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Facile synthesis of coumaronochromones through palladium-catalyzed intramolecular cross dehydrogenative coupling

Chang-Xue Gu [b], Jian-Guo Liu [a], Wen-Wen Chen [b, c, **], Ming-Hua Xu [a, b, *]

[a] Shenzhen Key Laboratory of Small Molecule Drug Discovery and Synthesis, Department of Chemistry, Southern University of Science and Technology, 1088 Xueyuan Boulevard, Shenzhen, 518055, China
[b] State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai, 201203, China
[c] The Education Ministry Key Lab of Resource Chemistry and Shanghai Key Laboratory of Rare Earth Functional Materials, Shanghai Normal University, 100 Guilin Road, Shanghai, 200234, China

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ABSTRACT

An efficient base-free palladium-catalyzed intramolecular cross dehydrogenative coupling of 2-aryloxy substituted 4-chromenones to access coumaronochromones has been achieved. A range of diversely substituted coumaronochromones can be facilely synthesized in good to excellent yields (up to 90%).

1. Introduction

Coumaronochromones, also named benzofuro[2,3-*b*][1]benzopyran-11-ones, are one subclass of isoflavones in nature [1]. Coumaronochromone derivatives exhibit a wide range of biological activities such as estrogenic, antibacterial, anti-HIV, antiplatelet, cytotoxicity against cancer cell lines, immunosuppressive and neuroprotective activities [2–8]. Some interesting examples of biologically active coumaronochromones are illustrated in Fig. 1. Lupinalbin A is a known phytoestrogen [2a], which also exerts anti-inflammatory activity on lipopolysaccharide-treated RAW264.7 cells [2b]. Hirtellanine A exhibits strong B lymphocyte suppression activity and T lymphocyte suppression activity [3]. Euchretin F is significantly active against AA- (arachidonic acid) and collagen-induced platelet aggregation [4], while Euchretin J shows moderate cytotoxicity in a human hepatoma cell line (59T) [5]. Moreover, Euchretin M inhibits HIV replication in H9 lymphocyte cells [4]. Recently, two new coumaronochromones (cristatone I and cristatone II) were isolated from *Celosia cristata*, and Cristatone II was found to display moderate cytotoxic activity against HeLa and BGC-823 cancer cell lines [6].

Despite their biological importance, synthetic methodologies to access the coumaronochromone nucleus remain largely undeveloped [9–13]. To the best of our knowledge, intramolecular oxidative annulation of the corresponding 2′-hydroxyisoflavones stands as the most conventional method to construct this framework, albeit often with low to moderate yields (Scheme 1). However, the need for pre-introduction of a hydroxy group onto the 2′-position poses severe limitations on the practical applicability of this method. Typically, the preparation of 2′-hydroxyisoflavone substrates requires a number of steps. For example, condensation of 2'-(methoxymethoxy)acetophenone and 2-(benzyloxy)benzaldehyde derivatives followed by hydroxyl deprotection/acetylation/oxidative rearrangement/cyclization and benzyl removal would ultimately deliver the corresponding 2′-hydroxyisoflavones in six steps

* Corresponding author. Shenzhen Key Laboratory of Small Molecule Drug Discovery and Synthesis, Department of Chemistry, Southern University of Science and Technology, 1088 Xueyuan Boulevard, Shenzhen, 518055, China.
** Corresponding author. State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai, 201203, China.
E-mail addresses: wenwen@shnu.edu.cn (W.-W. Chen), xumh@sustech.edu.cn (M.-H. Xu).

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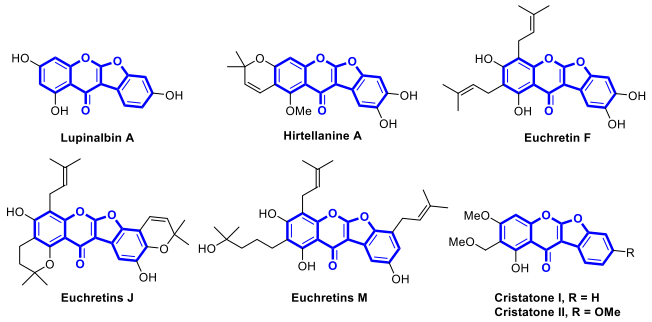
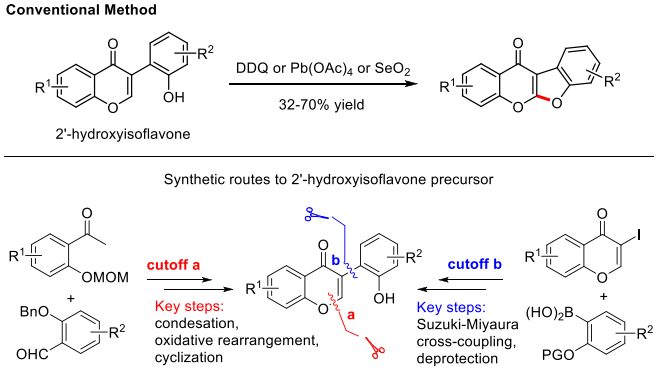


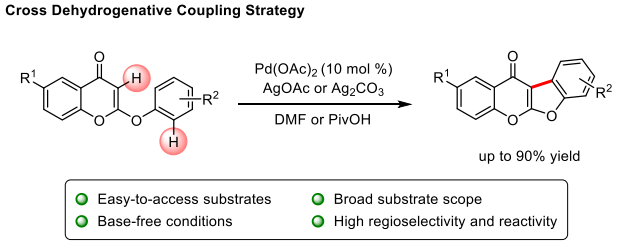
Fig. 1. Selected examples of bioactive coumaronochromone natural products.



Scheme 1. Conventional oxidative cyclization approach for the synthesis of coumaronochromones.

(Scheme 1, cutoff a) [10]. Alternatively, this precursor can be obtained by Suzuki-Miyaura cross-coupling (Scheme 1, cutoff b), however, both coupling partners are not commercially available and their preparation also takes steps [11,13]. Moreover, this intramolecular oxidative cyclization approach is not applicable to polyhydroxy-substituted 2′-hydroxyisoflavones, as the free hydroxy groups are highly susceptible to oxidation and would lead to substrate decomposition [10,11]. Therefore, the development of new and efficient synthetic methodologies with broad substrate scope is in high demand.

In the past decades, the oxidative cross dehydrogenative coupling (CDC) strategy has received increasing attention and proved to be a powerful method in organic synthesis because it provides an easy way to construct C–C bonds through oxidation of two C–H bonds by directly utilizing non-prefunctionalized starting materials [14]. Recently, we became interested in the synthesis of polyheterocyclic compounds for drug discovery and developed a series of Pd-catalyzed intramolecular CDC reactions for facile construction of a wide range of fused polyheterocycles such as coumestans [15], indolo[3,2-*c*]coumarins [15,16], indolo[3,2-*c*]quinolinones [16], indolo[3,2-*c*]pyrones [16], isoazacoumestans [17], and indolo[2,3-*c*]quinolinones [17] from readily available 4- or 3-substituted coumarins, quinolinones and pyrones, respectively. In considering the coumaronochromone framework, we envisaged that the molecule might be quickly assembled through direct connection of the two unfunctionalized C–H bonds under CDC conditions by forming the fused benzofuran ring (Scheme 2). Herein, we disclose our success on the development of this promising intramolecular CDC approach to construct a variety of coumaronochromones from 2-aryloxy substituted chromen-4-ones with a broad substrate scope in good yields.

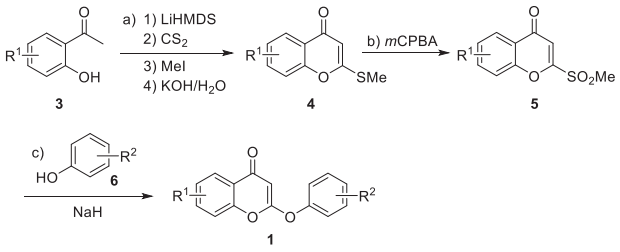


Scheme 2. Cross dehydrogenative coupling strategy for the synthesis of coumaronochromones.

2. Results and discussion

To implement our CDC strategy, we began our studies by looking into an easy synthetic route to access the starting material 2-aryloxy substituted 4-chromenones. To our delight, diversified 2-aryloxy substituted 4-chromenones (**1**) could be readily prepared through a three-step-synthesis (Scheme 3) [18]. Starting from the commercially available 2- hydroxyacetophenones **3**, 2-thiomethyl chromenones **4** was accessible on a multigram scale in good yields via ketene dithioacetal in a one-pot synthesis. Subsequent oxidation provided the desired 2-sulfonylchromenones **5** in almost quantitative yields, which were then converted to the desired 2-aryloxy-4*H*-4-chromenones **1** with substituted phenols **6** as the nucleophiles.

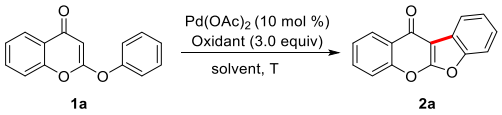
To test our hypothesis, we initially performed the intramolecular cross dehydrogenative coupling reaction of 2-phenoxy-4*H*-chromen-4-one (**1a**) with $Pd(OAc)_2$ as the catalyst, $Cu(OAc)_2$ as the oxidant and AcOH as the solvent at 100 °C in the absence of base [16,17] (Table 1, entry 1). Luckily, the desired product **2a** was detected, albeit in a very low yield (7% yield). Though the reaction yield is far from satisfactory, it suggests the potential of employing intramolecular CDC protocol to construct coumaronochromone frameworks. Encouraged by this result, a series of reactions were carried out to optimize the reaction parameters. Since the oxidant is one of the essential factor, $PhI(OAc)_2$, Ag_2O, Ag_2CO_3, and AgOAc were screened in AcOH (entries 2–5). Among them, AgOAc was found to be the best, and the desired coumaronochromone **2a** could be obtained in a greatly improved yield (61%) (entry 5). Gratifyingly, replacing AcOH with DMF as the solvent resulted in a further increase of the yield (75%) (entry 6). Unfortunately, rising temperature and reducing the amount of AgOAc is not beneficial to the reaction (entries 7, 8). When changing the solvent from DMF to PivOH accompanying with higher temperature (120 °C), a slight decrease of the reaction yield was observed (entry 9 vs entry 6). Utilizing air as the sole oxidant caused dramatic decrease of the yield (entry 10 vs entry 9). To our delight, the reaction could be



[a]Reagents and conditions: (a) LiHMDS (3.2 equiv), CS_2 (1.5 equiv), THF, -78 to 0 °C, 3.5 h; then MeI (2.2 equiv), THF, 0 °C to rt, 2 h; then KOH (10 M in H_2O), THF, reflux, 1.5 h; (b) *m*CPBA (2.5 equiv), CH_2Cl_2, 0 °C to rt, 3 h; (c) **6** (1.2 equiv), NaH (1.2 equiv), THF, 0 °C to rt, 2 h.

Scheme 3. Synthesis of 2-aryloxy substituted 4-chromenones **1**.

Table 1
Optimization of reaction conditions.[a]



entry	oxidant	Solvent	T (°C)	t (h)	yield[b] (%)
1	$Cu(OAc)_2$	AcOH	100	24	7
2	$PhI(OAc)_2$	AcOH	100	24	24
3	Ag_2O	AcOH	100	24	27
4	Ag_2CO_3	AcOH	100	24	31
5	AgOAc	AcOH	100	24	61
6	**AgOAc**	**DMF**	**100**	**24**	**75**
7	AgOAc	DMF	120	29	65
8[c]	AgOAc	DMF	120	29	50
9	AgOAc	PivOH	120	16	71
10	air	PivOH	120	16	38
11[d]	**Ag_2CO_3**	**PivOH**	**120**	**10**	**72**
12[e]	Ag_2CO_3	PivOH	120	52	71

[a] Reaction conditions: a mixture of substrate **1a** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol, 10 mol %), and oxidant (0.60 mmol, 3 equiv) in 1.0 mL of solvent was stirred at 100 °C or 120 °C.
[b] Isolated yield.
[c] 2.0 equiv of AgOAc.
[d] 1.5 equiv of Ag_2CO_3.
[e] 1.0 equiv of Ag_2CO_3.

greatly accelerated with Ag_2CO_3 as the oxidant in PivOH, affording a comparable 72% yield (entry 11 vs entry 6). Interestingly, the amount of oxidant plays an important role on the reaction rate. With reduced amount of Ag_2CO_3, the reaction became very slow (entry 12 vs entry 11). Notably, base usually exhibited remarkable impact in the CDC reactions [19] and the base-free conditions can tolerate base-sensitive functional groups or substrates.

With the optimized conditions in entry 6 (Method A) and entry 9 (Method B) of Table 1, we then commenced to investigate the substrate scope of the reaction. As illustrated in Table 2, a wide range of 2-aryloxy substituted 4-chromenones bearing diverse electronic properties with substituents on either phenyl ring of the 4-chromenone nucleus or the C-2 substituted aryloxy are generally well tolerated in this palladium-catalyzed intramolecular CDC reaction, affording a broad scope of coumaronochromone products in good to excellent yields (**2b**-**2u**). The two methods exhibited different reactivity for varying substrates. It is likely that Method B is more suitable for the substrates having electron-donating groups in the C-2 substituted aryloxy moiety and electron-withdrawing group on the 4-chromenone nucleus, giving the corresponding products **2b**, **2c**, **2e**-**2h**, **2r**, **2s**, and **2u** in good to excellent yields (64–90% yields). Moreover, the reaction time could be shortened to less than 7 h. However, the use of the same reaction conditions for substrates bearing a strong electron-withdrawing group CF_3 at the C4′ position led to a dramatic drop of the reaction yield (**2d**, **2t**). In contrast, Method A provided product **2d** and **2t** with a better yield after 24 h (**2d**, 65%; **2t**, 47%). In most cases of substrates with both electron-rich 4-chromenone core and aryloxys, Method A is likely somewhat more efficient than Method B (**2i**, **2j**, **2k**, and **2p,** 72–87% yields). It was also found that Method B could give **2n** and **2o** containing electron-deficient aryloxy in better yield when compared to Method A. Interestingly, the tyrosine moiety can be incorporated, leading to the coumaronochromone product **2q** bearing a chiral alanine substitutent on the benzofuran ring. It is notable that the presence of a *meta*-OMe substituent would lead to a sole isomer (**2f**, **2l** and **2m**), while a *meta*-Me substituent resulted in a mixture of two regioisomers with a higher preference for the less hindered products (**2g** and **2j**) which are separable by column chromatography in good yields.

The utility of the reaction was demonstrated by conducting a scale-up synthesis (Scheme 4). On gram-scales, the reaction of **1p** under the conditions of method B proceeded well to provide the product **2p** in comparable yield (53%).

To showcase the synthetic application of this protocol, we carried out the synthesis of natural product Lupinalbin A. As illustrated in Scheme 5, exposure of product **2m** to BBr_3 in DCM at 45 °C for 24 h could readily furnish Lupinalbin A in 54% yield. To the best of our knowledge, this is among the shortest routes and best yields for the synthesis of Lupinalbin A [10,12,13].

A possible reaction mechanism was proposed as shown in Scheme 6. Similar to our previous work [15], the initial palladation of substrate **1** is assumed to preferably occur at the C-3 position of the coumaronochromone nucleus to form Pd(II) intermediate A. Subsequently, C–H activation proceeds presumably through a concerted metalation–deprotonation mechanism to generate the key intermediate **C**, which undergoes reductive elimination to yield the intramolecular cross dehydrogenative coupling product **2** while releasing the Pd(0) species. The active Pd(II) catalyst is regenerated by means of the oxidant Ag(I) salt.

3. Conclusion

In summary, we have successfully developed an efficient Pd-catalyzed base-free intramolecular cross dehydrogenative coupling (CDC) reaction to furnish a wide range of coumaronochromones in good to excellent yields. This CDC strategy provides a convenient and facile route to access structurally diversified coumaronochromones for medicinal chemistry. High atom-economy efficiency, good functional group compatibility, broad substrate scope and nontoxic-reagent usage make this method promising in construction and identifying more coumaronochromones with potent bioactivities.

4. Experimental section

4.1. General

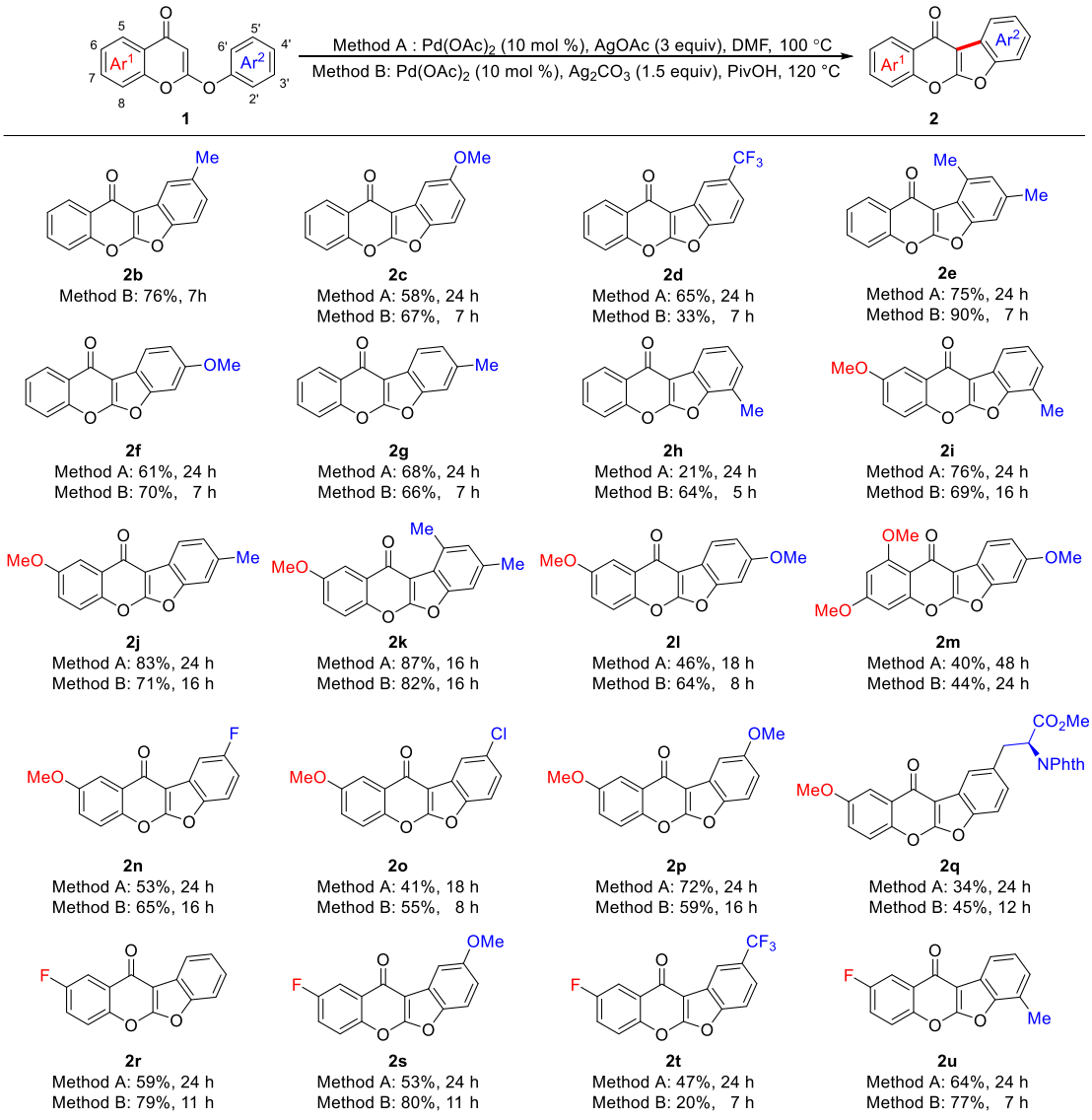
NMR spectra were recorded on spectrometer (400 or 600 MHz for ^1H and 125 or 150 MHz for ^{13}C). Chemical shift values are given in ppm and referred as the internal standard to TMS (tetramethylsilane). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; dd, doublet of doublets and br s, broad singlet. The coupling constants.

(*J*) are reported in Hertz (Hz). HRMS were recorded on a Q-TOF mass spectrometer with ESI resource. Flash column chromatography was performed over silica gel 300–400 mesh, and the eluent was a mixture of PE and EtOAc.

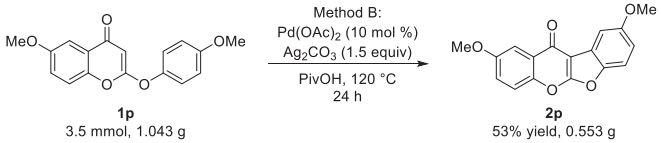
4.2. General procedures for intramolecular CDC reaction to access coumaronochromone *2*

Method A: To a 15 mL vessel was added compound **1** (0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 10 mol %), AgOAc (99.6 mg, 0.6 mmol, 3 equiv) and DMF (1.0 mL). Then the reaction mixture was stirred at 100 °C for 16–48 h with the progress monitored by TLC (PE/EtOAc = 10/1). After completion, the reaction mixture was cooled to room temperature and diluted with EtOAc (10 mL) and water (10 mL), and extracted with EtOAc (15 mL×3). The isolated organic layer was washed by Brine (10 mL) and dried by Na_2SO_4. After removal of solvent, the residue was purified by silica gel column chromatography with PE/EtOAc as the eluent (15/1 to 5/1) to give desired product **2**.

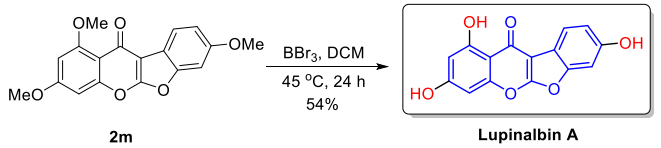
Table 2
Pd-catalyzed intramolecular CDC reaction of 2-aryloxy substituted 4-chromenones.[a]



[a] Reaction conditions for Method A: **1** (0.20 mmol), $Pd(OAc)_2$ (10 mol %) and AgOAc (0.60 mmol, 3 equiv) in 1.0 mL of DMF at 100 °C; Method B: **1** (0.20 mmol), $Pd(OAc)_2$ (10 mol %) and Ag_2CO_3 (0.30 mmol, 1.5 equiv) in 1.0 mL of PivOH at 120 °C.



Scheme 4. Gram-scale CDC reaction.

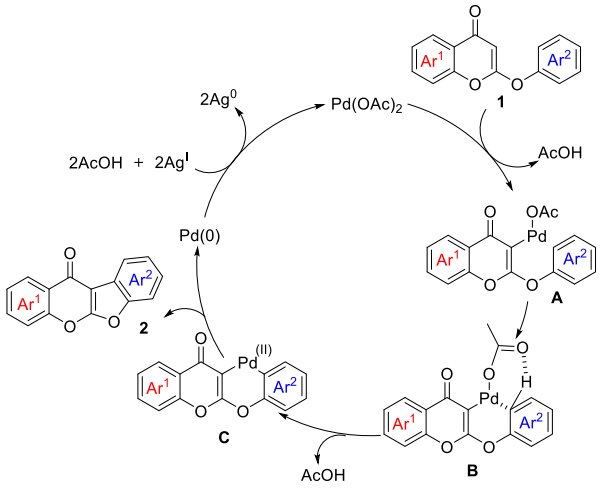


Scheme 5. Synthesis of natural product Lupinalbin A.

Method B: To a 15 mL vessel was added compound **1** (0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 10 mol %), Ag_2CO_3 (82.8 mg, 0.3 mmol, 1.5 equiv) and PivOH (1.0 mL). Then the reaction mixture was stirred at 120 °C for 5–24 h with the progress monitored by TLC (PE/EtOAc = 10/1). After completion, the reaction mixture was cooled to room temperature and diluted with EtOAc (10 mL). Excess $NaHCO_3$ (aq.) was then added to neutralize PivOH. After stirring the mixture for 10 min, the residue was washed with aqueous $NaHCO_3$ and extracted with EtOAc (15 mL×3). The isolated organic layer was washed by brine (10 mL) and dried by Na_2SO_4. After removal of solvent, the residue was purified by silica gel column chromatography with PE/EtOAc as the eluent (15/1 to 5/1) to give desired product **2**.

*4.2.1. 11H-benzofuro[2,3-b]chromen-11-one (**2a**)*

White solid, Method A: 35.4 mg, 75% yield, Method B: 34.0 mg, 72% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (dd, J = 7.9, 1.6 Hz, 1H),



Scheme 6. Proposed mechanism of the CDC reaction.

8.23–8.17 (m, 1H), 7.74 (ddd, J = 8.5, 7.2, 1.7 Hz, 1H), 7.65–7.60 (m, 1H), 7.57–7.50 (m, 2H), 7.46–7.37 (m, 2H). HRMS (ESI): Calcd for $C_{15}H_9NO_4[M+H]^+$: 237.0546, found 237.0547.

*4.2.2. 9-methyl-11H-benzofuro[2,3-b]chromen-11-one (**2b**)*

White solid, Method B: 38.0 mg, 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 8.0 Hz, 1H), 7.96 (s, 1H), 7.70 (dd, J = 8.0, 7.2 Hz, 1H), 7.58 (d, J = 8.3 Hz, 1H), 7.49 (dd, J = 7.6, 7.6 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 8.3 Hz, 1H), 2.47 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 165.4, 153.4, 147.7, 135.2, 133.4, 126.7, 126.4, 125.8, 124.2, 123.0, 122.1, 118.0, 110.7, 99.6, 21.5. HRMS (ESI): Calcd for $C_{16}H_{11}O_3[M+H]^+$: 251.0703. found 251.0704.

*4.2.3. 9-methoxy-11H-benzofuro[2,3-b]chromen-11-one (**2c**)*

White solid, Method A: 30.9 mg, 58% yield, Method B: 35.6 mg, 67% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41–8.34 (m, 1H), 7.72–7.69 (m, 1H), 7.62 (d, J = 2.4 Hz, 1H), 7.57 (d, J = 8.3 Hz, 1H), 7.49 (dd, J = 7.5, 7.2 Hz, 1H), 7.38 (d, J = 9.0 Hz, 1H), 6.90 (dd, J = 9.0, 2.6 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 165.5, 157.7, 153.3, 143.8, 133.5, 126.6, 125.8, 124.0, 123.7, 117.9, 113.7, 111.9, 104.8, 100.0, 56.1. HRMS (ESI): Calcd for $C_{16}H_{11}O_4[M+H]^+$: 267.0652, found 267.0651.

*4.2.4. 9-(trifluoromethyl)-11H-benzofuro[2,3-b]chromen-11-one (**2d**)*

White solid, Method A: 39.5 mg, 65% yield, Method B: 20.0 mg, 33% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.39 (dd, J = 7.9, 1.5 Hz, 1H), 7.80–7.73 (m, 1H), 7.68–7.62 (m, 3H), 7.56–7.52 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 165.9, 153.5, 150.7, 134.0, 128.2 (q, $^2J_{CF}$ = 32.5 Hz), 126.9, 126.3, 124.3 (q, $^1J_{CF}$ = 271.3 Hz), 124.0, 123.6, 122.7 (q, $^3J_{CF}$ = 3.3 Hz), 119.7 (q, $^3J_{CF}$ = 3.3 Hz), 118.1, 111.8, 99.4. HRMS (ESI): Calcd for $C_{16}H_8F_3O_3[M+H]^+$: 305.0420, found 305.0421.

*4.2.5. 8,10-dimethyl-11H-benzofuro[2,3-b]chromen-11-one (**2e**)*

White solid, Method A: 39.6 mg, 75% yield, Method B: 47.5 mg, 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 7.8 Hz, 1H), 7.71 (dd, J = 7.6, 7.6 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.49 (dd, J = 7.5, 7.5 Hz, 1H), 7.13 (s, 1H), 7.00 (s, 1H), 2.99 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 165.1, 152.8, 149.9, 136.2, 133.7, 133.3, 128.1, 127.0, 125.8, 124.3, 120.2, 117.7, 108.8, 100.7, 21.68, 21.65. HRMS (ESI): Calcd for $C_{17}H_{13}O_3[M+H]^+$: 265.0859, found 265.0859.

*4.2.6. 8-methoxy-11H-benzofuro[2,3-b]chromen-11-one (**2f**)*

White solid, Method A: 32.5 mg, 61% yield, Method B: 37.2 mg, 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 7.9 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.70 (dd, J = 11.1, 4.0 Hz, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.49 (dd, J = 8.0, 8.0 Hz, 1H), 7.07 (d, J = 2.0 Hz, 1H), 7.00 (dd, J = 8.5, 2.1 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 164.9, 158.6, 153.2, 150.3, 133.3, 126.6, 125.8, 124.2, 122.3, 118.0, 116.0, 112.8, 99.8, 97.1, 56.0. HRMS (ESI): Calcd for $C_{16}H_{11}O_4[M+H]^+$: 267.0652, found 267.0653.

*4.2.7. 8-methyl-11H-benzofuro[2,3-b]chromen-11-one (**2g**)*

White solid, Method A: 34.0 mg, 68% yield, Method B: 33.0 mg, 66% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (dd, J = 7.9, 1.5 Hz, 1H), 8.02 (d, J = 7.9 Hz, 1H), 7.69 (dd, J = 7.1, 1.5 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.51–7.47 (m, 1H), 7.32 (s, 1H), 7.22 (d, J = 7.8 Hz, 1H), 2.48 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 165.1, 153.3, 149.7, 136.0, 133.4, 126.7, 126.4, 125.8, 124.2, 121.6, 120.4, 118.0, 111.5, 99.8, 21.9. HRMS (ESI): Calcd for $C_{16}H_{11}O_3[M+H]^+$: 251.0703, found 251.0703.

*4.2.8. 7-methyl-11H-benzofuro[2,3-b]chromen-11-one (**2h**)*

White solid, Method A: 10.5 mg, 21% yield, Method B: 32.0 mg, 64% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (dd, J = 7.9, 1.2 Hz, 1H), 7.97 (d, J = 7.6 Hz, 1H), 7.74–7.66 (m, 1H), 7.58 (d, J = 8.3 Hz, 1H), 7.49 (dd, J = 7.5, 7.2 Hz, 1H), 7.29 (dd, J = 7.6, 7.6 Hz, 1H), 7.15 (d, J = 7.4 Hz, 1H), 2.53 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 165.1, 153.3, 148.3, 133.4, 126.73, 126.66, 125.8, 125.3, 124.2, 122.6, 121.5, 119.5, 117.9, 99.9, 14.9. HRMS (ESI): Calcd for $C_{16}H_{11}O_3[M+H]^+$: 251.0703, found 251.0703.

*4.2.9. 2-methoxy-7-methyl-11H-benzofuro[2,3-b]chromen-11-one (**2i**)*

White solid, Method A: 42.6 mg, 76% yield, Method B: 38.6 mg, 69% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 7.6 Hz, 1H), 7.76 (d, J = 2.8 Hz, 1H), 7.52 (d, J = 9.1 Hz, 1H), 7.35–7.26 (m, 2H), 7.18 (d, J = 7.5 Hz, 1H), 3.93 (s, 3H), 2.54 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 165.2, 157.5, 148.4, 147.8, 126.7, 125.3, 124.9, 122.7, 122.6, 121.5, 119.5, 119.2, 106.7, 99.5, 56.1, 14.9. HRMS (ESI): Calcd for $C_{17}H_{13}O_4[M+H]^+$: 281.0808, found 281.0808.

*4.2.10. 2-methoxy-8-methyl-11H-benzofuro[2,3-b]chromen-11-one (**2j**)*

White solid, Method A: 46.3 mg, 83% yield, Method B: 39.8 mg, 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 2.8 Hz, 1H), 7.49 (d, J = 9.1 Hz, 1H), 7.30 (s, 1H), 7.26–7.20 (m, 2H), 3.92 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 165.1, 157.4, 149.7, 147.7, 135.9, 126.3, 124.8, 122.5, 121.6, 120.4, 119.1, 111.5, 106.6, 99.3, 56.1, 21.9. HRMS (ESI): Calcd for $C_{17}H_{13}O_4[M+H]^+$: 281.0808, found 281.0808.

*4.2.11. 2-methoxy-8,10-dimethyl-11H-benzofuro[2,3-b]chromen-11-one (**2k**)*

White solid, Method A: 51.2 mg, 87% yield, Method B: 48.2 mg, 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 2.3 Hz, 1H), 7.48 (d, J = 9.0 Hz, 1H), 7.29–7.22 (m, 1H), 7.11 (s, 1H), 6.98 (s, 1H), 3.91 (s, 3H), 2.98 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 165.1, 157.4, 149.9, 147.2, 136.1, 133.6, 128.0, 124.9, 122.6, 120.2, 118.8, 108.7, 106.8, 100.2, 56.0, 21.7, 21.6. HRMS (ESI): Calcd for $C_{18}H_{15}O_4[M+H]^+$: 295.0965, found 295.0965.

*4.2.12. 2,8-dimethoxy-11H-benzofuro[2,3-b]chromen-11-one (**2l**)*

White solid, Method A: 27.3 mg, 46% yield, Method B: 38.0 mg, 64% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, J = 8.5 Hz, 1H), 7.77 (s, 1H), 7.53 (d, J = 9.0 Hz, 1H), 7.29 (d, J = 9.0 Hz, 1H), 7.09 (s, 1H), 7.03 (d, J = 8.5 Hz, 1H), 3.94 (s, 3H), 3.89 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.7, 165.0, 158.6, 157.4, 150.4, 147.7, 124.9, 122.6, 122.4,

119.2, 116.0, 112.7, 106.6, 99.4, 97.2, 56.2, 56.0. HRMS (ESI): calcd for $C_{17}H_{13}O_5$ $[M+H]^+$: 297.0758, found: 297.0756.

4.2.13. 1,3,8-trimethoxy-11H-benzofuro[2,3-b]chromen-11-one (**2m**)

White solid, Method A: 26.1 mg, 40% yield, Method B: 28.8 mg, 44% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (d, J = 8.5 Hz, 1H), 7.07 (s, 1H), 7.01 (d, J = 8.6 Hz, 1H), 6.63 (s, 1H), 6.47 (s, 1H), 3.99 (s, 3H), 3.92 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.8, 163.6, 163.4, 161.9, 158.3, 157.2, 150.3, 122.2, 116.8, 112.6, 109.0, 99.9, 97.1, 96.9, 93.7, 56.6, 56.02, 55.98. HRMS (ESI): calcd for $C_{18}H_{15}O_6$ $[M+H]^+$: 327.0863, found: 327.0862.

4.2.14. 2-fluoro-11H-benzofuro[2,3-b]chromen-11-one (**2n**)

White solid, Method A: 30.1 mg, 53% yield, Method B: 36.9 mg, 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 5.9 Hz, 1H), 7.74 (d, J = 2.5 Hz, 1H), 7.52 (d, J = 9.1 Hz, 1H), 7.47 (dd, J = 8.8, 3.6 Hz, 1H), 7.29 (dd, J = 9.2, 2.9 Hz, 1H), 7.09 (dd, J = 8.9, 6.8 Hz, 1H), 3.93 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 165.9, 160.5 (d, J = 240.0 Hz), 157.6, 147.8, 145.4, 124.7, 124.3 (d, J = 11.3 Hz), 122.9, 119.2, 112.8 (d, J = 26.3 Hz), 112.2 (d, J = 8.8 Hz), 108.6 (d, J = 26.3 Hz), 106.8, 99.4, 56.2. HRMS (ESI): Calcd for $C_{16}H_{10}FO_4[M+H]^+$: 285.0558, found 285.0559.

4.2.15. 9-chloro-2-methoxy-11H-benzofuro[2,3-b]chromen-11-one (**2o**)

White solid, Method A: 24.6 mg, 41% yield, Method B: 33.1 mg, 55% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.76 (d, J = 2.8 Hz, 1H), 7.54 (d, J = 9.1 Hz, 1H), 7.46 (d, J = 8.7 Hz, 1H), 7.35 (d, J = 8.7 Hz, 1H), 7.31 (dd, J = 9.0, 2.8 Hz, 1H), 3.95 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.6, 165.7, 157.7, 147.9, 147.7, 131.1, 125.6, 124.7, 124.5, 123.0, 121.9, 119.3, 112.3, 106.8, 98.9, 56.2. HRMS (ESI): calcd for $C_{16}H_{10}ClO_4$ $[M+H]^+$: 301.0262, found: 301.0264.

4.2.16. 2,9-dimethoxy-11H-benzofuro[2,3-b]chromen-11-one (**2p**)

White solid, Method A: 42.6 mg, 72% yield, Method B: 34.9 mg, 59% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 2.7 Hz, 1H), 7.62 (d, J = 2.1 Hz, 1H), 7.48 (d, J = 9.1 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 7.24 (dd, J = 9.1, 2.9 Hz, 1H), 6.90 (dd, J = 8.9, 2.3 Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 165.5, 157.6, 157.4, 147.7, 143.8, 124.7, 123.7, 122.5, 119.1, 113.5, 111.8, 106.7, 104.9, 99.5, 56.11, 56.06. HRMS (ESI): Calcd for $C_{17}H_{13}O_5$ $[M+H]^+$: 297.0757, found 297.0759.

4.2.17. methyl(S)-2-(1,3-dioxoisoindolin-2-yl)-3-(2-methoxy-11-oxo-11H-benzofuro[2,3-b]chromen-9-yl) propanoate (**2q**)

White solid, Method A: 33.8 mg, 34% yield, Method B: 44.8 mg, 45% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.84–7.72 (m, 3H), 7.70–7.63 (m, 2H), 7.51 (d, J = 9.0 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.28 (d, J = 2.1 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 5.22 (dd, J = 11.5, 4.8 Hz, 1H), 3.94 (s, 3H), 3.81 (s, 3H), 3.77 (dd, J = 14.5, 4.6 Hz, 1H), 3.72–3.64 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.7, 169.3, 167.6, 165.5, 157.5, 148.4, 147.8, 134.29, 134.26, 131.7, 126.1, 124.8, 123.7, 123.5, 122.7, 122.5, 119.2, 111.2, 106.8, 99.2, 56.2, 53.9, 53.1, 34.8. HRMS (ESI): Calcd for $C_{28}H_{20}NO_8$ $[M+H]^+$: 498.1184, found: 498.1184.

4.2.18. 2-fluoro-11H-benzofuro[2,3-b]chromen-11-one (**2r**)

White solid, Method A: 30.0 mg, 59% yield, Method B: 40.1 mg, 79% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (d, J = 8.6 Hz, 1H), 8.05 (dd, J = 8.2, 3.1 Hz, 1H), 7.64 (dd, J = 9.1, 4.1 Hz, 1H), 7.56 (d, J = 7.7 Hz, 1H), 7.48–7.40 (m, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.0, 165.5, 160.2 (d, J = 246.0 Hz), 149.4 (d, J = 22.7 Hz), 125.8, 125.7 (d, J = 7.4 Hz), 125.6, 122.8, 122.2, 121.5, 121.3, 120.0 (d, J = 8.0 Hz), 112.1 (d, J = 24.0 Hz), 111.4, 99.5. ^{19}F NMR (564 MHz, $CDCl_3$): δ −114.38 ~ −114.40 (m). HRMS (ESI): Calcd for $C_{15}H_8FO_3$ $[M+H]^+$: 255.0452, found 255.0453.

4.2.19. 2-fluoro-9-methoxy-11H-benzofuro[2,3-b]chromen-11-one (**2s**)

White solid, Method A: 30.1 mg, 53% yield, Method B: 45.4 mg, 80% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (dd, J = 8.2, 3.1 Hz, 1H), 7.66 (d, J = 2.7 Hz, 1H), 7.62 (dd, J = 9.1, 4.1 Hz, 1H), 7.47–7.42 (m, 2H), 6.96 (dd, J = 9.0, 2.7 Hz, 1H), 3.91 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.0, 165.7, 160.1 (d, J = 246.0 Hz), 157.9, 149.3, 143.9, 125.6 (d, J = 6.9 Hz), 123.5, 121.4 (d, J = 25.1 Hz), 119.9 (d, J = 8.1 Hz), 114.1, 112.1, 112.0 (d, J = 8.0 Hz), 104.9, 99.8, 58.2. ^{19}F NMR (564 MHz, $CDCl_3$): δ −114.46 ~ −114.46 (m). HRMS (ESI): Calcd for $C_{16}H_{10}FO_4[M+H]^+$: 285.0558, found 285.0559.

4.2.20. 2-fluoro-9-(trifluoromethyl)-11H-benzofuro[2,3-b]chromen-11-one (**2t**)

White solid, Method A: 30.2 mg, 47% yield, Method B: 12.9 mg, 20% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.06 (dd, J = 8.1, 3.1 Hz, 1H), 7.72–7.68 (m, 2H), 7.66 (dd, J = 4.5 Hz, 4.5 Hz, 1H), 7.49 (ddd, J = 9.1, 7.3, 3.1 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.7, 166.1, 160.3 (d, J = 246.9 Hz), 150.8, 149.4, 128.4 (q, $^2J_{CF}$ = 32.6 Hz), 125.6 (d, J = 7.4 Hz), 124.3 (q, $^1J_{CF}$ = 270.1 Hz), 123.3, 123.1 (q, $^3J_{CF}$ = 3.1 Hz), 121.8 (d, J = 25.2 Hz), 120.1 (d, J = 8.0 Hz), 119.8 (q, $^3J_{CF}$ = 3.8 Hz), 112.3 (d, J = 24.6 Hz), 111.9, 99.2. ^{19}F NMR (564 MHz, $CDCl_3$): δ −61.33 (s), −113.63 ~ −113.67 (m). HRMS (ESI): Calcd for $C_{16}H_7F_4O_3$ $[M+H]^+$: 323.0326, found 323.0327.

4.2.21. 2-fluoro-7-methyl-11H-benzofuro[2,3-b]chromen-11-one (**2u**)

White solid, Method A: 34.3 mg, 64% yield, Method B: 41.3 mg, 77% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (dd, J = 8.2, 3.1 Hz, 1H), 7.99 (d, J = 7.5 Hz, 1H), 7.62 (dd, J = 9.1, 4.1 Hz, 1H), 7.46–7.42 (m, 1H), 7.33 (dd, J = 7.6, 7.6 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 2.56 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.0 (d, J = 1.5 Hz), 165.3, 160.1 (d, J = 246.0 Hz), 149.3, 148.5, 127.1, 125.7 (d, J = 7.1 Hz), 125.5, 122.3, 121.6, 121.3 (d, J = 25.4 Hz), 119.9 (d, J = 8.4 Hz), 119.6, 112.1 (d, J = 24.5 Hz), 99.7, 15.0. ^{19}F NMR (564 MHz, $CDCl_3$): δ −114.51 ~ −114.54 (m). HRMS (ESI): Calcd for $C_{16}H_{10}FO_3$ $[M+H]^+$: 269.0608, found 269.0609.

4.3. General procedures for the synthesis of natural product Lupinalbin A

A solution of CDC product **2m** (32.6 g, 0.1 mmol) in 2 mL DCM was cooled to 0 °C and was treated with boron tribromide (2 mL, 1M in DCM). The reaction mixture was stirred at 45 °C for 24 h. Then the reaction mixture was cooled to room temperature and quenched with $NaHCO_3$ (aq.) (10 mL). After extracted with EtOAc (30 mL×3), the combined organic phases were dried by anhydrous Na_2SO_4 and concentrated. The product Lupinalbin A was isolated by flash chromatograph (petroleum ether/ethyl acetate = 4/1) as white solid (15.3 mg, 54% yield).

4.3.1. 1,3,8-trimethoxy-11H-benzofuro[2,3-b]chromen-11-one (Lupinalbin A)

White solid, 15.3 mg, 54% yield. ^{1}H NMR (600 MHz, Acetone-d_6) δ 12.98 (s, 1H), 9.51 (br, 1H), 8.95 (br, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.13 (s, 1H), 7.02 (d, J = 8.3 Hz, 1H), 6.59 (s, 1H), 6.37 (s, 1H). ^{13}C NMR (150 MHz, Acetone-d_6) δ179.6, 165.7, 164.3, 164.0, 157.2, 156.1, 151.4, 122.3, 115.2, 114.6, 104.5, 100.7, 99.6, 98.4, 95.6. HRMS (ESI): Calcd for $C_{15}H_9O_6$ $[M+H]^+$: 285.0394, found: 285.0391.

Declaration of competing interest

The authors declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work. We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132048.

Supplementary Material

Supplementary data (Copies of NMR spectra) related to this article can be found at https://doi.org/10.1016.xxxx.xx.

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