

ORGANIC LETTERS
Supporting Information

Oxidative Umpolung α -Alkylation of Ketones

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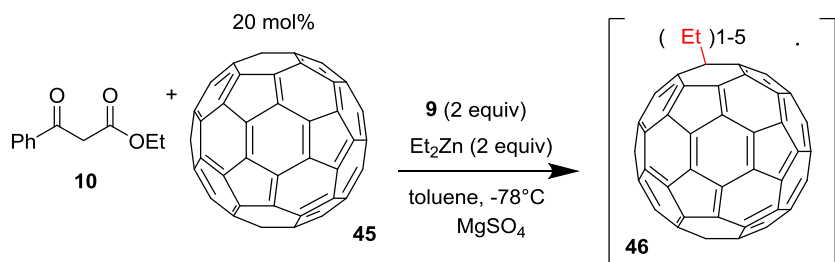
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Table of Content

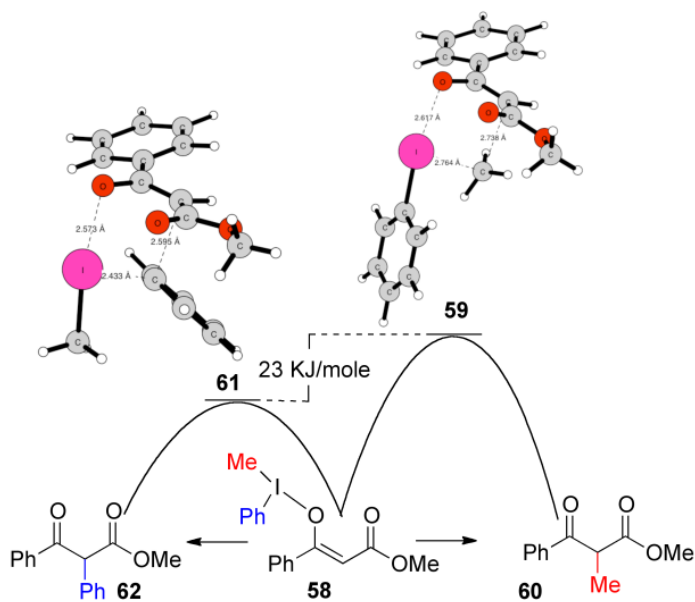
1.Schemes S1 and S2, discussion of DFT calculation results	2
2. General Information	5
3. Optimization Experiments including Table S1	6
4. General Procedures and Characterization Data	10
5. Mechanistic Studies	57
6. Computational Results	69
7. References for experimental section	73

1. Scheme S1 and Discussion of the DFT Calculation Results

Scheme S1. Radical trapping experiment using C₆₀ (45)



Scheme S2. DFT calculated transitions states for phenyl (61) and methyl (59) transfer from 58



Discussion

A focused DFT-based computational study of the reaction was carried out to further elucidate the mechanism. Specifically, we were interested in whether the proposed mixed phenyl-methyl-iodine(III) **50** (Scheme 3, path c) would be able to selectively transfer the methyl group, or if the proposed path c instead would result in formation of the phenyl-substituted product. Based on earlier computational studies,^{1,2} we constructed a model system, consisting of a mixed alkyl-aryl iodine(III) enolate **50** (Scheme S1).

To avoid complications arising from multiple conformations of the ethyl ester we employed the methyl ester **58** of **50** in this study.³ The DFT calculations were carried out using the B3LYP functional⁴ with added D3 corrections⁵ and the LACVP** basis set.⁶ As expected, the transition state for the transfer of the phenyl moiety i.e. **61** to give **62** was found to be similar to the one reported by Norrby et al.¹ for the analogous diphenyl-iodoenolate fragment, with a C-C distance

of 2.59 Å, I-C distance 2.43 and I-O distance 2.57 Å and a single imaginary frequency (239i cm⁻¹). The transition state **59** for the transfer of the methyl group to afford **60** was found to have a slightly longer C-C distance of 2.74 Å, a slightly longer I-C distance 2.76 Å, a similar I-O distance 2.62 Å and a single imaginary frequency (281i cm⁻¹). The energy of the transition state **59** for methyl transfer was 20 kJ/mol higher than the transition state **61** for transfer of the phenyl moiety, calculated as the difference in Gibbs Free energies at 195K (-78 °C). Employment of implicit solvation (PB-SCRF,⁷ benzene) resulted in a marginally larger energy difference (23 kJ/mol). As only methyl transfer is observed in the reaction, these results rule out path c, leaving path a as the only plausible alternative.

References for Computational section

- (1) Norrby, P.-O.; Petersen, T. B.; Bielawski, M.; Olofsson, B. *Chem. Eur. J.* **2010**, *16*, 8251.
- (2) Malmgren, J.; Santoro, S.; Jalalian, N.; Himo, F.; Olofsson, B. *Chem. Eur. J.* **2013**, *19*, 10334.
- (3) XYZ coordinates, SCF, PB-SCRF, Gibbs free energies (195K and 298K) and depictions of the two TS structures are available as Supporting Information.
- (4) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372. (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
- (5) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H.; *J. Chem. Phys.* **2010**, *132*, 154104.
- (6) LACVP** uses the 6-31G** basis set for all light elements and the Hay–Wadt ECP and basis set for iodine; see: Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299.
- (7) Marten, B.; Kim, K.; Cortis, C.; Friesner, R. A.; Murphy, R. B.; Ringnalda, M. N.; Sitkoff, D.; Honig, B. *J. Phys. Chem.* **1996**, *100*, 11775.

2.General Information

All reactions were carried out using oven-dried (120 °C) or heat gun dried glassware under a positive pressure of dry argon. All commercially available reagents were used without further purification. The chemical [hydroxy(tosyloxy)iodo]benzene(Koser's reagent) was handled in the dark. The reactions were magnetically stirred and monitored by thin layer chromatography using Merck Silica Gel 60 F254 plates and visualized by fluorescence quenching under UV light. In addition, TLC plates were stained using potassium permanganate. Chromatographic purification of products (column chromatography) was performed on silica 32-63, 60 Å using a forced flow of eluent at 0.3-0.5 bar. Concentration under reduced pressure was performed by rotary evaporation at 40 °C at the appropriate pressure. Yields refer to chromatographically purified compounds.

All 1,3-diketo products were isolated in pure form. While the enclosed NMR spectra, of course, show a mixture of keto and enol form in varying proportions depending on compound structure, concentration and solvent, only the data for the major keto form has been tabulated.

NMR spectra: NMR spectra were recorded on a Bruker Avance III 400 spectrometer operating at 400 MHz (^1H) and 101 MHz (^{13}C); or a Bruker Avance I 300 spectrometer operating at 300 MHz (^1H) and 75 MHz (^{13}C); or on a Bruker DPX200 spectrometer operating at 200 MHz (^1H) and 50 MHz (^{13}C). Chemical shifts (δ) are reported in ppm with the solvent resonance as the internal standard relative to chloroform (δ 7.26) for ^1H , and chloroform (δ 77.0) for ^{13}C ; or THF (δ 3.62, 1.79) for ^1H , and THF (δ 68.03, 26.19) for ^{13}C . All ^{13}C spectra were measured with complete proton decoupling. Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, dq = doublet of quartet; coupling constants in Hz.

IR spectra: recorded on a Bruker FT-IR (as thin film). Absorptions are given in wavenumbers (cm^{-1}).

Mass spectra: High resolution mass spectra were recorded by the MS service at Technion. ESI-MS (m/z): was recorded on a Waters Micromass LCT premier instrument at 70eV in the positive or negative mode using 70% acetonitrile/30% water at 0.2 mL flowrate.

ESR: Spectra were recorded on a Bruker EMX-10/12 X-band ($\nu = 9.4$ GHz) digital EPR spectrometer equipped with Bruker N_2 -temperature controller. Samples were irradiated with the focused and filtered ($\lambda > 300\text{nm}$) light of high-pressure mercury lamp (1 kW) (ARC lamp power supply model 69920) in resonator of EPR spectrometer.

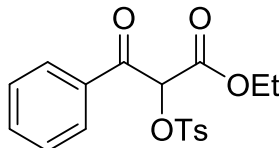
3. Optimization Experiments

Table S1. Optimization of the Reaction^a

Entry	Oxidant	Alk-M)	additive	T/°C	Product	Yield (Cons.)/%
1	3	Me ₃ Al	none	RT	-	NR
2	4	Me ₃ Al	None	RT	-	NR
3	5	Me ₃ Al	None	RT	-	NR
4	6	Me ₃ Al	None	RT	-	NR
5	7	Me ₃ Al	None	RT	-	NR
6	8	Me ₃ Al	None	RT	-	NR
7	9	Me ₃ Al	None	-78	2a	18 (18)
8	9	Me ₃ Al	MgSO ₄	-78	2a	49 (100)
9	9	Me ₃ Al	4Å MS	-78	2a	47 (100)
10	9	Me ₂ Zn	MgSO ₄	-78	2a	80 (100)
11	9	Et ₂ Zn	MgSO ₄	-78	2b	28 (100)
12	9	Et ₂ Zn	MgSO ₄ /ethanol amine	-78	2b	50 (100)

^a 2 equiv of organometal and oxidant were used in all reactions. ^b 1 equiv

Tosylation of β -ketoester (**10**)¹



Ethyl 3-oxo-3-phenylpropanoate **10** (0.37 mmol, 0.07 g) was dissolved in anhydrous toluene (0.9 mL, 0.4 M) under positive argon flow. [hydroxy(tosyloxy)iodo]benzene (0.92 mmol, 0.36 g) was added in the dark. After 1 h stirring at ambient temperature, the mixture was cooled to -78 °C and diethylzinc in toluene (1.5 M, 0.92 mmol, 0.61 mL) was added at once. The mixture was allowed to stir at -78 °C for 18 h, in the dark. Reaction was quenched by addition of water, followed by filtration of the slurry through a Celite® frit and rinse with DCM. The product was purified by a column chromatography (5-15% EtOAc/Hexane) to furnish ethyl 3-oxo-3-phenyl-2-(tosyloxy)propanoate as an oil (0.10 g, 80%).

¹H NMR (400 MHz, CDCl₃) δ 7.92 (d, J = 7.9 Hz, 2 H), 7.78 (d, J = 8.1 Hz, 2 H), 7.60 (t, J = 7.4 Hz, 1 H), 7.45 (t, J = 7.7 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 5.98 (s, 1 H), 4.18 (m, 2 H), 2.43 (s, 3 H), 1.17 (t, J = 7.1 Hz, 3 H).

¹³C NMR (101 MHz, CDCl₃) δ 188.21, 164.17, 145.65, 134.37, 133.32, 132.43, 129.83, 129.40, 128.74, 128.30, 78.07, 62.83, 21.68, 13.79.

The data is consistent with those reported in the literature (reference 1)

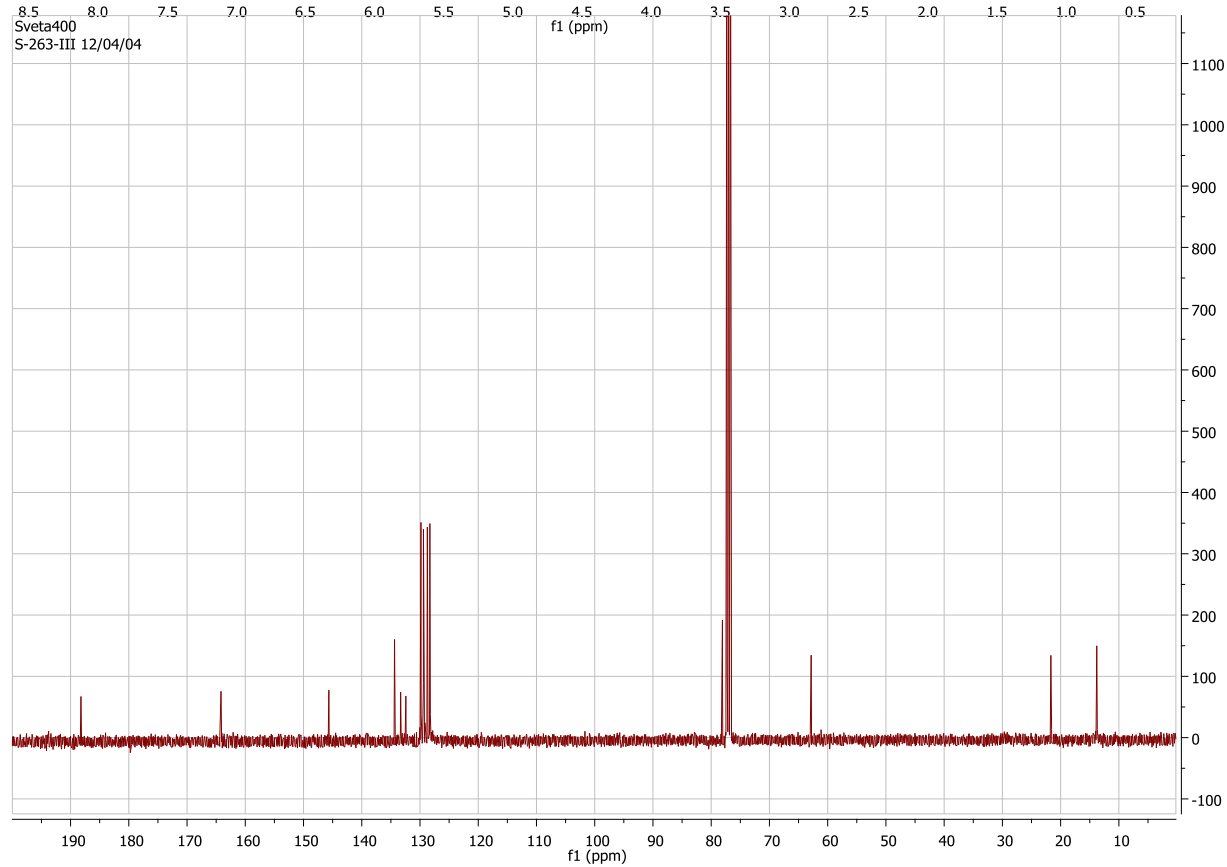
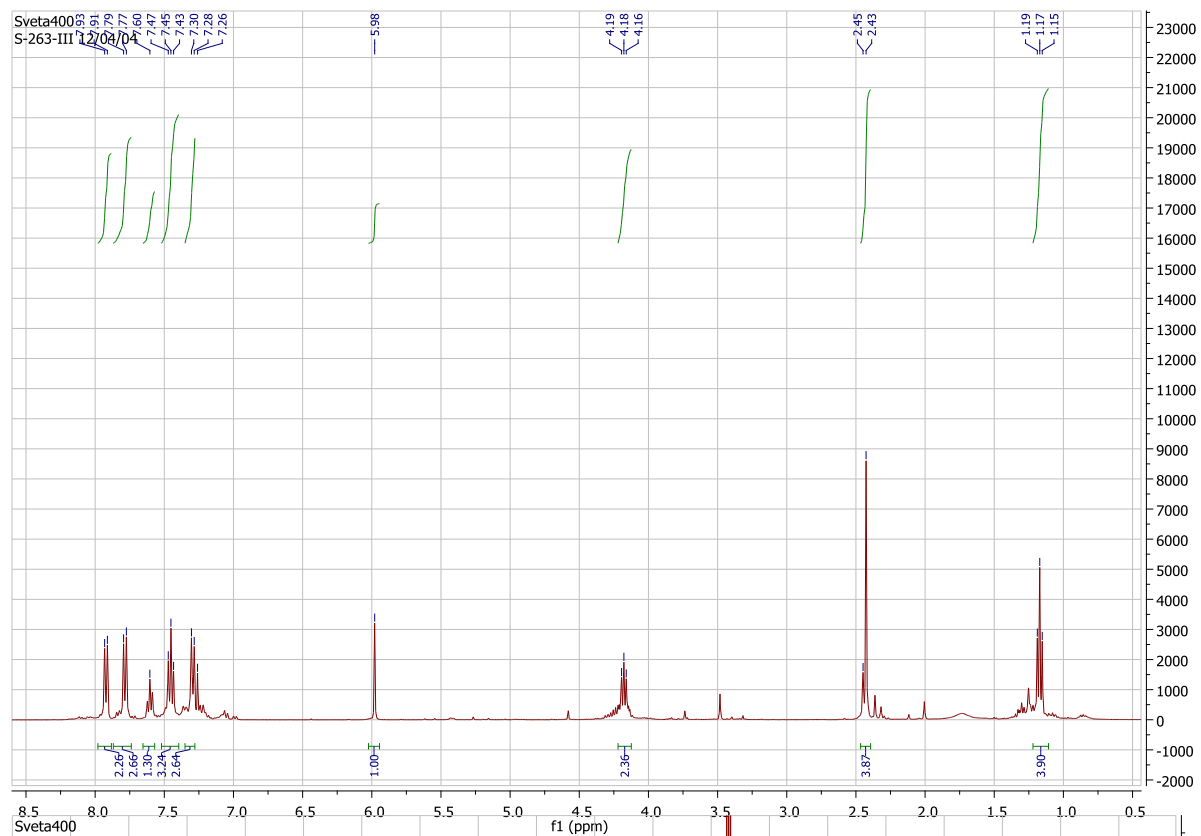


Table 1, entry 1/Table S1, Entry 7

Ethyl 2-oxocyclohexane-1-carboxylate (0.59 mmol, 0.1 g) was dissolved in anhydrous DCM (1.2 mL, 0.5 M) under positive argon flow. [hydroxy(tosyloxy)iodo]benzene (1.48 mmol, 0.57 g) was added in the dark. The mixture was cooled to -78 °C and trimethylaluminum in hexane (2M, 1.77 mmol, 0.89 mL) was added at once. The mixture was allowed to stir at -78 °C for 18 h, in the dark. Reaction was quenched by addition of water, followed by filtration of the slurry through a Celite® frit and rinse with DCM. The product was purified by a column chromatography (5% EtOAc/Hexane) to furnish **2a** as an oil (0.02 g, 18%). For characterization data see below.

Table 1, entry 2/Table S1, Entry 8

Ethyl 2-oxocyclohexane-1-carboxylate (0.24 mmol, 40 mg) was dissolved in anhydrous DCM (1.2 mL, 0.5 M) under positive argon flow. The mixture was cooled to -78 °C and [hydroxy(tosyloxy)iodo]benzene (0.6 mmol, 0.24 g) and MgSO₄ (0.96 mmol, 0.12 g) were added in the dark. After 15 min, trimethylaluminum in hexane (2M, 0.6 mmol, 0.3 mL) was added at once. The mixture was allowed to stir at -78 °C for 18 h, in the dark. Reaction was quenched by addition of water, followed by filtration of the slurry through a Celite® frit and rinse with DCM. The product was purified by a column chromatography (5% EtOAc/Hexane) to furnish **2a** as an oil (0.023 g, 49%). For characterization data see below.

Table 1, entry 3/Table S1, Entry 9

Ethyl 2-oxocyclohexane-1-carboxylate (0.24 mmol, 0.04 g) was dissolved in anhydrous DCM (1.2 mL, 0.5 M) under positive argon flow. The mixture was cooled to -78 °C and [hydroxy(tosyloxy)iodo]benzene (0.6 mmol, 0.24 g) and molecular sieves 4 Å were added in the dark. After 15 min, trimethylaluminum in hexane (2M, 0.6 mmol, 0.3 mL) was added at once. The mixture was allowed to stir at -78 °C for 18 h, in the dark. Reaction was quenched by addition of water, followed by filtration of the slurry through a Celite® frit and rinse with DCM. The product was purified by a column chromatography (5% EtOAc/Hexane) to furnish **2a** as an oil (0.022 g, 47%). For characterization data see below.

Table 1, entry 4/Table S1, Entry 10

Ethyl 2-oxocyclohexane-1-carboxylate (0.59 mmol, 0.1 g) was dissolved in anhydrous toluene (1.5 mL, 0.4 M) under positive argon flow. [hydroxy(tosyloxy)iodo]benzene (1.47 mmol, 0.58 g) and MgSO₄ (5.88 mmol, 0.71 g) were added in the dark. After ½ h the mixture was cooled to -78 °C and dimethylzinc in toluene (1.2M, 1.47 mmol, 1.2 mL) was added at once. The mixture was allowed to stir at -78 °C for 18 h, in the dark. Reaction was quenched by addition of water, followed by filtration of the slurry through a Celite® frit and rinse with DCM. The product was purified by a column chromatography (5-15% EtOAc/Hexane) to furnish **2a** as an oil (0.095 g, 80%). For characterization data see below.

Table 1, entry 5/Table S1, Entry 11

As entry 12, but in the absence of ethanolamine. Product isolated as an oil (14.5 mg, yield 28%).

Table 1, entry 6/Table S1, Entry 12

According to Procedure B (see below for description).

4. General Procedures and Characterization Data

Characterization data

All known compounds had NMR spectra consistent with published data. For several known compounds full characterization was performed and the data are included here. Unknown compounds were fully characterized.

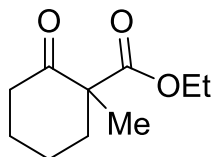
Coupling Procedure A

Ethyl 3-oxo-3-phenylpropanoate (0.58 mmol, 110 mg, 1.0 equiv.) was dissolved in anhydrous toluene (1.45 mL, 0.4 M) under positive argon flow. After cooling to -78 °C, [hydroxy(tosyloxy)iodo]benzene (1.16 mmol, 0.45 g, 2.0 equiv.) and freshly dried MgSO₄ (2.9 mmol, 0.35 g, 5.0 equiv.) were added in the dark. Then a solution of dimethylzinc in toluene (1.2 M, 1.16 mmol, 0.97 mL, 2.0 equiv.) was added at once. The mixture was allowed to stir at -78 °C for 18 h, in the dark. Reaction was quenched by addition of water, followed by filtration of the slurry through a Celite® frit and rinse with DCM. The alkylated product was purified by a column chromatography (5-15% EtOAc/Hexane) to furnish **11a** as an oil (110 mg, 92%). For characterization data see below.

Coupling Procedure B

Ethyl 3-oxo-3-phenylpropanoate (0.5 mmol, 96 mg, 1.0 equiv.) was dissolved in anhydrous toluene (1.25 mL, 0.4 M) under positive argon flow. After cooling to -78 °C, [hydroxy(tosyloxy)iodo]benzene (2.0 mmol, 0.78 g, 4.0 equiv.) and freshly dried MgSO₄ (2.5 mmol, 0.30 g, 5.0 equiv.) were added in the dark. Then a solution of ethanolamine (0.5 mmol, 0.03 g, 1.0 equiv.) was added, followed by a solution of diethylzinc in toluene (1.5 M, 2.0 mmol, 1.3 mL, 4.0 equiv.) at once. The mixture was allowed to stir at -78 °C for 18 h, in the dark. Reaction was quenched by addition of water, followed by filtration of the slurry through a Celite® frit and rinse with DCM. The alkylated product was purified by a column chromatography (5-10% EtOAc/Hexane) to furnish **11b** as an oil (88 mg, 80%). For characterization data see below.

Ethyl 1-methyl-2-oxocyclohexanecarboxylate (2a)²



The compound was prepared according to procedure A and purified by column chromatography (5-15% EtOAc/Hexane) to give the product as an oil (95 mg, 80 %).

R_f = 0.56 (20% EtOAc/Hexane).

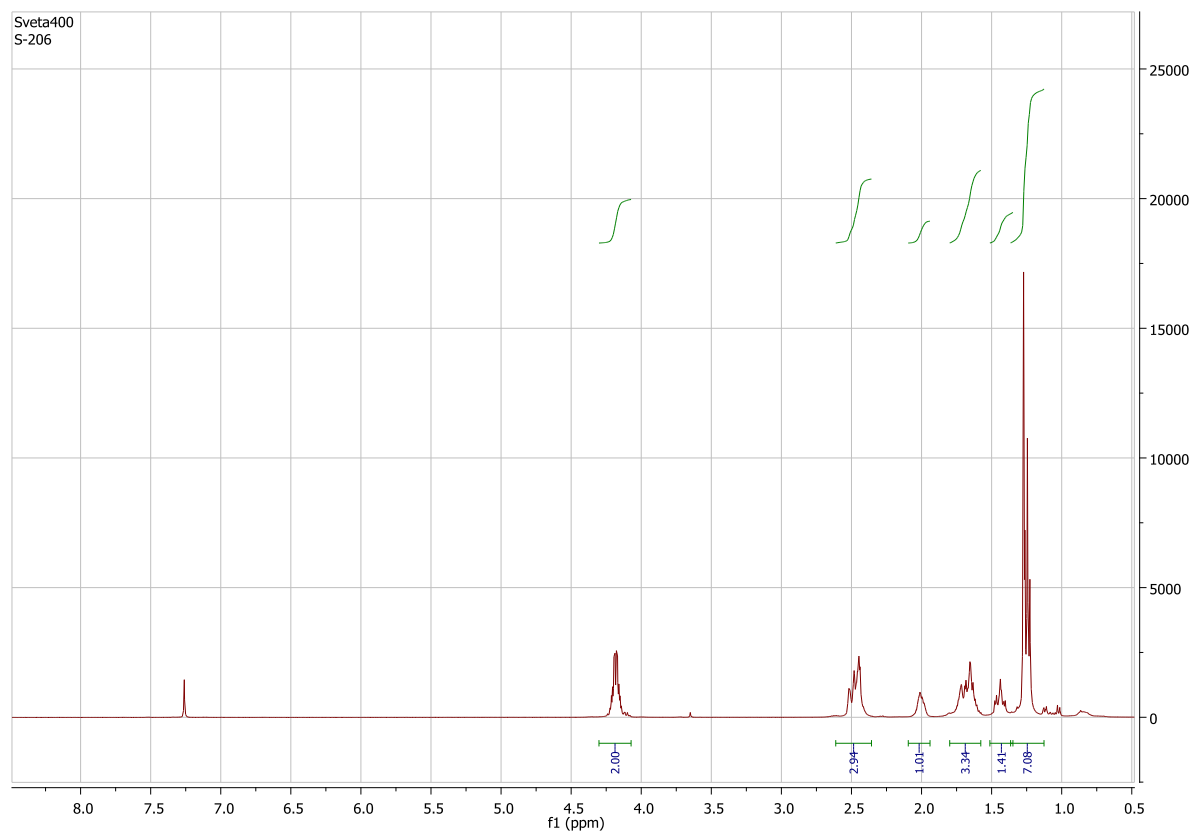
¹H NMR (400 MHz, CDCl₃) δ 4.18 (m, 2 H), 2.47 (m, 3 H), 2.01 (m, 1 H), 1.68 (m, 3 H), 1.44 (m, 1 H), 1.26 (m, 6 H).

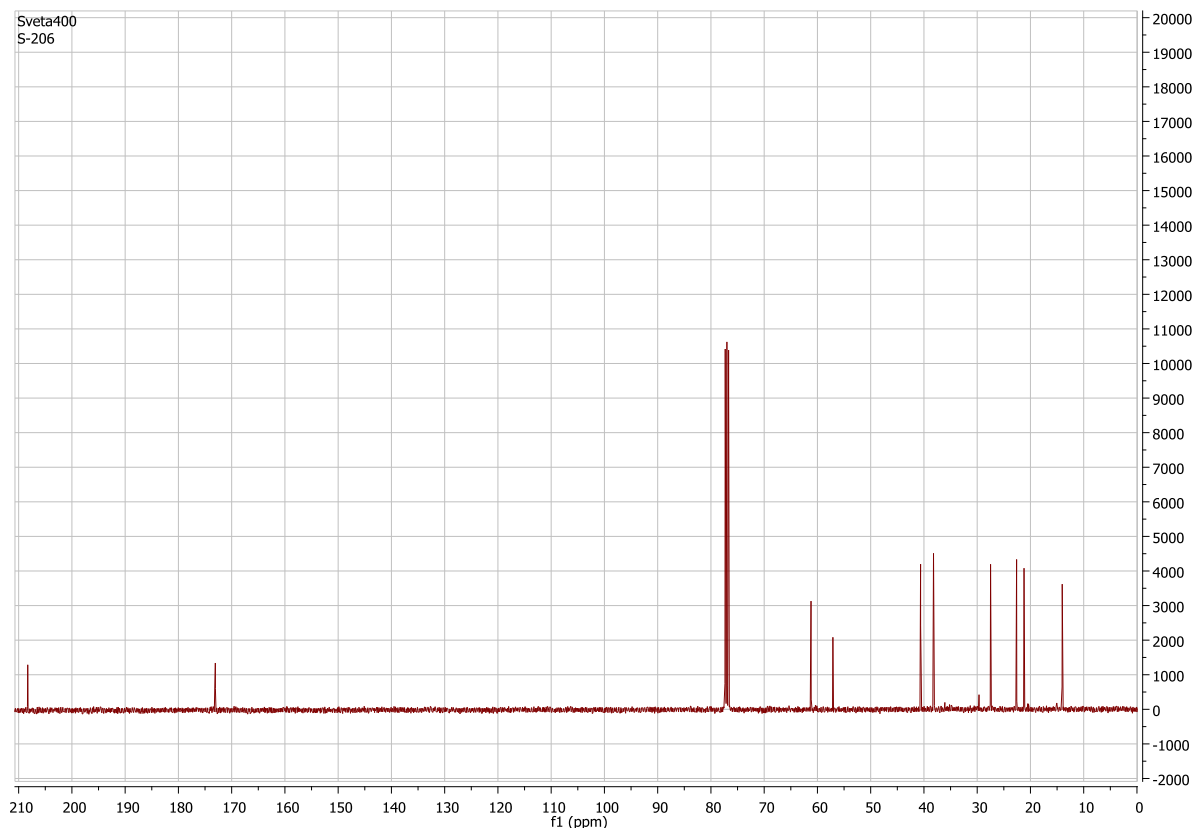
^{13}C NMR (101 MHz, CDCl_3) δ 208.29, 173.06, 61.20, 57.10, 40.63, 38.20, 27.49, 22.60, 21.20, 14.04.

IR: (thin film) ν 2937, 2866, 1711, 1450, 1374, 1339, 1301, 1254, 1215, 1152, 1117, 1085, 1019, 989 cm^{-1} .

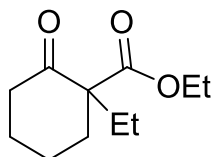
HRMS (ESI) m/z : calcd for $\text{C}_{10}\text{H}_{16}\text{O}_3$, $[\text{M}+\text{Na}]$, 207.0997; found 207.1026.

The data is consistent with those reported in the literature (reference 2)





Ethyl 1-ethyl-2-oxocyclohexanecarboxylate (2b)³



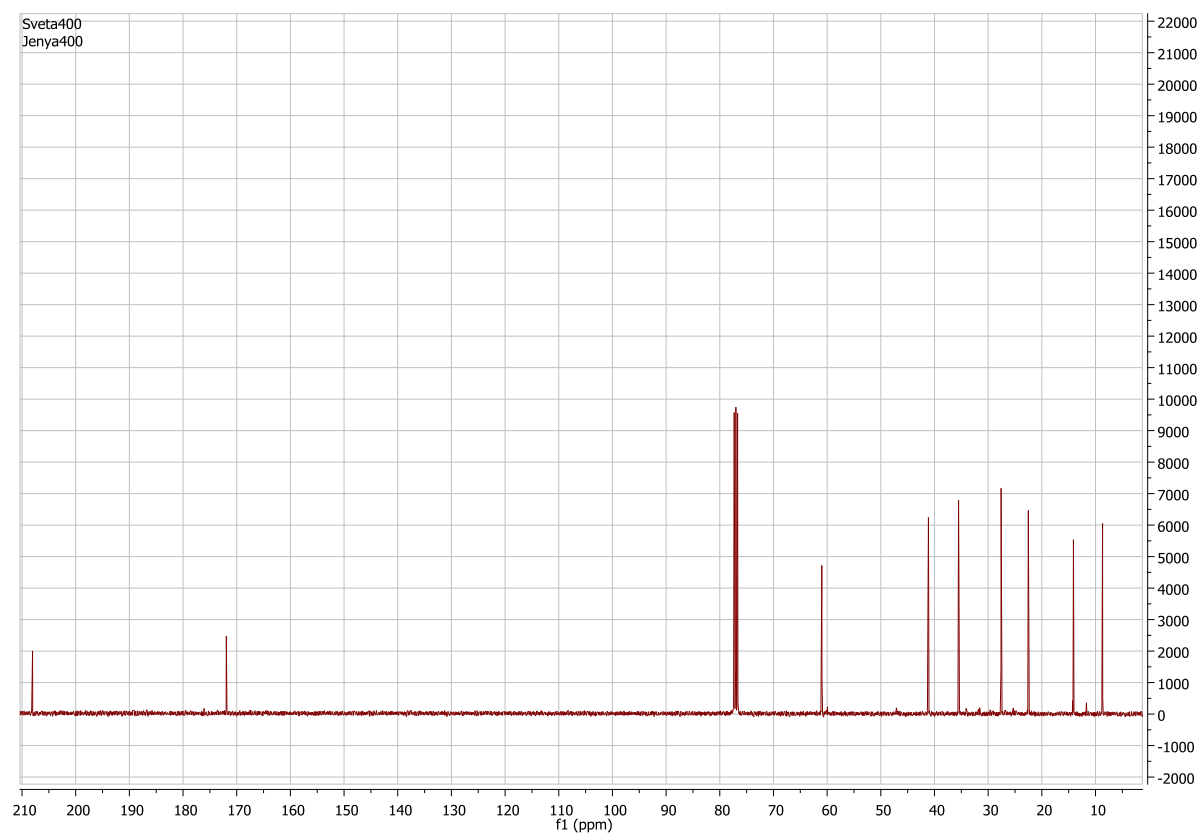
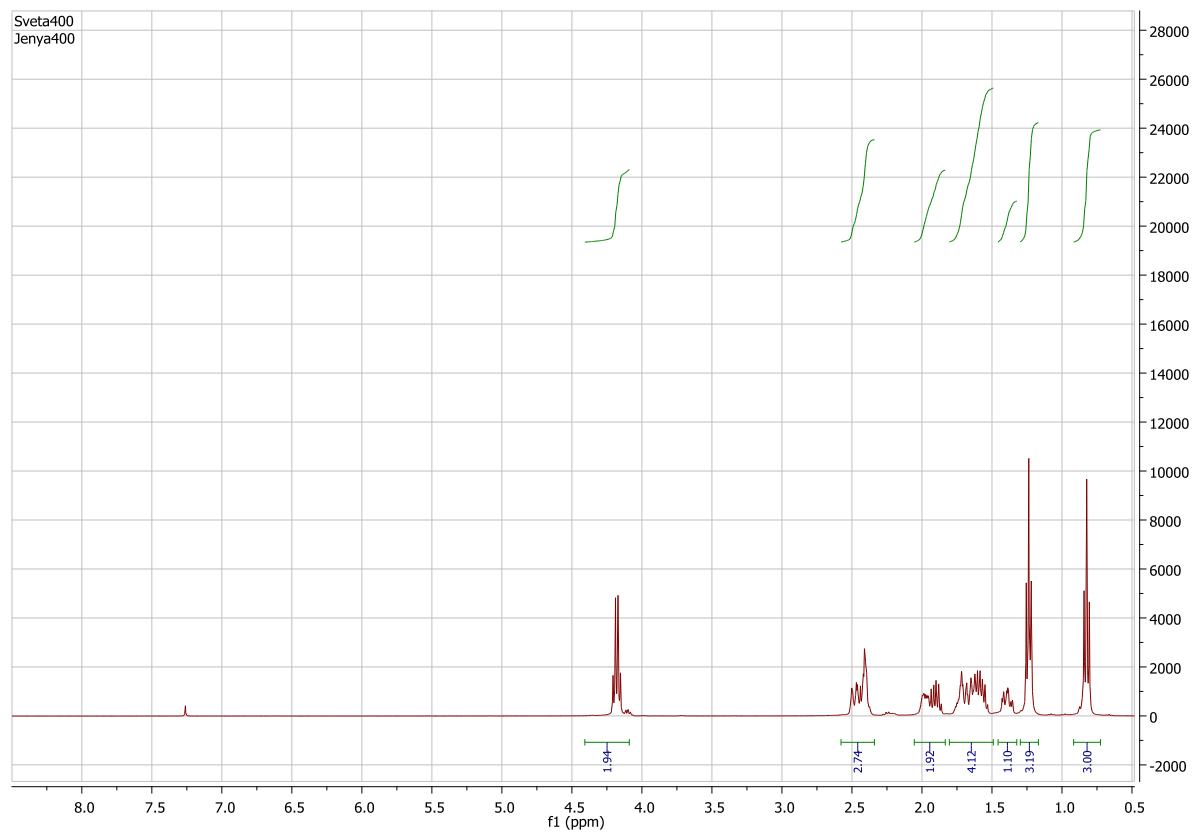
The compound was prepared according to procedure B and purified by column chromatography (5-10% EtOAc/Hexane) to give the product as an oil (26 mg, 50%).

R_f = 0.61 (20% EtOAc/Hexane).

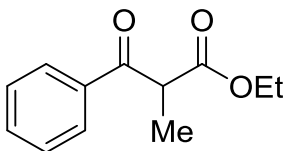
¹H NMR (400 MHz, CDCl₃) δ 4.18 (q, J = 7.1 Hz, 2 H), 2.53 – 2.35 (m, 3 H), 2.03 – 1.85 (m, 2 H), 1.76 – 1.53 (m, 4 H), 1.48 – 1.34 (m, 1 H), 1.24 (dd, J = 8.8 Hz, 5.5 Hz, 3 H), 0.82 (t, J = 7.5 Hz, 3 H).

¹³C NMR (101 MHz, CDCl₃) δ 208.04, 171.94, 61.11, 60.98, 41.13, 35.51, 27.59, 27.57, 22.52, 14.11, 8.68.

The data is consistent with those reported in the literature (reference 3)



Ethyl 2-methyl-3-oxo-3-phenylpropanoate (11a)⁴



The compound was prepared according to procedure A and purified by column chromatography (5-15% EtOAc/Hexane) to give the product as an oil (110 mg, 92%).

R_f = 0.55 (20% EtOAc/Hexane).

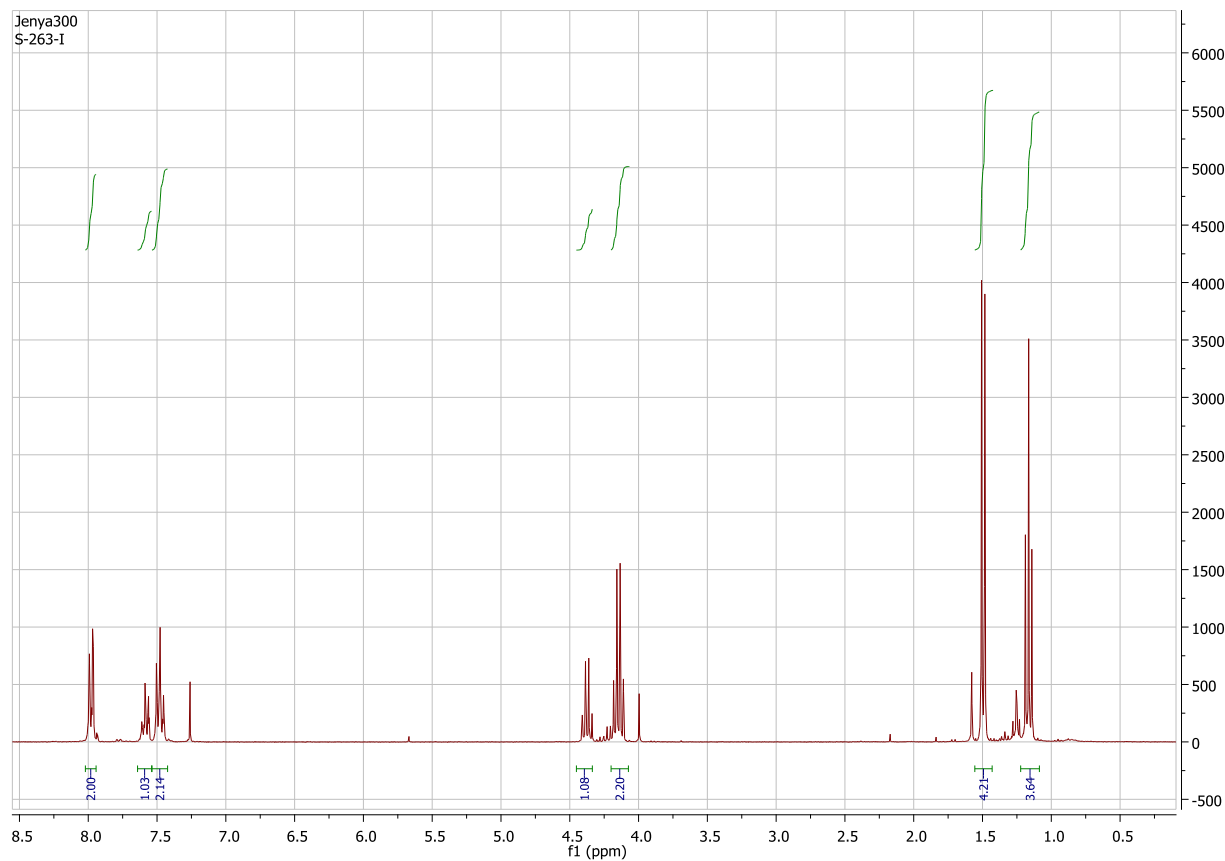
¹H NMR (300 MHz, CDCl₃) δ 7.97 (d, J = 8.1 Hz, 2 H), 7.58 (t, J = 7.5 Hz, 1 H), 7.47 (t, J = 8.3 Hz, 2 H), 4.36 (q, J = 7.1 Hz, 1 H), 4.14 (q, J = 7.1 Hz, 2 H), 1.49 (d, J = 7.1 Hz, 2 H), 1.15 (t, J = 7.1 Hz, 3H).

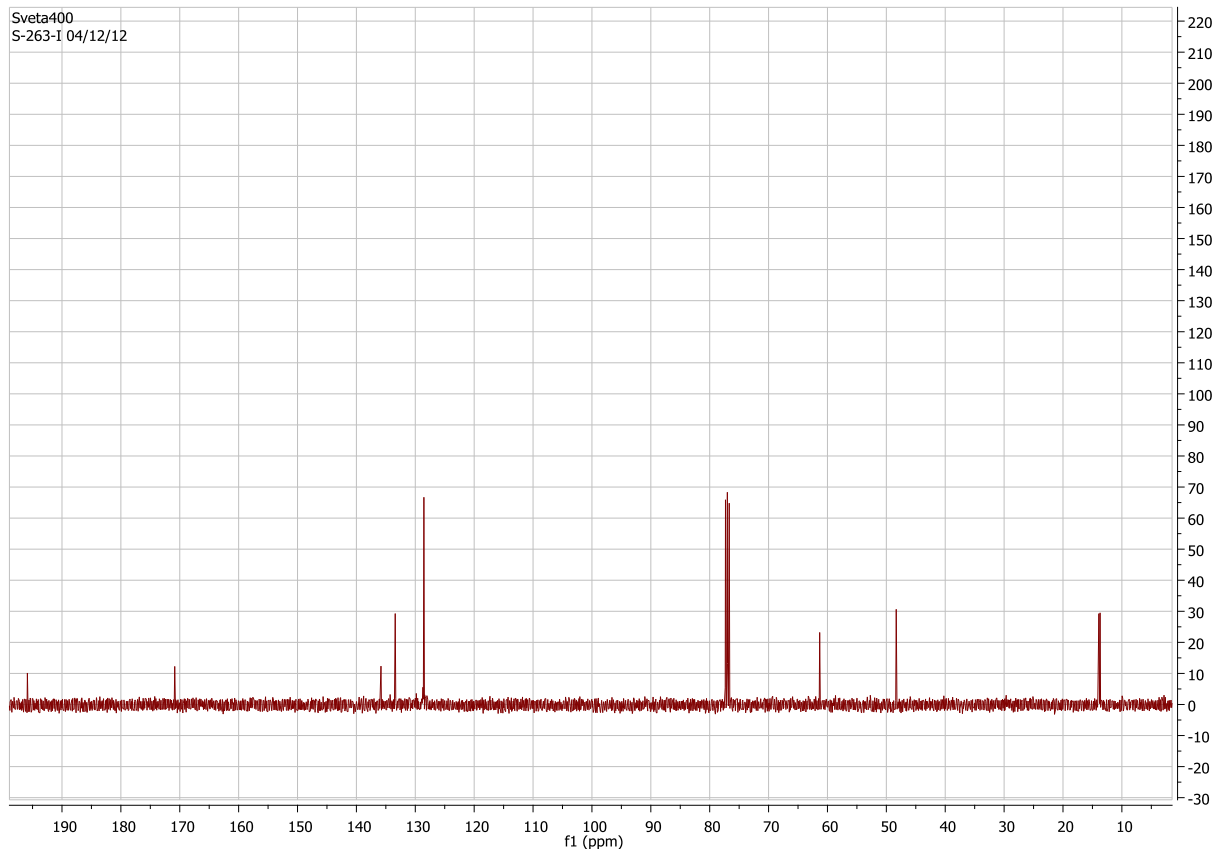
¹³C NMR (101 MHz, CDCl₃) δ 195.88, 170.85, 135.82, 133.40, 128.68, 128.54, 61.32, 48.32, 13.91, 13.70.

IR: (thin film) ν 2984, 2939, 1735, 1684, 1592, 1450, 1370, 1184, 1089, 1029, 963, 767, 693, 586 cm⁻¹.

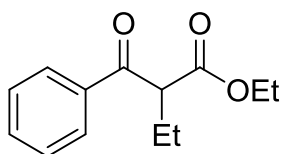
HRMS (ESI) m/z : calcd for C₁₂H₁₄O₃, [M+1], 207.1021; found 207.1026.

The data is consistent with those reported in the literature (reference 4)





Ethyl 2-benzoylbutanoate (11b)⁵



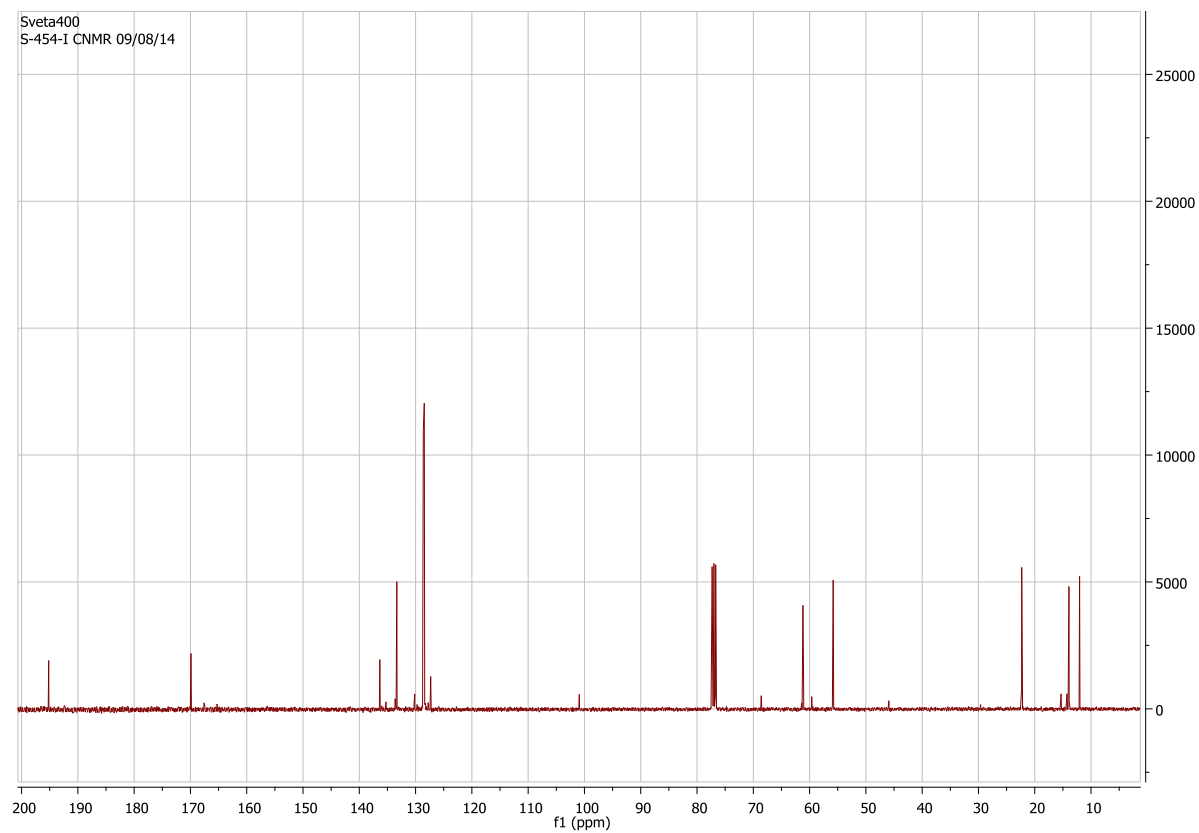
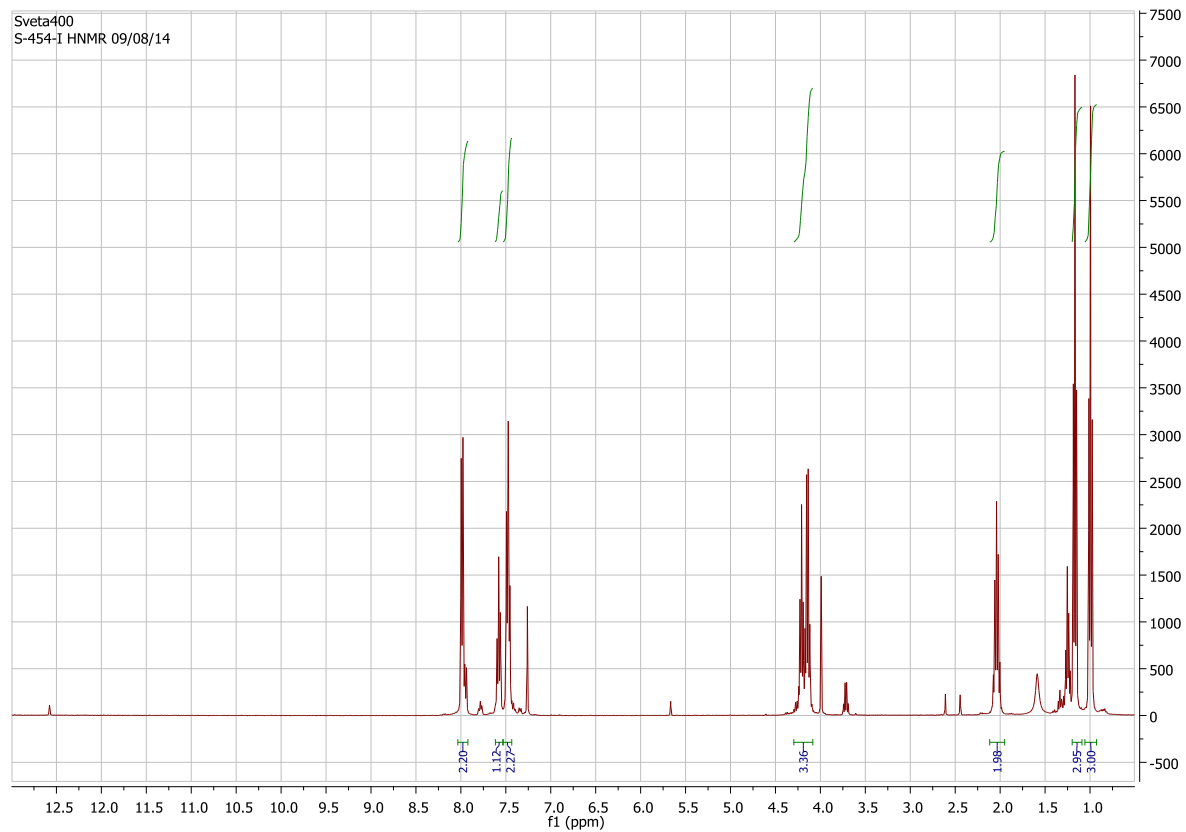
The compound was prepared according to procedure B and purified by column chromatography (5-10% EtOAc/Hexane) to give the product as an oil (95 mg, 86%).

R_f = 0.56 (20% EtOAc/Hexane).

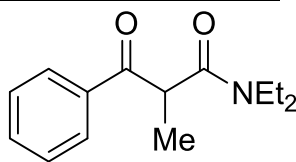
¹H NMR (400 MHz, CDCl₃) δ 7.93 (d, J = 7.8 Hz, 2 H), 7.52 (t, J = 7.3 Hz, 1 H), 7.41 (t, J = 7.6 Hz, 2 H), 4.18 (m, 1 H + 2 H), 1.98 (q, J = 7.3 Hz, 2 H), 1.11 (t, J = 7.1 Hz, 3 H), 0.94 (t, J = 7.4 Hz, 3 H).

¹³C NMR (101 MHz, CDCl₃) δ 195.31, 170.04, 136.47, 133.48, 128.77, 128.59, 61.31, 55.92, 22.45, 14.12, 12.17.

The data is consistent with those reported in the literature (reference 5)



N,N-diethyl-2-methyl-3-oxo-3-phenylpropanamide (13)⁶



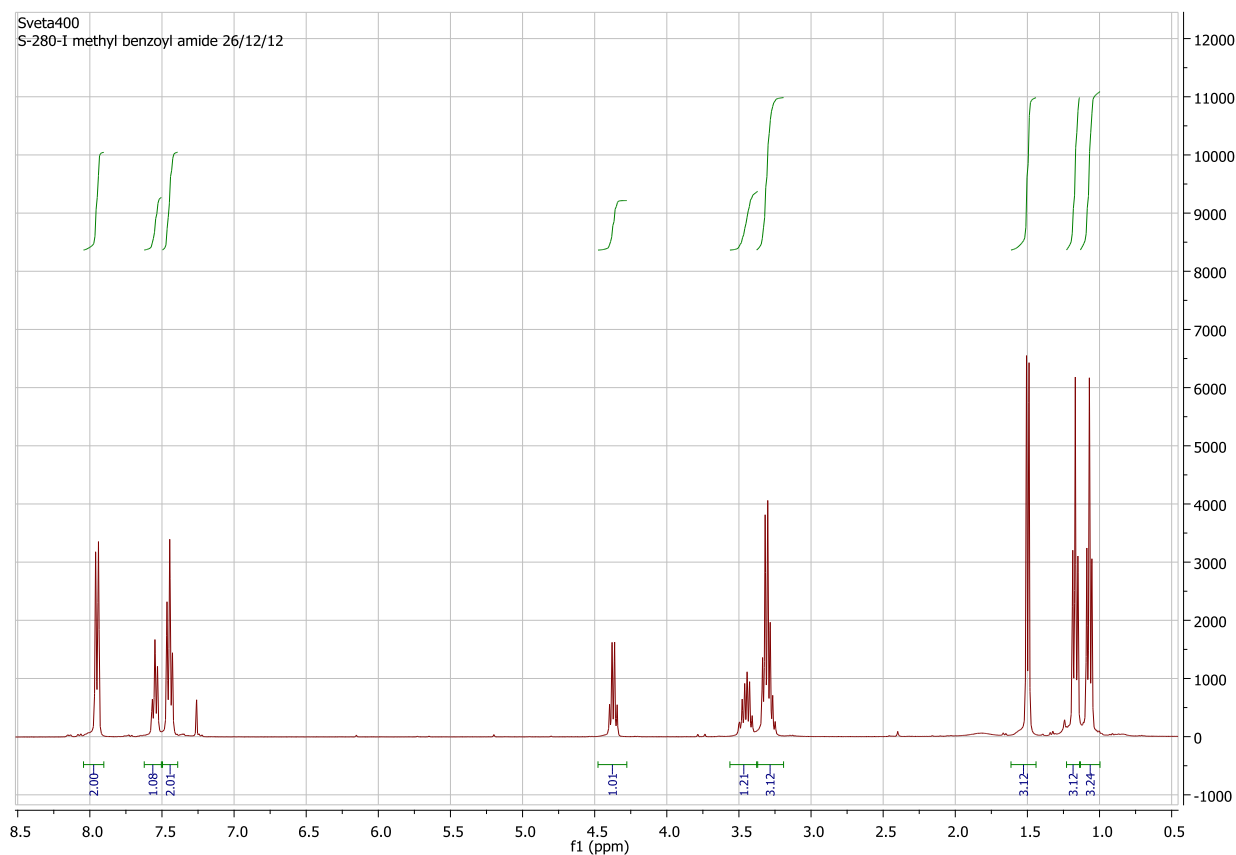
The compound was prepared according to procedure A and purified by column chromatography (10-30% EtOAc/Hexane) to give the product as an oil (82 mg, 88%).

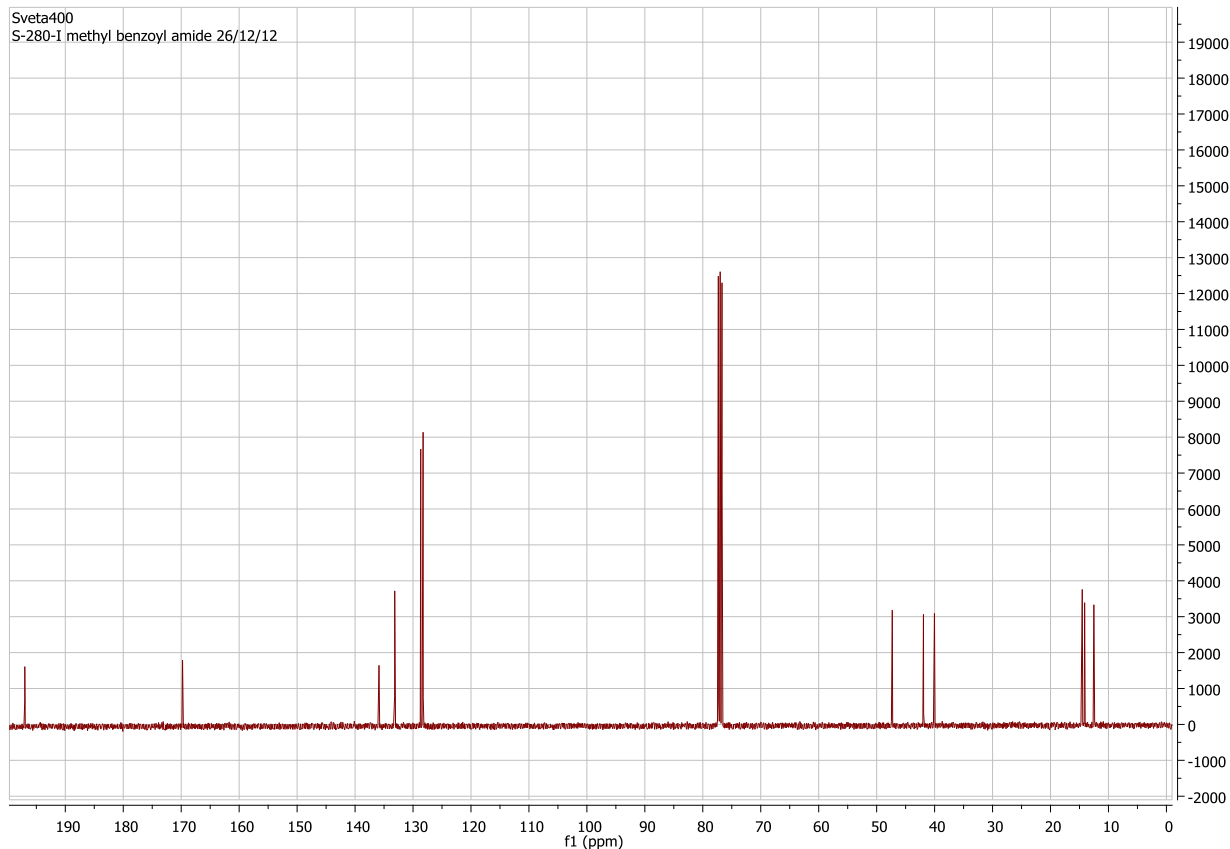
R_f = 0.14 (20% EtOAc/Hexane).

¹H NMR (400 MHz, CDCl₃) δ 7.95 (d, J = 8.0 Hz, 2 H), 7.55 (t, J = 7.0 Hz, 1 H), 7.45 (t, J = 7.6 Hz, 2 H), 4.37 (q, J = 7.0 Hz, 1 H), 3.45 (dq, J = 14.1 Hz, 7.1 Hz, 1 H), 3.30 (m, 3 H), 1.50 (d, J = 7.0 Hz, 3 H), 1.17 (t, J = 7.1 Hz, 3 H), 1.07 (t, J = 7.1 Hz, 3 H).

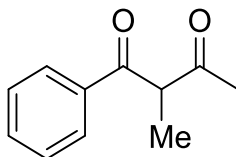
¹³C NMR (101 MHz, CDCl₃) δ 196.99, 169.77, 135.87, 133.16, 128.67, 128.26, 47.31, 41.92, 40.03, 14.52, 14.11, 12.52.

The data is consistent with those reported in the literature (reference 6)





2-Methyl-1-phenylbutane-1,3-dione (15)⁷



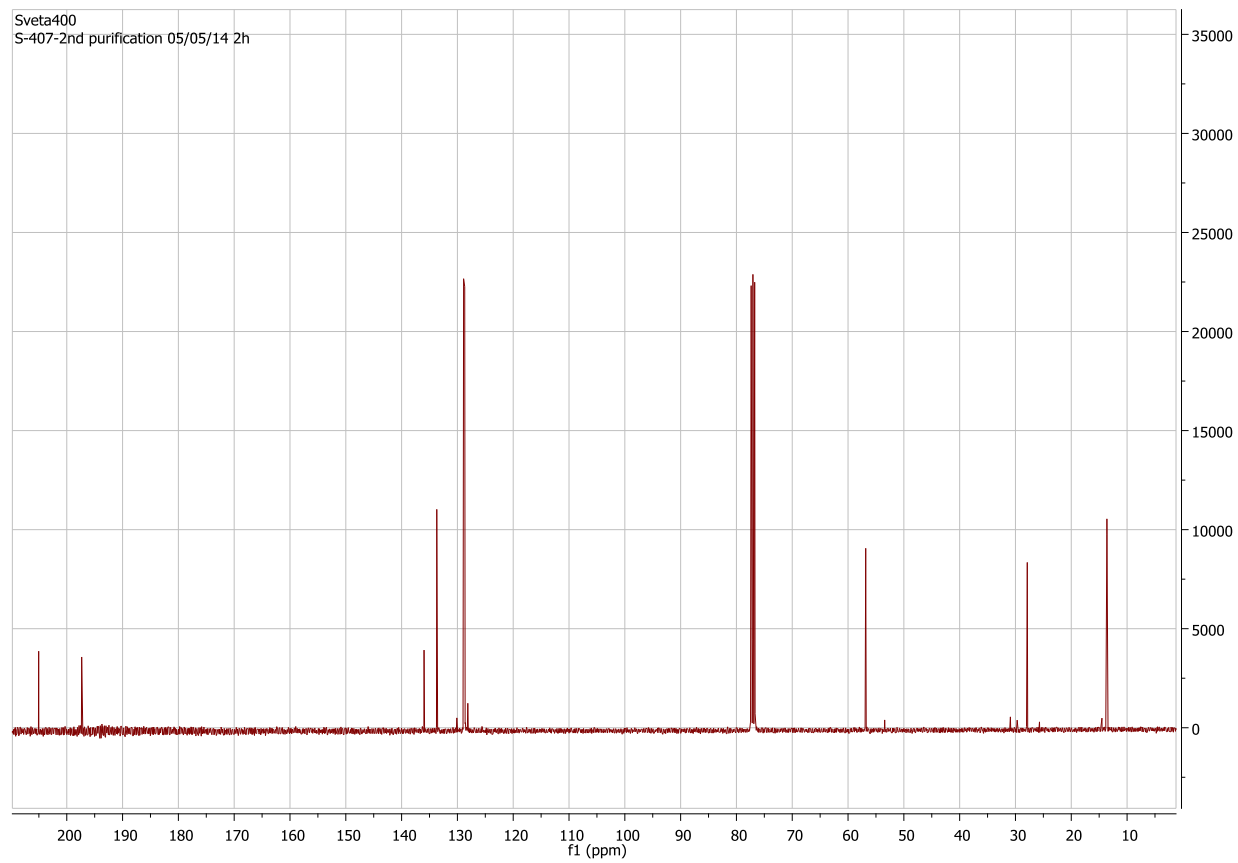
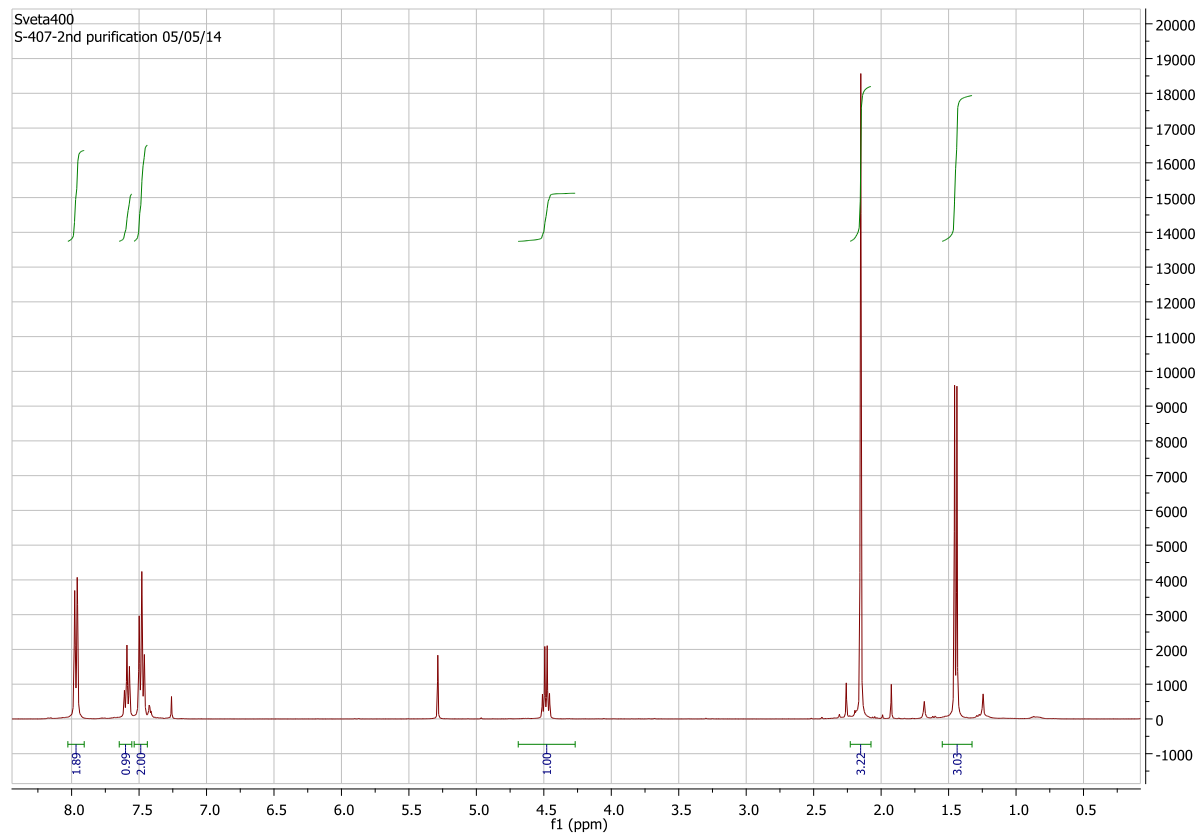
The compound was prepared according to procedure A and purified by column chromatography (10% EtOAc/Hexane) to give the product as an oil (58 mg, 66%).

$R_f = 0.38$ (DCM).

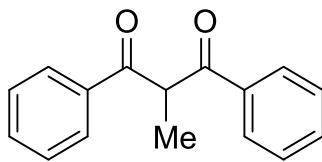
¹H NMR (400 MHz, CDCl₃) δ 7.97 (d, $J = 7.4$ Hz, 2 H), 7.59 (t, $J = 7.4$ Hz, 1 H), 7.48 (t, $J = 7.7$ Hz, 2 H), 4.48 (q, $J = 7.0$ Hz, 1 H), 2.15 (s, 3 H), 1.45 (d, $J = 7.0$ Hz, 3 H).

¹³C NMR (101 MHz, CDCl₃) δ 205.03, 197.33, 135.98, 133.69, 128.89, 128.69, 56.84, 27.88, 13.62.

The data is consistent with those reported in the literature (reference 7)



2-Methyl-1,3-diphenylpropane-1,3-dione (17a)⁸



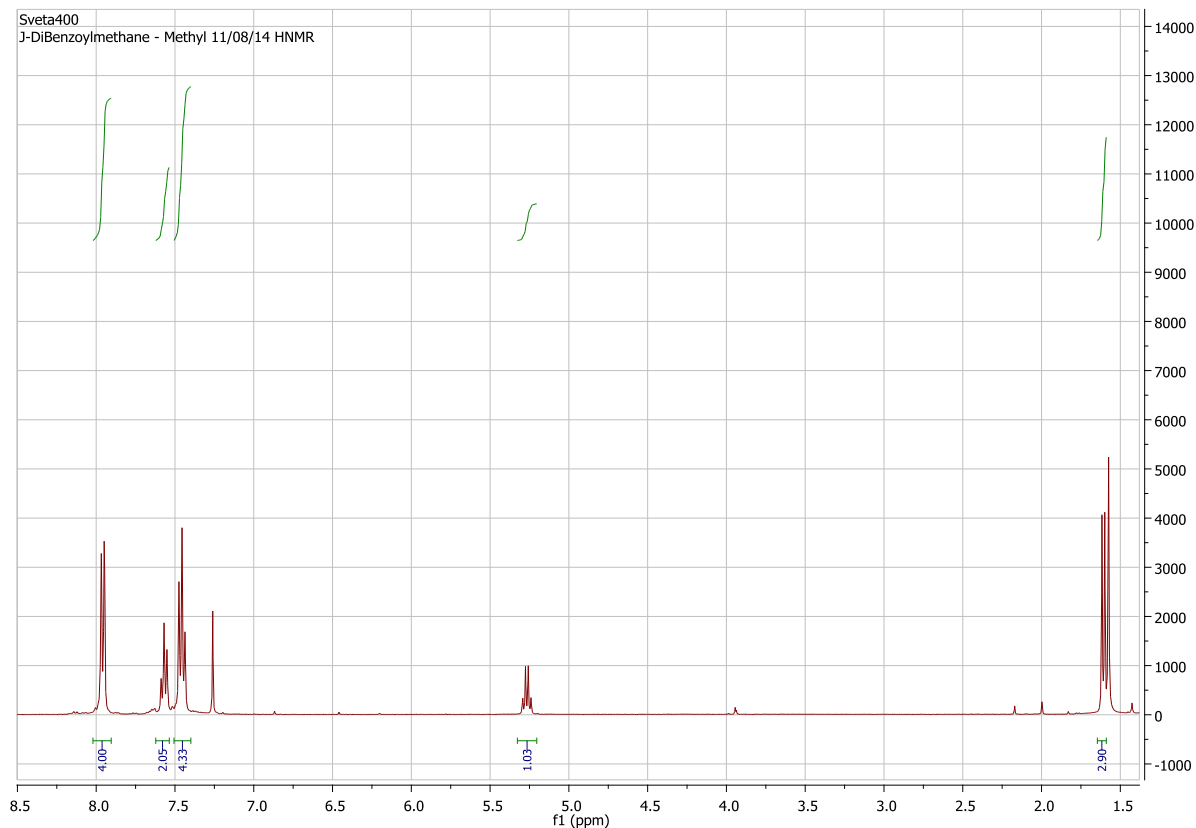
The compound was prepared according to procedure A and purified by column chromatography (5-10% EtOAc/Cyclohexane) to give the product as a solid (84 mg, 76%).

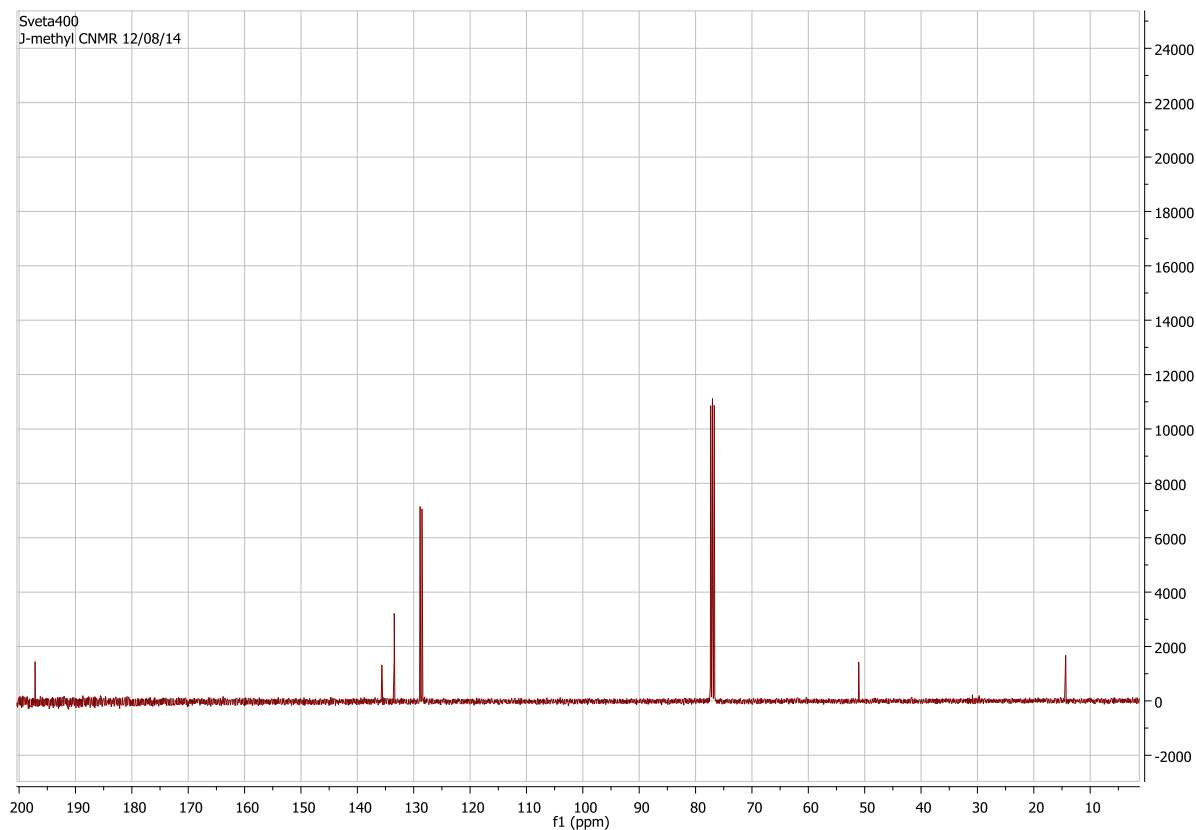
$R_f = 0.49$ (DCM).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.91 (d, $J = 7.4$ Hz, 4 H), 7.52 (t, $J = 7.4$ Hz, 2 H), 7.40 (t, $J = 7.7$ Hz, 4 H), 5.23 (m, 1 H), 1.56 (d, $J = 7.0$ Hz, 3 H).

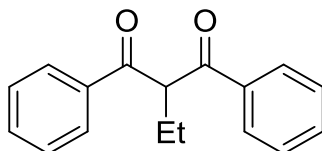
$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 197.17, 135.63, 133.45, 128.86, 128.51, 51.02, 14.34.

The data is consistent with those reported in the literature (reference 8)





2-Ethyl-1,3-diphenylpropane-1,3-dione (17b)⁹



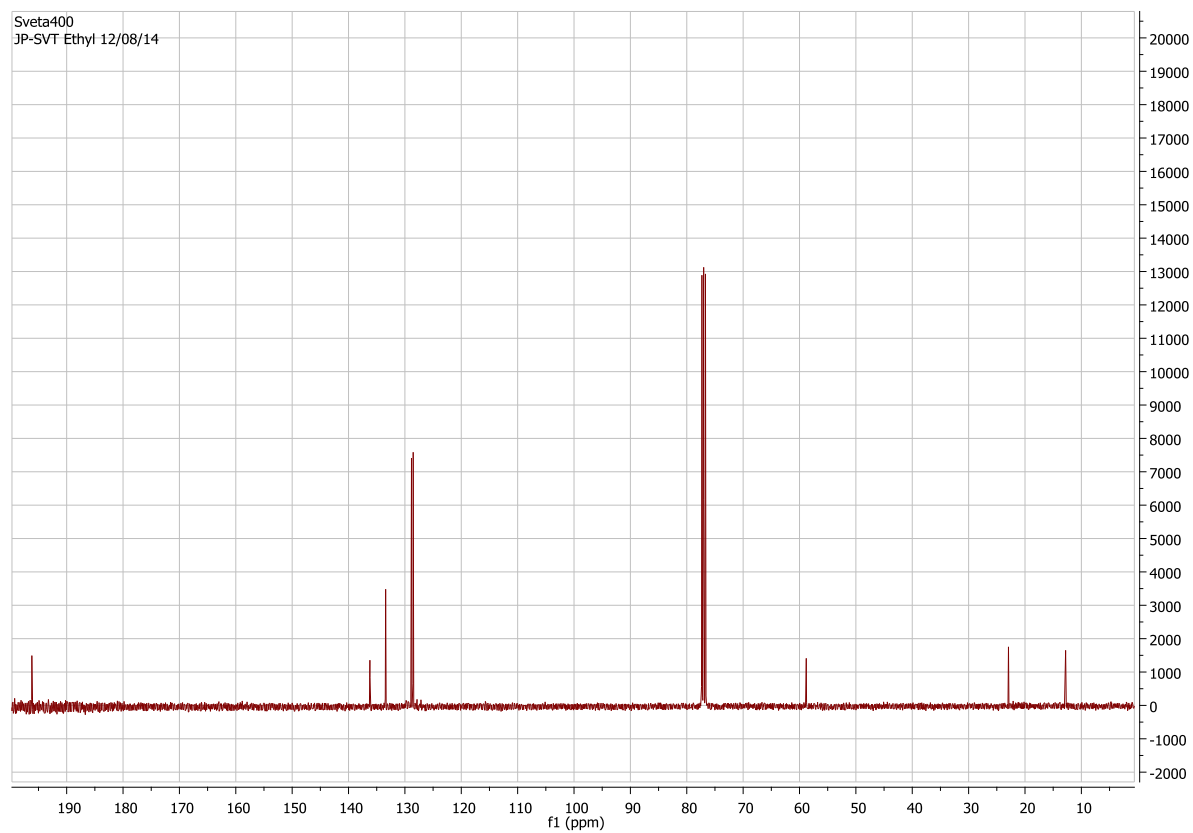
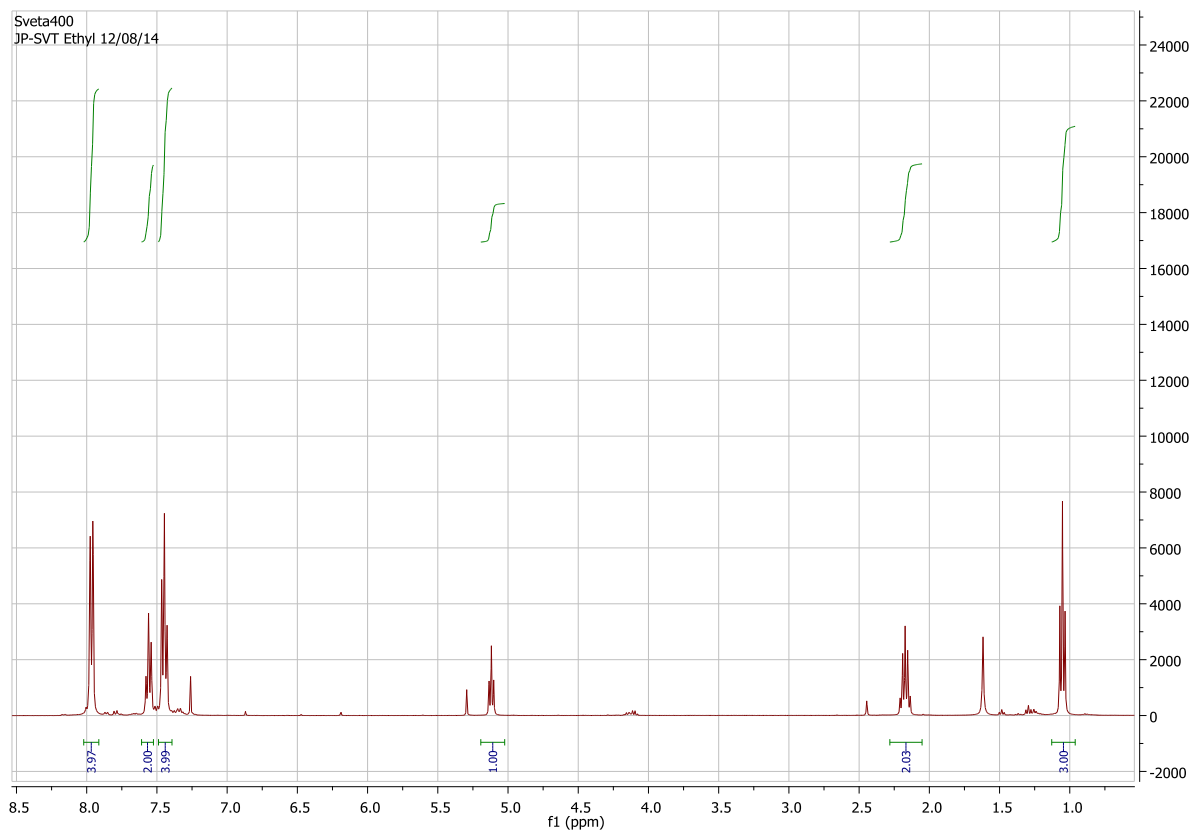
The compound was prepared according to procedure A and purified by column chromatography (5-10% EtOAc/Hexane) to give the product as a solid (80 mg, 65%).

R_f = 0.36 (10% EtOAc/Hex).

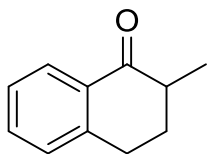
¹H NMR (400 MHz, CDCl₃) δ 7.97 (d, J = 7.4 Hz, 4 H), 7.56 (t, J = 7.4 Hz, 2 H), 7.45 (t, J = 7.7 Hz, 4 H), 5.12 (t, J = 6.6 Hz, 1 H), 2.17 (q, J = 7.3 Hz, 2 H), 1.05 (t, J = 7.4 Hz, 3 H).

¹³C NMR (101 MHz, CDCl₃) δ 196.18, 136.21, 133.41, 128.83, 128.53, 58.80, 22.93, 12.80.

The data is consistent with those reported in the literature (reference 9)



2-Methyl-3,4-dihydronaphthalen-1(2H)-one (19a)¹⁰



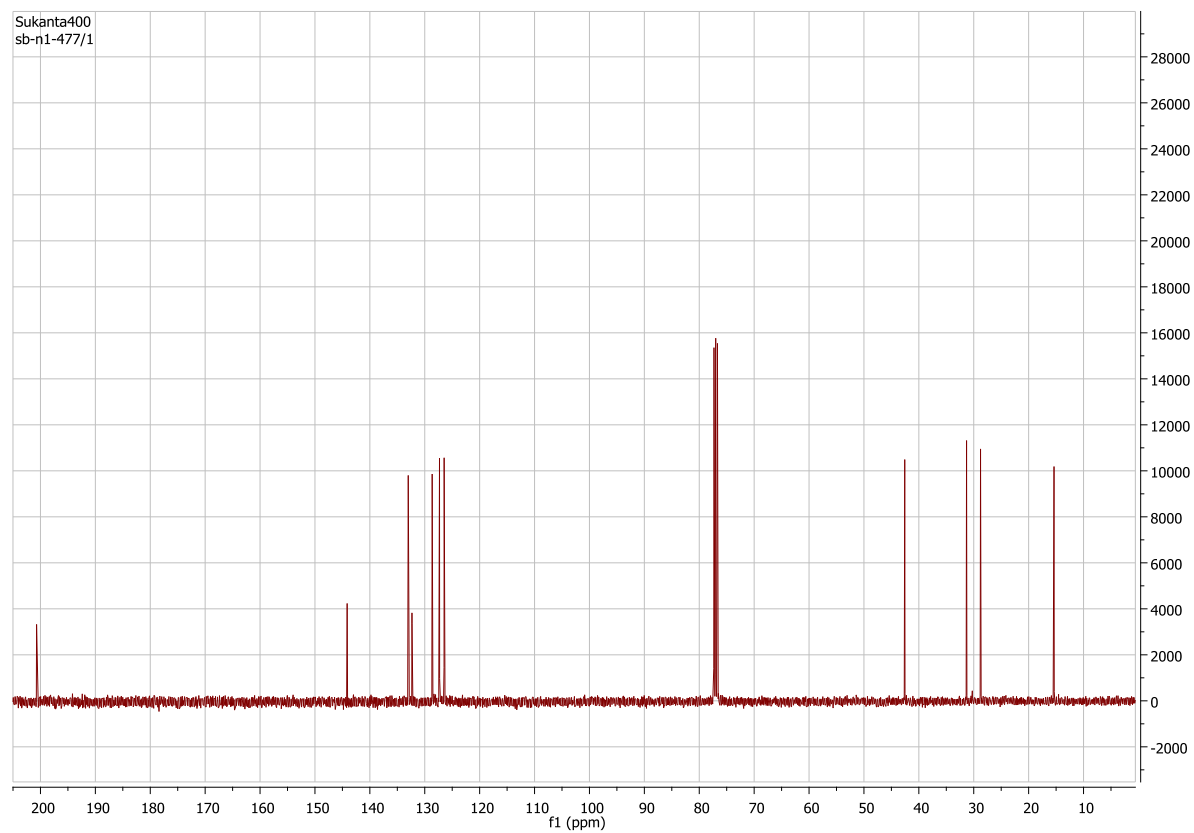
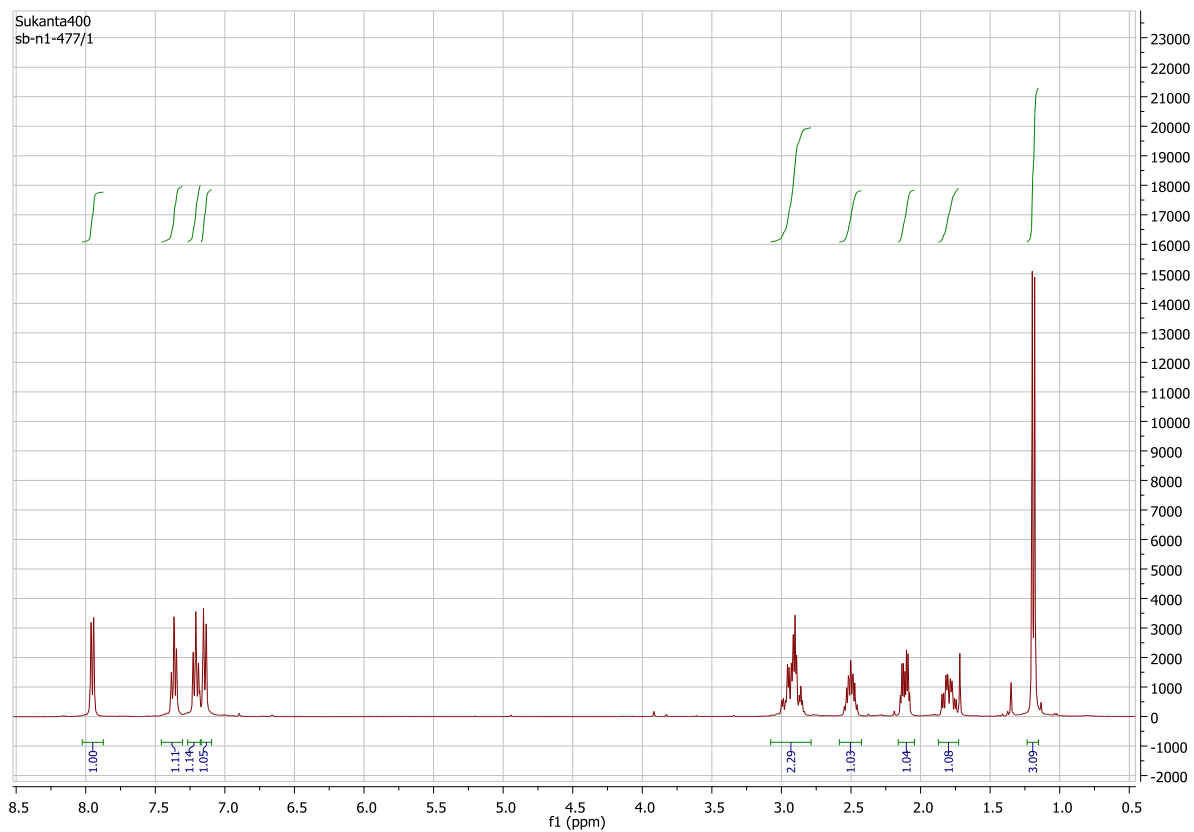
((3,4-Dihydronaphthalen-1-yl)oxy)trimethylsilane (0.5 mmol, 0.11 g) and MeLi in ether (1.5 M, 0.6 mmol, 0.4 mL) were combined in a Schlenk flask under positive argon flow at ambient temperature. Following 30 min of stirring, the volatiles were removed at r.t., under reduced pressure (10 torr), for 30 min. The formed lithium enolate (white solid) was dissolved in anhydrous toluene (0.3 M, 1.5 mL) and cooled to -78 °C. [hydroxy(tosyloxy)iodo]benzene (1 mmol, 0.39 g) and freshly dried MgSO₄ (2.5 mmol, 0.3 g) were added in the dark. After 15 min dimethylzinc in toluene (1.2 M, 1 mmol, 0.83 mL) was added at once. The mixture was allowed to stir at -78 °C for 18 h, in the dark. Reaction was quenched by addition of water, followed by filtration of the slurry through a Celite® frit and rinse with Et₂O. The material was purified by a column chromatography (5-10% EtOAc/Hexane) to give the product as an oil (55 mg, 68 %).

R_f = 0.45 (5% EtOAc/Hexane).

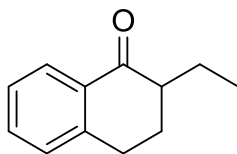
¹H NMR (400 MHz, CDCl₃) δ 7.95 (d, J = 7.8 Hz, 1 H), 7.37 (t, J = 7.4 Hz, 1 H), 7.21 (t, J = 7.5 Hz, 1 H), 7.14 (d, J = 7.6 Hz, 1 H), 2.92 (qt, J = 16.7 Hz, 4.6 Hz, 2 H), 2.50 (m, 1 H), 2.11 (dq, J = 13.2 Hz, 4.4 Hz, 1 H), 1.80 (ddd, J = 24.6 Hz, 11.9 Hz, 4.9 Hz, 1 H), 1.19 (d, J = 6.8 Hz, 3 H).

¹³C NMR (101 MHz, CDCl₃) δ 200.71, 144.13, 133.01, 132.33, 128.65, 127.31, 126.47, 42.57, 31.31, 28.76, 15.38.

The data is consistent with those reported in the literature (reference 10)



2-Ethyl-3,4-dihydronaphthalen-1(2H)-one (19b)¹⁰



Option 1: ((3,4-Dihydronaphthalen-1-yl)oxy)trimethylsilane (0.5 mmol, 0.11 g) and MeLi in ether (1.5 M, 0.6 mmol, 0.4 mL) were combined in a Schlenk flask under positive argon flow at ambient temperature. Following 30 min of stirring, the volatiles were removed at r.t. under reduced pressure (10 torr), for 30 min. Lithium enolate (white solid) was dissolved in anhydrous toluene (0.3 M, 1.5 mL) and cooled to -78 °C. [hydroxy(tosyloxy)iodo]benzene (1 mmol, 0.39 g) and freshly dried MgSO₄ (2.5 mmol, 0.3 g) were added in the dark. After 15 min diethylzinc in toluene (1.5 M, 1 mmol, 0.67 mL) was added at once. The mixture was allowed to stir at -78 °C for 18 h, in the dark. Reaction was quenched by addition of water, followed by filtration of the slurry through a Celite® frit and rinse with Et₂O. The material was purified by a column chromatography (2-10% EtOAc/Hexane) to give the product **as an oil (60 mg, 70%)**.

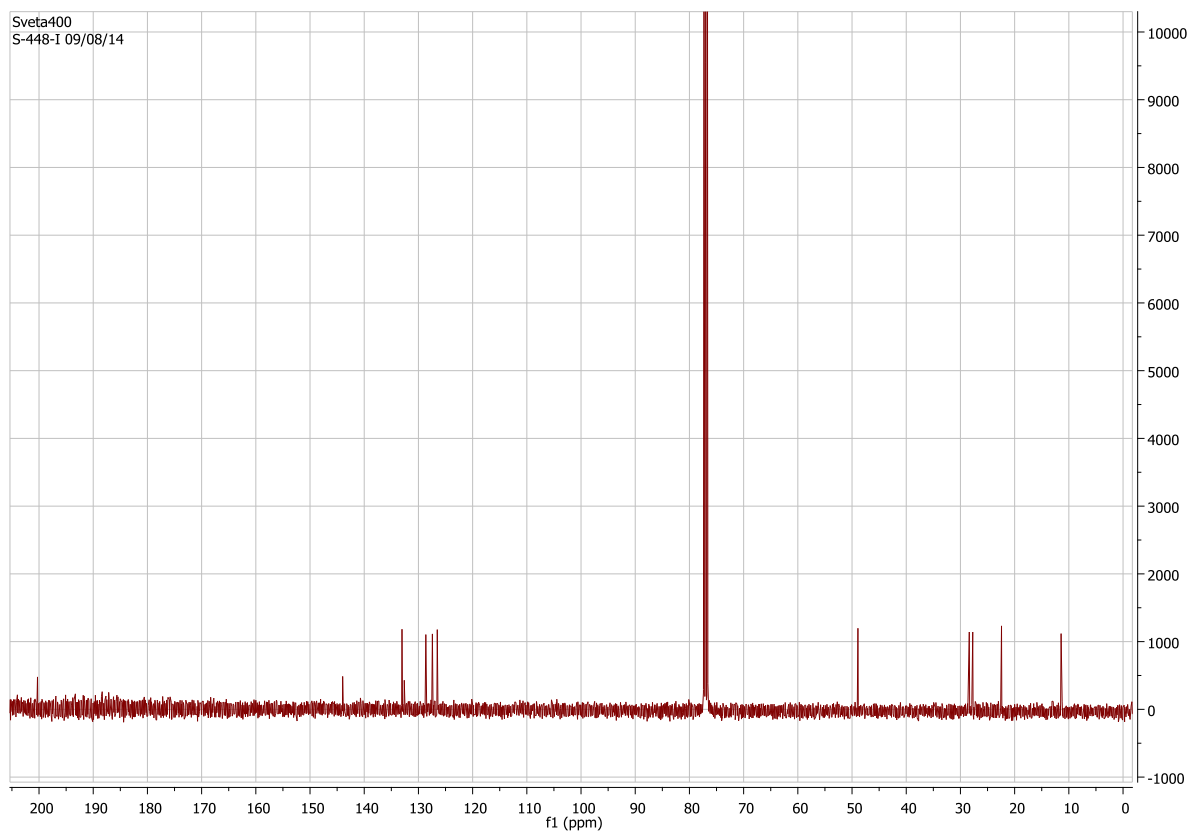
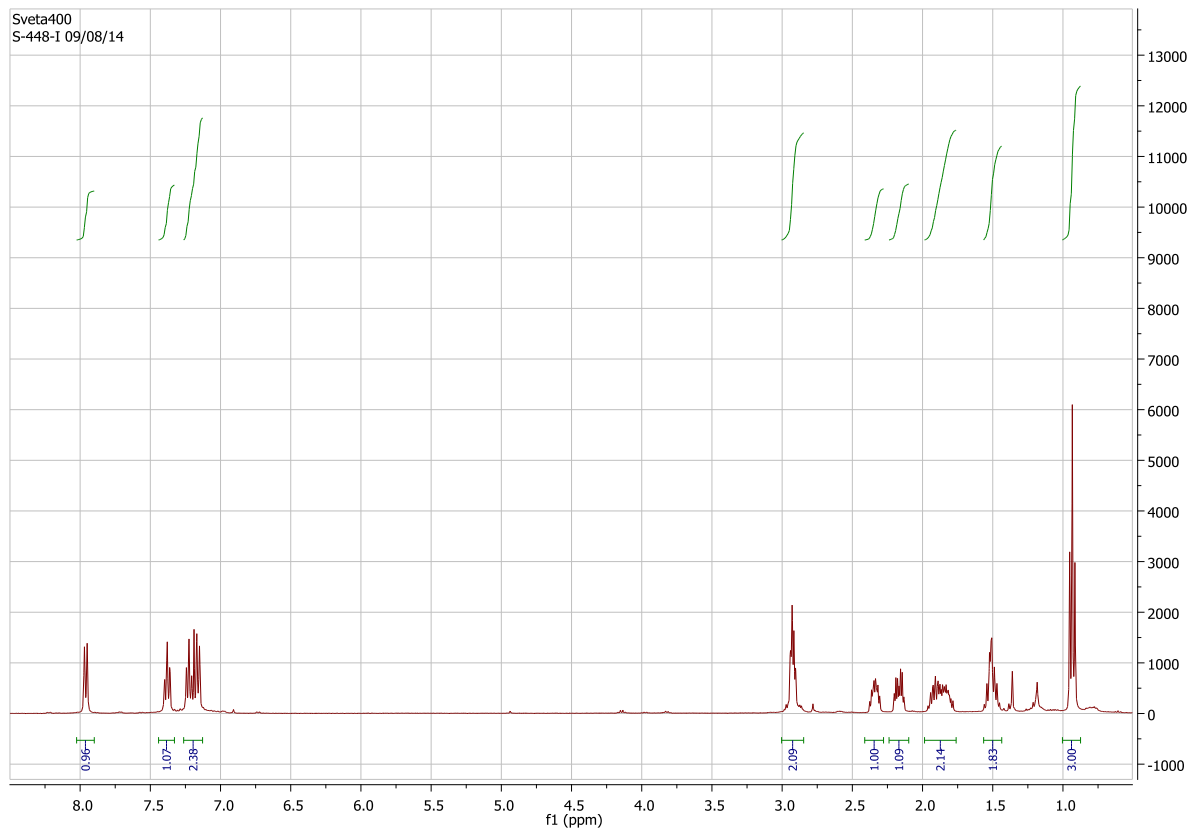
Option 2: Hexamethyldisilazane (freshly distilled) (1.03 mmol, 0.15 g) was dissolved in a dry toluene (0.4 M, 2.6 mL). After cooling to 0-5 °C, *n*BuLi in hexane (1.6M, 1.32 mmol, 0.82 mL) was added dropwise over 5 min. After cooling to -78 °C 3,4-dihydronaphthalen-1(2H)-one (tetralone) (1.03 mmol, 0.14 mL) in 1 mL toluene was added dropwise for 5 min. After 30 min, [hydroxy(tosyloxy)iodo]benzene (4.12 mmol, 1.6 g) and freshly dried MgSO₄ (5.15 mmol, 0.64 g) were added in the dark and allowed to stir for 15 min. Solution of diethylzinc in toluene (1.5 M, 4.14 mmol, 2.75 mL) was added at once. The mixture was allowed to stir at -78 °C for 18 h, in the dark. Reaction was quenched by addition of water, followed by filtration of the slurry through a Celite® frit and rinse with Et₂O. The material was purified by a column chromatography (5-10% EtOAc/Hexane) to give the product **as an oil (77 mg, 50%)**.

R_f = 0.45 (5% EtOAc/Hexane).

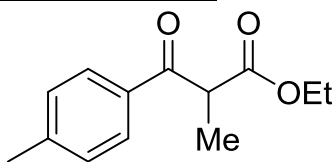
¹H NMR (400 MHz, CDCl₃) δ 7.96 (d, *J* = 7.7 Hz, 1 H), 7.38 (t, *J* = 7.0 Hz, 1 H), 7.20 (m, 2 H), 2.92 (dd, *J* = 9.7 Hz, 4.5 Hz, 2 H), 2.34 (ddd, *J* = 11.7 Hz, 7.5 Hz, 4.9 Hz, 1 H), 2.17 (ddd, *J* = 13.9 Hz, 9.4 Hz, 4.6 Hz, 1 H), 1.86 (m, 2 H), 1.52 (td, *J* = 14.8 Hz, 7.4 Hz, 1 H), 0.93 (t, *J* = 7.5 Hz, 3 H).

¹³C NMR (101 MHz, CDCl₃) δ 200.28, 143.98, 133.03, 132.61, 128.63, 127.42, 126.52, 48.91, 28.37, 27.73, 22.42, 11.43.

The data is consistent with those reported in the literature (reference 10)



Ethyl 2-methyl-3-oxo-3-(p-tolyl)propanoate (30a)¹¹



The compound was prepared according to procedure A and purified by column chromatography (5-15% EtOAc/Hexane) to give the product as an oil (120 mg, 87%).

R_f = 0.52 (20% EtOAc/Hexane).

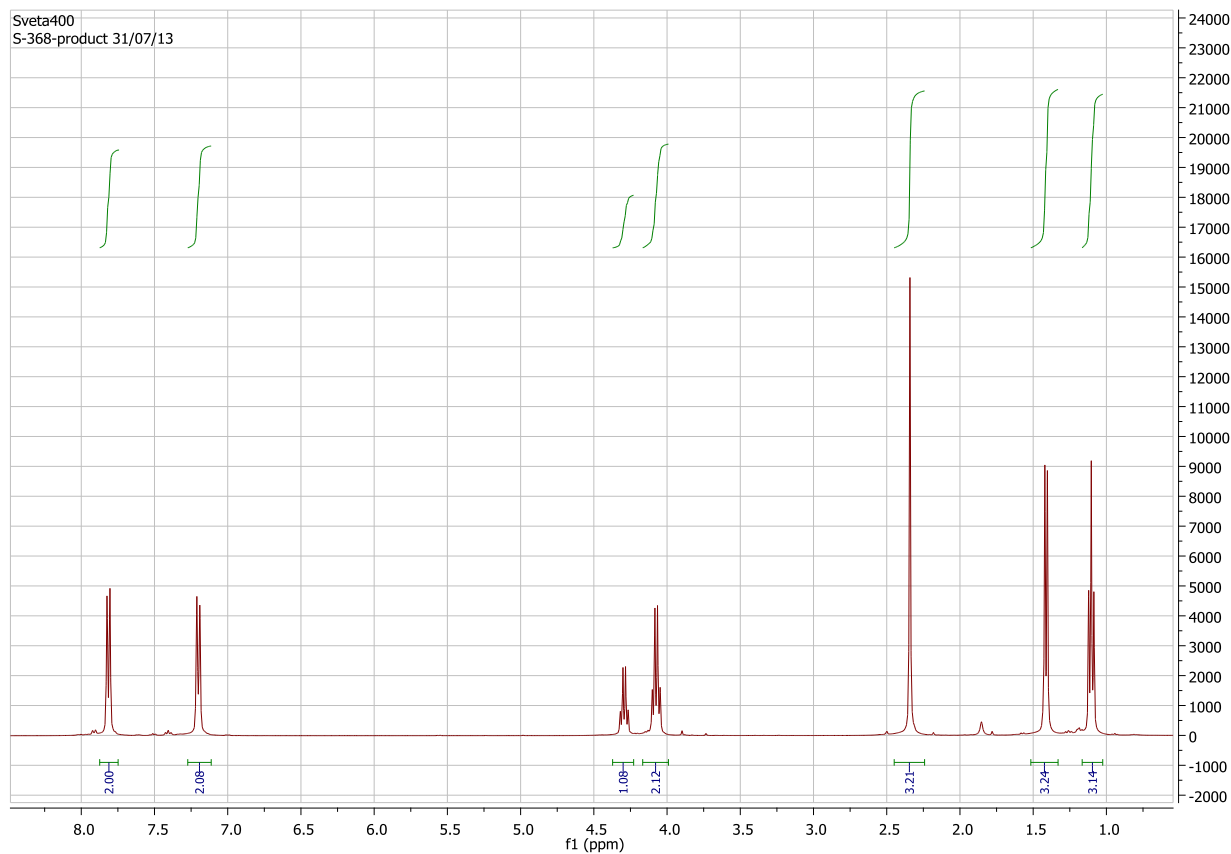
¹H NMR (400 MHz, CDCl₃) δ 7.81 (d, J = 8.1 Hz, 2 H), 7.20 (d, J = 8.0 Hz, 2 H), 4.29 (q, J = 7.1 Hz, 1 H), 4.07 (q, J = 7.1 Hz, 2 H), 2.34 (s, 3 H), 1.41 (d, J = 7.1 Hz, 3 H), 1.10 (t, J = 7.1 Hz, 3 H).

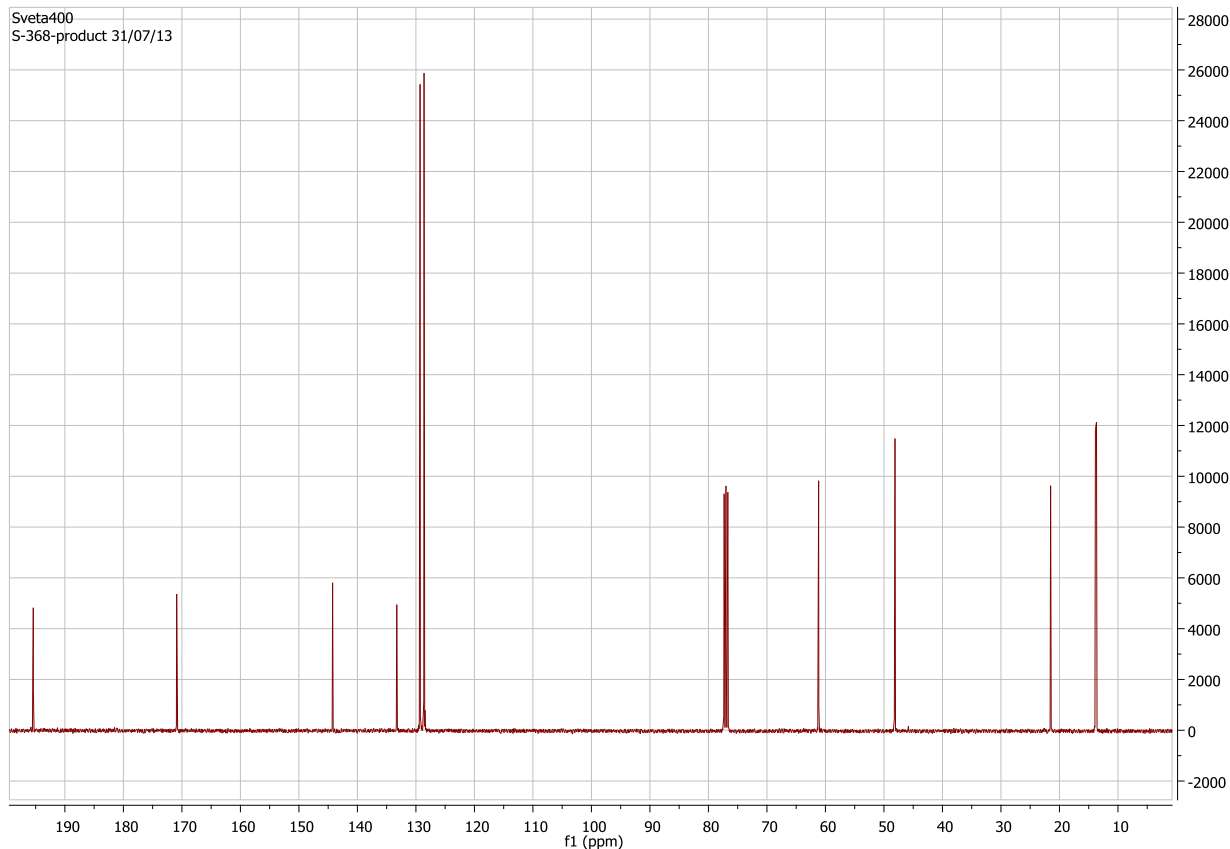
¹³C NMR (101 MHz, CDCl₃) δ 195.40, 170.89, 144.24, 133.26, 129.29, 128.61, 61.16, 48.11, 21.51, 13.85, 13.67.

IR: (thin film) ν 2984.07, 2939.39, 1732.62, 1679.64, 1605.71, 1451.26, 1372.24, 1294.41, 1182.17, 1081.90, 1031.61, 957.68, 741.28 cm⁻¹.

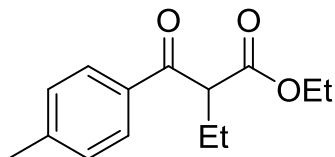
HRMS (ESI) m/z : calcd for C₁₃H₁₆O₃, [M+1], 221.1178; found 221.1199.

The data is consistent with those reported in the literature (reference 11)





Ethyl 2-(4-methylbenzoyl)butanoate (30b)¹²



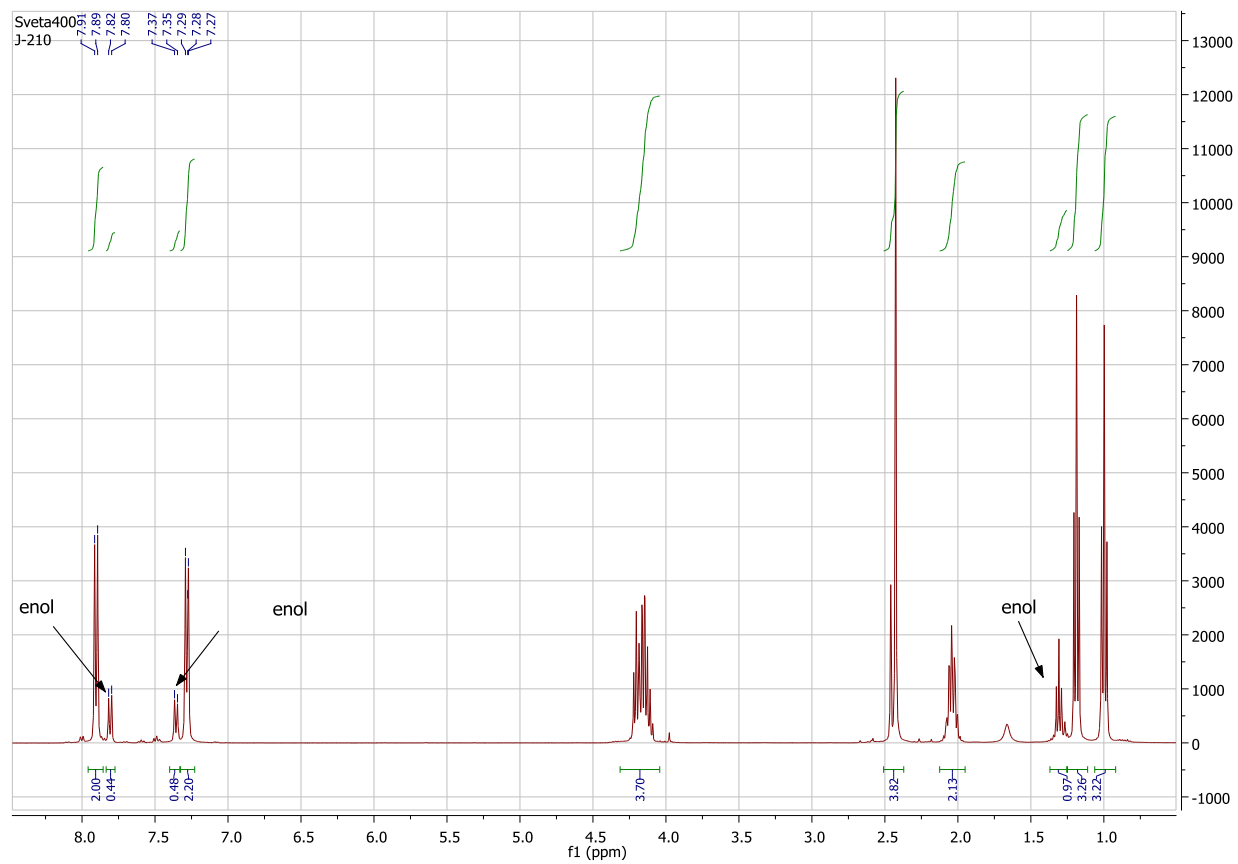
The compound was prepared according to procedure B and purified by column chromatography (10-15% EtOAc/Hexane) to give the product as an oil (100 mg, 85%).

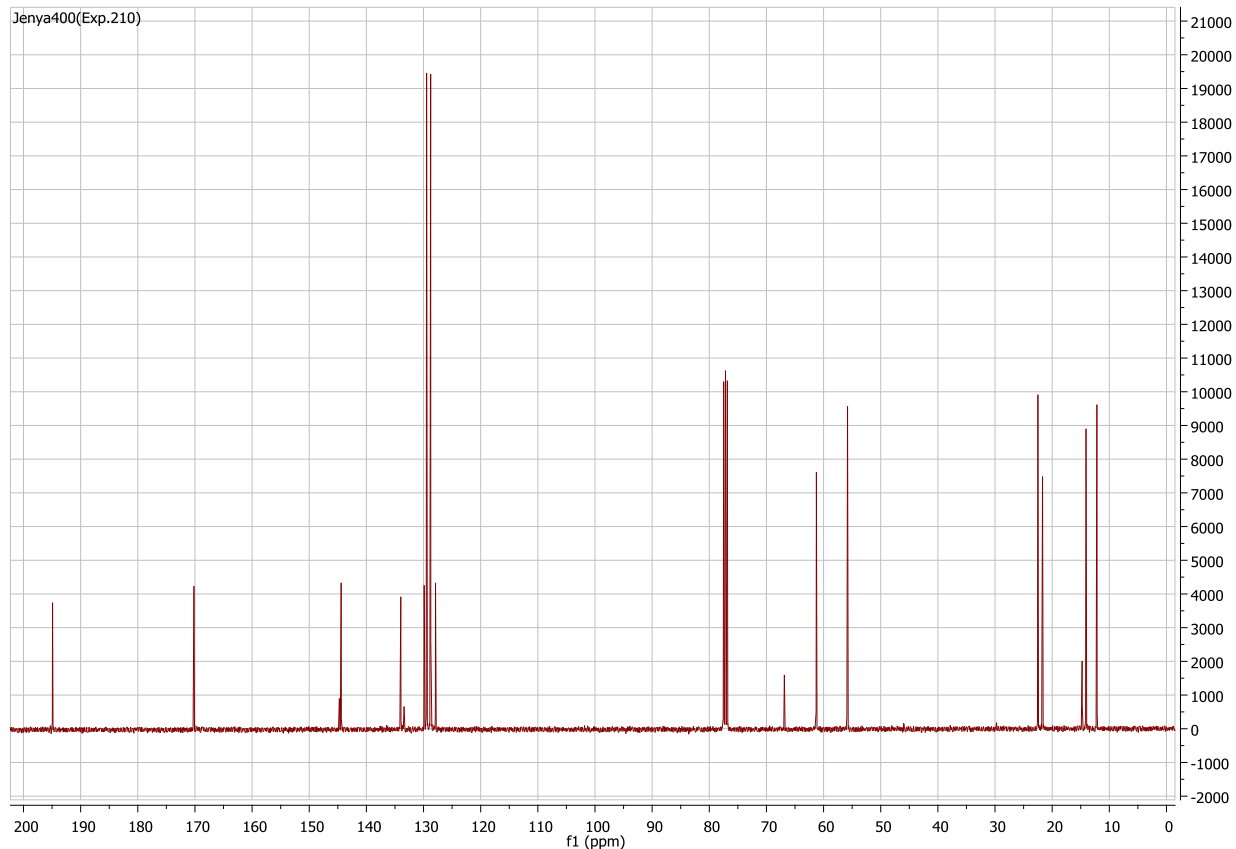
R_f = 0.64 (20% EtOAc/Hexane).

¹H NMR (400 MHz, CDCl₃) δ 7.83 (d, J = 7.9 Hz, 2 H), 7.21 (d, J = 8.0 Hz, 2 H), 4.09 (m, 3 H), 2.35 (s, 3 H), 1.97 (m, 2 H), 1.11 (t, J = 7.1 Hz, 3 H), 0.92 (t, J = 7.4 Hz, 3 H).

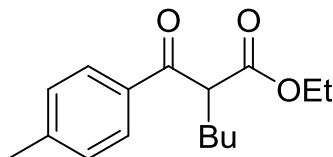
¹³C NMR (101 MHz, CDCl₃) δ 194.92, 170.17, 144.41, 133.98, 129.46, 128.75, 61.26, 55.81, 22.49, 21.69, 14.08, 12.17.

The data is consistent with those reported in the literature (reference 12)





Ethyl 2-(4-methylbenzoyl)hexanoate (30c)



The compound was prepared according to procedure B, employing dibutylzinc in toluene 0.8 M (instead of diethylzinc), and purified by column chromatography (5-10% EtOAc/Hexane) to give the product as an oil (71 mg, 54%).

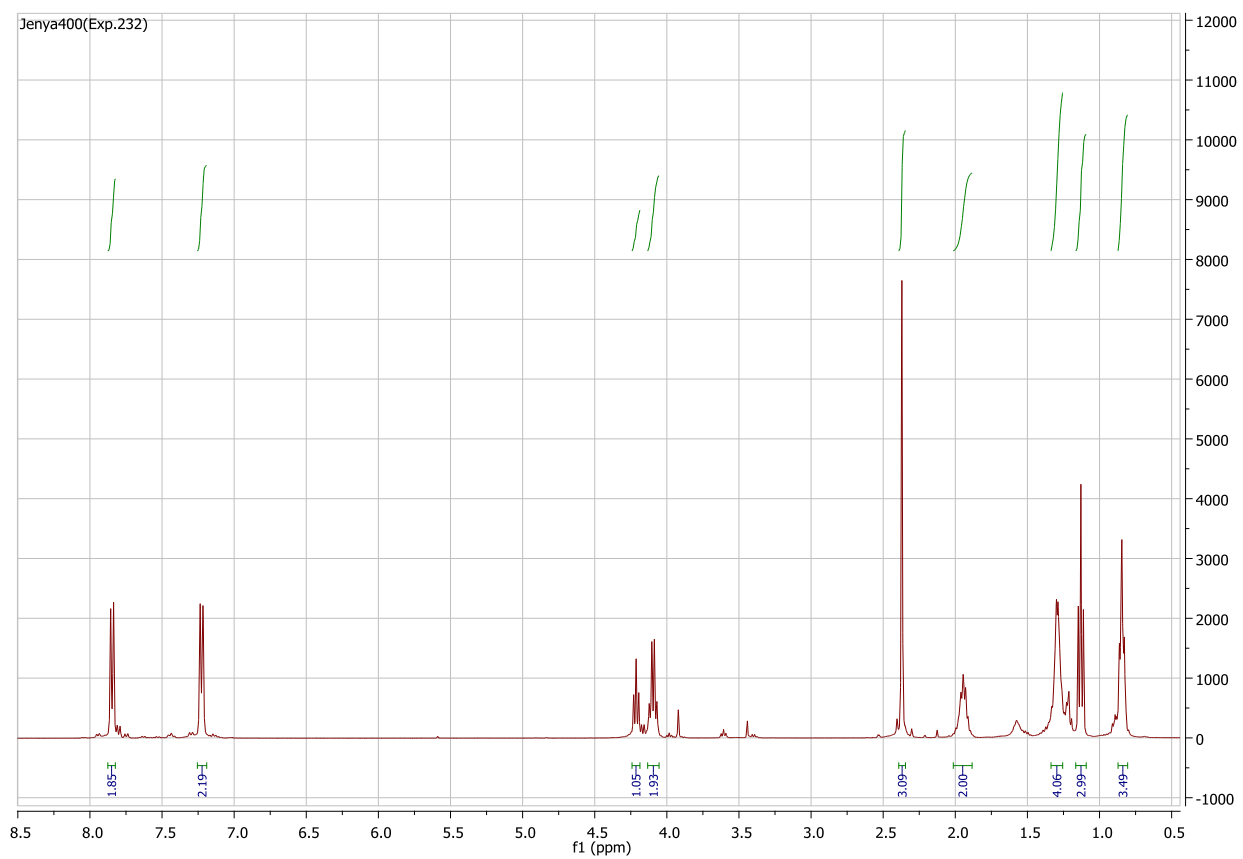
R_f = 0.62 (20% EtOAc/Hexane).

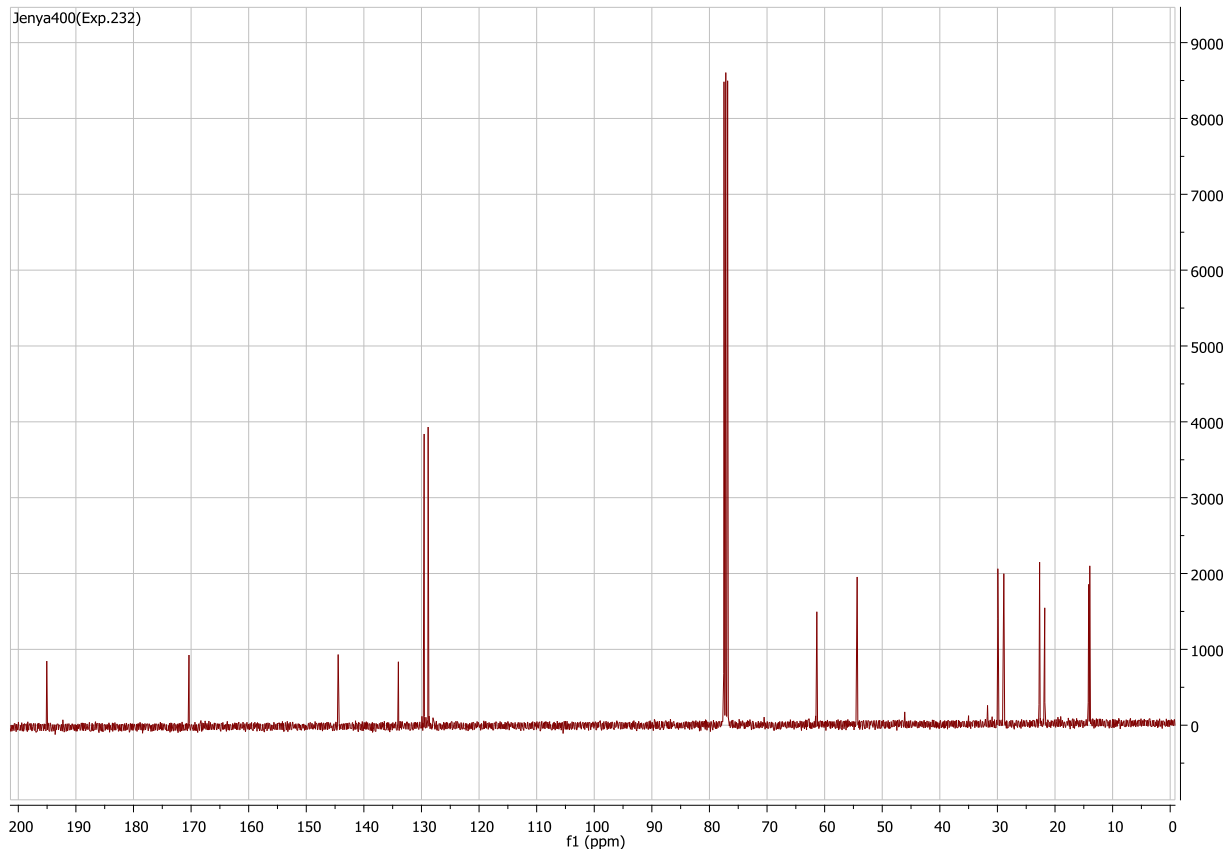
¹H NMR (400 MHz, CDCl₃) δ 7.85 (d, *J* = 8.0 Hz, 2 H), 7.23 (d, *J* = 7.6 Hz, 2 H), 4.21 (t, *J* = 7.2 Hz, 1 H), 4.10 (q, *J* = 7.1 Hz, 2 H), 2.37 (s, 3 H), 1.94 (dd, *J* = 12.8 Hz, 6.2 Hz, 2 H), 1.28 (m, 4 H), 1.13 (t, *J* = 7.1 Hz, 3 H), 0.85 (dd, *J* = 14.2 Hz, 7.6 Hz, 3 H).

¹³C NMR (101 MHz, CDCl₃) δ 195.06, 170.36, 144.46, 134.01, 129.53, 128.84, 61.35, 54.35, 29.93, 28.89, 22.68, 21.78, 14.15, 13.96.

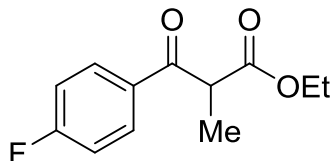
IR: (thin film) ν 3025, 2964, 2868, 1730, 1680, 1603, 1460, 1230, 1183, 1022, 762, 427 cm⁻¹.

HRMS (ESI) *m/z*: calcd for C₁₆H₂₂O₃, [M+1], 263.1647; found 263.1600.





Ethyl 3-(4-fluorophenyl)-2-methyl-3-oxopropanoate (31a)⁴



The compound was prepared according to procedure A and purified by column chromatography (5-15% EtOAc/Hexane) to give the product as an oil (82 mg, 82%).

R_f = 0.50 (20% EtOAc/Hexane).

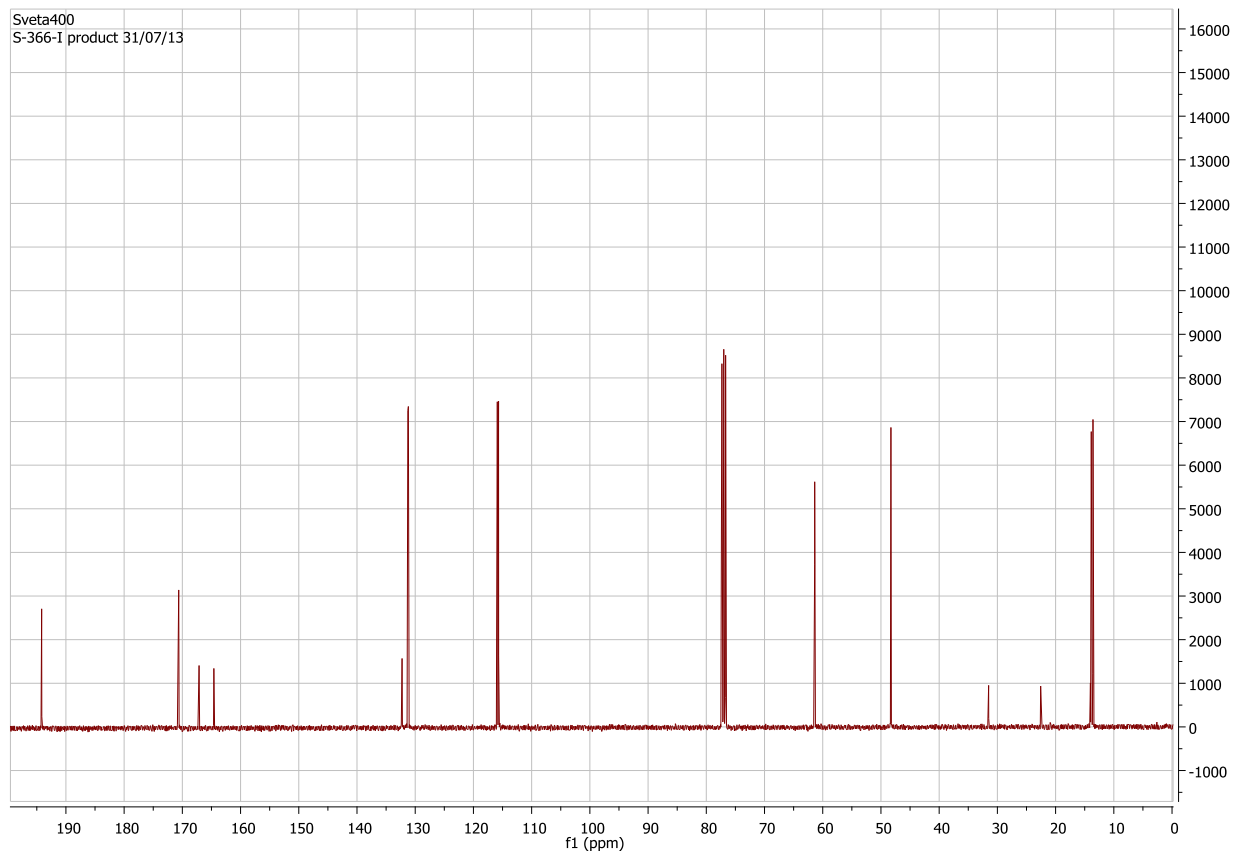
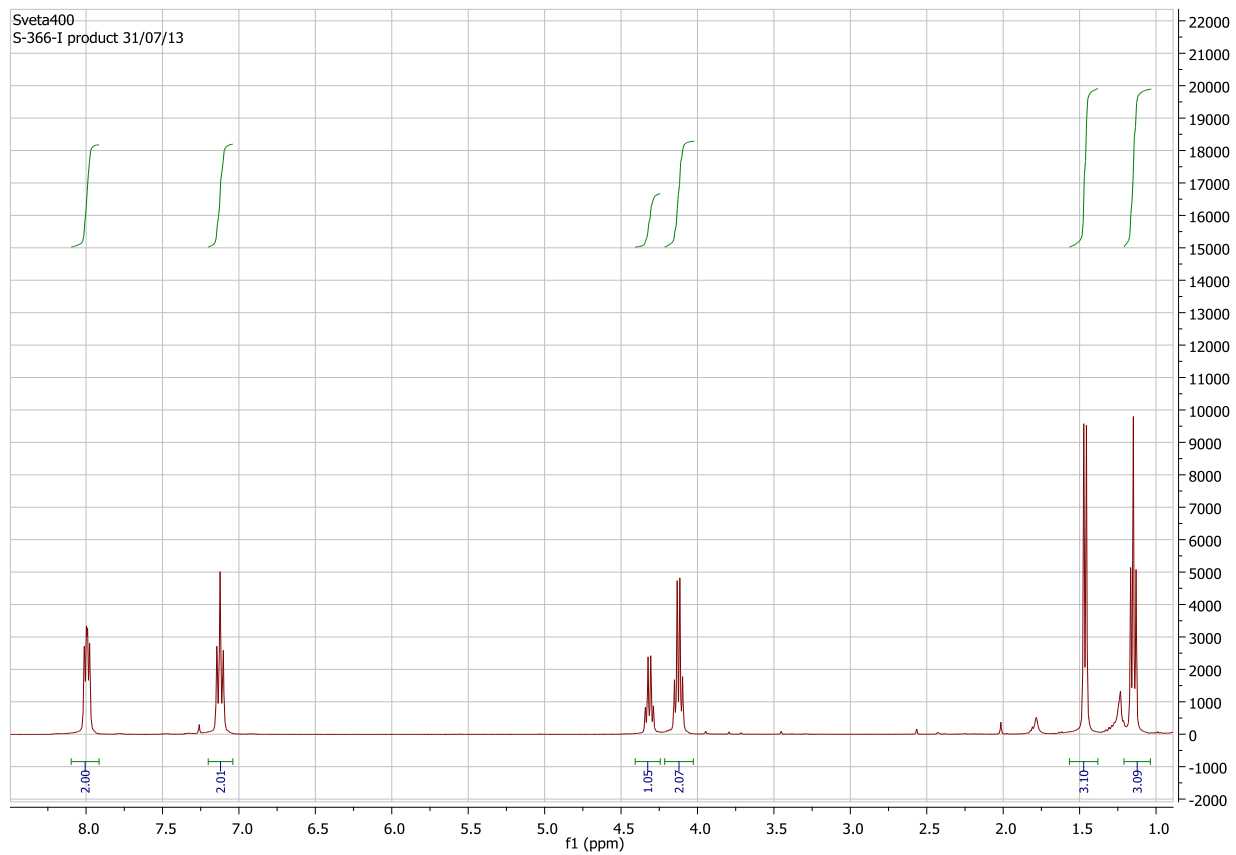
¹H NMR (400 MHz, CDCl₃) δ 7.99 (dd, *J* = 8.4, 5.5 Hz, 2 H), 7.12 (t, *J* = 8.5 Hz, 2 H), 4.31 (q, *J* = 7.0 Hz, 1 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 1.46 (d, *J* = 7.1 Hz, 3 H), 1.15 (t, *J* = 7.1 Hz, 3 H).

¹³C NMR (101 MHz, CDCl₃) δ 194.16, 170.62, 167.13, 164.59, 132.28, 132.25, 131.27, 131.17, 115.90, 115.68, 61.38, 48.29, 13.88, 13.58.

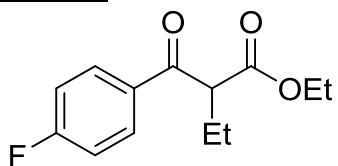
IR: (thin film) ν 2986, 2941, 1734, 1685, 1595, 1506, 1453, 1408, 1372, 1330, 1297, 1185, 1156, 1080, 1031, 964, 849, 635, 601, 506 cm⁻¹.

HRMS (ESI) *m/z*: calcd for C₁₂H₁₃FO₃, [M+Na], 247.0746; found 247.0794.

The data is consistent with those reported in the literature (reference 4)



Ethyl 2-(4-fluorobenzoyl)butanoate (31b)



The compound was prepared according to procedure B and purified by column chromatography (5% EtOAc/Hexane) to give the product as an oil (101 mg, 85%).

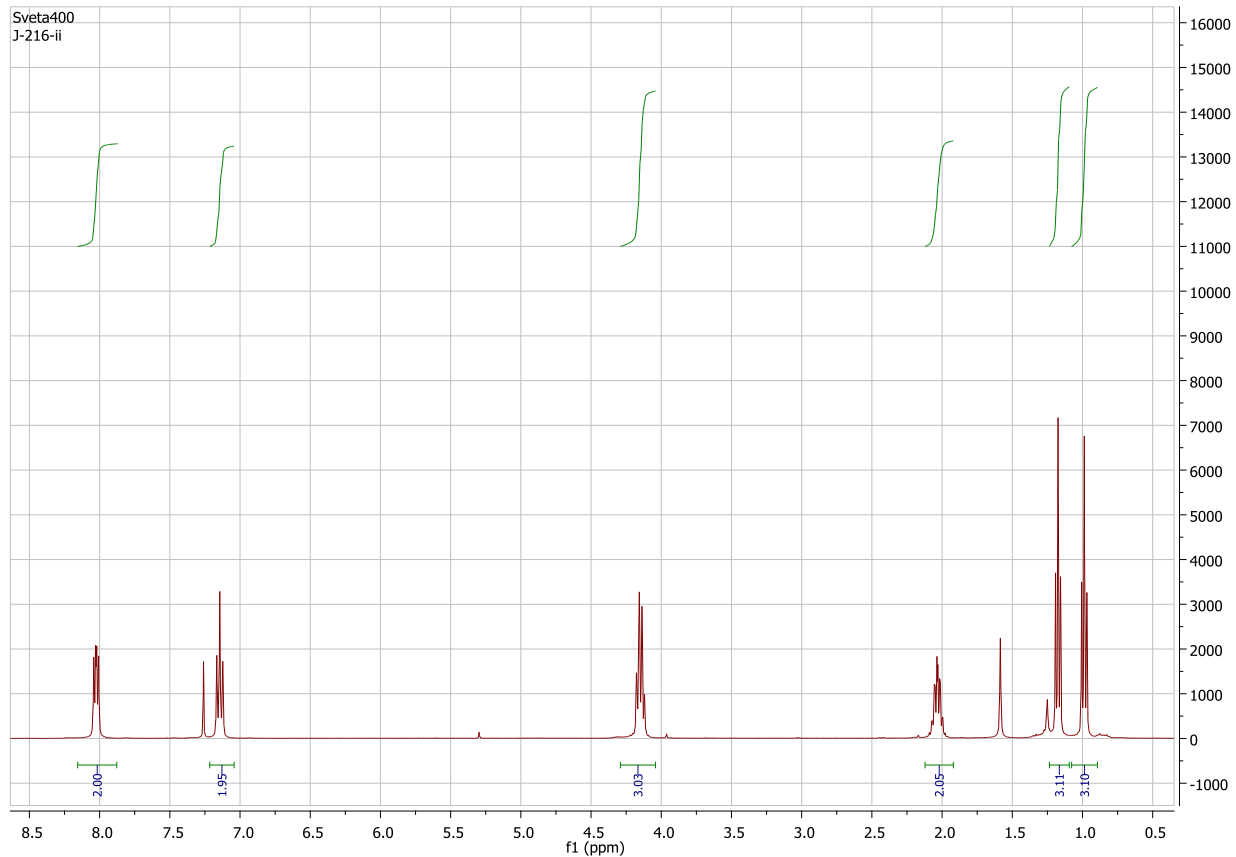
R_f = 0.41 (10% EtOAc/Hexane).

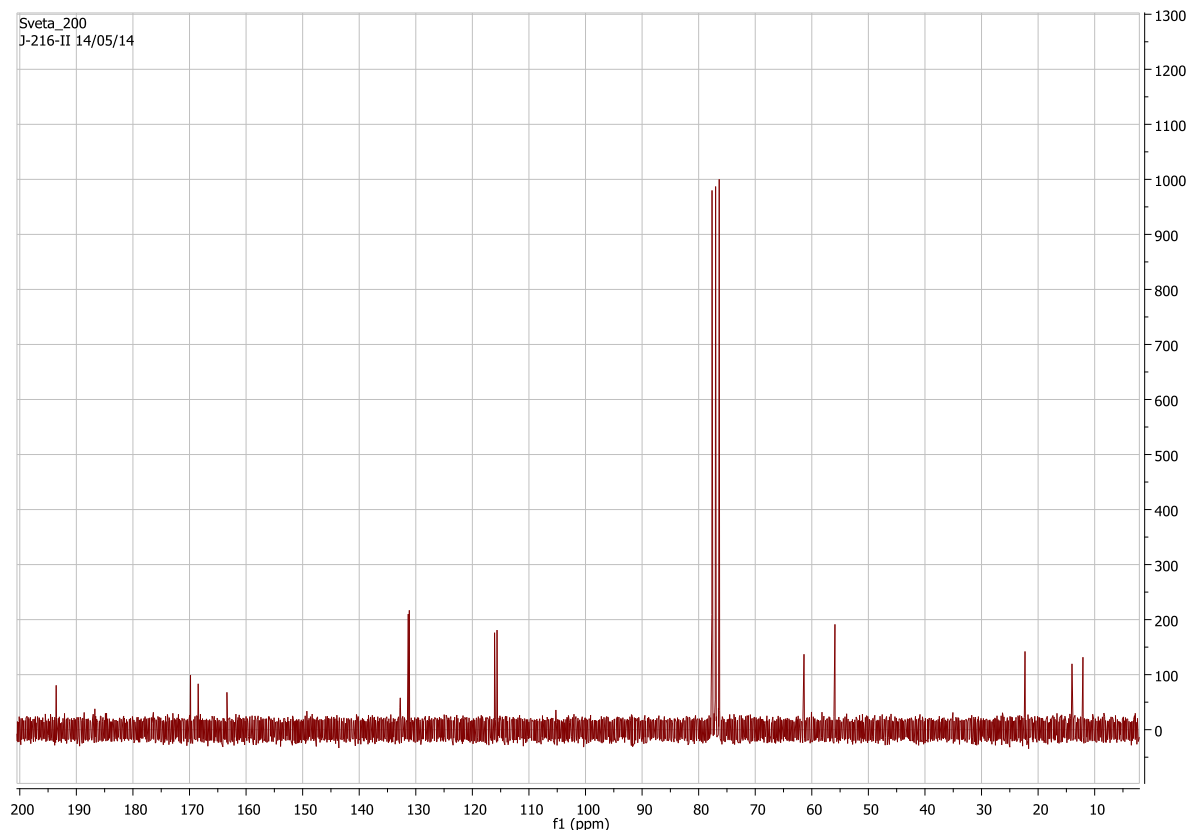
^1H NMR (400 MHz, CDCl_3) δ 8.00 (dt, J = 14.1 Hz, 7.0 Hz, 2 H), 7.12 (t, J = 8.6 Hz, 2 H), 4.13 (dt, J = 13.7 Hz, 7.0 Hz, 3 H), 2.01 (m, 2 H), 1.15 (t, J = 7.1 Hz, 3 H), 0.97 (t, J = 7.4 Hz, 3 H).

^{13}C NMR (50 MHz, CDCl_3) δ 193.57, 169.82, 168.46, 163.38, 131.33, 131.15, 116.08, 115.64, 61.38, 55.91, 22.31, 14.01, 12.07.

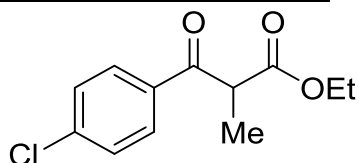
IR: (thin film) ν 2972, 2935, 2878, 1734, 1682, 1597, 1508, 1456, 1212, 1155, 1093, 993, 847, 580, 502 cm^{-1} .

HRMS (ESI) m/z : calcd for $\text{C}_{13}\text{H}_{15}\text{FO}_3$, $[\text{M}+1]$, 239.1083; found 239.1082.





Ethyl 3-(4-chlorophenyl)-2-methyl-3-oxopropanoate (32)⁴



The compound was prepared according to procedure A and purified by column chromatography (5-15% EtOAc/Hexane) to give the product as an oil (93 mg, 80%).

R_f = 0.50 (20% EtOAc/Hexane).

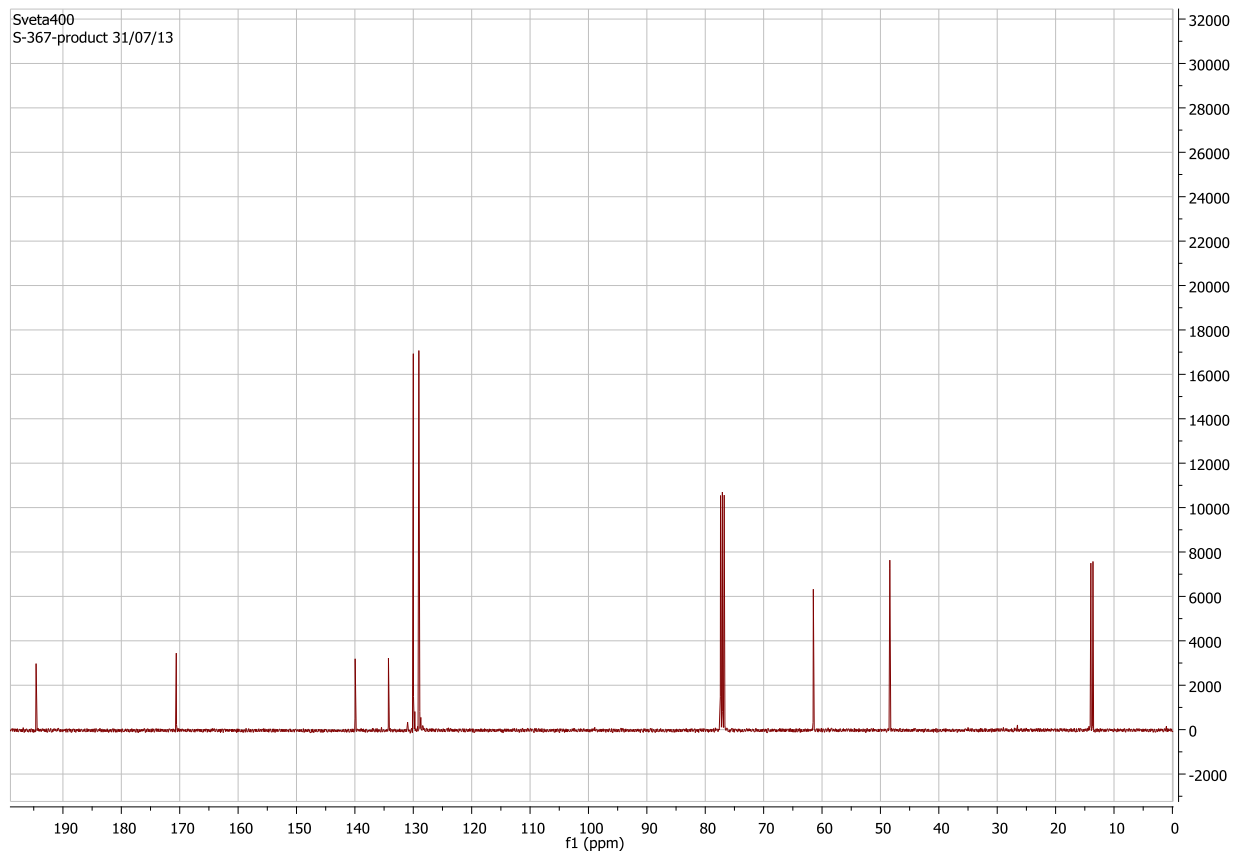
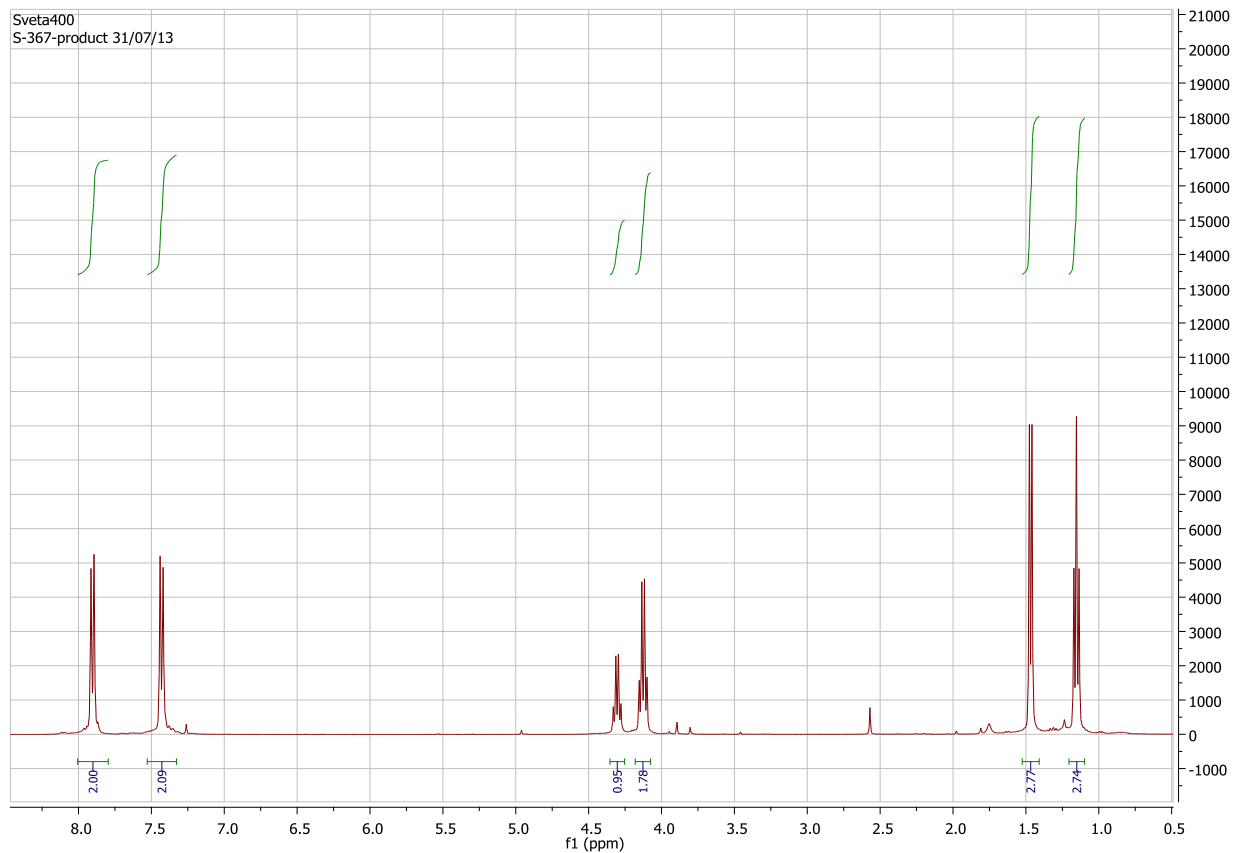
¹H NMR (400 MHz, CDCl₃) δ 7.90 (d, J = 8.4 Hz, 2 H), 7.43 (d, J = 8.4 Hz, 2 H), 4.30 (q, J = 7.0 Hz, 1 H), 4.13 (q, J = 7.1 Hz, 2 H), 1.47 (d, J = 7.0 Hz, 3 H), 1.15 (t, J = 7.1 Hz, 3 H).

¹³C NMR (101 MHz, CDCl₃) δ 194.59, 170.59, 139.95, 134.25, 129.99, 129.05, 61.49, 48.39, 13.96, 13.60.

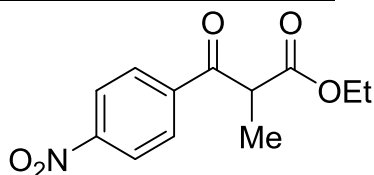
IR: (thin film) ν 2983.71, 2939.24, 1732.09, 1684.50, 1585.96, 1451.73, 1393.30, 1372.90, 1281.06, 1213.76, 1181.04, 1089.20, 1010.74, 957.94, 843.41, 757.89 cm⁻¹.

HRMS (ESI) m/z : calcd for C₁₂H₁₃ClO₃, [M+1], 241.0632; found 241.0631.

The data is consistent with those reported in the literature (reference 4)



Ethyl 2-methyl-3-(4-nitrophenyl)-3-oxopropanoate (33a)¹³



The compound was prepared according to procedure A and purified by column chromatography (15% EtOAc/Hexane) to give the product as an oil (110 mg, 92 %).

R_f = 0.40 (20% EtOAc/Hexane).

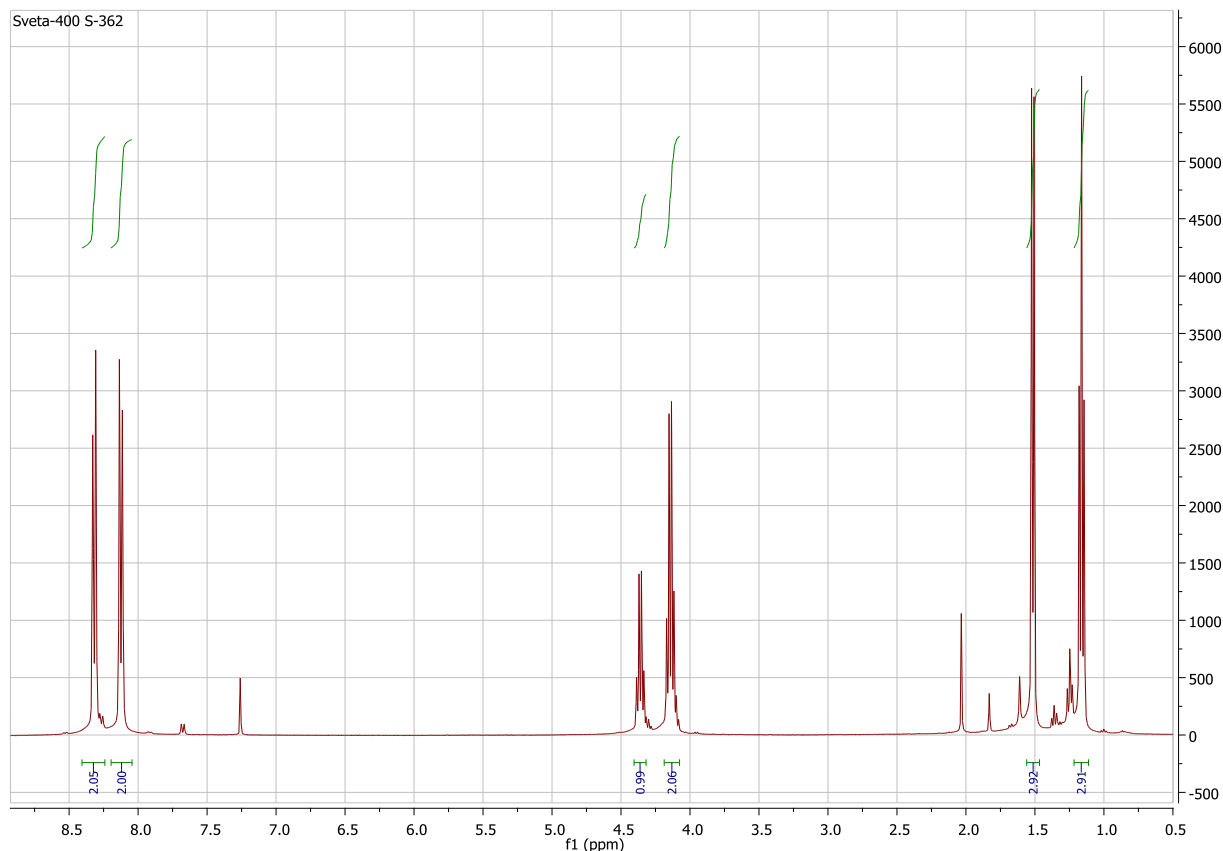
¹H NMR (400 MHz, CDCl₃) δ 8.32 (d, *J* = 8.5 Hz, 2 H), 8.12 (d, *J* = 8.6 Hz, 2 H), 4.36 (q, *J* = 7.0 Hz, 1 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 1.52 (d, *J* = 7.0 Hz, 3 H), 1.16 (t, *J* = 7.1 Hz, 3 H).

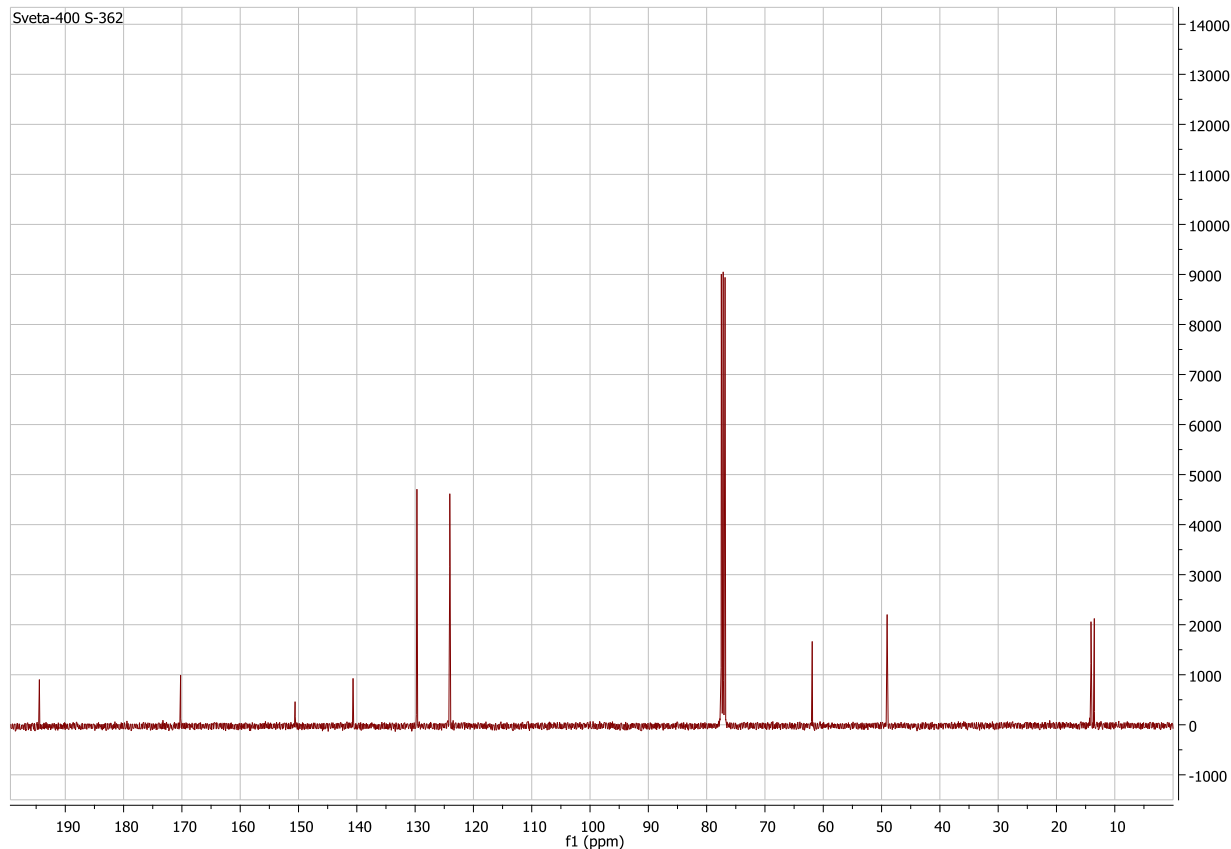
¹³C NMR (101 MHz, CDCl₃) δ 194.44, 170.23, 150.59, 140.65, 129.69, 124.06, 61.89, 49.04, 14.08, 13.51.

IR: (thin film) ν 2986, 2941, 1734, 1693, 1602, 1525, 1453, 1342, 1218, 1180, 1081, 1032, 964, 855, 711, 509 cm⁻¹.

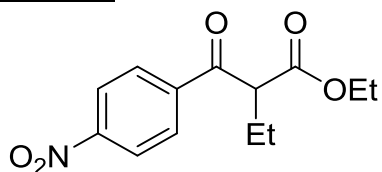
HRMS (ESI) *m/z*: calcd for C₁₂H₁₃NO₅, [M+1], 252.0872 ; found 253.0856.

The data is consistent with those reported in the literature (reference 13)





Ethyl 2-(4-nitrobenzoyl)butanoate (33b)



The compound was prepared according to procedure B and purified by column chromatography (10-15% EtOAc/Hexane) to give the product as an oil (44 mg, 33%).

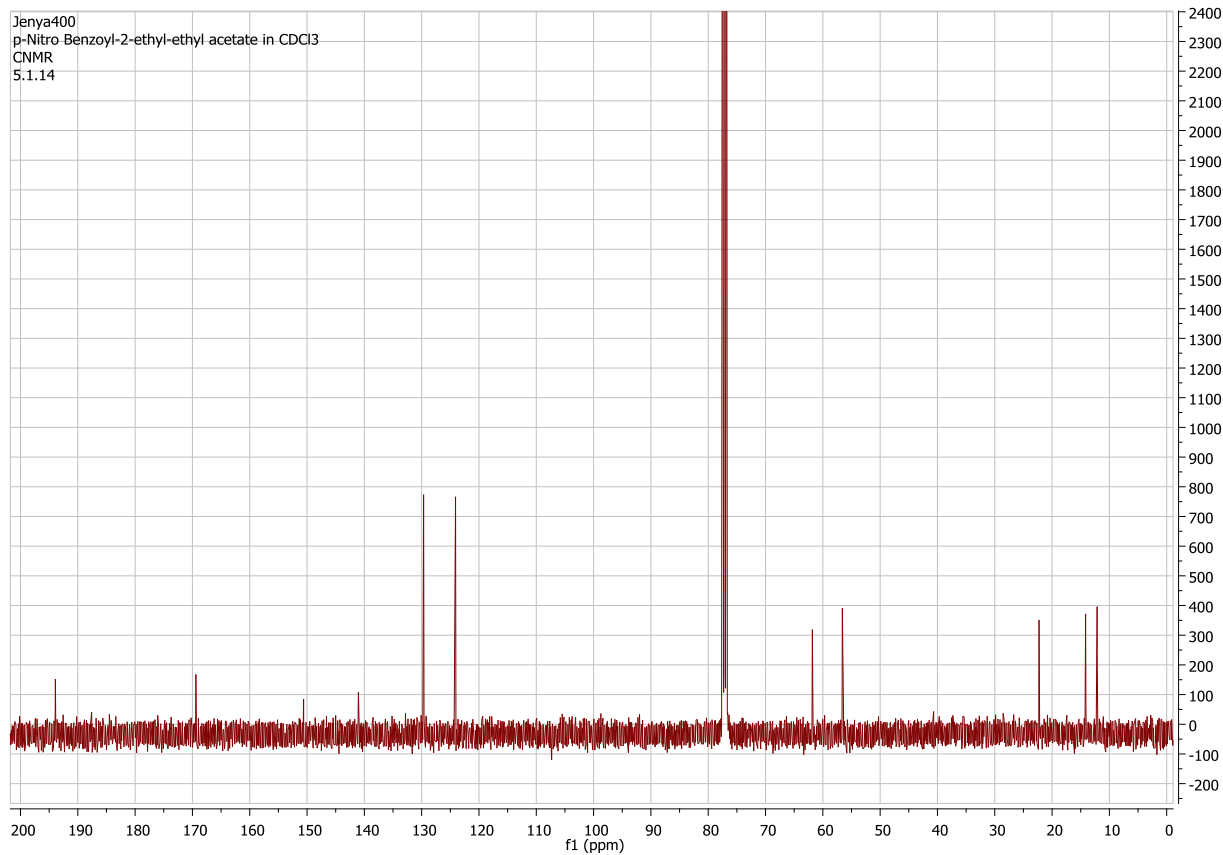
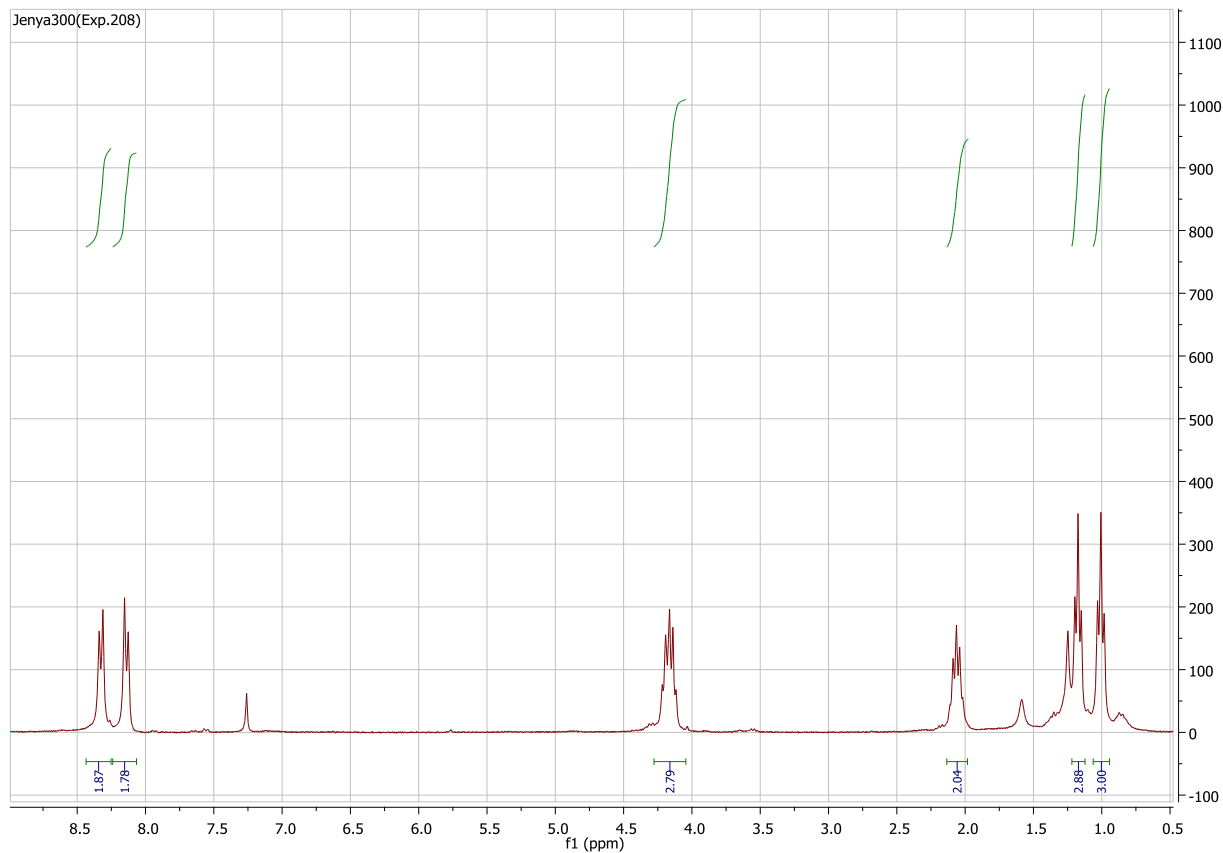
R_f = 0.5 (20% EtOAc/Hexane).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.33 (d, J = 8.3 Hz, 2 H), 8.14 (d, J = 8.2 Hz, 2 H), 4.17 (dt, J = 14.2 Hz, 7.1 Hz, 3 H), 2.06 (m, 2 H), 1.17 (t, J = 7.0 Hz, 3 H), 1.01 (t, J = 7.3 Hz, 3 H).

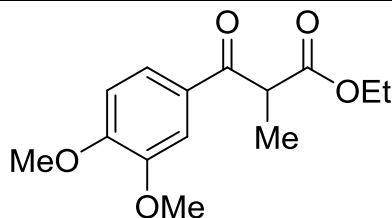
$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 193.91, 169.39, 150.61, 141.04, 129.66, 124.09, 61.83, 56.60, 22.27, 14.15, 12.14.

IR: (thin film) ν 2972, 2934, 1732, 1692, 1525, 1461, 1344, 1254, 1213, 1176, 1109, 996, 851, 706 cm^{-1} .

HRMS (ESI) m/z : calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_5$, $[\text{M}+\text{Na}]$, 288.0848; found 288.0830.



Ethyl 3-(3,4-dimethoxyphenyl)-2-methyl-3-oxopropanoate (34a)



The compound was prepared according to procedure A and purified by column chromatography (10-20% EtOAc/Hexane) to give the product as an oil (110 mg, 90%).

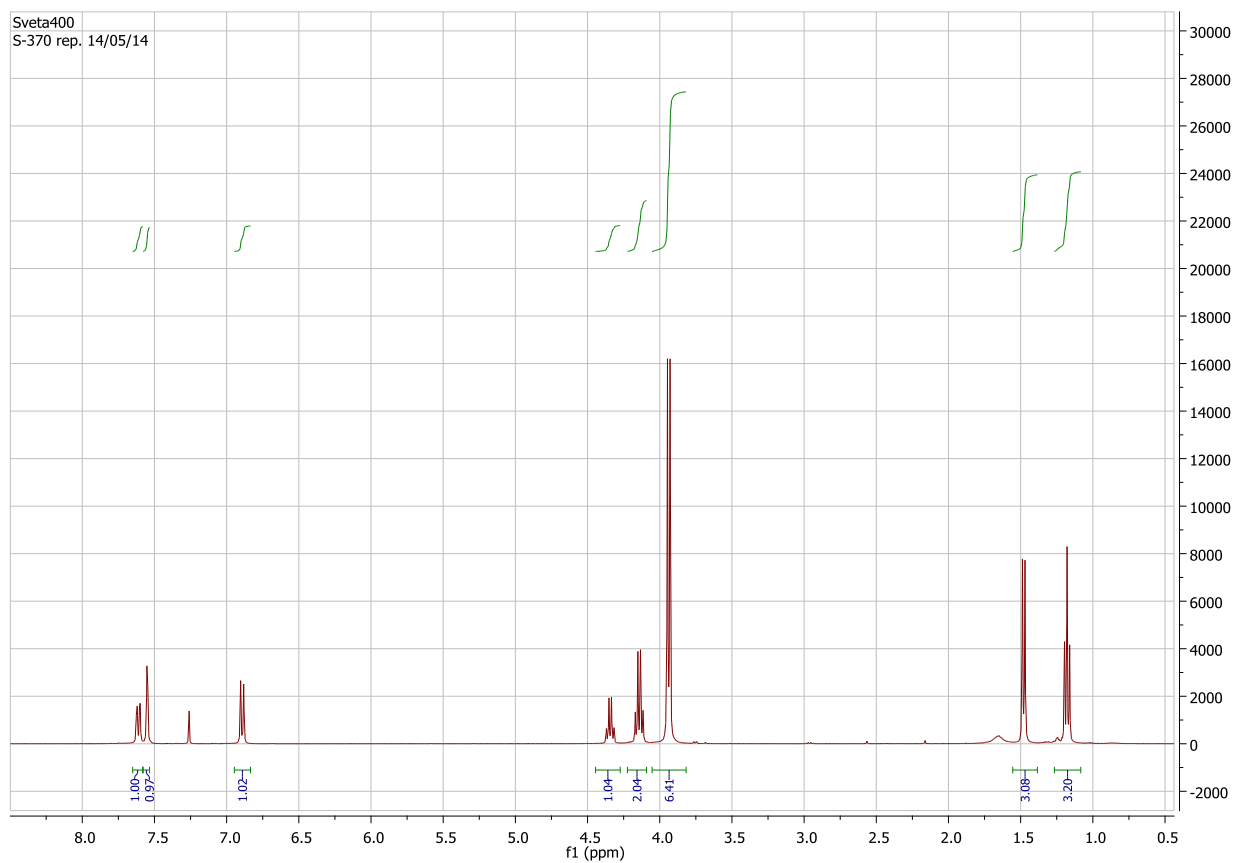
R_f = 0.18 (20% EtOAc/Hexane).

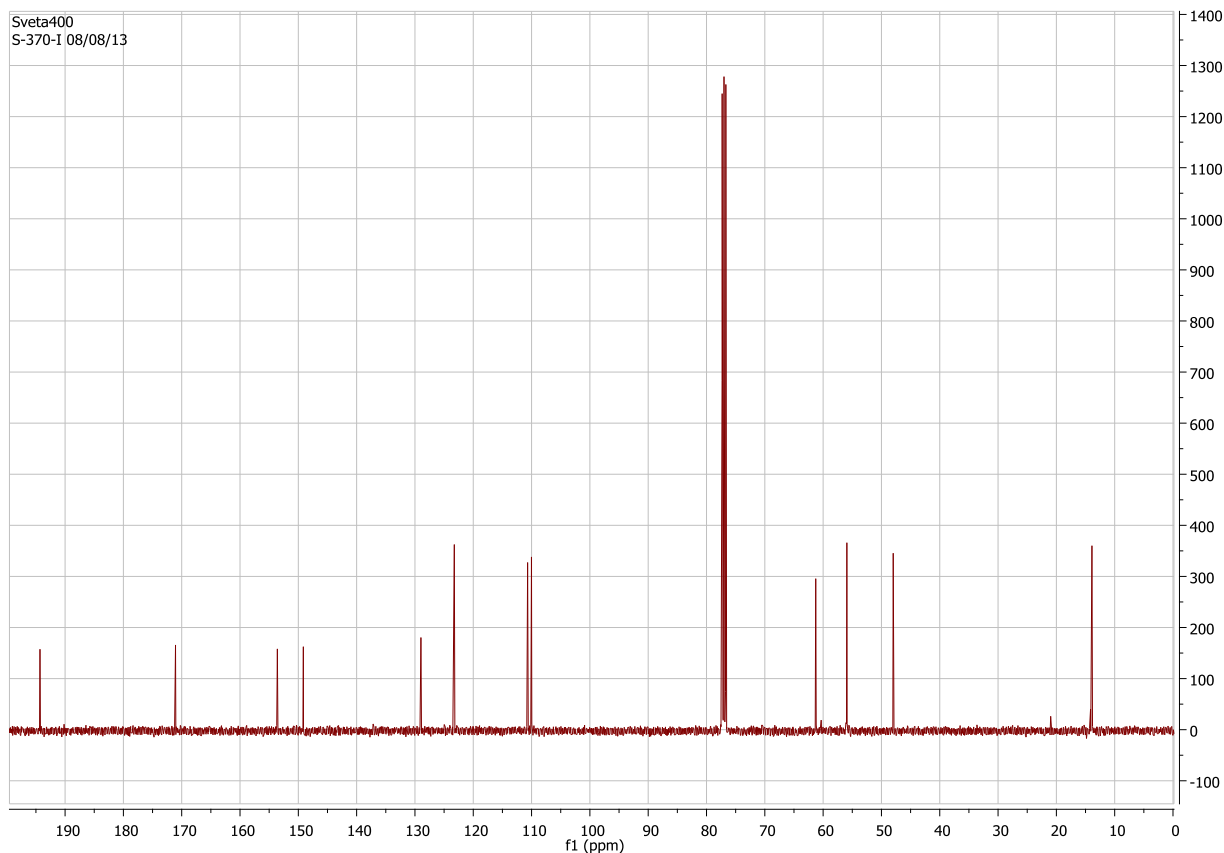
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.60 (dd, J = 8.4 Hz, 1.3 Hz, 1 H), 7.54 (s, 1 H), 6.89 (d, J = 8.4 Hz, 1 H), 4.34 (q, J = 7.0 Hz, 1 H), 4.14 (dd, J = 14.0 Hz, 6.9 Hz, 2 H), 3.93 (d, J = 7.3 Hz, 6 H), 1.47 (d, J = 7.0 Hz, 3 H), 1.17 (t, J = 7.1 Hz, 3 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 194.30, 171.06, 153.59, 149.14, 128.97, 123.25, 110.68, 110.02, 61.27, 56.05, 55.93, 47.98, 13.97, 13.90.

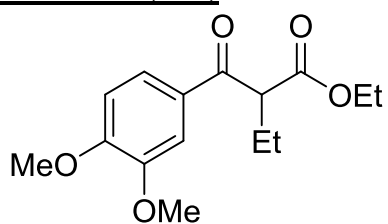
IR: (thin film) ν 2923.78, 2843.31, 1729.22, 1669.16, 1579.62, 1509.35, 1453.82, 1414.15, 1258.88, 1204.48, 1148.95, 1084.34, 1014.08, 849.74, 804.41, 760.20 cm^{-1} .

HRMS (ESI) m/z : calcd for $\text{C}_{14}\text{H}_{18}\text{O}_5$, $[\text{M}+1]$, 267.1232; found 267.1240.





Ethyl 2-(3,4-dimethoxybenzoyl)butanoate (34b)



The compound was prepared according to procedure B and purified by column chromatography (10-15% EtOAc/Hexane) to give the product as an oil (86 mg, 61%).

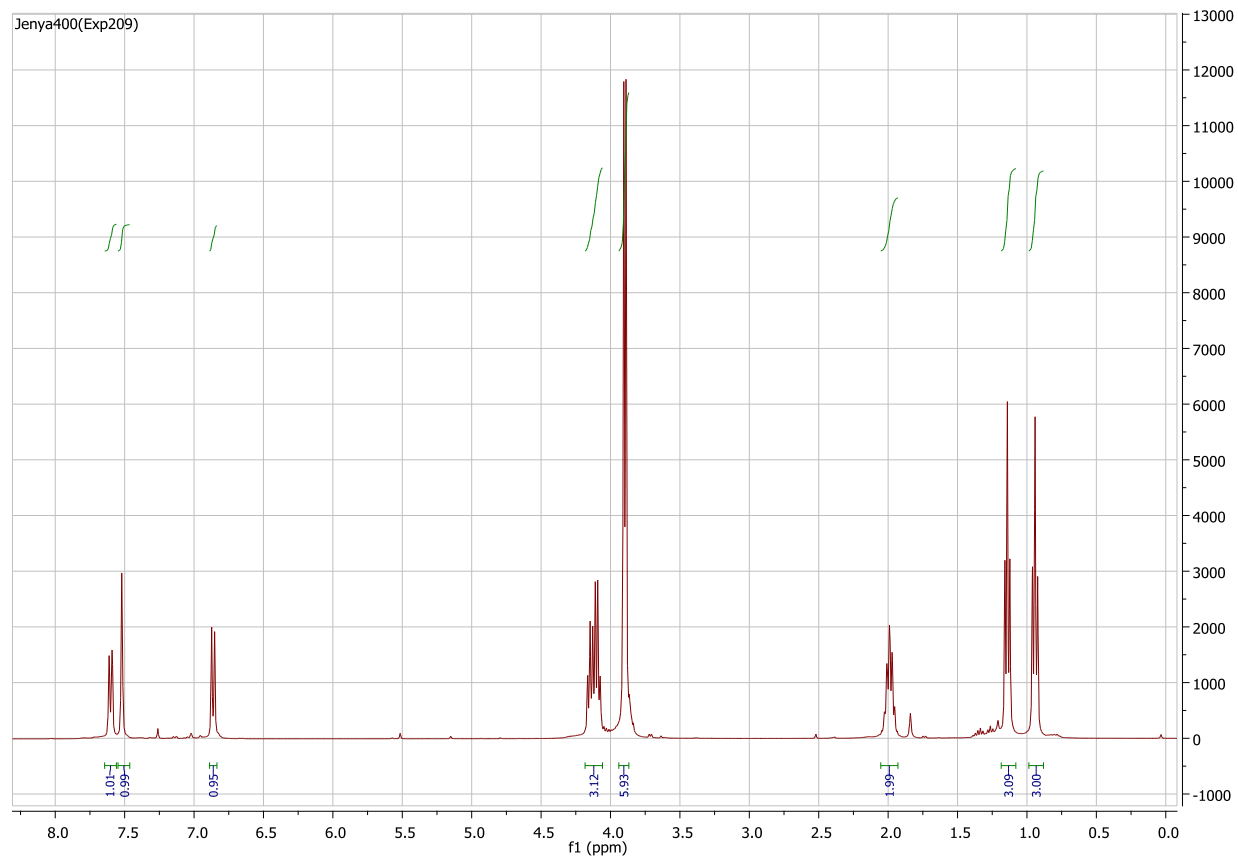
R_f = 0.23 (20% EtOAc/Hexane).

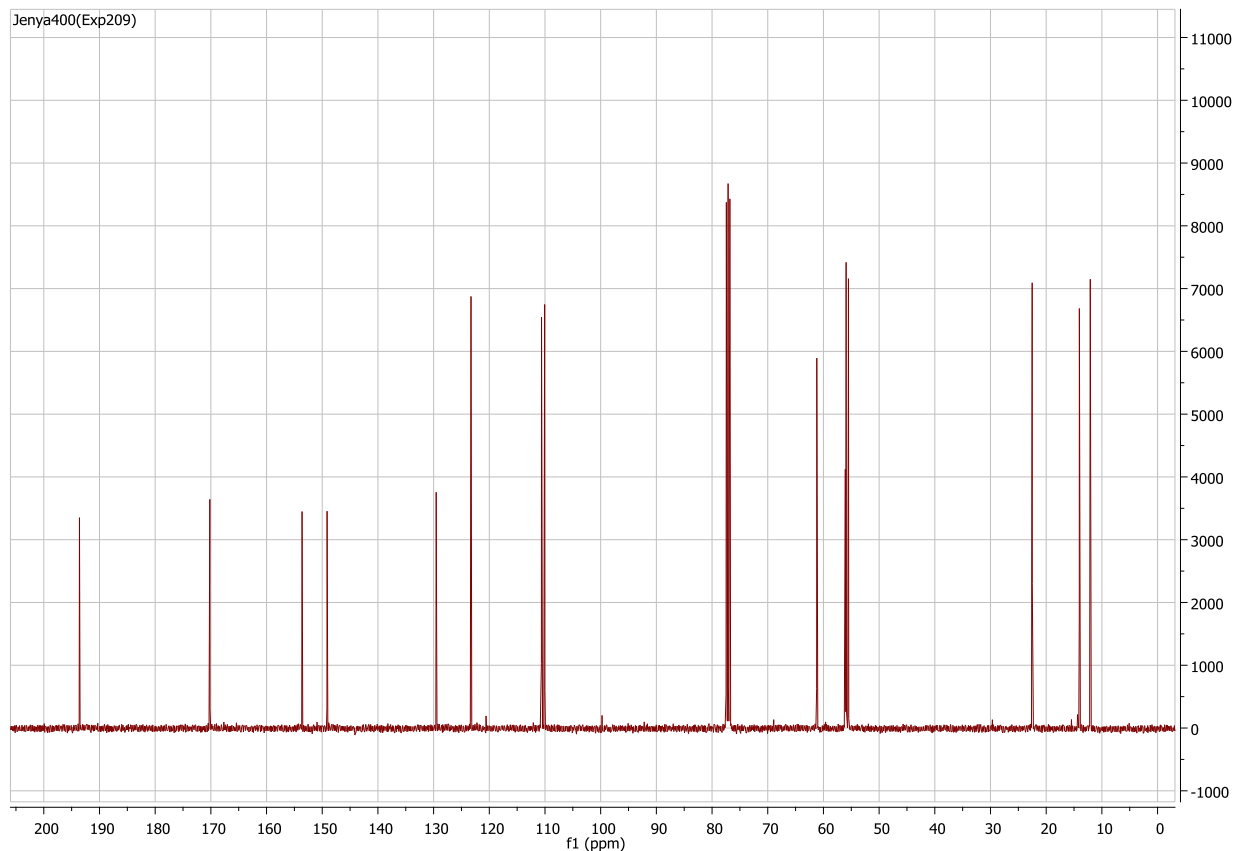
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.60 (d, J = 8.4 Hz, 1 H), 7.52 (s, 1 H), 6.86 (d, J = 8.4 Hz, 1 H), 4.12 (m, 2 H + 1 H), 3.90 (d, J = 6.4 Hz, 6 H), 1.99 (m, 2 H), 1.14 (t, J = 7.1 Hz, 3 H), 0.94 (t, J = 7.4 Hz, 3 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 193.64, 170.23, 153.67, 149.18, 129.58, 123.33, 120.63, 110.67, 110.10, 99.80, 61.24, 56.11, 55.97, 55.55, 22.56, 14.41, 14.09, 12.13.

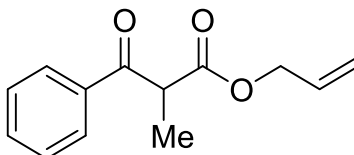
IR: (thin film) ν 2937.55, 2935.79, 1726.18, 1684.88, 1599.93, 1453.49, 1294.46, 1218.32, 1175.52, 1097.26, 1013.79, 902.18, 739.73 cm^{-1} .

HRMS (ESI) m/z : calcd for $\text{C}_{15}\text{H}_{20}\text{O}_5$, $[\text{M}+1]$, 281.1389; found 281.1396.





Allyl 2-methyl-3-oxo-3-phenylpropanoate (35a)¹⁴



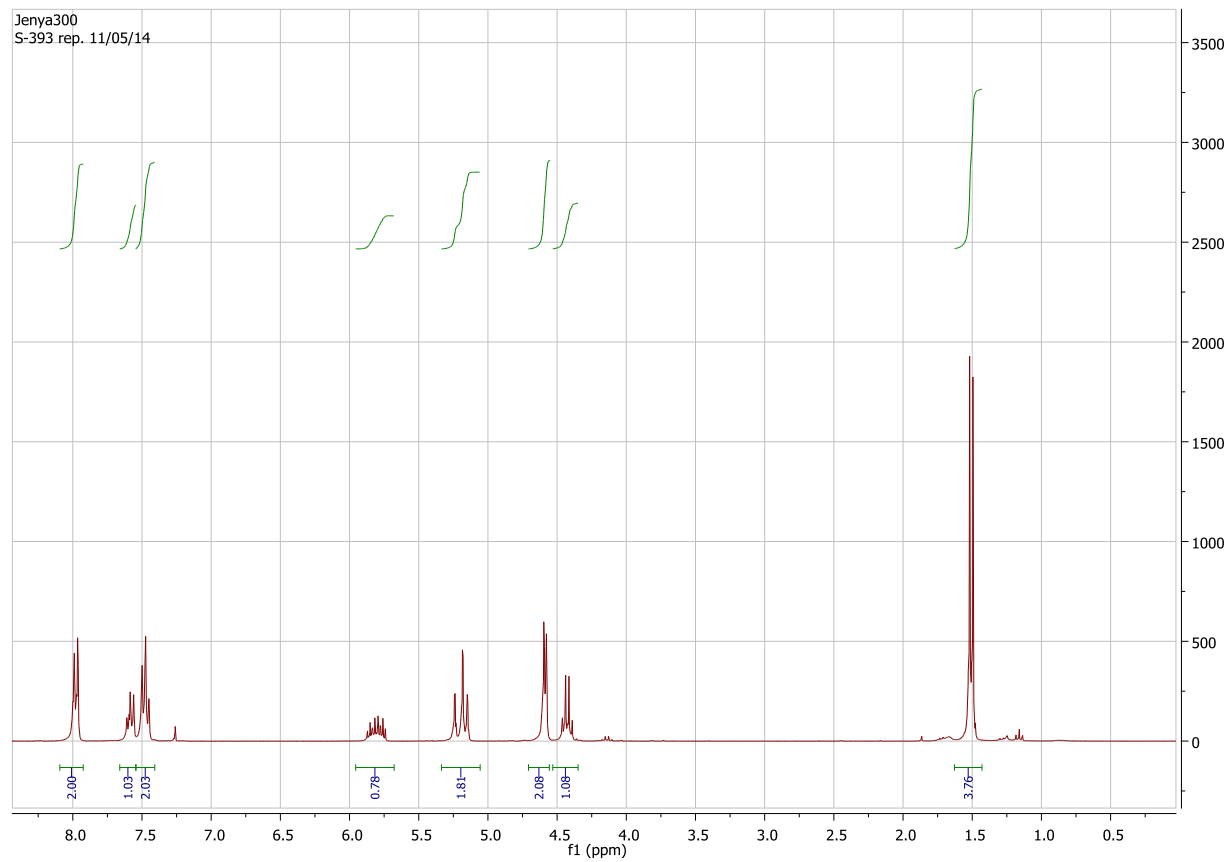
The compound was prepared according to procedure A and purified by column chromatography (10% EtOAc/Hexane) to give the product as an oil (78 mg, 92%).

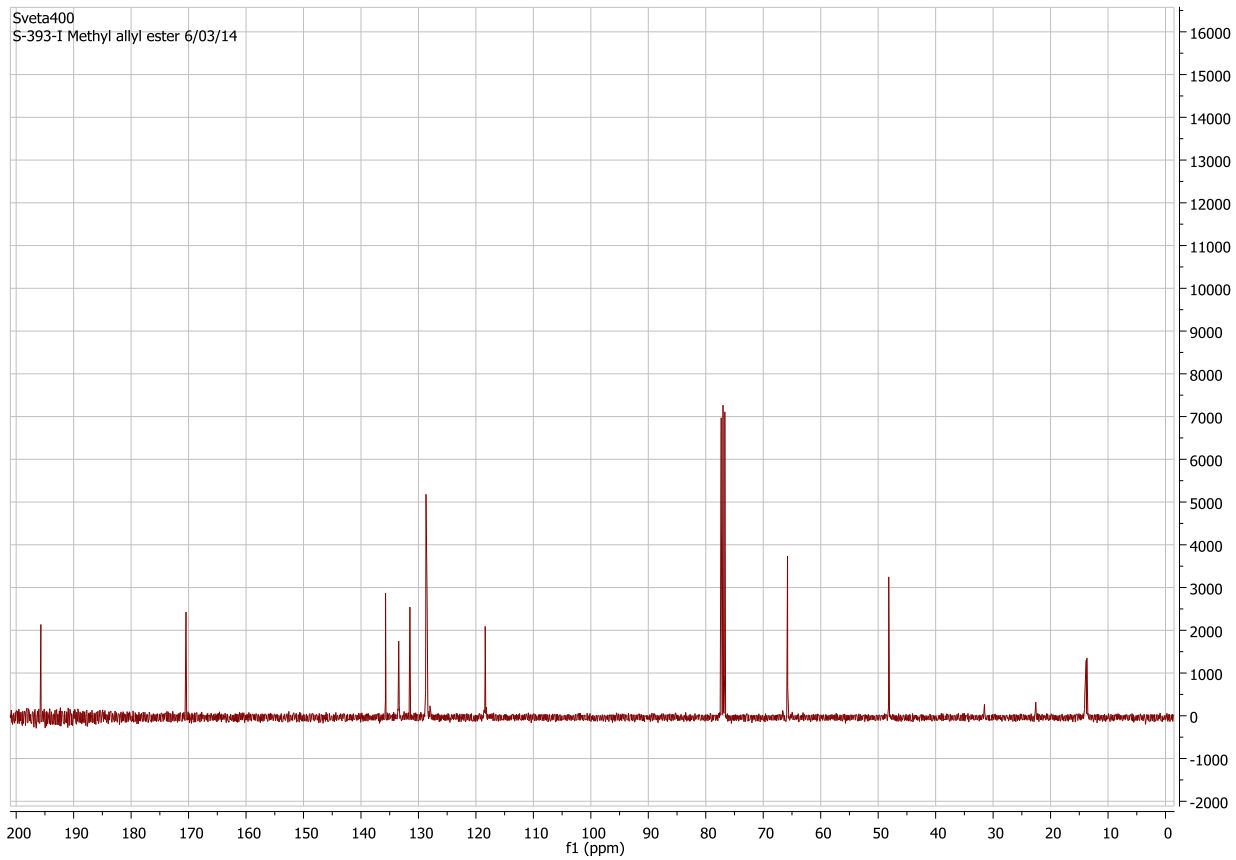
R_f =0.57 (DCM).

¹H NMR (300 MHz, CDCl₃) δ 7.98 (d, J = 7.1 Hz, 2 H), 7.57 (t, J = 7.5 Hz, 1 H), 7.48 (t, J = 7.2 Hz, 2 H), 5.80 (m, 1 H), 5.19 (m, 2 H), 4.59 (ddd, J = 5.7 Hz, 2.7 Hz, 1.3 Hz, 2 H), 4.42 (q, J = 7.1 Hz, 1 H), 1.50 (d, J = 7.1 Hz, 3 H).

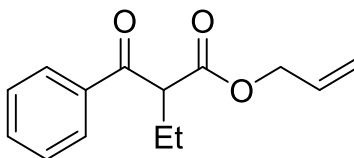
¹³C NMR (101 MHz, CDCl₃) δ 195.70, 170.44, 135.72, 133.43, 131.48, 128.69, 128.59, 128.50, 118.38, 65.77, 48.16, 48.09, 13.80, 13.68.

The data is consistent with those reported in the literature (reference 14)





Allyl 2-benzoylbutanoate (35b)



The compound was prepared according to procedure B and purified by column chromatography (10% EtOAc/Hexane) to give the product as an oil (64 mg, 93%).

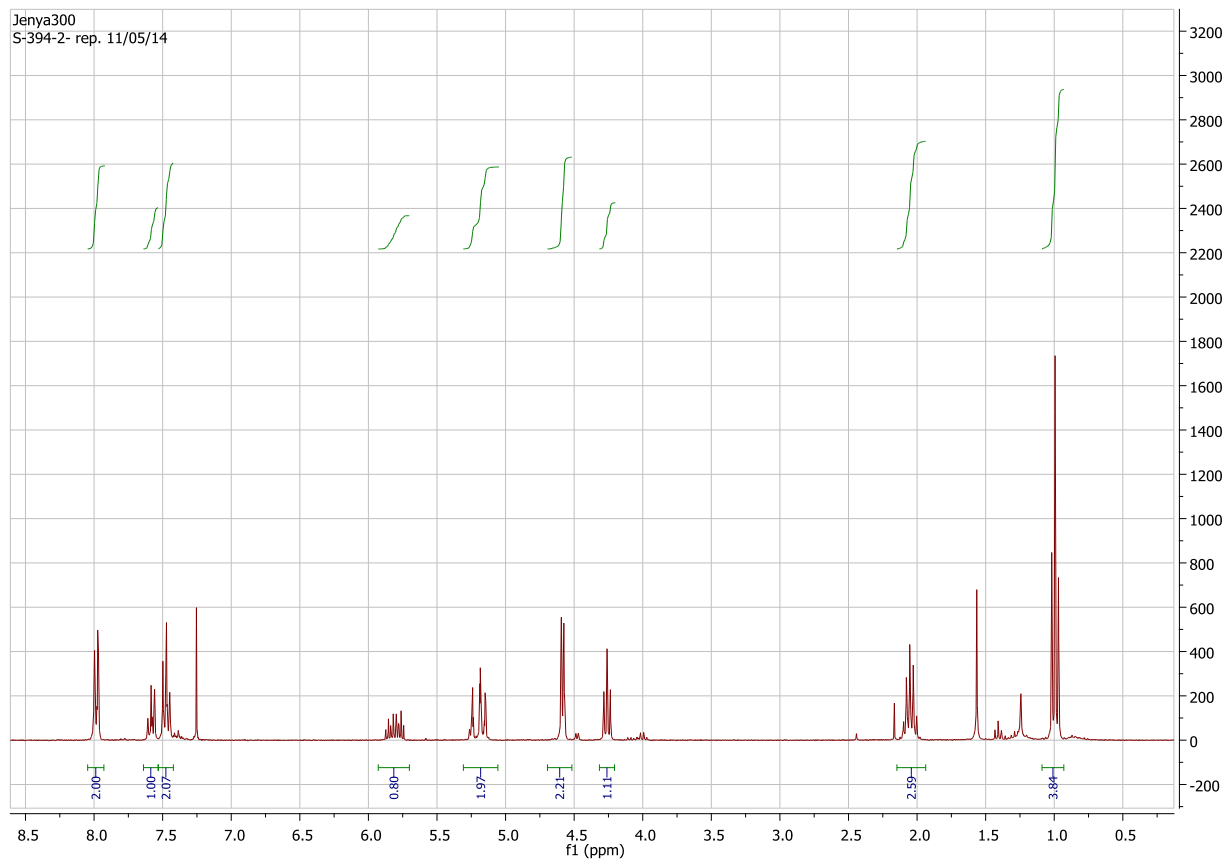
R_f = 0.61 (DCM).

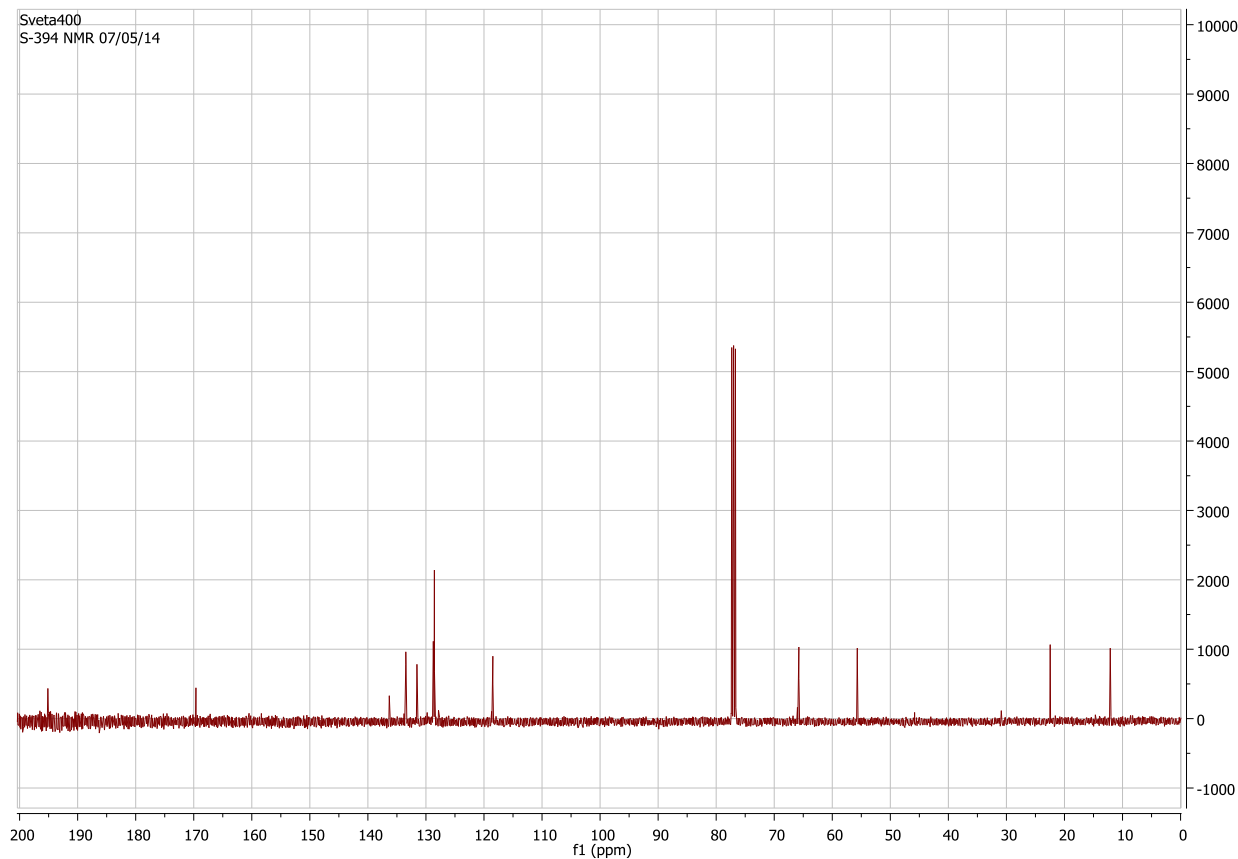
$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.97 (d, J = 7.1 Hz, 2 H), 7.57 (t, J = 7.2 Hz, 1H), 7.46 (ddt, J = 7.2 Hz, 2 H), 5.79 (ddt, J = 17.2 Hz, 10.5 Hz, 5.7 Hz, 1 H), 5.18 (m, 2H), 4.57 (dt, J = 5.7 Hz, 1.4 Hz, 2 H), 4.26 (t, J = 7.2 Hz, 1 H), 2.04 (m, 2H), 0.98 (t, J = 7.4 Hz, 3 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 195.13, 169.62, 136.31, 133.47, 131.55, 128.78, 128.72, 128.55, 118.47, 65.76, 55.69, 22.46, 12.11.

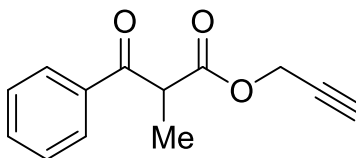
IR: (thin film) ν 3032, 2963, 1739, 1688, 1621, 1451, 1263, 1188, 1094, 1014 cm^{-1} .

HRMS (ESI) m/z : calcd for $\text{C}_{14}\text{H}_{16}\text{O}_3$, $[\text{M}+1]$, 233.1178; found 233.1168.





Prop-2-yn-1-yl 2-methyl-3-oxo-3-phenylpropanoate (36)



The compound was prepared according to procedure A and purified by column chromatography (10% EtOAc/Hexane) to give the product as an oil (100 mg, 93%).

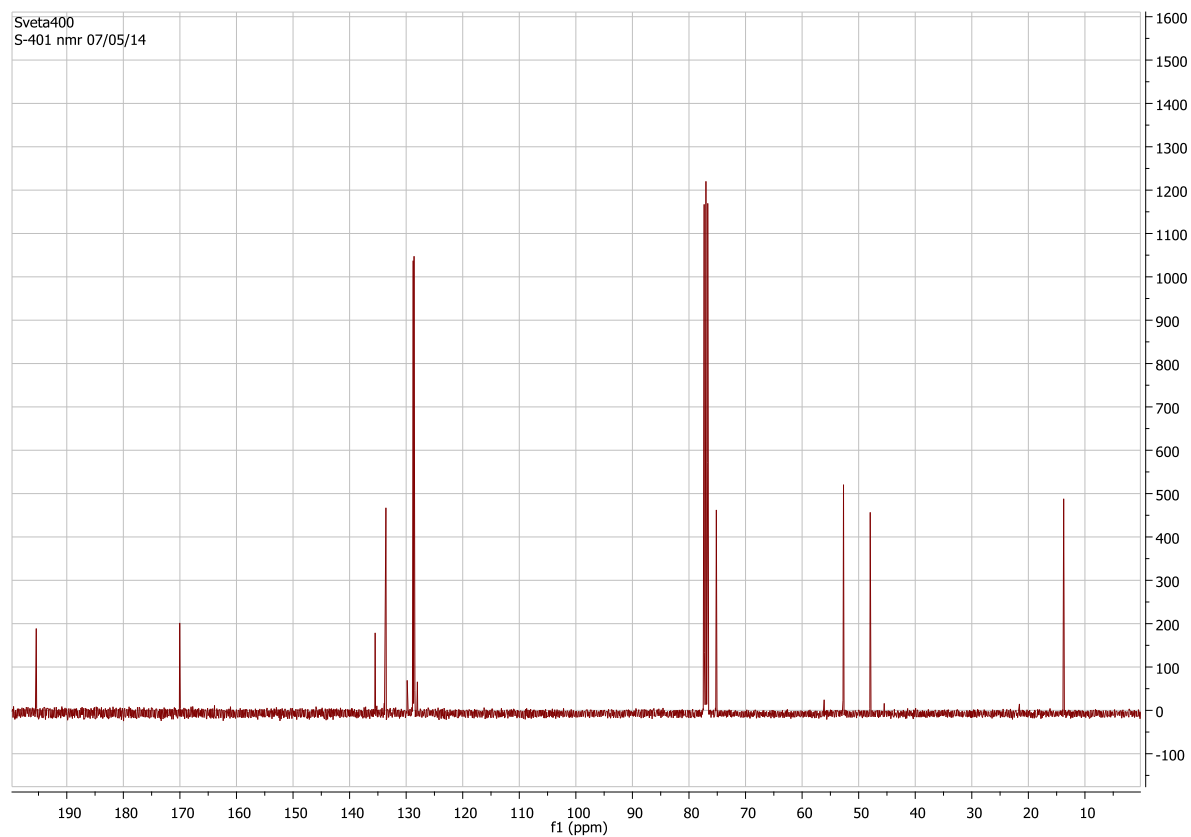
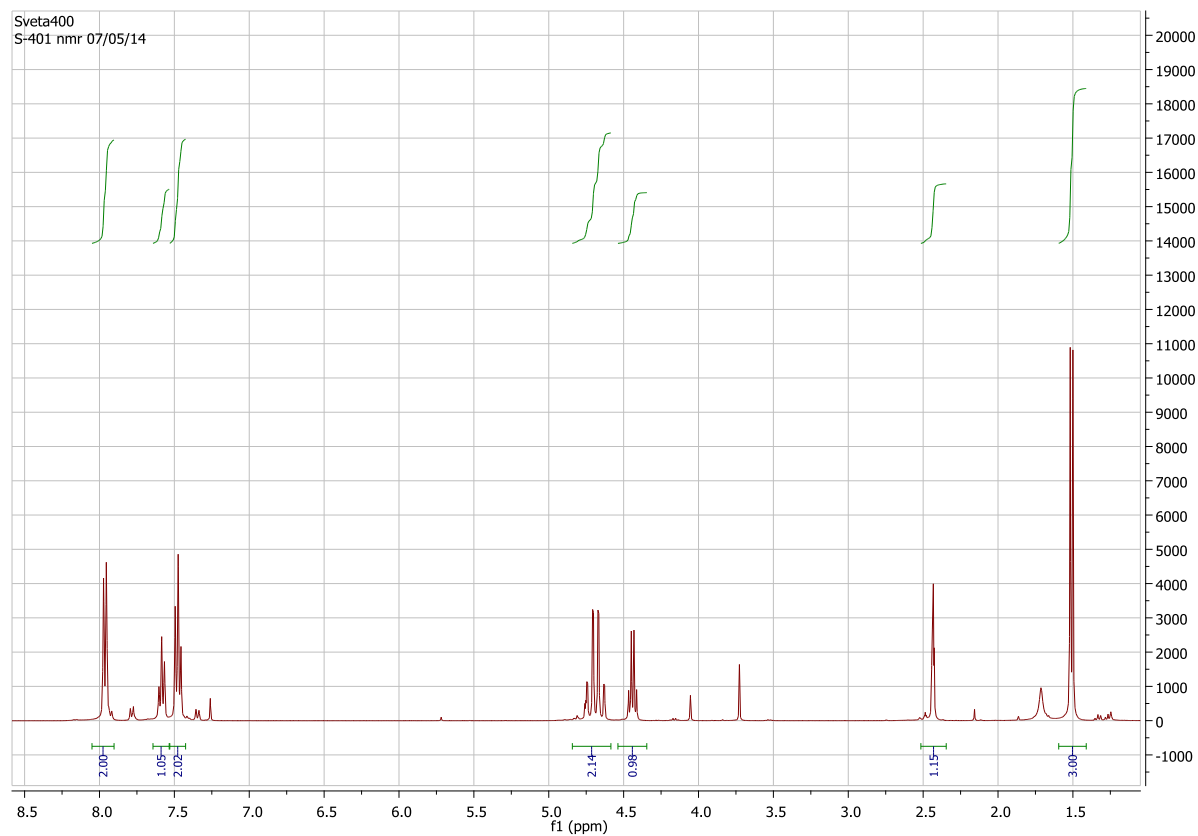
$R_f = 0.57$ (DCM).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.95 (dd, $J = 7.3$ Hz, 6.2 Hz, 2 H), 7.58 (t, $J = 7.4$ Hz, 1 H), 7.47 (t, $J = 7.7$ Hz, 2 H), 4.69 (qd, $J = 15.6$ Hz, 2.4 Hz, 2 H), 4.44 (q, $J = 7.1$ Hz, 1 H), 2.43 (t, $J = 2.5$ Hz, 1 H), 1.51 (d, $J = 7.1$ Hz, 3 H).

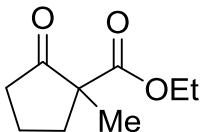
$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 195.39, 170.04, 135.48, 133.58, 128.76, 128.60, 75.16, 52.68, 47.96, 13.75.

IR: (thin film) ν 3285, 2991, 2944, 2129, 1742, 1683, 1592, 1449, 1372, 1280, 1171, 1078, 959. cm^{-1} .

HRMS (ESI) m/z : calcd for $\text{C}_{13}\text{H}_{12}\text{O}_3$, $[\text{M}+1]$, 216.0786; found 216.0763.



Ethyl 1-methyl-2-oxocyclopentanecarboxylate (37a)²



The compound was prepared according to procedure A and purified by column chromatography (5-10% EtOAc/Hexane) to give the product as an oil (160 mg, 82%).

R_f = 0.53 (20% EtOAc/Hexane).

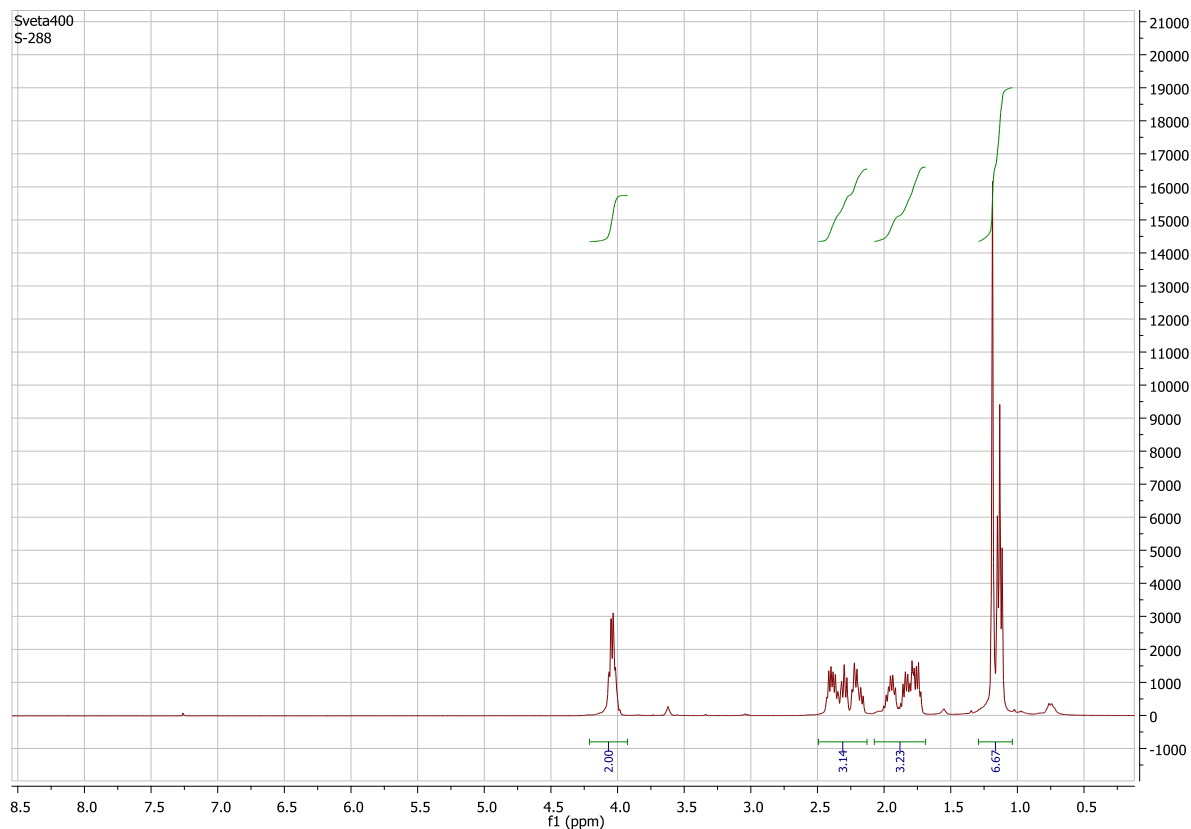
¹H NMR (400 MHz, CDCl₃) δ 4.04 (m, 2 H), 2.30 (m, 3 H), 1.84 (m, 3 H), 1.15 (m, 6 H).

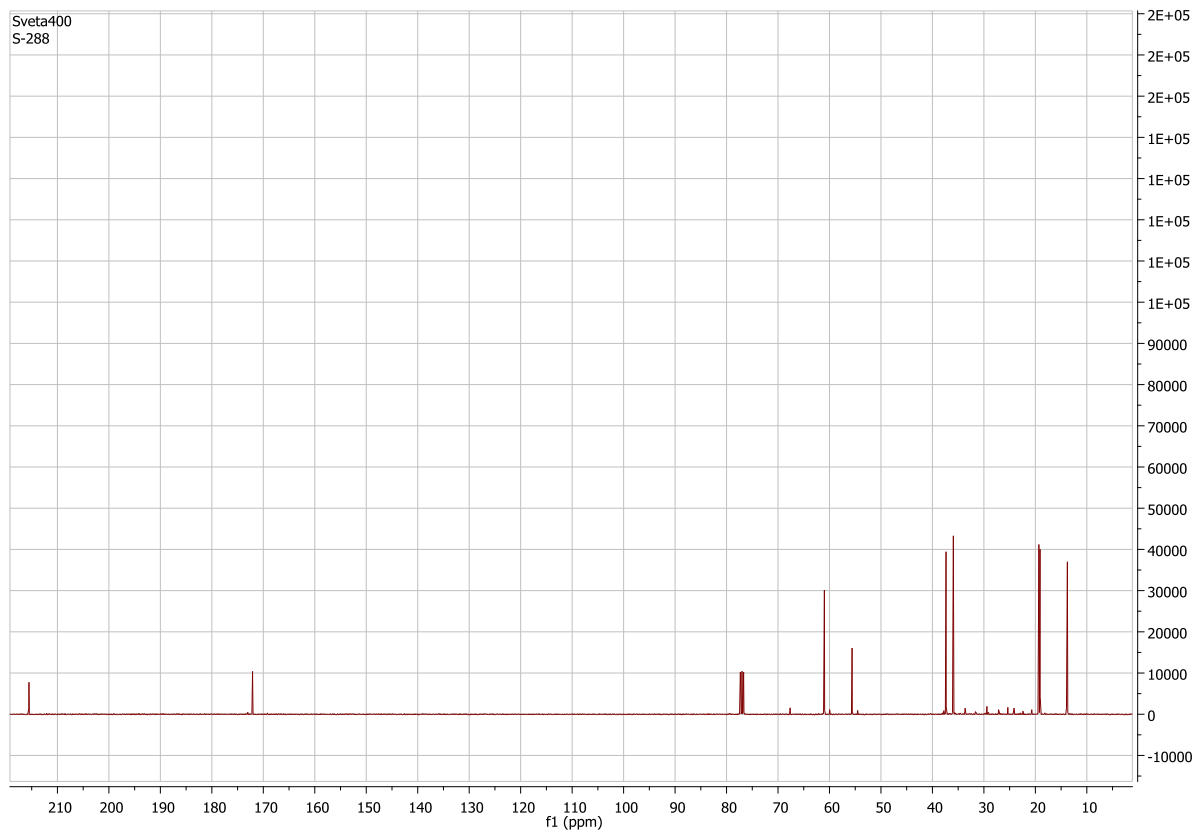
¹³C NMR (101 MHz, CDCl₃) δ 215.53, 172.09, 60.99, 55.61, 37.36, 35.94, 19.32, 19.09, 13.78.

IR: (thin film) ν 2973.65, 1743.96, 1725.44, 1450.58, 1373.52, 1265.91, 1234.59, 1148.11, 1061.64, 1026.82, 944.43, 860.20, 814.33 cm⁻¹.

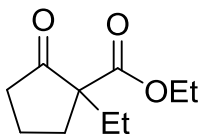
HRMS (ESI) m/z: calcd for C₉H₁₄O₃, [M+1], 171.1021; found 171.1029.

The data is consistent with those reported in the literature (reference 2)





Ethyl 1-ethyl-2-oxocyclopentanecarboxylate (37b)³



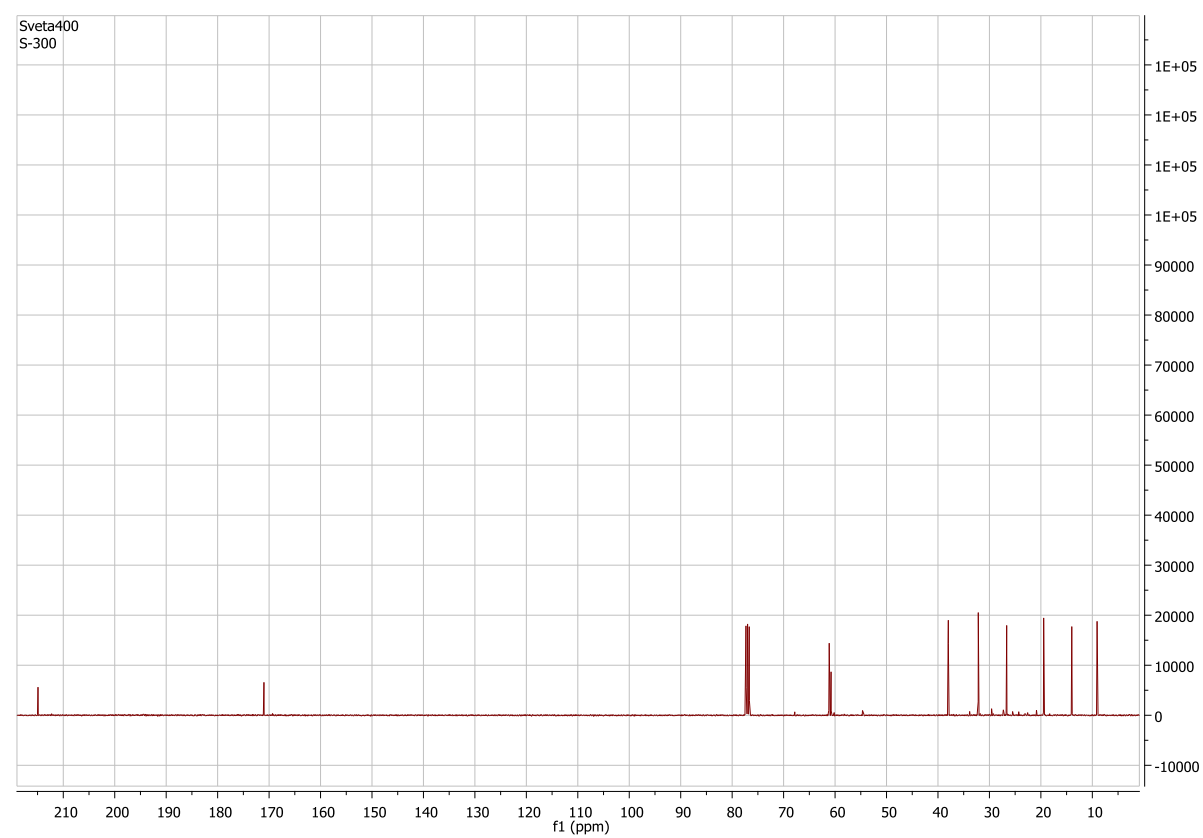
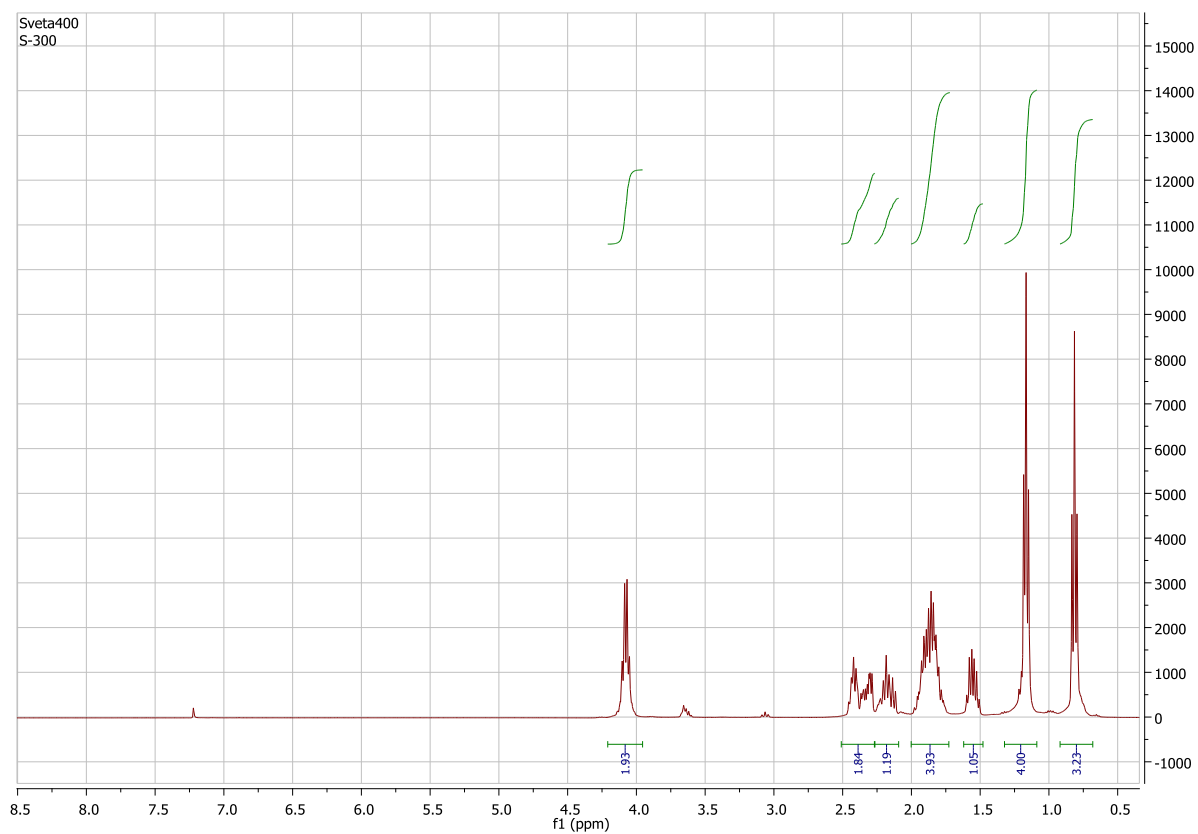
The compound was prepared according to procedure A and purified by column chromatography (5-15% EtOAc/Hexane) to give the product as an oil (78 mg, 74%).

R_f = 0.59 (20% EtOAc/Hexane).

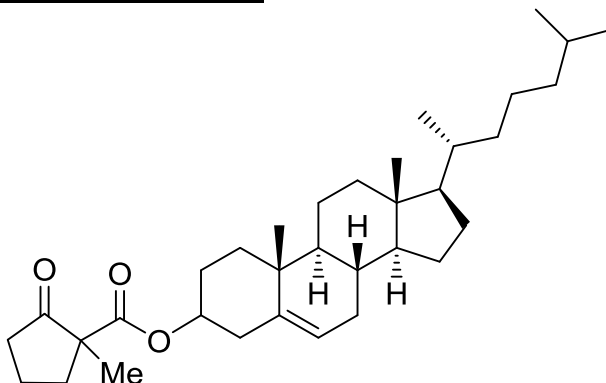
¹H NMR (400 MHz, CDCl₃) δ 4.11 (m, 2 H), 2.41 (m, 2 H), 2.20 (tt, J = 19.6 Hz, 9.8 Hz, 1 H), 1.90 (m, 4 H), 1.59 (dq, J = 14.6 Hz, 7.4 Hz, 1 H), 1.22 (dt, J = 14.2 Hz, 7.1 Hz, 3 H), 0.85 (t, J = 7.4 Hz, 3 H).

¹³C NMR (101 MHz, CDCl₃) δ 214.91, 171.00, 61.14, 60.78, 37.99, 32.16, 26.65, 19.45, 13.99, 9.07.

The data is consistent with those reported in the literature (reference 3)



(8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl 1-methyl-2-oxocyclopentanecarboxylate (38)



The compound was prepared according to procedure A and purified by column chromatography (10% EtOAc/Hexane) to give the product as a white solid (84 mg, 80%).

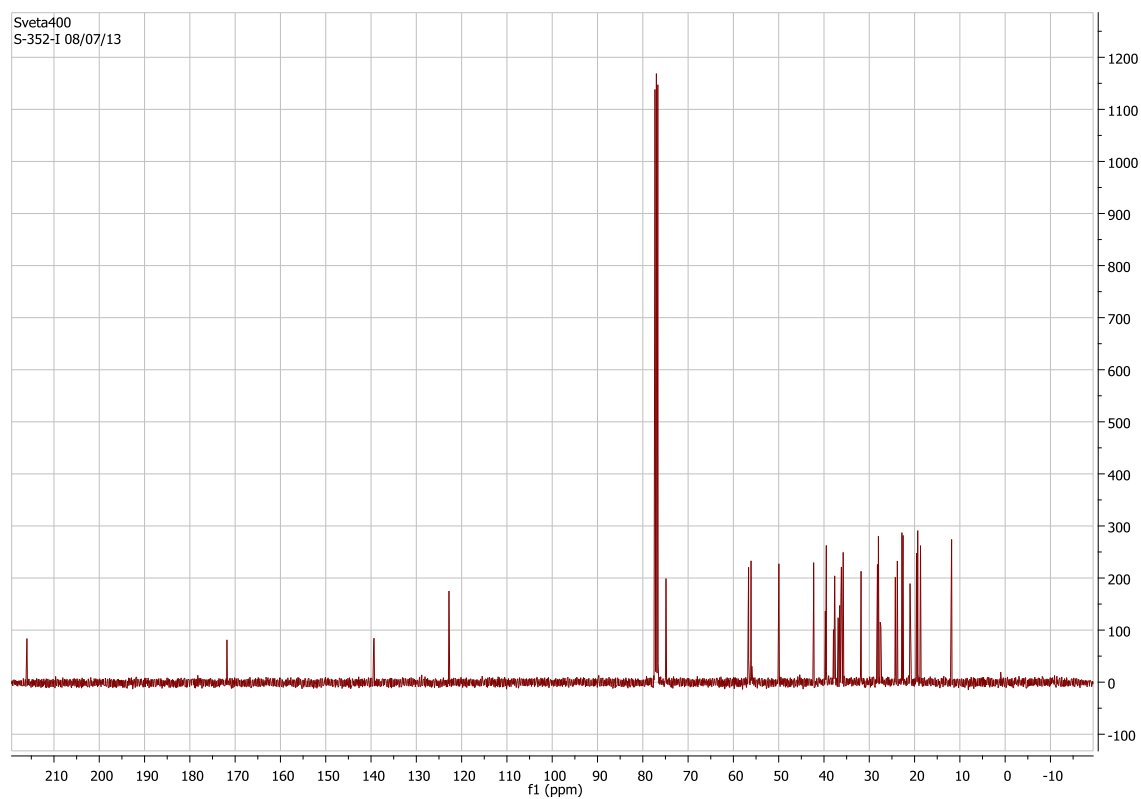
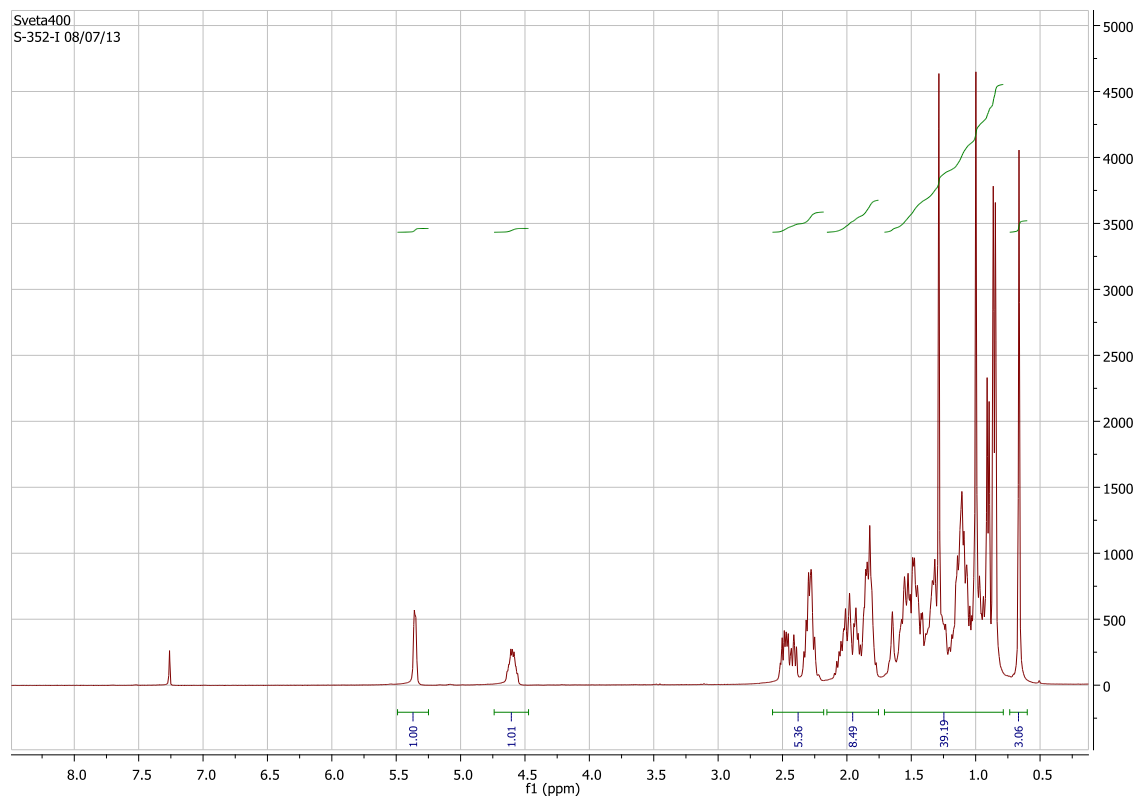
R_f = 0.35 (20% EtOAc/Hexane).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.35 (d, J = 3.7 Hz, 1 H), 4.70 – 4.47 (m, 1 H), 2.61 – 2.36 (m, 2 H), 2.36 – 2.20 (m, 3 H), 2.11 – 1.75 (m, 8 H), 1.73 – 0.77 (m, 36 H), 0.68 (d, J = 16.4 Hz, 3 H).

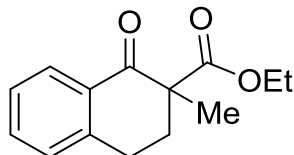
$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 215.97, 171.81, 139.41, 139.33, 122.79, 74.88, 56.65, 56.11, 55.94, 49.96, 42.28, 39.69, 39.49, 37.73, 37.64, 36.88, 36.84, 36.53, 36.28, 36.26, 36.16, 35.76, 31.87, 31.81, 28.20, 27.98, 27.60, 27.44, 24.25, 23.80, 22.79, 22.54, 21.00, 19.58, 19.30, 18.69, 11.82.

IR: (thin film) ν 958.74, 2935.26, 2866.96, 1745.70, 1723.04, 1464.23, 1374.63, 1268.91, 1162.85, 1062.96, 997.74, 940.41, 802.77 cm^{-1} .

HRMS (ESI) m/z : calcd for $\text{C}_{34}\text{H}_{54}\text{O}_3$, $[\text{M}+1]$, 511.4151; found 511.4198.



Ethyl 2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (39a)¹⁵



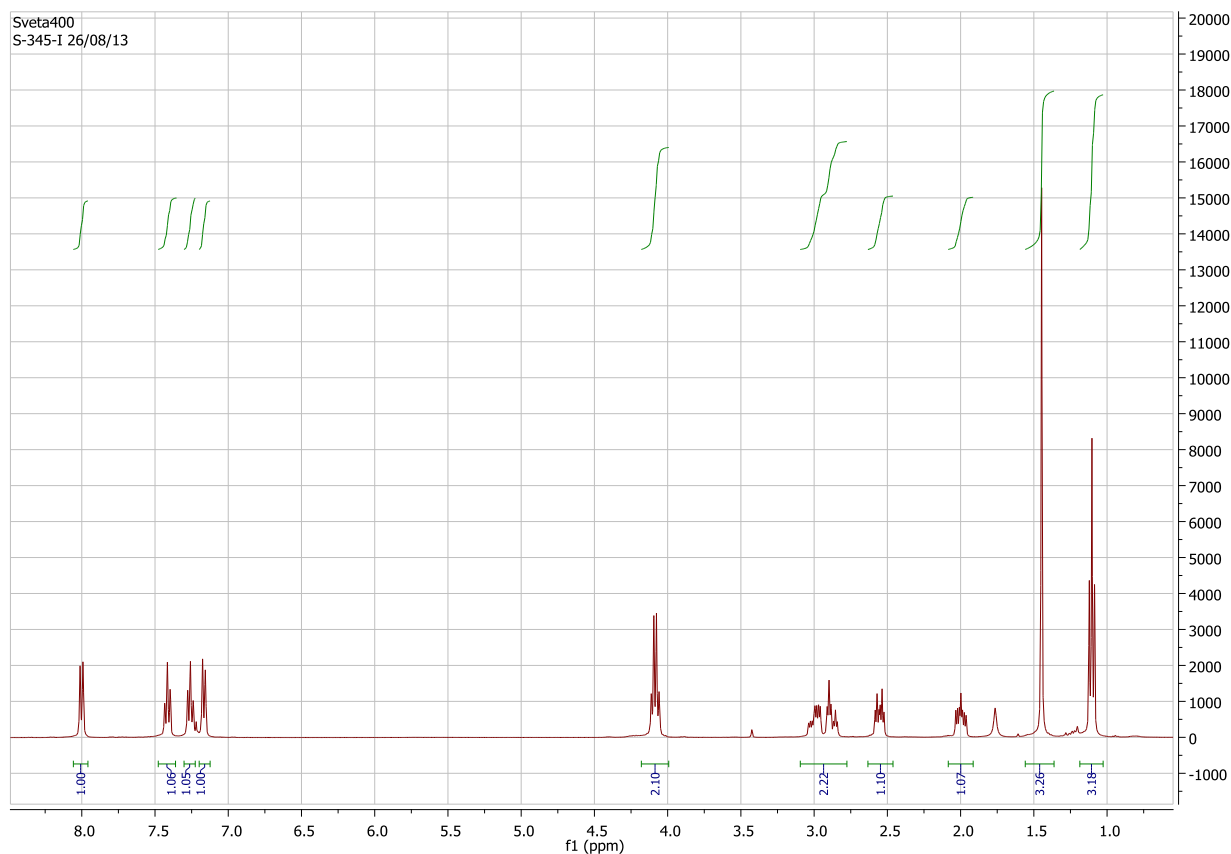
The compound was prepared according to procedure A and purified by column chromatography (5-15% EtOAc/Hexane) to give the product as an oil (80 mg, 93%).

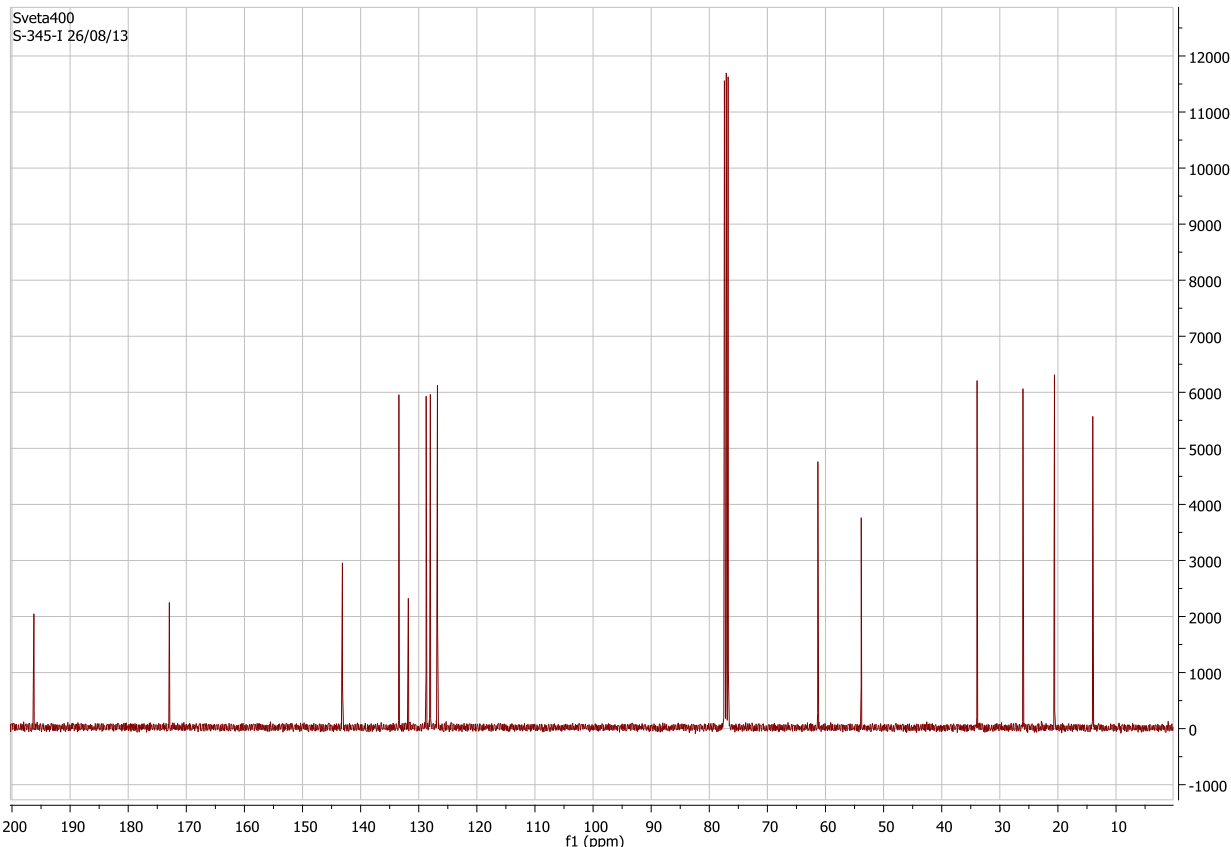
R_f =0.56 (20% EtOAc/Hexane).

¹H NMR (400 MHz, CDCl₃) δ 8.00 (d, J = 7.8 Hz, 1 H), 7.42 (t, J = 7.5 Hz, 1 H), 7.26 (t, J = 7.5 Hz, 1 H), 7.17 (d, J = 7.6 Hz, 1 H), 4.09 (q, 2 H), 2.94 (m, 2 H), 2.57 (m, 1 H), 2.01 (m, 1 H), 1.45 (s, 3 H), 1.12 (t, 3 H).

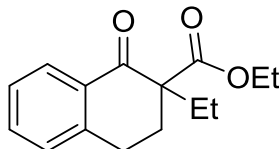
¹³C NMR (101 MHz, CDCl₃) δ 196.23, 172.92, 143.13, 133.41, 131.79, 128.72, 128.00, 126.78, 61.31, 53.85, 33.91, 26.02, 20.59, 14.00.

The data is consistent with those reported in the literature (reference 15)





Ethyl 2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (39b)



The compound was prepared according to procedure A and purified by column chromatography (5-15% EtOAc/Hexane) to give the product as an oil (20 mg, 27%).

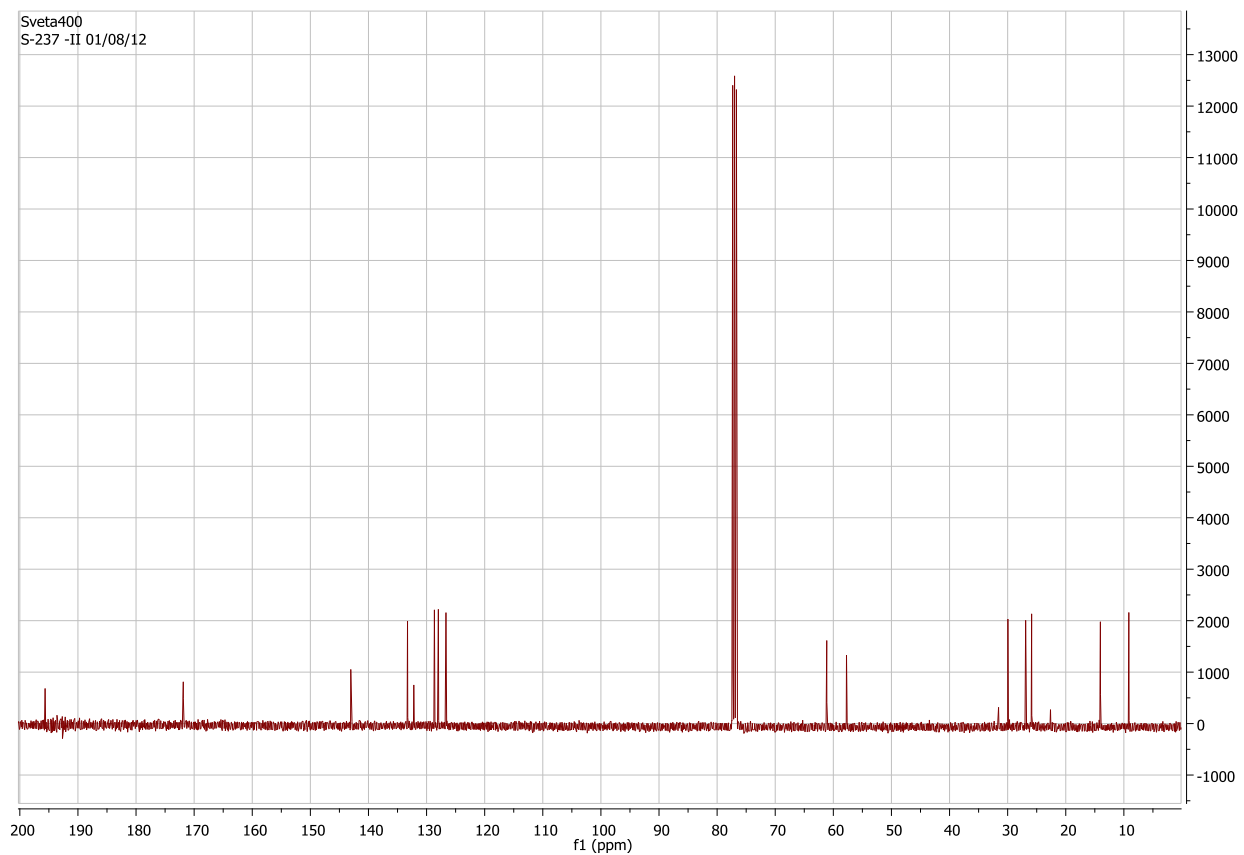
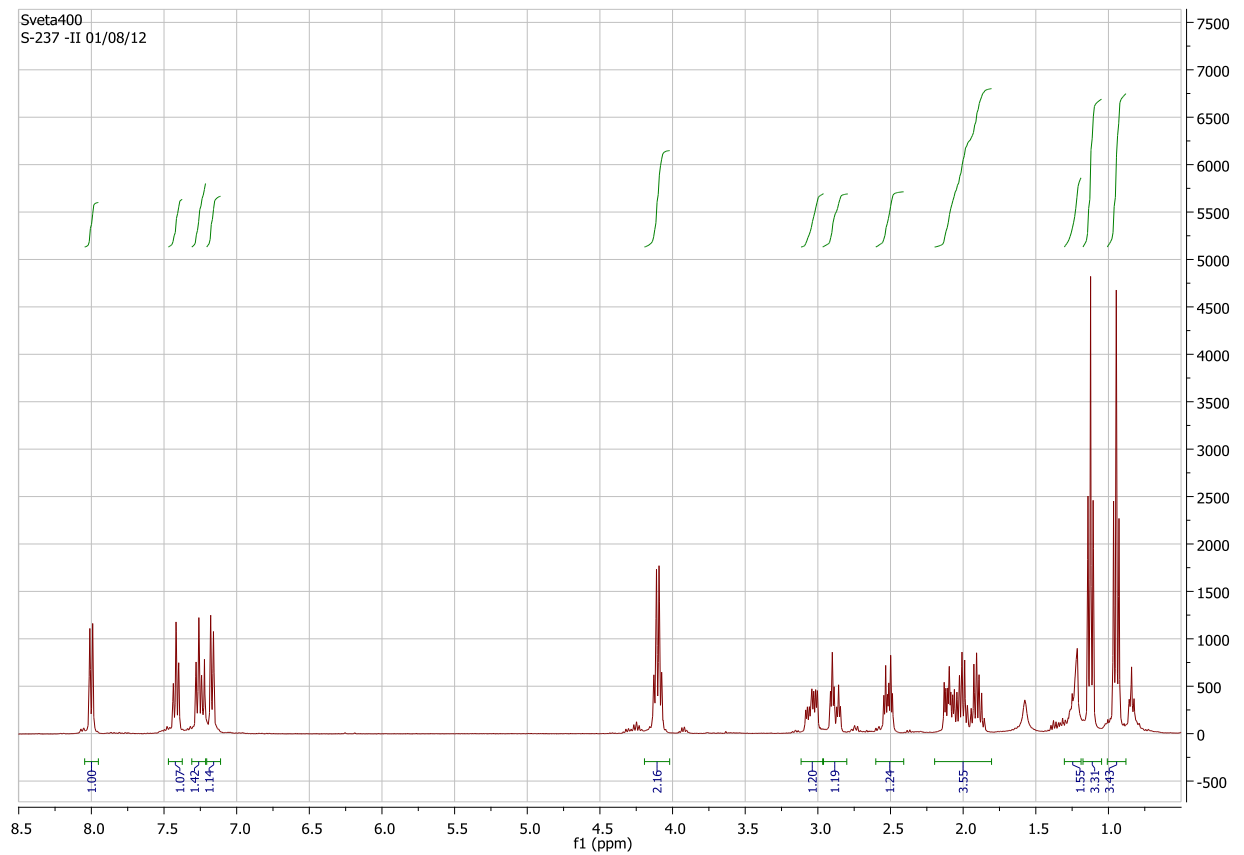
R_f = 0.54 (20% EtOAc/Hexane).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.00 (d, J = 7.8 Hz, 1 H), 7.42 (t, J = 7.4 Hz, 1 H), 7.25 (dd, J = 15.3 Hz, 7.7 Hz, 1 H), 7.17 (d, J = 7.6 Hz, 1 H), 4.10 (q, J = 7.1 Hz, 2 H), 3.04 (m, 1 H), 2.88 (dt, J = 17.4 Hz, 5.0 Hz, 1 H), 2.52 (dt, J = 13.6 Hz, 5.0 Hz, 1 H), 2.01 (m, 3 H), 1.12 (t, J = 7.1 Hz, 3 H), 0.95 (t, J = 7.4 Hz, 3 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 195.65, 171.87, 143.04, 133.28, 132.20, 128.65, 127.97, 126.66, 61.13, 57.74, 29.96, 26.91, 25.87, 14.04, 9.15.

IR: (thin film) ν 2937.55, 2935.79, 1726.18, 1684.88, 1599.93, 1453.49, 1294.46, 1218.32, 1175.52, 1097.26, 1013.79, 902.18, 739.73 cm^{-1} .

HRMS (ESI) m/z : calcd for $\text{C}_{15}\text{H}_{18}\text{O}_3$, $[\text{M}+1]$, 247.1334; found 247.1324.



5. Mechanistic Studies

Reaction of Koser's reagent with dimethylzinc

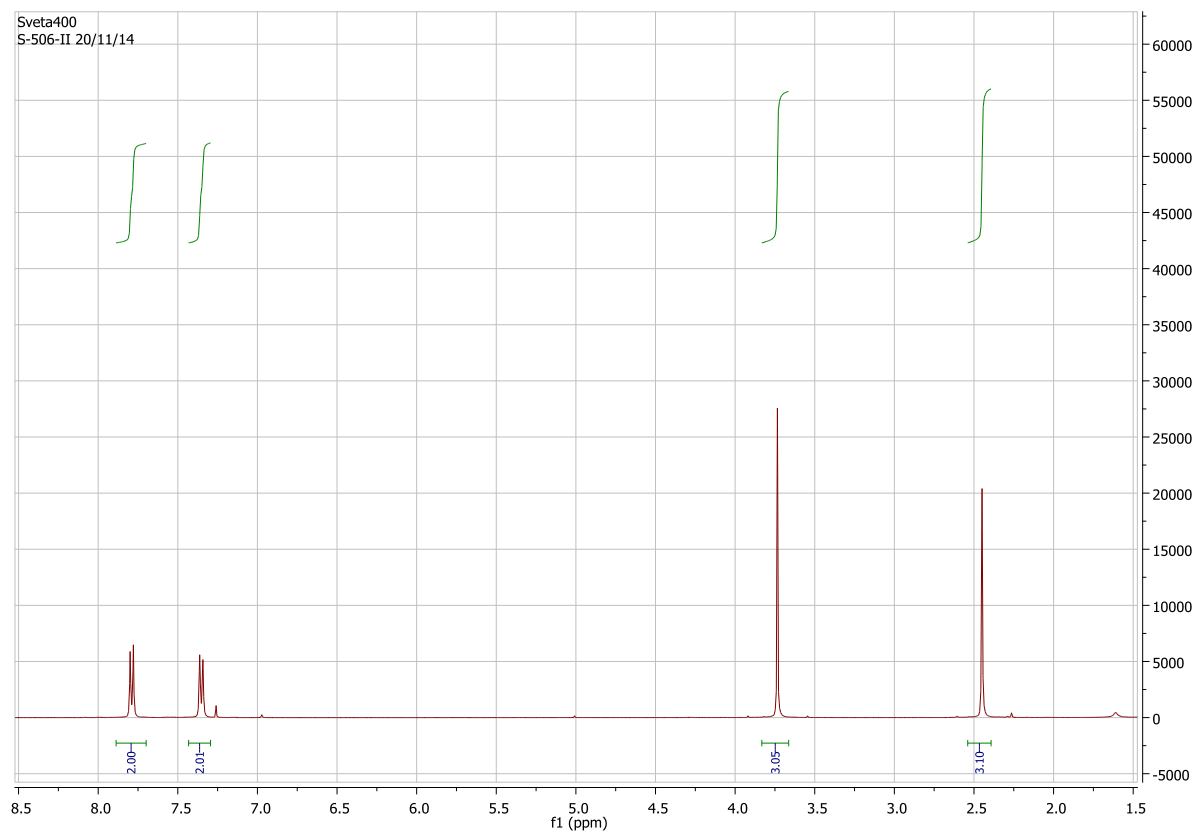
[Hydroxy(tosyloxy)iodo]benzene(0.2 gr, 0.51 mmol) and Me_2Zn solution in toluene (0.7 mL, 0.83 mmol, 1.2 M) were combined in DCM (1.3 mL, 0.4 M) under inert conditions at -78°C . After 4 h stirring at -78°C , the reaction was quenched with water, and the organics extracted with Et_2O (x3), and dried over brine and Na_2SO_4 . Methyl tosylate was isolated as pale yellow oil (0.07 gr, 78% yield) upon short column chromatography using 30% Et_2O /Pentane.

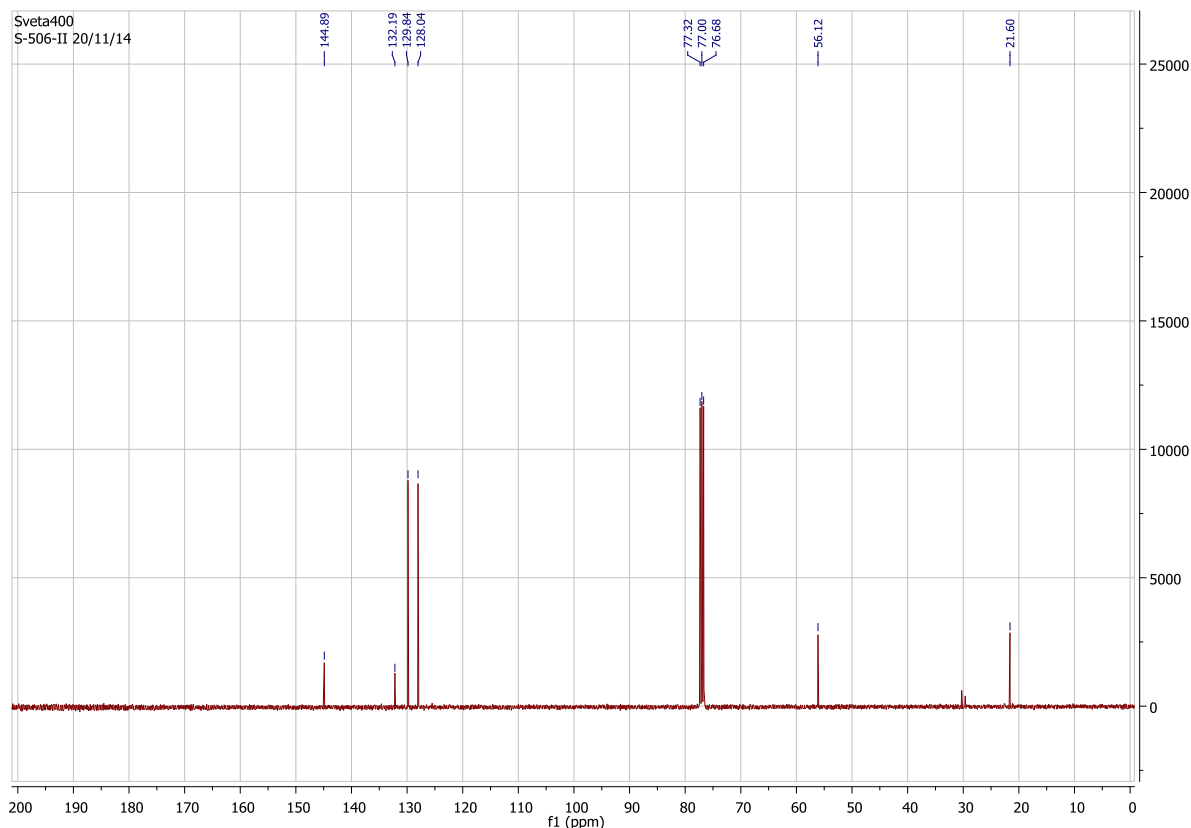
$R_f = 0.25$ (20% Et_2O /Pentane)

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.79 (d, $J = 8.3$ Hz, 2 H), 7.35 (d, $J = 8.1$ Hz, 2 H), 3.73 (s, 3 H), 2.45 (s, 3 H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 144.89, 132.19, 129.84, 128.04, 56.12, 21.60.

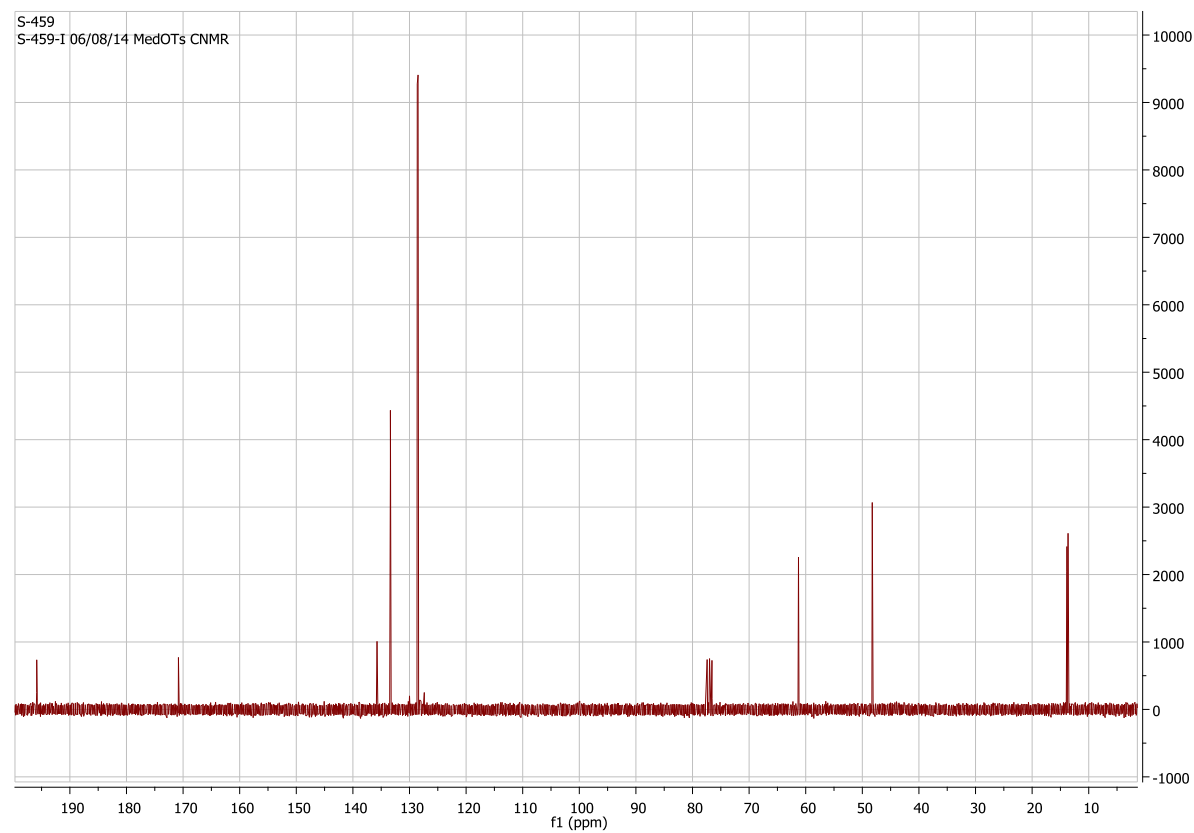
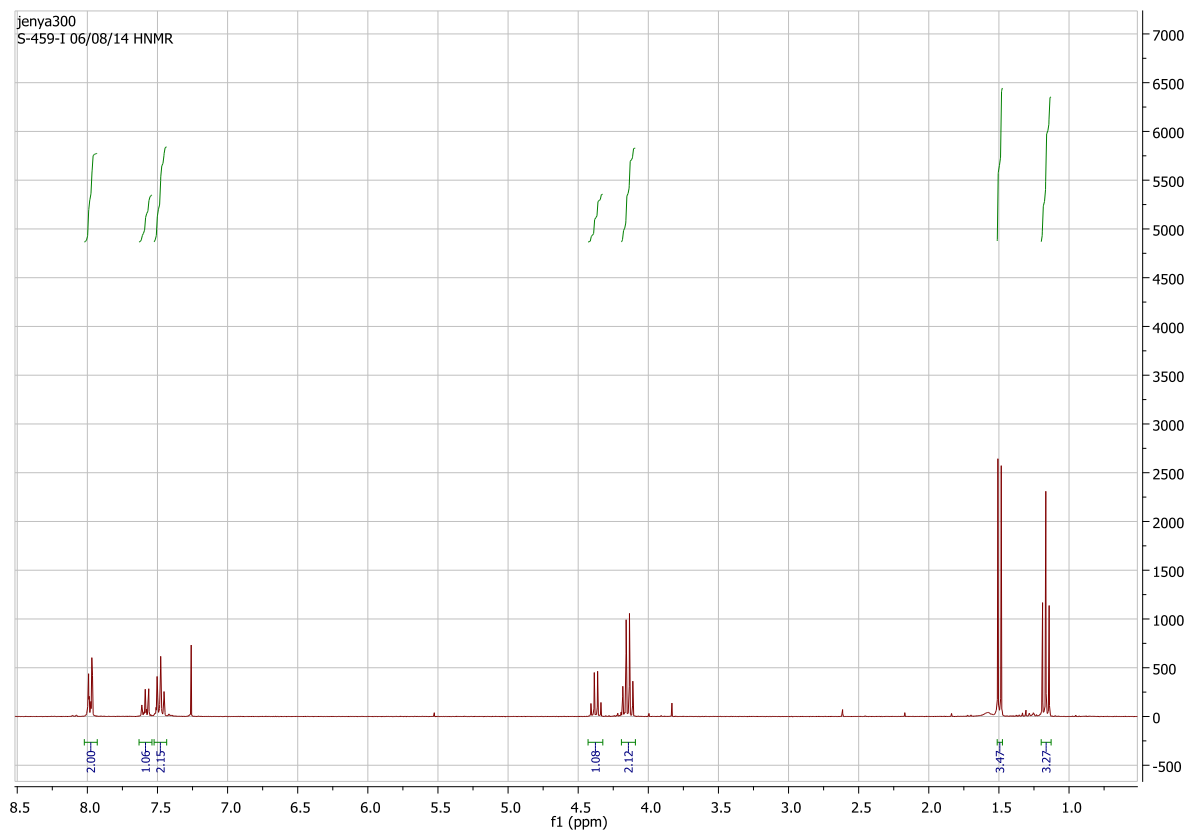
Data in accordance with commercially available reagent.

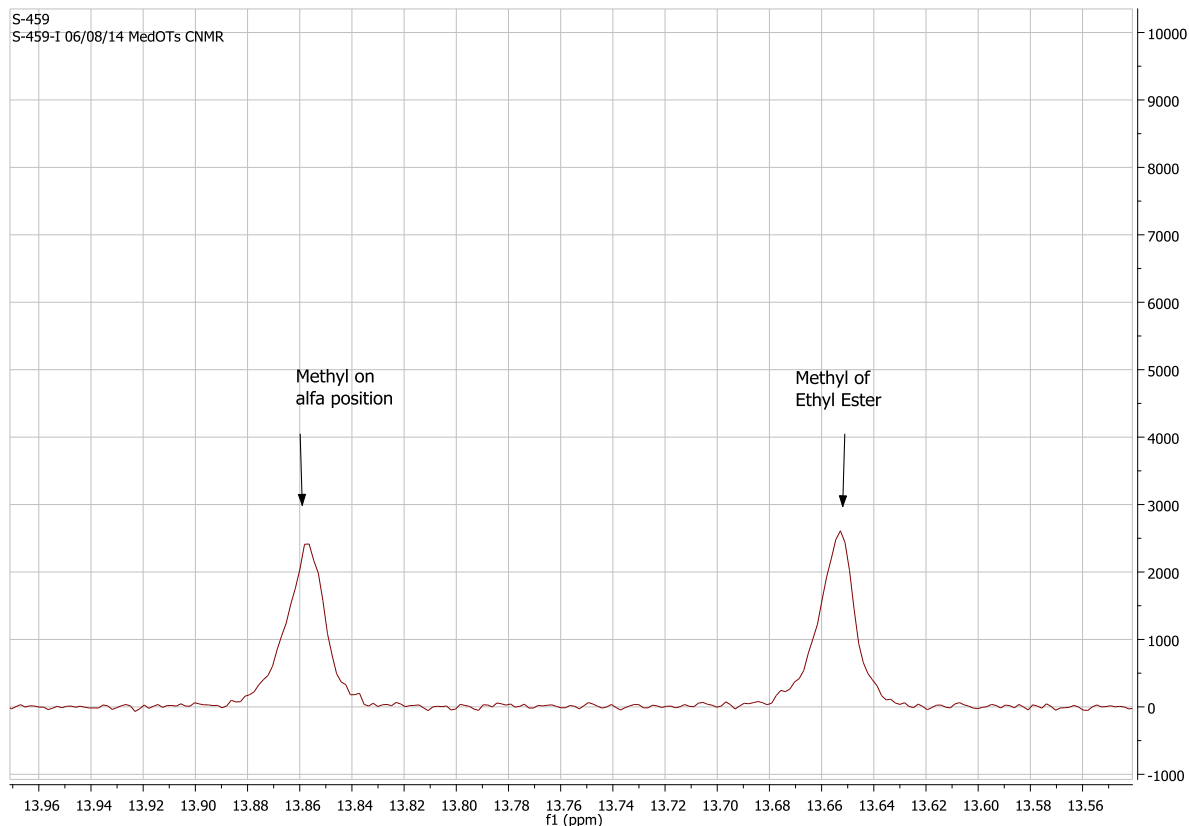




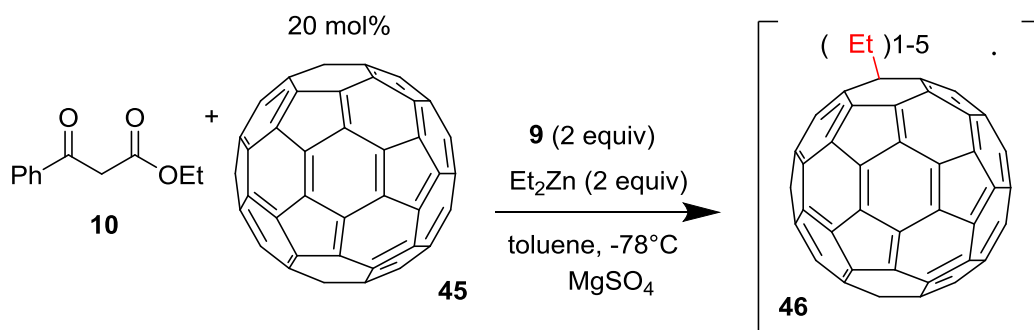
Study on the influence of deuterated methyltosylate

Ethyl 2-methyl-3-oxo-3-phenylpropanoate (0.5 mmol, 0.096 g) was dissolved in anhydrous toluene (1.5 mL, 0.3 M) under positive argon flow. The mixture was cooled to -78 °C and [hydroxy(tosyloxy)iodo]benzene **9** (1.0 mmol, 0.39 g) and freshly dried MgSO₄ (2.5 mmol, 0.3 g) were added in the dark. After 5 min, MeOTs-*d*₃¹⁶ (0.75 mmol, 0.14 g) was added. This followed by addition of dimethylzinc in toluene (1.2 M, 1.0 mmol, 0.83 mL). The mixture was allowed to stir at -78 °C for 18 h, in the dark. Reaction was quenched by addition of water, followed by filtration of the slurry through a Celite® frit and rinse with Et₂O. Product **11a** was purified on column chromatography (10% EtOAc/Hexane) as an oil (93 mg, 93%). Methyl-*d*₃ insertion was not observed (no multiplet peak of the methyl on ¹³C NMR; accurate integration of methyl on ¹H NMR). For tabulated characterization data see above **11a**.





C₆₀ radical trapping experiment



C₆₀ (0.0027 mmol, 2 mg, 0.2 equiv.) in 1 mL of toluene and ethyl 3-oxo-3-phenylpropanoate **10** (0.014 mmol, 2.6 mg, 1.0 equiv.) were placed in a dry Schlenk flask under positive argon flow. After cooling to -78 °C, [hydroxy(tosyloxy)iodo]benzene (0.028 mmol, 11 mg, 2.0 equiv.) and freshly dried MgSO₄ (0.07 mmol, 8.4 mg, 5.0 equiv.) were added in the dark. After 15 min, diethylzinc in toluene (1.5 M, 19 µL, 2 equiv.) was added, followed by 18 h stirring in the dark at -78 °C. The content of reaction mixture was moved to a dry NMR tube under positive argon flow and capped under inert conditions. The ESR and HRMS were measured.

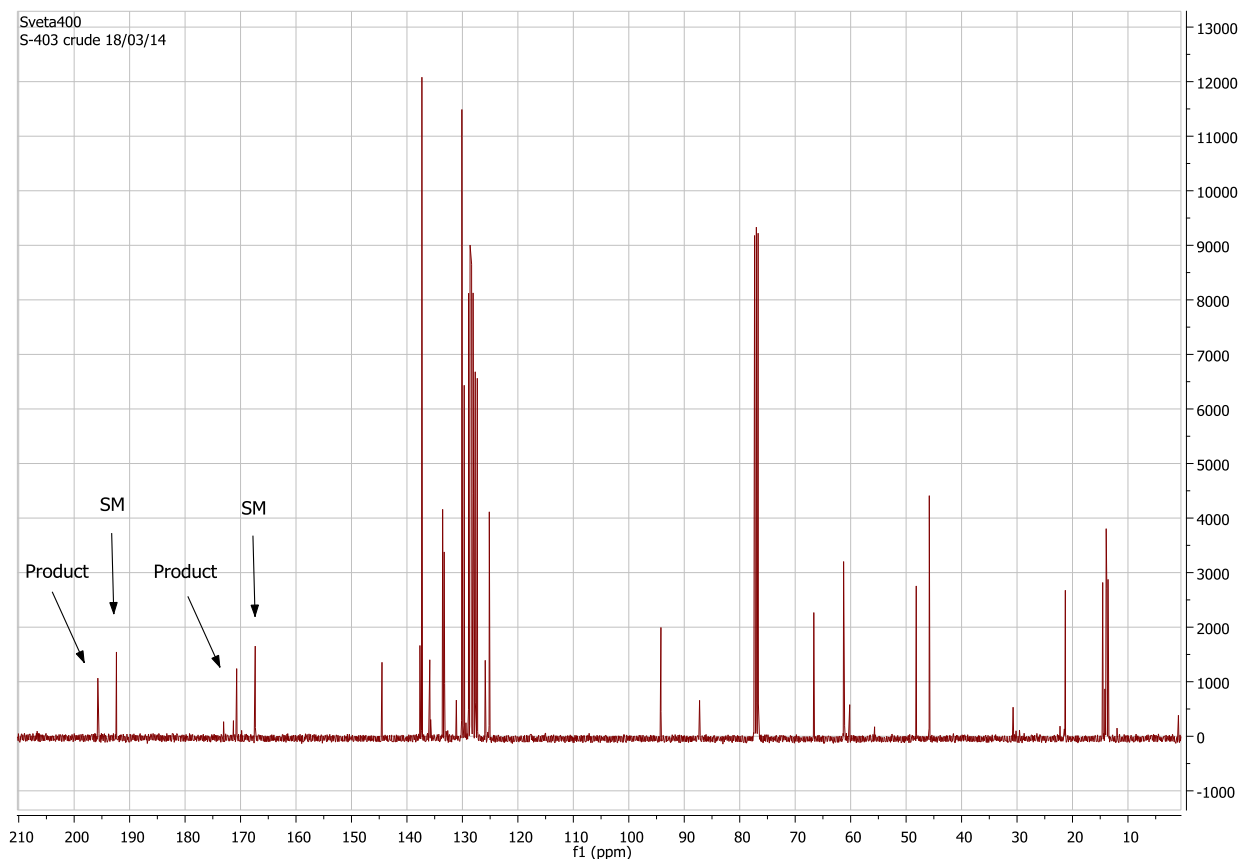
Eq. 2 – 1,4-cyclopentadiene experiment

The compound was prepared according to procedure A, with addition of 1,4-cyclohexadiene (2 equiv.) along with MgSO_4 . The product was obtained following column chromatography (5-15% EtOAc/Hexane) as an oil (110 mg, 85%).

Crossover experiment (scheme 4)

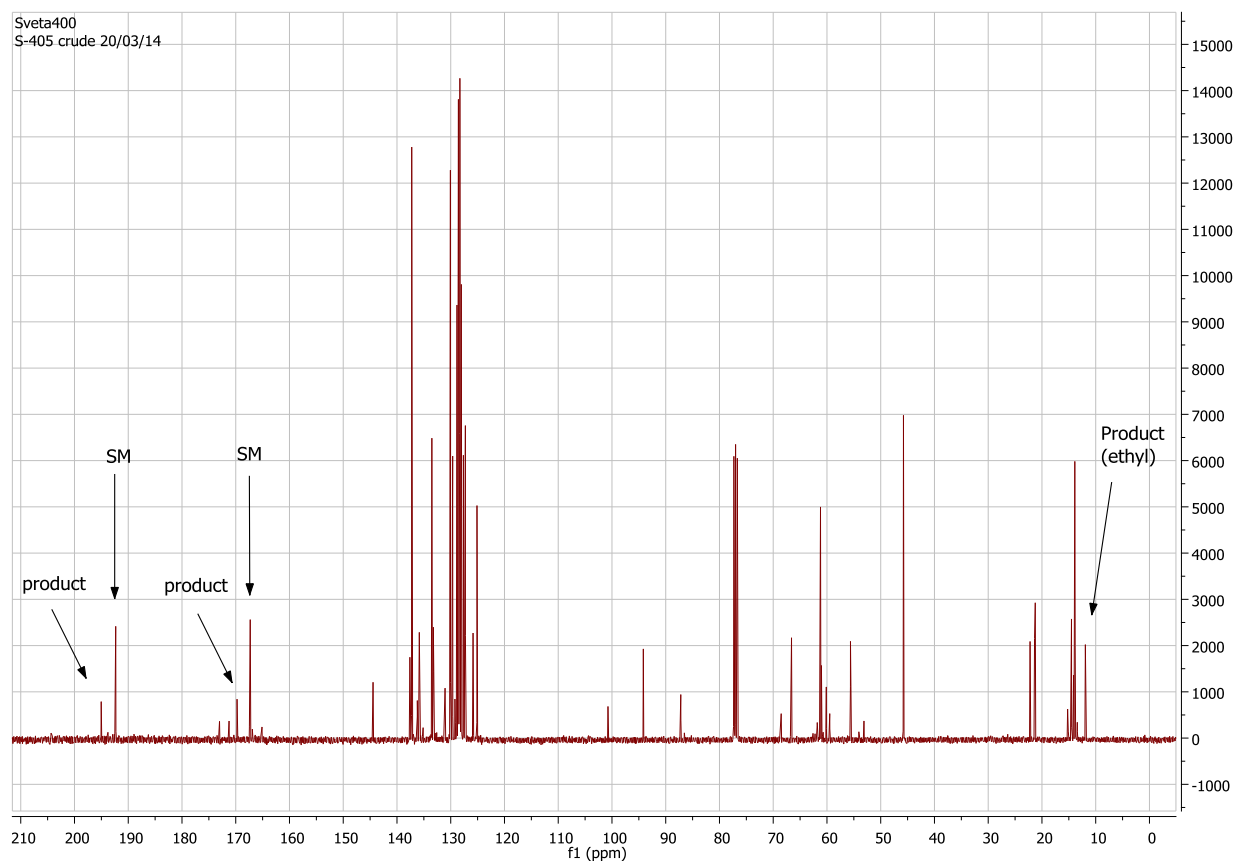
Experiment 1:

Flask 1: Ethyl 3-oxo-3-phenylpropanoate (0.5 mmol, 0.96 g, 1.0 equiv.) was dissolved in anhydrous toluene (0.8 M, 0.6 mL) under positive argon flow. After cooling to $-78\text{ }^\circ\text{C}$, freshly dried MgSO_4 (1.5 mmol, 0.18 g, 3.0 equiv.) and solution of dimethylzinc in toluene (1.2 M, 0.65 mmol, 0.54 mL, 1.3 equiv.) were added. Flask 2: under inert conditions [hydroxy(tosyloxy)iodo]benzene (0.65 mmol, 0.25 g, 1.3 equiv.) and anhydrous toluene (0.4 M, 1.25 mL) were added in the dark. A solution of diethylzinc in toluene (1.5 M, 0.65 mmol, 0.43 mL, 1.3 eq) followed. After 8 h stirring at $-78\text{ }^\circ\text{C}$, content of flask 2 was cannulated to flask 1. The mixture was allowed to stir at $-78\text{ }^\circ\text{C}$ for 13 h, in the dark. Reaction was quenched by addition of water, followed by filtration of the slurry through a Celite® frit and rinse with Et_2O . NMR spectra of the crude mixture show about 40% conversion to product **11a**, while the rest is unreacted reactant **10**.



Experiment 2:

The experiment was repeated according to crossover procedure 1 switching the dimethylzinc and diethylzinc reagents. NMR spectra of the crude mixture show about 30% conversion to product **11b**, while the rest is unreacted reactant **10**.



Zinc Enolate (47) – NMR experiment in d_8 -THF/toluene

Procedure:

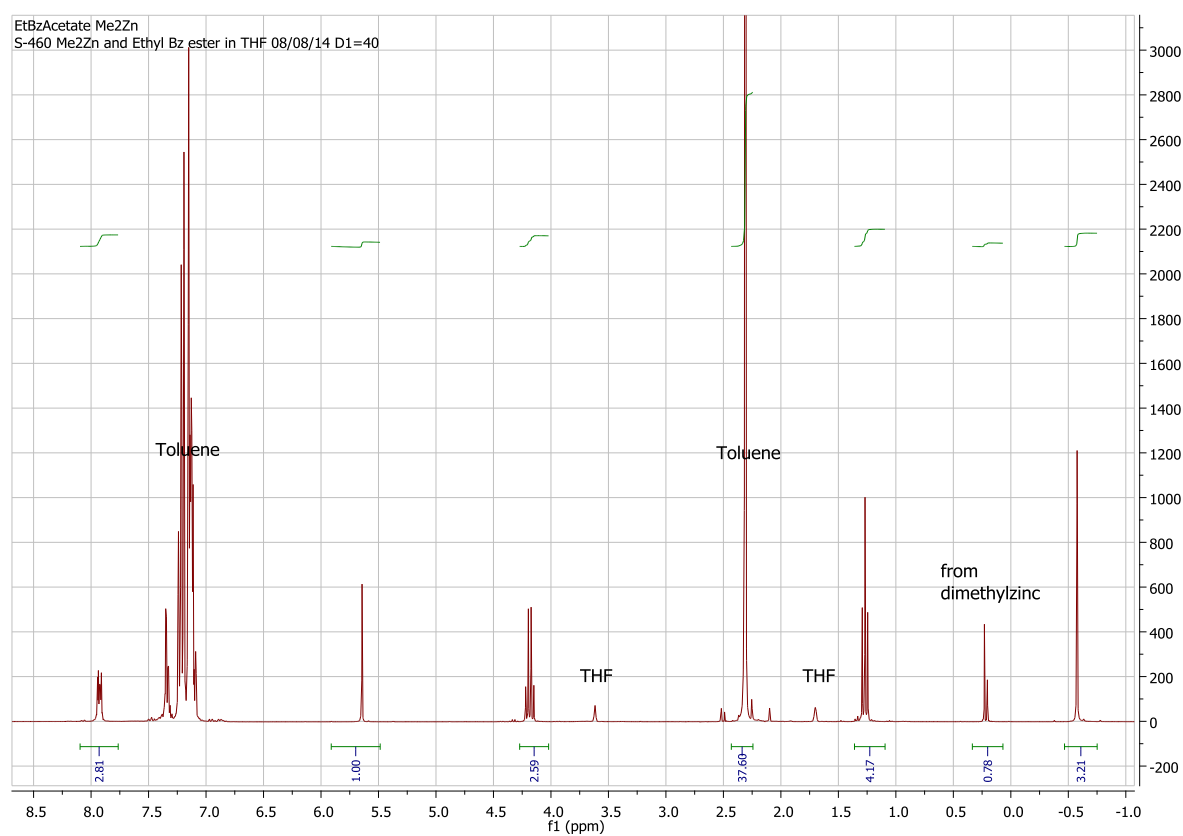
Under a positive argon pressure, ethyl 3-oxo-3-phenylpropanoate (0.1 mmol, 0.02 g), Me_2Zn in toluene (1.2 M, 0.11 mmol, 0.092 mL) and $\text{THF-}d_8$ (0.75 mL) were combined in a NMR tube. NMR acquisition on Bruker Avance I 300 spectrometer was performed immediately.

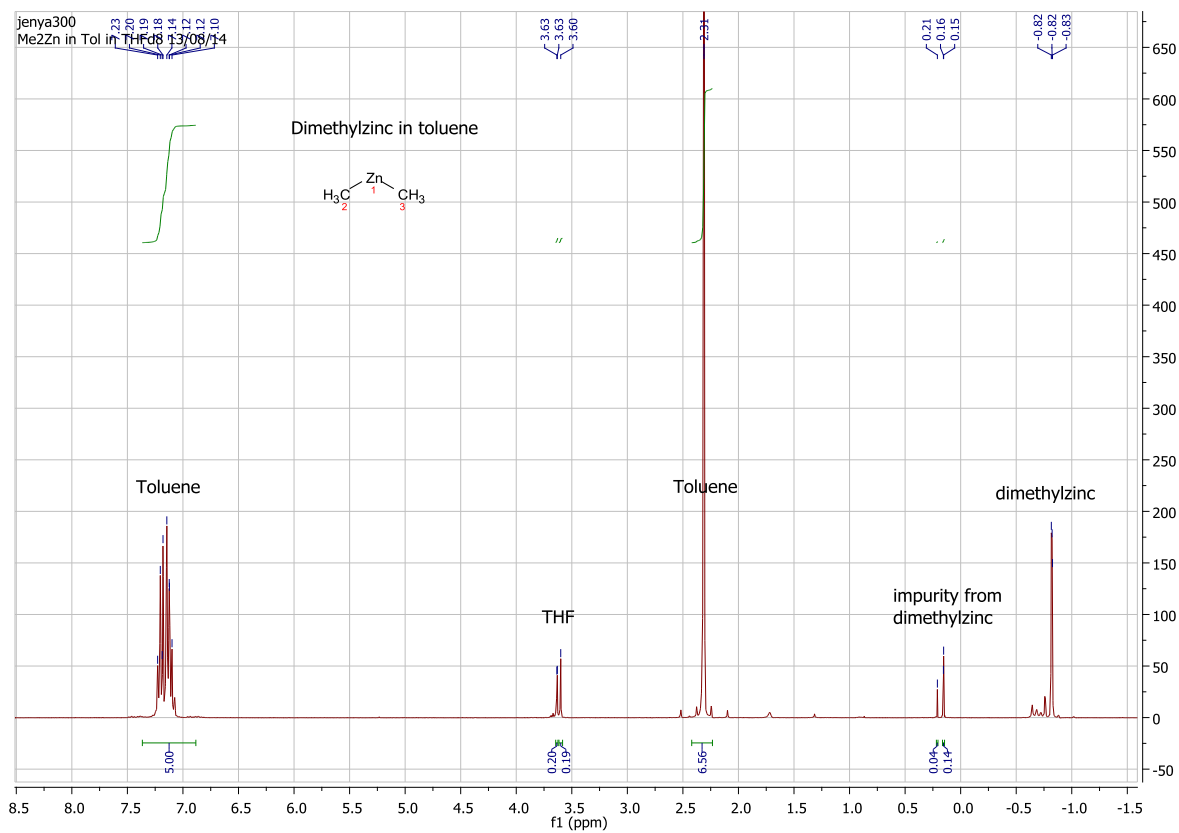
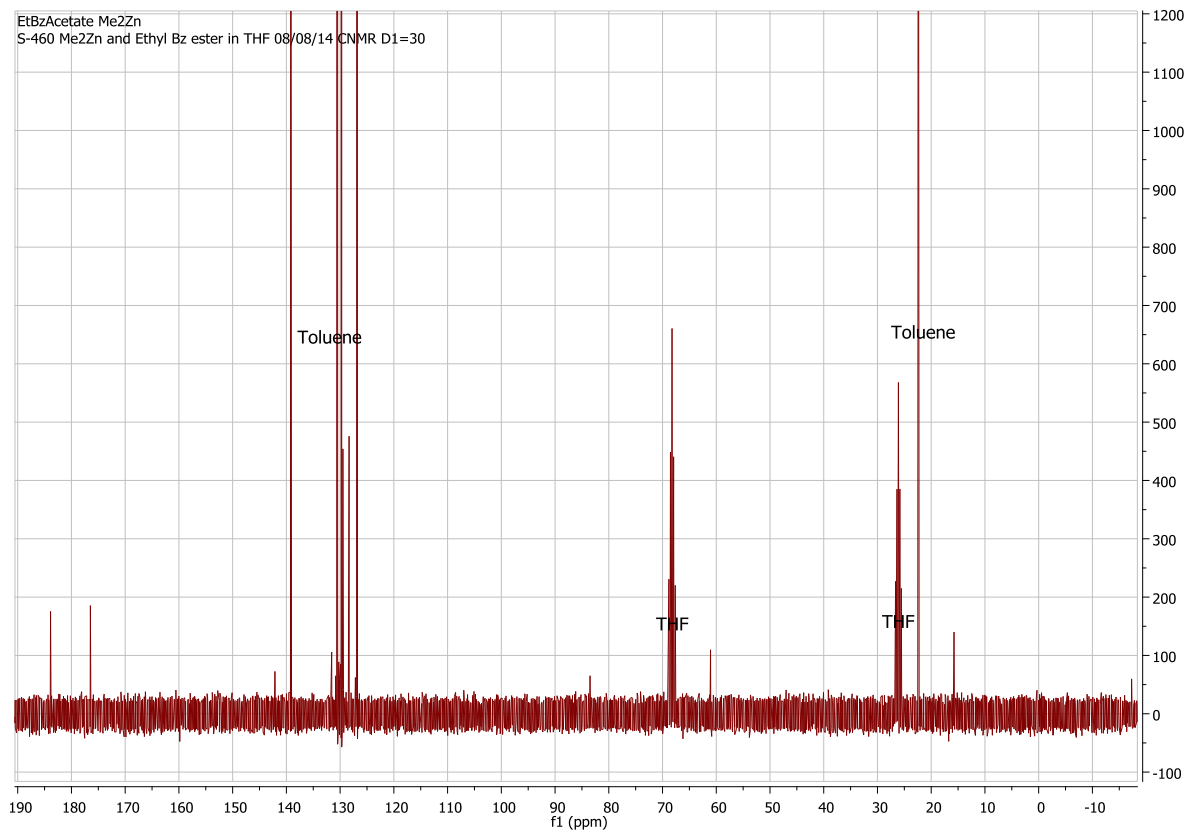
^1H NMR (300 MHz, THF): δ 7.93 (m, 1 H), 7.24-7.09 (m, 3H + 5H of toluene), 5.64 (s, 1 H), 4.18 (q, $J = 7.1$ Hz, 2H), 3.62 (s, 1H), 1.28 (t, $J = 7.1$ Hz, 3H), -0.58 (s, 3H).

^{13}C NMR (75 MHz, THF): δ 183.89, 176.47, 142.14, 131.56, 129.46, 128.33, 83.49, 61.07, 15.75, -17.29.

Me_2Zn in Toluene 1.2 M solution in $\text{THF-}d_8$:

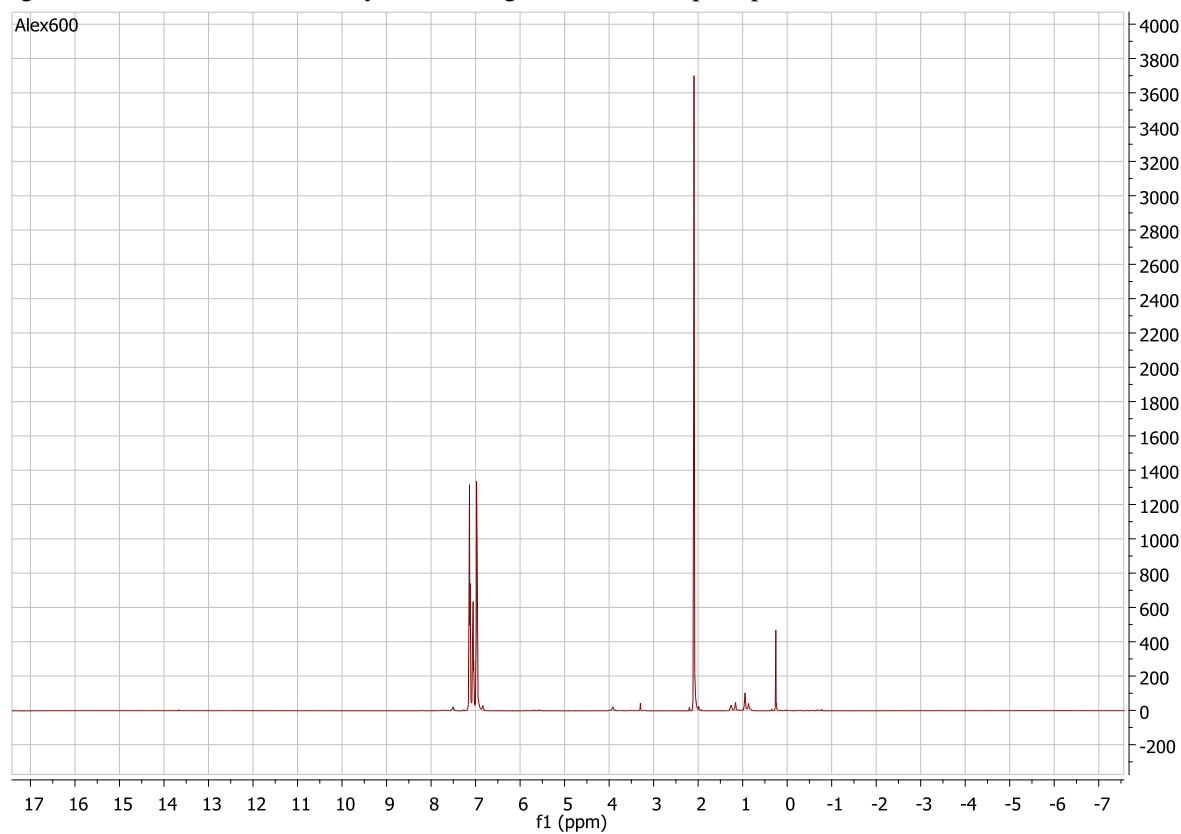
^1H NMR (300 MHz, THF): δ -0.82 (s, 6 H).



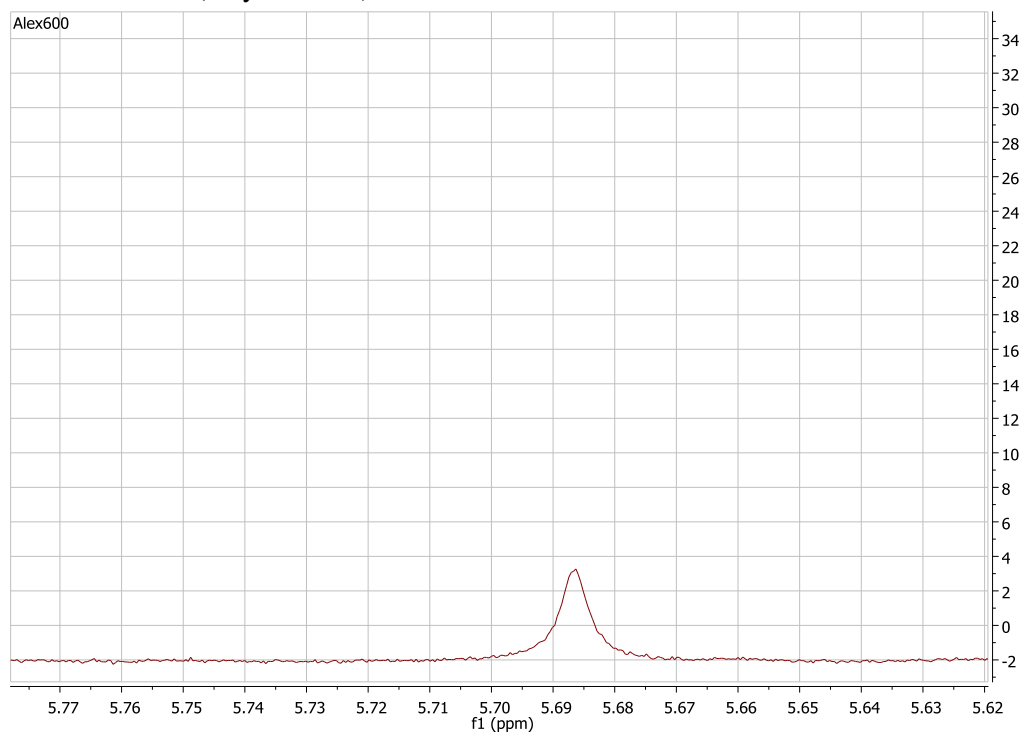


Enolate formation in toluene at -78 °C ^1H NMR measured at 600 MHz.

NMR measured 1 h after mixing of **10** and dimethylzinc at -78 °C in toluene. Disappearance of the signals from **10** can be clearly seen. Large amounts of precipitate observed. Gas evolution observed.

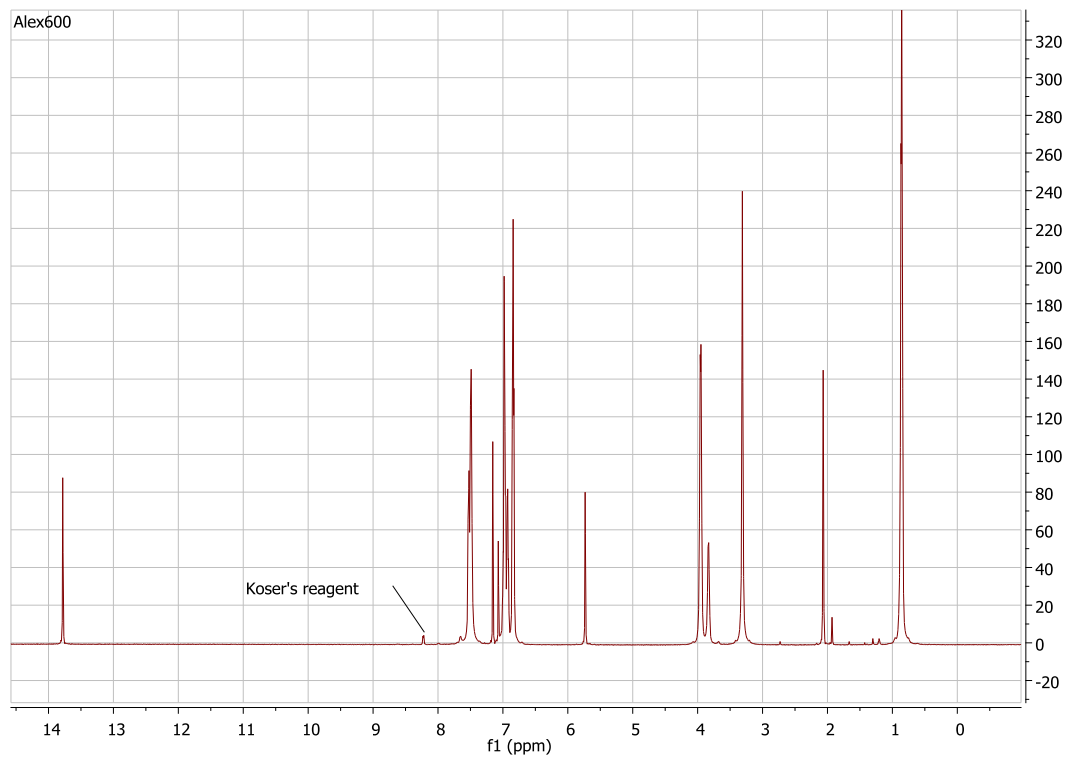


Zoom in at 5.69 (vinyl $=\text{C}-\text{H}$)

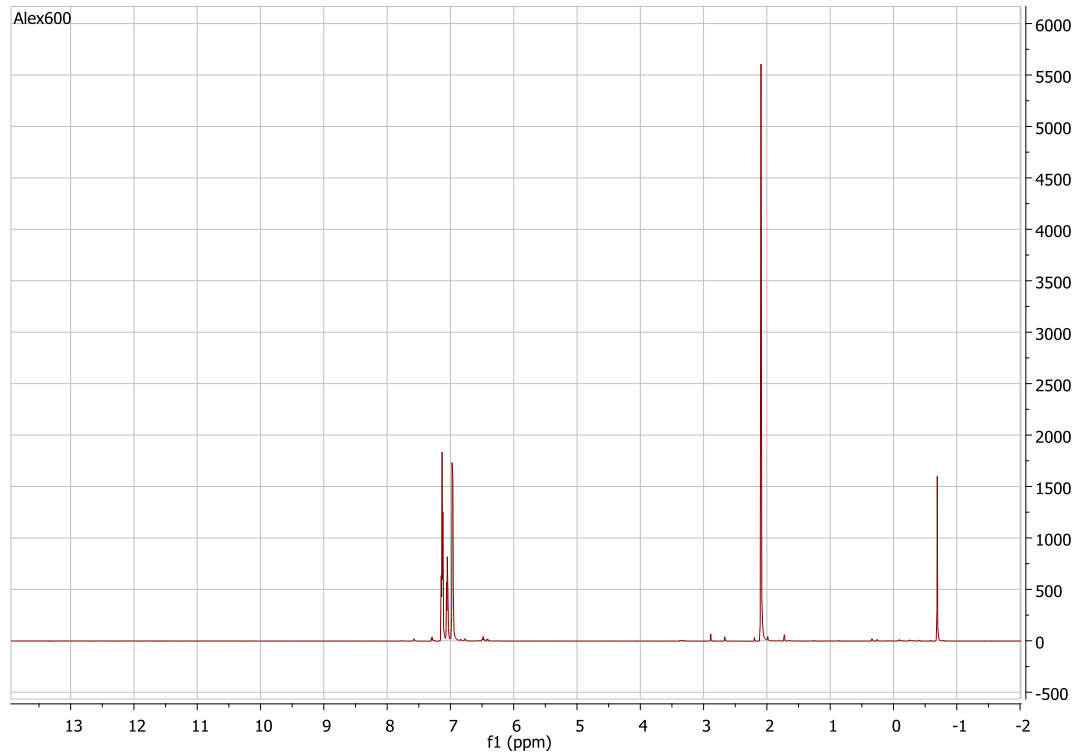


Reaction monitoring in toluene at -78 °C by ^1H NMR measured at 600 Mhz.

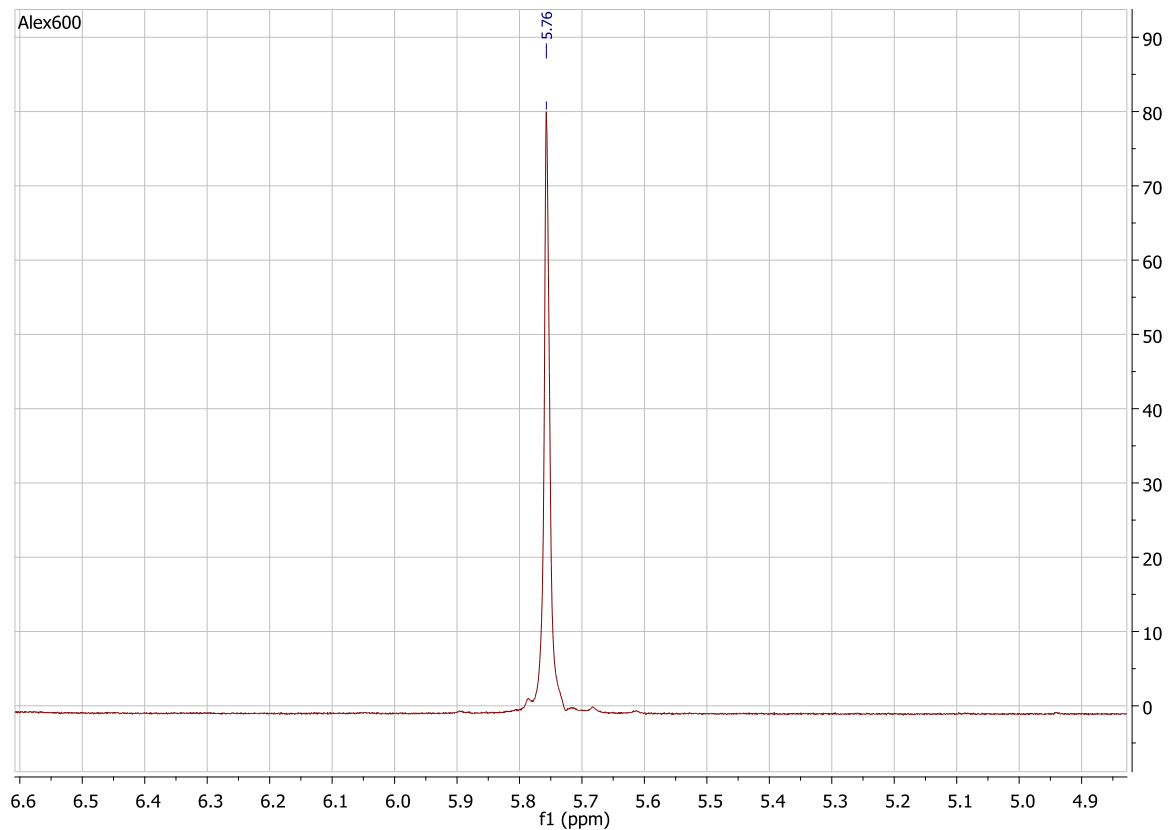
Heterogeneous mixture of **10** and Koser's reagent **11** 30 minutes after mixing of the reagents and before addition of dimethylzinc. Enol form of **10** can be clearly seen at 13.81 ppm and at 5.76. No product formation may be observed. Koser's reagent is almost insoluble. Small signal from Koser's reagent may be observed at 8.25 ppm (indicated).



One hour after addition of excess dimethylzinc. Dimethylzinc signal can be observed at -0.8 ppm. All other signals have totally disappeared. Large amounts of precipitate are observed.

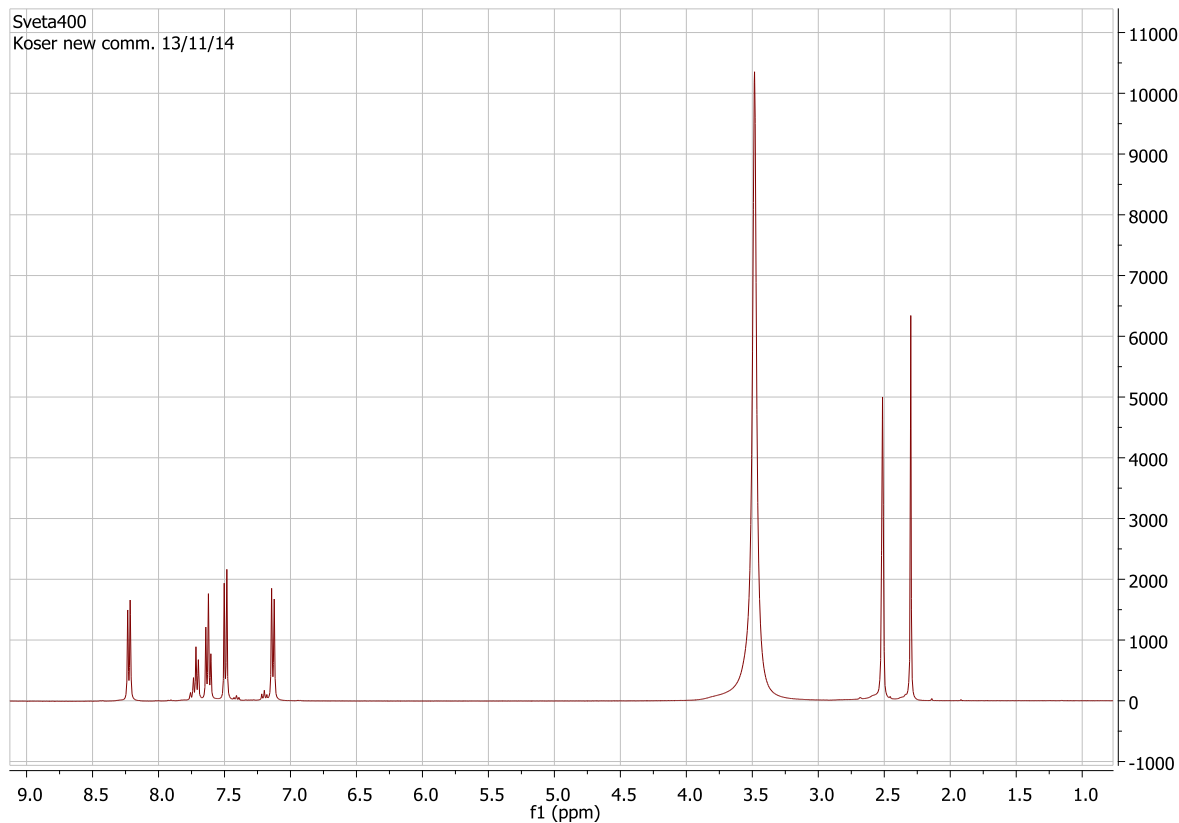


Zoom in on the vinylic region of the spectra. Only the enol form of **10** can be observed.



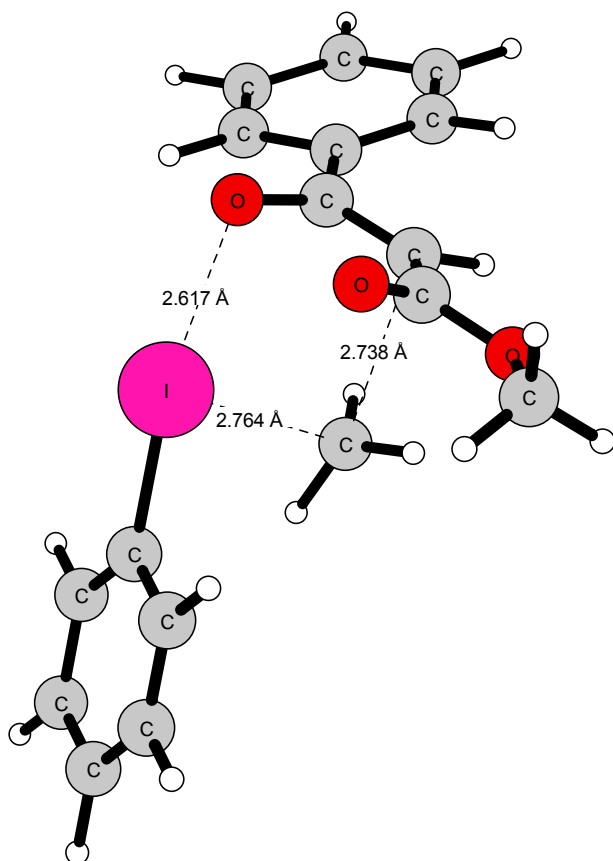
Role of the dehydrating reagent.

While the role of the dehydrating reagent, molecular sieves or magnesium sulfate, is not clear, it may protect the reaction from adventitious water (similar to the Sharpless epoxidation, *J. Am. Chem. Soc.* **1987**, 109, 5165-5180) or from water present in the Koser reagent. See attached below a ^1H NMR spectrum of a freshly opened container of commercial Koser reagent recorded in d_6 -DMSO from a freshly opened ampule. Note the large water signal at 3.5 ppm.



6. Computational Results

Transition state for transfer of the methyl group

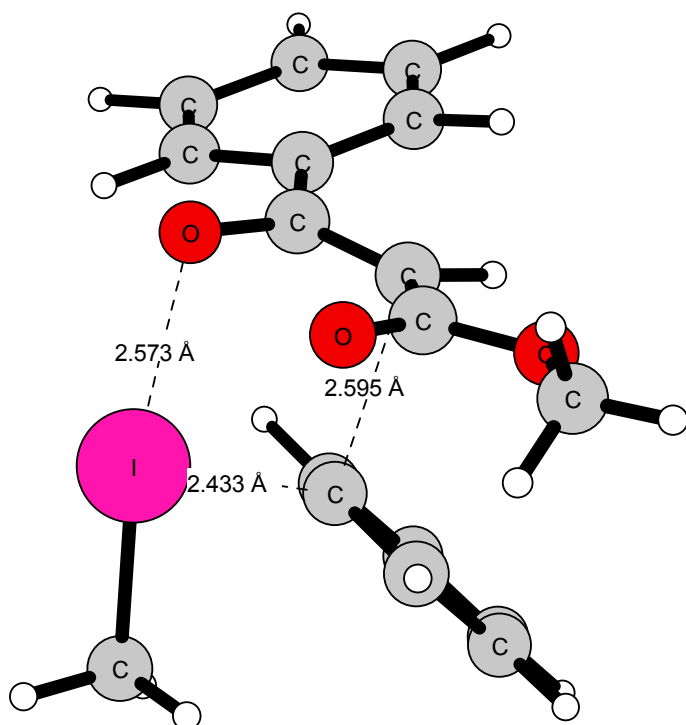


E_scf: -894.972884
Total Gibbs free energy (298K): -894.771856
Total Gibbs free energy (195 K): -894.747544
Solution phase energy (benzene): -895.024225
Five lowest frequencies -281.03 14.39 21.76 32.33 38.58 48.86

C1	0.0374173827	-0.0298733378	-0.0629993386
C35	-0.1727867436	-0.1377171900	2.6650261474
I2	2.5845962092	-0.0451156779	2.5100074348
O16	2.0683298249	1.1292561586	0.2286433920
C3	2.4754261565	-0.8368068322	4.4903582391
C4	2.4971639988	-2.2216632609	4.6831871914
C5	2.3716264856	0.0265752034	5.5853848876
C6	2.4257131320	-2.7399179602	5.9774332498
C7	2.2979464076	-0.5001480859	6.8772070521
C8	2.3265451762	-1.8814952718	7.0744961737

H9	2.2709211728	-2.2883132635	8.0797739043
H10	2.2207512088	0.1720684723	7.7268475748
H11	2.3551607276	1.1015028638	5.4350812524
H12	2.5731698839	-2.8901621071	3.8314710895
H13	2.4468995733	-3.8156233894	6.1261270398
C14	0.8340112716	1.1399921572	-0.0288766986
C15	0.5531241503	-1.3819210755	-0.1380046962
O17	-0.4899495227	-2.2797068961	0.0011920749
O18	1.7052222623	-1.7586626517	-0.2673910308
C19	-0.1004633718	-3.6540294395	-0.0681137742
H20	-1.0175233053	-4.2324260281	0.0555606307
H21	0.3659571616	-3.8817114722	-1.0314999636
H22	0.6159971781	-3.9013351369	0.7220066809
C23	-1.0198006159	5.0246576186	-0.3087239333
C24	0.2196257024	4.8598727574	0.3154088793
C25	0.8037521610	3.5975822242	0.3860652588
C26	0.1538539569	2.4771351674	-0.1533154406
C27	-1.0850058056	2.6546098717	-0.7877509555
C28	-1.6671818195	3.9196132209	-0.8652961879
H29	-1.4743543053	6.0097212051	-0.3686443488
H30	0.7313409110	5.7178882721	0.7428271664
H31	1.7730825421	3.4501930079	0.8506164915
H32	-1.5850002963	1.8079202092	-1.2480503955
H33	-2.6225151119	4.0441761741	-1.3674626532
H34	-1.0408075677	0.0600053005	-0.0939653215
H36	-0.5967498492	0.8171029070	2.3844408905
H37	-0.5897230429	-1.0202280223	2.1984916934
H38	0.1264120455	-0.2419582013	3.7004186969

Transition state for transfer of the phenyl group



E_scf: -894.975800
 Total Gibbs free energy (298K): -894.778738
 Total Gibbs free energy (195K): -894.755033
 Solution phase energy (benzene): -895.033182
 Five lowest frequencies: -238.94 20.79 31.14 42.22 50.22 69.71

XYZ coordinates

C2	-0.2733730541	0.0118159705	0.2088889155
C24	0.1609206950	0.0010146739	2.7669147137
I1	2.1233589093	-0.0175605137	-0.2119240880
C3	-0.8617039726	1.2535726091	0.0218096289
C4	-0.9114584814	-1.1877075358	-0.0732451265
C5	-2.1837377791	1.2866789661	-0.4329190569
C6	-2.2326259699	-1.1284643711	-0.5280881707
C7	-2.8687329118	0.1018697483	-0.7089874300
H9	-3.8927402978	0.1367951282	-1.0680628753
H10	-2.7601454001	-2.0554422262	-0.7368734750
H11	-0.4190841057	-2.1398864065	0.0922415134
H12	-0.3256349717	2.1672365915	0.2556078887
H13	-2.6739766912	2.2478317442	-0.5627549366
C14	0.9996045957	-1.1214134315	2.6091891128

C15	0.6069318646	1.3782539037	2.7619257043
O16	2.1751514544	-1.0574657362	2.1412336354
O17	-0.4406445606	2.2055489849	3.0985178301
O18	1.7042624602	1.8284390877	2.4671233615
C19	-0.1153480672	3.5963058362	3.1339102433
H20	-1.0364778664	4.1118290076	3.4112445264
H21	0.6700366352	3.7991568216	3.8688515614
H22	0.2376182114	3.9479497065	2.1584732218
C23	-0.6289521957	-5.0860760849	3.0821986728
C25	0.5193037454	-4.8624373312	2.3188271527
C26	1.0387337444	-3.5755136855	2.2010597062
C27	0.4136631501	-2.4883895988	2.8317742260
C28	-0.7314703744	-2.7263524828	3.6066554319
C29	-1.2477745575	-4.0153686646	3.7307486822
H29	-1.0351727519	-6.0896097349	3.1771527086
H30	1.0104563515	-5.6927563733	1.8182314108
H31	1.9375022705	-3.3807913539	1.6249295101
H32	-1.2123388071	-1.9073487522	4.1320740697
H33	-2.1323987147	-4.1857554313	4.3384095754
H34	-0.8800949856	-0.1432384591	3.0216856147
C35	1.4818579728	0.5738383918	-2.2199119385
H36	2.3500288896	0.4974482542	-2.8750040385
H37	0.6923356831	-0.1120885174	-2.5245079758
H38	1.1088979939	1.5956319149	-2.1754326016

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