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Chiral hypervalent iodine-catalyzed enantioselective oxidative Kita spirolactonization of 1-naphthol derivatives and one-pot diastereo-selective oxidation to epoxyspirolactones

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ABSTRACT

We demonstrate here the rational design of a conformationally flexible C_2-symmetric iodosylarene **8g** based on secondary $n-\sigma^*$ or hydrogen-bonding interactions as a chiral catalyst for the enantioselective Kita oxidative spirolactonization of 1-naphthol derivatives **5**. Iodosylarenes **8** were generated in situ from iodoarenes **7** and *m*CPBA as a co-oxidant. Furthermore, epoxyspirolactone **15** was obtained by the one-pot oxidation of **5** with *m*CBPA in the presence of **7g**. Thus, the enantioselective oxidation of **5** to **6** and the successive enantio- and diastereo-selective oxidation of **5** to **15** proceeded in good yields when we controlled the amount of *m*CPBA.

1. Introduction

Over the past two decades, hypervalent iodine compounds have been the focus of great attention due to their mild and chemoselective oxidizing properties and the fact that they are environmentally benign compared to toxic metal reagents.[1] However, the stoichiometric use of hypervalent iodine compounds has been limited because of their potentially shock-sensitive explosiveness and/or poor solubility in common organic solvents.[1] Thus, the development of hypervalent iodine-catalyzed oxidation reactions with co-oxidants is needed.[1,2] In particular, the development of chiral hypervalent iodine-catalyzed enantioselective oxidative coupling reactions is one of the most challenging areas in asymmetric organocatalysis.[3,4] There are some examples of in situ-generated chiral iodosylarene(I(III)) or iodylarene(I(V)) catalysis with *meta*-chloroperbenzoic acid (*m*CPBA)[5] as a co-oxidant (Fig. 1).[4] Wirth and co-workers reported the enantioselective α-oxysulfonylation of ketones with **1** as a precatalyst.[4a] Quideau and co-workers reported the enantioselective hydroxylative dearomatization of 2-methyl-1-naphthol with **2** as a precatalyst.[4b] However, the enantioselectivity has been modest. Recently, Kita and co-workers reported the enantioselective oxidative dearomatization of

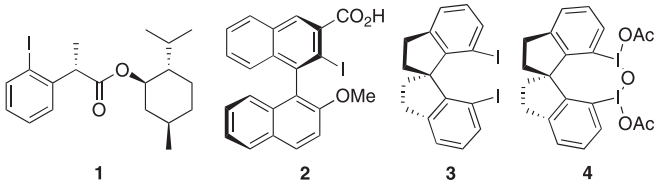
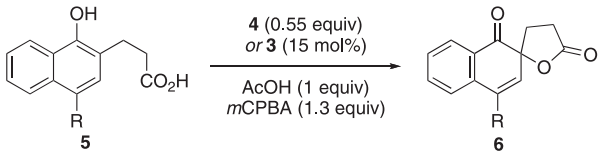


Figure 1. Chiral iodoarene precatalysts **1**–**3** and iodosylarene **4**.

1-naphthol derivatives **5** to spirolactones **6** with high enantioselectivities (up to 86% ee) using stoichiometric chiral iodine(III) reagent **4**, which has a conformationally rigid 1,1-spiroindanone backbone (Scheme 1).[6] They also succeeded in the catalytic use of **4** (30 mol % based on iodine) that was generated in situ from **3** and *m*CPBA in the presence of acetic acid, although the enantioselectivity was reduced to 69% ee (Scheme 1).[6]



Scheme 1. Enantioselective oxidative spirolactonization of 1-naphthols (**5**) reported by Kita and co-workers.[6]

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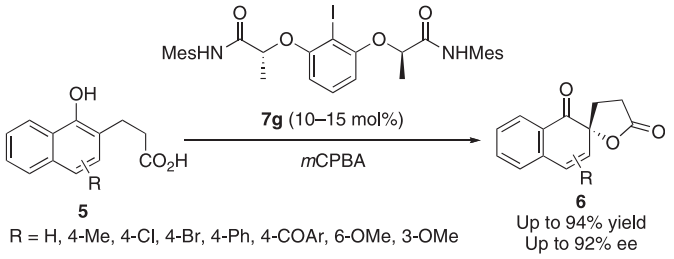
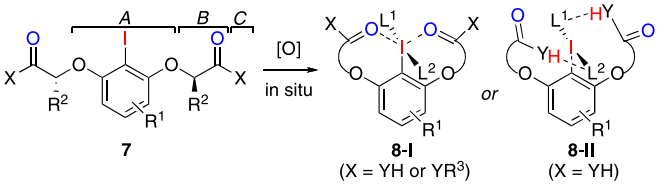
Very recently, we reported conformationally flexible C_2-symmetric chiral iodoarenes **7g** as a highly effective precatalyst for the enantioselective Kita oxidative spirolactonization (Scheme 2).[7] In this report, we described a detailed investigation of enantioselective oxidative spirolactonization. A broad range of substrates and higher enantioselectivities of up to 92% ee were achieved using iodosylarene **8g** generated in situ from **7g** and *m*CPBA. To the best of our knowledge, the present catalysis provides the highest asymmetric induction among previous chiral hypervalent iodine-catalyzed enantioselective oxidative reactions.[3,4,6] Furthermore, we briefly highlight here the synthetic utility of the present oxidation. The selective oxidation of **5** to spirolactones **6** and the successive oxidation of **5** to epoxyspirolactones **15** proceeded in good yields when we controlled the amount of *m*CPBA.



Scheme 2. In situ-generated **8g**-catalyzed enantioselective oxidative spirolactonization of **5** with *m*CPBA.[7]

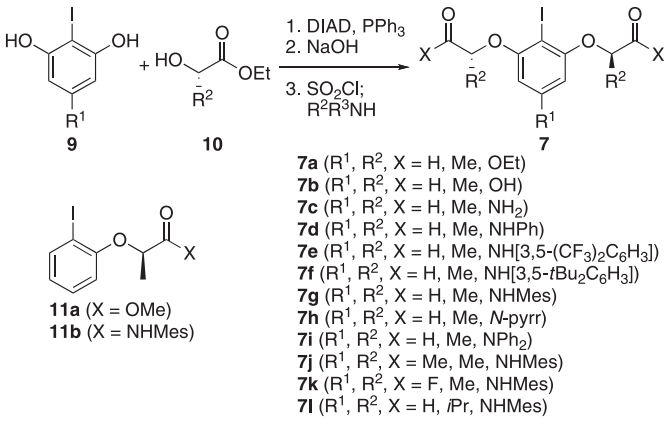
2. Results and discussion

C_2-Symmetric chiral iodoarenes **7** consist of three units, including an iodoaryl moiety (**A**), chiral linkers (**B**), and subfunctional groups (**C**) (Scheme 3). These units can be easily combined to give a wide variety of chiral iodoarenes **7**. The iodosylarenes **8** generated in situ from iodoarenes **7** were expected to exhibit intramolecular $n-\sigma^*$ interactions between the electron-deficient iodine(III) center (C–I σ^* orbital) of **A** and the Lewis-basic group of **C** (lone pair n), such as carbonyl groups (**8-I**).[1,8] Alternatively, intramolecular hydrogen-bonding interactions between the acidic hydrogen of **C** (COY–H) and the ligand (L, such as an acetoxy group) of iodine(III) might also be generated (**8-II**). We envisioned that a suitable chiral environment might be constructed around the iodine(III) center of **8** via such intramolecular interactions.



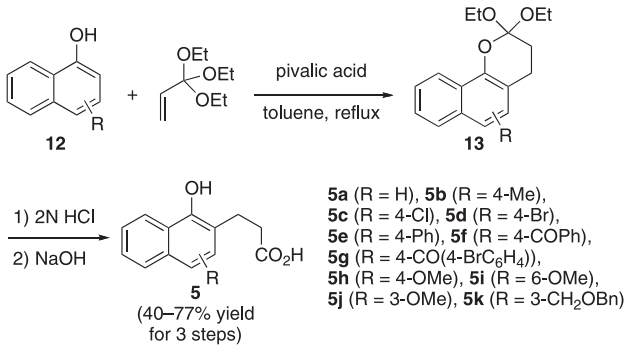
Scheme 3. Design of conformationally flexible iodoarenes **7** (precatalyst) and iodosylarenes **8** (catalyst).

Chiral iodoarenes **7** were easily prepared in two or three steps from 2-iodoresorcinol (Scheme 4). The Mitsunobu reaction of 2-iodoresorcinol (**9**, R^1=H)[9] with (−)-ethyl lactate (**10**, R^2=Me) gave C_2-symmetric chiral iodoarene **7a** in 90% yield. Hydrolysis of **7a** gave **7b** quantitatively without epimerization. Treatment of **7b** with thionyl chloride followed by several amines gave the corresponding amides **7c**–**i** in good yields. **7j**–**l**, **11a**,[3g] and **11b** were also prepared in a similar manner.



Scheme 4. Synthesis of chiral iodoarenes **7** and **11**.

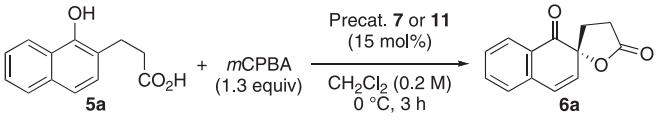
The starting materials **5** used in this study were prepared in good yields in three steps from readily available 1-napthols **12** (Scheme 5).[6b] Treatment of **12** with triethyl orthoacrylate in the presence of pivalic acid afforded diethoxychromane **13**.[10] Acid hydrolysis of **13** furnished dihydrocoumarin, which was transformed to **5** by hydrolysis.



Scheme 5. Synthesis of 1-naphthol derivatives **5**.

The chiral iodoarenes **7** were examined for use as precatalysts for the enantioselective oxidative spirolactonization of **5a** to spirolactone **6a** in the presence of *m*CPBA as a co-oxidant under Kita's conditions (Table 1).[6] The use of diester **7a** and

Table 1
Precatalyst screening for the oxidative spirolactonization of **5a**[a]



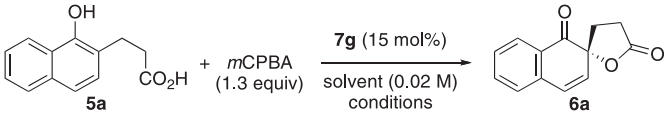
Entry	Precat. **7** or **11**	Yield[b] (%)	ee[c] (%)
1	**7a**	27	23
2	**7b**	26	43
3	**7c**	40	70
4	**7d**	25	77
5	**7e**	53	75
6	**7f**	36	84
7	**7g**	64	82
8	**7h**	37	51
9	**7i**	39	52
10	**7j**	37	50
11	**7k**	47	80
12	**7l**	70	83
13	**11a**	24	13
14	**11b**	42	32

[a] The reactions were performed with 0.05 mmol of **5a** and 1.3 equiv of *m*CPBA in the presence of **7** or **11** (15 mol %).
[b] Isolated yield of **6a** by column chromatography is shown.
[c] The ee values of **6a** were determined by chiral stationary phase HPLC.

dicarboxylic acid **7b** gave (+)-**6a** with 23% ee and 43% ee, respectively (entries 1 and 2). In contrast, the use of bis(primary amide) **7c** gave (+)-**6a** with 70% ee (entry 3), and the use of bis(*N*-aryl amide)s **7d**–**g** further increased the enantioselectivity (entries 4–7). Bis(*N*-mesityl amide) **7g** was the best precatalyst with respect to activity and enantioselectivity (entry 7, 64% yield, 82% ee). The use of tertiary amides, such as **7h** and **7i** gave moderate enantioselectivities (entries 8 and 9). Bis(*N*-mesityl amide) **7j** bearing a methyl group at the *para*-position of the iodoaryl moiety (**A**) gave modest enantioselectivity (entry 10). In contrast, the use of F-substituted **7k** gave (+)-**6a** with 80% ee (entry 11). Bis(*N*-mesityl amide) **7l** bearing an ^{i}Pr group on the chiral linker (**B**) also gave high enantioselectivity and high catalytic activity as well as **5g** (entry 12). Meanwhile, C_2-unsymmetrical iodoarenes, such as monoester **11a**[3g] and mono(*N*-mesityl amide) **11b** gave low enantioselectivities (entries 13 and 14). Thus, the C_2-symmetric chirality in **8** was essential for the present enantioselective oxidative spirolactonization.

Next, we optimized the reaction conditions with **7g** (Table 2). Enantioselectivity was enhanced at lower temperatures and under diluted conditions (entries 2 and 3). The highest enantioselectivity (92% ee) was observed in chloroform (entries 5 and 6). Notably, high or good enantioselectivities were observed regardless of the polarity of the solvent (entries 5–12). In particular, (+)-**6a** was obtained in 82% yield with 85% ee in nitromethane (entry 9). In contrast, almost no reaction occurred when the reaction was performed in tetrahydrofuran or diethyl ether (entries 13 and 14).

Table 2
Optimization of the reaction conditions[a]

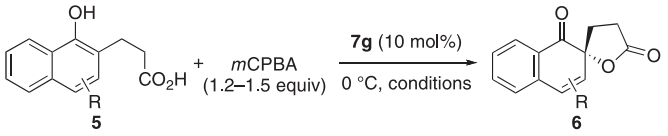


Entry	Solvent	Conditions	Yield[b] (%)	ee[c] (%)
1	CH_2Cl_2[d]	0 °C, 3 h	64	82
2	CH_2Cl_2	0 °C, 5 h	56	88
3	CH_2Cl_2	−20 °C, 48 h	75	90
4	CH_2Cl_2	25 °C, 5 h	70	83
5[e]	$CHCl_3$	0 °C, 18 h	60	92
6	$CHCl_3$	−20 °C, 48 h	55	92
7	Toluene	0 °C, 5 h	46	77
8	CH_3CN	0 °C, 5 h	23	83
9	CH_3NO_2	0 °C, 5 h	82	85
10	EtOAc	0 °C, 5 h	14	81
11	CF_3CH_2OH	0 °C, 5 h	66	70
12	$(CF_3)_2CHOH$	0 °C, 5 h	63	41
13	THF	0 °C, 5 h	<5	n.d.
14	Et_2O	0 °C, 5 h	<5	n.d.
15	$CHCl_3$–CH_3NO_2[f]	0 °C, 5 h	65	90

[a] Unless otherwise noted, the reactions were performed with 0.05 mmol of **5a** and 1.3 equiv of *m*CPBA in the presence of **7g** (15 mol %).
[b] Isolated yield of **6a** by column chromatography is shown.
[c] The ee values of **6a** were determined by chiral stationary phase HPLC.
[d] Reaction was performed in CH_2Cl_2 (0.5 mL, 0.2 M).
[e] The reaction was performed with 1.0 mmol of **5a** and 1.2 equiv of *m*CPBA.
[f] Reaction was performed in $CHCl_3$–CH_3NO_2 (2/1, v/v, 0.02 M) mixed solvents.

To explore the generality and substrate scope of the present spirolactonization, several 1-naphthol derivatives **5** were examined as substrates under optimized conditions using **7g** (10 mol %) and *m*CPBA (1.2–1.5 equiv) (Table 3). The oxidation of 4-substituted naphthol derivatives **5b**–**g** gave the corresponding spirolactones **6b**–**g** in good to high yields with high enantioselectivities (entries 1–6). Fortunately, nearly enantiomerically pure **6d**–**f** were obtained after a single

Table 3
Scope and limitations of the spirolactonization reaction[a]



Entry	**6**	Conditions	Yield[b] (%)	ee[c] (%)
1	(+)-**6b**	$CHCl_3$–CH_3NO_2,[d] 17 h	59	84
2	(+)-**6c**	$CHCl_3$, 30 h	72	90
3	(+)-**6d**	$CHCl_3$, 16 h	67	85 (98)
4	(+)-**6e**	$CHCl_3$, 27 h	62	87 (98)
5	(*R*)-(−)-**6f**	$CHCl_3$–CH_3NO_2,[d] 16 h	94	83 (>99)
6	(−)-**6g**	$CHCl_3$, 30 h	88	91
7	(±)-**6h**	$CHCl_3$–CH_3NO_2,[d] 7 h	28	0
8	(+)-**6i**	$CHCl_3$–CH_3NO_2,[d] 18 h	40	87
9	(+)-**6j**	$CHCl_3$–CH_3NO_2,[d] 24 h	3	88
10	(+)-**6k**	$CHCl_3$, 18 h	53	91

[a] The reactions were performed with 0.05 mmol of **5** and 1.2–1.5 equiv of *m*CPBA in the presence of **7g** (10 mol %).
[b] Isolated yield of **6** by column chromatography is shown.
[c] The ee values of **6** were determined by chiral stationary phase HPLC. Ee value in parentheses is that obtained after single recrystallization.
[d] Reaction was performed in $CHCl_3$–CH_3NO_2 (2/1, v/v) mixed solvents.

recrystallization (≥98% ee, entries 3–5).[11] The absolute stereochemistry of (−)-**6f** was determined to be (*R*) based on the X-ray crystal analysis (>99% ee, entry 5, Fig. 2). Notably, the oxidation of 4-benzoylnaphthol derivative **5f** gave **6f** in 94% yield with 83% ee (entry 5). In sharp contrast, according to Kita's report, **4** gave racemic **6f**.[6b] Although the oxidation of 4-methoxynaphthol derivative **5h** gave racemic **6h** (entry 8), as did Kita's reagent **4**,[6] **7g** gave (+)-**6i** with 87% ee, for the oxidation of 6-methoxynaphthol derivative **5i** (entry 8). Unfortunately, 3-methoxynaphthol derivative **5j** gave (+)-**6j** in very low yield (entry 9). Notably, the oxidation of 3-benzyloxymethyl-substituted **5k** gave (+)-**6k** in good yield with 91% ee (entry 10). Analogs of **6k** may become new chiral intermediate candidates in enantioselective total syntheses of Lactonamycin.[12]

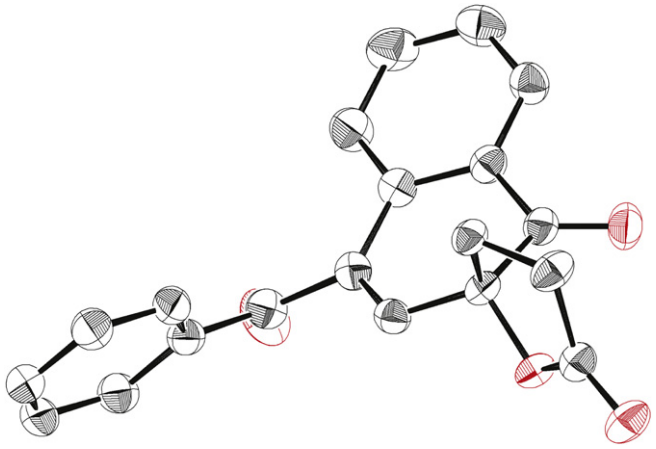
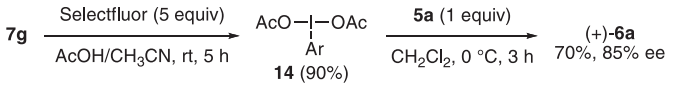


Figure 2. ORTEP drawing of (*R*)-(−)-**6f** (>99% ee).

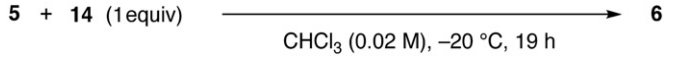
Iodosylarene diacetate **14**, which was analogous to **8g**, was isolated through the oxidation of **7g** with Selectfluor.[6] Treatment of **5a** with 1 equiv of **14** in dichloromethane at 0 °C gave (+)-**6a** with 85% ee (Scheme 6 and entry 1 in Table 2). Thus, iodine(III) generated in situ from **7** should be the actual oxidant species for the present catalytic oxidation.



Scheme 6. Preparation of iodosylarene **14** from **7g** and the oxidation of **5a** with **14**.

Next, stoichiometric oxidations of **5** with 1 equiv of **14** were investigated under optimal conditions (Table 4). The oxidation of **5a**, **5b**, **5i**, and **5k** gave corresponding spirolactone (+)-**6** in high yields and with high enantioselectivities (entries 1–3 and 5). Furthermore, (+)-**6j** was obtained in 87% yield with 95% ee for the stoichiometric oxidation of **5j** (entry 4).

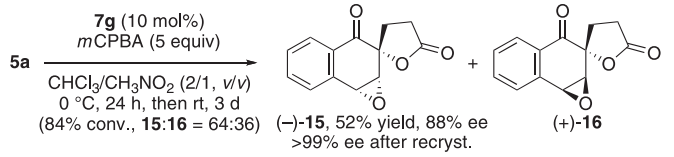
Table 4
Stoichiometric oxidation of **5** with iodosylarene **14**[a]



Entry	6	Yield[b] (%)	ee[c] (%)
1	(+)-**6a**	70	90
2	(+)-**6b**	85	89
3	(+)-**6i**	89	90
4	(+)-**6j**	87	95
5	(+)-**6k**	75	94

[a] The reactions were performed with 0.05 mmol of **5** and 0.05 mmol of **14**.
[b] Isolated yield of **6** by column chromatography is shown.
[c] The ee values of **6** were determined by chiral stationary phase HPLC.

Oxidation of **5a** with 5 equiv of *m*CPBA in the presence of 10 mol% of **7g** gave epoxyspirolactone (−)-**15** in good yield. (Scheme 7). Enantiomerically pure (−)-**15** was obtained after



Scheme 7. One-pot oxidation of **5a** to epoxyspirolactone (−)-**15**.

a single recrystallization. Thus, the selective oxidation of **5** to spirolactone **6** and the successive enantio- and diastereo-selective oxidation of **5** to epoxyspirolactone **15** proceeded in good yields when we controlled the amount of *m*CPBA.[13] The relative stereochemistry of **15** was determined by the X-ray crystal analysis of (±)-**15** (Fig. 3).

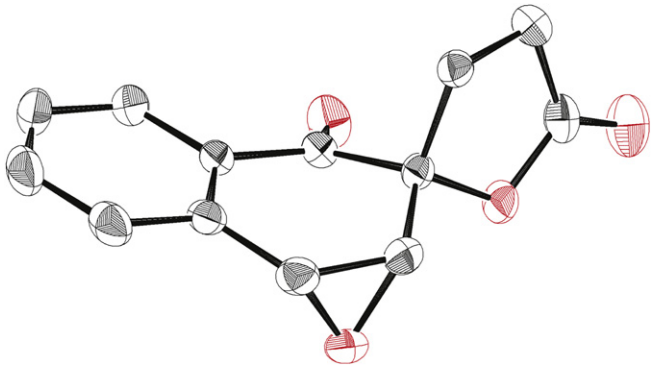
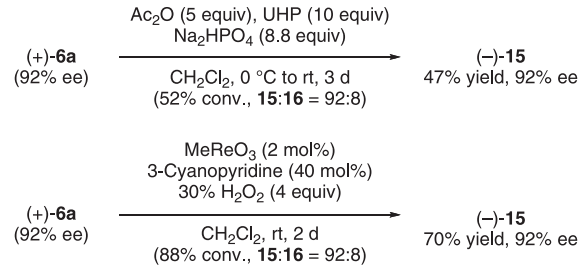


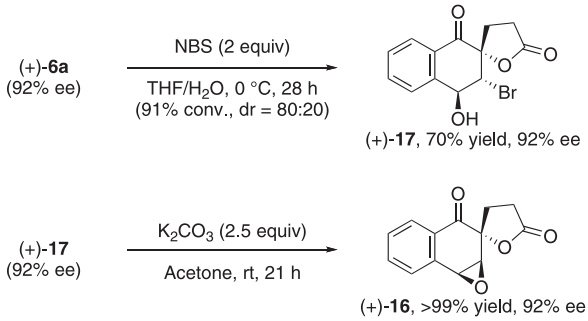
Figure 3. ORTEP drawing of (±)-**15**.

Epoxyspirolactone (−)-**15** could also be obtained by the epoxidation of unsaturated spirolactone (+)-**6a** with in situ-generated peracetic acid[14] or $MeReO_3$–H_2O_2[15] in good yield and with higher diastereoselectivity (Scheme 8).



Scheme 8. Epoxidation of (+)-**6a** to epoxyspirolactone (−)-**15**.

Bromohydrin spirolactone (+)-**17** was obtained in high yield and high diastereoselectivity by treatment of (+)-**6a** with NBS in aqueous THF (Scheme 9).[16] Treatment of (+)-**17** with K_2CO_3 gave epoxyspirolactone (+)-**16**, which was a diastereomer of (−)-**15** (Scheme 9). Thus, both of the enantioenriched epoxyspirolactones (−)-**15** and (+)-**16** could be obtained selectively from **6a** in good yields (Schemes 8 and 9).



Scheme 9. Conversion of (+)-**6a** to bromohydrin spirolactone (+)-**17**, and conversion of (+)-**17** to epoxyspirolactone (+)-**16**.

3. Conclusion

In summary, we have demonstrated the rational design of a conformationally flexible iodosylarene **8g** as a chiral catalyst based on secondary n–σ^* or hydrogen-bonding interactions for the enantioselective Kita oxidative spirolactonization. In a similar way, it is likely that several precatalysts for other enantioselective oxidative transformations will be found in the library of **7**. Furthermore, we have briefly highlighted the synthetic utility of the present oxidation. Epoxyspirolactone **15** was obtained by the one-pot oxidation of **5a** with *m*CPBA in the presence of **7g**. Thus, the enantioselective oxidation of **5** to **6** and the successive enantio- and diastereo-selective oxidation of **5** to **15** proceeded in good yields when we controlled the amount of *m*CPBA. Additionally, unsaturated spirolactones **6** could be easily transformed to epoxyspirolactones **15** and bromohydrin spirolactones **17** in good yields and with high diastereoselectivities. Basic treatment of **17** gave epoxyspirolactone **16**, which is diastereomer of **15**. Thus, both of the enantioenriched epoxyspirolactones **15** and **16** could be obtained selectively from unsaturated spirolactone **6** in good yields. Studies to elucidate the detailed mechanism of oxidative spirolactonization are currently underway.

4. Experimental section

4.1. General methods

^{1}H NMR spectra were measured on a Varian Gemini-2000 (300 MHz), Varian INOVA-500 (500 MHz) or a JEOL ECS-400 (400 MHz) spectrometer at ambient temperature. Data were recorded as follows: chemical shift in parts per million from

internal tetramethylsilane on the δ scale, multiplicity (s=singlet; d=doublet; t=triplet; q=quartet; m=multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a Varian Gemini-2000 (75 MHz), Varian INOVA-500 (125 MHz) or JEOL ECS-400 (100 MHz) spectrometers. Chemical shifts were recorded in parts per million from the solvent resonance employed as the internal standard (deuterochloroform at 77.00 ppm). High-performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-10 AD coupled diode array-detector SPD-MA-10A-VP and chiral column of Daicel CHIRALCEL OD-H (4.6 mm×25 cm) AD-3 (4.6 mm×25 cm). For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254} 0.25 mm) were used. The products were purified by column chromatography on silica gel (E. Merck Art. 9385). In experiments that required dry solvents, tetrahydrofuran (THF), dichloromethane, and toluene were purchased from Wako as the 'anhydrous' and stored over 4A molecular sieves. Other solvents were purchased from Aldrich or Wako and used without further purification. Other simple chemicals were analytical-grade and obtained commercially and used without further purification.

4.2. Synthesis of chiral iodoarenes 7a–l (Scheme 4)

*4.2.1. (2R,2′R)-Diethyl 2,2′-(2-iodo-1,3-phenylene)bis(oxy)dipropanoate (**7a**).* To a solution of 2-iodoresorcinol[9] (**9**, 2.36 g, 10.0 mmol), PPh_3 (6.56 g, 25.0 mmol) and (−)-lactic acid ethylester (**10**, 2.80 mL, 25.0 mmol) in THF (50 mL) was added slowly diisopropyl azodicarboxylate (DIAD, 1.9 M in toluene, 25.0 mmol, 13.2 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature. After stirring for 6 h, the resulting mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: hexane–EtOAc=15:1) to give **7a** (3.93 g, 9.0 mmol) in 90% yield. Colorless oil; TLC, R_f=0.33 (hexane–EtOAc=4:1); IR (neat) 2985, 1753, 1587, 1461, 1252, 1135 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24 (t, J=7.2 Hz, 6H), 1.70 (d, J=6.8 Hz, 6H), 4.18–4.24 (m, 4 h), 4.75 (q, J=6.8 Hz, 2H), 6.37 (d, J=8.4 Hz, 2H), 7.13 (t, J=8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (2C), 18.5 (2C), 61.2 (2C), 74.2 (2C), 80.6, 106.9 (2C), 129.4, 158.2 (2C), 171.6 (2C); HRMS (FAB$^+$) m/z calcd for $C_{16}H_{22}IO_6$ (M+H) 437.0461, found 437.0462; $[\alpha]_D^{26}$ −21.6 (c 1.0, $CHCl_3$).

*4.2.2. (2R,2′R)-2,2′-(2-Iodo-1,3-phenylene)bis(oxy)dipropanoic acid (**7b**).* To a solution of **7a** (3.93 g, 9.0 mmol) in THF (25.0 mL) and MeOH (25.0 mL) was added 2 M NaOH (25 mL) and stirred overnight at room temperature. The reaction mixture was cooled to 0 °C, quenched with 1 M HCl and extracted with EtOAc. The organic layers were dried over anhydrous $MgSO_4$ and the solvents were removed in vacuo to give analytically pure **7b** (3.42 g, 9.0 mmol) in >99% yield. White solid; TLC, R_f=0.15 (hexane–EtOAc–$CHCl_3$=1:2:1 with a few drops of AcOH); IR (KBr) 3600–2700, 2525, 1715, 1581, 1458, 1252 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.54 (d, J=6.8 Hz, 6H), 4.84 (q, J=6.8 Hz, 2H), 6.42 (d, J=8.0 Hz, 2H), 7.21 (t, J=8.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 18.4 (2C), 72.8 (2C), 79.6, 105.9 (2C), 129.7, 157.8 (2C), 172.7 (2C); HRMS (FAB$^+$) m/z calcd for $C_{12}H_{13}IO_6$ (M) 379.9757, found 329.9755; $[\alpha]_D^{26}$ −6.4 (c 1.0, THF).

*4.2.3. (2R,2′R)-2,2′-(2-Iodo-1,3-phenylene)bis(oxy)dipropan amide (**7c**).* A solution of **7b** (190 mg, 0.50 mmol) in $SOCl_2$ (4.0 mL) was refluxed for 1 h. To the resulting mixture was added benzene (2×2 mL), and excess reagents were removed in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL), and to the resulting mixture was added excess NH_3 gas with cooling (−78 °C). The resulting mixture was stirred at −78 °C for 2 h, and gradually warmed to room temperature. After stirring for overnight, the reaction mixture was poured into 1 M HCl and extracted with $CHCl_3$. The organic layers were dried over anhydrous $MgSO_4$ and the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: hexane–EtOAc=1:2) to give **7c** (0.15 g, 0.4 mmol) in 79% yield. White solid; TLC, R_f=0.13 (hexane–EtOAc–$CHCl_3$=1:2:1); IR (KBr) 3455, 3398, 3217, 1709, 1460, 1251, 1111 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.47 (d, J=6.8 Hz, 6H), 4.68 (q, J=6.8 Hz, 2H), 6.51 (d, J=8.0 Hz, 2H), 7.24 (t, J=8.0 Hz, 1H), 7.30 (s, 2H), 7.42 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 18.6 (2C), 74.8 (2C), 80.6, 106.7 (2C), 129.9, 157.5 (2C), 172.9 (2C); HRMS (FAB$^+$) m/z calcd for $C_{12}H_{16}IN_2O_4$ (M+H) 379.0155, found 379.0152; $[\alpha]_D^{26}$ −120.9 (c 1.0, $CHCl_3$).

*4.2.4. (2R,2′R)-2,2′-(2-Iodo-1,3-phenylene)bis(oxy)bis(N-phenylpropanamide) (**7d**).* This compound was prepared as **7c** from **7b** with aniline in 69% yield. White solid; TLC, R_f=0.37 (hexane–EtOAc=1:1); IR (KBr) 3402, 1685, 1600, 1529, 1439, 1242, 1104 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.75 (d, J=6.4 Hz, 6H), 4.96 (q, J=6.4 Hz, 2H), 6.60 (d, J=8.4 Hz, 2H), 7.16 (t, J=8.0 Hz, 2H), 7.33 (t, J=8.4 Hz, 1H), 7.37 (t, J=8.0 Hz, 4H), 7.66 (d, J=8.0 Hz, 4H), 8.79 (br s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.3 (2C), 76.1 (2C), 80.7, 107.2 (2C), 119.8 (4C), 124.7 (2C), 129.1 (4C), 130.8, 137.2 (2C), 156.7 (2C), 168.9 (2C); HRMS (FAB$^+$) m/z calcd for $C_{24}H_{24}IN_2O_4$ (M+H) 531.0781, found 531.0794; $[\alpha]_D^{25}$ −229.4 (c 1.0, $CHCl_3$).

*4.2.5. (2R,2′R)-2,2′-(2-Iodo-1,3-phenylene)bis(oxy)bis(N-(3,5-bis(trifluoromethyl)phenyl)propanamide) (**7e**).* This compound was prepared as **7c** from **7b** with 3,5-di-trifluoromethylaniline in 80% yield. White solid; TLC, R_f=0.57 (hexane–EtOAc=1:1); IR (KBr) 3367, 1701, 1543, 1460, 1383, 1279, 1132 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.77 (d, J=6.8 Hz, 6H), 5.00 (q, J=6.8 Hz, 2H), 6.64 (d, J=8.4 Hz, 2H), 7.38 (t, J=8.4 Hz, 2H), 7.67 (s, 2H), 8.17 (s, 4H), 9.03 (br s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.1 (2C), 76.1 (2C), 80.9, 107.6 (2C), 118.1 (2C), 119.5 (4C), 123.0 (d, J_{C-F}=271 Hz, 4C), 131.1, 132.3 (q, J_{C-F}=33 Hz, 4C), 138.6 (2C), 156.5 (2C), 169.5 (2C); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −62.8; HRMS (FAB$^+$) m/z calcd for $C_{28}H_{20}F_{12}IN_2O_4$ (M+H) 803.0276, found 803.0272; $[\alpha]_D^{26}$ −147.3 (c 1.0, $CHCl_3$).

*4.2.6. (2R,2′R)-2,2′-(2-Iodo-1,3-phenylene)bis(oxy)bis(N-(3,5-ditertbutylphenyl)propanamide) (**7f**).* This compound was prepared as **7c** from **7b** with 3,5-di-*tert*-butylaniline in 62% yield. White solid; TLC, R_f=0.64 (hexane–EtOAc=1:1); IR (KBr) 3382, 3290, 2962, 1690, 1669, 1457, 1248, 1113 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34 (s, 36H), 1.75 (d, J=6.8 Hz, 6H), 4.93 (q, J=6.8 Hz, 2H), 6.62 (d, J=8.4 Hz, 2H), 7.19 (s, 2H), 7.33 (t, J=8.4 Hz, 2H), 7.51 (s, 4H), 8.72 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.3 (2C), 31.3 (12C), 34.9 (4C), 76.4 (2C), 80.7, 107.2 (2C), 114.4 (4C), 118.9 (2C), 130.8, 136.6 (2C), 151.8 (4C), 156.9 (2C), 168.8 (2C); HRMS (FAB$^+$) m/z calcd for $C_{40}H_{56}IN_2O_4$ (M+H) 755.3285, found 755.3277; $[\alpha]_D^{26}$ −180.9 (c 1.0, $CHCl_3$).

*4.2.7. (2R,2′R)-2,2′-(2-Iodo-1,3-phenylene)bis(oxy)bis(N-mesitylpropanamide) (**7g**).* This compound was prepared as **7c** from **7b** with mesitylaniline in 78% yield. White solid; TLC, R_f=0.42 (hexane–EtOAc=1:1); IR (KBr) 3255, 1673, 1528, 1463, 1256, 1138 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.77 (d, J=6.8 Hz, 6H), 2.15 (s, 12H), 2.26 (s, 6H), 5.00 (q, J=6.8 Hz, 2H), 6.64 (d, J=8.4 Hz, 2H), 6.86 (s, 4H), 7.34 (t, J=8.4 Hz, 1H), 8.02 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.2 (4C), 18.7 (2C), 20.8 (2C), 76.0 (2C), 80.4, 107.0 (2C), 128.9 (4C), 130.0 (2C), 130.6, 135.0 (4C), 137.1 (2C), 156.9 (2C), 169.6 (2C); HRMS (FAB$^+$) m/z calcd for $C_{30}H_{36}IN_2O_4$ (M+H) 615.1720, found 615.1717; $[\alpha]_D^{26}$ −116.1 (c 1.0, $CHCl_3$).

*4.2.8. (2R,2′R)-2,2′-(2-Iodo-1,3-phenylene)bis(oxy)bis(1-(pyrrolidin-1-yl)propan-1-one) (**7h**).* This compound was prepared as **7c** from **7b** with pyrrolidine in >99% yield. White solid; TLC, R_f=0.19 (hexane–EtOAc–$CHCl_3$=1:2:1); IR (KBr) 2980, 2875, 1650, 1461, 1428, 1255, 1103 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.55–1.92 (m,

8H), 1.68 (d, J=6.8 Hz, 6H), 3.31 (dt, J=6.8, 11.2 Hz, 2H), 3.42–3.53 (m, 4H), 3.72 (dt, J=6.8, 11.2 Hz, 2H), 4.83 (q, J=6.8 Hz, 2H), 6.46 (d, J=8.0 Hz, 2H), 7.16 (t, J=8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.4 (2C), 23.2 (2C), 26.5 (2C), 46.3 (2C), 46.8 (2C), 76.5 (2C), 78.5, 106.0 (2C), 130.3, 157.6 (2C), 169.3; HRMS (FAB$^+$) m/z calcd for $C_{20}H_{28}IN_2O_4$ (M+H) 487.1094, found 487.1092; $[\alpha]_D^{25}$ −161.0 (c 1.0, $CHCl_3$).

*4.2.9. (2R,2′R)-2,2′-(2-Iodo-1,3-phenylene)bis(oxy)bis(N,N-diphenylpropanamide) (**7i**).* This compound was prepared as **7c** from **7b** with diphenylamine in 72% yield. White solid; TLC, R_f=0.37 (hexane–EtOAc=1:1); IR (KBr) 3600–3200, 3448, 1686, 1491, 1458, 1247, 1092 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.62 (d, J=6.4 Hz, 6H), 4.88 (q, J=6.4 Hz, 2H), 6.40 (d, J=8.4 Hz, 2H), 7.11 (t, J=8.4 Hz, 2H), 7.20–7.32 (m, 20H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.1 (2C), 73.6 (2C), 83.0, 108.8 (2C), 126.1 (m, 8C), 130.0 (m, 13C), 141.0 (m, 2C), 142.0 (m, 2C), 158.0 (2C), 170.5 (2C); HRMS (FAB$^+$) m/z calcd for $C_{36}H_{32}IN_2O_4$ (M+H) 683.1407, found 683.1407; $[\alpha]_D^{26}$ −30.8 (c 1.0, $CHCl_3$).

*4.2.10. (2R,2′R)-2,2′-(2-Iodo-5-methyl-1,3-phenylene)bis(oxy)bis(N-mesitylpropanamide) (**7j**).* This compound was prepared as **7g** from 2-iodo-5-methylresorcinol. White solid; TLC, R_f=0.56 (hexane–EtOAc–$CHCl_3$=1:2:1); IR (KBr) 3234, 2918, 1668, 1578, 1508, 1440, 1239, 1108 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.77 (d, J=6.8 Hz, 6H), 2.14 (s, 12H), 2.26 (s, 6H), 2.35 (s, 3H), 4.98 (q, J=6.8 Hz, 2H), 6.48 (s, 2H), 6.90 (s, 4H), 7.97 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.2 (4C), 18.8 (2C), 20.9 (2C), 21.8, 76.0 (2C), 76.2, 108.1 (2C), 129.0 (4C), 130.0 (2C), 135.0 (4C), 137.2 (2C), 141.4, 156.6 (2C), 169.7 (2C); HRMS (FAB$^+$) m/z calcd for $C_{31}H_{38}IN_2O_4$ (M+H) 629.1876, found 629.1870; $[\alpha]_D^{23}$ −94.9 (c 1.0, $CHCl_3$).

*4.2.11. (2R,2′R)-2,2′-(5-Fluoro-2-iodo-1,3-phenylene)bis(oxy)bis(N-mesitylpropanamide) (**7k**).* This compound was prepared as **7g** from 5-fluoro-2-iodoresorcinol. Pale purple solid; TLC, R_f=0.60 (hexane–EtOAc–$CHCl_3$=1:2:1); IR (KBr) 3246, 2920, 1668, 1609, 1508, 1431, 1211, 1105 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.78 (d, J=6.8 Hz, 6H), 2.16 (s, 12H), 2.27 (s, 6H), 4.94 (q, J=6.8 Hz, 2H), 6.46 (d, J=10.1 Hz, 2H), 6.91 (s, 4H), 7.94 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.3 (4C), 18.6 (2C), 20.9 (2C), 73.5, 76.4 (2C), 95.4 (d, J_{C-F}=27 Hz, 2C), 129.0 (4C), 129.9 (2C), 135.0 (4C), 137.4 (2C), 157.2 (d, J_{C-F}=13 Hz, 2C), 165.0 (d, J_{C-F}=247 Hz), 169.0 (2C); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −107.8; HRMS (FAB$^+$) m/z calcd for $C_{30}H_{35}FIN_2O_4$ (M+H) 633.1626, found 633.1612; $[\alpha]_D^{22}$ −122.2 (c 0.6, $CHCl_3$).

*4.2.12. (2R,2′R)-2,2′-(2-Iodo-1,3-phenylene)bis(oxy)bis(N-mesityl-3-methylbutanamide) (**7l**).* Compound **7l** was prepared as **7g** in 30% yield (three steps). Yellow solid; TLC, R_f=0.48 (hexane–EtOAc=1:1); IR (KBr) 3376, 3246, 2967, 2921, 1665, 1459, 1246, 1079 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J=7.2 Hz, 6H), 1.31 (d, J=7.2 Hz, 6H), 2.05 (s, 12H), 2.24 (s, 6H), 2.45–2.52 (m, 2H), 4.73 (q, J=6.8 Hz, 2H), 6.62 (d, J=8.4 Hz, 2H), 6.86 (s, 4H), 7.28 (t, J=8.4 Hz, 1H), 7.60 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.6 (2C), 18.5 (4C), 19.1 (2C), 20.8 (2C), 31.7 (2C), 79.3, 84.4 (2C), 106.5 (2C), 129.0 (4C), 130.0 (2C), 130.6, 134.8 (4C), 137.1 (2C), 157.6 (2C), 168.4 (2C); HRMS (FAB$^+$) m/z calcd for $C_{34}H_{44}IN_2O_4$ (M+H) 671.2346, found 671.2342; $[\alpha]_D^{26}$ −63.7 (c 1.0, $CHCl_3$).

*4.2.13. (R)-Methyl 2-(2-iodophenoxy)propanoate (**11a**)[3g].* Compound **11a** was prepared as **7a** from 2-iodophenol with (−)-lactic acid methylester in 80% yield. Pale yellow oil; TLC, R_f=0.40 (hexane–EtOAc=4:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.69 (d, J=6.9 Hz, 3H), 3.75 (s, 3H), 4.88 (q, J=6.9 Hz, 1H), 6.64–6.77 (m, 2H), 7.24 (t, J=7.8 Hz, 1H), 7.77 (dd, J=1.8, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 18.6, 52.3, 74.1, 87.2, 113.3, 123.5, 129.3, 139.7, 156.5, 172.0.

*4.2.14. (R)-2-(2-Iodophenoxy)-N-mesitylpropanamide (**11b**).* Compound **11b** was prepared as **7g** from in 88% yield. Yellow solid; TLC, R_f=0.55 (hexane–EtOAc=1:1); IR (KBr) 3277, 1658, 1521, 1473, 1224, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.77 (d, J=6.8 Hz, 3H), 2.14 (s, 6H), 2.27 (s, 3H), 4.96 (q, J=6.8 Hz, 1H), 6.80 (t, J=7.6 Hz, 1H), 6.90–6.96 (m, 3H), 7.34 (t, J=7.6 Hz, 1H), 7.82 (dd, J=1.6, 7.6 Hz, 1H), 8.00 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.3 (2C), 18.7, 20.9, 75.8, 87.2, 113.1, 123.8, 129.0 (2C), 129.8, 130.0, 135.1 (2C), 137.2, 139.7, 155.1, 169.8; HRMS (FAB$^+$) m/z calcd for $C_{18}H_{21}INO_2$ (M+H) 410.0617, found 410.0609; $[\alpha]_D^{25}$ +52.1 (c 1.0, $CHCl_3$).

4.3. Synthesis of 1-napthol derivatives 5 (Scheme 5)

*4.3.1. 3-(1-Hydroxynaphthalen-2-yl)propanoic acid (**5a**)[6,10].* To a stirred solution of 1-naphtol (**12a**, 4.33 g, 30 mmol) and triethyl orthoacrylate (6.0 ml, 48 mmol) in toluene (100 ml) was added pivalic acid (1.53 g, 15 mmol) and the resulting mixture was refluxed for 1 day. The resulting mixture was poured into 1 M NaOH (30 mL), extracted with Et_2O (twice) and washed with brine. The combined organic layers were dried over anhydrous Na_2SO_4 and solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: hexane–EtOAc=15:1) to give **13a** (8.17 g, 30 mmol, >99% yield) as colorless oil. To a solution of **13a** (8.17 g, 30 mmol) in Et_2O (80 ml) was added 2 M HCl (40 ml) and the resulting mixture was stirred for overnight at room temperature. The resulting mixture was extracted with EtOAc (twice) and washed with brine. The combined organic layers were dried over anhydrous Na_2SO_4 and solvents were removed in vacuo. To a solution of the crude product in THF (30 mL) and MeOH (30 ml) was added 2 N NaOH (40 mL) and the resulting mixture was stirred overnight at room temperature. The resulting mixture was poured into 1 N HCl (100 mL), extracted with EtOAc (twice) and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$ and solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: hexane–EtOAc=4:1 to 1:2) to give **5a** (4.05 g, 18.7 mmol) in 62% yield (2 steps). White solid; TLC, R_f=0.27 (hexane–EtOAc–$CHCl_3$=1:2:1 with a few drops of AcOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.86–2.89 (m, 2H), 3.02–3.06 (m, 2H), 7.17 (d, J=8.4 Hz, 1H), 7.39 (d, J=8.4 Hz, 1H), 7.40–7.47 (m, 2H), 7.65 (br s, 1H), 7.73–7.76 (m, 1H), 8.24–8.27 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.1, 34.7, 120.0, 120.7, 122.1, 125.3, 125.7, 125.9, 127.3, 128.1, 133.7, 149.2, 180.5.

*4.3.2. 3-(1-Hydroxy-4-methylnaphthalen-2-yl)propanoic acid (**5b**).* This compound was prepared as **5a** from 4-methylnaphthalen-1-ol (**12b**) in 62% yield (three steps). White solid; TLC, R_f=0.50 (hexane–EtOAc–$CHCl_3$=1:2:1 with a few drops of AcOH); IR (film) 3500–3200, 3010, 1765, 1703, 1387, 1147 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.57 (s, 3H), 2.85 (t, J=6.9 Hz, 2H), 2.99 (t, J=6.9 Hz, 2H), 6.99 (s, 1H), 7.44–7.49 (m, 2H), 7.84–7.88 (m, 1H), 8.24–8.28 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.7, 24.0, 34.7, 119.5, 122.7, 123.8, 125.0, 125.7, 126.0, 126.6, 128.4, 132.5, 147.7, 180.3; HRMS (FAB$^+$) m/z calcd for $C_{14}H_{15}O_3$ (M+H) 231.1021, found 231.1025.

*4.3.3. 3-(4-Chloro-1-hydroxynaphthalen-2-yl)propanoic acid (**5c**).* This compound was prepared as **5a** from 4-chloronaphthalen-1-ol (**12c**) in 40% yield (three steps). White solid; TLC, R_f=0.50 (hexane–EtOAc–$CHCl_3$=1:2:1 with a few drops of AcOH); IR (KBr) 3500–3200, 1691, 1595, 1449, 1381, 1259 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.57 (t, J=7.8 Hz, 2H), 2.98 (t, J=7.8 Hz, 2H), 7.48 (s, 1H),

7.54–7.63 (m, 2H), 8.03 (d, J=7.3 Hz, 1H), 8.27 (d, J=7.3 Hz, 1H), 9.48 (br s, 1H), 12.18 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 25.0, 34.0, 120.5, 122.5, 122.7, 123.5, 125.8, 126.5, 126.8, 128.5, 129.4, 149.1, 174.1; HRMS (FAB$^+$) m/z calcd for $C_{13}H_{12}ClO_3$ (M+H) 251.0475, found 251.0479.

*4.3.4. 3-(4-Bromo-1-hydroxynaphthalen-2-yl)propanoic acid (**5d**)*[6]. This compound was prepared as **5a** from 4-bromonaphthalen-1-ol (**12d**) in 71% yield (3 steps). Yellow solid; TLC, R_f=0.50 (hexane–EtOAc–$CHCl_3$=1:2:1 with a few drops of AcOH); IR (KBr) 3500–3200, 1692, 1595, 1449, 1378, 1241 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.87–2.90 (m, 2H), 3.00–3.03 (m, 2H), 7.48 (s, 1H), 7.51 (dt, J=1.2, 7.2 Hz, 1H), 7.56 (dt, J=1.2, 7.2 Hz, 1H), 7.50–7.70 (br s, 1H), 8.08 (d, J=7.2 Hz, 1H), 8.25 (d, J=7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.8, 34.6, 113.4, 121.0, 122.8, 126.1, 126.7, 127.1, 127.3, 131.4, 131.7, 149.4, 180.3; HRMS (FAB$^+$) m/z calcd for $C_{13}H_{11}BrO_3$ (M) 293.9892, found 293.9896.

*4.3.5. 3-(1-Hydroxy-4-phenylnaphthalen-2-yl)propanoic acid (**5e**).* This compound was prepared as **5a** from 4-phenylnaphthalen-1-ol (**12e**) in 73% yield (three steps). Pale yellow solid; TLC, R_f=0.50 (hexane–EtOAc–$CHCl_3$=1:2:1 with a few drops of AcOH); IR (KBr) 3500–3200, 1699, 1578, 1391, 1304, 1220 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.59 (t, J=7.5 Hz, 2H), 3.03 (t, J=7.5 Hz, 2H), 7.23 (s, 1H), 7.39–7.51 (m, 7H), 7.73 (d, J=7.5 Hz, 2H), 8.28 (d, J=7.5 Hz, 1H), 9.25 (br s, 1H), 12.05 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 25.3, 34.3, 121.3, 122.4, 124.8, 125.0, 125.5, 125.6, 126.9, 128.4 (2C), 129.6, 129.9 (2C), 130.6, 131.0, 140.4, 149.2, 174.4; HRMS (FAB$^+$) m/z calcd for $C_{19}H_{17}O_3$ (M+H) 293.1178, found 293.1174.

*4.3.6. 3-(4-Benzoyl-1-hydroxynaphthalen-2-yl)propanoic acid (**5f**)*[6]. This compound was prepared as **5a** from (4-hydroxynaphthalen-1-yl)(phenyl)methanone (**12f**) in 77% yield (three steps). White solid; TLC, R_f=0.50 (hexane–EtOAc–$CHCl_3$=1:2:1 with a few drops of AcOH); IR (KBr) 3500–3200, 1685, 1562, 1503, 1269, 1242 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.55 (t, J=7.3 Hz, 2H), 2.99 (t, J=7.3 Hz, 2H), 7.40–7.57 (m, 5H), 7.67 (t, J=7.3 Hz, 1H), 7.74 (d, J=8.3 Hz, 2H), 8.21 (d, J=8.3 Hz, 1H), 8.34 (d, J=7.8 Hz, 1H), 10.10 (br s, 1H), 12.10 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 25.2, 33.9, 119.8, 122.4, 125.2, 125.3, 125.5, 126.1, 127.0, 128.6 (2C), 129.9 (2C), 131.2, 132.7, 133.8, 138.9, 153.4, 174.0, 196.2; HRMS (FAB$^+$) m/z calcd for $C_{20}H_{17}O_4$ (M+H) 321.1127, found 321.1133.

*4.3.7. 3-(4-(4-Bromobenzoyl)-1-hydroxynaphthalen-2-yl)propanoic acid (**5g**).* This compound was prepared as **5a** from (4-bromophenyl)(4-hydroxynaphthalen-1-yl)methanone (**12g**) in 70% yield (three steps). Pale yellow solid; TLC, R_f=0.50 (hexane–EtOAc–$CHCl_3$=1:2:1 with a few drops of AcOH); IR (KBr) 3500–3200, 1716, 1699, 1628, 1570, 1509, 1260 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.55 (t, J=7.3 Hz, 2H), 2.99 (t, J=7.3 Hz, 2H), 7.52 (s, 1H), 7.52–7.57 (m, 2H), 7.66 (d, J=8.2 Hz, 2H), 7.74 (d, J=8.7 Hz, 2H), 8.23–8.27 (m, 1H), 8.33–8.36 (m, 1H), 10.18 (br s, 1H), 12.16 (br s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 25.1, 33.9, 119.8, 122.4, 125.2, 125.3 (2C), 125.5, 126.7, 127.2, 131.2, 131.6 (2C), 131.9 (2C), 134.3, 137.9, 153.7, 174.0, 196.1; HRMS (FAB$^+$) m/z calcd for $C_{20}H_{15}BrO_4$ (M) 398.0154, found 398.0155.

*4.3.8. 3-(1-Hydroxy-4-methoxynaphthalen-2-yl)propanoic acid (**5h**)*[6]. This compound was prepared as **5a** from 4-methoxynaphthalen-1-ol (**12h**) in 54% yield (three steps). White solid; TLC, R_f=0.50 (hexane–EtOAc–$CHCl_3$=1:2:1 with a few drops of AcOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.89 (t, J=6.4 Hz, 2H), 3.04 (t, J=6.4 Hz, 2H), 3.95 (s, 3H), 6.49 (s, 1H) 7.18–7.28 (br s, 1H), 7.45 (t, J=8.4 Hz, 1H), 7.50 (t, J=8.4 Hz, 1H), 8.14 (d, J=8.4 Hz, 1H), 8.21 (d, J=8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.5, 34.7, 55.7, 105.5, 119.6, 121.6, 122.0, 125.3, 125.4, 126.0, 126.7, 142.7, 149.7, 180.3.

*4.3.9. 3-(1-Hydroxy-6-methoxynaphthalen-2-yl)propanoic acid (**5i**).* This compound was prepared as **5a** from 6-methoxynaphthalen-1-ol (**12i**) in 60% yield (three steps). Yellow solid; TLC, R_f=0.50 (hexane–EtOAc–$CHCl_3$=1:2:1 with a few drops of AcOH); IR (KBr) 3542, 3484, 1686, 1418, 1360, 1229, 1163 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.50–2.53 (m, 2H), 2.91 (t, J=7.3 Hz, 2H), 3.84 (s, 3H), 7.07 (dd, J=2.8, 9.2 Hz, 1H) 7.17–7.26 (m, 3H), 8.08 (d, J=9.0 Hz, 1H), 9.07 (br s, 1H), 12.10 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 25.2, 34.4, 55.1, 105.7, 117.0, 118.2, 119.5, 120.6, 123.6, 129.1, 134.6, 149.7, 156.8, 174.4; HRMS (FAB$^+$) m/z calcd for $C_{14}H_{15}O_4$ (M+H) 247.0970, found 247.0965.

*4.3.10. 3-(1-Hydroxy-3-methoxynaphthalen-2-yl)propanoic acid (**5j**).* This compound was prepared as **5a** from 3-methoxynaphthalen-1-ol (**12j**) in 40% yield (three steps). Pale brown solid; TLC, R_f=0.46 (hexane–EtOAc–$CHCl_3$=1:2:1 with a few drops of AcOH); IR (KBr) 3394, 3406, 2943, 1697, 1446, 1406, 1268, 1116 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.42 (t, J=8.0 Hz, 2H), 2.98 (t, J=8.0 Hz, 2H), 3.87 (s, 3H), 6.87 (s, 1H), 7.27 (t, J=7.3 Hz, 1H), 7.37 (t, J=7.3 Hz, 1H), 7.69 (d, J=7.8 Hz, 1H), 8.08 (d, J=8.2 Hz, 1H), 9.20 (br s, 1H), 12.19 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 19.1, 33.5, 55.5, 97.8, 113.9, 121.2, 121.9, 122.4, 125.9, 126.4, 133.2, 150.4, 156.5, 174.8; HRMS (FAB$^+$) m/z calcd for $C_{14}H_{15}O_4$ (M+H) 247.0970, found 247.0971.

*4.3.11. 3-(3-(Benzyloxymethyl)-1-hydroxynaphthalen-2-yl)propanoic acid (**5k**).* This compound was prepared as **5a** from 3-benzyloxymethylnaphthalen-1-ol (**12k**) in 53% yield (three steps). Pale yellow solid; TLC, R_f=0.38 (hexane–EtOAc–$CHCl_3$=1:2:1 with a few drops of AcOH); IR (KBr) 3233, 2874, 1696, 1362, 1250, 1033 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.84 (t, J=5.0 Hz, 1H), 3.11 (t, J=5.0 Hz, 1H), 4.56 (s, 2H), 4.65 (s, 2H), 7.24–7.46 (m, 8H), 7.71–7.73 (m, 1H), 8.22–8.23 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.0, 34.2, 71.5, 72.0, 119.9, 122.0, 122.4, 125.5, 125.7, 126.2, 127.3, 127.8, 128.1 (2C), 128.5 (2C), 132.9, 134.2, 137.7, 150.4, 180.8; HRMS (FAB$^+$) m/z calcd for $C_{21}H_{21}O_4$ (M+H) 337.1440, found 337.1434.

4.4. Preparation of iodosylarene 14 (Scheme 6)[6]

A solution of **7g** (61.5 mg, 0.1 mmol) and Selectfluor® (177 mg, 0.5 mmol) in AcOH (1 mL) and CH_3CN (3.2 mL) was stirred for 5 h at room temperature. After CH_3CN was evaporated in vacuo, water was added to the residue and the resulting solution was extracted with CH_2Cl_2 (twice), and washed with water. The combined organic layers were dried over anhydrous Na_2SO_4. The solvents were removed in vacuo to give **14** (66 mg, 0.09 mmol, contained ca. 10% of **7g**) in 90% yield. White powder; IR (film) 3317, 3008, 1677, 1517, 1464, 1252, 1094 cm^{-1}; The ^{1}H and ^{13}C NMR spectra of **14** were assigned by using a combination of 2D NMR experiments, which included HMQC and HMBC studies: ^{1}H NMR ($CDCl_3$, 400 MHz, Ar^1=Iodoarene, Ar^2=Mesitylene) δ 1.50 (s, 6H, IOCOCH_3), 1.80–1.90 (br s, 12H, 2-CH_3–Ar^2), 1.88 (d, J=6.5 Hz, 6H, –OCH(CH_3)CO–), 2.21 (s, 6H, 4-CH_3–Ar^2), 5.15 (q, J=6.5 Hz, 2H, –OCH(CH$_3$)CO–), 6.79 (s, 4H, 3H–Ar^2), 6.94 (d, J=8.5 Hz, 2H, 3H–Ar^1), 7.57 (t, J=8.5 Hz, 1H, 4H–Ar^1), 8.34 (s, 2H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.6 (4C), 19.4 (2C), 19.5 (2C), 20.9 (4C), 76.2 (2C), 103.5, 106.3 (2C), 129.0 (4C), 129.6 (4C), 134.9 (2C), 136.5, 137.4 (2C), 156.0 (2C), 169.6 (2C), 176.7 (2C); HRMS (FAB$^+$) m/z calcd for $C_{32}H_{38}IN_2O_6$ (M–OAc) 673.1775, found 673.1779.

4.5. Representative procedure for 8g-catalyzed enantioselective oxidative dearomatization of 5 with mCPBA (Tables 1–3)

*4.5.1. (+)-1′H,3H-Spiro[furan-2,2′-naphthalene]-1′,5(4H)-dione (**6a**, Table 2, entry 3)*[6]. A solution of **5a** (216 mg, 1.0 mmol), **7g** (92.2 mg, 0.15 mmol, 15 mol %), and *m*CPBA (269 mg, 1.2 mmol, 1.2 equiv) in $CHCl_3$ (50 mL) was stirred at 0 °C. After 18 h, the resulting mixture poured into aqueous $Na_2S_2O_3$ (20 mL) and aqueous $NaHCO_3$, and extracted with $CHCl_3$ (two times). The organic layers were dried over anhydrous $MgSO_4$ and solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: hexane–EtOAc=10:1 to 4:1) to give **6a** (129 mg, 0.6 mmol) in 60% yield. White solid; TLC, R_f=0.46 (hexane–EtOAc–$CHCl_3$=1:2:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.18 (ddd, J=9.6, 11.0, 13.5 Hz, 1H), 2.49 (ddd, J=1.8, 9.6, 13.5 Hz, 1H), 2.60 (ddd, J=1.8, 9.6, 17.6 Hz, 1H), 2.92 (ddd, J=9.6, 11.0, 17.6 Hz, 1H), 6.21 (d, J=10.4 Hz, 1H), 6.66 (d, J=10.4 Hz, 1H), 7.26 (d, J=8.0 Hz, 1H), 7.41 (t, J=8.0 Hz, 1H), 7.62 (t, J=8.0 Hz, 1H), 8.02 (d, J=8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.5, 31.2, 83.4, 127.3, 127.8, 127.9, 127.9, 129.0, 132.3, 135.7, 136.8, 176.5, 196.5; HPLC (OD-H column), hexane–^{i}PrOH=85:15 as eluent, 1.0 mL/min, t_R=19.4 min (major), 25.1 min (minor); $[\alpha]_D^{26}$ +181.7 (*c* 1.2, $CHCl_3$) for 92% ee.

4.6. Representative procedure for the stoichiometric oxidation of 5 with 14 (Scheme 6 and Table 4)

A solution of **5a** (10.8 mg, 0.05 mmol) and **14** (36.6 mg, 0.05 mmol) in $CHCl_3$ (2.5 mL) was stirred at −20 °C. After 19 h, the resulting mixture poured into aqueous $Na_2S_2O_3$ (5 mL) and aqueous $NaHCO_3$, and extracted with $CHCl_3$ (two times). The organic layers were dried over anhydrous $MgSO_4$ and solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: hexane–EtOAc=10:1 to 4:1) to give **6a** (7.5 mg, 0.035 mmol) in 70% yield and 90% ee.

*4.6.1. (+)-4′-Methyl-1′H,3H-spiro[furan-2,2′-naphthalene]-1′,5(4H)-dione (**6b**; Table 3, entry 1 and Table 4, entry 2).* Colorless amorphous; TLC, R_f=0.40 (hexane–EtOAc=1:1); IR (film) 3027, 1783, 1696, 1599, 1453, 1175 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.12–2.24 (m, 1H), 2.21 (s, 3H), 2.41 (ddd, J=1.8, 9.6, 13.3 Hz, 1H), 2.59 (ddd, J=1.8, 9.6, 17.6 Hz, 1H), 2.91 (ddd, J=9.6, 11.4, 17.6 Hz, 1H), 6.03 (s, 1H), 7.40–7.46 (m, 2H), 7.69 (dt, J=1.4, 7.8 Hz, 1H), 8.05 (dd, J=1.4, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.3, 26.8, 31.5, 83.5, 124.8, 127.3, 127.9, 128.7, 129.0, 133.1, 135.6, 137.9, 176.5, 196.8; HRMS (FAB$^+$) m/z calcd for $C_{14}H_{13}O_3$ (M+H) 229.0865, found 229.0862; HPLC (AD-3 column), hexane–^{i}PrOH=85:15 as eluent, 0.7 mL/min, t_R=20.8 min (minor), 25.3 min (major); $[\alpha]_D^{26}$ +102.4 (*c* 0.61, $CHCl_3$) for 84% ee.

*4.6.2. (+)-4′-Chlorospiro[tetrahydrofuran-2,2′-(1′H-naphthaline)]-1′,5-dione (**6c**; Table 3, entry 2).* White solid; TLC, R_f=0.43 (hexane–EtOAc=1:1); IR (film) 3018, 1788, 1700, 1595, 1454, 1293 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.23 (ddd, J=9.6, 11.0, 13.4 Hz, 1H), 2.45 (ddd, J=2.3, 9.6, 13.4 Hz, 1H), 2.62 (ddd, J=2.3, 9.6, 17.9 Hz, 1H), 2.91 (ddd, J=9.6, 11.0, 17.9 Hz, 1H), 6.40 (s, 1H), 7.52 (dt, J=1.8, 7.4 Hz, 1H), 7.70–7.79 (m, 2H), 8.06 (d, J=7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.5, 31.5, 83.4, 126.1, 127.3, 128.1, 129.1, 130.1, 131.8, 134.5, 135.8, 175.7, 194.7; HRMS (FAB$^+$) m/z calcd for $C_{13}H_{10}ClO_3$ (M+H) 249.0318, found 249.0316; HPLC (OD-H column), hexane–^{i}PrOH=85:15 as eluent, 1.0 mL/min, t_R=18.4 min (major), 22.2 min (minor); $[\alpha]_D^{24}$ +99.0 (*c* 0.89, $CHCl_3$) for 90% ee.

*4.6.3. (+)-4′-Bromospiro[tetrahydrofuran-2,2′-(1′H-naphthaline)]-1′,5-dione (**6d**; Table 3, entry 3)*[6]. Recrystallization of **6d** (85% ee) was carried out in the solution of CH_3CN at room temperature to give colorless crystal (low ee). The enantioselectivities of the mother liquid was 98% ee. White solid; TLC, R_f=0.43 (hexane–EtOAc=1:1); IR (film) 3029, 1791, 1699, 1592, 1453, 1187 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.24 (ddd, J=9.6, 11.0, 13.5 Hz, 1H), 2.46 (ddd, J=2.3, 9.6, 13.5 Hz, 1H), 2.62 (ddd, J=2.3, 9.6, 17.9 Hz, 1H), 2.90 (ddd, J=9.6, 11.0, 17.9 Hz, 1H), 6.67 (s, 1H), 7.49–7.53 (m, 1H), 7.73–7.78 (m, 2H), 8.05 (d, J=7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.5, 31.2, 84.2, 122.5, 127.0, 128.0, 128.8, 130.1, 133.4, 135.1, 135.9, 175.7, 194.7; HRMS (FAB$^+$) m/z calcd for $C_{13}H_{10}BrO_3$ (M+H) 292.9813, found 292.9814; HPLC (OD-H column), hexane–^{i}PrOH=85:15 as eluent, 1.0 mL/min, t_R=18.8 min (major), 22.3 min (minor); $[\alpha]_D^{26}$ +91.8 (*c* 1.6, $CHCl_3$) for 98% ee.

*4.6.4. (+)-4′-Phenyl-1′H,3H-spiro[furan-2,2′-naphthalene]-1′,5 (4H)-dione (**6e**; Table 3, entry 4).* Recrystallization of **6e** (87% ee) was carried out in the solution of ^{i}PrOH at room temperature to give colorless crystal (98% ee). TLC, R_f=0.47 (hexane–EtOAc=1:1); IR (film) 3027, 1783, 1687, 1593, 1280, 1176 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.27 (ddd, J=9.6, 11.0, 13.3 Hz, 1H), 2.54 (ddd, J=2.3, 9.6, 13.3 Hz, 1H), 2.63 (ddd, J=2.3, 9.6, 17.6 Hz, 1H), 2.93 (ddd, J=9.6, 11.0, 17.6 Hz, 1H), 6.12 (s, 1H), 7.15 (d, J=7.3 Hz, 1H), 7.34–7.50 (m, 6H), 7.56 (dt, J=1.4, 7.3 Hz, 1H), 8.10 (dd, J=1.4, 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.7, 31.5, 83.7, 127.4, 127.6, 128.2, 128.4, 128.6 (2C), 128.7 (2C), 128.9, 130.6, 135.3, 137.4, 137.6, 139.8, 176.3, 196.4; HRMS (FAB$^+$) m/z calcd for $C_{19}H_{15}O_3$ (M+H) 291.1021, found 291.1021; HPLC (OD-H column), hexane–^{i}PrOH=85:15 as eluent, 1.0 mL/min, t_R=20.0 min (minor), 31.2 min (major); $[\alpha]_D^{26}$ +115.9 (*c* 0.19, $CHCl_3$) for 98% ee.

*4.6.5. (−)-(R)-4′-Benzoyl-1′H,3H-spiro[furan-2,2′-naphthalene]-1′,5 (4H)-dione (**6f**; Table 3, entry 5)*[6]. Colorless crystal; TLC, R_f=0.40 (hexane–EtOAc=1:1); IR (KBr) 3069, 2944, 1783, 1692, 1591, 1455, 1190 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.27 (ddd, J=9.6, 11.0, 13.3 Hz, 1H), 2.52 (ddd, J=1.8, 9.6, 13.3 Hz, 1H), 2.63 (ddd, J=1.8, 9.6, 17.6 Hz, 1H), 2.92 (ddd, J=9.6, 11.0, 17.6 Hz, 1H), 6.39 (s, 1H), 7.41 (d, J=7.8 Hz, 1H), 7.46–7.52 (m, 3H), 7.60–7.67 (m, 2H), 7.96 (d, J=7.3 Hz, 2H), 8.12 (dd, J=1.4, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.3, 31.2, 82.7, 126.9, 127.4, 128.5, 128.9 (2C), 129.8, 130.1 (2C), 134.0, 134.2, 134.3, 135.8, 136.0, 1375, 175.8, 194.5, 195.2; HRMS (FAB$^+$) m/z calcd for $C_{20}H_{15}O_4$ (M+H) 319.0970, found 319.0971; HPLC (OD-H column), hexane–^{i}PrOH=85:15 as eluent, 1.0 mL/min, t_R=32.4 min (major, *R*), 40.2 min (minor, *S*); $[\alpha]_D^{26}$ −35.2 (*c* 0.41, $CHCl_3$) for >99% ee.

*4.6.6. X-ray crystallographic analysis of (−)-**6f** (Fig. 2).* Recrystallization of (−)-**6f** (83% ee) was carried out in the solution of ^{i}PrOH at room temperature to give colorless crystal (>99% ee). Mp: 153–155 °C. Crystal data: formula $C_{20}H_{14}O_4$, M=318.31, colorless, crystal dimensions 0.50×0.40×0.20 mm^3, orthorhombic, space group $P2_12_12_1$, a=5.4071(16) Å, b=10.164(3) Å, c=28.448 (8) Å, V=1563.4(8) Å^3, Z=4, D_{calcd}=1.352 g/cm^3, F(000)=664, μ (Mo Kα)=0.094 mm^{-1}, T=173(2) K. X-ray crystallographic analysis was performed with a Bruker SMART APEX diffractometer (graphite monochromator, Mo Kα radiation, λ=0.71073 Å) and the structure was solved by direct methods and expanded using Fourier techniques (Sir97 and SHELXL[17]). 11,371 reflections collected, 3876 independent reflections with $I>2\sigma(I)$ ($2\theta_{max}$=28.33°), and 265 parameters were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. R_1=0.0411 and wR_2=0.0848, GOF=1.017. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-758468 for (−)-**6f**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2

1EZ, UK [fax: int. code +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk].

*4.6.7. (−)-4′-(4-Bromobenzoyl)-1′H,3H-spiro[furan-2,2′-naphthalene]-1′,5(4H)-dione (**6g**; Table 3, entry 6).* White solid; TLC, R_f=0.43 (hexane−EtOAc=1:1); IR (film) 3027, 1793, 1698, 1669, 1585, 1278, 1172 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.27 (ddd, J=9.6, 11.0, 13.3 Hz, 1H), 2.52 (ddd, J=1.8, 9.6, 13.3 Hz, 1H), 2.63 (ddd, J=1.8, 9.6, 17.6 Hz, 1H), 2.92 (ddd, J=9.6, 11.0, 17.6 Hz, 1H), 6.38 (s, 1H), 7.37 (d, J=7.8 Hz, 1H), 7.50 (dt, J=0.9, 7.8 Hz, 1H), 7.60−7.66 (m, 3H), 7.83 (d, J=8.7 Hz, 2H), 8.12 (dd, J=1.4, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.2, 31.2, 82.5, 126.8, 127.3, 128.6, 129.8, 129.9, 131.4 (2C), 132.3 (2C), 133.7, 134.2, 134.7, 135.8, 137.2, 175.7, 193.5, 195.0; HRMS (FAB$^+$) m/z calcd for $C_{20}H_{14}BrO_4$ (M+H) 397.0075, found 397.0079; HPLC (OD-H column), hexane−^{i}PrOH=85:15 as eluent, 1.0 mL/min, t_R=44.3 min (major), 49.7 min (minor); $[\alpha]_D^{24}$ −44.0 (c 1.83, $CHCl_3$) for 84% ee.

*4.6.8. 4′-Methoxyspiro[tetrahydrofuran-2,2′-(1′H-naphthaline)]-1′,5-dione (**6h**; Table 3, entry 7)*[6]. White solid; TLC, R_f=0.33 (hexane−EtOAc=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.17 (ddd, J=9.6, 11.0, 13.6 Hz, 1H), 2.49 (ddd, J=2.3, 9.6, 13.6 Hz, 1H), 2.61 (ddd, J=2.3, 9.6, 17.6 Hz, 1H), 2.95 (ddd, J=9.6, 11.0, 17.6 Hz, 1H), 3.84 (s, 3H), 5.17 (s, 1H), 7.46 (t, J=7.6 Hz, 1H), 7.67 (t, J=7.6 Hz, 1H), 7.74 (d, J=7.6 Hz, 1H), 8.00 (d, J=7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.6, 33.0, 55.1, 83.8, 99.9, 123.1, 127.2, 127.5, 129.4, 134.6, 135.3, 152.0, 176.6, 195.7.

*4.6.9. (+)-6′-Methoxy-1′H,3H-spiro[furan-2,2′-naphthalene]-1′,5(4H)-dione (**6i**; Table 3, entry 8 and Table 4, entry 3).* White solid; TLC, R_f=0.27 (hexane−EtOAc=1:1); IR (KBr) 3027, 1787, 1683, 1597, 1273, 1176 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.17 (ddd, J=9.6, 11.0, 13.3 Hz, 1H), 2.40 (ddd, J=2.2, 9.6, 13.3 Hz, 1H), 2.61 (ddd, J=2.2, 9.6, 17.6 Hz, 1H), 2.95 (ddd, J=9.6, 11.0, 17.6 Hz, 1H), 3.94 (s, 3H), 6.21 (d, J=9.6 Hz, 1H), 6.60 (d, J=9.6 Hz, 1H), 6.72 (d, J=2.8 Hz, 1H), 6.91 (dd, J=2.8, 8.7 Hz, 1H), 8.01 (d, J=8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.8, 31.6, 55.7, 82.8, 112.9, 114.2, 120.6, 127.9, 130.5, 133.3, 139.1, 165.6, 176.3, 194.8; HRMS (FAB$^+$) m/z calcd for $C_{14}H_{13}O_4$ (M+H) 245.0814, found 245.0810; HPLC (AD-3 column), hexane−^{i}PrOH=85:15 as eluent, 0.7 mL/min, t_R=33.8 min (minor), 39.6 min (major); $[\alpha]_D^{25}$ +146.8 (c 0.06, $CHCl_3$) for 87% ee.

*4.6.10. (+)-3′-Methoxy-1′H,3H-spiro[furan-2,2′-naphthalene]-1′,5(4H)-dione (**6j**; Table 3, entry 9 and Table 4, entry 4).* Pale yellow solid; TLC, R_f=0.50 (hexane−EtOAc=1:1); IR (KBr) 3027, 1792, 1691, 1650, 1191, 1168 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.34−2.48 (m, 2H), 2.70 (ddd, J=5.0, 9.6, 17.6 Hz, 1H), 2.87 (ddd, J=8.2, 10.6, 17.6 Hz, 1H), 3.82 (s, 3H), 5.73 (s, 1H), 7.15 (d, J=7.3 Hz, 1H), 7.23 (dt, J=0.9, 7.3 Hz, 1H), 7.54 (dt, J=1.4, 7.3 Hz, 1H), 7.95 (d, J=7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.4, 30.5, 55.8, 82.8, 98.3, 124.7, 126.4, 126.8, 128.1, 136.0, 138.2, 157.6, 176.6, 195.2; HRMS (FAB$^+$) m/z calcd for $C_{14}H_{13}O_4$ (M+H) 245.0814, found 245.0814; HPLC (AD-3 column), hexane−^{i}PrOH=85:15 as eluent, 0.7 mL/min, t_R=28.2 min (minor), 29.9 min (major); $[\alpha]_D^{26}$ +98.2 (c 0.53, $CHCl_3$) for 95% ee.

*4.6.11. (+)-3′-(Benzyloxymethyl)-1′H,3H-spiro[furan-2,2′-naphthalene]-1′,5(4H)-dione (**6k**; Table 3, entry 10 and Table 4, entry 5).* Colorless amorphous; TLC, R_f=0.43 (hexane−EtOAc=1:1); IR (film) 1784, 1697, 1600, 1455, 1290, 1180, 1097 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.30−2.37 (m, 1H), 2.43−2.55 (m, 2H), 2.69−2.79 (m, 1H), 4.25 (d, J=12.8 Hz, 1H), 4.36 (d, J=12.8 Hz, 1H), 4.60 (s, 2H), 6.70 (s, 1H), 7.25 (d, J=7.8 Hz, 1H) 7.30−7.40 (m, 6H), 7.62 (t, J=7.8 Hz, 1H), 7.98 (d, J=7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.1, 30.4, 68.9, 73.3, 85.8, 124.6, 126.7, 127.7, 127.8 (2C), 128.0 (2C), 128.5 (2C), 128.6 135.6, 136.8, 137.5, 140.0, 176.6, 196.9; HRMS (FAB$^+$) m/z calcd for $C_{21}H_{19}O_4$ (M+H) 335.1283, found 335.1292; HPLC (OD-H column), hexane−^{i}PrOH=85:15 as eluent, 1.0 mL/min, t_R=27.4 min (minor), 69.0 min (major); $[\alpha]_D^{23}$ +156.2 (c 0.5, $CHCl_3$) for 94% ee.

4.7. One-pot oxidation of 5a to epoxyspirolactone (−)-15 (Scheme 7)

*4.7.1. (−)-(1a′R,2R,7b′R)-1a′H,3H-Spiro[furan-2,2′-naphtho[1,2-b]oxirene]-3′,5(4H,7b′H)-dione (**15**).* A solution of **5a** (10.8 mg, 0.05 mmol), **7g** (4.6 mg, 0.0075 mmol, 10 mol %), and mCPBA (43.1 mg, 0.25 mmol, 1.3 equiv) in $CHCl_3$ (1.7 mL) and CH_3NO_2 (1.7 mL) mixed solvents was stirred at 0 °C for 24 h and at room temperature for 72 h. The solvents were removed in vacuo. The conversion of **5a** to epoxyspirolactones **15** and **16** (84% conv.) and the diastereomeric ratio (**15**–**16**=64:36) were determined by ^{1}H NMR analysis of the crude mixture. The residue was purified by flash column chromatography on silica gel (eluent: hexane−EtOAc=10:1 to 2:1) to give (−)-**15** (6.0 mg, 0.026 mmol) as a single compound in 52% yield. Recrystallization of (−)-**15** (88% ee) was carried out in the solution of EtOH at room temperature to give colorless thin needles (>99% ee). TLC, R_f=0.13 (hexane−EtOAc=1:1); IR (film) 1793, 1706, 1210, 1181 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.04−2.11 (m, 1H), 2.27−2.36 (m, 1H), 2.57−2.73 (m, 2H), 3.92 (d, J=4.2 Hz, 1H), 4.18 (d, J=4.2 Hz, 1H), 7.53−7.57 (m, 1H), 7.64−7.69 (m, 2H), 8.00 (d, J=7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.5, 28.7, 52.4, 55.9, 85.2, 129.0, 129.7, 130.0 (2C), 134.5, 137.8, 175.7, 191.6; HRMS (FAB$^+$) m/z calcd for $C_{13}H_{11}O_4$ (M+H) 231.0657, found 231.0657; HPLC (OD-H column), hexane−EtOH=4:1 as eluent, 1.0 mL/min, t_R=19.8 min (major), 26.2 min (minor); $[\alpha]_D^{24}$ −73.8 (c 1.6, $CHCl_3$) for 92% ee.

*4.7.2. X-ray crystallographic analysis of (±)-**15** (Fig. 3).* Recrystallization of (±)-**15** was carried out in the solution of EtOH at room temperature to give colorless crystal. Mp: 199−201 °C. Crystal data: formula $C_{13}H_{10}O_4$, M=230.21, colorless, crystal dimensions 0.20×0.10×0.10 mm^3, orthorhombic, space group Pbca, a=8.8107 (19) Å, b=11.238(2) Å, c=21.064(4) Å, V=2085.6(8) Å^3, Z=8, D_{calcd}=1.466 g/cm^3, F(000)=960, μ(Mo Kα)=0.110 mm^{-1}, T=143(2) K. X-ray crystallographic analysis was performed with a Bruker SMART APEX diffractometer (graphite monochromator, Mo Kα radiation, λ=0.71073 Å) and the structure was solved by direct methods and expanded using Fourier techniques (Sir97 and SHELXL[17]). 15,230 reflections collected, 2807 independent reflections with $I>2\sigma(I)$ ($2\theta_{max}$=29.18°), and 162 parameters were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. R_1=0.0446 and wR_2=0.1271, GOF=1.061. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-769543 for (±)-**15**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: int. code +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk].

4.8. Epoxidation of (+)-6a to (−)-15 with in situ-generated peracid from UHP and Ac_2O (Scheme 8)[14]

To a stirred mixture of urea hydrogen peroxide (47 mg, 0.5 mmol), sodium hydrogen phosphate (62.5 mg, 0.44 mmol) and (+)-**6a** (92% ee; 10.8 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL) was added acetic anhydride (24 μL, 0.25 mmol) dropwise at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for additional 3 days. The resulting mixture was diluted with $CHCl_3$ and washed with brine. The aqueous layer was extracted with $CHCl_3$, and the combined organic layers were dried over anhydrous Na_2SO_4 and solvents were removed in

vacuo. The conversion (52%) of **6a** to epoxyspirolactones and the diastereomeric ratio (92:8) were determined by ^{1}H NMR analysis of the crude mixture. The residue was purified by flash column chromatography on silica gel (eluent: hexane–EtOAc=5:1) to give (−)-**15** (92% ee; 5.4 mg, 0.024 mmol) as a single compound in 47% yield.

4.9. Re-catalyzed epoxidation of (+)-6a to (−)-15 with H_2O_2 (Scheme 8)[15]

To a solution of (+)-**6a** (92% ee; 21.4 mg, 0.1 mmol), $MeReO_3$ (5 μg, 2 μmol) and 3-cyanopyridine (4.2 mg, 0.04 mmol) in CH_2Cl_2 (0.25 mL) was added slowly 30 wt % H_2O_2 (41.2 μL, 0.4 mmol) at room temperature. After stirring for 48 h at ambient temperature, the resulting mixture was diluted with $CHCl_3$ and washed with brine. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over anhydrous Na_2SO_4 and solvents were removed in vacuo. The conversion (88%) of **6a** to epoxyspirolactones and the diastereomeric ratio (92:8) were determined by ^{1}H NMR analysis of the crude mixture. The residue was purified by flash column chromatography on silica gel (eluent: hexane–EtOAc=5:1) to give (−)-**15** (92% ee; 16.0 mg, 0.07 mmol) in 70% yield.

4.10. Oxidation of (+)-6a with NBS to bromohydrin spirolactone (+)-17 [16]

To a solution of (+)-**6a** (92% ee; 10.7 mg, 0.05 mmol) in THF (0.25 mL) was added water (0.25 mL) at 0 °C until the solution became cloudy. NBS (recrystallized, 17.8 g, 0.10 mmol) was then added and the reaction was allowed to stir for 28 h at 0 °C. The resulting mixture was diluted with EtOAc and washed with brine. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over anhydrous Na_2SO_4 and solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: hexane–EtOAc=10:1 to 4:1) to give (+)-**16** (92% ee; 10.9 mg, 0.035 mmol) in 70% yield. White amorphous; TLC, R_f=0.20 (hexane–EtOAc=1:1); IR (film) 1793, 1699, 1602, 1456, 1210, 1175 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.39–2.47 (m, 1H), 2.81–2.86 (m, 2H), 3.01 (d, J=4.1 Hz, 1H), 3.09–3.17 (m, 1H), 4.47 (d, J=9.2 Hz, 1H), 5.33 (dd, J=4.1, 9.2 Hz, 1H), 7.51 (t, J=7.8 Hz, 1H), 7.73 (t, J=7.8 Hz, 1H), 7.81 (d, J=7.8 Hz, 1H), 8.07 (d, J=7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.5, 28.5, 63.3, 70.1, 86.1, 127.4, 128.2, 128.4, 129.0, 135.7, 142.1, 175.5 188.5; HRMS (FAB$^+$) m/z calcd for $C_{13}H_{12}BrO_4$ (M+H) 310.9919, found 310.9926; HPLC (OD-H column), hexane–EtOH=4:1 as eluent, 1.0 mL/min, t_R=8.6 min (major), 9.7 min (minor); $[\alpha]_D^{22}$ +137.8 (c 0.6, $CHCl_3$) for 92% ee.

4.11. Conversion of bromohydrin (+)-17 to epoxyspirolactone (+)-16 (Scheme 9)

To a solution of (+)-**17** (92% ee; 12.4 mg, 0.04 mmol) in acetone (0.8 mL) was added K_2CO_3 (13.8 mg, 0.1 mmol) at room temperature, and the resulting mixture was stirred for 21 h at ambient temperature. The resulting mixture was filtered through Celite, and the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: hexane–EtOAc=10:1 to 4:1) to give (+)-**16** (92% ee; 9.1 mg, 0.04 mmol) in >99% yield. White solid; TLC, R_f=0.34 (hexane–EtOAc=1:1); IR (film) 3028, 1795, 1698, 1605, 1303, 1185 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.43–2.49 (m, 1H), 2.71–2.80 (m, 1H), 2.95–3.06 (m, 2H), 3.93 (d, J=3.7 Hz, 1H), 4.17 (d, J=3.7 Hz, 1H), 7.54 (t, J=7.8 Hz, 1H), 7.62–7.70 (m, 2H), 7.99 (d, J=7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.7, 28.4, 52.7, 57.8, 80.7, 129.0, 129.6, 130.0 (2C), 134.4, 137.7, 175.6, 190.6; HRMS (FAB$^+$) m/z calcd for $C_{13}H_{11}O_4$ (M+H) 231.0657, found 231.0659; HPLC (OD-H column), hexane–^{i}PrOH=85:15 as eluent, 1.0 mL/min, t_R=24.9 min (major), 28.1 min (minor); $[\alpha]_D^{24}$ +197.7 (c 0.8, $CHCl_3$) for 92% ee.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.04.060. These data include MOL files and InChIKeys of the most important compounds described in this article.

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