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Supporting Information

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α-Amino Acids Induce Large Rate Accelerations in Aqueous Biphasic Lewis Acid-Catalyzed Michael Additions.**

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1. General experimental details

Deionized water was used in all reactions. All metal triflates and α-amino acids are commercially available compounds and used as received from the supplier. Purification of products was done by flash column chromatography performed on normal phase silica gel, 35-70 μ, 60Å. The enantiomeric excess of the optically active compounds were analyzed by chiral HPLC (CHIRALPAK AD-H). Purity has been documented by providing a ^{13}C-NMR spectrum for each of the products (see below). All products are known compounds and gave consistent ^{1}H- and ^{13}C-NMR data. References: **1**[1], **2**[2], **3**[1], 3-acetylheptane-2,6-dione[1], 3-acetyl-4-phenylheptane-2,6-dione.[3] ethyl 2-oxo-1-(3-oxobutyl)cyclopentanecarboxylate[1], ethyl 3-oxo-2-(3-oxocyclohexyl)-butanoate[4] and 3-(3-oxocyclopentyl)pentane-2,4-dione.[5]

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[1] J. Christoffers, *J. Chem. Soc., Perkin Trans. 1,* **1997**, 3141

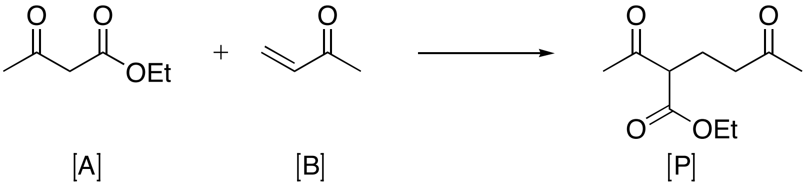
[2] A. Soriente, R. Arienzo, M. De Rosa, L. Palombi, A. Spinella, A. Scettri, *Green Chemistry*, **1999**, 1, 157

[3] P. P. Baruah; A. Boruah; D. Prajapati; J. S. Sandhu, *Ind. J. Chem., Sec. B: Org. Chem. Incl. Med. Chem.,* **1998**, 37B(5), 425

[4] K. Majima, R. Takita, A. Okada, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.,* **2003**, 125, 15837

[5] J. Comelles, M. Moreno-Mañas, E. Pérez, A.Roglans, M. R. Sebastián, A. Vallribera, *J. Org. Chem.*, **2004**, 69, 6834

2. Derivation of rate constants from second order rate equation



Rate of formation of products = k[A][B]

[A] = [B] i.e. we use 1:1 ratio of ethyl acetoacetate and methyl vinyl ketone

$$
\begin{aligned}
&d[P]/dt = k'[A]^2 \\
&[P]_t = [A]_0 - [A]_t \\
&d([A]_0 - [A]_t)/dt = k'[A]^2 \\
&-d[A]_t/dt = k'[A]^2 \\
&-\int d[A]_t/[A]^2 = k'\int dt \\
&\{1/[A]_t\} = k't \\
&k't = 1/[A]_t - 1/[A]_0
\end{aligned}
$$

The ^{1}H-NMR shows the ratio of ethyl acetoacetate to product at time t.

If k'_{+L} and k'_{-L} are the rate constants for the reaction in the presence and absence of ligand, respectively, then the relative rate is k'_{+L}/k'_{-L}

3. Determination of rate constants (Figure 1)

All reactions were performed at 25 ± 0.5 °C. To a mixture of D-alanine (0.06 mmol, 0.12 equiv.) was added NaOH (0.06 M, 0.12 equiv.) and the mixture was stirred for 15 min. Yb(OTf)$_3$ (0.05 mmol, 0.10 equiv.), ethyl acetoacetate (0.5 mmol, 1 equiv.) and methyl vinyl ketone (0.5 mmol, 1 equiv.) were then added. The reaction mixtures were stirred vigorously for 30, 60 and 120 min. respectively. The reaction was diluted with water and extracted with ethyl acetate (10 mL). The organic phase was dried over MgSO$_4$, filtered and concentrated. The crude mixture was analyzed by ^{1}H-NMR (acetone-d_6), which afforded the ratios of ethyl acetoacetate **A** to adduct **1** (Figure S1). All experiments were performed two times, and listed values are averages. $\mathbf{A}_0$=100%, $1/[\mathbf{A}]_0$=2.00, $\mathbf{A}_{30}$=80%, $1/[\mathbf{A}]_{30}$=2.50, $\mathbf{A}_{60}$=62%, $1/[\mathbf{A}]_{60}$=3.24, $\mathbf{A}_{120}$=49%, $1/[\mathbf{A}]_{120}$=4.12. The reactions were performed with good reproducibility and a standard deviation, σ, of 0.07. When plotting 1/[**A**] against time, a straight line, typical for a second-order reaction, is obtained from which the reaction rate can be calculated (Figure S2). The rate constant for the ligand-free reaction was obtained in an identical way.[6] All 1/[**A**]-values for the reactions with ligand were decreased with 1.0186 so that the same intercept as the ligand-free reaction was achieved. By making the sound assumption that the reactions have the same initial mechanism, the rate constants can be compared for the first 2 hours. The relative rate was then obtained by using the formula $k_{\mathrm{rel}} = k'_{+\mathrm{L}}/k'_{-\mathrm{L}}$, which gave a k_{rel} value of 138 for the reaction.

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[6] R. Ding, K. Katebzadeh, L. Roman, K-E. Bergquist, U. M. Lindström, *J. Org. Chem.*, **2006**, 71, 352

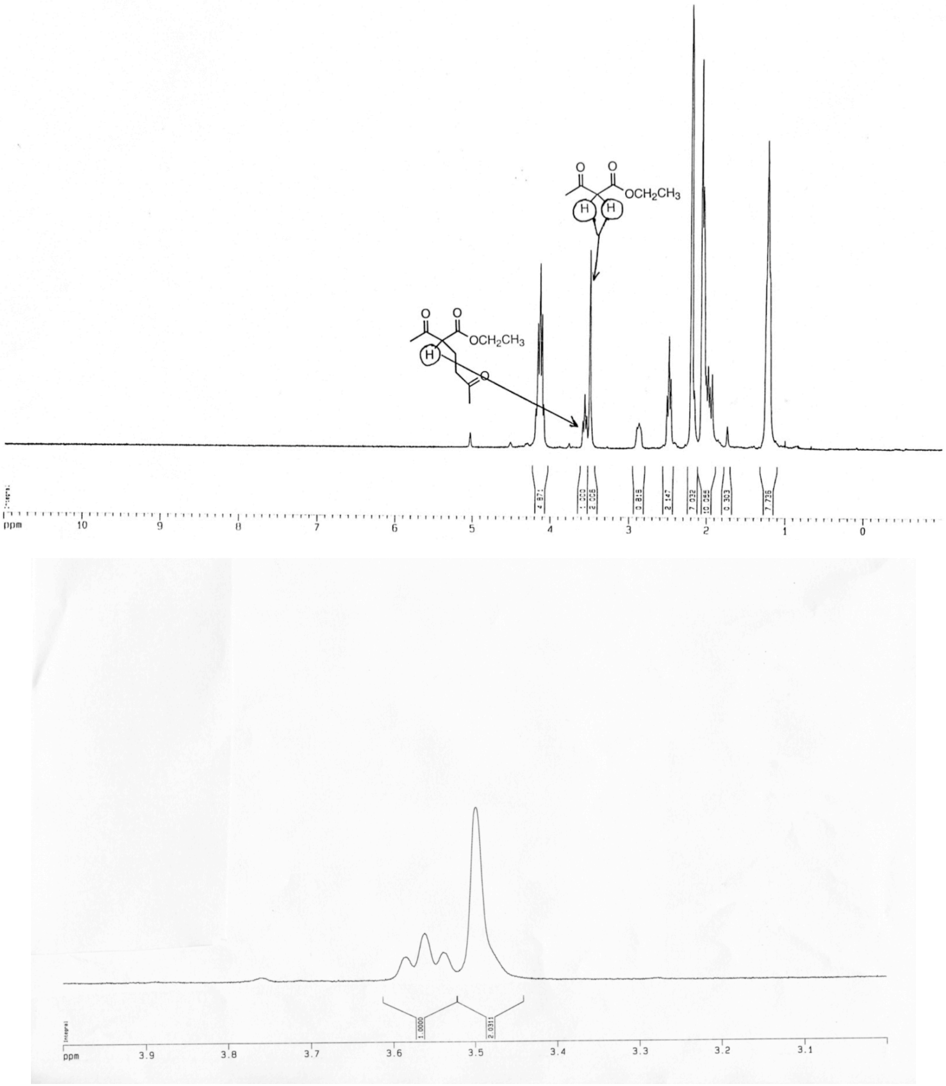


Figure S1. Reactions were analyzed for conversion of ethyl acetoacetate into product by integrating the peaks of α-protons in the ^{1}H-NMR (400 MHz, acetone-d_6).

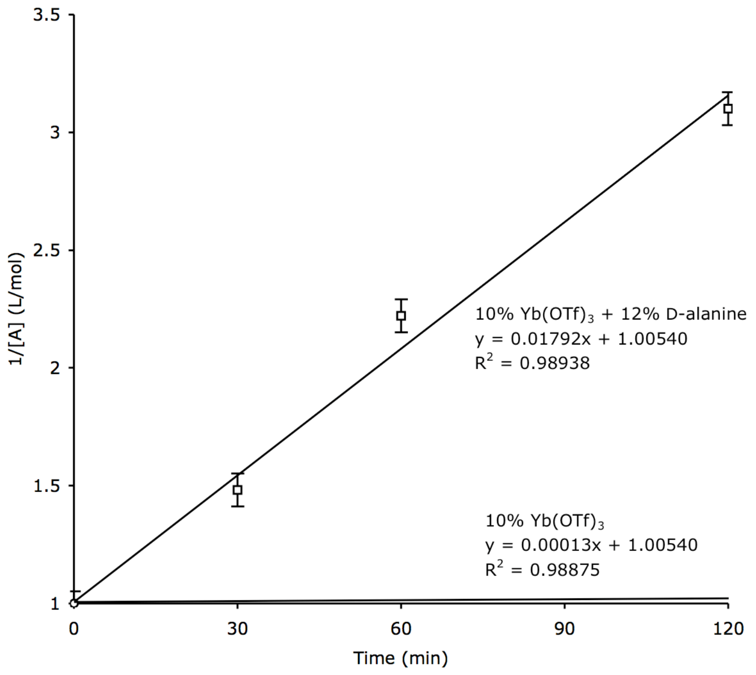


Figure S2. Plot showing an excellent fit of experimental data to the second order rate equation.

4. Typical procedure for Michael additions in aqueous suspension catalyzed by Yb(OTf)$_3$/D-alanine (Table 1, procedure A and B)

Procedure A

3-Acetylheptane-2,6-dione:

D-alanine (10.7 mg, 0.12 mmol) and ytterbium triflate (62.0 mg, 0.1 mmol) were stirred in aqueous NaOH (0.12 M, 1.0 mL) for 15 minutes. Acetylacetone (103 μL, 1 mmol) and methyl vinyl ketone (89 μL 1.1 mmol) were then added. The reaction mixture was stirred vigorously for 2 h at 60 °C. The reaction was diluted with water and extracted with ethyl acetate (10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (heptane/ethyl acetate 2:1), which afforded 3-acetylheptane-2,6-dione (153 mg, 90%).

Procedure B

3-(3-Oxocyclohexyl)pentane-2,4-dione (2):

D-alanine (21.4 mg, 0.24 mmol) and ytterbium triflate (124.0 mg, 0.2 mmol) were stirred in aqueous NaOH (0.12 M, 2.0 mL) for 15 minutes. Acetylacetone (103 μL, 1 mmol) and 2-cyclohexen-1-on (290 μL, 3 mmol) were then added. The reaction mixture was stirred vigorously for 24 h at 60 °C. The reaction was diluted with water and extracted with ethyl acetate (10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (heptane/ethyl acetate 2:1), which afforded 3-(3-oxocyclohexyl)pentane-2,4-dione (184 mg, 94%).

5. Typical procedure for Yb(OTf)$_3$-catalyzed Michael additions using various amino acids as ligands (Scheme 2)

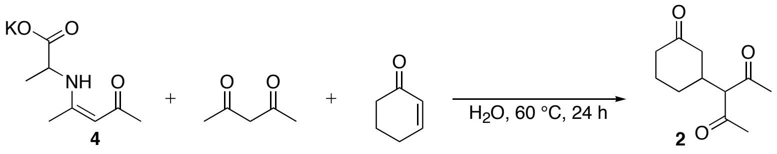
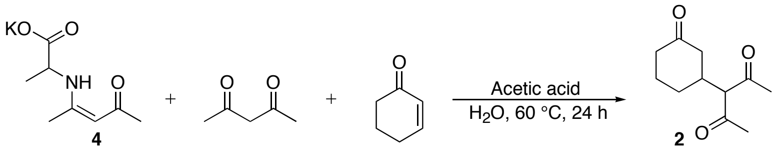
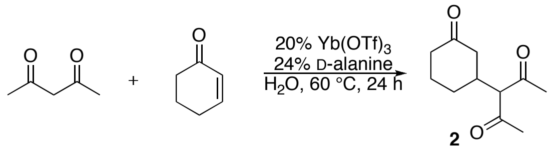
3-(3-oxocyclohexyl)pentane-2,4-dione (2):

To a mixture of D-alanine (21.4 mg, 0.24 mmol) and ytterbium triflate (124.0 mg, 0.2 mmol) in deionized water (1.5 mL) was added NaOH (0.2 M) until the solution reached pH 6.5. Acetylacetone (103 μL, 1 mmol) and 2-cyclohexen-1-one (290 μL, 3 mmol) were then added. The reaction mixture was stirred vigorously for 22 h at 40 °C. The reaction was diluted with water and extracted with ethyl acetate (10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (heptane/ethyl acetate 2:1) and analyzed for enantiomeric excess by chiral HPLC (2-propanol/hexane 1:6.5).

6. Catalyst recycling experiment on gram scale

D-alanine (67.1 mg, 0.75 mmol) and ytterbium triflate (389.0 mg, 0.63 mmol) were stirred in aqueous NaOH (0.12 M, 6 mL) in a round bottom flask for 15 minutes at room temperature. Ethyl 2-oxocyclohexanecarboxylate (1.0 mL, 6.27 mmol) and methyl vinyl ketone (559 μL, 6.90 mmol) were added. The reaction flask was sealed and the reaction mixture stirred vigorously at 60 °C for 8.5 h. The solution was transferred to a separatory funnel, which allowed facile separation of the organic phase from the water phase. The aqueous catalytic phase was poured back into the reaction flask, which was charged with another batch of reactants as described above. The organic phase was diluted with 2 mL of ethyl acetate, dried over $MgSO_4$, filtered and concentrated to give **3**. The crude was analyzed by ^{1}H-NMR (acetone-d_6). The experiment was performed 5 times and each cycle gave >98% conversion of starting material into **3** (see section 9 below for NMR spectra). The catalyst-free reaction was performed in an identical way (except that ^{1}H-NMR analysis was performed in $CDCl_3$) and gave no observable conversion of starting material.

7. Experimental comparing the organocatalyzed and the $Yb(OTf)_3$/D-alanine catalyzed Michael reaction

Reactions	NMR yield (%)	ee (%)
	23	7
	33	11
	94[a]	53

[a] Isolated yield.

We wanted to show that the Michael addition did not proceed by an organocatalytic mechanism. By synthesizing enamine **4**[7] and subjecting it to our reaction conditions we were able to get a strong indication that an organocatalyzed reaction did not have any significant influence, since it gave much lower yields and ee's compared to the $Yb(OTf)_3$/D-alanine catalyzed Michael addition.

Organocatalyzed reaction without acid

3-(3-oxocyclohexyl)pentane-2,4-dione (2)

Compound **4**[7] (50.2 mg, 0.24 mmol) was stirred in H_2O (1 mL) and then acetylacetone (78 μL, 0.76 mmol) and 2-cyclohexene-1-one (291 μL, 3.0 mmol) were added. The reaction mixture was stirred vigorously for 24 h at 60 °C. The reaction was diluted with water and extracted with ethyl acetate (10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The crude mixture was analyzed for conversion by ^{1}H-NMR ($CDCl_3$) and for enantiomeric excess by chiral HPLC (2-propanol/hexane 1:6.5), which afforded 23% conversion and 7% ee.

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[7] G. Gal, J. M. Chemerda, D. F. Reinhold, R. M. Purick, *J. Org. Chem.,* **1977**, 42, 142

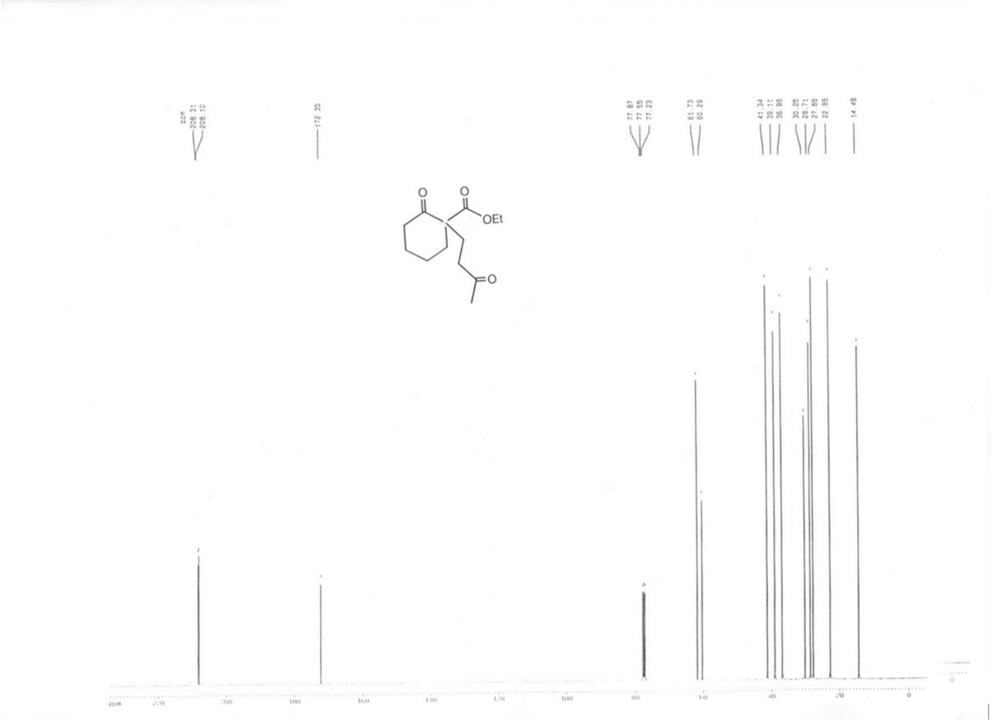
Organocatalyzed reaction with acetic acid

3-(3-oxocyclohexyl)pentane-2,4-dione (2)

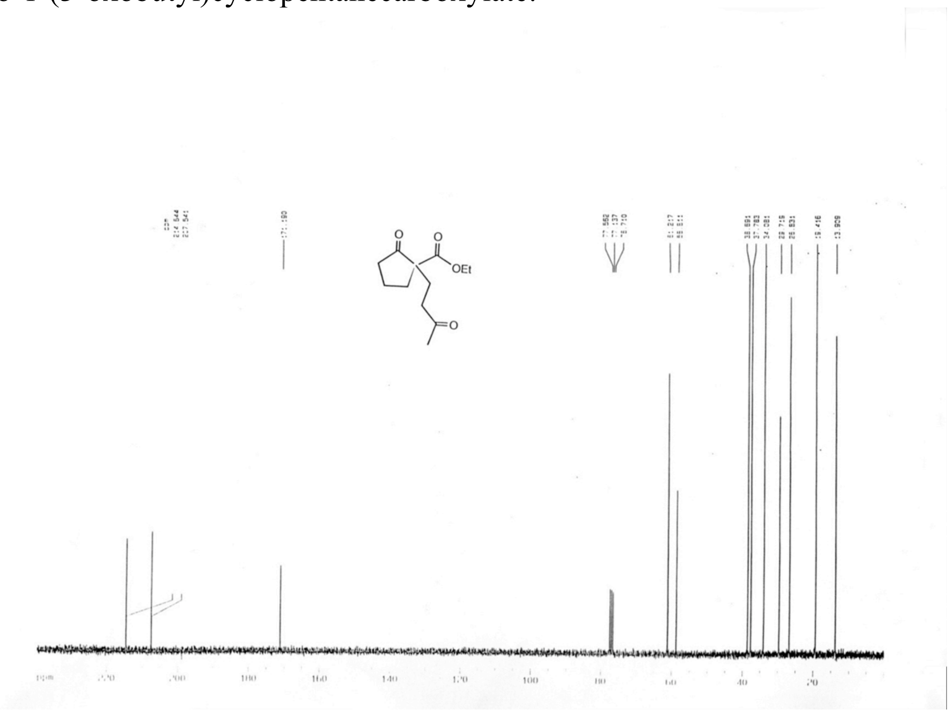
Compound 4[7] (50.2 mg, 0.24 mmol) was stirred in H_2O (1 mL) and then acetic acid (19.5 μL, 0.34 mmol), acetylacetone (78 μl, 0.76 mmol) and 2-cyclohexene-1-one (291 μL, 3.0 mmol) were added. The reaction mixture was stirred vigorously for 24 h at 60 °C. The reaction was diluted with water and extracted with ethyl acetate (10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The crude mixture was analyzed for conversion by ^{1}H-NMR ($CDCl_3$) and for enantiomeric excess by chiral HPLC (2-propanol/hexane 1:6.5), which afforded 33% conversion and 11% ee.

8. ^{13}C-NMR spectra confirming purity of products

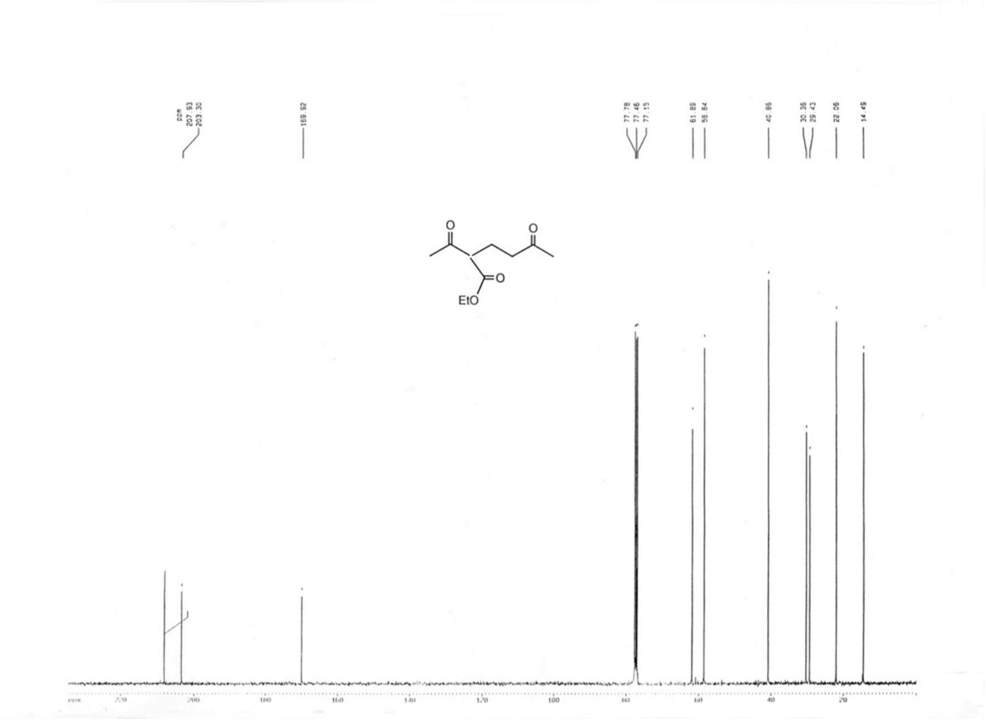
Ethyl 2-oxo-1-(3-oxobutyl)cyclohexanecarboxylate:



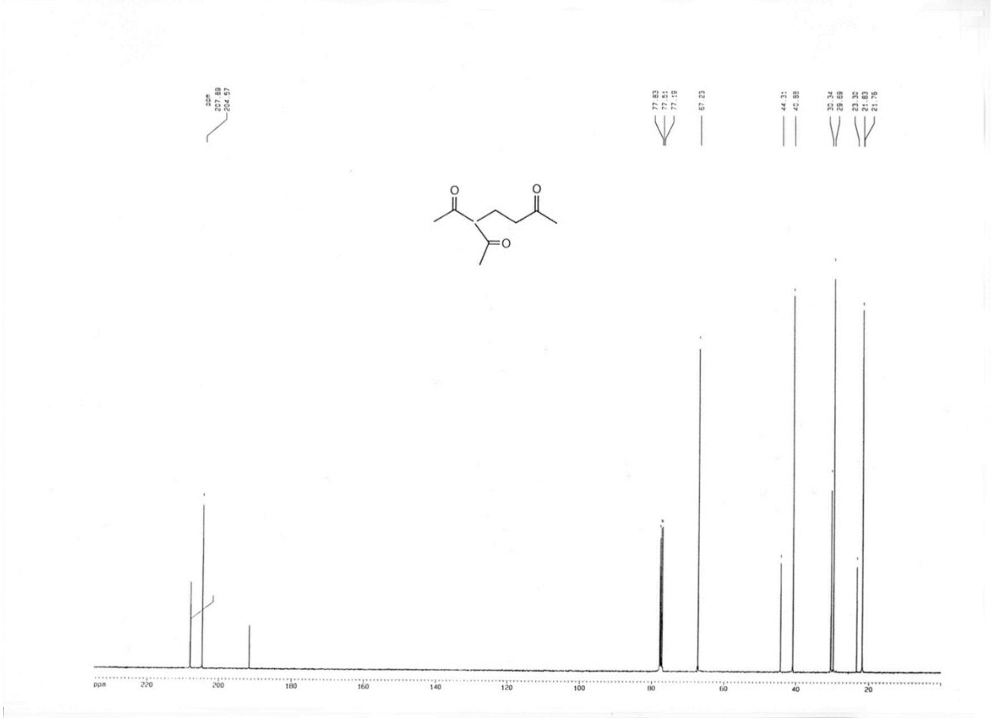
Ethyl 2-oxo-1-(3-oxobutyl)cyclopentanecarboxylate:



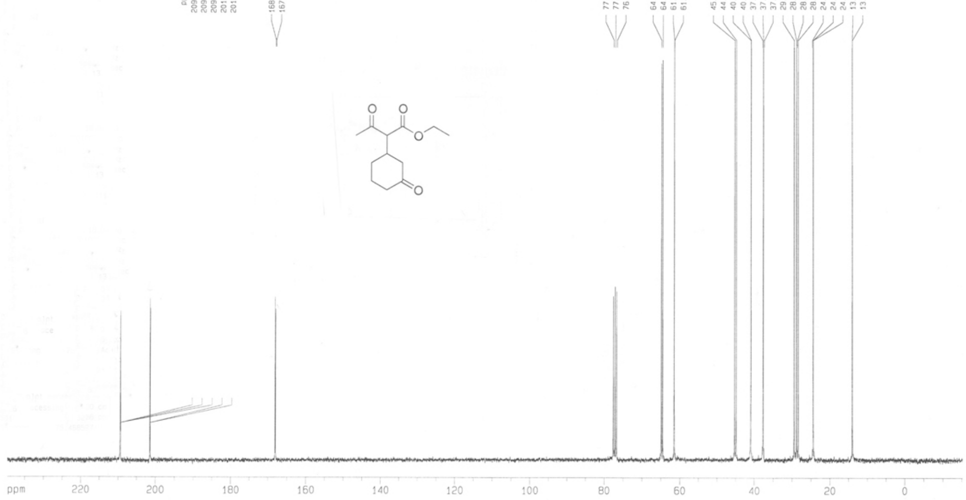
Ethyl 2-acetyl-5-oxohexanoate:



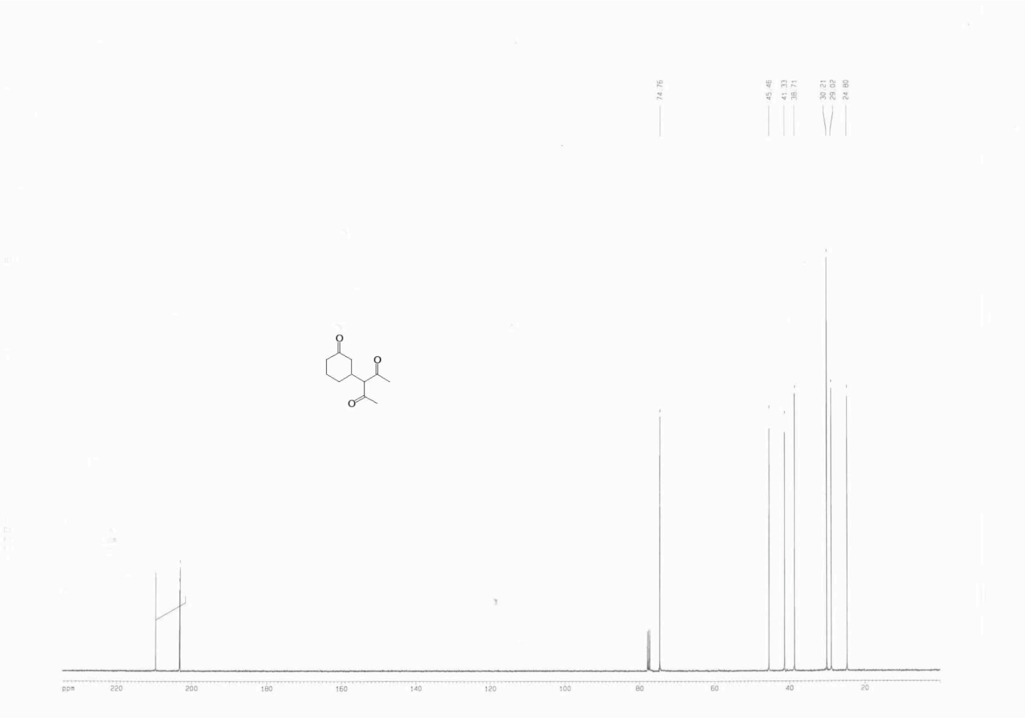
3-Acetylheptane-2,6-dione (mixture of tautomers):



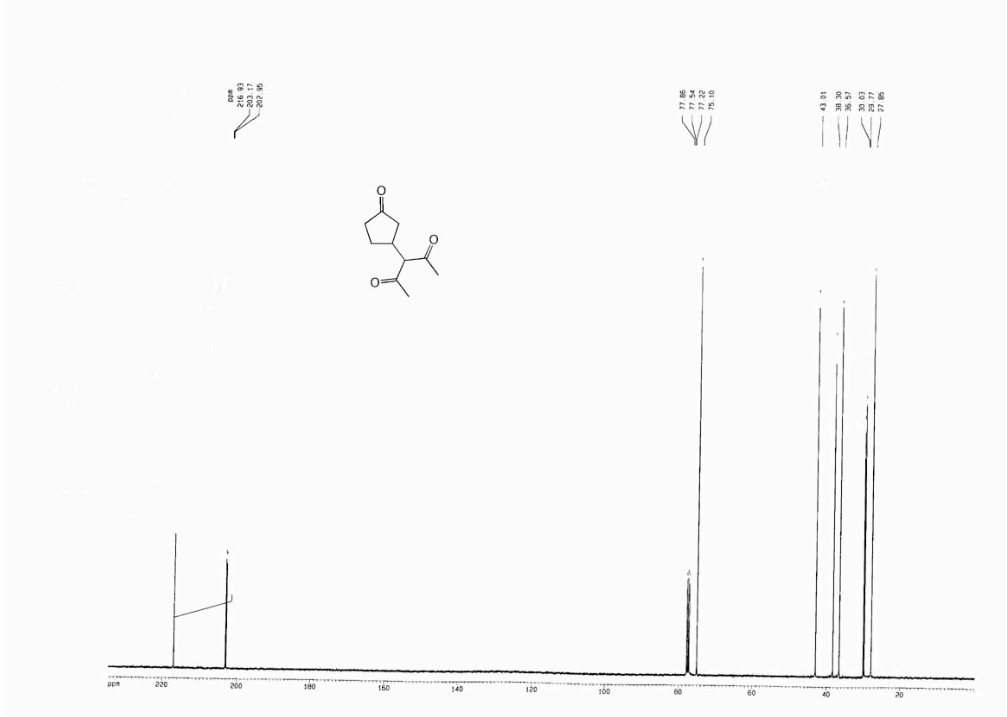
Ethyl 3-oxo-2-(3-oxocyclohexyl)butanoate:



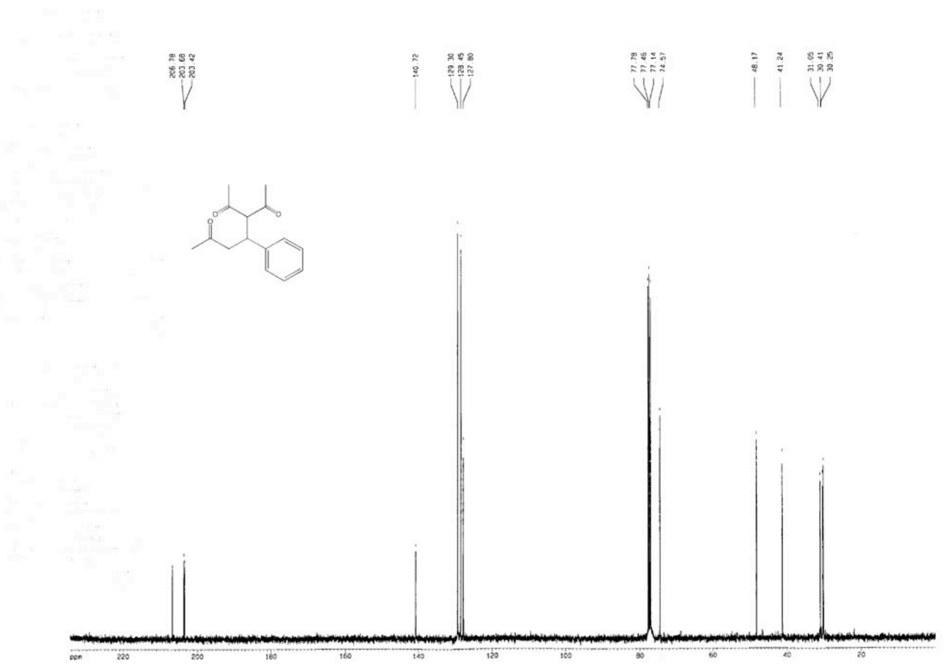
3-(3-Oxocyclohexyl)pentane-2,4-dione:



3-(3-Oxocyclopentyl)pentane-2,4-dione:

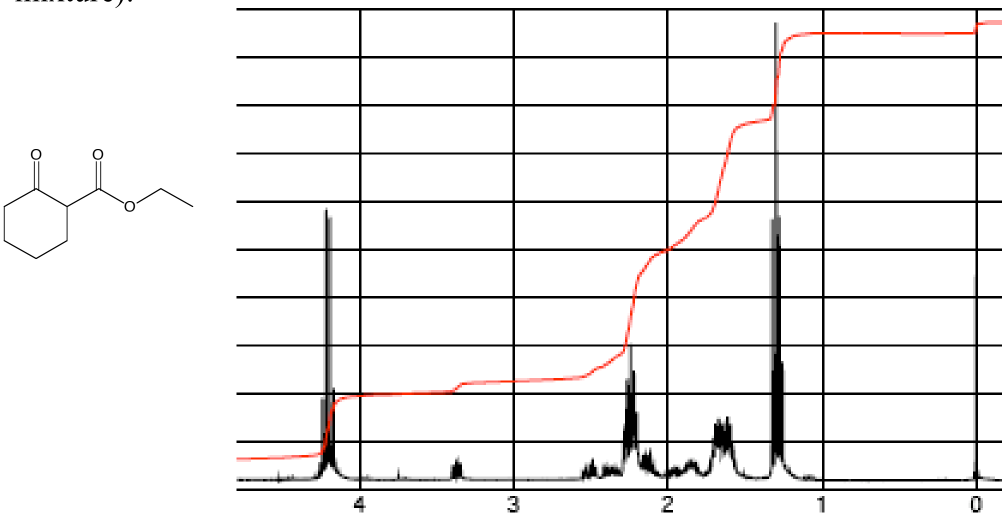


3-Acetyl-4-phenylheptane-2,6-dione:

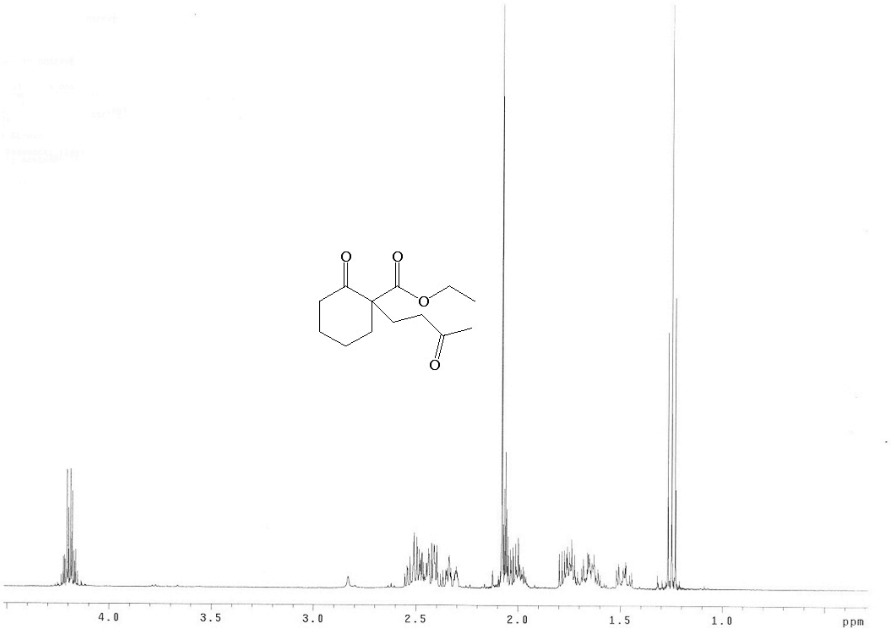


9. ^{1}H-NMR spectra confirming conversion of starting material into **3** in the recycling experiment

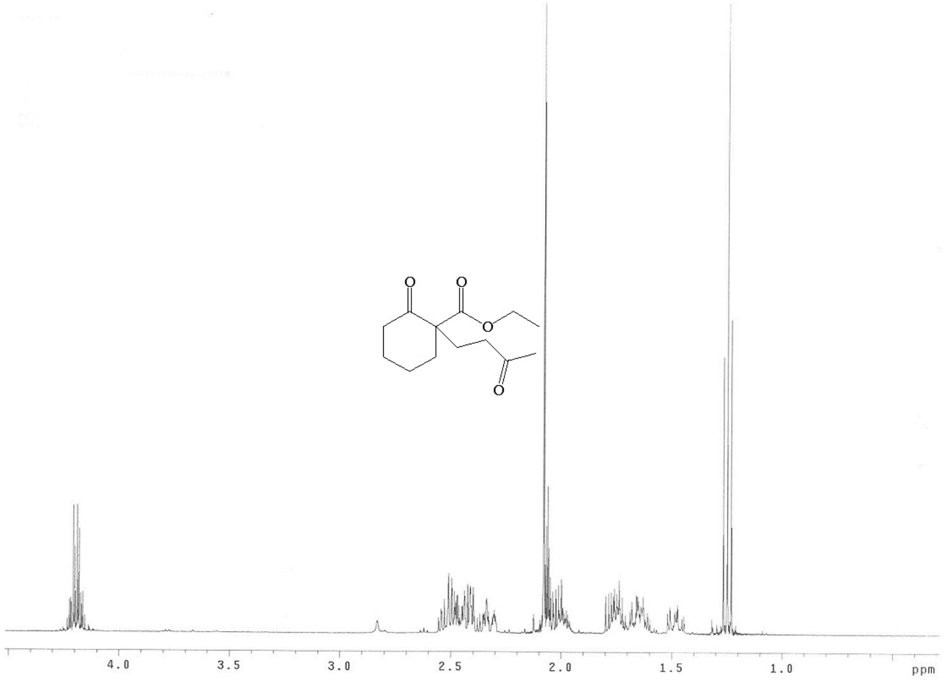
Reference spectrum of ethyl 2-oxocyclohexanecarboxylate from Sigma-Aldrich (keto-enol mixture):



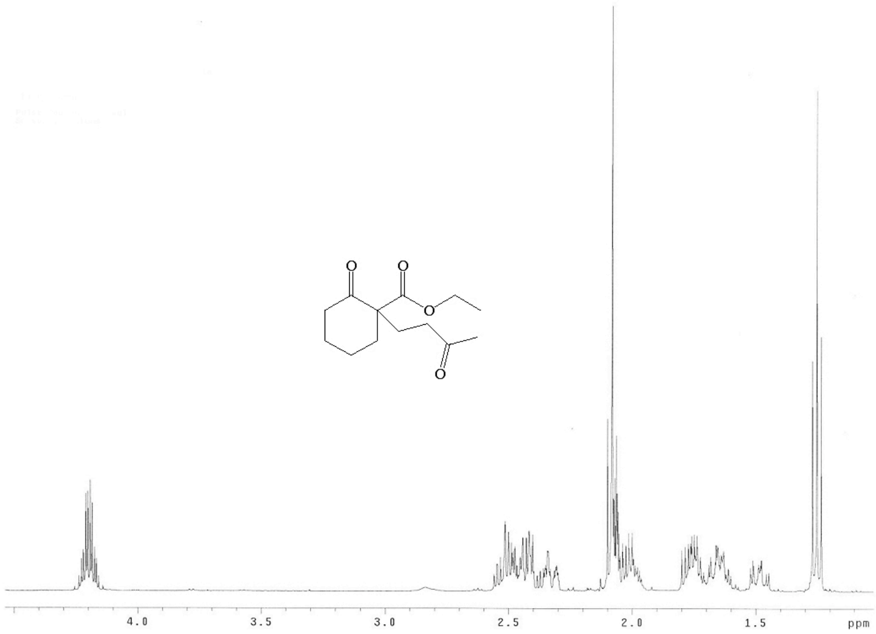
Ethyl 2-oxo-1-(3-oxobutyl)cyclohexanecarboxylate, cycle 1:



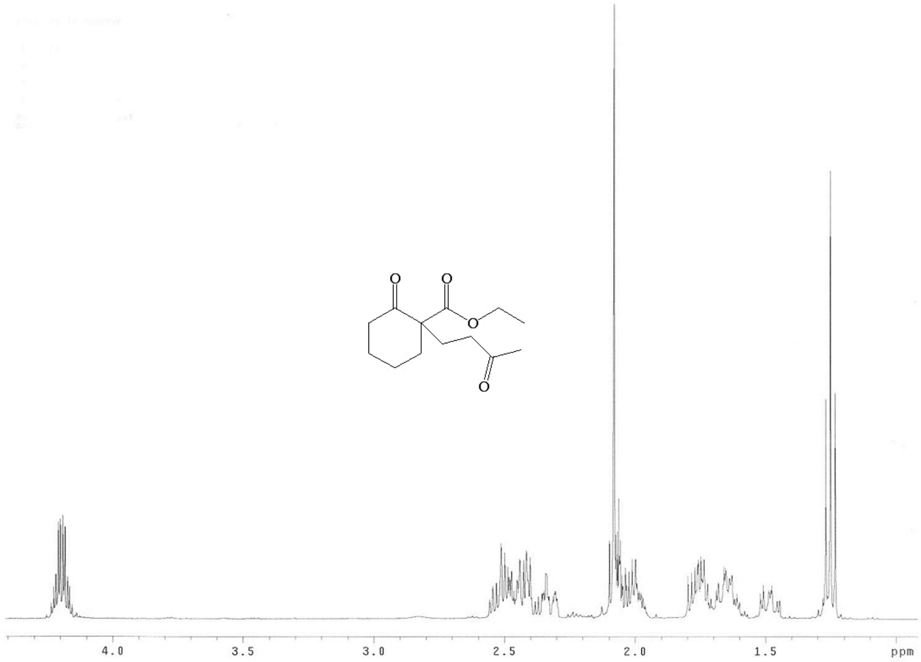
Ethyl 2-oxo-1-(3-oxobutyl)cyclohexanecarboxylate, cycle 2:



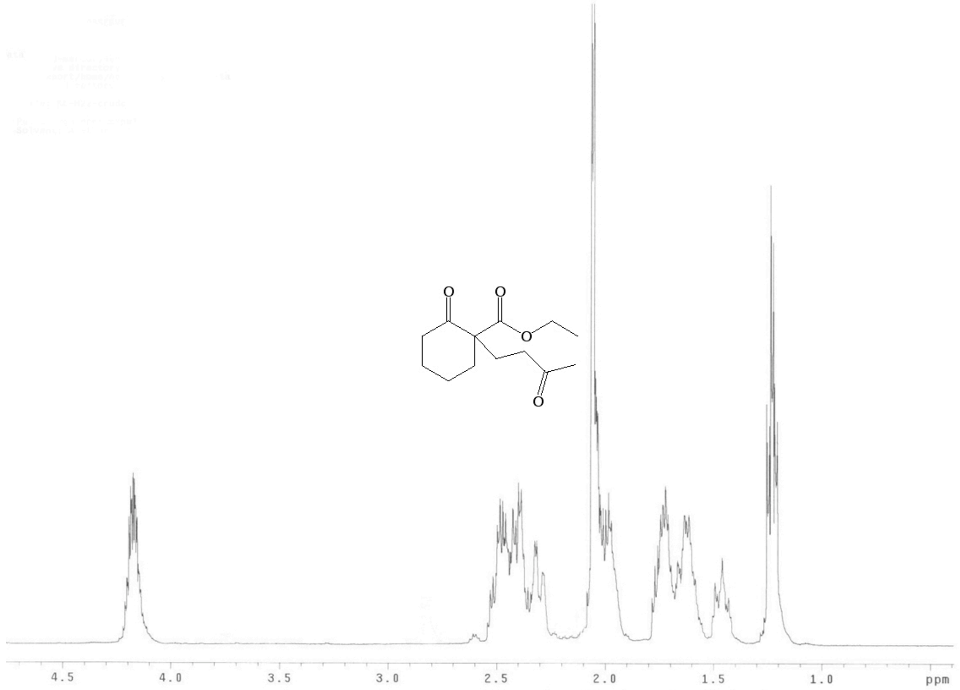
Ethyl 2-oxo-1-(3-oxobutyl)cyclohexanecarboxylate, cycle 3:



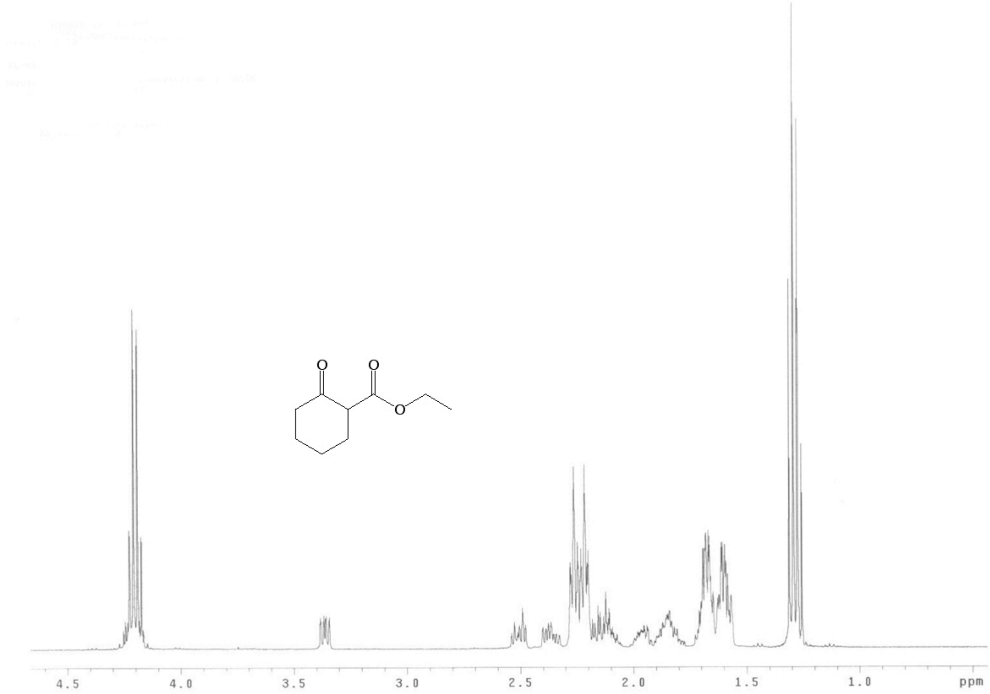
Ethyl 2-oxo-1-(3-oxobutyl)cyclohexanecarboxylate, cycle 4:



Ethyl 2-oxo-1-(3-oxobutyl)cyclohexanecarboxylate, cycle 5 (poorer resolution because it was run on a lower frequency spectrometer):



Ethyl 2-oxocyclohexanecarboxylate, recovered from reaction run without catalyst and identical to starting material (see reference spectrum from Sigma-Aldrich):



Reference spectrum of ethyl 2-oxocyclohexanecarboxylate from Sigma-Aldrich (keto-enol mixture):