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DBU-mediated regioselective intramolecular cyclization/dehydration of *ortho* diketo phenoxyethers: a synthesis of 2,3-substituted γ-benzopyranones

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ABSTRACT

The regioselective cyclization/dehydration sequence of *ortho* diketo phenoxyethers induced by DBU has been explored. The results demonstrated a high degree of selectivity with preference for 6-*exo*-*trig* cyclization leading to the formation of γ-benzopyranone derivatives in good yield.

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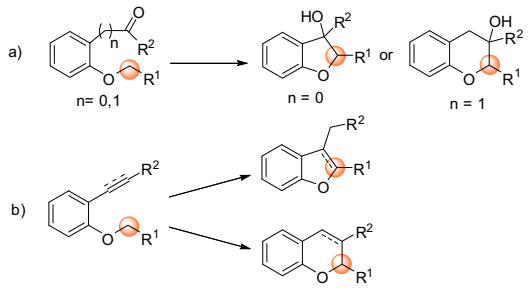
1. Introduction

Benzofuran and benzopyran scaffolds are widely distributed in many naturally occurring compounds, and show a wide range of biological activities, for instance, insecticidal, analgesic, antibacterial, anticancer, anti-HIV, antimicrobial, and antioxidant properties.[1] Additionally, they constitute versatile building blocks for entry into more complex molecules of biological interest.[2] Owing to their biologically and structurally interesting properties, various synthetic routes toward benzofuran and benzopyran derivatives have been developed over the years.[3] Among them, the attachment of the furanyl or pyranyl portion, formed by intramolecular cyclization, onto the existing benzenoid rings is probably one of the most direct and potentially versatile routes to assemble these ring systems.[3–11] This cyclization requires *ortho* substituted phenol or phenoxy derivatives as precursors and the reaction can proceed either through carbon–oxygen bond formation or carbon–carbon bond formation in the key step. In an intramolecular carbon–oxygen bond annulation, the oxygen in the common phenol derivatives was used as a nucleophile to attack electrophilic substituents.[4] Although the corresponding benzofurans or benzopyrans were obtained in good yield, the substituents on the ensuing heterocyclic rings were mostly simple aryl or alkyl group thus greatly limiting further functionalization to a more complex skeleton.[4]

The intramolecular carbon–carbon bond formation to construct these heterocycles is an alternative route, which holds potential synthetic utility in expanding the scope of functional group variability onto benzofurans or benzopyrans (Scheme 1).[5–11]



Scheme 1. Intramolecular carbon–carbon bond cyclization of *ortho* substituted phenyl ether.

In this mode of cyclization, the methylene group on the phenoxyether was used to cyclize onto the *ortho* electrophilic substituent, including a carbonyl group, alkene, and alkyne. Among these, the annulation reaction involving a carbonyl functionality as electrophile

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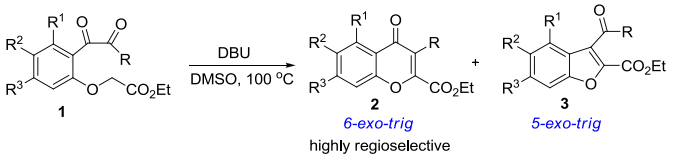
was the most typical route to construct these two heterocycles (Scheme 1a). Different ring sizes could be obtained by placing the carbonyl group into a suitable position, and promotion of cyclization was effectively done by generation of a carbanion using bases,[5] or a radical by photochemical hydrogen atom abstraction.[6] Even though, this route provided efficient and reliable formation of the requisite benzofurans or benzopyrans, the precise position of the carbonyl group on the substrate can make synthesis difficult in practice. On the other hand, regioselective formation by using an alkene and alkyne as electrophiles demonstrated the simplicity and expediency of preparation of precursors because the specific nucleophilic site is not vital (Scheme 1b). While in such cases regiochemical selectivity between five-membered and six-membered cyclization processes could occur leading to different ring sizes, numerous examples demonstrated excellent regioselectivity in product formation depending on substrates and conditions. Liang demonstrated the exclusive formation of 2-aroyl-3-vinyl-benzofuran by way of utilizing palladium catalyzed cyclization/isomerization of a propargylic arene.[7] Terada reported phosphazene base-catalyzed intramolecular carbon–carbon bond cyclization with highly selective formation of 2-substituted 3-benzylbenzofurans from *ortho* alkynyl phenylethers.[8] Recently, Wang nicely expanded the intramolecular carbon–carbon bond formation to an alkene or alkyne of an *ortho* phenoxyether by intramolecular nucleophilic attack of the carbanion generated by *t*-BuOK.[9] Remarkably, the cyclized products could be formed in high regioselectivity depending on alkene or alkyne used. When alkenes were used, the 6-*endo-trig* cyclization was formed to give the benzopyrans.[9b] In contrast, when alkynes were used, 5-*exo-dig* pathway to yield the benzofurans was exclusively observed.[9a]

Despite the fact that the regioselective cyclization simplifies the substrate formation and the carbonyl group offers high proficiency as an electrophilic site for benzofuran or benzopyran construction, the intramolecular carbon–carbon bond formation using related *ortho* dicarbonyl precursors has not been the subject of a detailed study to date. There have been scarce examples on the use of *ortho* dicarbonyl phenylethers with limited substituents in the synthesis of these heterocycles. Ruchirawat reported the synthesis of 2-arylbenzofurans via the in situ formation of aryl α-keto esters from the rearrangement of an aromatic cyanohydrin carbonate ester induced by LDA.[10] Roengsamran, in the synthesis of dehydrorotenoids, reported the generation of benzopyranones by treatment of an aryl diketone intermediate with aqueous sulfuric acid.[11] The limited substituent patterns and insufficient data of the carbon–carbon bond cyclization to dicarbonyl systems in the formation of benzofurans or benzopyrans prompted us to investigate the effect of different substituents on their regioselectivity. We focused our work on the utilization of the carbon–carbon bond formation by the base induced intramolecular cyclization reaction of an *ortho* diketo phenoxyether tethered with a carboxylic ester (i.e., **1**). The use of a carboxylic ester not only serves as an activating group for the generation of a carbanion, but its functionality could also be easily manipulated for further synthesis. In this study, we found that the intramolecular cyclization induced by DBU demonstrated a high degree of regioselectivity toward the 6-*exo-trig* cyclization with concomitant extrusion of H_2O, thus providing a two-step sequence of intramolecular carbon–carbon bond cyclization/dehydration to 2,3-substituted γ-benzopyranone **2**[12] in one-pot (Scheme 2).

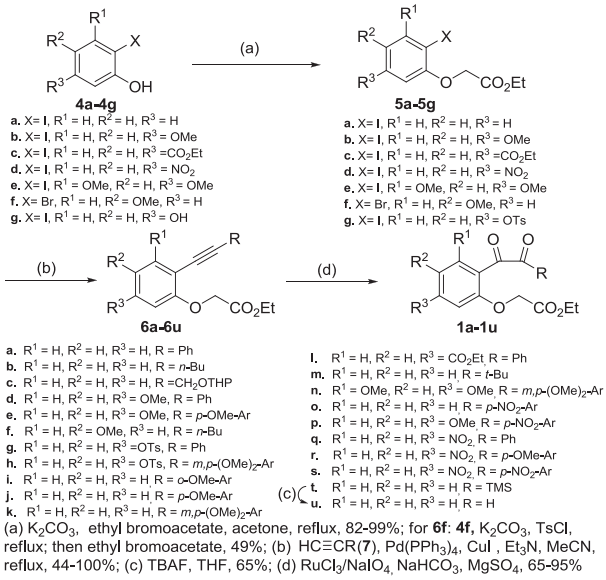


Scheme 2. Regioselective intramolecular cyclization/dehydration of *ortho* diketo phenoxyether using DBU.

2. Results and discussion

2.1. Preparation of diketo precursors

We began our investigation by preparing the desired diketo precursor **1**, which could be accomplished in three steps from halophenols **4a–g** (Scheme 3).



Scheme 3. Preparation of dione phenoxyethers.

Firstly, the phenols **4a–f** were deprotonated with K_2CO_3 and then alkylated with ethyl 2-bromoacetate to furnish the phenoxyacetates **5a–f** in excellent yield (82–99%). Ethyl 2-(2-iodo-5-(tosyloxy)phenoxy)acetate **5g** was, in turn, prepared in a consecutive manner from **4g** by treatment with TsCl and K_2CO_3 in refluxing acetone overnight and further refluxing with ethyl 2-bromoacetate (**5**) for an additional 3 h. Afterward, the phenoxyacetates **5a–g** were subjected to Sonogashira cross coupling reaction with a variety of terminal alkynes (**7**) in the presence of CuI, $Pd(PPh_3)_4$, and Et_3N in MeCN providing alkynyl phenoxyethers **6a–u** in good to excellent yield (44–100%). The third step in the synthesis involved the oxidation of the alkyne moiety to dicarbonyls. In this regard, the alkynyl phenoxyether **6a** was used for investigating oxidation reaction conditions.[13] The Wacker type oxidation, in which molecular oxygen as the stoichiometric sole oxidant and catalytic $PdBr_2$ and $CuBr_2$ were used,[14] could produce product **1a** in 58%. The $RuO_2/NaIO_4$[15] system was able to produce **1a** in moderate yield (40%), but a better result could be obtained by $RuCl_3/NaIO_4$ in the presence of $NaHCO_3/MgSO_4$[11] providing the corresponding product in excellent yield (96%) within 1 h. The increase in yield is presumably the result of the buffered reaction conditions.[16] With this latter reaction condition, the conversion of various substituted alkynes **6a–r** to the corresponding diketo phenoxyethers **1a–r** was completed within 1–3 h in good to excellent yield (65–95% yield). However, oxidation of compound **6s** led to an unidentified complex mixture, presumably due to the instability of the substrate. In addition, with alkynyl phenoxyethers **6t** and **6u**, containing the TMS and H terminus, the reactions produced the 2-(2-ethoxy-2-oxoethoxy) benzoic acid **8** as the only product isolated by column chromatography in 74% and 88%, respectively.[17] The ensuing diketones **1t** and **1u** probably underwent photolysis resulting in the oxidative carbon–carbon bond cleavage to give the carboxylic acid **8**.[13e]

2.2. Investigation of base induced cyclization reaction

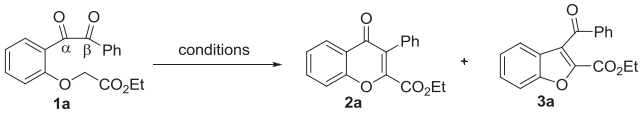
When commencing the investigation, we first explored the intramolecular carbon–carbon bond cyclization/dehydration sequence with compound **1a** as a model substrate. Thus, the cyclization of diketo phenoxyether **1a** would lead to 3-carbonylated benzofuran-2-carboxylate ester **2a** via 5-*exo*-*trig* cyclization or 3-substituted benzopyranone-2-carboxylate ester **3a** via 6-*exo*-*trig* cyclization. We initially examined the reaction of **1a** in a variety of basic conditions. As can be seen in Table 1 in all cases where the reaction occurred, the 6-*exo* cyclization product was predominant.

When the substrate **1a** was subjected to DMAP in DMF, cyclization did not occur at all even at 100 °C (entry 1). The use of phosphazene base P4-*t*-Bu gave no reaction in refluxing toluene or decomposition in DMSO at 100 °C (entries 2 and 3). When the substrate **1a** reacted with NaOEt in EtOH at room temperature, only recovered starting material was found (entry 4); however, when the reaction was heated at reflux, the reaction could not proceed to completion, but three different cyclized products were formed along with 35% of the recovered starting material (entry 5). This condition could induce cyclization followed by dehydration to give rise to benzopyranone **2a** (14%), benzofuran **3a** (7%), and 6-*exo* cyclized alcohol **II** (11% yield). The preference for the 6-*exo*-*trig* pathway was also observed when heating **1a** with NaH in refluxing toluene in which the 6-*exo* cyclized alcohol **II** was obtained in 18% yield together with benzopyranone **2a** (4%), benzofuran **3a** (9%), and the recovered starting material (44%) (entry 6). Using *t*-BuOK in THF (entry 7), which was effectively employed in similar systems,[9] did not work well with our substrate. Only 9% of benzopyranone product **2a** was accompanied by major decomposition. When **1a** was treated with K_2CO_3 in DMF at 100 °C for 24 h, intramolecular carbon–carbon bond cyclization occurred with complete loss of H_2O to deliver **2a** and **3b** in 36% and 4%, respectively (entry 8). The low combined yield of products could be due to the long reaction time at high temperature to achieve the full conversion. Gratifyingly, the use of DBU in DMF at 100 °C gave complete conversion within 3 h to provide the corresponding cyclization/dehydration products. The regioselectivity toward 6-*exo*-*trig* cyclized product **2a** could be observed in 57% yield together with a small amount of 5-*exo*-*trig* cyclized product **3a** in 3% (entry 9).

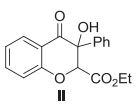
We next continued to investigate the regioselectivity of the DBU mediated cyclization/dehydration sequence with respect to solvents (entries 9–13). By switching to non-polar solvent toluene, the reaction required a long reaction time to complete, and the regioselectivity toward a 6-*exo*-*trig* cyclized product was drastically diminished to give only 41% of **2a** along with 24% of **3a** (entry 10). By contrast, in polar solvents, the reactions were complete in much shorter time, within 3 h in DMF and MeCN, 8 h in EtOH, and 1 h in DMSO (entries 9–13). Moreover, the regioselectivity of the reaction in polar solvents also displayed higher selectivity toward a 6-*exo*-*trig* cyclized product **2a** than that of in toluene.[19] Furthermore, when comparing polar solvents, DMSO showed excellent selectivity giving a 6-*exo*-*trig* cyclized product **2a** in 84% yield with a barely detectable amount of 5-*exo*-*trig* cyclized product **3a** (3%) (entries 9, 11–13). We also examined the effect of DBU in DMSO at room temperature (entry 14) as well as catalytic DBU (entry 15). In both cases, the reactions proceeded with concomitant loss of H_2O, but reaction times were exceedingly long. A significant amount of starting material could be isolated after 3 days, thus making these conditions (entries 14 and 15) impractical for synthesis.

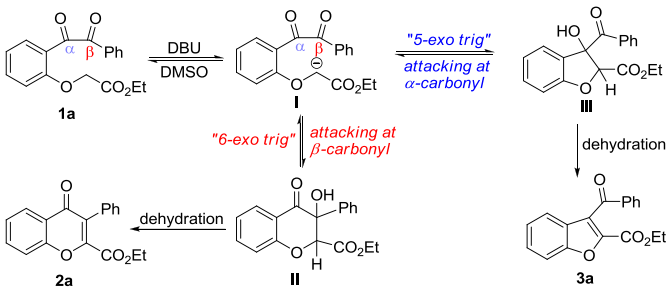
A plausible mechanism is described in Scheme 4. The present molecular cyclization was most probably initiated by the generation of a carbanion intermediate via deprotonation of the most acidic proton by base. Carbanion **I** thus formed then underwent nucleophilic attack to the β-carbonyl through intramolecular 6-*exo*-*trig* cyclization, followed by dehydration to yield benzopyranone derivative **2a**. The dehydration was presumably driven by the formation of the more conjugated α,β unsaturated keto ester. The benzofuran regioisomer **3a**, conversely, derived from the cyclization of carbanion to the α-carbonyl through intramolecular 5-*exo*-*trig* pathway.

Table 1
Investigation of the cyclization of **1a** under various basic conditions



Entry	Reagents	Solvent	*T* (°C)	Time[a]	Yield[b] (%) **2a**	Yield[b] (%) **3a**
1	DMAP	DMF	100	24 h	No Rx	
2	P4-*t*-Bu	DMSO	100	4 h	Complex mixture	
3	P4-*t*-Bu	Toluene	Reflux	24 h	No Rx	
4	NaOEt	EtOH	rt	24 h	No Rx	
5	NaOEt	EtOH	Reflux	24 h[c]	14[d]	7
6	NaH	Toluene	Reflux	24 h[c]	4[e]	9
7	*t*-BuOK	THF	Reflux	20 h	9	—
8	K_2CO_3	DMF	100	24 h	36	4
9	DBU	DMF	100	3 h	57	4
10	DBU	Toluene	Reflux	24 h	41	24
11	DBU	MeCN	Reflux	3 h	45	13
12	DBU	EtOH	Reflux	8 h	30	8
13	DBU	DMSO	100	1 h	84	3
14	DBU	DMSO	rt	3 days[c]	23	3
15	0.25 equiv DBU	DMSO	100	3 days[c]	48	2

[a] Determined by monitoring the consumption of stating material by TLC.
[b] Isolated yield.
[c] The reaction was not completed.
[d] Along with 11% of alcohol **II**[18] and 35% of recovered starting material. 
[e] Along with 18% of alcohol **II** and 44% of recovered starting material.



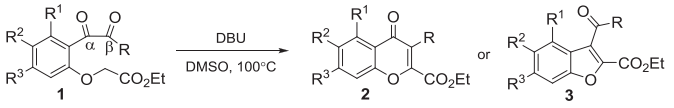
Scheme 4. Proposed mechanism for an intramolecular carbon–carbon bond cyclization/dehydration reaction.

2.3. Exploring substrate variation

After finding the optimal reaction condition (DBU, DMSO, 100 °C) for the cyclization of **1a**, we further examined the scope and limitation of the DBU induced 6-*exo*-*trig* cyclization with a series of *ortho* diketo phenoxyether derivatives. We found that the intramolecular cyclization/dehydration sequence induced by DBU demonstrated a high degree of regioselectivity. In most cases, the corresponding cyclization/dehydration adducts were formed favoring benzopyranone **2** in good yield; nonetheless, the influence of the steric and electronic effect to the cyclization mode could apparently be recognized as shown in Table 2.

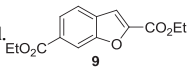
The simple phenoxyether containing alkyl or simple phenyl substituents on the β-carbonyl (entries 1–3, and entry 13) provided the regioselective formation of benzopyranones with the exception of entry 13 (R=*t*-Bu). The introduction of a *t*-Bu group at the β-carbonyl induced the opposite regioselectivity, giving rise to

Table 2
Intramolecular cyclization/dehydration reaction of various *ortho* diketo phenoxyether **1** with DBU



Entry	1	R^1	R^2	R^3	R	Time (h)	2, Yield[a]	3, Yield[a]
1	1a	H	H	H	Ph	1	84%	3%
2	1b	H	H	H	*n*-Bu	1	74%	—
3	1c	H	H	H	CH_2OTHP	2	73%	—
4	1d	H	H	OMe	Ph	1	78%	—
5	1e	H	H	OMe	*p*-OMe–Ar	1	70%	—
6	1f	H	OMe	H	*n*-Bu	1	73%	—
7	1g	H	H	OTs	Ph	1	56%	—
8	1h	H	H	OTs	*m*,*p*-$(OMe)_2$–Ar	1	56%	—
9	1i	H	H	H	*o*-OMe–Ar	3	61%	—
10	1j	H	H	H	*p*-OMe–Ar	1	57%	13%
11	1k	H	H	H	*m*,*p*-$(OMe)_2$–Ar	1	53%	16%
12	1l	H	H	CO_2Et	Ph	1	54%	12%[b]
13	1m	H	H	H	*t*-Bu	4	—	42%
14	1n	OMe	H	OMe	*m*,*p*-$(OMe)_2$–Ar	2	—	64%
15	1o	H	H	H	*p*-NO_2–Ar	3[c]	—	—
16	1p	H	H	OMe	*p*-NO_2–Ar	1[c]	—	—

[a] Isolated yield.
[b] Along with the formation of **9** in 14% yield.
[c] Complex mixture was obtained.



9

benzofuran **3m**. The steric bulkiness of the *t*-Bu substituent most probably hindered the attack of the carbanion at the β-carbonyl and directed the attack to the less hindered α-carbonyl. The longer reaction time required for completion of **3m** (4 h) inferred the difficulty in product formation compared to the shorter reactions used in 6-*exo*-*trig* formation.

When placing a variety of substituents on both the phenoxyether and phenyl rings on the β-carbonyl, the reactions yielded benzopyranones **2** without detectable amounts of benzofurans **3** on both TLC and ^{1}H NMR of crude product (entries 2–9). The *meta* substituent on the phenoxyether also has no obvious influence on the regioselectivity toward cyclization as demonstrated by phenoxyethers **1b** and **1f** in which benzopyranones **2b** and **2f** were exclusively formed in comparable product yield (entries 2 and 6).

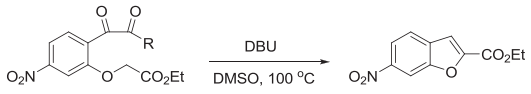
The influence of electronic effects toward cyclization was detected when the substrate contained an electron-donating group, *p*-OMe–Ar at the β-carbonyl. When substrate **1j** was subjected to the DBU-cyclization condition, besides the major product benzopyranone **2j** in 57% yield, a minor amount of benzofuran **3j** (13%) was also obtained. This outcome could be ascribed by the electron donating nature through the resonance effect of the *para* OMe group decreasing the electrophilicity of the β-carbonyl thus attenuating the regioselectivity toward 6-*exo*-*trig* cyclization. Along the same line, in the presence of electron withdrawing CO_2Et on R^3, the cyclization resulted in 54% of benzopyranone **1l** together with 12% of benzofuran **3l**. In this circumstance, the electron withdrawing property of CO_2Et in turn enhanced the electrophilicity of α-carbonyl thus leading to the competitive formation of 5-*exo*-*trig* to give benzofuran **3l**.

On the basis of our results, it seemed that the *ortho* phenoxyether tether on substrates **1** played a significant role in the product selectivity by donating an electron through resonance effect thus weakening the electrophilicity of the α-carbonyl. As a consequence, the mode of cyclization then was directed to 6-*exo*-*trig* cyclization to give benzopyranones **2**. Such effect of the *ortho* phenoxyether was supported by the use of substrate **1e** bearing a *p*-OMe–Ar on both β-carbonyl (R group) and a *para*-substituent on phenoxyether (entry 5, Table 2). In this case, each OMe group could equally donate an electron to its adjacent carbonyl, but only the 6-*exo*-*trig* benzopyranone **2e** was formed. Thus, this result could be inferred to the contribution of resonance effect from *ortho* phenoxyether tether.

The resonance effect of substituents in the *meta* and *para* positions were also investigated. The additional OMe group in the *meta* position on the β-carbonyl substituent exhibited a slight influence on product selectivity as seen in entries 11 and 12. The *m*,*p*-$(OMe)_2$–Ar group gave 53% of benzopyranone **1k** with 16% of benzofuran **3k**, whereas the *p*-OMe–Ar group provided 57% of benzopyranone **1j** with 13% of benzofuran **3j**.

Surprisingly, the placement of an OMe group in the *ortho* position of both phenoxyether and phenyl rings on the β-carbonyl gave contrasting results to our expectation (entries 9 and 14). When the *o*-OMe–Ar group was placed at the β-carbonyl (entry 9), the benzopyranone **2i** was received exclusively without contamination of the expected benzofuran **3i**, which should theoretically be formed as the result of the weakening electrophilicity of the β-carbonyl by an *ortho* donating resonance effect. These results could be explained by the concept of steric inhibition of the resonance effect.[20] The introduction of the OMe group at the *ortho* position contributed to the steric hindrance, and blocked the attainment of coplanarity between the β-carbonyl group and the phenyl ring. As a consequent, resonance from the *o*-OMe–Ar group to the β-carbonyl was inhibited and made the β-carbonyl more resemble an isolated carbonyl, which was more susceptible toward the generated carbanion, resulting in the preference for 6-*exo* formation. The same rationalization could be applied for the formation of 5-*exo* benzofuran **3n**. The OMe group at R^1 on the phenoxyether forced the α-carbonyl away from the plane of the aromatic ring inhibiting the effect of resonance from the phenoxyether, while the β-carbonyl, which had no *ortho* substituent feasibly gained resonance effect from the *m*,*p*-$(OMe)_2$–Ar substituent. As a result, the α-carbonyl was more electrophilic, thus giving benzofuran **3n** as sole product.

We also examined the effect of the strong electron withdrawing NO_2 substituent on both phenoxyether and phenyl rings on the β-carbonyl. Of many reports, examples were mostly illustrated with moderate electron-withdrawing groups while the nitro substituted substrates were scarcely examined.[3–11] Hence it drew us to explore the effect of such a strong group toward the cyclization. The introduction of NO_2 functionality on phenyl ring located on the β-carbonyl (R group) (entries 15 and 16, Table 2) resulted in decomposition as observed by both TLC and ^{1}H NMR spectroscopy of the crude product. These results could be attributed to the instability under base at high temperature of these nitro compounds.[4a] Interestingly, when placing the NO_2 group on R^3, the reaction exclusively provided 5-*exo*-*trig* benzofuran **10** (Scheme 5).



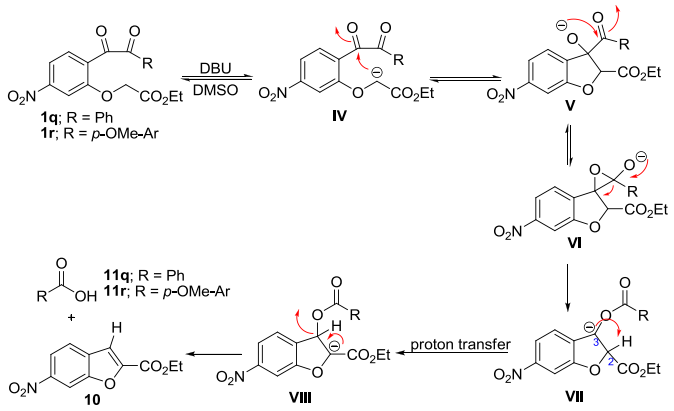
1q; R = Ph
1r; R = *p*-OMe-Ar

10; from **1q**, 75%
from **1r**, 80%

Scheme 5. The generation of nitro benzofuran **10** from **1q** and **1r**.

These results indicated that the very strong electron withdrawing nature of the NO_2 group greatly enhanced the electrophilic nature of the α-carbonyl and overrode the donating effect of the *ortho* ether tethering. Further, the absence of the keto side chain on the C-3 position on the NO_2 substituted benzofuran **10** could be the result of a strong electron withdrawing property of the nitro group as ascribed in the next scheme (Scheme 6).

The interpretation of the reaction mechanism for the formation of **10** could be rationally illustrated as follows (Scheme 6). Initially, the carbon–carbon bond formation of carbanion **IV** to α-carbonyl by 5-*exo*-*trig* cyclization gave rise to the formation of alkoxide **V**, which could further react with the adjacent carbonyl to provide the alkoxy epoxide intermediate **VI**. The ring opening of the epoxide led to the



Scheme 6. Proposed reaction mechanism for the formation of nitro benzofuran from **1q** and **1r**.

rearrangement of the oxygen to give the ester group with the α-carbanion on C-3 (intermediate **VII**). The strong withdrawing effect of the *para* nitro substituent probably helped stabilize the given anion through resonance effect, thus promoting the formation of intermediate **VII**. The proton transfer and subsequent loss of carboxylate would afford the benzofuran **10**. This rationale was confirmed by the fact that we were able to isolate the corresponding carboxylic acid, benzoic acid **11q**, and *para* methoxybenzoic acid **11r**, which were derived from the eliminated carboxylate anion.[21] The proposed mechanism also corresponds to the moderately electron-withdrawing CO_2Et group at R^3 in which we also observed some of benzofuran **9** (entry 12, Table 2) in 14% yield.

The formation of benzofuran or benzopyranone products was supported by their ^1H NMR and ^{13}C NMR spectra. The structural difference between benzopyranones **2** and benzofurans **3** could be deduced by the chemical shift of the carbonyl carbon and the aromatic proton close to the carbonyl group. In benzopyranones **2**, the ^{13}C NMR of the carbonyl appeared in the range δ_C 176–178 ppm presumably due to the delocalization of electrons through benzopyranone system. This chemical shift corresponded to those reported carbonyl chemical shifts of ^{13}C NMR in benzopyranone-4-one derivatives.[5] The aromatic proton on C-5 appeared far downfield in the range δ_H 8.1–8.4 ppm as the result of the deshielding effect from the carbonyl group to the *peri* proton. In benzofurans **3**, the ^{13}C NMR of the carbonyl located in the range δ_C 190–207 ppm resembling the chemical shift of the regular isolated ketone carbonyl. This chemical shift could be explained by the diminishing of the delocalization through the carbonyl group from the fully aromatized benzofuran system. Further, the aromatic proton on C-4 was observed at 7.6–7.9 ppm indicating the absence of a deshielding effect from the carbonyl functionality. Additionally, all resulting structures were reconfirmed by HMBC correlation. The benzopyranone systems showed a strong correlation between the aromatic proton on C-5 and the carbonyl on C-4; whereas, there was no HMBC correlation between the aromatic proton on C-4 and the carbonyl group on benzofuran systems as shown in Fig. 1.

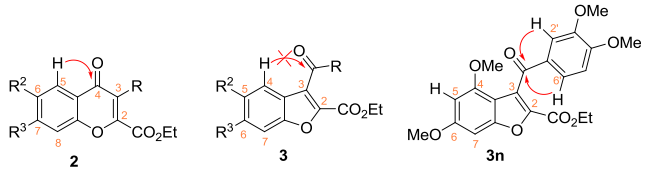


Fig. 1. The HMBC correlation of benzopyranones **2** and benzofurans **3**.

For compound **3n**, which had no H at R^1, the structure of benzofuran was inferred from the carbonyl ketone at 189.7 ppm, hence resembling the isolated ketone as found in benzofuran structure **3**. Further rationalization was made from a strong HMBC correlation between the 2′ and 6′ protons and the carbonyl ketone confirming the structure of benzofuran **3n**.

3. Conclusion

In conclusion, the regioselective intramolecular cyclization/dehydration sequence of *ortho* diketo pheoxyethers to afford benzopyranones, specifically γ-benzopyranones, has been developed. This method has illustrated a practical protocol starting from iodo or bromo phenol derivatives through a sequence of Sonogashira cross coupling, oxidation of alkyne to dione and DBU-induced cyclization. The 6-*exo*-*trig* pathway was exclusive or dominant in most substrates except the substrate containing a strong electron withdrawing NO_2 group at R^3, OMe substituent at R^1 (*ortho* substituent), or a steric bulky *t*-Bu on R group. The approach may deserve further attention as a complement to the conventional benzopyran syntheses because it expands the synthetic potential by way of using the carbonyl and ester moieties on the benzopyranones **2**. Moreover, the construction of 3-substituted γ-benzopyranone, especially those with a substituted phenyl group, is noteworthy since the products possess the isoflavone core, which are rich in nature and have diverse biological effects. Thus the present method potentially offer practical access to both simple isoflavone natural products and advanced isoflavones, such as rotenoid natural products.[22]

4. Experimental section

4.1. General

Commercial grade reagents and solvents were used as received from the supplier except where indicated otherwise. 2-Iodophenol (**4a**),[23] 2-iodo-5-methoxyphenol (**4b**),[24] ethyl-3-hydroxy-4-iodobenzoate (**4c**),[25] 2-iodo-5-nitrophenol (**4d**),[26] 2-iodo-3,5-dimethoxyphenol (**4e**),[27] 2-bromo-4-methoxyphenol (**4f**),[28] 4-iodobenzene-1,3-diol (**4g**),[29] 1-ethynyl-4-methoxybenzene (**7e**),[30] 4-ethynyl-1,2-dimethoxybenzene (**7h**),[29] 1-ethynyl-2-methoxybenzene (**7i**),[31] and 1-ethylnyl-4-nitrobenzene (**7o**), were prepared according to the literature. Tetrahydrofuran (THF), dichloromethane (DCM), acetonitrile (MeCN), and toluene were purified by pressure filtration through activated alumina. All glassware was oven-dried at 110 °C for 2 h or more. Thin layer chromatography was performed on Merck precoated silica gel $60F_{254}$ plates. Silica gel 60 (Silicycle, 230–400 mesh) was used for flash column chromatography and Silica gel $60PF_{254}$ (Merck) was used for preparative thin layer chromatography. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or MeOD-d_4 with 300 and 400 MHz NMR spectrometers. ^1H NMR and ^{13}C NMR chemical shifts (δ) were reported in units of parts per million (ppm), relative to tetramethylsilane (TMS) as internal standard at δ equal to zero ppm. Coupling constants (J) were reported in Hertz (Hz). Infrared spectra measured using an FT-IR spectrometer and were reported in cm^{-1}. High resolution mass spectra (HRMS) and electron-impacted mass spectra (EI-MS) were measured on a mass spectrometer.

4.2. General procedure for preparation of ethyl-2-(2-iodophenoxy) acetate derivatives

To a stirred solution of *ortho* halophenol derivative **4** (1.0 equiv) and potassium carbonate (K_2CO_3) (1.0 equiv) in acetone (4 mL/mmol of substrate) was added ethyl-2-bromoacetate (1.02 equiv) at room temperature. The reaction mixture was stirred at reflux until complete conversion as indicated by TLC. The resulting mixture was allowed to cool to room temperature, filtered through Celite, washed with excess EtOAc (three times), and concentrated under

reduced pressure. Unless otherwise noted, the crude residue was purified to obtain the pure product.

*4.2.1. Ethyl-2-(2-iodophenoxy)acetate (**5a**).*[32] 2-Iodophenol (**4a**) (1.3 g, 5.8 mmol), K_2CO_3 (0.8 g, 5.8 mmol), and ethyl-2-bromoacetate (0.65 mL, 5.9 mmol) were used. The reaction mixture was refluxed for 4 h and then worked up to obtain the title compound **5a** (1.8 g, 99% yield) as a yellow oil, which was pure to use for the next step without further purification; IR (neat) 2981, 1756, 1471, and 1194 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, 3H, J=7.1 Hz), 4.25 (q, 2H, J=7.1 Hz), 4.68 (s, 2H), 6.72 (d, 1H, J=7.8 Hz), 6.73 (t, 1H, J=7.6 Hz), 7.26 (td, 1H, J=7.8 and 1.5 Hz), and 7.77 (d, 1H, J=7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 156.2, 139.3, 129.0, 123.1, 112.0, 86.0, 65.9, 61.0, and 13.8; HRMS calcd for $[(C_{10}H_{11}IO_3)+H]^+$: 306.9826. Found: 306.9822.

*4.2.2. Ethyl-2-(2-iodo-5-methoxyphenoxy)acetate (**5b**).* 2-Iodo-5-methoxyphenol (**4b**) (3.9 g, 15.6 mmol), K_2CO_3 (2.2 g, 15.6 mmol), and ethyl-2-bromoacetate (1.8 mL, 16.0 mmol) were used. The reaction mixture was refluxed for 6 h. Purification by column chromatography (SiO_2, 10% EtOAc/hexane) provided the title compound **5b** (4.5 g, 86% yield) as a yellow oil; IR (neat) 2980, 1755, 1578, 1304, and 1164 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, 3H, J=7.1 Hz), 3.74 (s, 3H), 4.24 (q, 2H, J=7.1 Hz), 4.64 (s, 2H), 6.32 (s, 1H), 6.34 (d, 1H, J=8.5 Hz), and 7.61 (d, 1H, J=8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 160.9, 157.1, 139.2, 108.0, 100.3, 74.9, 66.1, 61.2, 55.2, and 13.9; HRMS calcd for $[(C_{11}H_{13}IO_4)+H]^+$: 336.9931. Found: 336.9943.

*4.2.3. Ethyl-3-(2-ethoxy-2-oxoethoxy)-4-iodobenzoate (**5c**).* Ethyl-3-hydroxy-4-iodobenzoate (**4c**) (220 mg, 0.75 mmol), K_2CO_3 (104 mg, 0.75 mmol), and ethyl-2-bromoacetate (54 μL, 0.77 mmol) were used. The reaction mixture was refluxed for 6 h. Purification by column chromatography (SiO_2, 10% EtOAc/hexane) provided the title compound **5c** (281 mg, 99% yield) as a yellow oil; IR (neat) 2988, 2924, 1756, 1714, and 1239 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, 3H, J=7.1 Hz), 1.38 (t, 3H, J=7.1 Hz), 4.28 (q, 2H, J=7.1 Hz), 4.36 (q, 2H, J=7.1 Hz), 4.75 (s, 2H), 7.35 (s, 1H), 7.41 (d, 1H, J=8.0 Hz), and 7.87 (d, 1H, J=8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 165.7, 156.8, 139.8, 132.0, 124.2, 112.5, 93.0, 66.3, 61.5, 61.3, 14.3 and 14.1; HRMS calcd for $[(C_{13}H_{15}IO_5)+Na]^+$: 400.9856. Found: 400.9856.

*4.2.4. Ethyl-2-(2-iodo-5-nitrophenoxy)acetate (**5d**).* 2-Iodo-5-nitrophenol (**4d**) (1.6 g, 6.1 mmol), K_2CO_3 (0.8 g, 6.1 mmol), and ethyl-2-bromoacetate (0.7 mL, 6.2 mmol) were used. The reaction mixture was refluxed for 6 h. Purification by column chromatography (SiO_2, 10% EtOAc/hexane) provided the title compound **5d** (2.0 g, 92% yield) as a yellow solid; mp 84–86 °C; IR (neat) 2922, 1753, 1524, 1467, and 1204 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (t, 3H, J=7.0 Hz), 4.39 (q, 2H, J=7.0 Hz), 4.81 (s, 2H), 7.52 (s, 1H), 7.64 (d, 1H, J=8.3 Hz), and 8.01 (d, 1H, J=8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 157.6, 149.0, 140.6, 117.9, 107.1, 97.0, 66.4, 61.4, and 14.5; HRMS calcd for $[(C_{10}H_{10}INO_5)]$: 350.9598. Found: 350.9598.

*4.2.5. Ethyl-2-(2-iodo-3,5-dimethoxyphenoxy)acetate (**5e**).* 2-Iodo-3,5-dimethoxyphenol (**4e**) (60 mg, 0.21 mmol), K_2CO_3 (29 mg, 0.21 mmol), and ethyl 2-bromoacetate (38 mg, 0.22 mmol) were used. The reaction mixture was refluxed for 3 h. Purification by preparative thin layer chromatography (SiO_2, 20% EtOAc/hexane) provided the title compound **5e** (69 mg, 90% yield) as a yellow solid; mp 74–75 °C; IR (neat) 2793, 1755, 1582, 1199, 1162, 1127, and 1017 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, 3H, J=7.1 Hz), 3.79 (s, 3H), 3.86 (s, 3H), 4.26 (q, 2H, J=7.1 Hz), 4.66 (s, 2H), 6.04 (s, 1H), and 6.16 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 161.9, 160.0, 158.4, 92.5, 92.1, 66.6, 61.4, 56.5, 55.5, and 14.1; HRMS calcd for $[(C_{12}H_{15}IO_5)+Na]^+$: 388.9856. Found: 388.9857.

*4.2.6. Ethyl-2-(2-bromo-4-methoxyphenoxy)acetate (**5f**).* 2-Bromo-4-methoxyphenol (**4f**) (25.0 g, 124 mmol), K_2CO_3 (17.0 g, 124 mmol), and ethyl-2-bromoacetate (14.0 mL, 125 mmol) were used. The reaction mixture was refluxed for 2 h. Purification by column chromatography (SiO_2, 10% EtOAc/hexane) provided the title compound **5f** (29.1 g, 82% yield) as a yellow oil; IR (neat) 2982, 1755, 1733, 1490, 1192, 1083, and 1034 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, 3H, J=7.1 Hz), 3.74 (s, 3H), 4.24 (q, 2H, J=7.1 Hz), 4.61 (s, 2H), 6.76 (d, 1H, J=9.0 Hz), 6.84 (d, 1H, J=9.0 Hz), and 7.10 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 154.9, 148.7, 118.8, 115.7, 113.5, 113.1, 67.3, 61.2, 55.6, and 14.0; HRMS calcd for $[(C_{11}H_{13}BrO_4)+Na]^+$: 310.9889. Found: 310.9879.

4.3. Ethyl-2-(2-iodo-5-(tosyloxy)phenoxy)acetate (5g)

To a stirred solution of 4-iodobenzene-1,3-diol (**4g**) (1.2 g, 5.0 mmol) and potassium carbonate (K_2CO_3) (2.1 g, 14.9 mmol) in 20 mL of acetone was added *p*-toluene sulfonylchloride (TsCl) (0.9 g, 5.0 mmol) at room temperature. The reaction mixture was stirred at reflux for 20 h, and then 577 μL (5.21 mmol) of ethyl-2-bromoacetate was added. The resulting mixture was stirred for an additional 3 h, then allowed to cool to room temperature, filtered through Celite, washed with excess EtOAc (three times), and concentrated under reduced pressure. Purification by column chromatography (SiO_2, 5% EtOAc/hexane) provided the title compound **5g** (1.2 g, 49% yield) as a pale yellow oil; IR (neat) 2982, 1756, 1590, 1471, 1373, 1192, 1178, 1091, and 950 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, 3H, J=7.1 Hz), 2.47 (s, 3H), 4.37 (q, 2H, J=7.1 Hz), 4.59 (s, 2H), 6.33 (dd, 1H, J=8.5 and 1.7 Hz), 6.46 (s, 1H), 7.32 (d, 2H, J=8.1 Hz), 7.66 (d, 1H, J=8.5 Hz), and 7.70 (d, 2H, J=8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 157.3, 150.5, 145.7, 139.7, 129.9, 128.6, 128.5, 117.0, 107.3, 84.1, 66.3, 61.7, 21.7, and 14.1; HRMS calcd for $[(C_{17}H_{17}IO_6S)+Na]^+$: 498.9683. Found: 498.9665.

4.4. General procedure for Sonogashira coupling

To a solution of the aryl halide substrate (1.0 equiv) in a dry solution of Et_3N (2 mL/mmol of substrate) and MeCN (2 mL/mmol of substrate) was added the terminal alkyne substrate (1.1 equiv), copper iodide (CuI) (0.1 equiv), and tetrakis (triphenylphosphine) palladium [$Pd(PPh_3)_4$] (0.05 equiv). The reaction mixture was stirred at reflux under argon atmosphere overnight. The resulting mixture was filtered through Celite and washed with excess EtOAc. The combined organic solvent was removed under reduced pressure and the crude product was purified to provide the desire product.

*4.4.1. Ethyl-2-(2-(phenylethynyl)phenoxy)acetate (**6a**).*[8] Compound **5a** (2.00 g, 6.53 mmol), phenylacetylene (730 mg, 7.19 mmol), CuI (124 mg, 0.65 mmol), and $Pd(PPh_3)_4$ (376 mg, 0.33 mmol) were used. Purification by column chromatography (SiO_2, 10% EtOAc/hexane) provided the title compound **6a** (1.80 g, 100% yield) as a yellow oil; IR (neat) 2982, 1757, 1497, and 1193 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 3H, J=7.1 Hz), 4.25 (q, 2H, J=7.1 Hz), 4.72 (s, 2H), 6.81 (d, 1H, J=8.3 Hz), 6.97 (t, 1H, J=7.5 Hz), 7.22–7.35 (m, 4H), 7.50 (dd, 1H, J=7.5 and 1.7 Hz), and 7.54–7.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 158.5, 135.2, 133.5, 131.6, 129.4, 128.2, 128.1, 123.6, 121.8, 113.4, 93.9, 85.4, 66.6, 61.1, and 14.0; HRMS calcd for $[(C_{18}H_{16}O_3)+H]^+$: 281.1172. Found: 281.1170.

*4.4.2. Ethyl-2-(2-(hex-1-ynyl)phenoxy)acetate (**6b**).* Compound **5a** (1.25 g, 4.08 mmol), hex-1-yne (369 mg, 4.49 mmol), CuI (78 mg, 0.41 mmol), and $Pd(PPh_3)_4$ (228 mg, 0.20 mmol) were used.

Purification by column chromatography (SiO_2, 10% EtOAc/hexane) provided the title compound **6b** (1.07 g, 100% yield) as a yellow oil; IR (neat) 2932, 1759, 1736, 1491, 1189, and 749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.75 (t, 3H, J=7.0 Hz), 1.28 (t, 3H, J=7.1 Hz), 1.50 (sext, 2H, J=7.0 Hz), 1.62 (pent, 2H, J=7.0 Hz), 2.46 (t, 2H, J=7.0 Hz), 4.26 (q, 2H, J=7.1 Hz), 4.69 (s, 2H), 6.77 (d, 1H, J=8.0 Hz), 6.93 (t, 1H, J=7.5 Hz), 7.19 (t, 1H, J=8.0 Hz), and 7.39 (d, 1H, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 158.2, 133.7, 128.5, 121.6, 114.2, 113.0, 95.1, 76.2, 66.3, 61.2, 30.8, 21.9, 19.4, 14.1, and 13.6; HRMS calcd for $[(C_{16}H_{20}O_3)+H]^+$: 261.1485. Found: 261.1474.

*4.4.3. Ethyl-2-(2-(3-(tetrahydro-2H-pyran-2-yloxy)prop-1-ynyl) phenoxy)acetate (**6c**).* Compound **5a** (125 mg, 0.41 mmol), 2-(prop-2-ynyloxy)tetrahydro-2*H*-pyran (63 mg, 0.45 mmol), CuI (8 mg, 40 μmol), and $Pd(PPh_3)_4$ (24 mg, 20 μmol) were used. Purification by column chromatography (SiO_2, 10% EtOAc/hexane) provided the title compound **6c** (93 mg, 71% yield)/as a yellow oil; IR (neat) 2939, 1757, 1491, and 1195 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, 3H, J=7.1 Hz), 1.53–1.81 (m, 6H), 3.53–3.60 (m, 1H), 3.86–3.94 (m, 1H), 4.26 (q, 2H, J=7.1 Hz), 4.54 (d, 2H, J=3.2 Hz), 4.70 (s, 2H), 4.95 (t, 1H, J=3.2 Hz), 6.78 (d, 1H, J=7.5 Hz), 6.94 (td, 1H, J=7.5 and 0.85 Hz), 7.22–7.28 (m, 1H), and 7.44 (dd, 1H, J=7.5 and 1.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 158.6, 134.0, 129.6, 121.6, 112.7, 96.7, 89.7, 81.7, 66.2, 62.0, 61.3, 54.9, 30.3, 29.6, 25.4, 19.1, and 14.1; HRMS calcd for $[(C_{18}H_{22}O_5)+Na]^+$: 341.1359. Found: 341.1363.

*4.4.4. Ethyl-2-(5-methoxy-2-(phenylethynyl)phenoxy)acetate (**6d**).* Compound **5b** (500 mg, 1.49 mmol), phenylacetylene (168 mg, 1.64 mmol), CuI (29 mg, 0.15 mmol), and $Pd(PPh_3)_4$ (87 mg, 74 μmol) were used. Purification by column chromatography (SiO_2, 10% EtOAc/hexane) provided the title compound **6d** (465 mg, 100% yield) as a yellow oil; IR (neat) 2981, 1759, 1610, 1508, 1301, 1195, and 1167 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (t, 3H, J=7.1 Hz), 3.67 (s, 3H), 4.15 (q, 2H, J=7.1 Hz), 4.61 (s, 2H), 6.28 (s, 1H), 6.42 (d, 1H, J=8.5 Hz), 7.19 (t, 3H, J=6.8 Hz), 7.32 (d, 1H, J=8.5 Hz), and 7.44 (d, 2H, J=6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 160.7, 159.4, 134.2, 131.3, 128.1, 127.7, 123.7, 106.3, 105.7, 100.5, 92.4, 85.3, 66.2, 61.2, 55.3, and 14.0; HRMS calcd for $[(C_{19}H_{18}O_4)+Na]^+$: 333.1097. Found: 333.1094.

*4.4.5. Ethyl-2-(5-methoxy-2-((4-methoxyphenyl)ethynyl)phenoxy) acetate (**6e**).* Compound **5b** (500 mg, 1.49 mmol), 1-ethynyl-4-methoxybenzene (220 mg, 1.64 mmol), CuI (29 mg, 0.15 mmol), and $Pd(PPh_3)_4$ (87 mg, 74 μmol) were used. Purification by column chromatography (SiO_2, 10% EtOAc/hexane) provided the title compound **6e** (436 mg, 85% yield) as a colorless oil; IR (neat) 2937, 1757, 1610, 1515, 1246, and 1194 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, 3H, J=7.1 Hz), 3.80 (s, 3H), 3.82 (s, 3H), 4.27 (q, 2H, J=7.1 Hz), 4.72 (s, 2H), 6.39 (s, 1H), 6.53 (d, 1H, J=8.5 Hz), 6.86 (d, 2H, J=8.5 Hz), 7.41 (d, 1H, J=8.5 Hz), and 7.41 (d, 2H, J=8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 160.5, 159.3, 159.2, 134.1, 132.8, 115.9, 113.8, 106.5, 106.2, 100.7, 92.4, 83.9, 66.4, 61.3, 55.4, 55.2, and 14.1; HRMS calcd for $[(C_{20}H_{20}O_5)+H]^+$: 341.1384. Found: 341.1374.

*4.4.6. Ethyl-2-(2-(phenylethynyl)-5-(tosyloxy)phenoxy)acetate (**6g**).* Compound **5g** (1.10 g, 2.30 mmol), phenylacetylene (252 mg, 2.54 mmol), CuI (42 mg, 0.23 mmol), and $Pd(PPh_3)_4$ (125 mg, 0.12 mmol) were used. The reaction mixture was refluxed overnight under argon atmosphere and then worked up to give the crude compound. Purification by column chromatography (SiO_2, 10% EtOAc/hexane) provided the title compound **6g** (1.00 g, 100% yield) as a yellow oil; IR (neat) 2983, 1757, 1594, 1501, 1374, 1179, 1192, 1091, and 953 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, 3H, J=7.1 Hz), 2.43 (s, 3H), 4.26 (q, 2H, J=7.1 Hz), 4.61 (s, 2H), 6.54 (s, 1H), 6.55 (d, 1H, J=8.6 Hz), 7.20–7.45 (m, 6H), 7.50 (br s, 2H), and 7.69 (d, 2H, J=7.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 158.9, 149.8, 145.6, 133.8, 131.6, 129.8, 128.5, 128.4, 128.2, 123.0, 121.1, 115.3, 112.4, 107.6, 94.8, 84.1, 66.1, 61.5, 21.6, and 14.1; HRMS calcd for $[(C_{25}H_{22}O_6S)+H]^+$: 451.1210. Found: 451.1195.

*4.4.7. Ethyl-2-(2-((3,4-dimethoxyphenyl)ethynyl)-5-(tosyloxy) phenoxy)acetate (**6h**).* Compound **5g** (1.00 g, 2.10 mmol), 4-ethynyl-1,2-dimethoxybenzene (386 mg, 2.31 mmol), CuI (41 mg, 0.21 mmol), and $Pd(PPh_3)_4$ (121 mg, 0.11 mmol) were used. Purification by column chromatography (SiO_2, 10% EtOAc/hexane) provided the title compound **6h** (890 mg, 81% yield) as a light brown oil; IR (neat) 2967, 2214, 1756, 1514, 1191, 1178, 1133, and 1023 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, 3H, J=7.1 Hz), 2.43 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 4.25 (q, 2H, J=7.1 Hz), 4.60 (s, 2H), 6.51 (s, 1H), 6.55 (d, 1H, J=8.4 Hz), 6.82 (d, 1H, J=8.4 Hz), 7.07 (s, 1H), 7.13 (d, 1H, J=8.4 Hz), 7.30 (d, 2H, J=8.1 Hz), 7.36 (d, 1H, J=8.4 Hz), and 7.68 (d, 2H, J=8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 158.5, 149.4, 148.4, 145.5, 133.4, 131.7, 129.6, 128.3, 128.2, 124.8, 115.1, 115.0, 114.1, 112.5, 110.8, 107.3, 94.9, 82.5, 65.9, 61.3, 55.7, 55.6, 21.5, and 13.9; HRMS calcd for $[(C_{27}H_{26}O_8S)+H]^+$: 511.1421. Found: 511.1432.

*4.4.8. Ethyl-2-(2-((4-methoxyphenyl)ethynyl)phenoxy)acetate (**6j**).*[8] Compound **5a** (500 mg, 1.63 mmol), 1-ethynyl-4-methoxy benzene (240 mg, 1.80 mmol), CuI (31 mg, 0.16 mmol), and $Pd(PPh_3)_4$ (95 mg, 89 μmol) were used. Purification by column chromatography (SiO_2, 15% EtOAc/hexane) provided the title compound **6j** (433 mg, 85% yield) as a yellow oil; IR (neat) 2924, 1758, 1510, and 1194 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, 3H, J=7.1 Hz), 3.82 (s, 3H), 4.27 (q, 2H, J=7.1 Hz), 4.74 (s, 2H), 6.85 (t, 1H, J=8.3 Hz), 6.87 (d, 2H, J=8.3 Hz), 6.98 (t, 1H, J=7.5 Hz), 7.23 (d, 1H, J=8.8 Hz), and 7.50 (d, 3H, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 159.6, 158.3, 133.4, 133.1, 129.2, 121.8, 115.6, 113.9, 113.2, 112.6, 94.0, 84.0, 66.5, 61.3, 55.3, and 14.2; HRMS calcd for $[(C_{19}H_{18}O_4)+H]^+$: 311.1278. Found: 311.1283.

*4.4.9. Ethyl-2-(2-((3,4-dimethoxyphenyl)ethynyl)phenoxy)acetate (**6k**).* Compound **5a** (1.00 g, 3.27 mmol), 4-ethynyl-1,2-dimethoxy benzene (583 mg, 3.59 mmol), CuI (62 mg, 0.33 mmol), and $Pd(PPh_3)_4$ (182 mg, 0.16 mmol) were used. Purification by column chromatography (SiO_2, 15% EtOAc/hexane) provided the title compound **6k** (1.03 g, 93% yield) as a pale yellow solid; mp 67–68 °C; IR (neat) 2972, 2837, 2208, 1755, 1514, 1218, 1195, 1109, and 1019 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, 3H, J=7.1 Hz), 3.87 (s, 3H), 3.89 (s, 3H), 4.25 (q, 2H, J=7.1 Hz), 7.73 (s, 2H), 6.81 (d, 2H, J=8.3 Hz), 6.95 (t, 1H, J=7.5 Hz), 7.11 (s, 1H), 7.15 (d, 1H, J=8.3 Hz), 7.25 (t, 1H, J=7.5 Hz), and 7.50 (d, 1H, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 158.0, 149.2, 148.3, 133.1, 129.0, 124.6, 121.5, 115.4, 114.2, 113.4, 112.6, 110.7, 93.9, 83.6, 66.0, 60.9, 55.6, 55.5, and 13.8; HRMS calcd for $[(C_{20}H_{20}O_5)+Na]^+$: 363.1203. Found: 363.1200.

*4.4.10. Ethyl-3-(2-ethoxy-2-oxoethoxy)-4-(phenylethynyl)benzoate (**6l**).* Compound **5c** (936 mg, 2.48 mmol), phenylacetylene (280 mg, 2.79 mmol), CuI (48 mg, 0.25 mmol), and $Pd(PPh_3)_4$ (144 mg, 0.12 mmol) were used. Purification by column chromatography (SiO_2, 7% EtOAc/hexane) provided the title compound **6l** (877 mg, 100% yield) as a red oil; IR (neat) 2982, 1760, 1717, 1417, 1291, and 1199 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, 3H, J=7.0 Hz), 1.39 (t, 3H, J=7.0 Hz), 4.29 (q, 2H, J=7.0 Hz), 4.37 (q, 2H, J=7.0 Hz), 4.79 (s, 2H), 7.35 (br s, 3H), 7.48 (br s, 1H), 7.57 (br t, 3H, J=7.9 Hz), and 7.68 (d, 1H, J=7.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 165.8, 158.1, 133.3, 131.8, 131.1, 128.7, 128.3, 123.0, 122.8, 118.1, 113.1, 96.7, 84.8, 66.1, 61.5, 61.3, 14.3, and 14.2; HRMS alcd for $[(C_{21}H_{20}O_5)+Na]^+$: 375.1203. Found: 375.1208.

*4.4.11. Ethyl-2-(2-(3,3-dimethylbut-1-ynyl)phenoxy)acetate (**6m**).* Compound **5a** (480 mg, 1.57 mmol), 3,3-dimethylbut-1-yne (200 μL, 1.72 mmol), CuI (30 mg, 0.16 mmol), and $Pd(PPh_3)_4$ (87 mg, 78 μmol) were used. Purification by column

chromatography (SiO_2, 10% EtOAc/hexane) provided the title compound **6m** (371 mg, 90% yield) as a pale yellow oil; IR (neat) 2969, 1760, 1492, and 1188 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, 3H, J=7.1 Hz), 1.34 (s, 9H), 4.27 (q, 2H, J=7.1 Hz), 4.67 (s, 2H), 6.81 (d, 1H, J=8.0 Hz), 6.93 (t, 1H, J=7.5 Hz), 7.19 (t, 1H, J=8.0 Hz), and 7.36 (d, 1H, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 158.3, 133.7, 128.6, 121.9, 114.0, 112.4, 103.4, 74.7, 66.7, 61.2, 31.0, 28.2, and 14.2; HRMS calcd for $[(C_{16}H_{20}O_3)+H]^+$: 261.1485. Found: 261.1484.

*4.4.12. Ethyl-2-(2-((3,4-dimethoxyphenyl)ethynyl)-3,5-dimethoxy phenoxy)acetate (**6n**).* Compound **5e** (57 mg, 0.16 mmol), 4-ethynyl-1,2-dimethoxybenzene (28 mg, 0.17 mmol), CuI (3 mg, 15 μmol), and $Pd(PPh_3)_4$ (9 mg, 8 μmol) were used. Purification by preparative thin layer chromatography (SiO_2, 10% EtOAc/hexane) provided the title compound **6n** (39 mg, 61% yield) as a yellow solid; mp 131–132 °C; IR (neat) 2915, 2836, 1761, 1517, 1202, 1145, and 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (t, 3H, J=7.1 Hz), 3.80 (s, 3H), 3.88 (s, 6H), 3.90 (s, 3H), 4.25 (q, 2H, J=7.1 Hz), 4.71 (s, 2H), 6.05 (s, 1H), 6.16 (s, 1H), 7.82 (d, 1H, J=8.3 Hz), 7.12 (s, 1H), and 7.17 (d, 1H, J=8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 161.8, 161.0, 160.4, 148.9, 148.3, 124.6, 116.3, 114.2, 110.7, 96.7, 95.6, 92.5, 91.6, 79.9, 66.4, 61.1, 56.0, 55.8, 55.7, 55.3, and 14.0; HRMS calcd for $[(C_{22}H_{24}O_7)+Na]^+$: 423.1412. Found: 423.1418.

*4.4.13. Ethyl-2-(2-((4-nitrophenyl)ethynyl)phenoxy)acetate (**6o**).* Compound **5a** (100 mg, 0.33 mmol), 1-ethynyl-4-nitrobenzene (50 mg, 0.36 mmol), CuI (6 mg, 32 μmol), and $Pd(PPh_3)_4$ (19 mg, 16 μmol) were used. Purification by column chromatography (SiO_2 10% EtOAc/hexane) provided the title compound **6o** (85 mg, 79% yield) as a yellow oil; IR (neat) 2924, 1756, 1592, 1342, and 1193 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, 3H, J=7.0 Hz), 4.30 (q, 2H, J=7.0 Hz), 4.74 (s, 2H), 6.83 (d, 1H, J=8.3 Hz), 7.02 (t, 1H, J=7.5 Hz), 7.34 (t, 1H, J=8.0 Hz), 7.53 (d, 1H, J=8.0 Hz), 7.71 (d, 2H, J=8.0 Hz), and 8.21 (d, 2H, J=8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 158.7, 146.9, 139.8, 135.2, 133.8, 132.3, 130.7, 123.6, 121.8, 112.4, 92.1, 91.0, 66.0, 61.5, and 14.1; HRMS calcd for $[(C_{18}H_{15}NO_5)+Na]^+$: 348.0842. Found: 348.0838.

*4.4.14. Ethyl-2-(5-methoxy-2-((4-nitrophenyl)ethynyl)phenoxy) acetate (**6p**).* Compound **5b** (500 mg, 1.49 mmol), 1-ethynyl-4-nitrobenzene (243 mg, 1.64 mmol), CuI (29 mg, 0.15 mmol), and $Pd(PPh_3)_4$ (87 mg, 74 μmol) were used. Purification by column chromatography (SiO_2, 10% EtOAc/hexane) provided the title compound **6p** (404 mg, 76% yield) as an orange oil; IR (neat) 2980, 2937, 2212, 1758, 1591, 1514, and 1341 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, 3H, J=7.1 Hz), 3.83 (s, 3H), 4.30 (q, 2H, J=7.1 Hz), 4.72 (s, 2H), 6.38 (s, 1H), 6.56 (d, 1H, J=8.5 Hz), 7.45 (d, 1H, J=8.5 Hz), 7.67 (d, 2H, J=8.4 Hz), and 8.20 (d, 2H, J=8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 161.8, 159.9, 146.6, 134.7, 132.0, 131.0, 123.6, 106.4, 104.7, 100.1, 91.5, 91.1, 66.0, 61.5, 55.6, and 14.2; HRMS calcd for $[(C_{19}H_{17}NO_6)+H]^+$: 356.1129. Found: 356.1127.

*4.4.15. Ethyl-2-(5-nitro-2-(phenylethynyl)phenoxy)acetate (**6q**).* Compound **5d** (220 mg, 0.63 mmol), phenylacetylene (70 mg, 0.69 mmol), CuI (12 mg, 63 μmol), and $Pd(PPh_3)_4$ (36 mg, 31 μmol) were used. Purification by column chromatography (SiO_2, 10% EtOAc/hexane) provided the title compound **6q** (171 mg, 84% yield) as a yellow oil; IR (neat) 2984, 2216, 1756, 1519, 1339, and 1202 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, 3H, J=7.1 Hz), 4.32 (q, 2H, J=7.1 Hz), 4.83 (s, 2H), 7.39 (br s, 3H), 7.57–7.64 (m, 3H), 7.66 (s, 1H), and 7.89 (d, 1H, J=8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 158.3, 147.6, 133.5, 131.8, 129.0, 128.3, 122.3, 120.3, 116.6, 107.2, 98.9, 83.8, 66.0, 61.6, and 14.0; HRMS calcd for $[(C_{18}H_{15}NO_5)+H]^+$: 326.1023. Found: 326.1023.

*4.4.16. Ethyl-2-(2-((4-methoxyphenyl)ethynyl)-5-nitrophenoxy) acetate (**6r**).* Compound **5d** (100 mg, 0.28 mmol), 1-ethynyl-4-methoxybenzene (63 mg, 0.31 mmol), CuI (7 mg, 28 μmol), and $Pd(PPh_3)_4$ (22 mg, 14 μmol) were used. Purification by column chromatography (SiO_2, 10% EtOAc/hexane) provided the title compound **6r** (131 mg, 96% yield) as a yellow oil; IR (neat) 2927, 2212, 1755, 1513, 1343, and 1200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, 3H, J=7.1 Hz), 3.85 (s, 3H), 4.31 (q, 2H, J=7.1 Hz), 4.82 (s, 2H), 6.90 (d, 2H, J=8.4 Hz), 7.54 (d, 2H, J=8.4 Hz), 7.61 (d, 1H, J=8.4 Hz), 7.66 (s, 1H), and 7.88 (d, 1H, J=8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 160.4, 158.2, 147.4, 133.5, 133.3, 121.0, 116.8, 114.5, 114.1, 107.4, 99.6, 82.9, 66.2, 61.7, 55.3, and 14.1; HRMS calcd for $[(C_{19}H_{17}NO_6)+H]^+$: 356.1129 Found: 356.1126.

*4.4.17. Ethyl-2-(5-nitro-2-((4-nitrophenyl)ethynyl)phenoxy) acetate (**6s**).* Compound **5d** (100 mg, 0.28 mmol), 1-ethynyl-4-nitrobenzene (62 mg, 0.31 mmol), CuI (7 mg, 28 μmol), and $Pd(PPh_3)_4$ (22 mg, 14 μmol) were used. Purification by column chromatography (SiO_2, 10% EtOAc/hexane) provided the title compound **6s** (62 mg, 44% yield) as a yellow oil; IR (neat) 3112, 2925, 1739, 1595, 1516, and 1343 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, 3H, J=7.2 Hz), 4.33 (q, 2H, J=7.2 Hz), 4.84 (s, 2H), 7.68 (d, 2H, J=7.1 Hz), 7.75 (d, 2H, J=8.3 Hz), 7.92 (d, 1H, J=8.5 Hz), and 8.26 (d, 2H, J=8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 158.8, 148.5, 147.5, 133.9, 132.6, 129.3, 123.7, 119.1, 116.7, 107.0, 96.3, 88.5, 65.9, 61.9 and 14.1; HRMS calcd for $[(C_{18}H_{14}N_2O_7)+H]^+$: 370.0796. Found: 370.0795.

*4.4.18. (2-((Trimethylsilyl)ethynyl)phenoxy)methyl propionate (**6t**).*[32b] Compound **5a** (71 mg, 0.23 mmol), ethynyltrimethylsilane (36 μL, 0.26 mmol), CuI (4 mg, 23 μmol), and $Pd(PPh_3)_4$ (13 mg, 11 μmol) were used. Purification by column chromatography (SiO_2, 10% EtOAc/hexane) provided the title compound **6t** (53 mg, 83% yield) as a yellow oil; IR (neat) 2961, 2158, 1760, 1489, and 1189 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.27 (s, 9H), 1.30 (t, 3H, J=7.1 Hz), 4.27 (q, 2H, J=7.1 Hz), 4.70 (s, 2H), 6.79 (d, 1H, J=8.2 Hz), 6.94 (td, 1H, J=7.6 and 0.9 Hz), 7.24 (td, 1H, J=8.2 and 1.7 Hz), and 7.45 (dd, 1H, J=7.6 and 1.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 158.8, 134.1, 129.7, 121.7, 113.3, 100.7, 99.0, 66.4, 61.2, 29.6, 14.1, and −0.1; HRMS calcd for $[(C_{15}H_{20}O_3Si)+H]^+$: 277.1255 Found: 277.1247.

4.5. Ethyl-2-(2-(hex-1-ynyl)-4-methoxyphenoxy)acetate (6f)

To a solution of compound **5f** (2.00 g, 6.92 mmol) in a dry solution of Et_3N (14 mL) and MeCN (14 mL) were added hex-1-yne (1.6 mL, 13.8 mmol), CuI (66 mg, 0.35 mmol), and $Pd(PPh_3)_4$ (192 mg, 0.17 mmol). The reaction mixture was stirred at reflux under argon atmosphere overnight. The resulting mixture was then filtered through Celite and washed with excess EtOAc. All volatile organic solvent was removed under reduced pressure and the crude product was purified by column chromatography (SiO_2, 15% EtOAc/hexane) to provide the title compound **6f** (1.0 g, 51% yield) as a yellow oil; IR (neat) 2933, 1758, 1735, 1496, 1187, 1073, 1035 and 801 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 3H, J=7.0 Hz), 1.29 (t, 3H, J=7.1 Hz), 1.40–1.70 (m, 4H), 2.46 (t, 2H, J=7.0 Hz), 3.75 (s, 3H), 4.25 (q, 2H, J=7.1 Hz), 4.65 (s, 2H), 6.74 (d, 1H, J=9.1 Hz), 6.80 (d, 1H, J=9.1 Hz), and 6.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 154.4, 152.9, 118.2, 116.1, 115.5, 114.6, 95.3, 76.2, 67.7, 61.1, 55.7, 30.8, 22.0, 19.4, 14.1, and 13.6; HRMS calcd for $[(C_{17}H_{22}O_4)+Na]^+$: 313.1410. Found: 313.1411.

4.6. Ethyl-2-(2-((2-methoxyphenyl)ethynyl)phenoxy)acetate (6i)

To a solution of compound **5a** (100 mg, 0.33 mmol) in a dry solution of Et_3N (0.7 mL) and MeCN (0.7 mL) were added 1-ethynyl-2-methoxybenzene (48 mg, 0.36 mmol), CuI (13 mg, 65 μmol), and $Pd(PPh_3)_4$ (38 mg, 33 μmol). The reaction mixture was stirred at reflux under argon atmosphere for 2 days. The resulting mixture

was filtered through Celite and washed with excess EtOAc. The combined organic phase was concentrated under reduced pressure. Purification by flash silica gel column chromatography using 10% EtOAc/hexane mixture as an eluent provided the title compound **6i** (66 mg, 65% yield) as a yellow oil; IR (neat) 2928, 1756, 1498, and 1197 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, 3H, J=7.1 Hz), 3.93 (s, 3H), 4.27 (q, 2H, J=7.1 Hz), 4.79 (s, 2H), 6.88 (t, 1H, J=8.2 Hz), 6.95 (d, 1H, J=7.2 Hz), 7.00 (t, 2H, J=7.5 Hz), 7.26 (t, 1H, J=10.2 Hz), 7.29 (t, 1H, J=8.2 Hz), and 7.54 (d, 2H, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 159.9, 158.4, 133.6, 133.5, 129.6, 129.3, 121.9, 120.4, 120.3, 114.0, 112.6, 110.6, 90.4, 89.3, 66.7, 61.1, 55.7, and 14.1; HRMS calcd for $[(C_{19}H_{18}O_4)+Na]^+$: 333.1097. Found: 333.1107.

4.7. Ethyl-2-(2-ethynylphenoxy)acetate (6u)[32b]

To a stirred solution of compound **6t** (50 mg, 0.16 mmol) in THF (6 mL) at 0 °C was added tetra-*n*-butyl-ammonium fluoride (TBAF) (74 mg, 0.16 mmol) in THF (2 mL). After 10 min at 0 °C, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford the title compound **6u** (25 mg, 68% yield) as a pale yellow oil, which was pure to use in the next step without further purification; IR (neat) 3280, 2924, 1756, 1489, and 1199 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, 3H, J=7.1 Hz), 3.32 (s, 1H), 4.26 (q, 2H, J=7.1 Hz), 4.73 (s, 2H), 6.78 (d, 1H, J=8.1 Hz), 6.96 (td, 1H, J=7.6 and 0.9 Hz), 7.29 (td, 1H, J=8.1 and 1.7 Hz), and 7.48 (dd, 1H, J=7.6 and 1.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 134.4, 130.1, 121.6, 112.5, 81.6, 79.6, 66.1, 61.4, 29.7 and 14.1; HRMS calcd for $[(C_{12}H_{12}O_3)+H]^+$: 205.0786. Found: 205.0789.

4.8. General procedure for oxidation of alkynes to 1,2-diketones

To a solution of the alkyne substrate (1.0 equiv), $NaHCO_3$ (0.08 equiv), $MgSO_4$ (0.25 equiv), and $NaIO_4$ (3.0 equiv) in a mixture of 3:3:4 of $MeCN/CCl_4/H_2O$ (5 mL/mmol of substrate) was added (0.01 equiv) of a 0.01 M stock solution of $RuCl_3$ in water. The reaction mixture was stirred at room temperature until completion and then extracted with EtOAc two times. The combined organic layer was washed with H_2O and brine, dried over $NaSO_4$ (s), and concentrated. Unless otherwise noted, the crude residue was purified to obtain the title compound as pure product.

*4.8.1. Ethyl-2-(2-(2-oxo-2-phenylacetyl)phenoxy)acetate (**1a**).* Alkyne **6a** (103 mg, 0.37 mmol), $NaHCO_3$ (3 mg, 29 μmol), $MgSO_4$ (11 mg, 92 μmol), $NaIO_4$ (237 mg, 1.10 mmol), and a 0.01 M $RuCl_3$ solution (370 μL, 4 μmol) were used. The reaction mixture was stirred for 30 min. Purification by column chromatography (SiO_2, 20% EtOAc/hexane) provided the title compound **1a** (109 mg, 95% yield) as pale a yellow oil; IR (neat) 2976, 1755, 1681, 1598, and 1199 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (t, 3H, J=7.1 Hz), 4.07 (q, 2H, J=7.1 Hz), 4.39 (s, 2H), 6.85 (d, 1H, J=8.4 Hz), 7.19 (t, 1H, J=7.6 Hz), 7.49 (t, 2H, J=7.6 Hz), 7.59 (t, 1H, J=7.6 Hz), 7.61 (t, 1H, J=8.1 Hz), 7.95 (d, 2H, J=8.1 Hz), and 8.05 (d, 1H, J=7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.3, 193.1, 167.5, 158.6, 136.2, 133.9, 132.8, 130.9, 129.7, 128.6, 124.5, 122.6, 113.2, 65.9, 61.4, and 14.0; HRMS calcd for $[(C_{18}H_{16}O_5)+H]^+$: 313.1071. Found: 313.1080.

*4.8.2. Ethyl-2-(2-(2-oxohexanoyl)phenoxy)acetate (**1b**).* Alkyne **6b** (739 mg, 2.84 mmol), $NaHCO_3$ (19 mg, 0.23 mmol), $MgSO_4$ (85 mg, 0.71 mmol), $NaIO_4$ (1.8 g, 8.52 mmol), and a 0.01 M $RuCl_3$ solution (2.8 mL, 28 μmol) were used. The reaction mixture was stirred for 2 h. Purification by column chromatography (SiO_2, 20% EtOAc/hexane) provided the title compound **1b** (539 mg, 65% yield) as a pale yellow oil; IR (neat) 2960, 1760, 1667, 1598, 1200, and 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 3H, J=7.5 Hz), 1.28 (t, 3H, J=7.1 Hz), 1.41 (sext, 2H, J=7.5 Hz), 1.69 (pent, 2H, J=7.5 Hz), 2.90 (t, 2H, J=7.5 Hz), 4.25 (q, 2H, J=7.1 Hz), 4.59 (s, 2H), 6.87 (d, 1H, J=7.6 Hz), 7.13 (t, 1H, J=7.6 Hz), 7.54 (t, 1H, J=7.6 Hz), and 7.82 (d, 1H, J=7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 194.8, 167.5, 158.0, 135.5, 130.8, 124.0, 122.5, 112.8, 65.9, 61.5, 37.0, 24.6, 22.2, 14.0, and 13.8; HRMS calcd for $[(C_{16}H_{20}O_5)+Na]^+$: 315.1203. Found: 315.1199.

*4.8.3. Ethyl-2-(2-(2-oxo-3-(tetrahydro-2H-pyran-2yloxy) propanoyl) phenoxy)acetate (**1c**).* Alkyne **6c** (50 mg, 0.16 mmol), $NaHCO_3$ (1.1 mg, 13 μmol), $MgSO_4$ (5 mg, 39 μmol), $NaIO_4$ (103 mg, 0.47 mmol), and a 0.01 M $RuCl_3$ solution (160 μL, 1.6 μmol) were used. The reaction mixture was stirred at room temperature for 2 h and then worked up to obtain the title compound **1c** (44 mg, 78% yield) as a pale yellow oil, which was pure to use for next step without further purification; IR (neat) 2925, 1733, 1597, 1458, 1199, and 1074 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, 3H, J=7.1 Hz), 1.49–1.79 (m, 6H), 3.52 (d, 1H, J=11.3 Hz), 3.83 (t, 1H, J=9.4 and 10.9 Hz), 4.27 (q, 2H, J=7.1 Hz), 4.65 (s, 2H), 4.77 (m, 3H), 6.88 (d, 1H, J=8.3 Hz), 7.15 (t, 1H, J=7.5 Hz), 7.57 (t, 1H, J=8.3 Hz), and 7.88 (d, 1H, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.2, 194.3, 167.6, 158.4, 136.0, 130.5, 123.9, 122.5, 112.9, 98.4, 68.6, 66.1, 61.8, 61.6, 30.0, 25.3, 18.7, and 14.1; HRMS calcd for $[(C_{18}H_{22}O_7)+Na]^+$: 373.1258. Found: 373.1254.

*4.8.4. Ethyl-2-(5-methoxy-2-(2-oxo-2-phenylacetyl)phenoxy) acetate (**1d**).* Alkyne **6d** (260 mg, 0.84 mmol), $NaHCO_3$ (5 mg, 67 μmol), $MgSO_4$ (26 mg, 0.21 mmol), $NaIO_4$ (545 mg, 2.51 mmol), and a 0.01 M $RuCl_3$ solution (850 μL, 8 μmol) were used. The reaction mixture was stirred for 1 h. Purification by column chromatography (SiO_2, 10% EtOAc/hexane) provided the title compound **1d** (235 mg, 81% yield) as a yellow solid; mp 81–82 °C; IR (neat) 2924, 1756, 1679, 1595, and 1166 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (t, 3H, J=7.1 Hz), 3.78 (s, 3H), 4.01 (q, 2H, J=7.1 Hz), 4.30 (s, 2H), 6.29 (s, 1H), 6.65 (d, 1H, J=8.8 Hz), 7.42 (t, 2H, J=7.4 Hz), 7.54 (t, 1H, J=7.2 Hz), 7.87 (d, 2H, J=7.4 Hz), and 7.99 (d, 1H, J=8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.3, 192.7, 166.9, 166.2, 160.2, 133.3, 132.7, 132.3, 129.1, 128.2, 117.1, 107.6, 98.9, 65.3, 60.9, 55.4, and 13.6; HRMS calcd for $[(C_{19}H_{18}O_6)+H]^+$: 343.1176. Found: 343.1166.

*4.8.5. Ethyl-2-(5-methoxy-2-(2-(4-methoxyphenyl)-2-oxoacetyl) phenoxy)acetate (**1e**).* Alkyne **6e** (200 mg, 0.59 mmol), $NaHCO_3$ (4 mg, 47 μmol), $MgSO_4$ (18 mg, 0.15 mmol), $NaIO_4$ (379 mg, 1.76 mmol), and a 0.01 M $RuCl_3$ solution (600 μL, 6 μmol) were used. The reaction mixture was stirred for 1 h. Purification by column chromatography (SiO_2, 20% EtOAc/hexane) provided the title compound **1e** (208 mg, 95% yield) as a colorless solid; mp 117–118 °C; IR (neat) 2923, 1755, 1663, 1595, and 1165 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (t, 3H, J=7.0 Hz), 3.75 (s, 3H), 3.77 (s, 3H), 4.01 (q, 2H, J=7.0 Hz), 4.29 (s, 2H), 6.23 (s, 1H), 6.60 (d, 1H, J=8.7 Hz), 6.86 (d, 2H, J=8.3 Hz), 7.80 (d, 2H, J=8.3 Hz), and 7.94 (d, 1H, J=8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.3, 192.6, 167.5, 166.4, 164.1, 160.6, 132.8, 131.9, 126.1, 117.9, 113.9, 107.9, 99.6, 66.0, 61.4, 55.8, 55.5, and 14.0; HRMS calcd for $[(C_{20}H_{20}O_7)+H]^+$: 373.1282. Found: 373.1281.

*4.8.6. Ethyl-2-(4-methoxy-2-(2-oxohexanoyl)phenoxy)acetate (**1f**).* Alkyne **6f** (30 mg, 0.10 mmol), $NaHCO_3$ (0.7 mg, 8 μmol), $MgSO_4$ (3.1 mg, 26 μmol), $NaIO_4$ (66 mg, 0.31 mmol), and 0.01 M $RuCl_3$ (104 μL, 1 μmol) were used. The reaction mixture was stirred at room temperature for 30 min and then worked up to obtain the title compound **6f** (16 mg, 48% yield) as a pale yellow oil; IR (neat) 2929, 1758, 1714, 1664, 1493, 1193, and 1063 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 3H, J=7.4 Hz), 1.29 (t, 3H, J=7.1 Hz), 1.40 (sext, 2H, J=7.4 Hz), 1.68 (pent, 2H, J=7.4 Hz), 2.88 (t, 2H, J=7.4 Hz), 3.81 (s, 3H), 4.25 (q, 2H, J=7.1 Hz), 4.52 (s, 2H), 6.86 (d, 1H, J=9.1 Hz), 7.11 (dd, 1H, J=9.1 and 3.2 Hz), and 7.33 (t, 1H, J=3.2 Hz);

^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 194.5, 167.9, 154.9, 152.6, 124.6, 122.9, 115.3, 113.0, 66.9, 61.4, 55.8, 31.1, 24.6, 22.2, 14.0, and 13.8; HRMS calcd for $[(C_{17}H_{22}O_6)+H]^+$: 323.1485. Found: 323.1489.

*4.8.7. Ethyl-2-(2-(2-oxo-2-phenylacetyl)-5-(tosyloxy)phenoxy) acetate (**1g**).* Alkyne **6g** (55 mg, 0.12 mmol), $NaHCO_3$ (1 mg, 10 μmol), $MgSO_4$ (4 mg, 30 μmol), $NaIO_4$ (73 mg, 0.37 mmol), and $RuCl_3$ (122 μL, 1 μmol) were used. The reaction mixture was stirred for 1 h. Purification by preparative thin layer chromatography (SiO_2, 20% EtOAc/hexane) provided the title **1g** (36 mg, 63% yield) as a yellow oil; IR (neat) 2983, 1756, 1678, 1597, 1377, 1192, 1090, and 954 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, 3H, *J*=7.1 Hz), 2.46 (s, 3H), 4.07 (q, 2H, *J*=7.1 Hz), 4.32 (s, 2H), 6.65 (s, 1H), 6.68 (d, 1H, *J*=8.7 Hz), 7.35 (d, 2H, *J*=8.0 Hz), 7.48 (d, 1H, *J*=7.4 Hz), 7.51 (d, 1H, *J*=7.6 Hz), 7.62 (dd, 1H, *J*=7.6 and 7.4 Hz), 7.73 (d, 2H, *J*=8.0 Hz), and 7.89–7.98 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.0, 192.6, 166.7, 159.3, 155.1, 146.0, 134.1, 132.5, 132.2, 131.8, 130.0, 129.7, 128.7, 128.5, 123.0, 116.1, 107.8, 65.8, 61.6, 21.7, and 13.9; HRMS calcd for $[(C_{25}H_{22}O_8S)+Na]^+$: 505.0928. Found: 505.0920.

*4.8.8. Ethyl-2-(2-(2-(3,4-dimethoxyphenyl)-2-oxoacetyl)-5-(tosyloxy)phenoxy)acetate (**1h**).* Alkyne **6h** (1.20 g, 2.35 mmol), $NaHCO_3$ (16 mg, 0.2 mmol), $MgSO_4$ (71 mg, 0.6 mmol), $NaIO_4$ (1.5 g, 7.05 mmol), and 0.01 M $RuCl_3$ (2.4 mL, 24 μmol) were used. The reaction mixture was stirred for 1 h. Purification by column chromatography (SiO_2, 30% EtOAc/hexane) provided the title compound **1h** (1.0 g, 81% yield) as a pale yellow oil; IR (neat) 2973, 1754, 1663, 1596, 1261, 1192, and 1019 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, 3H, *J*=7.2 Hz), 2.46 (s, 3H), 3.95 (s, 6H), 4.11 (q, 2H, *J*=7.2 Hz), 4.36 (s, 2H), 6.66 (s, 1H), 6.69 (d, 1H, *J*=8.2 Hz), 6.91 (d, 1H, *J*=8.2 Hz), 7.34 (d, 2H, *J*=7.7 Hz), 7.46 (d, 1H, *J*=8.2 Hz), 7.54 (s, 1H), 7.73 (d, 2H, *J*=7.7 Hz), and 7.92 (d, 1H, *J*=8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.2, 191.6, 166.8, 159.2, 154.9, 154.2, 149.2, 146.0, 132.3, 131.8, 130.0, 128.5, 125.6, 125.5, 123.3, 116.0, 110.6, 110.2, 107.9, 65.9, 61.6, 56.1, 56.0, 21.7, and 14.0; HRMS calcd for $[(C_{27}H_{26}O_{10}S)+H]^+$: 543.1319. Found: 543.1314.

*4.8.9. Ethyl-2-(2-(2-(2-methoxyphenyl)-2-oxoacetyl)phenoxy) acetate (**1i**).* Alkyne **6i** (30 mg, 97 μmol), $NaHCO_3$ (0.6 mg, 8 μmol), $MgSO_4$ (3 mg, 25 μmol), $NaIO_4$ (64 mg, 0.29 mmol), and a 0.01 M $RuCl_3$ solution (100 μL, 1 μmol) were used. The reaction mixture was stirred for 1 h and the crude product was purified by preparative thin layer chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound **1i** (28 mg, 87% yield) as a pale yellow oil; IR (neat) 2937, 1756, 1658, 1596, 1484, and 1279 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (t, 3H, *J*=7.1 Hz), 3.62 (s, 3H), 4.06 (q, 2H, *J*=7.1 Hz), 4.40 (s, 2H), 6.85 (d, 1H, *J*=8.3 Hz), 6.95 (d, 1H, *J*=8.3 Hz), 7.10 (t, 1H, *J*=8.3 Hz), 7.18 (t, 1H, *J*=7.6 Hz), 7.56 (br s, 2H), 8.05 (d, 1H, *J*=7.6 Hz), and 8.12 (d, 1H, *J*=7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.3, 191.9, 167.7, 160.5, 158.6, 135.6, 135.3, 130.8, 130.5, 123.8, 123.5, 122.3, 121.1, 112.4, 66.2, 61.3, 55.8, and 14.0; HRMS calcd for $[(C_{19}H_{18}O_6)+Na]^+$: 365.0996. Found: 365.0989.

*4.8.10. Ethyl-2-(2-(2-(4-methoxyphenyl)-2-oxoacetyl)phenoxy) acetate (**1j**).* Alkyne **6j** (26 mg, 84 μmol), $NaHCO_3$ (0.6 mg, 7 μmol), $MgSO_4$ (3 mg, 21 μmol), $NaIO_4$ (85 mg, 0.25 mmol), and a 0.01 M $RuCl_3$ solution (90 μL, 1 μmol) were used. The reaction mixture was stirred for 1 h and the crude product was purified by preparative thin layer chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound **1j** (29 mg, 94% yield) as a pale yellow oil; IR (neat) 2924, 1756, 1666, 1596, and 1258 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, 3H, *J*=7.1 Hz), 3.88 (s, 3H), 4.10 (q, 2H, *J*=7.1 Hz), 4.41 (s, 2H), 6.85 (d, 1H, *J*=8.5 Hz), 6.97 (d, 2H, *J*=8.5 Hz), 7.18 (t, 1H, *J*=7.5 Hz), 7.57 (t, 1H, *J*=7.7 Hz), 7.93 (d, 2H, *J*=8.5 Hz), and 8.02 (d, 1H, *J*=7.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.5, 192.0, 167.7, 164.2, 158.6, 136.0, 132.1, 131.0, 125.8, 124.8, 122.6, 114.0, 113.3, 66.0, 61.4, 55.5, and 14.0; HRMS calcd for $[(C_{19}H_{18}O_6)+H]^+$: 343.1176. Found: 343.1183.

*4.8.11. Ethyl-2-(2-(2-(3,4-dimethoxyphenyl)-2-oxoacetyl) phenoxy) acetate (**1k**).* Alkyne **6k** (800 mg, 2.35 mmol), $NaHCO_3$ (16 mg, 0.19 mmol), $MgSO_4$ (71 mg, 0.59 mmol), $NaIO_4$ (1.51 g, 7.06 mmol), and $RuCl_3$ (2.4 mL, 24 μmol) were used. The reaction mixture was stirred for 1 h and the crude product was purified by column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound **1k** (653 mg, 75% yield) as a bright yellow solid; IR (neat) 2939, 1755, 1662, 1596, 1265, 1195, and 1020 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, 3H, *J*=6.9 Hz), 3.94 (s, 6H), 4.09 (q, 2H, *J*=6.9 Hz), 4.42 (s, 2H), 6.85 (d, 1H, *J*=8.4 Hz), 6.90 (d, 1H, *J*=8.4 Hz), 7.17 (t, 1H, *J*=7.5 Hz), 7.48–7.48 (m, 3H), 8.01 (d, 1H, *J*=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.2, 192.0, 167.5, 158.5, 153.9, 149.1, 135.9, 130.8, 125.8, 125.4, 124.7, 122.4, 113.2, 110.6, 110.2, 65.9, 61.3, 56.0, 55.9, and 13.9; HRMS calcd for $[(C_{20}H_{20}O_7)+Na]^+$: 395.1101. Found: 395.1090.

*4.8.12. Ethyl-3-(2-ethoxy-2-oxoethoxy)-4-(2-oxo-2-phenylacetyl) benzoate (**1l**).* Alkyne **6l** (214 mg, 0.61 mmol), $NaHCO_3$ (4 mg, 49 μmol), $MgSO_4$ (18 mg, 0.15 mmol), $NaIO_4$ (391 mg, 1.82 mmol), and a 0.01 M $RuCl_3$ solution (610 μL, 6 μmol) were used. The reaction mixture was stirred for 2 h. Purification by column chromatography (SiO_2, 20% EtOAc/hexane) provided the title compound **1l** (198 mg, 85% yield) as a yellow oil; IR (neat) 2983, 1721, 1678, 1420, and 1196 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (t, 3H, *J*=6.9 Hz), 1.29 (t, 3H, *J*=6.9 Hz), 3.96 (q, 2H, *J*=6.9 Hz), 4.29 (q, 2H, *J*=6.9 Hz), 4.37 (s, 2H), 7.40 (t, 3H, *J*=10.7 and 7.2 Hz), 7.52 (t, 1H, *J*=6.9 Hz), 7.73 (d, 1H, *J*=7.8 Hz), 7.85 (d, 2H, *J*=7.2 Hz), and 7.95 (d, 1H, *J*=7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.7, 191.4, 166.1, 164.0, 157.1, 136.0, 133.1, 131.5, 129.9, 128.7, 127.7, 126.8, 122.2, 113.0, 64.7, 60.7, 60.4, 13.2, and 12.9; HRMS calcd for $[(C_{21}H_{20}O_7)+Na]^+$: 407.1101. Found: 407.1106.

*4.8.13. Ethyl-2-(2-(3,3-dimethyl-2-oxobutanoyl)phenoxy)acetate (**1m**).* Alkyne **6m** (100 mg, 0.38 mmol), $NaHCO_3$ (3 mg, 31 μmol), $MgSO_4$ (11 mg, 96 μmol), $NaIO_4$ (244 mg, 1.15 mmol), and a 0.01 M $RuCl_3$ solution (400 μL, 4 μmol) were used. The reaction mixture was stirred for 1 h. Purification by column chromatography (SiO_2, 15% EtOAc/hexane) provided the title compound **1m** (45 mg, 91% yield) as a pale yellow oil; IR (neat) 2967, 2927, 1756, 1597, 1458, and 1194 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, 3H, *J*=7.1 Hz), 1.33 (s, 9H), 4.26 (q, 2H, *J*=7.1 Hz), 4.62 (s, 2H), 6.83 (d, 1H, *J*=8.2 Hz), 7.14 (t, 1H, *J*=7.5 and 8.2 Hz), 7.55 (t, 1H, *J*=7.5 and 8.2 Hz), and 7.94 (d, 1H, *J*=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.4, 194.7, 167.9, 158.2, 135.9, 130.6, 122.4, 121.8, 112.8, 66.0, 61.6, 42.0, 26.5, and 14.0; HRMS calcd for $[(C_{16}H_{20}O_5)+H]^+$: 293.1384. Found: 293.1383.

*4.8.14. Ethyl-2-(2-(2-(3,4-dimethoxyphenyl)-2-oxoacetyl)-3,5-dimethoxyphenoxy)acetate (**1n**).* Alkyne **6n** (1.38 g, 3.5 mmol), $NaHCO_3$ (23 mg, 0.28 mmol), $MgSO_4$ (104 mg, 0.86 mmol), $NaIO_4$ (2.2 g, 10.35 mmol), and 0.01 M $RuCl_3$ solution (3.5 mL, 35 μmol) were used. The reaction mixture was stirred for 30 h. Purification by column chromatography (SiO_2, 15% EtOAc/hexane) provided the title compound **1n** (988 mg, 67% yield) as a pale yellow solid; mp 118–120 °C; IR (neat) 2940, 2843, 1754, 1613, 1598, 1580, 1131, and 1020 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, 3H, *J*=7.1 Hz), 3.70 (s, 3H), 3.82 (s, 3H), 3.93 (s, 3H), 3.95 (s, 3H), 4.17 (q, 2H, *J*=7.1 Hz), 4.51 (s, 2H), 6.02 (s, 1H), 6.15 (s, 1H), 6.92 (d, 1H, *J*=8.4 Hz), and 7.59 (d, 2H, *J*=8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.6, 190.8, 167.8, 165.5, 162.9, 161.0, 153.3, 148.7, 126.0, 125.1, 111.1, 110.1, 108.6, 92.5, 91.9, 66.2, 61.3, 55.9, 55.8 (×2), 55.5, and 13.9; HRMS calcd for $[(C_{22}H_{24}O_9)+Na]^+$: 455.1312. Found: 455.1306.

*4.8.15. Ethyl-2-(2-(2-(4-nitrophenyl)-2-oxoacetyl)phenoxy)acetate (**1o**).* Alkyne **6o** (20 mg, 61 μmol), $NaHCO_3$ (0.4 mg, 5 μmol), $MgSO_4$ (2 mg, 15 μmol), $NaIO_4$ (39 mg, 0.18 mmol), and a 0.01 M $RuCl_3$

solution (60 μL, 1 μmol) were used. The reaction mixture was stirred for 1 h and then worked up to obtain the title compound **1o** (19 mg, 86% yield) as a yellow oil, which was used for next step without further purification; IR (neat) 2923, 1756, 1598, and 1200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, 3H, J=7.0 Hz), 4.09 (q, 2H, J=7.0 Hz), 4.41 (s, 2H), 6.86 (d, 1H, J=8.4 Hz), 7.23 (t, 1H, J=7.8 Hz), 7.63 (t, 1H, J=7.8 Hz), 8.05 (d, 1H, J=7.8 Hz), 8.14 (d, 2H, J=8.0 Hz), and 8.34 (d, 2H, J=8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.3, 190.8, 167.0, 158.5, 150.7, 137.5, 136.7, 131.0, 130.8, 123.9, 123.8, 122.8, 112.9, 65.6, 61.6, and 14.0; HRMS calcd for $[(C_{18}H_{15}NO_7)+H]^+$: 358.0921. Found: 358.0919.

*4.8.16. Ethyl-2-(5-methoxy-2-(2-(4-nitrophenyl)-2-oxoacetyl) phenoxy)acetate (**1p**).* Alkyne **6p** (173 mg, 0.49 mmol), $NaHCO_3$ (3 mg, 39 μmol), $MgSO_4$ (1 mg, 0.12 mmol), $NaIO_4$ (314 mg, 1.46 mmol), and a 0.01 M $RuCl_3$ solution (490 μL, 5 μmol) were used. The reaction mixture was stirred for 2 h. Purification by column chromatography (SiO_2, 20% EtOAc/hexane) provided the title compound **1p** (158 mg, 83% yield) as a yellow solid; mp 151–153 °C; IR (neat) 2923, 1760, 1686, 1592, 1526, and 1210 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, 3H, J=7.1 Hz), 3.89 (s, 3H), 4.09 (q, 2H, J=7.1 Hz), 4.38 (s, 2H), 6.30 (s, 1H), 6.74 (d, 1H, J=8.7 Hz), 8.08 (d, 1H, J=8.7 Hz), 8.11 (d, 2H, J=8.4 Hz), and 8.32 (d, 2H, J=8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.9, 191.4, 167.0, 166.8, 160.5, 150.6, 137.8, 133.0, 130.6, 123.7, 117.1, 108.0, 99.3, 65.6, 61.6, 55.9, and 14.0; HRMS calcd for $[(C_{19}H_{17}NO_8)+H]^+$: 388.1027. Found: 388.1012.

*4.8.17. Ethyl-2-(5-nitro-2-(2-oxo-2-phenylacetyl)phenoxy)acetate (**1q**).* Alkyne **6q** (140 mg, 0.43 mmol), $NaHCO_3$ (3 mg, 34 μmol), $MgSO_4$ (14 mg, 0.11 mmol), $NaIO_4$ (289 mg, 1.29 mmol), and a 0.01 M $RuCl_3$ solution (450 μL, 4 μmol) were used. Purification by preparative thin layer chromatography (SiO_2, 20% EtOAc/hexane) provided the title compound **1q** (134 mg, 83% yield) as a yellow oil; IR (neat) 2927, 1754, 1679, 1532, and 1199 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, 3H, J=7.0 Hz), 4.10 (q, 2H, J=7.0 Hz), 4.52 (s, 2H), 7.52 (t, 2H, J=7.5 Hz), 7.66 (t, 1H, J=7.2 Hz), 7.71 (s, 1H), 7.98 (dd, 3H, J=14.4 and 7.5 Hz), and 8.14 (d, 1H, J=8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.5, 191.6, 166.5, 158.2, 151.9, 134.4, 132.0, 129.8, 129.5, 128.8, 117.1, 108.3, 65.9, 61.8, and 13.9; HRMS calcd for $[(C_{18}H_{15}NO_7)+H]^+$: 358.0921. Found: 358.0925.

*4.8.18. Ethyl-2-(2-(2-(4-methoxyphenyl)-2-oxoacetyl)-5-nitro phenoxy)acetate (**1r**).* Alkyne **6r** (495 mg, 1.39 mmol), $NaHCO_3$ (9 mg, 0.11 mmol), $MgSO_4$ (42 mg, 0.35 mmol), $NaIO_4$ (892 mg, 4.17 mmol), and a 0.01 M $RuCl_3$ solution (1.4 mL, 14 μmol) were used. The reaction mixture was stirred for 2 h. Purification by column chromatography (SiO_2, 20% EtOAc/hexane) provided the title compound **1r** (480 mg, 89% yield) as a yellow oil; IR (neat) 2926, 1753, 1671, 1598, 1532, and 1203 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, 3H, J=7.1 Hz), 3.90 (s, 3H), 4.14 (q, 2H, J=7.1 Hz), 4.53 (s, 2H), 7.00 (d, 2H, J=8.6 Hz), 7.70 (s, 1H), 7.96 (d, 2H, J=8.6 Hz), 8.02 (d, 1H, J=8.5 Hz), and 8.12 (d, 1H, J=8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.6, 190.4, 166.7, 164.7, 158.3, 151.9, 132.4, 132.2, 130.1, 125.1, 117.2, 114.2, 108.5, 66.2, 61.9, 55.6 and 14.0; HRMS calcd for $[(C_{19}H_{17}NO_8)+H]^+$: 388.1027. Found: 388.1036.

4.9. Procedure for DBU-induced cyclization reaction

To a solution of the diketone **1** (1.0 equiv) in DMSO (5 mL/mmol of substrate) was added 1.1 equiv of diazabicycloundecene (DBU) dropwise. The reaction mixture was heated at 100 °C until completion as indicated by TLC. The reaction mixture was quenched with a saturated NH_4Cl solution and extracted three times with EtOAc. The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated under reduce pressure. After the organic solvent was removed the crude residue was purified to obtain the pure product.

*4.9.1. Ethyl-4-oxo-3-phenyl-4H-chromene-2-carboxylate (**2a**)[33] and ethyl-3-benzoylbenzofuran-2-carboxylate (**3a**).* The diketone **1a** (320 mg, 1.02 mmol) and DBU (200 μL, 1.13 mmol) were used. The reaction mixture was heated for 1 h. Purification by preparative thin layer chromatography (SiO_2, 20% EtOAc/hexane) provided the title compound **2a** (253 mg, 84% yield) as a white solid and compound **3a** (19 mg, 3% yield) as a pale yellow solid; **2a**: mp 86–88 °C; IR (neat) 2983, 1736, 1650, 1617, 1465, and 1296 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, 3H, J=7.1 Hz), 4.15 (q, 2H, J=7.1 Hz), 7.29–7.32 (m, 2H), 7.37–7.46 (m, 4H), 7.56 (d, 1H, J=8.5 Hz), 7.75 (t, 1H, J=7.8 Hz), 8.25 (d, 1H, J=7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 161.6, 155.4, 150.8, 134.4, 131.2, 129.6, 128.3, 128.0, 126.2, 125.8, 125.6, 123.6, 118.3, 62.3, and 13.3. HRMS calcd for $[(C_{18}H_{14}O_4)+Na]^+$: 317.0784. Found: 317.0783.

Compound **3a**: mp 85–86 °C; IR (neat) 2924, 1729, 1659, 1579, 1299, and 1147 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.00 (t, 3H, J=7.1 Hz), 4.17 (q, 2H, J=7.1 Hz), 7.34 (t, 1H, J=7.3 Hz), 7.45–7.68 (m, 6H), and 7.92 (d, 2H, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.7, 158.6, 154.6, 137.4, 134.8, 133.8, 129.4, 128.7, 128.4, 125.7, 124.6, 123.9, 122.1, 112.4, 61.9, and 13.5. HRMS calcd for $[(C_{18}H_{14}O_4)+Na]^+$: 317.0784. Found: 317.0788.

*4.9.2. Ethyl-3-butyl-4-oxo-4H-chromene-2-carboxylate (**2b**).* The diketone **1b** (100 mg, 0.34 mmol) and DBU (71 μL, 0.38 mmol) were used. The reaction mixture was heated for 1 h. Purification by preparative thin layer chromatography (SiO_2, 20% EtOAc/hexane) provided the title compound **2b** (69 mg, 74% yield) as a pale yellow oil; IR (neat) 2958, 2927, 1734, 1647, 1617, 1467, 1294, and 1414 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 3H, J=7.1 Hz), 1.35–1.61 (m, 4H), 1.48 (t, 3H, J=7.1 Hz), 2.85 (t, 2H, J=7.1 Hz), 4.48 (t, 2H, J=7.1 Hz), 7.39 (t, 1H, J=7.6 Hz), 7.51 (d, 1H, J=7.6 Hz), 7.70 (t, 1H, J=7.6 Hz), and 8.18 (d, 1H, J=7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 161.6, 155.3, 149.1, 134.1, 128.0, 125.9, 125.2, 122.8, 118.2, 62.4, 31.4, 24.2, 22.9, 14.1, and 13.8; HRMS calcd for $[(C_{16}H_{18}O_4)+Na]^+$: 297.1097. Found: 297.1089.

*4.9.3. Ethyl-4-oxo-3-((tetrahydro-2H-pyran-2-yloxy)methyl)-4H-chromene-2-carboxylate (**2c**).* The diketone **1c** (43 mg, 0.12 mmol) and DBU (25 μL, 0.13 mmol) were used. The reaction mixture was heated for 2 h. Purification by preparative thin layer chromatography (SiO_2, 30% EtOAc/hexane) provided the title compound **2c** (29 mg, 73% yield) as a pale yellow oil; IR (neat) 2942, 1740, 1652, 1467, 1239, and 1025 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.43–1.84 (m, 9H), 3.53–3.61 (m, 1H), 3.92 (t, 1H, J=10.2 Hz), 4.48 (q, 2H, J=7.1 Hz), 4.71 (d, 1H, J=11.1 Hz), 4.81 (br s, 1H), 5.01 (d, 1H, J=11.1 Hz), 7.44 (t, 1H, J=7.8 Hz), 7.53 (dd, 1H, J=8.0 and 0.4 Hz), 7.72 (t, 1H, J=7.8 Hz), and 8.22 (d, 1H, J=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 161.2, 155.4, 134.3, 126.0, 125.6, 123.4, 122.1, 118.3, 116.5, 98.9, 62.7, 61.8, 58.6, 30.4, 25.4, 19.1, and 13.9; HRMS calcd for $[(C_{18}H_{20}O_6)+H]^+$: 355.1152. Found: 355.1161.

*4.9.4. Ethyl-7-methoxy-4-oxo-3-phenyl-4H-chromene-2-carboxylate (**2d**).* The diketone **1d** (180 mg, 0.53 mmol) and DBU (110 μL, 0.58 mmol) were used. The reaction mixture was heated for 1 h. Purification by preparative thin layer chromatography (SiO_2, 20% EtOAc/hexane) provided the title compound **2d** (136 mg, 78% yield) as a yellow solid; mp 130–132 °C; IR (neat) 2977, 1735, 1621, 1438, and 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, 3H, J=7.1 Hz), 3.91 (s, 3H), 4.12 (q, 2H, J=7.1 Hz), 6.96 (d, 1H, J=2.3 Hz), 7.01 (dd, 1H, J=8.8 and 2.3 Hz), 7.28–7.30 (m, 2H), 7.38–7.44 (m, 3H), and 8.13 (d, 1H, J=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 164.7, 161.7, 157.3, 150.4, 131.5, 129.7, 128.2, 128.0, 127.6, 126.1, 117.6, 115.4, 100.2, 62.3, 55.9, and 13.3; HRMS calcd for $[(C_{19}H_{16}O_5)+H]^+$: 325.1071. Found: 325.1062.

*4.9.5. Ethyl-7-methoxy-3-(4-methoxyphenyl)-4-oxo-4H-chromene-2-carboxylate (**2e**).* The diketone **1e** (88 mg, 0.23 mmol) and DBU

(50 μL, 0.26 mmol) were used. The reaction mixture was heated for 1 h. Purification by preparative thin layer chromatography (SiO_2, 20% EtOAc/hexane) provided the title compound **2e** (57 mg, 70% yield) as a colorless solid; mp 117–118 °C; IR (neat) 2981, 1733, 1609, 1438, and 1246 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (t, 3H, J=7.1 Hz), 3.83 (s, 3H), 3.90 (s, 3H), 4.16 (q, 2H, J=7.1 Hz), 6.93–7.00 (m, 4H), 7.23 (d, 2H, J=8.8 Hz), and 8.13 (d, 1H, J=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 164.6, 161.9, 159.7, 157.3, 150.3, 131.0, 127.6, 125.6, 123.5, 117.6, 115.3, 113.6, 100.1, 62.2, 55.8, 55.2, and 13.5; HRMS calcd for $[(C_{20}H_{18}O_6)+H]^+$: 355.1176. Found: 355.1173.

*4.9.6. Ethyl-3-butyl-6-methoxy-4-oxo-4H-chromene-2-carboxylate (**2f**).* The diketone **1f** (31 mg, 96 μmol) and DBU (14 μL, 106 μmol) were used. The reaction mixture was heated for 1 h. Purification by preparative thin layer chromatography (SiO_2, 15% EtOAc/hexane) provided the title compound **2f** (21 mg, 73% yield) as a pale yellow oil; IR (neat) 2953, 1729, 1635, 1488, 1275, 1243, and 817 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 3H, J=7.1 Hz), 1.30–1.60 (m, 4H), 1.45 (t, 3H, J=7.1 Hz), 2.86 (t, 2H, J=7.1 Hz), 3.90 (s, 3H), 4.46 (q, 2H, J=7.1 Hz), 7.29 (dd, 1H, J=9.2 and 3.0 Hz), 7.45 (d, 1H, J=9.2 Hz), and 7.53 (d, 1H, J=3.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 161.7, 157.0, 150.2, 149.0, 127.2, 124.6, 123.4, 119.8, 104.6, 62.4, 55.8, 31.5, 24.3, 22.9, 14.1, and 13.9; HRMS calcd for $[(C_{17}H_{20}O_5)+Na]^+$: 327.1203 Found:327.1206.

*4.9.7. Ethyl-4-oxo-3-phenyl-7-(tosyloxy)-4H-chromene-2-carboxylate (**2g**).* The diketone **1g** (35 mg, 73 μmol) and DBU (11 μL, 79 μmol) were used. The reaction mixture was heated for 1 h. Purification by preparative thin layer chromatography (SiO_2, 15% EtOAc/hexane) provided the title compound (18 mg, 56% yield) as an off-white solid; mp 108–110 °C; IR (neat) 2926, 1740, 1651, 1615, 1258, 1222, 1117, and 1089 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (t, 3H, J=7.1 Hz), 2.47 (s, 3H), 4.13 (q, 2H, J=7.1 Hz), 7.03 (d, 1H, J=8.7 Hz), 7.26 (br s, 2H), 7.31–7.45 (m, 6H), 7.76 (d, 2H, J=8.1 Hz), and 8.16 (d, 1H, J=8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 161.3, 155.7, 153.6, 151.2, 146.1, 131.8, 130.8, 130.1, 129.6, 128.5, 128.4, 128.2, 128.1, 126.2, 122.3, 120.2, 112.2, 62.6, 21.7, 14.3; HRMS calcd for $[(C_{25}H_{20}O_7S)+H]^+$: 465.1003. Found: 465.0999.

*4.9.8. Ethyl-3-(3,4-dimethoxyphenyl)-4-oxo-7-(tosyloxy)-4H-chromene-2-carboxylate (**2h**).* The diketone **1h** (75 mg, 0.14 mmol) and DBU (23 μL, 0.15 mmol) were used. The reaction mixture was heated for 1 h. Purification by preparative thin layer chromatography (SiO_2, 25% EtOAc/hexane) provided the title compound (41 mg, 56% yield) as a pale yellow solid; mp 126–128 °C; IR (neat) 2937, 1736, 1655, 1614, 1513, 1377, 1265, 1176, and 1021 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (t, 3H, J=7.1 Hz), 2.47 (s, 3H), 3.87 (s, 3H), 3.91 (s, 3H), 4.18 (q, 2H, J=7.1 Hz), 6.80–6.87 (m, 2H), 6.91 (d, 1H, J=8.2 Hz), 7.03 (dd, 1H, J=8.8 and 2.2 Hz), 7.33–7.38 (m, 3H), 7.75 (d, 2H, J=8.2 Hz), and 8.16 (d, 1H, J=8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 161.5, 155.7, 153.6, 151.4, 149.7, 148.8, 146.1, 131.8, 130.0, 128.4, 128.1, 125.5, 123.0, 122.9, 122.2, 113.0, 112.1, 110.9, 62.6, 55.9 (×2), 21.8, 13.6; HRMS calcd for $[(C_{27}H_{24}O_4S)+H]^+$: 525.1238 Found: 525.1219.

*4.9.9. Ethyl-3-(2-methoxyphenyl)-4-oxo-4H-chromene-2-carboxylate (**2i**).* The diketone **1i** (18 mg, 50 μmol) and DBU (10 μL, 55 μmol) were used. The reaction mixture was heated for 3 h. Purification by preparative thin layer chromatography (SiO_2, 25% EtOAc/hexane) provided the title compound **2i** (11 mg, 61% yield) as a pale yellow oil; **2i**: IR (neat) 2926, 1738, 1651, 1464, 1244, and 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (t, 3H, J=7.0 Hz), 3.74 (s, 3H), 4.14 (q, 2H, J=7.0 Hz), 6.95 (d, 1H, J=8.1 Hz), 7.02 (t, 1H, J=7.5 Hz), 7.19 (d, 1H, J=7.4 Hz), 7.37 (t, 1H, J=7.9 Hz), 7.44 (t, 1H, J=7.5 Hz), 7.59 (d, 1H, J=8.5 Hz), 7.73 (t, 1H, J=7.9 Hz), and 8.24 (d, 1H, J=8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 161.6, 156.9, 155.5, 150.9, 134.3, 131.1, 129.8, 126.3, 125.5, 123.7, 123.2, 120.9, 120.4, 118.4, 110.7, 62.1, 55.6, and 13.5; HRMS calcd for $[(C_{19}H_{16}O_5)+Na]^+$: 347.0889. Found: 347.0884.

*4.9.10. Ethyl-3-(4-methoxyphenyl)-4-oxo-4H-chromene-2-carboxylate (**2j**) and ethyl-3-(4-methoxybenzoyl) benzofuran-2-carboxylate (**3j**).* The diketone **1j** (28 mg, 80 μmol) and DBU (17 μL, 88 μmol) were used. The reaction mixture was heated for 1 h. Purification by preparative thin layer chromatography (SiO_2, 25% EtOAc/hexane) provided the title compound **2j** (15 mg, 57% yield) as a pale colorless solid and compound **3j** (4 mg, 13% yield) as a pale yellow solid; **2j**: mp 86–87 °C; IR (neat) 2935, 2833, 1738, 1652, 1466, and 1247 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (t, 3H, J=7.1 Hz), 3.85 (s, 3H), 4.18 (q, 2H, J=7.1 Hz), 6.97 (d, 2H, J=8.7 Hz), 7.25 (d, 2H, J=8.7 Hz), 7.45 (t, 1H, J=8.0 Hz), 7.57 (d, 1H, J=8.0 Hz), 7.74 (td, 1H, J=8.0 and 1.6 Hz), and 8.26 (dd, 1H, J=8.0 and 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 161.9, 159.8, 155.5, 150.8, 134.3, 131.0, 126.3, 125.5, 125.3, 123.7, 123.3, 118.3, 113.7, 62.4, 55.2, and 13.5; HRMS calcd for $[(C_{19}H_{16}O_5)+H]^+$: 325.1071. Found: 325.1071.

Compound **3j**: mp 83–85 °C; IR (neat) 2924, 1728, 1659, 1599, and 1247 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (t, 3H, J=7.1 Hz), 3.88 (s, 3H), 4.22 (q, 2H, J=7.1 Hz), 6.94 (d, 2H, J=8.6 Hz), 7.32 (t, 1H, J=7.5 Hz), 7.50 (d, 1H, J=7.5 Hz), 7.54 (t, 1H, J=7.5 Hz), 7.66 (d, 1H, J=8.5 Hz), and 7.89 (d, 2H, J=8.5 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 189.1, 164.3, 158.7, 154.7, 142.3, 131.9, 130.5, 128.3, 126.8, 126.3, 124.4, 122.1, 113.9, 112.4, 61.8, 55.6, and 13.7; HRMS calcd for $[(C_{19}H_{16}O_5)+H]^+$: 325.1071. Found: 325.1066.

*4.9.11. Ethyl-3-(3,4-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxylate (**2k**) and ethyl 3-(3,4-dimethoxybenzoyl)benzofuran-2-carboxylate (**3k**).* The diketone **1k** (640 mg, 1.72 mmol) and DBU (285 mL, 1.89 mmol) were used. The reaction mixture was heated for 1 h. Purification by column chromatography (SiO_2, 15% EtOAc/hexane) provided the title compound **2k** (322 mg, 53% yield) as a pale yellow solid along with compound **3k** (101 mg, 16% yield) as an off-white solid; **2k**; mp 138–140 °C; IR (neat) 2937, 1734, 1650, 1615, 1515, 1464, and 1299 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, 3H, J=7.0 Hz), 3.80 (s, 3H), 3.82 (s, 3H), 4.09 (q, 2H, J=7.0 Hz), 6.76 (d, 1H, J=8.2 Hz), 6.81 (s, 1H), 6.83 (d, 1H, J=8.2 Hz), 7.34 (t, 1H, J=7.9 Hz), 7.47 (d, 1H, J=7.9 Hz), 7.65 (t, 1H, J=7.9 Hz), and 8.16 (d, 1H, J=7.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 161.8, 155.3, 151.0, 149.2, 148.6, 134.3, 126.1, 125.5, 125.0, 123.6, 123.5, 122.2, 118.2, 113.0, 110.8, 62.3, 55.8 (×2), and 13.5; HRMS calcd for $[(C_{20}H_{18}O_6)+Na]^+$: 377.0996. Found: 377.0988.

Compound **3k**; mp 164–165 °C; IR (neat) 2937, 1728, 1658, 1584, 1301, 1273, 1262, 1174, and 1146 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (t, 3H, J=7.1 Hz), 3.94 (s, 6H), 4.23 (q, 2H, J=7.1 Hz), 6.83 (d, 1H, J=8.4 Hz), 7.27–7.36 (m, 2H), 7.48–7.57 (m, 2H), 7.65 (d, 1H, J=7.0 Hz), 7.66 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.1, 158.7, 154.5, 154.1, 149.3, 142.2, 130.4, 128.3, 126.8, 126.1, 125.6, 124.4, 122.0, 112.4, 110.2, 109.9, 61.8, 56.1, 56.0, and 13.7; HRMS calcd for $[(C_{20}H_{18}O_6)+Na]^+$: 377.0996. Found: 377.0992.

*4.9.12. Diethyl-4-oxo-3-phenyl-4H-chromene-2,7-dicarboxylate (**2l**), diethyl-3-benzoylbenzofuran-2,6-dicarboxylate (**3l**), and diethyl benzofuran-2,6-dicarboxylate (**9**).* The diketone **1l** (148 mg, 0.39 mmol) and DBU (82 μL, 0.42 mmol) were used. The reaction mixture was heated for 1 h. Purification by preparative thin layer chromatography (SiO_2, 20% EtOAc/hexane) provided the title compound **2l** (39 mg, 54% yield) as a colorless solid, compound **3l** (9 mg, 12% yield) as a pale yellow solid, and compound **9** (7 mg, 14% yield) as a colorless solid; **2l**: mp 103–104 °C; IR (neat) 2983, 1724, 1653, 1429, 1278, and 1203 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, 3H, J=7.1 Hz), 1.45 (t, 3H, J=7.1 Hz), 4.16 (q, 2H, J=7.1 Hz), 4.46 (q, 2H, J=7.1 Hz), 7.29–7.32 (m, 2H), 7.41–7.46 (m, 3H), 8.07 (dd, 1H, J=8.3 and 1.3 Hz), and 8.29 (t, 2H, J=8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 164.8, 161.3, 155.0,

151.4, 135.9, 130.9, 129.6, 128.5, 128.2, 126.6, 126.3, 126.2, 125.9, 120.2, 62.6, 61.9, 14.2 and 13.4; HRMS calcd for $[(C_{21}H_{18}O_6)+Na]^+$: 389.0996. Found: 389.1001.

Compound **3l**: mp 113–115 °C; IR (neat) 2922, 2847, 1670, 1720 and 1301 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (t, 3H, J=7.1 Hz), 1.44 (t, 3H, J=7.1 Hz), 4.18 (q, 2H, J=7.1 Hz), 4.44 (q, 2H, J=7.1 Hz), 7.49 (t, 2H, J=8.0 Hz), 7.64 (d, 2H, J=8.3 Hz), 7.91 (d, 2H, J=7.8 Hz), 8.04 (dd, 1H, J=8.3 and 1.3 Hz), and 8.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.1, 165.8, 158.2, 154.0, 145.0, 137.2, 134.0, 130.6, 130.3, 129.4, 128.7, 125.5, 125.2, 121.9, 114.1, 62.2, 61.5, 14.3, and 14.5; HRMS calcd for $[(C_{21}H_{18}O_6)+Na]^+$: 389.0996. Found: 389.1001.

Compound **9**: mp 76–78 °C; IR (neat) 2982, 2919, 1715, 1291, 1181 and 1016 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (q, 6H, J=6.3 Hz), 4.37 (q, 4H, J=6.7 Hz), 7.48 (s, 1H), 7.66 (d, 1H, J=8.2 Hz), 7.94 (d, 1H, J=8.2 Hz), and 8.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 159.1, 155.0, 148.1, 130.8, 129.7, 124.7, 122.4, 113.9, 113.2, 61.7, 61.3, and 14.2; HRMS calcd for $[(C_{14}H_{14}O_5)+Na]^+$: 285.0734. Found: 285.0734.

*4.9.13. Ethyl-3-pivaloylbenzofuran-2-carboxylate (**3m**).* The diketone **1m** (41 mg, 0.14 mmol) and DBU (30 μL, 0.15 mmol) were used. The reaction mixture was heated for 4 h. Purification by preparative thin layer chromatography (SiO_2 30% EtOAc/hexane) provided the title compound **3m** (16 mg, 42% yield) as a pale yellow oil; IR (neat) 2973, 1713, 1696, 1586, 1296, and 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 9H), 1.41 (t, 3H, J=7.1 Hz), 4.43 (q, 2H, J=7.1 Hz), 7.33 (td, 1H, J=8.0 and 7.3 Hz), 7.49 (m, 2H), and 7.60 (d, 1H, J=9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9, 158.8, 154.4, 128.2, 127.7, 126.0, 124.2, 122.1, 112.5, 61.9, 45.3, 29.6, 26.8, and 14.2; HRMS calcd for $[(C_{16}H_{18}O_4)+H]^+$: 275.1239. Found: 275.1277.

*4.9.14. Ethyl-3-(3,4-dimethoxybenzoyl)-4,6-dimethoxybenzofuran-2-carboxylate (**3n**).* The diketone **1n** (62 mg, 0.14 mmol) and DBU (22 μL, 0.16 mmol) were used. The reaction mixture was heated for 2 h. Purification by preparative thin layer chromatography (SiO_2 25% EtOAc/hexane) provided the title compound **3n** (38 mg, 64% yield) as a pale yellow oil; IR (neat) 2939, 1711, 1589, 1508, 1259, and 1151 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (t, 3H, J=7.1 Hz), 3.68 (s, 3H), 3.87 (s, 3H), 3.93 (s, 3H), 3.96 (s, 3H), 4.21 (q, 2H, J=7.1 Hz), 6.30 (s, 1H), 6.70 (s, 1H), 6.81 (d, 1H, J=8.4 Hz), 7.30 (d, 1H, J=8.4 Hz), and 7.66 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.7, 162.6, 158.7, 156.8, 154.9, 153.7, 149.1, 139.5, 130.5, 126.5, 125.5, 111.1, 110.0, 109.9, 95.6, 87.9, 61.4, 56.1, 56.0, 55.9, 55.8, and 13.9; HRMS calcd for $[(C_{22}H_{22}O_8)+Na]^+$: 437.1207. Found: 437.1215.

*4.9.15. Ethyl-6-nitro benzofuran-2-carboxylate (**10**).* The diketone **1q** (50 mg, 0.14 mmol) and DBU (30 μL, 0.15 mmol) were used. The reaction mixture was heated for 1 h. Purification by preparative thin layer chromatography (SiO_2, 10% EtOAc/hexane) provided the title compound **10** (24 mg, 75% yield) as a pale yellow solid and 5 mg (37%) of benzoic acid (**11q**). The benzofuran **10** can also be produced from diketone **1r** as following: the diketone **1r** (400 mg, 1.03 mmol) and DBU (215 μL, 1.14 mmol) were used. The reaction mixture was heated for 1 h. Purification by preparative thin layer chromatography (SiO_2, 20% EtOAc/hexane) provided the title compound **10** (194 mg, 80% yield) as a pale yellow solid and 55 mg (41%) of *para* methoxybenzoic acid (**11r**) as brown needles; **10**: mp 112–115 °C; IR (neat) 3106, 2987, 1732, 1716, 1516, and 1290 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (t, 3H, J=7.1 Hz), 4.49 (q, 2H, J=7.1 Hz), 7.61 (s, 1H), 7.83 (d, 1H, J=8.7 Hz), 8.24 (dd, 1H, J=8.7 and 1.9 Hz), and 8.50 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 154.1, 150.2, 147.1, 132.4, 123.1, 119.2, 112.9, 108.8, 62.2, and 14.2; HRMS Calcd for $[C_{11}H_9NO_5]$: 235.0475. Found: 235.0471.

Compound **11q**: mp 123–125 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 6.26 (s, 1H), 7.45 (t, 2H, J=7.8 Hz), 7.59 (t, 1H, J=7.8 Hz), and 8.11 (d, 2H, J=7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.8, 130.2, and 128.6.

Compound **11r**: mp 181–183 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.86 (s, 3H), 6.20 (s, 1H), 6.91 (d, 2H, J=8.2 Hz), and 8.05 (d, 2H, J=8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 163.9, 132.2, 121.4, 113.7, and 55.4.

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Supplementary data

^1H NMR and ^{13}C NMR data. Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2013.07.104.

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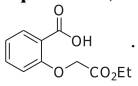
17. The crude NMR spectrum showed a mixture of 2-(2-ethoxy-2-oxoethoxy) benzoic acid **8** and a small amount of corresponding diketone derivative **1p** or **1q**. However, after column chromatography, the only isolated compound was  . IR (neat) 3266, 2929, 1729, 1603, and 1220 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, 3H, J=7.1 Hz), 4.35 (q, 2H, J=7.1 Hz), 4.83 (s, 2H), 6.94 (dd, 1H, J=8.3 and 0.8 Hz), 7.19 (td, 1H, J=7.8 and 0.8 Hz), 7.56 (td, 1H, J=7.8 and 1.8 Hz), and 8.21 (dd, 1H, J=7.8 and 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 164.9, 156.2, 134.8, 134.2, 123.2, 123.1, 112.8, 66.3, 62.5, and 14.0; HRMS calcd for $[(C_{11}H_{12}O_5)+H]^+$: 225.0758. Found: 225.0755.
18. Spectroscopic data of **II**: IR (neat) 3462, 2982, 1740, 1697, 1608, 1462, 1297, 1185 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (t, 3H, J=7 Hz) 1.21 (3H, t, J=7. 1 Hz), 4.19 (2H, q, J=7.1 Hz), 4.50 (s), 5.30 (1H,s), 6.97 (1H, dd, J=8.3, 0.5 Hz), 7. 07 (1H, td, J=7.6 and 1.0 Hz), 7.35–7.30 (3H,m), 7.55–7.50 (3H,m), and 7.87 (1H, dd, J=7.8, 1.7 Hz),; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 168.1, 158.9, 138.3, 136.9, 128.9, 128.8, 126.9, 125.8, 122.2, 119.5, 117.6, 82.3, 74.3, 61.9, and 13.8; HRMS calcd for $[(C_{20}H_{18}O_6)+H]^+$: 355.0890. Found: 355.0890.
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