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Water opportunities: catalyst and solvent in Mukaiyama aldol addition of Rawal's diene to carbonyl derivatives

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ABSTRACT

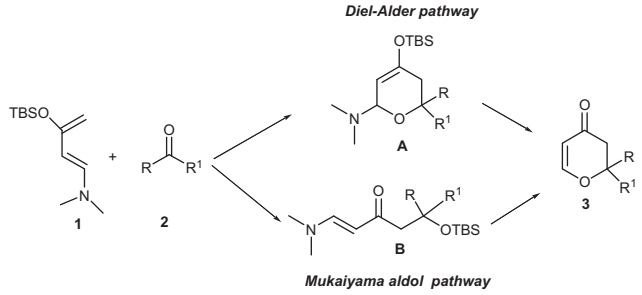
Addition reactions between Rawal's diene and different carbonyl compounds are rapidly and efficiently promoted by water. No catalyst or any other additive, water as an eco-friendly medium, clean reaction conditions, a simple work-up, and short reaction times are the salient features in this procedure. The protocol is general, proceeding well with moderate to good yields for various aldehydes and activated ketones. Based on the experimental ^{1}H NMR results, a Mukaiyama aldol mechanism was proposed as the reaction pathway, affording open chain products.

1. Introduction

Traditionally, the use of water as a reaction medium in organic processes has often been rejected. The idea that water had an adverse effect on most organic reactions was mainly attributed to the scant solubility of organic substrates in water, with the belief that solubility was a prerequisite for reactivity, in addition to the incompatibility between water molecules and some functional groups present in the reactants themselves. This belief was challenged by the studies done by Breslow[1] and Grieco,[2] which highlighted the positive effect of water on the rate and selectivity of Diels–Alder reactions. Further studies by Sharpless et al.[3] greatly increased the interest in water as a solvent, introducing the concept of 'on water' conditions, which provide with a substantial reaction rate acceleration for cases where the reactants are insoluble in water. Since then, the list of organic processes performed efficiently in water has been expanded including an increasing number of different types of reactions.[4]

Water is a unique solvent: inexpensive, readily available, and environmentally acceptable, providing opportunities for clean processes and simplicity of reaction conditions. Furthermore, reactions performed in water can not only be faster and more selective than in conventional organic solvents but also exhibit unique reactivity and selectivity leading to novel assembly processes. In recent years, studies focused on finding new water-compatible and reusable catalysts, strengthened by a growing development of catalyst-free processes,[5] with water used both as medium and as reaction promoter, keeping in mind that 'the best catalyst is no catalyst'[6] in order to accomplish clearer and cleaner synthesis.

Based on the above observations, and our interest in highlighting the potential of water in important C–C bond forming processes,[7] we investigated the reaction between electron-rich diene, Rawal's diene (**1**), and carbonyl compounds in water under catalyst-free conditions (Scheme 1). The reaction is a powerful tool in organic synthesis offering very convenient and rapid access to highly functionalized frameworks. Rawal and Huang[8] reported a study on the solvent acceleration in the hetero Diels–Alder (HDA) reaction of diene **1** with a range of carbonyl derivatives in absence



Scheme 1. Two possible pathways for HDA reaction of carbonyl compounds with electron-rich dienes.

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of Lewis acid catalysts, demonstrating the positive role of the hydrogen bonding interactions on the observed rate acceleration in protic solvents.

There are two different reaction pathways for the reaction between an electron-rich diene, such as Rawal's diene, and a carbonyl compound depending on the catalyst used and reaction conditions (Scheme 1). These paths are classified into two mechanisms; the Mukaiyama aldol reaction and concerted [4+2] cycloaddition. The concerted Diels–Alder pathway has been identified in the hydrogen bonding-promoted reactions reported by Rawal[8] with tested solvents.

To the best of our knowledge, a catalyst-free aqueous HDA reaction between carbonyl compounds and electron-rich dienes has not been reported to date, probably due to the stereotypical notion of these dienes susceptibility to water.

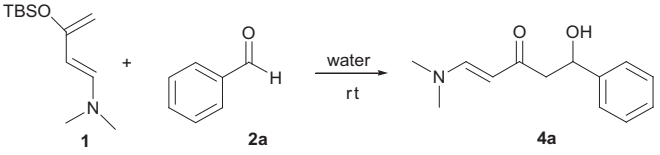
Encouraged by the reported favorable effect of a protic solvent on the HDA reaction efficiency, we envisaged the feasibility of developing a convenient and alternative synthetic procedure involving water molecules as the hydrogen-bond (HB) promoting. Our goal was not only to use water as a simple substitute for conventional organic solvents, but also to assess the influence of novel reaction medium on the reaction both as efficiency of the process and as feasible different mechanistic pathway (Scheme 1).

Herein, we report the first uncatalyzed addition reaction between Rawal's diene **1** and various carbonyl compounds using water as both reaction medium and as a hydrogen-bond donor species to activate the carbonyl compound.

2. Results and discussion

The coupling of the 1-amino-3-siloxybutadiene (Rawal's diene) **1** with benzaldehyde **2a** was conducted as a model screening reaction and the results are summarized in Table 1.

Table 1
Screening studies of catalyst-free aqueous reaction addition between Rawal's diene (**1**) and benzaldehyde (**2a**)

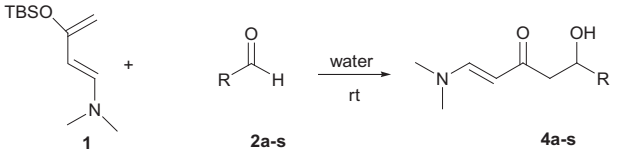


Entry[a]	**1**/**2a** (equiv)	Reaction time (min)	Volume (mL)	Yield (%)[b]
1	1.0/1.0	60	1.5	64
2	1.0/1.2	60	1.5	65
3	1.2/1.0	60	1.5	90
4	1.2/1.0	30	1.5	61
5	1.2/1.0	90	1.5	92
6	1.2/1.0	60	0.5	90
7	1.2/1.0	60	10.8	68
8[c]	1.2/1.0	60	6	83

[a] All reactions were run at atmospheric pressure in deionized water under vigorous stirring on a 0.25 mmol scale. For details, see the Experimental section. The use of tap water gives the same reaction yields.
[b] Yields refer to isolated, chromatographically pure product **4a** and are the average of two experiments.
[c] The reaction was performed on 1 mmol scale.

At the outset of this screening, equimolar amounts of **1** and **2a** were allowed to react using pure water (1.5 mL) as solvent and under vigorous stirring at room temperature without the use of any type of catalyst. Under these conditions, the reaction proceeded cleanly giving the Mukaiyama-type aldol adduct **4a** in a comforting yield (entry 1, Table 1) along with a limited quantity of silyl-protected aldol adduct (<8%) and of the diene solvolysis

Table 2
Catalyst-free aqueous reaction addition of Rawal's diene **1** with aldehydes **2**



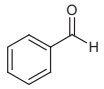
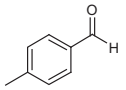
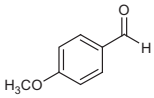
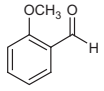
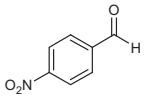
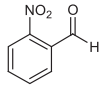
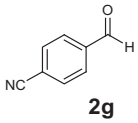
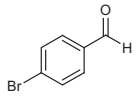
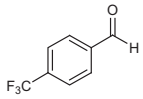
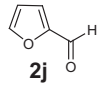
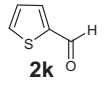
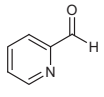
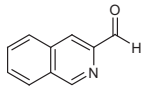
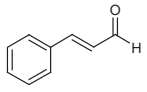
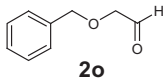
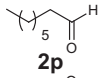
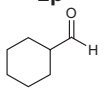
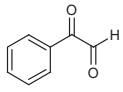
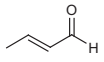
Entry[a]	RCHO	Reaction time (h)	Yield (%)[b]
1	 **2a**	1	90
2	 **2b**	1	88
3	 **2c**	3	75
4	 **2d**	3	56
5	 **2e**	1	87
6	 **2f**	1	84
7	 **2g**	3	67
8	 **2h**	0.5	89
9	 **2i**	1	93
10	 **2j**	3	70
11	 **2k**	3	66
12	 **2l**	0.5	92

Table 2 (*continued*)

Entry[a]	RCHO	Reaction time (h)	Yield (%)[b]
13	 **2m**	3	65
14	 **2n**	3	59
15[c]	 **2o**	1	56
16	 **2p**	1	84
17	 **2q**	1	88
18[d]	 **2r**	1	69
19	 **2s**	3	44

[a] Reaction conditions: **1** (0.30 mmol) and **2** (0.25 mmol) in pure deionized water (1.5 mL) at room temperature. For details, see the Experimental section.

[b] All the yields refer to isolated chromatographically pure compounds, whose structures were confirmed by ^{1}H and ^{13}C NMR data, IR spectra, and mass spectrometry (see Experimental section). The yields are the average of two experiments.

[c] The silyl-protected aldol adduct was obtained in 22% yield.

[d] The silyl-aldol adduct was obtained in 30% yield.

byproduct (13%). There was no evidence of the cycloaddition product **3a**. The rest of material is unreacted starting material.

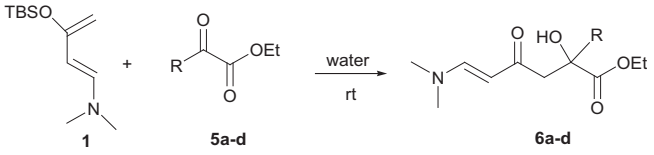
Of special interest was the fact that the diene **1** was compatible with the aqueous environment under our reaction conditions. Indeed the competitive hydrolysis diene reaction didn't surpass the desired addition reaction in aqueous medium, and the water itself could be a suitable protic solvent for pushing the reaction.

In hope to achieve higher conversion, the effects of molar ratio of **1** to **2a** were examined in detail. Whereas the reaction yield did not appreciably vary increasing the amount of **2a** (entry 2, Table 1), changing to the molar ratio **1**/**2a** in 1.2/1 significantly improved the adduct yield (entry 3, Table 1). Therefore, only a modest excess of **1** was required for an efficient conversion. A variation of the reaction times (entries 3–5, Table 1) revealed that 1 h proved to be the most suitable reaction time (entry 5, Table 1) and indeed prolonging the reaction time did not improve the yield (entry 5, Table 1). Next, the influence of the solubility of reacting species in aqueous medium on the reaction efficiency was investigated ranging from complete (entry 7, Table 1) to partial (entry 3, Table 1) to almost no solubility (entry 6, Table 1). The results demonstrated that when the reaction mixture remained heterogeneous, the process appeared to benefit from it (entry 3, Table 1). In order to investigate the role of water, the reaction was performed neat under identical reaction conditions, such as entry 3 of Table 1. Under these conditions, the ^{1}H NMR spectrum of the crude reaction mixture revealed the formation of the cycloadduct A from the concerted Diels–Alder pathway in low conversion (36%) and there was no evidence of the formation of **4a**, thereby highlighting the potential benefits from water as a reaction medium in this process. Additional experiment was performed on 1 mmol scale reaction demonstrating the validity for scaling up the procedure (entry 8, Table 1).

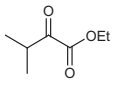
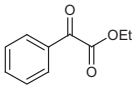
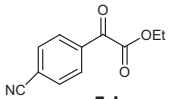
Encouraged by these preliminary results, the scope and limitations of this reaction with respect to the aldehyde component was further investigated. A series of aromatic and aliphatic aldehydes were reacted with Rawal's diene **1** using the optimized conditions in entry 3 of Table 1. In all cases the reactions were quite fast, they smoothly proceeded to just reach the corresponding aldol products **4** in moderate to good yields together with a limited quantity of silyl-protected aldol adduct (<10%) as summarized in Table 2.

The reaction worked well with aromatic aldehydes bearing either electron-donating or electron-withdrawing groups, although the conversion observed with these latter groups was inferior. The expected aldol adduct **4** was obtained as only reaction product with a yield ranging from 56 to 93% (entries 2–9, Table 2). Heteroaromatic aldehydes also demonstrated to be viable substrates in this reaction, giving the corresponding aldol from good (entry 12, Table 2) to moderate yields (entries 10, 11, and 13, Table 2). Although the reaction of conjugated aldehydes proceeded in aqueous solvent, the yields of desired product were more moderate (entries 14 and 19, Table 2). Our protocol was then applied to aliphatic aldehydes. When *n*-octylaldehyde or cyclohexylcarboxyaldehyde were reacted, the corresponding aldols **4p** and **4q** were obtained in good yield (entries 16 and 17, respectively, Table 2). When benzyloxyacetaldehyde **2o** and glyoxalate **2r** were used, they were also suitable substrates for our procedure but they provided the Mukaiyama aldol adduct with increasing amount of silyl-protected product.

Table 3
Catalyst-free water-promoted Mukaiyama aldol reactions of Rawal's diene **1** with representative pyruvate esters **5a–d**



1 **5a-d** **6a-d**

Entry[a]	Ketoester	Reaction time (h)	Yield (%)[b]
1	 **5a**	1	Quant.
2	 **5b**	1	91
3	 **5c**	1	90
4	 **5d**	3	85

[a] Reaction conditions: **1** (0.30 mmol) and **5** (0.25 mmol) in pure deionized water (1.5 mL) at room temperature. For details, see the Experimental section.

[b] All the yields refer to isolated chromatographically pure compounds, whose structures were confirmed by ^{1}H and ^{13}C NMR data, IR spectra, and mass spectrometry (see Experimental section). The yields are the average of two experiments.

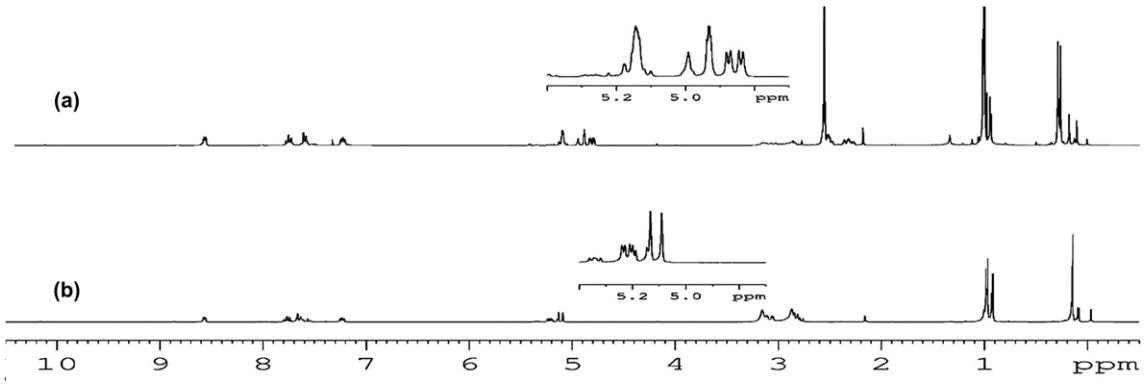


Fig. 1. ^{1}H NMR spectra in $CDCl_3$ of reaction addition of Rawal's diene **1** with aldehyde **2l** performed in different H-bonding solvents: (a) $CDCl_3$; (b) D_2O.

As a further aspect, we were curious to check if our procedure could be extended to ketones, generally considered less reactive. Initial approach showed that diene **1** was not reactive in the reaction conditions with a simple ketone as cyclohexanone, but the reaction with ethyl pyruvate **5a** led to similar levels of success when employed with benzaldehyde (entry 1, Table 3). The reaction went to completion in just 1 h at room temperature under vigorous stirring and gave the adduct of Mukaiyama-aldol pathway in quantitative yield.

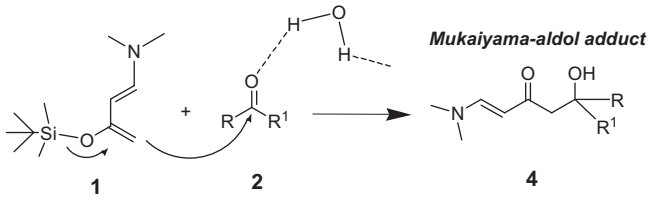
Similarly, other ketonic substrates **5** bearing a different acyl moiety (isopropyl or phenyl instead of methyl) reacted smoothly with **1**, providing the aldol adduct **6** in good yield (entries 2–4, Table 3).

Finally to clarify whether water-mediated reaction proceeded by Mukaiyama-aldol pathway or the Diels–Alder pathway (Scheme 1), we performed some experiments by monitoring the reaction using ^{1}H NMR analysis. Rawal and Huang[8] have reported that the reaction between carbonyl compounds and diene **1** in hydrogen-bonding solvents proceeds by a rapid cycloaddition resulting in clean formation of the expected cycloadduct **A** (Scheme 1), which could then be transformed to a more stable product, such as alcohol **4** or dihydro-4-pyrone **3** depending on the work-up conditions. We carried out the addition reaction between 2-pyridine carboxyaldehyde **2l** and diene **1** as a model reaction in, respectively, D_2O and $CDCl_3$ media, in order to directly examine the reaction mixture by NMR analysis without any work-up procedure (Fig. 1).

The ^{1}H NMR spectrum of the crude reaction mixture in D_2O showed the disappearance of the aldehyde after 30 min, but it was not easy to analyze for examining the product structure. Then, we decided to pour and shake the reaction mixture in sufficient $CDCl_3$ checking the ^{1}H NMR spectrum of corresponding organic phase (Fig. 1b). As shown in Fig. 1, a different behavior was observed performing the reaction in the two different solvents $CDCl_3$ and D_2O (compare a and b, Fig. 1). In the case of the reaction carried out in $CDCl_3$ (Fig. 1a), the ^{1}H NMR spectrum revealed the exclusive formation of the intermediate **A** proceeding through a concerted [4+2] mechanism in complete agreement with literature data.[8] On the other hand, performing the reaction in D_2O under our reaction conditions (Fig. 1b), ^{1}H NMR spectrum clearly indicated the generation of a different compound identified as the aldol product **4** without the observation of a detectable cyclization intermediate.

These results demonstrated that the aqueous addition reaction followed the Mukaiyama-aldol pathway and the isolated product **4** did not come from a possible transformation of cycloadduct **A** following the work-up.

Then, under our reaction conditions, the water played a key role as reaction promoter and activated the oxygen of the carbonyl compound through hydrogen bonding. The diene **1** then attacked the activated carbonyl compound to form the new carbon–carbon bond through a Mukaiyama-aldol pathway (Scheme 2) yielding the aldol adduct **4**.



Scheme 2. Proposed mechanism for the water-promoted addition reaction between Rawal's diene **1** and carbonyl compound **2**.

3. Conclusion

Our study aims to add a further contribution to the fascinating field of catalyst-free water-promoted organic reactions by including a reaction traditionally carried out under strictly anhydrous conditions. We have demonstrated the successful role played by neat water both catalyst and reaction medium in a carbon–carbon bond formation reaction as the addition reaction between Rawal's diene, notoriously water sensitive, and carbonyl compounds.

The reaction is, in general, very clean giving good to moderate yields with excellent selectivity under mild reaction conditions and short reaction times. In addition, the reaction scope is substantial and aromatic or aliphatic carbonyl compounds could be successfully applied. It is interesting to observe the remarkable difference between the protic solvents water and those reported by Rawal[8] as effective reaction promoters. Studies by ^{1}H NMR analysis indicate that the reaction solvent influences the reaction pathway: using water as reaction medium the reaction follows the Mukaiyama-aldol pathway affording the Mukaiyama aldol adduct as only isolated product. On the other hand, with other H-bonding solvents a rapid cycloaddition takes place following the Diels–Alder pathway. Therefore, water as novel reaction medium is not only an alternative H-bonding promoter solvent for the addition reaction between Rawal's diene and a carbonyl compound, but it also offers the opportunity for directly getting different reaction products.

To the best of our knowledge, this is the first example of Mukaiyama aldol reaction of Rawal's diene with carbonyl compounds using pure water as reaction medium and promoter without the presence of any catalyst, additive or co-solvents. Currently, studies are actively underway to expand the synthetic utility to the optically active addition products.

4. Experimental section

4.1. General method

Unless otherwise mentioned, all commercial reagents were obtained from commercial suppliers and used without further purification. Thin-layer chromatography was performed on Merck Kieselgel 60 (0.25 mm) in appropriate solvent. Visualization was accomplished with ultraviolet light (254 nm) and/or an alcoholic *p*-anisaldehyde solution, followed by heating. Column chromatography was carried out using silica gel 60 (70–230 mesh ASTM, Merck). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 250 (250.13 MHz for ^{1}H, 62.89 MHz for ^{13}C), Bruker DRX 300 (300 MHz for ^{1}H; 75 MHz for ^{13}C) and Bruker DRX 400 (400 MHz for ^{1}H; 100 MHz for ^{13}C). *J* values are given in hertz. The ^{1}H chemical shifts were referenced to the solvent peak: $CDCl_3$ (7.26 ppm), and the ^{13}C chemical shifts were referenced to the solvent peak: $CDCl_3$ (77.0 ppm). Melting points were determined in open capillary tubes using an Electro Thermal 9100 series apparatus. Mass spectra were recorded on a Micromass Quattro micro API mass spectrometer using electrospray (ES^{+}) ionization technique. IR spectra were recorded on an FT-IR instrument (Bruker Vector 22). Elemental analyses were performed on the Flash EA 1112 Series with Thermal Conductivity Detector (Thermo Electron Corporation).

4.2. Typical experimental procedure

A mixture of carbonyl compound (0.25 mmol) and diene **1** (0.30 mmol) was suspended in pure deionized water (1.5 mL) and vigorously stirred at room temperature for the indicate time (Tables 1–3). After completion of the reaction, as indicated by TLC, the water was simply removed by evaporation or alternatively EtOAc (3×5 mL) could be used with, which to extract the organic material from the aqueous layer. The collected organic phases were dried with anhydrous magnesium sulfate, filtered, and the solvent evaporated in vacuo. Purification was accomplished by column chromatography on silica gel using chloroform/methanol mixture as eluent.

4.3. NMR analysis of 4l

To a solution of 2-pyridine carboxyaldehyde **2l** (0.125 mmol) in D_2O (0.75 mL) was added diene **1** (0.15 mmol) at room temperature. After stirring for 30 min, the reaction mixture was extracted with $CDCl_3$ (1.0 mL) and organic phase was directly analyzed by ^{1}H NMR spectroscopy. The spectroscopic data showed exclusive formation of **3l**.

4.4. Analytical data for new compounds among the products

4.4.1. (E)-1-(Dimethylamino)-5-hydroxy-5-phenylpent-1-en-3-one ***4a****.* Pale yellow oil; (found: C, 71.23; H, 7.84; N, 6.37. $C_{13}H_{17}NO_2$ requires C, 71.21; H, 7.81; N, 6.39); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58 (d, *J*=11.3 Hz, 1H), 7.41–7.38 (m, 2H), 7.37–7.33 (m, 2H), 7.28–7.18 (m, 1H), 5.13 (dd, *J*=3.2, 11.3 Hz, 1H), 3.10 (br s, 3H), 2.82 (br s, 3H), 2.77 (dd, *J*=2.8, 13.3 Hz, 1H), 2.72–2.65 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.1, 153.3, 143.7, 128.2 (×2), 127.1, 125.7 (×2), 96.3, 71.2, 49.1, 44.9, 37.0; IR (liquid film, cm^{-1}) 3370, 2916, 2809, 1645, 1558, 1418, 1362, 1276, 1101, 762, 702; *m*/*z* 220 $(M+1)^+$, 242 $(M+Na)^+$.

4.4.2. (E)-1-(Dimethylamino)-5-hydroxy-5-p-tolylpent-1-en-3-one ***4b****.* Yellow oil; (found: C, 72.04; H, 8.19; N, 6.03. $C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.00); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.55 (d, *J*=12.3 Hz, 1H), 7.27 (d, *J*=8.7 Hz, 2H), 7.13 (d, *J*=8.7 Hz, 2H), 5.06 (dd, *J*=2.7, 9.0 Hz, 1H), 4.99 (d, *J*=12.3 Hz, 1H), 3.07 (br s, 3H), 2.79 (br s, 3H), 2.74 (dd, *J*=3.3, 15.6 Hz, 1H), 2.65 (dd, *J*=9.0, 15.6 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.2, 153.2, 140.8, 136.4, 128.8 (×2), 125.7 (×2), 95.9, 71.0, 48.2, 44.8, 37.1, 20.7; IR (liquid film, cm^{-1}) 3372, 2920, 1645, 1557, 1419, 1361, 1278, 1097; *m*/*z* 233 (M^+).

4.4.3. (E)-1-(Dimethylamino)-5-hydroxy-5-(4-methoxyphenyl) pent-1-en-3-one ***4c****.* Yellow oil; (found: C, 67.48; H, 7.70; N, 5.64. $C_{14}H_{19}NO_3$ requires C, 67.45; H, 7.68; N, 5.62); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58 (d, *J*=12.4 Hz, 1H), 7.31 (d, *J*=8.0 Hz, 2H), 6.87 (d, *J*=8.0 Hz, 2H), 5.07–5.03 (m, 1H), 4.99 (d, *J*=12.4 Hz, 1H), 3.79 (s, 3H), 3.09 (br s, 3H), 2.80 (br s, 3H), 2.73 (dd, 1H, *J*=3.5, 15.7 Hz), 2.65 (dd, *J*=9.0, 15.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.7, 160.1, 154.6, 133.4, 128.2 (×2), 115.0 (×2), 97.5, 72.3, 56.6, 50.0, 46.4, 38.5; IR (liquid film, cm^{-1}) 3372, 2920, 1645, 1557, 1419, 1361, 1278, 1097; *m*/*z* 272 $(M+Na)^+$.

4.4.4. (E)-1-(Dimethylamino)-5-hydroxy-5-(2-methoxyphenyl) pent-1-en-3-one ***4d****.* Yellow oil; (found: C, 67.47; H, 7.66; N, 5.64. $C_{14}H_{19}NO_3$ requires C, 67.45; H, 7.68; N, 5.62); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56–7.52 (m, 2H), 7.24–7.20 (m, 1H), 7.00–6.95 (m, 1H), 6.84 (d, *J*=8.0 Hz, 1H), 5.40 (dd, *J*=2.4, 9.3 Hz, 1H), 5.04 (d, *J*=12.6 Hz, 1H), 3.82 (s, 3H), 3.08 (br s, 3H), 2.91–2.80 (m, 4H), 2.59 (dd, *J*=9.3, 15.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.89 MHz): δ 197.9, 156.0, 153.2, 132.2, 128.1, 126.6, 120.8, 110.0, 96.6, 66.3, 55.2, 47.1, 45.1, 37.1; IR (liquid film, cm^{-1}) 3372, 2937, 1645, 1568, 1418, 1239, 1095; *m*/*z* 272 $(M+Na)^+$.

4.4.5. (E)-1-(Dimethylamino)-5-hydroxy-5-(4-nitrophenyl) pent-1-en-3-one ***4e****.* Yellow solid, mp 129–131 °C; (found: C, 59.11; H, 6.12; N, 10.62. $C_{13}H_{16}N_2O_4$ requires C, 59.08; H, 6.10; N, 10.60); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.20 (d, *J*=9.0 Hz, 2H), 7.62–7.56 (m, 3H), 5.21 (dd, *J*=3.3, 9.3 Hz, 1H), 4.99 (d, *J*=12.0 Hz, 1H), 3.13 (br s, 3H), 2.83 (br s, 3H), 2.80–2.77 (m, 1H), 2.64 (dd, *J*=9.3, 15.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.89 MHz): δ 196.2, 153.5, 152.9, 151.4, 126.5 (×2), 123.6 (×2), 94.8, 70.6, 48.8, 45.2, 37.2; IR (liquid film, cm^{-1}) 3333, 2922, 1644, 1557, 1345, 1096; *m*/*z* 265 $(M+1)^+$.

4.4.6. (E)-1-(Dimethylamino)-5-hydroxy-5-(2-nitrophenyl) pent-1-en-3-one ***4f****.* Yellow solid, mp 119–121 °C; (found: C, 59.05; H, 6.07; N, 10.58. $C_{13}H_{16}N_2O_4$ requires C, 59.08; H, 6.10; N, 10.60); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (d, *J*=8.0 Hz, 1H), 7.93 (dd, *J*=1.5, 8.0 Hz, 1H), 7.68–7.61 (m, 2H), 7.41 (dt, *J*=1.5, 8.0 Hz, 1H) 5.59 (dd, *J*=2.0, 9.1 Hz, 1H), 5.00 (d, *J*=12.8 Hz, 1H), 3.14 (br s, 3H), 3.13–3.04 (m, 1H), 2.85 (br s, 3H), 2.56 (dd, *J*=9.1, 14.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.89 MHz): δ 196.9, 153.7, 147.3, 139.4, 133.5, 128.5, 127.8, 124.1, 96.3, 67.5, 46.9, 45.1, 37.1; IR (liquid film, cm^{-1}) 3337, 2920, 1645, 1563, 1524, 1361, 1278; *m*/*z* 265 $(M+1)^+$, 287 $(M+Na)^+$.

4.4.7. 4-((E)-5-(Dimethylamino)-1-hydroxy-3-oxo pent-4-enyl)benzonitrile ***4g****.* Pale yellow solid, mp 130–132 °C; (found: C, 68.81; H, 6.58; N, 11.44. $C_{14}H_{16}N_2O_2$ requires C, 68.83; H, 6.60; N, 11.47); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.61–7.55 (m, 3H), 7.50 (d, *J*=9.0 Hz, 2H), 5.14 (dd, *J*=3.0, 9.0 Hz, 1H), 4.96 (d, *J*=12.0 Hz, 1H), 3.10 (br s, 3H), 2.82 (br s, 3H), 2.76 (dd, *J*=2.7, 16.0 Hz, 1H), 2.61 (dd, *J*=9.1, 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 196.2, 153.4, 149.3, 132.0 (×2), 126.6 (×2), 118.9, 110.7, 94.9, 70.8, 47.7, 45.0, 37.1; IR (liquid film, cm^{-1}) 3322, 2918, 2226, 1644, 1557, 1418, 1361, 1278, 1097; *m*/*z* 245 $(M+1)^+$, 267 $(M+Na)^+$.

4.4.8. (E)-5-(4-Bromophenyl)-1-(dimethylamino)-5-hydroxypent-1-en-3-one ***4h****.* Yellow solid, mp 87–89 °C; (found: C, 52.34; H, 5.40; N, 4.72. $C_{13}H_{16}BrNO_2$ requires C, 52.36; H, 5.41; N, 4.70); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56 (d, *J*=12.4 Hz, 1H), 7.43 (d, *J*=8.0 Hz, 2H), 7.25 (d, *J*=8.0 Hz, 2H), 5.04 (dd, *J*=2.8, 9.6 Hz, 1H), 4.97 (d, *J*=12.4 Hz, 1H), 3.08 (br s, 3H), 2.79 (br s, 3H), 2.72 (dd, *J*=2.9, 16.0 Hz, 1H), 2.60

(dd, J=9.2, 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.7, 153.2, 142.9, 131.2 (×2), 127.5 (×2), 120.7, 95.4, 70.6, 48.4, 45.0, 37.0; IR (liquid film, cm^{-1}) 3344, 2923, 1643, 1560, 1419, 1362, 1277, 1094; m/z 320 $(M+Na)^+$.

4.4.9. (E)-1-(Dimethylamino)-5-(4-(trifluoromethyl)phenyl)-5-hydroxypent-1-en-3-one ***4i***. Yellow solid, mp 79–81 °C; (found: C, 58.55; H, 5.63; N, 4.91. $C_{14}H_{16}F_3NO_2$ requires C, 58.53; H, 5.61; N, 4.88); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.59–7.54 (m, 3H), 7.49 (d, J=7.8 Hz, 2H), 5.14 (dd, J=3.3, 9.6 Hz, 1H), 4.97 (d, J=12.0 Hz, 1H), 3.08 (br s, 3H), 2.80 (br s, 3H), 2.78–2.73 (m, 1H), 2.63 (dd, J=9.3, 15.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 196.5, 153.3, 147.8, 129.8, 125.9(×2), 125.1(×2), 122.3, 95.1, 70.8, 48.2, 45.0, 37.3; IR (liquid film, cm^{-1}) 3343, 2919, 1645, 1563, 1420, 1326, 1277, 1118; m/z 288 $(M+1)^+$.

4.4.10. (E)-1-(Dimethylamino)-5-(furan-2-yl)-5-hydroxypent-1-en-3-one ***4j***. Yellow oil; (found: C, 63.17; H, 7.26; N, 6.71. $C_{11}H_{15}NO_3$ requires C, 63.14; H, 7.23; N, 6.69); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.56 (d, J=12.5 Hz, 1H), 7.33 (d, J=0.84 Hz, 1H), 6.29–6.27 (m, 1H), 6.24–6.22 (m, 1H), 5.09 (dd, J=4.0, 8.1 Hz, 1H), 5.00 (d, J=12.5 Hz, 1H), 3.07 (br s, 3H), 3.03–2.77 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.4, 156.2, 153.2, 141.7, 110.2, 106.0, 95.1, 65.3, 45.3, 45.0, 37.3; IR (liquid film, cm^{-1}) 3361, 2927, 1647, 1560, 1420, 1362, 1276, 1100; m/z 232 $(M+Na)^+$.

4.4.11. (E)-1-(Dimethylamino)-5-hydroxy-5-(thiophen-2-yl) pent-1-en-3-one ***4k***. Yellow oil; (found: C, 58.62; H, 6.68; N, 6.20. $C_{11}H_{15}NO_2S$ requires C, 58.64; H, 6.71; N, 6.22); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.57 (d, J=12.7 Hz, 1H), 7.19 (dd, J=1.6, 4.8 Hz, 1H), 6.94–6.86 (m, 2H), 5.33 (dd, J=3.9, 8.0 Hz, 1H), 5.00 (d, J=12.7 Hz, 1H), 3.07 (br s, 3H), 2.85–2.78 (m, 5H); ^{13}C NMR ($CDCl_3$, 62.89 MHz): δ 196.7, 153.4, 147.9, 126.3, 124.1, 122.8, 95.4, 67.8, 48.1, 45.2, 37.0; IR (liquid film, cm^{-1}) 3350, 2926, 1645, 1568, 1418, 1360, 1274, 1097; m/z 226 $(M+1)^+$, 248 $(M+Na)^+$.

4.4.12. (E)-1-(Dimethylamino)-5-hydroxy-5-(pyridin-2-yl) pent-1-en-3-one ***4l***. Yellow oil; (found: C, 65.41; H, 7.31; N, 12.69. $C_{12}H_{16}N_2O_2$ requires C, 65.43; H, 7.32; N, 12.72); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.50 (d, J=4.5 Hz, 1H), 7.70–7.62 (m, 1H), 7.58–7.44 (m, 2H), 7.17–7.10 (m, 1H), 5.15 (dd, J=3.6, 8.4 Hz, 1H), 5.03 (d, J=12.9 Hz, 1H), 3.07 (br s, 3H), 2.99 (dd, J=3.6, 15.6 Hz, 1H), 2.79–2.68 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.3, 162.7, 153.4, 148.3, 136.9, 122.1, 120.4, 97.0, 71.7, 47.2, 44.8, 36.9; IR (liquid film, cm^{-1}) 3359, 2953, 2927, 2809, 1645, 1568, 1471, 1418, 1275, 1108; m/z 221 $(M+1)^+$.

4.4.13. (E)-1-(Dimethylamino)-5-hydroxy-5-(quinolin-2-yl) pent-1-en-3-one ***4m***. Brown oil; (found: C, 71.07; H, 6.69; N, 10.38. $C_{16}H_{18}N_2O_2$ requires C, 71.09; H, 6.71; N, 10.36); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 8.16 (d, J=8.4 Hz, 1H), 8.09 (d, J=8.4 Hz, 1H), 7.82 (d, J=8.0 Hz, 1H), 7.75–7.68 (m, 2H), 7.62–7.50 (m, 2H), 5.38 (dd, J=3.7, 8.5 Hz, 1H), 5.08 (d, J=12.6 Hz, 1H), 3.09–3.01 (m, 1H), 3.08 (br s, 3H), 2.86 (dd, J=8.5, 15.3 Hz, 1H), 2.80 (br s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.5, 162.9, 153.4, 146.6, 137.1, 129.6, 128.5, 127.6, 127.4, 126.2, 118.6, 96.1, 71.9, 48.0, 44.9, 37.0; IR (liquid film, cm^{-1}) 3367, 2917, 1645, 1558, 1418, 1360, 1276, 1101; m/z 271 $(M+1)^+$.

4.4.14. (1E,6E)-1-(Dimethylamino)-5-hydroxy-7-phenylhepta-1,6-dien-3-one ***4n***. Pale orange oil; (found: C, 73.41; H, 7.79; N, 5.74. $C_{15}H_{19}NO_2$ requires C, 73.44; H, 7.81; N, 5.71); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62 (d, J=12.4 Hz, 1H), 7.39 (d, J=8.0 Hz, 2H), 7.31 (m, 2H), 7.22 (m, 1H), 6.65 (d, J=15.6 Hz, 1H), 6.26 (dd, J=6.4, 15.6 Hz, 1H), 5.05 (d, J=12.4 Hz, 1H), 4.72 (m, 1H), 3.12 (br s, 3H), 2.84 (br s, 3H), 2.72 (dd, J=2.4, 16.0 Hz, 1H), 2.59 (dd, J=8.8, 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.1, 153.1, 136.9, 131.2, 129.5, 128.4(×2), 127.3, 126.4(×2), 95.9, 69.8, 46.7, 45.0, 37.1; IR (liquid film, cm^{-1}) 3330, 2911, 1644, 1557, 1418, 1361, 1274, 1111; m/z 245 $(M)^+$.

4.4.15. (E)-6-(Benzyloxy)-1-(dimethylamino)-5-hydroxyhex-1-en-3-one ***4o***. Yellow oil; (found: C, 68.40; H, 8.01; N, 5.30. $C_{15}H_{21}NO_3$ requires C, 68.42; H, 8.04; N, 5.32); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (d, J=13.2 Hz, 1H), 7.36–7.28 (m, 5H), 5.04 (d, J=13.2 Hz, 1H), 4.58 (s, 2H), 4.27–4.21 (m, 1H), 3.52 (dd, J=6, 9.6 Hz, 1H), 3.49 (dd, J=6, 9.6 Hz, 1H), 3.09 (br s, 3H), 2.82 (br s, 3H), 2.62 (dd, J=3.6, 15.6 Hz, 1H), 2.55 (dd, J=8.4, 15.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.0, 153.1, 138.2, 128.3(×2), 127.7 (×2), 127.6, 96.3, 73.8, 73.7, 68.2, 45.0, 43.4, 37.2; IR (liquid film, cm^{-1}) 3386, 2919, 1646, 1557, 1420, 1361, 1275, 1112; m/z 264 $(M+1)^+$, 286 $(M+Na)^+$.

4.4.16. (E)-1-(Dimethylamino)-5-hydroxydodec-1-en-3-one ***4p***. Yellow oil; (found: C, 69.69; H, 11.30; N, 5.82. $C_{14}H_{27}NO_2$ requires C, 69.66; H, 11.27; N, 5.80); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.59 (d, J=13.5 Hz, 1H), 5.02 (d, J=13.5 Hz, 1H), 4.02–3.94 (m, 1H), 3.10 (br s, 3H), 2.83 (br s, 3H), 2.57 (dd, J=2.7, 16.2 Hz, 1H), 2.38 (dd, J=9.3, 16.2 Hz, 1H), 1.65–1.38 (m, 13H), 0.99 (t, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.89 MHz): δ 198.1, 152.9, 95.9, 68.9, 46.9, 45.0, 37.2, 37.0, 31.9, 29.7, 29.3, 25.7, 22.7, 14.2; IR (liquid film, cm^{-1}) 3390, 2926, 2855, 1645, 1627, 1558, 1418, 1361, 1278, 1096; m/z 242 $(M+1)^+$, 264 $(M+Na)^+$.

4.4.17. (E)-5-Cyclohexyl-1-(dimethylamino)-5-hydroxypent-1-en-3-one ***4q***. Yellow oil; (found: C, 69.26; H, 10.31; N, 6.25. $C_{13}H_{23}NO_2$ requires C, 69.29; H, 10.29; N, 6.22); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (d, J=12.0 Hz, 1H), 5.02 (d, J=12.6 Hz, 1H), 3.76–3.72 (m, 1H), 3.09 (br s, 3H), 2.82 (br s, 3H), 2.56 (dd, J=2.6, 15.6 Hz, 1H), 2.39 (dd, J=9.5, 15.6 Hz, 1H), 1.9–1.6 (m, 5H), 1.40–0.97 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.4, 152.8, 96.0, 73.1, 44.9, 43.6, 43.2, 37.0, 28.8, 28.4, 26.5, 26.2, 26.1; IR (liquid film, cm^{-1}) 3399, 2924, 2851, 1651, 1558, 1418, 1361, 1275, 1110; m/z 226 $(M+1)^+$, 248 $(M+Na)^+$.

4.4.18. (E)-6-(Dimethylamino)-2-hydroxy-1-phenylhex-5-ene-1,4-dione ***4r***. Brown oil; (found: C, 67.98; H, 6.90; N, 5.65. $C_{14}H_{17}NO_3$ requires C, 68.00; H, 6.93; N, 5.66); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 (d, J=7.6 Hz, 2H), 7.64 (d, J=12.4 Hz, 1H), 7.59 (m, 1H), 7.49 (t, J=7.6 Hz, 2H), 5.48 (dd, J=3.6, 8.0 Hz, 1H), 5.08 (d, J=12.4 Hz, 1H), 3.11 (br s, 3H), 2.89–2.81 (m, 4H), 2.73 (dd, J=8.0, 15.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 201.2, 193.9, 153.3, 134.0, 133.4, 128.8 (×2), 128.7 (×2), 95.7, 71.5, 44.9, 42.2, 37.1; IR (liquid film, cm^{-1}) 3356, 2925, 2459, 1645, 1568, 1419, 1364, 1275, 1112; m/z 248 $(M+1)^+$, 270 $(M+Na)^+$.

4.4.19. (1E,6E)-1-(Dimethylamino)-5-hydroxocta-1,6-dien-3-one ***4s***. Brown oil; (found: C, 65.56; H, 9.38; N, 7.66. $C_{10}H_{17}NO_2$ requires C, 65.54; H, 9.35; N, 7.64); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56 (d, J=13.2 Hz, 1H), 5.75–5.65 (m, 1H), 5.50 (dd, J=5.6, 15.2 Hz, 1H), 5.00 (d, J=13.2 Hz, 1H), 4.48–4.42 (m, 1H), 3.08 (br s, 3H), 2.82 (br s, 3H), 2.71–2.44 (m, 2H), 1.68 (d, J=5.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.5, 153.0, 132.8, 126.3, 96.7, 70.0, 46.7, 45.4, 37.1, 17.9; IR (liquid film, cm^{-1}) 3396, 2919, 1628, 1568, 1422, 1361, 1264, 1115; m/z 184 $(M+1)^+$.

4.4.20. (E)-Ethyl-6-(dimethylamino)-2-hydroxy-2-methyl-4-oxohex-5-enoate ***6a***. Pale yellow oil; (found: C, 57.65; H, 8.37; N, 6.09. $C_{11}H_{19}NO_4$ requires C, 57.62; H, 8.35; N, 6.11); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.53 (d, J=12.3 Hz, 1H), 4.97 (d, J=12.3 Hz, 1H), 4.18 (q, J=6.6 Hz, 2H), 3.07 (br s, 3H), 3.04 (d, J=15.9 Hz, 1H), 2.80 (br s, 3H), 2.60 (d, J=15.9 Hz, 1H), 1.38 (s, 3H), 1.25 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 195.8, 176.0, 153.1, 95.6, 73.6, 61.3, 48.8, 45.2, 37.0, 25.9, 14.2; IR (liquid film, cm^{-1}) 3412, 2981, 1738, 1645, 1628, 1574, 1421, 1365, 1228, 1110; m/z 230 $(M+1)^+$, 252 $(M+Na)^+$.

4.4.21. (E)-Ethyl-6-(dimethylamino)-2-hydroxy-2-isoproyl-4-oxohex-5-enoate ***6b***. Orange oil; (found: C, 60.65; H, 8.98; N, 5.42. $C_{13}H_{23}NO_4$ requires C, 60.68; H, 9.01; N, 5.44); ^{1}H NMR ($CDCl_3$,

300 MHz): δ 7.54 (d, J=12.9 Hz, 1H), 5.01 (d, J=12.9 Hz, 1H), 4.20 (q, J=7.5 Hz, 2H), 3.05 (br s, 3H), 2.93 (d, J=15.9 Hz, 1H), 2.80 (br s, 3H), 2.66 (d, J=15.9 Hz, 1H), 1.98–1.85 (m, 1H), 1.26 (t, J=7.5 Hz, 3H), 0.95 (d, J=7.2 Hz, 3H), 0.91 (d, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.89 MHz): δ 196.2, 175.8, 153.1, 96.1, 78.9, 61.4, 46.3, 45.1, 37.2, 36.0, 17.0, 16.5, 14.2; IR (liquid film, cm^{-1}) 3451, 2968, 2879, 1723, 1646, 1568, 1421, 1362, 1278, 1093; *m*/*z* 258 $(M+1)^+$, 280 $(M+Na)^+$.

4.4.22. (E)-Ethyl-6-(dimethylamino)-2-hydroxy-4-oxo-2-phenylhex-5-enoate ***6c***. Yellow oil; (found: C, 65.94; H, 7.24; N, 4.79. $C_{16}H_{21}NO_4$ requires C, 65.96; H, 7.27; N, 4.81); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.57–7.45 (m, 3H), 7.31–7.20 (m, 3H), 4.98 (d, J=12.5 Hz, 1H), 4.12 (q, J=7.5 Hz, 2H), 3.42 (d, J=16.5 Hz, 1H), 3.01 (br s, 3H), 2.80 (d, J=16.5 Hz, 1H), 2.75 (br s, 3H), 1.15 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.89 MHz): δ 196.0, 174.4, 153.4, 141.3, 128.1 (×2), 127.5, 124.9 (×2), 95.2, 77.4, 61.6, 49.7, 44.9, 36.9, 13.8; IR (liquid film, cm^{-1}) 3374, 2980, 1728, 1645, 1568, 1421, 1365, 1267, 1093; *m*/*z* 292 $(M+1)^+$, 314 $(M+Na)^+$.

4.4.23. (E)-Ethyl-2-(4-cyanophenyl)-6-(dimethylamino)-2-hydroxy-4-oxohex-5-enoate ***6d***. Yellow solid, mp 107–109 °C; (found: C, 64.51; H, 6.35; N, 8.84. $C_{17}H_{20}N_2O_4$ requires C, 64.54; H, 6.37; N, 8.86); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.73 (d, J=8.3 Hz, 2H), 7.64–7.56 (m, 3H), 5.00 (d, J=12.5 Hz, 1H), 4.19 (q, J=7.1 Hz, 2H), 3.4 (d, J=16.3 Hz, 1H), 3.09 (br s, 3H), 2.82 (d, J=16.3 Hz, 1H), 2.82 (br s, 3H), 1.21 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.89 MHz): δ 194.9, 173.3, 162.1, 153.6, 146.5, 132.0 (×2), 125.9 (×2), 118.9, 111.4, 95.3, 77.4, 62.0, 49.9, 45.6, 36.8; IR (liquid film, cm^{-1}) 3414, 2983, 2931, 228.8, 1732, 1644, 1557, 1417, 1366, 1217, 1093, 1019; *m*/*z* 317 $(M+1)^+$, 339 $(M+Na)^+$.

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References and notes

1. (a) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816–7817; (b) Breslow, R.; Maitra, U. *Tetrahedron Lett.* **1983**, *24*, 1901–1904; (c) Breslow, R.; Maitra, U. *Tetrahedron Lett.* **1984**, *25*, 1239–1240; (d) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159–164; (e) Breslow, R. *Acc. Chem. Res.* **2004**, *37*, 471–478.
2. (a) Grieco, P. A.; Garner, P.; He, Z. *Tetrahedron Lett.* **1983**, *24*, 1897–1900; (b) Grieco, P. A.; Yoshida, K.; Garner, P. *J. Org. Chem.* **1983**, *48*, 3137–3139.
3. Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275–3279.
4. For reviews about the state of the art of water as solvent in organic reactions: (a) Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis* **1994**, *8*, 741–760; (b) Li, C.-J.; Chang, T. H. *Organic Reactions in Aqueous Media*; Wiley: New York, NY, 1997; (c) Grieco, P. A. *Organic Synthesis in Water*; Blackie Academic and Professional: London, 1998; (d) Demko, Z. P.; Sharpless, K. B. *J. Org. Chem.* **2001**, *66*, 7945–7950; (e) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751–2771; (f) Reichardt, C. *Solvent and Solvent Effects in Organic Chemistry*, 3rd ed.; Wiley-VCH: Weinheim, 2002; (g) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095–3166; (h) Pirrung, M. C. *Chem.—Eur. J.* **2006**, *12*, 1312–1317; (i) Li, C.-J.; Chang, T. H. *Comprehensive Organic Reactions in Aqueous Media*, 2nd ed.; Wiley: New York, NY, 2007; (j) Raj, M.; Singh, V. K. *Chem. Commun.* **2009**, 6687–6703; (k) Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009**, *109*, 725–748; (l) Butler, R. N.; Coyne, A. G. *Chem. Rev.* **2010**, *110*, 6302–6337; (m) Rueping, M.; Theissmann, T. *Chem. Sci.* **2010**, *1*, 473–476.
5. Selected examples: (a) Loh, T.-P.; Feng, L.-C.; Wei, L.-L. *Tetrahedron* **2000**, *56*, 7309–7312; (b) Naik, S.; Bhattacharjya, G.; Talukdar, B.; Patel, B. K. *Eur. J. Org. Chem.* **2004**, *6*, 1254–1260; (c) Deb, M. L.; Bhuyan, P. J. *Tetrahedron Lett.* **2006**, *47*, 1441–1443; (d) Habib, P. M.; Kavala, V.; Kuo, C.-W.; Yao, C.-F. *Tetrahedron Lett.* **2008**, *49*, 7005–7007; (e) Halimehjani, Z. A.; Saidi, M. R. *Tetrahedron Lett.* **2008**, *49*, 1244–1248; (f) Habib, P. M.; Kavala, V.; Raju, B. R.; Kuo, C.-W.; Huang, W.-C.; Yao, C.-F. *Eur. J. Org. Chem.* **2009**, *26*, 4503–4514; (g) Halimehjani, Z. A.; Aryanasab, F.; Saidi, M. R. *Tetrahedron Lett.* **2009**, *50*, 1441–1443; (h) Sreedhar, B.; Reddy, P. S.; Reddy, M. A. *Synthesis* **2009**, *10*, 1732–1738; (i) Williams, D. B. G.; Cullen, A.; Fourie, A.; Henning, H.; Lawton, M.; Mommsen, W.; Nangu, P.; Parker, J.; Renison, A. *Green Chem.* **2010**, *12*, 1919–1921; (j) Alam, J.; Keller, T. H.; Loh, T.-P. *J. Am. Chem. Soc.* **2010**, *132*, 9546–9548; (k) Jung, E. J.; Park, B. H.; Lee, Y. R. *Green Chem.* **2010**, *12*, 2003–2011; (l) Curti, C.; Battistini, L.; Zanardi, F.; Rassu, G.; Zambrano, V.; Pinna, L.; Casiraghi, G. *J. Org. Chem.* **2010**, *75*, 8681–8684; (m) Zhang, X.; Jia, X.; Wang, J.; Fan, X. *Green Chem.* **2011**, *13*, 413–418.
6. Bigi, F.; Carloni, S.; Ferrari, L.; Maggi, R.; Mazzacani, A.; Sartori, G. *Tetrahedron Lett.* **2001**, *42*, 5203–5205.
7. (a) De Rosa, M.; Soriente, A. *Eur. J. Org. Chem.* **2010**, *6*, 1029–1032; (b) De Rosa, M.; Soriente, A. *Tetrahedron* **2010**, *66*, 2981–2986.
8. (a) Huang, Y.; Rawal, V. H. *Org. Lett.* **2010**, *2*, 3321–3323; (b) Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 9662–9663.