Supplementary Information

Enamine/Carbene Cascade Catalysis in the Diastereo- and Enantioselective Synthesis of Functionalized Cyclopentanones

Kerem E. Ozboya and Tomislav Rovis*

Department of Chemistry, Colorado State University, Fort Collins, CO USA 80523

rovis@lamar.colostate.edu

Contents:

Materials and Methods

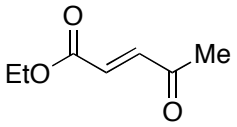
All reactions were carried out under an atmosphere of argon with magnetic stirring. HPLC grade Chloroform preserved with pentane was purchased from Fisher Scientific. Column chromatography was performed on SiliCycle®SilicaFlash® P60, 40-63μm 60A. Thin layer chromatography was performed on SiliCycle® 250μm 60A plates. Visualization was accomplished with UV light or p-anisaldehyde stain followed by heating. This stain is highly recommended, with starting material typically staining orange, intermediate as brown, and final product as a dark blue.

^{1}H NMR spectra were obtained on Varian 300 or 400 MHz spectrometers at ambient temperature. Data is reported as follows: chemical shift in parts per million (δ, ppm) from $CDCl_3$ (7.26 ppm), toluene-d8 (7.09, 7.0, 6.98, 2.09 ppm) or benzene-d6 (7.16 ppm) multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constants(Hz).
^{13}C NMR was recorded on Varian 300 or 400 MHz spectrometers (at 75 or 100 MHz) at ambient temperature. Chemical shifts are reported in ppm from $CDCl_3$ (77.2 ppm) or toluene-d_8 (137.86 (1), 129.4 (3), 128.33 (3), 125.49 (3), 20.4 (5) ppm).

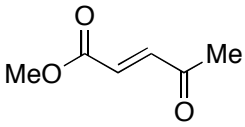
Varian CP-3800 Gas Chromatograph was used to determine diastereomeric and enantiomeric ratios. For the achiral column, Varian CP-Sil 8CB (15m X 0.25mm) was used. For the chiral column, Chiraldex BDM-1 was used, unless otherwise stated.

Aldehydes **1a-f** were purchased from Aldrich. Aldehyde **1g** was prepared according to literature procedure.[1]

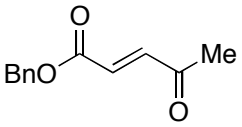
[1] Y. Kiyotsuka and Y. Kobayashi, *J. Org. Chem.*, 2009, **74**, 7489.



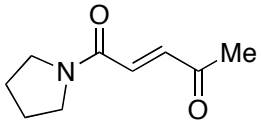
2a



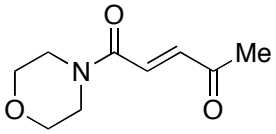
2h



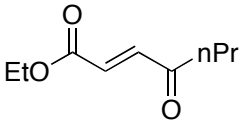
2i



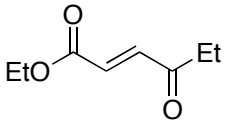
2j



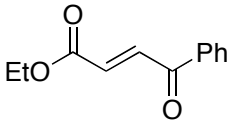
2k



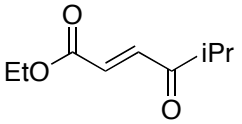
2l



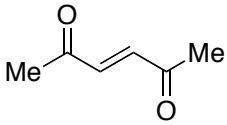
2m



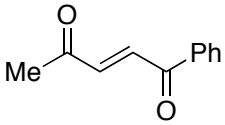
2n



2o



2p



2q

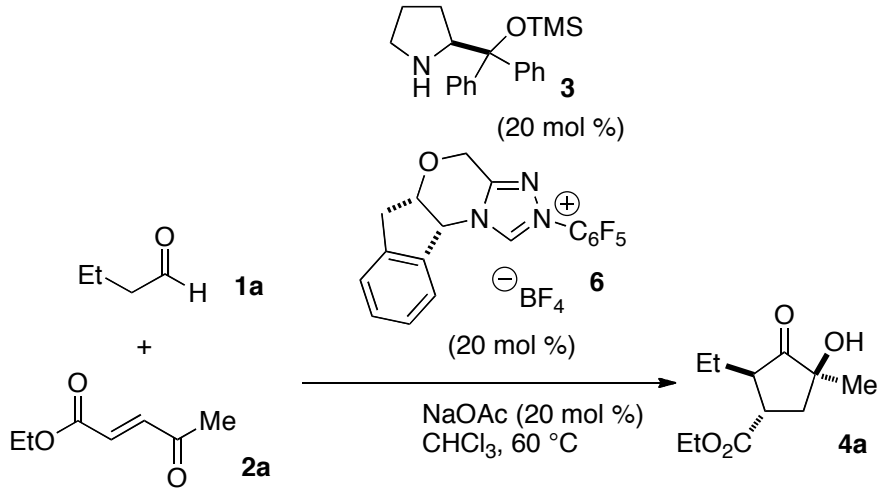
Keto-esters 2 were prepared with the following protocols:
2a,[2] **2h**,[3] **2i**,[4] **2j-k**,[5] **2l-p**,[2] and **2q**.[6]

Amine catalyst **3** was prepared with the established protocol.[7]
Triazolium catalyst **5** and **6** were prepared according to literature procedure.[8]

---

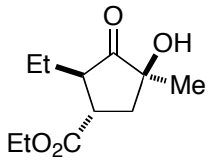
[2] K. A. Runcie and R. J. K. Taylor, *Chem. Commun*., 2002, 974.
[3] P. F. Schuda, C. B. Ebner and S. J. Potlock, *Synthesis*, 1987, 1055.
[4] S. Gérard, M. Raoul and J. Sapi, *Eur. J. Org. Chem*., 2006, 2440.
[5] J. L. Zigterman, J. C. S. Woo, S. D. Walker, J. S. Tedrow, C. J. Borths, E. E. Bunel and M. M. Faul*, J. Org. Chem*., 2007, **72**, 8870.
[6] J.-Q. Yu and E. J. Corey*, J. Am. Chem. Soc*., 2003, **125**, 3232.
[7] M. Marigo, T. C. Wabnitz, D. Fielenbach and K. A. Jørgensen*, Angew. Chem. Int. Ed*., 2005, **44**, 794.
[8] H. U. Vora, S. P. Lathrop, N. T. Reynolds, M. S. Kerr, J. Read de Alaniz and T. Rovis, *Org. Synth*., 2010, **87,** 350.

Representative Procedures

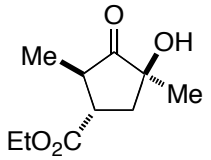


General procedure for synthesis of 4a:
25 mg (0.17 mmol) of Keto-Ester **2a** is added to an oven-dried 10mL round bottom flask. 11mg (0.2 equiv., 0.03 mmol) of amine catalyst **3** and 14 mg (0.2 equiv., 0.03 mmol) of triazolium **6** are then added. 1 ml of $CHCl_3$ is added and argon is bubbled into the mixture. 20 µl (1.2-1.5 equiv, 0.2 mmol) of butyraldehyde (**1a**) is then added, followed by 2.5mg (0.2 equiv, 0.03 mmol) of NaOAc. The reaction is outfitted with a reflux condenser and stir bar, and heated to 60 °C for 12 hours. The reaction is cooled to room temperature and filtered through a small plug (1 in) of silica gel, washing with DCM and EtOAc. The solution is concentrated and purified by column chromatography, eluting with 10% EtOAc/DCM to 50% EtOAc/Hexanes through silica gel. Fractions were collected and concentrated to provide the desired product.

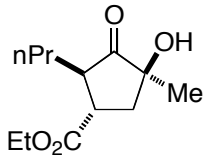
Characterization Data



(1*S*,2*R*,4*S*)-ethyl 2-ethyl-4-hydroxy-4-methyl-3-oxocyclopentanecarboxylate (4a) Rf= 0.3 (10% Ethyl Acetate/Dichloromethane); 28 mg (72%), 94% ee, 19:1:<1:<1 dr $[\alpha]_D^{21}$ = -40.83 (c = 0.0024 g/ml, $CHCl_3$) **GC Analysis** CP-Sil 8CB column at 110 °C, 1 ml/min. Major: 12.07min. Minor: 12.95 min, 13.84 min, 15.14 min. BDM-1 column at 130 °C, 1 ml/min. Major: 24.35 min. Minor: 23.81 min. **^{1}H NMR**: (300 MHz; $CDCl_3$): δ_H 4.16-4.23 (2 H, q), 2.98 (1 H, d, *J* 7.2), 2.33 (1 H, ddd, *J* =13.7, 7.2 and 0.3), 1.94 (1 H, d, *J* =10.5), 1.63 (1 H, d, *J* =7.3), 1.33 (3 H, d, *J* =0.8), 1.25-1.33 (3 H, t, J = 7.2), 0.92 (3 H, td, *J* =7.5 and 0.8).. **^{13}C NMR**: (100 MHz, $CDCl_3$) δ216.7, 174.8, 75.7, 60.9, 51.7, 42.3, 39.3, 23.0, 22.1, 14.1, 10.8. **IR** (NaCl, neat): 3465, 2971, 2937, 2878, 1733, 1519, 1447, 1378, 1298, 1234, 1177**. HRMS**: (ESI-) calcd for $C_{12}H_{20}O_4$, 227.1289. Found 227.1291.

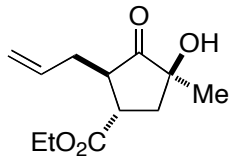


(1*S*,2*R*,4*S*)-ethyl 4-hydroxy-2,4-dimethyl-3-oxocyclopentanecarboxylate (4b) Rf= 0.3 (10% Ethyl Acetate/Dichloromethane); 28 mg (78%), 88% ee, 24:1.5:1 dr $[\alpha]_D^{21}$ = -101.82(c = 0.0011 g/ml, $CHCl_3$) **GC Analysis** CP-Sil 8CB column at 110 °C, 1 ml/min. Major: 7.54min. Minor: 8.22, 9.46 min. BDM-1 column at 130 °C, 1 ml/min. Major: 17.33 min. Minor: 16.82 min. **^{1}H NMR**: (300 MHz, CDCl3) δ 4.20 (q, 2H), 2.84 (q, 1H), 2.61 (m, 1H), 2.34 (dd, 1H), 1.94 (t, 1H), 1.35 (s, 3H), 1.29 (s, 3H), 1.24 (t, 3H). **^{13}C NMR**: (100 MHz, $CDCl_3$) δ 217.4, 174.5, 61.2, 46.07, 45.4, 39.3, 23.5, 14.4, 13.9. **IR** (NaCl, neat): 3436, 2980, 2938, 1732, 1520, 1450, 1376, 1181**. HRMS**: (ESI-) calcd for $C_{11}H_{26}O_4$, 213.1249. Found 213.1256.

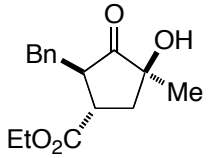


(1*S*,2*R*,4*S*)-ethyl 4-hydroxy-4-methyl-3-oxo-2-propylcyclopentanecarboxylate(4c) Rf= 0.3 (10% Ethyl Acetate/Dichloromethane); 31 mg (76%), 95% ee, 33:1:1 dr $[\alpha]_D^{21}$ = -56.97(c = 0.0033 g/ml, $CHCl_3$) **GC Analysis** CP-Sil 8CB column at 110 °C, 1 ml/min. Major: 19.66min. Minor: 20.77, 22.00 min. BDM-1 column at 100 °C, 2 ml/min. Major: 112.04 min. Minor: 113.74 min. **^{1}H NMR**: (300 MHz, $CDCl_3$) δ 4.20 (q, 2H), 2.95 (q, 1H), 2.66 (m, 1H), 2.33 (dd, 1H), 1.92 (m, 1H), 1.72 (m, 1H), 1.49 (m, 1H), 1.33 (s, 3H), 1.28 (t, 3H), 0.90 (t, 3H). **^{13}C NMR**: (100 MHz, $CDCl_3$) δ 217.3, 175.1, 61.2, 50.2, 43.4,

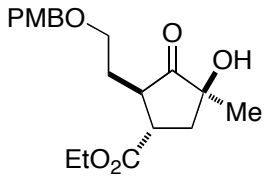
39.7, 31.9, 23.2, 20.1, 14.4, 14.2. **IR** (NaCl, neat): 3448, 2964, 1734, 1377, 1178, 1038, 756 cm^{-1}**. HRMS**: (ESI-) calcd for $C_{12}H_{20}O_4$, 227.1289. Found 227.1291.



(1*S*,2*R*,4*S*)-ethyl 2-allyl-4-hydroxy-4-methyl-3-oxocyclopentanecarboxylate (4e)
Rf = 0.39 (10% Ethyl Acetate/Dichloromethane); 37 mg (97%), 85% ee, 15:1:0.2:0.2 dr, $[\alpha]_D^{21}$ = -67.23 (c = 0.0047 g/ml, $CHCl_3$) **GC Analysis:** CP-Sil 8CB at 110 °C, 1 ml/min. Major 16.70 min. Minor: 18.16 min, 20.74 min, 21.11 min. HPLC Analysis: ChiralPak IA column at 97% Hexanes/iPrOH, 1 ml/min. Major: 14.346 min. Minor: 12.338 min. **^{1}H NMR**: (300 MHz, $CDCl_3$): δ 5.73-5.61 (m, 1H), 5.12-5.00 (m, 2H), 4.20-4.13 (m, 2H), 2.98 (td, *J* = 10.3, 7.2 Hz, 1H), 2.77 (ddd, *J* = 10.2, 7.3, 4.8 Hz, 1H), 2.56-2.50 (m, 1H), 2.33 (dtd, *J* = 13.6, 6.8, 1.9 Hz, 2H), 1.91 (ddd, *J* = 13.7, 10.4, 0.4 Hz, 1H), 1.33 (d, *J* = 0.7 Hz, 3H), 1.33-1.24 (m, 3H). **^{13}C NMR**: (100 MHz, $CDCl_3$): δ 216.0, 174.5, 134.3, 117.7, 75.6, 60.9, 49.9, 42.2, 39.3, 33.4, 23.0, 14.1 **IR** (NaCl, neat): 3457, 2979, 2930, 1734, 1641, 1520, 1444, 1378, 1227, 1179 cm^{-1}. **HRMS**: (APCI+) Calc'd for $C_{12}H_{18}O_4$, 227.1278. Found 227.1276.

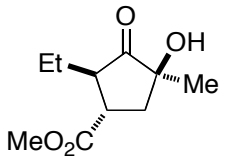


(1*S*,2*R*,4*S*)-ethyl 2-benzyl-4-hydroxy-4-methyl-3-oxocyclopentanecarboxylate (4f)
Rf = 0.21 (5% Ethyl Acetate/Dichloromethane); 25 mg (50%), 89% ee, 9:1:0.2:0.2 dr, $[\alpha]_D^{21}$ = -126.92 (c = 0.0013 g/ml, $CHCl_3$) **HPLC Analysis** Chiracel IC at 95% Hexanes/iProH. Major 13.36 min. Minor: 11.36 min **^{1}H-NMR** (300 MHz; $CDCl_3$): δ 7.32-7.14 (m, 5H), 3.98-3.83 (m, 2H), 3.19 (dd, *J* = 13.7, 4.5 Hz, 1H), 3.04-2.89 (m, 2H), 2.81 (dd, *J* = 13.7, 7.2 Hz, 1H), 2.30-2.23 (m, 1H), 1.91-1.83 (m, 2H), 1.33 (s, 3H), 1.15-1.11 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR**: (100 MHz, $CDCl_3$): δ 215.9, 174.6, 138.3, 129.55, 128.55, 126.72, 75.8, 61.1, 52.5, 42.8, 39.7, 35.4, 23.1, 14.2. **IR** (NaCl, neat): 3442, 2980, 1732, 1496, 1454, 1377, 1178, 1045. **HRMS**: (APCI+) Calc'd for $C_{16}H_{19}O_4$, 275.1289. Found 275.1292.

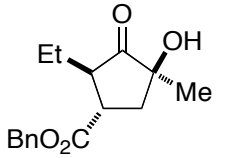


(1*S*,2*R*,4*S*)-ethyl 4-hydroxy-2-(2-((4-methoxybenzyl)oxy)ethyl)-4-methyl-3-oxocyclopentanecarboxylate (4g)
Rf = 0.31 (5% Ethyl Acetate/Dichloromethane); 37mg (59%), 90% ee, 9:1:0.2:0.2 dr,

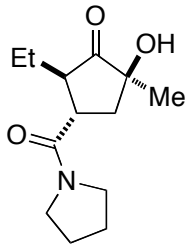
$[\alpha]_D^{21}$ = -42.61 (c = 0.0023 g/ml, $CHCl_3$) **HPLC Analysis** Chiracel IC at 95% Hexanes/iProH. Major 13.64 min. Minor: 16.34 min **^{1}H-NMR** (300 MHz; $CDCl_3$): δ 7.23 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.36 (d, *J* = 4.0 Hz, 2H), 4.13 (dd, *J* = 11.6, 7.1 Hz, 3H), 3.80 (s, 3H), 3.55 (td, *J* = 4.8, 2.1 Hz, 2H), 3.09 (d, *J* = 7.2 Hz, 1H), 2.78 (s, 1H), 2.38-2.34 (m, 1H), 2.04 (d, *J* = 5.4 Hz, 3H), 1.88 (dd, *J* = 13.7, 10.6 Hz, 2H), 1.31 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H).**^{13}C NMR**: (100 MHz, $CDCl_3$): δ 216.5, 191.3, 180.5, 174.5, 159.1, 130.0, 129.2, 113.8, 113.7, 72.4, 67.1, 60.9, 55.2, 47.7, 42.7, 39.8, 29.0, 22.7, 14.1 **IR** (NaCl, neat): 3445, 2936, 1730, 1611, 1514, 1444, 1376, 1301, 1247, 1174. **HRMS**: (ESI-) Calc'd for $C_{19}H_{25}0_6$, 349.1657. Found 349.1663.



(1*S*,2*R*,4*S*)-methyl 2-ethyl-4-hydroxy-4-methyl-3-oxocyclopentanecarboxylate (4h) Rf= 0.24 (10% Ethyl Acetate/Dichloromethane); 38 mg (97%), 89% ee, 33:1:1:nd dr $[\alpha]_D^{21}$ = -62.32 (c = 0.0043 g/ml, $CHCl_3$) **GC Analysis** CP-Sil 8CB column at 110 °C, 1 ml/min. Major: 8.33 min. Minor: 8.98, 9.51 min. BDM-1 column at 130 °C, 1 ml/min. Major: 18.72 min. Minor: 18.31 min. **^{1}H NMR**: (300 MHz, $CDCl_3$) δ 3.7 (s, 3H), 2.99 (q, 1H), 2.62 (m, 1H), 2.32 (dd, 1H), 1.93 (m, 1H), 1.77 (m, 1H), 1.63 (m, 2H), 1.33 (s, 3H), 0.91 (t, 3H). **^{13}C NMR**: (100 MHz, $CDCl_3$) δ 216.3, 175.6, 52.4, 52.1, 42.4, 39.6, 23.1, 22.2, 10.9. **IR** 3456, 2970, 1737, 1439, 1377, 1170, 1032. **HRMS**: (ESI-) Calc'd for $C_{10}H_{16}O_4$, 199.0976. Found 199.0979.

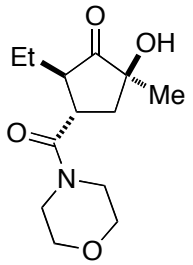


(1*S*,2*R*,4*S*)-benzyl 2-ethyl-4-hydroxy-4-methyl-3-oxocyclopentanecarboxylate (4i) Rf= 0.31 (10% Ethyl Acetate/Dichloromethane); 24 mg (58%), 85% ee, 17:1 dr $[\alpha]_D^{21}$ = -65.38 (c = 0.0013 g/ml, $CHCl_3$) **GC Analysis** CP-Sil 8CB column at 140 °C, 3 ml/min. Major: 17.98 min. Minor: 19.92 min. HPLC Analysis : Chiralcel IC column 95:5 Hexanes/Isopropanol, 1ml/min. Major: 11.03 min. Minor: 9.89 min. **^{1}H NMR**: (300 MHz, $CDCl_3$) δ 7.36 (bs, 5H), 5.18 (s, 2H), 3.06 (q, 1H), 2.65 (m, 1H), 2.32 (dd, 1H), 1.94 (m, 1H), 1.62 (m, 2H), 1.32 (s, 3H), 0.89 (t, 3H). **^{13}C NMR**: (100 MHz, $CDCl_3$) δ 216.7, 174.9, 135.8, 128.8, 128.6, 128.4, 67.0, 51.9, 42.6, 39.5, 23.1, 22.3, 11.0. **IR** (NaCl, neat): 3448, 3034, 2969, 2935, 2878, 1734, 1455, 1385 cm^{-1}**. HRMS**: (ESI-) calcd for $C_{16}H_{19}O_4$, 275.1289. Found 275.1292.



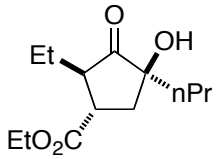
(2*S*,4*S*,5*R*)-5-ethyl-2-hydroxy-2-methyl-4-(pyrrolidine-1-carbonyl)cyclopentanone (4j)

Rf= 0.27 (50% Ethyl Acetate/Dichloromethane); 30 mg (70%), 97% ee, 8:1:0.3:0.1 dr, $[\alpha]_D^{21}$ = -40.0 (c = 0.0017 g/ml, $CHCl_3$) **GC Analysis** CP-Sil 8CB at 140 °C, 3 ml/min. Major: 12.52 min. Minor: 10.08min, 9.59 min,. BDM1 column at 170 °C, 3ml/min. Major: 20.23 min. Minor: 19.75 min. **^{1}H NMR**: (300 MHz, $CDCl_3$) δ 3.52 (quint, *J* = 6.6 Hz, 4H), 3.08 (m, 1H), 2.94 (m, 1H), 2.25 (dd, *J* = 6.9 Hz, 1H), 1.97-1.81 (m, 5H), 1.71 (m, 2H), 1.54 (m, 1H), 1.34 (s, 3H), 0.89 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR**: (100 MHz, $CDCl_3$) δ 217.8, 172.3, 52.4, 46.8, 46.3, 42.1, 39.5, 26.2, 24.5, 23.4, 21.9, 11.3 **IR** (NaCl, neat): 3354, 2969, 2876, 1746, 1622, 1518, 1452, 1343, 1255, 1229, 1165cm^{-1}**. HRMS**: (ESI+) Calcd for $C_{13}H_{22}NO_3$, 240.1594. Found 240.1596.



(2*S*,4*S*,5*R*)-5-ethyl-2-hydroxy-2-methyl-4-(morpholine-4-carbonyl)cyclopentanone (4k)

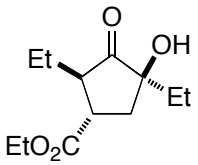
Rf= 0.30 (100% Ethyl Acetate); 37 mg (99%), 98% ee, 9:1:0.4:0.1 dr, $[\alpha]_D^{21}$ = -44.23 (c = 0.0052 g/ml, $CHCl_3$) **GC Analysis** CP-Sil 8CB at 140 °C, 3 ml/min. Major: 14.49 min. Minor: 12.83min, 12.01 min, 12.45 min. BDM1 column at 160 °C, 3ml/min. Major: 41.07 min. Minor: 40.48 min. **^{1}H NMR**: (300 MHz, $CDCl_3$) δ 3.68 (m, 8H), 3.17 (m, 1H), 3.01 (m, 1H), 2.19 (dd, J = 6.9, 13.5 Hz, 1H), 1.81 (m, 2H), 1.55 (m, 1H), 1.33 (s, 3H), 0.89 (t, J = 7.5 Hz, 3H) **^{13}C NMR**: (100 MHz, $CDCl_3$) δ 217.0, 191.3, 172.0, 75.84, 66.9, 51.8, 45.9, 42.6, 39.8, 39.5, 23.1, 21.7, 11.1 **IR** (NaCl, neat): 3383, 2966, 1745, 1638, 1438, 1240, 1117 cm^{-1}**. HRMS**: (ESI+) XX



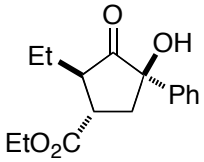
(1*S*,2*R*,4*S*)-ethyl 2-ethyl-4-hydroxy-3-oxo-4-propylcyclopentanecarboxylate (4l)

Rf= 0.24 (10% Ethyl Acetate/Dichloromethane); 19 mg (53%), 85% ee, 16:1 dr $[\alpha]_D^{21}$ = -70.0 (c = 0.0008 g/ml, $CHCl_3$) **GC Analysis** CP-Sil 8CB at 110 °C, 1 ml/min. Major: 32.66min. Minor: 35.76 min. BDM-1 column at 130 °C, 1 ml/min. Major: 55.68 min.

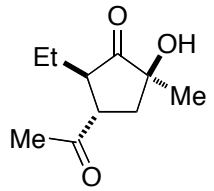
Minor: 54.01 min. **^{1}H NMR**: (300 MHz, $CDCl_3$) δ 4.20 (q, 2H), 2.95 (q, 1H), 2.60 (m, 1H), 2.20 (dd, 1H), 2.02 (m, 1H), 1.79 (m, 1H), 1.60 (m, 3H), 1.50 (m, 2H) 1.29 (t, 3H), 0.92 (m, 6H). **^{13}C NMR**: (100 MHz, $CDCl_3$) δ 217.2, 175.1, 61.2, 52.5, 42.5, 38.9, 37.2, 21.9, 16.9, 14.6, 14.4,11.1. **IR** (NaCl, neat): 3437, 2957, 2865, 1720, 1462, 1377, 1232, 1191 cm^{-1}**. HRMS**: (ESI-) calcd for $C_{13}H_{21}O_4$, 241.1445. Found 241.1442.



(1*S*,2*R*,4*S*)-ethyl 2,4-diethyl-4-hydroxy-3-oxocyclopentanecarboxylate (4m)
Rf= 0.21 (10% Ethyl Acetate/Dichloromethane); 42 mg (76%), 81% ee, 55:1:1 dr $[\alpha]_D^{21}$ = -56.82(c = 0.0022 g/ml, $CHCl_3$) **GC Analysis** CP-Sil 8CB at 110 °C, 1 ml/min. Major: 20.19 min. Minor: 22.52, 24.50 min. BDM-1 column at 130 °C, 1 ml/min. Major: 35.16 min. Minor: 34.54 min. **^{1}H NMR**: (300 MHz, $CDCl_3$) δ 4.20 (q, 2H), 2.94 (q, 1H), 2.61 (m, 1H), 2.21 (dd, 1H), 1.99 (m, 1H), 1.78 (m, 1H), 1.60 (m, 3H), 1.29 (t, 3H), 0.92 (t, 3H). **^{13}C NMR**: (100 MHz, $CDCl_3$) δ 217.3, 175.2, 61.2, 52.6, 42.4, 36.7, 29.6, 21.9, 14.4, 11.1, 7.8. **IR** (NaCl, neat): 3467, 2970, 2938, 2880, 1734, 1518, 1462, 1378, 1231, 1179, 1035, 995, 947 cm^{-1}**. HRMS**: (ESI-) calcd for $C_{12}H_{20}O_4$, 227.1289. Found 227.1292.

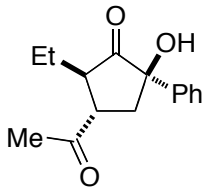


(1*S*,2*R*,4*R*)-ethyl 2-ethyl-4-hydroxy-3-oxo-4-phenylcyclopentanecarboxylate (4n)
Rf= 0.71 (10% Ethyl Acetate/Dichloromethane); 39 mg (95%), 83% ee, 4.4:1:<1:<1 dr $[\alpha]_D^{21}$ = -62.50 (c = 0.002 g/ml, $CHCl_3$) **GC Analysis** CP-Sil 8CB at 170 °C, 2 ml/min. Major: 6.40min. Minor: 6.50, 7.96, 7.86 min. **HPLC Analysis** : Chiralcel IC column 95:5 Hexanes/Isopropanol, 1ml/min. Major: 9.43 min. Minor: 10.13 min. **^{1}H NMR**: (300 MHz, $CDCl_3$) δ 7.35 (bs, 5H), 4.15 (m, 2H), 3.13 (q, 1H), 2.83 (m, 1H), 2.60 (dd, 1H), 2.30 (m, 0.5H), 1.74 (m, 1H), 1.27 (q, 3H), 0.98 (t, 3H). **^{13}C NMR**: (100 MHz, $CDCl_3$) δ 215.7, 174.7, 141.2, 128.7, 128.2, 125.6, 61.3, 53.9, 42.8, 42.0, 22.0, 14.4, 11.0. **IR** (NaCl, neat): 3442, 3062, 2973, 2938, 2878, 1733, 1496, 1448, 1376 cm^{-1}**. HRMS**: (ESI+) calcd for $C_{16}H_{20}O_4Na$, 299.1254. Found 299.1256.



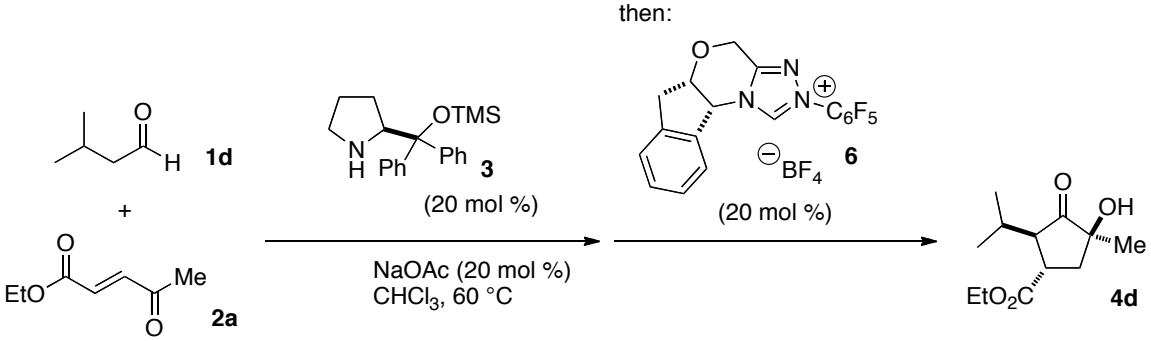
(2*S*,4*S*,5*R*)-4-acetyl-5-ethyl-2-hydroxy-2-methylcyclopentanone (4p)

Rf= 0.3 (10% Ethyl Acetate/Dichloromethane); 24mg (58%), 68% ee, 9:1:0.4:0.6 dr, $[\alpha]_D^{21}$ = -56.0 (c = 0.0025g/ml, $CHCl_3$) **GC Analysis** [CP-Sil 8CB] at 110 °C, 1 ml/min. Major: 6.96. Minor: 7.37 min, 8.05 min, 8.38 min. **HPLC Analysis**: Chiracel IC column at 98% Hexanes/Isopropanol, 1ml/min. Major: 33.32 min. Minor: 27.89 min. **^{1}H NMR**: (300 MHz; $CDCl_3$): δ 3.17 (td, *J* = 10.2, 7.4 Hz, 1H), 2.78-2.71 (m, 1H), 2.36 (dd, *J* = 13.5, 7.4 Hz, 1H), 2.27 (s, 3H), 2.01-2.00 (m, 1H), 1.77-1.66 (m, 2H), 1.62-1.52 (m, 2H), 1.31 (s, 3H), 0.88 (t, *J* = 7.5 Hz, 3H).**^{13}C NMR**: (100 MHz, $CDCl_3$): δ 217.1, 208.9, 75.9, 49.9, 49.8, 39.4, 29.5, 22.9, 22.1, 11.0 **IR** (NaCl, neat): 3442, 2971, 2931, 1741, 1702, 1437, 1386, 1267, 1226, 1162 cm^{-1}**. HRMS**: (ESI-) calcd for $C_{10}H_{15}O_3$, 183.1027. Found 183.1027.



(2*R*,4*S*,5*R*)-4-acetyl-5-ethyl-2-hydroxy-2-phenylcyclopentanone (4q)
Rf= 0.12 (10% Ethyl Acetate/Dichloromethane); 12mg (35%), % ee, 4:1:0.4:0.6 dr, $[\alpha]_D^{21}$ = -104 (c = 0.003g/ml, $CHCl_3$) **GC Analysis**: CP-Sil 8CB at 170 °C and 3 ml/min. Major: 25.108 min. Minor: 26.679 min, 30.489 min, 35.243 min. **HPLC Analysis** Chiracel IC column at 95% Hexanes/iPrOH, 1 ml/min. Major: 11.248 min. Minor 12.768 min. **^{1}H NMR**: (300 MHz; $CDCl_3$): δ 7.41-7.27 (m, 5H), 3.33 (td, *J* = 11.0, 6.7 Hz, 1H), 2.95 (dt, *J* = 10.9, 5.6 Hz, 1H), 2.66-2.56 (m, 2H), 2.32-2.24 (m, 3H), 2.02 (ddd, *J* = 13.6, 11.5, 2.0 Hz, 1H), 1.86-1.76 (m, 1H), 1.74-1.64 (m, 1H), 1.64-1.57 (m, 1H), 0.96-0.88 (m, 3H).**^{13}C NMR**: (100 MHz, $CDCl_3$) δ215.9, 208.4, 140.9, 128.5, 128.0, 125.2, 80.2, 52.3, 49.8, 41.9, 29.7, 21.7, 11.0 **IR** (NaCl, neat): 3410, 3061, 3029, 2966, 2934, 2877, 2252, 1956, 1744, 1708, 1600, 1518, 1495, 1448, 1367, 1217 cm^{-1}**.**

Procedure for the synthesis of **4d:**

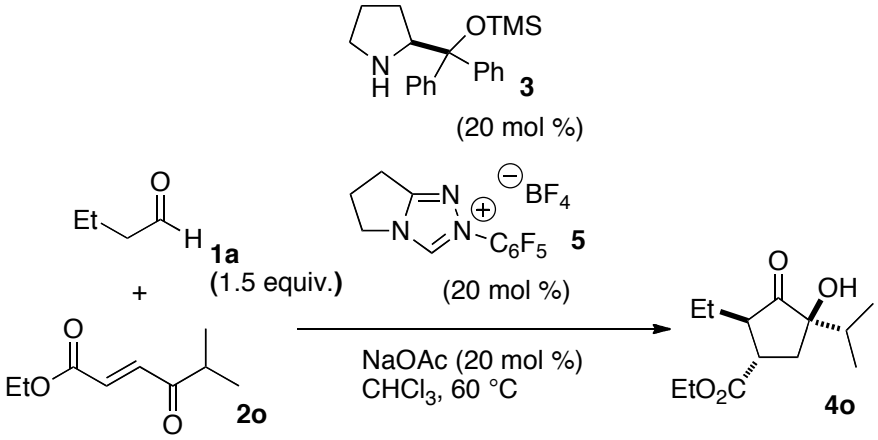


(1*S*,2*R*,4*S*)-ethyl 4-hydroxy-2-isopropyl-4-methyl-3-oxocyclopentanecarboxylate (4d)
In a 5 ml round bottom flask, 25 mg of **2a** (0.17 mmol) was combined with 10 mg of **3** (0.2 equiv, 0.03 mmol) and 1.7 µl of AcOH (0.2 equiv., 0.03 mmol) and dissolved in 1 ml of chloroform. The reaction was stirred at 60 °C for 3 hours. The reaction was cooled to

room temperature and 14 mg of **6** (0.2 equiv., 0.03 mmol) and 5 mg of sodium acetate (0.4 equiv., 0.06 mmol) were added. The reaction was stirred at 60 °C for an additional 4 hours. The reaction was cooled to room temperature and filtered through a plug of silica gel, washing with DCM then EtOAc. The filtrate was concentrated and purified by column chromatography, eluting with 10% EtOAc/DCM to 50% EtOAc/Hexanes through silica gel. Isolated a yellow oil.

Rf= 0.35 (10% Ethyl Acetate/Dichloromethane); 49 mg (90%), 88% ee, 24:1:0.1 dr, $[\alpha]_D^{21}$ = -66.96 (c = 0.0046 g/ml, $CHCl_3$) **GC Analysis** CP-Sil 8CB column at 90 °C, 2 ml/min. Major: 24.48 min. Minor: 26.62 min, 27.69 min. BDM1 column at 130 °C, 2ml/min. Major: 18.48 min. Minor: 17.71 min. **^{1}H NMR**: (300 MHz, $CDCl_3$) δ 4.20 (q, *J* = 6.9, 2H), 3.08 (q, *J* = 7.5, 1H), 2.72 (dd, *J* = 3.9, 9.9, 1H), 2.92 (dd, *J* = 7.5, 13.8, 1H), 2.25 (m, 1H), 1.90 (m, 2H), 1.31 (s, 3H), 1.29 (t, *J* = 7.2, 3H), 0.97 (d, *J* = 6.9, 3H), 0.91 (d, *J* = 6.9, 3H). **^{13}C NMR**: (100 MHz, $CDCl_3$) δ 216.7, 175.7, 61.2, 56.7, 39.9, 39.6, 27.9, 22.9, 20.3, 18.8, 14.3 **IR** (NaCl, neat): 3472, 2967, 2876, 1735, 1519, 1466, 1378, 1338, 1239, 1177 cm^{-1}**. HRMS**: (ESI-) Calcd for $C_{12}H_{19}O_4$, 227.1289. Found 227.1291.

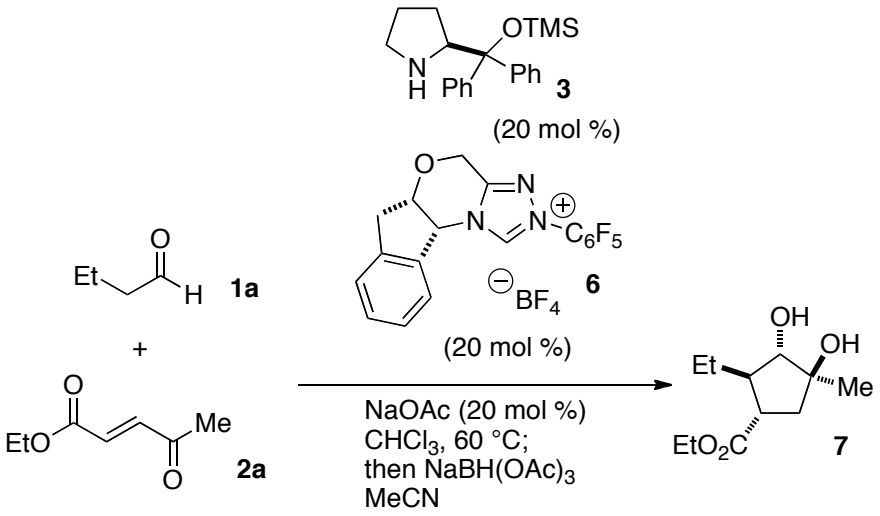
Procedure for the synthesis of **4o**:



(1*S*,2*R*,4*R*)-ethyl 2-ethyl-4-hydroxy-4-isopropyl-3-oxocyclopentanecarboxylate (4o)
In a 5 ml round bottom flask, combined 25 mg of **2o** (0.15 mmol) with 10 mg of **3** (0.2 equiv., 0.03 mmol) and 11 mg of **5** (0.2 equiv., 0.03 mmol). Dissolved in 1 ml of $CHCl_3$ and bubbled Ar into the reaction mixture for 1 minute. Added 20 µl of butyraldehyde (**1a**, 1.5 equiv., 0.22 mmol) and 2.5 mg of NaOAc (0.2 equiv., 0.03 mmol). Stirred at 80 °C for 4 hours. Cooled to room temperature and filtered through a plug of silica gel, washing with DCM then EtOAc. Concentrated the filtrate and purified by column chromatography, eluting with 10% EtOAc/DCM through 50% EtOAc/Hexanes through silica gel. Isolated a yellow solid (mixture of diastereomers).

Rf= 0.3 (10% Ethyl Acetate/Dichloromethane); 25 mg (69%), 51% ee, 18:1:0.1:0.7 dr, $[\alpha]_D^{21}$ = -44.50 (c = 0.004 g/ml, $CHCl_3$) **GC Analysis** CP-Sil 8CB at 110 °C, 1 ml/min. Major: 27.97min. Minor: 28.35 min, 30.41 min, 32.16 min. BDM1 column at 130 °C, 2ml/min. Major: 26.85 min. Minor: 27.55 min. **^{1}H NMR**: (300 MHz, $CDCl_3$) δ 4.21 (q, *J* = 7.2, 2H), 2.93 (q, *J* = 7.2, 1H), 2.54 (q, *J* = 5.7, 1H), 2.01 (m, 3H), 1.83 (m, 2H), 1.60 (m, 1H), 1.29 (t, *J* = 6.9, 3H), 0.98 (d, *J* = 6.9, 3H), 0.90 (t, *J* = 7.5, 3H), 0.83 (d, *J* = 6.9, 3H). **^{13}C NMR**: (100 MHz, $CDCl_3$) δ 217.6, 175.2, 81.4, 61.2, 53.9, 42.2, 33.4, 33.3, 21.5, 17.7, 16.2, 14.4, 10.9 **IR** (NaCl, neat): 3467, 2967, 2878, 1735, 1466, 1377, 1233, 1180 cm^{-1}**. HRMS**: (ESI-) calcd for $C_{13}H_{21}O_4$, 241.1445. Found 241.1444.

Procedure for diol **7**:

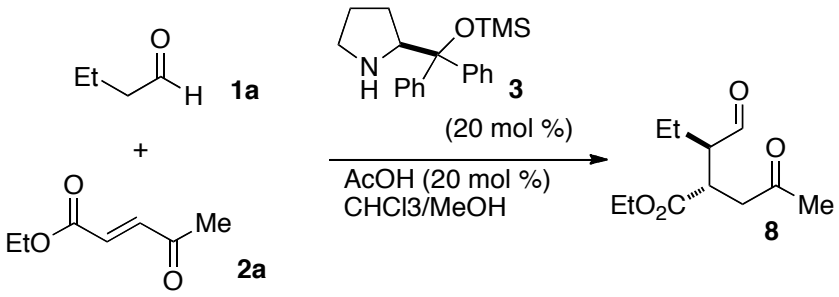


(1*S*,2*R*,3*S*,4*S*)-ethyl 2-ethyl-3,4-dihydroxy-4-methylcyclopentanecarboxylate (7)
In a 5 ml round bottom flask, 25 mg (0.17 mmol) of **2a** was combined with 10 mg of **3** (0.2 equiv., 0.03 mmol) and 14 mg of **6** (0.2 equiv., 0.03 mmol). This mixture was taken up in $CHCl_3$ and bubbled with Ar for 1 minute. 18 µl of butyraldehyde (**1a**, 1.2 equiv., 0.2 mmol) and 2.5 mg of NaOAc (0.2 equiv, 0.03 mmol) were added and the reaction was stirred at 60 °C for 5 hours. The reaction was cooled to room temperature and 40 mg of $NaBH(OAc)_3$ (1.1 equiv., 0.19 mmol) and 1 ml of acetonitrile were added. The suspension was stirred at room temperature overnight. The reaction mixture was filtered through silica gel, eluting with EtOAc. The filtrate was concentrated and purified by column chromatography, eluting with 100% EtOAc through silica gel. Isolated a yellow oil.

Rf= 0.22 (100% Ethyl Acetate); 31mg (84%), 88% ee, 35:1:<1:<1 dr, $[\alpha]_D^{21}$ = -67.33 (c = 0.0015 g/ml, $CHCl_3$) **GC Analysis** CP-Sil 8CB at 130 °C, 1 ml/min. Major: 8.69min. Minor: 5.6 min, 7.33 min, 5.12 min. BDM1 column at 120 °C, 2ml/min. Major: 62.36 min. Minor: 61.63 min. **^{1}H NMR**: (300 MHz, $CDCl_3$) δ_H 4.13 (2 H, q, *J* 7.0, A), 3.55 (1 H, d, *J* 6.8, B), 2.60 (1 H, d, *J* 8.7, C), 1.99 (3 H, m, *J* 8.7, D), 1.65 (1 H, d, *J* 7.4, E), 1.54 (1 H, d, *J* 7.3, F), 1.31 (3 H, sG), 1.22-1.27 (3 H, mH), 0.94 (3 H, t, *J* 7.4, I). **^{13}C NMR**: (100 MHz, $CDCl_3$) δC 176.0, 84.4, 80.1, 60.6, 51.2, 44.5, 41.3, 26.5, 22.9, 14.1, 11.8 **IR**

(NaCl, neat): 3421, 2964, 2934, 2877, 1729, 1519, 1458, 1376, 1179 cm^{-1}**. HRMS**: (ESI+) calcd for $C_{11}H_{21}O_4$, 217.1434. Found 217.1444.

Procedure for Aldehyde **8:**

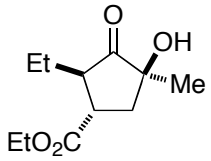


(2*S*,3*R*)-ethyl 3-formyl-2-(2-oxopropyl)pentanoate (8) [9]
In a 5 ml round bottome flask, combined 200 mg of **2a** (1.41 mmol) with 45 mg of **3** (0.1 equiv, 0.14 mmol). Dissolved in 6 ml of $CHCl_3$ and 1 ml of MeOH, added 0.15 ml of butyraldehyde (**1a**, 1.2 equiv., 1.69 mmol) and 2 drops of acetic acid. Stirred at 60 °C for 5 hours. Cooled to room temperature and concentrated. Purified by column chromatography, eluting with 10% EtOAc/Hexanes through silica gel. Isolated as a mixture of diastereomers. Product is a yellow oil.

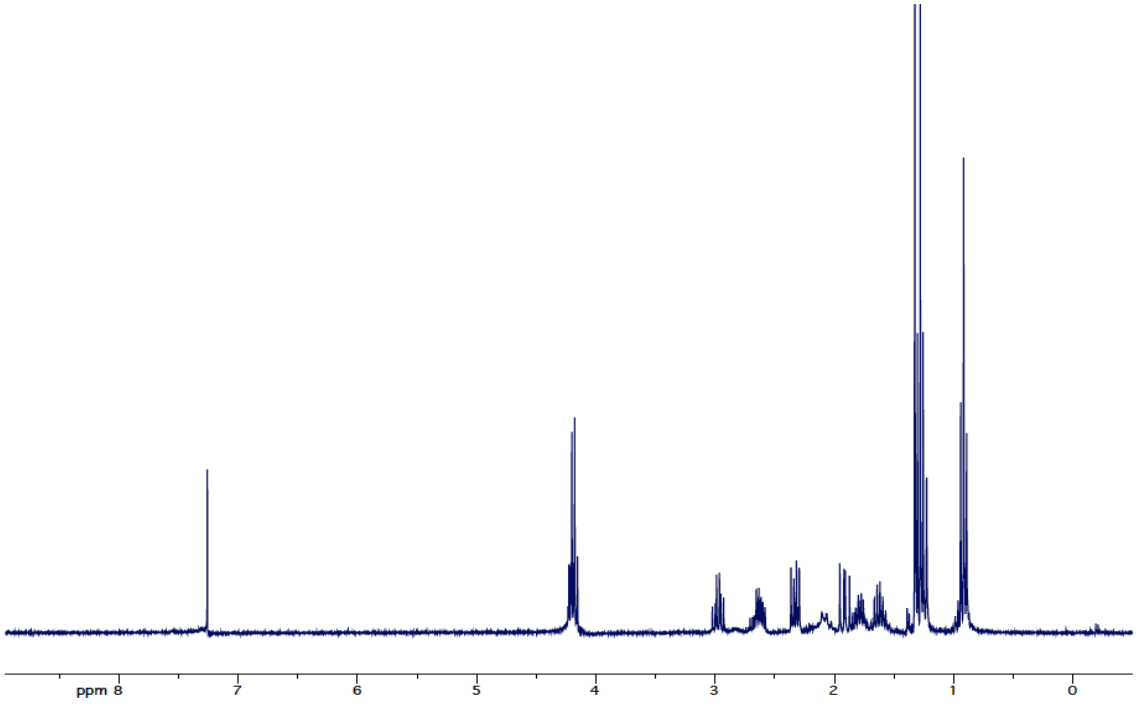
Rf= 0.45 (10% Ethyl Acetate/Dichloromethane); 301mg (99%), 96% ee, 1.1:1 dr, $[\alpha]_D^{21}$ = +20.8 (c = 0.005 g/ml, $CHCl_3$) **GC Analysis**. **^{1}H NMR**: (300 MHz, $CDCl_3$) δ_H 9.65 (1 H, s), 4.10-4.18 (2 H, m), 3.29-3.39 (1 H, m), 2.97 (1 H, ddd, *J* 25.6, 17.9 and 9.3), 2.53-2.59 (1 H, m), 2.36-2.53 (1 H, m), 2.17-2.22 (3 H, s), 1.70-1.80 (1 H, m), 1.40-1.54 (2 H, m), 1.22-1.32 (3 H, m), 0.94-1.00 (3 H, m). **^{13}C NMR**: (100 MHz, $CDCl_3$) δ206.3, 206.1, 202.4, 191.3, 178.7, 18.3, 173.2, 172.9, 61.1, 54.1, 47.8, 47.4, 41.9, 41.5, 41.3, 39.3, 30.0, 29.9, 22.7, 21.9, 19.4, 14.0, 12.0, **IR** (NaCl, neat): 2971, 2881, 1720, 1463, 1369, 1165, 1045 cm^{-1}**. HRMS**: (ESI+) calcd for $C_{11}H_{19}O_4$, 215.1278. Found 215.1270.

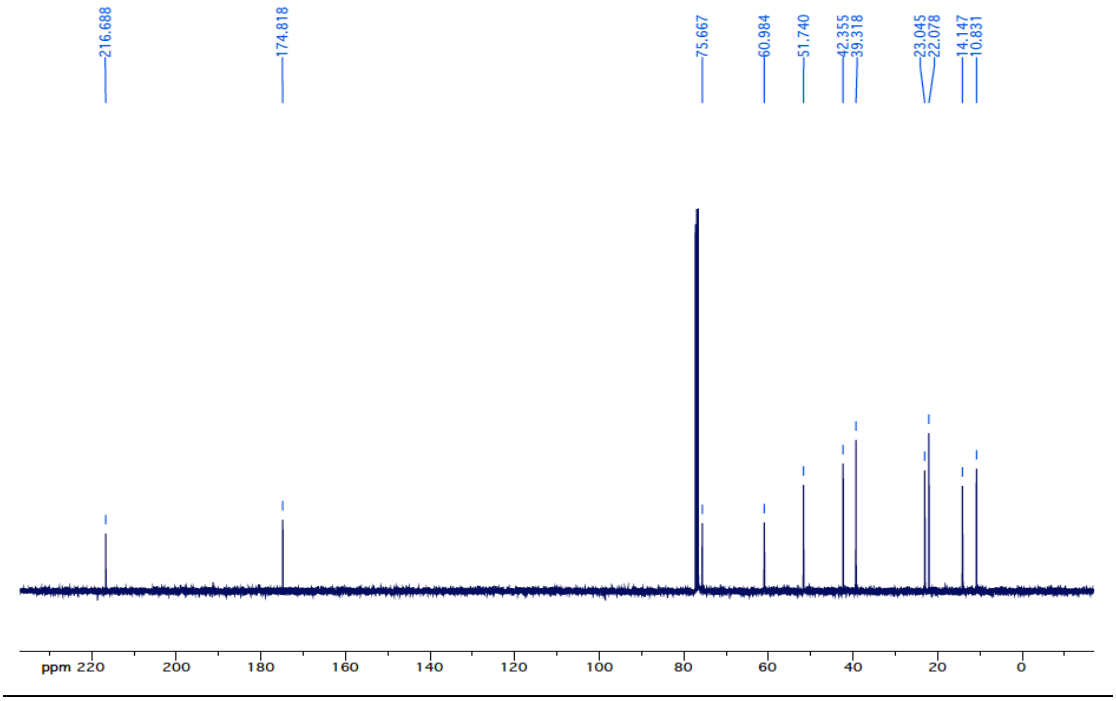
[9] J. Wang, A. Ma and D. Ma, *Org Lett.*, 2008, **10**, 5425.

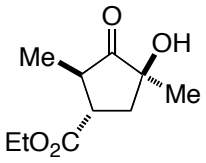
^{1}H and ^{13}C Spectra



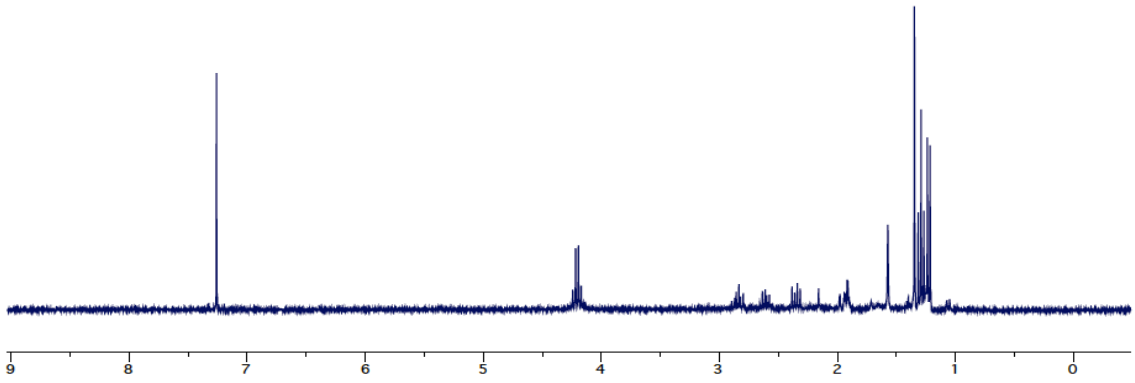
4a

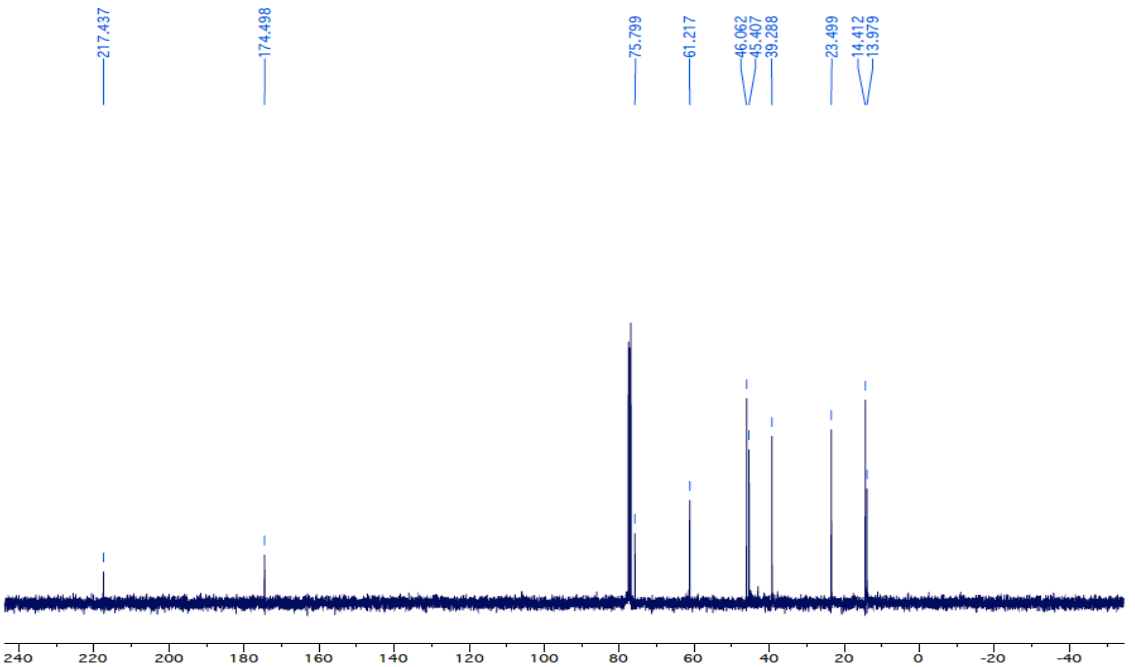


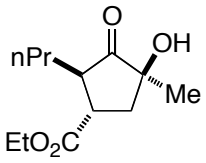



O
OH
Me
Me
EtO2C

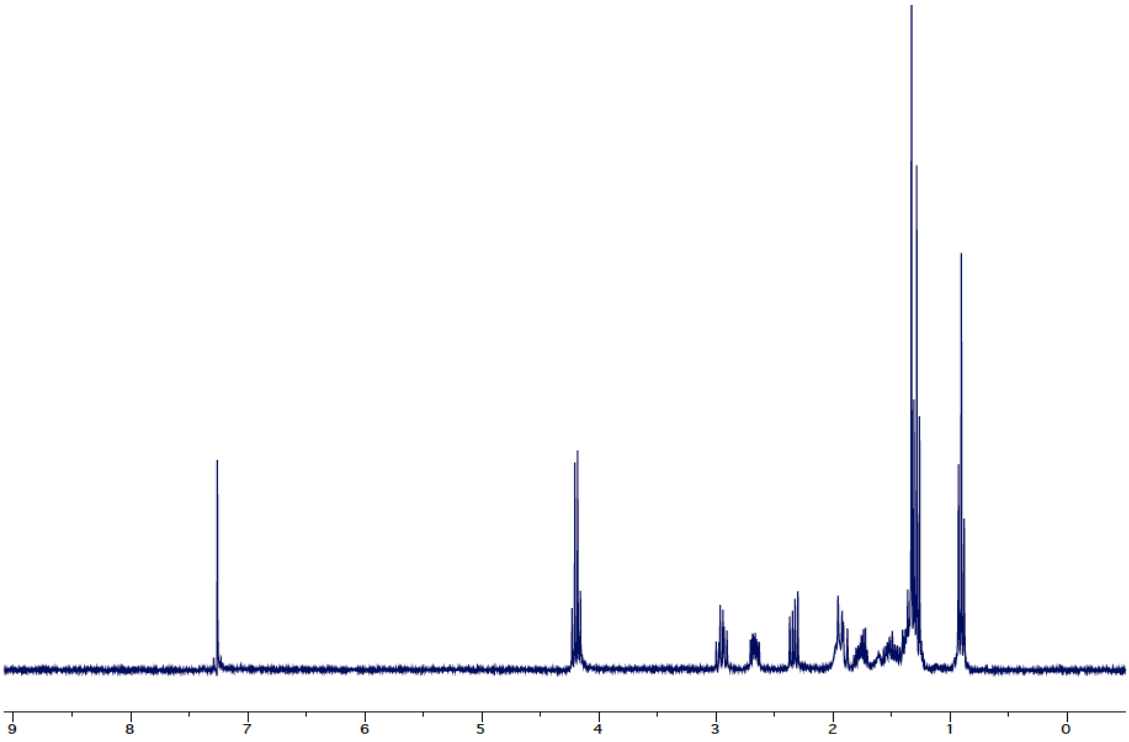
4b


9
8
7
6
5
4
3
2
1
0

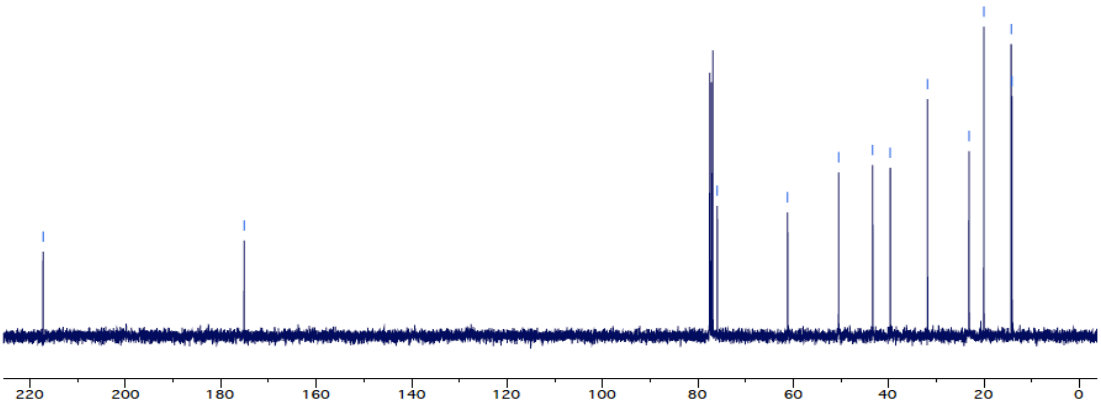

217.437
174.498
75.799
61.217
46.062
45.407
39.288
23.499
14.412
13.979
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40

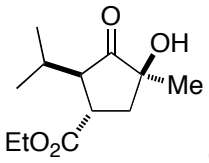

O
OH
nPr
Me
EtO2C

4c

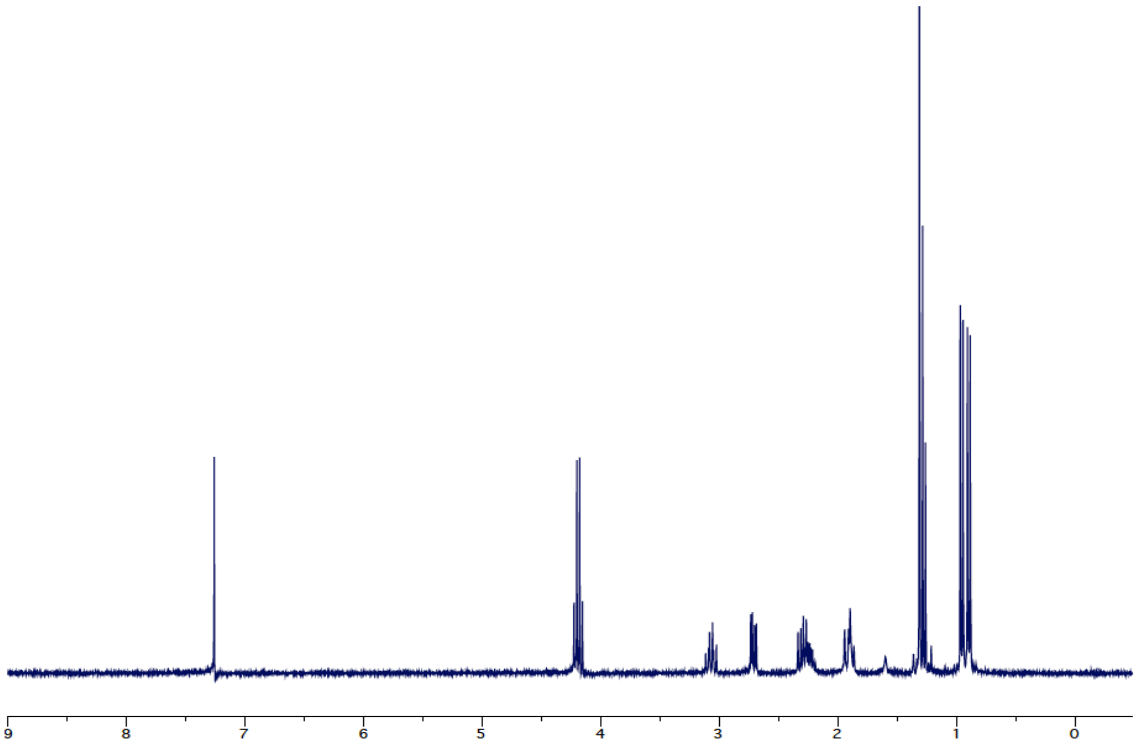

9
8
7
6
5
4
3
2
1
0

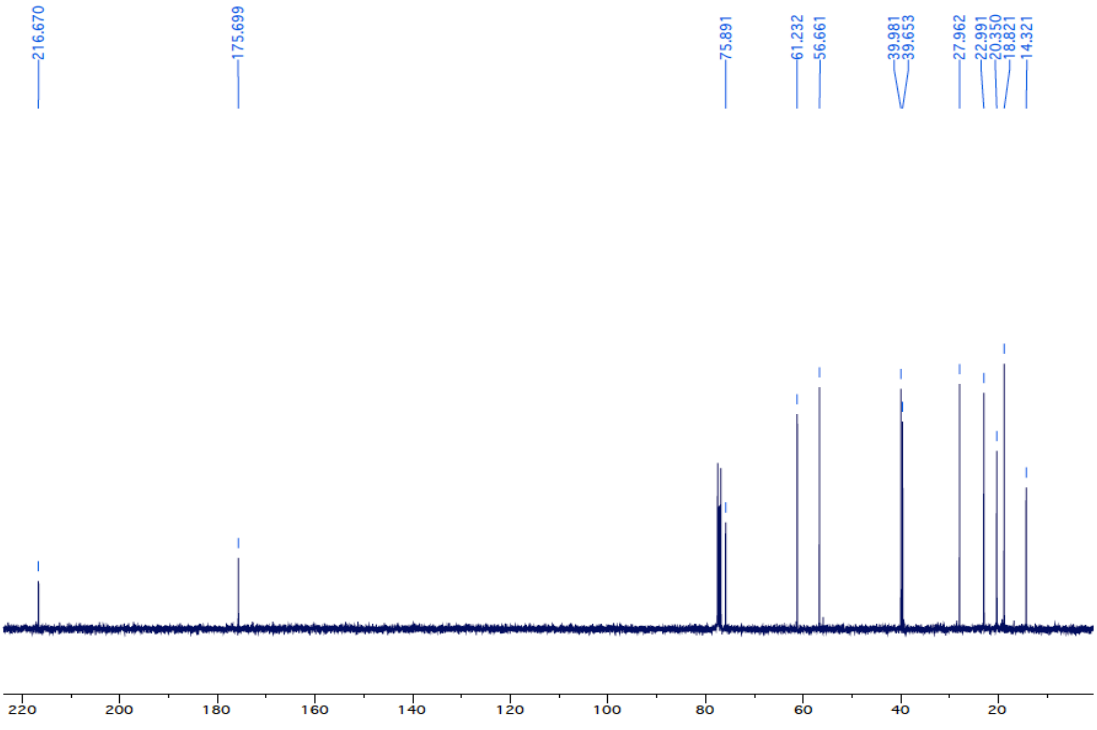

217.253
175.116
75.945
61.218
50.523
43.387
39.691
31.913
23.193
20.096
14.359
14.195

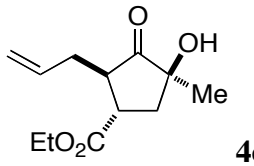

220
200
180
160
140
120
100
80
60
40
20
0


O
OH
Me
EtO2C

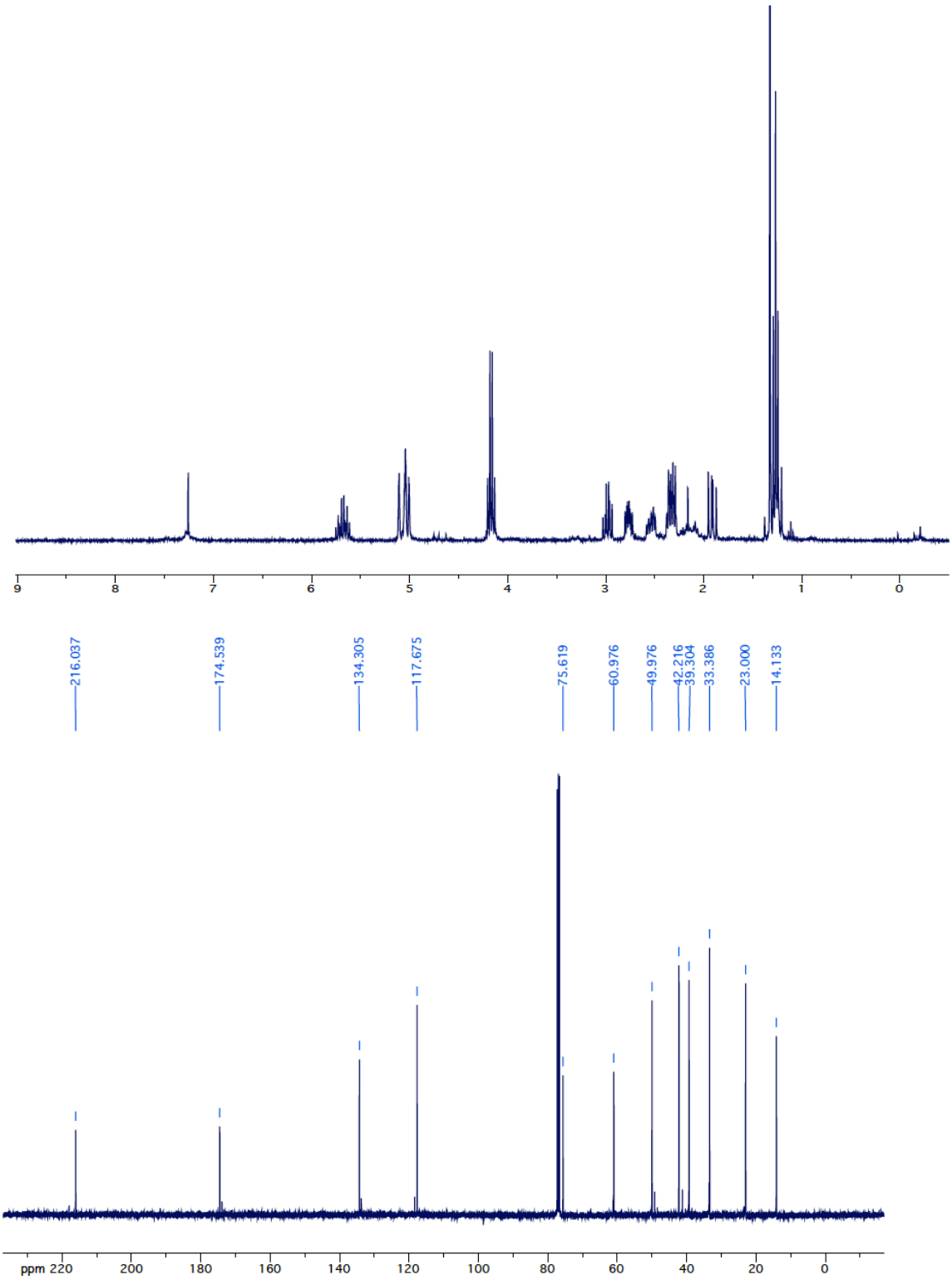
4d

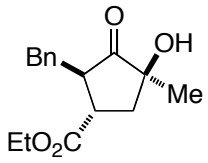

9
8
7
6
5
4
3
2
1
0


216.670
175.699
75.891
61.232
56.661
39.981
39.653
27.962
22.991
20.350
18.821
14.321
220
200
180
160
140
120
100
80
60
40
20

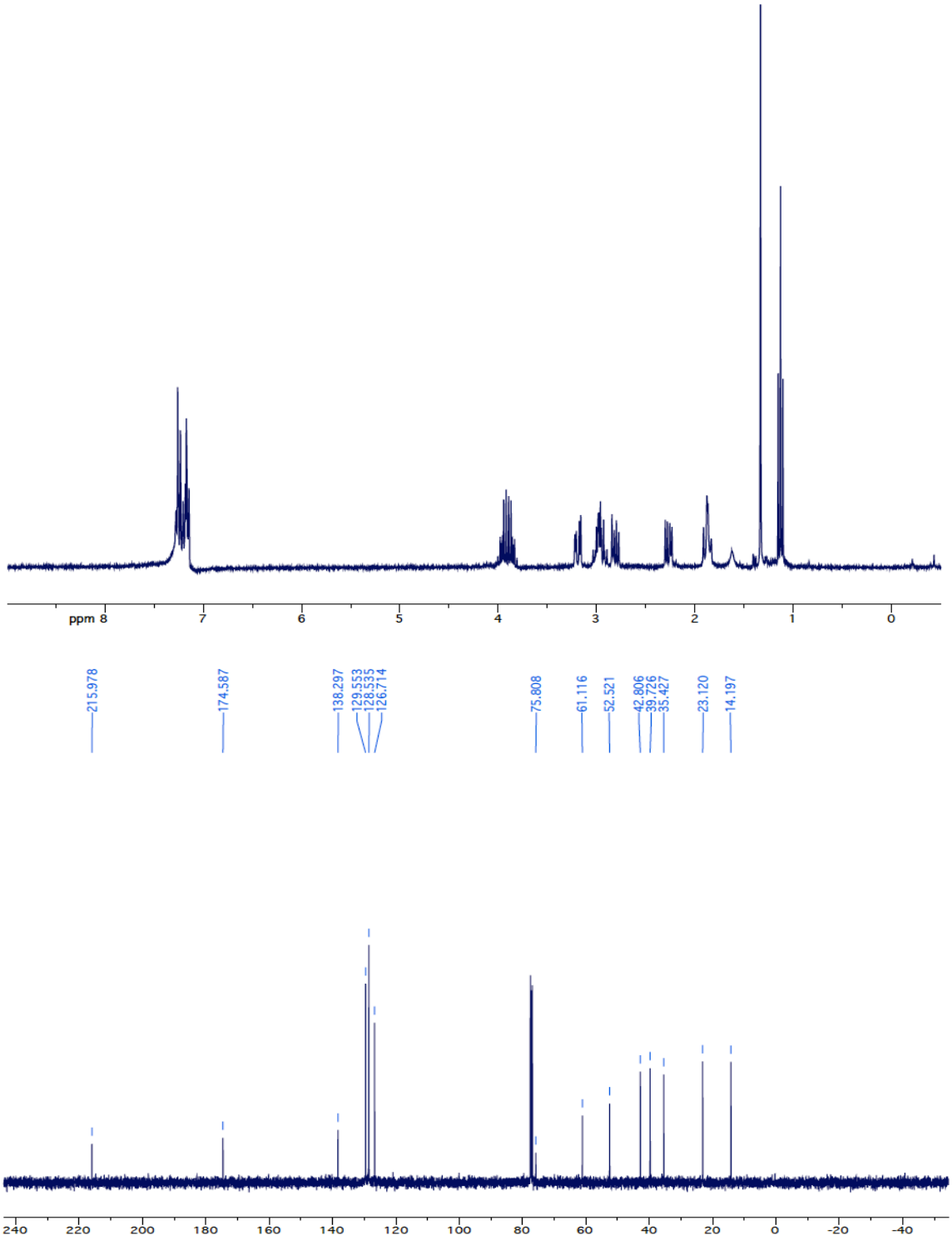

O
OH
Me
EtO2C

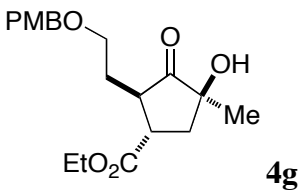
4e


9
8
7
6
5
4
3
2
1
0
216.037
174.539
134.305
117.675
75.619
60.976
49.976
42.216
39.304
33.386
23.000
14.133
ppm 220
200
180
160
140
120
100
80
60
40
20
0

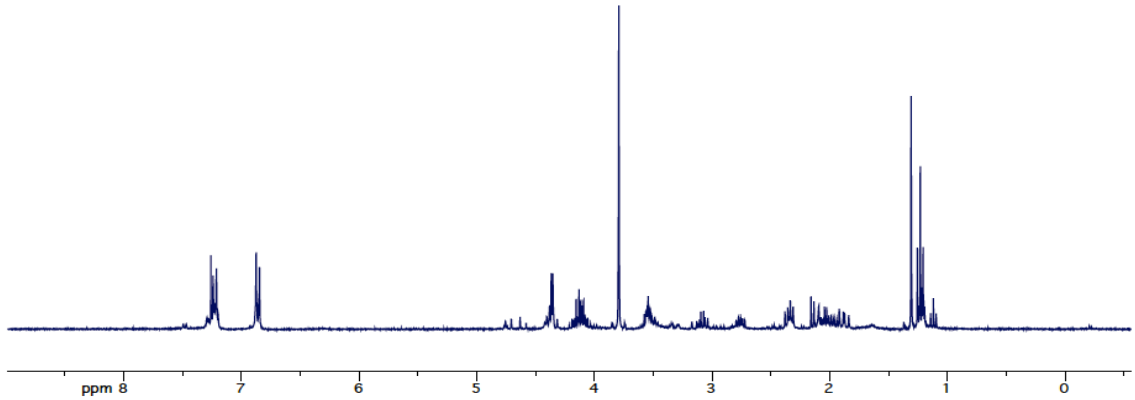

O
OH
Bn
Me
EtO2C

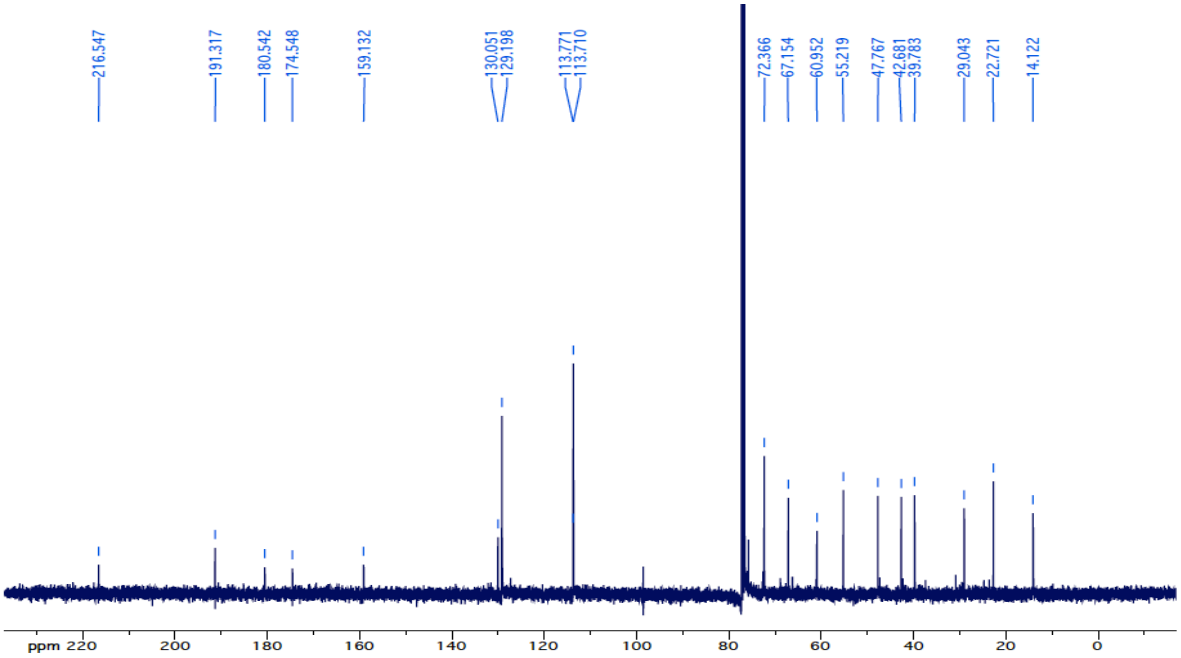
4f

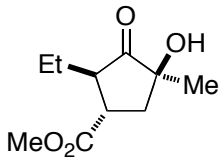

ppm 8
7
6
5
4
3
2
1
0
215.978
174.587
138.297
129.553
128.535
126.714
75.808
61.116
52.521
42.806
39.726
35.427
23.120
14.197
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40


PMBO
O
OH
Me
EtO2C

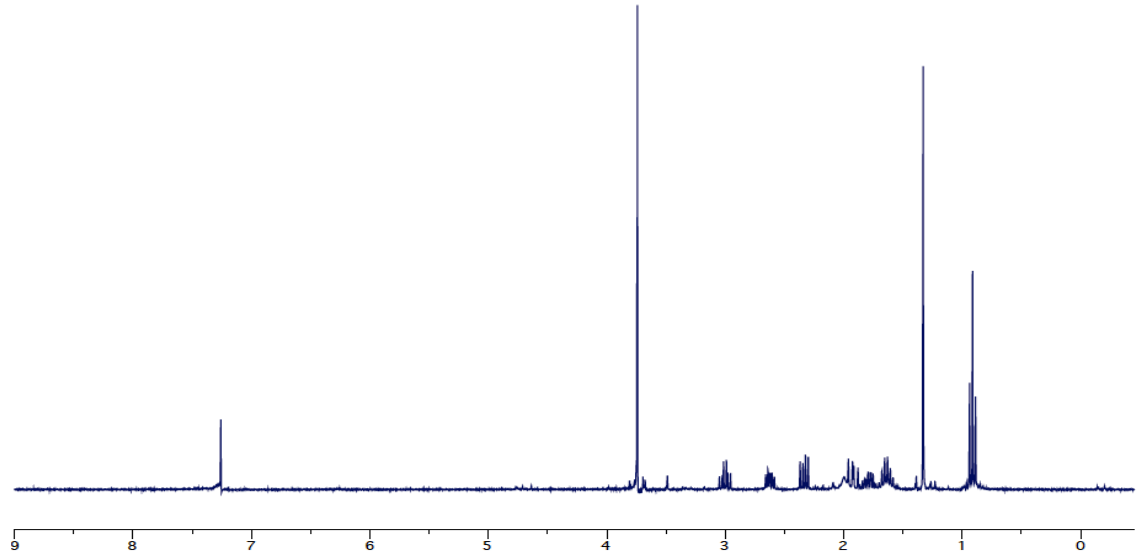
4g

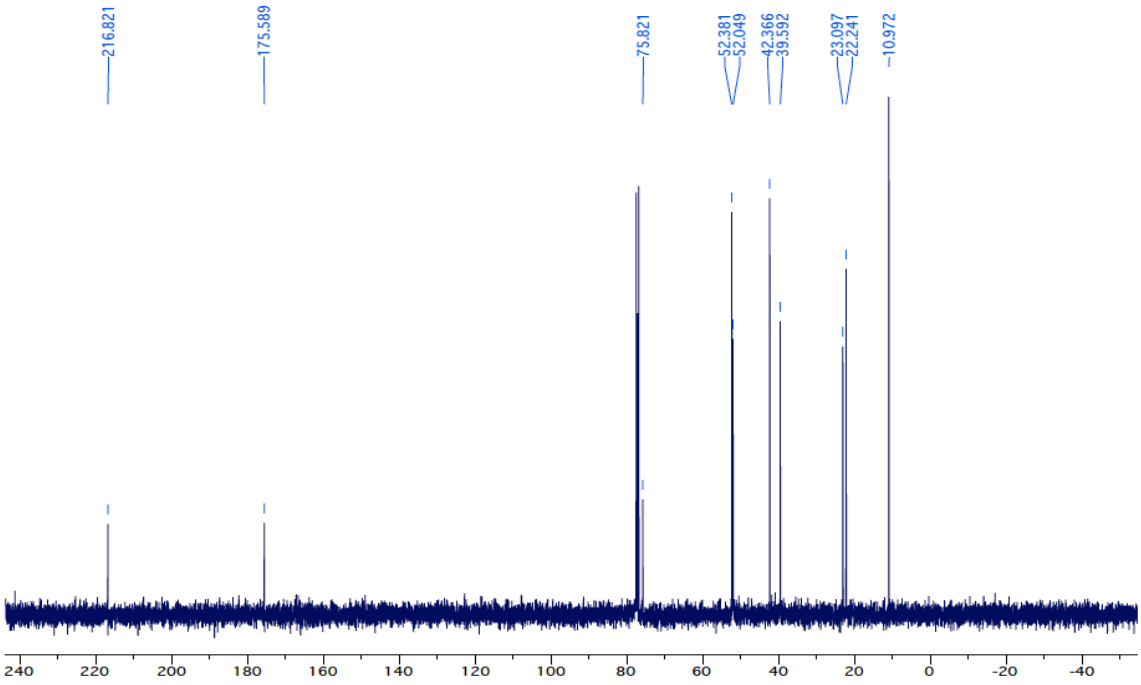

ppm 8
7
6
5
4
3
2
1
0

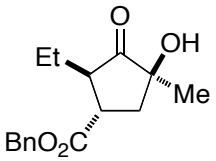

216.547
191.317
180.542
174.548
159.132
130.051
129.198
113.771
113.710
72.366
67.154
60.952
55.219
47.767
42.681
39.783
29.043
22.721
14.122
ppm 220
200
180
160
140
120
100
80
60
40
20
0


O
OH
Et
Me
MeO2C

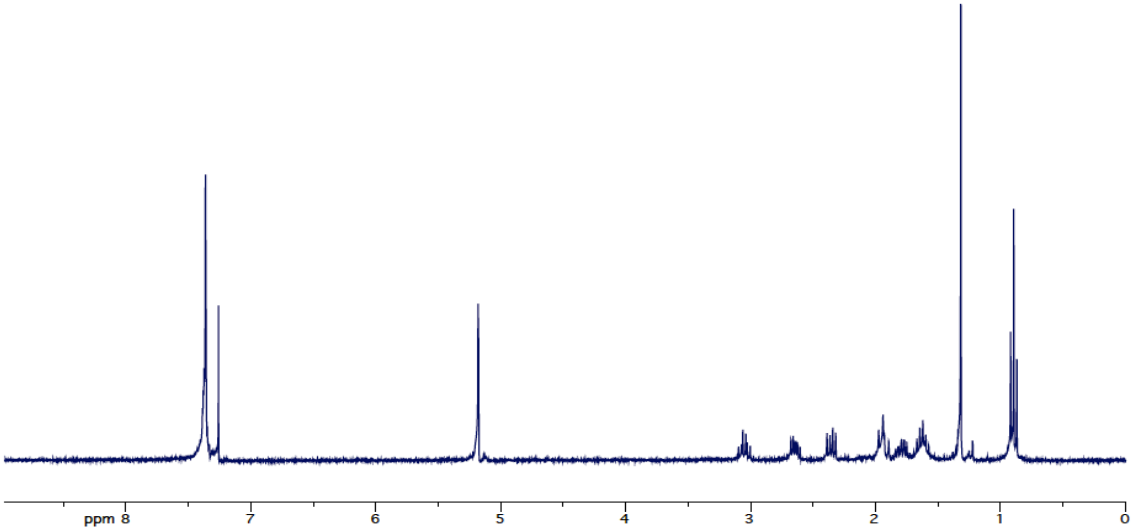
4h


9
8
7
6
5
4
3
2
1
0

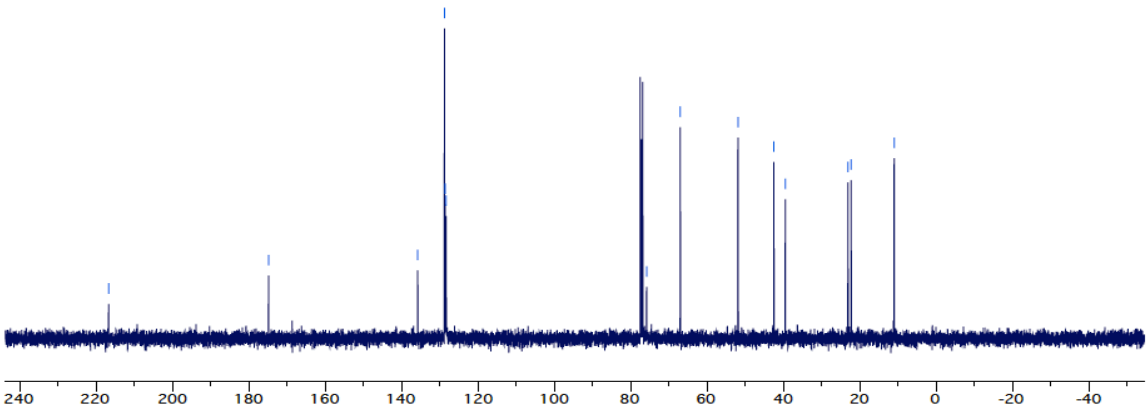

216.821
175.589
75.821
52.381
52.049
42.366
39.592
23.097
22.241
10.972
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40

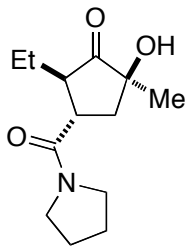

O
Et
OH
Me
BnO2C

4i

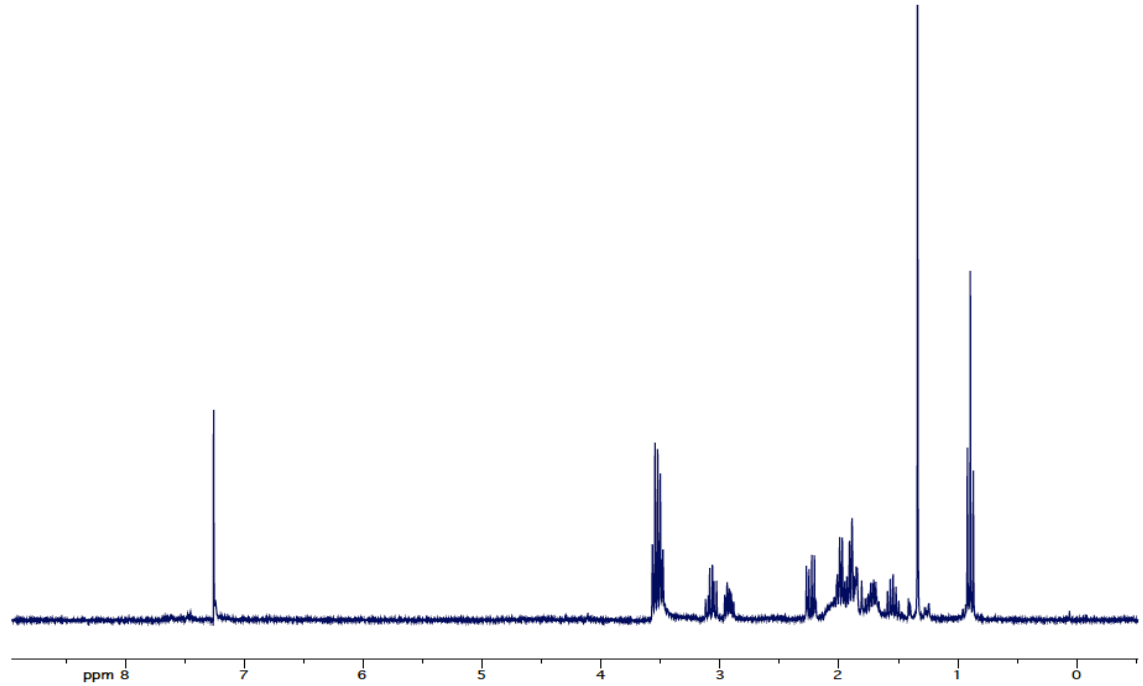

ppm 8
7
6
5
4
3
2
1
0

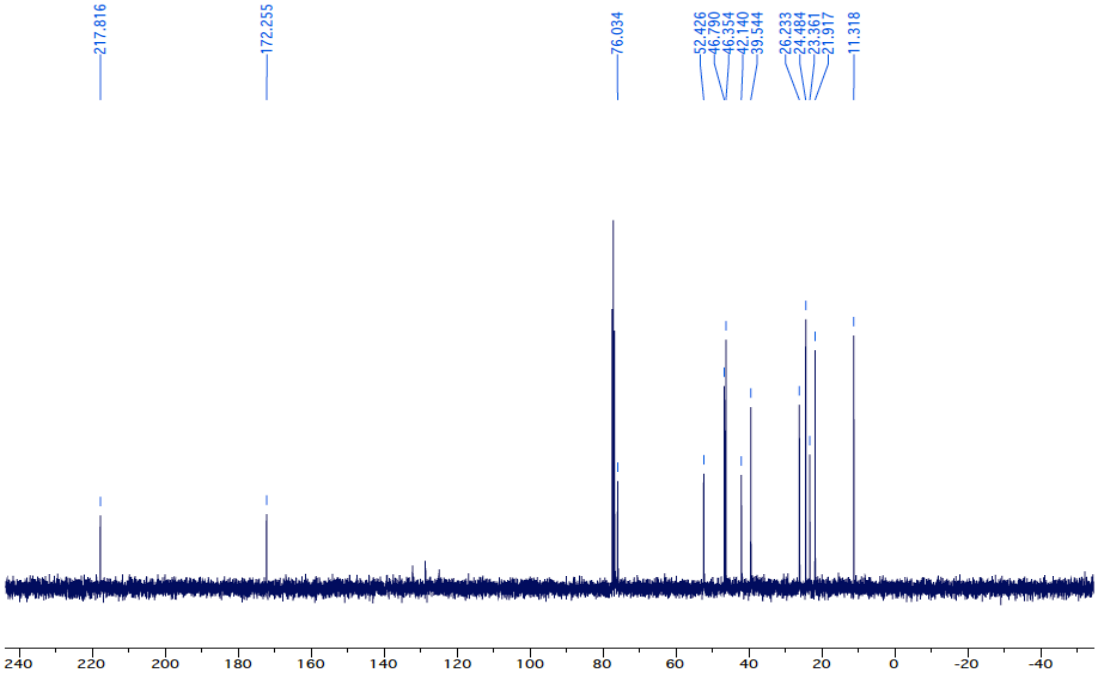

216.745
174.861
135.800
128.808
128.589
128.364
75.873
67.040
51.944
42.548
39.541
23.139
22.318
11.045

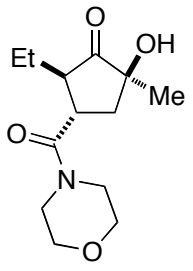

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40


O
OH
Et
Me
O
N

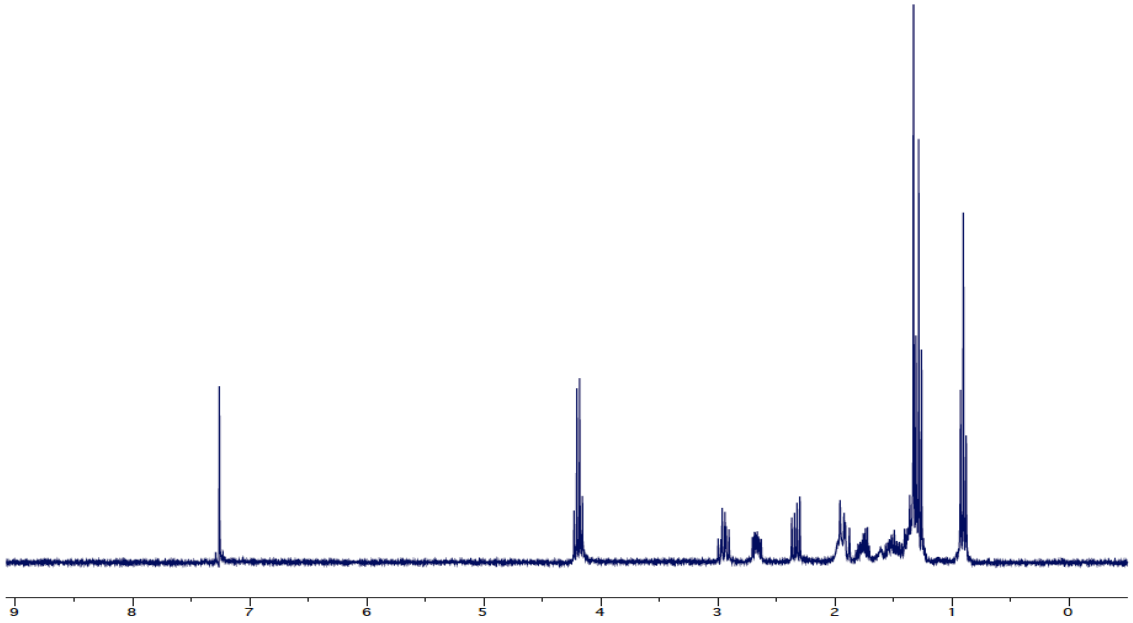
4j

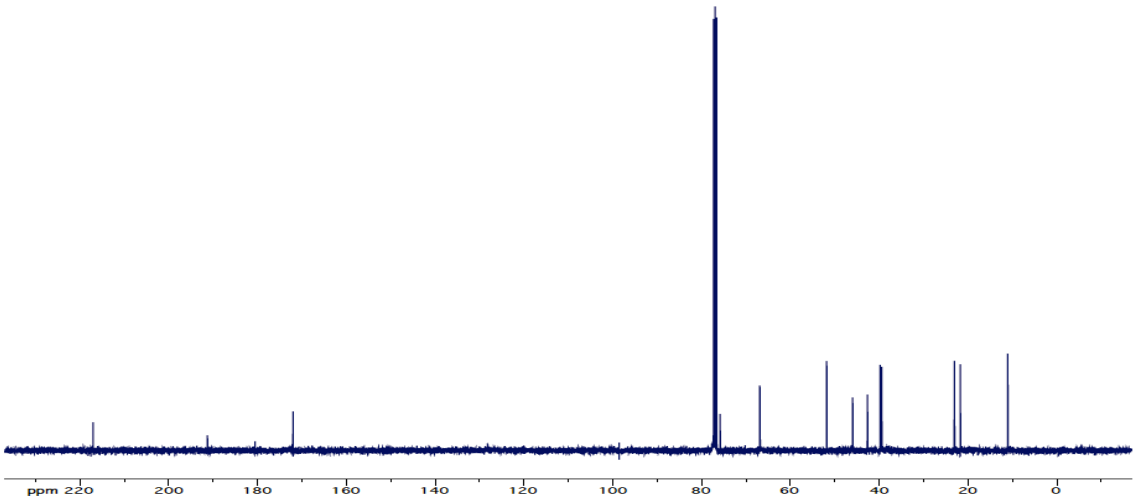

ppm 8
7
6
5
4
3
2
1
0

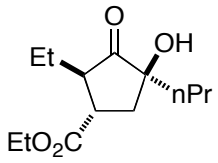

217.816
172.255
76.034
52.426
46.790
46.354
42.140
39.544
26.233
24.484
23.361
21.917
11.318
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40


O
OH
Et
Me
O
N
O

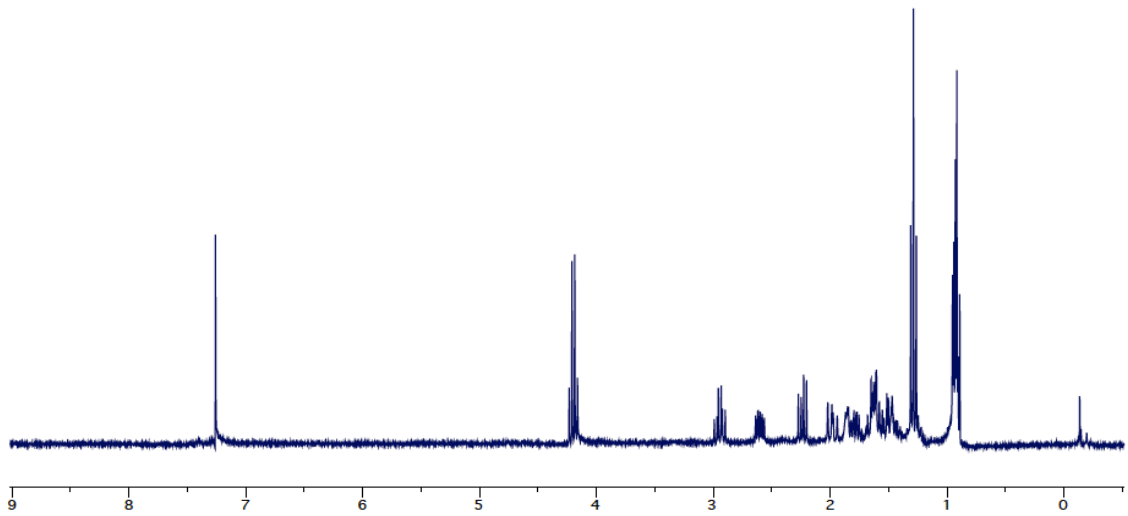
4k

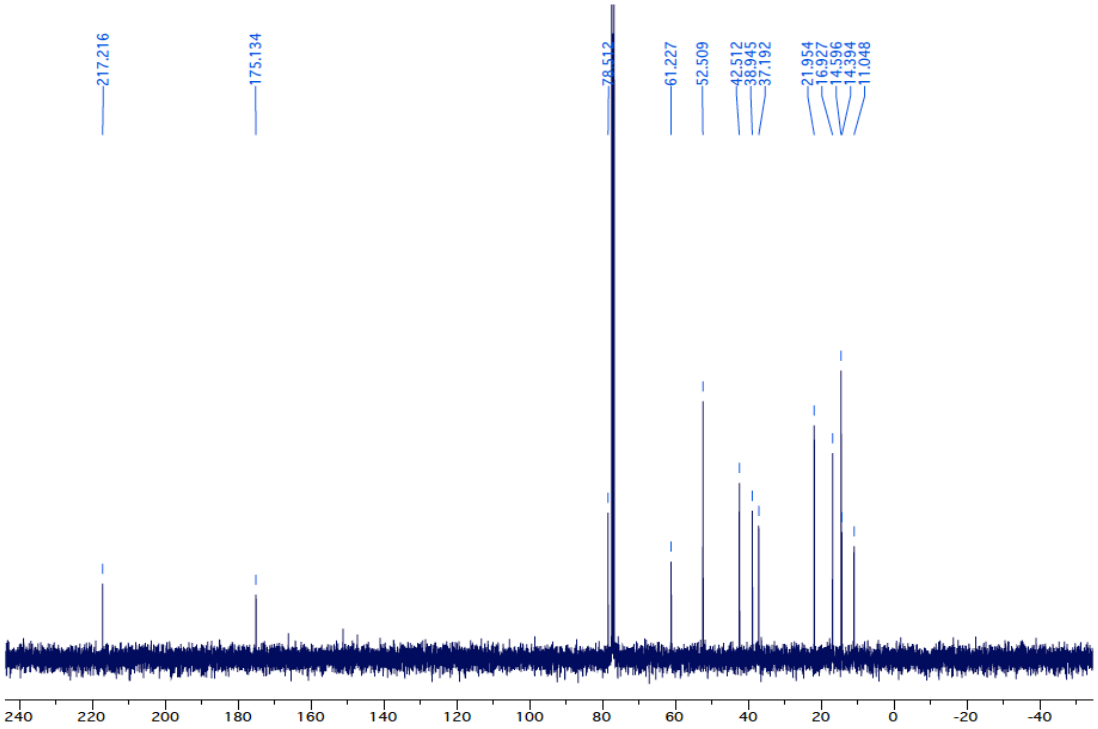

9
8
7
6
5
4
3
2
1
0

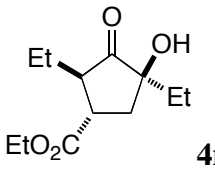

ppm 220
200
180
160
140
120
100
80
60
40
20
0


O
OH
Et
nPr
EtO2C

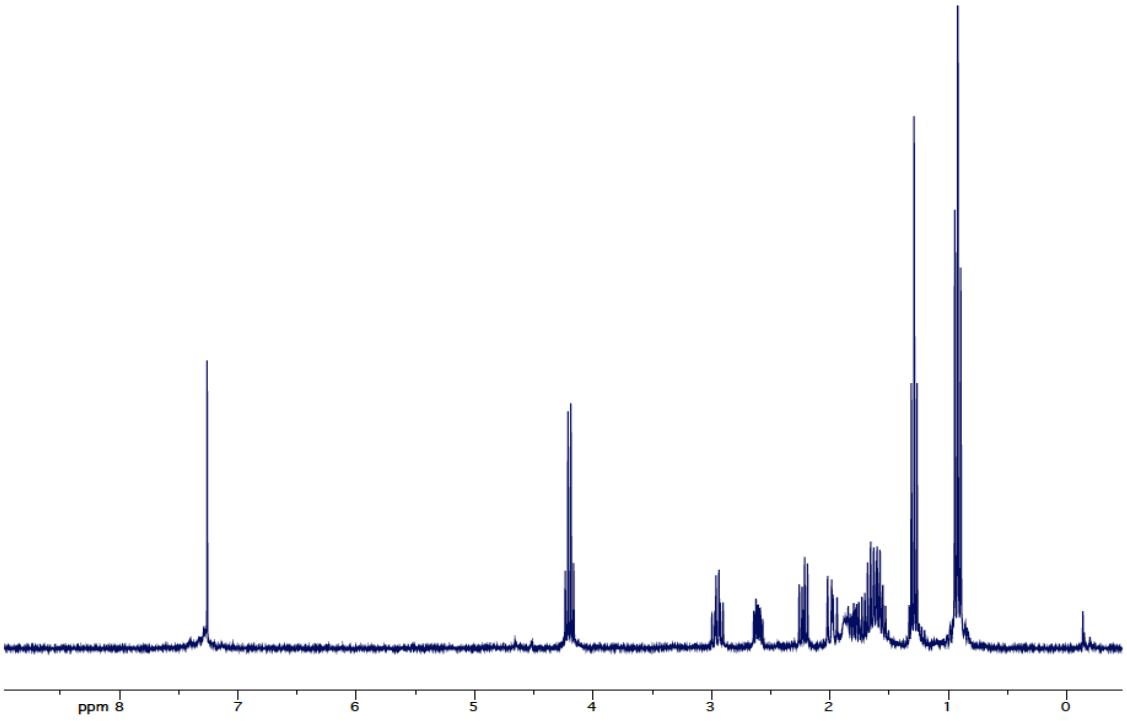
4l

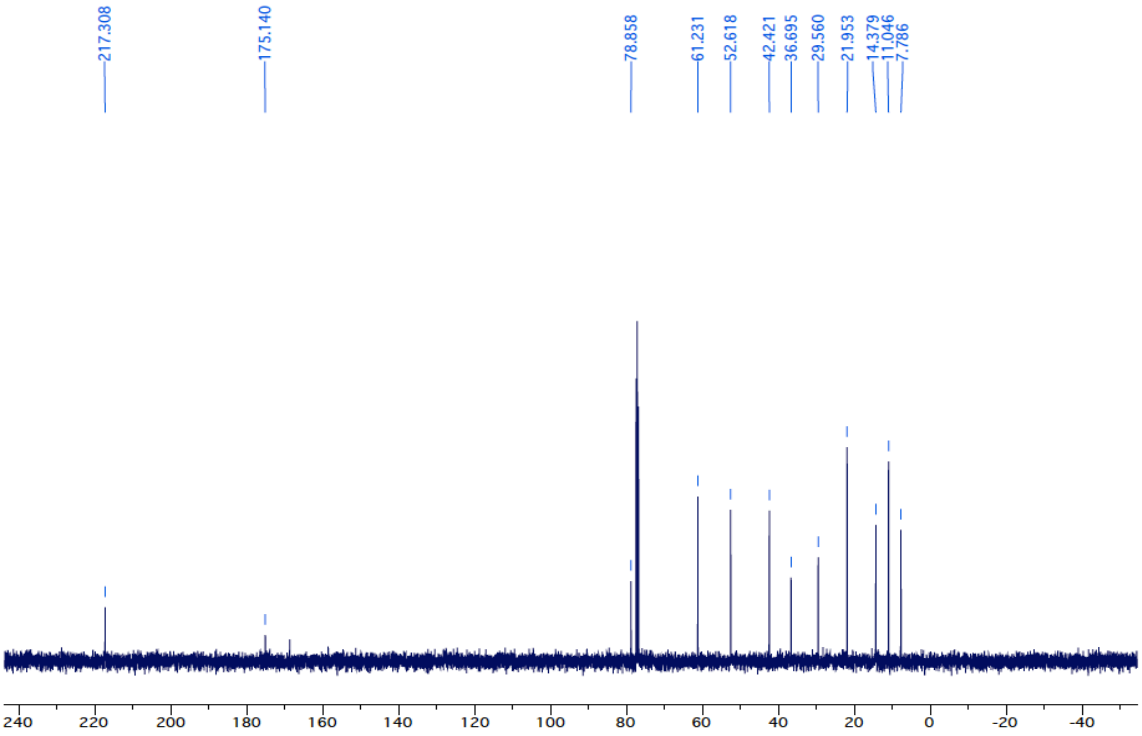

9
8
7
6
5
4
3
2
1
0

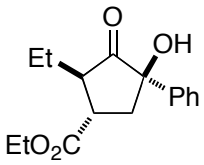

217.216
175.134
78.512
61.227
52.509
42.512
38.945
37.192
21.954
16.927
14.596
14.394
11.048
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40


O
OH
Et
Et
EtO2C

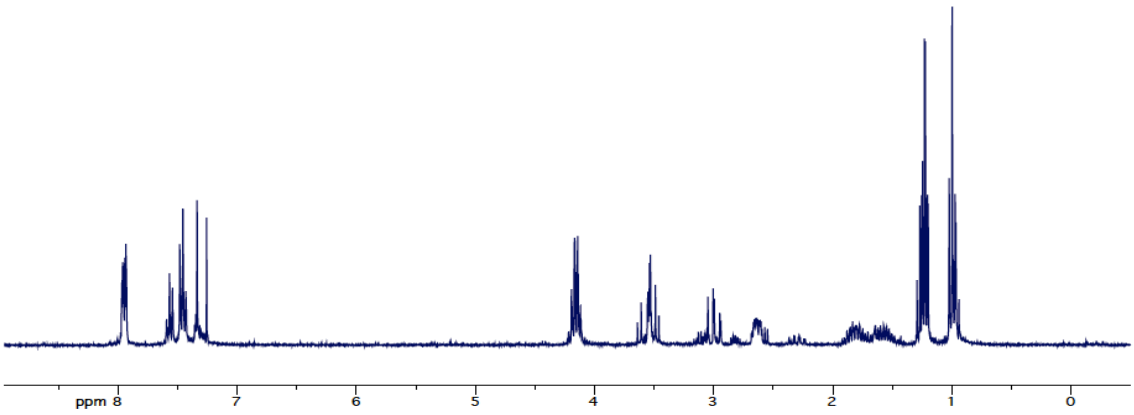
4m

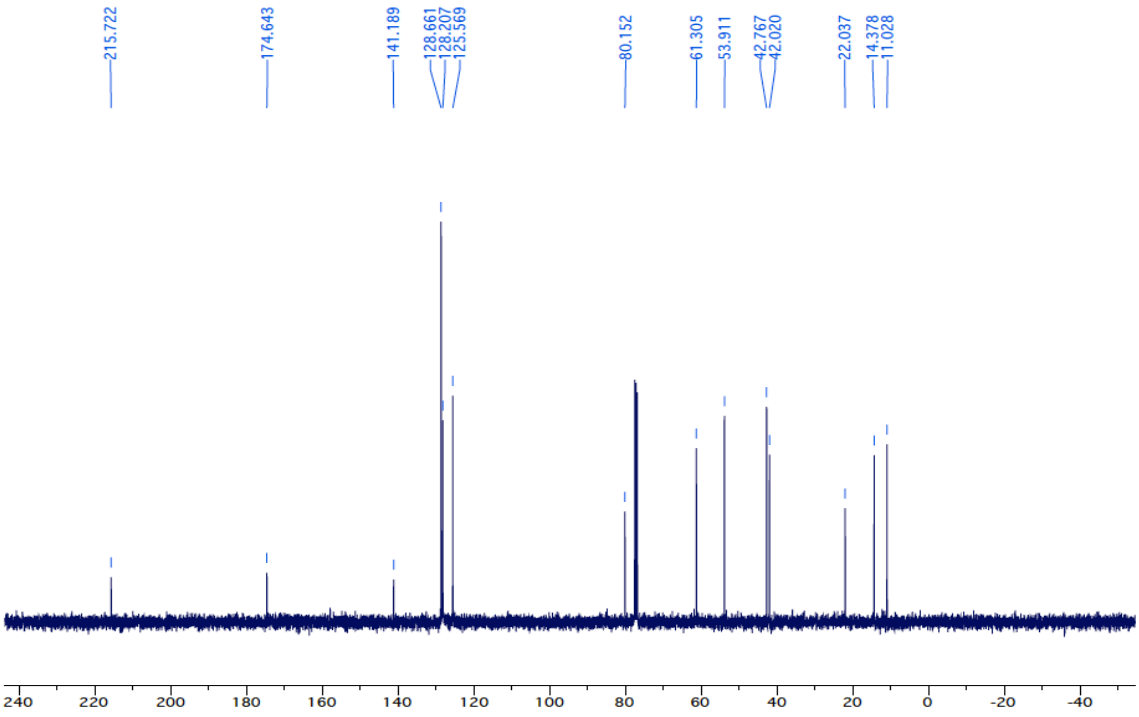

ppm 8
7
6
5
4
3
2
1
0

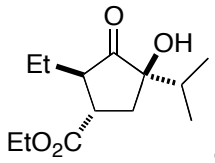

217.308
175.140
78.858
61.231
52.618
42.421
36.695
29.560
21.953
14.379
11.046
7.786
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40


O
OH
Et
Ph
EtO2C

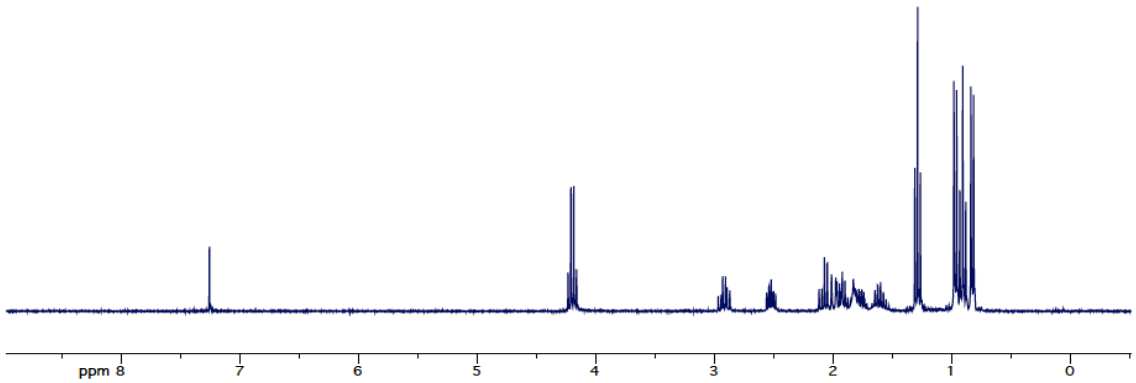
4n

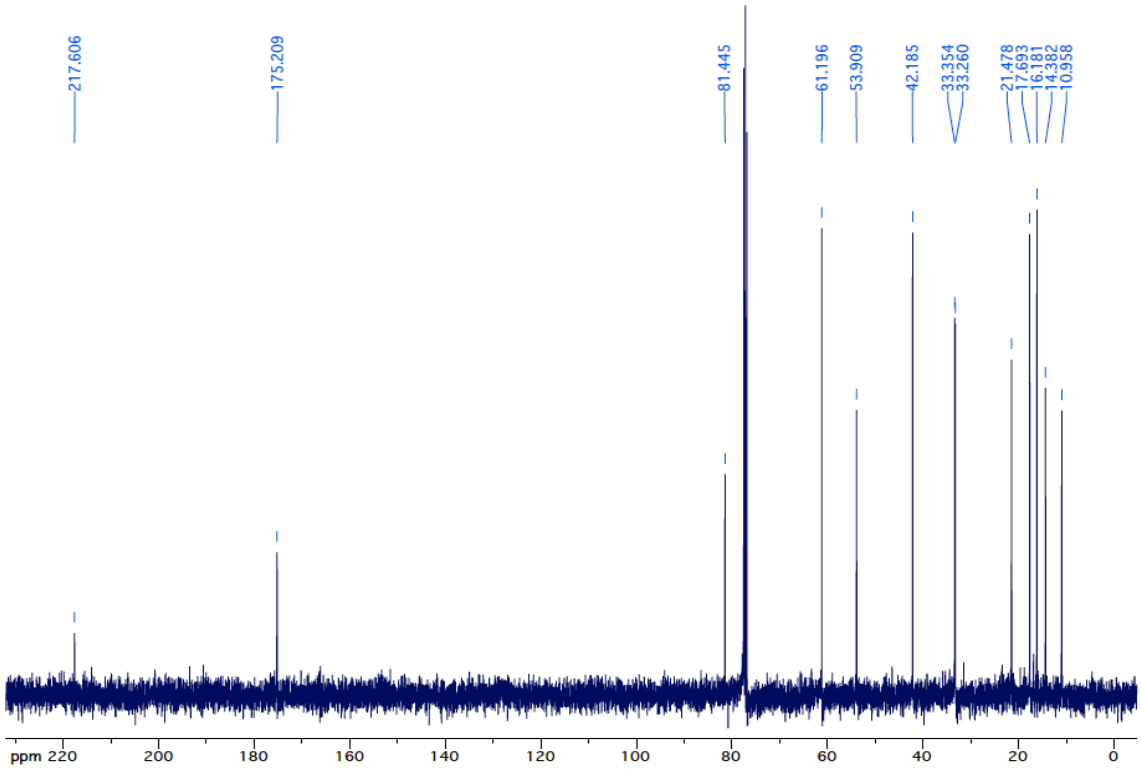

ppm 8
7
6
5
4
3
2
1
0

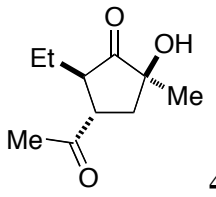

215.722
174.643
141.189
128.661
128.207
125.569
80.152
61.305
53.911
42.767
42.020
22.037
14.378
11.028
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40


O
OH
Et
EtO2C

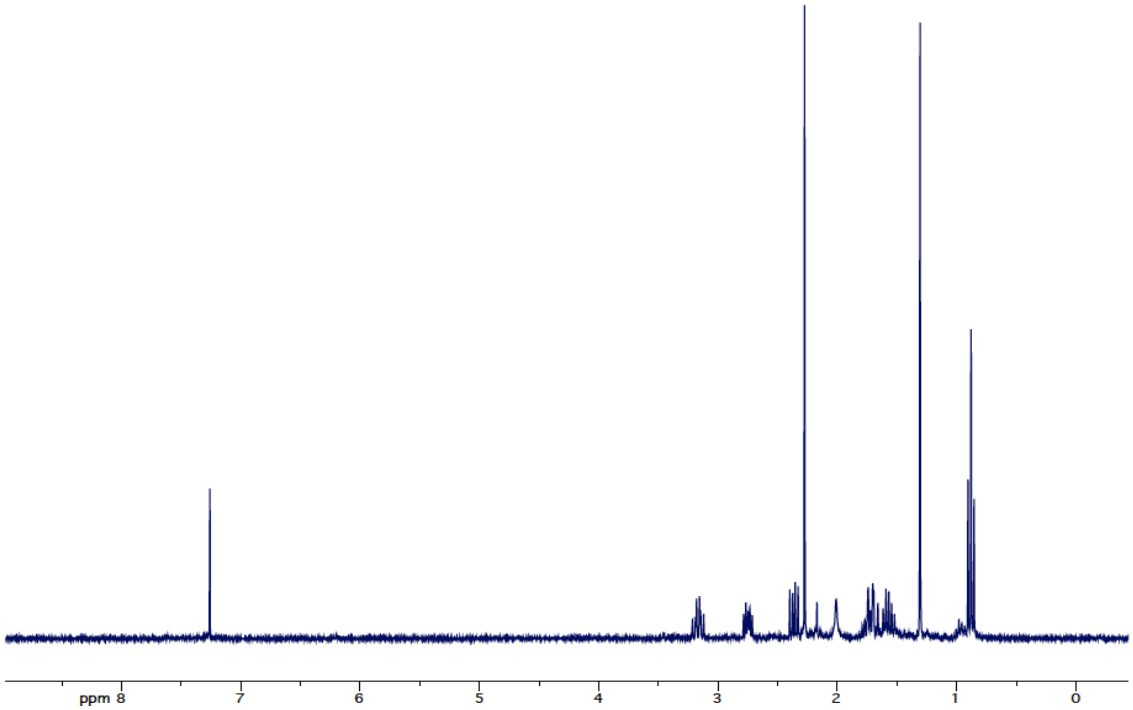
4o

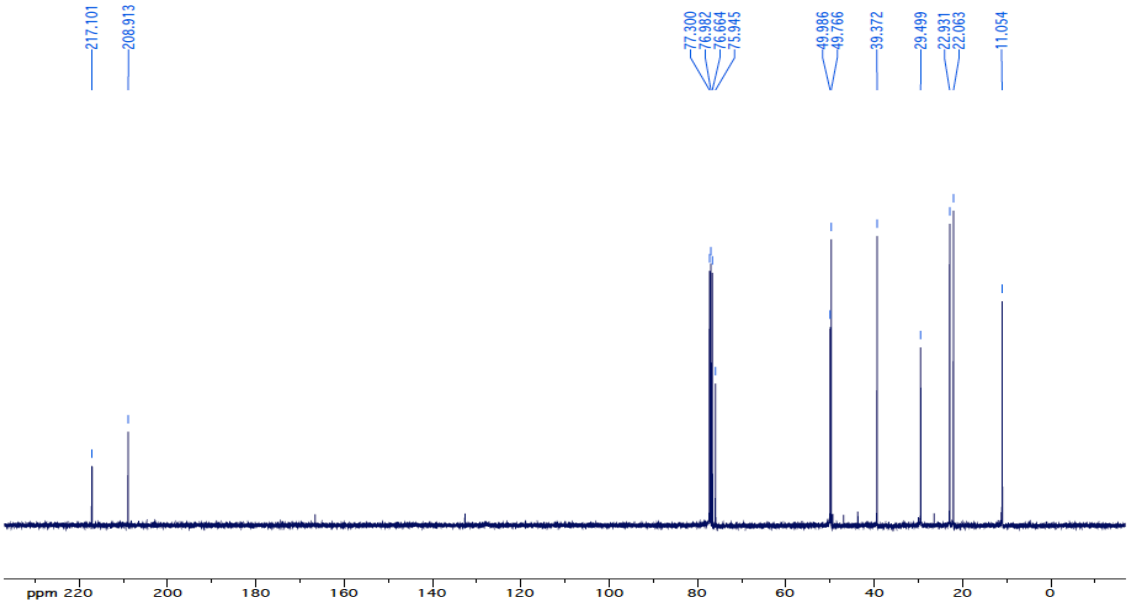

ppm 8
7
6
5
4
3
2
1
0

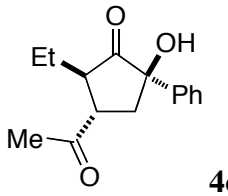

217.606
175.209
81.445
61.196
53.909
42.185
33.354
33.260
21.478
17.693
16.181
14.382
10.958
ppm 220
200
180
160
140
120
100
80
60
40
20
0


O
Et
OH
Me
Me
O

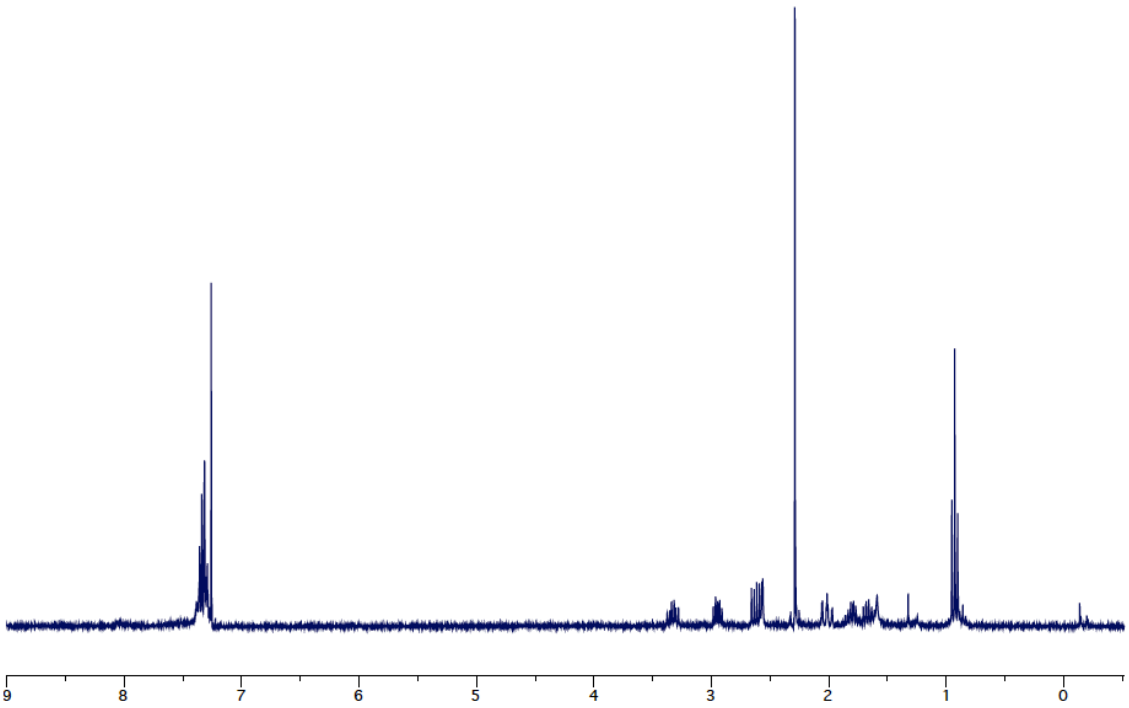
4p

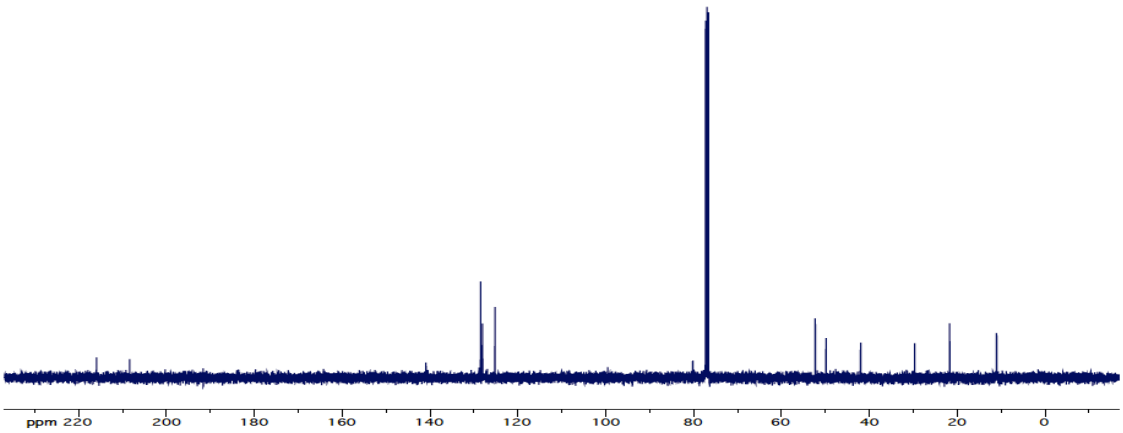

ppm 8
7
6
5
4
3
2
1
0

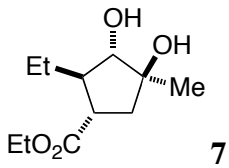

217.101
208.913
77.300
76.982
76.664
75.945
49.986
49.766
39.372
29.499
22.931
22.063
11.054
ppm 220
200
180
160
140
120
100
80
60
40
20
0


O
OH
Et
Ph
Me
O

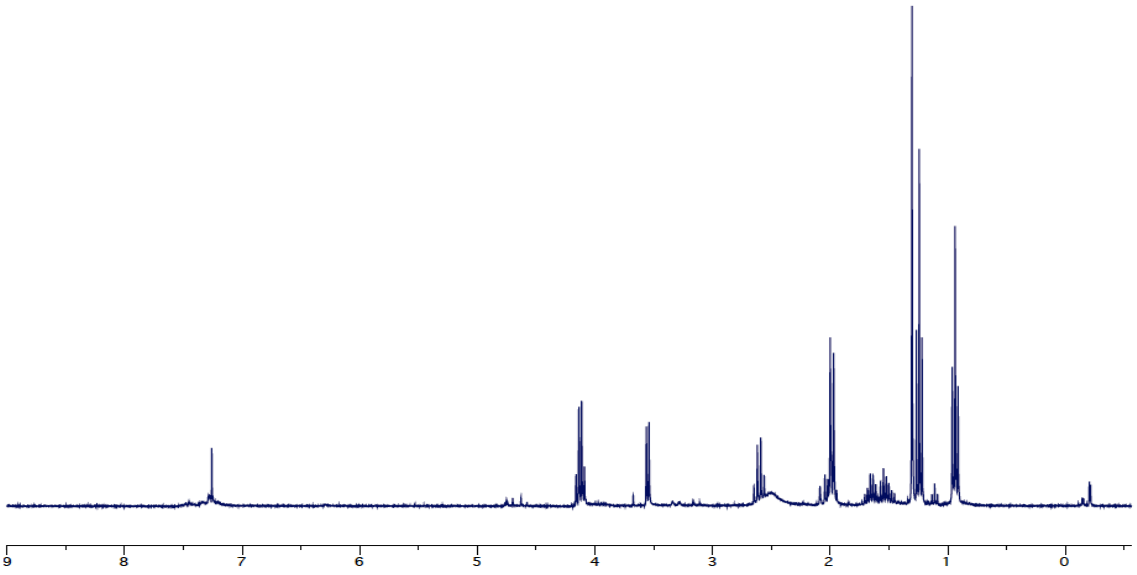
4q

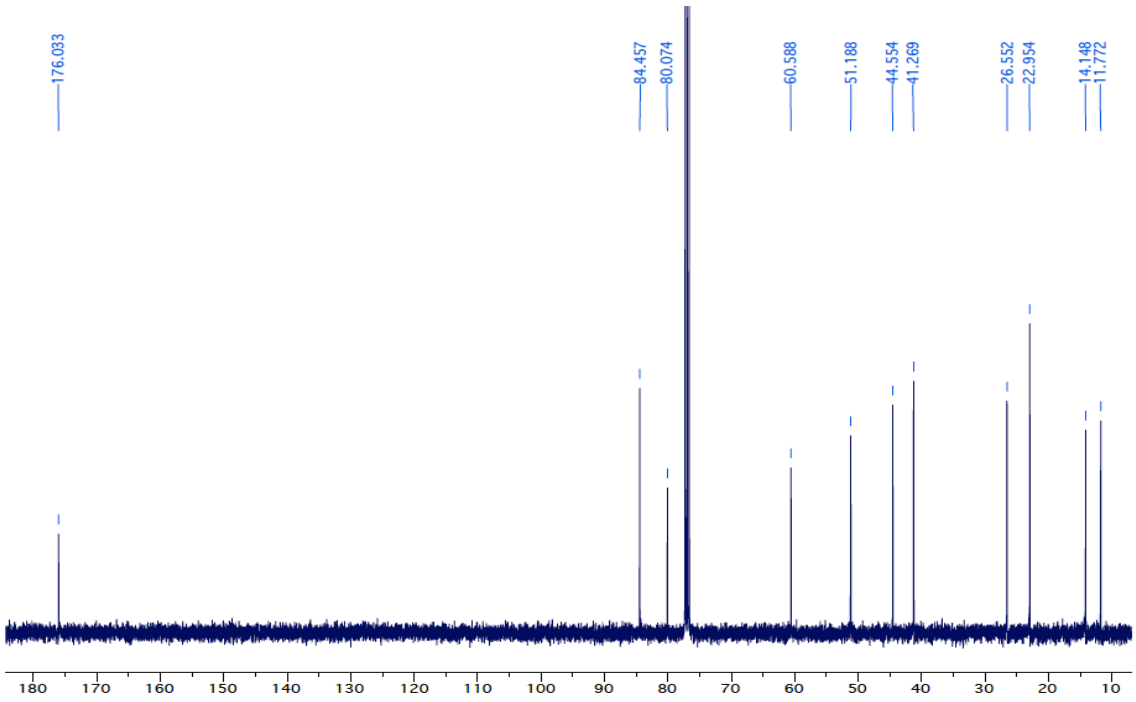

9
8
7
6
5
4
3
2
1
0

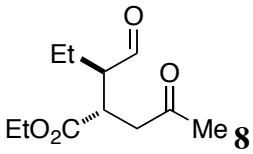

ppm 220
200
180
160
140
120
100
80
60
40
20
0


OH
OH
Et
Me
EtO2C

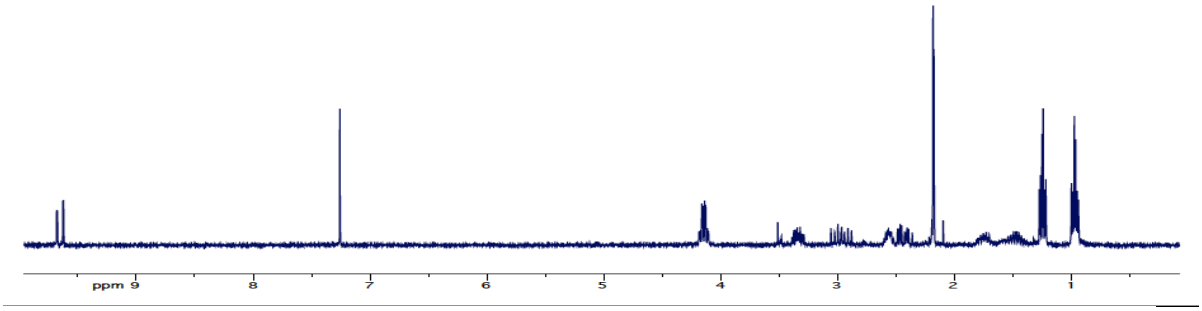
7

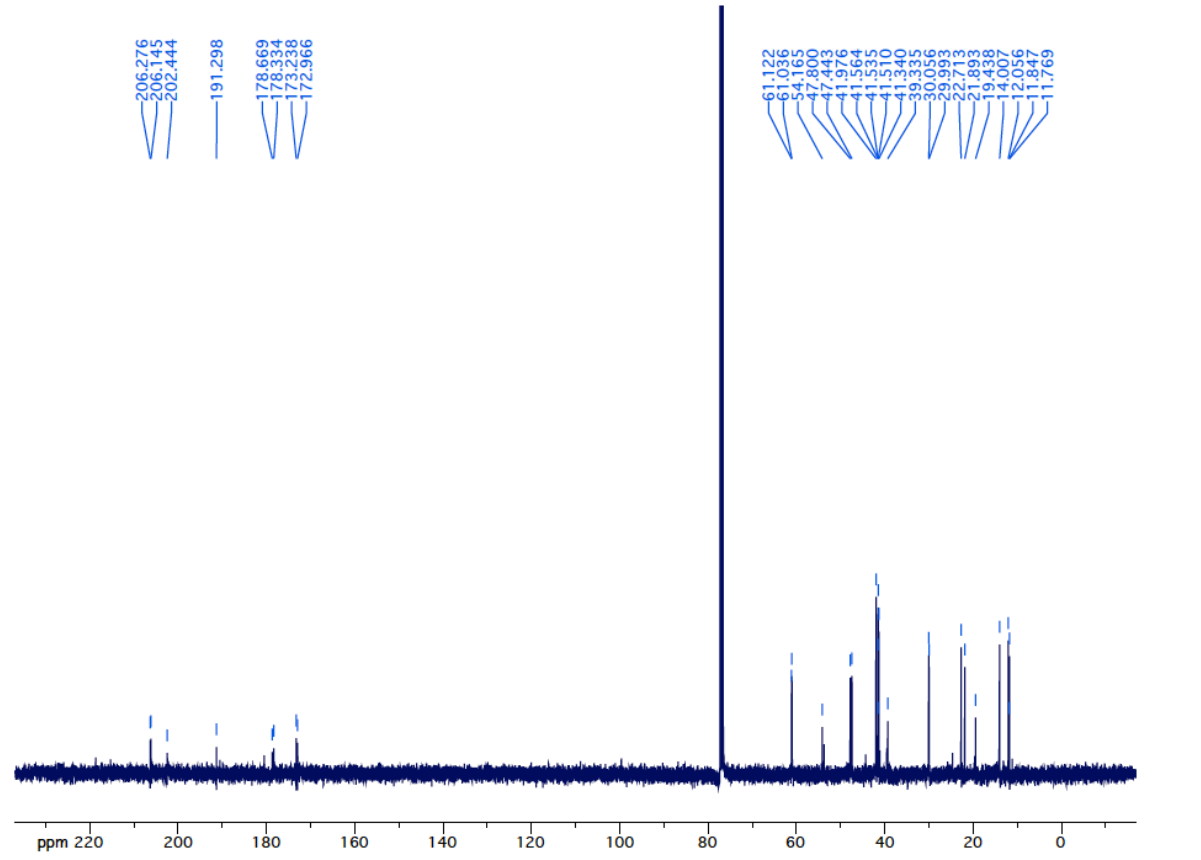

9
8
7
6
5
4
3
2
1
0


176.033
84.457
80.074
60.588
51.188
44.554
41.269
26.552
22.954
14.148
11.772
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

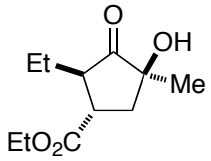

O
Et
O
EtO2C
Me

8

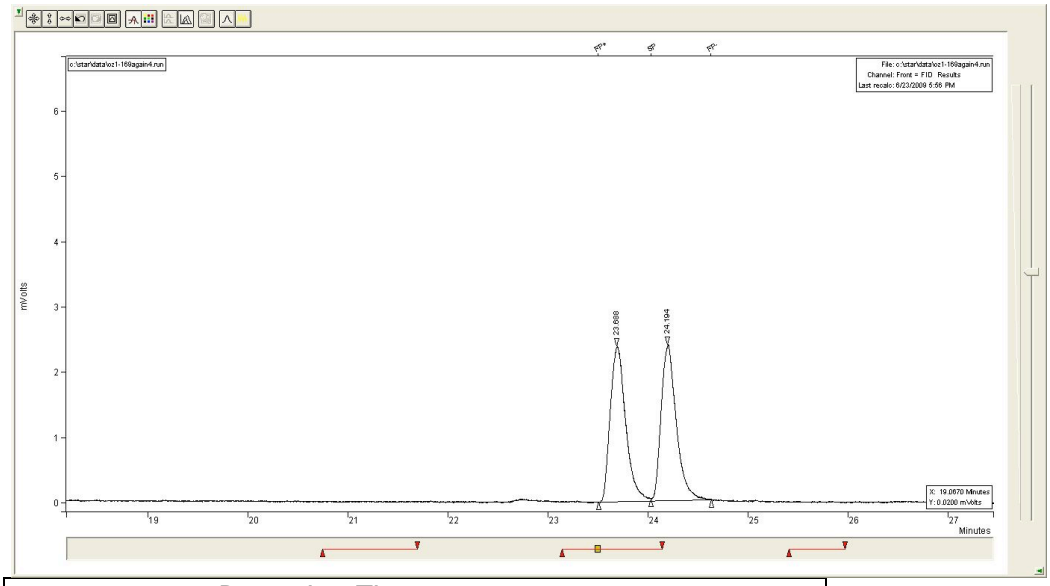

ppm 9
8
7
6
5
4
3
2
1


206.276
206.145
202.444
191.298
178.669
178.334
173.238
172.966
61.122
61.036
54.165
47.800
47.443
41.976
41.564
41.535
41.510
41.340
39.335
30.056
29.993
22.713
21.893
19.438
14.007
12.056
11.847
11.769
ppm 220
200
180
160
140
120
100
80
60
40
20
0

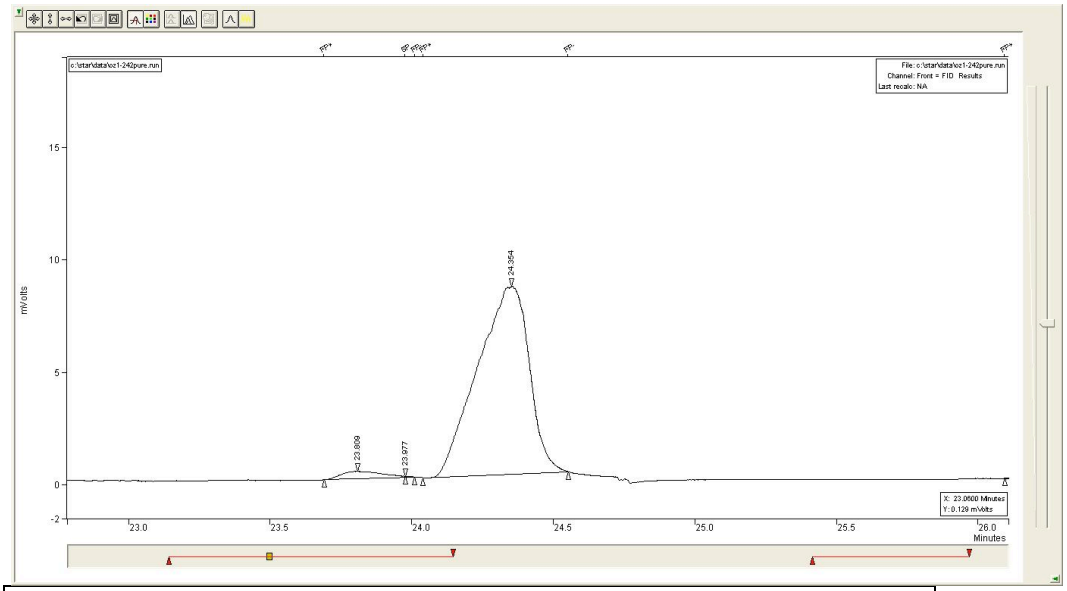
GC and HPLC traces



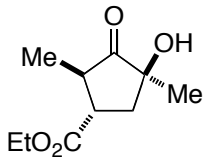
4a



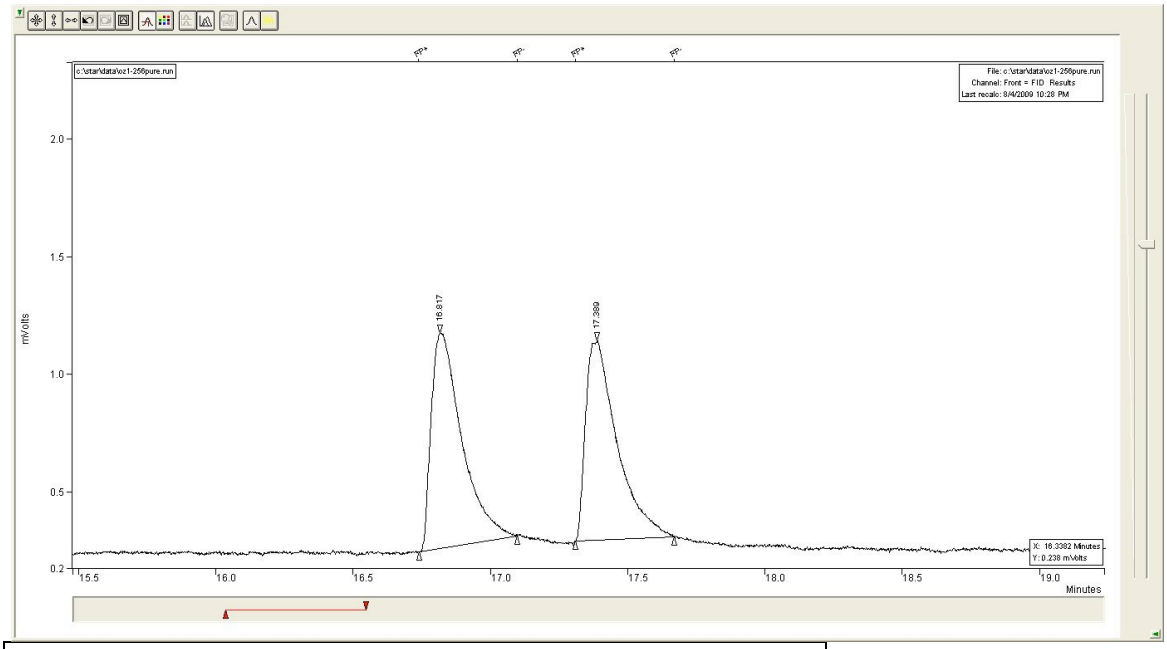
	Retention Time (min)	Area (mVolts*s)
Peak1	23.688	25.6
Peak2	24.194	25.1



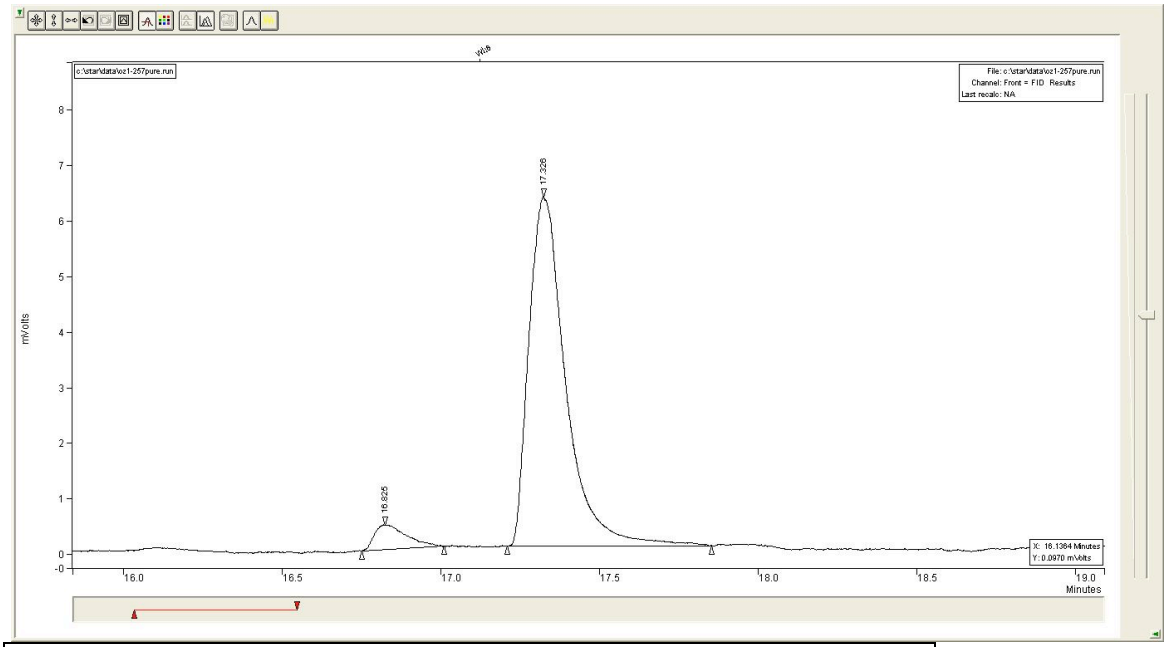
	Retention Time (min)	Area (mVolts*s)
Peak1	23.631	9.8
Peak2	24.224	168



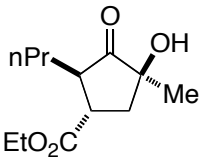
4b



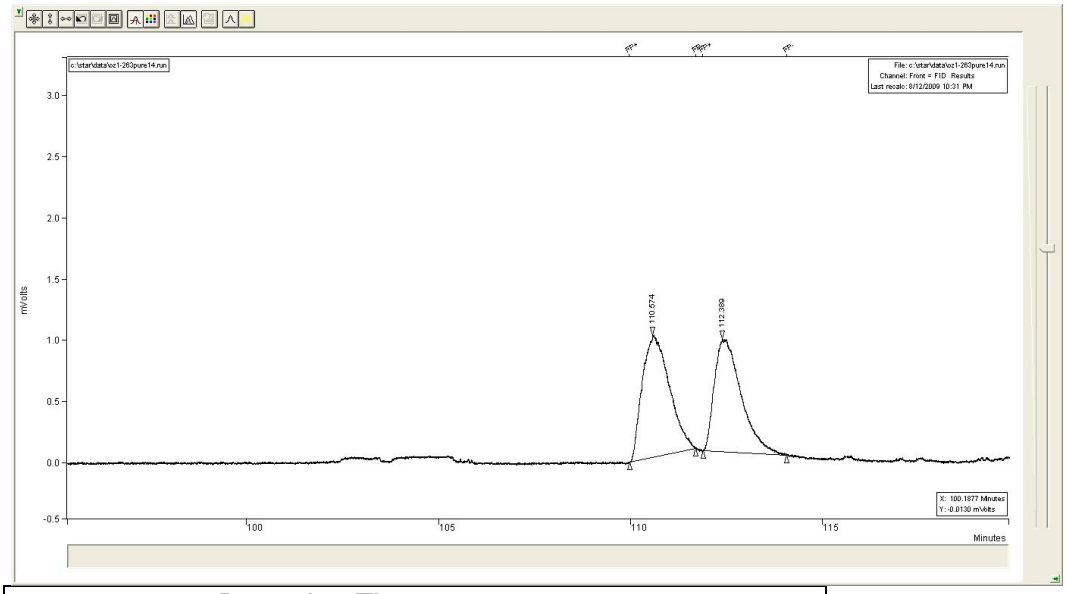
	Retention Time (min)	Area (mVolts*s)
Peak1	16.817	7.08
Peak2	17.389	6.79



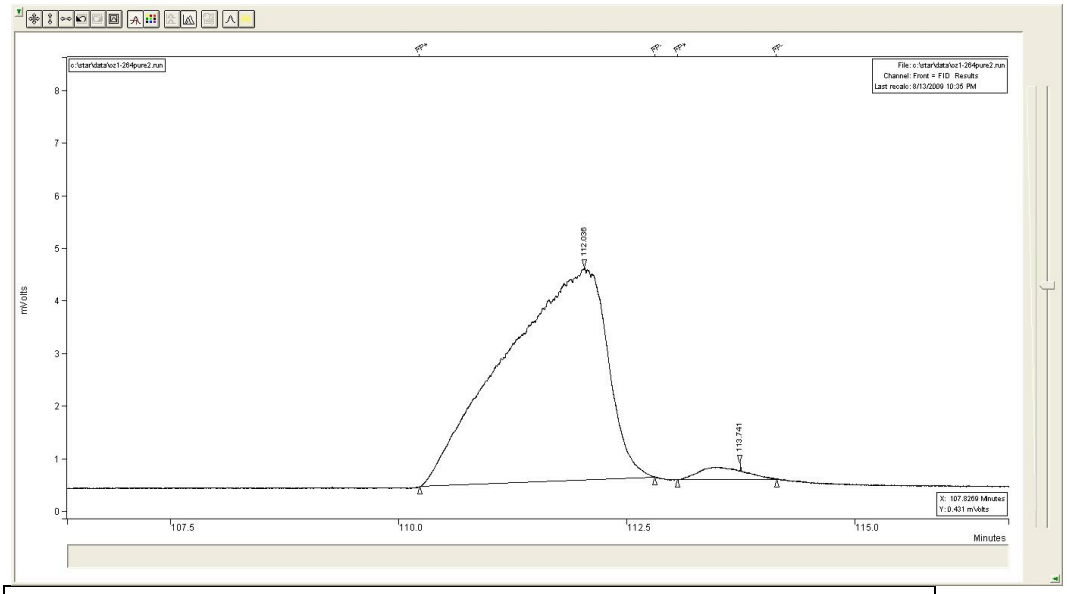
	Retention Time (min)	Area (mVolts*s)
Peak1	16.825	3.13
Peak2	17.326	50.7



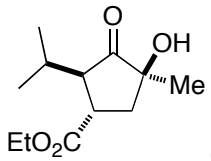
4c



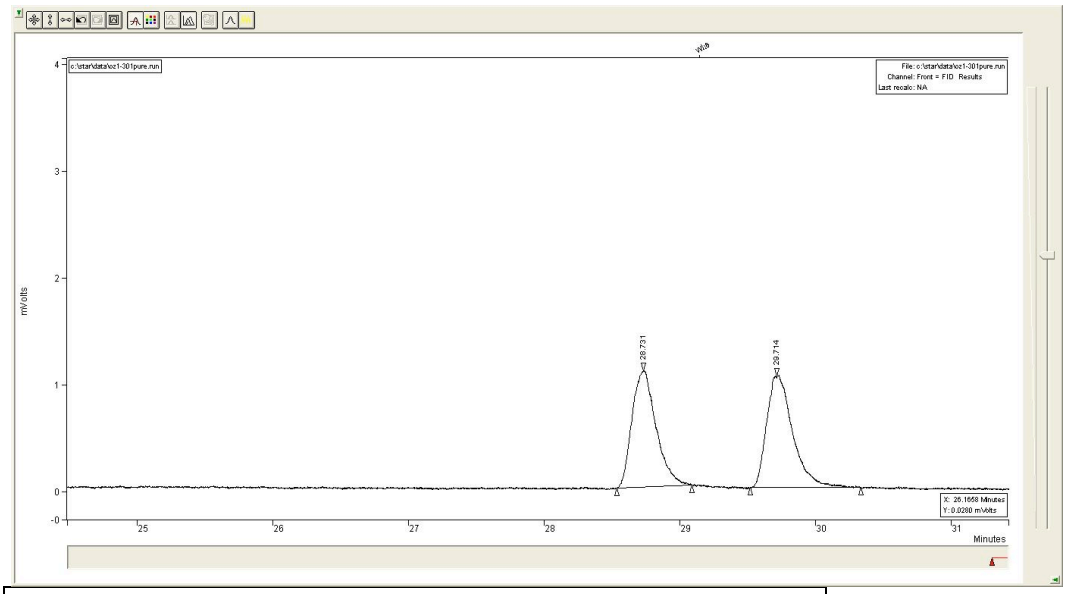
	Retention Time (min)	Area (mVolts*s)
Peak1	110.57	45
Peak2	112.389	44.6



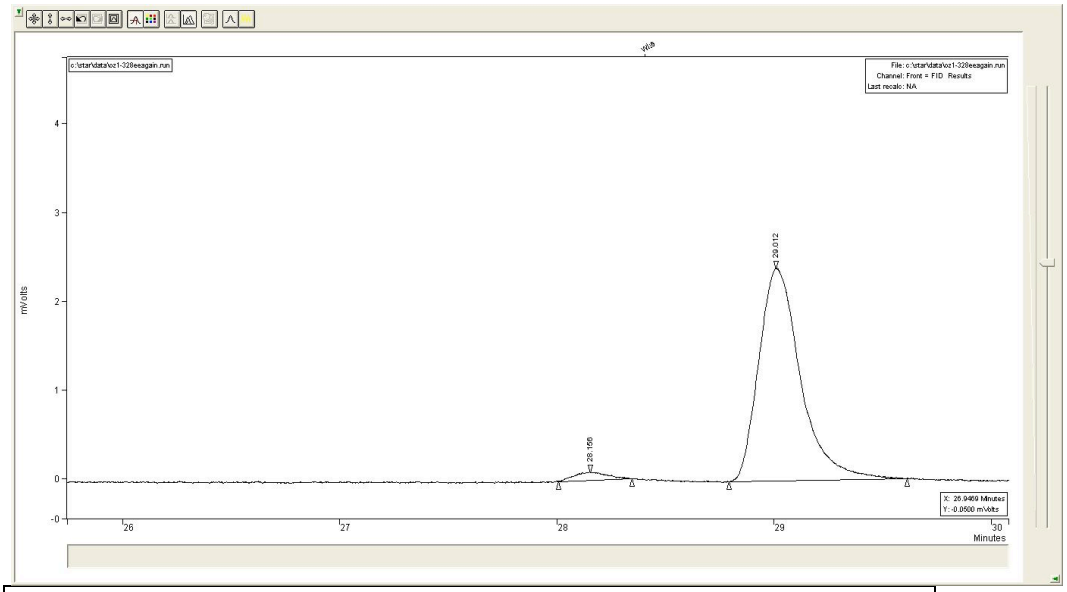
	Retention Time (min)	Area (mVolts*s)
Peak1	113.036	313
Peak2	113.741	7.49



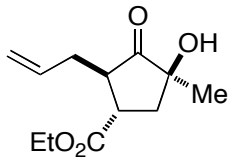
4d



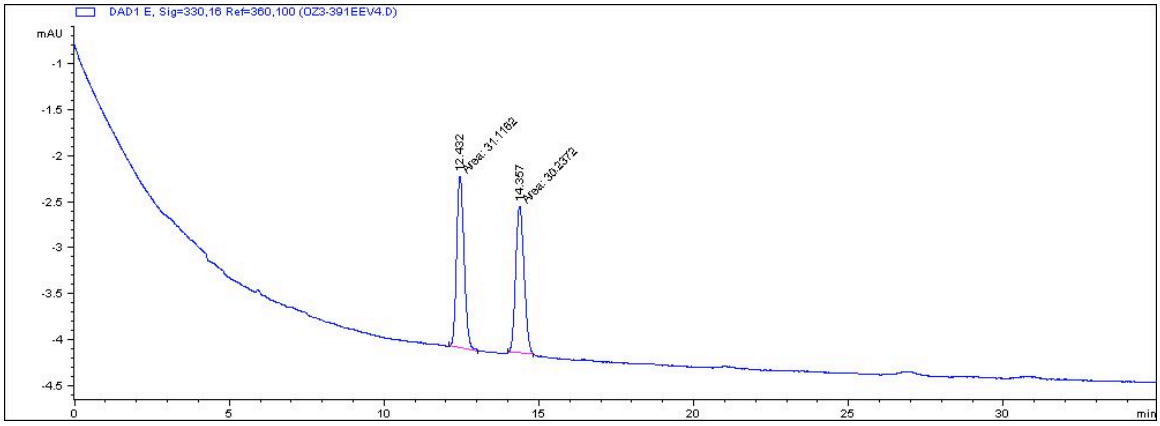
	Retention Time (min)	Area (mVolts*s)
Peak1	28.731	13.5
Peak2	29.714	14



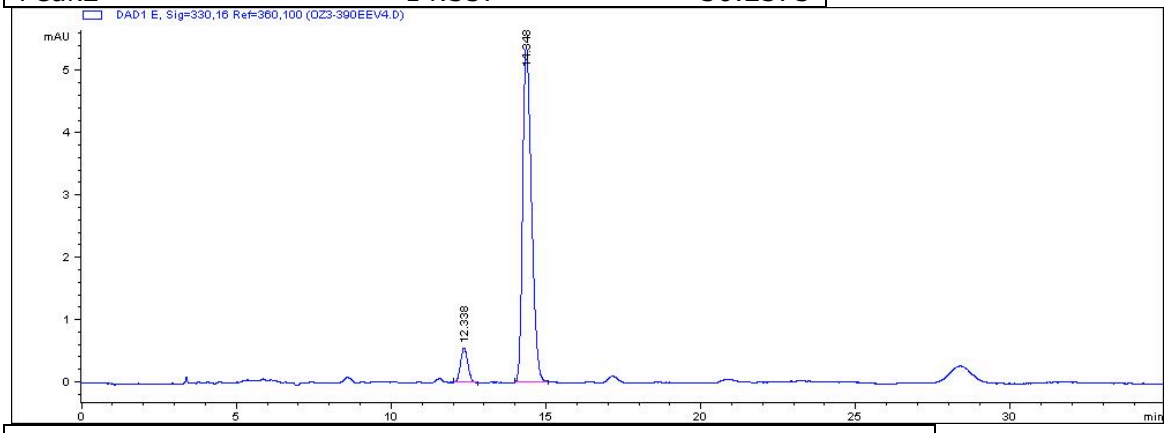
	Retention Time (min)	Area (mVolts*s)
Peak1	28.156	0.978
Peak2	29.012	32



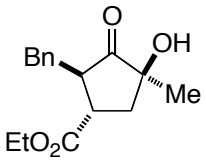
4e



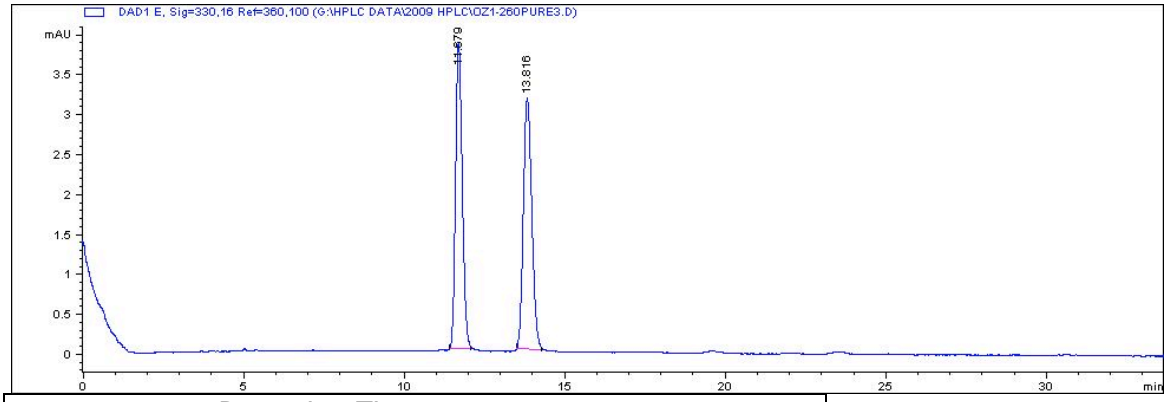
	Retention Time (min)	Area (mAu*s)
Peak1	12.432	31.1162
Peak2	14.357	30.2373



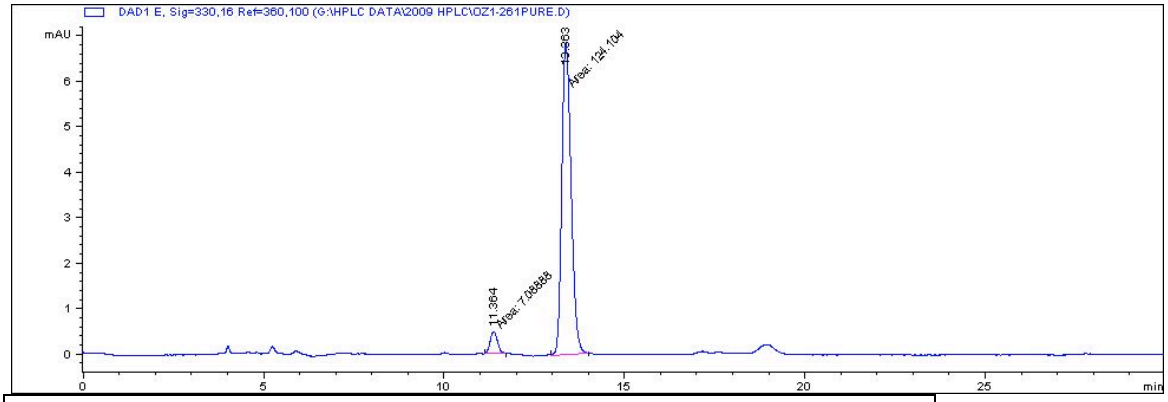
	Retention Time (min)	Area (mAu*s)
Peak1	12.338	8.9438
Peak2	14.346	107.83



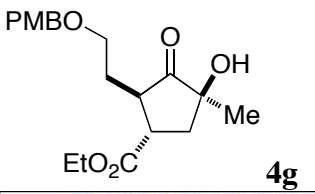
4f



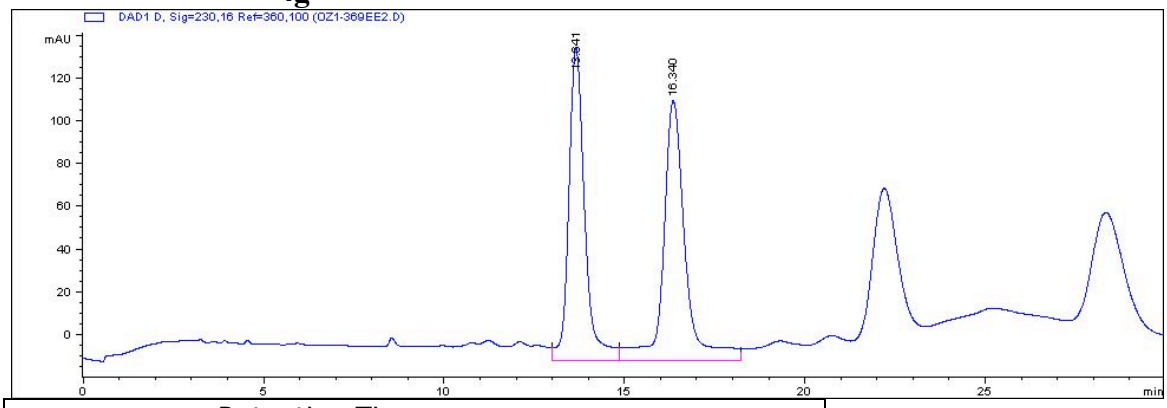
	Retention Time (min)	Area (mAU*s)
Peak1	11.679	56.1959
Peak2	13.816	57.3378



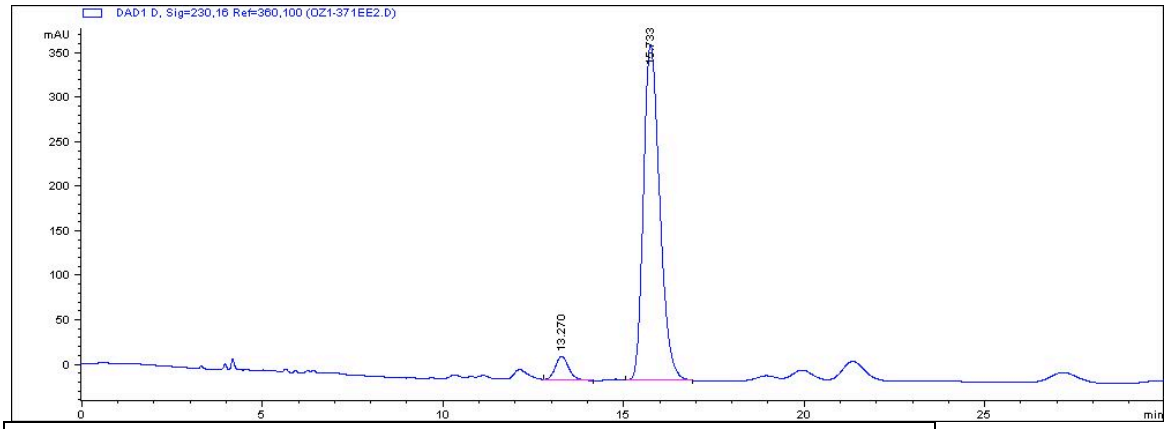
	Retention Time (min)	Area (mAu*s)
Peak1	11.363	6.8983
Peak2	13.363	123.133



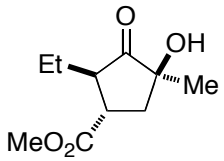
4g



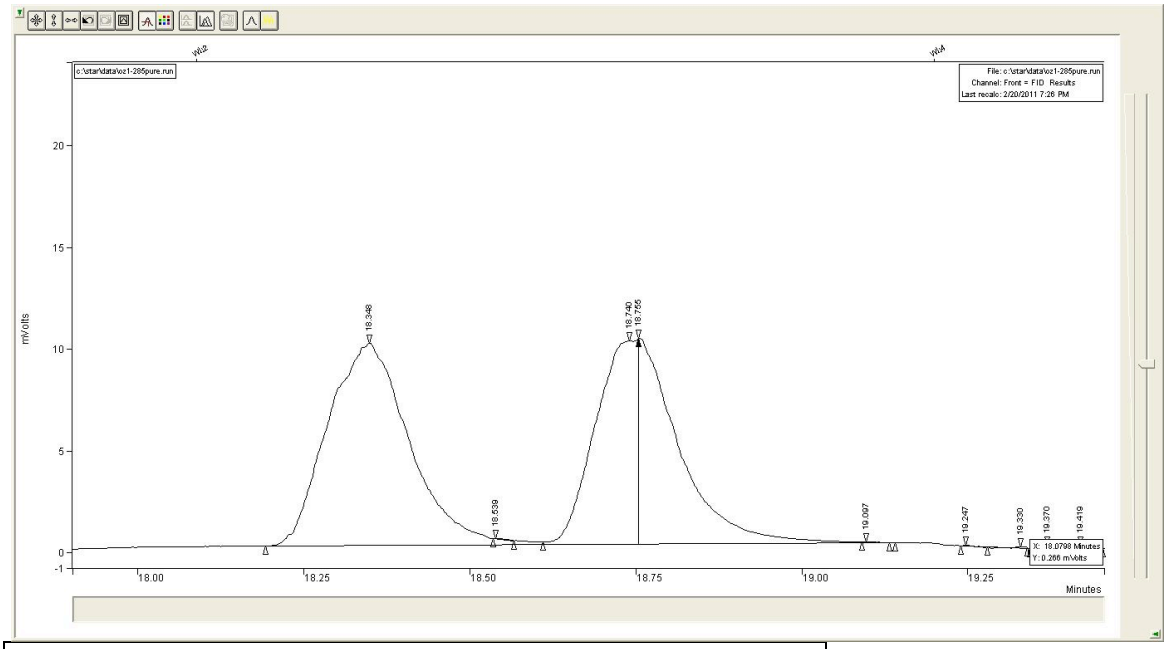
	Retention Time (min)	Area (mAu*s)
Peak1	13.641	3843.1
Peak2	16.34	3869.4



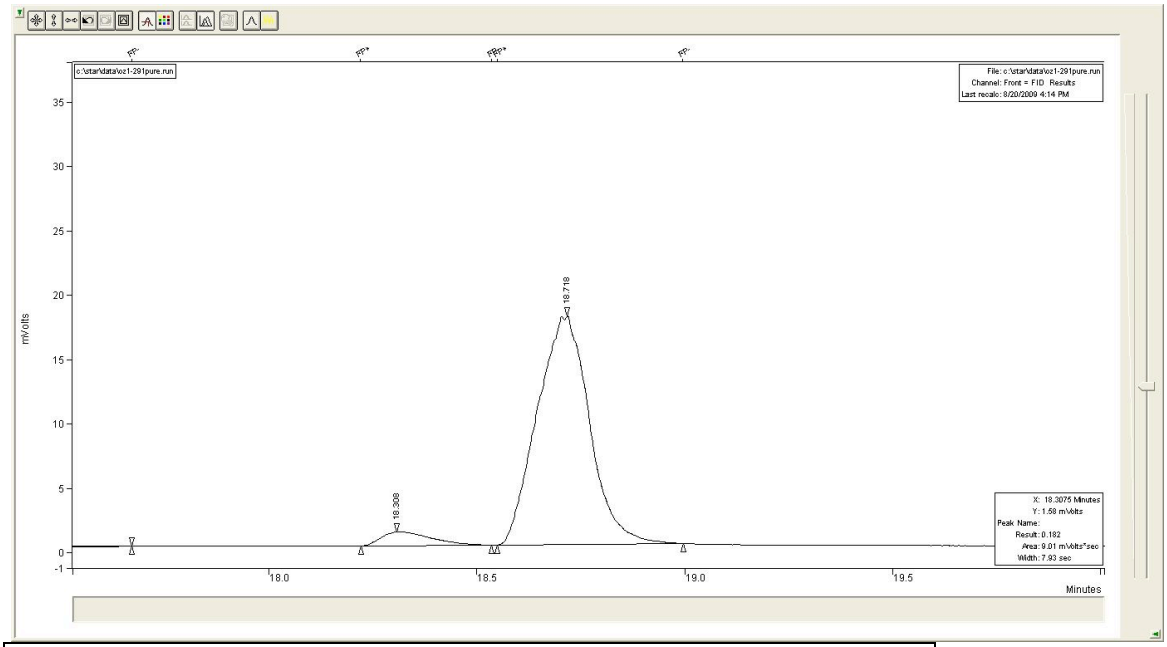
	Retention Time (min)	Area (mAu*s)
Peak1	13.27	692.8
Peak2	15.733	11850.1



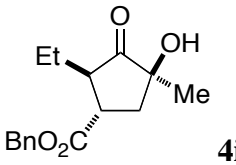
4h



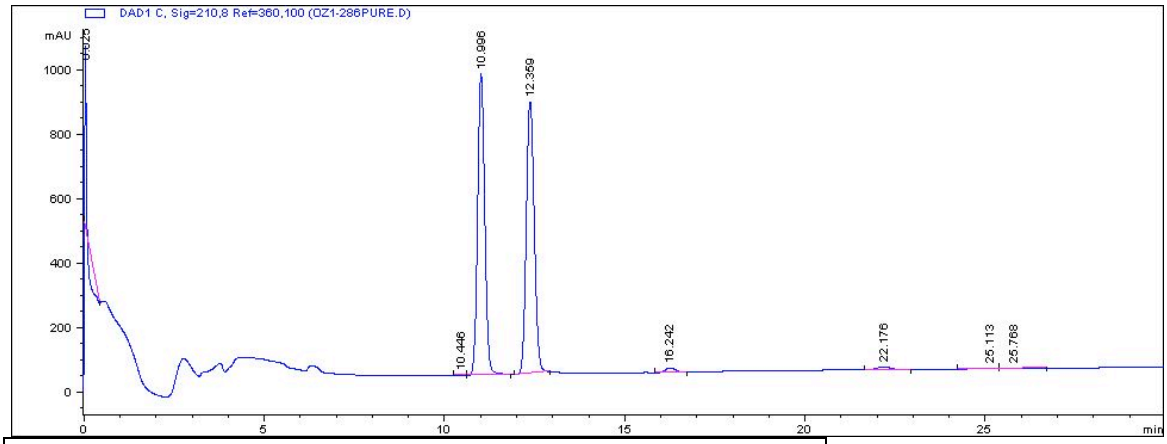
	Retention Time (min)	Area (mVolts*s)
Peak1	18.348	81.4
Peak2	18.751	84



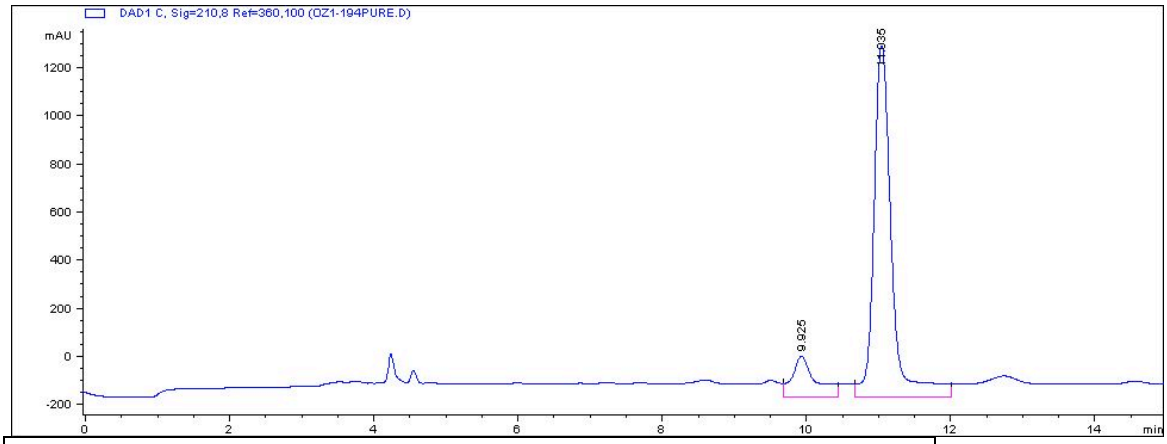
	Retention Time (min)	Area (mVolts*s)
Peak1	18.308	9.01
Peak2	18.718	155



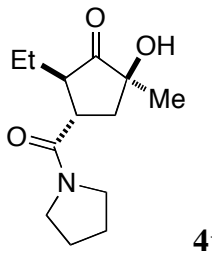
4i



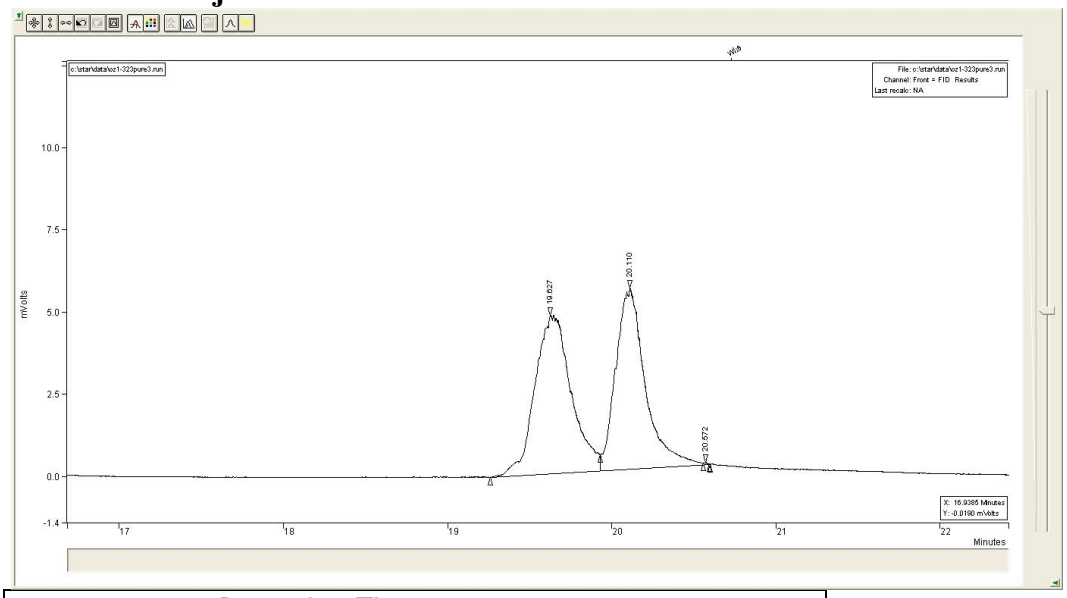
	Retention Time (min)	Area (mAU*s)
Peak1	10.996	12892.1
Peak2	12.359	12733.8



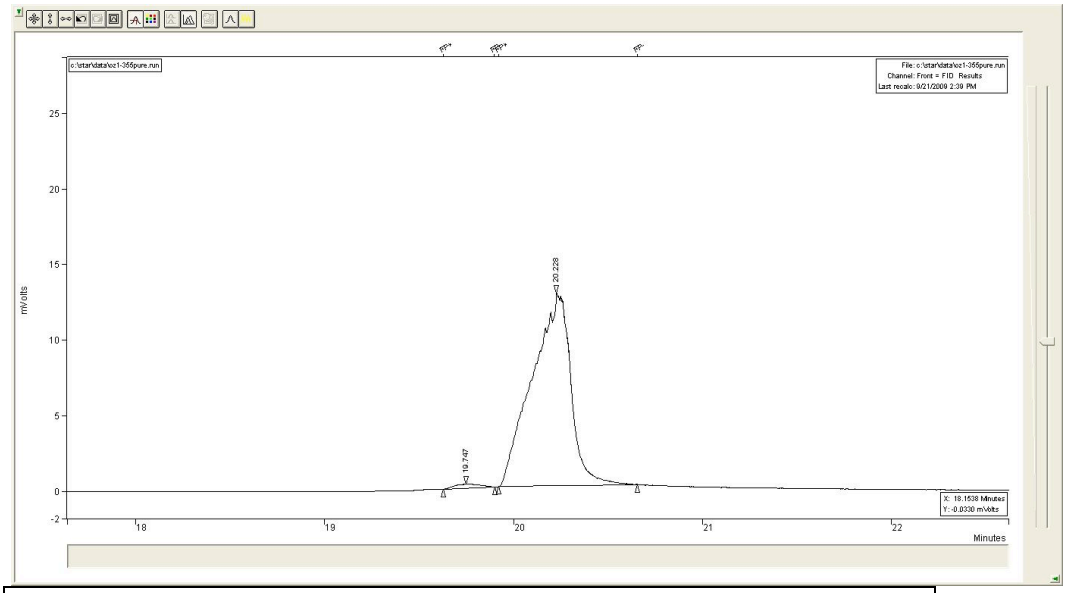
	Retention Time (min)	Area (mAU*s)
Peak1	9.925	1633.68
Peak2	11.035	20446.5



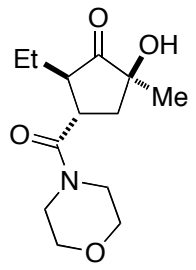
4j



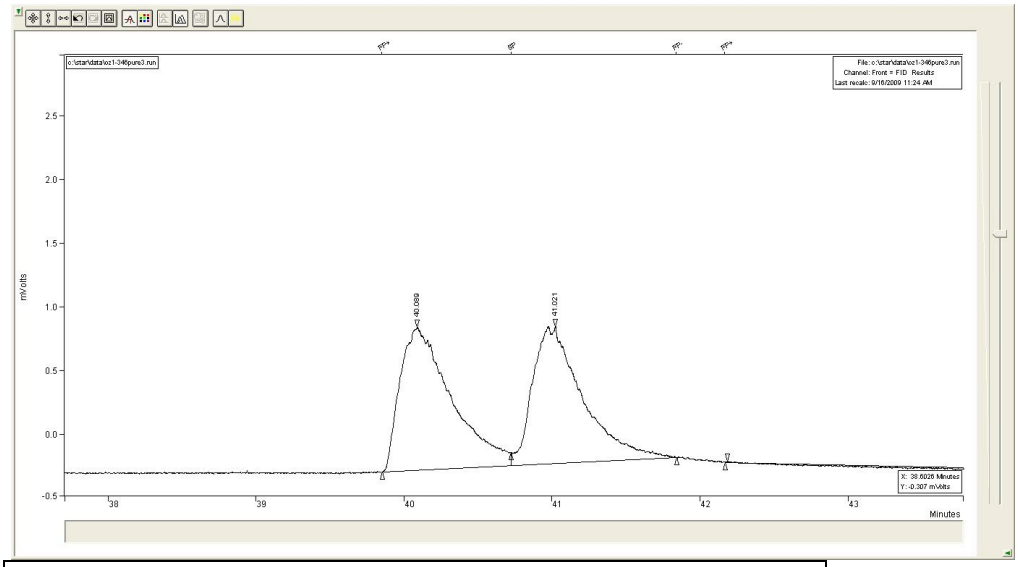
	Retention Time (min)	Area (mVolts*s)
Peak1	19.627	70
Peak2	20.11	68.7



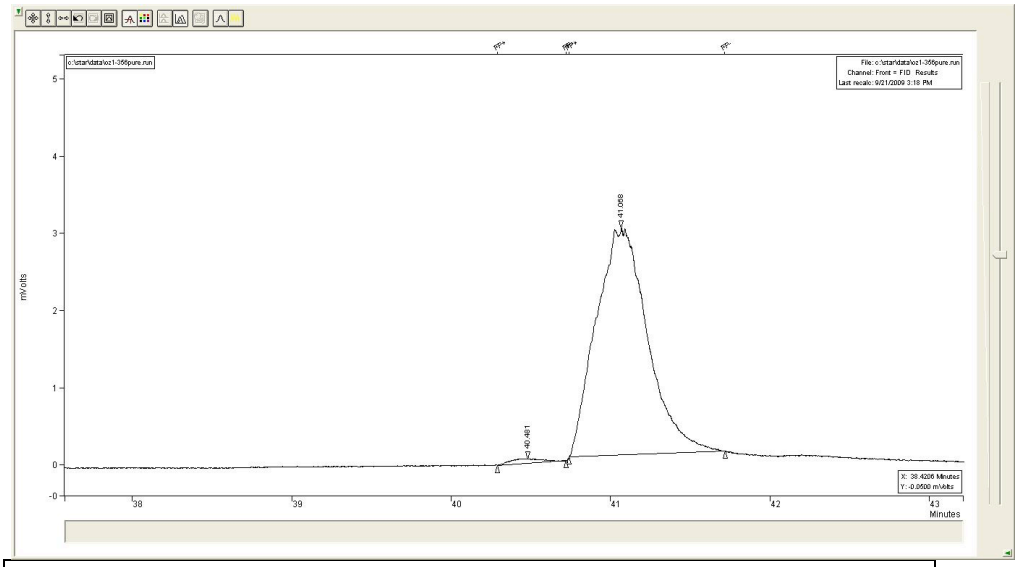
	Retention Time (min)	Area (mVolts*s)
Peak1	19.747	2.54
Peak2	20.228	180



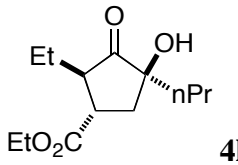
4k



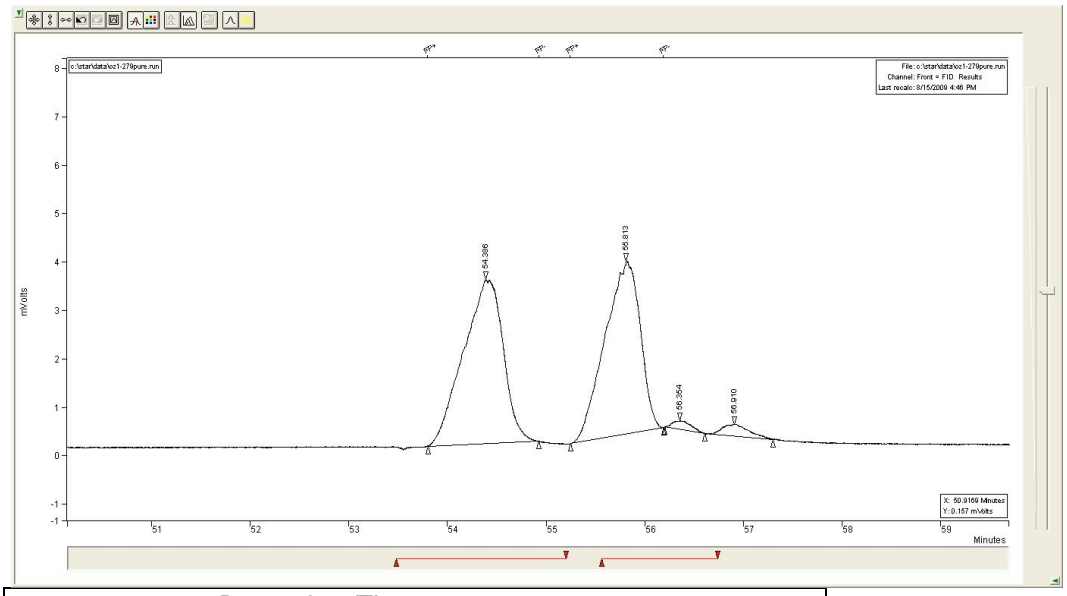
	Retention Time (min)	Area (mVolts*s)
Peak1	40.089	27
Peak2	41.021	25.2



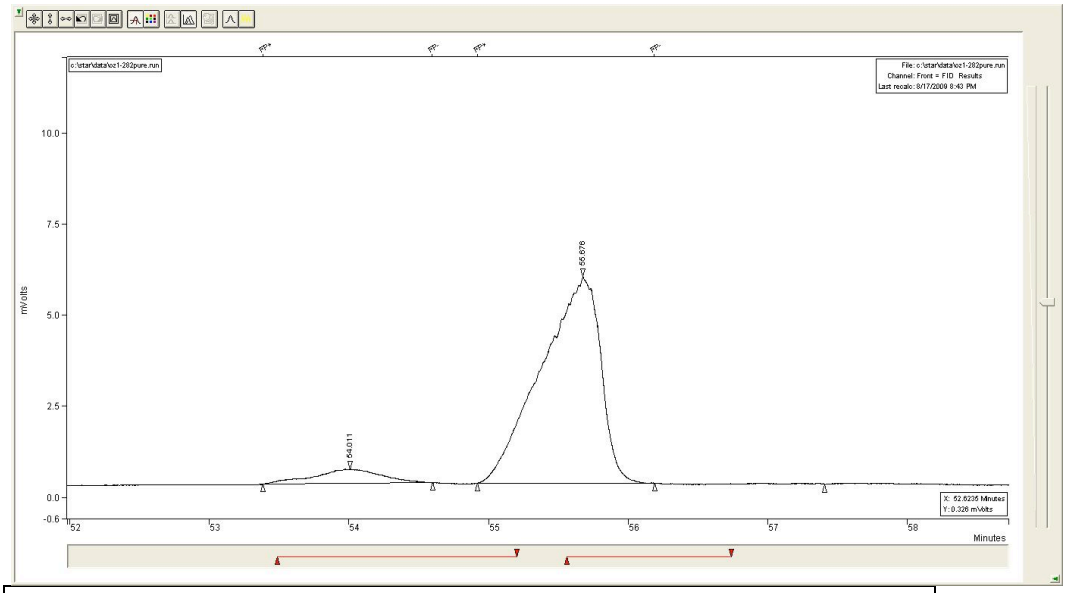
	Retention Time (min)	Area (mVolts*s)
Peak1	40.481	0.801
Peak2	41.068	66



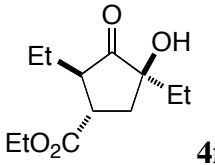
4l



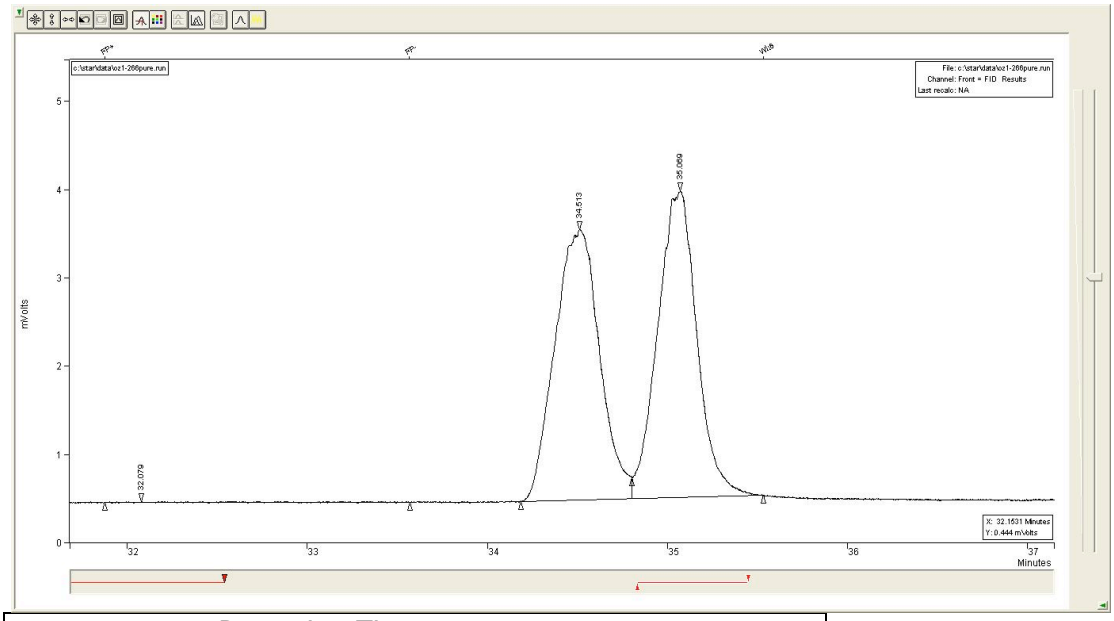
	Retention Time (min)	Area (mVolts*s)
Peak1	54.386	94.9
Peak2	55.813	88.6



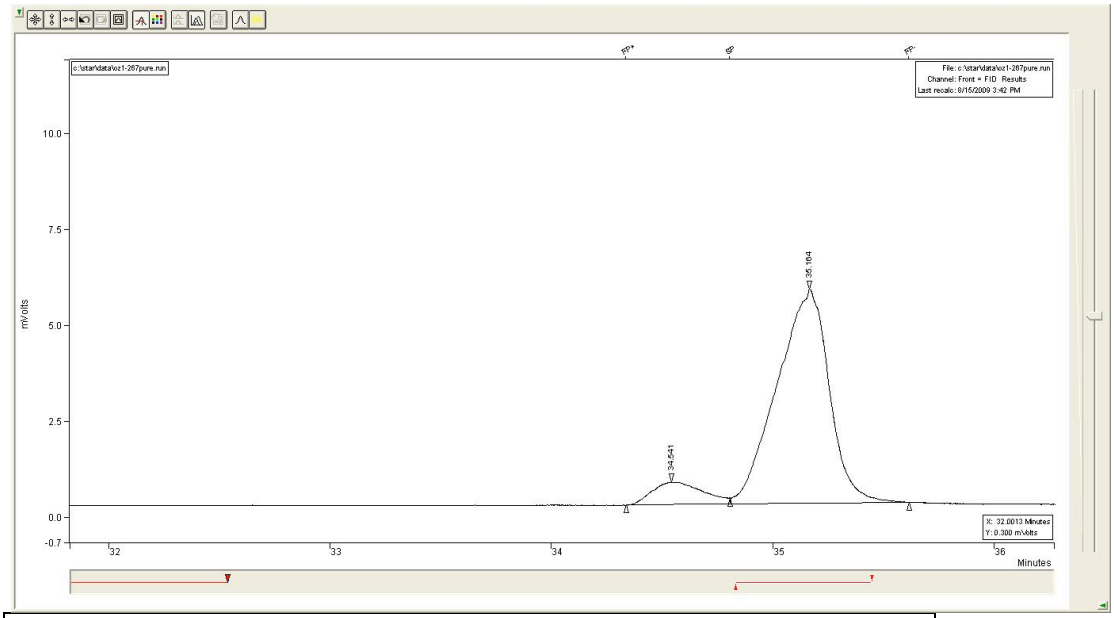
	Retention Time (min)	Area (mVolts*s)
Peak1	54.011	13.3
Peak2	55.676	167



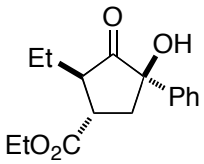
4m



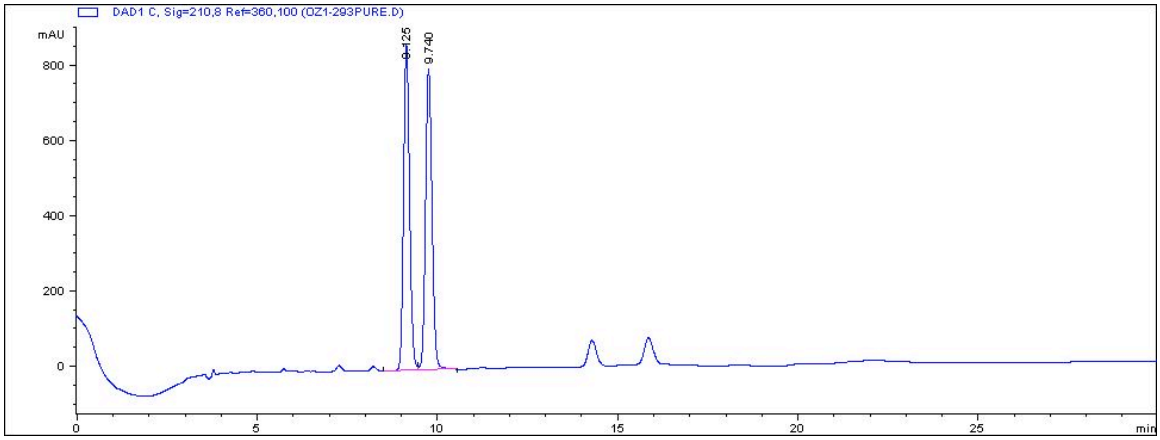
	Retention Time (min)	Area (mVolts*s)
Peak1	34.513	53
Peak2	35.069	52.6

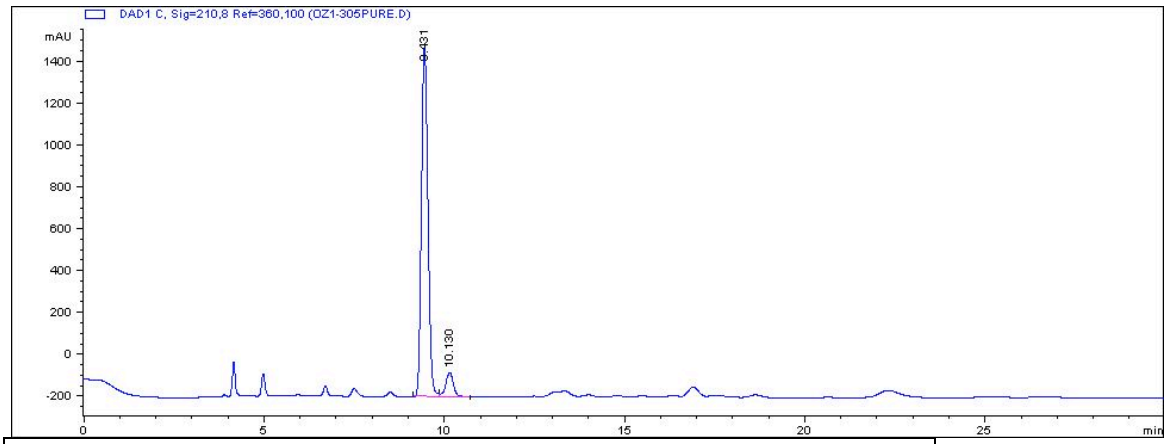


	Retention Time (min)	Area (mVolts*s)
Peak1	34.541	9.31
Peak2	35.164	91.1

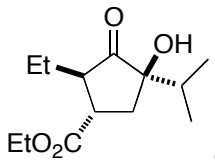


4n

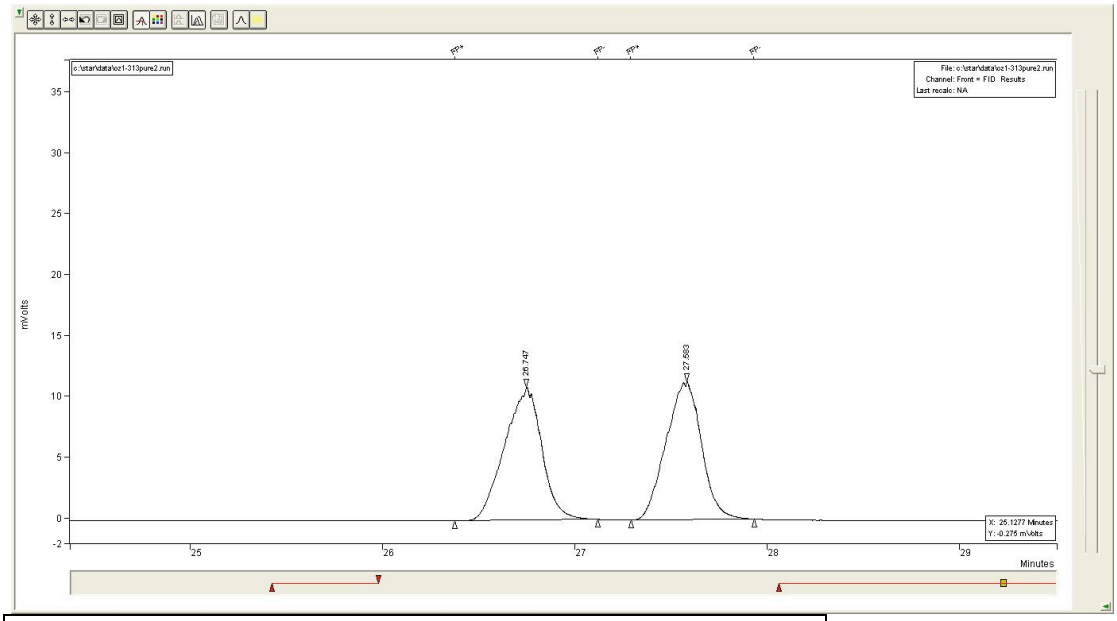




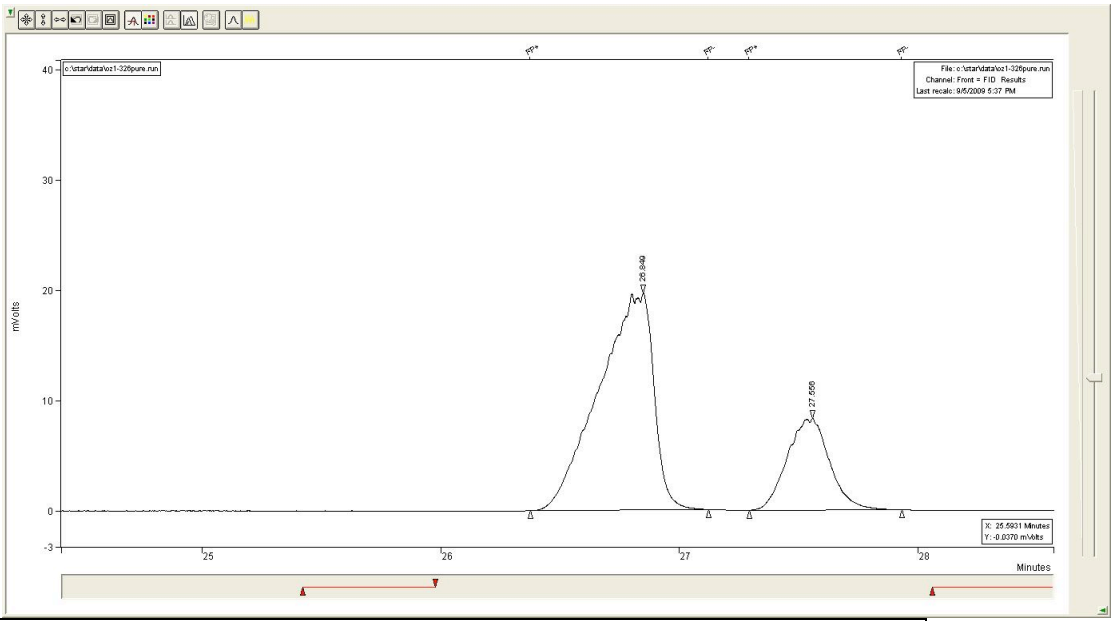
	Retention Time (min)	Area (mAU*s)
Peak1	9.431	5412.71
Peak2	10.14	492.78



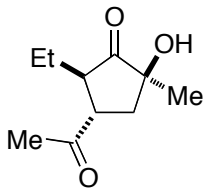
4o



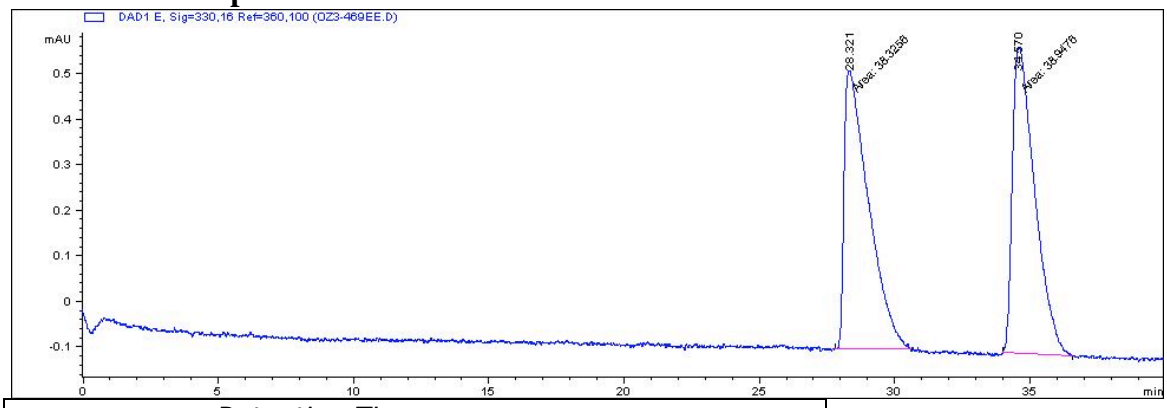
	Retention Time (min)	Area (mVolts*s)
Peak1	26.747	146
Peak2	27.583	145



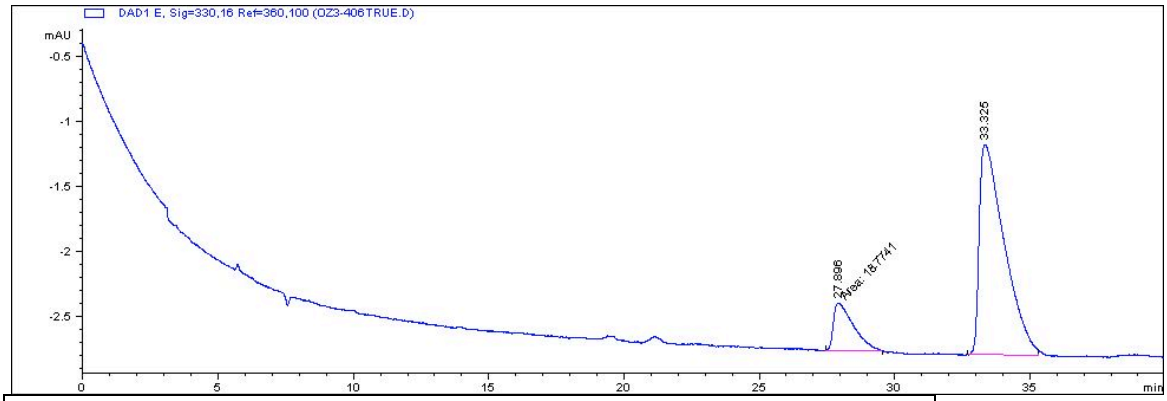
	Retention Time (min)	Area (mVolts*s)
Peak1	26.849	314
Peak2	27.556	101



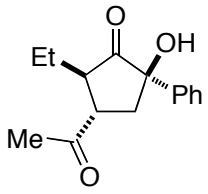
4p



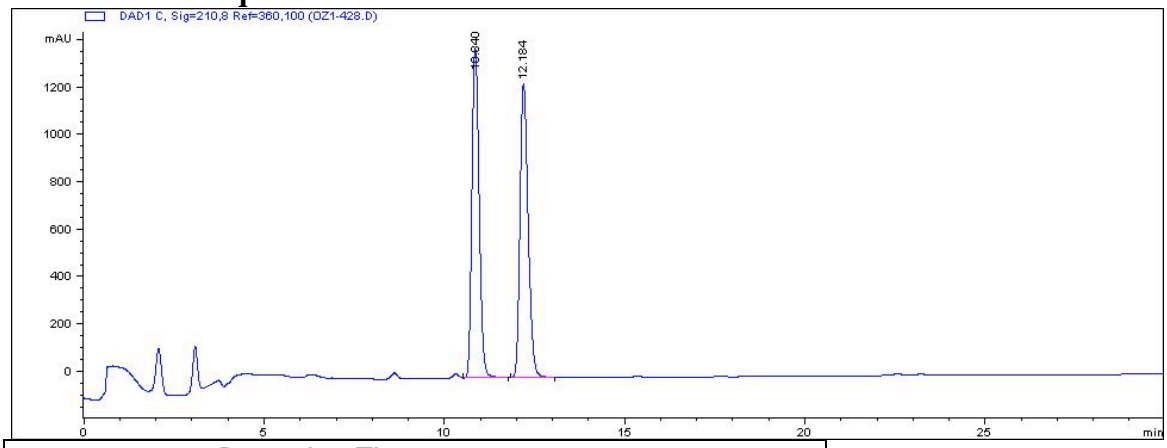
	Retention Time (min)	Area (mAu*s)
Peak1	28.319	38.6
Peak2	34.58	38.6



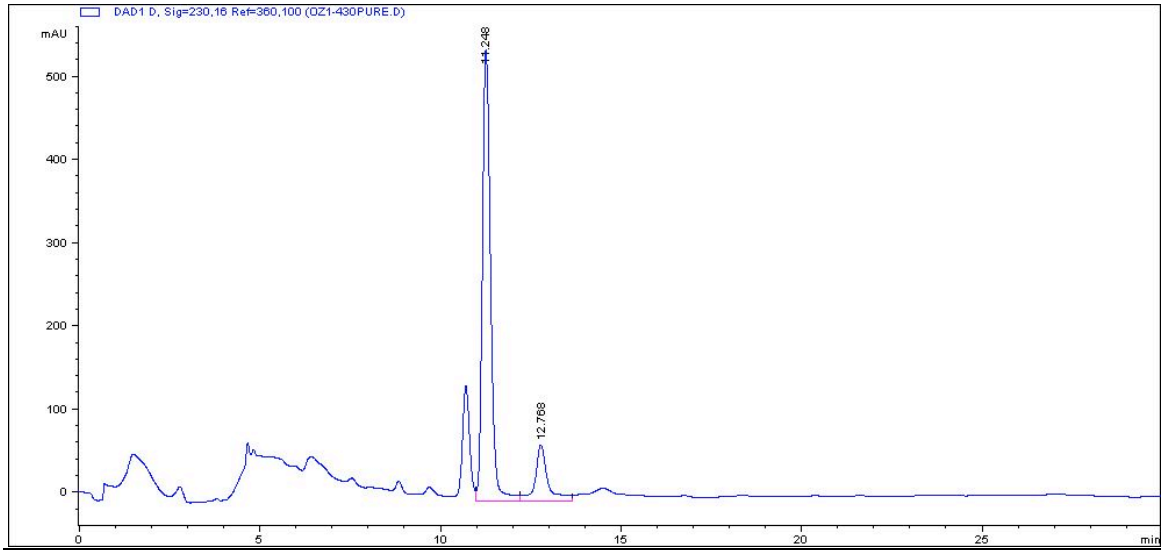
	Retention Time (min)	Area (mAu*s)
Peak1	27.896	19.4485
Peak2	33.316	105.36



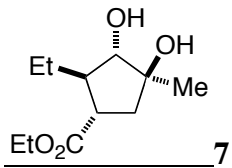
4q



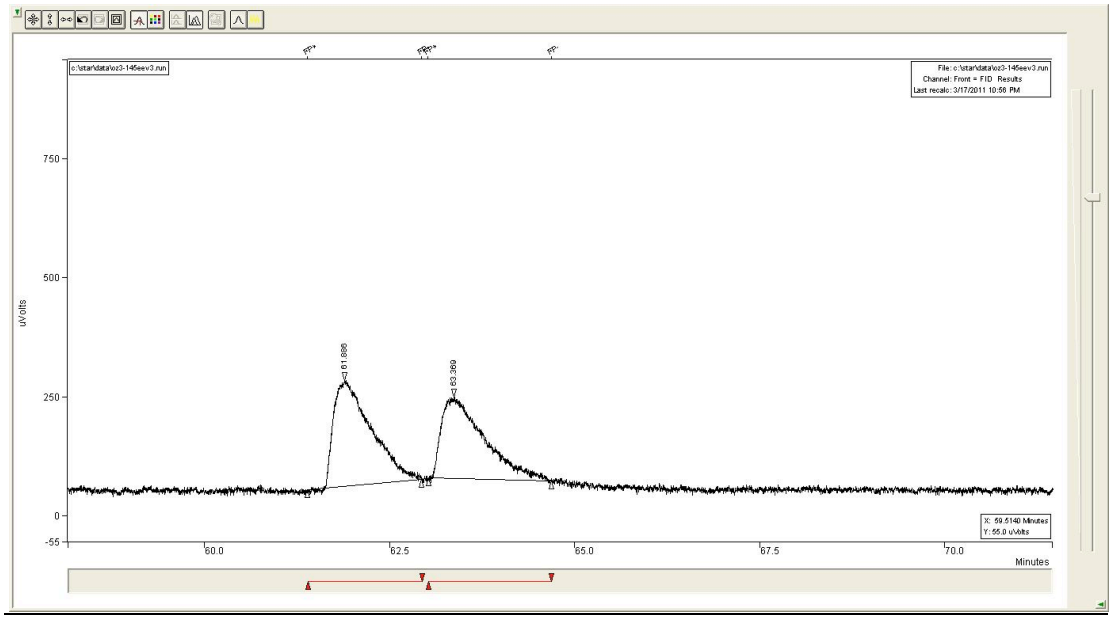
	Retention Time (min)	Area (mAu*s)
Peak1	10.841	5912
Peak2	12.185	5997.3



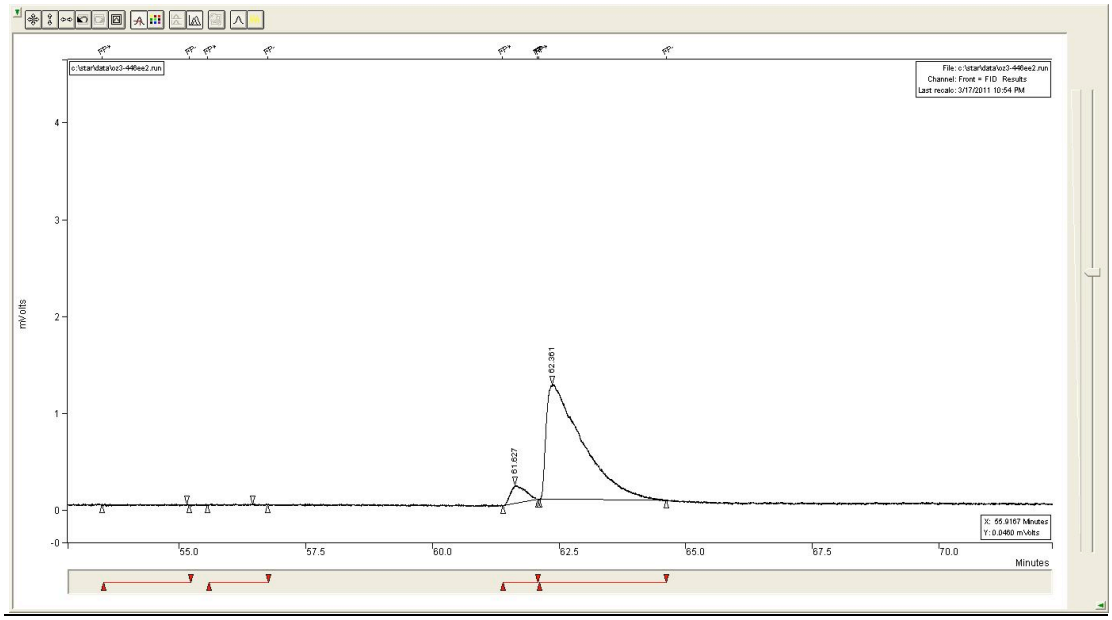
	Retention Time (min)	Area (mAu*s)
Peak1	11.248	8665.3
Peak2	12.768	1749.6



7

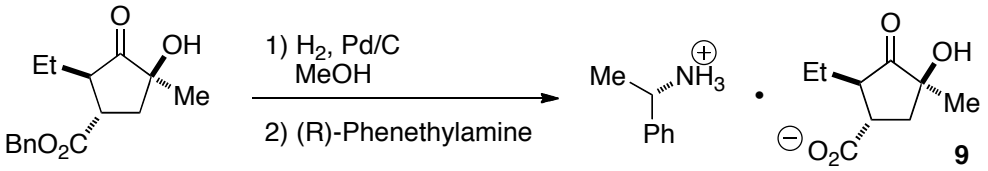


	Retention Time (min)	Area (mVolts*s)
Peak1	61.886	0.78
Peak2	63.369	0.72



	Retention Time (min)	Area (mVolts*s)
Peak1	61.627	3.78
Peak2	62.361	59

X-Ray Crystal Structure and Data



Procedure:
4i was combined with 10% Palladium on Carbon (10 wt%) and suspended in dry methanol. An atmosphere (1 atm) of H_2 was introduced via balloon and stirred at room temperature overnight. The reaction was filtered through a plug of celite and concentrated to an oil. This crude oil was then dissolved in DCM and the amine (1 equiv.) was added. The reaction was concentrated and the product was recrystallized by slow evaporation from methanol.

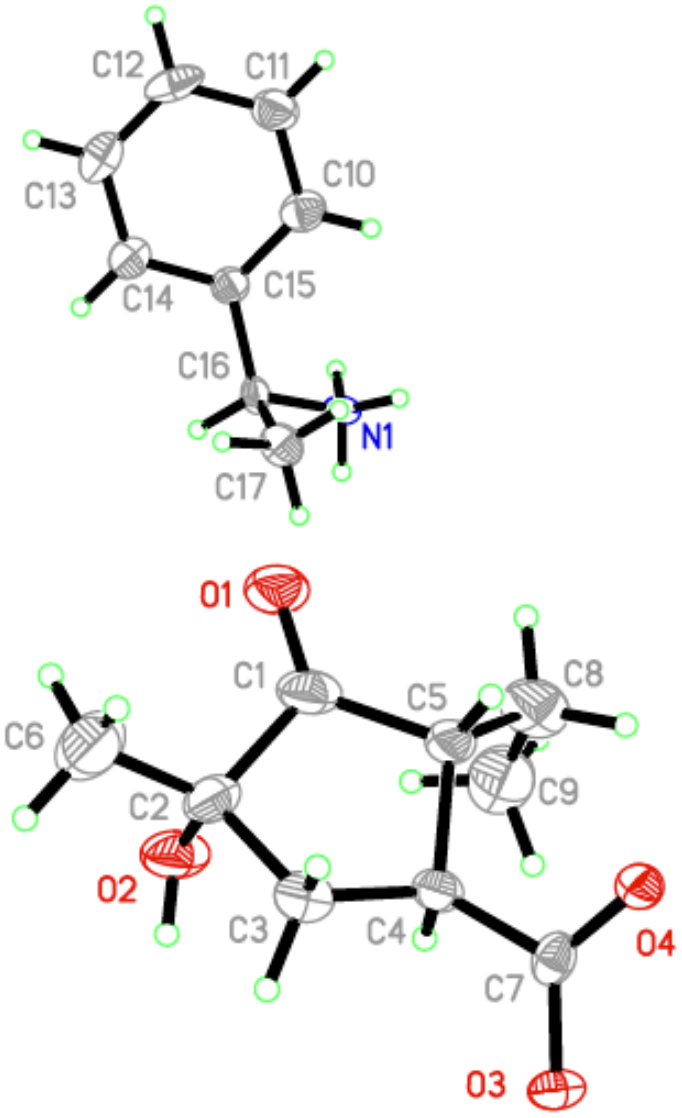

C12
C11
C13
C10
C14
C15
C16
N1
C17
O1
C1
C5
C8
C6
C9
C2
O2
C3
C4
O4
C7
O3

_Table 1. Crystal data and structure refinement for Rovis99_0m.

Identification code	rovis99_0m	
Empirical formula	$C_{17}H_{25}NO_4$	
Formula weight	307.38	
Temperature	120 K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 6.1775(5) Å	α= 90°.
	b = 13.7872(10) Å	β= 90°.
	c = 19.8051(14) Å	γ = 90°.
Volume	1686.8(2) $Å^3$	
Z	4	
Density (calculated)	1.210 Mg/m^3	
Absorption coefficient	0.086 mm^{-1}	
F(000)	664	
Crystal size	0.20 x 0.11 x 0.06 mm^3	
Theta range for data collection	1.80 to 24.41°.	
Index ranges	-7<=h<=7, -15<=k<=16, -23<=l<=23	
Reflections collected	24929	
Independent reflections	2773 [R(int) = 0.1599]	
Completeness to theta = 24.41°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9950 and 0.9835	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2773 / 0 / 204	
Goodness-of-fit on F^2	1.005	
Final R indices [I>2sigma(I)]	R1 = 0.0559, wR2 = 0.1031	
R indices (all data)	R1 = 0.1341, wR2 = 0.1311	
Absolute structure parameter	-1(2)	
Largest diff. peak and hole	0.191 and -0.253 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for Rovis99_0m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	1189(7)	5403(3)	2272(2)	36(1)
C(2)	2746(7)	5442(3)	1665(2)	32(1)
C(3)	1591(7)	4816(3)	1137(2)	30(1)
C(4)	442(7)	4023(3)	1557(2)	25(1)
C(5)	-428(7)	4592(3)	2162(2)	30(1)
C(6)	3355(10)	6445(3)	1442(2)	56(2)
C(7)	-1185(7)	3485(3)	1119(2)	23(1)
C(8)	-945(8)	4013(4)	2802(2)	44(1)
C(9)	849(9)	3380(3)	3045(2)	53(2)
C(10)	6989(8)	4591(3)	9518(2)	33(1)
C(11)	6401(8)	5494(3)	9768(2)	38(1)
C(12)	7823(9)	6258(3)	9735(2)	43(1)
C(13)	9829(9)	6134(4)	9452(2)	46(1)
C(14)	10428(8)	5231(3)	9207(2)	36(1)
C(15)	9024(7)	4455(3)	9239(2)	25(1)
C(16)	9717(6)	3510(3)	8924(2)	23(1)
C(17)	8800(7)	3376(3)	8215(2)	30(1)
N(1)	9017(5)	2659(2)	9347(1)	22(1)
O(1)	1297(5)	5923(2)	2760(2)	47(1)
O(2)	4568(5)	4940(2)	1949(2)	45(1)
O(3)	-396(4)	2840(2)	731(1)	24(1)
O(4)	-3154(5)	3710(2)	1143(1)	27(1)

Table 3. Bond lengths [Å] and angles [°] for Rovis99_0m.

C(1)-O(1)	1.206(5)
C(1)-C(5)	1.514(6)
C(1)-C(2)	1.540(6)
C(2)-O(2)	1.437(5)
C(2)-C(6)	1.499(6)
C(2)-C(3)	1.532(6)
C(3)-C(4)	1.545(5)
C(4)-C(7)	1.521(6)
C(4)-C(5)	1.530(5)
C(5)-C(8)	1.532(6)
C(7)-O(4)	1.256(5)
C(7)-O(3)	1.272(5)
C(8)-C(9)	1.490(6)
C(10)-C(15)	1.386(6)
C(10)-C(11)	1.388(6)
C(11)-C(12)	1.373(6)
C(12)-C(13)	1.371(7)
C(13)-C(14)	1.387(6)
C(14)-C(15)	1.379(5)
C(15)-C(16)	1.506(5)
C(16)-N(1)	1.505(4)
C(16)-C(17)	1.526(5)

O(1)-C(1)-C(5)	126.2(4)
O(1)-C(1)-C(2)	124.8(4)
C(5)-C(1)-C(2)	109.0(4)
O(2)-C(2)-C(6)	111.3(4)
O(2)-C(2)-C(3)	111.1(3)
C(6)-C(2)-C(3)	115.9(4)
O(2)-C(2)-C(1)	99.6(3)
C(6)-C(2)-C(1)	114.8(4)
C(3)-C(2)-C(1)	102.8(4)
C(2)-C(3)-C(4)	104.2(3)
C(7)-C(4)-C(5)	117.7(4)

C(7)-C(4)-C(3)	110.0(3)
C(5)-C(4)-C(3)	102.7(3)
C(1)-C(5)-C(4)	105.0(4)
C(1)-C(5)-C(8)	113.8(4)
C(4)-C(5)-C(8)	117.0(4)
O(4)-C(7)-O(3)	124.5(4)
O(4)-C(7)-C(4)	119.9(4)
O(3)-C(7)-C(4)	115.6(4)
C(9)-C(8)-C(5)	114.7(4)
C(15)-C(10)-C(11)	120.1(5)
C(12)-C(11)-C(10)	120.3(5)
C(13)-C(12)-C(11)	120.2(4)
C(12)-C(13)-C(14)	119.7(5)
C(15)-C(14)-C(13)	120.9(4)
C(14)-C(15)-C(10)	118.9(4)
C(14)-C(15)-C(16)	118.3(4)
C(10)-C(15)-C(16)	122.7(4)
N(1)-C(16)-C(15)	111.3(3)
N(1)-C(16)-C(17)	108.1(3)
C(15)-C(16)-C(17)	112.3(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for Rovis99_0m. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

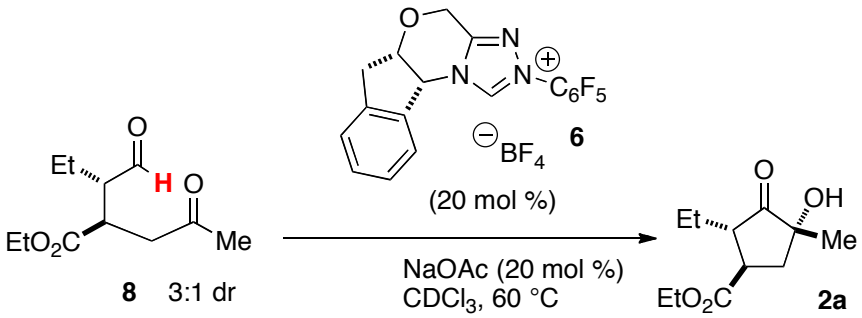
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	28(3)	40(3)	40(3)	-14(3)	-1(2)	12(3)
C(2)	30(3)	26(3)	39(3)	-10(2)	-5(2)	2(2)
C(3)	31(3)	33(3)	28(2)	-2(2)	1(2)	5(2)
C(4)	22(3)	29(3)	24(2)	-6(2)	2(2)	3(2)
C(5)	22(3)	36(3)	33(3)	-15(2)	1(2)	-1(2)
C(6)	79(4)	40(3)	50(3)	-7(3)	8(3)	-15(3)
C(7)	28(3)	21(3)	19(2)	3(2)	-2(2)	-7(2)
C(8)	43(3)	64(4)	25(3)	-10(2)	-3(2)	1(3)
C(9)	65(4)	57(4)	37(3)	0(3)	1(3)	-10(3)
C(10)	39(3)	26(3)	33(3)	4(2)	-1(2)	3(3)
C(11)	42(3)	35(3)	38(3)	1(2)	11(3)	4(3)
C(12)	66(4)	20(3)	43(3)	-3(2)	-4(3)	12(3)
C(13)	52(4)	29(3)	58(3)	-1(3)	2(3)	-10(3)
C(14)	40(3)	29(3)	39(3)	-4(2)	4(2)	-4(3)
C(15)	26(3)	22(3)	27(2)	2(2)	0(2)	2(2)
C(16)	19(2)	22(2)	29(2)	3(2)	4(2)	-4(2)
C(17)	35(3)	36(3)	20(2)	5(2)	4(2)	-1(2)
N(1)	23(2)	22(2)	21(2)	-4(2)	3(2)	4(2)
O(1)	34(2)	57(2)	49(2)	-32(2)	2(2)	-2(2)
O(2)	27(2)	54(2)	54(2)	-29(2)	-7(2)	8(2)
O(3)	26(2)	24(2)	23(2)	-8(1)	-2(1)	6(2)
O(4)	19(2)	27(2)	34(2)	-10(1)	1(1)	0(2)

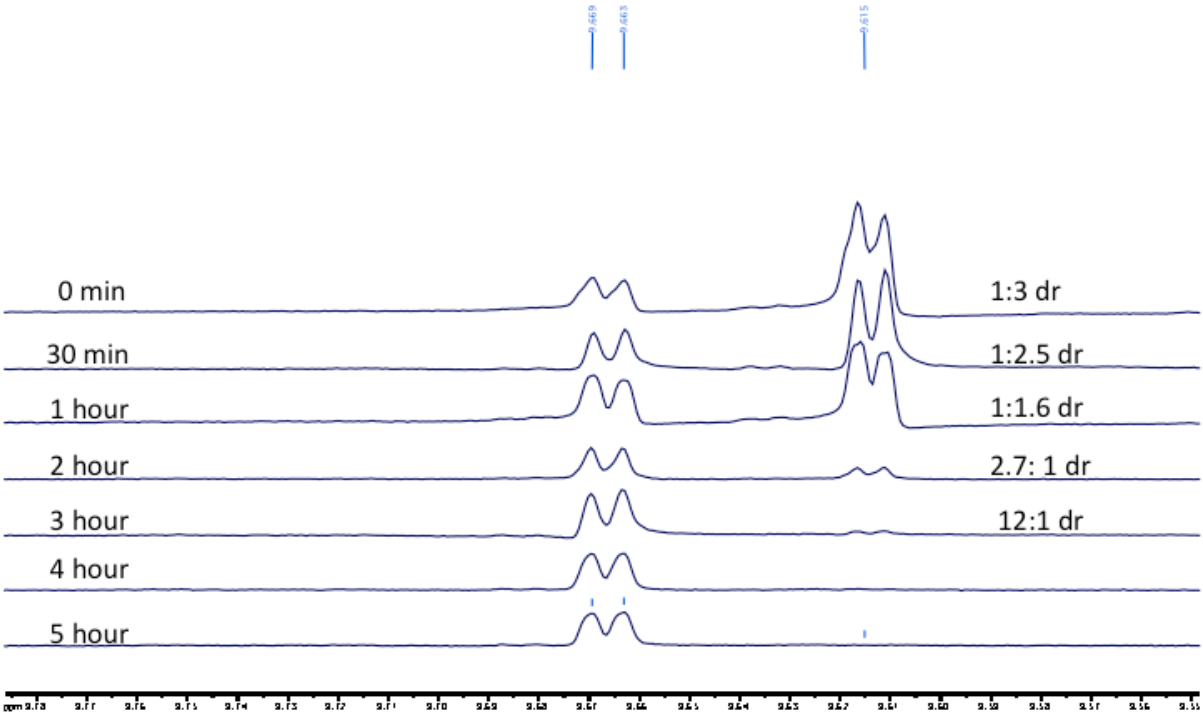
Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for Rovis99_0m.

	x	y	z	U(eq)
H(3A)	2622	4530	826	36
H(3B)	551	5196	884	36
H(4)	1530	3560	1718	30
H(5)	-1783	4897	2017	36
H(6A)	4503	6407	1117	84
H(6B)	3831	6814	1826	84
H(6C)	2121	6755	1242	84
H(8A)	-1322	4464	3159	53
H(8B)	-2204	3611	2716	53
H(9A)	2190	3732	3026	80
H(9B)	945	2815	2763	80
H(9C)	570	3187	3502	80
H(10)	6017	4077	9539	39
H(11)	5038	5582	9958	46
H(12)	7424	6861	9905	51
H(13)	10785	6654	9424	56
H(14)	11796	5148	9019	43
H(16)	11301	3505	8895	28
H(17A)	7248	3403	8233	46
H(17B)	9245	2759	8040	46
H(17C)	9329	3883	7927	46
H(1A)	7626	2533	9269	33
H(1B)	9201	2798	9782	33
H(1C)	9809	2142	9239	33
H(2)	5129	4598	1659	67

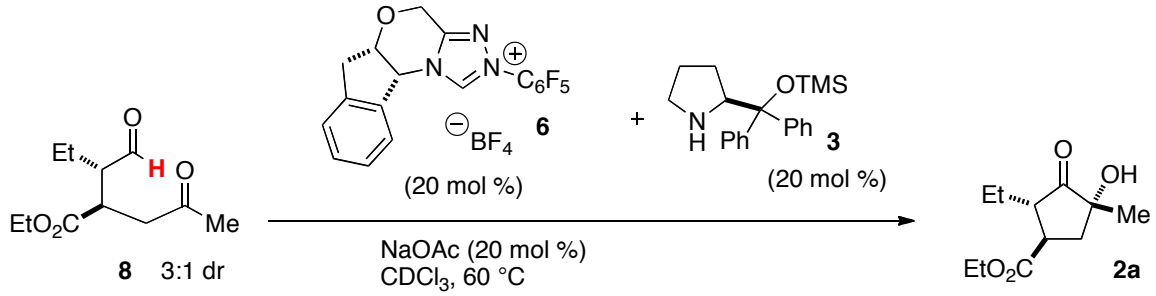
NMR Studies

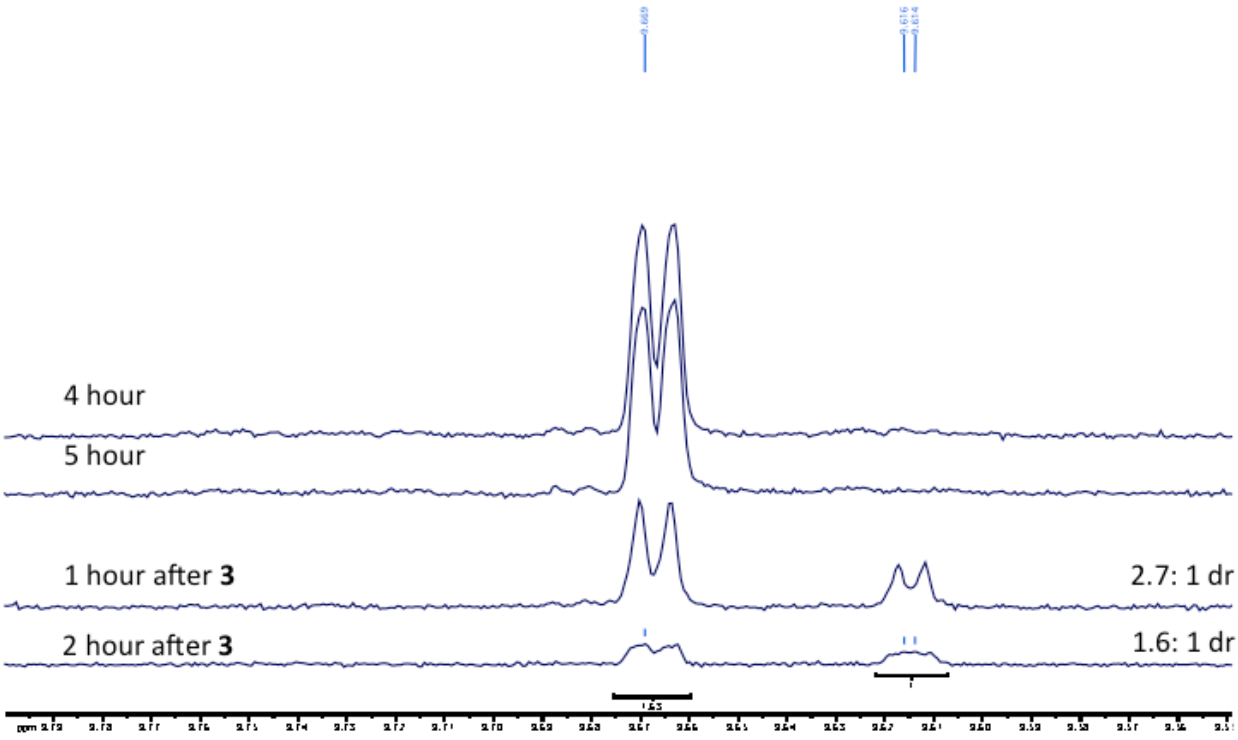
Procedure:
In a 1 dram vial, 25 mg of **8** (0.12 mmol) was combined with 9 mg of **6** (0.2 equiv, 0.02 mmol), 2 mg of NaOAc (0.2 equiv., 0.02 mmol), and 7 mg trimethoxybenzene (internal standard, 0.3 equiv., 0.04 mmol). This mixture was taken up in CDCl3 and transferred to an NMR tube. The tube was heated in an oil bath at 60 °C. Spectra was taken at intervals throughout the reaction.



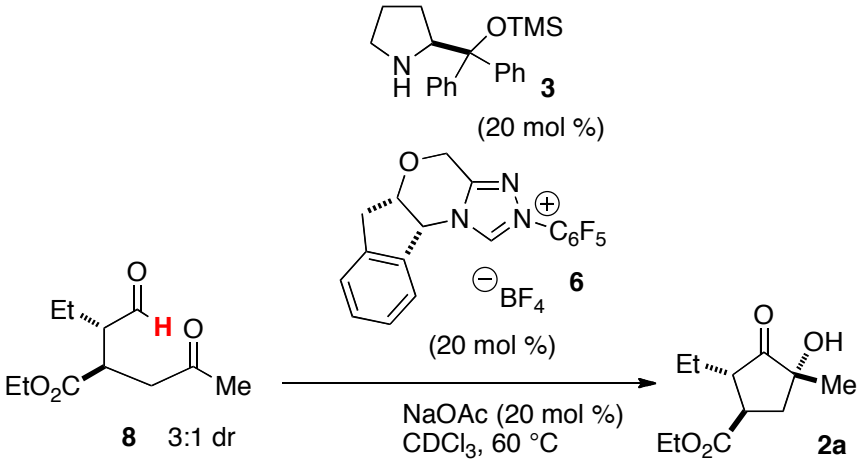


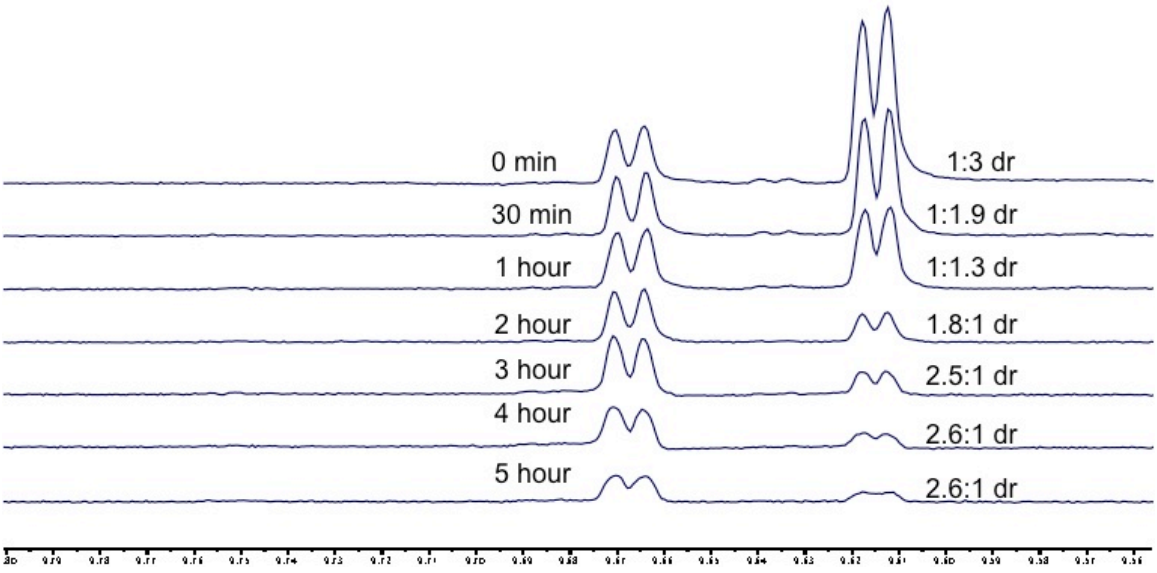
After 5 hours, 6.5 mg of **3** (0.2 equiv., 0.02 mmol) was added and continued heating.





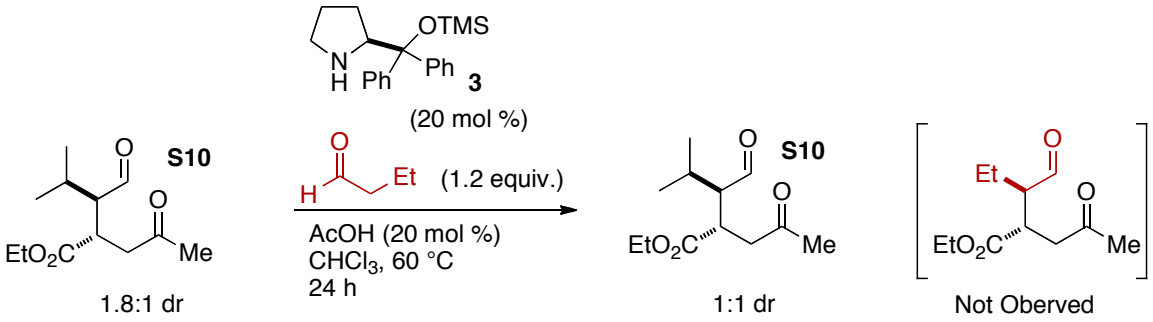
This experiment was repeated, but with amine catalyst **3** present from the beginning.



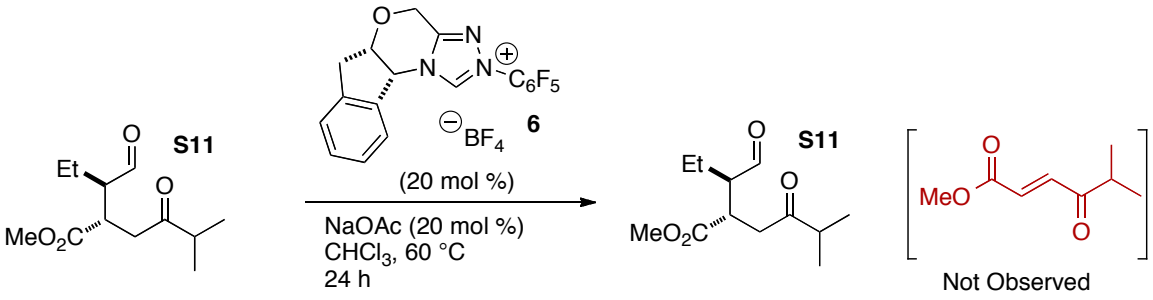


Crossover Experiments

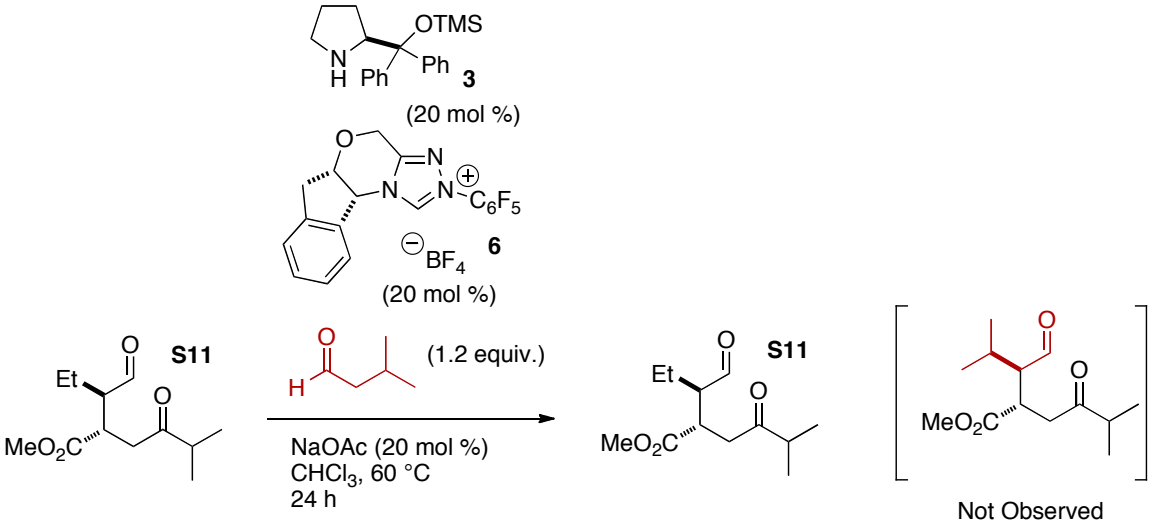
To determine if a retro-Michael was responsible for low diastereoselectivity, a crossover experiment was conducted by heating the intermediate aldehyde with a different aldehyde starting material in the presence of the amine catalyst. No crossover product was observed, indicating that the amine catalyst is not responsible for this pathway.



To determine if the NHC catalyst played a role in the retro-Michael, compound **S11** was exposed catalyst **6**, base, and heat for one day. If the retro-Michael occurred, we would expect formation of starting material **2**. None was observed. Note that the combination of the isopropylketone with bulky catalyst **6** does not provide the benzoin product.



In case the combination of the amine catalyst and the NHC catalyst was responsible, S11 was exposed to both catalysts, isovaleraldehyde, and heat for 1 day. No crossover product was observed.



From these results, we are confident that a retro-Michael is not a factor in this new cascade reaction.