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Synthesis of Polycyclic Cyclohexadienone through the Alkoxy-oxylactonization and Dearomatization of 3'-Hydroxy-[1,1'-biphenyl]-2-carboxylic acids Promoted by Hypervalent Iodine

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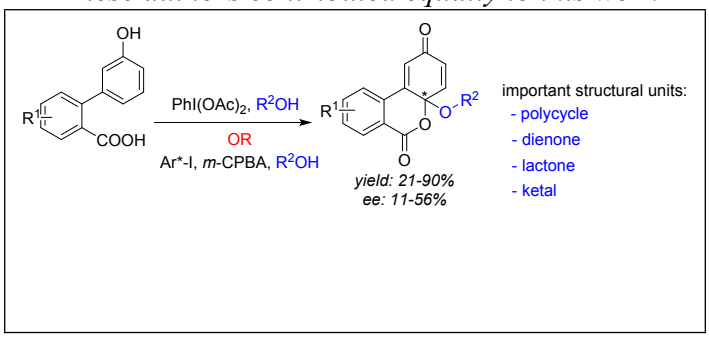


ABSTRACT

Hypervalent iodine simultaneously promoted alkoxy-oxylactonization and dearomatization of 3'-hydroxy-[1,1'-biphenyl]-2-carboxylic acid have been developed using stoichiometric $PhI(OAc)_2$ or a catalytic amount of chiral aryl-λ^3-iodane generated *in situ*. This reaction provides a concise method to synthesize diversely polycyclic cyclohexadienones as potential inhibitors of DNA polymerase under mild reaction conditions.

INTRODUCTION

Cyclohexadienones are acclaimed for their use in diverse biologically active natural products and pharmaceuticals, in particular, dehydroaltenusin with benzopyrolactone structure, found to be an effective inhibitor of DNA polymerase.[1,2] Instances include the meds dexamethasone, (+)-puupehenone and dehydroaltenusin

(Figure 1). Recently, aryliodine-catalyzed oxidative dearomatization reactions of *para*-phenols have a time-honored intensifying interest as target synthesis with the cyclohexadienones moiety as a key functional group.[3] In addition, Kita reported the synthesis of spirocyclohexanones from *para*-phenols following intramolecular oxylactonizations of the carboxylic acids.[4] For the time being, chiral iodine(III) catalysts have been utilized to achieve asymmetric spirocyclizations of *ortho*-substituted naphthol derivatives with high enantioselectivity.[5] However, studies on *para*-phenols alkoxy-oxylactonization reactions are relatively rare. The need for aforesaid lactonized products has inspired the expansion of methodologies for their synthesis. For a chemist, a low toxic synthetic approach utilizing metal-free reagents such as hypervalent iodine reagents compared with metal-based reagents is a highly fascinating means for accessing poly heterocycles.

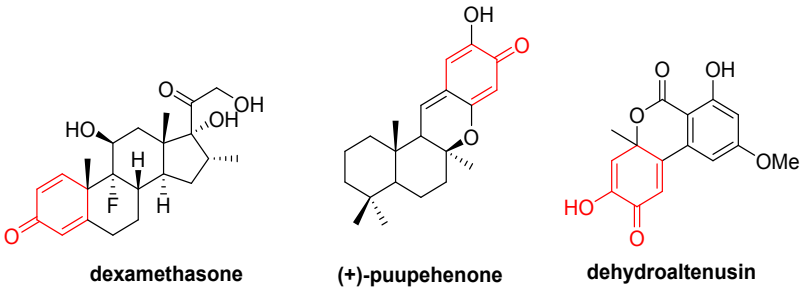
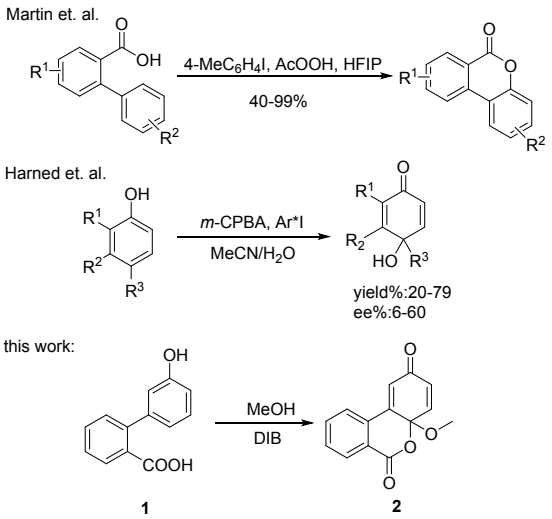


Figure 1. Cyclohexadienone-containing natural products.

In recent years, hypervalent iodine reagents can be used for the alkoxylation or hydroxylation of *para*-phenols[6] and oxylactonizations of benzoic acids.[7] For instance, Martin and co-workers reported a synthesis of tricyclic benzolactones due to a big energy gap between HOMO and LUMO frontier orbitals using catalytic amounts of aryliodine and peracetic acid as terminal oxidant.[7a] And in 2013, Harned and coworkers established a strategy to access *para*-quinols with low to moderate enantioselectivity from oxidative dearomatization reactions of phenols utilizing a newly designed 8-iodotetralone and tartaric acid based chiral aryl iodide catalyst.[6a] According to Martin and Harned's reports, it takes two steps to synthesize the methoxy-cyclohexadienones. In defiance of these advances, some concerns still linger

in this heartening field. Thereby, it is vitally important to explore new approaches to scale up this area. To the best of our knowledge, there has been no single report of using hypervalent iodine reagents for the construction of methoxy- cyclohexadienones (**2**, Scheme 1). In the continuation of our ongoing lab interest[8] and also premised on the antecedent information, we report mild and user-friendly one-step synthesis polycyclic cyclohexadienone from 3'-hydroxy-[1,1'-biphenyl]-2-carboxylic acid by utilizing $PhI(OAc)_2$ (DIB) and MeOH (Scheme 1).

Scheme 1. **Previous Work and Methoxy-oxylactonization**

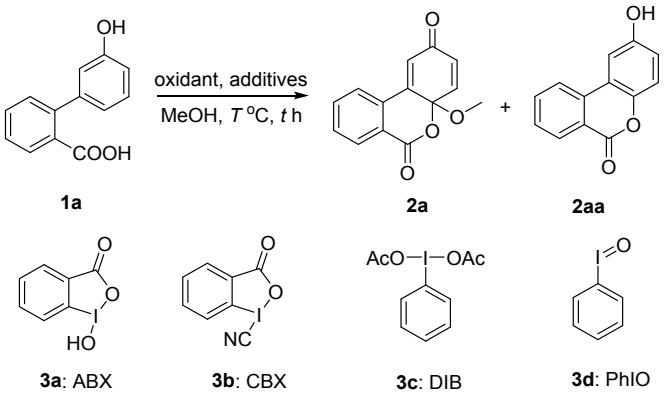


RESULTS AND DISCUSSION

To investigate our supposition, we primarily chose 3'-hydroxy-[1,1'-biphenyl]-2-carboxylic acid (**1a**) as a model substrate. The efficiencies of various hypervalent iodine reagents in the MeOH solvent were examined to explore various reaction conditions. Selected findings from this investigation are itemized in Table 1. To our delight, the desired product **2a** could be synthesized in 16% and 31% yields with the use of PhIO and DIB, respectively, while ABX and CBX did not respond to produce the desired product (Table 1, entries 1-4). When the experiment was conducted in a less polar medium such as DCM instead of methanol, a lactonization product **2aa** without dearomatization was obtained in 11% yield (Table 1, entry 5). After that concentration effect of DIB and MeOH were tested (Table 1, entries 6-12), the best result of 72% yield was obtained when added 2.8 eq.

DIB and 1mL MeOH. Subsequently, the effects of reaction time and temperature were investigated. Both raising and lowering time and temperature resulted in the decreased yield correspondingly (Table 1, entries 13-17). Thereafter, different additives and their amounts were subjected to the rection in order to get improved yield (Table 1, entries 18-26). Among these, 5 Å of molecular sieve as an additive provided the best yield in 78%.

Table 1. Optimization of Reaction Conditions[a]



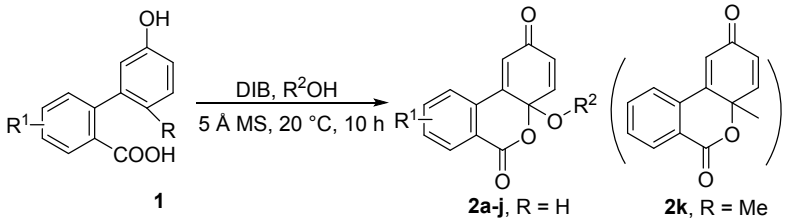
Entry	Oxidant (equiv)	MeOH (mL)	Additives[b]	*T* (°C)	Yield[c] (%)
1	ABX(1.2)	1		20	0
2	CBX(1.2)	1		20	0
3	PhIO(1.2)	1		20	16
4	DIB(1.2)	1		20	31
5[d]	DIB(1.2)	1		20	11
6	DIB(1.8)	1		20	40
7	DIB(2.2)	1		20	61
8	DIB(2.5)	1		20	69
9	DIB(2.8)	1		20	72
10	DIB(3.0)	1		20	67
11	DIB(2.8)	0.5		20	68
12	DIB(2.8)	1.5		20	57
13	DIB(2.8)	1		0	65
14	DIB(2.8)	1		30	69
15	DIB(2.8)	1		50	58
16[e]	DIB(2.8)	1		20	61
17[f]	DIB(2.8)	1		20	56
18	**DIB(2.8)**	**1**	**5Å MS**	**20**	**78**
19	DIB(2.8)	1	4 Å MS	20	71
20	DIB(2.8)	1	3 Å MS	20	69
21	DIB(2.8)	1	Et_3N	20	0

23	DIB(2.8)	1	Na_2CO_3	20	35
24	DIB(2.8)	1	CF_3COOH	20	31
25	DIB(2.8)	1	CH_3COOH	20	26
26	DIB(2.8)	1	$FeCl_3$	20	47

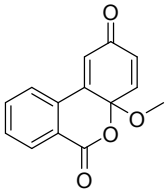
[a] Conditions: **1a** (0.3 mmol), oxidant (specified) in MeOH for 10 h. [b] 20 wt% of additives. [c] Yield determined by ^{1}H-NMR using anisole ether as an internal standard. [d] DCM replaced MeOH. [e] Reaction for 5 h. [f] Reaction for 15 h.

With the optimal conditions for alkoxy-oxylactonization and dearomatization in hand, the scope of the reaction was investigated. An inspection of the differently substituted substrates disclosed that all 3'-hydroxy-[1,1'-biphenyl]-2-carboxylic acid derivatives underwent alkoxy-oxylactonization and dearomatization to generate **2a**–**k** in moderate to high yields ranging from 48% to 80%. Results depicted in Table 2 reveal that this reaction is highly sensitive to the size of the aliphatic part of alcohol. Increasing the size of R^2OH had a negative effect (**2a**-**d**), and no products were obtained in the cases of **2e** and **2f**. The effects of both electrons donating and withdrawing group on various position of phenyl ring were also studied. For electron-withdrawing groups, *para*-nitro showed a high yield of 72% (**2h**) compared to *para*-fluorine (**2g**). In the case of an inductively electron-donating methyl group, *meta*-position was found to be more favourable than that of *ortho*-position (**2i** and **2j**). In addition, this method can also be employed successfully to synthesize the mother core (**2k**) of dehydroaltenusin in moderate yield.

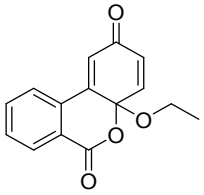
Table 2. Scope of 3'-Hydroxy-[1,1'-biphenyl]-2-carboxylic Acids[a]



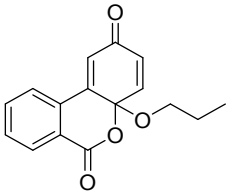
1 **2a-j**, R = H **2k**, R = Me



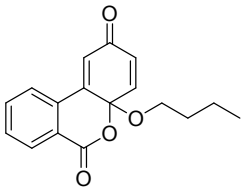
2a, 78%[b]



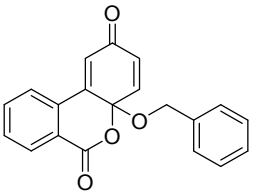
2b, 69%



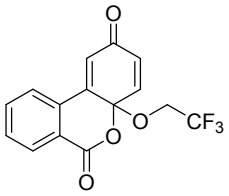
2c, 65%



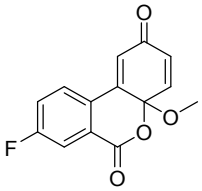
2d, 48%



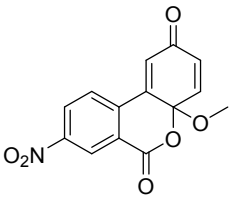
2e, 0%



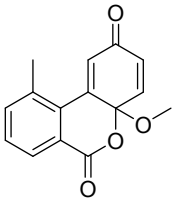
2f, 0%



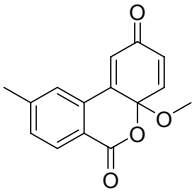
2g, 49%



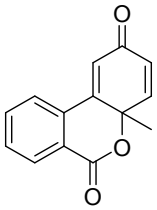
2h, 72%



2i, 69%



2j, 80%



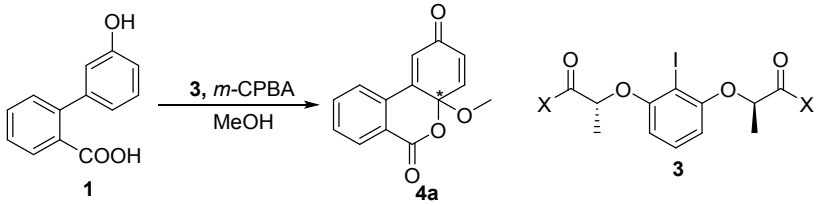
2k, 75%[c]

[a] Conditions: **1** (0.3 mmol), 20 wt% 5 Å MS and DIB (0.84 mmol) in R^2OH (1 mL) at 20°C for 10 h. [b] Isolated yield by silica gel column chromatography. [c] DCM replaced MeOH.

Inspired from the our afore substrate generality, next, observations were designed to approach enantioselective alkoxy-oxylactonization and dearomatization of 3'-hydroxy-[1,1'-biphenyl]-2-carboxylic acid by utilizing a series of chiral iodoarenes as a catalyst with *m*-CPBA in MeOH at 20 °C, respectively, and results are tabulated in Table 3. Initially, oxygen and nitrogen moieties based chiral iodoarenes **3a-d** were subjected to this transformation. Gratifyingly, we found that the chiral iodoarene **3d**, incorporating a bulky phenyl group and as various H-bond donor, afforded better enantioselectivity. Next, alternative chiral iodoarene precursors possessing different substituted groups of phenylamide were considered (**3e-h**). It is worth noting that introducing an electron-donating group such as -Me, on the phenyl appears more beneficial for enantioselectivity than that of electron-withdrawing groups such as -F, -Cl, or $-CF_3$. Encouraged by this result, a variety of chiral iodoarenes, possessing different methyl substitution on phenylamide, were prepared (**3i-n**) and their effects on this changeover under afore mentioned reaction conditions

were analyzed. Among these, **3l** provided the highest level of enantioselectivity.

Table 3. Optimization of the Chiral Organoiodine[a]



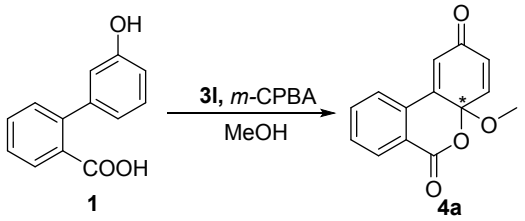
3a (X = OEt): 22% yield[b], 4% ee[c]	**3h** (X = NHNap): 14% yield, 31% ee
3b (X = OH): 18% yield, 10% ee	**3i** (X = NH(3,5-Me_2-Ph)): 18% yield, 40% ee
3c (X = NHPr: 20% yield,11% ee	**3j** (X = NHMes): 15% yield, 15% ee
3d (X = NHPh): 13% yield, 36% ee	**3k** (X = NH(2-Me-Ph)): 17% yield, 23% ee
3e (X = NH(4-CF_3-Ph)): 17% yield, 31% ee	**3l** (X = NH(4-Me-Ph)): 22% yield, 41% ee
3f (X = NH(2,3-F-Cl-Ph)): 17% yield, 25% ee	**3m** (X = NH(3,4,5-Me_3-Ph)): 17% yield, 41% ee
3g (X = NH(2,3-Me-F-Ph)): 11% yield, 38% ee	**3n** (X = NH(4-*i*Pr-Ph)): 20% yield, 37 % ee

[a] Conditions: **1a** (0.3 mmol), **3** (specified, 20 mol%) and *m*-CPBA (0.45 mmol) in MeOH (1 mL) at 20°C for 10 hours. [b] Yield determined by ^{1}H-NMR using anisole ether as an internal standard. [c] By HPLC analysis (chiralpack AD-H).

After screening of catalysts, tricyclic aryl iodide **3l** as a lead structure, efforts were made to investigate its optimal conditions for this catalytic asymmetric oxidative dearomatization and results are detailed in Table 4. Initially, catalyst uploading was investigated using 3'-hydroxy-[1,1'-biphenyl]-2-carboxylic acid **1a** with 1.5 equiv of *m*-CPBA in MeOH for 10 hours and the best result of 22% yield with 41% *ee* was obtained in the presece of 0.2 equiv of **3l** (Table 4, entries 1-5). Subsequently, the effects of amounts of *m*-CPBA and reaction time were tested (Table 4, entries 6-12). As the amount of *m*-CPBA decreases, an improvement in *ee* value along with a fall in the yield was observed (Table 4, entry 7). An increase in reaction output resulted in the foremost result of 58% yield with 43% *ee* at 30 hours (Table 4, entry 11). Lowered the temperature, both the yield and *ee* dropped correspondingly (Table 4, entries 13-15). After that, different additives were subjected to the afore optimal reaction conditions to improve both *ee* and yield. Unfortunately, all additives resulted

in a negative impact (Table 4, entries 16-22). Basic additive such as Et_3N found quencher to the reaction while a negative effect was noticed for either acidic or neutral additives. From these experimental data, we determined the optimized conditions to be using 3'-hydroxy-[1,1'-biphenyl]-2-carboxylic acid **1a** as a model substrate, 1.5 equiv *m*-CPBA as an oxidant and 0.2 equivalents of tricyclic aryl iodide **3l** as a catalyst in MeOH for 30 hours.

Table 4. Optimization of Reaction Conditions[a]

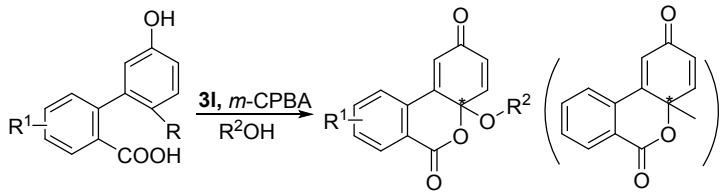


Entry	**3l** (equiv)	*m*-CPBA (equiv)	Additives (0.2 equiv)	*t* (h)	*ee*[b] (%)	Yield (%)
1	0.05	1.5		10	34	15
2	0.1	1.5		10	38	17
3	0.15	1.5		10	39	18
4	0.2	1.5		10	41	22
5	0.3	1.5		10	40	27
6	0.2	1		10	36	6
7	0.2	1.2		10	43	14
8	0.2	1.8		10	38	23
9	0.2	2		10	37	25
10	0.2	1.2		20	42	30
11	**0.2**	**1.2**		**30**	**43**	**58**
12	0.2	1.2		40	39	55
13[d]	0.2	1.2		30	40	40
14[e]	0.2	1.2		30	41	24
15[f]	0.2	1.2		30	39	16
16	0.2	1.2	Et_3N	30	0	0
17	0.2	1.2	3Å	30	38	40
18	0.2	1.2	4Å	30	37	43
19	0.2	1.2	5Å	30	36	55
20	0.2	1.2	H_2O	30	37	47
21	0.2	1.2	Na_2SO_4	30	34	49
22	0.2	1.2	CH_3COOH	30	35	53

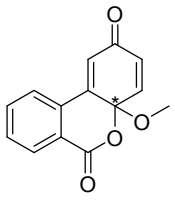
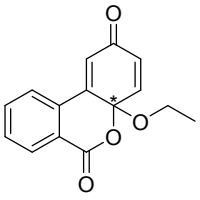
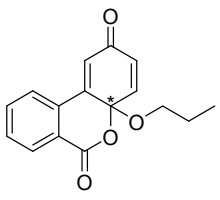
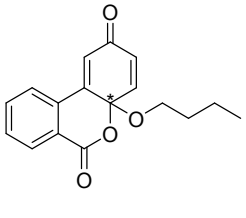
[a] Conditions: **1a** (0.3 mmol), **3l** (specified, 20 mol%) and *m*-CPBA (specified) in MeOH (1 mL) at 20 °C. [b] By HPLC analysis (chiralpack AD-H). [c] Yield determined by ^{1}H-NMR using anisole ether as an internal standard. [d] Reaction at 0 °C. [e] Reaction at -10 °C. [f] Reaction at -30 °C.

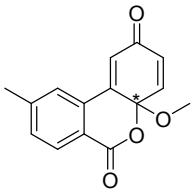
On the basis of the reaction conditions optimized in Table 4, the substrate generality of the asymmetric alkoxy-oxylactonization and dearomatization reaction was explored. Initially, the effect of the nucleophilic organic moiety of alchol was probed. An increase in the size of R^2OH demonstrated a considerable steric effect. A prominent decrease in yield from 58% to 21% along with moderate level of enantioselectivities ranging from 40% to 50% *ee* caused when sterically hindered alcohols were investigated (Table 5, **4a-d**). After that, effects of position and substituents were examined. Electron-donating groups such as methyl both at *meta*- and *ortho*- positions provided close enantioselectivities while electron-withdrawing groups such as *para*-fluorine that enhance the nucleophilic character of carboxylate anion showed a considerable increase in yield and ee (Table 5, **4e-g**). When DCM replaced MeOH, methyl substituted substrate led to formation of **4h** in yield of 61% with 13% *ee* as well.

Table 5. Scope of of 3'-Hydroxy-[1,1'-biphenyl]-2-carboxylic Acids[a]

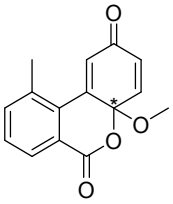


1 **4a-g**, R = H **4h**, R = Me

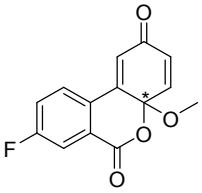
			
4a, 58% yield[b], 43% ee[c]	**4b**, 55% yield, 52% ee	**4c**, 27% yield, 50% ee	**4d**, 21% yield, 40% ee



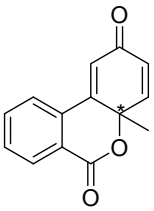
4e, 42% yield, 15% ee



4f, 31% yield, 11% ee



4g, 42% yield, 23% ee

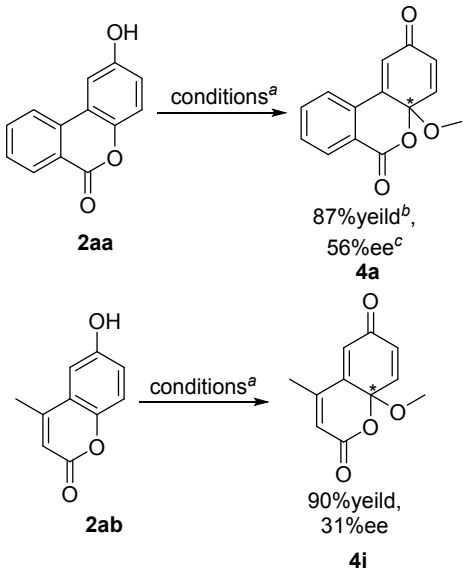


4h, 61% yield[d], 13% ee

[a] Conditions: **1** (0.3 mmol), **3l** (0.06 mmol) and *m*-CPBA (0.36 mmol) in R^2OH (1 mL) at 20 °C for 30 h. [b] Isolated yield by silica gel column chromatography. [c] By HPLC analysis (chiralpack AD-H). [d] DCM replaced MeOH.

Controlled investigations were made to explore the reaction mechanism and to confirm the reaction intermediate. The alkoxy-dearomatization of lactone phenol resulted in both higher enantioselectivity and yield (**4a**, 56% *ee*, 87% yield) than the corresponding 3'-hydroxy-[1,1'-biphenyl]-2-carboxylic acid which confirms that reaction proceeds via lactone phenol intermediate. The 6-hydroxy-4-methylcoumarin substrate was also examined leading to the corresponding product in good yield (**4i**, 31% *ee*, 90% yield) that further strengthen our hypothesis (Scheme 2).

Scheme 2. Alkoxy-dearomatization of Lactone Phenols



[a] Conditions: **1** (0.3 mmol), **3l** (0.06 mmol) and *m*-CPBA (0.36 mmol) in MeOH (1 mL) at 20 °C for 30 h. [b] Isolated yield by silica gel column chromatography. [c] By HPLC analysis (chiralpack AD-H).

In an effort to glean insights into the mechanism, ^1H NMR analysis was

employed to detect the interaction of electron-deficiency iodine(III) and substrates. N-acyl aniline have been reported interacting with hypervalent iodine(III) at the *para*-carbon of aniline by Nicolaou[9] and the hypervalent iodide has been separated successfully. Similarly, for this electron-rich phenol, two nucleophilic sites were considered, i.e. basic oxygen of hydroxyl and *para*-carbon of phenol. In starting material structure (**1a**), the three aryl hydrogen atoms of phenol appeared multiplet signal peaks in displace of 6.72-6.75 ppm (Figure 2, 1). When we mixed starting material **1a** and DIB, the ^{1}H NMR spectrum showed three new signal peaks very soon which correspond to three aryl hydrogen atoms of phenol moieties: H^1 singlet peak of 6.70 ppm; H^2 doublet peak of 6.63 ppm with coupling constant J = 7.5 Hz; H^3 doublet peak of 6.82 ppm with coupling constant J = 7.5 Hz. No interaction with aryl carbon of phenol was observed. Thus, the adduct of starting materials and DIB was speculated to form as in line 2 of Figure 2. The sample was tested again after ten minutes, and the hydrogen content of hydroxyl signal significantly reduced (Figure 2, 3). Ten hours later, the adduct disappeared (Figure 2, 4) and the lactone **2aa** was generated, which was confirmed by comparing the ^{1}H NMR spectra.

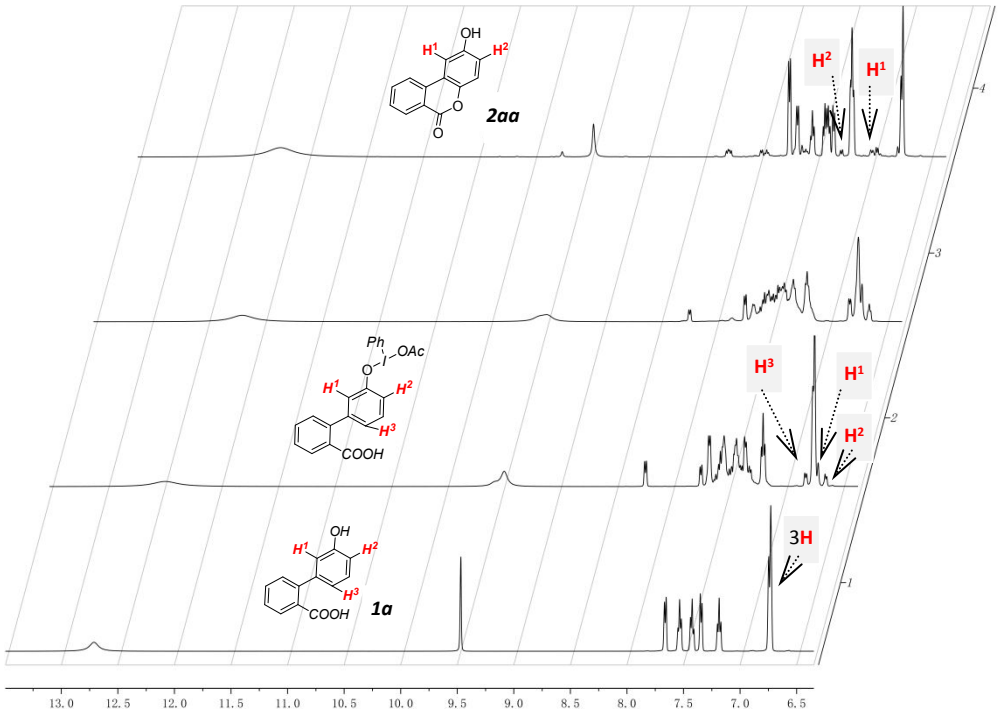


Figure 2. ^{1}H NMR analysis for mechanism insight. (1) **1a**; (2) mixing **1a** and DIB, no wait; (3) mixing **1a** and DIB for 10 min; (4) mixing **1a** and DIB for 10 h.

Based on the isolated intermediate **2aa** and above NMR-identification, a plausible mechanism pathway for this catalytic dearomatization of alkoxy-oxylactonizations process as well as asymmetric inductivity is proposed (Figure 3). At first, oxygen of phenolic hydroxyl attacks the iodine of DIB in a nucleophilic way to give adduct **A**, and *para*-position of phenol therefore gets reactive to permit the σ-bond shift from carboxyl, which leads to cleavage of OAc group, reduction of iodine(III) and formation of dienone. Then, a flash rearomatization process undergoes to form **2aa** through 1,5-H shift. Repeatedly, oxygen of phenolic hydroxyl attacks again by the iodine(III) and RO^- exchanges subsequentially to give rise to the final product with release of PhI and HOAc. Enantioselectively, with *m*-CPBA and chiral aryl iodine instead of DIB, a similar process could experience to reach enantiomer excessive product. The *ee* values of the enantioselective conversion are generally low in all cases, similar to asymmetric *para*-dearomatization of phenols (up to 60% *ee*).[7a] One possible reason might be that the prochiral center of starting materials is far away from the chiral center of hypervalent iodine species.

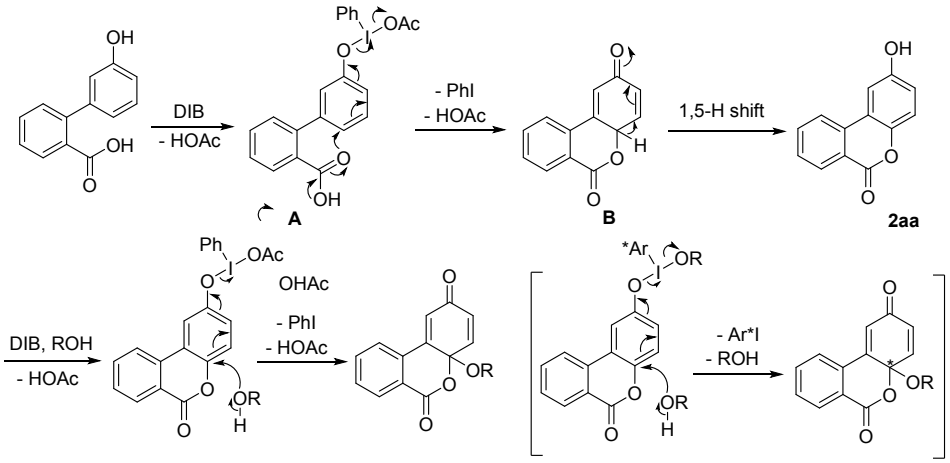


Figure 3. Proposed reaction mechanism.

CONCLUSION

In summary, we have developed an alkoxy-oxylactonization and dearomatization reaction of 3'-hydroxy-[1,1'-biphenyl]-2-carboxylic acid derivatives under optimized conditions in which DIB acts as a double Umpolung reagent to promote dioxygenation of electron-rich aryl carbon. We have described a polycyclic cyclohexadienone derivatives one-step synthesis using DIB. We also have described

an enantioselective reaction using a catalytic amount of chiral hypervalent iodine precursors. Moreover, we found alkoxy-dearomatization of lactone phenols reaction gave higher enantioselectivity. This method provides an efficient access to various interesting enantioenriched cyclohexadienone in acceptable yields and moderate enantioselectivity. The further improvement of enantiomer excess and applications of this strategy using other nucleophile are underway.

EXPERIMENTAL SECTION

General Information. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution on a Bruker Avance 500 spectrometer at 20~25 °C. ^{1}H NMR spectra were reported in parts per million using tetramethylsilane TMS (δ = 0.00 ppm) as an internal standard. The data of ^{1}H NMR are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (*J*, Hz), and integration. ^{13}C NMR spectra were reported in parts per million using solvent $CDCl_3$ (δ = 77.2 ppm) as an internal standard, The data of ^{13}C NMR are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constants (*J*, Hz). High resolution mass spectra (HRMS) were obtained with a Q-TOF MS spectrometer. High-performance liquid chromatography (HPLC) analysis was performed, equipped with a UV/Vis detector employing chiral columns. Reactions were monitored by TLC and column chromatography was performed using silica gel. Commercially available reagents were used without further purification unless otherwise specified.

General Procedure for Synthesis of 1.[10]

For starting materials: 3'-hydroxy-[1,1'-biphenyl]-2-carboxylic acid, 3'-hydroxy-5-methyl-[1,1'-biphenyl]-2-carboxylic acid, 3'-hydroxy-6-methyl-[1,1'-biphenyl]-2-carboxylic acid and 5'-hydroxy-2'-methyl-[1,1'-biphenyl]-2-carboxylic acid.

(i) To a solution of bromobenzoate (10 mmol), 2 *N* Na_2CO_3 (10 mL, 2 equiv) and (3-hydroxyphenyl)boronic acid (10 mmol, 1 equiv) in toluene (50 mL) was added $Pd(dppf)Cl_2$ (0.5 mmol, 5 mol %) under argon. After stirring for 14 h, the solvent was removed by vacuum and the mixture was purified by silica-gel column

chromatography (10:1 petroleum ether: EtOAc) to give colourless oil liquid biphenyl-carboxylate (90% yield). (ii) To a solution of biphenyl-carboxylate (9 mmol) in THF (25.0 mL) and MeOH (25.0 mL) was added 2 *N* NaOH (25 mL, 5.6 equiv) and stirred overnight at room temperature. The reaction mixture was cooled to 0 °C, quenched with 1 *N* HCl until pH reached to 2, and extracted with EtOAc (30 mL × 3). The organic layers were dried over anhydrous $MgSO_4$ and the solvents were removed in vacuo to give pure solid biphenyl-carboxylic acid with quantative yield.

For starting materials: 5-fluoro-3'-hydroxy-[1,1'-biphenyl]-2-carboxylic acid and 3'-hydroxy-5-nitro-[1,1'-biphenyl]-2-carboxylic acid.

(i) To a solution of bromobenzoate (10 mmol), *t*-BuOK (20 mmol, 2 equiv) and (3-hydroxyphenyl)boronic acid (10 mmol, 1 equiv) in THF (50 mL) was added $Pd_2(dba)_3$ (0.5 mmol, 5 mol %) under argon. After stirring for 14 h, the solvent was removed by vacuum and the mixture was purified by chromatography (10:1 petroleum ether: EtOAc) to give colourless oil liquid biphenyl-carboxylate (80% yield). (ii) To a solution of biphenyl-carboxylate (8 mmol) in THF (25.0 mL) and MeOH (25.0 mL) was added 2 *N* NaOH (25.0 mL, 6.2 equiv) and stirred overnight at room temperature. The reaction mixture was cooled to 0 °C, quenched with 1 *N* HCl until pH reached to 2 and extracted with EtOAc (30 mL × 3). The organic layers were dried over anhydrous $MgSO_4$ and the solvents were removed in vacuo to give pure solid biphenyl-carboxylic acid with quantative yield.

General Procedure for Synthesis of 2.

To a round-bottom flask was charged with **1** (0.3 mmol), ROH (1 mL), 20 wt% 5 Å MS and DIB (0.84 mmol, 2.8 equiv) in sequence successively. Then the resulting mixture was stirred under closed conditions at 20 °C (water bath temperature) for 10 h. The reaction was quenched with saturated solution of $Na_2S_2O_3$ (1 mL). The organic phase was separated, and the aqueous layer was extracted with DCM (5 mL × 3). The combined organic solution was dried with Mg_2SO_4 and concentrated in vacuo. The resulting residue was purified by a column chromatography (20:1 petroleum ether: EtOAc) to give racemic **2**.

General Procedure for Synthesis of 3.[11,8d]

To a solution of 2-iodoresorcinol (2.36 g, 10.0 mmol), PPh_3 (6.56 g, 25.0 mmol) and (-)-lactic acid ethylester (2.95 g, 25.0 mmol) in THF (50 mL) was added slowly diisopropyl azodicarboxylate (DIAD, 1.9 M in toluene, 13.2 mL, 25.0 mmol) 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 silica-gel column chromatography (30:1 petroleum ether: EtOAc) to give colorless oil **3a** (3.93 g, 9.0 mmol) in 90% yield. To a solution of **3a** (3.93 g, 9.0 mmol) in THF (25.0 mL) and MeOH (25.0 mL) was added 2N NaOH (25 mL) and stirred overnight at room temperature. The reaction mixture was cooled to 0 °C, quenched with 1 *N* HCl and extracted with EtOAc (30 mL × 3). The organic layers were dried over anhydrous $MgSO_4$ and the solvents were removed in vacuo to give pure white solid **3b** (3.42 g, 9.0 mmol) in 99% yield. To a solution of **3b** (0.87 g, 2.29 mmol) in DCM (10 mL) and DMF (1 drop) was added $SOCl_2$ (1.32 mL, 18.32 mmol, 8 equiv) and the mixture was stirred overnight under argon. The resulting mixture was concentrated under vacuum. Then the residue was dissolved in DCM (6 mL) at 0 °C and amine derivative (4.17 mmol, 1.8 equiv) was added. After 0.5 h, Et_3N (1.16 mL, 8.34 mmol) was added. Stirring continued overnight, and the reaction mixture was poured into aqueous HCl (1 M, 20 mL) and extracted with brine and DCM (10 mL × 2). The organic layers were dried with $MgSO_4$, filtered and the solvent was removed under vacuum to give solid product **3c-n**.

General Procedure for Synthesis of 4.

To a round-bottom flask was charged with **1** or lactone phenols (0.3 mmol), ROH (1 mL), 20 % **3l** and *m*-CPBA (0.36 mmol, 1.2 equiv) in sequence successively. Then the resulting mixture was stirred under closed conditions at 20 ^oC (water bath temperature) for 30 h. The reaction was quenched with saturated solution of $Na_2S_2O_3$ (1 mL). The organic phase was separated, and the aqueous layer was extracted with DCM (5 mL × 3). The combined organic solution was dried with Mg_2SO_4 and concentrated in vacuo. The resulting residue was purified by a column chromatography (20:1 petroleum ether: EtOAc) to give optically active **4**.

^{1}H- and ^{13}C-NMR Analytical Data

*2-Hydroxy-6H-benzo[c]chromen-6-one (**2aa**)*:[7a] 7.03 mg, 0.033 mmol, 11% yield, mp 195-196 °C yellowish solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.74 (s, 1H), 8.26 (m, 2H), 7.93 (t, J = 8 Hz, 1H), 7.67 (t , J = 8 Hz, 1H), 7.61 (s, 1H), 7.27 (d, J = 9 Hz, 1H), 7.00 (d, J = 9 Hz, 1H); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_9O_3$ 213.0546; Found 213.0539.

*4a-Methoxy-6H-benzo[c]chromene-2,6(4aH)-dione (**2a** and **4a**)*. **2a**: 56.9 mg, 0.234 mmol, 78% yield, yellowish solid, mp 145-146 °C; **4a**: 42.3 mg, 0.174 mmol, 58% yield, 43% *ee*, [α] $^{20}_D$ +66.5 (*c* 0.16, $CHCl_3$); **4a**: 63.4 mg, 0.261 mmol,87% yield, 56% *ee* from **2aa**, [α] $^{20}_D$ +118.1 (*c* 0.21, $CHCl_3$), chiralpack AD-H, hexane/*i*-PrOH = 92/8, flow rate = 1.0 mL/min, 254nm, major isomer : t_R = 26.052 min, minor isomer : t_R = 30.415 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, J = 7.5 Hz, 1H), 7.76 (t, J = 7.5 Hz, 1H), 7.72 (d, J = 7.5 Hz, 1H), 7.65 (t , J = 7.5 Hz, 1H), 7.06 (d, J = 10 Hz, 1H), 6.70 (s, 1H), 6.47 (d, J = 10 Hz, 1H), 3.36 (s, 3H), 2.04 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz,$CDCl_3$) δ 184.6, 162.3, 145.1, 140.3, 134.9, 133.0, 131.7, 130.7, 124.5, 124.1, 95.3, 52.1, 18.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{11}O_4$ 243.0652; Found 243.0659.

*4a-Ethoxy-6H-benzo[c]chromene-2,6(4aH)-dione (**2b** and **4b**)*. **2b**: 53.2 mg, 0.207 mmol, 69% yield, yellowish solid, mp 149-151 °C; **4b**: 42.4 mg, 0.165 mmol, 55% yield, 52% *ee*, [α] $^{20}_D$ +55.8 (*c* 0.12, $CHCl_3$), chiralpack AD-H, hexane/*i*-PrOH = 92/8, flow rate = 1.0 mL/min, 254nm, major isomer : t_R = 19.286 min, minor isomer : t_R = 22.435 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, J = 7.5 Hz, 1H), 7.73 (t, J = 7.5 Hz, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.06 (d, J = 10 Hz, 1H), 6.67 (s, 1H), 6.42 (d, J = 10 Hz, 1H), 3.78-7.72 (m, 1H), 3.56-3.51 (m, 1H), 1.03 (t, J = 7 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz,$CDCl_3$) δ 184.6, 162.4, 145.5, 140.9, 134.8, 133.1, 131.6, 130.5, 130.4, 124.5, 124.1, 123.8, 95.0, 60.6, 15.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{13}O_4$ 257.0808; Found 257.0807.

*4a-Propoxy-6H-benzo[c]chromene-2,6(4aH)-dione (**2c** and **4c**)*. **2c**: 52.8 mg, 0.195 mmol, 65% yield, yellowish oil; **4c**: 21.9 mg, 0.081 mmol, 27% yield, 50% *ee*, [α] $^{20}_D$ +78.9 (*c* 0.14, $CHCl_3$), chiralpack AD-H, hexane/*i*-PrOH = 92/8, flow rate =

1.0 mL/min, 254nm, major isomer : t_R = 16.968 min, minor isomer : t_R = 19.522 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8 Hz, 1H), 7.73-7.68 (m, 2H), 7.60 (t, *J* = 10 Hz, 1H), 7.03 (t, *J* = 10 Hz, 1H), 6.66 (s, 1H), 6.40 (d, *J* = 10 Hz, 1H), 3.64-3.60 (m, 1H), 3.41-3.37 (m, 1H), 1.40-1.36 (m, 2H), 0.63 (t, *J* = 7 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz,$CDCl_3$) δ 184.6, 162.4, 145.5, 141.0, 134.8, 133.0, 131.6, 130.4, 130.4, 124.6, 124.1, 123.7, 94.9, 66.3, 22.8, 10.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{15}O_4$ 271.0965; Found 271.0962.

*4a-Butoxy-6H-benzo[c]chromene-2,6(4aH)-dione (**2d** and **4d**)*. **2d**: 41.1 mg, 0.144 mmol, 48% yield, yellowish oil; **4d** : 17.9 mg, 0.063 mmol, 21% yield, 40% *ee*, $[\alpha]^{20}_D$ +66.3 (*c* 0.178, $CHCl_3$), chiralpack AD-H, hexane/*i*-PrOH = 92/8, flow rate = 1.0 mL/min, 254nm, major isomer: t_R = 14.996 min, minor isomer: t_R = 16.645 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.5 Hz, 1H), 7.74-7.69 (m, 2H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 10 Hz, 1H), 6.68 (s, 1H), 6.43 (d, *J* = 10 Hz, 1H), 3.71-3.67 (m, 1H), 3.47-3.43 (m, 1H), 1.41-1.35 (m, 2H), 1.11-1.07 (m, 2H), 0.73 (t, *J* = 7 Hz, 3H)); ^{13}C{^{1}H} NMR (125 MHz,$CDCl_3$) δ 184.7, 162.5, 145.6, 141.0, 134.8, 133.1, 131.6, 130.4, 30.4, 124.6, 124.2, 123.8, 95.0, 64.5, 31.5, 18.9, 13.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{17}O_4$ 285.1121; Found 285.1113.

*8-Fluoro-4a-methoxy-6H-benzo[c]chromene-2,6(4aH)-dione (**2g** and **4g**)*. **2g**: 38.4 mg, 0.147 mmol, 49% yield, yellowish solid, mp 163-165 °C; **4g**: 32.9 mg, 0.126 mmol, 42% yield, 23% *ee*, $[\alpha]^{20}_D$ +47.9 (*c* 0.146, $CHCl_3$), chiralpack AD-H, hexane/*i*-PrOH = 92/8, flow rate = 1.0 mL/min, 254nm, major isomer: t_R = 23.070 min, minor isomer : t_R = 30.656 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 8 Hz, 5.5 Hz, 1H), 7.37 (dd, *J* = 8 Hz, 2 Hz, 1H), 7.32 (dt, *J* = 8 Hz, 2 Hz, 1H), 7.07 (d, *J* = 10 Hz, 1H), 6.66 (d, *J* = 1.5 Hz, 1H), 6.47 (dd, *J* = 10 Hz, 1.5 Hz, 1H), 3,38 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz,$CDCl_3$) δ 184.2, 166.6 (d, J = 256 Hz), 161.4, 144.1, 140.2, 135.8 (d, J = 10 Hz), 133.9 (d, J = 10 Hz), 130.9, 124.8, 120.5, 119.2 (d, J = 22 Hz), 111.6 (d, J = 24 Hz), 95.3, 52.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{10}FO_4$ 261.0558; Found 261.0551.

*4a-Methoxy-8-nitro-6H-benzo[c]chromene-2,6(4aH)-dione (**2h**):* 62.2 mg, 0.216 mmol, 72% yield, yellow solid, mp 186-187 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.03

(s, 1H), 8.59-8.56 (dd, *J* = 8.5 Hz, 2 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.13 (d, *J* = 10 Hz, 1H), 6.79 (s, 1H), 6.52 (d, *J* = 10 Hz, 1H), 3.42 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 183.8, 160.5, 149.6, 142.9, 139.8, 138.4, 131.2, 129.2, 126.3, 126.3, 125.9, 125.6, 95.4, 52.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{10}NO_6$ 288.0503; Found 288.0501.

*4a-Methoxy-10-methyl-6H-benzo[c]chromene-2,6(4aH)-dione (**2i** and **4f**)*. **2i**: 53.2 mg, 0.207 mmol, 69% yield, yellowish solid, mp 154-156 °C; **4f**: 23.9 mg, 0.093 mmol, 31% yield, 11% *ee*, [α] $^{20}_{D}$ +12.5 (*c* 0.08, $CHCl_3$), chiralpack AD-H, hexane/*i*-PrOH = 97/3, flow rate = 1.0 mL/min, 254nm, major isomer: t_R = 31.945 min, minor isomer: t_R = 33.547 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.04 (d, J = 10 Hz, 1H), 6.58 (s, 1H), 6.47 (d, J = 10 Hz, 1H), 3.32 (s, 3H), 2.58 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz,$CDCl_3$) δ 184.6, 162.6, 144.5, 140.5, 137.8, 136.5, 131.8, 130.4, 130.3, 128.9, 128.4, 125.1, 94.9, 51.9, 21.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{13}O_4$ 257.0808; Found 257.0814.

*4a-Methoxy-9-methyl-6H-benzo[c]chromene-2,6(4aH)-dione (**2j** and **4e**)*. **2j**: 61.7 mg, 0.24 mmol, 80% yield, yellowish solid, mp 156-156 °C; **4e**: 32.4 mg, 0.126 mmol, 42% yield, 15% *ee*, [α] $^{20}_{D}$ +26.6 (*c* 0.128, $CHCl_3$), chiralpack AD-H, hexane/*i*-PrOH = 95/5, flow rate = 1.0 mL/min, 254nm, major isomer: t_R = 28.596 min, minor isomer: t_R = 37.726 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7 Hz, 1H), 7.48 (s, 1H), 7.43 (d, *J* = 7 Hz, 1H), 7.04 (d, *J* = 10 Hz, 1H), 6.66 (s, 1H), 6.44 (d, *J* = 10 Hz, 1H), 3.34 (s, 3H), 2.49 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125MHz,$CDCl_3$) δ 184.6, 162.3, 146.2, 145.3, 140.4, 132.9, 132.7, 130.8, 130.7, 124.9, 123.8, 121.4, 95.2, 52.1, 22.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{13}O_4$ 257.0808; Found 257.0800.

*4a-Methyl-6H-benzo[c]chromene-2,6(4aH)-dione **(2k** and **4h)***. **2k** (DCM as solvent): 51.1 mg, 0.225 mmol, 75% yield, yellowish solid, mp 138-140 °C; **4h** (DCM as solvent): 41.5 mg, 0.183 mmol, 61% yield, 13% *ee*, [α] $^{20}_{D}$ +48.6 (*c* 0.122, $CHCl_3$), chiralpack AD-H, hexane/*i*-PrOH = 92/8, flow rate = 1.0 mL/min, 254nm, minor isomer : t_R = 26.134 min, major isomer : t_R = 33.090 min; ^{1}H NMR (500 MHz, $CDCl_3$)

δ 8.22 (d, *J* = 7.5 Hz, 1H), 7.78 - 7.72 (m, 2H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 10 Hz, 1H), 6.67 (s, 1H), 6.33 (d, *J* = 10 Hz, 1H), 1.68 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125MHz,$CDCl_3$) δ 184.8, 162.7, 150.1, 147.8, 135.0, 133.7, 131.9, 130. 9, 127.8, 124.5, 123.9, 123.2, 76.9, 29.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{11}O_3$ 227.0703; Found 227.0699.

*8a-Methoxy-4-methyl-2H-chromene-2,6(8aH)-dione (***4i***)*: 55.9 mg, 0.270 mmol, 90% yield, 31% *ee*, yellowish solid, mp 74-76 °C, $[\alpha]_D^{20}$ +33.9 (*c* 0.18, $CHCl_3$), chiralpack AD-H, hexane/*i*-PrOH = 96/4, flow rate = 1.0 mL/min, 254nm, minor isomer : t_R = 24.617 min, major isomer : t_R = 25.619 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (d, *J* = 10 Hz, 1H), 6.40 (m, 2H), 6.10 (s, 1H), 3.40 (s, 3H), 2.18 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz,$CDCl_3$) δ 184.7, 161.4, 147.7, 145.8, 141.5, 130.4, 125.8, 120.9, 94.8, 52.2, 17.81; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{11}O_4$ 207.0652; Found 207.0645.

ASSOCIATED CONTENT

Supporting Information

Supporting Information is available free of charge on the ACS Publications website at 1H-NMR Spectra for Mechanism Insight; HPLC, 1H-NMR, 13C-NMR and HRMS spectra for **2** and **4**

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