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I_2-Catalyzed Direct α-Hydroxylation of β-Dicarbonyl Compounds with Atmospheric Oxygen under Photoirradiation

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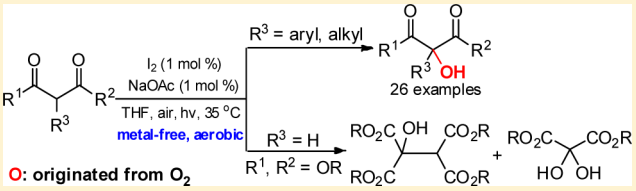
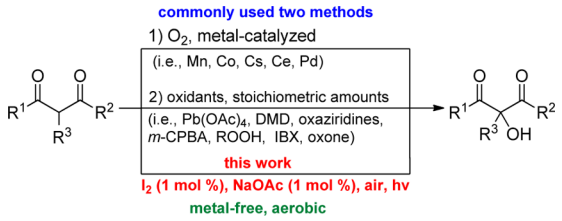
Supporting Information

ABSTRACT: An I_2-catalyzed hydroxylation of β-dicarbonyl moieties using air as the oxidant under photoirradiation has been developed for the easy preparation of α-hydroxy-β-dicarbonyl compounds. The transformation was completed with only 1 mol % of I_2. With α-unsubstituted malonates, the hydroxylated dimerization product was afforded as the predominant product along with a minor product, α,α-dihydroxyl malonate.



The α-hydroxy-β-dicarbonyl compounds are useful synthetic intermediates and common structural units in many natural products and pharmaceutical compounds.[1] To date, a number of methods have been developed to prepare the α-hydroxy-β-dicarbonyl moieties.[2] Recently, the asymmetric α-hydroxylation of β-dicarbonyl compounds has gained increased attention.[3] The commonly used strategy is the direct oxidation of the corresponding β-dicarbonyl compounds with various oxidants (i.e., MoOPH,[4] OsO_4,[5] $Pb(OAc)_4$,[6] *m*-CPBA,[7] DMD,[8] oxaziridines,[9] IBX,[10] oxone,[11] ROOH,[3d,12] H_2O_2[13]), or molecular oxygen catalyzed by a transition-metal catalyst (i.e., Mn,[14] Co,[15] Cs,[16] Ce,[17] Pd[18]) (Scheme 1). Nevertheless, the

Scheme 1



required stoichiometric amounts of organic oxidants or heavy metals present disadvantages of high costs of materials and the need to dispose of toxic byproducts. Thus, from an economical and ecological point of view, the air oxidation of β-dicarbonyl compounds catalyzed by Mn, Co, Ce, Cs, and Pd salts is optimal. However, these reactions are still limited by the restricted scope of substrates, the requirement for a metal catalyst loading of at least 5 mol %, and the need for an oxygen atmosphere (1 atm). Recently, the direct transformation of β-ketoesters to α-hydroxymalonate with molecular oxygen catalyzed by CaI_2 under photoirradiation through a tandem oxidation/rearrangement process was reported. In this procedure, the substrates were limited to the α-unsubstituted β-ketoesters.[2c] The combination of I_2 and *t*-BuOK has been reported to initiate the oxidative degradation of arylacetoacetates to generate α-ketoesters as the major product accompanied by the formation of minor α-hydroxylation products (<10% yield).[19] In view of the limitations of the existing methods, we report here a metal-free and air oxidative methodology for the α-hydroxylation of β-dicarbonyl moieties catalyzed by I_2 under photoirradiation (Scheme 1).

The use of I_2 as an inexpensive and efficient reagent in organic transformations has been well documented.[20] We recently reported a directly air oxidative α-hydroxylation of α-substituted diethyl malonates using I_2 and NaOAc (0.2 equiv for each) in THF.[21] However, only the Michael adducts of malonates with enones were used in the research. In continuation of our research on I_2 chemistry,[21,22] we attempted to explore a general methodology to realize the α-hydroxylation of other common β-dicarbonyl compounds using an I_2/NaOAc system.

We commenced our investigation of the hydroxylation of β-ketoester **1a** by stirring together at room temperature a mixture of **1a** (1 mmol), NaOAc (0.2 mmol), and iodine (0.2 mmol) in THF (10 mL). In our initial studies, we noted that the reaction had poor reproducibility. Sometimes **1a** could be completely transformed to **2a** within 12 h, while at other times a low conversion of **1a** to **2a** (<25%) was achieved even after stirring for 4 days. Later on, we determined that conversion was related to the light intensity. The reaction proceeded better under strong light than in the dark. When the reaction was carried out under the irradiation of a 300 W high pressure lamp at 35 °C, the reaction was completed within 1 h and gave the desired product **2a** in 95% yield. We then proceeded to optimize the other conditions of the transformation (Table 1).

The influence of the molar ratio of **1a**:I_2:base on the reaction was first investigated (Table 1, entries 1−4). The results showed that 1 mol % of I_2 and 1 mol % of NaOAc were enough to give a high yield of **2a** (94%, entry 4), albeit a longer reaction

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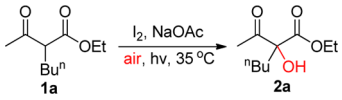
Table 1. Optimization of Reaction Conditions for the Synthesis of 2a[a]



entry	base	molar ratio [1a:I_2:base]	solvent	time (h)	yield[b] (%)
1	NaOAc	1:0.2:0.2	THF	1	95
2	NaOAc	1:0.05:0.05	THF	2	93
3	NaOAc	1:0.02:0.02	THF	3	94
4	**NaOAc**	**1:0.01:0.01**	**THF**	**4**	**94**
5	NaOAc	1:0.01:0.01	THF	48	trace[c]
6	NaOAc	1:0:0.01	THF	4	0
7	NaOAc	1:0.01:0	THF	4	0
8	Na_2CO_3	1:0.01:0.01	THF	5	93
9	NaOH	1:0.01:0.01	THF	10	92
10	TEA	1:0.01:0.01	THF	10	trace
11	pyridine	1:0.01:0.01	THF	10	trace
12	NaOAc	1:0.01:0.01	dioxane	10	19
13	NaOAc	1:0.01:0.01	EtOAc	10	29
14	NaOAc	1:0.01:0.01	$CHCl_3$	10	15
15	NaOAc	1:0.01:0.01	CH_3CN	10	10
16	NaOAc	1:0.01:0.01	EtOH	10	13
17	NaOAc	1:0.01:0.01	DMF	10	88
18	NaOAc	1:0.01:0.01	DMSO	10	trace

[a]Unless otherwise noted, all the reactions were performed with **1a** (1 mmol) and proper additives in 10 mL of solvents, simultaneously bubbled with air through a capillary column and irradiated with a 300 W high pressure mercury lamp at 35 °C. [b]Isolated yield. [c]The reaction was carried out under dark conditions.

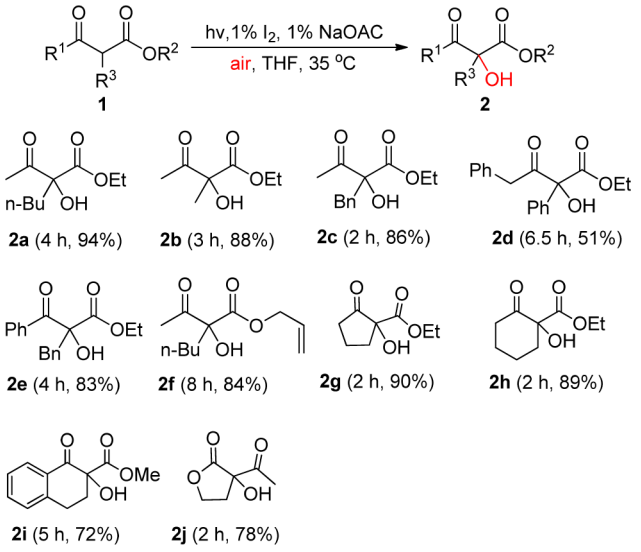
time (4 h) was needed. Both I_2 and NaOAc were essential for the successful hydroxylation of **1a** (Table 1, entries 6 and 7). Photoirradiation also played an essential role; that is, only a trace conversion to **2a** occurred under dark conditions after 48 h (Table 1, entry 5). Other organic or inorganic bases were also examined. The inorganic bases such as Na_2CO_3 or NaOH were the more efficient base (Table 1, entries 8 and 9). Attempts to use triethylamine or pyridine were unsuccessful, generating only traces of **2a** (Table 1, entries 10 and 11). Among the typical solvents, THF was found to be the most effective. Although DMF afforded an acceptable 88% yield of **2a**, the solvent had a high boiling point and was hard to remove. Overall, the most efficient and environmentally friendly method to prepare a high yield of **2a** involved using only 1 mol % of I_2 and 1 mol % of NaOAc in THF under photoirradiation (Table 1, entry 4). Compared to our previous work,[21] the reaction time was shortened (4 h vs 48 h) and the loading of iodine was decreased greatly (1% vs 20%).

Under the optimal reaction conditions, we examined the scope and generality of this kind of transformation using various β-ketoester compounds (Scheme 2). 2-Alkyl β-ketoesters **1a**–**c**, **1e**, and **1f** were efficiently converted to the corresponding tertiary alcohols **2a**–**c**, **2e**, and **2f** in excellent yields within 2–8 h (83–94%). The double bonds were also tolerated in this reaction (**2f**). In the case of the product **2d**, the yield was only 51% due to the incomplete conversion of **1d** and formation of some byproducts. Gratifyingly, the cyclic substrates also gave the alcohol products **2g**–**2j** in good yields (72–90%).

The use of 2-substituted malonates **3** demonstrated the broad applicability of the I_2-catalyzed hydroxylation (Scheme 3). The reaction proceeded smoothly to afford the corresponding α-hydroxylated products **4a**–**4k** (except **4f**) in moderate to excellent yields (56–96%). Although a hydroxyl group could be successively introduced to 2-propargyl malonate **3e** to produce **4e** in 90% yield, 2-allyl malonate **3f** failed to give the expected product **4f**. Alkynyl, carbonyl, nitro, and cyano groups were also compatible with the reaction conditions (**4e** and **4g**–**i**). Furthermore, 2-aminodo substituted malonates **3j** and **3k** also gave the α-hydroxyl malonates **4j**[23] and **4k**[23] in moderate yields.

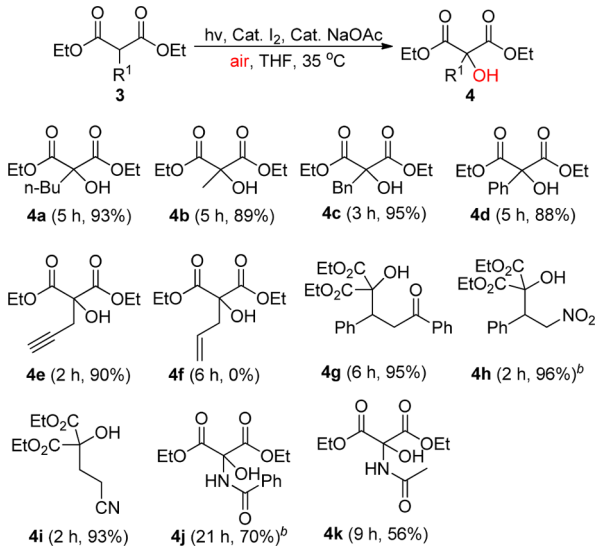
To demonstrate the further synthetic utility of this hydroxylation system, more 1,3-dicarbonyl compounds were

Scheme 2. I_2-Catalyzed α-Hydroxylation of 2-Substituted β-Keto Esters[a]



[a]Reaction conditions: **1** (1 mmol), I_2 (0.01 mmol), NaOAc (0.01 mmol), THF (10 mL), and 300 W high pressure mercury lamp.

Scheme 3. I_2-Catalyzed α-Hydroxylation of 2-Substituted Malonates[a]



[a]Reaction conditions: **1** (1 mmol), I_2 (0.01 mmol), NaOAc (0.01 mmol), THF (10 mL), and 300 W high pressure mercury lamp. [b] 0.05 mmol of I_2 and 0.05 mmol of NaOAc were used.

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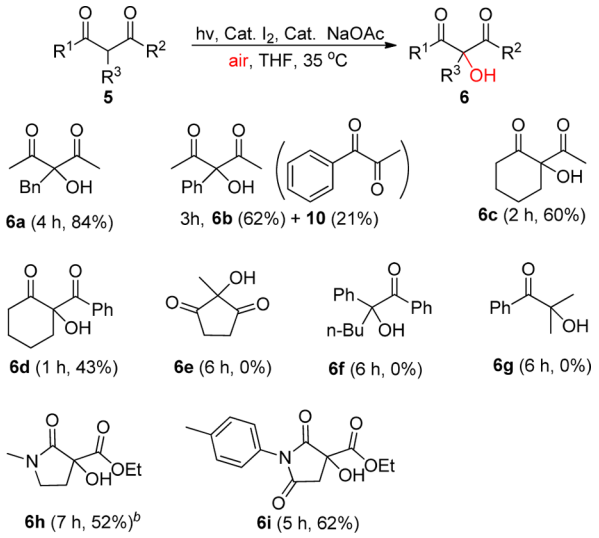
tested (Scheme 4). β-Diketones **5a**−**5d** were smoothly transformed to **6a**−**6d**. As for 3-phenyl acetylacetone **5b**, the

Scheme 4. α-Hydroxylation of β-Dicarbonyl Compounds Catalyzed by I_2[a]

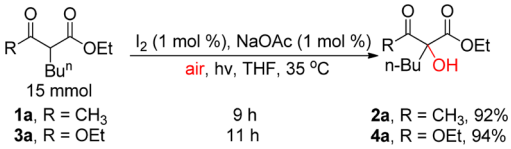


[a]Reaction conditions: **1** (1 mmol), I_2 (0.01 mmol), NaOAc (0.01 mmol), THF (10 mL), and 300 W high pressure mercury lamp. [b] 0.05 mmol of I_2 and 0.05 mmol of NaOAc were used.

desired hydroxylated product **6b** was obtained in 62% yield along with the formation byproduct **10**[24] in 21% yields. Although the quantitative conversion of **5c** and **5d** was observed on TLC, the isolated yields of products **6c** and **6d** were relatively low. The cyclic β-diketone **5e** and the simple ketones **5f** and **5g**, with only one carbonyl group failed to give the product. Fortunately, α-ethoxycarbonyl cyclic amides **5h** and **5i** both produced the corresponding products **6h** and **6i** in 52% and 62% yields, respectively.

In order to show the practicality of the developed method, we further performed large-scale I_2-catalyzed hydroxylation with 15 mmol of **1a** or **3a** in 30 mL of THF (Scheme 5). In

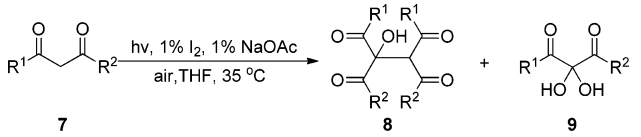
Scheme 5

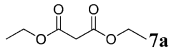
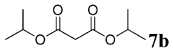
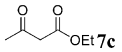
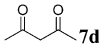


order to reduce the use of solvent, the concentration was 5 times to that of the 1 mmol scale. An excellent yield of **2a** (92%) and **4a** (94%) also could be achieved according to the same procedure although the complete conversion needed a longer time (9 and 11 h, respectively).

In the above I_2-catalyzed hydroxylation, only the α-substituted β-dicarbonyl compounds were investigated. We questioned if the reaction could proceed with α-unsubstituted β-dicarbonyl compounds under similar conditions. Consequently, we treated the diethyl malonate **7a** with 1 mol % of I_2 and 1 mol % of NaOAc in THF under the similar conditions (Table 2). After 4.5 h, complete conversion of **7a** was observed and a main product **8a** along with minor product **9a** was isolated. Through NMR and HRMS spectroscopy analysis, **8a**

Table 2. Aerobic Oxidation of Unsubstituted β-Dicarbonyl Compounds Catalyzed by I_2[a]



entry	Substrate	time (h)	product yield (%)[b]	
1	 7a	7	**8a** (70)[25]	**9a** (22)
2	 7b	4	**8b** (68)[25]	**9b** (16)
3	 7c	6	100% conversion, complex mixture	
4	 7d	3	100% conversion, complex mixture	

[a]A mixture of **7** (1 mmol), I_2, and NaOAc in 10 mL of THF was irrradiated with 300 W high pressure mercury lamp at 35 °C, simultaneously bubbled air through a capillary column. [b]Isolated yields.

was identified as the hydroxylated dimerization product and **9a** was α,α-dihydroxyl diethyl malonate. In comparison to the $Mn(OAc)_3$-catalyzed dimerization of malonate in HOAc with the addition of large amounts of Ac_2O and KOAc,[25] our procedure was a much greener approach with easier handling. The dehydration of the alcohol **8a** could easily afford the tetra-acceptor-substituted alkene,[25] which possessed unique electronic properties and was difficult to prepare. Diisopropyl malonate **7b** could also afford the hydroxylated dimerization product **8b** and α,α-dihydroxyl diisopropyl malonate **9b**. When ethyl acetoacetate **7c** and acetylacetone **7d** were employed in the reaction, TLC indicated that complete conversion to a single product had occurred. However, the NMR analysis showed both of the products were present as complex mixtures.

The reaction mechanism for the generation of α-hydroxy-β-dicarbonyl compounds **2**, **4**, and **6** is similar to our previous research.[21] In the presence of I_2 and NaOAc, the β-dicarbonyl compounds **1** are transformed to the crucial intermediate **A**, which undergoes homolytic cleavage of the C−I bond to generate the carbon radical **B** (Scheme 6). Insertion of molecular oxygen to the species **B** followed by coupling with iodine radical furnishes the iodoperoxide **D**. Homolytic O−O bond cleavage of **D** produces oxygen radical **E**, and follow-up trapping by the iodine radical forms hypoiodite **F**, which acts as a good electrophonic reagent (I^+). **F** reacts with the β-dicarbonyl compound **1**, **3**, or **5** to afford α-hydroxyl product **2**, **4**, or **6** and the intermediate **A**, which undergoes the next cycle. The photoirradiation is favorable to the key step of C−I bond cleavage, which results in an obvious acceleration effect on the reaction and low demand of the iodine catalyst. For the α-unsubstituted malonates, elimination of HOI from **D** affords **G**, which reacts with malonate to generate **8** or water to form **9**, respectively. Reaction of HOI with malonate provides **H**, which enters into the next catalytic cycle.

In summary, we have developed an I_2-catalyzed air oxidation of β-dicarbonyl compounds under photoirradiation for the easy preparation of α-hydroxy-β-dicarbonyl compounds. The present method shows wide applicability and good functional group tolerance. It is particularly noteworthy that the method is

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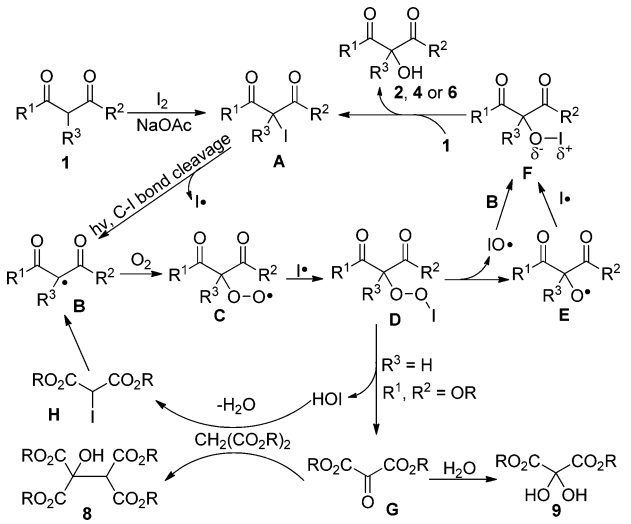
Scheme 6. Possible Reaction Mechanism[a]



[a]One of the reviewers proposed an alternative mechanism. They thought that peroxy radical **C** would abstract a hydrogen atom from the solvent THF, but not combine with the iodine radical to form iodoperoxide **D** (see Supporting Information for the mechanism discussion).

consistent with the principles of green chemistry due to its metal-free conditions, low loading of catalyst, and the use of atmospheric oxygen as the oxidant, which makes the synthesis more efficient, economical, and ecologically friendly.

EXPERIMENTAL SECTION

General Procedure for the I_2-Catalyzed Direct α-Hydroxylation of β-Dicarbonyl Compounds. The reaction was performed on an XPA-7 photochemical reactor (http://www.njxu.com). A mixture of the β-dicarbonyl compounds (**1**, **3**, **5**, or **7**, 1 mmol), I_2 (0.01 mmol, 10 μL × 1 mol·mL^{-1} THF solution of I_2), and NaOAc (0.01 mmol, 10 μL × 1 mol·mL^{-1} aqueous solution of NaOAc) were stirred in 10 mL of THF in a quartz tube (ø 18 mm × 180 mm) at 35 °C under the irradiation of a 300 W high pressure mercury lamp for a given time. Simultaneously, the solution was bubbled with an air pump through a capillary column. Upon completion of the reaction detected by TLC, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether) to provide the corresponding products **2**, **4**, **6**, **8**, or **9**.

2a:[17b] Colorless oil, 189.1 mg, 94%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21−4.31 (m, 2H), 4.17 (s, 1H), 2.29 (s, 3H), 2.04−2.14 (m, 1H), 1.86−1.96 (m, 1H), 1.30 (t, J = 7.2 Hz, 3H), 1.18−1.40 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.2, 171.1, 84.3, 62.7, 35.0, 25.3, 24.8, 22.8, 14.2, 14.0.

2b:[18a] Colorless oil, 141.2 mg, 88%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.26 (q, J = 7.2 Hz, 2H), 4.19 (s, 1H), 2.28 (s, 3H), 1.60 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.0, 171.4, 81.0, 62.7, 24.2, 21.8, 14.0.

2c:[18a] Colorless oil, 203.4 mg, 86%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20−7.30 (m, 5H), 4.23 (q, J = 7.2 Hz, 2H), 4.06 (s, 1H), 3.42 (d, J = 14.2 Hz, 1H), 3.18 (d, J = 14.2 Hz, 1H), 2.29 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.1, 170.6, 134.7, 130.2, 128.3, 127.2, 84.3, 62.9, 40.8, 25.2, 14.1.

2d: Colorless oil, 152.8 mg, 51%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57−7.61 (m, 2H), 7.37−7.44 (m, 3H), 7.20−7.28 (m, 3H), 7.02−7.05 (m, 2H), 4.71 (s, 1H), 4.33 (dq, J = 10.7, 7.1 Hz, 1H), 4.24 (dq, J = 10.7, 7.1 Hz, 1H), 3.86 (s, 2H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.3, 170.6, 135.8, 133.8, 129.7, 128.9, 128.6, 128.5, 127.0, 126.7, 84.6, 63.3, 43.9, 14.1; HRMS-MALDI-TOF m/z: [M+Na]$^+$ Calcd for $C_{18}H_{18}NaO_4$ 321.1103; Found 321.1097.

2e: Colorless oil, 247.0 mg, 83%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95−7.99 (m, 2H), 7.59 (tt, J = 7.4, 1.3 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.20−7.25 (m, 3H), 7.05−7.11 (m, 2H), 4.21 (q, J = 7.1 Hz, 2H), 4.19 (s, 1H), 3.56 (d, J = 14.1 Hz, 1H), 3.44 (d, J = 14.2 Hz, 1H), 1.17 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.9, 171.6, 134.5, 134.3, 133.6, 130.5, 129.5, 128.7, 128.2, 127.2, 82.5, 62.8, 42.0, 14.0; HRMS-MALDI-TOF m/z: [M+K]$^+$ Calcd for $C_{18}H_{18}KO_4$ 337.0842; Found 337.0837.

2f: Colorless oil, 179.9 mg, 84%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (ddt, J = 17.0, 10.4, 5.8 Hz, 1H), 5.27−5.38 (m, 2H), 4.68 (d, J = 5.8 Hz, 2H), 4.18 (s, 1H), 2.29 (s, 3H), 2.05−2.15 (m, 1H), 1.88−1.98 (m, 1H), 1.15−1.40 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.1, 170.7, 131.1, 119.6, 84.4, 66.9, 35.1, 25.3, 24.8, 22.7, 13.9; HRMS-MALDI-TOF m/z: [M+Na]$^+$ Calcd for $C_{11}H_{18}NaO_4$ 237.1103; Found 237.1110.

2g:[18a] Colorless oil, 155.1 mg, 90%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19−4.34 (m, 2H), 3.68 (s, 1H), 2.43−2.56 (m, 3H), 2.05−2.18 (m, 3H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.6, 171.7, 79.8, 62.6, 35.9, 34.9, 18.4, 14.1.

2h:[18a] Colorless oil, 165.1 mg, 89%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.33 (s, 1H), 4.25 (q, J = 7.2 Hz, 2H), 2.52−2.73 (m, 3H), 2.00−2.11 (m, 1H), 1.79−1.93 (m, 2H), 1.63−1.77 (m, 2H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.4, 170.1, 80.7, 62.1, 38.9, 37.6, 27.0, 22.0, 14.0.

2i:[18b] Pale yellow solid, 158 mg, 72%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (dd, J = 7.9, 1.2 Hz, 1H), 7.54 (td, J = 7.5, 1.4 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 4.38 (s, 1H), 3.75 (s, 3H), 3.07−3.21 (m, 2H), 2.72 (dt, J = 13.6, 5.0 Hz, 1H), 2.25 (ddd, J = 13.6, 8.7, 6.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.6, 171.2, 144.1, 134.5, 130.2, 129.0, 128.3, 127.1, 77.8, 53.1, 32.8, 25.6.

2j:[17a] Colorless oil, 112.7 mg, 78%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.54 (ddd, J = 9.0, 8.3, 4.8 Hz, 1H), 4.47 (dt, J = 9.1, 7.3 Hz, 1H), 4.22 (s, 1H), 2.72 (ddd, J = 13.5, 7.3, 4.9 Hz, 1H), 2.41 (ddd, J = 13.5, 8.2, 7.3 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.0, 174.7, 81.3, 66.3, 34.1, 24.7.

4a:[2c] Colorless oil, 214.8 mg, 93%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.26 (q, J = 7.1 Hz, 4H), 3.73 (s, 1H), 2.02 (t, J = 7.8 Hz, 2H), 1.29 (t, J = 7.1 Hz, 6H), 1.22−1.39 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 79.1, 62.4, 34.4, 25.3, 22.7, 14.1, 14.0.

4b:[23] Colorless oil, 168.9 mg, 89%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.26 (q, J = 7.1 Hz, 4H), 3.77 (s, 1H), 1.63 (s, 3H), 1.29 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 76.1, 62.5, 21.6, 14.0.

4c:[18a] Colorless oil, 251.9 mg, 95%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20−7.30 (m, 5H), 4.25 (q, J = 7.1 Hz, 4H), 3.73 (s, 1H), 3.35 (s, 2H), 1.29 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 134.7, 130.4, 128.1, 127.2, 79.3, 62.6, 40.5, 14.1.

4d:[18b] Colorless oil, 221 mg, 88%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62−7.67 (m, 2H), 7.34−7.41 (m, 3H), 4.34 (s, 1H), 4.35 (dq, J = 10.7, 7.1 Hz, 2H), 4.27 (dq, J = 10.7, 7.1 Hz, 2H), 3.35 (s, 2H), 1.30 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 136.0, 128.6, 128.0, 126.7, 80.0, 63.0, 14.0.

4e: Colorless oil, 191.7 mg, 90%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.22−4.38 (m, 4H), 4.04 (s, 1H), 2.98 (d, J = 2.6 Hz, 2H), 2.05 (t, J = 2.7 Hz, 1H), 1.31 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 77.8, 77.7, 71.5, 63.0, 26.0, 14.0; HRMS-MALDI-TOF m/z: [M+Na]$^+$ Calcd for $C_{10}H_{14}NaO_5$ 237.0739; Found 237.0741.

4g:[21] White solid, 363.5 mg, 95%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J = 7.2 Hz, 2H), 7.51 (t, J = 7.3 Hz, 1H), 7.42 (d, J = 7.3 Hz, 2H), 7.41 (t, J = 7.3 Hz, 2H), 7.21 (t, J = 7.3 Hz, 2H), 7.16 (d, J = 7.2 Hz, 1H), 4.45 (dd, J = 10.2, 2.9 Hz, 1H), 4.23−4.33 (m, 2H), 4.05 (dq, J = 10.7, 7.1 Hz, 1H), 4.01 (s, 1H), 3.98 (dq, J = 10.7, 7.1 Hz, 1H), 3.72 (dd, J = 17.4, 10.2 Hz, 1H), 3.37 (dd, J = 17.4, 3.1 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 170.0, 169.5, 138.6, 137.0, 133.1, 129.6, 128.6, 128.20, 128.18, 127.5, 82.0, 63.0, 62.8, 44.8, 40.3, 14.1, 13.9.

4h: Yellow oil, 312.7 mg, 96%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−741 (m, 2H), 7.27−7.31 (m, 3H), 4.95 (dd, J = 13.1, 4.4 Hz, 1H), 4.85 (dd, J = 13.1, 10.1 Hz, 1H), 4.48 (dd, J = 10.1, 4.4 Hz, 1H), 4.34 (dq, J = 10.7, 7.1 Hz, 1H), 4.29 (dq, J = 10.7, 7.2 Hz, 1H), 4.06

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(dq, J = 10.7, 7.1 Hz, 1H), 4.04 (s, 1H), 3.97 (dq, J = 10.7, 7.2 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H), 1.10 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 168.5, 134.5, 129.4, 128.71, 128.67, 80.3, 76.6, 63.4, 63.2, 47.2, 14.0, 13.8; HRMS-MALDI-TOF m/z: $[M+Na]^+$ Calcd for $C_{15}H_{19}NNaO_7$ 348.1059; Found 348.1053.

4i: Colorless oil, 212.2 mg, 93%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30 (q, J = 7.1 Hz, 4H), 3.91 (s, 1H), 2.47−2.52 (m, 2H), 2.39−2.44 (m, 2H), 1.31 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 118.9, 77.2, 63.2, 30.4, 14.0, 11.7; HRMS-MALDI-TOF m/z: $[M+H]^+$ Calcd for $C_{10}H_{16}NO_5$ 230.1029; Found 230.1023.

4j:[23] Colorless oil, 205.3 mg, 70%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (br, 1H), 7.83−7.86 (m, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.4 Hz, 2H), 5.27 (s, 1H), 4.36 (q, J = 7.1 Hz, 4H), 1.31 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 166.9, 132.6, 132.5, 128.8, 127.4, 80.3, 63.8, 14.0; HRMS-MALDI-TOF m/z: $[M+H]^+$ Calcd for $C_{14}H_{18}NO_6$ 296.1134; Found 296.1131.

4k:[23] Colorless oil, 131.2 mg, 56%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (br, 1H), 5.20 (s, 1H), 4.32 (q, J = 7.1 Hz, 4H), 2.06 (s, 3H), 1.29 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 167.0, 80.0, 63.6, 22.8, 13.9; HRMS-MALDI-TOF m/z: $[M+H]^+$ Calcd for $C_9H_{16}NO_6$ 234.0978; Found 234.0972.

6a:[17a] Pale yellow oil, 172.9 mg, 84%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18−7.30 (m, 5H), 4.70 (s, 1H), 3.28 (s, 2H), 2.23 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.8, 134.6, 130.1, 128.4, 127.2, 91.1, 41.9, 25.7.

6b:[23] Pale yellow oil, 118.2 mg, 62%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.51 (m, 2H), 7.36−7.44 (m, 3H), 5.28 (s, 1H), 2.29 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.2, 136.6, 129.1, 129.0, 126.0, 89.1, 26.4.

6c:[11] Colorless oil, 94.1 mg, 60%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.62 (s, 1H), 2.61−2.78 (m, 2H), 2.40−2.48 (m, 1H), 2.24 (s, 3H), 2.02−2.13 (m, 1H), 1.64−1.96 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.1, 207.6, 85.5, 39.5, 38.5, 27.4, 25.6, 21.8.

6d:[11] Yellow solid, 94.5 mg, 43%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02−8.06 (m, 2H), 7.55 (tt, J = 7.4, 1.3 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 4.82 (s, 1H), 2.69−2.87 (m, 3H), 2.07−2.17 (m, 1H), 1.64−1.84 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.2, 198.0, 134.7, 133.3, 129.9, 128.5, 85.2, 40.2, 40.0, 27.6, 22.1.

6h: Colorless oil, 96.9 mg, 52%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21−4.36 (m, 2H), 3.85 (br, 1H), 3.39−3.55 (m, 2H), 2.93 (s, 3H), 2.59 (ddd, J = 13.5, 7.6, 3.3 Hz, 1H), 2.22 (ddd, J = 13.5, 8.8, 7.3 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 171.0, 78.0, 62.7, 46.2, 31.0, 30.5, 14.1; HRMS-MALDI-TOF m/z: $[M+Na]^+$ Calcd for $C_8H_{13}NNaO_4$ 210.0742; Found 210.0737.

6i: White solid, 172.8 mg, 62%, mp 137−138 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 8.2 Hz, 2H), 4.30−4.45 (m, 2H), 4.18 (s, 1H), 3.34 (d, J = 18.2 Hz, 1H), 3.04 (d, J = 18.2 Hz, 1H), 2.39 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 172.6, 169.6, 139.3, 130.0, 128.7, 126.1, 76.2, 64.0, 40.7, 21.3, 14.1; HRMS-MALDI-TOF m/z: $[M+H]^+$ Calcd for $C_{14}H_{16}NO_5$ 278.1029; Found 278.1023.

8a:[25] Colorless oil, 116.6 mg, 70%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.52 (s, 1H), 4.40 (s, 1H), 4.27−4.35 (m, 4H), 4.24 (q, J = 7.1 Hz, 4H), 1.31 (t, J = 7.1 Hz, 6H), 1.28 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 166.6, 78.8, 63.2, 62.2, 56.5, 13.9; HRMS-MALDI-TOF m/z: $[M+H]^+$ Calcd for $C_{14}H_{23}O_9$ 335.1342; Found 335.1346.

8b:[25] Colorless oil, 132.4 mg, 68%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03−5.18 (m, 4H), 4.43 (s, 1H), 4.36 (s, 1H), 1.25−1.29 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 166.2, 78.7, 71.1, 69.9, 56.6, 21.63, 21.61, 21.57, 21.48; HRMS-MALDI-TOF m/z: $[M+H]^+$ Calcd for $C_{18}H_{31}O_9$ 391.1968; Found 391.1973.

9a: Colorless oil, 41.5 mg, 22%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.78 (s, 2H), 4.35 (q, J = 7.1 Hz, 4H), 1.33 (q, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 90.2, 63.6, 14.0. HRMS-MALDI-TOF m/z: $[M+H]^+$ Calcd for $C_7H_{13}O_6$ 193.0712; Found 193.0707.

9b: Colorless oil, 35.6 mg, 16%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.16 (hept, J = 6.3 Hz, 2H), 4.80 (s, 2H), 1.30 (d, J = 6.3 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 90.1, 71.7, 21.5. HRMS-MALDI-TOF m/z: $[M+H]^+$ Calcd for $C_9H_{17}O_6$ 221.1025; Found 221.1018.

10: Colorless oil, 30.6 mg, 21%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00−8.03 (m, 2H), 7.65 (tt, J = 7.4, 1.3 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 2.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.7, 191.5, 134.7, 131.9, 130.5, 129.0, 26.5.

Large Scale Preparation of 2a and 4a. A mixture of the β-dicarbonyl compounds (**1a** or **3a**, 15 mmol), I_2 (38.1 mg, 0.15 mmol), and NaOAc (12.3 mg, 0.15 mmol) were stirred in 30 mL of THF in a quartz tube (ø 28 mm × 180 mm) at 35 °C under the irradiation of a 300 W high pressure mercury lamp for a given time. Simultaneously, the solution was bubbled with an air pump through a capillary column. After the reaction was completed, most of the solvent was removed *in vacuo*, and 40 mL of water were added. To the mixture was added saturated $Na_2S_2O_3$ until the disappearance of umber, and then the mixture was extracted with dichloromethane (30 mL × 3). The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether) to provide the corresponding α-hydroxylmalonate **2a** (2.78 g, 92%) or **4a** (3.26 g, 94%).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra of all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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