

# Enantioselective Construction of Tetrasubstituted Stereogenic Carbons through Brønsted Base Catalyzed Michael Reactions: $\alpha'$ -Hydroxy Enones as Key Enolate Equivalent

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## 1. Materials and general techniques

**General experimental:** All non-aqueous reactions were performed using oven-dried glassware and were magnetically stirred unless otherwise stated. Yields refer to chromatographically purified and spectroscopically pure compounds, unless otherwise stated.

**Solvents and reagents:** All reagents bought from commercial sources were used as sold. Organic solvents were evaporated under reduced pressure using a Büchi rotary evaporator. Anhydrous dichloromethane was dried over  $\text{CaH}_2$ , and diethyl ether and tetrahydrofuran were dried by filtration through activated alumina (powder  $\approx$  150 mesh, pore size 58 Å, basic, Sigma aldrich) columns.

**Chromatography:** Reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F254 plates and visualised by fluorescence quenching under UV light. In addition, TLC plates were stained with a dipping solution of potassium permanganate (1 g) in 100 ml of water (limited lifetime), followed by heating. Chromatographic purification was performed on ROCC 60 silica gel 40-63  $\mu\text{m}$ .

**Melting points:** Melting points were obtained on a Stuart SHP3 melting point apparatus and microscope and are uncorrected.

**Mass spectra:** MS spectra were recorded on an ESI-ion trap Mass spectrometer (Agilent 1100 series LC/MSD, SL model)

**Infrared spectra:** Infrared spectra were recorded on a Bruker Alpha FT-IR spectrometer as a thin film. Only selected maximum absorbances are reported.

**NMR spectra:** NMR spectra were recorded using a Bruker Avance 300 MHz, 400 MHz or 500 MHz spectrometer, chemical shifts ( $\delta$ ) are quoted in parts per million referenced to the residual solvent peak. The multiplicity of each signal is designated using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; brs, broad singlet. Coupling constants ( $J$ ) are reported in Hertz (Hz).

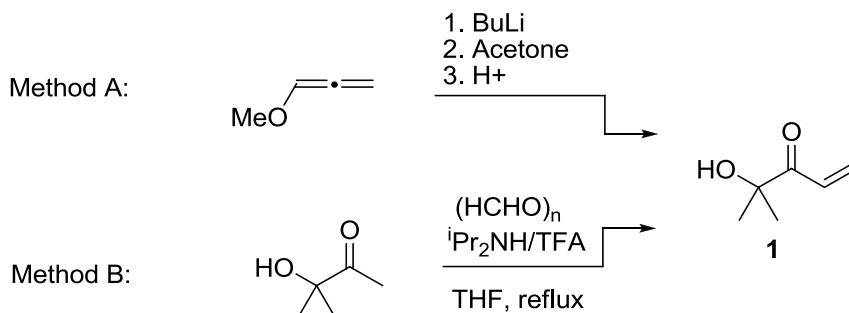
**Determination of enantiomeric excesses:** Enantiomeric excesses were determined using analytical high performance liquid chromatography (HPLC) performed on either a Waters 600 (Photodiode Array Detector Waters 2996) or a Jasco MD2010 equipped with photodiode array UV detector and CD detector systems (column and solvent conditions are given with the compound).

**Optical rotations:** Optical rotations were recorded using a Jasco P-2000 polarimeter; specific rotation (SR) ( $[\alpha]_D$ ) are reported in  $10^{-1} \text{ deg}\cdot\text{cm}^2\cdot\text{g}^{-1}$ ; concentrations ( $c$ ) are quoted in g/100 mL;  $D$  refers to the D-line of sodium (589 nm); temperatures ( $T$ ) are given in degree Celsius ( $^{\circ}\text{C}$ ).

## 2. Experimental procedures, analytical and spectroscopic data

### 2.1. Preparation of $\alpha'$ -oxy enones

#### 2.1.1. Preparation of $\alpha'$ -hydroxy enone **1**<sup>1</sup>



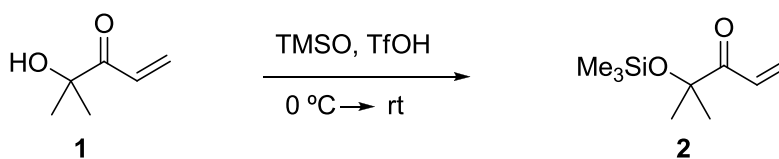
**METHOD A:**<sup>1</sup> To a solution of methoxypropadiene (3.50 g, 50 mmol) in dry Et<sub>2</sub>O (100 mL) at -40°C, nBuLi (2.5 M in hexanes, 22 mL, 55 mmol) was added under nitrogen and the reaction was stirred at -40°C for 10 min. Then, acetone (4.04 mL, 55 mmol) in dry Et<sub>2</sub>O (55 mL) was added within 5 min. The reaction was stirred at the same temperature for 0.5 h and quenched with H<sub>2</sub>O (100 mL). The resulting mixture was allowed to warm to room temperature and extracted with Et<sub>2</sub>O (3 x 100 mL). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford 2-methyl-3-methoxy-3,4-pentadien-2-ol as a yellow liquid (5.65 g) (82%) that was employed in the next step without further purification.

The material from previous step (2-methyl-3-methoxy-3,4-pentadien-2-ol, 5.65 g, 44 mmol) was added dropwise to 5% aq H<sub>2</sub>SO<sub>4</sub> (110 mL) at 0°C and the mixture was stirred for 1.5 h. After this time the reaction was allowed to warm to room temperature and the solution was saturated with solid NaCl. The mixture was extracted with Et<sub>2</sub>O (5 x 60 mL) and the combined extracts were washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed to give a yellow oil which upon distillation afforded the enone as a colorless liquid (4.42 g) (88%) b.p. 45°C (13 mmHg); IR (neat, cm<sup>-1</sup>) 3445 (OH), 1693 (C=O); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  6.73 (dd, 1H, CH, J= 9.5 Hz, J'= 16.8 Hz), 6.50 (dd, 1H, HCH, J= 2.2 Hz, J'= 16.8 Hz), 5.82 (dd, 1H, HCH, J= 2.2 Hz, J'= 10.3 Hz), 1.38 (s, 6H, 2CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  202.3, 131.1, 128.8, 75.4, 26.1

**METHOD B:**<sup>2</sup> Commercially available 3-hydroxy-3-methyl-2-butanone (1 equiv., 5.3 mL, 50 mmol) and paraformaldehyde (2 equiv., 3 g, 100 mmol) were added to a solution of iPr<sub>2</sub>NH (2 equiv., 14.0 mL, 100 mmol) and TFA (2.5 equiv., 9.6 mL, 125 mmol) in THF (250 mL). The mixture was refluxed and paraformaldehyde (2 equiv., 3 g, 100 mmol) was added every 2 h three times. The mixture was stirred at reflux overnight and then was cooled to room temperature. CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was added and the mixture was washed with 1N HCl (75 mL), 1N NaOH (75 mL) and brine (75 mL), and the organic layer was dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure (230 mbar/ bath 40 °C). The residue was purified by flash column chromatography on silica gel (eluent: diethyl ether) to afford 4-hydroxy-4-methylpent-1-en-3-one (**1**) as colorless oil. Yield: 5.0 g, 44.5 mmol, 89%.

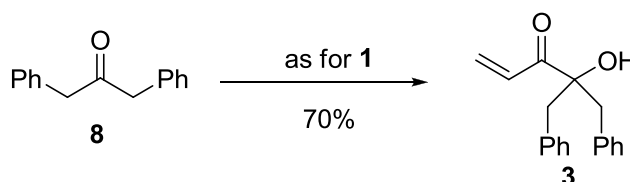


### 2.1.2. Preparation of 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one (**2**)<sup>3</sup>



3-(Trimethylsilyl)-2-oxazolidinone (TMSO) (1.5 equiv., 3.4 mL, 22.5 mmol) and 3 drops of trifluoromethanesulfonic acid were added to enone **1** (1 equiv., 1.68 g, 15 mmol). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with pentane (20 mL) and subsequently washed with water (20 mL) and NaHCO<sub>3</sub> sat. (20 mL), dried with MgSO<sub>4</sub> and concentrated under reduced pressure to afford the title compound (**2**) as colorless oil. Yield: 2.6 g, 14.0 mmol, 93%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>),  $\delta$  = 7.03 (dd,  $J$  = 17.3, 10.4 Hz, 1H), 6.38 (dd,  $J$  = 17.3, 2.1 Hz, 1H), 5.72 (dd,  $J$  = 10.4, 2.1 Hz, 1H), 1.37 (s, 6H), 0.14 (s, 9H).

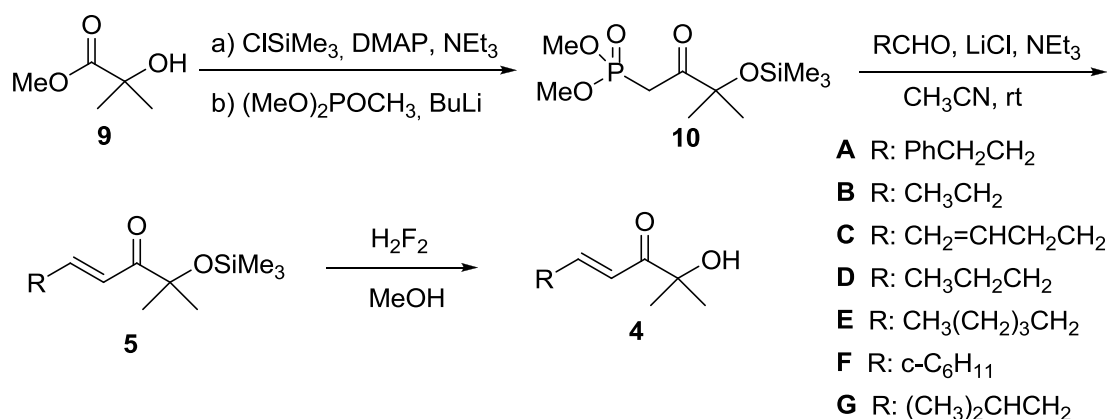
### 2.1.3. Preparation of $\alpha'$ -hydroxy enone **3**



The same procedure as for enone **1** was employed, but this time starting from 1,3-dimethylacetone **8** (9.25 g, 44 mmol) and allowing the reaction mixture to stir overnight (16 h) for the hydrolysis step. The solid crude material was purified by flash chromatography (silica gel, hexane-EtOAc 20:1) (8.20 g) (70%). m.p. 89-91 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.29 – 7.19 (m, 10H), 6.98 (dd,  $J$ =10.4 Hz,  $J$ =17.0 Hz, 1H), 6.40 (dd,  $J$ =1.7 Hz,  $J$ =17.0 Hz, 1H), 5.83 (dd,  $J$ =1.7 Hz,  $J$ =10.4 Hz, 1H), 3.76 (s, 1H), 3.22 (d,  $J$ =14.0 Hz, 2H), 3.13 (d,  $J$ =14.0 Hz, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  200.9, 135.3, 130.7, 130.3, 129.9, 128.1, 126.9, 81.6, 44.3.

### 2.1.4. Preparation of alkyl-substituted $\alpha'$ -hydroxy enones **4A-G**.

(Palomo et al. *J. Am. Chem. Soc.* **2004**, 126, 9188; *J. Am. Chem. Soc.* **2005**, 127, 4154)



STEP 1: Preparation of (3-methyl-2-oxo-3-trimethylsilyloxybutyl)phosphonic acid dimethyl ester **10**.

(Adapted from: a) P. Sampson, V. Roussis, G. J. Drtina, F. L. Koerwitz, D. F. Wiemer, *J. Org. Chem.* **1986**, *51*, 2525-2529, and b) D. G. McCarthy, C. C. Collins, J. P. O'Driscoll, S. E. Lawrence, *J. Chem. Soc., Perkin Trans. 1* **1999**, 3667-3675).

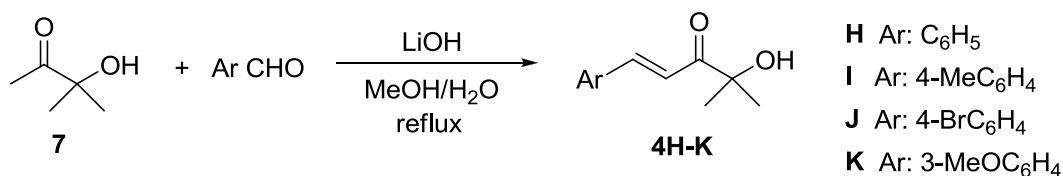
Methyl 2-hydroxyisobutyrate (6.9 mL, 60 mmol) was added under a nitrogen atmosphere to a solution of dimethyl amino pyridine (1.22 g, 10 mmol), triethylamine (10 mL, 50 mmol) and trimethylchlorosilane (6.3 mL, 50 mmol) in 50 mL of dichloromethane. The reaction mass was stirred at room temperature for 24 hours. After filtering over celite to remove the salt, the filtrate was diluted with diethyl ether (150 mL) and the resulting solution was washed with brine (1 x 50 mL) and water (1 x 50 mL). The solvent was removed under reduced pressure to give the triethylsilyl ether. Yield: 12.6 g (92%). No further purification is needed. Dimethyl methyl phosphonate (13.8 mL, 130 mmol, 2.5 eq) in dry THF (40 mL) was added drop-wise to a cold solution of *n*BuLi (1.6 M in hexanes, 79 mL, 130 mmol) in dry THF (80 mL) at -78 °C under a nitrogen atmosphere. After stirring the resulting solution for 30 min, a solution of the crude triethylsilyl ether prepared above (12 g, 51 mmol) in dry THF (100 mL) was added dropwise at -78 °C. The mixture was stirred at the same temperature (-78 °C) for 3h and then quenched at this temperature with saturated ammonium chloride solution (200 mL). After allowing reaction mass to come to room temperature, it was extracted with diethyl ether (3 x 250 mL), dried over MgSO<sub>4</sub> and the solvent was evaporated under reduced pressure to get the title compound. Yield: 14.6 g (99 %). It was used for the next step without further purification.

#### STEP 2: Preparation of enones **5A-G** and their desilylation to **4A-G**:

Dried LiCl (1.17 g, 27 mmol) and Et<sub>3</sub>N (3.8 mL, 27 mmol) were added successively to a solution of (3-methyl-2-oxo-3-trimethylsilyloxybutyl)phosphonic acid dimethyl ester (7.95 g, 27 mmol) in dry MeCN (67 mL). The resulting milky suspension was stirred for 15 min at room temperature and the corresponding aliphatic aldehyde (27 mmol) was added drop-wise. The mixture was stirred for 40 h, diluted with water and extracted with Et<sub>2</sub>O. The organic layer was dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The crude was dissolved in methanol (200 mL) and a solution of hydrofluoric acid (HF) (48% in water, 5 mL) was added. The resulting mixture was stirred 0.5 h at room temperature and then was neutralized by addition of saturated solution of NaHCO<sub>3</sub>. The reaction mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 100 mL) and the combined organic layers were dried over MgSO<sub>4</sub> and evaporated to afford the crude desilylated product that was purified by flash chromatography (silica gel, hexane-EtOAc 40:1).

#### 2.1.5. Preparation of aryl-substituted $\alpha'$ -hydroxy enones **4H-K**.

(Palomo et al. *J. Am. Chem. Soc.* **2004**, *126*, 9188; *J. Am. Chem. Soc.* **2005**, *127*, 4154)



3-Hydroxy-3-methyl-2-butanone **7** (5.0 g, 49 mmol) was dissolved in a mixture of MeOH (120 mL) and H<sub>2</sub>O (40 mL). Freshly distilled aldehyde (87.5 mmol) was then added followed by LiOH·H<sub>2</sub>O (10.28 g, 245 mmol). The reaction was stirred at reflux for 3 h, and after removal of MeOH under reduced pressure, the aqueous residue was diluted with H<sub>2</sub>O (40 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 100 mL). The CH<sub>2</sub>Cl<sub>2</sub> extracts were combined, dried over MgSO<sub>4</sub> and concentrated. The crude product was purified by column chromatography (silica gel, hexane-EtOAc 50:1).

## Representative data of $\alpha'$ -hydroxy enones 4

### (E)-2-Hydroxy-2-methyl-7-phenyl-hept-4-en-3-one (4A)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.28–7.21 (m, 6H), 6.41 (d,  $J=15.5$  Hz, 1H), 3.98 (s, 1H), 2.8 (t,  $J=8$  Hz, 2H), 2.59 (m, 2H), 1.34 (s, 6H).

### (E)-2-Hydroxy-2-methylhept-4-en-3-one (4B)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.15 (m, 1H), 6.38 (d,  $J=15$  Hz, 1H), 4.0 (s, 1H), 2.27 (m, 2H), 1.36 (s, 6H), 1.08 (t,  $J=6.0$  Hz, 3H).

### (E)-2-hydroxy-2-methylnona-4,8-dien-3-one (4C)

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.14 (dt,  $J=15.4, 6.7$  Hz, 1H), 6.43 (dt,  $J=15.3, 1.5$  Hz, 1H), 5.80 (ddt,  $J=16.6, 10.2, 6.4$  Hz, 1H), 5.13 – 4.97 (m, 2H), 3.96 (s, 1H), 2.45 – 2.32 (m, 2H), 2.32 – 2.14 (m, 2H), 1.38 (s, 6H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  202.4, 145.0, 137.0, 122.8, 115.9, 75.3, 32.1, 26.5.

### (E)-2-Hydroxy-2-methyloct-4-en-3-one (4D)

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.12 (dt,  $J=15.3, 7.0$  Hz, 1H), 6.40 (dt,  $J=15.3, 1.5$  Hz, 1H), 3.98 (s, 1H), 2.22 (qd,  $J=7.3, 1.5$  Hz, 2H), 1.50 (h,  $J=7.3$  Hz, 2H), 1.36 (s, 6H), 0.92 (t,  $J=7.4$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  202.5, 151.0, 122.5, 75.3, 53.6, 34.9, 26.5, 21.4, 13.8.

### (E)-2-Hydroxy-2-methyldec-4-en-3-one (4E)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.16 (td,  $J=7.0$  Hz,  $J=15.3$  Hz, 1H), 6.42 (dt,  $J=1.5$  Hz,  $J=15.3$  Hz, 1H), 2.26 (qd,  $J=1.5$  Hz,  $J=7.3$  Hz, 2H), 1.55 – 1.43 (m, 2H), 1.39 (s, 6H), 1.36 – 1.30 (m, 5H), 0.90 (t,  $J=7.0$  Hz, 3H).

### (E)-1-Cyclohexyl-4-hydroxy-4-methylpent-1-en-3-one (4F)

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.10 (dd,  $J=15.5, 7.0$  Hz, 1H), 6.36 (dd,  $J=15.5, 1.4$  Hz, 1H), 4.00 (s, 1H), 2.18 (m, 1H), 1.85 – 1.64 (m, 4H), 1.38 (s, 6H), 1.33 – 1.10 (m, 4H), 0.91 – 0.81 (m, 2H).

### (E)-2-Hydroxy-2,7-dimethyloct-4-en-3-one (4G)

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.13 (dt,  $J=15.1, 7.5$  Hz, 1H), 6.40 (dt,  $J=15.3, 1.4$  Hz, 1H), 3.98 (s, 1H), 2.15 (ddd,  $J=7.4, 6.8, 1.4$  Hz, 2H), 1.80 (dp,  $J=13.4, 6.7$  Hz, 1H), 1.39 (s, 6H), 0.94 (d,  $J=6.7$  Hz, 6H).

### (E)-2-Hydroxy-2-methyl-5-phenylpent-4-en-3-one (4H)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.83 (d,  $J=15.7$  Hz, 1H), 7.58 (m, 2H), 7.40 (m, 3H), 7.02 (d,  $J=15.4$  Hz, 1H), 4.00 (s, 1H), 1.45 (s, 6H).

### (E)-4-Hydroxy-4-methyl-1-(p-tolyl)pent-1-en-3-one (4I)

The enone was prepared according to general procedure from 3-hydroxy-3-methyl-2-butanone and 4-methylbenzaldehyde (3.4 mL, 60 mmol). 4.4 g (75%);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.84 (d,  $J=15.6$  Hz, 1H), 7.50 (dd,  $J=7.3, 1.1$  Hz, 2H), 7.29 – 7.16 (m, 2H), 6.99 (d,  $J=15.7$  Hz, 1H), 2.39 (s, 3H), 1.46 (s, 7H).

### (E)-1-(4-Bromophenyl)-4-hydroxy-4-methylpent-1-en-3-one<sup>4</sup> (4J)

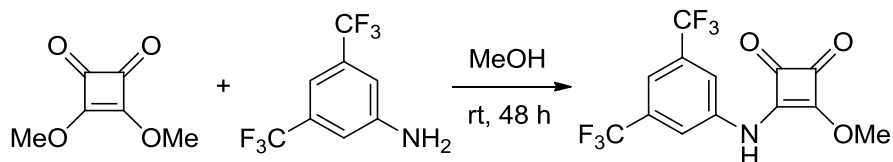
The enone was prepared according to general procedure from 3-hydroxy-3-methyl-2-butanone and 4-bromobenzaldehyde (10 g, 60 mmol). 6.5 g (85%); yellow oil;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.77 (d,  $J=16.0$  Hz, 1H), 7.54 (d,  $J=8.5$  Hz, 2H), 7.46 (d,  $J=8.5$  Hz, 2H), 7.03 (d,  $J=15.5$  Hz, 1H), 3.88 (s, 1H), 1.46 (s, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  202.4, 144.3, 133.3, 132.4, 130.1, 125.5, 119.1, 75.7, 26.6.

**(E)-4-Hydroxy-1-(3-methoxyphenyl)-4-methylpent-1-en-3-one (4K)**

The enone was prepared according to general procedure from 3-hydroxy-3-methyl-2-butanone and 3-methoxybenzaldehyde (6.6 mL, 60 mmol). 4.6 g (75%); yellow oil; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.75 (d, J = 15.7 Hz, 1H), 7.25 (d, J = 7.9 Hz, 1H), 7.19 – 7.03 (m, 3H), 6.92 (ddd, J = 8.2, 2.6, 1.0 Hz, 1H), 3.78 (s, 3H), 1.44 (s, 6H).

## 2.2. Preparation of catalysts

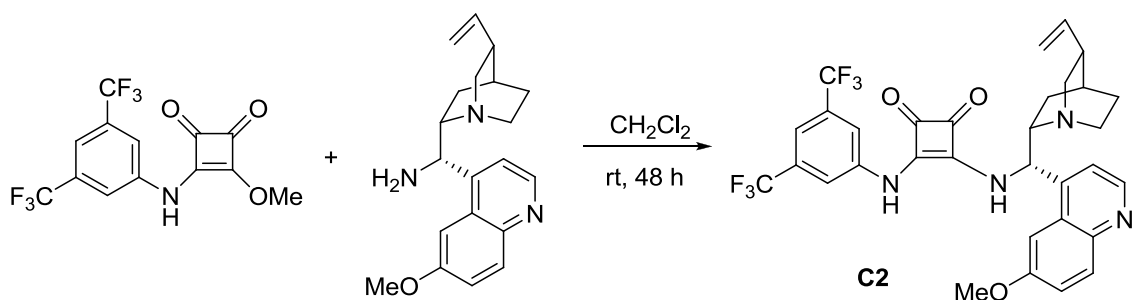
### a) Preparation of common squaric ester monoamide intermediate



To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (1.42 g, 10.0 mmol) in MeOH (20 mL) was added 3,5-bis(trifluoromethyl)aniline (1.56 mL, 10.0 mmol). The reaction mixture was stirred at room temperature for 48 h. The formed precipitate was filtered and dried in vacuo to give desired product (2.25 g, 6.6 mmol, 66%). m.p. 179-181 °C. All spectroscopic data were identical to those reported in literature.<sup>55</sup>

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 11.18 (s, 1H), 8.04 (s, 2H), 7.78 (s, 1H), 4.41 (s, 3H).

### b) Preparation of Catalyst C2<sup>5</sup>

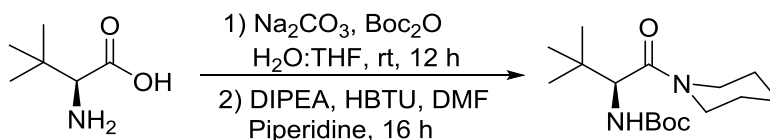


To a solution of squaric ester monoamide prepared as above (339 mg, 1.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) 9-amino-9-deoxyepiquinine<sup>6</sup> (323 mg, 1.0 mmol) was added. The reaction mixture was stirred for 48 h at room temperature, the solvent evaporated, and the product submitted to purification by silica gel column chromatography. White solid (441 mg, 0.70 mmol, 70% yield); m.p. 224-225 °C. All spectroscopic data were identical to those reported in literature.<sup>5</sup>

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 9.88 (br s, 1H), 8.80 (d, *J* = 4.5 Hz, 1H), 8.36 (br s, 1H), 8.04 – 7.86 (m, 3H), 7.76 (d, *J* = 10.0 Hz, 1H), 7.67 (d, *J* = 4.5 Hz, 1H), 7.58 (s, 1H), 7.47 (d, *J* = 6.8 Hz, 1H), 6.19 – 5.73 (m, 2H), 5.13 – 4.92 (m, 2H), 3.95 (s, 3H), 3.52-3.42 (m, 1H), 3.30- 3.25 (m, 1H) 2.77 – 2.58 (m, 2H), 2.35 – 2.20 (m, 1H), 1.60 – 1.47 (m, 4H), 0.66 (m, 1H).

### b) Preparation of Catalyst C3

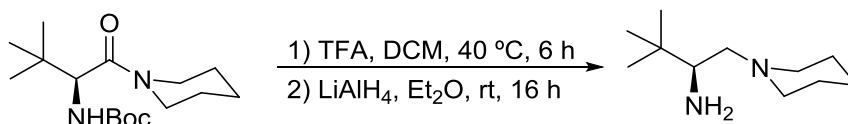
Step 1) Protection of the amine and amide formation<sup>7</sup>



Na<sub>2</sub>CO<sub>3</sub> (2.12 g, 20 mmol, 2 equiv.) and Boc<sub>2</sub>O (3.3g, 15 mmol, 1.5 equiv.) were added to a solution of *t*-leucine (1.31 g, 10 mmol, 1 equiv.) in water (20 mL) and THF (5 mL) at 0 °C. After stirring for 12 h at room temperature HCl (10 %) was added until pH 2 and the mixture was extracted with EtOAc (3 x 30 mL). The aqueous phases were united and washed with brine (50 mL) and dried over MgSO<sub>4</sub>, after which the solvent was removed under reduced pressure. The residue was then redissolved in dry DMF dissolution (20 mL) and DIPEA (2.58 g, 20 mmol, 2 equiv.) and HBTU (5.7 gm 15 mmol, 1,5 equiv.) were added. After stirring for 1 h piperidine (0.94 g, 11 mmol, 1.1 equiv.) was added and the mixture was stirred for further 16 h. The reaction was quenched adding HCl 1 M (20 mL) and the mixture was extracted with EtOAc (2 x 20 mL). The organic phases were united and washed with a HCl 1 M and brine (20 mL) and dried over MgSO<sub>4</sub>, after which the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ EtOAc 85/15) to afford *tert*-butyl (S)-(3,3-dimethyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)carbamate as a white solid. Yield: 2.5 g, 8.3 mmol, 83%. All spectroscopic data were identical to those reported in the literature.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ= 0.98 (s, 9H), 1.43 (s, 9H), 1.52 – 1.62 (m, 6H), 3.46 – 3.69 (m, 4 H), 4.54 (d, *J* = 9.7 Hz, 1H), 5.38 (d, *J* = 9.6 Hz, 1H).

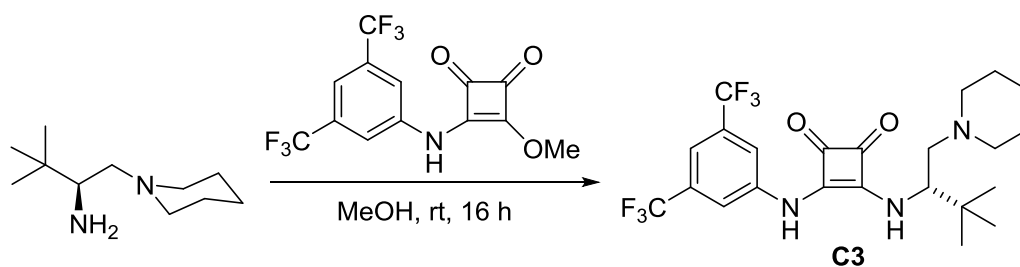
#### Step 2) Deprotection and reduction<sup>7</sup>



Previously obtained amide (2.5 g, 8 mmol, 1 equiv.) was dissolved in a mixture of CH<sub>2</sub>Cl<sub>2</sub> (8 mL) and trifluoroacetic acid (2 mL) and stirred at 40 °C until no more starting material was observed by TLC (eluting with hexane/ EtOAc 70/30). The solvent was then removed under reduced pressure and the residue was redissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The solution was washed with NaOH (40 %), dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure obtaining the aminoamide as a yellow oil. The aminoamide was then dissolved in dry diethyl ether (10 mL) and was added dropwise over a suspension of lithium aluminiumhydride (879 mg, 24 mmol, 3 equiv.) in diethyl ether (40 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred at the same temperature for some minutes and afterwards it was stirred at room temperature for 16 h. The reaction was quenched adding water (1.2 mL), NaOH 15 % (1,2 mL) and water (3.6 mL) at 0 °C. The result was filtered and the liquid was extracted with diethyl ether (2 x 10 mL). The combined organic layers were dried over MgSO<sub>4</sub> and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ EtOAc 1/1) to afford (S)-3,3-dimethyl-1-(piperidin-1-yl)butan-2-amine as yellow oil. Yield: 1.16 g, 6.8 mmol, 92%. All spectroscopic data were identical to those reported in the literature.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ= 2.66 (dd, *J* = 11.0, 2.5 Hz, 1H), 2.52 (d, *J* = 12.3 Hz, 4H), 2.28 (dd, *J* = 12.3, 2.8 Hz, 3H), 2.13 (dd, *J* = 12.1, 11.2 Hz, 1H), 1.61-1.53 (m, 4H), 1.44 – 1.42 (m, 2H), 0.90 (s, 9H).

#### Step 3) Formation of catalyst **C3**<sup>8</sup>



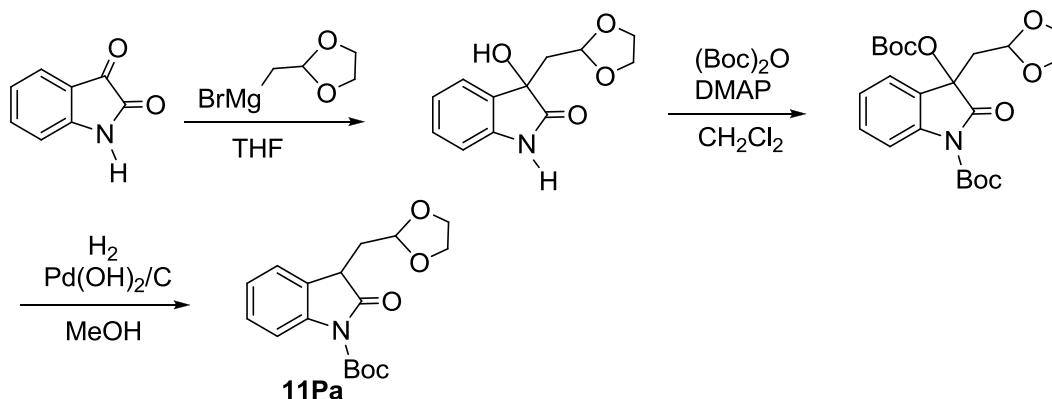
To a solution of the diamine (780 mg, 4,6 mmol, 1 equiv.) in methanol (30 mL) the squaric ester monoamide obtained above (1.56 g, 4,6 mmol, 1 equiv.) was added and the mixture was stirred until complete disappearance of the starting amide as monitored by TLC (16 h). The formed white precipitate was filtered and washed with  $\text{CH}_2\text{Cl}_2$  to afford essentially pure **C3** as a white solid. m. p. 246–248 °C. Yield: 1.29 g, 2.6 mmol, 59%. All spectroscopic data were identical to those reported in the literature.<sup>8</sup>

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  10.09 (s, 1H), 8.08 (s, 2H), 7.64 (s, 1H), 4.07 – 3.93 (m, 1H), 2.49 – 2.04 (m, 5H), 1.51 – 1.22 (m, 6H), 0.93 (s, 9H).

## 2.3. Preparation of pronucleophiles

### 2.3.1. Preparation of oxindoles 11

a) Oxindoles **11Aa**, **11Ac**, **11Ba**, **11Ca**, **11Da**, **11Dd**, **11Eb**, **11Ga**, **11Gc**, **11Gd**, **11Ha**, **11Ia**, **11Ja**, **11Pa** were prepared according to the following representative procedure:<sup>9</sup>



#### ***tert*-Butyl 3-(1,3-dioxolan-2-ylmethyl)-2-oxoindoline-1-carboxylate (**11Pa**)**

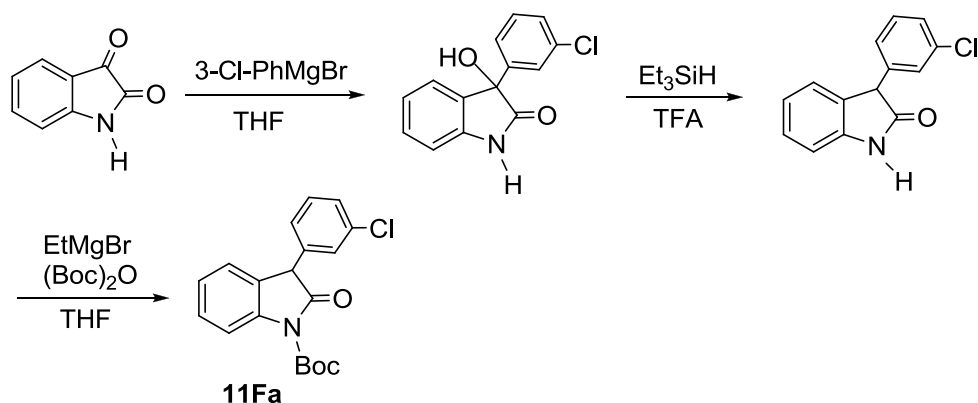
A solution of (1,3-dioxolan-2-ylmethyl)magnesium bromide in THF (0.5M, 40 mL, 20 mmol) was added to a stirred cold (-40 °C) suspension of isatin (1.47 g, 10 mmol) in THF (30 mL) under an atmosphere of N<sub>2</sub>. The mixture was allowed to warm to room temperature and was stirred until isatin was consumed. The reaction mixture was diluted with ether, cooled in an ice-bath, and then quenched with 1N HCl. The aqueous layer was extracted with ether and the combined organic layers were washed with water and brine and then dried over Na<sub>2</sub>SO<sub>4</sub>. After the removal of solvent, purification by flash column chromatography (hexane/ethyl acetate 1/1) was carried out to give the hydroxy oxindole in 35% yield (0.83 g) as an orange solid.

This pure compound (0.83 g, 3.53 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (35 mL) and cooled to 0 °C. To this solution were added DMAP (43 mg, 0.35 mmol) and (Boc)<sub>2</sub>O (1.7 g, 7.8 mmol) and the mixture was stirred at room temperature for 12 h. The reaction mixture was then cooled to 0 °C and quenched with saturated aqueous NH<sub>4</sub>Cl. The aqueous layer was extracted with ethyl acetate, the combined organic layers were washed with 0.5N HCl and saturated solution of NaHCO<sub>3</sub> and then dried over Na<sub>2</sub>SO<sub>4</sub>. After the removal of solvent, purification by flash column chromatography (hexane/ethyl acetate 10/1) afforded Boc-protected indole in 63% yield (960 mg) as a yellow solid.

This compound (900 mg, 2.07 mmol) was dissolved in methanol (25 mL). Pd(OH)<sub>2</sub>/C (422 mg) was added to this solution, and the resulting mixture was stirred under hydrogen atmosphere (balloon) for 4 h at room temperature. The reaction mixture was then passed through celite to remove Pd(OH)<sub>2</sub>/C. After the removal of solvent, the crude product was purified by flash column chromatography (hexane/ethyl acetate 10/1) to give **11Pa** in 35% yield (229 mg).

b) Oxindole **11Fa** was prepared according to the following representative procedure:<sup>9</sup>





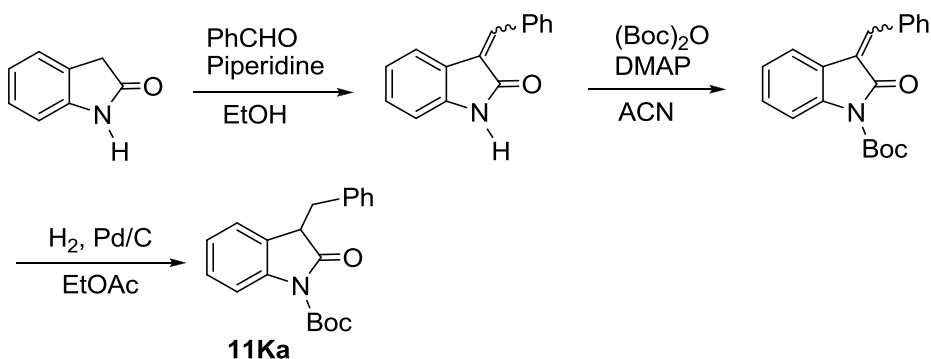
***tert*-Butyl 3-(3-chlorophenyl)-2-oxindole-1-carboxylate (**11Fa**)**

A solution of 3-chlorophenylmagnesium bromide in THF (1M, 25 mL, 25 mmol) was added to a stirred cold (-40 °C) suspension of isatin (1.47 g, 10 mmol) in THF (30 mL) under an atmosphere of N<sub>2</sub>. The mixture was allowed to warm to room temperature and was stirred until isatin was consumed. The reaction mixture was diluted with ether, cooled in an ice-bath, and then quenched with 1N HCl. The aqueous layer was extracted with ether and the combined organic layers were washed with water and brine and then dried over Na<sub>2</sub>SO<sub>4</sub>. After the removal of solvent, purification by flash column chromatography (hexane/ethyl acetate 5/1) was carried out to give the corresponding hydroxy oxindole in 94% yield (2.45 g) as a white solid.

A mixture of this pure compound (520 mg, 2 mmol), Et<sub>3</sub>SiH (698 mg, 6 mmol), and TFA (684 mg, 6 mmol) was heated at 110-120 °C in a sealed tube for 41 h. Excess Et<sub>3</sub>SiH and TFA were evaporated and the resulting residue was purified by flash chromatography (hexane/ethyl acetate 5/1) to afford the chlorophenyl derivative (448 mg, 92%).

This compound (327 mg, 1.34 mmol) was dissolved in THF (7 mL). To this solution were added EtMgBr (1M, 1.34 mL, 1.34 mmol) and (Boc)<sub>2</sub>O (323 mg, 1.48 mmol) at -40 °C, and then allowed to stir at room temperature for 4 h. The reaction mixture was diluted with ether and then quenched with saturated aqueous NH<sub>4</sub>Cl. The aqueous layer was extracted with ether and the combined organic layers were washed with water and brine and then dried over Na<sub>2</sub>SO<sub>4</sub>. After the removal of solvent, purification by flash column chromatography (hexane/ethyl acetate 20/1) was carried out to afford **11Fa** in 85% yield (392 mg) as a white foam.

c) Oxindoles **11Ka** and **11La** were prepared according to the following representative procedure:<sup>10</sup>



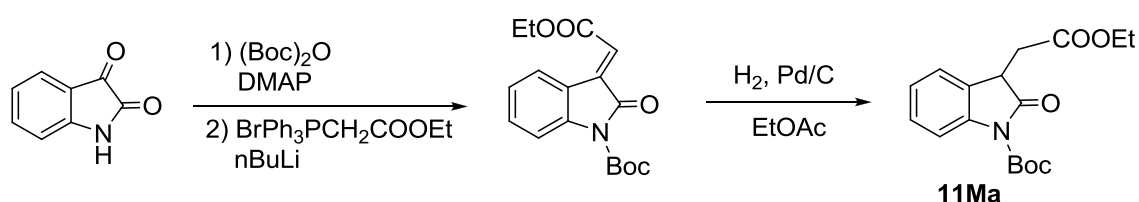
### ***tert*-Butyl 3-benzyl-2-oxoindoline-1-carboxylate (**11Ka**)**

To a solution of oxindole (2.66 g, 20 mmol) in EtOH (20 mL) were added benzaldehyde (2.33 g, 22 mmol) and piperidine (3.41 g, 40 mmol). The reaction was then heated to reflux for 2.5 h. After cooling to 0 °C, the orange-colored precipitate formed was filtered, washed with cold EtOH and dried under vacuum. Crude phenylmethylene derivative is obtained in 65% yield (2.86 g) and used in next step without further purification.

The crude material (2.86 g, 12.92 mmol) was dissolved in acetonitrile (80 mL) and cooled to 0 °C. To this solution were added DMAP (159 mg, 1.3 mmol) and (Boc)<sub>2</sub>O (2.97 g, 13.6 mmol) and the mixture was stirred at room temperature for 12 h. The reaction mixture was then cooled to 0 °C and quenched with saturated aqueous NH<sub>4</sub>Cl. The aqueous layer was extracted with ethyl acetate, the combined organic layers were washed with 0.5N HCl and saturated solution of NaHCO<sub>3</sub> and then dried over Na<sub>2</sub>SO<sub>4</sub>. After the removal of solvent, crude Boc-protected indole is obtained in 98% yield (4.05 g) and used in next step without further purification.

This compound (4.0 g, 12.45 mmol) was dissolved in ethyl acetate (125 mL). Pd/C (2.1 g) was added to this solution, and the resulting mixture was stirred under hydrogen atmosphere (balloon) for 12 h at room temperature. The reaction mixture was then passed through celite to remove Pd/C. After the removal of solvent, the crude product was purified by flash column chromatography (hexane/ethyl acetate 20/1) to give **11Ka** in 94 % yield (3.78 g).

d) Oxindole **11Ma** was prepared according to the following representative procedure:<sup>11</sup>



### ***tert*-Butyl 3-(2-ethoxy-2-oxoethyl)-2-oxoindoline-1-carboxylate (**11Ma**)**

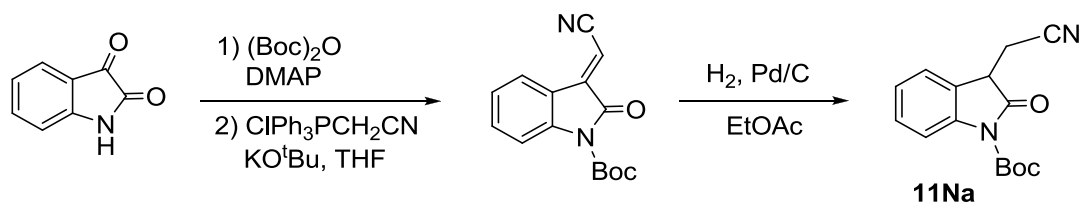
A mixture of isatin (1.47 g, 10 mmol) and DMAP (122 mg, 1 mmol) in THF (14 mL) was cooled in an ice-bath with stirring and a solution of (Boc)<sub>2</sub>O (2.62 g, 12 mmol) in THF (6 mL) was added slowly. The solution was stirred for 2 h to give the Boc-protected isatin solution in THF.

In another flask (ethoxycarbonylmethyl)triphenylphosphonium bromide (4.29 g, 10 mmol) in THF (30 mL) was cooled in an ice-bath and *n*BuLi (2.5 M, 4 mL, 10 mmol) was added. The mixture was stirred at 0 °C for 30 minutes.

The previously prepared Boc-protected isatin solution was added slowly at 0 °C to the second flask and the resulted mixture was stirred at room temperature for 60 minutes. The reaction was quenched with water, extracted with ethyl acetate and dried over Na<sub>2</sub>SO<sub>4</sub>. Removing of the solvent under reduced pressure gave the crude product, which was purified by flash column chromatography (hexane/ethyl acetate 20/1) to provide the pure oxindole intermediate in 33% yield (1.06 g).

This pure compound (0.75 g, 2.36 mmol) was dissolved in ethyl acetate (30 mL). Pd/C (0.4 g) was added to this solution, and the resulting mixture was stirred under hydrogen atmosphere (balloon) for 6 h at room temperature. The reaction mixture was then passed through celite to remove Pd/C. After the removal of solvent, the crude product was purified by flash column chromatography (hexane/ethyl acetate 15/1) to give **11Ma** in 30% yield (225 mg).

d) Oxindole **11Na** was prepared according to the following representative procedure:<sup>11</sup>



***tert*-Butyl 3-(cyanomethyl)-2-oxindoline-1-carboxylate (**11Na**)**

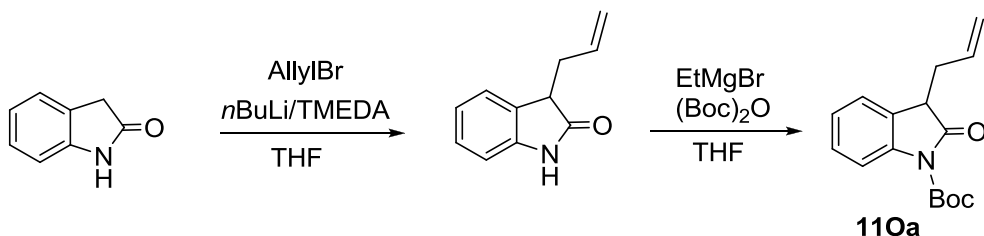
A mixture of isatin (736 mg, 5 mmol) and DMAP (61 mg, 0.5 mmol) in THF (7 mL) was cooled in an ice-bath with stirring and a solution of (Boc)<sub>2</sub>O (1.31 g, 6 mmol) in THF (3 mL) was added slowly. The solution was stirred for 2 h to give the Boc-protected isatin solution in THF.

In another flask (cyanomethyl)triphenylphosphonium chloride (1.68 g, 5 mmol) and KO<sup>t</sup>Bu (0.56 g, 5.5 mmol) were dissolved under ice-bath in THF (10 mL) and stirred for 30 minutes.

The previously prepared Boc-protected isatin solution was added slowly at 0 °C to the second flask and the resulted solution was stirred at room temperature for another 30 minutes. The reaction was quenched with water, extracted with ethyl acetate and dried over Na<sub>2</sub>SO<sub>4</sub>. Removing the solvent under reduced pressure gave the crude product, which was purified by flash column chromatography (hexane/ethyl acetate 20/1) to provide the pure oxindole intermediate in 50% yield (0.68 g).

This pure compound (0.4 g, 1.48 mmol) was dissolved in ethyl acetate (20 mL). Pd/C (0.25 g) was added to this solution, and the resulting mixture was stirred under hydrogen atmosphere (balloon) for 12 h at room temperature. The reaction mixture was then passed through celite to remove Pd/C. After the removal of solvent, the crude product was purified by flash column chromatography (hexane/ethyl acetate 20/1) to give **11Na** in 93% yield (373 mg).

e) Oxindole **11Oa** was prepared according to the following representative procedure:<sup>12</sup>



***tert*-Butyl 3-allyl-2-oxindoline-1-carboxylate (**11Oa**)**

To a solution of oxindole (4.0 g, 30 mmol) in THF (100 mL) at -78 °C was added *n*BuLi (24 mL, 2.5M in hexanes) and TMEDA (9.0 mL, 60 mmol) and the resulting solution was stirred for 2 h. Allyl bromide (2.8 mL, 33 mmol) was then added dropwise and the solution was slowly warmed up to -20 °C and stirred for 1 h at that temperature before it was brought to room temperature. The reaction was then quenched with aq. NH<sub>4</sub>Cl (200 mL) and extracted with ethyl ether (3 x 50 mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, and concentrated in *vacuo*. Purification through silica gel (hexane/ethyl acetate 4/1) gave 3-allyloxindole (4.42 g, 85%).

This compound (346 mg, 2 mmol) was dissolved in THF (10 mL). To this solution were added EtMgBr (1M, 2 mL, 2 mmol) and (Boc)<sub>2</sub>O (480 mg, 2.2 mmol) at -40 °C, and then allowed to stir at room temperature for 4 h. The reaction mixture was diluted with ether and then quenched with saturated aqueous NH<sub>4</sub>Cl. The aqueous layer was extracted with ether and the combined organic layers were washed with water and brine and then dried over Na<sub>2</sub>SO<sub>4</sub>. After the

removal of solvent, purification by flash column chromatography (hexane/ethyl acetate 20/1) was carried out to afford **11Oa** in 80% yield (437 mg).

Representative NMR data of oxindoles prepared:

***tert*-Butyl 2-oxo-3-phenylindoline-1-carboxylate (11Aa)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.95 (d, *J*=8.4 Hz, 1H), 7.40 – 7.30 (m, 4H), 7.23 – 7.17 (m, 4H), 4.75 (s, 1H), 1.65 (s, 9H).

***tert*-Butyl 5-methoxy-2-oxo-3-phenylindoline-1-carboxylate (11Ac)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.87 (d, *J*=8.9 Hz, 1H), 7.39 – 7.30 (m, 3H), 7.23 – 7.21 (m, 2H), 6.91 (ddd, *J*=9.0 Hz, *J*=2.7 Hz, *J*=0.8 Hz, 1H), 6.74 (dd, *J*=2.7 Hz, *J*=1.1 Hz, 1H), 4.72 (s, 1H), 3.79 (s, 3H), 1.64 (s, 9H).

***tert*-Butyl 2-oxo-3-*p*-tolylindoline-1-carboxylate (11Ba)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.94 (d, *J*=8.4 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.21 – 7.16 (m, 4H), 7.10 (d, *J*=8.2 Hz, 2H), 4.71 (s, 1H), 2.35 (s, 3H), 1.65 (s, 9H).

***tert*-Butyl 3-(4-methoxyphenyl)-2-oxoindoline-1-carboxylate (11Ca)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.94 (d, *J*=8.3 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.19 – 7.12 (m, 4H), 6.89 (d, *J*=8.8 Hz, 2H), 4.69 (s, 1H), 3.81 (s, 3H), 1.65 (s, 9H).

***tert*-Butyl 3-(4-fluorophenyl)-2-oxoindoline-1-carboxylate (11Da)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.95 (d, *J*=8.2 Hz, 1H), 7.42 – 7.37 (m, 1H), 7.23 – 7.16 (m, 4H), 7.02 – 7.08 (m, 2H), 4.73 (s, 1H), 1.65 (s, 9H).

***tert*-Butyl 5-fluoro-3-(4-fluorophenyl)-2-oxoindoline-1-carboxylate (11Dd)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.94 – 7.91 (m, 1H), 7.18 – 7.14 (m, 2H), 7.09 – 7.02 (m, 3H), 6.88 – 6.86 (m, 1H), 4.69 (s, 1H), 1.62 (s, 9H).

***tert*-Butyl 3-(3-methoxyphenyl)-5-methyl-2-oxoindoline-1-carboxylate (11Eb)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.81 (d, *J*=8.3 Hz, 1H), 7.28 (t, *J*=8.0 Hz, 1H), 7.17 (dt, *J*=8.3 Hz, *J*=0.8 Hz, 1H), 7.00 (s<sub>b</sub>, 1H), 6.87 (ddd, *J*=8.3 Hz, *J*=2.5 Hz, *J*=0.8 Hz, 1H), 6.80 (d, *J*=7.6 Hz, 1H), 6.75 (t, *J*=2.1 Hz, 1H), 4.67 (s, 1H), 3.80 (s, 3H), 2.34 (s, 3H), 1.65 (s, 9H).

***tert*-Butyl 3-(3-chlorophenyl)-2-oxoindoline-1-carboxylate (11Fa)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.00 (d, *J* = 8 Hz, 1H), 7.44 – 7.39 (m, 1H), 7.31 – 7.29 (m, 2H), 7.24 – 7.14 (m, 4H), 4.74 (s, 1H), 1.68 (s, 9H).

***tert*-Butyl 3-methyl-2-oxoindoline-1-carboxylate (11Ga)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.83 (d, *J*=7.8 Hz, 1H), 7.34 – 7.24 (m, 2H), 7.17 (td, *J*=7.5 Hz, *J*=1.0 Hz, 1H), 5.08 (q, *J*=7.6 Hz, 1H), 1.67 (s, 9H), 1.54 (d, *J*=7.6 Hz, 3H).

***tert*-Butyl 5-methoxy-3-methyl-2-oxoindoline-1-carboxylate (11Gc)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.76 – 7.74 (m, 1H), 6.85 – 6.82 (m, 2H), 3.83 (s, 3H), 3.55 (q, *J*=7.6 Hz, 1H), 1.66 (s, 9H), 1.53 (d, *J*=7.6 Hz, 3H).

***tert*-Butyl 5-fluoro-3-methyl-2-oxoindoline-1-carboxylate (11Gd)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.81 – 7.78 (m, 1H), 7.00 – 6.95 (m, 2H), 3.54 (q, *J*= 7.6 Hz, 1H), 1.63 (s, 9H), 1.51 (d, *J* = 7.6 Hz, 3H).

***tert*-Butyl 3-ethyl-2-oxoindoline-1-carboxylate (11Ha)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.83 (d, *J*=8.2 Hz, 1H), 7.34 – 7.25 (m, 2H), 7.17 (td, *J*=1.0 Hz, *J*=7.5 Hz, 1H), 3.55 (t, *J*=5.7 Hz, 1H), 2.15 – 2.00 (m, 2H), 1.67 (s, 9H), 0.94 (t, *J*=7.4 Hz, 3H).

***tert*-Butyl 3-hexyl-2-oxoindoline-1-carboxylate (11Ia)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.83 (d, *J*=8.2 Hz, 1H), 7.43 – 7.08 (m, 3H), 3.56 (t, *J*=5.9 Hz, 1H), 2.03 – 1.89 (m, 2H), 1.66 (s, 9H), 1.39 – 1.15 (m, 8H), 0.85 (t, *J*=7.0 Hz, 1H).

***tert*-Butyl 3-isobutyl-2-oxoindoline-1-carboxylate (11Ja)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.84 (d, *J*=8.2 Hz, 1H), 7.33 – 7.25 (m, 2H), 7.16 (td, *J*=1.0 Hz, *J*=7.5 Hz, 1H), 3.57 (t, *J*=7.0 Hz, 1H), 2.13 – 2.02 (m, 1H), 1.95 – 1.86 (m, 1H), 1.76 – 1.69 (m, 1H), 1.66 (s, 9H), 1.00 (d, *J*=6.6 Hz, 3H), 0.98 (d, *J*=6.6 Hz, 3H).

***tert*-Butyl 3-benzyl-2-oxoindoline-1-carboxylate (11Ka)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.75 (d, *J* = 8.0 Hz, 1H), 7.30-7.21 (m, 4H), 7.17-7.15 (m, 2H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.74 (d, *J* = 7.5 Hz, 1H), 3.83 (dd, *J* = 9.2 Hz and 4.4 Hz, 1H), 3.51 (dd, *J* = 13.6 Hz and 4.4 Hz, 1H), 2.96 (dd, *J* = 13.6 Hz and 9.2 Hz, 1H), 1.64 (s, 9H).

***tert*-Butyl 3-*p*-methoxybenzyl-2-oxoindoline-1-carboxylate (11La)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.75 (d, *J*=8.2 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.09 – 7.02 (m, 3H), 6.83 – 6.79 (m, 3H), 3.81 – 3.78 (m, 1H), 3.80 (s, 3H), 3.45 (dd, *J*=4.5 Hz, *J*=13.8 Hz, 1H), 2.95 (dd, *J*=8.9 Hz, *J*=13.8 Hz, 1H), 1.65 (s, 9H).

***tert*-Butyl 3-(2-ethoxy-2-oxoethyl)-2-oxoindoline-1-carboxylate (11Ma)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.83 (d, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 4.11 – 4.05 (m, 2H), 3.88 (dd, *J* = 7.0 Hz and 4.6 Hz, 1H), 3.07 (dd, *J* = 17.0 Hz and 4.6 Hz, 1H), 2.93 (dd, *J* = 17.0 Hz and 7.0 Hz, 1H), 1.64 (s, 9H), 1.17 (t, *J* = 7.2 Hz, 3H).

***tert*-Butyl 3-(cyanomethyl)-2-oxoindoline-1-carboxylate (11Na)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 3.81 (dd, *J* = 9.0 Hz and 4.8 Hz, 1H), 3.13 (dd, *J* = 16.8 Hz and 4.8 Hz, 1H), 2.75 (dd, *J* = 16.8 Hz and 9.0 Hz, 1H), 1.64 (s, 9H).

***tert*-Butyl 3-allyl-2-oxoindoline-1-carboxylate (11Oa)**

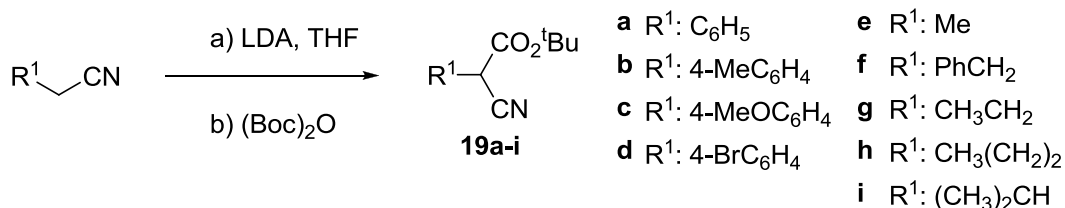
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.83 (d, *J*=7.9 Hz, 1H), 7.34 – 7.28 (m, 2H), 7.18 – 7.14 (m, 1H), 5.83 – 5.72 (m, 1H), 5.16 – 5.08 (m, 2H), 3.65 – 3.62 (m, 1H), 2.89 – 2.82 (m, 1H), 2.69 – 2.62 (m, 1H), 1.66 (s, 9H).

***tert*-Butyl 3-(1,3-dioxolan-2-ylmethyl)-2-oxoindoline-1-carboxylate (11Pa)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.80 (d, *J* = 8.0 Hz, 1H), 7.39 – 7.33 (m, 1H), 7.30 – 7.26 (m, 1H), 7.19 – 7.11 (m, 1H), 5.14 (dd, *J* = 6.0 Hz and 3.6 Hz, 1H), 3.95 – 3.91 (m, 1H), 3.87 – 3.79 (m, 3H), 3.71 (t, *J* = 6.0 Hz, 1H), 2.42 (ddd, *J* = 14.3 Hz, 6.0 Hz and 3.6 Hz, 1H), 2.21 (dt, *J* = 14.3 Hz and 6.0 Hz, 1H), 1.63 (s, 9H).

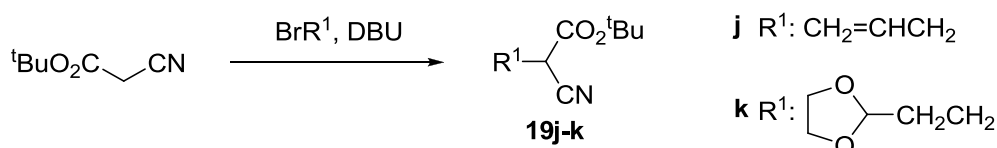
### 2.3.2. Preparation of $\alpha$ -cyanoacetates **19**

#### General procedure for the preparation of cyanoacetates **19a-i**<sup>13</sup>



A solution of nitrile (10 mmol) in THF (10 mL) was added dropwise to a solution of LDA (25 mmol, 2.5 equiv.) in THF (30 mL) cooled to  $-78^\circ\text{C}$ . The reaction mixture was allowed to stir at  $-78^\circ\text{C}$  for 45 min. and then at room temperature for an additional 45 minutes. The reaction mixture was then cooled to  $-78^\circ\text{C}$  and a solution of di-*tert*-butyl dicarbonate (2.62 g, 12 mmol, 1.2 equiv.) in THF (10 mL) was added *via* syringe. The reaction mixture was stirred at  $-78^\circ\text{C}$  for 16 hours. The reaction mixture was quenched with saturated ammonium chloride (20 mL) and extracted with diethyl ether (3 x 50 mL). The organic layer was washed with 1N HCl (30 mL), brine (30 mL) and dried with MgSO<sub>4</sub>. The solvent was removed under reduced pressure and the resulting crude oil was purified using silica gel chromatography (EtOAc:hexane 1:20) to yield the desired cyanoester **19**.

#### General procedure for the preparation of cyanoacetates **19j-k**<sup>14</sup>



A solution of the corresponding alkyl bromide (10 mmol) in benzene (10 mL) was added to a stirred solution of *tert*-butyl cyanoacetate (1.43 mL, 10 mmol) and DBU (1.5 mL, 10 mmol) in benzene (50 mL). The reaction mixture was stirred at room temperature for 15 h, then washed with water, and the organic layer was dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure and the resulting crude oil was purified using silica gel chromatography (EtOAc:hexane 1:20) to yield the desired cyanoester **19**.

Representative NMR data of cyanoacetate products prepared:

##### *tert*-Butyl 2-cyano-2-phenylacetate (**19a**)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.53 – 7.29 (m, 5H), 4.61 (s, 1H), 1.44 (s, 9H).

##### *tert*-Butyl 2-cyano-2-(4-methylphenyl)acetate (**19b**)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.32 (d, *J* = 8 Hz, 2H), 7.20 (d, *J* = 8 Hz, 2H), 4.57 (s, 1H), 2.36 (s, 3H), 1.44 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  164.0, 138.9, 129.8, 127.6, 127.5, 116.1, 84.2, 44.3, 27.6, 21.0.

##### *tert*-Butyl 2-cyano-2-(4-methoxyphenyl)acetate (**19c**)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.36 – 7.32 (m, 2H), 6.93 – 6.89 (m, 2H), 4.55 (s, 1H), 3.80 (s, 3H), 1.43 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  164.1, 160.0, 128.9, 122.4, 116.2, 114.5, 84.2, 55.2, 43.9, 27.6.

##### *tert*-Butyl 2-(4-bromophenyl)-2-cyanoacetate (**19d**)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.52 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 4.58 (s, 1H), 1.44 (s, 9H).

**tert-Butyl 2-cyanopropanoate (19e)**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.43 (q,  $J$  = 7.4 Hz, 1H), 1.52 (d,  $J$  = 7.4 Hz, 3H), 1.47 (s, 9H).

**tert-Butyl 2-cyano-3-phenylpropanoate (19f)**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42 – 7.20 (m, 5H), 3.63 (dd,  $J$  = 8.3, 6 Hz, 1H), 3.28 – 3.12 (m, 2H), 1.44 (s, 9H).

**tert-Butyl 2-cyanobutanoate (19g)**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.36 (t,  $J$  = 7.5 Hz, 1H), 1.97 – 1.88 (m, 2H), 1.48 (s, 9H), 1.10 (t,  $J$  = 7.5 Hz, 3H).

**tert-Butyl 2-cyanopentanoate (19h)**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.38 (t,  $J$  = 7.2 Hz, 1H), 1.90 – 1.84 (m, 2H), 1.58 – 1.49 (m, 2H), 1.48 (s, 9H), 0.96 (t,  $J$  = 7.4 Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  165.2, 116.9, 83.7, 38.3, 31.8, 27.7, 20.0, 13.2 .

**tert-Butyl 2-cyano-3-methylbutanoate (19i)**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.27 (d,  $J$  = 5.2 Hz, 1H), 2.41 – 2.29 (m, 1H), 1.48 (s, 9H), 1.10 (d,  $J$  = 7 Hz, 3H), 1.07 (d,  $J$  = 7 Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  164.8, 115.7, 83.7, 46.3, 29.9, 27.7, 20.6, 18.7.

**tert-Butyl 2-cyano-4-pentenoate (19j)**

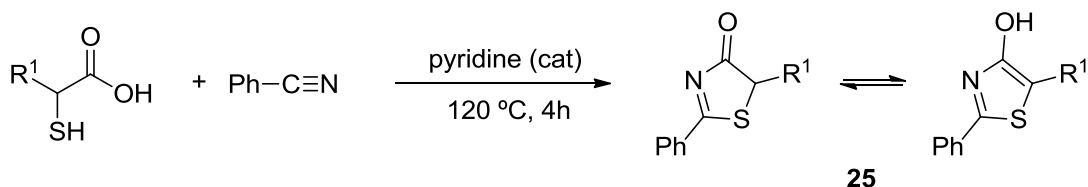
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.85 – 5.75 (m, 1H), 5.26 – 5.20 (m, 2H), 3.45 (t,  $J$  = 6.8 Hz, 1H), 2.65 – 2.61 (m, 2H), 1.48 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  164.4, 131.6, 119.7, 116.4, 84.1, 38.3, 33.9, 27.8.

**tert-Butyl 2-cyano-4-(1,3-dioxolan-2-yl)butyrate (19k)**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.92 (t,  $J$  = 4.2 Hz, 1H), 4.00 – 3.93 (m, 2H), 3.91 – 3.83 (m, 2H), 3.54 (dd,  $J$  = 8.4, 6 Hz, 1H), 2.12 – 1.97 (m, 2H), 1.94 – 1.81 (m, 2H), 1.50 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  164.9, 116.8, 103.2, 84.0, 65.0, 64.9, 38.2, 30.5, 27.8, 24.1.

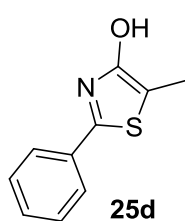
### 2.3.3. Preparation of racemic thiazol-4(5H)-ones **25**

#### Method A.<sup>15, 16</sup>



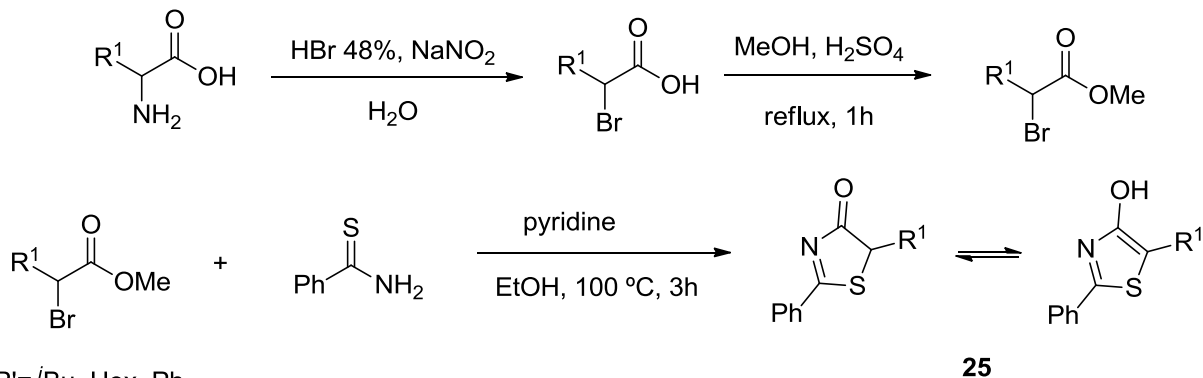
In an inert atmosphere, benzonitrile (1 equiv.) was treated with the corresponding  $\alpha$ -mercaptocarboxylic acid (1 eq.) and pyridine (20 mol %). The mixture was stirred for 4 h at 120 °C. During this time, a yellow mass was formed which was collected by filtration and washed with methanol.

#### 5-Methyl-2-phenylthiazol-4-ol (**25d**)



The title compound **25d** was prepared from benzonitrile (1.0 mL, 10 mmol) and mercaptolactic acid (1.06 g, 10 mmol) according to the general procedure A. The resulting solid was washed with methanol. Yellow solid; yield: 1.3 g, 6.7 mmol, 67%. m. p. 202–204 °C. <sup>1</sup>H NMR (300 MHz, DMSO),  $\delta$ : 10.30 (s, 1H), 7.82–7.74 (m, 2H), 7.49–7.37 (m, 3H), 2.21 (s, 3H). <sup>13</sup>C NMR (75 MHz, DMSO),  $\delta$ : 158.8, 158.2, 133.4, 129.4, 129.1, 124.8, 102.6, 9.1. UPLC-DAD-QTOF: C<sub>10</sub>H<sub>10</sub>NOS [M+H]<sup>+</sup> calcd.: 192.0483, found: 192.0482.

#### Method B.<sup>17, 18</sup>



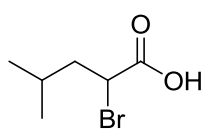
R' = *i*Bu, Hex, Ph

The bromoacids 2-bromooctanoic acid (R<sup>1</sup> = Hex) and  $\alpha$ -bromophenylacetic acid (R<sup>1</sup> = Ph) are commercially available, whereas 2-bromo-4-methylpentanoic acid (R<sup>1</sup> = *i*Bu) and 2-bromo-3-phenylpropanoic acid (R<sup>1</sup>: PhCH<sub>2</sub>) were prepared as follows:<sup>19</sup>

The corresponding amino acid (40 mmol, 1 equiv.) is solubilized in 48% HBr (40 mL) and 36 mL water. The reaction mixture is cooled to 0 °C and a solution of NaNO<sub>2</sub> (4.4 g, 64 mmol, 1.6 equiv.) in 10 mL water was added dropwise. The mixture was stirred for 2.5 h at room temperature, then concentrated to remove acid vapor, and extracted with Et<sub>2</sub>O (4 × 10 mL). The organic layers were washed with water, brine, dried over MgSO<sub>4</sub>, and concentrated under reduced pressure yielding 2-bromo-3-phenylpropanoic acid as colorless oil, which was used without further purification.<sup>20</sup> Yield: 98%



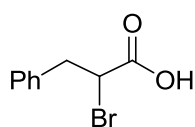
## 2-Bromo-4-methylpentanoic acid



The title compound was prepared from L-leucine (5.25 g, 40 mmol) according to the General Procedure. Yield: 7.91 g, 40 mmol, 100 %.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$  = 4.29 (t,  $J$  = 7.6 Hz, 1H), 1.93 (t,  $J$  = 7.1 Hz, 2H), 1.82 (td,  $J$  = 13.9, 13.3, 6.4 Hz, 1H), 0.95 (dd,  $J$  = 13.5, 6.5 Hz, 9H).<sup>7</sup>

## 2-Bromo-3-phenylpropanoic acid



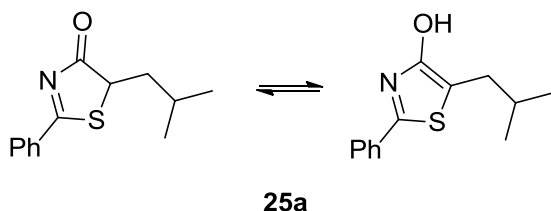
The title compound was prepared from L-phenylalanine (6.6 g, 40 mmol) according to the general procedure. Yield: 9.27 g, 40 mmol, 100 %.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.43 – 7.18 (m, 5H), 4.43 (t,  $J$  = 7.7 Hz, 1H), 3.47 (dd,  $J$  = 13.6, 7.6 Hz, 1H), 3.25 (dd,  $J$  = 14.2, 7.2 Hz, 1H).<sup>21</sup>

The  $\alpha$ -bromoacid was treated with a solution of concentrated sulphuric acid (30  $\mu\text{L}/\text{mmol}$ ) in methanol (2 mL/mmol) and refluxed for one hour. The solution was cooled to room temperature and concentrated in vacuo.  $\text{Et}_2\text{O}$  was added and the organic layer was washed with 5% aqueous solution of  $\text{NaHCO}_3$  followed by brine, dried over  $\text{MgSO}_4$  and concentrated in vacuo.

A mixture of the corresponding  $\alpha$ -bromo methyl ester (1.1 equiv.), thioamide (1 equiv.) and pyridine (1 equiv.) was stirred under argon and slowly heated to 100–110  $^\circ\text{C}$  until the mixture solidified. After 3 h, ethanol (15 mL) was added and the mixture was stirred at room temperature for 30 min. After filtration the crude product was washed with ethanol.

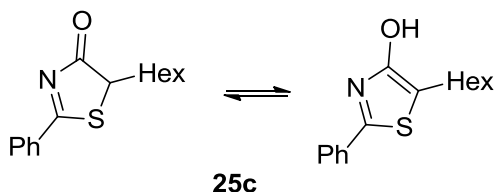
## 5-Isobutyl-2-phenylthiazol-4(5H)-one (keto form); 5-isobutyl-2-phenylthiazol-4-ol (enol form) (25a)



The title compound **25a** was prepared from methyl 2-bromo-4-methylpentanoate (2.3 g, 11 mmol) and thioamide (1.4 g, 10 mmol) according to the general procedure B. The resulting solid was washed with ethanol. Yellow solid; yield: 1.7 g, 7.3 mmol, 73%. m. p. 125–127  $^\circ\text{C}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 8.20

– 8.10 (m, 1H), 7.88 – 7.80 (m, 1H), 7.72 – 7.61 (m, 1H), 7.57 – 7.48 (m, 1H), 7.47 – 7.35 (m, 1H), 4.26 (dd,  $J$  = 11.0, 4.1 Hz, 1H) (ceto form), 2.63 (d,  $J$  = 7.0 Hz, 2H) (enol form), 2.28 – 2.09 (m, 2H) (ceto form), 2.03 – 1.85 (m, 1H) (enol form), 1.83 – 1.66 (m, 1H) (ceto form), 1.12 – 0.91 (m, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 196.1, 194.2, 161.1, 158.4, 135.0, 133.0, 132.2, 129.7, 129.0, 129.0, 128.8, 125.7, 108.3, 54.0, 42.5, 33.3, 30.2, 28.2, 23.0, 22.2, 21.4. UPLC-DAD-QTOF:  $\text{C}_{13}\text{H}_{16}\text{NOS}$   $[\text{M}+\text{H}]^+$  calcd.: 234.0953, found: 234.0960.

## 5-Hexyl-2-phenylthiazol-4(5H)-one (ceto form); 5-hexyl-2-phenylthiazol-4-ol (enol form) (25c)

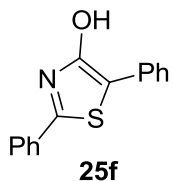


The title compound **25c** was prepared from methyl 2-bromooctanoate (2.6 g, 11 mmol) and thioamide (1.4 g, 10 mmol) according to the general procedure B. The resulting solid was washed with ethanol. Yellow solid; yield: 1.7 g, 6.5 mmol, 65%. m. p. 77–80  $^\circ\text{C}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 8.93 –

8.83 (m, 1H), 8.16 – 8.07 (m, 2H), 7.87 – 7.76 (m, 1H), 7.71 – 7.60 (m, 1H), 7.56 – 7.46 (m, 3H), 7.46 – 7.29 (m, 2H), 4.25 (dd,  $J$  = 9.2, 4.2 Hz, 1H) (ceto form), 2.73 (t,  $J$  = 7.5 Hz, 2H) (enol form), 2.33 – 2.17 (m, 1H), 1.97 – 1.78 (m, 1H), 1.71 – 1.56 (m, 1H), 1.56 – 1.08 (m, 13H), 1.05 – 0.57

(m, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 196.2, 193.7, 157.6, 135.0, 132.2, 129.6, 129.0, 128.7, 127.4, 125.6, 109.9, 55.6, 33.0, 31.5, 31.4, 30.9, 28.7, 28.6, 27.9, 24.3, 22.5, 22.4, 14.0, 13.9. UPLC-DAD-QTOF:  $\text{C}_{15}\text{H}_{20}\text{NOS}$   $[\text{M}+\text{H}]^+$  calcd.: 262.1266, found: 262.1265.

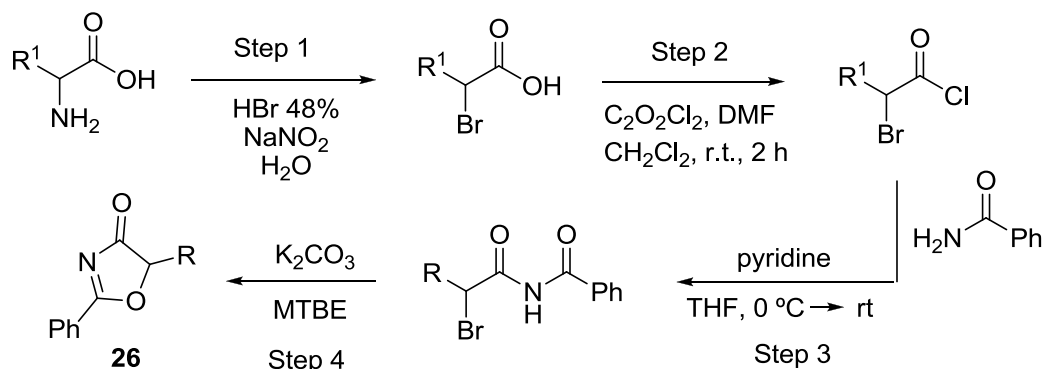
#### 2,5-Diphenylthiazol-4-ol (**25f**)



The title compound **25f** was prepared from methyl 2-bromo-2-phenylacetate (2.5 g, 11 mmol) and thioamide (1.4 g, 10 mmol) according to the general procedure B. The resulting solid was washed with ethanol. Yellow solid; yield: 1.9 g, 7.7 mmol, 77%. m. p. 214-216 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 8.01 – 7.90 (m, 2H), 7.89 – 7.79 (m, 2H), 7.54 – 7.32 (m, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 145.8, 141.4, 129.8, 128.8, 128.5, 127.1, 126.4, 126.1, 125.5, 109.5.

UPLC-DAD-QTOF:  $\text{C}_{15}\text{H}_{12}\text{NOS}$   $[\text{M}+\text{H}]^+$  calcd.: 254.0640, found: 254.0647.

### 2.3.4. Preparation of racemic oxazol-4(5*H*)-ones **26**



#### Step 1) Preparation of 2-bromoacids

The bromoacids were commercially available or prepared as indicated above.

#### Step 2) Preparation of $\alpha$ -bromoacylchlorides

A solution of oxalyl chloride (1.2 equiv.) in dry dichloromethane (0.5 mL/mmol) was added slowly to a stirred solution of the corresponding bromoacid (1 eq.) in dichloromethane (0.5 mL/mmol) at 0 °C, then 2 drops of DMF were added. Gas evolution was observed, and the system was allowed to stir at room temperature for 2 additional hours. Volatiles were removed under reduced pressure and the resulting crude material was subjected to synthetic step 3

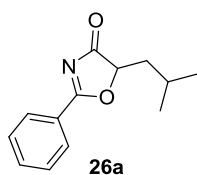
#### Step 3) Synthesis of $\alpha$ -bromo imides

To a solution/suspension of benzamide (1.2 g, 10 mmol, 1.0 eq.) and pyridine (0.81 mL, 10 mmol, 1.0 eq.) in THF (12.5 mL) was added the corresponding  $\alpha$ -bromoacylchloride (1.0 eq.) dropwise over 5 min at 0 °C. The resulting suspension was stirred overnight at rt and diluted with EtOAc. The mixture was acidified to ca. pH 2 with 1N HCl aq. and the phases were separated. The aqueous phase was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with water (3 x 20 mL) and brine (20 mL), dried over  $\text{MgSO}_4$ , and filtered. Volatiles were removed under reduced pressure. The imide product was purified by flash chromatography on silica gel (eluting with hexane/ ethyl acetate 90/10).

#### Step 4) Synthesis of oxazol-4(5*H*)-ones **26**<sup>22, 23</sup>

A suspension of  $\text{K}_2\text{CO}_3$  (2.0 g, 20 mmol, 2.0 equiv.) in methyl *tert*-butylether (MTBE) (20 mL) was refluxed for 2 h to remove water using a Dean-Stark trap. The suspension was cooled to rt and the corresponding imide was added in one portion. The resulting mixture was refluxed overnight and cooled to rt. Inorganic salts were filtered through a celite pad with suction and the filter cake was washed with EtOAc. The combined organic layers were concentrated in vacuo. The crude material was purified by flash chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20).

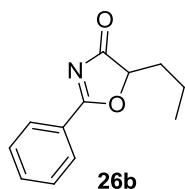
### 5-Isobutyl-2-phenyloxazol-4(5H)-one (26a)



The title compound **26a** was prepared from benzamide (1.2 g, 10 mmol) and 2-bromo-4-methylpentanoyl chloride (2.13 g, 10 mmol) according to the general procedure. The crude material was purified by flash chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20). White solid. Yield: 1.2 g, 5.4 mmol, 54%. m. p.= 57–59 °C. All spectroscopic data were identical to those reported in the literature.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$  = 8.26 – 8.15 (m, 2H), 7.74 – 7.63 (m, 1H), 7.59 – 7.47 (m, 2H), 4.79 (dd,  $J$  = 10.0, 3.5 Hz, 1H), 2.11 – 1.82 (m, 2H), 1.77 – 1.62 (m, 1H), 1.04 (d,  $J$  = 6.4 Hz, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ),  $\delta$  = 192.2, 186.3, 135.1, 130.0, 128.9, 125.9, 80.8, 40.2, 25.5, 22.8, 21.9. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{13}\text{H}_{16}\text{NO}_2$  ( $\text{M}+\text{H}^+$ ), 218.1181; found, 218.1183.

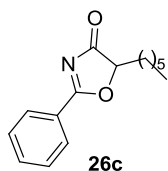
### 2-Phenyl-5-propyloxazol-4(5H)-one (26b)



The title compound **26b** was prepared from benzamide (1.2 g, 10 mmol) and 2-bromopentanoyl chloride (2.0 g, 10 mmol) according to the general procedure. The crude material was purified by flash chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20). White solid. Yield: 480 mg, 2.4 mmol, 24%. m. p.= 55–56 °C.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$  = 8.27 – 8.18 (m, 2H), 7.76 – 7.65 (m, 1H), 7.60 – 7.47 (m, 2H), 4.79 (dd,  $J$  = 7.7, 4.5 Hz, 1H), 2.15 – 2.00 (m, 1H), 1.93 – 1.78 (m, 1H), 1.56 (dq,  $J$  = 14.8, 7.5 Hz, 2H), 1.00 (t,  $J$  = 7.4 Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ),  $\delta$  = 192.33, 186.92, 135.54, 130.48, 129.35, 126.26, 82.17, 33.55, 18.52, 13.99. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{12}\text{H}_{14}\text{NO}_2$  ( $\text{M}+\text{H}^+$ ), 204.1021; found, 204.1024.

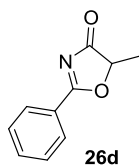
### 5-Hexyl-2-phenyloxazol-4(5H)-one (26c)



The title compound **26c** was prepared from benzamide (1.2 g, 10 mmol) and 2-bromooctanoyl chloride (2.42 g, 10 mmol) according to the general procedure. The crude material was purified by flash chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20). White solid. Yield: 800 mg, 3.3 mmol, 33%. m. p. 69–70 °C.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$  = 8.23 (dd,  $J$  = 8.4, 1.3 Hz, 2H), 7.76 – 7.63 (m, 1H), 7.54 (t,  $J$  = 7.7 Hz, 2H), 4.78 (dd,  $J$  = 7.6, 4.5 Hz, 1H), 2.19 – 2.00 (m, 1H), 1.86 (td,  $J$  = 14.8, 7.6 Hz, 1H), 1.51 (dt,  $J$  = 15.7, 6.9 Hz, 2H), 1.33 (ddd,  $J$  = 11.2, 8.1, 4.5 Hz, 6H), 0.87 (t,  $J$  = 6.7 Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ),  $\delta$  = 191.87, 186.45, 135.09, 130.02, 128.89, 125.80, 81.90, 31.39, 31.11, 28.70, 24.53, 22.43, 13.94. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{15}\text{H}_{20}\text{NO}_2$  ( $\text{M}+\text{H}^+$ ), 246.1494; found, 246.1491.

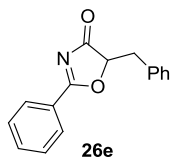
### 5-Methyl-2-phenyloxazol-4(5H)-one (26d)



The title compound **26d** was prepared from benzamide (1.2 g, 10 mmol) and 2-bromopropanoyl chloride (1.7 g, 10 mmol) according to the general procedure. The crude material was purified by flash chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20). White solid; yield: 1.1 g, 6.2 mmol, 62%. m. p.= 68–70 °C. All spectroscopic data were identical to those reported in the literature.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$  = 8.15 – 7.99 (m, 2H), 7.64 – 7.46 (m, 1H), 7.46 – 7.35 (m, 2H), 4.72 (q, 1H), 1.49 (d,  $J$  = 7.1 Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ),  $\delta$  = 192.0, 185.8, 134.8, 129.6, 128.5, 125.4, 77.6, 16.0. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{10}\text{H}_{10}\text{NO}_2$  ( $\text{M}+\text{H}^+$ ), 176.0712; found, 176.0717.

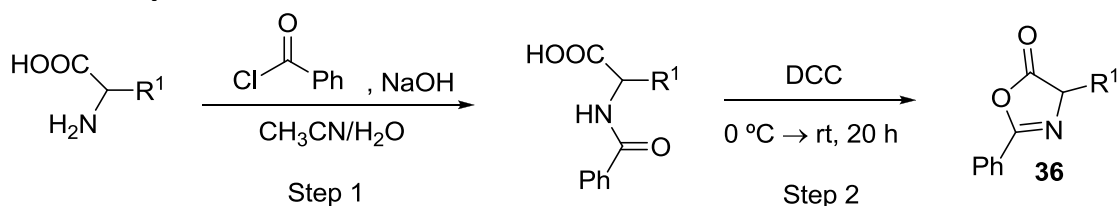
#### 5-Benzyl-2-phenyloxazol-4(5H)-one (26e)



The title compound **26e** was prepared from benzamide (1.2 g, 10 mmol) and 2-bromooctanoyl chloride (2.47 g, 10 mmol) according to the general procedure. The crude material was purified by flash chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20). White solid; yield: 850 mg, 3.4 mmol 34%. m. p. 97–98 °C. All spectroscopic data were identical to those reported in the literature.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$  = 8.13 (dd,  $J$  = 5.2, 3.3 Hz, 2H), 7.70 – 7.62 (m, 1H), 7.49 (dd,  $J$  = 10.6, 4.8 Hz, 2H), 7.29 – 7.20 (m, 5H), 4.98 (dd,  $J$  = 7.6, 4.0 Hz, 1H), 3.43 (dd,  $J$  = 14.8, 4.0 Hz, 1H), 3.12 (dd,  $J$  = 14.8, 7.6 Hz, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ),  $\delta$  = 190.85, 186.44, 135.17, 134.64, 130.00, 129.27, 128.89, 128.61, 127.31, 125.61, 81.93, 37.25. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{16}\text{H}_{14}\text{NO}_2$  ( $\text{M}+\text{H}^+$ ), 252.1025; found, 252.1024.

### 2.3.5. Preparation of racemic azlactones **36**<sup>24</sup>



**STEP 1:** The corresponding racemic amino acid (1 equiv.) and NaOH (4 eq.) were dissolved in H<sub>2</sub>O/CH<sub>3</sub>CN (75/25, 0.3 M). After cooling to 0 °C, benzoyl chloride (1.05 equiv.) was added dropwise at this temperature. After the addition was complete, the mixture was stirred for additional 2 h at 0 °C. Subsequently, the mixture was allowed to warm to RT and was stirred for one additional hour. All volatiles were then removed under reduced pressure before conc. HCl was added to cause precipitation. The mixture was filtered and the filter cake was washed with ice-cold diethylether.

#### *N*-Benzoyl-*D,L*-phenylglycine

*D,L*-Phenylglycine (1.51 g, 10 mmol) was treated with NaOH (1.62 g, 40 mmol) and benzoyl chloride (1.22 mL, 10.5 mmol) to yield a white solid which was used as such in the next step (2.03 g, 7.97 mmol, 80%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), δ: 7.86 – 7.77 (m, 2H), 7.57 – 7.32 (m, 8H), 7.08 (d, *J* = 7.0 Hz, 1H), 5.80 (d, *J* = 6.7 Hz, 1H).

#### *N*-Benzoyl-*D,L*-phenylalanine

*D,L*-Phenylalanine (1.65 g, 10 mmol) was treated with NaOH (1.62 g, 40 mmol) and benzoyl chloride (1.22 mL, 10.5 mmol) to yield a white solid which was used as such in the next step (2.38 g, 8.82 mmol, 88%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), δ: 8.14 – 8.06 (m, 2H), 7.73 – 7.57 (m, 2H), 7.53 – 7.38 (m, 2H), 7.35 – 7.19 (m, 5H), 6.53 (d, *J* = 8.4 Hz, 1H), 5.16 – 5.03 (m, 1H), 3.34 (ddd, *J* = 30.5, 13.8, 5.5 Hz, 2H).

#### *N*-Benzoyl-*D,L*-leucine

*D,L*-Leucine (1.31 g, 10 mmol) was treated with NaOH (1.62 g, 40 mmol) and benzoyl chloride (1.22 mL, 10.5 mmol) to yield a white solid which was used as such in the next step (2.01 g, 8.51 mmol, 85%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), δ: 7.87 – 7.75 (m, 2H), 7.63 – 7.41 (m, 3H), 6.49 (d, *J* = 7.8 Hz, 1H), 4.91 – 4.77 (m, 1H), 1.93 – 1.63 (m, 3H), 1.00 (d, *J* = 6.1 Hz, 6H).

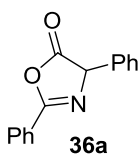
#### *N*-Benzoyl-*D,L*-valine

*D,L*-Valine (1.17 g, 10 mmol) was treated with NaOH (1.62 g, 40 mmol) and benzoyl chloride (1.22 mL, 10.5 mmol) to yield a white solid which was used as such in the next step (1.99 g, 9.01 mmol, 90%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), δ: 9.03 (s, 1H), 7.85 – 7.77 (m, 2H), 7.63 – 7.40 (m, 3H), 6.69 (d, *J* = 8.5 Hz, 1H), 4.82 (dd, *J* = 8.5, 4.8 Hz, 1H), 2.45 – 2.28 (m, 1H), 1.05 (t, *J* = 7.2 Hz, 6H).

**Step 2:** The corresponding *N*-substituted amino acid (5 mmol, 1 equiv.) was suspended in CH<sub>2</sub>Cl<sub>2</sub> (50 mL, 10 mL/mmol), the mixture was cooled to 0 °C and DCC (1.08 g, 5.25 mmol, 1.05 equiv.) was added portionwise. After complete addition the mixture was allowed to warm to RT and was stirred for additional 20 h at this temperature. A precipitate was filtered off and

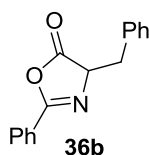
the filtrate was concentrated *in vacuo*. The product was purified by silica gel column chromatography using hexane/ethyl acetate (95:5).

#### 2,4-Diphenyloxazol-5(4H)-one (36a)<sup>25</sup>



The title compound was prepared from *N*-benzoyl-*D,L*-phenylglycine (1.28 g, 5 mmol) according to the general procedure. Yellow solid; yield: 737 mg, 3.11 mmol, 62%. m.p. 104-105 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), δ: 8.24 – 7.94 (m, 2H), 7.67 – 7.49 (m, 3H), 7.48 – 7.34 (m, 5H), 5.53 (s, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>), δ: 176.4, 162.8, 133.6, 133.3, 129.1, 129.1, 128.9, 128.8, 128.3, 127.6, 127.4, 127.0, 68.3. UPLC-DAD-QTOF: C<sub>15</sub>H<sub>12</sub>NO<sub>2</sub> [M+H]<sup>+</sup> calcd.: 238.0863, found: 238.0860.

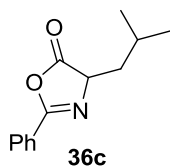
#### 4-Benzyl-2-phenyloxazol-5(4H)-one (36b)<sup>26</sup>



The title compound was prepared from *N*-benzoyl-*D,L*-phenylalanine (1.35 g, 5 mmol) according to the general procedure. White solid; yield: 759 g, 3.02 mmol, 60%. m.p. 69-71 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), δ: 7.97 – 7.88 (m, 2H), 7.59 – 7.40 (m, 3H), 7.32 – 7.17 (m, 5H), 4.69 (dd, *J* = 6.7, 5.0 Hz, 1H), 3.38 (dd, *J* = 14.0, 5.0 Hz, 1H), 3.19 (dd, *J* = 14.0, 6.7 Hz, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>), δ: 177.8, 161.9, 135.5, 132.9, 129.8, 128.9, 128.6, 128.1, 127.4, 125.9, 66.7, 37.5. UPLC-

DAD-QTOF: C<sub>16</sub>H<sub>14</sub>NO<sub>2</sub> [M+H]<sup>+</sup> calcd.: 252.1025, found: 252.1029.

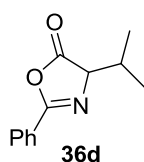
#### 4-Isobutyl-2-phenyloxazol-5(4H)-one (36c)



The title compound was prepared from *N*-benzoyl-*D,L*-leucine (1.35 g, 5 mmol) according to the general procedure. White solid; yield: 944 mg, 3.75 mmol, 75%. m.p. 53-55 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), δ: 8.04 – 7.97 (m, 2H), 7.62 – 7.44 (m, 3H), 4.41 (dd, *J* = 8.9, 5.7 Hz, 1H), 2.07 (dp, *J* = 13.2, 6.6 Hz, 1H), 1.85 (ddd, *J* = 13.5, 7.7, 5.7 Hz, 1H), 1.68 (ddd, *J* = 13.7, 8.9, 6.4 Hz, 1H), 1.03 (t, *J* = 6.8 Hz, 6H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>), δ: 179.2, 161.6, 134.8, 132.8,

128.9, 128.0, 64.1, 40.9, 25.4, 22.9, 22.3. UPLC-DAD-QTOF: C<sub>13</sub>H<sub>16</sub>NO<sub>2</sub> [M+H]<sup>+</sup> calcd.: 218.1181, found: 218.1182.

#### 4-Isopropyl-2-phenyloxazol-5(4H)-one (36d)



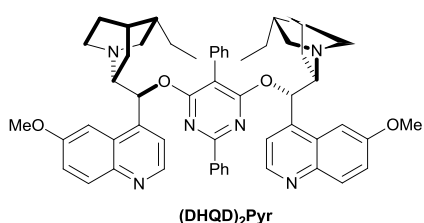
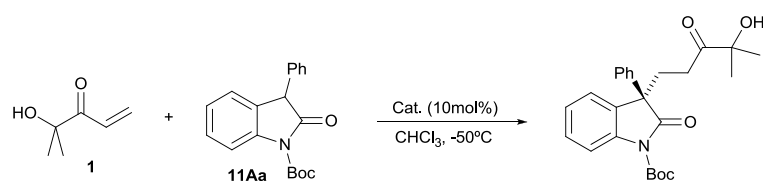
The title compound was prepared from *N*-benzoyl-*D,L*-valine (2.21 g, 10 mmol) according to the general procedure. White solid; yield: 1.56 g, 7.65 mmol, 77%. m.p. 44-47 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), δ: 8.06 – 7.97 (m, 2H), 7.62 – 7.54 (m, 1H), 7.53 – 7.44 (m, 2H), 4.29 (d, *J* = 4.5 Hz, 1H), 2.59 – 2.24 (m, 1H), 1.15 (d, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>), δ: 177.8, 161.8, 132.8, 128.9, 128.0, 126.1, 70.8, 31.4, 18.9, 17.7. UPLC-DAD-QTOF: C<sub>12</sub>H<sub>14</sub>NO<sub>2</sub>

[M+H]<sup>+</sup> calcd.: 204.1025, found: 204.1025.

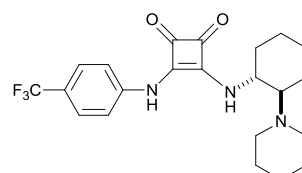




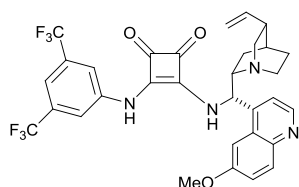
Table SI-2: Reaction between oxindole **11Aa** and hydroxy enone **1**.



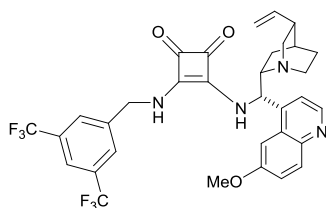
100% conversion  
96% e.e.



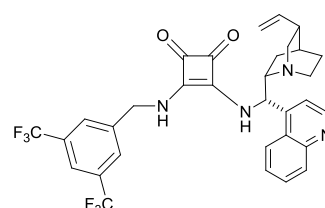
82% conversion  
78% e.e. (-60 °C)



100% conversion  
34% e.e.

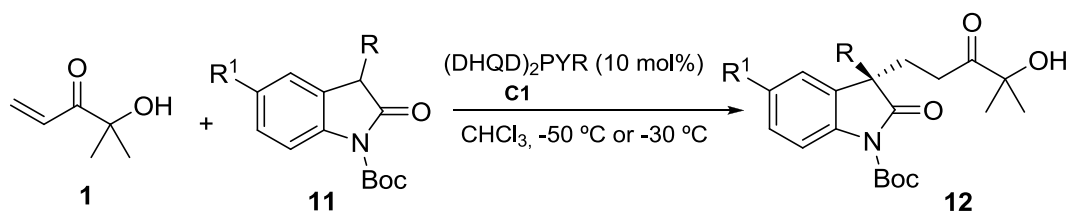


100% conversion  
6% e.e.



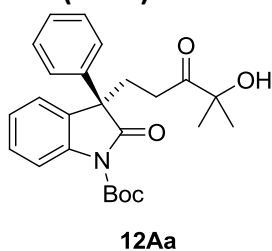
100% conversion  
20% e.e.

## 2.4.2. Catalytic conjugate addition of 3-substituted oxindoles **11** to **1**



(DHQD)<sub>2</sub>Pyr **C1** (10 mol%) was added to a solution of N-Boc-3-substituted oxindole **11** (0.3 mmol) and  $\alpha'$ -hydroxy enone **1** (0.9 mmol) in CHCl<sub>3</sub> (3.6 mL) cooled to the corresponding temperature and the resulting solution was stirred at the same temperature until the reaction was complete (it was monitored by TLC). The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed twice with 0.1N HCl and the organic layer was dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure and the product was purified by column chromatography.

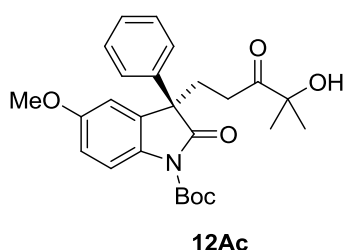
**(R)-tert-Butyl 3-(4-hydroxy-4-methyl-3-oxopentyl)-2-oxo-3-phenylindoline-1-carboxylate (12Aa)**



Prepared according to the general procedure starting from N-Boc-3-phenyl-2-oxoindole **11Aa** (92.7 mg, 0.3 mmol) at  $-50^{\circ}\text{C}$ . The title compound was obtained as a 98:2 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 20/1 to 1/1) to give the title compound as a white solid. Yield: 95% (120.6 mg). m.p.=  $102 - 103^{\circ}\text{C}$ .  $[\alpha]_{\text{D}}^{22} = +50.7^{\circ}$  ( $c=1$ , 96% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.95 (d,  $J=8.1$  Hz, 1H), 7.41 – 7.23 (m, 8H), 3.45 (s, 1H), 2.84 – 2.75 (m, 1H), 2.61 – 2.47 (m, 2H), 2.33 – 2.23 (m, 1H), 1.65 (s, 9H), 1.26 (s, 3H), 1.17 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 213.2, 176.5, 149.2, 139.8, 139.3, 130.1, 128.9, 128.8, 127.8, 126.9, 124.8, 115.4, 84.7, 76.3, 56.1, 31.8, 30.9, 28.1, 26.4, 26.3. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{25}\text{H}_{30}\text{NO}_5$  ( $\text{M}+\text{H}^+$ ), 424.2124; found, 424.2132.

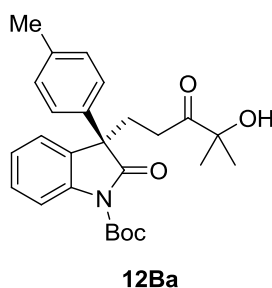
**(R)-tert-butyl 3-(4-hydroxy-4-methyl-3-oxopentyl)-5-methoxy-2-oxo-3-phenylindoline-1-carboxylate (12Ac)**



Prepared according to the general procedure starting from N-Boc-5-methoxy-3-phenyl-2-oxoindole **11Ac** (101.7 mg, 0.3 mmol) at  $-50^{\circ}\text{C}$ . The title compound was obtained as a 98:2 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 20/1 to 1/1) to give the title compound as a white solid. Yield: 89% (121.2 mg). m.p.=  $106 - 109^{\circ}\text{C}$ .  $[\alpha]_{\text{D}}^{21} = +57.9^{\circ}$  ( $c=1$ , 96% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.88 (d,  $J=8.9$  Hz, 1H), 7.34 – 7.29 (m, 5H), 6.91 (dd,  $J=8.9$  Hz,  $J=2.6$  Hz, 1H), 6.77 (d,  $J=2.6$  Hz, 1H), 3.81 (s, 3H), 3.47 (s, 1H), 2.85 – 2.76 (m, 1H), 2.59 – 2.48 (m, 2H), 2.34 – 2.25 (m, 1H), 1.65 (s, 9H), 1.28 (s, 3H), 1.19 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 213.2, 176.5, 157.1, 149.2, 139.3, 133.1, 131.5, 128.8, 127.8, 126.9, 116.3, 113.6, 110.9, 84.5, 76.3, 56.4, 55.7, 31.6, 30.9, 28.1, 26.5, 26.3. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{26}\text{H}_{32}\text{NO}_6$  ( $\text{M}+\text{H}^+$ ), 454.2230; found, 454.2226.

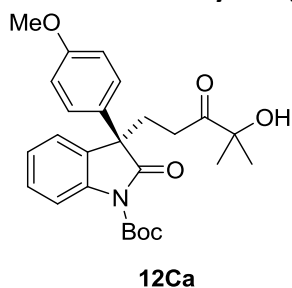
**(R)-tert-Butyl 3-(4-hydroxy-4-methyl-3-oxopentyl)-2-oxo-3-p-tolylindoline-1-carboxylate (12Ba)**



Prepared according to the general procedure starting from N-Boc-3-p-methylphenyl-2-oxoindole **11Ba** (32.3 mg, 0.1 mmol) at  $-50^{\circ}\text{C}$ . The title compound was obtained as a 95:5 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 20/1 to 1/1) to give the title compound as a white solid. Yield: 87% (114.3 mg). m.p.=  $83 - 85^{\circ}\text{C}$ .  $[\alpha]_{\text{D}}^{23} = +37.7^{\circ}$  ( $c=1$ , 90% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.85 (d,  $J=8.1$  Hz, 1H), 7.31 – 7.27 (m, 1H), 7.16 – 7.11 (m, 4H), 7.04 (d,  $J=8.1$  Hz, 2H), 3.38 (s, 1H), 2.72 – 2.64 (m, 1H), 2.49 – 2.37 (m, 2H), 2.23 (s, 3H), 2.21 – 2.14 (m, 1H), 1.55 (s, 9H), 1.17 (s, 3H), 1.08 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 213.2, 176.6, 149.2, 139.8, 137.6, 136.3, 130.3, 129.5, 128.8, 126.8, 124.7, 124.6, 115.4, 84.6, 76.3, 55.8, 31.7, 30.9, 28.1, 26.4, 26.3, 20.9. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{26}\text{H}_{32}\text{NO}_5$  ( $\text{M}+\text{H}^+$ ), 438.2280; found, 438.2283.

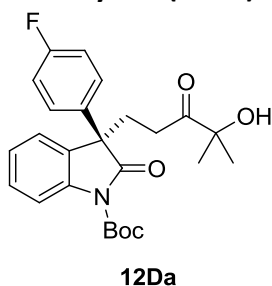
**(*R*)-tert-Butyl 3-(4-hydroxy-4-methyl-3-oxopentyl)-3-(4-methoxyphenyl)-2-oxindoline-1-carboxylate (12Ca)**



Prepared according to the general procedure starting from N-Boc-3-*p*-methoxyphenyl-2-oxindole **11Ca** (101.7 mg, 0.3 mmol) at  $-50^{\circ}\text{C}$ . The title compound was obtained as a 95:5 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 20/1 to 1/1) to give the title compound as a white solid. Yield: 89% (121.2 mg). m.p.=  $65-67^{\circ}\text{C}$ .  $[\alpha]_{\text{D}}^{23} = +47.1^{\circ}$  ( $c=1$ , 90% *ee*,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.95 (d,  $J=8.3$  Hz, 1H), 7.41 – 7.37 (m, 1H), 7.26 – 7.20 (m, 4H), 6.85 (d,  $J=8.9$  Hz, 2H), 3.78 (s, 3H), 3.47 (s, 1H), 2.79 – 2.71 (m, 1H), 2.57 – 2.46 (m, 2H), 2.30 – 2.21 (m, 1H), 1.64 (s, 9H), 1.26 (s, 3H), 1.17 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 213.2, 176.7, 159.1, 149.2, 139.8, 131.3, 130.2, 128.8, 128.1, 124.8, 124.7, 115.4, 114.1, 84.7, 76.3, 55.4, 55.3, 31.8, 30.9, 28.1, 26.4, 26.3. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{26}\text{H}_{32}\text{NO}_6$  ( $\text{M}+\text{H}^+$ ), 454.2230; found, 454.2225.

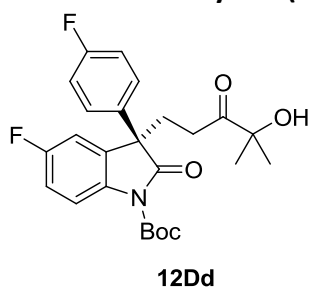
**(*R*)-tert-Butyl 3-(4-fluorophenyl)-3-(4-hydroxy-4-methyl-3-oxopentyl)-2-oxindoline-1-carboxylate (12Da)**



Prepared according to the general procedure starting from N-Boc-3-*p*-fluorophenyl-2-oxindole **11Da** (98.1 mg, 0.3 mmol) at  $-50^{\circ}\text{C}$ . The title compound was obtained as a 98:2 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 20/1 to 1/1) to give the title compound as a white solid. Yield: 92% (121.8 mg). m.p.=  $61-63^{\circ}\text{C}$ .  $[\alpha]_{\text{D}}^{23} = +66.9^{\circ}$  ( $c=1$ , 96% *ee*,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.96 (d,  $J=8.2$  Hz, 1H), 7.43 – 7.41 (m, 1H), 7.39 – 7.20 (m, 4H), 7.01 (t,  $J=8.6$  Hz, 2H), 3.41 (s, 1H), 2.80 – 2.72 (m, 1H), 2.58 – 2.46 (m, 2H), 2.28 – 2.19 (m, 1H), 1.65 (s, 9H), 1.26 (s, 3H), 1.17 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 213.1, 176.3, 163.5, 161.1, 149.1, 139.8, 135.1, 129.7, 129.1, 128.8, 128.7, 124.9, 124.7, 115.7, 115.5, 84.9, 76.3, 55.5, 32.07, 30.9, 28.1, 26.4, 26.3. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{25}\text{H}_{29}\text{FNO}_5$  ( $\text{M}+\text{H}^+$ ), 442.2030; found, 442.2036.

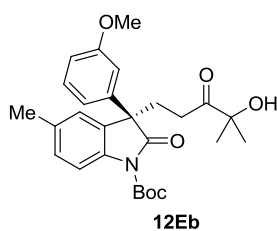
**(*R*)-tert-Butyl 5-fluoro-3-(4-fluorophenyl)-3-(4-hydroxy-4-methyl-3-oxopentyl)-2-oxindoline-1-carboxylate (12Dd)**



Prepared according to the general procedure starting from N-Boc-5-fluoro-3-*p*-fluorophenyl-2-oxindole **11Dd** (103.5 mg, 0.3 mmol) at  $-50^{\circ}\text{C}$ . The title compound was obtained as a 97:3 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 20/1 to 1/1) to give the title compound as a white solid. Yield: 91% (125.4 mg). m.p.=  $107-110^{\circ}\text{C}$ .  $[\alpha]_{\text{D}}^{21} = +53.4^{\circ}$  ( $c=0.5$ , 94% *ee*,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.96 (dd,  $J=9.0$  Hz,  $J=4.6$  Hz, 1H), 7.31 – 7.26 (m, 2H), 7.10 (td,  $J=8.9$  Hz,  $J=2.7$  Hz, 1H), 7.06 – 7.00 (m, 2H), 6.94 (dd,  $J=7.6$  Hz,  $J=2.7$  Hz, 1H), 3.38 (s<sub>br</sub>, 1H), 2.80 – 2.69 (m, 1H), 2.56 – 2.46 (m, 2H), 2.33 – 2.22 (m, 1H), 1.64 (s, 9H), 1.27 (s, 3H), 1.20 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 212.9, 175.9, 161.3, 158.8, 149.0, 135.7, 134.5, 131.9, 131.8, 128.7, 128.6, 117.0, 116.9, 115.9, 115.8, 115.7, 115.6, 112.2, 111.9, 85.1, 76.4, 55.7, 31.8, 30.8, 28.0, 26.5, 26.4. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{25}\text{H}_{28}\text{F}_2\text{NO}_5$  ( $\text{M}+\text{H}^+$ ), 460.1936; found, 460.1938.

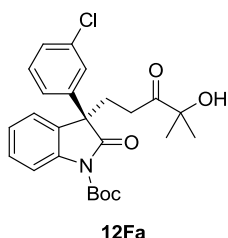
**(R)-tert-Butyl 3-(3-hydroxy-4-methyl-3-oxopentyl)-3-(3-methoxyphenyl)-5-methyl-2-oxoindoline-1-carboxylate (12Eb)**



Prepared according to the general procedure starting from N-Boc-5-methyl-3-*m*-methoxyphenyl-2-oxoindole **11Eb** (105.9 mg, 0.3 mmol) at  $-50\text{ }^{\circ}\text{C}$ . The title compound was obtained as a 96:4 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 20/1 to 1/1) to give the title compound as a colorless oil. Yield: 88% (123.6 mg).  $[\alpha]_{\text{D}}^{21} = +43.0^{\circ}$  ( $c=1$ , 92% *ee*,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.80 (d,  $J=8.3$  Hz, 1H), 7.28 – 7.16 (m, 2H), 7.01 (s, 1H), 6.92 – 6.81 (m, 3H), 3.78 (s, 3H), 3.49 (s, 1H), 2.80 – 2.72 (m, 1H), 2.57 – 2.47 (m, 2H), 2.37 (s, 3H), 2.33 – 2.24 (m, 1H), 1.65 (s, 9H), 1.27 (s, 3H), 1.18 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 213.4, 176.5, 159.8, 149.2, 141.0, 137.3, 134.5, 130.1, 129.7, 129.4, 125.1, 119.3, 115.1, 113.5, 112.5, 84.5, 76.3, 56.1, 55.2, 31.6, 30.9, 28.1, 26.4, 26.3, 21.1. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{27}\text{H}_{34}\text{NO}_6$  ( $\text{M}+\text{H}^+$ ), 468.2386; found, 468.2381.

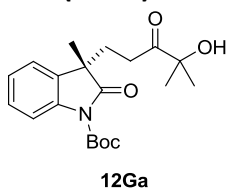
**(R)-tert-Butyl 3-(3-chlorophenyl)-3-(4-hydroxy-4-methyl-3-oxopentyl)-2-oxoindoline-1-carboxylate (12Fa)**



Prepared according to the general procedure starting from N-Boc-3-*m*-chlorophenyl-2-oxoindole **11Fa** (103.2 mg, 0.3 mmol) at  $-50\text{ }^{\circ}\text{C}$ . The title compound was obtained as a 99:1 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 20/1 to 1/1) to give the title compound as an oil. Yield: 85% (117.6 mg).  $[\alpha]_{\text{D}}^{21} = +58.3^{\circ}$  ( $c=0.5$ , 98% *ee*,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.87 (d,  $J=8.2$  Hz, 1H), 7.33 (td,  $J=7.8$  Hz,  $J=1.4$  Hz, 1H), 7.25 – 7.11 (m, 6H), 3.31 (s, 1H), 2.71 – 2.62 (m, 1H), 2.49 – 2.37 (m, 2H), 2.20 – 2.11 (m, 1H), 1.57 (s, 9H), 1.17 (s, 3H), 1.08 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 211.1, 174.1, 147.2, 139.5, 138.0, 132.9, 128.1, 127.4, 127.3, 126.3, 125.4, 123.4, 123.1, 122.9, 113.7, 83.1, 74.5, 54.0, 30.0, 29.0, 26.2, 24.6, 24.5. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{25}\text{H}_{29}\text{ClNO}_5$  ( $\text{M}+\text{H}^+$ ), 458.1734; found, 458.1738.

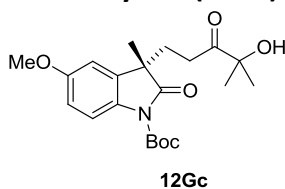
**(S)-tert-Butyl 3-(4-hydroxy-4-methyl-3-oxopentyl)-3-methyl-2-oxoindoline-1-carboxylate (12Ga)**



Prepared according to the general procedure starting from N-Boc-3-methyl-2-oxoindole **11Ga** (74.1 mg, 0.3 mmol) at  $-30\text{ }^{\circ}\text{C}$ . The title compound was obtained as a 95:5 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 20/1 to 1/1) to give the title compound as a white solid. Yield: 90% (97.5 mg). m.p. =  $90\text{--}92\text{ }^{\circ}\text{C}$ .  $[\alpha]_{\text{D}}^{22} = +25.4^{\circ}$  ( $c=0.5$ , 90% *ee*,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.83 (d,  $J=8.2$  Hz, 1H), 7.33 – 7.27 (m, 1H), 7.18 (d,  $J=4.3$  Hz, 2H), 3.48 (s, 1H), 2.48 – 2.36 (m, 1H), 2.28 – 2.10 (m, 3H), 1.66 (s, 9H), 1.44 (s, 3H), 1.25 (s, 3H), 1.15 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 213.3, 178.7, 149.2, 139.0, 131.9, 128.4, 124.7, 122.6, 115.1, 84.5, 76.3, 47.8, 32.2, 30.6, 28.1, 26.4, 26.3, 24.9. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{20}\text{H}_{28}\text{NO}_5$  ( $\text{M}+\text{H}^+$ ), 362.1967; found, 362.1962.

**(S)-tert-Butyl 3-(4-hydroxy-4-methyl-3-oxopentyl)-5-methoxy-3-methyl-2-oxoindoline-1-carboxylate (12Gc)**

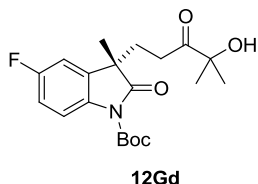


Prepared according to the general procedure starting from N-Boc-3-methyl-2-oxoindole **11Gc** (83.1 mg, 0.3 mmol) at  $-30\text{ }^{\circ}\text{C}$ . The title compound was obtained as a 95:5 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel

(eluting with hexane/ ethyl acetate 20/1 to 1/1) to give the title compound as a white solid. Yield: 92% (108.0 mg). m.p.= 94–97 °C.  $[\alpha]_D^{21} = +8.9^\circ$  ( $c=0.5$ , 92% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.77 (d,  $J=8.9$  Hz, 1H), 6.83 (dd,  $J=8.9$  Hz,  $J=2.7$  Hz, 1H), 6.75 (d,  $J=2.7$  Hz, 1H), 3.82 (s, 3H), 3.47 (s, 1H), 2.51 – 2.40 (m, 1H), 2.27 – 2.12 (m, 3H), 1.66 (s, 9H), 1.44 (s, 3H), 1.28 (s, 3H), 1.18 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 213.4, 178.7, 157.2, 149.3, 133.3, 132.2, 116.1, 113.0, 108.9, 84.4, 76.3, 55.7, 48.2, 32.2, 30.6, 28.1, 26.5, 26.3, 24.9. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{21}\text{H}_{30}\text{NO}_6$  ( $\text{M}+\text{H}^+$ ), 392,2073; found, 392.2076.

### (S)-tert-Butyl 5-fluoro-3-(4-hydroxy-4-methyl-3-oxopentyl)-3-methyl-2-oxoindoline-1-carboxylate (12Gd)

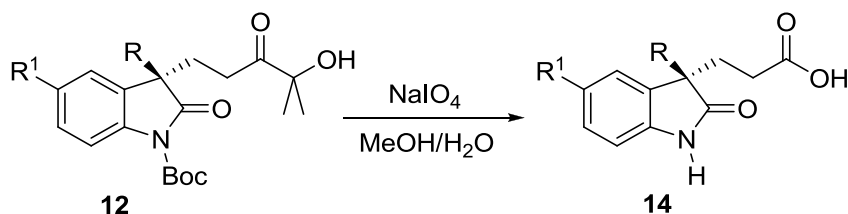


Prepared according to the general procedure starting from N-Boc-5-fluoro-3-methyl-2-oxoindole **11Gd** (79.5 mg, 0.3 mmol) at  $-30^\circ\text{C}$ . The title compound was obtained as a 95:5 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 20/1 to 1/1) to give the title compound as a colorless oil. Yield: 86% (97.8 mg).  $[\alpha]_D^{23} = +24.5^\circ$  ( $c=0.5$ ,

86% ee,  $\text{CH}_2\text{Cl}_2$ ).

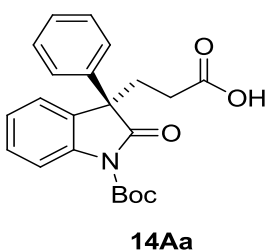
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.84 (dd,  $J=8.9$  Hz,  $J=4.6$  Hz, 1H), 7.01 (td,  $J=8.9$  Hz,  $J=2.7$  Hz, 1H), 6.92 (dd,  $J=7.6$  Hz,  $J=2.7$  Hz, 1H), 3.45 (s, 1H), 2.50 – 2.41 (m, 1H), 2.29 – 2.12 (m, 3H), 1.66 (s, 9H), 1.44 (s, 3H), 1.28 (s, 3H), 1.20 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 213.1, 178.2, 161.4, 158.9, 149.1, 134.8, 134.0, 133.9, 116.6, 116.5, 115.0, 114.8, 110.3, 110.0, 84.8, 76.4, 48.1, 32.2, 30.5, 28.1, 26.5, 26.4, 24.7. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{20}\text{H}_{27}\text{FNO}_5$  ( $\text{M}+\text{H}^+$ ), 380.1873; found, 380.1876.

## 2.4.3. Elaboration of adducts 12 into carboxylic acids 14



A suspension of sodium periodate  $\text{NaIO}_4$  (321 mg, 1.5 mmol) in water (0.75 mL) was added to a solution of the corresponding  $\alpha$ -hydroxy ketone **12** (0.3 mmol) in methanol (1.5 mL). The mixture was stirred at room temperature until the reaction was complete (monitored by TLC). Then the solvent was removed under reduced pressure. Water (4.5 mL) was added to the crude product and the resulting mixture was extracted with  $\text{Et}_2\text{O}$  (3 x 6 mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and the solvent was evaporated to afford the corresponding carboxylic acid. The crude product was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 10/1 to 1/2).

### 3-((R)-1-(tert-butoxycarbonyl)-2-oxo-3-phenylindolin-3-yl)propanoic acid (14Aa)

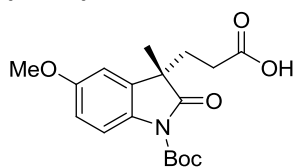


Prepared according to the general procedure starting from  $\alpha$ -hydroxy ketone **12Aa** (126.9 mg, 0.3 mmol). The title compound was obtained as a colorless oil. Yield: 98% (112.2 mg).  $[\alpha]_D^{22} = +60.5^\circ$  ( $c=1$ , 96% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.97 (d,  $J=8.2$  Hz, 1H), 7.42 – 7.22 (m, 8H), 2.88 – 2.80 (m, 1H), 2.58 – 2.50 (m, 1H), 2.34 – 2.26 (m, 1H), 2.11 – 2.02 (m, 1H), 1.64 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 178.2, 176.2, 149.1, 139.9, 139.1, 129.8, 128.9, 128.8, 127.8, 127.0,

124.8, 124.7, 115.5, 84.7, 55.9, 32.7, 29.6, 28.1. MS (ESI,  $m/z$ ): calcd for  $C_{22}H_{24}NO_5$  ( $M+H^+$ ), 382.1624; found, 380.1494.

**3-((*S*)-1-(*tert*-butoxycarbonyl)-5-methoxy-3-methyl-2-oxoindolin-3-yl)propanoic acid (**14Gc**)**

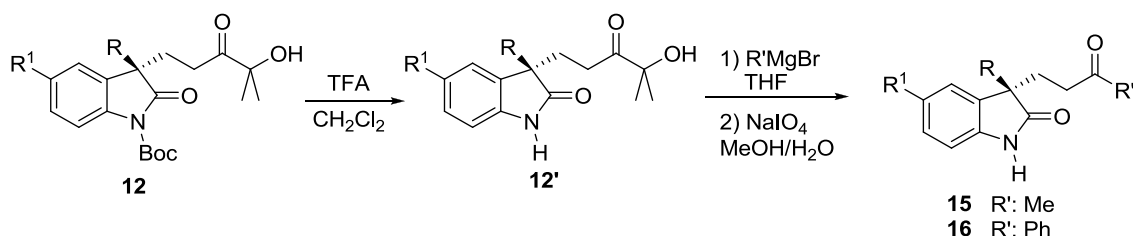


**14Gc**

Prepared according to the general procedure starting from  $\alpha$ -hydroxy ketone **12Gc** (117.4 mg, 0.3 mmol). The title compound was obtained as a colorless oil. Yield: 94% (98.5 mg).  $[\alpha]_D^{21} = +14.1^\circ$  ( $c=1$ , 92% *ee*,  $CH_2Cl_2$ ).

$^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  = 7.77 (d,  $J=8.9$  Hz, 1H), 6.83 (dd,  $J=8.9$  Hz,  $J=2.7$  Hz, 1H), 6.75 (d,  $J=2.7$  Hz, 1H), 3.82 (s, 3H), 2.32 – 2.16 (m, 2H), 2.12 – 1.95 (m, 2H), 1.65 (s, 9H), 1.44 (s, 3H).  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  = 178.5, 178.1, 157.1, 149.2, 133.0, 132.4, 116.1, 113.0, 108.9, 84.3, 55.6, 48.1, 33.4, 29.3, 28.1, 24.6. MS (ESI,  $m/z$ ): calcd for  $C_{18}H_{24}NO_6$  ( $M+H^+$ ), 350.1604; found, 350.1442.

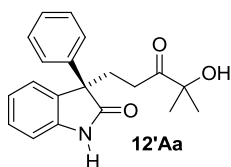
**2.4.4. Elaboration of adducts 12 into ketones 15 and 16**



Trifluoroacetic acid (0.85 mL) was added to a solution of N-Boc derivative **12** (1.25 mmol) in  $CH_2Cl_2$  (8.5 mL) at room temperature and the resulting solution was stirred at the same temperature until the reaction was complete (monitored by TLC). The reaction mixture was diluted with ethyl acetate (20 mL) and neutralized at 0 °C with  $NaHCO_3$  (saturated solution). The organic layer was separated and the aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over  $MgSO_4$  and evaporated under reduced pressure. The crude material **12'** was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 20/1 to 1/1).

$R'MgBr$  (1.5 mmol) was added to a solution of the corresponding  $\alpha$ -hydroxy ketone **12'** (0.3 mmol) in dry THF (1.5 mL) at 0 °C and the resulting solution was stirred at room temperature until the reaction was complete (monitored by TLC). Then  $NH_4Cl$  (saturated solution, 3 mL) was added at 0 °C and the resulting mixture was extracted with  $CH_2Cl_2$  (3 x 5 mL). The solvents were removed under reduced pressure and the residue thus obtained was subjected to oxidative scission by treatment with  $NaIO_4$ , under the same conditions reported above. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 20/1 to 1/1).

**(*R*)-3-(4-Hydroxy-4-methyl-3-oxopentyl)-3-phenylindolin-2-one (**12'Aa**)**

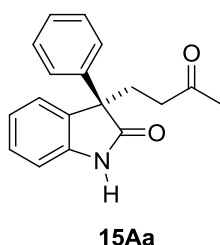


**12'Aa**

Prepared according to the general procedure starting from N-Boc derivative **12Aa** (529 mg, 1.25 mmol). The title compound was isolated as a colorless oil. Yield: 92% (372 mg).  $[\alpha]_D^{23} = +58.3^\circ$  ( $c=1$ , 96% *ee*,  $CH_2Cl_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.84 (s, 1H), 7.40 – 7.24 (m, 6H), 7.19 (d,  $J$ =7.2 Hz, 1H), 7.09 (t,  $J$ =7.5 Hz, 1H), 6.96 (d,  $J$ =7.7 Hz, 1H), 3.62 (s, 1H), 2.77 – 2.68 (m, 1H), 2.65 – 2.53 (m, 2H), 2.38 – 2.30 (m, 1H), 1.26 (s, 3H), 1.18 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 213.7, 180.7, 140.8, 139.3, 132.3, 128.8, 128.6, 127.6, 126.7, 125.0, 123.0, 110.3, 76.4, 56.3, 30.8, 30.7, 26.4, 26.3.

### (*R*)-3-(3-Oxobutyl)-3-phenylindolin-2-one (15Aa)

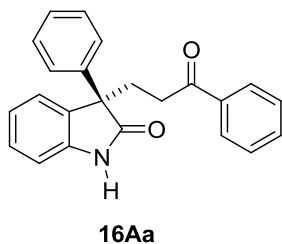


Prepared according to the general procedure starting from  $\alpha$ -hydroxy ketone **12'Aa** (97.0 mg, 0.3 mmol) and  $\text{MeMgBr}$  (3.2 M, 0.47 mL, 1.5 mmol). The title compound was isolated as a white solid. Yield: 82% (68.7 mg). m.p.=144 – 146°C.  $[\alpha]_{\text{D}}^{22}$  = + 75.9° ( $c$ =0.5, 96% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 9.31 (s, 1H), 7.39 – 7.24 (m, 6H), 7.16 (d,  $J$ =7.4 Hz, 1H), 7.08 (t,  $J$ =7.5 Hz, 1H), 6.98 (d,  $J$ =7.8 Hz, 1H), 2.73 – 2.66 (m, 1H), 2.61 – 2.54 (m, 1H), 2.48 – 2.40 (m, 1H), 2.21 – 2.14 (m, 1H), 2.03 (s, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 207.6, 181.1, 140.0, 139.5, 132.5, 128.7, 128.4, 124.5, 126.8, 124.9, 122.9, 110.4, 56.2, 38.6, 30.7, 30.0. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{18}\text{H}_{18}\text{NO}_2$  ( $\text{M}+\text{H}^+$ ), 280.1338; found, 280.1341.

### (*R*)-3-(3-Oxo-3-phenylpropyl)-3-phenylindolin-2-one (16Aa)

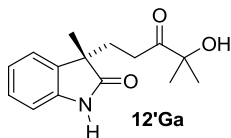


Prepared according to the general procedure starting from  $\alpha$ -hydroxy ketone **12'Aa** (97.0 mg, 0.3 mmol) and  $\text{PhMgBr}$  (1 M, 1.5 mL, 1.5 mmol). The title compound was isolated as a colorless oil. Yield: 71% (72.7 mg).  $[\alpha]_{\text{D}}^{22}$  = + 39.3° ( $c$ =1, 96% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 9.37 (s, 1H), 7.83 (d,  $J$ =7.2 Hz, 2H), 7.53 – 7.00 (m, 12H), 3.05 – 2.97 (m, 1H), 2.94 – 2.86 (m, 1H), 2.78 – 2.68 (m, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 199.2, 181.2, 141.0, 139.5, 136.6,

133.1, 132.6, 128.8, 128.5, 128.0, 127.6, 126.9, 124.9, 122.9, 110.5, 56.4, 33.7, 31.5. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{23}\text{H}_{20}\text{NO}_2$  ( $\text{M}+\text{H}^+$ ), 342.1494; found, 342.1491.

### (*S*)-3-(4-Hydroxy-4-methyl-3-oxopentyl)-3-methylindolin-2-one (12'Ga)

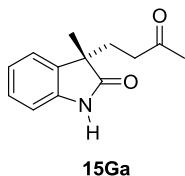


Prepared according to the general procedure starting from N-Boc derivative **12Ga** (452 mg, 1.25 mmol). The title compound was isolated as a colorless oil. Yield: 90% (293 mg).  $[\alpha]_{\text{D}}^{21}$  = + 20.0° ( $c$ =1, 90% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.52 (s, 1H), 7.14 (td,  $J$ =7.7 Hz,  $J$ =1.3 Hz, 1H), 7.08 (d,  $J$ =7.4 Hz, 1H), 6.98 (td,  $J$ =7.5 Hz,  $J$ =1.0 Hz, 1H), 6.86 (d,  $J$ =7.7 Hz, 1H), 3.53 (s, 1H), 2.42 – 2.31 (m, 1H), 2.17 – 1.97 (m, 3H), 1.35 (s, 3H), 1.17 (s, 3H), 1.07 (s, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 213.6, 182.5, 140.3, 133.5, 128.1, 123.2, 122.8, 109.9, 76.3, 48.1, 31.5, 30.6, 26.4, 26.2, 23.8.

### (*S*)-3-Methyl-3-(3-oxobutyl)indolin-2-one (15Ga)

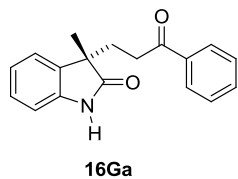


Prepared according to the general procedure starting from  $\alpha$ -hydroxy ketone **12'Ga** (78.0 mg, 0.3 mmol) and  $\text{MeMgBr}$  (3.2 M, 0.47 mL, 1.5 mmol). The title compound was isolated as a white solid. Yield: 80% (52.3mg). m.p.= 130–133 °C.  $[\alpha]_{\text{D}}^{21}$  = + 30.2° ( $c$ =1, 90% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 9.24 (s, 1H), 7.23 (td,  $J$ =7.6 Hz,  $J$ =1.3 Hz, 1H), 7.15 (d,  $J$ =6.9 Hz, 1H), 7.06 (td,  $J$ =7.5 Hz,  $J$ =1.0 Hz, 1H), 6.98 (d,  $J$ =7.7 Hz, 1H), 2.36 – 2.28 (m, 1H), 2.21 – 2.10 (m, 2H), 2.09 – 2.01 (m, 1H), 2.00 (s, 3H), 1.43 (s, 3H).

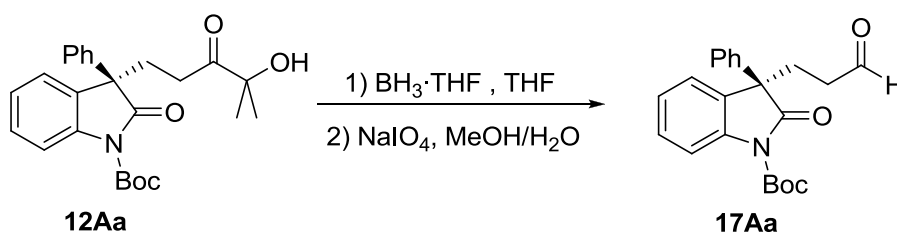
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 207.7, 183.1, 140.5, 133.7, 128.2, 123.0, 122.7, 110.0, 48.0, 38.6, 31.7, 29.9, 23.7. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{13}\text{H}_{16}\text{NO}_2$  ( $\text{M}+\text{H}^+$ ), 218.1181; found, 218.1185.

### (S)-3-Methyl-3-(3-oxo-3-phenylpropyl)indolin-2-one (16Ga)



Prepared according to the general procedure starting from  $\alpha$ -hydroxy ketone **12'Ga** (78.0 mg, 0.3 mmol) and PhMgBr (1 M, 1.5 mL, 1.5 mmol). The title compound was isolated as an oil. Yield: 75% (62.6 mg).  $[\alpha]_D^{21} = -4.3^\circ$  ( $c=1$ , 90% *ee*, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 8.38 (s, 1H), 7.83 – 7.81 (m, 2H), 7.54 – 7.49 (m, 1H), 7.41 – 7.37 (m, 2H), 7.25 – 7.21 (m, 2H), 7.07 (td,  $J=7.5$  Hz,  $J=1.0$  Hz, 1H), 6.95 (d,  $J=7.6$  Hz, 1H), 2.95 – 2.87 (m, 1H), 2.60 – 2.52 (m, 1H), 2.40 – 2.26 (m, 2H), 1.49 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 199.2, 182.5, 140.2, 136.6, 133.8, 133.0, 128.5, 128.1, 128.2, 123.1, 122.8, 109.8, 48.1, 33.6, 32.3, 23.8. MS (ESI,  $m/z$ ): calcd for C<sub>18</sub>H<sub>18</sub>NO<sub>2</sub> ( $M+H^+$ ), 280.1338; found, 280.1336.

### 2.4.5. Elaboration of adduct **12Aa** into aldehyde **17Aa**



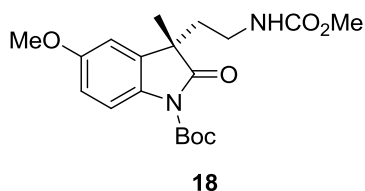
### (R)-tert-Butyl 3-(2-formylethyl)-2-oxo-3-phenylindoline-1-carboxylate (17Aa)

BH<sub>3</sub>·THF complex (1 M, 0.6 mL, 0.6 mmol) was added to a solution of  $\alpha$ -hydroxy ketone **12Aa** (126.9 mg, 0.3 mmol) in dry THF (0.9 mL) at 0 °C and the resulting solution was stirred at the same temperature for 2 h. Then MeOH (1 mL) was added and the resulting mixture was stirred at room temperature for 30 min. The solvents were removed under reduced pressure and the residue thus obtained was subjected to oxidative scission by treatment with NaIO<sub>4</sub>, under the same conditions reported above. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 20/1 to 1/1) to give the title compound as a white solid. Yield: 91% (99.9 mg). m.p.=109–111 °C.  $[\alpha]_D^{23} = +71.2^\circ$  ( $c=1$ , 94% *ee*, CHCl<sub>3</sub>). Lit<sup>27</sup> for enantiomer  $[\alpha]_D^{23} = -63.67^\circ$  ( $c=1$ , 90% *ee*, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 9.65 (s, 1H), 7.97 (d,  $J=8.2$  Hz, 1H), 7.42 – 7.21 (m, 7H), 2.86 – 2.79 (m, 1H), 2.58 – 2.51 (m, 1H), 2.46 – 2.37 (m, 1H), 2.21 – 2.13 (m, 1H), 1.65 (s, 9H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 200.3, 176.3, 149.1, 139.9, 130.0, 128.9, 128.8, 127.8, 127.0, 124.8, 124.7, 115.4, 84.7, 55.8, 39.4, 30.3, 28.1. MS (ESI,  $m/z$ ): calcd for C<sub>22</sub>H<sub>24</sub>NO<sub>4</sub> ( $M+H^+$ ), 366.1705; found, 366.1701.



## 2.4.6. Synthesis of (–)-esermethole

### Methyl 2-((S)-1(*tert*-butoxycarbonyl)-5-methoxy-3-methyl-2-oxindolin-3-yl)ethylcarbamate (**18**)

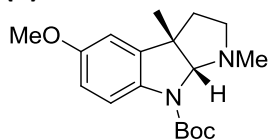


A round-bottomed flask equipped with a rubber septum and a refluxed condenser, under nitrogen atmosphere, was charged with the carboxylic acid **14Gc** (419 mg, 1.2 mmol), 2 mL of toluene, and triethylamine (0.17 mL, 1.21 mmol). Diphenylphosphorylazide (0.26 mL, 1.2 mmol) was added dropwise via syringe, and the resulting solution was heated at 80 °C for 2 h. The reaction mixture was cooled to 50 °C, then

methanol (0.50 mL) was added and the resulting mixture was stirred at 50 °C for 14 h. The reaction mixture was allowed to cool to room temperature and the solvents were removed by rotary evaporation. The resulting oil was diluted with 20 mL of Et<sub>2</sub>O, 10 mL of water, and 5 mL of saturated solution of Na<sub>2</sub>CO<sub>3</sub>. The aqueous layer was separated and extracted with three 20 mL portions of Et<sub>2</sub>O, and the combined organic layers were washed with 20 mL of saturated solution of NaCl solution, dried over MgSO<sub>4</sub>, filtered and evaporated. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 10/1 to 1/1) to give the title compound as an oil. Yield: 87% (395 mg).  $[\alpha]_D^{23} = -8.1^\circ$  (*c*=1, 90% *ee*, CH<sub>2</sub>Cl<sub>2</sub>).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.75 (d, *J*=8.8 Hz, 1H), 6.81 (dd, *J*=8.8 Hz, *J*=2.6 Hz, 1H), 6.76 (d, *J*=2.6 Hz, 1H), 4.65 (s<sub>br</sub>, 1H), 3.80 (s, 3H), 3.57 (s, 3H), 3.06 – 2.88 (m, 2H), 2.23 – 2.15 (m, 1H), 2.07 – 1.97 (m, 1H), 1.63 (s, 9H), 1.40 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 179.0, 157.1, 156.7, 149.2, 133.2, 132.1, 116.1, 112.9, 108.9, 84.1, 55.6, 51.9, 47.6, 38.4, 37.3, 28.1, 25.2. MS (ESI, *m/z*): calcd for C<sub>19</sub>H<sub>27</sub>N<sub>2</sub>O<sub>6</sub> (*M*+H<sup>+</sup>), 379.1869; found, 379.1871.

### (–)-Esermethole

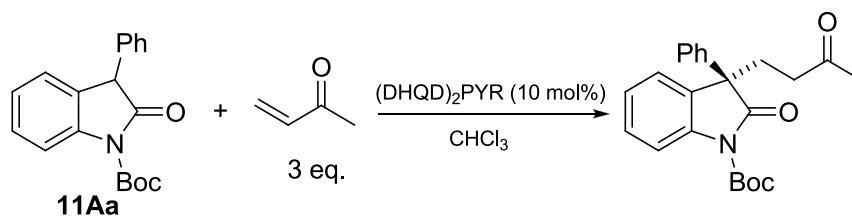


LAH (161 mg, 4.25 mmol) was added to a solution of oxindole **18** (321.7 mg, 0.85 mmol) in dry THF (30 mL) at room temperature. The resulting mixture was heated to reflux for 2 h and then allowed to cool to room temperature. Ethyl acetate (100 mL) and saturated aqueous NaHCO<sub>3</sub> (50 mL) were added. The aqueous layer was separated and extracted

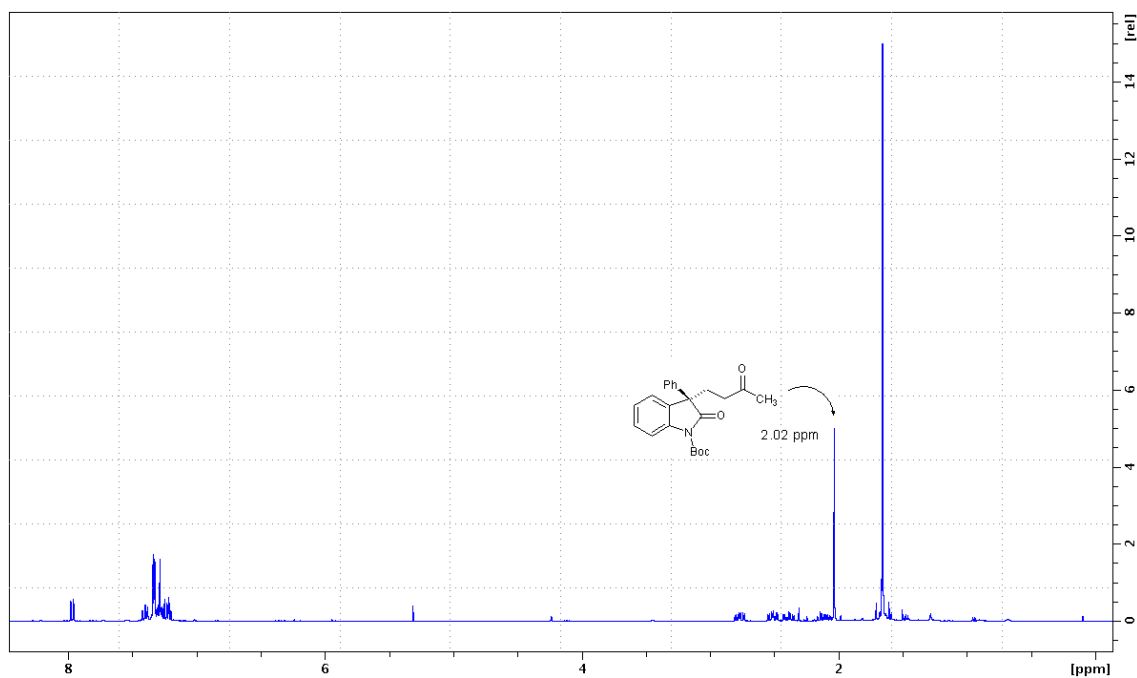
with ethyl acetate (3 x 20 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 20/1) afforded the title product as an oil. Yield: 90% (178 mg).  $[\alpha]_D^{23} = -112.2^\circ$  (*c*=1, 90% *ee*, C<sub>6</sub>H<sub>6</sub>); Literature:<sup>28</sup>  $[\alpha]_D^{24} = -140.1^\circ$  (*c* 1.0, C<sub>6</sub>H<sub>6</sub>, 99% *ee*). Literature data for the opposite enantiomer:<sup>29</sup>  $[\alpha]_D^{24} = +132^\circ$  (*c* 0.85, C<sub>6</sub>H<sub>6</sub>, 96% *ee*).

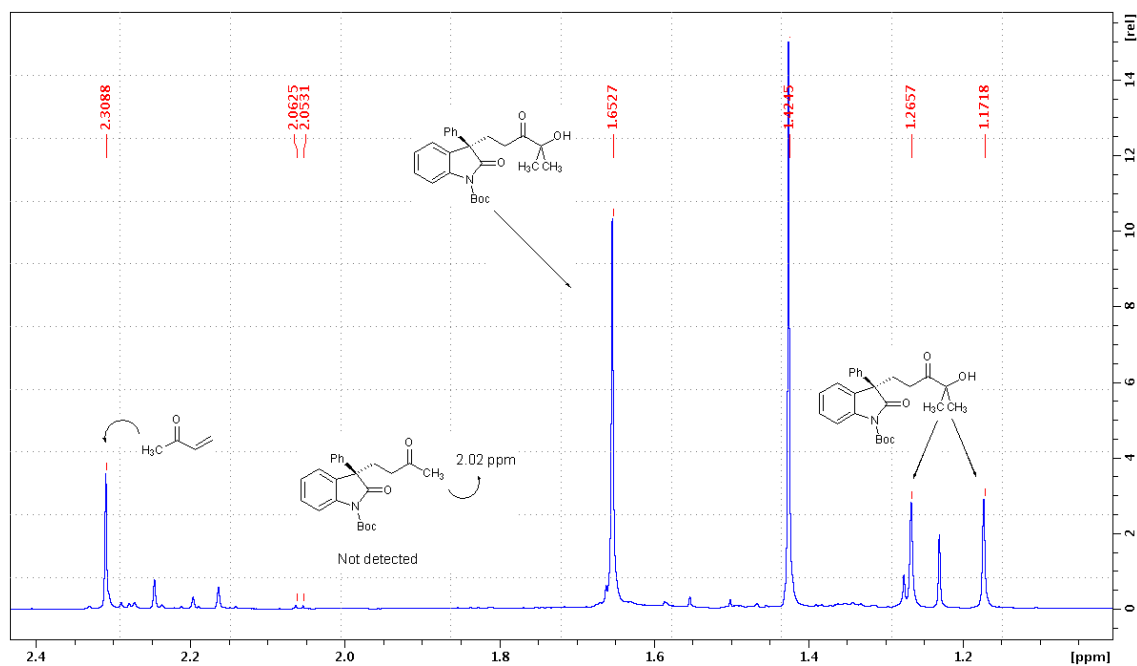
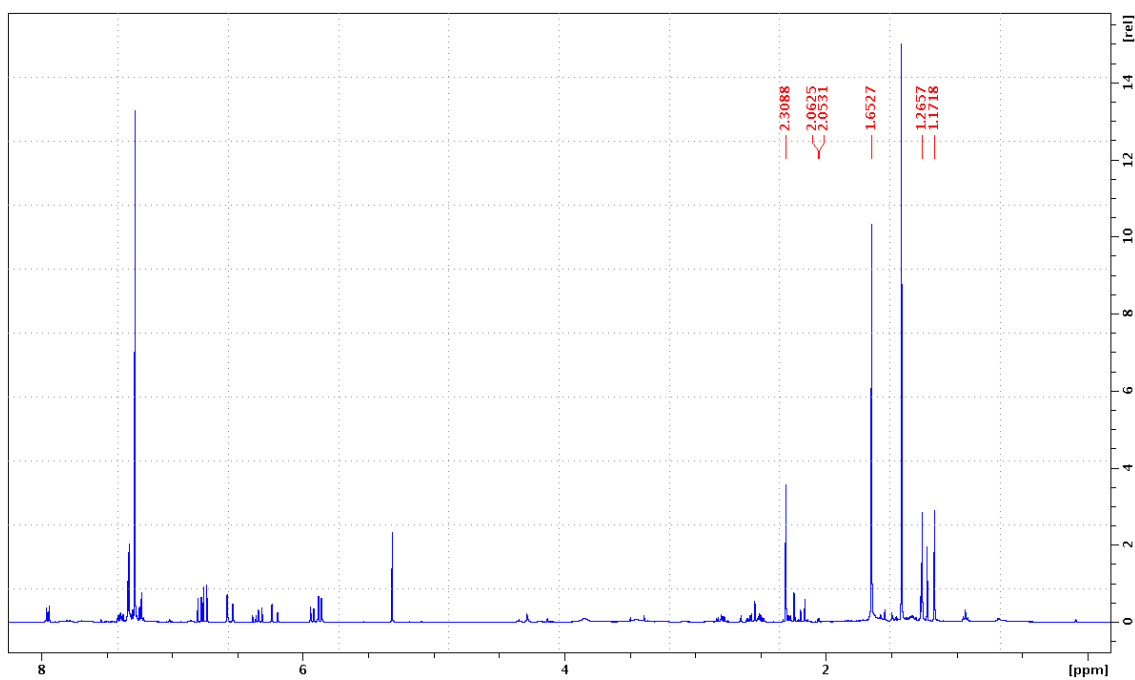
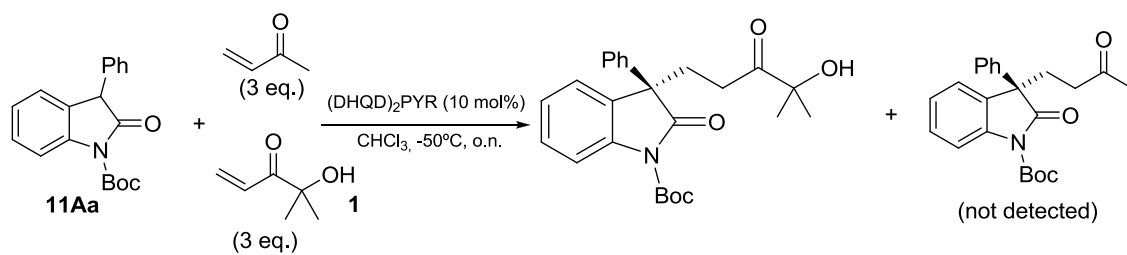
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 6.68 – 6.64 (m, 2H), 6.37 (d, *J*=8.2 Hz, 1H), 4.11 (s, 1H), 3.75 (s, 3H), 2.91 (s, 3H), 2.80 – 2.75 (m, 1H), 2.67 – 2.61 (m, 1H), 2.56 (s, 3H), 2.00 – 1.97 (m, 2H), 1.45 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 153.1, 146.4, 138.1, 112.3, 109.8, 107.6, 98.2, 56.0, 53.1, 52.8, 40.7, 38.0, 37.9, 27.4. MS (ESI, *m/z*): calcd for C<sub>18</sub>H<sub>27</sub>N<sub>2</sub>O<sub>3</sub> (*M*+H<sup>+</sup>), 319.2022; found, 319.2025.

### 2.4.7. Parallel and competitive experiments with methyl vinyl ketone

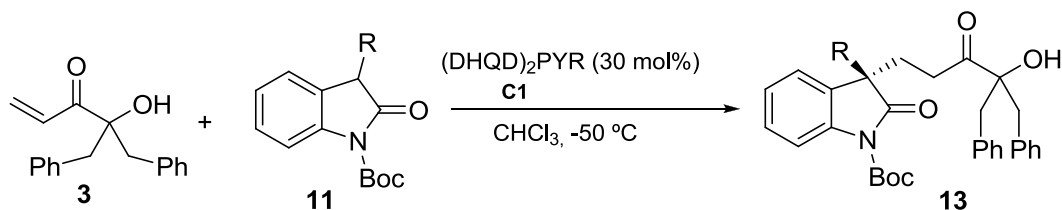


T (°C)	t (h)	Conversion (%)	ee (%)
-50	48	0	---
-30	24	35	---
0	18	100	50



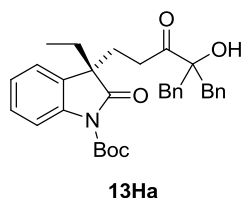


### 2.4.8. Addition of oxindoles **11** to $\alpha'$ -hydroxy enone **3**



(DHQD)<sub>2</sub>PYR **C1** (30 mol%, 26.4 mg, 0.03 mmol) was added to a solution of N-Boc-3-substituted oxindole **11** (0.1 mmol) and  $\alpha'$ -hydroxy enone **3** (79.9 mg, 0.3 mmol) in CHCl<sub>3</sub> cooled to -50 °C and the resulting solution was stirred at the same temperature until the reaction was complete (it was monitored by TLC). The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed twice with 0.1N HCl and the organic layer was dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure and the product was purified by column chromatography.

#### (S)-tert-Butyl 3-(4-benzyl-4-hydroxy-3-oxo-5-phenylpentyl)-3-ethyl-2-oxoindoline-1-carboxylate (**13Ha**)

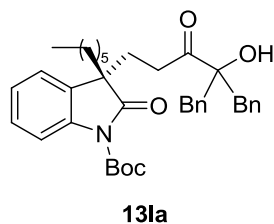


Prepared according to the general procedure starting from N-Boc-3-ethyl-2-oxoindol **11Ha** (26.1 mg, 0.1 mmol) and hydroxy enone **3** (79.9 mg, 0.3 mmol) in CHCl<sub>3</sub> (0.4 mL) at -50 °C. The title compound was obtained as a 92:8 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 50/1 to 10/1) to give the title compound as an oil.

Yield: 86% (45.4 mg). [ $\alpha$ ]<sub>D</sub><sup>25</sup> = +12.1° (c=2.0, 84% ee, CH<sub>2</sub>Cl<sub>2</sub>).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.87 (d, *J*=7.9 Hz, 1H), 7.36 – 7.13 (m, 10H), 7.05 – 7.00 (m, 3H), 3.23 (s, 1H), 3.03 – 2.89 (m, 4H), 2.33 – 2.24 (m, 1H), 2.00 – 1.89 (m, 3H), 1.85 – 1.64 (m, 2H), 1.70 (s, 9H), 0.62 (t, *J*=7.4 Hz, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  212.5, 178.2, 149.2, 139.8, 135.5, 135.5, 130.1, 130.1, 130.0, 128.3, 128.2, 127.0, 126.9, 124.6, 122.7, 114.9, 84.4, 82.6, 52.6, 44.9, 44.5, 33.0, 31.7, 30.9, 28.2, 8.5. MS (ESI, *m/z*): calcd for C<sub>33</sub>H<sub>38</sub>NO<sub>5</sub> (M+H<sup>+</sup>), 528.2750; found, 528.2745.

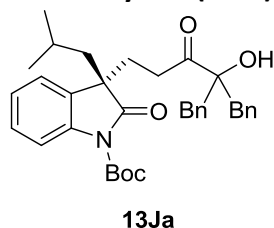
#### (S)-tert-Butyl 3-(4-benzyl-4-hydroxy-3-oxo-5-phenylpentyl)-3-hexyl-2-oxoindoline-1-carboxylate (**13la**)



Prepared according to the general procedure starting from N-Boc-3-hexyl-2-oxoindol **11la** (31.7 mg, 0.1 mmol) and hydroxy enone **3** (79.9 mg, 0.3 mmol) in CHCl<sub>3</sub> (0.4 mL) at -50 °C. The title compound was obtained as a 8:92 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 20/1 to 1/1) to give the title compound as an oil. Yield: 81% (47.2 mg). [ $\alpha$ ]<sub>D</sub><sup>25</sup> = +7.1° (c=1.5, 84% ee, CH<sub>2</sub>Cl<sub>2</sub>).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.87 (d, *J*=8.2 Hz, 1H), 7.36 – 7.14 (m, 10H), 7.05 – 7.00 (m, 3H), 3.23 (s, 1H), 3.02 (d, *J*=13.7 Hz, 1H), 2.96 – 2.89 (m, 3H), 2.33 – 2.24 (m, 1H), 2.01 – 1.61 (m, 7H), 1.70 (s, 9H), 1.23 – 1.13 (m, 6H), 0.84 (t, *J*=7.0 Hz, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  212.5, 178.3, 149.2, 139.7, 135.3, 130.3, 130.1, 130.0, 129.9, 128.3, 128.2, 128.21, 127.0, 126.9, 124.6, 122.7, 114.9, 84.4, 82.6, 52.0, 44.9, 44.5, 38.6, 32.9, 31.4, 31.3, 29.3, 28.2, 24.0, 22.6, 14.0. MS (ESI, *m/z*): calcd for C<sub>37</sub>H<sub>46</sub>NO<sub>5</sub> (M+H<sup>+</sup>), 584.3376; found, 584.3371.

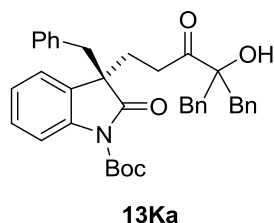
**(*R*)-tert-Butyl 3-(4-benzyl-4-hydroxy-3-oxo-5-phenylpentyl)-3-isobutyl-2-oxoindoline-1-carboxylate (13Ja)**



Prepared according to the general procedure starting from N-Boc-3-isobutyl-2-oxoindol **11Ja** (28.9 mg, 0.1 mmol) and hydroxy enone **3** (79.9 mg, 0.3 mmol) in  $\text{CHCl}_3$  (0.4 mL) at  $-50^\circ\text{C}$ . The title compound was obtained as a 11:89 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 50/1 to 10/1) to give the title compound as an oil. Yield: 80% (44.5 mg).  $[\alpha]_{\text{D}}^{25} = +13.1^\circ$  ( $c=1.5$ , 78% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.87 (d,  $J=7.9$  Hz, 1H), 7.34 – 7.13 (m, 10H), 7.03 – 7.01 (m, 3H), 3.25 (s, 1H), 3.01 (d,  $J=13.8$  Hz, 1H), 2.94 – 2.91 (m, 3H), 2.34 – 2.25 (m, 1H), 2.07 – 1.87 (m, 3H), 1.76 – 1.65 (m, 3H), 1.69 (s, 9H), 0.70 (d,  $J=6.6$  Hz, 3H), 0.63 (d,  $J=6.6$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  212.4, 178.3, 149.3, 139.6, 135.3, 135.2, 130.5, 130.1, 129.9, 128.3, 128.2, 127.0, 126.9, 124.5, 123.0, 115.0, 84.4, 82.6, 51.5, 46.8, 44.9, 44.6, 33.4, 32.5, 28.2, 25.1, 24.2, 22.9. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{35}\text{H}_{42}\text{NO}_5$  ( $\text{M}+\text{H}^+$ ), 556.3063; found, 556.3061.

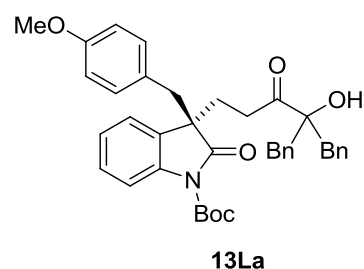
**(*R*)-tert-Butyl 3-benzyl-3-(4-benzyl-4-hydroxy-3-oxo-5-phenylpentyl)-2-oxoindoline-1-carboxylate (13Ka)**



Prepared according to the general procedure starting from N-Boc-3-benzyl-2-oxoindol **11Ka** (32.3 mg, 0.1 mmol) and hydroxy enone **3** (79.9 mg, 0.3 mmol) in  $\text{CHCl}_3$  (0.4 mL) at  $-50^\circ\text{C}$ . The title compound was obtained as a 97:3 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 50/1 to 10/1) to give the title compound as an oil. Yield: 86% (50.7 mg).  $[\alpha]_{\text{D}}^{25} = +0.7^\circ$  ( $c=0.5$ , 94% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.59 (d,  $J=7.8$  Hz, 1H), 7.30 – 6.98 (m, 16H), 6.76 – 6.74 (m, 2H), 3.19 (s, 1H), 3.15 – 2.89 (m, 6H), 2.38 – 2.30 (m, 1H), 2.19 – 2.12 (m, 1H), 2.03 – 1.85 (m, 2H), 1.60 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  212.4, 177.5, 148.7, 139.8, 135.3, 135.3, 134.8, 130.1, 130.0, 129.7, 129.0, 128.4, 128.3, 127.7, 127.0, 126.9, 126.8, 124.2, 123.2, 114.8, 84.1, 82.6, 54.0, 45.8, 45.0, 44.4, 33.4, 29.9, 28.1. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{38}\text{H}_{40}\text{NO}_5$  ( $\text{M}+\text{H}^+$ ), 590.2906; found, 590.2909.

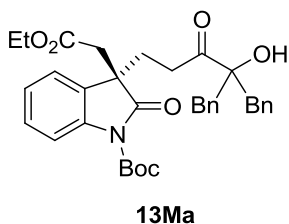
**(*R*)-tert-Butyl 3-(4-methoxybenzyl)-3-(4-benzyl-4-hydroxy-3-oxo-5-phenylpentyl)-2-oxoindoline-1-carboxylate (13La)**



Prepared according to the general procedure starting from N-Boc-3-*p*-methoxybenzyl-2-oxoindol **11La** (35.3 mg, 0.1 mmol) and hydroxy enone **3** (79.9 mg, 0.3 mmol) in  $\text{CHCl}_3$  (0.4 mL) at  $-50^\circ\text{C}$ . The title compound was obtained as a 5:95 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 50/1 to 10/1) to give the title compound as an oil. Yield: 82% (50.8 mg).  $[\alpha]_{\text{D}}^{25} = +3.2^\circ$  ( $c=0.5$ , 90% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.62 (d,  $J=7.8$  Hz, 1H), 7.30 – 7.14 (m, 10H), 7.06 – 6.97 (m, 3H), 6.69 – 6.66 (m, 2H), 6.61 – 6.57 (m, 2H), 3.22 (s, 3H), 3.09 – 3.01 (m, 2H), 2.91 – 2.86 (m, 4H), 2.38 – 2.30 (m, 1H), 2.17 – 2.09 (m, 1H), 2.01 – 1.85 (m, 2H), 1.61 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  212.4, 177.7, 158.4, 148.7, 139.8, 135.3, 130.8, 130.1, 130.0, 129.1, 127.0, 126.9, 126.8, 124.2, 123.2, 114.9, 113.1, 84.0, 82.6, 55.0, 54.1, 44.9, 44.4, 33.4, 29.8, 28.1. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{39}\text{H}_{42}\text{NO}_6$  ( $\text{M}+\text{H}^+$ ), 620.3012; found, 620.3015.

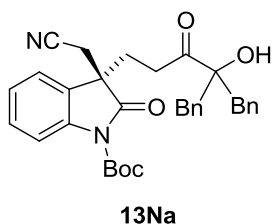
**(*R*)-tert-Butyl 3-((ethoxycarbonyl)methyl)-3-(4-benzyl-4-hydroxy-3-oxo-5-phenylpentyl)-2-oxoindoline-1-carboxylate (13Ma)**



Prepared according to the general procedure starting from N-Boc-3-ethoxycarbonylmethyl-2-oxoindol **11Ma** (31.9 mg, 0.1 mmol) and hydroxy enone **3** (79.9 mg, 0.3 mmol) in  $\text{CHCl}_3$  (0.4 mL) at  $-50^\circ\text{C}$ . The title compound was obtained as a 97:3 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 50/1 to 10/1) to give the title compound as an oil. Yield: 78% (45.7 mg).  $[\alpha]_D^{24} = +12.2^\circ$  ( $c=0.75$ , 94% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.88 (d,  $J=8.0$  Hz, 1H), 7.36 – 7.12 (m, 10H), 7.04 – 7.01 (m, 3H), 3.90 – 3.80 (m, 2H), 3.14 (s, 1H), 3.04 – 2.89 (m, 5H), 2.71 (d,  $J=16.2$  Hz, 1H), 2.31 – 2.22 (m, 1H), 2.02 – 1.94 (m, 1H), 1.86 – 1.80 (m, 1H), 1.79 – 1.67 (m, 1H), 1.69 (s, 9H), 1.00 (t,  $J=7.2$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  212.3, 177.2, 169.1, 149.2, 140.1, 135.2, 135.2, 130.0, 129.9, 129.3, 128.7, 128.4, 128.3, 127.1, 127.0, 124.5, 122.2, 115.1, 84.3, 82.7, 60.7, 48.9, 44.9, 44.7, 41.8, 32.4, 32.0, 28.2, 13.7. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{35}\text{H}_{40}\text{NO}_7$  ( $\text{M}+\text{H}^+$ ), 586.2805; found, 586.2803.

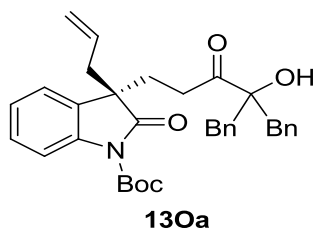
**(*R*)-tert-Butyl 3-(4-benzyl-4-hydroxy-3-oxo-5-phenylpentyl)-3-(cyanomethyl)-2-oxoindoline-1-carboxylate (13Na)**



Prepared according to the general procedure starting from N-Boc-3-cyanomethyl-2-oxoindol **11Na** (27.2 mg, 0.1 mmol) and hydroxy enone **3** (79.9 mg, 0.3 mmol) in  $\text{CHCl}_3$  (0.4 mL) at  $-50^\circ\text{C}$ . The title compound was obtained as a 96:4 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 50/1 to 10/1) to give the title compound as an oil. Yield: 80% (43.1 mg).  $[\alpha]_D^{23} = +4.4^\circ$  ( $c=0.5$ , 92% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.89 (d,  $J=8.2$  Hz, 1H), 7.43 – 7.39 (m, 1H), 7.29 – 7.21 (m, 8H), 7.12 – 7.05 (m, 4H), 3.03 (d,  $J=13.7$  Hz, 1H), 3.01 (d,  $J=13.7$  Hz, 1H), 2.90 (d,  $J=13.7$  Hz, 1H), 2.90 (s, 1H), 2.88 (d,  $J=13.7$  Hz, 1H), 2.19 – 2.11 (m, 1H), 2.00 – 1.84 (m, 3H), 1.68 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  212.2, 175.0, 148.6, 139.2, 135.2, 130.0, 129.9, 129.7, 128.5, 128.4, 127.2, 127.2, 127.1, 125.2, 123.1, 115.6, 115.5, 85.2, 82.7, 48.4, 45.0, 44.7, 33.1, 29.9, 28.1, 26.2. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{33}\text{H}_{35}\text{N}_2\text{O}_5$  ( $\text{M}+\text{H}^+$ ), 539.2546; found, 539.2548.

**(*R*)-tert-Butyl 3-allyl-3-(4-benzyl-4-hydroxy-3-oxo-5-phenylpentyl)-2-oxoindoline-1-carboxylate (13Oa)**

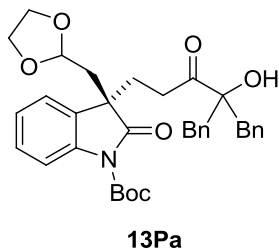


Prepared according to the general procedure starting from N-Boc-3-allyl-2-oxoindol **11Oa** (27.3 mg, 0.1 mmol) and hydroxy enone **3** (79.9 mg, 0.3 mmol) in  $\text{CHCl}_3$  (0.4 mL) at  $-50^\circ\text{C}$ . The title compound was obtained as a 94:6 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 50/1 to 10/1) to give the title compound as a white solid. Yield: 83% (44.8 mg). m.p. =  $130 - 132^\circ\text{C}$ .  $[\alpha]_D^{24} = +14.6^\circ$  ( $c=1$ , 88% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.85 (d,  $J=7.9$  Hz, 1H), 7.26 – 7.13 (m, 10H), 7.04 – 7.02 (m, 3H), 5.44 – 5.32 (m, 1H), 5.01 – 4.94 (m, 2H), 3.18 (s, 1H), 3.03 – 2.89 (m, 4H), 2.53 (dd,  $J=7.8$  Hz,  $J=13.5$  Hz, 1H), 2.44 (dd,  $J=6.8$  Hz,  $J=13.5$  Hz, 1H), 2.34 – 2.25 (m, 1H), 2.00 – 1.82 (m, 3H), 1.68 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  212.5, 177.5, 149.1, 139.5, 135.3, 131.3, 130.1, 130.0,

129.7, 128.4, 128.3, 127.0, 126.9, 124.5, 123.0, 119.6, 114.9, 84.4, 82.6, 52.0, 44.9, 44.5, 42.8, 33.0, 30.3, 28.2. MS (ESI,  $m/z$ ): calcd for  $C_{34}H_{38}NO_5$  ( $M+H^+$ ), 540.2750; found, 540.2753.

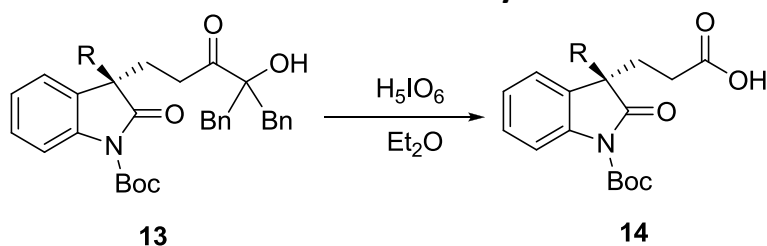
**(*R*)-tert-Butyl 3-((1,3-dioxolan-2-yl)methyl)-3-(4-benzyl-4-hydroxy-3-oxo-5-phenylpentyl)-2-oxoindoline-1-carboxylate (13Pa)**



Prepared according to the general procedure starting from N-Boc-3-((1,3-dioxolan-2-yl)methyl)-2-oxoindol **11Pa** (31.9 mg, 0.1 mmol) and hydroxy enone **3** (79.9 mg, 0.3 mmol) in  $CHCl_3$  (0.4 mL) at  $-50^\circ C$ . The title compound was obtained as a 2:98 mixture of enantiomers. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 50/1 to 10/1) to give the title compound as a white solid. Yield: 76% (44.5 mg). m.p.=  $84 - 87^\circ C$ .  $[\alpha]_D^{24} = +19.8^\circ$  ( $c=0.5$ , 96% ee,  $CH_2Cl_2$ ).

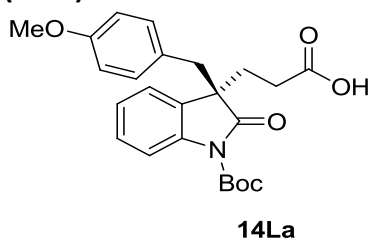
$^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.87 (d,  $J=7.9$  Hz, 1H), 7.36 – 7.00 (m, 13H), 4.59 (dd,  $J=2.8$  Hz,  $J=7.3$  Hz, 1H), 3.80 – 3.75 (m, 1H), 3.72 – 3.56 (m, 3H), 3.22 (s, 1H), 3.00 (d,  $J=13.8$  Hz, 1H), 2.93 – 2.89 (m, 3H), 2.34 – 2.26 (m, 2H), 2.12 (dd,  $J=2.8$  Hz,  $J=14.2$  Hz, 1H), 2.00 – 1.85 (m, 2H), 1.79 – 1.73 (m, 1H), 1.69 (s, 9H).  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  212.3, 177.6, 149.4, 139.8, 135.3, 135.2, 130.1, 130.0, 129.3, 128.4, 128.3, 128.2, 127.0, 126.9, 124.3, 123.1, 115.1, 101.4, 84.1, 82.6, 64.9, 64.4, 48.9, 44.9, 44.5, 41.6, 32.3, 32.2, 28.2. MS (ESI,  $m/z$ ): calcd for  $C_{35}H_{40}NO_7$  ( $M+H^+$ ), 586.2805; found, 586.2801.

### 2.4.9. Elaboration of adducts **13** into carboxylic acids **14**



Periodic acid  $\text{H}_5\text{IO}_6$  (684 mg, 3 mmol) was added to a solution of the corresponding  $\alpha$ -hydroxy ketone (0.3 mmol) in  $\text{Et}_2\text{O}$  (9 mL) and the reaction mixture was stirred at room temperature overnight. Then, the reaction mixture was filtered through a pad of silica gel. The solvent was evaporated to afford the corresponding carboxylic acid. The crude product was purified by flash column chromatography on silica gel (eluting with hexane/diethyl ether 1/1).

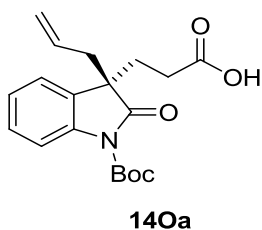
#### 3-((*R*)-1-(*tert*-Butoxycarbonyl)-3-(4-methoxybenzyl)-2-oxoindolin-3-yl)propanoic acid (**14La**)



Prepared according to the general procedure starting from  $\alpha$ -hydroxy ketone **13La** (185.9 mg, 0.3 mmol). The title compound was obtained as a colorless oil. Yield: 87% (111 mg).  $[\alpha]_{\text{D}}^{25} = +10.7^\circ$  ( $c=2$ , 90% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.62 (d,  $J=8.0$  Hz, 1H), 7.36–7.12 (m, 3H), 6.74–6.71 (m, 2H), 6.62–6.59 (m, 2H), 3.71 (s, 3H), 3.14 (d,  $J=13.2$  Hz, 1H), 2.99 (d,  $J=13.2$  Hz, 1H), 2.49–2.40 (m, 1H), 2.29–2.15 (m, 2H), 1.99–1.89 (m, 1H), 1.59 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  177.9, 177.6, 158.4, 148.7, 139.9, 130.9, 128.8, 128.5, 126.8, 124.3, 123.4, 115.0, 113.1, 84.1, 55.1, 54.2, 44.7, 31.5, 29.31, 28.0. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{24}\text{H}_{28}\text{NO}_6$  ( $\text{M}+\text{H}^+$ ), 426.1917; found, 426.1920.

#### 3-((*R*)-1-(*tert*-Butoxycarbonyl)-3-allyl-2-oxoindolin-3-yl)propanoic acid (**14Oa**)



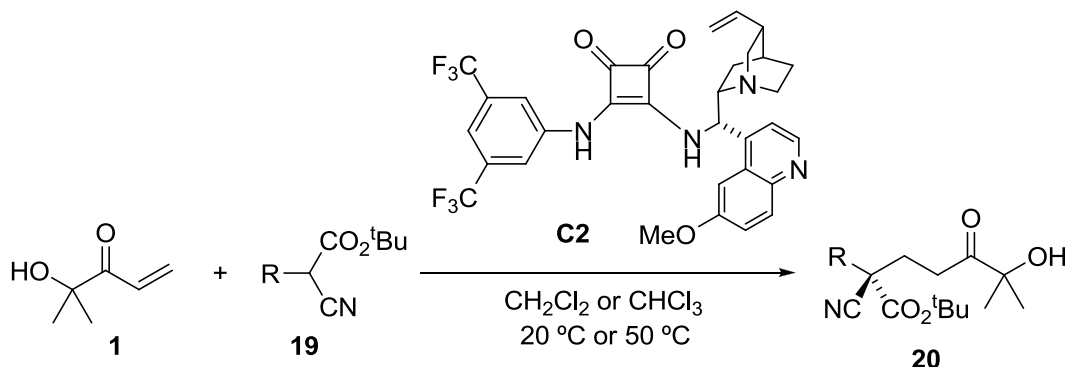
Prepared according to the general procedure starting from  $\alpha$ -hydroxy ketone **13Oa** (161.9 mg, 0.3 mmol). The title compound was obtained as a colorless oil. Yield: 90% (93.2mg).  $[\alpha]_{\text{D}}^{25} = +15.0^\circ$  ( $c=0.5$ , 88% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.84 (d,  $J=8.1$  Hz, 1H), 7.37–7.28 (m, 2H), 7.20–7.16 (m, 1H), 5.51–5.40 (m, 1H), 5.05–4.97 (m, 2H), 2.64–2.52 (m, 2H), 2.36–2.27 (m, 1H), 2.22–2.11 (m, 2H), 1.99–1.89 (m, 1H), 1.66 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  178.3, 177.5, 149.0, 139.7, 131.2, 129.4, 128.6, 124.60, 123.1, 119.8, 115.1, 84.5, 52.3, 42.8, 31.9, 29.1, 28.1. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{19}\text{H}_{24}\text{NO}_5$  ( $\text{M}+\text{H}^+$ ), 346.1654; found, 346.1658.



## 2.5. Reactions involving $\alpha$ -cyanoacetates **19**

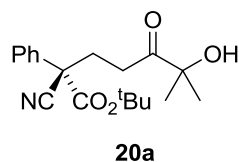
### 2.5.1. Catalytic conjugate addition of $\alpha$ -cyanoacetates **19** to **1**.



GENERAL PROCEDURE A:  $\alpha$ -substituted cyanoacetate **19** (0.3 mmol), hydroxy enone **1** (0.9 mmol) and catalyst **C2** (18.9 mg, 0.03 mmol) were stirred in  $\text{CH}_2\text{Cl}_2$  (1.2 mL) at room temperature. After the stated reaction time, the product **20** was purified by flash chromatography on silica gel (eluting with hexane/ ethyl acetate 20/1 to 10/1).

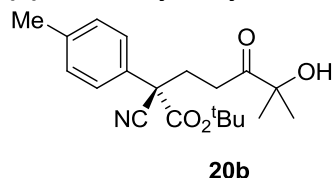
GENERAL PROCEDURE B:  $\alpha$ -substituted cyanoacetate **19** (0.9 mmol), hydroxy enone **1** (0.3 mmol) and catalyst **C2** (18.9 mg, 0.03 mmol) were stirred in  $\text{CHCl}_3$  (1.2 mL) at  $50\text{ }^\circ\text{C}$ . After the stated reaction time, the product **20** was purified by flash chromatography on silica gel (eluting with hexane/ ethyl acetate 20/1 to 10/1).

#### (*S*)-*tert*-Butyl 2-cyano-6-hydroxy-6-methyl-5-oxo-2-phenylheptanoate (**20a**)



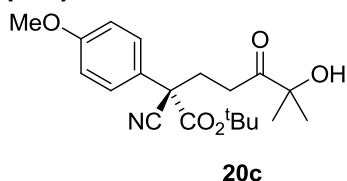
Prepared according to general procedure A starting from **19a** (65.1 mg, 0.3 mmol). The title compound was isolated as a colorless oil. Yield: 90% (89.4 mg).  $[\alpha]_{\text{D}}^{24} = +7.1^\circ$  ( $c=1.5$ , 96% *ee*,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.56 – 7.53 (m, 2H), 7.47 – 7.38 (m, 3H), 3.46 ( $s_{\text{br}}$ , 1H), 2.85 – 2.74 (m, 1H), 2.69 – 2.60 (m, 2H), 2.53 – 2.42 (m, 1H), 1.45 (s, 9H), 1.39 (s, 3H), 1.34 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 212.4, 165.8, 134.2, 129.2, 129.0, 125.9, 118.3, 84.7, 76.4, 54.0, 31.8, 27.6, 26.6, 26.5. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{19}\text{H}_{26}\text{NO}_4$  ( $\text{M}+\text{H}^+$ ), 332.1862; found, 332,1865.

#### (*S*)-*tert*-Butyl 2-cyano-6-hydroxy-6-methyl-5-oxo-2-*p*-tolylheptanoate (**20b**)



Prepared according to general procedure A starting from **19b** (69.3 mg, 0.3 mmol). The title compound was isolated as a colorless oil. Yield: 93% (96.0 mg).  $[\alpha]_{\text{D}}^{24} = +4.8^\circ$  ( $c=1.5$ , 96% *ee*,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.41 (d,  $J=8.4$  Hz, 2H), 7.23 (d,  $J=8.4$  Hz, 2H), 3.48 ( $s_{\text{br}}$ , 1H), 2.82 – 2.73 (m, 1H), 2.68 – 2.58 (m, 2H), 2.51 – 2.42 (m, 1H), 2.38 (s, 3H), 1.45 (s, 9H), 1.39 (s, 3H), 1.34 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 212.5, 166.0, 138.9, 131.2, 129.9, 125.8, 118.5, 84.6, 76.4, 53.7, 31.8, 31.7, 27.6, 26.6, 26.5, 21.0. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{20}\text{H}_{28}\text{NO}_4$  ( $\text{M}+\text{H}^+$ ), 346.2018; found, 346.2023.

**(S)-tert-Butyl 2-cyano-6-hydroxy-2-(4-methoxyphenyl)-6-methyl-5-oxoheptanoate (20c)**

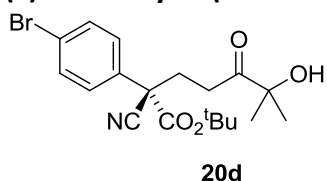


Prepared according to general procedure A starting from **19c** (74.1 mg, 0.3 mmol). The title compound was isolated as a colorless oil. Yield: 85% (92.1 mg).  $[\alpha]_D^{24} = +2.2^\circ$  ( $c=1.4$ , 96% *ee*,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.46 (d,  $J=9.0$  Hz, 2H), 6.95 (d,  $J=9.0$  Hz, 2H), 3.85 (s, 3H), 3.47 (s<sub>b</sub>, 1H), 2.81 – 2.72 (m, 1H), 2.68 – 2.57

(m, 2H), 2.51 – 2.42 (m, 1H), 1.45 (s, 9H), 1.39 (s, 3H), 1.34 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 212.5, 166.1, 159.9, 127.2, 126.0, 118.6, 114.5, 84.6, 76.4, 55.4, 53.3, 31.8, 31.7, 27.6, 26.6, 26.5. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{20}\text{H}_{28}\text{NO}_5$  ( $\text{M}+\text{H}^+$ ), 362.1967; found, 362.1962.

**(S)-tert-Butyl 2-(4-bromophenyl)-2-cyano-6-hydroxy-6-methyl-5-oxoheptanoate (20d)**

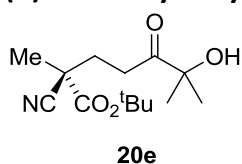


Prepared according to general procedure A starting from **19d** (88.8 mg, 0.3 mmol). The title compound was isolated as a colorless oil. Yield: 82% (100.8 mg).  $[\alpha]_D^{24} = +2.0^\circ$  ( $c=1.3$ , 94% *ee*,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.58 (d,  $J=8.8$  Hz, 2H), 7.43 (d,  $J=8.8$  Hz, 2H), 3.39 (s<sub>b</sub>, 1H), 2.83 – 2.74 (m, 1H), 2.68 – 2.59 (m, 2H), 2.48 – 2.40 (m, 1H), 1.45 (s, 9H), 1.39 (s, 3H), 1.35 (s, 3H).  $^{13}\text{C}$  NMR (100

MHz,  $\text{CDCl}_3$ )  $\delta$  = 212.2, 165.4, 133.4, 132.4, 127.7, 123.4, 117.9, 85.2, 76.4, 53.6, 31.8, 31.7, 27.6, 26.6, 26.5. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{19}\text{H}_{25}\text{BrNO}_4$  ( $\text{M}+\text{H}^+$ ), 410.0967; found, 410.0972.

**(R)-tert-Butyl 2-cyano-6-hydroxy-2,6-dimethyl-5-oxoheptanoate (20e)**

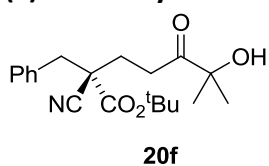


Prepared according to general procedure B starting from **19e** (139.5 mg, 0.9 mmol). The title compound was isolated as a colorless oil. Yield: 73% (58.8 mg).  $[\alpha]_D^{24} = +4.7^\circ$  ( $c=1.8$ , 98% *ee*,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 3.45 (s<sub>b</sub>, 1H), 2.84 (ddd,  $J=17.9$  Hz,  $J=10.5$  Hz,  $J=5.3$  Hz, 1H), 2.73 (ddd,  $J=17.9$  Hz,  $J=10.5$  Hz,  $J=5.2$  Hz, 1H), 2.25 (ddd,

$J=14.2$  Hz,  $J=10.5$  Hz,  $J=5.2$  Hz, 1H), 2.09 (ddd,  $J=14.2$  Hz,  $J=10.5$  Hz,  $J=5.3$  Hz, 1H), 1.61 (s, 3H), 1.54 (s, 9H), 1.42 (s, 3H), 1.41 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 212.3, 167.7, 119.7, 84.3, 76.4, 43.9, 31.8, 31.6, 27.8, 26.7, 26.6, 23.6. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{14}\text{H}_{24}\text{NO}_4$  ( $\text{M}+\text{H}^+$ ), 270.1705; found, 270.1710.

**(S)-tert-Butyl 2-benzyl-2-cyano-6-hydroxy-6-methyl-5-oxoheptanoate (20f)**

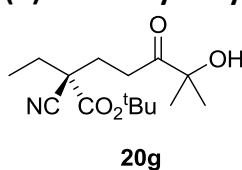


Prepared according to general procedure A starting from **19f** (208.2 mg, 0.9 mmol). The title compound was isolated as a colorless oil. Yield: 92% (95.4 mg).  $[\alpha]_D^{24} = +9.2^\circ$  ( $c=1.5$ , 98% *ee*,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.35 (s<sub>b</sub>, 5H), 3.44 (s<sub>b</sub>, 1H), 3.22 (d,  $J=13.6$  Hz, 1H), 3.08 (d,  $J=13.6$  Hz, 1H), 2.87 (ddd,  $J=17.9$  Hz,  $J=10.9$  Hz,  $J=5.0$  Hz,

1H), 2.68 (ddd,  $J=17.9$  Hz,  $J=11.0$  Hz,  $J=4.9$  Hz, 1H), 2.32 (ddd,  $J=14.0$  Hz,  $J=10.9$  Hz,  $J=4.9$  Hz, 1H), 2.09 (ddd,  $J=14.0$  Hz,  $J=11.0$  Hz,  $J=5.0$  Hz, 1H), 1.41 (s, 9H), 1.41 (s, 3H), 1.40 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 212.2, 166.9, 133.9, 130.1, 128.6, 127.9, 118.8, 84.6, 76.4, 51.0, 43.1, 31.6, 31.3, 27.7, 26.7, 26.6. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{20}\text{H}_{28}\text{NO}_4$  ( $\text{M}+\text{H}^+$ ), 346.2018; found, 346.2015.

**(R)-tert-Butyl 2-cyano-2-ethyl-6-hydroxy-6-methyl-5-oxoheptanoate (20g)**



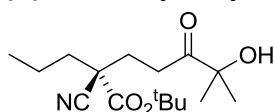
Prepared according to general procedure B starting from **19g** (152.4 mg, 0.9 mmol). The title compound was isolated as a colorless oil. Yield: 70% (59.6 mg).  $[\alpha]_D^{24} = +5.2^\circ$  ( $c=0.8$ , 98% *ee*,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 3.46 (s<sub>b</sub>, 1H), 2.86 (ddd,  $J=17.9$  Hz,  $J=10.7$  Hz,  $J=5.2$  Hz, 1H), 2.67 (ddd,  $J=17.9$  Hz,  $J=10.9$  Hz,  $J=5.1$  Hz, 1H), 2.21 (ddd,

$J=14.2$  Hz,  $J=10.7$  Hz,  $J=5.1$  Hz, 1H), 2.10 (ddd,  $J=14.2$  Hz,  $J=10.9$  Hz,  $J=5.2$  Hz, 1H), 2.04 – 1.95 (m,

1H), 1.90 – 1.81 (m, 1H), 1.54 (s, 9H), 1.42 (s, 3H), 1.41 (s, 3H), 1.12 (t,  $J=7.4$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 212.4, 167.4, 118.9, 84.3, 76.4, 50.5, 31.6, 31.0, 30.7, 27.8, 26.7, 26.6, 9.7. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{15}\text{H}_{26}\text{NO}_4$  ( $\text{M}+\text{H}^+$ ), 284.1862; found, 284.1865.

**(R)-tert-Butyl 2-cyano-6-hydroxy-6-methyl-5-oxo-2-propylheptanoate (20h)**

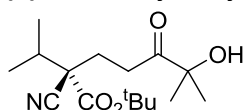


**20h**

Prepared according to general procedure B starting from **19h** (165.0 mg, 0.9 mmol). The title compound was isolated as a colorless oil. Yield: 74% (65.7 mg).  $[\alpha]_{\text{D}}^{24} = +3.8^\circ$  ( $c=0.9$ , 98% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 3.46 ( $s_b$ , 1H), 2.86 (ddd,  $J=17.9$  Hz,  $J=10.7$  Hz,  $J=5.2$  Hz, 1H), 2.66 (ddd,  $J=17.9$  Hz,  $J=10.9$  Hz,  $J=5.1$  Hz, 1H), 2.21 (ddd,  $J=14.2$  Hz,  $J=10.7$  Hz,  $J=5.1$  Hz, 1H), 2.10 (ddd,  $J=14.2$  Hz,  $J=10.9$  Hz,  $J=5.2$  Hz, 1H), 1.91 (ddd,  $J=13.4$  Hz,  $J=12.1$  Hz,  $J=4.9$  Hz, 1H), 1.75 (ddd,  $J=13.4$  Hz,  $J=12.1$  Hz,  $J=4.9$  Hz, 1H), 1.69 – 1.62 (m, 1H), 1.53 (s, 9H), 1.45 – 1.38 ( $m_{\text{hidden}}$ , 1H), 1.42 (s, 3H), 1.41 (s, 3H), 1.00 (t,  $J=7.3$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 212.4, 167.6, 119.1, 84.3, 76.4, 49.7, 39.5, 31.6, 31.1, 27.8, 26.7, 26.5, 18.8, 13.8. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{16}\text{H}_{28}\text{NO}_4$  ( $\text{M}+\text{H}^+$ ), 298.2018; found, 298.2021.

**(S)-tert-Butyl 2-cyano-6-hydroxy-2-isopropyl-6-methyl-5-oxoheptanoate (20i)**

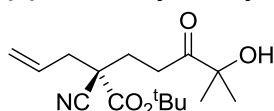


**20i**

Prepared according to general procedure B starting from **19i** (165.0 mg, 0.9 mmol). The title compound was isolated as a colorless oil. Yield: 74% (66.0 mg).  $[\alpha]_{\text{D}}^{24} = +5.4^\circ$  ( $c=1.0$ , 98% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 3.51 ( $s_b$ , 1H), 2.85 (ddd,  $J=17.8$  Hz,  $J=11.2$  Hz,  $J=4.9$  Hz, 1H), 2.59 (ddd,  $J=17.8$  Hz,  $J=11.2$  Hz,  $J=4.9$  Hz, 1H), 2.23 – 2.07 (m, 3H), 1.54 (s, 9H), 1.41 (s, 3H), 1.39 (s, 3H), 1.14 (d,  $J=6.8$  Hz, 3H), 1.09 (d,  $J=6.8$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 212.5, 167.7, 118.0, 84.3, 76.4, 55.4, 35.1, 31.8, 29.0, 27.8, 26.7, 26.6, 18.9, 17.7. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{16}\text{H}_{28}\text{NO}_4$  ( $\text{M}+\text{H}^+$ ), 298.2018; found, 298.2015.

**(S)-tert-Butyl 2-allyl-2-cyano-6-hydroxy-6-methyl-5-oxoheptanoate (20j)**

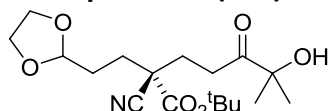


**20j**

Prepared according to general procedure A starting from **19j** (163.2 mg, 0.9 mmol). The title compound was isolated as a colorless oil. Yield: 71% (62.7 mg).  $[\alpha]_{\text{D}}^{24} = +0.6^\circ$  ( $c=1.0$ , 98% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 5.89 – 5.79 (m, 1H), 5.30 – 5.25 (m, 2H), 3.45 (s, 1H), 2.86 (ddd,  $J=17.9$  Hz,  $J=10.6$  Hz,  $J=5.2$  Hz, 1H), 2.73 – 2.64 (m, 2H), 2.57 – 2.52 (m, 1H), 2.22 (ddd,  $J=14.2$  Hz,  $J=10.6$  Hz,  $J=5.1$  Hz, 1H), 2.11 (ddd,  $J=14.2$  Hz,  $J=10.8$  Hz,  $J=5.2$  Hz, 1H), 1.52 (s, 9H), 1.42 (s, 3H), 1.41 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 212.3, 166.9, 130.3, 121.1, 118.6, 84.6, 76.4, 49.3, 41.5, 31.5, 30.4, 27.8, 26.7, 26.6. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{16}\text{H}_{26}\text{NO}_4$  ( $\text{M}+\text{H}^+$ ), 296.1862; found, 296.1859.

**(R)-tert-Butyl 2-cyano-2-[2-(1,3-dioxolan-2-yl)ethyl]-6-hydroxy-6-methyl-5-oxoheptanoate (20k)**

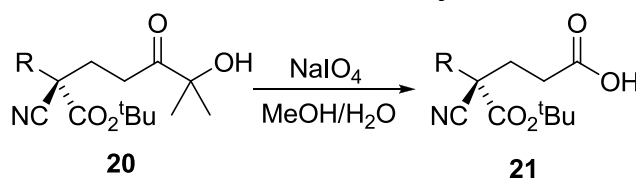


**20k**

Prepared according to general procedure B starting from **19k** (216.9 mg, 0.9 mmol). The title compound was isolated as a colorless oil. Yield: 81% (86.7 mg).  $[\alpha]_{\text{D}}^{24} = +2.5^\circ$  ( $c=1.4$ , 98% ee,  $\text{CH}_2\text{Cl}_2$ ).

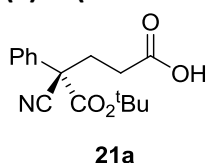
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 4.93 (t,  $J=4.1$  Hz, 1H), 4.00 – 3.94 (m, 2H), 3.92 – 3.86 (m, 2H), 3.46 ( $s_b$ , 1H), 2.86 (ddd,  $J=17.9$  Hz,  $J=10.6$  Hz,  $J=5.2$  Hz, 1H), 2.68 (ddd,  $J=17.9$  Hz,  $J=10.7$  Hz,  $J=5.1$  Hz, 1H), 2.22 (ddd,  $J=14.2$  Hz,  $J=10.6$  Hz,  $J=5.1$  Hz, 1H), 2.14 (ddd,  $J=14.2$  Hz,  $J=10.7$  Hz,  $J=5.2$  Hz, 1H), 2.09 – 2.01 (m, 1H), 1.99 – 1.90 (m, 2H), 1.79 – 1.70 (m, 1H), 1.53 (s, 9H), 1.41 (s, 3H), 1.40 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 212.3, 167.2, 118.7, 103.0, 84.5, 76.4, 65.0, 49.1, 31.6, 31.2, 30.9, 29.6, 27.8, 26.6, 26.5. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{18}\text{H}_{30}\text{NO}_6$  ( $\text{M}+\text{H}^+$ ), 356.2073; found, 356.2078.

## 2.5.2. Elaboration of adducts **20** into carboxylic acids **21**



A suspension of sodium periodate  $\text{NaIO}_4$  (321 mg, 1.5 mmol) in water (0.75 mL) was added to a solution of the corresponding  $\alpha$ -hydroxy ketone **20** (0.3 mmol) in methanol (1.5 mL). The mixture was stirred at room temperature until the reaction was complete (monitored by TLC). Then the solvent was removed under reduced pressure. Water (4.5 mL) was added to the crude product and the resulting mixture was extracted with  $\text{Et}_2\text{O}$  (3 x 6 mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and the solvent was evaporated to afford the corresponding carboxylic acid **21**.

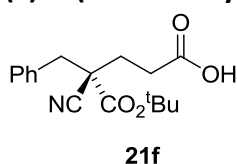
### (S)-4-(tert-Butoxycarbonyl)-4-cyano-4-phenylbutanoic acid (**21a**)



Prepared according to the general procedure starting from hydroxy ketone **20a** (99.4 mg, 0.3 mmol). The title compound was isolated as a white solid. Yield: 95% (82.5 mg). m.p.=54 - 57°C.  $[\alpha]_{\text{D}}^{24} = +7.4^\circ$  ( $c=1$ , 96% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.55 – 7.52 (m, 2H), 7.46 – 7.38 (m, 3H), 2.71 – 2.41 (m, 4H), 1.44 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 177.8, 165.7, 134.1, 129.3, 129.0, 125.9, 118.0, 84.8, 53.8, 32.5, 30.2, 27.6. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{16}\text{H}_{20}\text{NO}_4$  ( $\text{M}+\text{H}^+$ ), 290.1392; found, 290.1240.

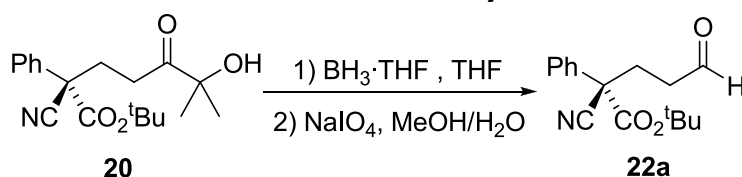
### (S)-4-(tert-Butoxycarbonyl)-4-cyano-5-phenylpentanoic acid (**21f**)



Prepared according to the general procedure starting from hydroxy ketone **20f** (103.6 mg, 0.3 mmol). The title compound was isolated as an oil. Yield: 93% (84.6 mg).  $[\alpha]_{\text{D}}^{24} = +5.4^\circ$  ( $c=1$ , 98% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.34 (s, 5H), 3.21 (d,  $J=13.6$  Hz, 1H), 3.08 (d,  $J=13.6$  Hz, 1H), 2.70 (ddd,  $J=16.7$  Hz,  $J=11.5$  Hz,  $J=5.1$  Hz, 1H), 2.48 (ddd,  $J=16.7$  Hz,  $J=11.6$  Hz,  $J=5.0$  Hz, 1H), 2.35 (ddd,  $J=13.9$  Hz,  $J=11.5$  Hz,  $J=5.0$  Hz, 1H), 2.18 (ddd,  $J=13.9$  Hz,  $J=11.6$  Hz,  $J=5.1$  Hz, 1H), 1.41 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 177.6, 166.8, 133.9, 130.1, 128.6, 127.9, 118.6, 84.8, 50.9, 43.1, 32.0, 30.1, 27.7. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{17}\text{H}_{22}\text{NO}_4$  ( $\text{M}+\text{H}^+$ ), 304.1549; found, 304.1387.

## 2.5.3. Elaboration of adduct **20a** into aldehyde **22a**

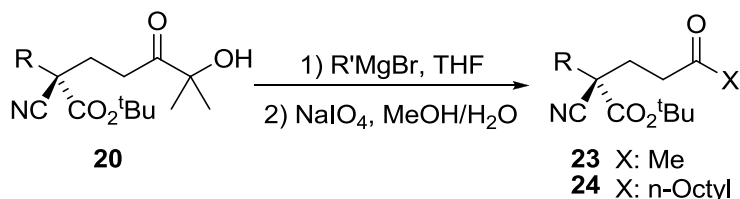


### (S)-tert-Butyl 2-cyano-4-formyl-2-phenylbutanoate (**22a**)

$\text{BH}_3 \cdot \text{THF}$  complex (1 M, 0.6 mL, 0.6 mmol) was added to a solution of  $\alpha$ -hydroxy ketone **20a** (99.4 mg, 0.3 mmol) in dry THF (0.9 mL) at 0°C and the resulting solution was stirred at the same temperature for 2 h. Then MeOH (1 mL) was added and the resulting mixture was stirred at room temperature for 30 min. The solvents were removed under reduced pressure and the residue thus obtained was subjected to oxidative scission by treatment with  $\text{NaIO}_4$ , under the same conditions reported above. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 20/1 to 1/1) to give the title compound as an oil. Yield: 85% (69.7 mg).  $[\alpha]_{\text{D}}^{22} = +6.2^\circ$  ( $c=1$ , 96% ee,  $\text{CH}_2\text{Cl}_2$ ).

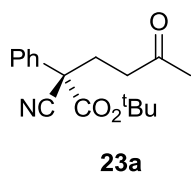
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 9.76 (s, 1H), 7.55 – 7.51 (m, 2H), 7.45 – 7.36 (m, 3H), 2.74 – 2.42 (m, 4H), 1.44 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 199.3, 165.8, 134.2, 129.2, 129.0, 126.0, 118.2, 84.8, 53.8, 39.9, 30.2, 27.5. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{16}\text{H}_{20}\text{NO}_3$  ( $\text{M}+\text{H}^+$ ), 274.1443; found, 274.1441.

#### 2.5.4. Elaboration of adducts **20** into ketones **23** and **24**



MeMgBr or *n*-OctMgBr (1.5 mmol) was added to a solution of the corresponding  $\alpha$ -hydroxy ketone **20** (0.3 mmol) in dry THF (1.5 mL) at  $0^\circ\text{C}$  and the resulting solution was stirred at room temperature until the reaction was finished (monitored by TLC). Then  $\text{NH}_4\text{Cl}$  (saturated solution, 3 mL) was added at  $0^\circ\text{C}$  and the resulting mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 5 mL). The solvents were removed under reduced pressure and the residue thus obtained was subjected to oxidative scission by treatment with  $\text{NaIO}_4$ , under the same conditions reported above. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 20/1 to 1/1).

##### (*S*)-*tert*-Butyl 2-cyano-5-oxo-2-phenylhexanoate (**23a**)

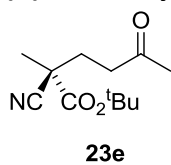


Prepared according to the general procedure starting from hydroxy ketone **20a** (99.4 mg, 0.3 mmol) and MeMgBr. The title compound was isolated as an oil. Yield: 78% (67.3 mg).  $[\alpha]_{\text{D}}^{25} = +4.2^\circ$  ( $c=1$ , 96% *ee*,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.54 – 7.51 (m, 2H), 7.45 – 7.36 (m, 3H), 2.68 – 2.38 (m, 4H), 2.15 (s, 3H), 1.43 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 206.0, 165.9, 134.4, 129.2, 128.9, 125.9, 118.4, 84.6, 53.9, 39.4, 31.5, 30.0, 27.6. MS

(ESI,  $m/z$ ): calcd for  $\text{C}_{17}\text{H}_{22}\text{NO}_3$  ( $\text{M}+\text{H}^+$ ), 288.1600; found, 288.1597.

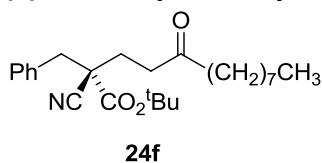
##### (*R*)-*tert*-Butyl 2-cyano-2-methyl-5-oxohexanoate (**23e**)



Prepared according to the general procedure starting from hydroxy ketone **20e** (80.8 mg, 0.3 mmol) and MeMgBr. The title compound was isolated as an oil. Yield: 75% (50.7 mg).  $[\alpha]_{\text{D}}^{22} = +3.9^\circ$  ( $c=1$ , 98% *ee*,  $\text{CHCl}_3$ ). Lit.<sup>30</sup>  $[\alpha]_{\text{D}}^{20} = +2.7^\circ$  ( $c=5$ , 81% *ee*,  $\text{CHCl}_3$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 2.71 (ddd,  $J=17.9$  Hz,  $J=10.9$  Hz,  $J=5.1$  Hz, 1H), 2.59 (ddd,  $J=17.9$  Hz,  $J=10.9$  Hz,  $J=5.1$  Hz, 1H), 2.20 (ddd,  $J=14.2$  Hz,  $J=10.9$  Hz,  $J=5.1$  Hz, 1H), 2.20 (s, 3H), 2.02 (ddd,  $J=14.2$  Hz,  $J=10.9$  Hz,  $J=5.1$  Hz, 1H), 1.58 (s, 3H), 1.52 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 205.9, 167.8, 119.8, 84.1, 43.8, 39.2, 31.5, 30.0, 27.9, 23.5. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{12}\text{H}_{20}\text{NO}_3$  ( $\text{M}+\text{H}^+$ ), 226.1443; found, 226.1446.

##### (*S*)-*tert*-Butyl 2-benzyl-2-cyano-5-oxotridecanoate (**24f**)



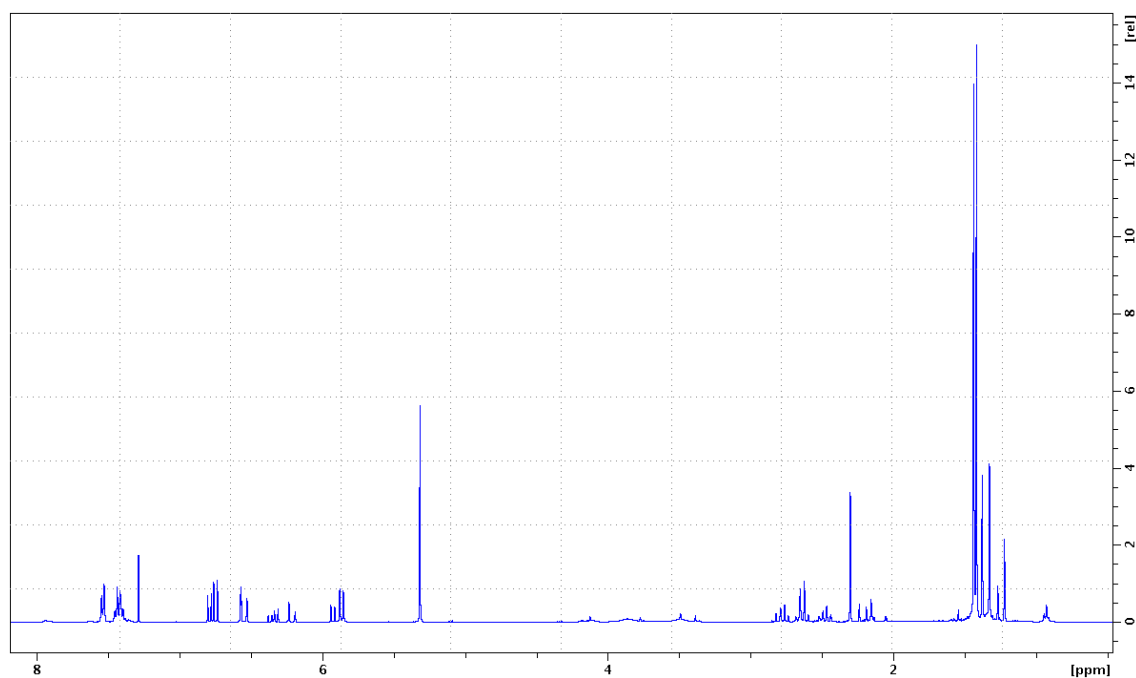
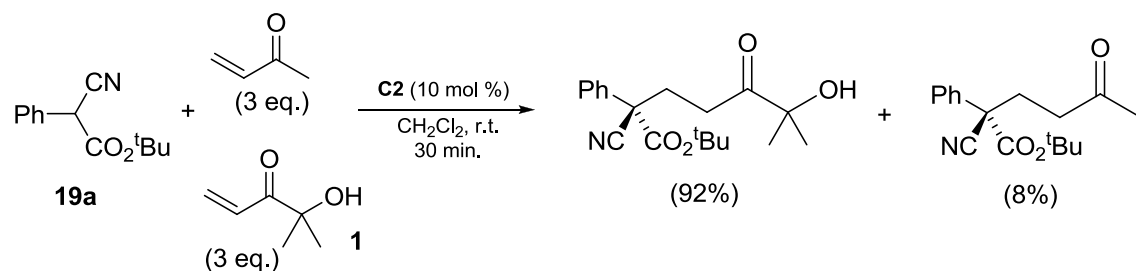
Prepared according to the general procedure starting from hydroxy ketone **20f** (103.6 mg, 0.3 mmol) and *n*-OctMgBr. The title compound was isolated as an oil. Yield: 73% (87.5 mg).  $[\alpha]_{\text{D}}^{23} = +5.8^\circ$  ( $c=1$ , 98% *ee*,  $\text{CH}_2\text{Cl}_2$ ).

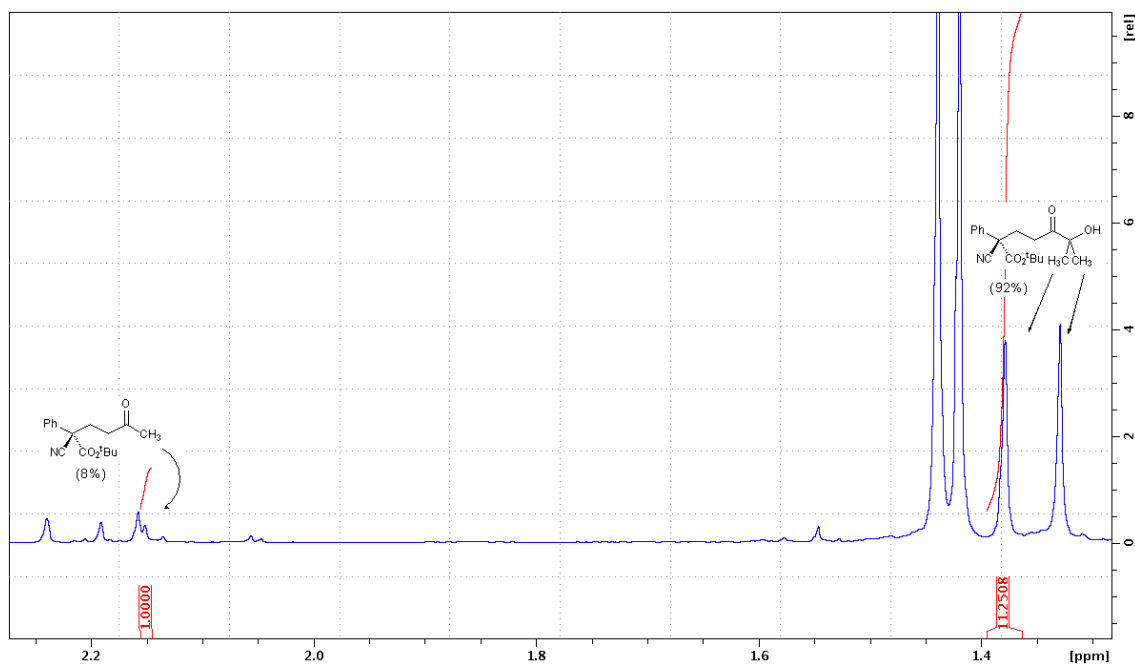
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.34 ( $s_b$ , 5H), 3.19 (d,  $J=13.6$  Hz, 1H), 3.06 (d,  $J=13.6$  Hz, 1H), 2.73 (ddd,  $J=17.5$  Hz,  $J=11.2$  Hz,  $J=4.8$  Hz, 1H), 2.48 (ddd<sub>hidden</sub>,  $J=17.5$  Hz,  $J=11.4$  Hz,  $J=4.9$  Hz, 1H), 2.43 (t,  $J=7.6$  Hz, 3H), 2.28 (ddd,  $J=14.1$  Hz,  $J=11.2$  Hz,  $J=4.9$  Hz, 1H),

2.12 (ddd,  $J=14.1$  Hz,  $J=11.4$  Hz,  $J=4.8$  Hz, 1H), 1.62-1.56 (m, 2H), 1.40 (s, 9H), 1.29 (s<sub>b</sub>, 10H), 0.90 (t,  $J=6.9$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 208.4, 167.0, 134.1, 130.1, 128.5, 127.8, 119.0, 84.4, 51.0, 43.1, 43.0, 38.2, 31.8, 31.2, 29.3, 29.2, 29.1, 27.7, 23.8, 22.6, 14.1. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{25}\text{H}_{38}\text{NO}_3$  ( $\text{M}+\text{H}^+$ ), 400.2852; found, 400.2856.

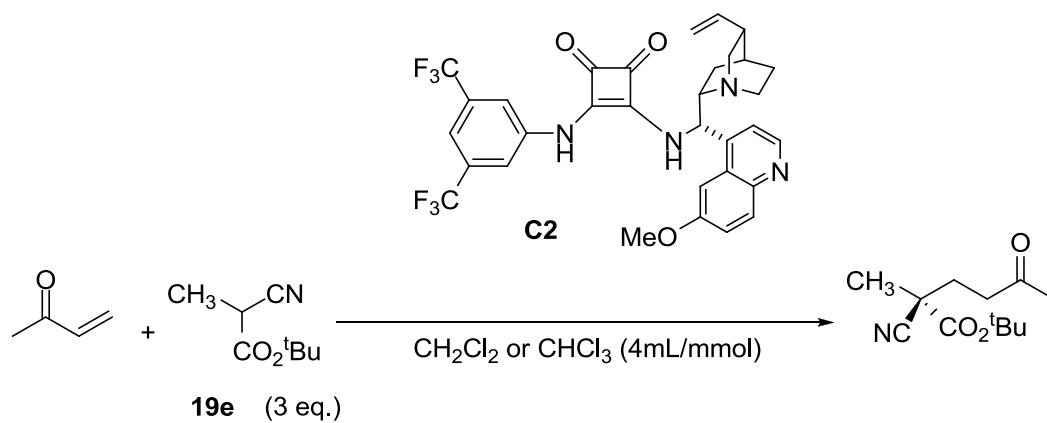
### 2.5.5. Experiments with MVK and other typical Michael acceptors.

Hydroxy enone **1** versus methyl vinyl ketone in conjugate addition with *tert*-butyl 2-cyano-2-phenylacetate **19a**



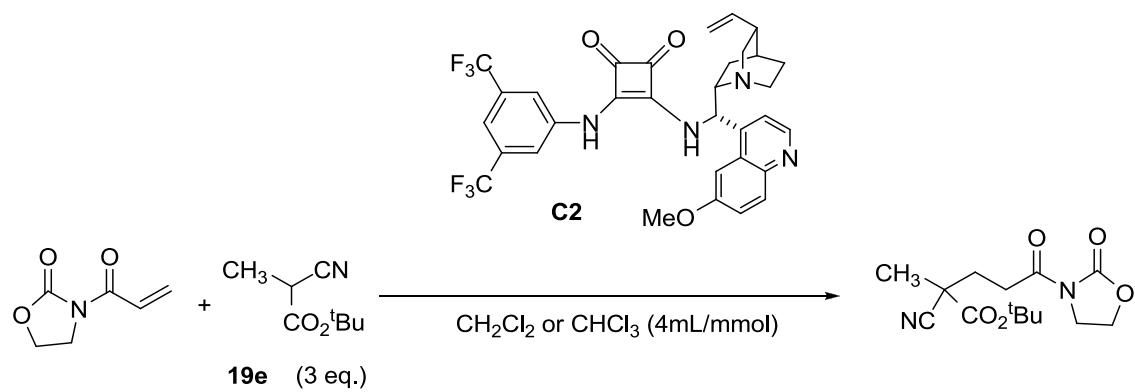


Screening of typical enoyl systems in conjugate addition with *tert*-butyl 2-cyanopropanoate **19e** and **C2**

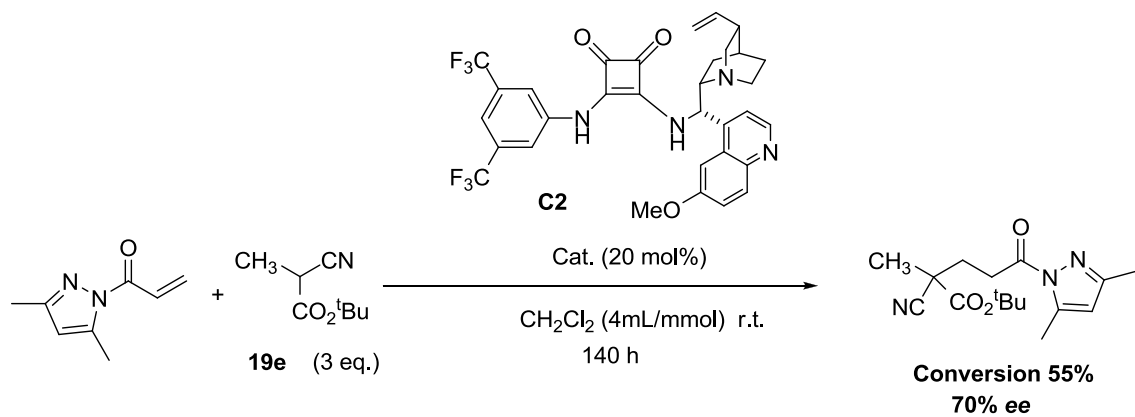


Cat (mol%)	t (h)	T (°C)	ee (%)	Conversion (%)
20	120	20	88	50
10	26	50		50
10	51	50		56
10	67	50	84	59



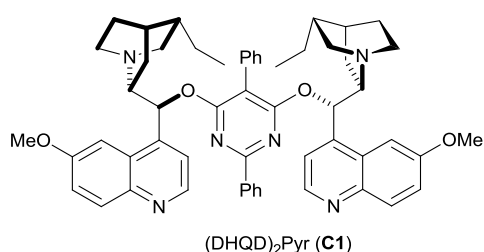
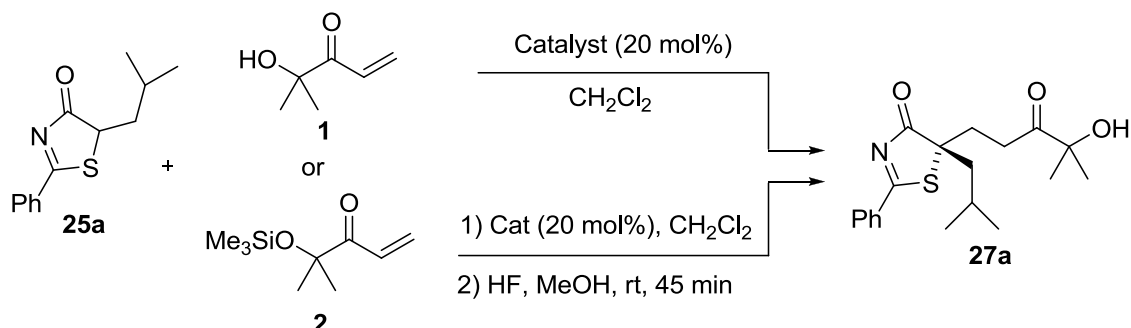


Cat (mol%)	t (h)	T (°C)	ee (%)	Conversion (%)
20	120	20	76	50
10	26	50		34
10	42	50		37
10	118	50	68	41

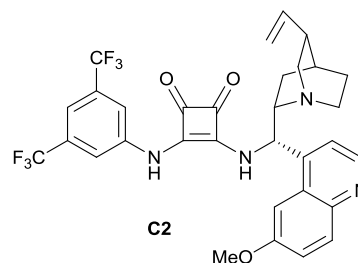


## 2.6. Reactions involving thiazol-4(5*H*)-ones **25**

### 2.6.1. Catalyst screening

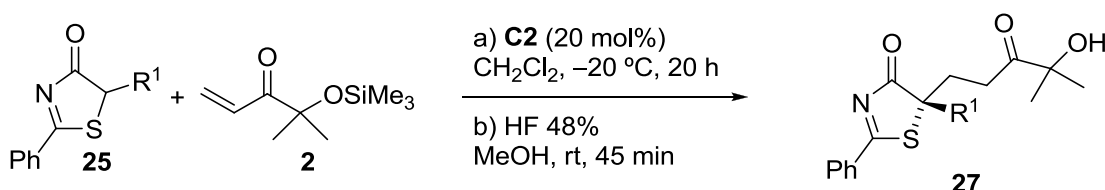


with **1**:  $-40\text{ }^\circ\text{C}$ , 48 h, racemic  
with **2**:  $0\text{ }^\circ\text{C}$ , 24 h, no reaction



with **1**:  $-40\text{ }^\circ\text{C}$ , 24 h, 72%, 36% ee  
with **2**:  $-40\text{ }^\circ\text{C}$ , 24 h, 64%, 98% ee

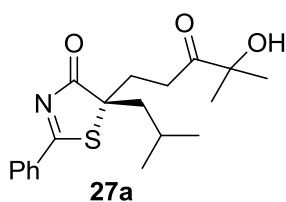
### 2.6.2. Catalytic conjugate addition of thiazol-4(5*H*)-ones to enone **2**.



To a mixture of the corresponding thiazolone **25** (1 equiv., 0.3 mmol) and enone **2** (3.0/1.5 equiv., 0.6/0.45 mmol), in dichloromethane (0.9 mL) at  $-20\text{ }^\circ\text{C}$ , the catalyst **C2** (20 mol%, 0.06 mmol, 38 mg) was added. The resulting suspension was stirred at the same temperature, until consumption of the thiazolone (monitored by  $^1\text{H-NMR}$ ). Then, 3 mL of methanol and 0.6 mL of HF 48% were added at the corresponding temperature and the mixture was warmed to room temperature and stirred for 45 min. The reaction was treated at  $0\text{ }^\circ\text{C}$  with saturated aqueous solution of  $\text{NaHCO}_3$  until neutralization. The product was extracted from the aq. phase with  $\text{CH}_2\text{Cl}_2$  and the combined organic phases were dried with  $\text{MgSO}_4$ . Evaporation of the solvent under reduced pressure gave the crude product, which was purified by flash column chromatography (eluting with hexane/ ethyl acetate 80/20).

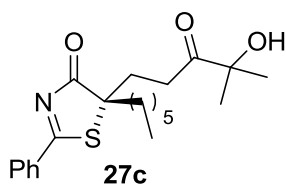
**General procedure for the racemic reactions.** Racemic reactions were conducted following the procedure for the asymmetric version using 4-hydroxy-4-methylpent-1-en-3-one (3 equiv.), but at  $0\text{ }^\circ\text{C}$  and by using TEA (20 mol%) as catalyst.

#### 5-(4-Hydroxy-4-methyl-3-oxopentyl)-5-isobutyl-2-phenylthiazol-4(5H)-one (27a)



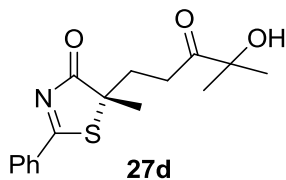
The title compound **27a** was prepared from 5-isobutyl-2-phenylthiazol-4(5H)-one (**25a**) (70.0 mg, 0.3 mmol) and enone **2** (83.8 mg, 0.45 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a colorless oil. Yield: 77.1 mg, 0.22 mmol, 74%.  $[\alpha]_D^{25} = -11.4$  ( $c = 1.00$ , 98% ee,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 8.19 – 8.11 (m, 2H), 7.73 – 7.63 (m, 1H), 7.57 – 7.48 (m, 2H), 3.50 (s, 1H), 2.55 – 2.44 (m, 2H), 2.43 – 2.31 (m, 1H), 2.31 – 2.17 (m, 1H), 2.12 – 1.99 (m, 1H), 1.96 – 1.85 (m, 1H), 1.86 – 1.70 (m, 1H), 1.29 (s, 3H), 1.24 (s, 3H), 0.96 (d,  $J = 6.5$  Hz, 3H), 0.86 (d,  $J = 6.5$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 213.0, 195.5, 195.4, 135.2, 132.0, 129.1, 128.9, 76.4, 68.0, 47.9, 32.6, 30.6, 26.5, 26.5, 25.9, 24.5, 22.9. UPLC-DAD-QTOF:  $\text{C}_{19}\text{H}_{26}\text{NO}_3\text{S}$   $[\text{M}+\text{H}]^+$  calcd.: 348.1633, found: 348.1638.

#### 5-Hexyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-2-phenylthiazol-4(5H)-one (27c)



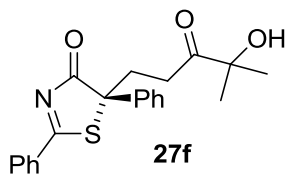
The title compound **27c** was prepared from 5-hexyl-2-phenylthiazol-4(5H)-one (**25c**) (78.4 mg, 0.3 mmol) and enone **2** (83.8 mg, 0.45 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a colorless oil. Yield: 80.0 mg, 0.21 mmol, 71%.  $[\alpha]_D^{25} = +2.0$  ( $c = 1.00$ , 92% ee,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 8.20 – 8.09 (m, 2H), 7.74 – 7.63 (m, 1H), 7.57 – 7.48 (m, 2H), 3.51 (s, 1H), 2.59 – 2.48 (m, 2H), 2.47 – 2.33 (m, 1H), 2.33 – 2.21 (m, 1H), 2.05 – 1.91 (m, 2H), 1.29 (s, 3H), 1.27 – 1.14 (m, 11H), 0.82 (t,  $J = 6.9$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 213.0, 195.5, 194.9, 135.2, 132.0, 129.0, 128.9, 76.4, 69.1, 39.5, 31.8, 31.4, 31.0, 29.0, 26.5, 26.5, 25.0, 22.4, 13.9. UPLC-DAD-QTOF:  $\text{C}_{21}\text{H}_{30}\text{NO}_3\text{S}$   $[\text{M}+\text{H}]^+$  calcd.: 376.1946, found: 376.1947.

#### 5-(4-Hydroxy-4-methyl-3-oxopentyl)-5-methyl-2-phenylthiazol-4(5H)-one (27d)



The title compound **27d** was prepared from 5-Methyl-2-phenylthiazol-4-ol (**25d**) (57.7 mg, 0.3 mmol) and enone **2** (83.8 mg, 0.45 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a colorless oil. Yield: 70.5 mg, 0.23 mmol, 77%.  $[\alpha]_D^{25} = -14.7$  ( $c = 1.00$ , 96% ee,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 8.23 – 8.01 (m, 2H), 7.78 – 7.62 (m, 1H), 7.62 – 7.46 (m, 1H), 3.48 (s, 1H), 2.60 – 2.47 (m, 2H), 2.39 – 2.28 (m, 2H), 1.74 (s, 3H), 1.31 (s, 3H), 1.28 (s, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 212.8, 195.1, 194.9, 135.3, 132.0, 129.1, 128.9, 76.4, 63.6, 32.9, 31.4, 26.7, 26.6, 26.5. UPLC-DAD-QTOF:  $\text{C}_{16}\text{H}_{20}\text{NO}_3\text{S}$   $[\text{M}+\text{H}]^+$  calcd.: 306.1164, found: 306.1172.

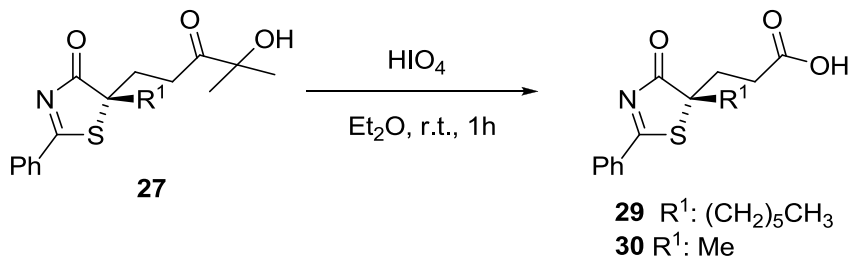
#### 5-(4-Hydroxy-4-methyl-3-oxopentyl)-2,5-diphenylthiazol-4(5H)-one (27f)



The title compound **27f** was prepared from 2,5-diphenylthiazol-4-ol (**25f**) (76.0 mg, 0.3 mmol) and enone **2** (83.8 mg, 0.45 mmol) according to the general procedure, but at  $-10$  °C. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a colorless oil. Yield: 73.5 mg, 0.20 mmol, 67%.  $[\alpha]_D^{25} = +54.7$  ( $c = 1.00$ , 88% ee,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 8.20 – 8.09 (m, 2H), 7.73 – 7.63 (m, 1H), 7.55 – 7.45 (m, 5H), 7.40 – 7.28 (m, 2H), 3.54 (s, 1H), 2.92 – 2.51 (m, 4H), 1.28 (s, 3H), 1.27 (s, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 212.9, 194.7, 192.8, 138.1, 135.4, 131.7, 129.0, 128.9,

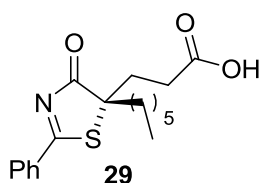
128.9, 128.4, 126.6, 76.4, 70.6, 33.1, 31.6, 26.4, 26.4. UPLC-DAD-QTOF: C<sub>21</sub>H<sub>22</sub>NO<sub>3</sub>S [M+H]<sup>+</sup> calcd.: 368.1320, found: 368.1324.

### 2.6.3. Elaboration of adducts **27** into carboxylic acids **29-31**



The corresponding adduct **27** (0.2 mmol, 1 eq.) was dissolved in (1 mL) of diethyl ether and periodic acid (1.2 mmol, 273.5 mg, 1.2 eq.) was added slowly. The reaction was stirred at room temperature until completion (TLC analysis, 1h). After completion, reaction was quenched with 10% aqueous sodium sulfite (5 mL) and washed with diethyl ether (5 mL). The aqueous phase was acidified to pH 2 with HCl 3M saturated with sodium chloride and extracted with ethyl acetate (3x 10 mL). The organic layer was dried over MgSO<sub>4</sub> and the solvent evaporated under reduced pressure to give the crude carboxylic acid.

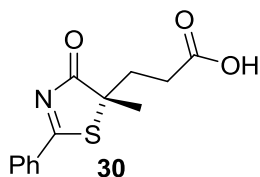
#### 3-(5-Hexyl-4-oxo-2-phenyl-4,5-dihydrothiazol-5-yl)propanoic acid (**29**)



The title compound was prepared from 5-hexyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-2-phenylthiazol-4(5H)-one (**27c**) (75.1 mg, 0.2 mmol) according to the general procedure. Orange oil. Yield: 63.3 mg, 0.19 mmol, 95%.  $[\alpha]_D^{25} = +3.7$  (*c* = 0.82, 92% ee, MeOH). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>),  $\delta$ : 8.19 – 8.07 (m, 2H), 7.73 – 7.61 (m, 1H), 7.58 – 7.48 (m, 2H), 2.53 – 2.18 (m, 4H), 2.12 – 1.90 (m, 2H), 1.56 – 1.11 (m, 8H), 0.82 (t, *J* = 6.6 Hz, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>),  $\delta$ :

195.7, 194.2, 177.9, 135.4, 131.7, 129.0, 128.9, 68.9, 39.0, 32.8, 31.3, 29.5, 28.9, 25.0, 22.4, 13.9. UPLC-DAD-QTOF: C<sub>18</sub>H<sub>24</sub>NO<sub>3</sub>S [M+H]<sup>+</sup> calcd.: 334.1477, found: 334.1479.

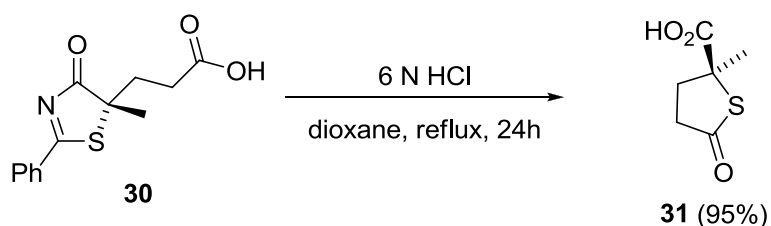
#### 3-(5-Methyl-4-oxo-2-phenyl-4,5-dihydrothiazol-5-yl)propanoic acid (**30**)



The title compound was prepared from 5-(4-hydroxy-4-methyl-3-oxopentyl)-5-methyl-2-phenylthiazol-4(5H)-one (**27d**) (61.1 mg, 0.2 mmol) according to the general procedure. Orange oil. Yield: 49.5 mg, 0.19 mmol, 94%.  $[\alpha]_D^{25} = -11.2$  (*c* = 0.72, 96% ee, MeOH). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>),  $\delta$ : 8.21 – 8.03 (m, 2H), 7.82 – 7.62 (m, 1H), 7.64 – 7.43 (m, 2H), 2.59 – 2.20 (m, 4H), 1.74 (s, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>),  $\delta$ :

194.9, 194.8, 177.5, 135.3, 132.0, 129.1, 128.9, 63.4, 33.9, 29.9, 26.3. UPLC-DAD-QTOF: C<sub>13</sub>H<sub>14</sub>NO<sub>3</sub>S [M+H]<sup>+</sup> calcd.: 264.0694, found: 264.0701.

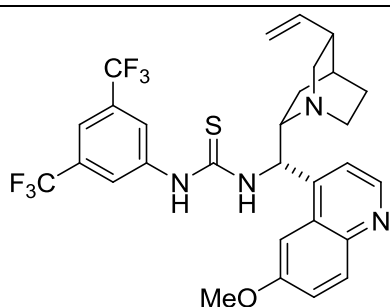
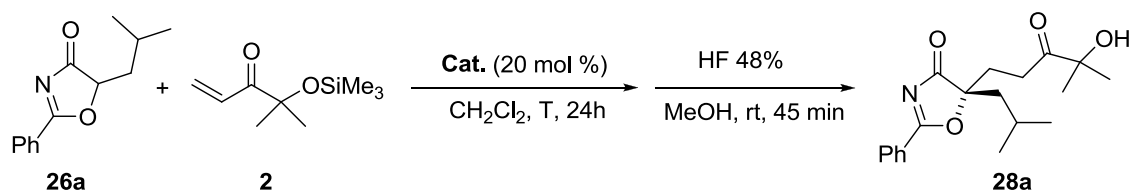
### Conversion of thiazolone **30** into thiolactone **31**



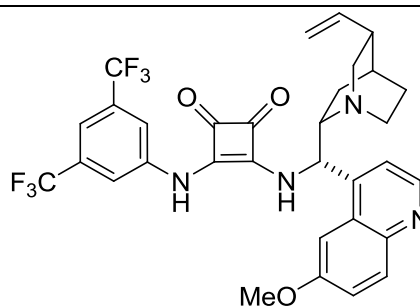
3-(5-methyl-4-oxo-2-phenyl-4,5-dihydrothiazol-5-yl)propanoic acid (**30**) (67.2 mg, 0.22 mmol, 1equiv.) was dissolved in a mixture of dioxane (1.2 mL) and HCl 6N (12 equiv., 0.44 mL, 2.64 mmol). The resulting solution was stirred refluxing for 24 h. After this period the cooled reaction mixture was treated with water and the product was extracted from the aq. phase with  $\text{CH}_2\text{Cl}_2$  and the combined organic phases were dried with  $\text{MgSO}_4$ . Evaporation of the solvent under reduced pressure gave the crude product, which was purified by flash column chromatography (eluting with ethyl acetate/hexane 4/1). Colorless oil. Yield: 33.7 mg, 0.21 mmol, 95%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 3.12 – 2.92 (m, 1H), 2.81 – 2.65 (m, 2H), 2.17 – 2.03 (m, 1H), 1.82 (s, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 206.3, 179.0, 59.1, 42.1, 35.6, 25.8. HRMS (ESI):  $\text{C}_6\text{H}_9\text{O}_3\text{S}$   $[\text{M}+\text{H}]^+$  calcd.: 161.0272, found: 161.0286.

## 2.7. Reactions involving oxazol-4(5*H*)-ones 26

### 2.7.1. Catalyst screening (Table SI-3)

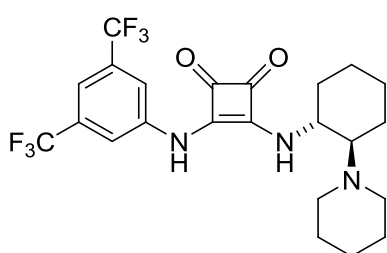


-20 °C, 72 %, 12 % ee

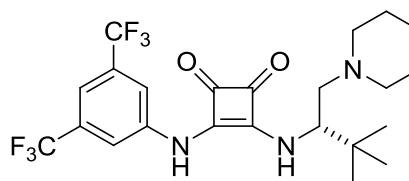


**C2**

20 °C, 80 %, 73 % ee

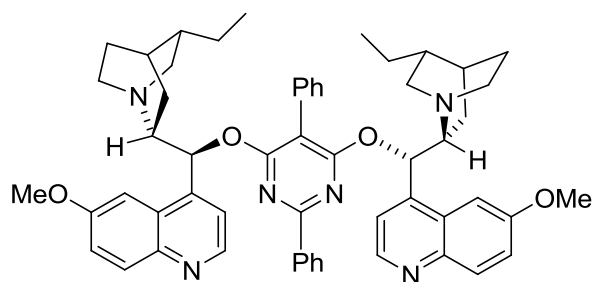


-20 °C, 79 %, -50 % ee



**C3**

20 °C, 80 %, 93 % ee

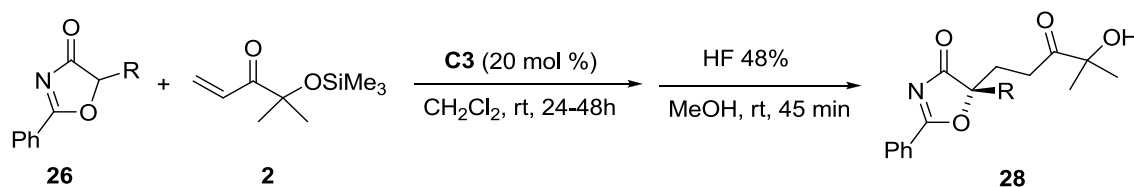


**(DHQD)<sub>2</sub>PYR, C1**

20 °C, Conv.: 23 %

The reactions were performed on a 0.30 mmol scale in  $\text{CH}_2\text{Cl}_2$  (0.9 ml) using 3 equiv. of enone **2**. Yields after chromatography. ee determined by HPLC.

## 2.7.2. Catalytic conjugate addition of oxazol-4(5H)-ones **26** to enone **2**



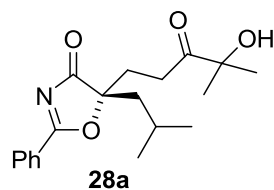
To a mixture of the corresponding oxazolone **26** (1 equiv., 0.3 mmol) and the enone **2** (83.9 mg, 3.0 equiv., 0.9 mmol), in dichloromethane (0.9 mL) at room temperature the catalyst **C3** (20 mol%) was added. The resulting suspension was stirred at the same temperature, until consumption of the oxazolone (monitored by  $^1\text{H-NMR}$ ). Then, 3 mL of methanol and 0.6 mL of aqueous HF 48% were added and the mixture was stirred for 45 min. The reaction was treated at 0 °C with saturated aqueous solution of  $\text{NaHCO}_3$  until pH 7. The product was extracted from the aq. phase with  $\text{CH}_2\text{Cl}_2$  (3 x 3 mL) and the combined organic phases were dried with  $\text{MgSO}_4$ . Evaporation of the solvent under reduced pressure gave the title products **28**, which were purified by flash column chromatography (eluent: hexane: ethyl acetate 80:20).

### General procedure for the racemic reactions

Racemic reactions were conducted at room temperature following the procedure for the asymmetric version using enone **1** (3 equiv.) and TEA (20 mol %) as the catalyst.

#### (*R*)-5-(4-Hydroxy-4-methyl-3-oxopentyl)-5-isobutyl-2-phenyloxazol-4(5H)-one (**28a**)

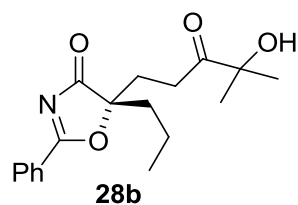
The title compound **28a** was prepared from 5-isobutyl-2-phenyloxazol-4(5H)-one (**26a**) (65.2 mg, 0.3 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one (**2**) (167 mg, 0.9 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a colorless oil. Yield: 79 mg, 0.24 mmol, 80 %.  $[\alpha]_{\text{D}}^{21} = +10.67^\circ$  ( $c = 1.00$ , 93% *ee* as determined by chiral HPLC,  $\text{CH}_2\text{Cl}_2$ ).



$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta = 8.22 - 8.09$  (m, 2H), 7.73 – 7.61 (m, 1H), 7.57 – 7.46 (m, 2H), 3.56 (s, 1H), 2.57 – 2.47 (m, 1H), 2.38 – 2.23 (m, 1H), 2.22 – 2.08 (m, 1H), 2.04 – 1.84 (m, 2H), 1.82 – 1.64 (m, 2H), 1.25 (s, 3H), 1.21 (s, 3H), 0.88 (dd,  $J = 10.0, 6.4$  Hz, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ),  $\delta = 212.7, 193.4, 185.6, 130.0, 129.0, 125.4, 90.2, 76.4, 60.3, 44.4, 29.7, 29.0, 26.4, 23.9, 23.3, 14.1$ . MS (ESI,  $m/z$ ): calcd for  $\text{C}_{19}\text{H}_{26}\text{NO}_4$  ( $\text{M}+\text{H}^+$ ), 332.1862; found, 332.1866.

#### (*S*)-5-(4-Hydroxy-4-methyl-3-oxopentyl)-2-phenyl-5-propyloxazol-4(5H)-one (**28b**)

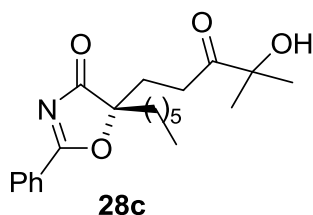
The title compound **28b** was prepared from 2-phenyl-5-propyloxazol-4(5H)-one (**26b**) (60.9 mg, 0.3 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one (**2**) (167 mg, 0.9 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a colourless oil. Yield: 52 mg, 0.26 mmol, 86 %.  $[\alpha]_{\text{D}}^{23} = +58.42^\circ$  ( $c = 1.00$ , 92% *ee* as determined by chiral HPLC,  $\text{CH}_2\text{Cl}_2$ ).



$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta = 8.29 - 8.15$  (m, 2H), 7.77 – 7.64 (m, 1H), 7.55 (t,  $J = 7.7$  Hz, 2H), 3.62 (s, 1H), 2.59 (t,  $J = 7.7$  Hz, 2H), 2.40 – 2.13 (m, 2H), 1.93 (ddd,  $J = 10.0, 5.8, 4.0$  Hz, 2H), 1.40 – 1.15 (m, 8H), 0.90 (t,  $J = 7.3$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ),  $\delta = 212.72, 193.10$ ,

185.69, 135.29, 129.99, 128.93, 125.34, 90.29, 76.34, 37.94, 29.36, 29.14, 26.42, 16.21, 13.70. MS (ESI,  $m/z$ ): calcd for  $C_{18}H_{24}NO_4$  ( $M+H^+$ ), 318.1705; found, 318.1697.

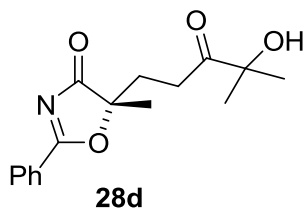
#### (S)-5-Hexyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-2-phenyloxazol-4(5H)-one (28c)



The title compound **28c** was prepared from 5-hexyl-2-phenyloxazol-4(5H)-one (**26c**) (73.6 mg, 0.3 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one (**2**) (167 mg, 0.9 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a colorless oil. Yield: 61 mg, 0.24 mmol, 79 %.  $[\alpha]_D^{21} = +10.60^\circ$  ( $c = 1.00$ , 97% ee as determined by chiral HPLC,  $CH_2Cl_2$ ).

$^1H$  NMR (300 MHz,  $CDCl_3$ ),  $\delta = 8.26 - 8.07$  (m, 2H), 7.76 – 7.60 (m, 1H), 7.51 (t,  $J = 7.7$  Hz, 2H), 2.55 (t,  $J = 7.7$  Hz, 2H), 2.41 – 2.09 (m, 2H), 1.89 (d,  $J = 3.9$  Hz, 2H), 1.34 – 1.08 (m, 14H), 0.78 (t,  $J = 6.7$  Hz, 3H).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ),  $\delta = 213.35$ , 193.76, 186.34, 135.93, 130.65, 129.59, 126.01, 90.95, 76.99, 36.55, 31.89, 30.03, 29.80, 29.49, 27.08, 23.29, 22.93, 14.46. MS (ESI,  $m/z$ ): calcd for  $C_{21}H_{30}NO_4$  ( $M+H^+$ ), 360.2175; found, 360.2170.

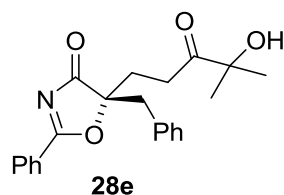
#### (S)-5-(4-Hydroxy-4-methyl-3-oxopentyl)-5-methyl-2-phenyloxazol-4(5H)-one (28d)



The title compound **28d** was prepared from 5-methyl-2-phenyloxazol-4(5H)-one (**26d**) (52.6 mg, 0.3 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one (**2**) (167 mg, 0.9 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a colourless oil. Yield: 65 mg, 0.23 mmol, 75 %.  $[\alpha]_D^{21} = +25.63^\circ$  ( $c = 1.00$ , 92% ee as determined by chiral HPLC,  $CH_2Cl_2$ ).

$^1H$  NMR (300 MHz,  $CDCl_3$ ),  $\delta = 8.30 - 8.14$  (m, 2H), 7.77 – 7.66 (m, 1H), 7.55 (t,  $J = 7.7$  Hz, 2H), 2.59 (t,  $J = 7.5$  Hz, 2H), 2.46 – 2.13 (m, 3H), 1.62 (s, 4H), 1.32 (s, 3H), 1.28 (s, 4H).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ),  $\delta = 212.47$ , 193.36, 185.42, 135.42, 130.17, 129.05, 87.14, 30.40, 29.37, 26.57, 22.31. MS (ESI,  $m/z$ ): calcd for  $C_{16}H_{20}NO_4$  ( $M, H^+$ ), 290.1392; found; 290.1381.

#### 5-Benzyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-2-phenyloxazol-4(5H)-one (28e)

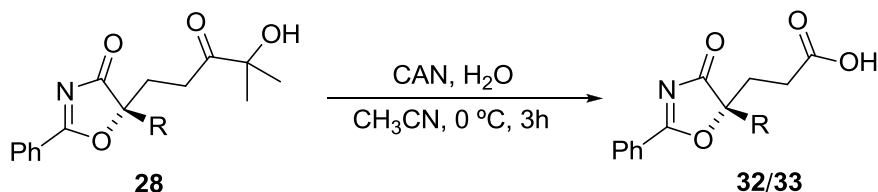


The title compound **28e** was prepared from 5-benzyl-2-phenyloxazol-4(5H)-one (**26e**) (75.4 mg, 0.3 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one (**2**) (167 mg, 0.9 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a white solid. Yield: 80 mg, 0.22 mmol, 73 %. m. p. 106-108  $^\circ C$ .  $[\alpha]_D^{23} = +44.63^\circ$  ( $c = 1.00$ , 96% ee as determined by chiral HPLC,  $CH_2Cl_2$ ).

$^1H$  NMR (300 MHz,  $CDCl_3$ ),  $\delta = 8.12 - 7.99$  (m, 2H), 7.64 (t,  $J = 7.5$  Hz, 1H), 7.46 (t,  $J = 7.7$  Hz, 2H), 7.14 (d,  $J = 6.0$  Hz, 5H), 3.61 (s, 1H), 3.20 (s, 2H), 2.60 (dd,  $J = 10.8, 5.3$  Hz, 2H), 2.34 (dd,  $J = 15.2, 7.5$  Hz, 2H), 1.26 (s, 3H), 1.22 (s, 3H).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ),  $\delta = 212.62$ , 192.37, 185.43, 135.19, 132.82, 129.84, 128.84, 128.25, 127.37, 125.15, 90.08, 76.37, 42.19, 29.27, 29.15, 26.41. MS (ESI,  $m/z$ ): calcd for  $C_{22}H_{24}NO_4$  ( $M, H^+$ ), 366.1705; found, 366.1708.

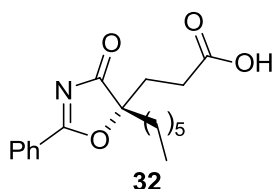


### 2.7.3. Elaboration of adducts **28** to carboxylic acids **32/33**



To a stirred solution of the ketol (**28**) (0.8 mmol) in acetonitrile (10 mL) at 0 °C a solution of cerium ammonium nitrate (CAN) (3 eq., 1.46 g, 2.7 mmol) in water (5 mL) was added dropwise and the mixture was stirred at the same temperature until starting **28** disappeared (TLC hex/EtOAc 60/40). Water was then added (3 mL) and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 10 mL), after which the organic phases were combined, dried over MgSO<sub>4</sub> and concentrated. The crude material was purified by flash chromatography on silica gel (Eluent with CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5) obtaining the desired product.

#### (*R*)-3-(5-Hexyl-4-oxo-2-phenyl-4,5-dihydrooxazol-5-yl)propanoic acid (**32**)

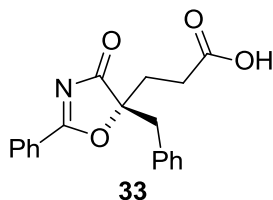


The title compound **32** was prepared from (*S*)-5-hexyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-2-phenyloxazol-4(5*H*)-one (**28c**) according to the general procedure. Yellow oil. Yield: 208 mg, 0.66 mmol, 82 %.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ = 8.22 – 8.15 (m, 2H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 2H), 2.37 – 2.27 (m, 2H), 1.96 – 1.84 (m, 2H), 1.34 – 1.14 (m, 10H), 0.81 (t, *J* = 6.6 Hz, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 193.00, 185.82, 176.87, 135.35, 130.10, 128.96, 127.36, 125.40,

90.21, 35.77, 31.31, 30.61, 28.91, 27.95, 22.66, 22.36, 13.86. MS (ESI, *m/z*): calcd for C<sub>18</sub>H<sub>24</sub>NO<sub>4</sub> (*M*+H<sup>+</sup>), 318.1705; found, 318.1691.

#### (*R*)-3-(5-Benzyl-4-oxo-2-phenyl-4,5-dihydrooxazol-5-yl)propanoic acid (**33**)



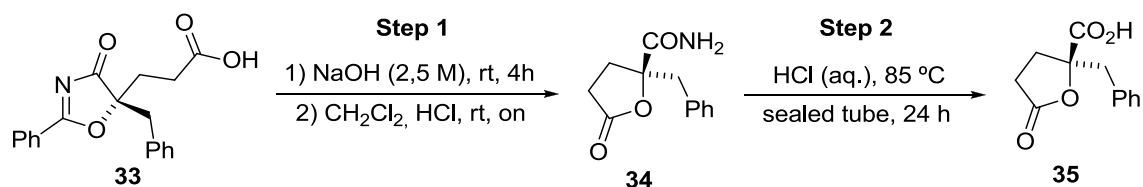
The title compound **33** was prepared from (*S*)-5-benzyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-2-phenyloxazol-4(5*H*)-one (**28e**) according to the general procedure. Yellow oil. Yield: 217 mg, 0.67 mmol, 84%.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ = 8.12 – 8.02 (m, 2H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.17 (s, 5H), 3.22 (s, 2H), 2.41 – 2.29 (m, 4H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 192.62, 185.91, 177.24, 135.64, 133.11, 130.23, 129.20, 128.65, 127.78, 90.30, 42.27, 30.59, 28.35.

MS (ESI, *m/z*): calcd for C<sub>19</sub>H<sub>18</sub>NO<sub>4</sub> (*M*+H<sup>+</sup>), 324.1236; found, 324.1227.

### 2.7.4. Assignment of stereochemistry

The configuration of adduct **33** was established by chemical correlation and comparison of chiroptical data with literature values as shown below. The configuration of the remaining adducts from the catalytic addition of oxazol-4(5*H*)-ones **26** to **2** was assigned by assuming a uniform reaction mechanism and also by correlation of retention times on HPLC.



**Step 1:** (*R*)-2-benzyl-5-oxotetrahydrofuran-2-carboxamide (**34**)<sup>31</sup>: The acid **33** (0.6 mmol) was dissolved in a 2.5 M aqueous solution of NaOH (6 mL) and stirred at room temperature for 4 h. Then CH<sub>2</sub>Cl<sub>2</sub> was added and the mixture was acidified to pH1 using a concentrated aqueous solution of HCl. The phases were separated and the aqueous phase was extracted with EtOAc (2 x 10 mL). The organic phases were united and the solvent was eliminated under reduced pressure. The crude was then redissolved in CH<sub>2</sub>Cl<sub>2</sub> (12 mL) and a concentrated aqueous solution of HCl (0.12 mL) was added, letting the mixture to stir at room temperature overnight. The organic phase was washed with an aqueous saturated solution of NaHCO<sub>3</sub> (3 x 10 mL), dried over MgSO<sub>4</sub> and the solvent was eliminated under reduced pressure, obtaining (*R*)-2-benzyl-5-oxotetrahydrofuran-2-carboxamide (**34**) as a white solid, which was used in the next step without further purification. Yield: 112 mg, 0.51 mmol, 85 %. m. p. 165–168 °C.

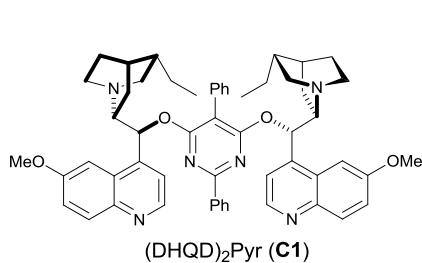
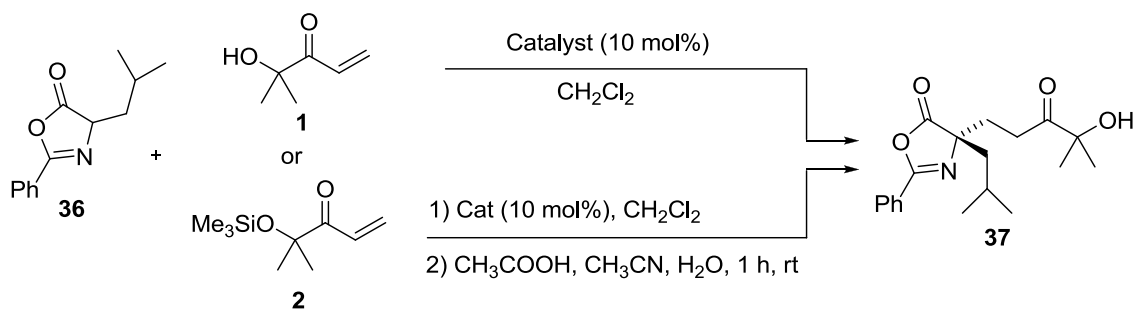
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ = 7.40 – 7.15 (m, 5H), 6.26 (s, 1H), 5.66 (s, 1H), 3.29 (d, *J* = 14.1 Hz, 1H), 3.09 (d, *J* = 14.1 Hz, 1H), 2.67 – 2.49 (m, 1H), 2.49 – 2.27 (m, 2H), 2.18 – 1.97 (m, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 175.39, 174.20, 133.88, 130.44, 128.57, 127.50, 87.72, 43.40, 29.90, 28.11. MS (ESI, *m/z*): calcd for C<sub>12</sub>H<sub>14</sub>NO<sub>3</sub> (M, H<sup>+</sup>), 220.0974; found, 220.0981.

**Step 2:** (*R*)-2-benzyl-5-oxotetrahydrofuran-2-carboxylic acid (**35**)<sup>32</sup>: The (*R*)-2-benzyl-5-oxotetrahydrofuran-2-carboxamide **34** (0.31 mmol) was dissolved in aqueous concentrated HCl solution (2 mL) and heated at 85 °C in a sealed tube for 24 h. The reaction mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL) and the combined organic phases were dried over MgSO<sub>4</sub> and the solvent eliminated under reduced pressure obtaining a brown solid. The solid was triturated with diethylether obtaining the desired (*R*)-2-benzyl-5-oxotetrahydrofuran-2-carboxylic acid (**35**) as a white solid. Yield: 43 mg, 0.19 mmol, 62%. m. p. 101–104 °C. [α]<sub>D</sub><sup>26</sup> = –2.73° (*c* = 1.00, acetone) ([α]<sub>D</sub><sup>20</sup> Lit<sup>33</sup> = –5.3° (*c* = 1.97, acetone). All spectroscopic data were identical to those reported in the literature.

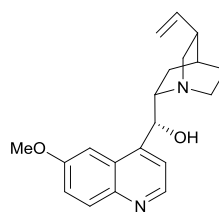
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ = 7.35 – 7.24 (m, 5H), 3.40 (d, *J* = 14.4 Hz, 1H), 3.15 (d, *J* = 14.4 Hz, 1H), 2.57 – 2.43 (m, 2H), 2.39 – 2.25 (m, 1H), 2.24 – 2.06 (m, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 175.67, 175.49, 133.42, 130.57, 128.64, 127.62, 85.80, 42.14, 29.96, 27.93.

## 2.8. Reactions involving azlactones 36

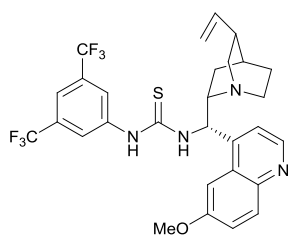
### 2.8.1. Catalyst screening (Table SI-4)



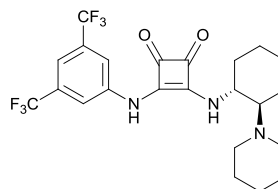
with **1**: -40 °C, 0% ee  
with **2**: -20 °C, 20% ee



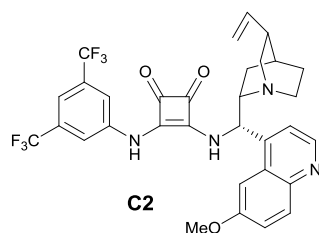
Quinine  
with **2**: -40 °C, 3% ee



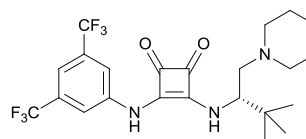
with **2**: -40 °C, 74% ee



with **2**: -20 °C, 82% ee

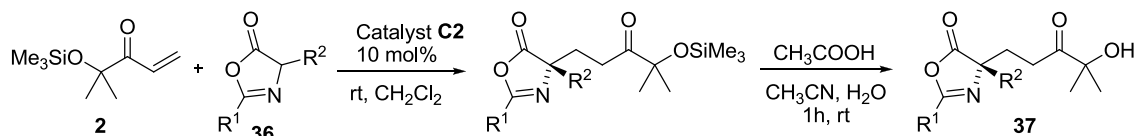


with **2**: -20 °C, 88% ee



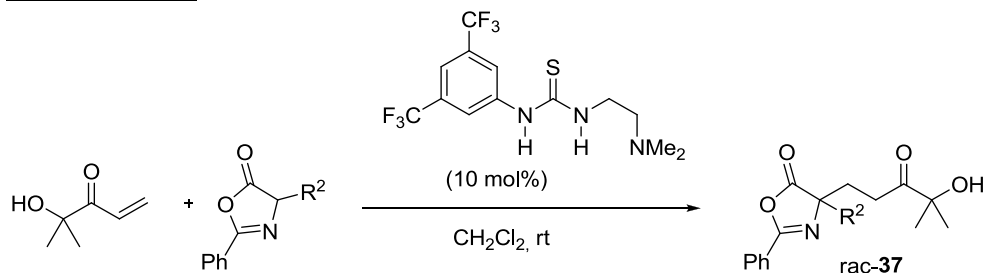
with **2**: 0 °C, 90% ee

## 2.8.2. Catalytic conjugate addition of azlactones **36** to **2**. General Procedure



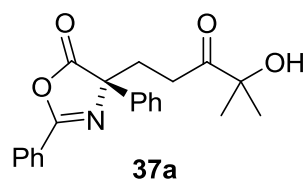
To a mixture of the corresponding azlactone **36** (1 eq., 0.2 mmol) and the  $\alpha'$ -silyloxy enone **2** (1.5 eq., 0.3 mmol) in dichloromethane (0.4 mL) catalyst **C2** was added at room temperature. The mixture was stirred at the same temperature, until consumption of the azlactone (monitored by  $^1\text{H-NMR}$ ). The reaction mixture was then quenched with 1M HCl (10 mL) and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 20 mL). The combined organic layers were dried with  $\text{MgSO}_4$ , filtered and the solvent was evaporated under reduced pressure. For the desilylation the crude was dissolved in  $\text{CH}_3\text{CN}$  (1 mL) and,  $\text{H}_2\text{O}$  (0.5 mL) and glacial acetic acid (0.3 mL) were added. The reaction mixture was stirred for 1 h at room temperature and it was quenched with  $\text{NaHCO}_3$  saturated aqueous solution (20 mL). The organic solvent was evaporated by reduced pressure and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 20 mL). The combined organic layers were dried over  $\text{MgSO}_4$ , filtered and the solvent was evaporated under reduced pressure. The crude was purified by flash column chromatography on silica gel to afford the expected adducts.

### Racemic variant<sup>34</sup>



To a mixture of the corresponding azlactone **36** (1 eq., 0.2 mmol) and the  $\alpha'$ -hydroxy enone **1** (1.5 eq., 0.3 mmol) in dichloromethane (0.4 mL) the achiral thiourea catalyst was added at room temperature. The mixture was stirred at the same temperature, until consumption of the azlactone (monitored by  $^1\text{H-NMR}$ ). The reaction mixture was then quenched with 1M HCl (10 mL) and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 20 mL). The combined organic layers were dried over  $\text{MgSO}_4$ , filtered and the solvent was evaporated under reduced pressure. The crude was purified by flash column chromatography on silica gel to afford the expected adducts.

### **(R)-4-(4-Hydroxy-4-methyl-3-oxopentyl)-2,4-diphenyloxazol-5(4H)-one (37a)**

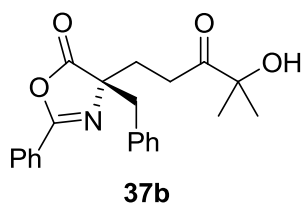


The title compound **37a** was prepared from 2,4-diphenyloxazol-5(4H)-one **36a** (47.5 mg, 0.2 mmol) and  $\alpha'$ -silyloxy enone **2** (55.9 mg, 0.3 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 90/10) to give the title compound as a yellow oil. Yield: 50.2 mg, 0.14 mmol, 71%.  $[\alpha]_D^{25} = -108.0$  ( $c = 2.3$ , 90% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 8.11 – 8.05 (m, 2H), 7.69 – 7.59 (m, 3H), 7.56 – 7.50 (m, 2H), 7.39 (m, 3H), 3.57 (s, 1H), 2.80 – 2.38 (m, 4H), 1.32 (s, 3H), 1.26 (s, 3H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ),  $\delta$ :

213.1, 178.5, 160.9, 137.3, 133.3, 129.1, 129.1, 128.8, 128.4, 126.0, 125.8, 76.6, 73.2, 34.6, 30.5, 26.7. UPLC-DAD-QTOF:  $C_{21}H_{22}NO_4$   $[M+H]^+$  calcd.: 352.1549, found: 352.1551.

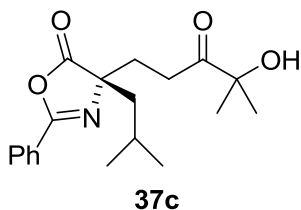
**(R)-4-Benzyl-4-(4-hydroxy-4-methyl-3-oxopentyl)-2-phenyloxazol-5(4H)-one (37b)**



The title compound **37b** was prepared from 4-benzyl-2-phenyloxazol-5(4H)-one **36b** (50.3 mg, 0.2 mmol) and  $\alpha'$ -silyloxy enone **2** (55.9 mg, 0.3 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 90/10) to give the title compound as a yellow oil. Yield: 40.6 mg, 0.14 mmol, 72%.  $[\alpha]_D^{25} = -70.5$  ( $c = 2.2$ , 88% ee,  $CH_2Cl_2$ ).

$^1H$  NMR (300 MHz,  $CDCl_3$ ),  $\delta$ : 7.86 – 7.80 (m, 2H), 7.58 – 7.50 (m, 1H), 7.47 – 7.40 (m, 2H), 7.16 (m, 5H), 3.56 (s, 1H), 3.31 – 3.12 (m, 2H), 2.71 – 2.51 (m, 2H), 2.45 – 2.28 (m, 2H), 1.32 (s, 3H), 1.30 (s, 3H).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ),  $\delta$ : 213.0, 179.4, 160.6, 134.0, 133.0, 130.3, 128.9, 128.4, 128.0, 127.6, 125.5, 76.6, 73.8, 43.9, 31.2, 30.4, 26.8. UPLC-DAD-QTOF:  $C_{22}H_{24}NO_4$   $[M+H]^+$  calcd.: 366.1700, found: 366.1709.

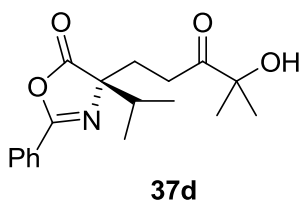
**(R)-4-(4-Hydroxy-4-methyl-3-oxopentyl)-4-isobutyl-2-phenyloxazol-5(4H)-one (37c)**



The title compound **37c** was prepared from 4-isobutyl-2-phenyloxazol-5(4H)-one **36c** (43.4 mg, 0.2 mmol) and  $\alpha'$ -silyloxy enone **2** (55.9 mg, 0.3 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 90/10) to give the title compound as a yellow oil. Yield: 50.6 mg, 0.15 mmol, 75%.  $[\alpha]_D^{25} = -28.7$  ( $c = 2.2$ , 92% ee,  $CH_2Cl_2$ ).

$^1H$  NMR (300 MHz,  $CDCl_3$ ),  $\delta$ : 8.12 – 7.89 (m, 2H), 7.64 – 7.56 (m, 1H), 7.55 – 7.47 (m, 2H), 3.55 (s, 1H), 2.62 – 2.44 (m, 2H), 2.29 – 2.11 (m, 2H), 1.97 (dd,  $J = 14.0, 5.5$  Hz, 1H), 1.82 (dd,  $J = 14.0, 7.1$  Hz, 1H), 1.62 (dq,  $J = 12.6, 6.7$  Hz, 1H), 1.32 (s, 3H), 1.30 (s, 3H), 0.88 (dd,  $J = 10.4, 6.6$  Hz, 6H).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ),  $\delta$ : 213.1, 180.7, 160.3, 133.1, 129.1, 128.6, 125.8, 76.6, 72.0, 46.2, 32.5, 29.9, 26.7, 25.0, 24.3, 23.3. UPLC-DAD-QTOF:  $C_{19}H_{26}NO_4$   $[M+H]^+$  calcd.: 332.1856, found: 332.1860.

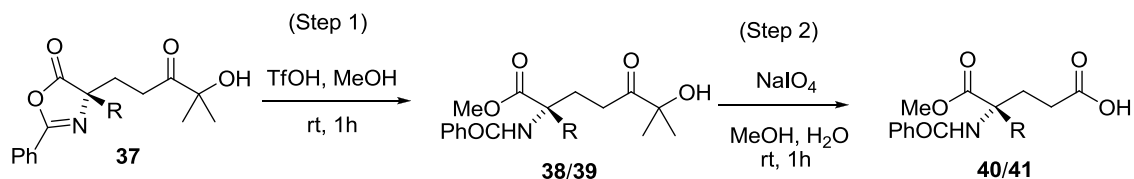
**(R)-4-(4-Hydroxy-4-methyl-3-oxopentyl)-4-isopropyl-2-phenyloxazol-5(4H)-one (37d)**



The title compound **37d** was prepared from 4-isopropyl-2-phenyloxazol-5(4H)-one **36d** (40.6 mg, 0.2 mmol) and  $\alpha'$ -silyloxy enone **2** (55.9 mg, 0.3 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 90/10) to give the title compound as a yellow oil. Yield: 49 mg, 0.15 mmol, 77%.  $[\alpha]_D^{25} = +0.7$  ( $c = 0.65$ , 90% ee,  $CH_2Cl_2$ ).

$^1H$  NMR (300 MHz,  $CDCl_3$ ),  $\delta$ : 8.04 – 7.98 (m, 2H), 7.63 – 7.56 (m, 1H), 7.54 – 7.47 (m, 2H), 3.50 (s, 1H), 2.54 – 2.45 (m, 2H), 2.39 – 2.28 (m, 1H), 2.26 – 2.13 (m, 2H), 1.31 (s, 3H), 1.29 (s, 3H), 1.06 (d,  $J = 6.8$  Hz, 3H), 0.97 (d,  $J = 6.8$  Hz, 3H).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ),  $\delta$ : 213.2, 180.1, 160.7, 133.1, 129.1, 128.2, 125.7, 76.5, 75.6, 35.2, 30.3, 28.9, 26.8, 16.9. UPLC-DAD-QTOF:  $C_{18}H_{24}NO_4$   $[M+H]^+$  calcd.: 318.1700, found: 318.1705.

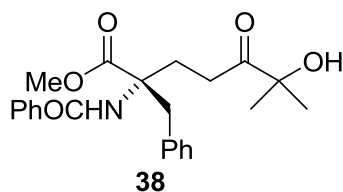
### 2.8.3. Elaboration of adducts **37** into carboxylic acids **40/41**



(Step 1): To a solution of  $\alpha$ -hydroxy ketone **37** (0.5 mmol) in MeOH (2.5 mL, 5 mL/mmol) 2 drops of triflic acid were added and the solution was stirred at room temperature until completion of reaction (1 h). After that the solvent was removed under reduced pressure, and the crude material was purified by flash column chromatography on silica gel.

(Step 2): The residue obtained in the previous step was dissolved in MeOH and to this solution a suspension of sodium periodate  $\text{NaIO}_4$  (535 mg, 2.5 mmol, 5 equiv.) in water (1.5 mL) was added. The reaction mixture was stirred at room temperature until completion of reaction (1 h). The solvent was then removed under reduced pressure, water (4.5 mL) was added to the residue and the resulting mixture was extracted with  $\text{Et}_2\text{O}$  (3 x 6 mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and the solvent was evaporated to afford the corresponding carboxylic acid. The crude was purified by flash column chromatography on silica gel.

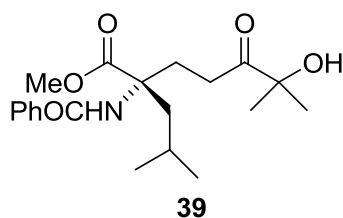
#### (*R*)-Methyl 2-benzamido-2-benzyl-6-hydroxy-6-methyl-5-oxoheptanoate (**38**)



The title compound **38** was prepared from (*R*)-4-(4-hydroxy-4-methyl-3-oxopentyl)-4-isobutyl-2-phenyloxazol-5(4*H*)-one **37b** (183 mg, 0.5 mmol) following the general procedure. The reaction mixture was stirred for 1 h until completion of reaction. After evaporating the organic solvent the crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a white foam. Yield: 199 mg, 0.5 mmol, >99%.  $[\alpha]_D^{25} = -52.3$  ( $c = 1.01$ ,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 7.71 – 7.65 (m, 2H), 7.54 – 7.38 (m, 3H), 7.19 (m, 2H), 7.04 – 6.96 (m, 3H), 3.87 (d,  $J = 13.8$  Hz, 1H), 3.84 (s, 3H), 3.26 (d,  $J = 13.5$  Hz, 1H), 3.10 – 2.96 (m, 1H), 2.77 – 2.57 (m, 1H), 2.50 – 2.32 (m, 2H), 1.29 (d,  $J = 3.9$  Hz, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 213.7, 173.7, 166.9, 136.1, 134.9, 131.9, 129.9, 128.9, 128.5, 127.3, 126.9, 76.5, 65.7, 53.2, 40.9, 30.9, 29.9, 26.7, 26.7. UPLC-DAD-QTOF:  $\text{C}_{23}\text{H}_{28}\text{NO}_5$   $[\text{M}+\text{H}]^+$  calcd.: 398.1962 found: 398.1967.

#### (*R*)-Methyl 2-benzamido-6-hydroxy-2-isobutyl-6-methyl-5-oxoheptanoate (**39**)

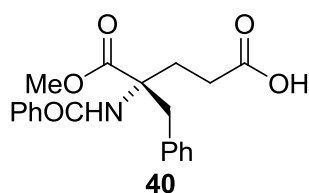


The title compound **39** was prepared from (*R*)-4-(4-hydroxy-4-methyl-3-oxopentyl)-4-isobutyl-2-phenyloxazol-5(4*H*)-one **37c** (166 mg, 0.5 mmol). The reaction mixture was stirred for 1 h until completion of reaction. After evaporating the organic solvent the crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a white foam.

Yield: 174 mg, 0.48 mmol, 95%.  $[\alpha]_D^{25} = +4.5$  ( $c = 0.75$ ,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 7.83 – 7.78 (m, 2H), 7.55 – 7.43 (m, 3H), 7.33 (s, 1H), 3.83 (s, 3H), 3.55 (s, 1H), 2.97 – 2.85 (m, 1H), 2.73 – 2.51 (m, 2H), 2.38 – 2.21 (m, 2H), 1.83 (dd,  $J = 14.2$ , 7.6 Hz, 1H), 1.60 (dd,  $J = 13.6$ , 7.1 Hz, 1H), 1.29 (s, 6H), 0.85 (dd,  $J = 26.6$ , 6.6 Hz, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 213.6, 175.6, 166.2, 134.9, 131.9, 128.9, 126.9, 76.5, 63.9, 53.2, 43.8, 30.8, 30.6, 26.8, 26.7, 25.1, 23.9, 22.8. UPLC-DAD-QTOF:  $\text{C}_{20}\text{H}_{30}\text{NO}_5$   $[\text{M}+\text{H}]^+$  calcd.: 364.2124, found: 364.2124.

#### (*R*)-4-Benzamido-4-benzyl-5-methoxy-5-oxopentanoic acid (**40**)

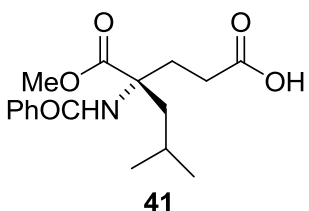


The title compound **40** was prepared from (*R*)-4-benzyl-4-(4-hydroxy-4-methyl-3-oxopentyl)-2-phenyloxazol-5(4*H*)-one **37b** (199 mg, 0.5 mmol, 1 eq.) and NaIO<sub>4</sub> (535 mg, 2.5 mmol, 5 eq.) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 60/40) to give the title compound as a white foam. Yield: 160 mg, 0.45 mmol, 89% over two steps.  $[\alpha]_D^{25} =$

$-14.8$  ( $c = 2.6$ , CH<sub>2</sub>Cl<sub>2</sub>).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>),  $\delta$ : 7.74 – 7.65 (m, 2H), 7.55 – 7.43 (m, 1H), 7.40 (m, 2H), 7.22 – 7.15 (m, 2H), 7.09 – 6.99 (m, 3H), 3.91 (d,  $J = 13.6$  Hz, 2H), 3.82 (s, 3H), 3.23 (d,  $J = 13.5$  Hz, 2H), 3.15 – 3.05 (m, 1H), 2.51 – 2.31 (m, 2H), 2.26 – 2.14 (m, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>),  $\delta$ : 178.0, 173.5, 167.3, 136.0, 134.8, 131.9, 129.8, 128.8, 128.5, 127.2, 127.1, 65.7, 53.1, 40.7, 30.4, 29.5. UPLC-DAD-QTOF: C<sub>20</sub>H<sub>22</sub>NO<sub>5</sub> [M+H]<sup>+</sup> calcd.: 356.1492, found: 356.1496.

#### (*R*)-4-Benzamido-4-(methoxycarbonyl)-6-methylheptanoic acid (**41**)

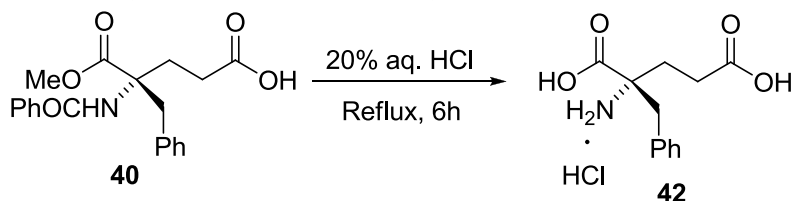


The title compound **41** was prepared from (*R*)-4-(4-hydroxy-4-methyl-3-oxopentyl)-4-isobutyl-2-phenyloxazol-5(4*H*)-one **37c** (182 mg, 0.5 mmol, 1 eq.) and NaIO<sub>4</sub> (535 mg, 2.5 mmol, 5 eq.) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 60/40) to give the title compound as a white foam. Yield: 138 mg, 0.43 mmol, 86% over two steps.  $[\alpha]_D^{25} =$

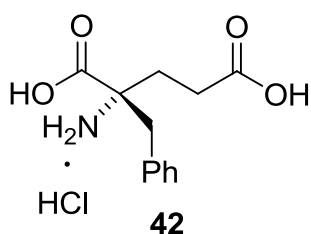
$-77.0$  ( $c = 0.5$ , CH<sub>2</sub>Cl<sub>2</sub>).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>),  $\delta$ : 7.81 – 7.76 (m, 2H), 7.53 – 7.32 (m, 3H), 3.80 (s, 3H), 3.02 – 2.88 (m, 1H), 2.67 (dd,  $J = 14.2$ , 5.3 Hz, 1H), 2.38 – 2.03 (m, 3H), 1.78 (dd,  $J = 14.2$ , 7.6 Hz, 1H), 1.57 (m, 1H), 0.88 (d,  $J = 6.7$  Hz, 3H), 0.78 (d,  $J = 6.6$  Hz, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>),  $\delta$ : 178.2, 175.3, 166.5, 134.7, 131.9, 128.9, 127.1, 63.9, 53.2, 43.7, 31.2, 29.3, 25.0, 23.9, 22.7. UPLC-DAD-QTOF: C<sub>17</sub>H<sub>24</sub>NO<sub>5</sub> [M+H]<sup>+</sup> calcd.: 322.1649, found: 322.1653.

#### 2.8.4. Synthesis of glutamic acid analogue **42**<sup>35</sup>



#### 2-(*R*)-Benzylglutamic acid hydrochloride (**42**)



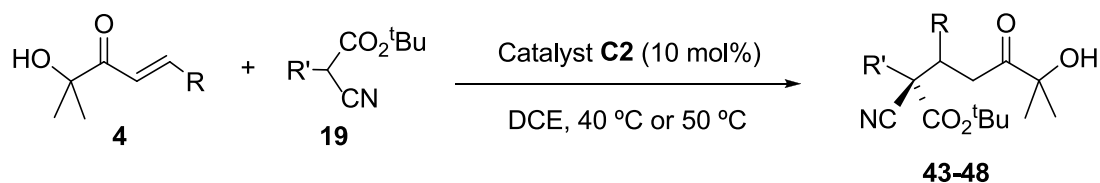
(*R*)-4-Benzamido-4-benzyl-5-methoxy-5-oxopentanoic acid (**40**) (355 mg, 0.75 mmol) was treated with 5 mL of 20% HCl for 4 h at reflux. After standing overnight in the refrigerator, the resulting crystals of benzoic acid were removed by filtration and the filtrate was washed twice with diethyl ether. The solution was evaporated to dryness in vacuo. The residue was dissolved in a small amount of water and the solution was evaporated to dryness again in order to remove any trace of HCl. Finally, the product was dried

overnight in the lyophilizator to obtain a white solid. Yield: 151 mg, 0.64 mmol, 85 %. m. p. 195–199 °C.  $[\alpha]_D^{25} = -0.98$  ( $c = 3.3$ , 4N HCl); Literature data for the opposite enantiomer:  $[\alpha]_D^{25} = +1.44$  ( $c = 6.39$ , 4N HCl).<sup>36</sup>

$^1\text{H}$  NMR (300 MHz,  $\text{D}_2\text{O}$ ),  $\delta$ : 7.50 – 7.38 (m, 3H), 7.36 – 7.30 (m, 2H), 3.46 (d,  $J = 14.4$  Hz, 1H), 3.14 (d,  $J = 14.4$  Hz, 1H), 2.70 – 2.50 (m, 2H), 2.46 – 2.32 (m, 1H), 2.30 – 2.16 (m, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{D}_2\text{O}$ ),  $\delta$ : 174.9, 172.5, 132.8, 130.6, 129.6, 128.7, 63.9, 41.3, 30.7, 28.6.



## 2.9. Addition of $\alpha$ -cyanoacetates **19** to $\beta$ -substituted $\alpha$ -hydroxy enones **4**



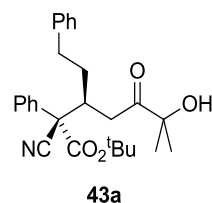
### General Procedure

To a mixture of the corresponding cyanoacetate (0.1 mmol, 1 equiv.) and  $\alpha$ -hydroxy enone **4** (0.3 mmol, 3 equiv.) in 1,2-dichloroethane (DCE, 0.4 mL), catalyst **C2** (6.31 mg, 0.01 mmol) was added. The resulting mixture was stirred at 40 °C, unless otherwise stated, until consumption of the cyanoacetate (monitored by  $^1\text{H-NMR}$ ). The reaction was treated with HCl 1N and the product was extracted with  $\text{CH}_2\text{Cl}_2$  and the combined organic phases were dried with  $\text{MgSO}_4$ . Evaporation of the solvent under reduced pressure gave the crude product as a mixture of diastereomers in all cases higher than 95:5 as indicated in Table 5. After purification by flash column chromatography (eluent hexane/ ethyl acetate 95/5) the product was isolated in essentially diastereomerically pure form.

### General procedure for the racemic reactions:

Racemic reactions were conducted following the procedure for the asymmetric version, but using as catalyst DBU (20 mol%) and running the reaction at 70 °C.

#### (2*S*,3*S*)-*tert*-Butyl 2-cyano-6-hydroxy-6-methyl-5-oxo-3-phenethyl-2-phenylheptanoate (**43a**)

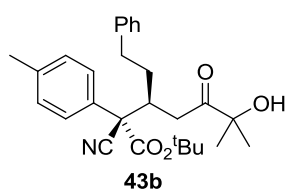


Prepared according to the general procedure starting from hydroxyketone **4A** (65.5 mg, 0.3 mmol) and *tert*-butyl 2-cyano-2-phenylacetate) **19a** (21.7 mg, 0.1 mmol). The title compound was isolated as an oil. Yield: 90% (39 mg).  $[\alpha]_{\text{D}}^{25} = +44.8$  ( $c=1.00$ , 96% *ee*,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.56 – 7.54 (m, 2H), 7.42 – 7.36 (m, 3H), 7.20 – 7.10 (m, 3H), 6.92 – 6.90 (m, 2H), 3.60 (brs, 1H), 3.40 – 3.35 (m, 1H), 2.95 (dd,  $J = 18.8$  Hz and 7.6 Hz, 1H), 2.83 (dd,  $J = 18.8$  Hz and 2.6 Hz, 1H), 2.45 – 2.38 (m, 1H), 2.21 – 2.12 (m, 1H), 1.60 – 1.46 (m, 2H), 1.43 (s, 3H), 1.41 (s, 3H), 1.37 (s, 9H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  211.6, 166.0, 141.12, 133.4, 129.1, 129.0, 128.3, 128.1, 126.4, 125.9, 117.7, 84.7, 76.4, 60.7, 39.5, 39.2, 33.7, 33.4, 27.4, 26.8, 26.7. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{27}\text{H}_{34}\text{NO}_4$  ( $\text{M}+\text{H}^+$ ), 436.2488; found, 436.2485.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-3 hexane/isopropanol 90/10, flow rate= 0.5 mL/min at 10 °C, retention times: 23.5 min (minor.) and 24.7 min (major.)).

#### (2*S*,3*S*)-*tert*-Butyl 2-cyano-6-hydroxy-6-methyl-5-oxo-3-phenethyl-2-(*p*-tolyl)heptanoate (**43b**)

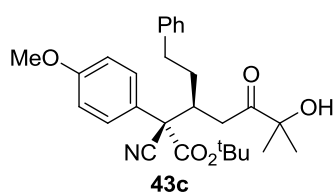


The title compound was prepared from *tert*-butyl 2-cyano-2-(*p*-tolyl)acetate **19b** (23 mg, 0.1 mmol) and (*E*)-2-hydroxy-2-methyl-7-phenylhept-4-en-3-one **4A** (65 mg, 0.3 mmol) according to the general procedure. Diastereomeric ratio as determined in the crude material 99:1. Yield of pure major diastereomer after column chromatography purification (colourless oil): 95% (43 mg).  $[\alpha]_{\text{D}}^{24} = +40.0^\circ$  ( $c=1.9$ , 99% *ee*,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.55 – 7.39 (m, 2H), 7.22 – 7.07 (m, 5H), 7.02 – 6.80 (m, 2H), 3.59 (s, 1H), 3.40 – 3.28 (m, 1H), 2.92 (dd,  $J = 18.6$ , 7.6 Hz, 1H), 2.79

(dd,  $J = 18.6, 2.7$  Hz, 1H), 2.53 – 2.39 (m, 1H), 2.19 (m, 1H), 1.59 (m, 1H), 1.53 – 1.45 (m, 1H) 1.42 (s, 3H), 1.40 (s, 3H), 1.37 (s, 9H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  211.9, 166.4, 141.4, 139.1, 130.6, 123.0, 128.5, 128.4, 126.5, 126.1, 118.0, 84.8, 76.6, 60.6, 39.8, 39.4, 33.9, 33.7, 27.7, 27.0, 26.9, 21.2. UPLC-DAD-QTOF:  $\text{C}_{28}\text{H}_{36}\text{NO}_4$   $[\text{M}+\text{H}]^+$  calcd.: 450.2344, found: 450.2347.

The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralcel AD-H hexane/isopropanol 98/2, flow rate= 1 mL/min, retention times: 49.9 min (minor.) and 57.5 min (major.)). Channel Descr.: PDA 210 nm.

**(2S,3S)-*tert*-Butyl 2-cyano-6-hydroxy-2-(4-methoxyphenyl)-6-methyl-5-oxo-3-phenethylheptanoate (43c)**

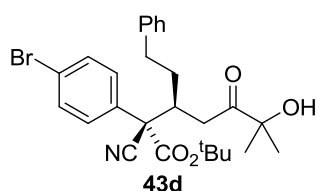


The title compound was prepared from *tert*-butyl 2-cyano-2-(4-methoxyphenyl)acetate **19c** (25 mg, 0.1 mmol) and (*E*)-2-hydroxy-2-methyl-7-phenylhept-4-en-3-one **4A** (65 mg, 0.3 mmol) according to the general procedure. Diastereomeric ratio as determined in the crude material 98:2. Yield of pure major diastereomer after column chromatography purification

(colourless oil): 92% (43 mg).  $[\alpha]_{\text{D}}^{24} = +37.0^\circ$  ( $c=1.4$ , 96% *ee*,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.57 – 7.36 (m, 2H), 7.17 (m, 3H), 7.04 – 6.72 (m, 4H), 3.82 (s, 3H), 3.58 (s, 1H), 3.36 – 3.26 (m, 1H), 2.92 (dd,  $J = 18.6, 7.6$  Hz, 1H), 2.78 (dd,  $J = 18.6, 2.7$  Hz, 1H), 2.47 – 2.34 (m, 1H), 2.27 – 2.13 (m, 1H), 1.43 (s, 3H), 1.40 (s, 3H), 1.37 (s, 9H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  211.9, 166.5, 160.1, 141.4, 128.5, 127.9, 126.2, 125.5, 118.1, 114.6, 84.8, 76.6, 60.3, 55.5, 39.8, 39.4, 33.9, 33.7, 27.7, 27.1. UPLC-DAD-QTOF:  $\text{C}_{28}\text{H}_{36}\text{NO}_5$   $[\text{M}+\text{H}]^+$  calcd.: 466.2593, found: 466.2589.

The enantiomeric purity of the major diastereoisomer was determined by HPLC analysis (Daicel Chiralcel AD-3 hexane/isopropanol 90/10, flow rate= 0.5 mL/min, retention times: 25.4 min (minor.) and 31.4 min (major.)). Channel Descr.: PDA 210 nm.

**(2S,3S)-*tert*-Butyl 2-(4-bromophenyl)-2-cyano-6-hydroxy-6-methyl-5-oxo-3-phenethylheptanoate (43d)**

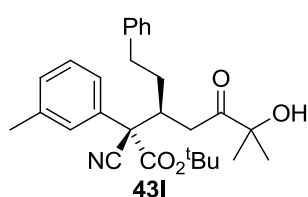


The title compound was prepared from *tert*-butyl 2-cyano-2-(4-bromophenyl)acetate **19d** (30 mg, 0.1 mmol) and (*E*)-2-hydroxy-2-methyl-7-phenylhept-4-en-3-one **4A** (65 mg, 0.3 mmol) according to the general procedure. Diastereomeric ratio as determined in the crude material 99:1. Yield of pure major diastereomer after column chromatography purification (colourless oil): 89% (46 mg).

$[\alpha]_{\text{D}}^{24} = +32.1^\circ$  ( $c=1.0$ , 94% *ee*,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.53 – 7.47 (m, 2H), 7.42 – 7.36 (m, 2H), 7.24 – 7.14 (m, 3H), 6.97 – 6.90 (m, 2H), 3.50 (s, 1H), 3.33 (m, 1H), 2.94 (dd,  $J = 18.7, 7.3$  Hz, 1H), 2.80 (dd,  $J = 18.7, 2.8$  Hz, 1H), 2.50 – 2.37 (m, 1H), 2.22 (m, 1H), 1.43 (s, 3H), 1.41 (s, 3H), 1.37 (s, 9H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  211.7, 165.8, 141.0, 132.7, 132.4, 128.5, 128.4, 128.3, 126.2, 123.4, 117.4, 85.3, 76.6, 60.6, 39.7, 39.1, 33.9, 33.4, 27.6, 27.0, 26.9. UPLC-DAD-QTOF:  $\text{C}_{27}\text{H}_{33}\text{NO}_4\text{Br}$   $[\text{M}+\text{H}]^+$  calcd.: 514.1593, found: 514.1594.

The enantiomeric purity of the major diastereoisomer was determined by HPLC analysis (Daicel Chiralcel AD-H hexane/isopropanol 90/10, flow rate= 1 mL/min, retention times: 11.1 min (minor.) and 13.9 min (major.)). Channel Descr.: PDA 210 nm.

**(2S,3S)-*tert*-Butyl 2-cyano-6-hydroxy-6-methyl-5-oxo-3-phenethyl-2-(*m*-tolyl)heptanoate (43I)**

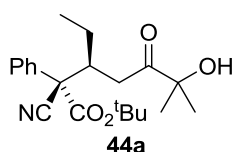


The title compound was prepared from *tert*-butyl 2-cyano-2-(*m*-tolyl)acetate **19I** (23 mg, 0.1 mmol) and (*E*)-2-hydroxy-2-methyl-7-phenylhept-4-en-3-one **4A** (65 mg, 0.3 mmol) according to the general procedure. Diastereomeric ratio as determined in the crude material 99:1. Yield of pure major diastereomer after column

chromatography purification (colourless oil): 89% (40 mg).  $[\alpha]_D^{24} = +30.6^\circ$  ( $c=2.5$ , 98% *ee*,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34 (m, 2H), 7.27 (m, 2H), 7.22 – 7.11 (m, 3H), 6.95 – 6.87 (m, 2H), 3.58 (s, 1H), 3.39 – 3.29 (m, 1H), 2.93 (dd,  $J = 18.6, 7.5$  Hz, 1H), 2.81 (dd,  $J = 18.6, 2.8$  Hz, 1H), 2.47 – 2.37 (m, 1H), 2.36 (s, 3H), 2.17 (ddd,  $J = 13.7, 10.7, 6.3$  Hz, 1H), 1.63 – 1.54 (m, 1H), 1.53 – 1.45 (m, 1H), 1.43 (s, 3H), 1.40 (s, 3H), 1.37 (s, 9H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  211.9, 166.3, 141.4, 139.2, 133.4, 129.9, 129.2, 128.5, 128.4, 127.2, 126.1, 123.6, 118.0, 84.9, 76.6, 60.9, 39.8, 39.4, 33.9, 33.6, 27.7, 27.0, 27.0, 21.7. UPLC-DAD-QTOF:  $\text{C}_{28}\text{H}_{36}\text{NO}_4$   $[\text{M}+\text{H}]^+$  calcd.: 450.2644, found: 450.2640.

The enantiomeric purity of the major diastereoisomer was determined by HPLC analysis (Phenomenex Lux  $3\mu$  Cellulose-4 hexane/isopropanol 96/4, flow rate= 1.0 mL/min, retention times: 9.9 min (minor.) and 10.9 min (major.)). Channel Descr.: PDA 207 nm.

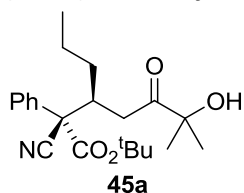
#### (2S,3S)-*tert*-Butyl 2-cyano-3-ethyl-6-hydroxy-6-methyl-5-oxo-2-phenylheptanoate (44a)



The title compound was prepared from *tert*-butyl 2-cyano-2-phenylacetate **19a** (22 mg, 0.1 mmol) and (*E*)-2-hydroxy-2-methylhept-4-en-3-one **4B** (43 mg, 0.3 mmol) according to the general procedure. Diastereomeric ratio as determined in the crude material 96:4. Yield of pure major diastereomer after column chromatography purification (colourless oil): 95% (35 mg).  $[\alpha]_D^{23} = +19.4^\circ$  ( $c=1.15$ , 92% *ee*,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.62 – 7.55 (m, 2H), 7.46 – 7.32 (m, 3H), 3.62 (s, 1H), 3.33 – 3.22 (m, 1H), 2.86 (dd,  $J = 18.8, 7.6$  Hz, 1H), 2.71 (dd,  $J = 18.7, 2.5$  Hz, 1H), 1.43 (s, 3H), 1.39 (s, 3H), 1.37 (s, 9H), 1.31 – 1.13 (m, 2H), 0.67 (t,  $J = 7.5$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  211.8, 166.3, 133.8, 129.3, 129.1, 126.6, 118.0, 84.8, 76.6, 61.0, 40.6, 38.9, 27.7, 27.1, 27.0, 24.6, 11.6. UPLC-DAD-QTOF:  $\text{C}_{21}\text{H}_{30}\text{NO}_4$   $[\text{M}+\text{H}]^+$  calcd.: 360.2175, found: 360.2171.

The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Phenomenex Lux  $3\mu$  Cellulose-4 hexane/isopropanol 99/01, flow rate= 1.0 mL/min, retention times: 26.8 min (minor.) and 27.8 min (major.)). Processed Channel Descr.: PDA 207 nm.

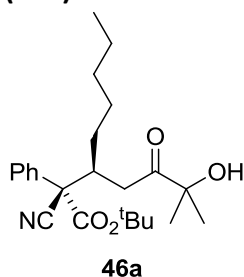
#### (2S,3S)-*tert*-Butyl 6-hydroxy-2-isocyano-6-methyl-5-oxo-2-phenyl-3-propylheptanoate (45a)



The title compound was prepared from *tert*-butyl 2-cyano-2-phenylacetate **19a** (22 mg, 0.1 mmol) and (*E*)-2-hydroxy-2-methyloct-4-en-3-one **4X** (47 mg, 0.3 mmol) according to the general procedure. Diastereomeric ratio as determined in the crude material 99:1. Yield of pure major diastereomer after column chromatography purification (colourless oil): 90% (33 mg).  $[\alpha]_D^{24} = +27.9^\circ$  ( $c=1.4$ , 92% *ee*,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.68 – 7.52 (m, 2H), 7.52 – 7.33 (m, 3H), 3.62 (s, 1H), 3.33 (qd,  $J = 7.2, 2.7$  Hz, 1H), 2.84 (dd,  $J = 18.7, 7.2$  Hz, 1H), 2.72 (dd,  $J = 18.7, 2.7$  Hz, 1H), 1.42 (s, 3H), 1.38 (s, 3H), 1.37 (s, 9H), 1.27 – 1.13 (m, 2H), 1.10 – 0.92 (m, 2H), 0.71 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  211.8, 166.3, 133.9, 129.3, 129.1, 126.6, 118.0, 84.8, 76.5, 61.1, 39.5, 39.1, 34.1, 27.7, 27.0, 27.0, 20.3, 14.2. UPLC-DAD-QTOF:  $\text{C}_{22}\text{H}_{32}\text{NO}_4$   $[\text{M}+\text{H}]^+$  calcd.: 374.2331, found: 374.2339.

The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralcel AD-H hexane/isopropanol 98/2, flow rate= 1.0 mL/min, retention times: 22.2 min (major.) and 29.7 min (minor.)). Processed Channel Descr.: PDA 210 nm.

#### (2S,3S)-*tert*-Butyl 2-cyano-6-hydroxy-6-methyl-5-oxo-3-pentyl-2-phenylheptanoate (46a)



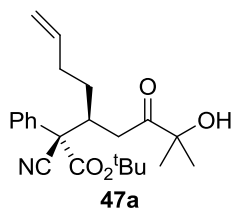
Prepared according to the general procedure starting from hydroxyketone **4D** (55.3 mg, 0.3 mmol) and *tert*-butyl 2-cyano-2-phenylacetate **19a** (21.7 mg, 0.1 mmol). The title compound was

isolated as an oil. Yield: 85% (34.1 mg).  $[\alpha]_D^{26} = +25.0^\circ$  ( $c=1$ , 94% *ee*,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.59 – 7.55 (m, 2H), 7.42 – 7.34 (m, 3H), 3.70 (s, 1H), 3.34 – 3.28 (m, 1H), 2.86 (dd,  $J=7.5$  Hz,  $J=18.7$  Hz, 1H), 2.71 (dd,  $J=2.4$  Hz,  $J=18.7$  Hz, 1H), 1.40 (s, 3H), 1.37 (s, 3H), 1.36 (s, 9H), 1.20 – 0.87 (m, 8H), 0.73 (t,  $J=7.1$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  211.6, 166.1, 133.7, 129.0, 128.9, 126.4, 117.8, 84.6, 76.4, 60.9, 39.4, 39.1, 31.6, 27.4, 26.9, 26.7, 26.5, 22.2, 13.8. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{24}\text{H}_{36}\text{NO}_4$  ( $\text{M}+\text{H}^+$ ), 402.2644; found, 402.2641.

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA hexane/isopropanol 98/2, flow rate= 1 mL/min at 10 °C, retention times: 26.8 min (major.) and 30.3 min (minor.)).

**(2S,3S)-*tert*-Butyl 2-cyano-3-(3-hydroxy-3-methyl-2-oxobutyl)-2-phenylhept-6-enoate (47a)**

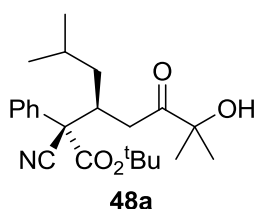


The title compound was prepared from *tert*-butyl 2-cyano-2-phenylacetate **19a** (22 mg, 0.1 mmol) and (*E*)-2-hydroxy-2-methylnona-4,8-dien-3-one **4C** (50 mg, 0.3 mmol) according to the general procedure. Diastereomeric ratio as determined in the crude material 99:1. Yield of pure major diastereomer after column chromatography purification (colourless oil): Yield: 93% (36 mg).  $[\alpha]_D^{23} = +29.4^\circ$  ( $c=1.7$ , 96% *ee*,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.58 (m, 2H), 7.51 – 7.34 (m, 3H), 5.62 – 5.49 (m, 1H), 4.93 – 4.77 (m, 1H), 3.58 (s, 1H), 3.39 – 3.26 (m, 1H), 2.94 – 2.73 (m, 2H), 1.84 – 1.61 (m, 2H), 1.42 (s, 3H), 1.38 (s, 3H), 1.37 (s, 9H), 1.33 – 1.23 (m, 2H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  211.7, 166.2, 137.5, 133.7, 129.3, 129.2, 127.1, 126.6, 117.9, 115.4, 85.0, 76.6, 61.0, 39.6, 39.0, 31.3, 31.2, 27.7, 27.0, 27.0. UPLC-DAD-QTOF:  $\text{C}_{23}\text{H}_{32}\text{NO}_4$   $[\text{M}+\text{H}]^+$  calcd.: 386.2331, found: 386.2320.

The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralcel AD-3 hexane/isopropanol 95/5, flow rate= 0.5 mL/min, retention times: 19.4 min (major.) and 21.9 min (minor.)). Channel Descr.: PDA 207 nm.

**(2S,3S)-*tert*-Butyl 2-cyano-6-hydroxy-3-isobutyl-6-methyl-5-oxo-2-phenylheptanoate (48a)**



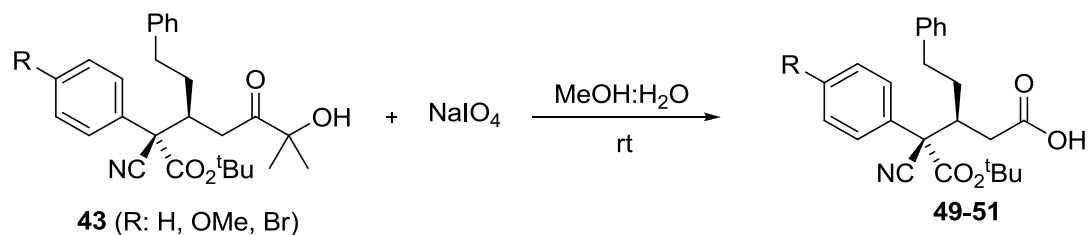
The title compound was prepared from *tert*-butyl 2-cyano-2-phenylacetate **19a** (22 mg, 0.1 mmol) and (*E*)-2-hydroxy-2,7-dimethyloct-4-en-3-one **4F** (51 mg, 0.3 mmol) according to the general procedure. Diastereomeric ratio as determined in the crude material 95:5. Yield of pure major diastereomer after column chromatography purification (colourless oil): 82% (32 mg).  $[\alpha]_D^{23} = +32.6^\circ$  ( $c=1.2$ , 83% *ee*,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.57 (m, 2H), 7.46 – 7.35 (m, 3H), 3.62 (s, 1H), 3.41 (m, 1H), 2.81 – 2.74 (m, 2H), 1.41 (s, 3H), 1.37 (s, 3H), 1.36 (s, 9H), 1.23 – 1.18 (m, 1H), 1.10 (m, 1H), 0.96 (m, 1H), 0.74 (t,  $J = 6.7$  Hz, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  211.7, 166.4, 134.0, 129.2, 129.1, 126.7, 84.9, 76.5, 61.5, 41.8, 40.3, 37.4, 27.7, 27.0, 27.0, 25.4, 24.0, 21.4. UPLC-DAD-QTOF:  $\text{C}_{23}\text{H}_{34}\text{NO}_4$   $[\text{M}+\text{H}]^+$  calcd.: 388.2488, found: 388.2491.

The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Phenomenex Lux 3 $\mu$  Cellulose-2 hexane/isopropanol 98/2, flow rate= 1 mL/min, retention times: 10.3 min (minor.) and 12.7 min (major.)). Channel Descr.: PDA 207 nm.

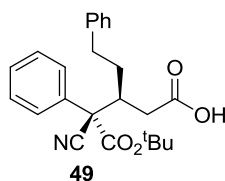
## 2.10. Elaboration of adducts 43-48

### a) To afford carboxylic acids 49-51



A suspension of sodium periodate  $\text{NaIO}_4$  (342 mg, 1.6 mmol) in water (0.8 mL) was added to a solution of the corresponding  $\alpha$ -hydroxy ketone adduct **43** (0.2 mmol) in methanol (1 mL). The mixture was stirred at room temperature until the reaction was complete (monitored by TLC, 48 h). Then the solvent was removed under reduced pressure. Water (4.5 mL) was added to the residue and the resulting mixture was extracted with  $\text{Et}_2\text{O}$  (3 x 6 mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and the solvent was evaporated to afford the corresponding carboxylic acid **49-51**.

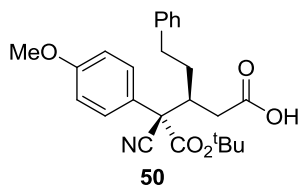
#### (3*S*,4*S*)-5-(*tert*-Butoxy)-4-cyano-5-oxo-3-phenethyl-4-phenylpentanoic acid (**49**)



The title compound was prepared from (2*S*,3*S*)-*tert*-Butyl 2-cyano-6-hydroxy-6-methyl-5-oxo-3-phenethyl-2-phenylheptanoate **43a** (87 mg, 0.2 mmol) following the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a white foam.

Yield: 57 mg, 0.14 mmol, 72%.  $[\alpha]_{\text{D}}^{23} = +24.1^\circ$  ( $c=0.4$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.53 (m, 2H), 7.44 – 7.31 (m, 3H), 7.16 (m, 3H), 6.99 – 6.86 (m, 2H), 3.17 (dq,  $J = 10.1, 5.6$  Hz, 1H), 2.75 – 2.69 (m, 2H), 2.61 (ddd,  $J = 13.8, 10.3, 5.6$  Hz, 1H), 2.31 (ddd,  $J = 13.7, 10.1, 7.0$  Hz, 1H), 1.67 – 1.51 (m, 2H), 1.40 (s, 9H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  178.1, 166.1, 141.1, 133.5, 129.3, 129.2, 128.5, 128.5, 126.6, 126.2, 117.5, 85.1, 60.7, 41.0, 37.9, 33.5, 33.4, 27.7 UPLC-DAD-QTOF:  $\text{C}_{24}\text{H}_{28}\text{NO}_4$   $[\text{M}+\text{H}]^+$  calcd.: 394.2018, found: 394.2022.

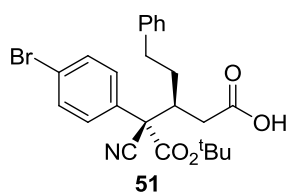
#### (3*S*,4*S*)-5-(*tert*-Butoxy)-4-cyano-4-(4-methoxyphenyl)-5-oxo-3-phenethylpentanoic acid (**50**)



The title compound was prepared from ((2*S*,3*S*)-*tert*-Butyl 2-cyano-6-hydroxy-2-(4-methoxyphenyl)-6-methyl-5-oxo-3-phenethylheptanoate **43c** (93 mg, 0.2 mmol) following the general procedure. The reaction mixture was stirred for 48 h until completion of reaction. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a white foam.

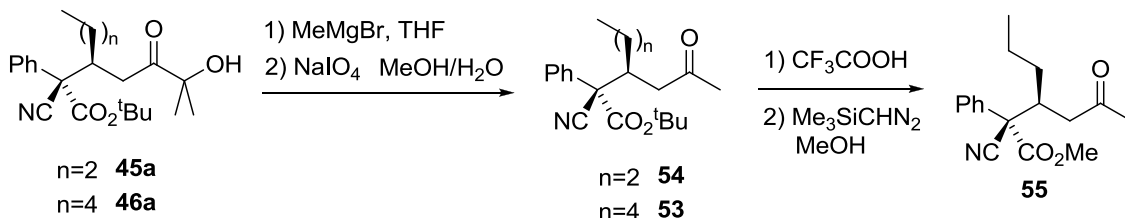
Yield: 68 mg, 0.16 mmol, 80%.  $[\alpha]_{\text{D}}^{24} = +26.8^\circ$  ( $c=1.05$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.45 – 7.38 (m, 2H), 7.17 (m, 3H), 6.98 – 6.83 (m, 4H), 3.82 (s, 3H), 3.15 – 3.04 (m, 1H), 2.71 – 2.65 (m, 2H), 2.64 – 2.54 (m, 1H), 2.32 (ddd,  $J = 13.7, 9.5, 7.5$  Hz, 1H), 1.64 – 1.53 (m, 2H), 1.39 (s, 9H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  177.2, 166.1, 159.9, 141.0, 128.3, 127.7, 125.9, 125.1, 117.4, 114.4, 84.8, 59.8, 55.3, 40.8, 37.5, 33.2, 27.5. UPLC-DAD-QTOF:  $\text{C}_{25}\text{H}_{30}\text{NO}_5$   $[\text{M}+\text{H}]^+$  calcd.: 424.2124, found: 424.2122.

**(3S,4S)-4-(4-Bromophenyl)-5-(tert-butoxy)-4-cyano-5-oxo-3-phenethylpentanoic acid (51)**



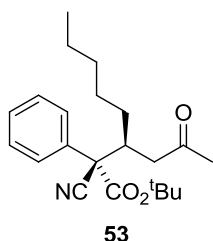
The title compound was prepared from (2*R*,3*S*)-*tert*-butyl 2-(4-bromophenyl)-6-hydroxy-2-isocyano-6-methyl-5-oxo-3-phenethylheptanoate **43d** (103 mg, 0.2 mmol) following the general procedure. The reaction mixture was stirred for 48 h until completion of reaction. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a white foam. Yield: 66 mg, 0.14 mmol, 70%.  $[\alpha]_D^{24} = +30.1^\circ$  ( $c=0.6$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.49 (m, 2H), 7.37 (m, 2H), 7.26 – 7.12 (m, 3H), 7.00 – 6.90 (m, 2H), 3.12 (dq,  $J = 9.1, 6.1, 5.7$  Hz, 1H), 2.76 – 2.67 (m, 2H), 2.68 – 2.56 (m, 1H), 2.36 (ddd,  $J = 13.7, 9.7, 7.2$  Hz, 1H), 1.65 (dq,  $J = 13.4, 4.1$  Hz, 1H), 1.56 – 1.46 (m, 1H), 1.40 (s, 9H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  177.9, 165.7, 140.8, 132.6, 132.4, 128.6, 128.5, 128.3, 126.3, 123.5, 117.0, 85.5, 60.3, 40.9, 37.7, 33.4, 33.2, 27.6. UPLC-DAD-QTOF:  $\text{C}_{24}\text{H}_{27}\text{NO}_4\text{Br}$   $[\text{M}+\text{H}]^+$  calcd.: 472.1123, found: 472.1126.

**b) To afford ketones 53-55**



$\text{MeMgBr}$  (3.2 M in  $\text{MeTHF}$ , 0.47 mL, 1.5 mmol) was added to a solution of the corresponding  $\alpha$ -hydroxy ketone **45a/46a** (0.3 mmol) in dry THF (1.5 mL) at  $0^\circ\text{C}$  and the resulting solution was stirred at room temperature until the reaction was finished (monitored by TLC). Then  $\text{NH}_4\text{Cl}$  (saturated solution, 3 mL) was added at  $0^\circ\text{C}$  and the resulting mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 5 mL). The solvents were removed under reduced pressure and the residue thus obtained was subjected to oxidative scission by treatment with  $\text{NaIO}_4$ , under the same conditions reported above. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 25/1 to 10/1) to afford pure ketones **53/54**.

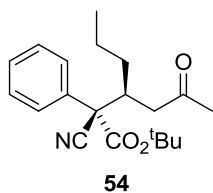
**(2S,3S)-*tert*-Butyl 2-cyano-3-(2-oxopropyl)-2-phenyloctanoate (53)**



358.2380.

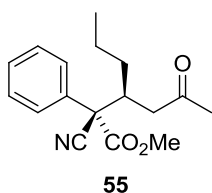
The title compound was prepared from **46a** (0.12 g, 0.3 mmol) following the general procedure to give an oil. Yield: 80.4 mg (75%).  $[\alpha]_D^{25} = +32.9^\circ$  ( $c=1.5$ , 94% *ee*,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.61 – 7.58 (m, 2H), 7.44 – 7.36 (m, 3H), 3.26 – 3.20 (m, 1H), 2.71 (dd,  $J=7.2$  Hz,  $J=17.8$  Hz, 1H), 2.63 (dd,  $J=3.0$  Hz,  $J=17.8$  Hz, 1H), 2.22 (s, 3H), 1.39 (s, 9H), 1.19 – 0.95 (m, 8H), 0.77 (t,  $J=6.9$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  205.4, 166.2, 133.8, 129.0, 128.8, 126.5, 117.8, 84.5, 61.0, 47.0, 39.5, 31.7, 31.5, 30.2, 27.5, 26.6, 22.3, 13.8. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{22}\text{H}_{32}\text{NO}_3$  ( $\text{M}+\text{H}^+$ ): 358.2382; found,

**(2*S*,3*S*)-tert-Butyl 2-cyano-5-oxo-2-phenyl-3-propylhexanoate (**54**)**



The title compound was prepared from **45a** (159 mg, 0.43 mmol, 1 equiv.) following the general procedure to give an oil. Yield: 90 mg, 0.27 mmol, 64%.  $[\alpha]_D^{23} = +35.4^\circ$  ( $c=0.85$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.70 – 7.47 (m, 2H), 7.37 (m, 3H), 3.33 – 3.12 (m, 1H), 2.68 (dd,  $J = 17.8, 7.0$  Hz, 1H), 2.58 (dd,  $J = 17.8, 3.2$  Hz, 1H), 2.17 (s, 3H), 1.35 (s, 9H), 1.12 (m, 3H), 1.00 – 0.87 (m, 1H), 0.68 (t,  $J = 6.6$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  205.5, 166.3, 133.9, 129.1, 128.9, 126.6, 117.9, 84.6, 61.2, 47.1, 39.4, 33.9, 30.3, 27.6, 20.3, 14.2. UPLC-DAD-QTOF:  $\text{C}_{20}\text{H}_{28}\text{NO}_3$   $[\text{M}+\text{H}]^+$  calcd.: 330.2069, found: 330.2072.

**Determination of the stereochemistry. Conversion of tert-butyl ester **54** into methyl ester **55****



A solution of *t*-Butyl ester **54** (70 mg, 0.21 mmol) in trifluoroacetic acid (1.0 mL) was stirred for 1h at room temperature. After evaporating all volatile compounds carboxylic acid was obtained and the residue was dissolved in MeOH (1 mL). Trimethylsilyldiazomethane (2M in diethyl ether, 0.8 mL) was added and the reaction mixture was stirred for 30 min at room temperature. Then all volatile compounds were evaporated and the crude material was purified by flash column chromatography (eluting with hexane/ethyl acetate 95:5) to afford the desired methyl ester. Yield: 43 mg, 0.15 mmol, 71%.  $[\alpha]_D^{23} = +45.0^\circ$  ( $c=0.85$ ,  $\text{CHCl}_3$ ) [Literature data for the opposite enantiomer (2*S*,3*R*):  $[\alpha]_D^{25} = -53^\circ$  ( $c=0.85$ ,  $\text{CHCl}_3$ ).<sup>37</sup> Spectroscopic data were essentially identical to those reported:<sup>37</sup>  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.60 (m, 2H), 7.41 (qd,  $J = 6.3, 5.8, 2.4$  Hz, 3H), 3.73 (s, 3H), 3.32 – 3.22 (m, 1H), 2.70 (dd,  $J = 17.8, 6.8$  Hz, 1H), 2.61 (dd,  $J = 17.7, 3.9$  Hz, 1H), 2.19 (s, 3H), 1.15 (m, 3H), 1.03 – 0.96 (m, 1H), 0.71 (t,  $J = 6.6$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  205.5, 168.2, 133.4, 129.4, 129.3, 126.9, 117.6, 60.1, 54.1, 47.0, 40.0, 33.7, 30.3, 20.4, 14.2. UPLC-DAD-QTOF:  $\text{C}_{17}\text{H}_{22}\text{NO}_3$   $[\text{M}+\text{H}]^+$  calcd.: 288.1600, found: 288.1605.

## 2.11. Addition of oxazol-4(5*H*)-ones **26** to $\beta$ -substituted $\alpha$ -hydroxy enones **4**

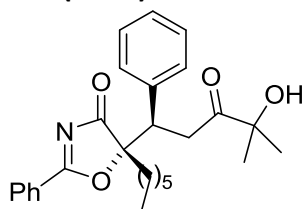
### General procedure (asymmetric version)

To a mixture of the corresponding oxazolone **26** (1 eq., 0.15 mmol) and the corresponding enone **4** (3.0 eq., 0.45 mmol), in 1,2-dichloroethane (0.45 mL) at 70 °C, catalyst **C2** (9.5 mg, 10 mol%) was added. The resulting mixture was stirred at the same temperature until consumption of the starting oxazolone as monitored by  $^1\text{H}$ -NMR. The crude product was purified by flash column chromatography (eluent: hexane/ ethyl acetate 80/20).

### General procedure (racemic version)

The same above procedure was followed except that reactions were run at 50 °C and DBU was used as the catalyst instead of **C2**.

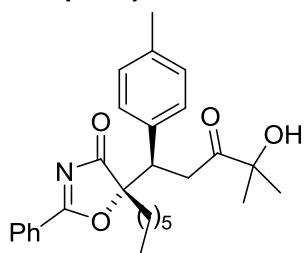
### (*S*)-5-Hexyl-5-((*R*)-4-hydroxy-4-methyl-3-oxo-1-phenylpentyl)-2-phenyloxazol-4(5*H*)-one (**56Hc**)



The title compound **56Hc** was prepared from 5-hexyl-2-phenyloxazol-4(5*H*)-one (**26c**) (37 mg, 0.15 mmol) and (*E*)-4-hydroxy-4-methyl-1-phenylpent-1-en-3-one (**4H**) (79 mg, 0.45 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound essentially as a sole diastereomer. Yellow oil. Yield: 53 mg, 0.123 mmol, 83%.  $[\alpha]_{\text{D}}^{25} = -49.9$  ( $c = 1.00$ , 96% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 8.22 – 8.10 (m, 2H), 7.74 – 7.65 (m, 1H), 7.58 – 7.48 (m, 2H), 7.32 – 7.12 (m, 5H), 3.90 (dd,  $J = 10.7, 3.4$  Hz, 1H), 3.39 (s, 1H), 3.30 (dd,  $J = 17.5, 10.7$  Hz, 1H), 2.74 (dd,  $J = 17.5, 3.3$  Hz, 1H), 2.00 – 1.81 (m, 1H), 1.81 – 1.64 (m, 1H), 1.21 (s, 3H), 1.18 – 1.07 (m, 8H), 1.03 (s, 3H), 0.82 – 0.71 (m, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 210.9, 193.0, 185.8, 137.4, 135, 123.0, 129.0, 128.4, 127.7, 125.3, 93.0, 76.3, 46.2, 36.0, 35.2, 31.3, 28.9, 26.0, 22.7, 22.3, 13.8. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{27}\text{H}_{34}\text{NO}_4$  ( $\text{M}+\text{H}^+$ ), 436.2488; found, 436.2475.

### (*S*)-5-Hexyl-5-((*R*)-4-hydroxy-4-methyl-3-oxo-1-(*p*-tolyl)pentyl)-2-phenyloxazol-4(5*H*)-one (**56Lc**)

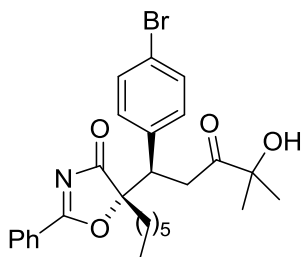


The title compound **56Lc** was prepared from 5-hexyl-2-phenyloxazol-4(5*H*)-one (**26c**) (37 mg, 0.15 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one (**4L**) (92 mg, 0.45 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a mixture of diastereomers in a 12:1 ratio. Yellow oil. Yield: 55 mg, 0.120 mmol, 80%.  $[\alpha]_{\text{D}}^{25} = -53.6$  ( $c = 1.00$ , 96% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 8.23 – 8.13 (m, 2H), 7.78 – 7.63 (m, 1H), 7.60 – 7.48 (m, 2H), 7.16 (d,  $J = 8.1$  Hz, 2H), 7.04 (d,  $J = 7.9$  Hz, 2H), 3.86 (dd,  $J = 10.8, 3.3$  Hz, 1H), 3.27 (dd,  $J = 17.4, 10.8$  Hz, 1H), 2.70 (dd,  $J = 17.4, 3.3$  Hz, 1H), 2.24 (s, 3H), 1.21 (s, 3H), 1.13 (m, 8H), 1.04 (s, 3H), 0.81 – 0.72 (m, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 210.9, 193.2, 185.8, 137.3, 135.3, 134.3, 130.0, 129.1, 129.0, 128.8, 125.3, 93.2, 76.3, 45.8, 36.1, 35.2, 31.3, 28.9, 26.0, 22.7, 22.3, 21.0, 13.8. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{28}\text{H}_{36}\text{NO}_4$  ( $\text{M}+\text{H}^+$ ), 450.2644; found, 450.2626.



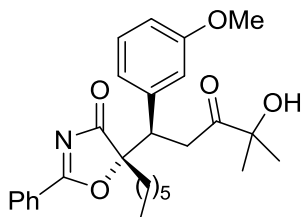
**(S)-5-((R)-1-(4-Bromophenyl)-4-hydroxy-4-methyl-3-oxopentyl)-5-hexyl-2-phenyloxazol-4(5H)-one (56Jc)**



The title compound **56Jc** was prepared from 5-hexyl-2-phenyloxazol-4(5H)-one (**26c**) (37 mg, 0.15 mmol) and 4-bromo-4-((trimethylsilyl)oxy)pent-1-en-3-one (**4J**) (83.8 mg, 0.45 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a mixture of diastereomers in a 11:1 ratio. White solid. Yield: 60 mg, 0.117 mmol, 78%. m. p. 125-127 °C.  $[\alpha]_D^{25} = -57.3$  ( $c = 1.00$ , 96% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 8.10 (dd,  $J = 8.3, 1.3$  Hz, 2H), 7.68 – 7.59 (m, 1H), 7.46 (t,  $J = 7.7$  Hz, 2H), 7.32 (d,  $J = 8.3$  Hz, 1H), 7.16 (d,  $J = 8.4$  Hz, 2H), 3.82 (dd,  $J = 10.9, 3.1$  Hz, 1H), 3.69 (s, 1H), 3.30 (dd,  $J = 18.0, 10.9$  Hz, 1H), 2.76 (dd,  $J = 17.9, 3.1$  Hz, 1H), 1.88 – 1.85 (m, 1H), 1.70 – 1.57 (m, 1H), 1.10 – 1.00 (m, 14H), 0.75 – 0.65 (m, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 210.9, 192.6, 185.7, 136.6, 135.3, 131.2, 130.5, 129.8, 128.9, 124.8, 121.4, 92.6, 76.3, 45.3, 35.9, 34.9, 31.0, 28.6, 25.8, 25.8, 22.4, 22.1, 13.6. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{27}\text{H}_{33}\text{BrNO}_4$  ( $\text{M}+\text{H}^+$ ), 514.1593; found, 514.1594.

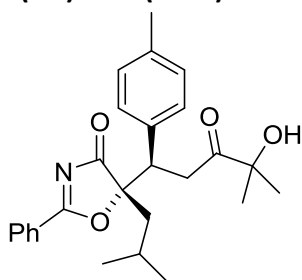
**(S)-5-Hexyl-5-((R)-4-hydroxy-1-(3-methoxyphenyl)-4-methyl-3-oxopentyl)-2-phenyloxazol-4(5H)-one (56Kc)**



The title compound **56Kc** was prepared from 5-hexyl-2-phenyloxazol-4(5H)-one (**26c**) (37 mg, 0.15 mmol) and 3-methoxy-4-((trimethylsilyl)oxy)pent-1-en-3-one (**4K**) (83.8 mg, 0.45 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a mixture of diastereomers in a 12:1 ratio. Yellow oil. Yield: 57 mg, 0.122 mmol, 81%.  $[\alpha]_D^{25} = -54.4$  ( $c = 1.00$ , 96% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 8.18 (dd,  $J = 8.4, 1.4$  Hz, 2H), 7.74 – 7.64 (m, 1H), 7.54 (dd,  $J = 8.4, 7.1$  Hz, 2H), 7.16 (t,  $J = 7.9$  Hz, 1H), 6.91 – 6.80 (m, 2H), 6.72 (ddd,  $J = 8.3, 2.6, 0.9$  Hz, 1H), 3.86 (dd,  $J = 10.6, 3.3$  Hz, 1H), 3.74 (s, 3H), 3.41 (s, 1H), 3.26 (dd,  $J = 17.5, 10.7$  Hz, 1H), 2.69 (dd,  $J = 17.4, 3.3$  Hz, 1H), 1.94 – 1.80 (m, 1H), 1.79 – 1.64 (m, 1H), 1.20 (s, 3H), 1.17 – 1.06 (m, 8H), 1.05 (s, 3H), 0.80 – 0.73 (m, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 210.8, 193.0, 185.99, 159.3, 139.0, 135.3, 130.0, 129.3, 129.0, 125.3, 121.2, 115.2, 112.7, 93.0, 76.3, 55.10, 46.2, 36.0, 35.1, 31.3, 28.9, 26.0, 22.7, 22.3, 13.8. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{28}\text{H}_{36}\text{NO}_5$  ( $\text{M}+\text{H}^+$ ), 466.2593; found, 466.2577.

**(S)-5-((R)-4-hydroxy-4-methyl-3-oxo-1-(p-tolyl)pentyl)-5-isobutyl-2-phenyloxazol-4(5H)-one (56La)**

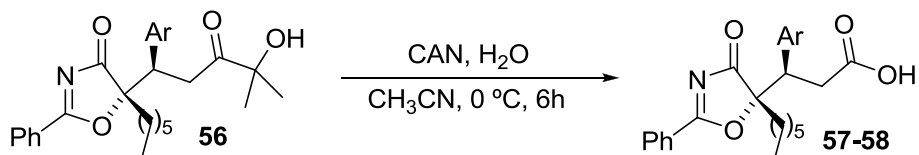


The title compound **56La** was prepared from 5-isobutyl-2-phenyloxazol-4(5H)-one (**26a**) (62.6 mg, 0.15 mmol) and (E)-4-hydroxy-4-methyl-1-(p-tolyl)pent-1-en-3-one (**4L**) (92 mg, 0.45 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a mixture of diastereomers in a 12:1 ratio. Yield: 43 mg (foam), 0.101 mmol, 67%.  $[\alpha]_D^{25} = -45.4$  ( $c = 1.00$ , 99% ee,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 8.18 – 8.08 (m, 2H), 7.74 – 7.62 (m, 1H), 7.52 (dd,  $J = 8.3, 7.2$  Hz, 2H), 7.17 – 7.08 (m, 2H), 7.05 – 6.95 (m, 2H), 3.85 (dd,  $J = 10.8, 3.3$  Hz, 1H), 3.45 – 3.24 (m, 2H), 2.72 (dd,  $J = 17.5, 3.3$  Hz, 1H), 2.21 (s, 3H), 1.80 (dd,  $J = 6.2, 4.2$  Hz, 2H), 1.64 – 1.52 (m, 1H),

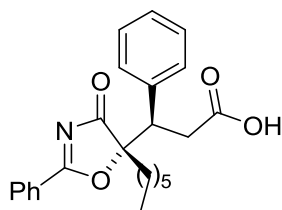
1.23 (s, 3H), 1.04 (s, 3H), 0.86 (d,  $J = 6.6$  Hz, 3H), 0.77 (d,  $J = 6.6$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 211.1, 193.4, 185.7, 137.2, 135.2, 134.0, 129.9, 129.0, 128.8, 125.4, 92.8, 76.3, 46.3, 43.6, 35.8, 26.0, 24.1, 23.8, 20.9. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{26}\text{H}_{32}\text{NO}_4$  ( $\text{M}+\text{H}^+$ ), 422.2331; found, 422.2314.

## 2.12. Elaboration of adducts **56** into carboxylic acids **57-58**<sup>38</sup>



To a stirred solution of the  $\beta$ -arilketol (**56**) (0.4 mmol) in acetonitrile (5 mL) at 0 °C a solution of cerium ammonium nitrate (CAN) (3 eq., 0.73 g, 1.35 mmol) in water (2.5 mL) was added dropwise and the mixture was stirred at the same temperature until starting **56** disappeared (TLC hex/EtOAc 70/30). Water was then added (1.5 mL) and the mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 5 mL), after which the organic phases were combined, dried over  $\text{MgSO}_4$  and concentrated. The crude material was purified by flash chromatography on silica gel (Eluting with hexane:EtOAc 80:20) obtaining the desired product.

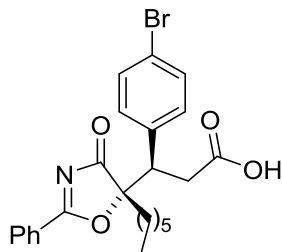
### (*R*)-3-((*S*)-5-Hexyl-4-oxo-2-phenyl-4,5-dihydrooxazol-5-yl)-3-phenylpropanoic acid (**57**)



The title compound **57** was prepared from adduct **56Gc** (152 mg, 0.35 mmol) according to the general procedure. Yield: 120 mg (foam), 0.30 mmol, 86 %.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.26 (bs, 1H), 8.21 – 8.13 (m, 2H), 7.69 (t,  $J = 7.5$  Hz, 1H), 7.52 (t,  $J = 7.7$  Hz, 2H), 7.30 – 7.18 (m, 5H), 3.68 (dd,  $J = 11.2$ , 3.8 Hz, 1H), 2.79 (dd,  $J = 16.1$ , 11.2 Hz, 1H), 2.61 (dd,  $J = 16.1$ , 3.8 Hz, 1H), 1.91 – 1.76 (m, 1H), 1.72 – 1.55 (m, 1H), 1.19 – 1.05 (m, 8H), 0.76 (t,  $J = 6.8$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 192.8, 185.8, 175.6, 136.7, 135.33, 129.92, 128.92, 128.34, 127.71, 125.05, 92.68, 46.97, 34.78, 34.56, 31.18, 28.75, 22.48, 22.20, 13.74. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{24}\text{H}_{28}\text{NO}_4$  ( $\text{M}+\text{H}^+$ ), 394.2018; found, 394.2003.

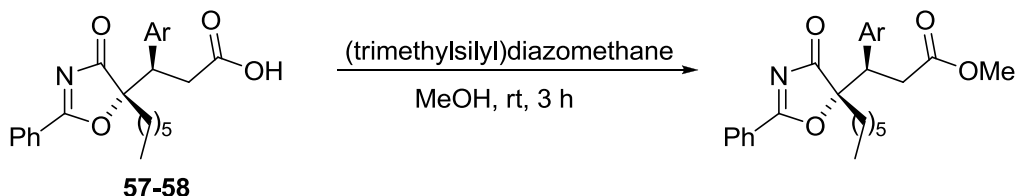
### (*R*)-3-(4-Bromophenyl)-3-((*S*)-5-hexyl-4-oxo-2-phenyl-4,5-dihydrooxazol-5-yl)propanoic acid (**58**)



The title compound **58** was prepared from adduct **56Ic** (411.6 mg, 0.3 mmol) according to the general procedure. Yield: 94 mg (foam), 0.20 mmol, 80 %.

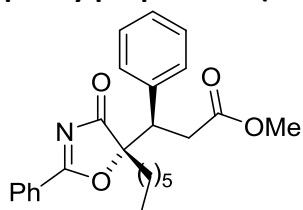
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.23 – 8.15 (m, 2H), 7.78 – 7.67 (m, 1H), 7.55 (t,  $J = 7.7$  Hz, 2H), 7.41 (d,  $J = 8.1$  Hz, 2H), 7.17 (d,  $J = 8.1$  Hz, 2H), 3.64 (dd,  $J = 11.2$ , 3.9 Hz, 1H), 2.75 (dd,  $J = 16.2$ , 11.2 Hz, 1H), 2.61 (dd,  $J = 16.2$ , 3.9 Hz, 1H), 1.81 (dt,  $J = 14.5$ , 6.7 Hz, 1H), 1.70 – 1.53 (m, 2H), 1.20 – 1.06 (m, 8H), 0.77 (t,  $J = 6.8$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 192.6, 185.9, 175.1, 136.0, 135.60, 131.7, 130.7, 130.0, 129.1, 125.0, 121.9, 92.4, 46.5, 34.9, 34.6, 31.3, 28.9, 22.6, 22.3, 13.9. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{24}\text{H}_{27}\text{BrNO}_4$  ( $\text{M}+\text{H}^+$ ), 472.1123; found, 472.1109.

## General procedure for the preparation of the esters



The corresponding acid (0.25 mmol) was dissolved in MeOH (7.5 mL) and a solution of (trimethylsilyl)diazomethane in diethyl ether (2M) (3.0 equiv., 0.38 mL, 0.75 mmol) was added dropwise, observing the coloration of the mixture. The reaction mixture was stirred for further 3 h and disappearance of the acid was checked by TLC (hexane/ EtOAc 1/1). The reaction mixture was concentrated and the crude material was purified by flash chromatography on silica gel (Eluting with hexane:EtOAc 90:10) obtaining the desired product.

### Methyl **(R)-3-((S)-5-hexyl-4-oxo-2-phenyl-4,5-dihydrooxazol-5-yl)-3-phenylpropanoate (57')**

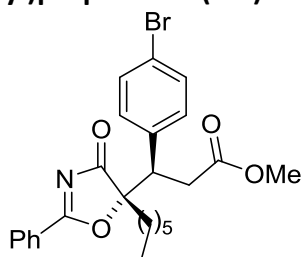


The title compound was prepared from the corresponding acid (**57**) (102 mg, 0.25 mmol) according to the general procedure. Yellow oil. Yield: 99 mg, 0.24 mmol, 97%.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 8.26 – 8.12 (m, 2H), 7.74 – 7.63 (m, 1H), 7.53 (dd,  $J$  = 8.4, 7.1 Hz, 2H), 7.34 – 7.17 (m, 5H), 3.72 (dd,  $J$  = 11.2, 4.1 Hz, 1H), 3.42 (s, 3H), 2.79 (dd,  $J$  = 15.6, 11.2 Hz, 1H), 2.62 (dd,  $J$  = 15.7, 4.1 Hz, 1H), 1.91 – 1.76 (m, 1H), 1.70 – 1.55 (m, 1H), 1.21 – 1.04 (m, 8H), 0.75 (t,  $J$  = 6.6 Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 192.9, 185.8, 170.8, 137.0, 135.2, 129.9, 128.9, 128.3, 127.7, 125.2, 92.6, 51.5, 47.4, 34.9, 34.7, 31.2, 28.8, 22.5, 22.2, 13.7. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{25}\text{H}_{30}\text{NO}_4$  ( $\text{M}+\text{H}^+$ ), 408.2175; found, 408.2155.

The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 80/20, flow rate = 1.0 mL/min, retention times: 18.6 min (min.) and 24.5 min (major.)).

### Methyl **(R)-3-(4-bromophenyl)-3-((S)-5-hexyl-4-oxo-2-phenyl-4,5-dihydrooxazol-5-yl)propanoate (58')**

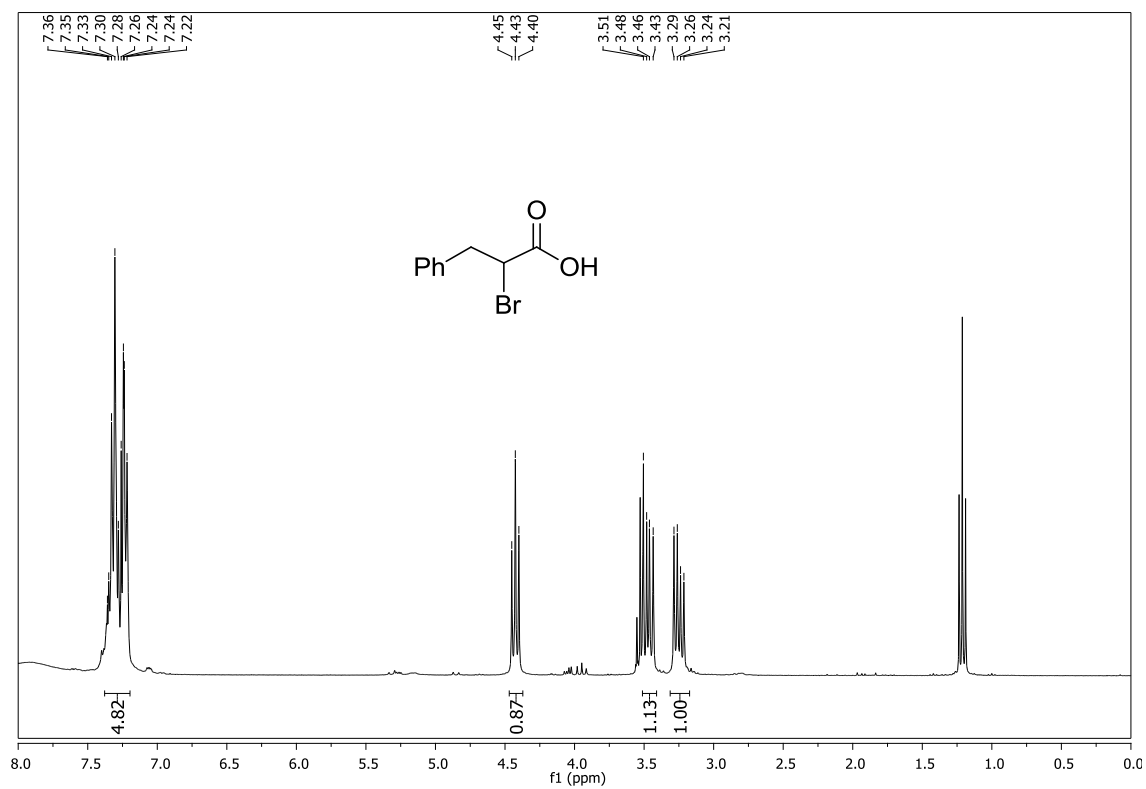


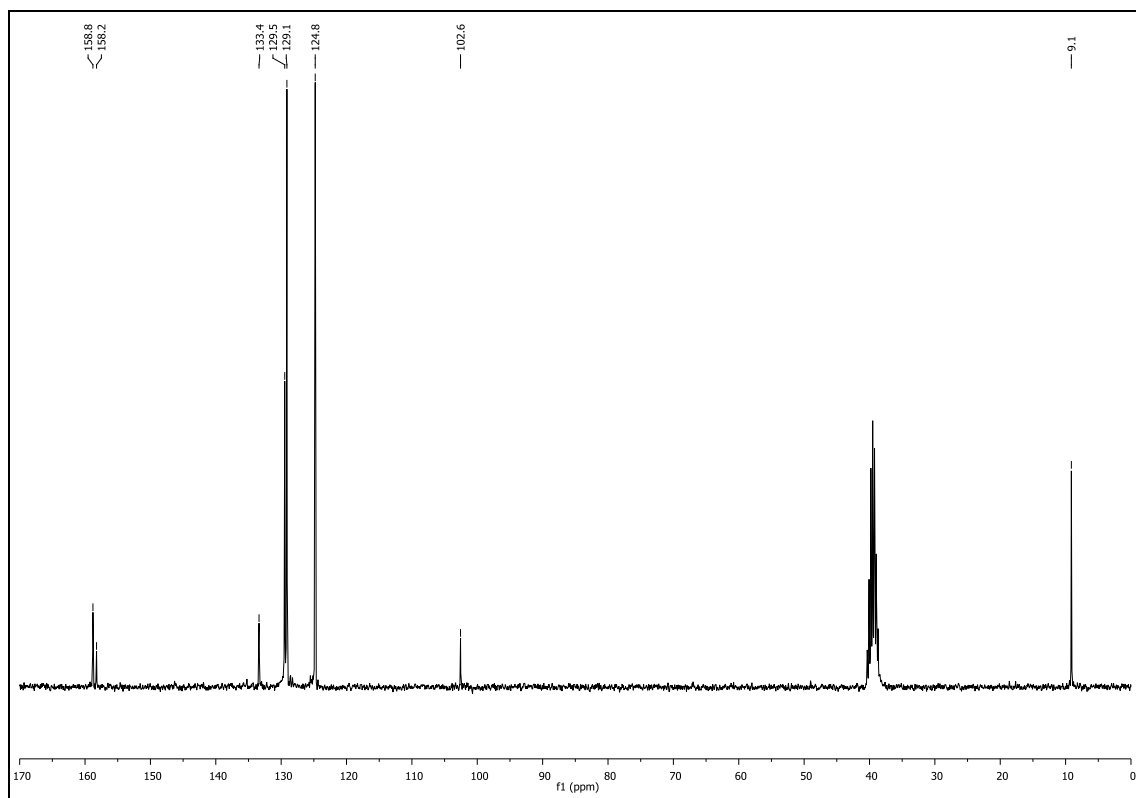
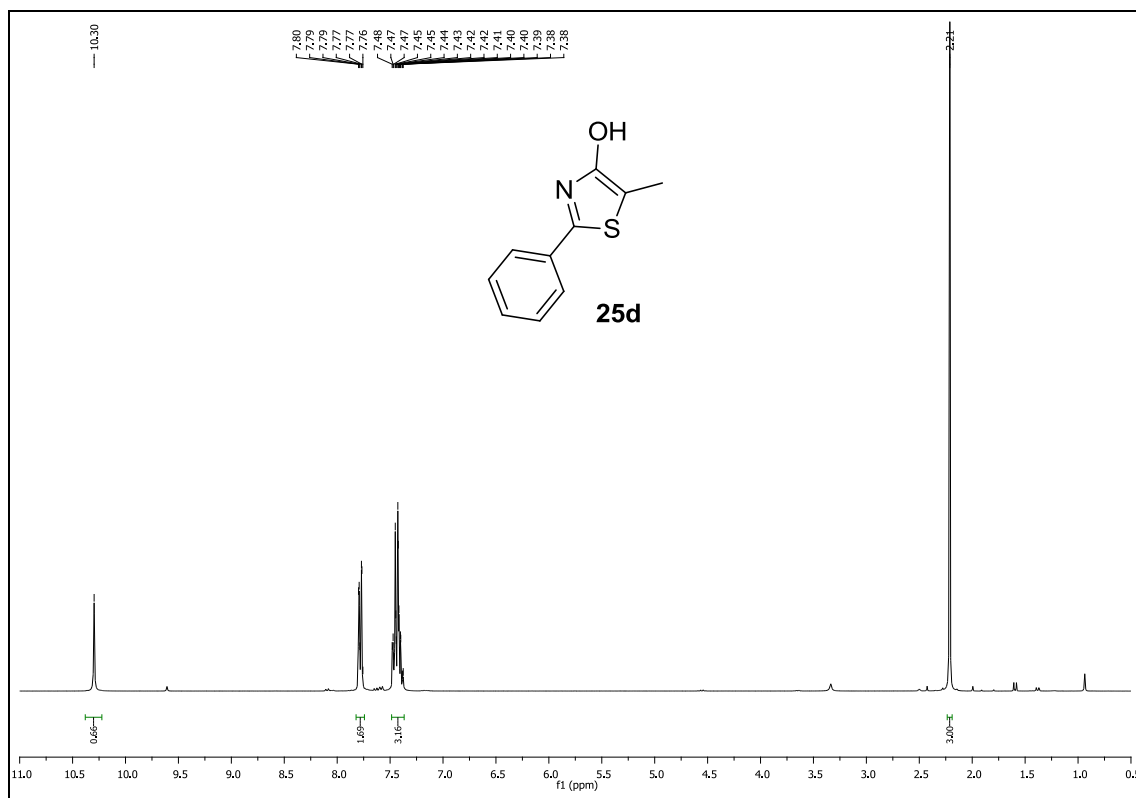
The title compound was prepared from the corresponding acid (**58**) (71 mg, 0.15 mmol) according to the general procedure. Yellow oil. Yield: 63 mg, 0.13 mmol, 87%.

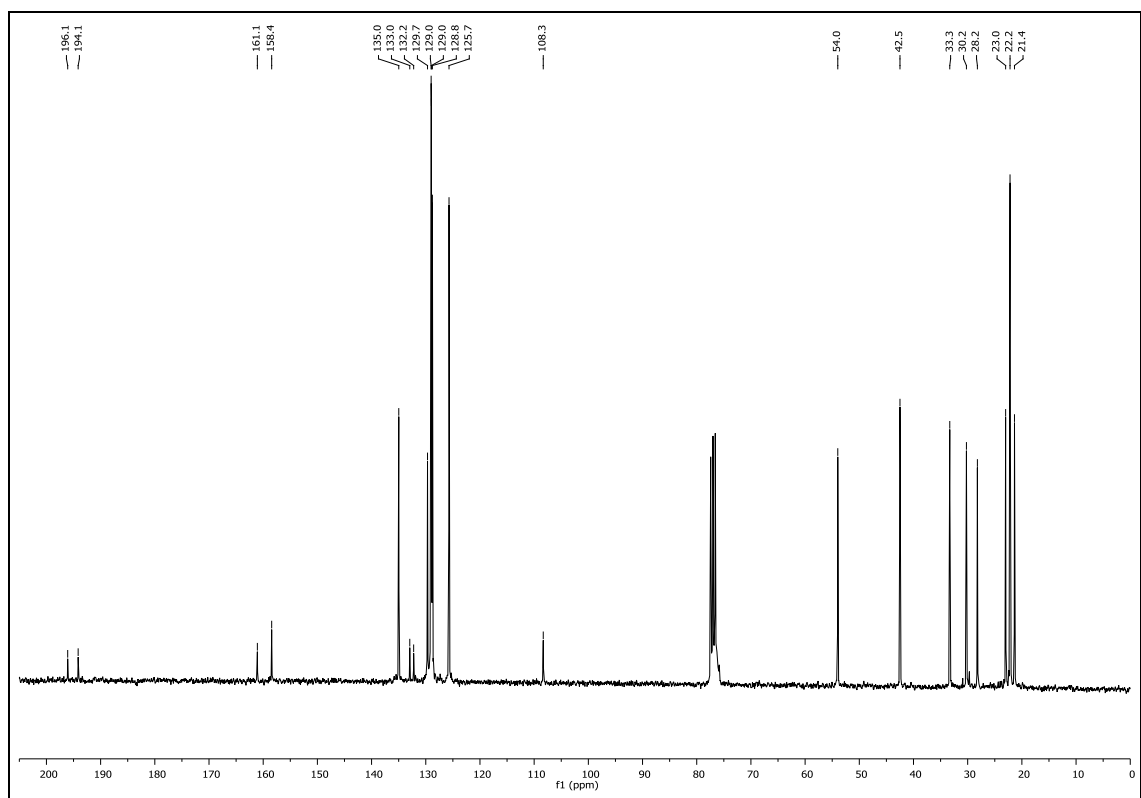
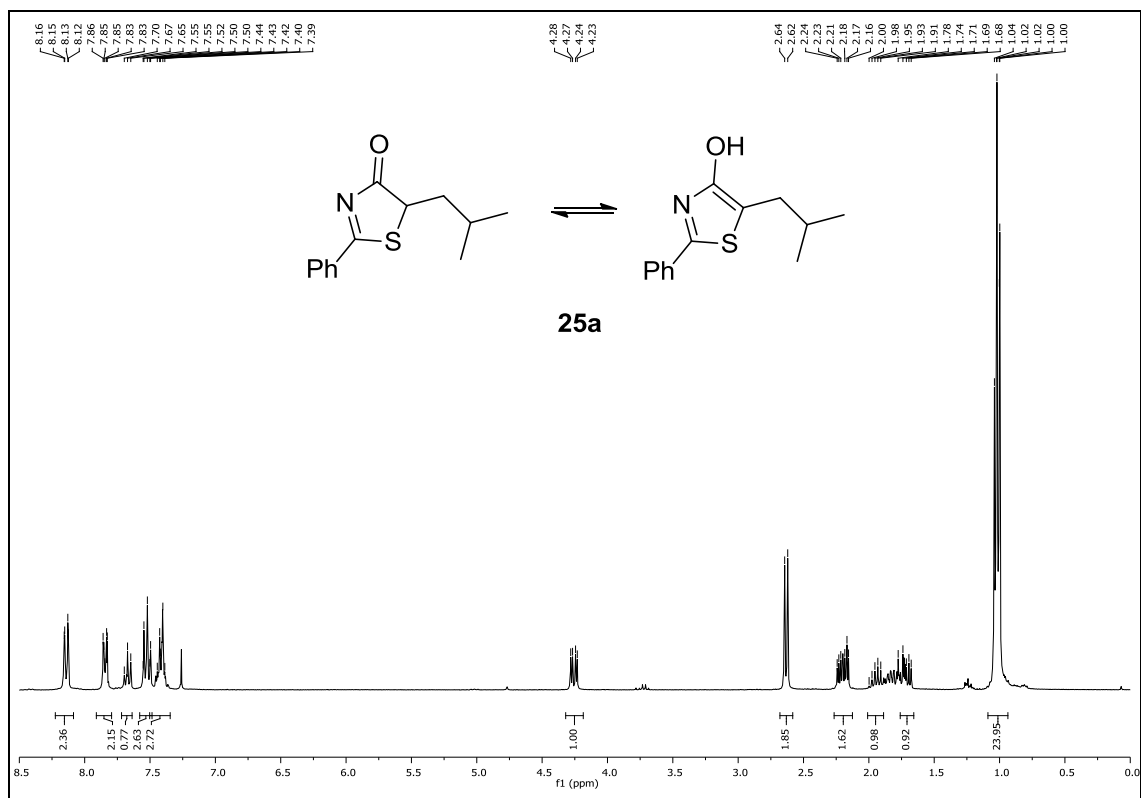
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 8.26 – 8.19 (m, 2H), 7.80 – 7.71 (m, 1H), 7.59 (dd,  $J$  = 8.4, 7.2 Hz, 2H), 7.47 (d,  $J$  = 8.4 Hz, 2H), 7.24 (d,  $J$  = 8.5 Hz, 2H), 3.73 (dd,  $J$  = 11.3, 4.0 Hz, 1H), 3.50 (s, 3H), 2.79 (dd,  $J$  = 15.8, 11.3 Hz, 1H), 2.65 (dd,  $J$  = 15.8, 4.1 Hz, 1H), 1.95 – 1.79 (m, 1H), 1.74 – 1.58 (m, 1H), 1.25 – 1.07 (m, 8H), 0.81 (t,  $J$  = 6.8 Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 192.6, 185.9, 170.7, 136.2, 135.5, 131.6, 130.7, 130.0, 129.1, 125.2, 121.8, 92.3, 51.8, 46.8, 35.0, 34.6, 31.3, 28.9, 22.6, 22.3, 13.8. MS (ESI,  $m/z$ ): calcd for  $\text{C}_{25}\text{H}_{29}\text{BrNO}_4$  ( $\text{M}+\text{H}^+$ ), 486.1280; found, 486.1258.

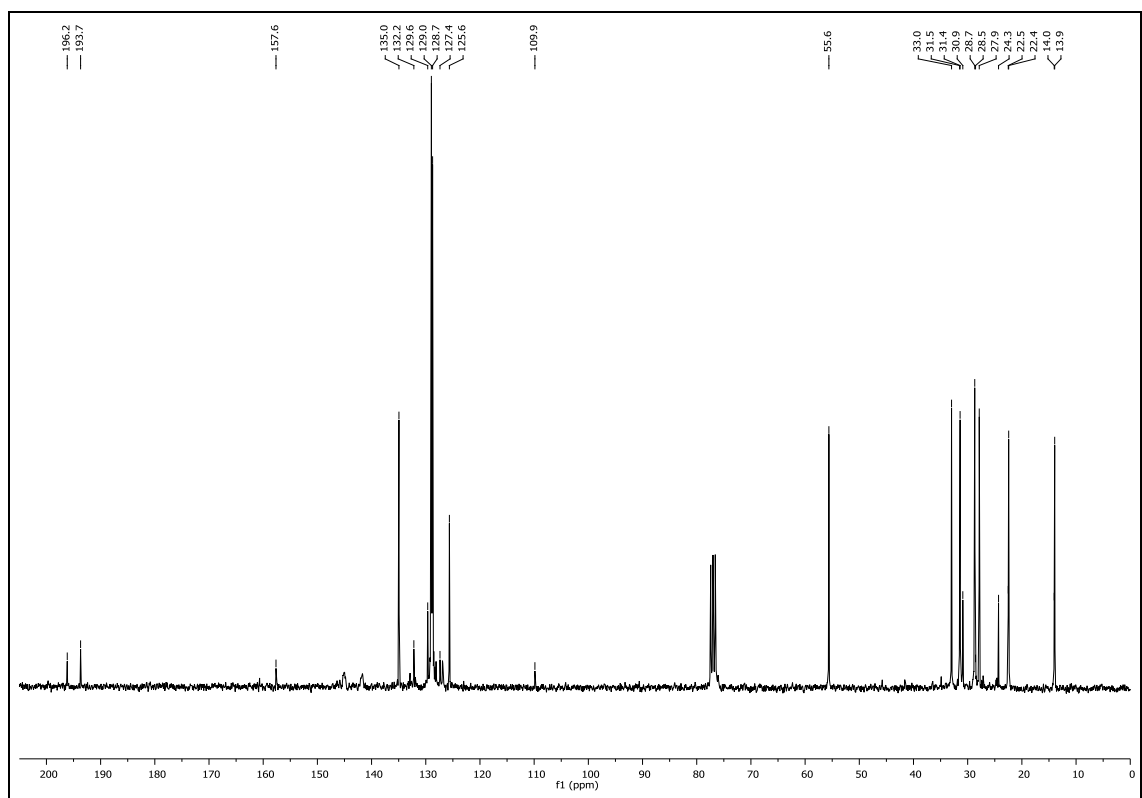
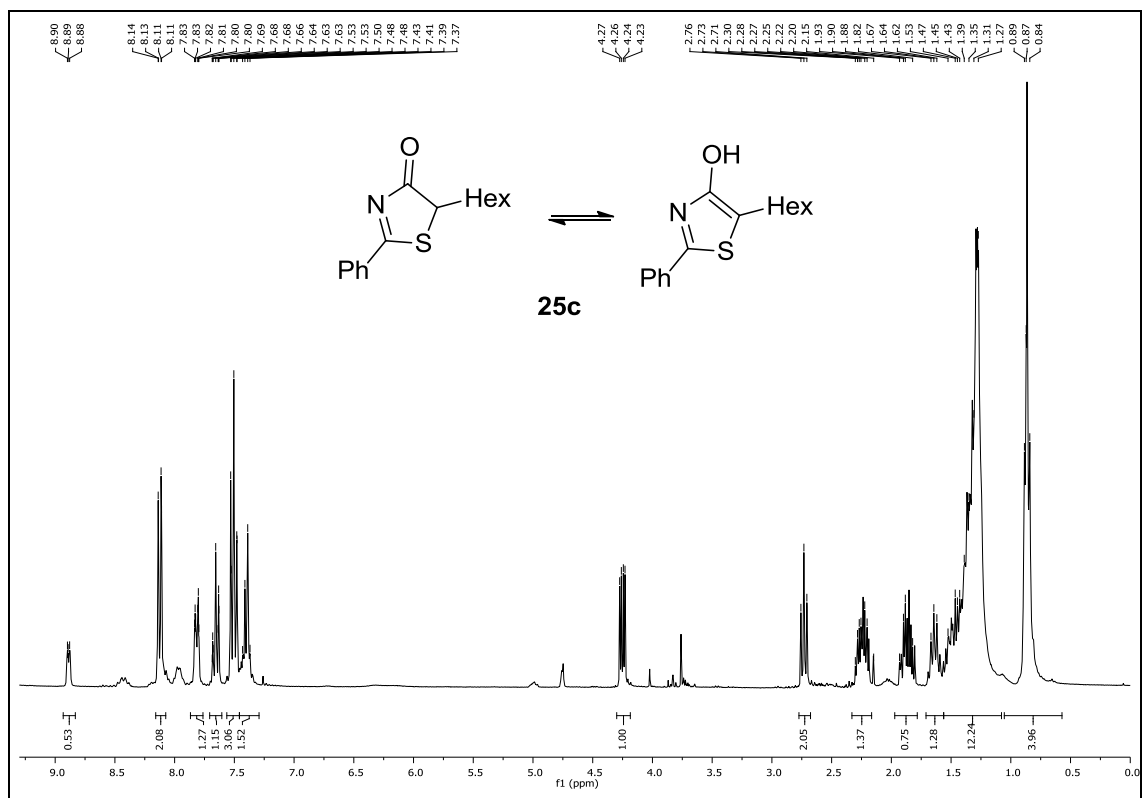
The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 80/20, flow rate = 1.0 mL/min, retention times: 14.2 min (min.) and 15.8 min (major.)).

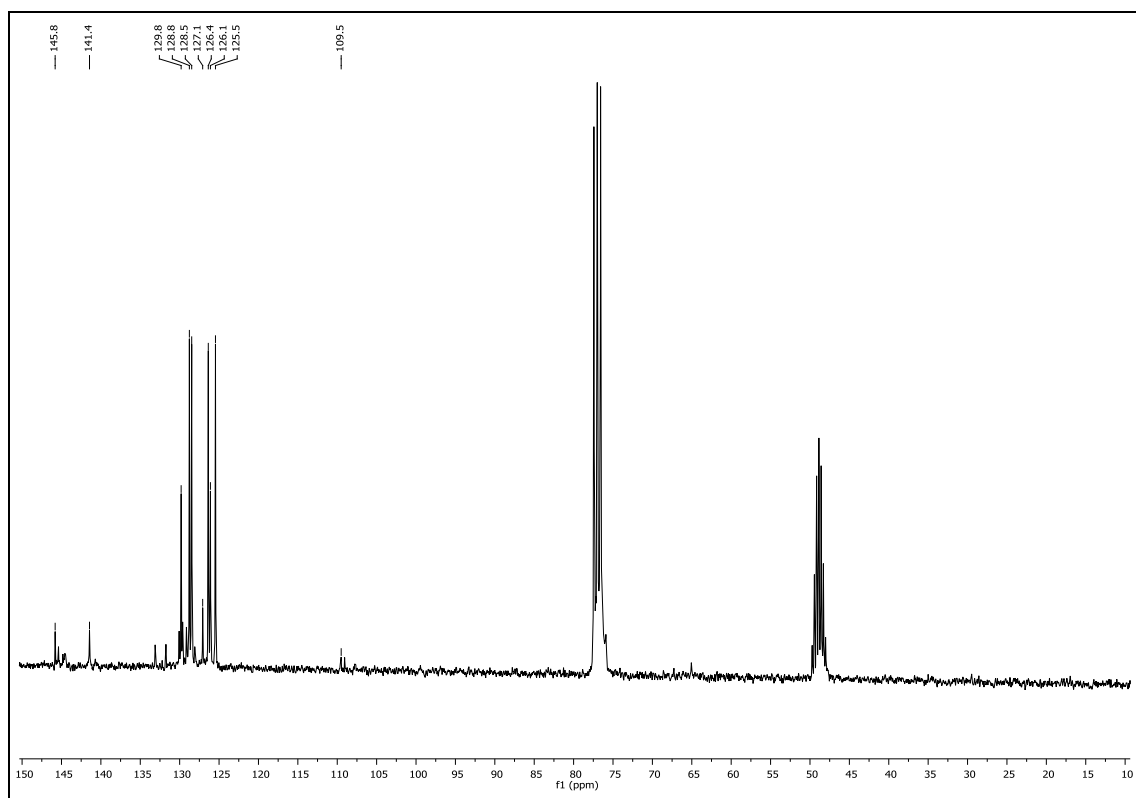
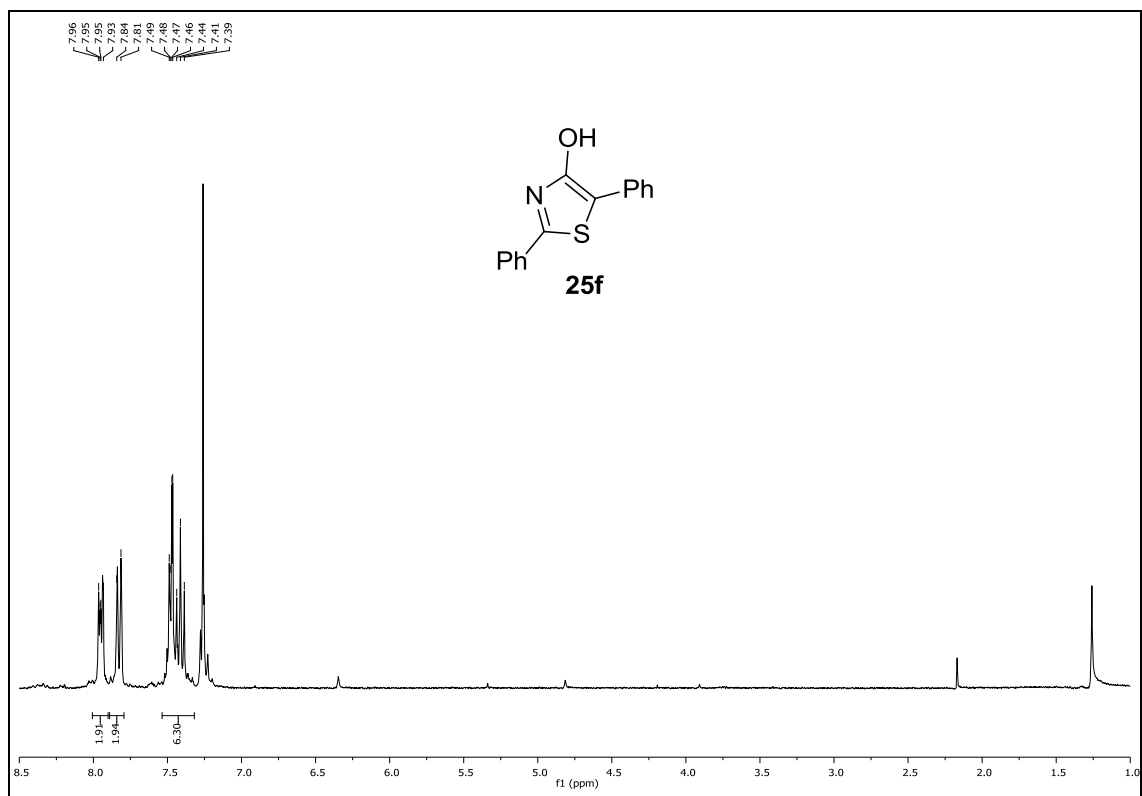
### 3. NMR spectra of representative compounds



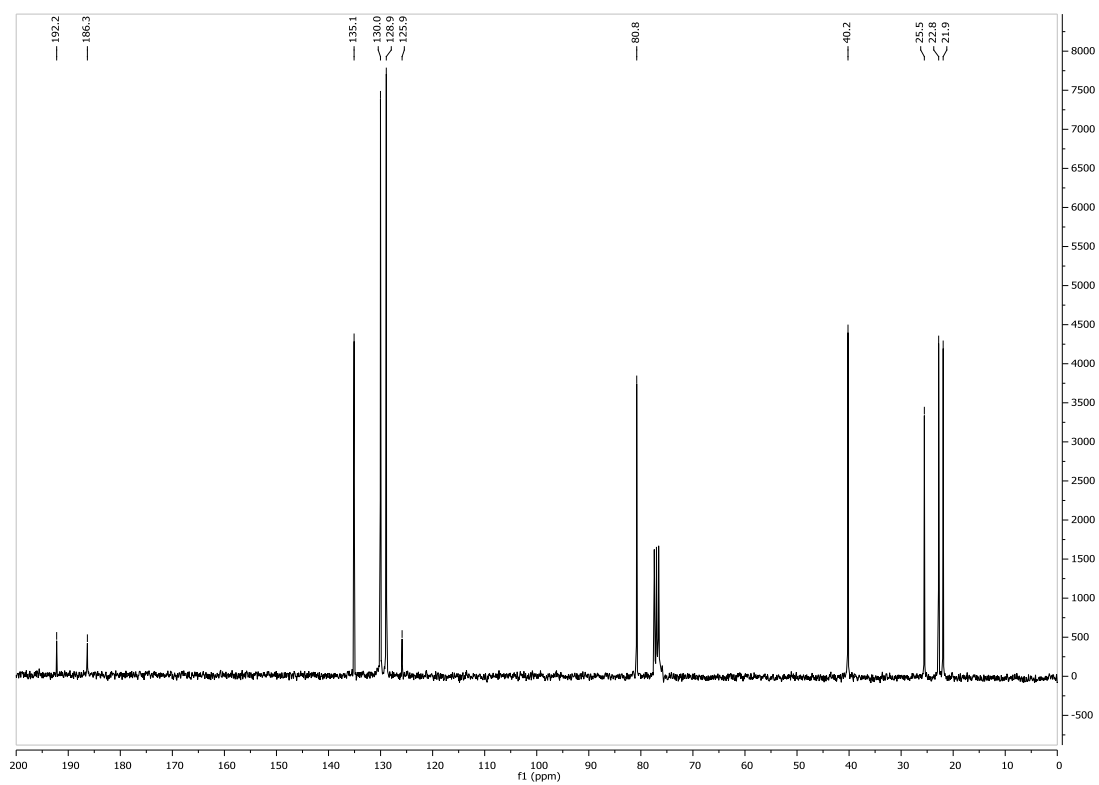
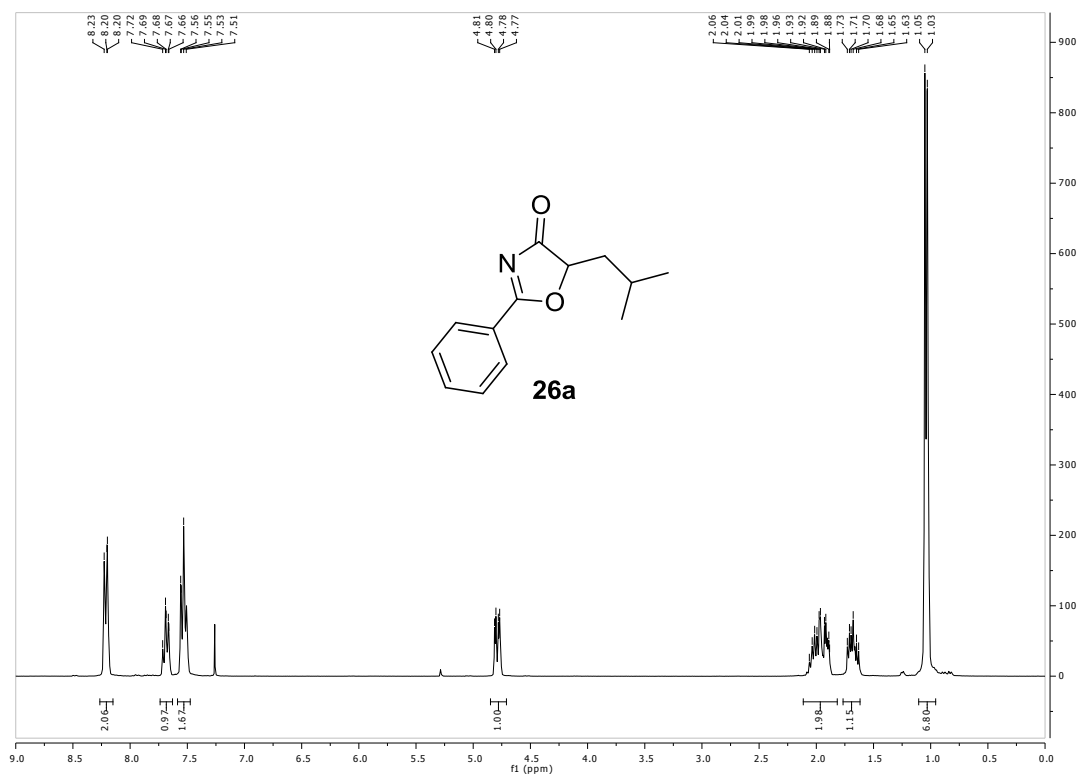


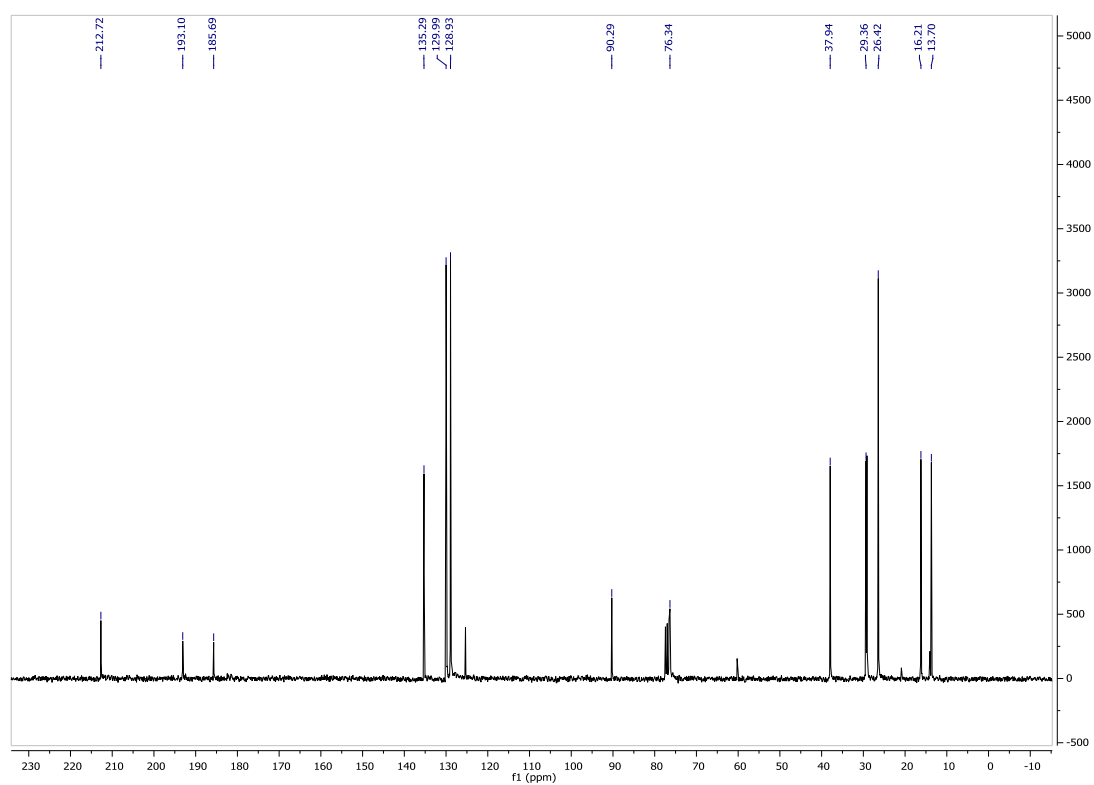
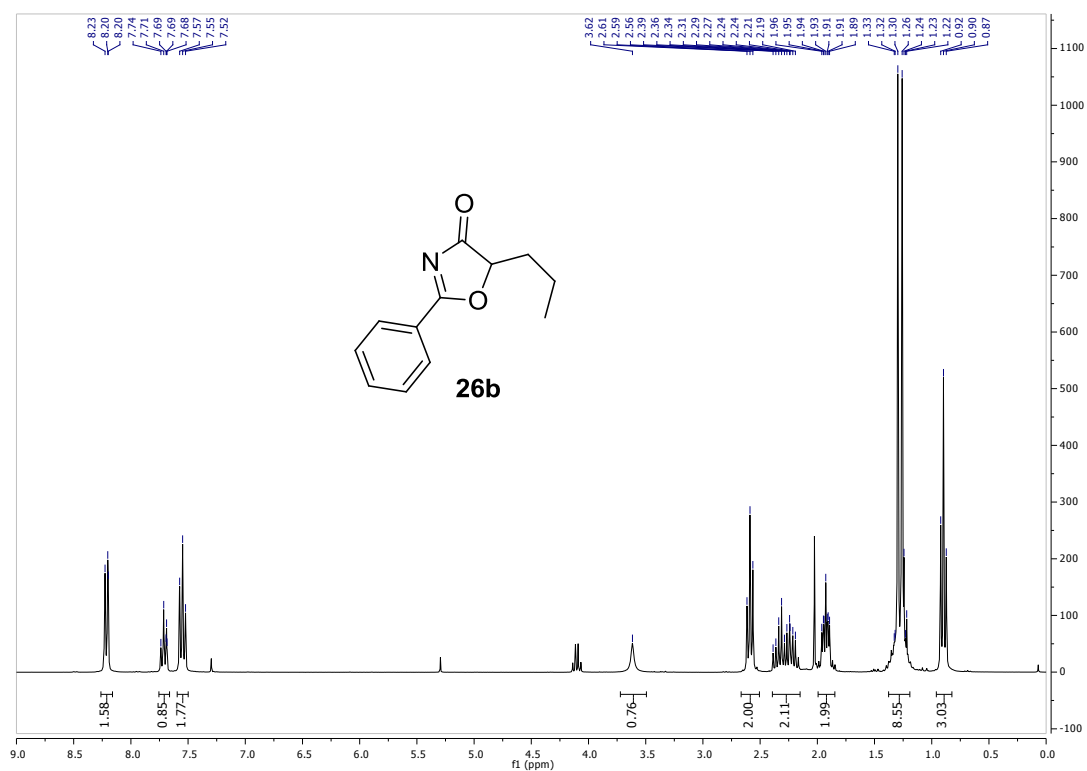


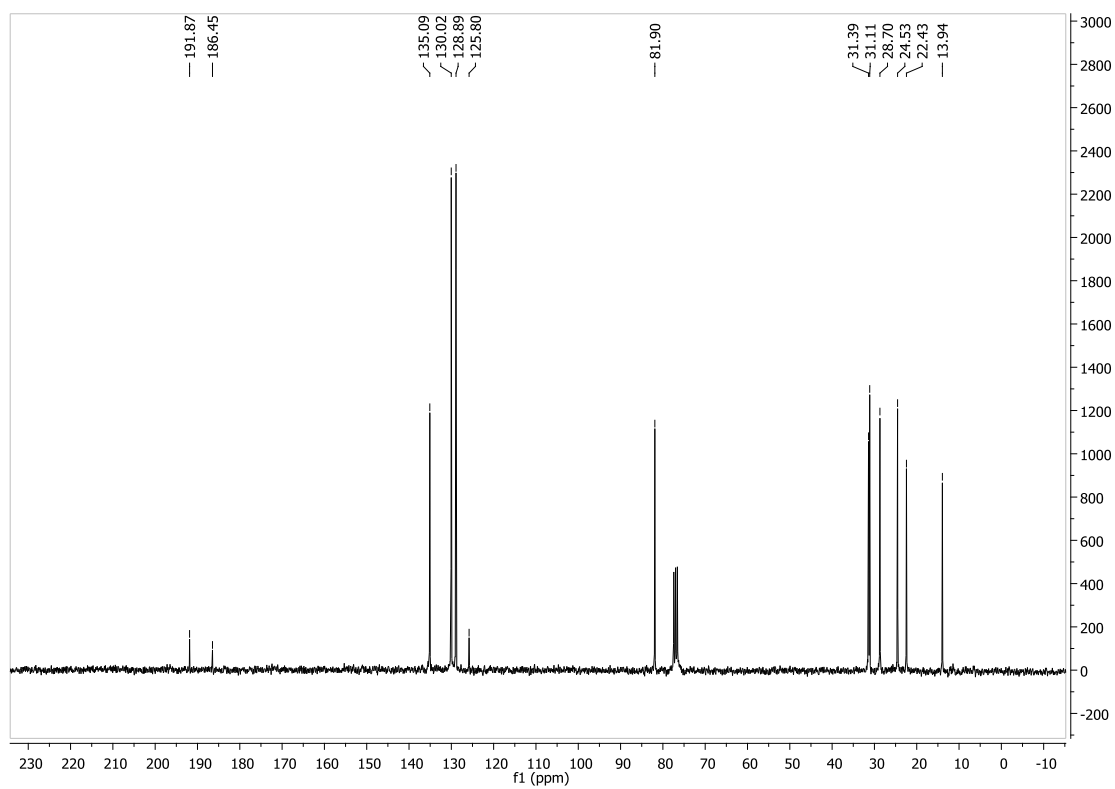
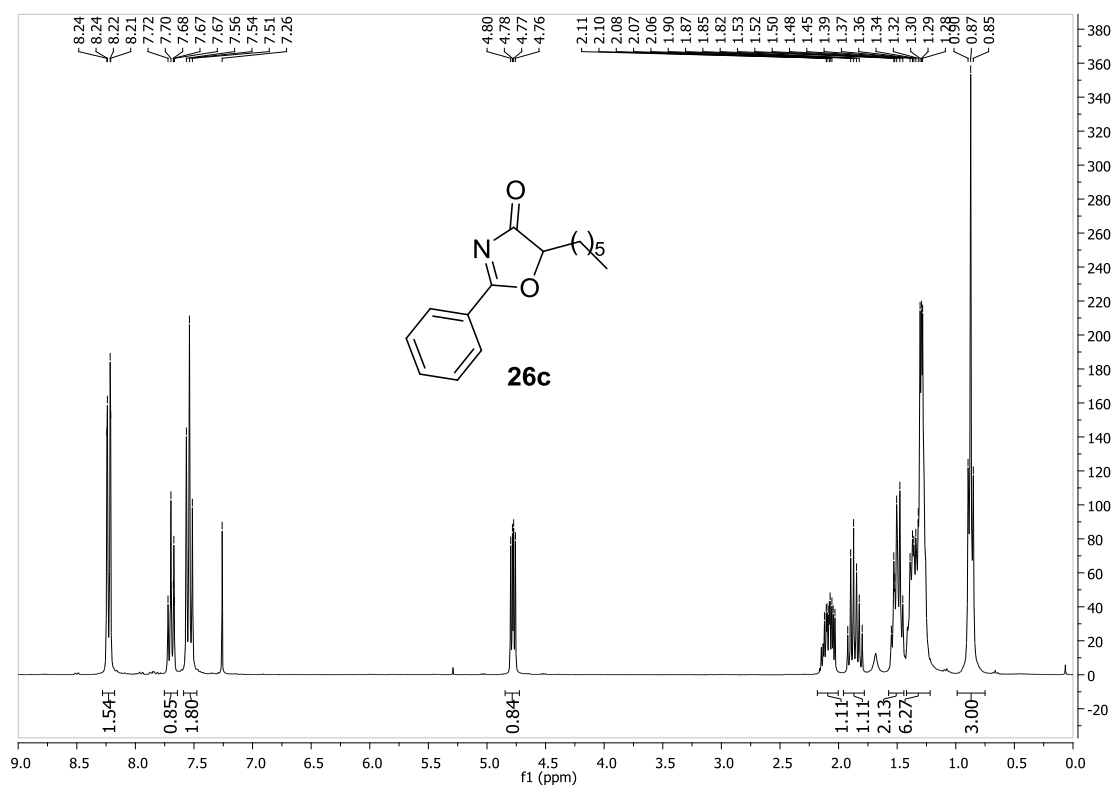


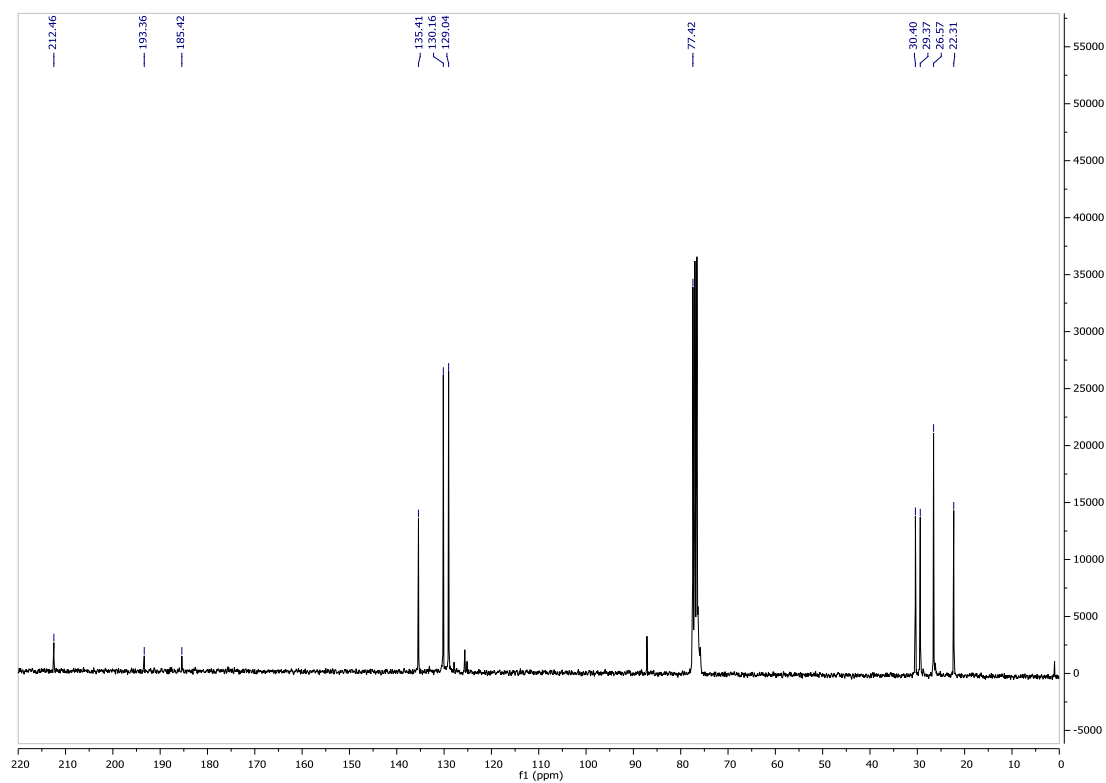
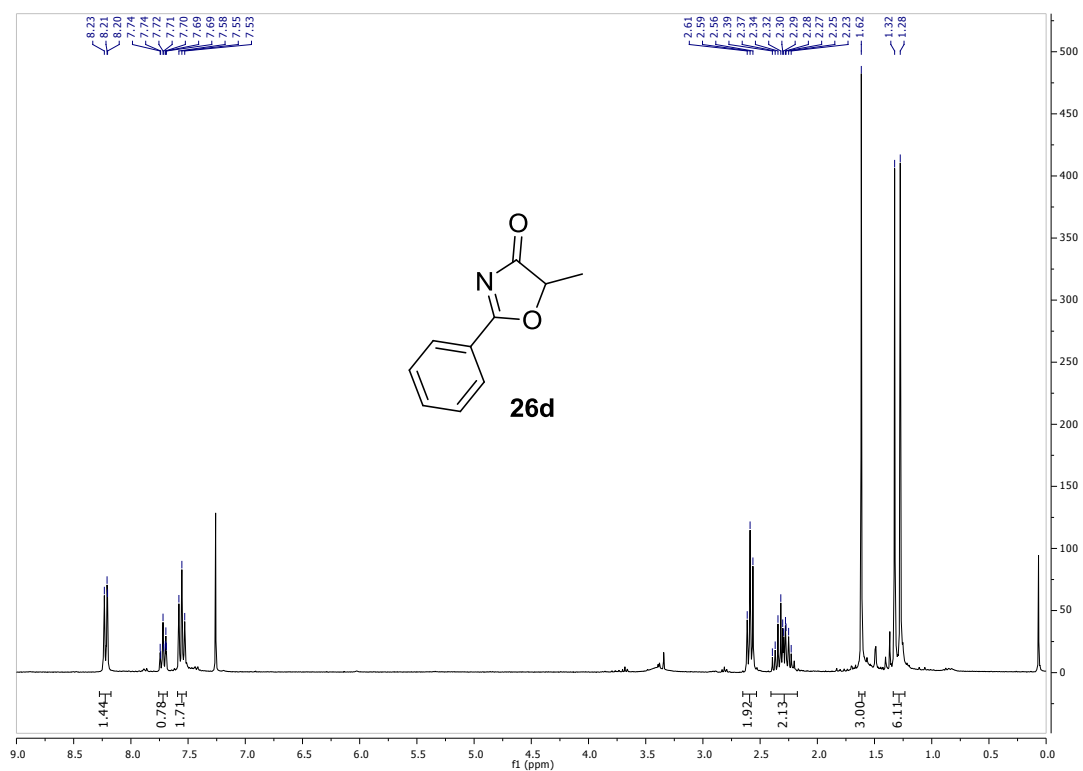


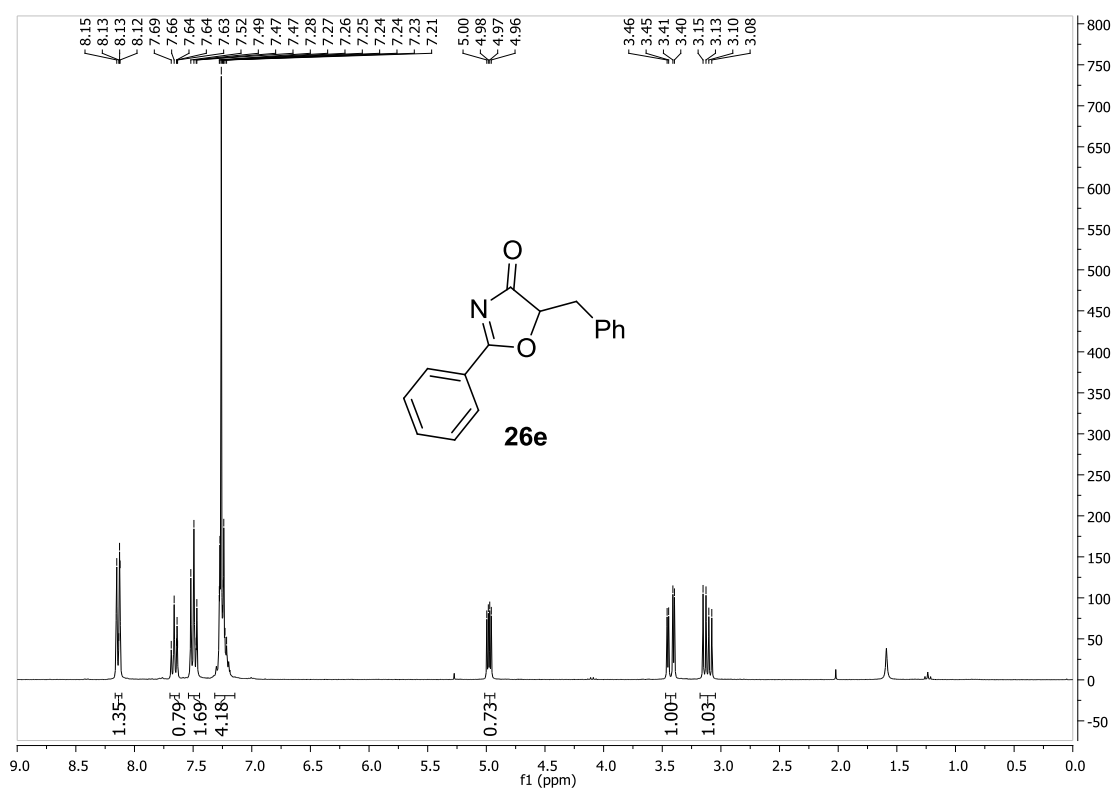


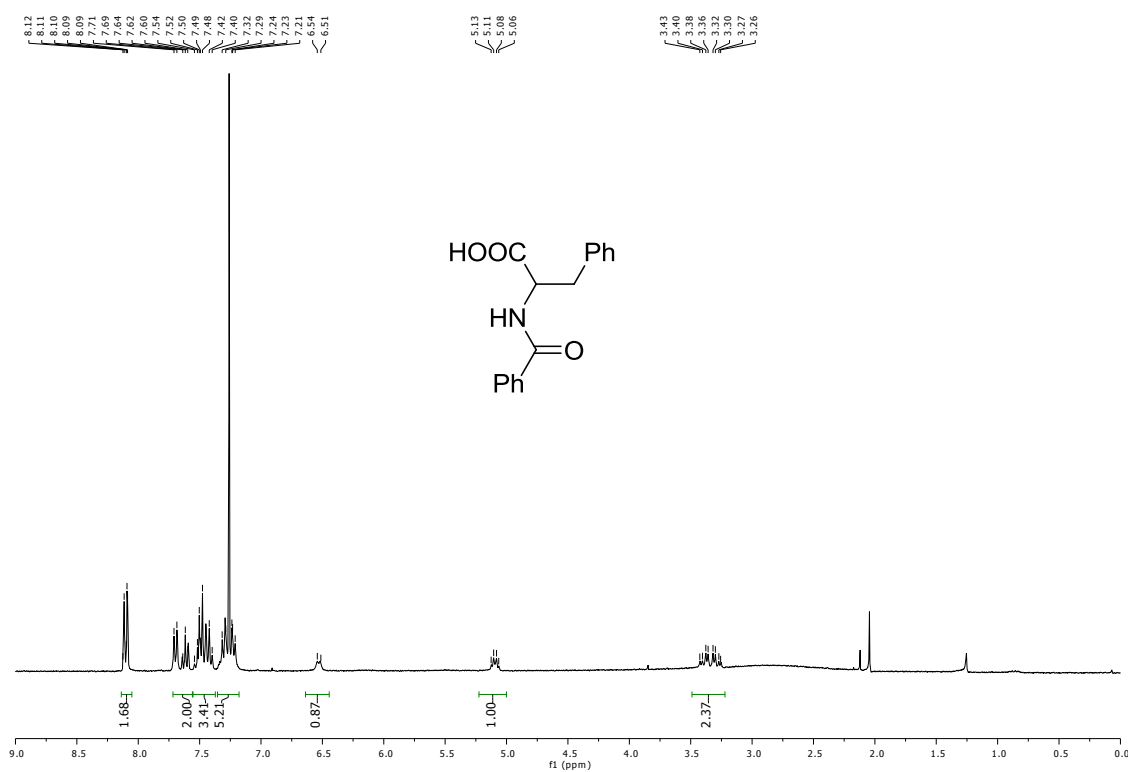
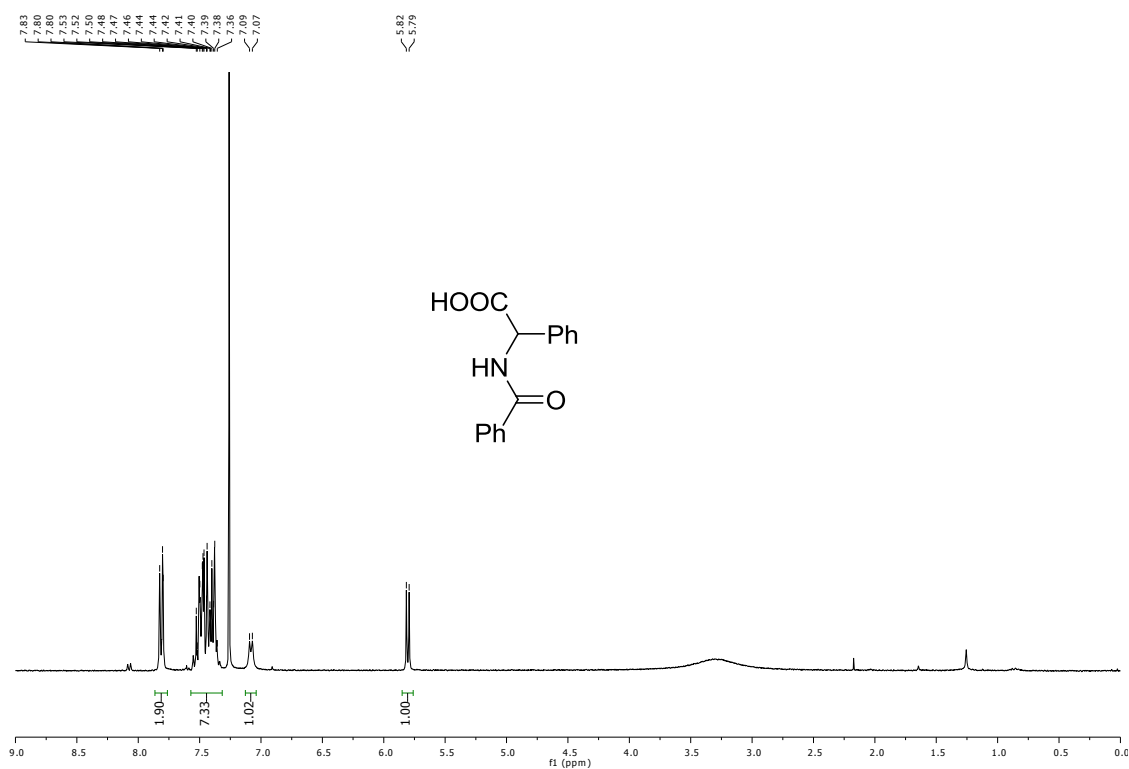


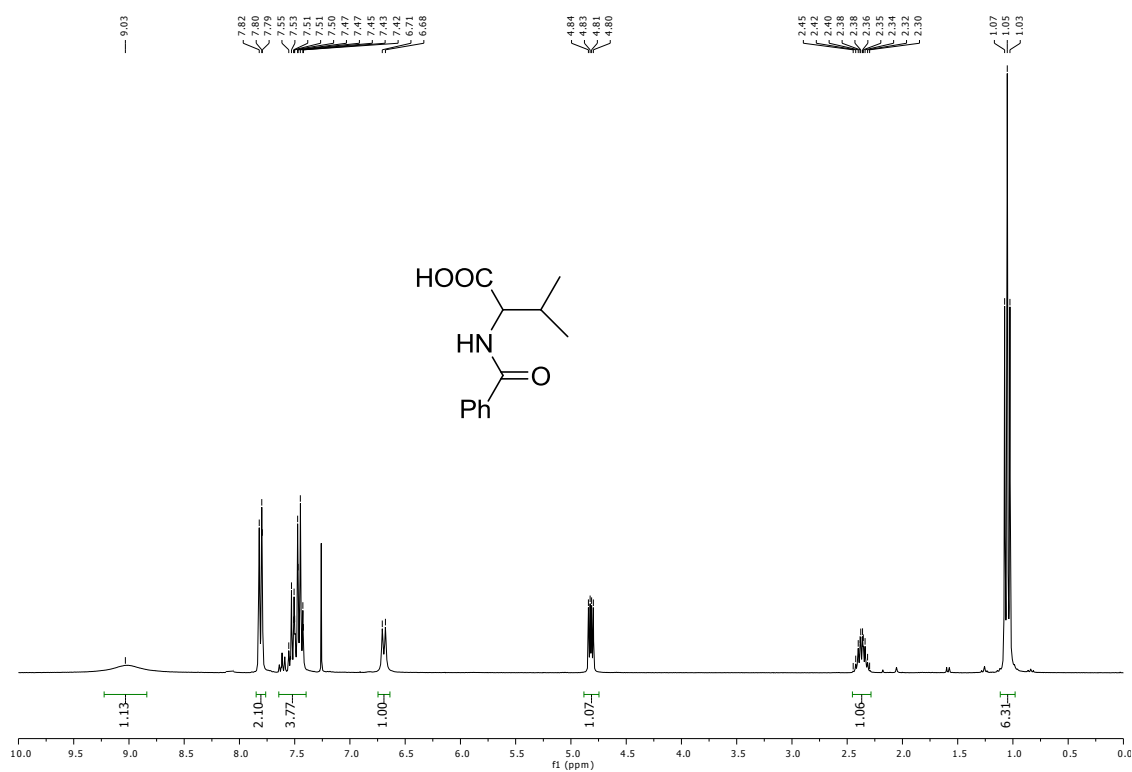
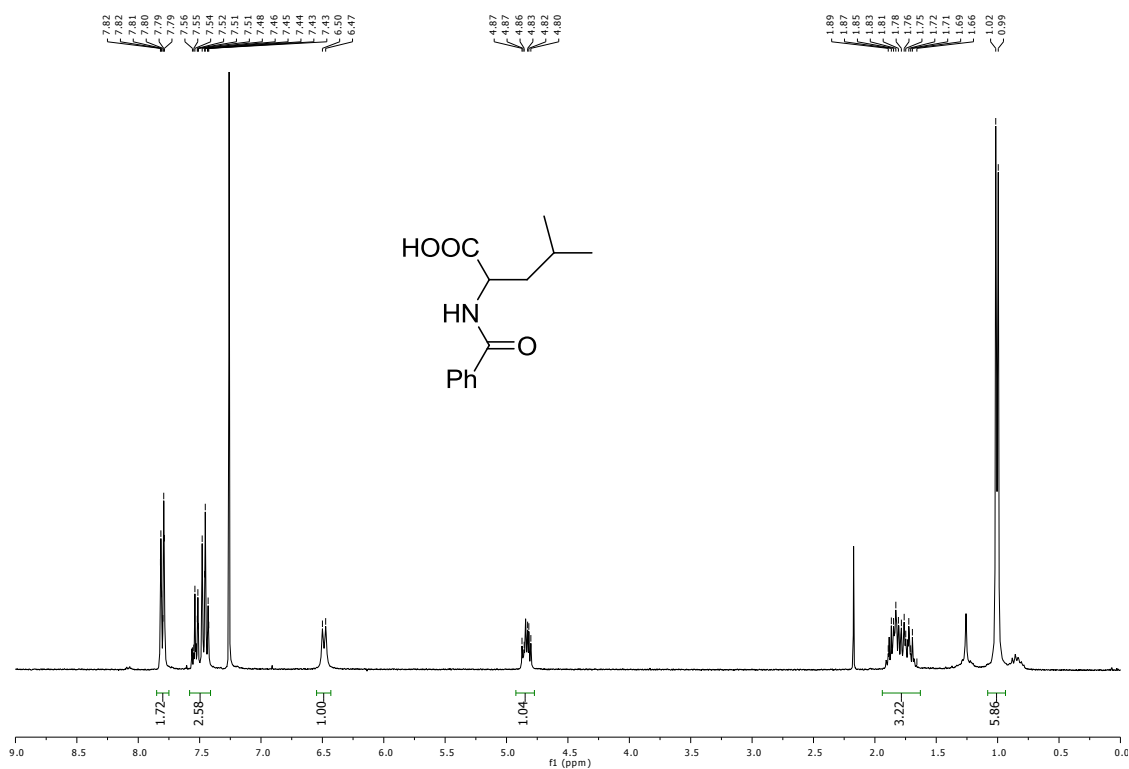


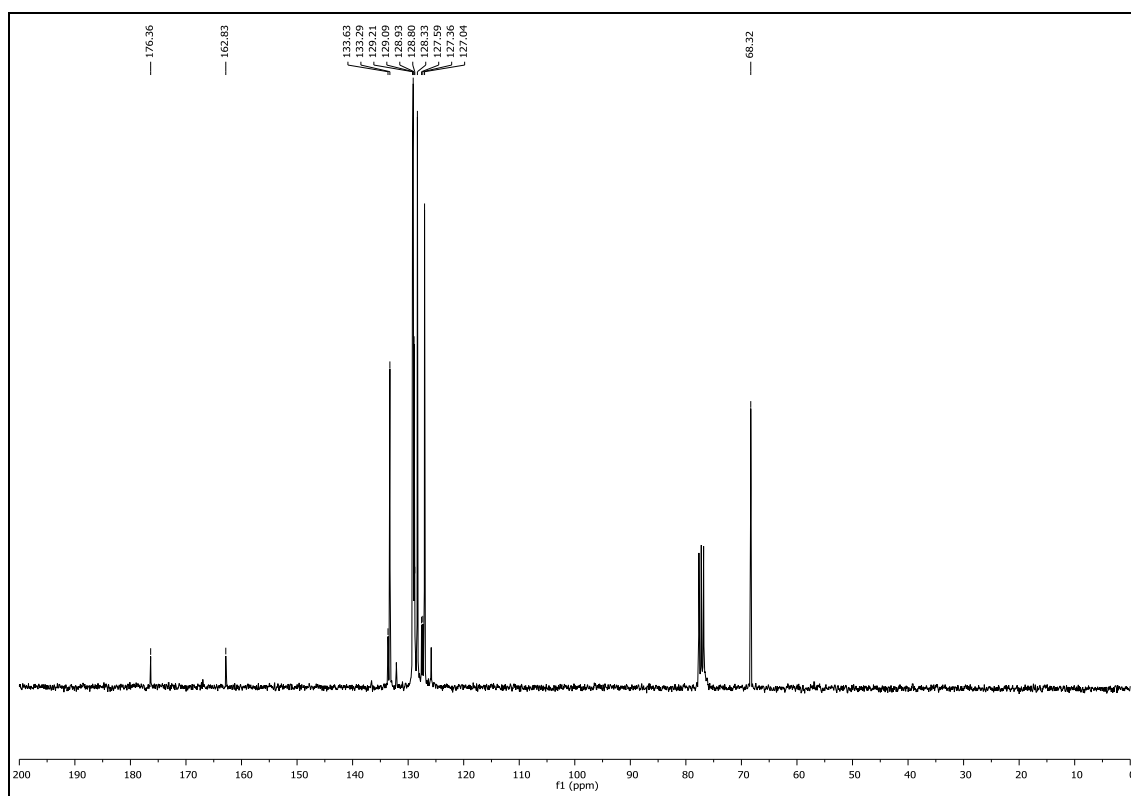
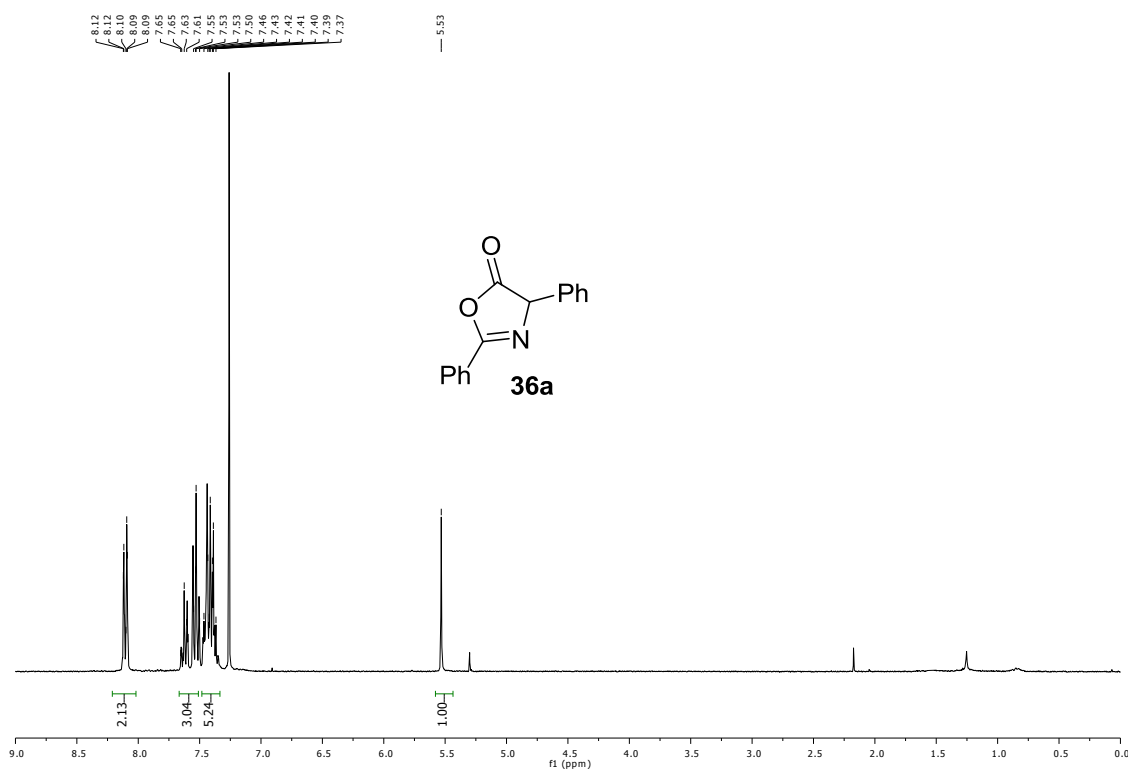




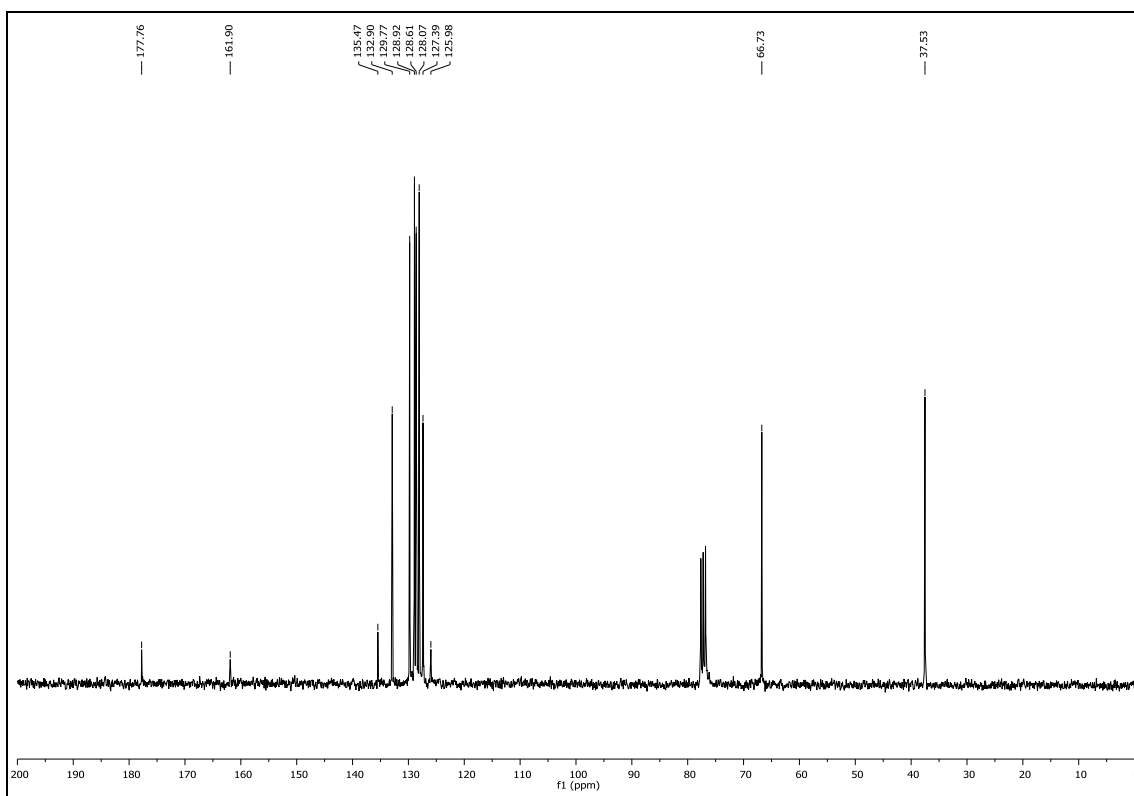
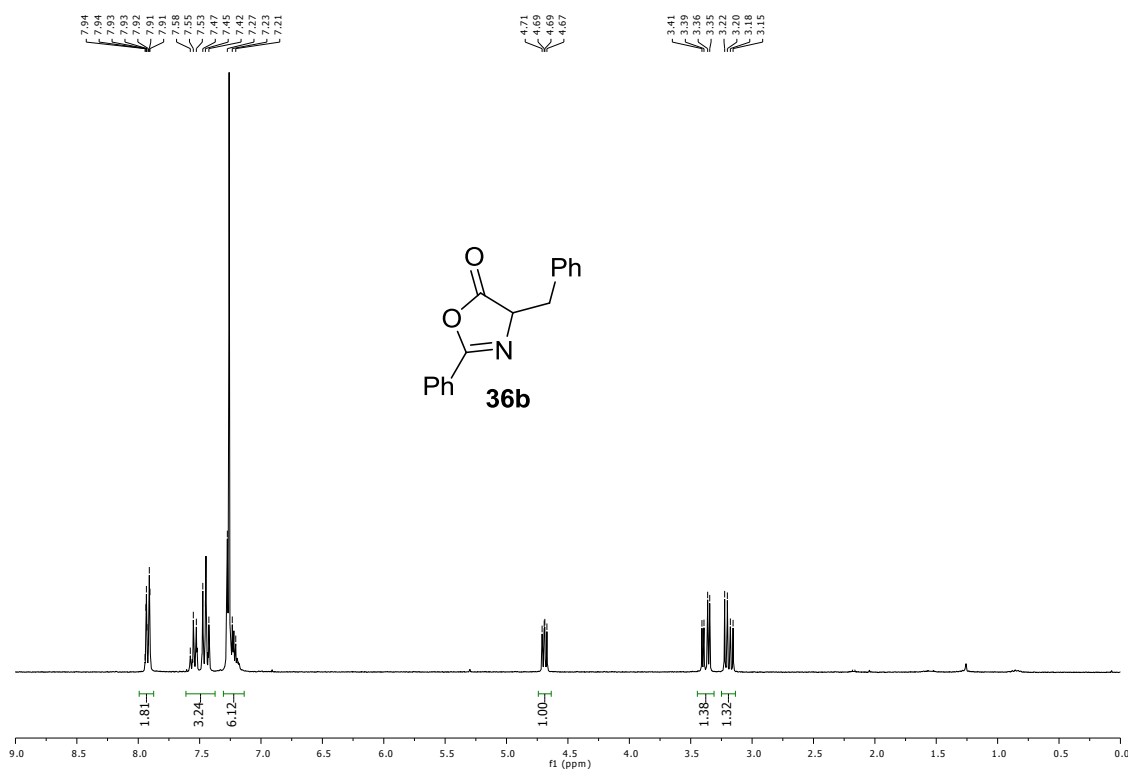


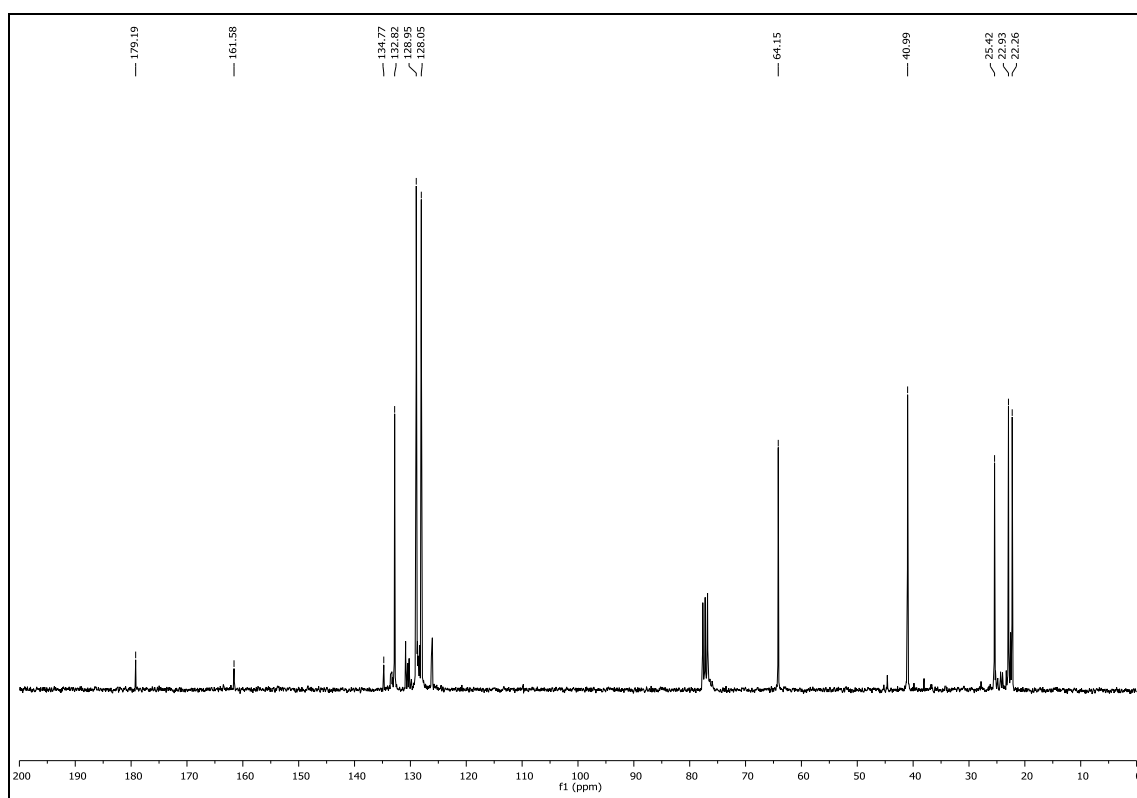
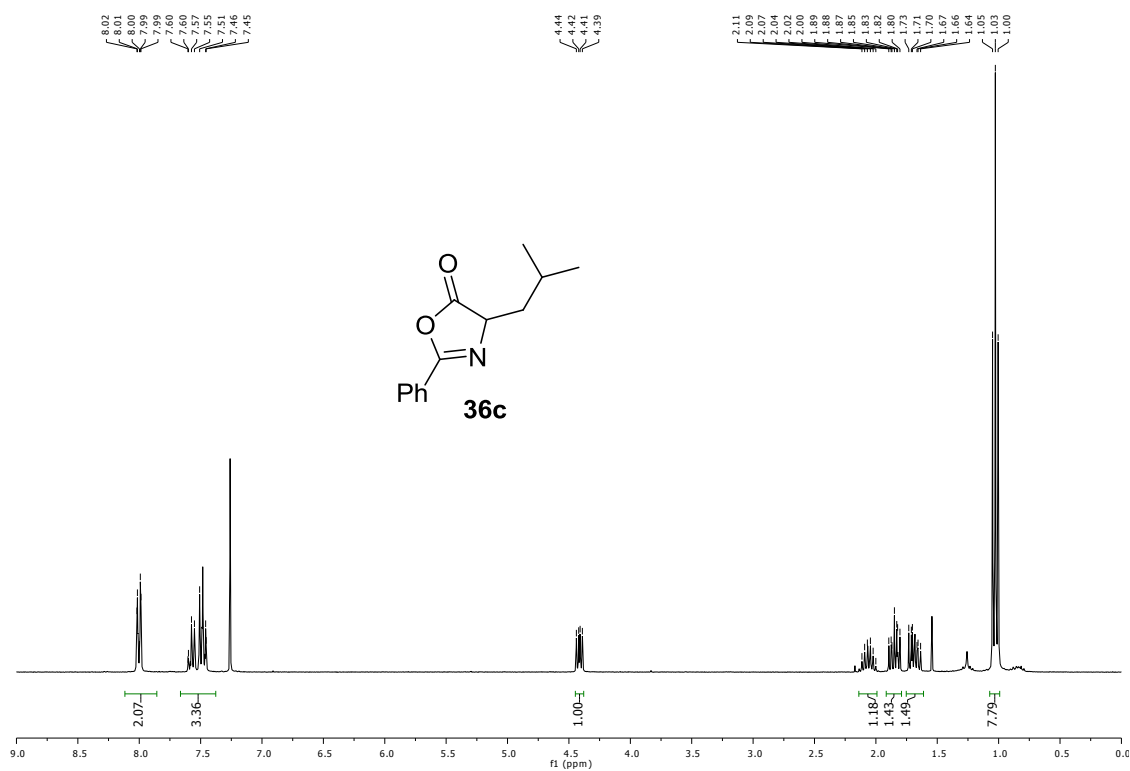


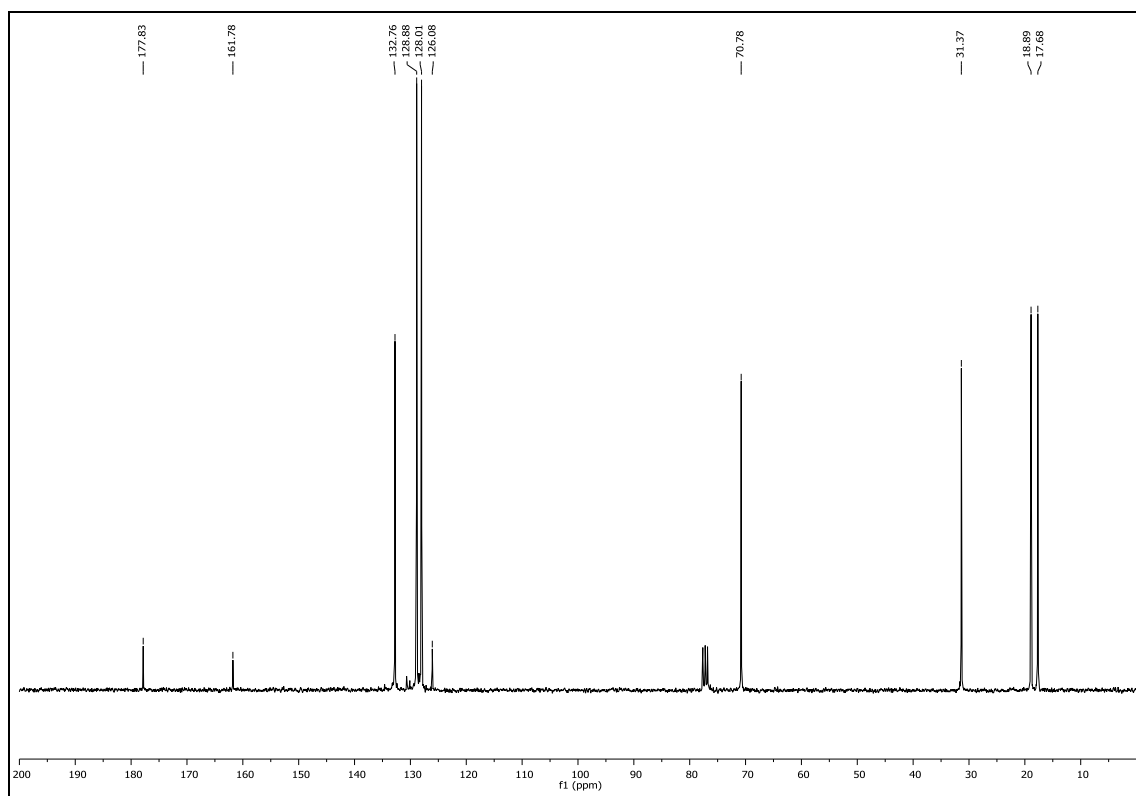
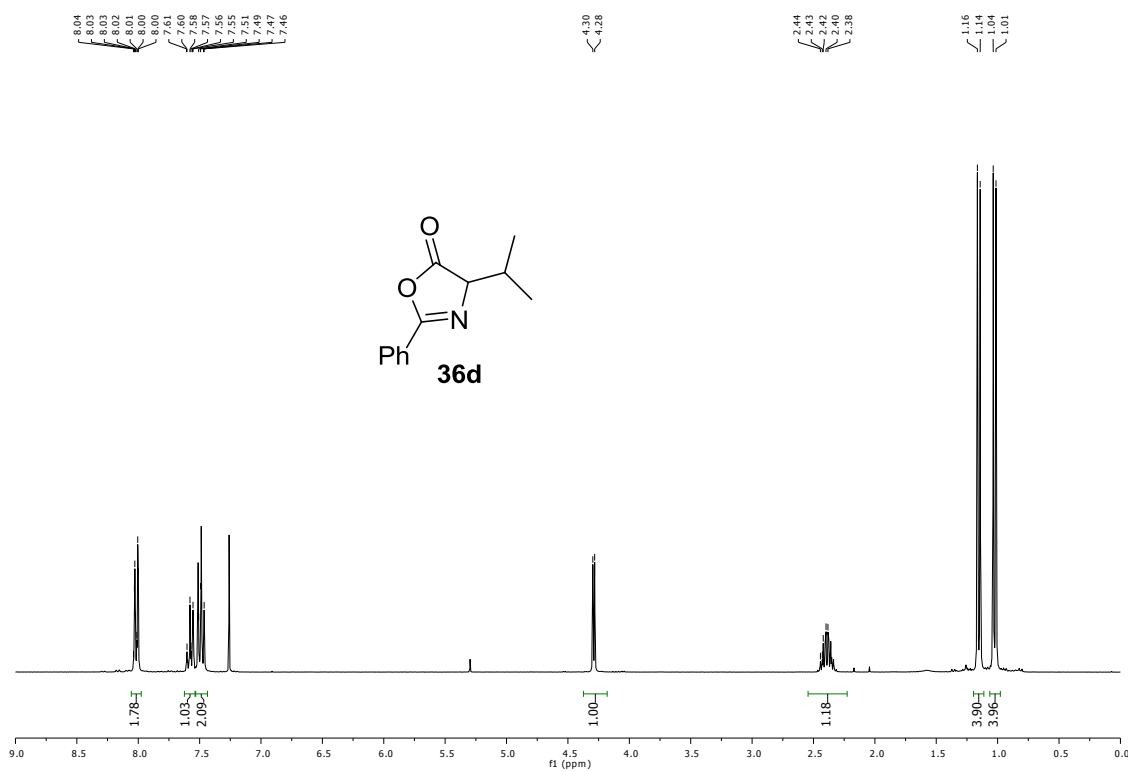


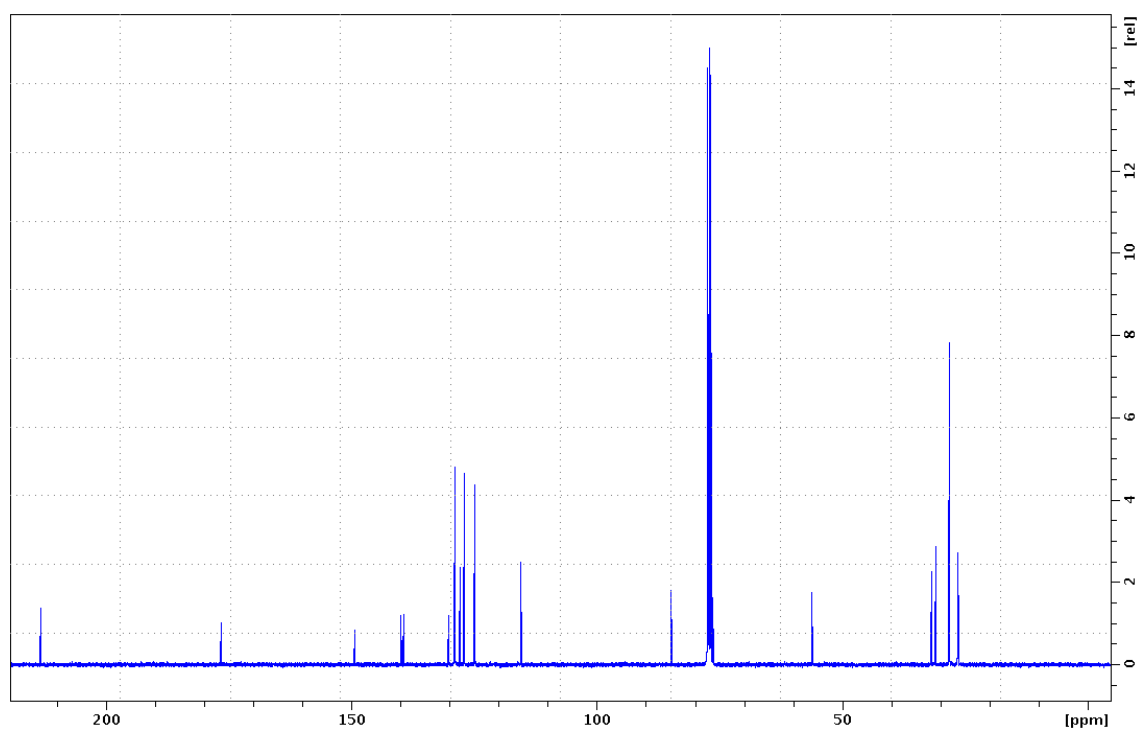
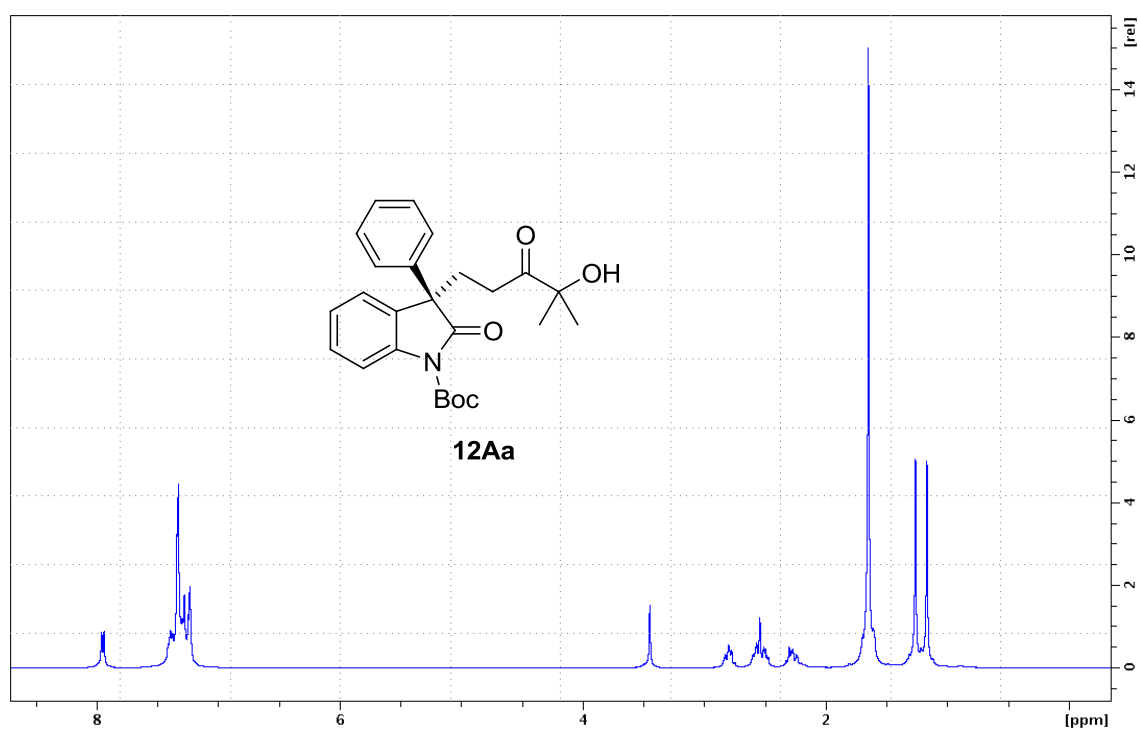


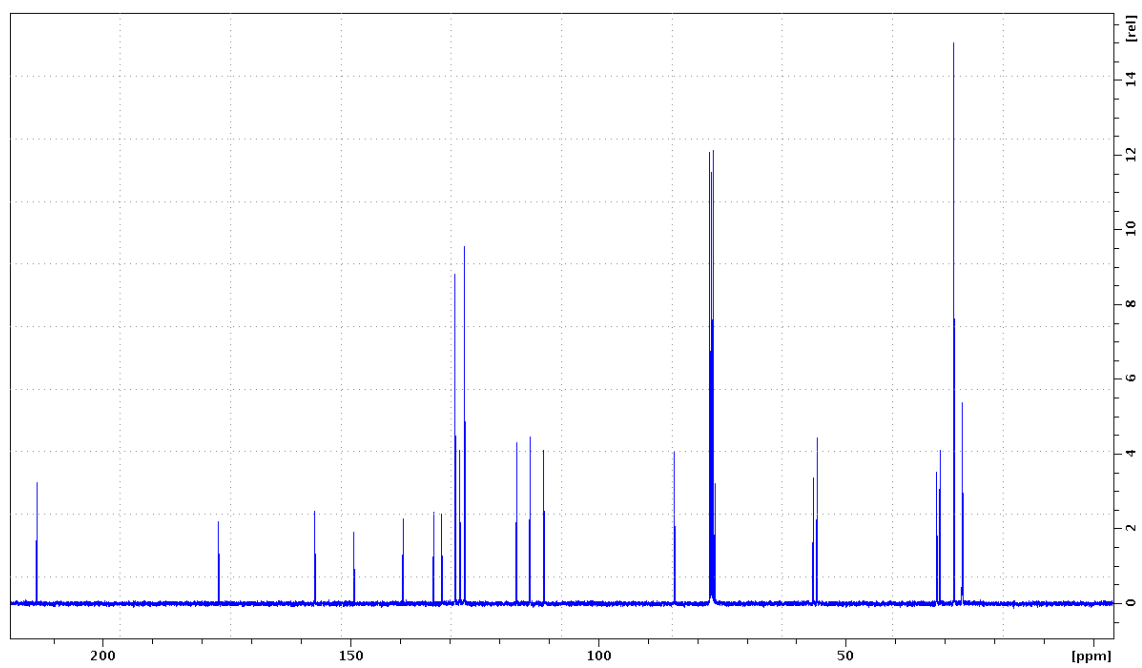
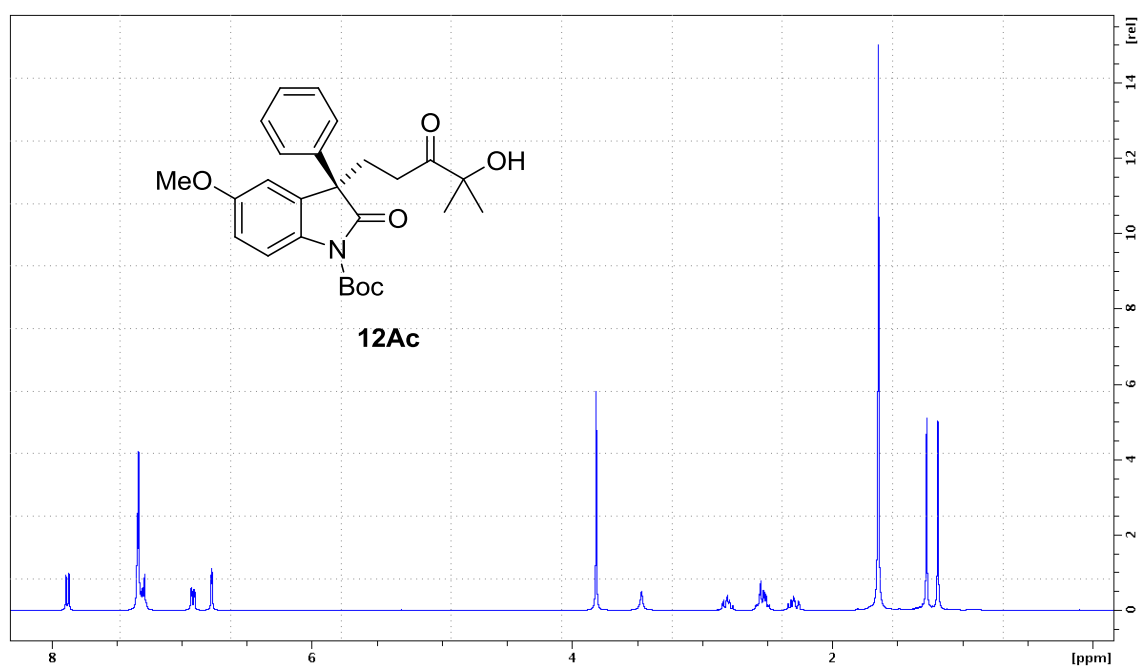


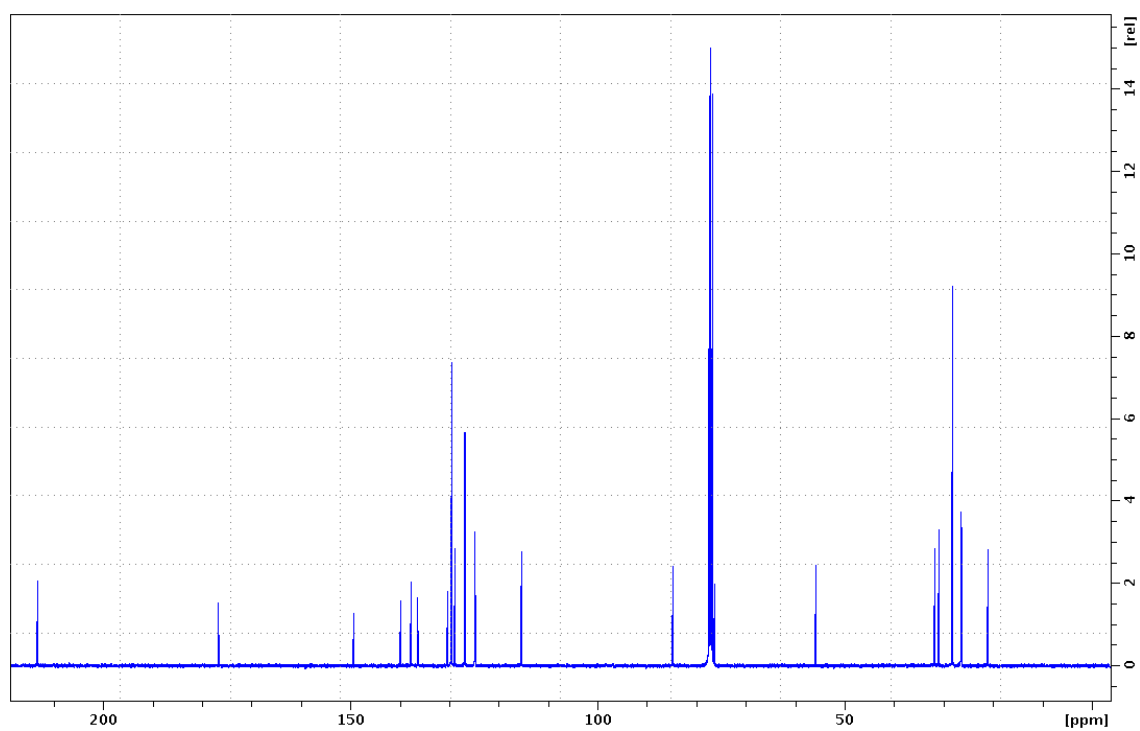
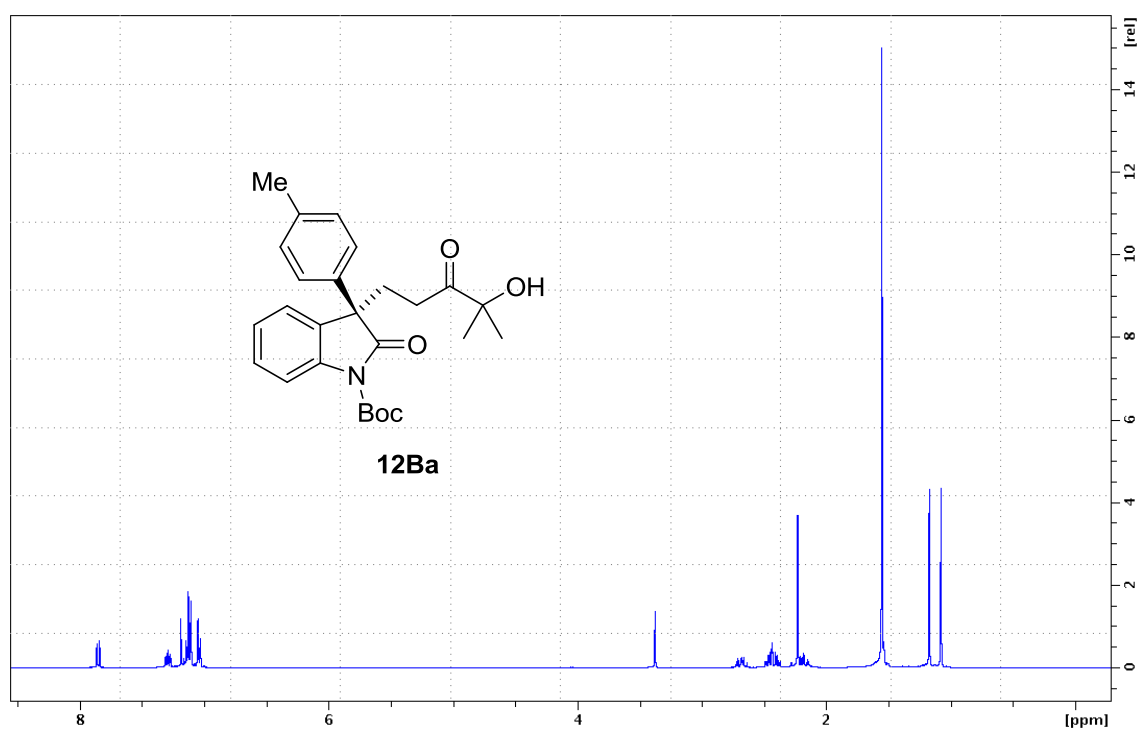


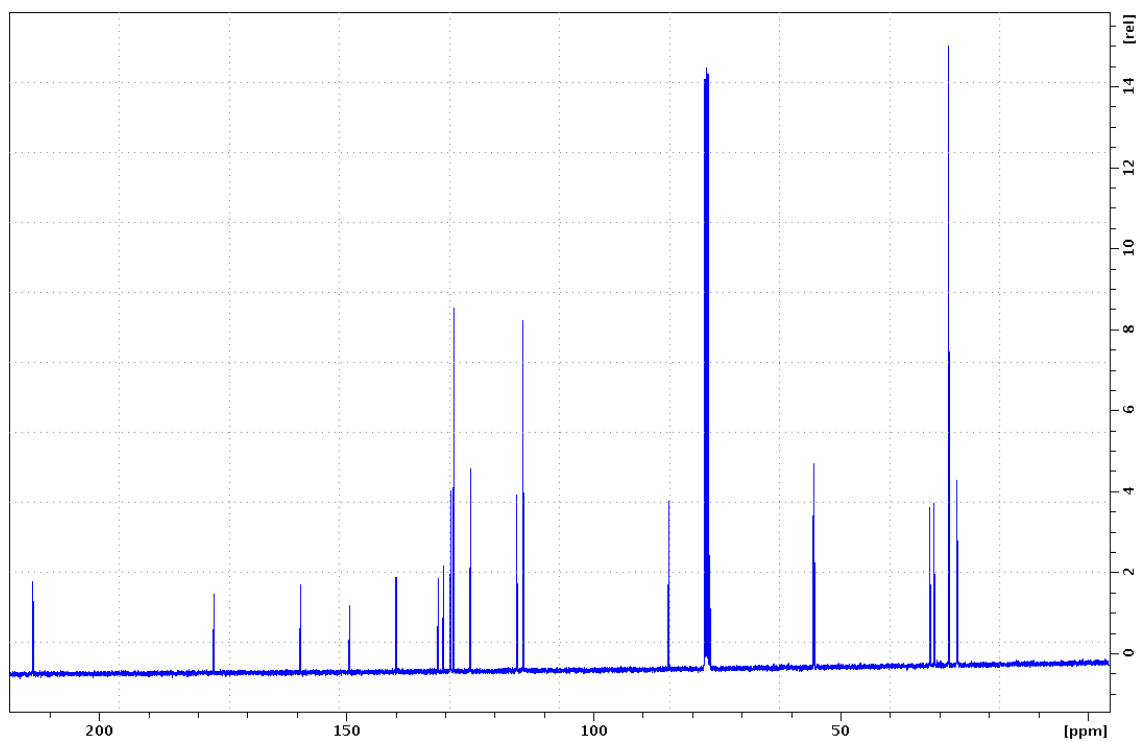
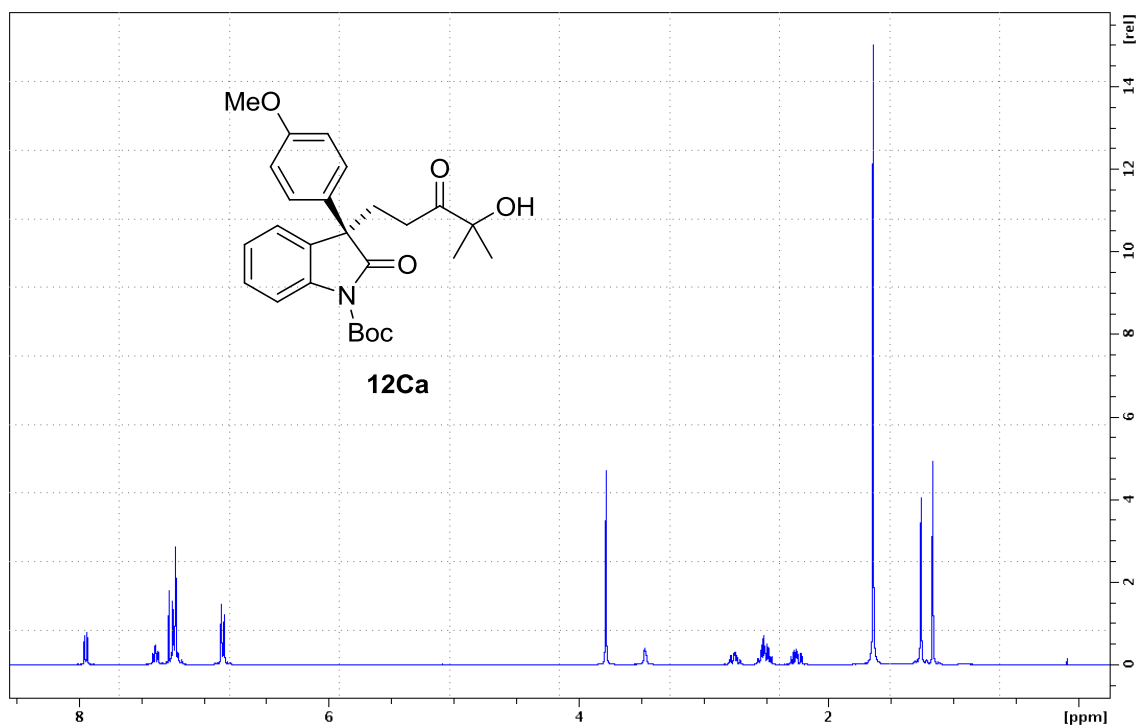


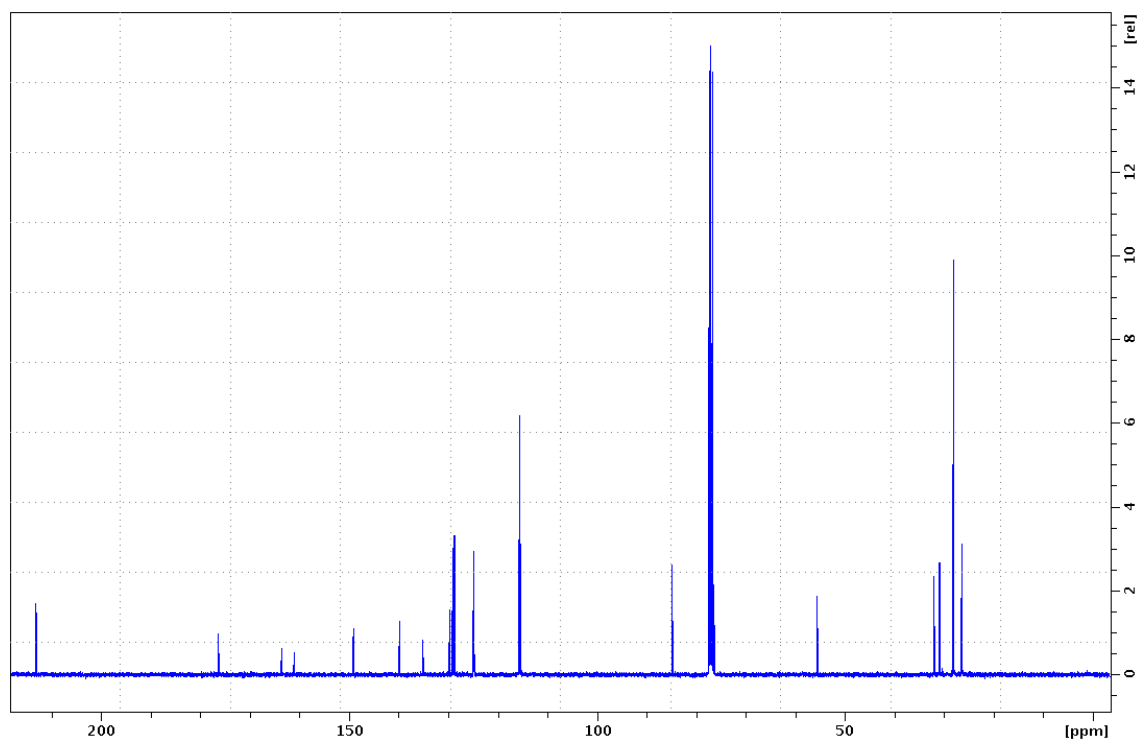
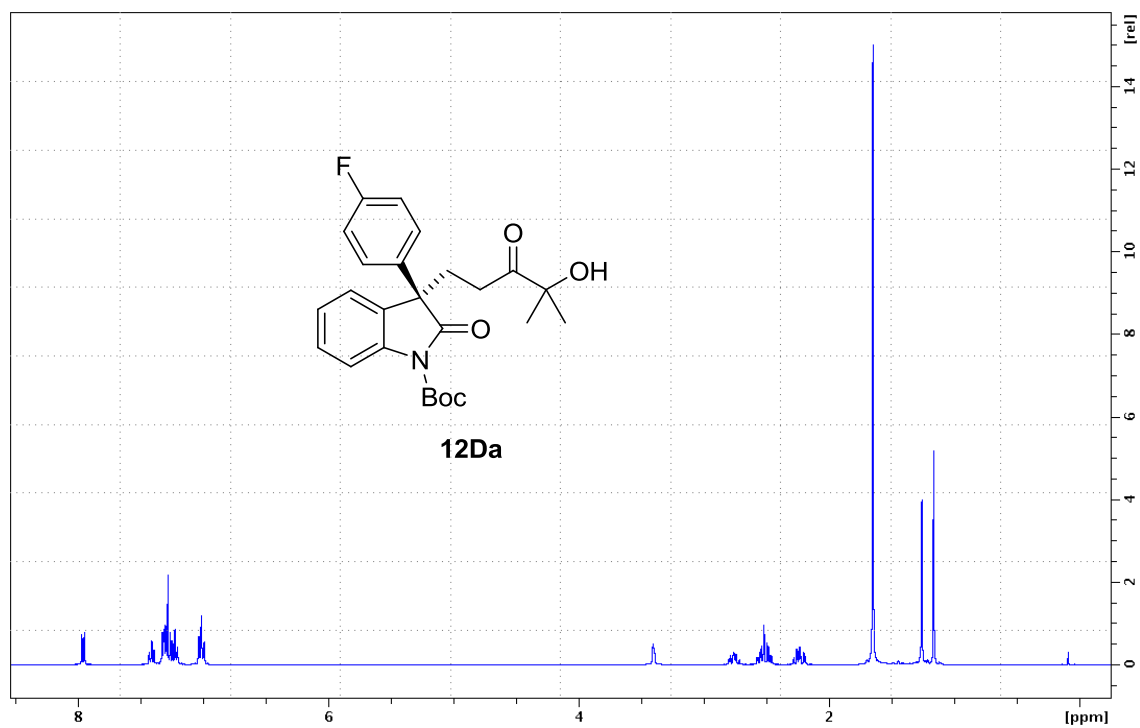




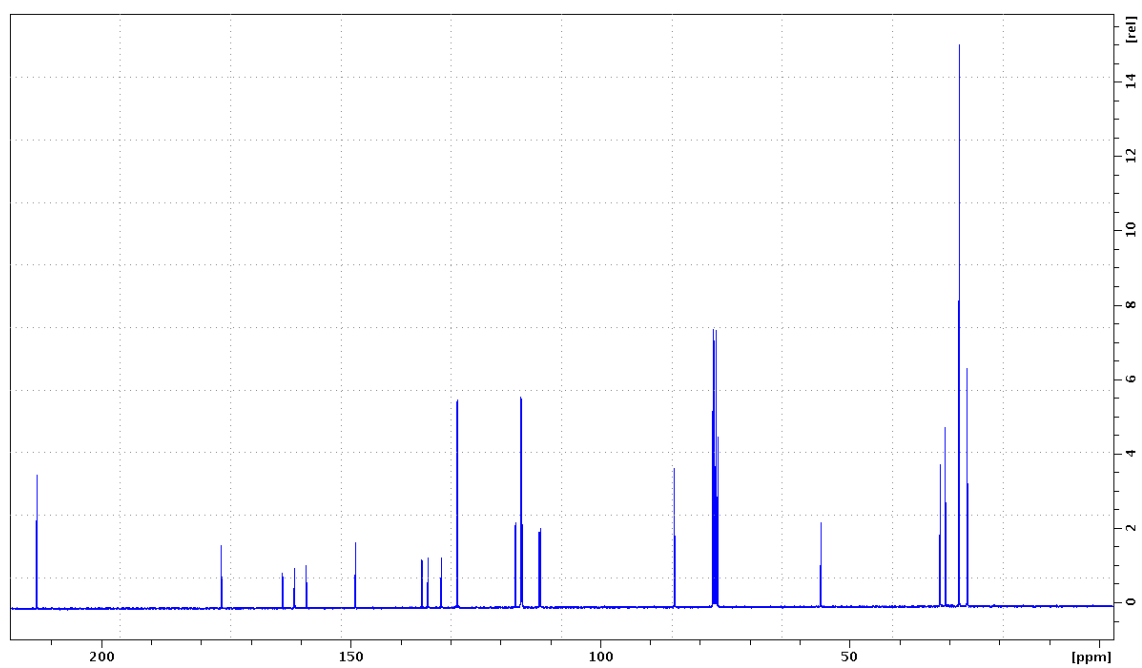
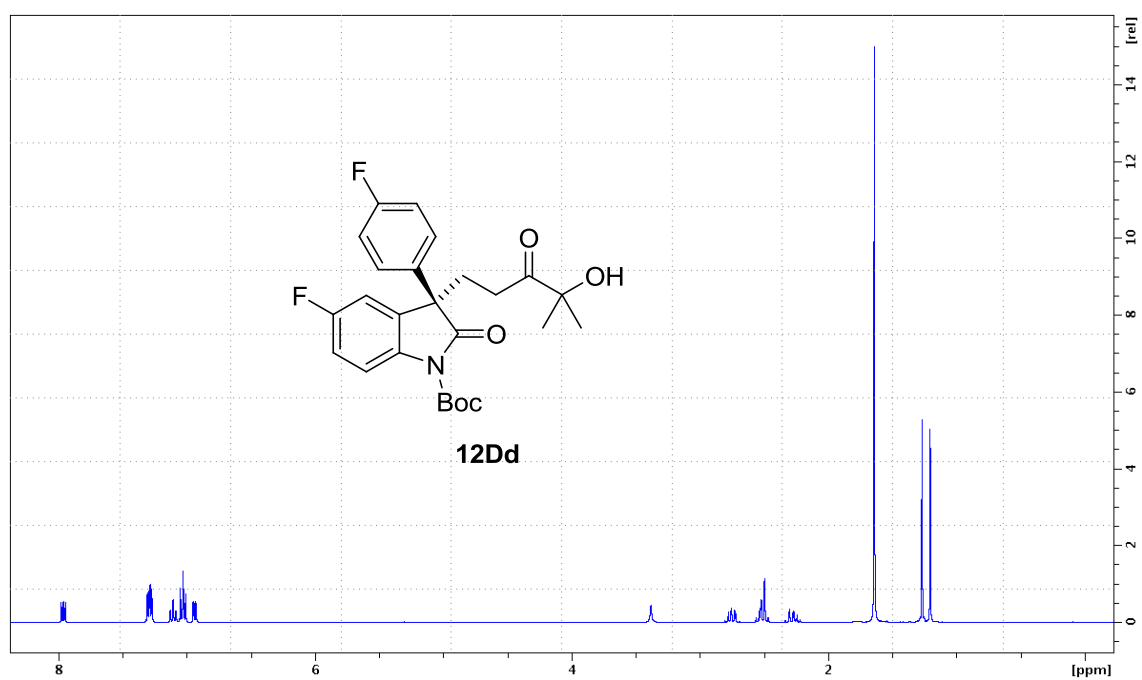


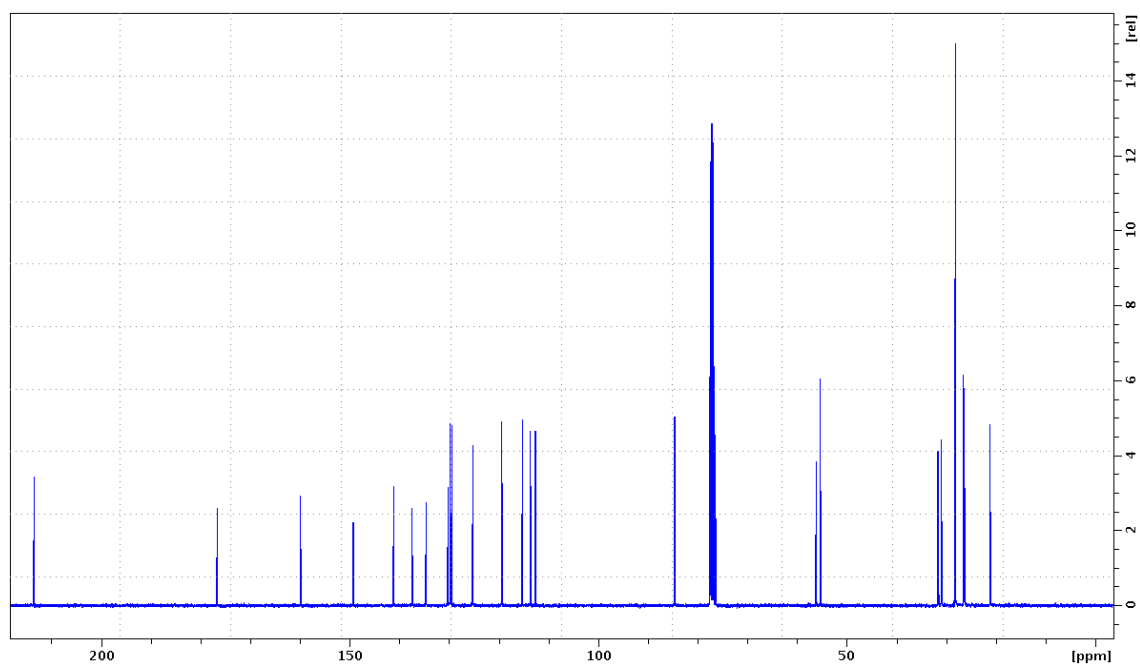
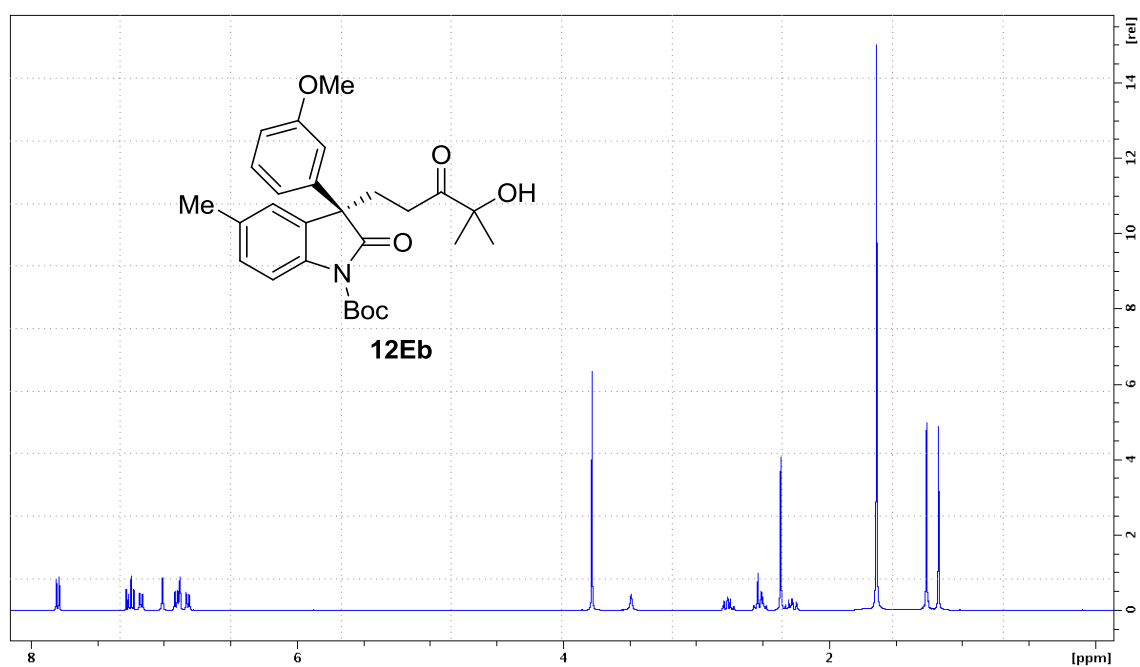


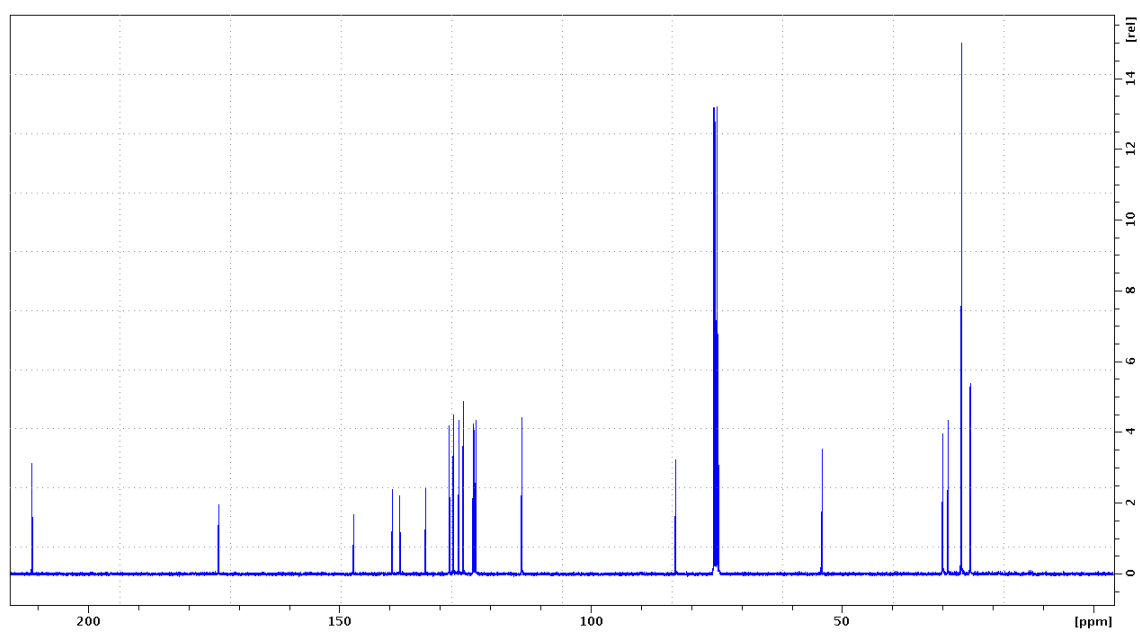
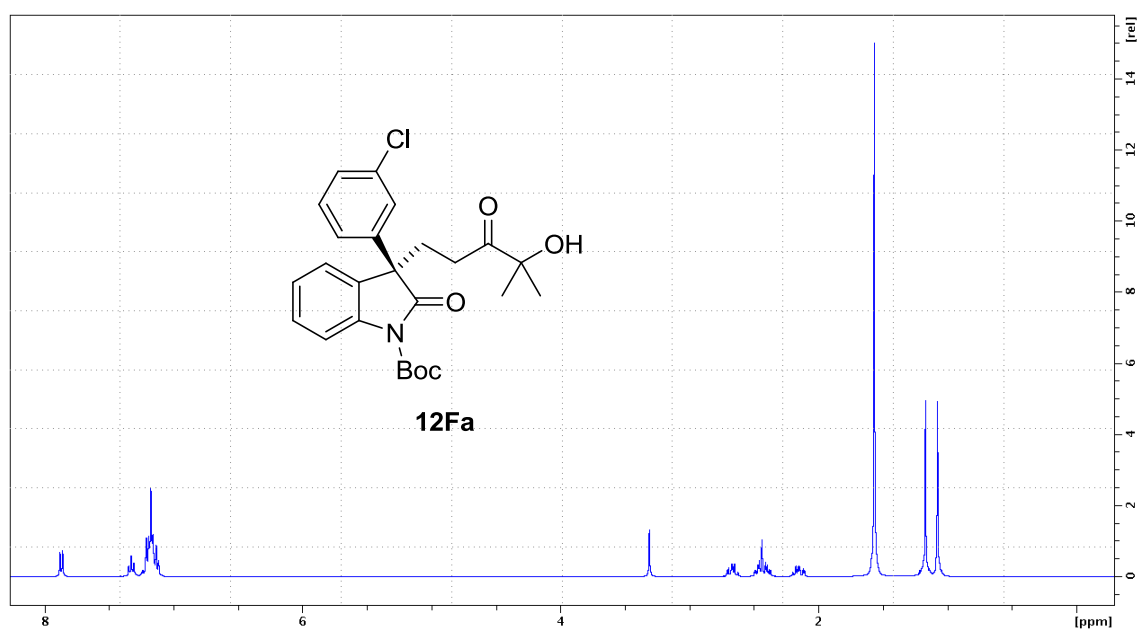


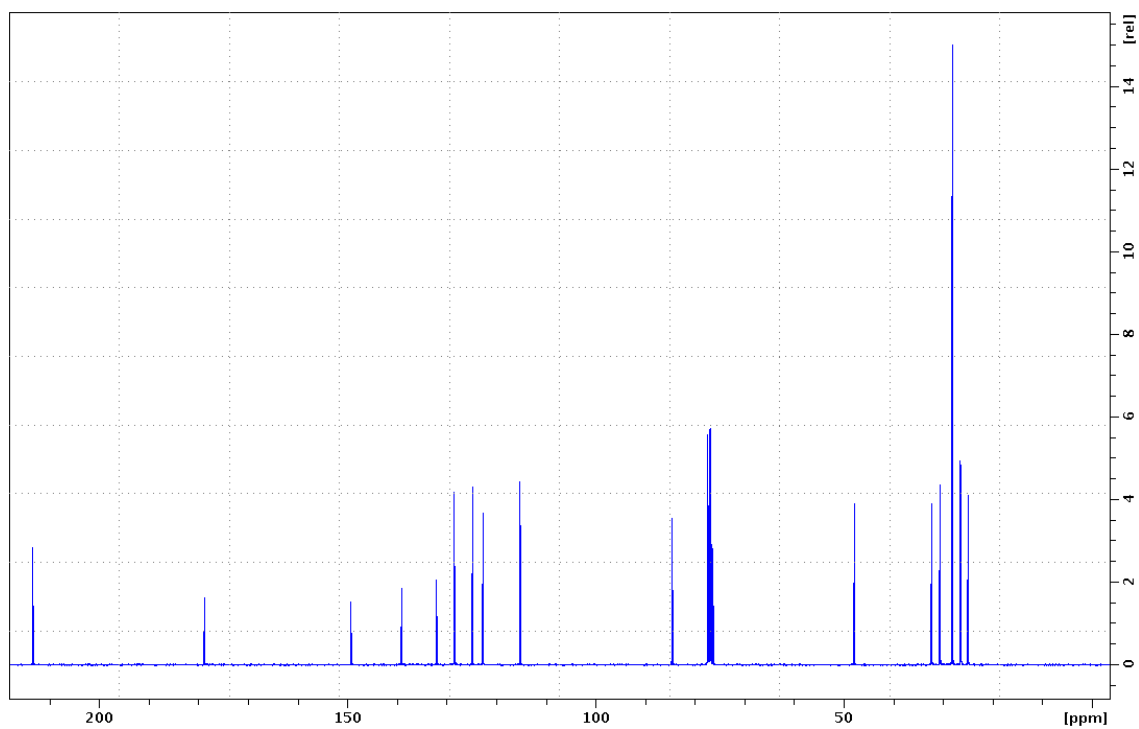
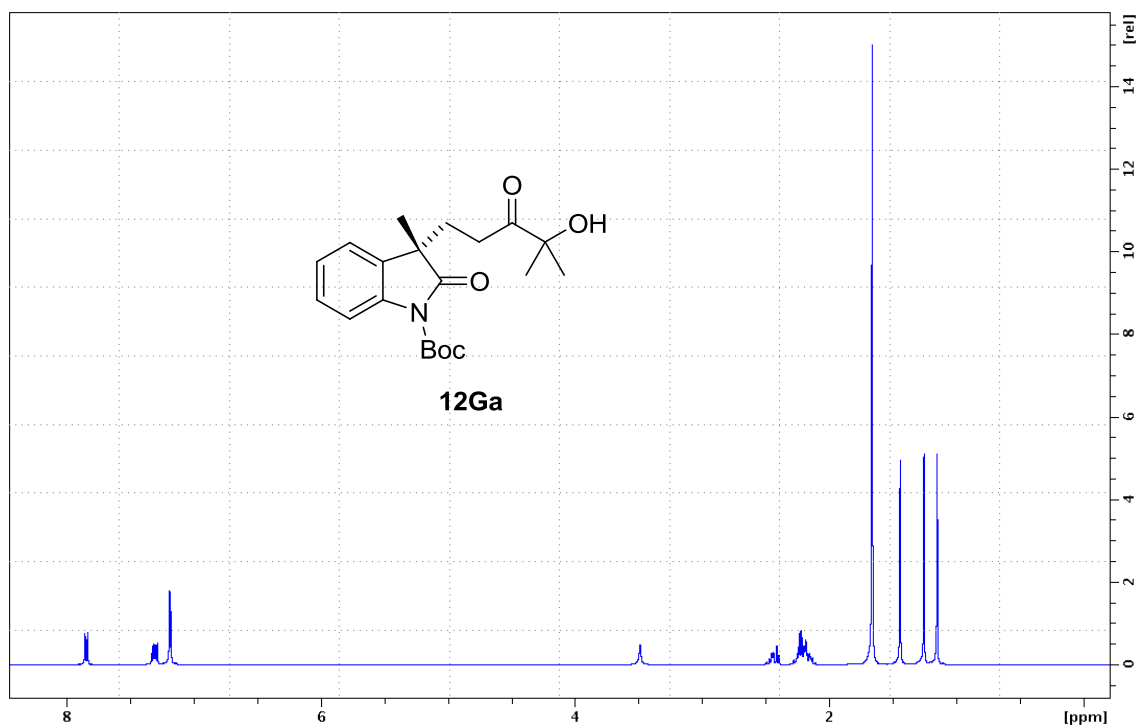


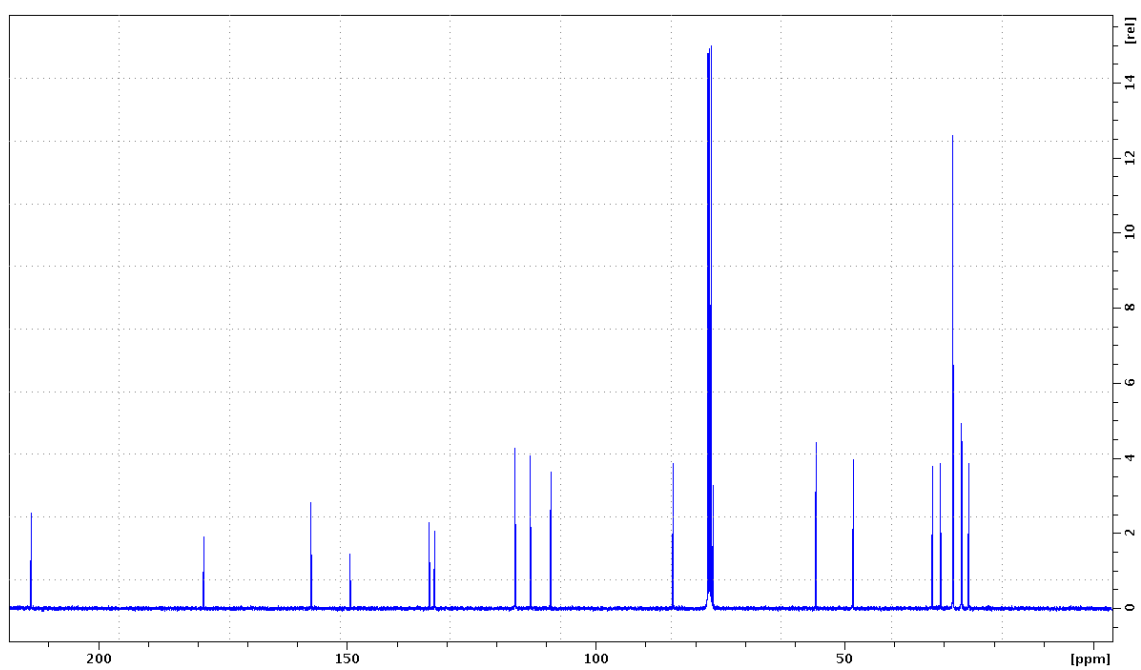
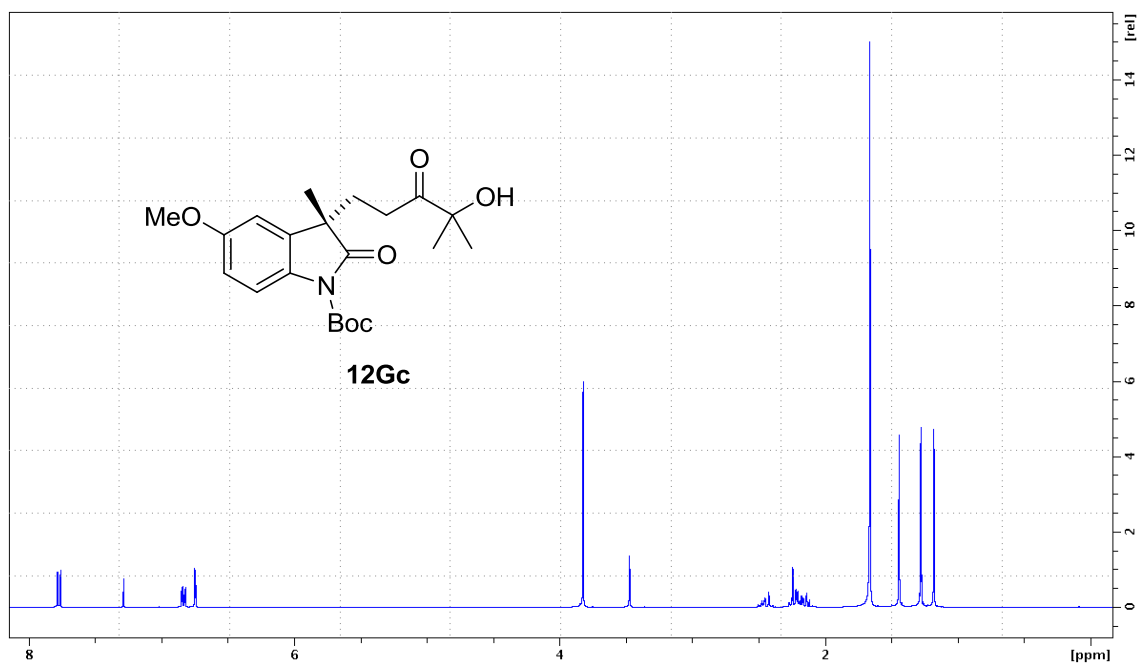


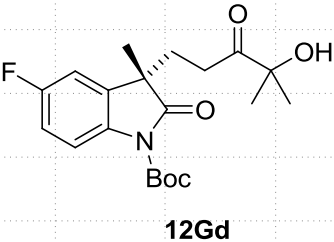


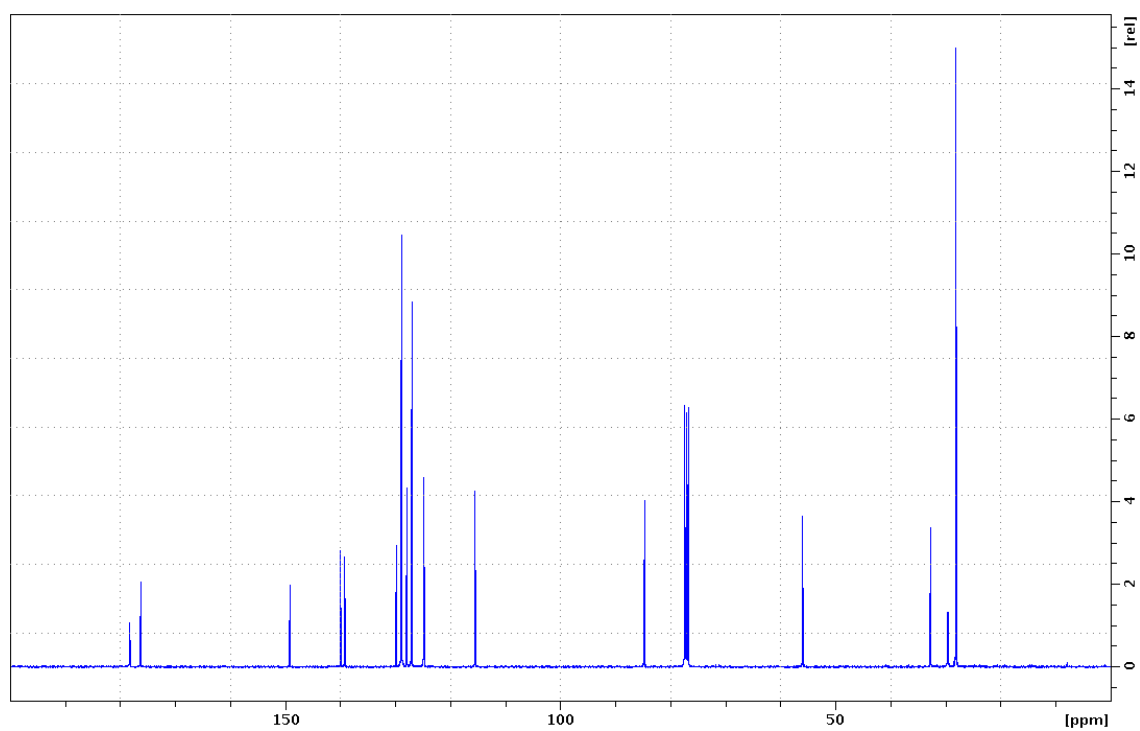
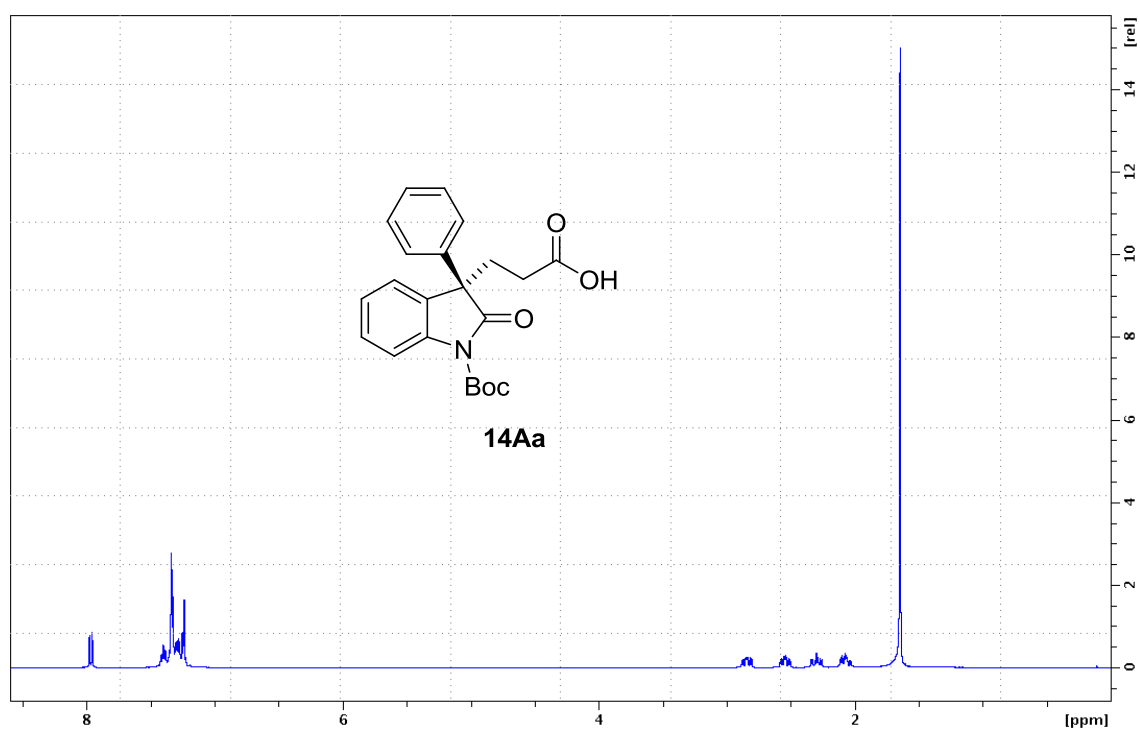


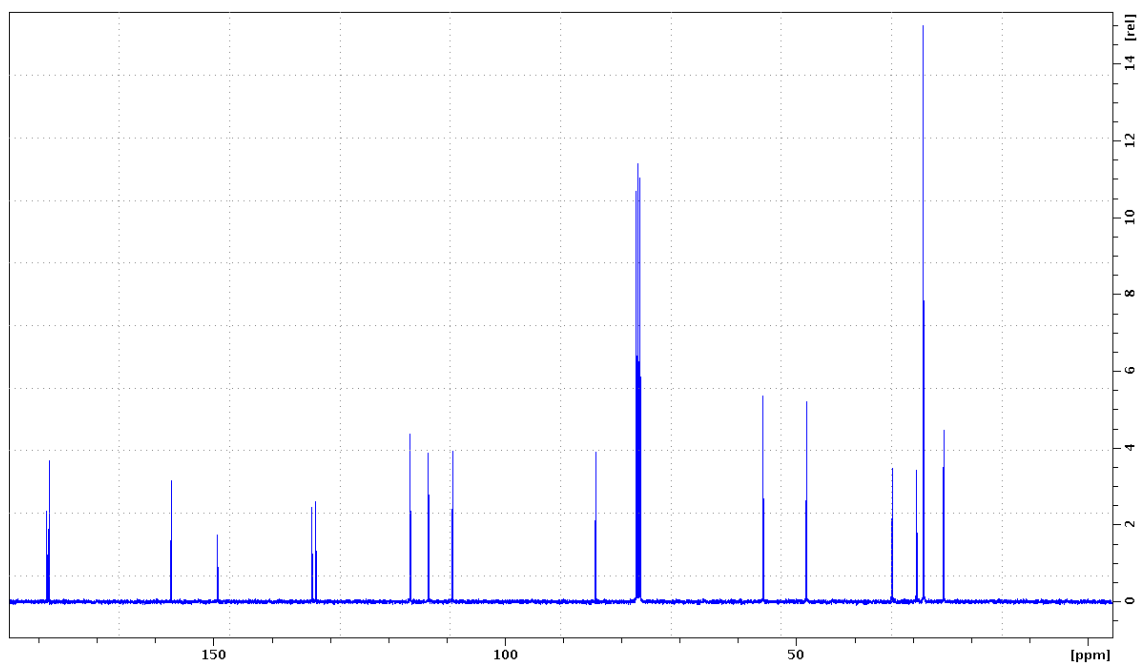
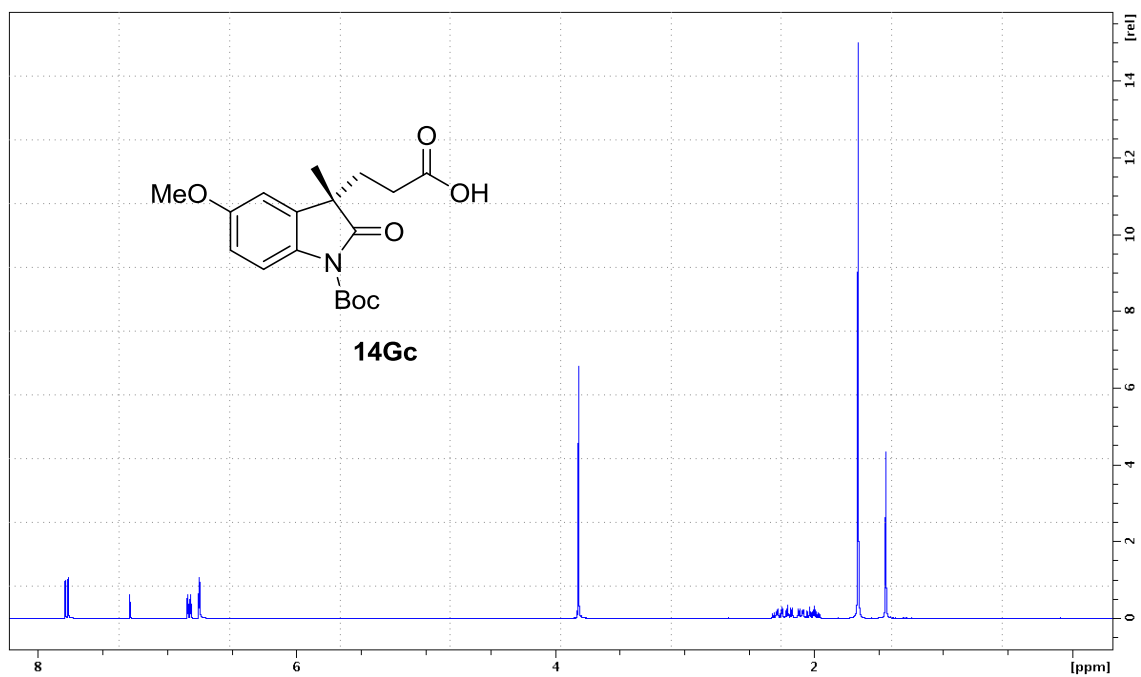




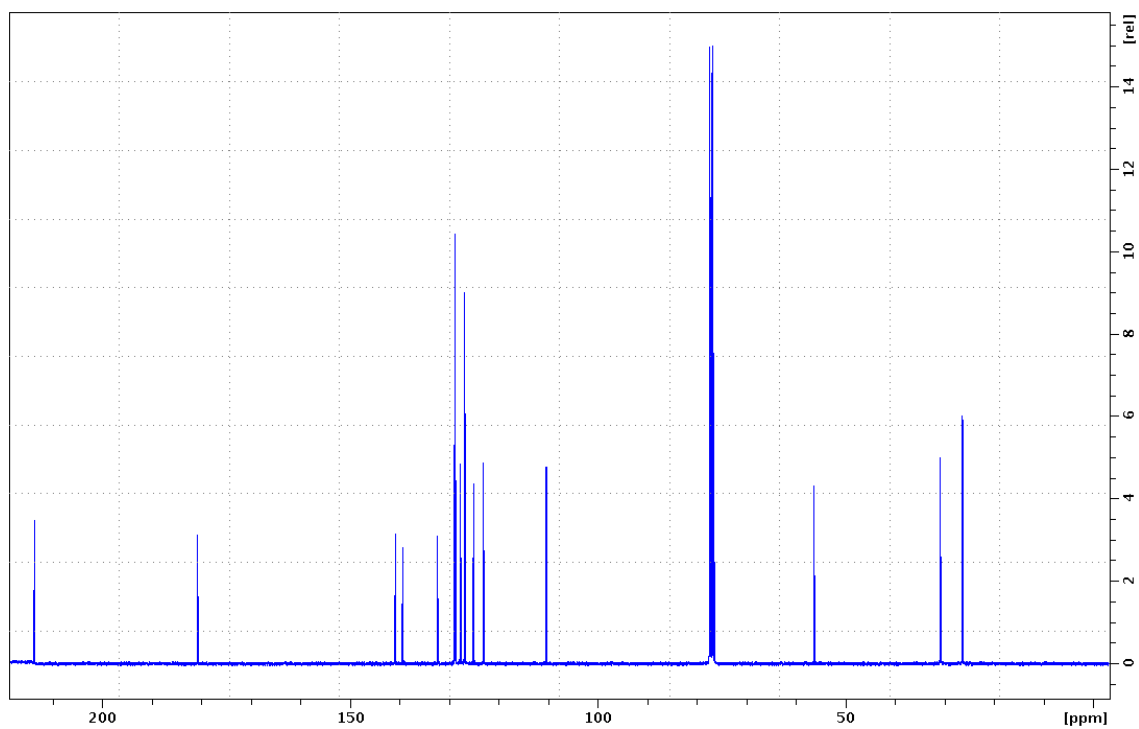
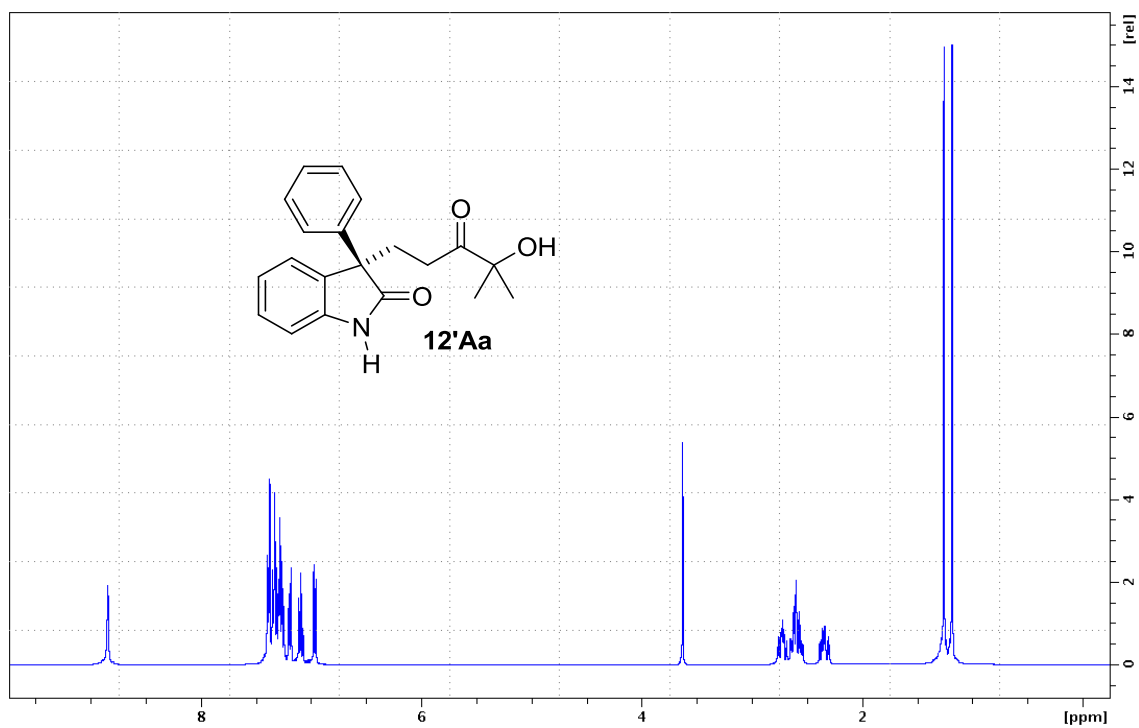


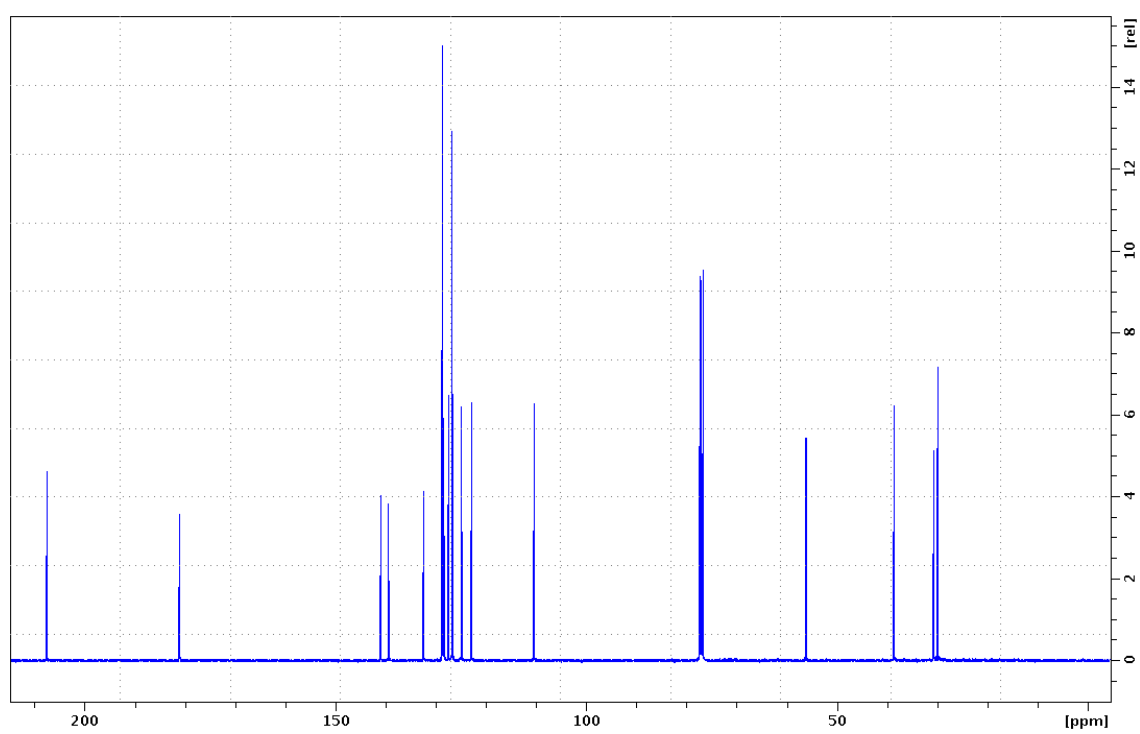
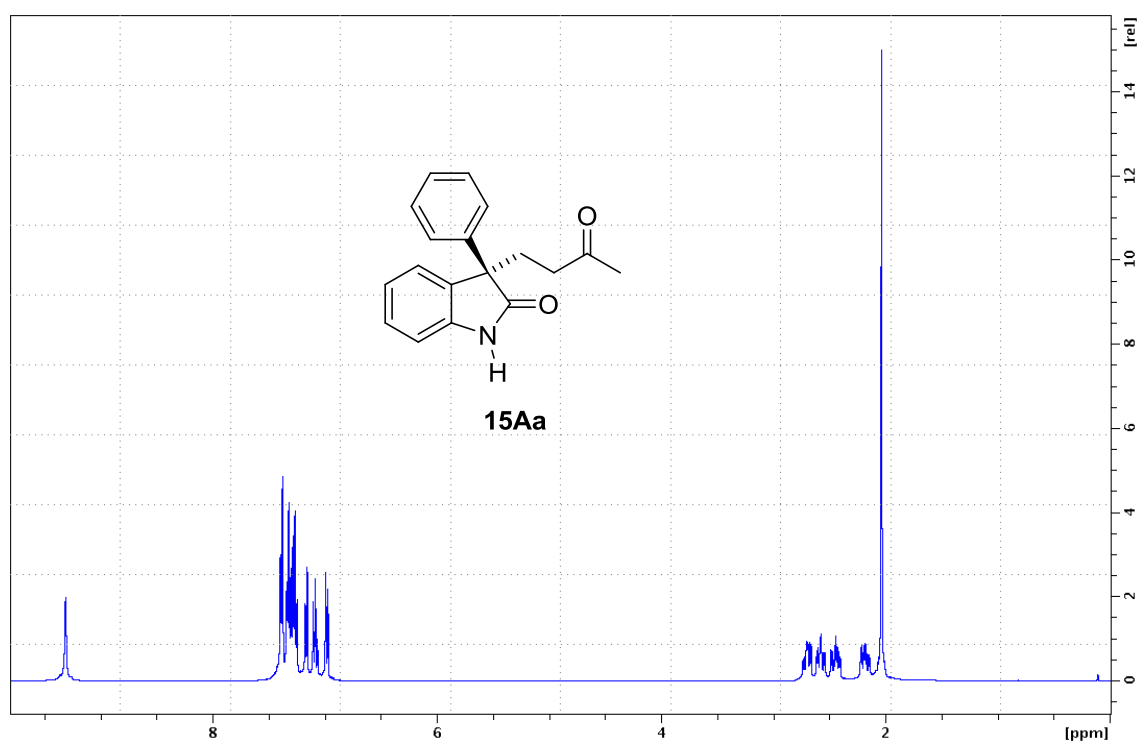


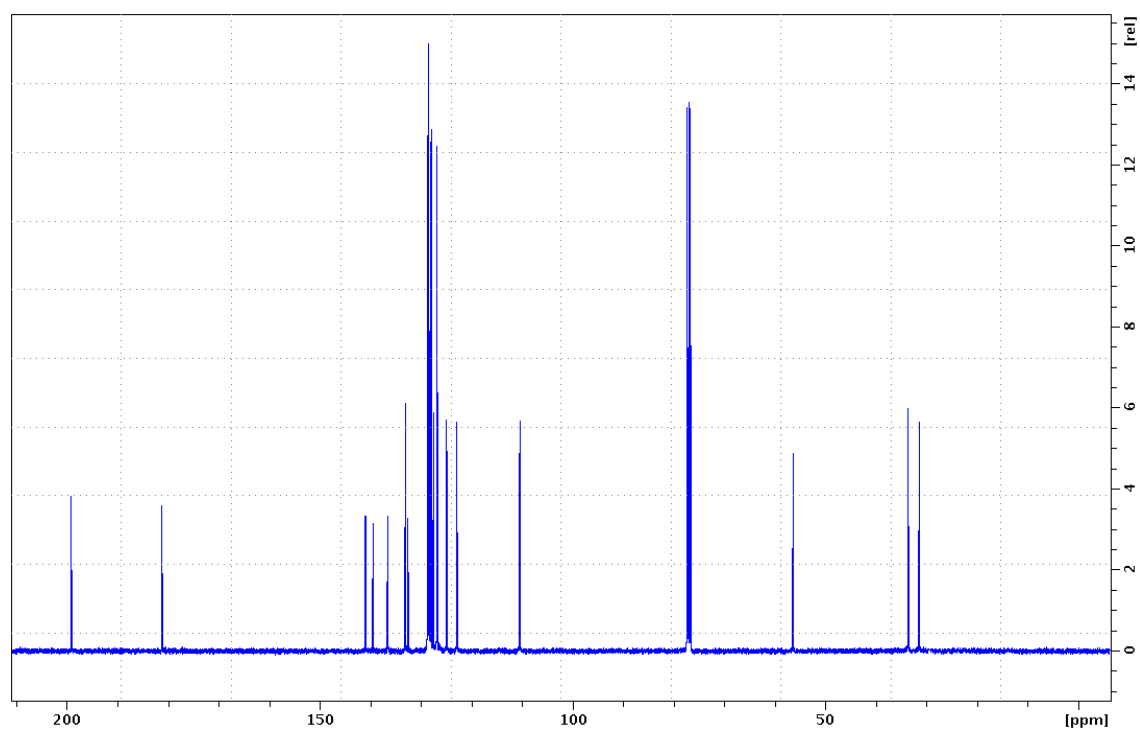
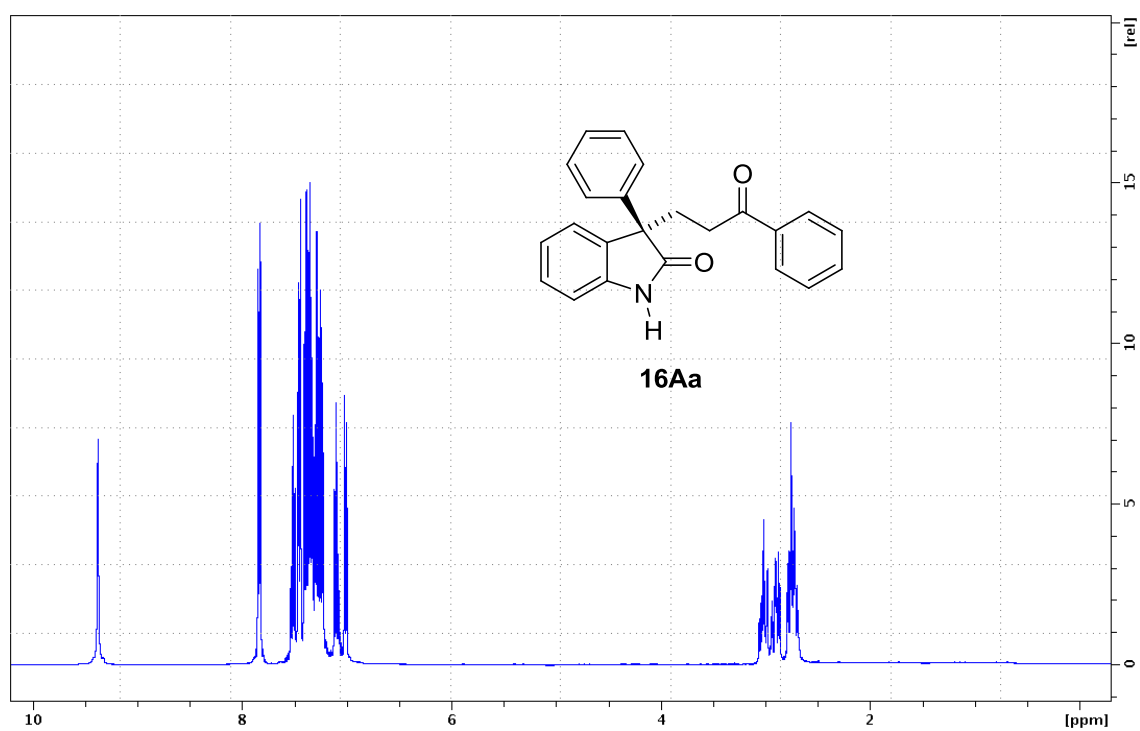


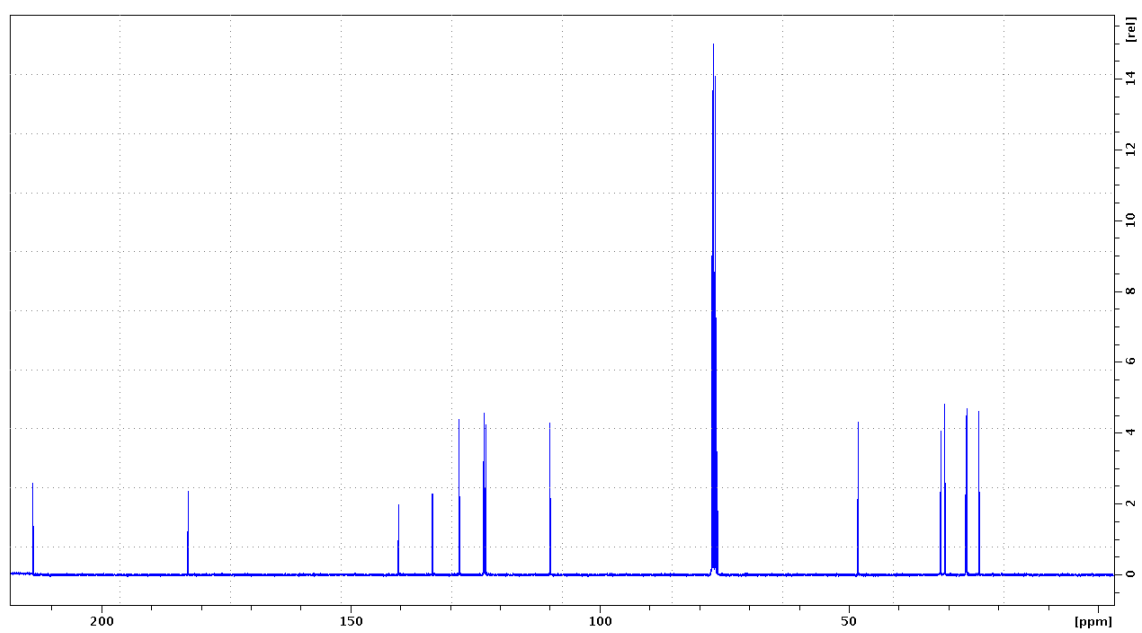
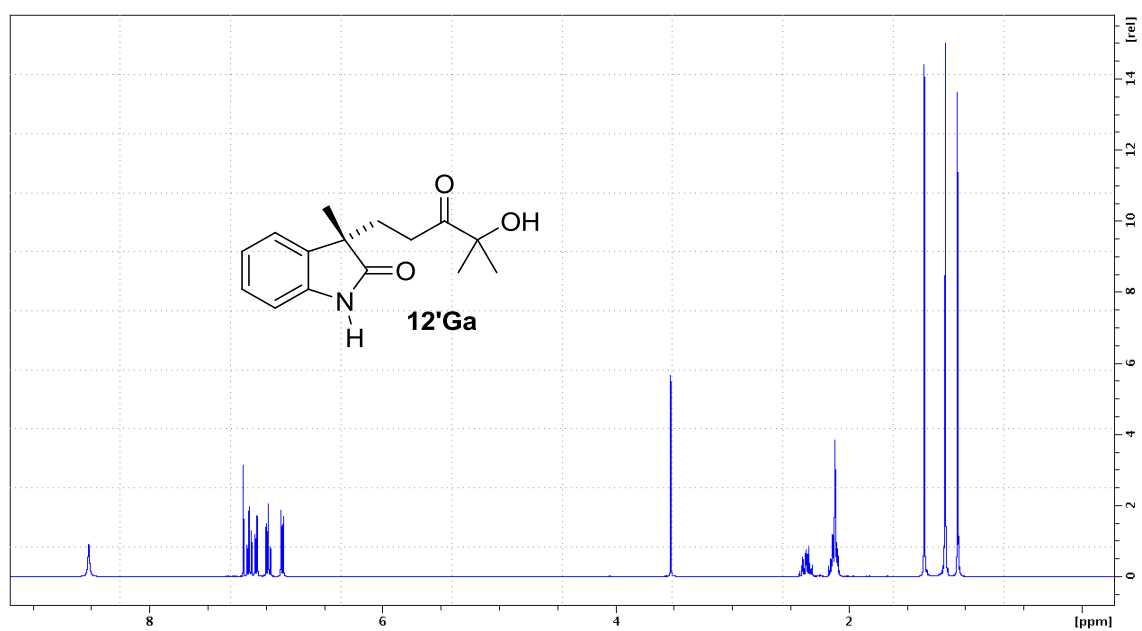


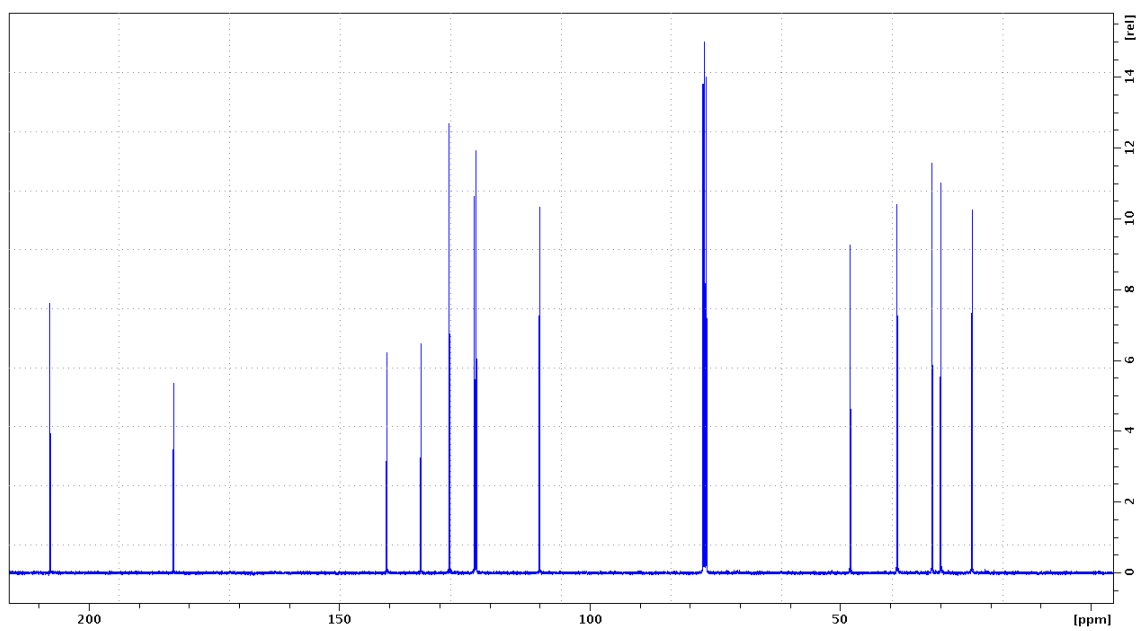
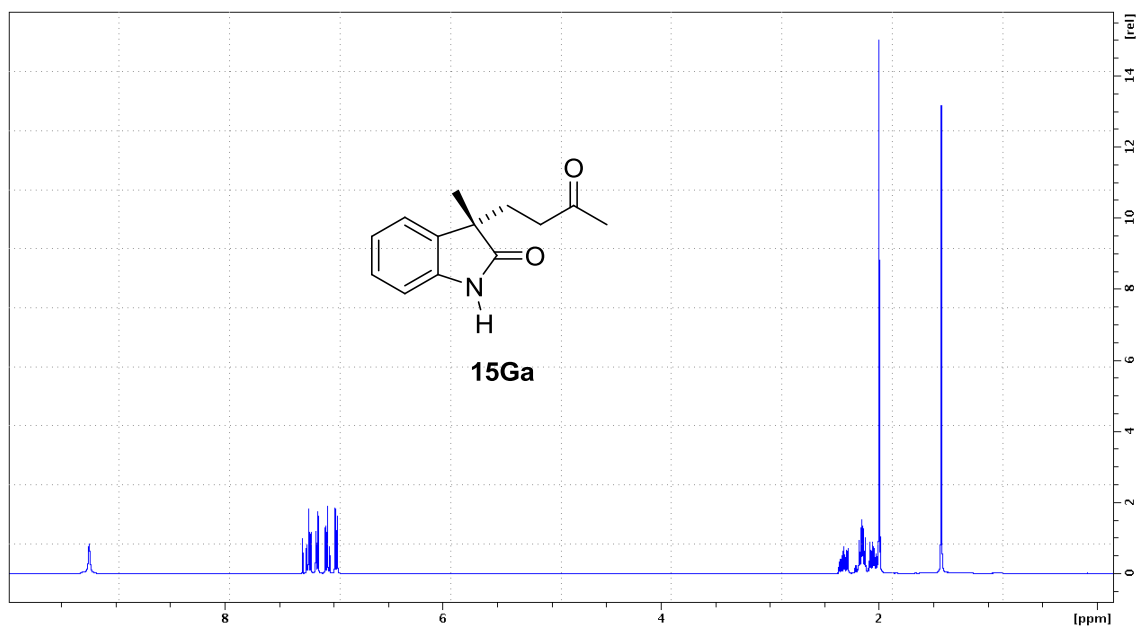


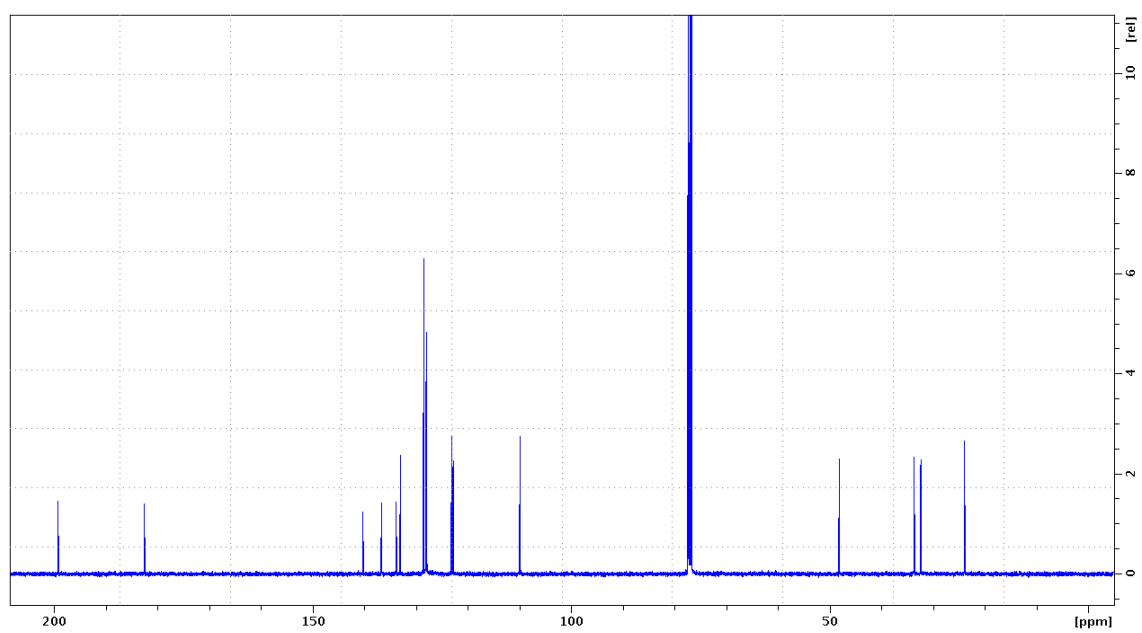
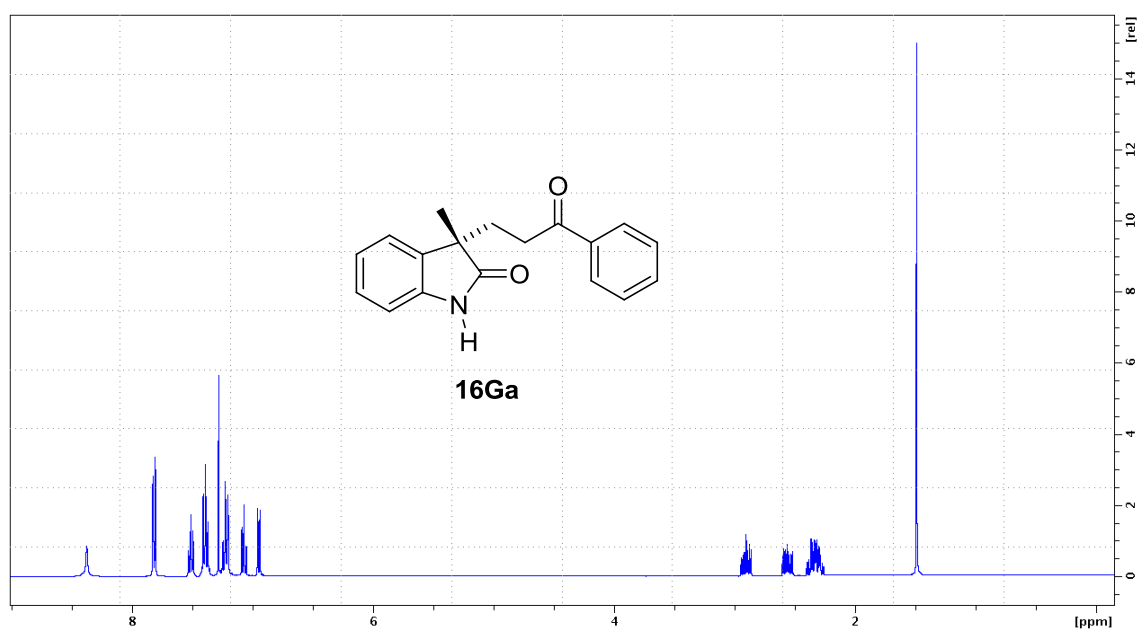


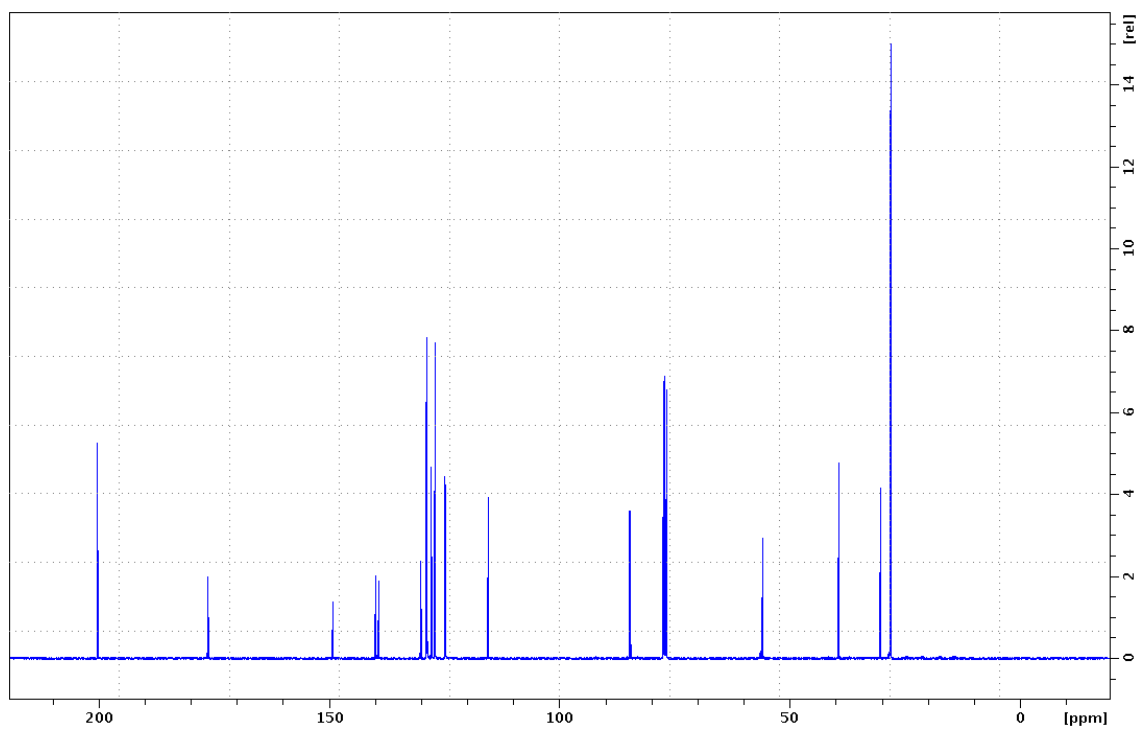
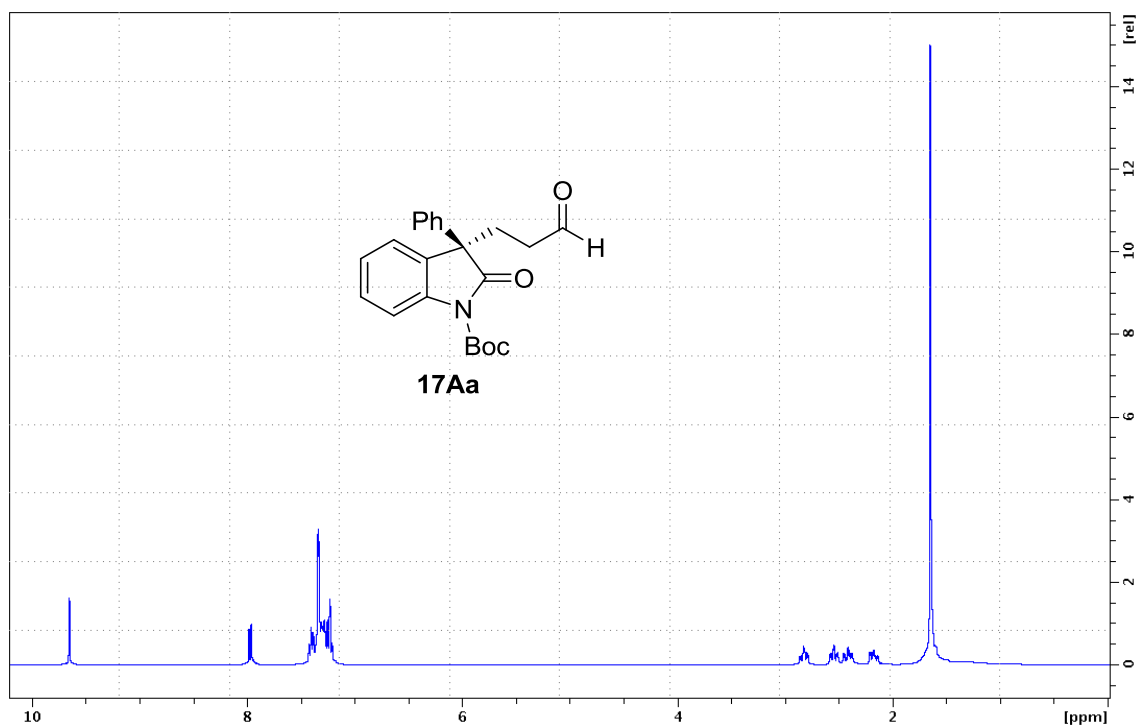


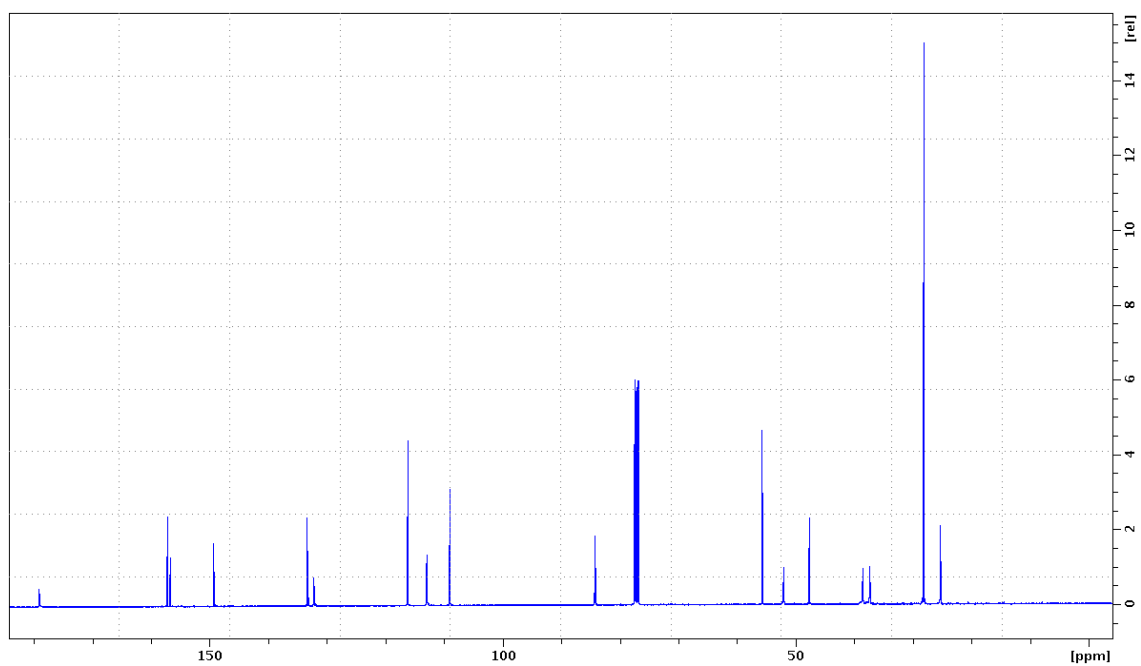
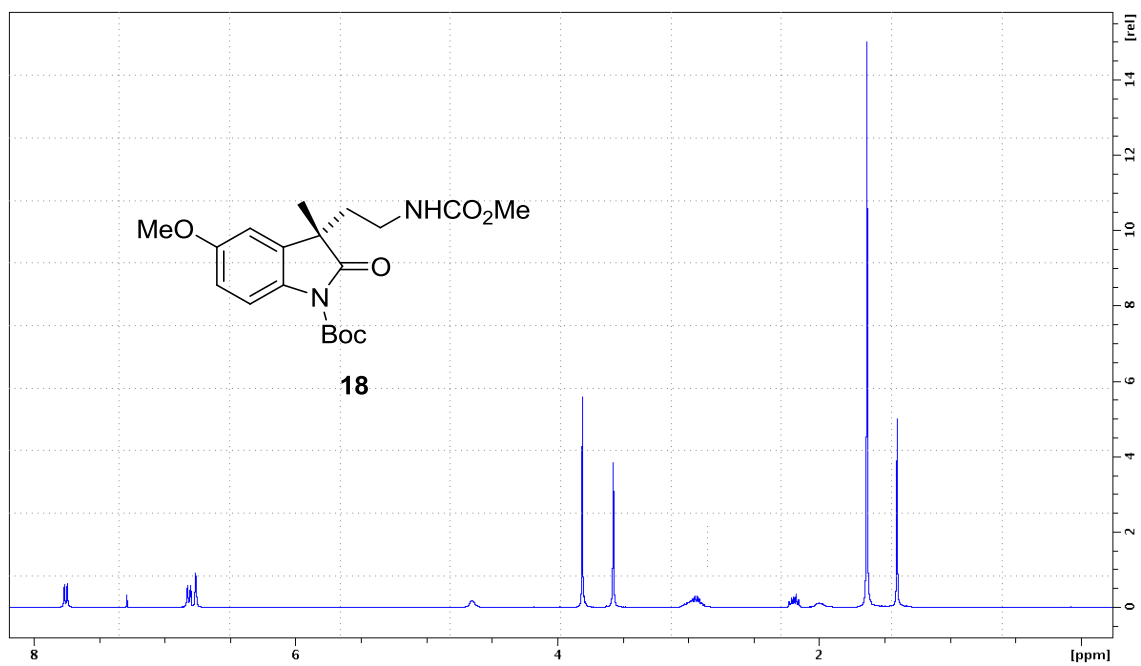




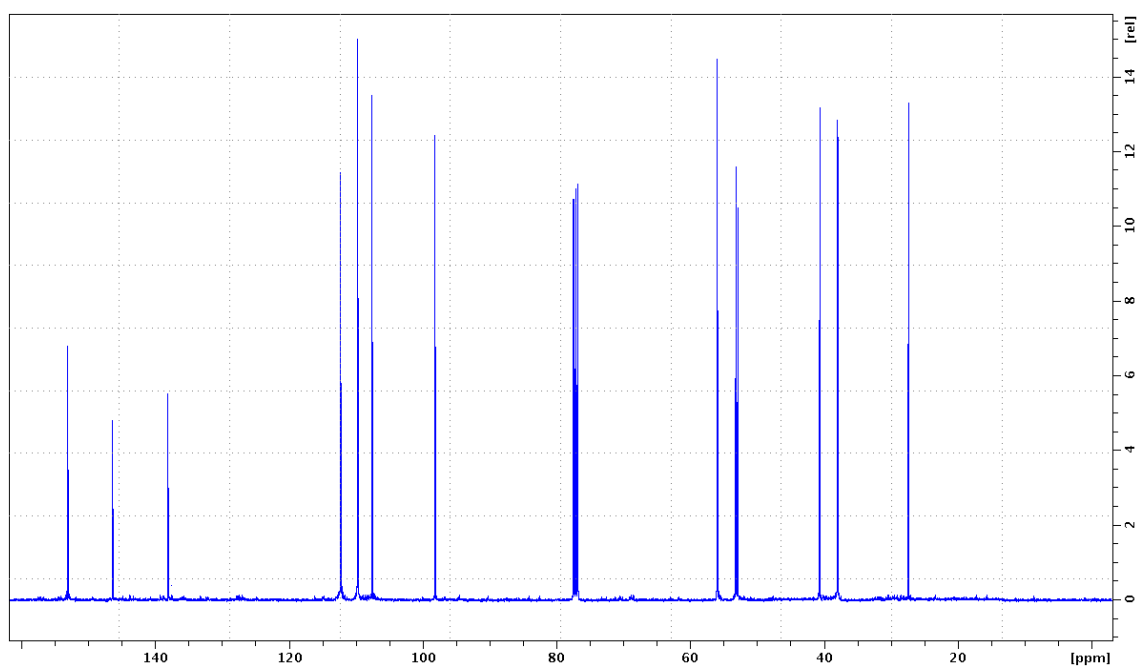
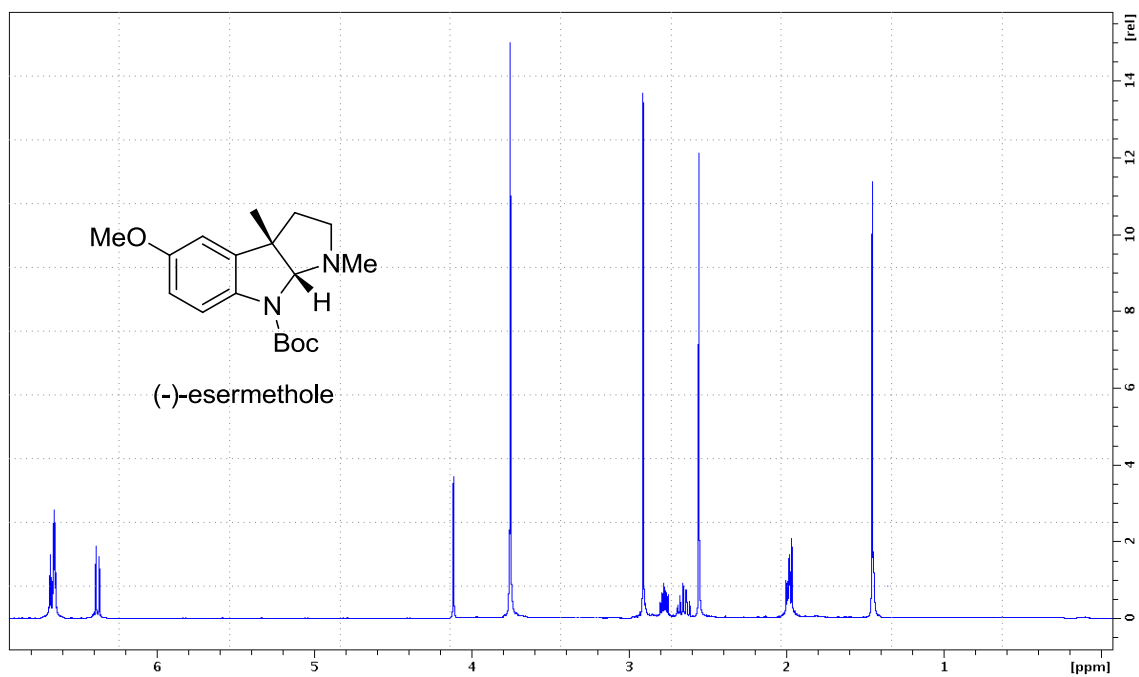


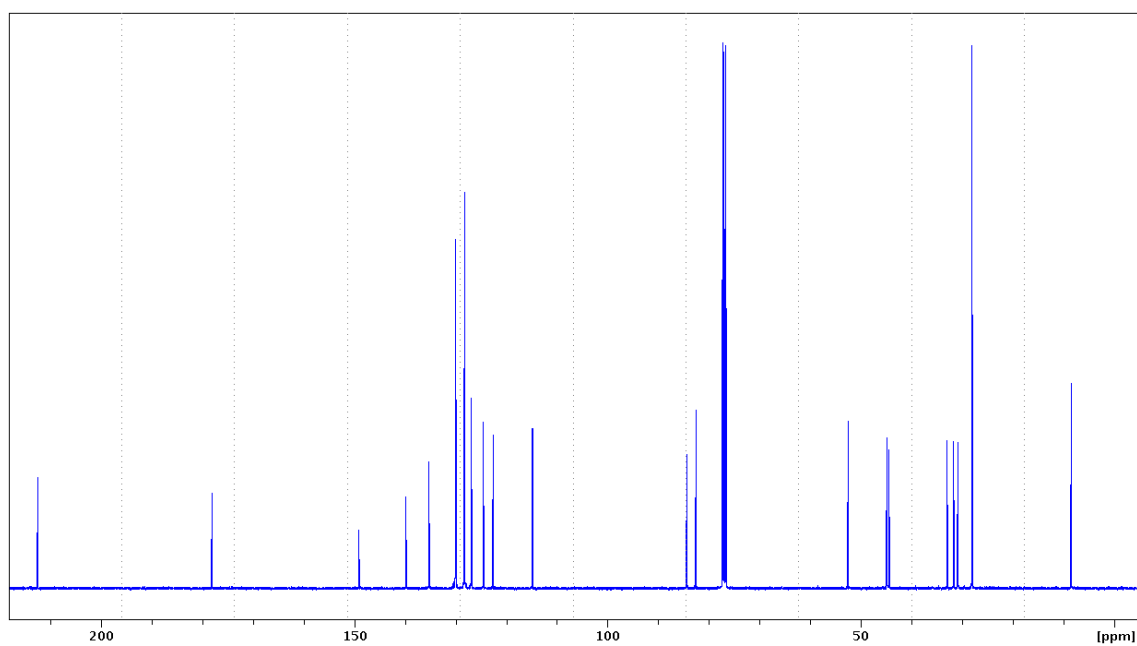
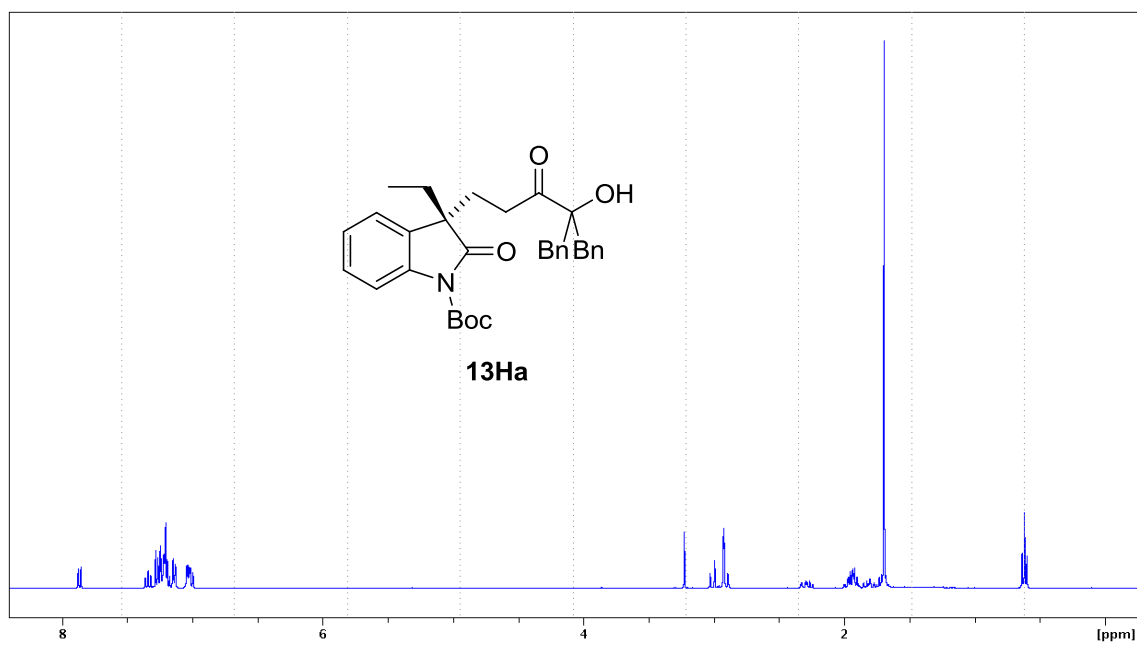


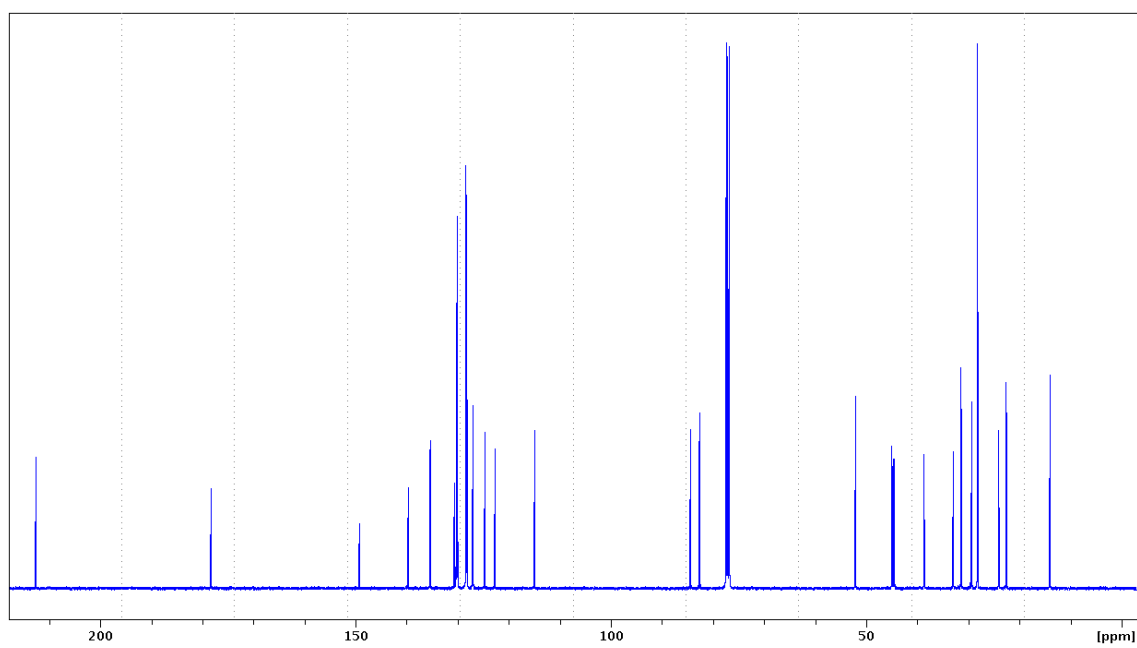
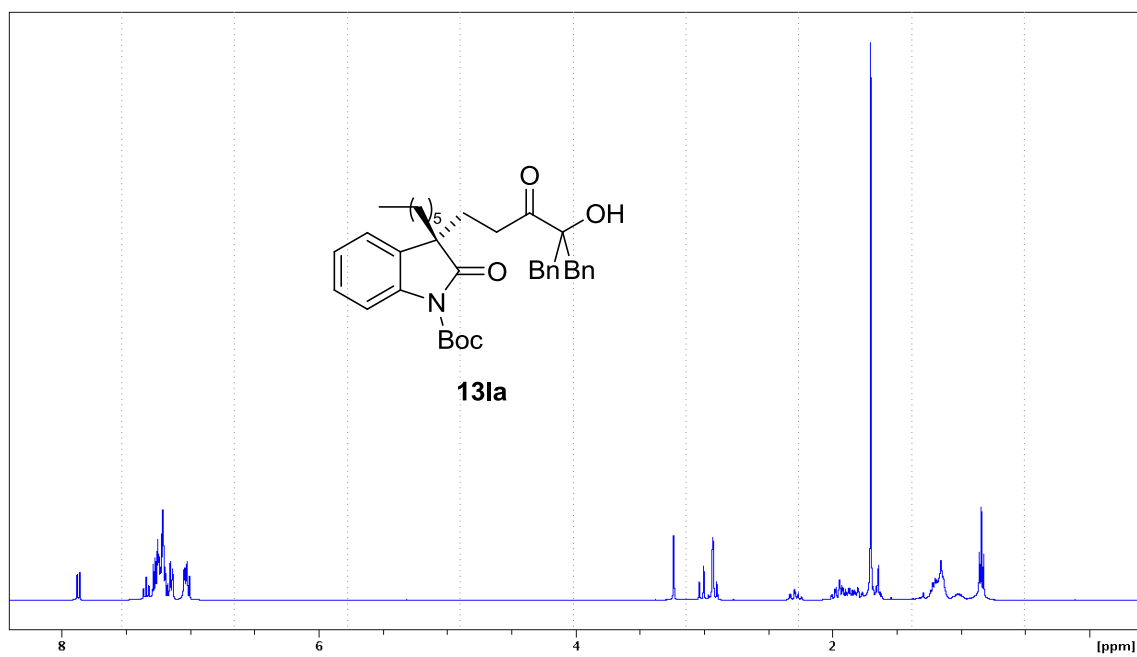


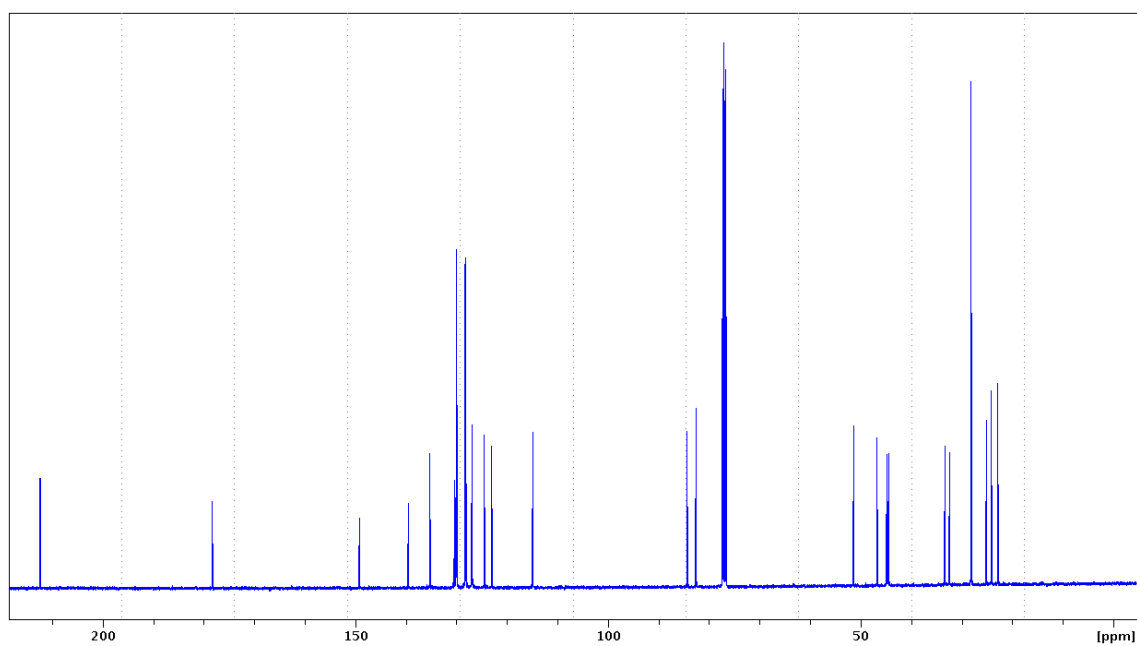
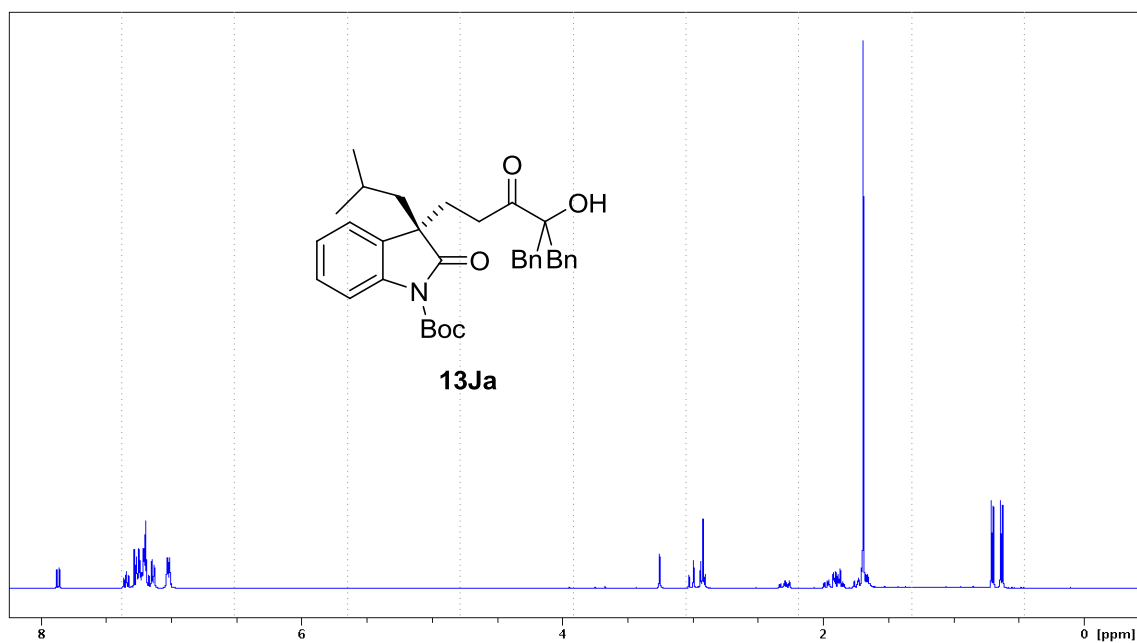


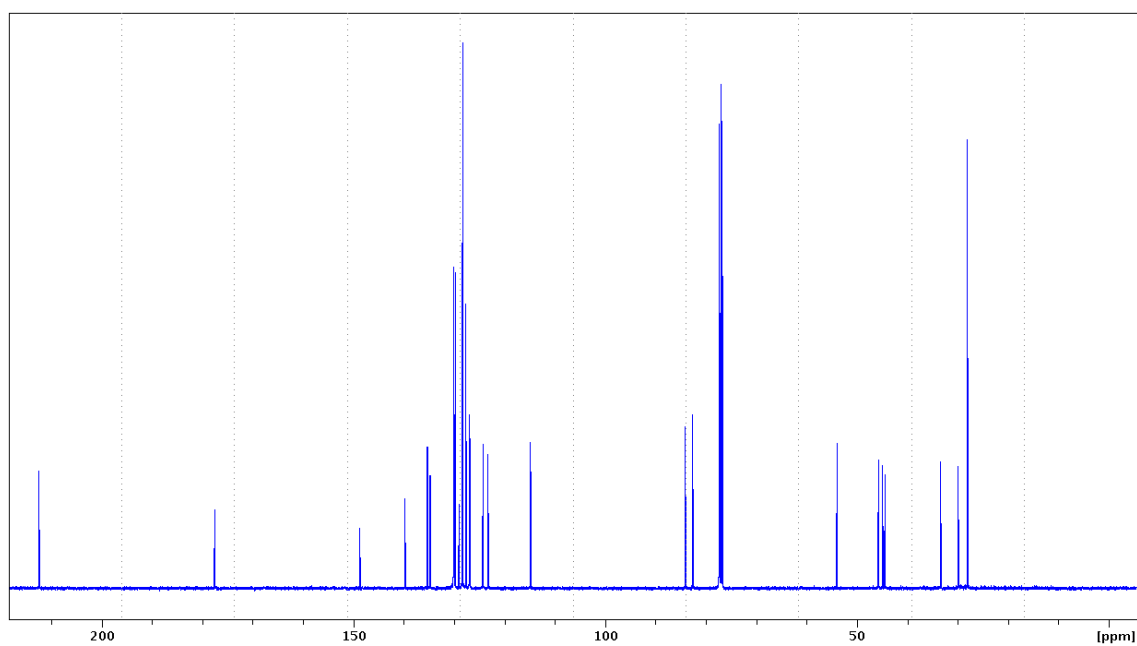
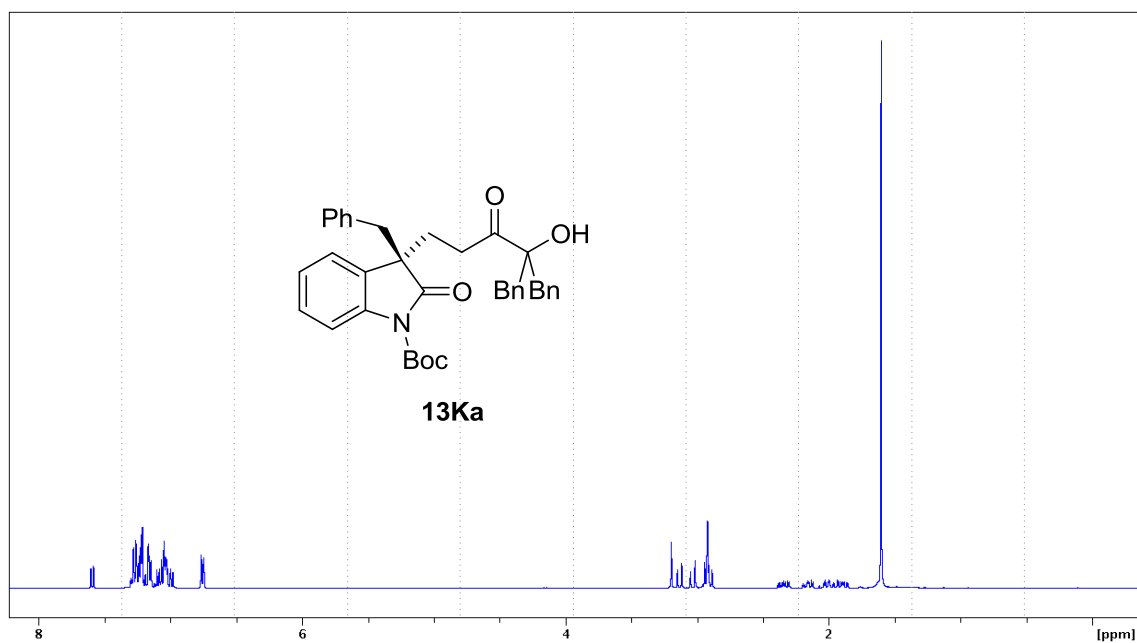


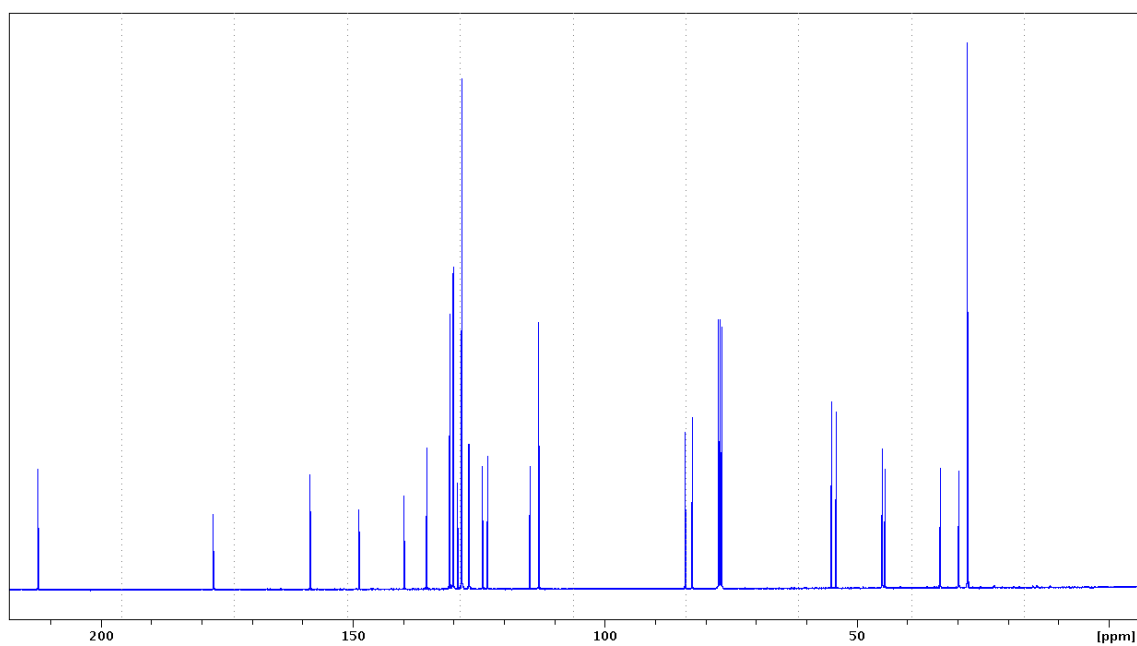
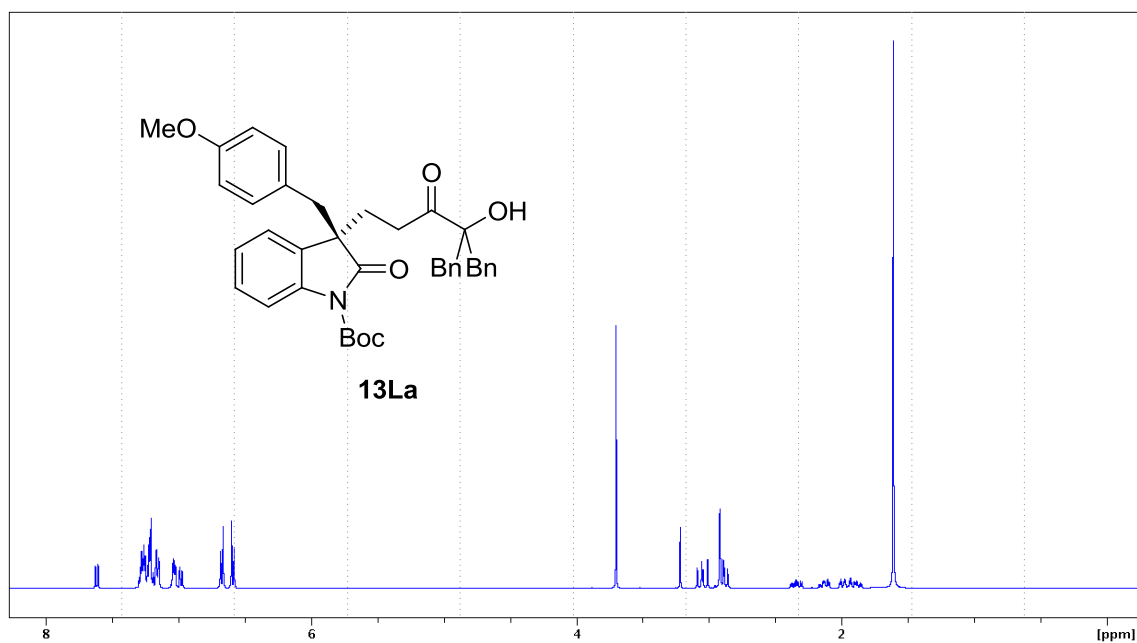


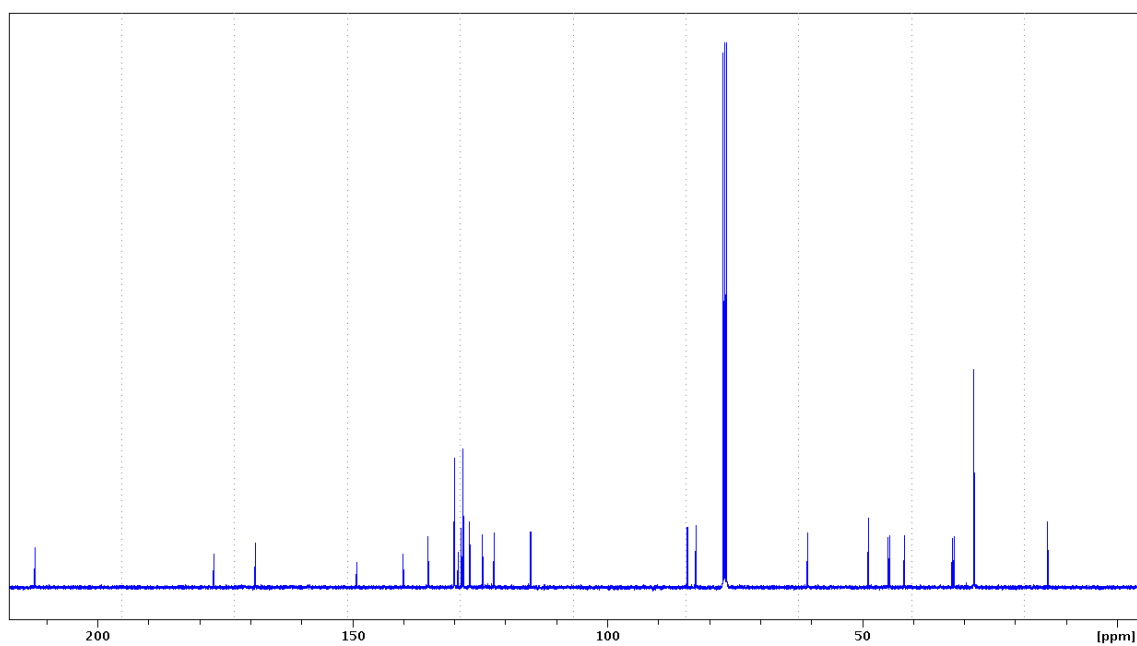
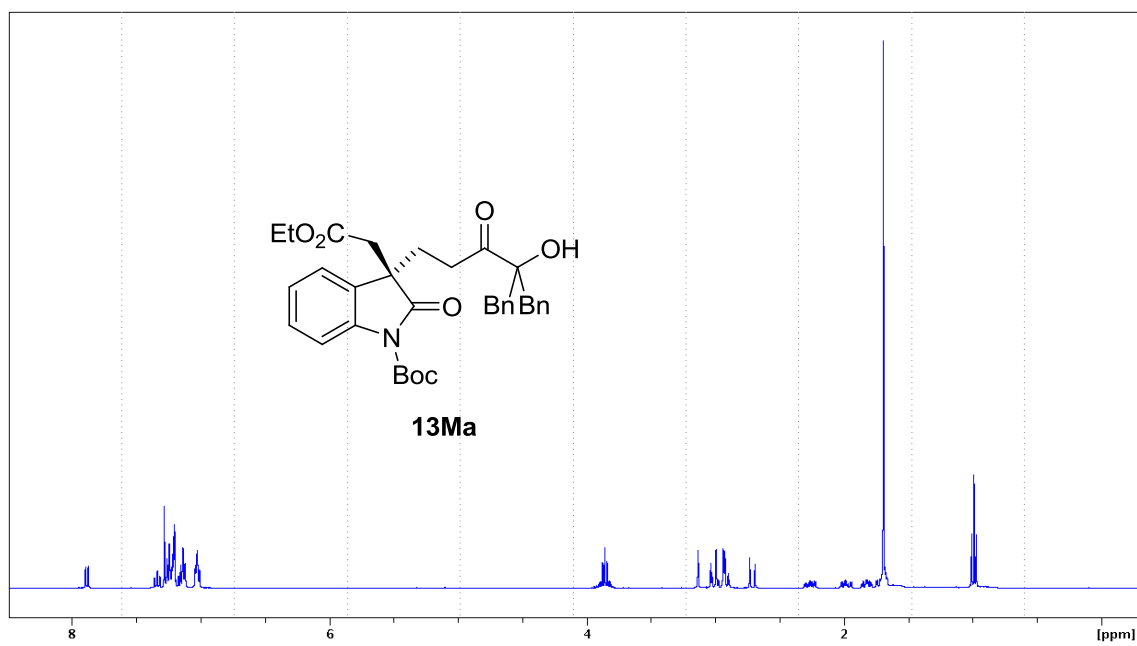


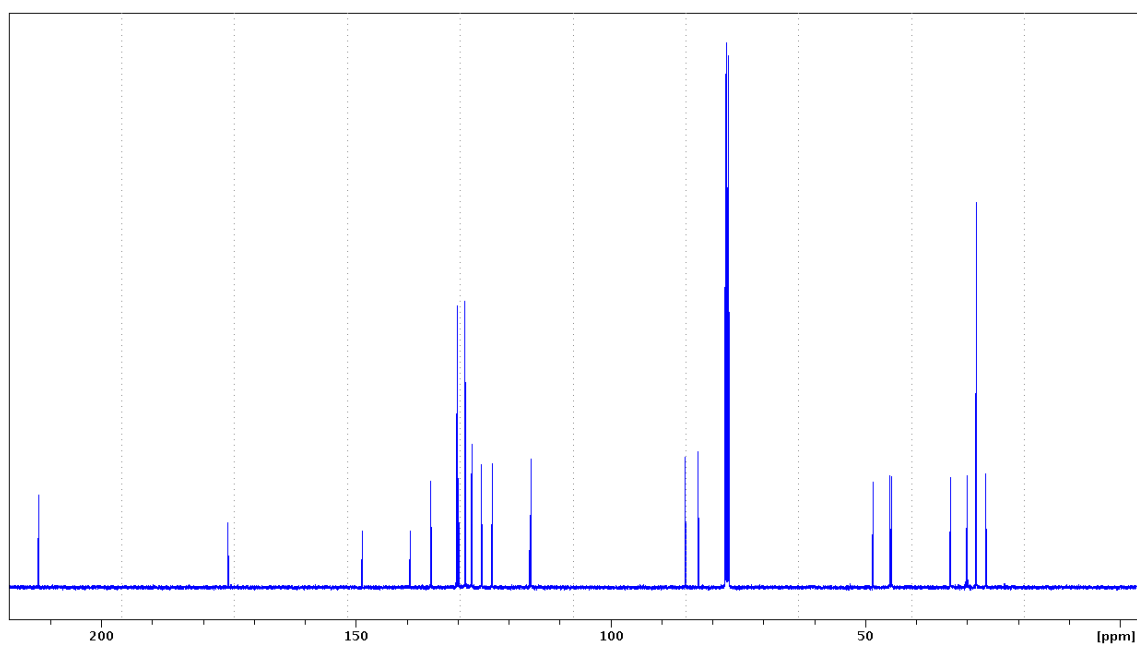
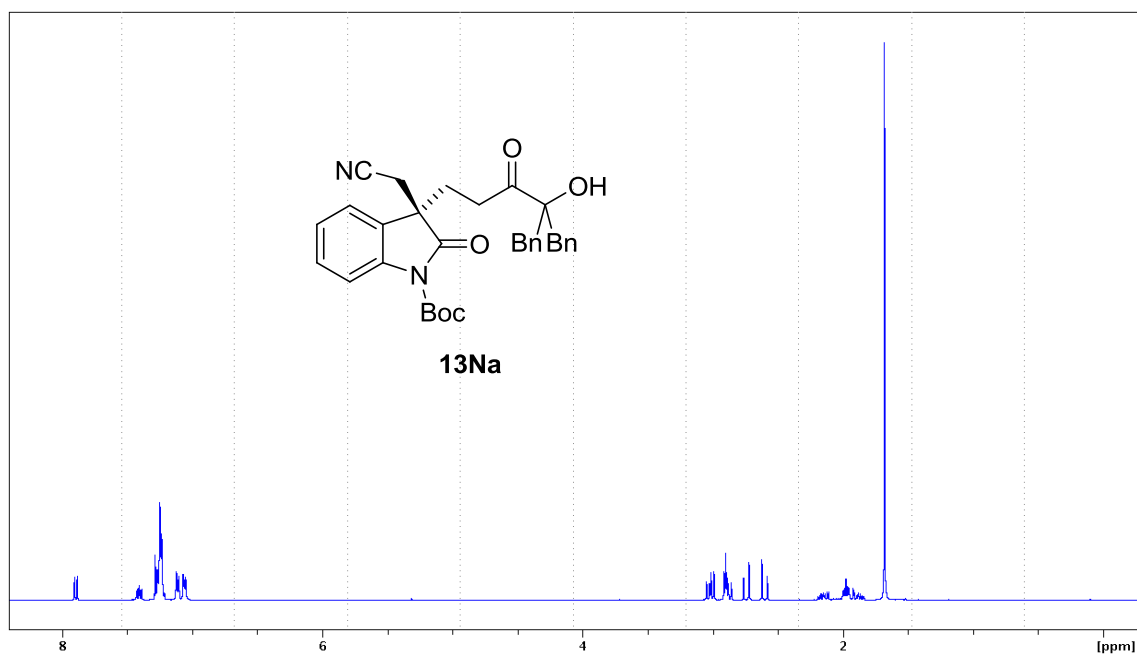




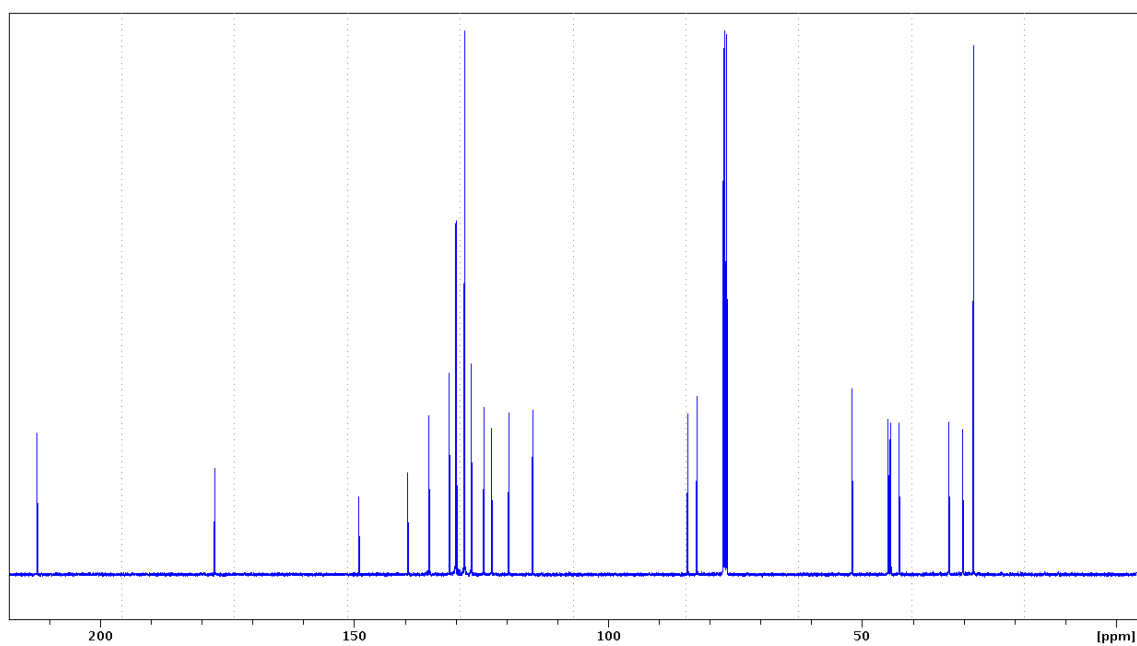
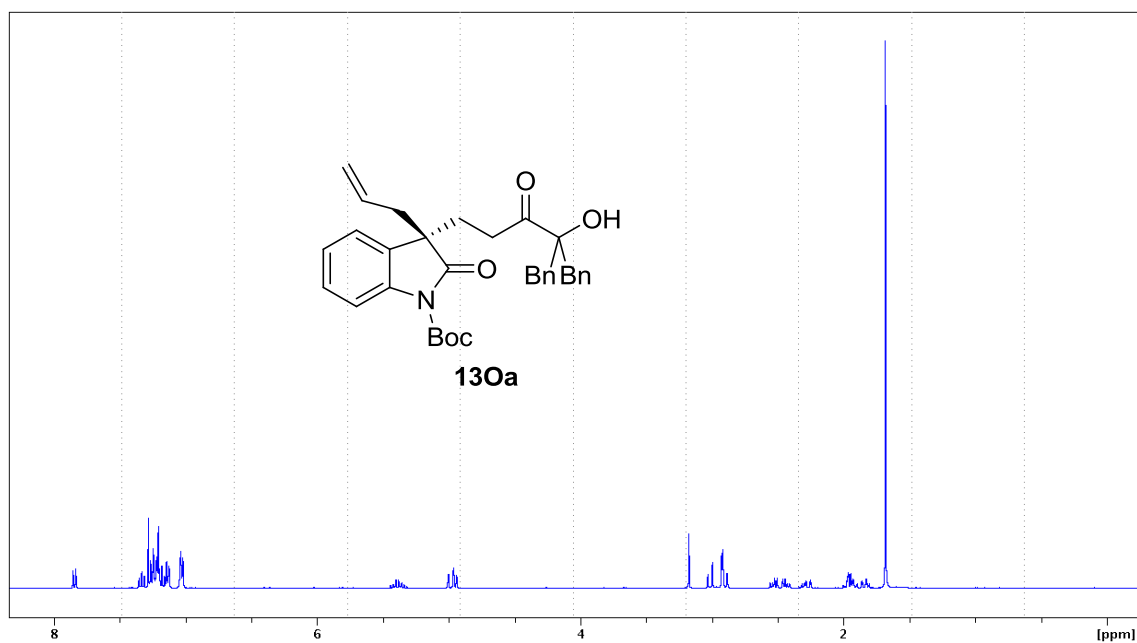


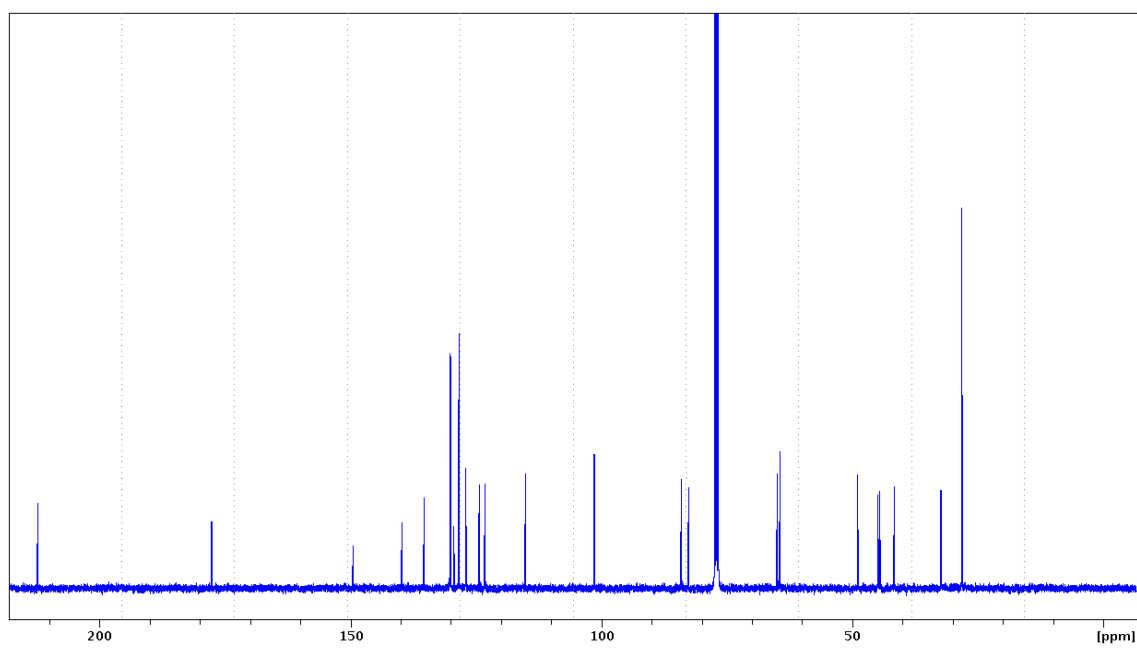
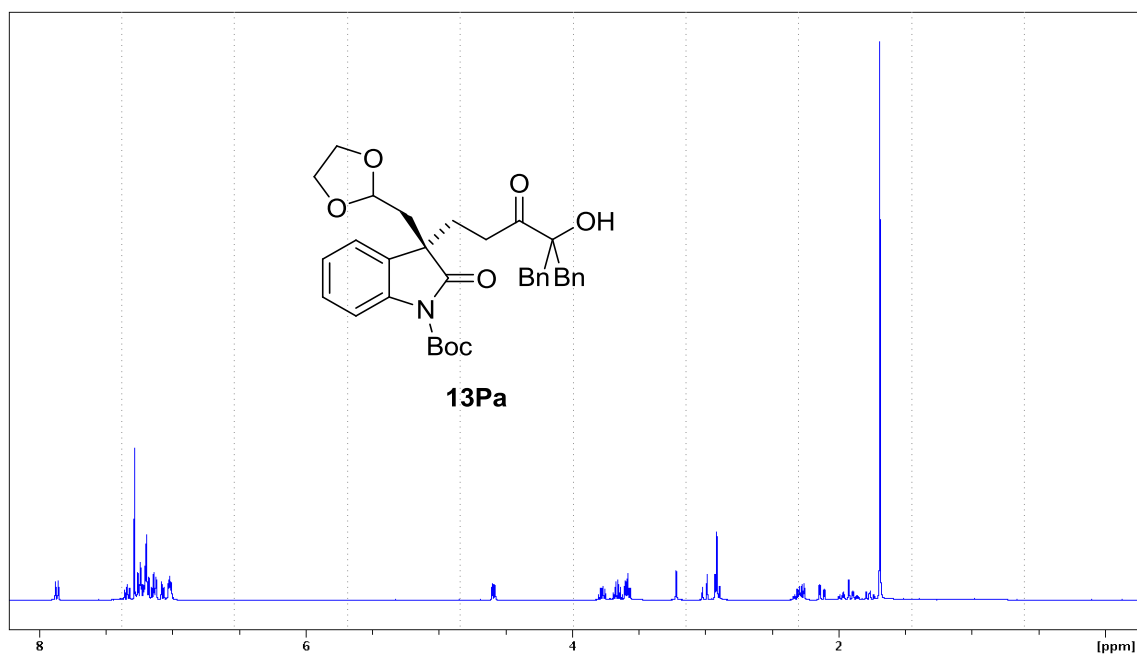


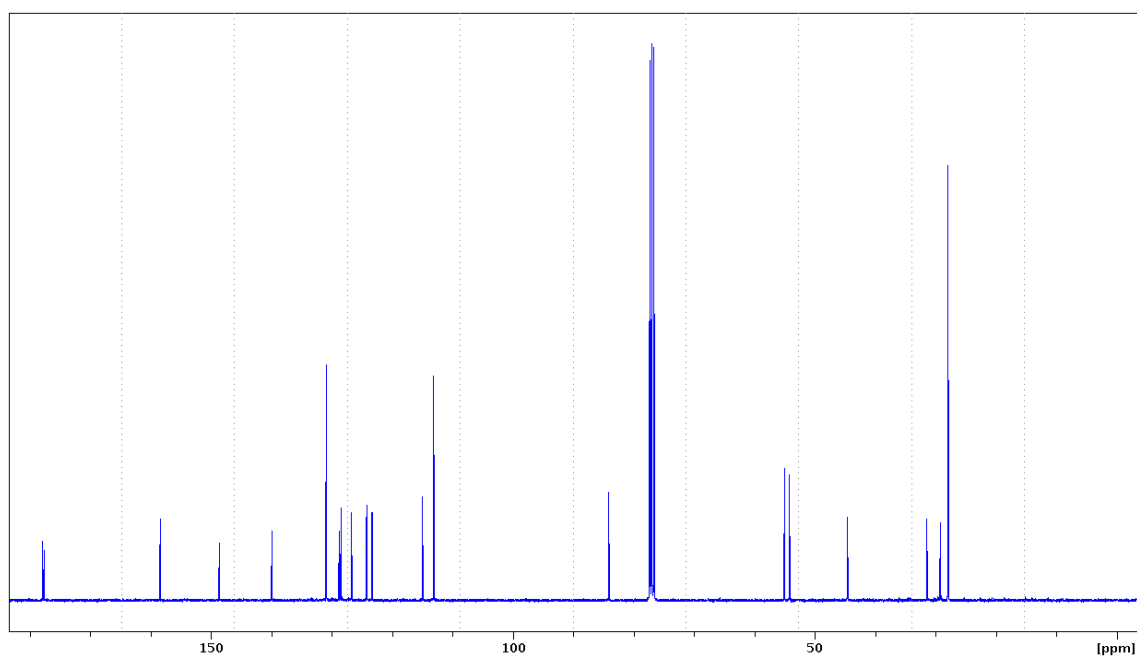
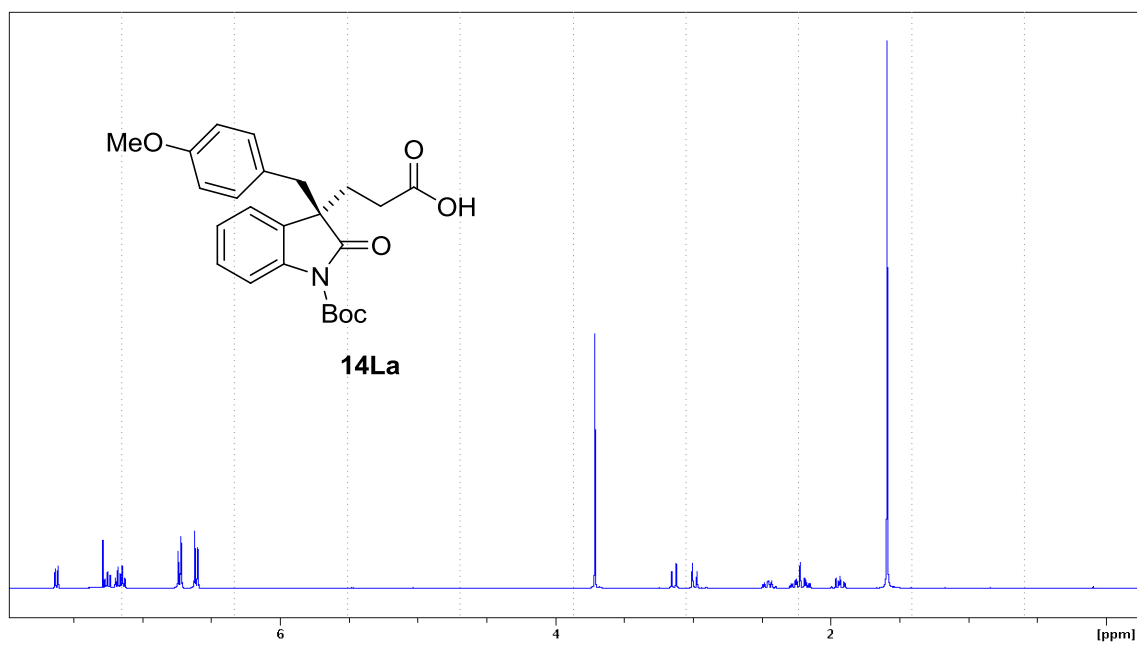


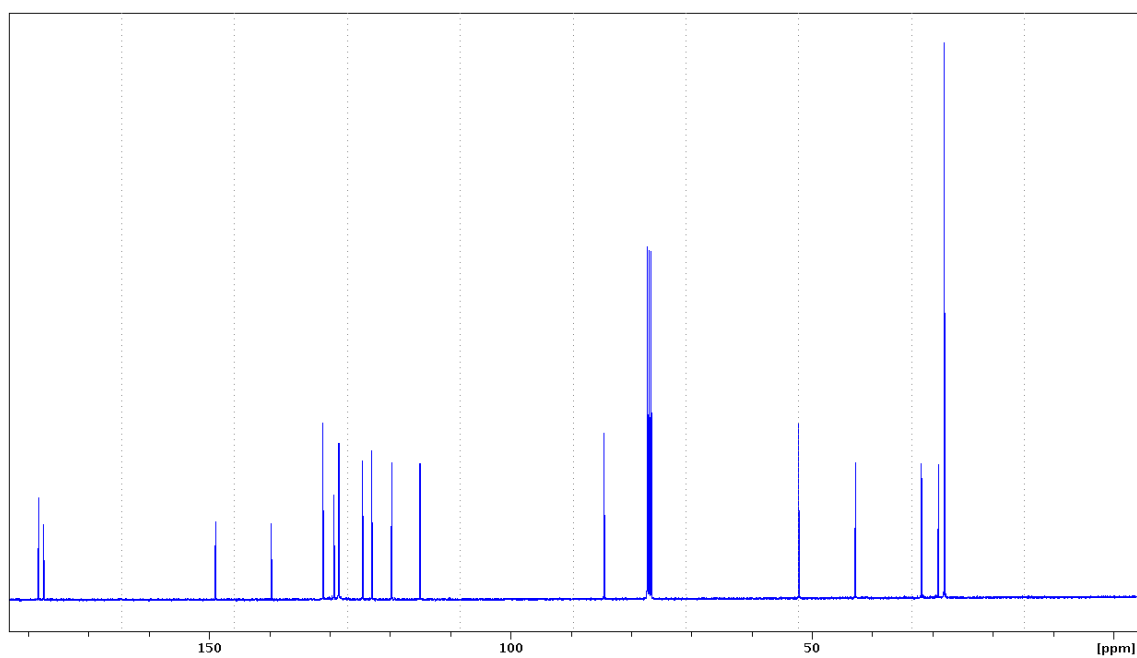
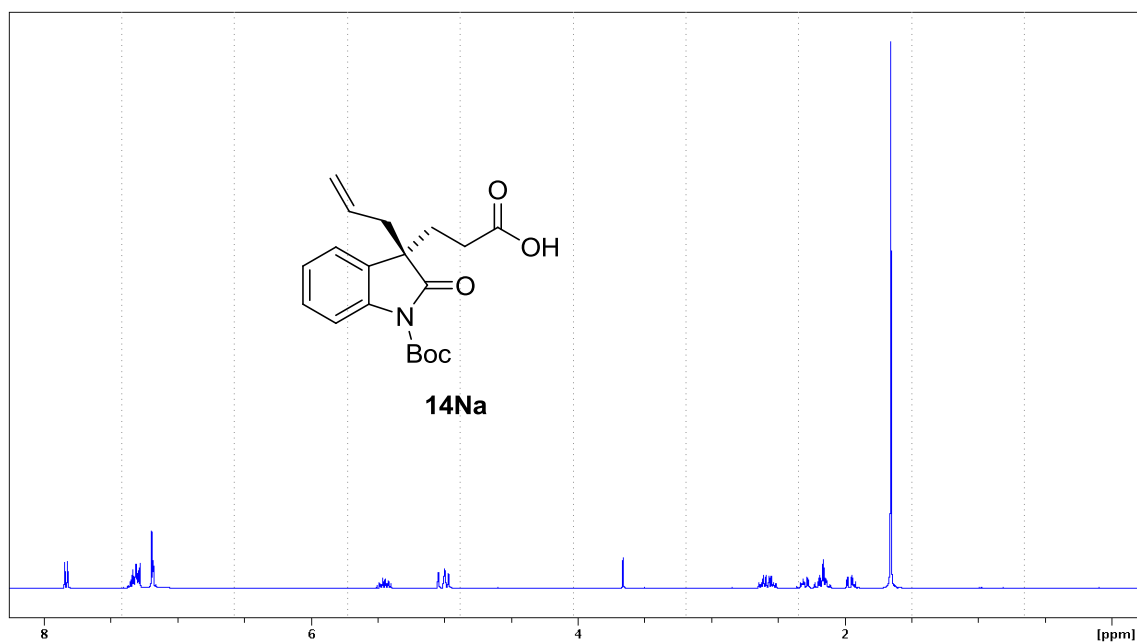


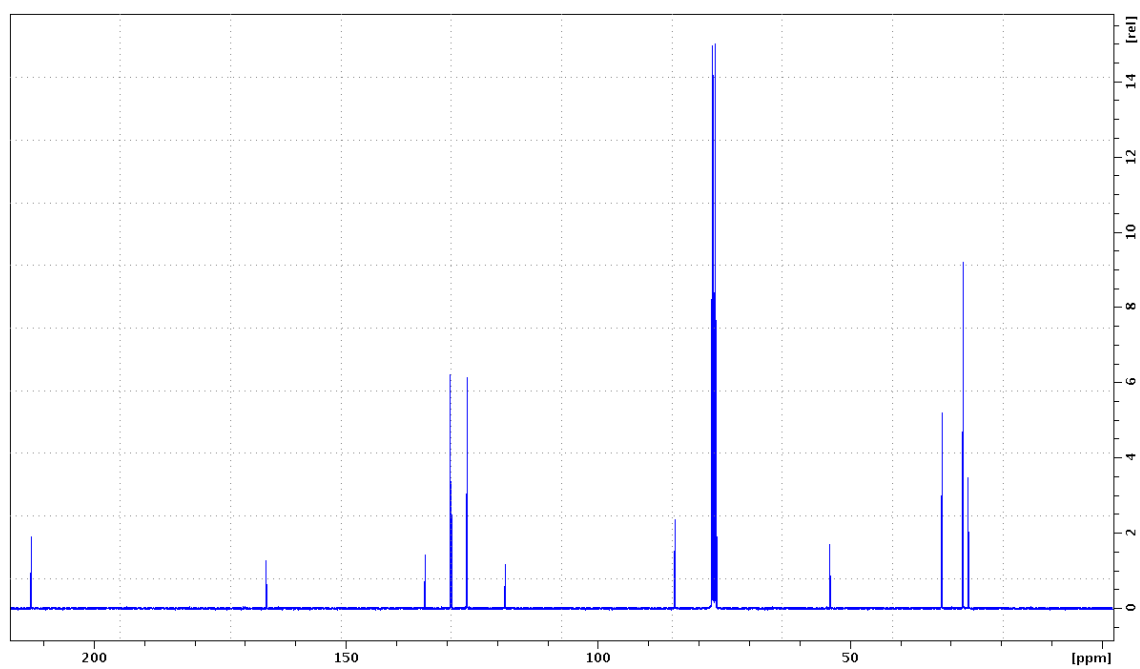
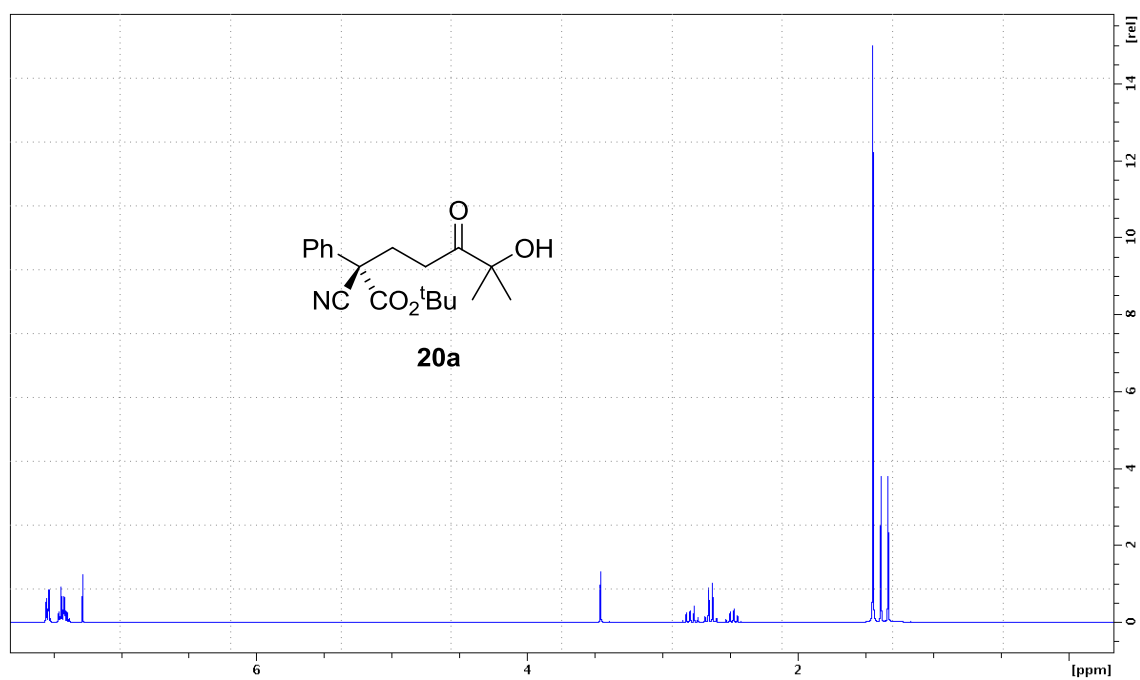


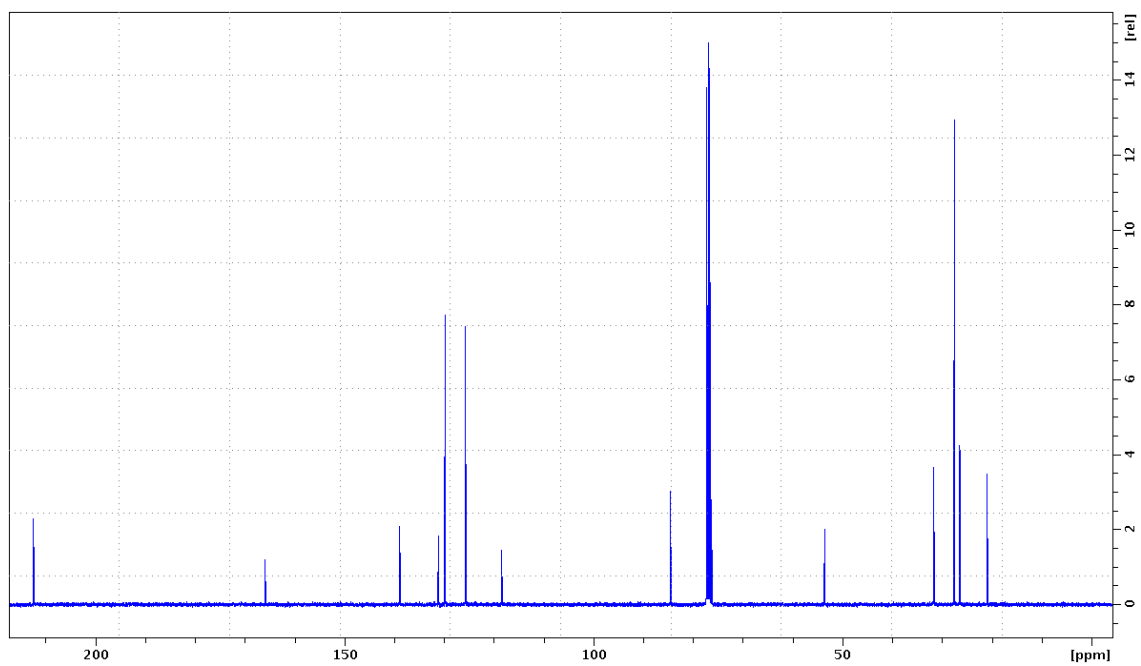
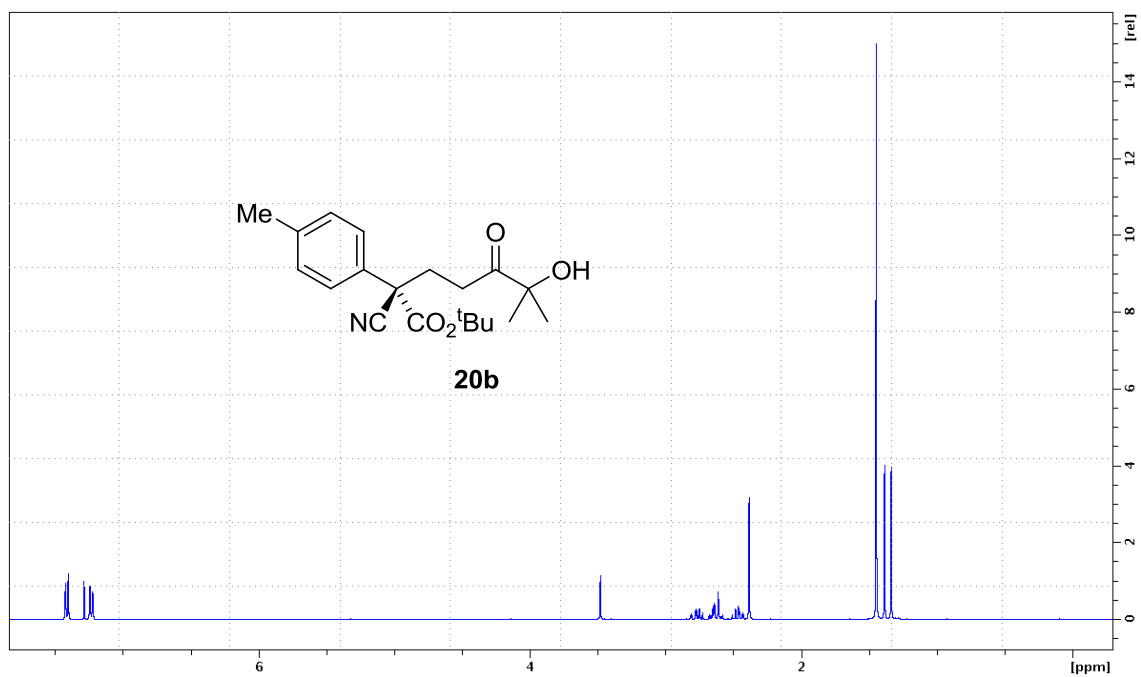


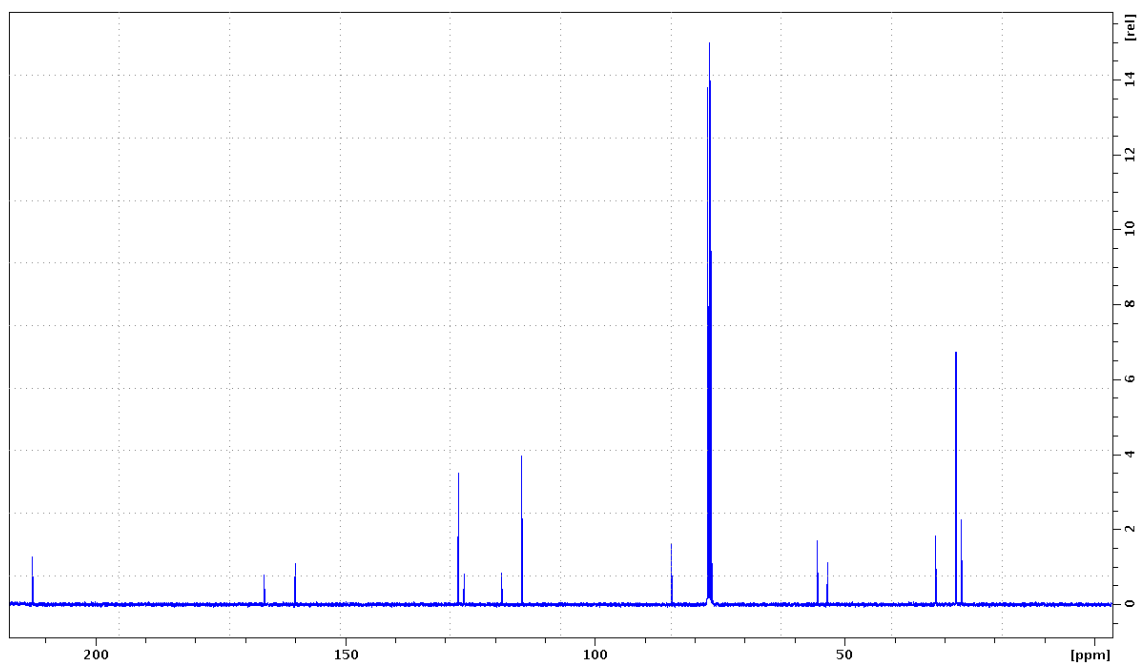
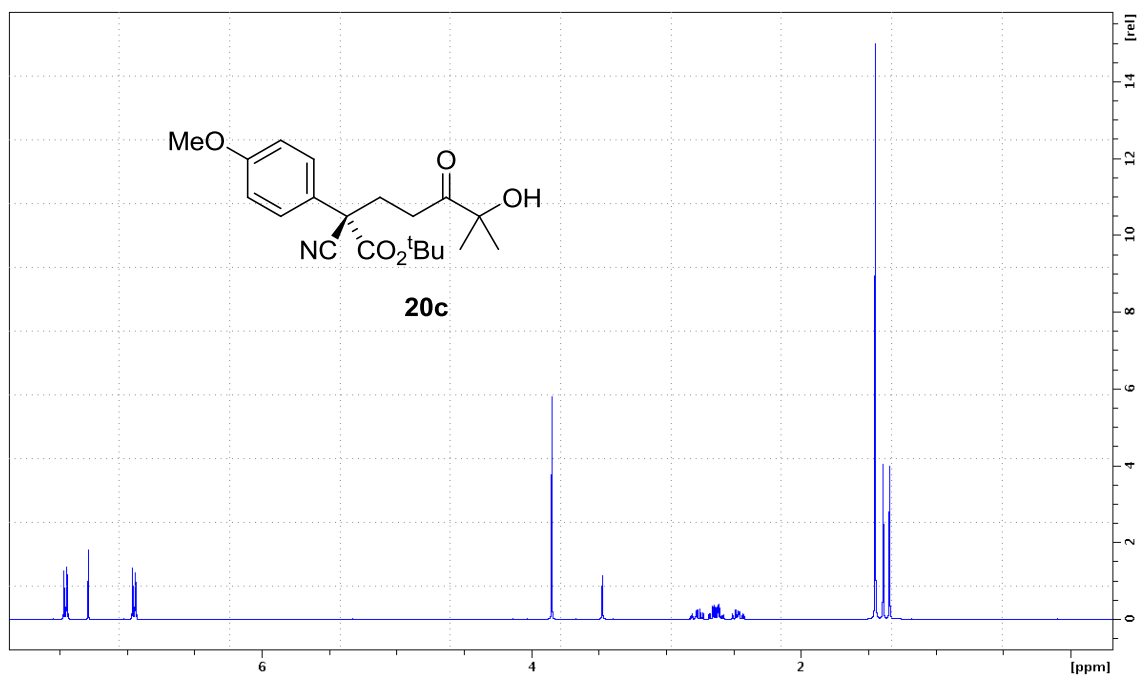


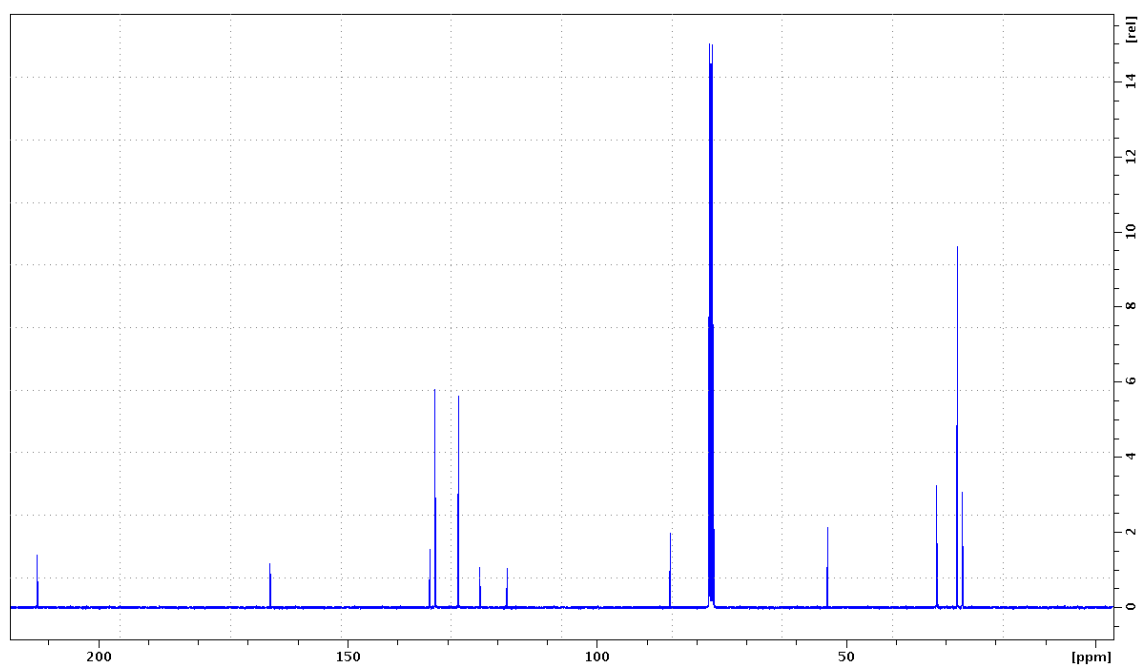
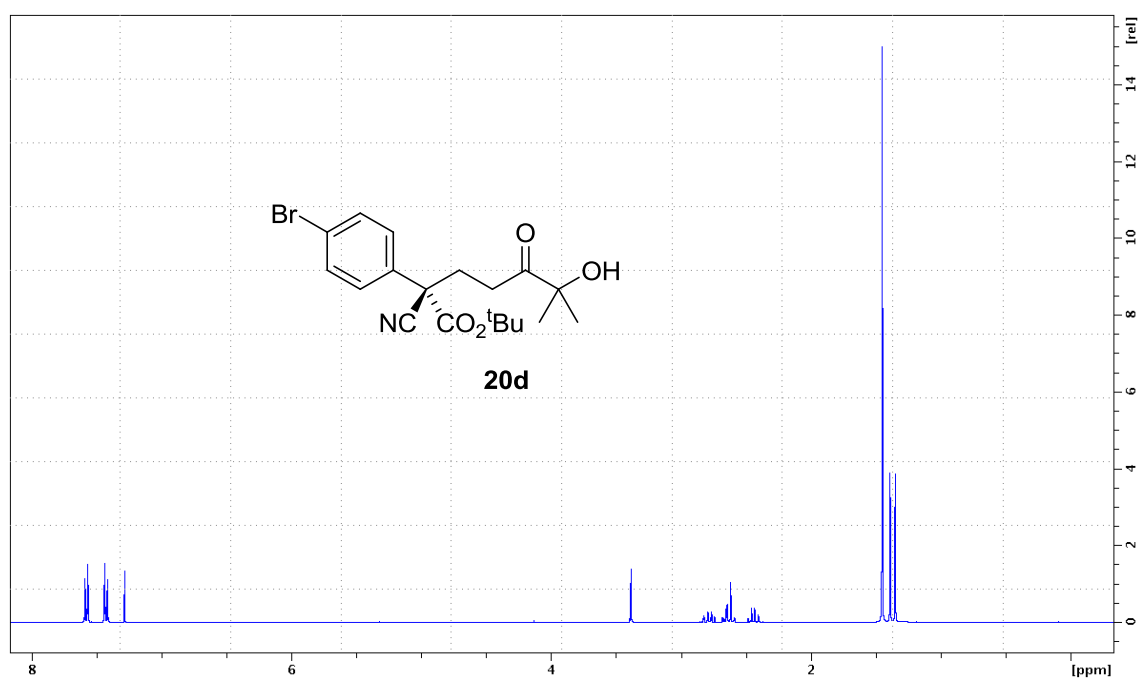




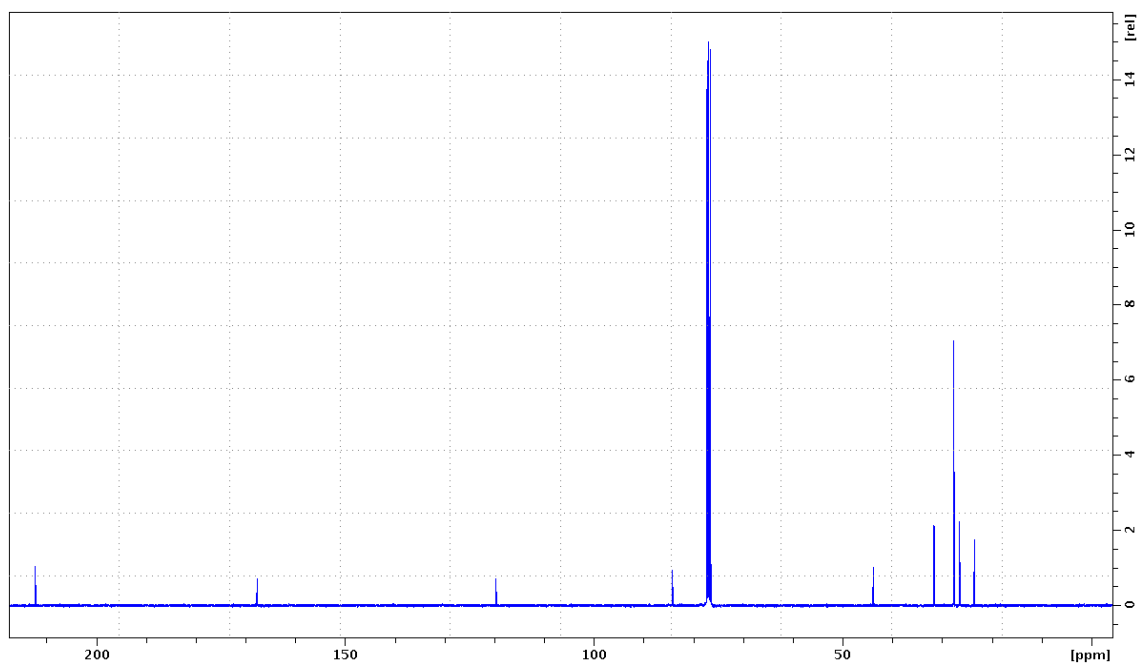
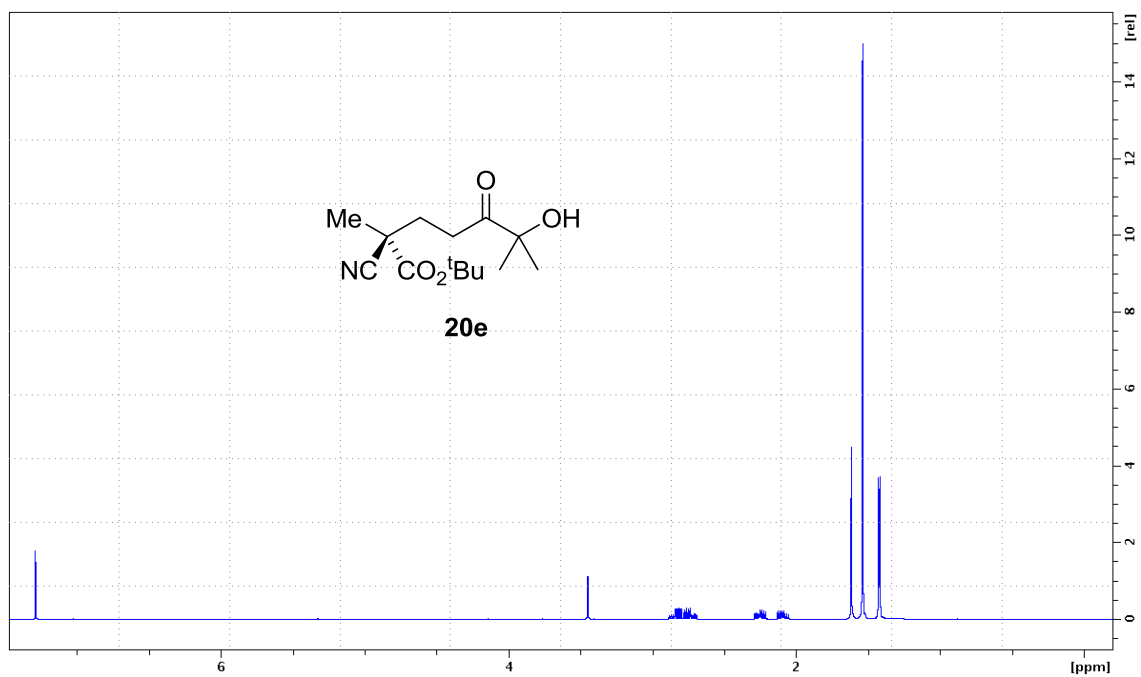


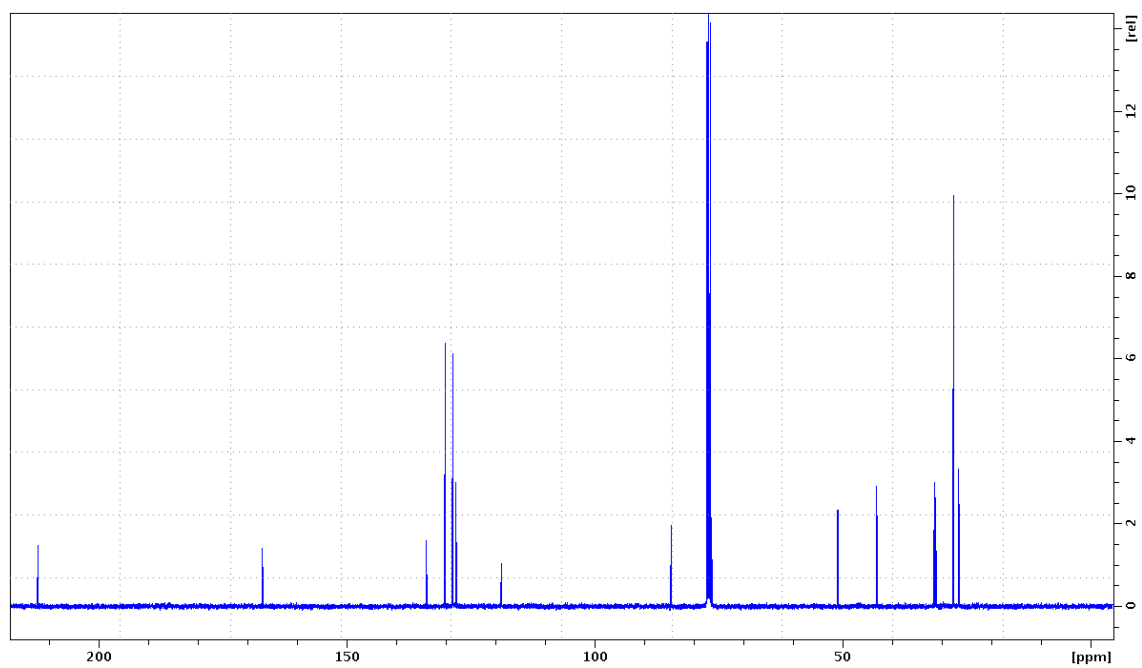
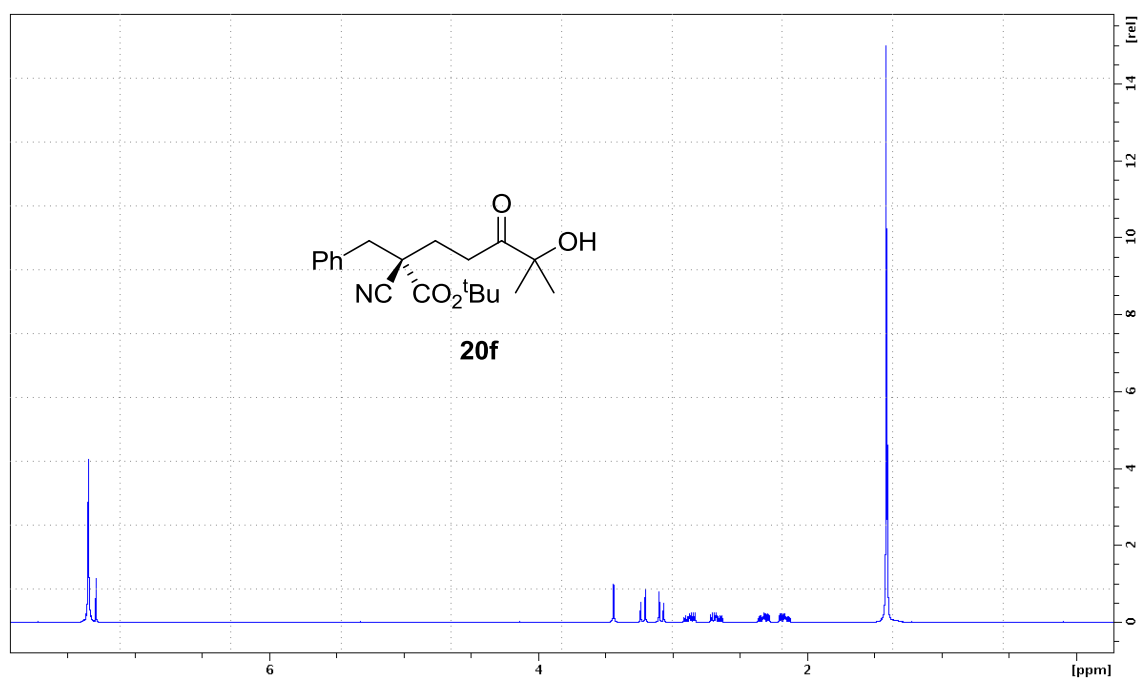


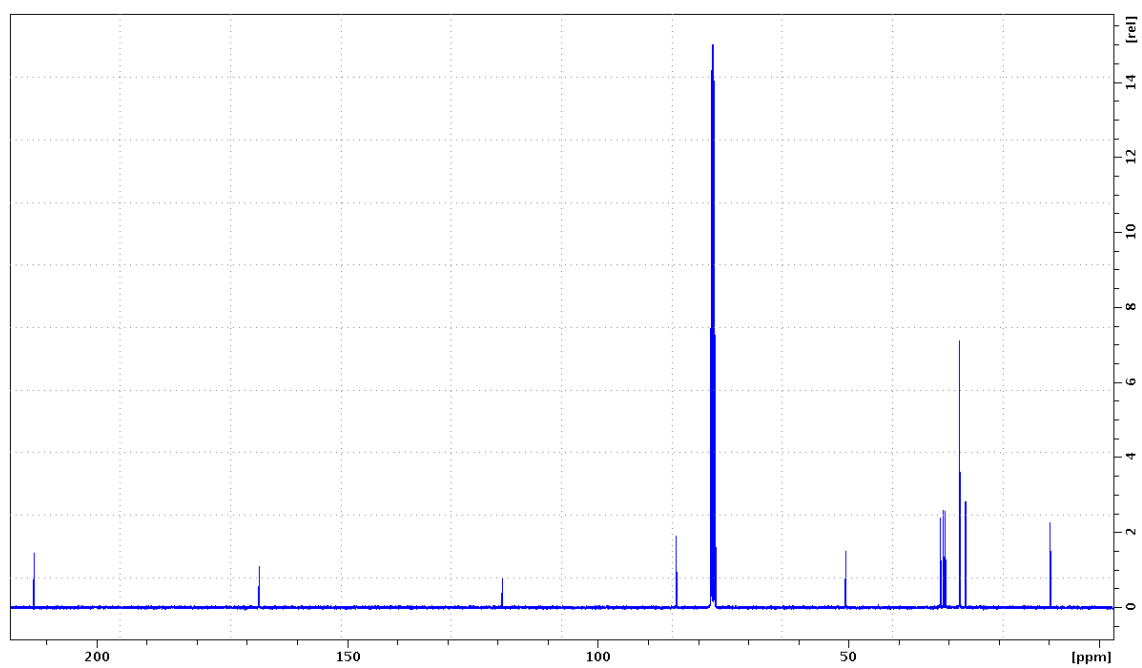
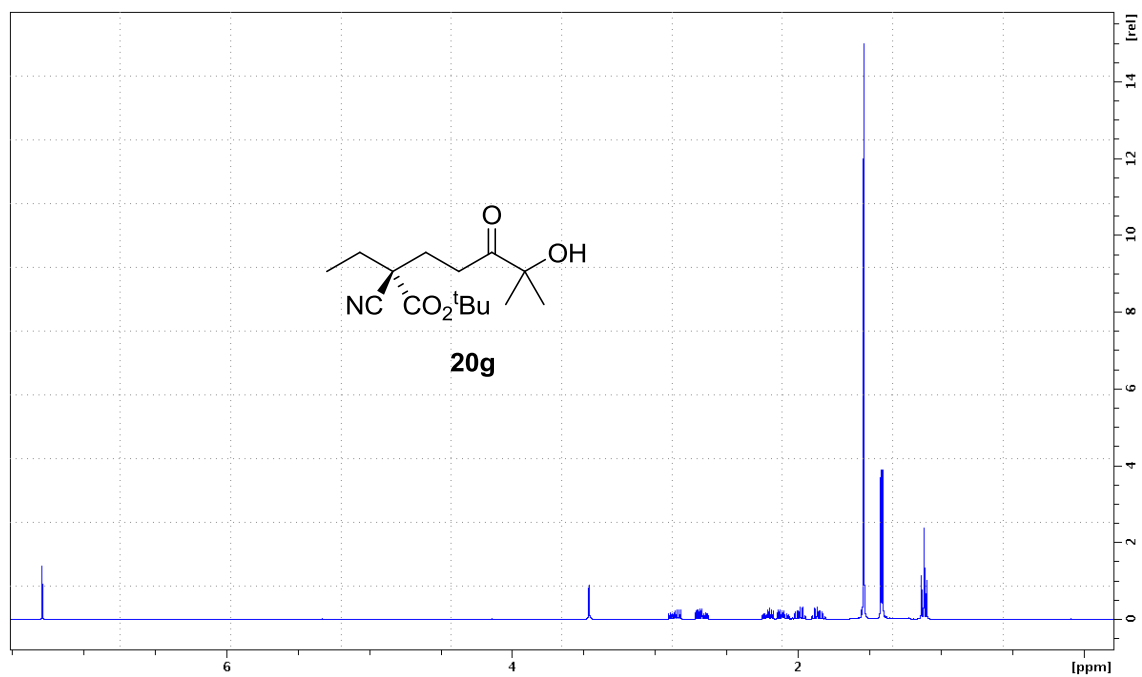


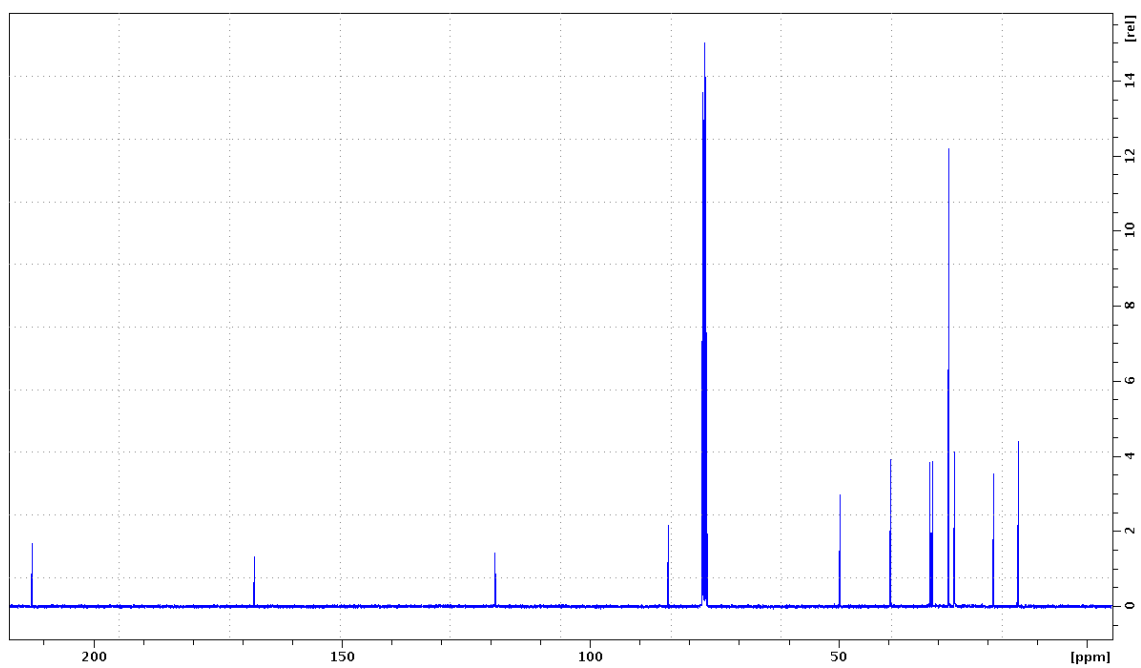
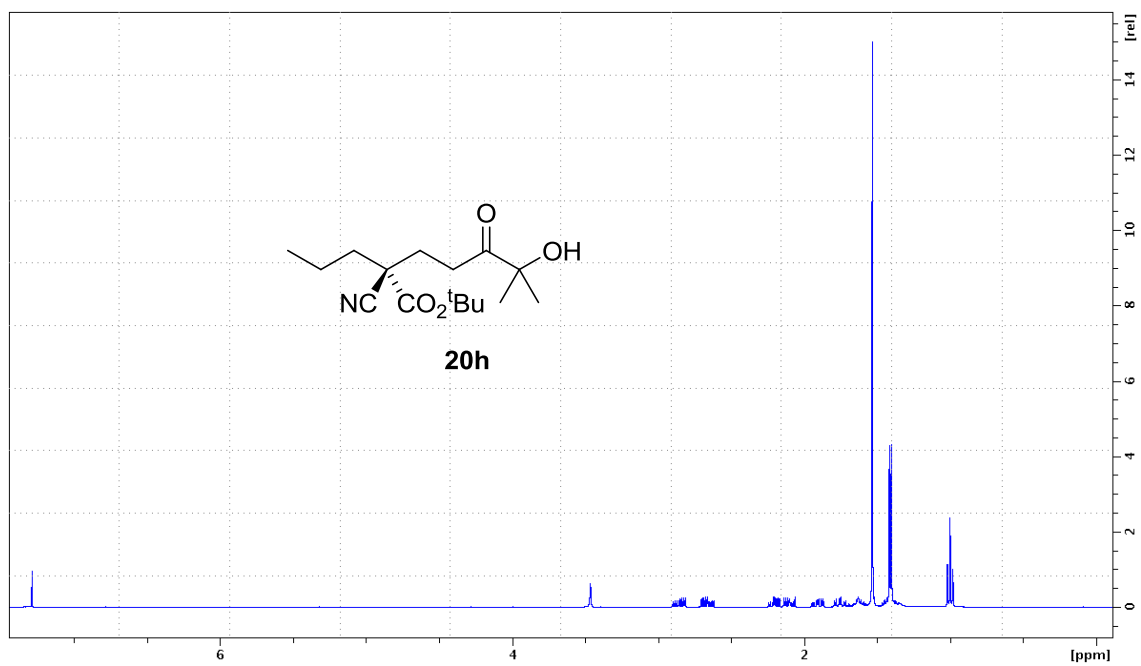


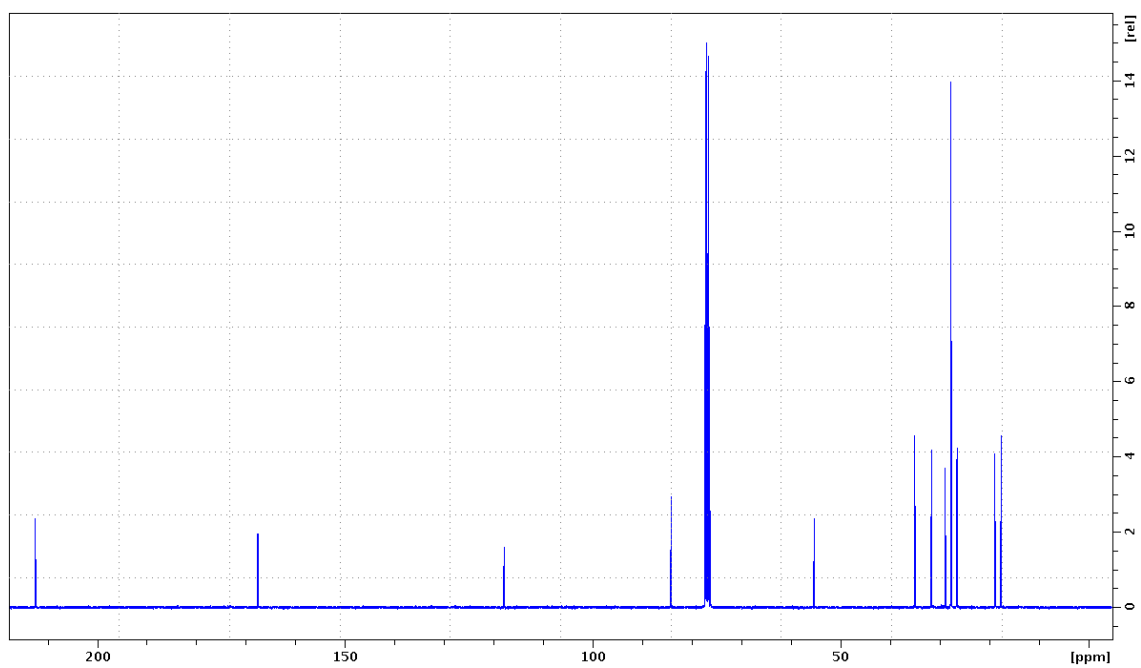
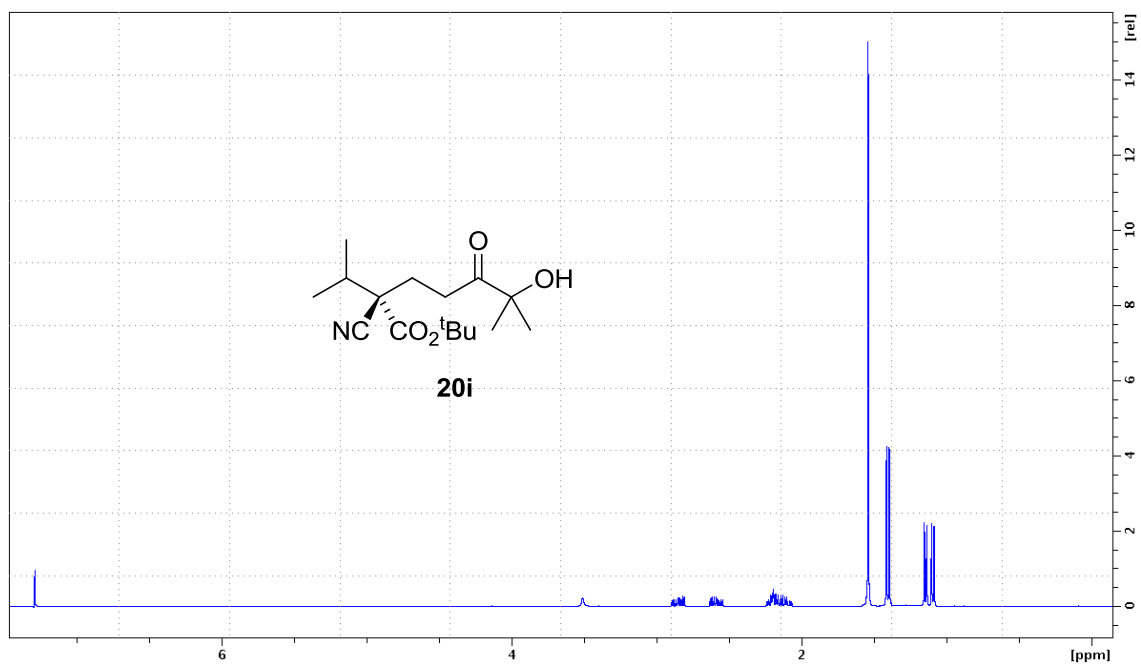


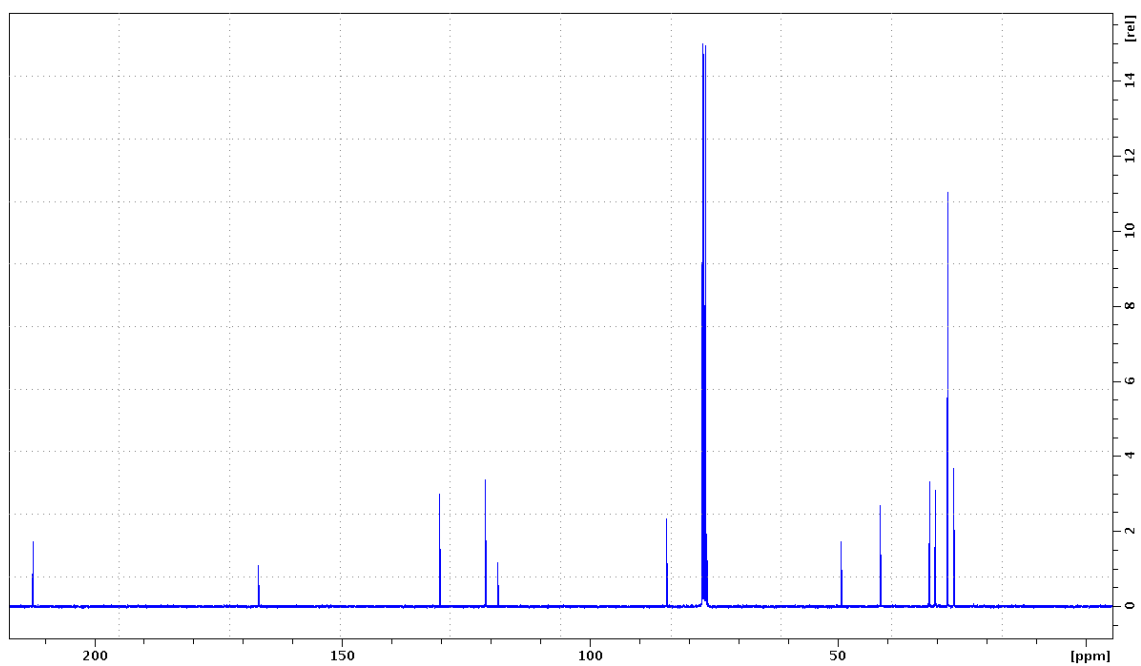
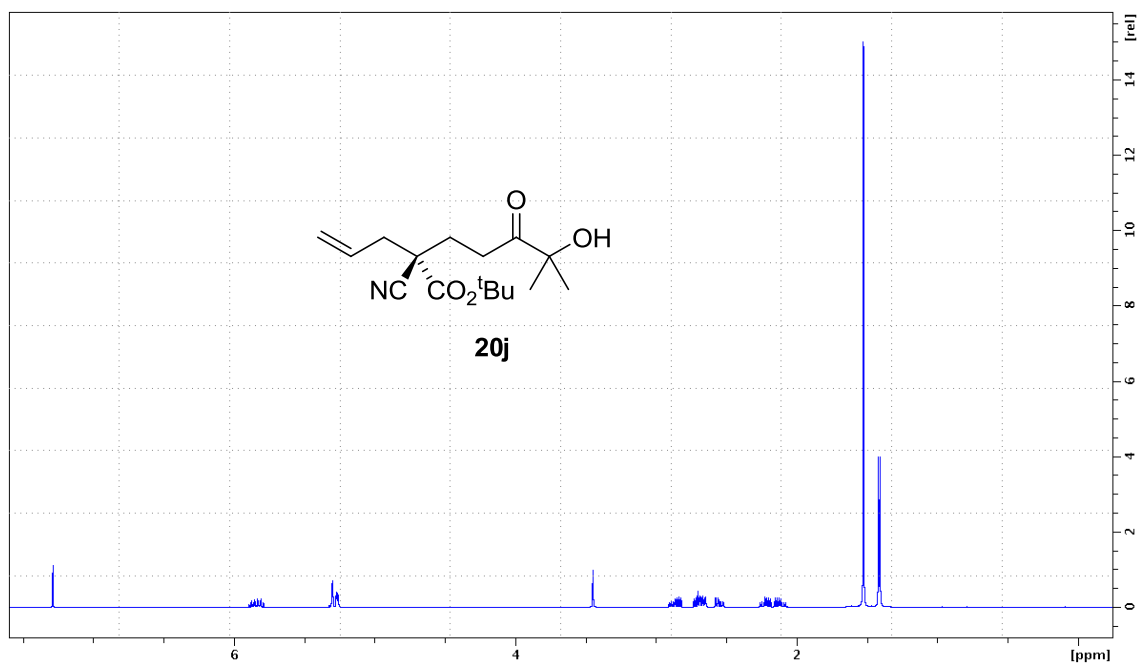


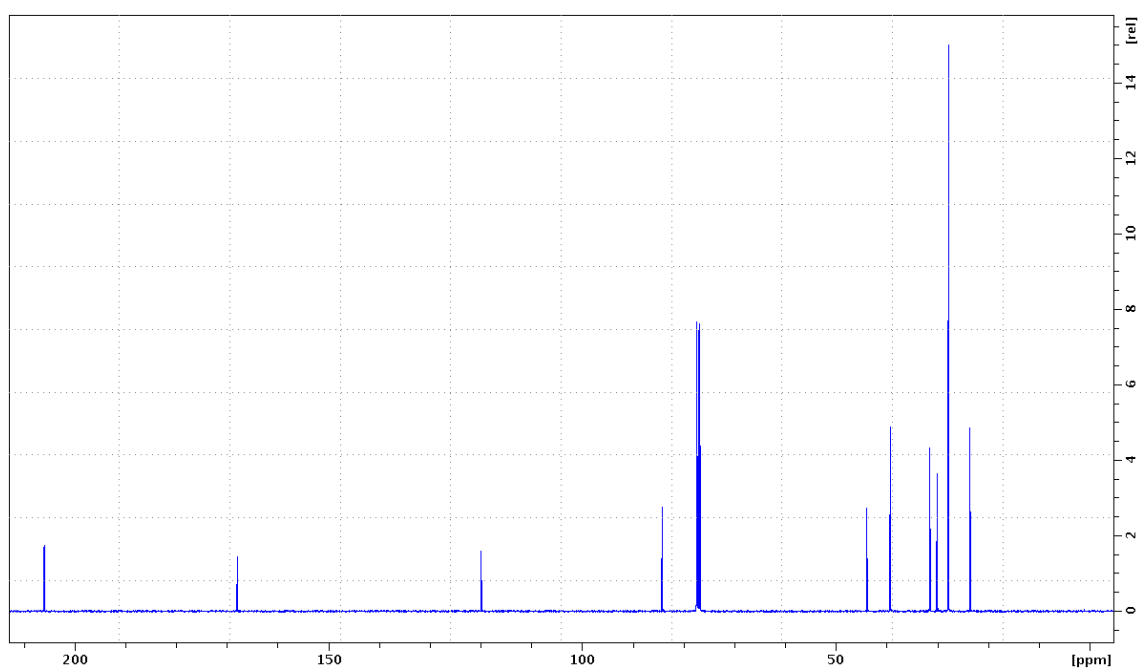
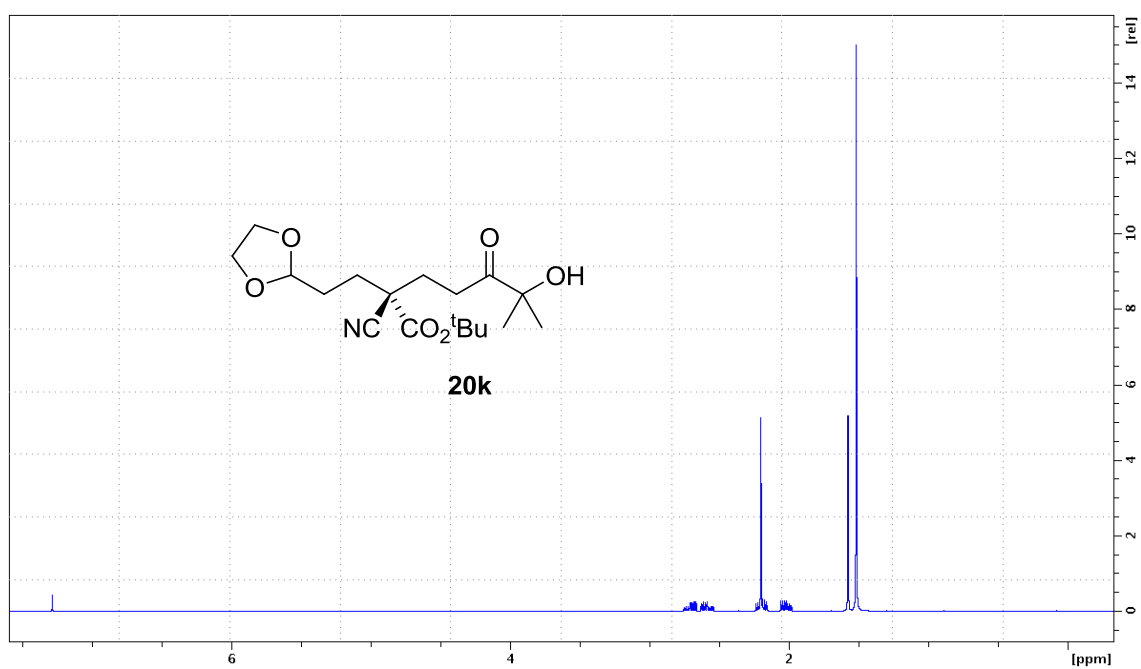


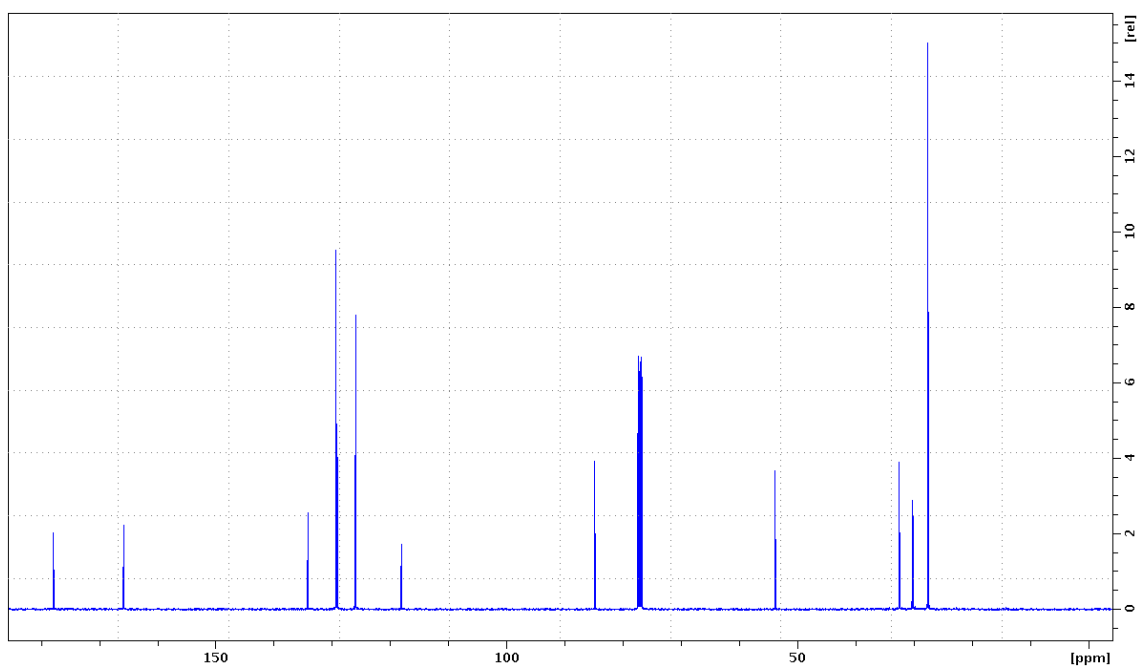
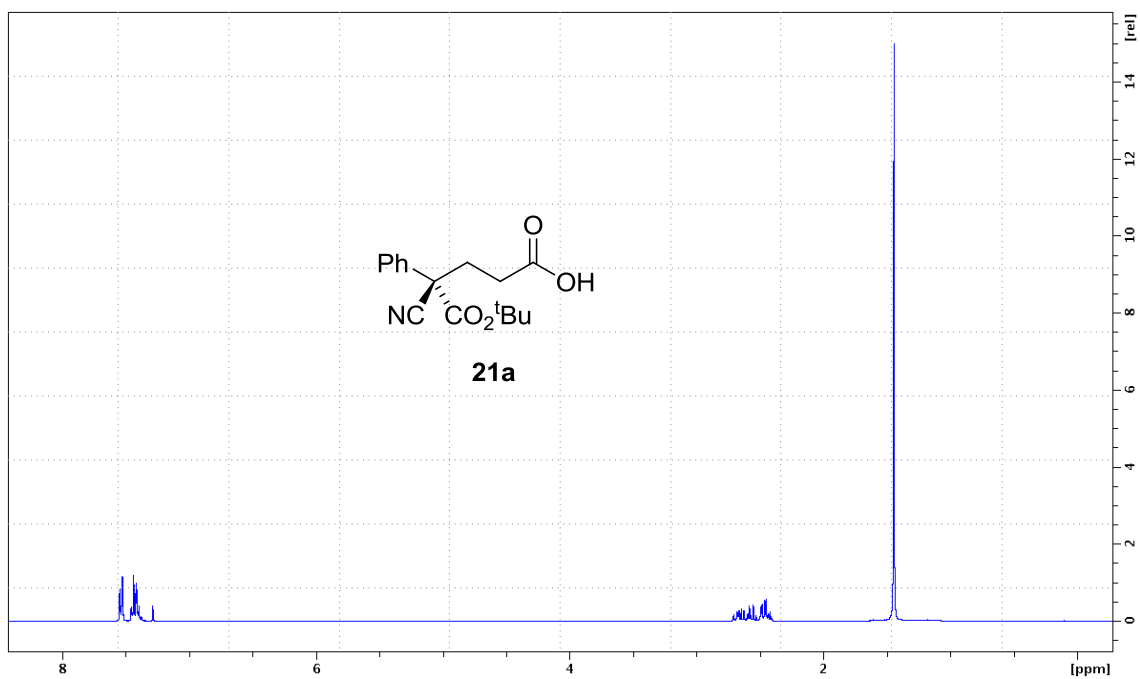




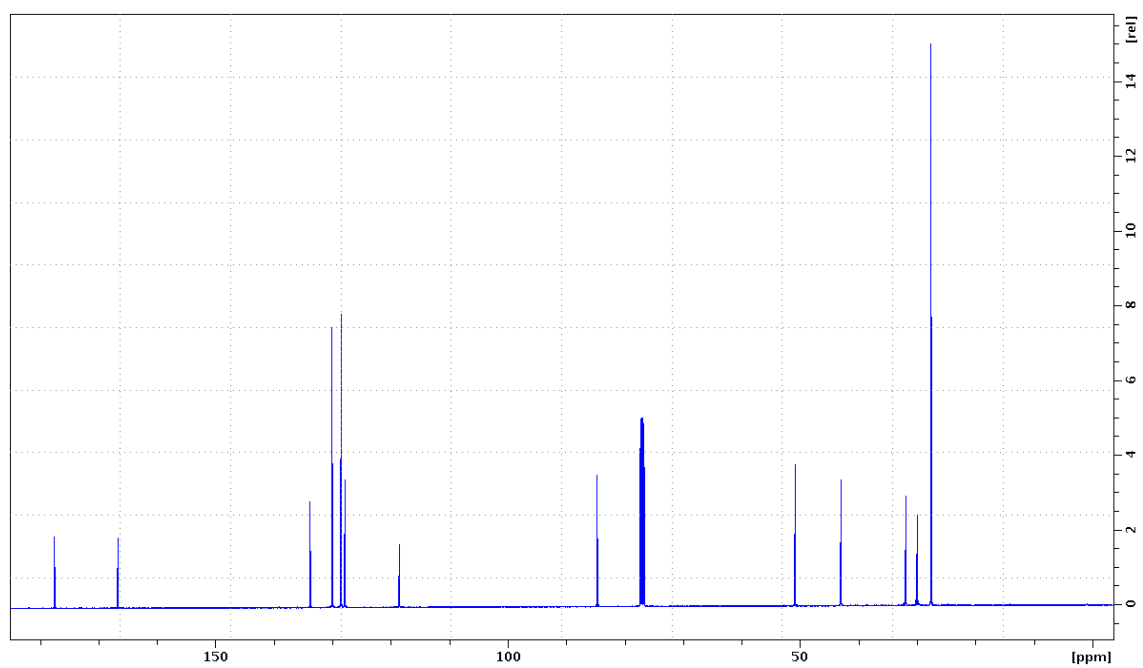
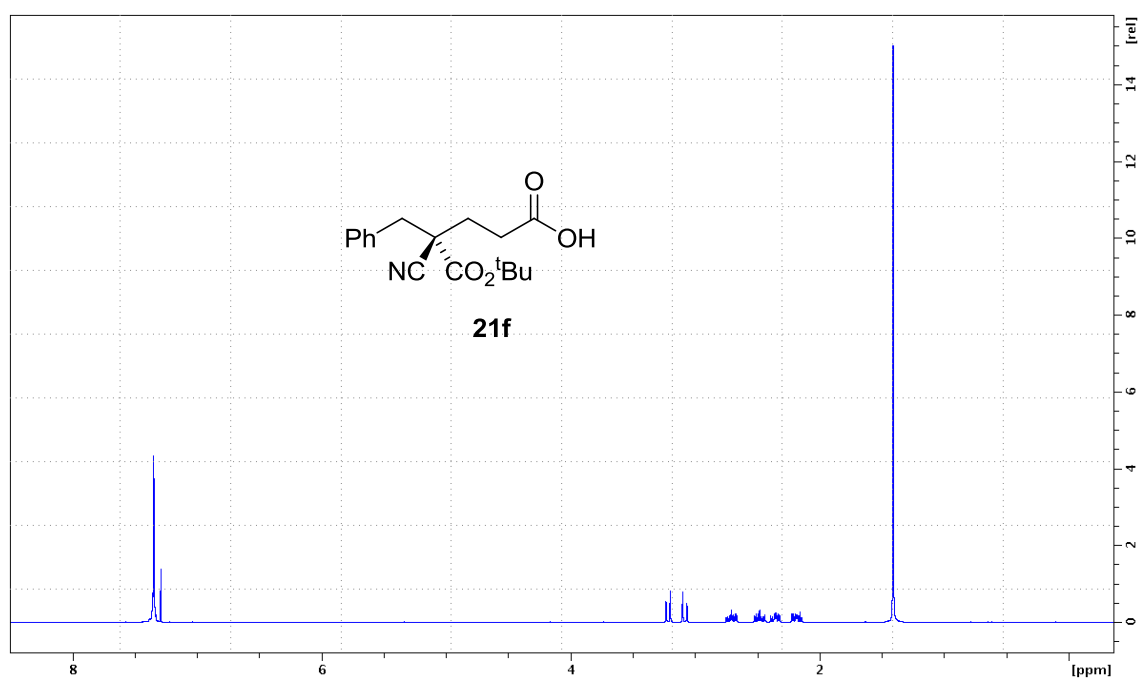


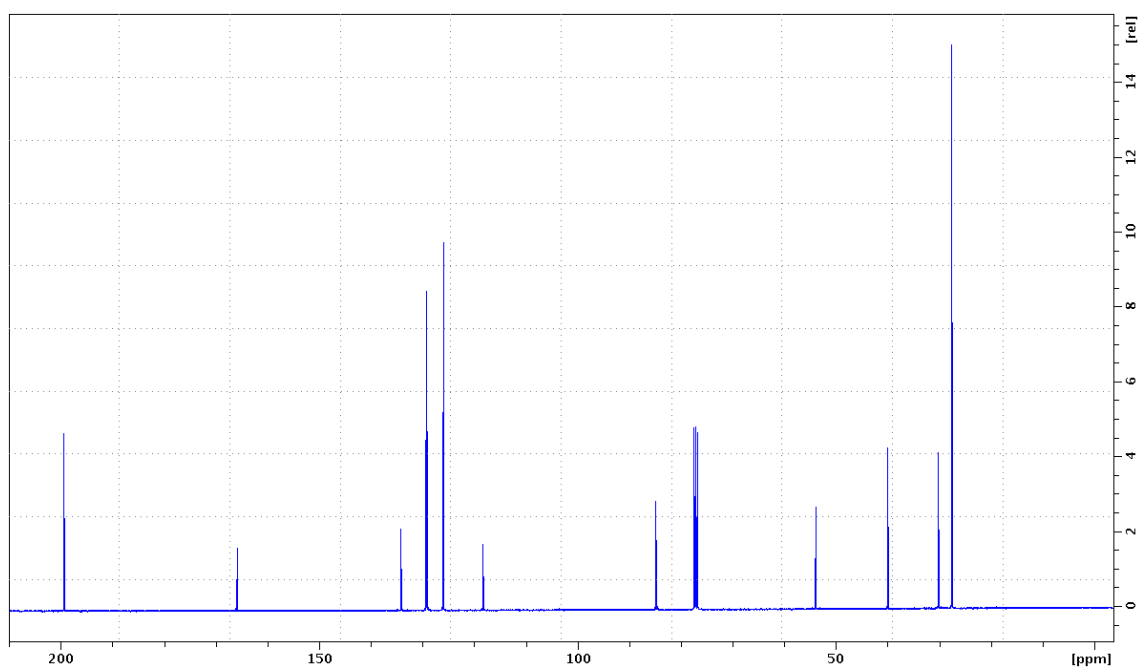
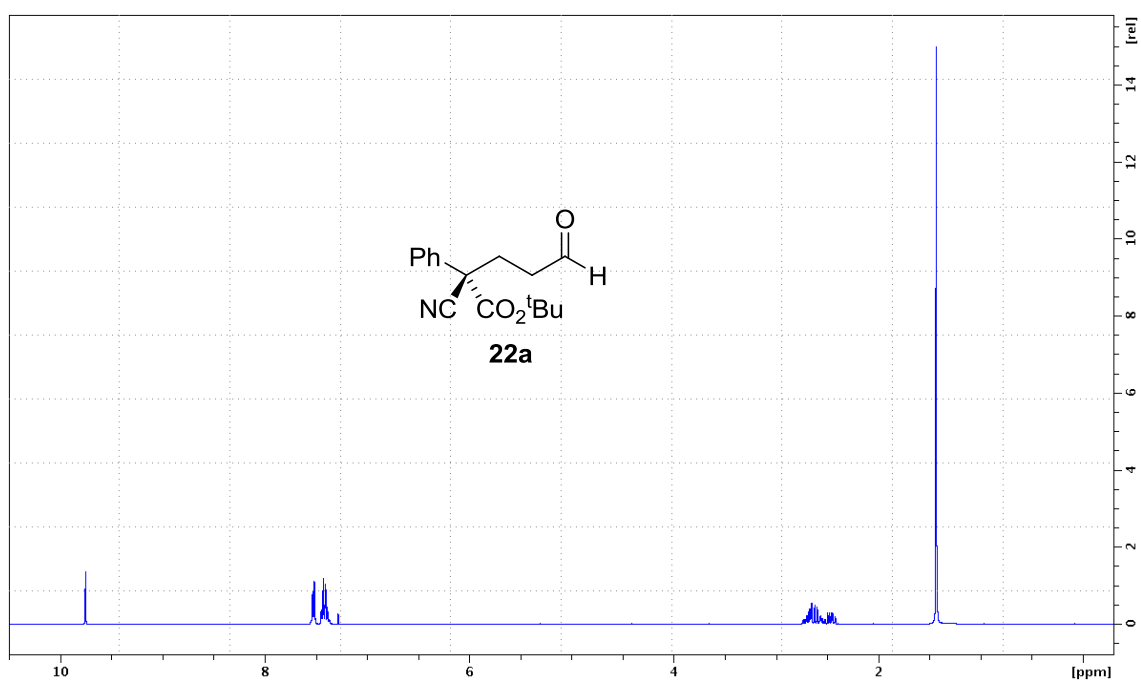


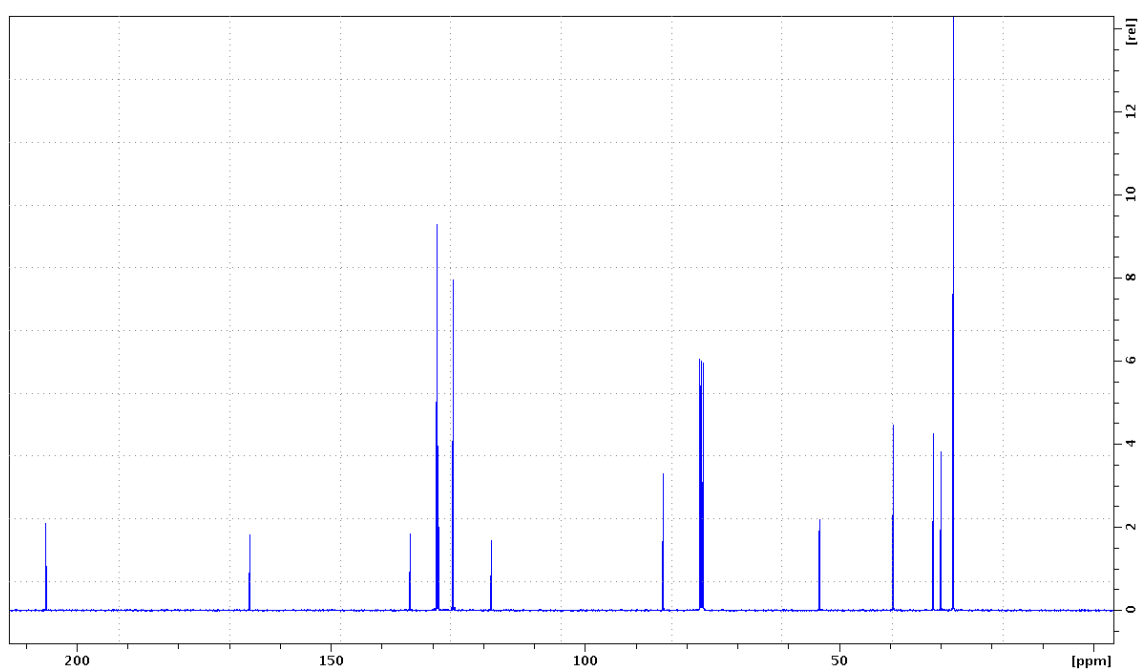
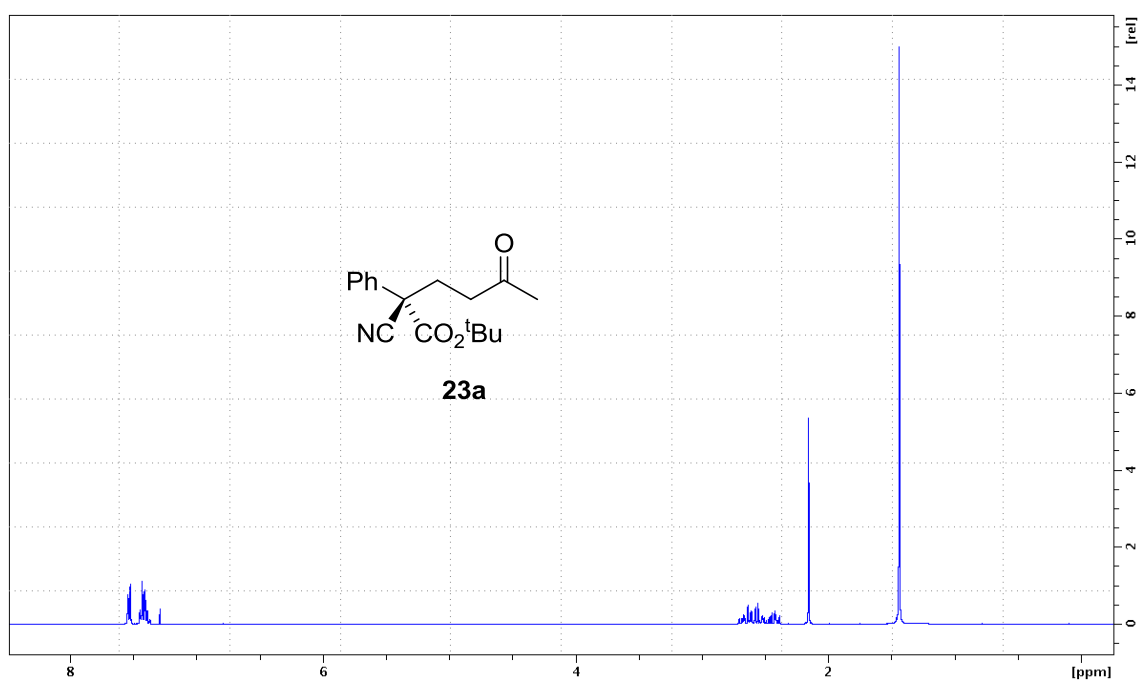


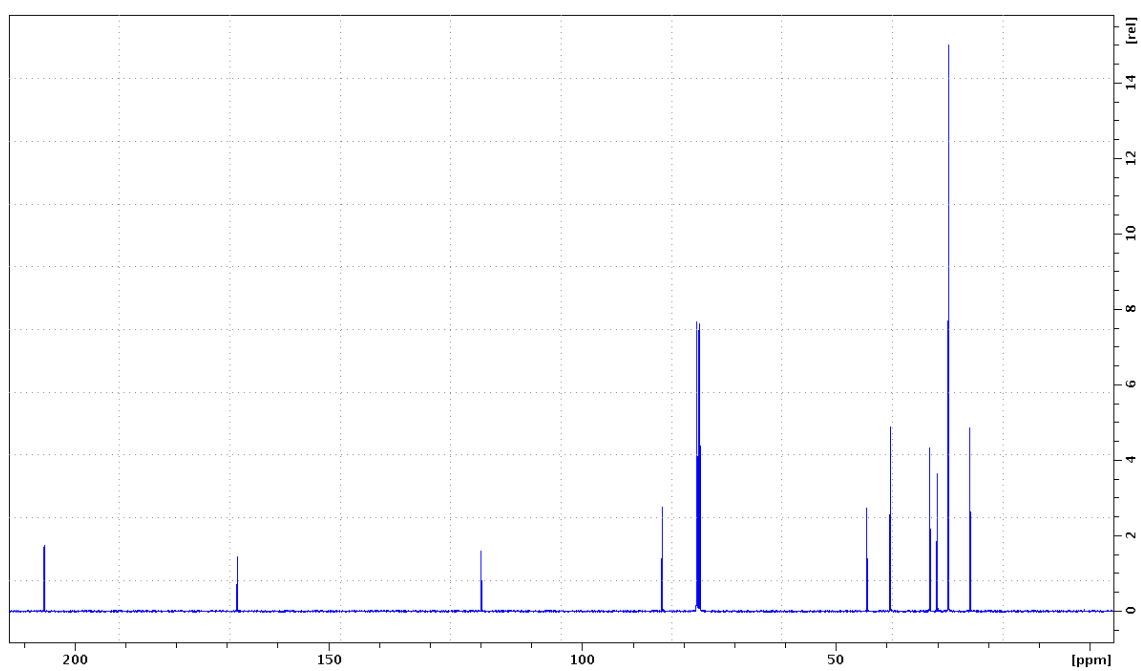
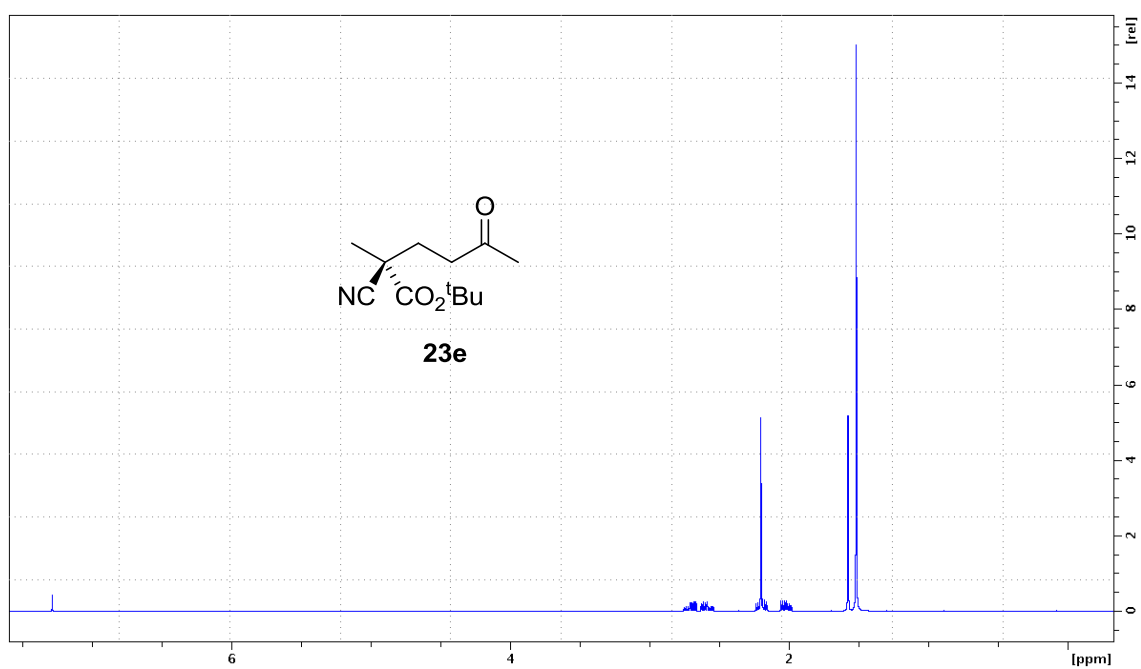


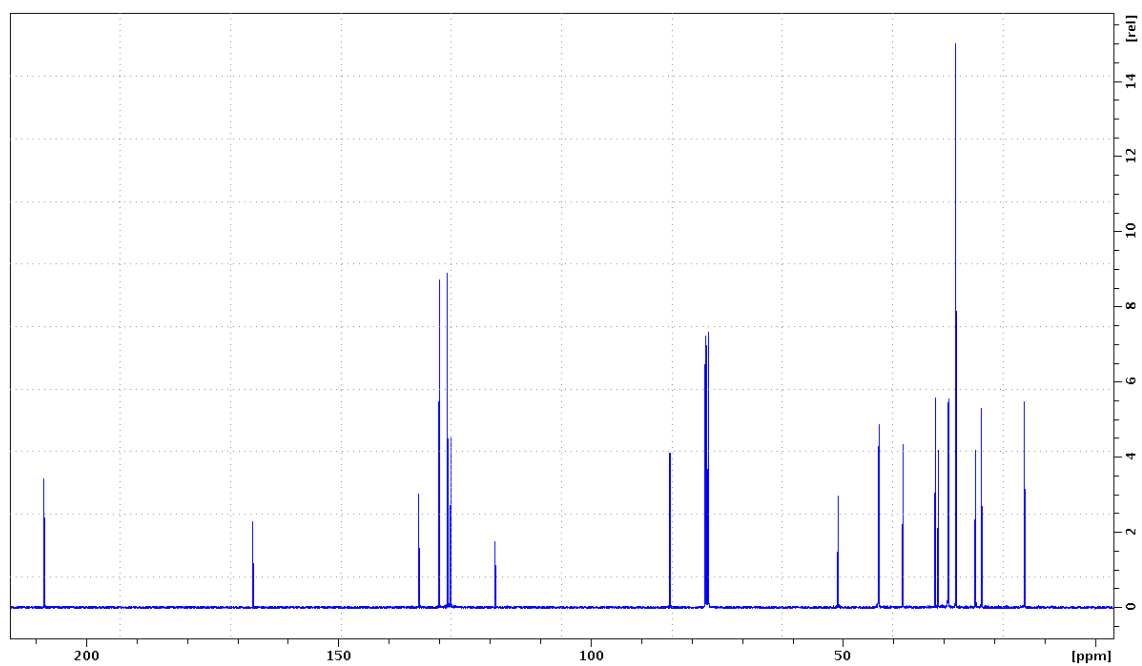
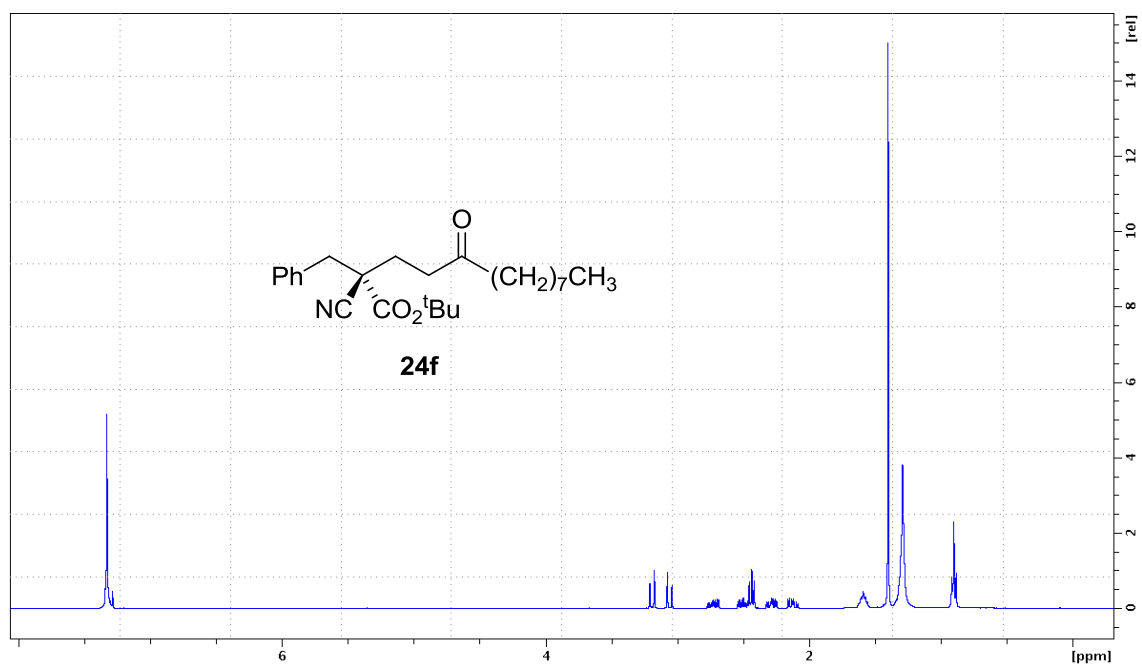


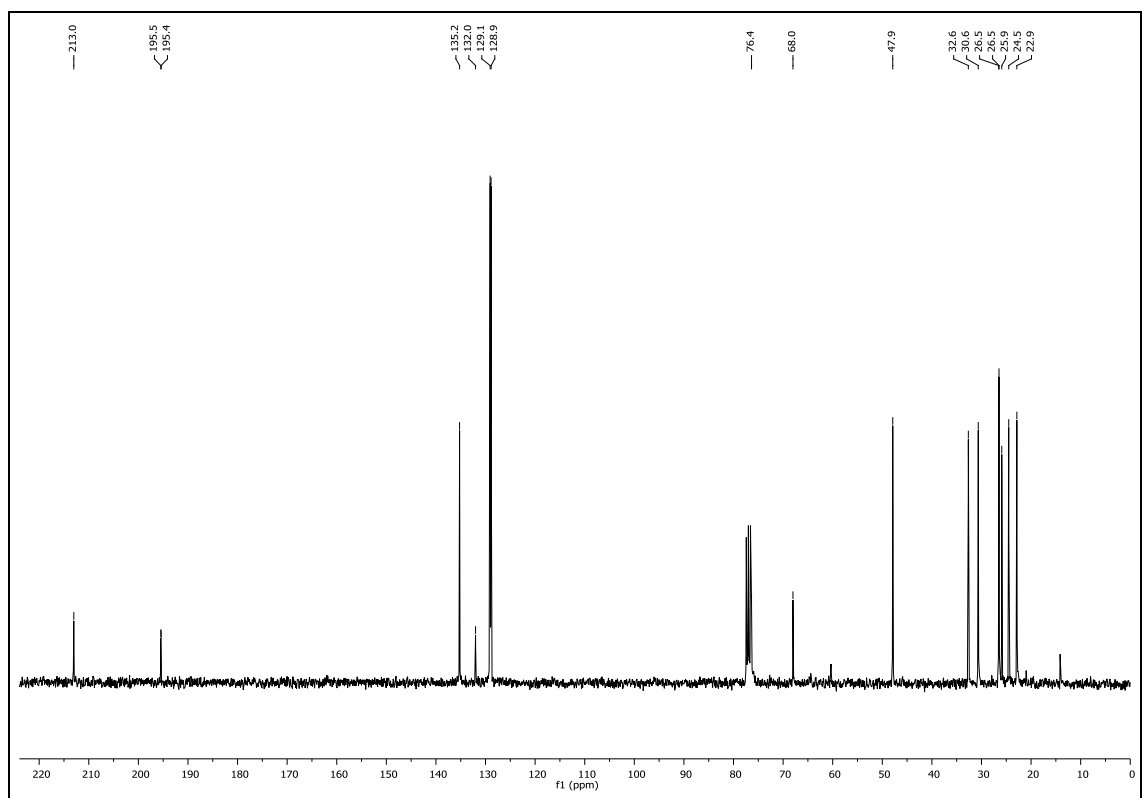
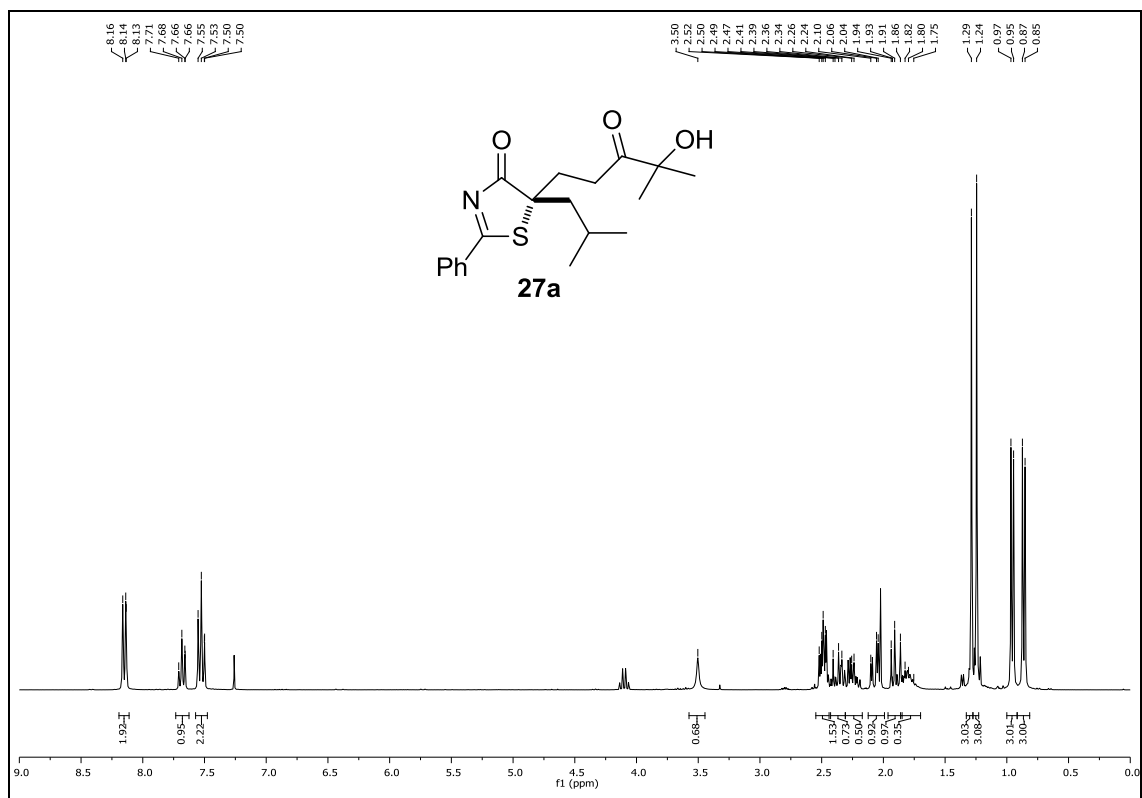


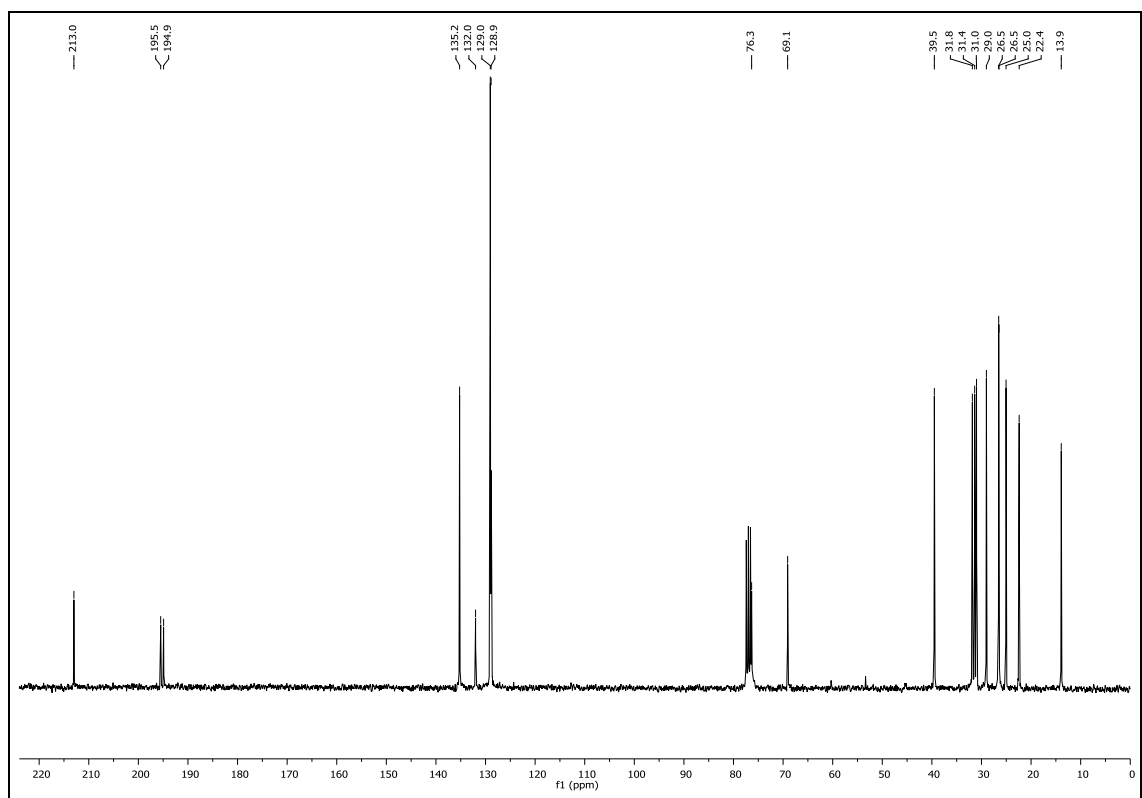
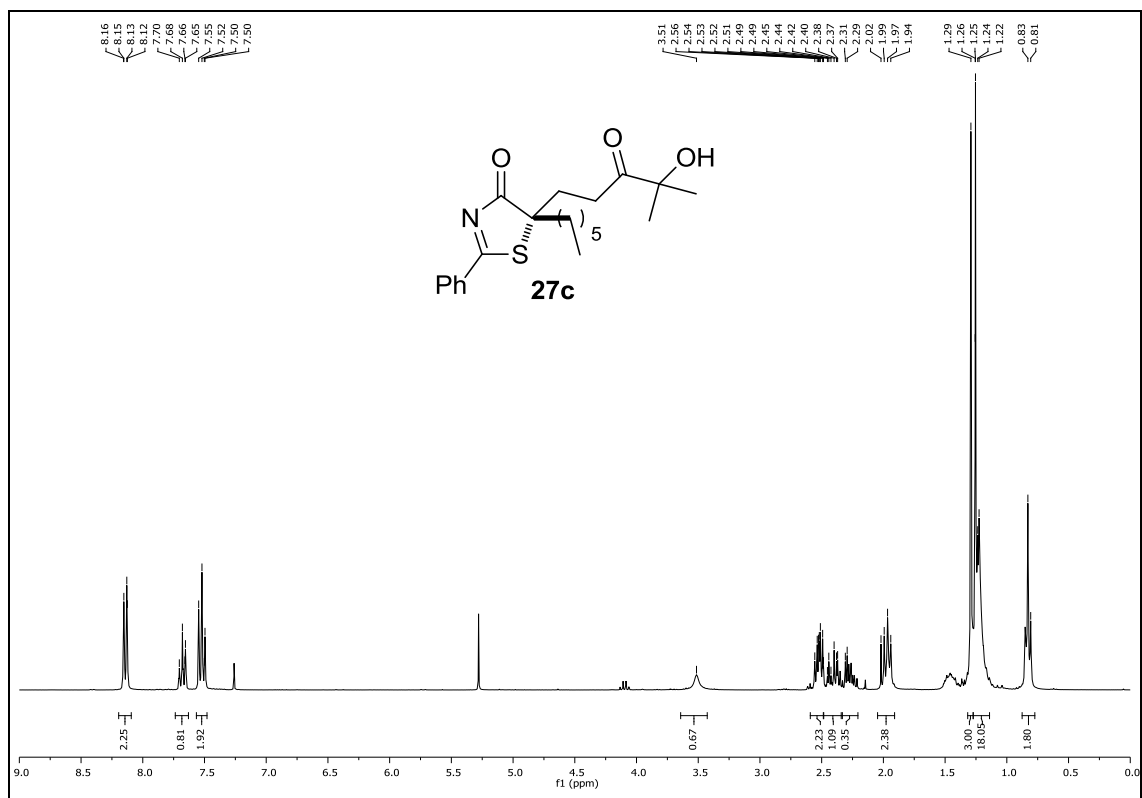


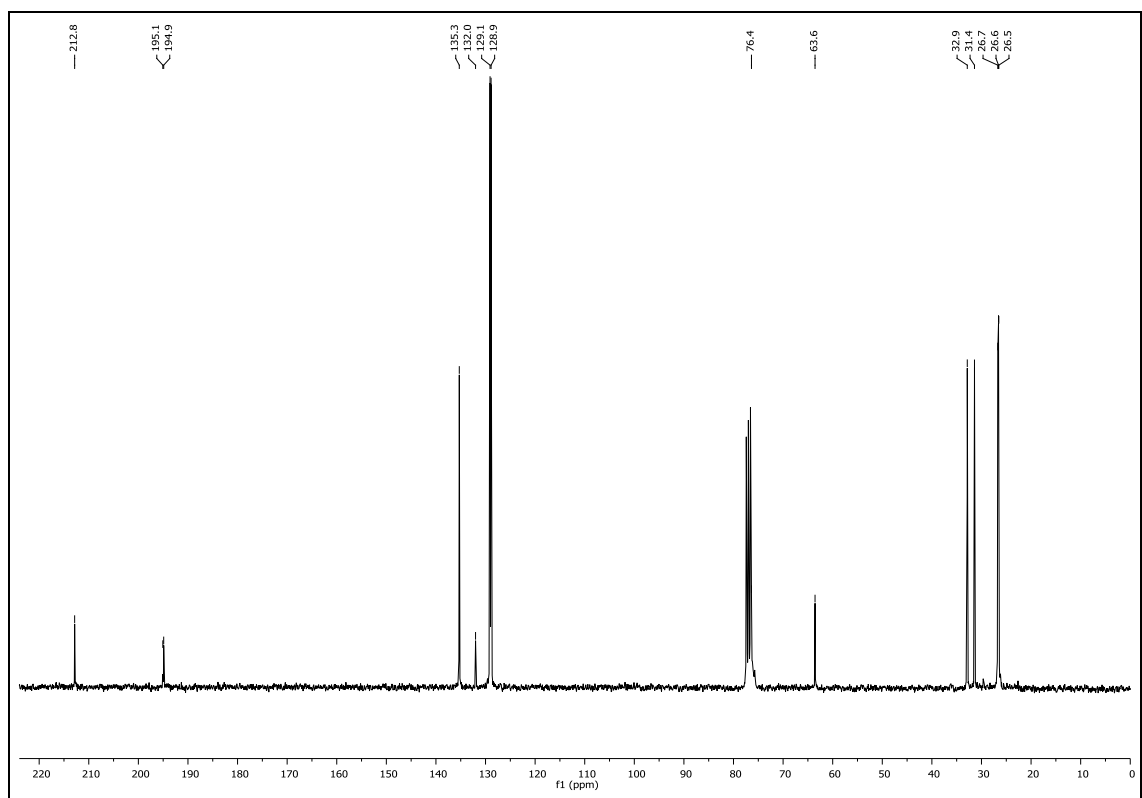
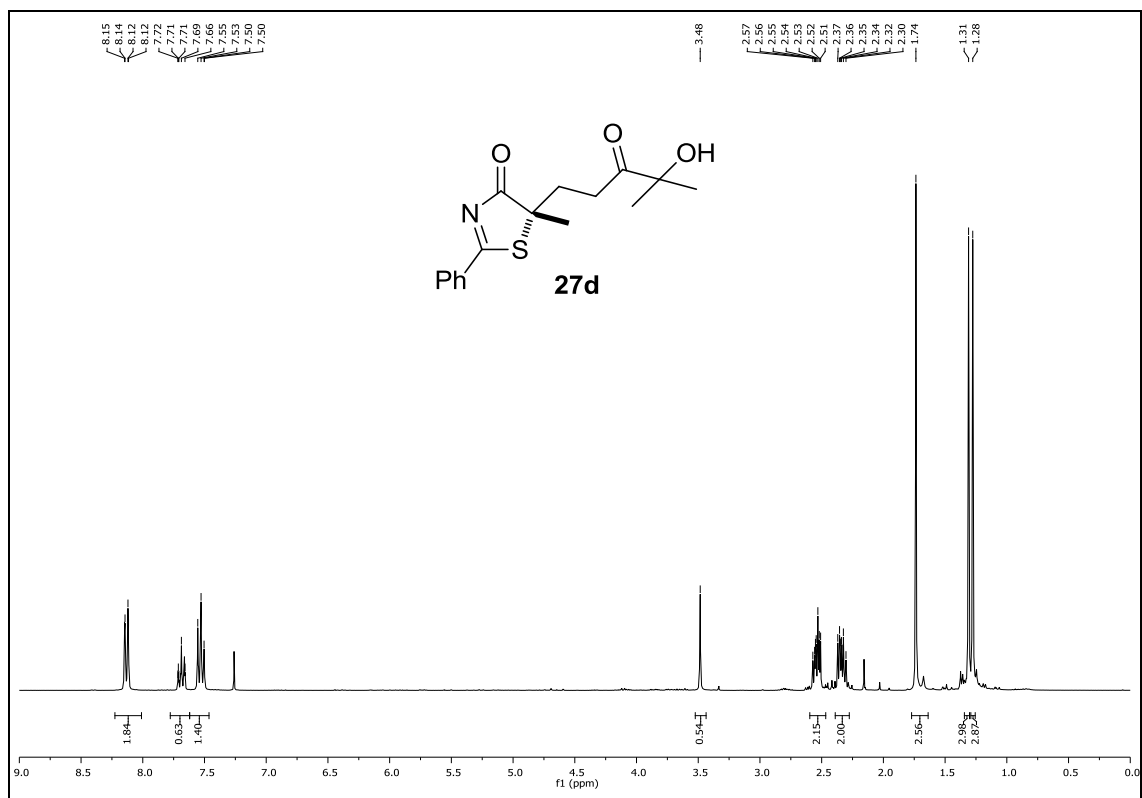




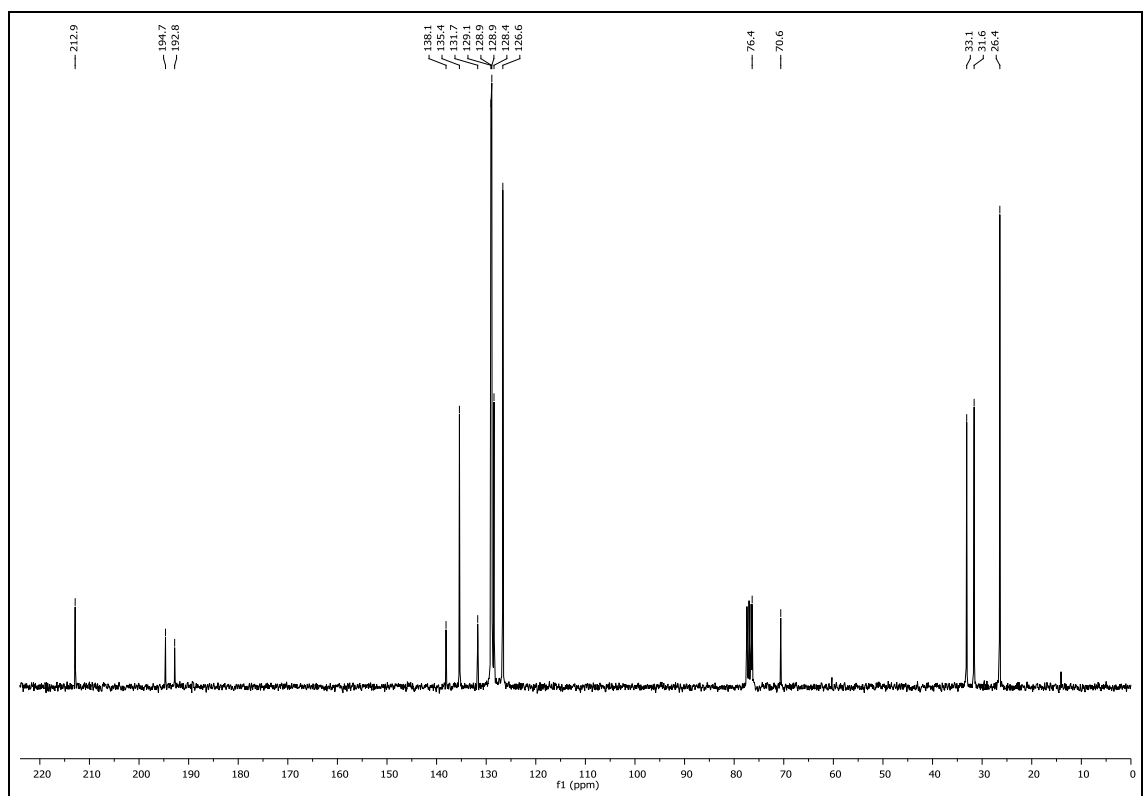
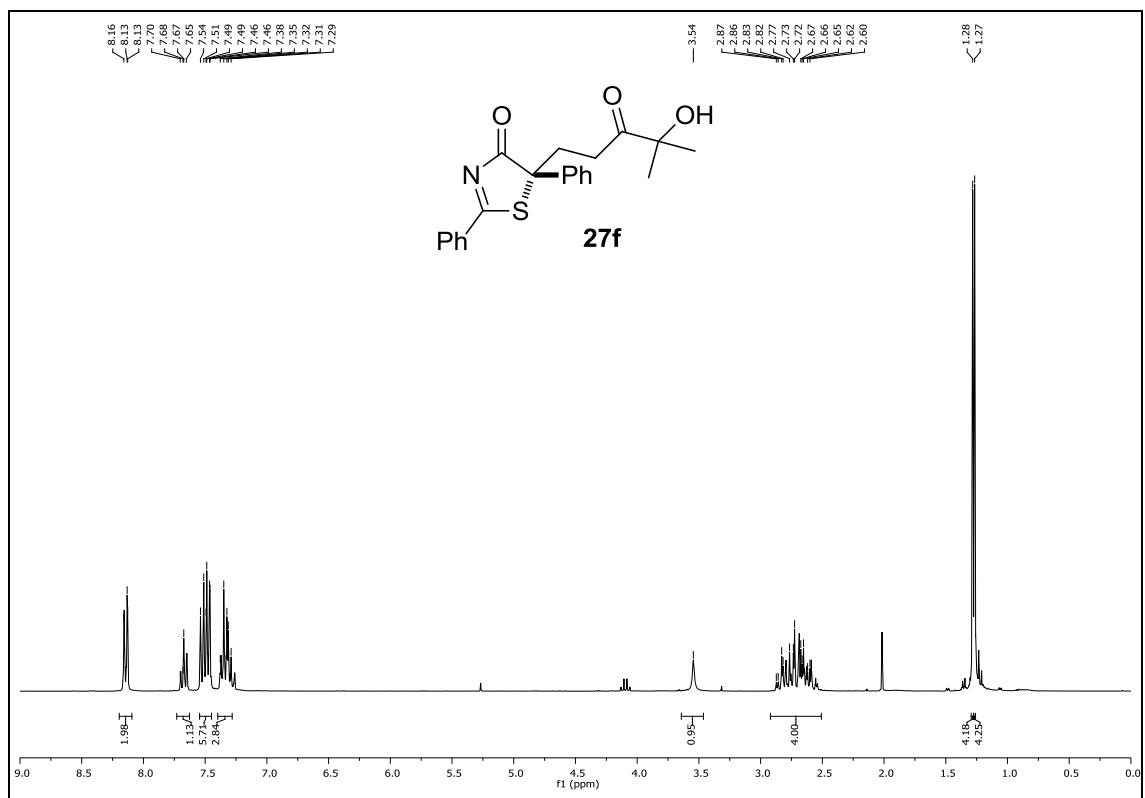


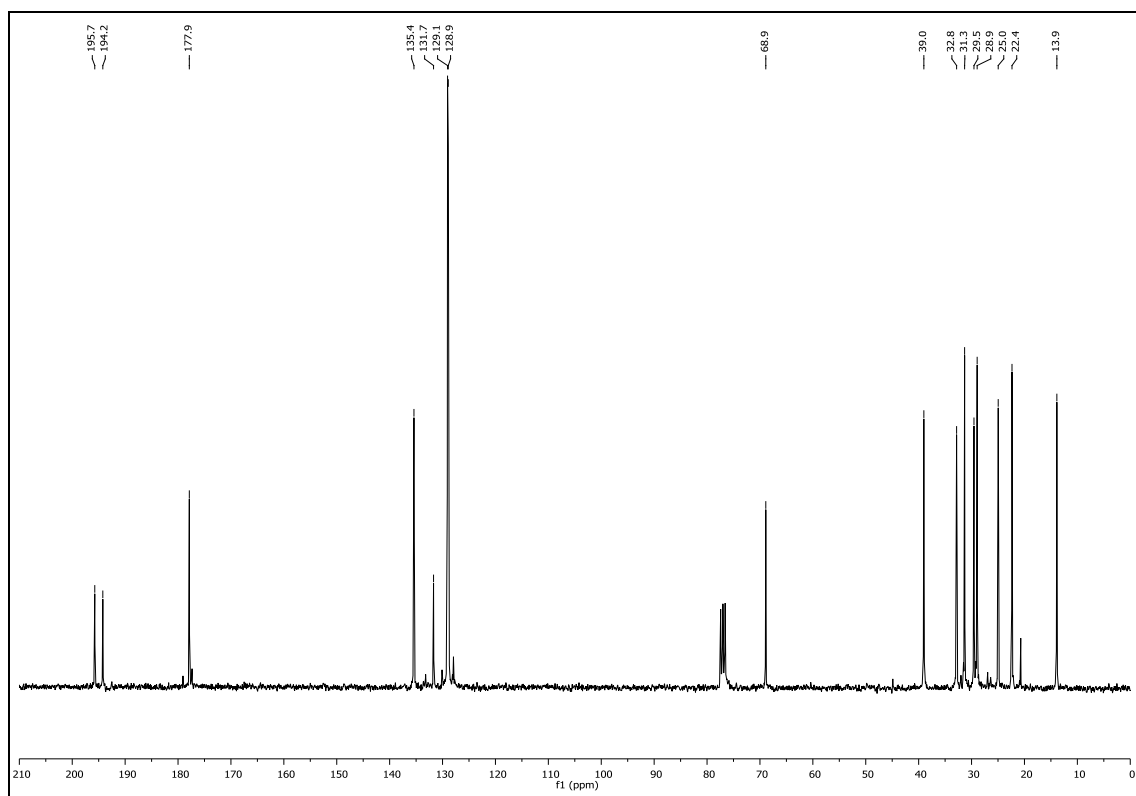
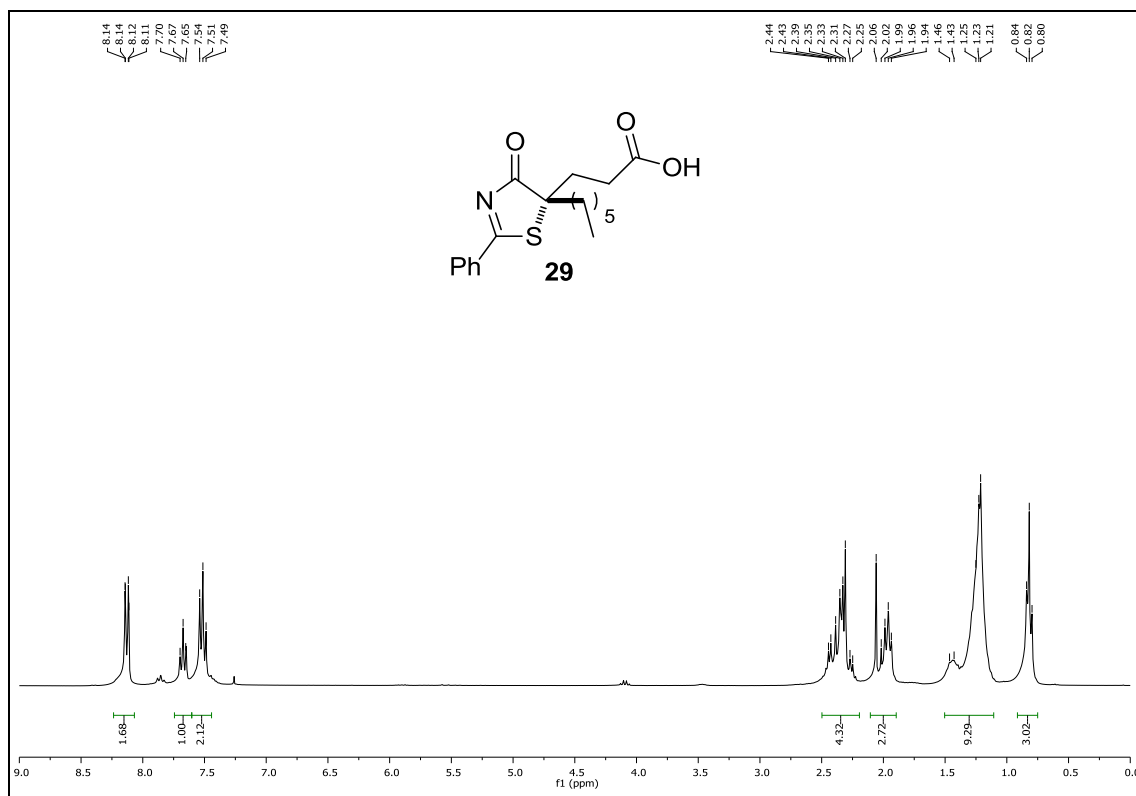


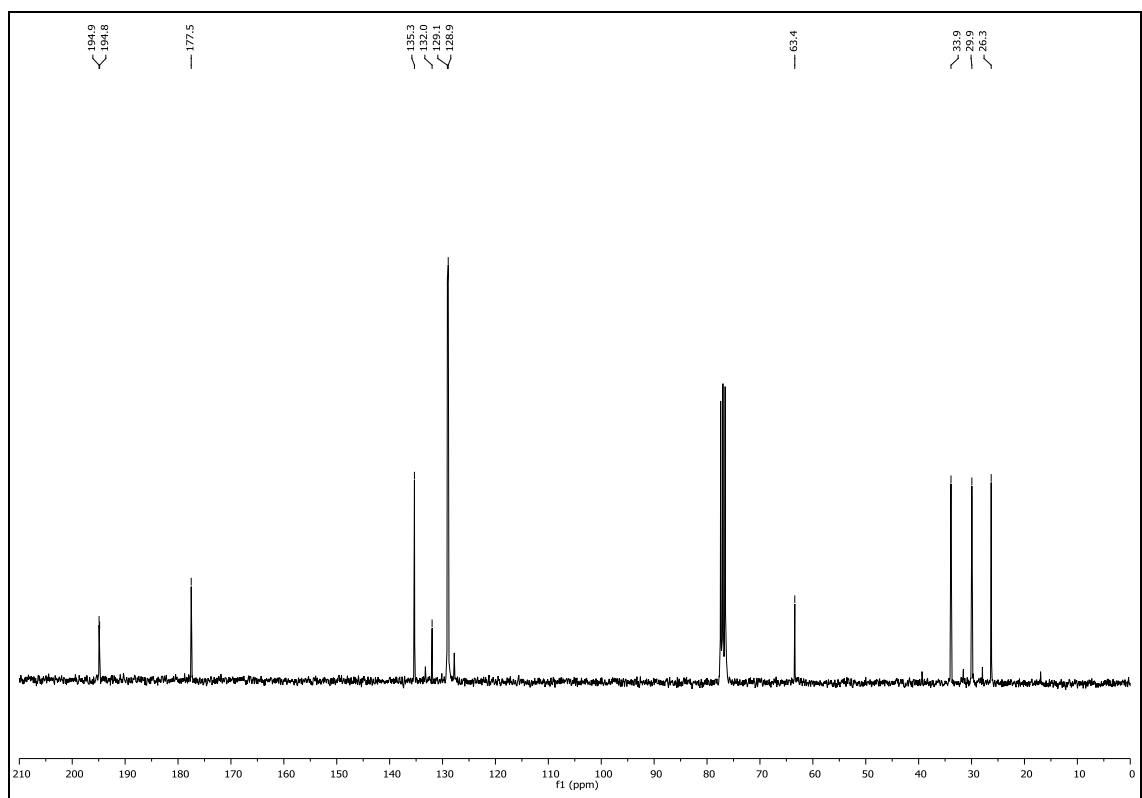
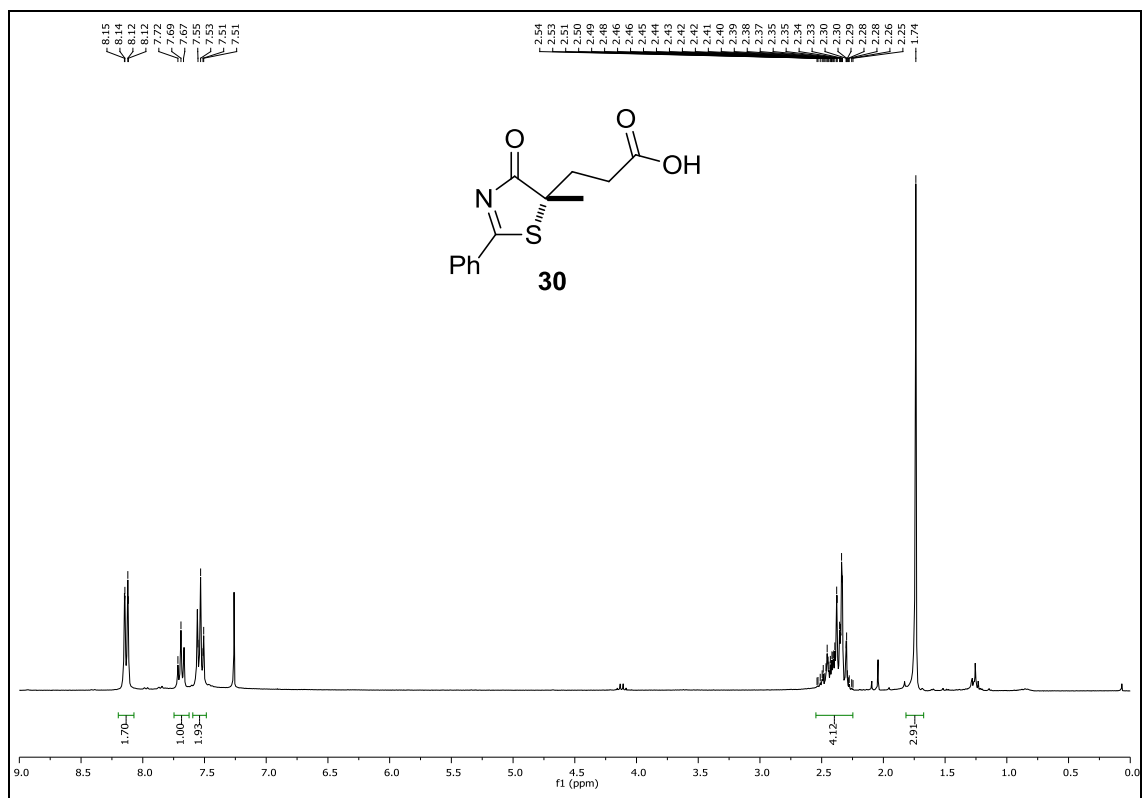


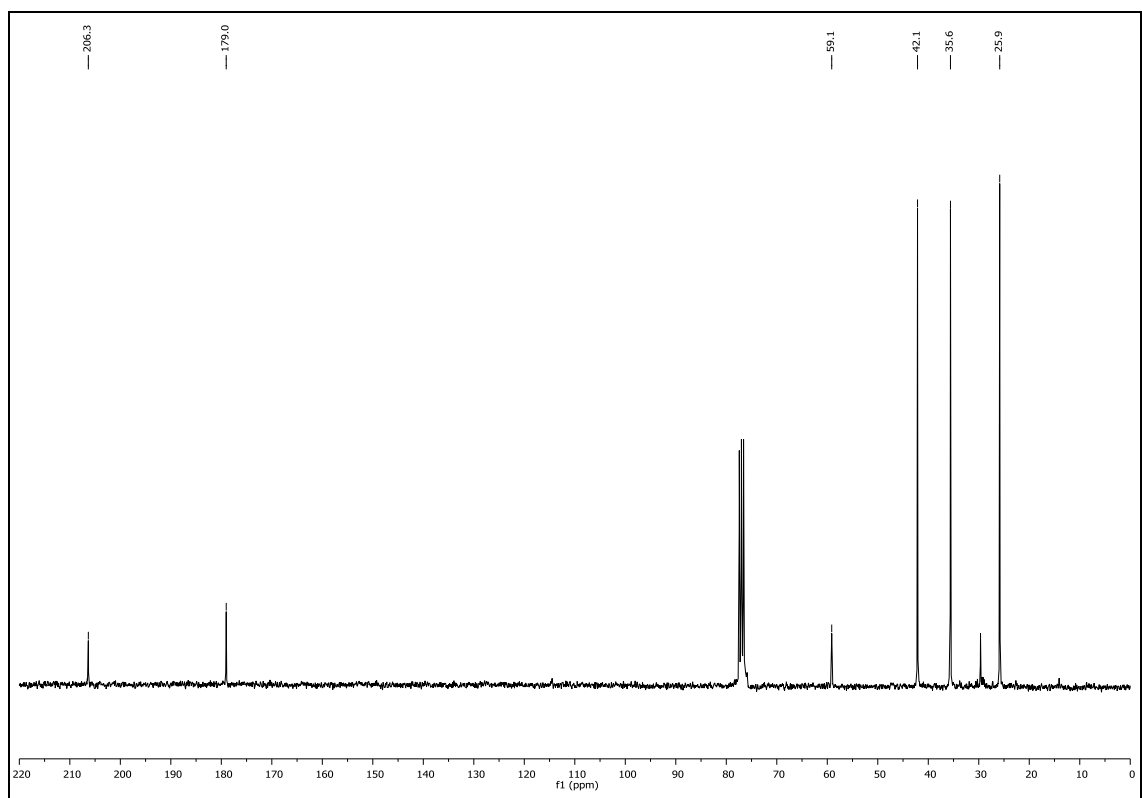
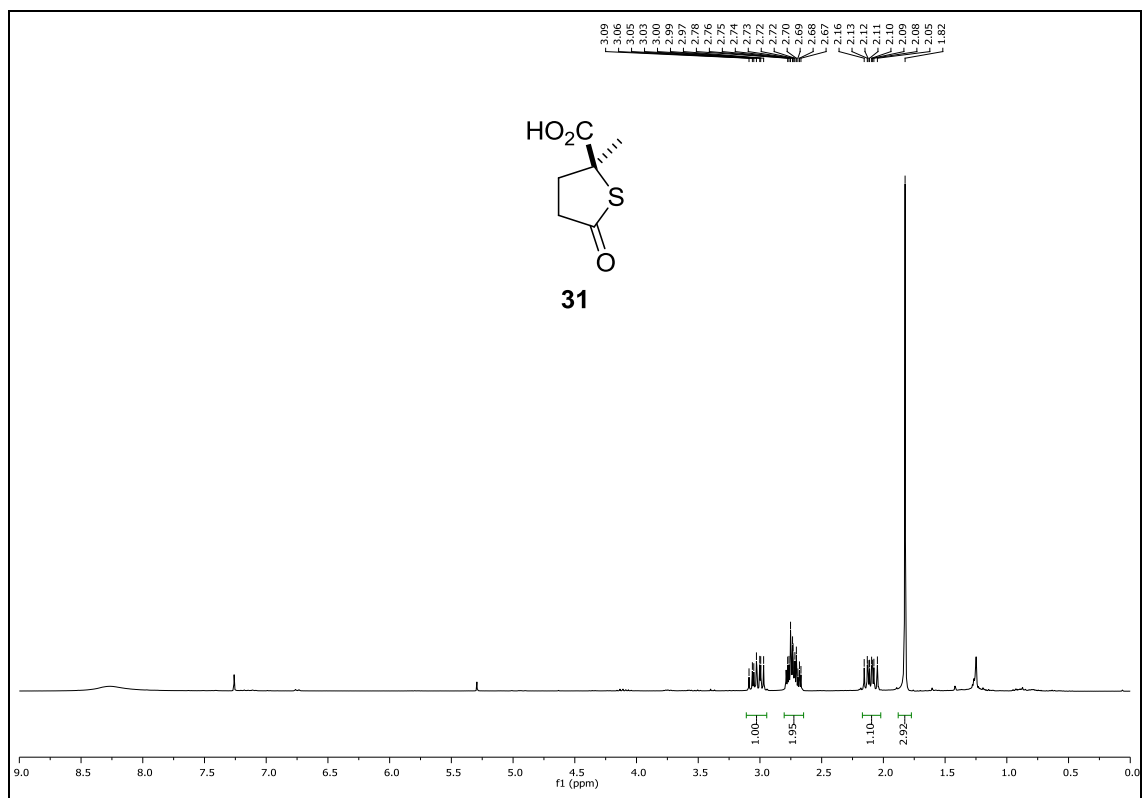


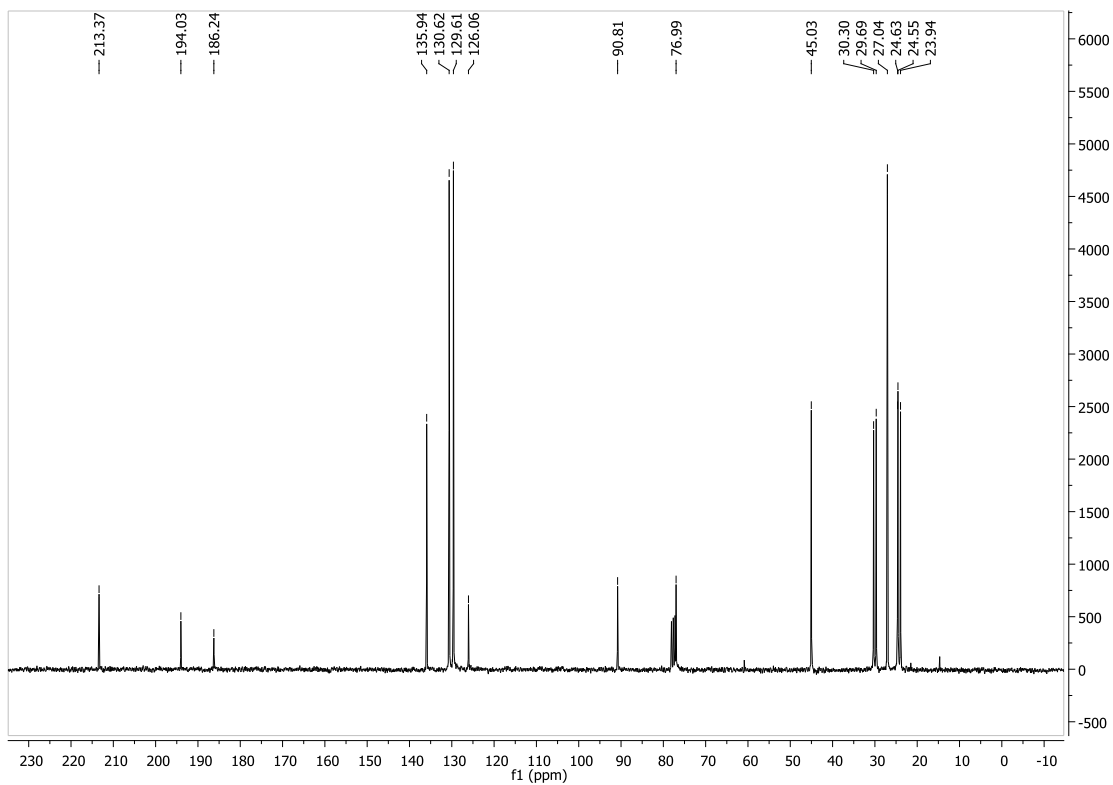
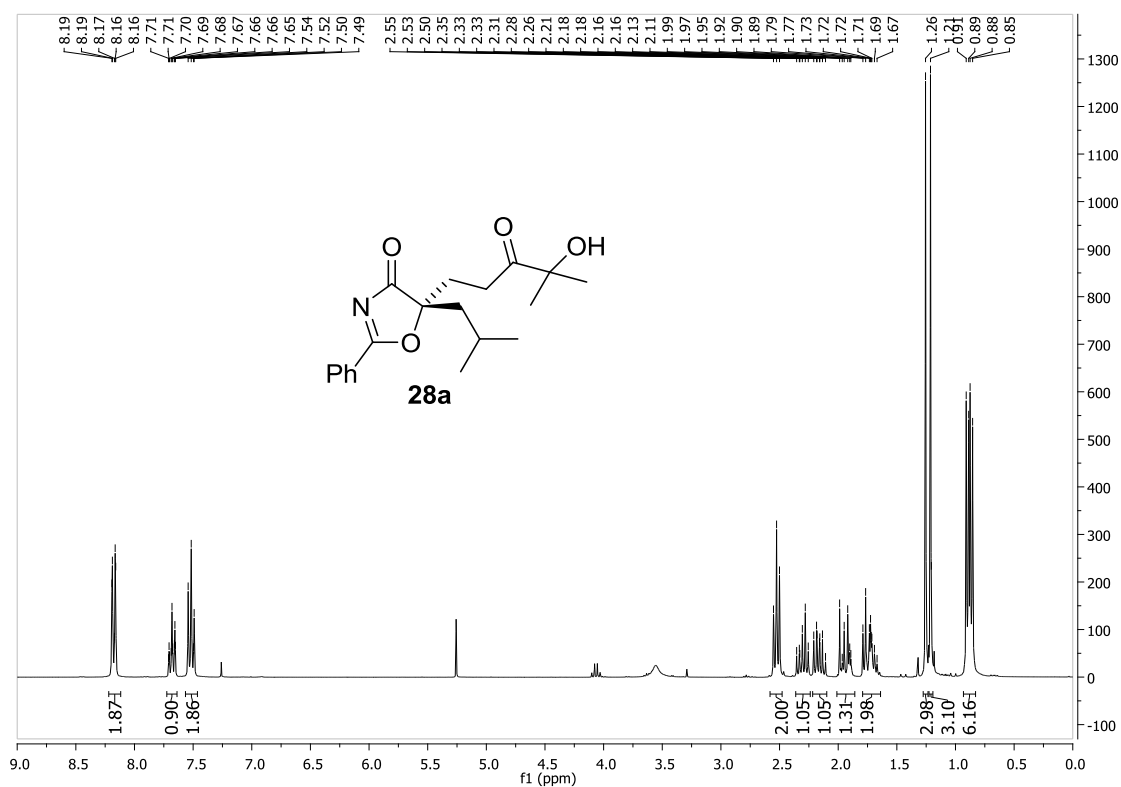


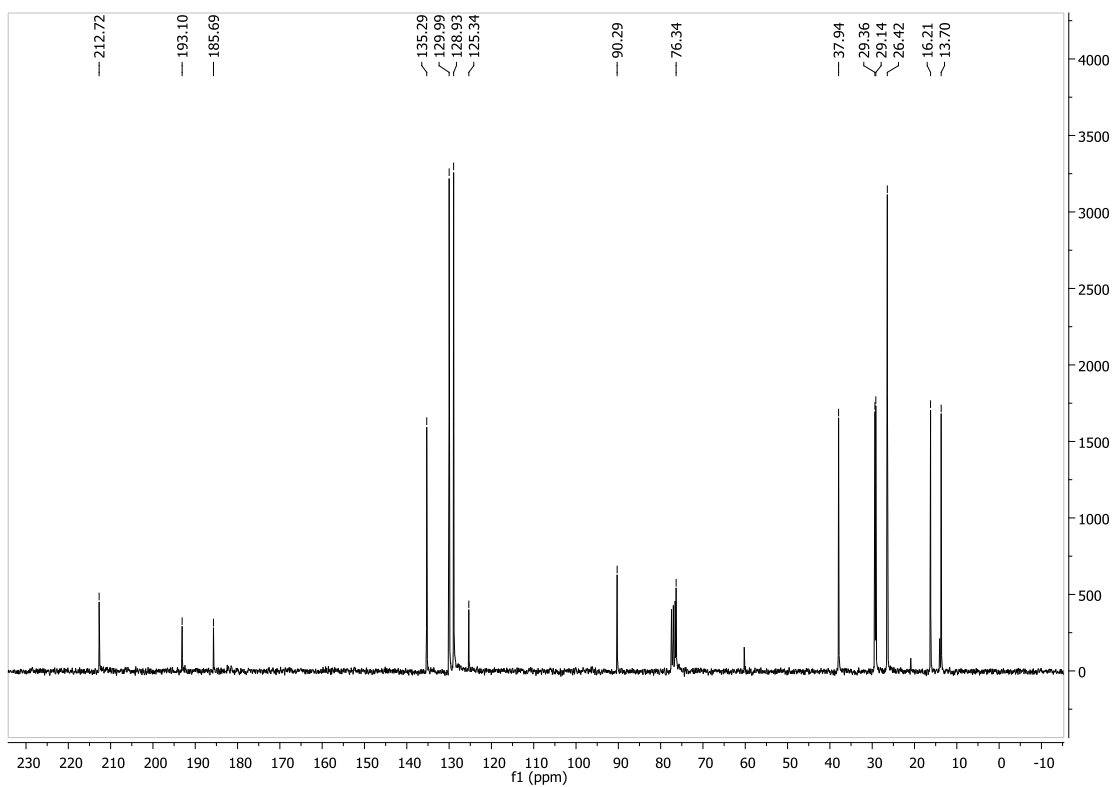
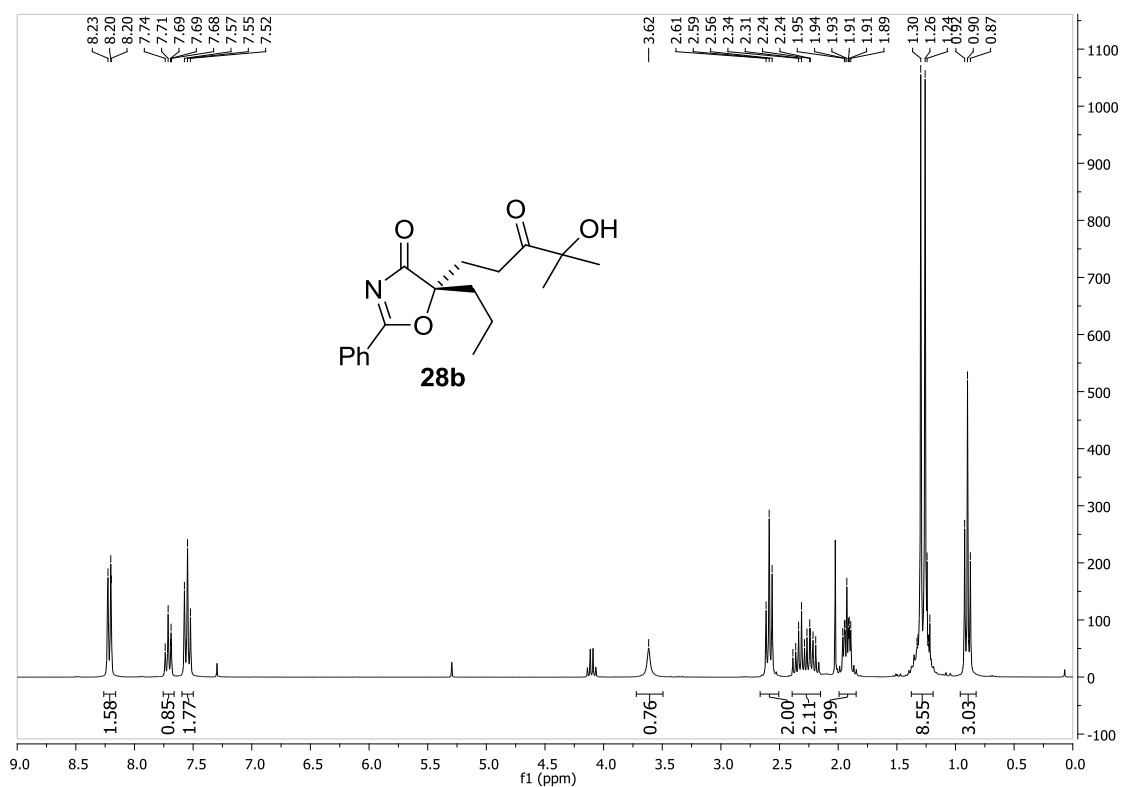


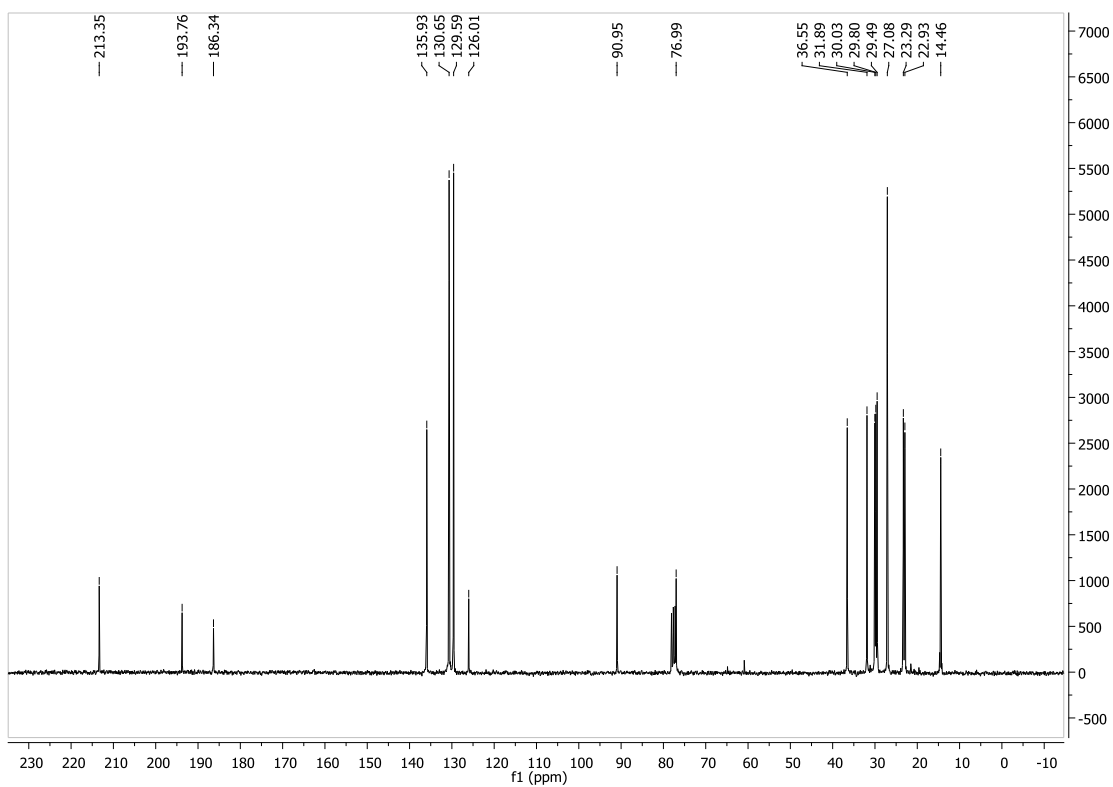
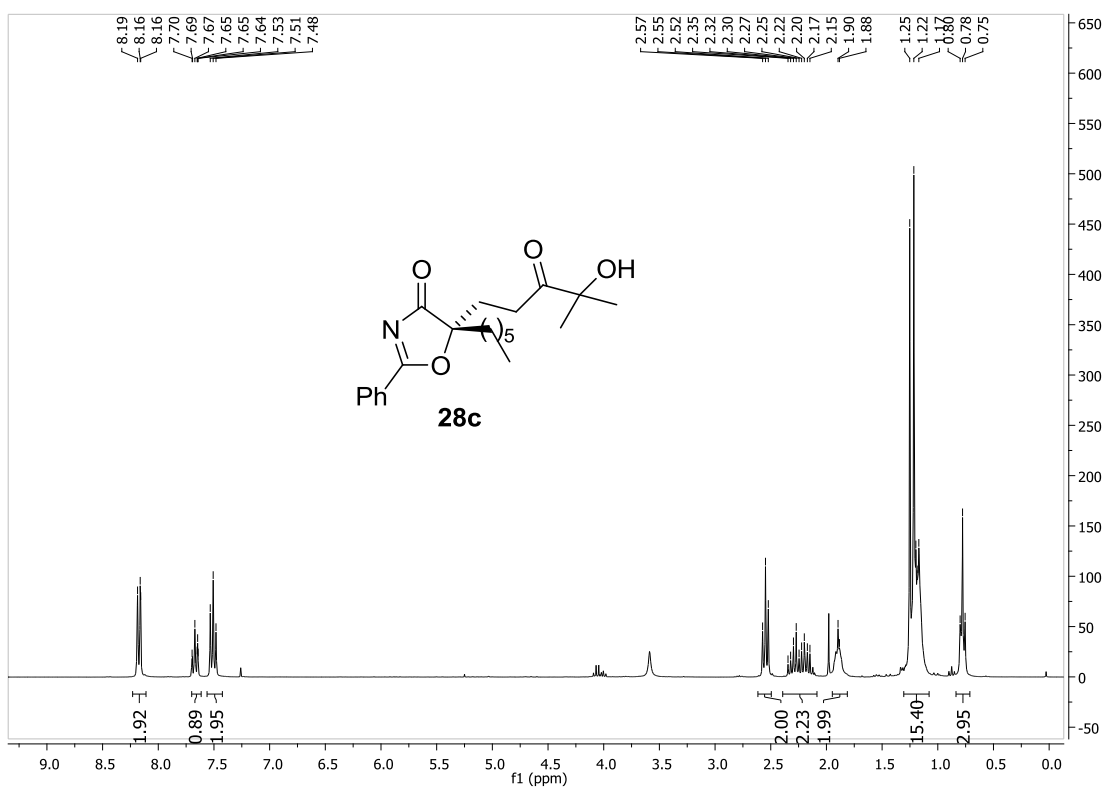


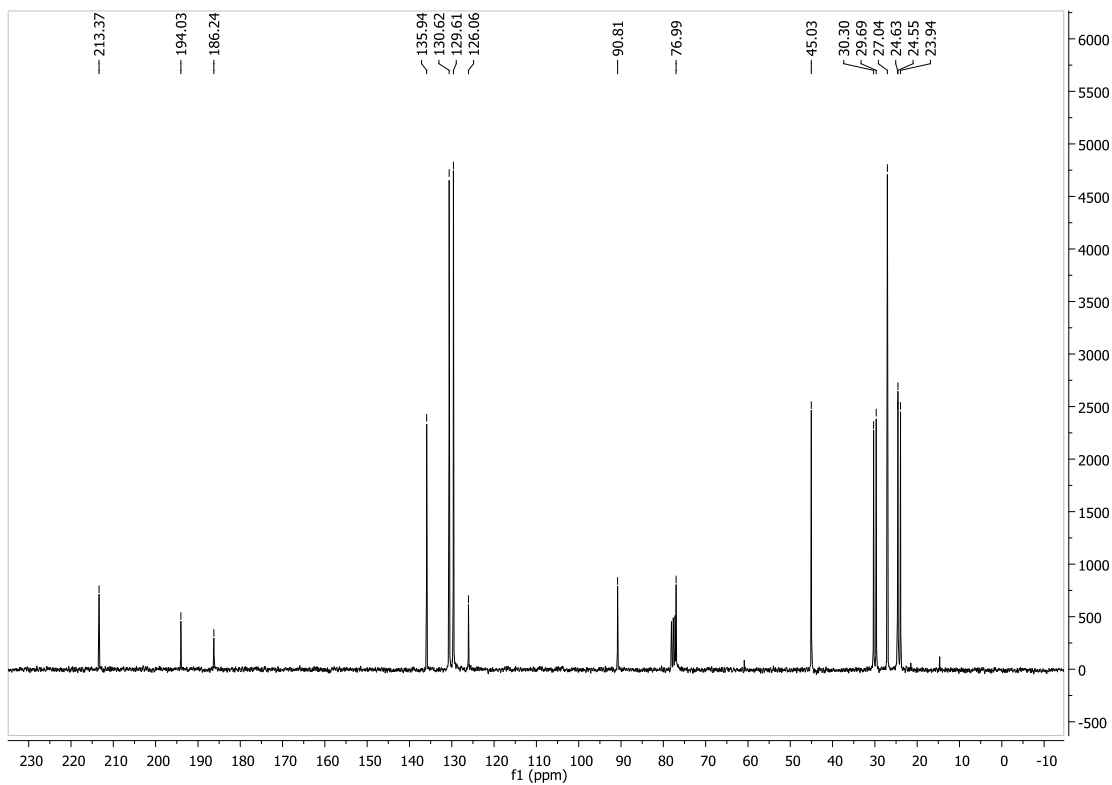
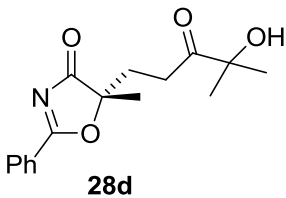




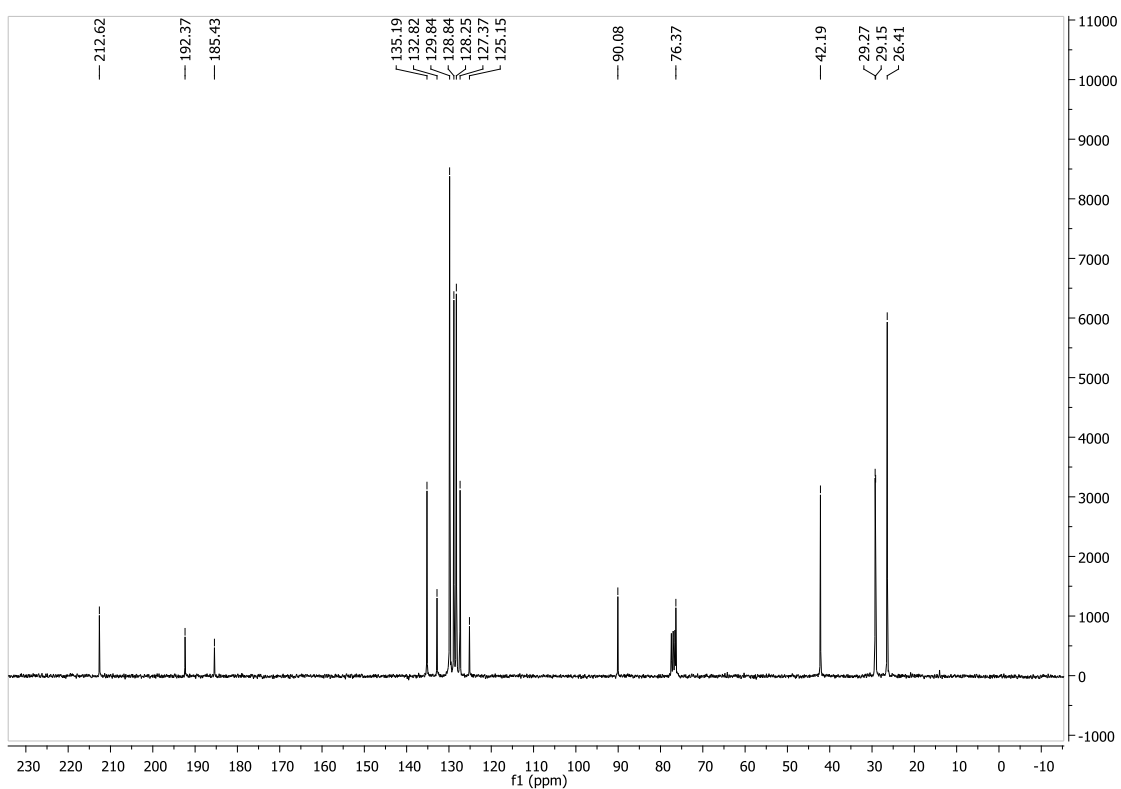
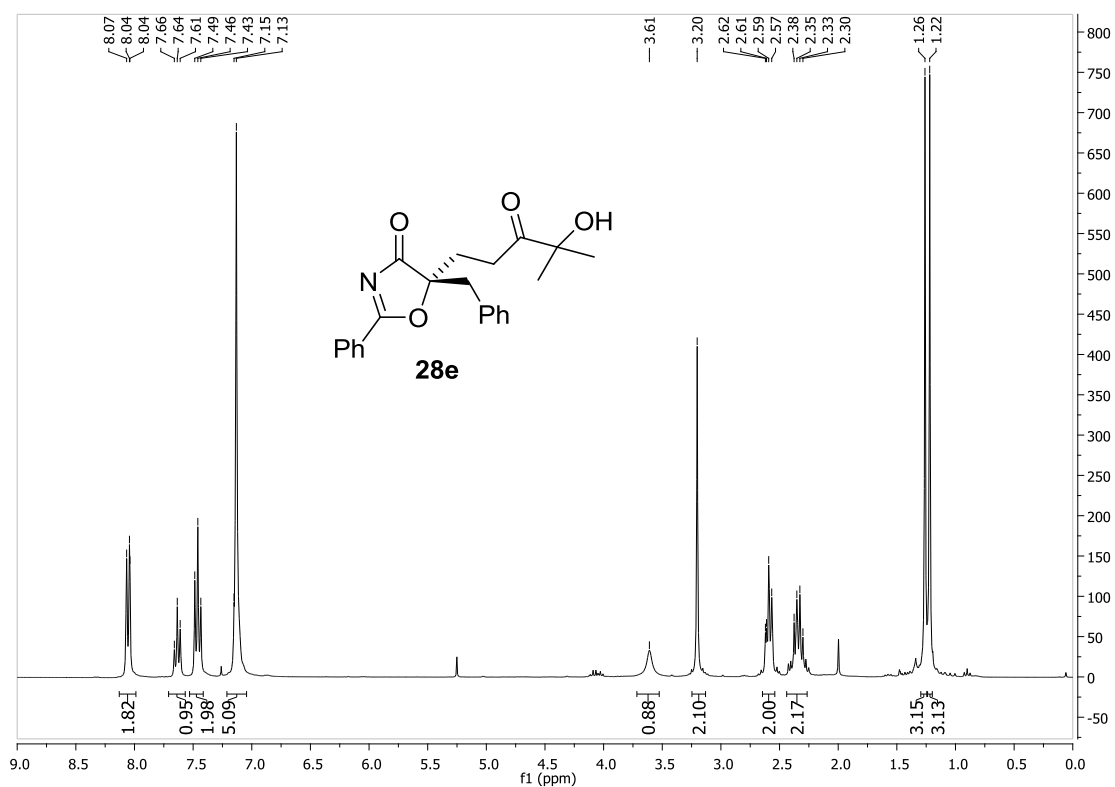


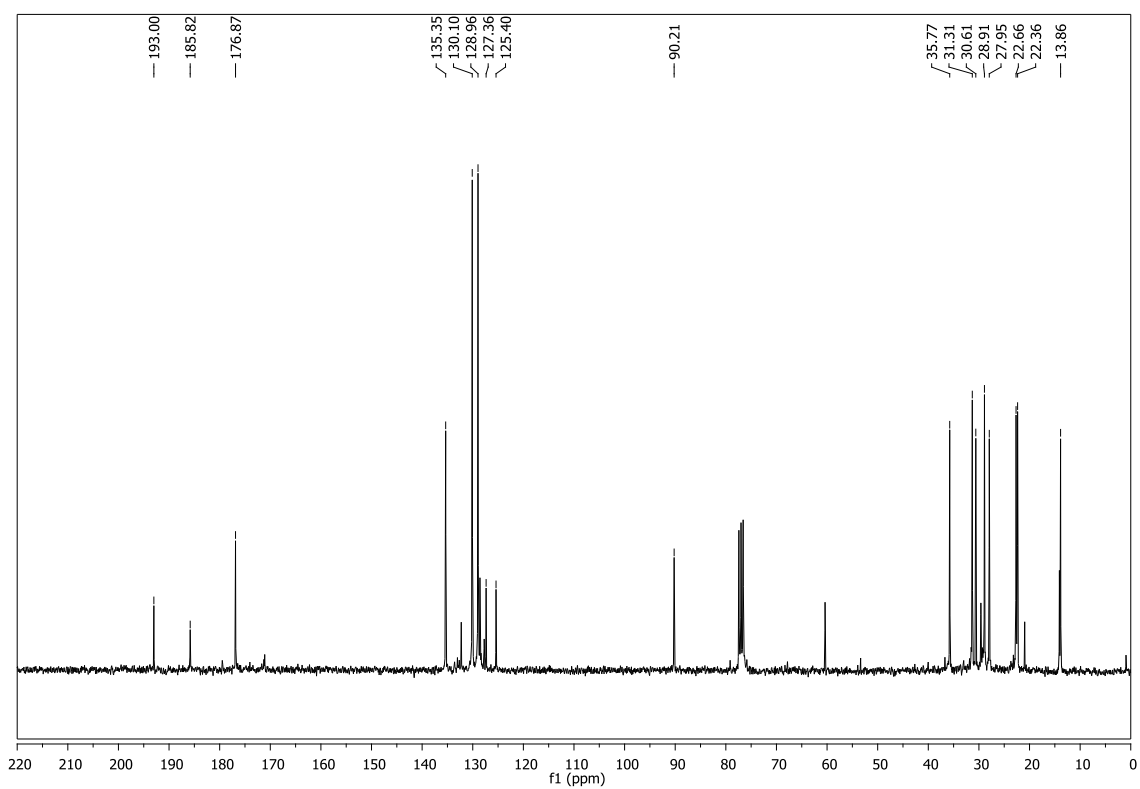
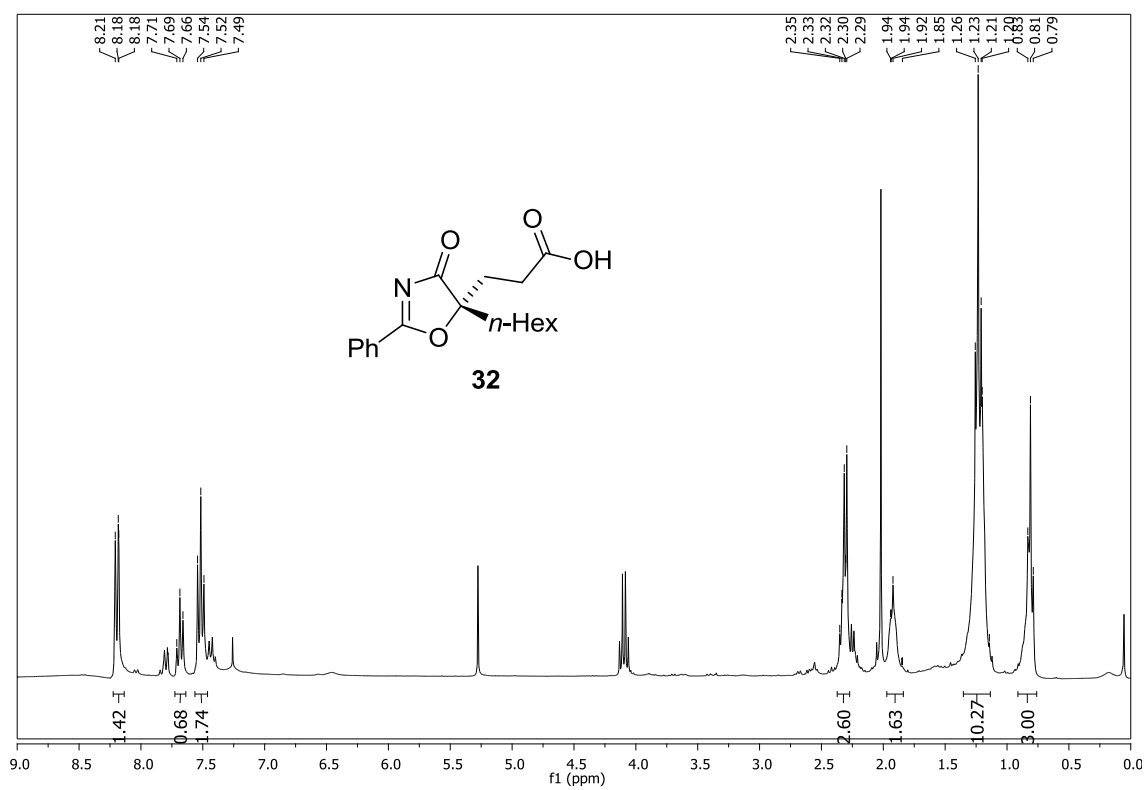


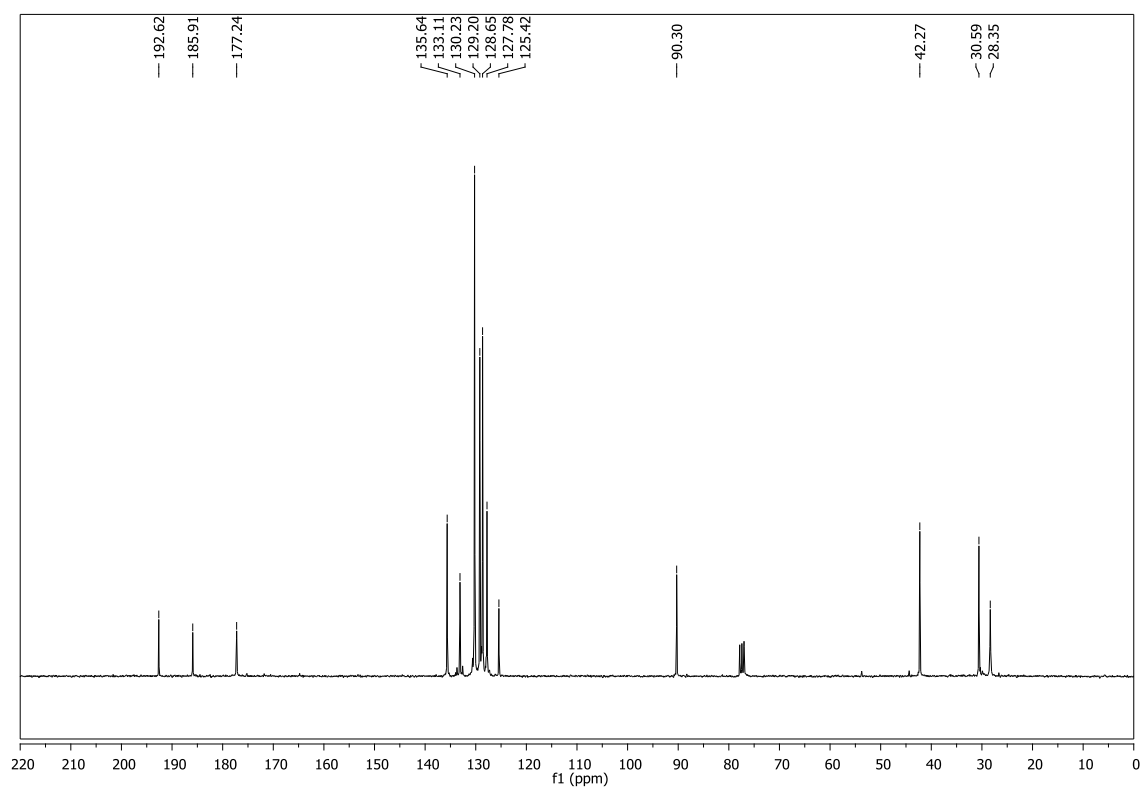
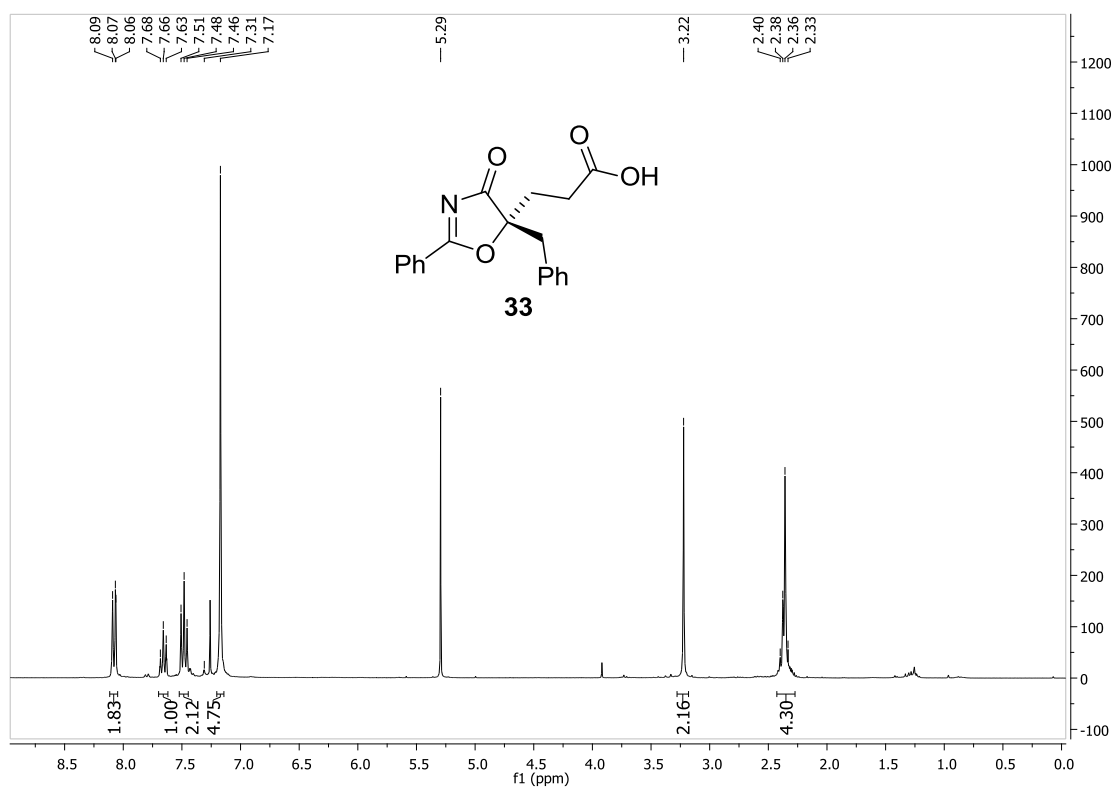


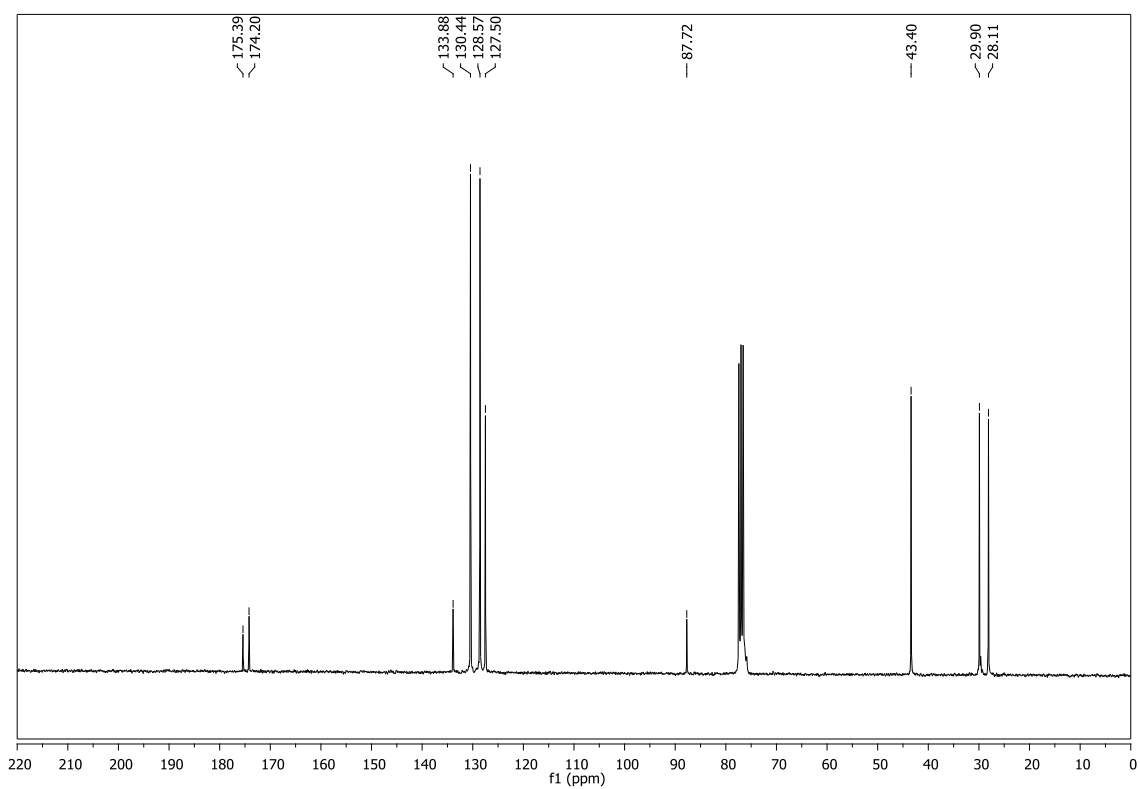
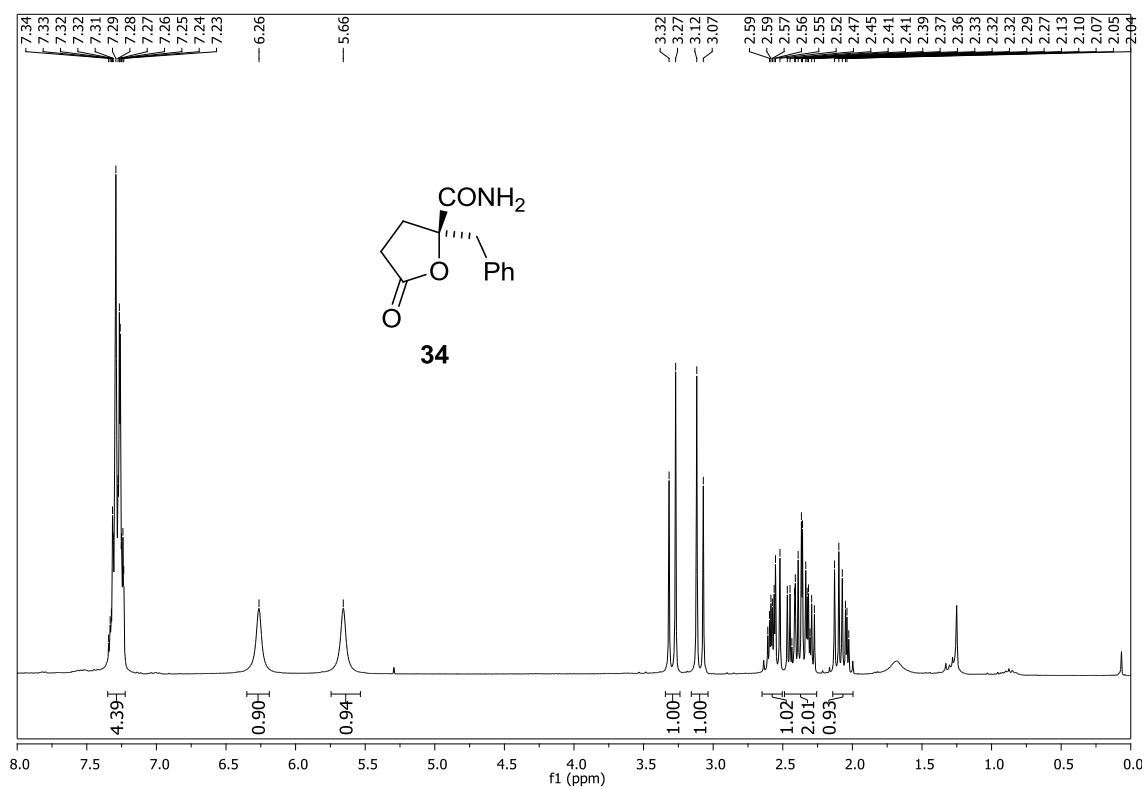


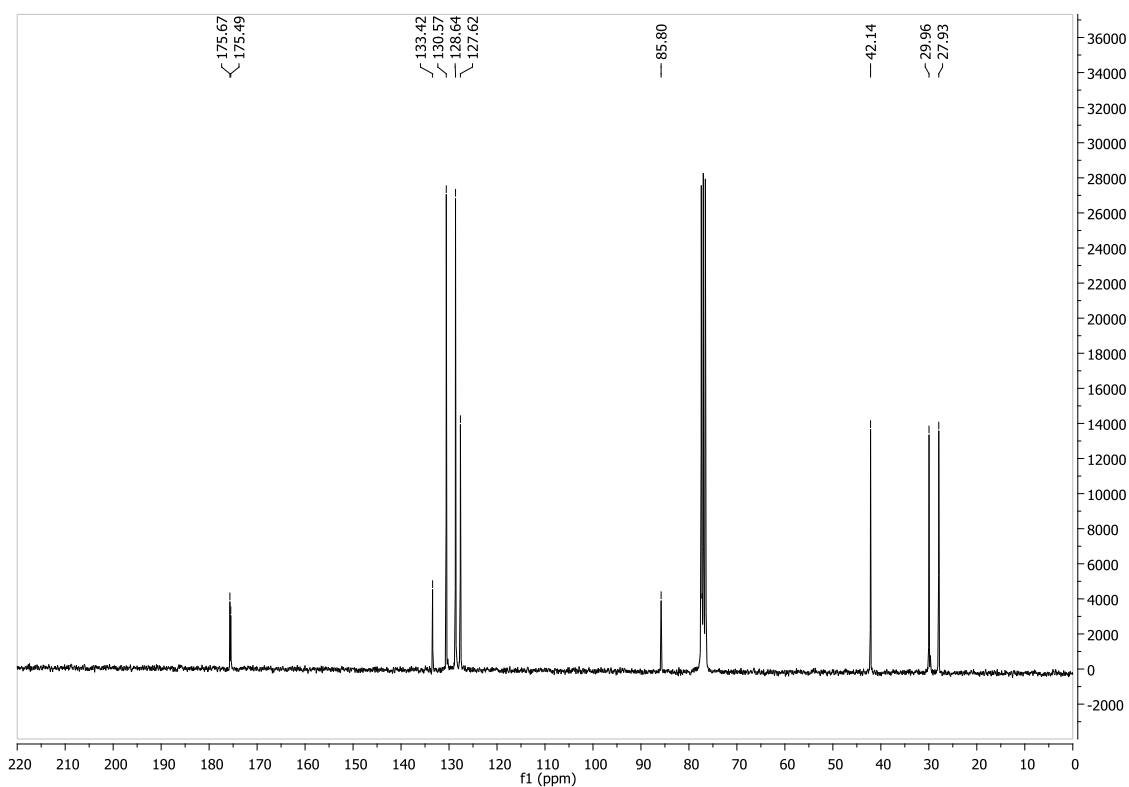
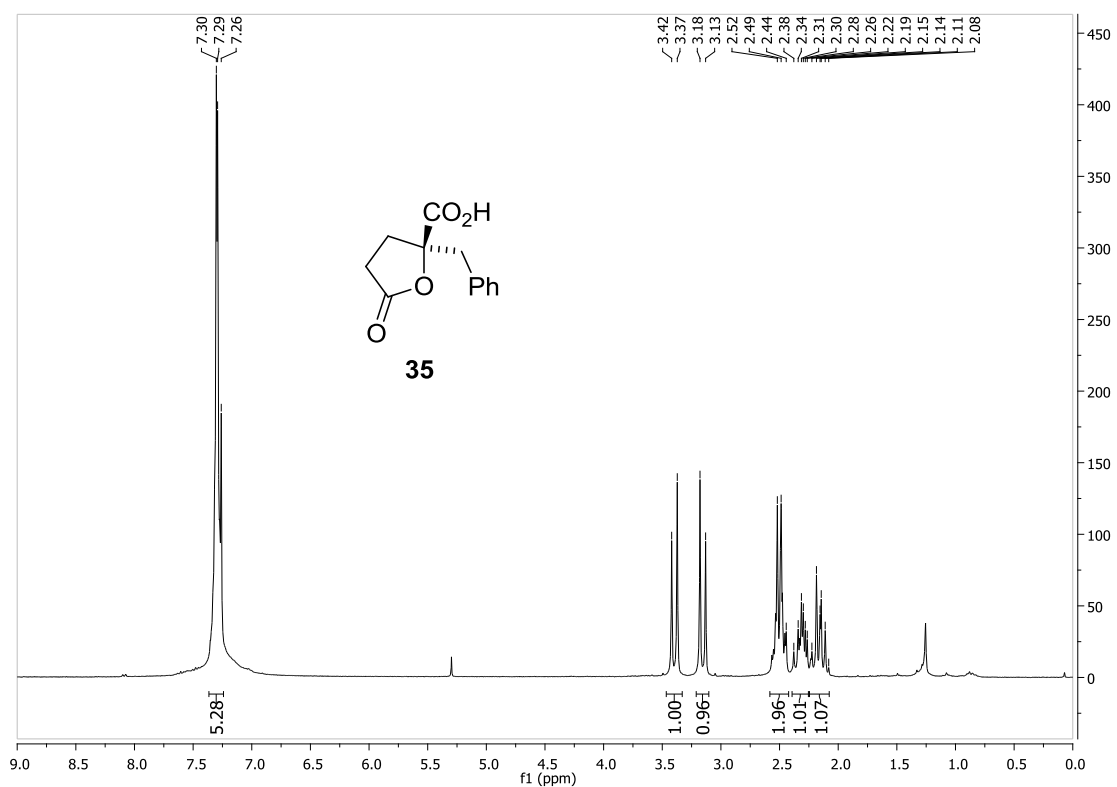


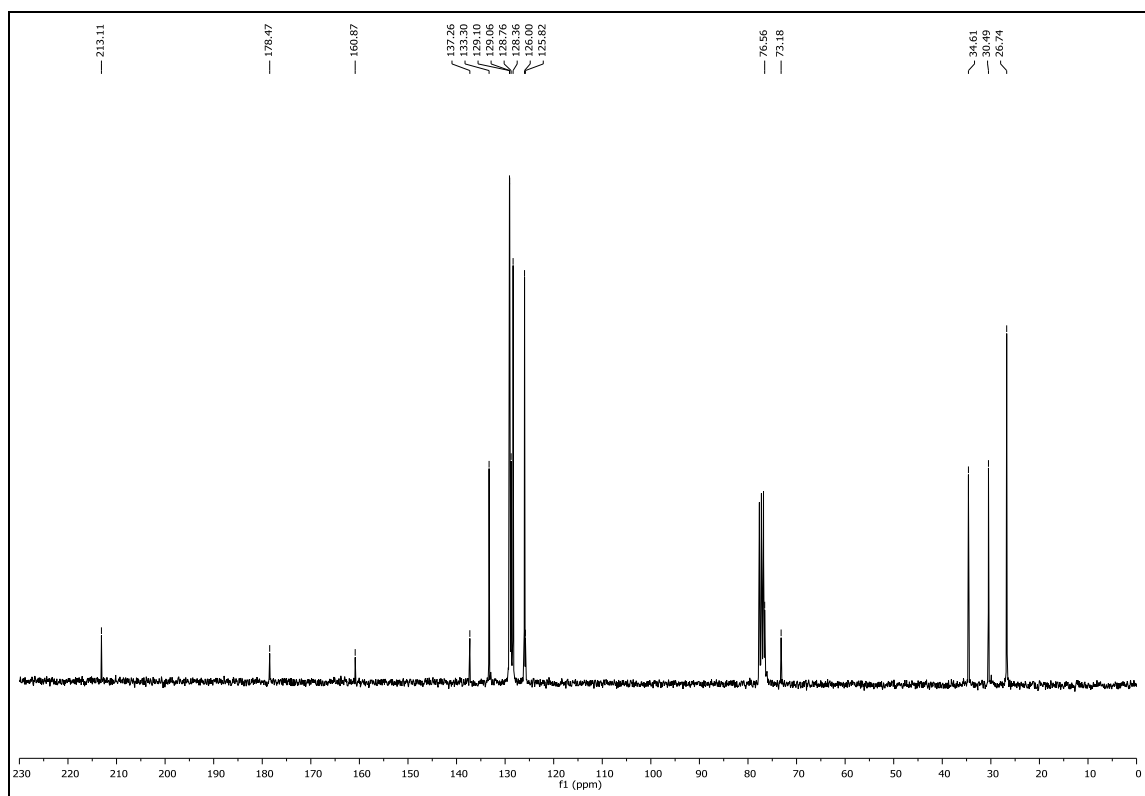
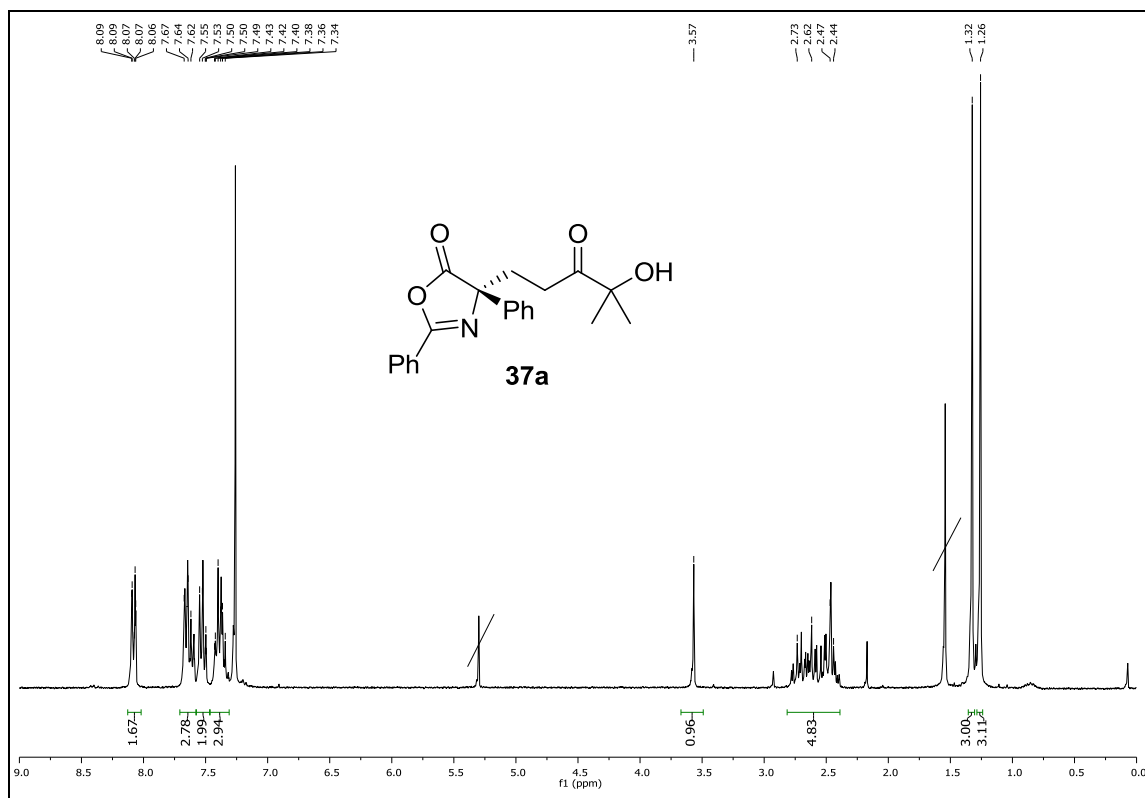


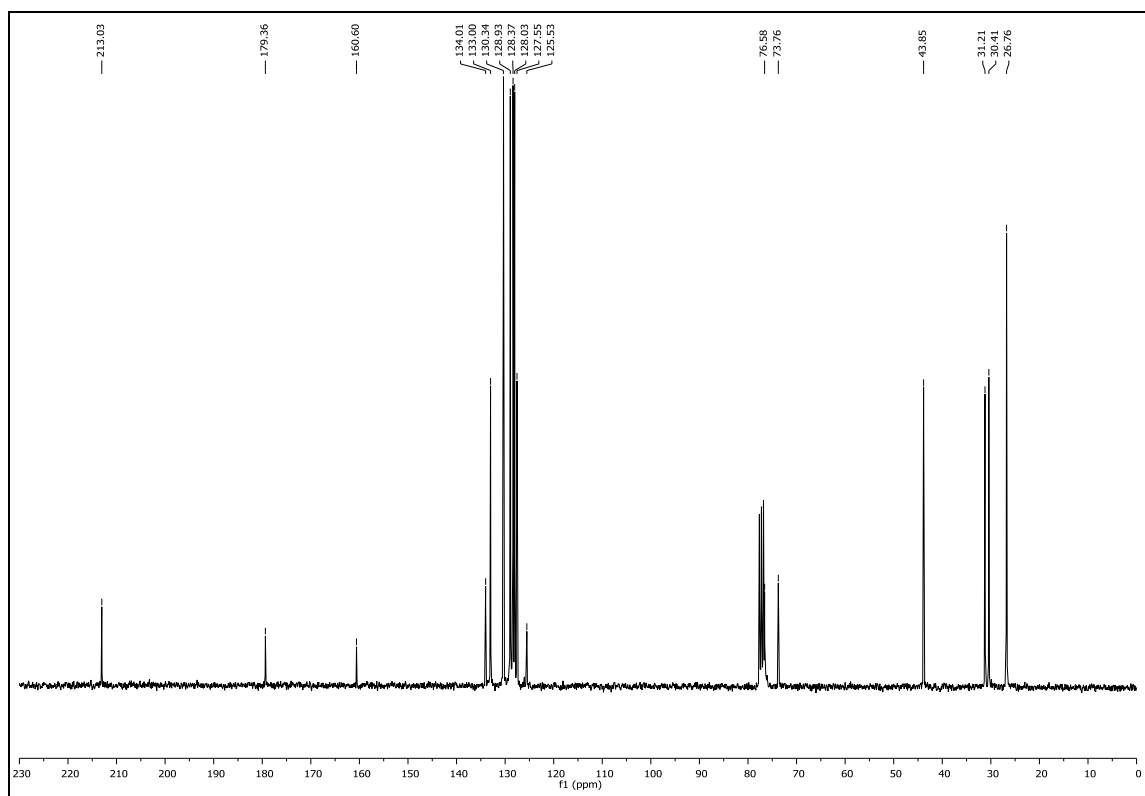
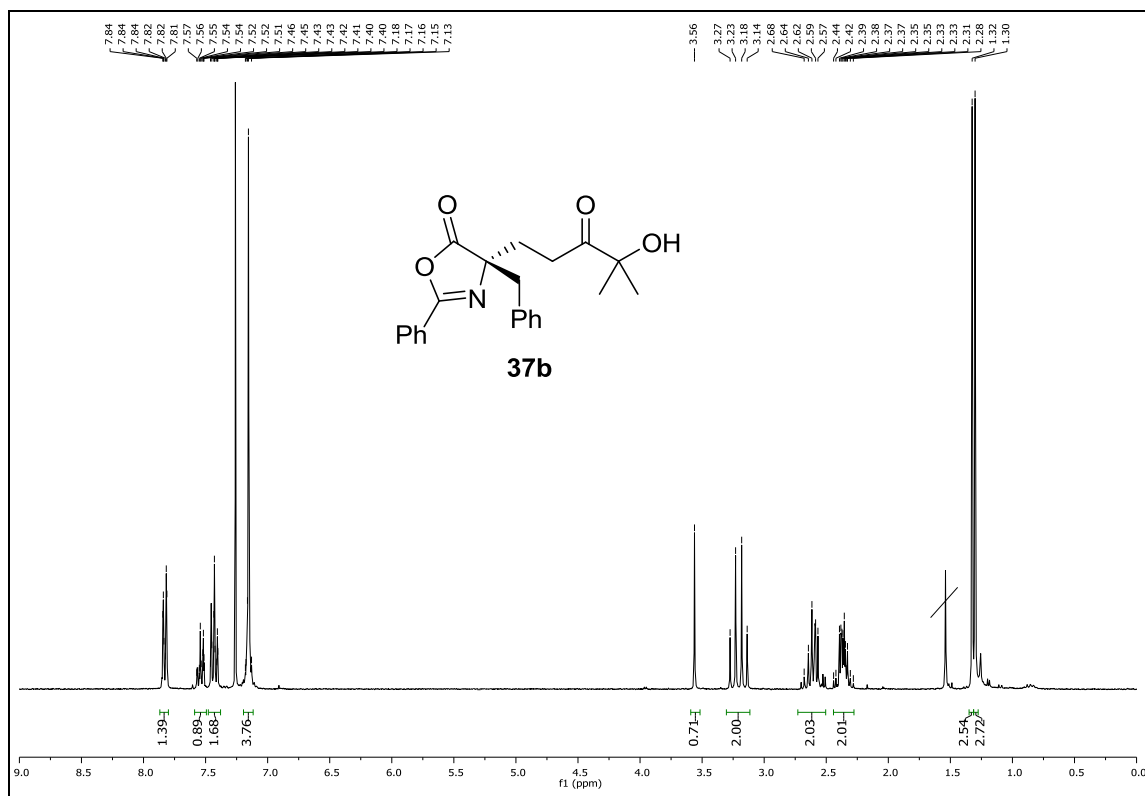


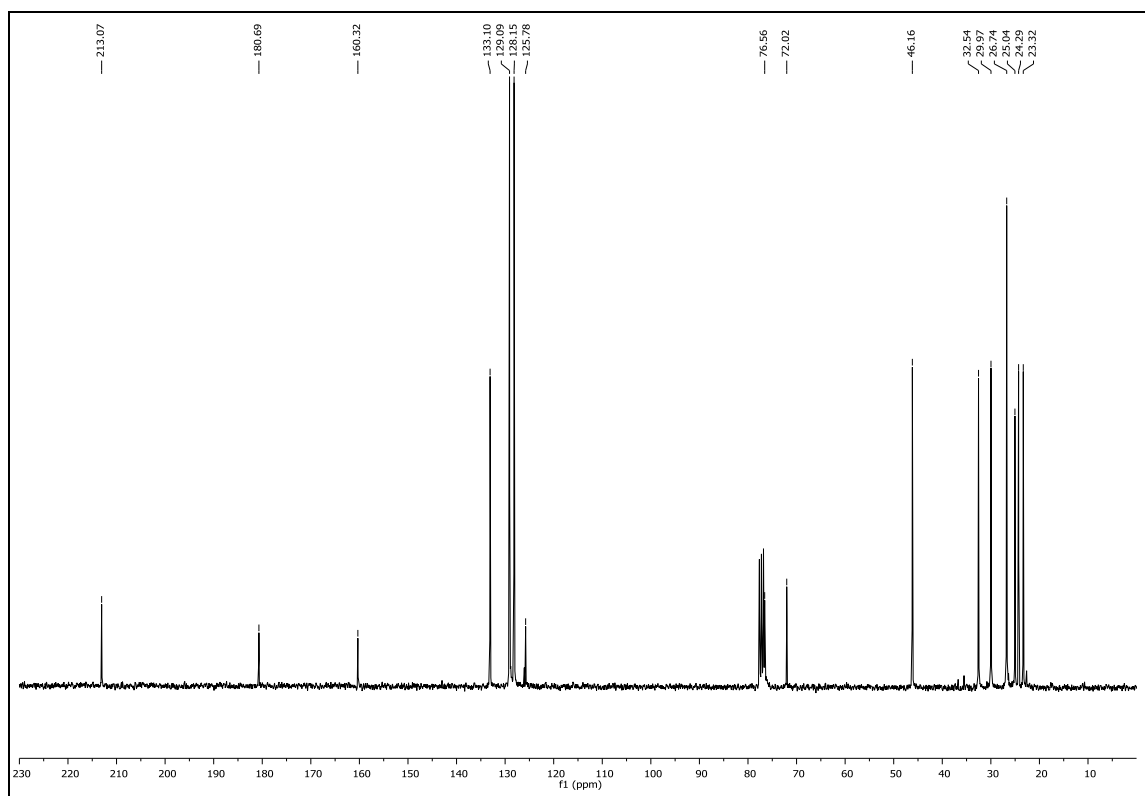
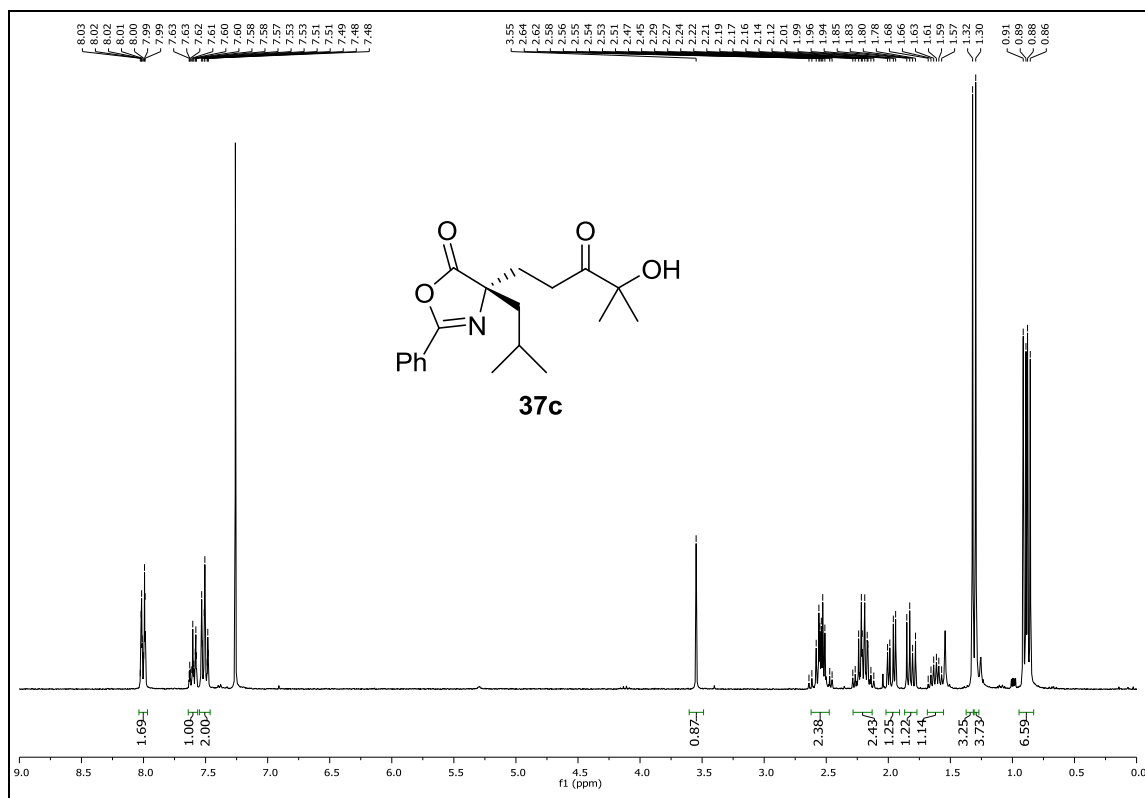




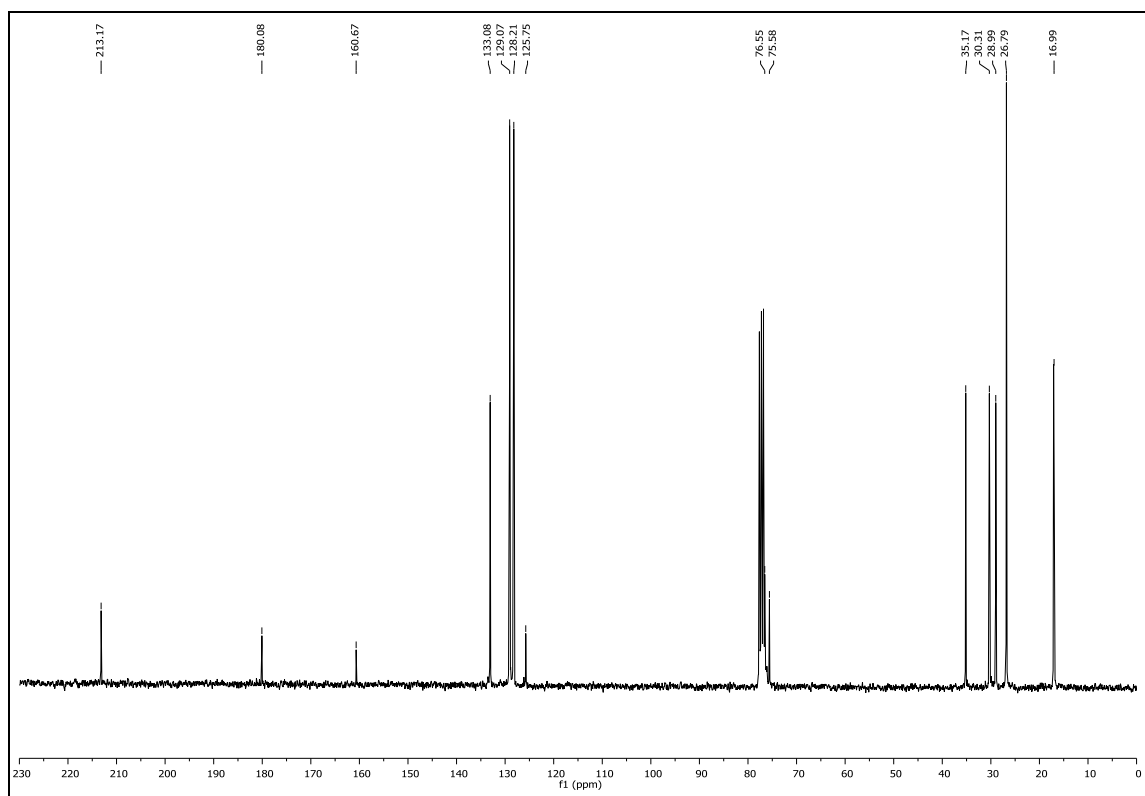
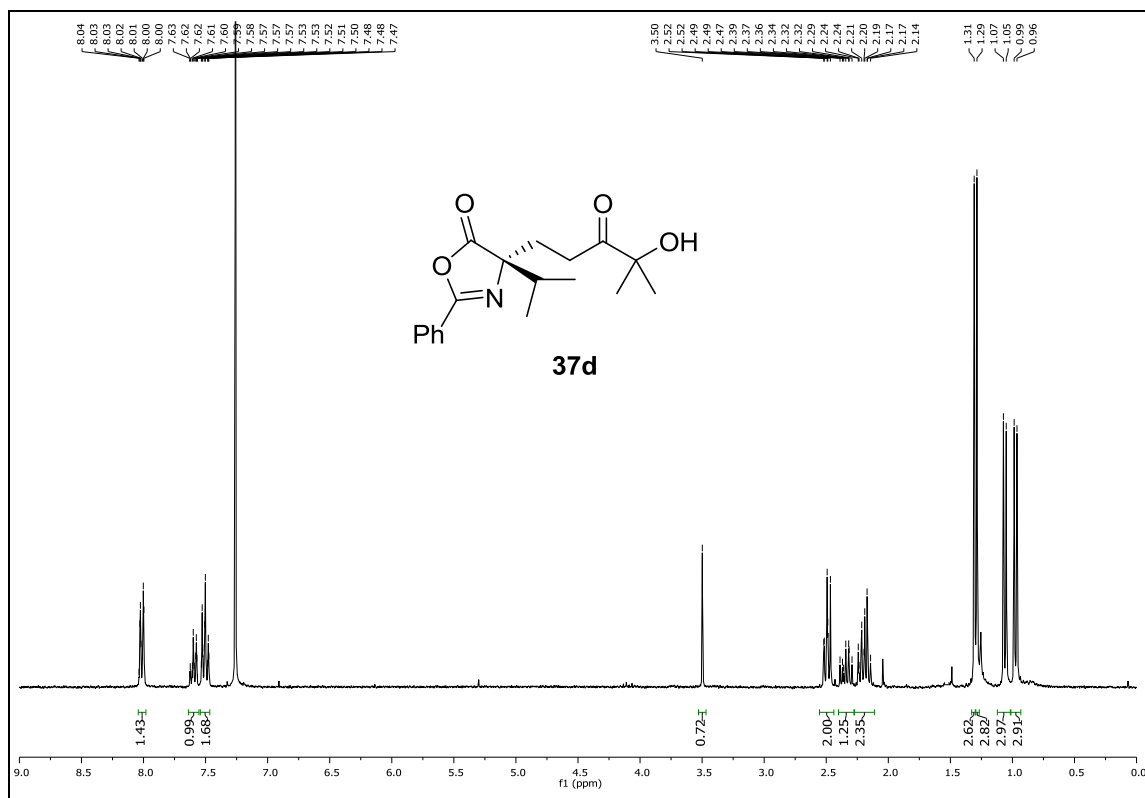


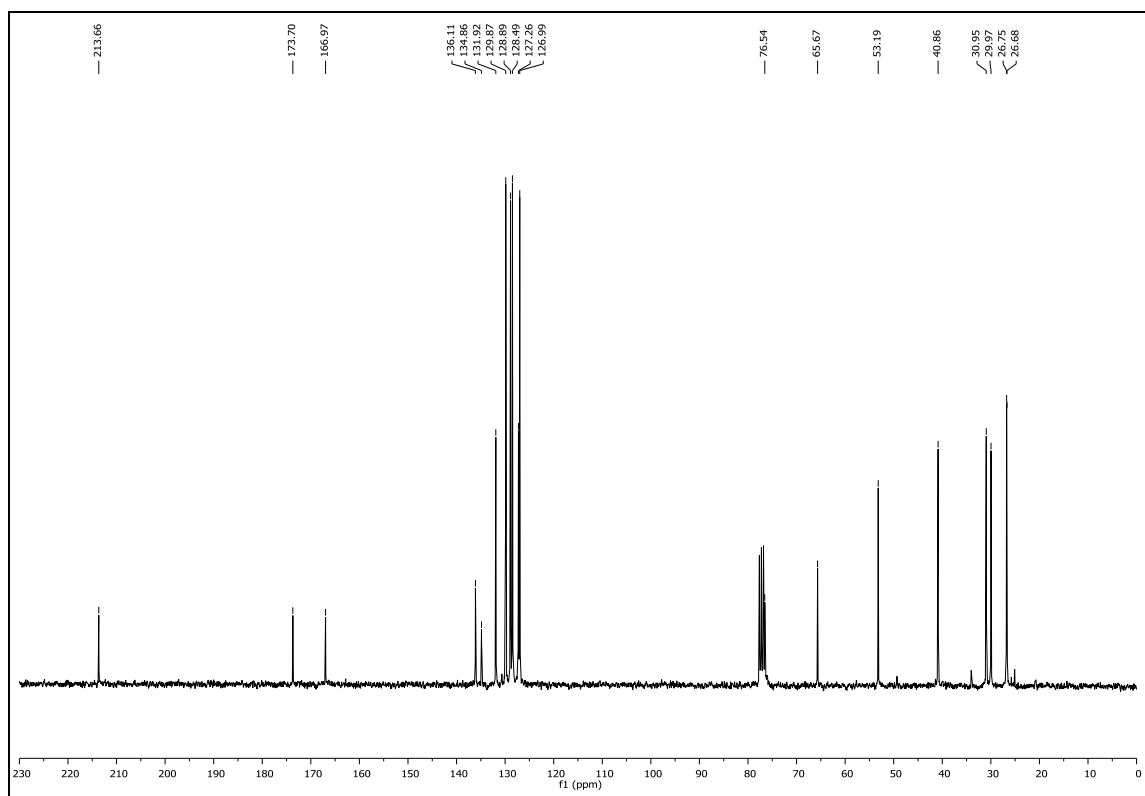
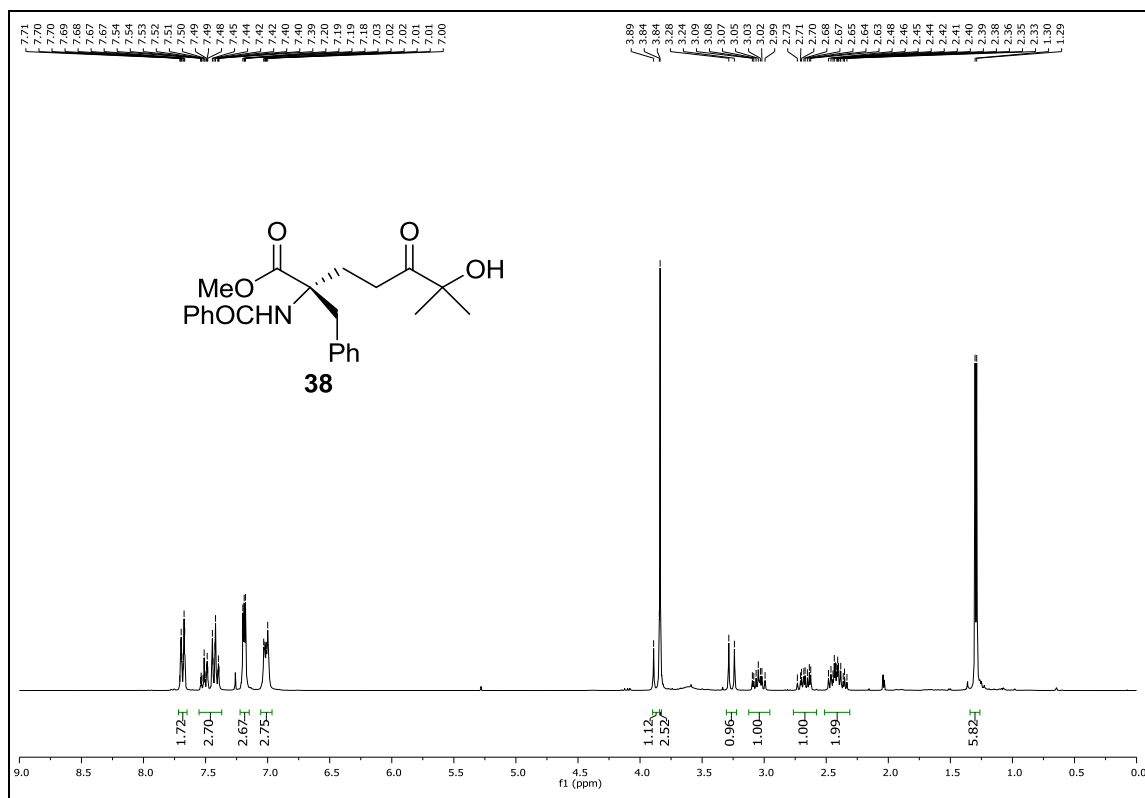


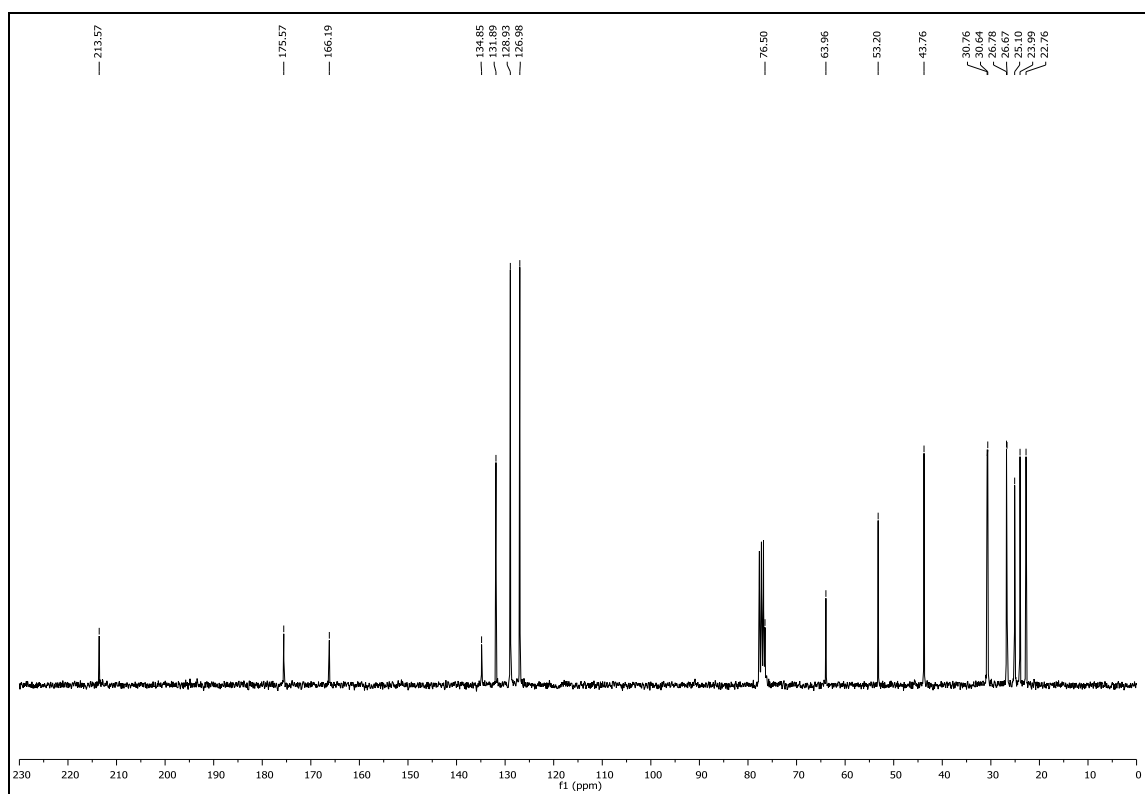
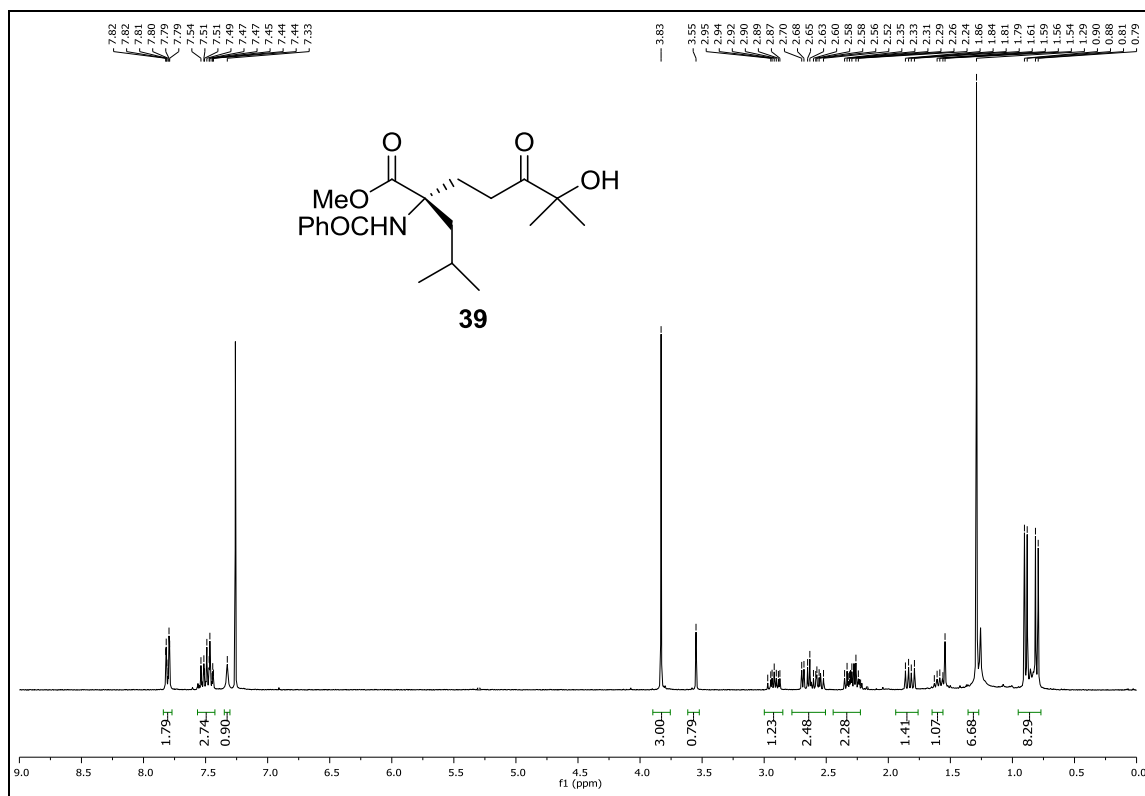


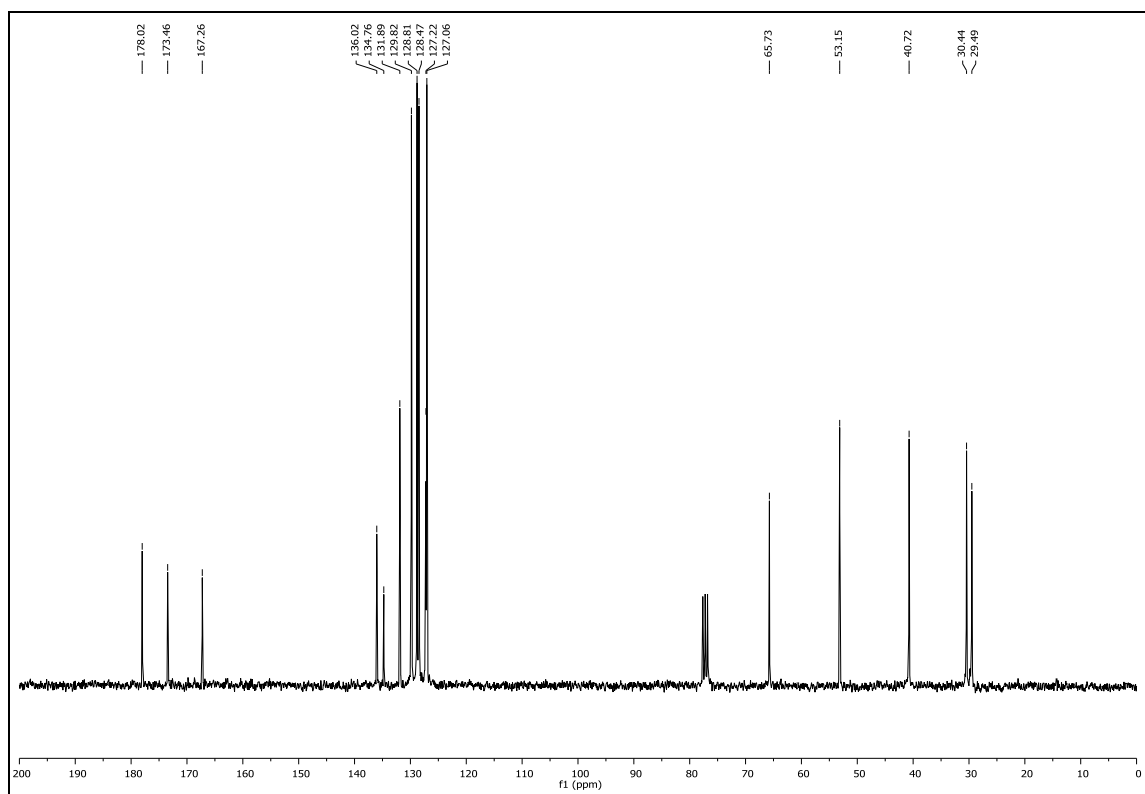
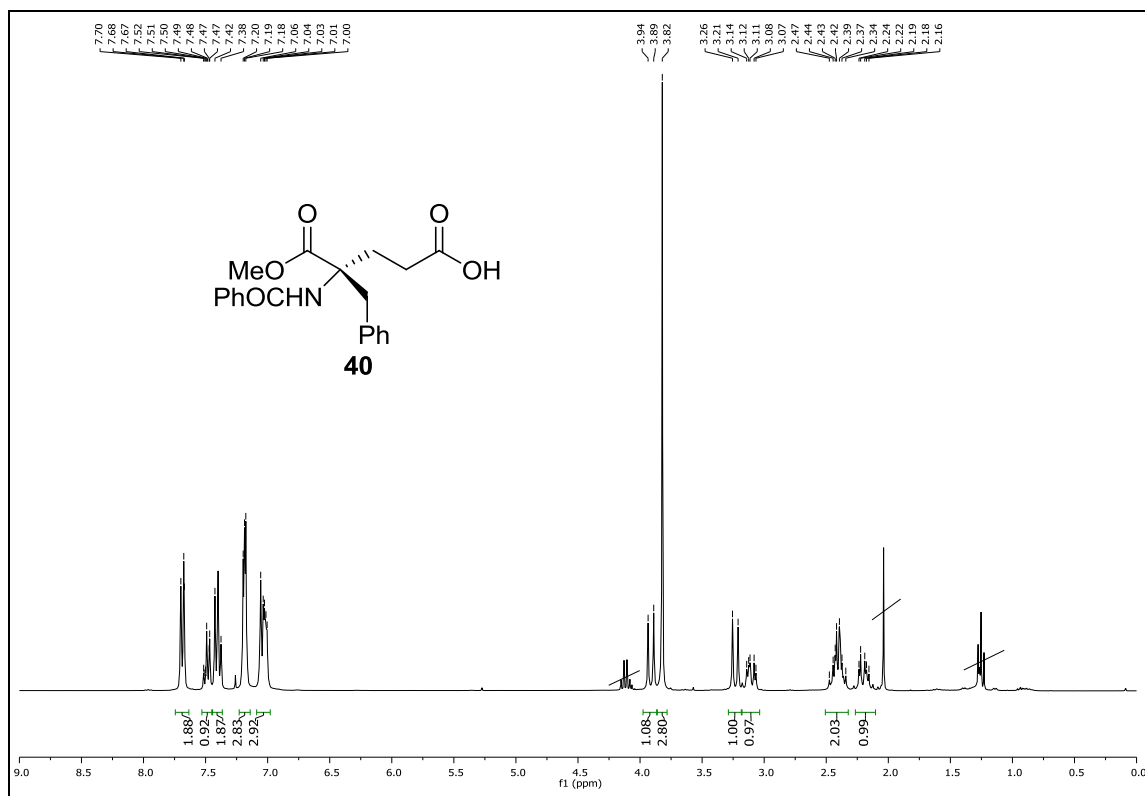


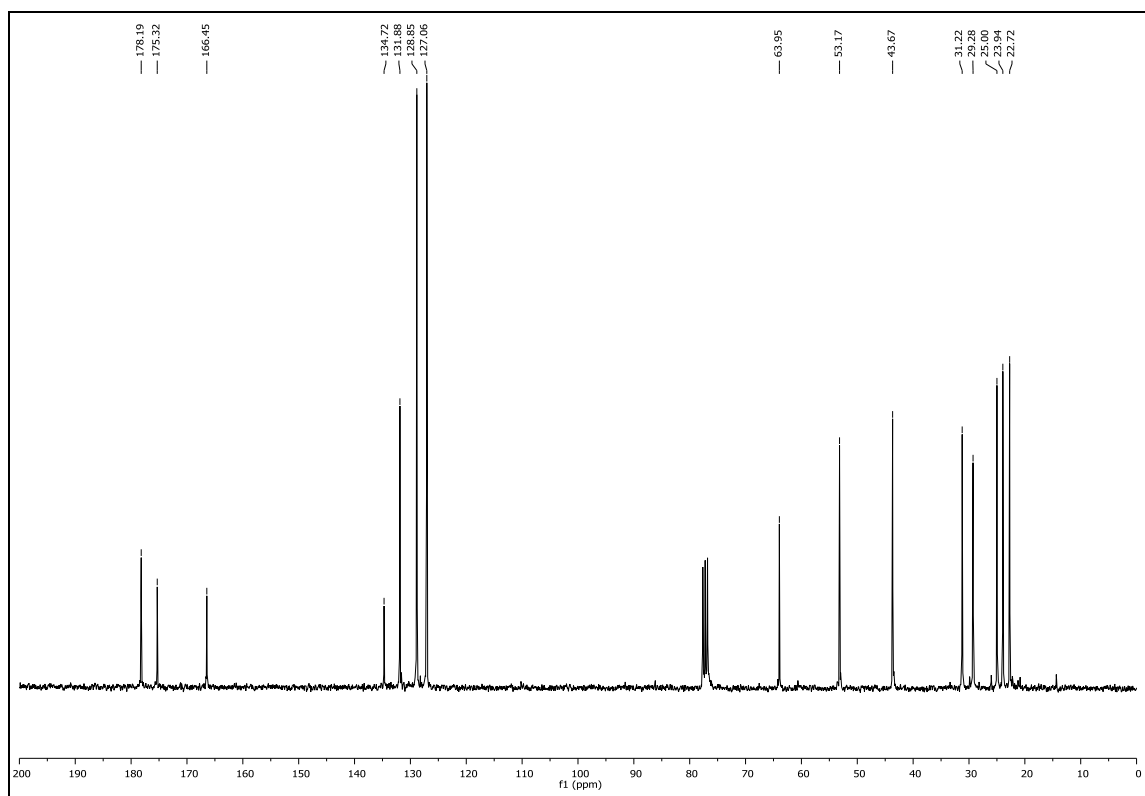
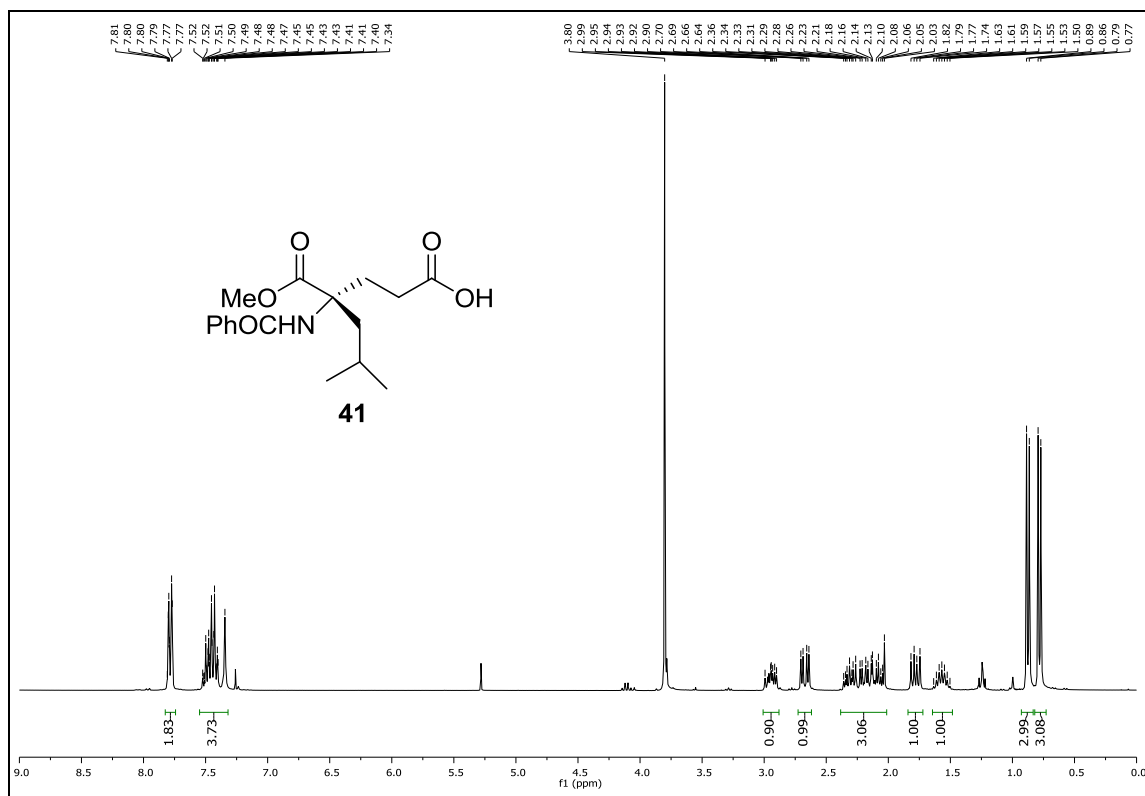


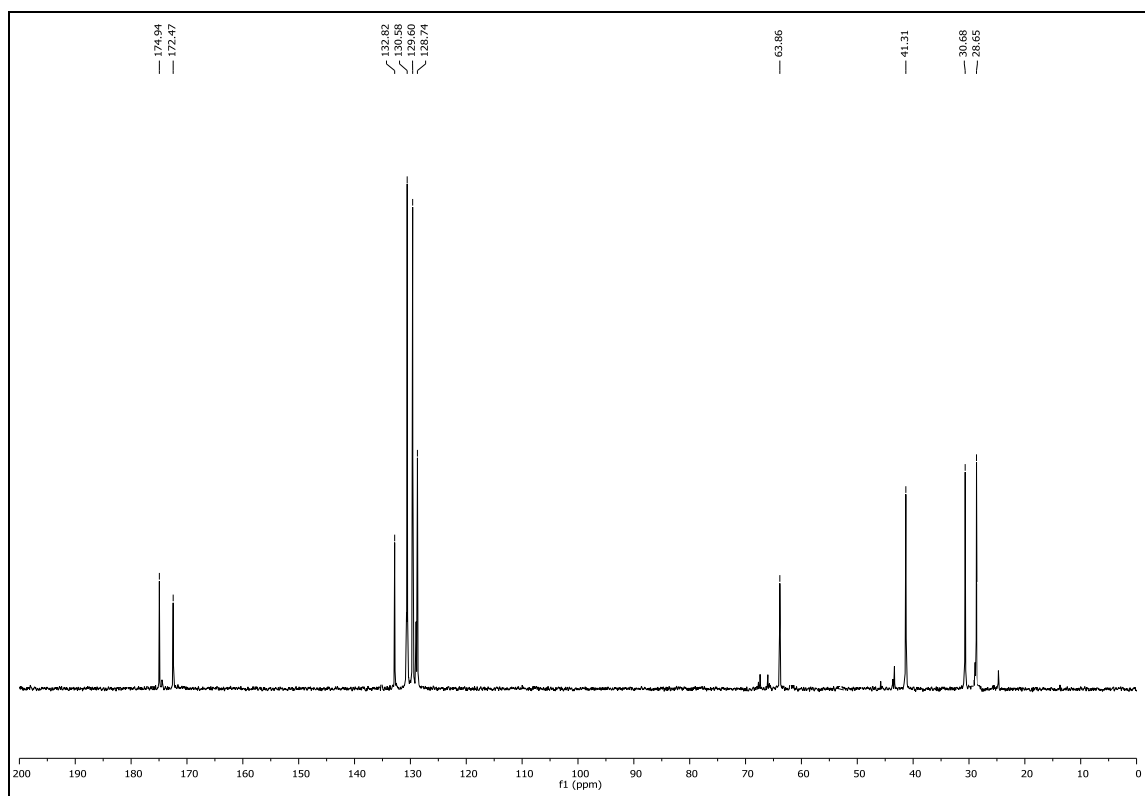
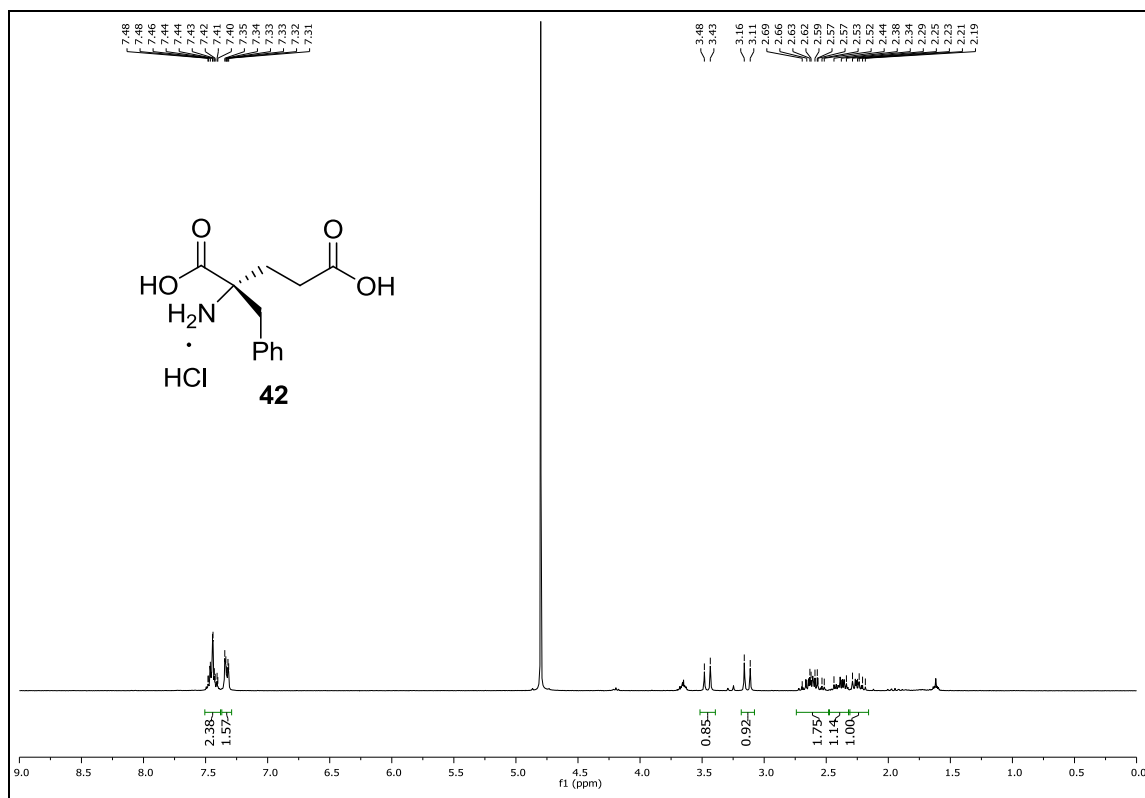


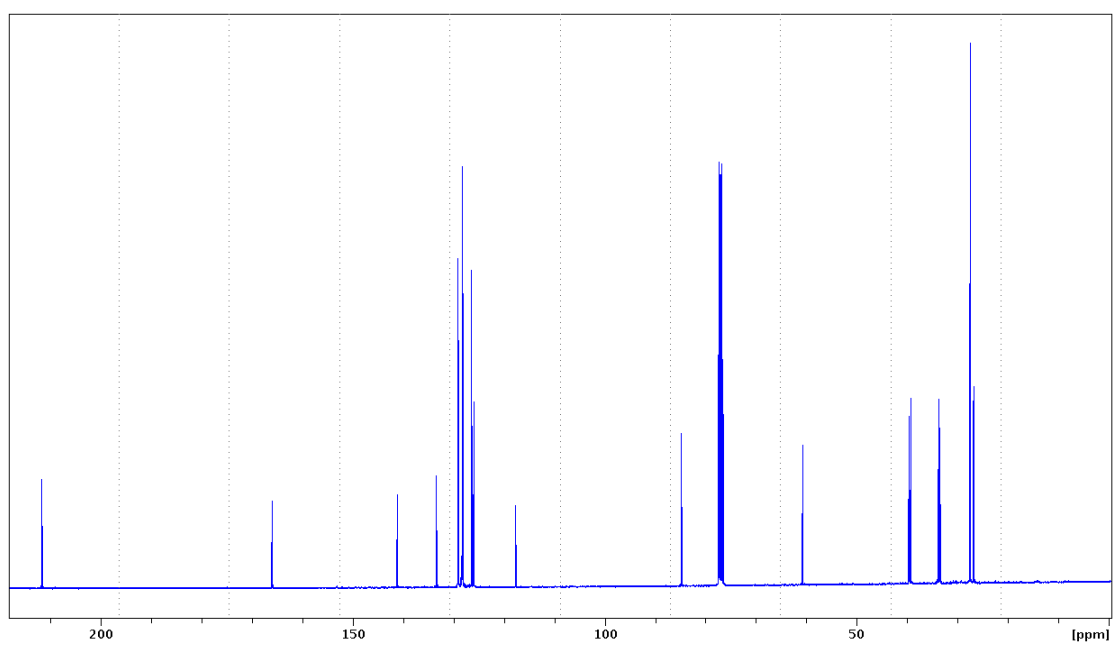
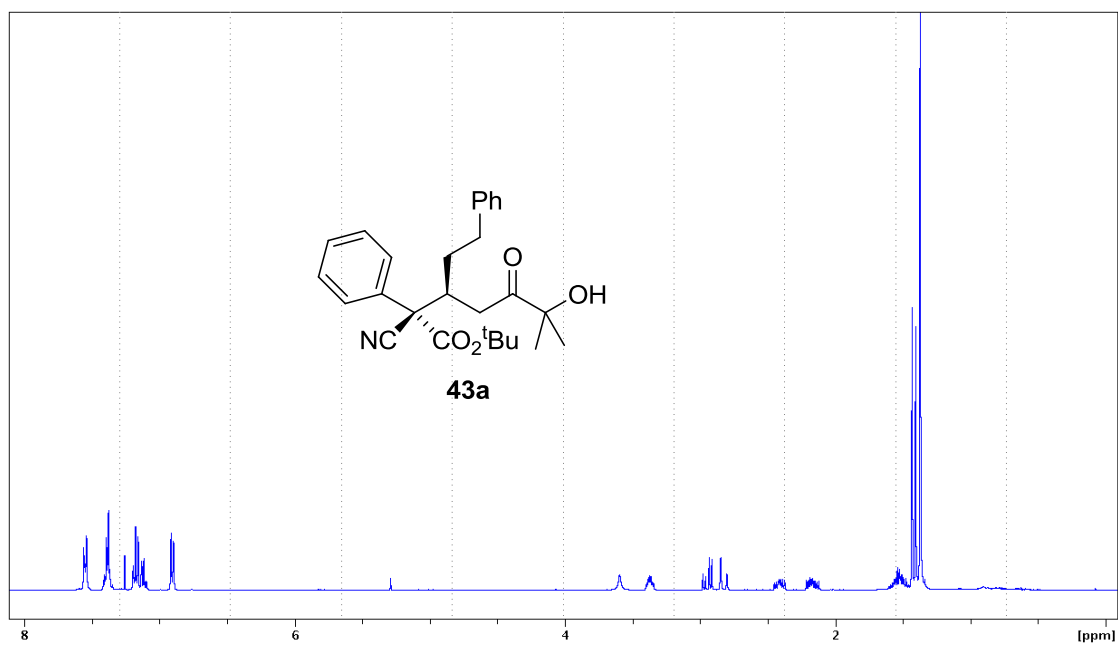


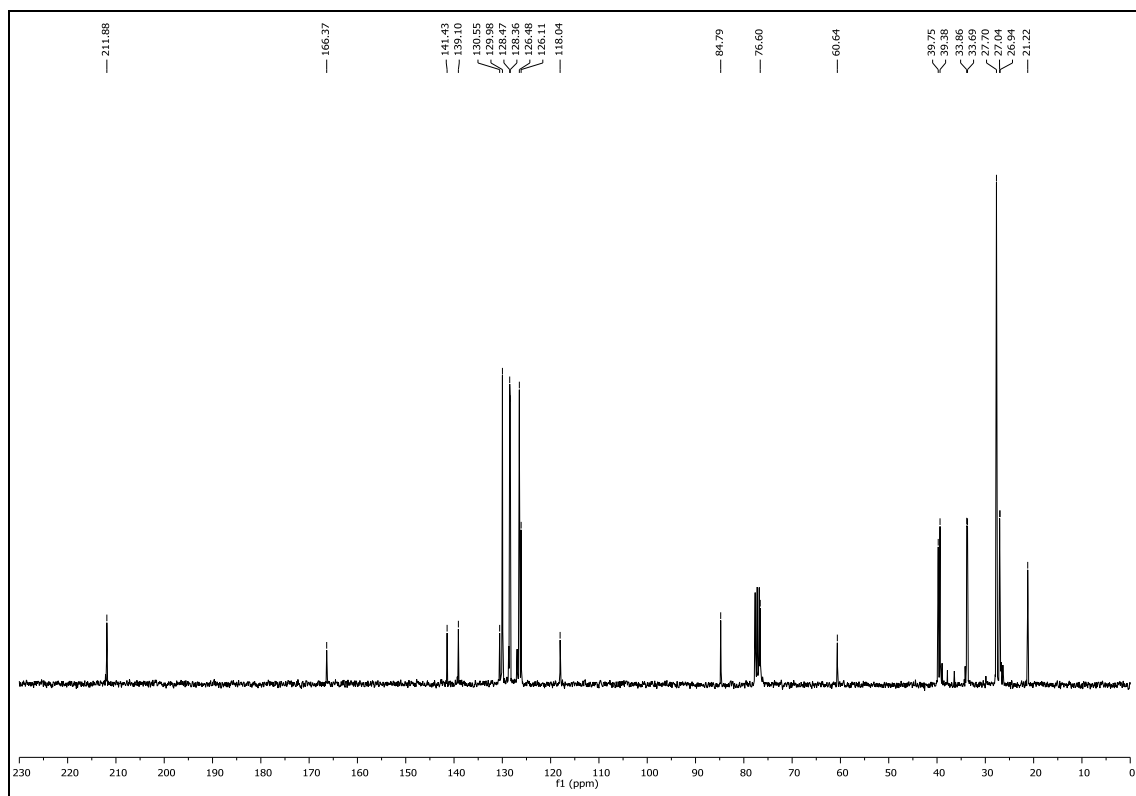
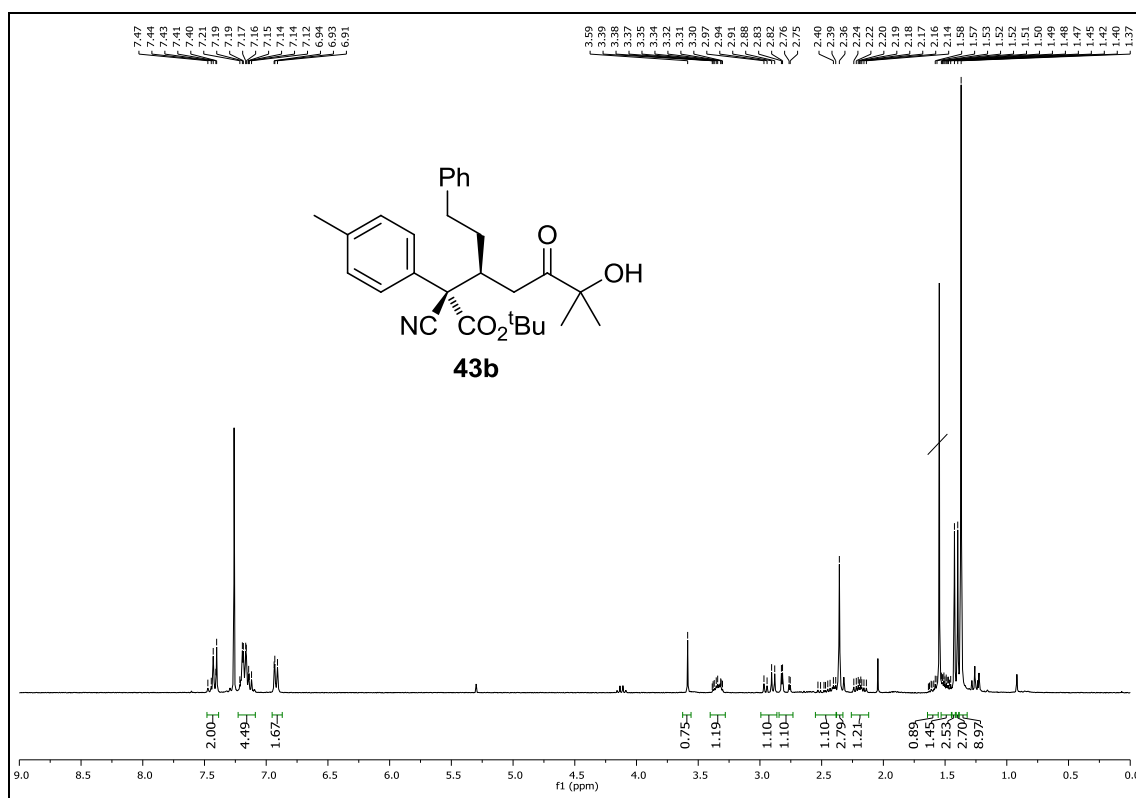




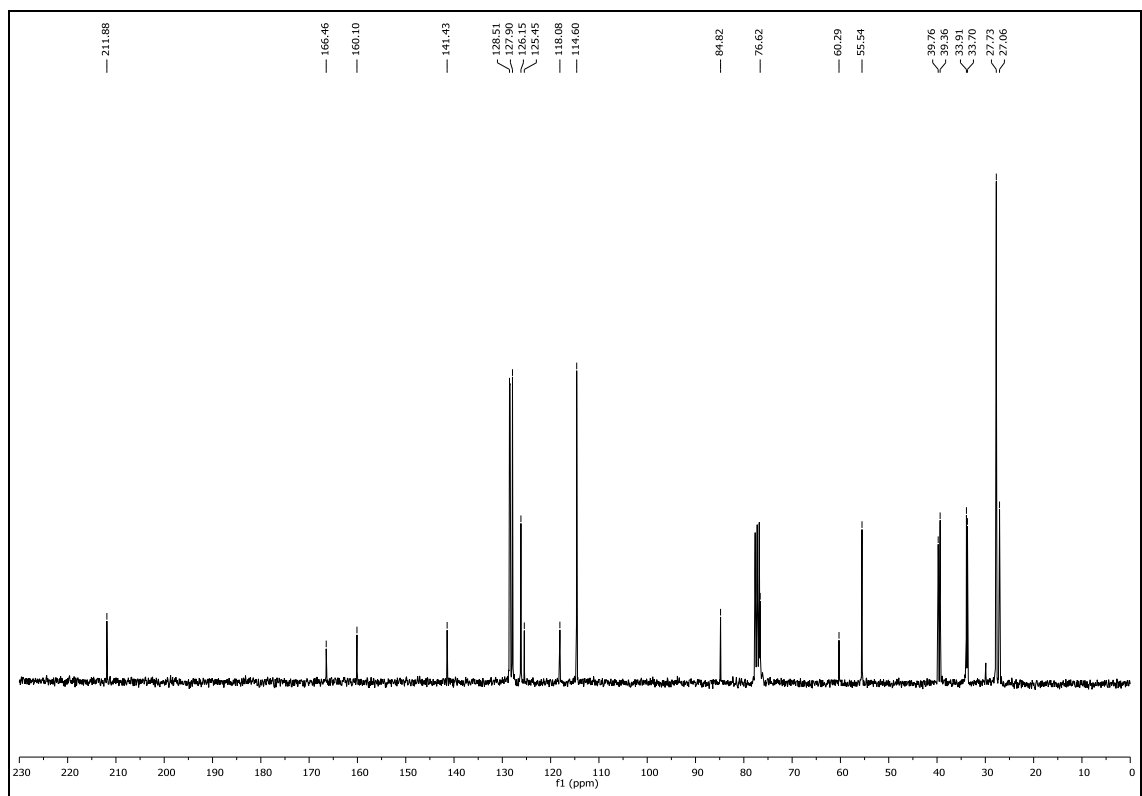
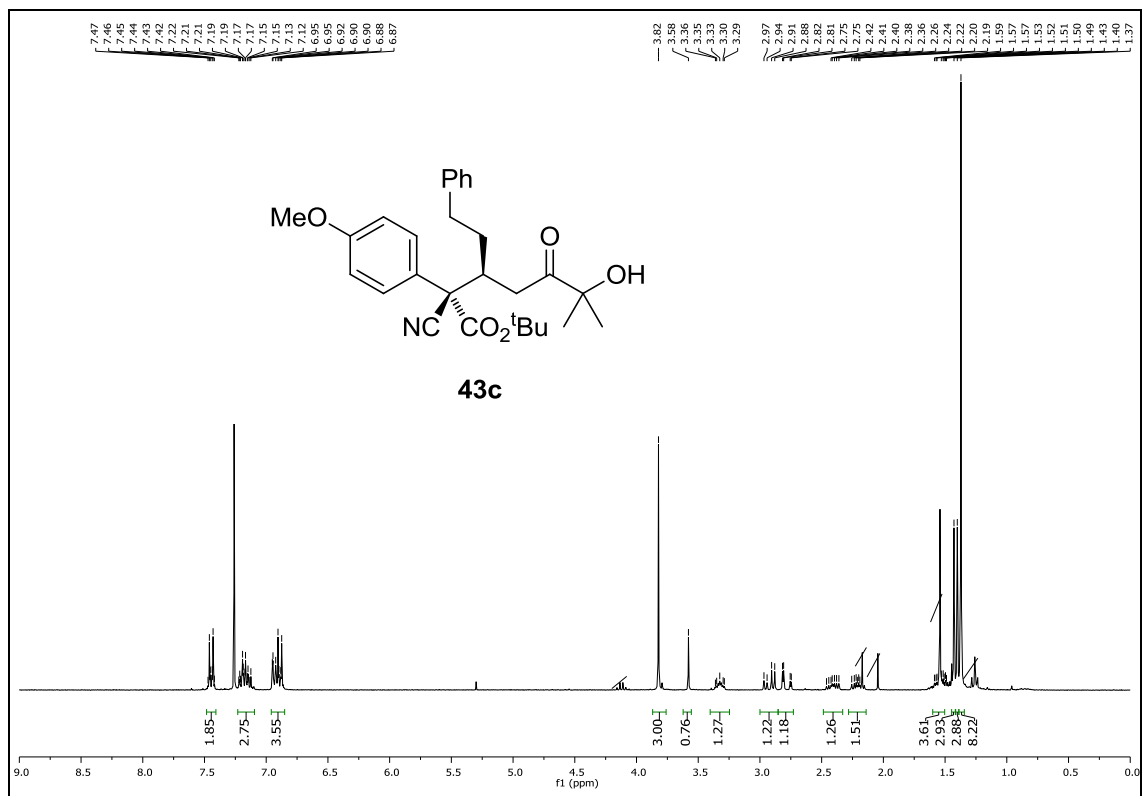


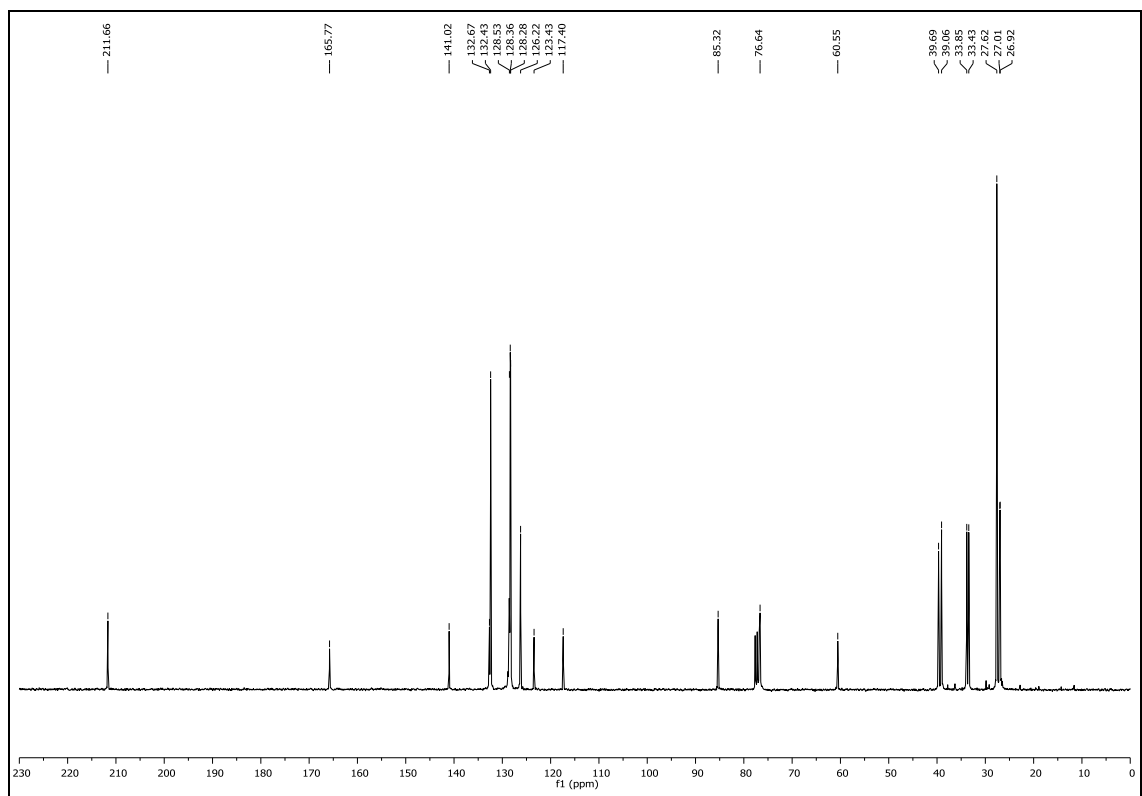
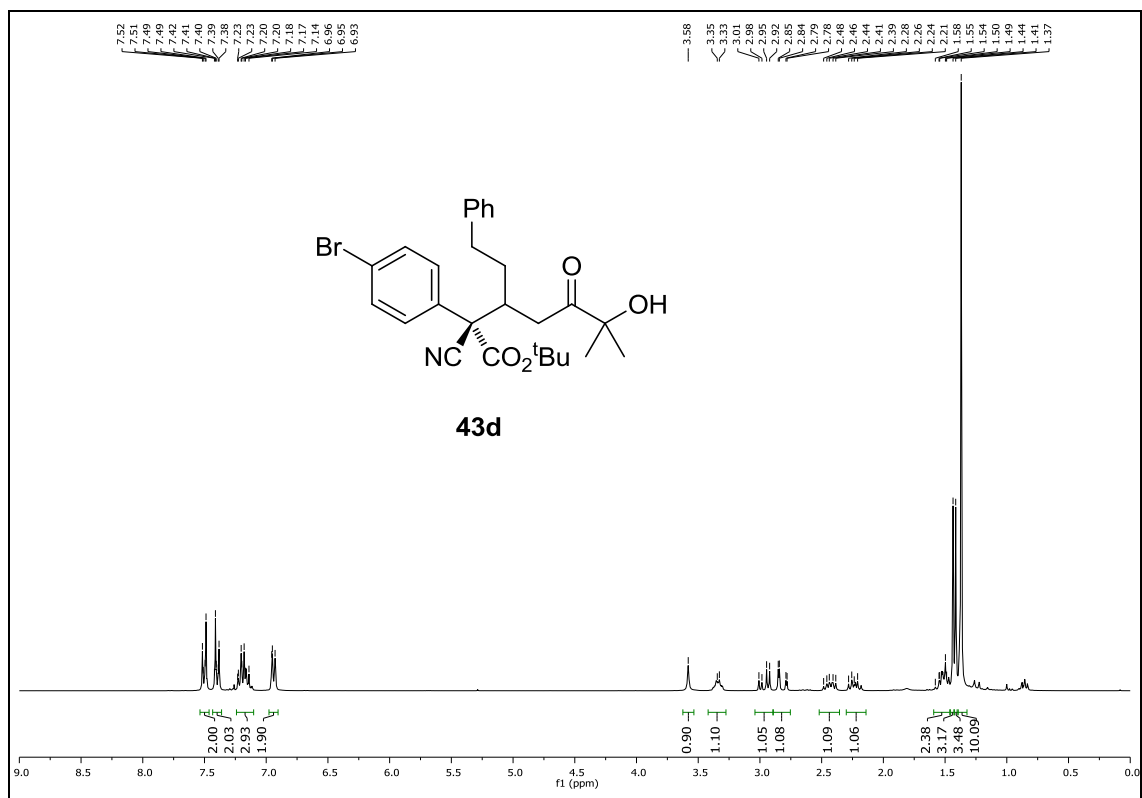


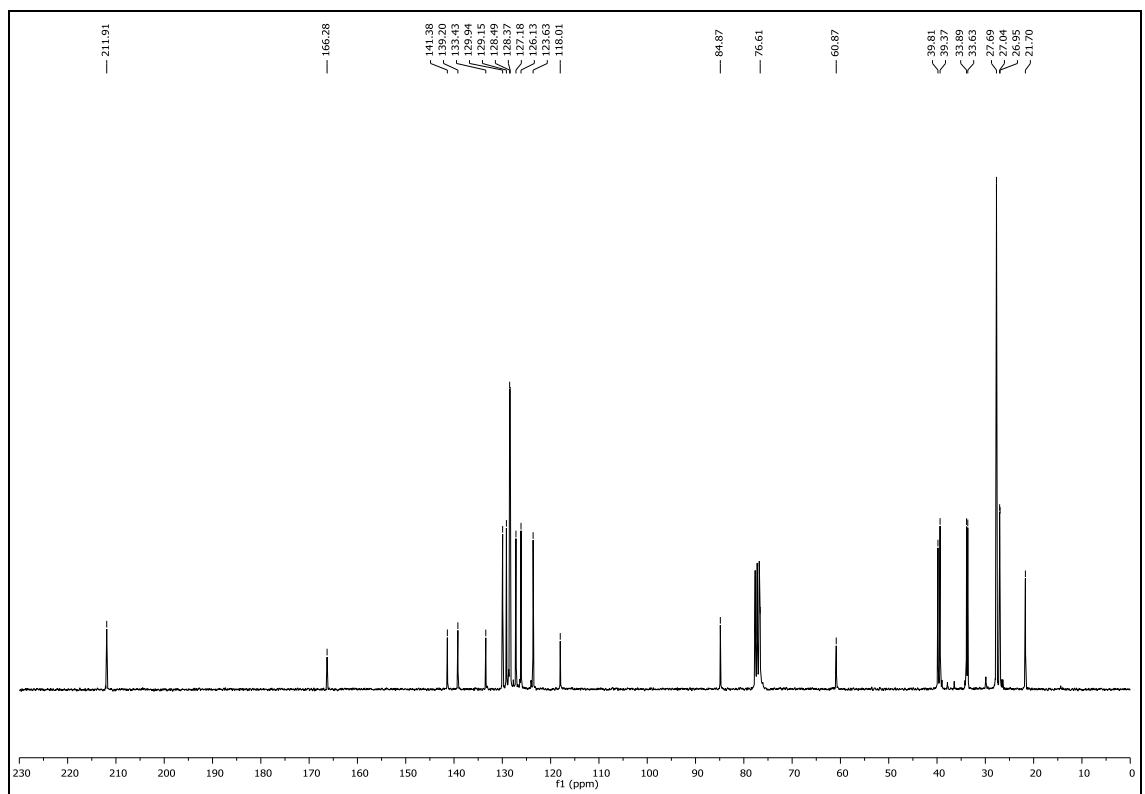
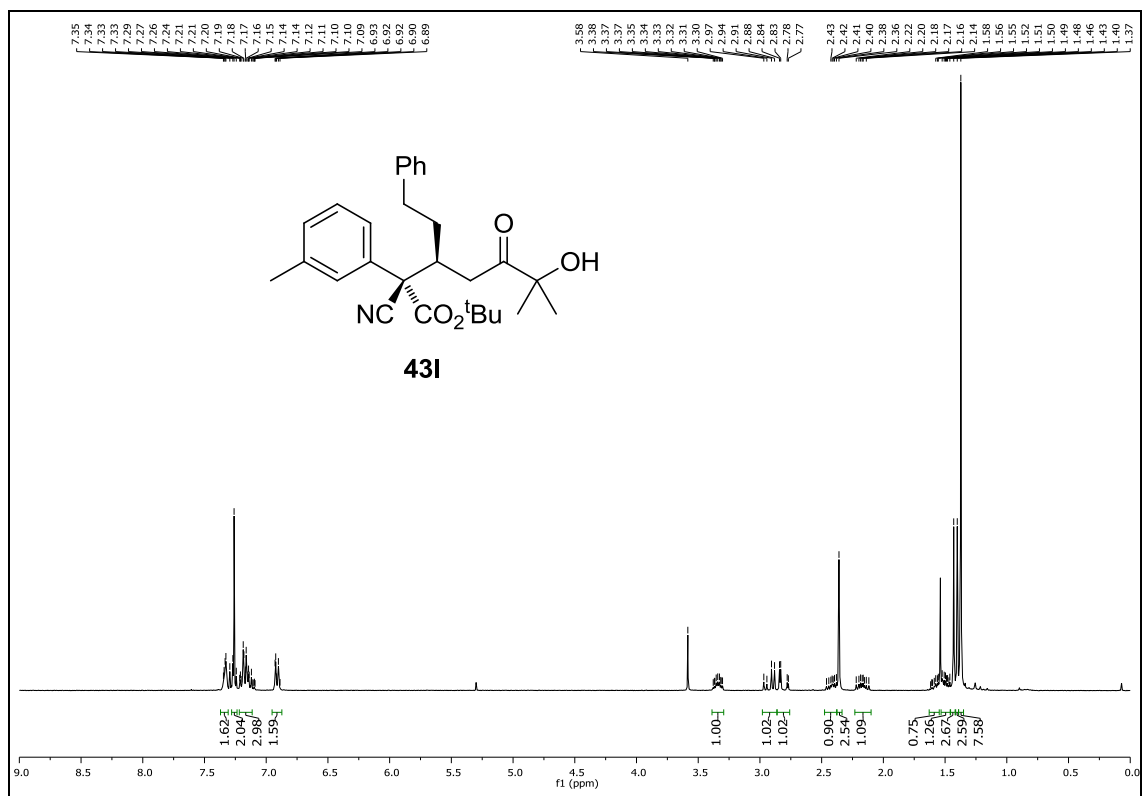


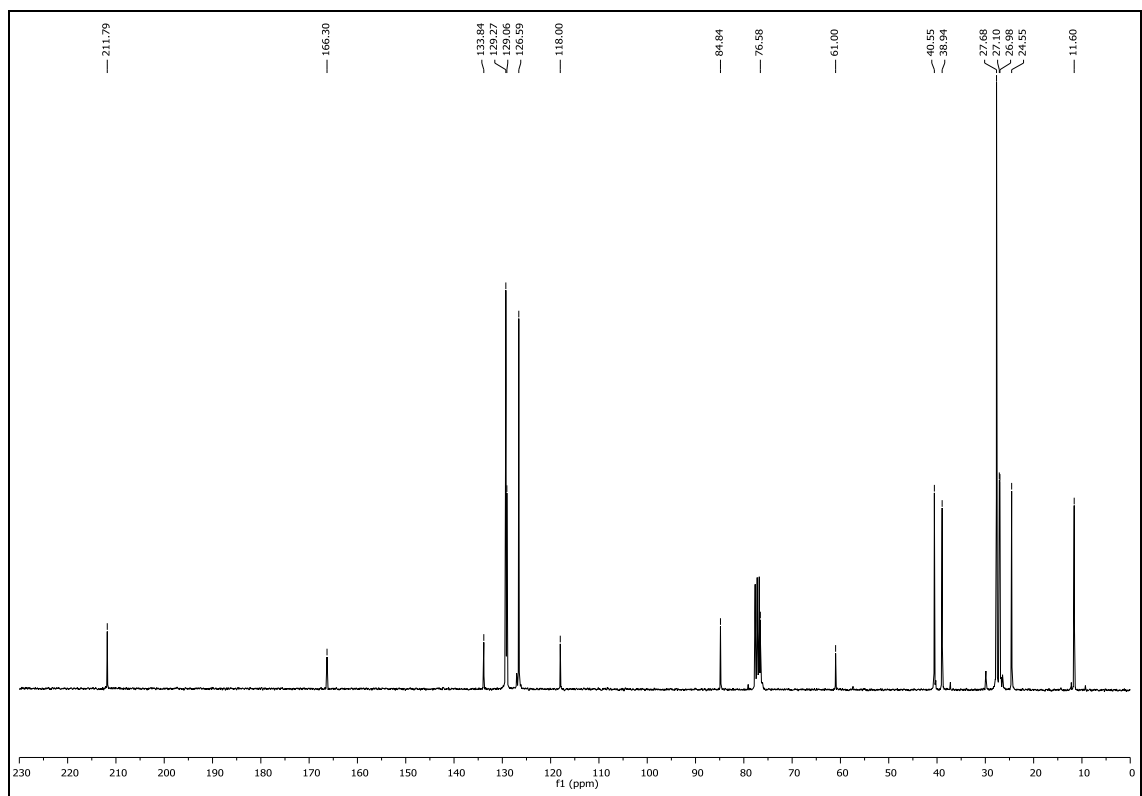
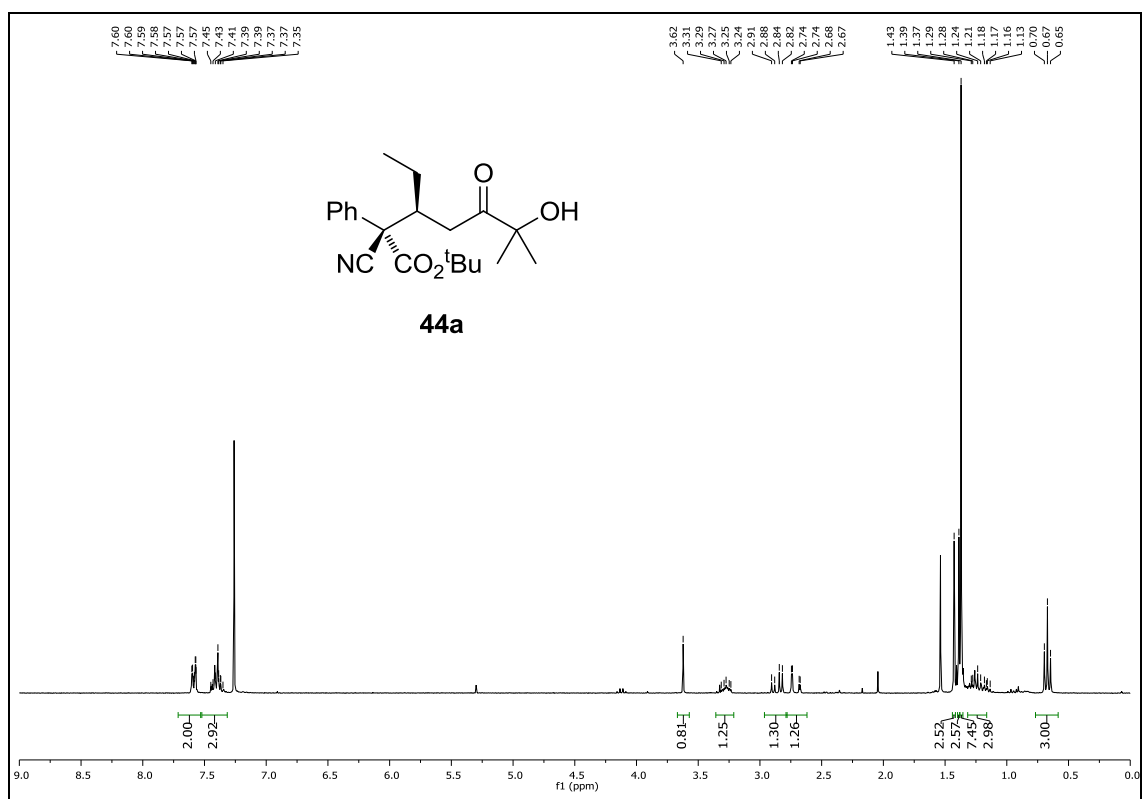


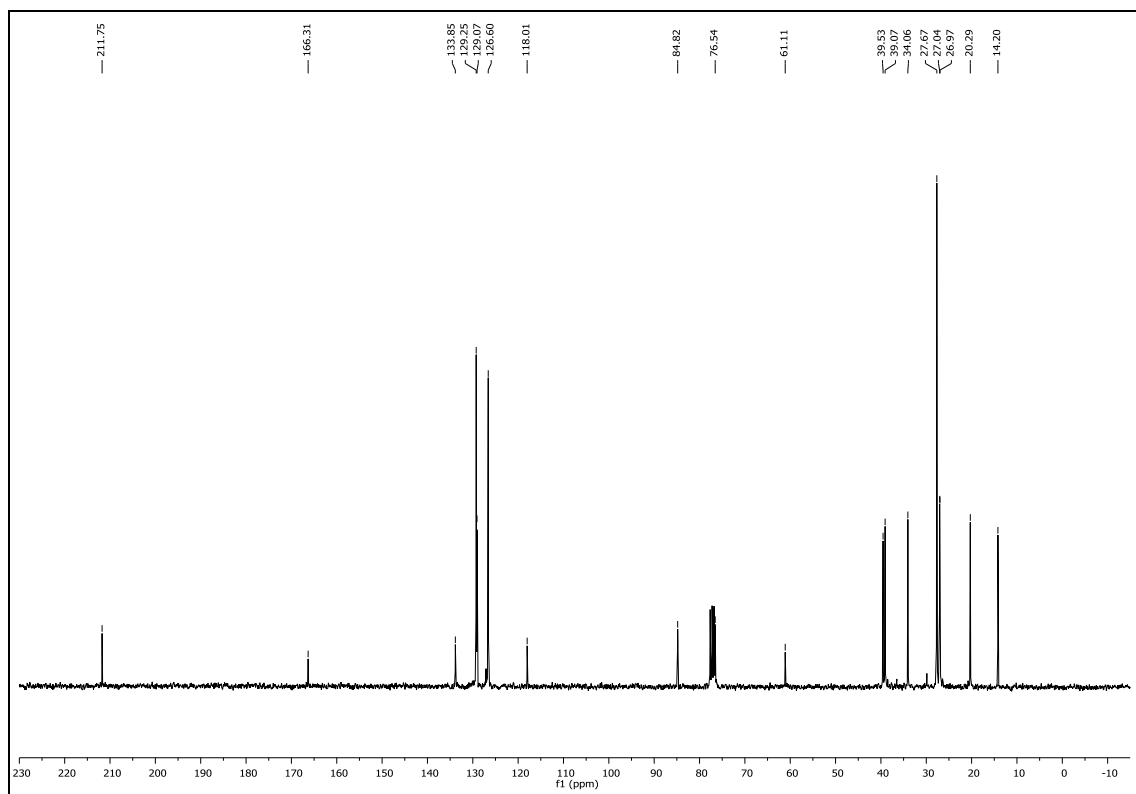
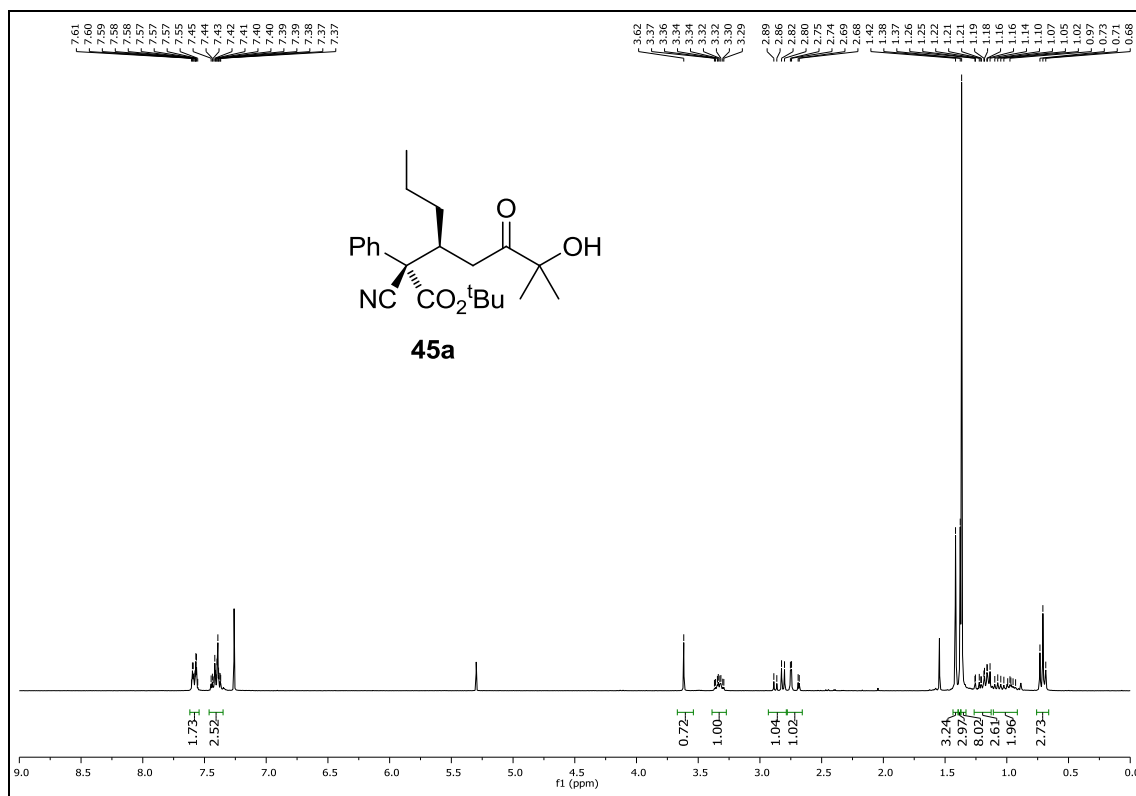


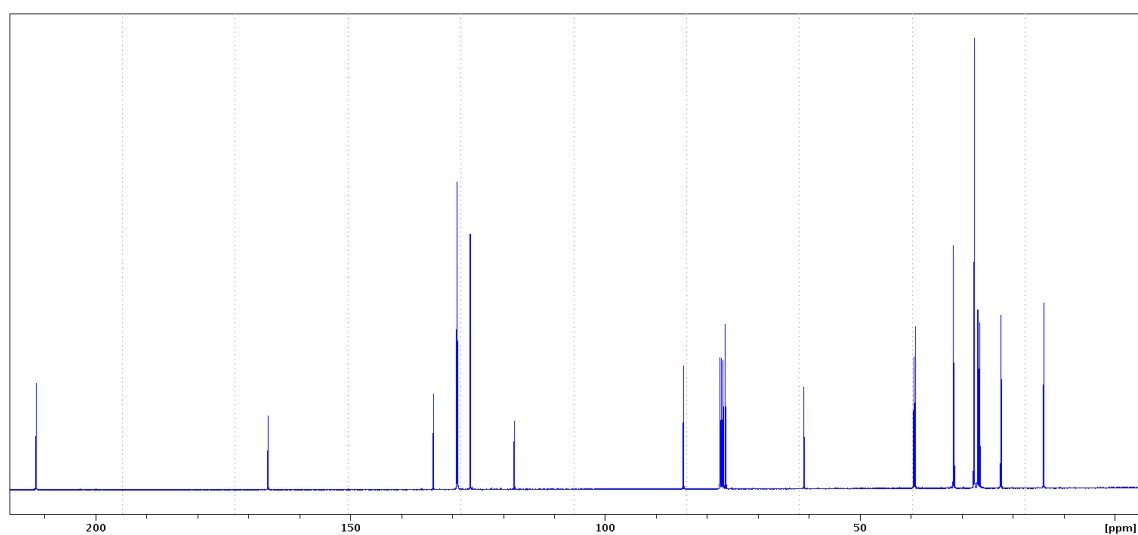
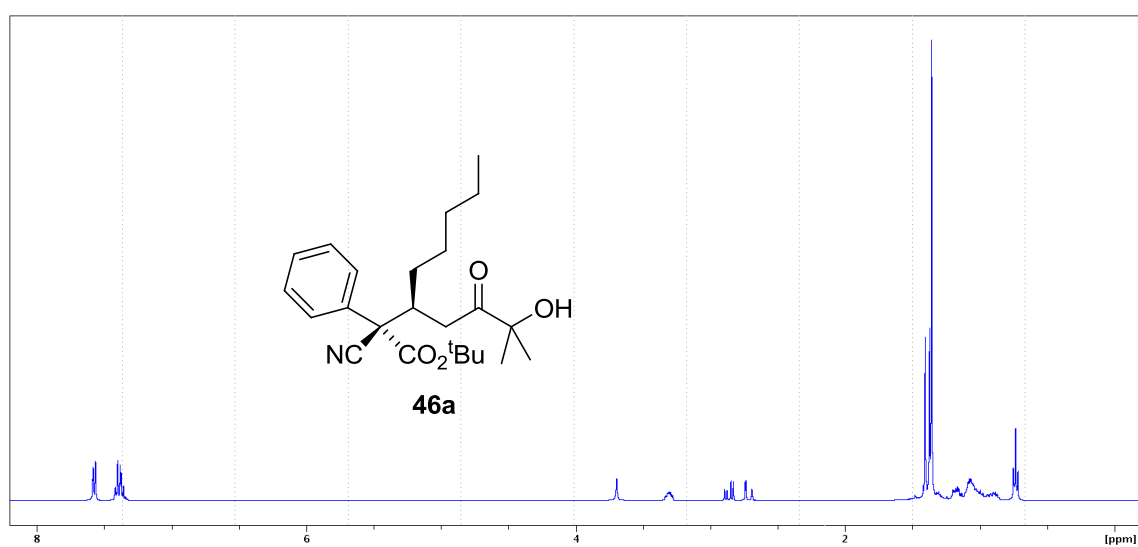


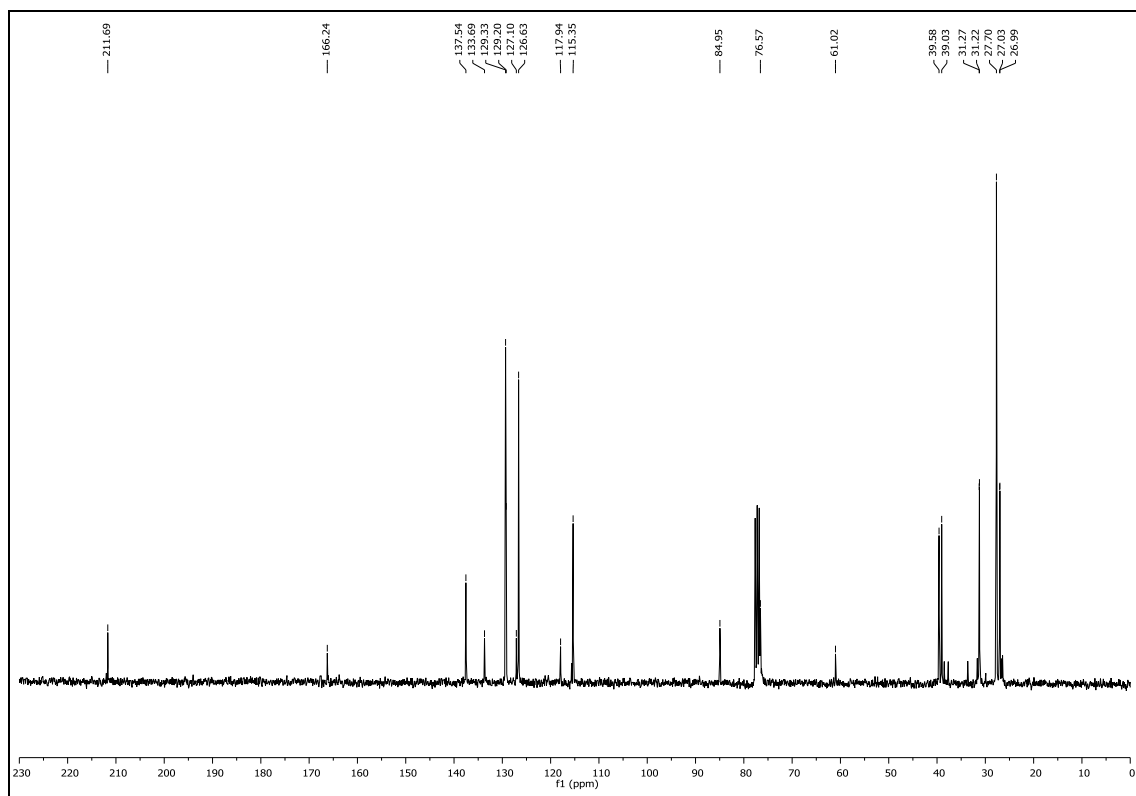
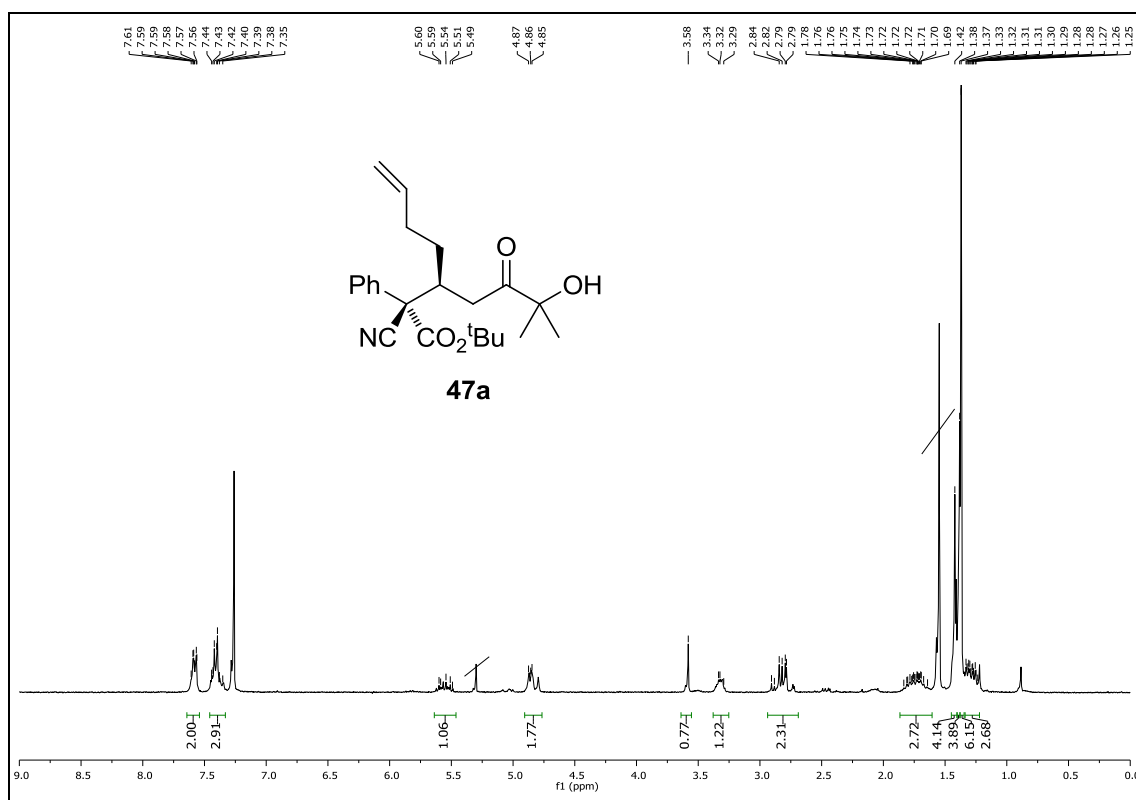


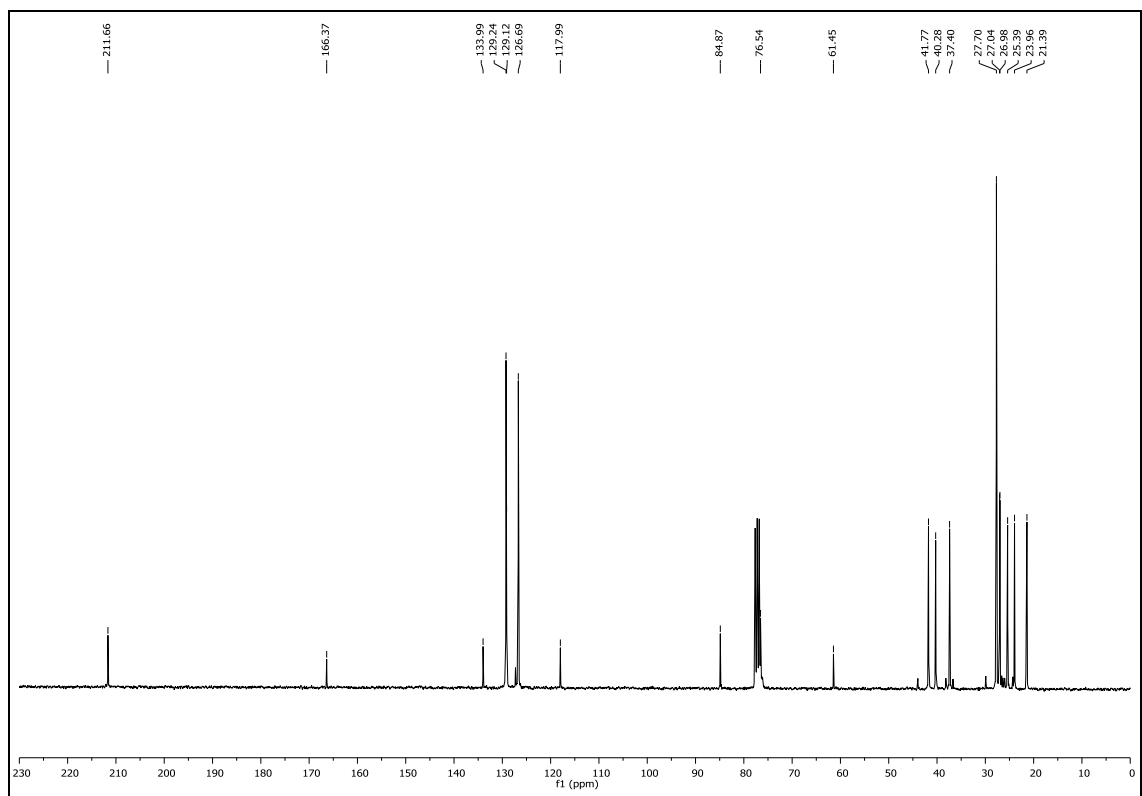
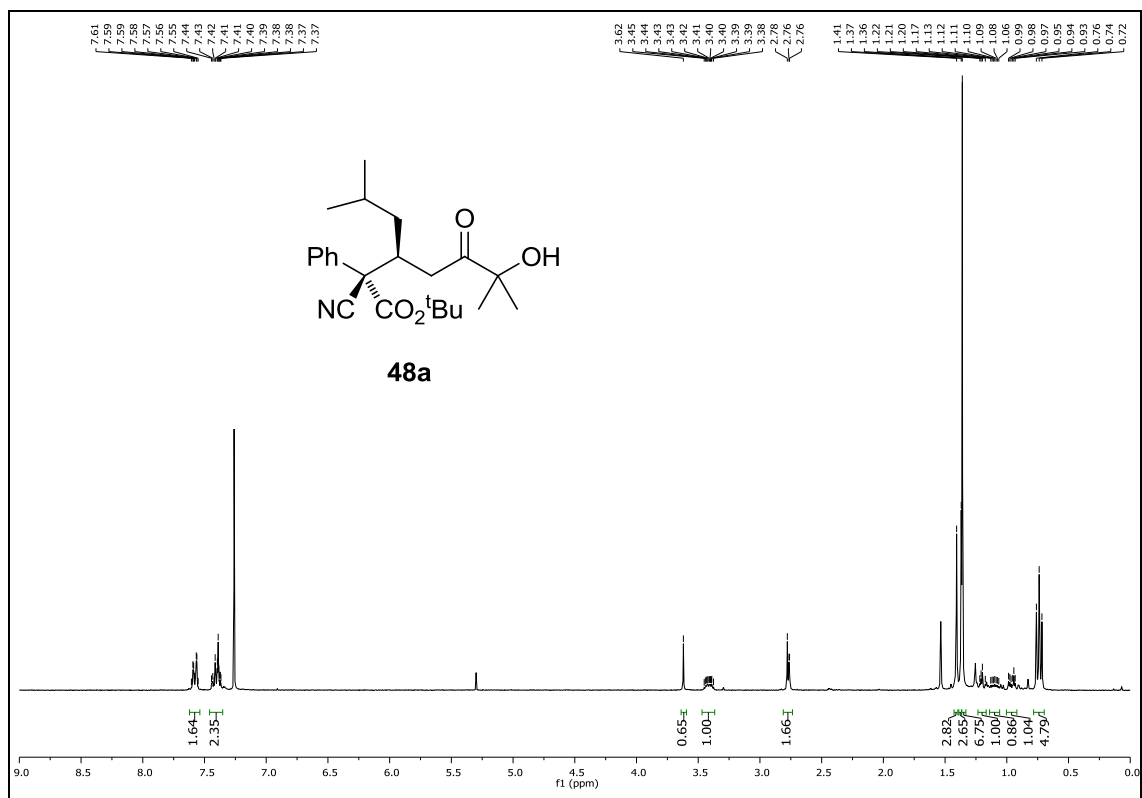




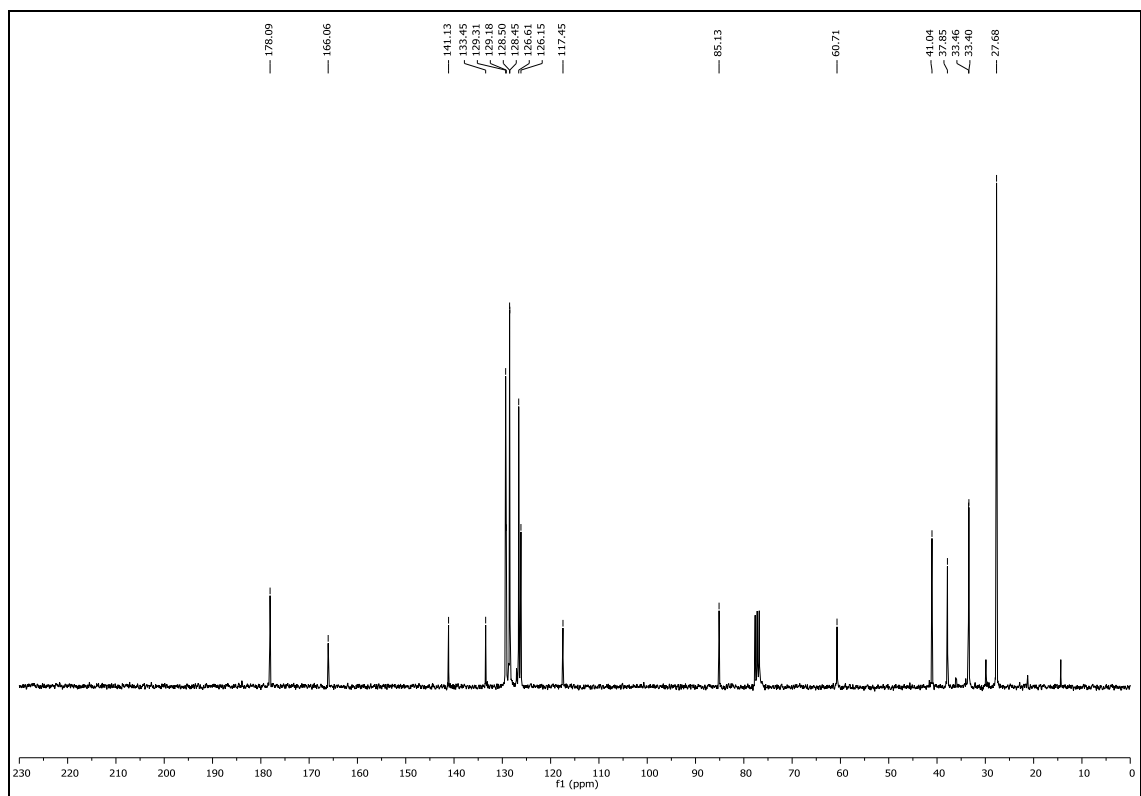
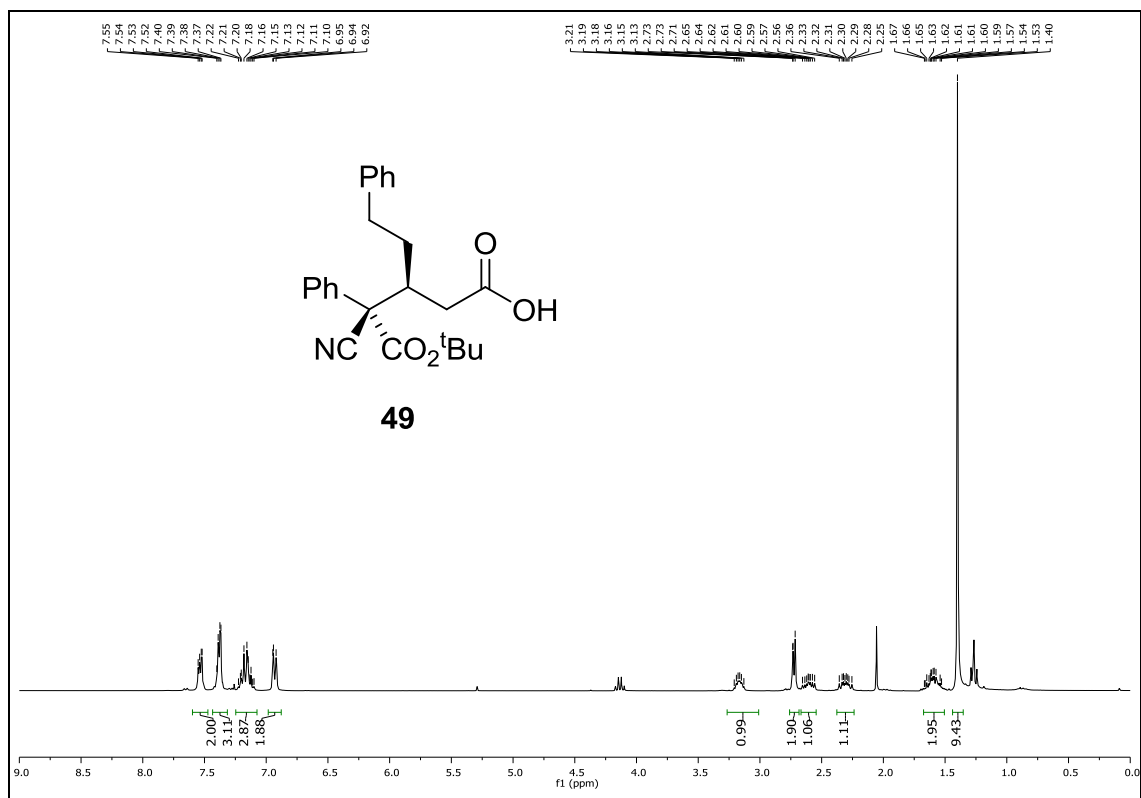


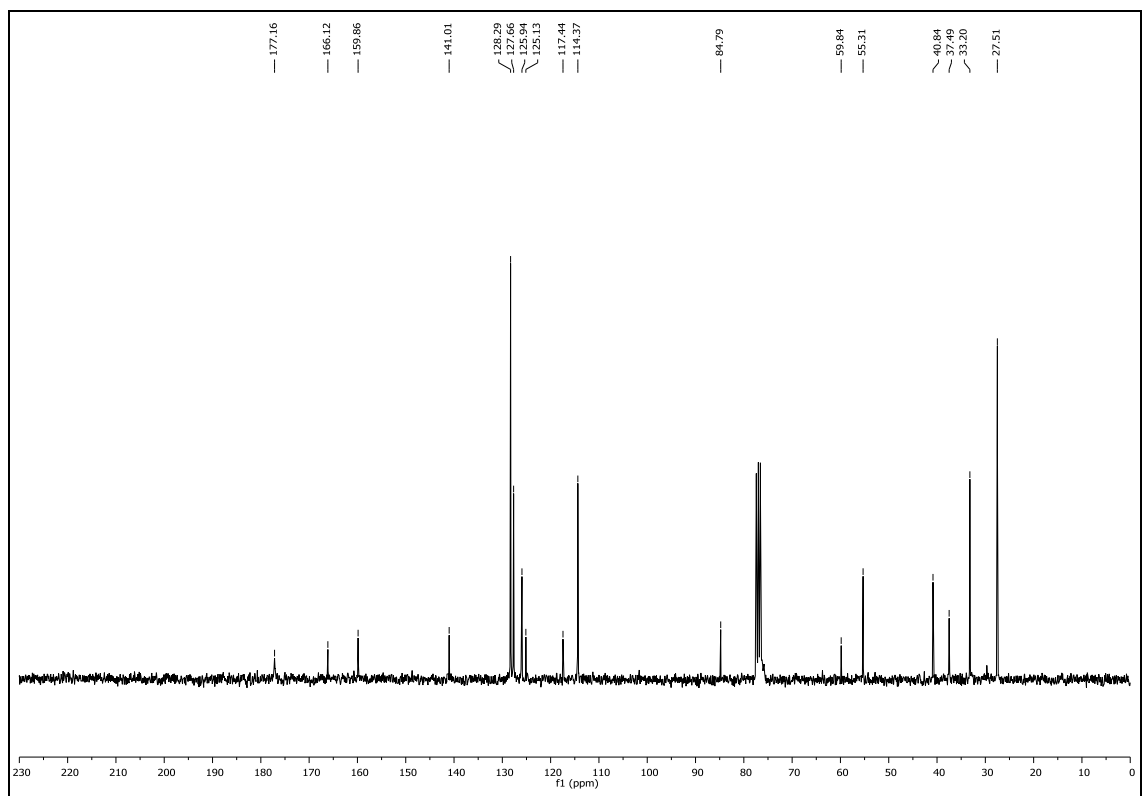
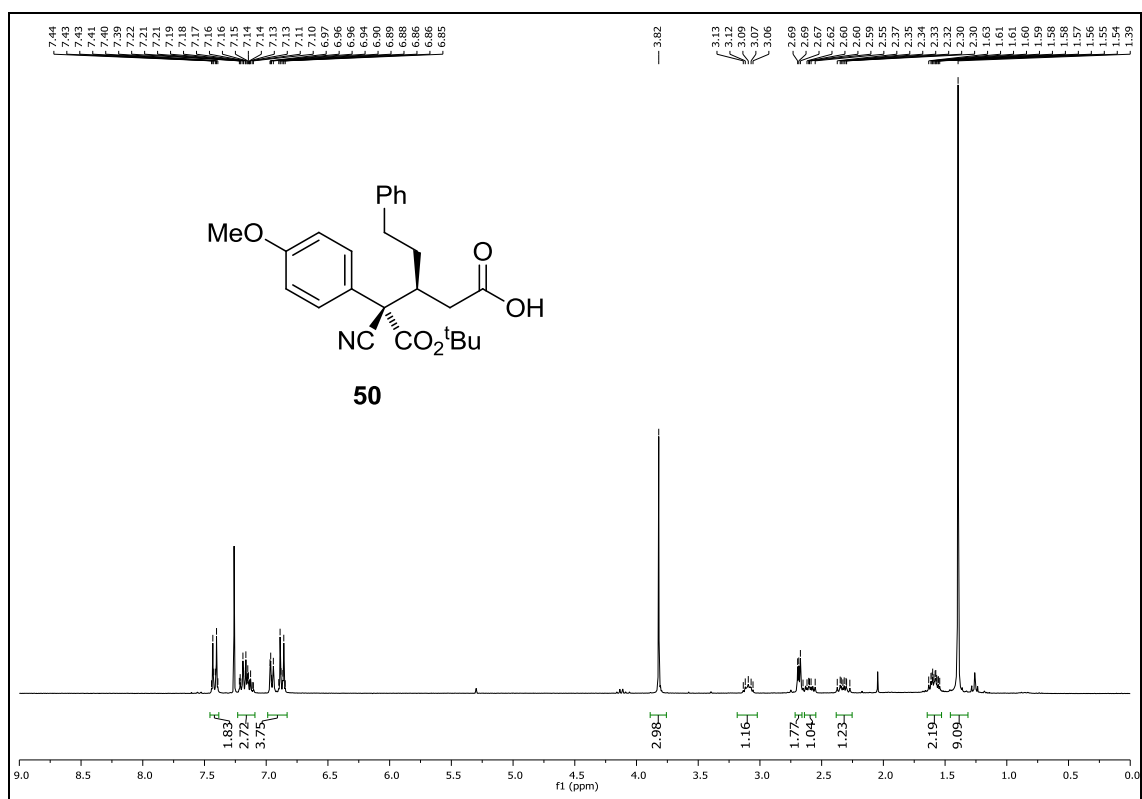


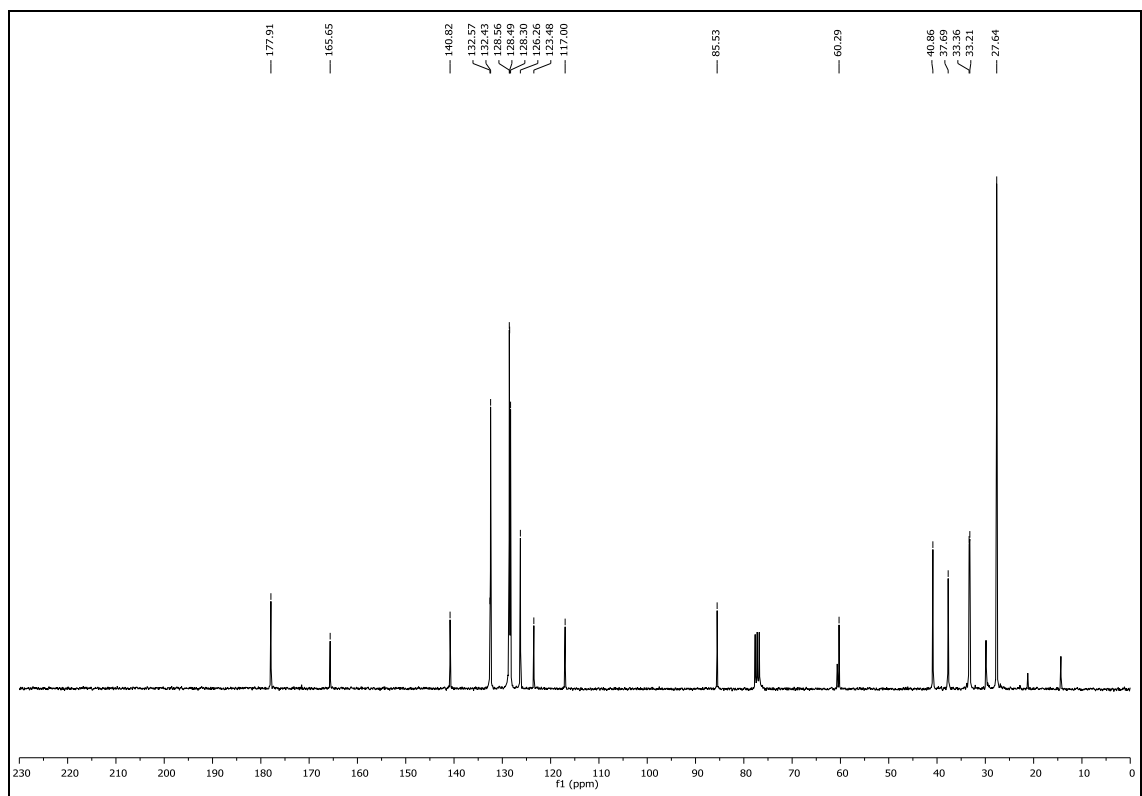
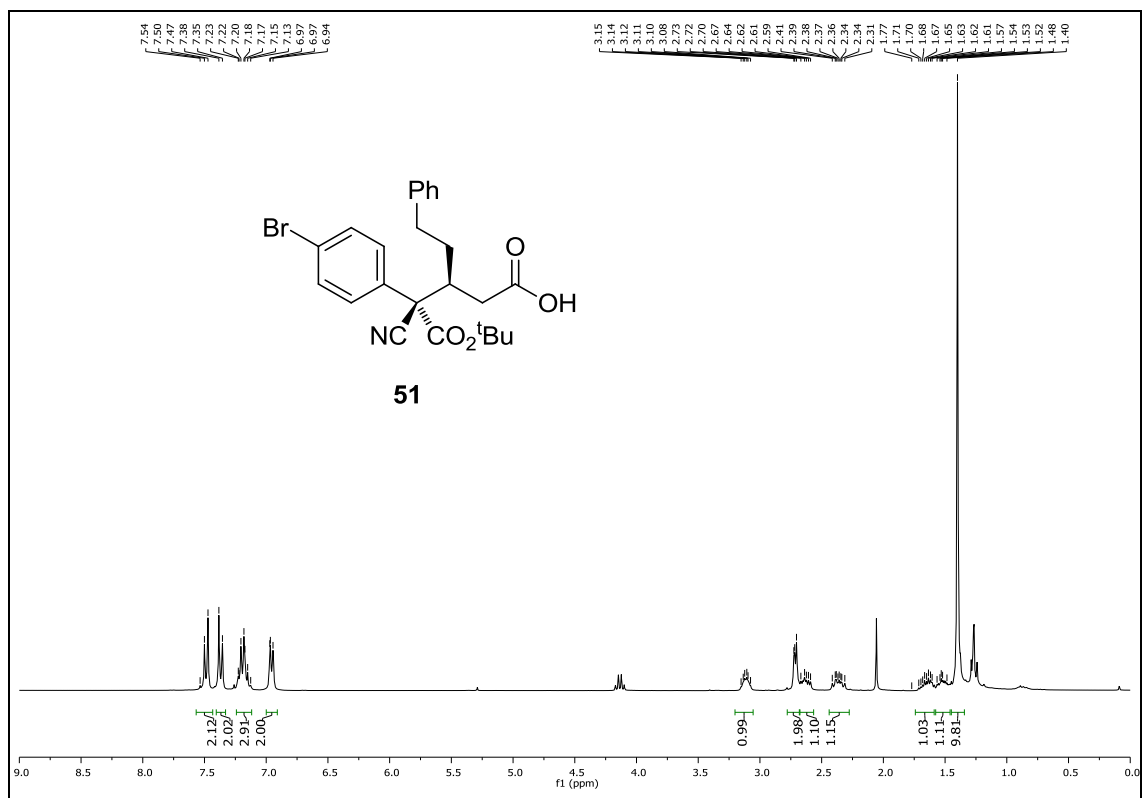


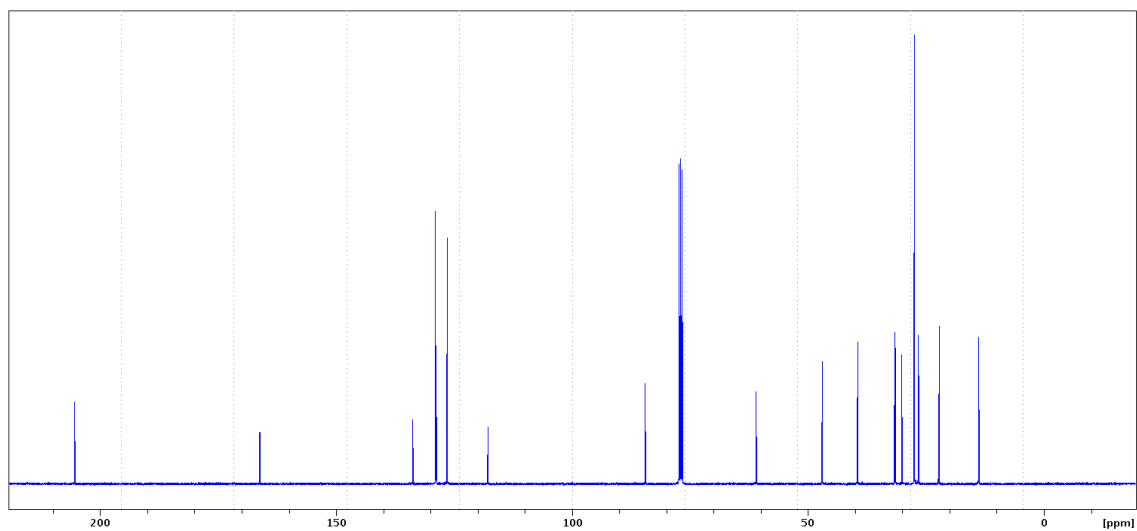
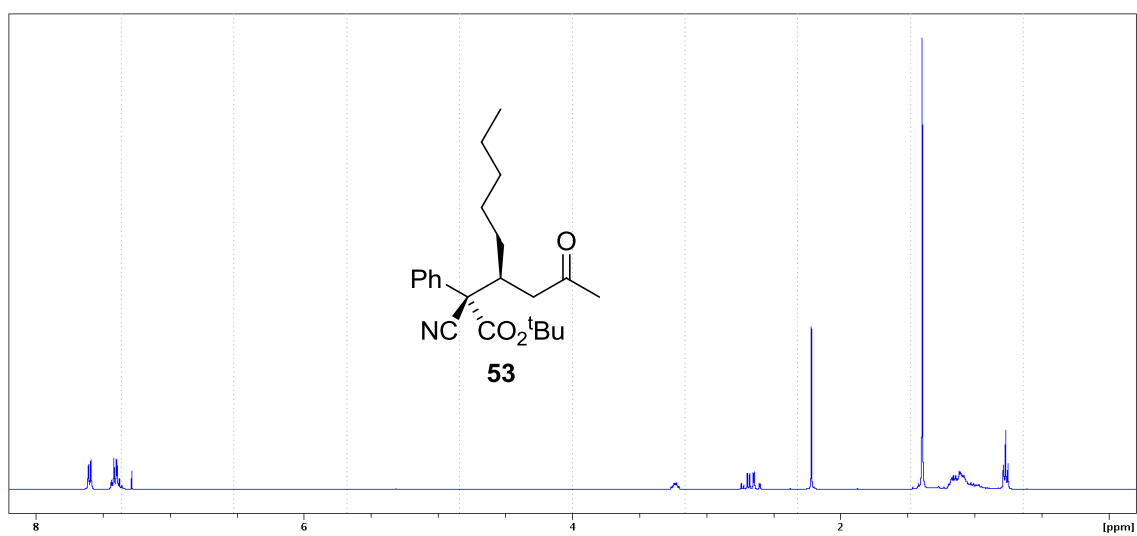


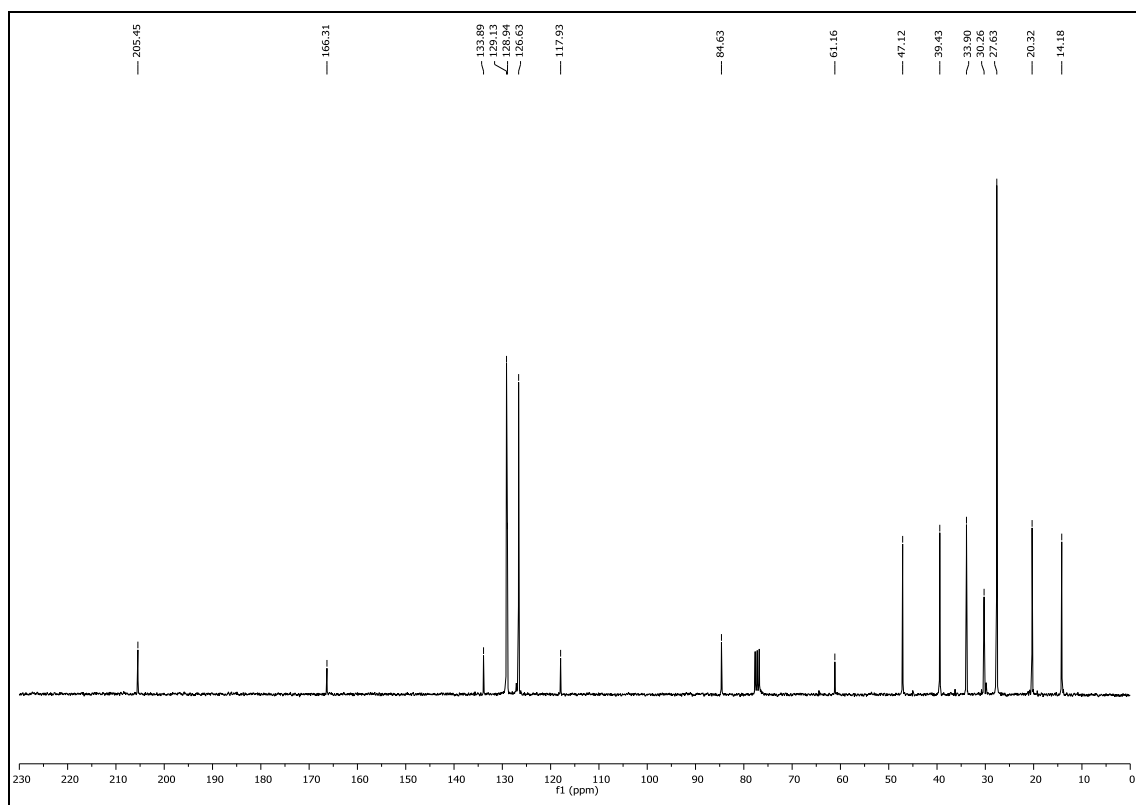
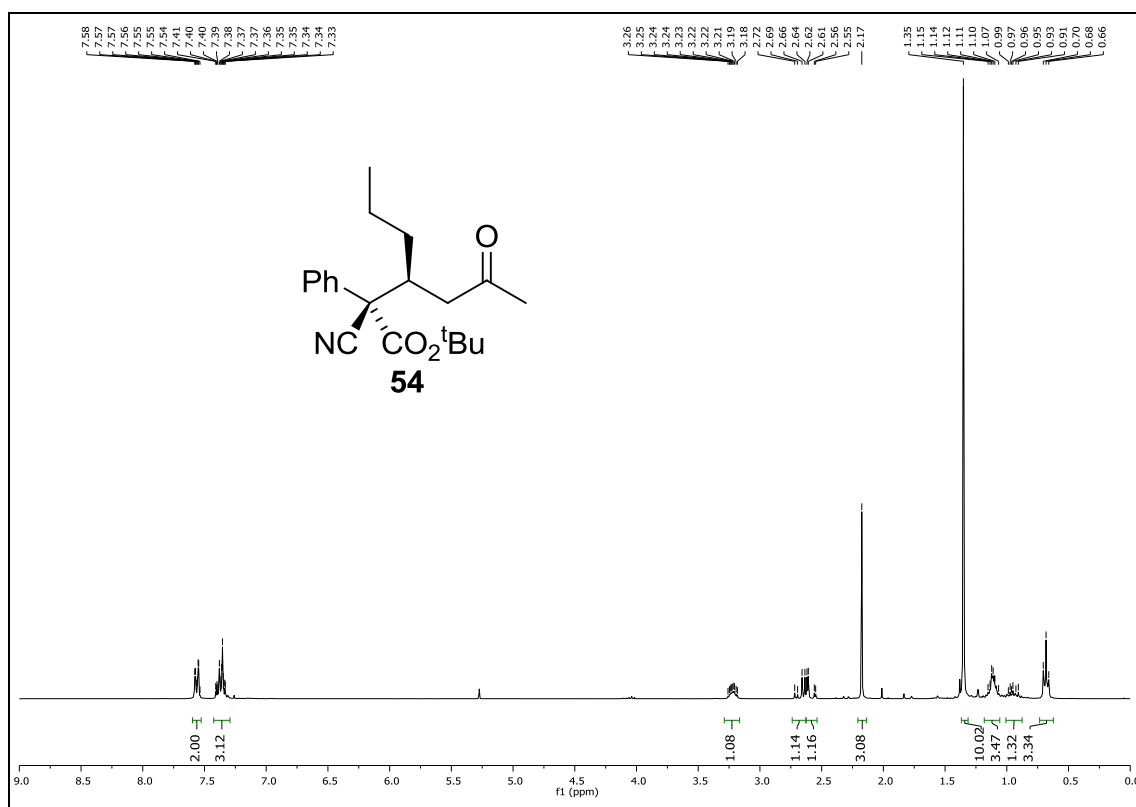


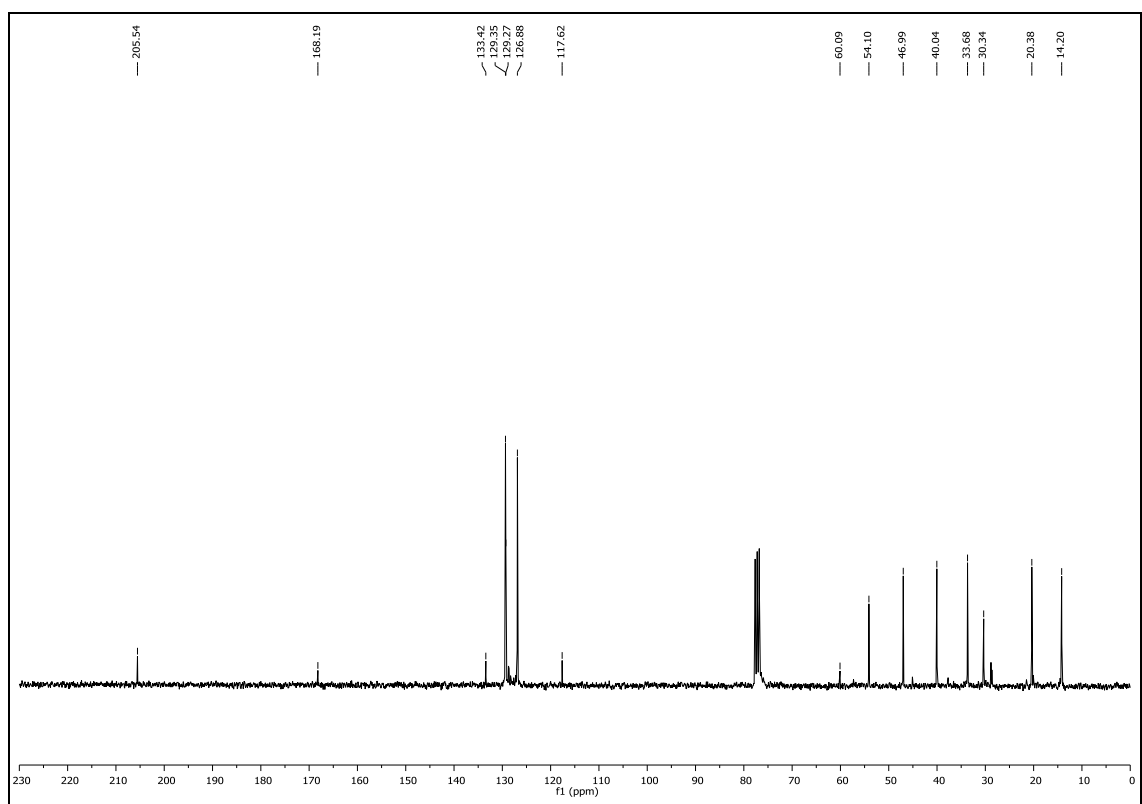
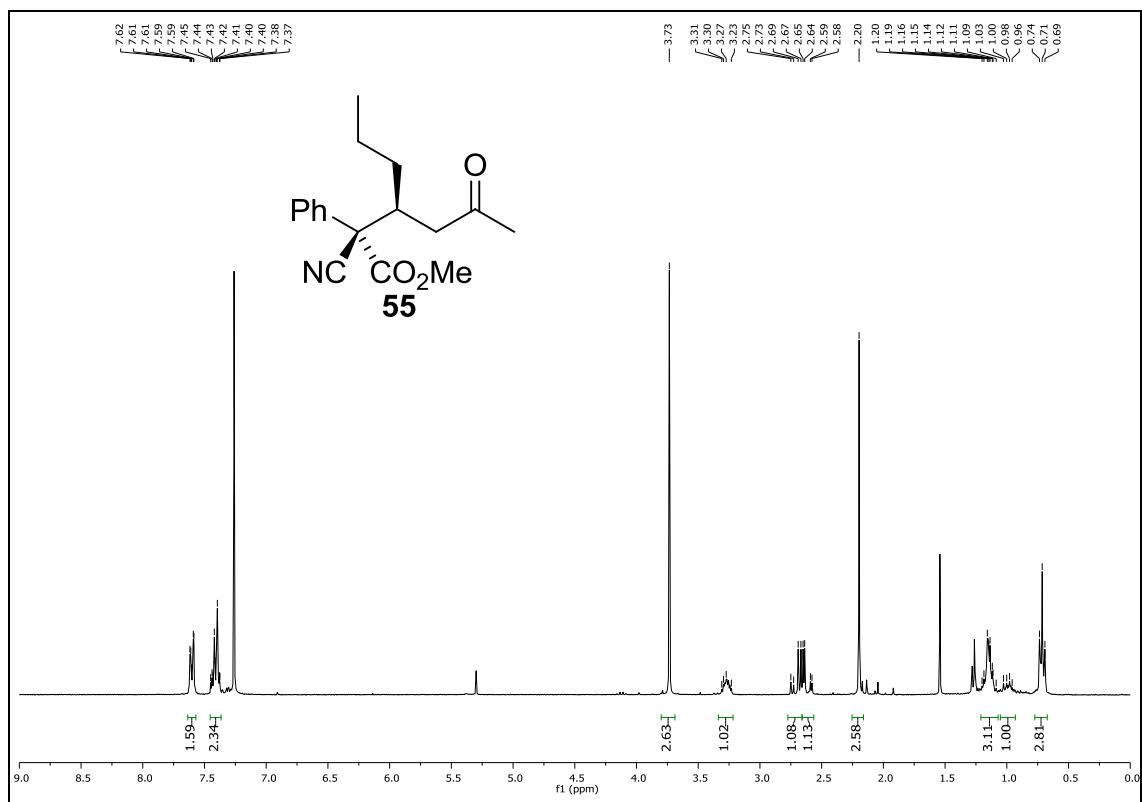


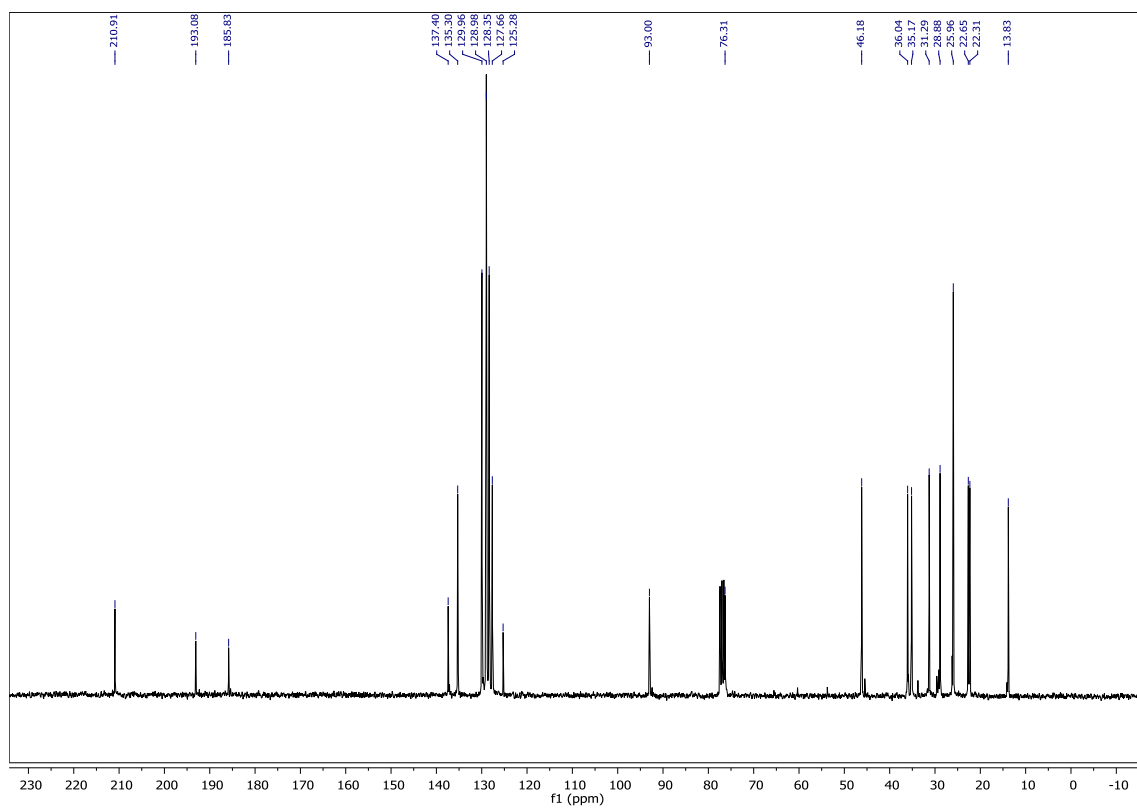
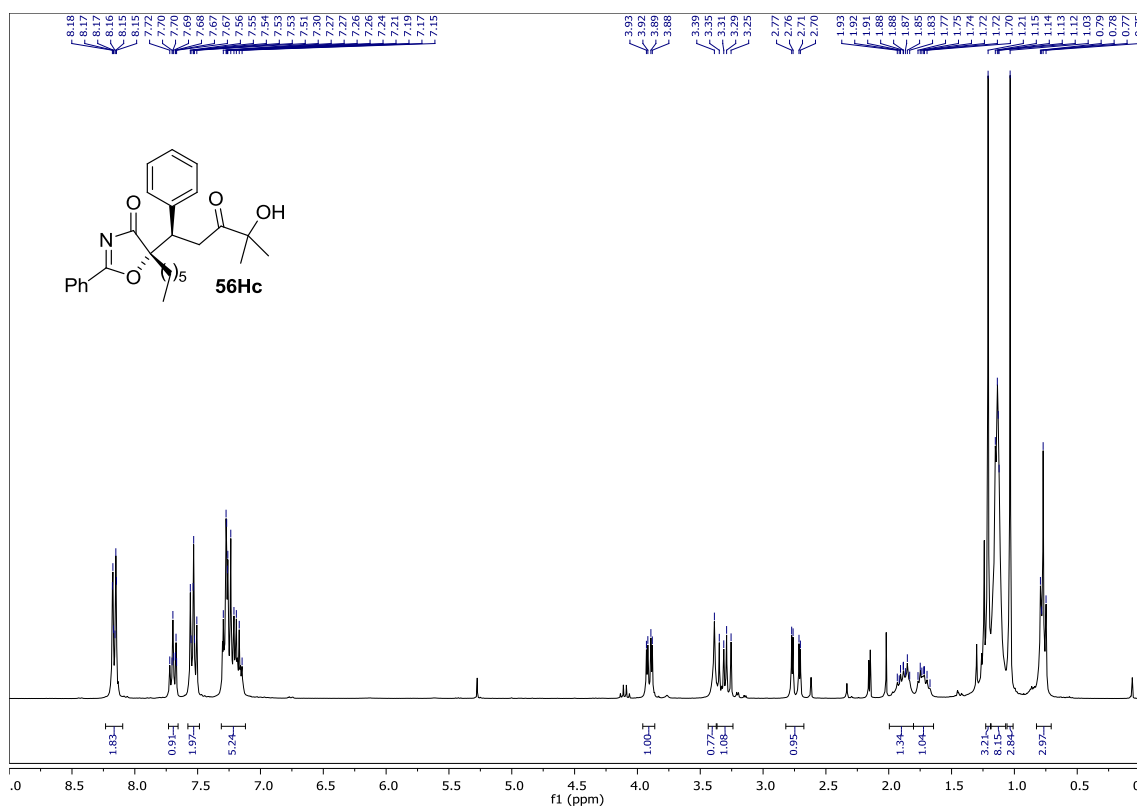


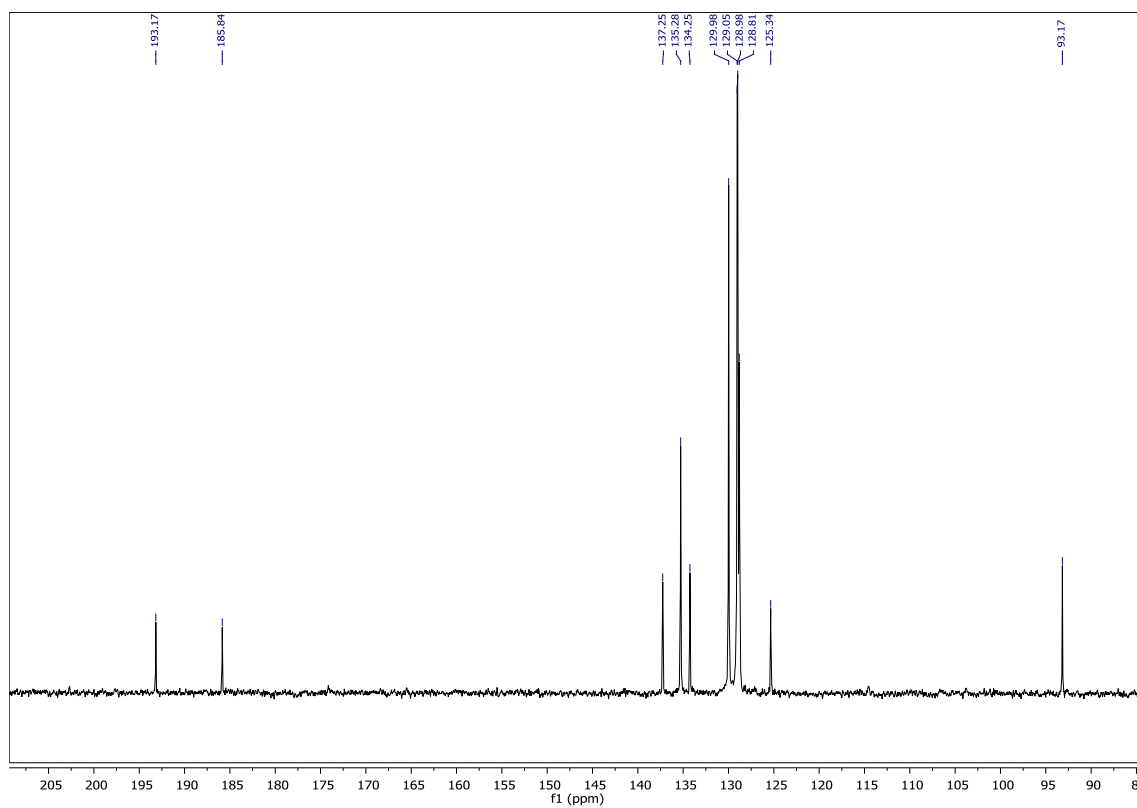
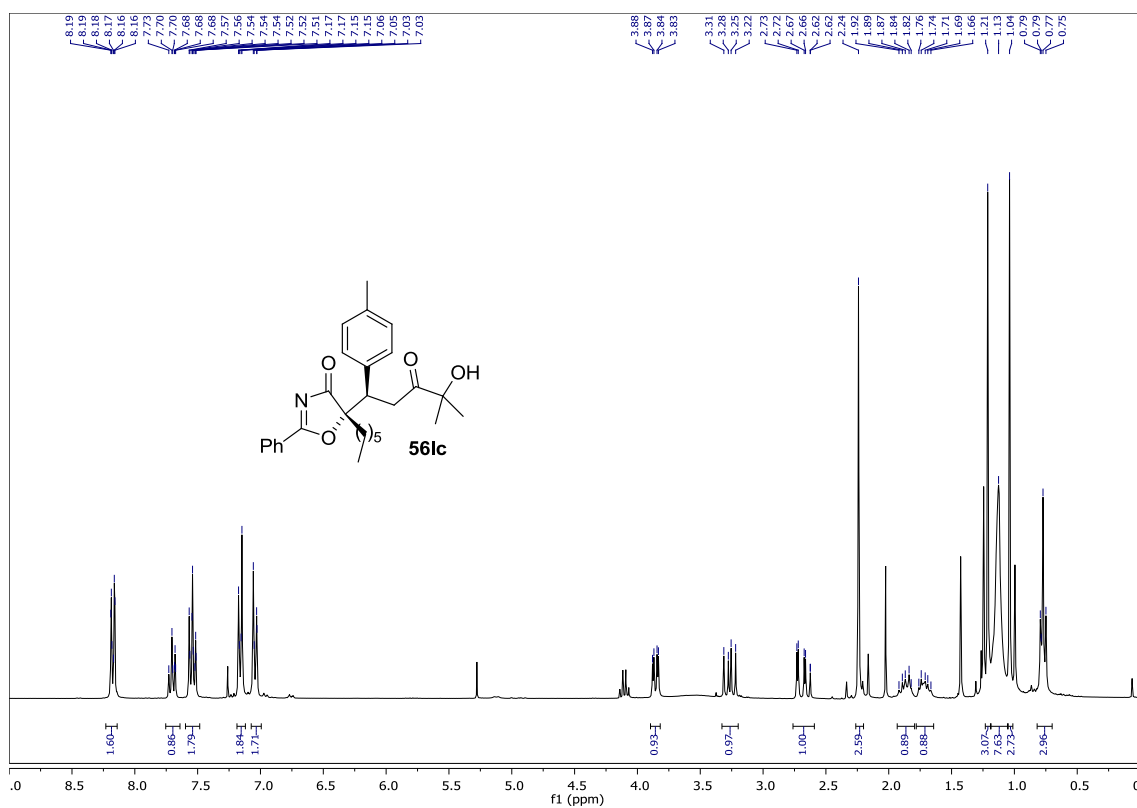




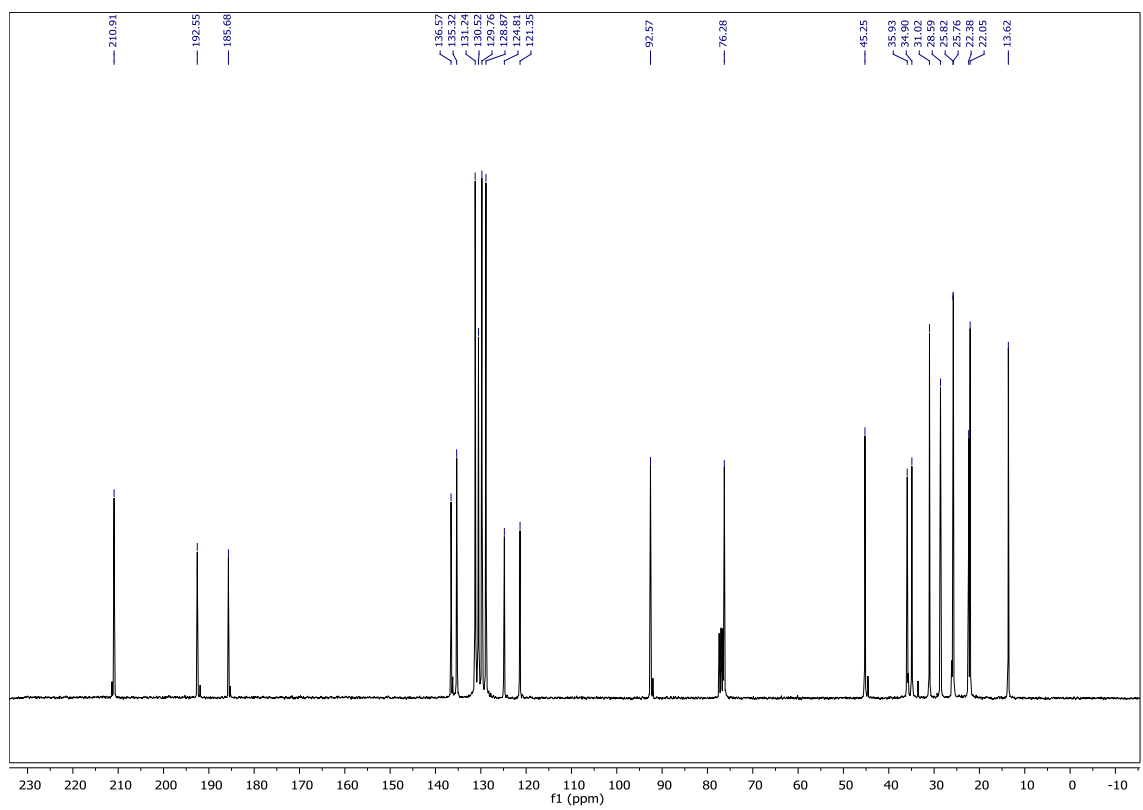
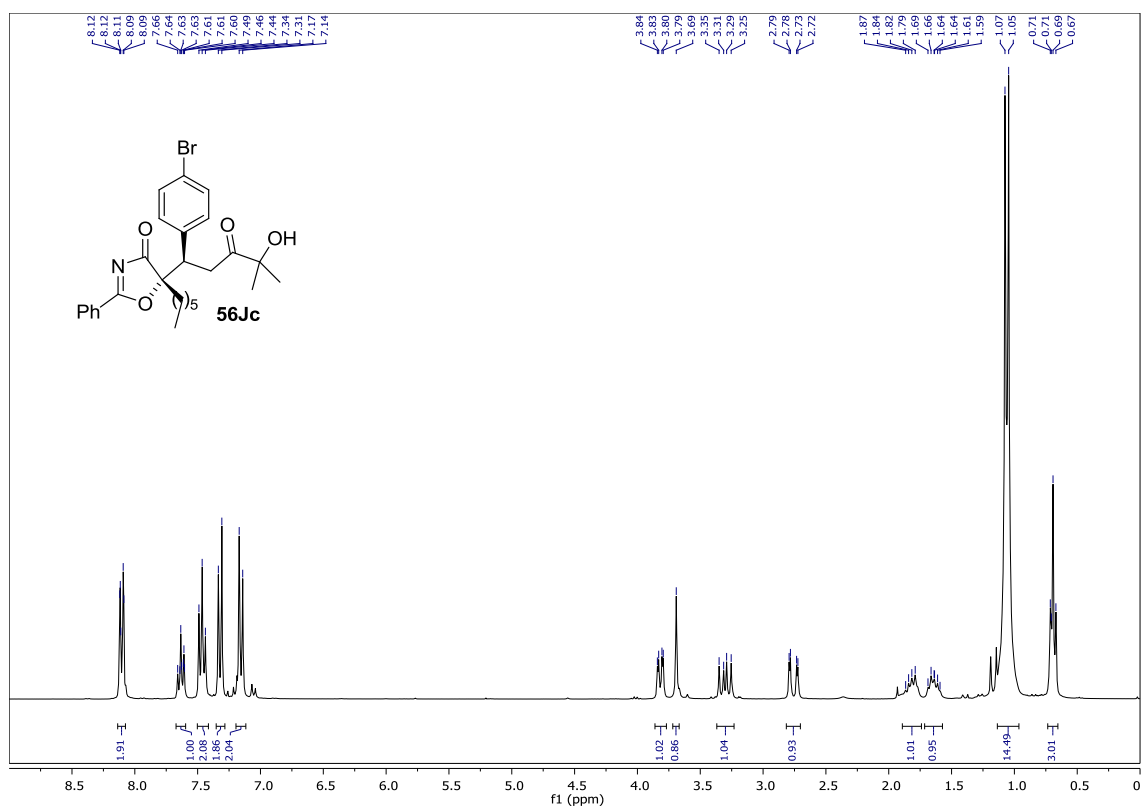


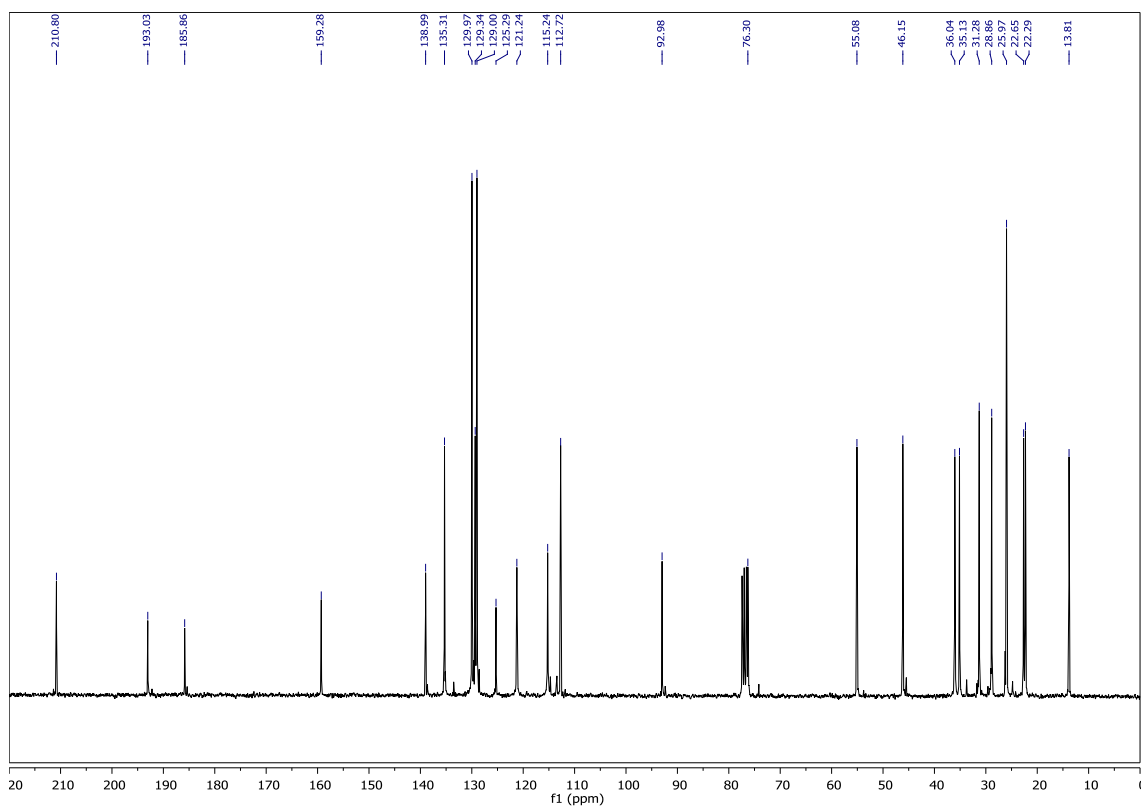
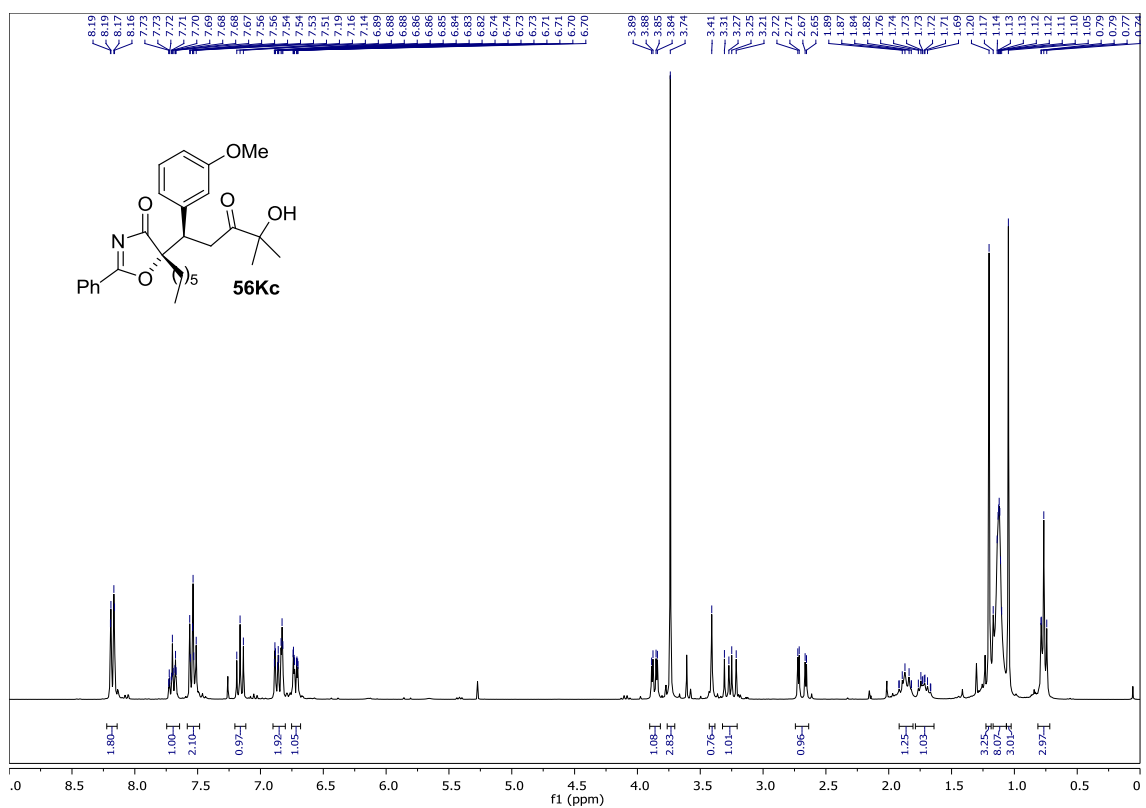


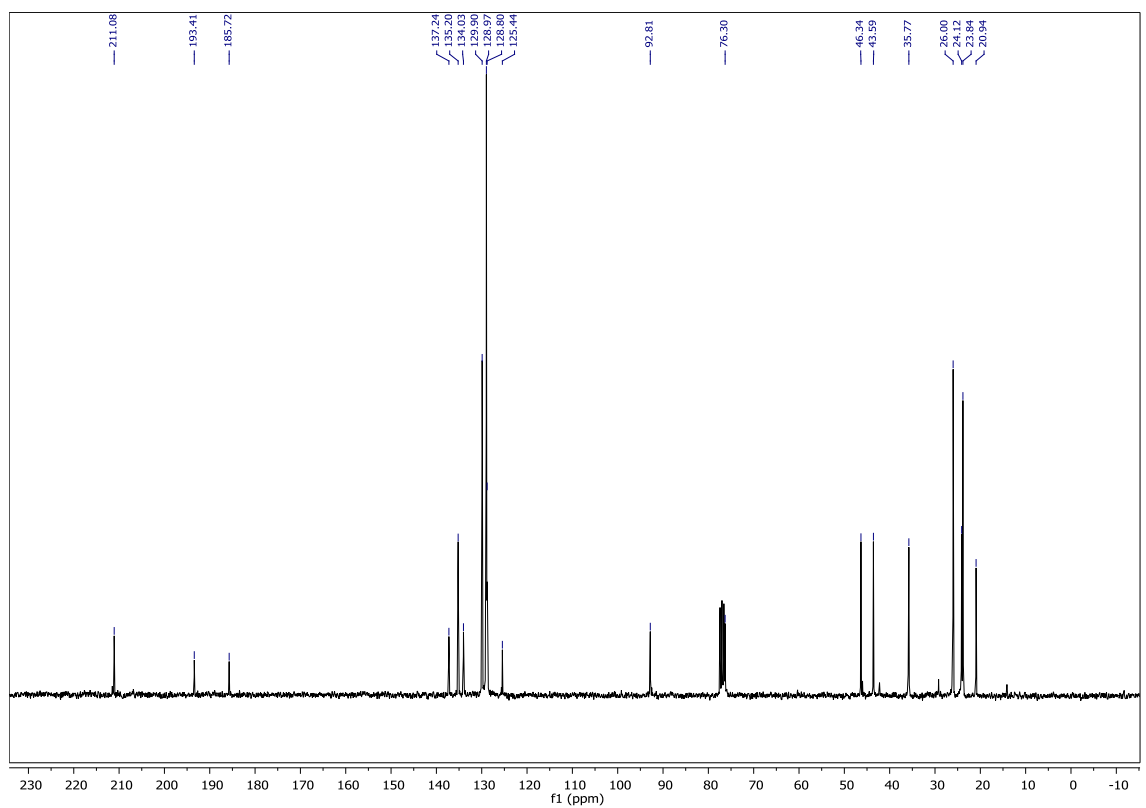
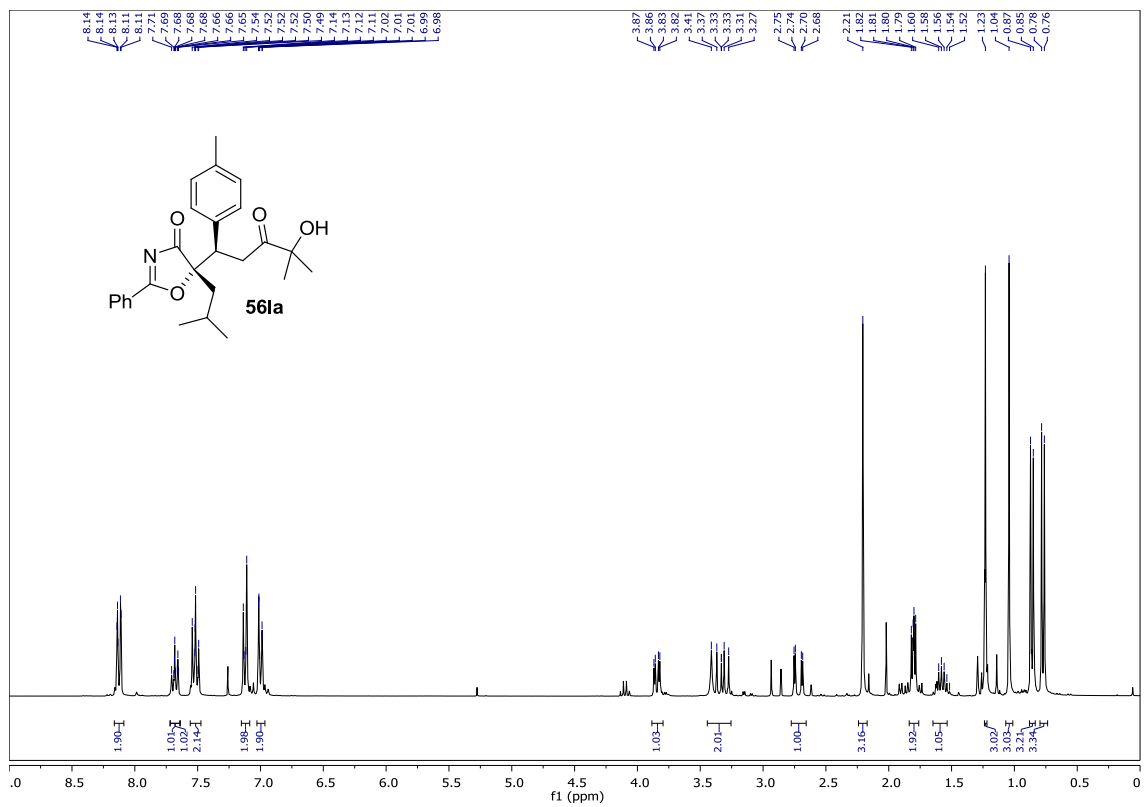


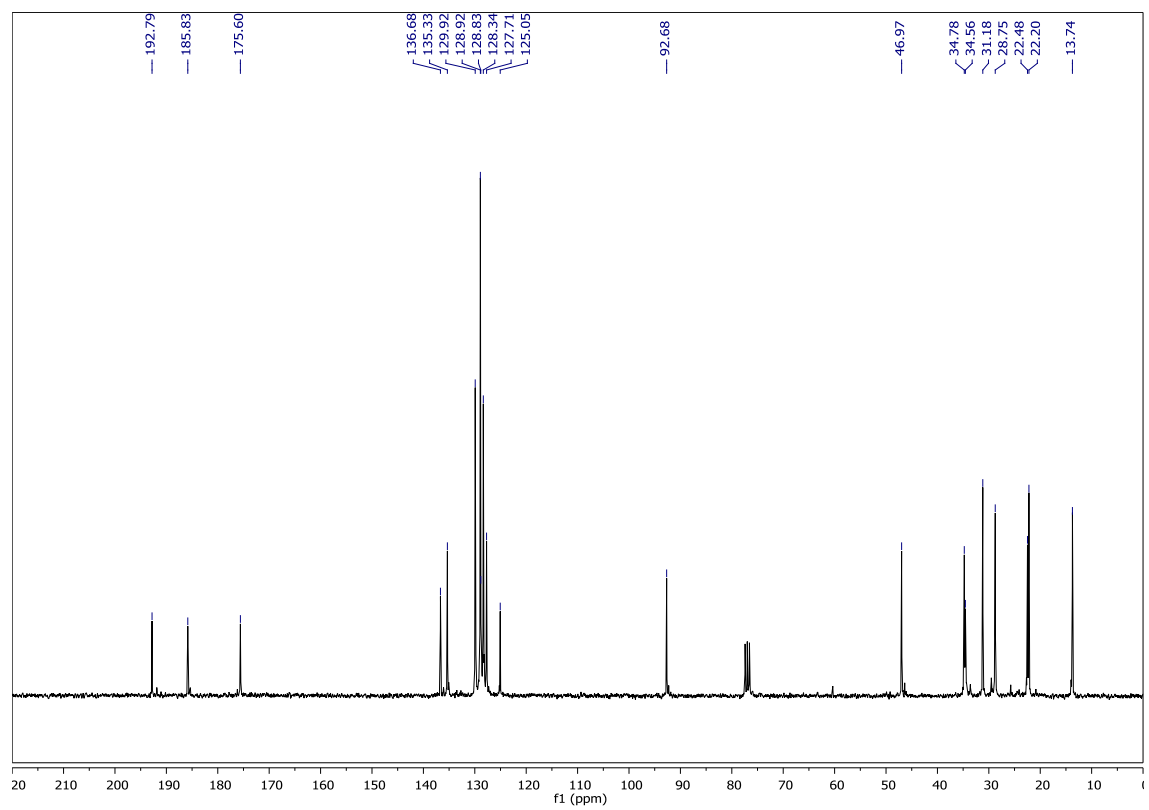
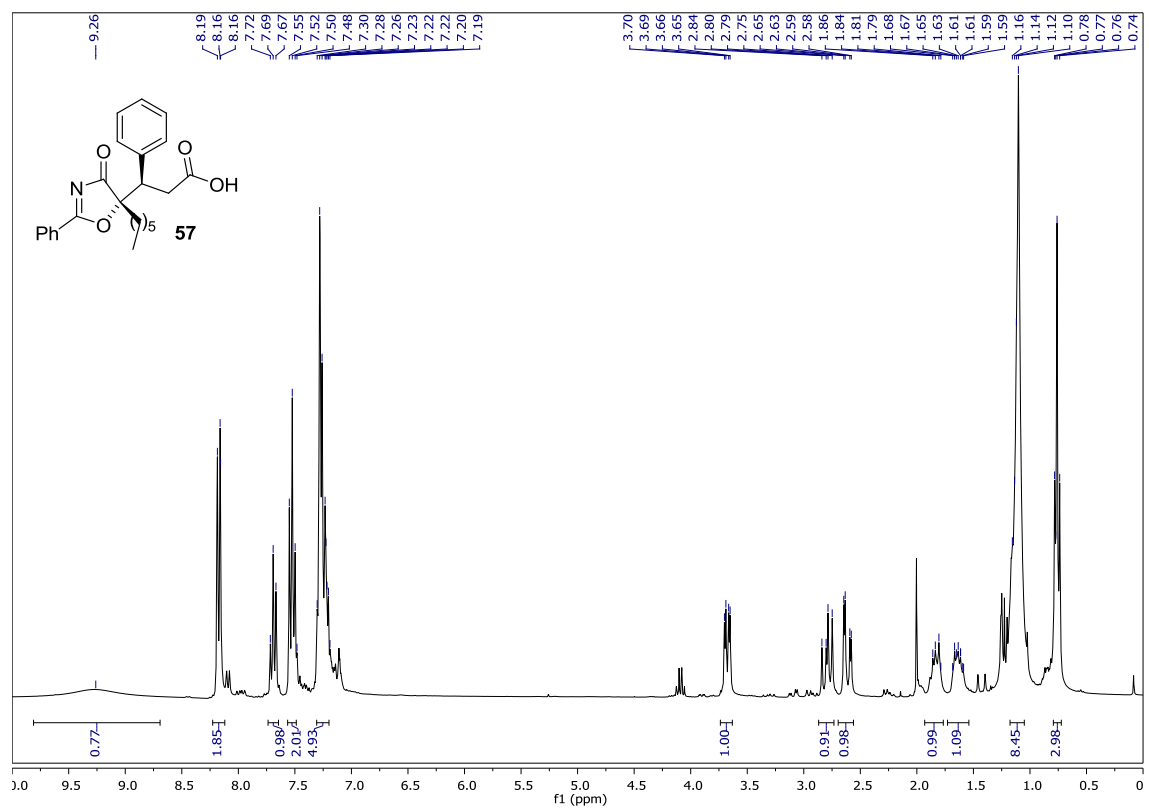


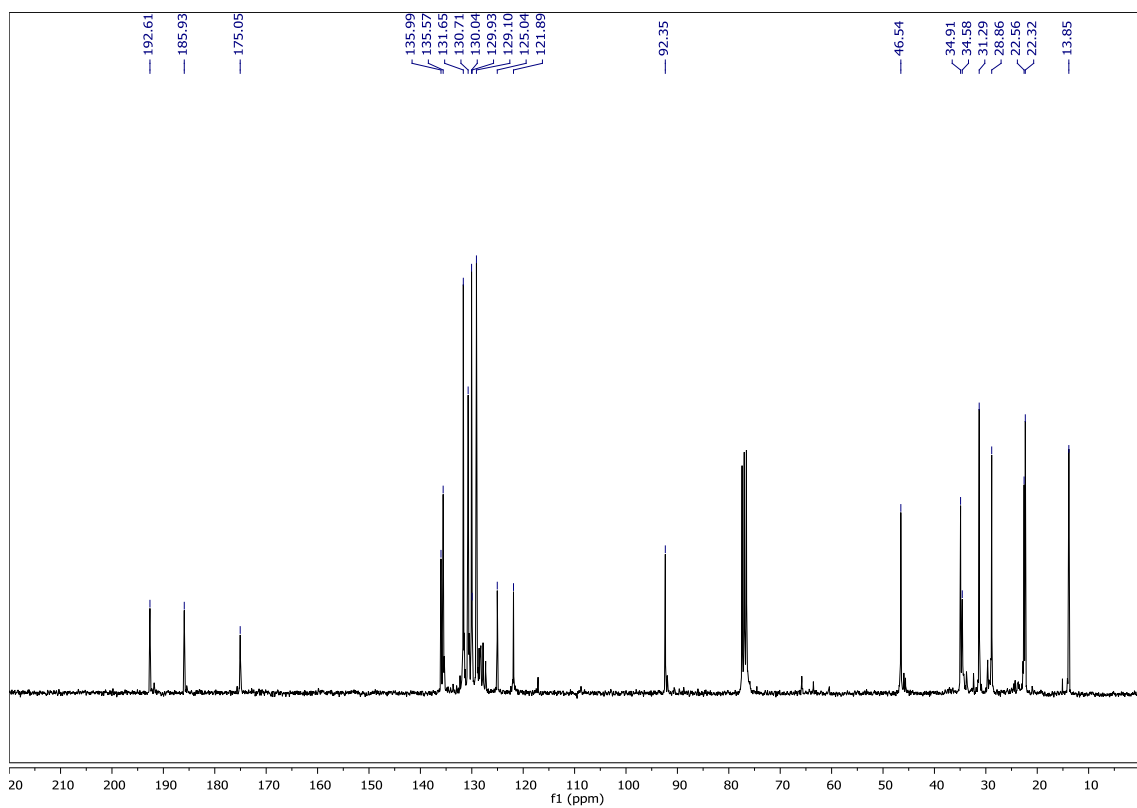
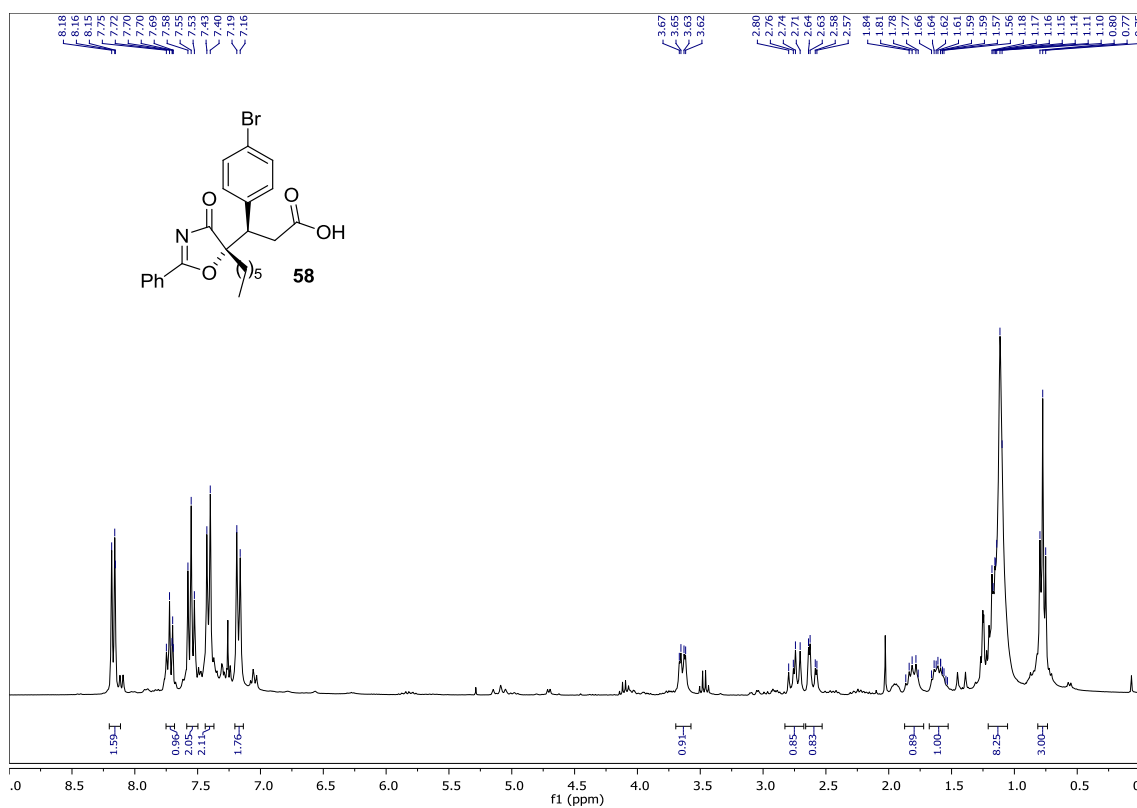


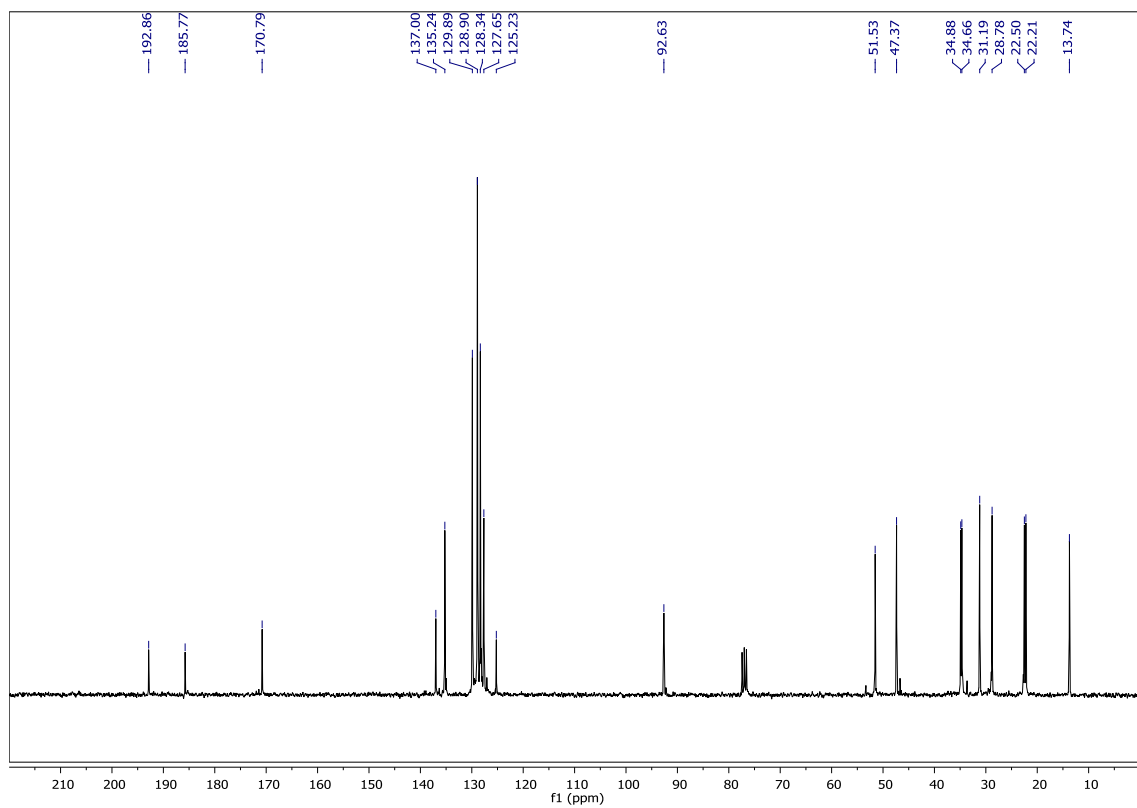
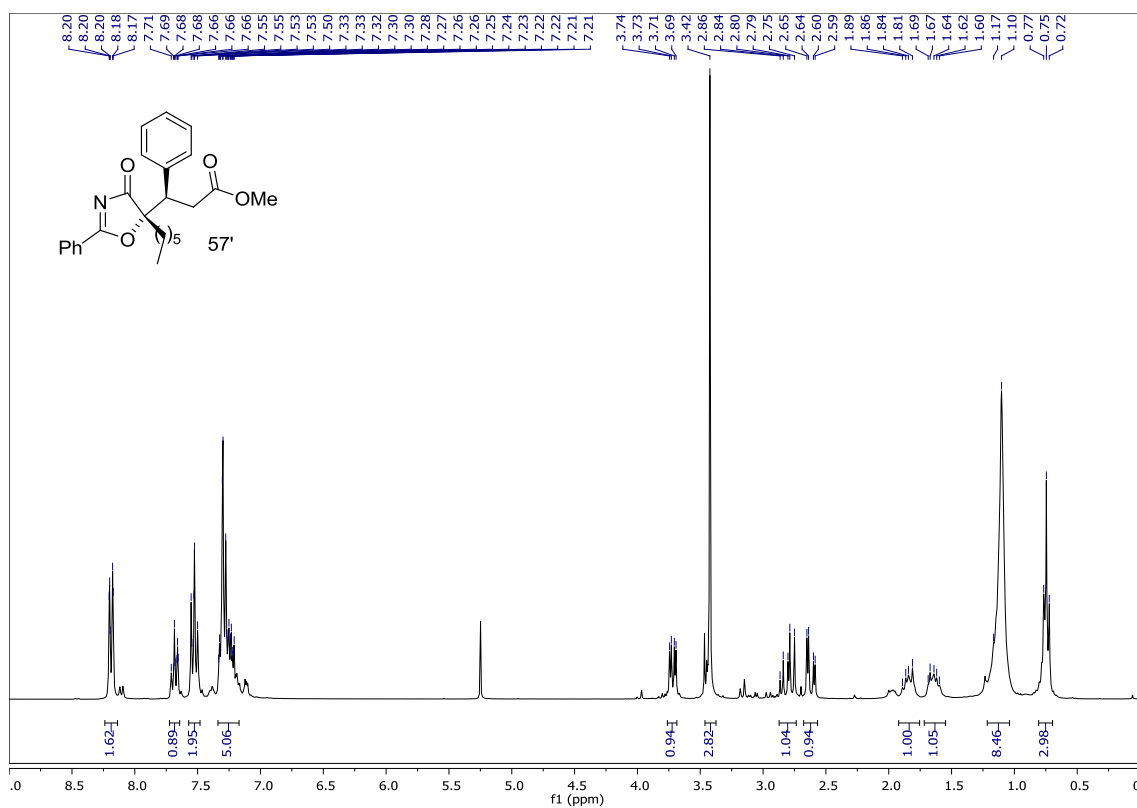


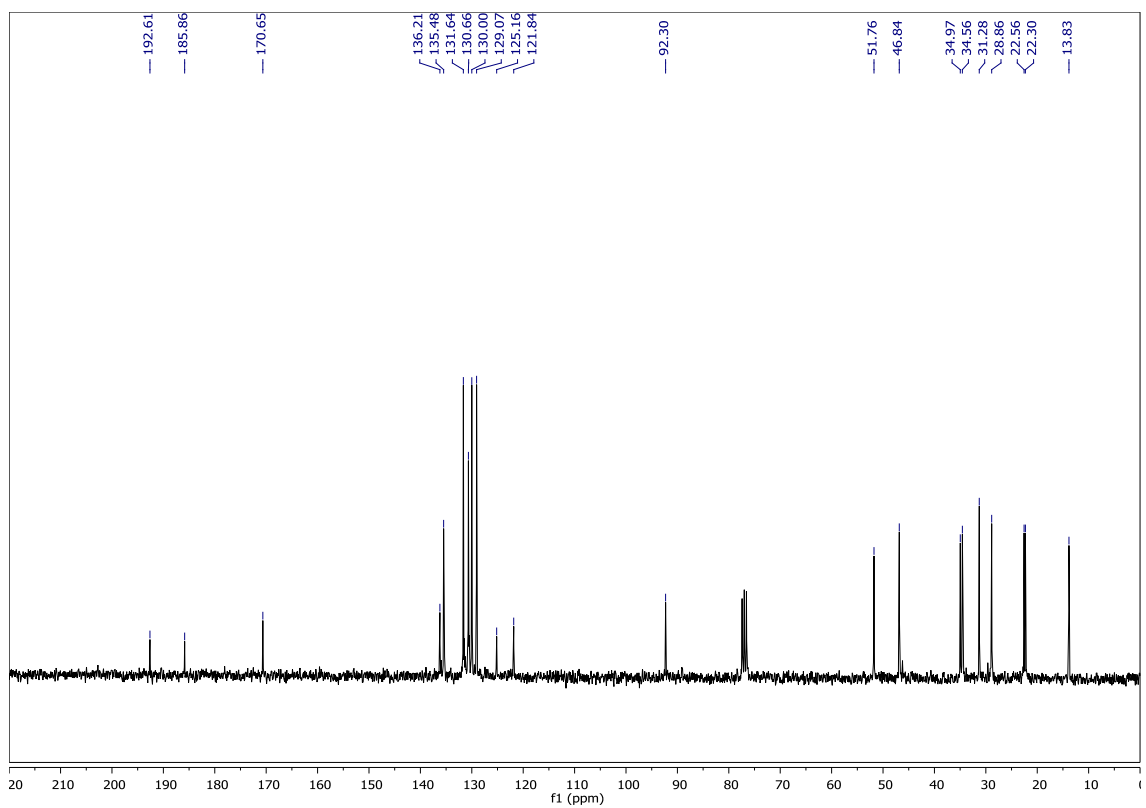
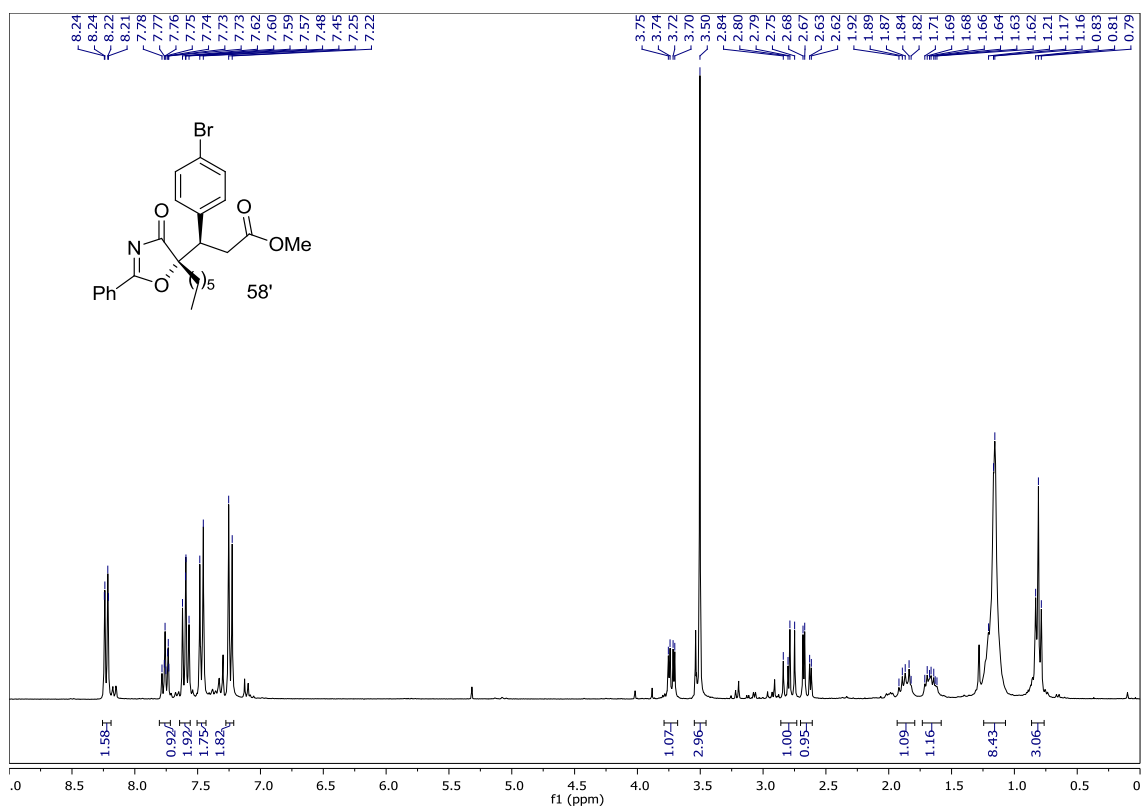




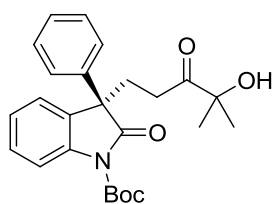






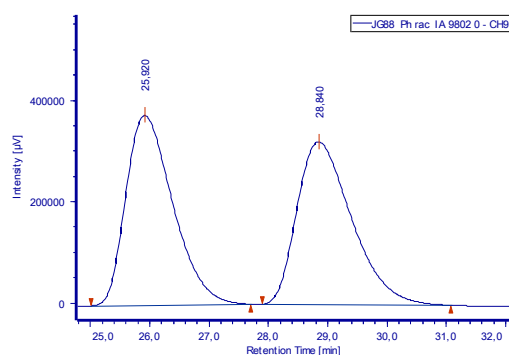


#### 4. HPLC chromatograms of representative compounds

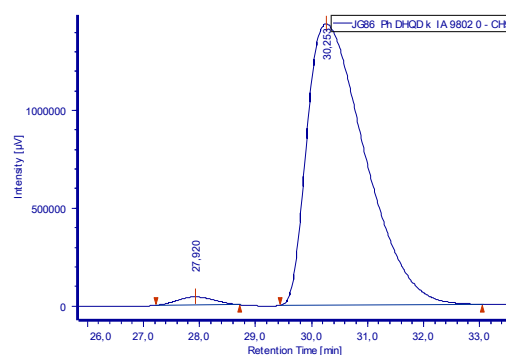


**12Aa**

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA hexane/isopropanol 98/2, flow rate= 1 mL/min, retention times: 27.9 min (minor.) and 30.2 min (major.)).

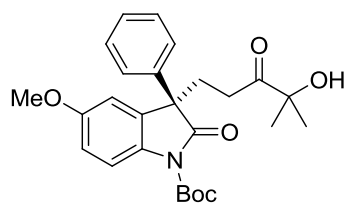


PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	25,920	20511543	373251	50,057	53,852
Unknown	9	28,840	20465200	319848	49,943	46,148



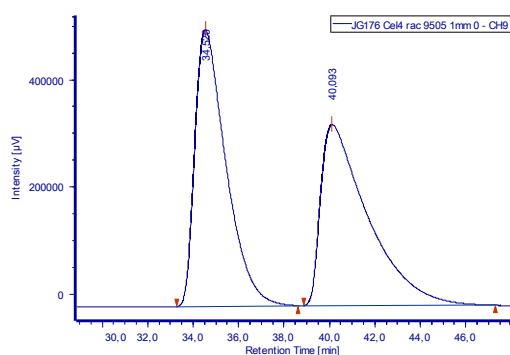
PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	27,920	1935788	41751	1,846	2,828
Unknown	9	30,253	102936340	1434679	98,154	97,172



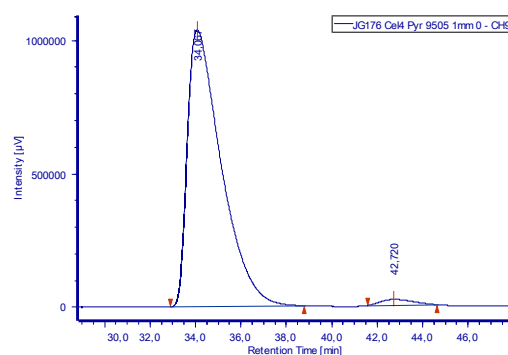


**12Ac**

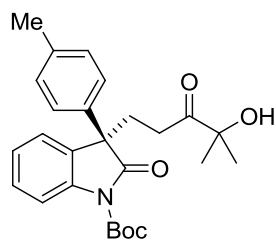
The enantiomeric purity was determined by HPLC analysis (Phenomenex Lux 3u Cellulose-4, hexane/isopropanol 95/5, flow rate= 1 mL/min, retention times: 34.1 min (major.) and 42.7 min (minor.)



PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	34,520	48740953	513881	50,189	60,457
Unknown	9	40,093	48373054	336107	49,811	39,543

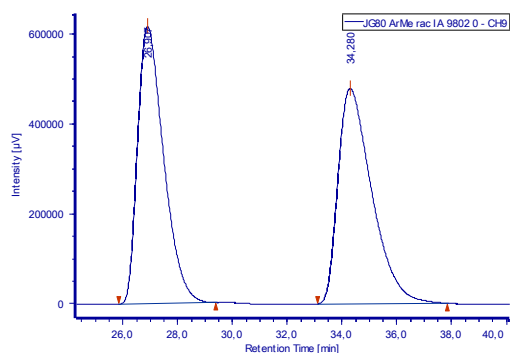


PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	34,067	106853234	1035525	98,033	97,945
Unknown	9	42,720	2144039	21730	1,967	2,055

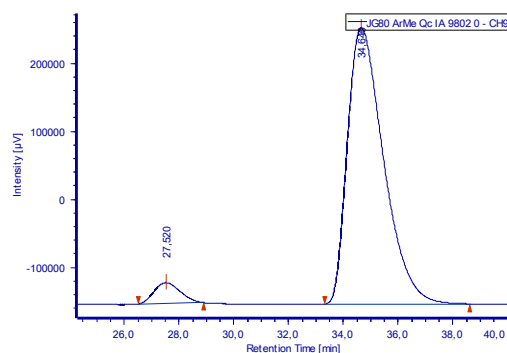


**12Ba**

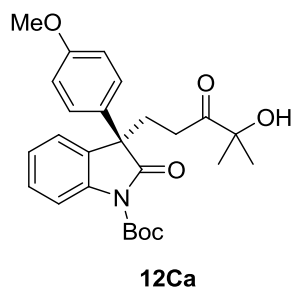
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA hexane/isopropanol 98/2, flow rate= 1 mL/min, retention times: 27.4 min (minor.) and 34.3 min (major.)).



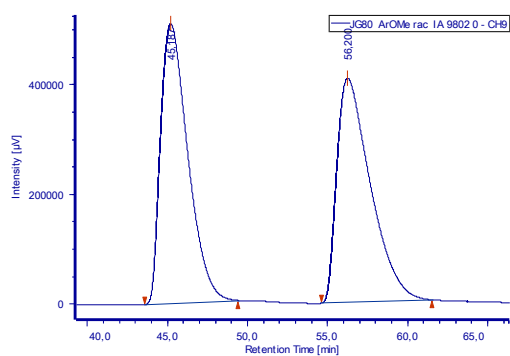
PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	26,907	40596805	615465	49,891	56,291
Unknown	9	34,280	40774355	477891	50,109	43,709



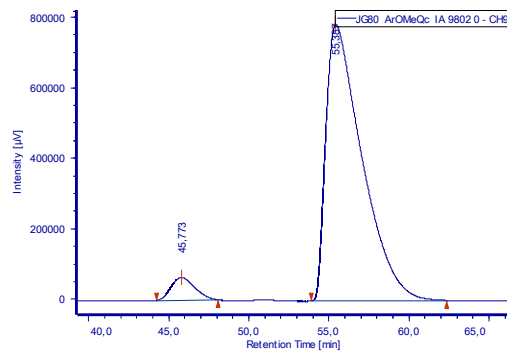
PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	27,520	2022276	30496	5,185	7,006
Unknown	9	34,640	36976558	404787	94,815	92,994



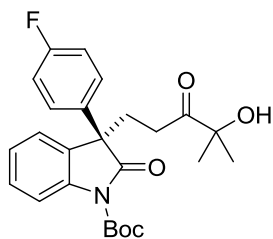
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA hexane/isopropanol 98/2, flow rate= 1 mL/min, retention times: 45.8 min (minor.) and 55.4 min (major.))



PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	45,187	59913148	507678	50,365	55,502
Unknown	9	56,200	59044452	407026	49,635	44,498

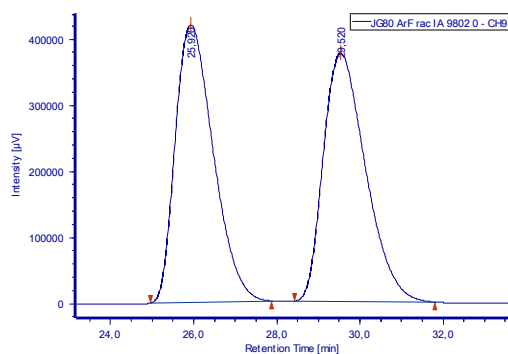


PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	45,773	6651729	64107	5,158	7,575
Unknown	9	55,387	122295601	782184	94,842	92,425

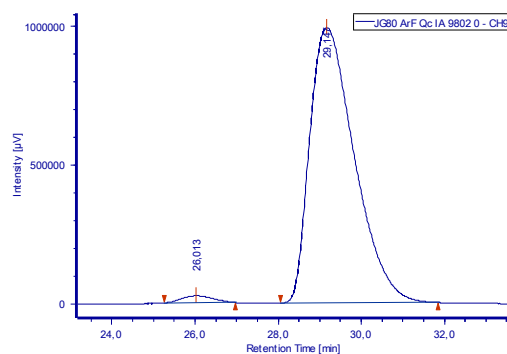


**12Da**

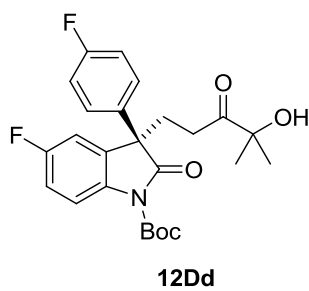
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA hexane/isopropanol 98/2, flow rate= 1 mL/min, retention times: 26.0 min (minor.) and 29.1 min (major.)).



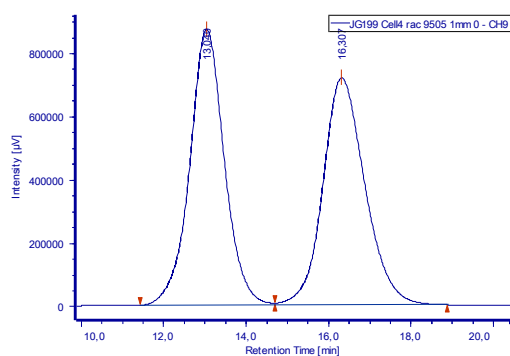
PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	25,920	26522646	418215	50,122	52,802
Unknown	9	29,520	26393349	373830	49,878	47,198



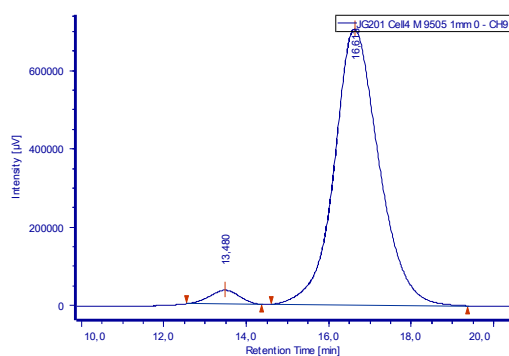
PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	26,013	1329040	25275	1,777	2,499
Unknown	9	29,147	73476262	985952	98,223	97,501



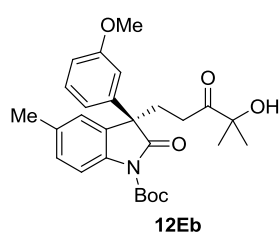
The enantiomeric purity was determined by HPLC analysis (Phenomenex Lux 3u Cellulose-4, hexane/isopropanol 95/05, flow rate= 1 mL/min, retention times: 13.5 min (minor.) and 16.6 min (major.)



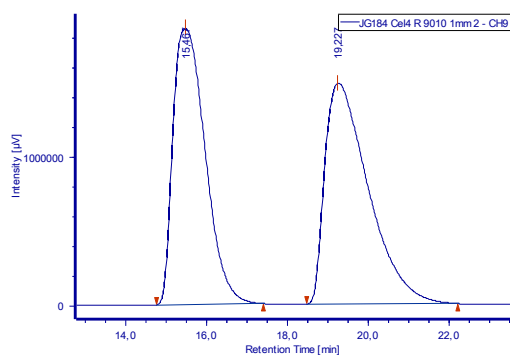
PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	13,040	50733690	870009	50,078	54,858
Unknown	9	16,307	50576053	715905	49,922	45,142



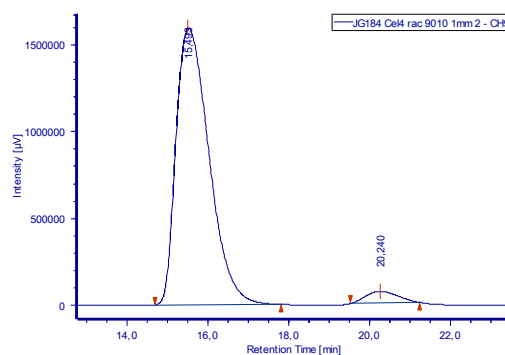
PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	13,480	1772755	35344	3,259	4,787
Unknown	9	16,613	52626094	702927	96,741	95,213



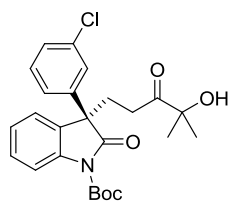
The enantiomeric purity was determined by HPLC analysis (Phenomenex Lux 3u Cellulose-4, hexane/isopropanol 90/10, flow rate= 1 mL/min, retention times: 15.5 min (major.) and 20.2 min (minor.)).



PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	15,467	102359064	1850826	48,010	55,544
Unknown	9	19,227	110845574	1481377	51,990	44,456

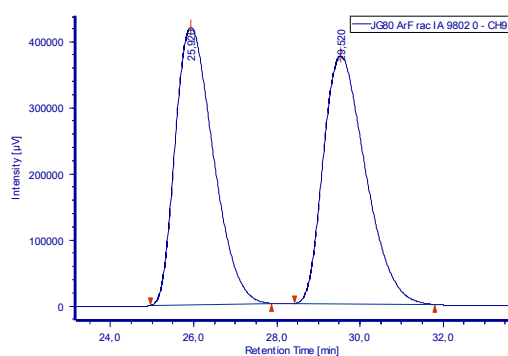


PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	15,493	89925856	1587482	96,067	95,956
Unknown	9	20,240	3681878	66904	3,933	4,044

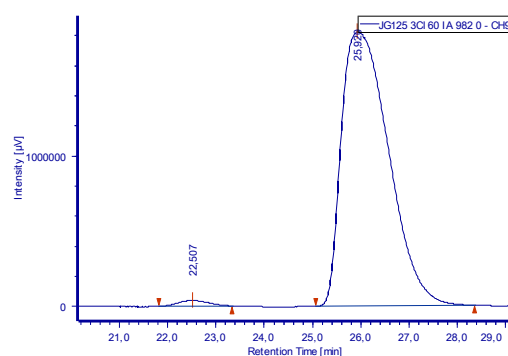


**12Fa**

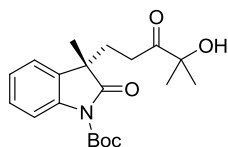
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA hexane/isopropanol 98/2, flow rate= 1 mL/min, retention times: 22.5 min (minor.) and 25.9 min (major.)..



PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	22,280	89944952	1645375	48,658	51,804
Unknown	9	26,080	94907414	1530779	51,342	48,196



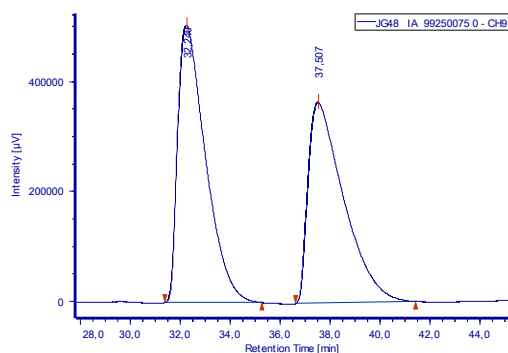
PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	22,507	1662619	37653	1,332	2,024
Unknown	9	25,920	123183631	1822417	98,668	97,976



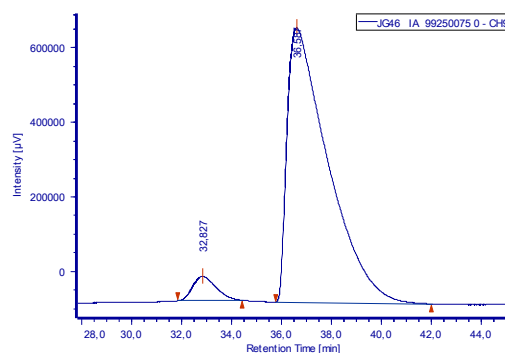
**12Ga**

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA hexane/isopropanol 99.25/0.75, flow rate= 1 mL/min, retention times: 32.8 min (minor.) and 36.6 min (major.)

)).

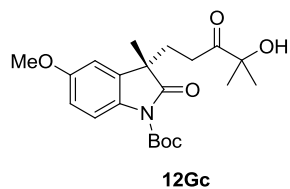


PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	32,240	38735518	502913	51,821	57,954
Unknown	9	37,507	36013303	364859	48,179	42,046

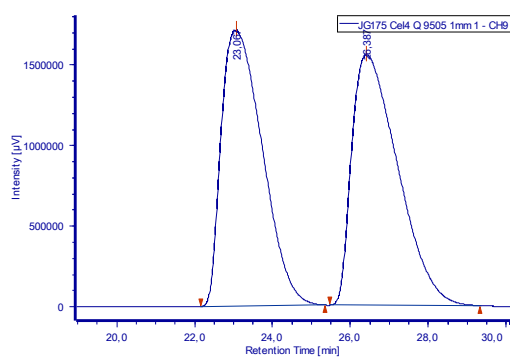


PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	32,827	4180149	64692	4,791	8,107
Unknown	9	36,587	83063476	733317	95,209	91,893

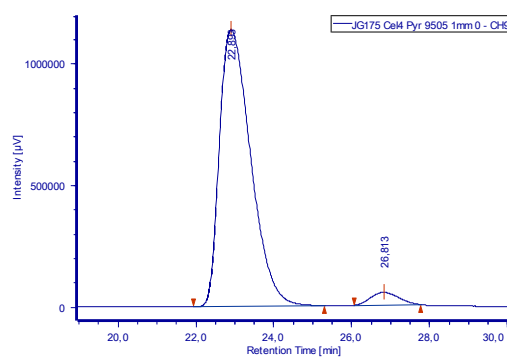




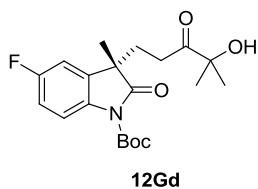
The enantiomeric purity was determined by HPLC analysis (Phenomenex Lux 3u Cellulose-4, hexane/isopropanol 95/5, flow rate= 1 mL/min, retention times: 22.9 min (major.) and 26.8 min (minor.)).



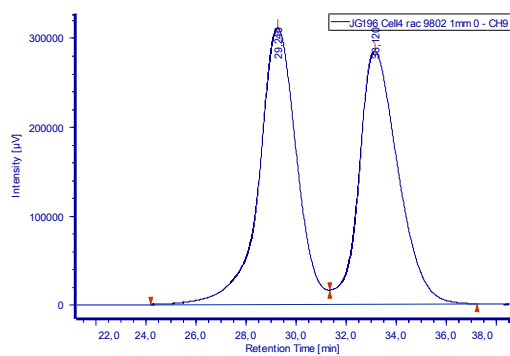
PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	23,067	125228913	1711867	49,612	52,440
Unknown	9	26,387	127187226	1552570	50,388	47,560



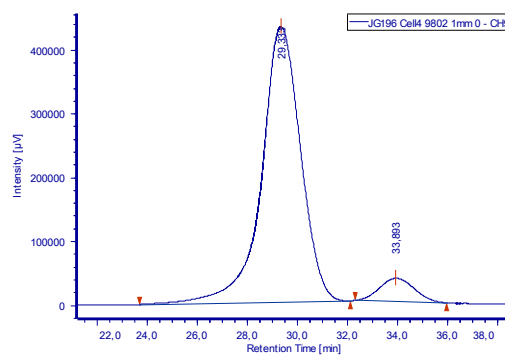
PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	22,893	63106728	1135864	96,067	95,640
Unknown	9	26,813	2583651	51779	3,933	4,360



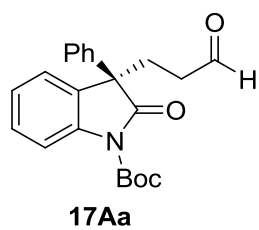
The enantiomeric purity was determined by HPLC analysis (Phenomenex Lux 3u Cellulose-4, hexane/isopropanol 98/2, flow rate= 1 mL/min, retention times: 29.3 min (major.) and 33.9 min (minor.)).



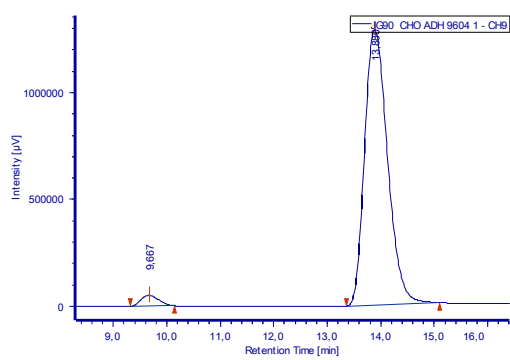
PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	29,240	32277615	309827	51,425	52,208
Unknown	9	33,120	30489038	283625	48,575	47,792



PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	29,333	46467850	429966	93,012	92,225
Unknown	9	33,893	3491212	36247	6,988	7,775

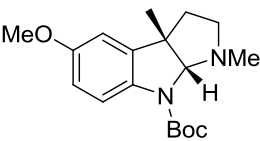


The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-3 hexane/isopropanol 96/4, flow rate= 1 mL/min, retention times: 9.7 min (minor.) and 13.9 min (major.)).

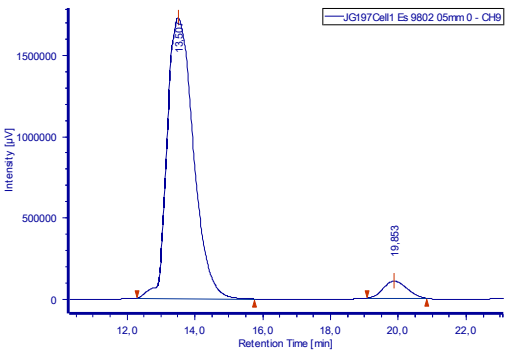


PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	9,667	1174211	50552	2,983	3,790
Unknown	9	13,880	38191401	1283414	97,017	96,210

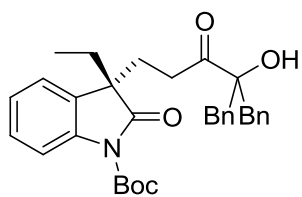
(-)-esermethole



The enantiomeric purity was determined by HPLC analysis (Phenomenex Lux 3u Cellulose-1, hexane/isopropanol 98/2, flow rate= 0.5 mL/min, retention times: 13.5 min (major.) and 19.8 min (minor.)).

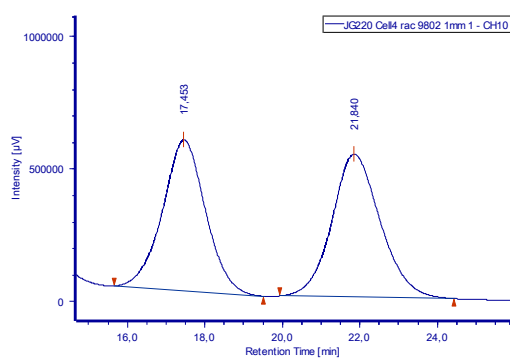


PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	13,507	92327753	1720147	94,792	94,278
Unknown	9	19,853	5072154	104406	5,208	5,722

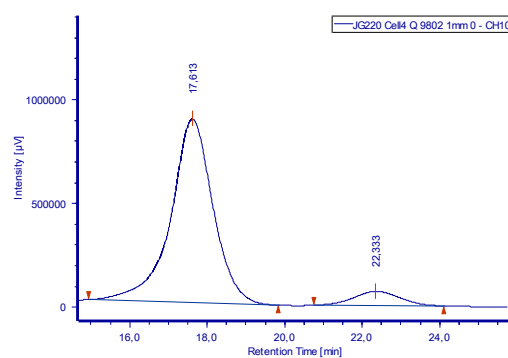


**13Ha**

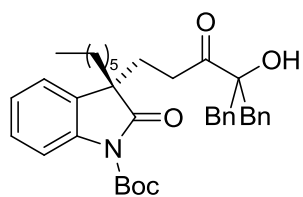
The enantiomeric purity was determined by HPLC analysis (Phenomenex Lux 3u Cellulose-4, hexane/isopropanol 98/2, flow rate= 1 mL/min, retention times: 17.6 min (major.) and 22.3 min (minor.)).



Peak Name	CH	tR	Area	Height	Area%	Height%
Unknown	10	17,453	43721222	567129	48,371	51,345
Unknown	10	21,840	46665571	537418	51,629	48,655

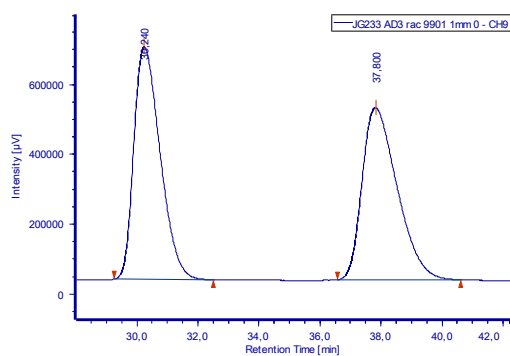


Peak Name	CH	tR	Area	Height	Area%	Height%
Unknown	10	17,613	67075876	882975	92,122	92,739
Unknown	10	22,333	5736082	69129	7,878	7,261

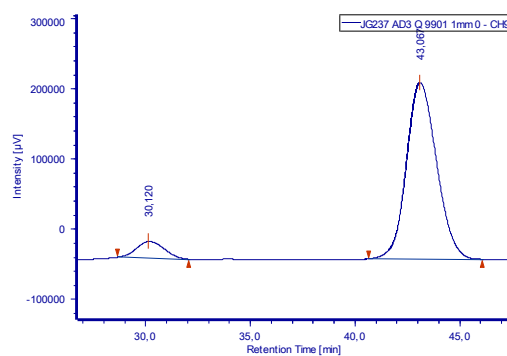


**13la**

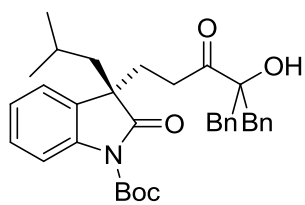
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-3, hexane/isopropanol 99/1, flow rate= 1 mL/min, retention times: 30.1 min (minor.) and 43.1 min (major.)).



Peak Name	CH	tR	Area	Height	Area%	Height%
Unknown	9	31,040	66740789	708699	51,045	55,489
Unknown	9	44,467	64008397	568497	48,955	44,511

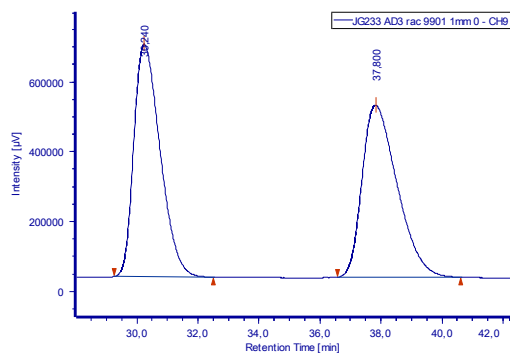


Peak Name	CH	tR	Area	Height	Area%	Height%
Unknown	9	30,120	2175489	23612	7,996	8,604
Unknown	9	43,067	25031090	250832	92,004	91,396

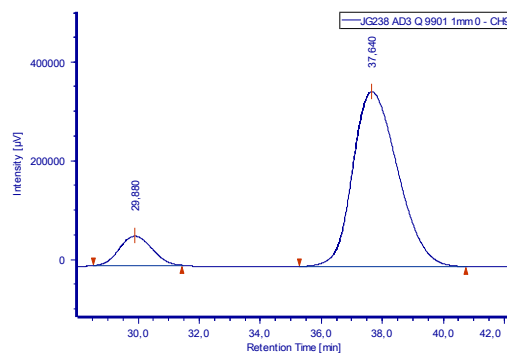


**13Ja**

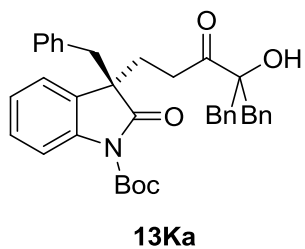
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-3 hexane/isopropanol 99/1, flow rate= 1 mL/min, retention times: 29.9 min (minor.) and and 37.6 min (major.)).



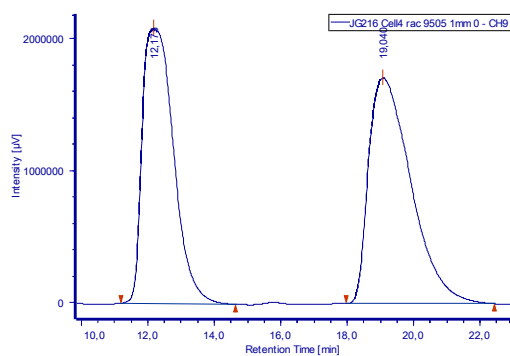
Peak Name	CH	tR	Area	Height	Area%	Height%
Unknown	9	30,240	39686040	663447	50,340	57,453
Unknown	9	37,800	39149959	491316	49,660	42,547



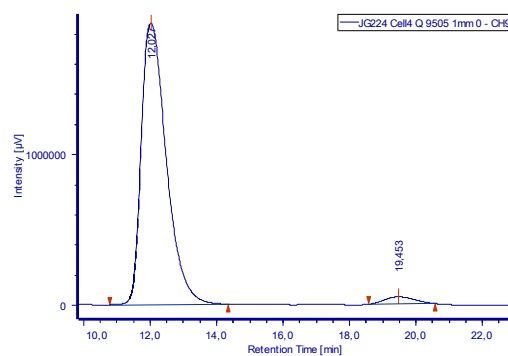
Peak Name	CH	tR	Area	Height	Area%	Height%
Unknown	9	29,880	4387544	59028	10,848	14,340
Unknown	9	37,640	36058961	352602	89,152	85,660



The enantiomeric purity was determined by HPLC analysis (Phenomenex Lux 3u Cellulose-4, hexane/isopropanol 95/5, flow rate= 1 mL/min, retention times: 12.0 min (major.) and 19.5 min (minor.)).

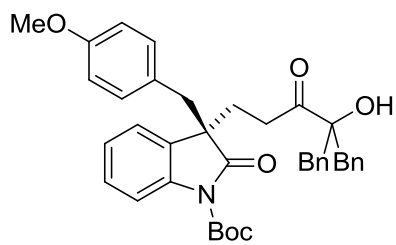


Peak Name	CH	tR	Area	Height	Area%	Height%
Unknown	9	12,173	135440813	2078375	47,333	54,937
Unknown	9	19,040	150702142	1704814	52,667	45,063



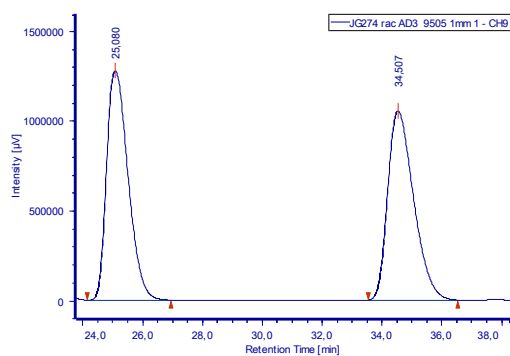
Peak Name	CH	tR	Area	Height	Area%	Height%
Unknown	9	12,027	97052279	1862114	97,051	97,528
Unknown	9	19,453	2949548	47205	2,949	2,472



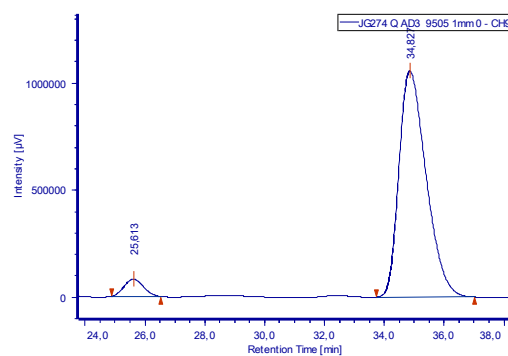


**13La**

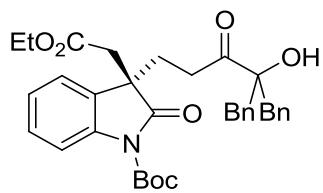
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-3 hexane/isopropanol 95/5, flow rate= 1 mL/min, retention times: 25.6 min (minor.) and and 34.8 min (major.)).



Peak Name	CH	tR	Area	Height	Area%	Height%
Unknown	9	25,080	63440760	1272289	50,157	54,788
Unknown	9	34,507	63043650	1049902	49,843	45,212

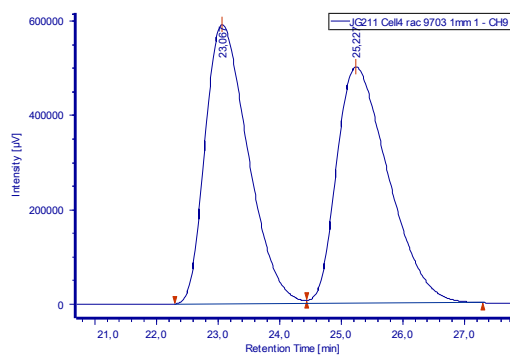


Peak Name	CH	tR	Area	Height	Area%	Height%
Unknown	9	25,613	3593394	79971	5,149	7,068
Unknown	9	34,827	66189763	1051553	94,851	92,932

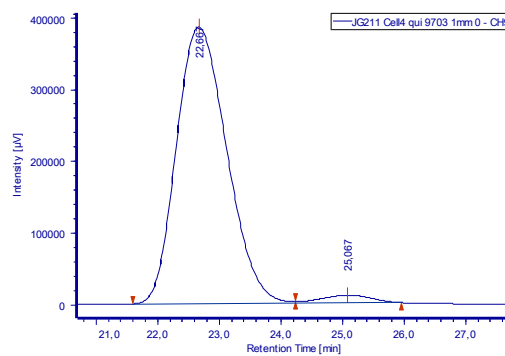


**13Ma**

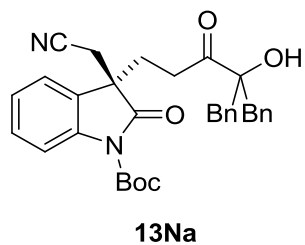
The enantiomeric purity was determined by HPLC analysis (Phenomenex Lux 3u Cellulose-4, hexane/isopropanol 97/3, flow rate= 1 mL/min, retention times: 22.7 min (major.) and 25.1 min (minor.)).



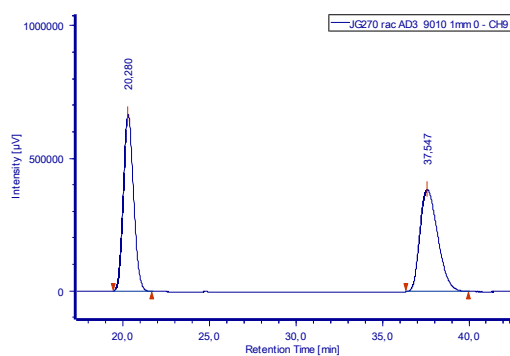
Peak Name	CH	tR	Area	Height	Area%	Height%
Unknown	9	23,067	28499086	590467	49,400	54,164
Unknown	9	25,227	29190822	499676	50,600	45,836



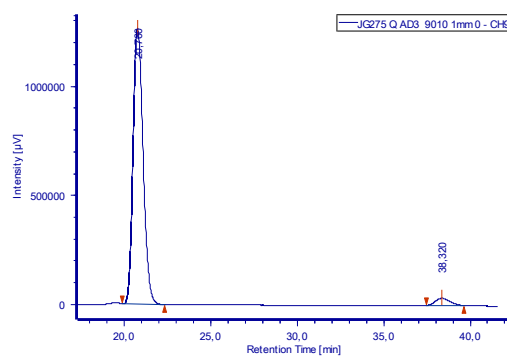
Peak Name	CH	tR	Area	Height	Area%	Height%
Unknown	9	22,667	21796307	384306	97,265	97,256
Unknown	9	25,067	612929	10845	2,735	2,744



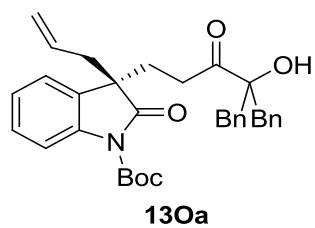
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-3 hexane/isopropanol 90/10, flow rate= 1 mL/min, retention times: 20.8 min (major.) and and 38.3 min (minor.)).



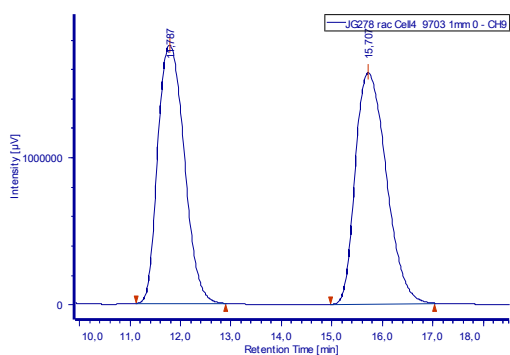
Peak Name	CH	tR	Area	Height	Area%	Height%
Unknown	9	20,280	27342831	664401	49,963	63,409
Unknown	9	37,547	27383619	383405	50,037	36,591



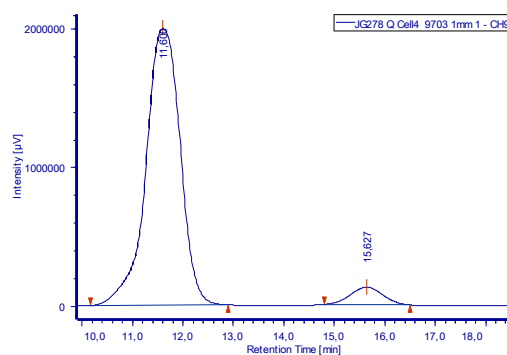
Peak Name	CH	tR	Area	Height	Area%	Height%
Unknown	9	20,760	50888357	1258390	96,328	97,428
Unknown	9	38,320	1939925	33223	3,672	2,572



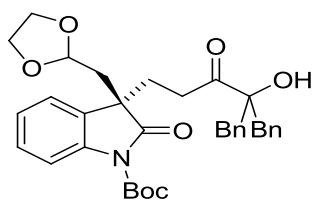
The enantiomeric purity was determined by HPLC analysis (Phenomenex 3u Cellulose-4, hexane/isopropanol 97/3, flow rate= 1 mL/min, retention times: 11.6 min (major.) and 15.6 min (minor.).



Peak Name	CH	tR	Area	Height	Area%	Height%
Unknown	9	11,787	63557612	1753055	48,795	52,772
Unknown	9	15,707	66697511	1568899	51,205	47,228

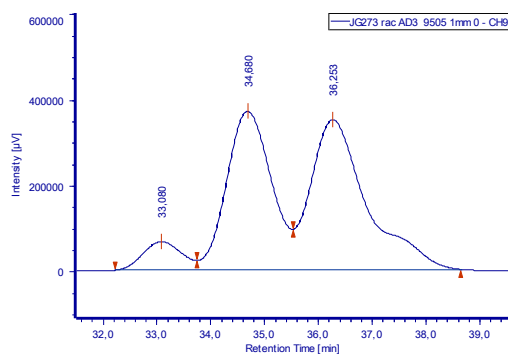


Peak Name	CH	tR	Area	Height	Area%	Height%
Unknown	9	11,600	93943642	1992172	94,341	94,027
Unknown	9	15,627	5634839	126542	5,659	5,973

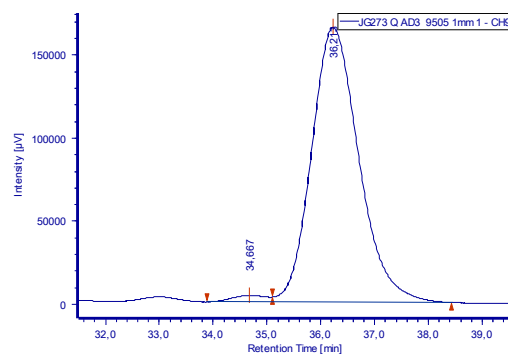


**13Pa**

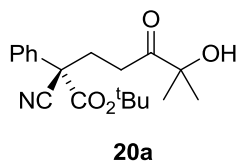
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-3 hexane/isopropanol 95/5, flow rate= 1 mL/min, retention times: 34.7 min (minor.) and 36.2 min (major.)).



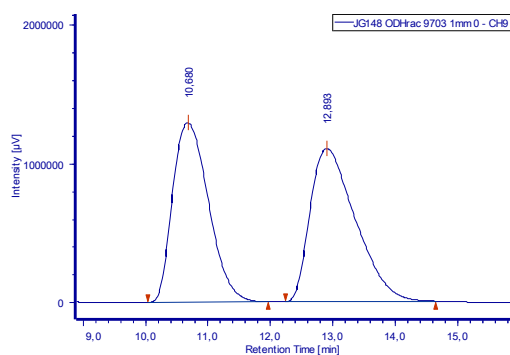
Peak Name	CH	tR	Area	Height	Area%	Height%
Unknown	9	33,080	3290113	65879	6,603	8,405
Unknown	9	34,680	21275991	368891	42,702	47,066
Unknown	9	36,253	25257800	348998	50,694	44,528



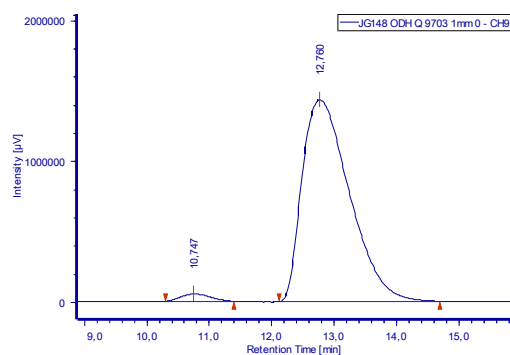
Peak Name	CH	tR	Area	Height	Area%	Height%
Unknown	9	34,667	177124	3976	1,728	2,354
Unknown	9	36,213	10071325	164974	98,272	97,646



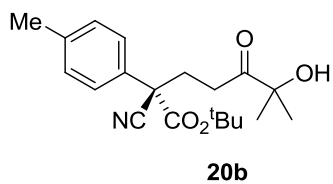
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H hexane/isopropanol 97/3, flow rate= 1 mL/min, retention times: 10.7 min (minor.) and 12.8 min (major.)).



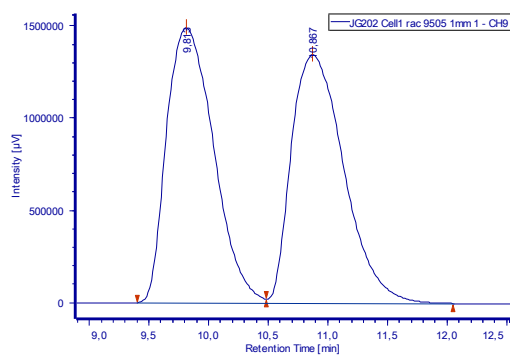
PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	10,680	51350592	1286509	48,251	54,016
Unknown	9	12,893	55073413	1095219	51,749	45,984



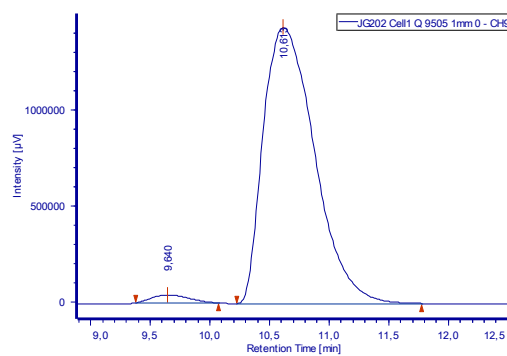
PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	10,747	1726633	52768	2,243	3,558
Unknown	9	12,760	75257086	1430247	97,757	96,442



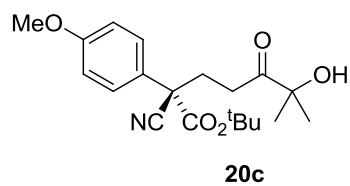
The enantiomeric purity was determined by HPLC analysis (Phenomenex Lux 3u Cellulose-1 hexane/isopropanol 95/05, flow rate= 1 mL/min, retention times: 9.6 min (minor.) and 10.6 min (major.)).



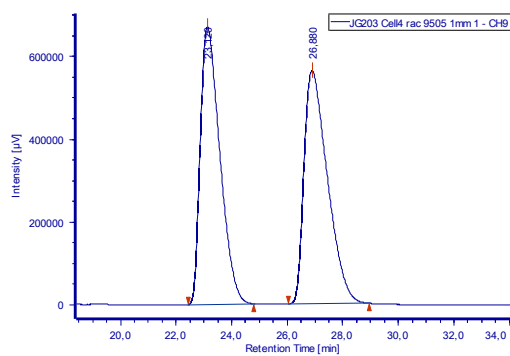
PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	9,813	40737029	1484645	49,756	52,517
Unknown	9	10,867	41135869	1342349	50,244	47,483



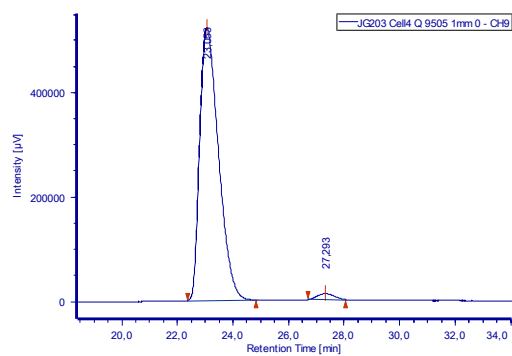
PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	9,640	902821	41844	2,064	2,838
Unknown	9	10,613	42828767	1432796	97,936	97,162



The enantiomeric purity was determined by HPLC analysis (Phenomenex Lux 3u Cellulose-4 hexane/isopropanol 95/05, flow rate= 1 mL/min, retention times: 23.1 min (major.) and 27.3 min (minor.)).

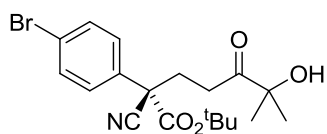


PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	23,120	32636207	669008	49,819	54,337
Unknown	9	26,880	32873058	562214	50,181	45,663



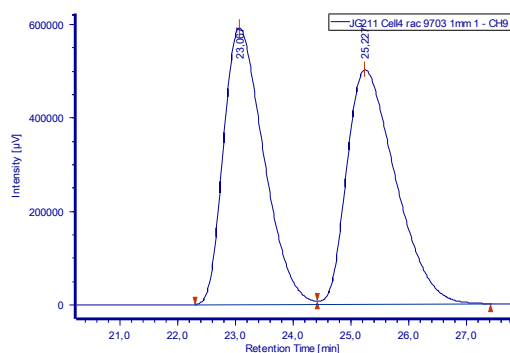
PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	23,053	24347381	520005	98,060	97,834
Unknown	9	27,293	481793	11512	1,940	2,166



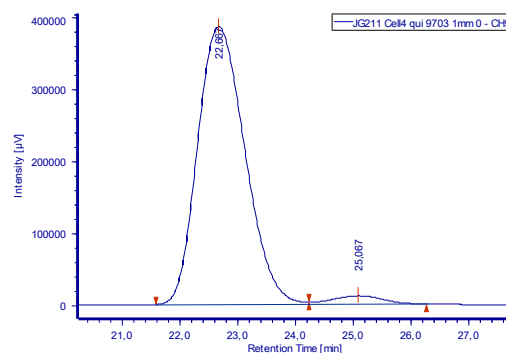


**20d**

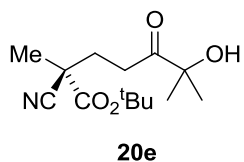
The enantiomeric purity was determined by HPLC analysis (Phenomenex Lux 3u Cellulose-4 hexane/isopropanol 97/03, flow rate= 1 mL/min, retention times: 22.7 min (major.) and 25.13 min (minor.)).



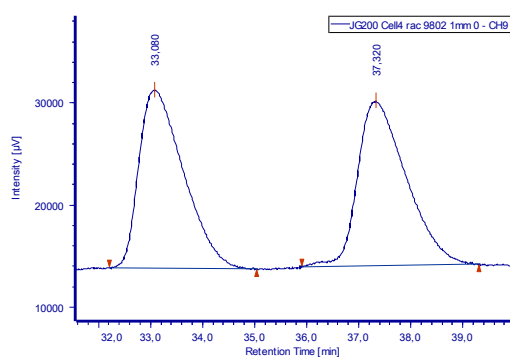
PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	23,067	28500038	590557	49,326	54,151
Unknown	9	25,227	29278675	500018	50,674	45,849



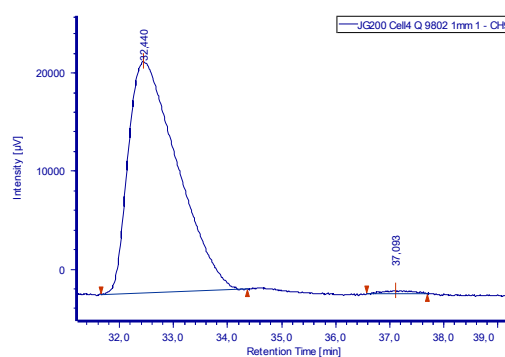
PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	22,667	21848018	384591	96,930	97,087
Unknown	9	25,067	691961	11540	3,070	2,913



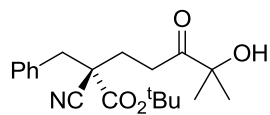
The enantiomeric purity was determined by HPLC analysis (Phenomenex Lux 3u Cellulose-4 hexane/isopropanol 98/02, flow rate= 1 mL/min, retention times: 32.4 min (major.) and 37.1 min (minor.)).



PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	33,080	1029758	17394	49,674	51,962
Unknown	9	37,320	1043271	16080	50,326	48,038

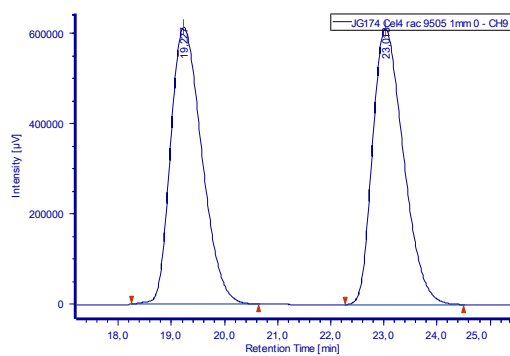


Peak Name	CH	tR	Area	Height	Area%	Height%
Unknown	9	32,440	1480892	23561	99,146	98,511
Unknown	9	37,093	12757	356	0,854	1,489

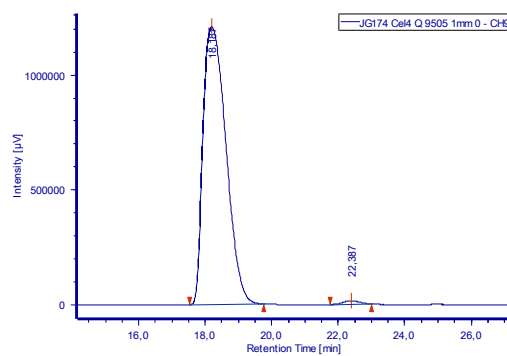


**20f**

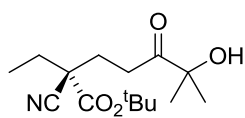
The enantiomeric purity was determined by HPLC analysis (Phenomenex Lux 3u Cellulose-4 hexane/isopropanol 95/05, flow rate= 1 mL/min, retention times: 18.2 min (major.) and 22.4 min (minor.)).



PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	19,227	24896850	610698	50,388	50,107
Unknown	9	23,013	24513280	608092	49,612	49,893

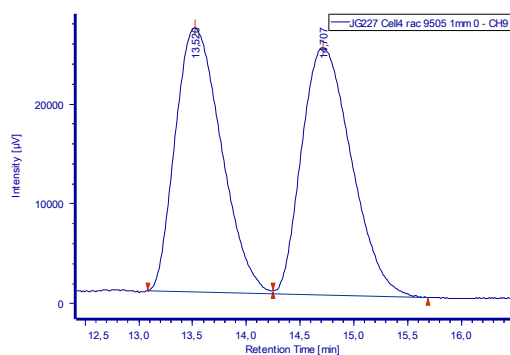


PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	18,187	57563679	1205240	99,064	98,687
Unknown	9	22,387	543872	16041	0,936	1,313

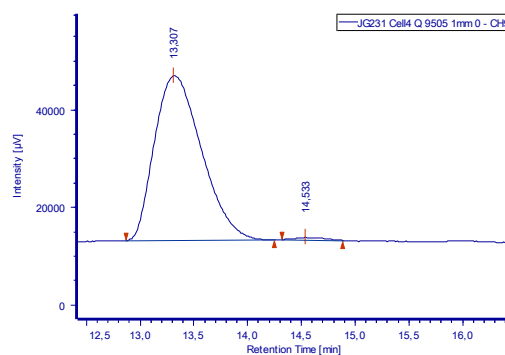


**20g**

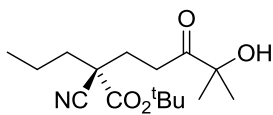
The enantiomeric purity was determined by HPLC analysis (Phenomenex Lux 3u Cellulose-4 hexane/isopropanol 95/05, flow rate= 1 mL/min, retention times: 13.3 min (major.) and 14.5 min (minor.)).



PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	13,520	784363	26354	49,822	51,604
Unknown	9	14,707	789955	24717	50,178	48,396

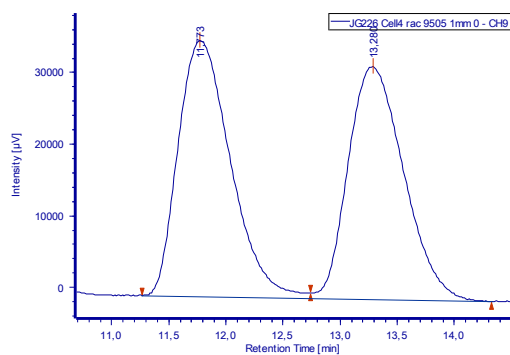


PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	13,307	1028199	33616	98,959	98,348
Unknown	9	14,533	10815	565	1,041	1,652

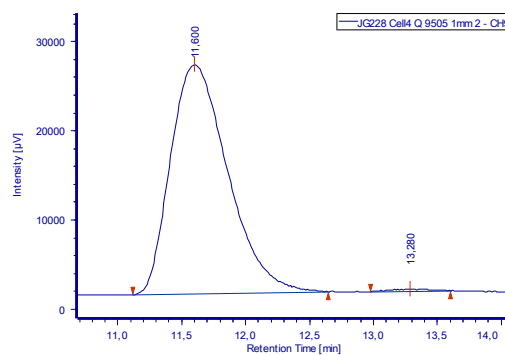


20h

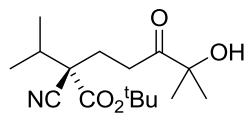
The enantiomeric purity was determined by HPLC analysis (Phenomenex Lux 3u Cellulose-4 hexane/isopropanol 95/05, flow rate= 1 mL/min, retention times: 11.6 min (major.) and 13.3 min (minor.)).



PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	11,773	1133063	35666	50,827	52,407
Unknown	9	13,280	1096191	32389	49,173	47,593

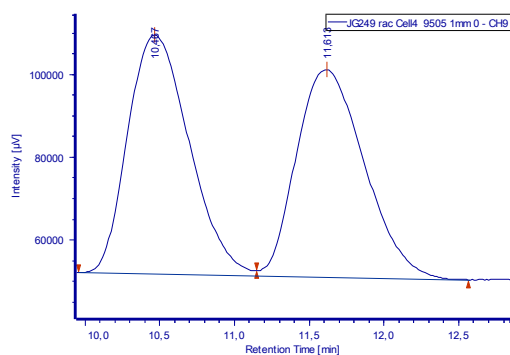


PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	11,600	795731	25615	99,256	98,995
Unknown	9	13,280	5964	260	0,744	1,005

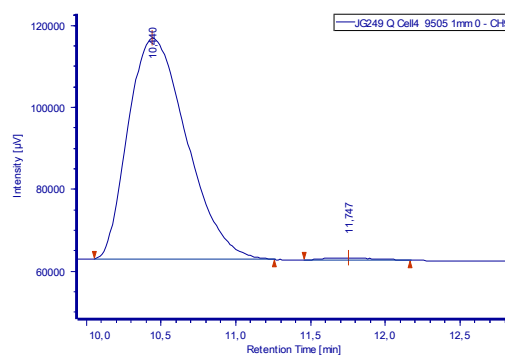


**20i**

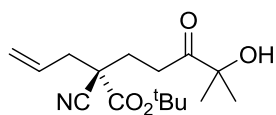
The enantiomeric purity was determined by HPLC analysis (Phenomenex Lux 3u Cellulose-4 hexane/isopropanol 95/05, flow rate= 1 mL/min, retention times: 10.4 min (major.) and 11.7 min (minor.)).



PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	10,467	1639142	57557	50,990	53,500
Unknown	9	11,613	1575512	50026	49,010	46,500

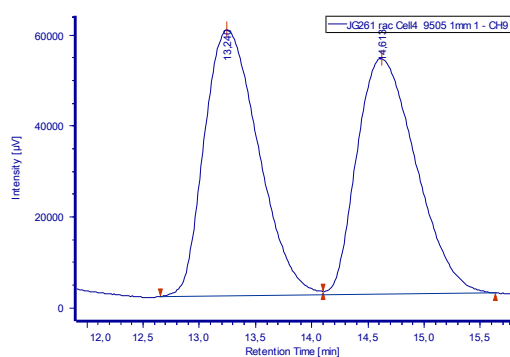


PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	10,440	1457426	53680	99,209	99,053
Unknown	9	11,747	11614	513	0,791	0,947

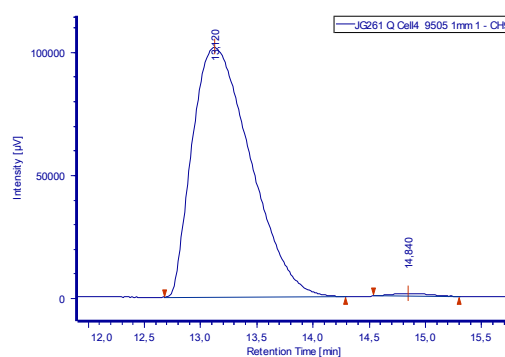


**20j**

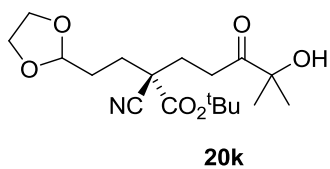
The enantiomeric purity was determined by HPLC analysis (Phenomenex Lux 3u Cellulose-4 hexane/isopropanol 95/05, flow rate= 1 mL/min, retention times: 13.1 min (major.) and 14.8 min (minor.)).



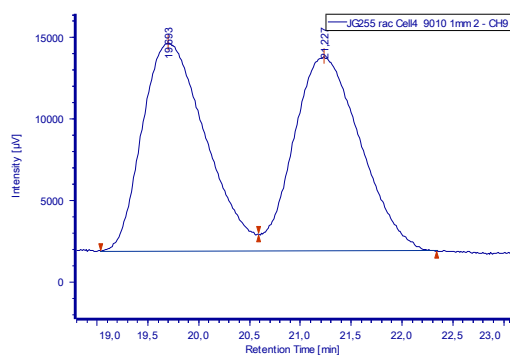
PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	13,240	1947175	58273	50,814	53,009
Unknown	9	14,613	1884771	51658	49,186	46,991



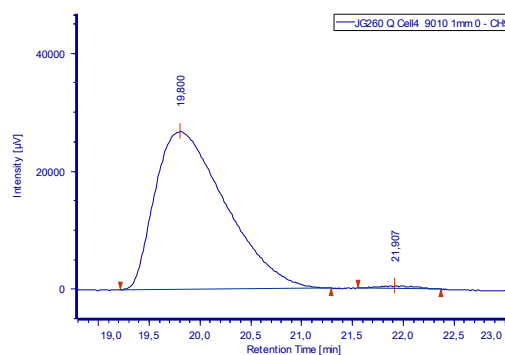
PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	13,120	3643939	101237	99,247	98,891
Unknown	9	14,840	27650	1136	0,753	1,109



The enantiomeric purity was determined by HPLC analysis (Phenomenex Lux 3u Cellulose-4 hexane/isopropanol 90/10, flow rate= 1 mL/min, retention times: 19.8 min (major.) and 21.9 min (minor.)).

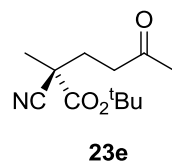


PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	19,693	551403	12763	50,436	51,758
Unknown	9	21,227	541863	11896	49,564	48,242

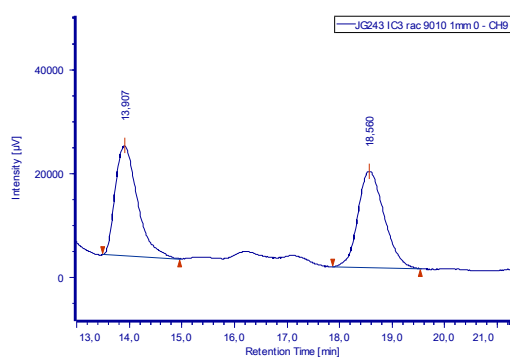


PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	19,800	1282238	26625	99,030	98,424
Unknown	9	21,907	12562	426	0,970	1,576

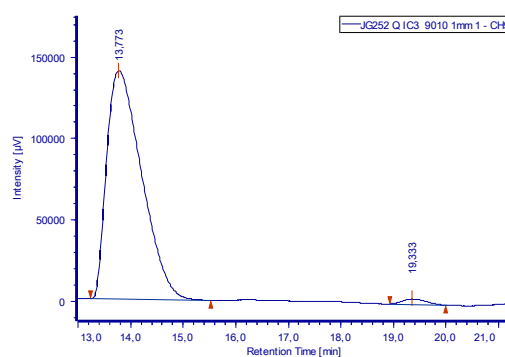




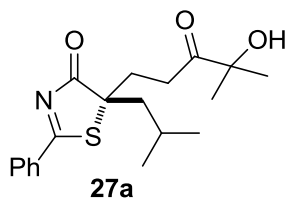
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC-3 hexane/isopropanol 90/10, flow rate= 1 mL/min, retention times: 13.7 min (major.) and 19.3 min (minor.)).



PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	13,907	621173	21097	49,179	53,315
Unknown	9	18,560	641908	18474	50,821	46,685

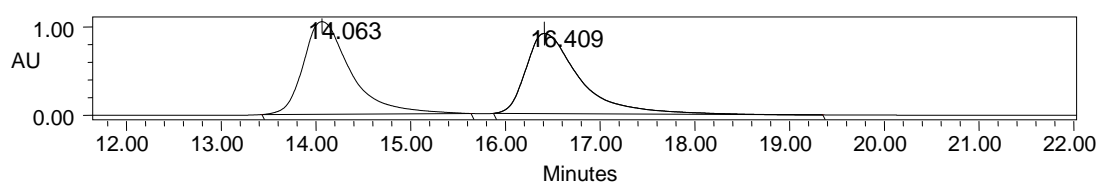


PeakName	CH	tR	Area	Height	Area%	Height%
Unknown	9	13,773	6452565	140109	98,420	97,683
Unknown	9	19,333	103588	3324	1,580	2,317



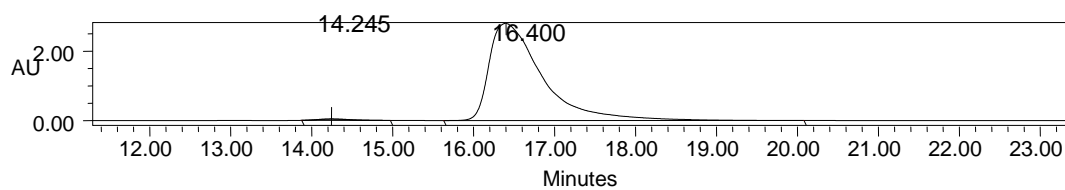
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90/10, flow rate= 1.0 mL/min, retention times: 14.0 min (min.) and 16.4 min (major.). Processed Channel Descr.: 272.0 nm.)

**Rac-27a**

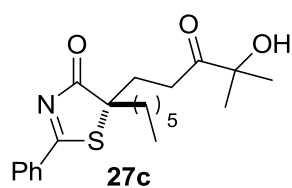


	Retention Time	% Area
1	14.063	50.60
2	16.409	49.40

**27a**

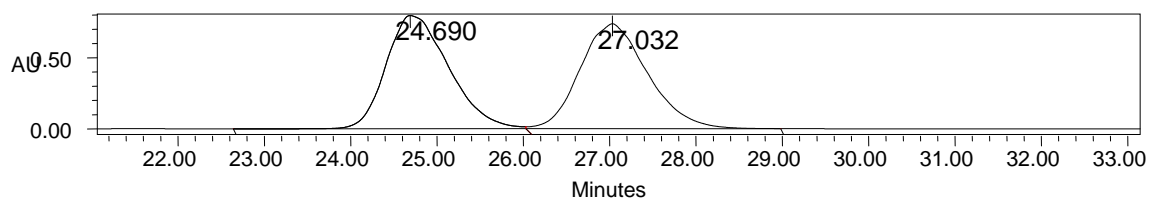


	Retention Time	% Area
1	14.245	0.88
2	16.400	99.12



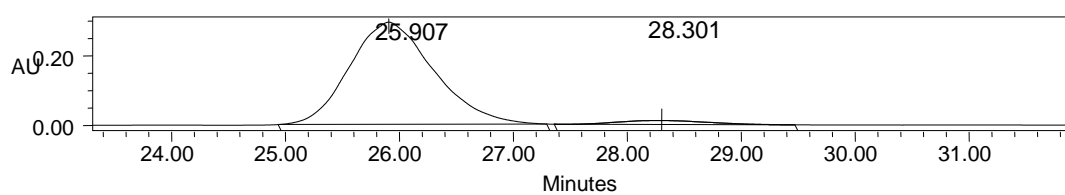
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 90/10, flow rate= 1.0 mL/min, retention times: 24.7 min (major.) and 27.0 min (min.). Processed Channel Descr.: 272.0 nm.)

**Rac-27c**

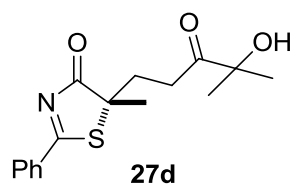


	Retention Time	% Area
1	24.690	50.03
2	27.032	49.97

**27c**

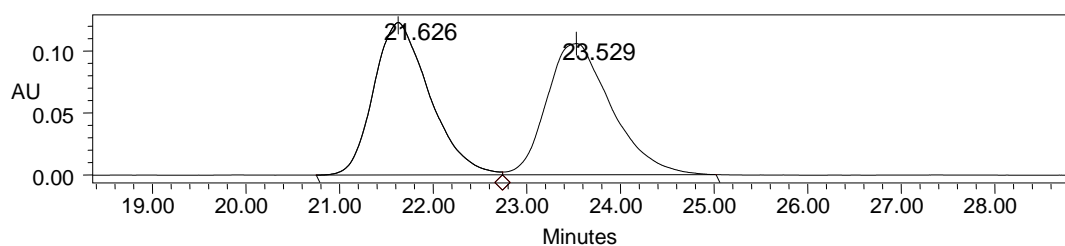


	Retention Time	% Area
1	25.907	96.00
2	28.301	4.00



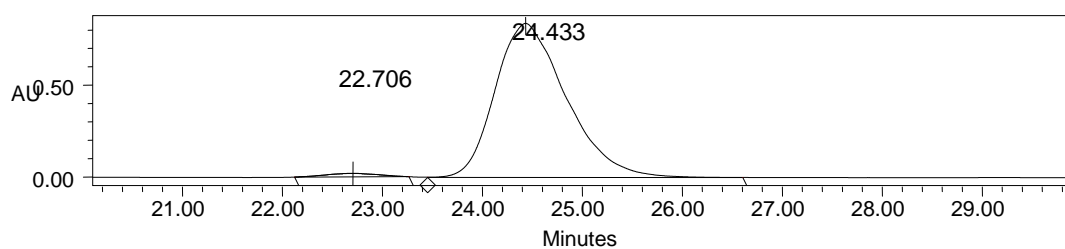
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 80/20, flow rate= 1.0 mL/min, retention times: 21.6 min (min.) and 23.5 min (major.). Processed Channel Descr.: 272.0 nm.)

**Rac-27d**

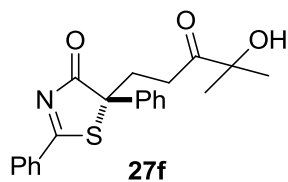


	Retention Time	% Area
1	21.626	50.09
2	23.529	49.91

**27d**

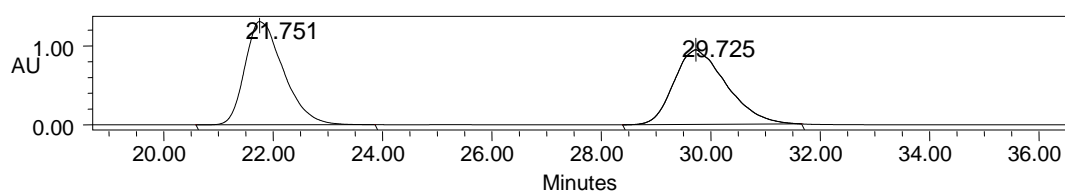


	Retention Time	% Area
1	22.706	1.65
2	24.433	98.35



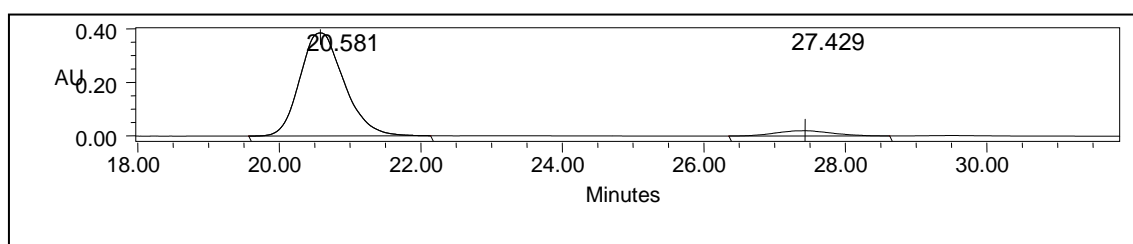
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 80/20, flow rate= 1.0 mL/min, retention times: 21.7 min (major.) and 29.7 min (min.). Processed Channel Descr.: 272.0 nm.)

**Rac-27f**

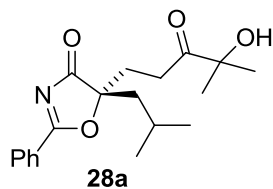


	Retention Time	% Area
1	21.751	50.39
2	29.725	49.61

**27f**

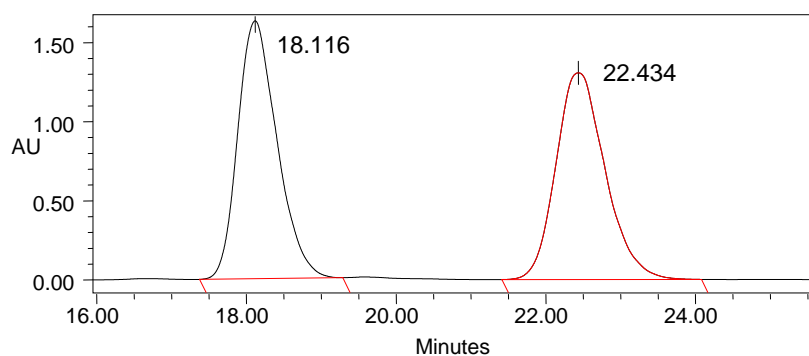


	Retention Time	% Area
1	20.581	93.87
2	27.429	6.13



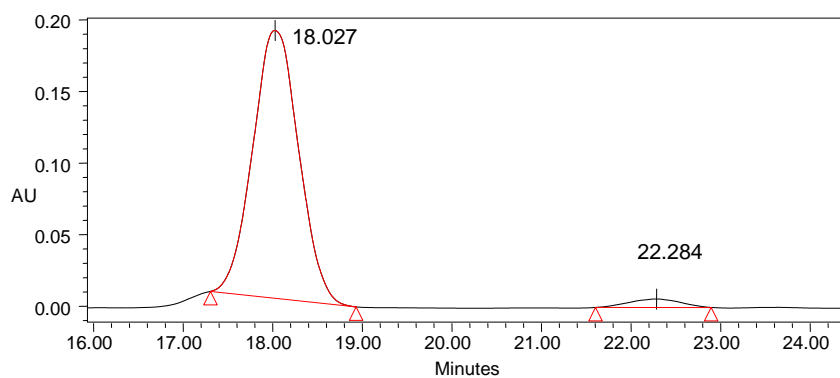
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 85/15, flow rate= 1 mL/min, retention times: 18.1 min (major.) and 22.4 min (min.). Processed Channel descr.: PDA 260 nm).

rac-**28a**

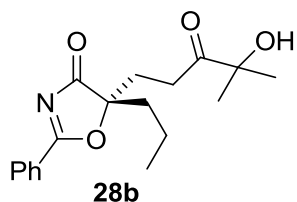


	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	18.116	59260735	49.83	1629621
2	PDA 260.0 nm	22.434	59667978	50.17	1305917

**28a**

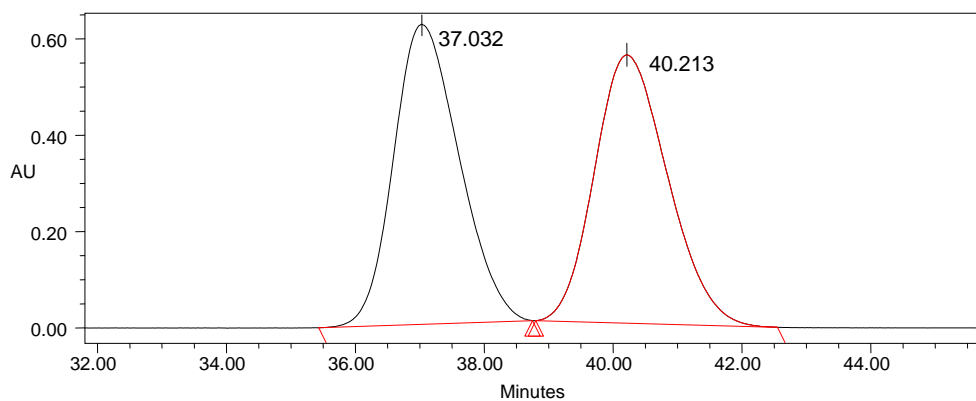


	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	18.027	6700761	96.59	187065
2	PDA 260.0 nm	22.284	236344	3.41	5894



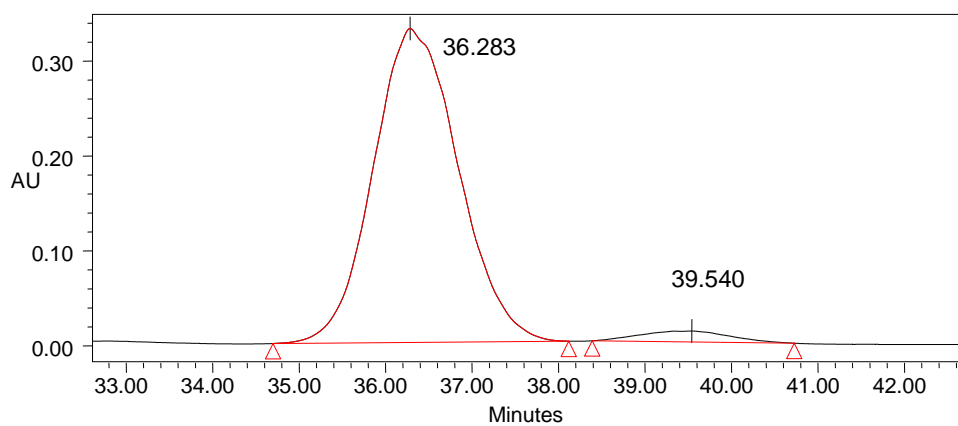
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 90/10, flow rate= 1 mL/min, retention times: 36.3 min (major.) and 39.5 min (min.). Processed Channel descr.: PDA 260 nm).

**rac-28b**

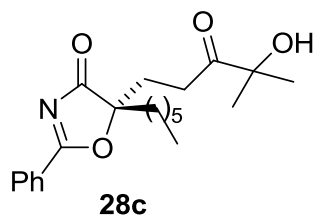


	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	37.032	44049090	50.05	622372
2	PDA 260.0 nm	40.213	43956027	49.95	556604

**28b**

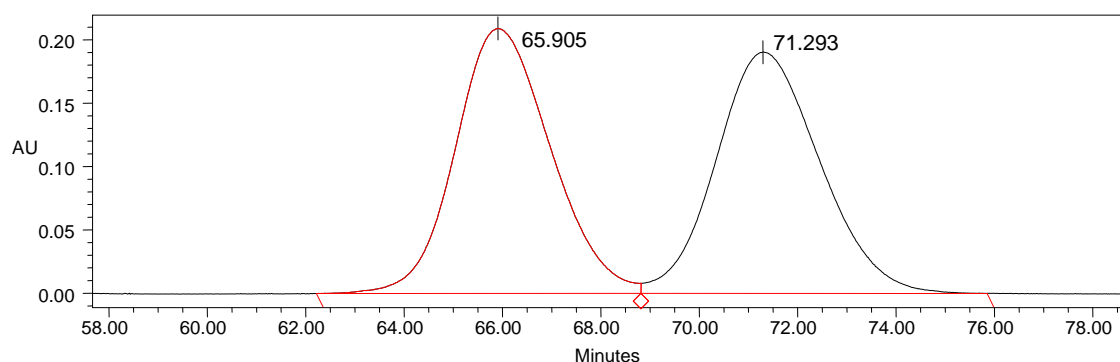


	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	36.283	22643618	96.48	330773
2	PDA 260.0 nm	39.540	826705	3.52	11595



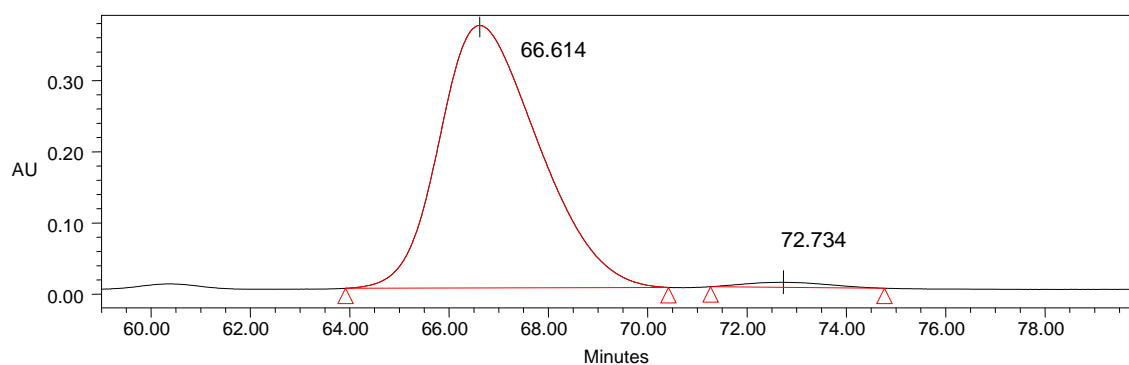
The enantiomeric purity of was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 95/5, flow rate= 1 mL/min, retention times: 66.6 min (major.) and 72.7 min (min.). Processed Channel descr.: PDA 260 nm).

**rac-28c**



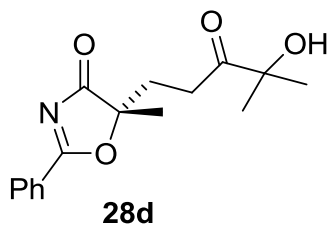
	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	65.905	28191425	50.22	209121
2	PDA 260.0 nm	71.293	27942136	49.78	190342

**28c**



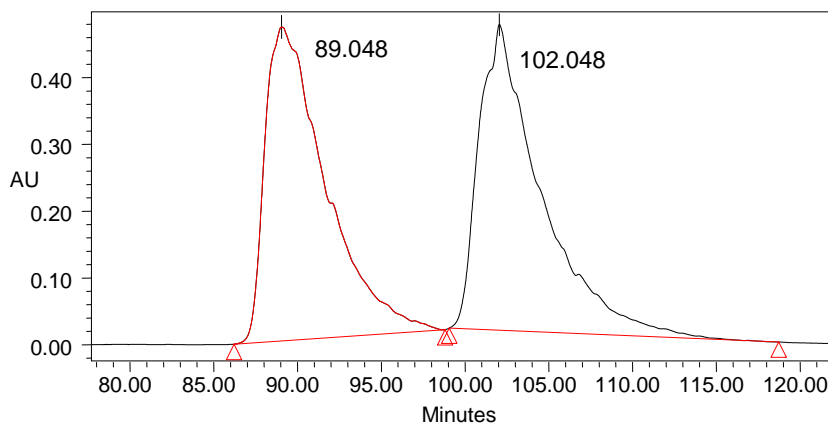
	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	66.614	51179803	98.42	368486
2	PDA 260.0 nm	72.734	820824	1.58	7110





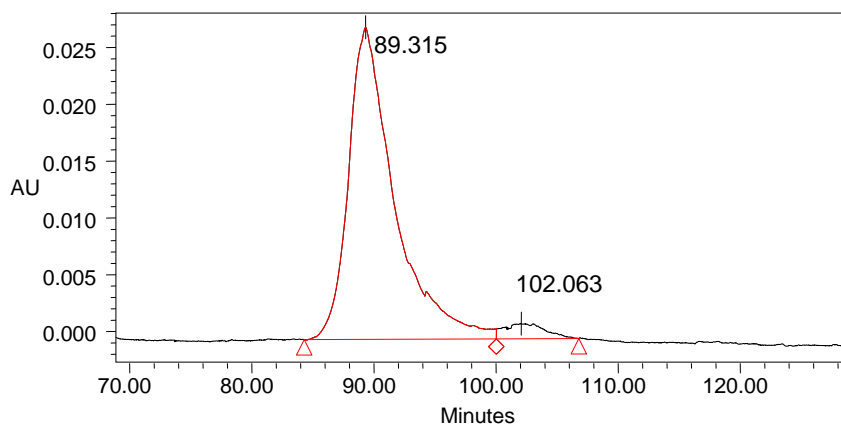
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 98/82 flow rate= 1 mL/min, retention times: 50.2 min (major.) and 56.3 min (min.). Processed Channel descr.: PDA 260 nm).

rac-**28d**

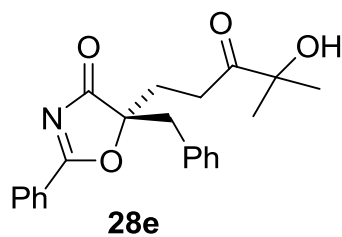


	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	89.048	118497342	50.16	469984
2	PDA 260.0 nm	102.048	117740828	49.84	458109

**28d**

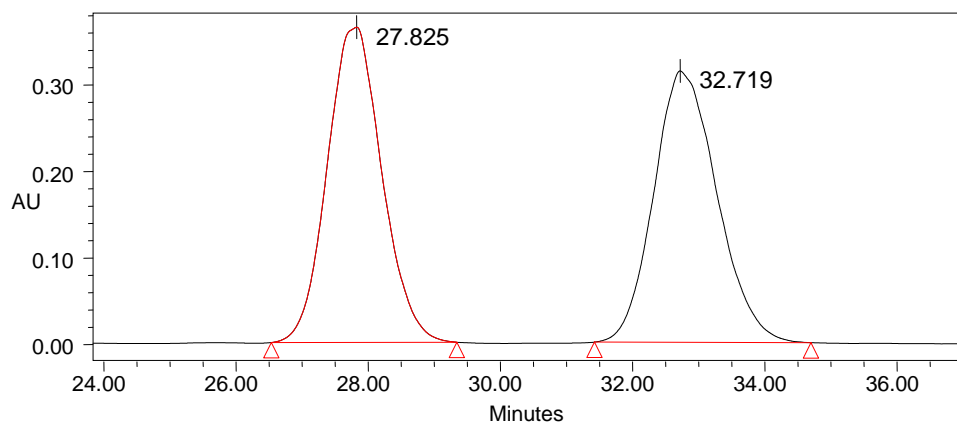


	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	89.315	7180567	95.79	27471
2	PDA 260.0 nm	102.063	315618	4.21	1329



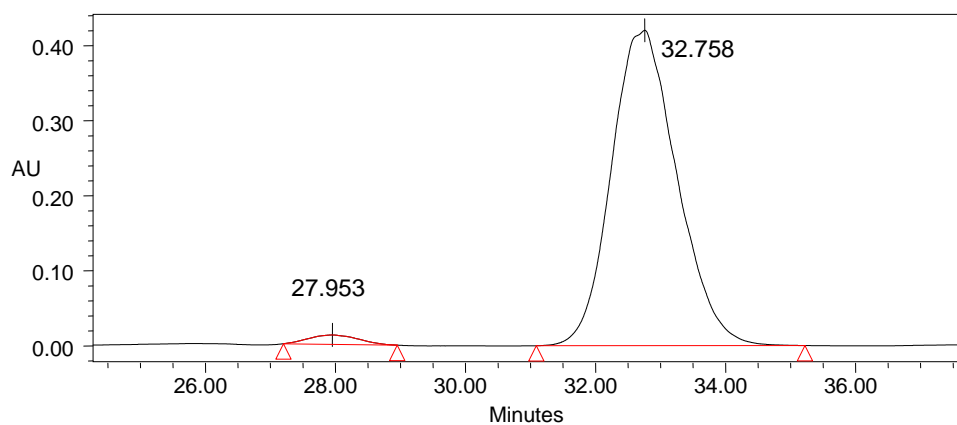
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 85/15, flow rate= 1 mL/min, retention times: 28.0 min (min.) and 32.8 min (major.). Processed Channel descr.: PDA 260 nm).

rac-**28e**

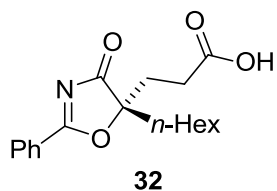


	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	27.825	20941551	50.07	364212
2	PDA 260.0 nm	32.719	20880273	49.93	313597

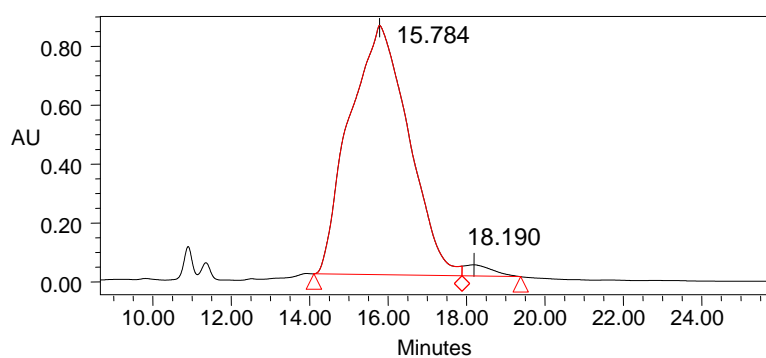
**28e**



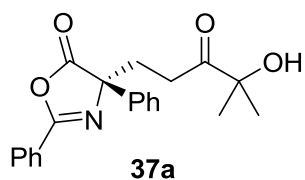
	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	27.953	660767	2.19	12549
2	PDA 260.0 nm	32.758	29507186	97.81	420246



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/ethanol 70/30, flow rate= 0.5 mL/min, retention times: 15.8 min (major.) and 18.2 min (min.). Processed Channel descr.: PDA 260 nm).

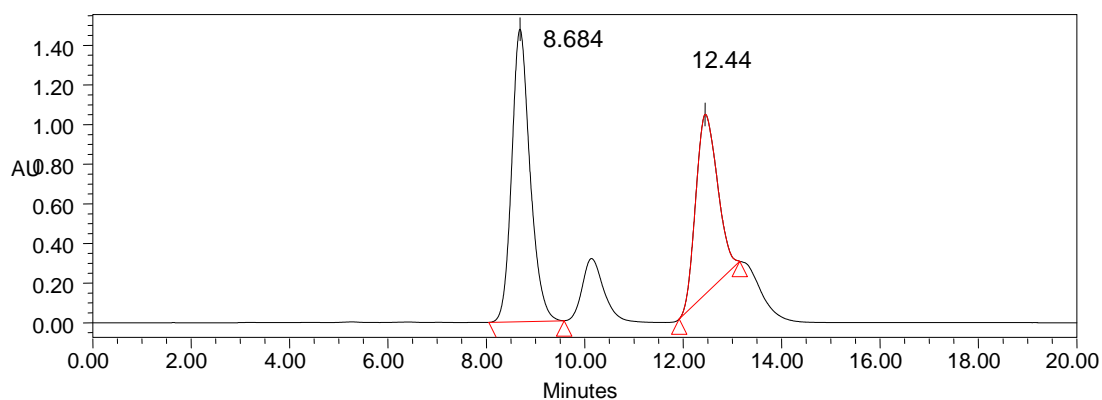


	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	15.784	88764669	97.89	846380
2	PDA 260.0 nm	18.190	1910539	2.11	38140



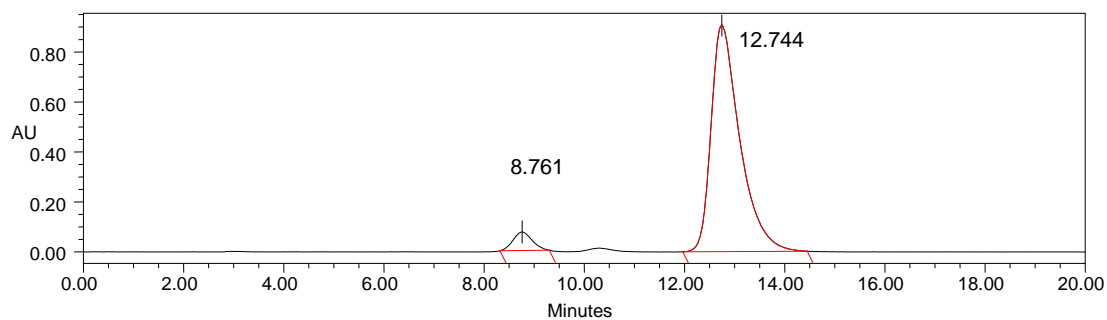
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90/10, flow rate= 1.0 mL/min, retention times: 8.7 min (min.) and 12.4 min (major.). Processed Channel Descr.: PDA 254 nm).

**rac-37a**

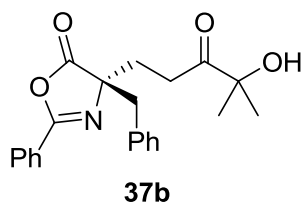


	Retention Time	% Area
2	12.444	42.07
1	8.684	57.93

**37a**

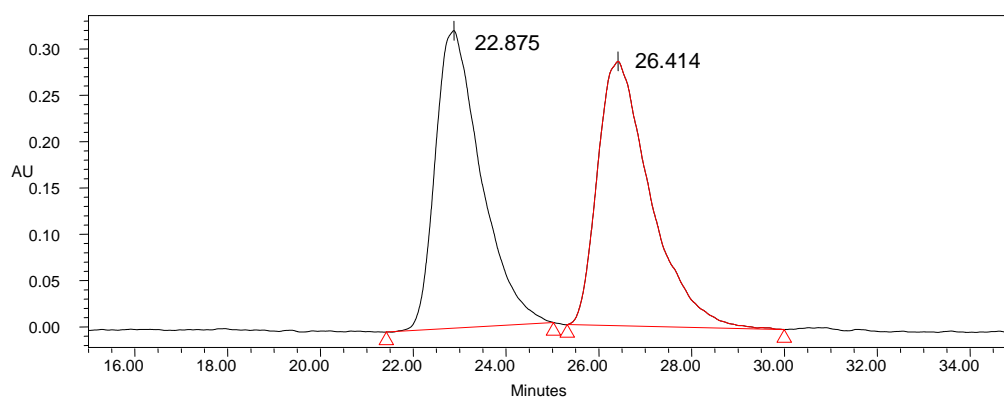


	Retention Time	% Area
2	12.744	94.90
1	8.761	5.10



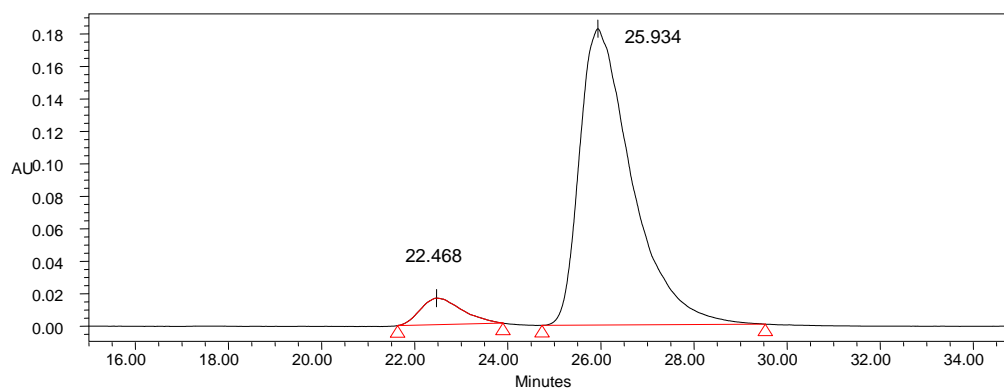
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 95/5, flow rate= 1.0 mL/min, retention times: 22.9 min (min.) and 26.4 min (major.). Processed Channel Descr.: 254 nm).

**rac-37b**

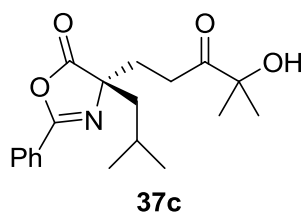


	Retention Time	% Area
2	26.414	50.65
1	22.875	49.35

**37b**

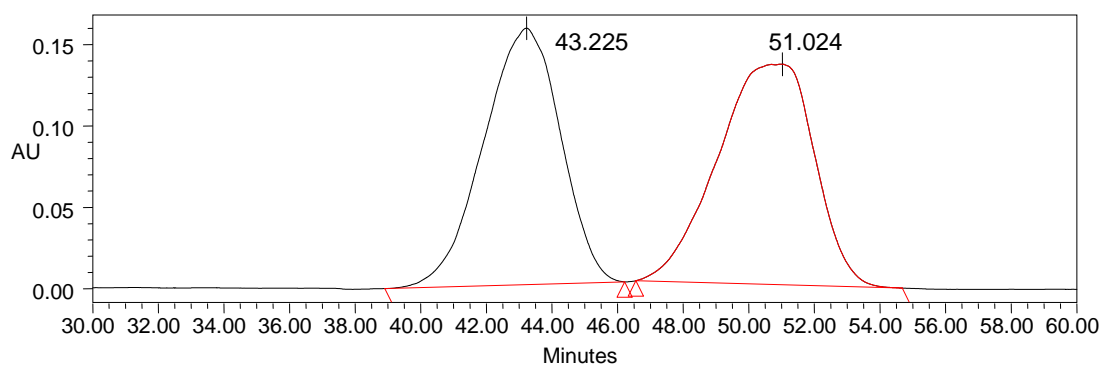


	Retention Time	% Area
1	22.468	6.15
2	25.934	93.85



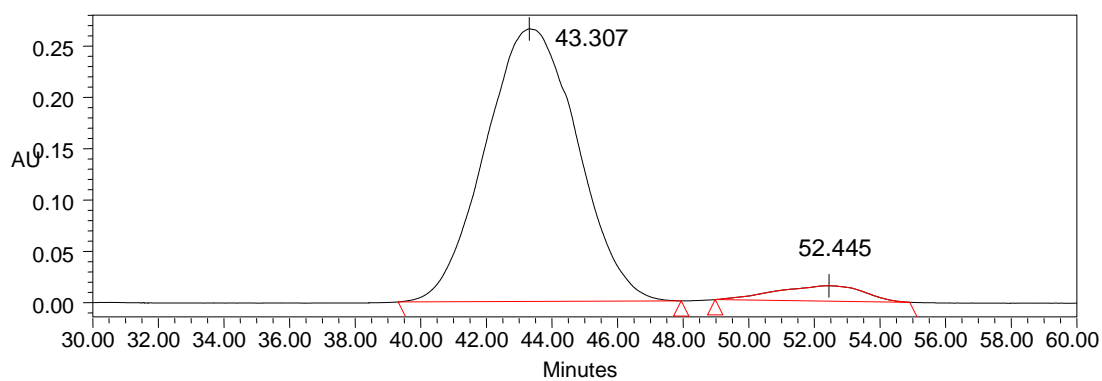
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 99/1, flow rate= 1.0 mL/min, retention times: 43.2 min (mayor.) and 51.0 min (min.). Processed Channel Descr.: 254 nm).

rac-**37c**

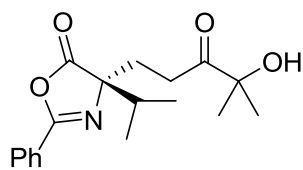


	Retention Time	% Area
2	51.024	51.95
1	43.225	48.05

**37c**



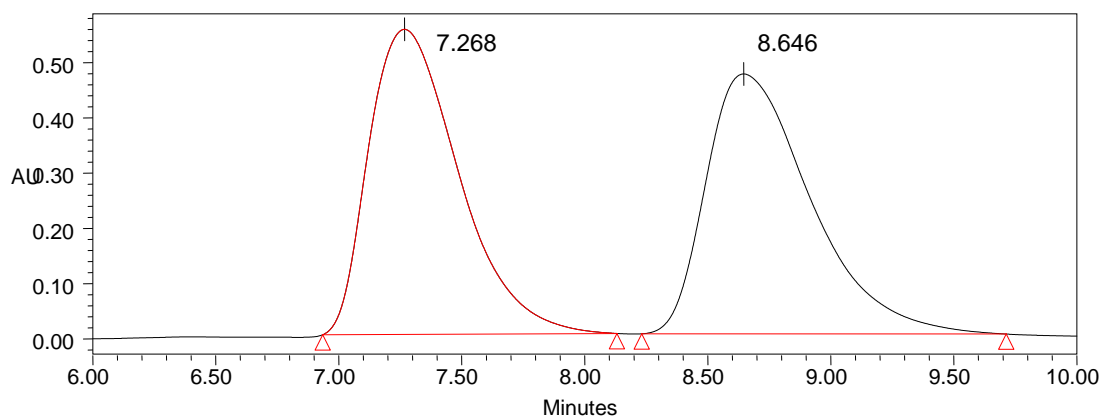
	Retention Time	% Area
2	52.491	4.37
1	43.307	95.63



**37d**

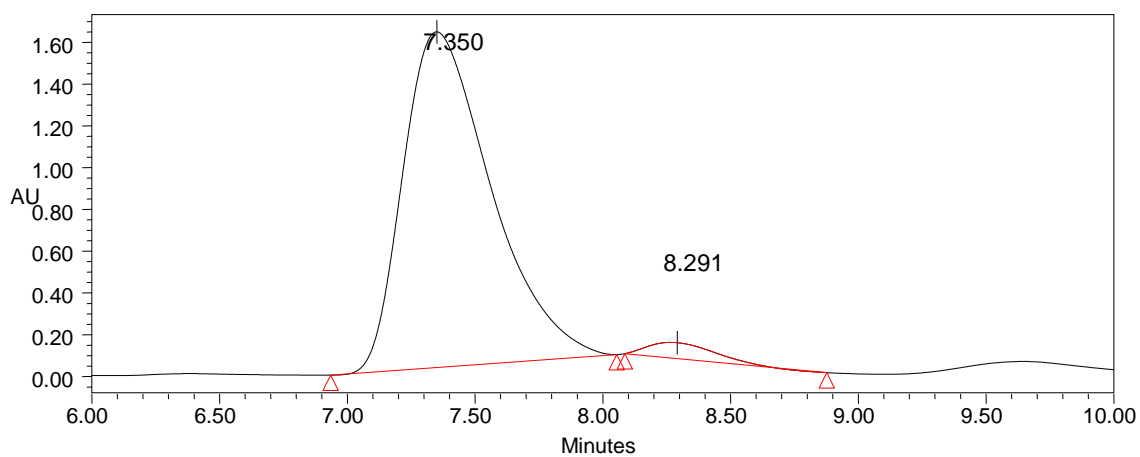
The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 90/10, flow rate= 1.0 mL/min, retention times: 7.3 min (major.) and 8.6 min (min.). Processed Channel Descr.: 254 nm).

**rac-37d**

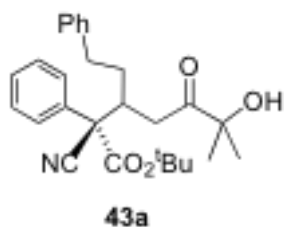


	Retention Time	% Area
2	8.646	49.48
1	7.268	50.52

**37d**



	Retention Time	% Area
2	8.290	4.82
1	7.350	95.18

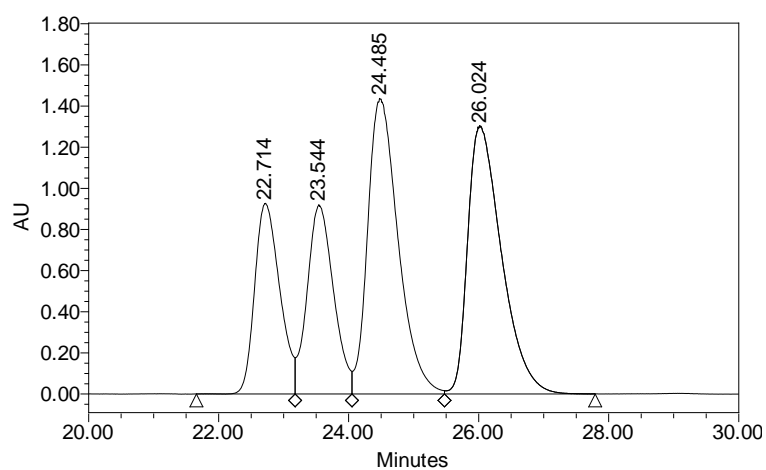


PDA 209.0 nm, Daicel Chiralpak AD3

90 : 10 hex : ipr, f: 0.5 mL/min, 10 °C

Processed Channel Descr.: PDA 209.0 nm

	Retention Time	Area	% Area	Height
1	22.714	24775154	17.14	926316
2	23.544	25841902	17.88	917248
3	24.485	46819083	32.39	1434780
4	26.024	47133939	32.60	1301938

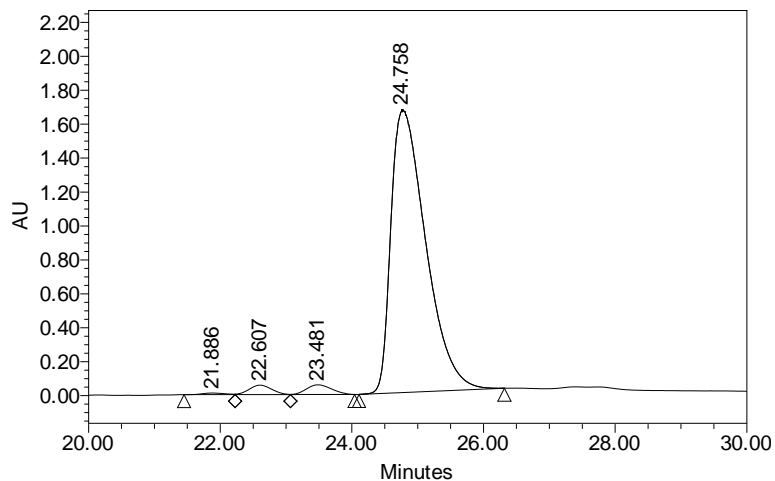


PDA 209.0 nm, Daicel Chiralpak AD3

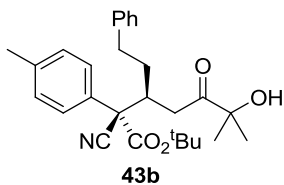
90 : 10 hex : ipr, f: 0.5 mL/min, 10 °C

Processed Channel Descr.: PDA 209.0 nm

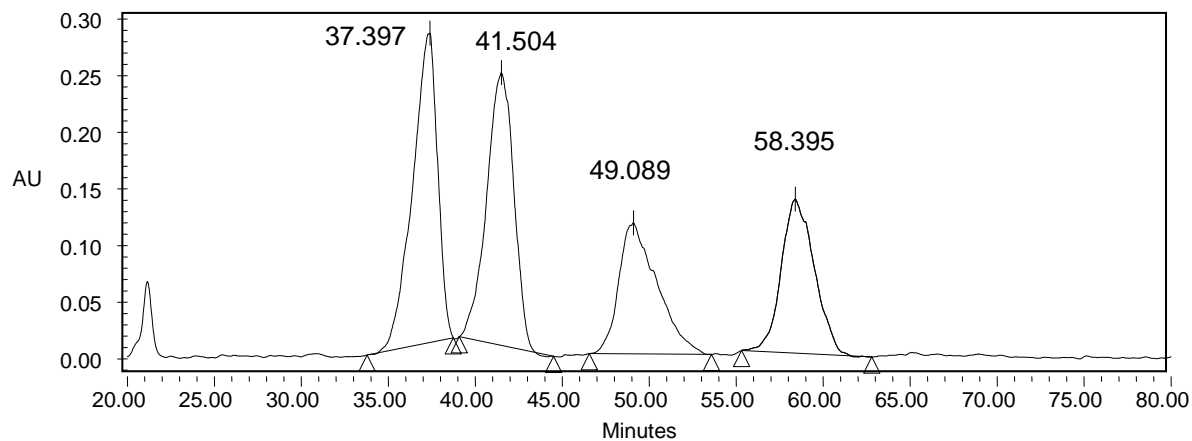
	Retention Time	Area	% Area	Height
1	21.886	210126	0.33	9214
2	22.607	1304069	2.03	55276
3	23.481	1503226	2.34	56833
4	24.758	61188267	95.30	1669002



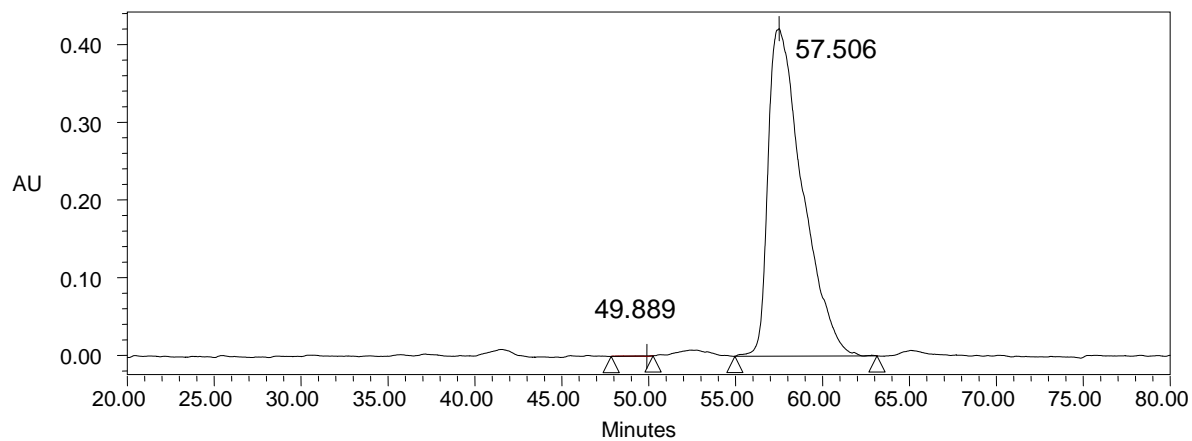


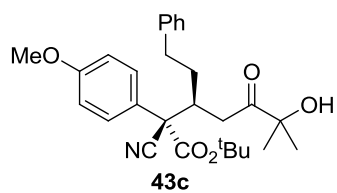


	Retention Time	% Area
1	37.397	30.58
2	41.504	29.48
3	49.089	19.74
4	58.395	20.19

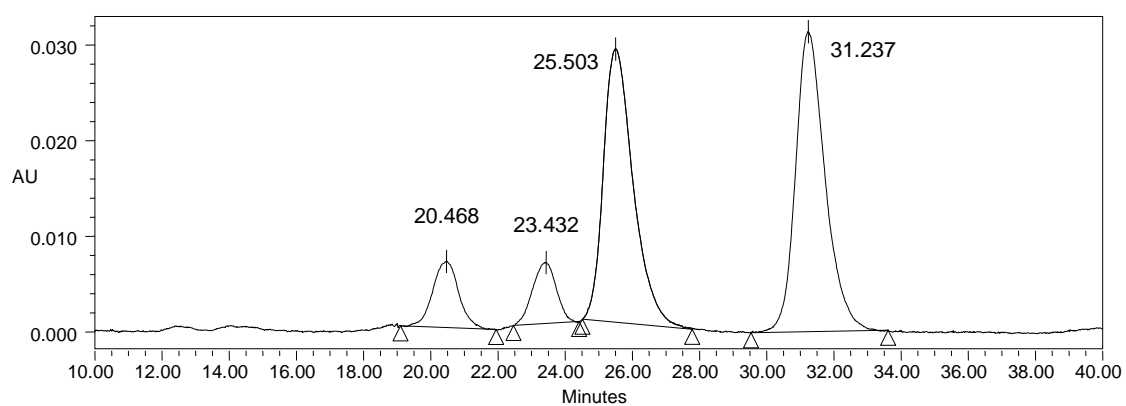


	Retention Time	% Area
2	57.506	99.95
1	49.889	0.05

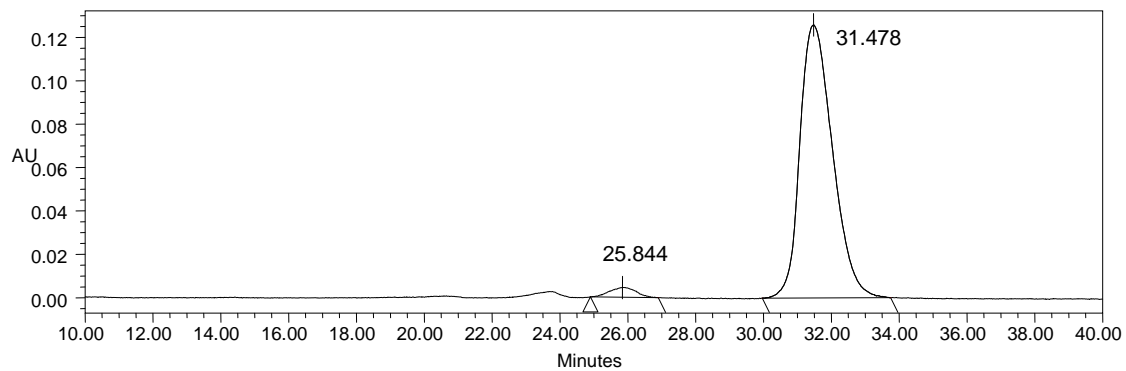


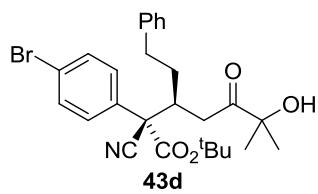


	Retention Time	% Area
1	20.468	8.49
2	23.432	7.15
3	25.503	40.40
4	31.237	43.95

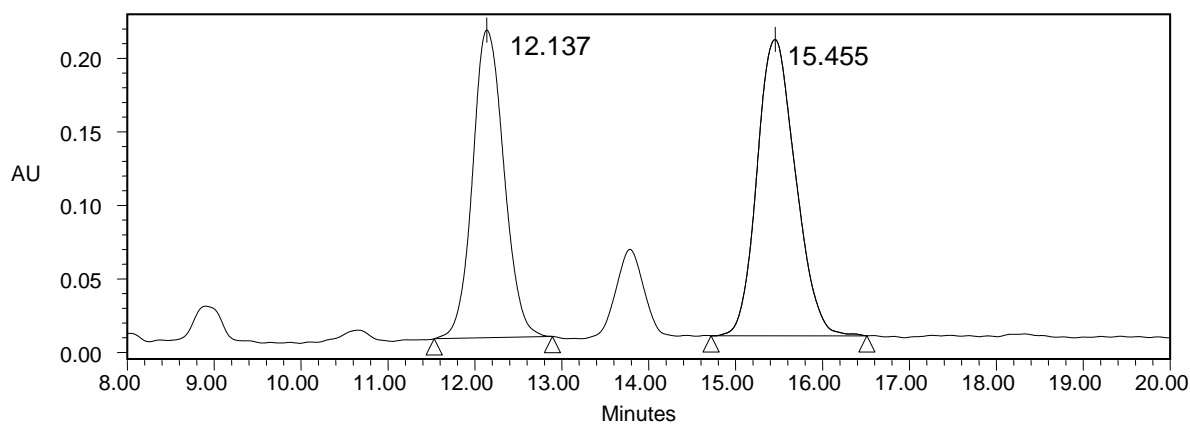


	Retention Time	% Area
2	31.478	97.17
1	25.844	2.83

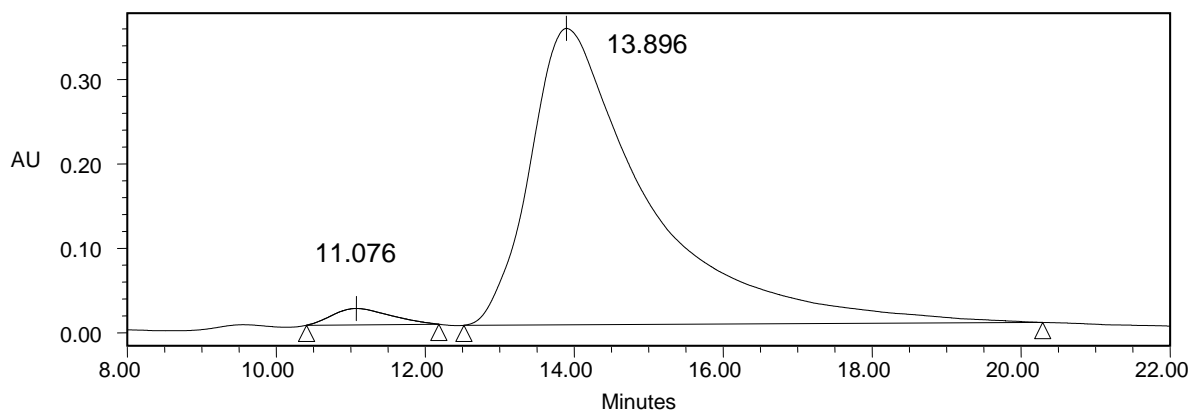


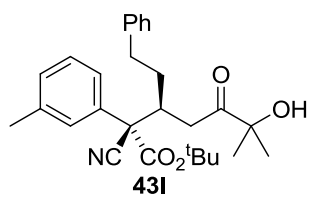


	Retention Time	% Area
2	15.455	54.15
1	12.137	45.85



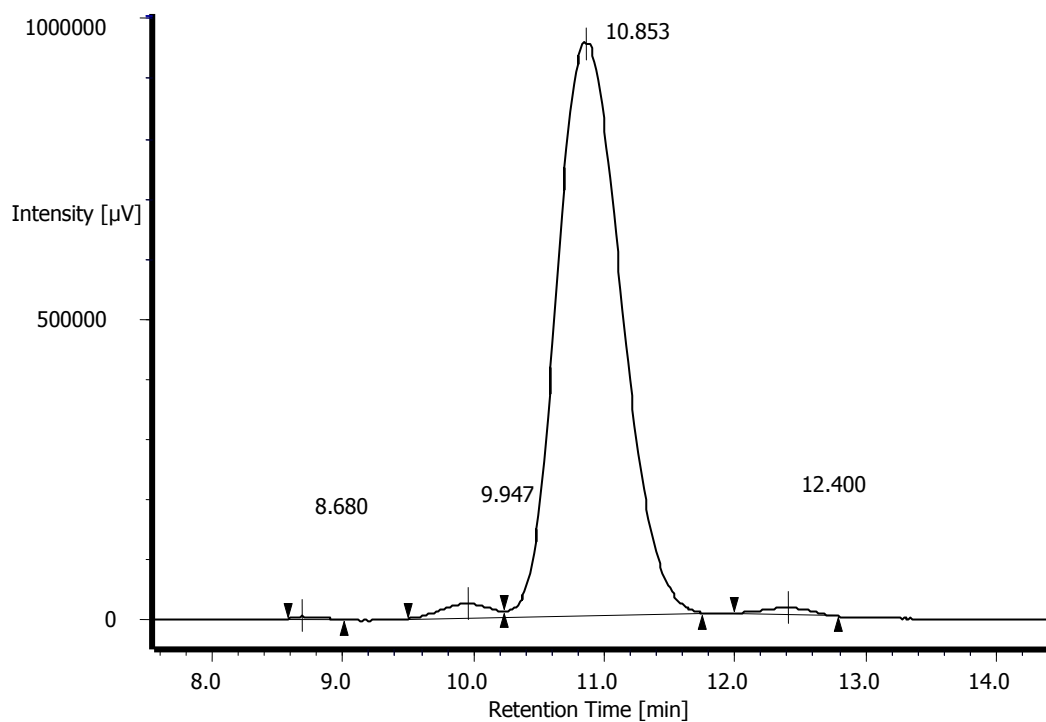
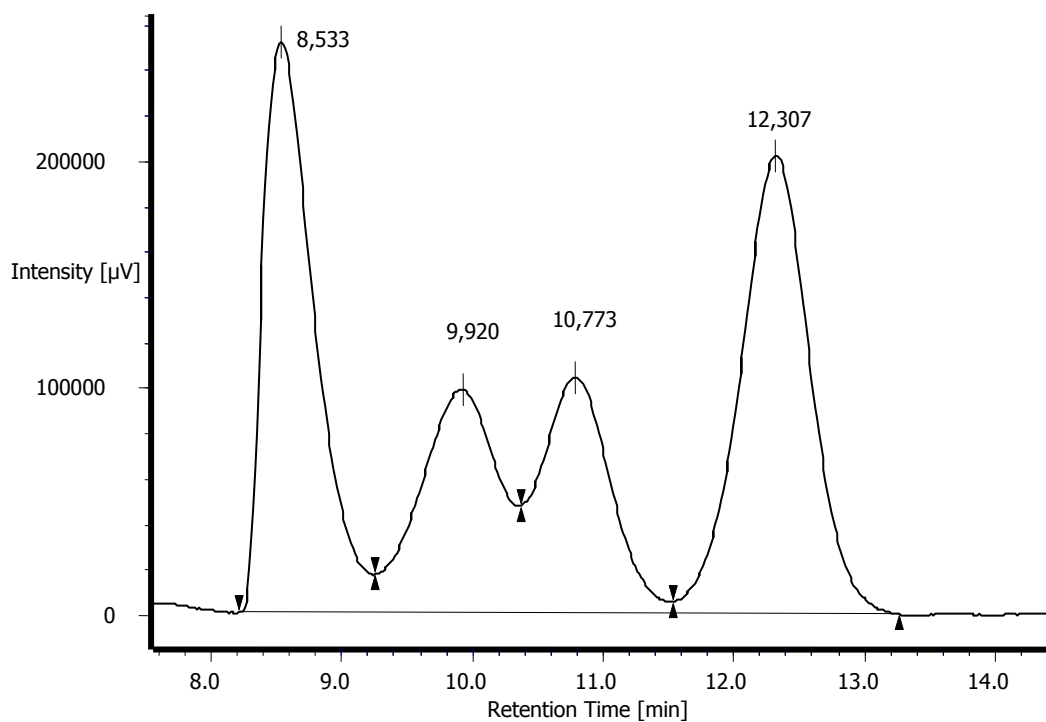
	Retention Time	% Area
2	13.896	97.23
1	11.076	2.77

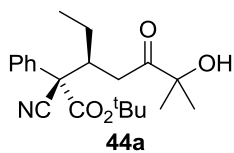




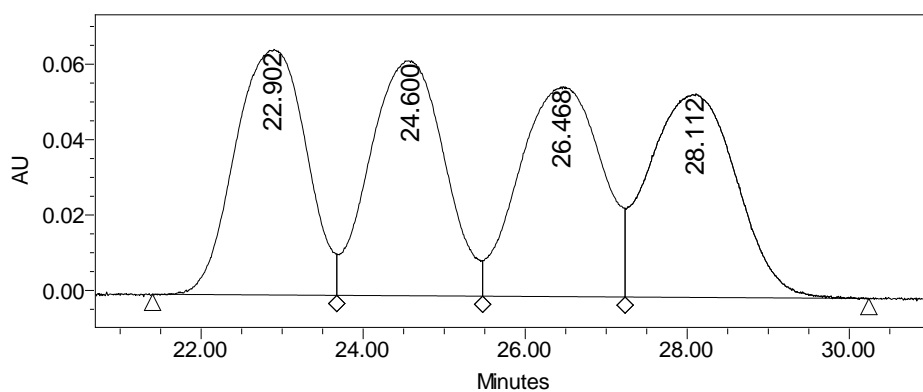
	Retention Time	% Area
1	8.533	30.82
2	9.920	18.33
3	10.773	17.36
4	12.307	33.49

	Retention Time	% Area
1	8.680	0.19
2	9.947	1.81
3	10.853	97.15
4	12.400	0.85

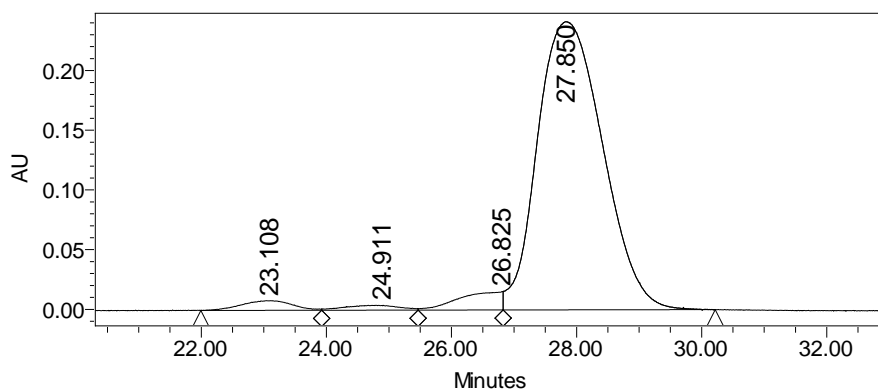


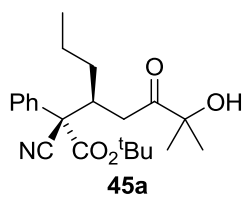


	Retention Time	% Area
1	22.902	24.80
2	24.600	24.96
3	26.468	24.74
4	28.112	25.50

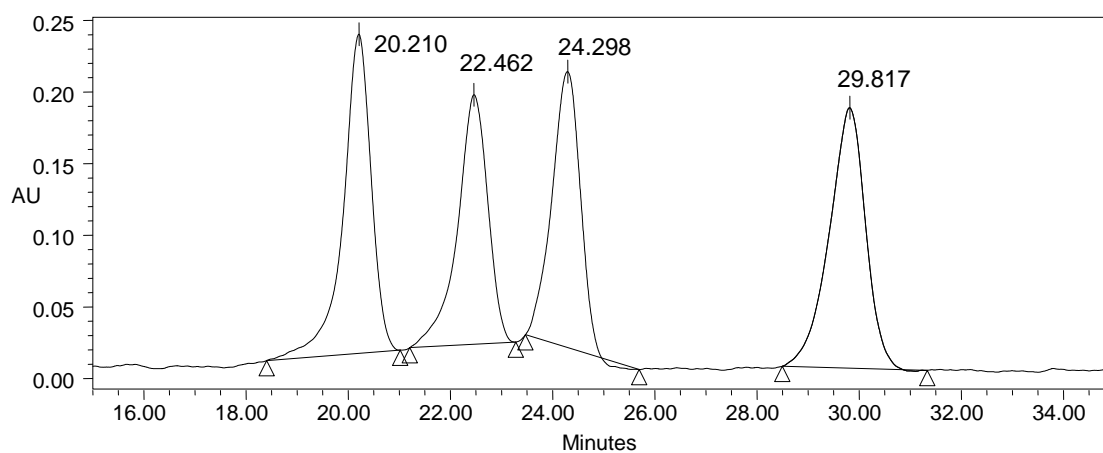


	Retention Time	% Area
1	23.108	2.40
2	24.911	1.28
3	26.825	3.86
4	27.850	92.46

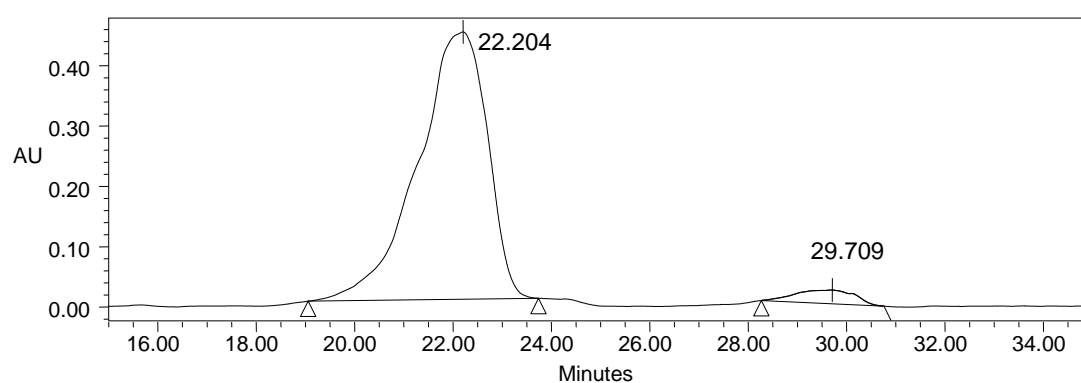


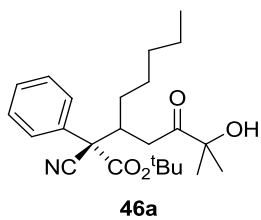


	Retention Time	% Area
1	20.210	26.37
2	22.462	22.26
3	24.298	23.42
4	29.817	27.95



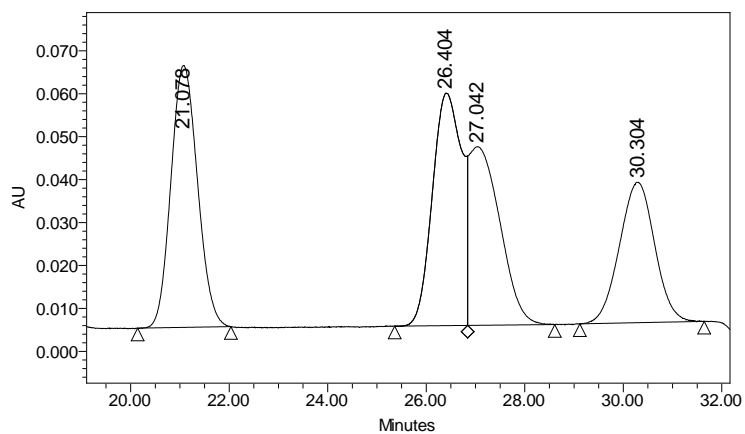
	Retention Time	% Area
2	29.709	4.15
1	22.204	95.85



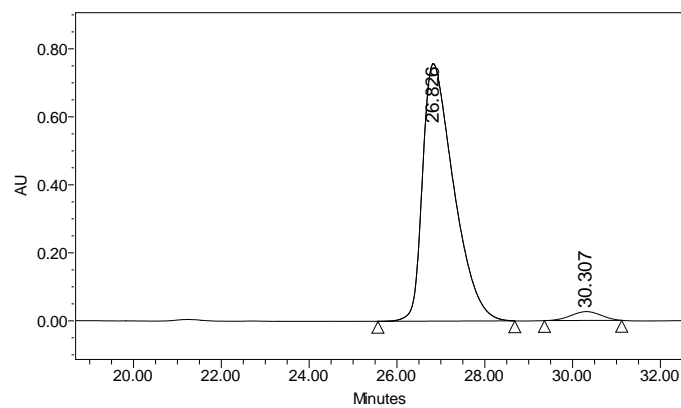


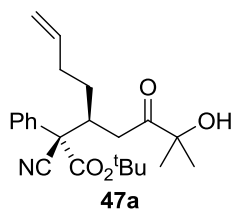
PDA 209.0 nm, Daicel Chiralpak IA  
 98 : 2 hex : ipr, f: 1 mL/min, 10 °C  
 Processed Channel Descr.: PDA 207.0 nm

	Retention Time	Area	% Area	Height
1	21.078	2284855	28.66	61000
2	26.404	2257614	28.32	54154
3	27.042	1804471	22.63	41573
4	30.304	1626112	20.40	32706

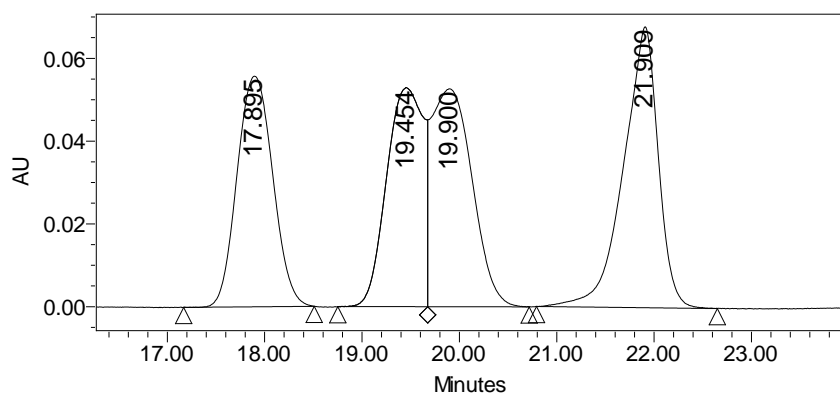


	Retention Time	Area	% Area	Height
1	26.826	37233829	96.79	756889
2	30.307	1235725	3.21	26045

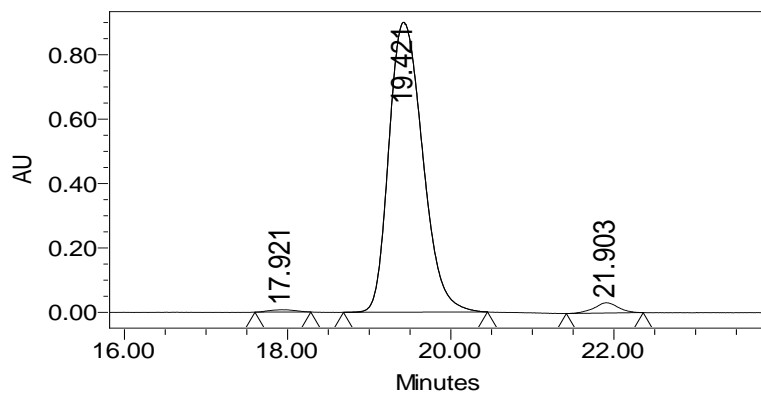




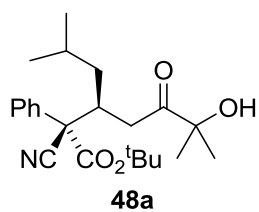
	Retention Time	% Area
1	17.895	23.63
2	19.454	23.08
3	19.900	25.35
4	21.909	27.93



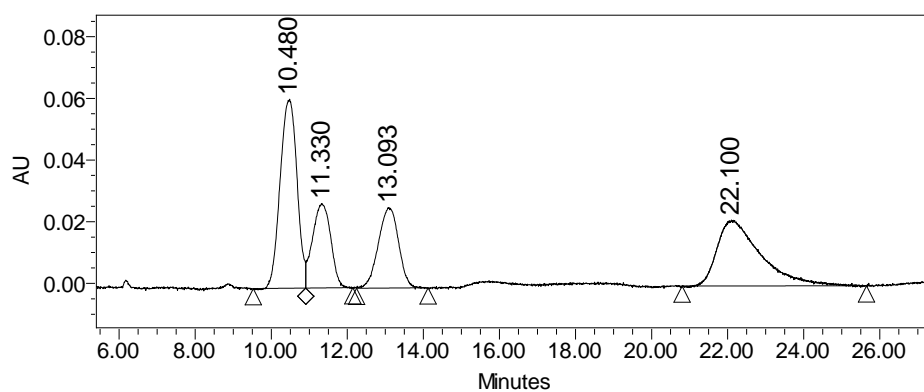
Retention Time	% Area
17.921	0.59
19.421	96.96
21.903	2.46



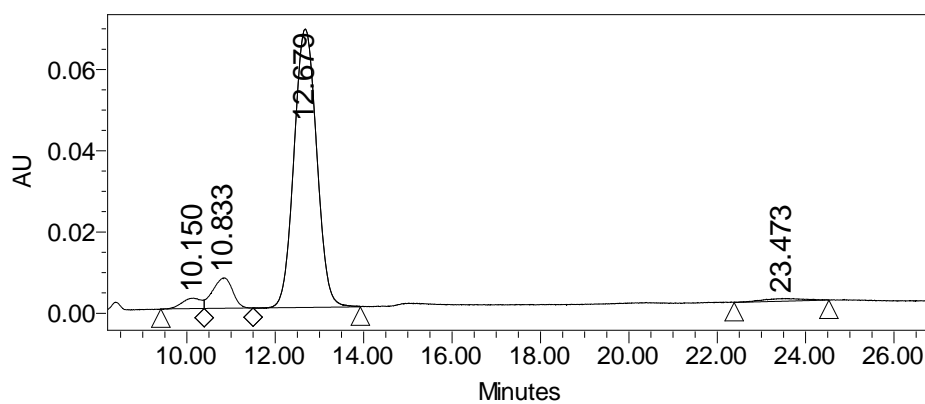


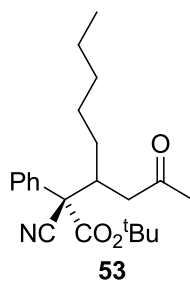


Retention Time	Area	% Area	Height
10.480	1891116	34.63	61128
11.330	909383	16.65	27227
13.093	962892	17.63	26106
22.100	1697485	31.08	21292

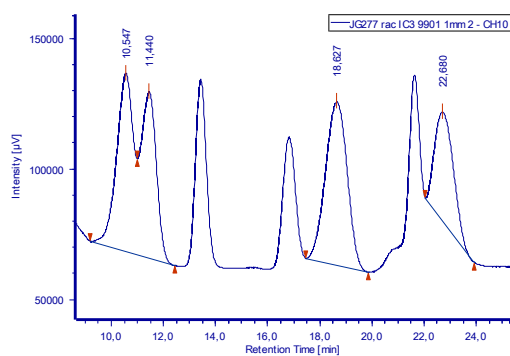


	Retention Time	Area	% Area	Height
1	10.150	78393	2.81	2583
2	10.833	233367	8.37	7495
3	12.679	2435231	87.29	68521
4	23.473	42748	1.53	623

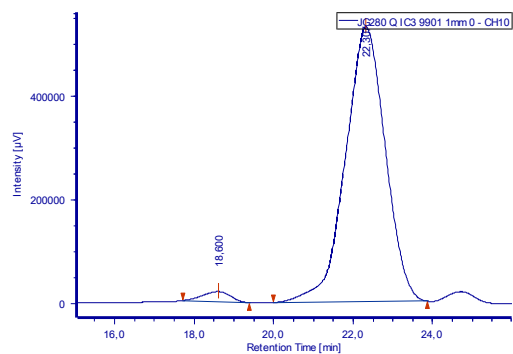




The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC-3 hexane/isopropanol 99/1, flow rate= 1 mL/min, retention times: 18.6 min (minor.) and 22.3 min (major.)).



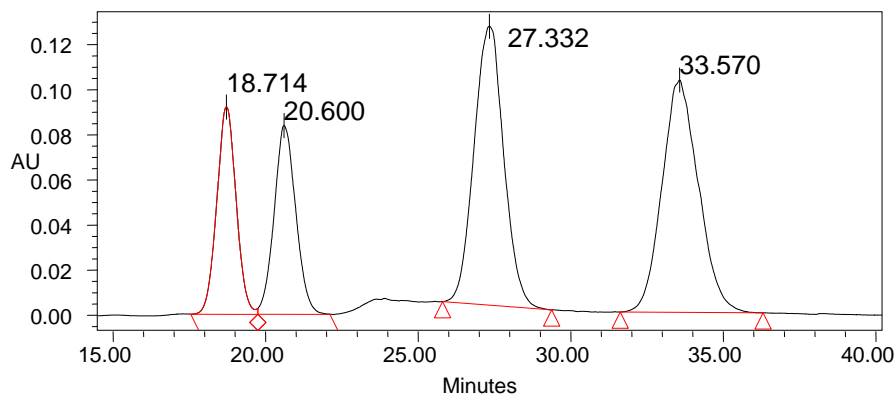
Peak Name	CH	tR	Area	Height	Area%	Height%
Unknown	10	10,547	3026063	68059	26,750	28,901
Unknown	10	11,440	2613000	63438	23,098	26,938
Unknown	10	18,627	3605500	62507	31,872	26,543
Unknown	10	22,680	2067962	41489	18,280	17,618



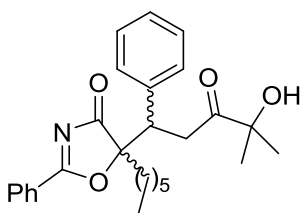
Peak Name	CH	tR	Area	Height	Area%	Height%
Unknown	10	18,600	955552	19746	2,528	3,594
Unknown	10	22,307	36845690	529689	97,472	96,406

## rac-56Hc

The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 90/10, flow rate= 1.0 mL/min, retention times: 18.7 min (min.) and 20.5 min (major.)).

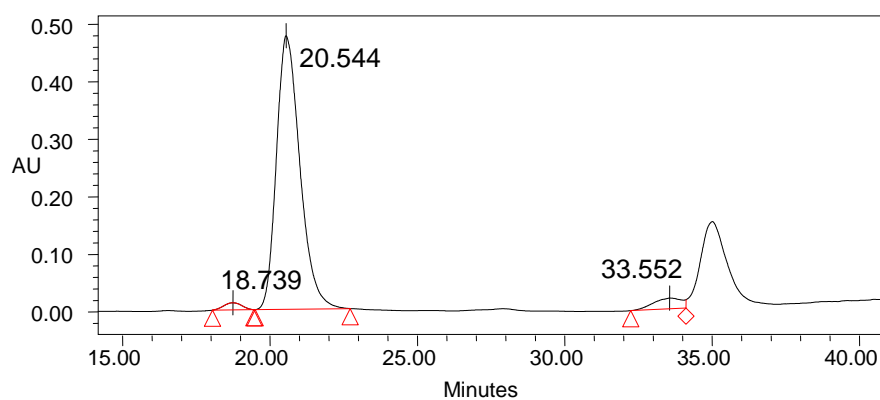


### Processed Channel Descr.: PDA 250.0 nm

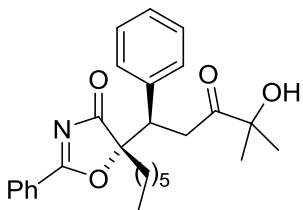


	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 250.0 nm	18.714	4063858	16.17	91873
2	PDA 250.0 nm	20.600	4126524	16.42	83675
3	PDA 250.0 nm	27.332	8387860	33.38	123623
4	PDA 250.0 nm	33.570	8553447	34.03	102997

## 56Hc

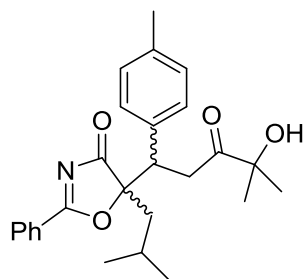


### Processed Channel Descr.: PDA 250.0 nm



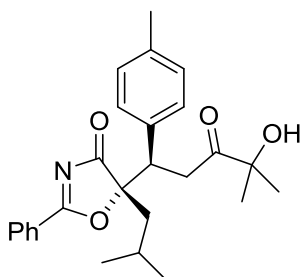
	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 250.0 nm	18.739	525473	1.87	12484
2	PDA 250.0 nm	20.544	26371608	93.69	475634
3	PDA 250.0 nm	33.552	1251363	4.45	18581

The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 98/2, flow rate= 1.0 mL/min, retention times: 18.8 min (min.) and 21.7 min (major.)).



	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	18.475	7978927	14.51	79920
2	PDA 260.0 nm	22.200	8161399	14.85	73067
3	PDA 260.0 nm	26.150	19563172	35.58	131901
4	PDA 260.0 nm	34.573	19272657	35.06	96637

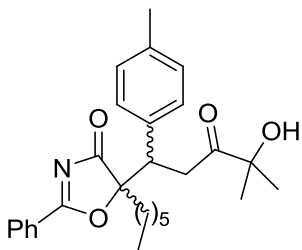
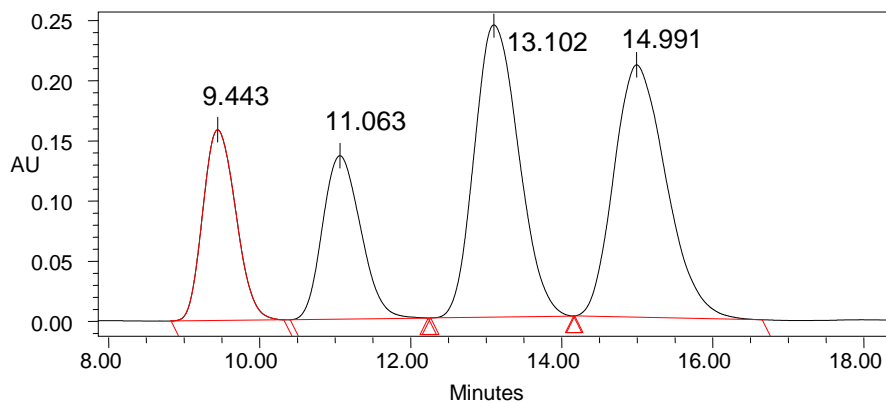
Chromatogram showing absorbance (AU) versus time (Minutes). The x-axis ranges from 15.00 to 45.00 minutes. The y-axis ranges from 0.00 to 0.25 AU. A major peak is labeled at 21.675 minutes. Other labeled peaks are at 18.768, 29.951, and 36.486 minutes. Red triangles mark the baseline at approximately 19.5, 20.5, 27.5, 30.0, 35.0, and 42.5 minutes.



	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 250.0 nm	18.768	95933	0.31	2270
2	PDA 250.0 nm	21.675	28488836	92.62	249852
3	PDA 250.0 nm	29.951	72674	0.24	1021
4	PDA 250.0 nm	36.486	2102577	6.84	12072

## rac-56Lc

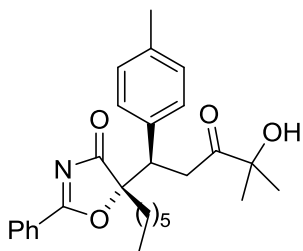
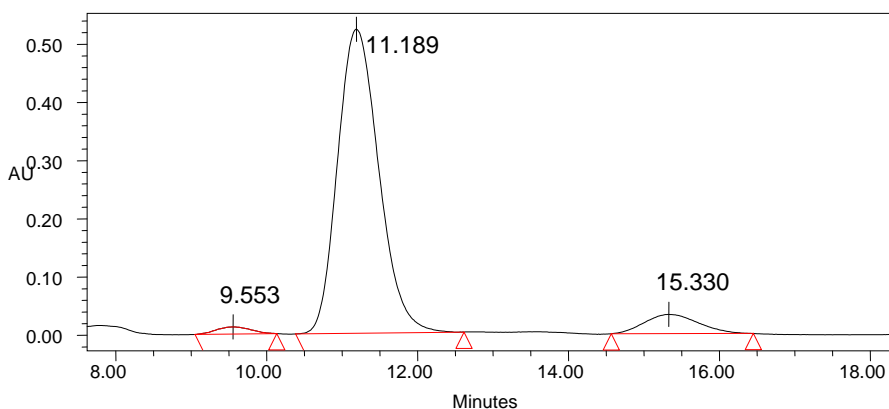
The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 80/20, flow rate= 1.0 mL/min, retention times: 9.5 min (min.) and 11.2 min (major.)).



### Processed Channel Descr.: PDA 260.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	9.443	4821848	16.27	158449
2	PDA 260.0 nm	11.063	4762599	16.07	135827
3	PDA 260.0 nm	13.102	9941986	33.54	242748
4	PDA 260.0 nm	14.991	10115316	34.13	209634

## 56Lc

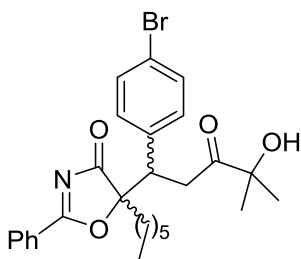
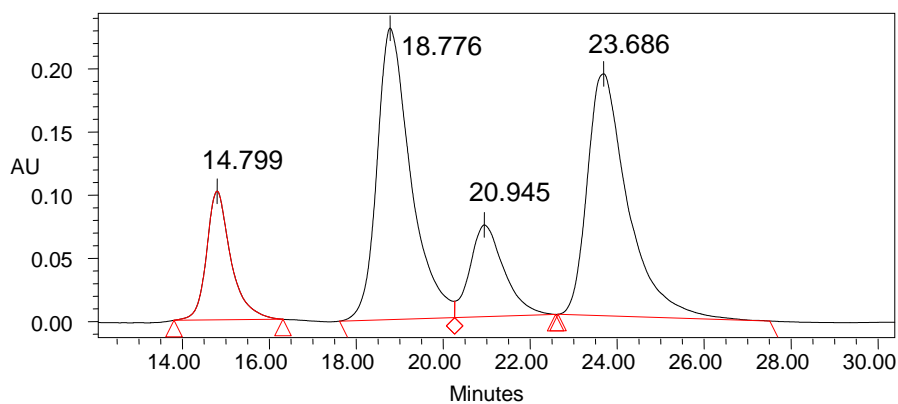


### Processed Channel Descr.: PDA 260.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	9.553	393868	1.81	12294
2	PDA 260.0 nm	11.189	19794059	90.72	522490
3	PDA 260.0 nm	15.330	1631914	7.48	33016

### rac-56Jc

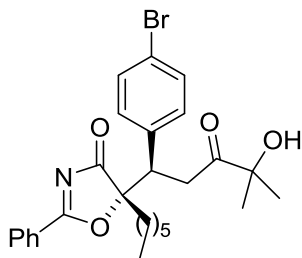
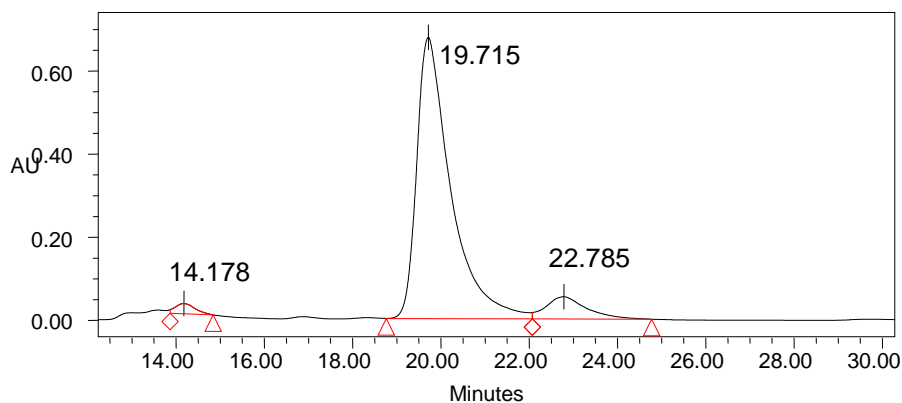
The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90/10, flow rate= 1.0 mL/min, retention times: 14.2 min (min.) and 19.7 min (major.)).



#### Processed Channel Descr.: PDA 250.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 250.0 nm	14.799	3969749	12.11	101829
2	PDA 250.0 nm	18.776	12466053	38.02	230608
3	PDA 250.0 nm	20.945	3933109	12.00	72592
4	PDA 250.0 nm	23.686	12417080	37.87	191382

### 56Jc

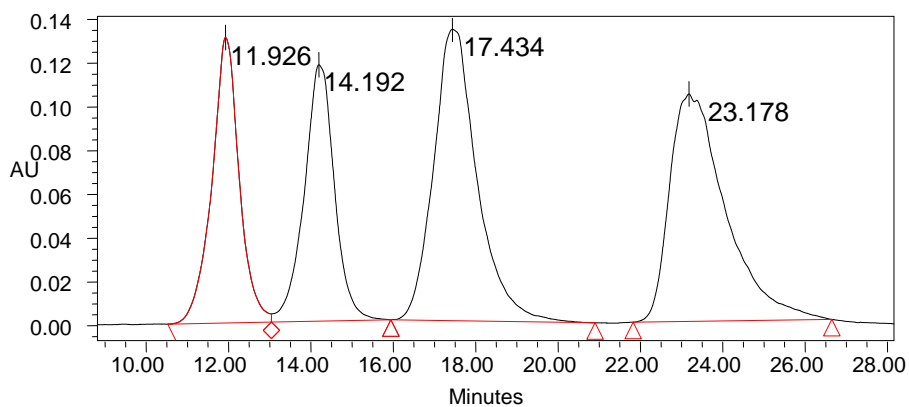


#### Processed Channel Descr.: PDA 250.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	14.178	770917	1.91	24589
2	PDA 260.0 nm	19.715	36266603	89.65	676831
3	PDA 260.0 nm	22.785	3418193	8.45	53620

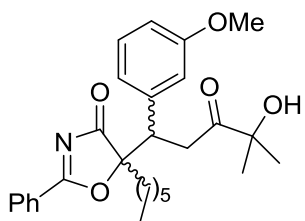
## rac-56Kc

The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 95/5, flow rate= 1.0 mL/min, retention times: 11.9 min (min.) and 14.0 min (major.)).

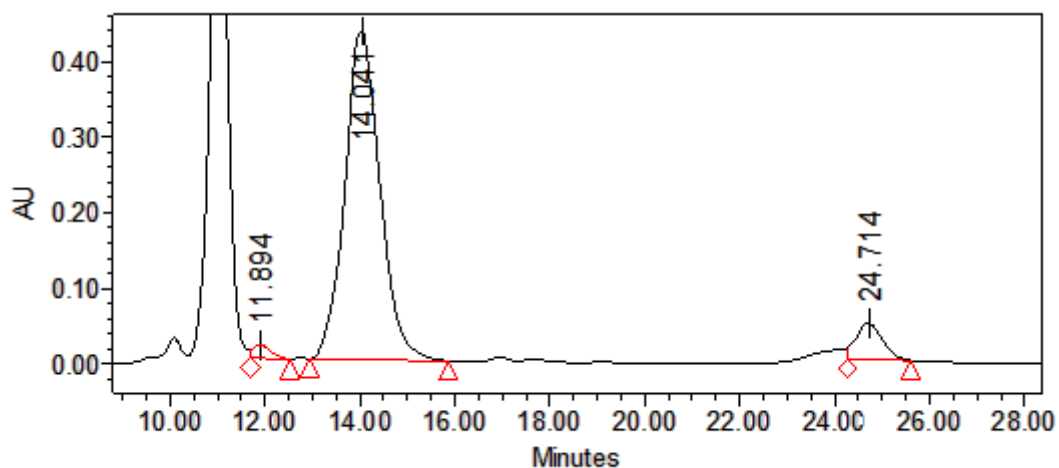


### Processed Channel Descr.: PDA 250.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 250.0 nm	11.926	6047064	19.11	130505
2	PDA 250.0 nm	14.192	5984595	18.92	117190
3	PDA 250.0 nm	17.434	9791771	30.95	133192
4	PDA 250.0 nm	23.178	9812962	31.02	103965

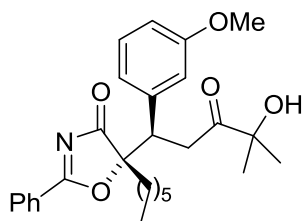


## 56Kc

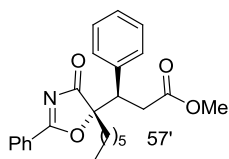
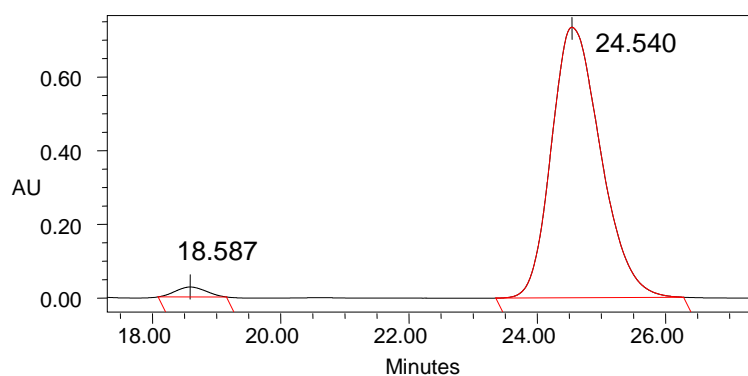


### Processed Channel Descr.: PDA 250.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 255.0 nm	11.894	467820	1.89	17667
2	PDA 255.0 nm	14.041	22358074	90.56	433708
3	PDA 255.0 nm	24.714	1861859	7.54	47868



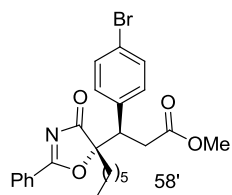
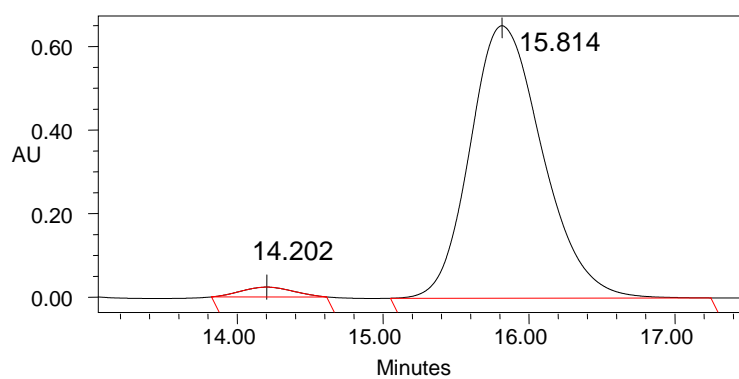
57'



Processed Channel Descr.: PDA 260.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	18.587	876506	2.18	27004
2	PDA 260.0 nm	24.540	39250164	97.82	734325

58'



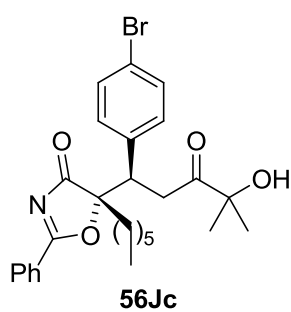
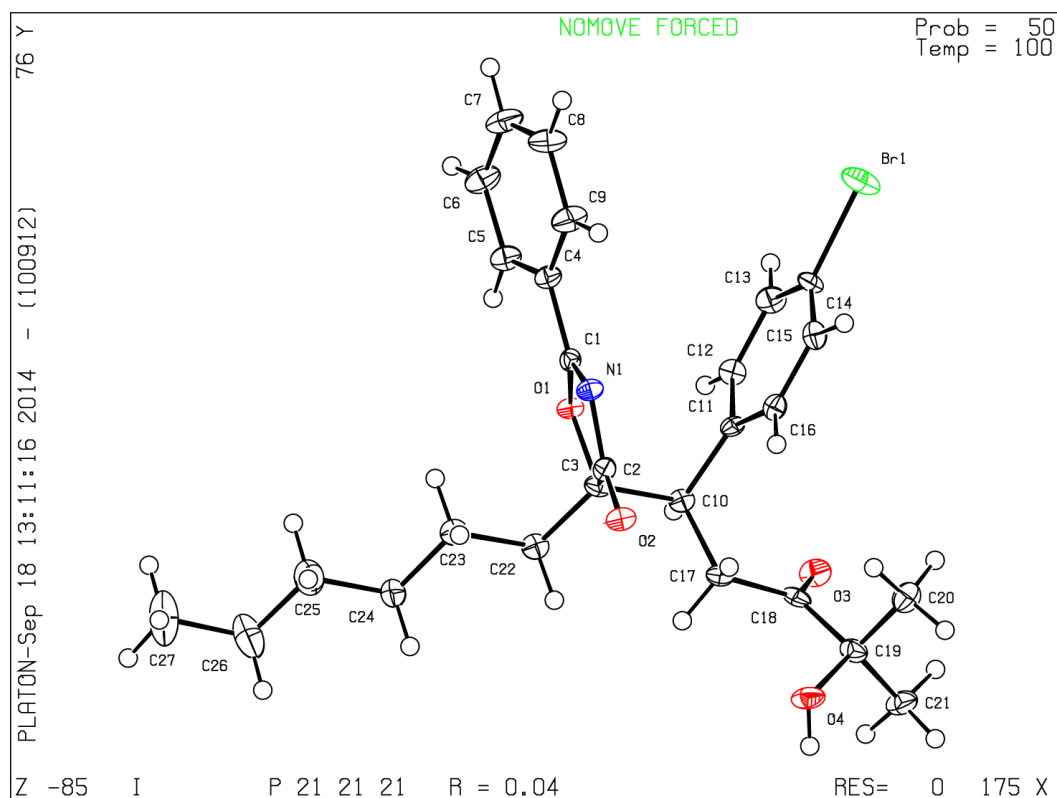
Processed Channel Descr.: PDA 260.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 260.0 nm	14.202	578170	2.50	23483
2	PDA 260.0 nm	15.814	22544216	97.50	651906



## 5. X-Ray analysis: ORTEP diagram of compound 56Jc

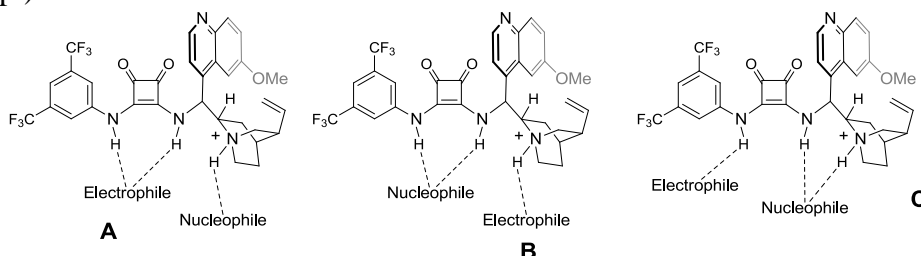
Cambridge Crystallographic Data Centre deposition numbers CCDC 1025058



## 6. Computational studies

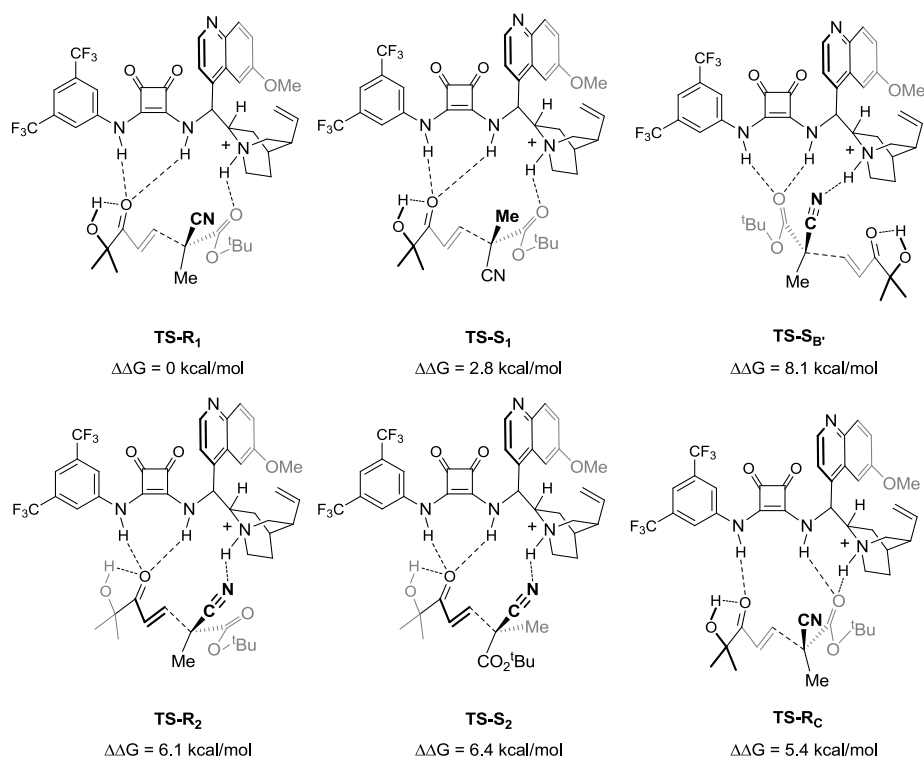
All structures were optimized using the functional B3LYP<sup>39</sup> and the 6-31G\* basis set as implemented in Gaussian 09.<sup>40</sup> DFT has been shown to reliably predict enantioselectivities in asymmetric organocatalyzed reactions.<sup>41</sup> All energy minima and transition structures were characterized by frequency analysis. The stationary points were characterized by frequency calculations in order to verify that they have the right number of negative eigenvalues. The intrinsic reaction coordinates (IRC)<sup>42</sup> were followed to verify the energy profiles connecting each transition state to the correct associated local minima. The energies reported in this work include single-point calculations at M06-2X/6-311++G\*\* level on the IEF-PCM solvation model (solvent = dichloromethane),<sup>43</sup> using the previously optimized gas-phase structures (B3LYP/6-31G\*).

We carried out an extensive search for different H-bond combination patterns in line with the proposed activation ternary complexes **A**, **B**, and **C**, as in Figure S1 (see manuscript).



**Figure S1.** Previously proposed activation ternary complexes.

Only transition structures belonging to **A**-type activation (**TS-R<sub>1</sub>**, **TS-S<sub>1</sub>**, **TS-R<sub>2</sub>** and **TS-S<sub>2</sub>**) are predicted to have feasible energies (Figure S2), whereas a single structure of too high energy presented pattern **C** (**TS-R<sub>C</sub>**), and no plausible structure of type **B** was located. In what can be considered the saddle point closest to **B** (**TS-S<sub>B</sub>**), the cyanoacetate is activated by three H-bonds, while the electrophilic hydroxyenone remains non-bonded. This structure can be discarded, as it presents too high energy, and predicts the formation of the wrong *S* enantiomer. The corresponding TS for the formation of the *R* enantiomer could not be located.



**Figure S2.** Lowest in energy transition states located in this study. Relative Gibbs energies (kcal/mol) for the solvent model (CH<sub>2</sub>Cl<sub>2</sub>) are shown.

**Table SI-5.** Energies of the structures involved in the computational study.

	<b>G</b> (M06-2X/6-311++G**, IEF-PCM, CH <sub>2</sub> Cl <sub>2</sub> )	relative <b>G</b>	Frequency
<b>Transition States in Figure 6</b>			
<b>TS-R<sub>1</sub></b>	-3104.470112	0	-311.6
<b>TS-S<sub>1</sub></b>	-3104.465609	2.83	-194.0
<b>TS-R<sub>2</sub></b>	-3104.460460	6.06	-195.2
<b>TS-S<sub>2</sub></b>	-3104.459971	6.36	-104.4
<b>TS-S<sub>B'</sub></b>	-3104.457132	8.15	-371.1
<b>TS-R<sub>c</sub></b>	-3104.451775	11.51	-198.1
<b>Structures in Figure 4</b>			
<b>19e</b>	-360.071203		
<b>59</b>	-306.353223		
<b>1</b>	-384.917547		
<b>MVK</b>	-231.138280		
<b>TS-19e+59</b>	-666.399678	15.5	-276.4
<b>TS-19e+1</b>	-744.970910	11.1	-155.5
<b>TS-19e+MVK</b>	-591.181233	17.7	-315.5

## Cartesian Coordinates of the structures involved in the computational study

### TS-R<sub>1</sub>

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	1	0	2.752133	2.548579	3.131656
2	1	0	-1.320494	-0.563770	-0.767164
3	1	0	-3.335417	-0.618065	-1.789669
4	1	0	2.732683	0.849815	2.654112
5	1	0	-2.904747	-2.297886	2.162326
6	1	0	1.864390	2.309027	0.967437
7	1	0	2.867820	4.295130	1.563310
8	1	0	3.144057	3.951759	-0.147687
9	1	0	3.212474	1.817859	-0.935043
10	1	0	0.960763	0.195135	-0.843144
11	1	0	-6.708089	-2.448173	0.147230
12	1	0	5.529383	1.701661	-0.726278
13	1	0	5.408601	0.337385	0.372643
14	1	0	5.194792	4.340889	1.953104
15	1	0	5.457597	4.105899	0.228178
16	1	0	5.060745	2.324682	3.522252
17	1	0	5.054361	0.699302	2.847777
18	1	0	6.522923	2.247670	1.506178
19	7	0	1.428496	-0.026552	0.041839
20	6	0	-2.954194	-1.416011	0.182229
21	6	0	-3.759236	-1.130498	-0.932630
22	6	0	-3.510908	-2.072478	1.289607
23	6	0	-5.436003	-3.201122	2.421071
24	6	0	1.039792	-1.263533	2.273476
25	6	0	-0.407565	-1.748638	2.380561
26	6	0	0.712265	-0.721981	0.945690
27	6	0	-0.624827	-1.152200	1.022832
28	7	0	-1.614469	-1.011049	0.115131
29	6	0	-5.665133	-2.158441	0.154740
30	6	0	-4.857918	-2.433836	1.258172
31	6	0	-5.965931	-1.129260	-2.113494
32	6	0	-5.100075	-1.501403	-0.938618
33	6	0	2.896175	-0.070825	0.066283
34	6	0	3.505122	1.348173	0.006454
35	6	0	3.218089	1.809808	2.476888
36	7	0	2.905820	2.259335	1.068992
37	6	0	3.423741	3.665738	0.865867
38	6	0	5.048084	1.354399	0.192373
39	6	0	4.950879	3.692806	1.105434
40	6	0	4.752640	1.733179	2.654696
41	6	0	5.436594	2.258026	1.378254
42	9	0	-5.263460	-4.533733	2.267699
43	9	0	-4.859169	-2.857267	3.589780
44	9	0	-6.766706	-2.989851	2.545771
45	9	0	-5.254944	-1.050855	-3.259870
46	9	0	-6.555795	0.076287	-1.933538
47	8	0	2.049387	-1.272703	2.968597
48	8	0	-1.076405	-2.337694	3.205616
49	9	0	-6.957445	-2.025059	-2.308594
50	6	0	3.450825	-0.919624	-1.078107
51	7	0	4.431032	-2.421726	-3.282445
52	6	0	4.257129	-2.081733	-0.841485
53	6	0	3.159232	-0.582677	-2.383520
54	6	0	3.658436	-1.369033	-3.450222
55	6	0	4.734217	-2.783976	-2.002830
56	1	0	2.525870	0.263868	-2.629759
57	1	0	3.391479	-1.101482	-4.470102
58	1	0	3.168854	-0.523216	1.018290
59	6	0	4.605271	-2.573528	0.440522

60	1	0	4.227141	-2.125321	1.352622
61	6	0	5.406914	-3.695267	0.578699
62	6	0	5.893908	-4.376005	-0.567043
63	1	0	6.521073	-5.253161	-0.462820
64	6	0	5.554933	-3.924699	-1.821592
65	1	0	5.902440	-4.432787	-2.714830
66	8	0	5.679276	-4.078514	1.857804
67	6	0	6.436791	-5.260693	2.074277
68	1	0	5.946999	-6.141581	1.641478
69	1	0	6.496377	-5.380918	3.156605
70	1	0	7.451803	-5.174581	1.666299
71	6	0	-0.608283	3.995497	-0.540560
72	6	0	-0.594892	3.632154	0.868481
73	6	0	-1.956416	3.804977	2.937213
74	8	0	0.251814	2.895108	1.408910
75	8	0	-1.661672	4.122919	1.525598
76	6	0	-2.190012	2.300595	3.101105
77	1	0	-2.970594	1.959295	2.414525
78	1	0	-2.525025	2.091136	4.121758
79	1	0	-1.278623	1.733838	2.911132
80	6	0	-3.250092	4.584930	3.184722
81	1	0	-4.039399	4.247266	2.507471
82	1	0	-3.092992	5.655560	3.025554
83	1	0	-3.588738	4.432591	4.213493
84	6	0	-0.832831	4.324821	3.839370
85	1	0	-1.125914	4.213081	4.887950
86	1	0	-0.652140	5.387385	3.648918
87	1	0	0.091156	3.770755	3.674346
88	6	0	0.579384	3.647108	-1.230314
89	7	0	1.516893	3.316785	-1.847544
90	6	0	-1.312218	5.258689	-1.013126
91	1	0	-2.288166	5.347148	-0.532677
92	1	0	-1.459428	5.227813	-2.096878
93	1	0	-0.741338	6.165603	-0.779614
94	6	0	-0.414809	0.777223	-4.443686
95	1	0	0.993923	2.428523	-4.520087
96	1	0	0.552939	1.747167	-6.102569
97	1	0	-0.579799	2.808334	-5.247549
98	1	0	-1.342948	-0.004413	-6.236077
99	1	0	-2.032500	-0.655957	-4.739858
100	1	0	-2.449201	0.989201	-5.258819
101	1	0	-2.007877	2.764378	-3.437436
102	1	0	-2.802580	3.102412	-1.100478
103	1	0	-1.732797	1.725343	-0.542774
104	8	0	0.601674	-0.219805	-4.449800
105	6	0	0.171524	2.025006	-5.115241
106	6	0	-1.643572	0.250055	-5.215326
107	1	0	0.493666	-0.670094	-3.591331
108	8	0	-0.400496	0.168925	-2.132390
109	6	0	-0.820448	1.035787	-2.970780
110	6	0	-1.663088	2.118672	-2.636911
111	6	0	-1.965659	2.447610	-1.317153

## TS-S<sub>1</sub>

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	1	0	2.803653	2.307325	3.270735
2	1	0	-1.357903	-0.503435	-0.742645
3	1	0	-3.407083	-0.459620	-1.689837
4	1	0	2.719144	0.654355	2.659859
5	1	0	-2.777406	-2.694005	1.948525
6	1	0	1.832028	2.266518	1.113512
7	1	0	2.843443	4.175842	1.833859
8	1	0	3.159719	3.969813	0.114303

9	1	0	3.158030	1.893242	-0.856236
10	1	0	0.943140	0.239686	-0.843180
11	1	0	-6.632986	-2.715722	0.031133
12	1	0	5.469896	1.875641	-0.696697
13	1	0	5.419035	0.378702	0.218453
14	1	0	5.159847	4.141304	2.304566
15	1	0	5.454507	4.141223	0.569489
16	1	0	5.102817	1.936600	3.606970
17	1	0	5.044646	0.418649	2.718953
18	1	0	6.519680	2.131528	1.574057
19	7	0	1.432931	-0.052288	0.004852
20	6	0	-2.930297	-1.521162	0.131837
21	6	0	-3.781330	-1.109111	-0.905785
22	6	0	-3.422785	-2.358829	1.141862
23	6	0	-5.290990	-3.628468	2.211808
24	6	0	1.121353	-1.492307	2.121473
25	6	0	-0.314809	-2.014151	2.220365
26	6	0	0.745719	-0.832479	0.863289
27	6	0	-0.582185	-1.285667	0.935361
28	7	0	-1.604121	-1.064835	0.081523
29	6	0	-5.607293	-2.371739	0.063279
30	6	0	-4.755137	-2.770476	1.092330
31	6	0	-6.016663	-1.044655	-2.028658
32	6	0	-5.104762	-1.536238	-0.934590
33	6	0	2.899056	-0.067340	0.003385
34	6	0	3.478081	1.367180	0.047600
35	6	0	3.228809	1.610881	2.545604
36	7	0	2.893156	2.183202	1.187923
37	6	0	3.415884	3.597543	1.106926
38	6	0	5.027971	1.398948	0.183068
39	6	0	4.938366	3.609411	1.374191
40	6	0	4.763782	1.475323	2.674677
41	6	0	5.431795	2.153845	1.464030
42	9	0	-6.373635	-4.338662	1.823316
43	9	0	-4.368609	-4.503532	2.659707
44	9	0	-5.671280	-2.875404	3.269279
45	9	0	-5.338119	-0.784906	-3.169335
46	9	0	-6.644257	0.099743	-1.675008
47	8	0	2.151560	-1.545190	2.783252
48	8	0	-0.947379	-2.701238	2.994637
49	9	0	-6.977027	-1.946824	-2.322199
50	6	0	-0.578009	1.114184	-4.383849
51	1	0	0.796427	2.795778	-4.465691
52	1	0	0.255345	2.200934	-6.043353
53	1	0	-0.834836	3.186181	-5.052178
54	1	0	-1.538369	0.379440	-6.177657
55	1	0	-2.155015	-0.362818	-4.691491
56	1	0	-2.645117	1.287268	-5.120813
57	1	0	-2.215540	3.000579	-3.231194
58	1	0	-2.921367	3.239954	-0.870231
59	1	0	-1.839164	1.821978	-0.402845
60	8	0	0.480161	0.165297	-4.469777
61	6	0	-0.065003	2.411741	-5.018846
62	6	0	-1.813810	0.576518	-5.137602
63	1	0	0.389028	-0.370274	-3.661132
64	8	0	-0.474716	0.405810	-2.107446
65	6	0	-0.949899	1.283536	-2.890601
66	6	0	-1.828830	2.326219	-2.474773
67	6	0	-2.144057	2.541908	-1.152601
68	6	0	-0.585984	4.184898	-0.216161
69	6	0	-0.541431	3.548153	1.063523
70	6	0	-1.792518	3.349364	3.205033
71	8	0	0.326028	2.715415	1.435548
72	8	0	-1.590998	3.874728	1.848790
73	6	0	-1.981097	1.829345	3.168384
74	1	0	-2.787969	1.564898	2.478133
75	1	0	-2.257195	1.466408	4.163512
76	1	0	-1.067073	1.326441	2.852851
77	6	0	-3.087830	4.044035	3.635074
78	1	0	-3.907231	3.777604	2.962148
79	1	0	-2.967536	5.130420	3.611371

80	1	0	-3.359146	3.742041	4.651024
81	6	0	-0.632170	3.769975	4.114027
82	1	0	-0.856006	3.493709	5.149254
83	1	0	-0.493072	4.854665	4.073212
84	1	0	0.295533	3.280594	3.815518
85	6	0	0.558878	4.043457	-1.182671
86	1	0	1.084117	3.102463	-1.001826
87	1	0	1.278961	4.871151	-1.118403
88	1	0	0.192501	4.013622	-2.215224
89	6	0	-1.432622	5.312037	-0.394879
90	7	0	-2.119370	6.231449	-0.613249
91	6	0	3.459612	-0.814694	-1.208211
92	7	0	4.474945	-2.106080	-3.528471
93	6	0	4.354380	-1.926568	-1.067413
94	6	0	3.100365	-0.427326	-2.482584
95	6	0	3.620844	-1.107854	-3.609765
96	6	0	4.844568	-2.520236	-2.282988
97	1	0	2.393728	0.376845	-2.663412
98	1	0	3.305075	-0.799269	-4.604043
99	1	0	3.195043	-0.584624	0.914686
100	6	0	4.778043	-2.467039	0.171427
101	1	0	4.392857	-2.108111	1.119304
102	6	0	5.666384	-3.529848	0.217946
103	6	0	6.167272	-4.100124	-0.981330
104	1	0	6.862800	-4.929905	-0.948995
105	6	0	5.754759	-3.602928	-2.195539
106	1	0	6.111015	-4.028229	-3.127663
107	8	0	6.006359	-3.966347	1.461596
108	6	0	6.854420	-5.100540	1.586649
109	1	0	6.417015	-5.987584	1.112872
110	1	0	6.953425	-5.279420	2.657765
111	1	0	7.848006	-4.914380	1.160176

## TS-R<sub>2</sub>

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	1	0	2.885818	-2.529393	-3.329381
2	1	0	-0.834701	0.116328	1.168095
3	1	0	-2.614922	0.289236	2.529317
4	1	0	2.940030	-0.874970	-2.720777
5	1	0	-2.508595	2.532867	-1.153223
6	1	0	2.212945	-2.493440	-1.072313
7	1	0	3.151197	-4.397152	-1.914019
8	1	0	3.588068	-4.187485	-0.220899
9	1	0	3.762039	-2.122266	0.712428
10	1	0	1.526841	-0.620874	0.948327
11	1	0	-6.004588	2.661408	1.361267
12	1	0	6.050455	-1.960110	0.286343
13	1	0	5.810496	-0.531202	-0.704522
14	1	0	5.434616	-4.425872	-2.514043
15	1	0	5.859509	-4.303495	-0.810193
16	1	0	5.153185	-2.308379	-3.926480
17	1	0	5.235417	-0.730688	-3.151946
18	1	0	6.809952	-2.365439	-2.062995
19	7	0	1.900671	-0.215760	0.089935
20	6	0	-2.406221	1.348136	0.658756
21	6	0	-3.090605	0.960944	1.822900
22	6	0	-3.023295	2.221260	-0.249079
23	6	0	-5.013940	3.540161	-0.999373
24	6	0	1.269446	1.233621	-1.938260
25	6	0	-0.144034	1.799778	-1.800661
26	6	0	1.083070	0.570935	-0.644456
27	6	0	-0.234951	1.038611	-0.509986
28	7	0	-1.115774	0.834006	0.488123
29	6	0	-5.003214	2.296621	1.170510
30	6	0	-4.313441	2.678229	0.019834
31	6	0	-5.075043	1.066883	3.350983

32	6	0	-4.375527	1.434146	2.069377
33	6	0	3.354105	-0.164517	-0.099920
34	6	0	3.957603	-1.579766	-0.216284
35	6	0	3.428991	-1.849330	-2.669984
36	7	0	3.254644	-2.404738	-1.278117
37	6	0	3.775497	-3.818608	-1.231052
38	6	0	5.475806	-1.562154	-0.554852
39	6	0	5.275481	-3.834041	-1.607481
40	6	0	4.939521	-1.772567	-2.996574
41	6	0	5.741125	-2.383638	-1.831006
42	9	0	-5.913606	4.368028	-0.419250
43	9	0	-4.153563	4.301697	-1.701095
44	9	0	-5.699958	2.786211	-1.893345
45	9	0	-4.606100	-0.088141	3.873261
46	9	0	-6.406145	0.919293	3.168911
47	8	0	2.186646	1.271611	-2.754227
48	8	0	-0.857395	2.541838	-2.442251
49	9	0	-4.913607	2.020950	4.297372
50	6	0	0.977652	-3.122865	3.132458
51	1	0	1.770250	-4.235212	1.445719
52	1	0	2.425681	-4.713574	3.036557
53	1	0	0.800577	-5.221097	2.547076
54	1	0	1.287649	-3.770235	5.176087
55	1	0	0.119349	-2.445689	5.016008
56	1	0	-0.356741	-4.097086	4.580832
57	1	0	-1.282567	-4.303835	2.232661
58	1	0	-3.185390	-3.405049	0.953676
59	1	0	-2.335477	-1.782116	0.789922
60	8	0	2.057924	-2.187171	3.183058
61	6	0	1.524785	-4.404552	2.497096
62	6	0	0.468569	-3.379438	4.564791
63	1	0	1.610468	-1.323381	3.106642
64	8	0	-0.029303	-1.233392	2.084939
65	6	0	-0.157760	-2.475629	2.293378
66	6	0	-1.271621	-3.269851	1.902617
67	6	0	-2.278087	-2.825517	1.073593
68	1	0	-1.822312	-5.459461	-0.578624
69	1	0	-2.255921	-5.268722	-2.285495
70	1	0	-3.430544	-4.867046	-1.035475
71	6	0	-1.870100	-3.395784	-1.220198
72	6	0	-2.610373	-2.288106	-1.823042
73	6	0	-4.806513	-1.759408	-2.832961
74	8	0	-2.182790	-1.142522	-1.934580
75	8	0	-3.855802	-2.685357	-2.197829
76	6	0	-2.368200	-4.827515	-1.286645
77	6	0	-0.491720	-3.202022	-1.120128
78	7	0	0.662198	-3.095154	-0.938497
79	6	0	-5.164036	-0.622385	-1.872124
80	1	0	-4.295887	0.002997	-1.670993
81	1	0	-5.539132	-1.026936	-0.926384
82	1	0	-5.947825	0.003536	-2.309359
83	6	0	-4.228470	-1.237909	-4.153358
84	1	0	-3.939211	-2.074545	-4.797606
85	1	0	-3.356377	-0.608224	-3.977355
86	1	0	-4.988035	-0.650307	-4.679129
87	6	0	-6.022070	-2.654051	-3.090623
88	1	0	-5.756272	-3.489089	-3.745495
89	1	0	-6.819044	-2.077035	-3.569238
90	1	0	-6.407210	-3.062169	-2.151474
91	1	0	3.513254	0.346457	-1.048448
92	6	0	4.056750	0.627869	1.007843
93	7	0	5.333259	2.041130	3.122881
94	6	0	4.561834	1.952518	0.776586
95	6	0	4.203018	0.088714	2.270388
96	6	0	4.841360	0.833068	3.291851
97	6	0	5.201439	2.605896	1.888406
98	1	0	3.828068	-0.900738	2.513560
99	1	0	4.947034	0.394688	4.283070
100	6	0	5.728035	3.908387	1.707775
101	1	0	6.204791	4.374216	2.563588
102	6	0	4.475074	2.643207	-0.456508



103	1	0	3.973985	2.225486	-1.322707
104	6	0	5.000620	3.918798	-0.595150
105	6	0	5.637416	4.558832	0.499404
106	1	0	6.048340	5.555520	0.393329
107	8	0	4.862722	4.487500	-1.823946
108	6	0	5.308361	5.822137	-2.020072
109	1	0	4.794626	6.523514	-1.351290
110	1	0	5.061327	6.067805	-3.053397
111	1	0	6.392556	5.914904	-1.878138

## TS-S<sub>2</sub>

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	7	0	1.866753	-0.204416	0.065180
2	6	0	-1.726528	2.677886	0.131748
3	6	0	-2.616895	2.580037	1.214369
4	6	0	-1.913803	3.679844	-0.831361
5	6	0	-3.232149	5.590133	-1.769839
6	6	0	1.988922	1.305740	-2.017778
7	6	0	0.825275	2.296181	-2.043203
8	6	0	1.452115	0.775201	-0.756421
9	6	0	0.349050	1.647404	-0.779026
10	7	0	-0.680195	1.745350	0.089939
11	6	0	-3.882446	4.465457	0.370435
12	6	0	-2.989332	4.558390	-0.696336
13	6	0	-4.597346	3.393695	2.518830
14	6	0	-3.682713	3.467053	1.324409
15	6	0	3.200924	-0.802238	-0.053990
16	6	0	3.105980	-2.333712	-0.217985
17	6	0	2.858587	-2.369530	-2.731303
18	7	0	2.233553	-2.713500	-1.401041
19	6	0	1.949105	-4.194089	-1.349577
20	6	0	4.487720	-3.016909	-0.410288
21	6	0	3.280370	-4.978880	-1.411716
22	6	0	4.178824	-3.161605	-2.891955
23	6	0	4.434976	-3.980065	-1.611692
24	6	0	-0.315503	-2.616661	2.904684
25	6	0	-0.357484	-4.014936	2.280259
26	6	0	-0.861843	-2.624405	4.345454
27	6	0	-1.095307	-1.575854	2.059966
28	6	0	-2.428663	-1.880762	1.666938
29	6	0	-3.142901	-1.156993	0.742519
30	6	0	-2.927031	-2.095051	-1.472787
31	6	0	-1.530875	-2.054362	-1.540539
32	7	0	-0.360386	-1.997562	-1.561751
33	6	0	-3.731885	-1.105835	-2.291724
34	6	0	-3.458011	-3.384103	-1.057616
35	6	0	-5.590247	-4.627834	-0.903448
36	6	0	-5.508342	-4.924543	0.598984
37	6	0	-5.114624	-5.815253	-1.749154
38	6	0	-7.014502	-4.223590	-1.294969
39	6	0	4.104151	-0.422223	1.123645
40	7	0	5.725917	0.266034	3.359608
41	6	0	5.083786	0.621841	0.999778
42	6	0	3.981468	-1.054467	2.344418
43	6	0	4.809304	-0.674212	3.428858
44	6	0	5.871597	0.914286	2.168360
45	6	0	6.857494	1.928700	2.095125
46	6	0	5.321291	1.367015	-0.180138
47	6	0	6.294004	2.354750	-0.213891
48	6	0	7.073670	2.638339	0.937048
49	6	0	7.371688	4.072000	-1.493666
50	1	0	3.429646	-5.547930	-0.488960
51	1	0	2.111713	-2.630173	-3.483796
52	1	0	-0.715003	1.007617	0.806499

53	1	0	-2.471697	1.810305	1.964490
54	1	0	2.999249	-1.287961	-2.773544
55	1	0	-1.231419	3.776228	-1.671065
56	1	0	1.275005	-2.247631	-1.359647
57	1	0	1.282022	-4.405670	-2.186579
58	1	0	1.389258	-4.377969	-0.431540
59	1	0	2.575032	-2.742696	0.646216
60	1	0	1.270149	-0.460089	0.853336
61	1	0	-4.712475	5.155150	0.457504
62	1	0	4.765406	-3.548696	0.503571
63	1	0	5.259465	-2.258645	-0.579568
64	1	0	3.254627	-5.700828	-2.233361
65	1	0	-0.274304	-3.319627	4.952672
66	1	0	4.122439	-3.825997	-3.759905
67	1	0	5.008437	-2.470907	-3.069786
68	1	0	5.384571	-4.516410	-1.695719
69	9	0	-4.010126	5.095412	-2.760333
70	9	0	-3.867974	6.678751	-1.278856
71	9	0	-2.085052	6.009843	-2.337524
72	9	0	-4.234818	4.276712	3.477670
73	9	0	-4.590641	2.168276	3.088072
74	8	0	2.947304	1.018553	-2.727111
75	8	0	0.453323	3.192295	-2.773352
76	9	0	-5.874799	3.680967	2.185358
77	1	0	-0.129025	-3.972856	1.212572
78	1	0	0.373534	-4.652648	2.787169
79	1	0	-1.343319	-4.473142	2.376877
80	1	0	-0.780103	-1.627178	4.789341
81	1	0	-1.911692	-2.928555	4.378994
82	1	0	-2.854682	-2.805626	2.038838
83	1	0	-4.197899	-1.347978	0.588530
84	1	0	-2.771032	-0.212236	0.365964
85	8	0	1.057614	-2.211086	2.928779
86	1	0	1.013067	-1.238408	2.903800
87	8	0	-0.484788	-0.493007	1.822305
88	1	0	-3.949452	-1.475961	-3.301609
89	1	0	-3.196329	-0.157517	-2.394153
90	1	0	-4.693270	-0.902403	-1.811845
91	8	0	-2.795280	-4.289939	-0.555415
92	8	0	-4.812212	-3.430479	-1.233204
93	1	0	-4.493569	-5.202632	0.883231
94	1	0	-6.187518	-5.745796	0.851464
95	1	0	-5.813701	-4.045878	1.176648
96	1	0	-4.093438	-6.093079	-1.488185
97	1	0	-5.152215	-5.560203	-2.812974
98	1	0	-5.771841	-6.675157	-1.582368
99	1	0	-7.064956	-3.974001	-2.358637
100	1	0	-7.338424	-3.349672	-0.722220
101	1	0	-7.709885	-5.044940	-1.096831
102	1	0	3.249385	-1.838100	2.509046
103	1	0	4.698487	-1.181573	4.386036
104	1	0	3.634023	-0.393370	-0.966006
105	1	0	7.435430	2.124800	2.991909
106	1	0	4.747282	1.217234	-1.087740
107	1	0	7.834511	3.409130	0.912602
108	8	0	6.436470	3.006759	-1.399875
109	1	0	7.139901	4.878613	-0.787334
110	1	0	7.285387	4.452815	-2.511818
111	1	0	8.399731	3.727444	-1.324717

# TS-S<sub>B'</sub>

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	9	0	-8.408690	-1.804267	0.634717
2	9	0	-7.452620	-2.881644	-0.992277
3	9	0	-5.843494	3.316405	0.411370
4	6	0	3.096709	-4.462648	-2.689798

5	6	0	4.264616	-3.618100	-2.130125
6	6	0	3.913896	-3.134901	-0.702275
7	6	0	4.428091	-2.381105	-3.031166
8	8	0	0.092948	-4.577735	-0.031663
9	9	0	-6.834505	-3.249697	1.058312
10	9	0	-7.338305	2.633237	-1.014000
11	8	0	-3.118484	-4.056962	0.162759
12	1	0	2.784837	-1.055794	-3.708036
13	1	0	-1.916886	0.113309	0.177875
14	1	0	-4.543719	-2.537046	0.415857
15	1	0	0.944753	-3.987335	-2.558457
16	1	0	-7.663633	0.344421	-0.294255
17	1	0	-3.549920	1.571357	-0.434161
18	1	0	3.442669	-0.635236	-2.126625
19	1	0	4.494144	-2.685883	-4.081501
20	1	0	5.183051	-4.210947	-2.113975
21	1	0	1.805689	-3.550472	-0.518454
22	1	0	0.378932	-0.280720	0.289298
23	9	0	-5.302730	3.050016	-1.673303
24	1	0	1.274216	-1.649962	-2.157461
25	1	0	1.749380	-3.248972	-3.962999
26	1	0	4.033967	-3.935711	0.030961
27	1	0	4.582396	-2.319305	-0.404788
28	1	0	3.383087	-4.927846	-3.637373
29	1	0	2.835666	-5.268824	-1.997621
30	1	0	5.334066	-1.814493	-2.802408
31	7	0	0.613235	-1.271578	0.221979
32	6	0	-3.877961	-0.509693	0.031995
33	6	0	-4.289023	0.794388	-0.274650
34	6	0	-4.841761	-1.515193	0.203174
35	6	0	-7.222121	-2.286641	0.199770
36	6	0	-0.627641	-3.595806	0.112484
37	6	0	-2.126695	-3.354311	0.164719
38	6	0	-0.425170	-2.129176	0.221877
39	6	0	-1.819813	-1.897573	0.194547
40	7	0	-2.496296	-0.730522	0.159803
41	6	0	-6.610939	0.109099	-0.210092
42	6	0	-6.191298	-1.191390	0.076639
43	6	0	-6.040642	2.520121	-0.671417
44	6	0	-5.644444	1.096011	-0.386904
45	6	0	2.053521	-1.591573	0.320315
46	6	0	2.440858	-2.681326	-0.697757
47	6	0	3.213213	-1.466625	-2.792791
48	7	0	2.105701	-2.269318	-2.135870
49	6	0	1.872446	-3.539577	-2.917548
50	8	0	5.830939	0.688767	-2.358547
51	6	0	4.825739	1.943710	-4.132143
52	6	0	2.980706	3.032876	-1.860857
53	8	0	3.794475	1.022366	-0.901213
54	6	0	1.919626	3.174312	-0.949973
55	6	0	3.892928	1.966615	-1.744613
56	6	0	6.107620	3.084380	-2.266687
57	6	0	5.168555	1.920998	-2.637324
58	1	0	4.375464	2.894202	-4.431003
59	1	0	3.134584	3.780124	-2.632098
60	1	0	1.510016	4.167539	-0.785400
61	1	0	6.353883	3.042376	-1.201463
62	1	0	7.038047	2.997356	-2.836837
63	1	0	5.654384	4.057723	-2.477038
64	1	0	5.740054	1.797621	-4.716105
65	1	0	4.127826	1.140003	-4.384288
66	1	0	1.988867	2.562835	-0.054145
67	1	0	5.417784	0.424989	-1.509371
68	6	0	-0.564683	2.473203	-0.284189
69	6	0	-1.316984	4.007655	1.525384
70	1	0	-0.404705	4.531733	-2.143252
71	6	0	-0.298378	3.558291	-2.624640
72	6	0	0.299211	1.198948	-2.125558
73	8	0	-0.633152	1.456040	0.437385
74	6	0	0.088370	2.507202	-1.590745
75	7	0	0.499353	0.138698	-2.569517

76	1	0	-1.244582	3.320881	-3.123047
77	8	0	-0.976305	3.683627	0.116212
78	1	0	0.480984	3.630175	-3.389369
79	6	0	-0.114835	3.708846	2.425247
80	1	0	0.776310	4.230768	2.064413
81	1	0	0.095278	2.639634	2.468619
82	1	0	-0.327456	4.061356	3.439369
83	6	0	-2.571727	3.253412	1.968805
84	1	0	-2.391263	2.179788	2.018863
85	1	0	-3.409607	3.449687	1.295006
86	1	0	-2.862143	3.599484	2.966055
87	6	0	-1.587572	5.511750	1.451235
88	1	0	-0.702548	6.048266	1.098052
89	1	0	-1.851106	5.892727	2.442057
90	1	0	-2.415601	5.721627	0.768640
91	1	0	2.560331	-0.665174	0.043085
92	6	0	2.453836	-1.988910	1.747227
93	7	0	3.053657	-2.768457	4.419220
94	6	0	2.111183	-3.228922	2.247808
95	6	0	3.138422	-1.075007	2.619331
96	6	0	3.404209	-1.533483	3.958202
97	6	0	2.433977	-3.572054	3.582761
98	1	0	1.581866	-3.956149	1.640260
99	1	0	2.158409	-4.555398	3.961082
100	6	0	4.066539	-0.667196	4.861902
101	1	0	4.251772	-1.041884	5.862928
102	6	0	3.558020	0.227229	2.253501
103	1	0	3.423525	0.621800	1.252042
104	6	0	4.199911	1.046991	3.168267
105	6	0	4.457429	0.597477	4.488499
106	1	0	4.959972	1.237514	5.203595
107	8	0	4.553266	2.284347	2.713290
108	6	0	5.266569	3.154312	3.578235
109	1	0	6.221268	2.718247	3.898392
110	1	0	4.678660	3.422120	4.465671
111	1	0	5.464015	4.055993	2.996909

## TS-R<sub>c</sub>

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	1	0	-6.015958	-3.083934	-1.035057
2	1	0	-4.850953	-1.210937	-2.118057
3	1	0	-5.068960	-4.002936	1.171943
4	1	0	-3.897959	-3.673940	-2.351057
5	1	0	-4.286963	-4.856939	-1.108057
6	1	0	-1.736955	-2.067945	0.583943
7	1	0	-2.570954	-1.432943	-1.733057
8	1	0	-1.796959	-3.481945	-1.315057
9	1	0	-2.332961	-4.349944	0.125943
10	6	0	5.062058	2.780037	-0.008057
11	6	0	0.770055	1.692048	0.124943
12	6	0	-0.581946	1.328052	0.147943
13	6	0	5.411052	0.667036	-1.087057
14	6	0	-3.122953	-1.191942	-0.820057
15	6	0	-3.610956	-2.386940	1.345943
16	9	0	6.896061	3.996032	0.867943
17	9	0	5.562063	5.040036	-0.493057
18	8	0	-2.031942	2.926056	1.386943
19	9	0	5.732047	-1.154965	-2.570057
20	9	0	4.902062	4.580037	1.525943
21	8	0	1.146060	3.902047	1.281943
22	1	0	-3.705953	-1.388940	1.776943
23	1	0	-3.098958	-3.012942	2.074943
24	1	0	-5.780956	-2.398935	1.322943
25	1	0	-5.226952	-0.689936	-0.483057
26	1	0	6.996056	2.064032	-0.646057

27	1	0	1.562051	0.108046	-0.838057
28	1	0	3.036059	3.265042	0.548943
29	1	0	3.657049	-0.533959	-1.404057
30	1	0	-0.696951	-0.451948	-0.813057
31	9	0	7.425051	0.176031	-2.231057
32	6	0	0.496058	2.961049	0.873943
33	6	0	-0.981943	2.524053	0.913943
34	6	0	5.604061	4.101035	0.478943
35	6	0	3.690057	2.539041	0.076943
36	6	0	4.047051	0.402040	-1.017057
37	6	0	3.175054	1.339042	-0.436057
38	6	0	6.340049	-0.377966	-1.646057
39	6	0	-2.704949	0.234057	-0.412057
40	7	0	-2.671956	-2.265943	0.167943
41	7	0	1.815053	1.007045	-0.404057
42	7	0	-1.248949	0.252054	-0.309057
43	6	0	5.935055	1.859035	-0.587057
44	6	0	-5.011957	-2.847937	-0.672057
45	6	0	-4.959958	-2.958937	0.863943
46	9	0	6.797047	-1.205968	-0.677057
47	6	0	-3.977960	-3.820939	-1.270057
48	6	0	-4.635953	-1.404938	-1.065057
49	6	0	-2.609959	-3.579943	-0.593057
50	1	0	-1.793953	-1.382945	4.289943
51	1	0	1.147052	0.741047	3.266943
52	1	0	1.739038	-4.647954	3.934943
53	1	0	2.737037	-4.926957	2.499943
54	1	0	-1.461951	-0.473946	5.776943
55	1	0	1.403046	-1.521953	6.251943
56	1	0	-0.964955	-2.169947	5.652943
57	1	0	0.961051	0.196048	6.349943
58	1	0	2.274049	-0.321956	5.275943
59	6	0	-1.072953	-1.234947	5.093943
60	7	0	-0.253963	-5.212949	0.723943
61	6	0	2.175039	-4.168955	3.050943
62	6	0	0.324044	-2.416951	2.660943
63	1	0	2.872041	-3.404957	3.400943
64	6	0	1.294049	-0.598953	5.675943
65	6	0	0.174051	0.484050	3.695943
66	6	0	0.343038	-4.461951	1.389943
67	8	0	-0.713955	-1.983948	2.136943
68	6	0	0.283048	-0.782951	4.542943
69	6	0	1.115041	-3.543953	2.152943
70	1	0	-0.547949	0.356052	2.891943
71	1	0	-0.146946	1.320051	4.324943
72	8	0	0.885045	-1.880952	3.757943
73	1	0	2.474039	-4.104956	-0.928057
74	1	0	2.875042	-3.130957	-3.755057
75	1	0	1.977046	-1.580955	0.786943
76	1	0	1.588042	-3.223954	-4.983057
77	1	0	1.861046	-1.714955	-4.088057
78	1	0	0.162037	-5.114950	-2.017057
79	1	0	1.765036	-5.225954	-2.758057
80	1	0	3.207043	-2.890958	1.113943
81	6	0	0.770038	-4.785952	-2.864057
82	8	0	-0.465957	-2.803949	-3.332057
83	1	0	-0.451955	-1.876949	-3.032057
84	1	0	0.331037	-5.167951	-3.790057
85	6	0	0.841042	-3.260952	-2.946057
86	6	0	2.303043	-2.596956	0.590943
87	6	0	2.049042	-3.137955	-0.682057
88	6	0	1.178043	-2.555953	-1.608057
89	8	0	0.638047	-1.391951	-1.482057
90	6	0	1.861043	-2.806955	-4.009057
91	6	0	-3.246947	1.214059	-1.461057
92	7	0	-4.238942	2.870061	-3.546057
93	6	0	-4.393944	2.039062	-1.226057
94	6	0	-2.637946	1.284057	-2.697057
95	6	0	-3.168944	2.122059	-3.706057
96	6	0	-4.845942	2.848063	-2.326057
97	1	0	-1.741948	0.707055	-2.903057

98	1	0	-2.684944	2.159057	-4.681057
99	1	0	-3.117948	0.492058	0.564943
100	6	0	-5.981940	3.677066	-2.142057
101	1	0	-6.302939	4.274067	-2.989057
102	6	0	-6.650940	3.725068	-0.942057
103	1	0	-7.515938	4.369070	-0.835057
104	6	0	-6.194942	2.939067	0.147943
105	6	0	-5.090944	2.117064	0.002943
106	1	0	-4.756946	1.582063	0.882943
107	8	0	-6.785942	2.934068	1.374943
108	6	0	-7.863940	3.828071	1.620943
109	1	0	-7.563937	4.873070	1.476943
110	1	0	-8.141940	3.676072	2.664943
111	1	0	-8.729940	3.607073	0.983943

## 19e

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-0.860457	-0.756678	0.000151
2	1	0	-0.757704	-1.835118	0.000161
3	6	0	-2.140962	-0.204768	0.000063
4	7	0	-3.231969	0.239601	-0.000076
5	6	0	0.290563	0.061641	-0.000012
6	8	0	0.371392	1.299144	-0.000009
7	8	0	1.458092	-0.710626	-0.000228
8	6	0	2.670060	0.034034	0.000084
9	1	0	2.756430	0.672400	0.886121
10	1	0	2.756155	0.673632	-0.885067
11	1	0	3.477813	-0.701636	-0.000513

## 59

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-1.355684	-0.630496	-0.000071
2	1	0	-1.326651	-1.717317	-0.000191
3	6	0	-0.056651	0.078034	-0.000037
4	6	0	1.207512	-0.767689	0.000070
5	1	0	1.178099	-1.428796	0.881987
6	1	0	1.178151	-1.428998	-0.881717
7	6	0	-2.516981	0.032952	0.000051
8	1	0	-3.470789	-0.483828	0.000021
9	1	0	-2.530442	1.118788	0.000156
10	8	0	0.054891	1.301216	-0.000022
11	8	0	2.356419	0.037844	-0.000022
12	1	0	2.011979	0.950868	0.000018

## 1

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	1.588316	-0.658893	0.000067
2	1	0	1.292091	-1.702848	0.000145
3	6	0	0.520147	0.370135	0.000026
4	6	0	-0.956295	-0.072504	-0.000015
5	6	0	2.881531	-0.316282	-0.000022
6	1	0	3.669004	-1.062535	-0.000023
7	1	0	3.174951	0.729200	-0.000135

8	8	0	0.769341	1.573770	0.000003
9	8	0	-1.762381	1.095851	-0.000201
10	1	0	-1.124583	1.834855	-0.000103
11	6	0	-1.262067	-0.884303	-1.272844
12	1	0	-1.037969	-0.292558	-2.164997
13	1	0	-2.328029	-1.129653	-1.283562
14	1	0	-0.695755	-1.818554	-1.318014
15	6	0	-1.262172	-0.884017	1.272983
16	1	0	-0.695811	-1.818231	1.318454
17	1	0	-2.328121	-1.129422	1.283635
18	1	0	-1.038216	-0.292046	2.165015

## MVK

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	2.014340	-0.104129	0.000052
2	1	0	2.923060	-0.697049	-0.000079
3	1	0	2.114600	0.977454	-0.000145
4	6	0	0.801409	-0.665308	0.000012
5	1	0	0.682582	-1.746039	-0.000059
6	6	0	-0.442398	0.161928	-0.000075
7	8	0	-0.404771	1.386460	0.000020
8	6	0	-1.751810	-0.596953	0.000002
9	1	0	-1.809439	-1.248949	-0.879386
10	1	0	-2.592232	0.097942	-0.000346
11	1	0	-1.809655	-1.248264	0.879905

## TS-19e+59

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-0.004886	-1.037000	1.041866
2	1	0	0.743115	-0.966015	1.824866
3	1	0	-0.183906	-2.038996	0.665866
4	6	0	-1.069869	-0.139979	1.023866
5	1	0	-1.009851	0.790020	1.583866
6	6	0	-2.219873	-0.355957	0.223866
7	8	0	-2.413892	-1.331953	-0.544134
8	6	0	-3.367853	0.671066	0.286866
9	1	0	-2.987834	1.656058	-0.029134
10	1	0	-3.703851	0.783072	1.329866
11	6	0	1.476120	-0.707029	-0.508134
12	1	0	0.782120	-0.720015	-1.340134
13	6	0	2.325098	-1.833045	-0.395134
14	7	0	2.972079	-2.799058	-0.259134
15	6	0	2.024145	0.578960	-0.126134
16	8	0	2.985149	0.781942	0.612866
17	8	0	1.272165	1.601975	-0.634134
18	6	0	1.668191	2.915967	-0.224134
19	1	0	2.675196	3.151948	-0.580134
20	1	0	1.652193	3.010968	0.864866
21	1	0	0.945204	3.597982	-0.672134
22	8	0	-4.424861	0.243086	-0.542134
23	1	0	-4.051878	-0.589921	-0.911134

## TS-19e+1

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	1	0	2.641887	-1.789084	-1.762088
2	1	0	4.251907	-1.094130	-1.482088
3	1	0	3.526876	-2.169110	-0.272088
4	1	0	1.642957	0.645944	-2.037088
5	1	0	3.295974	1.260897	-1.820088
6	1	0	1.991990	1.831934	-0.765088
7	1	0	3.068944	0.218903	1.495912
8	1	0	0.363902	-1.258019	-1.220088
9	1	0	-0.670110	-1.672990	1.646912
10	1	0	-1.303134	-2.509972	0.191912
11	8	0	3.620947	0.324888	0.673912
12	6	0	3.309899	-1.379103	-0.998088
13	6	0	2.381965	0.956923	-1.294088
14	6	0	2.690933	-0.164086	-0.289088
15	8	0	1.501928	-0.356052	1.778912
16	6	0	1.405922	-0.568049	0.518912
17	6	0	0.323906	-1.130018	-0.142088
18	6	0	-0.858107	-1.589984	0.575912
19	1	0	-0.621962	3.495009	1.020912
20	1	0	-0.251984	2.743998	-0.563088
21	1	0	-1.857963	3.459044	-0.275088
22	1	0	-2.551071	-0.325936	1.613912
23	6	0	-1.024978	2.923020	0.185912
24	8	0	-1.477014	1.679033	0.750912
25	8	0	-2.045034	0.983050	-1.324088
26	6	0	-1.960040	0.781047	-0.128088
27	7	0	-4.238114	-1.815888	-0.604088
28	6	0	-3.399096	-1.192912	-0.090088
29	6	0	-2.315076	-0.498943	0.563912

## TS-19e+MVK

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-0.461041	-1.016998	0.968022
2	1	0	0.219956	-0.986935	1.815022
3	1	0	-0.666949	-2.015017	0.592022
4	6	0	-1.513126	-0.095095	0.904022
5	1	0	-1.467211	0.820910	1.487022
6	6	0	-2.601109	-0.279195	0.002022
7	8	0	-2.704020	-1.240204	-0.797978
8	6	0	-3.725205	0.759701	0.020022
9	1	0	-4.684159	0.257613	0.198022
10	1	0	-3.797249	1.236695	-0.963978
11	1	0	-3.588277	1.537714	0.776022
12	6	0	1.037932	-0.725859	-0.450978
13	1	0	0.391932	-0.725919	-1.321978
14	6	0	1.876037	-1.863782	-0.321978
15	7	0	2.507127	-2.836724	-0.170978
16	6	0	1.619814	0.552194	-0.076978
17	8	0	2.559797	0.736281	0.692022
18	8	0	0.923719	1.588130	-0.630978
19	6	0	1.346598	2.896169	-0.225978
20	1	0	2.382581	3.082265	-0.520978
21	1	0	1.263587	3.018162	0.857022
22	1	0	0.680534	3.595108	-0.734978



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