Water mediated trapping of active methylene intermediates generated by IBX-induced oxidation of Baylis–Hillman adducts with nucleophiles†

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Water proved to be an efficient solvent for oxidation of a Baylis–Hillman adduct with IBX. The generated product, a methylene intermediate, could be trapped *in situ* by many nucleophiles in water, such as styrenes, β-dicarbonyl compounds, benzamide and less reactive indoles. This strategy offers an alternative way to methylenylation of β-dicarbonyl compounds with formaldehyde for the formation of a methylene intermediate, thus allows the use of some nucleophiles that are chemically unstable to formaldehyde. The use of water as solvent, good recycling ability of IBX oxidant and wide substrate scopes make these reactions very attractive from the viewpoint of green chemistry.

Introduction

Domino reactions offer preparatively simple and elegant solutions for complex synthetic problems.[1] The efficiency of this concept relies on linking together single reaction steps, thus avoiding separation and purification procedures after each step. In a domino reaction, a product is assembled according to a cascade of elementary chemical reactions. The challenge is to conduct the reaction in a suitable way that allows the pre-equilibrated elementary reactions to channel into the main product and not yield side products.[2] For this purpose, many efforts have been devoted to optimization of reaction conditions, and among all the parameters that might affect the domino reaction, solvent is particularly important.

Nowadays, organic reactions in water are of current interest in organic synthesis.[3] In addition to environmental and economical advantages, unique reactivity and selectivity that are not achieved in organic solvents are often observed in water, and several interesting and useful reactions have been exploited using water as the solvent. The unique capability of water as a solvent for developing new reactions has also been demonstrated by recent observations of some multi-component domino reactions.[4] Water was proved to be crucial in these domino reactions because it is either able to accelerate the reaction rate or is capable of stabilizing or destabilizing a reactive intermediate.

Inspired by using water as solvent, we have recently developed a water-mediated catalyst-free three-component reaction of formaldehyde, styrene and β-dicarbonyl compound that generated a 5,6-dihydropyran derivative in moderate to good yields (Scheme 1).[5] The plausible reaction pathway involves (i) formation of a methylene intermediate from formaldehyde and β-dicarbonyl compound through a Knoevenagel reaction (step **R-1**), and (ii) trapping of the intermediate with styrene by means of an *oxo* Diels–Alder reaction (step **R-2**). So, this reaction could be classified as a domino Knoevenagel/*oxo* Diels–Alder reaction that has been extensively investigated by Tietze and the others.[6] The use of water as solvent for this type of domino reaction has, in fact, been investigated by some pioneers. For example, Majumdar[7] and his co-workers have recently reported a catalyst-free intramolecular domino Knoevenagel/*oxo* Diels–Alder reaction of terminal alkynes and 4-hydroxy dithiocoumarin using water as solvent. Because of the well known acceleration effect of water on Diels–Alder reactions, it is reasonable to expect that the use of water as solvent should be partially responsible for the accomplishment of these domino reactions.

Despite fascinating results, the reported domino Knoevenagel/*oxo* Diels–Alder reaction has two drawbacks: (i) forming a methylene intermediate is quite difficult when the reactivity of β-dicarbonyl compounds is poor for the Knoevenagel reaction of formaldehyde (step **R-1**); however, in the case of reactive substrate, due to generation of large amount of a side-product through a domino Knoevenagel/Michael reaction pathway (Scheme 1, step **R-3**), excess amount of β-dicarbonyl compounds and formaldehyde has to be used in order to obtain a good yield; (ii) owing to the use of formaldehyde as methylenylation reagent, the trapping reagent has to be chemically inert to formaldehyde, otherwise extra effort has to be paid for inhibiting the side reaction between trapping reagent and formaldehyde (see the case of **R-4** in Scheme 1). In order to solve these problems, an alternative method that is able to generate a methylene intermediate without the use of formaldehyde is desired.

In the search for a new method, we were attracted by the Baylis–Hillman adduct, which is a very useful synthetic intermediate[8] and can be oxidized to the desired methylene

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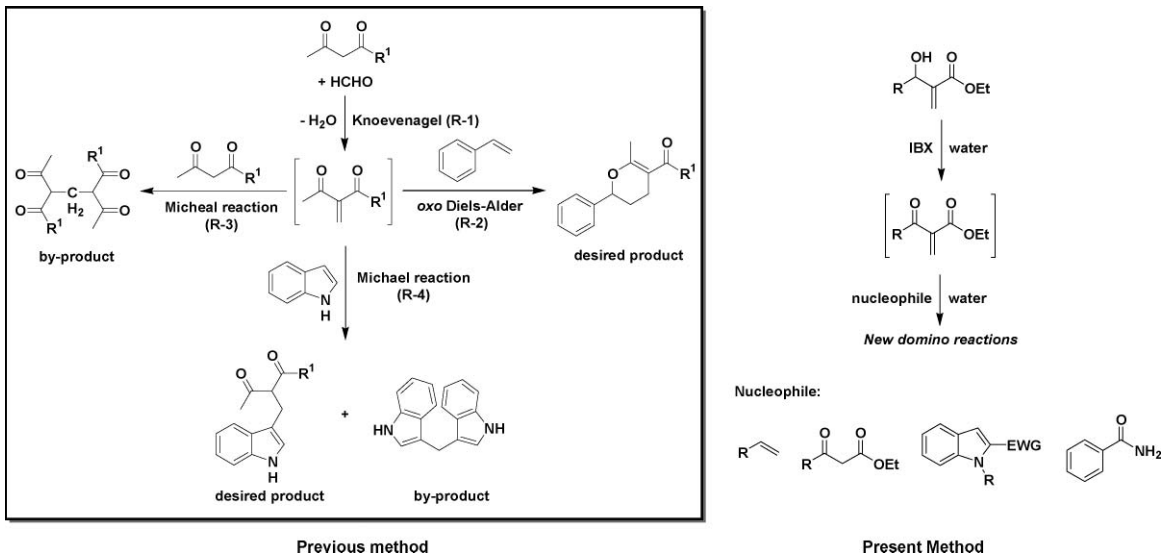


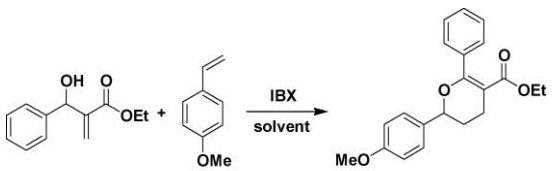
Scheme 1 Generation and trapping of the methylene intermediate.

intermediate in the presence of IBX (iodoxybenzoic acid),[9] Dess–Martin periodinane,[10] Swern[11] or Jones oxidants.[12] In particular, high selectivity and mild conditions of IBX-induced oxidation of Baylis–Hillman adduct allow *in situ* trapping of the generated 2-methylene-1,3-dicarbonyl compounds with a suitable nucleophile.[13] Indeed, some domino reactions have been developed based on oxidation of Baylis–Hillman adducts using IBX as oxidant, such as the one-pot oxidative Michael reaction of Baylis–Hillman adducts with indoles,[14] oxidative 1,2-acetoxysulfenylation,[15] and oxidative bromohydroxylation.[16] Encouraged by these domino reactions, we decided to use the oxidation of a Baylis–Hillman adduct to replace Knoevenagel reaction of formaldehyde for the purpose of generating a methylene intermediate. In particular, we observed that the good compatibility of IBX oxidant with water might allow the use of water as solvent for developing some new domino reactions based on oxidation of a Baylis–Hillman adduct.[17] In this paper, we will report some outcomes obtained by using a combination of water and IBX as solvent/oxidant, including Baylis–Hillman adduct-participant one-pot oxidative *oxo* Diels–Alder reaction with olefins, oxidative Michael reaction with β-dicarbonyl compounds or less-reactive indoles and oxidative aza-Michael reaction with benzamide. Compared with our previous domino reactions based on methylenylation of β-dicarbonyl compounds with formaldehyde, which are also capable of affording the analogous products, better yields, wider substrate generality and easier control of the selectivity were obtained in the present domino reactions.

Results and discussion

Initially, in order to confirm feasibility of generating a methylene intermediate by means of IBX-induced oxidation of a Baylis–Hillman adduct, ethyl-3-hydroxy-2-methylene-3-phenylpropionate (**1a**) was heated in water in the presence of 1.2 equv. amount of IBX. As we expected, after 3 h of reaction at 60 °C, **1a** was completely consumed, and the desired product, ethyl 2-benzoylacrylate, was formed exclusively. This

Table 1 IBX-induced oxidative *oxo* Diels–Alder reaction of **1a** with **2a** in different solvents[a]



1a *2a* *3a*

Entry	Solvent	**1a**/**2a**/IBX	Temp./°C	Time/h	Yield[b] (%)
1	H_2O	1.0/1.3/1.3	90	3.0	72
2	$ClCH_2CH_2Cl$	1.0/1.3/1.3	90	3.0	15
3	CH_3CN	1.0/1.3/1.3	90	3.0	63
4	Toluene	1.0/1.3/1.3	90	3.0	trace
5	Dioxane	1.0/1.3/1.3	90	3.0	trace
6	$[BMIm]BF_4$	1.0/1.3/1.3	90	3.0	10
7	H_2O	1.0/1.0/1.0	90	3.0	57
8	H_2O	1.0/1.0/1.5	90	3.0	57
9	H_2O	1.0/1.3/1.3	60	3.0	40
10	H_2O	1.0/1.3/1.3	90	1.5	53
11[c]	H_2O	1.0/1.3/1.3	90	3.0	71

[a] **1a**: 0.3 mmol, solvent: 1 ml. [b] Yield was calculated with respect to Baylis–Hillman adduct. [c] Regenerated IBX was used.

result encouraged us to investigate the possibility of developing some new domino reactions on the basis of *in situ* trapping of the methylene intermediate with a suitable nucleophile. To realize this idea, two points have to be taken into consideration: (i) owing to the presence of IBX in the system, the trapping reagent has to be chemically inert for this oxidant; and (ii) in view of the fact that water was used as reaction solvent here, performance of the trapping reaction should not be affected by water. Out of these considerations, the first nucleophile we tested was 4-methoxystyrene (**2a**), which has been proven to be capable of affording an *oxo* Diels–Alder adduct with the analogous methylene intermediate in water.[5a] As shown in Table 1, oxidative *oxo* Diels–Alder reaction of **1a** with **2a** proceeded well in water using IBX as oxidant, and the desired

product, ethyl-6-phenyl-3,4-dihydro-2-(4-methoxyphenyl)-2*H*-pyran-5-carboxylate (**3a**), was obtained in 72% yield (entry 1). Importantly, water was proved to be a preferable solvent for this domino reaction, because when the other tested solvents, such as 1,2-dichloroethane, acetonitrile, toluene, dioxane and an ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIm]BF_4), were used under identical conditions, the reaction yields were inferior to that obtained in water (entries 2 to 6). When the reaction was performed in the presence of equimolar amounts of **1a**, **2a** and IBX, only 57% yield was obtained (entry 7). Fortunately, only slight excess amounts of **2a** and IBX were sufficient to improve the reaction yield to the maximum (entries 1, 7 and 8). Further investigations revealed that the reaction was also affected by temperature and reaction time, and the optimal conditions are 90 °C and 3 h (entries 1, 9 and 10).

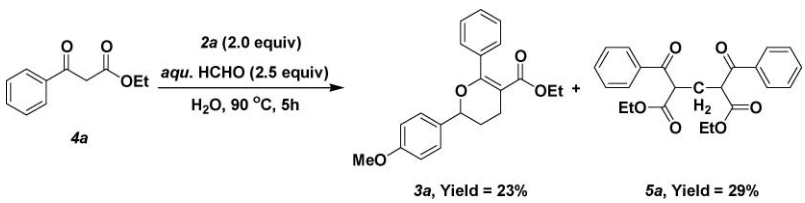
When IBX was used as oxidant, a by-product, 2-iodobenzoic acid, could be formed during the reaction. There are two liquid phases in the reaction system including (i) an aqueous phase that is the reaction medium, and (ii) an organic phase mainly composed of the un-reacted **2a** and the formed product **3a**. Because of the poor solubility of 2-iodobenzoic acid in both liquid phases, a large amount of white solid could be precipitated out at the end of the reaction. Separation of this solid could be realized by filtration and subsequent washing with a mixture of ethyl acetate and heptane (v/v = 1/1). Thus, this system allows an easy and quantitative recovery of the concomitant 2-iodobenzoic acid. After regeneration according to a known procedure,[18] the recycling of 2-iodobenzoic acid was proved to be successful in the model domino reaction (entry 11). With this method, greenness of the model domino reaction was significantly improved in terms of minimization of waste. Considering the fact that the reaction was conducted in water, it is not incongruous to classify the model reaction as a green method for the synthesis of **3a**.

It should be noted that **3a** could also be prepared by a known method, three-component reaction of ethyl benzoylacetate (**4a**), **2a** and formaldehyde in water. From the viewpoint of practical synthesis, the three-component reaction should be much more effective than the present method because of good availability of substrate and low cost. However, this domino Knoevenagel/*oxo* Diels–Alder reaction is not always clean and applicable because of the presence of a side reaction, domino Knoevenagel/Michael reaction of β-dicarbonyl compound and formaldehyde. In order to get a direct comparison, the three-component reaction of **4a**, **2a** and formaldehyde was also investigated in water. As shown in Scheme 2, **3a** was obtained only in 23% yield although large excess amounts of formaldehyde and **2a** were used. The low yield mainly resulted from an extensive formation of a by-product, **5a**, generated through a domino Knoevenagel/Michael reaction of **4a** and formaldehyde. On the basis of this result, we can conclude at this stage that, for the synthesis of **3a**, the model reaction in Table 1 is much more efficient than the previous reported method from the viewpoints of atom-economy and minimization of waste. This result clearly indicated the necessity and effectiveness of the model reaction for organic synthesis.

With these results in hand, we then investigated substrate scope of the IBX-induced oxidative *oxo* Diels–Alder reactions of Baylis–Hillman adducts with olefins in water. As shown in Table 2, many Baylis–Hillman adducts could be used in the presence of **2a**. Generally, Baylis–Hillman adducts obtained from an aromatic aldehyde with an electron-withdrawing group gave higher yields than the one with an electron-donating group (entries 1 to 5). An aliphatic aldehyde-dervied Baylis–Hillman adduct, **1g**, could also be used in this domino reaction (entry 6). In particular, the reaction was proved to be tolerable for some heterocyclic moieties, such as 2-furyl and 2-thienyl (**1h** and **1i**, entries 7 and 8). Table 3 shows the results of using some Baylis–Hillman adducts prepared from benzaldehyde and different acrylates. Generally, the reaction yield decreased with increase of the size of ester groups. This may result from the increased hydrophobicity of the Baylis–Hillman adducts.

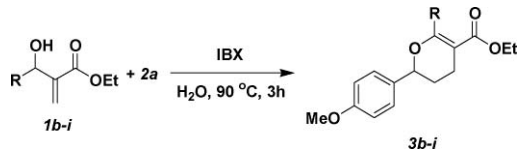
Reactivity of other olefins in this reaction was also investigated, and the results are listed in Table 4. A general tendency could be found, and that is styrenes with an electron-donating group in the aromatic ring have higher reactivity toward cyclization than the one with an electron-withdrawing group (entries 1 to 3). The presence of a methyl group in the α-position of styrene was proved to be helpful for increasing the reaction yield (entries 4 and 5). An alkyl vinyl ether, **2g**, was also applicable in this reaction, but the yield obtained is slightly inferior to that of styrene type substrates (entry 6). In order to know whether it is possible to apply this method to practical synthesis, we also carried out a reaction on a 10 mmol scale. And as shown in Table 4, an 85% yield was obtained for the reaction of **1a** and **2d** (entry 3). Although an increased amount of IBX was used in this case, the good performance of this reaction on a large scale demonstrated that our method is, indeed, applicable for practical synthesis. It should also be noted that, at the end of the 10 mmol scale reaction, 2-iodobenzoic acid was recovered in 98% yield. It further proves the system to be a good example of green synthesis.

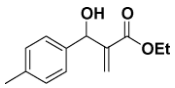
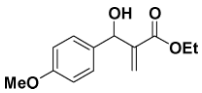
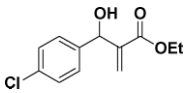
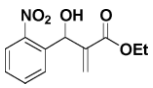
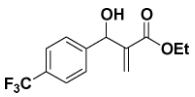
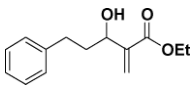
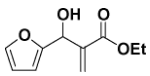
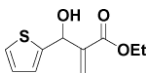
The promising results obtained in the above-mentioned tables encouraged us to investigate the possibility of linking other types of reactions together with oxidation of Baylis–Hillman adducts in water. We then changed the nucleophile from olefins to β-dicarbonyl compounds that might be able to trap the methylene intermediate through a Michael type reaction.[19] As shown in Table 5, after a few condition optimizations, the



Scheme 2 Three-component reaction of **2a**, formaldehyde and **4a** in water.

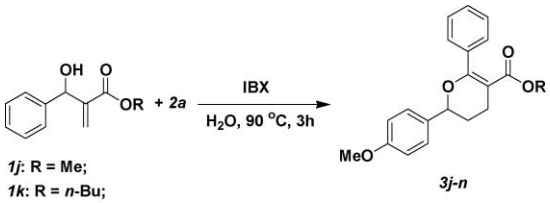
Table 2 IBX-induced oxidative *oxo* Diels–Alder reaction of different Baylis–Hillman adducts with **2a** in water[a]



Entry	Baylis–Hillman adduct		Product	Yield[b] (%)
1		**1b**	**3b**	59
2		**1c**	**3c**	60
3		**1d**	**3d**	70
4		**1e**	**3e**	73
5		**1f**	**3f**	70
6		**1g**	**3g**	66
7		**1h**	**3h**	40
8		**1i**	**3i**	73

[a] Baylis–Hillman alcohol: 0.3 mmol, water: 1.0 ml, Baylis–Hillman alcohol/**2a**/IBX = 1.0/1.3/1.3; temperature: 90 °C; reaction time: 3.0 h; [b] yield was calculated with respect to Baylis–Hillman adduct.

Table 3 Effect of ester groups on the IBX-induced oxidative *oxo* Diels–Alder reaction of Baylis–Hillman adducts with **2a** in water[a]



1j: R = Me;
1k: R = *n*-Bu;
1l: R = *t*-Bu;
1m: R = cyclohexyl;
1n: R = *iso*-octyl.

Entry	Baylis–Hillman adduct	Product	Yield[b] (%)
1	**1j**	**3j**	70
2	**1k**	**3k**	60
3	**1l**	**3l**	65
4	**1m**	**3m**	53
5[c]	**1n**	**3n**	39

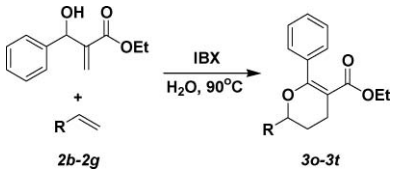
[a] Baylis–Hillman alcohol: 0.3 mmol, water: 1.0 ml, Baylis–Hillman alcohol/**2a**/IBX = 1.0/1.3/1.3; Temperature: 90 °C. Reaction time: 3.0 h. [b] Yield was calculated with respect to Baylis–Hillman adduct. [c] Reaction time: 5h.

yield of an IBX-induced oxidative Michael reaction of **1a** with ethyl 4-methoxybenzoylacetate, **4b**, could be improved to the maximum value, 80%. And the obtained product, a polycarbonyl compound **5b**, has the desired structure. Some organic solvents, such as toluene, 1,2-dichloroethane, and acetonitrile were also examined and it was found that they are all ineffective for this reaction, indicating the great ability of water solvent for this domino reaction. It should be noted that although the product could be prepared by a three-component reaction of **4a**, **4b** and formaldehyde, owing to the presence of two "ABB" type side reactions, **4a** + **4a** + HCHO and **4b** + **4b** + HCHO, controlling the selectivity to **5b** and isolating the desired product from others that have close polarities and boiling points would be a great challenge. So, the synthesis of **5b**-type axial-unsymmetric polycarbonyl compounds is not easy, and until now, only a few indirect methods are available in literature (see supporting information, Scheme S1†).[19,20] Attracted by the great ability of the IBX-induced oxidative Michael reaction of Baylis–Hillman adducts, we then examined the substrate generality of this reaction in water. As shown in Table 5, many axial-unsymmetric polycarbonyl compounds were prepared in good to excellent yields. It should be noted that all the products generated in Table 5 might be easily converted to the corresponding Hantzsch adducts in the presence of an amine,[21] indicating again the potential effectiveness of this reaction for organic synthesis.

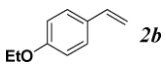
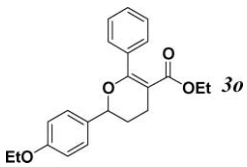
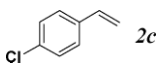
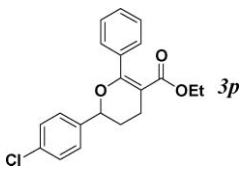
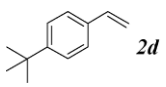
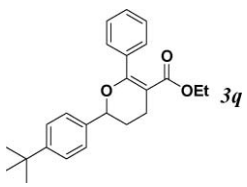
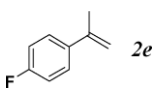
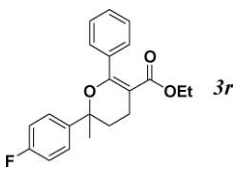
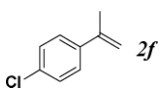
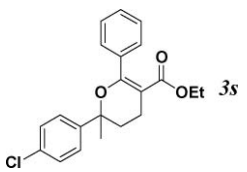
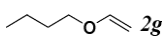
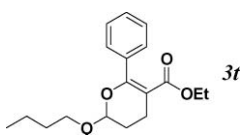
Another nucleophile we used to trap the methylene intermediate generated from the Baylis–Hillman adduct is indoles. In fact, Yadav and his co-workers[14] have reported an oxidative Michael reaction of Baylis–Hillman adduct with indoles using IBX as oxidant. However, a few problems are still present for this domino reaction. First, Yadav's procedure was performed in an organic solvent, acetonitrile, that is detrimental for the environment. Second, only highly reactive indoles, such as unsubstituted indole, 2-methylindole and 5-bromoindole, were examined in the reported system, and no information is available for less-reactive indole derivatives.

In order to overcome these problems, we decided to re-evaluate the reaction using water and less-reactive indoles as solvent and substrates, respectively. As shown in Table 6, the oxidative Michael reaction of a Baylis–Hillman adduct, **1a**, with ethyl indole-2-carboxylate (**6a**) proceeded very well, and the desired product was obtained in 67% yield after 10 h of reaction in water. Importantly, when acetonitrile was used as solvent, only trace amount of product was obtained under identical conditions, indicating the existence of an acceleration effect of water for this reaction. Other Baylis–Hillman adducts were also examined in the reaction of **6a**, and in all the cases, moderate to good yields were obtained. 2-Phenylindoles, such as 1-methyl-2-phenylindole (**6b**) and 1-ethyl-2-phenylindole (**6c**) were also applied in this reaction, and it was found that the yields are even better than that obtained by using **6a** as substrate. From these results, we can conclude that our method not only avoids the use of acetonitrile as solvent, but also is efficient for the reactions of less-reactive indoles.

Table 4 IBX-induced oxidative *oxo* Diels–Alder reaction of **1a** with different olefins in water[a]



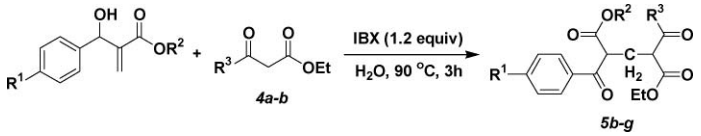
2b-2g *3o-3t*

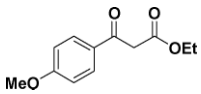
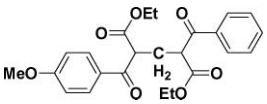
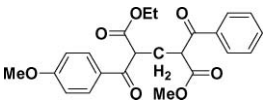
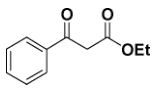
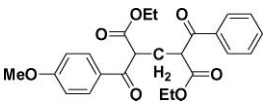
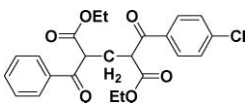
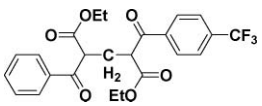
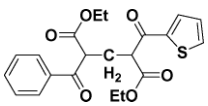
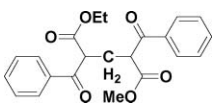
Entry	Olefin		Time/h	Product		Yield[b] (%)
1	 *2b*	**2b**	3	 *3o*	**3o**	69
2	 *2c*	**2c**	5	 *3p*	**3p**	53
3	 *2d*	**2d**	4	 *3q*	**3q**	67 (85)[c]
4	 *2e*	**2e**	3	 *3r*	**3r**	80
5	 *2f*	**2f**	4	 *3s*	**3s**	74
6	 *2g*	**2g**	5	 *3t*	**3t**	39

[a] Baylis–Hillman alcohol: 0.3 mmol, water: 1.0 ml, Baylis–Hillman alcohol/olefin/IBX = 1.0/1.3/1.3; Reaction temperature: 90 °C. [b] Yield was calculated with respect to Baylis–Hillman adduct. [c] Yield was obtained in a 10 mmol scale, **1a**/IBX/**2d** = 1.0/1.9/1.3.

Good results obtained in the above-mentioned domino reactions encouraged us to further extend this strategy in organic synthesis. It is well known that amide or urea can be used as Michael donor in developing an aza-Michael reaction. Unfortunately, due perhaps to the poor reactivities of amide and urea, this type of reaction generally requires assistance of a strong acid or noble metal catalyst, or has to be carried out under harsh conditions.[22] As a result, aza-Michael reactions of amides or ureas have been rarely used in organic synthesis. We were attracted by this reaction because of the following points: (i) good chemical stability of amide to IBX that allows an uneventful use of this oxidant in the presence of an amide; (ii) good compatibility of aza-Michael reaction with water solvent that offers a good chance to use this type of reaction in trapping of the methylene intermediate; and (iii) high reactivity of the methylene intermediate as a Michael acceptor that might allow aza-Michael reaction of amide to proceed under relatively mild conditions. In light of the above-mentioned

Table 5 IBX-induced oxidative Michael reaction of Baylis–Hillman adducts with β-ketoesters in water[a]



Entry	Baylis–Hillman adduct	β-ketone ester		Product		Yield[b] (%)
1	**1a**		**4b**		**5b**	80
2[c]	**1a**		**4b**		**5b**	67
3[d]	**1a**		**4b**		**5b**	55
4[e]	**1a**		**4b**		**5b**	53
5[f]	**1a**		**4b**		**5b**	49
6[g]	**1a**		**4b**		**5b**	18
7[h]	**1a**		**4b**		**5b**	21
8	**1j**		**4b**		**5c**	70
9	**1c**		**4a**		**5b**	75
10	**1d**		**4a**		**5d**	77
11	**1f**		**4a**		**5e**	81
12	**1i**		**4a**		**5f**	70
13	**1j**		**4a**		**5g**	73

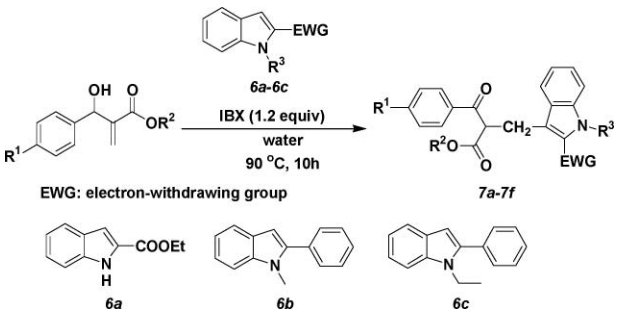
[a] Baylis–Hillman adduct: 0.3 mmol, solvent: 1 ml, **1a**/β-ketoester/IBX = 1.0/1.2/1.2, Reaction temperature: 90 °C; Reaction time: 3.0 h. [b] Yield was calculated with respect to Baylis–Hillman adduct. [c] **1a**/β-dicarbonyl compound/IBX = 1.0/1.0/1.0. [d] Reaction temperature: 60 °C. [e] Reaction time: 1.5 h. [f] Reaction solvent: toluene. [g] Reaction solvent: CH_3CN. [h] Reaction solvent: $ClCH_2CH_2Cl$.

considerations, amide might be a suitable nucleophile to trap the methylene intermediate generated by means of oxidation of Baylis–Hillman adducts with IBX in water. As shown in Scheme 3, an IBX-induced oxidative aza-Michael reaction of Baylis–Hillman adduct **1a** with benzamide (**8a**) was investigated in water, and as we expected, a 63% yield was obtained in 90 °C without using a catalyst. Because of the presence of four organic functional groups, phenyl, amide, ketocarbonyl and ester, it is reasonable to expect that the obtained products have good potential to act as synthetic intermediates in the future. It should also be noted that trying to synthesize the analogous product by a three-component reaction of **4a**, formaldehyde and **8a** in water failed, indicating again the necessity of the present strategy to generate the active methylene intermediate for developing domino organic reactions.

Conclusion

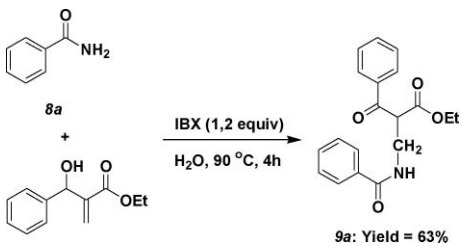
IBX-induced oxidation of Baylis–Hillman adducts was proposed as an alternative way to methylenylation of β-dicarbonyl compounds with formaldehyde for the generation of active methylene intermediates. The use of water as solvent allows easy trapping of these intermediates with appropriate nucleophiles, such as styrenes, β-dicarbonyl compounds, benzamide and less-reactive indoles, which generated many complex skeletons that are either difficult to prepare by conventional methods or

Table 6 IBX-induced oxidative Michael of Baylis–Hillman alcohol with less-reactive indoles[a]



Entry	Baylis–Hillman adduct	Indole	Product	Yield[b] (%)
1	**1j**	**6a**	**7a**	67
2[c]	**1j**	**6a**	**7a**	< 5
3	**1a**	**6a**	**7b**	65
4	**1b**	**6a**	**7c**	62
5	**1d**	**6a**	**7d**	59
6[d]	**1c**	**6b**	**7e**	72
7[d]	**1c**	**6c**	**7f**	67

[a] Baylis–Hillman adduct: 0.30 mmol, indole: 0.33 mmol, water: 1 ml. [b] Yield was calculated with respect to Baylis–Hillman adduct. [c] Reaction solvent: CH_3CN. [d] Reaction time: 12 h.



Scheme 3 IBX-induced oxidative aza-Michael reaction of Baylis–Hillman adducts with benzamide in water (**1a**: 0.30 mmol, **8a**: 0.33 mmol, water: 1.0 ml).

unprecedented in literature. Because of the fact that (i) the by-product of IBX, 2-iodobenzoic acid, could be recycled, and (ii) the use of water as solvent, the system developed here could be considered as environmentally benign for organic synthesis.

Experimental section

All reactions were conducted in a 10 mL V-type flask equipped with triangle magnetic stirring. In a typical reaction, water (1.0 g) was mixed with **2a** (52 mg, 0.4 mmol), **1a** (62 mg, 0.3 mmol) and IBX (109 mg, 0.4 mmol) under air. The mixture was stirred for 3 h at 90 °C. After reaction, the mixture was extracted with ethyl acetate (2 mL × 3). The obtained ester phases were then combined together and concentrated under reduced pressure. The product was obtained by preparative TLC using a mixed solution of ethyl acetate and petro ether as eluting solvent (normally, the ratio of ethyl acetate/petroether is 1/10). Procedures for the other reactions and physicochemical data of the products are available in the Electronic Supporting Information.†

Spectroscopic data for the products

3-Ethoxycarbonyl-2-phenyl-6-(4-methoxyphenyl)-5,6-dihydropyran (3a). white solid, mp = 91–92 °C, ^{1}H NMR ($CDCl_3$): 0.93 (t, J = 7.2 Hz, 3H), 1.92–2.05 (m, 1H), 2.15–2.25 (m, 1H), 2.45–2.58 (m, 1H), 2.66–2.76 (m, 1H), 3.79 (s, 3H), 3.95 (q, J = 6.8 Hz, 2H), 4.98 (dd, J_a = 2.0 Hz, J_b = 10.4 Hz, 1H), 6.88 (td, J_a = 2.0 Hz, J_b = 9.6 Hz, 2H), 7.27–7.35 (m, 5H), 7.36–7.41 (m, 2H); ^{13}C NMR: 13.7, 23.1, 29.3, 55.3, 59.9, 78.7, 103.9, 113.9, 127.4, 127.6, 128.7, 129.0, 132.8, 136.9, 159.4, 163.2, 168.9. IR (cm^{-1}): 2980, 2955, 2934, 1689, 1618, 1597, 1515, 1446, 1372, 1287, 1250, 1205, 1178, 1159, 1095, 1034, 1002, 975, 832, 761, 699. HR-MS: m/z = 338.1550, calcd. for $C_{21}H_{22}O_4$ [M]: 338.1518.

3-Ethoxycarbonyl-2-(4-methylphenyl)-6-(4-methoxyphenyl)-5,6-dihydropyran (3b). colorless liquid, ^{1}H NMR ($CDCl_3$): 0.98 (t, J = 6.8 Hz, 3H), 1.90–2.02 (m, 1H), 2.13–2.22 (m, 1H), 2.34 (s, 3H), 2.45–2.55 (m, 1H), 2.68–2.76 (m, 1H), 3.79 (s, 3H), 3.98 (q, 7.2 Hz, 2H), 4.96 (dd, J_a = 1.6 Hz, J_b = 10.4 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 7.29 (dd, J_a = 2.8 Hz, J_b = 8.0 Hz, 4H); ^{13}C NMR: 13.9, 21.5, 23.2, 29.4, 55.3, 59.9, 78.6, 103.5, 113.9, 127.4, 128.4, 128.8, 132.9, 133.9, 139.0, 159.4, 163.5, 169.0. IR (cm^{-1}): 2979, 2954, 2933, 2838, 1687, 1613, 1514, 1461, 1445, 1370, 1353, 1287, 1250, 1205, 1179, 1159, 1093, 1036, 1000, 975, 909, 825, 760. HR-MS: m/z = 352.1699, calcd. for $C_{22}H_{24}O_4$ [M]: 352.1675.

3-Ethoxycarbonyl-2,6-di(4-methoxyphenyl)-5,6-dihydropyran (3c). white solid, mp = 76–78 °C, ^{1}H NMR ($CDCl_3$): 1.01 (t, J = 6.8 Hz, 3H), 1.90–2.02 (m, 1H), 2.14–2.22 (m, 1H), 2.44–2.55 (m, 1H), 2.68–2.77 (m, 1H), 3.77 (s, 3H), 3.79 (s, 3H), 4.00 (q, J = 6.8 Hz, 2H), 4.95 (dd, J_a = 1.6 Hz, J_b = 10.4 Hz, 1H), 6.84 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 8.8 Hz, 2H); ^{13}C NMR: 14.0, 23.4, 29.4, 55.3, 55.3, 59.9, 78.6, 103.1, 113.0, 113.9, 127.5, 129.1, 130.4, 132.8, 159.4, 160.4, 163.1, 169.1. IR (cm^{-1}): 2955, 2934, 2905, 2838, 1684, 1610, 1513, 1462, 1444, 1370, 1354, 1286, 1249, 1205, 1176, 1092, 1034, 976, 909, 834, 761. HR-MS: m/z = 368.1657, calcd. for $C_{22}H_{24}O_5$ [M]: 368.1624.

3-Ethoxycarbonyl-2-(4-chlorophenyl)-6-(4-methoxyphenyl)-5,6-dihydropyran (3d). colorless liquid, ^{1}H NMR ($CDCl_3$): 1.00 (t, J = 6.8 Hz, 3H), 1.91–2.02 (m, 1H), 2.14–2.24 (m, 1H), 2.45–2.56 (m, 1H), 2.67–2.77 (m, 1H), 3.77 (s, 3H), 3.98 (q, J = 6.8 Hz, 2H), 4.96 (dd, J_a = 2.0 Hz, J_b = 10.4 Hz, 1H), 6.88 (d, J = 8.8 Hz, 2H), 7.26–7.33 (m, 4H), 7.33–7.37 (m, 2H); ^{13}C NMR: 13.9, 23.2, 29.2, 55.3, 60.1, 78.9, 104.3, 114.0, 127.5, 127.9, 130.3, 132.5, 135.0, 135.3, 159.5, 162.2, 168.5. IR (cm^{-1}): 2979, 2956, 2934, 2904, 1690, 1618, 1515, 1370, 1287, 1250, 1205, 1178, 1160, 1092, 1135, 999, 976, 909, 831, 761. HR-MS: m/z = 372.1093, calcd. for $C_{21}H_{21}ClO_4$ [M]: 372.1128.

3-Ethoxycarbonyl-6-(4-methoxyphenyl)-2-(2-nitrophenyl)-5,6-dihydropyran (3e). colorless liquid, ^{1}H NMR ($CDCl_3$): 0.90 (t, J = 7.2 Hz, 3H), 2.05–2.17 (m, 1H), 2.18–2.27 (m, 1H), 2.53–2.64 (m, 1H), 2.69–2.78 (m, 1H), 3.76 (s, 3H), 3.89 (q, J = 6.8 Hz, 2H), 5.01 (dd, J_a = 2.0 Hz, J_b = 10.8 Hz, 1H), 6.87 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.8 Hz, 2H), 7.41 (dd, J_a = 1.2 Hz, J_b = 7.6 Hz, 1H), 7.47 (td, J_a = 1.2 Hz, J_b = 7.6 Hz, 1H), 7.58 (td, J_a = 1.2 Hz, J_b = 7.6 Hz, 1H), 8.06 (dd, J_a = 0.4 Hz, J_b = 8.0 Hz, 1H); ^{13}C NMR: 13.8, 22.7, 28.7, 55.3, 59.9, 79.8, 114.0,

124.2, 127.8, 129.4, 131.1, 132.2, 133.0, 133.1, 147.5, 159.7, 167.1. IR (cm^{-1}): 2980, 2957, 2934, 2905, 2838, 1694, 1639, 1608, 1525, 1444, 1350, 1287, 1250, 1205, 1179, 1097, 1035, 1000, 974, 909, 860, 833, 753, 698. HR-MS: m/z = 383.1393, calcd. for $C_{21}H_{21}NO_6$ [M]: 383.1369.

3-Ethoxycarbonyl-2-(4-trifluorophenyl)-6-(4-methoxyphenyl)-5,6-dihydropyran (3f). white solid, mp = 85–86 °C, ^{1}H NMR ($CDCl_3$): 0.95 (t, J = 6.8 Hz, 3H), 1.94–2.07 (m, 1H), 2.18–2.26 (m, 1H), 2.47–2.59 (m, 1H), 2.69–2.78 (m, 1H), 3.78 (s, 3H), 3.96 (q, J = 7.2 Hz, 2H), 4.99 (dd, J_a = 2.0 Hz, J_b = 10.4 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H); ^{13}C NMR: 13.7, 23.0, 29.1, 55.3, 60.1, 79.0, 104.9, 114.0, 122.7, 124.6, 124.6, 124.7, 124.7, 125.5, 127.4, 129.2, 129.3, 130.6, 131.0, 132.4, 140.5, 159.6, 161.9, 168.2. IR (cm^{-1}): 2981, 2958, 2936, 2906, 2840, 1693, 1633, 1613, 1516, 1326, 1286, 1251, 1166, 1126, 1093, 1068, 1036, 836, 761. HR-MS: m/z = 406.1429, calcd. for $C_{22}H_{21}F_3O_4$ [M]: 406.1392.

3-Ethoxycarbonyl-6-(4-methoxyphenyl)-2-(2-phenylethyl)-5,6-dihydropyran (3g). colorless liquid, ^{1}H NMR ($CDCl_3$): 1.29 (t, J = 6.8 Hz, 3H), 1.71–1.82 (m, 1H), 2.00–2.10 (m, 1H), 2.31–2.44 (m, 1H), 2.45–2.53 (m, 1H), 2.84–2.96 (m, 2H), 2.96–3.08 (m, 2H), 3.79 (s, 3H), 4.18 (q, J = 6.8 Hz, 2H), 4.74 (dd, J_a = 2.0 Hz, J_b = 10.4 Hz, 1H), 6.88 (d, J = 8.4 Hz, 2H), 7.13–7.20 (m, 3H), 7.21–7.29 (m, 4H); ^{13}C NMR: 14.5, 22.3, 29.3, 34.1, 35.4, 55.3, 59.8, 77.9, 101.6, 113.9, 125.9, 127.3, 128.3, 128.7, 133.1, 141.8, 159.4, 167.5, 168.2. IR (cm^{-1}): 3061, 3026, 2952, 2932, 2856, 2837, 1700, 1616, 1515, 1454, 1366, 1249, 1209, 1177, 1158, 1117, 1070, 1036, 829, 762, 700. HR-MS: m/z = 366.1858, calcd. for $C_{23}H_{26}O_4$ [M]: 366.1831.

3-Ethoxycarbonyl-2-(2-furyl)-6-(4-methoxyphenyl)-5,6-dihydropyran (3h). white solid, mp = 102–103 °C, ^{1}H NMR ($CDCl_3$): 1.11 (t, J = 7.2 Hz, 3H), 1.90–2.20 (m, 1H), 2.14–2.23 (m, 1H), 2.46–2.57 (m, 1H), 2.67–2.76 (m, 1H), 3.78 (s, 3H), 4.04–4.13 (m, 2H), 4.96 (dd, J_a = 2.0 Hz, J_b = 10.4 Hz, 1H), 6.89 (td, J_a = 2.8 Hz, J_b = 8.8 Hz, 2H), 6.98 (dd, J_a = 3.6 Hz, J_b = 4.8 Hz, 1H), 7.28–7.38 (m, 3H), 7.35 (dd, J_a = 0.8 Hz, J_b = 4.8 Hz, 1H); ^{13}C NMR: 14.0, 23.7, 29.2, 55.3, 60.3, 78.5, 104.7, 113.9, 126.4, 127.4, 129.2, 132.5, 137.5, 155.2, 159.4, 168.8. IR (cm^{-1}): 2983, 2961, 2933, 2906, 2938, 1708, 1645, 1616, 1585, 1561, 1518, 1482, 1465, 1369, 1343, 1292, 1253, 1209, 1177, 1087, 1031, 978, 911, 832, 760, 595. HR-MS: m/z = 328.1339, calcd. for $C_{19}H_{20}O_5$ [M]: 328.1311.

3-Ethoxycarbonyl-2-(2-thienyl)-6-(4-methoxyphenyl)-5,6-dihydropyran (3i). white solid, mp = 92–93 °C, ^{1}H NMR ($CDCl_3$): 1.16 (t, J = 7.2 Hz, 3H), 1.91–2.03 (m, 1H), 2.13–2.21 (m, 1H), 2.46–2.54 (m, 1H), 2.69–2.78 (m, 1H), 3.81 (s, 3H), 4.09–4.19 (m, 2H), 4.92 (dd, J_a = 2.0 Hz, J_b = 10.4 Hz, 1H), 6.42 (q, J = 1.6 Hz, 1H), 6.62 (d, J = 4.4 Hz, 1H), 6.90 (td, J_a = 2.8 Hz, J_b = 8.8 Hz, 2H), 7.31 (td, J_a = 2.8 Hz, J_b = 8.4 Hz, 2H), 7.42 (d, J = 1.2 Hz, 1H); ^{13}C NMR: 14.3, 23.5, 29.2, 55.3, 60.3, 78.3, 105.3, 111.1, 111.4, 113.9, 127.5, 132.5, 142.8, 148.7, 151.2, 159.5, 168.8. IR (cm^{-1}): 3106, 3009, 2978, 2957, 2935, 2900, 2840, 1707, 1615, 1518, 1464, 1425, 1365, 1338, 1289, 1250, 1200, 1176, 1075, 1032, 987, 948, 908, 834, 761, 718, 556. HR-MS: m/z = 344.1117, calcd. for $C_{19}H_{20}O_4S$ [M]: 344.1082.

3-Methoxycarbonyl-2-phenyl-6-(4-methoxyphenyl)-5,6-dihydropyran (3j). white solid, mp = 70–71 °C, ^{1}H NMR ($CDCl_3$): 1.92–2.02 (m, 1H), 2.15–2.25 (m, 1H), 2.46–2.56 (m, 1H), 2.67–2.75 (m, 1H), 3.49 (s, 3H), 3.76 (s, 3H), 4.97 (dd, J_a = 2.0 Hz, J_b = 10.4 Hz, 1H), 6.88 (dt, J_a = 2.0 Hz, J_b = 8.8 Hz, 2H), 7.29 (dt, J_a = 2.8 Hz, J_b = 8.4 Hz, 2H), 7.31–7.35 (m, 3H), 7.38–7.42 (m, 2H); ^{13}C NMR: 23.2, 29.3, 51.1, 55.3, 78.7, 103.5, 113.9, 127.5, 127.7, 128.8, 129.2, 132.7, 136.7, 159.5, 163.5, 169.2. IR (cm^{-1}): 2948, 1692, 1617, 1597, 1515, 1435, 1359, 1288, 1250, 1179, 1161, 1091, 1033, 953, 897, 832, 760, 699. HR-MS: m/z = 324.1354, calcd. for $C_{20}H_{20}O_4$ [M]: 324.1362.

Butyl 2-(4-methoxyphenyl)-3,4-dihydro-6-phenyl-2*H*-pyran-5-carboxylate (3k). colorless liquid, ^{1}H NMR ($CDCl_3$): 0.69 (t, J = 8.0 Hz, 3H), 0.95 (sext, J = 7.2 Hz, 2H), 1.13–1.24 (m, 2H), 1.84–1.94 (m, 1H), 2.07–2.15 (m, 1H), 2.38–2.48 (m, 1H), 2.60–2.69 (m, 1H), 3.69 (s, 3H), 3.76–3.88 (m, 2H), 4.89 (d, J = 9.2 Hz, 1H), 6.79 (d, J = 8.4 Hz, 2H), 7.19–7.26 (m, 5H), 7.29–7.34 (m, 2H); ^{13}C NMR: 13.8, 19.1, 23.2, 29.3, 30.4, 55.3, 63.9, 78.7, 103.9, 113.9, 127.4, 127.7, 128.8, 129.0, 132.8, 137.0, 159.4, 163.3, 169.0. IR (cm^{-1}): 2958, 2933, 2872, 1688, 1627, 1618, 1597, 1515, 1463, 1446, 1388, 1356, 1286, 1250, 1205, 1178, 1158, 1093, 1034, 1001, 978, 831, 761, 698. HR-MS: m/z = 366.1857, calcd. for $C_{23}H_{26}O_4$ [M]: 366.1831.

***tert*-Butyl 2-(4-methoxyphenyl)-3,4-dihydro-6-phenyl-2*H*-pyran-5-carboxylate (3l).** colorless liquid, ^{1}H NMR ($CDCl_3$): 1.16 (s, 9H), 1.90–2.02 (m, 1H), 2.14–2.23 (m, 1H), 2.41–2.53 (m, 1H), 2.67–2.76 (m, 1H), 3.77 (s, 3H), 4.95 (d, J = 10.4, 1H), 6.87 (d, J = 8.4 Hz, 2H), 7.26–7.35 (m, 5H), 7.36–7.42 (m, 2H); ^{13}C NMR: 23.3, 27.7, 29.4, 55.3, 78.6, 80.0, 105.5, 113.9, 127.5, 127.7, 128.8, 128.9, 132.9, 137.5, 159.4, 162.5, 168.4. IR (cm^{-1}): 2975, 2931, 2849, 1685, 1631, 1616, 1515, 1447, 1366, 1298, 1250, 1170, 1095, 1032, 977, 831, 763, 698. HR-MS: m/z = 366.1811, calcd. for $C_{23}H_{26}O_4$ [M]: 366.1831.

Cyclohexyl 2-(4-methoxyphenyl)-3,4-dihydro-6-phenyl-2*H*-pyran-5-carboxylate (3m). white solid, mp = 93–94 °C, ^{1}H NMR ($CDCl_3$): 0.90–1.30 (m, 5H), 1.35–1.60 (m, 4H), 1.62–1.74 (m, 1H), 1.92–2.03 (m, 1H), 2.15–2.24 (m, 1H), 2.46–2.57 (m, 1H), 2.68–2.78 (m, 1H), 3.78 (s, 3H), 4.64 (sept, J = 4.0 Hz, 1H), 4.98 (d, J = 9.2 Hz, 1H), 6.88 (d, J = 8.4 Hz, 2H), 7.25–7.35 (m, 5H), 7.37–7.44 (m, 2H); ^{13}C NMR: 23.3, 23.6, 23.7, 25.4, 29.4, 31.1, 31.5, 55.3, 72.3, 78.6, 104.3, 113.9, 127.5, 127.7, 128.9, 128.9, 132.8, 137.0, 159.4, 163.0, 168.3. IR (cm^{-1}): 2935, 2856, 1682, 1628, 1616, 1597, 1515, 1447, 1358, 1286, 1250, 1178, 1092, 1034, 977, 908, 829, 760, 697. HR-MS: m/z = 392.2020, calcd. for $C_{25}H_{28}O_4$ [M]: 392.1988.

2-Ethylhexyl 2-(4-methoxyphenyl)-3,4-dihydro-6-phenyl-2*H*-pyran-5-carboxylate (3n). colorless liquid, ^{1}H NMR ($CDCl_3$): 0.73 (dd, J_a = 7.2 Hz, J_b = 12.0 Hz, 3H), 0.86 (t, J = 6.8 Hz, 3H), 0.95–1.30 (m, 9H), 1.92–2.03 (m, 1H), 2.16–2.24 (m, 1H), 2.47–2.57 (m, 1H), 2.68–2.78 (m, 1H), 3.72–3.83 (m, 4H), 3.83–3.94 (m, 1H), 4.98 (d, J = 10.0 Hz, 1H), 6.88 (d, J = 8.4 Hz, 2H), 7.27–7.36 (m, 5H), 7.36–7.43 (m, 2H); ^{13}C NMR: 11.0, 11.0, 14.2, 23.0, 23.3, 23.5, 23.6, 29.0, 29.4, 30.2, 30.2, 38.6, 55.3, 66.5, 78.7, 103.9, 113.9, 127.5, 127.8, 128.8, 129.0, 132.8, 137.0, 159.4, 163.3, 169.1. IR (cm^{-1}): 2957, 2930, 2872, 2858, 1687, 1628, 1618, 1515, 1462, 1447, 1356, 1284, 1250, 1204,

1178, 1157, 1091, 1034, 1001, 979, 830, 760, 697. HR-MS: m/z = 422.2481, calcd. for $C_{27}H_{34}O_4$ [M]: 422.2457.

3-Ethoxycarbonyl-2-phenyl-6-(4-ethoxyphenyl)-5,6-dihydropyran (3o). white solid, 96–97 °C, ^{1}H NMR ($CDCl_3$): 0.93 (t, J = 7.2 Hz, 3H), 1.39 (t, J = 7.2 Hz, 3H), 1.92–2.03 (m, 1H), 2.16–2.24 (m, 1H), 2.46–2.57 (m, 1H), 2.68–2.78 (m, 1H), 3.95 (q, J = 7.2 Hz, 2H), 4.00 (q, J = 7.2 Hz, 2H), 4.98 (dd, J_a = 2.0 Hz, J_b = 10.4 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 7.26–7.35 (m, 5H), 7.37–7.43 (m, 2H); ^{13}C NMR: 13.8, 14.9, 23.2, 29.3, 59.9, 63.5, 78.8, 103.9, 114.5, 127.4, 127.7, 128.8, 128.9, 129.0, 132.6, 136.9, 158.8, 163.3, 169.0. IR (cm^{-1}): 2982, 2928, 2902, 1682, 1626, 1515, 1476, 1448, 1394, 1372, 1293, 1251, 1207, 1178, 1156, 1116, 1097, 1045, 813, 773, 761, 702. HR-MS: m/z = 352.1709, calcd. for $C_{22}H_{24}O_4$ [M]: 352.1675.

3-Ethoxycarbonyl-2-phenyl-6-(4-chlorophenyl)-5,6-dihydropyran (3p). colorless liquid, ^{1}H NMR ($CDCl_3$): 0.93 (t, J = 7.2 Hz, 3H), 1.89–2.05 (m, 1H), 2.47–2.61 (m, 1H), 2.68–2.77 (m, 1H), 3.95 (q, J = 7.2 Hz, 2H), 7.29–7.38 (m, 7H), 7.38–7.42 (m, 2H); ^{13}C NMR: 13.8, 22.9, 29.5, 60.0, 78.2, 104.2, 127.4, 127.7, 128.7, 128.9, 129.2, 133.8, 136.6, 139.1, 162.8, 168.7. IR (cm^{-1}): 2980, 2932, 2902, 2852, 1689, 1629, 1597, 1493, 1446, 1471, 1287, 1255, 1203, 1158, 1090, 1036, 1014, 977, 819, 760, 698. HR-MS: m/z = 342.1049, calcd. for $C_{20}H_{19}ClO_3$ [M]: 342.1023.

3-Ethoxycarbonyl-2-phenyl-6-(4-*tert*-butylphenyl)-5,6-dihydropyran (3q). white solid, mp = 104–105 °C, ^{1}H NMR ($CDCl_3$): 0.92 (t, J = 7.2 Hz, 3H), 1.30 (s, 9 H), 1.93–2.07 (m, 1H), 2.18–2.27 (m, 1H), 2.46–2.57 (m, 1H), 2.69–2.77 (m, 1H), 3.95 (q, J = 6.8 Hz, 2H), 5.01 (dd, J_a = 2.0 Hz, J_b = 10.4 Hz, 1H), 7.28–7.35 (m, 5H), 7.35–7.45 (m,. 4H); ^{13}C NMR: 13.8, 23.1, 29.3, 31.4, 34.6, 59.9, 78.9, 104.0, 125.5, 125.9, 127.7, 128.8, 129.0, 136.9, 137.6, 151.0, 163.3, 169.0. IR (cm^{-1}): 2984, 2958, 2903, 1688, 1624, 1594, 1372, 1287, 1155, 1096, 1031, 1000, 977, 922, 834, 761, 700. HR-MS: m/z = 364.2074, calcd. for $C_{24}H_{28}O_3$ [M]: 364.2038.

3-Ethoxycarbonyl-6-(4-fluorophenyl)-6-methyl-2-phenyl-5,6-dihydropyran (3r). colorless liquid, ^{1}H NMR ($CDCl_3$): 0.89 (t, J = 7.2 Hz, 3H), 1.61 (s, 3H), 1.97–2.07 (m, 1H), 2.17–2.32 (m, 2H), 2.48–2.59 (m, 1H), 3.88 (q, J = 7.2 Hz, 2H), 7.03 (t, J = 8.4 Hz, 2H), 7.35–7.40 (m, 5H), 7.41–7.45 (m, 2H); ^{13}C NMR: 13.7, 20.4, 28.9, 32.5, 59.8, 79.7, 103.4, 115.2, 115.4, 126.3, 126.3, 127.8, 128.5, 128.9, 129.0, 137.4, 140.8, 140.8, 160.6, 161.6, 163.1, 168.4. IR (cm^{-1}): 3059, 2980, 2933, 2902, 1690, 1631, 1600, 1510, 1447, 1371, 1297, 1264, 1230, 1201, 1151, 1096, 1033, 1015, 970, 924, 837, 762, 698. HR-MS: m/z = 340.1511, calcd. for $C_{21}H_{21}FO_3$ [M]: 340.1475.

3-Ethoxycarbonyl-6-methyl-2-phenyl-6-(4-chlorophenyl)-5,6-dihydropyran (3s). colorless liquid, ^{1}H NMR ($CDCl_3$): 0.89 (t, J = 6.8 Hz, 3H), 1.59 (s, 3H), 1.96–2.05 (m, 1H), 2.15–2.30 (m, 2H), 2.47–2.57 (m, 1H), 3.88 (q, J = 7.2 Hz, 2H), 7.28–7.34 (m, 3H), 7.34–7.40 (m, 3H), 7.40–7.45 (m, 2H); ^{13}C NMR: 13.7, 20.4, 28.8, 32.3, 59.8, 79.6, 103.5, 126.1, 127.8, 128.6, 128.7, 128.9, 130.0, 133.0, 137.3, 143.6, 161.5, 168.3. IR (cm^{-1}): 2980, 2933, 1689, 1632, 1596, 1492, 1447, 1396, 1372, 1295, 1261, 1152, 1094, 1033, 1013, 970, 828, 765, 740, 698. HR-MS: m/z = 356.1210, calcd. for $C_{21}H_{21}ClO_3$ [M]: 356.1179.

Ethyl 2-butoxy-3,4-dihydro-6-phenyl-2*H*-pyran-5-carboxylate (3t). colorless liquid, ^{1}H NMR ($CDCl_3$): 0.89–0.97 (m, 6H), 1.40 (sext, J = 7.6 Hz, 2H), 1.56–1.67 (m, 2H), 1.84–1.94 (m, 1H), 1.96–2.04 (m, 1H), 2.52 (dd, J_a = 6.0 Hz, J_b = 8.0 Hz, 2H), 3.61 (dd, J_a = 6.8 Hz, J_b = 16.0 Hz, 1H), 3.87–3.97 (m, 3H), 5.21 (bs, 1H), 7.31–7.37 (m, 5H); ^{13}C NMR: 13.7, 13.9, 18.5, 19.4, 26.1, 31.7, 59.8, 68.6, 98.4, 104.5, 127.7, 128.4, 128.8, 137.1, 159.8, 168.4. IR (cm^{-1}): 2959, 2935, 2872, 1692, 1634, 1447, 1370, 1339, 1291, 1245, 1153, 1125, 1057, 953, 900, 834, 761, 697. HR-MS: m/z = 304.1712, calcd. for $C_{18}H_{24}O_4$ [M]: 304.1675.

Diethyl 2-benzoyl-4-(4-methoxybenzoyl)glutarate (5b). white solid, mp = 80–81 °C, ^{1}H NMR ($CDCl_3$): 1.11 (dt, J_a = 4.4 Hz, J_b = 7.2 Hz, 3H), 1.22 (dt, J_a = 4.8 Hz, J_b = 7.2 Hz, 3H), 2.52–2.63 (m, 1.5H), 2.70–2.79 (m, 0.5H), 3.85 (d, J = 8.4 Hz, 3H), 4.06–4.15 (m, 2H), 4.16–4.27 (m, 2H), 4.49–4.56 (m, 2H), 6.95 (dd, J_a = 8.8 Hz, J_b = 14.8 Hz, 2H), 7.43–7.53 (m, 2H), 7.54–7.63 (m, 1H), 8.02–8.08 (m, 4H); ^{13}C NMR: 13.9, 13.9, 14.0, 14.0, 27.8, 28.4, 51.0, 51.3, 51.4, 51.6, 55.5, 55.5, 61.5, 61.5, 61.6, 61.6, 114.0, 128.4, 128.8, 128.9, 128.9, 131.1, 131.3, 133.7, 135.5, 136.0, 164.1, 164.1, 169.3, 169.5, 169.7, 169.8, 193.1, 193.5, 194.9, 195.2. IR (cm^{-1}): 2982, 2937, 1738, 1676, 1599, 1574, 1511, 1447, 1371, 1260, 1176, 1028, 961, 846, 692. HR-MS: m/z = 426.1646, calcd. for $C_{24}H_{26}O_7$ [M]: 426.1679.

1-Ethyl 5-methyl 4-benzoyl-2-(4-methoxybenzoyl)pentanedioate (5c). colorless liquid, ^{1}H NMR ($CDCl_3$): 1.12 (t, J = 7.2 Hz, 1.5H), 1.23 (t, = 7.2 Hz, 1.5H), 2.51–2.64 (m, 1.5H), 2.70–2.79 (m, 0.5H), 3.64 (s, 1.5H), 3.75(s, 1.5H), 3.86 (d, J = 7.2 Hz, 3H), 4.08–4.15 (m, 1H), 4.17–4.27 (m, 1H), 4.51 (t, J = 7.2 Hz, 0.5H), 4.56–4.63 (m, 1H), 4.67 (dd, J_a = 6.4 Hz, J_b = 8.4 Hz, 0.5H), 6.95 (dd, J_a = 8.8 Hz, J_b = 12.4 Hz, 2H), 7.44–7.54 (m, 2H), 7.56–7.64 (m, 1H), 8.02–8.10 (m, 4H); ^{13}C NMR: 13.9, 14.0, 14.2, 27.9, 28.5, 51.0, 51.1, 51.3, 51.4, 52.6, 55.5, 55.6, 61.6, 61.6, 114.0, 128.3, 128.8, 128.9, 128.9, 128.9, 131.3, 131.4, 131.9, 135.3, 135.8, 164.1, 169.5, 169.9, 169.9, 170.3, 193.1, 193.6, 194.9, 195.2. IR (cm^{-1}): 2981, 2955, 2843, 1743, 1679, 1600, 1576, 1512, 1447, 1356, 1308, 1260, 1202, 1175, 1028, 958, 845, 691. HR-MS: m/z = 412.1503, calcd. for $C_{23}H_{24}O_7$ [M]: 412.1522.

Diethyl 2-benzoyl-4-(4-chlorobenzoyl)glutarate (5d). white solid, 86–87 °C, ^{1}H NMR ($CDCl_3$): 1.11 (dt, J_a = 1.6 Hz, J_b = 6.8 Hz, 3H), 1.18–1.26 (m, 3H), 2.50–2.63 (m, 1.5 H), 2.69–2.79 (m, 0.5H), 4.05–4.15 (m, 2H), 4.16–4.28 (m, 2H), 4.48–4.66 (m, 2H), 7.41–7.53 (m, 4H), 4.56–4.64 (m, 1H), 8.01 (dd, J_a = 1.6 Hz, J_b = 8.8 Hz, 2H), 8.05 (d, J = 8.4 Hz, 2H); ^{13}C NMR: 13.9, 14.0, 14.0, 14.0, 14.2, 27.5, 28.1, 51.2, 51.3, 51.4, 51.5, 61.7, 61.7, 61.8, 61.8, 128.8, 128.8, 128.9, 129.2, 130.3, 130.4, 133.8, 133.9, 134.2, 135.4, 135.9, 140.4, 140.4, 169.1, 169.3, 169.4, 169.7, 193.7, 194.0, 194.7, 195.1. IR (cm^{-1}): 2983, 2938, 1740, 1685, 1590, 1448, 1400, 1370, 1251, 1198, 1159, 1094, 1031, 1014, 962, 846, 691. HR-MS: m/z = 430.1221, calcd. for $C_{23}H_{23}ClO_6$ [M]: 430.1183.

Diethyl 2-benzoyl-4-(4-trifluorobenzoylglutarate (5e). white solid, mp = 80–82 °C, ^{1}H NMR ($CDCl_3$): 1.12 (t, J = 7.2 Hz, 2H), 1.18–1.28 (m, 4H), 2.54–2.67 (m, 1.6H), 2.72–2.82 (m, 0.4H), 4.06–4.16 (m, 2H), 4.17–4.28 (m, 2H), 4.58 (t, J = 7.2 Hz, 0.6H), 4.66 (q, J = 1.4H), 7.44–7.54 (m, 2H), 7.56–7.64 (m, 1H),

7.72–7.81 (m, 2H), 8.05 (d, J = 7.6 Hz, 2H), 8.18 (d, J = 8.0 Hz, 2H); ^{13}C NMR: 13.8, 13.9, 14.0, 27.4, 28.0, 51.2, 51.3, 51.5, 51.8, 61.0, 61.8, 61.9, 61.9, 125.8, 125.8, 125.9, 125.9, 126.9, 128.8, 128.9, 128.9, 129.2, 129.3, 133.9, 134.7, 135.0, 135.3, 135.8, 138.2, 168.9, 169.2, 169.3, 169.7, 194.1, 194.4, 194.7, 195.1. IR (cm^{-1}): 2987, 2942, 1742, 1690, 1598, 1582, 1450, 1412, 1372, 1327, 1253, 1170, 1130, 1067, 1015, 963, 855, 690, 595. HR-MS: m/z = 464.1409, calcd. for $C_{24}H_{23}F_3O_6$ [M]: 464.1447.

Diethyl 2-benzoyl-4-(2-thenoyl)glutarate (5f). white solid, mp = 82–83 °C, ^{1}H NMR ($CDCl_3$): 1.10–1.27 (m, 6H), 2.56–2.67 (m, 1.5H), 2.70–2.79 (m, 0.5H), 4.06–4.16 (m, 2H), 4.18–4.28 (m, 2H), 4.42 (t, J = 7.2 Hz, 0.5H), 4.47 (dd, J_a = 6.0 Hz, J_b = 9.2 Hz, 0.5H), 4.54 (t, J = 7.6 Hz, 0.5H), 4.62 (dd, J_a = 5.6 Hz, J_b = 8.8 Hz, 0.5H), 7.13 (dd, J_a = 4.0 Hz, J_b = 4.8 Hz, 0.5H), 7.18 (dd, J_a = 4.0 Hz, J_b = 4.8 Hz, 0.5H), 7.44–7.53 (m, 2H), 7.55–7.64 (m, 1H), 7.69 (dd, J_a = 0.8 Hz, J_b = 4.8 Hz, 0.5H), 7.73 (dd, J_a = 1.2 Hz, J_b = 5.2 Hz, 0.5H), 7.93 (dd, J_a = 0.8 Hz, J_b = 4.0 Hz, 0.5H), 7.96 (dd, J_a = 0.8 Hz, J_b = 3.6 Hz, 0.5H), 8.02–8.08 (m, 2H); ^{13}C NMR: 13.9, 13.9, 14.0, 14.0, 27.8, 28.5, 51.2, 51.5, 52.5, 52.7, 61.7, 61.7, 61.8, 61.8, 128.5, 128.8, 128.8, 128.9, 133.8, 133.9, 134.0, 135.4, 135.4, 135.8, 142.7, 143.2, 168.9, 169.2, 169.3, 169.7, 187.4, 187.7, 194.8, 195.1. IR (cm^{-1}): 3094, 2982, 1735, 1660, 1516, 1447, 1412, 1369, 1355, 1252, 1188, 1159, 1094, 1059, 1030, 946, 852, 732, 692, 619, 590. HR-MS: m/z = 402.1102, calcd. for $C_{21}H_{22}O_6S$ [M]: 402.1137.

1-Ethyl 5-methyl 2,4-bisbenzoylpentanedioate (5g). white solid, mp = 86–88 °C, ^{1}H NMR ($CDCl_3$): 1.10 (t, J = 6.8 Hz, 1.4H), 1.23 (t, J = 7.2 Hz, 1.6H), 2.52–2.65 (m, 1.5H), 2.71–2.80 (m, 0.5H), 3.63 (s, 1.5H), 3.75 (s, 1.5H), 4.05–4.15 (m, 1H), 4.16–4.27 (m, 1H), 4.58 (td, Ja = 7.2 Hz, Jb = 20.4 Hz, 1H), 4.67 (quint, J = 6.8 Hz, 1H), 7.44–7.54 (m, 4H), 7.55–7.64 (m, 2H), 8.06 (d, J = 7.6 Hz, 4H); ^{13}C NMR: 13.9, 14.0, 14.2, 27.8, 28.3, 51.0, 51.3, 51.3, 51.5, 52.7, 61.7, 61.7, 128.8, 133.9, 133.9, 133.9, 135.3, 135.4, 135.8, 135.8, 169.3, 169.7, 169.8, 170.2, 194.8, 195.1. IR (cm^{-1}): 2953, 1745, 1680, 1596, 1581, 1449, 1436, 1372, 1256, 1203, 1186, 1164, 1094, 1068, 1037, 962, 781, 725, 692, 617. HR-MS: m/z = 382.1450, calcd. for $C_{22}H_{22}O_6$ [M]: 382.1416.

Methyl α-benzoyl-3-[2-(ethoxycarbonyl)-1*H*-indol-3-yl]propanoate (7a). red solid, mp = 140–141 °C, ^{1}H NMR ($CDCl_3$): 1.35 (t, J = 7.2 Hz, 3H), 3.53 (s, 3H), 3.79 (q, J = 4.4 Hz, 2H), 4.39 (dq, J_a = 2.0 Hz, J_b = 7.2, 2H), 4.29 (t, J = 7.2 Hz, 1H), 7.13 (td, J_a = 1.6 Hz, J_b = 6.0 Hz, 1H), 7.25–7.33 (m, 2H), 7.37 (t, J = 8.0 Hz, 2H), 7.50 (t, J = 7.6 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 7.2 Hz, 2H), 8.85 (bs, 1H); ^{13}C NMR: 14.4, 24.5, 52.5, 54.8, 61.0, 111.6, 120.5, 120.6, 121.2, 123.9, 125.8, 127.9, 128.6, 128.6, 133.4, 135.7, 136.3, 161.9, 170.1, 195.0. IR (cm^{-1}): 3314, 2943, 1725, 1687, 1541, 1461, 1435, 1340, 1282, 1256, 1232, 1210, 1159, 1020, 954, 779, 737, 692. HR-MS: m/z = 380.1493, calcd. for $C_{22}H_{22}NO_5$ [M + H$^+$]: 380.1498.

Ethyl α-benzoyl-3-[2-(ethoxycarbonyl)-1*H*-indol-3-yl]propanoate (7b). red solid, mp = 118–119 °C, ^{1}H NMR ($CDCl_3$): 0.99 (t, J = 7.2 Hz, 3H), 1.33 (t, J = 7.2 Hz, 3H), 3.80 (dd, J_a = 3.2 Hz, J_b = 8.0 Hz, 2H), 3.98 (q, J = 8.8 Hz, 2H), 4.38 (dq, J_a = 1.6 Hz, J_b = 7.2 Hz, 2H), 4.90 (t, J = 7.2 Hz, 1H), 7.11 (td, J_a = 0.8 Hz, J_b = 7.6 Hz, 1H), 7.23–7.29 (m, 2H), 7.36 (t, J = 8.0 Hz, 2H), 7.45–7.50 (m, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 7.2 Hz, 2H), 9.19 (bs, 1H); ^{13}C NMR: 55.1, 61.1, 61.4, 111.7, 120.4, 120.7, 121.2, 123.9, 125.7, 127.9, 128.5, 128.5, 128.6, 130.2, 133.4, 133.7, 135.9, 136.4, 162.2, 169.8, 195.2. IR (cm^{-1}): 3313, 2981, 1717, 1687, 1540, 1460, 1448, 1368, 1340, 1257, 1232, 1212, 1161, 1025, 741, 689. HR-MS: m/z = 394.1622, calcd. for $C_{23}H_{24}NO_5$ [M + H$^+$]: 394.1654.

Ethyl α-(4-methylbenzoyl)-3-[2-(ethoxycarbonyl)-1*H*-indol-3-yl]propanoate (7c). red solid, mp = 135–136 °C, ^{1}H NMR ($CDCl_3$): 0.99 (t, J = 7.2 Hz, 3H), 1.35 (t, J = 6.8 Hz, 3H), 2.36 (s, 3H), 3.77 (ddd, J_a = 8.0 Hz, J_b = 13.6 Hz, J_c = 20.0 Hz, 2H), 3.96 (q, J = 7.2 Hz, 2H), 4.38 (dq, J_a = 1.2 Hz, J_b = 7.2 Hz, 2H), 4.86 (t, J = 8.6 Hz, 1H), 7.12 (dt, J_a = 1.2 Hz, J_b = 6.4 Hz, 1H), 7.18 (d, J = 2.0 Hz, 2H), 7.24–7.34 (m, 2H), 7.76 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.0 Hz, 2H), 8.93 (bs, 1H); ^{13}C NMR: 13.8, 14.4, 21.7, 24.3, 55.0, 61.0, 61.4, 111.6, 120.4, 120.8, 121.3, 123.8, 125.7, 128.0, 128.8, 129.2, 133.9, 135.7, 144.3, 162.0, 169.8, 194.6. IR (cm^{-1}): 3319, 2980, 2934, 1715, 1688, 1607, 1537, 1455, 1371, 1339, 1257, 1214, 1168, 1100, 1019, 744. HR-MS: m/z = 430.1663, calcd. for $C_{24}H_{25}NNaO_5$ [M + Na$^+$]: 430.1630.

Ethyl α-(4-chlorobenzoyl)-3-[2-(ethoxycarbonyl)-1*H*-indol-3-yl]propanoate (7d). red solid, mp = 140–142 °C, ^{1}H NMR ($CDCl_3$): 1.00 (t, J = 7.2 Hz, 3H), 1.36 (t, J = 7.2 Hz, 3H), 3.77 (q, J = 2.0 Hz, 2H), 3.98 (q, J = 7.2 Hz, 2H), 4.39 (q, J = 6.8 Hz, 2H), 4.87 (t, J = 7.2 Hz, 1H), 7.12 (t, J = 7.2 Hz, 1H), 7.25–7.36 (m, 4H), 7.74 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 8.4 Hz, 2H), 8.99 (bs, 1H); ^{13}C NMR: 13.8, 14.4, 24.3, 55.0, 61.0, 61.5, 111.7, 120.4, 120.5, 121.2, 123.8, 125.8, 127.9, 128.0, 128.8, 130.0, 134.7, 135.7, 140.0, 161.9, 169.5, 194.1. IR (cm^{-1}): 3313, 2979, 1718, 1689, 1590, 1537, 1459, 1399, 1368, 1338, 1283, 1254, 1211, 1161, 1096, 1026, 981, 899, 835, 745, 685. HR-MS: m/z = 428.1270, calcd. for $C_{23}H_{23}ClNO_5$ [M + H$^+$]: 428.1265.

Ethyl α-(4-methoxybenzoyl)-3-(1-methyl-2-phenylindol-3-yl)-propanoate (7e). gum-like material, ^{1}H NMR ($CDCl_3$): 0.97 (t, J = 7.2 Hz, 3H), 3.38 (dd, J_a = 6.4 Hz, J_b = 10.8 Hz, 1H), 3.51 (s, 3H), 3.54 (dd, J_a = 6.4 Hz, J_b = 10.8 Hz, 1H), 3.81 (s, 3H), 3.84–3.96 (m, 2H), 4.46 (dd, J_a = 6.0 Hz, J_b = 7.6 Hz, 1H), 6.77 (td, J_a = 2.8 Hz, J_b = 8.8 Hz, 2H), 7.15 (t, J = 8.0 Hz, 1H), 7.23 (t, J = 8.4 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.34 (dd, J_a = 1.6 Hz, J_b = 8.0 Hz, 2H), 7.42–7.51 (m, 3H), 7.66 (td, J_a = 2.0 Hz, J_b = 7.2 Hz, 2H), 7.70 (d, J = 8.0 Hz, 1H); ^{13}C NMR: 13.8, 24.2, 30.7, 54.8, 55.5, 61.2, 109.3, 109.4, 113.7, 119.2, 119.5, 121.7, 127.5, 128.4, 128.6, 129.2, 130.7, 130.9, 131.9, 137.0, 138.7, 163.6, 169.8, 193.6. IR (cm^{-1}): 3054, 2977, 2936, 2841, 1733, 1676, 1600, 1575, 1511, 1468, 1366, 1332, 1260, 1230, 1172, 1028, 912, 843, 742, 704, 560. HR-MS: m/z = 442.2053, calcd. for $C_{28}H_{28}NO_4$ [M + H$^+$]: 442.2018.

Ethyl α-(4-methoxybenzoyl)-3-(1-ethyl-2-phenylindol-3-yl)-propanoate (7f). gum-like material, ^{1}H NMR ($CDCl_3$): 0.98 (t, J = 7.2 Hz, 3H), 1.13 (t, J = 6.8 Hz, 3H), 3.32 (dd, J_a = 6.4 Hz, J_b = 10.8 Hz, 1H), 3.51 (dd, J_a = 6.4 Hz, J_b = 10.8 Hz, 1H), 3.80 (s, 3H), 3.87–3.99 (m, 4H), 4.46 (dd, J_a = 6.0 Hz, J_b = 8.0 Hz, 1H), 6.75 (td, J_a = 2.8 Hz, J_b = 10.0 Hz, 2H), 7.14 (t, J = 8.0 Hz, 1H), 7.21 (dt, J_a = 1.2 Hz, J_b = 8.0 Hz, 1H), 7.29–7.35 (m, 3H), 7.42–7.51 (m, 3H), 7.62 (td, J_a = 2.8 Hz, J_b = 9.6 Hz, 2H), 7.70 (d, J = 8.0 Hz, 1H); ^{13}C NMR: 13.9, 15.4, 24.2, 38.5, 54.7, 55.5, 61.1, 109.5, 109.6, 113.6, 119.3, 119.4, 121.6, 127.8, 128.4, 128.7, 129.2, 130.7, 130.9, 132.1, 135.7, 138.2, 163.6, 169.8, 193.7. IR (cm^{-1}): 3055, 2978, 2935, 2841, 1734, 1676,

1600, 1575, 1511, 1464, 1341, 1261, 1232, 1217, 1172, 1028, 843, 743, 703. HR-MS: m/z = 456.2197, calcd. for $C_{29}H_{30}NO_4$ [M + H^+]: 456.2175.

Ethyl α-[(benzoylamino)methyl]-β-oxo-benzenepropanoate (9a). gum-like material, ^{1}H NMR (CD_3COCD_3): 1.13 (t, J = 7.2 Hz, 3H), 3.94–3.40 (m, 2H), 4.12 (q, J = 7.2 Hz, 2H), 5.06 (t, J = 7.2 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.50 (d, J = 7.2 Hz, 1H), 7.55 (t, J = 7.6 Hz, 2H), 7.85 (dd, J_a = 1.2 Hz, J_b = 8.4 Hz, 2H), 8.03 (bs, 1H), 8.12 (dd, J_a = 1.6 Hz, J_b = 7.2 Hz, 2H); ^{13}C NMR: 13.4, 39.3, 53.2, 61.1, 127.1, 128.3, 128.6, 128.9, 131.3, 133.8, 134.5, 136.3, 167.2, 168.6, 194.4. IR (cm^{-1}): 3346, 3063, 2982, 2938, 1736, 1683, 1648, 1599, 1580, 1532, 1487, 1449, 1370, 1294, 1257, 1211, 1184, 1158, 1096, 1027, 714, 692. HR-MS: m/z = 326.1366, calcd. for $C_{19}H_{20}NO_4$ [M + H^+]: 326.1392.

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