (m, 3H), 6.22 (d, *J* = 10.9 Hz, 1H), 5.62 (d, *J* = 11.0 Hz, 1H), 5.06 (d, *J* = 1.5 Hz, 1H), 2.28 (s, 3H); ^{13} C NMR (75 MHz, $CDCl_3$) δ 165.4, 150.1, 143.5, 136.7, 133.1, 131.9, 129.5, 129.4, 129.3, 128.3, 127.4, 126.8, 122.5, 83.5, 52.8, 21.3; HRMS (EI) Calcd. for $C_{18}H_{14}NO_4SCl_3$ $[M]^+$: 444.9709; Found: 444.9697; IR (KBr) ν_{max}/cm^{-1}: 3283, 2948, 1785, 1630, 1243, 1163, 736, 709.

N-((2-bromophenyl)(3,4-dichloro-5-oxo-dihydrofuran-2-yl)methyl)-4-methylbenzenesulfonamide ***(3ja)***

White solid, mp 178-179 °C; $[\alpha]_D^{20}$=-38 (c 0.1, CH_2Cl_2), yield 98 %; 12:1 dr, Enantiomeric excess: 92 %, determined by HPLC (Chiralcel OD-H column, hexane/ethanol= 90/10, flow rate 1 mL/min, UV detection at 220 nm), t_R (minor) = 10.5 min, t_R (major) =14.7 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.1 Hz, 2H), 7.46-7.43 (m, 1H), 7.20-7.18 (m, 1H), 7.10-7.00 (m, 4H), 6.35 (d, *J* = 10.9 Hz, 1H), 5.84 (d, *J* = 11.0 Hz, 1H), 5.07 (d, *J* = 1.2 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 150.3, 143.3, 136.6, 134.4, 132.6, 129.7, 129.3, 128.6, 128.0, 126.8, 126.4, 122.2, 83.5, 55.2, 21.3; HRMS (EI) Calcd. for $C_{18}H_{14}NO_4SCl_2Br$ $[M]^+$: 488.9204; Found: 488.9219; IR (KBr) ν_{max}/cm^{-1}: 3286, 2946, 1785, 1630, 1348, 1243, 1163, 658.

N-((3,4-dichloro-5-oxo-2,5-dihydrofuran-2-yl)(naphthalene-2-yl)methyl)-4-methylbenzenesulfonamide ***(3ka)*** White solid, mp 168-169 °C; $[\alpha]_D^{20}$=-12 (c 0.1, CH_2Cl_2), yield 95 %; 10:1 dr, Enantiomeric excess: 84 %, determined by HPLC (Chiralcel OD-H column, hexane/*i*-propanol= 90/10, flow rate 1 mL/min, UV detection at 220 nm), t_R (minor) = 22.6 min, t_R (major) =58.2 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* =

8.3 Hz, 1H), 7.86 (d, *J* = 7.9 Hz, 1H), 7.73 (d, *J* = 8.1Hz, 1H), 7.60-7.50 (m, 2H), 7.42-7.34 (m, 3H), 7.28-7.23 (m, 1H), 6.83 (d, *J* = 8.0 Hz, 2H), 6.43 (d, *J* = 10.5 Hz, 1H), 5.98 (d, *J* = 10.7 Hz, 1H), 5.14 (s, 1H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 150.0, 143.2, 136.8, 133.6, 130.9, 129.5, 129.3, 129.1, 128.9, 127.1, 126.7, 125.9, 125.3, 125.0, 122.6, 121.0, 84.0, 51.6, 21.2; HRMS (EI) Calcd. for $C_{22}H_{17}NO_4SCl_2$ $[M]^+$: 461.0255; Found: 461.0256; IR (KBr) ν_{max}/cm^{-1}: 3298, 2920, 1785, 1634, 1339, 1241, 1163, 735.

N-((3,4-dichloro-5-oxo-2,5-dihydrofuran-2-yl)(m-tolyl)methyl)-4-methylbenzenesulfonamide ***(3la)***

White solid, mp 75-76 °C; $[\alpha]_D^{20}$=-95 (c 0.1, CH_2Cl_2), yield 95 %; 4:1 dr, Enantiomeric excess: 85 %, determined by HPLC (Chiralcel OD-H column, hexane/ethanol= 95/5, flow rate 1 mL/min, UV detection at 220 nm), t_R (minor) = 16.5 min, t_R (major) =25.4 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.1 Hz, 2H), 7.15-7.10 (m, 3H), 7.09-6.99 (m, 2H), 6.88 (s, 1H), 5.50 (brs, 1H), 5.09 (d, *J* = 1.4Hz, 1H), 4.93 (dd, *J* = 10.0 Hz, 1.1 Hz, 1H), 2.35 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 149.9, 143.4, 138.6, 136.9, 135.6, 129.4, 129.3, 128.8, 127.6, 126.9, 123.9, 122.7, 84.5, 56.5, 21.3, 21.1; HRMS (EI) Calcd. for $C_{19}H_{17}NO_4SCl_2$ $[M]^+$: 425.0255; Found: 425.0276; IR (KBr) ν_{max}/cm^{-1}: 3281, 2923, 1785, 1631, 1339, 1234, 1162, 713.

N-((3,4-dibromo-5-oxo-2,5-dihydrofuran-2-yl)(phenyl)methyl)-4-methylbenzenesulfonamide ***(3ab)*** White solid, mp 116-117 °C; $[\alpha]_D^{20}$=-86 (c 0.1, CH_2Cl_2), yield 80 %; 3:1 dr, Enantiomeric excess: 89 %, determined by HPLC (Chiralcel OD-H column, hexane/*i*-propanol= 85/15, flow rate 1 mL/min, UV detection at 220 nm), t_R (minor) = 14.9 min, t_R (major) =19.4 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.2 Hz, 2H), 7.24-7.11 (m, 5H), 7.08 (d, *J* = 8.0 Hz, 2H), 5.36 (d, *J* = 10.1 Hz, 1H), 5.09 (d, *J* = 1.6 Hz, 1H), 5.02 (dd, *J* = 10.1 Hz, 1.5Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 145.4, 143.5, 137.1, 136.0, 130.8, 129.4, 128.9, 128.6, 127.0, 116.5, 87.0, 56.9, 21.4; HRMS (ESI) Calcd. for $C_{18}H_{15}Br_2NNaO_4S$ $[M+Na]^+$:

521.8981; Found: 521.8993; IR (KBr) ν_{max}/cm^{-1}: 3293, 2919, 1758, 1605, 1336, 1214, 1161, 702.

N-((3,4-dibromo-5-oxo-2,5-dihydrofuran-2-yl)(4-methoxyphenyl)methyl)-4-methylbenzenesulfonamide ***(3bb)*** White solid, yield 44 %; 6:1 dr, Enantiomeric excess: 90 %, determined by HPLC (Chiralcel AY-H column, hexane/ethanol/TFA= 55/45/0.1%, flow rate 0.6 mL/min, UV detection at 220 nm), t_R (minor) = 22.9 min, t_R (major) =47.9 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.50 (m, 4H), 6.91 (d, *J* =8.6 Hz, 2H), 6.64 (d, *J* = 8.7 Hz, 2H), 5.09 (d, *J* = 1.7 Hz, 1H), 4.97-4.91 (m, 2H), 3.72 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 145.5, 143.5, 137.1, 129.5, 128.3, 126.9, 123.4, 116.6, 114.2, 87.1, 58.1, 55.3, 21.4; HRMS (ESI) Calcd. for $C_{19}H_{17}Br_2NNaO_5S$ $[M+Na]^+$: 551.9086; Found: 551.9090; IR (KBr) ν_{max}/cm^{-1}: 3294, 2935, 1755, 1607, 1334, 1257, 1159, 733.

N-((R)-((S)-3,4-dibromo-5-oxo-2,5-dihydrofuran-2-yl)(p-tolyl)methyl)-4-methylbenzenesulfonamide ***(3cb)*** White solid, mp 166-167 ^oC; $[\alpha]_D^{20}$=-92 (c 0.1, CH_2Cl_2), yield 55 %; 5:1 dr, Enantiomeric excess: 86 %, determined by HPLC (Chiralcel OD-H column, hexane/ethanol= 92/8, flow rate 1 mL/min, UV detection at 220 nm), t_R (minor) = 15.4 min, t_R (major) =24.4 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.2 Hz, 2H), 7.09-6.99 (m, 6H), 5.60 (d, *J* = 10.0 Hz, 1H), 5.06 (d, *J* = 1.5Hz, 1H), 4.97 (d, *J* = 10.1 Hz, 1H), 2.33 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 145.5, 143.3, 138.4, 137.0, 132.9, 129.4, 129.3, 127.0, 126.8, 116.3, 87.2, 56.7, 21.4, 21.0; HRMS (EI) Calcd. for $C_{19}H_{17}NO_4SBr_2$ $[M]^+$: 512.9245; Found: 512.9232; IR (KBr) ν_{max}/cm^{-1}: 3315, 2960, 1763, 1600, 1323, 1224, 1162, 680.

N-((R)-(4-bromophenyl)(S)-3,4-dibromo-5-oxo-2,5-dihydrofuran-2-yl)methyl)-4-methylbenzenesulfonamide ***(3db)*** White solid, mp 201-202 ^oC; $[\alpha]_D^{20}$=-74 (c 0.1, CH_2Cl_2), yield 41 %; 3:1 dr, Enantiomeric excess: 88 %, determined by HPLC (Chiralcel OD-H column, hexane/ethanol= 92/8, flow rate 1 mL/min, UV detection at 220 nm), t_R (minor) = 20.2 min, t_R (major) =38.4 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45(d, *J* = 8.3 Hz, 2H), 7.33-7.30 (m, 2H), 7.09-7.04 (m, 4H), 5.85 (d, *J* = 10.3 Hz, 1H), 5.03 (d, *J* = 1.6 Hz, 1H), 4.98

(dd, *J* = 10.4 Hz, 1.4Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 145.3, 143.7, 136.8, 134.8, 131.9, 129.4, 128.8, 127.0, 122.7, 116.4, 87.0, 56.5, 21.4; HRMS (ESI) Calcd. for $C_{18}H_{14}Br_3NNaO_4S$ $[M+Na]^+$: 599.8086; Found: 599.8096; IR (KBr) ν_{max}/cm^{-1}: 3279, 2933, 1778, 1609, 1339, 1213, 1160, 723.

N-((R)-(4-chlorophenyl)(S)-3,4-dibromo-5-oxo-2,5-dihydrofuran-2-yl)methyl)-4-methylbenzenesulfonamid

*e **(3eb)*** White solid, mp 191-192 °C; $[\alpha]_D^{20}$=-98 (c 0.1, CH_2Cl_2), yield 41 %; 7:1 dr, Enantiomeric excess: 88 %, determined by HPLC (Chiralcel OD-H column, hexane/ethanol= 92/8, flow rate 1 mL/min, UV detection at 220 nm), t_R (minor) = 18.6 min, t_R (major) =35.7 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.5 Hz, 2H), 7.19-7.07 (m, 6H), 5.75 (d, *J* = 10.3 Hz, 1H), 5.03 (d, *J* = 1.5 Hz, 1H), 5.00 (d, *J* = 10.4 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 145.3, 143.7, 136.8, 134.6, 129.4, 129.0, 128.5, 127.0, 126.4, 116.5, 87.0, 56.4, 21.4; HRMS (ESI) Calcd. for $C_{18}H_{14}Br_2ClNNaO_4S$ $[M+Na]^+$: 555.8591; Found: 555.8588; IR (KBr) ν_{max}/cm^{-1}: 3296, 2921, 1759, 1602, 1338, 1217, 1158, 739.

N-((R)-((S)-3,4-dibromo-5-oxo-2,5dihydrofuran-2-yl)(4-fluorophenyl)methyl)-4-methylbenzenesulfonamid

*e **(3fb)*** White solid, mp 151-152 °C; $[\alpha]_D^{20}$=-85 (c 0.1, CH_2Cl_2), yield 51 %; 4:1 dr, Enantiomeric excess: 94 %, determined by HPLC (Chiralcel OD-H column, hexane/ethanol= 92/8, flow rate 1 mL/min, UV detection at 220 nm), t_R (minor) = 18.0 min, t_R (major) =31.7 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8. 2Hz, 2H), 7.22-7.17 (m, 2H), 7.12 (d, *J* = 8.1 Hz, 2H), 6.94-6.88 (m, 2H), 5.73 (d, *J* = 10.2 Hz, 1H), 5.06 (d, *J* = 1.6 Hz, 1H), 5.03 (d, *J* = 10.2 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 160.9 ($J_{C\text{-}F}$ = 246.9 Hz), 145.4, 143.6, 137.0, 131.9 ($J_{C\text{-}F}$ = 3.3 Hz), 129.4, 129.0 ($J_{C\text{-}F}$ = 8. 3Hz), 127.0, 116.4, 115.9 ($J_{C\text{-}F}$ = 21.6 Hz), 87.2, 56.4, 21.4; HRMS (EI) Calcd. for $C_{18}H_{14}NO_4FSBr_2$ $[M]^+$: 516.8994; Found: 516.8965; IR (KBr) ν_{max}/cm^{-1}: 3298, 2922, 1754, 1604, 1337, 1229, 1159, 728.

N-((R)-((S)-3,4-dibromo-5-oxo-2,5dihydrofuran-2-yl)(2-fluorophenyl)methyl)-4-methylbenzenesulfonamid

*e **(3gb)*** White solid, mp 168-169 °C; $[\alpha]_D^{20}$=-88 (c 0.1, CH_2Cl_2), yield 90 %; 4:1 dr, Enantiomeric excess:

91 %, determined by HPLC (Chiralcel OD-H column, hexane/ethanol= 97/3, flow rate 1 mL/min, UV detection at 220 nm), t_R (minor) = 39.2 min, t_R (major) =50.2 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8. Hz, 2H), 7.22-7.16 (m, 2H), 7.08 (d, *J* = 7.9 Hz, 2H), 7.01-6.90 (m, 2H), 5.73 (d, *J* = 10.9 Hz, 1H), 5.41 (d, *J* = 10.9 Hz, 1H), 5.03 (d, *J* = 1.7 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 157.6 (J_{C-F} = 244.4 Hz), 145.3, 143.6, 136.7, 130.2 (J_{C-F} = 8.4 Hz), 129.4, 128.3, 126.9, 124.7, 123.3, 116.4, 115.6 (J_{C-F} =21.6 Hz), 86.6, 50.7, 21.4; HRMS (ESI) Calcd. for $C_{18}H_{14}Br_2FNNaO_4S$ $[M+Na]^+$: 539.8887; Found: 539.8897; IR (KBr) ν_{max}/cm^{-1}: 3290, 2946, 1778, 1611, 1348, 1213, 1163, 675.

N-((R)-(2-chlorophenyl)((S)-3,4-dibromo-5-oxo-2,5-dihydrofuran-2-yl)-4-methylbenzenesulfonamide ***(3hb)***

White solid, mp 179-180 °C; $[\alpha]_D^{20}$=-57 (c 0.1, CH_2Cl_2), yield 90 %; 4:1 dr, Enantiomeric excess: 94 %, determined by HPLC (Chiralcel OD-H column, hexane/ethanol= 97/3, flow rate 1 mL/min, UV detection at 220 nm), t_R (minor) = 35.8 min, t_R (major) = 49.2 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.0 Hz, 2H), 7.32-7.28 (m, 1H), 7.22-7.08 (m, 2H), 7.04-7.01 (m, 3H), 6.30 (brs, 1H), 5.66 (d, *J* = 11.5 Hz, 1H), 5.06 (d, *J* = 1.4 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 145.8, 143.4, 136.8, 133.3, 131.9, 129.4, 129.3, 128.4, 127.4, 126.9, 126.5, 116.1, 86.1, 53.2, 21.3; HRMS (ESI) Calcd. for $C_{18}H_{18}Br_2ClN_2O_4S$ $[M+NH_4]^+$: 550.9037; Found: 550.9049; IR (KBr) ν_{max}/cm^{-1}: 3282, 2946, 1778, 1610, 1347, 1213, 1162, 675.

N-((R)-(2-bromophenyl)((S)-3,4-dibromo-5-oxo-2,5-dihydrofuran-2-yl)-4-methylbenzenesulfonamide ***(3ib)***

White solid, mp 186-187 °C; $[\alpha]_D^{20}$=-28 (c 0.1, CH_2Cl_2), yield 94 %; 10:1 dr, Enantiomeric excess: 93 %, determined by HPLC (Chiralcel OD-H column, hexane/ethanol= 92/8, flow rate 1 mL/min, UV detection at 220 nm), t_R (minor) = 15.2 min, t_R (major) =21.6 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.2 Hz, 2H), 7.46-7.43 (m, 1H), 7.11-7.10 (m, 1H), 7.08-7.01 (m, 4H), 6.19 (d, *J* = 11.1 Hz, 1H), 5.64 (d, *J* = 11.0 Hz, 1H), 5.07 (d, *J* = 1.3 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 145.8, 143.4, 136.7, 134.7, 132.7, 129.7, 129.3, 128.6, 128.0, 126.9, 122.4, 116.1, 86.0, 55.6, 21.3; HRMS (EI) Calcd. for

$C_{18}H_{14}NO_4SBr_3$ $[M]^+$: 576.8194; Found: 576.8134; IR (KBr) ν_{max}/cm^{-1}: 3291, 2945, 1778, 1610, 1347, 1212, 1163, 655.

N-((R)-((S)-3,4-dibromo-5-oxo-2,5dihydrofuran-2-yl)(naphthalene-2-yl)methyl)-4-methylbenzenesulfonamide ***(3jb)*** White solid, mp 105-106 °C; $[\alpha]_D^{20}$=-28 (c 0.1, CH_2Cl_2), yield 94 %; 10:1 dr, Enantiomeric excess: 93 %, determined by HPLC (Chiralcel OD-H column, hexane/ethanol= 92/8, flow rate 1 mL/min, UV detection at 220 nm), t_R (minor) = 15.2 min, t_R 9major) =21.6 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.5 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.63-7.51 (m, 2H), 7.39-7.36 (m, 3H), 7.30-7.28 (m, 1H), 6.87 (d, *J* = 8.0 Hz, 2H), 6.01 (d, *J* = 10.4 Hz, 1H), 5.86 (d, *J* = 10.4 Hz, 1H), 5.13 (d. *J* = 1.2 Hz, 1H), 2.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 145.6, 143.2, 136.8, 133.6, 131.1, 129.5, 129.2, 129.1, 128.9, 127.1, 126.7, 125.9, 125.2, 124.8, 121.0, 116.2, 86.4, 51.9, 21.2; HRMS (EI) Calcd. for $C_{22}H_{17}NO_4SBr_2$ $[M]^+$: 548.9245; Found: 548.9240; IR (KBr) ν_{max}/cm^{-1}: 3278, 3062, 1778, 1610, 1336, 1207, 1160, 666.

N-((R)-((S)-3,4-dibromo-5-oxo-2,5dihydrofuran-2-yl)(m-tolyl)methyl)-4-methylbenzenesulfonamide ***(3kb)*** White solid, mp 83-84 °C; $[\alpha]_D^{20}$=-88 (c 0.1, CH_2Cl_2), yield 76 %; 4:1 dr, Enantiomeric excess: 84 %, determined by HPLC (Chiralcel OD-H column, hexane/*i*-propanol= 85/15, flow rate 1 mL/min, UV detection at 220 nm), t_R (minor) = 11.7 min, t_R (major) =15.6 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.48 (m, 2H), 7.14-7.08 (m, 3H), 6.88 (s, 1H), 5.36 (d, *J* = 9.8 Hz, 1H), 5.07 (d, *J* = 1.5 Hz, 1H), 4.96 (dd, *J* = 10.1 Hz, 1.2 Hz, 1H), 2.33 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 145.5, 143.4, 138.6, 137.0, 135.8, 129.4, 129.2, 128.8, 127.6, 127.0, 123.9, 116.3, 87.1, 56.9, 21.4, 21.1; HRMS (EI) Calcd. for $C_{19}H_{17}NO_4SBr_2$ $[M]^+$: 512.9245; Found: 512.9227; IR (KBr) ν_{max}/cm^{-1}: 3284, 2920, 1766, 1608, 1339, 1215, 1159, 705.

N-((2-bromophenyl)(5-oxotetradrofuran-2-yl)methyl)-4-methylbenzenesulfonamide ***5*** To a solution of **3ja**

(129 mg, 0.26 mmol, 92% ee) in 1:1 THF/MeOH (2 mL) at 0 °C were added $NiCl_2 \cdot 6H_2O$ (187 mg, 0.79 mmol) and $NaBH_4$ (100 mg, 2.6 mmol). The reaction was quenched with the addition of saturated NH_4Cl until starting material disappeared. The mixture was then filtered, and the filtrate was concentrated, and the residue was extracted with ethyl acetate several times. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/EtOAc = 5/1 as eluent) to give **5** (47 mg, 43%) as a white solid. mp 129-130 ^oC; $[\alpha]_D^{20}$=-55 (c 0.1, CH_2Cl_2), yield 43 %; Enantiomeric excess: 91 %, determined by HPLC (Chiralcel OD-H column, hexane/ethanol= 92/8, flow rate 1 mL/min, UV detection at 220 nm), t_R (minor) = 17.8 min, t_R (major) =18.9 min. ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.1 Hz, 2H), 7.38-7.35 (m, 1H), 7.18-7.15 (m, 1H), 7.01-6.95 (m, 4H), 6.34 (brs, 1H), 5.03 (dd, *J*= 9.8 Hz, 2.1Hz, 1H), 4.66-4.62 (m, 1H), 2.57-2.31 (m, 4H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 143.1, 136.7, 136.2, 132.4, 129.2, 129.0, 128.7, 127.5, 126.8, 122.5, 81.8, 58.8, 28.3, 24.3, 21.3; HRMS (ESI) Calcd. for $C_{18}H_{18}BrNNaO_4S$ $[M+Na]^+$: 446.0032; Found: 446.0040; IR (KBr) ν_{max}/cm^{-1}: 3234, 2959, 1769, 1337, 1197, 1161, 690.

N-((1R, 2R)-1-(2-bromophenyl)-2,5-dihydroxypentyl)-4-methylbenzenesulfonamide ***6*** To a solution of **5** (31 mg, 0.73 mmol) in dry THF (1 mL) at 0 ^oC was added $LiBH_4$ (33 mg, 1.46 mmol), and the resulting mixture was stirred at 0 ^oC until starting material disappeared. Saturated aqueous NH_4Cl solution was added to quench the reaction. The solvent was extracted with ethyl acetate several times. The combined organic layers weredried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography(hexane/EtOAc = 5/1 as eluent) afforded **6** (28 mg, 90%) as a white solid, yield 90 %; Enantiomeric excess: 91 %, determined by HPLC (Chiralcel OD-H column, hexane/ethanol= 90/10, flow rate 1 mL/min, UV detection at 220 nm), t_R (major) = 16.8 min, t_R (minor) =19.9 min. ^1H NMR (300MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 7.7 Hz, 1H), 7.15 (d, *J* = 7.4 Hz, 1H), 7.05-6.93 (m, 4H), 6.26

(d, J = 8.2 Hz, 1H), 4.80 (dd, J = 8.1 Hz, 3.4 Hz, 1H), 3.74 (d, J = 3.4 Hz, 1H), 3.64 (d, J = 10.3 Hz, 1H), 3.55 (d, J = 10.3 Hz, 1H), 3.15 (brs, 1H), 2.28 (s, 3H), 1.64-1.58 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 137.9, 136.9, 132.5, 129.1, 128.8, 128.6, 127.2, 126.9, 122.8, 73.5, 62.5, 60.2, 31.0, 28.7, 21.3; HRMS (ESI) Calcd. for $C_{18}H_{23}NO_4SBr$ $[M+H]^+$: 428.0531; Found: 428.0534.

Supporting Information Available: copies of NMR spectra and HPLC analysis spectra of all compounds, X-ray structural data (cif) of compound **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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