Catalytic Asymmetric α-Alkylation of Aldehydes via a S_N2'-Type Addition-Elimination Pathway

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Electronic Supporting Information

Contents

1. General.

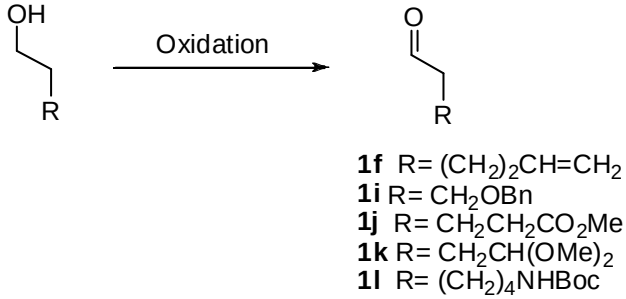
The ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively. The chemical shifts are reported in ppm relative to $CDCl_3$ (δ = 7.26) for ^{1}H NMR and relative to the central resonances of $CDCl_3$ (δ = 77.0) for ^{13}C NMR. Purification of reaction products was carried out by flash column chromatography using ROCC silica gel 60 (0.040-0.063mm, 230-400 mesh). Visualization was accomplished with a solution of phosphomolybdic acid (1 g) in 100 ml of ethanol (limited lifetime), followed by heating. Analytical high performance liquid chromatography (HPLC) was performed on Waters 600E chromatographs, equipped with diode array UV detector, using Daicel Chiralpak IC and OD-H columns. Optical rotations were recorded on a Perkin Elmer polarimeter. MS spectra were recorded on an ESI-ion trap Mass spectrometer (Agilent 1100 series LC/MSD, SL model).

2. Materials.

All solvents were of p.a. quality and were dried by standard procedures prior to use if necessary. Unless otherwise specified, materials were obtained from commercial sources and used without purification. Aldehydes were obtained from commercial sources, purified by distillation before usage, and stored in the fridge at -30ºC under argon, except aldehydes **1f**, **1i**, **1j**, **1k**, and **1l** that were prepared following the procedure described below. Catalyst **5a** was obtained from commercial sources and immediately before use was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$. The combined organic layers were dried over $MgSO_4$ and the solvent evaporated under reduce pressure.

3. Experimental Procedures, Analytical and Spectroscopic Data.

3.1. Preparation of aldehydes:



Aldehydes **1j** and **1k** were prepared according to procedures reported by Watanabe[1] and Tanaka[2] respectively.

3.1.1 Synthesis of aldehydes 1f, and 1i.

The following procedure adapted from Pérez-Castells *et al.*[3] was employed.

A solution of the corresponding alcohol (10 mmol) in dichloromethane (4 mL) was added to a suspension of PCC (15 mmol) in dichloromethane (15 mL) at 0ºC. The resulting mixture was stirred at room temperature until completion of the reaction (TLC). The reaction was diluted by addition of diethyl ether (50 mL) and filtered through a small pad of silica gel (and rinse with Et_2O). The solvent was removed under vacuum at room temperature. The crude product was distilled before usage.

3.1.2 Synthesis of Boc-protected 6-aminohexanal (1l).

The following procedure adapted from Cushman *et al.*[4] was employed.

CH_2Cl_2 (100 mL) and $(COCl)_2$ (3.9 mL, 46 mmol, 1.5 eq.) were successively placed in an oven dried three-necked flask and the solution was cooled to -60^{o}C under dry Ar. DMSO (4.8 mL, 68 mmol) in CH_2Cl_2 (15 mL) was added at a rate where a temperature below -60^{o}C was maintained. The mixture was then stirred for ca. 5 min followed by dropwise addition of a solution of the alcohol (31 mmol) in CH_2Cl_2 (25 mL) over a period of ca. 5 min. The mixture was stirred for an additional 25 min, then rapidly quenched with Et_3N (22 mL, 0.16 mol). The obtained white slurry was stirred for ca. 5 min and then allowed to

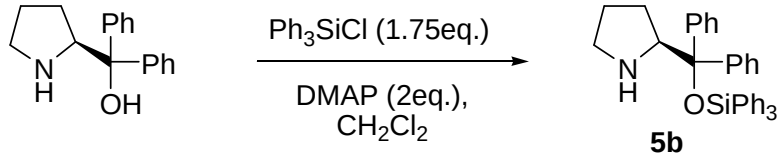
[1] Kai, K.; Takeuchi, J.; Kataoka, T.; Yokoyama, M.; Watanabe, N. *Tetrahedron* **2008**, 6760.
[2] Takeishi, K.; Sugishima, K.; Sasaki, K.; Tanaka, K. Chem. Eur. J. **2004**, *10*, 5681.
[3] Rosillo, M.; Arnáiz, E.; Abdi, D.; Blanco-Urgoiti, J.; Domínguez, G.; Pérez-Castells J. *Eur. J. Org. Chem.* **2008**, 3917.
[4] Xiao, X.; Antony, S.; Kohlhagen, G.; Pommierb, Y.; Cushman, M. *Bioorg. Med. Chem.* **2004**, *12*, 5147.

warm to room temperature. The reaction mixture was washed with water (300 mL) and the aqueous layer was extracted with Et_2O (300 mL). The combined organic layers were washed with brine (2 x 200 mL). The residue was subjected to flash chromatography (eluent: n-hexane/ethyl acetate 5:1), yielding a colorless oil (yield 90%).

3.2. Preparation of 2-(bromomethyl) acrylates 2-4.

2-(Bromomethyl) acrylates **2**, **3** and **4** were prepared by sequential Morita-Baylis-Hillman reaction, according to Ratovelomanana-Vidal,[5] and subsequent bromination, according to Hediger.[6]

3.3. Preparation of catalyst 5b.[7]

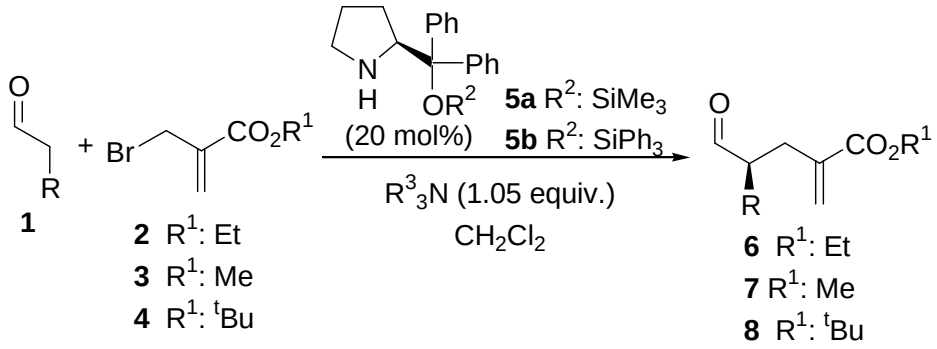


5b

To a solution of (S)-α,α-diphenylprolinol (20 mmol, 5.06g) in dry THF (40 mL) were successively added DMAP (4.88 g, 40 mmol, 2 eq.) and triphenylchlorosilane (10.4g, 35 mmol, 1.75 eq.). The mixture was refluxed for 20h, then cooled to room temperature and quenched with H_2O (10 mL). Solvents were evaporated and to the obtained solid CH_2Cl_2 (100 mL) and H_2O (100 mL) were added. The organic layer was dried ($MgSO_4$), the solvent was evaporated and the crude was purified by flash column chromatography (eluent: from CH_2Cl_2 to CH_2Cl_2/EtOH 95:5). Further crystallization from ethyl acetate afforded pure **5b** as a white solid (7.60g, 15 mmol, 75% yield).

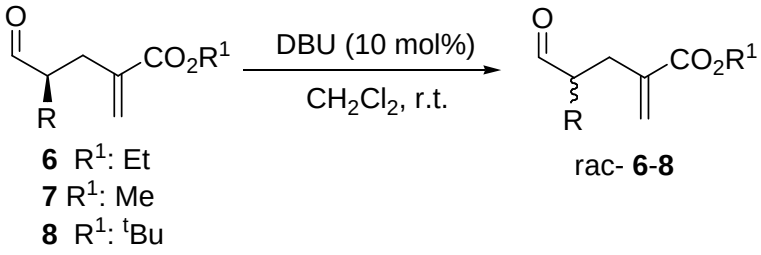
[5] Pautigny, C.; Jeulin, S.; Ayad, T.; Zhang, Z.; Genat, J.P.; Ratovelomanana-Vidal, V. *Adv. Synth. Catal.* **2008**, *350*, 2525..
[6] Hediger, M. E. *Bioorg. Med. Chem.* **2004**, *12*, 4995.
[7] Wang, Y.; Li, P.; Liang, X.; Ye, J. *Adv. Synth. Catal.* **2008**, *350*, 1383.

3.4. General procedure for the catalytic allylation of aldehydes with 2-4.



A solution of the corresponding α-bromomethyl acrylates **2**-**4** (0.5 mmol) and DMAP (or DABCO) (63 mg, 0.51 mmol) in CH_2Cl_2 (1.5 mL) was stirred at room temperature for 30 minutes and then was cooled to the specified temperature (Table 2). To this cooled solution were successively added freshly distilled aldehyde **1** (3 or 4 equiv.; see below) and catalyst **5** (0.1 mmol, 20 mol%). The mixture was stirred at specified temperature and time (see below), then diluted with dichloromethane (10 mL), washed with H_2O (10 mL), HCl 1N (10 mL) and brine (10 mL), and dried with anhydrous $MgSO_4$. The solvent was evaporated under vacuum and the crude material was purified by flash chromatography (eluent EtOAc/Hex from1:99 to 2:98).

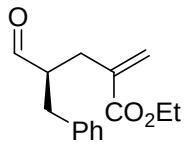
3.5. General procedure for the synthesis of racemic adducts.



To a solution of the corresponding optically active adducts **6**-**8** in CH_2Cl_2 was added DBU (10 mol%). The reaction was stirred at room temperature for 3h and afterwards quenched with H_2O and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with HCl 1N (10 mL) and dried ($MgSO_4$). The product was injected directly in the HPLC without further purification.

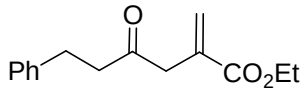
Data of adducts:

Ethyl (R)-4-benzyl-2-methylene-5-oxopentanoate (6a)

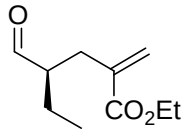


The title compound was prepared from hydrocinnamaldehyde **1a** (1.5 mmol, 3 eq.), ethyl α-bromomethyl acrylate **2** (0.50 mmol) and DMAP (0.51 mmol) at -10ºC for 48h according to the general procedure. Yield: 73 mg, 0.29 mmol, 59%. $[\alpha]_D^{25}$ = +13.7 (c 1.0, CH_2Cl_2, 93% ee). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 9.69 (d, 1H, J= 1.2 Hz), 7.29-7.16 (m, 5H, Ar), 6.24 (d, 1H, J= 1.2 Hz), 5.57 (d, 1H, J= 1.2 Hz), 4.20 (q, 2H, J= 7.2 Hz), 3.03-2.43 (m, 5H), 1.29 (t, 3H, J= 7.2 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 203.5, 166.6, 138.3, 137.6, 129.0, 128.6, 127.4, 126.5, 60.9, 51.9, 35.1, 14.1. The enantiomeric excess was determined by HPLC with Chiralpack IC column at 210nm (hexane/^{i}PrOH in the ratio of 90/10, flow rate = 0.5 mL/min tr= 21.07 min (minor), tr= 26.86 min (major)). HRMS: $C_{15}H_{19}O_3$ $[M+H]^+$ calcd.: 247.1334, found: 247.1351.

With DABCO, 5% of the Stetter adduct was identified. ^{1}H-NMR data of the product Ethyl 2-methylene-4-oxo-6-phenylhexanoate ($CDCl_3$, 200 MHz) δ: 7.31-7.20 (m, 5H), 6.33 (s, 1H), 5.73 (s, 1H), 4.83 (m, 2H), 4.25 (q, 2H, J= 7.2 Hz), 3.00 (m, 1H), 2.71 (m, 1H), 1.31(t, 3H, J= 7.2 Hz).

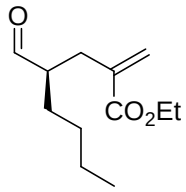


Ethyl (R)-4-formyl-2-methylenehexanoate (6b)



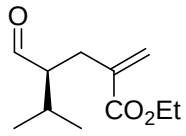
The title compound was prepared from butyraldehyde **1b** (1.5 mmol, 3 eq.), ethyl α-bromomethyl acrylate **2** (0.50 mmol) and DMAP (0.51 mmol) at -10ºC for 48h according to the general procedure. Yield: 58 mg, 0.31 mmol, 63%. $[\alpha]_D^{25}$ = +12.0 (c 1.0, CH_2Cl_2, 92% ee). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 9.61 (d, 1H, J= 2.4 Hz), 6.23 (d, 1H, J= 1.2 Hz), 5.59 (d, 1H, J= 1.2 Hz), 4.22 (q, 2H, J= 7.2 Hz), 2.71 (dd, 1H, J= 13.8, 7.2 Hz), 2.55-2.39 (m, 2H), 1.74-1.52 (m, 2H), 1.31 (t, 3H, J= 7.2 Hz), 0.95 (t, 3H, J= 7.5 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 204.1, 166.7, 137.9, 126.9, 60.8, 52.0, 31.0, 21.8, 14.1, 11.1. The enantiomeric excess was determined by HPLC with Chiralpack IC column at 210nm (hexane/^{i}PrOH in the ratio of 95/5, flow rate = 0.5 mL/min tr= 21.95 min (minor), tr= 25.66 min (major)). HRMS: $C_8H_{11}O_2$ $[M+H-C_2H_6O]^+$ calcd.: 139.0759, found: 139.0765.

Ethyl (R)-4-formyl-2-methyleneoctanoate (6c)



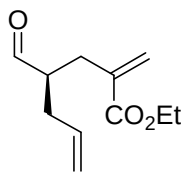
The title compound was prepared from hexanal **1c** (1.5 mmol, 3 eq.), ethyl α-bromomethyl acrylate **2** (0.50 mmol) and DMAP (0.51 mmol) at -10ºC for 48h according to the general procedure. Yield: 64 mg, 0.305 mmol, 61%. $[\alpha]_D^{25}$ = +18.4 (c 1.4, CH_2Cl_2, 94% ee). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 9.59 (d, 1H, J= 1.0 Hz), 6.21 (d, 1H, J= 0.9 Hz), 5.57 (d, 1H, J= 0.9 Hz), 4.20 (q, 2H, J= 7.2 Hz), 2.68 (dd, 1H, J= 14.0, 8.0 Hz), 2.53 (m, 1H), 2.41 (dd, 1H, J= 14.0, 6.2 Hz), 1.66-1.27 (m, 6H), 1.29 (t, 3H, J= 7.1 Hz), 0.88 (t, 3H, J= 6.6 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 204.1, 166.6, 137.9, 126.9, 60.8, 50.6, 31.4, 28.9, 28.5, 22.6, 14.1, 13.7. The enantiomeric excess was determined by HPLC with Chiralpack IC column at 216nm (hexane/^{i}PrOH in the ratio of 90/10, flow rate = 0.5 mL/min tr= 16.93 min (minor), tr= 18.58 min (major)). HRMS: $C_{10}H_{15}O_2$ $[M+H-C_2H_6O]^+$ calcd.: 167.1072, found: 167.1086.

Ethyl (R)-4-formyl-5-methyl-2-methylenehexanoate (6d)



The title compound was prepared from isovaleraldehyde **1d** (1.5 mmol, 4eq.), ethyl α-bromomethyl acrylate **2** (0.50 mmol) and DMAP (0.51 mmol) ato 0ºC for 60h according to the general procedure**.** Yield: 53 mg, 0.27 mmol, 54%. $[\alpha]_D^{25}$ = +12.2 (c 1.0, CH_2Cl_2, 90% ee). ^{1}H NMR (300 MHz, CDCl3) δ 9.64 (d, 1H, J = 2.9 Hz), 6.20 (s, 1H, J= 0.9 Hz), 5.58 (d, 1H. J = 0.9 Hz), 4.20 (q, 2H, J = 7.1 Hz), 2.74 – 2.35 (m, 3H), 2.11– 2.00 (m, 1H), 1.30 (t, 3H, J = 7.1 Hz), 1.01 (d, 6H, J = 6.9 Hz) .^{13}C NMR (75 MHz, CDCl3) δ 204.58, 166.76, 138.36, 126.90, 60.81, 56.74, 28.58, 28.45, 19.87, 19.63, 14.16. The enantiomeric excess was determined by HPLC with Chiralpack IC column at 210nm (hexane/^{i}PrOH in the ratio of 95/5, flow rate = 0.5 mL/min tr= 23.19 min (minor), tr= 25.19 min (major)). HRMS: $C_9H_{13}O_2$ $[M+H-C_2H_6O]^+$ calcd.: 153.0916, found: 153.0914.

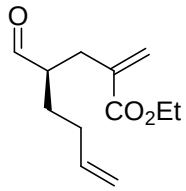
Ethyl (R)-4-formyl-2-methylenehept-6-enoate (6e)



The title compound was prepared from pent-4-enal **1e** (2.0 mmol, 4 eq.), ethyl α-bromomethyl acrylate **2** (0.50 mmol) and DMAP (0.51 mmol) at -20ºC for 60h according to the general procedure. Yield: 61 mg, 0.31 mmol, 63%. $[\alpha]_D^{25}$ = + 5.5 (c 1.0, CH_2Cl_2, 95% ee). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 9.65 (d, 1H, J= 1.2 Hz), 6.25 (d, 1H, J= 1.2 Hz), 5.82-5.69 (m, 1H), 5.60 (d,

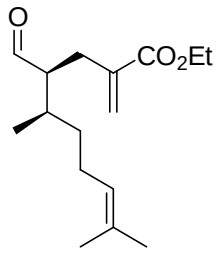
1H, J= 1.2 Hz), 5.10 (m, 2H), 4.21 (q, 2H, J= 7.2 Hz), 2.75-2.20 (m, 5H), 1.31 (t, 3H, J= 7.2 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 203.4, 166.6, 137.6, 134.4, 127.3, 117.6, 60.8, 49.8, 32.9, 30.9, 14.1. The enantiomeric excess was determined by HPLC with Chiralpack IC column at 212nm (hexane/^{i}PrOH in the ratio of 95/5, flow rate = 0.5 mL/min tr= 22.22 min (minor), tr= 24.38 min (major)). HRMS: $C_9H_{11}O_2$ $[M+H-C_2H_6O]^+$ calcd.: 151.0759, found: 151.0734.

Ethyl (R)-4-formyl-2-methyleneoct-7-enoate (6f)



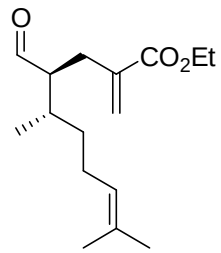
The title compound was prepared from hex-5-enal **1f** (2.0 mmol, 4 eq.), ethyl α-bromomethyl acrylate **2** (0.50 mmol) and DMAP (0.51 mmol) at -20ºC for 60h according to the general procedure. Yield: 72 mg, 0.345 mmol, 69%. $[\alpha]_D^{25}$ = + 11.0 (c 1.0, CH_2Cl_2, 93% ee). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 9.60 (d, 1H, J= 2.4 Hz), 6.21 (s, 1H), 5.81-5.68 (m, 1H), 5.57 (d, 1H, J= 1.2 Hz), 5.04-4.96 (m, 2H), 4.19 (q, 2H, J= 7.2 Hz), 2.69 (dd, 1H, J= 13.8, 7.8 Hz), 2.53 (m, 1H), 2.41 (dd, 1H, J= 14.0, 6.0 Hz), 2.08 (m, 2H), 1.74 (m, 1H), 1.52 (m, 1H), 1.28 (t, 3H, J= 7.2 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 203.2, 166.2, 137.6, 137.2, 126.7, 115.2, 60.5, 49.6, 31.2, 30.6, 27.7, 13.9. The enantiomeric excess was determined by HPLC with Chiralpack IC column at 210nm (hexane/^{i}PrOH in the ratio of 99/1, flow rate = 0.5 mL/min tr= 35.5 min (minor), tr= 39.9 min (major)). HRMS: $C_{10}H_{13}O_2$ $[M+H-C_2H_6O]^+$ calcd.: 165.0916, found: 165.0930.

Ethyl (4S,5R)-4-formyl-5,9-dimethyl-2-methylenedec-8-enoate (6g)



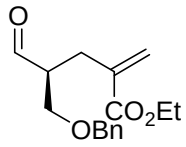
The title compound was prepared from (R)-(+)-citronellal **1g** (1.5 mmol, 3 eq.), ethyl α-bromomethyl acrylate **2** (0.50 mmol) and DMAP (0.51 mmol) at 20ºC for 48h according to the general procedure. Yield mixture: 90 mg, 0.34 mmol, 68% (diastereomeric ratio 75:25). ^{1}H NMR (mayor) (300 MHz, $CDCl_3$) δ 9.64 (d, 1H, J = 2.4 Hz), 6.21 (d, 1H, J= 0.9 Hz), 5.60 (d, 1H, J = 0.9 Hz), 5.08 (m, 1H), 4.21 (q, 2H, J = 6.9 Hz), 2.71–2.41 (m, 3H), 2.05–1.90 (m, 3H), 1.69 (s, 3H), 1.64 (s, 3H), 1.50 (m, 1H), 1.34 (t, 3H, J = 7.2 Hz), 0.95 (d, 2H, J= 6.9 Hz), 0.90 (m, 2H).

Ethyl (4S,5S)-4-formyl-5,9-dimethyl-2-methylenedec-8-enoate (6h)



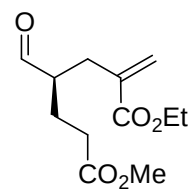
The title compound was prepared from (S)-(-)-citronellal **1h** (1.5 mmol, 3 eq.), ethyl α-bromomethyl acrylate **2** (0.50 mmol) and DMAP (0.51 mmol) at 20ºC for 48h according to the general procedure. Yield: 93 mg, 0.35 mmol, 70% (diastereomeric ratio 97:3). ^{1}H NMR (major) (300 MHz, $CDCl_3$) δ 9.71 (d, 1H, J= 2.6 Hz), 6.24 (d, 1H, J= 1.2 Hz), 5.62 (d, 1H, J= 1.2 Hz), 5.11 (m, 1H), 4.24 (q, 2H, J= 7.1 Hz), 2.76 (dd, 1H, J= 14.0, 8.8 Hz), 2.66–2.35 (m, 2H), 2.17–1.90 (m, 3H), 1.72 (s, 3H), 1.64 (s, 3H), 1.50 (m, 1H), 1.34 (t, 3H, J = 7.1 Hz), 1.04 (d, 2H, J = 6.9 Hz), 0.90 (m, 2H). ^{13}C NMR (major) (75 MHz, $CDCl_3$) δ 204.6, 166.7, 138.4, 131.9, 126.0, 123.9, 111.3, 60.8, 55.4, 34.2, 33.5, 28.78, 25.7, 17.7, 16.59, 14.2. HRMS: $C_{16}H_{26}O_3$ $[M+H]^+$ calcd.: 267.1960, found: 267.1963.

Ethyl (S)-5-(benzyloxy)-4-formyl-2-methylenepentanoate (6i)



The title compound was prepared from aldehyde **1i** (1.5 mmol, eq.), ethyl α-bromomethyl acrylate **2** (0.50 mmol) and DMAP (0.51 mmol) at -10ºC for 60h according to the general procedure. Yield: 81 mg, 0.29 mmol, 59%. $[\alpha]_D^{25}$ = +7.7 (c 0.5, CH_2Cl_2, 68% ee). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 9.78(d, 1H, J= 1.2 Hz), 7.38-7.30 (m, 5H, Ar), 6.25 (d, 1H, J= 1.2 Hz), 5.62 (d, 1H, J= 1.2 Hz), 4.52 (s, 2H), 4.23 (q, 2H, J= 7.2 Hz), 4.22 (ddd, 2H, J= 25.8, 9.6, 4.8 Hz), 2.88-2.50 (m, 3H), 1.32 (t, 3H, J= 7.2 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 202.6, 166.6, 137.8, 137.5, 128.4, 127.8, 127.6, 127.4, 73.3, 67.9, 60.8, 50.9, 29.7, 28.5, 14.1. The enantiomeric excess was determined by HPLC with Chiralpack IC column at 210nm (hexane/^{i}PrOH in the ratio of 95/5, flow rate = 0.5 mL/min tr= 43.2 min (minor), tr= 57.3 min (mayor)).

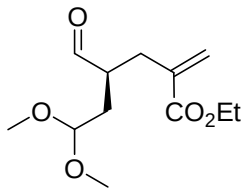
(R)-1-Ethyl 7-methy 4-formyl-2-methyleneheptanedioate (6j)



The title compound was prepared from methyl 5-oxopentanoate **1j** (1.5 mmol, 3 eq.), ethyl α-bromomethyl acrylate **2** (0.50 mmol) and DMAP (0.51 mmol) at –10 ºC for 60 hours according to the general procedure. Yield: 75 mg, 0.31 mmol, 62%. $[\alpha]_D^{25}$ = +3.2 (c 1.0, CH_2Cl_2, 90% ee). ^{1}H NMR (300 MHz, CDCl3) δ 9.62 (d, 1H, *J* = 2.1), 6.25 (d, 1H, *J* = 0.9), 5.62 (d, 1H, *J* = 1.1), 4.31 – 4.10 (m, 2H), 3.66 (d, 3H, *J* = 2.8), 2.80 – 2.53 (m, 2H), 2.48 – 2.28 (m, 3H), 1.96 (ddd, 1H, *J* = 4.8, 9.6, 22.5), 1.87 – 1.63 (m, 1H), 1.30 (t, 3H, *J* = 7.1), 0.92 – 0.81

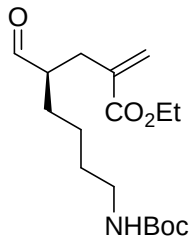
(m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.00, 173.19, 166.47, 135.46, 127.89, 60.91, 49.71, 31.43, 31.14, 23.47, 14.09. The enantiomeric excess was determined by HPLC with Chiralpack IC column at 220nm (hexane/^{i}PrOH in the ratio of 80/20, flow rate = 0.5 mL/min tr= 34.54 min, tr= 37.70 major).

Ethyl (S)-4-formyl-6,6-dimethoxy-2-methylenehexanoate (6k)



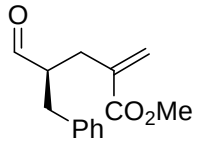
The title compound was prepared from 4,4-dimethoxybutanal **1k** (1.5 mmol), ethyl α-bromomethyl acrylate **2** (0.50 mmol) and DMAP (0.51 mmol) at –10 ºC for 60 hours according to the general procedure. Yield: 71 mg, 0,29 mmol, 58%. $[\alpha]_D^{25}$ = +5.4 (c1.0, CH_2Cl_2, 87% ee). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 9.69(d, 1H, J= 1.2 Hz), 7.29-7.16 (m, 5H, Ar), 6.24 (d, 1H, J= 1.2 Hz), 5.57 (d, 1H, J= 1.2 Hz), 4.20 (q, 2H, J= 7.2 Hz), 3.03-2.43 (m, 5H), 1.29 (t, 3H, J= 7.2 Hz). ^{13}C NMR (75 MHz, CDCl3) δ 203.03, 166.21, 137.47, 127.45, 103.08, 60.92, 53.85, 53.27, 46.62, 32.39, 31.69, 14.09. The enantiomeric excess was determined by HPLC with Chiralpack IC column at 220nm (hexane/^{i}PrOH in the ratio of 80/20, flow rate = 0.5 mL/min tr= 21.10 min, tr= 27.38 major).

Ethyl (R)-8-(tert-butoxycarbonylamino)-4-formyl-2-methyleneoctanoate (6l)



The title compound was prepared from N-Boc-amino-1-hexanal **1l** (1.5 mmol), ethyl α-bromomethyl acrylate **2** (0.50 mmol) and DMAP (0.51 mmol) at -10ºC for 60h according to the general procedure. Yield: 102 mg, 0.31 mmol, 62%. $[\alpha]_D^{25}$ = +15.4 (c 1.0, CH_2Cl_2, 94% ee). ^{1}H NMR (300 MHz, CDCl3) δ 9.58 (d, 1H, J = 2.5), 6.21 (d, 1H, J = 1.0), 5.57 (d, 1H, J = 1.1), 4.53 (s, 1H), 4.19 (q, 2H, J = 7.1), 3.18 – 3.00 (m, 2H), 2.67 (dd,1H, J = 7.5, 13.6), 2.59 – 2.45 (m, 1H), 2.39 (dd, 1H, J = 5.2, 13.5), 1.42 (s, 12H), 1.27 (dd, 5H, J = 6.7, 13.8,), 0.84 (dd, 1H, J = 4.3, 10.9,). ^{13}C NMR (75 MHz, CDCl3) δ 203.85, 166.62, 155.96, 137.71, 127.13, 60.88, 50.53, 40.20, 31.44, 30.07, 28.40, 24.00, 14.14. The enantiomeric excess was determined by HPLC with Chiralpack IC column at 210nm (hexane/^{i}PrOH in the ratio of 70/30, flow rate = 0.5 mL/min tr= 27.2 min (major), tr= 30.5 min (minor)).

Methyl (R) 4-benzyl-2-methylene-5-oxopentanoate (7a)

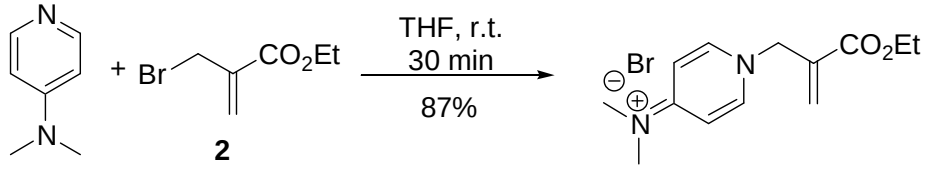


The title compound was prepared from hydrocinnamaldehyde **1a** (1.5 mmol), methyl α-bromomethyl acrylate **3** (0.50 mmol) and DMAP (0.51 mmol) at –10 ºC for 60 hours according to the general procedure. Yield: 66 mg, 0.28 mmol, 57%. $[\alpha]_D^{25}$ = + 6.2 (c 1.0, CH_2Cl_2, 94% ee). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: ^{1}H NMR (300 MHz, CDCl3) δ 9.66 (d, 1 H, *J* = 2.0 Hz), 7.38 – 7.08 (m, 5H), 6.23 (s, 1H), 5.57 (d, 1H, *J* = 1.1 Hz), 3.72 (s, 3H), 2.95 (tt, 2H, *J* = 4.8, 7.7 Hz), 2.81 – 2.66 (m, 2H), 2.44 (dd, 1H, *J* = 4.6, 14.6 Hz). ^{13}C NMR (75 MHz, CDCl3) δ 208.14, 203.35, 166.98, 138.16, 137.24, 128.95, 128.49, 127.58, 126.47, 51.86, 51.75, 35.04, 31.34. The enantiomeric excess was determined by HPLC with Chiralpack IC column at 220nm (hexane/^{i}PrOH in the ratio of 85/15, flow rate = 0.5 mL/min tr= 19.8 min, tr= 23.1 major).

3.6. Catalytic alkylation of butanal with preformed ammonium salt.

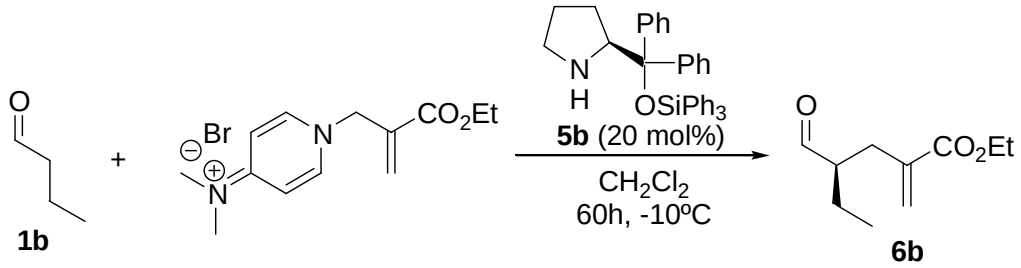
3.6.1. Generation and isolation of ammonium salt from bromide 2 and DMAP.

(Addapted from Mayr et al, *Chem. Eur. J.* **2010**, *16*, 1365-1371)



To a solution of the ethyl α-bromomethyl acrylate **2** (190 mg, 1.0 mmol) in THF (5 mL) at room temperature was added DMAP (126 mg, 1.1 mmol). After 1 min of stirring of the initial solution, a white solid appeared. The mixture was stirred for ca. 30 min. and afterwards the solid was filtered off and washed with THF giving 272 mg (87% yield) of the ammonium bromide salt as a white solid. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 8.64 (d, 2H, J= 7.8 Hz), 6.88 (d, 2H, J= 7.8 Hz), 6.87 (s, 1H), 6.58 (s, 1H), 5.31 (s, 2H), 4.18 (q, 2H, J= 7.0 Hz), 1.29 (t, 3H, J= 7.0 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 165.1, 156.3, 142.9, 134.0, 133.6, 107.7, 61.5, 57.5, 40.4, 14.0. Anal. calcd. for $C_{13}H_{19}BrN_2O_2$ (315.21): C, 49.54; H, 6.08; N, 8.89. Found: C, 49.36; H, 5.90; N, 9.09.

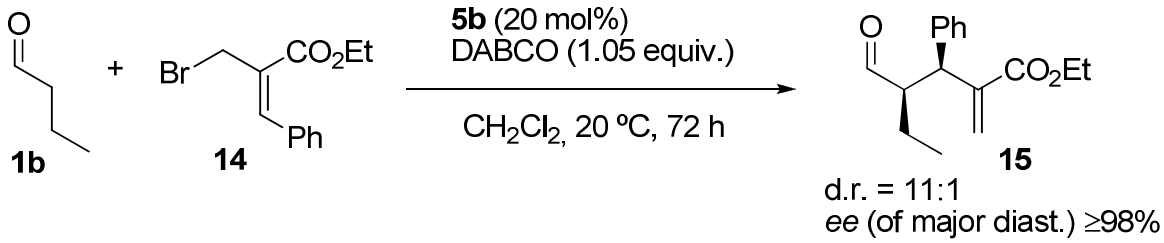
3.6.2. Catalytic allylation of butanal with the ammonium salt.



To a cooled solution of DMAP-**2** salt (61 mg, 0.19 mmol) were successively added freshly distilled butanal **1b** (52 μL, 0.58 mmol, 3 equiv.) and catalyst **5b** (19 mg, 0.038 mmol, 20 mol%). The mixture was stirred at -10 ºC for 60 h, then diluted with dichloromethane (10 mL), washed with H_2O (10 mL), HCl 1N (10 mL) and brine (10 mL), and dried with anhydrous $MgSO_4$. The solvent was evaporated under vacuum and the crude material was purified by flash chromatography (eluent EtOAc/Hex from1:99 to 2:98). Yield: 20 mg (0.11 mmol, 57 %); *ee* 90 %.

All physic and spectroscopic data of thus obtained product were identical to the sample obtained following the catalytic General Procedure above.

3.7. Catalytic alkylation of butanal with ethyl 2-(bromomethyl) cinnamate 14.

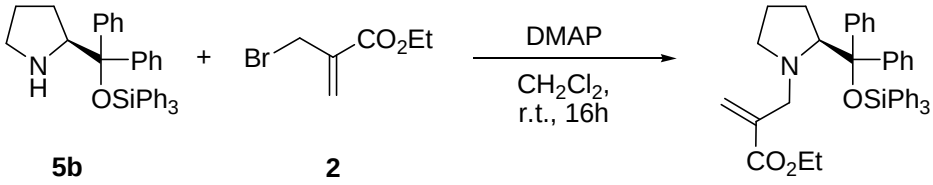


The General Procedure for the catalytic alkylation of aldehydes was followed, starting from butyraldehyde **1b** (5.36 mmol, 4 equiv., 704 μL), ethyl 2-(bromomethyl) cinnamate (1.34 mmol, 350 mg) and DABCO (1.36 mmol, 152 mg), at 0 ºC for 72 h. Only the shown regioisomer was detected as an 11:1 mixture of diastereomers. Yield: 139 mg, 0.53 mmol, 40%. ^{1}H-NMR (mayor) ($CDCl_3$, 300 MHz) δ: 9.50 (d, 1H, J= 4.2 Hz), 7.32-7.24 (m, 5H), 6.34 (s, 1H), 5.7 (s, 1H), 4.20-4.09 (m, 3H), 2,82 (m, 1H), 1.43-1.40 (m, 2H), 1.21 (t, 3H, J= 7.2 Hz), 0.81 (t, 3H, J= 7.2 Hz). ^{13}C-NMR (mayor) (75 MHz, $CDCl_3$) δ: 203.7, 166.3, 141.8, 139.6, 135.5, 128.6, 127.0, 125.5, 60.9, 56.7, 45.8, 21.2, 14.0, 11.1. The diastereomeric ratio (11:1) was determined by ^{1}H-NMR. The enantiomeric excess was

determined by HPLC with Chiralpack IC column at 210nm (hexane/$_i$PrOH in the ratio of 90/10, flow rate = 0.5 mL/min tr= 18.55 min (major), tr= 19.63 min (minor)).

3.8. Preparation of control sample by N-alkylation of catalyst 5b.

For control purposes, N-alkylation of pyrrolidine **5b** was carried out as follow:



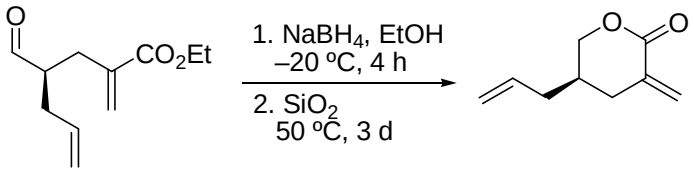
5b **2**

A solution of ethyl α-bromomethyl acrylate **2** (47.5 mg, 0.25 mmol) and DMAP (31.1 mg, 0.255 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 30 minutes and after this period catalyst **5b** was added (51 mg, 0.1 mmol). The mixture was stirred at room temperature for 16h and after this time, the reaction mixture was diluted with dichloromethane (5 mL), washed with H_2O (5 mL) and HCl 1N (5 mL), and dried with anhydrous $MgSO_4$. The solvent was evaporated and the crude compound was purified by flash chromatography (eluent EtOAc/Hex 1:5). Yield: 56 mg, 0.09 mmol, 90%. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.48-7.24 (m, 25H), 6.25 (s, 1H), 5.82 (d, 1H, J= 1.8 Hz), 4.11 (m, 2H), 3.86 (dd, 1H, J= 9.4, 3.6 Hz), 3.25 (m, 2H), 2.80 (m, 1H), 2.20-1.03 (m, 5H), 1.25 (t, 3H, J= 7.2 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.8, 144.6, 143.9, 139.2, 136.2, 135.5, 129.9, 129.5, 129.2, 127.4, 127.0, 126.9, 126.8, 125.1, 86.3, 72.6, 60.2, 58.2, 55.0, 29.7, 24.1, 14.1.

3.9. Elaboration of adducts:

3.9.1. Lactonization:

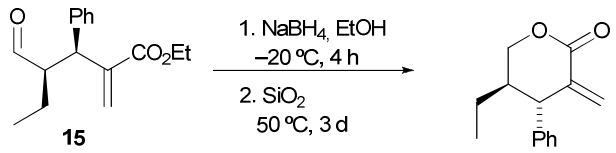
Synthesis of (R)-5-allyl-3-methylene-tetrahydropyran-2-one 10.[8]



6e **10**

115 mg (0,58 mmol, 1.0 equiv.) of **6e** was solved in 1.5 mL of EtOH. The solution was cooled to -20 °C and 7 mg (0.18 mmol) of $NaBH_4$ was added. The reaction mixture was stirred at this temperature for 4 h, then diluted with dichloromethane (10mL) and poured in H_2O (10 mL). Water phase was extracted three times with dichloromethane and the combined organic layers were dried with anhydrous $MgSO_4$. After evaporation of the solvents under vacuum the crude product was dissolved in 1.5 mL of dichloromethane. 250 mg of silica gel was added and the mixture stirred at 50ºC for 3 days. After filtration the solvent was evaporated under vacuum and the crude product was purified by column chromatography (eluent EtOAc/hexane 1:7) giving product **10** as viscous oil. Yield: 78 mg, 0.51 mmol, 89%. $[\alpha]_D^{25}$ = -2.0 (c 1.25, CH_2Cl_2, 99% ee) (Lit: $[\alpha]_D^{25}$ = -4.24 (c 1.25, CH_2Cl_2)[8]. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 6.46 (d, 1H, J= 2.1 Hz), 5.79 (m, 1H), 5.59 (d, 1H, J= 2.1 Hz), 5.07-5.03 (m, 2H), 4.32 (ddd, 1H, J= 11.2, 3.2, 2.1 Hz), 4.08 (ddd, 1H, J= 11.2, 8.4, 3.2 Hz), 2.81 (m, 1H), 2.36 (m, 1H), 2.16 (m, 3H). The enantiomeric excess was determined by HPLC with Chiralpack OD-H column at 220nm (hexane/^{i}PrOH in the ratio of 99/1, flow rate = 0.5 mL/min tr= 41.7 min (minor), tr= 42.6 min (major)). HRMS: $C_9H_{13}O_2$ $[M+H]^+$ calcd.: 153.0916, found: 153.0905.

Lactonization of adduct 15

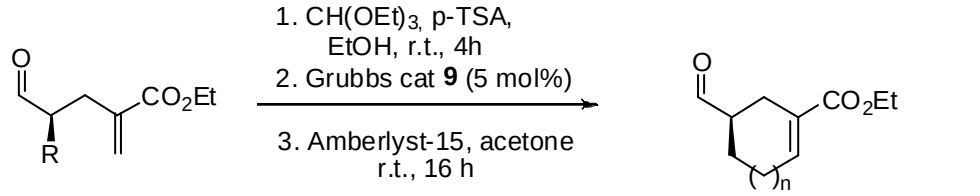


15

[8] Lukasz, L.; Richter, B.; Krawczyk, H.; Jørgensen, K. A. *J. Org. Chem*. **2008**, *73*, 8337.

The title compound was prepared from adduct **15** (82 mg, 0.31 mmol) following the same experimental procedure as for compound **10**. Overall yield after two steps: 47 mg, 0.22 mmol, 70%. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.36-7.14 (m, 5H), 6.61 (dd, 1H, J= 2.4, 1.2 Hz), 5.33 (dd, 1H, J= 2.4, 1.2 Hz), 4.45 (dd, 1H, J= 11.1, 3.6 Hz), 4.11 (dd, 1H, J= 11.1, 9.0 Hz), 2.08 (m, 1H), 1.49-1.15 (m, 2H), 0.89 (t, 3H, J= 7.2 Hz).

3.9.2. Ring closing metathesis: Synthesis of 11e and 11f.

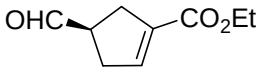


6e, 6f

(n=0) **11e** 72 %, 92 % *ee*
(n=1) **11f** 82 %, 94 % *ee*

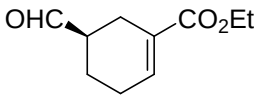
Triethyl orthoformate (83 μL, 0.5 mmol) and *p*TsOH·H_2O (19 mg, 0.1 mmol, 20 mol%) were added to a solution adduct **6e-6f** (0.5 mmol) in EtOH (5 mL). The mixture was stirred for 4 h at room temperature. After dilution with dichloromethane (10 mL) the mixture was washed with 1% aqueous NaOH (10 mL) and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporation of the solvent under reduced pressure gave the protected adduct as a brown oil, which was used as such in the next step. To a solution of this diethyl acetal protected aldehyde in dry dichloromethane (20 mL) and under Ar atmosphere, was added Grubbs second-generation catalyst **9** (22 mg, 5 mol%). The reaction mixture was refluxed for 12 h**,** afterwards diluted with dichloromethane (10 mL) and filtered through a small pad of silica gel (with dichloromethane rinsing). Evaporation of the solvent under reduced pressure gave an oil that was purified through column chromatography (eluent EtOAc/hexane 1:9). The metathesis product (0.4 mmol) was dissolved in acetone (3 mL) and H_2O (0.3 mL, 10 vol %). Amberlyst-15 (15 mg) was then added and the heterogeneous mixture was stirred for 16 h at room temperature. Dry molecular sieves (3Å) were then added and the mixture was stirred for and additional ca. 30 min. The solids were filtered off and washed with acetone. Evaporation of the solvent under reduced pressure gave pure compounds **11e** and **11f**.

Ethyl (R)-4-formylcyclopent-1-enecarboxylate (11e)



Overall yield from **6e** (0.5mmol): 60 mg, 0.36 mmol, 72%. $[\alpha]_D^{25}$ = -9.9 (c 1.0, CH_2Cl_2, 99% ee). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 9.69 (d, 1H, J= 1.5 Hz), 6.69 (t, 1H, J= 2.1 Hz), 4.21 (q, 2H, J= 7.2 Hz), 3.23-2.91 (m, 5H), 1.30 (t, 3H, J= 7.2 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 201.5, 164.4, 141.0, 135.0, 60.4, 48.7, 33.1, 31.7, 14.2. The enantiomeric excess was determined by HPLC with Chiralpack IC column at 210nm (hexane/^{i}PrOH in the ratio of 98/2, flow rate = 0.5 mL/min tr= 63.7 min (major), tr= 72.1 min (minor)).

Ethyl (R)-5-formylcyclohex-1-enecarboxylate (11f)



Overall yield from **6f** (0.29 mmol): 44 mg, 0.24 mmol, 82%. $[\alpha]_D^{25}$ = -5.1 (c 0.5, CH_2Cl_2, 94% ee). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 9.73 (s, 1H), 7.00 (m, 1H), 4.21 (q, 2H, J= 7.2 Hz), 2.63-1.59 (m, 7H), 1.30 (t, 3H, J= 7.2 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 203.2, 166.8, 138.9, 128.6, 60.5, 45.7, 24.3, 23.5, 21.1, 14.2. The enantiomeric excess was determined by HPLC with Chiralpack IC column at 220nm (hexane/^{i}PrOH in the ratio of 85/15, flow rate = 0.5 mL/min tr= 37.9 min (major), tr= 41.9 min (minor)). HRMS: $C_8H_9O_2$ $[M+H-C_2H_6O]^+$ calcd.: 137.0603, found: 137.0582.

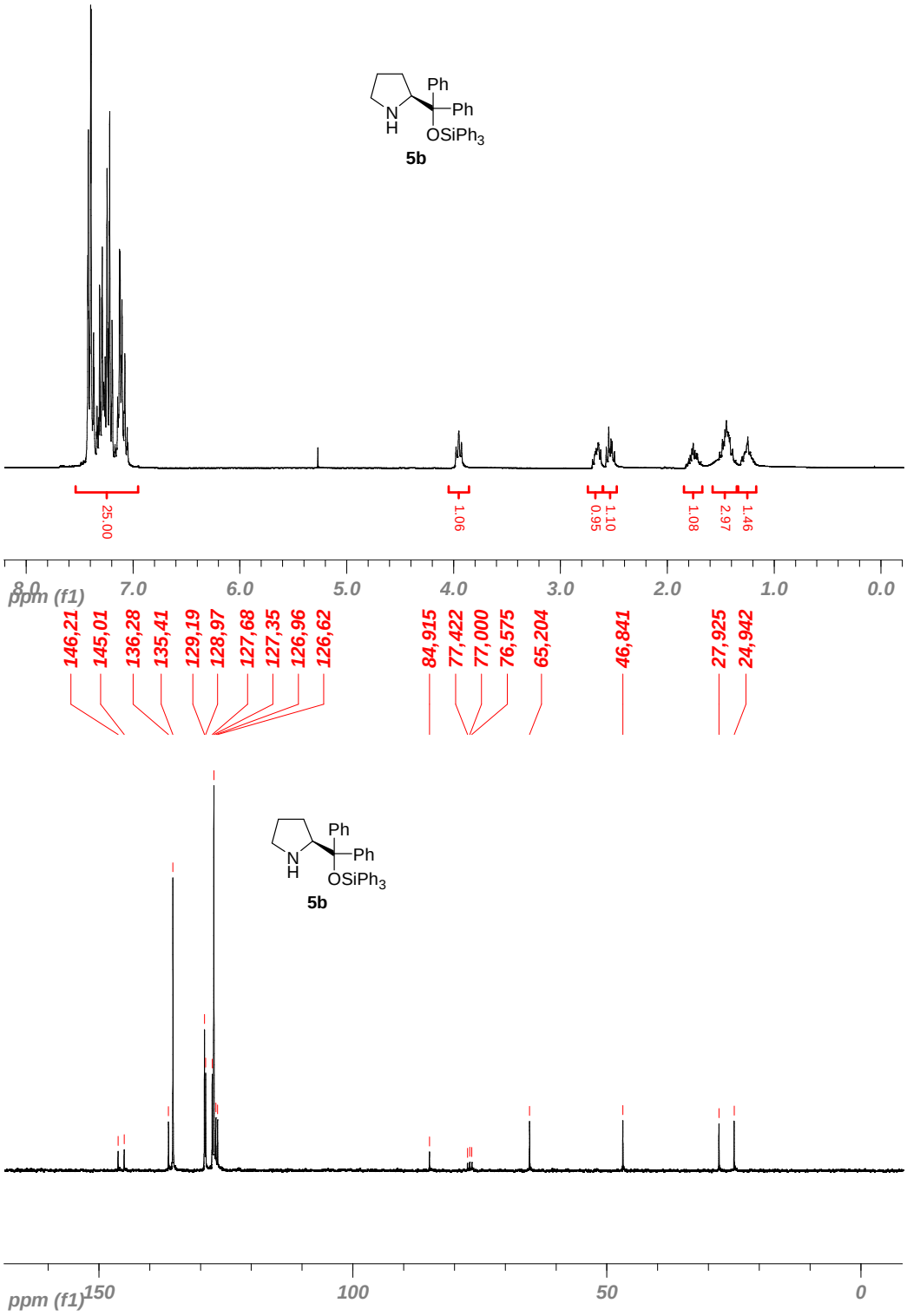
3.10. Stereochemical proofs

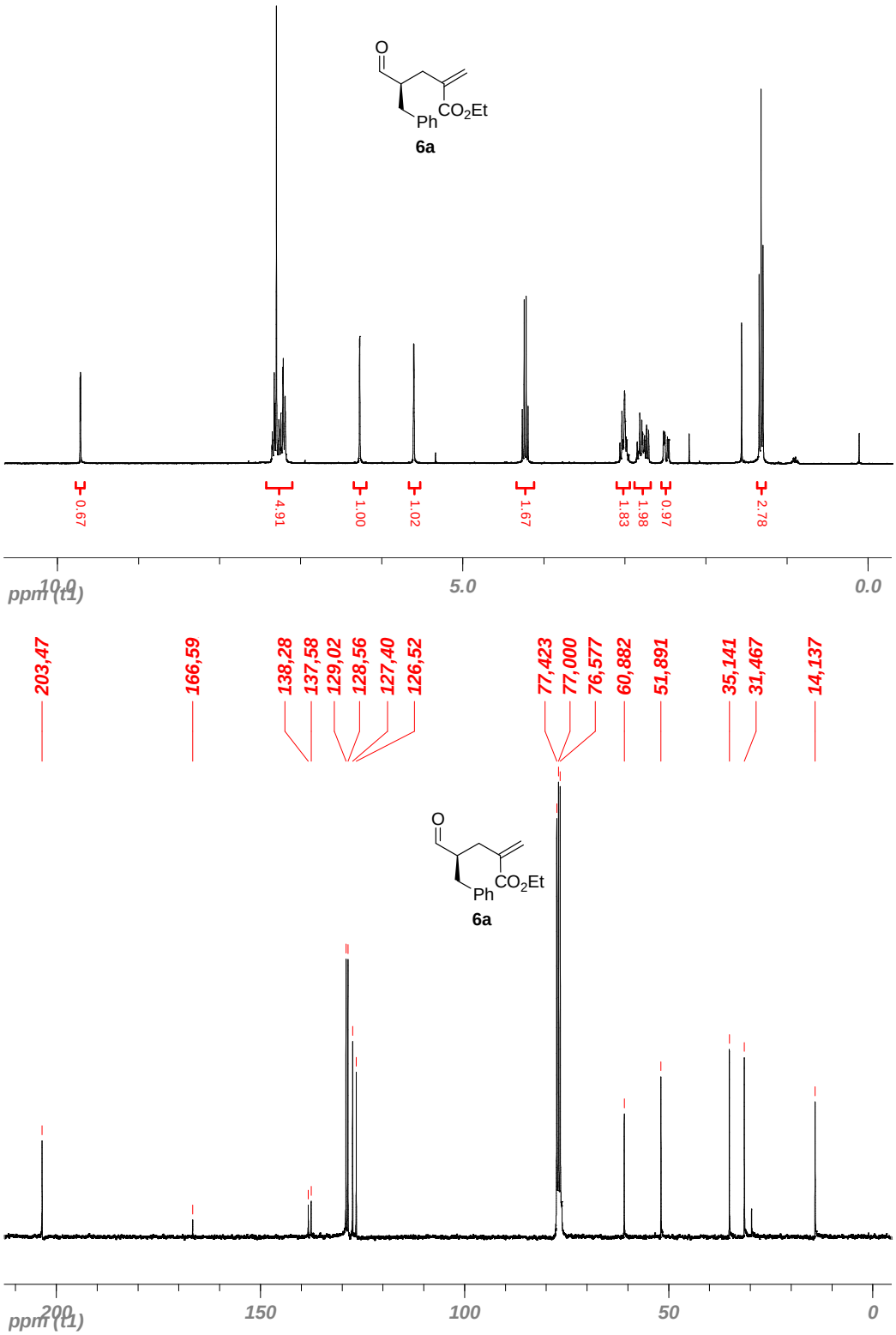
Absolute configuration of adduct **6e** was determined by comparison of chiroptic data of its lactone derivative **10** with literature data. Assignment was confirmed by comparison of the order of elution on HPLC with that reported.

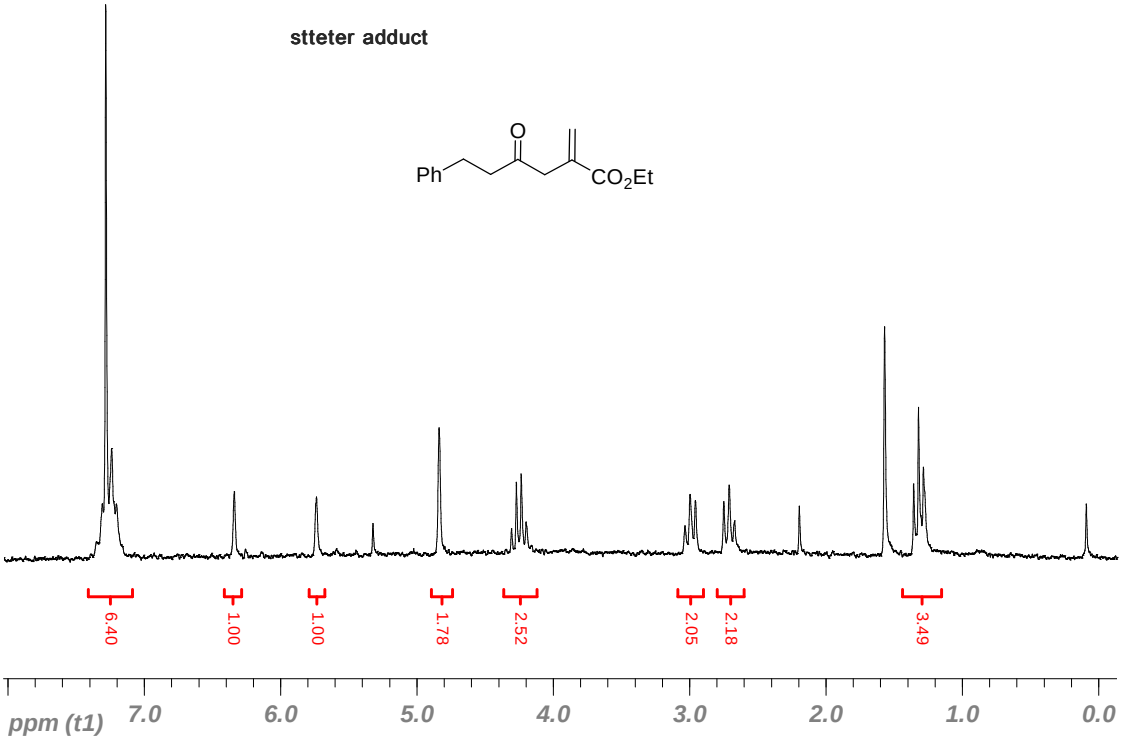
For the remaining adducts, absolute configuration was assumed on the basis of a uniform reaction mechanism.

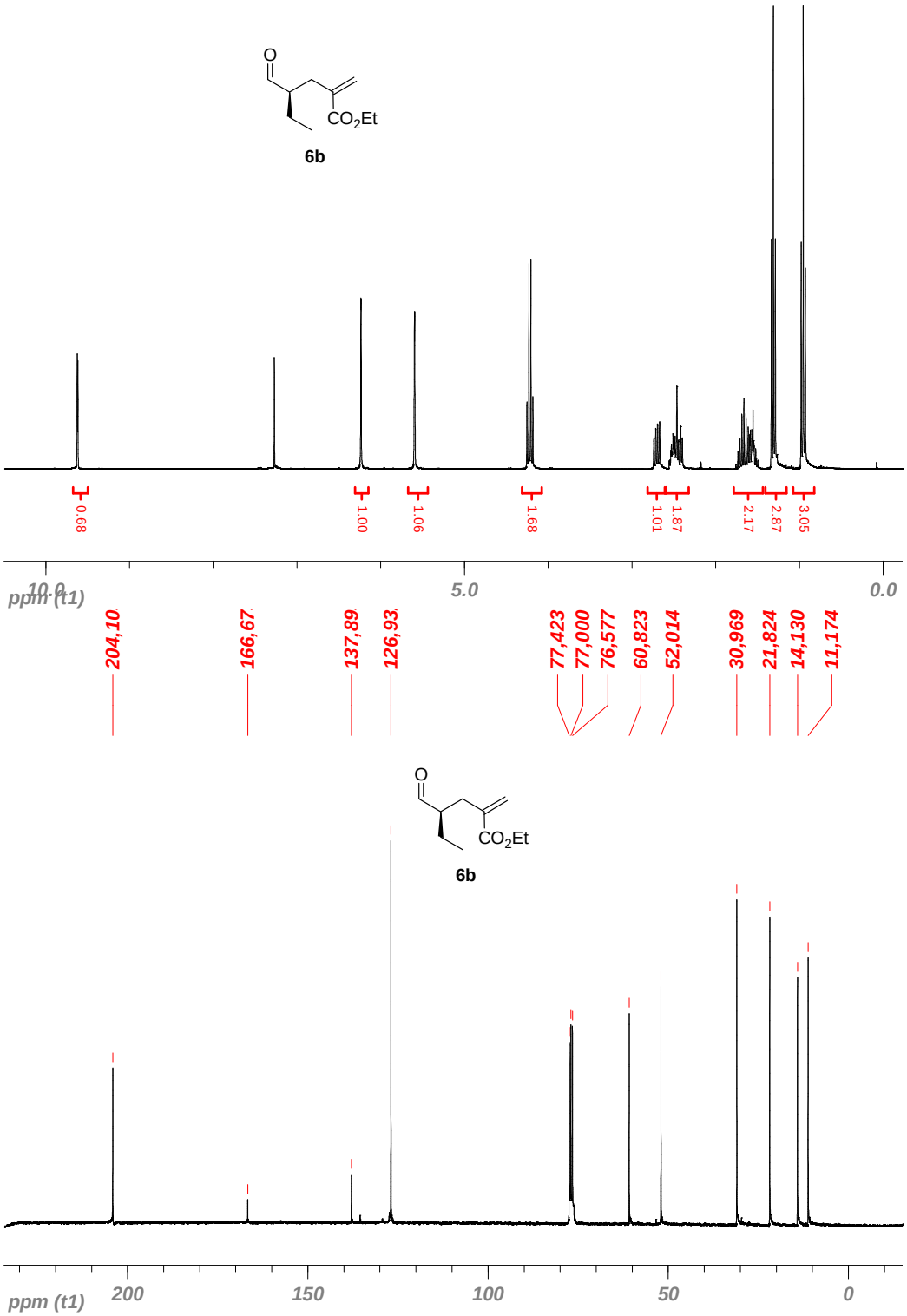
The relative configuration of lactone from adduct **15** (major diastereomer) was determined to be *trans* by selective NOE experiments and correlation of the value of the H4-H5 coupling constant.

4. ^{1}H and ^{13}C NMR Spectra




O
Ph
CO2Et
6a
0.67
4.91
1.00
1.02
1.67
1.83
1.98
0.97
2.78
10.0
5.0
0.0
ppm (t1)
203,47
166,59
138,28
137,58
129,02
128,56
127,40
126,52
77,423
77,000
76,577
60,882
51,891
35,141
31,467
14,137
O
Ph
CO2Et
6a
200
150
100
50
0
ppm (t1)


stteter adduct
O
Ph
CO2Et
6.40
1.00
1.00
1.78
2.52
2.05
2.18
3.49
ppm (t1)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0


O
CO2Et
6b
0.68
1.00
1.06
1.68
1.01
1.87
2.17
2.87
3.05
10.0
5.0
0.0
ppm (t1)
204,10
166,67
137,89
126,93
77,423
77,000
76,577
60,823
52,014
30,969
21,824
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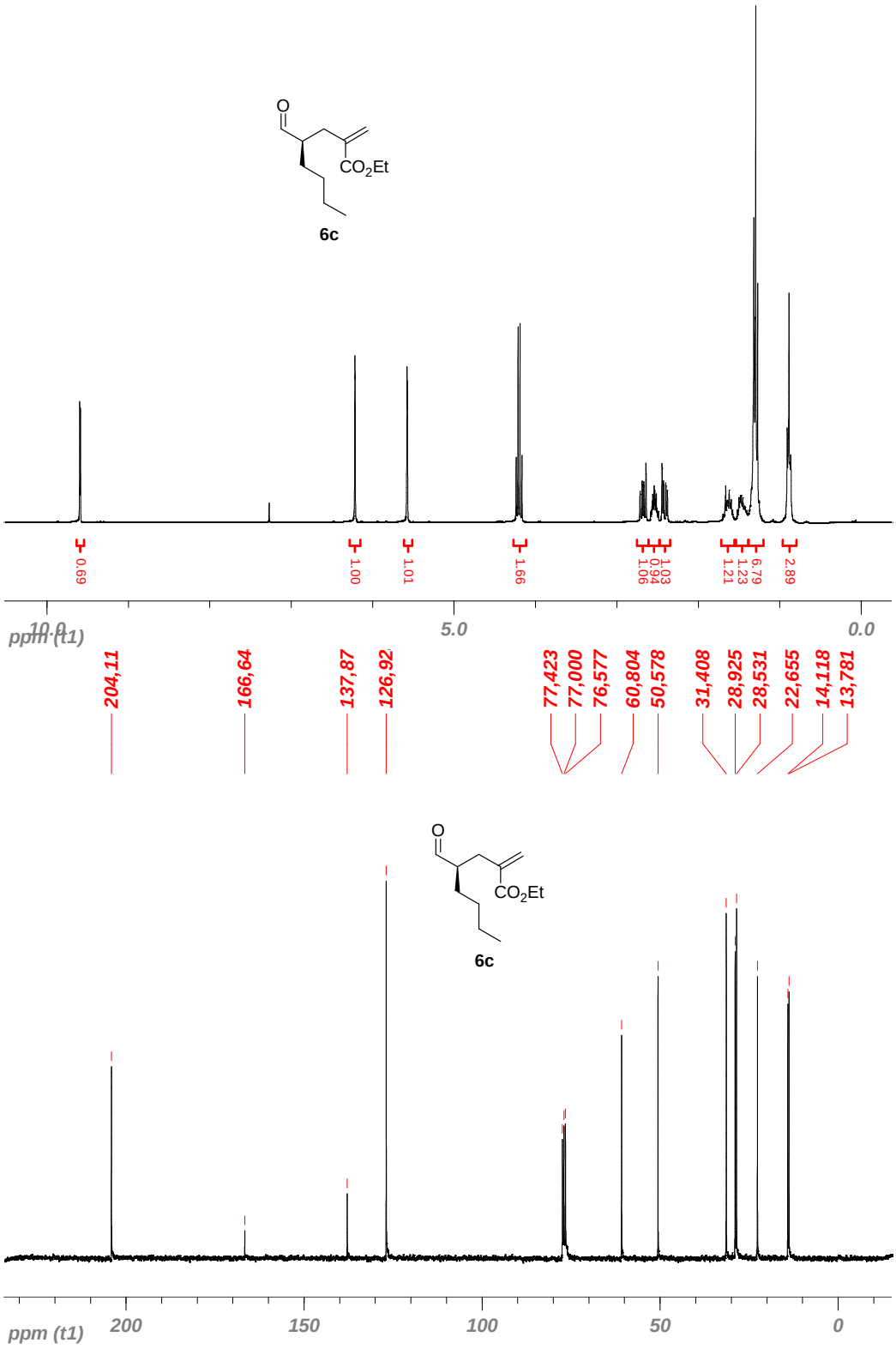
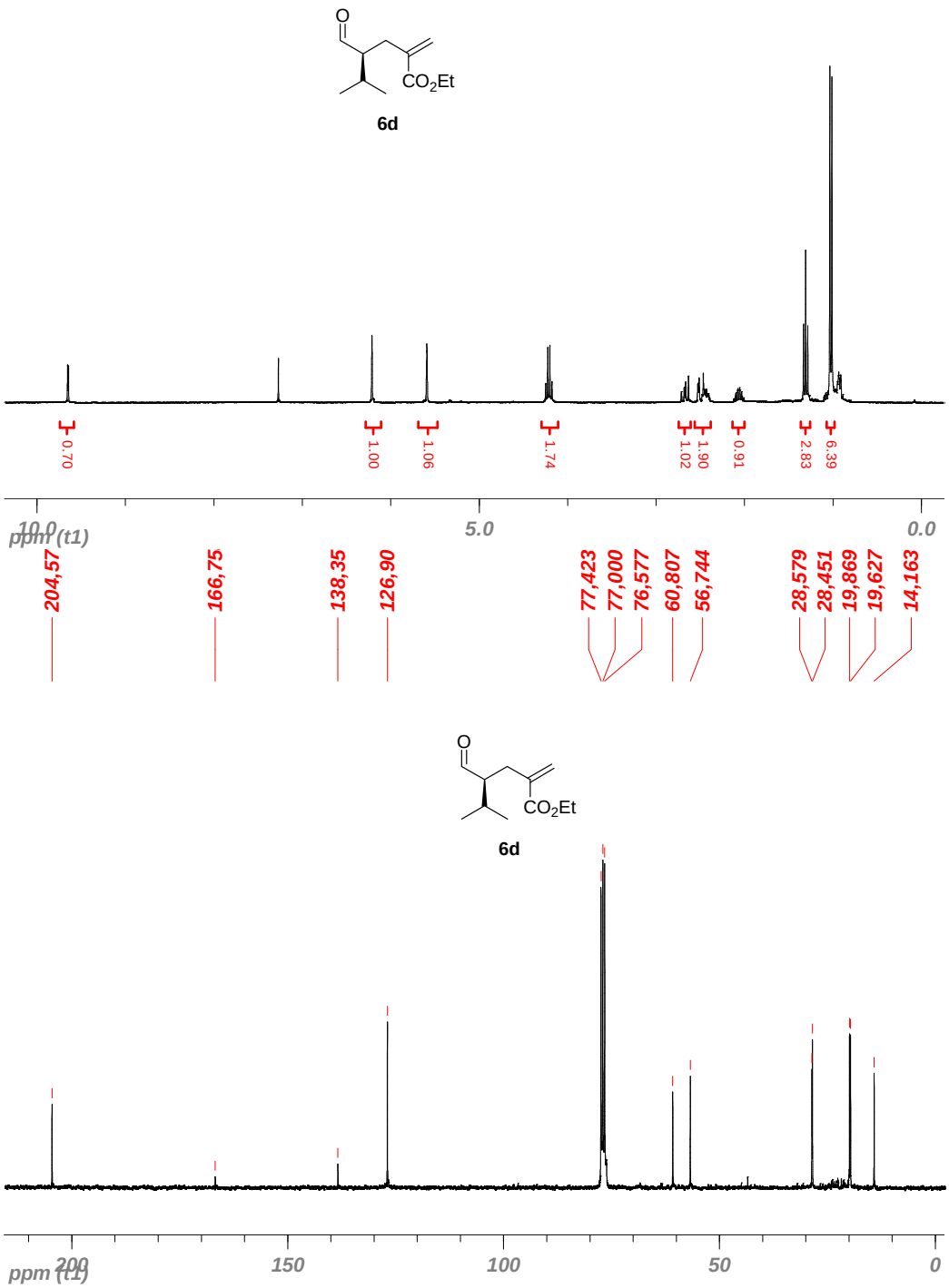
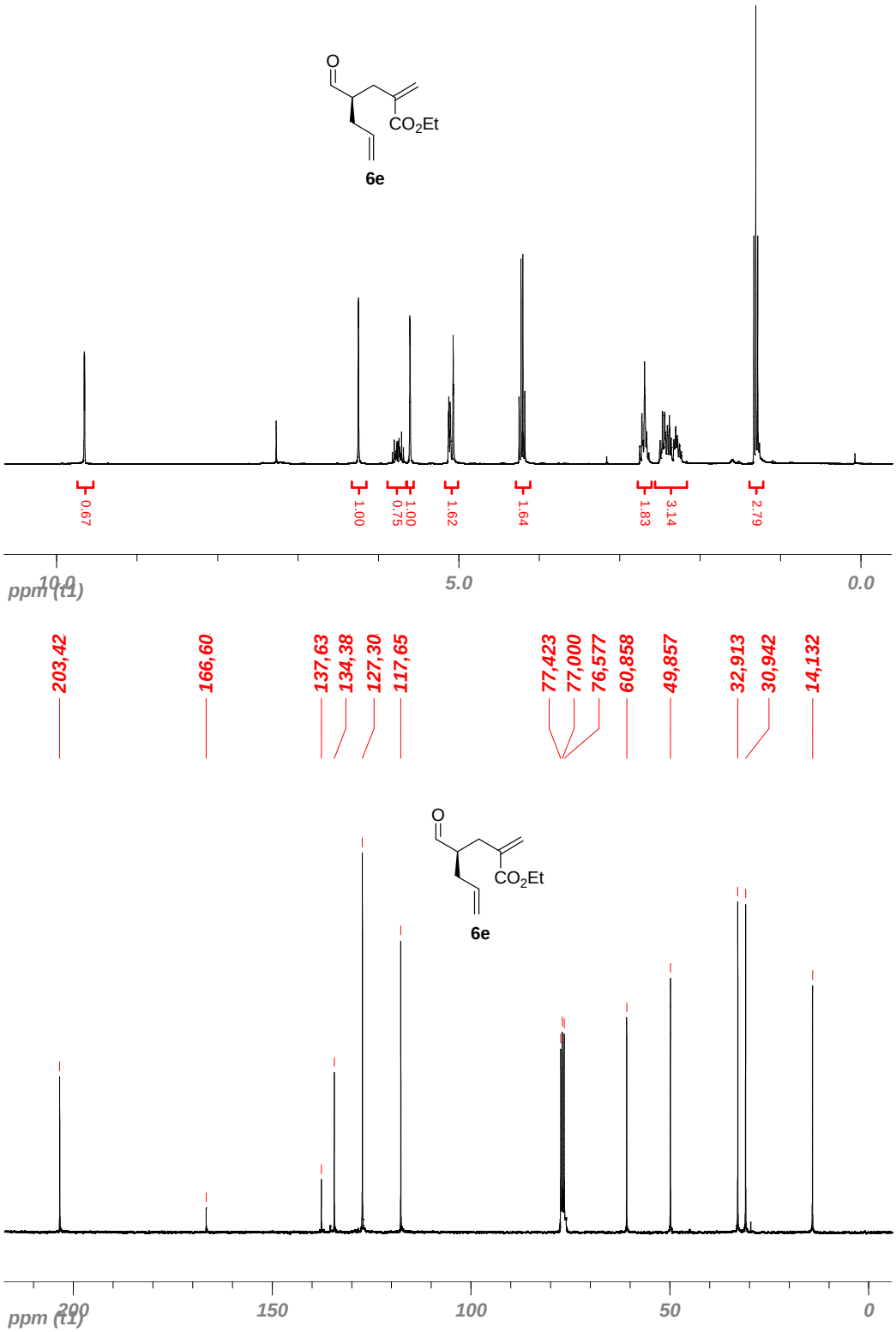
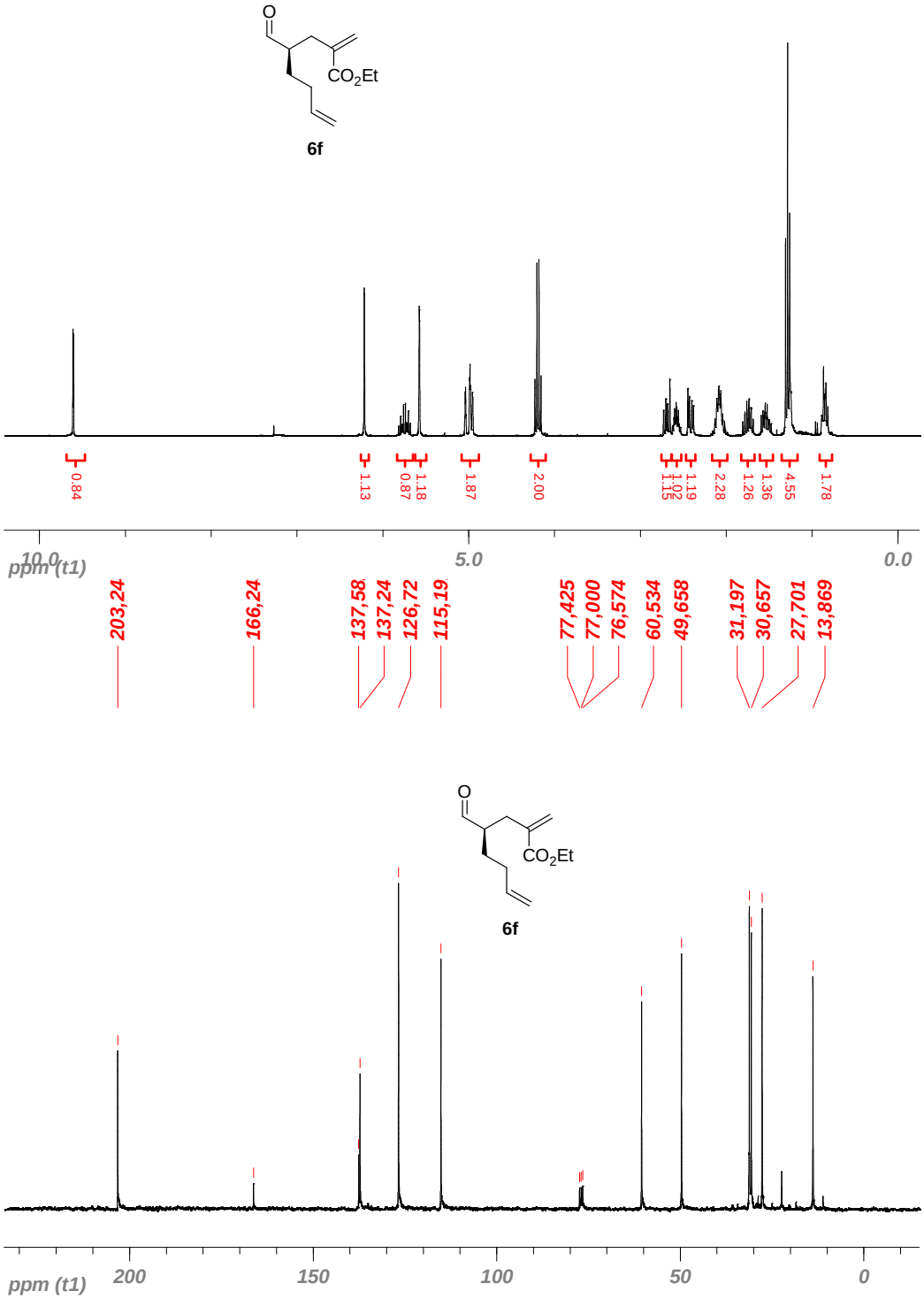
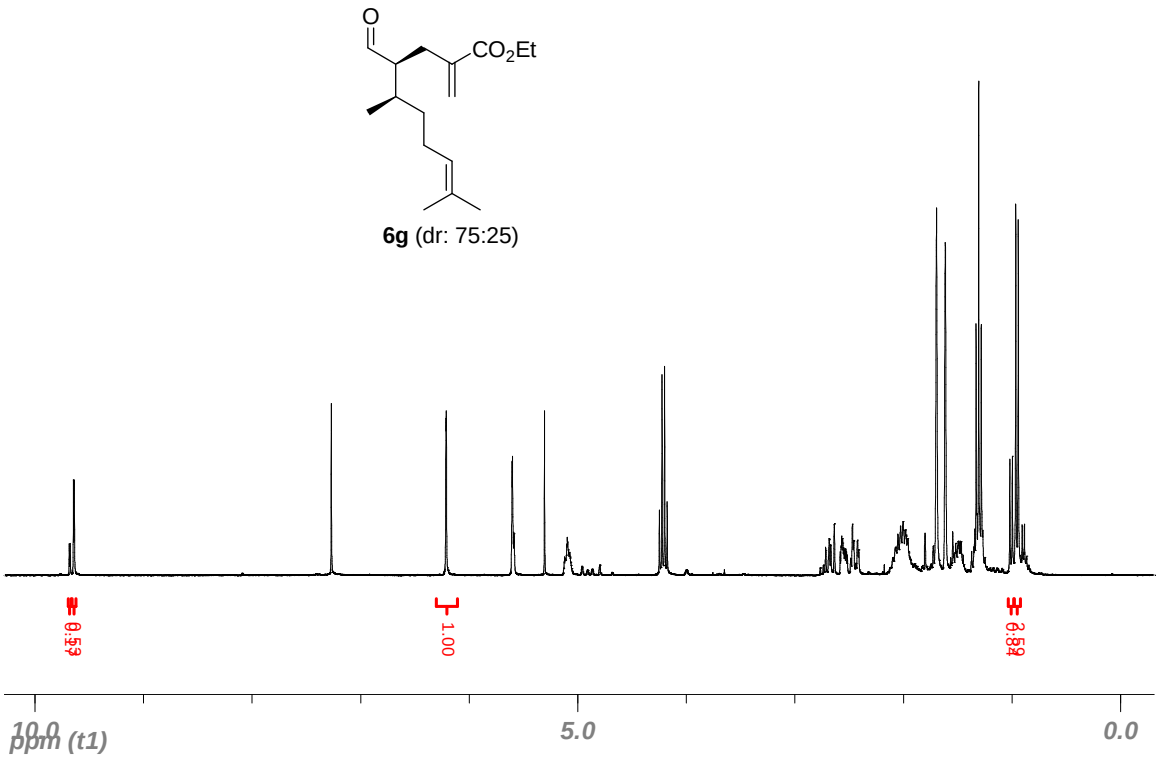
CO2Et
6b
ppm (t1)
200
150
100
50
0

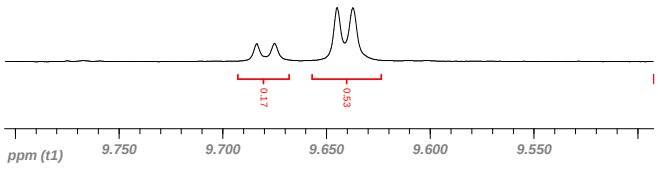

O
CO2Et
6c
0.69
1.00
1.01
1.66
1.03
0.94
1.06
6.79
1.23
1.21
2.89
10.0
5.0
0.0
ppm (t1)
204,11
166,64
137,87
126,92
77,423
77,000
76,577
60,804
50,578
31,408
28,925
28,531
22,655
14,118
13,781
O
CO2Et
6c
ppm (t1)
200
150
100
50
0

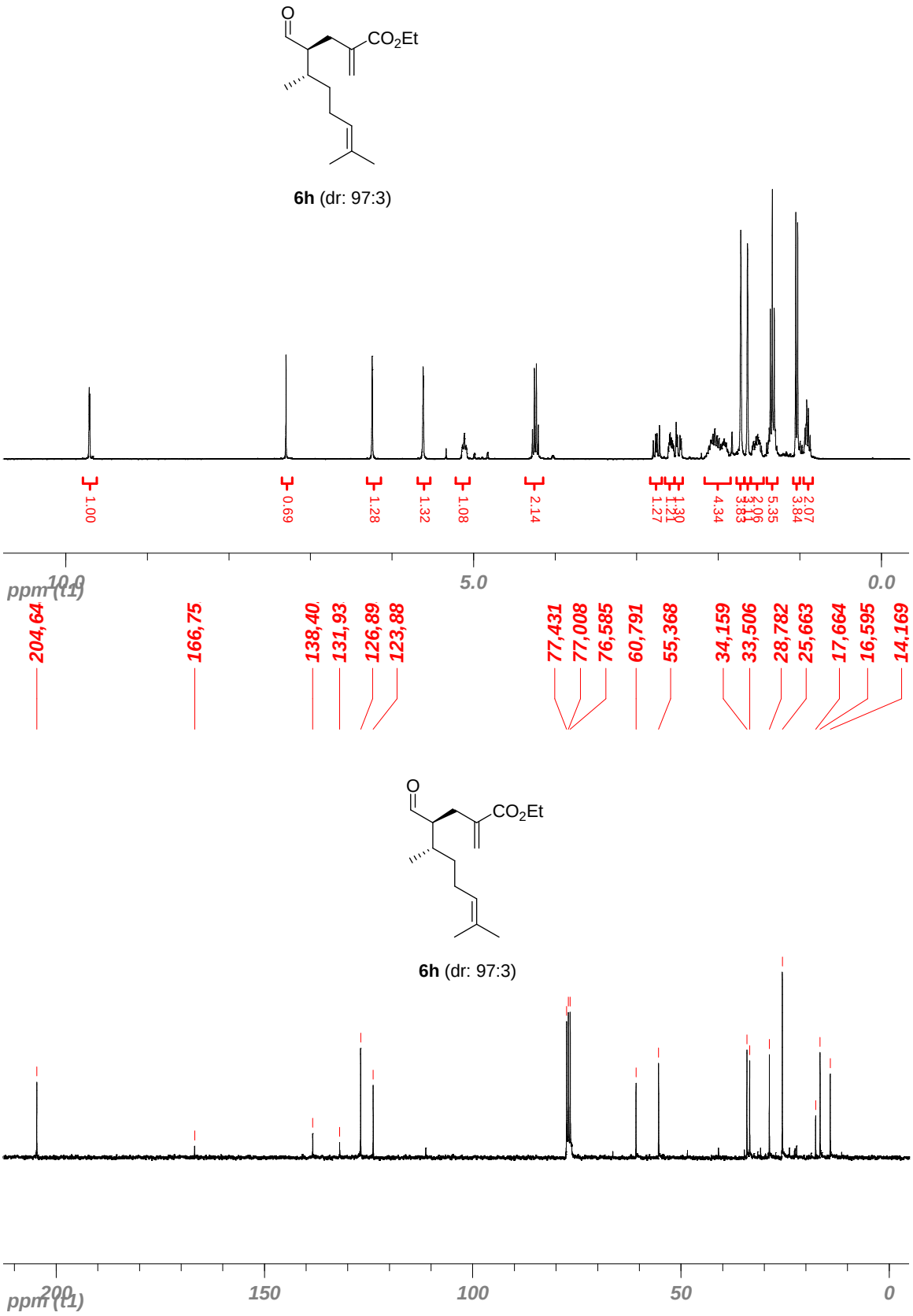

O
CO2Et
6d
0.70
1.00
1.06
1.74
1.02
1.90
0.91
2.83
6.39
10.0
5.0
0.0
ppm (t1)
204,57
166,75
138,35
126,90
77,423
77,000
76,577
60,807
56,744
28,579
28,451
19,869
19,627
14,163
O
CO2Et
6d
200
150
100
50
0
ppm (t1)

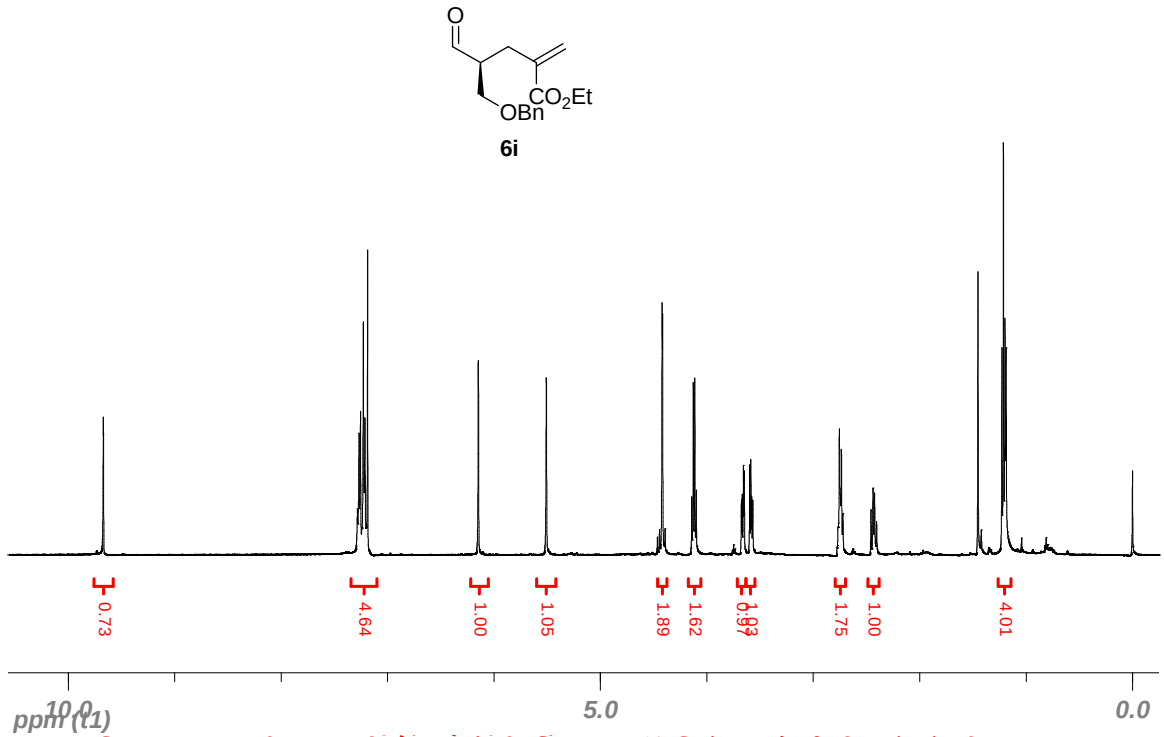

O
CO2Et
6e
0.67
1.00
1.00
0.75
1.62
1.64
1.83
3.14
2.79
10.0
5.0
0.0
ppm (t1)
203,42
166,60
137,63
134,38
127,30
117,65
77,423
77,000
76,577
60,858
49,857
32,913
30,942
14,132
O
CO2Et
6e
200
150
100
50
0
ppm (t1)

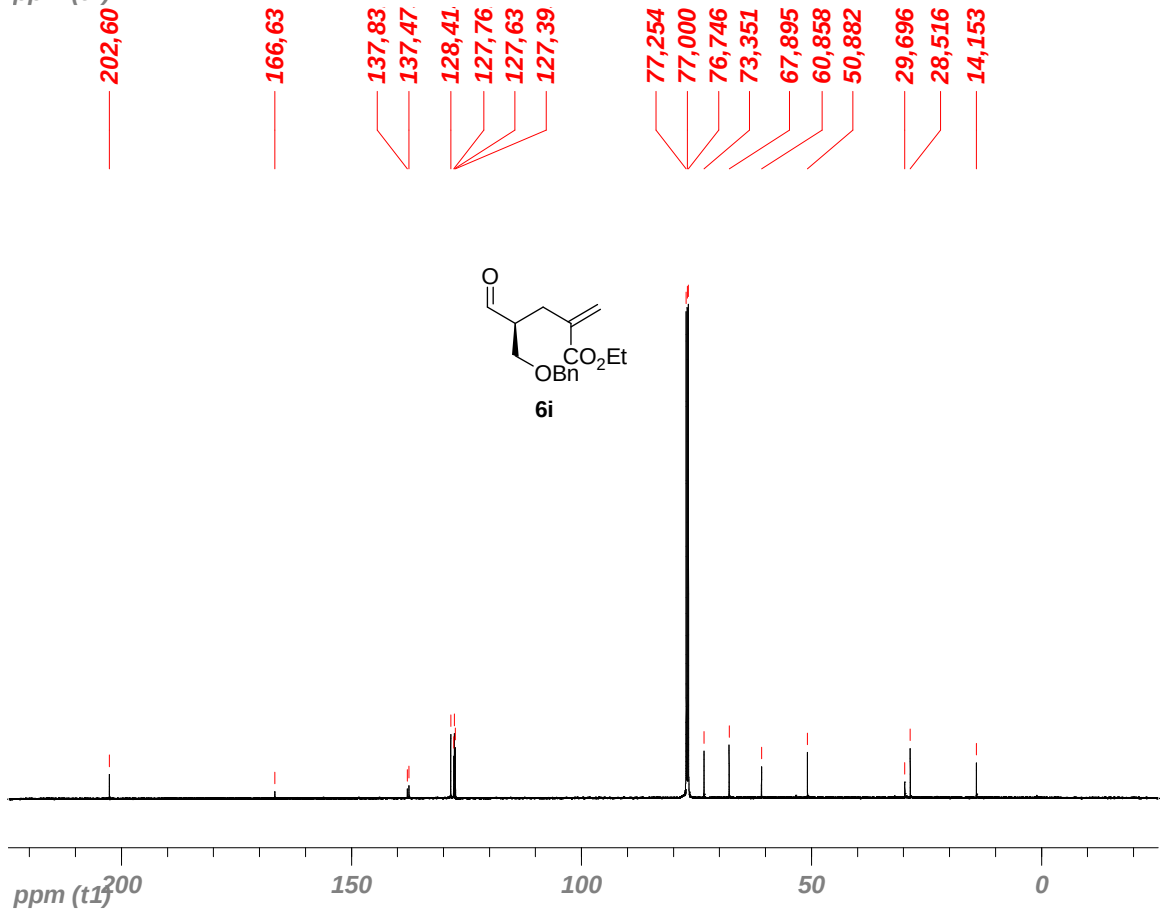

O
CO2Et
6f
0.84
1.13
0.87
1.18
1.87
2.00
1.02
1.15
1.19
2.28
1.26
1.36
4.55
1.78
10.0
5.0
0.0
ppm (t1)
203,24
166,24
137,58
137,24
126,72
115,19
77,425
77,000
76,574
60,534
49,658
31,197
30,657
27,701
13,869
O
CO2Et
6f
200
150
100
50
0
ppm (t1)

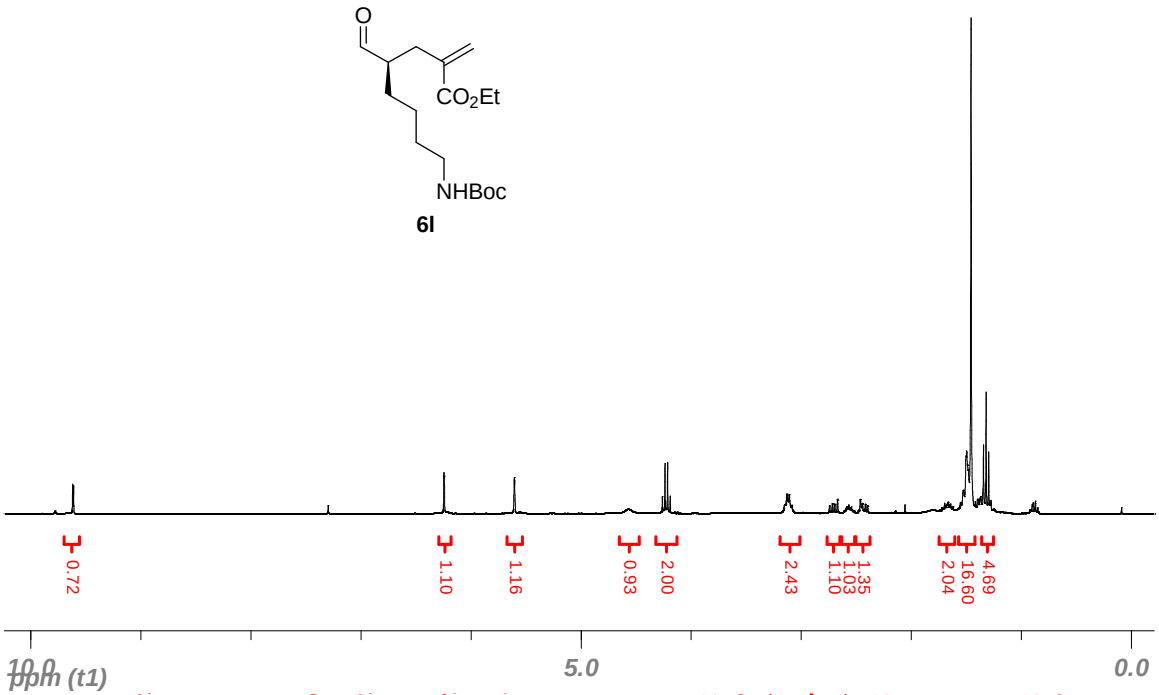

O
CO2Et
6g (dr: 75:25)
0.59
1.00
2.59
10.0
5.0
0.0
ppm (t1)

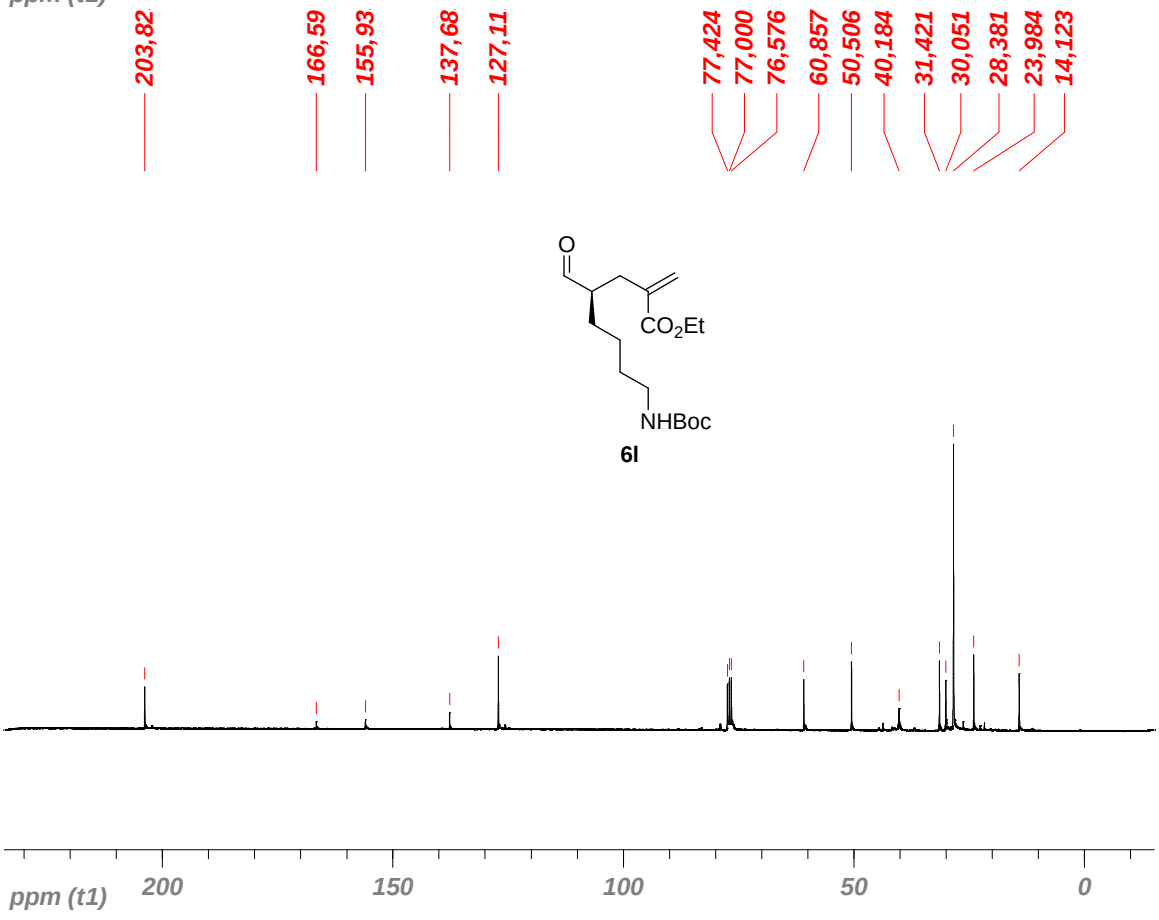

0.17
0.53
ppm (t1)
9.750
9.700
9.650
9.600
9.550

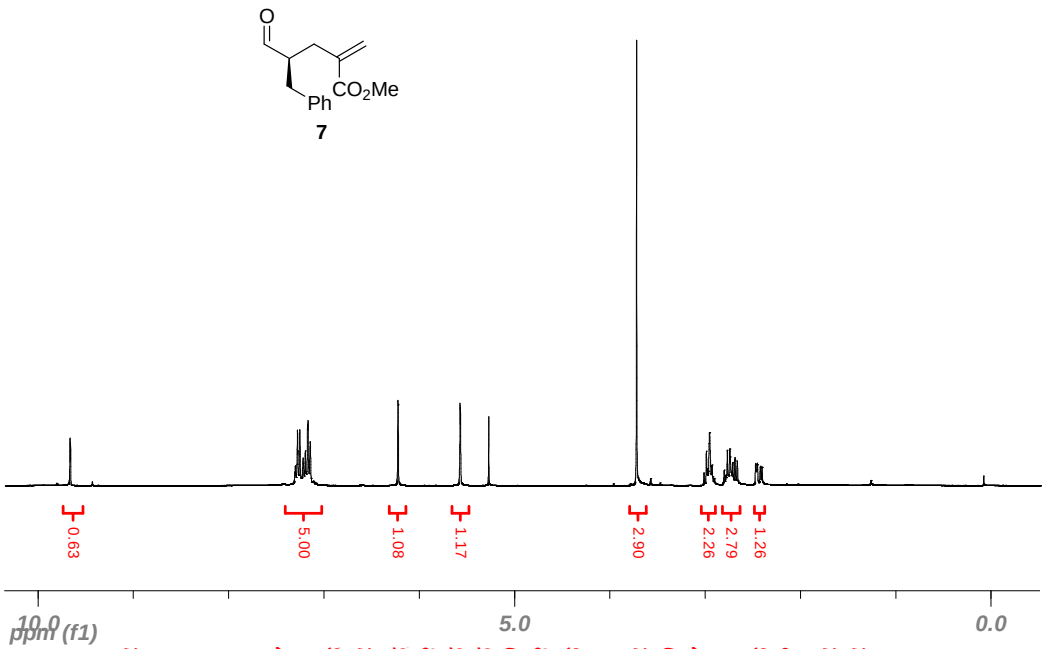

O
CO2Et
6h (dr: 97:3)
1.00
0.69
1.28
1.32
1.08
2.14
1.27
4.34
5.35
3.84
10.0
5.0
0.0
ppm (t1)
204,64
166,75
138,40
131,93
126,89
123,88
77,431
77,008
76,585
60,791
55,368
34,159
33,506
28,782
25,663
17,664
16,595
14,169
O
CO2Et
6h (dr: 97:3)
200
150
100
50
0
ppm (t1)

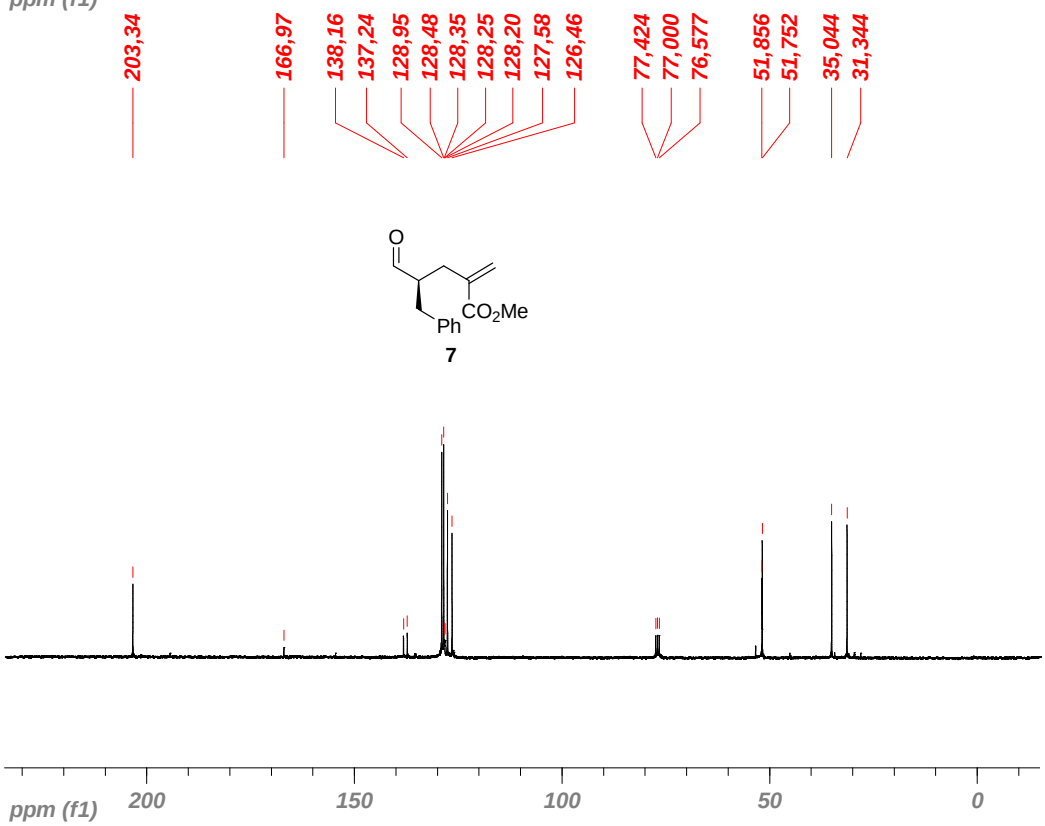

O
CO2Et
OBn
6i
0.73
4.64
1.00
1.05
1.89
1.62
0.97
1.03
1.75
1.00
4.01
10.0
5.0
0.0
ppm (t1)

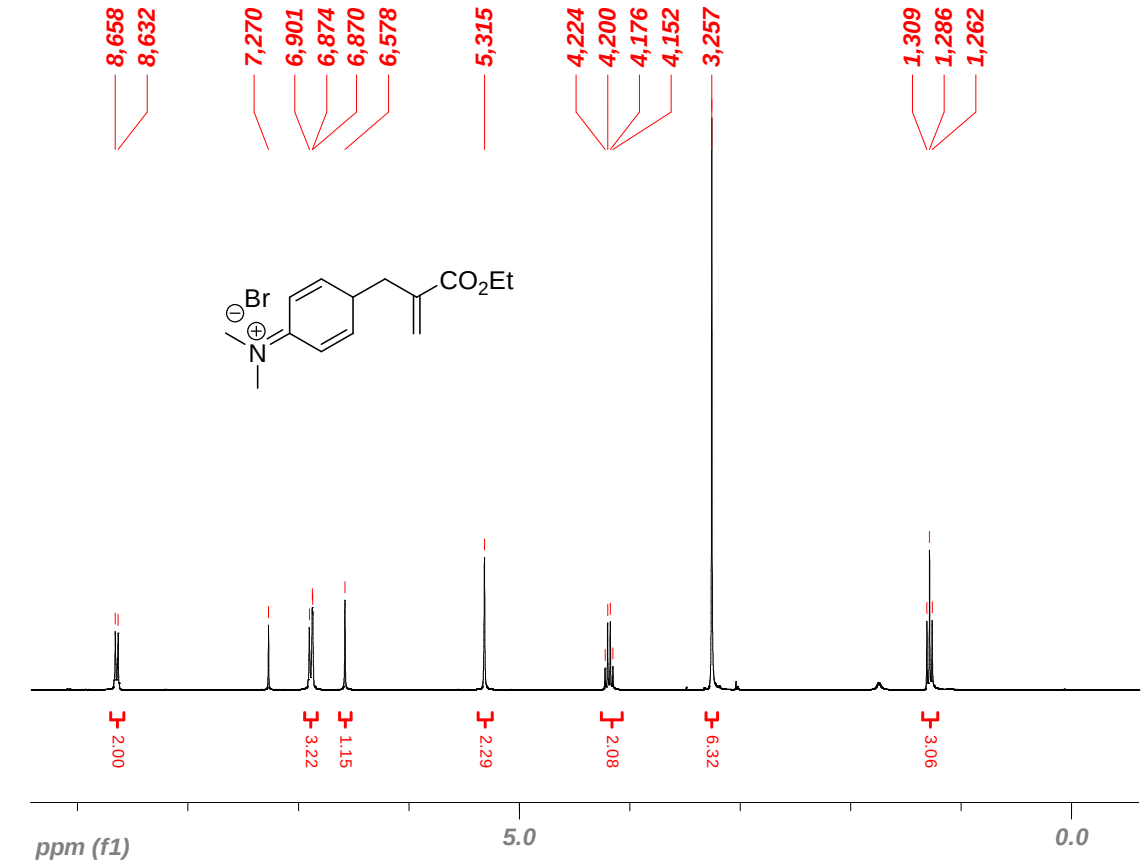

202,60
166,63
137,83
137,47
128,41
127,76
127,63
127,39
77,254
77,000
76,746
73,351
67,895
60,858
50,882
29,696
28,516
14,153
O
CO2Et
OBn
6i
200
150
100
50
0
ppm (t1)

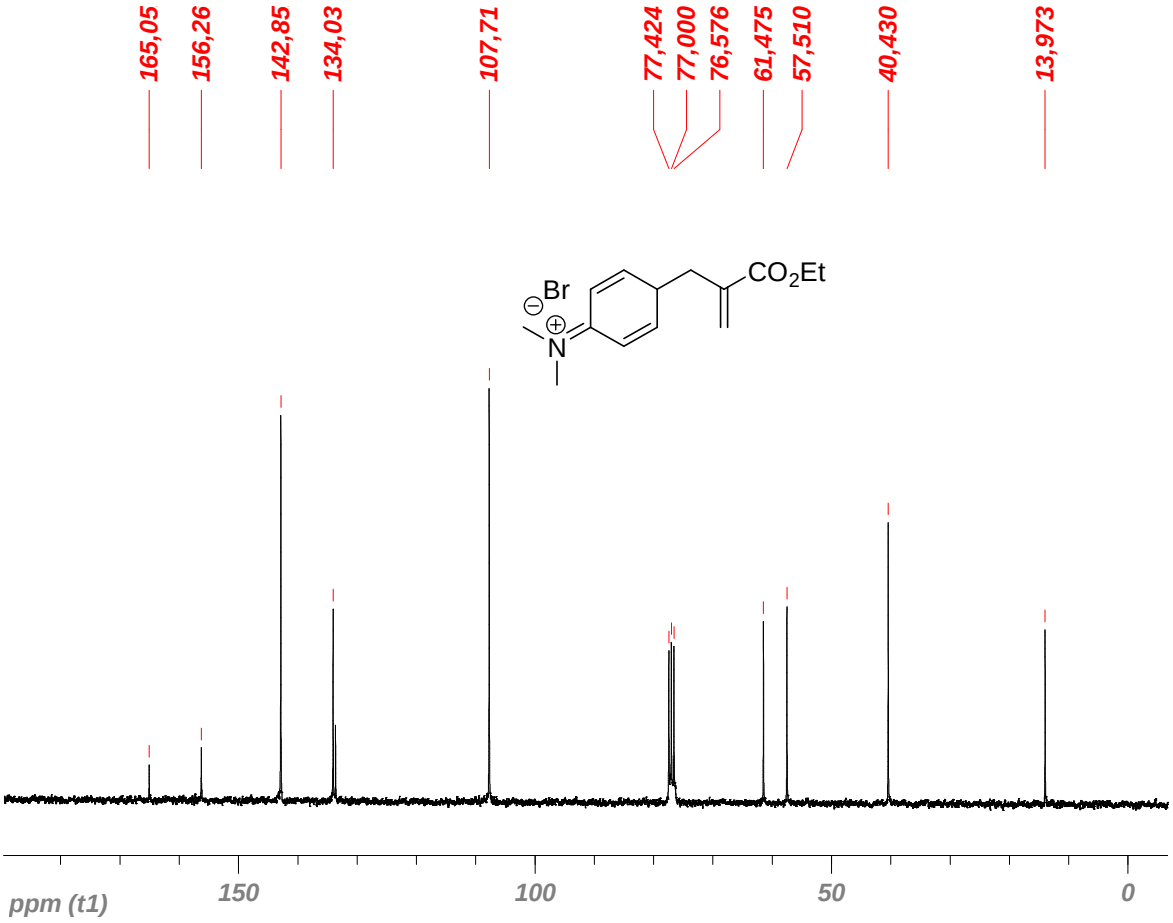

O
CO2Et
NHBoc
6l
0.72
1.10
1.16
0.93
2.00
2.43
1.35
1.03
1.10
2.04
16.60
4.69
10.0
5.0
0.0
ppm (t1)

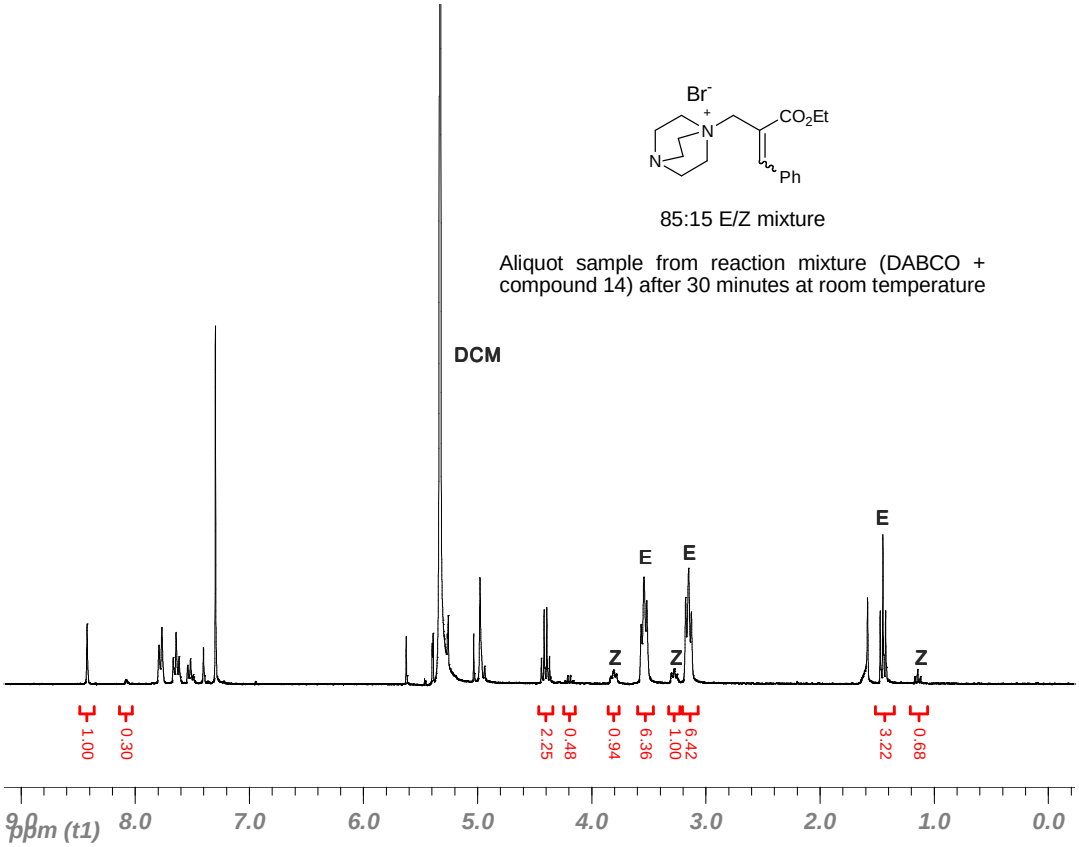

203,82
166,59
155,93
137,68
127,11
77,424
77,000
76,576
60,857
50,506
40,184
31,421
30,051
28,381
23,984
14,123
O
CO2Et
NHBoc
6l
200
150
100
50
0
ppm (t1)

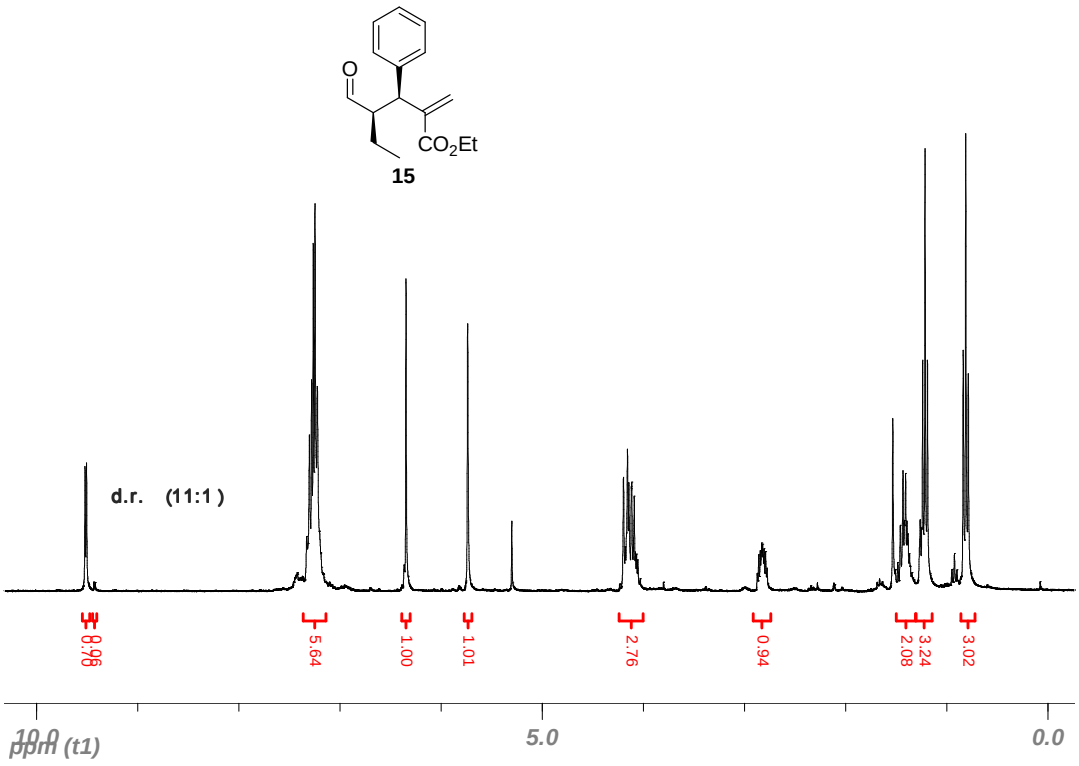

O
CO2Me
Ph
7
0.63
5.00
1.08
1.17
2.90
2.26
2.79
1.26
10.0
5.0
0.0
ppm (f1)

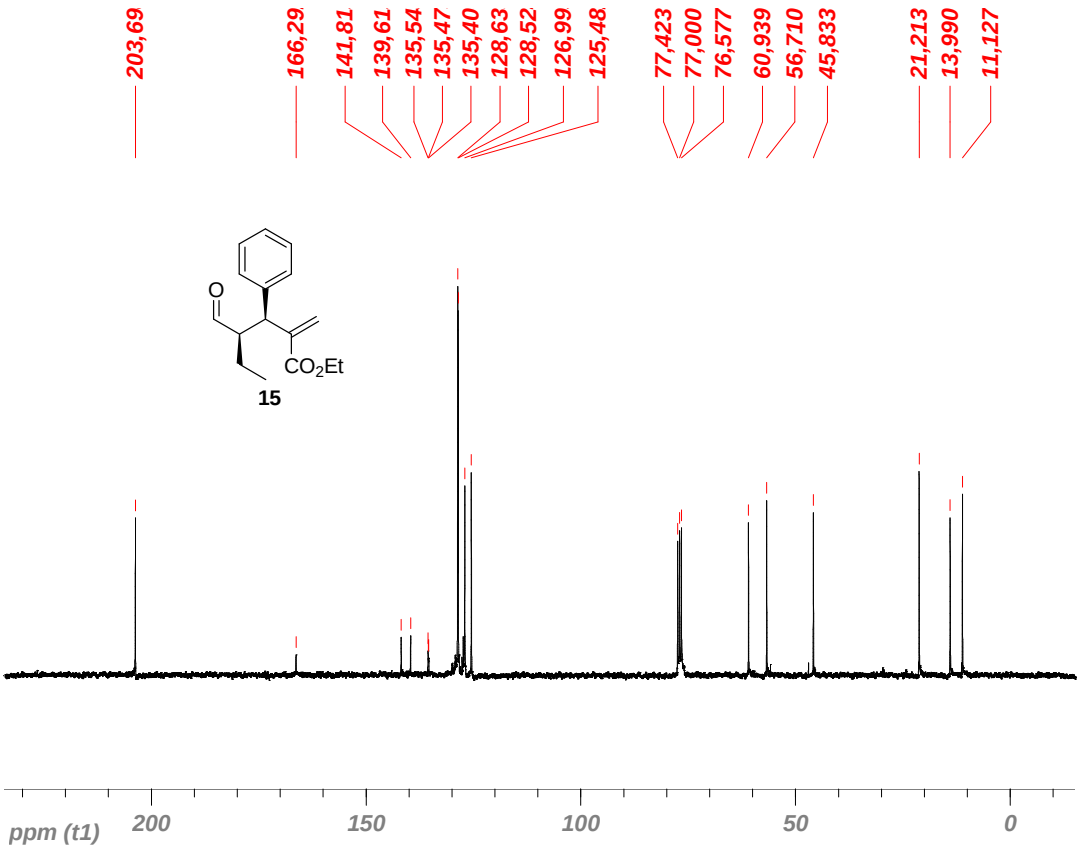

203,34
166,97
138,16
137,24
128,95
128,48
128,35
128,25
128,20
127,58
126,46
77,424
77,000
76,577
51,856
51,752
35,044
31,344
O
CO2Me
Ph
7
200
150
100
50
0
ppm (f1)

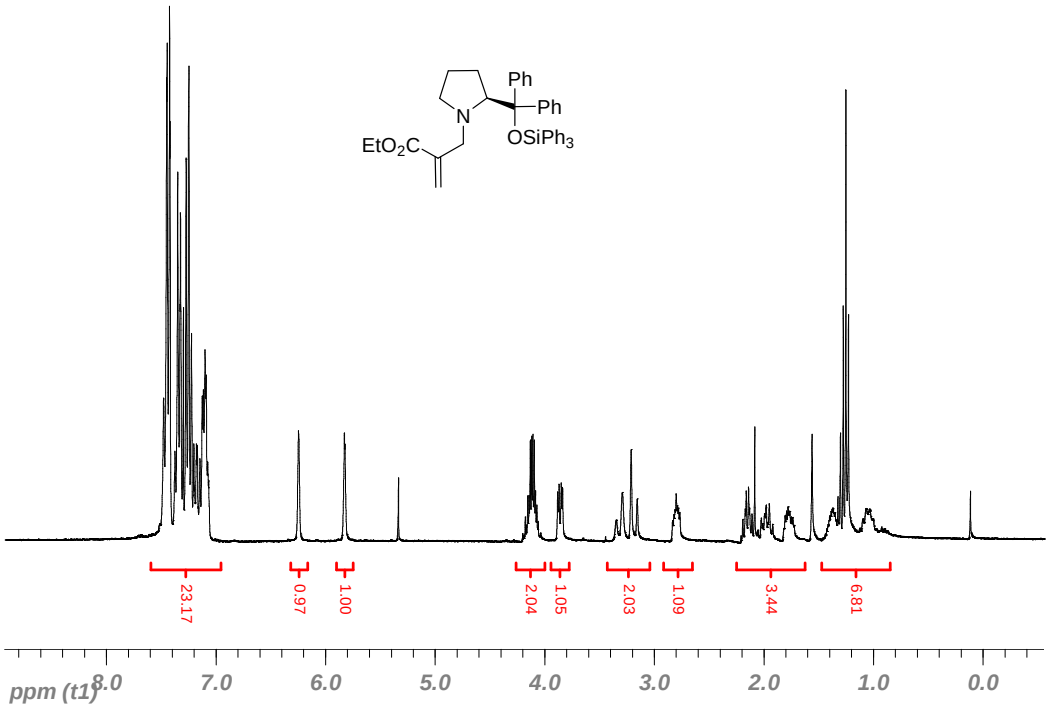

8,658
8,632
7,270
6,901
6,874
6,870
6,578
5,315
4,224
4,200
4,176
4,152
3,257
1,309
1,286
1,262
Br
N
CO2Et
2.00
3.22
1.15
2.29
2.08
6.32
3.06
ppm (f1)
5.0
0.0


165,05
156,26
142,85
134,03
107,71
77,424
77,000
76,576
61,475
57,510
40,430
13,973
Br
N
CO2Et
ppm (t1)
150
100
50
0

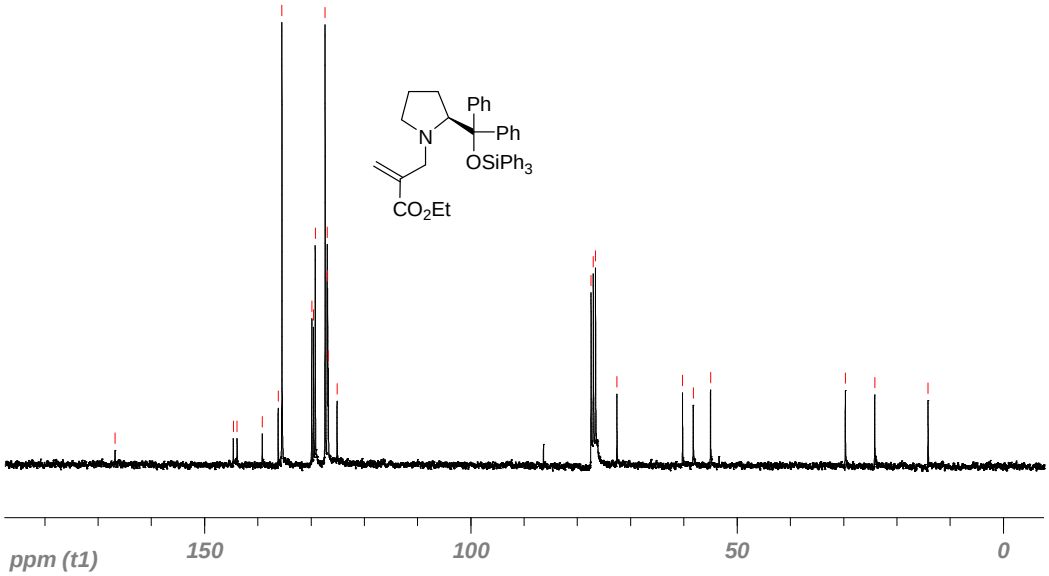

Br-
CO2Et
N
N
Ph
85:15 E/Z mixture
Aliquot sample from reaction mixture (DABCO + compound 14) after 30 minutes at room temperature
DCM
E
E
E
Z
Z
Z
1.00
0.30
2.25
0.48
0.94
6.36
1.00
6.42
3.22
0.68
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

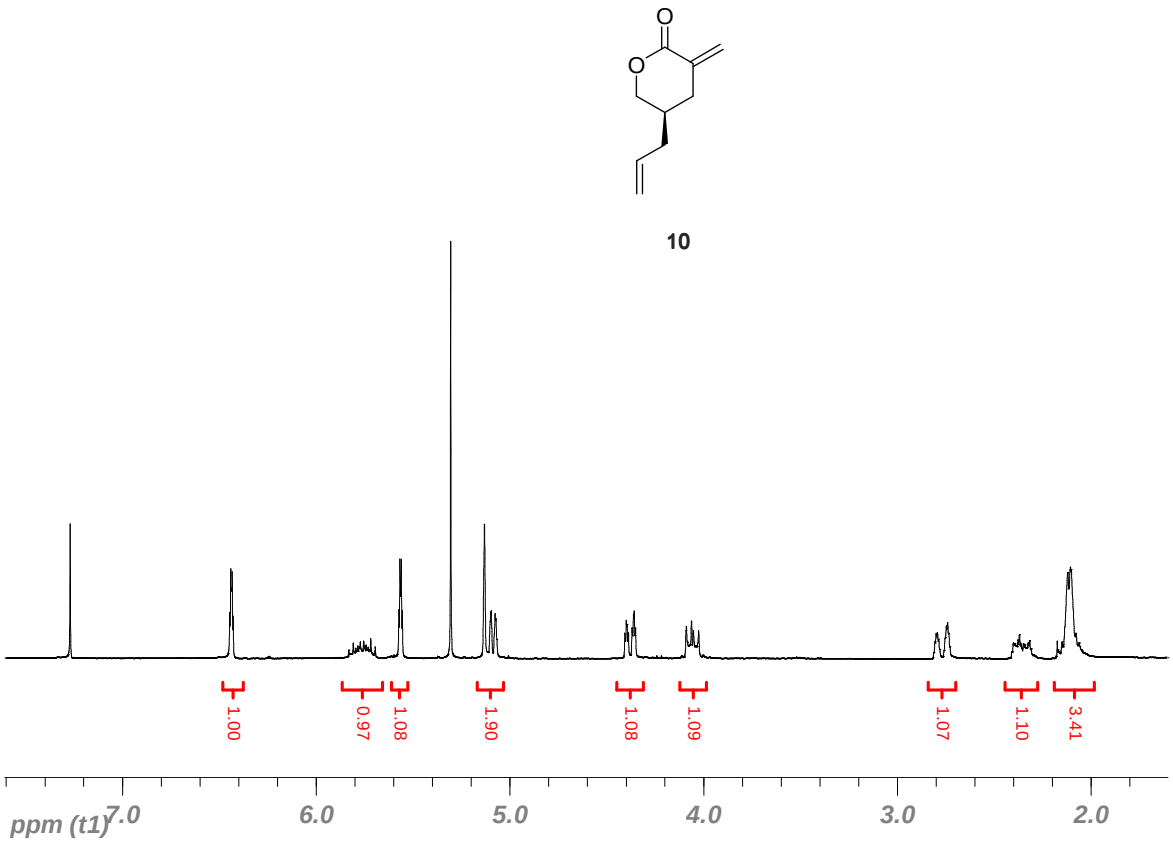

O
CO2Et
15
d.r. (11:1)
0.96
5.64
1.00
1.01
2.76
0.94
3.24
2.08
3.02
10.0
5.0
0.0
ppm (t1)

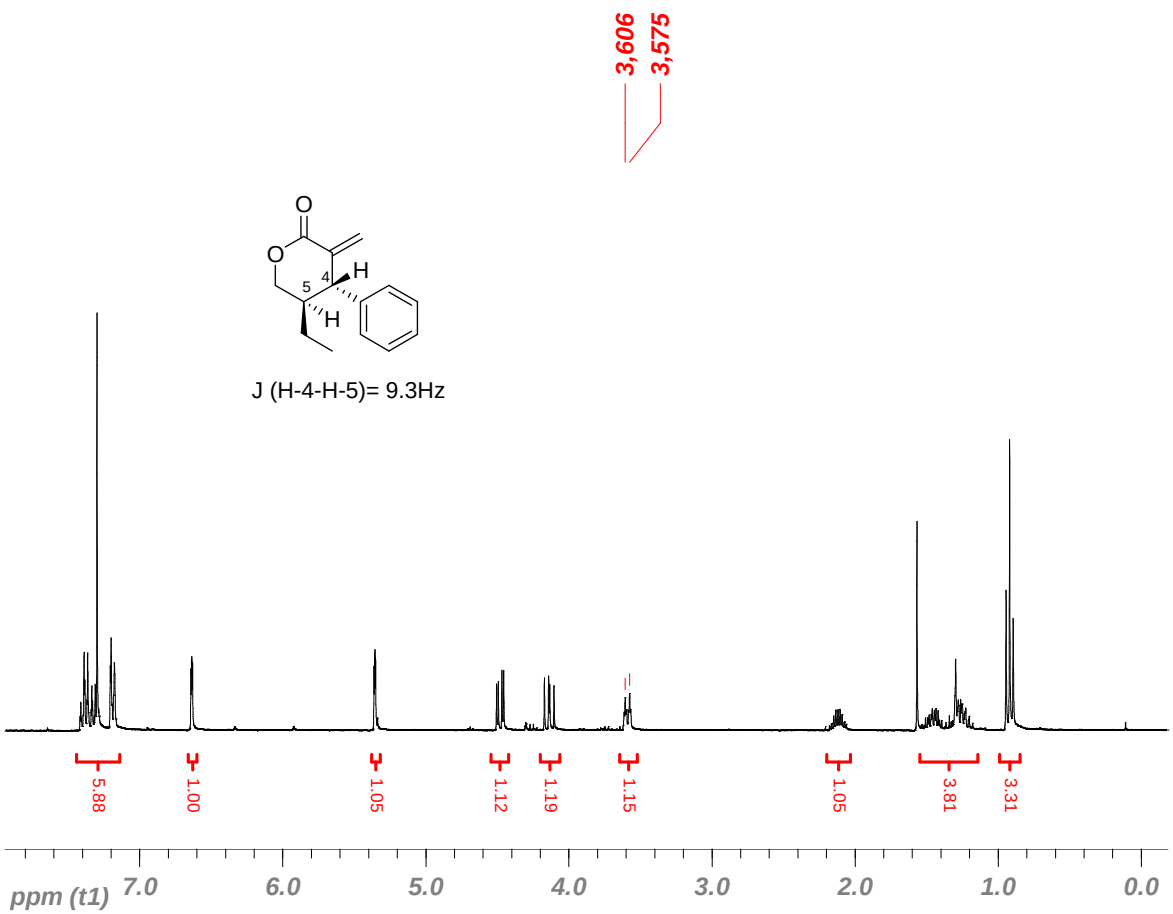

203,69
166,29
141,81
139,61
135,54
135,47
135,40
128,63
128,52
126,99
125,48
77,423
77,000
76,577
60,939
56,710
45,833
21,213
13,990
11,127
O
CO2Et
15
ppm (t1)
200
150
100
50
0

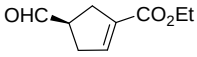


166,81 144,60 143,89 139,16 136,17 135,47 129,86 129,53 129,20 127,36 126,97 126,88 126,77 125,11 77,422 77,000 76,576 72,565 60,241 58,237 54,983 29,669 24,154 14,141

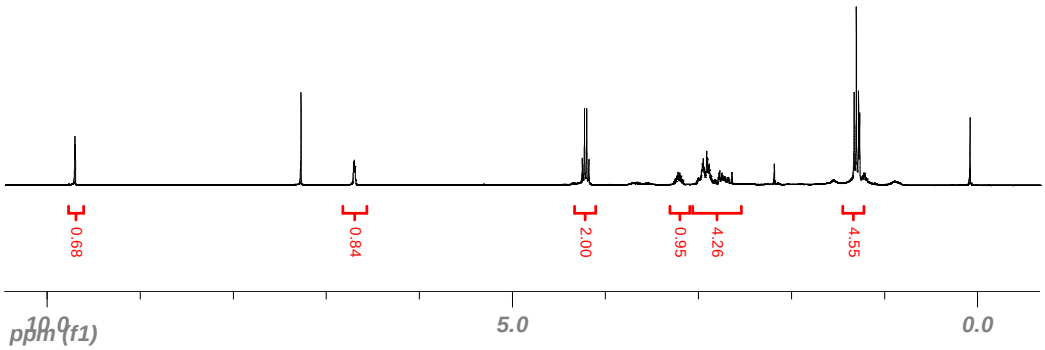



O
O
10
1.00
0.97
1.08
1.90
1.08
1.09
1.07
1.10
3.41
ppm (t1)
7.0
6.0
5.0
4.0
3.0
2.0

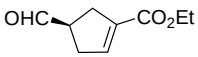

3,609
3,575
O
O
4
5
H
H
J (H-4-H-5)= 9.3Hz
5.88
1.00
1.05
1.12
1.19
1.15
1.05
3.81
3.31
ppm (t1)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0


OHC
CO2Et

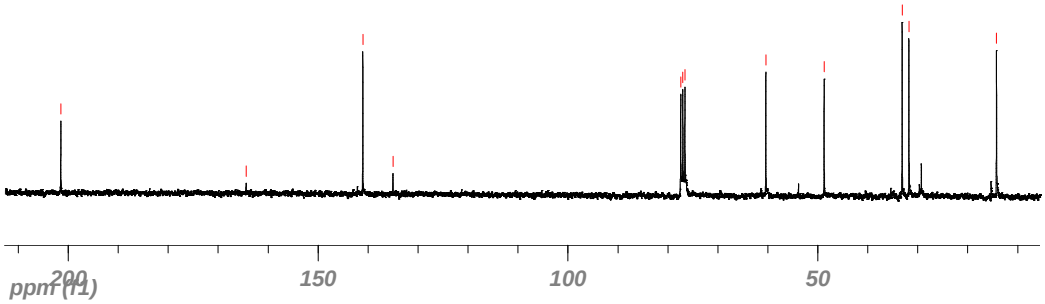
11e

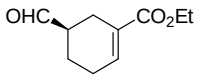

0.68
0.84
2.00
0.95
4.26
4.55
10.0
5.0
0.0
ppm (f1)


201,47
164,39
141,04
135,00
77,423
77,000
76,576
60,390
48,721
33,116
31,758
14,230

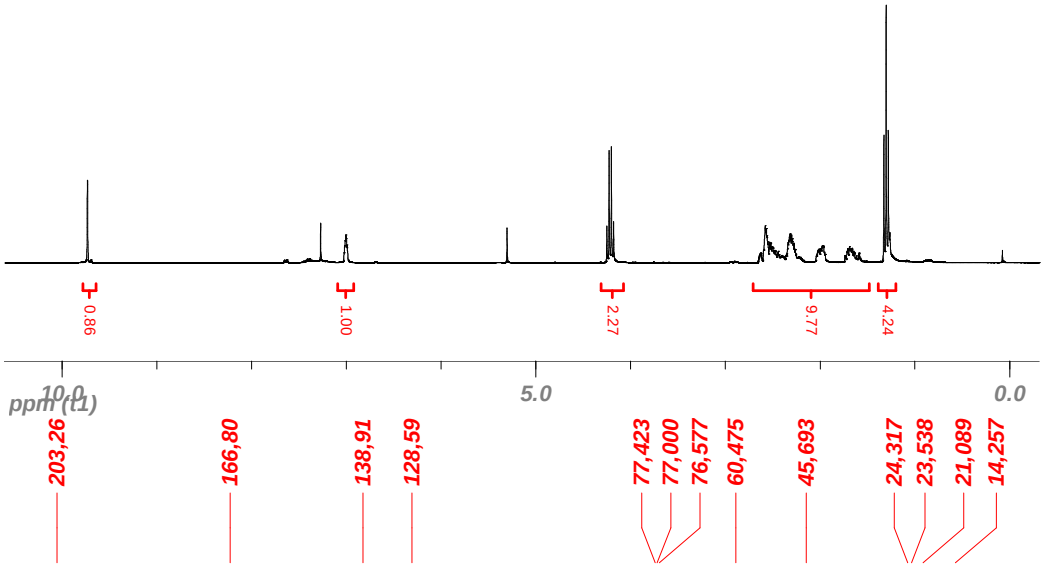

OHC
CO2Et

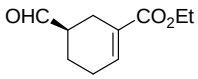
11e


200
150
100
50
ppm (f1)

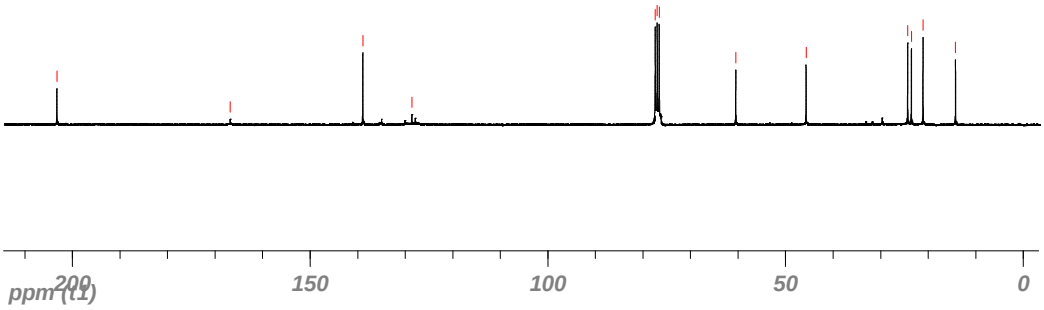

OHC
CO2Et

11f


0.86
1.00
2.27
9.77
4.24
10.0
5.0
0.0
ppm (t1)
203,26
166,80
138,91
128,59
77,423
77,000
76,577
60,475
45,693
24,317
23,538
21,089
14,257

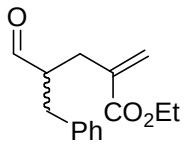

OHC
CO2Et

11f

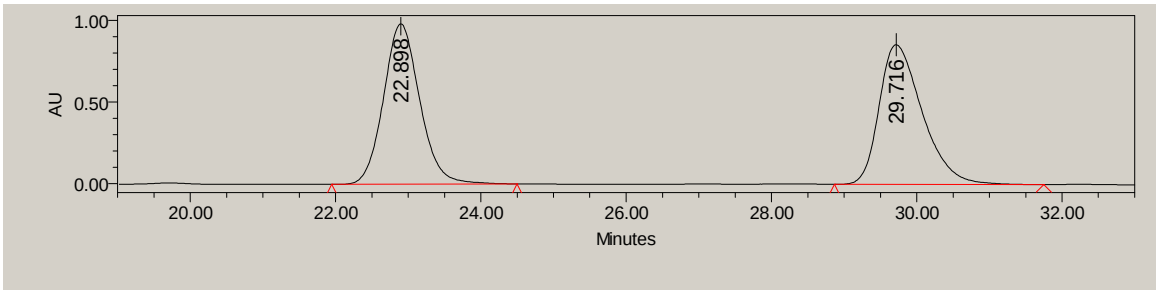

200
150
100
50
0
ppm (t1)

5. HPLC of compounds

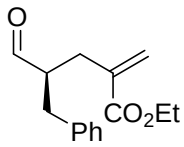
Chiralpak IC, 90:10 hexane:*i*PrOH, 0.5mL/min, λ=210nm



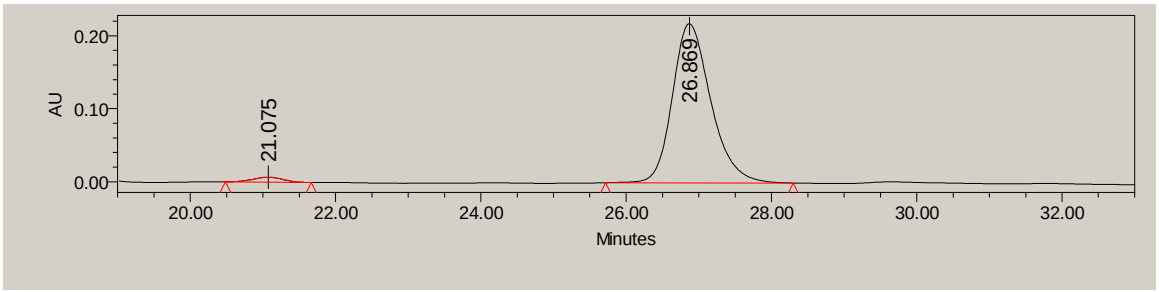
6a-rac



	Retention Time	% Area
1	22.898	49.10
2	29.716	50.90

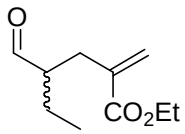


6a

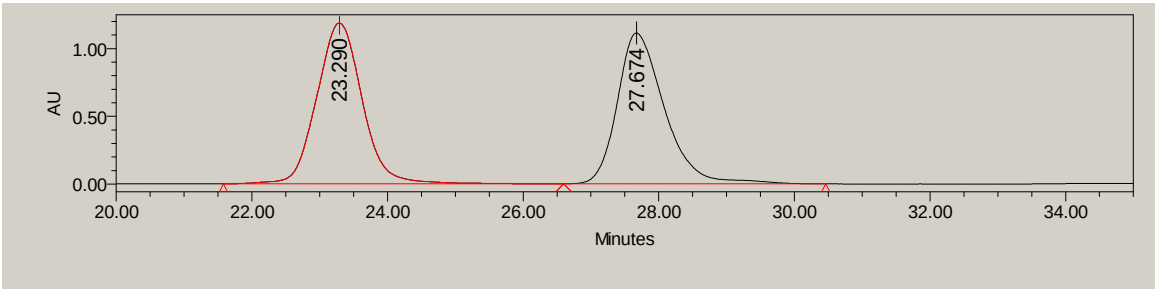


	Retention Time	% Area
2	26.869	96.53
1	21.070	3.47

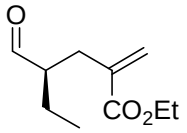
Chiralpak IC, 95:5 hexane:*i*PrOH, 0.5mL/min, λ=210nm



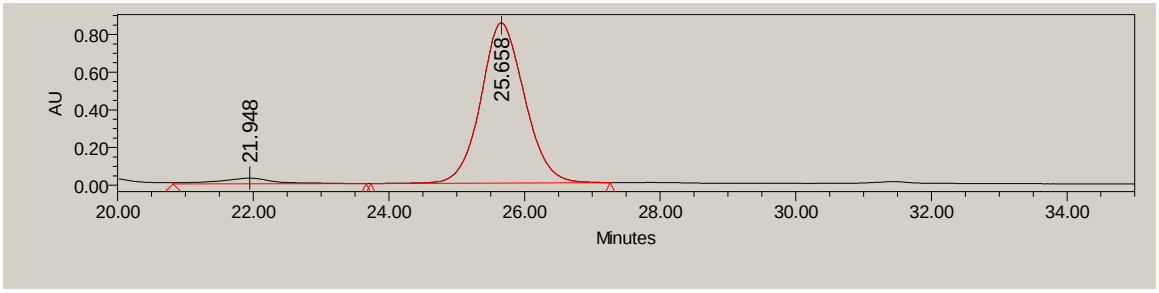
6b-rac



	Retention Time	% Area
1	23.290	50.68
2	27.674	49.32

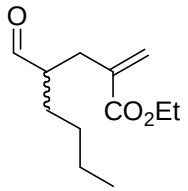


6b

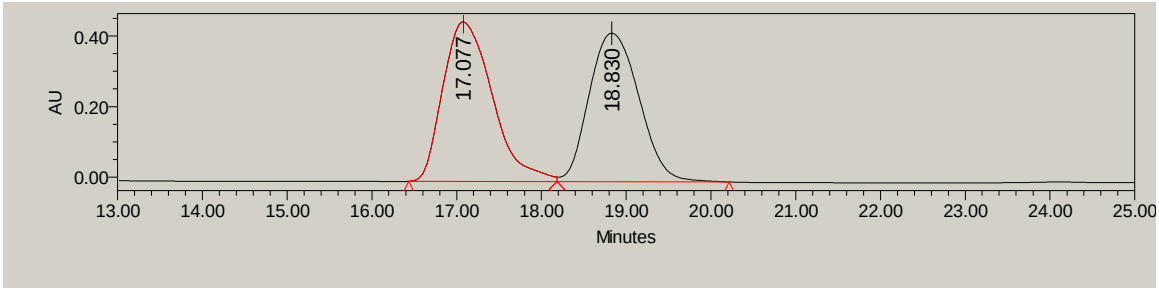


	Retention Time	% Area
2	25.658	95.72
1	21.948	4.28

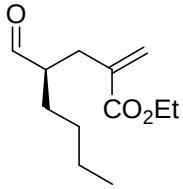
Chiralpak IC, 90:10 hexane:*i*PrOH, 0.5mL/min, λ=216nm



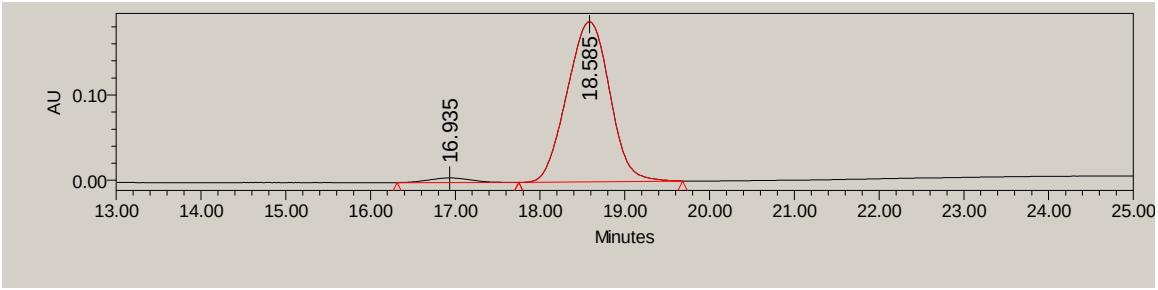
6c-rac



	Retention Time	% Area
1	17.077	51.58
2	18.830	48.42

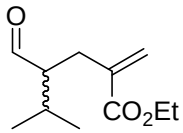


6c

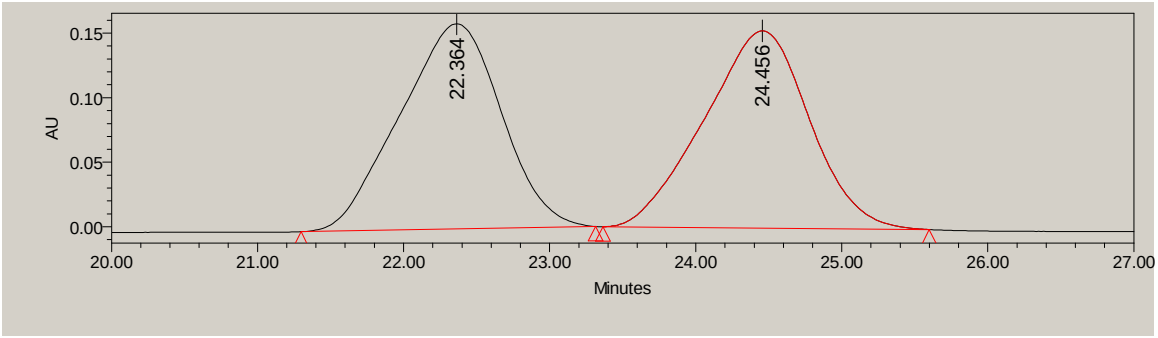


	Retention Time	% Area
2	18.585	97.35
1	16.935	2.65

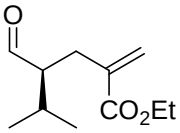
Chiralpak IC, 95:5 hexane:*i*PrOH, 0.5mL/min, λ=210nm



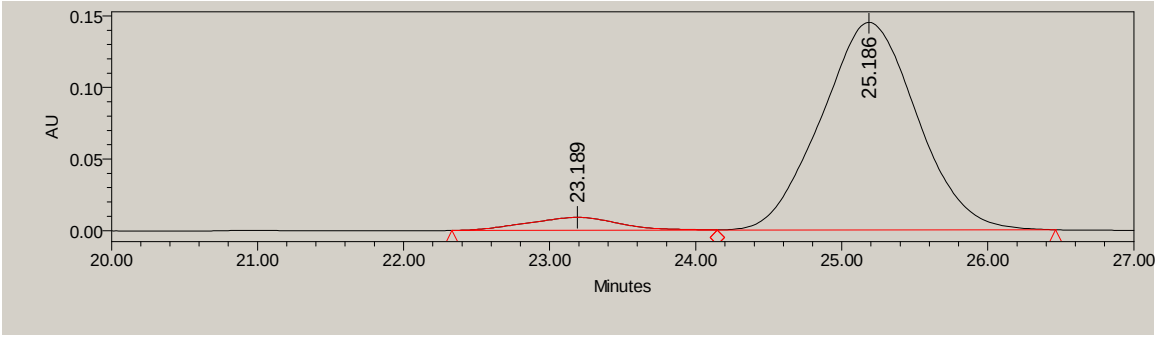
6d-rac



	Retention Time	% Area
1	22.364	49.96
2	24.456	50.04

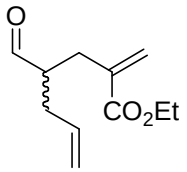


6d

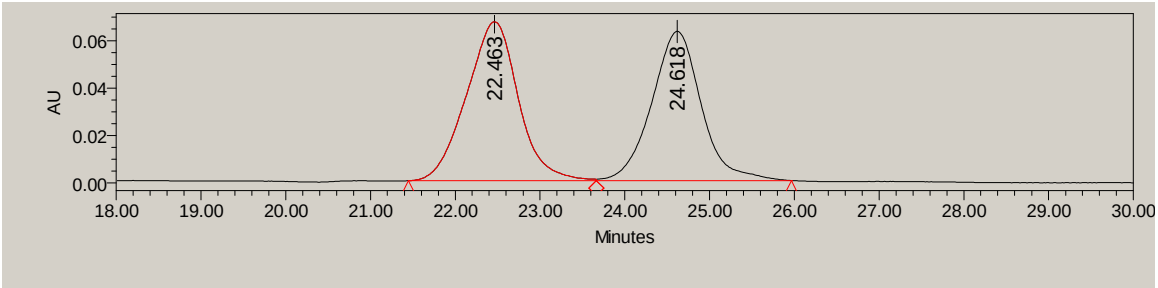


	Retention Time	% Area
1	23.189	5.70
2	25.186	94.30

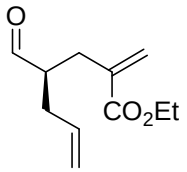
Chiralpak IC, 95:5 hexane:*i*PrOH, 0.5mL/min, λ=212nm



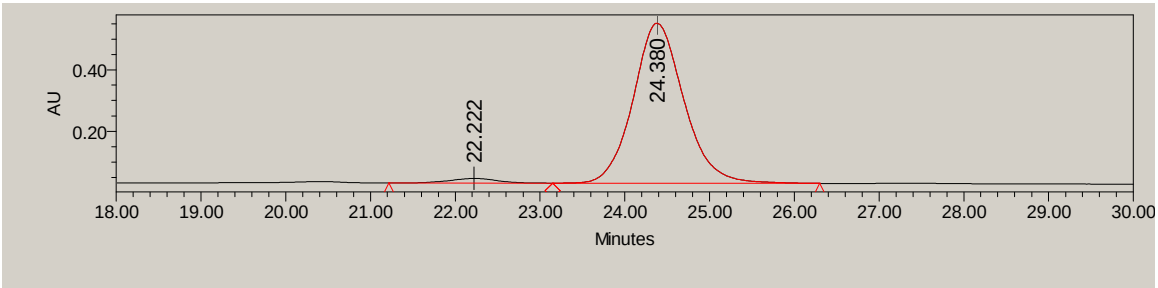
6e-rac



	Retention Time	% Area
1	22.463	52.72
2	24.618	47.28

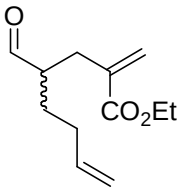


6e

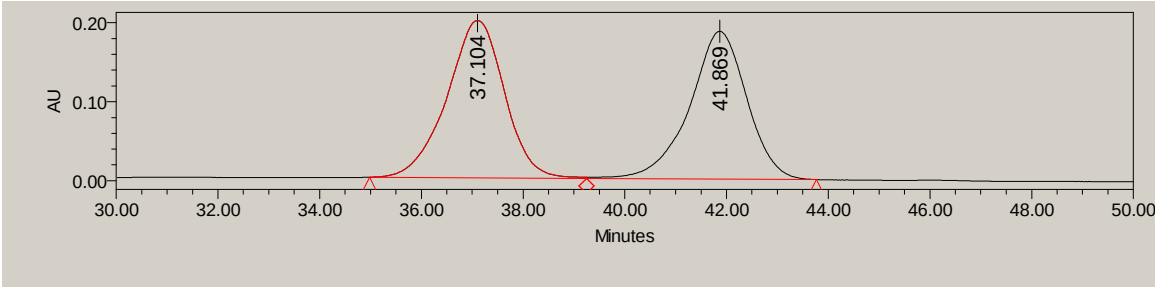


	Retention Time	% Area
2	24.380	97.32
1	22.222	2.68

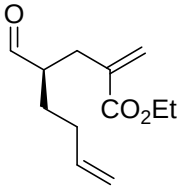
Chiralpak IC, 99:1 hexane:*i*PrOH, 0.5mL/min, λ=210nm



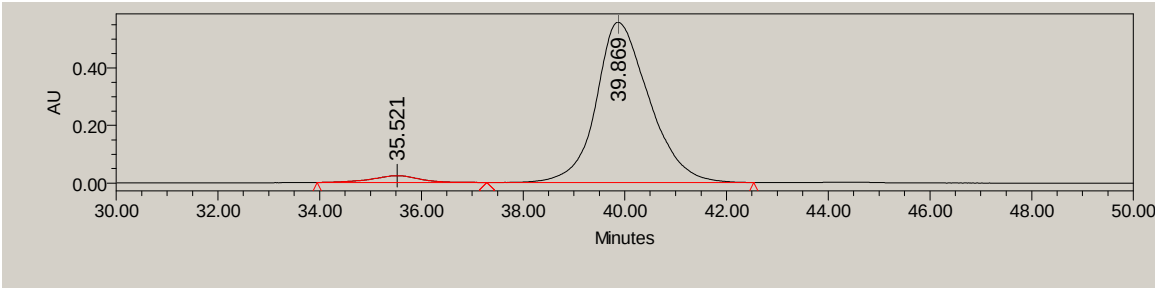
6f-rac



	Retention Time	% Area
1	37.104	51.61
2	41.869	48.39

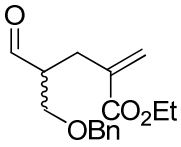


6f

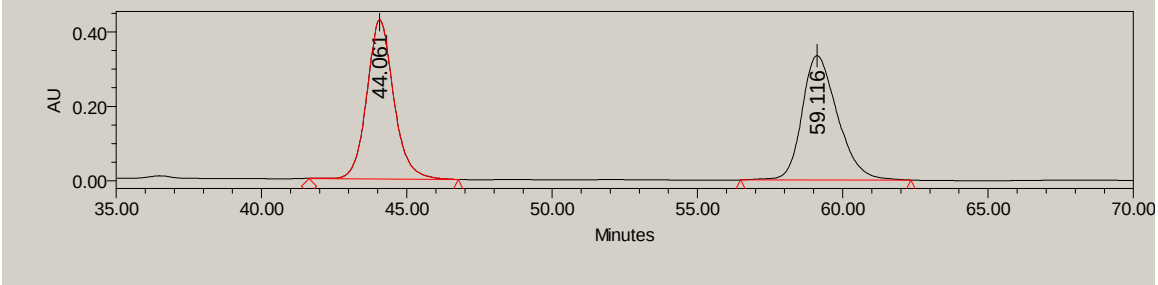


	Retention Time	% Area
1	35.521	3.60
2	39.869	96.40

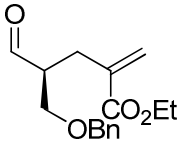
Chiralpak IC, 95:5 hexane:*i*PrOH, 0.5mL/min, λ=210nm



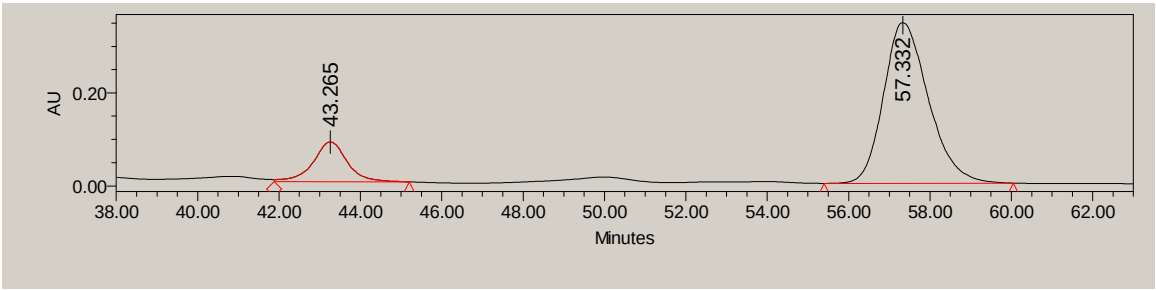
6i-rac



	Retention Time	% Area
1	44.061	49.32
2	59.116	50.68

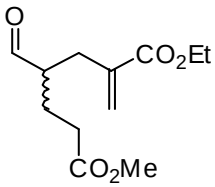


6i

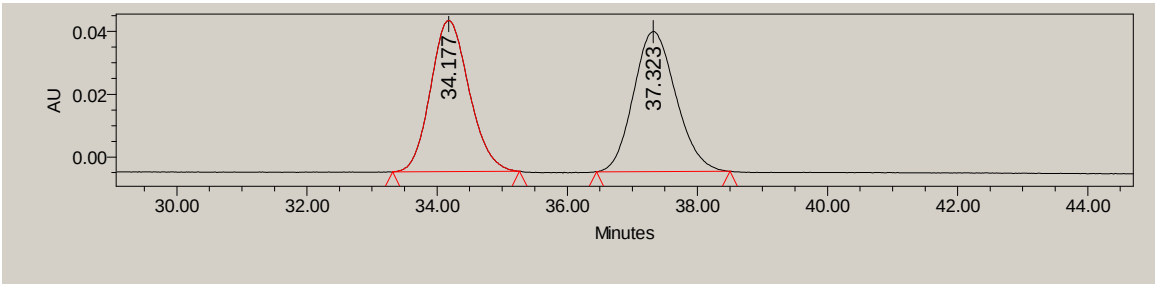


	Retention Time	% Area
1	43.265	15.94
2	57.332	84.06

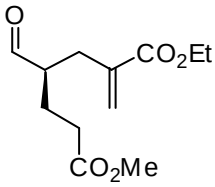
Chiralpak IC, 80:20 hexane:*i*PrOH, 0.5mL/min, λ=210nm



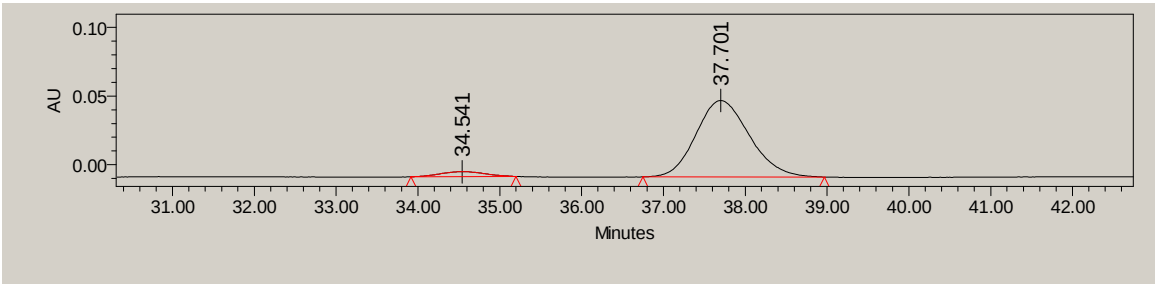
6j-rac



	Retention Time	% Area
1	34.177	49.50
2	37.323	50.50

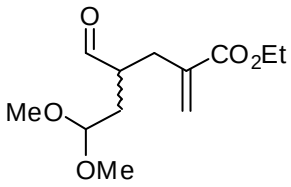


6j

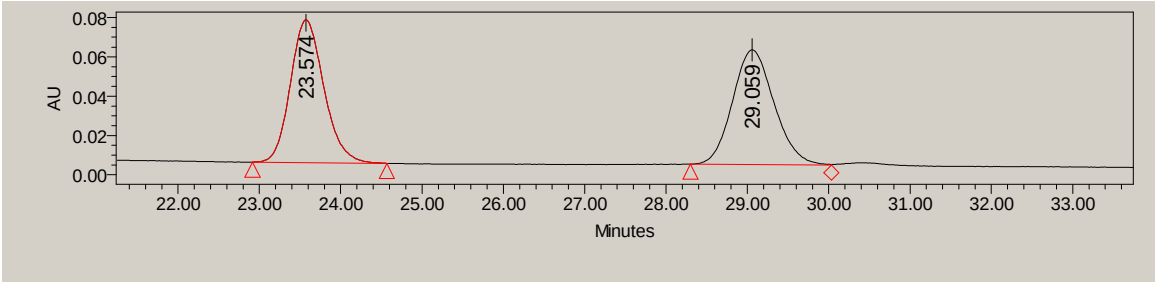


	Retention Time	% Area
1	34.541	5.09
2	37.701	94.91

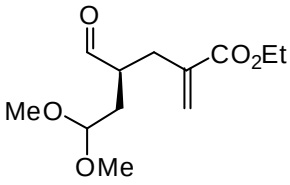
Chiralpak IC, 80:20 hexane:*i*PrOH, 0.5mL/min, λ=210nm



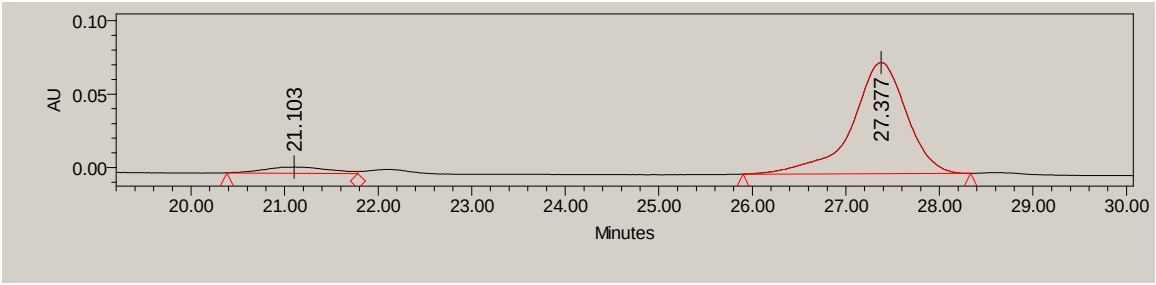
6k-rac



	Retention Time	% Area
1	23.574	50.03
2	29.059	49.97

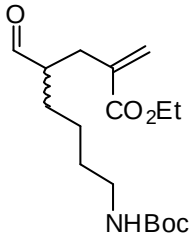


6k

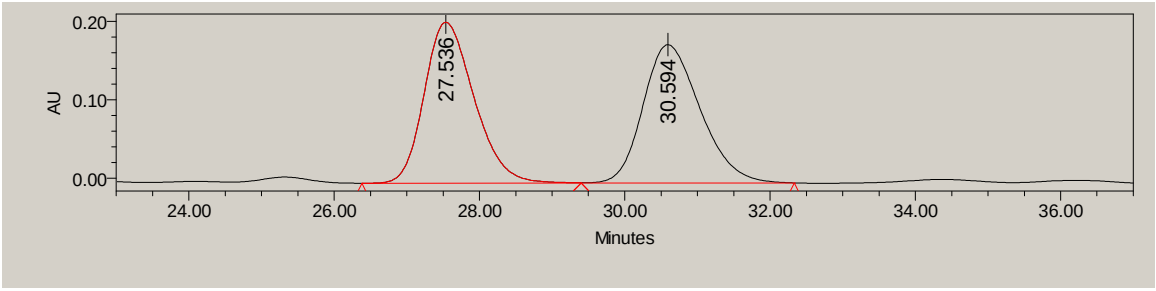


	Retention Time	% Area
2	21.103	6.32
1	27.377	93.68

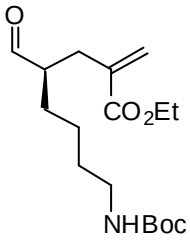
Chiralpak IC, 70:30 hexane:*i*PrOH, 0.5mL/min, λ=210nm



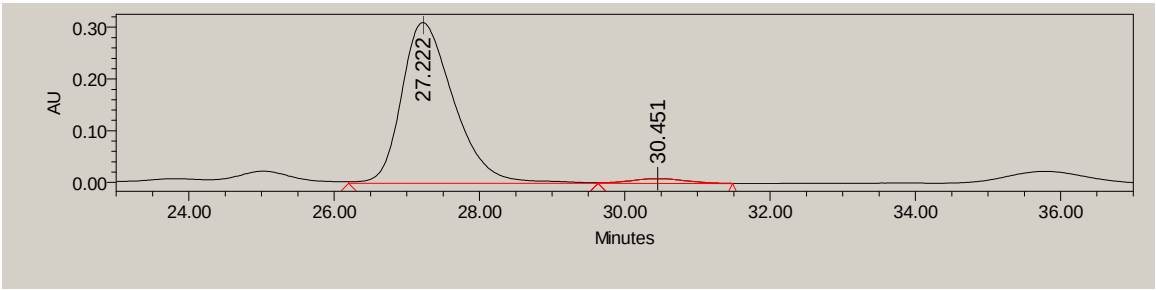
6l-rac



	Retention Time	% Area
1	27.536	50.39
2	30.594	49.61

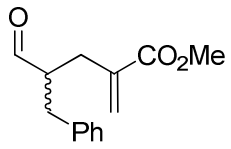


6l

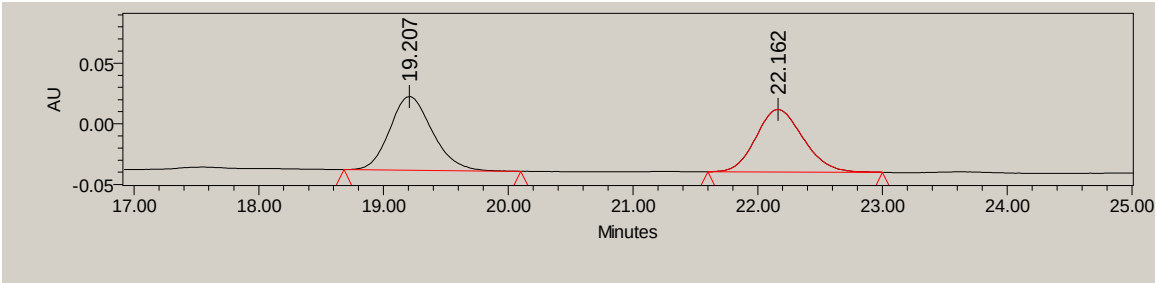


	Retention Time	% Area
2	30.451	3.03
1	27.222	96.97

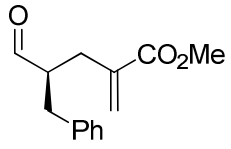
Chiralpak IC, 85:15 hexane:*i*PrOH, 0.5mL/min, λ=210nm



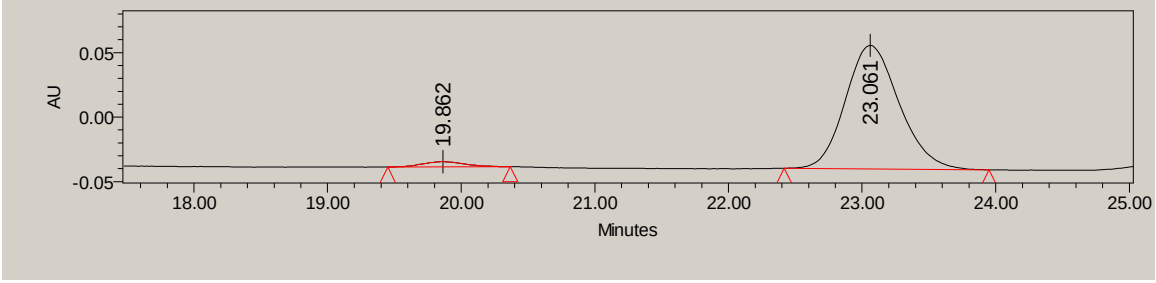
7a-rac



	Retention Time	% Area
2	22.162	48.37
1	19.207	51.63

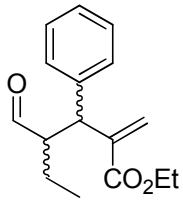


7a

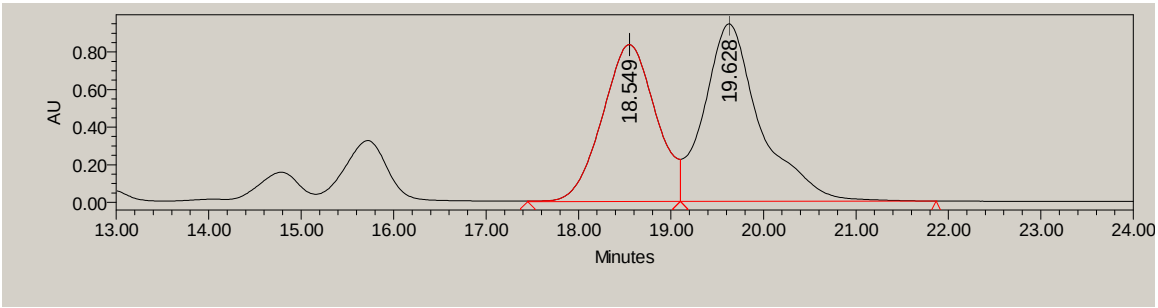


	Retention Time	% Area
1	19.862	3.23
2	23.061	96.77

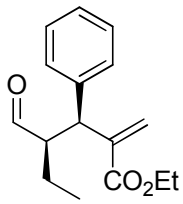
Chiralpak IC, 90:10 hexane:*i*PrOH, 0.5mL/min, λ=210nm



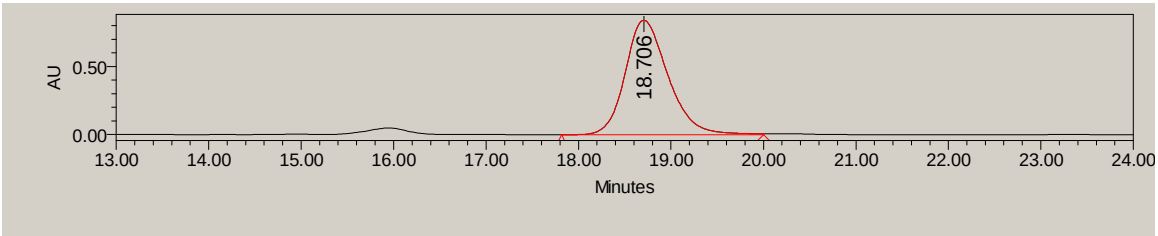
15-rac



	Retention Time	% Area
1	18.547	47.51
2	19.627	52.49

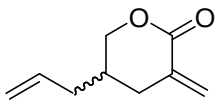


15

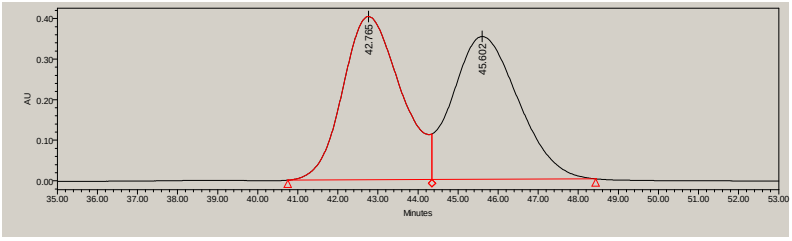


	Retention Time	% Area
1	18.706	100.00

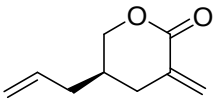
Chiralpak OD, 99:1 hexane:*i*PrOH, 0.5mL/min, λ=214nm



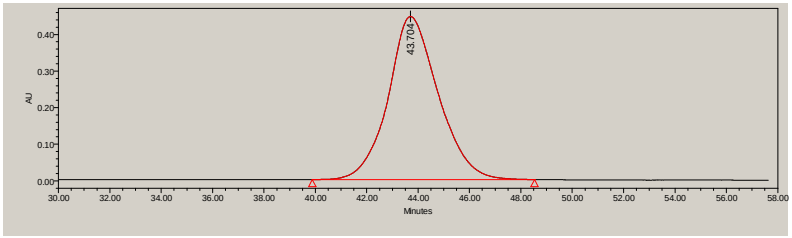
10-rac



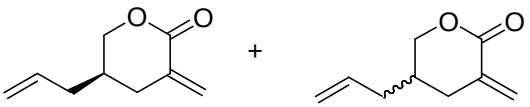
	Retention Time	% Area
1	42.765	50.35
2	45.602	49.65



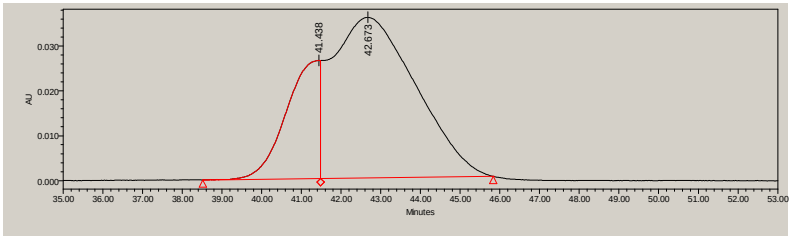
10



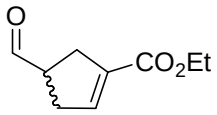
	Retention Time	% Area
1	43.704	100.00



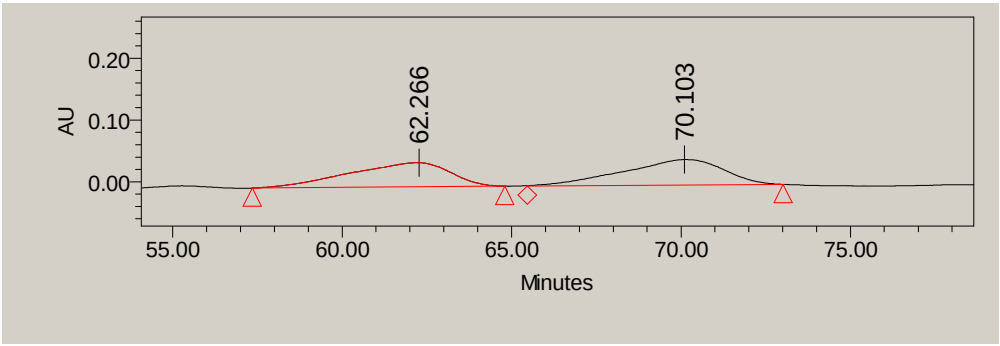
10 + **10**-rac



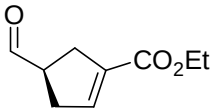
Chiralpak IC, 98:2 hexane:*i*PrOH:EtOH, 0.5mL/min, λ=210nm



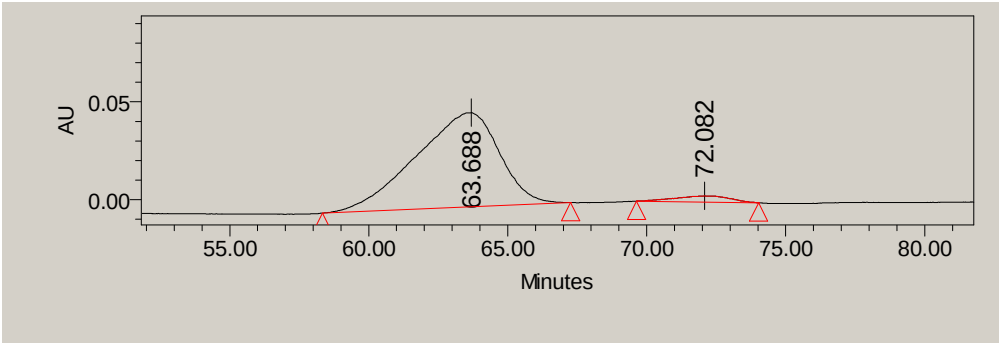
11e-rac



	Retention Time	% Area
1	62.266	48.79
2	70.103	51.21

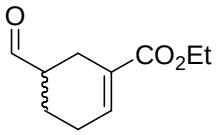


11e

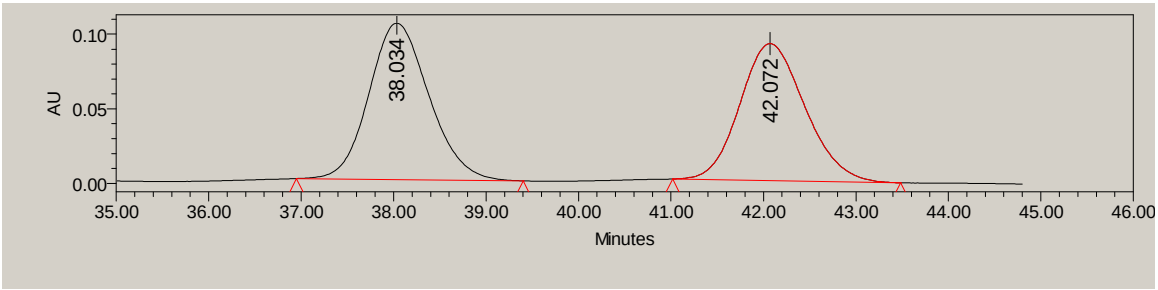


	Retention Time	% Area
1	63.688	95.94
2	72.082	4.06

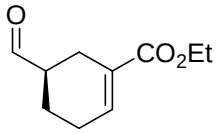
Chiralpak IC, 85:15 hexane:*i*PrOH, 0.5mL/min, λ=210nm



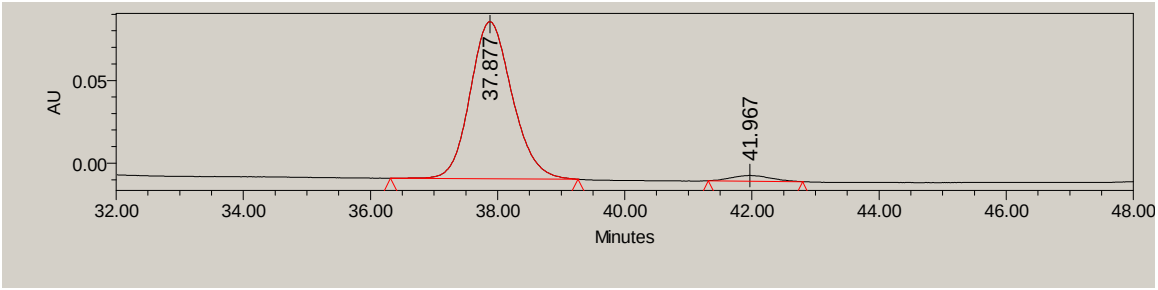
11f-rac



	Retention Time	% Area
2	42.072	48.72
1	38.034	51.28



11f



	Retention Time	% Area
1	37.877	96.78
2	41.967	3.22

6. Computational Methods

All reported structures were optimized at DFT level using the B3LYP[9] hybrid functional as implemented in Gaussian 09.[10] Optimizations were carried out using the standard 6-31G* basis set for all implied atoms H, C, N, O. All energy minima and transition structures were characterized by harmonic frequency analysis at the same level. The energies reported in this work include thermal and zero-point vibrational energy corrections (ZPVE) and are not scaled. The stationary points were characterized by frequency calculations in order to verify that they have the right number of negative eigenvalues. The intrinsic reaction coordinates (IRC)[11] were followed to verify the energy profiles connecting each TS to the correct associated local minima. Atomic charges and charge transfer values were calculated within the natural bond orbital (NBO) analysis.[12]

The transformation depicted in Figure S1 was considered for calculations, wherein the enamine derived from acetaldehyde and simple pyrrolidine, dimethylaminopyridine (DMAP), and methyl 2-bromomethyl acrylate are the intervening species. Based on previous experimental evidence, the whole transformation would involve two formal consecutive substitution reactions, namely (1) that of DMAP with 2-bromomethyl acrylate to yield the pyridium salt, and (2) substitution of the pyridinium moiety with the incoming enamine. Accordingly, both processes were calculated separately, and for each substitution event the feasibility of either S_N2 or S_N2' mechanism was studied.

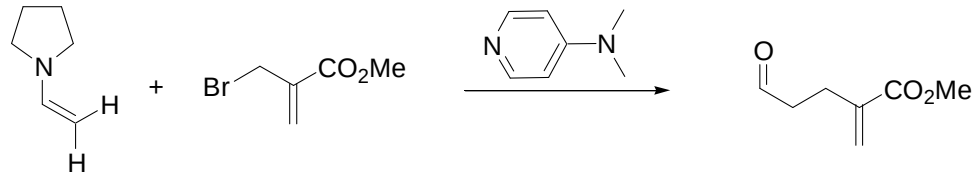


Figure S1. The model reaction considered for computational study.

Figure S2 shows the energy profiles corresponding to the S_N2 pathways. As the calculated values indicate, both processes are highly disfavored with exceedingly high activation energies of 20.7 (**TS1**) and 24.3 kcal/mol (**TS2**), respectively. This values are comparatively much higher than those corresponding to transition states for the S_N2' pathway (see below), and therefore the S_N2 mechanism could be ruled out.

---

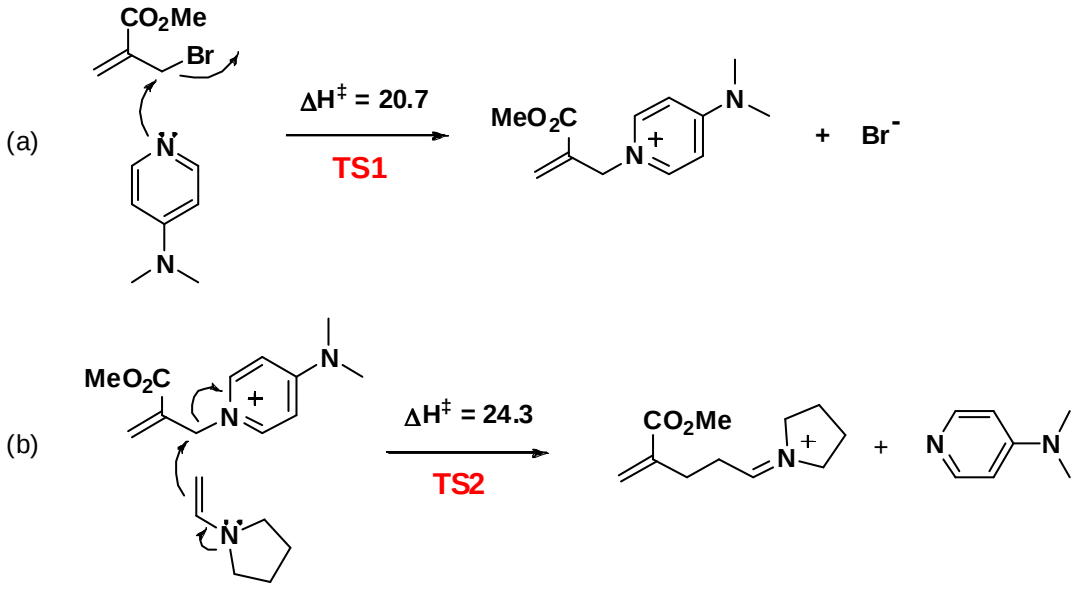
[9] (a) Lee, C.; Yang, W.; Parr, R.G. *Phys. Rev. B* **1988**, *37*, 785. (b) Becke, A.D. *J. Chem. Phys.* **1993**, *98*, 5648. (c) Kohn, W.; Becke, A.D.; Parr, R.G. *J. Phys. Chem.* **1996**, *100*, 12974.

[10] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Menucci, B., Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd,, J. J.; Brothers, E.; Kudin,. K. N.; Staroverov, V. N; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J.E.; Cross, J.B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R.E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09, Revision A.02, Gaussian, Inc., Wallingford CT, **2009**.

[11] Gonzalez, C.; Schlegel, H.B. *J. Phys. Chem.* **1990**, *94*, 5523.

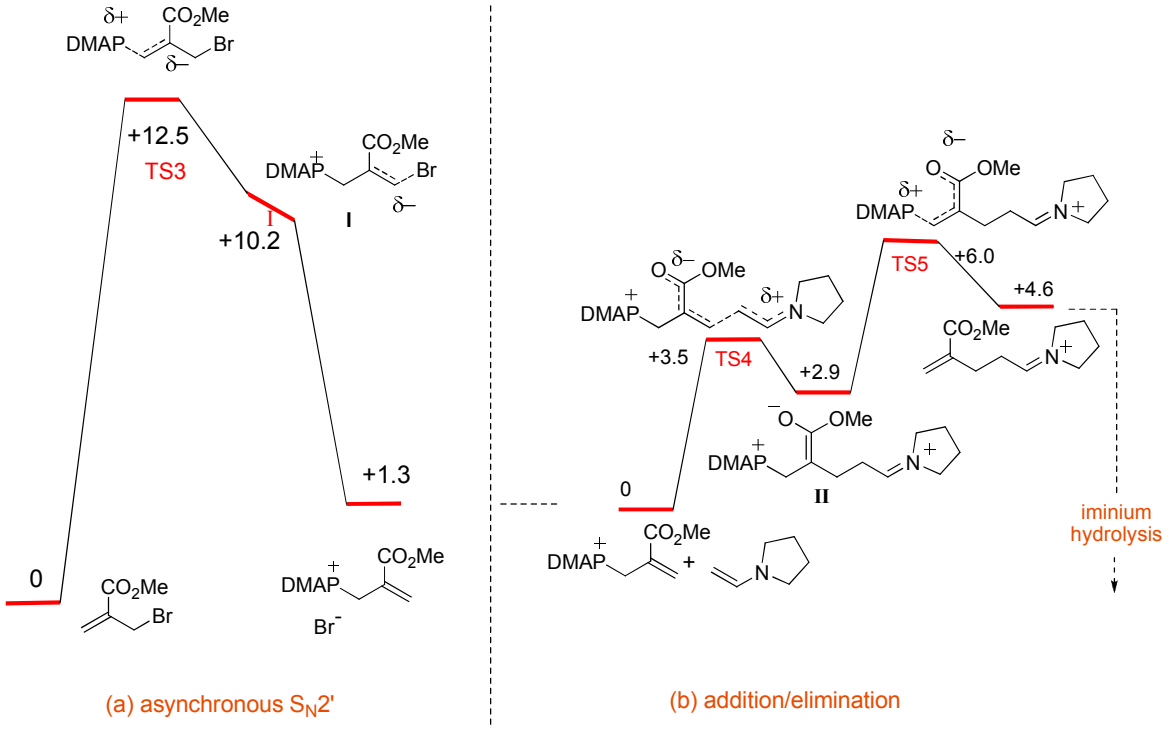
[12] (a) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735. (b) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.

Figure S2. S_N2 substitution mechanism for the two reaction steps.



Regarding the allylic displacement proposal (Figure S3), the calculations indicated that step (a), in which DMAP reacts with 2-bromomethyl acrylate, proceeds via an asynchronous S_N2' pathway, wherein the transition state carries a partial carbanion character and a "pseudointermediate" (**I**) can be identified. In its turn, step (b), in which the incoming enamine formally displaces the pyridinium moiety, proceeds via a two-step addition-elimination sequence. Thus, the 1,4–addition zwitterionic species **II** clearly appears as a reaction intermediate. It should be noted that the iminium product formed at the end of this process lies higher in energy than the starting pyridinium salt, and therefore subsequent hydrolysis of the iminium product with recovery of free pyrrolidine must account as the driven force for the whole transformation.

Figure S3. Minimum energy profile for the allylic substitution (S_N2') pathway.



Wiberg bond orders

The Wiberg bond orders and bond lengths corresponding to the significant breaking/forming bonds were also calculated for selected structures in Figure S3.

For step (a), these values (Table S1) are in agreement with a very asynchronous transition state (**TS3**), wherein bond **a** (N-C) is partially formed (BO = 0.53, 1.82 Å) before bond **d** (C-Br) starts to break (BO = 0.81, 2.13 Å). The reaction coordinate continues through a shoulder (**I**) showing partial maximum and minimum character, which contains a fully formed C-N bond and a partially broken C-Br bond.

For step (b), the Michael addition of enamine to the pyridinium adduct proceeds through transition state **TS4** (BO = 0.85 and 0.52) and renders the zwitterionic intermediate **II** with equally formed C-N (BO = 0.82, 1.54 Å) and C-C bonds (BO = 0.82, 1.68 Å). The elimination of DMAP from **II** renders the final iminium product through transition state **TS5**, which shows opposite bond orders to **TS4** (BO = 0.46 for C-N, and 0.89 for C-C). Noteworthy, the structure **I** (step a) presents mixed features of both the minimum **II** and the maximum **TS5** (see bond orders).

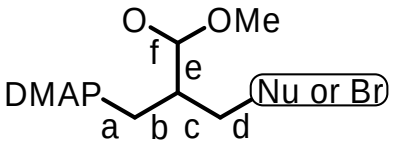
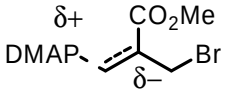
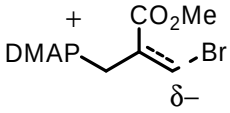
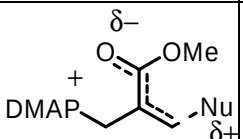
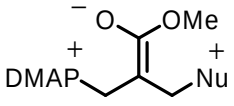
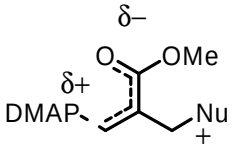


Table S1. Wiberg bond orders for the significant bonds of structures in Figure S3

		a	b	c	**d**	e	f
	**TS3**	**0.531**	1.308	1.157	**0.812**	1.138	1.624
	**I**	**0.827**	1.052	1.327	**0.616**	1.204	1.533
	**TS4**	**0.854**	1.042	1.354	**0.524**	1.170	1.581
	**II**	**0.825**	1.073	1.118	**0.818**	1.264	1.542
	**TS5**	**0.458**	1.394	1.042	**0.894**	1.153	1.637

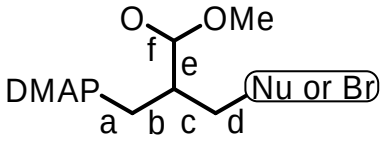
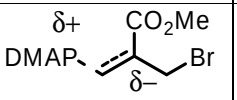
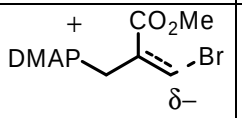
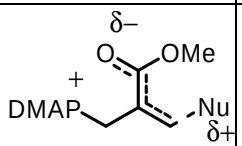
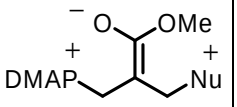
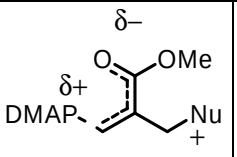


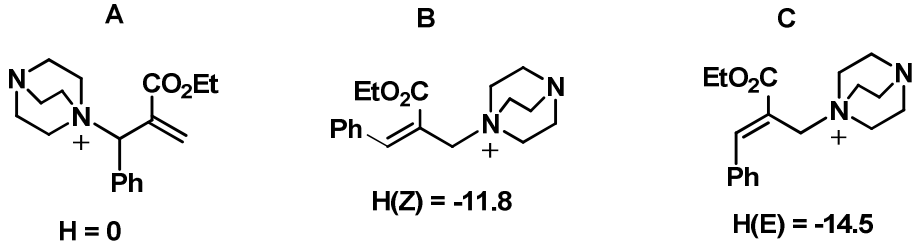
Table S2. Bond lengths in Å for the breaking/forming bonds of structures in Figure S2

		a	b	c	**d**	e	f
	**TS3**	1.82	1.41	1.45	2.13	1.45	1.23
	**I**	1.53	1.48	1.41	2.30	1.43	1.24
	**TS4**	1.52	1.49	1.41	1.99	1.44	1.23
	**II**	1.54	1.48	1.46	1.68	1.42	1.24
	**TS5**	1.91	1.40	1.49	1.62	1.45	1.23

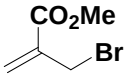
Reaction with β-substituted 2-(bromomethyl)acrylate

The energies for the three possible ammonium intermediate species resulting from the displacement of Br atom of the starting bromide **14** were calculated. Structures **B** and **C** resulted more stable than **A** by large. We presume that both **B** and **C** might arise from **14** via a double S_N2' process.

The prevalence of the bromide salts corresponding to structures **B** and **C** in solution was confirmed by ^1H NMR analysis of an aliquot taken from the reaction mixture of DABCO and **14** in CH_2Cl_2 (see ^1H NMR spectrum on page S31).



Cartesian Coordinates and absolute energies (in hartrees) of the structures discussed in the Main Text.



Standard orientation:

Atomic Type	Coordinates (Angstroms) X	Y	Z
C	-0.6050	-1.5370	1.3270
C	-0.4350	2.5460	0.5060
C	-0.7260	0.3890	-0.3950
C	-0.8350	-1.0720	-0.0730
C	-1.1590	-1.9100	-1.0670
H	-1.0730	-0.8950	2.0690
H	-0.9020	-2.5750	1.4670
H	-1.2540	-2.9790	-0.9030
H	-1.3290	-1.5310	-2.0690
H	0.4240	2.7570	-0.1360
H	-0.2920	2.9790	1.4960
H	-1.3380	2.9430	0.0360
O	-0.7950	0.8600	-1.5120
O	-0.5620	1.1310	0.7200
Br	1.3380	-1.4870	1.7960

Sum of electronic and thermal Enthalpies= -2916.762979
Sum of electronic and thermal Free Energies= -2916.809088

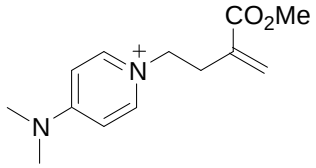
TS1

Standard orientation:

Atomic Type	Coordinates (Angstroms) X	Y	Z
C	2.9225	-0.7085	1.4285
C	3.2685	3.4715	1.7185
C	2.7345	1.5625	0.4605
C	2.8405	0.0765	0.3415
C	2.7115	-0.4405	-1.0335
H	3.0135	-0.2865	2.4215
H	2.9395	-1.7915	1.3425
H	3.0685	-1.4335	-1.2575
H	2.6215	0.2575	-1.8475
H	3.7435	3.9715	0.8715
H	3.8085	3.6855	2.6415
H	2.2285	3.8015	1.7935
O	2.1175	2.2595	-0.3285
O	3.3395	2.0465	1.5565
N	0.8365	-0.9475	-1.1215
Br	5.1975	0.2165	-1.4435
C	-0.1135	0.0035	-1.1285
H	0.2435	1.0235	-1.0095
C	0.4635	-2.2255	-1.2715
H	1.2625	-2.9625	-1.2725
C	-1.4565	-0.2875	-1.2725
H	-2.1665	0.5295	-1.2685
C	-1.8795	-1.6335	-1.4225
C	-0.8545	-2.6155	-1.4195

H	-1.0775	-3.6675	-1.5365
N	-3.1965	-1.9665	-1.5635
C	-3.5845	-3.3615	-1.7325
H	-3.2755	-3.9715	-0.8735
H	-3.1485	-3.7955	-2.6415
H	-4.6695	-3.4225	-1.8155
C	-4.2165	-0.9245	-1.5795
H	-4.0715	-0.2285	-2.4165
H	-4.2165	-0.3475	-0.6455
H	-5.1975	-1.3875	-1.6895

Sum of electronic and thermal Enthalpies= -3298.816030
Sum of electronic and thermal Free Energies= -3298.886938
Frequency: 382.3i



Standard orientation:

Atomic Type	Coordinates (Angstroms) X	Y	Z
C	4.2050	-0.5610	0.5550
C	2.7210	3.0370	2.1420
C	2.7590	1.4620	0.3860
C	3.3100	0.1670	-0.1240
C	2.8280	-0.2210	-1.5020
H	4.5640	-0.2440	1.5280
H	4.6170	-1.4830	0.1510
H	3.4010	-1.0680	-1.8870
H	2.9390	0.6120	-2.1990
H	3.0350	3.8600	1.4970
H	3.1800	3.1180	3.1270
H	1.6320	3.0280	2.2200
O	1.9940	2.1440	-0.2760
O	3.1920	1.7790	1.6070
N	1.3880	-0.6100	-1.5340
C	0.4350	0.2560	-1.9720
H	0.7850	1.2370	-2.2650
C	1.0100	-1.8440	-1.1020
H	1.8070	-2.4900	-0.7520
C	-0.8910	-0.0860	-2.0080
H	-1.5920	0.6530	-2.3710
C	-1.3240	-1.3740	-1.5730
C	-0.2960	-2.2510	-1.1070
H	-0.5190	-3.2490	-0.7550
N	-2.6180	-1.7420	-1.5980
C	-3.0220	-3.0760	-1.1400
H	-2.7630	-3.2260	-0.0860
H	-2.5500	-3.8600	-1.7420
H	-4.1020	-3.1730	-1.2410
C	-3.6440	-0.8110	-2.0840
H	-3.4610	-0.5330	-3.1270
H	-3.6760	0.0960	-1.4700
H	-4.6170	-1.2960	-2.0260

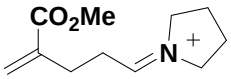
Sum of electronic and thermal Enthalpies= -726.951067
Sum of electronic and thermal Free Energies= -727.014603

TS2

Standard orientation:

Atomic Type	Coordinates (Angstroms) X	Y	Z
C	1.2360	0.5545	-1.4150
C	1.9460	1.7675	2.5300
C	5.6590	-1.7985	0.9200
C	4.8750	-0.6795	0.2140
C	1.3330	2.4165	0.3480
C	3.8990	-0.6055	-2.0640
C	1.1260	1.9715	-1.0740
C	4.8300	-2.7165	-1.1420
C	0.8000	2.9125	-1.9800
C	5.0750	-3.0915	0.3240
C	3.4810	0.7155	-2.0290
H	1.5340	-0.1685	-0.6770
H	1.0260	0.2225	-2.4190
H	0.6380	2.6675	-3.0260
H	0.7050	3.9495	-1.6780
H	3.9820	-0.3725	0.7720
H	4.0270	-3.2885	-1.6160
H	5.7410	-2.8385	-1.7420
H	3.8070	1.3695	-1.2280
H	5.7430	-3.9495	0.4240
H	4.1260	-3.3435	0.8110
H	2.7030	2.5495	2.6220
H	6.7240	-1.7185	0.6780
H	2.2690	0.8525	3.0260
H	5.5620	-1.7455	2.0070
H	1.0060	2.1275	2.9540
H	3.7110	-1.1965	-2.9600
H	5.4770	0.2175	0.0300
H	3.2580	1.1945	-2.9750
N	4.4680	-1.2855	-1.0680
O	1.1410	3.5465	0.7380
O	1.7620	1.4105	1.1420
N	-0.7790	0.0015	-0.8950
C	-0.9950	-1.2125	-0.3620
H	-0.1130	-1.8145	-0.1540
C	-1.8490	0.7645	-1.1630
H	-1.6460	1.7465	-1.5830
C	-3.1490	0.3645	-0.9200
H	-3.9570	1.0425	-1.1630
C	-2.2520	-1.7085	-0.0790
H	-2.3390	-2.6965	0.3530
C	-3.4010	-0.9165	-0.3560
N	-4.6600	-1.3555	-0.0960
C	-4.8710	-2.6795	0.4860
H	-4.3880	-2.7675	1.4670
H	-4.4860	-3.4715	-0.1680
H	-5.9400	-2.8425	0.6200
C	-5.8110	-0.5075	-0.3970
H	-5.8670	-0.2735	-1.4670
H	-5.7750	0.4315	0.1680
H	-6.7240	-1.0345	-0.1190

Sum of electronic and thermal Enthalpies= -1016.726193
Sum of electronic and thermal Free Energies= -1016.813039
Frequency: 422.4i



Standard orientation:

Atomic Type	Coordinates (Angstroms) X	Y	Z
C	-1.6030	-0.9865	-0.7515
C	-0.9060	2.9845	0.4335
C	3.3070	-0.6205	1.2495
C	2.1010	-0.3485	0.3365
C	-2.2750	1.5265	-0.8225
C	0.6940	-1.9545	-0.9255
C	-2.5280	0.1075	-1.2355
C	2.5360	-2.7655	0.4955
C	-3.5920	-0.1335	-2.0105
C	3.0980	-2.0665	1.7335
C	-0.2240	-0.9405	-1.4965
H	-1.4300	-0.8785	0.3235
H	-2.0720	-1.9625	-0.9165
H	-3.8490	-1.1375	-2.3385
H	-4.2380	0.6805	-2.3245
H	1.2540	0.0975	0.8645
H	1.9340	-3.6545	0.6935
H	3.3270	-3.0165	-0.2205
H	0.1900	0.0665	-1.4265
H	4.0220	-2.5375	2.0765
H	2.3730	-2.1055	2.5535
H	-0.7350	3.6545	-0.4115
H	4.2380	-0.5385	0.6795
H	-0.0150	2.9095	1.0575
H	3.3550	0.0985	2.0695
H	-1.7540	3.3515	1.0155
H	0.5080	-3.0075	-1.1405
H	2.3360	0.2715	-0.5325
H	-0.3910	-1.1805	-2.5535
N	1.6790	-1.7105	-0.1325
O	-2.9620	2.4715	-1.1365
O	-1.1680	1.6415	-0.0355

Sum of electronic and thermal Enthalpies= -634.671558
Sum of electronic and thermal Free Energies= -634.731413

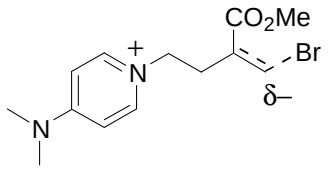
TS3

Standard orientation:

Atomic Type	Coordinates (Angstroms) X	Y	Z
C	3.1020	-0.4280	2.3075
C	3.3500	3.6780	1.4715
C	2.9250	1.5040	0.6545
C	2.8690	0.0890	0.9675
C	2.7040	-0.7910	-0.1265
H	3.0450	0.3150	3.0955
H	2.5450	-1.3270	2.5605
H	3.0920	-1.8010	-0.0055
H	2.8830	-0.3600	-1.1085

H	4.1020	3.8880	0.7055
H	3.6360	4.1400	2.4185
H	2.3890	4.0780	1.1295
O	2.6850	2.0060	-0.4415
O	3.2620	2.2790	1.7355
N	0.9720	-1.2570	-0.4235
Br	5.0620	-1.1880	2.6215
C	0.0120	-0.5420	0.1695
H	0.3790	0.2340	0.8405
C	0.6310	-2.2410	-1.2675
H	1.4530	-2.7850	-1.7265
C	-1.3300	-0.7810	-0.0455
H	-2.0570	-0.1640	0.4665
C	-1.7300	-1.8190	-0.9285
C	-0.6840	-2.5580	-1.5455
H	-0.8910	-3.3690	-2.2315
N	-3.0440	-2.0930	-1.1705
C	-3.4130	-3.1670	-2.0855
H	-3.0410	-4.1400	-1.7365
H	-3.0230	-2.9890	-3.0955
H	-4.5000	-3.2240	-2.1485
C	-4.0860	-1.3110	-0.5165
H	-4.0200	-0.2480	-0.7845
H	-4.0290	-1.3980	0.5755
H	-5.0620	-1.6800	-0.8345

Sum of electronic and thermal Enthalpies= -3298.829108
Sum of electronic and thermal Free Energies= -3298.900497
Frequency: 227.8i



Standard orientation:

Atomic Type	Coordinates (Angstroms) X	Y	Z
C	3.0230	-0.6640	1.4270
C	2.7390	3.5380	1.6830
C	2.4140	1.5620	0.4310
C	2.5270	0.1370	0.3770
C	2.2910	-0.4780	-0.9520
H	3.1810	-0.1830	2.3850
H	2.6640	-1.6850	1.5080
H	2.8940	-1.3810	-1.0830
H	2.5000	0.2210	-1.7650
H	3.2840	4.0490	0.8830
H	3.1560	3.8110	2.6540
H	1.6860	3.8340	1.6270
O	1.8910	2.2680	-0.4510
O	2.8860	2.1230	1.5850
N	0.8400	-0.9100	-1.1840
Br	5.1690	-1.4290	1.0660
C	-0.1250	0.0400	-1.1750
H	0.2420	1.0560	-1.0310
C	0.4920	-2.2050	-1.3320

H	1.3070	-2.9190	-1.3290
C	-1.4510	-0.2830	-1.3290
H	-2.1690	0.5250	-1.3170
C	-1.8640	-1.6390	-1.4820
C	-0.8180	-2.6020	-1.4740
H	-1.0080	-3.6610	-1.5810
N	-3.1790	-1.9550	-1.6260
C	-3.6920	-3.3170	-1.7220
H	-2.8890	-4.0490	-1.7110
H	-4.2560	-3.4450	-2.6540
H	-4.3590	-3.5340	-0.8780
C	-4.1930	-0.9020	-1.6260
H	-4.0150	-0.1770	-2.4290
H	-4.2240	-0.3690	-0.6680
H	-5.1690	-1.3590	-1.7930

Sum of electronic and thermal Enthalpies= -3298.831826
Sum of electronic and thermal Free Energies= -3298.901066

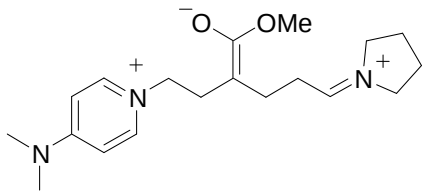
TS4

Standard orientation:

Atomic Type	Coordinates (Angstroms) X	Y	Z
C	1.3590	-1.2925	-0.2545
C	2.0840	2.7805	0.3915
C	6.4040	-0.0325	0.6825
C	5.1310	-0.2175	-0.1595
C	0.7240	1.1025	-0.5765
C	3.8910	-2.2795	-0.7585
C	0.4960	-0.3065	-0.7785
C	5.8100	-2.3575	0.8135
C	-0.6110	-0.6505	-1.7205
C	6.3760	-1.2175	1.6655
C	2.8770	-1.6415	-1.4915
H	1.9390	-1.0105	0.6185
H	0.9810	-2.3115	-0.2005
H	-0.4590	-1.6245	-2.1935
H	-0.7250	0.1035	-2.5035
H	4.2700	0.3325	0.2385
H	5.2940	-3.1295	1.3905
H	6.5970	-2.8385	0.2175
H	3.0610	-0.6245	-1.8215
H	7.3600	-1.4575	2.0755
H	5.7020	-1.0065	2.5035
H	2.1740	3.3575	-0.5325
H	7.2910	-0.0945	0.0425
H	3.0110	2.8285	0.9635
H	6.4250	0.9375	1.1855
H	1.2540	3.1835	0.9785
H	3.8460	-3.3575	-0.6075
H	5.2620	0.0815	-1.2055
H	2.3810	-2.2645	-2.2315
N	4.8580	-1.6685	-0.0835
O	-0.0280	2.0045	-0.9585
O	1.8770	1.3875	0.1065
N	-1.9840	-0.7415	-1.0705
C	-2.5870	0.3935	-0.6275
H	-2.0120	1.3035	-0.7735
C	-2.6140	-1.9295	-0.9085

H	-2.0930	-2.8025	-1.2845
C	-3.8450	-2.0325	-0.3105
H	-4.2880	-3.0145	-0.2195
C	-3.8190	0.3665	-0.0245
H	-4.2430	1.3065	0.3015
C	-4.5130	-0.8645	0.1625
N	-5.7280	-0.9225	0.7495
C	-6.3840	0.3025	1.2125
H	-6.5530	0.9995	0.3825
H	-5.7890	0.8045	1.9835
H	-7.3520	0.0465	1.6425
C	-6.4060	-2.2095	0.9215
H	-5.8110	-2.8915	1.5395
H	-6.6060	-2.6865	-0.0455
H	-7.3600	-2.0435	1.4215

Sum of electronic and thermal Enthalpies= -1016.759395
Sum of electronic and thermal Free Energies= -1016.841832
Frequency: 286.9i



Standard orientation:

Atomic Type	Coordinates (Angstroms) X	Y	Z
C	1.5030	-1.3085	-0.4085
C	2.2390	2.7375	0.3455
C	6.3590	-0.1715	0.8445
C	5.1270	-0.2785	-0.0705
C	0.8300	1.1085	-0.6515
C	3.8480	-2.2765	-0.7915
C	0.5870	-0.2705	-0.8915
C	5.7730	-2.4985	0.7455
C	-0.5350	-0.5825	-1.8075
C	6.2940	-1.4375	1.7185
C	2.7970	-1.5275	-1.4545
H	1.9490	-1.0455	0.5525
H	1.0330	-2.2935	-0.3135
H	-0.4060	-1.5335	-2.3335
H	-0.6950	0.2105	-2.5425
H	4.2490	0.2485	0.3145
H	5.2550	-3.3355	1.2175
H	6.5800	-2.8925	0.1155
H	3.1060	-0.5255	-1.7475
H	7.2610	-1.7125	2.1445
H	5.5840	-1.3045	2.5425
H	2.2970	3.3585	-0.5525
H	7.2760	-0.1715	0.2465
H	3.1860	2.7685	0.8885
H	6.3460	0.7495	1.4315
H	1.4310	3.1175	0.9775
H	3.7650	-3.3585	-0.7035
H	5.3150	0.0805	-1.0875
H	2.4100	-2.0715	-2.3175
N	4.8280	-1.7365	-0.1085

O	0.0840	2.0495	-0.9625
O	2.0250	1.3605	0.0105
N	-1.9050	-0.7225	-1.1165
C	-2.4260	0.3605	-0.4825
H	-1.8090	1.2555	-0.5255
C	-2.5950	-1.8845	-1.1145
H	-2.1350	-2.7135	-1.6415
C	-3.8110	-2.0175	-0.4895
H	-4.3050	-2.9785	-0.5275
C	-3.6410	0.3045	0.1545
H	-4.0040	1.2045	0.6315
C	-4.3970	-0.9035	0.1785
N	-5.5970	-0.9875	0.7965
C	-6.1690	0.1845	1.4615
H	-6.3280	1.0055	0.7535
H	-5.5210	0.5365	2.2735
H	-7.1330	-0.0855	1.8895
C	-6.3440	-2.2465	0.7905
H	-5.7770	-3.0475	1.2775
H	-6.5920	-2.5575	-0.2315
H	-7.2760	-2.1095	1.3385

Sum of electronic and thermal Enthalpies= -1016.760349
Sum of electronic and thermal Free Energies= -1016.843614

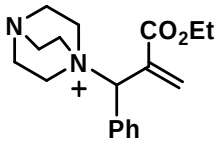
TS5

Standard orientation:

Atomic Type	Coordinates (Angstroms) X	Y	Z
C	1.6450	-1.0460	-0.7685
C	2.5260	2.8390	0.5005
C	6.4030	-0.4680	1.1175
C	5.2430	-0.3100	0.1205
C	1.0380	1.4300	-0.6915
C	3.9410	-2.0440	-1.0775
C	0.7750	0.0950	-1.1795
C	5.7420	-2.6880	0.4835
C	-0.3100	-0.0710	-2.0495
C	6.2200	-1.8840	1.6945
C	2.9830	-1.1050	-1.6705
H	1.9610	-0.9570	0.2755
H	1.1260	-2.0040	-0.8775
H	-0.3490	-0.9650	-2.6695
H	-0.6920	0.8230	-2.5315
H	4.3560	0.1640	0.5515
H	5.1590	-3.5800	0.7235
H	6.5770	-2.9700	-0.1675
H	3.3780	-0.0910	-1.7275
H	7.1400	-2.2940	2.1165
H	5.4540	-1.8900	2.4775
H	2.5680	3.5800	-0.3015
H	7.3620	-0.3920	0.5945
H	3.4940	2.7620	0.9985
H	6.3800	0.3090	1.8845
H	1.7570	3.1430	1.2155
H	3.8040	-3.1140	-1.2285
H	5.5160	0.2420	-0.7825
H	2.6950	-1.4430	-2.6695
N	4.8870	-1.7140	-0.2525
O	0.3140	2.4110	-0.8215

O	2.2480	1.5310	-0.0235
N	-1.9700	-0.4490	-1.1825
C	-2.3620	0.3740	-0.1945
H	-1.6860	1.1940	0.0295
C	-2.7710	-1.4690	-1.5265
H	-2.4220	-2.1030	-2.3385
C	-3.9780	-1.7200	-0.9055
H	-4.5700	-2.5630	-1.2375
C	-3.5540	0.2090	0.4805
H	-3.8130	0.9170	1.2575
C	-4.4210	-0.8670	0.1425
N	-5.6040	-1.0690	0.7825
C	-6.0330	-0.1550	1.8385
H	-6.1520	0.8690	1.4615
H	-5.3180	-0.1410	2.6695
H	-6.9950	-0.4870	2.2275
C	-6.4740	-2.1730	0.3885
H	-5.9730	-3.1410	0.5125
H	-6.7980	-2.0780	-0.6565
H	-7.3620	-2.1700	1.0195

Sum of electronic and thermal Enthalpies= -1016.755399
Sum of electronic and thermal Free Energies= -1016.839415
Frequency: 209.1i

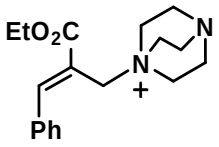


Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.117528	-0.446756	0.091087
2	6	0	3.950835	-1.379228	-0.582981
3	6	0	2.230749	-1.091205	1.038769
4	6	0	0.759234	-0.822267	1.280873
5	6	0	0.341954	-1.018940	2.539330
6	1	0	1.064700	-1.314016	3.293591
7	1	0	4.600638	-0.674572	-0.056924
8	1	0	4.147953	-2.378537	-0.186623
9	1	0	0.482813	-0.631889	-0.798263
10	1	0	-0.689996	-0.924572	2.852622
11	8	0	3.016426	-1.340882	1.924701
12	8	0	2.563080	-1.039625	-0.268296
13	7	0	-0.319098	1.124561	-0.014535
14	6	0	-1.200478	1.709901	1.072293
15	1	0	-0.796100	1.377032	2.029278
16	1	0	-2.192618	1.282176	0.933462
17	6	0	-1.209417	3.264405	0.934603
18	1	0	-0.673462	3.728476	1.767165
19	1	0	-2.239792	3.629650	0.959831
20	6	0	1.033629	1.826285	0.053232
21	1	0	1.696150	1.314576	-0.645940
22	1	0	1.412026	1.671386	1.064692
23	6	0	0.840928	3.336091	-0.277796
24	1	0	1.286637	3.578550	-1.246655
25	1	0	1.341426	3.947741	0.478031
26	6	0	-0.945807	1.455144	-1.362526
27	1	0	-1.854077	0.859536	-1.452167
28	1	0	-0.235120	1.118099	-2.121239
29	6	0	-1.214693	2.987222	-1.435447
30	1	0	-0.828120	3.388000	-2.376664
31	1	0	-2.288843	3.190484	-1.407365
32	7	0	-0.579347	3.685914	-0.317134
33	6	0	4.112863	-1.310746	-2.087296
34	1	0	3.915029	-0.302505	-2.466584
35	1	0	3.442549	-2.014579	-2.590542
36	1	0	5.141856	-1.573679	-2.352601

37	6	0	-1.409126	-1.231521	-0.089778
38	6	0	-3.679609	-2.831827	-0.581970
39	6	0	-2.462830	-1.293446	0.839647
40	6	0	-1.520748	-1.992879	-1.265550
41	6	0	-2.640397	-2.788014	-1.510260
42	6	0	-3.586513	-2.081003	0.591433
43	1	0	-2.427221	-0.737160	1.769234
44	1	0	-0.714321	-1.977198	-1.994875
45	1	0	-2.695736	-3.372305	-2.423709
46	1	0	-4.387893	-2.112510	1.323467
47	1	0	-4.553695	-3.448729	-0.766763

Sum of electronic and thermal Enthalpies= -960.224978
Sum of electronic and thermal Free Energies= -960.295821



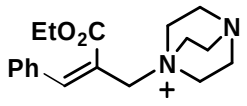
E

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.400129	1.073875	-0.041636
2	6	0	-4.118831	-2.098034	0.122311
3	6	0	-1.975069	-1.288466	-0.519128
4	6	0	-1.029388	-0.124199	-0.558541
5	6	0	0.261229	-0.416736	-1.280413
6	1	0	0.084737	-1.180351	-2.038895
7	1	0	-4.302217	-2.426119	-0.904265
8	1	0	-3.682189	-2.936304	0.673078
9	1	0	-2.355639	1.072565	0.479028
10	1	0	0.685193	0.468756	-1.747490
11	8	0	-1.694571	-2.372421	-1.009331
12	8	0	-3.134930	-1.019283	0.083666
13	6	0	-5.364911	-1.552991	0.788866
14	1	0	-5.778087	-0.711798	0.224075
15	1	0	-5.154951	-1.220577	1.810256
16	1	0	-6.124788	-2.339797	0.835064
17	7	0	1.407960	-0.973071	-0.412007

18	6	0	0.988571	-2.177916	0.419710
19	1	0	0.490842	-2.875846	-0.253172
20	1	0	0.249593	-1.812865	1.134897
21	6	0	2.530024	-1.407591	-1.344857
22	1	0	2.745381	-0.562422	-2.003381
23	1	0	2.127917	-2.223885	-1.949500
24	6	0	2.253058	-2.759782	1.118315
25	1	0	2.494589	-3.746444	0.713414
26	1	0	2.066603	-2.880141	2.189104
27	6	0	3.758643	-1.838624	-0.490610
28	1	0	4.587301	-1.138110	-0.626272
29	1	0	4.105039	-2.826363	-0.806628
30	6	0	1.947839	0.092977	0.527019
31	1	0	2.299594	0.914342	-0.101683
32	1	0	1.105590	0.453105	1.118757
33	6	0	3.081438	-0.534626	1.393410
34	1	0	3.977673	0.090067	1.344444
35	1	0	2.776281	-0.592489	2.441870
36	7	0	3.412088	-1.883563	0.930578
37	6	0	-0.711866	2.373043	-0.045412
38	6	0	0.528708	4.895721	0.071992
39	6	0	-0.044605	2.898605	-1.168998
40	6	0	-0.781148	3.158045	1.122207
41	6	0	-0.149472	4.397956	1.186873
42	6	0	0.565107	4.150041	-1.109411
43	1	0	-0.063991	2.363900	-2.114032
44	1	0	-1.328906	2.785820	1.984398
45	1	0	-0.203218	4.983647	2.099636
46	1	0	1.052908	4.553054	-1.992132
47	1	0	1.005241	5.870529	0.114565

Sum of electronic and thermal Enthalpies= -960.248068
Sum of electronic and thermal Free Energies= -960.320446



Z

Standard orientation:

Center	Atomic	Atomic	Coordinates (Angstroms)

Number	Number	Type	X	Y	Z
1	6	0	0.906851	-0.851985	-0.847009
2	6	0	2.401387	3.130790	0.164326
3	6	0	0.607097	1.654542	-0.330722
4	6	0	0.171927	0.294988	-0.784176
5	6	0	-1.204823	0.303707	-1.401449
6	1	0	-1.448512	1.299519	-1.771587
7	1	0	2.011643	3.833124	-0.577258
8	1	0	1.981886	3.401170	1.137971
9	1	0	-1.277284	-0.416746	-2.219978
10	8	0	-0.193033	2.570260	-0.192052
11	8	0	1.922514	1.794500	-0.181471
12	6	0	3.915441	3.082694	0.176847
13	1	0	4.307831	2.802116	-0.805130
14	1	0	4.284709	2.365975	0.916470
15	1	0	4.306444	4.072773	0.433016
16	7	0	-2.383966	-0.063793	-0.466159
17	6	0	-2.368231	0.733171	0.830554
18	1	0	-2.258553	1.782771	0.560121
19	1	0	-1.464930	0.430498	1.362658
20	6	0	-3.680658	0.243736	-1.199788
21	1	0	-3.629016	-0.261774	-2.167494
22	1	0	-3.686976	1.322417	-1.372480
23	6	0	-3.667682	0.410414	1.625659
24	1	0	-4.310095	1.293444	1.684122
25	1	0	-3.417638	0.117061	2.648991
26	6	0	-4.880945	-0.234199	-0.328648
27	1	0	-5.401376	-1.065074	-0.812962
28	1	0	-5.599912	0.580199	-0.205244
29	6	0	-2.367988	-1.540393	-0.119705
30	1	0	-2.442313	-2.084457	-1.065192
31	1	0	-1.396176	-1.751902	0.328629
32	6	0	-3.558713	-1.843897	0.840575
33	1	0	-4.149126	-2.677569	0.450503
34	1	0	-3.189955	-2.133644	1.828292
35	7	0	-4.423549	-0.672964	0.990706
36	1	0	0.433532	-1.653293	-1.418869
37	6	0	2.198867	-1.261542	-0.302940
38	6	0	4.645649	-2.250278	0.663910
39	6	0	2.888099	-2.285343	-0.986572
40	6	0	2.746255	-0.769786	0.898843
41	6	0	3.953582	-1.265983	1.377214
42	6	0	4.110441	-2.759283	-0.521409
43	1	0	2.464139	-2.696308	-1.899726
44	1	0	2.214773	-0.016513	1.466918

45	1	0	4.356558	-0.890198	2.313067
46	1	0	4.636722	-3.532875	-1.072042
47	1	0	5.591056	-2.629603	1.040508

Sum of electronic and thermal Enthalpies= -960.243773
Sum of electronic and thermal Free Energies= -960.315467