The Grob/Eschenmoser fragmentation of cycloalkanones bearing β-electron withdrawing groups: a general strategy to acyclic synthetic intermediates†

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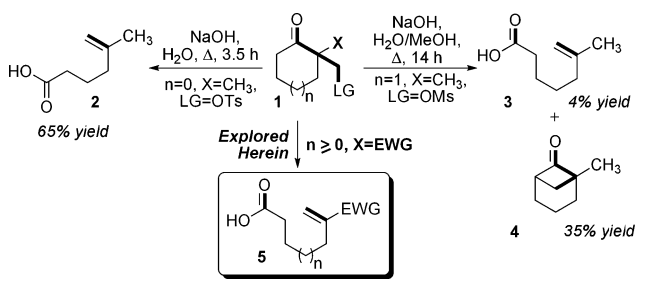
Introduction of a β-electron withdrawing group to cycloalkanones allows facile C–C bond fragmentation. The reaction has been demonstrated with a large range of ring sizes, bearing various leaving and electron withdrawing groups, and using a variety of nitrogen and oxygen containing nucleophiles (>30 examples). The application of fragmentation products to the preparation of substituted γ-lactones has been demonstrated. Mechanistic studies are reported which are suggestive of a Grob/Eschenmoser type reaction.

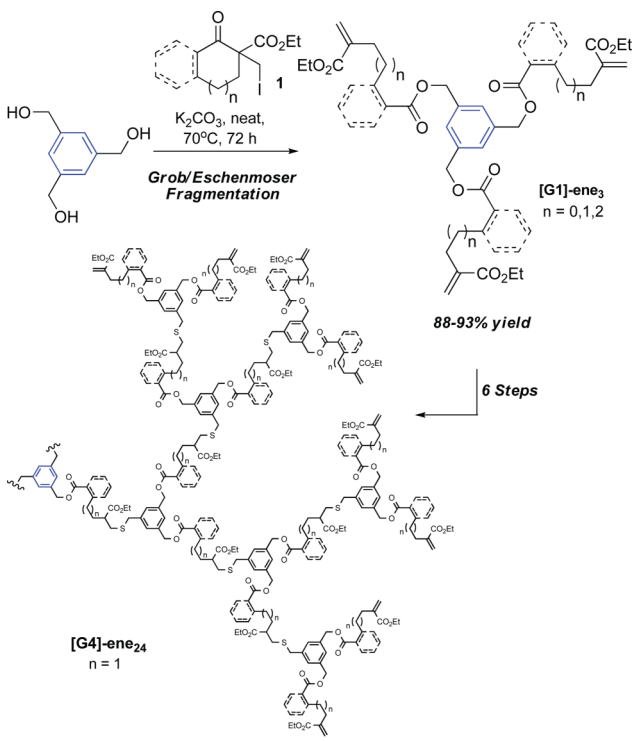
Introduction

Organic synthesis requires control over bond making and breaking events. Within the latter class fragmentations, as studied by Grob,[1] have lasting significance. In a large part this is due to the observation that cyclic structures can be fashioned, with chemo- and stereoselectively, then converted in a predictable manner to acyclic products.[2] This has been demonstrated in total synthesis,[3,4] and in the preparation of synthetic intermediates.[5] In the context of a program into the preparation of hyperbranched polymers we envisaged the use of C–C bond fragmentation with non-carbon nucleophiles to assemble a diverse modular array of materials. This strategy was inspired by the seminal studies of Eschenmoser who investigated the fragmentation of cyclopentyl tosylate **1**(n = 0)→**2** (Scheme 1).[6] Unfortunately due to the narrow scope of this reaction (*i.e.* **1**(n = 1)→**3**+**4**)[7] it required modification to be useful for our studies. We felt that by introducing a β-electron withdrawing group (*i.e.* **1**, X═EWG) inductive weakening of the fragmentable C–C bond should allow ring opening under mild conditions.



Scheme 1

Inspection of the literature supported this hypothesis with a number of undesired ring openings reported as minor side reactions with related substrates.[8] In addition the ester functionality introduces an equally conceivable retro-Dieckmann pathway for ring-opening (*vide infra*).[9–11] In the event, fragmentation—up to 24 times in a single transformation—enabled a novel approach to the synthesis of dendrimers, for example **[G4]-ene$_{24}$** (Scheme 2).[12]



Scheme 2

Concurrent to studies on the synthesis of dendrimers more general investigations into the fragmentation of β-ketoesters of type **1**, and the application of this reaction in organic synthesis, were undertaken. Herein we report an extensive survey of the nucleophilic C–C bond fragmentation of cycloalkanones bearing a β-electron withdrawing group. Exploration of the reaction mechanism and potential applications in synthesis are also described.

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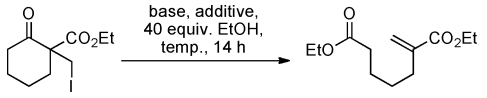
† Electronic supplementary information (ESI) available: ^{1}H- and ^{13}C-NMR spectra of all reported compounds as well as additional experimental procedures. See DOI: 10.1039/c0ob00632g

Table 1 Optimisation of fragmentation of cyclohexanone **1a**



1a **5a**

Entry	Base (equiv.)	Additive	Temp.	Yield%[a]
1	Et_3N (4)	5 mol% DMAP	70 °C	81
2	Et_3N (4)	—	70 °C	(52)
3	Pyridine (4)	—	70 °C	(3)
4	Imidazole (4)	—	70 °C	(32)
5	K_2CO_3 (4)	—	70 °C	(100)
6	K_2CO_3 (2)	—	rt	(100) 93

[a] Isolated yield, conversion in parentheses as judged by ^{1}H-NMR analysis.

Results and discussion

Reaction development and scope of nucleophiles

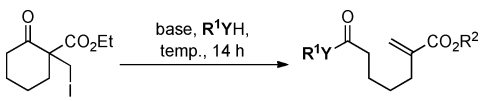
Studies commenced with the fragmentation of β-ketoester **1a**[13] using 5 mol% DMAP, triethylamine as the stoichiometric base, and ethanol as the nucleophile. To our satisfaction these conditions proved adequate providing diester **5a** in 81% isolated yield (Table 1, entry 1). To clarify the role of DMAP it was omitted and the reaction found to proceed, albeit more slowly, achieving 52% conversion after 14 h of heating at 70 °C (Table 1, entry 2). Pyridine and imidazole were not suitable bases (Table 1, entries 3 and 4), while K_2CO_3 gave complete conversion within 14 h (Table 1, entry 5). Further optimization revealed that two equivalents of K_2CO_3 were required, and that the reaction could be conducted at room temperature providing diester **5a** in 93% isolated yield (Table 1, entry 6).

Having developed conditions for the fragmentation of β-ketoester **1a** with ethanol, we targeted non-symmetrical diesters, materials better suited to subsequent chemoselective transformations. When examining alternate primary alcohols we found that *iso*-butanol fragmented **1a** effectively (Table 2, entry 1), while less hindered alcohols were plagued by concomitant transesterification reactions. This was eliminated, with benzylalcohol and *n*-butanol, by using a single equivalent of K_2CO_3 (Table 2, entries 2–3), while with methanol, the reaction had to be conducted at 0 °C (Table 2, entry 4a). When secondary alcohols were examined more forcing conditions were required to reach completion. For instance, *iso*-propanol fragmented cyclohexanone **1a** only after 96 h at 82 °C (Table 2, entry 5a). Finally, *tert*-butanol proved to be unsuitable (Table 2, entry 6).

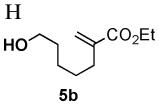
Rather than avoiding transesterification it was possible to conduct the reaction under conditions that favoured the one-pot fragmentation transesterification. In the case of methanol this was achieved with 2 equivalents of K_2CO_3 at room temperature providing the dimethyl ester in 82% isolated yield (Table 2, entry 4b). With *iso*-propanol the reaction gave reasonable yields of the diester after extended heating at 82 °C (Table 2, entry 5b).

Next the capacity of amines to fragment β-ketoester **1a** was explored. Previously optimised conditions used 40 equivalents of alcohol, however using these conditions it was difficult to separate the product from unreacted amine. This problem was circumvented by conducting the reaction with one equivalent of amine in dichloromethane at reflux, thus providing benzyl amide **5a** (Y═NH, R^1═Bn, R^2═Et) in 61% yield (Table 2,

Table 2 Fragmentation of cyclohexanone **1a** with alcohol and amines



1a **5a**

	Conditions		Product			
Entry[a]	Base (equiv.)	Temp.	R^1	Y	R^2	Yield%[b]
1	K_2CO_3 (2)	rt[c]	*i*-Bu	O	Et	63
2	K_2CO_3 (1)	rt	$PhCH_2$	O	Et	71
3	K_2CO_3 (1)	rt[c]	*n*-Bu	O	Et	65
4a	K_2CO_3 (1)	0 °C	Me	O	Et	81
4b	K_2CO_3 (2)	rt	Me	O	Me	82
5a	K_2CO_3 (1)	82 °C[c]	*i*-Pr	O	Et	57
5b	K_2CO_3 (2)	82 °C[d]	*i*-Pr	O	*i*-Pr	63
6	K_2CO_3 (2)	83 °C	*t*-Bu	O	Et	trace
7a[e]	K_2CO_3 (4)	40 °C	$PhCH_2$	NH	Et	61
7b[e]	K_2CO_3 (4)	40 °C	PMB	NH	Et	62
7c[e]	K_2CO_3 (4)	40 °C	MeBn	NH	Et	86
8a	NaOH (2)	40 °C	H	O	Et	68
8b	NaOH (4)[f]	70 °C	H	O	H	63
9	$NaBH_4$ (2.5)[f]	rt				60

5b

[a] 40 equivalents of R^1YH used except as noted. [b] Isolated yield following flash column chromatography. [c] 96 h to reach completion. [d] Conducted for 168 h. [e] 1 equivalent of R^1YH in CH_2Cl_2. [f] Conducted in ethanol.

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entry 7a). The transformation could also be achieved using *p*-methoxybenzylamine and methylbenzylamine (Table 2, entries 7b-c).

Finally, hydrolytic and reductive fragmentation was investigated. Using NaOH in dichloromethane it was possible to fragment β-ketoester **1a** to give the expected acid in 68% yield (Table 2, entry 8a). Increased stoichiometry of the hydroxide and temperature promoted subsequent hydrolysis, providing diacid **5a** (R^1═R^2═H, Y═O) in 63% isolated yield (Table 2, entry 8b). Extending the capacity to provide products with differentiated functionality we found that the reduction of ketone **1a** with $NaBH_4$ provided alcohol **5b** in 60% isolated yield (Table 2, entry 9).

Scope with regard to carbocycles

Attention now moved to the cycloalkanones suited to this reaction, of particular interest were ring systems incompatible with Grob/Eschenmoser type fragmentations.[14] Examining the scope of this reaction was intended to aid future studies in natural product[15] and novel dendrimer synthesis. To commence we probed the type of leaving group, finding that when the iodide was replaced by a bromide the reaction proceeded in similar yield, while the mesylate required elevated temperature to reach completion (Table 3, entries 1a–c). Similarly diiodide **1d** fragmented well, but only when heated at 70 °C (Table 3, entry 2).

The type of electron-withdrawing group in the β-position was examined with substrates **1e** and **f**. Replacing the ester with a nitrile (**1a** *cf.* **1e**) had no effect on the reaction (Table 3, entry 3), while fragmentation of the phenyl ketone **1f** proceeded more slowly and gave a lower isolated yield (Table 3, entry 4). The modest yield arose due to competing cleavage of the benzoyl group.

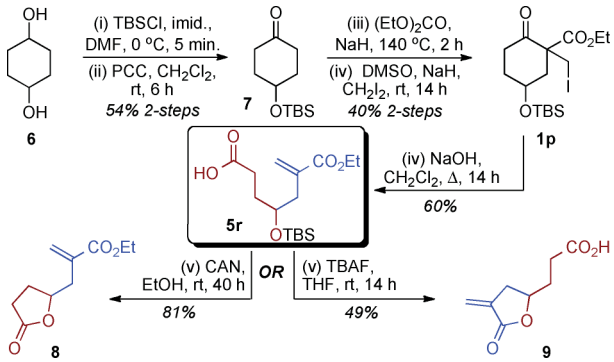
Cyclopentanone **1g** was fragmented by both ethanol (Table 3, entry 5a) and secondary amines such as benzylmethylamine, providing amide **5h** (Table 3, entry 5b), and dibenzylamine, providing amide **5i** (Table 3, entry 5c). Cycloheptanone **1j** reacted readily at room temperature to provide ester **5j** in 81% yield (Table 3, entry 6), while cyclododecanone **1k** gave the expected product **5k** in good yield (Table 3, entry 7). The bicyclic indanone **1l** fragmented under the general reaction conditions (Table 3, entry 8), while tetralone **1m** required heating (Table 3, entry 9a). Fragmentation of tetralone **1m** could also be achieved using amine nucleophiles to provide amide **5n** (Table 3, entry 9b).

Finally, cyclohexyl derivatives bearing an alkyl (**1o**), or protected alcohol (**1p**) functionality reacted readily under the standard conditions (Table 3, entries 10 and 11). The starting material for the latter reaction is accessible in enantiopure form,[16] thus providing a useful approach to homochiral intermediates, a possible application of which is introduced below.

Application to the synthesis of lactone building blocks

Substituted γ-lactones are well-represented motifs in bioactive and naturally occurring materials.[17] The capacity to fragment TBS protected cycloalkanone **1p**, provides the opportunity to develop the synthesis of such materials. In addition, since the de-symmetrisation of ketone **7** and subsequent acylation has been demonstrated[16] it should be possible to access optically pure fragmentation precursors, and hence γ-lactones, from this intermediate.[18]

To demonstrate this in a racemic context, studies commenced with the monoprotection of cyclohexan-1,4-diol **6** and oxidation using PCC to afford the symmetrical ketone **7**. Formation of the β-ketoester and introduction of the iodomethyl group then provided **1p**, which fragmented with NaOH (Table 2, entry 8a) to give the acid **5r** in 60% isolated yield (Scheme 3). When TBAF was used to remove the silyl protecting group spontaneous cyclisation with loss of ethanol gave the α-methylene γ-butyrolactone **9**. While deprotection using CAN delivered the isomeric γ-lactone **8** in high yield and selectivity.



Scheme 3 Application of fragmentation in the synthesis of γ-lactones.

One-pot alkylation/fragmentation

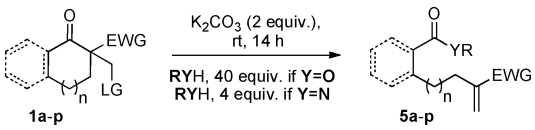
Through the course of our studies we found that traces of water caused fragmentation to proceed during the alkylation of the β-ketoester starting material. Exploiting this process we decided to investigate a one-pot alkylation fragmentation. When 3 equivalents of NaH were used in the alkylation, and an appropriate alcohol added after 14 h, this could be achieved in acceptable yields, and examples using cyclopentyl and cyclohexyl substrates are shown (Scheme 4).

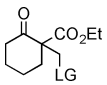
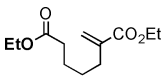
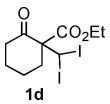
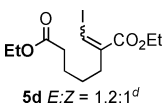
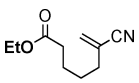
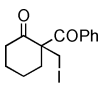
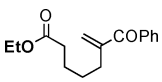
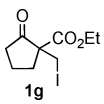
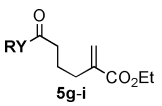
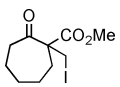
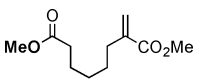
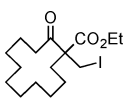
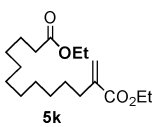
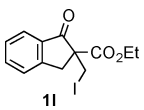
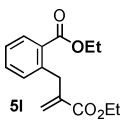
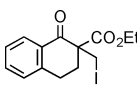
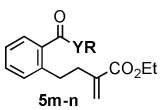
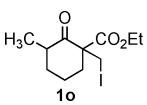
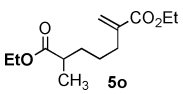
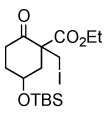
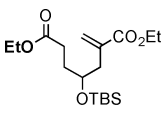
Scheme 4 One-pot alkylation fragmentation.

Mechanistic observations

Following examination of the scope of the reaction, studies into the reaction mechanism were undertaken. This reaction is most likely to resemble either a Grob-fragmentation or a retro-Dieckmann followed by elimination. In order to investigate these possibilities, competitive rate studies, monitored by ^{1}H-NMR, were undertaken (Fig. 1). When the reaction of the six membered β-ketoester **1a** with d_4-MeOH was compared to that of the seven membered **1j**, it was found that the former fragmented in less than 5 min, while the latter required 50 min (Fig. 1, graph A). A similar comparison of cyclohexanone **1a** to cyclopentanone **1g** was undertaken. At room temperature this was too fast to monitor, however at 0 °C we found that cyclopentanone **1g** reacted in under two minutes, and cyclohexanone **1a** in under four (Fig. 1, graph B). These studies demonstrate that the rate of reaction is related to ring size,

Table 3 Scope of Grob/Eschenmoser fragmentation with cycloalkanones **1a–p** bearing β-electron withdrawing groups



		Starting material		Product			
Entry	Nucleophile		LG		Y	R	Yield%[a]
1a	EtOH	 **1a-c**	I (**1a**)	 **5a**	—	—	93
1b	″		Br (**1b**)		—	—	92
1c[b]	″		OMs (**1c**)		—	—	73
2[b,c]	EtOH	 **1d**	—	 **5d** *E*:*Z* = 1.2:1[d]	—	—	80
3	EtOH	 **1e**	—	 **5e**	—	—	79
4[b,e]	EtOH	 **1f**	—	 **5f**	—	—	60[f]
5a	EtOH	 **1g**	—	 **5g-i**	O	Et	83 (**5g**)
5b[g]	$BnMeNH_2$		—		N	BnMe	80 (**5h**)
5c[g]	Bn_2NH		—		N	Bn_2	15 (**5i**)
6	MeOH	 **1j**	—	 **5j**	—	—	81
7	EtOH	 **1k**	—	 **5k**	—	—	68
8	EtOH	 **1l**	—	 **5l**	—	—	70
9a[b]	EtOH	 **1m**	—	 **5m-n**	O	Et	84 (**5m**)
9b[g]	PMB-NH_2		—		NH	PMB	52 (**5n**)
10	EtOH	 **1o**	—	 **5o**	—	—	65
11	EtOH	 **1p**	—	 **5p**	—	—	63

[a] Isolated yield following flash column chromatography. [b] Conducted under reflux. [c] Reaction time 4 h. [d] Stereoisomeric ratio determined by ^{1}H-NMR. [e] 48 h to reach completion. [f] 35% ethyl benzoate isolated. [g] 4 equiv. of amine and K_2CO_3, 20 mol% DMAP, CH_2Cl_2, Δ, 72 h.

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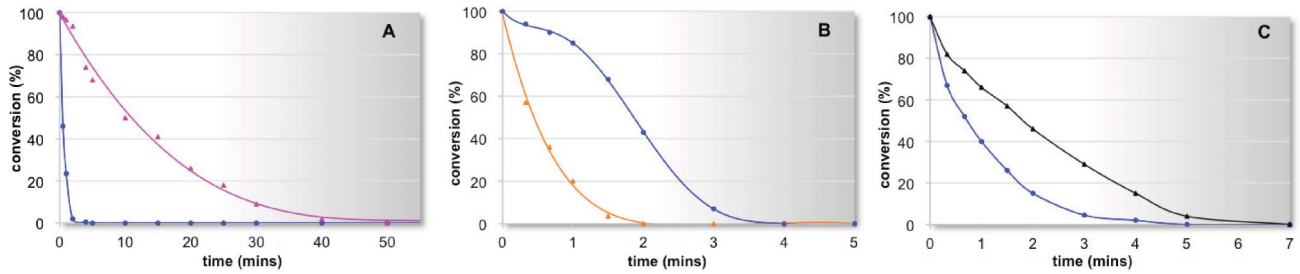

Fig. 1 **Graph A**: ● Cyclohexanone **1a**, ▲ Cycloheptanone **1j**. **Graph B**: ● Cyclohexanone **1a**, ▲ Cyclopentanone **1g**. **Graph C:** ● Iodide **1a**, ▲ Bromide **1b**.

as expected with a Grob-fragmentation, or a retro-Dieckmann reaction followed by rapid elimination. If the reaction proceeds by a rate determining retro-Dieckmann reaction, then bromide **1b** would react more quickly than iodide **1a**, due to its greater capacity to stabilise the developing negative charge. This was not the case with iodide **1a** reacting more quickly (Fig. 1, graph C) as expected with a process that involves concomitant departure of the leaving group. Thus it was observed that the rate is proportional to both ring size and leaving group in a fashion most supportive of a Grob fragmentation.

Conclusions

Fragmentation reactions have widespread applications in organic synthesis. We have demonstrated that, by introducing an electron-withdrawing group to an Eschenmoser fragmentation precursor, substrates formerly unreactive undergo facile reaction. The application of the products to the synthesis of substituted γ-lactones has been demonstrated, while previously we have used this reaction to prepare fourth generation dendrimers. Mechanistically, the reaction appears to occur by Grob-fragmentation, rather than a retro-Dieckmann/E_1cb sequence. Studies exploiting the applications of this reaction in total synthesis and hyperbranched polymer synthesis are ongoing.

Experimental

General experimental

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Bruker DRX400 operating at 400 MHz for proton and 100 MHz for carbon nuclei. Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer RXI FTIR spectrometer. Low resolution mass spectrometry (ESI) was performed on a Micromass Platform QMS spectrometer. High resolution mass spectra (HRMS) were recorded on a Bruker BioApex 47e FTMS fitted with an analytical electrospray source using NaI for accurate mass calibration. Melting points were measured on a Stuart hot-stage microscope apparatus. Flash column chromatography was performed on silica gel (Davisil LC60A, 40–63 μm silica media) using compressed air or nitrogen. Thin layer chromatography (TLC) was performed using aluminium-backed plates coated with 0.2 mm silica (Merck, DC-Platten, Kieselgel; 60 F_{254} plates). Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable stain followed by heating. Starting materials and reagents were purchased from Sigma–Aldrich and were used as supplied or, in the case of some liquids, distilled. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Ethanol and dichloromethane were distilled from calcium hydride. DMSO was dried over 4 Å molecular sieves.

Experimental procedures for the preparation of fragmentation precursors (1)

All fragmentation precursors (**1**) were prepared by alkylation of the corresponding 1,3-dicarbonyls. When the starting materials where not commercially available they where prepared from the corresponding ketone. Precursors **1a**,[19a] **1b**,[19b] **1g**, **1j**,[13] **1l**,[12] **1m**[19c] and **1p**[12] were synthesised as reported previously, while new precursors were accessed following either the procedures of Beckwith[13] in the case of **1d**, **1k**, and **1o**, Mu[20] in the case of **1f** or Bolm[21] followed by mesylation in the case of **1c** and **1e**. The generalised procedures can be found in the ESI†.

Ethyl 1-(((methylsulfonyl)oxy)methyl)-2-oxocyclohexanecarboxylate (1c)

R_f 0.4 (3 : 2, v/v EtOAc–hexane); IR ν_{max} 2944, 2871, 1714, 1453, 1359, 1209, 1178; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.28 (t, J = 7.0 Hz, 3H), 1.62–1.84 (m, 4H), 2.04–2.09 (m, 1H), 2.42–2.48 (m, 1H), 2.50–2.59 (m, 2H), 3.04 (s, 3H), 4.24 (q, J = 7.0 Hz, 2H), 4.36 (d, J = 10.0 Hz, 1H), 4.48 (d, J = 10.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.16, 21.90, 27.00, 33.20, 37.41, 40.85, 60.61, 62.36, 70.77, 168.86, 205.22; HRMS found $(M+H)^+$ 279.0900, $C_{11}H_{18}O_6S$ requires $(M+H)^+$ 279.0902; found $(M+NH_4)^+$ 296.1167, requires $(M+NH_4)^+$ 296.1168.

Ethyl 1-(diiodomethyl)-2-oxocyclohexanecarboxylate (1d)

R_f 0.5 (1 : 4, v/v EtOAc–hexane); IR ν_{max} 2944, 2867, 1715, 1648, 1597, 1451, 1251, 1200; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.28 (t, J = 7.0 Hz, 3H), 1.58–1.74 (m, 1H), 1.90–2.02 (m, 3H), 2.04–2.15 (m, 1H), 2.24–2.32 (m, 1H), 2.42–2.47 (m, 1H), 2.77–2.82 (m, 1H), 4.14–4.29 (m, 2H), 5.72 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ –25.82, 14.16, 22.55, 25.80, 35.01, 41.36, 62.96, 66.72, 165.34, 201.89; HRMS Found $(M+H)^+$, 436.9107, $C_{10}H_{14}I_2O_3$ requires $(M+H)^+$, 436.9111.

(1-Cyano-2-oxocyclohexyl)methyl methanesulfonate (1e)

R_f 0.4 (1 : 1, v/v EtOAc–hexane); IR ν_{max} 2943, 2872, 2241, 1731, 1452, 1360, 1315, 1178, 999; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.68–1.83 (m, 2H), 1.94–2.01 (m, 1H), 2.03–2.12 (m, 1H), 2.17–2.25 (m, 1H), 2.48–2.56 (m, 2H), 2.82–2.91 (m, 1H), 3.11 (s, 3H),

4.33 (d, J = 10.5 Hz, 1H), 4.53 (d, J = 10.5 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.78, 27.59, 31.66, 35.58, 37.84, 50.71, 68.29, 117.07, 200.53; HRMS found $(M+H)^+$ 232.0635, $C_9H_{13}NO_4S$ requires $(M+H)^+$ 232.0644; found $(M+NH_4)^+$ 249.0900, requires $(M+NH_4)^+$ 249.0909.

2-Benzoyl-2-(iodomethyl)cyclohexanone (1f)

R_f 0.5 (1 : 4, v/v EtOAc–hexane); IR ν_{max} 2957, 2928, 2873, 1747, 1713, 1682, 1465; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.45–1.51 (m, 1H), 1.72–1.83 (m, 2H), 1.93–2.09 (m, 2H), 2.19–2.30 (m, 1H), 2.46–2.54 (m, 1H), 2.99–3.04 (m, 1H), 3.58 (d, J = 10.5 Hz, 1H), 3.79 (d, J = 10.5 Hz, 1H), 7.39–7.44 (m, 2H), 7.52–7.55 (m, 1H), 7.81–7.84 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 10.87, 22.67, 29.58, 40.33, 43.31, 66.09, 128.97, 129.27, 133.60, 134.01, 195.00, 210.04; HRMS found $(M+Na)^+$ 365.0010, $C_{14}H_{15}IO_2$ requires $(M+Na)^+$ 365.0014.

Ethyl 1-(iodomethyl)-2-oxocyclododecanecarboxylate (1k)

R_f 0.6 (1 : 1, v/v CH_2Cl_2–hexane); IR ν_{max} 2923, 2861, 1743, 1706, 1468, 1441, 1242, 1149, 1027; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.21–1.37 (m, 18H), 1.96–2.16 (m, 4H), 3.01–3.09 (m, 1H), 3.49 (d, J = 11.0 Hz, 1H), 3.62 (dd, J = 11.0 Hz, 1.5 Hz, 1H), 4.15–4.30 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 8.13, 14.22, 18.40, 21.68, 21.90, 22.06, 22.73, 23.51, 26.27, 26.43, 30.08, 34.90, 62.13, 64.54, 170.45, 204.88; HRMS found $(M+H)^+$, 395.1072, $C_{16}H_{27}IO_3$ requires $(M+H)^+$, 395.1083.

Ethyl 1-(iodomethyl)-3-methyl-2-oxocyclohexanecarboxylate (1o)

R_f 0.4 (1 : 9, v/v EtOAc–hexane); IR ν_{max} 2979, 2935, 2871, 1739, 1710, 1454, 1372, 1275; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.04 (d, J = 6.5 Hz, 3H), 1.30 (t, J = 7.0 Hz, 3H), 1.45–1.53 (m, 1H), 1.62–1.74 (m, 1H), 1.77–1.85 (m, 1H), 2.04–2.17 (m, 2H), 2.32–2.40 (m, 1H), 2.59–2.68 (m, 1H), 3.64 (d, J = 10.0 Hz, 1H), 3.77 (dd, J = 10.0 Hz, 1.0 Hz, 1H), 4.24 (qd, J = 7.0 Hz, 2.0 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 7.44, 14.22, 15.27, 19.71, 35.25, 35.63, 42.68, 61.83, 62.25, 169.85, 207.43; HRMS found $(M+H)^+$ 325.0295, $C_{11}H_{17}IO_3$ requires $(M+H)^+$ 325.0301.

General experimental procedure for fragmentation with alcohols

A magnetically stirred solution of β-ketoester **1** (0.5 mmol) in dry alcohol (20 mmol), was reacted at the specified temperature with K_2CO_3 (1–2 equiv.) for a given period of time (for details see Tables 1, 2 and 3). The reaction mixture was filtered then evaporated and the resultant oil purified *via* flash column chromatography.

Diethyl 2-methyleneheptanedioate (5a, Table 1, entry 6)[22]

R_f 0.5 (CH_2Cl_2); IR ν_{max} 2982, 2939, 2869, 1718, 1631, 1464, 1446, 1370, 1237, 1136; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.18 (t, J = 7.0 Hz, 3H), 1.23 (t, J = 7.0 Hz, 3H), 1.42–1.46 (m, 2H), 1.55–1.61 (m, 2H), 2.22–2.27 (m, 4H), 4.05 (q, J = 7.0 Hz, 2H), 4.13 (q, J = 7.0 Hz, 2H), 5.45 (q, J = 1.0 Hz, 1H), 6.07 (t, J = 7.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.17, 14.21, 24.47, 27.85, 31.49, 34.09, 60.18, 60.54, 124.52, 140.52, 167.16, 173.55.

1-Ethyl 7-isobutyl 2-methyleneheptanedioate (5a, Table 2, entry 1)

R_f 0.5 (CH_2Cl_2); IR ν_{max} 2961, 2875, 1736, 1719, 1471, 1370, 1178, 1135; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.91 (d, J = 7.0 Hz, 6H), 1.29 (t, J = 7.0 Hz, 3H), 1.46–1.54 (m, 2H), 1.62–1.69 (m, 2H), 1.91 (nonet, J = 7.0 Hz, 1H), 2.29–2.34 (m, 4H), 3.84 (d, J = 7.0 Hz, 2H), 4.19 (q, J = 7.0 Hz, 2H), 5.51 (d, J = 1.0 Hz, 1H), 6.13 (d, J = 1.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.33, 19.21, 24.69, 27.85, 28.04, 31.63, 34.26, 60.71, 70.56, 124.67, 140.68, 167.32, 173.78; HRMS found $(M+H)^+$, 257.1752, $C_{14}H_{24}O_4$ requires $(M+H)^+$, 257.1753.

7-Benzyl 1-ethyl 2-methyleneheptanedioate (5a, Table 2, entry 2)

R_f 0.5 (CH_2Cl_2); IR ν_{max} 2981, 2940, 2868, 1736, 1716, 1631, 1456, 1179; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.20 (t, J = 7.0 Hz, 3H), 1.39–1.47 (m, 2H), 1.56–1.64 (m, 2H), 2.23 (t, J = 7.5 Hz, 2H), 2.30 (t, J = 7.5 Hz, 2H), 4.11 (q, J = 7.0 Hz, 2H), 5.03 (s, 2H), 5.42 (q, J = 1.0 Hz, 1H), 6.05 (t, J = 1.0 Hz, 1H), 7.19–7.27 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.23, 24.49, 27.88, 31.51, 34.07, 60.58, 66.11, 124.58, 128.18, 128.19, 128.56, 136.14, 140.53, 167.14, 173.33; HRMS found $(M+NH_4)^+$, 308.1857, $C_{17}H_{22}O_4$ requires $(M+NH_4)^+$, 308.1862.

7-Butyl 1-ethyl 2-methyleneheptanedioate (5a, Table 2, entry 3)

R_f 0.5 (CH_2Cl_2); IR ν_{max} 2960, 2937, 2873, 1734, 1718, 1631, 1464, 1178, 1136; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J = 7.5 Hz, 3H), 1.28 (t, J = 7.0 Hz, 3H), 1.36 (sext, J = 7.5 Hz, 2H), 1.45–1.53 (m, 2H), 1.55–1.68 (m, 4H), 2.30 (t, J = 7.5 Hz, 4H), 4.05 (t, J = 6.5 Hz, 2H), 4.18 (q, J = 7.0 Hz, 2H), 5.50 (d, J = 1.0 Hz, 1H), 6.12 (d, J = 1.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.79, 14.30, 19.25, 24.64, 28.00, 30.81, 31.61, 34.23, 60.68, 64.26, 124.64, 140.66, 167.29, 173.78; HRMS found $(M+H)^+$, 257.1749, $C_{14}H_{24}O_4$ requires $(M+H)^+$, 257.1753.

1-Ethyl 7-methyl 2-methyleneheptanedioate (5a, Table 2, entry 4a)[23]

R_f 0.5 (CH_2Cl_2); IR ν_{max} 2982, 2952, 2868, 1740, 1717, 1631, 1438, 1178, 1136; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J = 7.0 Hz, 3H), 1.42–1.50 (m, 2H), 1.57–1.65 (m, 2H), 2.25–2.30 (m, 4H), 3.61 (s, 3H), 4.15 (q, J = 7.0 Hz, 2H), 5.47 (d, J = 1.0 Hz, 1H), 6.09 (d, J = 1.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.22, 24.49, 27.91, 31.54, 33.85, 51.46, 60.60, 124.59, 140.56, 167.17, 173.99.

Dimethyl 2-methyleneheptanedioate (5a, Table 2, entry 4b)[19a]

R_f 0.4 (CH_2Cl_2); IR ν_{max} 2995, 2953, 2866, 1723, 1631, 1438, 1198, 1167, 1138; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.44–1.51 (m, 2H), 1.59–1.66 (m, 2H), 2.27–2.32 (m, 4H), 3.63 (s, 3H), 3.72 (s, 3H), 5.51 (q, J = 1.0 Hz, 1H), 6.11 (t, J = 1.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 24.52, 27.92, 31.61, 33.89, 51.53, 51.84, 124.96, 140.28, 167.69, 174.05.

1-Ethyl 7-isopropyl 2-methyleneheptanedioate (5a, Table 2, entry 5a)

R_f 0.4 (CH_2Cl_2); IR ν_{max} 2981, 2936, 2871, 1731, 1632, 1466, 1373, 1179, 1110; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.21 (d, J = 6.5 Hz, 6H), 1.28 (t, J = 7.0 Hz, 3H), 1.45–1.53 (m, 2H), 1.59–1.67 (m,

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2H), 2.25–2.32 (m, 4H), 4.19 (q, J = 7.0 Hz, 2H), 4.98 (sept, J = 6.5 Hz, 1H), 5.50 (q, J = 1.0 Hz, 1H), 6.12 (t, J = 1.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.32, 21.96, 24.68, 27.98, 31.64, 34.58, 60.69, 67.53, 124.64, 140.70, 167.31, 173.23; HRMS found $(M+H)^+$, 243.1592, $C_{13}H_{22}O_4$ requires $(M+H)^+$, 243.1596.

Diisopropyl 2-methyleneheptanedioate (5a, Table 2, entry 5b)

R_f 0.5 (CH_2Cl_2); IR ν_{max} 2981, 2938, 2871, 1732, 1715, 1631, 1374, 1180, 1109; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.22 (d, J = 6.0 Hz, 6H), 1.26 (d, J = 6.5 Hz, 6H), 1.45–1.53 (m, 2H), 1.60–1.68 (m, 2H), 2.26–2.32 (m, 4H), 4.99 (sept, J = 6.5 Hz, 1H), 5.05 (sept, J = 6.0 Hz, 1H), 5.48 (d, J = 1.0 Hz, 1H), 6.11 (d, J = 1.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.95, 21.98, 24.71, 28.03, 31.64, 34.62, 67.55, 68.04, 124.36, 141.10, 166.86, 173.26; HRMS found $(M+H)^+$ 257.1749, $C_{14}H_{24}O_4$ requires $(M+H)^+$ 257.1753.

General experimental procedure for fragmentation with amines

A magnetically stirred solution of β-ketoester **1** (0.5 mmol) in CH_2Cl_2 (5 mL) was treated with amine (1–4 equiv.), K_2CO_3 (4 equiv.) and DMAP (0–20 mol%) then brought to reflux for a given period of time (for details see Table 2, entry 7 and Table 3, entries 5b–c, 9b). The reaction mixture was filtered then evaporated and the resultant oil purified *via* flash column chromatography.

Ethyl 7-(benzylamino)-2-methylene-7-oxoheptanoate (5a, Table 2, entry 7a)

R_f 0.4 (1 : 1, v/v EtOAc–hexane); IR ν_{max} 3292, 2933, 2865, 1715, 1651, 1548, 1455, 1369, 1245, 1179, 1135; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J = 7.0 Hz, 3H), 1.40–1.48 (m, 2H), 1.62 (quint, J = 7.5 Hz, 2H), 2.16 (t, J = 7.5 Hz, 2H), 2.22–2.26 (m, 2H), 4.11 (q, J = 7.0 Hz, 2H), 4.36 (d, J = 5.5 Hz, 2H), 5.45 (q, J = 1.0 Hz, 1H), 5.77 (br s, 1H), 6.06 (t, J = 1.0 Hz, 1H), 7.17–7.28 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.32, 25.36, 28.18, 31.60, 36.53, 43.72, 60.73, 124.81, 127.61, 127.95, 128.82, 138.53, 140.63, 167.38, 172.80; HRMS found $(M+H)^+$, 290.1753, $C_{17}H_{23}NO_3$ requires $(M+H)^+$, 290.1756.

Ethyl 7-(4-methoxybenzylamino)-2-methylene-7-oxoheptanoate (5a, Table 2, entry 7b)

R_f 0.3 (1 : 1, v/v EtOAc–hexane); IR ν_{max} 3286, 2977, 2933, 2867, 1715, 1641, 1545, 1370, 1301, 1179, 1139; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J = 7.0 Hz, 3H), 1.44–1.52 (m, 2H), 1.62–1.69 (m, 2H), 2.19 (t, J = 7.5 Hz, 2H), 2.28 (t, J = 7.5 Hz, 2H), 3.76 (s, 3H), 4.15 (q, J = 7.0 Hz, 2H), 4.32 (d, J = 5.5 Hz, 2H), 5.49 (q, J = 1.0 Hz, 1H), 5.95 (br s, 1H), 6.11 (t, J = 1.0 Hz, 1H), 6.82 (d, J = 8.5 Hz, 2H), 7.16 (d, J = 8.5 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.26, 25.32, 28.11, 31.54, 36.44, 43.08, 55.34, 60.66, 114.11, 124.72, 129.20, 130.65, 140.57, 159.05, 167.31, 172.71; HRMS found $(M+H)^+$, 320.1856, $C_{18}H_{25}NO_4$ requires $(M+H)^+$, 320.1862.

Ethyl 2-methylene-7-oxo-7-(1-phenylethylamino)heptanoate (5a, Table 2, entry 7c)

R_f 0.4 (1 : 1, v/v EtOAc–hexane); IR ν_{max} 3232, 2983, 2915, 1711, 1620, 1555, 1510, 1242, 1145, 1022; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.20 (t, J = 7.0 Hz, 3H), 1.39 (d, J = 7.0 Hz, 3H), 1.37–1.44 (m, 2H), 1.54–1.62 (m, 2H), 2.11 (t, J = 7.5 Hz, 2H), 2.22 (t, J = 7.5 Hz, 2H), 4.10 (q, J = 7.0 Hz, 2H), 5.05 (quint, J = 7.0 Hz, 1H), 5.42 (q, J = 1.0 Hz, 1H), 5.95 (br d, J = 7.0 Hz 1H), 6.05 (t, J = 1.0 Hz, 1H), 7.14–7.26 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.24, 21.82, 25.28, 28.05, 31.51, 36.46, 48.62, 60.63, 124.69, 126.21, 127.28, 128.64, 140.56, 143.46, 167.30, 171.98; HRMS found $(M+H)^+$ 304.1911, $C_{18}H_{25}NO_3$ requires $(M+H)^+$ 304.1913.

6-(Ethoxycarbonyl)hept-6-enoic acid (5a, Table 2, entry 8a)

A magnetically stirred solution of β-ketoester **1a** (310 mg, 1 mmol) in CH_2Cl_2 (8 mL) was treated with NaOH (80 mg, 2 mmol) and then refluxed for 14 h. After cooling to room temperature the mixture was washed with HCl (3 × 10 mL of a 1 M aqueous solution). The combined aqueous fractions were extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic fractions dried ($MgSO_4$) and concentrated under reduced pressure. The resultant oil was purified *via* flash column chromatography to yield the title compound (136 mg, 68%).

R_f 0.2 (3 : 7, v/v EtOAc–hexane); IR ν_{max} 2982, 2940, 2871, 1714, 1630, 1412, 1301, 1180, 1136; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.29 (t, J = 7.0 Hz, 3H), 1.49–1.57 (m, 2H), 1.66 (quint, J = 7.5 Hz, 2H), 2.32 (t, J = 7.5 Hz, 2H), 2.37 (t, J = 7.5 Hz, 2H), 4.20 (q, J = 7.0 Hz, 2H), 5.52 (d, J = 1.5 Hz, 1H), 6.14 (d, J = 1.5 Hz, 1H), 10.25 (br s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.32, 24.30, 27.92, 31.63, 33.91, 60.78, 124.84, 140.56, 167.36, 179.81; HRMS found $(M+H)^+$, 201.1122, $C_{10}H_{16}O_4$ requires $(M+H)^+$, 201.1127.

2-Methyleneheptanedioic acid (5a, Table 2, entry 8b)[24]

A magnetically stirred solution of β-ketoester **1a** (310 mg, 1 mmol) and NaOH (160 mg, 4 mmol) in ethanol (3 mL) was refluxed for 14 h. After cooling to room temperature the mixture was acidified with HCl (5 mL of a 2 M aqueous solution) and extracted with EtOAc (3 × 7 mL). The combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. Recrystallisation from H_2O afforded the pure product (108 mg, 63%).

Mp. 89–90 °C; IR ν_{max} 2946, 2903, 1677, 1627, 1427, 1406, 1257, 925; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.52–1.60 (m, 2H), 1.64–1.71 (m, 2H), 2.33 (t, J = 7.0 Hz, 2H), 2.40 (t, J = 7.0 Hz, 2H), 5.66 (d, J = 1.0 Hz, 1H), 6.30 (d, J = 1.0 Hz, 1H), 11.62 (br s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 24.01, 27.66, 31.26, 33.72, 127.49, 139.61, 172.69, 180.09.

Ethyl 7-hydroxy-2-methyleneheptanoate (5b)

A magnetically stirred solution of β-ketoester **1a** (155 mg, 0.5 mmol) in EtOH (5 mL) was treated with $NaBH_4$ (47.5 mg, 1.25 mmol) for 14 h. The mixture was diluted with HCl (10 mL of a 0.5 M aqueous solution) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. The resultant oil was purified *via* flash column chromatography to yield the title compound (56 mg, 60%).

R_f 0.3 (3 : 7, v/v EtOAc–hexane); IR ν_{max} 3390, 2982, 2936, 2863, 1715, 1633, 1302, 1181; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.30 (t, J = 7.0 Hz, 3H), 1.37–1.43 (m, 2H), 1.47–1.52 (m, 3H), 1.55–1.62 (m, 2H), 2.31 (td, J = 7.5 Hz, 1.0 Hz, 2H), 3.64 (t, J = 7.0 Hz, 2H), 4.20 (q, J = 7.0 Hz, 2H), 5.51 (q, J = 1.0 Hz, 1H), 6.12 (t, J = 1.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.34, 25.48, 28.37, 31.97, 32.67, 60.71, 63.02, 124.49, 141.06, 167.49; HRMS found $(M+H)^+$ 187.1329, $C_{10}H_{18}O_3$ requires $(M+H)^+$ 187.1334.

Diethyl 2-(iodomethylene)heptanedioate (5d)

R_f *E-isomer*: 0.67, *Z-isomer*: 0.62 (1 : 4, v/v EtOAc–hexane); IR ν_{max} 2934, 1736, 1714, 1594, 1368, 1295, 1214, 1095; ^{1}H-NMR (400 MHz, $CDCl_3$) δ *E-isomer*: 1.25 (t, *J* = 7.0 Hz, 3H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.46–1.54 (m, 2H), 1.66–1.73 (m, 2H), 2.34 (t, *J* = 7.5 Hz, 2H), 2.49–2.53 (m, 2H), 4.13 (q, *J* = 7.0 Hz, 2H), 4.20 (q, *J* = 7.0 Hz, 2H), 7.77 (s, 1H) *Z-isomer*: 1.25 (t, *J* = 7.0 Hz, 3H), 1.35 (t, *J* = 7.0 Hz, 3H), 1.45–1.53 (m, 2H), 1.60–1.67 (m, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.42 (td, *J* = 7.5 Hz, 1.0 Hz, 2H), 4.12 (q, *J* = 7.0 Hz, 2H), 4.28 (q, *J* = 7.0 Hz, 2H), 6.71 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ *E-isomer*: 14.31, 14.42, 24.82, 27.40, 33.68, 34.29, 60.39, 61.44, 98.55, 143.62, 163.58, 173.65 *Z-isomer*: 14.31, 14.39, 24.33, 27.79, 34.08, 36.49, 60.46, 61.35, 81.48, 144.41, 167.15, 173.49; HRMS found $(M+H)^+$, 355.0400, $C_{12}H_{19}IO_4$ requires $(M+H)^+$, 355.0406.

Ethyl 6-cyanohept-6-enoate (5e)

R_f 0.8 (3 : 7, v/v EtOAc–hexane); IR ν_{max} 2983, 2940, 2223, 1732, 1622, 1251, 1185; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.0 Hz, 3H), 1.56–1.70 (m, 4H), 2.27 (t, *J* = 7.5 Hz, 2H), 2.33 (t, *J* = 7.5 Hz, 2H), 4.13 (q, *J* = 7.0 Hz, 2H), 5.72 (q, *J* = 1.0 Hz, 1H), 5.85 (d, *J* = 1.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.37, 24.02, 27.09, 33.96, 34.44, 60.53, 118.66, 122.96, 130.60, 173.35; HRMS found $(M+H)^+$ 182.1182, $C_{10}H_{15}NO_2$ requires $(M+H)^+$ 182.1181; found $(M+Na)^+$ 204.0997, requires $(M+Na)^+$ 204.1000.

Ethyl 6-benzoylhept-6-enoate (5f)

R_f 0.6 (1 : 4, v/v EtOAc–hexane); IR ν_{max} 2937, 2866, 1732, 1658, 1597, 1448, 1177, 982, 754, 708; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.0 Hz, 3H), 1.51–1.60 (m, 2H), 1.67–1.74 (m, 2H), 2.33 (t, *J* = 7.5 Hz, 2H), 2.49 (tt, *J* = 7.5 Hz, 1.0 Hz, 2H), 4.12 (q, *J* = 7.0 Hz, 2H), 5.60 (d, *J* = 1.0 Hz, 1H), 5.84 (q, *J* = 1.0 Hz, 1H), 7.41–7.45 (m, 2H), 7.51–7.55 (m, 1H), 7.73–7.74 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.25, 24.64, 27.67, 31.96, 34.12, 60.25, 125.60, 128.20, 129.51, 132.19, 137.90, 147.91, 173.58, 198.25; HRMS found $(M+H)^+$ 261.1486, $C_{16}H_{20}O_3$ requires $(M+H)^+$ 261.1491, found $(M+Na)^+$ 283.1305, requires $(M+Na)^+$ 283.1310.

Diethyl 2-methylenehexanedioate (5g)[15b]

R_f 0.6 (1 : 4, v/v EtOAc–hexane); IR ν_{max} 2982, 2939, 2875, 1735, 1630, 1463, 1447, 1372, 1180; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.0 Hz, 3H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.78–1.84 (m, 2H), 2.30–2.35 (m, 4H), 4.12 (q, *J* = 7.0 Hz, 2H), 4.18 (q, *J* = 7.0 Hz, 2H), 5.54 (q, *J* = 1.0 Hz, 1H), 6.17 (t, *J* = 1.0 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.17, 14.21, 23.56, 31.16, 33.60, 60.27, 60.65, 125.12, 139.93, 167.00, 173.37.

Ethyl 6-(benzyl(methyl)amino)-2-methylene-6-oxohexanoate (5h)

3 : 2 Ratio of rotamers; R_f 0.6 (1 : 1, v/v EtOAc–hexane); IR ν_{max} 2932, 1715, 1648, 1452, 1406, 1265, 1183, 1139, 1028; ^{1}H-NMR (400 MHz, $CDCl_3$) δ *major*: 1.29 (t, *J* = 7.0 Hz, 3H), 1.82–1.92 (m, 2H), 2.31–2.41 (m, 4H), 2.89 (s, 3H), 4.19 (q, *J* = 7.0 Hz, 2H), 4.58 (s, 2H), 5.56 (d, *J* = 1.0 Hz, 1H), 6.17 (d, *J* = 1.0 Hz, 1H), 7.13–7.37 (m, 5H) *minor*: 1.26 (t, *J* = 7.0 Hz, 3H), 1.82–1.92 (m, 2H), 2.31–2.41 (m, 4H), 2.94 (s, 3H), 4.19 (q, *J* = 7.0 Hz, 2H), 4.51 (s, 2H), 5.52 (d, *J* = 1.0 Hz, 1H), 6.13 (d, *J* = 1.0 Hz, 1H), 7.13–7.37 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ *major*: 14.28, 23.83, 31.46, 32.83, 34.80, 50.85, 60.69, 124.97, 127.36, 128.08, 128.63, 137.59, 140.40, 167.23, 172.69 *minor*: 14.26, 24.00, 31.39, 32.42, 34.00, 53.38, 60.66, 124.90, 126.35, 127.65, 128.99, 136.78, 140.33, 167.19, 173.06. HRMS found $(M+H)^+$, 290.1750, $C_{17}H_{23}NO_3$ requires $(M+H)^+$, 290.1756.

Ethyl 6-(dibenzylamino)-2-methylene-6-oxohexanoate (5i)

R_f 0.4 (3 : 7, v/v EtOAc–hexane); IR ν_{max} 3030, 2980, 2934, 1713, 1650, 1605, 1495, 1452, 1366, 1182, 1028; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.0 Hz, 3H), 1.81–1.86 (m, 2H), 2.72 (t, *J* = 7.5 Hz, 2H), 2.35 (t, *J* = 7.5 Hz, 2H), 4.11 (q, *J* = 7.0 Hz, 2H), 4.35 (s, 2H), 4.52 (s, 2H), 5.44 (q, *J* = 1.0 Hz, 1H), 6.05 (t, *J* = 1.0 Hz, 1H), 7.04–7.28 (m, 10H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 14.33, 24.12, 31.46, 32.65, 48.34, 50.05, 60.75, 125.04, 126.51, 126.86, 127.51, 127.74, 128.27, 128.42, 128.73, 129.09, 129.11, 136.71, 137.62, 139.89, 140.38, 167.26, 173.25; HRMS found $(M+Na)^+$, 388.1882, $C_{23}H_{27}NO_3$ requires $(M+Na)^+$, 388.1889.

Dimethyl 2-methyleneoctanedioate (5j)[15a]

R_f 0.4 (CH_2Cl_2); IR ν_{max} 2996, 2951, 2862, 1723, 1631, 1438, 1334, 1290, 1263, 1198, 1167; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.28–1.35 (m, 2H), 1.41–1.49 (m, 2H), 1.61 (quint, *J* = 7.5 Hz, 2H), 2.25–2.29 (m, 4H), 3.63 (s, 3H), 3.71 (s, 3H), 5.48 (d, *J* = 1.0 Hz, 1H), 6.09 (d, *J* = 1.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 24.76, 28.09, 28.71, 31.76, 34.03, 51.50, 51.81, 124.73, 140.61, 167.77, 174.17.

Diethyl 2-methylenetridecanedioate (5k)

R_f 0.7 (3 : 7, v/v EtOAc–hexane); IR ν_{max} 2928, 2856, 1737, 1719, 1631, 1466, 1370, 1252, 1179; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.23–1.32 (m, 18H), 1.41–1.47 (m, 2H), 1.59–1.63 (m, 2H), 2.38 (t, *J* = 7.5 Hz, 4H), 4.12 (q, *J* = 7.0 Hz, 2H), 4.20 (q, *J* = 7.0 Hz, 2H), 5.50 (q, *J* = 1.0 Hz, 1H), 6.11 (t, *J* = 1.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.37, 14.41, 25.14, 28.56, 29.29, 29.35, 29.39, 29.54, 29.57, 29.64, 32.00, 34.55, 60.29, 60.66, 124.23, 141.34, 167.58, 174.05; HRMS found $(M+H)^+$, 313.2366, $C_{18}H_{32}O_4$ requires $(M+H)^+$, 313.2379.

Ethyl 2-(2-(ethoxycarbonyl)allyl)benzoate (5l)[23]

R_f 0.4 (1 : 9, v/v EtOAc–hexane); IR ν_{max} 2982, 2938, 2906, 1719, 1633, 1602, 1578, 1448, 1367, 1259; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.0 Hz, 3H), 1.34 (t, *J* = 7.0 Hz, 3H), 4.01 (s, 2H), 4.19 (q, *J* = 7.0 Hz, 2H), 4.31 (q, *J* = 7.0 Hz, 2H), 5.19 (q, *J* = 1.5 Hz, 1H), 6.19 (q, *J* = 1.5 Hz, 1H), 7.23 (dd, *J* = 7.5 Hz, 1.0 Hz, 1H), 7.29 (td, *J* = 7.5 Hz, 1.0 Hz, 1H), 7.43 (td, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.90 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.26, 14.29, 36.04, 60.81, 60.97, 125.50, 126.62, 130.64, 130.85, 131.66, 131.97, 140.01, 140.56, 167.07, 167.52.

Ethyl 2-(3-(ethoxycarbonyl)but-3-enyl)benzoate (5m)

R_f 0.6 (1 : 4, v/v EtOAc–hexane); IR ν_{max} 2982, 2937, 2874, 1718, 1630, 1448, 1367, 1255, 1186, 1145, 1078; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.0 Hz, 3H), 1.38 (t, *J* = 7.0 Hz, 3H), 2.62 (td, *J* = 8.0 Hz, 0.5 Hz, 2H), 3.14 (t, *J* = 8.0 Hz, 2H), 4.21 (q, *J* = 7.0 Hz, 2H), 4.35 (q, *J* = 7.0 Hz, 2H), 5.51 (q, *J* = 1.0 Hz, 1H), 6.15 (t, *J* = 1.0 Hz, 1H), 7.23–7.27 (m, 2H), 7.41 (td, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.88 (dd, *J* = 7.5 Hz, 1.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$)

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δ 14.37, 14.45, 33.51, 33.85, 60.74, 60.96, 125.20, 126.18, 130.11, 130.74, 131.30, 131.95, 140.40, 143.23, 167.31, 167.76; HRMS found $(M+H)^+$, 277.1437, $C_{16}H_{20}O_4$ requires $(M+H)^+$, 277.1440.

Ethyl 4-(2-(4-methoxybenzylcarbamoyl)phenyl)-2-methylene-butanoate (5n)

R_f 0.3 (3 : 7, v/v EtOAc–hexane); IR ν_{max} 3245, 2931, 1709, 1634, 1511, 1452, 1251, 1178, 1028; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.28 (t, J = 7.0 Hz, 3H), 2.60–2.63 (m, 2H), 2.95–2.99 (m, 2H), 3.80 (s, 3H), 4.17 (q, J = 7.0 Hz, 2H), 4.55 (d, J = 5.5 Hz, 2H), 5.50 (d, J = 1.5 Hz, 1H), 6.09 (br s, 1H), 6.13 (d, J = 1.5 Hz, 1H), 6.88 (d, J = 9.0 Hz, 2H), 7.17–7.23 (m, 2H), 7.29 (d, J = 9.0 Hz, 2H), 7.32–7.36 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.37, 32.56, 33.84, 43.62, 55.46, 60.79, 114.33, 125.43, 126.25, 126.97, 129.44, 130.02, 130.48, 130.57, 136.61, 139.67, 140.24, 159.28, 167.34, 169.91; HRMS found $(M+H)^+$, 368.1862, $C_{22}H_{25}NO_4$ requires $(M+H)^+$, 368.1862.

Diethyl 2-methyl-6-methyleneheptanedioate (5o)

R_f 0.6 (CH_2Cl_2); IR ν_{max} 2980, 2938, 2874, 1731, 1632, 1464, 1371, 1301, 1267, 1153; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.14 (d, J = 7.0 Hz, 3H), 1.25 (t, J = 7.0 Hz, 3H), 1.29 (t, J = 7.0 Hz, 3H), 1.42–1.52 (m, 3H), 1.64–1.72 (m, 1H), 2.28–2.31 (m, 2H), 2.39–2.47 (m, 1H), 4.12 (q, J = 7.0 Hz, 2H), 4.20 (q, J = 7.0 Hz, 2H), 5.51 (q, J = 1.0 Hz, 1H), 6.13 (t, J = 1.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.35, 14.40, 17.19, 26.14, 31.84, 33.38, 39.51, 60.29, 60.72, 124.65, 140.75, 167.36, 176.83; HRMS found $(M+H)^+$, 243.1589, $C_{13}H_{22}O_4$ requires $(M+H)^+$, 243.1596.

Diethyl 4-(*tert*-butyldimethylsilyloxy)-2-methyleneheptanedioate (5p)

R_f 0.5 (1 : 9, v/v EtOAc–hexane); IR ν_{max} 2957, 2931, 2858, 1736, 1718, 1630, 1255, 1178, 1084; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.87 (s, 9H), 1.24 (t, J = 7.0 Hz, 3H), 1.30 (t, J = 7.0 Hz, 3H), 1.63–1.72 (m, 1H), 1.77–1.86 (m, 1H), 2.30–2.50 (m, 4H), 3.91 (quint d, J = 6.5 Hz, 1.5 Hz, 1H), 4.11 (q, J = 7.0 Hz, 2H), 4.21 (q, J = 7.0 Hz, 2H), 5.59 (d, J = 1.5 Hz, 1H), 6.21 (d, J = 1.5 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ –4.48, –4.31, 14.37 (2XC), 18.16, 26.00, 29.98, 31.79, 40.38, 60.39, 60.80, 69.87, 128.03, 137.48, 167.13, 173.89; HRMS found $(M+H)^+$, 359.2242, $C_{18}H_{34}O_5Si$ requires $(M+H)^+$, 359.2254.

1-Ethyl 6-methyl 2-methylenehexanedioate (5q)[15b]

R_f 0.5 (CH_2Cl_2); IR ν_{max} 2985, 2954, 1712, 1631, 1438, 1370, 1265, 909; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.30 (t, J = 7.0 Hz, 3H), 1.82 (quint, J = 7.5 Hz, 2H), 2.32–2.36 (m, 4H), 3.67 (s, 3H), 4.20 (q, J = 7.0 Hz, 2H), 5.54 (q, J = 1.0 Hz, 1H), 6.17 (t, J = 1.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.34, 23.73, 31.34, 33.51, 51.66, 60.81, 125.25, 140.10, 167.16, 173.93.

4-((*tert*-Butyldimethylsilyl)oxy)-6-(ethoxycarbonyl)hept-6-enoic acid (5r)

A magnetically stirred solution of β-ketoester **1p** (440 mg, 1 mmol) and NaOH (160 mg, 4 mmol) in ethanol (3 mL) was refluxed for 14 h. After cooling to room temperature the mixture was acidified with HCl (5 mL of a 2 M aqueous solution) and extracted with EtOAc (3 × 7 mL). The combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. The resultant residue was purified *via* flash column chromatography to produce the title compound (198 mg, 60%).

R_f 0.13 (1 : 4, v/v EtOAc–hexane); IR ν_{max} 2957, 2930, 2858, 1713, 1631, 1256, 1181, 1085; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.87 (s, 9H), 1.29 (t, J = 7.0 Hz, 3H), 1.64–1.73 (m, 1H), 1.79–1.87 (m, 1H), 2.36–2.51 (m, 4H), 3.91–3.97 (m, 1H), 4.20 (q, J = 7.0 Hz, 2H), 5.59 (d, J = 1.0 Hz, 1H), 6.21 (d, J = 1.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ –4.62, –4.34, 14.33, 18.12, 25.97, 29.66, 31.40, 40.32, 60.84, 69.75, 128.10, 137.40, 167.11, 180.02; HRMS found $(M+H)^+$ 331.1930, $C_{16}H_{30}O_5Si$ requires $(M+H)^+$ 331.1941; found $(M+Na)^+$ 353.1752, requires $(M+Na)^+$ 353.1760.

Ethyl 2-((5-oxotetrahydrofuran-2-yl)methyl)acrylate (8)

A magnetically stirred solution of **5r** (83 mg, 0.25 mmol) in dry ethanol (3 mL) was reacted with ceric ammonium nitrate (206 mg, 0.38 mmol) at room temperature for 40 h. The solvent was removed under reduced pressure, the residue re-dissolved in diethyl ether (10 mL) and washed with $NaHCO_3$ (10 mL of a saturated aqueous solution), H_2O (10 mL) and brine (10 mL). The organic fraction was dried ($MgSO_4$) and concentrated under reduced pressure. The resultant oil was purified *via* flash column chromatography to produce the title compound (40 mg, 81%).

R_f 0.7 (1 : 1, v/v Et_2O–CH_2Cl_2); IR ν_{max} 2984, 1774, 1713, 1633, 1179, 914, 732; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.31 (t, J = 7.0 Hz, 3H), 1.86–1.96 (m, 1H), 2.29–2.38 (m, 1H), 2.51–2.56 (m, 2H), 2.67–2.70 (m, 2H), 4.22 (q, J = 7.0 Hz, 2H), 4.72 (quint, J = 7.0 Hz, 1H), 5.74 (d, J = 1.0 Hz, 1H), 6.32 (J = 1.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.33, 27.79, 28.82, 38.05, 61.18, 79.03, 128.75, 135.48, 166.74, 176.91; HRMS found $(M+H)^+$ 199.0964, $C_{10}H_{14}O_4$ requires $(M+H)^+$ 199.0970.

3-(4-Methylene-5-oxotetrahydrofuran-2-yl)propanoic acid (9)

A magnetically stirred solution of **5r** (60 mg, 2 mmol) in dry THF (3 mL) was reacted with TBAF (0.2 mL of a 1 M solution in THF) at room temperature for 14 h. The reaction mixture was diluted with NH_4Cl (10 mL of a saturated aqueous solution) and extracted with EtOAc (3 × 10 mL). The combined organic fractions were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The resultant oil was purified *via* flash column chromatography to provide the title compound (17 mg, 49%).

R_f 0.03 (1 : 1, v/v EtOAc–hexane); IR ν_{max} 2928, 1758, 1696, 1629, 1420, 1359, 1172, 1026; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.87–1.97 (m, 1H), 2.32–2.40 (m, 1H), 2.53–2.58 (m, 2H), 2.68–2.70 (m, 2H), 4.74 (quint, J = 7.0 Hz, 1H), 5.89 (s, 1H), 6.48 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 27.81, 28.83, 37.60, 78.90, 122.87, 131.53, 171.59, 177.05; HRMS found $(M+H)^+$ 171.0653, $C_8H_{10}O_4$ requires $(M+H)^+$ 171.0657; found $(M+Na)^+$ 193.0474, requires $(M+Na)^+$ 193.0477.

General procedures for kinetic analysis

A magnetically stirred solution of the competing β-ketoesters **1** (0.7 mmol of each) in dry CD_3OD (56 mmol) was reacted with K_2CO_3 (2.8 mmol) at the specified temperature (see Fig. 1). At the specified times aliquots (100 μL) were removed and quenched by

addition of HCl (100 μL of a 3 M aqueous solution). The mixtures were extracted with $CDCl_3$ (0.7 mL) and analyzed by ^{1}H-NMR.

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