Domino Asymmetric Conjugate Addition-Conjugate Addition

Nicolas Germain, Doriane Schlaefli, Mathieu Chellat, Stéphane Rosset, Alexandre Alexakis

Department of Organic Chemistry. University of Geneva. Quai Ernest Ansermet, 30. 1211 Geneva 4, Switzerland.

Experimental section

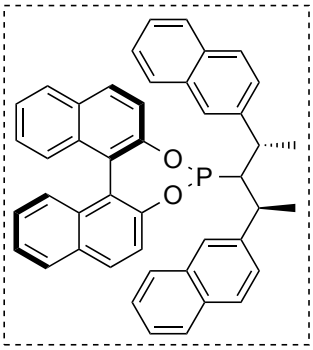
Table of contents

1) General remarks.

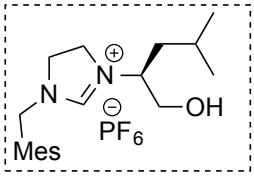
All NMR measurements were recorded on a Brücker 500 FT, Brücker 400 FT or Brüker 300 FT. The chemical shift (δ) is indicated in parts per million relative to residual $CHCl_3$ (set at 7.26 ppm for ^1H, 77.16 ppm for ^{13}C in $CDCl_3$). Coupling constants are given in Hertz and multiplicity is shown using the following acronym: s stands for singlet, d for doublet, t for triplet, q for quartet, dd for doublet of doublet, dt for doublet of triplet, brs for a broad signal and m for multiplet. Mass spectra (MS) were measured by ESI and High resolution mass spectra HRMS by Electrospray Ionisation (ESI) in the SMS service, Université de Genève. Optical rotations were obtained on a Perkin-Elmer 241 or 341 polarimeter at 20°C, d = 10 cm. Enantiomeric excesses were measured with chiral-GC (HP 6890 GC System, 10 psi H_2). Retention time (RT) are indicated in minutes. All commercial materials were used without further purification. All solvents were desiccated on drying column of aluminium oxide under nitrogen. Phosphoramidite stands as (11b*R*)-4-((2*S*,4*S*)-2,4-di(naphthalen-2-yl)pentan-3-yl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine.

The following ligands have been used in the ACA step:

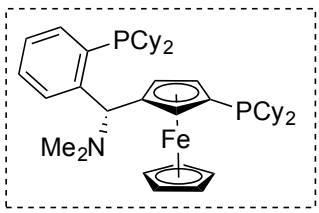
(11b*R*)-4-((2*S*,4*S*)-2,4-di(naphthalen-2-yl)pentan-3-yl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine (The Phosphoramidite Ligand)



3-(1-hydroxy-4-methylpentan-2-yl)-1-(2,4,6-trimethylbenzyl)-4,5-dihydro-1*H*-imidazol-3-ium

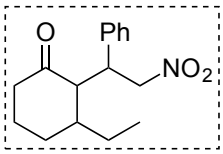


(R_P)-1-Dicyclohexylphosphino-2-[(*R*)-α-(dimethylamino)-2-(dicyclohexylphosphino)benzyl]ferrocene ((*R*),(*R*)-Taniaphos)



2) Procedures and compounds details

3-ethyl-2-(2-nitro-1-phenylethyl)cyclohexan-1-one. 5



A flame-dried schlenk tube was charged with the Phosphoramidite Ligand (0.03 equiv., 19.2 mg, 0.03 mmol) and copper thiophene carboxylate (0.02 equiv., 3.8 mg, 0.02 mmol). Dry diethyl ether (6 mL) was added and the solution was stirred under argon at room temperature for 20 minutes before being cooled down to -30 °C. To this, diethylzinc (1 M in hexanes, 1 equiv., 1 mL, 1 mmol) was added and allowed to react during 10 minutes. Cyclohexenone (1 equiv., 0.096 mL, 1 mmol) was added neat over 1 minutes. After 1 hour, the enantiomeric excess of the adduct of 1,4 addition was controlled on Chiral GC (Lipodex E, 70°C isothermal, RT = 9.0 min (*R*), 10.2 min (*S*), >99.5% ee (*R*)). After this, nitrostyrene (1.5 equiv., 224 mg, 1.5 mmol, in solution in dry dichloromethane (2 mL)) was added and the resulting mixture was allowed to stir at 0°C during 16 hours. The reaction was quenched with a saturated solution of ammonium chloride. The desired organic material was extracted with dichloromethane (three times). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The pure product was isolated by silica gel flash chromatography (Pentane/diethyl ether 95%) and a yellow oil was obtained in in 42% yield.

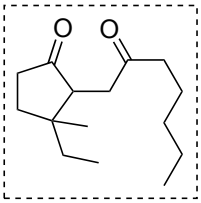
Mixture of diastereomers: 66:34 dr (determined by Gas Chromatography).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.2 (m, $5H_{ar}$), 4.97-4.89 (m, 1.30H) ppm

^{13}C NMR (133 MHz, $CDCl_3$) δ 213.4, 21.1, 137.8, 137.0, 129.3, 129.2, 128.8, 127.9, 127.9, 79.8, 78.5, 58.8, 57.1, 43.8, 43.7, 41.4, 41.0, 40.3, 40.0,29.7, 27.5, 25.7, 25.3, 249, 23.3, 23.0, 11.0, 10.6 ppm.

HRMS: Expected formula (C_{16} H_{21} N O_3) Observed *m/z* [M] 275.1520; Expected *m/z* (amu) 275.1521 (-0.1 ppm).

3-ethyl-3-methyl-2-(2-oxoheptyl)cyclopentan-1-one. **7a**



A flame-dried schlenk tube was charged with 3-(1-hydroxy-4-methylpentan-2-yl)-1-(2,4,6-trimethylbenzyl)-4,5-dihydro-1*H*-imidazol-3-ium (0.01 equiv., 2.7 mg, 0.006 mmol) and copper triflate (0.0075 equiv., 1.6 mg, 0.0045 mmol). Dry diethyl ether (2 mL) was then added and the suspension was stirred under argon at room temperature for 10 minutes and 5 minutes at -30°C. To this, ethylmagnesium bromide (3 M in diethyl ether, 1.2 equiv., 0.26 mL, 0.72 mmol) was added and allowed to react over 30 minutes. 3-methylcyclopentenone (1 equiv., 57.7 mg, 0.6 mmol, in solution in diethyl ether (4 mL)) was added over 15 minutes. After 4 hours, an aliquot was taken to determine the enantiomeric excess of 3-ethyl-3-methylcyclopentanone (Lipodex E, 60 °C isothermal, RT: 11.6 min, 13.3 min, 87% ee)[1]. 2-nitrohept-1-ene (1.2 equiv., 103 mg, 0.72 mmol, in solution in dry dichloromethane (2 mL)) was added at -30°C and the resulting the mixture was allowed to warm up to room temperature for additional 24 hours. The reaction was quenched with a 1 M solution of hydrochloric acid. The desired organic material was extracted with diethyl ether (three times). The organic phase was washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Silica gel flash chromatography (Petroleum ether/dichloromethane 90% to 60%) afforded the pure product in 64% yield.

Mixture of diastereomers: 66:34 dr (determined by Gas Chromatography).

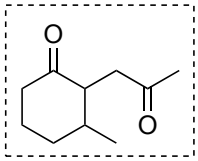
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.77-2.00 (m, 5H), 1.82-1.07 (m, 11H), 0.93-0.75 (m, 9H), 4.84 (dd, $^{3}J_{H\text{-}H}$ = 13.1, 10.8 Hz, 0.32H), 4.42 (dd, $^{3}J_{H\text{-}H}$ = 13.1, 4.4 Hz, 0.32H), 3.91-3.84 (m, 1H), 2.60-2.51 (m, 1H), 2.45-2.15 (m, 2H), 1.97-1.85 (m, 2H), 1.72-1.30 (m, 5H), 0.92 (t, $^{3}J_{H\text{-}H}$ = 7.4 Hz, 2H), 0.80 (t, $^{3}J_{H\text{-}H}$ = 7.4 Hz, H) ppm

[1] D. Martin, S. Kerli, M. d'Augustin, H. Clavier, M. Mauduit, A. Alexakis, *J. Am. Chem. Soc.* **2006**, *128*, 8416.

^{13}C NMR (133 MHz, $CDCl_3$) δ 219.1, 219.0, 209.7, 209.6, 57.4, 55.1, 43.6, 41.9, 41.6, 41.5, 37.1, 36.5, 34.6, 34.4, 33.6, 32.3, 31.5, 30.8, 29.2, 27.8, 26.5, 24.9, 23.7, 22.8, 22.6, 20.6, 19.8, 19.6, 18.9, 14.5, 14.1, 11.6, 8.7, 8.4 ppm.

HRMS: Expected formula (C_{15} H_{26} O_2) Observed *m/z* [M] 238.3711; Expected *m/z* (amu) 238.3710 (-1.1 ppm).

3-methyl-2-(2-oxopropyl)cyclohexan-1-one. 7ba



A flame-dried schlenk tube was charged with the Phosphoramidite Ligand (0.03 equiv., 8 mg, 0.015 mmol) and copper thiophene-2-carboxylate (0.02 equiv., 1.9 mg, 0.02 mmol). Dry diethyl ether (3 mL) was added and the solution was stirred under argon at room temperature for 20 minutes and 5 minutes at -30 °C. To this, trimethylaluminium (2 M in heptane, 1.4 equiv., 0.35 mL, 0.7 mmol) was added and allowed to react over 10 minutes, then cyclohexenone (1 equiv., 0.048 mL, 0.5 mmol) was slowly added over 1 minute. After 2 hours, an aliquot was taken to determine the enantiomeric excess of 3-methylcyclopentanone (Hydrodex-β-TBDMS, 40 °C for 5 min then 1 °C/min until 90 °C, RT = 41.8 min (*R*), 43.1 min (*S*), 95% ee (*R*)) then methyllithium (1.6 M in hexane, 1.4 equiv., 0.44 mL, 0.7 mmol) was added dropwise during 1 minute. After 10 minutes, 2-nitroprop-1-ene (2.0 equiv., 87 mg, 1 mmol, in solution in dry diethyl ether (2 mL)) was added over 1 hour and the resulting mixture was allowed to stir at 0°C for 3 hours. The reaction was quenched with a 2 M solution of hydrochloric acid and allowed to stir for 30 minutes. The desired organic material was extracted with dichloromethane (three times). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. Silica gel flash chromatography (Pentane/diethyl ether 95%) afforded the pure product in 84% yield.

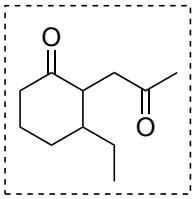
Mixture of diastereomers: 82:18 dr (determined by Gas Chromatography).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.90 (dd, $^{3}J_{H\text{-}H}$ = 17.1, 8.8 Hz, 1H), 2.75-2.69 (m, 1H), 2.41-2.32 (m, 3H), 2.26 (s, 3H), 2.11-2.04 (m, 1H), 1.90-1.85 (m, 1H), 1.71-1.50 (m, 3H), 1.04 (d, $^{3}J_{H\text{-}H}$ = 6.2 Hz, 3H) ppm.

^{13}C NMR (133 MHz, $CDCl_3$) δ 211.3, 208.0, 53.4, 41.4, 40.5, 39.1, 34.3, 30.5, 26.1, 20.7 ppm.

$[\alpha]_D$ -6.8 (c 1.7, $CHCl_3$).

3-ethyl-2-(2-oxopropyl)cyclohexan-1-one. 7bb



A flame-dried schlenk tube was respectively charged with (*R*),(*R*)-Taniaphos (0.06 equiv., 20.6 mg, 0.03 mmol) and copper chloride (0.05 equiv., 2.5 mg, 0.025 mmol). Diethyl ether (2.5 ml) was added and the solution was stirred under argon at room temperature for 30 minutes then cyclohexenone (1.0 equiv., 0.048 mL, 0.5 mmol, in solution in diethyl ether (2.5 mL)) was added slowly. After 10 minutes the reaction was cooled to 0 °C and ethylmagnesium bromide solution (3 M in diethyl ether, 1.2 equiv., 0.20 mL, 0.6 mmol) was added dropwise during 5 minutes. After 30 minutes, 2-nitroprop-1-ene (2.0 equiv., 87 mg, 1.0 mmol, in solution in dry diethyl ether (0.5 mL)) was added and the resulting mixture was allowed to stir at 0°C for 4 hours. The reaction was quenched during 30 minutes with a 2 M solution of hydrochloric acid. The desired organic material was extracted with dichloromethane (three times). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. After silica gel flash chromatography (Pentane/diethyl ether 95%), the pure product was obtained in 63% yield. Chiral GC (Chirasil Dex CB, 60°C with 1°C/min until 140°C, RT = 68.3 min (*R*), 69.7 min (*S*), 97% ee (*R*)).

Mixture of diastereomers: 86:14 dr (determined by Gas Chromatography).

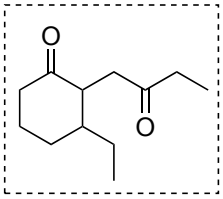
^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.91-2.78 (m, 2H), 2.41-2.32 (m, 3H), 2.26 (s, 3H), 2.13-2.05 (m, 1H), 1.97-1.92 (m, 1H), 1.64-1.44 (m, 3H), 1.32-1.25 (m, 2H), 0.92 (t, $^{3}J_{H\text{-}H}$ = 7.4 Hz, 3H) ppm.

^{13}C NMR (133 MHz, $CDCl_3$) δ 211.8, 208.1, 51.3, 44.7, 41.5, 40.3, 30.5, 30.0, 26.6, 26.0, 10.3 ppm.

$[\alpha]_D$ -8.5 (c 0.25, $CHCl_3$).

HRMS: Expected formula ($C_{11}H_{19}O_2$) Observed *m/z* $[M+H]^+$ 183.1375; Expected *m/z* (amu) 183.1380 (2.7 ppm).

3-ethyl-2-(2-oxobutyl)cyclohexan-1-one. 7bc



A flame-dried schlenk tube was respectively charged with (*R*),(*R*)-Taniaphos (0.06 equiv., 20.6 mg, 0.03 mmol) and copper chloride (0.05 equiv., 2.5 mg, 0.025 mmol). Dry diethyl ether (2.5 ml) was added and the solution was stirred under argon at room temperature for 30 minutes. To this, cyclohexenone (1 equiv., 0.048 mL, 0.5 mmol, in solution in diethyl ether (2.5 mL)) was added dropwise over 1 minute. After 10 minutes, the reaction was cooled down to 0 °C and ethylmagnesium bromide (3 M in diethyl ether, 1.2 equiv., 0.20 mL, 0.6 mmol) was added dropwise during 5 minutes. After 30 minutes, 2-nitrobut-1-ene (2.0 equiv., 101 mg, 1.0 mmol, in solution in dry diethyl ether (0.5 mL)) was added and the resulting mixture was allowed to stir at 0°C for 2 hours. The reaction was quenched with a 2 M solution of hydrochloric acid and the resulting colorless solution was stirred for 30 minutes. The desired organic material was extracted with dichloromethane (three times). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. After silica gel flash chromatography (Pentane/diethyl ether 95%) the pure product was isolated in 66% yield. Chiral GC (Hydrodex-b-3P, 80 °C with 1 °C/min until 140°C, RT = 52.4 min (*R*), 53.4 min (*S*), 97% ee (*R*)).

Mixture of diastereomers: 90:10 dr (determined by Gas Chromatography).

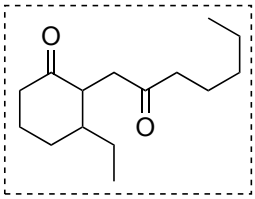
^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.87-2.80 (m, 2H), 2.00-2.28 (m, 5H), 2.13-1.91 (m, 2H), 1.66-1.44 (m, 3H), 1.31-1.22 (m, 2H), 1.08 (t, $^3J_{H-H}$ = 7.3 Hz, 3H), 0.92 (t, $^3J_{H-H}$ = 7.4 Hz, 3H) ppm.

^{13}C NMR (133 MHz, $CDCl_3$) δ 211.9, 210.7, 51.3, 44.7, 41.5, 39.1, 36.4, 30.0, 26.5, 25.9, 10.3, 7.8 ppm.

$[\alpha]_D$ -19.3 (c 0.5, $CHCl_3$).

HRMS: Expected formula ($C_{12}H_{20}O_2$) Observed *m/z* $[M+H]^+$ 197.1533; Expected *m/z* (amu) 197.1536 (1.3 ppm).

3-ethyl-2-(2-oxoheptyl)cyclohexan-1-one. 7bd



A flame-dried schlenk tube was respectively charged with the Phosphoramidite Ligand (0.03 equiv., 16 mg, 0.03 mmol) and copper thiophene-2-carboxylate (0.02 equiv., 3.8 mg, 0.03 mmol). Dry diethyl ether (6 mL) was added and the solution was stirred under argon at room temperature for 20 minutes before being cooled down to -30 °C. To this, diethylzinc (1 M in hexanes, 1 equiv., 1 mL, 1 mmol) was added and allowed to react during 10 minutes. Cyclohexenone (1 equiv., 0.096 mL, 1 mmol) was added neat over 1 minutes. After 1 hour, the enantiomeric excess of the adduct of 1,4 addition was controlled on Chiral GC (Lipodex E, 70°C isothermal, RT = 9.0 min (*R*), 10.2 min (*S*), >99.5% ee (*R*)). After this, 2-nitrohept-1-ene (1.5 equiv., 215 mg, 1.5 mmol, in solution in dry diethyl ether (2 mL)) was added and the resulting mixture was allowed to stir at 0°C during 1.5 hours. The reaction was quenched with a 2 M solution of hydrochloric acid and the resulting mixture was allowed to stir during 30 minutes. The desired organic material was extracted with dichloromethane (three times). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The pure product was isolated by silica gel flash chromatography (Pentane/diethyl ether 95%) and a yellow oil was obtained in in 82% yield.

Mixture of diastereomers: 88:12 dr (determined by Gas Chromatography).

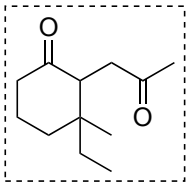
^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.85-2.78 (m, 1H), 2.60-2.19 (m, 5H), 2.10-1.87 (m, 2H), 1.63-1.41 (m, 6H), 1.34-1.24 (m, 6H), 0.98-0.86 (m, 6H) ppm.

^{13}C NMR (133 MHz, $CDCl_3$) δ 211.9, 210.4, 51.2, 44.7, 43.3, 41.5, 39.5, 31.4, 30.0, 26.6, 26.0, 23.5, 22.5, 13.9, 10.3 ppm.

$[\alpha]_D$ -12.3 (c 0.65, $CHCl_3$).

HRMS: Expected formula ($C_{15}H_{27}O_2$) Observed *m/z* $[M+H]^+$ 239.2005; Expected *m/z* (amu) 239.2006 (0.1 ppm).

3-ethyl-3-methyl-2-(2-oxopropyl)cyclohexan-1-one. **7ca**



A flame-dried schlenk tube was successively charged with 3-(1-hydroxy-4-methylpentan-2-yl)-1-(2,4,6-trimethylbenzyl)-4,5-dihydro-1*H*-imidazol-3-ium (0.01 equiv., 2.7 mg, 0.006 mmol) and copper triflate (0.0075 equiv., 1.6 mg, 0.0045 mmol). Dry ether (2 mL) was added and the solution was stirred under argon at room temperature for 10 minutes, and 10 minutes at -10 °C. To this, ethylmagnesium bromide (3 M in diethyl ether, 1.2 equiv., 0.26 mL, 0.72 mmol) was added and allowed to react over 30 minutes. 3-methylcyclohexenone (1 equiv., 57.7 mg, 0.6 mmol, in solution in diethyl ether (4 mL)) was added dropwise over 15 minutes. After 2 hours, a solution of 2-nitroprop-1-ene (1.2 equiv., 72.8 mg, 0.72 mmol, in solution in dry dichloromethane (2 mL)) was added at -10°C and the resulting the mixture was allowed to allowed to stir at 0°C for 2 hours. The reaction was quenched with a 1 M solution of hydrochloric acid. The desired organic material was extracted with diethyl ether (three times). The organic phase was eventually washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Silica gel flash chromatography (Petroleum ether/dichloromethane 90% then petroleum ether/diethylether 95%) afforded the pure product in 68% yield.

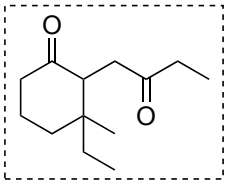
Mixture of diastereomers: 57:43 dr (determined by Gas Chromatography).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.00-2.80 (m, 2H), 2.63-2.54 (m, 1H), 2.45-2.43 (m, 1H), 2.35-2.31 (m, 2H), 2.12-2.02 (m, 1H), 1.98-1.93 (m, 1H), 1.87-1.72 (m, 2H), 1.56-1.46 (m, 1H), 1.36-1.24 (m, 2H), 1.06-1.02 (m, 3H), 0.95 (s, 1H), 0.88-0.84 (m, 2H), 0.79-0.70 (m, 3H) ppm (mixture of diastereomers).

^{13}C NMR (133 MHz, $CDCl_3$) δ 212.4, 211.7, 208.2, 208.2, 57.3, 53.4, 41.3, 41.1, 37.1, 37.0, 35.5, 34.9, 34.2, 30.7, 25.6, 5.1, 22.6, 22.5, 22.1, 20.5, 7.9, 7.4 ppm (mixture of diastereomers).

HRMS: Expected formula ($C_{12}H_{20}O_2$) Observed *m/z* [M] 196.1456; Expected *m/z* (amu) 196.1457 (-1.1 ppm).

3-ethyl-3-methyl-2-(2-oxobutyl)cyclohexan-1-one. 7cb



A flame-dried schlenk tube was respectively charged with 3-(1-hydroxy-4-methylpentan-2-yl)-1-(2,4,6-trimethylbenzyl)-4,5-dihydro-1*H*-imidazol-3-ium (0.01 equiv., 2.7 mg, 0.006 mmol) and copper triflate (0.0075 equiv., 1.6 mg, 0.0045 mmol). Dry ether (2 mL) is added and the solution was stirred under argon at room temperature for 10 minutes, and 10 minutes at -10 °C. To this, ethylmagnesium bromide (3 M in diethyl ether, 1.2 equiv., 0.28 mL, 0.72 mmol) was added and allowed to react over 30 minutes. 3-methylcyclohexenone (1 equiv., 66.6 mg, 0.6 mmol, in solution in diethyl ether (4 mL)) was added over 15 minutes. After 2 hours, a solution of 2-nitrobut-1-ene (1.2 equiv., 157.6 mg, 0.72 mmol, 77% in dry diethyl ether, in solution in dry dichloromethane (2 mL)) was added and the resulting mixture was allowed to stir at 0°C for 2 hours. The reaction was quenched with a 1 M solution of hydrochloric acid and the resulting solution was allowed to stir during 30 minutes. The desired organic material was extracted with dichloromethane (three times). The organic phase was eventually washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Silica gel flash chromatography (Petroleum ether/dichloromethane 90% then petroleum ether/diethylether 95%) afforded the pure product in 71% yield.

Mixture of diastereomers: 66:34 dr (determined by Gas Chromatography).

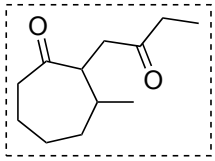
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.03 (dd, $^3J_{H-H}$ = 10.5, 2 Hz, 0.66H, major diastereomer), 3.00 (dd, $^3J_{H-H}$ = 10.5, 2 Hz, 0.34H, minor diastereomer), 2.94 (dd, $^3J_{H-H}$ = 17, 10.5 Hz, 0.34H, minor diastereomer), 2.86 (dd, $^3J_{H-H}$ = 17, 10.5 Hz, 0.66H, major diastereomer), 2.64 (m, 1H, two diastereomers), 2.5-2.42 (two q, $^3J_{H-H}$ = 7.5 Hz, 1H, two diastereomer), 2.38-2.30 (m, 2H, two diastereomers), 2.12 (dd, $^3J_{H-H}$ = 17, 2 Hz, 0.34H, minor diastereomer),

2.06 (dd, $^{3}J_{H\text{-}H}$ = 17, 2 Hz, 0.66H, major diastereomers), 1.98 (m, 0.66H, major diastereomer), 1.92 (m, 0.37H minor diastereomer), 1.82-1.76 (m, 1.32H, major diastereomer), 1.68-1.63 (m, 0.68H, minor diastereomer), 1.59 (m, 0.34H, minor diastereomer), 1.50 (m, 0.66H, major diastereomer), 1.37 (qd, $^{3}J_{H\text{-}H}$ = 8, 1.5 Hz, 1.32H, major diastereomer), 1.12 (qd, 7.5, 3.5 Hz, 0.68H, minor diastereomer), 1.06 (t, $^{3}J_{H\text{-}H}$ = 7.5 Hz, 3H, two diastereomer), 0.96 (s, 1.02H, minor diastereomer), 0.88 (t, $^{3}J_{H\text{-}H}$ = 7.5 Hz, 1.98H, major diastereomer), 0.76 (t, $^{3}J_{H\text{-}H}$ = 7.5 Hz, 1.02H, minor diastereomer), 0.70 (s, 1.98H, major diastereomer) ppm

^{13}C NMR (167 MHz, $CDCl_3$) δ 212.5, 211.7, 210.8, 210.7, 57.3, 53.4, 41.4, 41.3, 41.3, 41.2, 36.6, 35.9, 35.8, 35.5, 35.0, 34.2, 25.6, 25.1, 22.6, 22.2, 20.5, 7.9, 7.5 ppm.

HRMS: Expected formula ($C_{13}H_{22}O_2$) Observed *m/z* [M] 210.1613; Expected *m/z* (amu) 210.1614 (-0.5 ppm).

3-methyl-2-(2-oxobutyl)cycloheptan-1-one. 7da



A flame-dried schlenk tube was respectively charged with the Phosphoramidite Ligand (0.015 equiv., 48 mg, 0.075 mmol) and copper thiophene-2-carboxylate (0.01 equiv., 9.5 mg, 0.05 mmol). Dry diethyl ether (20 ml) was added and the solution was stirred under argon at room temperature for 20 minutes and 10 minutes at -30 °C. To this, trimethylaluminium (2 M in heptane, 1.4 equiv., 3.5 mL, 7 mmol) was added and allowed to react over 10 minutes. Cycloheptenone (1 equiv., 565 mg, 5 mmol, in solution in dry diethyl ether) was added dropwise during 5 minutes. After 2 hours, an analysis of the enantioselectivity of the 1-4 addition was done on Chiral GC (Lipodex E, 60°C isothermal, RT: 19.8min (*S*), 20.8min (*R*), 93% ee (*R*)) then methyllithium (1.6 M in diethyl ether, 1.4 equiv., 0.44 mL, 0.7 mmol) was added over 1 minute. After 10 minutes, 2-nitrobut-1-ene (2.0 equiv., 101 mg, 1 mmol, in solution in dry diethyl ether (2 mL)) was added over 30 minutes and the resulting mixture was allowed to stir at -10°C for 3 hours. The reaction was quenched with a 2 M solution of hydrochloric acid and the resulting mixture was allowed to stir during 30 minutes. The desired organic material was extracted with dichloromethane (three times). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. Silica gel flash chromatography (Pentane/diethyl ether 95%) afforded the pure product in 81% yield.

Mixture of diastereomers: 97:3 dr (determined by Gas Chromatography).

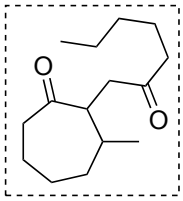
^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.06-2.93 (m, 2H), 2.76-2.69 (m, 1H), 2.51-2.37 (m, 4H), 1.88-1.66 (m, 4H), 1.46-1.27 (m, 3H), 1.02 (t, $^{3}J_{H\text{-}H}$ = 8 Hz, 3H), 0.97 (d, $^{3}J_{H\text{-}H}$ = 6.5 Hz, 3H) ppm.

^{13}C NMR (133 MHz, $CDCl_3$) δ 215.2, 210.8, 50.9, 43.4, 43.4, 37.4, 35.8, 34.6, 25.2, 23.1, 20.6, 7.6 ppm.

$[\alpha]_D$ -16.3 (c 0.60, $CHCl_3$)

HRMS: Expected formula ($C_{12}H_{20}O_2$) Observed *m/z* $[M+H]^+$ 197.1532; Expected *m/z* (amu) 197.1536 (2.1 ppm).

3-methyl-2-(2-oxoheptyl)cycloheptan-1-one. 7db



A flame-dried schlenk tube was respectively charged with the Phosphoramidite Ligand (0.03 equiv., 8 mg, 0.015 mmol) and copper thiophene-2-carboxylate (0.02 equiv., 1.9 mg, 0.01 mmol). Dry diethyl ether (3 ml) was added and the solution was stirred under argon at room temperature for 20 minutes and 10 minutes at -30 °C. To this, dimethylzinc (1.2 M in toluene, 1.1 equiv., 0.92 mL, 0.55 mmol) was added and allowed to react over 10 minutes. Cycloheptenone (1 equiv., 0.055 mL, 0.5 mmol) was added neat over 1 minutes. After 1 hours, an analysis of the enantioselectivity of the 1,4-addition was monitored by Chiral GC (Lipodex E, 60°C isothermal, RT: 19.8min (*S*), 20.8min (*R*), 99.5% ee (*R*)). 2-nitrohept-1-ene (1.5 equiv., 107 mg, 0.75 mmol, in solution in dry diethyl ether (0.5 mL)) was added and the resulting mixture was allowed to stir at 0°C for 1.5 hours. The reaction was quenched with a 2 M solution of hydrochloric acid and the resulting mixture was allowed to stir during 30 minutes. The desired organic material was extracted with dichloromethane (three times). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. Silica gel flash chromatography (5% of diethylether in Pentane) afforded the pure product in 72% yield.

Mixture of diastereomers: 92:8 dr (determined by Gas Chromatography).

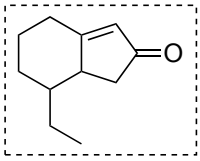
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 3.08-2.90 (m, 1H), 2.79-2.69 (m, 1H), 2.53-2.39 (m, 5H), 1.93-1.72 (m, 4H), 1.65-1.52 (m, 3H), 1.48-1.23 (m, 6H), 0.99 (d, $^{3}J_{H-H}$ = 6.5Hz, 3H), 0.99 (t, $^{3}J_{H-H}$ = 7.1Hz, 3H) ppm.

^{13}C NMR (133 MHz, $CDCl_3$) δ = 210.6, 50.9, 43.9, 43.5, 42.7, 37.5, 34.6, 31.4, 29.7, 25.2, 23.4, 23.1, 22.4, 20.6, 13.9 ppm.

$[\alpha]_D$ -4.0 (c 0.75, $CHCl_3$).

HRMS: Expected formula ($C_{15}H_{27}O_2$) Observed *m/z* $[M+H]^+$ 239.2011; Expected *m/z* (amu) 239.2006 (2.2 ppm).

7-ethyl-1,4,5,6,7,7a-hexahydro-2*H*-inden-2-one. 8



A flame-dried schlenk tube was respectively charged with (*R*),(*R*)-Taniaphos (0.06 equiv., 20.6 mg, 0.03 mmol) and copper triflate (0.05 equiv., 2.5 mg, 0.025 mmol). Dry diethyl ether (2.5 mL) is added and the solution was stirred under argon at room temperature for 30 minutes before the slow addition of cyclohexenone (1.0 equiv., 0.048 mL, 0.5 mmol, in solution in dry diethyl ether (2.5 mL)) over 5 minutes. After 10 minutes, the reaction was cooled down to 0 °C and ethylmagnesium bromide (3 M in diethyl ether, 1.2 equiv., 0.20 mL, 0.6 mmol) was added dropwise over 5 minutes and allowed to react during 30 minutes. 2-nitroprop-1-ene (2.0 equiv., 87 mg, 1.0 mmol, in solution in diethylether (0.5 mL)) was added and the resulting mixture was allowed to stir at 0°C for 4 hours. The reaction was quenched with a 2 M solution of hydrochloric acid and allowed to stir during 30 minutes. The desired organic material was extracted with dichloromethane (three times). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure (Chiral GC - Chirasil Dex CB, 60°C-1°C/min until 140°C, RT: 68.3min (*R*), 69.7min (*S*), 97% ee (*R*)). The crude material was directly used for the cyclization step by dissolving it in dry tetrahydrofuran (3 mL). A solution of potassium *t*-butanolate (1.1 equiv., 0.062 mg, 0.55 mmol) in tetrahydrofuran (2 mL) was added and after 3h, all the volatiles were removed under reduced pressure and replaced by dry diethyl ether. A saturated solution of ammonium chloride was then poured into the reaction mixture. The desired organic material was extracted with diethyl ether (three times). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. Silica gel flash chromatography (Pentane/diethyl ether 80%) afforded the pure product in 67% yield.

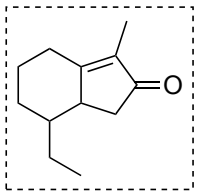
Mixture of diastereomers: 86:14 dr (determined by Gas Chromatography).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.81 (s, 1H), 2.80-2.76 (m, 1H), 2.56-2.49 (m, 1H), 2.37-2.33 (m, 1H), 2.25-1.91 (m, 5H), 1.61-1.52 (m, 1H), 1.45-1.35 (m, 1H),, 1.26-1.08 (m, 2H), 0.91 (t, $^{3}J_{H-H}$ = 7.4 Hz, 3H) ppm.

^{13}C NMR (133 MHz, $CDCl_3$) δ 209.2, 184.8, 126.8, 47.2, 47.1, 41.2, 30.9, 30.0, 27.8, 26.6, 11.1 ppm.

$[\alpha]_D$ -35.1 (c 0.85, $CHCl_3$).

7-ethyl-3-methyl-1,4,5,6,7,7a-hexahydro-2*H*-inden-2-one. 9



A flame-dried schlenk tube was respectively charged with (*R*),(*R*)-Taniaphos (0.06 equiv., 20.6 mg, 0.03 mmol) and copper chloride (0.05 equiv., 2.5 mg, 0.025 mmol). Dry diethyl ether (2.5 ml) was added and the solution was stirred under argon at room temperature for 30 minutes before the slow addition of cyclohexenone (1.0 equiv., 0.048 mL, 0.5 mmol, in solution in diethyl ether (2.5 mL)) over 5 minutes. After 10 minutes the reaction temperature was cooled down to 0 °C and ethylmagnesium bromide (3 M in diethyl ether, 1.2 equiv., 0.20 mL, 0.6 mmol) was added dropwise over 5 minutes and allowed to react during 30 minutes. To this, 2-nitrobut-1-ene (2.0 equiv., 101 mg, 1.0 mmol, in solution in dry diethyl ether (0.5 mL)) was added and the resulting mixture was allowed to stir at 0°C for 4 hours. The reaction was quenched with a 2 M solution of hydrochloric acid and

allowed to stir during 30 minutes. The desired organic material was extracted with dichloromethane (three times). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure (Chiral GC (Hydrodex-b-3P, 80 °C with 1 °C/min until 140°C, RT = 52.4 min (*R*), 53.4 min (*S*), 97% ee (*R*)). The crude material was directly used for the cyclization step by dissolving it in dry tetrahydrofuran (3 mL). A solution of potassium *t*-butanolate (1.1 equiv., 0.062 mg, 0.55 mmol) in tetrahydrofuran (2 mL) was added and after 3h, all the volatiles were removed under reduced pressure and replaced by dry diethyl ether. A saturated solution of ammonium chloride was then poured into the reaction mixture. The desired organic material was extracted with diethyl ether (three times). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. Silica gel flash chromatography (Pentane/diethyl ether 80%) afforded the pure product in 64% yield.

Mixture of diastereomers: 94:6 dr (determined by Gas Chromatography).

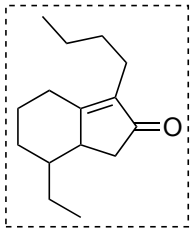
^{1}H-NMR (500 MHz, $CDCl_3$) δ = 2.84-2.80 (m, 1H), 2.54-2.49 (m, 1H), 2.30-2.23 (m, 1H), 2.10-1.99 (m, 3H), 1.97-1.92 (m, 1H), 1.67 (s, 3H), 1.40-1.00 (m, 5H), 0.91 (t, $^{3}J_{H\text{-}H}$ = 7.5 Hz, 3H) ppm.

^{13}C NMR (167 MHz, $CDCl_3$) δ = 209.5, 176.0, 133.2, 47.4, 46.0, 40.4, 30.8, 28.8, 28.2, 26.6, 11.4, 8.0 ppm.

$[\alpha]_D$ -31.4 (c 0.80, $CHCl_3$).

HRMS: Expected formula ($C_{12}H_{19}O$) Observed *m/z* $[M+H]^+$ 179.1432; Expected *m/z* (amu) 179.1430 (0.9 ppm).

3-butyl-7-ethyl-1,4,5,6,7,7a-hexahydro-2*H*-inden-2-one. 10



In a 5 ml flask, 3-ethyl-2-(2-oxoheptyl)cyclohexan-1-one (1.1 equiv., 62 mg, 0.55 mmol) was added to a 2% sodium hydroxide solution in a 1:1 mixture of methanol and water (1mL). After 30 hours, the desired organic material was extracted with diethyl ether (three times). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. Filtration through a short path of silica afforded the pure product in 70% yield.

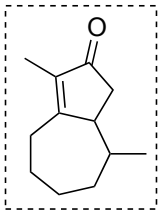
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 2.87-2.77 (m, 1H), 2.53-1.89 (m, 6H), 1.78-1.47 (m, 3H), 1.35-1.23 (m, 8H), 1.00-0.81 (m, 8H) ppm.

^{13}C NMR (133 MHz, $CDCl_3$) δ = 209.4, 208.9, 176.1, 174.1, 138.3, 137.3, 65.9, 47.3, 45.5, 44.2, 40.2, 39.6, 37.6, 31.1, 31.0, 30.4, 28.5, 28.4, 27.9, 27.5, 26.5, 22.6, 22.6, 22.4, 22.3, 20.2, 16.6, 15.3, 13.9, 11.9, 11.1 ppm.

$[\alpha]_D$ -3.8 (c 1.5, CH_3Cl)

HRMS: Expected formula ($C_{15}H_{25}O$) Observed *m/z* $[M+H]^+$ 221.1897; Expected *m/z* (amu) 221.1900 (1.1 ppm).

3,8-dimethyl-4,5,6,7,8,8a-hexahydroazulen-2(1*H*)-one. 11



In a 5 ml flask, a solution 3-methyl-2-(2-oxobutyl)cycloheptan-1-one (1 equiv., 23 mg, 0.12 mmol) in dry tetrahydrofuran (1 mL) was added to a solution of potassium *t*-butanolate (1.1 equiv., 14 mg, 0.13 mmol) in tetrahydrofuran (1 mL). After 3h, all the volatiles were removed under reduced pressure and replaced by diethyl ether. A saturated solution of ammonium chloride was poured into the reaction mixture. The desired organic material was extracted with diethyl ether (three times). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. Filtration through a short path of silica afforded the pure product in 81% yield.

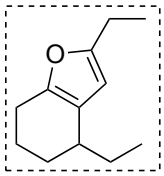
^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.64-2.47 (m, 4H), 2.15 (dd, $^{3}J_{H\text{-}H}$ = 18.1, 2.0 Hz, 1H), 1.96-1.90 (m, 1H), 1.82-1.65 (m, 3H), 1.67 (s, 3H), 1.43-1.26 (m, 3H), 1.05 (d, $^{3}J_{H\text{-}H}$ = 6.3 Hz, 3H) ppm.

^{13}C NMR (133 MHz, $CDCl_3$) δ 208.6, 177.5, 136.0, 49.4, 42.0, 40.4, 37.1, 30.5, 27.5, 24.6, 22.8, 7.8 ppm.

[α]$_D$ +9.4 (c 0.59, CH_3Cl)

HRMS: Expected formula ($C_{12}H_{18}O$) Observed *m/z* $[M+H]^+$ 179.1428; Expected *m/z* (amu) 179.1430 (1.3 ppm).

2,4-diethyl-4,5,6,7-tetrahydrobenzofuran. 12



In a microwave vial, hydrochloric acid (1.25 M in ethanol, 1 equiv., 0.20 mL, 0.255 mmol) was added to a solution of 3-ethyl-2-(2-oxobutyl)cyclohexan-1-one (1 equiv., 50 mg, 0.255 mmol) in absolute ethanol (2 mL). The mixture was heated at 110°C for 5 minutes (TLC (Petroleum ether/dichloromethane 9:1) showed the total conversion of the starting material). The crude mixture was diluted in ethyl acetate and sodium bicarbonate was used to neutralize the acid. The organic layer was then washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Highly volatile furan derivative was isolated by silica gel flash chromatography (Petroleum ether/dichloromethane 90%) in 67% yield as colorless oil.
No racemization is expected as of **13**. (All the chiral instruments failed in resolving the mixture of enantiomers)

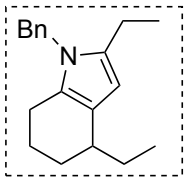
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (s, $1H_{furan}$), 2.64 (q, $^3J_{H\text{-}H}$ = 7.6 Hz, $2H_{furan\text{-}CH2\text{-}}$), 2.55 (t, $^3J_{H\text{-}H}$ = 5.2 Hz, $2H_{\text{-}CH\text{-}CH2\text{-}CH3}$), 2.47 (m, $1H_{furan\text{-}CH\text{-}}$), 1.98 (m, $2H_{\text{-}CH2\text{-}}$), 1.75 (m, $2H_{\text{-}CH2\text{-}}$), 1.40 (m, $2H_{\text{-}CH\text{-}CH2\text{-}CH3}$), 1.24 (t, $^3J_{H\text{-}H}$ = 7.2 Hz, $3H_{furan\text{-}CH2\text{-}CH3}$), 0.99 (t, $^3J_{H\text{-}H}$ = 7.2 Hz, $3H_{\text{-}CH\text{-}CH2\text{-}CH3}$) ppm

^{13}C NMR (133 MHz, $CDCl_3$) δ 155.5, 148.6, 121.8, 103.9, 34.8, 28.8, 28.4, 23.3, 21.7, 21.6, 12.5, 11.9 ppm

[α]$_D$ -45.7 (c 0.50, $CHCl_3$)

HRMS: Expected formula ($C_{12}H_{18}O_1Li$) Observed *m/z* $[M+Li]^+$ 185.1513; Expected *m/z* (amu) 185.1512 (0.7 ppm).

1-benzyl-2,4-diethyl-4,5,6,7-tetrahydro-1*H*-indole. 13



In a microwave vial, benzyl amine (5 equiv., 0.14 mL, 1.275 mmol) was added to a solution of enantiopure 3-ethyl-2-(2-oxobutyl)cyclohexan-1-one (1 equiv., 50 mg, 0.255 mmol) in acetic acid (1 mL). The mixture was heated at 170°C for 15 minutes (TLC (Petroleum ether/dichloromethane 9:1) showed the total conversion of the starting material). The reaction mixture was neutralized with a saturated solution of sodium bicarbonate. The organic phase is then washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The tetrahydrobenzopyrrole derivative was isolated by silica gel flash chromatography (Petroleum ether/dichloromethane 90%) in 79% yield as colorless oil. No racemization was measured (Chiral HPLC – OJ10_1A, RT: 3.88 min, 4.32 min, 99.5% ee).

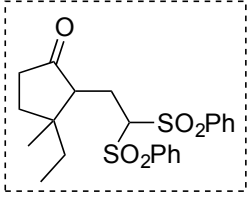
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.28 (m, $3H_{ar}$), 6.97-6.95 (m, $2H_{ar}$), 5.93 (s, $1H_{py}$), 5.02 (s, $2H_{benz}$), 2.60-2.59 (m, 1H), 2.57-2.49 (m, 2H), 2.48-2.45 (m, 2H), 2.02-1.85 (m, 3H), 1.78-1.70 (m, 1H), 1.49-1.38 (m, 2H), 1.27 (td, $^3J_{H\text{-}H}$ = 7.6, 1.2 Hz, 3H), 1.09 (td, $^3J_{H\text{-}H}$ = 7.2, 1.2 Hz, 3H) ppm

^{13}C NMR (133 MHz, $CDCl_3$) δ 139.1, 133.6, 128.7, 127.1, 127.0, 125.9, 121.3, 102.3, 46.5, 35.7, 29.3, 29.2, 22.2, 22.1, 19.7, 13.0, 12.1 ppm

[α]$_D$ -67.8 (c 0.50, $CHCl_3$)

HRMS: Expected formula ($C_{19}H_{25}N$) Observed *m/z* $[M+H]^+$ 268.2055; Expected *m/z* (amu) 268.2060 (-1.9 ppm).

2-(2,2-bis(phenylsulfonyl)ethyl)-3-isopropyl-2-methylcyclopentan-1-one. 14a



A flame-dried Schlenk flask was respectively charged with 3-(1-hydroxy-4-methylpentan-2-yl)-1-(2,4,6-trimethylbenzyl)-4,5-dihydro-1*H*-imidazol-3-ium (0.01 equiv., 2.7 mg, 0.006 mmol) and copper triflate (0.0075 equiv., 1.6 mg, 0.0045 mmol). Dry diethyl ether (2 mL) was added and the solution was stirred under argon at room temperature for 10 minutes. Ethylmagnesium bromide (3 M in diethyl ether, 1.2 equiv., 0.27 mL, 0.72 mmol) was added at -30°C and allowed to react over 30 minutes. 3-methylcyclopentenone (1 equiv., 57.7 mg, 0.6 mmol, in solution in diethyl ether (4 mL)) was added over 15 minutes. After 4 hours, a solution of 1,1-bis(phenylsulfonyl)ethane (1.2 equiv., 222 mg, 0.72 mmol, in solution in dichloromethane (2 mL)) was added and the resulting mixture was allowed to stir at 0°C for 2 hours. The reaction was quenched with a 1 M solution of hydrochloric acid. The desired organic material was extracted with diethyl ether (three times). The organic phase was eventually washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Pure ketone was isolated after silica gel flash chromatography (Petroleum ether/diethyl ether 10% to 50%) and the desired compound was further purified by trituration in diethyl ether to afford a pure white solid in 68% yield.

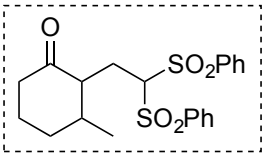
Mixture of diastereomers: 53:47 dr (determined by Gas Chromatography).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99-7.95 (m, 2H, two diastereomers), 7.93-7.90 (m, 2H, two diastereomers), 7.72-7.64 (m, 2H, two diastereomers), 7.60-7.53 (m, 4H, two diastereomers), 5.67 (dd, $^3J_{H-H}$ = 9.6, 2.0 Hz, 0.53H, major diastereomer), 5.52 (dd, $^3J_{H-H}$ = 9.2, 2.4 Hz, 0.47H, minor diastereomer), 2.70 (ddd, $^3J_{H-H}$ = 11.2, 4.0, 0.8 Hz, 0.53H, major diastereomer), 2.64 (ddd, $^3J_{H-H}$ = 11.2, 4.0, 1.2 Hz, 0.47H, minor diastereomer), 2.36-2.21 (m, 2H, two diastereomers), 2.18-1.99 (m, 2H, two diastereomers), 1.74-1.70 (m, 1H, two diastereomers), 1.60-1.53 (m, 2H, two diastereomers), 1.12 (s, 1.41H, minor diastereomer), 0.98 (t, $^3J_{H-H}$ = 7.6 Hz, 1.59 H, major diastereomer), 0.88-0.80 (m, 2.41H), 0.75 (s, 1.59H, major diastereomer) ppm

^{13}C NMR (133 MHz, $CDCl_3$) δ 220.3, 220.2, 138.2, 138.2, 138.1, 137.9, 134.7, 134.7, 134.5, 134.5, 129.9, 129.9, 129.5, 129.5, 129.2, 129.2, 12.2, 12.1, 79.6, 79.5, 56.6, 54.5, 43.1, 42.7, 35.2, 35.2, 33.2, 31.8, 31.1, 26.3, 24.8, 21.4, 20.9, 19.2, 8.6, 8.5 ppm. (mixture of diastereomers)

HRMS: Expected formula (C_{22} H_{26} O_5 S_2) Observed *m/z* $[M+H]^+$ 435.1292; Expected *m/z* (amu) 435.1294 (-0.5 ppm).

2-(2,2-bis(phenylsulfonyl)ethyl)-3-methylcyclohexan-1-one. <u>14ba(trimethylaluminum)</u>



A flame-dried Schlenk flask was respectively charged with Phosphoramidite (0.015 equiv., 48 mg, 0.075 mmol) and copper thiophene-2-carboxylate (0.001 equiv., 9.5 mg, 0.005 mmol). Dry diethyl ether (3 mL) was added and the solution was stirred under argon at room temperature for 20 minutes before being cooled down to -30 °C. To this, trimethylaluminium (2 M in heptane, 1.4 equiv., 3.5 mL, 7 mmol) was added and allowed to react over 10 minutes, then cyclohexenone (1 equiv., 0.48 mL, 5 mmol) was added neat over 1 minute. After 2 hours, the enantioselectivity of the 1,4-adduct was controlled using chiral Gas Chromatgraphy (Hydrodex-β-TBDMS, 40°C-5min-1°C/min until 90°C, RT: 41.8 min (*R*), 43.1 min (*S*), 96% ee (*R*)) them, methyllithium (1.6 M in diethyl ether, 1.4 equiv., 4.4 mL, 7 mmol) was added slowly over 5 minutes and allowd to react 30 minutes. To this, 1,1-bis(phenylsulfonyl)ethane (1.5 equiv., 2.32 g, 7.5 mmol, in solution in dichloromethane (15 mL)) was added over 5 minutes and the resulting mixture was allowed to stir at -30°C for 15 hours. The reaction was quenched with a 2 M solution of hydrochloric acid. The desired organic material was extracted with dichloromethane (three times). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. Silica gel flash chromatography (Pentane/ethyl acetate 80%) afforded the pure product in 82% yield.

Mixture of diastereomers: 95:5 dr (determined by Gas Chromatography).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.98-7.88 (m, 4H), 7.72-7.64 (m, 2H), 7.60-7.53 (m, 4H), 5.12 (dd, $^3J_{H-H}$ = 10.8, 2.6 Hz, 1H), 2.88 (td, $^3J_{H-H}$ = 10.6, 3.0 Hz, 1H), 2.41-2.17 (m, 5H), 2.05-1.97 (m, 1H), 1.84-1.80 (m, 1H), 1.64-1.47 (m, 2H), 1.08 (d, $^3J_{H-H}$ = 5.9 Hz, 3H) ppm.

^{13}C NMR (133 MHz, $CDCl_3$) δ 212.8, 138.3, 138.0, 134.6, 134.3, 131.1, 129.9, 129.6, 129.1, 129.0, 128.9, 80.9, 53.6, 41.9, 40.7, 34.2, 26.2, 23.8, 20.3 ppm.

$[\alpha]_D$ +6.6 (c 0.75, $CHCl_3$).

HRMS: Expected formula ($C_{21}H_{24}O_5S_2$) Observed *m/z* $[M+H]^+$ 421.1150; Expected *m/z* (amu) 421.1138 (2.9 ppm).

2-(2,2-bis(phenylsulfonyl)ethyl)-3-ethylcyclohexan-1-one. 14ba(dimethylzinc)

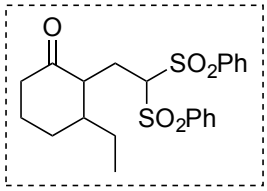
See **14bb** for the experimental procedure et **14ba(trimethylaluminum)** for characterization.

67% yield.

83:17 dr.

93% ee.

2-(2,2-bis(phenylsulfonyl)ethyl)-3-ethylcyclohexan-1-one. 14bb(diethylzinc)



A flame-dried schlenk tube was respectively charged with Phosphoramidite (0.03 equiv., 8 mg, 0.015 mmol) and copper thiophene-2-carboxylate (0.02 equiv., 1.9 mg, 0.01 mmol). Dry diethyl ether (4 mL) is added and the solution was stirred under argon at room temperature for 20 minutes and 10 minutes at -30 °C. To this, diethylzinc (1 M in hexane, 1 equiv., 1 mL, 0.5 mmol) was added and allowed to react over 10 minutes, then cyclohexenone (1 equiv., 0.048 mL, 0.5 mmol) was added over 1 minute. After 1 hour, the enantioselectivity of the 1,4-adduct was controlled using chiral Gas Chromatgraphy (Lipodex E, 70°C isothermal, RT = 9.0 min (*R*), 10.2 min (*S*), >99.5% ee (*R*)). 1,1-bis(phenylsulfonyl)ethane (1 equiv., 154 mg, 0.5 mmol, in solution in dichloromethane (1 mL)) was then added and the resulting mixture was allowed to stir at -30°C for 3 hours. The reaction was quenched with a 2 M solution of hydrochloric acid. The desired organic material was extracted with dichloromethane (three times). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. Silica gel flash chromatography (Pentane/ethyl acetate 80%) afforded the pure product in 75% yield.

Mixture of diastereomers: 88:12 dr (determined by Gas Chromatography).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.96-7.86 (m, 4H), 7.69-7.65 (m, 2H), 7.57-7.54 (m, 4H), 5.15 (dd, $^3J_{H-H}$ = 4.0, 4.0 Hz, 1H), 1.74 (td, $^3J_{H-H}$ = 12.0, 4.0 Hz, 1H), 2.38-2.29 (m, 4H), 2.18-2.02 (m, 1H), 1.92-1.75 (m, 2H), 1.62-1.32 (m, 4H), 0.94 (t, $^3J_{H-H}$ = 8 Hz, 3H) ppm.

^{13}C NMR (133 MHz, $CDCl_3$) δ 213.4, 138.3, 138.2, 129.7, 129.1, 129.1, 129.0, 80.7, 51.6, 46.3, 41.8, 29.5, 25.9, 25.8, 23.9, 10.3 ppm.

$[\alpha]_D$ -181 (c 1.0, $CHCl_3$).

HRMS: Expected formula ($C_{22}H_{26}O_5S_2$) Observed *m/z* [M] 434.12162; Expected *m/z* (amu) 434.12171 (0.21 ppm).

2-(2,2-bis(phenylsulfonyl)ethyl)-3-ethylcyclohexan-1-one. 14b (triethylaluminum)

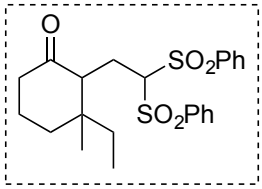
See **14ba** for the experimental procedure et **14bb(diethylzinc)** for characterization.

71% yield.

81:19 dr.

95% ee.

2-(2,2-bis(phenylsulfonyl)ethyl)-3-ethyl-3-methylcyclohexan-1-one. 14c



A flame-dried Schlenk flask was respectively charged with 3-(1-hydroxy-4-methylpentan-2-yl)-1-(2,4,6-trimethylbenzyl)-4,5-dihydro-1*H*-imidazol-3-ium (0.01 equiv., 2.7 mg, 0.006 mmol) and copper triflate (0.0075 equiv., 1.6 mg, 0.0045 mmol). Dry diethyl ether (2 mL) was added and the solution was stirred under argon at room temperature for 10 minutes and 10 minutes at -10 °C. To this, ethylmagnesium bromide (3 M in diethyl ether, 1.2 equiv., 0.26 mL, 0.72 mmol) was added and allowed to react over 30 minutes. 3-methylcyclohexenone (1 equiv., 66.6 mg, 0.6 mmol, in solution in diethyl ether (4 mL)) was added over 15 minutes. After 2 hours, 1,1-bis(phenylsulfonyl)ethane (1.2 equiv., 222 mg, 0.72 mmol, as a solution in dichloromethane 2 mL) was added and the resulting mixture was allowed to stir at -10°C for 2 hours. The reaction was quenched with a 1 M solution of hydrochloric acid. The desired organic material was extracted with diethyl ether (three times). The organic phase was eventually washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude mixture was purified by silica gel flash chromatography (Petroleum ether/diethylether 90% to 50%) to afford white solid in yield 85%.

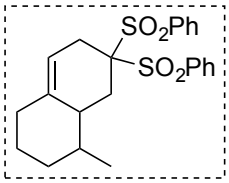
Mixture of diastereomers: 53:47 dr (determined by Gas Chromatography).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.83 (m, 4H, two diastereomers), 7.69-7.65 (m, 2H, two diastereomers), 7.57-7.53 (m, 4H, two diastereomers), 4.95 (dd, $^{3}J_{H\text{-}H}$ = 10.4, 2.4 Hz, 0.53H, major diastereomer), 4.80 (dd, $^{3}J_{H\text{-}H}$ = 10.8, 2.4 Hz, 0.47H, minor diastereomer), 3.13 (t, $^{3}J_{H\text{-}H}$ = 11.6 Hz, 1H), 2.52 (ddd, $^{3}J_{H\text{-}H}$ = 14.4, 11.6, 2.4 Hz, 0.47H, minor diatereomer), 2.38 (ddd, $^{3}J_{H\text{-}H}$ = 14.4, 11.2, 2.4 Hz, 0.53H, major diatereomer), 2.29-2.27 (m, 2H, two diastereomers), 2.22-2.10 (m, 1H, two diastereomers), 1.95-1.85 (m, 1H, two diastereomers), 1.81-1.68 (m, 2H, two diastereomers), 1.53-1.34 (m, 2H, two diastereomer), 1.2-0.99 (m, 2.41H, minor diastereomer), 0.96 (t, $^{3}J_{H\text{-}H}$ = 7.6 Hz, 1.59 H, major diastereomer), 0.76 (t, $^{3}J_{H\text{-}H}$ = 7.2 Hz, 1.41H, minor diastereomer), 0.64 (s, 1.59H, major diastereomer) ppm

^{13}C NMR (133 MHz, $CDCl_3$) δ 213.7, 212.8, 138.7, 138.4, 138.3, 134.8, 134.7, 134.5, 130.0, 129.8, 129.7, 129.3, 129.2, 129.1, 81.6, 81.0, 58.0, 54.4, 42.9, 42.4, 41.6, 41.5, 35.3, 34.9, 33.6, 25.1, 24.8, 22.6, 22.2, 20.9, 20.7, 19.6, 7.9, 7.3 ppm. (mixture of diastereomers)

HRMS: Expected formula (C_{23} H_{29} O_5 S_2) Observed *m/z* $[M+H]^+$ 449.1457; Expected *m/z* (amu) 449.1451 (1.4 ppm).

4-methyl-6,6-bis(phenylsulfonyl)-1,2,3,4,4a,5,6,7-octahydronaphthalene. 15



A flame-dried schlenk tube, 2-(2,2-bis(phenylsulfonyl)ethyl)-3-methylcyclohexan-1-one (1equiv., 84 mg, 0.2 mmol) was added portionwise at 0°C to a suspension of sodium hydride (1.1 equiv, 9 mg, 0.22 mmol) and dry dimethylformamide (1 mL). The resulting mixture was stirred 5 further minutes at 0°C and 10 minutes to room temperature. After this, triphenylphosphonium bromide (1.05 equiv., 75 mg, 0.21 mmol) was also added portionwise and dimethylformamide (1 mL) was used to dilute the reaction media. The reaction was allowed to proceed during 13 hours, to be eventually quenched with ammoniun chloride. The crude was extracted with dichloromethane. The organic layers was washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The desired product was isolated after silica gel flash chromoatography (Petroleum ether/Ethyl acetate 90% to 60%) to afford a white solid in 76% yield.

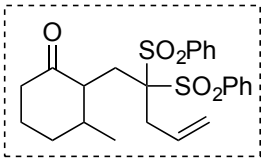
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (ddd, $^{3}J_{H\text{-}H}$ = 21.4, 8.4, 1.2 Hz, 4H), 7.73 (dtt, $^{3}J_{H\text{-}H}$ = 17.2, 7.6, 1.2 Hz, 2H), 7.62 (t, $^{3}J_{H\text{-}H}$ = 8.4 Hz, 2H), 7.55 (t, $^{3}J_{H\text{-}H}$ = 8Hz, 2H), 5.13 (dt, $^{3}J_{H\text{-}H}$ = 5.4, 2.2 Hz, 1H), 3.06 (dq, $^{3}J_{H\text{-}H}$ = 18.7, 2.8 Hz, 1H), 2.73 (ddd, $^{3}J_{H\text{-}H}$ = 13.8, 6.2, 2.5 Hz), 2.64 (ddq, $^{3}J_{H\text{-}H}$ = 18.5, 5.6, 2.4 Hz, 1H), 2.12 (m, 2H), 1.80 (m, 1H), 1.70 (m, 2H), 1.27 (m, 2H), 1.13 (m, 2H), 0.93 (d, $^{3}J_{H\text{-}H}$ = 5.6 Hz, 3H) ppm

^{13}C NMR (133 MHz, $CDCl_3$) δ 140.2, 137.6, 136.7, 134.5, 134.5, 131.7, 130.8, 128.7, 128.6, 113.3, 88.4, 40.9, 40.6, 35.3, 34.9, 29.9, 26.5, 26.3, 20.1 ppm.

$[\alpha]_D$ -89.6 (c 0.5, $CHCl_3$).

HMRS: Expected formula (C_{23} H_{26} O_4 S_2) Observed *m/z* $[M+NH_4]^+$ 448.1610; Expected *m/z* (amu) 448.1611 (-0.1 ppm).

2-(2,2-bis(phenylsulfonyl)pent-4-en-1-yl)-3-methylcyclohexan-1-one. 16



To a solution of 2-(2,2-bis(phenylsulfonyl)ethyl)-3-methylcyclohexan-1-one (1equiv., 84 mg, 0.2 mmol) in dry dimethylformamide (1 mL) in a flame-dried shlenk, sodium hydride (1.1 equiv., 9 mg, 0.22 mmol) was added under N_2 at 0°C. The mixture was stirred at 0 °C for 5 minutes and allowed to warm up to room temperature for 5 further minutes. After this, allyl iodide (1.05 equiv., 0.02 mL, 0.21 mmol, in solution in dry dimethylformamide (1 mL)) was added to the reaction mixture and the resulting solution was allowed to react during 13 hours at room temperature. The reaction was quenched with a solution of copper(II) sulfate. After addition of dichloromethane, the organic phase was washed successively with a saturated solution of sodium thiosulfate and brine (three times), dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford a yellow oil. The crude organic material was purified by silica gel flash chromatography (Petroleum ether/Ethyl acetate 90% to 50%) to afford the desired compound in 33% yield.

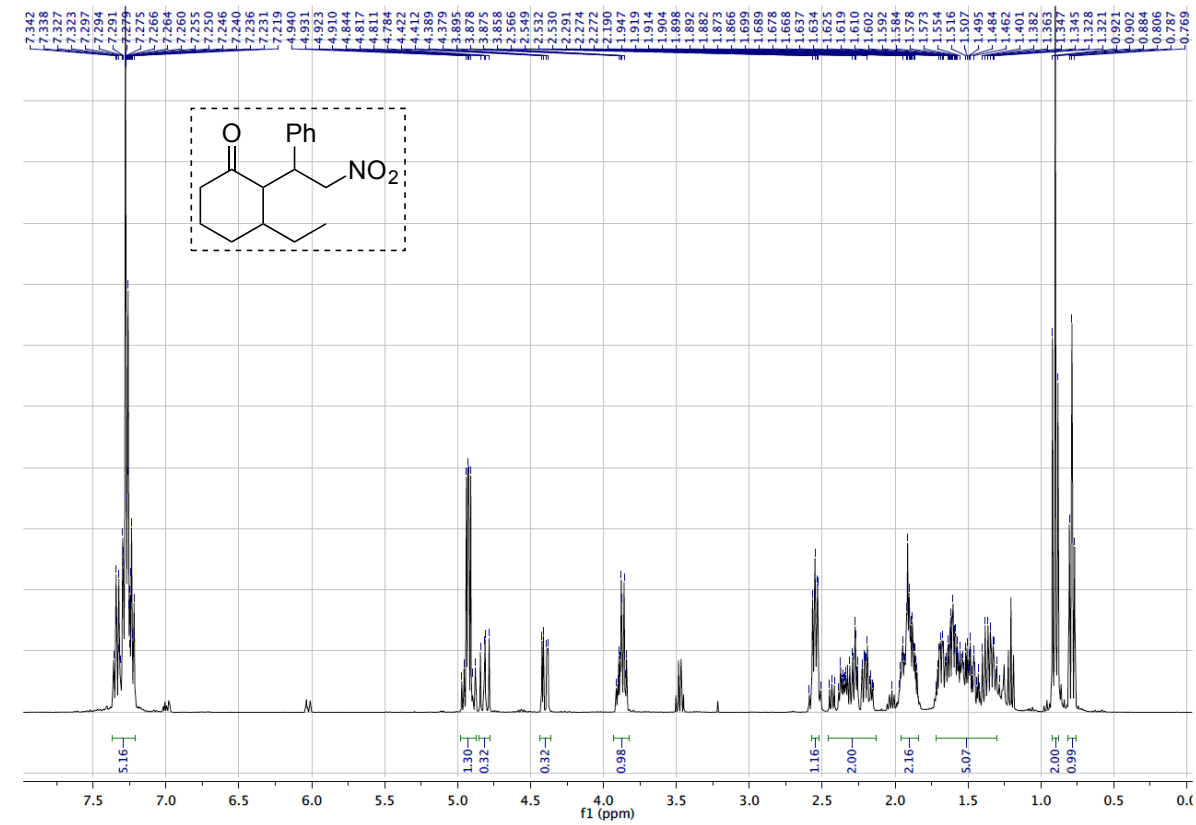
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, $^3J_{H-H}$ = 7.6 Hz, 2H), 7.97 (d, $^3J_{H-H}$ = 7.6 Hz, 2H), 7.75 (q, $^3J_{H-H}$ = 7.6), 7.61 (td, $^3J_{H-H}$ = 8, 2.4 Hz, 4H), 6.19 (dddd, $^3J_{H-H}$ = 17, 10.1, 8.5, 4.5 Hz, 1H), 5.05 (d, $^3J_{H-H}$ = 10 Hz, 1H), 4.93 (d, $^3J_{H-H}$ = 17.1 Hz, 1H), 3.10 (m, 2H), 2.91 (dd, $^3J_{H-H}$ = 15.5, 9 Hz, 1H), 2.68 (dd, $^3J_{H-H}$ = 15.9, 8.6 Hz, 1H), 2.45 (d, $^3J_{H-H}$ = 15.6 Hz, 1H), 2.36 (m, 2H), 2.02 (m, 1H), 1.85 (m, 2H), 1.60 (m, 4H), 1.25 (d, $^3J_{H-H}$ = 6.4 Hz, 3H) ppm

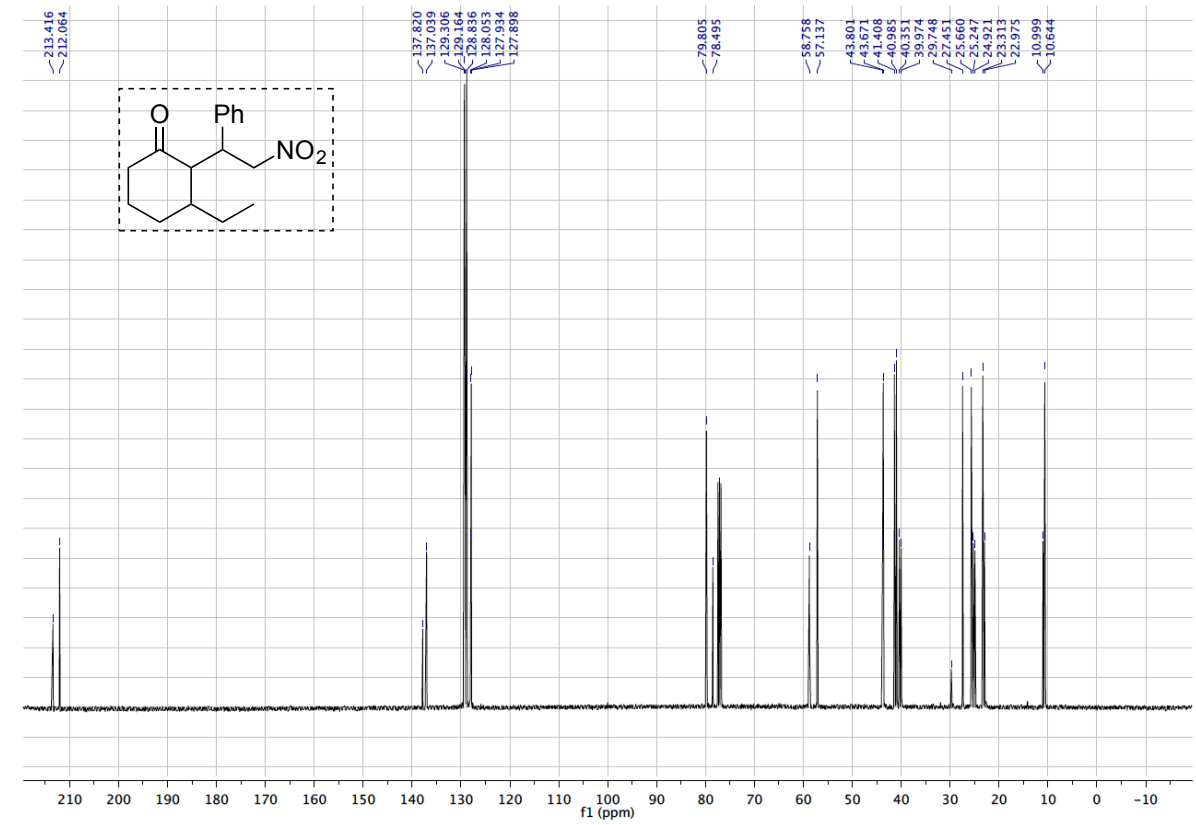
^{13}C NMR (167 MHz, $CDCl_3$) δ 212.8, 138.3, 136.6, 134.8, 134.7, 131.8, 131.6, 131.5, 128.9, 128.7, 119.8, 90.4, 53.4, 41.9, 41.8, 35.4, 34.8, 27.2, 27.2, 20.9 ppm.

$[\alpha]_D$ -167.7 (c 0.5, $CHCl_3$).

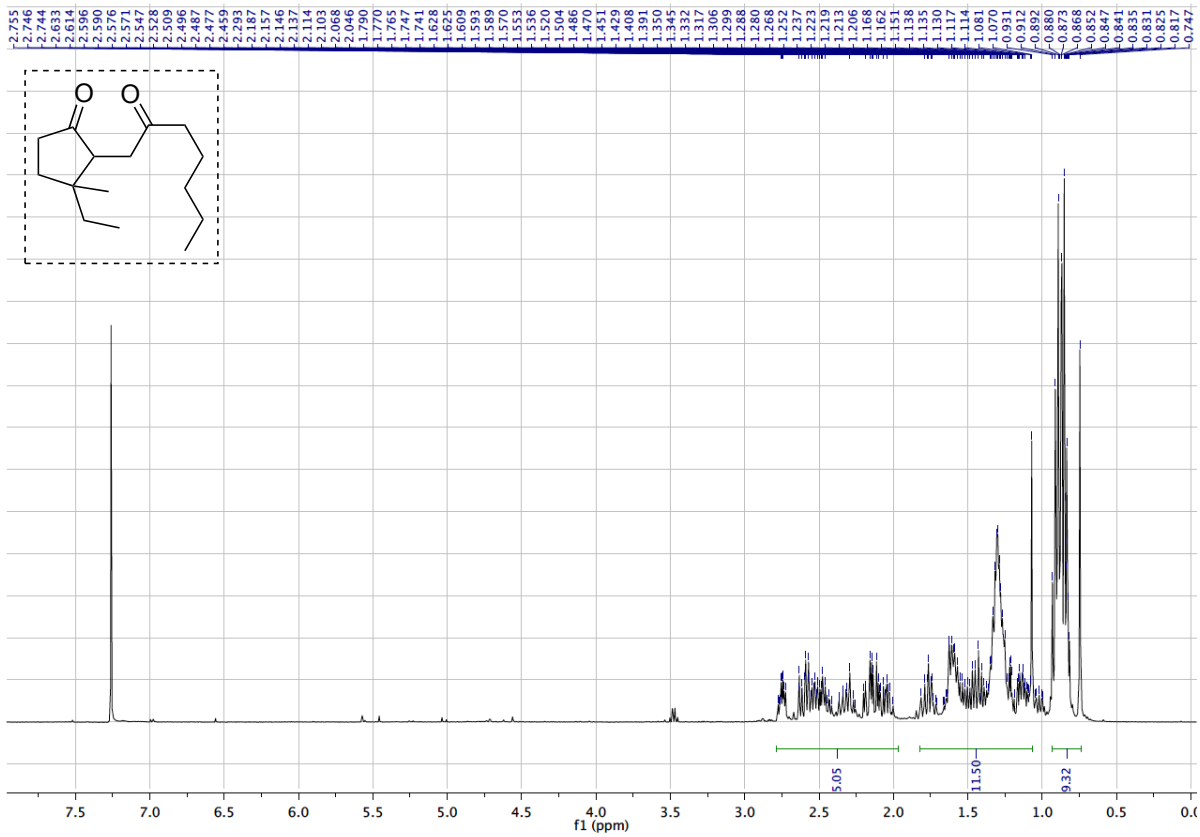
HRMS: Expected formula (C_{24} H_{28} O_5 S_2) Observed *m/z* $[M+H]^+$ 461.1442; Expected *m/z* (amu) 461.1451 (-1.9 ppm).

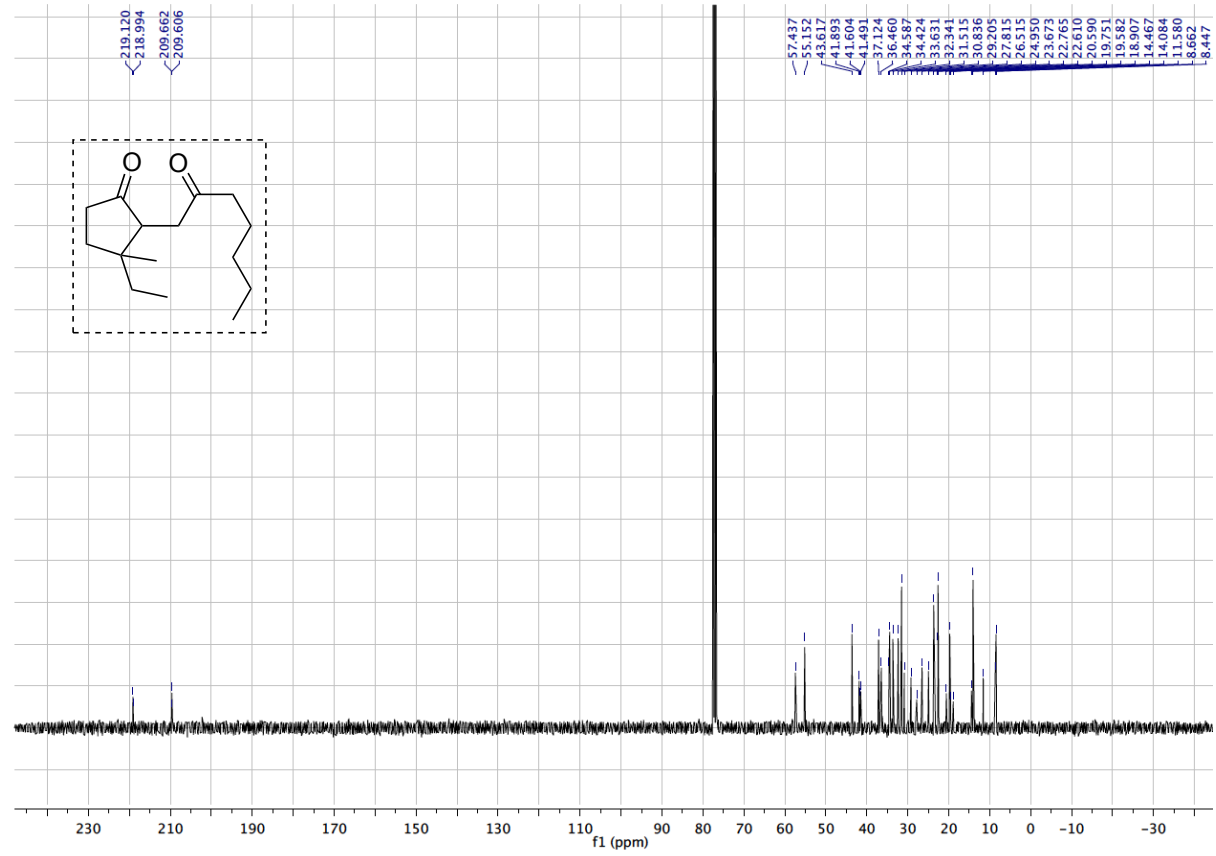
3-ethyl-2-(2-nitro-1-phenylethyl)cyclohexan-1-one. 5



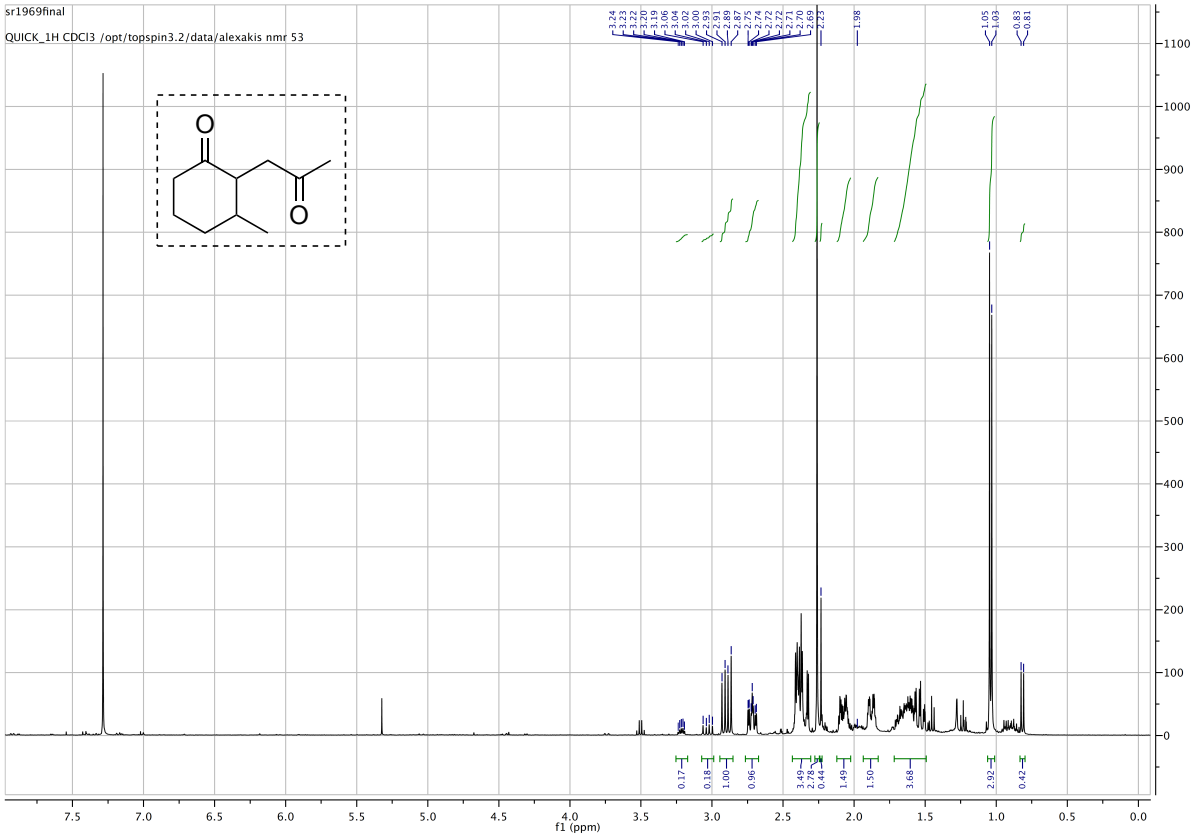


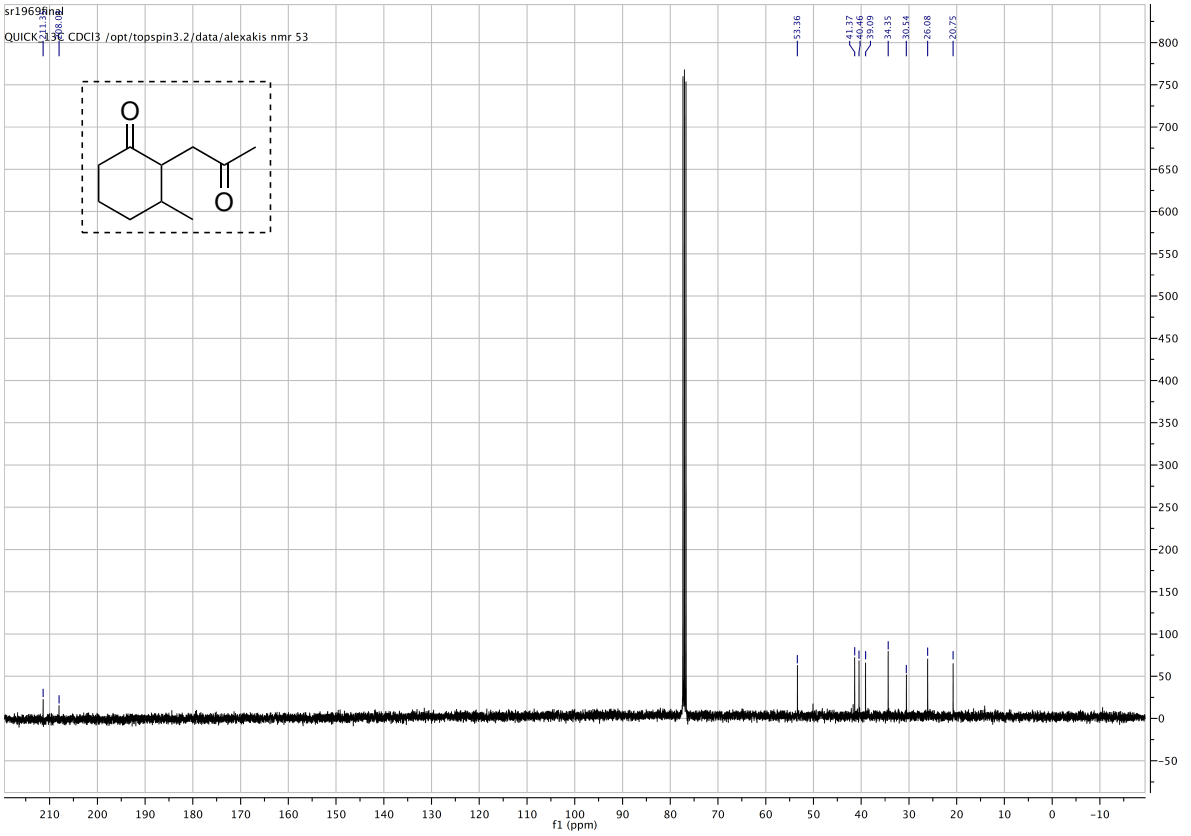
3-ethyl-3-methyl-2-(2-oxoheptyl)cyclopentan-1-one. **7a**



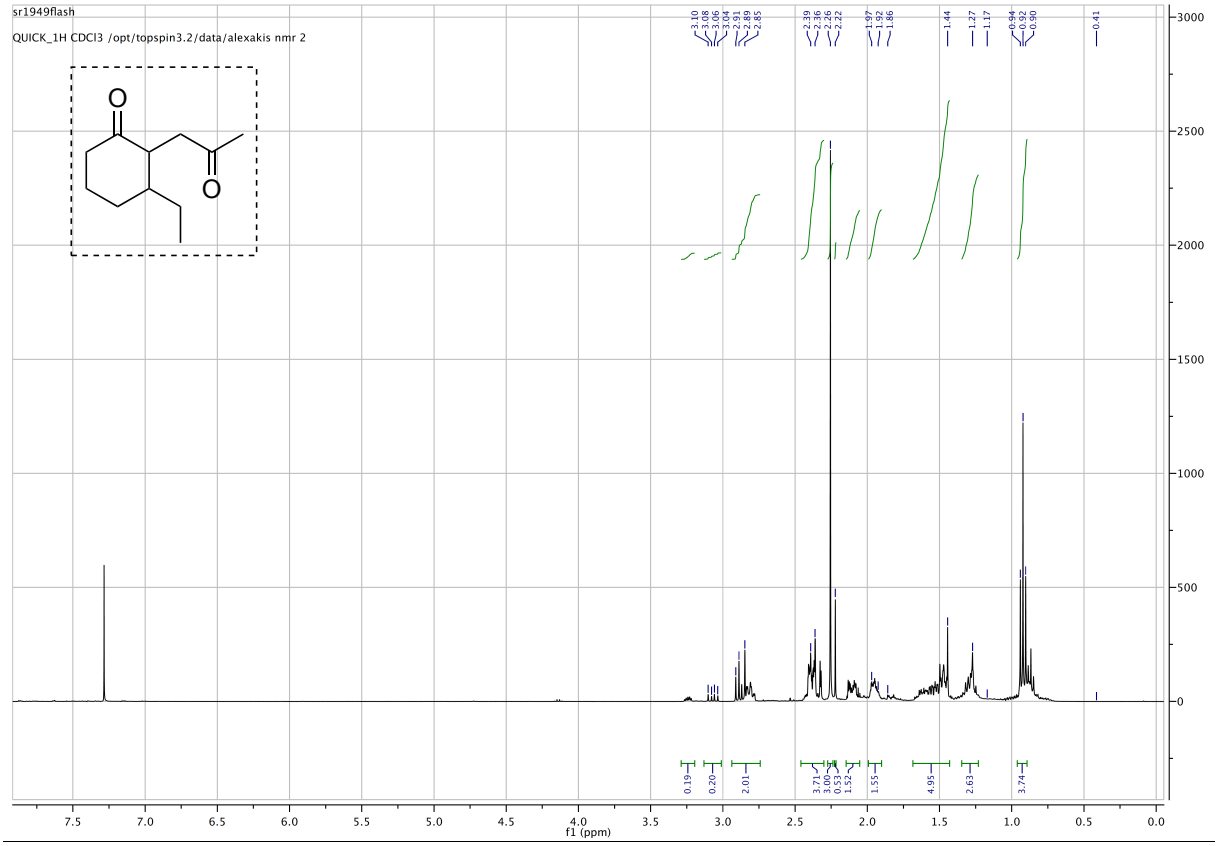


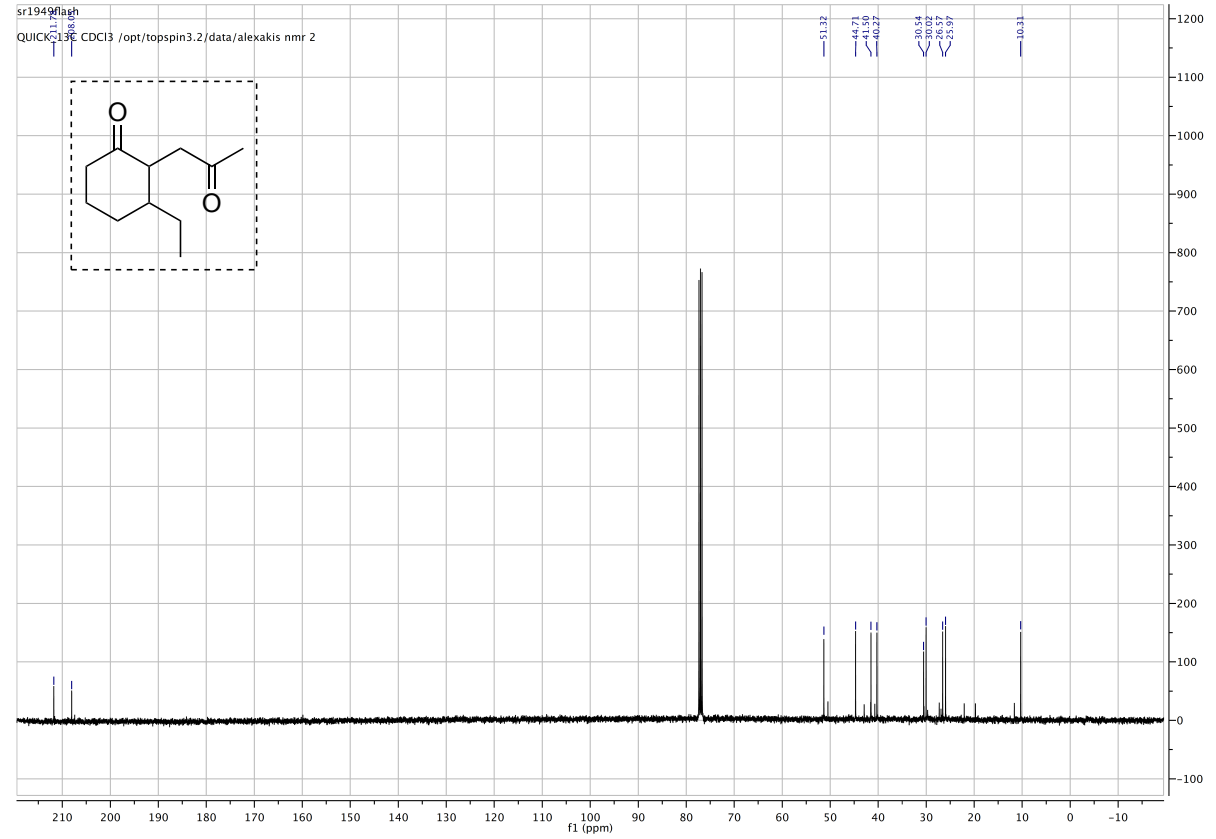
3-methyl-2-(2-oxopropyl)cyclohexan-1-one. 7ba



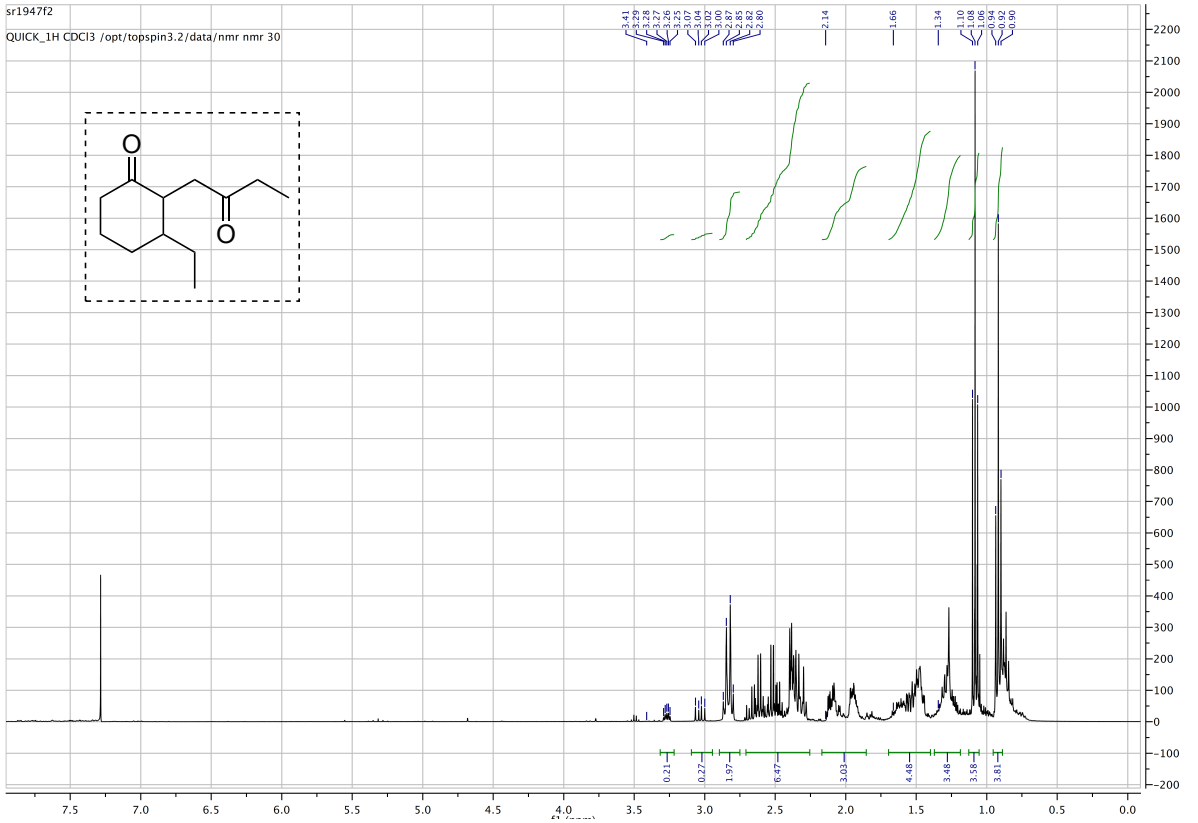


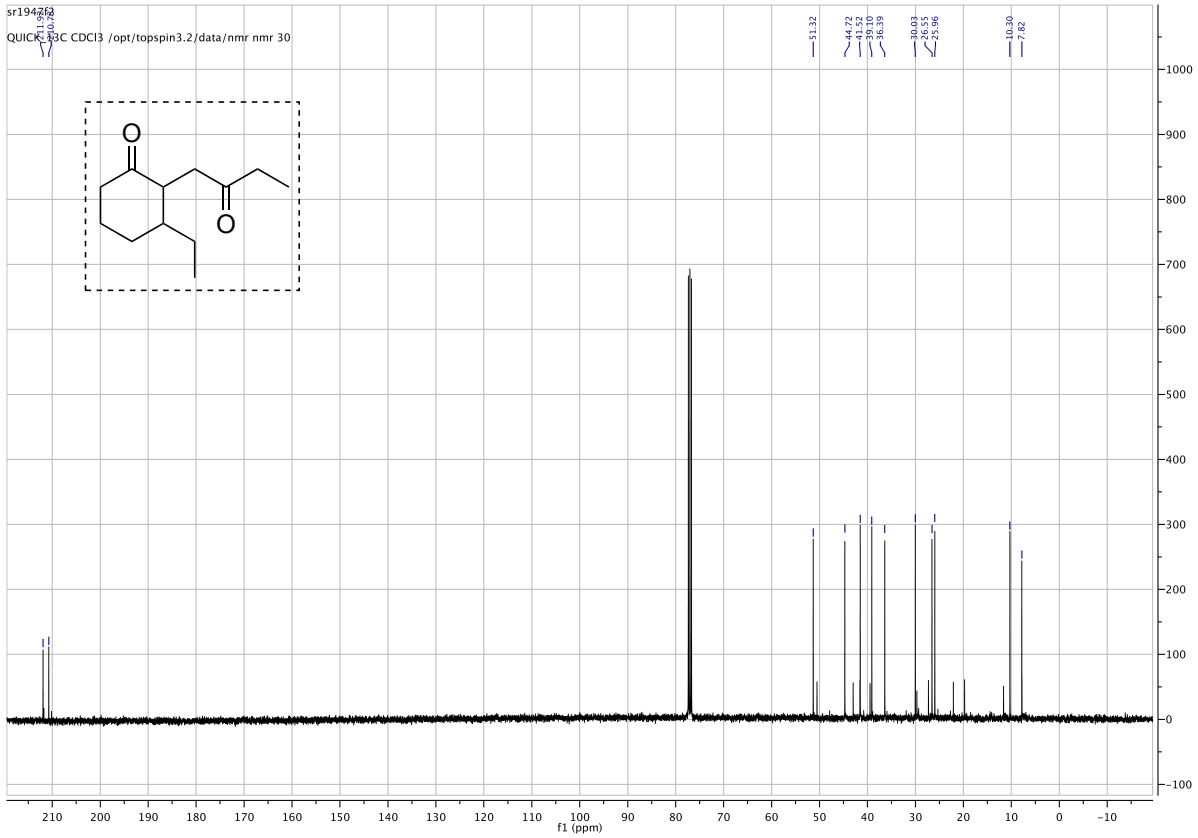
3-ethyl-2-(2-oxopropyl)cyclohexan-1-one. 7bb



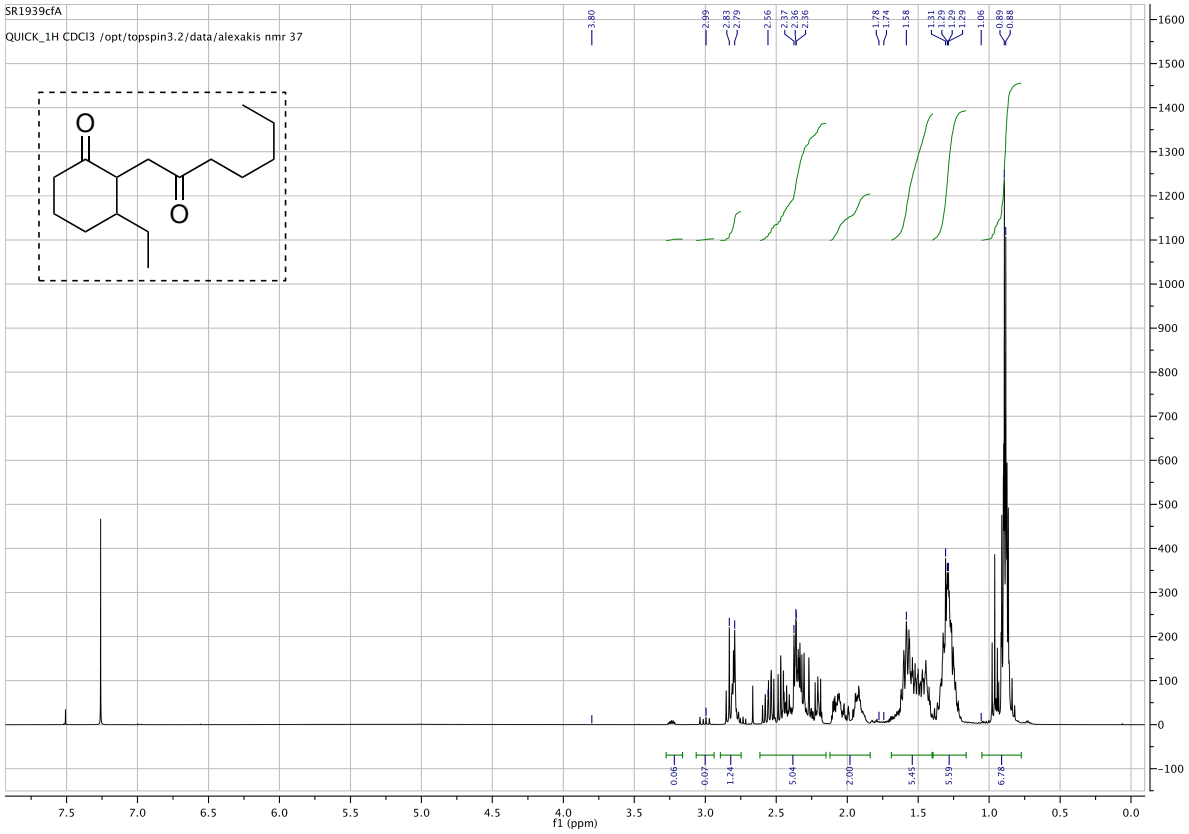


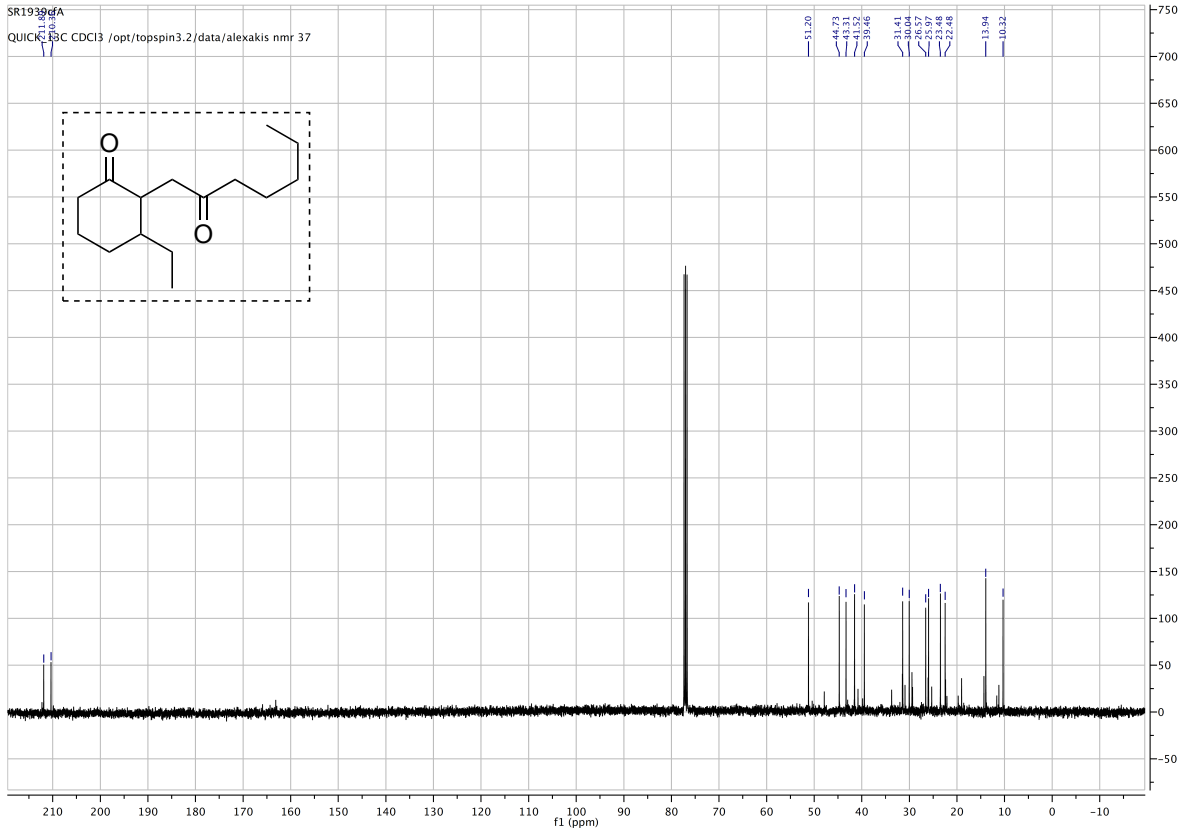
3-ethyl-2-(2-oxobutyl)cyclohexan-1-one. 7bc



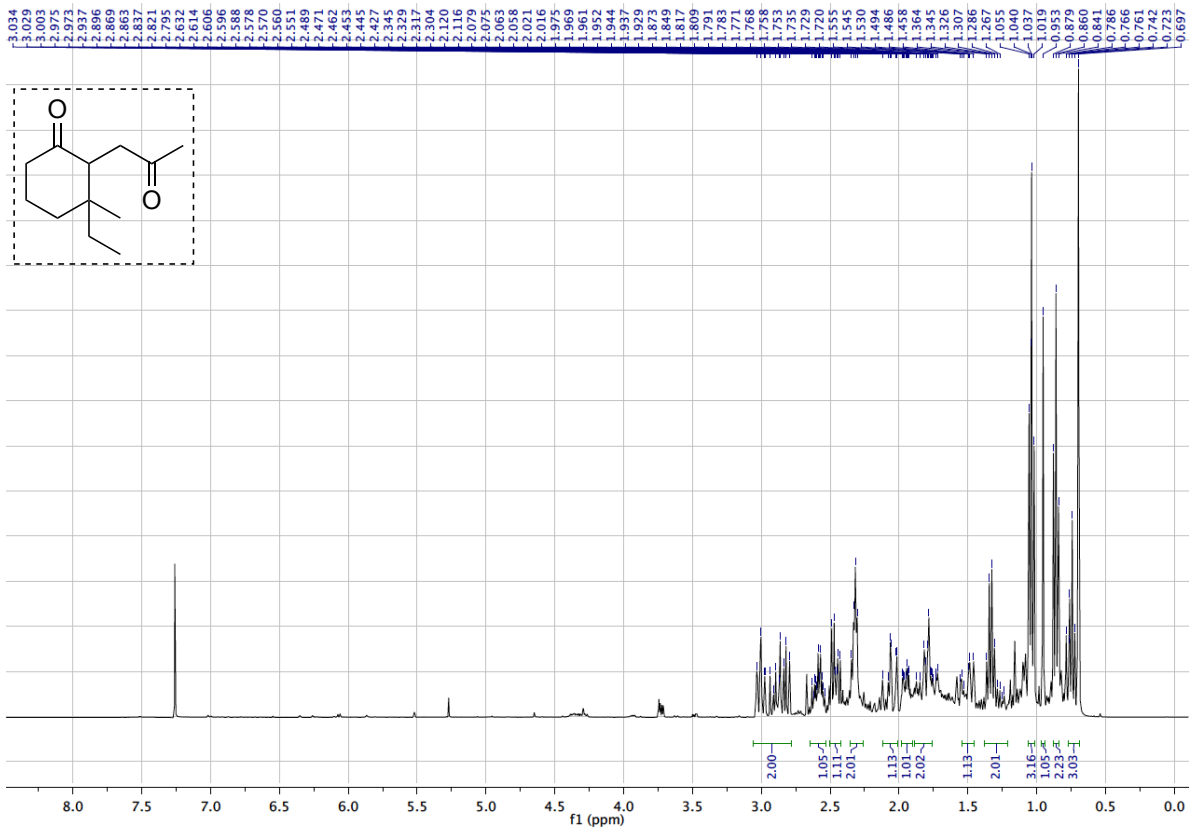


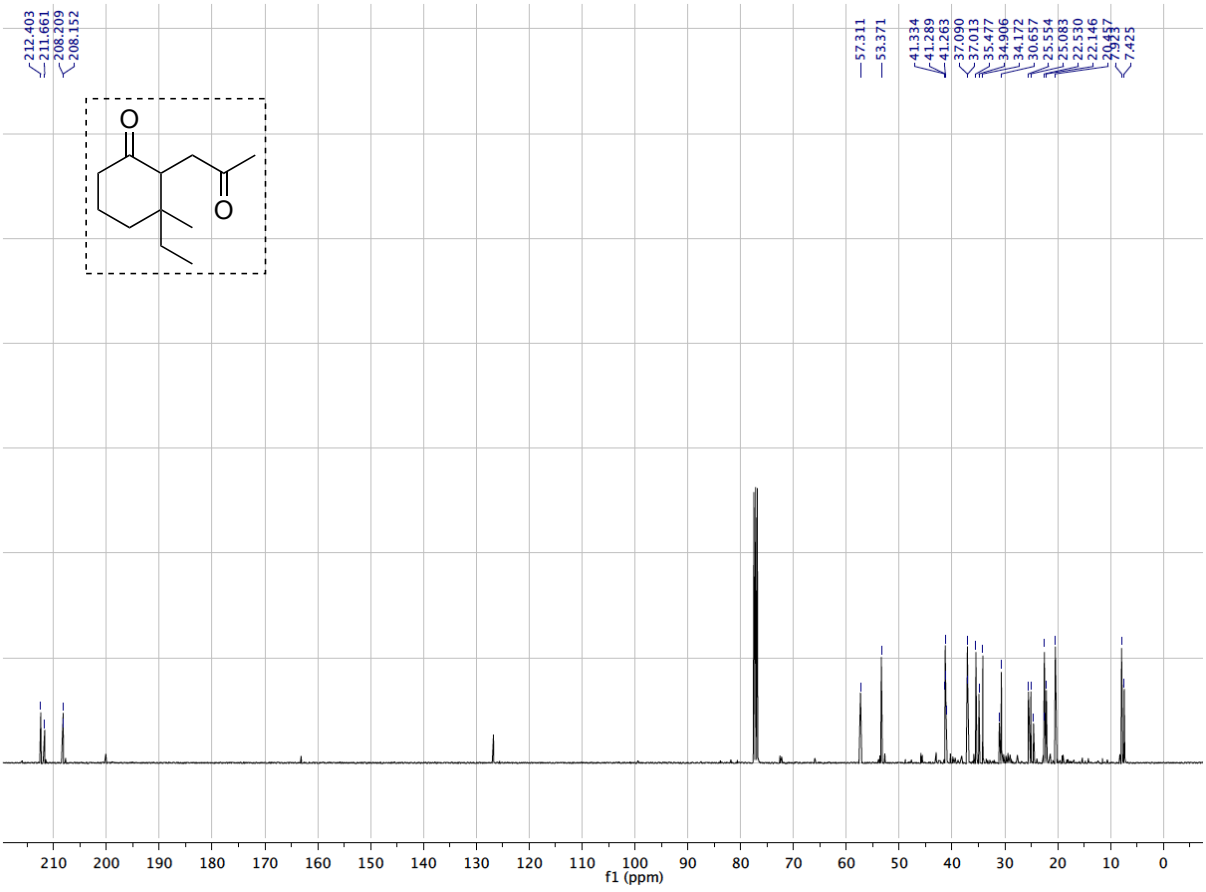
3-ethyl-2-(2-oxoheptyl)cyclohexan-1-one. 7bd



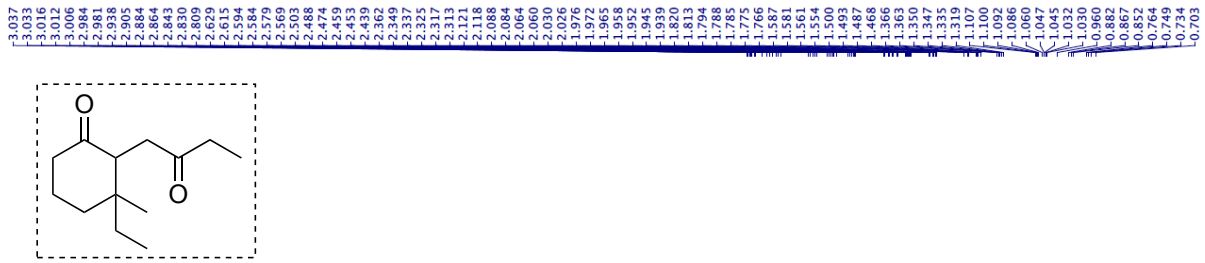


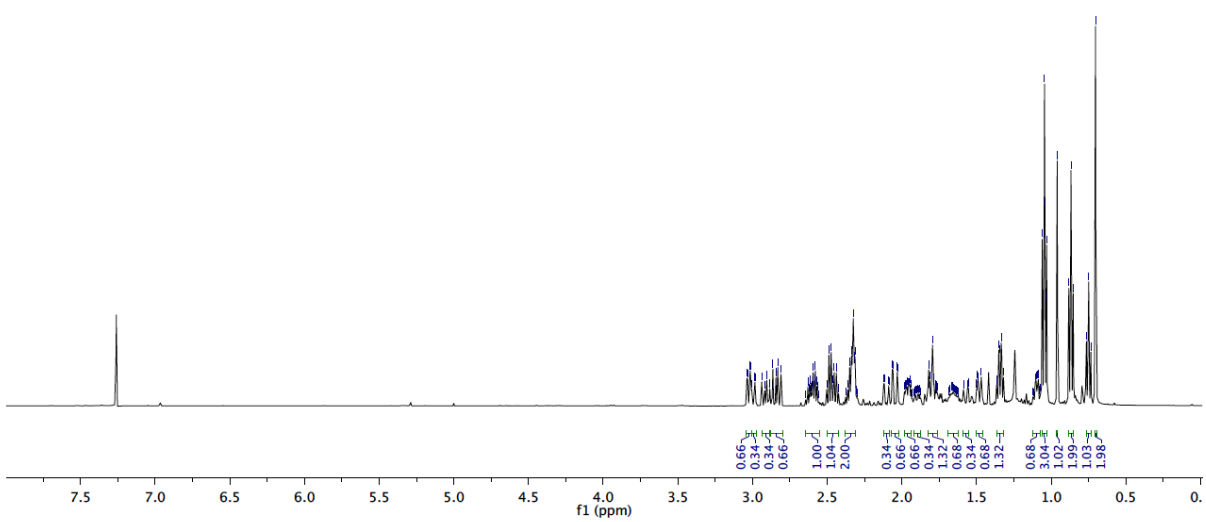
3-ethyl-3-methyl-2-(2-oxopropyl)cyclohexan-1-one. 7ca

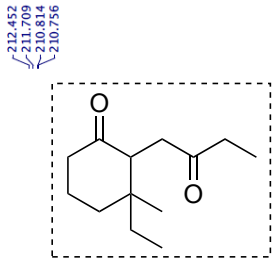




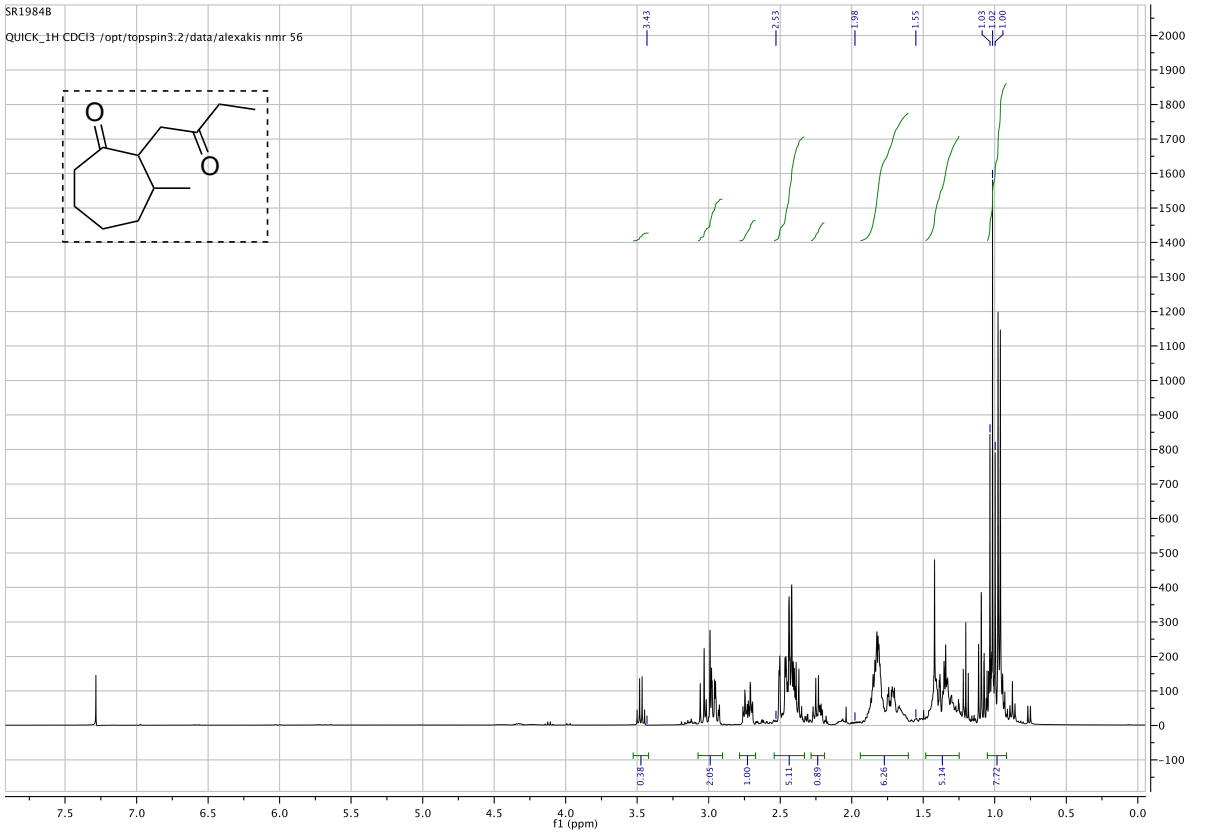
3-ethyl-3-methyl-2-(2-oxobutyl)cyclohexan-1-one. 7cb

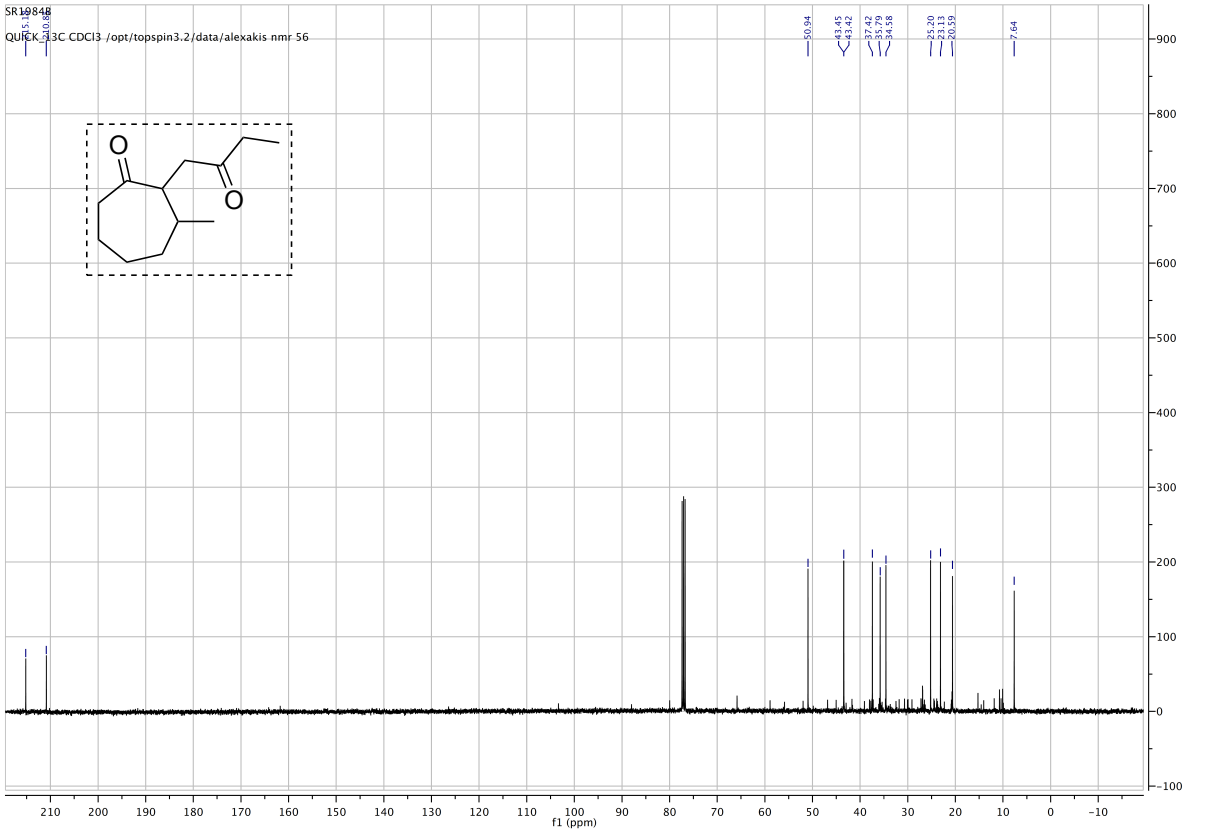




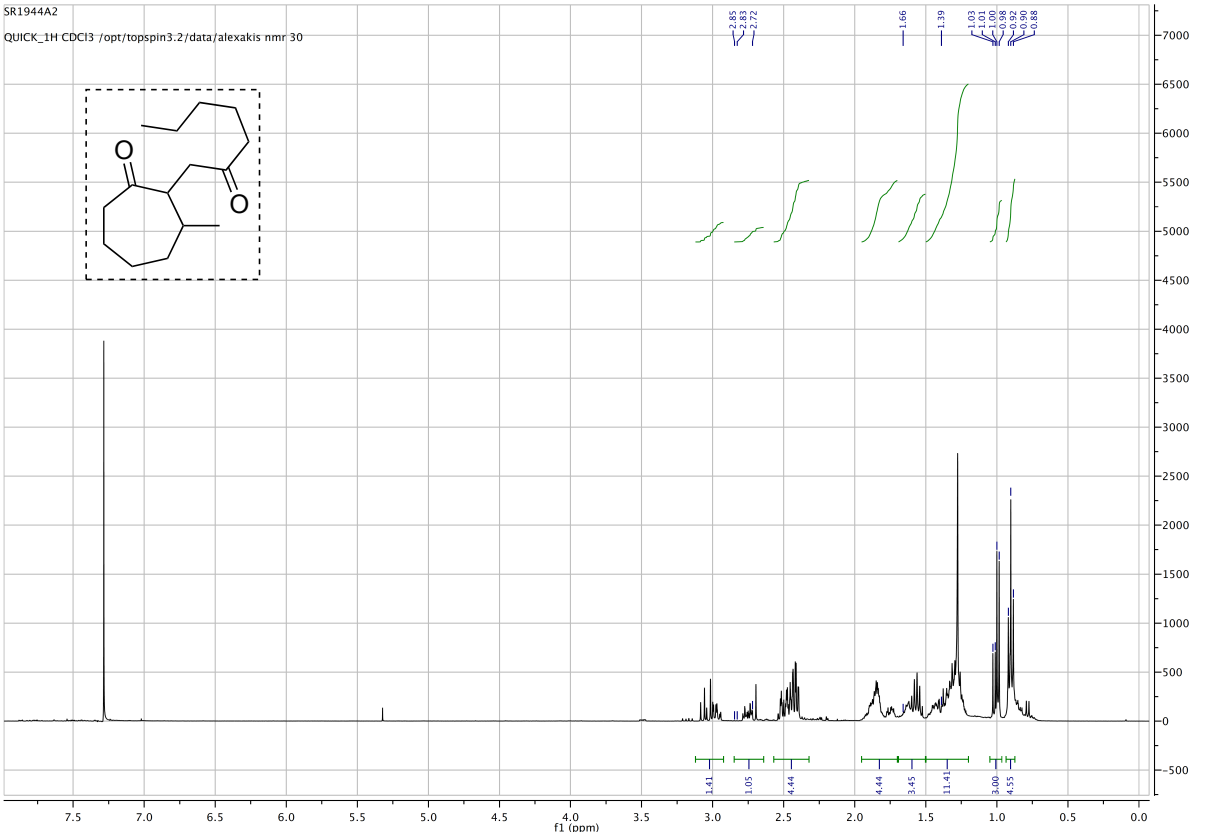


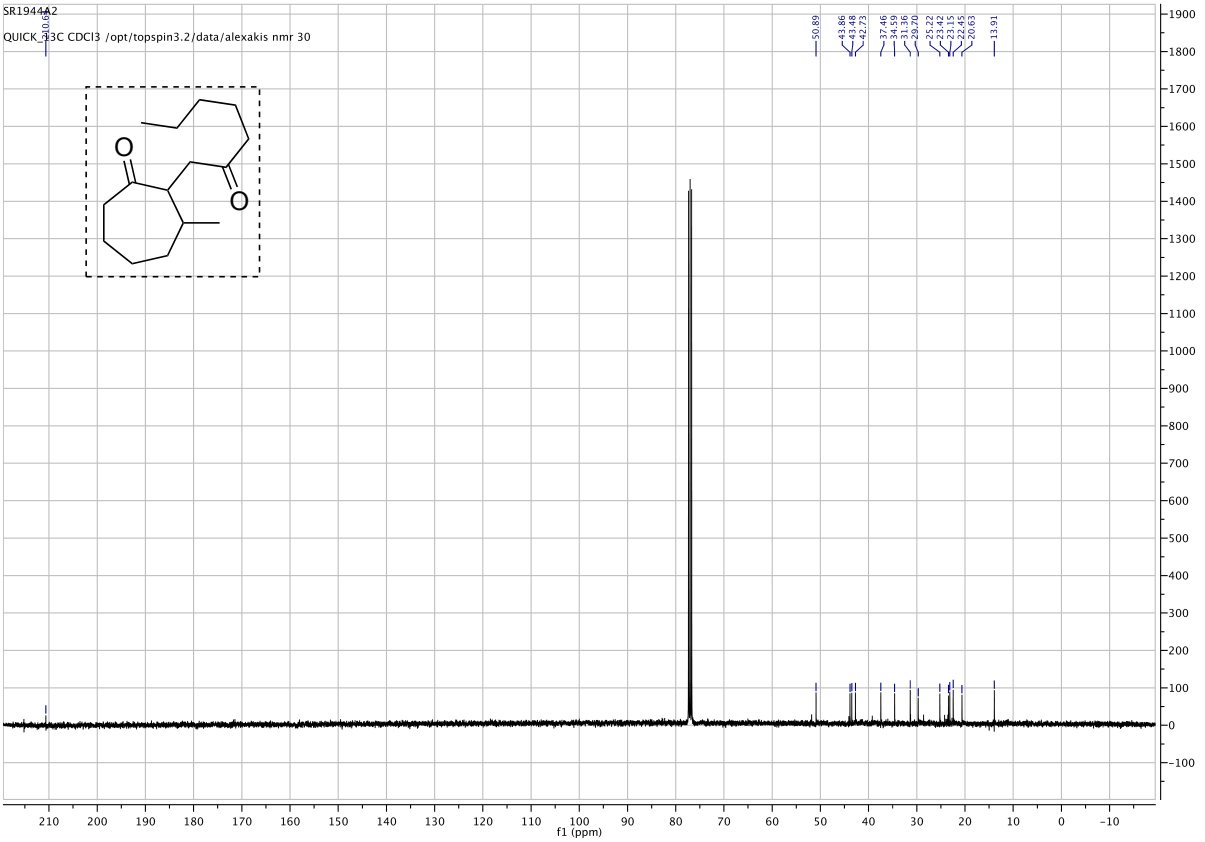
3-methyl-2-(2-oxobutyl)cycloheptan-1-on. 7da



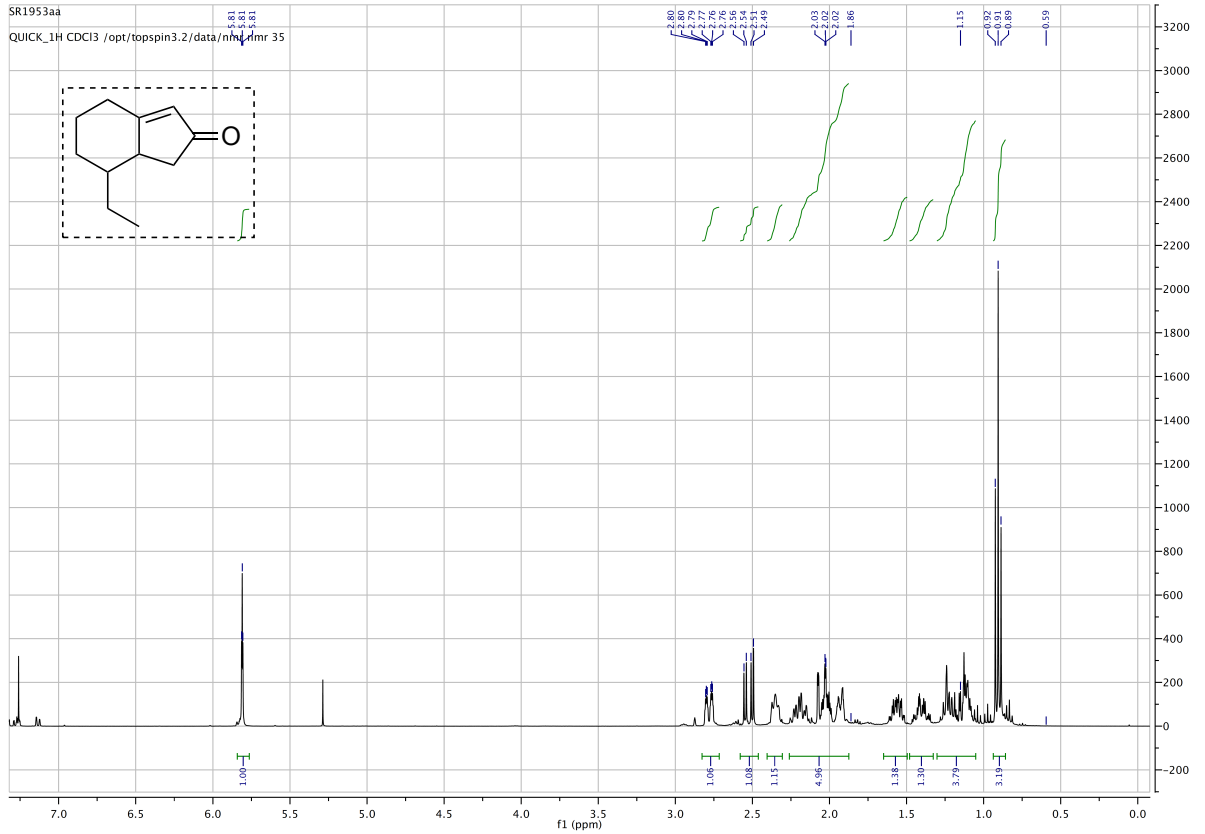


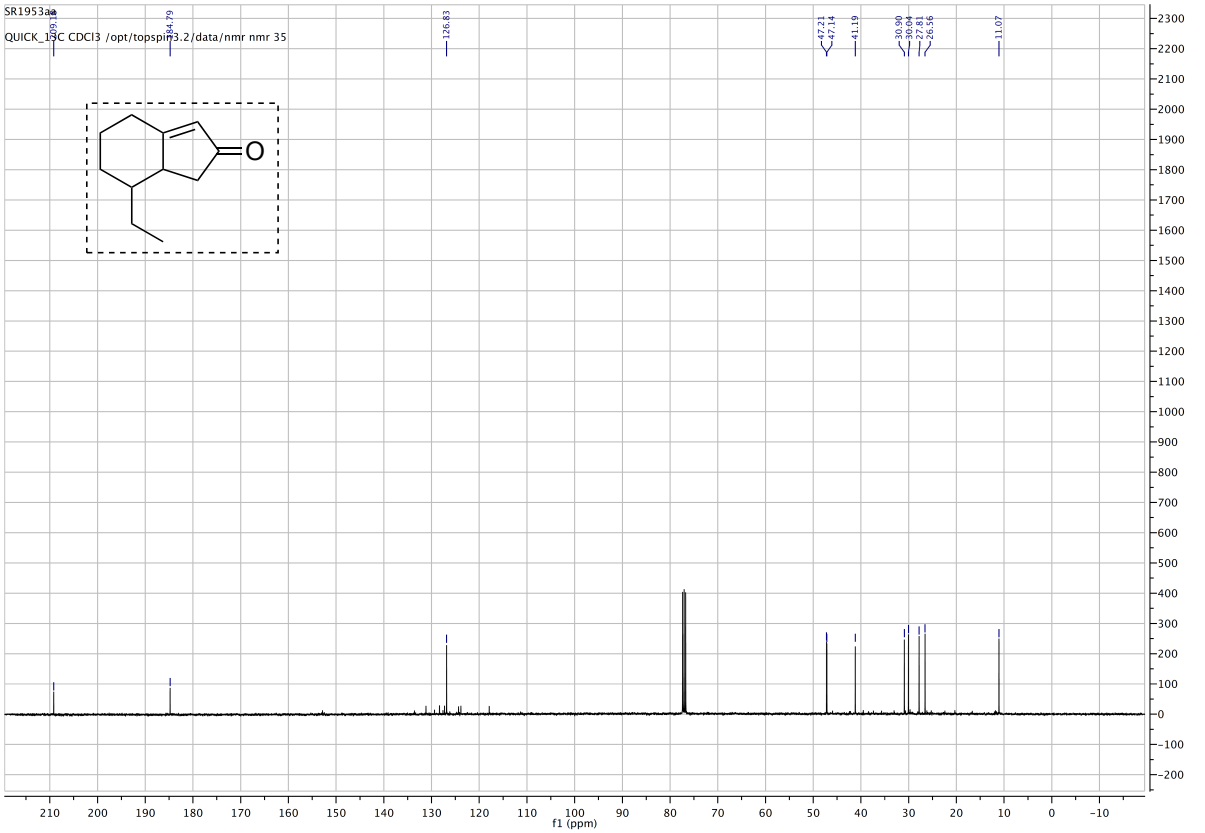
3-methyl-2-(2-oxoheptyl)cycloheptan-1-one. 7db



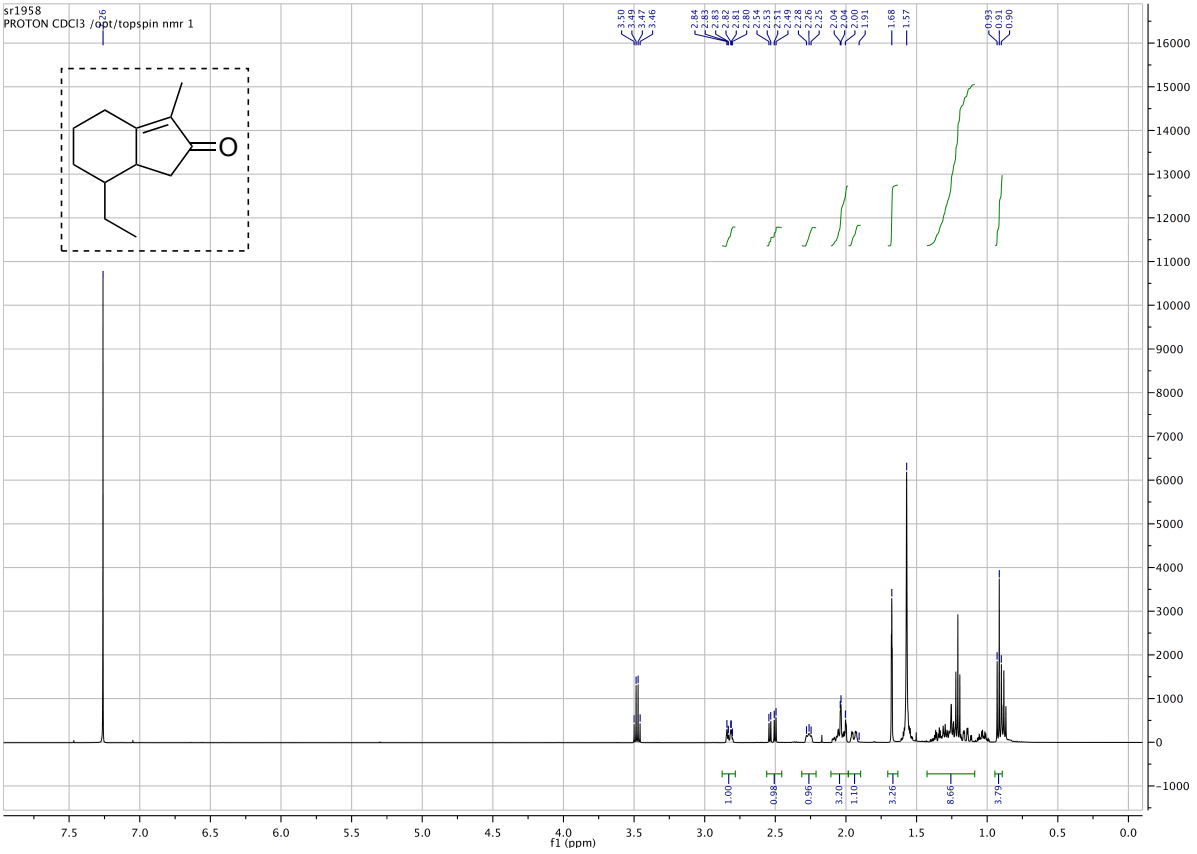


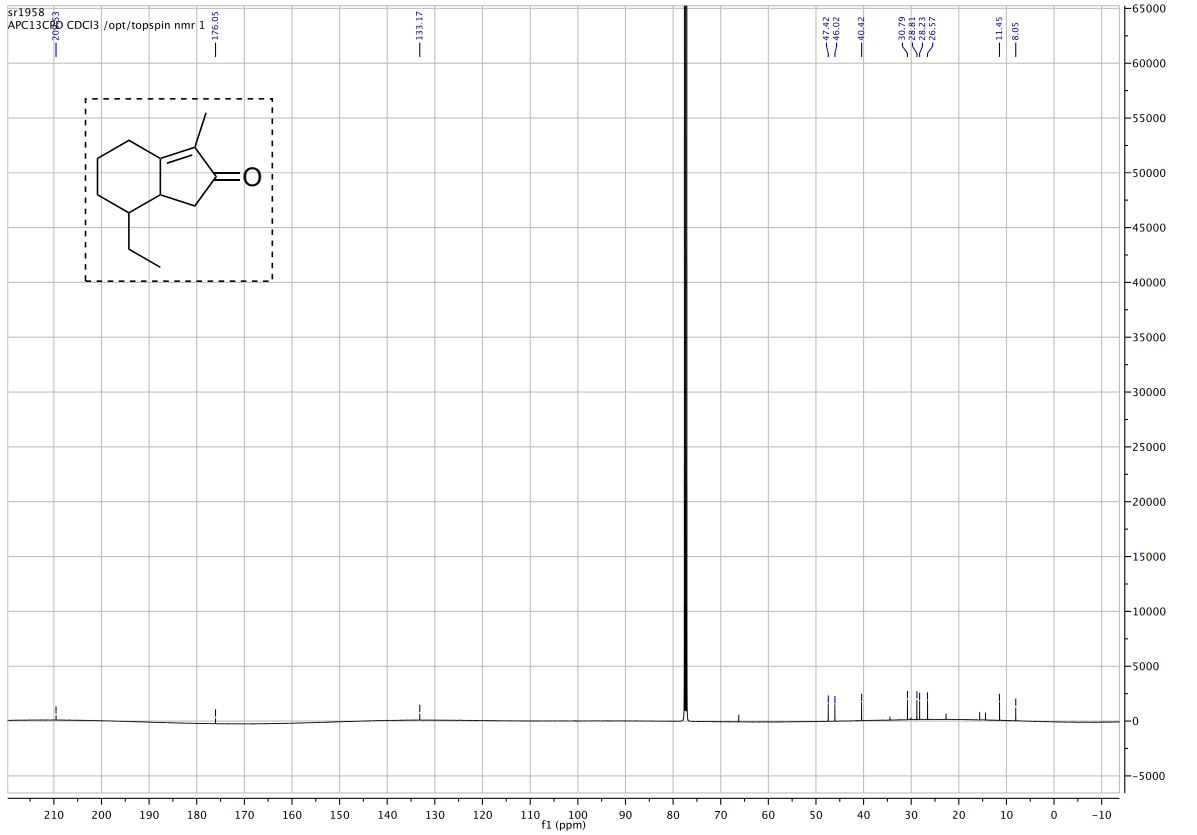
7-ethyl-1,4,5,6,7,7a-hexahydro-2*H*-inden-2-one. 8



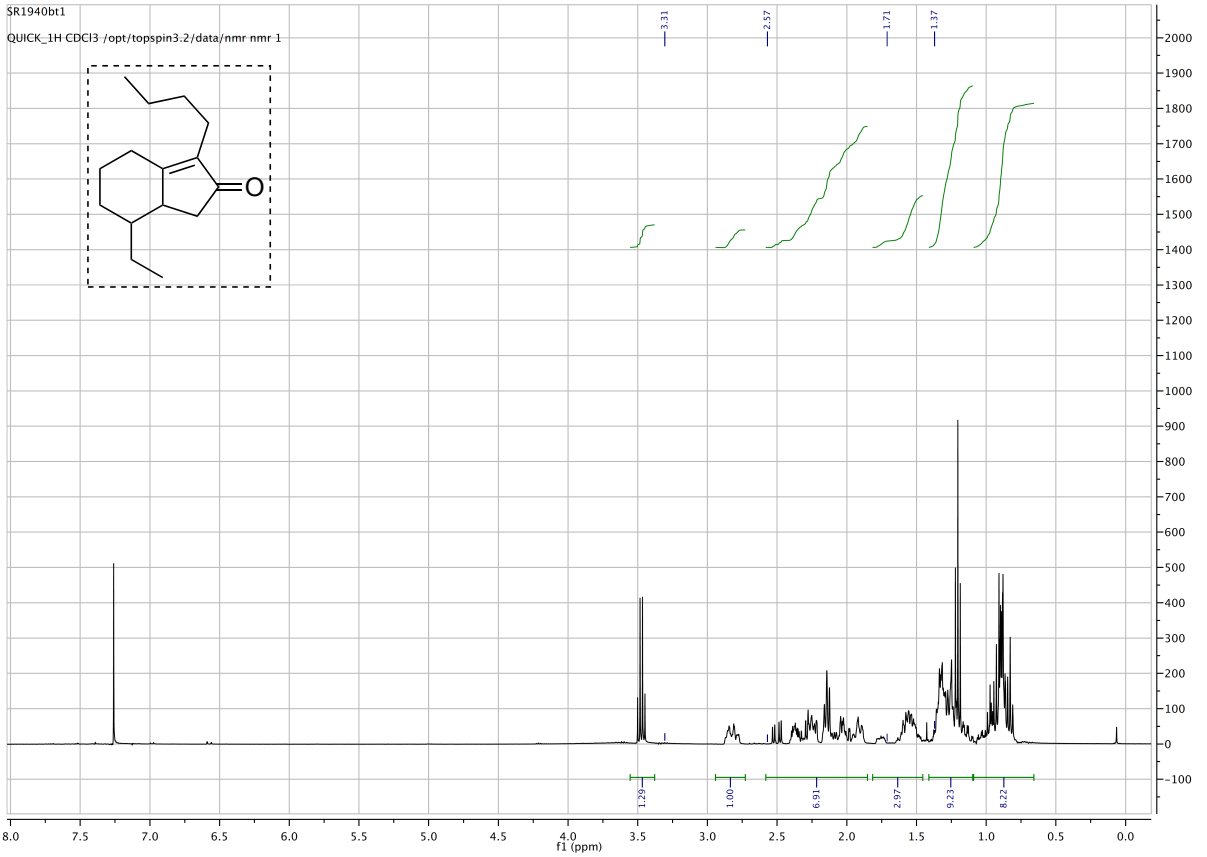


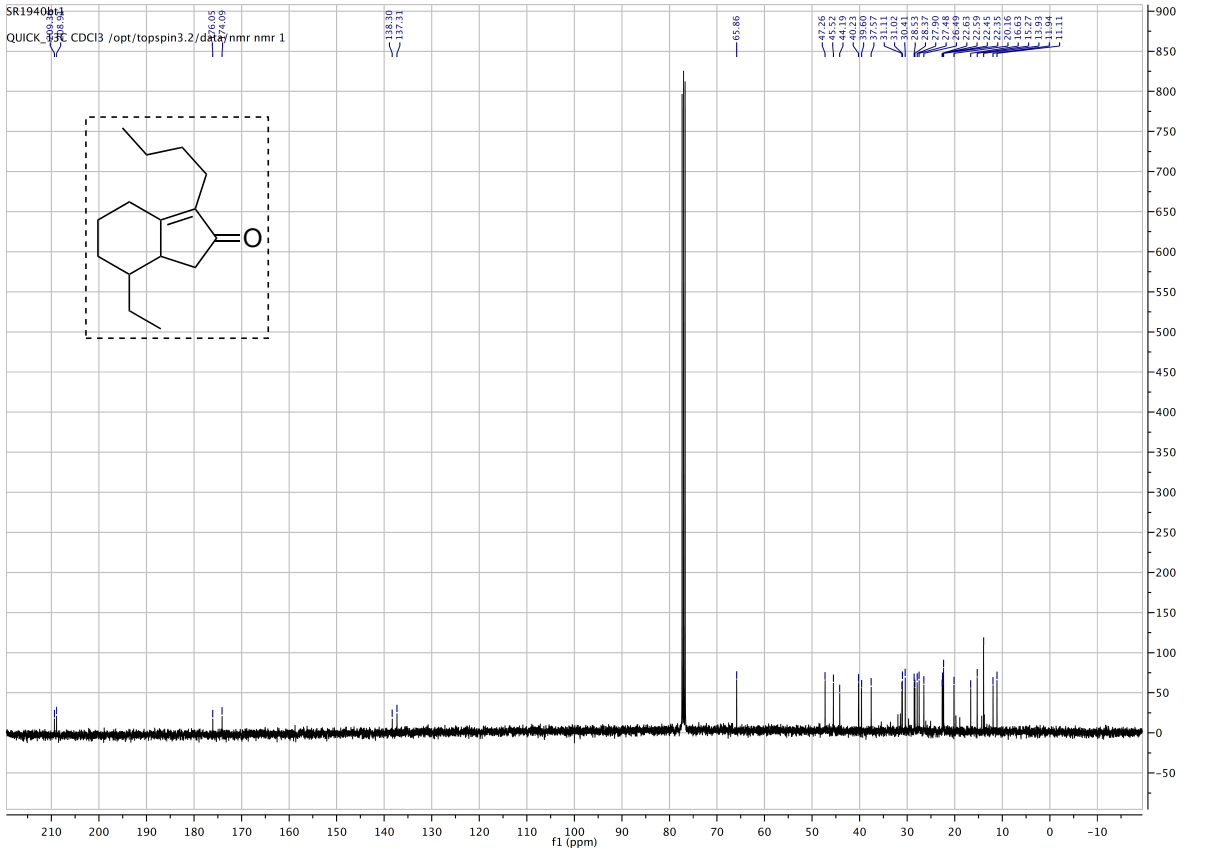
7-ethyl-3-methyl-1,4,5,6,7,7a-hexahydro-2*H*-ien-2-one. 9



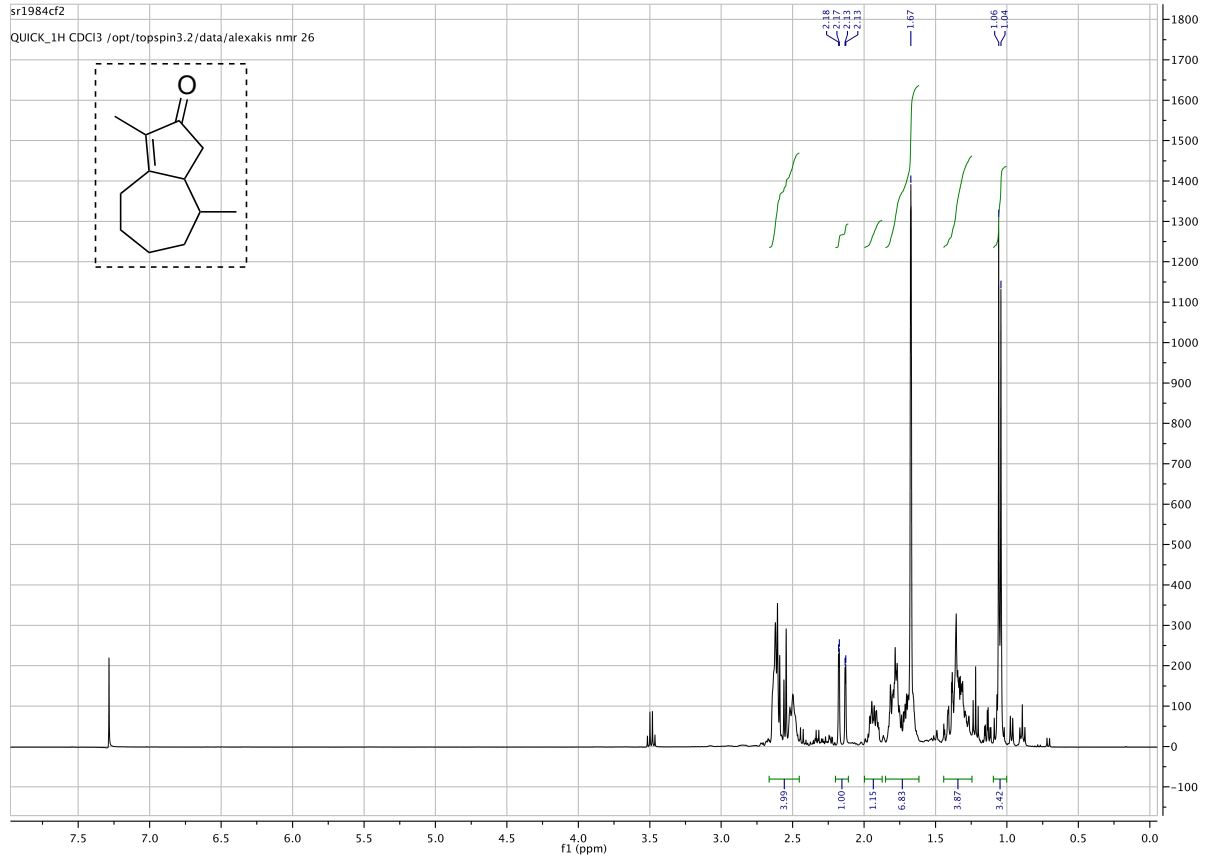


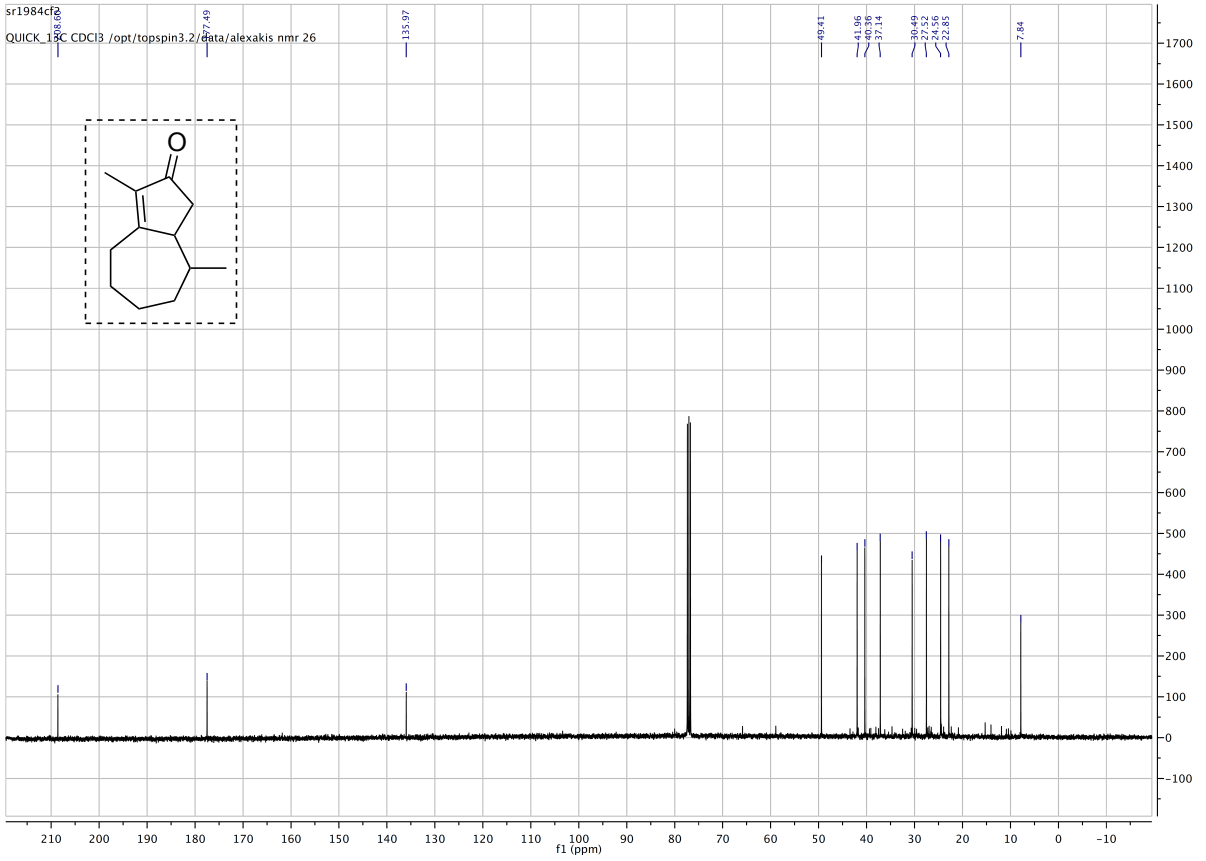
3-butyl-7-ethyl-1,4,5,6,7,7a-hexahydro-2*H*-inden-2-one. 10



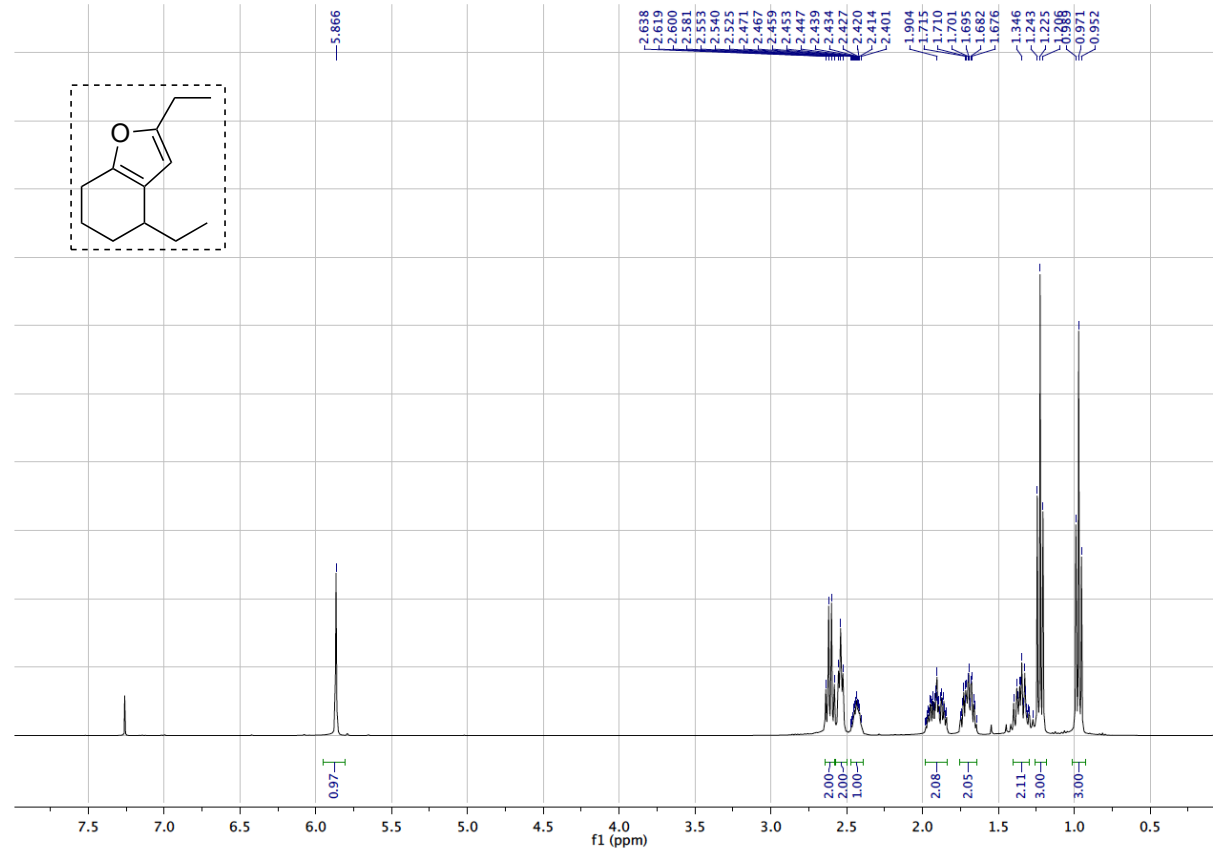


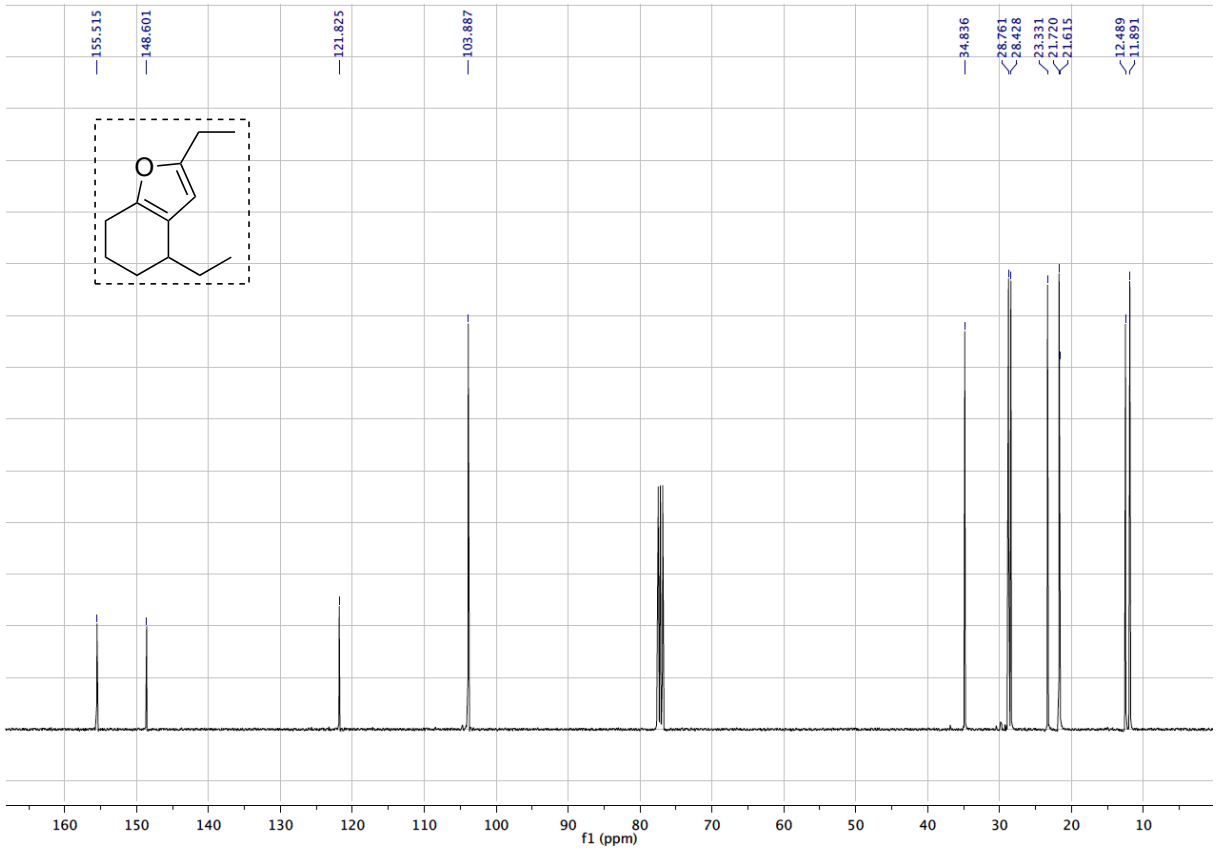
3,8-dimethyl-4,5,6,7,8,8a-hexahydroazulen-2(1*H*)-one. 11



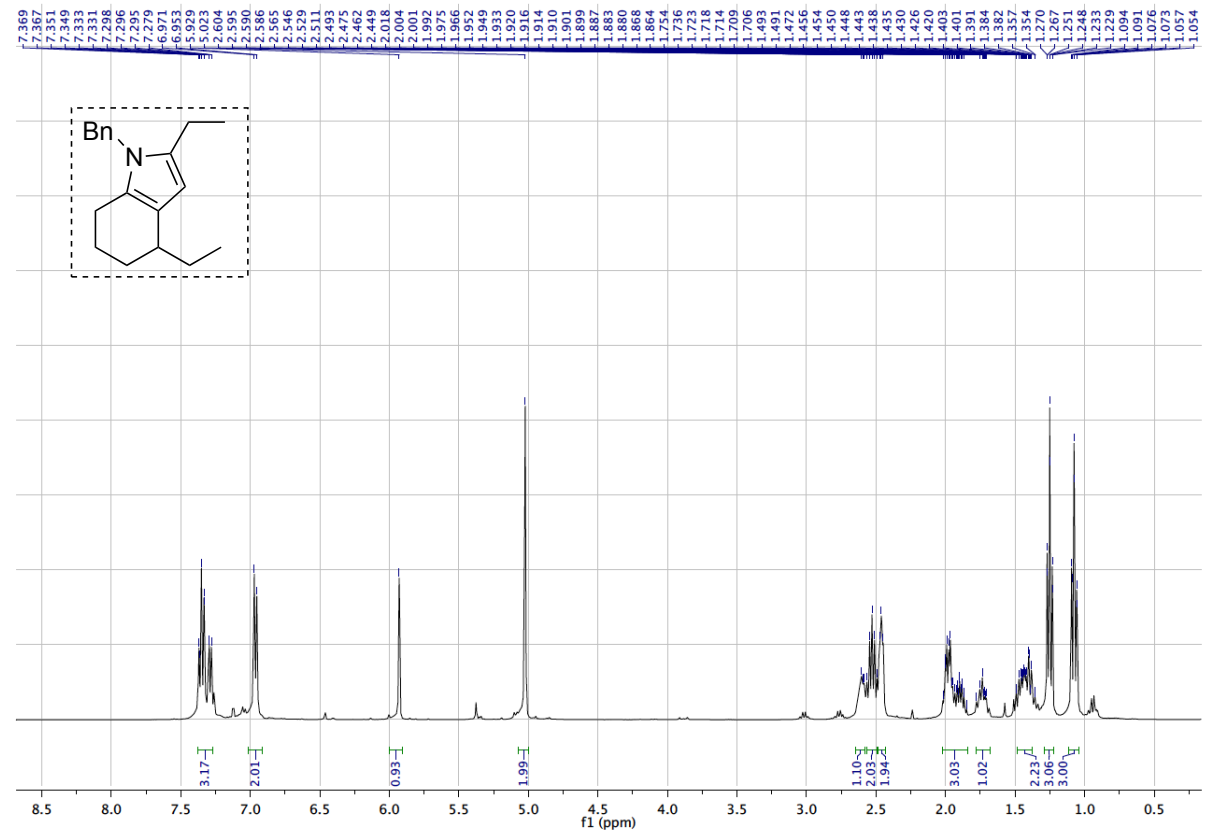


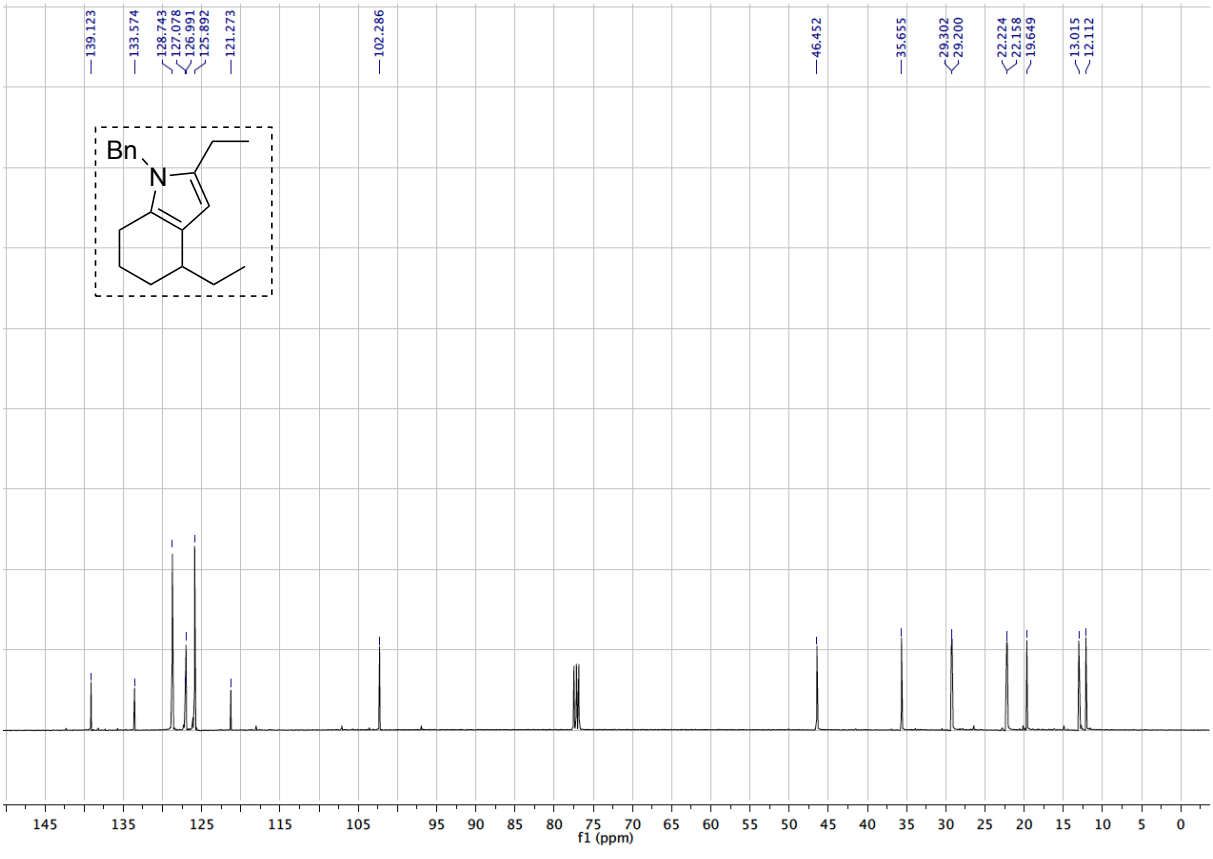
2,4-diethyl-4,5,6,7-tetrahydrobenzofuran. 12



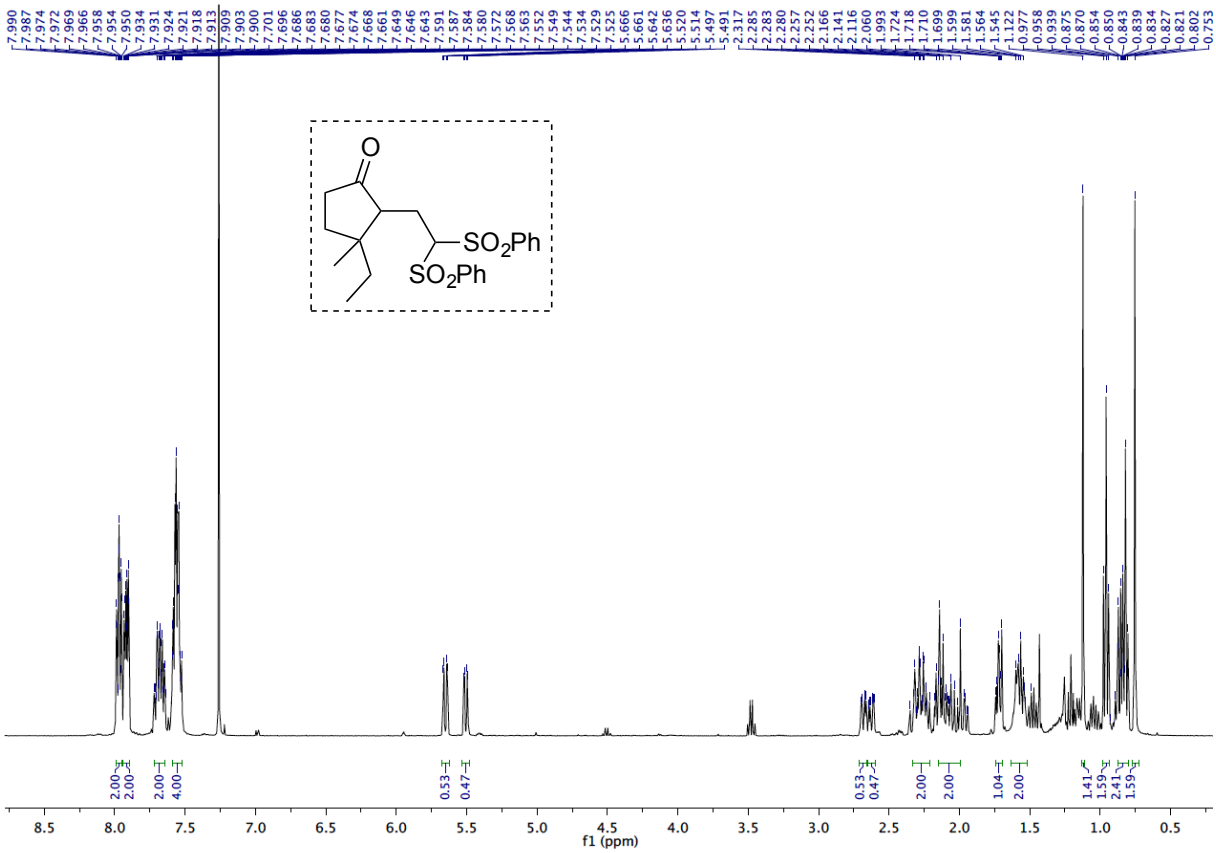


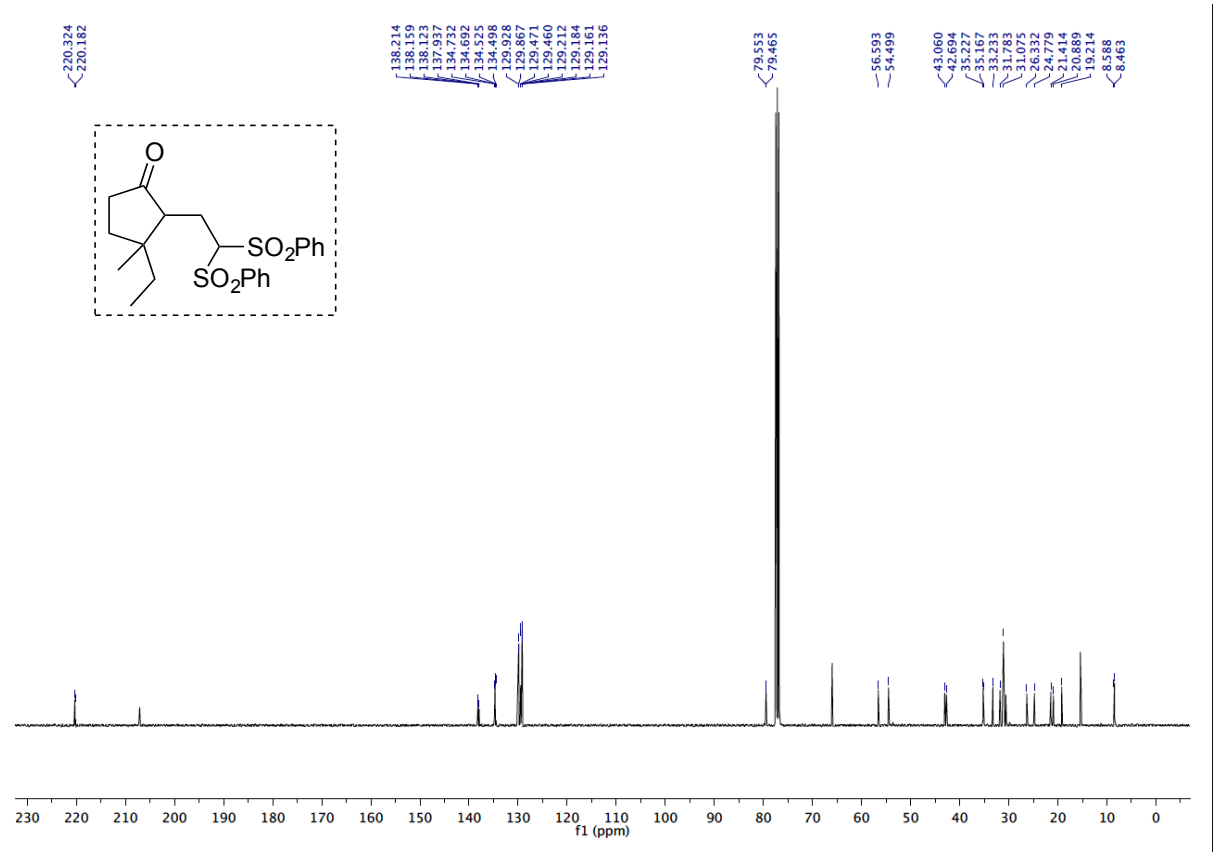
1-benzyl-2,4-diethyl-4,5,6,7-tetrahydro-1*H*-indole. 13



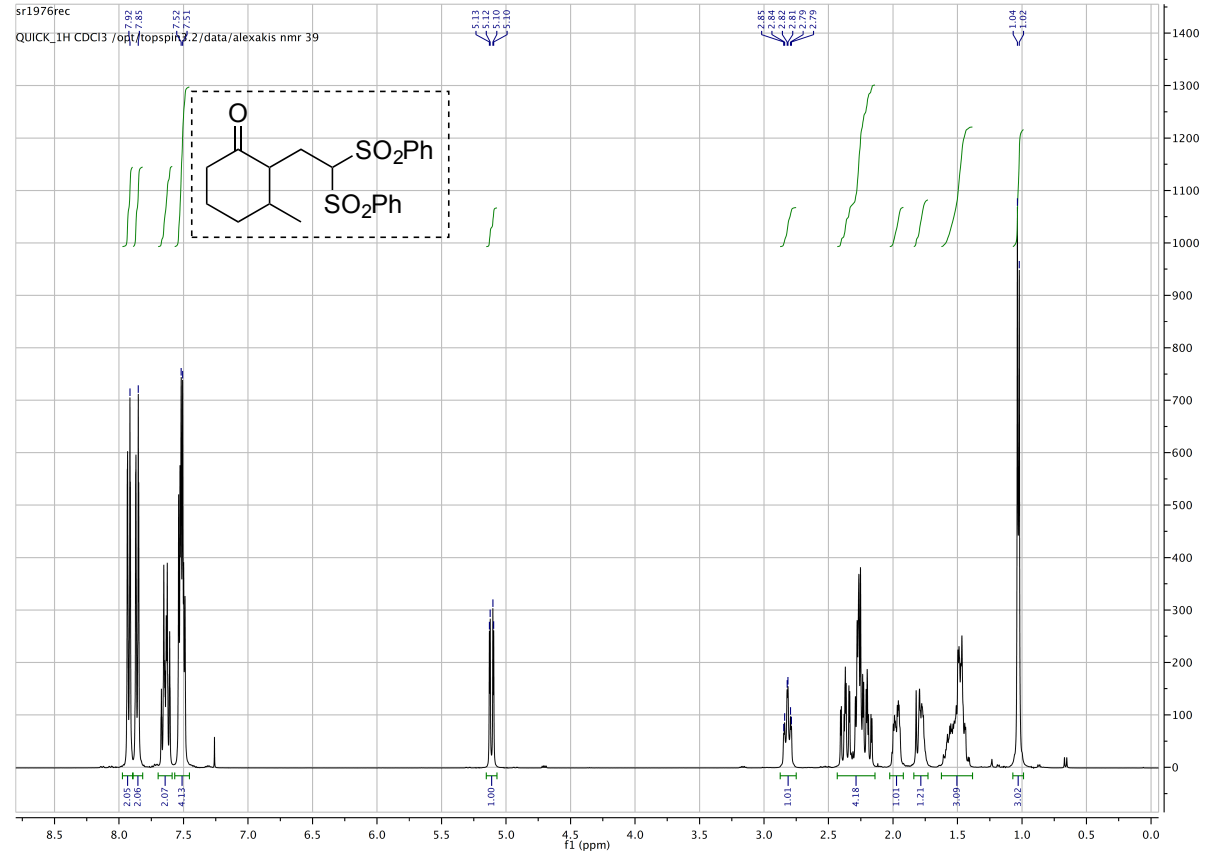


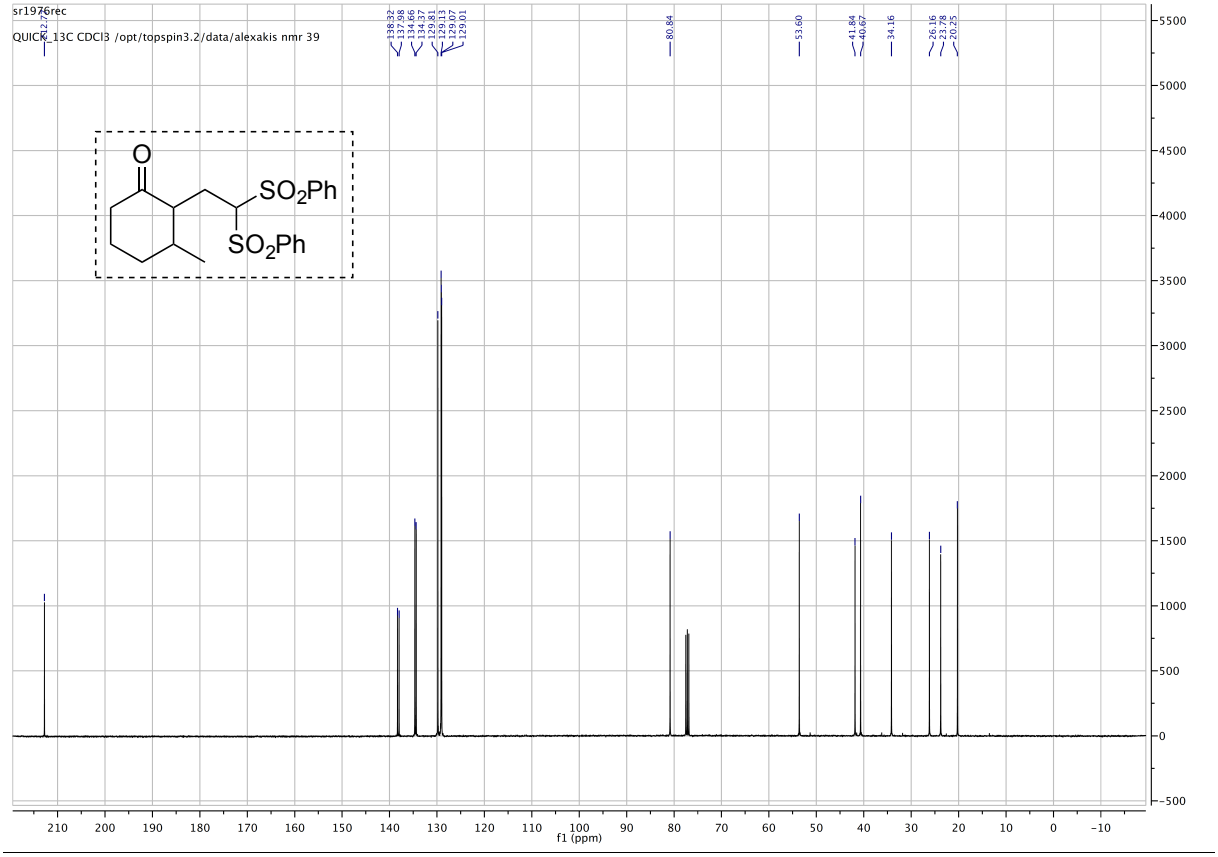
2-(2,2-bis(phenylsulfonyl)ethyl)-3-isopropyl-2-methylcyclopentan-1-one. 14a



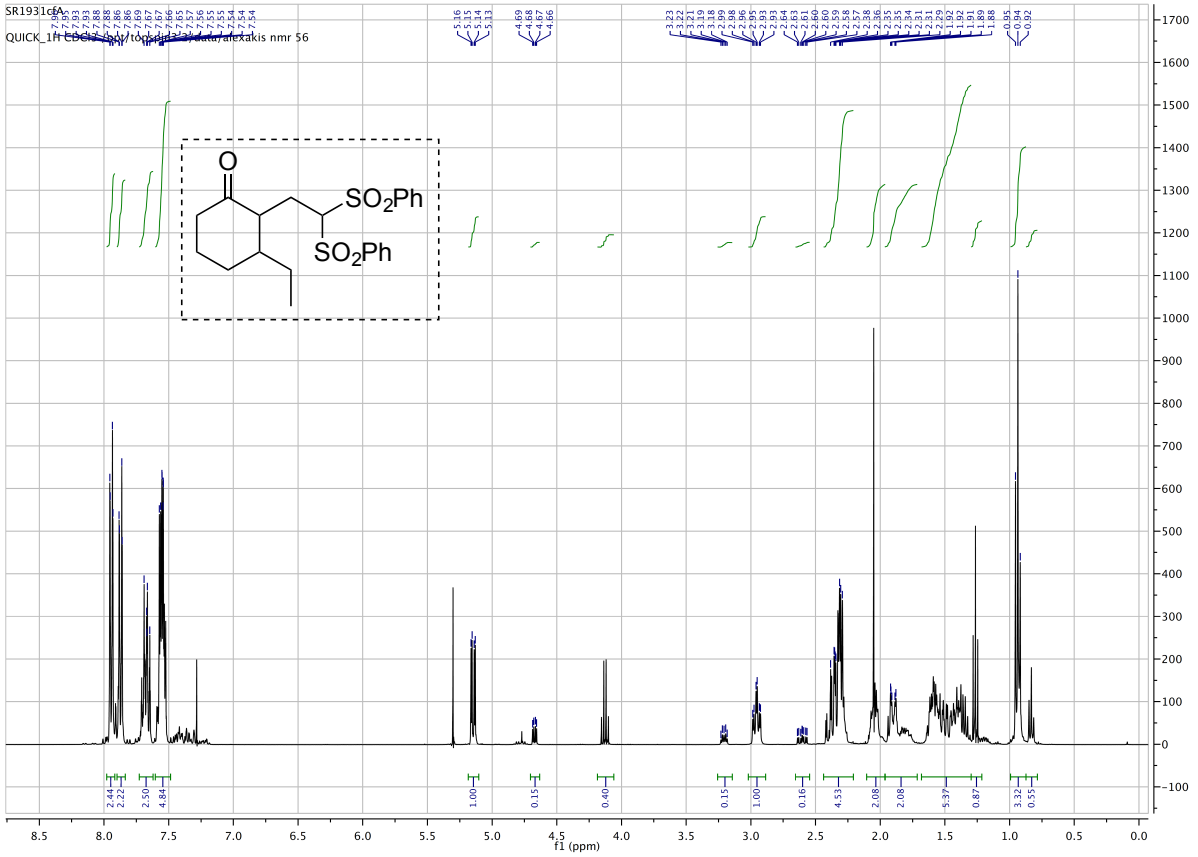


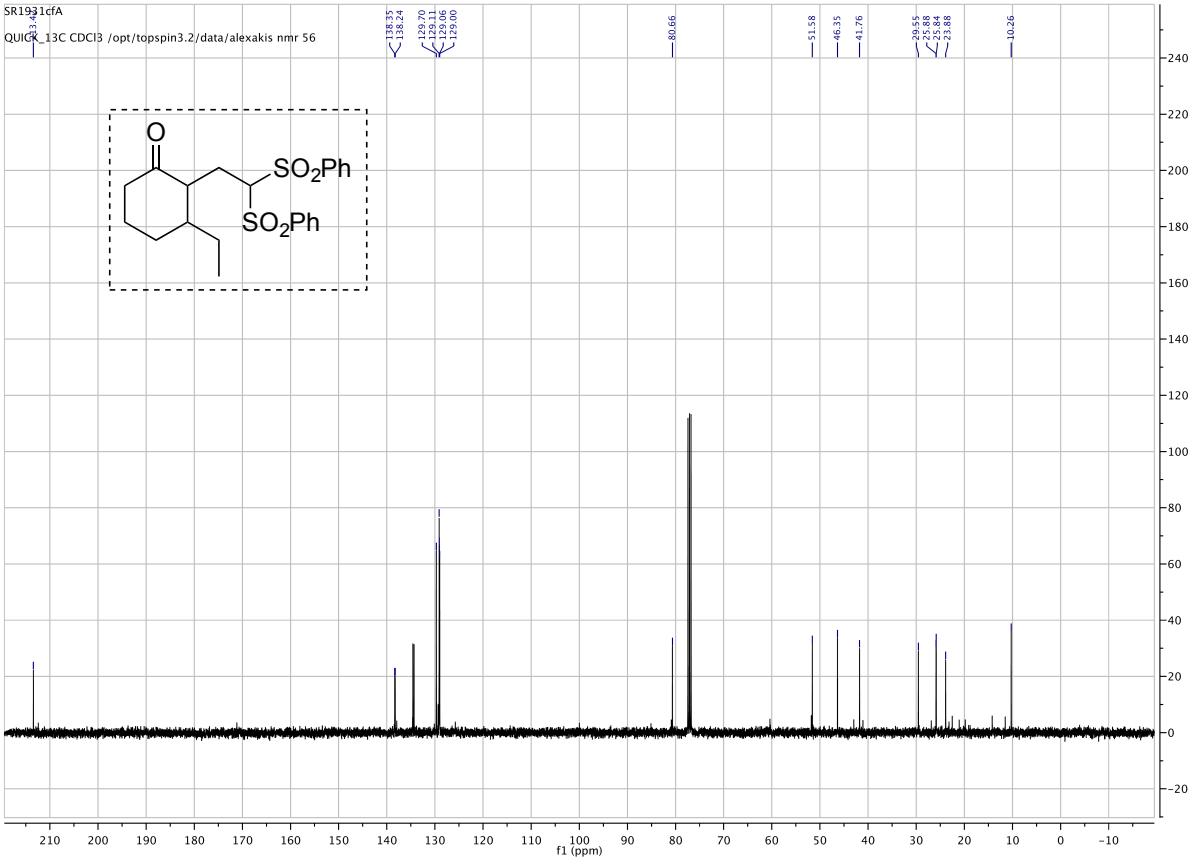
2-(2,2-bis(phenylsulfonyl)ethyl)-3-methylcyclohexan-1-one. <u>14ba</u>



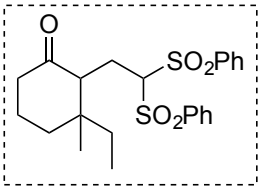


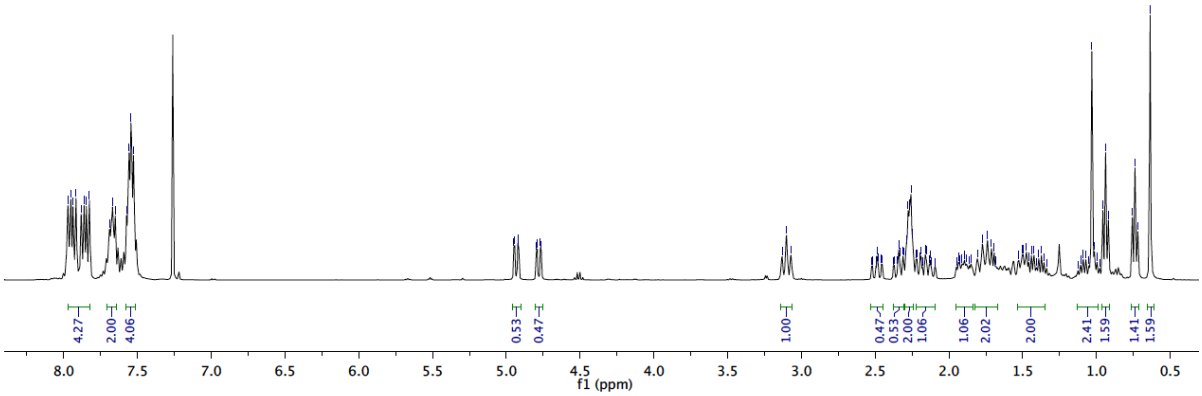
2-(2,2-bis(phenylsulfonyl)ethyl)-3-ethylcyclohexan-1-one. <u>14bb</u>

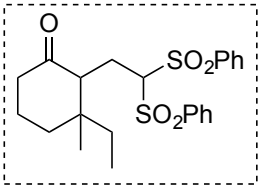


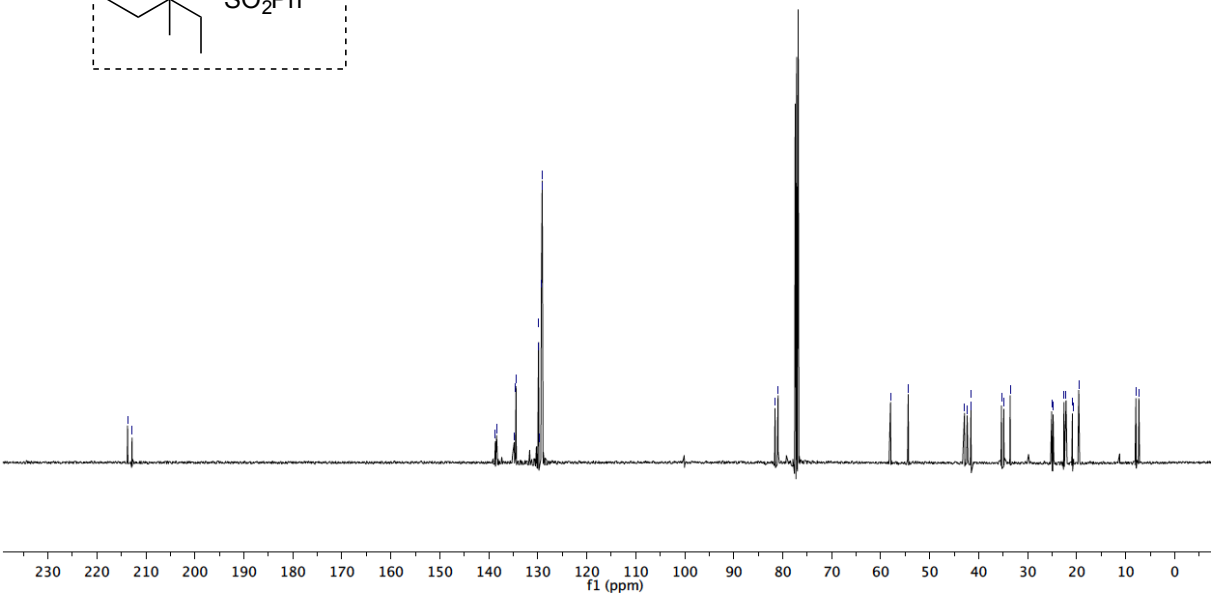


2-(2,2-bis(phenylsulfonyl)ethyl)-3-ethyl-3-methylcyclohexan-1-one. 14c

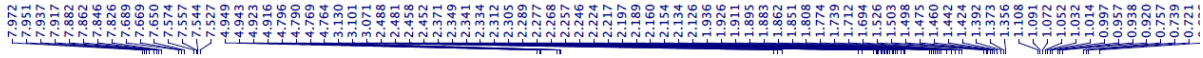


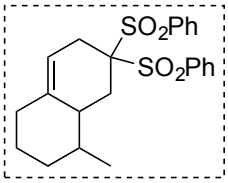


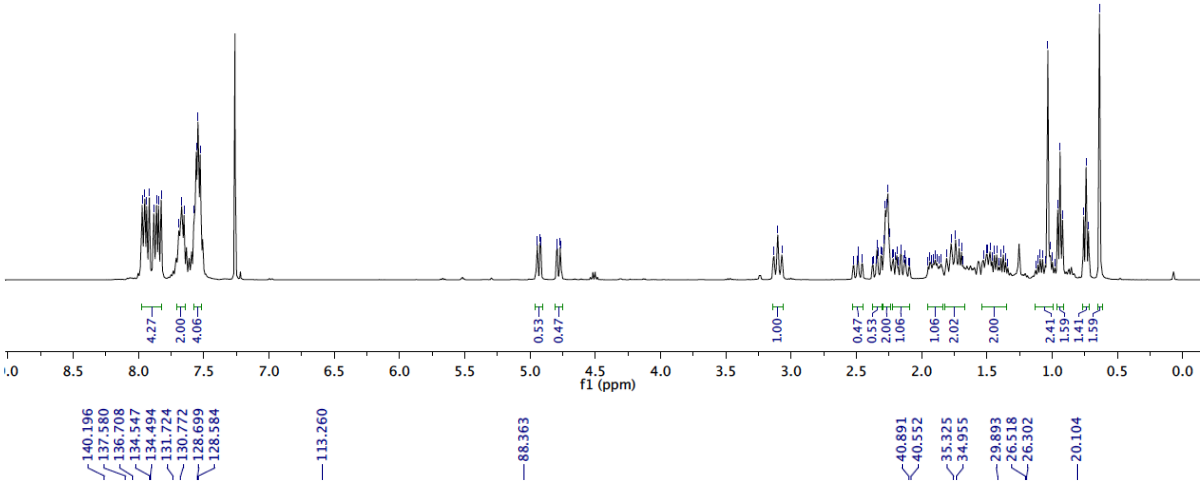


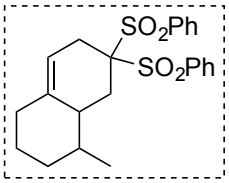


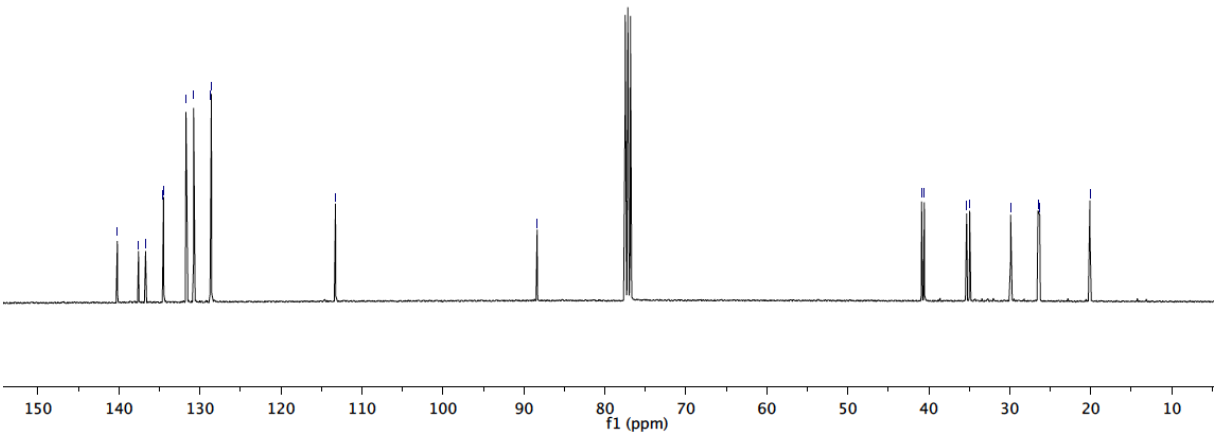
4-methyl-6,6-bis(phenylsulfonyl)-1,2,3,4,4a,5,6,7-octahydronaphthalene. 15











2-(2,2-bis(phenylsulfonyl)pent-4-en-1-yl)-3-methylcyclohexan-1-one. 16