

# Supporting Information

## Combination of Metal-Catalyzed Cycloisomerizations and Biocatalysis in Aqueous Media: Asymmetric Construction of Chiral Alcohols, Lactones and $\gamma$ -Hydroxy-Carbonyl Compounds

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## 1. General procedures

Compounds *trans*-[PdCl<sub>2</sub>{μ<sup>2</sup>-*N,S*-(PTA)=NP(=S)(OR)<sub>2</sub>}]<sub>2</sub> (**1-2**),<sup>1</sup> [AuCl(SMe<sub>2</sub>)] (**14**),<sup>2</sup> and *N*-tosylpent-4-yn-amide (**18**),<sup>3</sup> were prepared by following the methods described in the literature. Codex<sup>®</sup> KRED Screening Kit was purchased from Codexis. Laccase from *Trametes versicolor* and TEMPO were purchased from Aldrich. All other reagents and solvents were of the highest quality available. <sup>1</sup>H and <sup>13</sup>C NMR spectra were obtained using a Bruker DPX-300 (<sup>1</sup>H, 300.13 MHz; <sup>13</sup>C, 75 MHz) spectrometer for routine experiments. Gas chromatography (GC) analyses were performed on a Hewlett Packard 6890 Series II chromatograph. HPLC analyses were performed with a Hewlett Packard 1100 LC liquid chromatograph. Optical rotations were measured using a Perkin-Elmer 241 polarimeter and are quoted in units of 10<sup>-1</sup>deg cm<sup>2</sup> g<sup>-1</sup>.

## 2. Protocols

**General procedure for the metal-catalyzed cycloisomerization/hydrolysis of 4-pentyn-1-ol (5a) or 3-pentyn-1-ol (5b): Synthesis of 5-hydroxy-2-pentanone (7).** 25 mg (2.5 mol%) of catalyst **1** (*i.e.*, 5 mol% in Pd) and 1 mmol of **5a** (93  $\mu$ L) or **5b** (92  $\mu$ L) were added to 1 mL of water. The mixture was then stirred at 30 °C for 9 or 17 h, respectively, under air. The course of the reaction was monitored by regular sampling and analysis by GC. The crude of the reaction was extracted with diethyl ether (3 x 5 mL) and dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness in a vacuum concentrator to yield pure **7** in 95% yield. The identity of this compound was confirmed by <sup>1</sup>H-NMR analysis after comparison with reported spectra.

**General procedure for the one-pot synthesis of (R)-pentane-1,4-diol (8).** 6 mg (2.5 mol%) of catalyst **1** (*i.e.*, 5 mol% in Pd) and 23  $\mu$ L (0.25 mmol) of 4-pentyn-1-ol (**5a**) were added to 250  $\mu$ L of water. The mixture was then stirred at 30 °C for 9 h under air. Once completed the cycloisomerization/hydrolysis (GC analysis), the reaction mixture was diluted 4 times (substrate concentration = 250 mM) with a 125 mM potassium phosphate buffer pH 7.0 (1.25 mM MgSO<sub>4</sub>, 1mM NADP<sup>+</sup>), and <sup>t</sup>PrOH (175  $\mu$ L) and KRED-P2-B02 (21 mg, 100% w/w) was consecutively added. Then, the mixture was stirred at 30 °C for 24 h. After that time, an aliquot was extracted with ethyl acetate (2 x 500  $\mu$ L), the organic layers separated by centrifugation (90 sec, 13000 rpm), combined and finally dried over Na<sub>2</sub>SO<sub>4</sub>. Both conversion and enantiomeric excess of diol **8** were measured by GC using a chiral column after derivatization as diacetate with acetic anhydride. Then, brine (5 mL) was added to the mixture and the product extracted with ethyl acetate (2 x 10 mL). The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness in a vacuum concentrator to yield pure (*R*)-**8** in 90% yield and >99% ee. The identity of this compound was confirmed by <sup>1</sup>H-NMR analysis after comparison with reported spectra. Alternatively, (*R*)-pentane-1,4-diol (**8**) was also prepared starting from 3-pentyn-1-ol (**5b**) employing the aforementioned reaction procedure.

**General procedure for the stepwise conversion of 4-pentyn-1-ol (5a) or 3-pentyn-1-ol (5b) into (R)- $\gamma$ -valerolactone (9).** An identical procedure to that described above for the transformation of 4-pentyn-1-ol (**5a**) into (*R*)-pentane-1,4-diol (**8**) was followed (0.25 mmol-scale). Then, once the bioreduction (KRED-P2-B02) was accomplished, the reaction mixture was centrifuged and the supernatant diluted with 2 mL of 50 mM citrate buffer pH 5.5 (substrate concentration = 65 mM). Finally, TEMPO (10 mg, 0.06 mmol) and laccase from *Trametes versicolor* (10 mg; 10U/mg) were successively added and the mixture vigorously stirred in an open-to-air tube at room temperature overnight (alternatively, oxygen can be bubbled through the solution to minimize the reaction time). After completion of the reaction (TLC analysis), the crude was extracted with dichloromethane (2 x 5 mL), the combined organic phases dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated carefully (due to the

volatility of the resulting product) in a vacuum concentrator to yield (*R*)-**9** in 80% yield and >99% ee without the need for further purification (conversion and enantiomeric excess of **9** were measured by GC using a chiral column). The identity of this compound was confirmed by <sup>1</sup>H-NMR analysis after comparison with reported spectra. Alternatively, (*R*)- $\gamma$ -valerolactone (**9**) was also prepared starting from 3-pentyn-1-ol (**5b**) employing the aforementioned reaction procedure.

**General procedure for the metal-catalyzed cycloisomerization/hydrolysis of 4-pentynoic acid (10): Synthesis of levulinic acid (12).** 10 mg (5 mol%) of KAuCl<sub>4</sub> (**13**) and 50 mg (0.5 mmol) of 4-pentynoic acid (**10**) were added to 500  $\mu$ L of water. The mixture was then stirred at 50 °C for 45 min under air. The course of the reaction was monitored by regular sampling and analysis by GC. The crude of the reaction was extracted with diethyl ether (3 x 5 mL) and dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness in a vacuum concentrator to yield pure **12** in 95% yield. The identity of this compound was confirmed by <sup>1</sup>H-NMR analysis after comparison with reported spectra.

**General procedure for the one-pot synthesis of (*R*)- $\gamma$ -hydroxyvaleric acid (15).** 5 mg (5 mol%) of KAuCl<sub>4</sub> (**13**) and 25 mg (0.25 mmol) of 4-pentynoic acid (**10**) were added to 250  $\mu$ L of water. The mixture was then stirred at 50 °C for 45 min under air. Once completed the cycloisomerization/hydrolysis (GC analysis), the reaction mixture was diluted 4 times (substrate concentration = 250 mM) with a 125 mM potassium phosphate buffer pH 7.0 (1.25 mM MgSO<sub>4</sub>, 1mM NADP<sup>+</sup>), <sup>t</sup>PrOH (175  $\mu$ L) and DMSO (75  $\mu$ L). After 15 minutes of incubation, KRED-P1-A04 (21 mg, 100% w/w) was added and the mixture stirred at 250 rpm and 30 °C for 24 h. After this time, the crude was extracted with ethyl acetate (2 x 500  $\mu$ L), the organic layers separated by centrifugation (90 sec, 13000 rpm), combined and finally dried over Na<sub>2</sub>SO<sub>4</sub> to yield pure **15** in 95% yield. The conversion of the biotransformation was determined by GC meanwhile the enantiomeric excess of the resulting (*R*)- $\gamma$ -hydroxyvaleric acid (**15**) was measured by chiral GC after derivatization into  $\gamma$ -valerolactone. The identity of this compound was confirmed by NMR analysis.

**General procedure for the synthesis of isopropyl levulinate (16a).** 10 mg (5 mol%) of KAuCl<sub>4</sub> (**13**) and 50 mg (0.5 mmol) of 4-pentynoic acid (**10**) were added to 500  $\mu$ L of <sup>t</sup>PrOH. The mixture was then stirred at 50 °C for 11 h under air. The course of the reaction was monitored by regular sampling and analysis by GC. The crude of the reaction was extracted with diethyl ether (3 x 5 mL) and dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness in a vacuum concentrator to yield pure **16a** in quantitative yield. The identity of this compound was confirmed by NMR analysis. Alternatively, the aromatic levulinate **16b** could be also prepared by employing phenol under the aforementioned conditions.

**General procedure for the conversion of 4-pentynoic acid (10) into (*R*)- $\gamma$ -valerolactone (9).** 5 mg (5 mol%) of KAuCl<sub>4</sub> (**13**) and 25 mg (0.25 mmol) of 4-pentynoic acid (**10**) were added to 250

$\mu\text{L}$  of  $^i\text{PrOH}$ . The mixture was then stirred at  $50\text{ }^\circ\text{C}$  for 11 h under air. The course of the reaction was monitored by regular sampling and analysis by GC. Once completed the formal hydroalkoxylation of 4-pentynoic acid (GC analysis), the reaction mixture was diluted 4 times (substrate concentration = 250 mM) with a 125 mM potassium phosphate buffer pH 7.0 (1.25 mM  $\text{MgSO}_4$ , 1mM  $\text{NADP}^+$ ),  $^i\text{PrOH}$  (175  $\mu\text{L}$ ) and DMSO (75  $\mu\text{L}$ ). After 15 minutes of incubation, KRED-P1-B10 (21 mg, 100% w/w) was added and the mixture stirred at 250 rpm and  $30\text{ }^\circ\text{C}$  for 24 h. After this time, the crude was extracted with ethyl acetate ( $2 \times 500\text{ }\mu\text{L}$ ), the organic layers separated by centrifugation (90 sec, 13000 rpm), combined and finally dried over  $\text{Na}_2\text{SO}_4$  to yield pure (*R*)-**9** in 90% yield. Both conversion and enantiomeric excess were measured by GC using a chiral column. The identity of this compound was confirmed by  $^1\text{H-NMR}$  analyses after comparison with reported spectra. Alternatively, (*R*)- $\gamma$ -valerolactone (**9**) was also prepared starting from 4-pentynoic acid (**10**) and the corresponding aromatic alcohol (phenol) employing the aforementioned reaction procedure. In this occasion, the cyclization occurred once the resulting hydroxyester **17b** was extracted to an organic phase.

**General procedure for the metal-catalyzed cycloisomerization/hydrolysis of *N*-tosyl-pent-4-yn-amide (**18**): Synthesis of 4-oxo-*N*-tosylpentanamide (**19a**).** 10 mg (5 mol%) of  $\text{KAuCl}_4$  (**13**) and 125 mg (0.5 mmol) of *N*-tosyl-pent-4-yn-amide (**18**) were added to 500  $\mu\text{L}$  of water. The mixture was then stirred at  $50\text{ }^\circ\text{C}$  for 5 h under air. The course of the reaction was monitored by regular sampling and analysis by GC. The crude of the reaction was extracted with diethyl ether ( $3 \times 5\text{ mL}$ ) and dried over  $\text{Na}_2\text{SO}_4$  and evaporated to dryness in a vacuum concentrator. The identity of the resulting compound was elucidated by NMR analysis.

**General procedure for the one-pot synthesis of (*R*)-4-hydroxy-*N*-tosylpentanamide (**20a**).** 5 mg (5 mol%) of  $\text{KAuCl}_4$  (**13**) and 63 mg (0.25 mmol) of *N*-tosyl-pent-4-yn-amide (**18**) were added to 250  $\mu\text{L}$  of water. The mixture was then stirred at  $50\text{ }^\circ\text{C}$  for 5 h under air. Once completed the cycloisomerization/hydrolysis (TLC and NMR analyses), the reaction mixture was diluted 4 times (substrate concentration = 250 mM) with a 125 mM potassium phosphate buffer pH 7.0 (1.25 mM  $\text{MgSO}_4$ , 1mM  $\text{NADP}^+$ ),  $^i\text{PrOH}$  (175  $\mu\text{L}$ ) and DMSO (75  $\mu\text{L}$ ). After 15 minutes of incubation, KRED-P2-H07 (21 mg) was added and the mixture stirred at 250 rpm and  $30\text{ }^\circ\text{C}$  for 24 h. Then the crude was extracted with ethyl acetate ( $2 \times 500\text{ }\mu\text{L}$ ), the organic layers separated by centrifugation (90 sec, 13000 rpm), combined and finally dried over  $\text{Na}_2\text{SO}_4$ . Conversion and enantiomeric excess for the resulting (*R*)-4-hydroxy-*N*-tosylpentanamide (**20a**) were determined directly by HPLC. The identity of **20a** was elucidated by NMR analysis.

**General procedure for the metal-catalyzed cycloisomerization/aminolysis of 4-pentynoic acid (**10**): Synthesis of  $\gamma$ -keto amides **19b-h**.** 2 mg (1 mol%) of  $\text{KAuCl}_4$  (**13**) and 50 mg (0.5 mmol) of 4-pentynoic acid (**10**) were added to 0.5 mmol of the corresponding aromatic amine ( $\text{R-C}_6\text{H}_4\text{-NH}_2$ ). The obtained mixture was then stirred at  $50\text{ }^\circ\text{C}$  for 3 h under air. The course of the reaction was

monitored by regular sampling and analysis by GC. The crude of the reaction was extracted with diethyl ether (3 x 5 mL) and dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness in a vacuum concentrator. The identity of the resulting compounds was elucidated by NMR analysis.

**General procedure for the one-pot synthesis of  $\gamma$ -hydroxy amides **20b-h**.** 1 mg (1 mol%) of KAuCl<sub>4</sub> (**13**) and 25 mg (0.25 mmol) of 4-pentynoic acid (**10**) were added to 0.25 mmol of the corresponding aromatic amine (R-C<sub>6</sub>H<sub>4</sub>-NH<sub>2</sub>). The mixture was then stirred at 50 °C for 3 h under air. Once completed the cycloisomerization/aminolysis (GC analyses), the reaction mixture was diluted 4 times (substrate concentration = 250 mM) with a 125 mM potassium phosphate buffer pH 7.0 (1.25 mM MgSO<sub>4</sub>, 1mM NADP<sup>+</sup>), *i*PrOH (175  $\mu$ L) and DMSO (75  $\mu$ L). After 15 minutes of incubation, the corresponding KRED was added and the mixture stirred at 250 rpm and 30 °C for 24 h. Then the crude was extracted with ethyl acetate (2  $\times$  500  $\mu$ L), the organic layers separated by centrifugation (90 sec, 13000 rpm), combined and finally dried over Na<sub>2</sub>SO<sub>4</sub>. Conversion and enantiomeric excess for the resulting  $\gamma$ -hydroxy amides **20b-h** were determined directly by HPLC. The identity of  $\gamma$ -hydroxy amides **20b-h** was elucidated by NMR analysis.

### 3. Spectroscopic data

#### 4-Oxo-*N*-tosylpentanamide (19a)

White solid; mp = 155-156.5 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 2.17 (s, 3H), 2.46 (s, 3H), 2.52 (t, *J* = 6.2 Hz, 2H), 2.77 (t, *J* = 6.2 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.95 (d, *J* = 8.0 Hz, 2H), 8.56 (brs, 1H, NH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 20.1 (CH<sub>3</sub>), 28.1 (CH<sub>3</sub>), 29.2 (CH<sub>2</sub>), 36.4 (CH<sub>2</sub>), 127.7 (2CH), 129.1 (2CH), 136.6 (C), 144.6 (C), 171.3 (C), 207.8 (C); MS (ESI), *m/z* (%) = 292 [(M+Na)<sup>+</sup>, 100]; anal. calcd. for C<sub>12</sub>H<sub>15</sub>NO<sub>4</sub>S (269.3): C 53.52, H 5.61, N 5.20; found: C 53.29, H 5.66, N 5.44.

#### (*R*)-4-Hydroxy-*N*-tosylpentanamide (20a)

White solid; mp = 250-252 °C; [ $\alpha$ ]<sub>D</sub><sup>20</sup> = -3.4 (*c* 0.5, CHCl<sub>3</sub>); ee = >99%; <sup>1</sup>H NMR (300 MHz, MeOD): δ = 1.14 (d, *J* = 6.0 Hz, 3H), 1.67 (q, *J* = 7.5 Hz, 2H), 2.27 (dt, *J* = 3.0, 7.5 Hz, 2H), 2.41 (s, 3H), 3.71 (sextet, *J* = 6.1 Hz, 1H), 5.0 (brs, NH + OH), 7.28 (d, *J* = 8.1 Hz, 2H), 7.82 (d, *J* = 8.1 Hz, 2H); <sup>13</sup>C NMR (75 MHz, MeOD): δ = 20.1 (CH<sub>3</sub>), 22.1 (CH<sub>3</sub>), 34.9 (CH<sub>2</sub>), 35.6 (CH<sub>2</sub>), 66.9 (CH), 126.6 (2CH), 128.4 (2CH), 140.9 (C), 141.5 (C), 169.3 (C); MS (ESI), *m/z* (%) = 294 [(M+Na)<sup>+</sup>, 100]; anal. calcd. for C<sub>12</sub>H<sub>17</sub>NO<sub>4</sub>S (271.3): C 53.12, H 6.32, N 5.16; found: C 53.26, H 6.48, N 5.02.

#### 4-Oxo-*N*-phenylpentanamide (19b)

White solid; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 2.22 (s, 3H), 2.62 (t, *J* = 6.3 Hz, 2H), 2.90 (t, *J* = 6.3 Hz, 2H), 7.10 (t, *J* = 7.5 Hz, 1H), 7.32 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.50 (d, *J* = 7.5 Hz, 2H), 7.93 (brs, NH, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 30.0 (CH<sub>3</sub>), 31.0 (CH<sub>2</sub>), 38.6 (CH<sub>2</sub>), 119.8 (2CH), 124.3 (CH), 128.9 (2CH), 138.0 (C), 170.3 (C), 208.3 (C).

#### 4-Oxo-*N*-(*p*-tolyl)pentanamide (19c)

White solid; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 2.23 (s, 3H), 2.32 (s, 3H), 2.62 (t, *J* = 6.3 Hz, 2H), 2.90 (t, *J* = 6.3 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.61 (brs, NH, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 20.9 (CH<sub>3</sub>), 30.0 (CH<sub>3</sub>), 31.1 (CH<sub>2</sub>), 38.6 (CH<sub>2</sub>), 119.8 (2CH), 129.4 (2CH), 129.9 (C), 135.3 (C), 170.1 (C), 208.1 (C).

#### *N*-(4-Methoxyphenyl)-4-oxopentanamide (19d)

White solid; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 2.21 (s, 3H), 2.59 (t, *J* = 6.3 Hz, 2H), 2.87 (t, *J* = 6.3 Hz, 2H), 3.77 (s, 3H), 6.81 (d, *J* = 9.0 Hz, 2H), 7.39 (d, *J* = 9.0 Hz, 2H), 7.87 (brs, NH, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 30.0 (CH<sub>3</sub>), 30.7 (CH<sub>2</sub>), 38.6 (CH<sub>2</sub>), 55.5 (CH<sub>3</sub>), 114.0 (2CH), 121.7 (2CH), 131.1 (C), 156.3 (C), 170.2 (C), 208.3 (C).

#### *N*-(4-Fluorophenyl)-4-oxopentanamide (19e)

White solid; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 2.22 (s, 3H), 2.59 (t, *J* = 6.3 Hz, 2H), 2.89 (t, *J* = 6.3 Hz, 2H), 6.96 (d, *J* = 9.0 Hz, 2H), 7.40-7.46 (m, 2H), 8.13 (brs, NH, 1H); <sup>13</sup>C NMR (75 MHz,

CDCl<sub>3</sub>):  $\delta$  = 30.0 (CH<sub>3</sub>), 30.8 (CH<sub>2</sub>), 38.5 (CH<sub>2</sub>), 115.5 (d,  $^2J_{CF}$  = 22.5 Hz, *m*-C<sub>6</sub>H<sub>4</sub>F, 2CH), 121.6 (d,  $^3J_{CF}$  = 7.8 Hz, *o*-C<sub>6</sub>H<sub>4</sub>F, 2CH), 134.0 (C), 159.2 (d,  $^1J_{CF}$  = 242.9 Hz, *p*-C<sub>6</sub>H<sub>4</sub>F), 170.4 (C), 208.4 (C).

***N*-(4-Chlorophenyl)-4-oxopentanamide (19f)**

White solid; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.21 (s, 3H), 2.59 (t,  $J$  = 6.3 Hz, 2H), 2.86 (t,  $J$  = 6.3 Hz, 2H), 7.23 (d,  $J$  = 9.0 Hz, 2H), 7.44 (d,  $J$  = 9.0 Hz, 2H), 8.48 (brs, NH, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 29.9 (CH<sub>3</sub>), 30.7 (CH<sub>2</sub>), 38.4 (CH<sub>2</sub>), 121.0 (2CH), 128.8 (2CH), 129.2 (C), 136.8 (C), 170.6 (C), 208.7 (C).

***N*-(4-Bromophenyl)-4-oxopentanamide (19g)**

White solid; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.22 (s, 3H), 2.58 (t,  $J$  = 6.3 Hz, 2H), 2.87 (t,  $J$  = 6.3 Hz, 2H), 7.21 (d,  $J$  = 9.0 Hz, 2H), 7.51 (d,  $J$  = 9.0 Hz, 2H), 8.29 (brs, NH, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 30.0 (CH<sub>3</sub>), 30.8 (CH<sub>2</sub>), 38.4 (CH<sub>2</sub>), 116.5 (C), 121.3 (2CH), 131.8 (2CH), 137.2 (C), 170.5 (C), 208.5 (C).

***N*-(4-Iodophenyl)-4-oxopentanamide (19h)**

White solid; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.29 (s, 3H), 2.66 (t,  $J$  = 6.3 Hz, 2H), 2.95 (t,  $J$  = 6.3 Hz, 2H), 7.34 (d,  $J$  = 8.7 Hz, 2H), 7.65 (d,  $J$  = 8.7 Hz, 2H), 7.99 (brs, NH, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 30.1 (CH<sub>3</sub>), 31.2 (CH<sub>2</sub>), 38.6 (CH<sub>2</sub>), 87.3 (C), 121.6 (2CH), 137.8 (C), 137.9 (2CH), 170.5 (C), 208.5 (C).

**(*R*)-4-Hydroxy-*N*-phenylpentanamide (20b)**

White solid;  $[\alpha]_D^{20}$  = +44.2 (*c* 0.1, CHCl<sub>3</sub>); ee = >99%; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.22 (d,  $J$  = 5.7 Hz, 3H), 1.70-1.84 (m, 1H), 1.87-1.99 (m, 1H), 2.54 (t,  $J$  = 6.6 Hz, 2H), 2.93 (brs, OH, 1H), 3.85-3.97 (m, 1H), 7.08 (t,  $J$  = 7.5 Hz, 1H), 7.34 (t,  $J$  = 7.5 Hz, 2H), 7.53 (d,  $J$  = 7.5 Hz, 2H), 8.09 (brs, NH, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 23.7 (CH<sub>3</sub>), 34.1 (CH<sub>2</sub>), 34.2 (CH<sub>2</sub>), 67.6 (CH), 120.0 (2CH), 124.8 (CH), 129.0 (2CH), 137.9 (C), 172.2 (C); MS (ESI),  $m/z$  (%) = 194 [(M+H)<sup>+</sup>, 100], 216 [(M+Na)<sup>+</sup>, 20]; anal. calcd. for C<sub>11</sub>H<sub>15</sub>NO<sub>2</sub>: C 68.37, H 7.82, N 7.25; found: C 68.50, H 7.66, N 7.27.

**(*R*)-4-Hydroxy-*N*-(*p*-tolyl)pentanamide (20c)**

White solid;  $[\alpha]_D^{20}$  = +47.0 (*c* 0.1, CHCl<sub>3</sub>); ee = >99%; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.22 (d,  $J$  = 5.8 Hz, 3H), 1.70-2.00 (m, 2H), 2.30 (s, 3H), 2.54 (t,  $J$  = 6.3 Hz, 2H), 3.05 (brs, OH, 1H), 3.80-4.00 (m, 1H), 7.10 (d,  $J$  = 7.8 Hz, 2H), 7.38 (d,  $J$  = 7.8, Hz, 2H), 8.11 (brs, NH, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 20.9 (CH<sub>3</sub>), 23.7 (CH<sub>3</sub>), 34.1 (CH<sub>2</sub>), 34.3 (CH<sub>2</sub>), 67.5 (CH), 120.2 (2CH), 129.4 (2CH), 134.0 (C), 135.4 (C), 172.2 (C); MS (ESI),  $m/z$  (%) = 208 [(M+H)<sup>+</sup>, 100], 230 [(M+Na)<sup>+</sup>, 5]; anal. calcd. for C<sub>12</sub>H<sub>17</sub>NO<sub>2</sub>: C 69.54, H 8.27, N 6.76; found: C 69.40, H 8.45, N 6.48.

**(R)-4-Hydroxy-N-(4-methoxyphenyl)pentanamide (20d)**

White solid;  $[\alpha]_D^{20} = +42.5$  (*c* 0.1, CHCl<sub>3</sub>); ee = >99%; <sup>1</sup>H NMR (300 MHz, MeOD):  $\delta = 1.22$  (d, *J* = 6.3 Hz, 3H), 1.70-1.90 (m, 2H), 2.35-2.55 (m, 2H), 3.78 (s, 3H), 3.70-3.90 (m, 1H), 6.88 (d, *J* = 9.0 Hz, 2H), 7.44 (d, *J* = 9.0 Hz, 2H); <sup>13</sup>C NMR (75 MHz, MeOD):  $\delta = 22.1$  (CH<sub>3</sub>), 32.8 (CH<sub>2</sub>), 34.4 (CH<sub>2</sub>), 54.5 (CH<sub>3</sub>), 66.6 (CH), 113.5 (2CH), 121.7 (2CH), 131.4 (C), 156.5 (C), 172.9 (C); MS (ESI), *m/z* (%) = 224 [(M+H)<sup>+</sup>, 100], 246 [(M+Na)<sup>+</sup>, 10]; anal. calcd. for C<sub>12</sub>H<sub>17</sub>NO<sub>3</sub>: C 64.55, H 7.67, N 6.27; found: C 64.66, H 7.51, N 6.49.

**N-(4-Fluorophenyl)-4-hydroxypentanamide (20e)**

White solid;  $[\alpha]_D^{20} = +49.1$  (*c* 0.1, CHCl<sub>3</sub>); ee = >99%; <sup>1</sup>H NMR (300 MHz, MeOD):  $\delta = 1.22$  (d, *J* = 6.3 Hz, 3H), 1.70-1.90 (m, 2H), 2.35-2.60 (m, 2H), 3.80 (sextet, *J* = 6.3 Hz, 1H), 7.04 (t, *J* = 9.0 Hz, 2H), 7.55 (dd, *J* = 9.0, 9.0 Hz, 2H); <sup>13</sup>C NMR (75 MHz, MeOD):  $\delta = 22.1$  (CH<sub>3</sub>), 32.8 (CH<sub>2</sub>), 34.3 (CH<sub>2</sub>), 66.6 (CH), 114.8 (d, <sup>2</sup>*J*<sub>CF</sub> = 22.5 Hz, *m*-C<sub>6</sub>H<sub>4</sub>F, 2CH), 121.6 (d, <sup>3</sup>*J*<sub>CF</sub> = 7.8 Hz, *o*-C<sub>6</sub>H<sub>4</sub>F, 2CH), 134.8 (C), 159.2 (<sup>1</sup>*J*<sub>CF</sub> = 240.5 Hz, *p*-C<sub>6</sub>H<sub>4</sub>F), 173.0 (C); MS (ESI), *m/z* (%) = 212 [(M+H)<sup>+</sup>, 100]; anal. calcd. for C<sub>11</sub>H<sub>14</sub>FNO<sub>2</sub>: C 62.55, H 6.68, N 6.63; found: C 62.48, H 6.80, N 6.50.

**(R)-N-(4-Chloro)-4-hydroxypentanamide (20f)**

White solid;  $[\alpha]_D^{20} = +41.2$  (*c* 0.1, CHCl<sub>3</sub>); ee = >99%; <sup>1</sup>H NMR (300 MHz, MeOD):  $\delta = 1.22$  (d, *J* = 6.3 Hz, 3H), 1.70-1.90 (m, 2H), 2.40-2.60 (m, 2H), 3.70-3.90 (m, 1H), 7.30 (d, *J* = 9.0 Hz, 2H), 7.57 (d, *J* = 9.0 Hz, 2H); <sup>13</sup>C NMR (75 MHz, MeOD):  $\delta = 22.1$  (CH<sub>3</sub>), 32.9 (CH<sub>2</sub>), 34.2 (CH<sub>2</sub>), 66.5 (CH), 121.0 (2CH), 128.3 (2CH), 128.4 (C), 137.4 (C), 173.1 (C); MS (ESI), *m/z* (%) = 228 [(M+H)<sup>+</sup>, 100], 250 [(M+Na)<sup>+</sup>, 30]; anal. calcd. for C<sub>11</sub>H<sub>14</sub>ClNO<sub>2</sub>: C 58.03, H 6.20, N 6.15; found: C 58.27, H 6.11, N 6.26.

**(R)-N-(4-Bromo)-4-hydroxypentanamide (20g)**

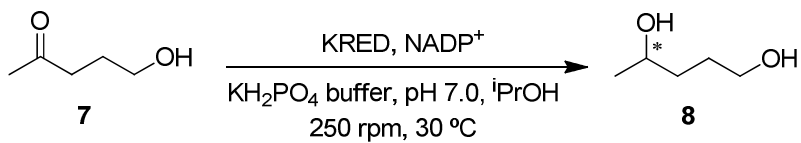
White solid;  $[\alpha]_D^{20} = +45.0$  (*c* 0.1, CHCl<sub>3</sub>); ee = >99%; <sup>1</sup>H NMR (300 MHz, MeOD):  $\delta = 1.22$  (d, *J* = 6.3 Hz, 3H), 1.70-1.90 (m, 2H), 2.40-2.60 (m, 2H), 3.81 (sextet, *J* = 6.3 Hz, 1H), 7.44 (d, *J* = 9.0 Hz, 2H), 7.53 (d, *J* = 9.0 Hz, 2H), 8.57 (brs, NH, 1H); <sup>13</sup>C NMR (75 MHz, MeOD):  $\delta = 22.1$  (CH<sub>3</sub>), 33.0 (CH<sub>2</sub>), 34.2 (CH<sub>2</sub>), 66.5 (CH), 115.9 (C), 121.4 (2CH), 131.3 (2CH), 137.9 (C), 169.1 (C); MS (ESI), *m/z* (%) = 294 [(M+Na)<sup>+</sup>, 80]; anal. calcd. for C<sub>11</sub>H<sub>14</sub>BrNO<sub>2</sub>: C 48.55, H 5.19, N 5.15; found: C 48.71, H 5.27, N 5.44.

**(R)-4-Hydroxy-N-(4-iodophenyl)pentanamide (20h)**

White solid;  $[\alpha]_D^{20} = +57.3$  (*c* 0.1, CHCl<sub>3</sub>); ee = >99%; <sup>1</sup>H NMR (300 MHz, MeOD):  $\delta = 1.22$  (d, *J* = 6.3 Hz, 3H), 1.70-1.90 (m, 2H), 2.30-2.60 (m, 2H), 3.70-3.90 (m, 1H), 7.39 (d, *J* = 9.0 Hz, 2H), 7.62 (d, *J* = 9.0 Hz, 2H); <sup>13</sup>C NMR (75 MHz, MeOD):  $\delta = 22.1$  (CH<sub>3</sub>), 33.0 (CH<sub>2</sub>), 34.2 (CH<sub>2</sub>), 66.5 (CH), 86.2 (C), 121.6 (2CH), 137.4 (2CH), 138.5 (C), 173.1 (C); MS (ESI), *m/z* (%) = 320 [(M+H)<sup>+</sup>, 100], 342 [(M+Na)<sup>+</sup>, 15]; anal. calcd. for C<sub>11</sub>H<sub>14</sub>INO<sub>2</sub>: C 41.40, H 4.42, N 4.39; found: C 41.29, H 4.61, N 4.45.

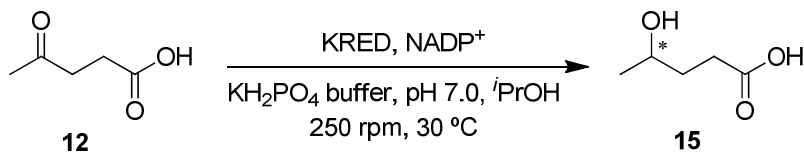
## 4. Enzymatic screening

**Table S1.** Enzymatic reduction of 5-hydroxypentan-2-one (**7**) using KREDs.<sup>a</sup>



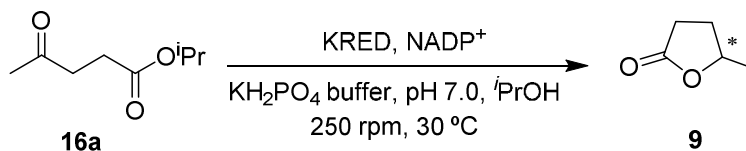
Entry	KRED	<i>c</i> (%) <sup>b</sup>	<i>ee</i> (%) <sup>c</sup>	Selectivity
1	P1-A04	>99	98	( <i>R</i> )
2	P1-B02	>99	85	( <i>R</i> )
3	P1-B05	25	15	( <i>S</i> )
4	P1-B10	>99	95	( <i>R</i> )
5	P1-B12	>99	89	( <i>R</i> )
6	P1-C01	>99	45	( <i>R</i> )
7	P1-H08	>99	38	( <i>R</i> )
8	P2-B02	>99	>99	( <i>R</i> )
9	P2-C02	>99	50	( <i>S</i> )
10	P2-C11	>99	39	( <i>S</i> )
11	P2-D03	>99	80	( <i>R</i> )
12	P2-D11	>99	47	( <i>R</i> )
13	P2-D12	>99	78	( <i>R</i> )
14	P2-G03	>99	80	( <i>R</i> )
15	P2-H07	>99	47	( <i>R</i> )
16	P3-B03	>99	98	( <i>S</i> )

<sup>a</sup> Reaction conditions: Substrate (20 mM) in KH<sub>2</sub>PO<sub>4</sub> buffer 125 mM (1.25 mM MgSO<sub>4</sub>, 1 mM NADP<sup>+</sup>) pH 7.0 (900 μL), KRED (2 mg), <sup>i</sup>PrOH (190 μL), for 24 h at 250 rpm and 30 °C. <sup>b</sup> Measured by GC. <sup>c</sup> Measured by chiral GC.

**Table S2.** Enzymatic reduction of levulinic acid (**12**) using KREDs.<sup>a</sup>

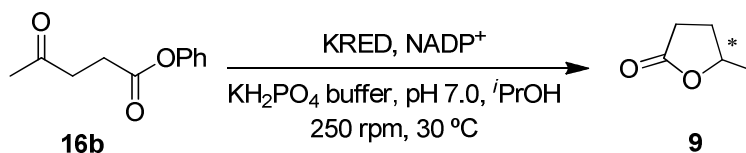
Entry	KRED	<i>c</i> (%) <sup>b</sup>	ee (%) <sup>c</sup>	Selectivity
1	P1-A04	>99	>99	( <i>R</i> )
2	P1-B02	>99	92	( <i>R</i> )
3	P1-B05	>99	70	( <i>R</i> )
4	P1-B10	>99	>99	( <i>R</i> )
5	P1-B12	>99	>99	( <i>R</i> )
6	P1-C01	>99	0	-
7	P1-H08	>99	70	( <i>R</i> )
8	P2-B02	>99	75	( <i>S</i> )
9	P2-C02	>99	30	( <i>S</i> )
10	P2-C11	>99	95	( <i>R</i> )
11	P2-D03	>99	40	( <i>R</i> )
12	P2-D11	>99	50	( <i>S</i> )
13	P2-D12	>99	20	( <i>R</i> )
14	P2-G03	>99	93	( <i>R</i> )
15	P2-H07	>99	>99	( <i>R</i> )
16	P3-B03	>99	80	( <i>S</i> )
17	P3-H12	>99	97	( <i>S</i> )
19	P2-G09	>99	90	( <i>S</i> )

<sup>a</sup> Reaction conditions: Substrate (20 mM) in KH<sub>2</sub>PO<sub>4</sub> buffer 125 mM (1.25 mM MgSO<sub>4</sub>, 1 mM NADP<sup>+</sup>) pH 7.0 (900 μL), KRED (2 mg), *i*PrOH (190 μL), for 24 h at 250 rpm and 30 °C. <sup>b</sup> Measured by GC. <sup>c</sup> Measured by chiral GC.

**Table S3.** Enzymatic reduction of isopropyl levulinate (**16a**) using KREDs.<sup>a</sup>

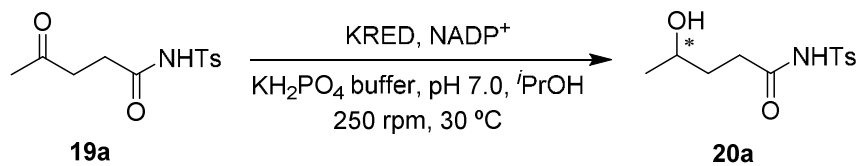
Entry	KRED	<i>c</i> (%) <sup>b</sup>	ee (%) <sup>c</sup>	Selectivity
1	P1-A04	>99	>99	( <i>R</i> )
2	P1-B02	>99	>99	( <i>R</i> )
3	P1-B05	>99	76	( <i>R</i> )
4	P1-B10	>99	>99	( <i>R</i> )
5	P1-B12	>99	>99	( <i>R</i> )
6	P1-C01	>99	0	-
7	P1-H08	>99	74	( <i>R</i> )
8	P2-B02	>99	86	( <i>S</i> )
9	P2-C02	>99	48	( <i>S</i> )
10	P2-C11	>99	>99	( <i>R</i> )
11	P2-D03	>99	74	( <i>R</i> )
12	P2-D11	>99	60	( <i>S</i> )
13	P2-D12	>99	16	( <i>R</i> )
14	P2-G03	>99	>99	( <i>R</i> )
15	P2-H07	>99	>99	( <i>R</i> )
16	P3-B03	>99	64	( <i>S</i> )
17	P3-H12	>99	96	( <i>S</i> )
18	P1-A12	>99	>99	( <i>R</i> )
19	P2-G09	>99	82	( <i>S</i> )

<sup>a</sup> Reaction conditions: Substrate (20 mM) in KH<sub>2</sub>PO<sub>4</sub> buffer 125 mM (1.25 mM MgSO<sub>4</sub>, 1 mM NADP<sup>+</sup>) pH 7.0 (900 μL), KRED (2 mg), <sup>t</sup>PrOH (190 μL), for 24 h at 250 rpm and 30 °C. <sup>b</sup> Measured by GC. <sup>c</sup> Measured by chiral GC.

**Table S4.** Enzymatic reduction of phenyl 4-oxopentanoate (**16b**) using KREDs.<sup>a</sup>

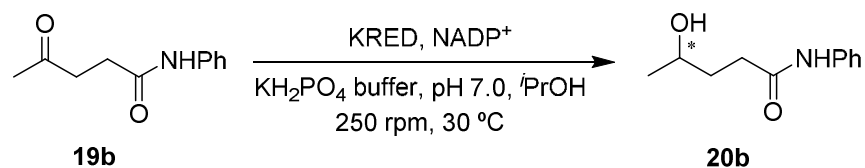
Entry	KRED	<i>c</i> (%) <sup>b</sup>	ee (%) <sup>c</sup>	Selectivity
1	P1-A04	>99	>99	( <i>R</i> )
2	P1-B02	>99	>99	( <i>R</i> )
3	P1-B05	>99	99	( <i>R</i> )
4	P1-B10	>99	>99	( <i>R</i> )
5	P1-B12	>99	>99	( <i>R</i> )
6	P1-C01	>99	0	-
7	P1-H08	>99	82	( <i>R</i> )
8	P2-B02	>99	98	( <i>S</i> )
9	P2-C02	>99	20	( <i>S</i> )
10	P2-C11	>99	>99	( <i>R</i> )
11	P2-D03	>99	74	( <i>R</i> )
12	P2-D11	>99	60	( <i>S</i> )
13	P2-D12	>99	5	( <i>R</i> )
14	P2-G03	>99	>99	( <i>R</i> )
15	P2-H07	>99	>99	( <i>R</i> )
16	P3-B03	>99	88	( <i>S</i> )
17	P3-H12	>99	96	( <i>S</i> )
18	P1-A12	>99	>99	( <i>R</i> )
19	P2-G09	>99	90	( <i>S</i> )

<sup>a</sup> Reaction conditions: Substrate (20 mM) in  $\text{KH}_2\text{PO}_4$  buffer 125 mM (1.25 mM  $\text{MgSO}_4$ , 1 mM  $\text{NADP}^+$ ) pH 7.0 (900  $\mu\text{L}$ ), KRED (2 mg),  $i\text{PrOH}$  (190  $\mu\text{L}$ ), for 24 h at 250 rpm and 30  $^\circ\text{C}$ . <sup>b</sup> Measured by GC. <sup>c</sup> Measured by chiral GC.

**Table S5.** Enzymatic reduction of 4-oxo-*N*-tosylpentanamide (**19a**) using KREDs.<sup>a</sup>

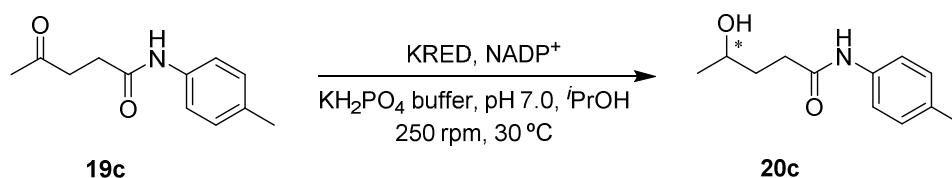
Entry	KRED	<i>c</i> (%) <sup>b</sup>	ee (%) <sup>c</sup>	Selectivity
1	P1-A04	52	30	( <i>R</i> )
2	P1-B02	15	-	-
3	P1-B05	0	-	-
4	P1-B10	8	-	-
5	P1-B12	43	25	( <i>R</i> )
6	P1-C01	10	-	-
7	P1-H08	3	-	-
8	P2-B02	7	-	-
9	P2-C02	0	-	-
10	P2-C11	37	20	( <i>R</i> )
11	P2-D03	3	-	-
12	P2-D11	0	-	-
13	P2-D12	41	40	( <i>R</i> )
14	P2-G03	21	-	-
15	P2-H07	96	>99	( <i>R</i> )
16	P3-B03	13	-	-
17	P3-H12	18	-	-

<sup>a</sup> Reaction conditions: Substrate (20 mM) in KH<sub>2</sub>PO<sub>4</sub> buffer 125 mM (1.25 mM MgSO<sub>4</sub>, 1 mM NADP<sup>+</sup>) pH 7.0 (900 μL), KRED (2 mg), *i*PrOH (190 μL), for 24 h at 250 rpm and 30 °C. <sup>b</sup> Measured by HPLC. <sup>c</sup> Measured by chiral HPLC.

**Table S6.** Enzymatic reduction of 4-Oxo-*N*-phenylpentanamide (**19b**) using KREDs.<sup>a</sup>

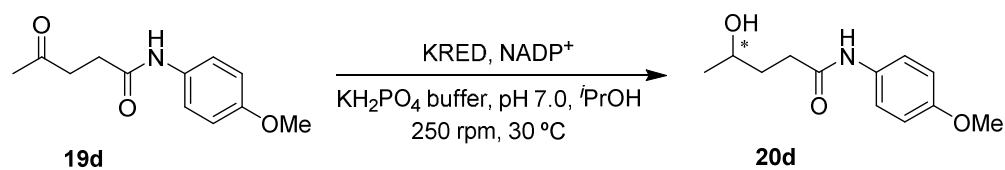
Entry	KRED	<i>c</i> (%) <sup>b</sup>	<i>ee</i> (%) <sup>c</sup>	Selectivity
1	P1-A04	>99	>99	( <i>R</i> )
2	P1-B02	80	96	( <i>R</i> )
3	P1-B05	87	40	( <i>R</i> )
4	P1-B10	92	>99	( <i>R</i> )
5	P1-B12	70	>99	( <i>R</i> )
6	P1-C01	97	55	( <i>S</i> )
7	P1-H08	65	95	( <i>R</i> )
8	P2-B02	50	75	( <i>S</i> )
9	P2-C02	67	82	( <i>S</i> )
10	P2-C11	80	99	( <i>R</i> )
11	P2-D03	50	-	-
12	P2-D11	83	76	( <i>S</i> )
13	P2-D12	97	82	( <i>R</i> )
14	P2-G03	82	>99	( <i>R</i> )
15	P2-H07	>99	>99	( <i>R</i> )
16	P3-B03	>99	>99	( <i>S</i> )
17	P1-A12	>99	>99	( <i>R</i> )
18	P3-H12	>99	>99	( <i>S</i> )

<sup>a</sup> Reaction conditions: Substrate (20 mM) in KH<sub>2</sub>PO<sub>4</sub> buffer 125 mM (1.25 mM MgSO<sub>4</sub>, 1 mM NADP<sup>+</sup>) pH 7.0 (900 μL), KRED (2 mg), <sup>i</sup>PrOH (190 μL), for 24 h at 250 rpm and 30 °C. <sup>b</sup> Measured by HPLC. <sup>c</sup> Measured by chiral HPLC.

**Table S7.** Enzymatic reduction of 4-Oxo-*N*-(*p*-tolyl)pentanamide (**19c**) using KREDs.<sup>a</sup>

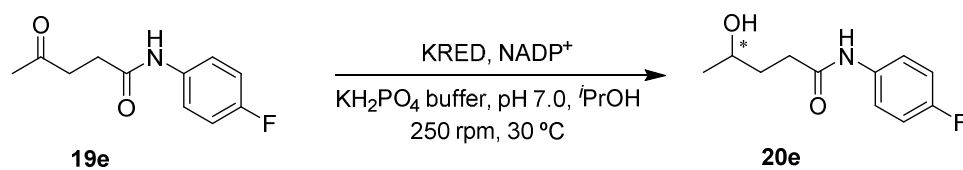
Entry	KRED	<i>c</i> (%) <sup>b</sup>	ee (%) <sup>c</sup>	Selectivity
1	P1-A04	>99	>99	( <i>R</i> )
2	P1-B02	65	86	( <i>R</i> )
3	P1-B05	86	60	( <i>R</i> )
4	P1-B10	90	>99	( <i>R</i> )
5	P1-B12	77	>99	( <i>R</i> )
6	P1-C01	86	28	( <i>S</i> )
7	P1-H08	66	94	( <i>R</i> )
8	P2-B02	52	12	( <i>S</i> )
9	P2-C02	76	40	( <i>S</i> )
10	P2-C11	86	>99	( <i>R</i> )
11	P2-D03	61	33	( <i>R</i> )
12	P2-D11	55	20	( <i>R</i> )
13	P2-D12	95	82	( <i>R</i> )
14	P2-G03	90	98	( <i>R</i> )
15	P2-H07	>99	>99	( <i>R</i> )
16	P3-B03	>99	99	( <i>S</i> )
17	P1-A12	>99	99	( <i>R</i> )
18	P3-H12	>99	98	( <i>S</i> )

<sup>a</sup> Reaction conditions: Substrate (20 mM) in KH<sub>2</sub>PO<sub>4</sub> buffer 125 mM (1.25 mM MgSO<sub>4</sub>, 1 mM NADP<sup>+</sup>) pH 7.0 (900 μL), KRED (2 mg), *i*PrOH (190 μL), for 24 h at 250 rpm and 30 °C. <sup>b</sup> Measured by HPLC. <sup>c</sup> Measured by chiral HPLC.

**Table S8.** Enzymatic reduction of *N*-(4-Methoxyphenyl)-4-oxopentanamide (**19d**) using KREDs.<sup>a</sup>

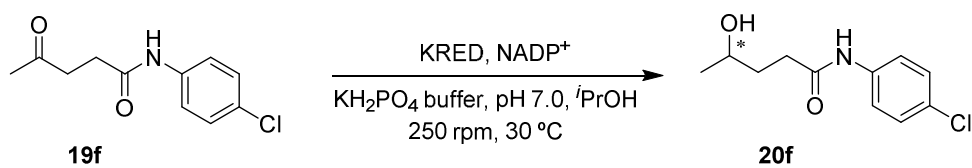
Entry	KRED	<i>c</i> (%) <sup>b</sup>	ee (%) <sup>c</sup>	Selectivity
1	P1-A04	>99	>99	( <i>R</i> )
2	P1-B02	71	>99	( <i>R</i> )
3	P1-B05	79	64	( <i>R</i> )
4	P1-B10	96	>99	( <i>R</i> )
5	P1-B12	90	>99	( <i>R</i> )
6	P1-C01	90	33	( <i>S</i> )
7	P1-H08	70	94	( <i>R</i> )
8	P2-B02	63	20	( <i>R</i> )
9	P2-C02	80	50	( <i>S</i> )
10	P2-C11	88	>99	( <i>R</i> )
11	P2-D03	60	20	( <i>R</i> )
12	P2-D11	77	5	( <i>S</i> )
13	P2-D12	83	80	( <i>R</i> )
14	P2-G03	85	>99	( <i>R</i> )
15	P2-H07	>99	>99	( <i>R</i> )
16	P3-B03	>99	>99	( <i>S</i> )
17	P1-A12	>99	>99	( <i>R</i> )
18	P3-H12	>99	>99	( <i>S</i> )

<sup>a</sup> Reaction conditions: Substrate (20 mM) in KH<sub>2</sub>PO<sub>4</sub> buffer 125 mM (1.25 mM MgSO<sub>4</sub>, 1 mM NADP<sup>+</sup>) pH 7.0 (900 μL), KRED (2 mg), *i*PrOH (190 μL), for 24 h at 250 rpm and 30 °C. <sup>b</sup> Measured by HPLC. <sup>c</sup> Measured by chiral HPLC.

**Table S9.** Enzymatic reduction of *N*-(4-Fluorophenyl)-4-oxopentanamide (**19e**) using KREDs.<sup>a</sup>

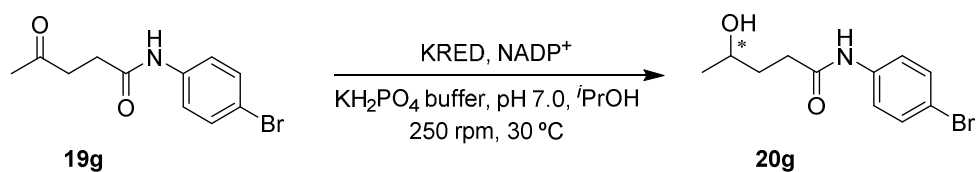
Entry	KRED	<i>c</i> (%) <sup>b</sup>	ee (%) <sup>c</sup>	Selectivity
1	P1-A04	>99	>99	( <i>R</i> )
2	P1-B02	63	46	( <i>R</i> )
3	P1-B05	42	2	( <i>R</i> )
4	P1-B10	54	62	( <i>R</i> )
5	P1-B12	31	32	( <i>R</i> )
6	P1-C01	91	58	( <i>S</i> )
7	P1-H08	28	12	( <i>R</i> )
8	P2-B02	32	90	( <i>S</i> )
9	P2-C02	40	92	( <i>S</i> )
10	P2-C11	53	36	( <i>R</i> )
11	P2-D03	25	44	( <i>S</i> )
12	P2-D11	59	89	( <i>S</i> )
13	P2-D12	49	42	( <i>R</i> )
14	P2-G03	51	46	( <i>R</i> )
15	P2-H07	>99	>99	( <i>R</i> )
16	P3-B03	>99	>99	( <i>S</i> )
17	P1-A12	>99	>99	( <i>R</i> )
18	P3-H12	>99	>99	( <i>S</i> )

<sup>a</sup> Reaction conditions: Substrate (20 mM) in KH<sub>2</sub>PO<sub>4</sub> buffer 125 mM (1.25 mM MgSO<sub>4</sub>, 1 mM NADP<sup>+</sup>) pH 7.0 (900 μL), KRED (2 mg), *i*PrOH (190 μL), for 24 h at 250 rpm and 30 °C. <sup>b</sup> Measured by HPLC. <sup>c</sup> Measured by chiral HPLC.

**Table S10.** Enzymatic reduction of *N*-(4-Chlorophenyl)-4-oxopentanamide (**19f**) using KREDs.<sup>a</sup>

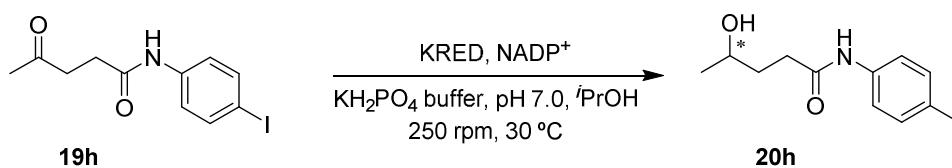
Entry	KRED	<i>c</i> (%) <sup>b</sup>	ee (%) <sup>c</sup>	Selectivity
1	P1-A04	>99	>99	( <i>R</i> )
2	P1-B02	37	96	( <i>R</i> )
3	P1-B05	66	32	( <i>R</i> )
4	P1-B10	93	>99	( <i>R</i> )
5	P1-B12	29	>99	( <i>R</i> )
6	P1-C01	99	30	( <i>S</i> )
7	P1-H08	71	30	( <i>R</i> )
8	P2-B02	67	76	( <i>S</i> )
9	P2-C02	99	82	( <i>S</i> )
10	P2-C11	72	>99	( <i>R</i> )
11	P2-D03	70	4	-
12	P2-D11	72	32	( <i>S</i> )
13	P2-D12	99	76	( <i>R</i> )
14	P2-G03	94	99	( <i>R</i> )
15	P2-H07	>99	>99	( <i>R</i> )
16	P3-B03	>99	>99	( <i>S</i> )
17	P1-A12	>99	>99	( <i>R</i> )
18	P3-H12	>99	98	( <i>S</i> )

<sup>a</sup> Reaction conditions: Substrate (20 mM) in KH<sub>2</sub>PO<sub>4</sub> buffer 125 mM (1.25 mM MgSO<sub>4</sub>, 1 mM NADP<sup>+</sup>) pH 7.0 (900 μL), KRED (2 mg), *i*PrOH (190 μL), for 24 h at 250 rpm and 30 °C. <sup>b</sup> Measured by HPLC. <sup>c</sup> Measured by chiral HPLC.

**Table S11.** Enzymatic reduction of *N*-(4-Bromophenyl)-4-oxopentanamide (**19g**) using KREDs.<sup>a</sup>

Entry	KRED	<i>c</i> (%) <sup>b</sup>	ee (%) <sup>c</sup>	Selectivity
1	P1-A04	>99	>99	( <i>R</i> )
2	P1-B02	48	96	( <i>R</i> )
3	P1-B05	64	34	( <i>R</i> )
4	P1-B10	93	>99	( <i>R</i> )
5	P1-B12	95	>99	( <i>R</i> )
6	P1-C01	99	26	( <i>S</i> )
7	P1-H08	67	93	( <i>R</i> )
8	P2-B02	63	78	( <i>S</i> )
9	P2-C02	72	86	( <i>S</i> )
10	P2-C11	99	>99	( <i>R</i> )
11	P2-D03	65	10	( <i>S</i> )
12	P2-D11	64	20	( <i>S</i> )
13	P2-D12	99	78	( <i>R</i> )
14	P2-G03	97	98	( <i>R</i> )
15	P2-H07	>99	>99	( <i>R</i> )
16	P3-B03	>99	>99	( <i>S</i> )
17	P1-A12	>99	88	( <i>R</i> )
18	P3-H12	>99	98	( <i>S</i> )

<sup>a</sup> Reaction conditions: Substrate (20 mM) in  $\text{KH}_2\text{PO}_4$  buffer 125 mM (1.25 mM  $\text{MgSO}_4$ , 1 mM  $\text{NADP}^+$ ) pH 7.0 (900  $\mu\text{L}$ ), KRED (2 mg), *i*PrOH (190  $\mu\text{L}$ ), for 24 h at 250 rpm and 30  $^\circ\text{C}$ . <sup>b</sup> Measured by HPLC. <sup>c</sup> Measured by chiral HPLC.

**Table S12.** Enzymatic reduction of *N*-(4-Iodophenyl)-4-oxopentanamide (**19h**) using KREDs.<sup>a</sup>

Entry	KRED	<i>c</i> (%) <sup>b</sup>	ee (%) <sup>c</sup>	Selectivity
1	P1-A04	>99	96	( <i>R</i> )
2	P1-B02	99	>99	( <i>R</i> )
3	P1-B05	81	51	( <i>R</i> )
4	P1-B10	84	>99	( <i>R</i> )
5	P1-B12	91	>99	( <i>R</i> )
6	P1-C01	99	48	( <i>S</i> )
7	P1-H08	75	92	( <i>R</i> )
8	P2-B02	98	90	( <i>S</i> )
9	P2-C02	>99	90	( <i>S</i> )
10	P2-C11	98	>99	( <i>R</i> )
11	P2-D03	97	24	( <i>S</i> )
12	P2-D11	98	10	( <i>S</i> )
13	P2-D12	95	84	( <i>R</i> )
14	P2-G03	99	98	( <i>R</i> )
15	P2-H07	99	>99	( <i>R</i> )
16	P3-B03	>99	>99	( <i>S</i> )
17	P1-A12	>99	98	( <i>R</i> )
18	P3-H12	>99	56	( <i>S</i> )

<sup>a</sup> Reaction conditions: Substrate (20 mM) in KH<sub>2</sub>PO<sub>4</sub> buffer 125 mM (1.25 mM MgSO<sub>4</sub>, 1 mM NADP<sup>+</sup>) pH 7.0 (900 μL), KRED (2 mg), <sup>i</sup>PrOH (190 μL), for 24 h at 250 rpm and 30 °C. <sup>b</sup> Measured by HPLC. <sup>c</sup> Measured by chiral HPLC.

## 5. Analytical data

In the following Tables S13-S19, all data corresponding to the GC analyses using a chiral or non-chiral column are shown. Assignment of the configuration for every peak is included where appropriate. Temperature program is given as follows, taking the hypothetical program 90/10/1/115/20/180 as a model: to start with an initial temperature of 90 °C / to maintain 90 °C during 10 min / to increase the temperature with a slope of 1 °C/min until to reach 115 °C / to increase the temperature with a slope of 20 °C/min until to reach the final 180 °C.

### 5.1. Step One: Cycloisomerization/Hydrolysis of alkyne derivatives

#### 5.1.1. GC Analyses for determination of conversion

The following column was used: Beta Dex (120 m × 0.25 mm × 0.25 μm).

**Table S13.** GC analyses data.

Substrate	T programme <sup>a</sup>	Retention time (min)	
		Substrate	Product
4-Pentyn-1-ol ( <b>5a</b> )	170/3/10/220	<b>5a</b> (4.6)	<b>7</b> (8.3)
3-Pentyn-1-ol ( <b>5b</b> )	170/3/10/220	<b>5b</b> (4.1)	<b>7</b> (8.3)
5-Pentynoic acid ( <b>10</b> )	110/8/20/220	<b>10</b> (3.5)	<b>12</b> (4.8)

<sup>a</sup> GC programme: initial temp. (°C) / time (min) / slope (°C/min) / final temp. (°C).

#### 5.1.2. TLC and <sup>1</sup>H-NMR analysis for determination of conversion

The cycloisomerization/hydrolysis of *N*-tosyl-pent-4-yn-amide (**18**) into 4-oxo-*N*-tosylpentanamide (**19a**) was followed by TLC. Then, complete conversion was confirmed by <sup>1</sup>H-NMR analysis.

### 5.2. Step Two: Enzymatic reduction of ketone derivatives

#### 5.2.1. GC Analysis for determination of conversion and enantiomeric excess in the bioreduction of **7**

The following column was used: CP-ChiraSil-DEX CB (25 m × 0.25 mm × 0.25 μm).

**Table S14.** GC analysis data.

Substrate	T programme <sup>a</sup>	Retention time (min)	
		Substrate	Product <sup>b</sup>
5-Hydroxy-2-pentanone ( <b>7</b> )	90/5/5/165/3/29/180	<b>7</b> (10.8)	13.8 for ( <i>R</i> )- <b>8</b> and 14.7 for ( <i>S</i> )- <b>8</b>

<sup>a</sup> Program: initial temp. (°C) / time (min) / slope (°C/min) / temp. (°C) / time (min) / slope (°C/min) / temp (°C). <sup>b</sup> Previously derivatized as diacetate with acetic anhydride.

### 5.2.2. GC Analysis for determination of conversion and enantiomeric excess in the biotransformation of **8** into **9**

The following column was used: Rt-bDEXse (30 m × 0.25 mm × 0.25 μm).

**Table S15.** GC analysis data.

Substrate	T programme <sup>a</sup>	Retention time (min)	
		Product	
1,4-Pentanediol ( <b>8</b> )	32/5/20/200	11.8 for ( <i>R</i> )- <b>9</b> and 11.9 for ( <i>S</i> )- <b>9</b>	

<sup>a</sup> Program: initial temp. (°C) / time (min) / slope (°C/min) / temp (°C).

### 5.2.3. GC Analysis for determination of conversion and enantiomeric excess in the bioreduction of **12**

The conversion for the bioreduction of **12** into **15** was followed by GC using a Beta Dex column (120 m × 0.25 mm × 0.25 μm).

**Table S16.** GC analysis data.

Substrate	T programme <sup>a</sup>	Retention time (min)	
		Substrate	Product
Levulinic acid ( <b>12</b> )	110/8/20/220	<b>12</b> (4.8)	<b>15</b> (5.2)

<sup>a</sup> GC programme: initial temp. (°C) / time (min) / slope (°C/min) / final temp. (°C).

The enantiomeric excess of the resulting  $\gamma$ -hydroxyvaleric acid (**15**) was determined by means of its transformation into  $\gamma$ -valerolactone (**9**). For this and after evaporation to dryness, the crude of the reaction mixture was dissolved in anhydrous dichloromethane and **15** lactonized in the presence of trifluoroacetic acid.<sup>4</sup> Then, the enantiomeric excess was determined as described above.

### 5.2.4. HPLC Analyses for determination of conversion and enantiomeric excess in the bioreduction of **19a**

Both conversion on the bioreduction of **19a** and the enantiomeric excess of the resulting **20a** were simultaneously analyzed using a column Chiralpak AD-H (25 cm × 4.6 mm I.D.), with a mixture of hexane:propan-2-ol (85:15), as eluent, flow 1.0 mL/min and 40 °C. Detection wavelength: 210 nm

**Table S17.** HPLC analyses data.

Compound	Retention time (min)	
	Ketone	Alcohol
4-Oxo- <i>N</i> -tosylpentanamide ( <b>19a</b> )	9.3 ( <b>19a</b> )	11.1 for ( <i>S</i> )- <b>20a</b> and 12.7 for ( <i>R</i> )- <b>20a</b>

### 5.2.5. HPLC Analyses for determination of conversion in the bioreduction of 19b-h

HPLC analyses to determine conversion were carried out in an Agilent chromatographic system, using a reversed phase column (Zorbax Eclipse XDB-C18, RR, 1.8  $\mu$ m, 4.6 x 50 mm, Agilent) and acetonitrile (MeCN) and 0.1% trifluoroacetic acid (TFA) in water as solvents. Samples were eluted with three linear gradients from 10% to 60% MeCN during 5.70 min, followed by another from 60% to 100% MeCN during 0.5 min and a third gradient from 100% to 10% MeCN during 1.90 min, at flow rate of 2 mL/min. Detection and spectral characterization of peaks [UV absorption maxima (from HPLC-diode array) at 210 nm] were performed with a diode array detector and ChemStation Rev.B.03.01 software (Agilent).

**Table S18.** HPLC analyses data.<sup>a</sup>

Compound	Retention time (min)	
	ketone	alcohol
4-Oxo- <i>N</i> -phenylpentanamide ( <b>19b</b> )	2.3	2.1
4-Oxo- <i>N</i> -( <i>p</i> -tolyl)pentanamide ( <b>19c</b> )	2.9	2.7
<i>N</i> -(4-Methoxyphenyl)-4-oxopentanamide ( <b>19d</b> )	2.2	2.1
<i>N</i> -(4-Fluorophenyl)-4-oxopentanamide ( <b>19e</b> )	2.7	2.4
<i>N</i> -(4-Chlororophenyl)-4-oxopentanamide ( <b>19f</b> )	3.6	3.3
<i>N</i> -(4-Bromophenyl)-4-oxopentanamide ( <b>19g</b> )	3.8	3.5
<i>N</i> -(4-Iodophenyl)-4-oxopentanamide ( <b>19h</b> )	4.2	3.8

<sup>a</sup> Detection wavelength: 210 nm.

### 5.2.6. HPLC Analyses for determination of enantiomeric excess (20b-h)

**Table S19.** HPLC analyses data.<sup>a</sup>

Compound	Column	Eluent (Hex/ <i>i</i> -PrOH)	Flow (mL/min)	T (°C)	Retention time (min)
<b>20b</b>	AD-H	90:10	0.6	40	13.5 ( <i>R</i> ), 14.2 ( <i>S</i> )
<b>20c</b>	AD-H	90:10	1.0	40	11.7 ( <i>R</i> ), 12.9 ( <i>S</i> )
<b>20d</b>	AD-H	85:15	1.0	40	9.2 ( <i>R</i> ), 10.2 ( <i>S</i> )
<b>20e</b>	AD-H	90:10	1.0	40	7.6 ( <i>R</i> ), 8.0 ( <i>S</i> )
<b>20f</b>	AD-H	90:10	1.0	40	9.8 ( <i>R</i> ), 10.8 ( <i>S</i> )
<b>20g</b>	AD-H	90:10	1.0	40	11.6 ( <i>R</i> ), 13.0 ( <i>S</i> )
<b>20h</b>	AD-H	90:10	1.2	40	12.3 ( <i>R</i> ), 14.1 ( <i>S</i> )

<sup>a</sup> Detection wavelength: 210 nm.

### 5.3. Assignment of absolute configuration

The assignment of the absolute configuration for the resulting optically active compounds was accomplished by comparing with analytical standards (sign of its specific rotation or retention time in GC analyses). This was the case of 1,4-pentanediol (**8**),  $\gamma$ -valerolactone (**9**) or  $\gamma$ -hydroxyvaleric acid (**15**, once converted into **9**). Regarding the unreported 4-hydroxy-*N*-tosylpentanamide (**20a**), several lipase catalyzed acylations (PS-C II and CAL-B lipases) of ( $\pm$ )-**20a** were carried out employing vinyl acetate and *tert*-butyl methyl ether as acyl donor and solvent, respectively. According to Kazlauskas' rule,<sup>5</sup> the (*R*)-enantiomer of **20a** is preferentially acylated which enabled to tentatively identify both enantiomers by chiral HPLC analysis. The assumed (*R*)-selectivity for KRED-P2-H07 towards **19a** is in good agreement with that exhibited for this enzyme and substrates **7**, **12** and **16a-b** (Tables S1-S4). Similarly, the absolute configuration of the resulting  $\gamma$ -hydroxy amides **20b-h** was tentatively assigned following the same strategy.

## 6. Copy of NMR spectra

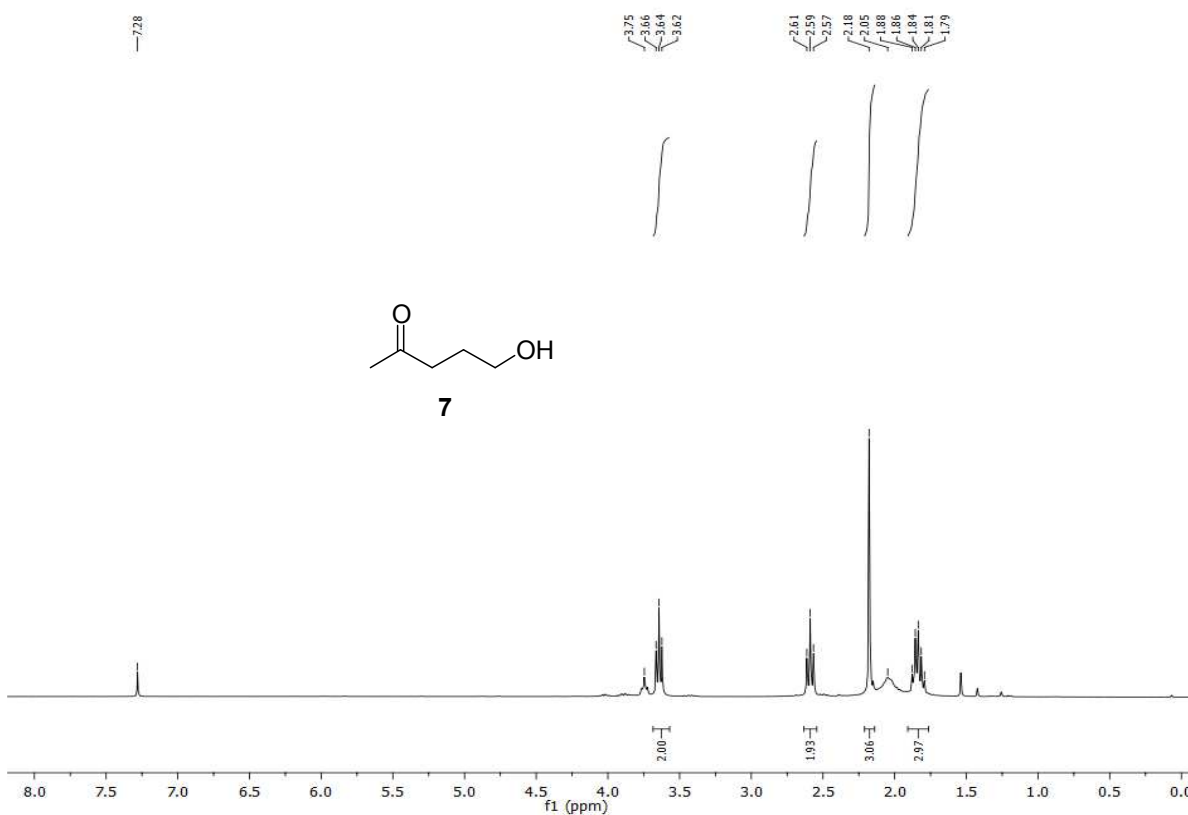


Figure S1. <sup>1</sup>H-NMR full chart for **7** in CDCl<sub>3</sub> (300 MHz)

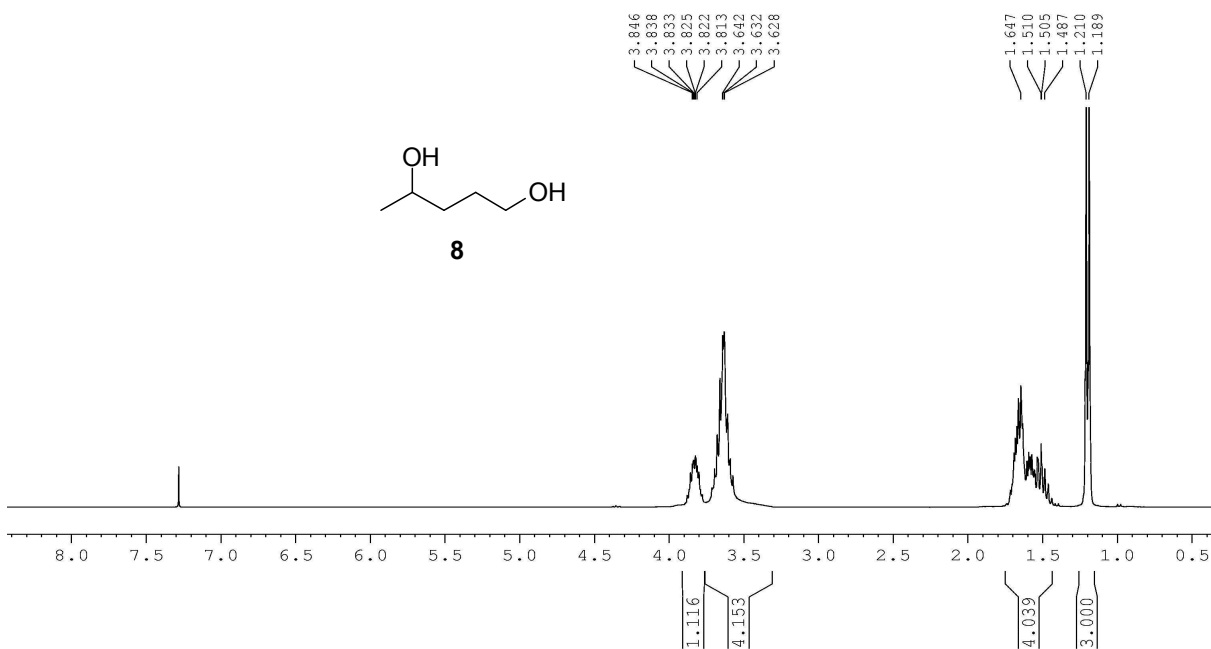
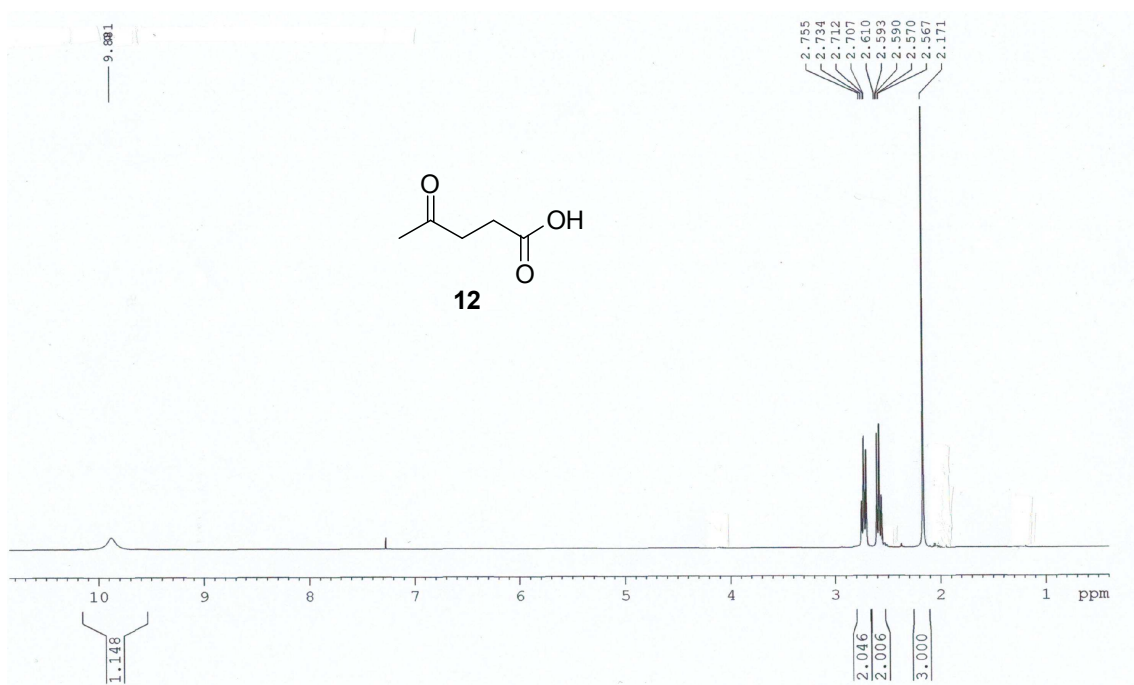
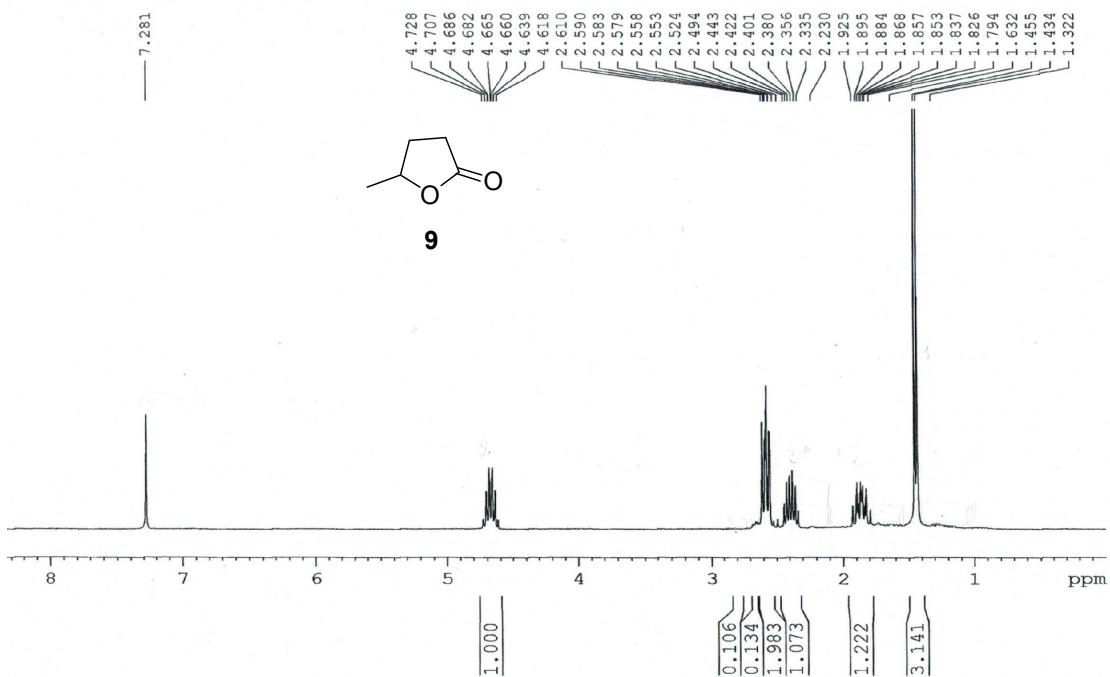
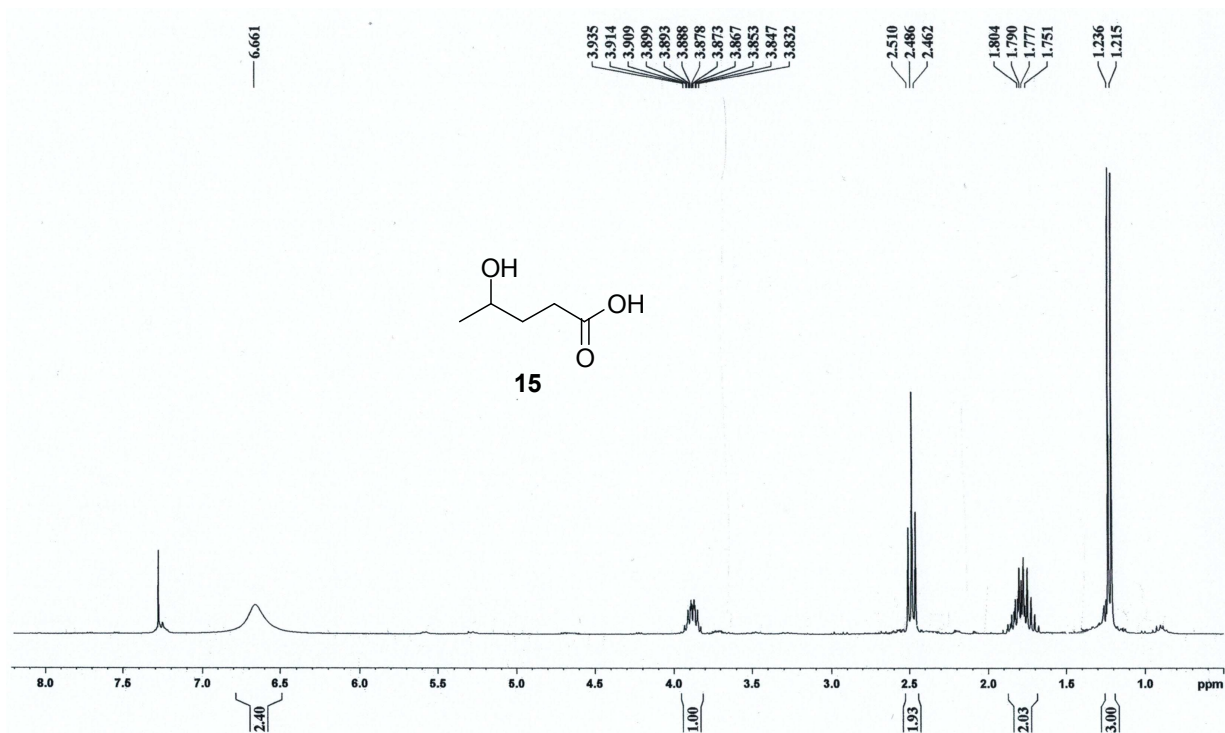
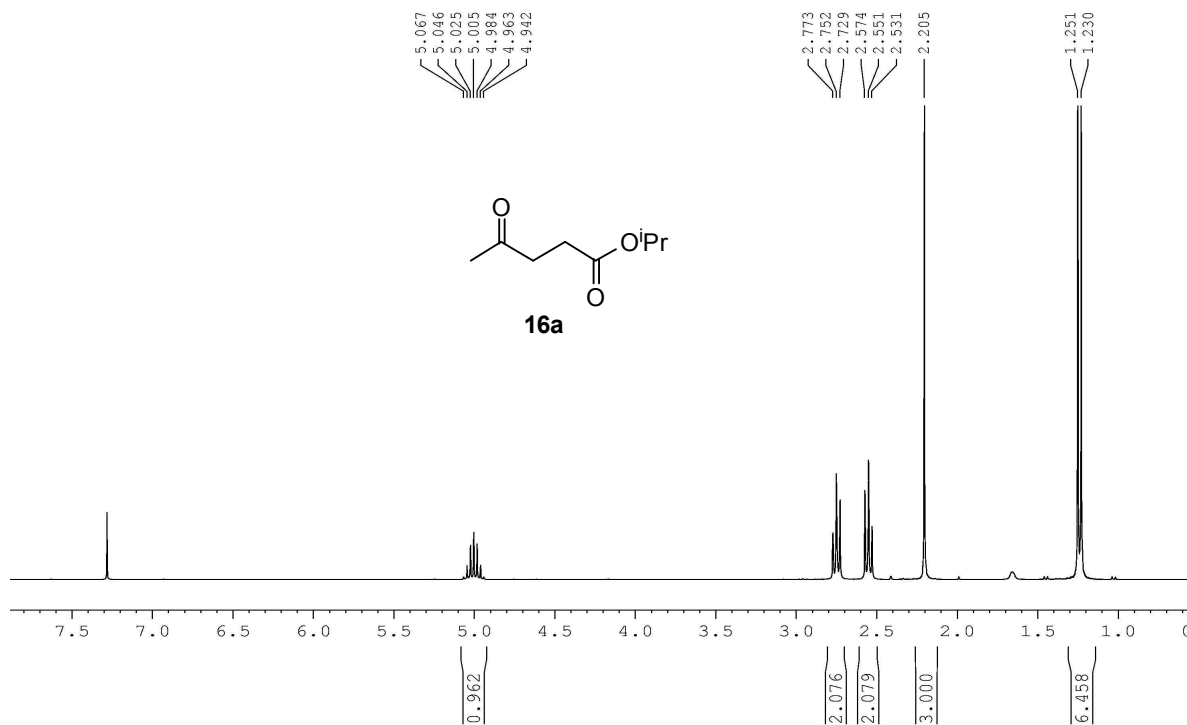


Figure S2. <sup>1</sup>H-NMR full chart for **8** in CDCl<sub>3</sub> (300 MHz)

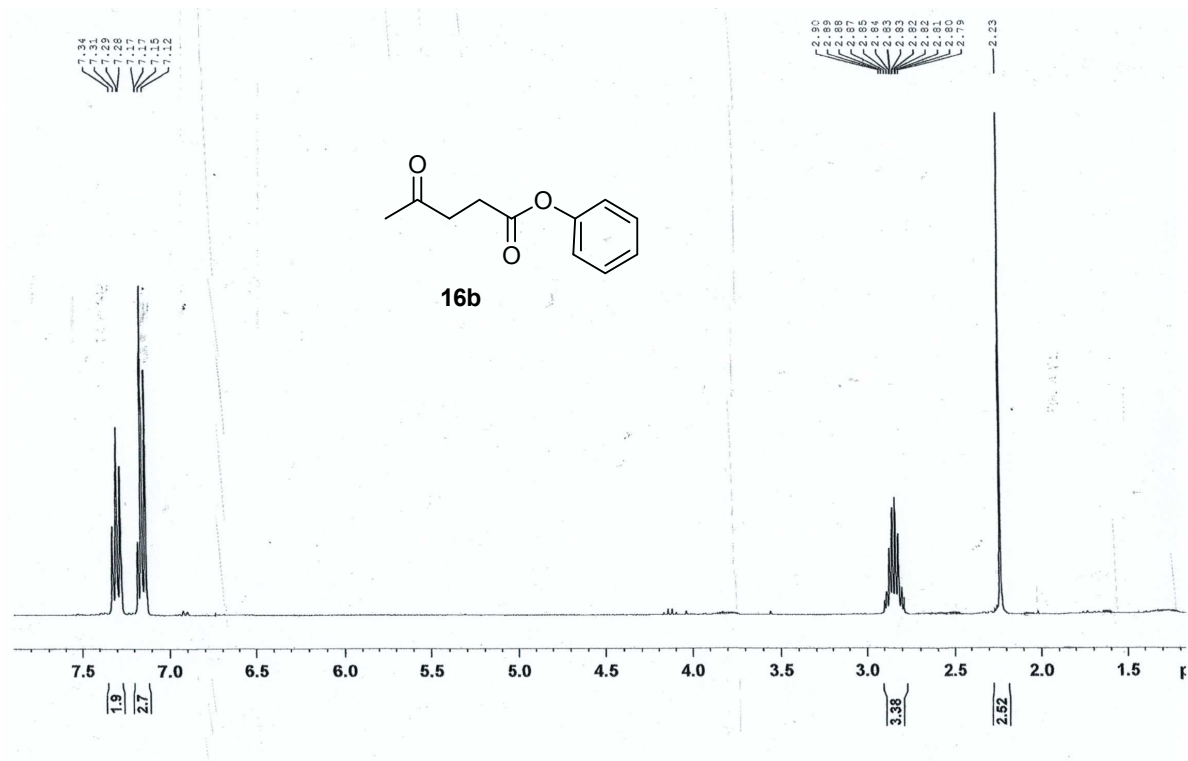




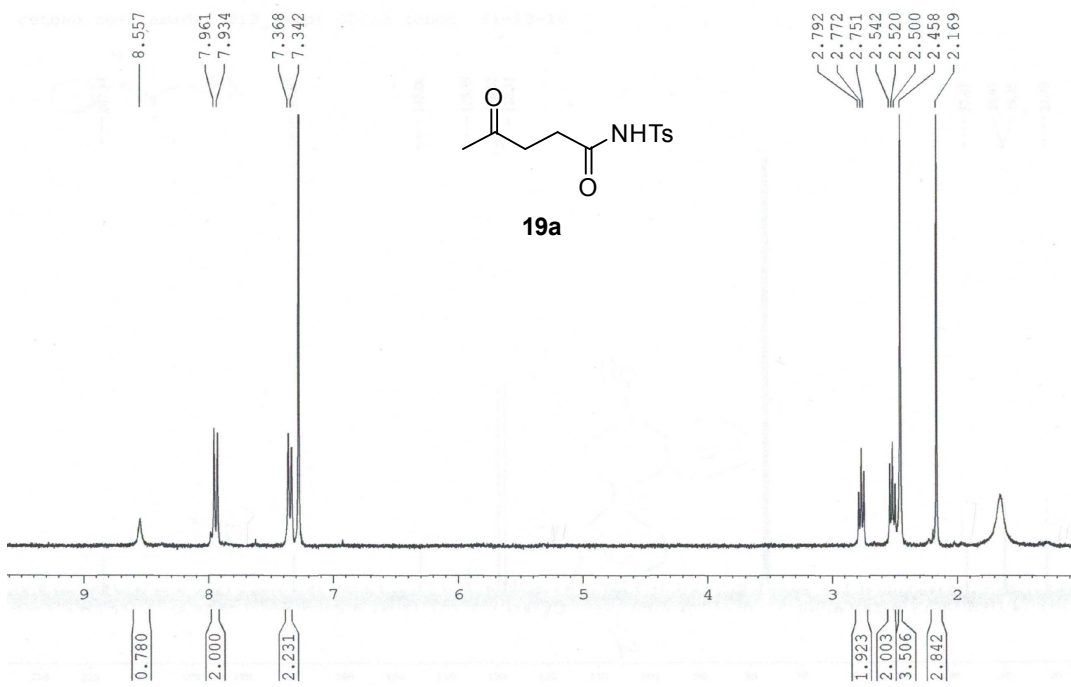
**Figure S5.** <sup>1</sup>H-NMR full chart for **15** in CDCl<sub>3</sub> (300 MHz)



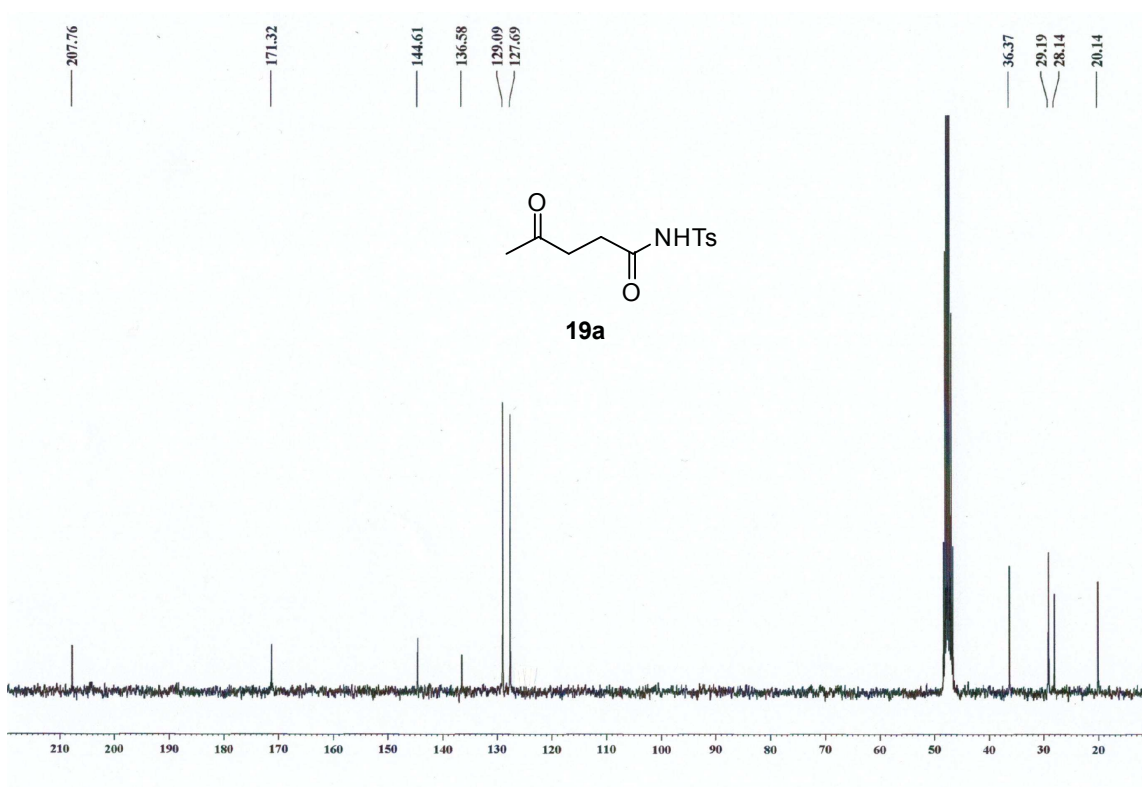
**Figure S6.** <sup>1</sup>H-NMR full chart for **16a** in CDCl<sub>3</sub> (300 MHz)



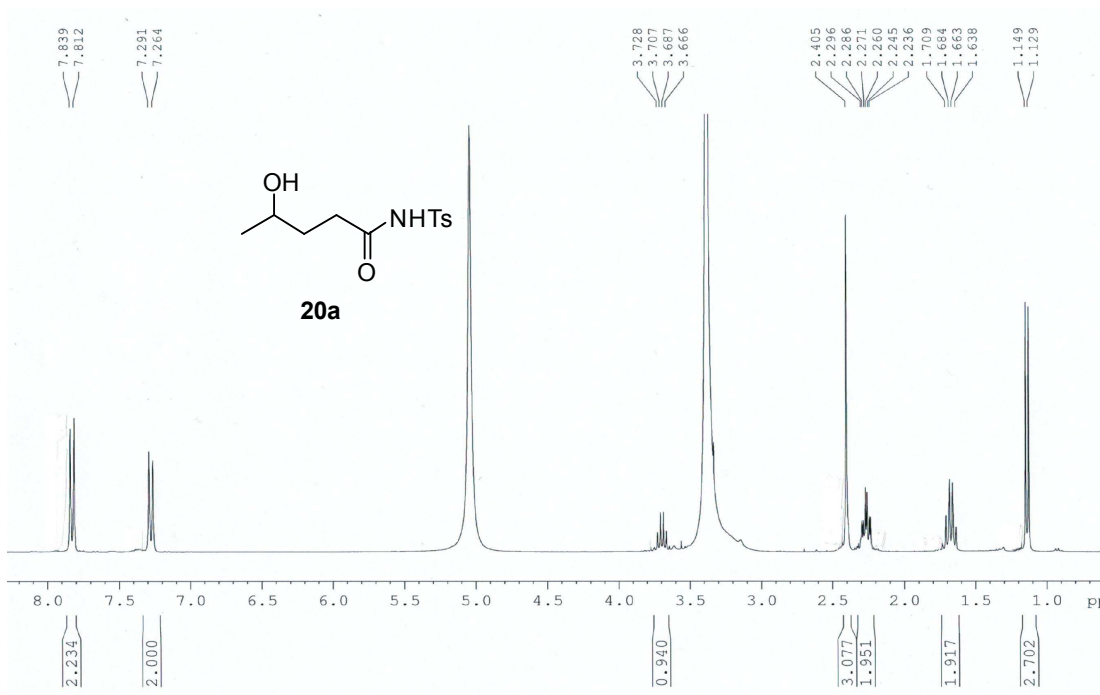
**Figure S7.** <sup>1</sup>H-NMR full chart for **16b** in CDCl<sub>3</sub> (300 MHz)



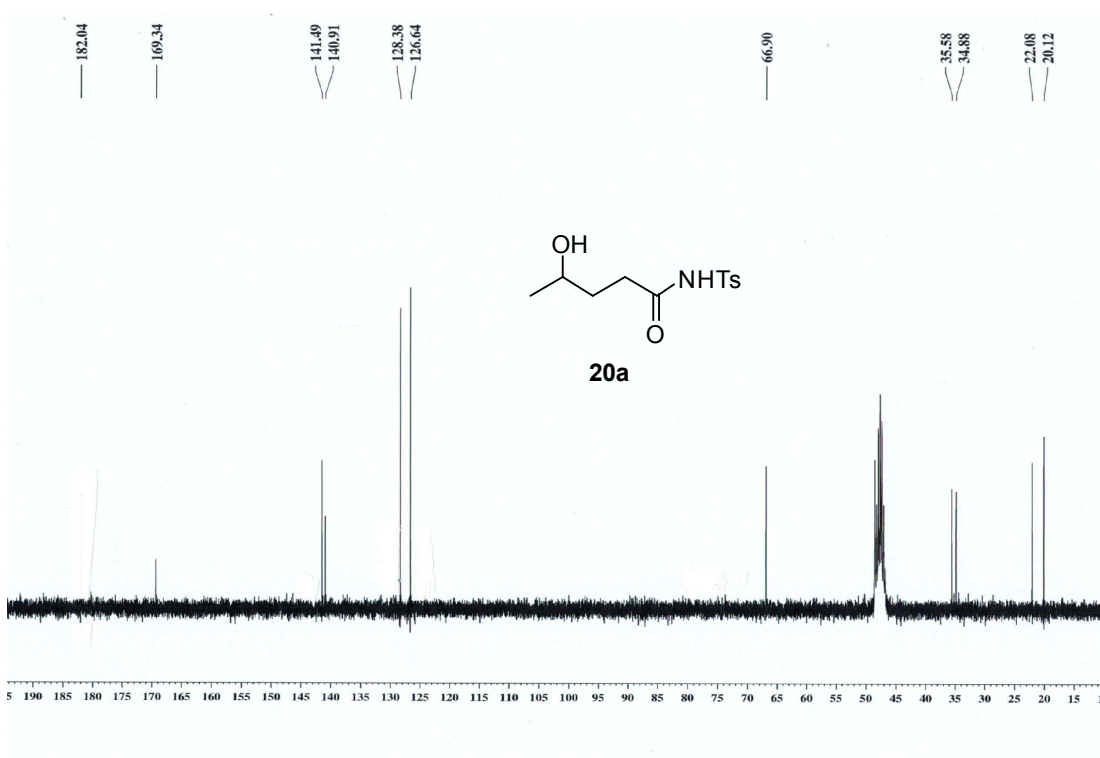
**Figure S8.**  $^1\text{H-NMR}$  full chart for **19a** in  $\text{CDCl}_3$  (300 MHz)



**Figure S9.**  $^{13}\text{C-NMR}$  full chart for **19a** in  $\text{CDCl}_3$  (75 MHz)



**Figure S10.** <sup>1</sup>H-NMR full chart for **20a** in MeOD (300 MHz)



**Figure S11.** <sup>13</sup>C-NMR full chart for **20a** in MeOD (75 MHz)

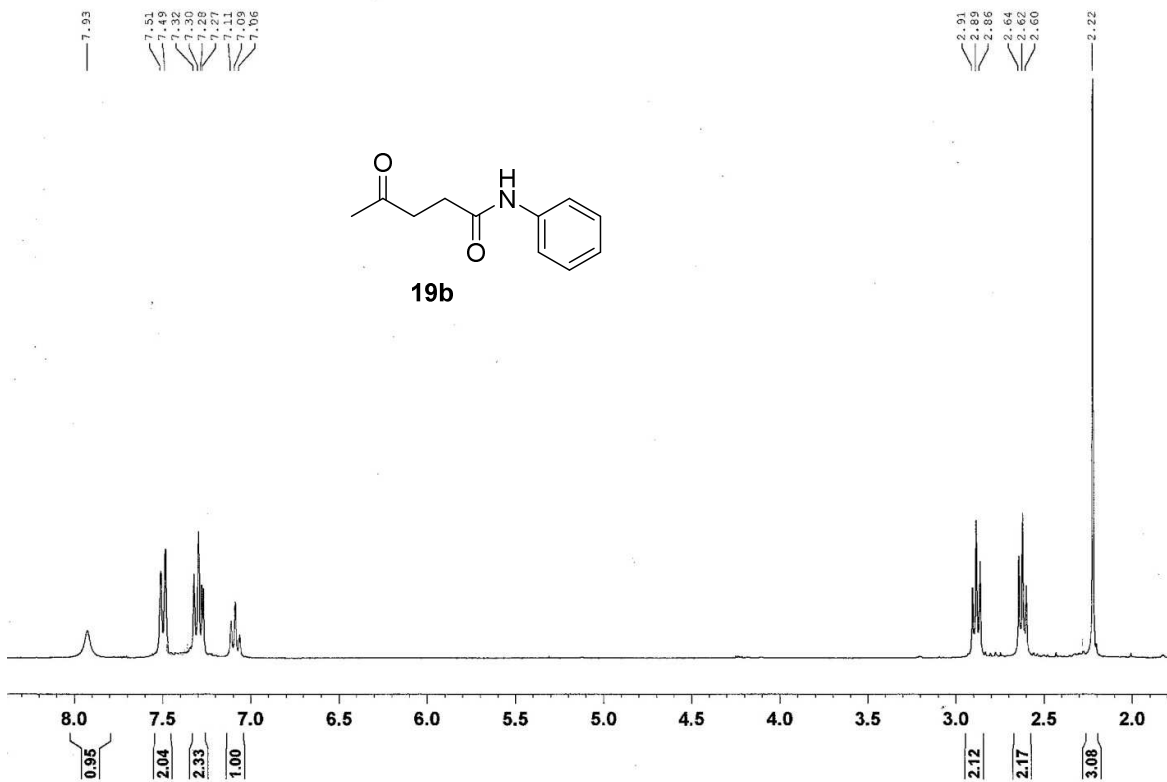


Figure S12. <sup>1</sup>H-NMR full chart for **19b** in CDCl<sub>3</sub> (300 MHz)

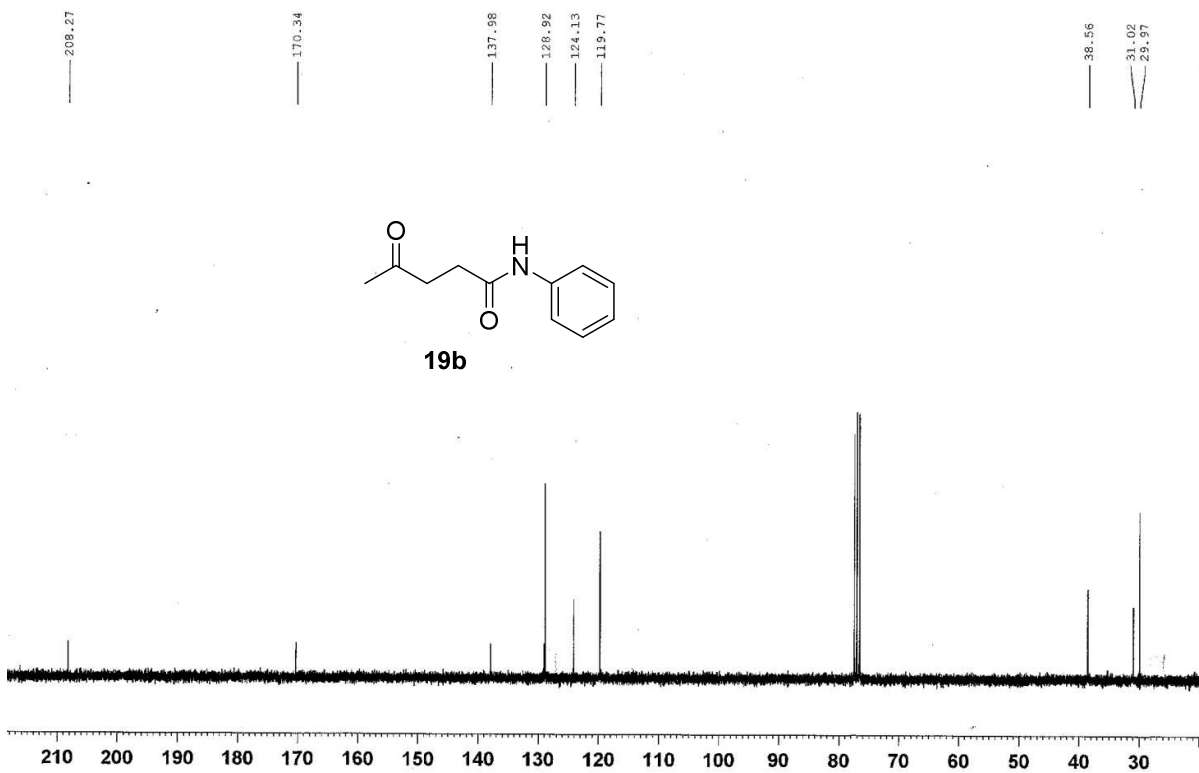


Figure S13. <sup>13</sup>C-NMR full chart for **19b** in MeOD (75 MHz)

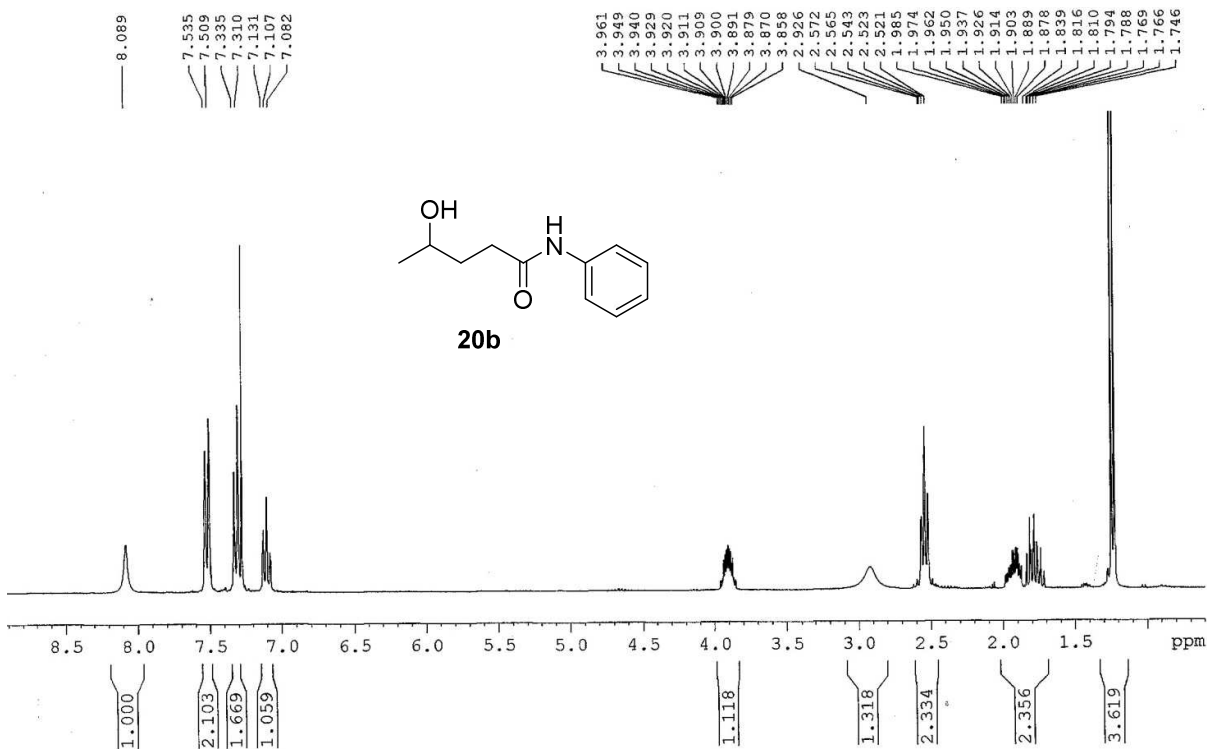


Figure S14. <sup>1</sup>H-NMR full chart for **20b** in CDCl<sub>3</sub> (300 MHz)

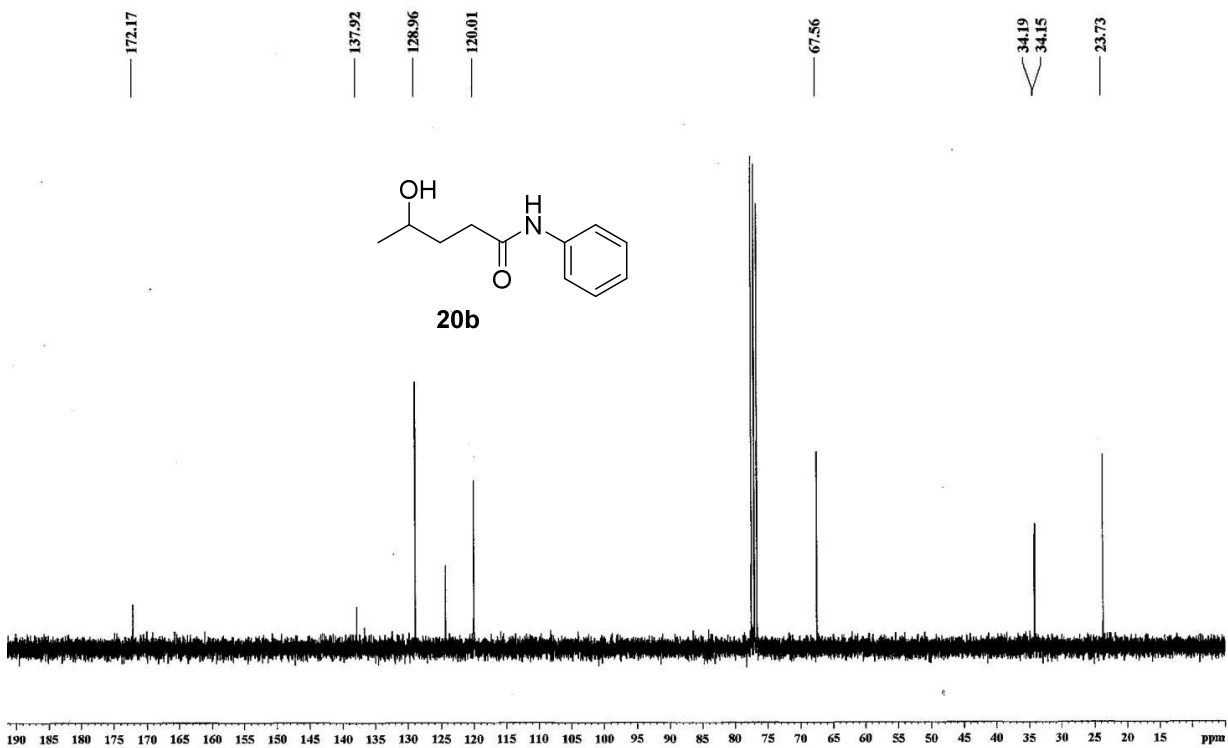


Figure S15. <sup>13</sup>C-NMR full chart for **20b** in CDCl<sub>3</sub> (75 MHz)

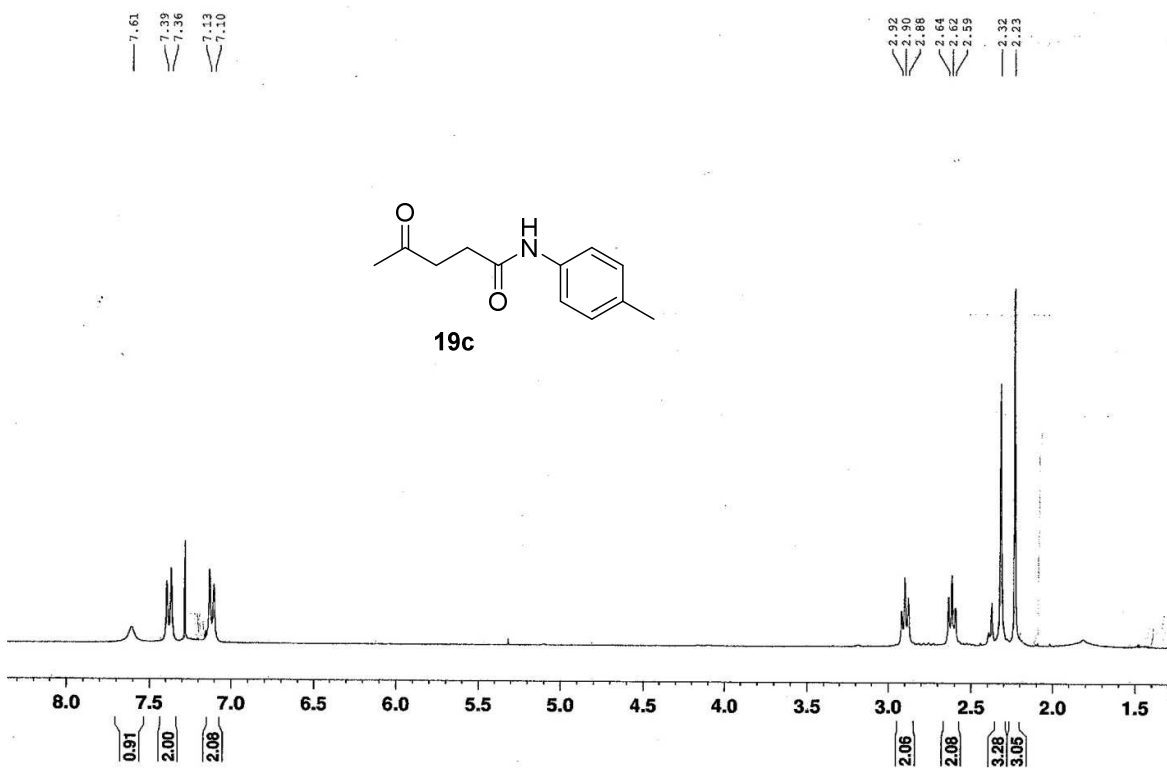


Figure S16.  $^1\text{H-NMR}$  full chart for **19c** in  $\text{CDCl}_3$  (300 MHz)

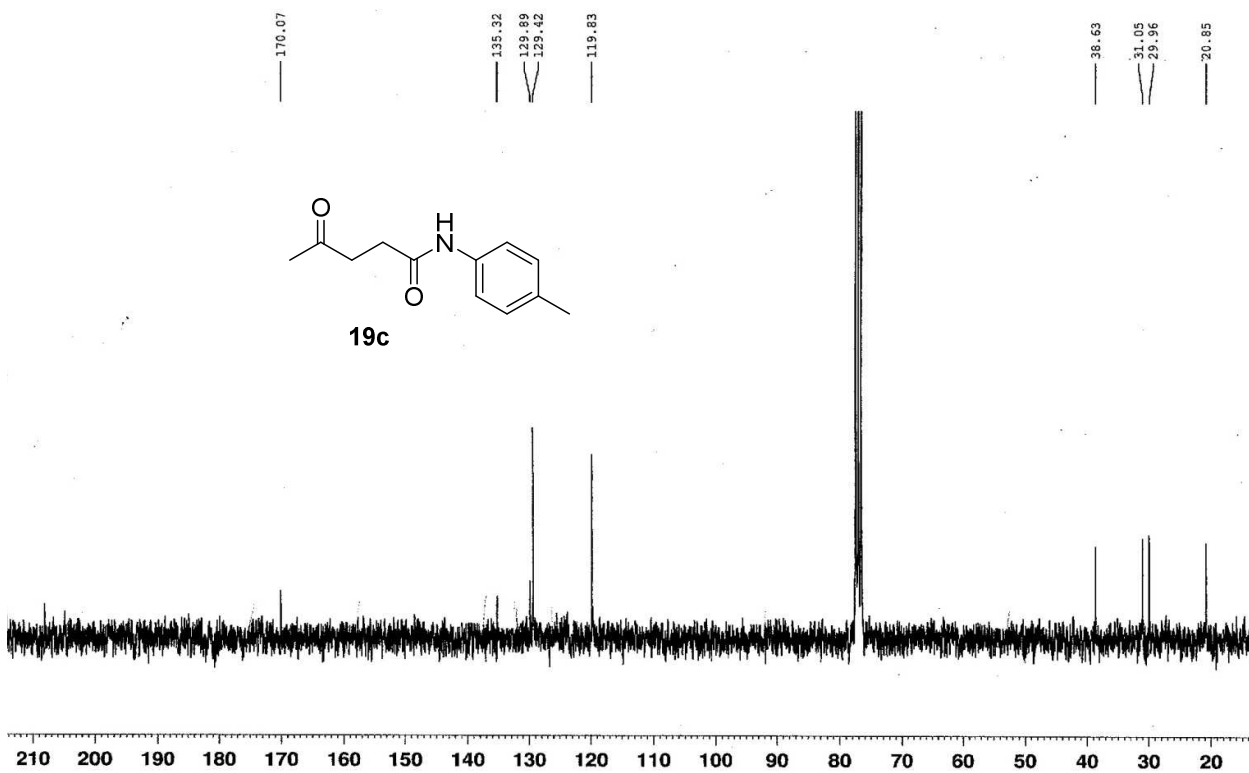


Figure S17.  $^{13}\text{C-NMR}$  full chart for **19c** in  $\text{CDCl}_3$  (75 MHz)

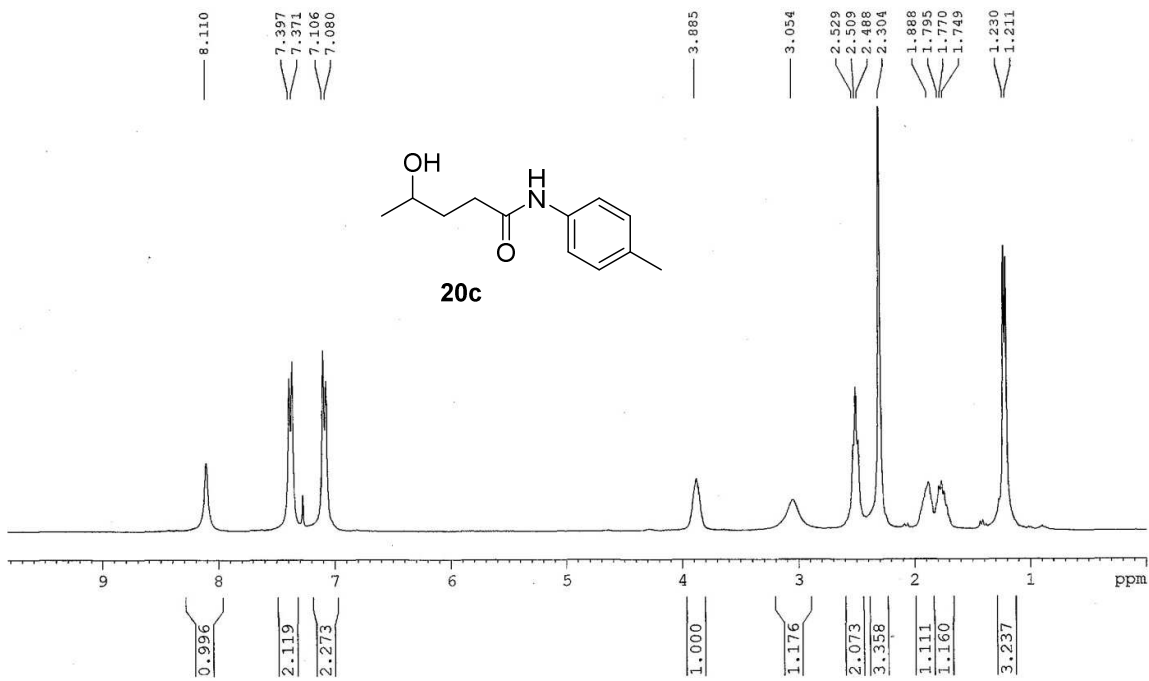


Figure S18. <sup>1</sup>H-NMR full chart for **20c** in CDCl<sub>3</sub> (300 MHz)

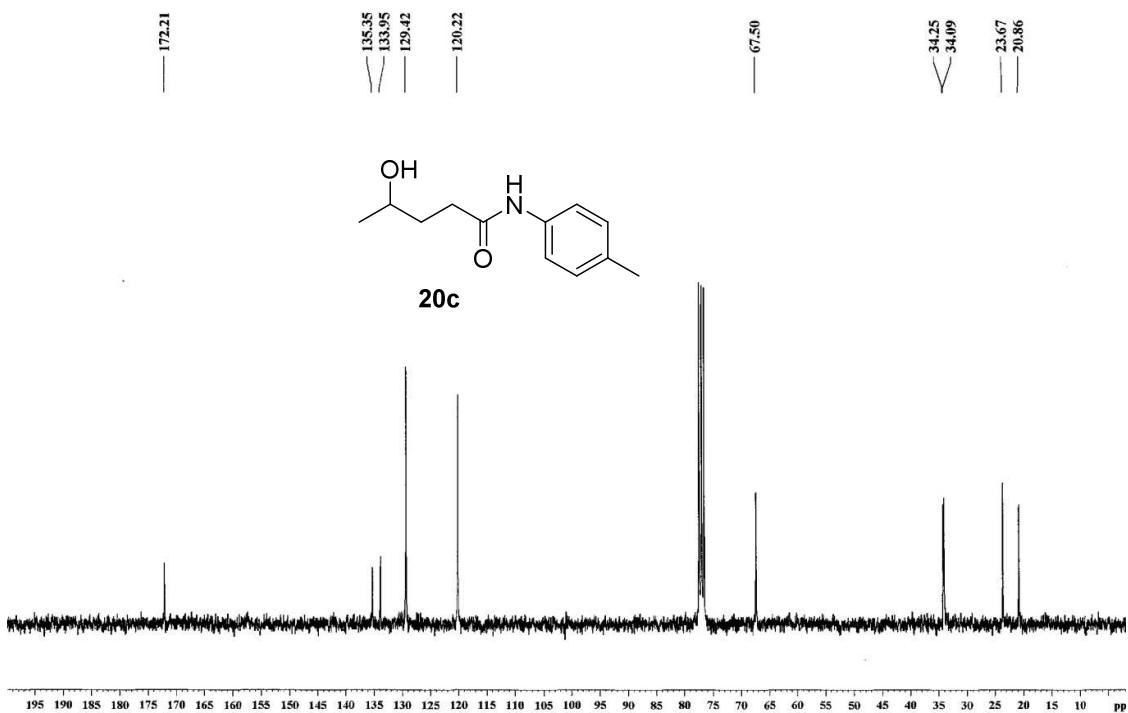


Figure S19. <sup>13</sup>C-NMR full chart for **20c** in CDCl<sub>3</sub> (75 MHz)

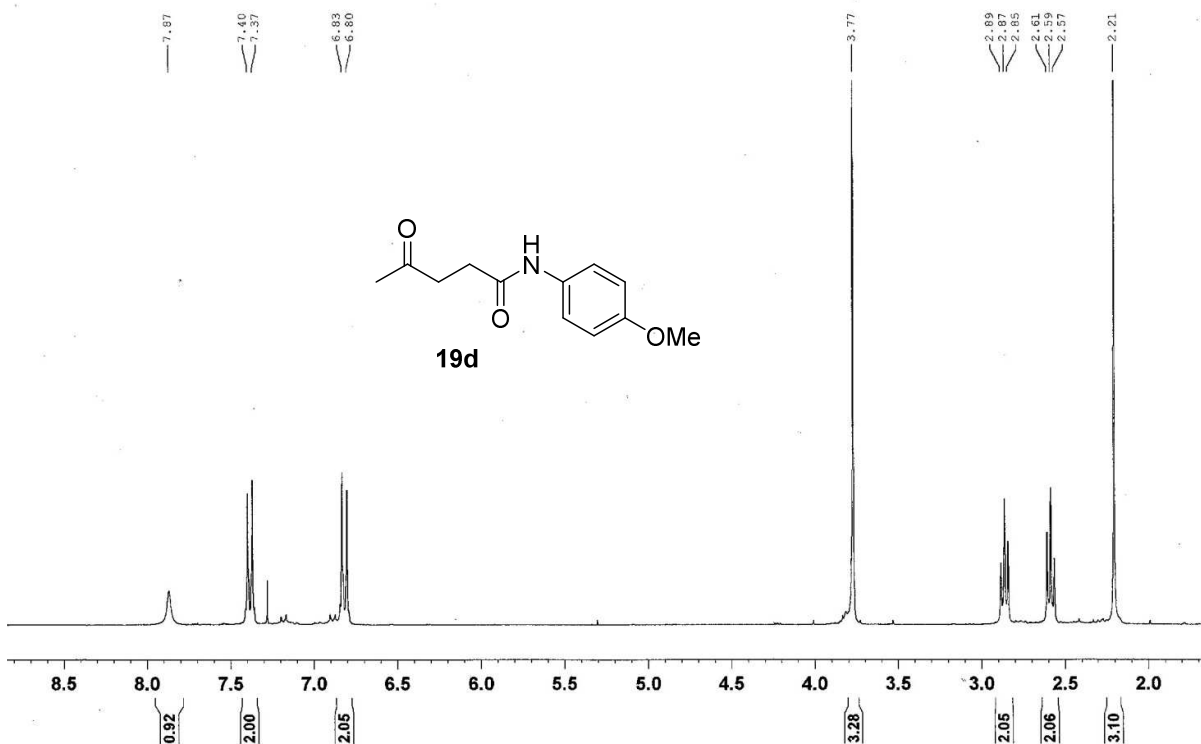


Figure S20. <sup>1</sup>H-NMR full chart for **19d** in CDCl<sub>3</sub> (300 MHz)

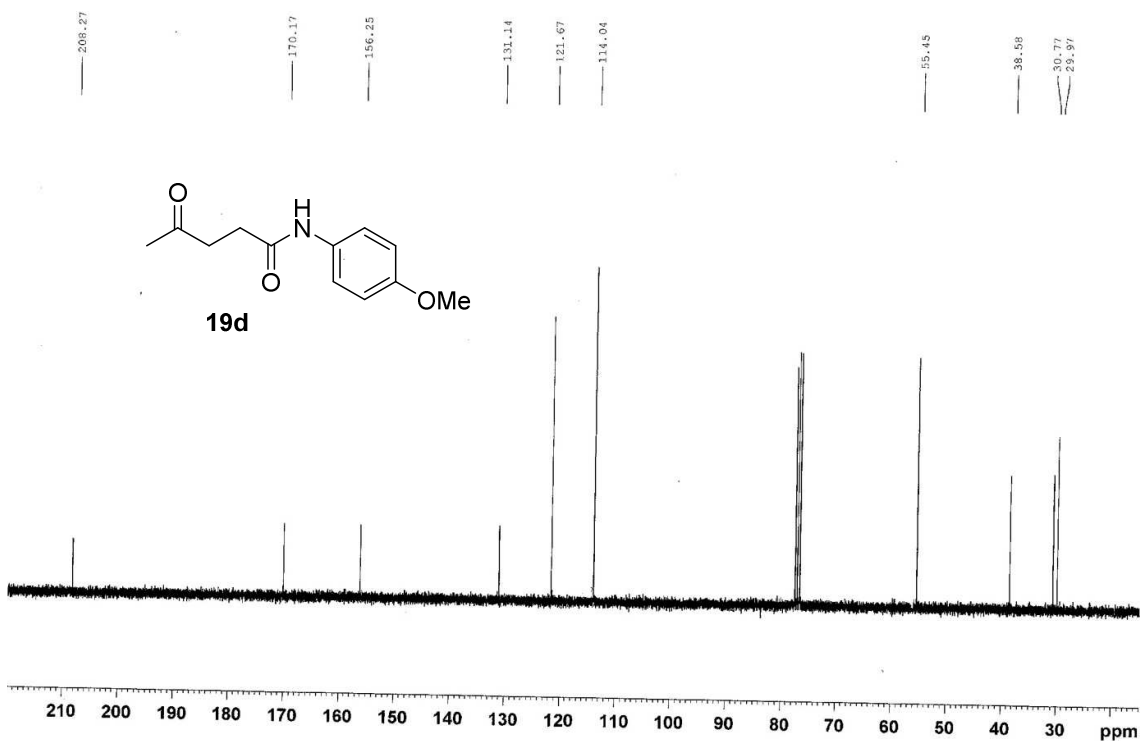


Figure S21. <sup>13</sup>C-NMR full chart for **19d** in CDCl<sub>3</sub> (75 MHz)

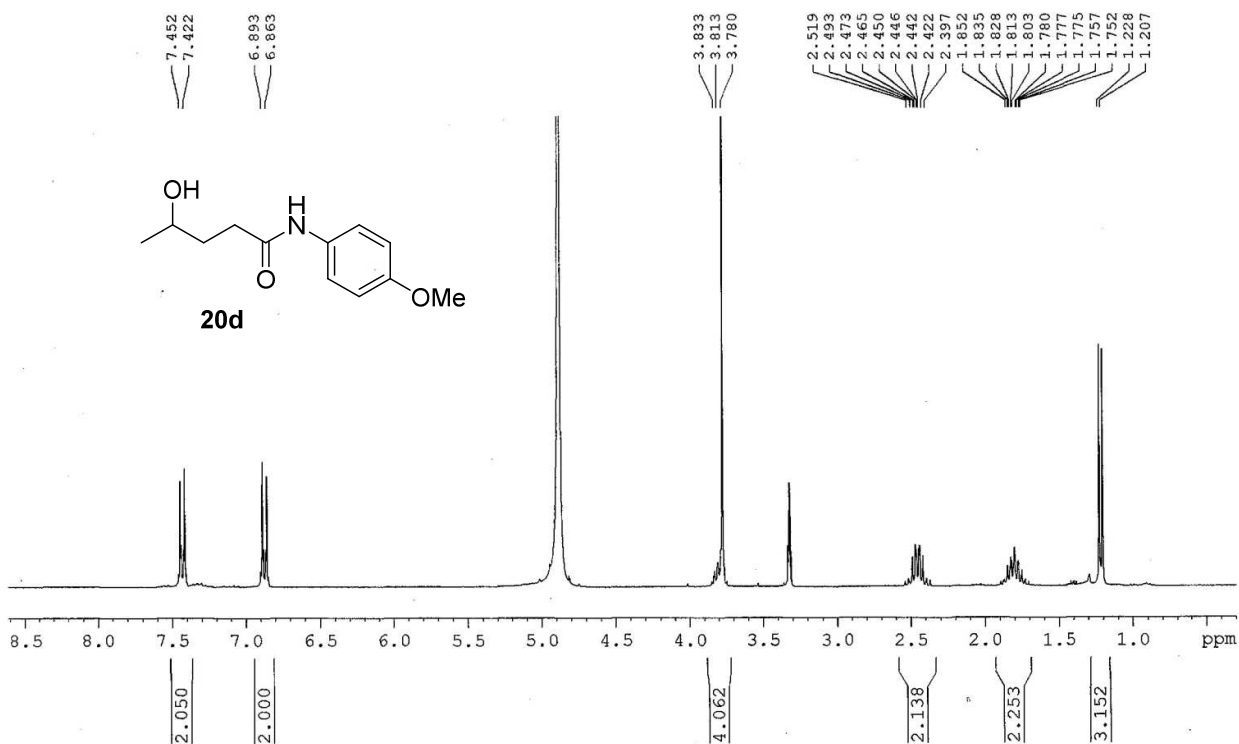


Figure S22. <sup>1</sup>H-NMR full chart for **20d** in MeOD (300 MHz)

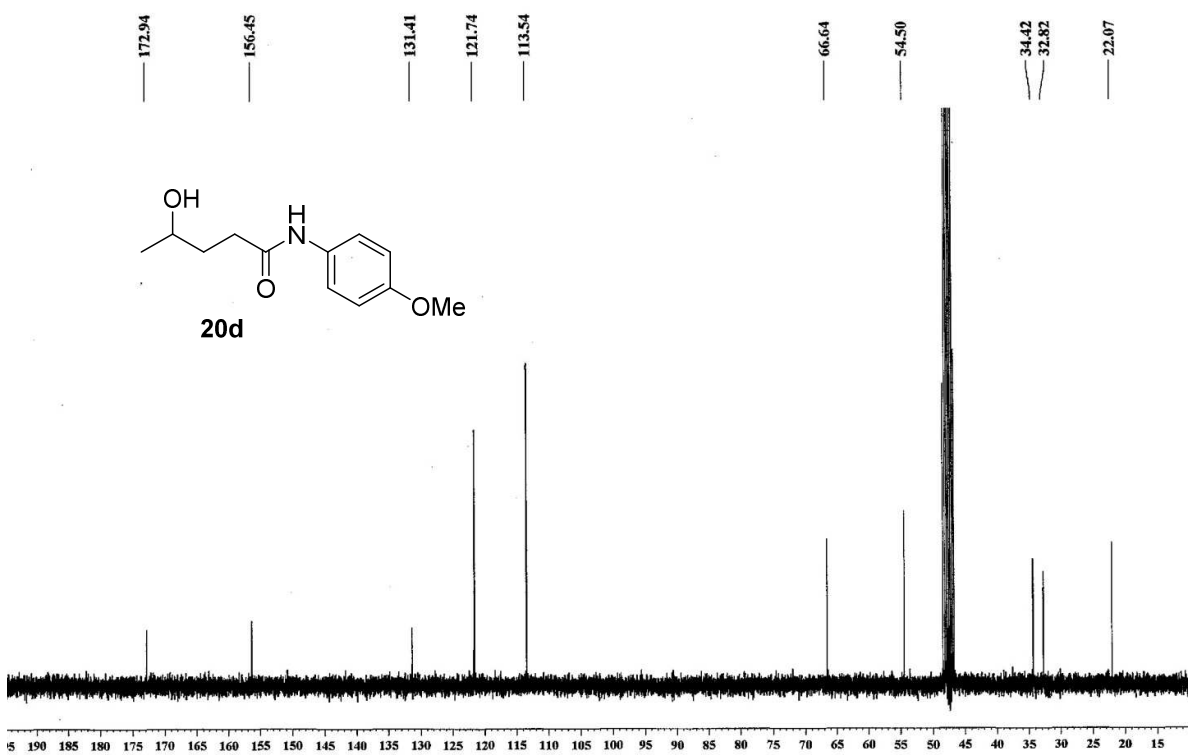


Figure S23. <sup>13</sup>C-NMR full chart for **20d** in MeOD (75 MHz)

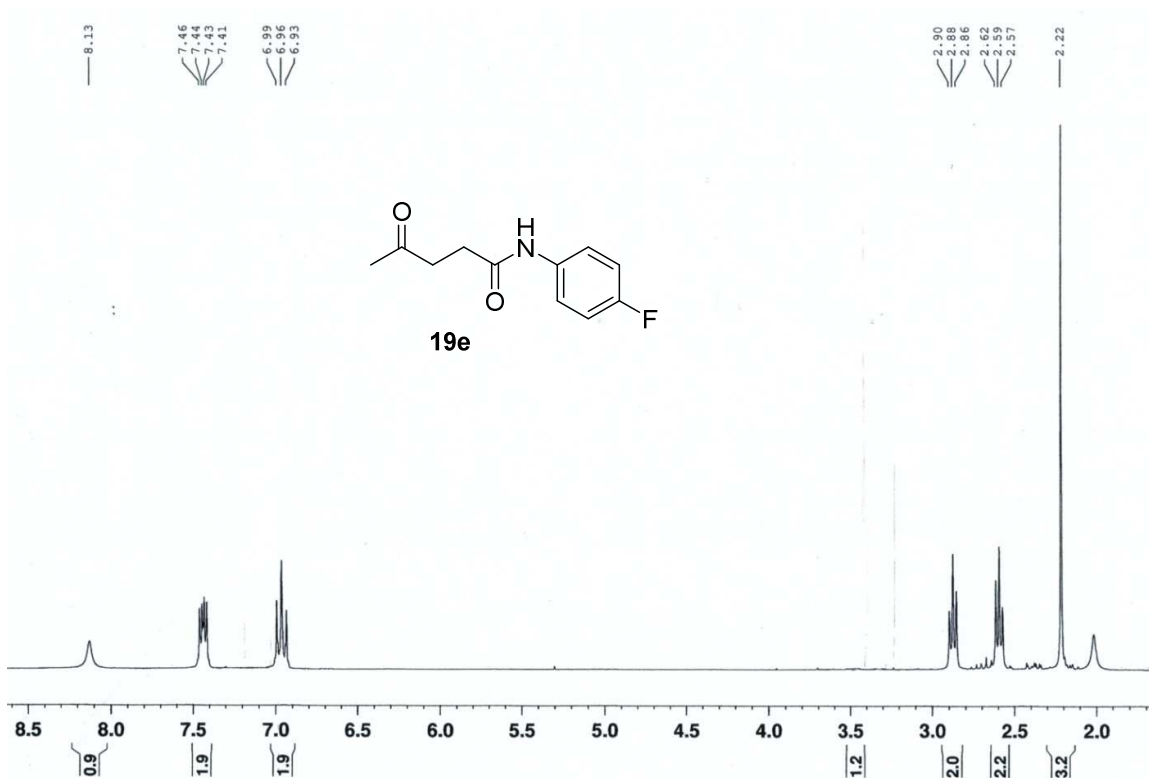


Figure S24. <sup>1</sup>H-NMR full chart for **19e** in CDCl<sub>3</sub> (300 MHz)

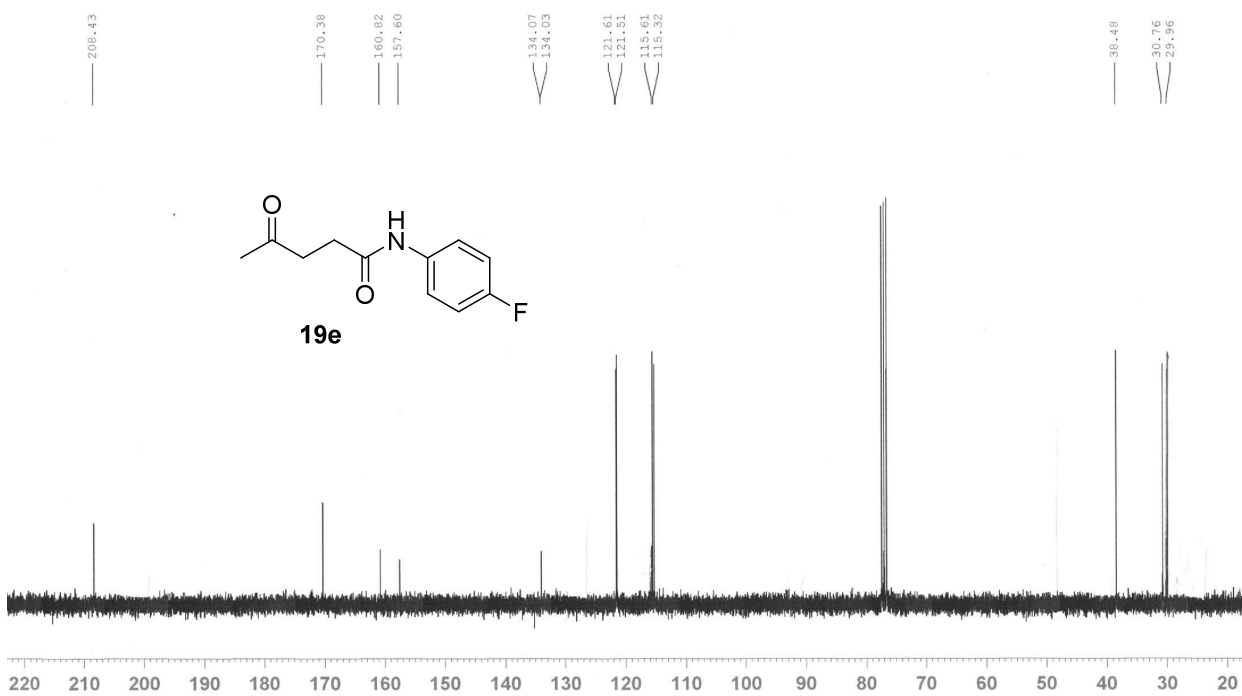


Figure S25. <sup>13</sup>C-NMR full chart for **19e** in CDCl<sub>3</sub> (75 MHz)



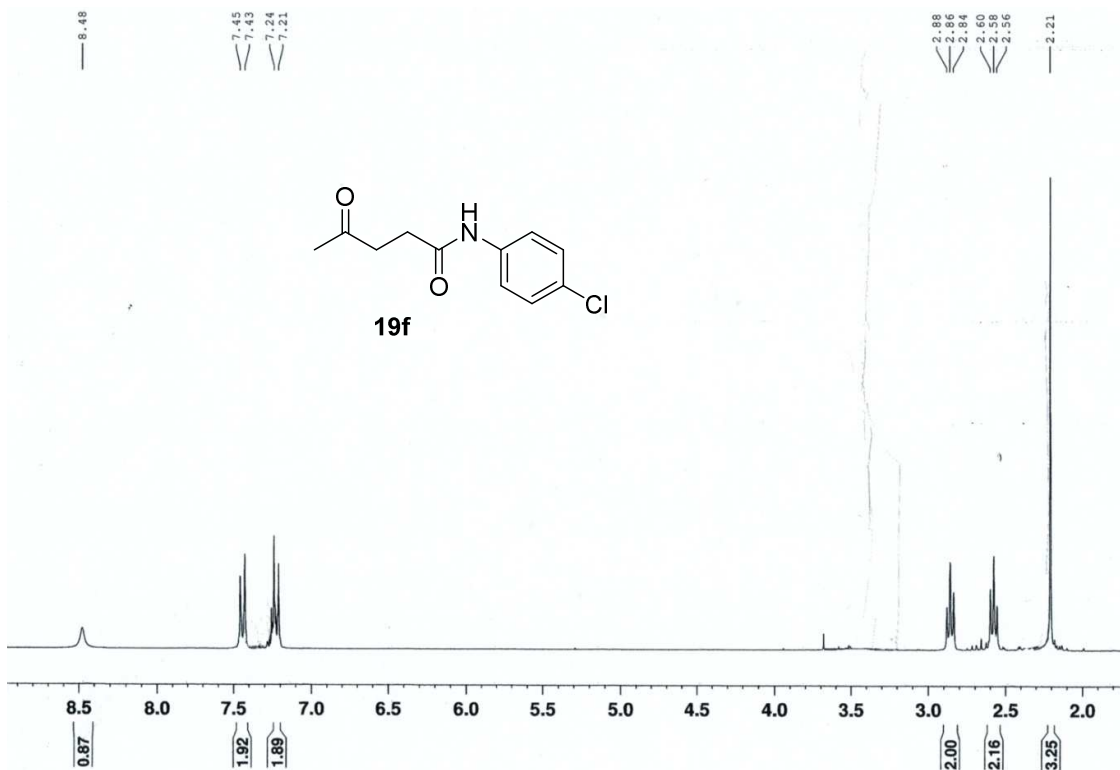


Figure S28. <sup>1</sup>H-NMR full chart for **19f** in CDCl<sub>3</sub> (300 MHz)

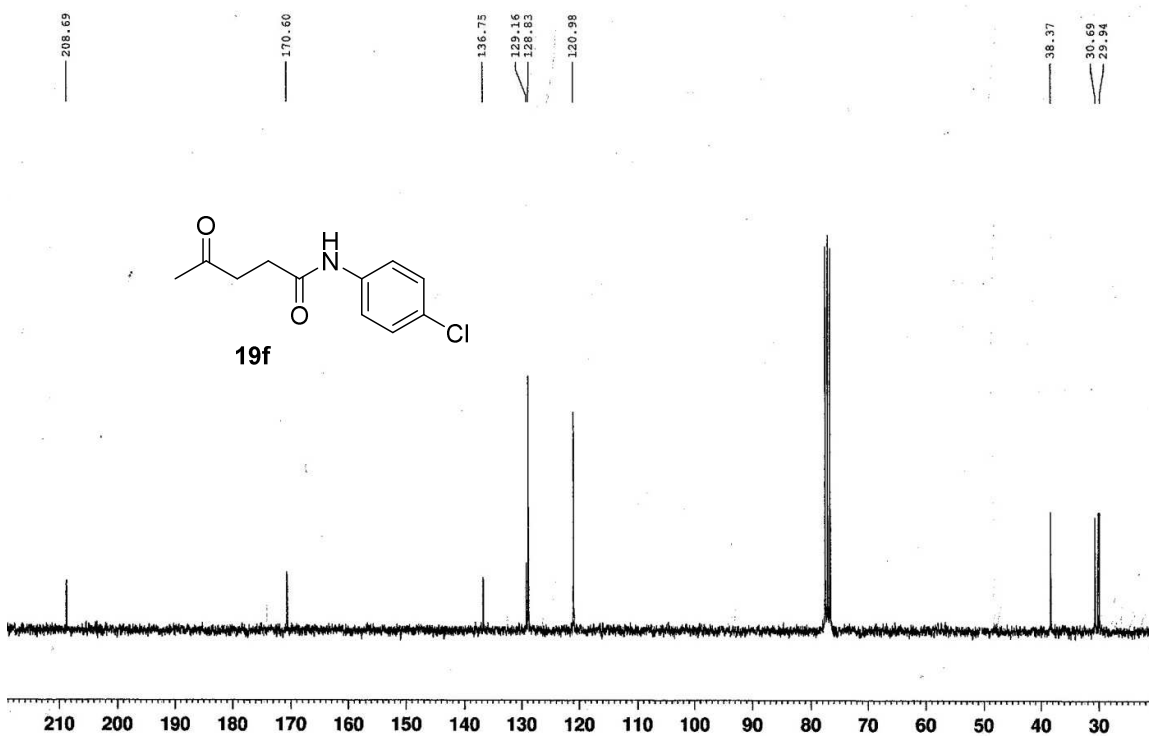


Figure S29. <sup>13</sup>C-NMR full chart for **19f** in CDCl<sub>3</sub> (75 MHz)

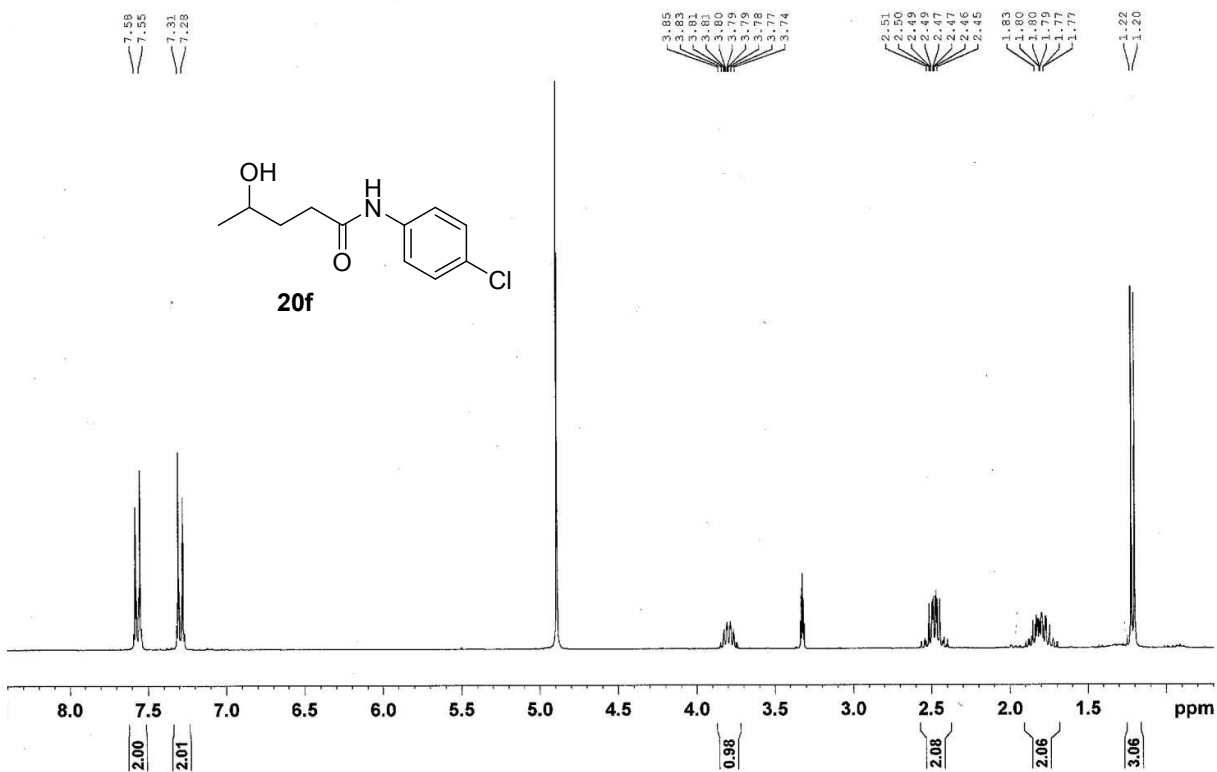


Figure S30. <sup>1</sup>H-NMR full chart for **20f** in MeOD (300 MHz)

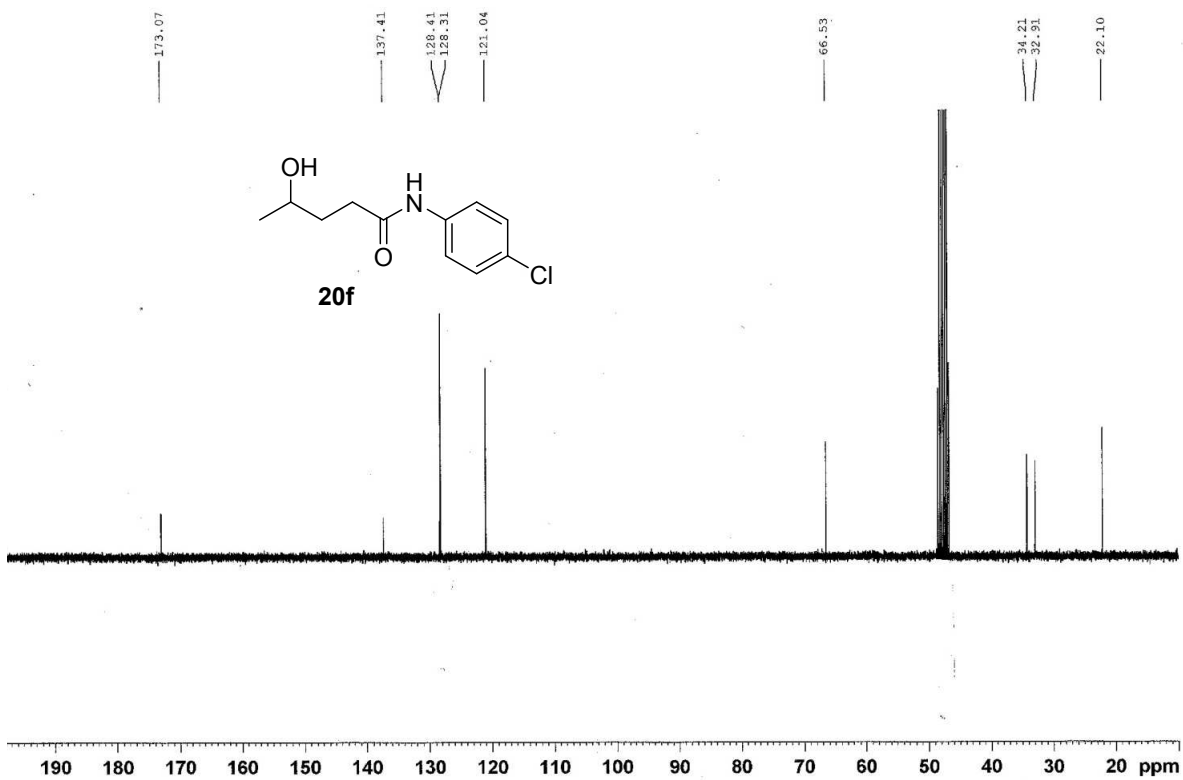
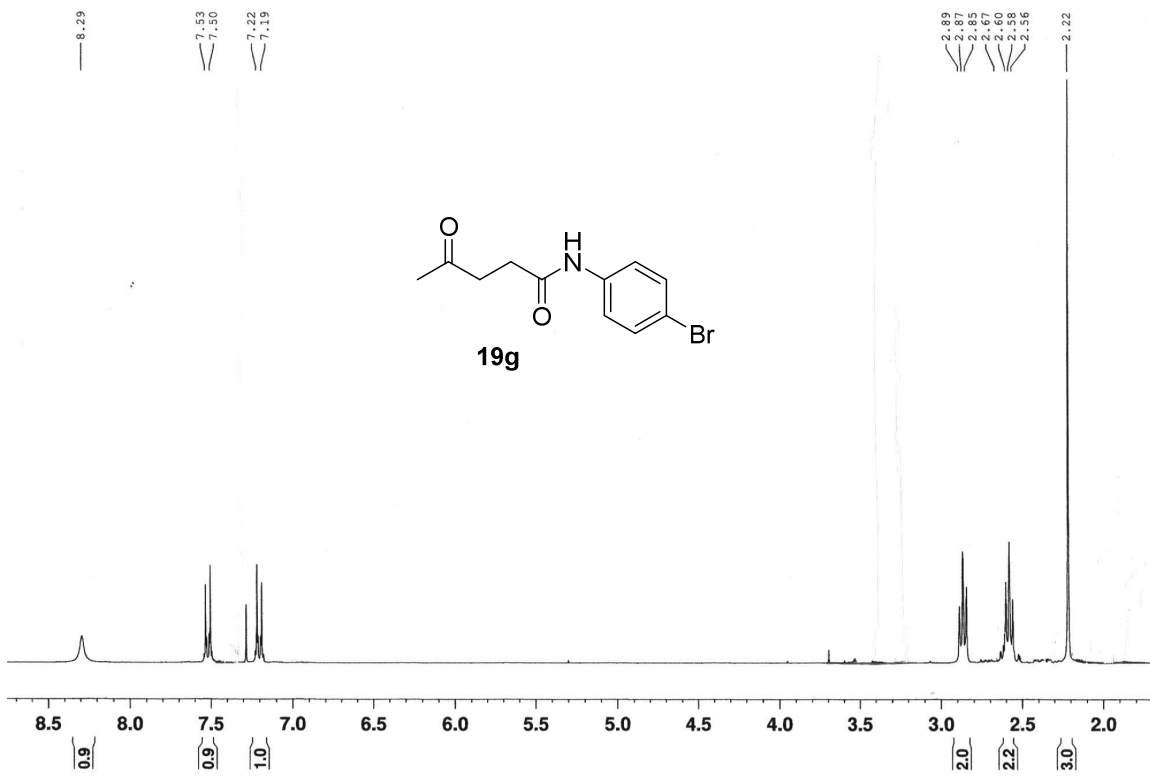
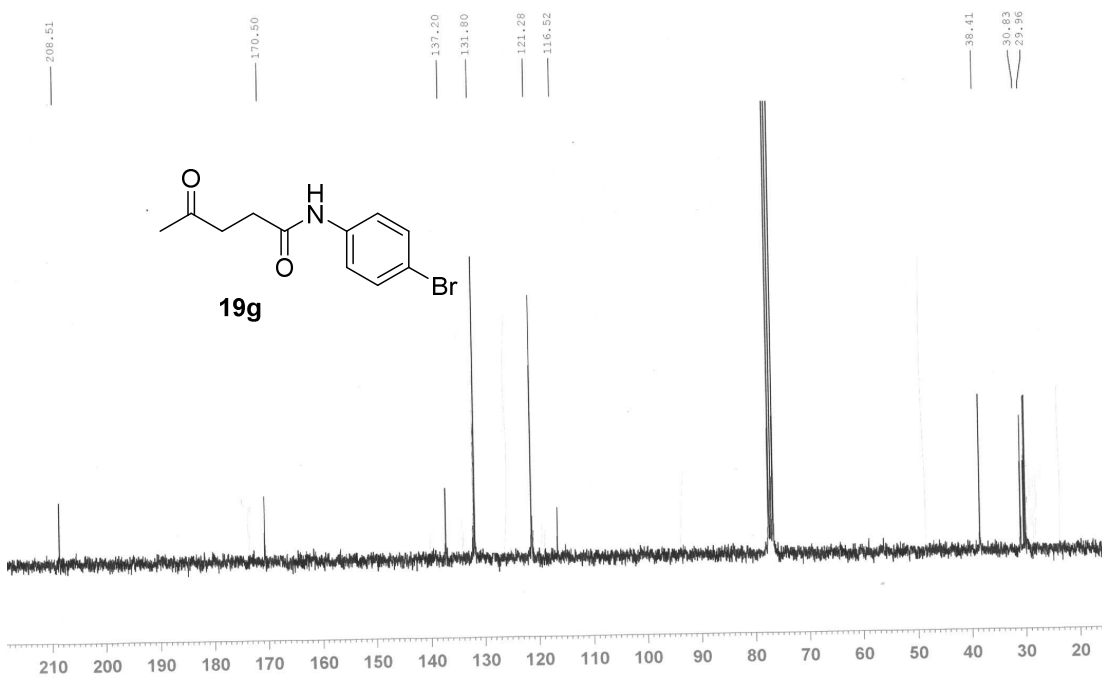


Figure S31. <sup>13</sup>C-NMR full chart for **20f** in MeOD (75 MHz)



**Figure S32.** <sup>1</sup>H-NMR full chart for **19g** in CDCl<sub>3</sub> (300 MHz)



**Figure S33.** <sup>13</sup>C-NMR full chart for **19g** in CDCl<sub>3</sub> (75 MHz)

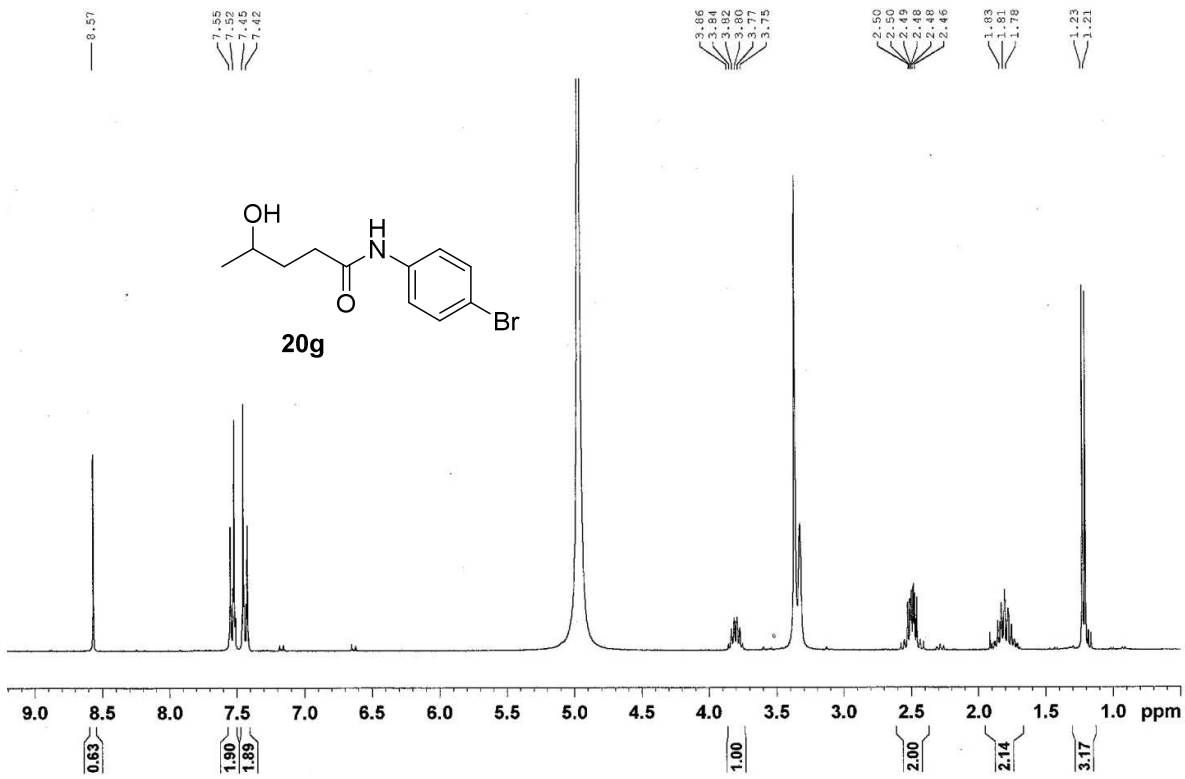


Figure S34. <sup>1</sup>H-NMR full chart for **20g** in MeOD (300 MHz)

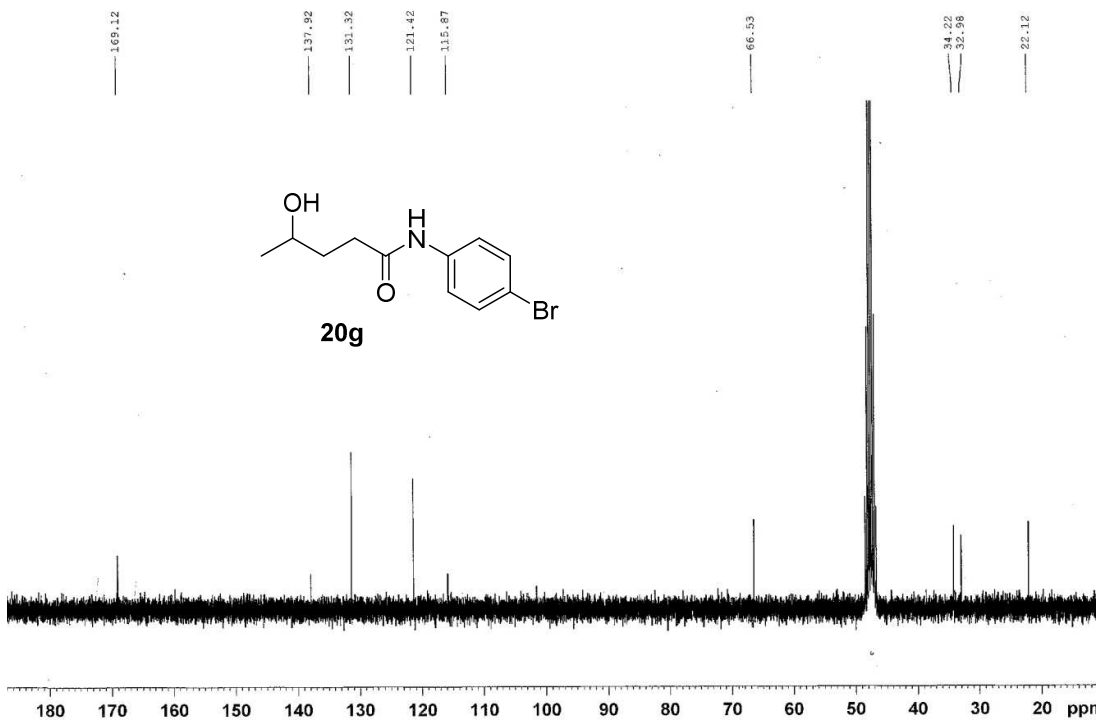


Figure S35. <sup>13</sup>C-NMR full chart for **20g** in MeOD (75 MHz)

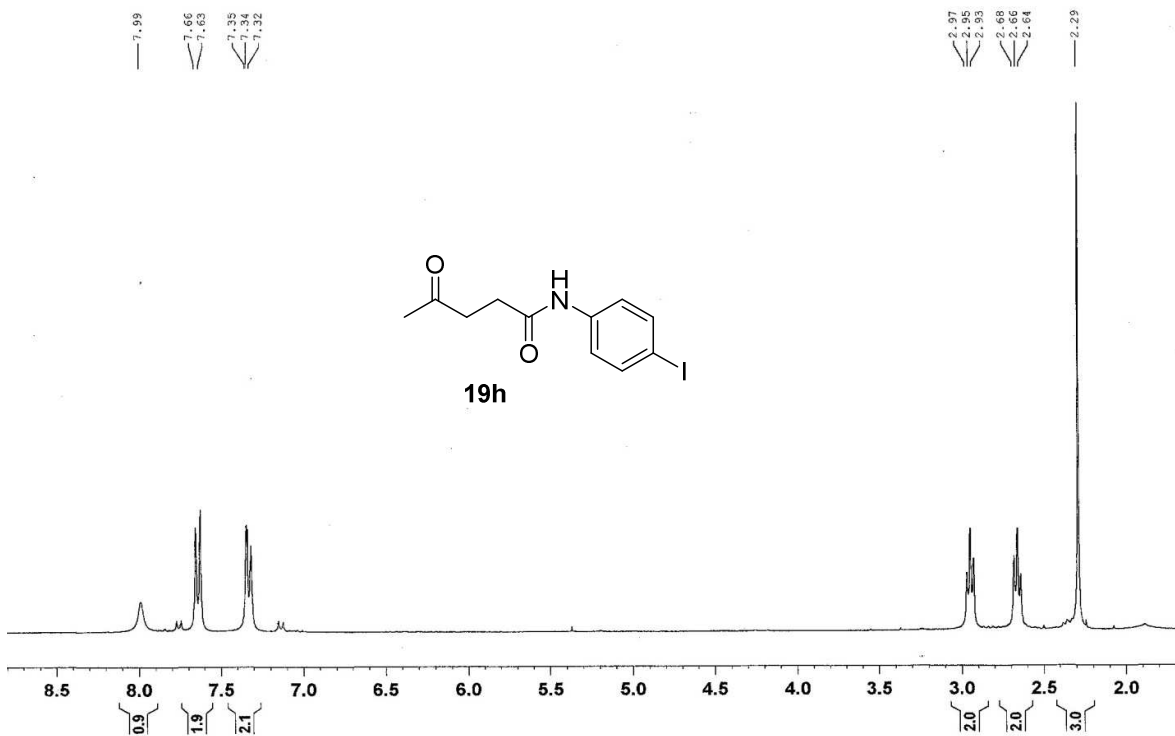


Figure S36. <sup>1</sup>H-NMR full chart for **19h** in CDCl<sub>3</sub> (100 MHz)

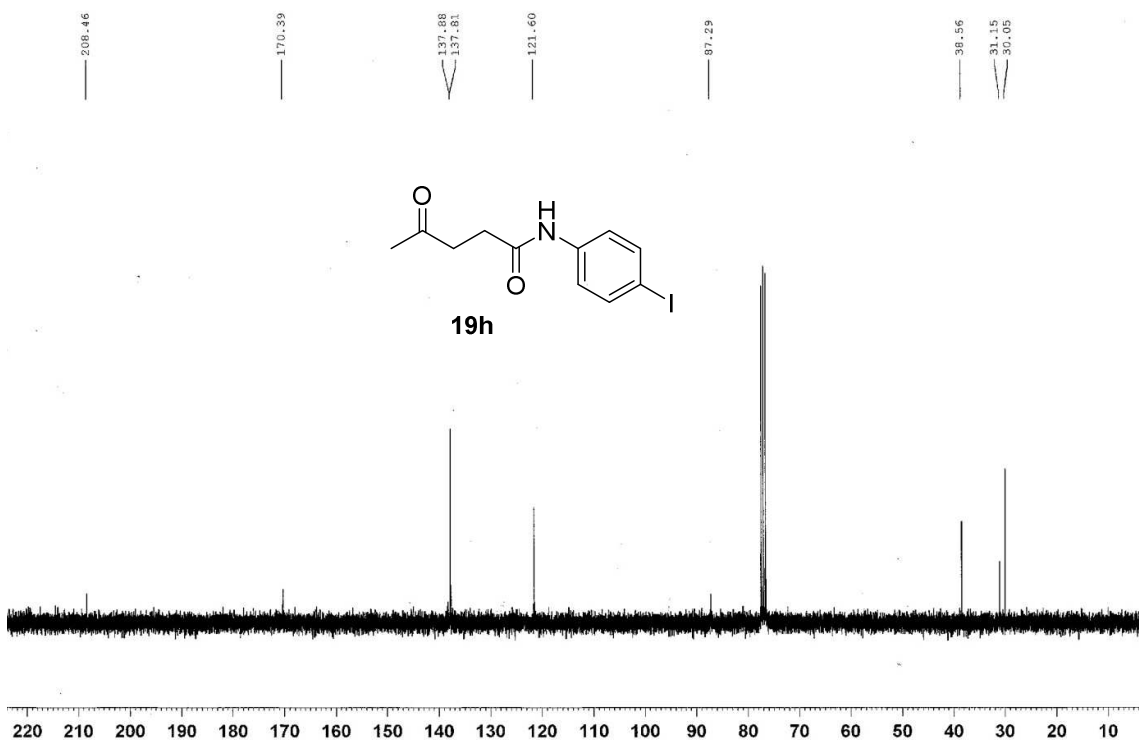
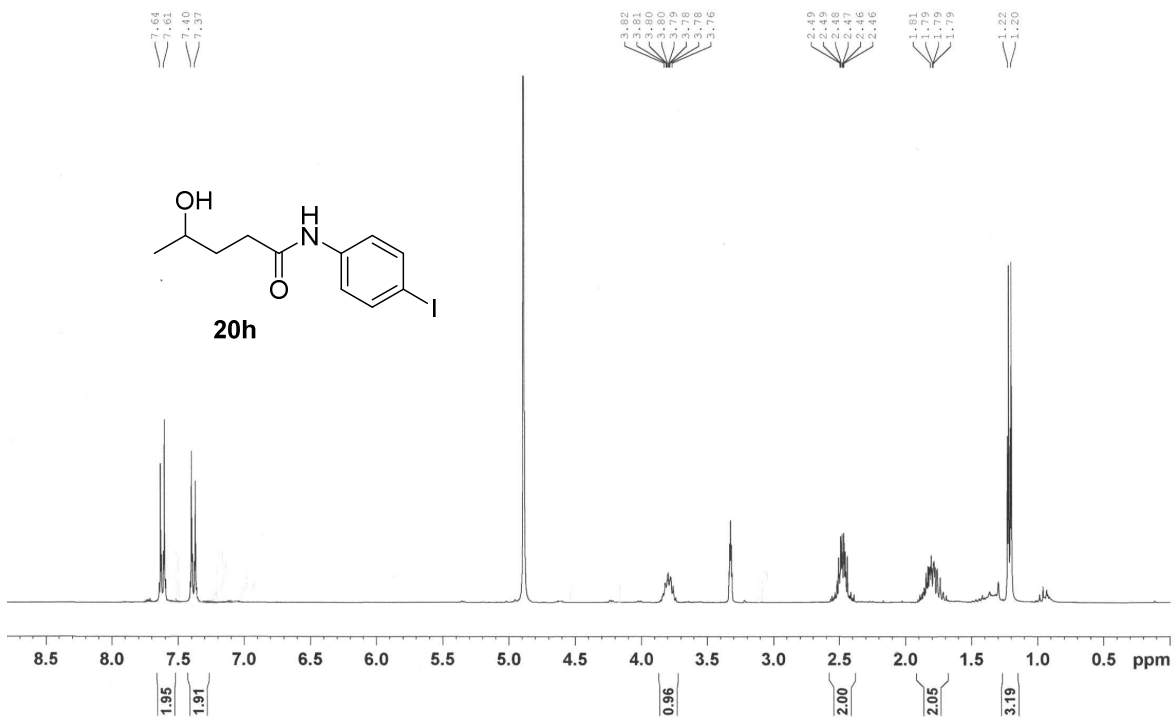
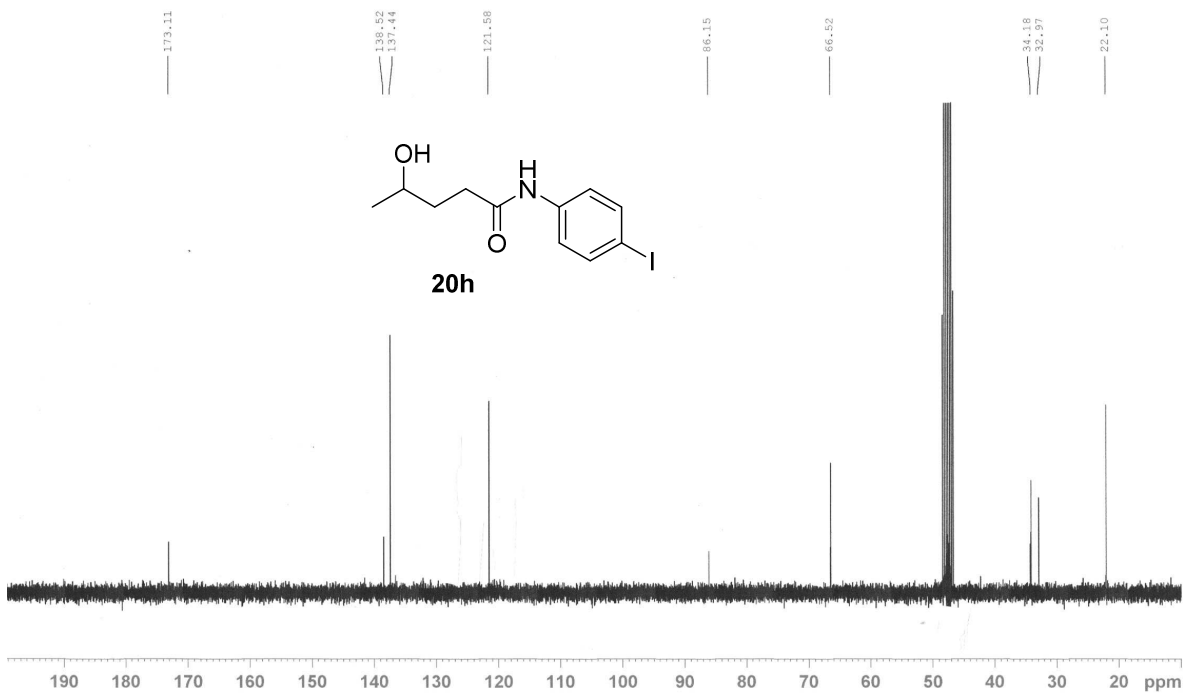


Figure S37. <sup>13</sup>C-NMR full chart for **19h** in CDCl<sub>3</sub> (75 MHz)

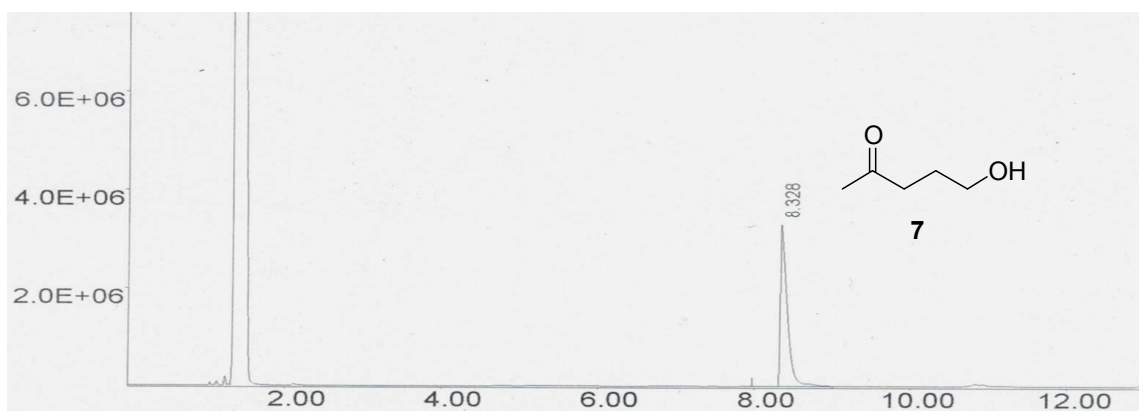
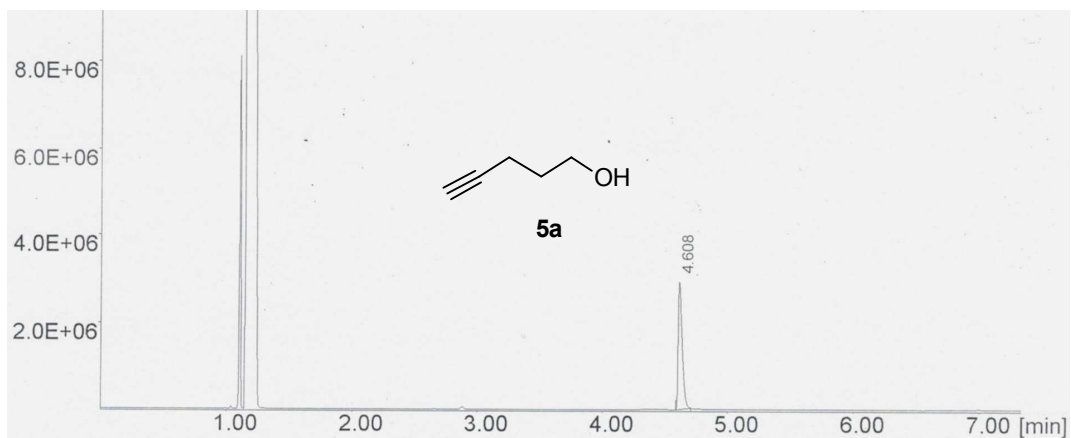


**Figure S38.** <sup>1</sup>H-NMR full chart for **20h** in MeOD (300 MHz)

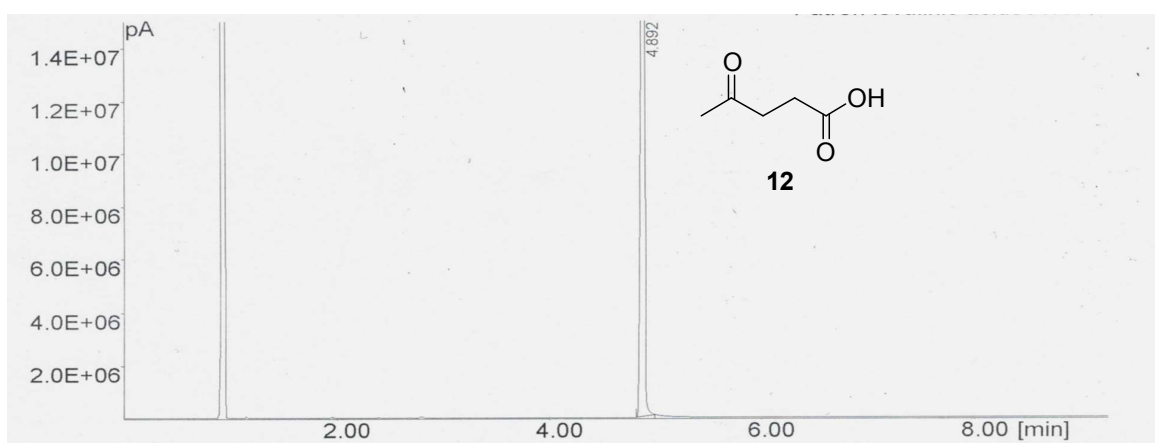
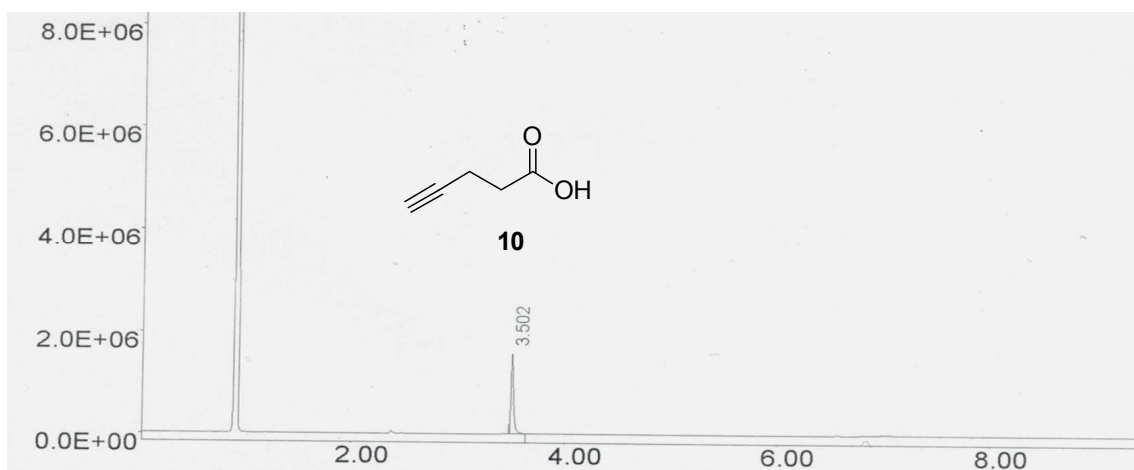


**Figure S39.** <sup>13</sup>C-NMR full chart for **20h** in MeOD (75 MHz)

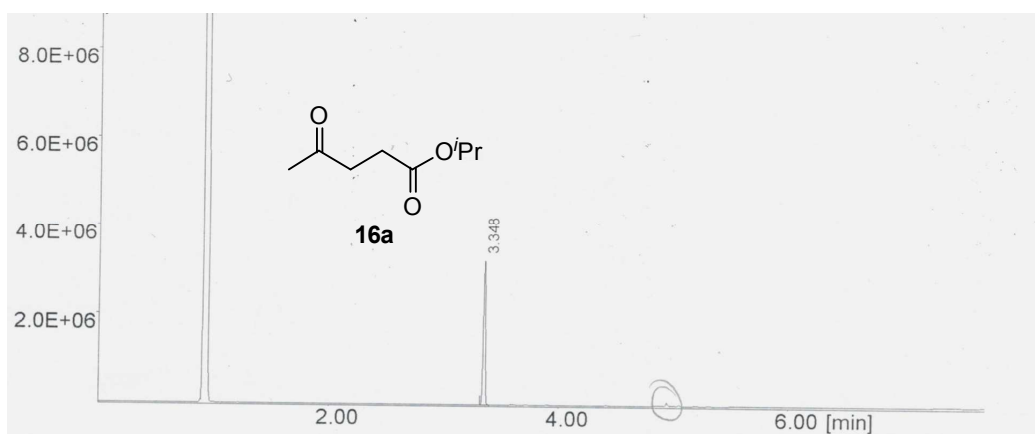
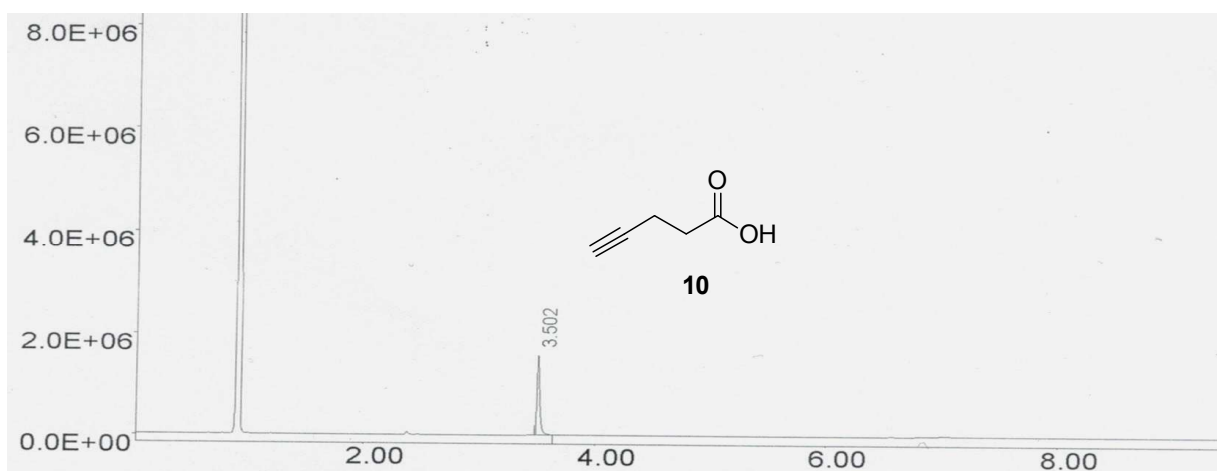
## 7. Appendix



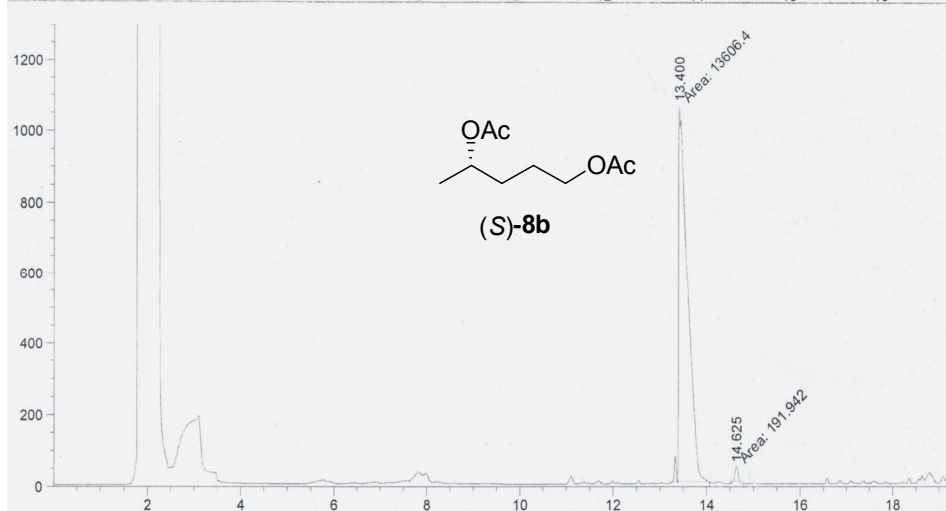
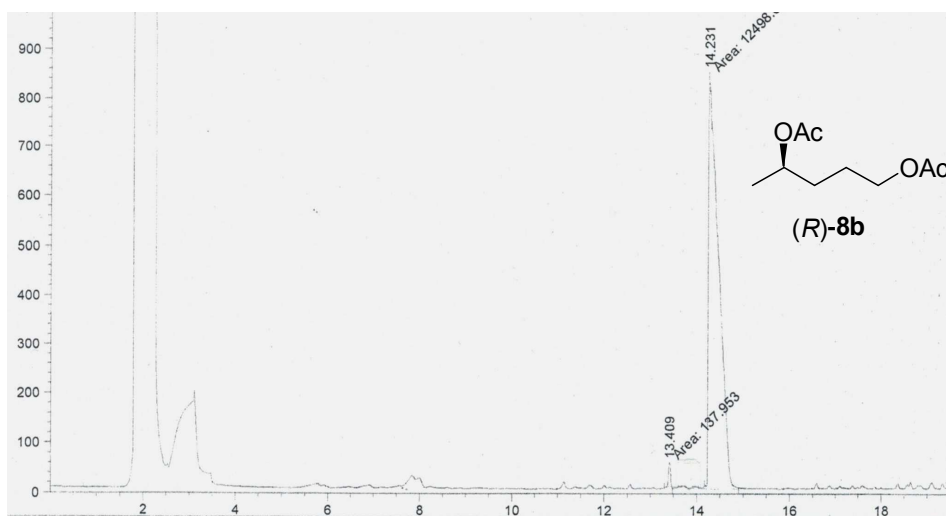
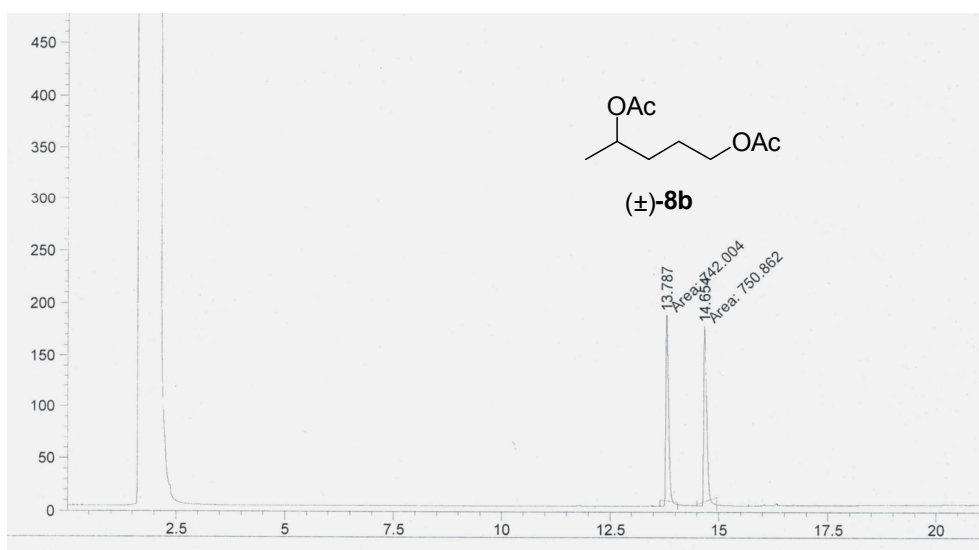
**Figure S40.** Standard of **5a** and in process GC monitoring for the cycloisomerization/hydrolysis of **5a** into **7**.



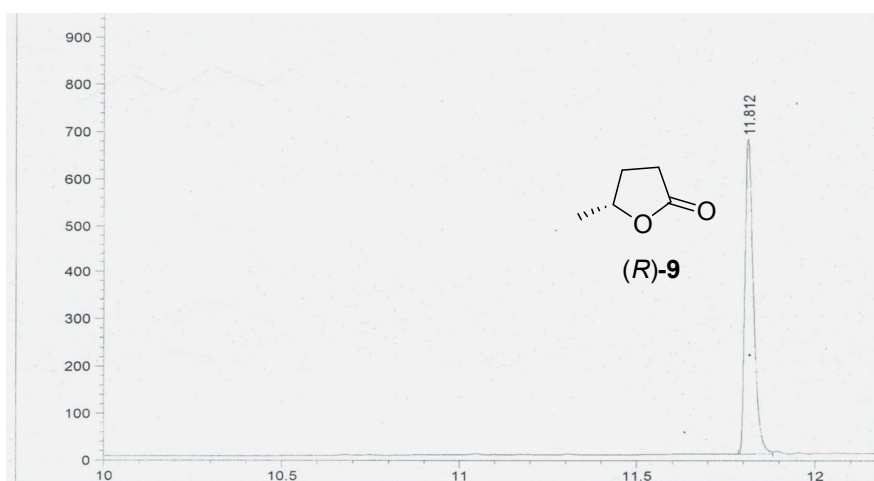
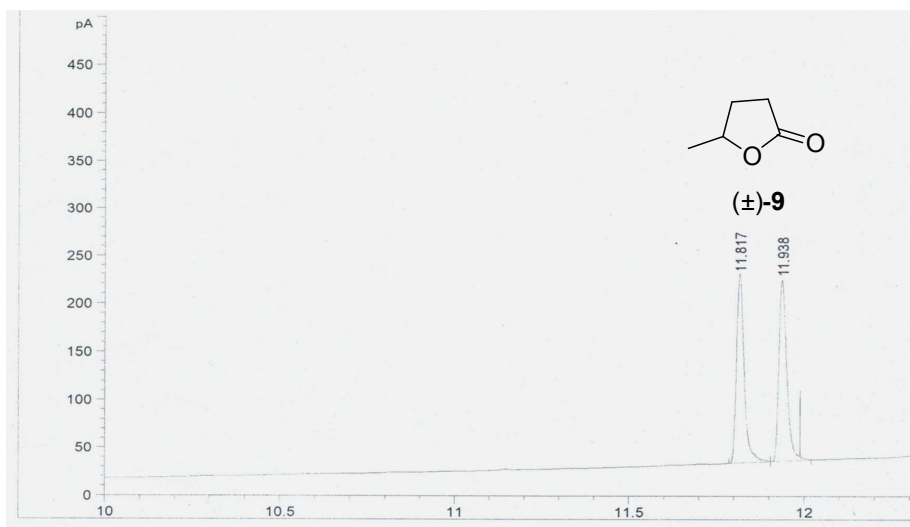
**Figure S41.** Standard of **10** and in process GC monitoring for the cycloisomerization/hydrolysis of **10** into **12**.



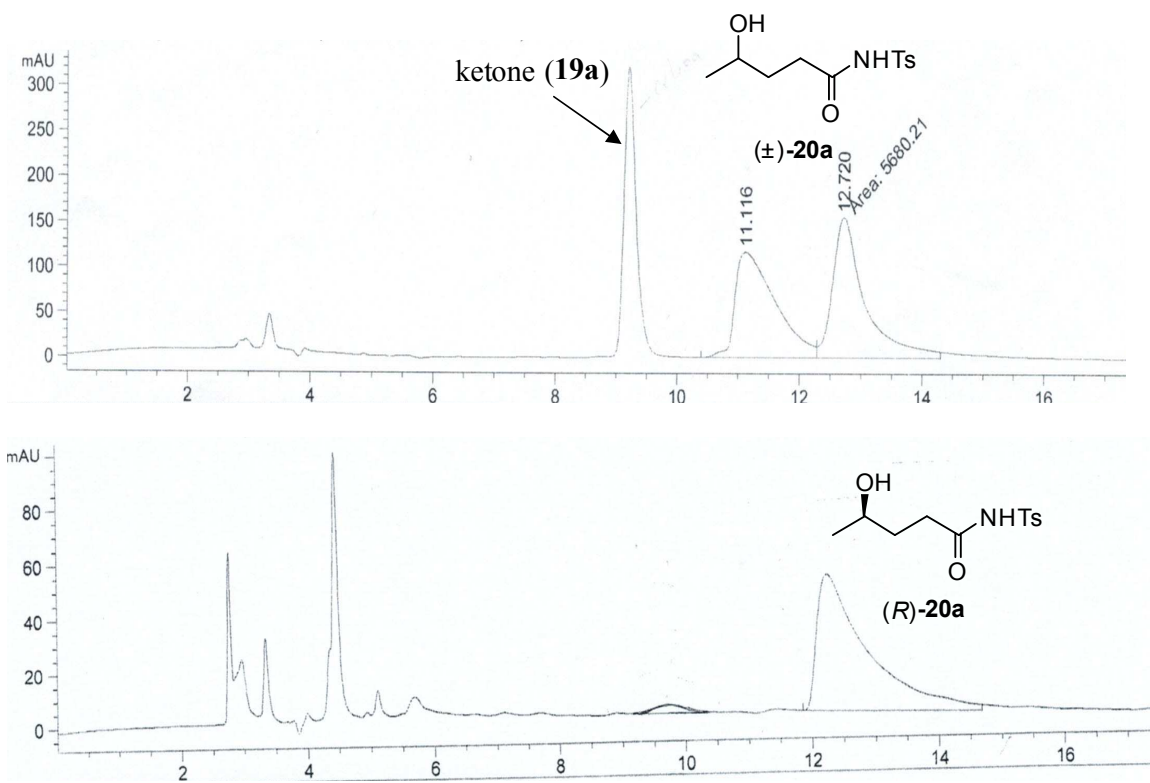
**Figure S42.** Standard of **10** and in process GC monitoring for the cycloisomerization of **10** and further esterification into **16a**.



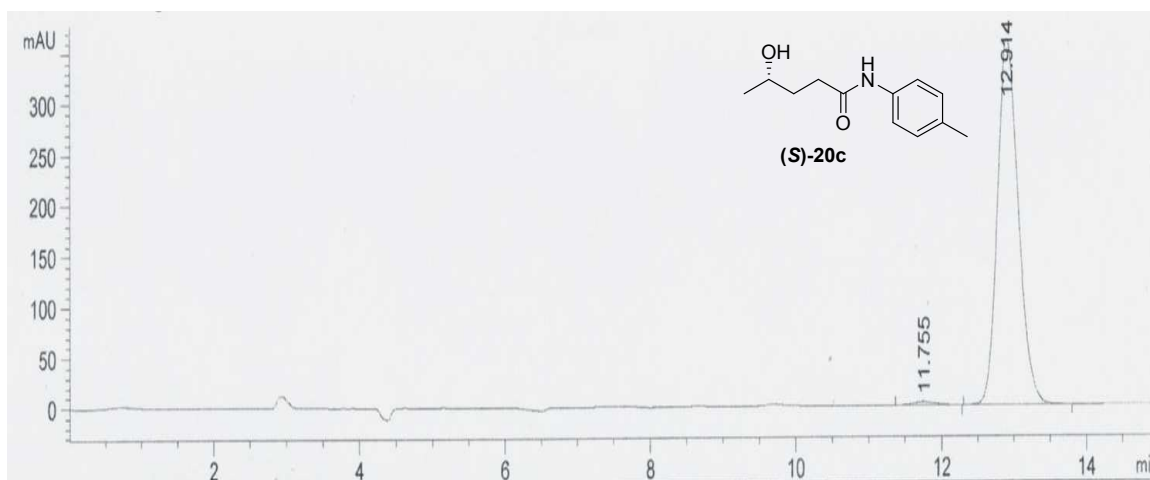
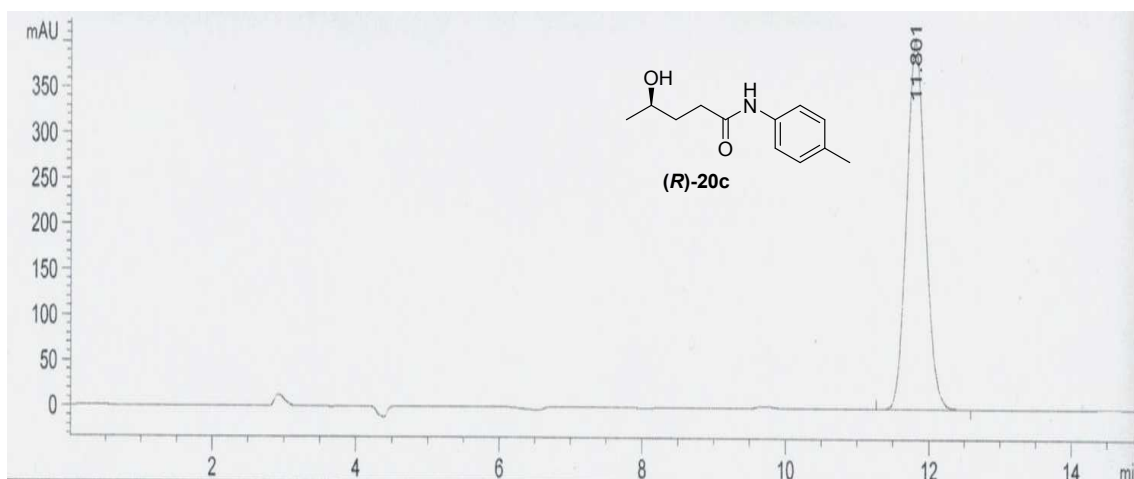
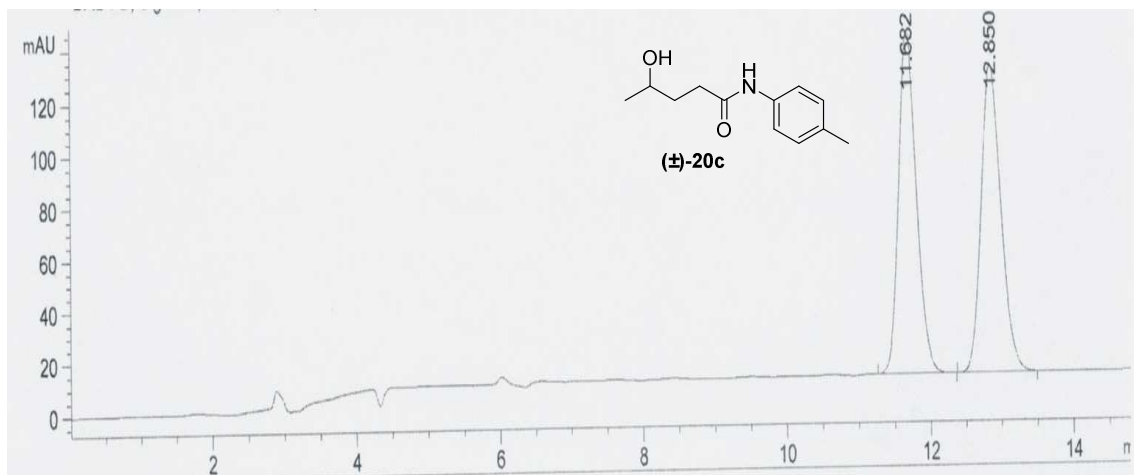
**Figure S43.** Determination of the enantiomeric excess of **8** in the sequential transformation of **5a** into **8** [Table S1, entries 1 (KRED-P1-A04) and 16 (KRED-P3-B03)].



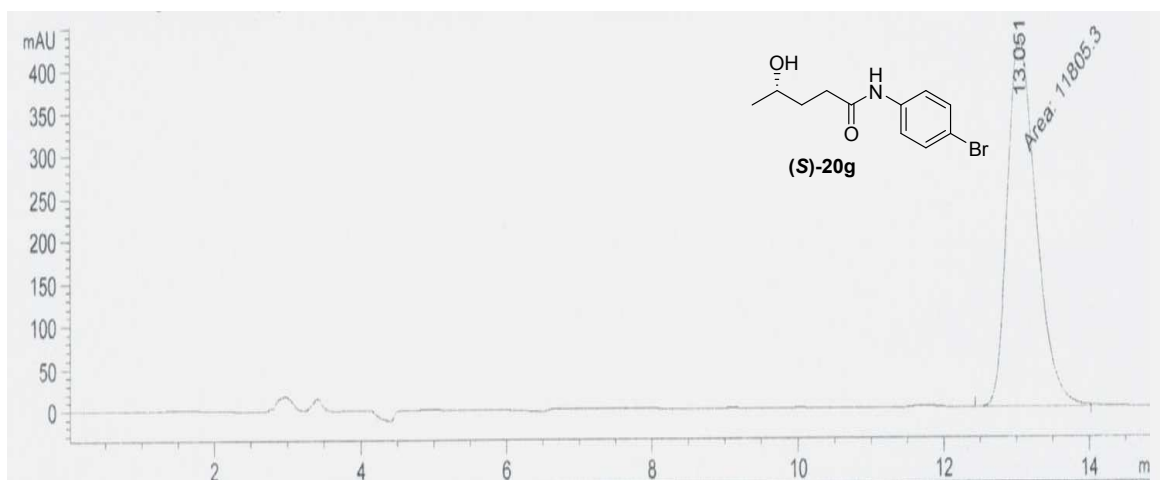
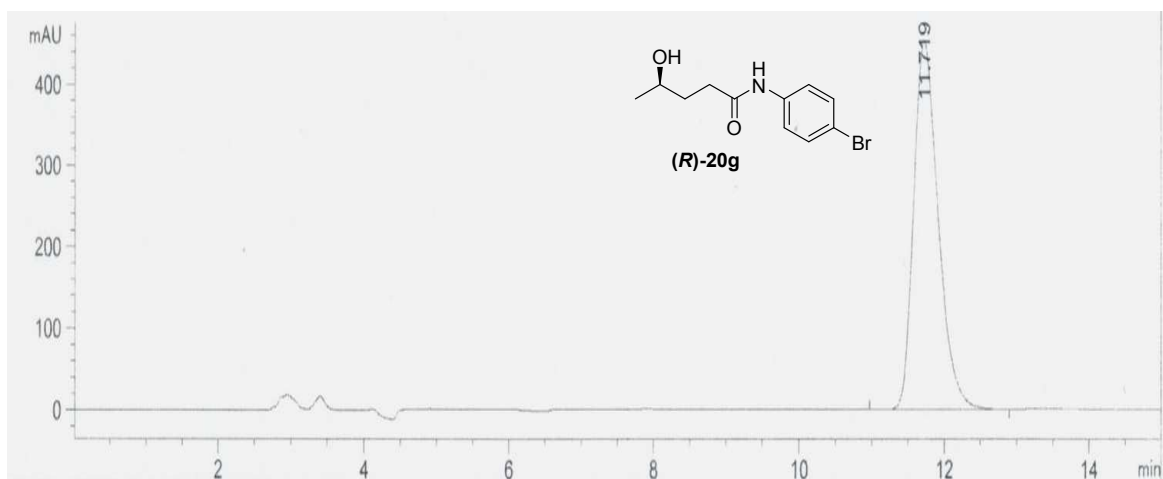
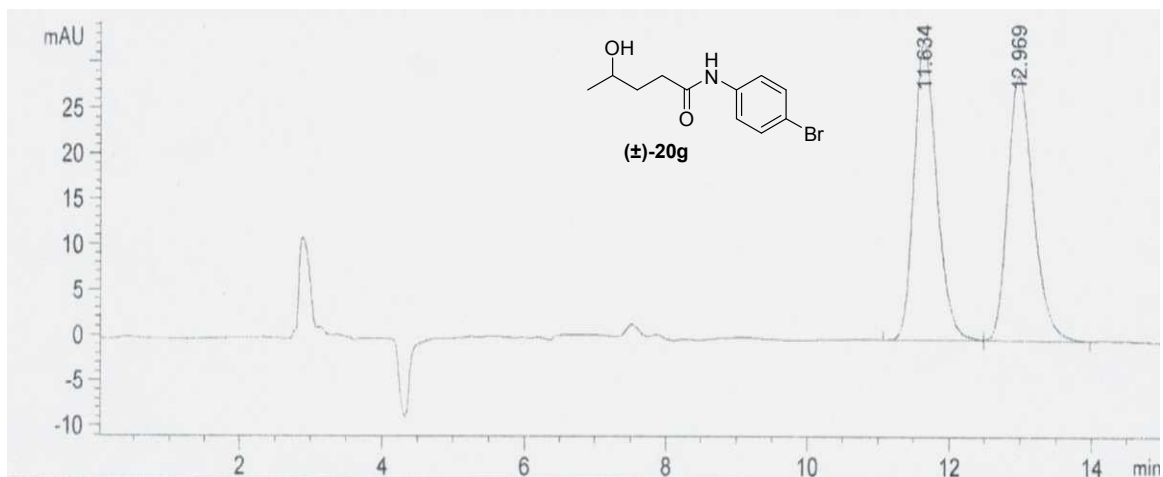
**Figure S44.** Determination of the enantiomeric excess of **9** in the sequential transformation of **10** into **9** [Table S3, entries 1 (KRED-P1-A04) and 17 (KRED-P3-H12)].



**Figure S45.** Standards of **19a** and **(±)-20a** and in process HPLC monitoring for the bioreduction of **19a** with KRED-P2-H07 (Table S5, entry 15).



**Figure S46.** Determination of the enantiomeric excess of **20c** in the bioreduction of **19c** with KRED-P1-A04 (Table S7, entry 1) and KRED-P3-B03 (Table S7, entry 16).



**Figure S47.** Determination of the enantiomeric excess of **20g** in the bioreduction of **19g** with KRED-P1-A04 (Table S11, entry 1) and KRED-P3-B03 (Table S11, entry 16).

## 8. References

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