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A Stereoselective and Practical Synthesis of (*E*)-α,β-Unsaturated Ketones from Aldehydes

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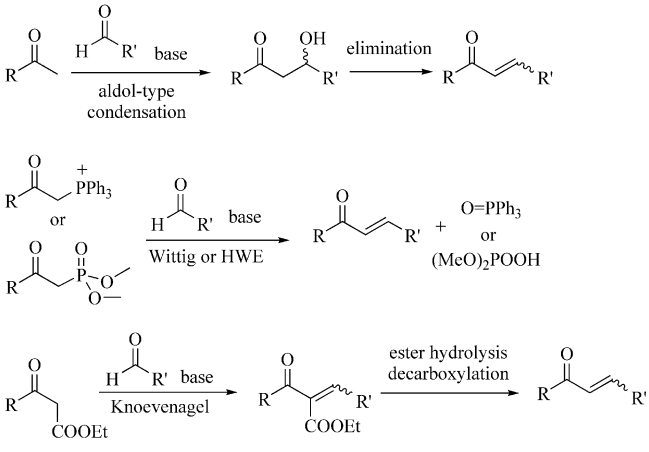
α,β-Unsaturated ketones can be prepared by reaction of differently substituted β-keto acids and aldehydes. The reaction is carried out under organocatalysis (β-alanine, 0.5 equiv.) and generates the enones with high *E* selectivity (>95 %). This version of the Verley–Doebner modification of the Knoevenagel reaction is a practical alternative to the classic Horner–Wadsworth–Emmons (HWE) reaction without the formation of high molecular weight byproducts. The process makes use of simple reagents and can be applied to large-scale synthesis under conditions compatible with atom-economy principles. Differently substituted aliphatic, aromatic, or heteroaromatic α,β-unsaturated ketones can be prepared. An example of a hydroformylation/Verley–Doebner Knoevenagel telescoped process is also described.

Introduction

α,β-Unsaturated ketones are important chemicals as intermediates or final products with different applications.[1] Several methods have been described for their preparation as aldol-type condensation followed by elimination,[2] acylation reactions,[3] transition-metal-catalyzed reactions,[4] Wittig, or Horner–Wadsworth–Emmons (HWE) reaction with alkoxy phosphoranes.[5] Some of these reactions suffer from being low (*E*)-stereoselective in the C–C bond formation, from the use of expensive or sensitive reagents that prevents the scale-up of the process, and from scarce atom economy. The most stereocontrolled Wittig or HWE reactions produce in fact high molecular weight byproducts. The Knoevenagel condensation between a β-keto ester and an aldehyde has also been applied to α,β-unsaturated ketone syntheses. After the condensation, the ester can be hydrolyzed and further decarboxylated to give the conjugated ketone.[6] However, mixtures of (*E*) and (*Z*) products are often obtained, limiting the application of this potentially useful and simple procedure (Scheme 1).



Scheme 1. Standard approaches for the synthesis of α,β unsaturated ketones.

Results and Discussion

Recently, List described a new protocol for the Knoevenagel reaction using malonic acid half ester in the presence of 10% DMAP to transform an aldehyde into the corresponding α,β-unsaturated ester in good yields with excellent (*E*)-stereoselectivity.[7] The possibility to apply an analogous approach to the synthesis of α,β-unsaturated ketones appeared to be useful to access this class of important compounds. In that case, the malonic acid half ester would be replaced by a β-keto acid that, reacting with an aldehyde, gives a ketol that is further transformable into the α,β-unsaturated ketone.

The main expected problem would be the low yield in the β-keto acid preparation due to decarboxylation, as previously reported.[8] To overcome this drawback, the reaction of the potassium salt of 2-oxobutanoic acid with aldehydes has also been described.[9] The condensation occurred in water in a very precise pH range (between 7.5 and 8.5) in order to prevent the self condensation of the aldehyde. A β-ketol is formed and further strong acidification (pH 1) generates directly the α,β-unsaturated ketone in a tele-

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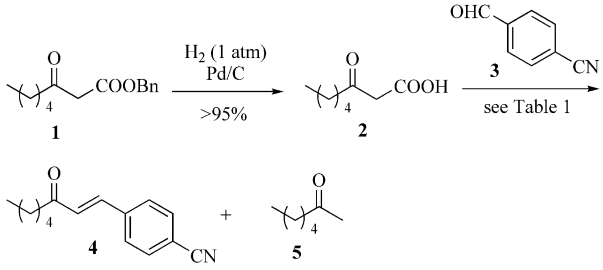
scoped process. As these conditions seemed to be not suitable for a large-scale application, we decided to investigate the application of a Knoevenagel-type protocol to the direct synthesis of α,β-unsaturated ketones that could be easily applied to a preparative level. In order to find the best conditions, the reaction between *p*-cyanobenzaldehyde (**3**) and 3-oxooctanoic acid (**2**) was investigated (Scheme 2). A practical approach towards a β-keto acid might be the hydrogenolysis of the corresponding β-keto benzyl ester. The synthesis of β-keto benzyl esters has been described although these products have been employed for different purposes.[10] Thus, compound **1**, prepared from hexanoic acid and malonic acid monobenzyl ester,[10] was hydrogenolyzed over Pd/C (10%) to give acid **2** in almost quantitative yield (Scheme 2).



Scheme 2. Preparation of α,β-unsaturated ketone **4**.

Simple filtration of the catalyst and evaporation of the solvent gave acid **2** pure enough to be directly used in the next step. Moreover, unlike in the previous descriptions,[8] pure product **2** was sufficiently stable to allow wide investigation of its reactivity.[11]

At first, conditions similar to those employed by List[7] were investigated. However, the presence of DMAP gave rapid decarboxylation of **2** with formation of large amounts of ketone **5** (Table 1, Entry 1). The first conditions published (use of pyridine as the solvent or as the base in DMF)[8] were also employed, but again the decarboxylation of **2** was the only reaction observed (Table 1, Entries 2 and 3). Using piperidine in DMF at 40 °C for 12 h, expected product **4** was obtained in 25% yield (Table 1, Entry 4). However, **4** was isolated as a single (*E*) isomer (as shown by 400 MHz ^{1}H NMR spectroscopic analysis), prompting us to investigate different reaction conditions to optimize the yield. An increase in the amount of acid **2** gave improved yields of compound **4** or **5**. In the presence of triethylamine, decarboxylation was exclusively observed (Table 1, Entry 6), and a complex mixture of products was obtained using a primary amine (Table 1, Entry 7). The replacement of DMF with toluene gave a further slight improvement (higher **4**/**5** ratio; Table 1, Entry 8), whereas the contemporary use of piperidine and acetic acid promoted decarboxylation (Table 1, Entry 9). The yield of **4** increased to 73% when the base was replaced by β-alanine (Table 1, Entries 10 and 11). The use of amino acids in aldol/Knoevenagel reactions is well precedented,[12] and β-alanine has been employed since 1925[13] in the Verley–Doebner modification of the Knoevenagel reaction for the synthesis of β-keto esters.[14] However, these conditions have never been applied to the synthesis of ketones.

A further improvement in the yield of **4** was achieved by removing the water that was formed during the reaction.[6] In the presence of dry Na_2SO_4 or 4 Å molecular sieves (MS), **4** was isolated in 84 and 86% yield, respectively (Table 1, Entries 12 and 13). The amount of β-alanine and β-keto acid could also be reduced up to 0.5 and 1.5 equiv., respectively, without observing a reduction in the yield of **4**[15] (Table 1, Entries 14 and 15). To speed up the reaction, the use of microwave dielectric heating was also attempted.[16] However, working at 40 °C in toluene (or without solvent), compound **4** was obtained in about 42% yield

Table 1. Optimization of reaction conditions for the synthesis of **4**.[a]

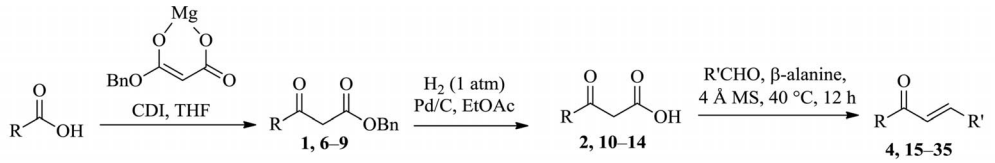
Entry	Solvent	Additive	Temperature [°C]	Time [h]	Product (% yield)[b]
1	DMF	DMAP (0.1 equiv.)	r.t.	2	**5** (50)
2	pyridine	–	r.t.	12	**5** (60)
3	DMF	pyridine (1 equiv.)	r.t.	12	**5** (60)
4	DMF	piperidine (0.5 equiv.)	40	12	**4** (25), **5** (30)
5	DMF	piperidine (0.5 equiv.)[c]	40	12	**4** (45), **5** (40)
6	DMF	TEA (0.5 equiv.)	40	2	**5** (70)
7	DMF	$C_4H_9NH_2$ (0.5 equiv.)	40	12	–
8	toluene	piperidine (0.5 equiv.)	40	12	**4** (45), **5** (10)
9	toluene	piperidine/AcOH (0.5 equiv.)	40	12	**4** (35), **5** (50)
10	toluene	β-alanine (1 equiv.)	40	12	**4** (67)
11	toluene	β-alanine (1 equiv.)[c]	40	12	**4** (73)
12	toluene	β-alanine (1 equiv.), Na_2SO_4 (4 equiv.)[c]	40	12	**4** (84)
13	toluene	β-alanine (1 equiv.), 4 Å MS[c]	40	12	**4** (86)
14	toluene	β-alanine (0.5 equiv.), 4 Å MS[d]	40	12	**4** (84)
15	toluene	β-alanine (0.5 equiv.), Na_2SO_4[d]	40	12	**4** (82)
16	toluene	β-alanine (1 equiv.), 4 Å MS, MW	40	2	**4** (44)
17	–	β-alanine (1 equiv.), 4 Å MS, MW	40	2	**4** (42)
18	toluene	L-alanine (1 equiv.), Na_2SO_4 (4 equiv.)	40	12	**4** (44)
19	toluene	L-proline (1 equiv.), Na_2SO_4 (4 equiv.)	40	12	**4** (50)
20	toluene	6-aminocaproic acid (1 equiv.), Na_2SO_4 (4 equiv.)	40	12	**4** (27)

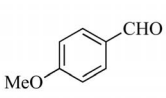
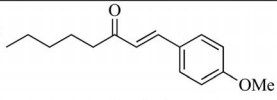
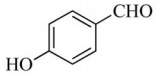
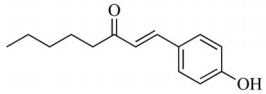
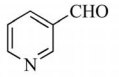
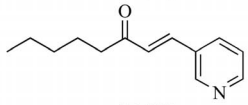
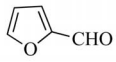
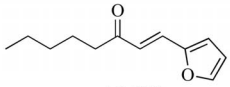
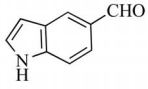
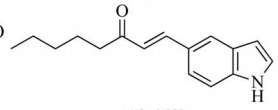
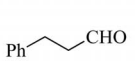
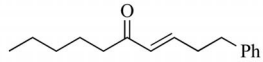
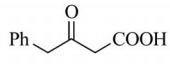
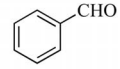
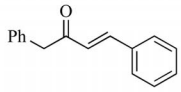
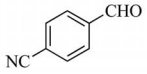
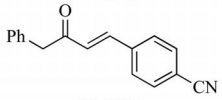
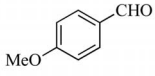
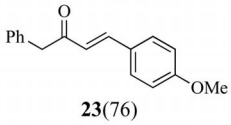
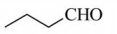
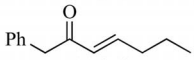
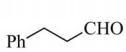
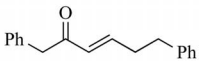
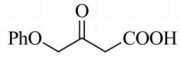
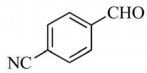
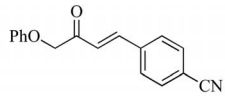
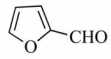
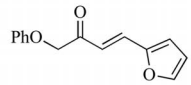
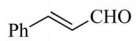
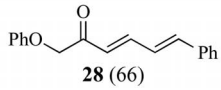
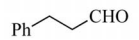
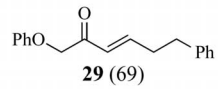
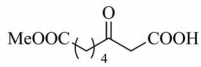
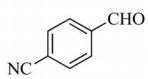
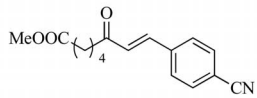
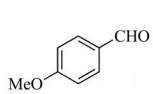
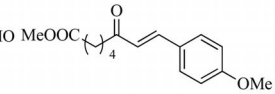
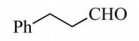
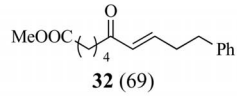
[a] If not differently stated, the reaction was carried out with 2 equiv. of acid **2** with respect to aldehyde **3**. [b] Yield of isolated and fully characterized compound. [c] 3 equiv. of **2** was used. [d] 1.5 equiv. of **2** was used.

after 2 h of irradiation (Table 1, Entries 16 and 17). Higher temperatures promoted decarboxylation. Finally, β-alanine was superior with respect to other amino acids investigated, including 6-aminocaproic acid, which has been described to give comparable results[13] (Table 1, Entries 18–20).

The previously optimized reaction conditions (toluene, 0.5 equiv. of β-alanine, 1.5 equiv. of β-keto acid, 4 Å MS, 40 °C, 12 h) were applied to different aldehydes and β-keto acids. All the β-keto acids (**10**–**14**, Table 2) employed were obtained in good yields by reaction of the corresponding

Table 2. Transformation of carboxylic acids into α,β-unsaturated ketones.

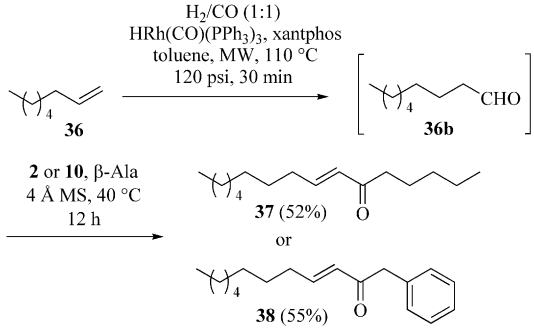


Entry	β-Ketoacid (% yield)[a]	Aldehyde	Product (% yield)[b]
1	**2** (81)		 **15** (55)
2	**2** (81)		 **16** (70)
3	**2** (81)		 **17** (75)
4	**2** (81)		 **18** (85)
5	**2** (81)		 **19** (69)
6	**2** (81)		 **20** (72)
7	 **10** (75)		 **21** (80)
8	**10** (75)		 **22** (80)
9	**10** (75)		 **23**(76)
10	**10** (75)		 **24** (51)
11	**10** (75)		 **25** (65)
12	 **11** (84)		 **26** (75)
13	**11** (84)		 **27** (85)
14	**11** (84)		 **28** (66)
15	**11** (84)		 **29** (69)
16	 **12** (73)		 **30** (73)
17	**12** (73)		 **31** (79)
18	**12** (73)		 **32** (69)
19	**13** (74)		**33** (52)
20	**13** (74)		**34** (70)
21	**13** (74)		**35** (58)
22	**14** (77)		[c]

[a] Overall yield starting from the corresponding carboxylic acid. [b] Yield of isolated and fully characterized product. [c] A complex mixture of products was formed. HPLC–MS analysis showed the presence of the expected ketone in about 10% yield.

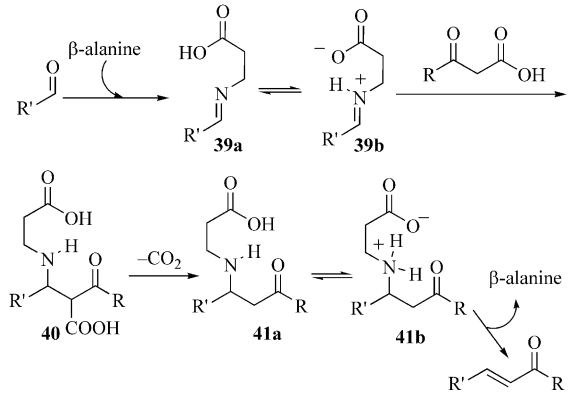
activated carboxylic acid with magnesium malonate monobenzyl ester[11] followed by hydrogenolysis. Aromatic aldehydes carrying either electron-withdrawing or electron-donating substituents gave good results (Table 2, Entries 1, 2, 7, 8, 12, 16, and 17) and even heterocyclic aldehydes (such as pyridine, furan, and indole aldehydes; Table 2, Entries 3, 4, 5, and 13) gave the corresponding α,β-unsaturated ketones in significant yields. The presence of different functional groups in the fragments originating from the acid or the aldehyde is also compatible with the process, and α,β-unsaturated ketones containing unprotected phenols, nitriles, carboxylates, and protected amines or alcohols can be prepared (Table 2, Entries 2, 8, 12, 16–21). Conjugated dienyl ketones (as compounds **28** and **35** in Table 2) can also be prepared starting from α,β-unsaturated aldehydes. The only limit observed was the low reactivity of aromatic β-keto acids such as 3-oxo-3-phenylpropionic acid (**14**; Table 2, Entry 22). However, chalcones (and chalconoids) produced with this type of acid could be easily obtained by alkaline condensation of acetophenones.[17] On the other hand, it is remarkable that the process works well with aliphatic β-keto acids and aliphatic aldehydes. Fully aliphatic α,β-unsaturated ketones are more difficult to obtain through aldol-type condensation/elimination because of regioselectivity problems in the enolization of the ketone and the self-condensation of the enolizable aldehyde.[18] Finally, products **15**–**35** were all obtained as (*E*) isomers (400 MHz NMR spectroscopic analysis, selectivity >95%).

This modification of the Verley–Doebner Knoevenagel reaction can be also applied under conditions analogous to the one-pot hydroformylation/decarboxylative Knoevenagel reaction sequence recently described by Breit for the synthesis of β-keto esters.[19] In our case, the telescoped process starts with hydroformylation of terminal alkene **36** (Scheme 3) under microwave dielectric heating.[20] After release of the syngas, β-alanine, 4 Å MS, and acid **2** or **10** were added, and the mixture was stirred at 40 °C for 12 h to give α,β-unsaturated ketone **33** or **38**, respectively, in 52 and 55% overall yield (Scheme 4).



Scheme 3. Telescoped hydroformylation/Verley–Doebner Knoevenagel reaction.

In light of the recent advances in understanding the role of organocatalysis in condensation reactions,[21] it is possible to propose a mechanism that may explain the influence of β-alanine in the process (Scheme 4). The aldehyde



Scheme 4. Proposed role of β-alanine in the condensation reaction.

reacts with the amino acid to form imine **39a**, which is in equilibrium with the more reactive iminium (zwitter)ion **39b**. Reaction of **39b** with the β-keto acid gives intermediate **40** at a pH value suitable to keep the carboxylic acid undissociated and ready for decarboxylation. Finally, the formation of zwitterion **41b** promotes the elimination reaction to form the (*E*) double bond and to regenerate the catalyst.

The proximity of opposite charges in **39b** or **41b** and the possibility of forming intramolecular H bonds in intermediates **39a**, **40**, or **41a** may explain the efficacy of β-alanine as the organocatalyst in the reaction.

Conclusions

In conclusion, we have developed a friendly protocol to carry out the Verley–Doebner modification of the Knoevenagel reaction with β-keto acids and aldehydes to produce α,β-unsaturated ketones. The process is based on the friendly preparation of β-keto acids by hydrogenolysis of the corresponding benzyl esters, and the reaction conditions allow significant reduction in the formation of byproducts. The method can be applied to the large-scale synthesis of differently substituted aliphatic, aromatic, or heteroaromatic α,β-unsaturated ketones.

Experimental Section

General Methods: The reactions were carried out in oven-dried glassware under a nitrogen atmosphere. Solvents were dried and purified by conventional methods prior use. Flash column chromatography was performed with Merck silica gel 60, 0.040–0.063 mm (230–400 mesh). Merck aluminum-backed plates precoated with silica gel 60 (UV_{254}) were used for thin-layer chromatography and were visualized by staining with $KMnO_4$. ^1H NMR and ^{13}C NMR spectra were recorded with a Bruker AC 400 MHz instrument at 400 and at 100 MHz, respectively. Low-resolution mass spectra were obtained with an Agilent 1100 LC–MS instrument in positive or negative mode, and HRMS were conducted at the Institut Fédératif de Recherche at the Louis Pasteur University, Strasbourg, France. GC–MS analysis was performed with a Varian-GC by using a CP 8944 column (30 m × 0.250 mm × 0.39 μm). For MW reactions, a CEM Discover

microwave oven equipped with an 80 or 10-mL tube for reactions under pressure was employed.

Benzyl 3-Oxooctanoate (1): Hexanoic acid (3 mL, 23.94 mmol) was dissolved in dry THF (42 mL) under an atmosphere of N_2 and 1,1′-carbonyldiimidazole (4.26 g, 26.33 mmol) was added, and the mixture was stirred at room temperature for 3 h (solution A). In a separate flask, to a solution of monobenzyl malonate (5.58 g, 28.73 mmol) in dry THF (42 mL) at 0 °C under an atmosphere of N_2 was dropwise added isopropylmagnesium chloride (2 M in THF, 28.73 mL, 57.46 mmol). After 30 min at 0 °C the solution was heated at 50 °C for 30 min and then cooled again to 0 °C at which time solution A was added dropwise. The mixture was left to warm to room temperature and then stirred for 16 h. The mixture was then quenched with 1 M HCl and extracted with Et_2O. The organic layer was washed with 1 M HCl (3 × 50 mL), $NaHCO_3$ (3 × 50 mL), and brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure The crude was purified by flash chromatography on silica gel (petroleum ether 40–60 °C/EtOAc, 9:1). Compound **1** (5.04 g, 85%) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.22 (m, 5 H, ArH), 5.06 (s, 2 H, CH_2), 3.35 (s, 2 H, CH_2), 2.37 (t, J = 7 Hz, 2 H, CH_2), 1.52–1.45 (m, 2 H, CH_2), 1.24–1.15 (m, 4 H, CH_2), 0.81 (t, J = 7 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.73, 166.46, 135.25, 128.02, 127.73, 127.61, 66.26, 48.55, 42.27, 30.65, 22.61, 21.84, 13.89 ppm. MS (ES+): m/z = 271 $[M + Na]^+$. HRMS (ES+): calcd. for $C_{15}H_{20}NaO_3$ 271.1310; found 271.1307.

Benzyl 3-Oxo-4-phenylbutanoate (6): Colorless oil: 5.06 g (79% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.18 (m, 10 H, ArH), 5.17 (s, 2 H, CH_2), 3.80 (s, 2 H, CH_2), 3.51 (s, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.78, 166.49, 134.83, 132.75, 129.14, 128:89, 128.45, 128.20, 128.06, 127.97, 126.96, 126.66, 66.75, 49.64, 47.78 ppm. MS (ES+): m/z = 291 $[M + Na]^+$. HRMS (ES+): calcd. for $C_{17}H_{16}NaO_3$ 291.0997; found 291.0995.

Benzyl 3-Oxo-4-phenoxybutanoate (7): White solid: 5.98 g (88% yield), m.p. 33–35 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.18 (m, 10 H, ArH), 5.17 (s, 2 H, CH_2), 3.80 (s, 2 H, CH_2), 3.51 (s, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.97, 166.24, 157.02, 134.80, 129.34, 129.24, 128.23, 128.09, 128.00, 121.58, 114.27, 114.15, 72.01, 66.86, 45.67 ppm. MS (ES+): m/z = 307 $[M + Na]^+$. HRMS (ES+): calcd. for $C_{17}H_{16}NaO_4$ 307.0946; found 307.0949.

1-Benzyl 8-Methyl 3-Oxooctanedioate (8): Colorless oil: 5.17 g (74% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.24 (m, 5 H, ArH), 5.07 (s, 2 H, CH_2), 3.55 (s, 3 H, CH_3), 3.38 (s, 2 H, CH_2), 2.44–2.41 (m, 2 H, CH_2), 2.20–2.17 (m, 2 H, CH_2), 1.51–1.48 (m, 4 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.66, 173.15, 166.52, 134.97, 128.11, 127.87, 126.37, 66.49, 50.95, 48.63, 41.95, 33.15, 23.67, 22.28 ppm. MS (ES+): m/z = 315 $[M + Na]^+$. HRMS (ES+): calcd. for $C_{16}H_{20}NaO_5$ 315.1208; found 315.1205.

Benzyl 4-(*tert*-Butoxycarbonylamino)-3-oxobutanoate (9): Colorless oil: 5.43 g (74% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (s, 5 H, ArH), 5.14 (s, 2 H, CH_2), 4.07 (s, 2 H, CH_2), 3.50 (s, 2 H, CH_2), 1.41 (s, 9 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.16, 166.02, 155.19, 134.66, 128.23, 128.13, 127.96, 79.78, 66.95, 50.18, 46.01, 27.85 ppm. MS (ES+): m/z = 330 $[M + Na]^+$. HRMS (ES+): calcd. for $C_{16}H_{21}NNaO_5$ 330.1317; found 330.1319.

Preparation of 3-Oxooctanoic Acid (2) as a Representative Procedure for Hydrogenolysis: A solution of **1** (1.5 g, 6.05 mmol) in EtOAc (30 mL) was stirred with 10% Pd/C (320 mg, 0.30 mmol) under an atmosphere of hydrogen (1 atm) at room temperature for 1 h. The mixture was filtered through Celite, and the solvent was evaporated under reduced pressure at 30 °C. Compound **2** was obtained as a white solid (908 mg, 95% yield). M.p. 69–72 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.39 (br. s, 1 H, COOH), 3.47 (s, 2 H, CH_2), 2.53–2.51 (m, 2 H, CH_2), 1.59–1.57 (m, 2 H, CH_2), 1.28–1.26 (m, 4 H, CH_2), 0.87–0.86 (m, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.65, 171.39, 47.58, 42.78, 30.66, 22.64, 21.91, 13.77 ppm. MS (ES+): m/z = 181 $[M + Na]^+$. HRMS (ES+): calcd. for $C_8H_{14}NaO_3$ 181.0841; found 181.0843.

3-Oxo-4-phenylbutanoic Acid (10): White solid: 1.02 g (95% yield), m.p. 58–60 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (br. s, 1 H, COOH), 7.33–7.18 (m, 5 H, ArH), 3.82 (s, 2 H, CH_2), 3.48 (s, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.84, 171.21, 132.53, 129.11, 128.99, 128.58, 128.26, 127.17, 49.77, 46.68 ppm. MS (ES+): m/z = 201 $[M + Na]^+$. HRMS (ES+): calcd. for $C_{10}H_{10}NaO_3$ 201.0528; found 201.0530.

3-Oxo-4-phenoxybutanoic Acid (11): White solid: 1.11 g (95% yield), m.p. 64–66 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (br. s, 1 H, COOH), 7.31–7.27 (m, 2 H, ArH), 7.02–6.86 (m, 3 H, ArH), 4.63 (s, 2 H, CH_2), 3.68 (s, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.25, 171.70, 157.88, 129.39, 129.24, 121.75, 114.24, 114.10, 72.02, 45.02 ppm. MS (ES+): m/z = 217 $[M + Na]^+$. HRMS (ES+): calcd. for $C_{10}H_{10}NaO_4$ 217.0477; found 217.0480.

8-Methoxy-3,8-dioxooctanoic Acid (12): White solid: 1.16 g (95% yield), m.p. 44–46 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.65 (br. s, 1 H, COOH), 3.60 (s, 3 H, CH_3), 3.44 (s, 2 H, CH_2), 2.55–2.53 (m, 2 H, CH_2), 2.28–2.26 (m, 2 H, CH_2), 1.58–1.56 (m, 4 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.73, 173.60, 170.87, 51.20, 47.87, 42.19, 33.23, 23.65, 22.26 ppm. MS (ES+): m/z = 225 $[M + Na]^+$. HRMS (ES+): calcd. for $C_9H_{14}NaO_5$ 225.0739; found 225.0736.

4-(*tert*-Butoxycarbonylamino)-3-oxobutanoic Acid (13): White solid: 1.25 g (95% yield), m.p. 94–96 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (br. s, 1 H, COOH), 5.35 (br. s, 1 H, NH), 4.16 (s, 2 H, CH_2), 3.50 (s, 2 H, CH_2), 1.42 (s, 9 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.73, 169.61, 155.65, 80.06, 50.12, 45.60, 27.84 ppm. MS (ES+): m/z = 240 $[M + Na]^+$. HRMS (ES+): calcd. for $C_9H_{15}NNaO_5$ 240.0848; found 240.0845.

3-Oxo-3-phenyl Propanoic Acid: (14) White solid: 1.02 g (77% yield), m.p. 79–80 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.11 (br. s, 1 H, COOH), 7.59 (m, 2 H, ArH), 7.16 (m, 3 H, ArH), 3.48 (s, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.72, 169.71, 132.88, 129.19, 128.94, 121.35, 52.12 ppm. MS (ES+): m/z = 187 $[M + Na]^+$. HRMS (ES+): calcd. for $C_9H_{19}NaO_3$ 187.0371; found 187.0375.

Preparation of (*E*)-4-(3-Oxooct-1-enyl)benzonitrile (4) as a Representative Procedure for the Modified Verley–Doebner Knoevenagel Condensation: Acid **2** (1.09 g, 6.9 mmol), **3** (0.60 g, 4.6 mmol), β-alanine (0.41 g, 4.6 mmol), 4 Å molecular sieves (0.4 g), and toluene (6 mL) were placed in a 25-mL vial. After closing the vial with a rubber septum, the mixture was heated at 40 °C for 12 h under magnetic stirring. The mixture was diluted with EtOAc (50 mL), washed with 1 N HCl (3 × 10 mL) and brine, dried with dry Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel (hexane/EtOAc, 9:1) to give **4** as a white solid (0.88 g, 84% yield). M.p. 80–81 °C. ^{1}H NMR (400 MHz, $CDCl_3$):[22] δ = 7.64–7.60 (m, 4 H, ArH), 7.47 (d, J = 16 Hz, 1 H, CH=), 6.76 (d, J = 16 Hz, 1 H, CH=), 2.62 (t, J = 7 Hz, 2 H, CH_2), 1.65–1.62 (m, 2 H, CH_2), 1.30–1.27 (m, 4 H, CH_2), 0.87–0.84 (m, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.47, 139.23, 139.08, 138.60, 132.19, 128.56, 128.19, 117.91, 112.94, 40.97, 30.98, 23.36, 22.02,

13.40 ppm. MS (ES+): *m*/*z* (%) = 250 [M + Na]$^+$. HRMS (ES+): calcd. for $C_{15}H_{17}NNaO$ 250.1208; found 250.1210.

(*E*)-1-(4-Methoxyphenyl)oct-1-en-3-one (15): Colorless oil: 59 mg (55% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.47 (m, 3 H, CH=, ArH), 6.89 (d, *J* = 8 Hz, 2 H, ArH), 6.60 (d, *J* = 16 Hz, 1 H, CH=), 3.82 (s, 3 H, CH_3), 2.61 (t, *J* = 7 Hz, 2 H, CH_2), 1.69–1.63 (m, 2 H, CH_2), 1.33–1.31 (m, 4 H, CH_2), 0.90–0.87 (m, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.30, 161.10, 141.66, 135.61, 129.50, 123.74, 113.98, 54.96, 40.40, 31.13, 23.80, 22.07, 13.51 ppm. MS (ES+): *m*/*z* = 255 [M + Na]$^+$. HRMS (ES+): calcd. for $C_{15}H_{20}NaO_2$ 255.1361; found 255.1364.

(*E*)-1-(4-Hydroxyphenyl)oct-1-en-3-one (16): White solid: 70 mg (70% yield), m.p. 112–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 16 Hz, 1 H, CH=), 7.43 (d, *J* = 8 Hz, 2 H, ArH), 6.86 (d, *J* = 8 Hz, 2 H, ArH), 6.60 (d, *J* = 16 Hz, 1 H, CH=), 6.46 (br. s, 1 H, OH), 2.63 (t, *J* = 7 Hz, 2 H, CH_2), 1.68–1.64 (m, 2 H, CH_2), 1.33–1.30 (m, 4 H, CH_2), 0.89–0.86 (m, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.35, 157.98, 142.50, 129.86, 126.56, 123.34, 115.64, 40.32, 31.10, 23.91, 22.04, 13.49 ppm. MS (ES+): *m*/*z* = 241 [M + Na]$^+$. HRMS (ES+): calcd. for $C_{14}H_{18}NaO_2$ 241.1204; found 241.1202.

(*E*)-1-(Pyridin-3-yl)oct-1-en-3-one (17): Light-yellow oil: 70 mg (75% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.73 (s, 1 H, ArH), 8.57 (s, 1 H, ArH), 7.82 (d, *J* = 8 Hz, 1 H, ArH), 7.49 (d, *J* = 16 Hz, 1 H, CH=), 7.31–7.28 (m, 1 H, ArH), 6.76 (d, *J* = 16 Hz, 1 H, CH=), 2.63 (t, *J* = 7 Hz, 2 H, CH_2), 1.68–1.63 (m, 2 H, CH_2), 1.32–1.30 (m, 4 H, CH_2), 0.89–0.85 (m, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.52, 150.53, 149.41, 137.93, 133.88, 130.03, 127.51, 123.34, 40.74, 31.01, 23.43, 22.03, 13.47 ppm. MS (ES+): *m*/*z* = 226 [M + Na]$^+$. HRMS (ES+): calcd. for $C_{13}H_{17}NNaO$ 226.1208; found 226.1211.

(*E*)-1-(Furan-2-yl)oct-1-en-3-one (18): Light-yellow solid: 75 mg (85% yield), m.p. 36–38 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (s, 1 H, ArH), 7.25 (d, *J* = 16 Hz, 1 H, CH=), 6.60–6.56 (m, 2 H, ArH, CH=), 6.42–6.41 (m, 1 H, ArH), 2.52 (t, *J* = 7 Hz, 2 H, CH_2), 1.63–1.56 (m, 2 H, CH_2), 1.28–1.25 (m, 4 H, CH_2), 0.84 (t, *J* = 6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.66, 150.71, 144.32, 127.96, 122.98, 114.98, 112.02, 40.92, 31.03, 23.64, 22.02, 13.45 ppm. MS (ES+): *m*/*z* = 215 [M + Na]$^+$. HRMS (ES+): calcd. for $C_{12}H_{16}NaO_2$ 215.1048; found 215.1045.

(*E*)-1-(1*H*-Indol-5-yl)oct-1-en-3-one (19): White solid: 76 mg (69% yield), m.p. 123–125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (br. s, 1 H, NH), 7.81 (s, 1 H, ArH), 7.69 (d, *J* = 16 Hz, 1 H, CH=), 7.44–7.36 (m, 2 H, ArH), 7.23–7.21 (m, 1 H, ArH), 6.72 (d, *J* = 16 Hz, 1 H, CH=), 6.57 (s, 1 H, ArH), 2.65 (t, *J* = 7 Hz, 2 H, CH_2), 1.70–1.67 (m, 2 H, CH_2), 1.35–1.33 (m, 4 H, CH_2), 0.91–088 (m, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.66, 144.04, 136.72, 127.83, 126.24, 125.05, 123.36, 122.26, 121.34, 111.22, 103.08, 40.33, 31.17, 23.94, 22.09, 13.53 ppm. MS (ES+): *m*/*z* = 264 [M + Na]$^+$. HRMS (ES+): calcd. for $C_{16}H_{19}NNaO$ 264.1364; found 264.1361.

(*E*)-1-Phenyldec-3-en-5-one (20): Colorless oil: 76 mg (72% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.15 (m, 5 H, ArH), 6.84–6.78 (m, 1 H, CH=), 6.08 (d, *J* = 16 Hz, 1 H, CH=), 2.78–2.75 (m, 2 H, CH_2), 2.54–2.46 (m, 4 H, CH_2), 1.59–1.56 (m, 2 H, CH_2), 1.31–1.27 (m, 4 H, CH_2), 0.89–086 (m, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.37, 145.33, 140.32, 130.35, 128.05, 127.91, 125.76, 39.72, 34.04, 33.67, 31.05, 23.57, 22.03, 13.49 ppm. MS (ES+): *m*/*z* = 253 [M + Na]$^+$. HRMS (ES+): calcd. for $C_{16}H_{22}NaO$ 253.1568; found 253.1566.

(*E*)-1,4-Diphenylbut-3-en-2-one (21): White solid: 82 mg (80% yield), m.p. 64–65 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 16 Hz, 1 H, CH=), 7.51–7.49 (m, 2 H, ArH), 7.37–7.25 (m, 8 H, ArH), 6.75 (d, *J* = 16 Hz, 1 H, CH=), 3.93 (s, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.87, 142.99, 134.04, 130.16, 129.09, 128.52, 128.37, 127.97, 126.59, 124.81, 47.99 ppm. MS (ES+): *m*/*z* = 245 [M + Na]$^+$. HRMS (ES+): calcd. for $C_{16}H_{14}NaO$ 245.0942; found 245.0945.

(*E*)-4-(3-Oxo-4-phenylbut-1-enyl)benzonitrile (22): White solid: 90 mg (79% yield), m.p. 106–108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.54 (m, 5 H, ArH, CH=), 7.35–7.23 (m, 5 H, ArH), 6.81 (d, *J* = 16 Hz, 1 H, CH=), 3.92 (s, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.18, 140.24, 138.35, 133.41, 132.19, 129.07, 128.49, 128.24, 127.43, 126.82, 117.90, 113.10, 48.40 ppm. MS (ES+): *m*/*z* = 270 [M + Na]$^+$. HRMS (ES+): calcd. for $C_{17}H_{13}NNaO$ 270.0895; found 270.0897.

(*E*)-4-(4-Methoxyphenyl)-1-phenylbut-3-en-2-one (23): White solid: 88 mg (76% yield), m.p. 93–95 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 16 Hz, 1 H), 7.44 (d, *J* = 8 Hz, 2 H), 7.34–7.23 (m, 5 H), 6.87 (d, *J* = 8 Hz, 2 H), 6.65 (d, *J* = 16 Hz, 1 H), 3.90 (s, 2 H), 3.80 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.86, 161.27, 142.79, 134.34, 129.72, 129.07, 128.32, 126.69, 126.49, 122.63, 113.99, 54.97, 47.88 ppm. MS (ES+): *m*/*z* = 275 [M + Na]$^+$. HRMS (ES+): calcd. for $C_{17}H_{16}NaO_2$ 275.1048; found 275.1045.

(*E*)-1-Phenylhept-3-en-2-one (24): Colorless oil: 44 mg (51% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.18 (m, 5 H, ArH), 6.89 (dt, *J* = 6, 16 Hz, 1 H, CH=), 6.12 (d, *J* = 16 Hz, 1 H, CH=), 3.80 (s, 2 H, CH_2), 2.15 (q, *J* = 6 Hz, 2 H, CH_2), 1.49–1.42 (m, 2 H, CH_2), 0.89 (t, *J* = 7 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.12, 147.97, 129.00, 128.22, 126.41, 122.51, 47.14, 34.05, 20.89, 13.22 ppm. MS (ES+): *m*/*z* = 211 [M + Na]$^+$. HRMS (ES+): calcd. for $C_{13}H_{16}NaO$ 211.1099; found 211.1096.

(*E*)-1,6-Diphenylhex-3-en-2-one (25): Colorless oil: 73 mg (63% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.11 (m, 10 H, ArH), 6.91 (dt, *J* = 6, 16 Hz, 1 H, CH=), 6.13 (d, *J* = 16 Hz, 1 H, CH=), 3.78 (s, 2 H, CH_2), 2.75 (t, *J* = 7 Hz, 2 H, CH_2), 2.50 (q, *J* = 7 Hz, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.75, 146.52, 140.20, 134.17, 129.48, 128.95, 128.21, 128.03, 127.87, 127.25, 126.39, 125.75, 47.19, 33.95, 33.58 ppm. MS (ES+): *m*/*z* = 273 [M + Na]$^+$. HRMS (ES+): calcd. for $C_{18}H_{18}NaO$ 273.1255; found 273.1258.

(*E*)-4-(3-Oxo-4-phenoxybut-1-enyl)benzonitrile (26): White solid: 91 mg (75% yield), m.p. 108–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 16 Hz, 1 H, CH=), 7.67–7.61 (m, 4 H, ArH), 7.29 (t, *J* = 7 Hz, 2 H, ArH), 7.14 (d, *J* = 16 Hz, 1 H, CH=), 6.99 (t, *J* = 7 Hz, 1 H, ArH), 6.91 (d, *J* = 8 Hz, 2 H, ArH), 4.75 (s, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.34, 157.31, 141.41, 138.16, 132.25, 129.34, 128.46, 123.44, 121.53, 117.83, 114.23, 113.47, 72.15 ppm. MS (ES+): *m*/*z* = 286 [M + Na]$^+$. HRMS (ES+): calcd. for $C_{17}H_{13}NNaO_2$ 286.0844; found 286.0847.

(*E*)-4-(Furan-2-yl)-1-phenoxybut-3-en-2-one (27): Light-yellow oil: 89 mg (85% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.48 (m, 1 H, ArH), 7.30–7.25 (m, 2 H, ArH, CH=), 6.99–6.85 (m, 5 H, ArH), 6.70–6.69 (m, 1 H, CH=), 6.47–6.46 (m, 1 H, ArH), 4.70 (s, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.23, 157.58, 145.00, 129.84, 129.23, 121.24, 117.91, 116.66, 114.29, 114.11, 112.35, 72.09 ppm. MS (ES+): *m*/*z* = 251 [M + Na]$^+$. HRMS (ES+): calcd. for $C_{14}H_{12}NaO_3$ 251.0684; found 251.0681.

(3*E*,5*E*)-1-Phenoxy-6-phenylhexa-3,5-dien-2-one (28): Yellow oil: 80 mg (66% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.27 (m, 8 H, ArH, CH=), 7.01–6.87 (m, 5 H, ArH, CH=), 6.61 (d, *J* = 16 Hz, 1 H, CH=), 4.70 (s, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz,

$CDCl_3$): δ = 195.70, 158.21, 144.06, 142.59, 135.48, 129.26, 129.05, 128.46, 126.99, 126.22, 123.95, 121.25, 114.26, 71.93 ppm. MS (ES+): *m*/*z* = 287 [M + Na]$^+$. HRMS (ES+): calcd. for $C_{18}H_{16}NaO_2$ 287.1048; found 287.1045.

(*E*)-1-Phenoxy-6-phenylhex-3-en-2-one (29): Colorless oil: 84 mg (69% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–6.96 (m, 9 H, ArH, CH=), 6.87 (d, *J* = 8 Hz, 2 H, ArH), 6.41 (d, *J* = 16 Hz, 1 H, CH=), 4.66 (s, 2 H, CH_2), 2.78 (t, *J* = 7 Hz, 2 H, CH_2), 2.58–2.53 (m, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.16, 157.53, 148.09, 140.14, 129.21, 128.11;127.92, 125.85, 125.59, 121.23, 114.27, 114.13, 71.60, 33.95, 33.82 ppm. MS (ES+): *m*/*z* = 289 [M + Na]$^+$. HRMS (ES+): calcd. for $C_{18}H_{18}NaO_2$ 289.1204; found 289.1201.

(*E*)-Methyl 8-(4-Cyanophenyl)-6-oxooct-7-enoate (30): White solid: 91 mg (73% yield), m.p. 97–99 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.57 (m, 4 H, ArH), 7.47 (d, *J* = 16 Hz, 1 H, CH=), 6.74 (d, *J* = 16 Hz, 1 H, CH=), 3.61 (s, 3 H, CH_3), 2.67–2.64 (m, 2 H, CH_2), 2.32–2.29 (m, 2 H, CH_2), 1.66–1.64 (m, 4 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.72, 173.32, 139.38, 138.48, 132.20, 128.39;128.13, 117.88, 113.01, 51.09, 40.44, 33.33, 24.00, 22.96 ppm. MS (ES+): *m*/*z* = 294 [M + Na]$^+$. HRMS (ES+): calcd. for $C_{16}H_{17}NNaO_3$ 294.1106; found 294,1109.

(*E*)-Methyl 8-(4-Methoxyphenyl)-6-oxooct-7-enoate (31): White solid: 100 mg (79% yield), m.p. 53–55 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.40 (m, 3 H, ArH, CH=), 6.82 (d, *J* = 8 Hz, 2 H, ArH), 6.53 (d, *J* = 16 Hz, 1 H, CH=), 3.75 (s, 3 H, CH_3), 3.58 (s, 3 H, CH_3), 2.59–2.56 (m, 2 H, CH_2), 2.29–2.26 (m, 2 H, CH_2), 1.63–1.61 (m, 4 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.32, 173.36, 161.11, 141.80, 129.49, 126.68, 123.49, 113.94, 54.88, 50.99, 39.76, 33.38, 24.12, 23.31 ppm. MS (ES+): *m*/*z* = 299 [M + Na]$^+$. HRMS (ES+): calcd. for $C_{16}H_{20}NaO_4$ 299.1259; found 299.1262.

(*E*)-Methyl 6-Oxo-10-phenyldec-7-enoate (32): Colorless oil: 76 mg (60% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.13 (m, 5 H, ArH), 6.80 (dt, *J* = 6, 16 Hz, 1 H, CH=), 6.06 (d, *J* = 16 Hz, 1 H, CH=), 3.63 (s, 3 H, CH_3), 2.75 (t, *J* = 7 Hz, 2 H, CH_2), 2.53–2.48 (m, 4 H, CH_2), 2.31–2.27 (m, 2 H, CH_2), 1.62–1.58 (m, 4 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.54, 173.41, 145.61, 140.25, 130.24, 128.06, 127.89, 125.77, 51.06, 39.16, 33.99, 33.65, 33.39, 24.07, 23.12 ppm. MS (ES+): *m*/*z* = 297 [M + Na]$^+$. HRMS (ES+): calcd. for $C_{17}H_{22}NaO_3$ 297.1467; found 297.1465.

(*E*)-*tert*-Butyl 2-Oxohept-3-enylcarbamate (33): Colorless oil: 54 mg (52% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (dt, *J* = 6, 16 Hz, 1 H, CH=), 6.09 (d, *J* = 16 Hz, 1 H, CH=), 5.34 (br. s, 1 H, NH), 4.17–4.16 (m, 2 H, CH_2), 2.21–2.13 (m, 2 H, CH_2), 1.49–1.42 (m, 11 H, CH_3, CH_2), 0.93–0.89 (m, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.02, 155.31, 148.65, 127.10, 79.27, 47.96, 34.19, 27.92, 20.78, 13.21 ppm. MS (ES+): *m*/*z* = 250 [M + Na]$^+$. HRMS (ES+): calcd. for $C_{12}H_{21}NNaO_3$ 250.1419; found 250.1415.

(*E*)-*tert*-Butyl 2-Oxo-6-phenylhex-3-enylcarbamate (34): Colorless oil: 93 mg (70% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.13 (m, 5 H, ArH), 6.93 (dt, *J* = 6, 16 Hz, 1 H, CH=), 6.10 (d, *J* = 16 Hz, 1 H, CH=), 5.35 (br. s, 1 H, NH), 4.14–4.13 (m, 2 H, CH_2), 2.76 (t, *J* = 7 Hz, 2 H, CH_2), 2.56–2.51 (m, 2 H, CH_2), 1.43 (s, 9 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.87, 155.27, 147.36, 139.97, 128.13, 127.87, 127.38, 125.88, 79.32, 48.02, 33.80, 27.91 ppm. MS (ES+): *m*/*z* = 312 [M + Na]$^+$. HRMS (ES+): calcd. for $C_{17}H_{23}NNaO_3$ 312.1576; found 312.1579.

***tert*-Butyl (3*E*,5*E*)-2-Oxo-6-phenylhexa-3,5-dienylcarbamate (35):** Yellow oil: 77 mg (58% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.31 (m, 6 H, ArH, CH=), 6.99–6.86 (m, 2 H, CH=), 6.27 (d, *J* = 16 Hz, 1 H, CH=), 5.39 (br. s, 1 H, NH), 4.23–4.22 (m, 2 H, CH_2), 1.44 (s, 9 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.77, 153.83, 143.47, 142.21, 135.21, 129.06, 128.46, 126.97, 125.85, 48.63, 27.92 ppm. MS (ES+): *m*/*z* = 310 [M + Na]$^+$. HRMS (ES+): calcd. for $C_{17}H_{21}NNaO_3$ 310.1419; found 310.1416.

Preparation of (*E*)-Hexadec-7-en-6-one (37) as a Representative Procedure for Telescoped Hydroformylation/Verley–Doebner Knoevenagel Reaction: 1-Octene (74 μL, 0.46 mmol) was dissolved in toluene (0.6 mL) followed by $(Ph_3P)_3Rh(CO)H$ (9 mg, 0.01 mmol) and xantphos (23 mg, 0.04 mmol). The yellow solution obtained was submitted to pressurized syngas (CO/H_2, 1:1) at 120 psi and heated for 30 min at 110 °C by microwave irradiation at 250 W (value previously settled on the microwave oven). The vessel was cooled, and the internal gas was released. Compound **2** (109 mg, 0.69 mmol), β-alanine (41 mg, 0.46 mmol), and 4 Å MS were added, and the reaction mixture was stirred at 40 °C for 12 h. The mixture was diluted with EtOAc and washed with 1 N HCl (3×) and brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel (petroleum ether 40–60 °C/EtOAc, 97:3). A colorless oil was obtained (56 mg, 52% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.79 (dt, *J* = 6, 16 Hz, 1 H, CH=), 6.05 (d, *J* = 16 Hz, 1 H, CH=), 2.49 (t, *J* = 7 Hz, 2 H, CH_2), 2.17 (q, *J* = 7 Hz, 2 H, CH_2), 1.60–1.56 (m, 2 H, CH_2), 1.45–1.41 (m, 2 H, CH_2), 1.29–1.24 (m, 14 H), 0.88–0.85 (m, 6 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.57, 146.88, 129.88, 39.64, 32.01, 31.39, 31.08, 28.91, 28.74, 27.69, 23.62, 22.20, 22.04, 13.63, 13.48 ppm. MS (ES+): *m*/*z* = 261 [M + Na]$^+$. HRMS (ES+): calcd. for $C_{16}H_{30}NaO$ 261.2194; found 261.2197.

(*E*)-1-Phenyldodec-3-en-2-one (38): Colorless oil: 63 mg, 55% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.18 (m, 5 H, ArH), 6.89 (dt, *J* = 6, 16 Hz, 1 H, CH=), 6.11 (d, *J* = 16 Hz, 1 H, CH=), 3.80 (s, 2 H, CH_2), 2.17 (q, *J* = 8 Hz, 2 H, CH_2), 1.35–1.23 (m, 12 H, CH_2), 0.88–0.84 (m, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.18, 148.32, 135.20, 128.99, 128.22, 126.40, 47.12, 32.06, 31.38, 28.88, 28.72, 27.61, 22.21, 13.64 ppm. MS (ES+): *m*/*z* = 281 [M + Na]$^+$. HRMS (ES+): calcd. for $C_{18}H_{26}NaO$ 281.1881; found 281.1884.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of compounds.

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