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PAPER

Base- and metal-free decarboxylative aldol reaction of β-ketoacids with glyoxylate hydrates and glyoxal monohydrates in water

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An environmental benign decarboxylative aldol reaction of β-ketoacids with glyoxylate and glyoxal monohydrates in water is reported. The reaction proceeds smoothly without any base and metal catalysts, affording the correspoding β-hydroxy ketones in high yields. A preliminary mechanism studies of this aldol transformation suggests a stepwise process involving nucleophilic addition of β-ketoacids to glyoxylate hydrates and glyoxal monohydrates followed by a subsequent decarboxylation reaction.

Introduction

The development of practical, atom-economical, and environmentally benign chemical reactions has become a vital consideration in current chemical research[1]. In this context, organic reactions in aqueous medium[2] have attracted more and more attention of synthetic chemists, because water is nonflammable, nontoxic and the most abundant solvent in nature. Although there are many potential advantages in terms of cost, safety, and environmental concerns when common organic solvents are replaced by water, it is still a challenge that the poor solubilities and reactivities of reactants in aqueous medium led to the deleterious effect on many organic transformations[3].

The aldol reaction is one of the most powerful methods for the formation of carbon-carbon bonds in organic synthesis[4]. Traditionally, the aldol reactions have been conducted in the presence of strong base or acid. However, under such conditions, the desired aldol adduct is afforded along with other side products derived from dehydration, dimerization, polymerization, or self-condensation. Catalytic aldol reactions which avoid dehydration in aqueous media have been widely studied, and many methods have been successfully applied to the synthesis of natural products and compounds of pharmaceutical significance[5]. In sharp contrast, examples of uncatalyzed aldol-type reactions in aqueous medium are rare. In 1986 Lubineau[6] demonstrated that silyl enol ethers reacted with carbonyl compounds in water without any catalyst to give the aldol products in low yields. Recently Dash and co-workers[7] reported an uncatalyzed aldol reaction of thiazolidinedione with aromatic aldehydes to afford the corresponding β-hydroxy carbonyl compounds. However, this method is limited by the scope and the accessibility of the required nucleophilic substrates. Thus, the development of new catalyst-free aldol reactions in aqueous medium for the construction of diverse aldol-products is still in high demand.

The decarboxylative transformations of β-ketoacids, which are catalyzed by enzymes, have proven to be the key step in the biosynthesis of natural tropinone, lycopodine alkaloids, and macrophomic acid[8]. The decarboxylative reaction of β-ketoacids provides a traceless means of activation with CO_2 as the only by-product for carbon-carbon bond-forming process. Inspired from nature, organic chemists have developed a variety of efficient carbon-carbon bond-forming reactions by empolying β-ketoacids as ketone enolate equivalents[9]. In this context, metal- and organcatalytic decarboxylative aldol reactions of β-ketoacids with aldehydes and ketones have been well established (Scheme 1a)[10]. However, the use of organic solvents has been the focus of all such studies. In sharp contrast, the implementation of the biomimetic decarboxylative aldol reactions in aqueous media, especially in pure water as a valuable synthetic tool still remains unexploited.

During our ongoing studies in the field of decarboxylative transformations of β-ketoacids[11], we have developed a useful base- and metal-free decarboxylative aldol reaction of β-ketoacids with glyoxylate hydrates and glyoxal monohydrates in aqueous medium (Scheme 1b). The notable features of this reaction are its operational simplicity, readily accessible starting materials, mild reaction conditions, low cost and eco-friendliness. Thus,

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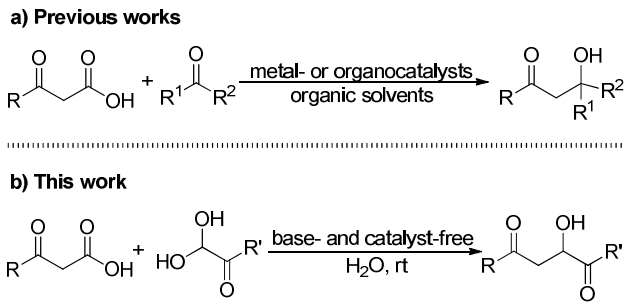
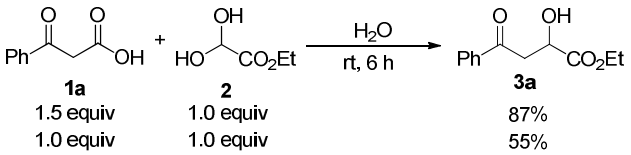
this protocol highly meets the criteria of Green Chemistry[12]. Herein, we report the results of our studies on this subject.



Scheme 1. The decarboxylative aldol reactions of *β*-ketoacids in organic solvents and water.

Results and discussion

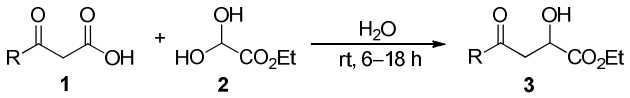
We initiated our investigation by conducting the decarboxylative aldol reaction between 3-oxo-3-phenylpropanoic acid **1a** and ethyl glyoxylate hydrate **2** in pure water (Scheme 2). To our delight, this aldol condensation could be carried out at room temperature for 6 h to afford the desired aldol product **3a** in 87% isolated yield in the absence of any Brønsted bases and metal complexes. Small amount of side product acetophenone, formed from a competing decarboxylation pathway, was observed. Notably the dehydration by-product was not detected in the reaction system. Next, when the amount of **1a** was reduced to 1.0 equivalent, the yield of **3a** was decreased dramatically to 55%. Thus, the optimized conditions for this reaction are summarized as follows: **1a** (0.3 mmol) and **2** (0.2mmol) at room temperature in pure water under air for 6 h.



Scheme 2. The decarboxylative aldol reaction of *β*-ketoacid **1a** with ethyl glyoxylate hydrate **2**.

With the optimized reaction conditions in hand, the scope of the decarboxylative aldol reaction was investigated by using a series of *β*-ketoacids, and the results were summarized in Table 1. The reaction of *ortho*-, *meta*-, and *para*-substitued phenyl *β*-ketoacids with ethyl glyoxylate hydrate **2** all proceeded smoothly, and the aldol adducts **3a**–**j** could be obtained in 81–90% yields (entries 1–10). It should be noted that the substrates with chlorine or bromine substituents on the phenyl ring are less reactive as the reaction time has been prolonged to 18 h, delivering the corresponding products **3k**–**n** in relatively lower yields (entries 11–14). The heteroaryl-substitued *β*-ketoacids could also be used as the nucleophile substrates, thus generating the desired products **3o** and **3p** in high yields (entries 15 and16). In addition, it was found that cyclic, linear, and branched alkyl-substituted *β*-ketoacids were also acceptable substrates and provided the corresponding aldol products **3q**–**u** in good yields (entries 17–21). This decarboxylative aldol reaction could also be performed on the decagram scale without losing efficiency, and the aldol product **3a** could be obtained by direct vacuum distillation (entry 22).

Table 1 Scope of the decarboxylative aldol reaction of *β*-ketoacids **1** with ethyl glyoxylate hydrate **2** [a]



Entry	R	Time (h)	Product	Yield (%) [b]
1	C_6H_5	6	**3a**	87
2	4-Me-C_6H_4	6	**3b**	85
3	3-Me-C_6H_4	6	**3c**	83
4	2-Me-C_6H_4	6	**3d**	87
5	2,4-Me_2-C_6H_3	6	**3e**	81
6	4-MeO-C_6H_4	6	**3f**	85
7	3-MeO-C_6H_4	6	**3g**	90
8	3,4,5-$(MeO)_3$-C_6H_3	12	**3h**	83
9	4-F-C_6H_4	6	**3i**	82
10	2-F-C_6H_4	6	**3j**	90
11	4-Cl-C_6H_4	18	**3k**	75
12	3-Cl-C_6H_4	18	**3l**	73
13	2-Cl-C_6H_4	18	**3m**	76
14	4-Br-C_6H_4	18	**3n**	74
15	2-Furyl	6	**3o**	92
16	3-Thienyl	6	**3p**	90
17	Phenethyl	12	**3q**	84
18	Cyclopropyl	12	**3r**	80
19	Cyclohexyl	12	**3s**	85
20	*n*-Propyl	12	**3t**	87
21	*t*-Butyl	12	**3u**	87
22[c]	C_6H_5	10	**3a**	85

[a] Reactions were performed with **1** (0.3 mmol) and **2** (0.2 mmol) in water (1.5 ml) at room temperature for 6–18 h. [b] Isolated yield. [c] Reaction was performed with 80 mmol of **2**.

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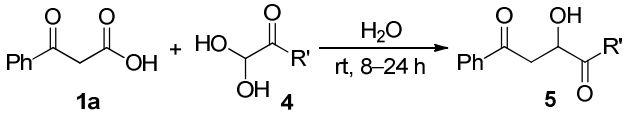
To further extend this base- and catalyst-free decarboxylative aldol reaction in water, we also used a variety of glyoxal monohydrates **4** as the electrophilic partners under the current reaction conditions. As shown in Table 2, the reaction of a series of phenyl-substituted glyoxal monohydrates with *β*-ketoacid **1a** worked well to afford the corresponding products **5a**–**g** in good to high yields (entries 1–7). 2-Naphthyl- and 2-thienyl-substituted glyoxal monohydrates also participated in this decarboxylative reaction well to give the aldol products **5h** and **5i** in the yield of 82% and 87%, respectively (entries 8 and 9). The aldol reactions of alkyl-substituted glyoxal monohydrates were also tested (entries 10 and 11). The desired adducts **5j** and **5k** were obtained in high yields. Furthermore, almost the same result was obtained when the aldol reaction of phenyl glyoxal monohydrate with *β*-ketoacid **1a** was scaled up to the gram scale (entry 12).

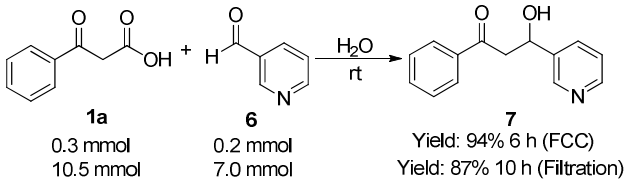
Table 2 The decarboxylative aldol reaction of *β*-ketoacid **1a** with a series of glyoxal monohydrates **4** [a]



Entry	R	Time (h)	Product	Yield (%) [b]
1	C_6H_5	8	**5a**	85
2	4-MeC_6H_4	8	**5b**	93
3	4-$MeOC_6H_4$	8	**5c**	92
4	4-FC_6H_4	8	**5d**	90
5	4-ClC_6H_3	16	**5e**	85
6	4-BrC_6H_4	24	**5f**	92
7	4-$NO_2C_6H_4$	16	**5g**	75
8	2-Naphthyl	16	**5h**	82
9	2-Thienyl	8	**5i**	87
10	Methyl	8	**5j**	92
11	*t*-Butyl	8	**5k**	88
12[c]	C_6H_5	16	**5a**	83

[a] Reactions were performed with **1a** (1 mmol) and **4** (0.67 mmol) in water (2 ml) at room temperature for 8–24 h. [b] Isolated yield. [c] Reaction was performed with 10 mmol of **4**.

Subsequently, we also investigated the aldol reaction of *β*-ketoacid **1a** with several aromatic aldehydes, including benzaldehyde, *p*-nitrobenzaldehyde and furaldehyde. Unfortunately these aromatic aldehydes were found to be insuitbale for this decarboxylative aldol reaction and no desired products were observed under the present standard conditions. Interestingly, nicotinaldehyde **6** could react with *β*-ketoacid **1a** in water to afford the *β*-hydroxy ketone **7** in excellent yields by flash column chromatography (FCC). In addition, when this aldol reaction was scaled up to the gram scale, the desired product **7** was also obtained in 87% yield by simple filtration (Scheme 3). We analysed the solutions of these aromatic aldehydes in D_2O by using ^1H and ^{13}C NMR, and found that nicotinaldehyde exists as partial hydrate species (aldehyde/hydrate = 10/1) in aqueous solution (see ESI). In contrast, for the other three aromatic aldehydes, the corresponding hydrates were undetectable on the timescale of the NMR experiment. These results indicate that the hydrate species of aldehydes is critically important to this aldol reaction.



Scheme 3. The decarboxylative aldol reaction of *β*-ketoacid **1a** with nicotinaldehyde **6**.

It is of great value to elucidate the mechanism of this biomimetic decarboxylative aldol reaction in neutral aqueous media, because the chemical environment is fairly similar to nature. To cast some light on the mechanism, NMR and ESI/MS methods were used to study this decarboxylative aldol reaction. It is noteworthy that the base- and metal-free aqueous conditions make NMR spectroscopic analysis of the crude reaction mixture very reliable and feasible in D_2O. By using *tert*-butyl substituted *β*-ketoacid **1u** and methyl glyoxylate hydrate **8** as substrates, we monitored the current aldol reaction *via* ^{13}C NMR (Figure 1). In comparison with the spectra of substrates and product (Figure 1: a, b, and c), an addition intermediate with new signals at 45.33, 52.77, 69.66, 170.50, 173.74, and 212.78 ppm was observed (Figure 1: d). However, all attempts to isolate this intermediate were unsuccessful. An ESI/MS analysis of this aldol reaction allowed further identification of the addition intermediate using the high-resolution mass data {HRMS (ESI) calcd for $C_{10}H_{16}O_6Na$ $[M + Na]^+$ 255.0839, found 255.0845} (Figure 1e). In the control experiment, we found that the corresponding ketone could not react with methyl glyoxylate hydrate to afford the desired product **9** under the standard conditions.

Based on these preliminary results, a stepwise process could be involved in this reaction system, in which nucleophilic addition of the *β*-ketoacids to glyoxylate hydrates and glyoxal monohydrates gave the addition intermediates, followed by the decarboxylation to afford the desired aldol products. These interesting findings may be helpful to further understand the mechanism of the decarboxylative reactions in biological systems[8].

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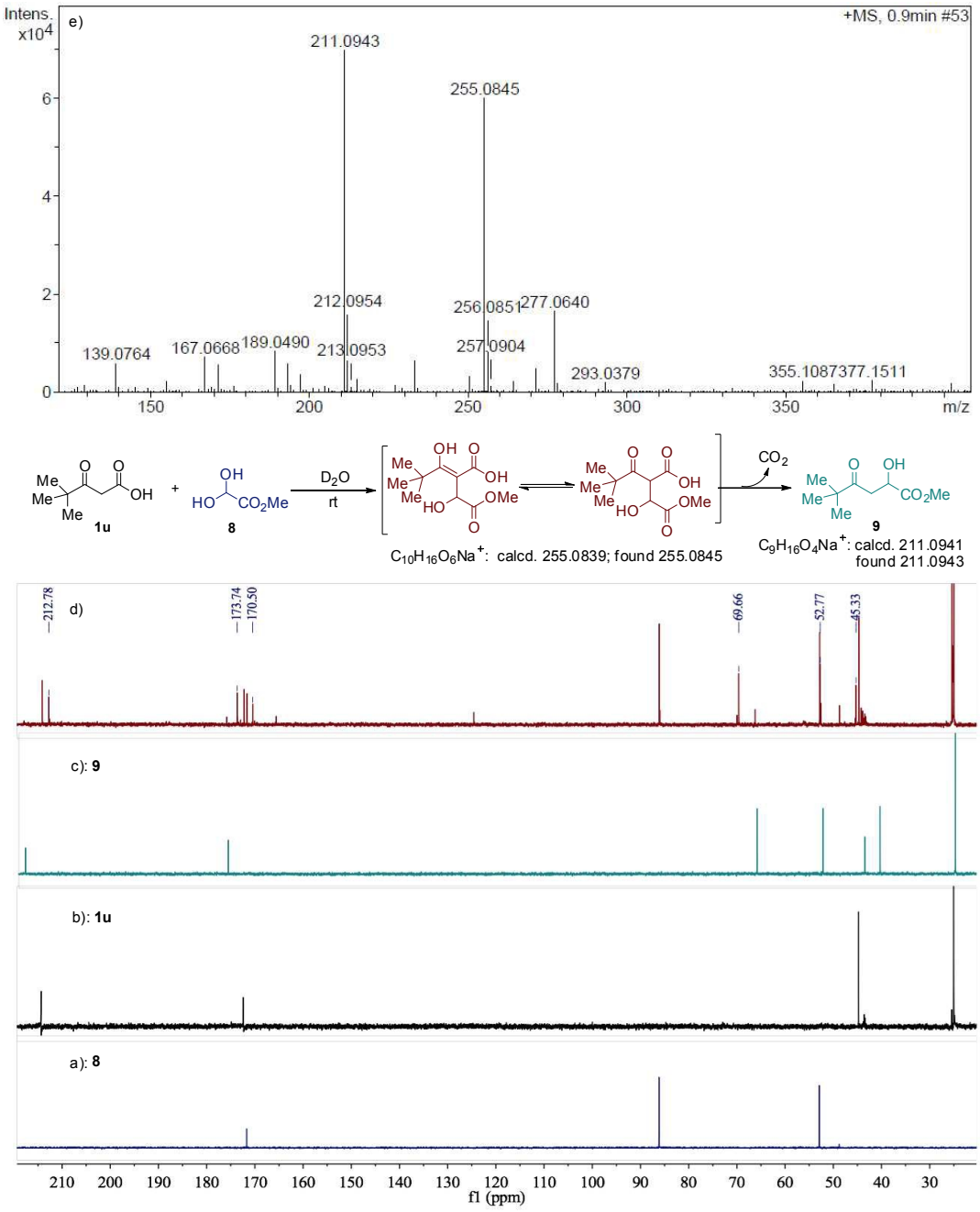

Figure 1 ^{13}C NMR spectra of the reactants, the aldol product, and the reaction mixture in D_2O (a–d) (bottom); the reaction equation (middle); as well as ESI/MS experiment of the reaction mixture (e) (top).

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Conclusions

In conclusion, we have successfully developed a decarboxylative aldol reaction of *β*-ketoacids with glyoxylate hydrates and glyxoal monohydrates in pure water. This synthetic protocol proves to be eco-friendly and cost-effective. In the absence of any base and metal catalysts, the reaction proceeded smoothly to afford the aldol adducts in good to high yields. Efforts are currently underway to elucidate the mechanistic details and to apply this reaction in bioorthogonal chemistry, the results of which will be reported in due course.

Experimental Section

^{1}H, ^{13}C and ^{19}F NMR were recorded at 400 MHz (^{1}H NMR), 100 MHz (^{13}C NMR), as well as 376 MHz (^{19}F NMR). Chemical shifts were reported in parts per million (ppm) from the solvent resonance as the internal standard ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), dt (doublet of triplets), br (broad). Coupling constants were reported in Hertz (Hz). High resolution mass spectrometry (HRMS) spectra were obtained on a micrOTOF-QII Instrument. IR spectra were recorded on an AVATAR 360 FT-IR spectrometer. Melting points were measured on a WRS-1A digital melting point apparatus and are uncorrected. All commercially available reagents were used without further purification. Analytical thin layer chromatography was performed on 0.20 mm silica gel plates. Silica gel (200–300 mesh) was used for flash chromatography. The ethyl glyoxylate and glyoxal monohydrates were synthesized according to the literature[13]. All the *β*-ketoacids were prepared according to the literature[11b].

General procedure for decarboxylative aldol reaction of *β*-ketoacids with glyoxylate hydrates

Glyoxylate hydrates **2** or **8** (0.2 mmol) was added to the suspension of *β*-ketoacid **1** (0.3 mmol) in water (1.5 mL). The ultimate suspension was stirred for 6 h at ambient temperature. The reaction mixture was extracted with ethyl acetate (15 mL × 3). The combined organic solvent was washed with saturated sodium bicarbonate (10 mL), brine (10 mL), dried over anhydrous sodium sulfate, and the solvent evaporated in vacuo. Purification of crude product by flash chromatography (petroleum ether/ethyl acetate: 6/1–3/1) gave the expected product.

The scaled-up decarboxylative aldol reaction of *β*-ketoacid 1a with ethyl glyoxylate hydrate

Ethyl glyoxylate hydrate **2** (9.6 g, 80 mmol) was added to the suspension of *β*-ketoacid **1a** (15.8 g, 96 mmol) in water (20 mL). The ultimate suspension was stirred for 10 h at ambient temperature. After completion of the reaction, water was evaporated under reduced pressure. Purification by vaccum distillation using a Vigreux column gave the desired product as a bright yellow oil (15.1 g, 85%); bp 153–157 °C/2 mmHg.

Ethyl 2-hydroxy-4-oxo-4-phenylbutanoate (3a)[14a]: 38.6 mg; 87% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.92 (m, 2H), 7.60-7.54 (m, 1H), 7.49-7.43 (m, 2H), 4.65 (dd, *J* = 9.4, 5.3 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.56–3.41 (m, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.66, 173.92, 136.54, 133.74, 128.82, 128.29, 67.32, 61.97, 42.30, 14.24.

Ethyl 2-hydroxy-4-oxo-4-(*p*-tolyl)butanoate (3b)[14a]: 40.1 mg; 85% yield; white solid; Mp: 51-52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 7.7 Hz, 2H), 4.58 (dd, *J* = 9.7, 5.8 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.47-3.33 (m, 3H), 2.34 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.20, 172.80, 143.54, 132.96, 128.36, 127.28, 66.28, 60.79, 41.01, 20.67, 13.11.

Ethyl 2-hydroxy-4-oxo-4-(*m*-tolyl)butanoate (3c): 39.2 mg; 83% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76-7.71 (m, 2H), 7.41-7.31 (m, 2H), 4.65 (dd, *J* = 5.6, 4.1 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.51-3.40 (m, 3H), 2.40 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.77, 172.80, 137.50, 135.44, 133.37, 127.65, 127.55, 124.40, 66.23, 60.81, 41.20, 20.31, 13.11; IR (KBr, *v*, cm^{-1}): 3480, 2982, 2924, 1738, 1682, 1591, 1367, 1273, 1205, 1101, 1039, 788, 690; HRMS (ESI) found: *m/z* 259.0944 [M + Na]$^+$; calcd. for $C_{13}H_{16}O_4$+Na 259.0941.

Ethyl 2-hydroxy-4-oxo-4-(*o*-tolyl)butanoate (3d): 41.1 mg; 87% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.65 (m, 1H), 7.42-7.37 (m, 1H), 7.30-7.23 (m, 2H), 4.63 (dd, *J* = 5.2, 4.4 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.45-3.36 (m, 3H), 2.51 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.10, 173.94, 138.70, 136.94, 132.12, 131.88, 128.85, 125.78, 67.43, 61.87, 44.83, 21.40, 14.16; IR (KBr, *v*, cm^{-1}): 3486, 2979, 2929, 1739, 1685, 1453, 1368, 1262, 1208,

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1099, 1037, 760; HRMS (ESI) found: *m/z* 259.0945 $[M + Na]^+$; calcd. for $C_{13}H_{16}O_4$+Na 259.0941.

Ethyl 4-(2,4-dimethylphenyl)-2-hydroxy-4-oxobutanoate (3e): 40.5 mg; 81% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.59 (m, 1H), 7.09-7.05 (m, 2H), 4.61 (dd, *J* = 9.9, 5.6 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.47-3.35 (m, 3H), 2.49 (s, 3H), 2.35 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.30, 172.95, 141.66, 138.27, 132.87, 132.02, 128.44, 125.38, 66.48, 60.77, 43.41, 20.66, 20.38, 13.13; IR (KBr, *v*, cm^{-1}): 3488, 2987, 2927, 2360, 1737, 1681, 1610, 1449, 1369, 1264, 1208, 1099, 1037, 762; HRMS (ESI) found: *m/z* 273.1099 $[M + Na]^+$; calcd. for $C_{14}H_{18}O_4$+Na 273.1097.

Ethyl 2-hydroxy-4-(4-methoxyphenyl)-4-oxobutanoate (3f) [14a]**:** 42.8 mg; 85% yield; white solid; Mp: 65-66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 4.63 (dd, *J* = 9.5, 5.4 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 3.50-3.36 (m, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.15, 173.85, 163.92, 130.53, 129.53, 113.85, 67.40, 61.77, 55.53, 41.77, 14.14.

Ethyl 2-hydroxy-4-(3-methoxyphenyl)-4-oxobutanoate (3g): 45.4 mg; 90% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.46 (m, 2H), 7.39-7.33 (m, 1H), 7.14-7.09 (m, 1H), 4.64 (dd, *J* = 5.5, 4.1 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 3.55-3.39 (m, 3H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.36, 173.81, 159.87, 137.78, 129.70, 120.87, 120.16, 112.29, 67.22, 61.87, 55.46, 42.32, 14.14; IR (KBr, *v*, cm^{-1}): 3490, 2980, 1738, 1683, 1591, 1437, 1262, 1204, 1101, 1038, 866, 789, 686; HRMS (ESI) found: *m/z* 275.0894 $[M + Na]^+$; calcd. for $C_{13}H_{16}O_5$+Na 275.0890.

Ethyl 2-hydroxy-4-oxo-4-(3,4,5-trimethoxyphenyl)butanoate (3h): 51.8 mg; 83% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (s, 2H), 4.63 (dd, *J* = 4.4, 4.0 Hz, 1H), 4.26 (q, *J* = 7.0 Hz, 2H), 3.89 (s, 9H), 3.53-3.37 (m, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.35, 173.81, 153.11, 143.08, 131.66, 105.72, 67.34, 61.90, 60.98, 56.32, 41.93, 14.15; IR (KBr, *v*, cm^{-1}): 3474, 2941, 2838, 1735, 1675, 1584, 1457, 1413, 1325, 1233, 1123, 1002, 890, 772; HRMS (ESI) found: *m/z* 335.1106 $[M + Na]^+$; calcd. for $C_{15}H_{20}O_7$+Na 2335.1101.

Ethyl 4-(4-fluorophenyl)-2-hydroxy-4-oxobutanoate (3i) [14b]**:** 39.3 mg; 82% yield; white solid; Mp: 62-64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.95 (m, 2H), 7.17-7.11 (m, 2H), 4.65 (dd, *J* = 8.9, 4.8 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.51 (dd, *J* = 17.4, 3.8 Hz, 1H), 3.42 (dd, *J* = 17.4, 6.0 Hz, 1H), 3.35 (d, *J* = 4.7 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.91, 173.75, 166.04 (d, *J* = 242.3 Hz), 132.93 (d, *J* = 2.9 Hz), 130.90 (d, *J* = 9.5 Hz), 115.86 (d, *J* = 20.9 Hz), 67.17, 61.93, 42.08, 14.12; ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.09 ~ -104.16 (m).

Ethyl 4-(2-fluorophenyl)-2-hydroxy-4-oxobutanoate (3j): 43.2 mg; 90% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.79 (m, 1H), 7.51-7.45 (m, 1H), 7.21-7.14 (m, 1H), 7.11-7.04 (m, 1H), 4.55 (dd, *J* = 9.6, 5.6 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.53-3.45 (m, 1H), 3.45-3.36 (m, 1H), 3.23 (d, *J* = 5.7 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.38 (d, *J* = 3.9 Hz), 172.84, 161.18 (d, *J* = 241.3 Hz), 134.20 (d, *J* = 9.2 Hz), 129.64 (d, *J* = 2.4 Hz), 123.91 (d, *J* = 12.6 Hz), 123.57 (d, *J* = 3.4 Hz), 115.73 (d, *J* = 21.9 Hz), 66.00 (d, *J* = 2.7 Hz), 60.85, 46.11 (d, *J* = 8.1 Hz), 13.10; ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.85 ~ -108.93 (m); IR (KBr, *v*, cm^{-1}): 3491, 2984, 2935, 1739, 1687, 1609, 1578, 1480, 1452, 1368, 1277, 1211, 1101, 1040, 767, 540, 513; HRMS (ESI) found: *m/z* 263.0692 $[M + Na]^+$; calcd. for $C_{12}H_{13}FO_4$+Na 263.0690.

Ethyl 4-(4-chlorophenyl)-2-hydroxy-4-oxobutanoate (3k) [14a]**:** 38.5 mg; 75% yield; white solid; Mp: 55-56 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.6 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 4.65 (dd, *J* = 9.3, 5.2 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.50 (dd, *J* = 17.4, 3.8 Hz, 1H), 3.41 (dd, *J* = 17.4, 6.0 Hz, 1H), 3.33 (d, *J* = 5.3 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.27, 173.70, 140.15, 134.79, 129.61, 129.06, 67.12, 61.99, 42.14, 14.14.

Ethyl 4-(3-chlorophenyl)-2-hydroxy-4-oxobutanoate (3l): 37.4 mg; 73% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.84-7.81 (m, 1H), 7.58-7.54 (m, 1H), 7.45-7.39 (m, 1H), 4.65 (d, *J* = 3.4 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.51 (dd, *J* = 17.5, 3.6 Hz, 1H), 3.42 (dd, *J* = 17.5, 5.9 Hz, 1H), 3.29 (d, *J* = 4.0 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.18, 172.67, 136.94, 134.04, 132.50, 129.04, 127.27, 125.27, 66.03, 60.99, 41.29, 13.11; IR (KBr, *v*, cm^{-1}): 3487, 2983, 2931, 1739, 1689, 1571, 1471, 1422, 1262, 1210, 1101, 1043, 789, 681; HRMS (ESI) found: *m/z* 279.0400 $[M + Na]^+$; calcd. for $C_{12}H_{13}ClO_4$+Na 279.0395.

Ethyl 4-(2-chlorophenyl)-2-hydroxy-4-oxobutanoate (3m): 39.0 mg; 76% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.52 (m, 1H), 7.41-7.30 (m, 3H), 4.61 (dd, *J* = 5.7, 4.4 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 3.51 (dd, *J* = 17.5, 4.2 Hz, 1H), 3.44 (dd, *J* = 17.5, 6.0 Hz, 1H), 3.30 (s, 1H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.97, 173.70, 138.31, 132.33, 131.26, 130.69, 129.53, 127.05, 67.28, 62.04, 46.52, 14.15; IR (KBr, *v*, cm^{-1}): 3487, 2983, 2359, 1738, 1701, 1588, 1432, 1365, 1268, 1206, 1100, 1034, 761; HRMS (ESI) found: *m/z* 279.0396 $[M + Na]^+$; calcd. for $C_{12}H_{13}ClO_4$+Na 279.0395.

Ethyl 4-(4-bromophenyl)-2-hydroxy-4-oxobutanoate (3n) [14b]**:** 44.5 mg; 74% yield; white solid; Mp: 66-67 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 4.64 (dd, *J* = 9.2, 5.1 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.49 (dd, *J* = 17.4, 3.8 Hz, 1H), 3.40 (dd, *J* = 17.4, 6.0 Hz, 1H), 3.32 (d, *J* = 5.3 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.45, 173.70, 135.19, 132.02, 129.70, 128.84, 67.09, 61.93, 42.15, 14.13.

Ethyl 4-(furan-2-yl)-2-hydroxy-4-oxobutanoate (3o) [14c]**:** 39.0 mg; 92% yield; white solid; Mp: 67-68 °C; ^{1}H NMR (400 MHz,

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$CDCl_3$) δ 7.60 (s, 1H), 7.24-7.21 (m, 1H), 6.56-6.53 (m, 1H), 4.63 (dd, *J* = 10.0, 5.6 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.42-3.24 (m, 3H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.15, 173.67, 152.37, 146.89, 117.92, 112.51, 67.05, 61.95, 42.03, 14.09.

Ethyl 2-hydroxy-4-oxo-4-(thiophen-3-yl)butanoate (3p): 41.1 mg; 90% yield; yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.55-7.52 (m, 1H), 7.34-7.30 (m, 1H), 4.62 (s, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.47-3.31 (m, 3H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.65, 172.70, 140.77, 131.82, 125.76, 125.65, 66.21, 60.89, 42.26, 13.10; IR (KBr, *v*, cm^{-1}): 3473, 3102, 2981, 1736, 1672, 1511, 1412, 1266, 1206, 1101, 1040, 866, 798, 636; HRMS (ESI) found: *m/z* 251.0346 $[M + Na]^+$; calcd. for $C_{10}H_{12}O_4S$+Na 251.0349.

Ethyl 2-hydroxy-4-oxo-6-phenylhexanoate (3q): 42.0 mg; 84% yield; yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23-7.18 (m, 2H), 7.14-7.08 (m, 3H), 4.40 (dd, *J* = 5.7, 4.2 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.16 (s, 1H), 2.89-2.69 (m, 6H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.34, 173.72, 140.70, 128.55, 128.31, 126.21, 66.98, 61.94, 46.09, 44.95, 29.36, 14.14; IR (KBr, *v*, cm^{-1}): 3485, 2979, 2933, 2128, 1720, 1450, 1374, 1264, 1211, 1099, 1033, 749, 701; HRMS (ESI) found: *m/z* 273.1097 $[M + Na]^+$; calcd. for $C_{14}H_{18}O_4$+Na 273.1097.

Ethyl 4-cyclopropyl-2-hydroxy-4-oxobutanoate (3r): 31.6 mg; 85% yield; colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 4.47 (dd, *J* = 5.9, 4.0 Hz, 1H), 4.28-4.20 (m, 2H), 3.25 (s, 1H), 3.11 (dd, *J* = 17.4, 3.9 Hz, 1H), 3.03 (dd, *J* = 17.4, 6.1 Hz, 1H), 1.97-1.90 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.10-1.06 (m, 2H), 0.95-0.90 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.41, 173.66, 67.04, 61.81, 46.42, 21.06, 14.14, 11.30; IR (KBr, *v*, cm^{-1}): 3496, 2985, 1738, 1698, 1391, 1265, 1205, 1094, 1030, 737; HRMS (ESI) found: *m/z* 209.0784 $[M + Na]^+$; calcd. for $C_9H_{14}O_4$+Na 279.0784.

Ethyl 4-cyclohexyl-2-hydroxy-4-oxobutanoate (3s): 36.5 mg; 80% yield; yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 4.45 (s, 1H), 4.26-4.18 (m, 2H), 3.25 (s, 1H), 2.99-2.88 (m, 2H), 2.34-2.31 (m, 1H), 1.85-1.64 (m, 5H), 1.30-1.15 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.70, 173.80, 67.10, 61.77, 51.03, 43.85, 28.14, 28.06, 25.77, 25.53, 25.49, 14.14; IR (KBr, *v*, cm^{-1}): 3487, 2931, 2856, 2360, 1739, 1712, 1449, 1377, 1260, 1207, 1107, 1032, 758; HRMS (ESI) found: *m/z* 251.1274 $[M + Na]^+$; calcd. for $C_{12}H_{20}O_4$+Na 251.1276.

Ethyl 2-hydroxy-4-oxoheptanoate (3t)[14d]**:** 32.7 mg; 87% yield; colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 4.45 (dd, *J* = 9.8, 5.5 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.23 (d, *J* = 5.2 Hz, 1H), 2.92 (dd, *J* = 17.3, 4.0 Hz, 1H), 2.86 (dd, *J* = 17.3, 6.1 Hz, 1H), 2.41 (t, *J* = 7.3 Hz, 2H), 1.64-1.55 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.57, 173.75, 67.03, 61.85, 45.86, 45.30, 16.97, 14.12, 13.61.

Ethyl 2-hydroxy-5,5-dimethyl-4-oxohexanoate (3u)[14e]**:** 35.2 mg; 87% yield; colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 4.44 (dd, *J* = 9.9, 4.9 Hz, 1H), 4.21 (q, *J* = 8.0 Hz, 2H), 3.29 (d, *J* = 5.5 Hz, 1H), 2.98 (d, *J* = 4.7 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.11 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.70, 173.94, 67.15, 61.68, 44.11, 40.35, 26.07, 14.11.

Methyl 2-hydroxy-5,5-dimethyl-4-oxohexanoate (9)[14i]: 72.5 mg; 82% yield; yellow oil; ^1H NMR (400 MHz, D_2O) δ 4.47 (t, *J* = 5.0 Hz, 1H), 3.63 (s, 3H), 3.08 (d, *J* = 5.1 Hz, 2H), 1.01 (s, 9H); ^{13}C NMR (101 MHz, D_2O) δ 218.06, 175.98, 66.30, 52.62, 43.93, 40.76, 25.15.

General procedure for decarboxylative aldol reaction of *β*-ketoacids with glyoxal monohydrates

A mixture of *β*-ketoacid **1a** (164.2 mg, 1 mmol) and glyoxal monohydrate **4** (0.67 mmol) was stirred in water (2 mL) at room temperature for 8 h. In most cases (except **5j** and **5k**), the solid product was directly filtered, washed with saturated sodium bicarbonate (20 mL) and dried under vacuum to afford the aldol products. Compounds **5j** and **5k** were purified by flash column chromatography (petroleum ether/ethyl acetate: 6/1–4/1).

2-hydroxy-1,4-diphenylbutane-1,4-dione (5a)[14h]**:** 145 mg; 85% yield; white solid; Mp: 90-92 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01-7.97 (m, 2H), 7.95-7.91 (m, 2H), 7.61-7.53 (m, 2H), 7.52-7.43 (m, 4H), 5.68 (s, 1H), 4.08 (s, 1H), 3.52-3.29 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.82, 197.19, 136.60, 135.14, 133.99, 133.62, 128.97, 128.76, 128.70, 128.35, 70.06, 43.56.

2-hydroxy-4-phenyl-1-(p-tolyl)butane-1,4-dione (5b)[14h]**:** 167.2 mg; 93% yield; white solid; Mp: 112-113 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95-7.87 (m, 4H), 7.59-7.53 (m, 1H), 7.47-7.41 (m, 2H), 7.31-7.27 (m, 2H), 5.66 (s, 1H), 4.04 (d, *J* = 5.8 Hz, 1H), 3.44-3.31 (m, 2H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.37, 197.17, 145.11, 136.69, 133.57, 130.90, 129.67, 128.87, 128.68, 128.35, 69.88, 43.87, 21.79.

2-hydroxy-1-(4-methoxyphenyl)-4-phenylbutane-1,4-dione (5c)[14h]**:** 175.3 mg; 92% yield; white solid; Mp: 120-121 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01-7.97 (m, 2H), 7.97-7.93 (m, 2H), 7.60-7.55 (m, 1H), 7.49-7.43 (m, 2H), 6.99-6.95 (m, 2H), 5.69-5.65 (m, 1H), 4.08 (d, *J* = 6.3 Hz, 1H), 3.88 (s, 3H), 3.42 (dd, *J* = 17.0, 7.9 Hz, 1H), 3.31 (dd, *J* = 17.0, 2.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.09, 197.34, 164.26, 136.70, 133.59, 131.18, 128.69, 128.36, 126.12, 114.22, 69.61, 55.60, 44.09.

1-(4-fluorophenyl)-2-hydroxy-4-phenylbutane-1,4-dione (5d)[14h]**:** 164.2 mg; 90% yield; white solid; Mp: 121-123 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07-8.03 (m, 2H), 7.95-7.93 (m, 2H), 7.59-7.57 (m, 1H), 7.47-7.44 (m, 2H), 7.19-7.14 (m, 2H), 5.61 (s, 1H), 4.11 (s, 1H), 3.46 (dd, *J* = 17.2, 7.1 Hz, 1H), 3.37 (dd, *J* = 17.2, 3.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.08 (s), 197.52 (s), 166.11 (d, *J* = 257.2 Hz), 136.51 (s),

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133.72 (s), 131.61 (d, *J* = 9.4 Hz), 130.13 (s), 128.74 (s), 128.34 (s), 116.15 (d, *J* = 21.2 Hz), 70.17 (s), 43.26 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.13~-103.27 (m).

1-(4-chlorophenyl)-2-hydroxy-4-phenylbutane-1,4-dione (5e)[14h]**:** 164.1 mg; 85% yield; white solid; Mp: 149-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.93 (m, 4H), 7.61-5.56 (m, 1H), 7.48-7.44 (m, 4H), 5.59 (s, 1H), 4.06 (s, 1H), 3.46 (dd, *J* = 17.3, 6.9 Hz, 1H), 3.38 (dd, *J* = 17.2, 3.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.55, 197.51, 140.42, 136.45, 133.78, 132.10, 130.25, 129.28, 128.75, 128.34, 70.29, 43.14.

1-(4-bromophenyl)-2-hydroxy-4-phenylbutane-1,4-dione (5f)[14h]**:** 201.2 mg; 90% yield; yellow solid; Mp: 155-157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.93 (m, 2H), 7.90-7.86 (m, 2H), 7.65-7.63 (m, 2H), 7.61-7.57 (m, 1H), 7.49-7.44 (m, 2H), 5.57 (s, 1H), 4.02 (s, 1H), 3.46 (dd, *J* = 17.2, 6.9 Hz, 1H), 3.38 (dd, *J* = 17.2, 3.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.74, 197.48, 136.47, 133.77, 132.56, 132.26, 130.31, 129.17, 128.75, 128.34, 70.34, 43.11.

2-hydroxy-1-(4-nitrophenyl)-4-phenylbutane-1,4-dione (5g)[14h]**:** 150.4 mg; 75% yield; yellow solid; Mp: 143-145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34-8.30 (m, 2H), 8.20-8.16 (m, 2H), 7.96-7.92 (m, 2H), 7.63-7.58 (m, 1H), 7.50-7.47 (m, 2H), 5.52-5.48 (m, 1H), 4.09 (s, 1H), 3.54 (d, *J* = 4.9 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.41, 198.04, 150.46, 139.23, 136.16, 134.02, 130.03, 128.82, 128.33, 123.91, 71.25, 42.22.

2-hydroxy-1-(naphthalen-2-yl)-4-phenylbutane-1,4-dione (5h)[14h]**:** 167.2 mg; 82% yield; yellow solid; Mp: 91-92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.04-8.02 (m, 1H), 7.98-7.91 (m, 4H), 7.89-7.85 (m, 1H), 7.64-7.60 (m, 1H), 7.59-7.53 (m, 2H), 7.47-7.41 (m, 2H), 5.85-5.81 (m, 1H), 4.11 (d, *J* = 6.1 Hz, 1H), 3.52-3.41 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.74, 197.31, 136.64, 135.94, 133.63, 132.43, 130.89, 130.66, 129.75, 129.04, 128.94, 128.70, 128.36, 127.87, 127.12, 124.10, 70.19, 43.79.

2-hydroxy-4-phenyl-1-(thiophen-2-yl)butane-1,4-dione (5i)[14h]**:** 151.4 mg; 87% yield; white solid; Mp: 114-116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98-7.96 (m, 3H), 7.74-7.72 (m, 1H), 7.61-7.57 (m, 1H), 7.49-7.45 (m, 2H), 7.19-7.16 (m, 1H), 5.45-5.40 (m, 1H), 4.01 (d, *J* = 6.6 Hz, 1H), 3.56 (dd, *J* = 17.3, 7.6 Hz, 1H), 3.45 (dd, *J* = 17.3, 3.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.02, 193.15, 139.88, 136.49, 135.04, 133.92, 133.76, 128.75, 128.40, 128.35, 71.54, 43.66.

3-hydroxy-1-phenylpentane-1,4-dione (5j)[14f]**:** 36.1 mg; 94% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.93 (m, 2H), 7.62-7.56 (m, 1H), 7.50-7.44 (m, 2H), 4.52 (d, *J* = 3.3 Hz, 1H), 3.85 (d, *J* = 4.3 Hz, 1H), 3.56 (dd, *J* = 17.6, 3.7 Hz, 1H), 3.40 (dd, *J* = 17.6, 6.1 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.71, 198.36, 136.31, 133.84, 128.77, 128.30, 73.91, 41.64, 25.65.

3-hydroxy-5,5-dimethyl-1-phenylhexane-1,4-dione (5k): 41.2 mg; 88% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98-7.94 (m, 2H), 7.62-7.56 (m, 1H), 7.50-7.45 (m, 2H), 5.08 (s, 1H), 3.62 (s, 1H), 3.35 (dd, *J* = 17.1, 7.2 Hz, 1H), 3.28 (dd, *J* = 17.1, 3.5 Hz, 1H), 1.28 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.77, 198.33, 136.68, 133.63, 128.72, 128.29, 69.80, 43.50, 42.44, 26.80. IR (KBr, *v*, cm^{-1}): 3422, 1735, 1702, 1450, 1365, 1260, 1205, 1154, 1036, 950, 758; HRMS (ESI) found: *m/z* 257.1144 $[M + Na]^+$; calcd. for $C_{14}H_{18}O_3$+Na 257.1148.

Procedure for decarboxylative aldol reaction of *β*-ketoacid 1a with nicotinaldehyde 6

nicotinaldehyde **6** (0.75 g, 7 mmol) was added to the suspension of *β*-ketoacid **1a** (1.7 g, 10.5 mmol) in water (15 mL). The ultimate suspension was stirred for 10 h at room temperature. The white precipitate was directly filtered, washed with saturated sodium bicarbonate (60 mL), and dried under vacuum to afford the desired product **7** (1.3 g, 87%) without further purification.

3-hydroxy-1-phenyl-3-(pyridin-3-yl)propan-1-one (7)[14g]**:** 1.3 g; 87% yield; white solid; Mp: 89-91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.48-8.44 (m, 1H), 7.94-7.91 (m, 2H), 7.82-7.78 (m, 1H), 7.59-7.54 (m, 1H), 7.47-7.41 (m, 2H), 7.30-7.25 (m, 1H), 5.38 (dd, *J* = 8.8, 3.3 Hz, 1H), 4.63 (s, 1H), 3.41 (dd, *J* = 17.6, 8.8 Hz, 1H), 3.32 (dd, *J* = 17.6, 3.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.52, 148.87, 147.65, 138.90, 136.52, 133.91, 133.88, 128.86, 128.28, 123.67, 67.93, 47.23.

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