Asymmetric synthesis of L-Carbidopa based on a highly enantioselective α-amination

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Supporting Information

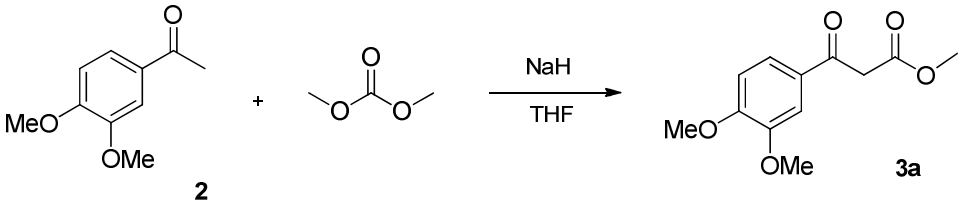
General information

GLC chromatographies were performed on a capilar column (5% biphenyl and 95 % dimethylpolysiloxane) of 15 m x 0.25 mm with stationary phase diameter of 0.25 μm. Column chromatographies were performed on silica gel (230-400 mesh). IR spectra were determined either by transmission or by Attenuated Total Reflectance mode (ATR). Enantiomeric excesses were determined, unless otherwise stated, by HPLC using a chiral column Chiracel Daicel-OD**.**

NMR spectra were recorded operating at 250MHz, 360MHz and 500 MHz. ^{13}C-NMR spectra were registered at 62.5 MHz. 2D NOESY spectra were recorded using a mixing time of 500 ms. For the diffusion data, 16 ^{1}H spectra were recorded using the bipolar-gradient LED pulse sequence with a diffusion time of 150 ms. To minimize convection effects, sample was spun to 20 Hz. Data were processed using the DOSY protocol included into the TOPSPINv1.3 software package (Bruker, Rheinstetten). Reactions at low temperature were performed in a cryothermostated bath. Elemental analyses are the average of two determinations.

General Preparation of β-Ketoesters and Synthesis of L-carbidopa

Synthesis of methyl 3-(3,4-dimethoxyphenyl)-3-oxopropanoate, 3a



In a 250 ml round bottom flask 7 ml (83.2 mmol) of dimethyl carbonate, 2.23 g (55.8 mmol) of NaH (60 % suspension) are dissolved in 50 ml of THF and very slowly a solution 5.00 g (27.8 mmol) de 1-(3,4-dimethoxyphenyl)ethanone, **2**, in 40 ml of THF is added. The mixture is heated to reflux 5 hours and the reaction is controlled by TLC using mixtures of hexanes:AcOEt (1:1). Reaction mixture is added to 100 ml of water and pH is adjusted to 9. The aqueous layer was extracted with DCM (2 x 200 mL) and the combined organic fractions were washed with more water. The organic phase was dried with MgSO4, filtered and concentrated and crude is purified with column chromatography using mixtures of hexanes:AcOEt (5:1) obtaining 6.40 g (26.9 mmol) of a white solid identified as **3a** with 97% yield.

^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): Keto (95%)-enol (5%), 3.67 (s, 3H, OCO-C$\underline{H}_3$), 3.70 (s, enol, 0.21H, OCO-C$\underline{H}_3$), 3.89 (s, 3H, OC$\underline{H}_3$), 3.91(s, 3H, OC$\underline{H}_3$), 3.93 (s, 2H, CO-C$\underline{H}_2$), 5.56 (s, enol, 0.05H, C=C$\underline{H}$), 6.85 (d, *J*= 8.5 Hz, enol, 0.05 H, aromatic $\underline{H}$), 6.86 (d, *J*= 8.3 Hz, 1H, aromatic $\underline{H}$), 7.35 (dd, *J*= 2.1 Hz, *J*= 8.5 Hz, enol, 0.05H, aromatic $\underline{H}$) 7.48 (d, *J*= 2.1 Hz, 1H, aromatic $\underline{H}$), 7.51 (dd, *J*= 2.1 Hz, *J*= 8.3, 1H, aromatic $\underline{H}$), 12.54 (s, enol, 0.05H, OH).

^{13}C [^{1}H] NMR ($CDCl_3$, 90 MHz) δ (ppm): 45.6 (CO-$\underline{C}H_2$), 51.6 (enol, OCO-$\underline{C}H_3$), 52.7 (OCO-$\underline{C}H_3$), 56.2 (OCH_3), 56.3 (OCH_3), 56.5 (enol, OCH_3), 56.6 (enol, OCH_3), 85.9 (enol, C=$\underline{C}$H), 109.0 (enol, aromatic $\underline{C}$), 110.3 (aromatic $\underline{C}$), 110.5 (aromatic $\underline{C}$), 110.9 (enol, (aromatic $\underline{C}$), 119.8 (enol, (aromatic $\underline{C}$), 123.8 (aromatic $\underline{C}$), 126.1 (enol, (aromatic $\underline{C}$), 129.4 (aromatic $\underline{C}$), 149.4 (aromatic $\underline{C}$), 154.1 (aromatic $\underline{C}$), 168.4 (O-C=O), 191.1 (C=O).

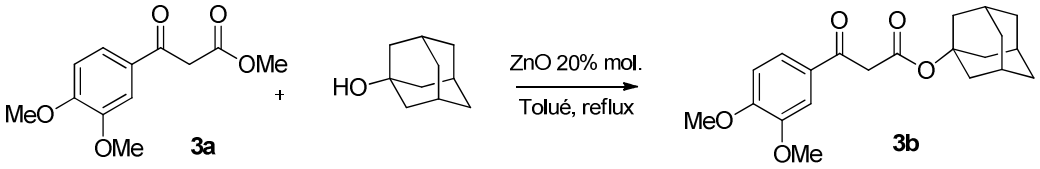
IR (ATR) υ (cm^{-1}): 3068 (arC-H st), 2980 (C-H st), 2949 (C-H st), 2839 (C-H st), 1732 (C=O st), 1667 (C=O st), 1583 (arC-C), 1510 (arC-C), 1419 (CH_3 δ as.), 1256 (C-O-C st as), 1243 (C-O-C st as), 1146 (C-O-C st as), 1018 (C-O-C st as).

Elemental analysis calculated for $C_{12}H_{14}O_5$: C: 60.50%, H: 5.92%. **Experimental**: C: 60.53%, H: 5.99%.

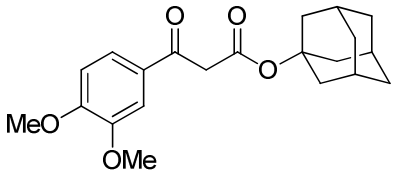
R_F (hexane:AcOEt (1:1))= 0.47.

Mp: 51-52 ºC.

General procedure for transesterification reaction



A round-bottom flask was charged with 3-(3,4-dimethoxyphenyl)-3-oxopropanoate 1 (18.9 g, 79.5 mmol), 1-adamantanol (15.81 g, 103.7 mmol, 1.3 equiv) in the presence of ZnO (1.34 g, 16.6 mmol, 20 mol %) and 200 mL of toluene for 24 h. The flask was fitted with a short-path distillation head and heated; distilling the methanol formed during the reaction. After 5 hours the TLC of the reaction mixture showed complete consumption of the β-ketoester. The reaction mixture was filtered through a plug of Celite to remove the catalyst. The filtrate was concentrated under reduced pressure and the crude residue was purified by column chromatography on silica gel, eluting with a mixture of n-hexane/ethyl acetate (3:1), affording 24.7 g (68.9 mmol) of the product as a white solid with 87% yield.



Adamantyl 3-(3,4-dimethoxyphenyl)-3-oxopropanoate, 3b

^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): Keto (96%)-enol (4%), 1.62 (s, 6H, CH_2CHCH_2ada), 2.07 (d, *J*= 2.9 Hz, 6H, CH_2CHCH_2ada), 2.13 (s, 3H, CH_2CHCH_2ada), 2.18 (s, 0.4H, enol, CH_2CHCH_2ada), 3.84 (s, 2H, CO-CH_2), 3.92 (s, 3H, OCH_3), 3.94(s, 3H, OCH_3), 5.49 (s, enol, 0.04H, C=CH), 6.88 (d, *J*= 8.3 Hz, 1H, aromatic H), 7.30 (d, *J*= 2.1 Hz, enol, 0.06H, aromatic H), 7.37 (dd, *J*= 2.1 Hz, *J*= 8.5 Hz, enol, 0.05H, aromatic H), 7.51-7.55 (m, 2H, aromatic H), 12.54 (s, 0.05 H, enol, OH).

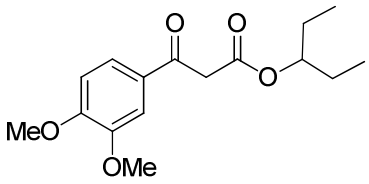
^{13}C [^{1}H] NMR ($CDCl_3$, 90 MHz) δ (ppm): 31.1 (enol, CH_2CHCH_2ada), 31.2 (CH_2CHCH_2ada), 36.4 (CH_2CHCH_2ada), 36.5 (enol, CH_2CHCH_2ada), 41.4 (CH_2CHCH_2ada), 41.9 (enol, CH_2CHCH_2ada), 47.6 ($COCH_2COO$ada), 56.3 (OCH_3), 56.4 (OCH_3), 65.1(enol, $COCH_2CH$), 81.3 (enol, $OCCH_3$), 82.3 ($OC(CH_2)_3$), 87.9 (enol, C=CH), 110.3 (aromatic C), 110.6 (aromatic C), 111.0 (enol, aromatic C), 123.8 (aromatic C), 129.8 (aromatic Cq), 149.4 (aromatic Cq), 153.9 (aromatic Cq), 166.9 (O-C=O), 191.8 (C=O).

IR (ATR) υ (cm^{-1}): 2908 (C-H st), 2850 (C-H st), 1728 (C=O st), 1673 (C=O st), 1585 (arC-C), 1514 (arC-C), 1254 (C-O-C st as), 1147 (C-O-C st as), 1053 (C-O-C st as), 1021 (C-O-C st as).

Elemental analysis calculated for $C_{21}H_{26}O_5$: C: 70.37%, H: 7.31%. **Experimental**: C: 70.23%, H: 7.41%

R_F (hexane:AcOEt (2:1))= 0.58.

Mp: 84-85 ºC.



Pentan-3-yl 3-(3,4-dimethoxyphenyl)-3-oxopropanoate, 3c

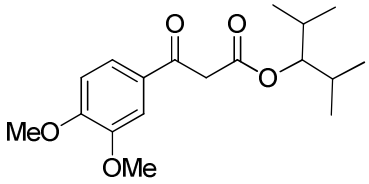
^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): Keto (94%)-enol (6%), %), 0.83 (t, *J*= 7.5 Hz, 6H, $CH_2C\underline{H}_3$), 0.91 (t, *J*= 7.5 Hz, 0.4H, enol, $CH_2C\underline{H}_3$), 1.50-1.58 (m, 4H, $C\underline{H}_2CH_3$), 1.59-1.64 (m, 0.2H, enol, $C\underline{H}_2CH_3$), 3.91(s, 2H, CO-$C\underline{H}_2$), 3.92 (d, *J*= 7.6 Hz, 6H, $OC\underline{H}_3$), 4.80 (quint , *J*= 6.6 Hz, 1H, $OC\underline{H}CH_2$), 4.88 (quint, *J*= 6.5 Hz, 0.06H, enol, $OC\underline{H}CH_2$), 5.58 (s, 0.06H, enol, C=C$\underline{H}$), 6.87 (d, *J*= 8.3 Hz, 1H, aromatic $\underline{H}$), 7.39 (dd, *J*= 8.5 Hz, *J*= 2.0 Hz, 0.06H, enol, aromatic $\underline{H}$), 7.52-7.56 (m, 2H, aromatic $\underline{H}$), 12.74 (s, 0.06 H, enol, OH).

^{13}C [^{1}H] NMR ($CDCl_3$, 90 MHz) δ (ppm): 9.81 ($CH_2\underline{C}H_3$), 9.95 (enol, $CH_2\underline{C}H_3$), 26.6 ($\underline{C}H_2CH_3$), 26.9 (enol, $\underline{C}H_2CH_3$), 46.4 (CO-$\underline{C}H_2$), 56.3 ($O\underline{C}H_3$), 56.4 ($O\underline{C}H_3$), 78.4 (CO-$\underline{C}$H), 86.6 (enol, C=$\underline{C}$H) , 109.0 (enol, aromatic $\underline{C}$), 110.34 (aromatic $\underline{C}$), 110.6 (aromatic $\underline{C}$), 123.8 (aromatic $\underline{C}$), 129.7 (aromatic $\underline{Cq}$), 149.5 (aromatic $\underline{Cq}$), 154.0 (aromatic $\underline{Cq}$), 167.9 (O-C=O), 191.45 (C=O).

IR (ATR) υ (cm^{-1}): 3080 (arC-H st), 2967 (C-H st), 2936 (C-H st), 2878 (C-H st), 2839 (C-H st), 1729 (C=O st), 1673 (C=O st), 1585 (arC-C), 1513 (arC-C), 1417 (CH_3 δ as.), 1317 (C-O-C st as), 1255 (C-O-C st as), 1148 (C-O-C st as), 1130 (C-O-C st as), 1020 (C-O-C st as).

Elemental analysis calculated for $C_{16}H_{22}O_5$: C: 65.29%, H: 7.53%. **Experimental**: C: 65.39%, H: 7.73%.

R_F (hexane:AcOEt (2:1))= 0.56.



2,4-dimethylpentan-3-yl 3-(3,4-dimethoxyphenyl)-3-oxopropanoate, 3d

^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): Keto (94%)-enol (6%), %), %), 0.81 (d, *J*= 6.7 Hz, 6H, CHC$\underline{H}_3$), 0.84 (d, *J*= 6.7 Hz, 6H, CHC$\underline{H}_3$), 0.90 (d, *J*= 3.8 Hz, 0.4H, enol, CHC$\underline{H}_3$), 0.91 (d, *J*= 3.8 Hz, 0.4H, enol, CHC$\underline{H}_3$), 1.86 (oct, *J*= 6.5 Hz, 2H, C$\underline{H}$CH$_3$), 1.91-1.99 (m, 0.12H, enol, C$\underline{H}$CH$_3$), 3.92 (s, 3H, OC$\underline{H}_3$), 3.94 (s, 3H, OC$\underline{H}_3$), 3.97(s, 2H, CO-C$\underline{H}_2$), 4.62 (t, *J*= 6.1 Hz, 1H, C$\underline{H}$CH), 4.71 (t, *J*= 6.2 Hz, 0.06H, enol, C$\underline{H}$CH), 5.60 (s, 0.06H, enol, C=C$\underline{H}$), 6.88 (d, *J*= 8.5 Hz, 1H, aromatic $\underline{H}$), 7.30 (d, *J*= 2.1 Hz, 0.06H, enol, aromatic $\underline{H}$), 7.41 (dd, *J*= 8.5, *J*= 2.0 Hz, 0.06H, enol, aromatic $\underline{H}$), 7.53 (d, *J*= 2.1 Hz, 1H, aromatic $\underline{H}$), 7.57 (dd, *J*= 8.5, *J*= 2.0 Hz, 1H, aromatic $\underline{H}$), 12.76 (s, 0.06 H, enol, OH).

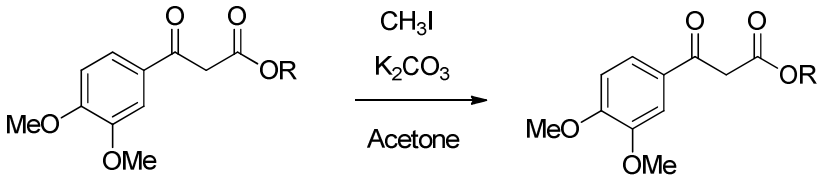
^{13}C [^{1}H] NMR ($CDCl_3$, 90 MHz) δ (ppm): 17.4 (CH$\underline{C}$H$_3$), 17.5 (enol, CH$\underline{C}$H$_3$), 19.8 (CH$\underline{C}$H$_3$), 19.9 (enol, CH$\underline{C}$H$_3$), 29.7 ($\underline{C}$HCH$_3$), 29.8 (enol, $\underline{C}$HCH$_3$), 46.2 (CO-$\underline{C}$H$_2$), 56.3 (O$\underline{C}$H$_3$), 56.4 (O$\underline{C}$H$_3$), 82.8 (enol, CO-$\underline{C}$H$_2$), 85.0 (CO-$\underline{C}$H$_2$), 86.3 (enol, C=$\underline{C}$H), 110.35 (aromatic $\underline{C}$), 110.71 (aromatic $\underline{C}$), 120.0 enol (aromatic $\underline{C}$), 124.0 (aromatic $\underline{C}$), 130.0 (aromatic $\underline{Cq}$), 149.5 (aromatic $\underline{Cq}$), 154.1 (aromatic $\underline{Cq}$), 168.0 (O-C=O), 191.4 (C=O).

IR (ATR) υ (cm^{-1}): 3082 (arC-H st), 2963 (C-H st), 2935 (C-H st), 2839 (C-H st), 1729 (C=O st), 1674 (C=O st), 1585 (arC-C), 1513 (arC-C), 1417 (CH_3 δ as.), 1322 (CH_3 δ as.), 1255 (CH_3 δ as.), 1128 (CH_3 δ as.), 1021 (CH_3 δ as.).

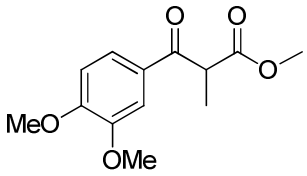
Elemental analysis calculated for $C_{18}H_{26}O_5$: C: 67.06%, H: 8.13%. **Experimental**: C: 67.02%, H: 8.43%.

R_F (hexane:AcOEt (2:1))= 0.60.

General procedure for methylation reaction



In a 50 ml round-bottom flash provided with a reflux condenser 12.50 mmol of β-ketoester is dissolved in 30 ml of dry acetone. After solution of starting material 13.76 mmol de K_2CO_3 and 18.12 mmol de iodomethane are added. The system is maintained at 40ºC with stirring up to 24 hours. After reaction completion (TLC) the solution is filtered, the crude is extracted with CH_2Cl_2 and washed with HCl 1M. Organic phase is dried with magnesium sulphate and purified with column chromatography using mixtures of hexane/AcOEt as eluent.



Methyl 3-(3,4-dimethoxyphenyl)- 2-methyl-3-oxopropanoate, 4a

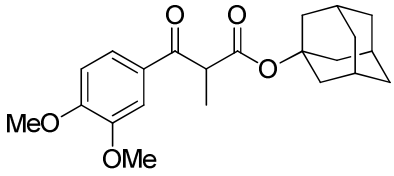
^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 1.47 (d, *J*= 7.1 Hz, 3H, COCHC<u>H</u>$_3$), 3.66 (s, 3H, COOC<u>H</u>$_3$), 3.91 (s, 3H, OC<u>H</u>$_3$), 3.93 (s, 3H, OC<u>H</u>$_3$), 4.36 (q, *J*= 7.1 Hz, 1H, COC<u>H</u>CH$_3$), 6.88 (d, *J*= 8.3 Hz, 1H, aromatic <u>H</u>), 7.53 (d, *J*= 2.0 Hz, 1H, aromatic <u>H</u>), 7.59 (dd, *J*= 8.4, *J*= 2.0 Hz, 1H, aromatic <u>H</u>).

^{13}C [^{1}H] NMR ($CDCl_3$, 90 MHz) δ (ppm): 14.3 (COCH<u>C</u>H$_3$), 48.0 (CO<u>C</u>HCH$_3$), 52.7 (COO<u>C</u>H$_3$), 56.2 (O<u>C</u>H$_3$), 56.4 (O<u>C</u>H$_3$), 110.3 (aromatic <u>C</u>), 110.9 (aromatic <u>C</u>), 123.6 (aromatic <u>C</u>), 129.1 (aromatic <u>Cq</u>), 149.5 (aromatic <u>Cq</u>), 154.0 (aromatic <u>Cq</u>), 171.8 (O-C=O), 194.6 (C=O).

IR (ATR) υ (cm^{-1}): 3059 (arC-H st), 2974 (C-H st), 2948 (C-H st), 2845 (C-H st), 1742 (C=O st), 1660 (C=O st), 1582 (arC-C), 1512 (arC-C), 1460 (CH_3 δ as.), 1250 (C-O-C st as), 1156 (C-O-C st as), 1052 (C-O-C st as), 1015 (C-O-C st as).

R_F (hexane:AcOEt (2:1))= 0.25.

Yield: 99%.



Adamantyl 3-(3,4-dimethoxyphenyl)-2-methyl-3-oxopropanoate, 4b

^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm):): 1.39 (d, *J*= 7.0 Hz, 3H, COCHC<u>H</u>$_3$), 1.56 (t, *J*= 2.8 Hz, 6H, CH-C<u>H</u>$_2$ada), 1.96 (d, *J*= 2.8 Hz, 6H, C-C<u>H</u>$_2$ada), 2.07 (s, 3H, C<u>H</u>-CH$_2$ada), 3.89 (s, 3H, OC<u>H</u>$_3$), 3.91 (s, 3H, OC<u>H</u>$_3$), 4.17 (q, *J*= 7.0 Hz, 1H, COC<u>H</u>CH$_3$), 6.85 (d, *J*= 8.4 Hz, 1H, aromatic <u>H</u>), 7.51 (d, *J*= 2.0 Hz, 1H, aromatic <u>H</u>), 7.58 (dd, *J*= 8.4 Hz, *J*= 2.0 Hz, aromatic <u>H</u>).

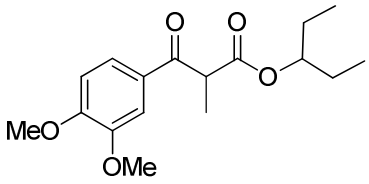
^{13}C [^{1}H] NMR ($CDCl_3$, 90 MHz) δ (ppm): 14.0 (COCH<u>C</u>H$_3$), 31.0 (<u>C</u>H-CH$_2$ada), 36.3 (CH-<u>C</u>H$_2$ada), 41.2 (C-<u>C</u>H$_2$ada), 49.5 (CO<u>C</u>HCH$_3$), 56.2 (O<u>C</u>H$_3$), 56.3 (O<u>C</u>H$_3$), 81.7 (<u>C</u>-CH$_2$ada), 110.1 (aromatic <u>C</u>), 111.0 (aromatic <u>C</u>), 123.5 (aromatic <u>C</u>), 129.4 (aromatic <u>Cq</u>), 149.1 (aromatic <u>Cq</u>), 153.5 (aromatic <u>Cq</u>), 170.2 (O-C=O), 194.7 (C=O).

IR (ATR) υ (cm^{-1}): 2910 (C-H st), 2851 (C-H st), 1736 (C=O st), 1670 (C=O st), 1593 (arC-C), 1514 (arC-C), 1451 (CH_3 δ as.), 1260 (C-O-C st as), 1187 (C-O-C st as), 1102 (C-O-C st as), 1018 (C-O-C st as).

R_F (hexane:AcOEt (2:1))= 0.64.

Mp = 78-78.5ºC (AcOEt)

Yield: 99%.



Pentan-3-yl 3-(3,4-dimethoxyphenyl)-2-methyl-3-oxopropanoate, 4c

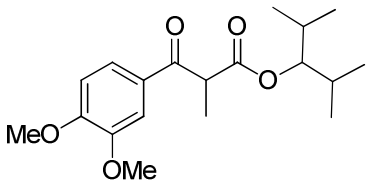
^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 0.69 (t, *J*= 7.4 Hz, 3H, $CH_2C\underline{H}_3$), 0.77 (t, *J*= 7.4 Hz, 3H, $CH_2C\underline{H}_3$), 1.38-1.53 (abs. com., 7H, $COCHC\underline{H}_3$, $C\underline{H}_2CH_3$), 3.91 (s, 3H, $OC\underline{H}_3$), 3.92 (s, 3H, $OC\underline{H}_3$), 4.32 (q, *J*= 7.0 Hz, 1H, $COC\underline{H}CH_3$), 4.72 (quin, *J*= 5.6 Hz, 1H, $OC\underline{H}CH_2$), 6.86 (d, *J*= 8.4 Hz, 1H, aromatic H), 7.53 (d, *J*= 2 Hz, 1H, aromatic H), 7.61 (dd, *J*= 8.4, *J*= 2.0 Hz, 1H, aromatic H).

^{13}C [^{1}H] NMR ($CDCl_3$, 90 MHz) δ (ppm): 9.6 ($CH_2\underline{C}H_3$), 9.7 ($CH_2\underline{C}H_3$), 14.2 ($COCH\underline{C}H_3$), 26.5 ($\underline{C}H_2CH_3$), 26.6 ($\underline{C}H_2CH_3$), 48.7 ($CO\underline{C}HCH_3$), 56.3 ($O\underline{C}H_3$), 56.4 ($O\underline{C}H_3$), 78.1 ($CO\underline{C}HCH_2$), 110.3 (aromatic C), 111.0 (aromatic C), 123.5 (aromatic C), 129.5 (aromatic Cq), 149.4 (aromatic Cq), 153.8 (aromatic Cq), 171.4 (O-C=O), 194.5 (C=O).

IR (ATR) υ (cm^{-1}): 2967 (C-H st), 2937 (C-H st), 2878 (C-H st), 2840 (C-H st), 1727 (C=O st), 1674 (C=O st), 1584 (arC-C), 1513 (arC-C), 1416 (CH_3 δ as.), 1259 (C-O-C st as), 1154 (C-O-C st as), 1020 (C-O-C st as)**.**

R_F (hexane:AcOEt (2:1))= 0.56.

Yield: 96%.



2,4-dimethylpentan-3-yl 3-(3,4-dimethoxyphenyl)-2-methyl-3-oxopropanoate, 4d

^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 0.66 (d, *J*= 6.7 Hz, 3H, $CHC\underline{H}_3$), 0.71 (d, *J*= 6.7 Hz, 3H, $CHC\underline{H}_3$), 0.74 (d, *J*= 6.7 Hz, 3H, $CHC\underline{H}_3$), 0.80 (d, *J*= 6.7 Hz, 3H, $CHC\underline{H}_3$), 1.49 (d, *J*= 7.0 Hz, 3H,

COCHC$\underline{H}_3$), 1.79 (oct, *J*= 6.8 Hz, 2H, C$\underline{H}$CH$_3$), 3.91 (s, 3H, OC$\underline{H}_3$), 3.92 (s, 3H, OC$\underline{H}_3$), 4.40 (q, *J*= 7.0 Hz, 1H, COC$\underline{H}$CH$_3$), 4.54 (t, *J*= 6.0 Hz, 1H, C$\underline{H}$CH), 6.87 (d, *J*= 8.4 Hz, 1H, aromatic $\underline{H}$), 7.55 (d, *J*= 2 Hz, 1H, aromatic $\underline{H}$), 7.64 (dd, *J*= 8.4, *J*= 2.0 Hz, 1H, aromatic $\underline{H}$).

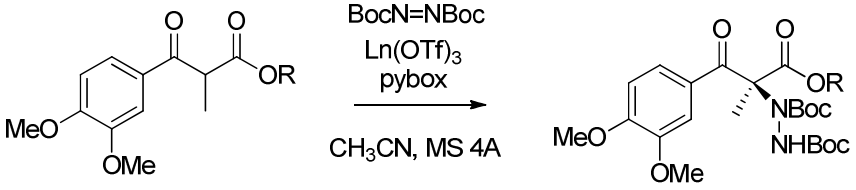
^{13}C [^{1}H] NMR (CDCl$_3$, 90 MHz) δ (ppm): 14.3 (COCH$\underline{C}$H$_3$), 17.2 (CH$\underline{C}$H$_3$), 17.3 (CH$\underline{C}$H$_3$), 19.7 (CH$\underline{C}$H$_3$), 19.8 (CH$\underline{C}$H$_3$), 29.7 ($\underline{C}$HCH$_3$), 29.8 ($\underline{C}$HCH$_3$), 48.5 (CO$\underline{C}$HCH$_3$), 56.3 (O$\underline{C}$H$_3$), 56.4 (O$\underline{C}$H$_3$), 84.1 ($\underline{C}$HCH), 110.3 (aromatic $\underline{C}$), 111.0 (aromatic $\underline{C}$), 123.7 (aromatic $\underline{C}$), 129.7 (aromatic $\underline{Cq}$), 149.8 (aromatic $\underline{Cq}$), 153.9 (aromatic $\underline{Cq}$), 171.3 (O-C=O), 194.5 (C=O).

IR (ATR) υ (cm^{-1}): 2964 (C-H st), 2936 (C-H st), 2875 (C-H st), 2839 (C-H st), 1730 (C=O st), 1675 (C=O st), 1585 (arC-C), 1514 (arC-C), 1417 (CH$_3$ δ as.), 1259 (C-O-C st as), 1130 (C-O-C st as), 1021 (C-O-C st as)**.**

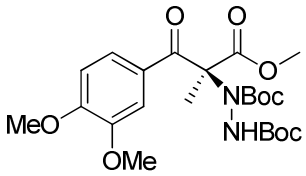
R$_F$ (hexane:AcOEt (2:1))= 0.63.

Yield: 98%.

General procedure for Michael addition



A solution of Ln(OTf)$_3$ (0.017 mmol) and pybox (0.023 mmol) in acetonitrile (1.5 mL) was stirred overnight in the presence of 4 Å molecular sieves under inert atmosphere. The mixture was placed at the selected temperature. Then, the ketoester (0.184 mmol) and the electrophile (0.298 mmol) were sequentially added. The mixture was stirred for the time indicated in the tables (TLC monitoring), and the product was chromatographed through a silica gel column with hexanes:ethyl acetate as eluent.



(*S*)-di-*tert*-butyl 1-(1-(3,4-dimethoxyphenyl)-3-methoxy-2-methyl-1,3-dioxopropan-2-yl)hydrazine-1,2-dicarboxylate, 5a

^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 1.13-1.49 (abs. complex., 18H, ^{t}Bu Boc), 1.80 (broad d, CH_3CNH), 3.83 (s, 3H, $COOCH_3$), 3.90 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.23 (s, 1H, CqNH), 6.93 (broad t, *J*=11.5 Hz, 1H, aromatic H), 8.02 (d, *J*= 20.1 Hz, 1H, aromatic H), 8.30 (dd, *J*= 46.1 Hz, *J*= 7.9 Hz, 1H, aromatic H).

^{13}C [^{1}H] NMR ($CDCl_3$, 90 MHz) δ (ppm): 20.9, 21.4, 21.5, 27.6, 28.2, 28.4, 53.3, 53.4, 56.3, 56.4, 56.7, 76.8, 78.0, 81.6, 81.8, 83.3, 85.2, 109.9, 110.5, 112.0, 112.3, 124.0, 124.9, 127.3, 127.7, 148.8, 152.9, 153.2, 156.1, 156.8, 170.9, 171.1, 190.9, 191.5.

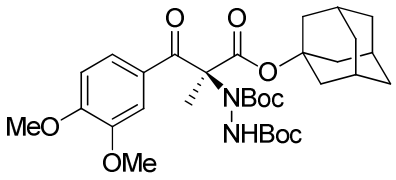
IR (ATR) υ (cm^{-1}): 3295 (NH st), 2974 (C-H st), 2936 (C-H st), 1722 (C=O st), 1677 (C=O st), 1592 (arC-C), 1514 (arC-C), 1456 (arC-C), 1364 (C-N st), 1268 (C-O-C st as), 1250 (C-O-C st as), 1156 (C-O-C st as), 1117 (C-O-C st as), 1024 (C-O-C st as), 959 (arC-H δ oop), 894 (arC-H δ oop), 812 (arC-H δ oop), 768 (arC-H δ oop).

Elemental analysis calculated for $C_{23}H_{34}N_2O_9$: C: 57.25%, H: 7.10%, N: 5.81%. **Experimental:** C: 57.62%, H: 7.40%, N: 5.82%.

R_F (hexà:AcOEt (2:1))= 0.31.

Mp = 144-145ºC.

Enantiomeric excess was determined by HPLC analysis using a mixture of hexanes: isopropanol (98.5: 1.5) at 0,4 ml/min as eluent. As a stationary phase a Chiralcel Daicel-AD (0.46 cm ϕ x 25 cm) column is used. 10 μl of a solution (concentration 1 mg/ml) of racemic mixture of **5a** (50:50) shows two peaks: t_r(*S*)= 5.574 min, i t_r(*R*)= 20.635 min.



(*S*)-di-*tert*-butyl 1-(1-(3,4-dimethoxyphenyl)-3-adamantyloxy-2-methyl-1,3-dioxopropan-2-yl)hydrazine-1,2-dicarboxylate, 5b

^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 0.84 (m, 1H), 1.13-2.18 (abs. complex., 32H), 3.94 (broad s, 6H, OCH_3), 6.17 (s, 1H, CqNH), 6.93 (m, 1H, aromatic H), 8.01 (d, *J*= 17.6 Hz, 1H, aromatic H), 8.31 (dd, *J*= 52.0 Hz, *J*= 8.1 Hz, 1H, aromatic H).

^{13}C [^{1}H] NMR ($CDCl_3$, 90 MHz) δ (ppm): 21.0, 21.7, 27.8, 28.2, 28.5, 31.2, 36.4, 41.5, 56.2, 56.6, 76.5, 81.5, 82.9, 83.1, 84.9, 110.3, 111.9, 112.3, 124.8, 148.6, 156.3, 156.8, 168.6, 190.9, 191,6.

IR (ATR) υ (cm^{-1}): 3309 (NH st), 2975 (C-H st), 2909 (C-H st), 2851 (C-H st), 1731 (C=O st), 1709 (C=O st), 1678 (C=O st), 1593 (arC-C), 1514 (arC-C), 1456 (arC-C), 1367 (C-N st), 1261 (C-O-C st as), 1240 (C-O-C st as), 1153 (C-O-C st as), 1114 (C-O-C st as), 1040 (C-O-C st as), 1021 (C-O-C st as), 965 (arC-H δ oop), 884 (arC-H δ oop), 768 (arC-H δ oop).

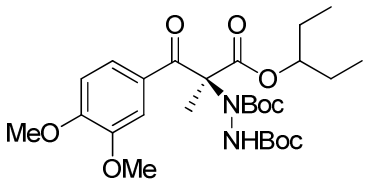
Elemental analysis calculated for $C_{32}H_{46}N_2O_9$: C: 63.77%, H: 7.69%, N: 4.65%. **Experimental:** C: 63.73%, H: 7.88%, N: 4.62%.

R_F (hexà:AcOEt (2:1))= 0.6.

$[\alpha]_D^{20}$= -111.2 (c= 2.6, $CHCl_3$), <99.9% e.e. (*R*)

Mp = 97-98ºC.

Enantiomeric excess was determined by HPLC analysis using a mixture of hexanes: isopropanol (96:04) at 1 ml/min as eluent. As a stationary phase a Chiralcel Daicel-OD (0.46 cm ϕ x 25 cm) column is used. 10 µl of a solution (concentration 1 mg/ml) of racemic mixture of **5b** (50:50) shows two peaks: t_r(*S*)= 5.64 min, i t_r(*R*)= 10.14 min.



(*S*)-di-*tert*-butyl 1-(1-(3,4-dimethoxyphenyl)-3-(pentan-3-yloxy)-2-methyl-1,3-dioxopropan-2-yl)hydrazine-1,2-dicarboxylate, 5c

^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 0.78-2.00 (abs. complex., 31H), 3.93 (s aparent, 6H, OC<u>H</u>$_3$), 4.88 (s aparent, 1 H, OC<u>H</u>CH_2), 6.16 (s, 1H, CqN<u>H</u>), 6.93 (s aparent, 1H, aromatic <u>H</u>), 8.03 (d, *J*= 17.0 Hz, 1H, aromatic <u>H</u>), 8.32 (dd, *J*= 45.0 Hz, *J*= 7.2 Hz, 1H, aromatic <u>H</u>).

^{13}C [^{1}H] NMR ($CDCl_3$, 90 MHz) δ (ppm): 9.9, 10.0, 10.1, 11.7, 14.4, 14.6, 15.3, 18.0, 19.1, 20.7, 21.0, 21.7, 22.3, 22.9, 23.0, 23.1, 25.6, 25.7, 26.5, 26.7, 26.9, 27.7, 28.2, 28.5, 29.4, 29.7, 31.9, 34.8, 35.0, 36.4, 41.6, 47.1, 56.3, 56.6, 56.7, 76.8, 77.6, 77.7, 79.7, 81.6, 81.8, 83.0, 85.0, 110.0, 110.4, 112.1, 112.5, 112.7, 124.0, 124.9, 127.7, 128.1, 148.9, 152.8, 153.1, 155.9, 156.2, 156.9, 170.1, 190.4, 191.3.

IR (ATR) υ (cm^{-1}): 3305 (NH st), 3083 (arC-H st), 2971 (C-H st), 2936 (C-H st), 2879 (C-H st), 1730 (C=O st), 1715 (C=O st), 1678 (C=O st), 1593 (arC-C), 1513 (arC-C), 1458 (arC-C), 1367 (C-N st), 1262 (C-O-C st as), 1240 (C-O-C st as), 1151 (C-O-C st as), 1101 (C-O-C st as), 1021 (C-O-C st as), 929 (arC-H δ oop), 895 (arC-H δ oop), 768 (arC-H δ oop).

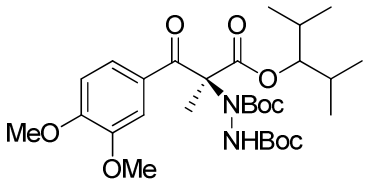
Elemental analysis calculated for $C_{27}H_{42}N_2O_9$: C: 60.21%, H: 7.86%, N: 5.20%. **Experimental:** C: 60.73%, H: 8.11%, N: 5.29%.

R_F (hexà:AcOEt (2:1))= 0.52.

$[\alpha]_D$= +131.2º (c= 2.8, $CHCl_3$), 97.5% e.e. (*S*)

Mp = 66-68ºC.

Enantiomeric excess was determined by HPLC analysis using a mixture of hexanes: isopropanol (95: 5) at 1 ml/min as eluent. As a stationary phase a Chiralcel Daicel-OD (0.46 cm ϕ x 25 cm) column is used. 10 µl of a solution (concentration 1 mg/ml) of racemic mixture of **5c** (50:50) shows two peaks: $t_r(S)$= 7.39 min, i $t_r(R)$= 10.49 min.



(*S*)-di-*tert*-butyl 1-(1-(3,4-dimethoxyphenyl)-3-(2,4-dimethylpentan-3-yloxy)-2-methyl-1,3-dioxopropan-2-yl)hydrazine-1,2-dicarboxylate, 5d

^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 0.85-1.71 (abs. complex., 32H), 1.83 (d aparent, *J*=13 Hz, 3H), 1.94 (sept aparent, *J*= 6.6Hz, 2H, C<u>H</u>CH_3), 3.94 (s aparent, 6H, OC<u>H</u>$_3$), 4.73 (m, 1 H, C<u>H</u>CH), 6.20 (s, 1H, CqN<u>H</u>), 6.94 (m, 1H, aromatic <u>H</u>), 8.05 (d, *J*= 20.2 Hz, 1H, aromatic <u>H</u>), 8.37 (dd, *J*= 57.0 Hz, *J*= 8.1 Hz, 1H, aromatic <u>H</u>).

^{13}C [^{1}H] NMR ($CDCl_3$, 90 MHz) δ (ppm): 8.7, 11.7, 14.4, 15.4, 17.5, 17.7, 17.8, 18.1, 20.0, 20.1, 21.3, 22.0, 23.0, 23.1, 24.8, 25.8, 26.5, 27.7, 28.3, 28.5, 29.4, 29.7, 29.7, 29.9, 29.9, 30.0, 31.3, 32.2, 33.9, 34.7, 47.1, 56.3, 56.4, 56.6, 56.8, 77.6, 78.3, 81.6, 81.7, 83.1, 85.1, 86.0, 109.6, 110.0, 110.5, 112.2, 112.6, 112.7, 124.0, 125.0, 127.7, 128.2, 148.9, 152.8, 153.1, 155.8, 156.1, 156.3, 157.0, 170.2, 170.3, 190.2, 191.1.

IR (ATR) υ (cm^{-1}): 3306 (NH st), 2967 (C-H st), 2934 (C-H st), 2875 (C-H st), 1733 (C=O st), 1705 (C=O st), 1680 (C=O st), 1593 (arC-C), 1514 (arC-C), 1459 (arC-C), 1367 (C-N st), 1262 (C-O-C st as), 1240 (C-O-C st as), 1152 (C-O-C st as), 1111 (C-O-C st as), 1022 (C-O-C st as), 943 (arC-H δ oop), 898 (arC-H δ oop), 768 (arC-H δ oop).

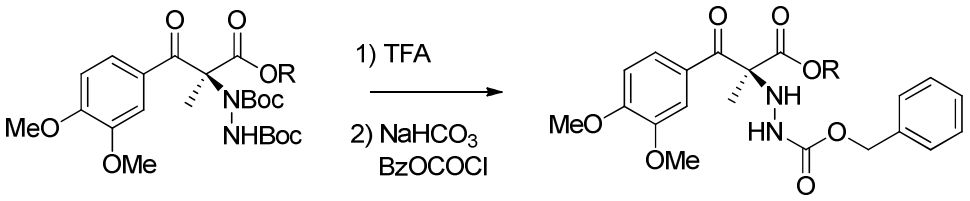
Elemental analysis calculated for $C_{29}H_{46}N_2O_9$: C: 61.46%, H: 8.18%, N: 4.94%. **Experimental:** C: 61.94%, H: 8.51%, N: 4.95%.

R_F (hexà:AcOEt (2:1))= 0.57.

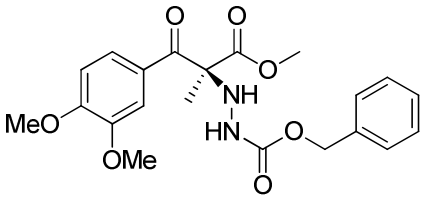
Mp = 183-185 ºC.

Enantiomeric excess was determined by HPLC analysis using a mixture of hexanes: isopropanol (98: 02) at 0.8 ml/min as eluent. As a stationary phase a Daicel Chiralpack AD-H (0.46 cm ϕ x 25 cm) column is used. 10 μl of a solution (concentration 1 mg/ml) of racemic mixture of **6d** (50:50) shows two peaks $t_r(S)$= 10.489 min, i $t_r(R)$= 17.500 min. A mixture of hexanes: isopropanol (97: 03) at 1 ml/min as eluent racemic mixture of **5d** (50:50) shows two peaks $t_r(S)$= 6.342 min, i $t_r(R)$= 8.298 min.

General procedure for deprotection/protection reaction



In a 25 ml round-bottom flask provided with magnetic stirring, 10.7 mmol of Michael adduct is dissolved in 8 ml of trifluoroacetic acid (107 mmol). The reaction is monitored by TLC. After consumption of starting material, the reaction is quenched with $NaHCO_3$ until pH=6.5. Crude is extracted with CH_2Cl_2 and the organic phase is dried and evaporated. The crude obtained is solved in a 100 ml round-bottom flask with 50 ml of THF. To the resulting solution is added 11.8 mmol of $NaHCO_3$ and 11.8 mmol of benzyl chloroformate. System is maintained stirred at room temp. 30 minutes. HCl 1M is added (pH 4) and crude is extracted with CH_2Cl_2. The organic phase is dried with MgSO4, filtered and concentrated and crude is purified with column chromatography using mixtures of hexanes: AcOEt (4:1).



(*S*)-benzyl 2-(1-(3,4-dimethoxyphenyl)-3-methoxy-2-methyl-1,3-dioxopropan-2-yl)hydrazinecarboxylate, 6a

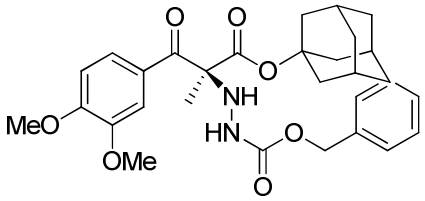
^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 1.67 (s, 3H, C$\underline{H}_3$CNH), 3.65 (s, 3 H, COOC$\underline{H}_3$), 3.85 (s, 3H, OC$\underline{H}_3$), 3.87 (s, 3H, OC$\underline{H}_3$), 4.89 (s, 1H, N$\underline{H}$COOPh), 5.06 (d, *J*=12.5 Hz, 1H, COC$\underline{H}_2$Ph), 6.62 (s, 1H, CqN$\underline{H}$), 6.79 (broad s, 1H, aromatic $\underline{H}$), 7.28 (s, 5 H, $CH_2\underline{Ph}$), 7.61 (broad s, 1H, aromatic $\underline{H}$), 7.73 (dd, *J*= 8.5 Hz, *J*= 2.0 Hz, 1H, aromatic $\underline{H}$).

^{13}C [^{1}H] NMR ($CDCl_3$, 90 MHz) δ (ppm): 19.7 ($\underline{C}H_3CNH$), 53.1 ($COO\underline{C}H_3$), 56.2 ($O\underline{C}H_3$), 56.5 ($O\underline{C}H_3$), 67.3 ($CO\underline{C}H_2Ph$), 73.1 (Cq), 110.2 (aromàtic $\underline{C}$), 112.0 (aromàtic $\underline{C}$), 124.5 (aromàtic $\underline{C}$), 127.1 (aromàtic $\underline{Cq}$), 128.4 ($CH_2\underline{Ph}$), 128.5 ($CH_2\underline{Ph}$), 128.7 ($CH_2\underline{Ph}$), 136.2 ($\underline{C}qPh$), 149.0 (aromàtic $\underline{Cq}$), 153.7 (aromàtic $\underline{Cq}$), 157.4 ($\underline{C}OOCH_2$), 171.8 ($\underline{C}OOCH_3$), 194.4 (C=O).

IR (ATR) υ (cm^{-1}): 3337 (NH st), 3247 (NH st) , 3011 (arC-H st), 2947 (C-H st), 1745 (C=O st), 1714 (C=O st), 1655 (C=O st), 1582 (arC-C), 1510 (arC-C), 1266 (C-O-C st as), 1127 (C-O-C st as), 1109 (C-O-C st as), 1039 (C-O-C st sim), 1017 (C-O-C st sim)**.**

R_F (hexà:AcOEt (2:1))= 0.30.

Mp = 109-110 ºC.



(*S*)-benzyl 2-(1-(3,4-dimethoxyphenyl)-3-adamatyloxy-2-methyl-1,3-dioxopropan-2-yl)hydrazinecarboxylate, 6b

^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 1.58 (s, 6 H, $CHC\underline{H}_2$ ada), 1.64 (s, 3H, $C\underline{H}_3CNH$), 1.98 (s, 6 H, $CC\underline{H}_2$ Ada), 2.10 (s, 3H, $C\underline{H}CH_2$ ada), 3.90 (s, 3H, $OC\underline{H}_3$), 3.93 (s, 3H, $OC\underline{H}_3$), 4.84 (s, 1H, $N\underline{H}COOPh$), 5.10 (broad s, 2H, $COC\underline{H}_2Ph$), 6.48 (s, 1H, $CqN\underline{H}$), 6.83 (broad s, 1H, aromatic $\underline{H}$), 7.32 (s, 5 H, $CH_2\underline{Ph}$), 7.62 (broad s, 1H, aromatic $\underline{H}$), 7.76 (dd, *J*= 8.5 Hz, *J*= 2.0 Hz, 1H, aromatic $\underline{H}$).

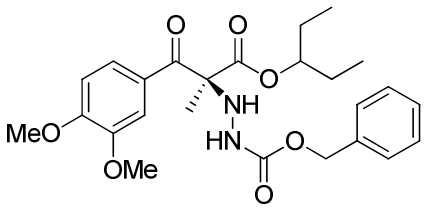
^{13}C [^{1}H] NMR ($CDCl_3$, 90 MHz) δ (ppm): 19.8 ($\underline{C}H_3CNH$), 31.1 ($\underline{C}HCH_2ada$), 36.2 ($CH\underline{C}H_2ada$), 41.2 ($CH\underline{C}H_2ada$), 56.3 ($O\underline{C}H_3$), 56.4 ($O\underline{C}H_3$), 67.5 ($CO\underline{C}H_2Ph$), 73.6 (Cq), 83.7 ($COO\underline{C}ada$), 110.2 (aromàtic $\underline{C}$), 112.2 (aromàtic $\underline{C}$), 124.6 (aromàtic $\underline{C}$), 127.7 (aromàtic $\underline{Cq}$), 128.5 ($CH_2\underline{Ph}$), 128.5 ($CH_2\underline{Ph}$), 128.8 ($CH_2\underline{Ph}$), 136.4 ($\underline{C}qPh$), 149.0 (aromàtic $\underline{Cq}$), 153.6 (aromàtic $\underline{Cq}$), 157.4 ($\underline{C}OOCH_2$), 170.0 ($\underline{C}OOCada$), 195.0 (C=O).

IR (ATR) υ (cm^{-1}): 3321 (NH st), 2909 (C-H st), 2851 (C-H st), 1725 (C=O st), 1676 (C=O st), 1593 (arC-C), 1513 (arC-C), 1259 (C-O-C st as), 1167 (C-O-C st as), 1131 (C-O-C st as), 1045 (C-O-C st sim), 1021 (C-O-C st sim)**.**

Elemental analysis calculated for $C_{30}H_{36}N_2O_7$: C: 67.15%, H: 6.76%, N: 5.22%. **Experimental**: C: 67.32%, H: 6.83%, N: 5.28%.

R_F (hexà:AcOEt (2:1))= 0.51.

Mp = 60-61 ºC.



(*S*)-benzyl 2-(1-(3,4-dimethoxyphenyl)-3-(pentan-3-yloxy)-2-methyl-1,3-dioxopropan-2-yl)hydrazinecarboxylate, 6c

^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 0.67 (t, *J*=7.6 Hz, 3 H, $CHCH_2C\underline{H}_3$), 0.73 (t, *J*=7.5 Hz, 3 H, $CHCH_2C\underline{H}_3$), 1.46 (sept, *J*= 6.0 Hz, 4H, $CHC\underline{H}_2CH_3$), 1.68 (s, 3 H $C\underline{H}_3CNH$), 3.88 (s, 3H, $OC\underline{H}_3$), 3.9 (s, 3H, $OC\underline{H}_3$), 4.77 (quint, *J*= 6 Hz, 1H, $C\underline{H}CH_2CH_3$), 4.91 (s, 1H, $N\underline{H}COOPh$), 5.09 (s, 2H, $COC\underline{H}_2Ph$), 6.43 (s, 1H, $CqN\underline{H}$), 6.79 (broad s, 1H, aromatic $\underline{H}$), 7.30 (s, 5 H, $CH_2\underline{Ph}$), 7.66 (broad s, 1H, aromatic $\underline{H}$), 7.76 (dd, *J*= 8.5 Hz, *J*=2.0 Hz , 1H, aromatic $\underline{H}$).

^{13}C [^{1}H] NMR ($CDCl_3$, 90 MHz) δ (ppm): 9.5 ($CHCH_2\underline{C}H_3$), 9.6 ($CHCH_2\underline{C}H_3$), 19.8 ($\underline{C}H_3CNH$), 26.1 ($CH\underline{C}H_2CH_3$), 26.2 ($CH\underline{C}H_2CH_3$), 56.2 ($O\underline{C}H_3$), 56.3 ($O\underline{C}H_3$), 67.5 ($CO\underline{C}H_2Ph$), 73.4 (Cq), 79.5 ($COO\underline{C}H(CH_2)_2$), 110.2 (aromatic $\underline{C}$), 112.3 (aromatic $\underline{C}$), 124.8 (aromatic $\underline{C}$), 127.7 (aromatic $\underline{Cq}$), 128.4 ($CH_2\underline{Ph}$), 128.5 ($CH_2\underline{Ph}$), 128.8 ($CH_2\underline{Ph}$), 136.3 ($\underline{C}qPh$), 149.0 (aromàtic $\underline{Cq}$), 153.7 (aromàtic $\underline{Cq}$), 157.5 ($\underline{C}OOCH_2$), 172.0 ($\underline{C}OOCH$), 194.1 (C=O).

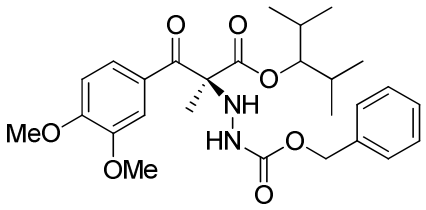
IR (ATR) υ (cm^{-1}): 3324 (NH st), 2967 (C-H st), 2937 (C-H st), 1722 (C=O st), 1676 (C=O st), 1512 (arC-C), 1455 (arC-C), 1258 (C-O-C st as), 1167 (C-O-C st as), 1101 (C-O-C st as), 1021 (C-O-C st sim), 913 (C-O-C st sim)**.**

$[\alpha]_D^{20}$= +39.5 (c= 1.75, $CHCl_3$), 97.5% e.e. (*S*).

R_F (hexà:AcOEt (2:1))= 0.44.

Mp = 86-88ºC.

Enantiomeric excess was determined by HPLC analysis using a mixture of hexanes: isopropanol (80: 20) at 1 ml/min as eluent. As a stationary phase a Daicel Chiralpack AD-H (0.46 cm ϕ x 25 cm) column is used. 10 μl of a solution (concentration 1 mg/ml) of racemic mixture of **6c** (50:50) shows two peaks t_r(*S*)= 21.601 min, i t_r(*R*)= 27.987 min.



(*S*)-benzyl 2-(1-(3,4-dimethoxyphenyl)-3--(2,4-dimethylpentan-3-yloxy)-2-methyl-1,3-dioxopropan-2-yl)hydrazine carboxylate, 6d

^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm):): 0.66-0.89 (m, 12H), 1.73 (s, 3H, C$\underline{H}_3$CNH), 1.84 (oct, *J*= 6.8 Hz, 2H, C$\underline{H}$CH$_3$), 3.90 (s, 3H, OC$\underline{H}_3$), 3.91 (s, 3H, OC$\underline{H}_3$), 4.64 (t, *J*= 5.8 Hz, 1H, COC$\underline{H}$CH$_3$), 4.68 (s, 1H, N$\underline{H}$COOPh), 5.10 (s, 2H, COC$\underline{H}_2$Ph), 6.35 (s, 1H, CqN$\underline{H}$), 6.80 (s aparent, 1H, aromatic $\underline{H}$), 7.30-7.36 (m, 5 H, CH$_2\underline{Ph}$), 7.73 (s aparent, 1H, aromatic $\underline{H}$), 7.96 (d, *J*= 8.4 Hz, 1H, aromatic $\underline{H}$).

^{13}C [^{1}H] NMR ($CDCl_3$, 90 MHz) δ (ppm): 17.6 (CH$\underline{C}$H$_3$), 19.9 (CH$\underline{C}$H$_3$), 20.0 ($\underline{C}$H$_3$CNH), 29.8 ($\underline{C}$HCH$_3$), 56.3 (O$\underline{C}$H$_3$), 56.4 (O$\underline{C}$H$_3$), 67.5 (CO$\underline{C}$H$_2$Ph), 74.3 (Cq), 84.3 (CO$\underline{C}$HCH), 110.2 (aromatic $\underline{C}$), 112.6 (aromatic $\underline{C}$), 125.4 (aromatic $\underline{C}$), 127.8 (aromatic $\underline{Cq}$), 128.5 (CH$_2\underline{Ph}$), 128.6 (CH$_2\underline{Ph}$), 128.8 (CH$_2\underline{Ph}$), 136.3 ($\underline{C}$qPh), 148.8 (aromatic $\underline{Cq}$), 153.8 (aromatic $\underline{Cq}$), 157.6 ($\underline{C}$OOCH$_2$), 171.3 ($\underline{C}$OOCCH$_3$), 193.9 (C=O).

IR (ATR) υ (cm^{-1}): 3324 (NH st), 3033 (arC-H st), 3003 (arC-H st), 2962 (C-H st), 2934 (C-H st), 2875 (C-H st), 1722 (C=O st), 1711 (C=O st), 1676 (C=O st), 1595 (arC-C), 1510 (arC-C), 1437 (arC-C), 1256 (C-O-C st as), 1168 (C-O-C st as), 1150 (C-O-C st as), 1099 (C-O-C st as), 1022 (C-O-C st sim).

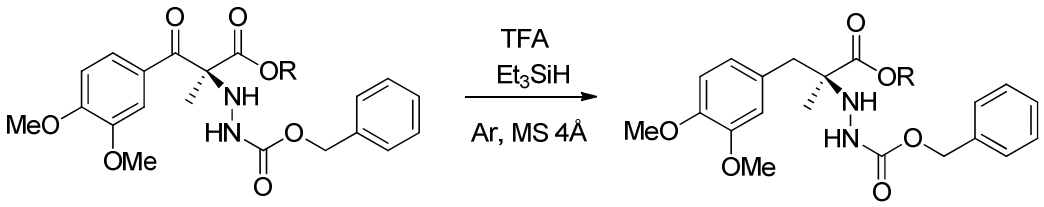
R_F (hexà:AcOEt (2:1))= 0.48.

Mp = 115-116.5ºC.

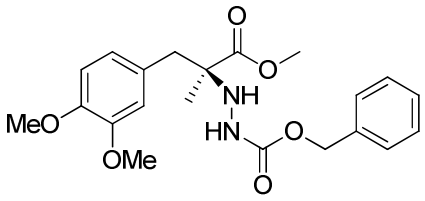
Yield= 85%.

Enantiomeric excess was determined by HPLC analysis using a mixture of hexanes: isopropanol (98: 02) at 0.8 ml/min as eluent. As a stationary phase a Daicel Chiralpack AD-H (0.46 cm ϕ x 25 cm) column is used. 10 µl of a solution (concentration 1 mg/ml) of racemic mixture of **6d** (50:50) shows two peaks t_r(*S*)= 14.327 min, i t_r(*R*)= 19.003 min.

General procedure for deoxygenation reaction



In a 50 ml round-bottom flask provided with magnetic stirring, 12.1 mmol of deprotected Michael adduct is dissolved under Argon atmosphere in 14 ml of trifluoroacetic acid (180 mmol). After 5 minutes 8 ml (62.1 mmol) of triethylsilane is added and the reaction is monitored by TLC. After consumption of starting material, CH_2Cl_2 is added and the reaction is quenched with $NaHCO_3$ until no observation of bubbles. Crude is extracted with CH_2Cl_2 and the organic with MgSO4, filtered and concentrated and crude is purified with column chromatography using mixtures of hexanes: AcOEt: NEt_3 (2:1:0,1).



(*S*)-benzyl 2-(3-(3,4-dimethoxyphenyl)-1-methoxy-2-methyl-1-oxopropan-2-yl)hydrazinecarboxylate, 7a

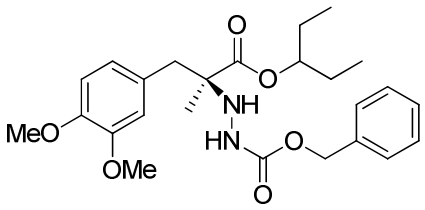
^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 1.38 (s, 3H, C$\underline{H}_3$CNH), 2.97 (dd, *J*= 13.74 Hz, *J*= 54.31 Hz, 2H, ArC$\underline{H}_2$Cq), 3.70 (s, 3 H, COOC$\underline{H}_3$), 3.84 (s, 6H, OC$\underline{H}_3$), 4.18 (s, 1H, N$\underline{H}$COOPh), 5.11 (t, *J*=9.21 Hz, 2H, COC$\underline{H}_2$Ph), 6.45 (s, 1H, CqN$\underline{H}$), 6.68 (dd, *J*= 8.0 Hz, *J*=1.9 Hz, 1H, aromatic $\underline{H}$), 6.69 (s aparent, 1H, aromatic $\underline{H}$), 6.76 (d, *J*=8.0 Hz, 1H, aromatic $\underline{H}$), 7.18-7.43 (m, 5 H, $CH_2\underline{Ph}$).

^{13}C [^{1}H] NMR ($CDCl_3$, 90 MHz) δ (ppm): 21.6 ($\underline{C}H_3$CNH), 43.8 (Ar$\underline{C}H_2$), 52.4 (COO$\underline{C}H_3$), 56.1 (O$\underline{C}H_3$), 66.4 (CO$\underline{C}H_2$Ph), 67.2 (Cq), 111.4 (aromatic $\underline{C}$), 113.2 (aromatic $\underline{C}$), 122.7 (aromatic $\underline{C}$), 127.9 (aromatic $\underline{Cq}$), 128.5 ($CH_2\underline{Ph}$), 128.6 ($CH_2\underline{Ph}$), 128.9 ($CH_2\underline{Ph}$), 136.5 ($\underline{C}$qPh), 148.5 (aromatic $\underline{Cq}$), 149.0 (aromatic $\underline{Cq}$), 157.2 ($\underline{C}OOCH_2$), 175.8 ($\underline{C}OOCH_3$).

IR (ATR) υ (cm^{-1}): 3309 (NH st), 2949 (C-H st), 2834 (C-H st), 1721 (C=O st), 1582 (arC-C), 1514 (arC-C), 1259 (C-O-C st as), 1236 (C-O-C st as), 1141 (C-O-C st as), 1098 (C-O-C st as), 1025 (C-O-C st sim), 1017 (C-O-C st sim).

Elemental analysis calculated for $C_{21}H_{26}N_2O_6$: C: 62.67%, H: 6.51%, N: 6.96%. **Experimental**: C: 62.45%, H: 6.53%, N: 6.96%.

R_F (hexà:AcOEt (1:1))= 0.35.



(*S*)-benzyl 2-(3-(3,4-dimethoxyphenyl)-1-(pentan-3-yloxy)-2-methyl-1-oxopropan-2-yl)hydrazinecarboxylate, 7c

^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 0.83 (t, *J*=7.4 Hz, 3 H, $CHCH_2C\underline{H}_3$), 0.90 (t, *J*=7.4 Hz, 3 H, $CHCH_2C\underline{H}_3$), 1.36 (s, 3 H $C\underline{H}_3CNH$), 1.49-1.67 (m, 4H, $CHC\underline{H}_2CH_3$), 2.99 (dd, *J*= 13.8 Hz, *J*= 64.0 Hz, 2H, $ArC\underline{H}_2Cq$), 3.84 (s, 6H, $OC\underline{H}_3$), 4.14 (s, 1H, $N\underline{H}COOPh$), 4.76 (quint, *J*= 5.7 Hz, 1H, $C\underline{H}CH_2CH_3$), 5.03-5.19 (m, 2H, $COC\underline{H}_2Ph$), 6.49 (s, 1H, $CqN\underline{H}$), 6.75 (s, 2H, aromatic $\underline{H}$), 6.79 (s, 1H, aromatic $\underline{H}$), 7.26-7.37 (m, 5 H, $CH_2\underline{Ph}$).

^{13}C [^{1}H] NMR ($CDCl_3$, 90 MHz) δ (ppm): 9.6 ($CHCH_2\underline{C}H_3$), 9.8 ($CHCH_2\underline{C}H_3$), 21.8 ($\underline{C}H_3CNH$), 26.2 ($CH\underline{C}H_2CH_3$), 26.4 ($CH\underline{C}H_2CH_3$), 46.3 ($Ar\underline{C}H_2$), 56.1 ($O\underline{C}H_3$), 56.2 ($O\underline{C}H_3$), 66.1 ($CO\underline{C}H_2Ph$), 67.2 (Cq), 78.5 ($COO\underline{C}H(CH_2)_2$), 111.3 (aromatic $\underline{C}$), 113.1 (aromatic $\underline{C}$), 122.6 (aromatic $\underline{C}$), 128.0 (aromatic $\underline{Cq}$), 128.4 ($CH_2\underline{Ph}$), 128.5 ($CH_2\underline{Ph}$), 128.8 ($CH_2\underline{Ph}$), 136.6 ($\underline{C}qPh$), 148.4 (aromatic $\underline{Cq}$), 149.0 (aromatic $\underline{Cq}$), 157.3 ($\underline{C}OOCH_2$), 175.4 ($\underline{C}OOCH$).

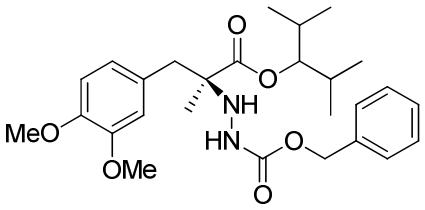
IR (ATR) υ (cm^{-1}): 3312 (NH st), 3064 (arC-H st), 3032 (arC-H st), 2967 (C-H st), 2937 (C-H st), 2878 (C-H st), 1712 (C=O st), 1514 (arC-C), 1454 (arC-C), 1259 (C-O-C st as), 1142 (C-O-C st as), 1094 (C-O-C st as), 1026 (C-O-C st sim), 913 (C-O-C st sim)**.**

Elemental analysis calculated for $C_{25}H_{34}N_2O_6$: C: 65.48%, H: 7.47%, N: 6.11%. **Experimental**: C: 65.09%, H: 7.60%, N:6.17 %.

$[\alpha]_D^{20}$= +25.3 (c= 2.13, $CHCl_3$), 97.5% e.e. (*S*).

R_F (hexà:AcOEt (1:1))= 0.47.

Enantiomeric excess was determined by HPLC analysis using a mixture of hexanes: isopropanol (80: 20) at 1 ml/min as eluent. As a stationary phase a Daicel Chiralpack AD-H (0.46 cm ϕ x 25 cm) column is used. 10 μl of a solution (concentration 1 mg/ml) of racemic mixture of **7c** (50:50) shows two peaks t_r(*S*)= 11.737 min, i t_r(*R*)= 13.515 min.



(*S*)-benzyl 2-(3-(3,4-dimethoxyphenyl)-1-(2,4-dimethylpentan-3-yloxy)-2-methyl-1-oxopropan-2-yl)hydrazinecarboxylate, 7d

^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 0.84 (dd, *J*= 6.8 Hz, *J*= 8.6 Hz, 6H, CHCH($C\underline{H}_3$)$_2$), 0.89 (dd, *J*= 6.8 Hz, *J*= 8.5 Hz, 6H, CH($C\underline{H}_3$)$_2$), 1.30 (s, 3 H $C\underline{H}_3$CNH), 1.89-1.97 (m, 2H, CHC$\underline{H}$(CH_3)$_2$), 2.99 (dd, *J*= 14.0 Hz, *J*= 50.4 Hz, 2H, ArC$\underline{H}_2$Cq), 3.83 (s, 3H, OC$\underline{H}_3$), 3.85 (s, 3H, OC$\underline{H}_3$), 4.20 (s ample, 1H, N$\underline{H}$COOPh), 4.64 (t, *J*= 6.1 Hz, 1H, C$\underline{H}$CH(CH_3)$_2$), 5.11 (s, 2H, COC$\underline{H}_2$Ph), 6.51 (s, 1H, CqN$\underline{H}$), 6.74 (d, *J*= 8.2 Hz, 1H, aromatic $\underline{H}$), 6.81 (dd, *J*= 1.8 Hz, *J*= 9.7 Hz, 1H, aromatic $\underline{H}$), 6.91 (s ample, 1H, aromatic $\underline{H}$), 7.28-7.33 (m, 5 H, $CH_2\underline{Ph}$).

^{13}C [^{1}H] NMR ($CDCl_3$, 90 MHz) δ (ppm): 17.5 (CHCH($\underline{C}H_3$)$_2$), 17.9 (CHCH($\underline{C}H_3$)$_2$), 20.0 (CHCH($\underline{C}H_3$)$_2$), 21.8 ($\underline{C}H_3$CqNH), 29.7 (CH$\underline{C}$H(CH_3)$_2$), 42.0 (Ar$\underline{C}H_2$Cq), 56.1 (O$\underline{C}H_3$), 56.2 (O$\underline{C}H_3$), 66.2 (CO$\underline{C}H_2$Ph), 67.1 ($CH_3\underline{C}$qNH), 84.6 ($\underline{C}$HCH(CH_3)$_2$), 111.1 (aromatic $\underline{C}$), 114.2 (aromatic $\underline{C}$), 123.1 (aromatic $\underline{C}$), 127.9 (aromatic $\underline{Cq}$), 128.2 ($CH_2\underline{Ph}$), 128.4 ($CH_2\underline{Ph}$), 128.7 ($CH_2\underline{Ph}$), 136.6 ($\underline{C}$qPh), 148.3 (aromatic $\underline{Cq}$), 148.8 (aromatic $\underline{Cq}$), 157.2 ($\underline{C}OOCH_2$), 175.7 ($\underline{C}$OOCH).

IR (ATR) υ (cm^{-1}): 3313 (NH st), 3064 (arC-H st), 3032 (arC-H st), 2963 (C-H st), 2935 (C-H st), 2875 (C-H st), 1713 (C=O st), 1514 (arC-C), 1453 (arC-C), 1259 (C-O-C st as), 1143 (C-O-C st as), 1027 (C-O-C st sim), 898 (C-O-C st sim), 737 (arC-H δ oop), 697 (arC-H δ oop)**.**

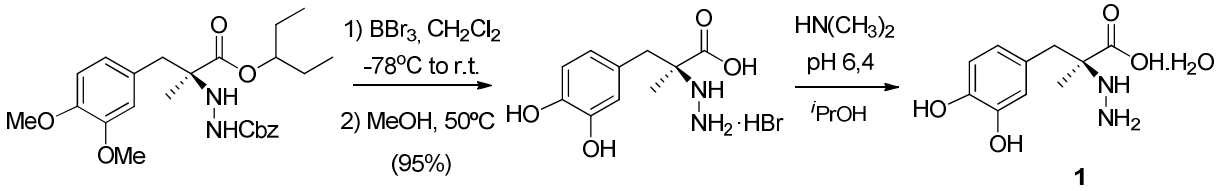
Elemental analysis calculated for $C_{27}H_{38}N_2O_6$: C: 66.64%, H: 7.87%, N: 5.76%. **Experimental**: C: 65.39%, H: 8.03%, N: 5.64%.

R_F (hexà:AcOEt (1:1))= 0.49.

Yield= 55%.

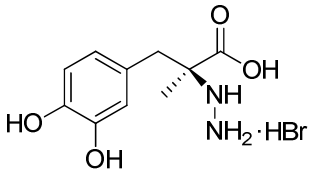
Enantiomeric excess was determined by HPLC analysis using a mixture of hexanes: isopropanol (80: 20) at 1 ml/min as eluent. As a stationary phase a Daicel Chiralpack AD-H (0.46 cm ϕ x 25 cm) column is used. 10 μl of a solution (concentration 1 mg/ml) of racemic mixture of **7d** (50:50) shows two peaks t_r(*S*) = 9.180 min, i t_r(*R*) = 11.011 min.

Synthesis of L-Carbidopa



In a 250 ml round-bottom flask provided with magnetic stirring 3.51g (7.65 mmol) of **7c** is dissolved under Argon atmosphere in 76 ml of CH_2Cl_2. At -78ºC 7.37 ml (76.5 mmol) of BBr_3 are added and system is stirred at room temperature 24 hours. 20 ml of water are added very carefully stirring at the same time. After 1 hour phases are separated and aqueous phase is extracted with $CHCl_3$ and AcOEt. Aqueous phase is liophilizated obtaining 9 g of a brown solid which is dissolved in 50 ml of MeOH and heated at 50ºC with stirring up to 12 hours. After evaporation 2,23g (7,26 mmol) of a brown solid is obtained (95% yield) which is in agreement with the *L*-Carbidopa hydrobromic salt.

To get the monohydrate derivative, the hydrobromic salt is dissolved in the minimum quantity of isopropanol and pH is adjusted up to 6.4 adding very slowly dimethylamine (2M in THF) yielding a grey precipitate which is in agreement with the formation of the *L*-Carbidopa monohydrate product.



(*S*)-3-(3,4-dihydroxyphenyl)-2-hydrazinyl-2-methylpropanoic acid hydrobromide,

^{1}H NMR (D_2O, 400 MHz) δ (ppm):): 1.35 (s, 3H, $C\underline{H}_3CNH$), 2.85 (dd, *J*= 14.2 Hz, *J*= 60.1 Hz, 2H, $ArC\underline{H}_2Cq$), 6.50 (d, *J*= 8.0 Hz, 1H, aromatic <u>H</u>), 6.58 (broad s, 1H, aromatic <u>H</u>), 6.68 (d, *J*= 8.0 Hz, 1H, aromatic <u>H</u>).

^{13}C [^{1}H] NMR (D_2O, 100.5 MHz) δ (ppm):): 18.7 ($\underline{C}H_3CqNH$), 41.3 ($Ar\underline{C}H_2Cq$), 65.5 ($CH_3\underline{C}qNH$), 116.0 (aromatic <u>C</u>), 117.5 (aromatic <u>C</u>), 122.4 (aromatic <u>C</u>), 125.7 (aromatic <u>Cq</u>), 143.3 (aromatic <u>Cq</u>), 143.6 (aromatic <u>Cq</u>), 174.7 (<u>C</u>OOH).

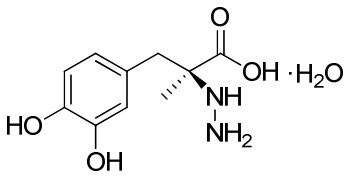
IR (ATR) υ (cm^{-1}): 3204 (NH st, OH st), 1716 (C=O st), 1602 (arC-C), 1442 (arC-C), 1193 (C-O-C st as), 1057 (C-O-C st sim)**,** 882 (arC-H δ oop), 723 (arC-H δ oop, NH δ).

MS high resolution theoric: m/z=227.1026 (100%), m/z=228.1060 (11.9%) i m/z=229.1069 (1.5%). **Experimental**: m/z=227.1031 (100%), m/z=228.1067 (14.9%) i m/z=229.1090 (2.0%).

ESI$^+$=m/z= 227.0 for $[M+H]^+$ (theoric m/z= 226 per [M]); **m/z=** 283.1 per $[M+K+H_2O]^+$.

$[\alpha]_D^{25}$= -7.5 (c= 1, methanol), 97.5% e.e.

Yield: 95%.



(*S*)-3-(3,4-dihydroxyphenyl)-2-hydrazinyl-2-methylpropanoic acid hydrate,

^{1}H NMR (DMSO, 400 MHz) δ (ppm):): 1.11 (s, 3H, C<u>H</u>$_3$CNH), 2.71 (broad dd, *J*= 12.2 Hz, *J*= 42.1 Hz, 2H, ArC<u>H</u>$_2$Cq), 6.41 (broad s, 1H, aromatic <u>H</u>), 6.55 (broad s, 1H, aromatic <u>H</u>), 6.61 (broad s, 1H, aromatic <u>H</u>).

^{13}C [^{1}H] NMR (DMSO, 100.5 MHz) δ (ppm):): 20.4 (<u>C</u>H$_3$CqNH), 41.4 (Ar<u>C</u>H$_2$Cq), 65.6 (CH$_3$<u>Cq</u>NH), 115.4 (aromatic <u>C</u>), 118.2 (aromatic <u>C</u>), 121.4 (aromatic <u>C</u>), 127.2 (aromatic <u>Cq</u>), 143.3 (aromatic <u>Cq</u>), 145.2 (aromatic <u>Cq</u>), 174.9 (<u>C</u>OOH).

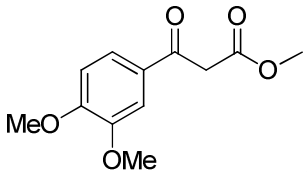
IR (ATR) υ (cm^{-1}): 3201 (NH st, OH st), 3087 (arC-H st), 2360 (), 2341 (), 1627 (C=O st), 1690 (arC-C), 1452 (arC-C), 1221 (C-O-C st as), 1123 (C-O-C st sim)**,** 855 (arC-H δ oop), 776 (arC-H δ oop, NH δ).

MS high resolution theoric: m/z=227.1026 (100%), m/z=228.1060 (11.9%) i m/z=229.1069 (1.5%). **Experimental**: m/z=227.1030 (100%), m/z=228.1078 (28.5.9%) i m/z=229.1153 (5.1%).

$[\alpha]_D^{25}$= -11.8 (c= 0,5, methanol), 97.5% e.e. (lit[127]= **$[\alpha]_D^{26}$=** -13.82 (c= 0.3, methanol), 100% e.e). *S* configuration.

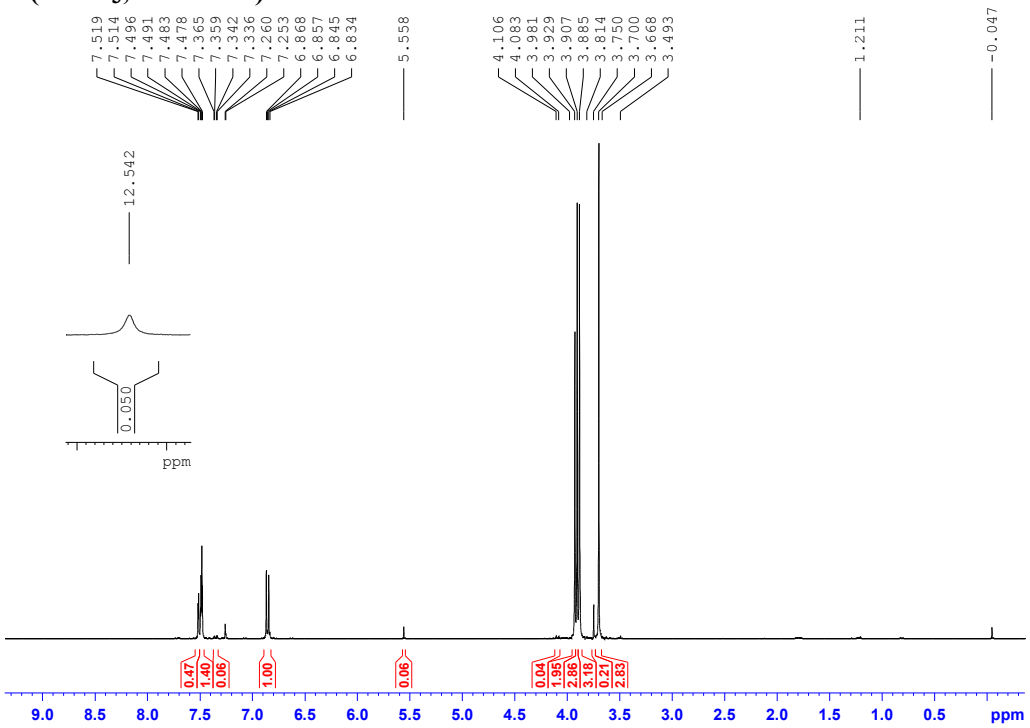
Mp. = >205ºC descompose.

NMR SPECTRA

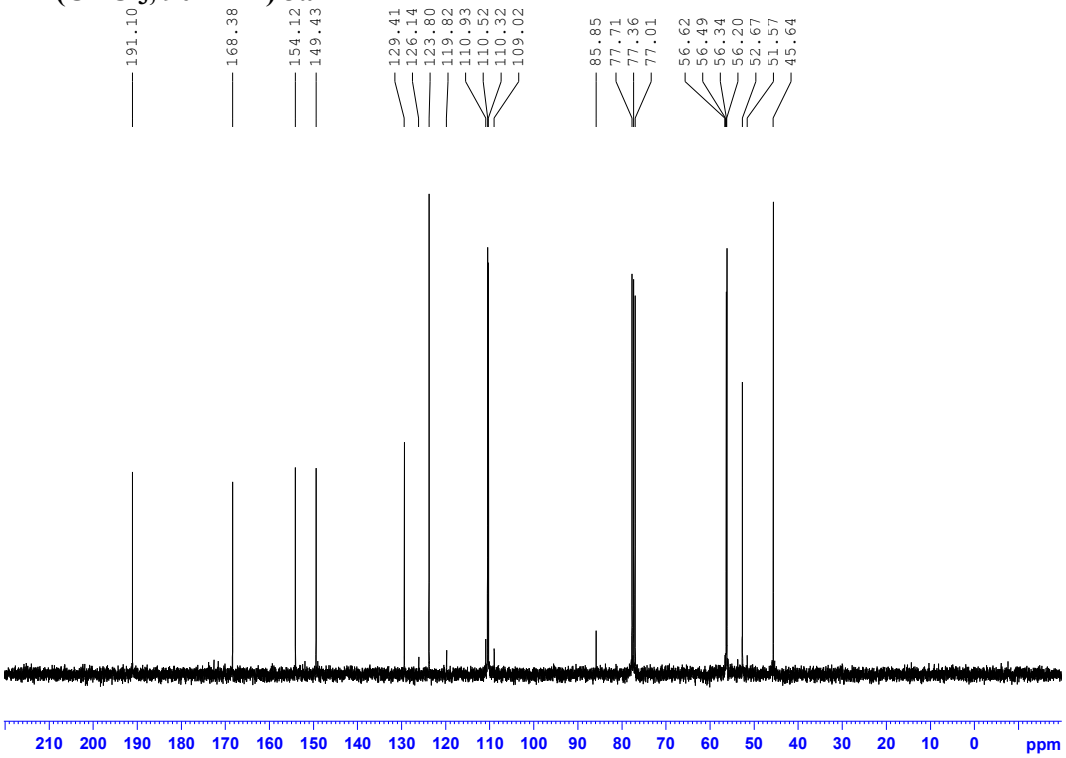


3a

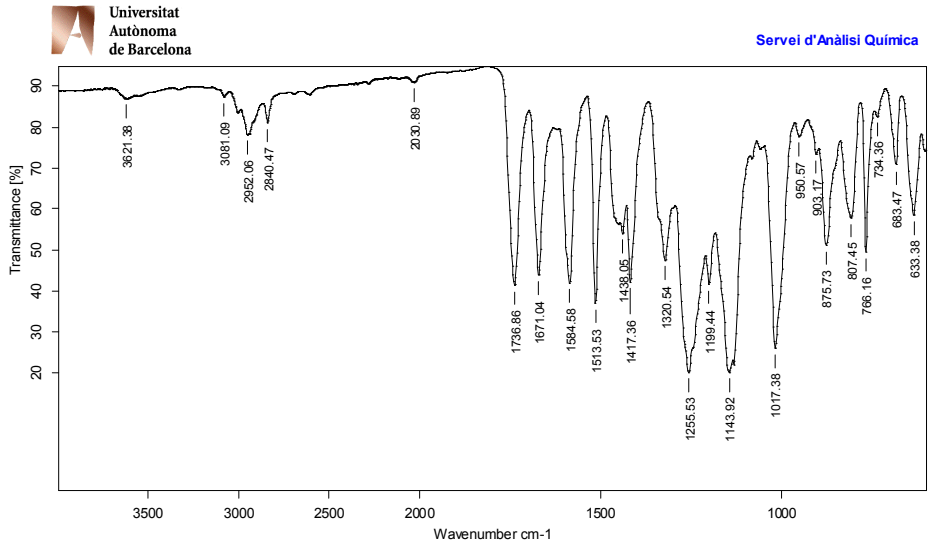
^{1}H NMR ($CDCl_3$, 360 MHz) 3a

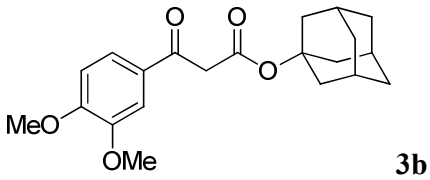


^{13}C NMR ($CDCl_3$, 90 MHz) 3a



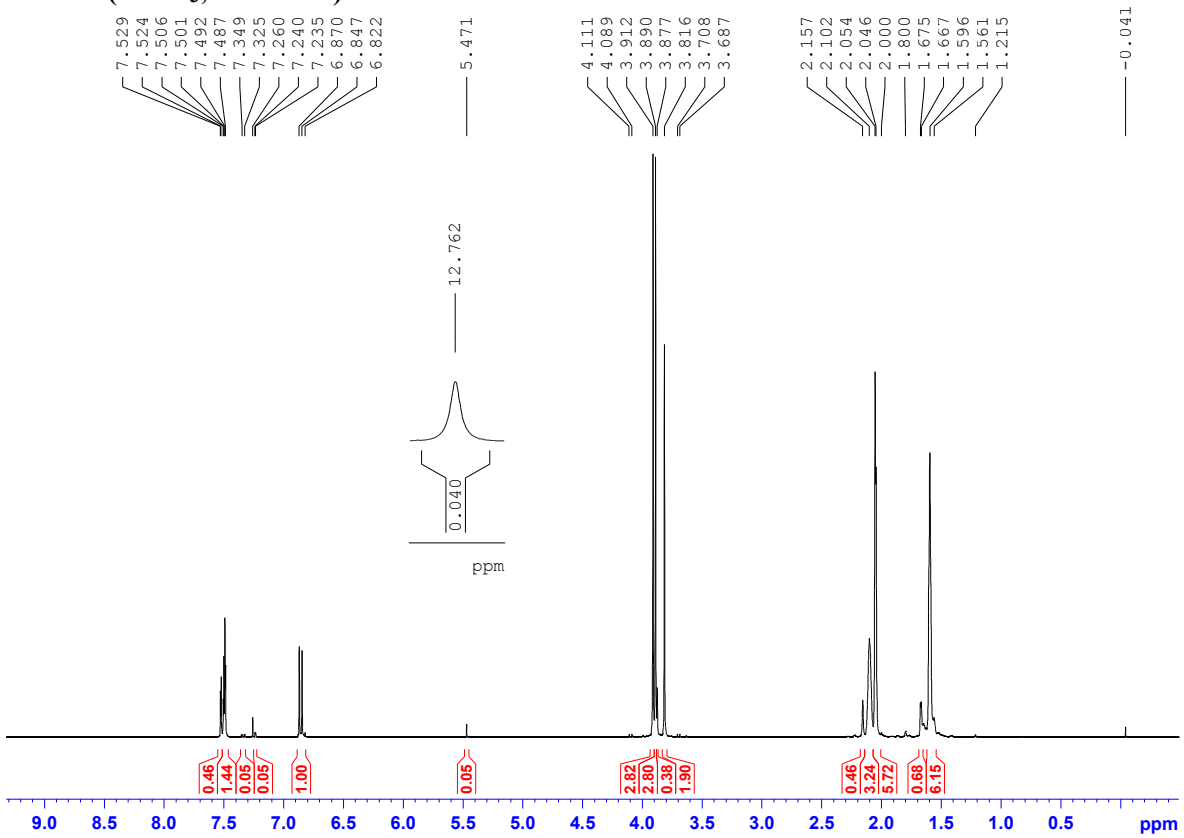
IR (ATR) 3a



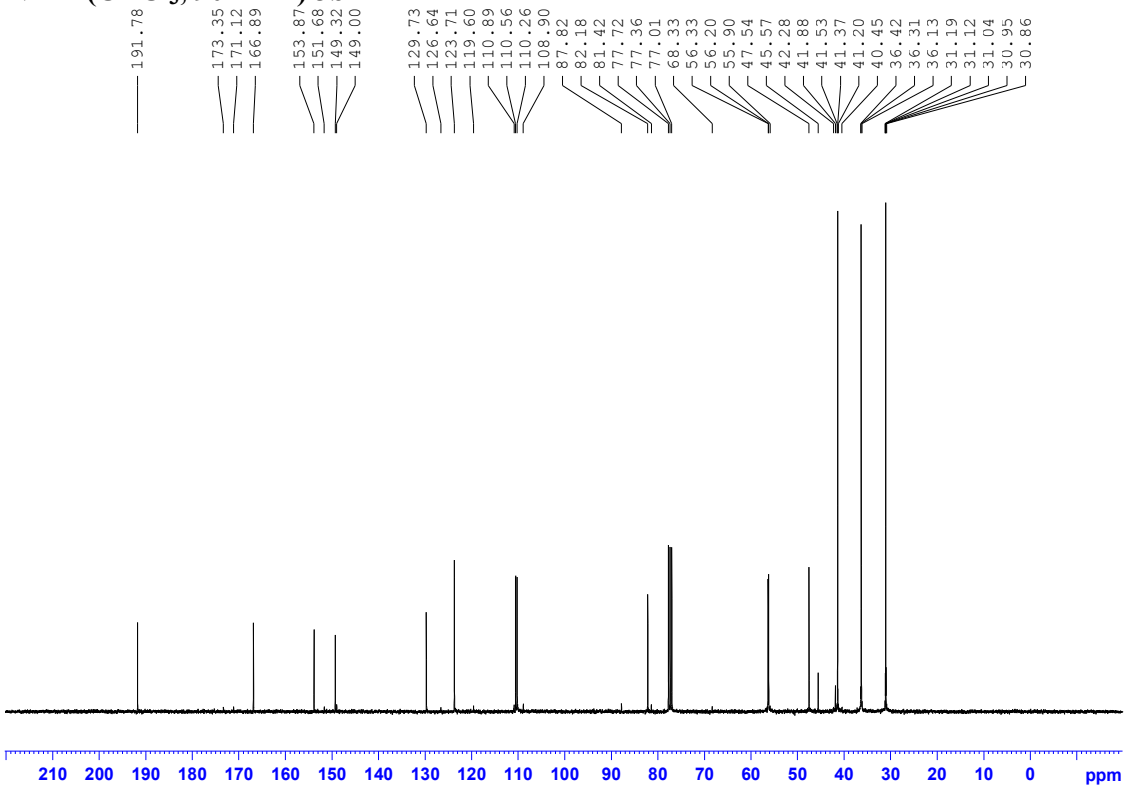


3b

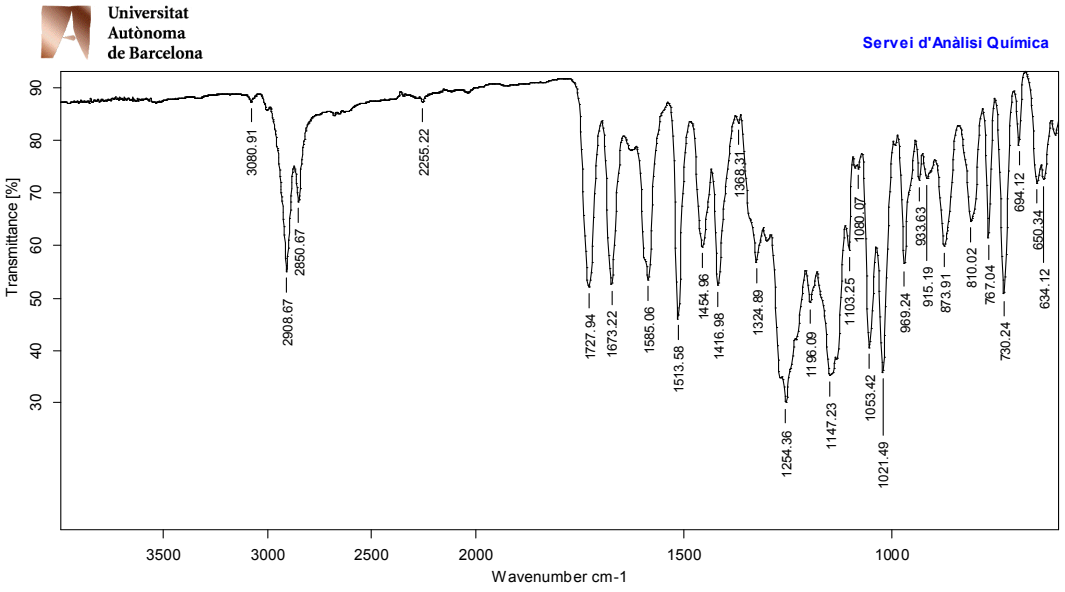
^{1}H NMR ($CDCl_3$, 360 MHz) 3b

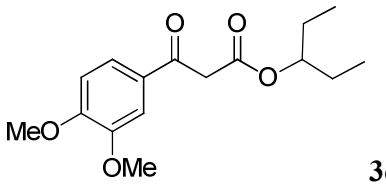


^{13}C NMR ($CDCl_3$, 90 MHz) 3b



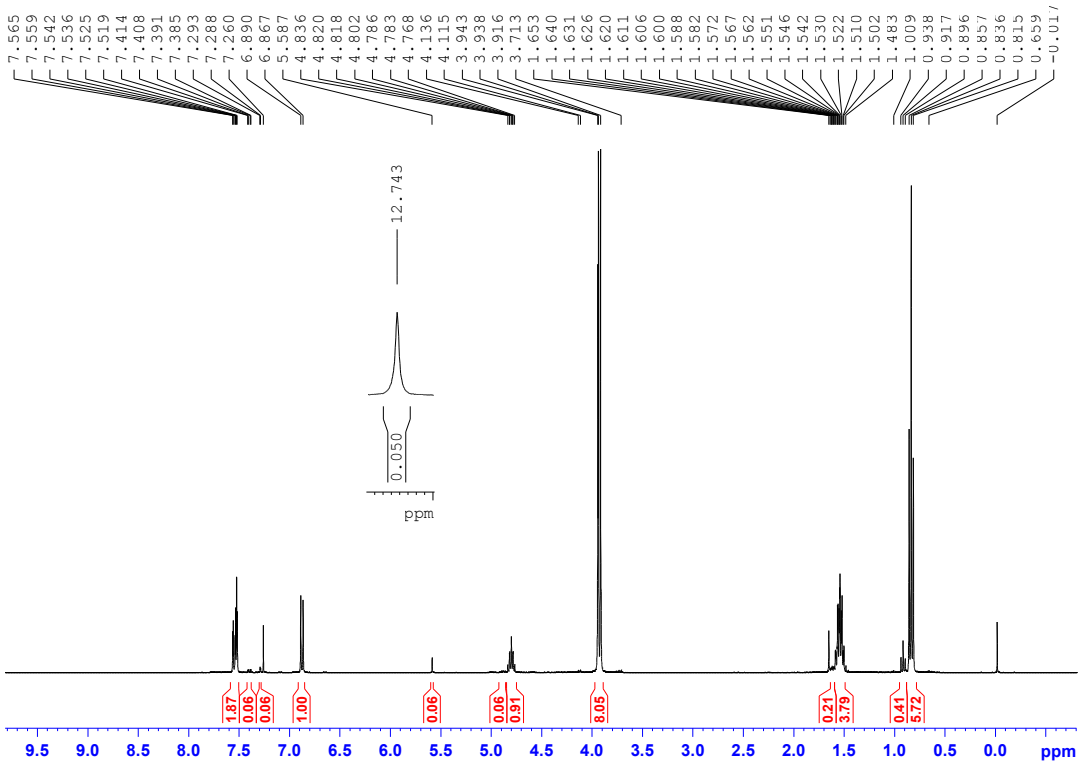
IR (ATR) 3b



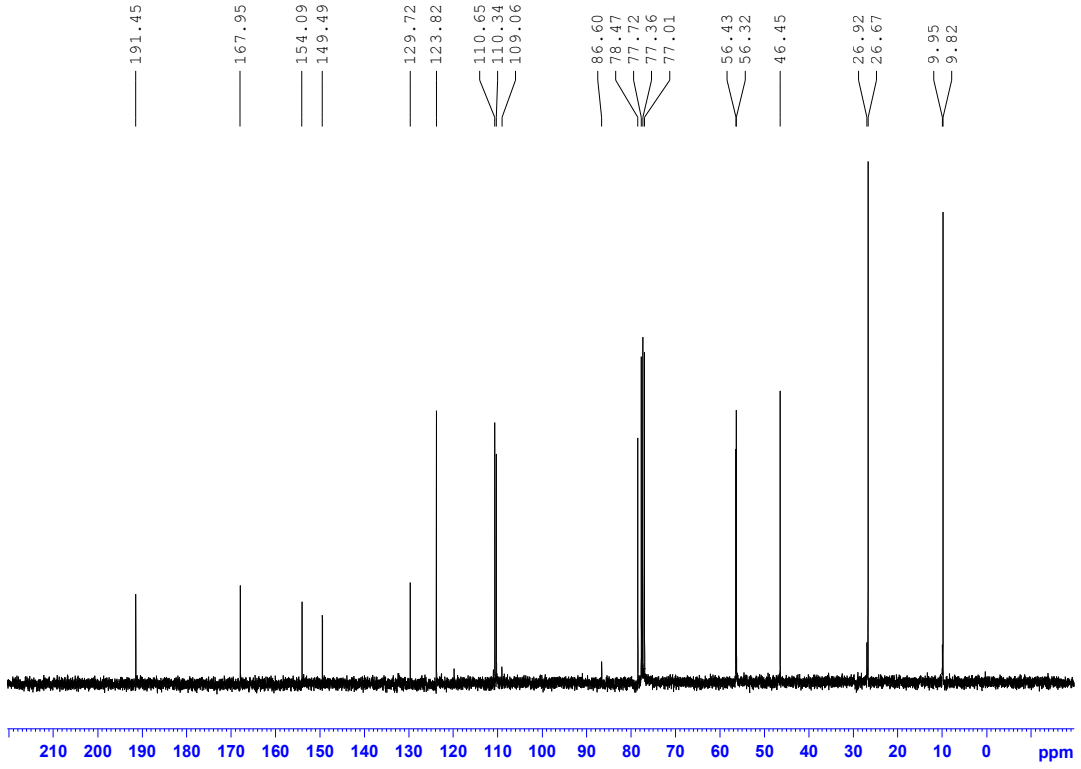


3c

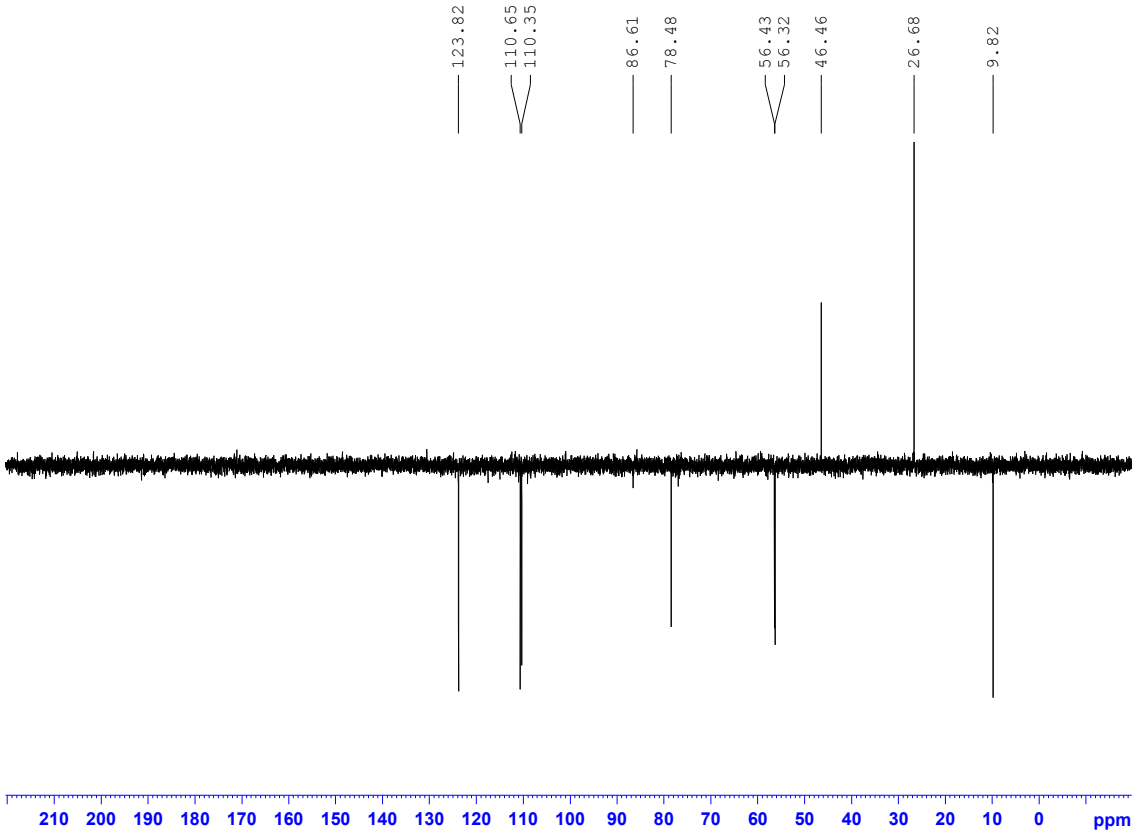
^{1}H NMR ($CDCl_3$, 360 MHz) 3c



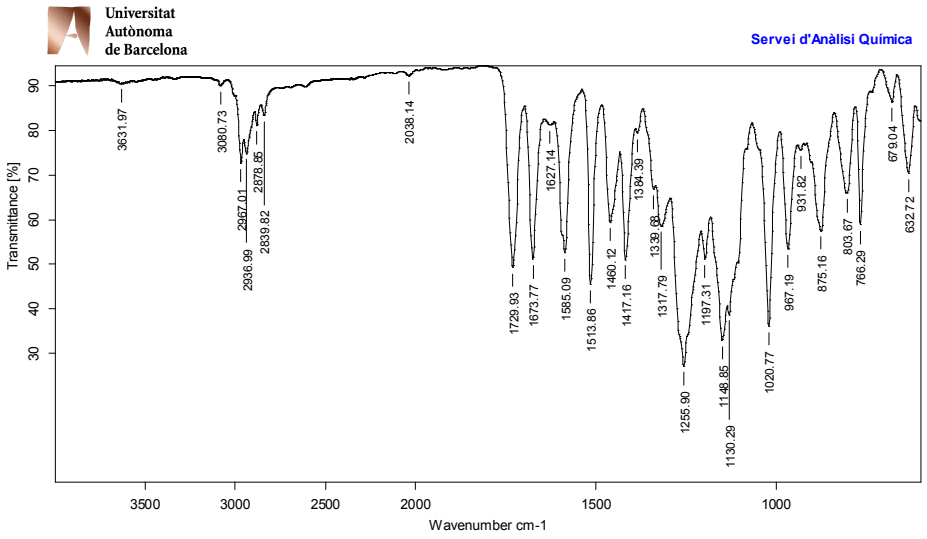
^{13}C NMR ($CDCl_3$, 90 MHz) 3c

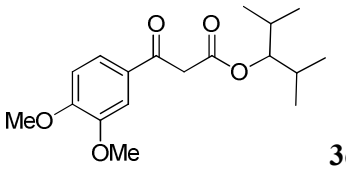


^{13}C-DEPT-135 ($CDCl_3$, 62.5 MHz) 3c



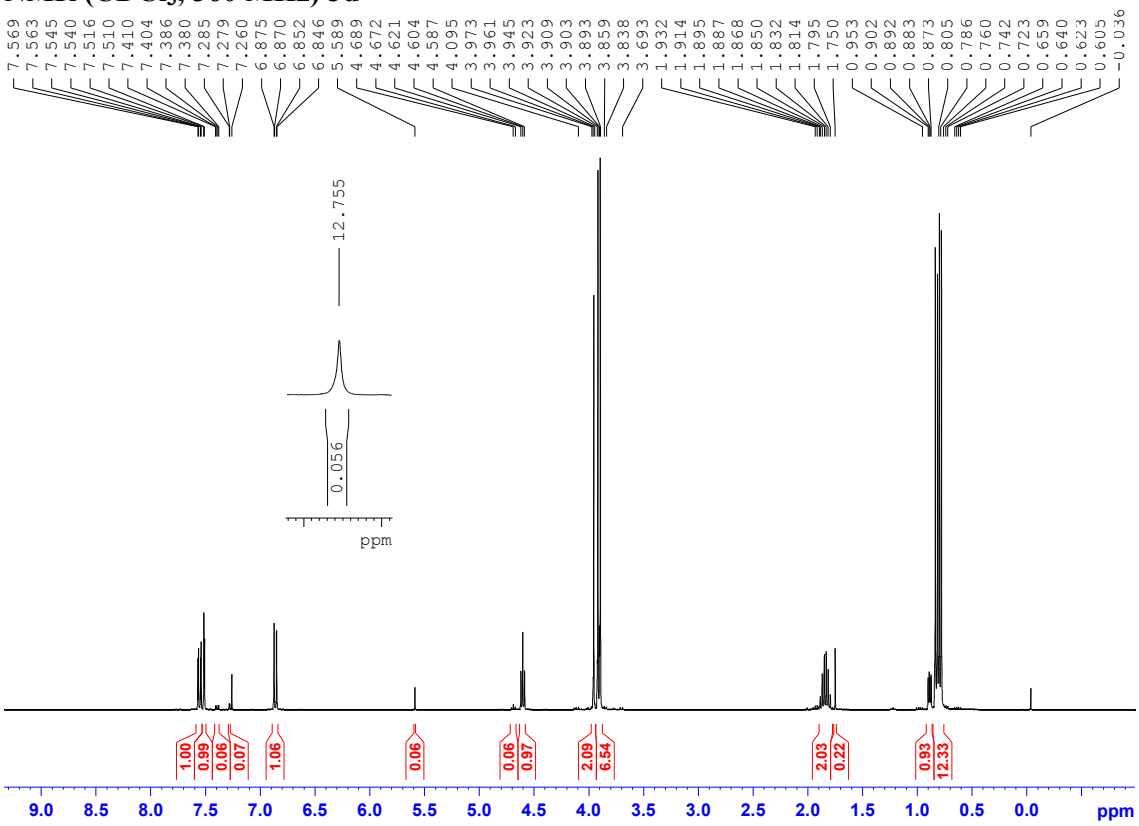
IR (ATR) 3c



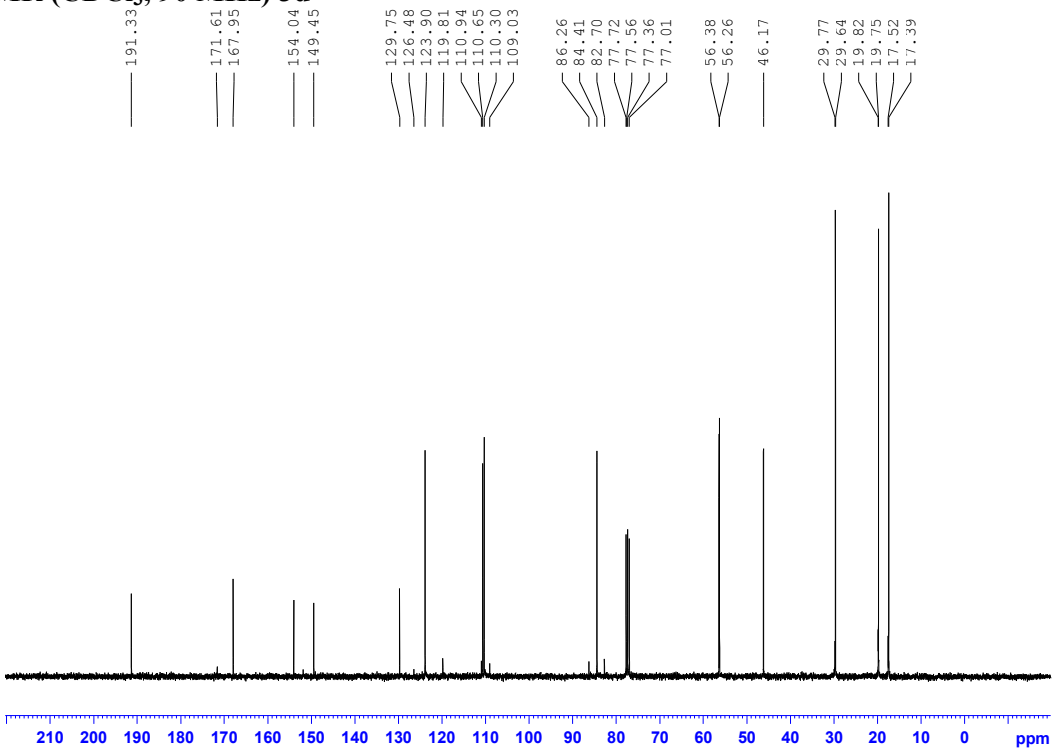


3d

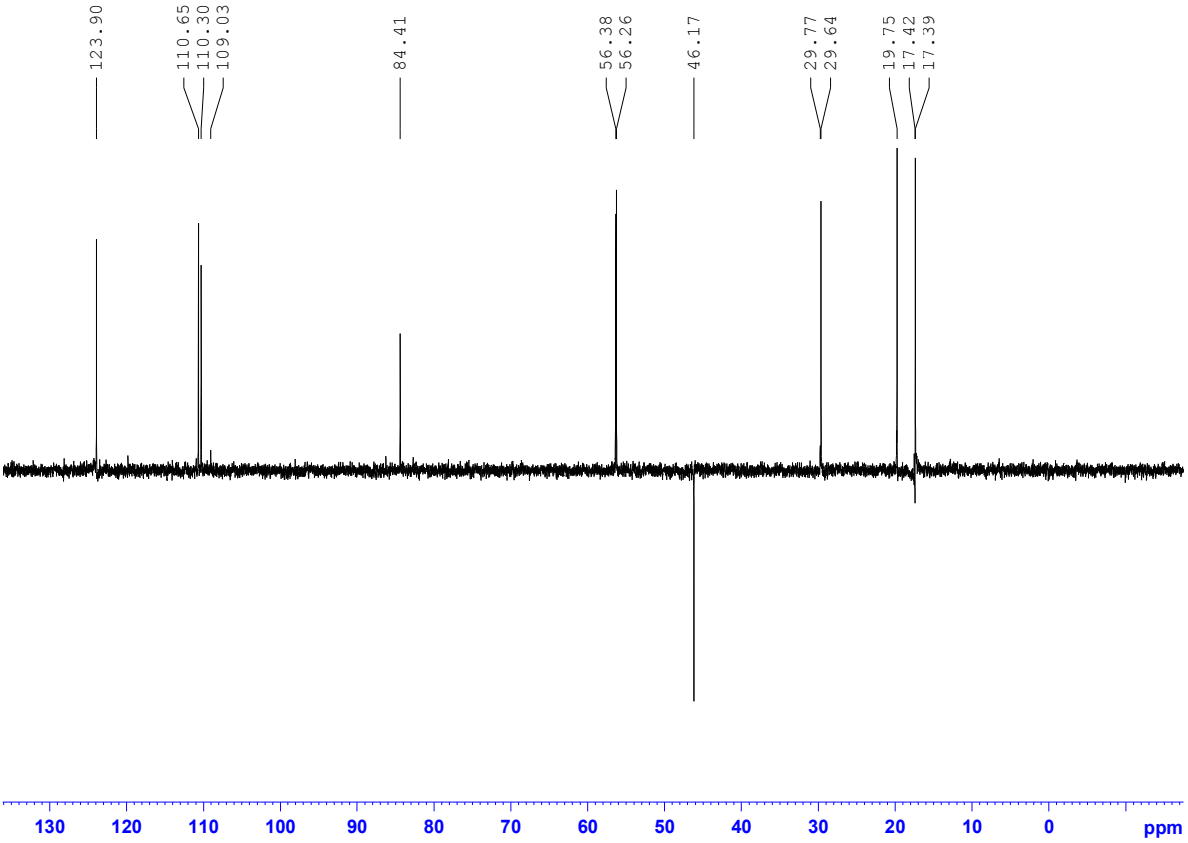
^{1}H NMR ($CDCl_3$, 360 MHz) 3d



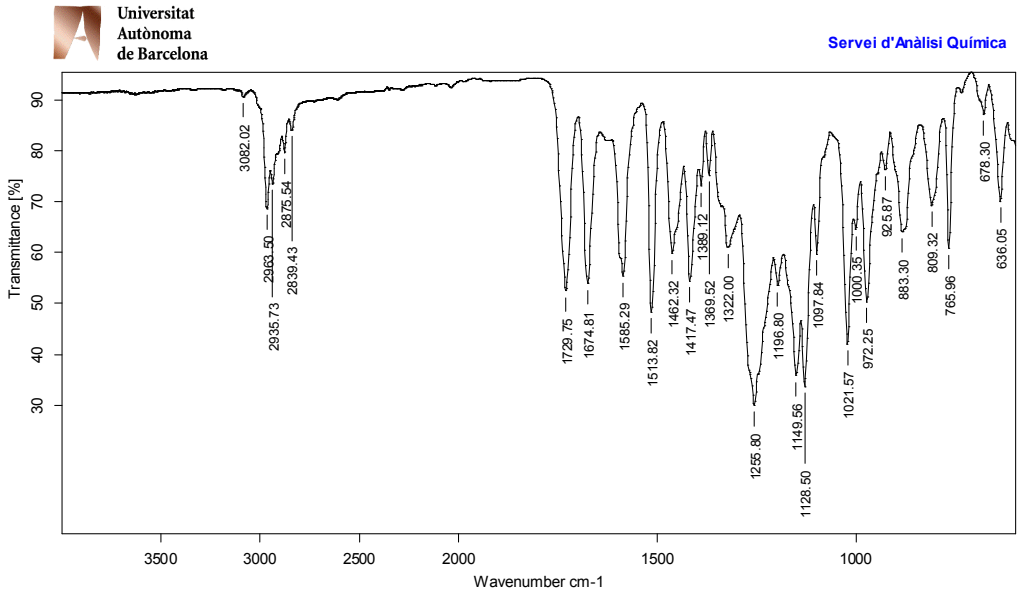
^{13}C NMR ($CDCl_3$, 90 MHz) 3d

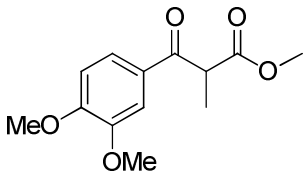


^{13}C-DEPT-135 ($CDCl_3$, 62.5 MHz) 3d



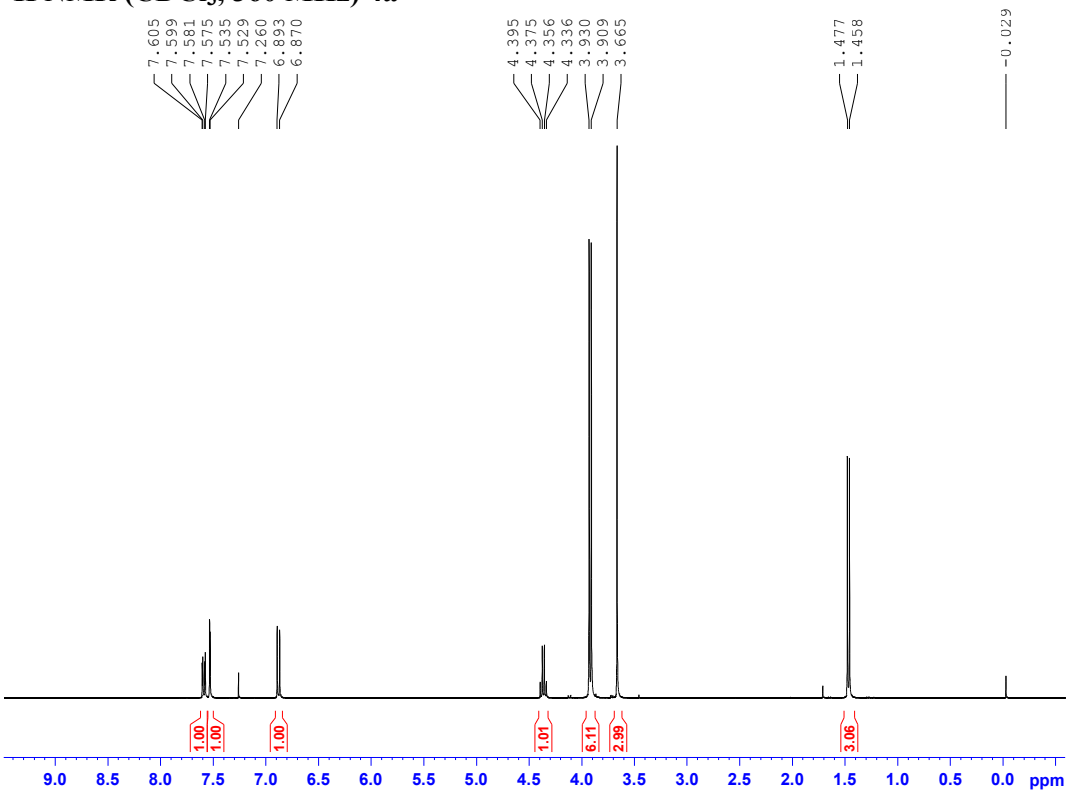
IR (ATR) 3d



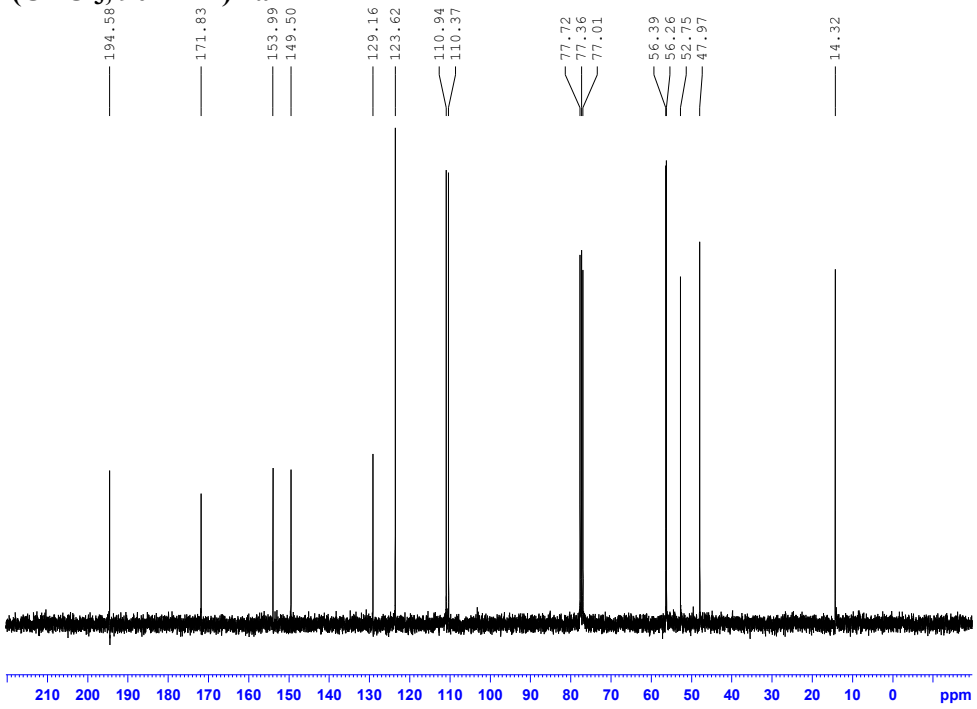


4a

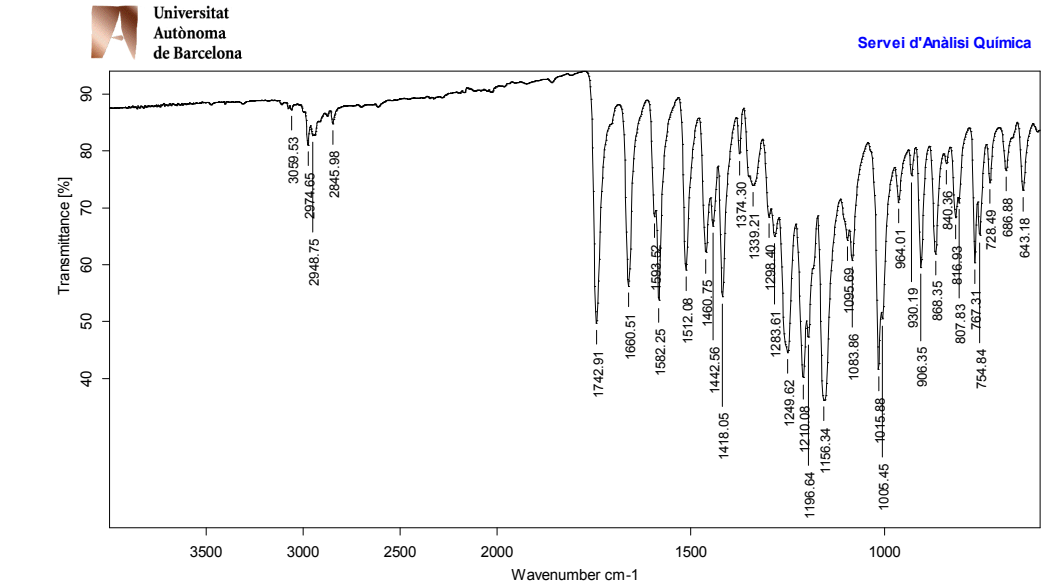
^{1}H NMR ($CDCl_3$, 360 MHz) 4a

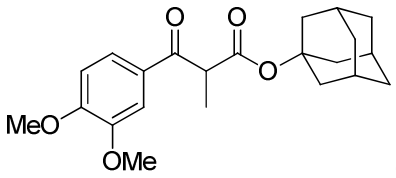


^{13}C NMR ($CDCl_3$, 90 MHz) 4a



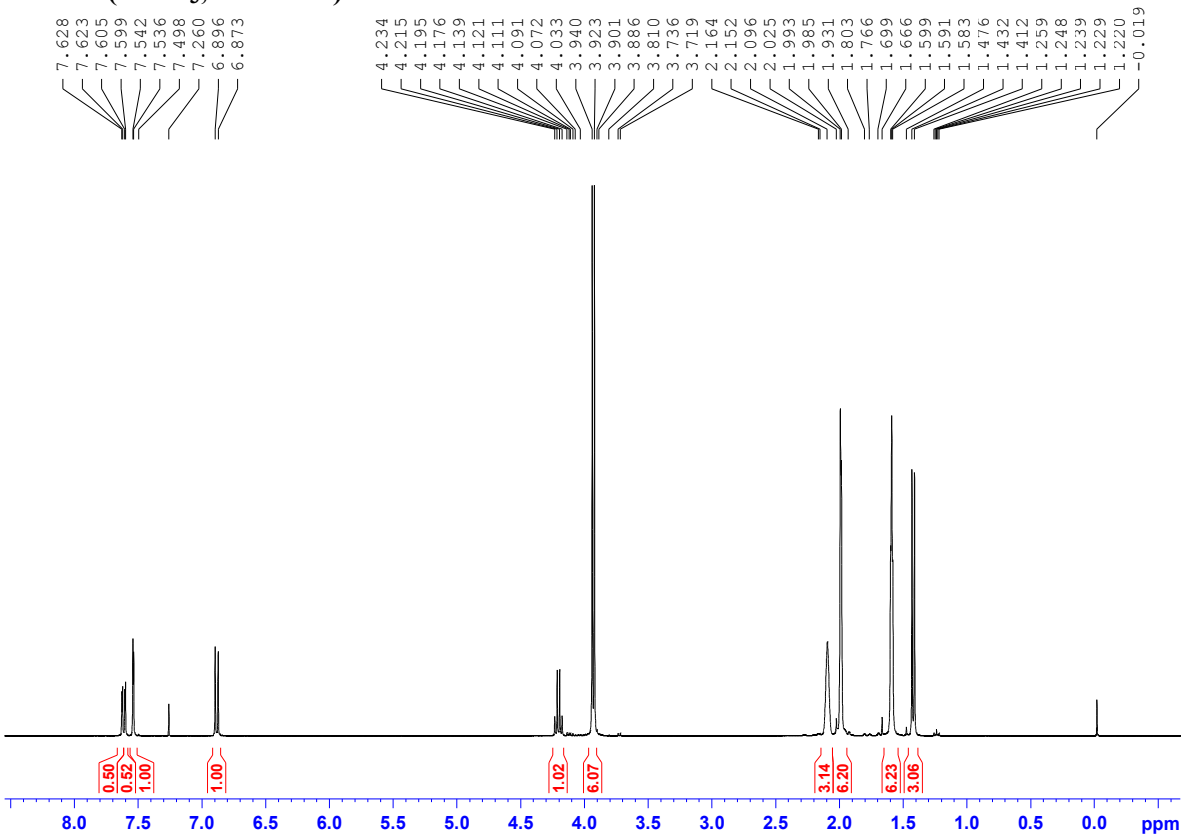
IR (ATR) 4a



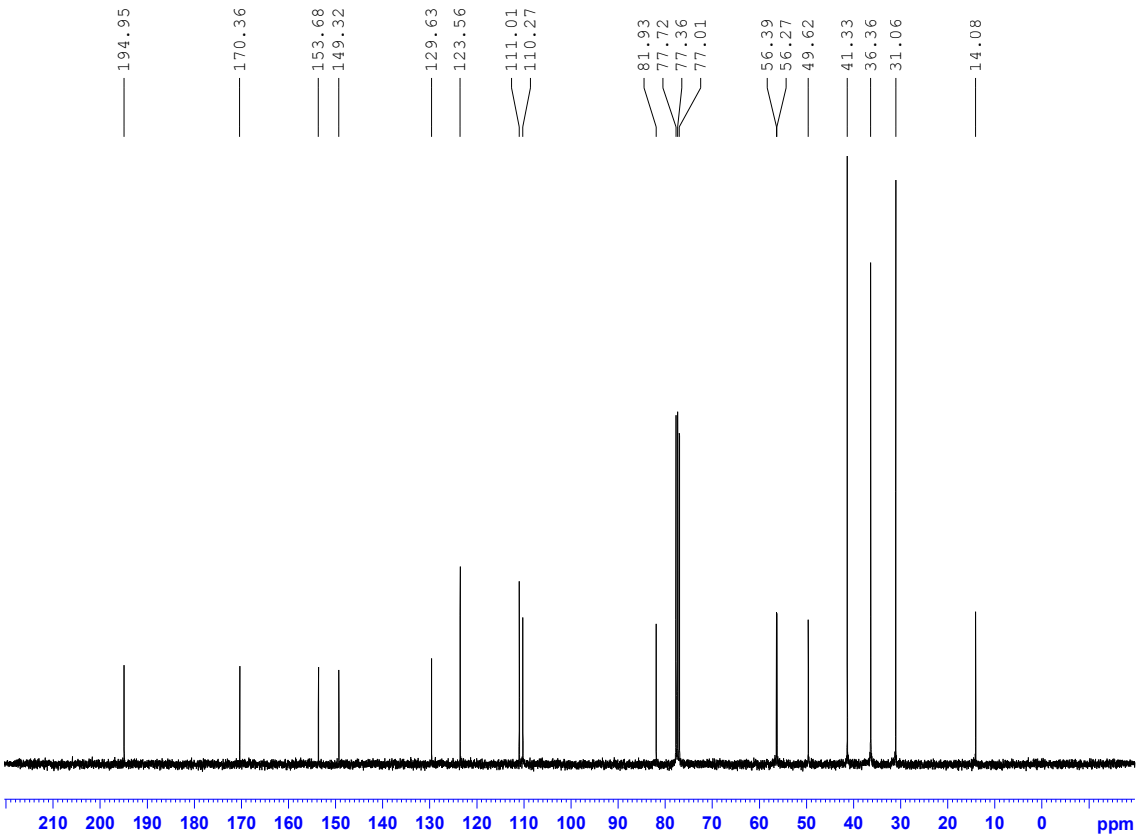


4b

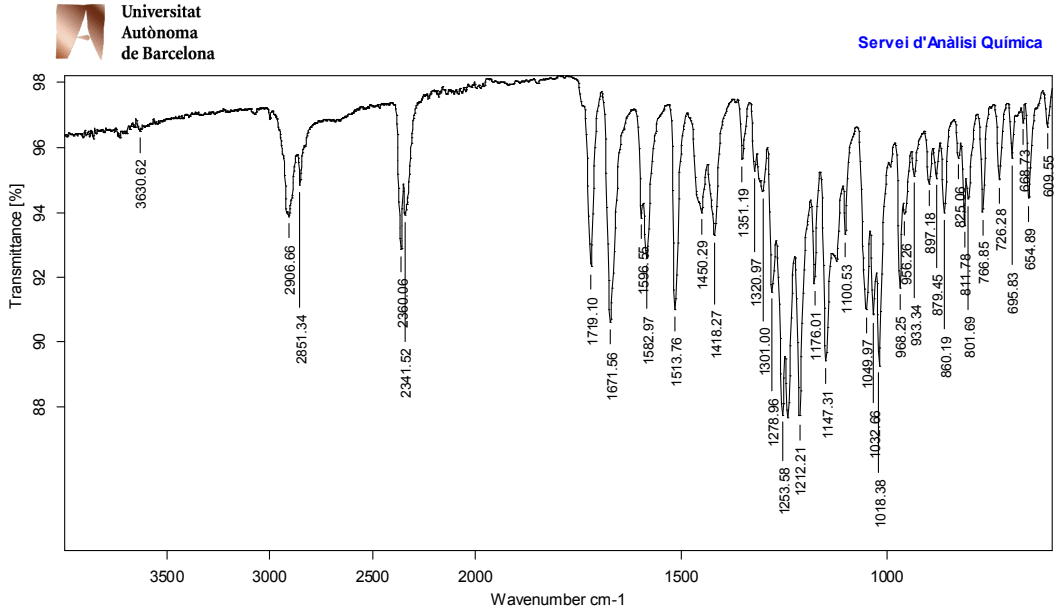
^{1}H NMR ($CDCl_3$, 360 MHz) 4b

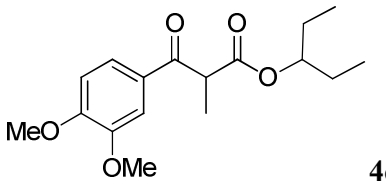


^{13}C NMR ($CDCl_3$, 90 MHz) 4b



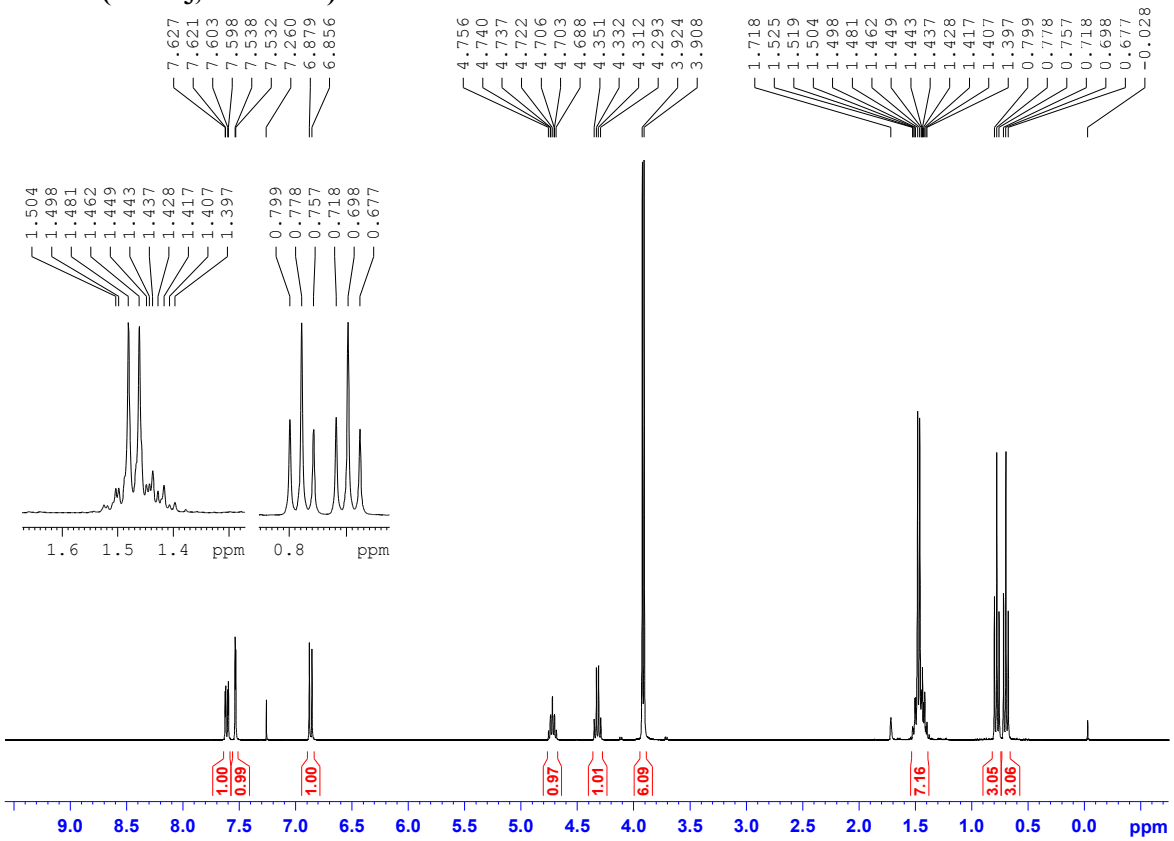
IR (ATR) 4b



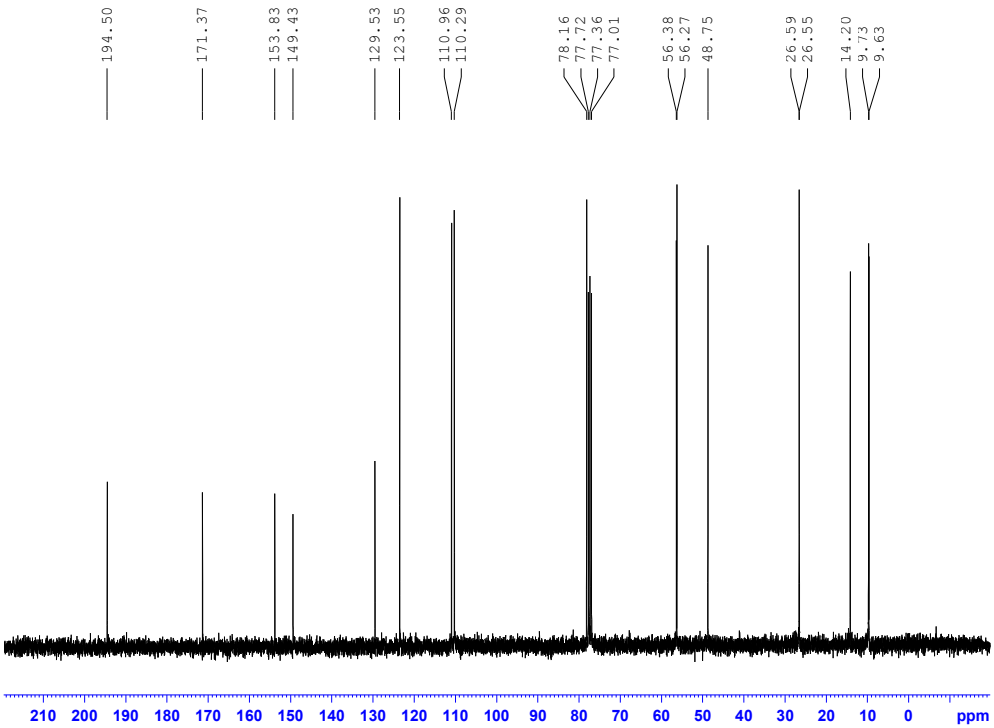


4c

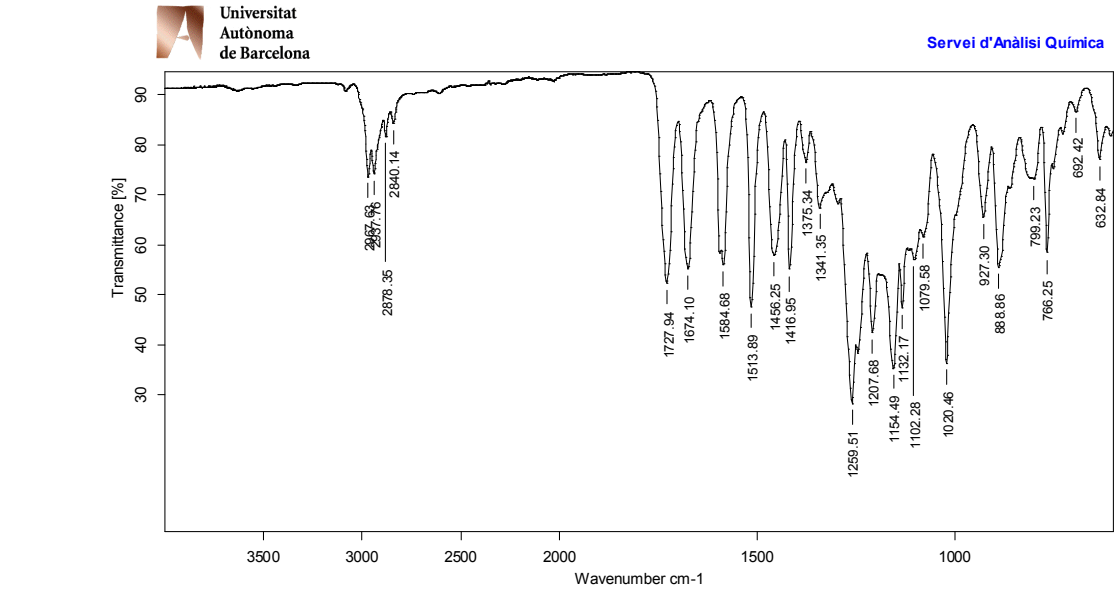
^{1}H NMR ($CDCl_3$, 360 MHz) 4c

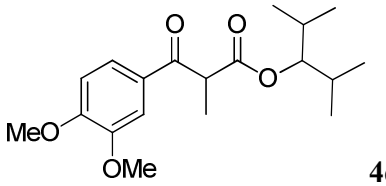


^{13}C NMR ($CDCl_3$, 90 MHz) 4c



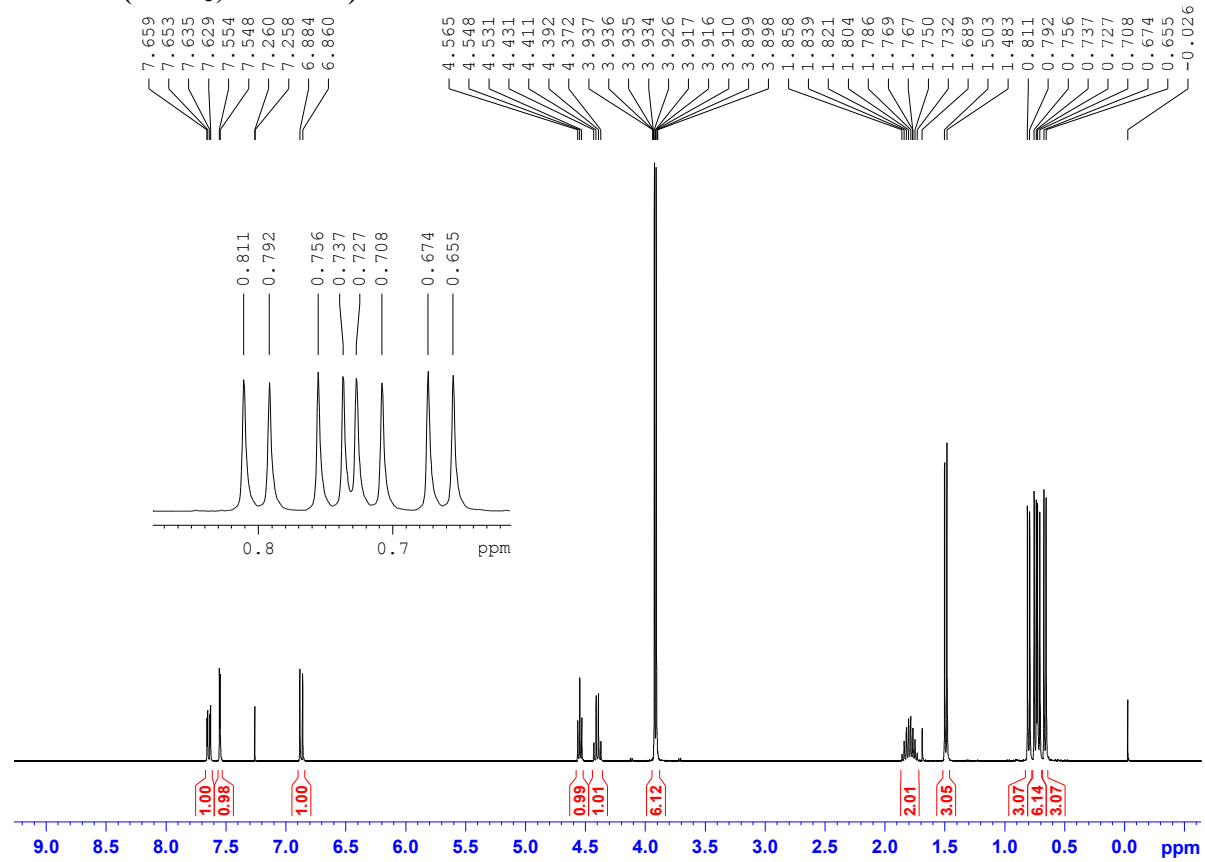
IR (ATR) 4c



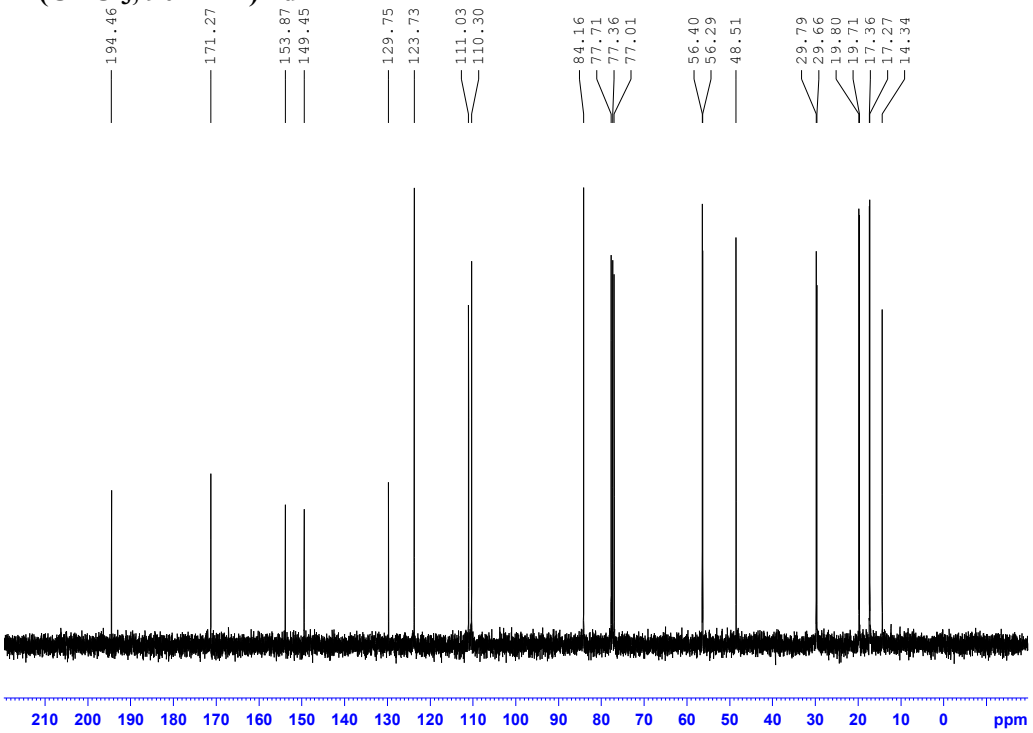


4d

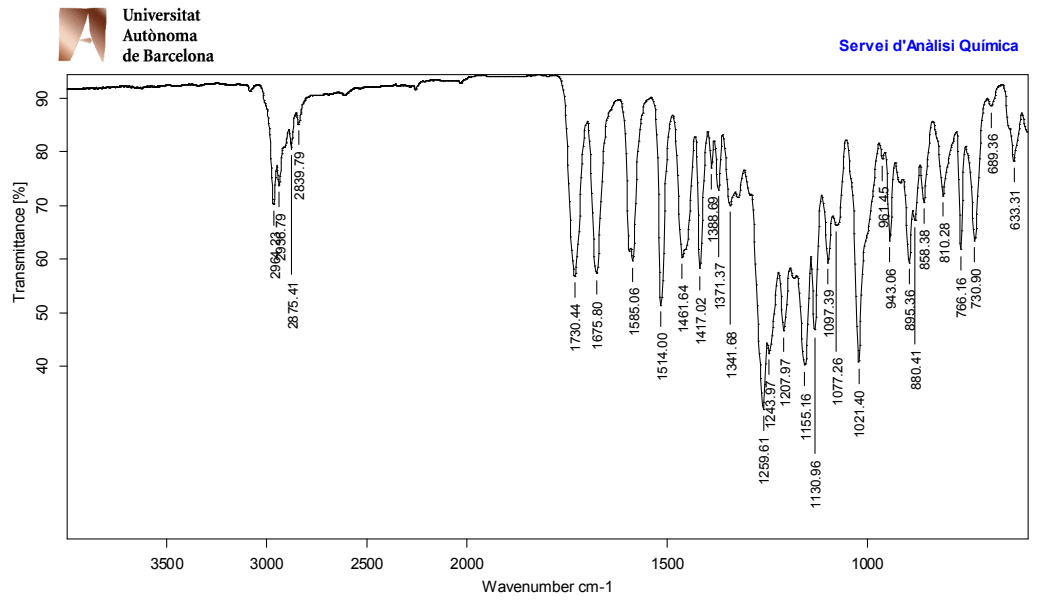
^{1}H NMR ($CDCl_3$, 360 MHz) 4d

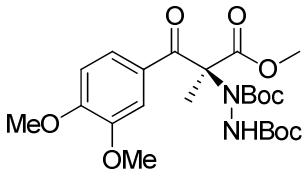


^{13}C NMR ($CDCl_3$, 90 MHz) 4d



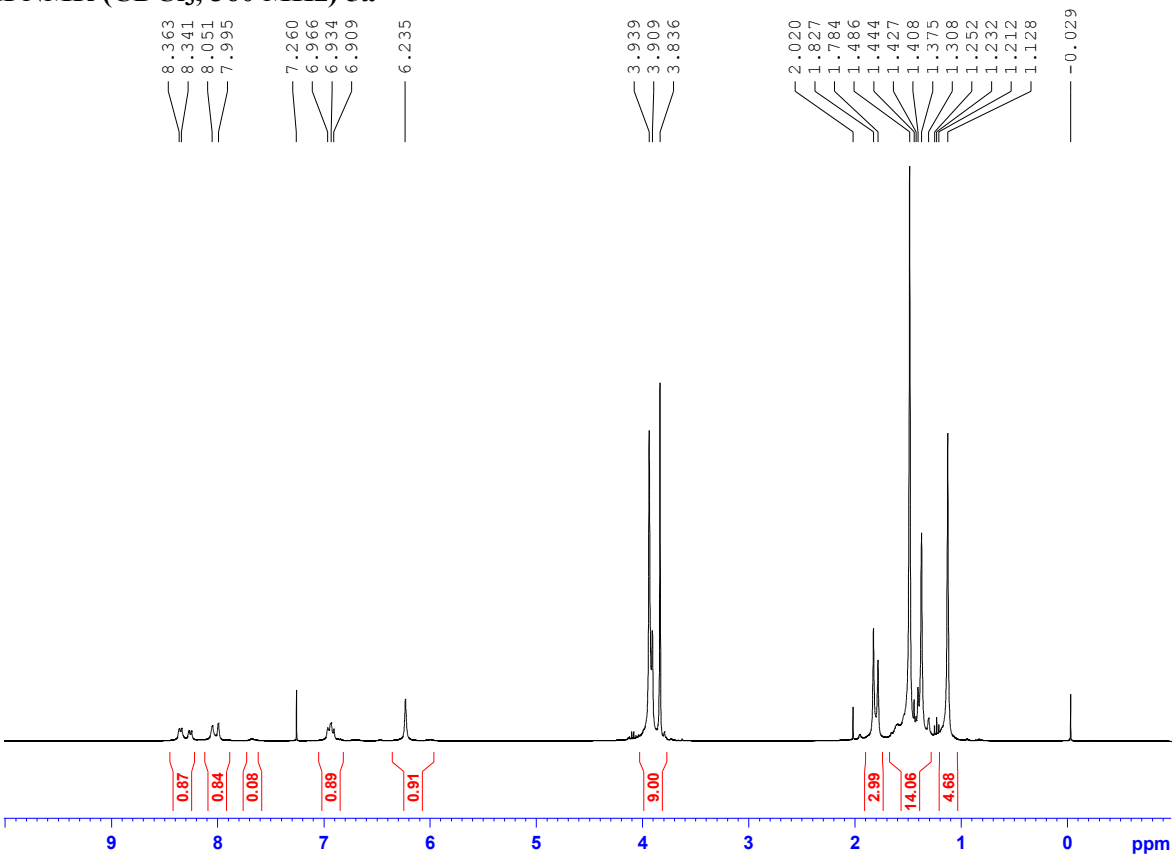
IR (ATR) 4d



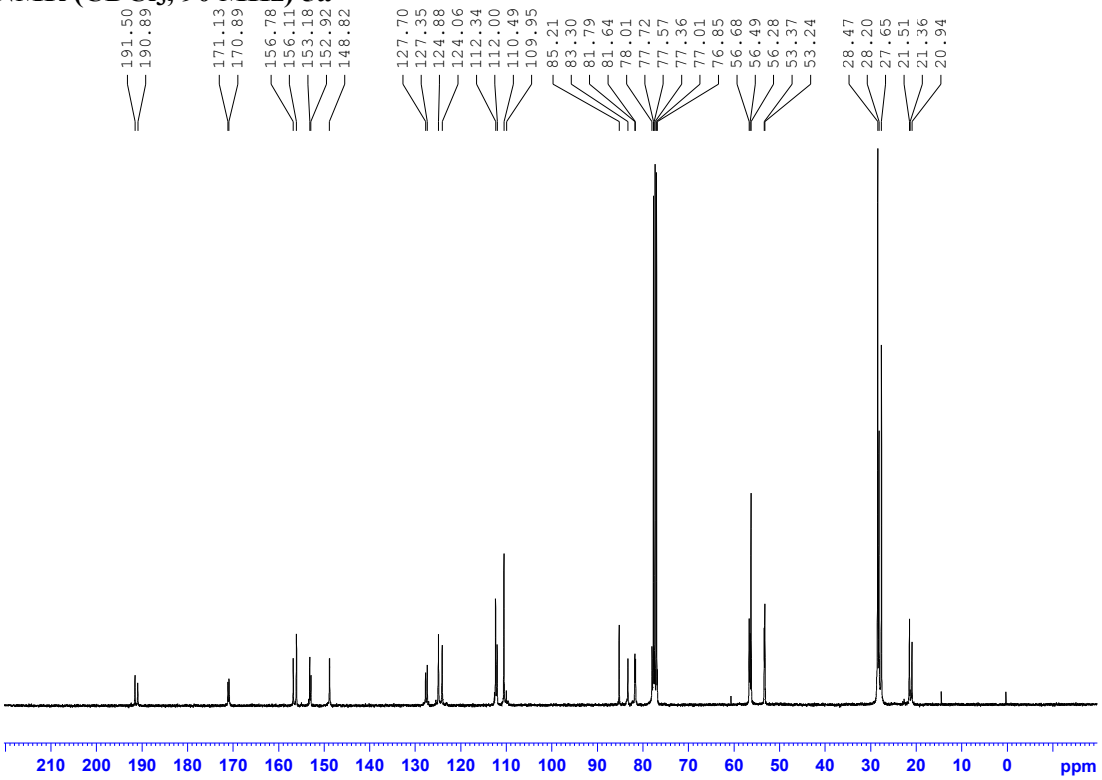


5a

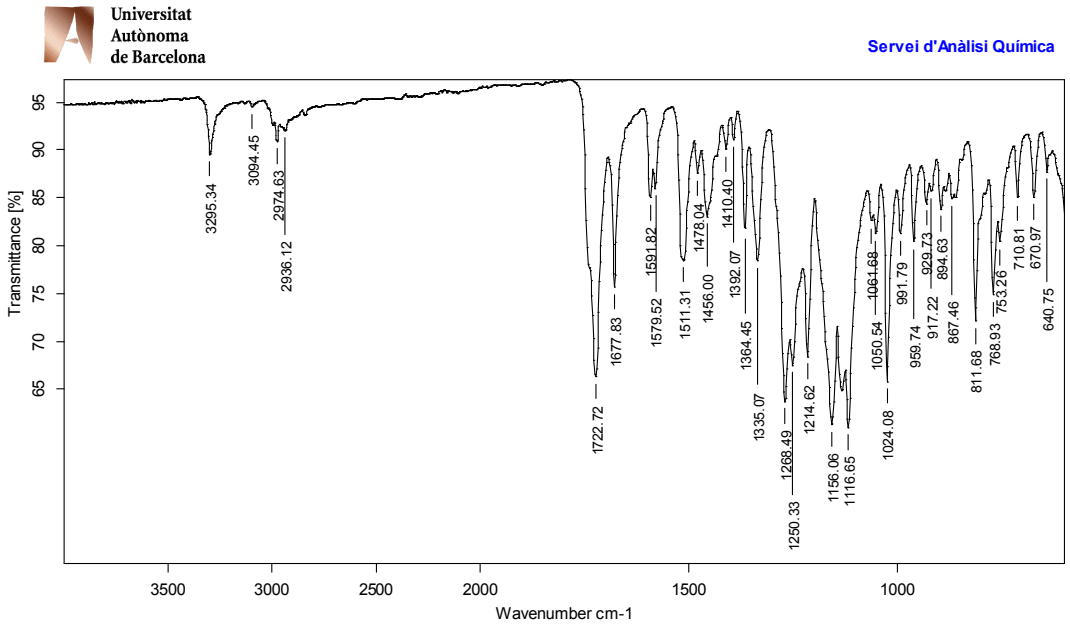
^{1}H NMR ($CDCl_3$, 360 MHz) 5a



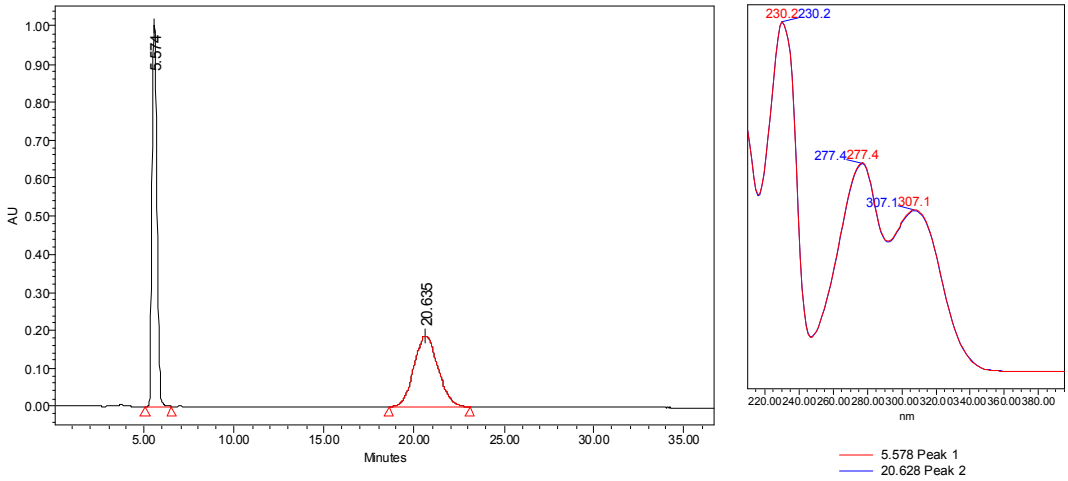
^{13}C NMR ($CDCl_3$, 90 MHz) 5a



IR (ATR) 5a

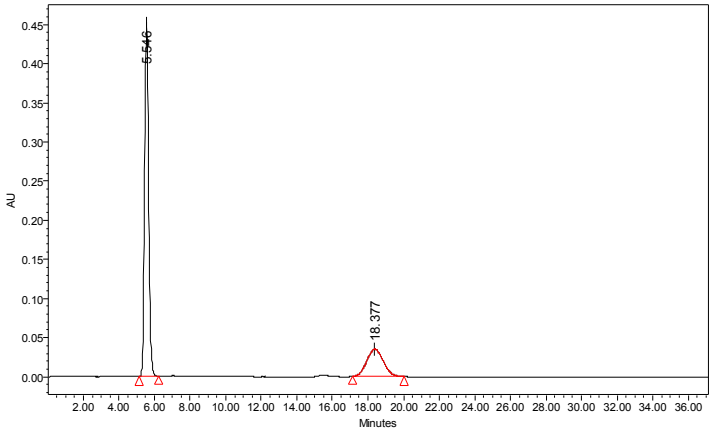


HPLC chromatogram of racemic mixture of 5a.

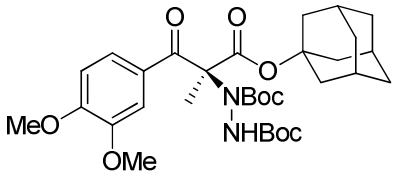


	Name	Retention Time	Area	% Area	Height	Int Type	Peak Type
1		5.574	17479407	50.07	1003567	BB	Unknown
2		20.635	17431739	49.93	186034	BB	Unknown

HPLC chromatogram 50% ee of 5a.

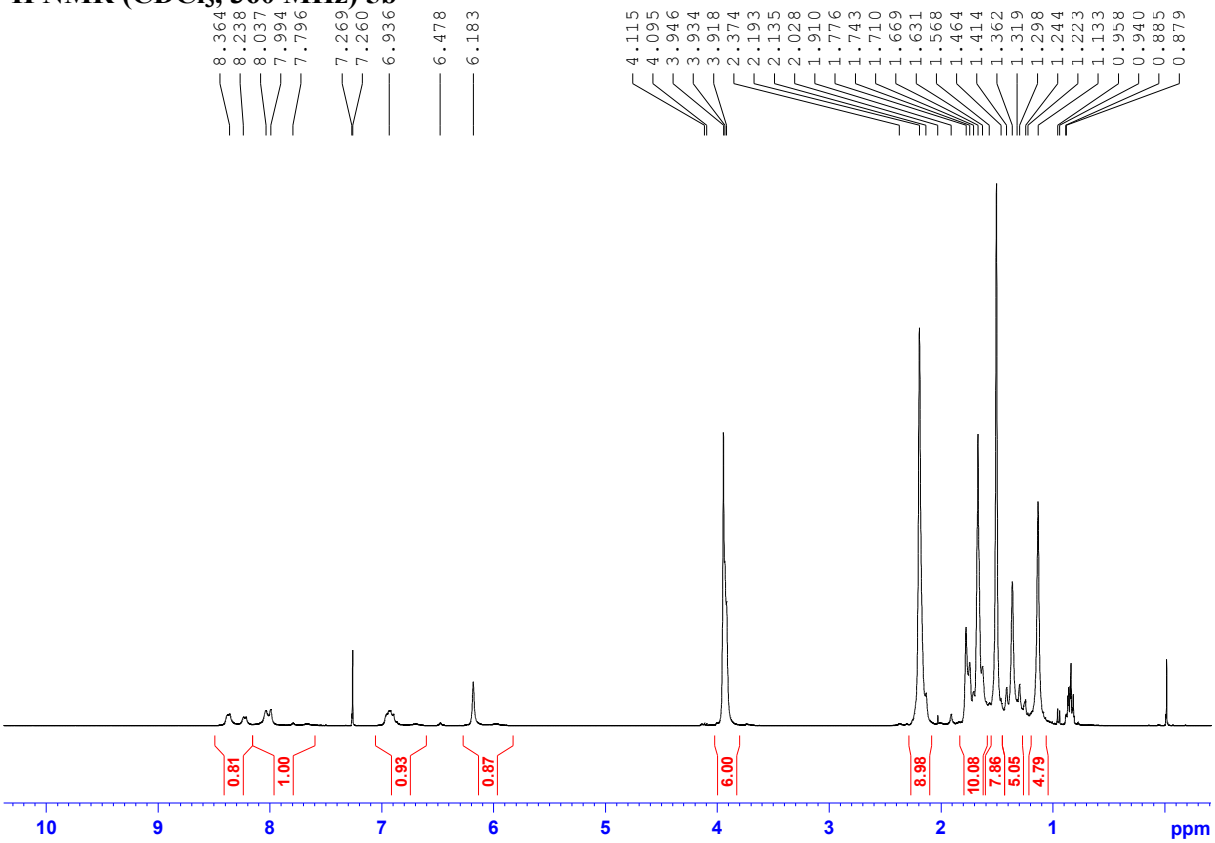


	Name	Retention Time	Area	% Area	Height	Int Type	Peak Type
1		5.546	7070788	75.59	452468	BB	Unknown
2		18.377	2283195	24.41	35008	Bb	Unknown

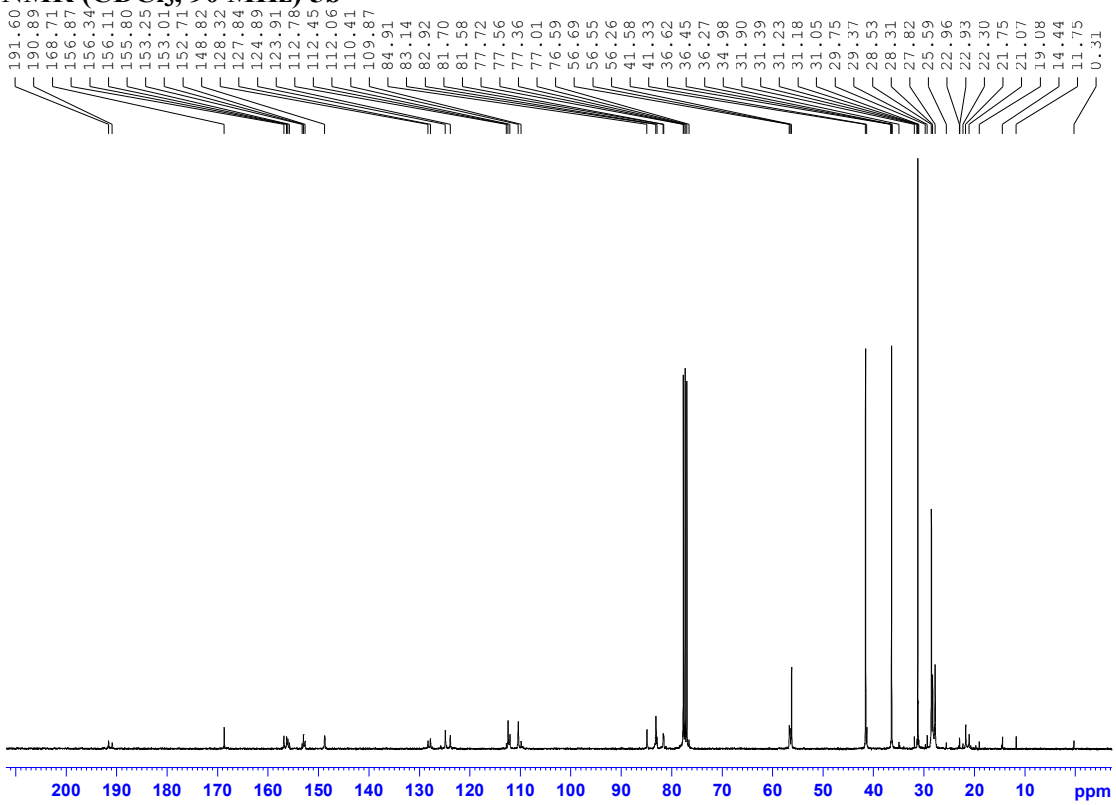


5b

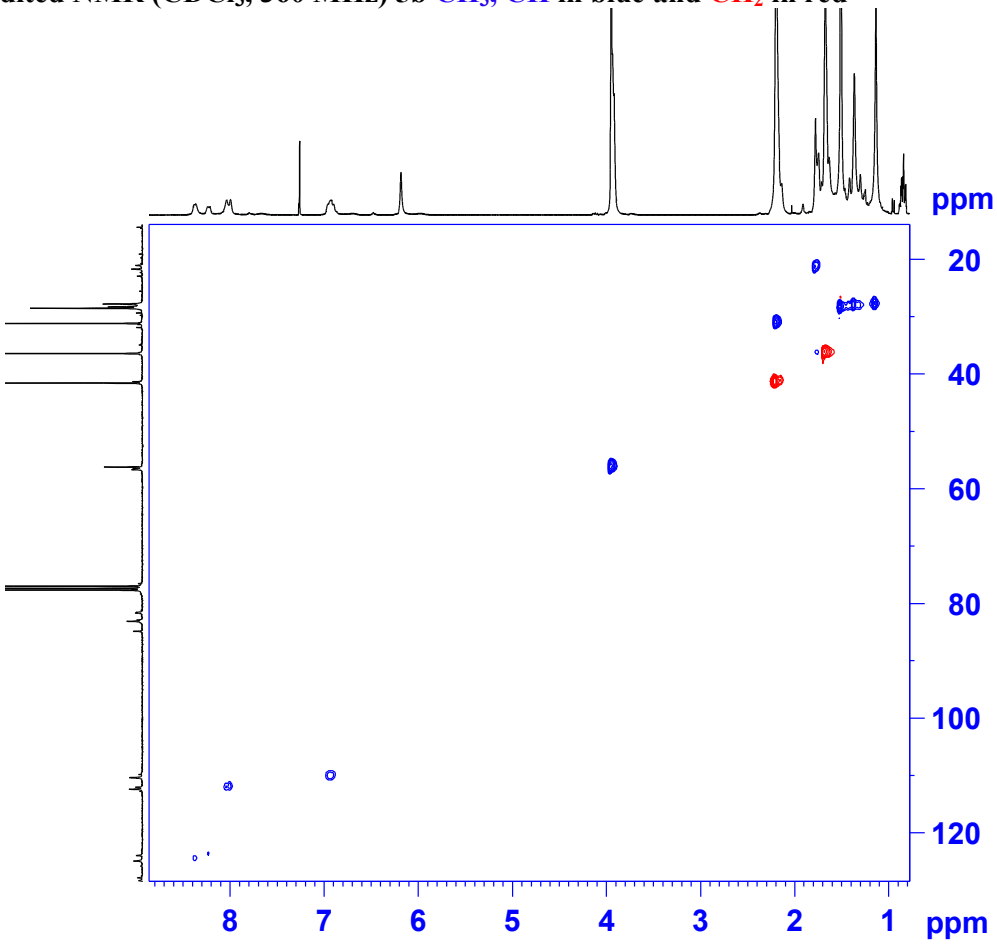
^{1}H NMR ($CDCl_3$, 360 MHz) 5b



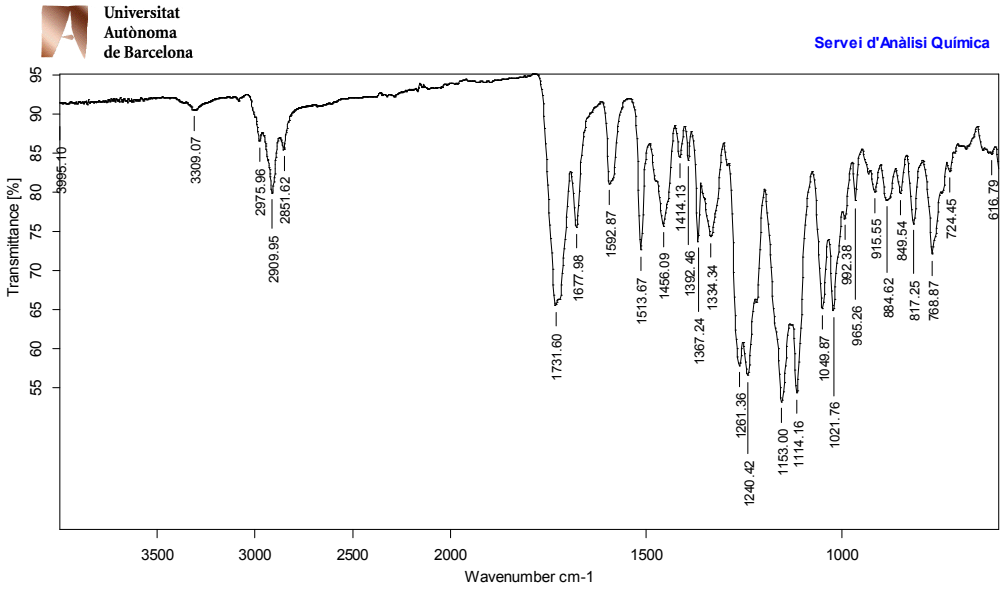
^{13}C NMR ($CDCl_3$, 90 MHz) 5b



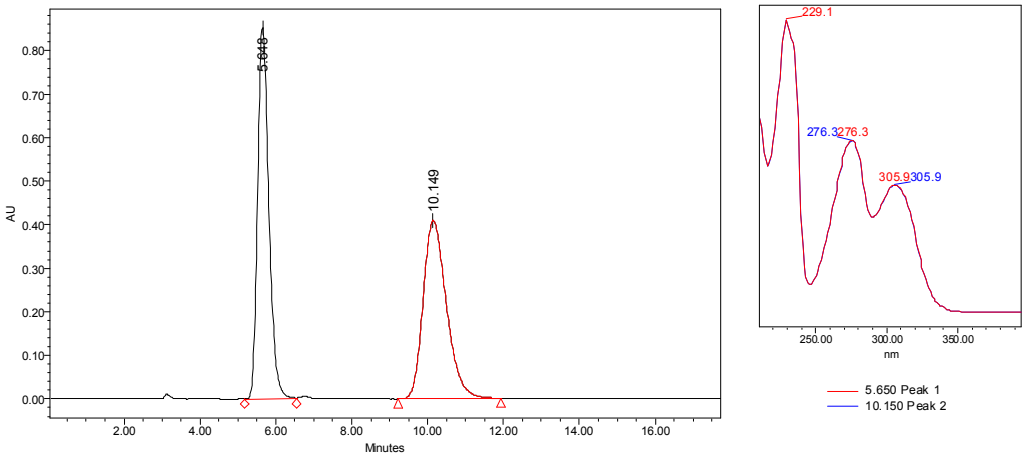
HSQC edited NMR ($CDCl_3$, 360 MHz) 5b CH_3, CH in blue and CH_2 in red



IR (ATR) 5b

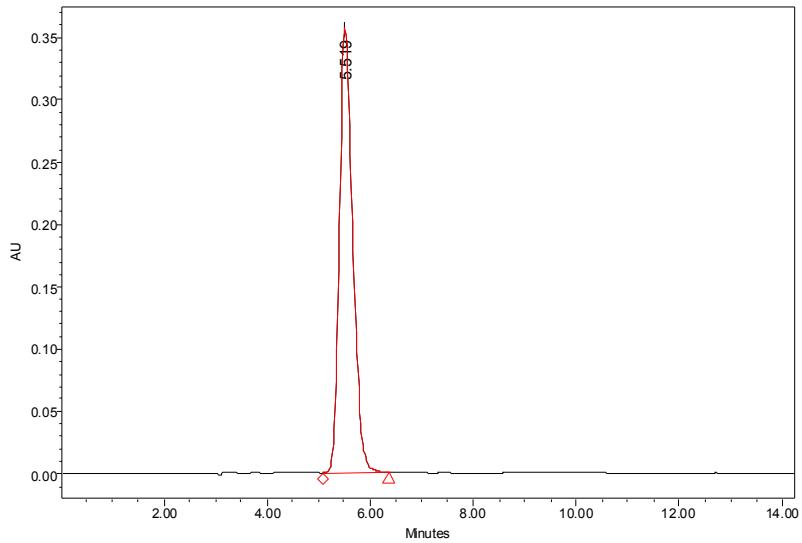


HPLC chromatogram of racemic mixture of 5b.

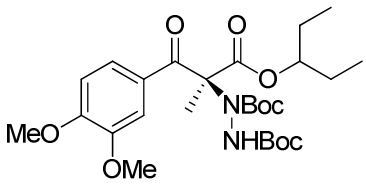


	Name	Retention Time	Area	% Area	Height	Int Type
1		5.648	17652889	50.29	853699	VV
2		10.149	17447648	49.71	409682	BB

HPLC chromatogram >99% ee of 5b.

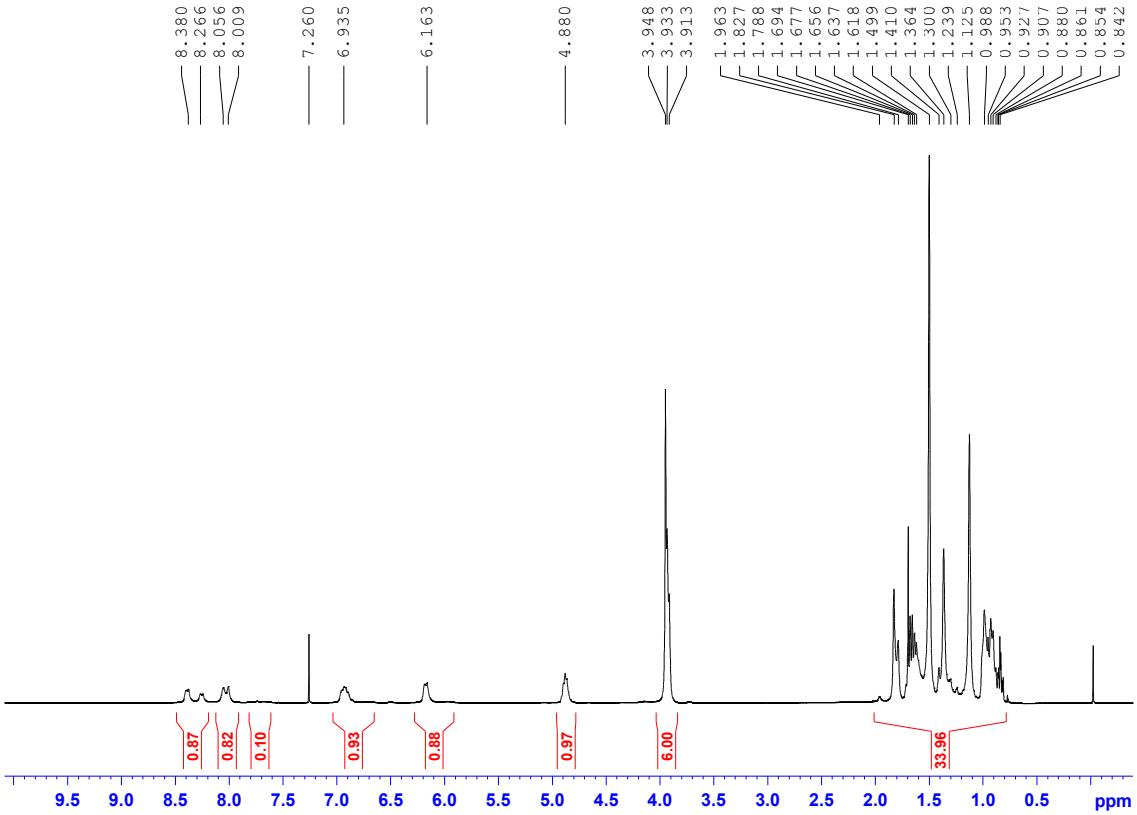


	Name	Retention Time	Area	% Area	Height	Int Type
1		5.519	6459590	100.00	357147	VB

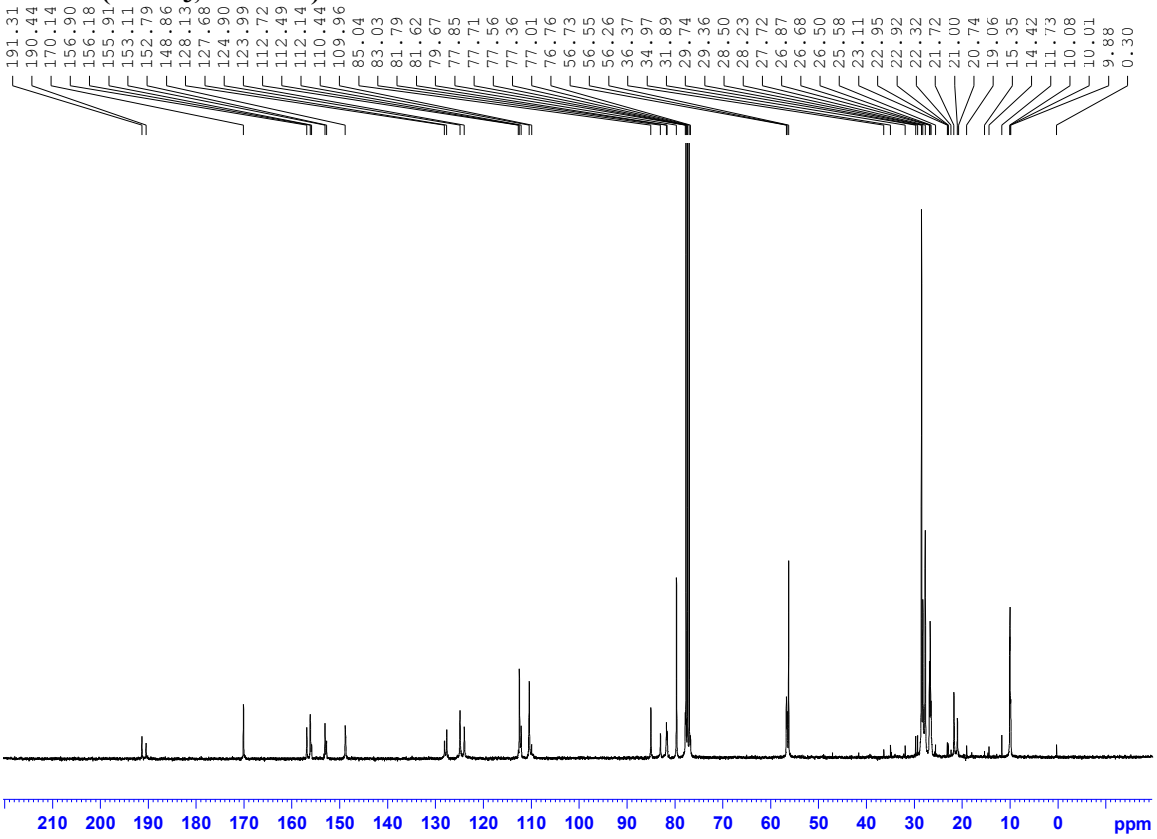


5c

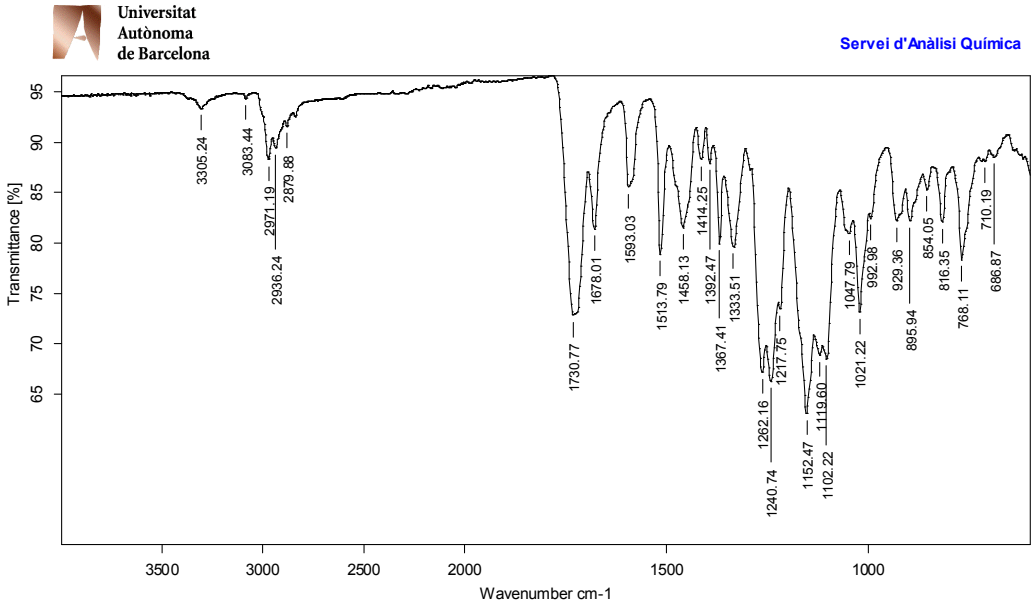
^{1}H NMR ($CDCl_3$, 360 MHz) 5c



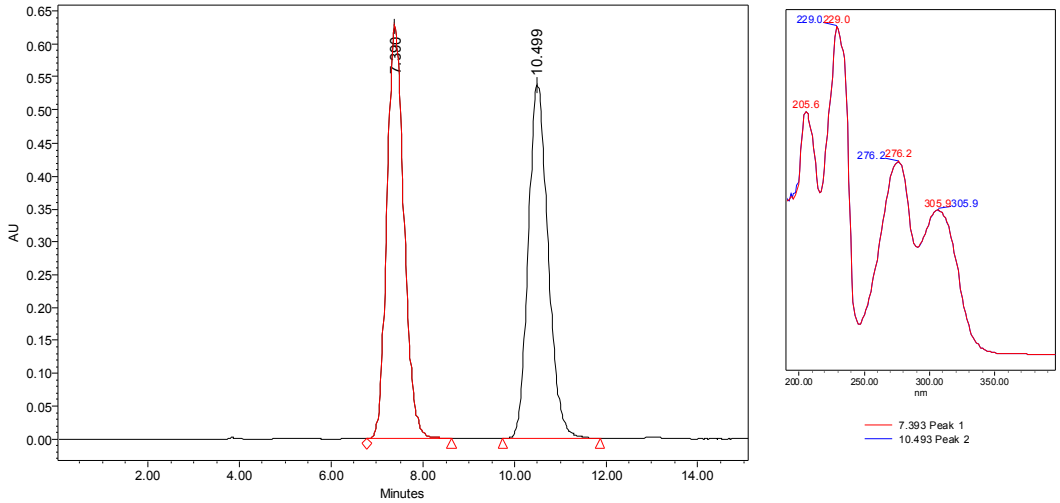
^{13}C NMR ($CDCl_3$, 90 MHz) 5c



IR (ATR) 5c

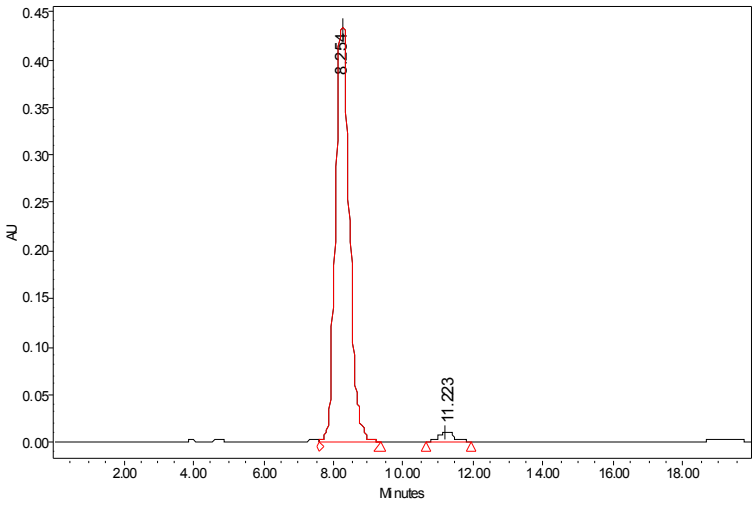


HPLC chromatogram of racemic mixture of 5c.



	Name	Retention Time	Area	% Area	Height	Int Type
1		7.390	16281516	50.03	626929	VB
2		10.499	16261866	49.97	536981	BB

HPLC chromatogram 95% ee of 5c.



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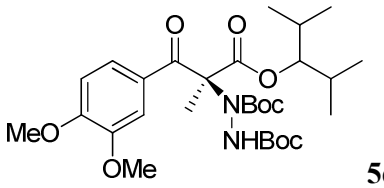
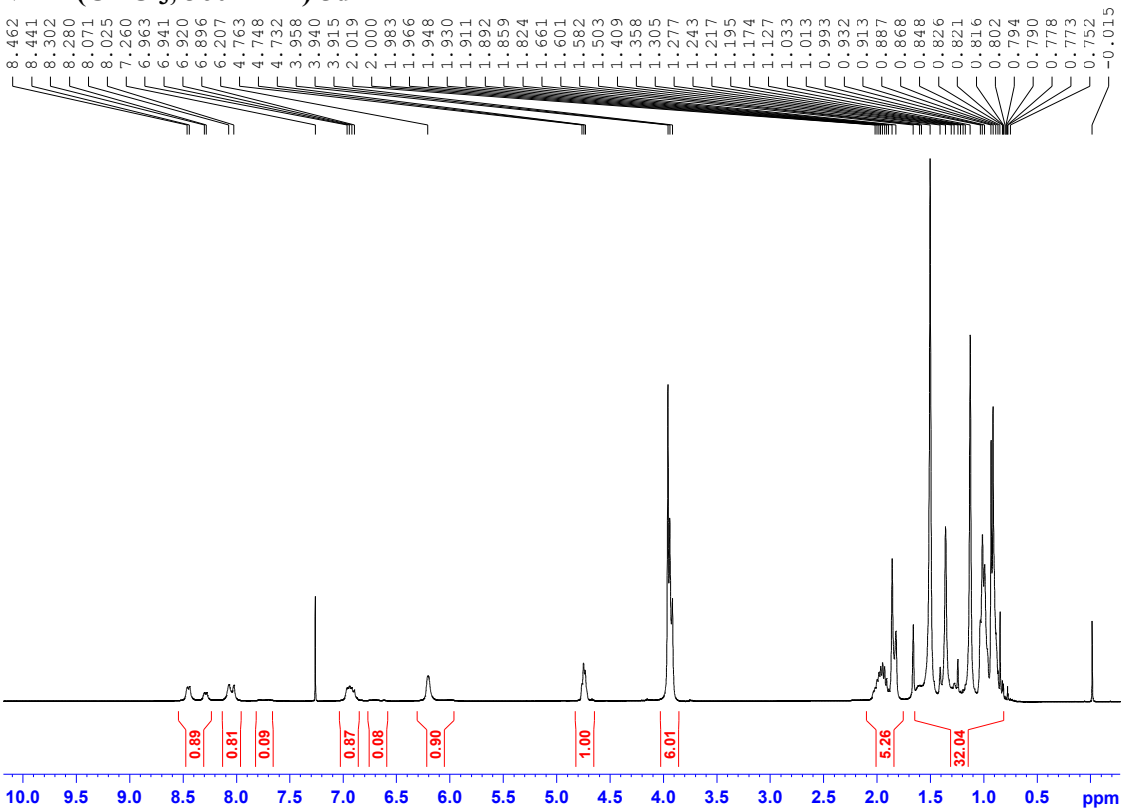
1		8.254	11916938	97.58	434999	VB
2		11.223	295970	2.42	9962	BB

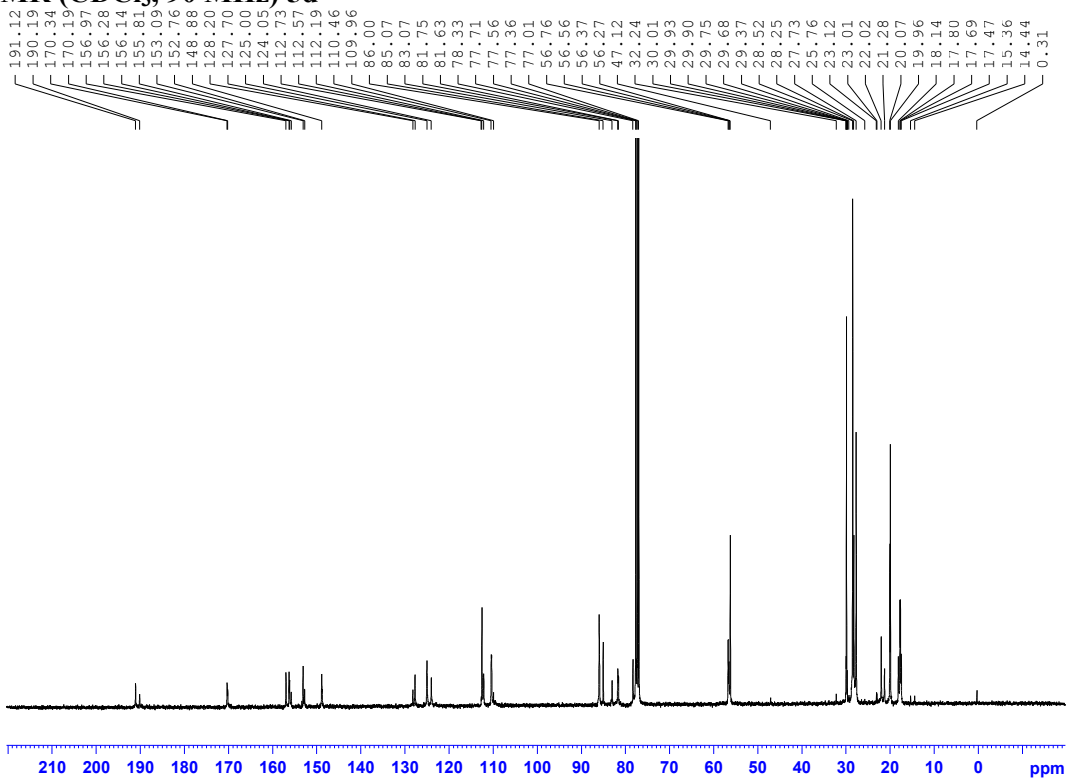


5d

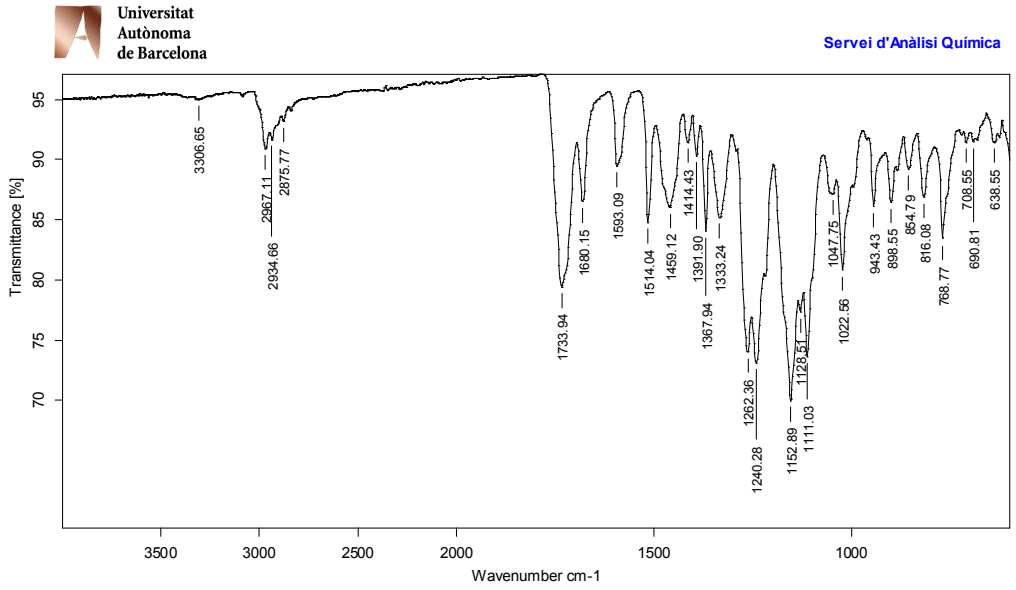
^{1}H NMR ($CDCl_3$, 360 MHz) 5d



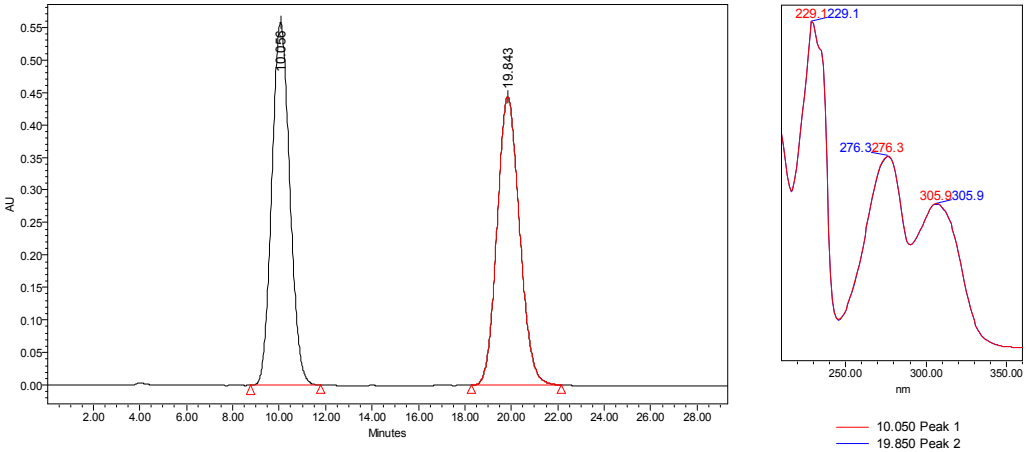
^{13}C NMR ($CDCl_3$, 90 MHz) 5d



IR (ATR) 5d

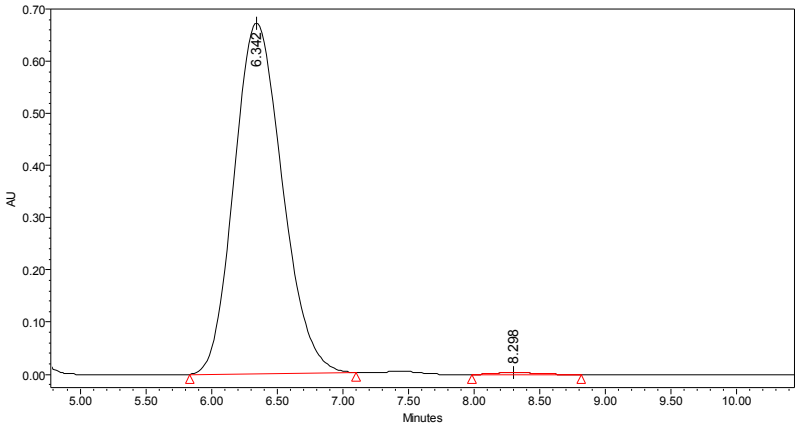


HPLC chromatogram of racemic mixture of 5d.

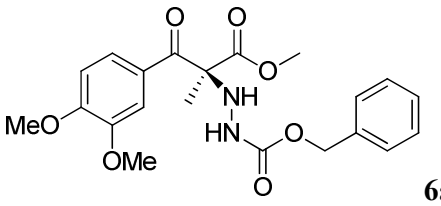


Name	Retention Time	Area	% Area	Height	Int Type
	10.056	30001043	50.09	557654	BB
Name	Retention Time	Area	% Area	Height	Int Type
	19.843	29897154	49.91	443319	BB

HPLC chromatogram 99% ee of 5d.

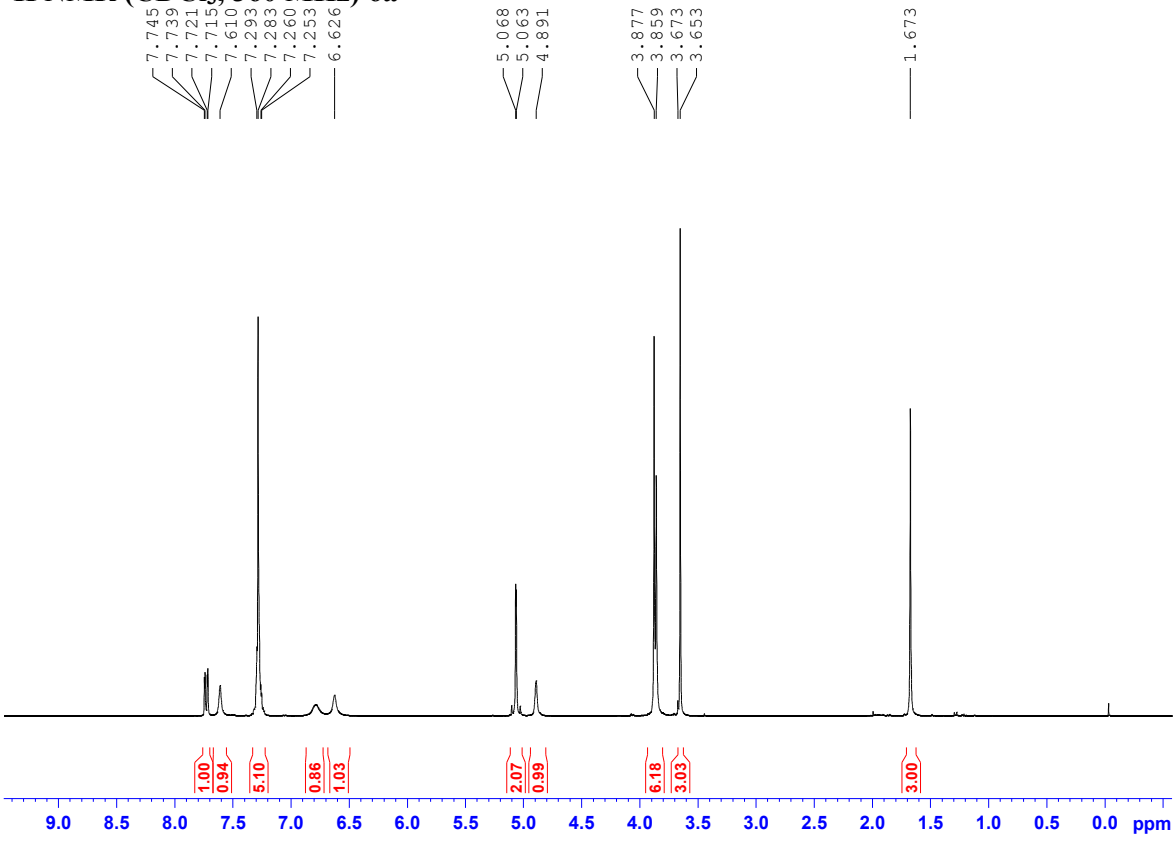


	Name	Retention Time	Area	% Area	Height	Int Type
1		6.342	17189130	99.46	673187	bb
	Name	Retention Time	Area	% Area	Height	Int Type
2		8.298	93573	0.54	3718	bb

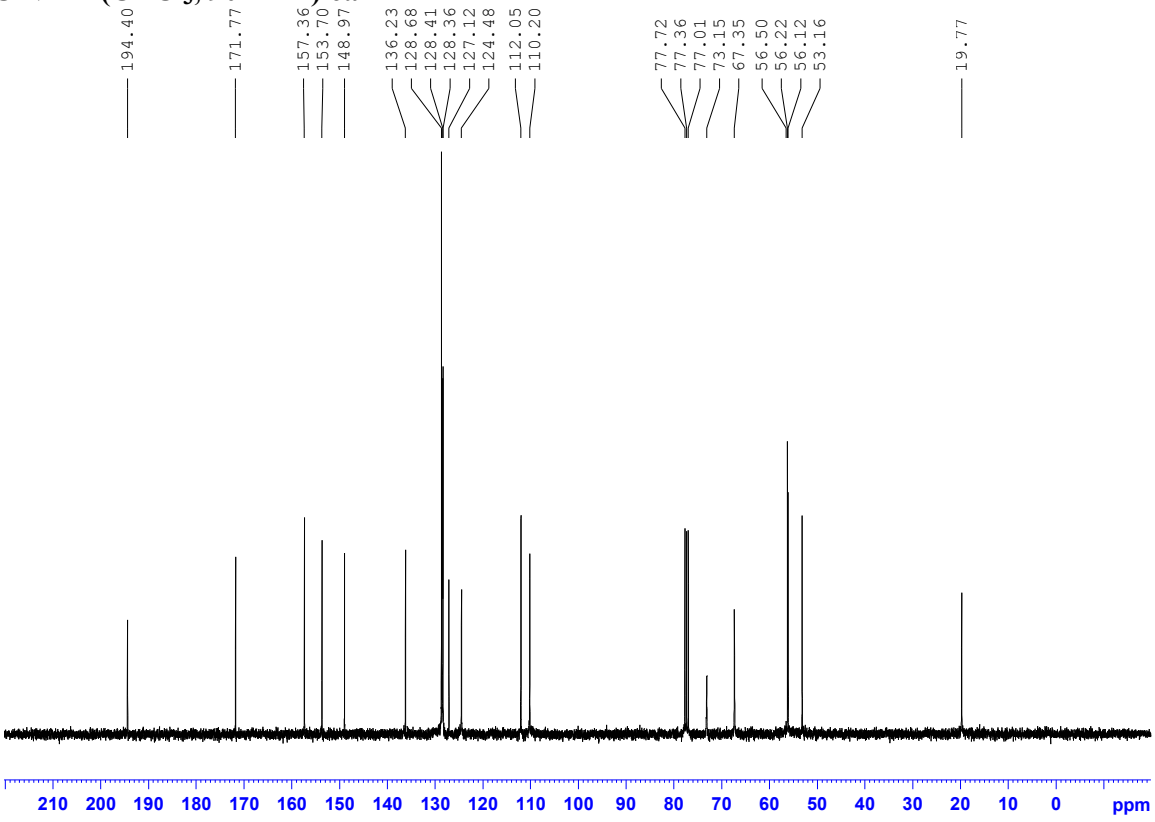


6a

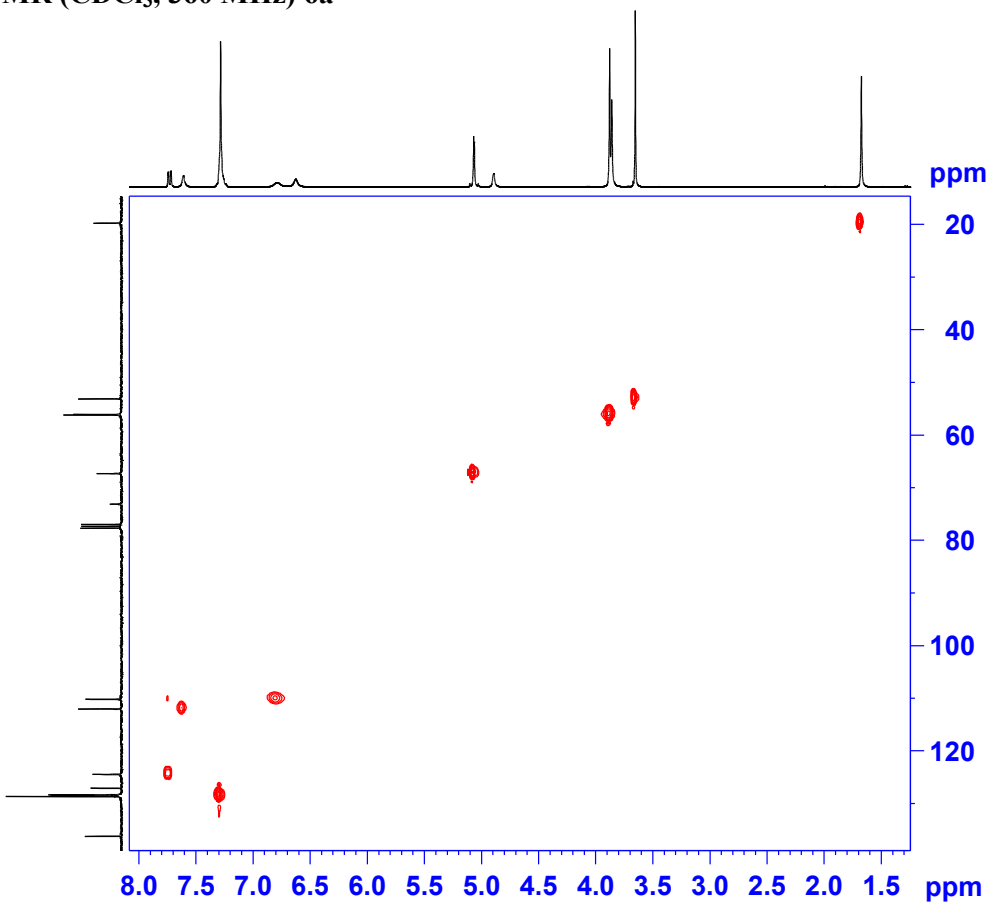
^{1}H NMR ($CDCl_3$, 360 MHz) 6a



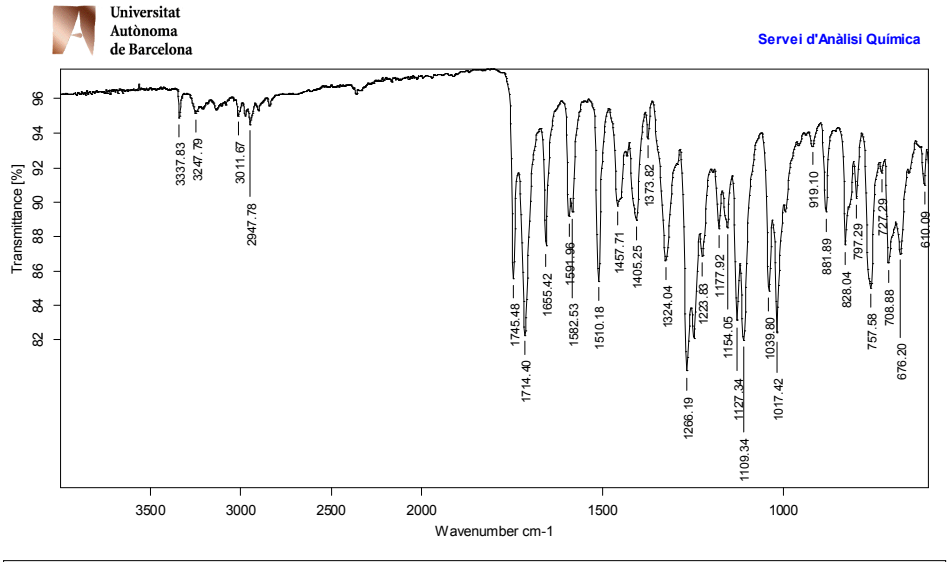
^{13}C NMR ($CDCl_3$, 90 MHz) 6a

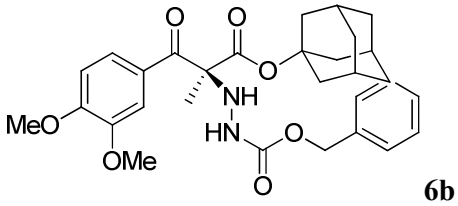


HSQC NMR ($CDCl_3$, 360 MHz) 6a



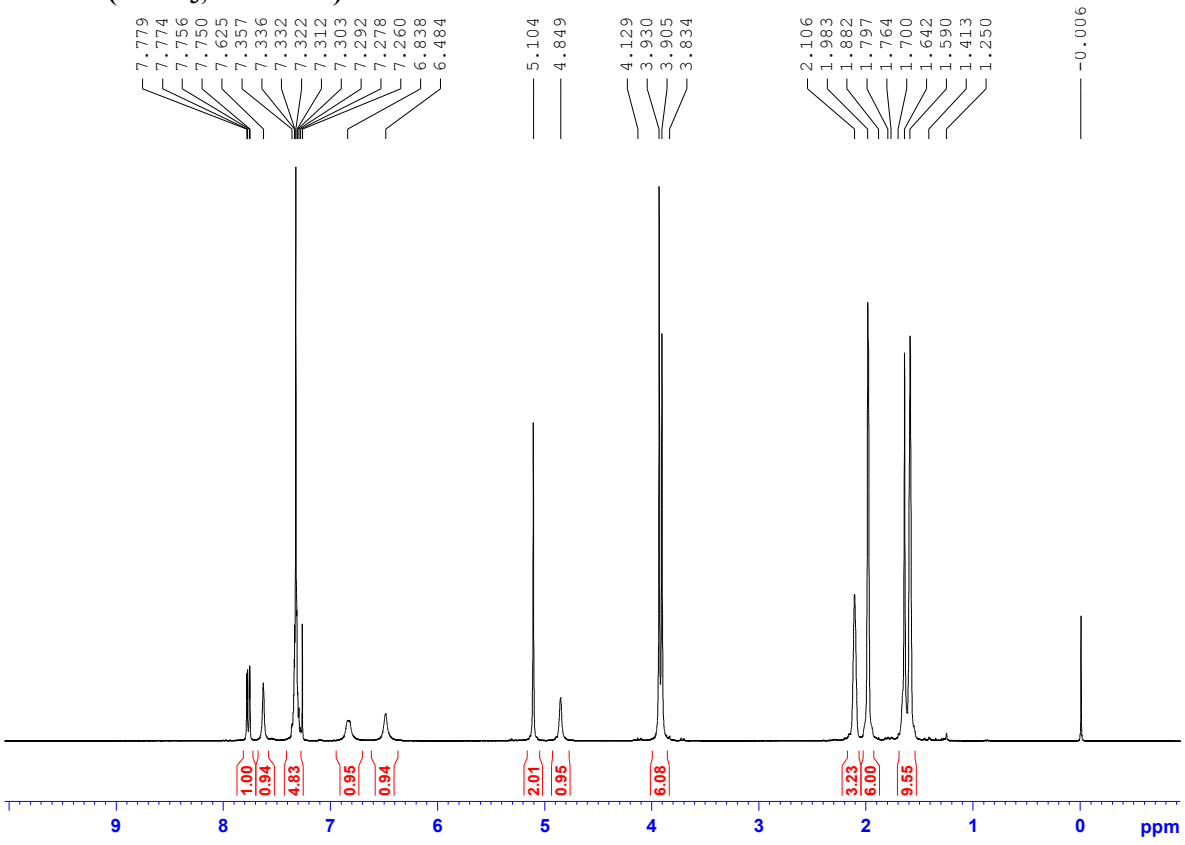
IR (ATR) 6a



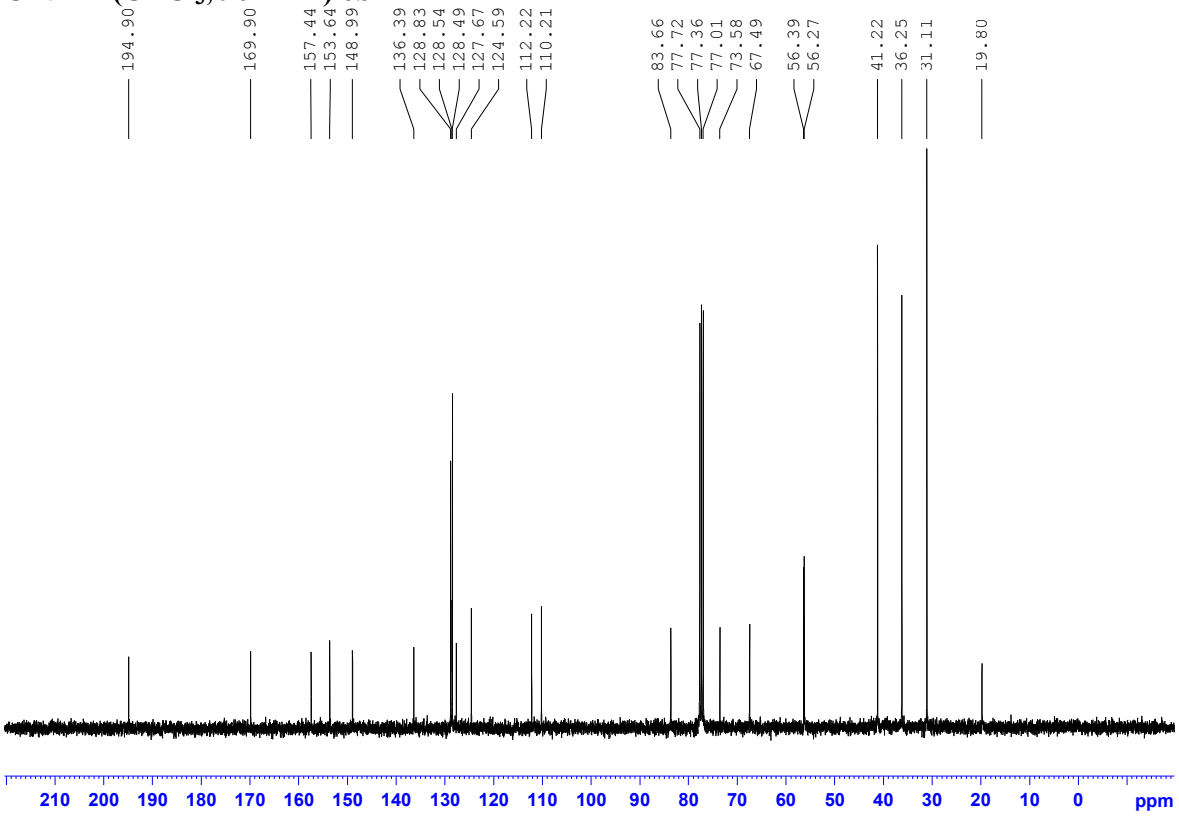


6b

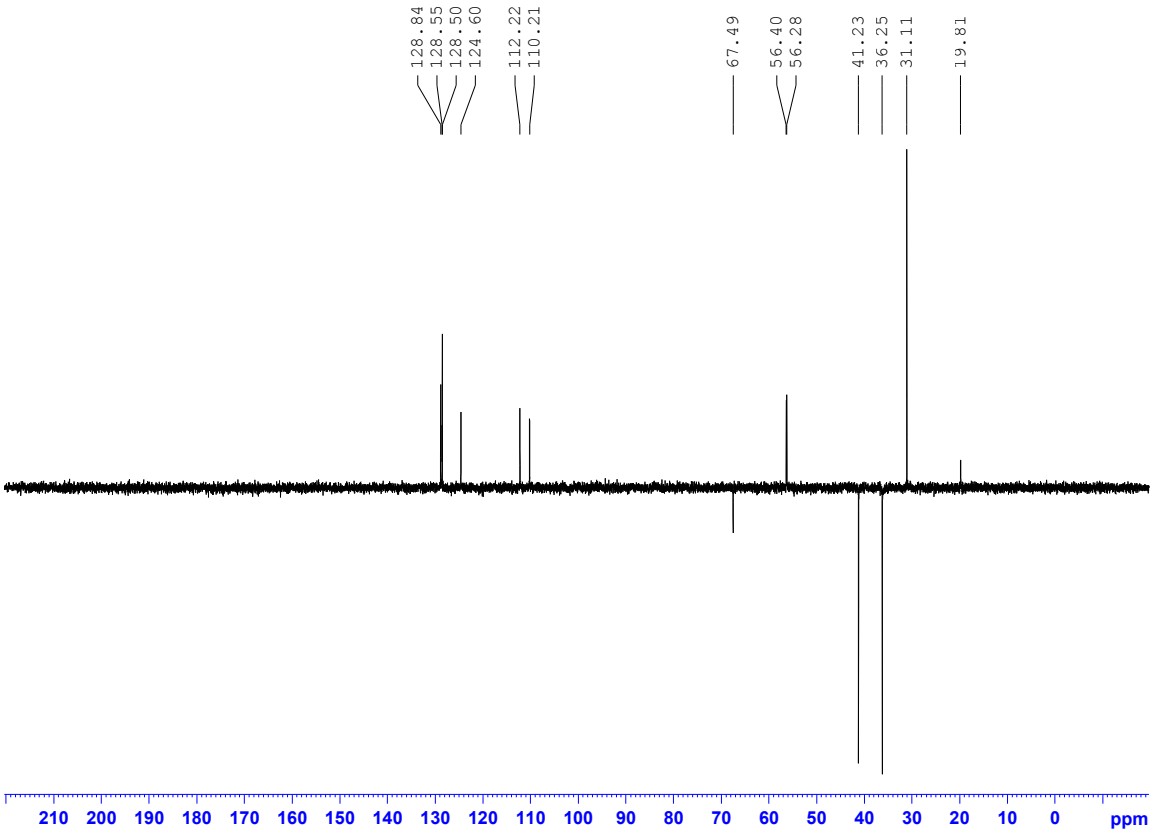
^{1}H NMR ($CDCl_3$, 360 MHz) 6b



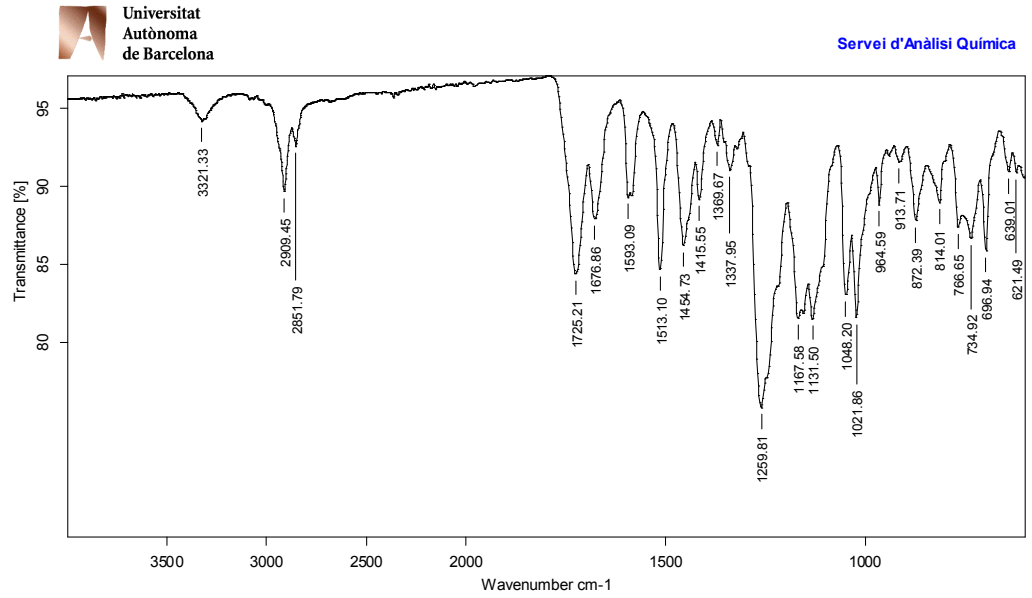
^{13}C NMR ($CDCl_3$, 90 MHz) 6b

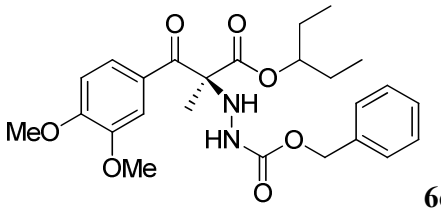


^{13}C-DEPT-135 ($CDCl_3$, 62.5 MHz) 6b



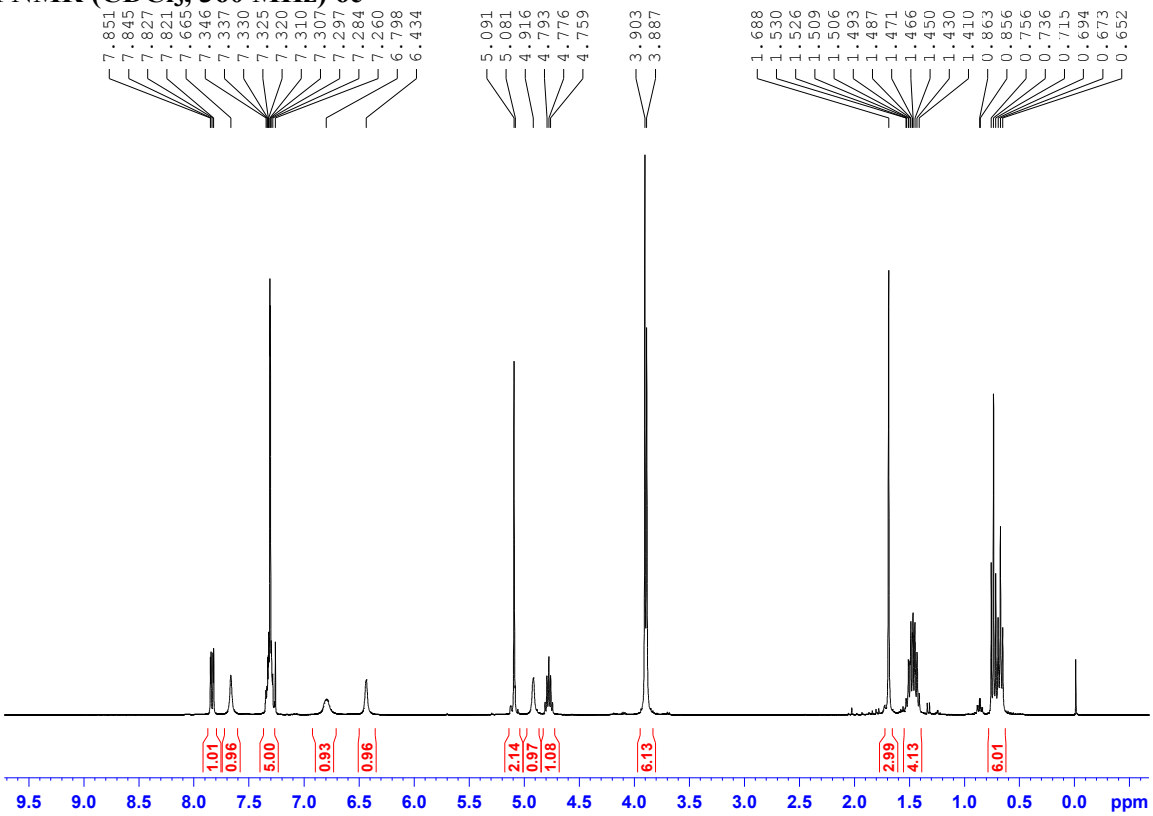
IR (ATR) 6b



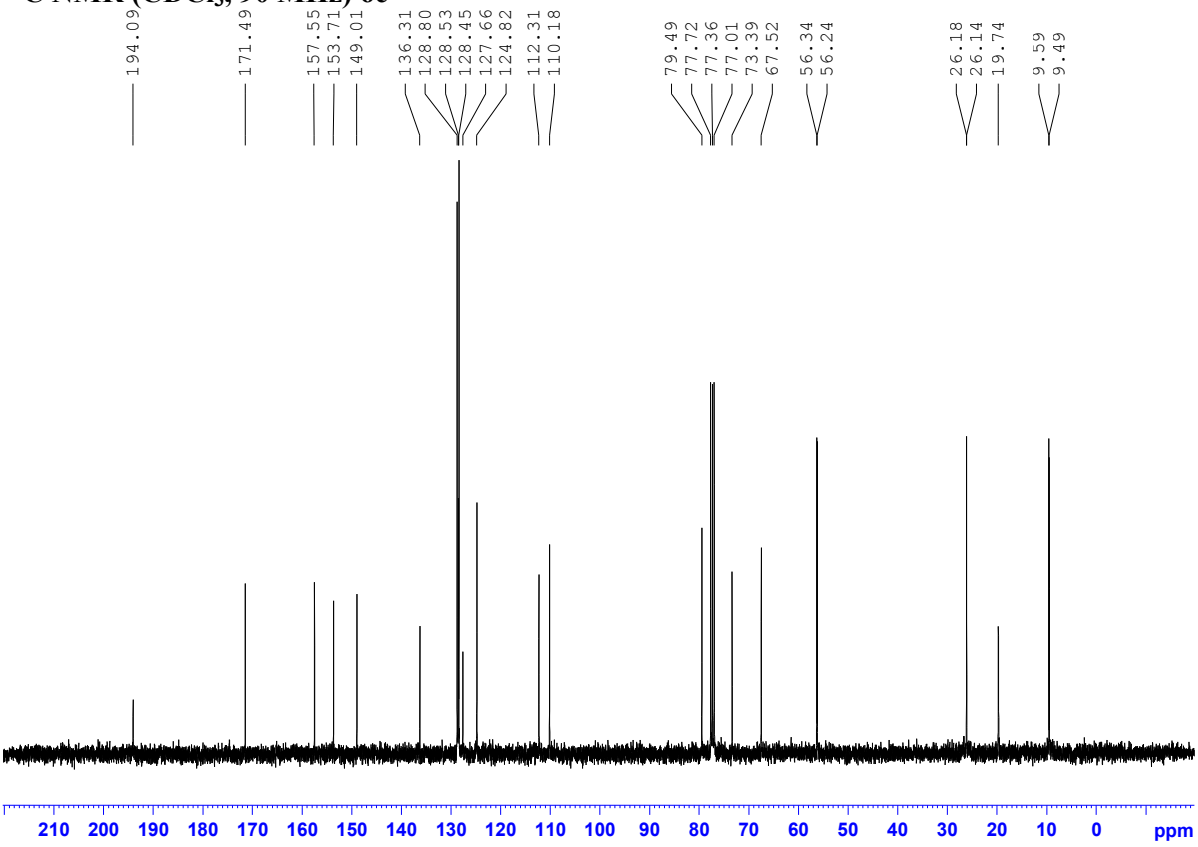


6c

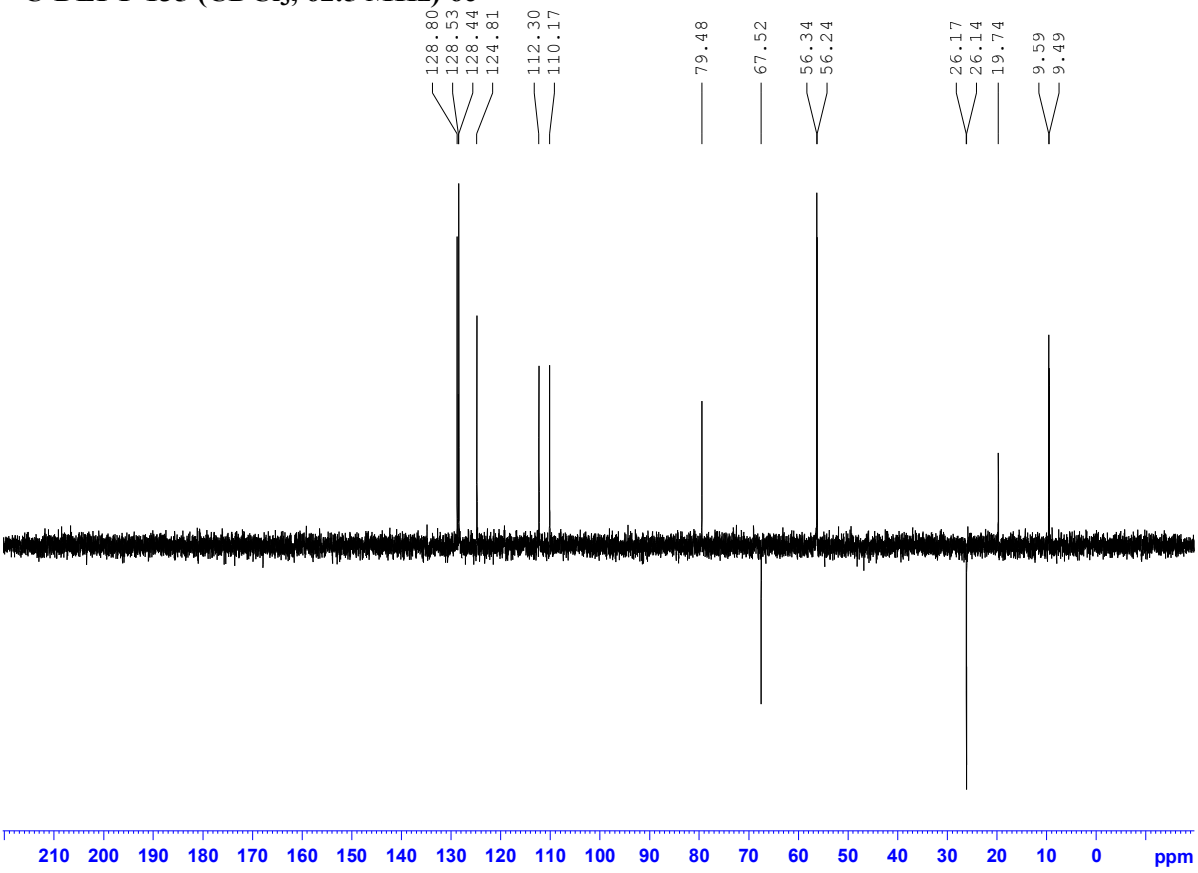
^{1}H NMR ($CDCl_3$, 360 MHz) 6c



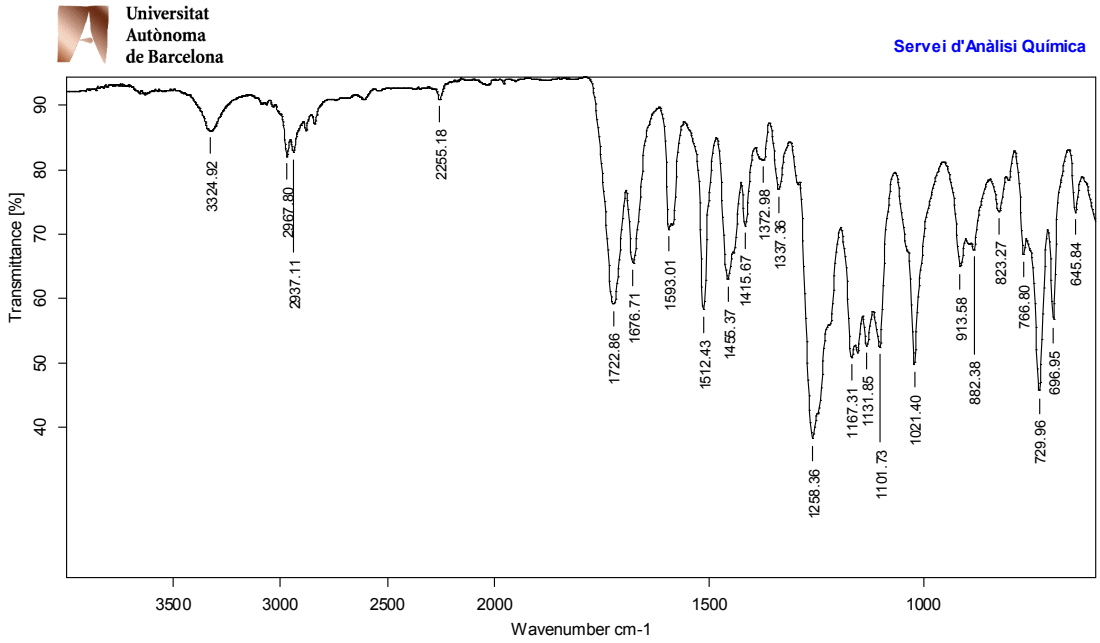
^{13}C NMR ($CDCl_3$, 90 MHz) 6c



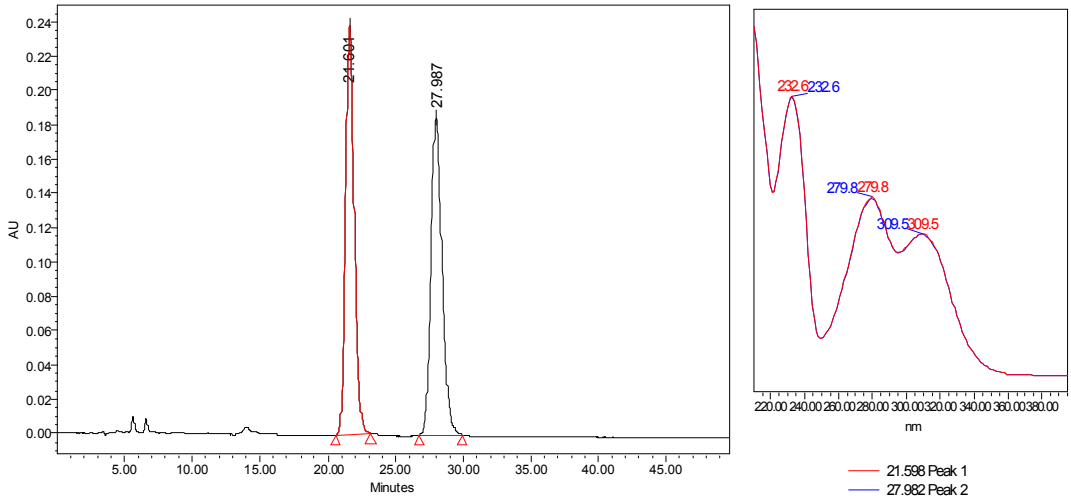
^{13}C-DEPT-135 ($CDCl_3$, 62.5 MHz) 6c



IR (ATR) 6c

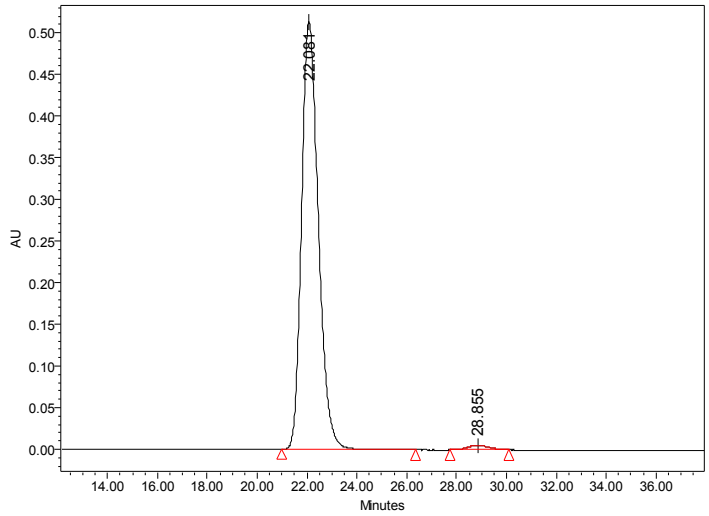


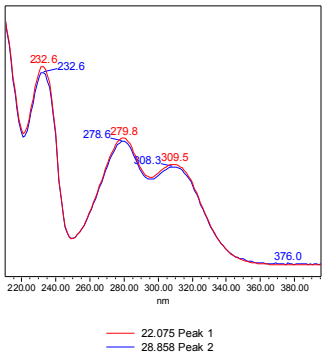
HPLC chromatogram of racemic mixture of 6c.



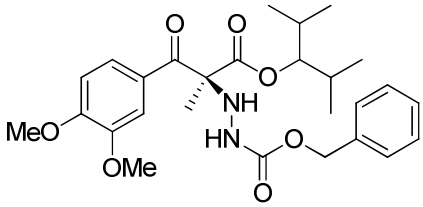
	Name	Retention Time	Area	% Area	Height	Int Type
1		21.601	10698755	50.04	238396	BB
2		27.987	10679922	49.96	185373	BB

HPLC chromatogram 97.5% ee of 6c.



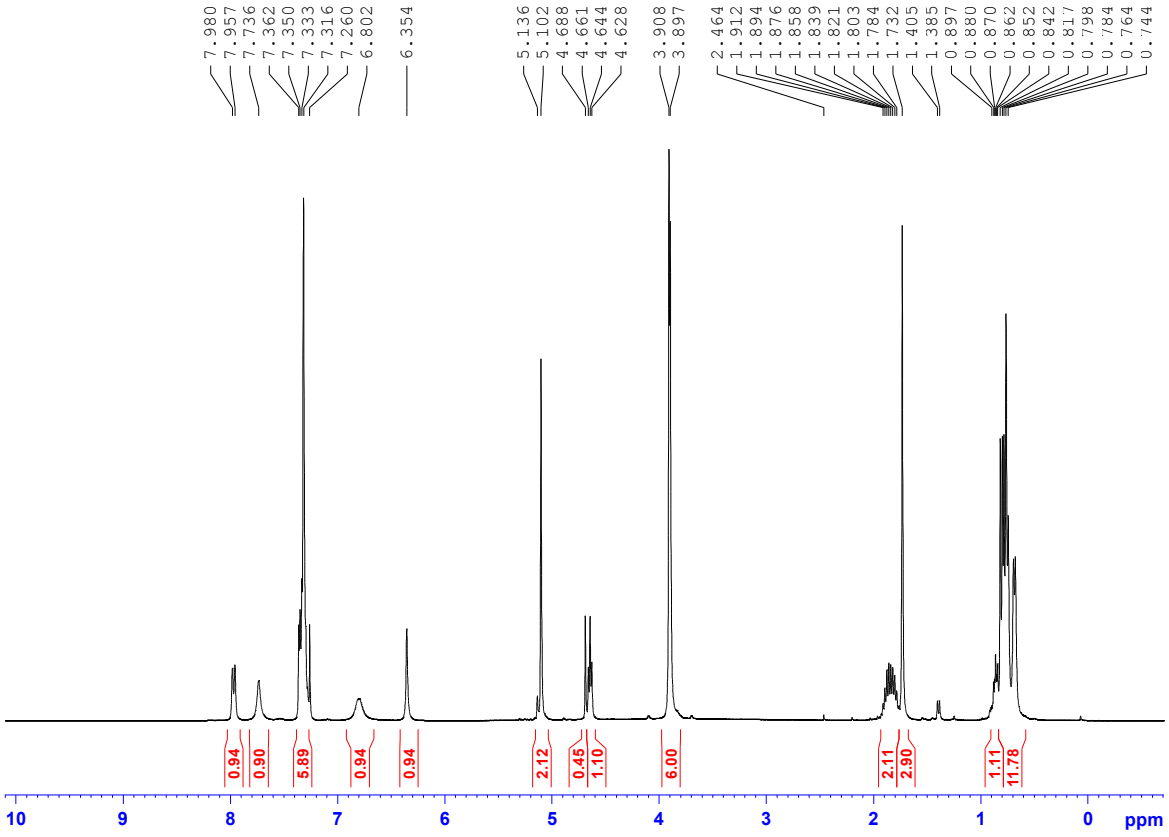


	Name	Retention Time	Area	% Area	Height
1		22.081	23976318	98.65	513396
2		28.855	328887	1.35	5680

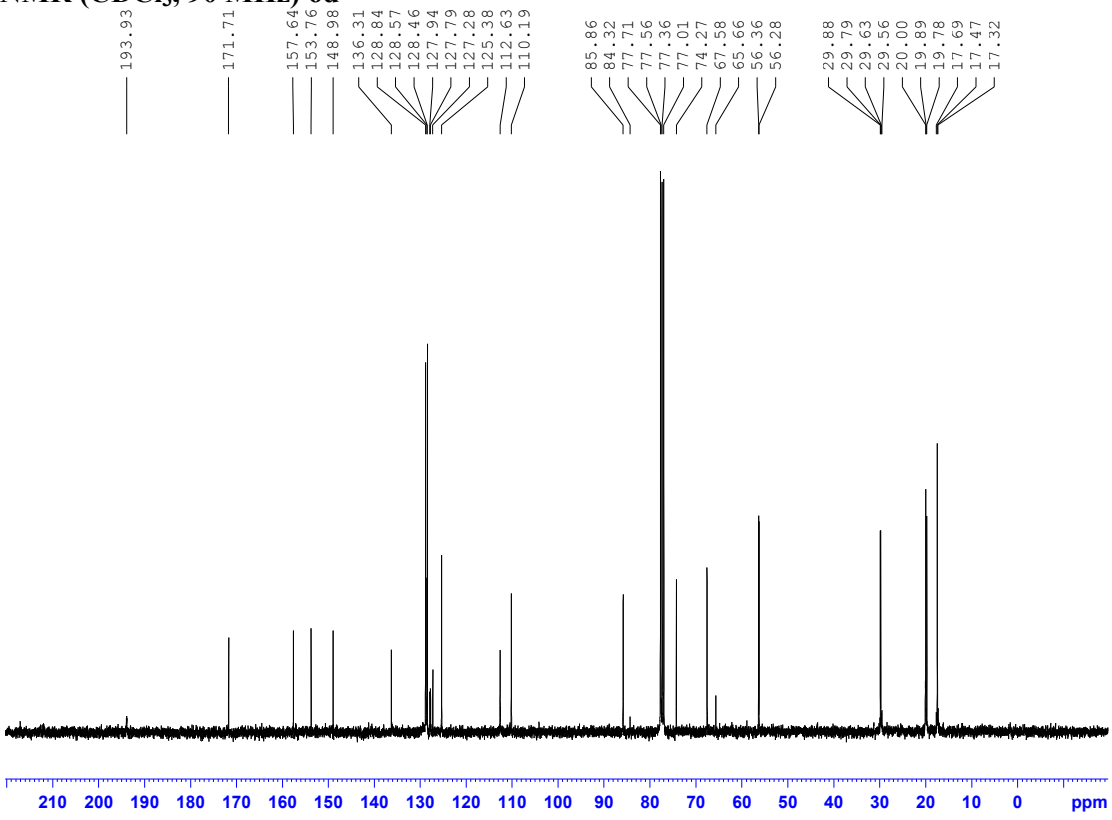


6d

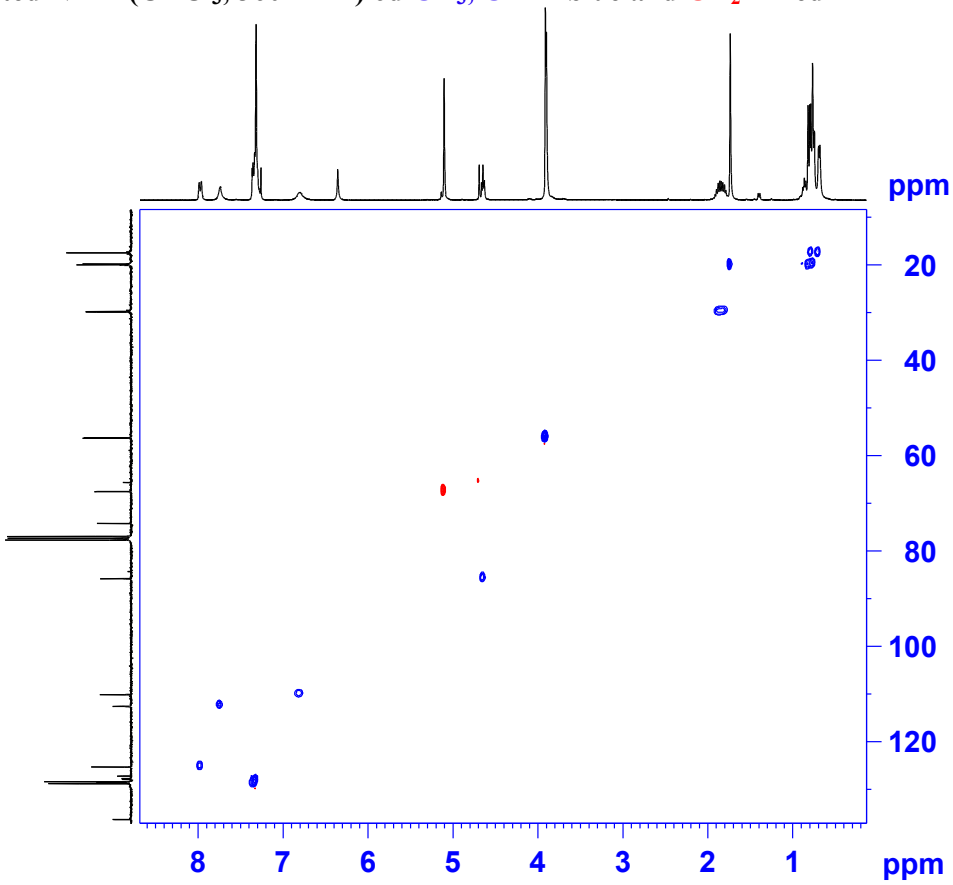
^{1}H NMR ($CDCl_3$, 360 MHz) 6d



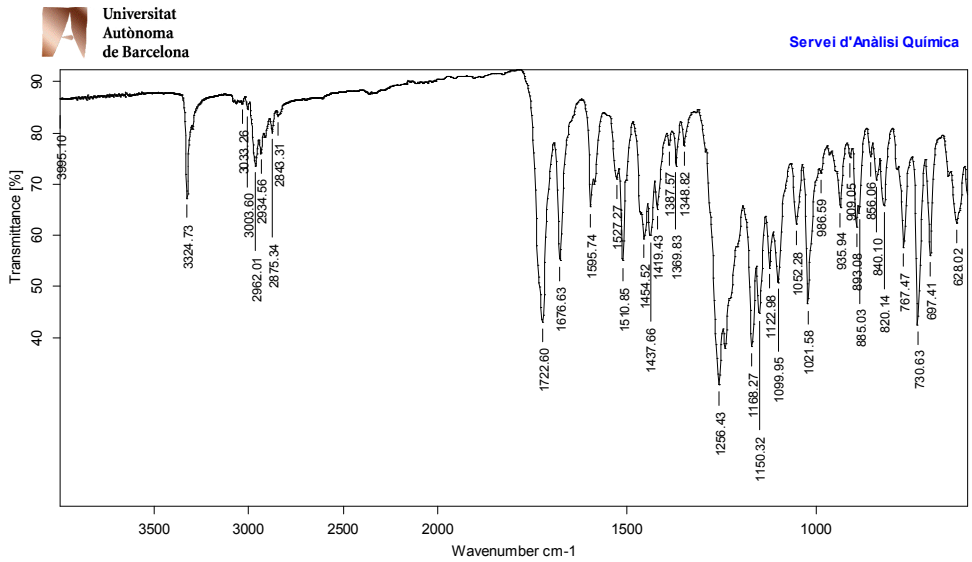
^{13}C NMR ($CDCl_3$, 90 MHz) 6d



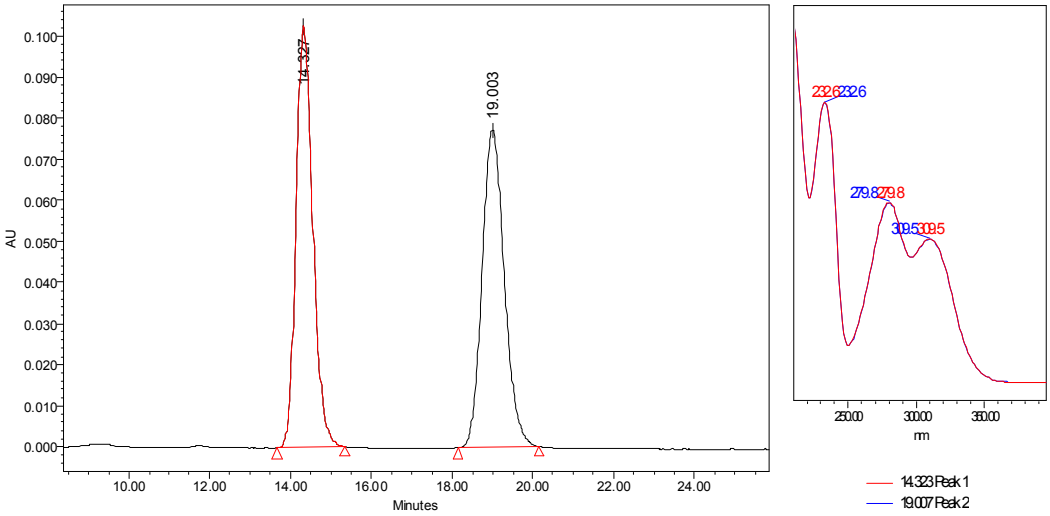
HSQC edited NMR ($CDCl_3$, 360 MHz) 6d CH_3, CH in blue and CH_2 in red



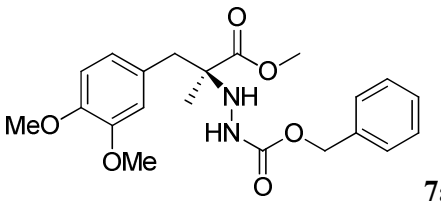
IR (ATR) 6d



HPLC chromatogram of racemic mixture of 6d.

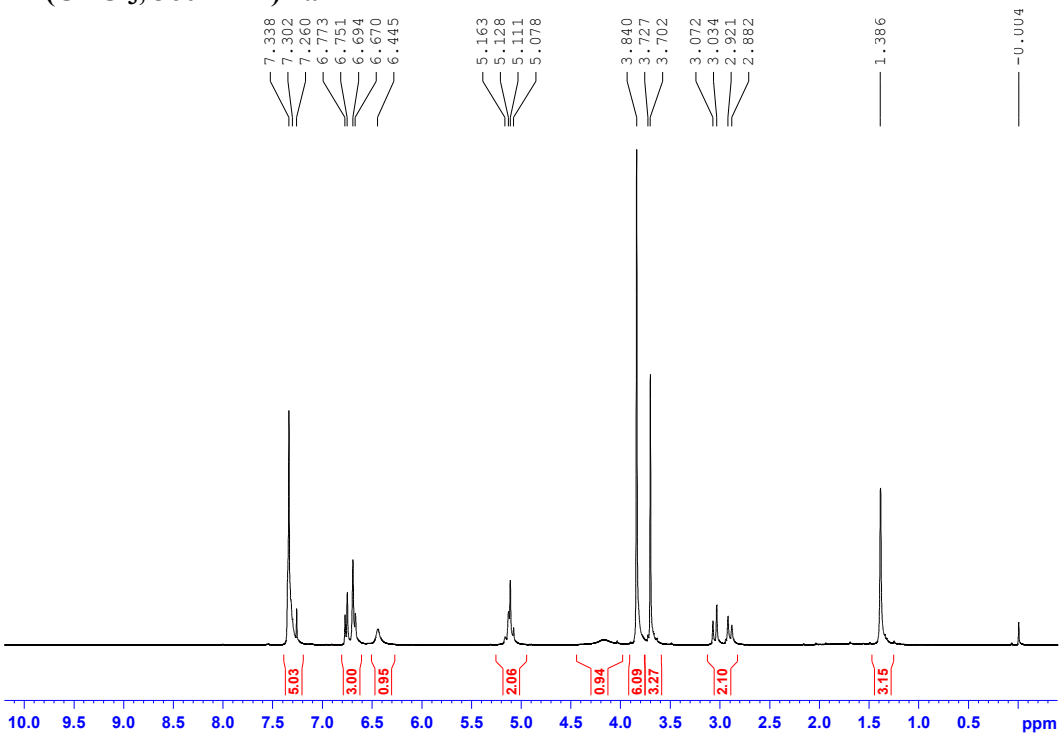


	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	14.327	2965867	50.05	102571	BB	Unknown
2	19.003	2959556	49.95	77390	BB	Unknown

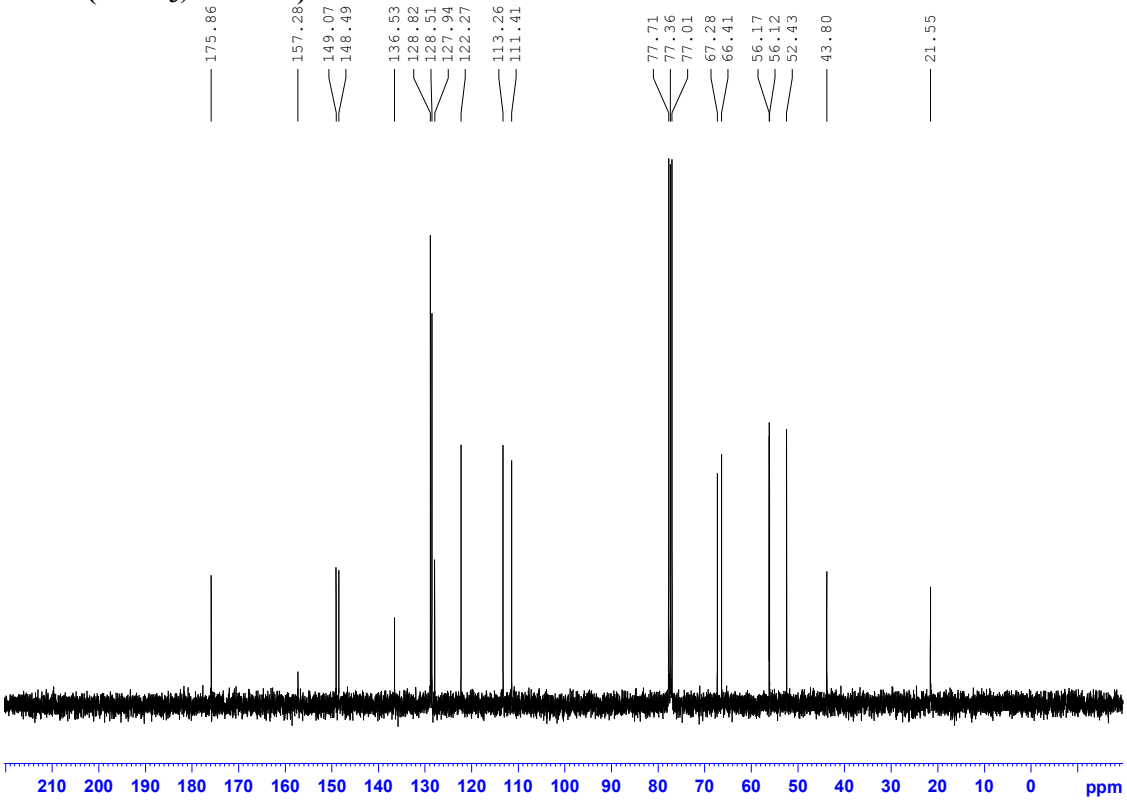


7a

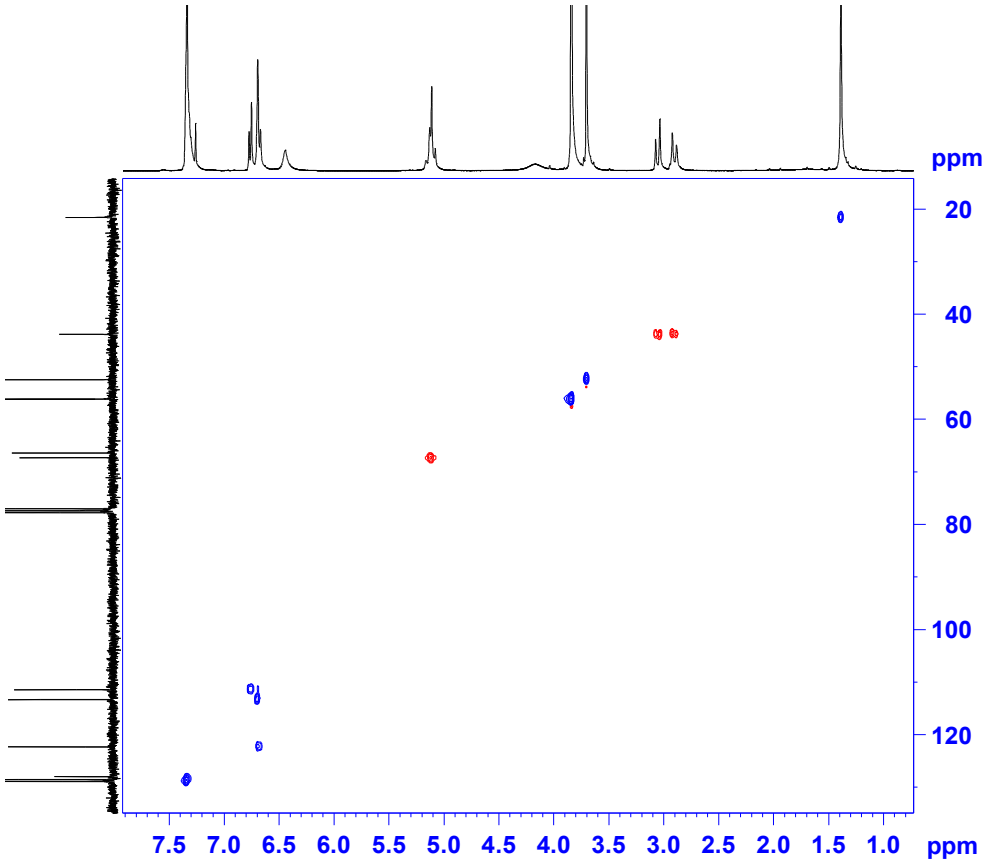
^{1}H NMR ($CDCl_3$, 360 MHz) 7a



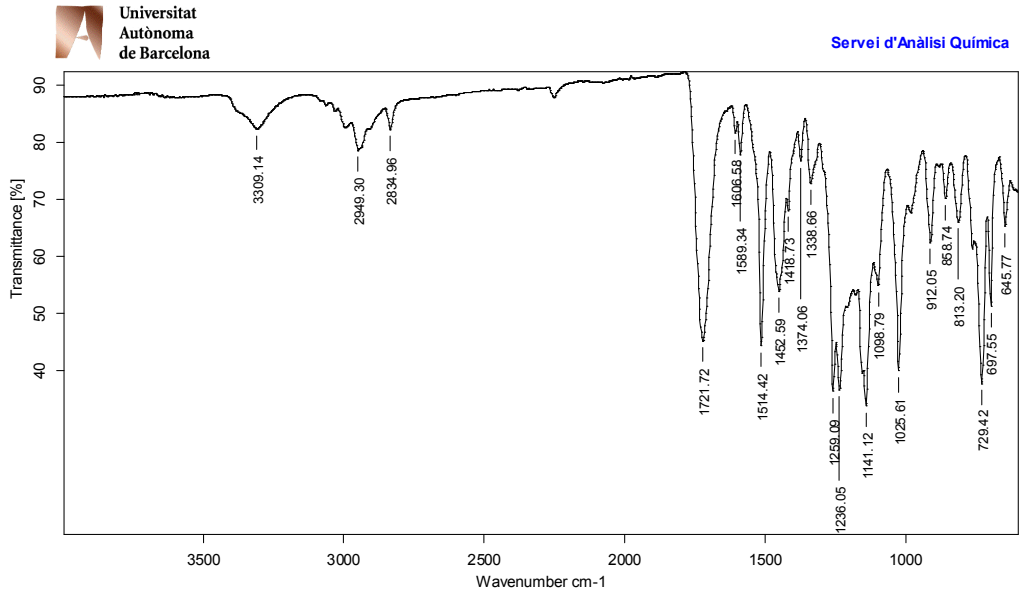
^{13}C NMR ($CDCl_3$, 90 MHz) 7a

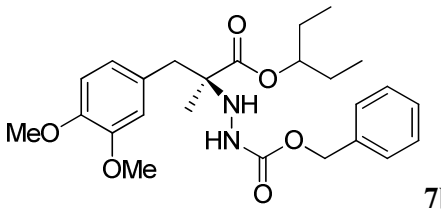


HSQC edited NMR ($CDCl_3$, 360 MHz) 7a CH_3, CH in blue and CH_2 in red



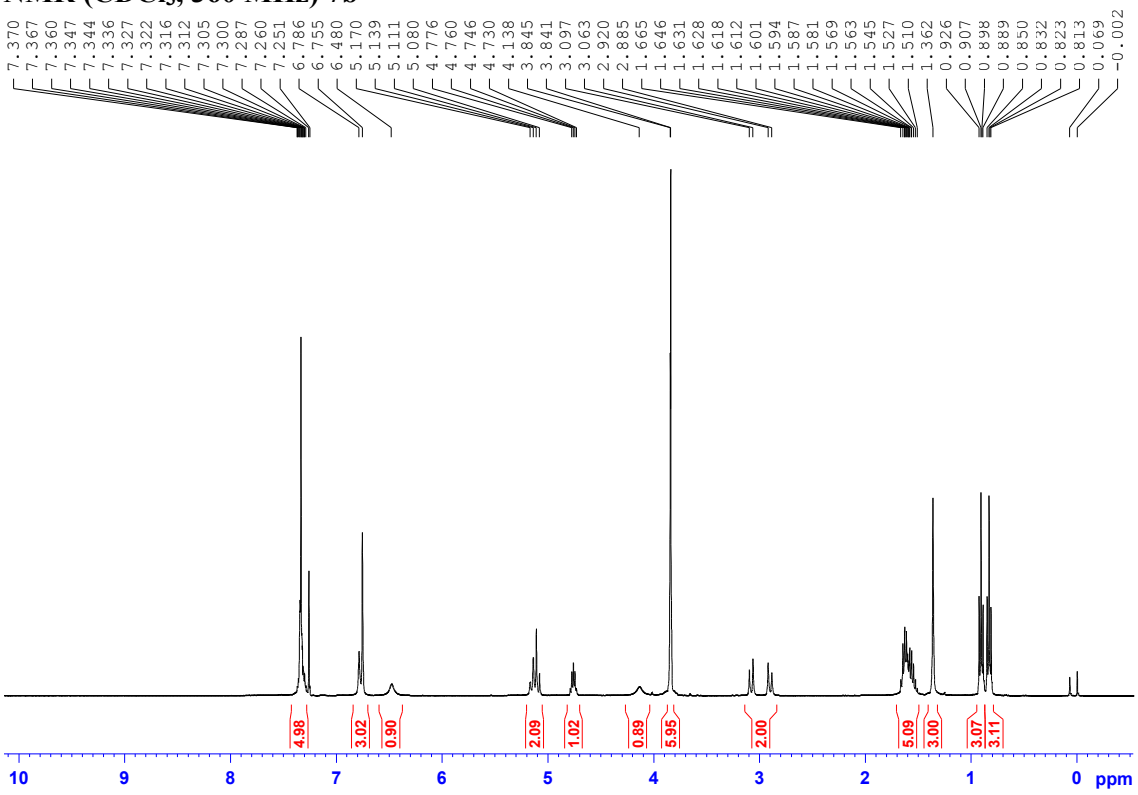
IR (ATR) 7a



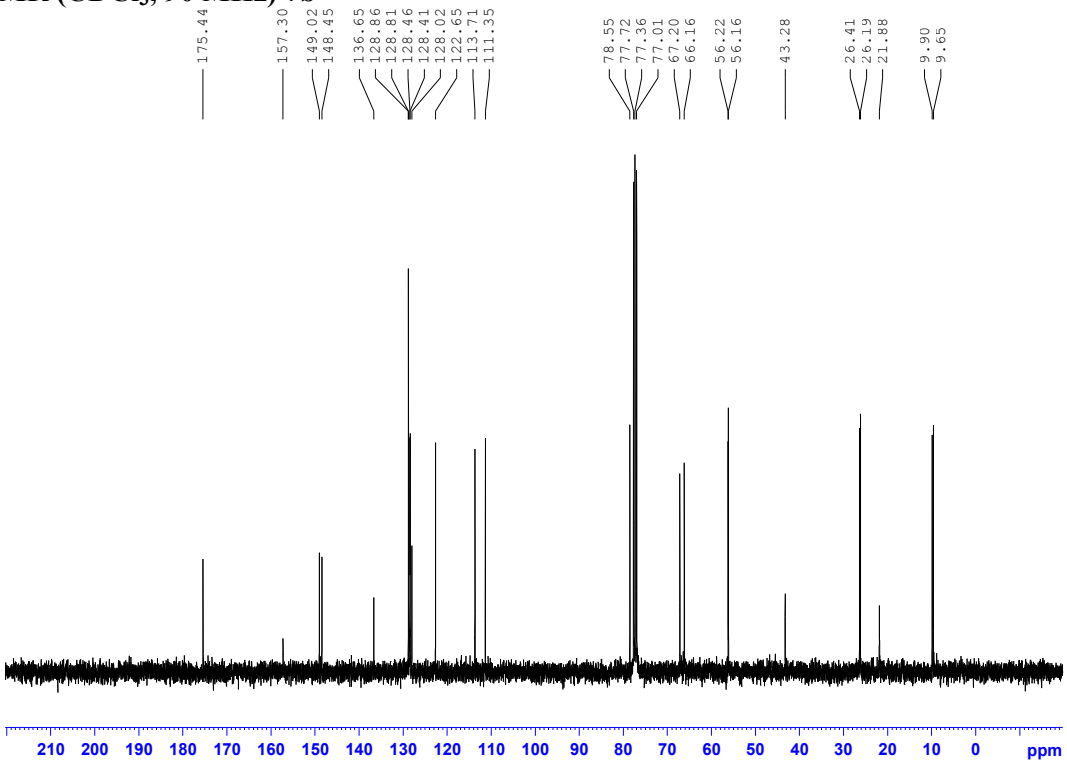


7b

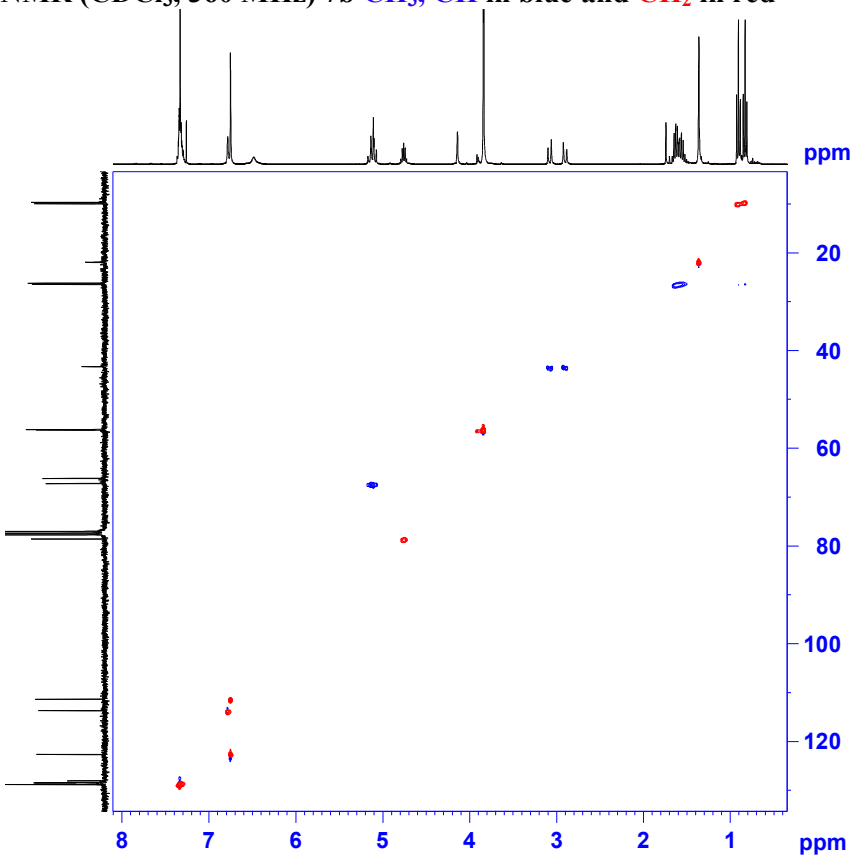
^{1}H NMR ($CDCl_3$, 360 MHz) 7b



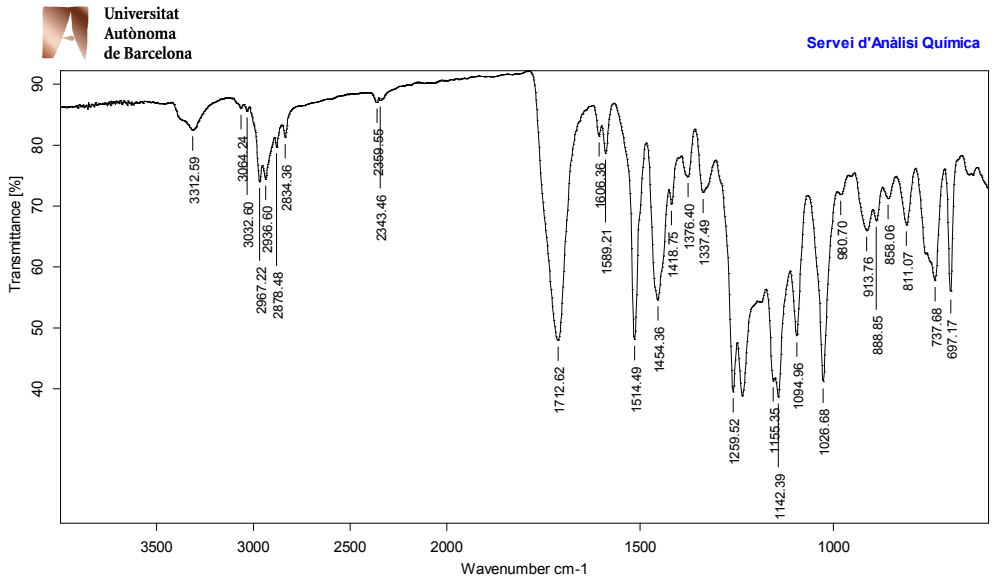
^{13}C NMR ($CDCl_3$, 90 MHz) 7b



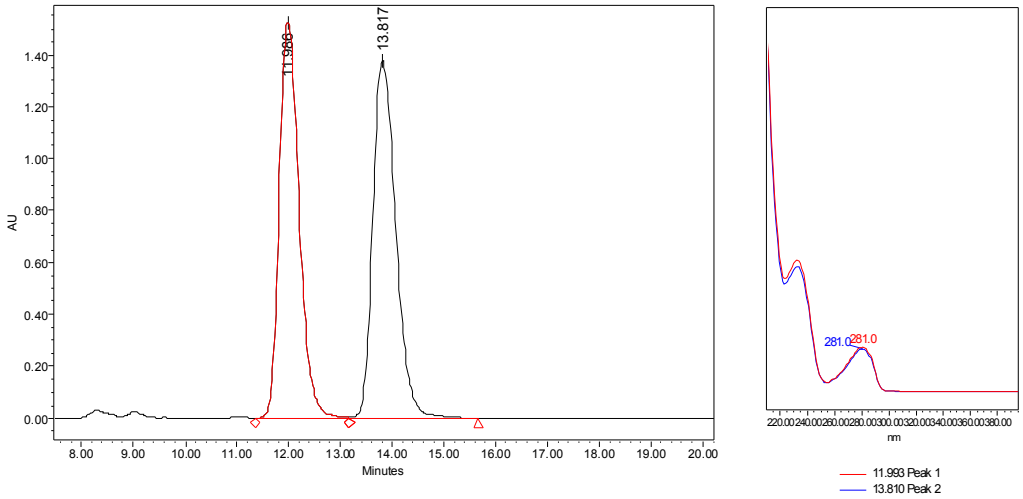
HSQC edited NMR ($CDCl_3$, 360 MHz) 7b CH_3, CH in blue and CH_2 in red



IR (ATR) 7b

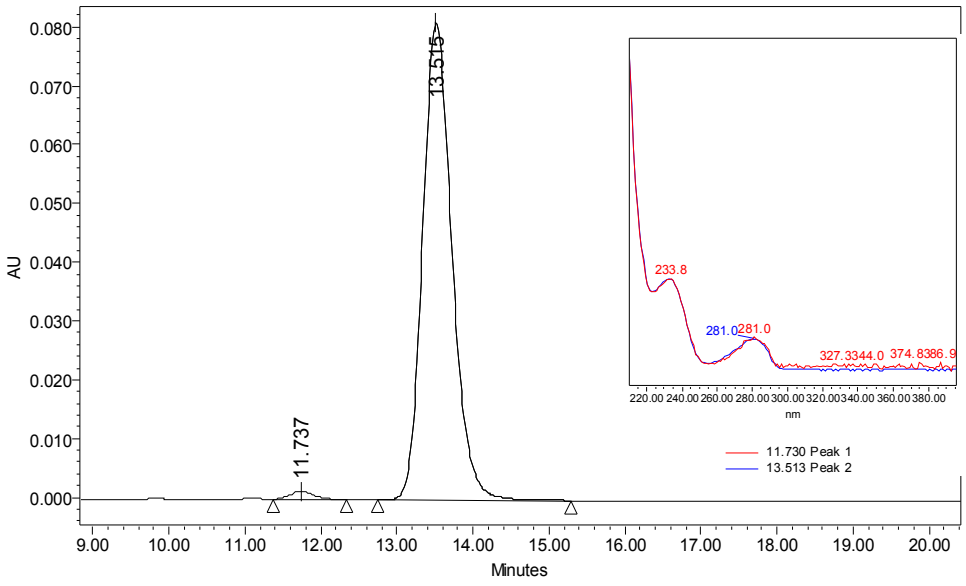


HPLC chromatogram of racemic mixture of 7c.

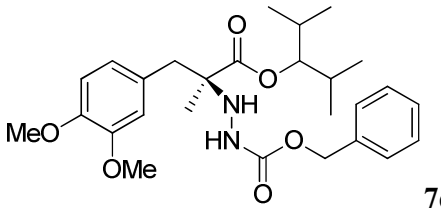


	Name	Retention Time	Area	% Area	Height	Int Type
1		11.986	41148393	49.29	1523776	VV
2		13.817	42329443	50.71	1376635	VB

HPLC chromatogram 97.5% ee of 7c.

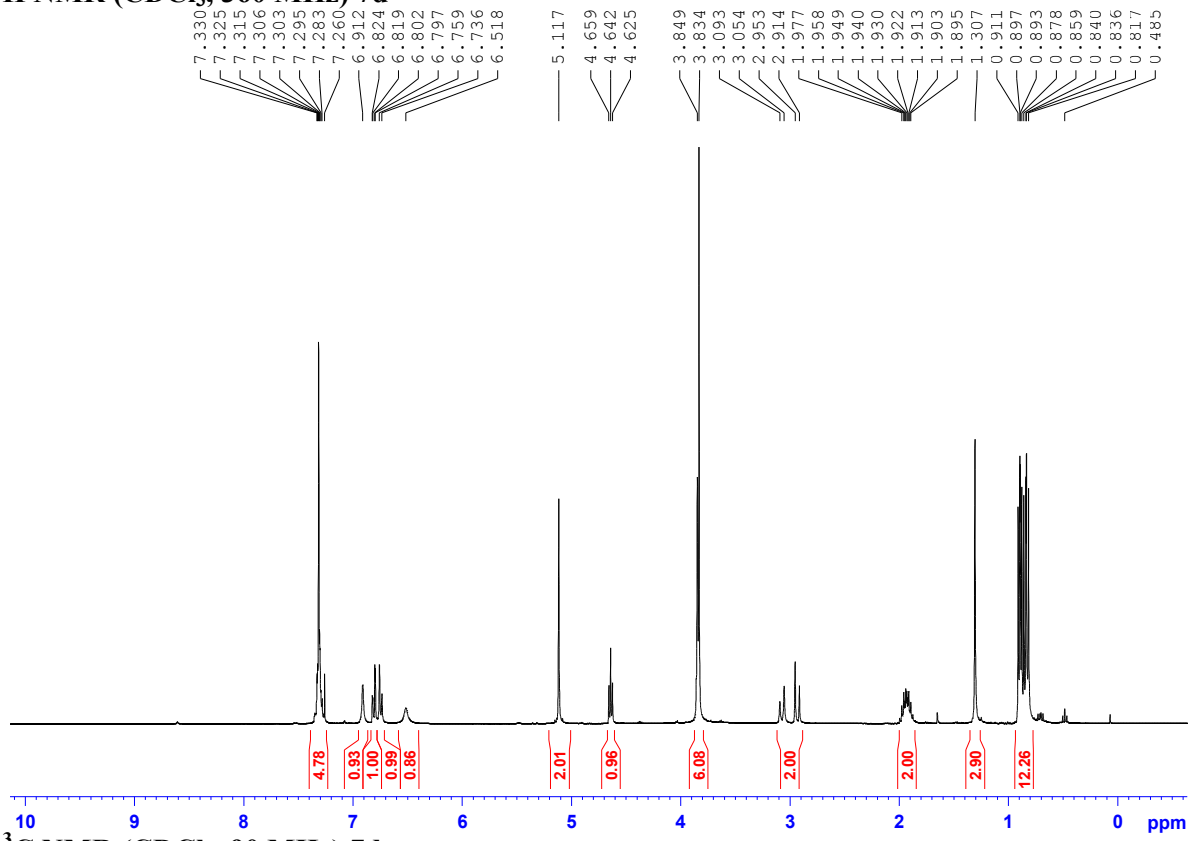


	Name	Retention Time	Area	% Area	Height	Int Type
1		11.737	29431	1.34	1332	bb
2		13.515	2172533	98.66	81240	bb

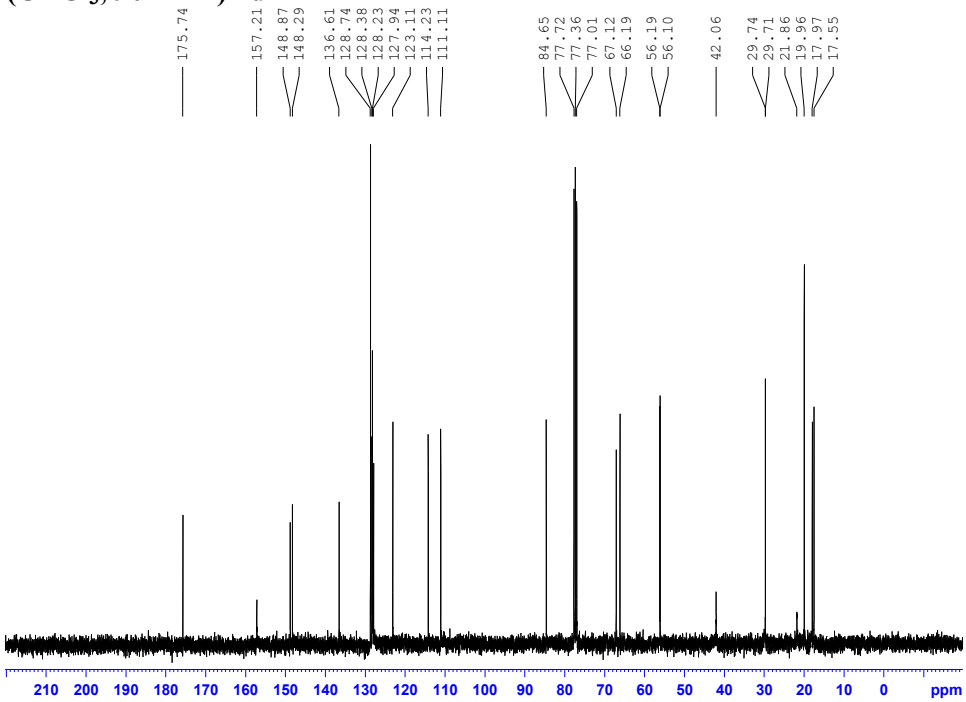


7d

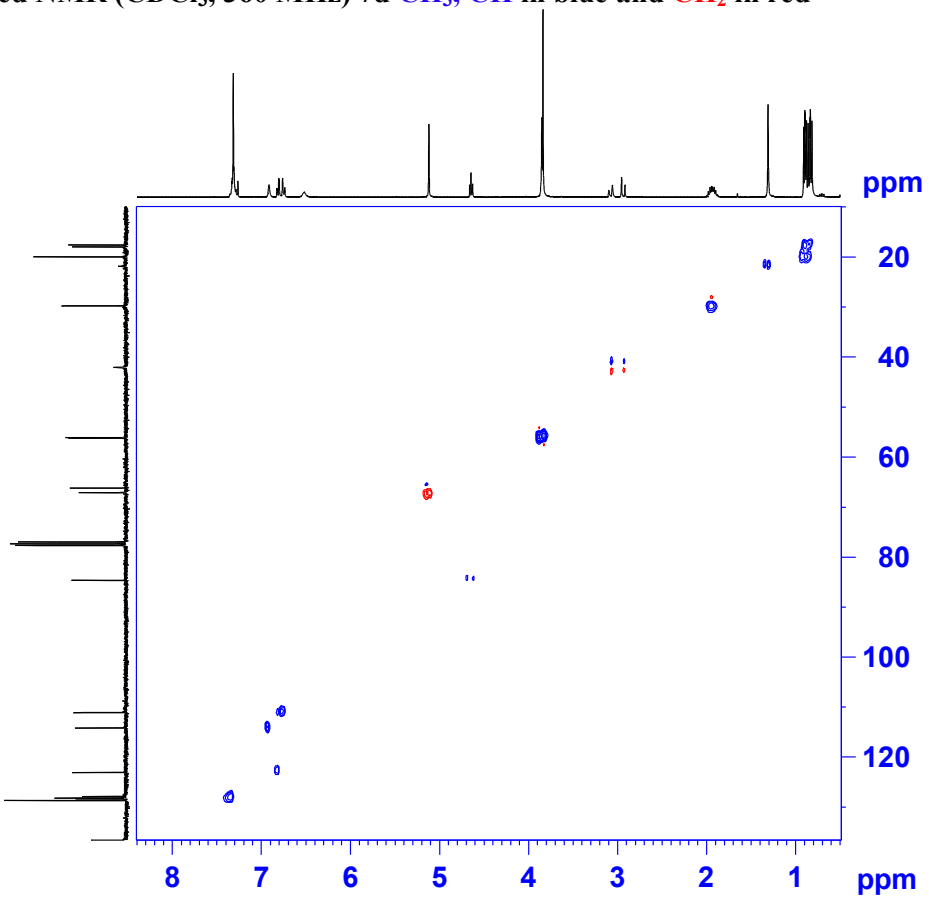
^{1}H NMR ($CDCl_3$, 360 MHz) 7d



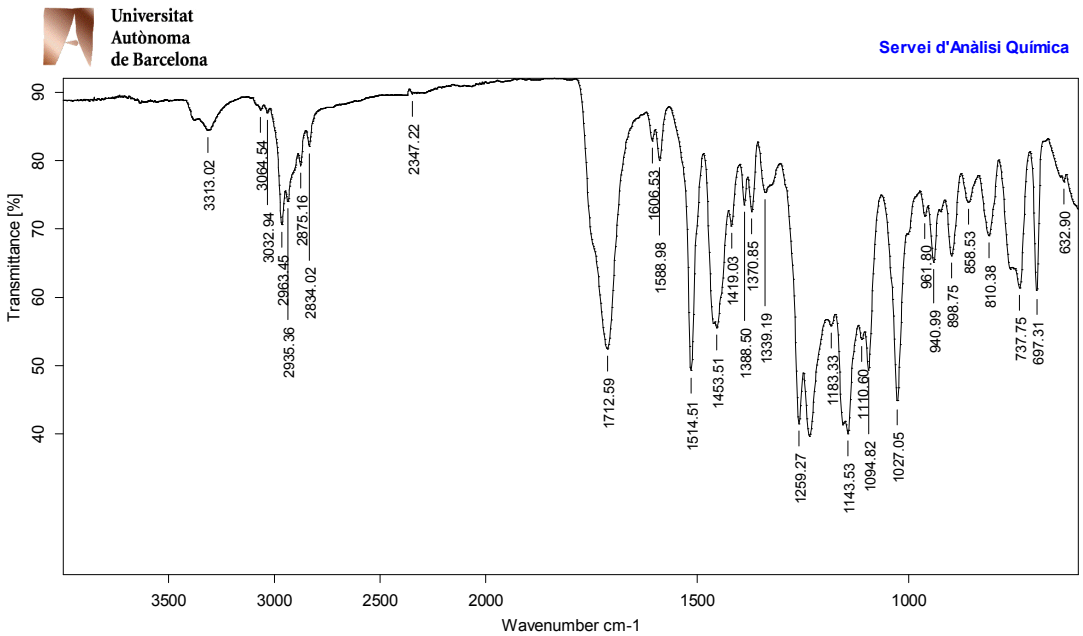
^{13}C NMR ($CDCl_3$, 90 MHz) 7d



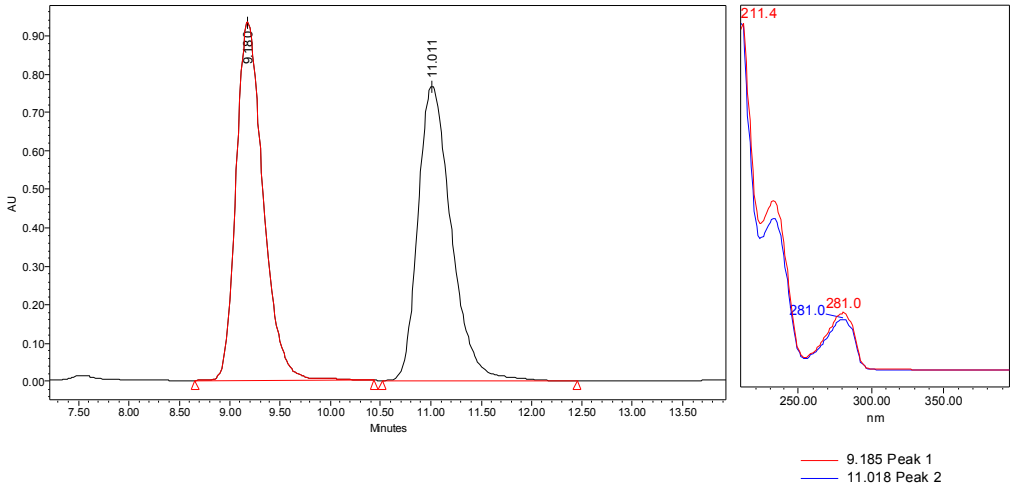
HSQC edited NMR ($CDCl_3$, 360 MHz) 7d CH_3, CH in blue and CH_2 in red



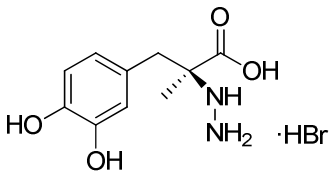
IR (ATR) 7d



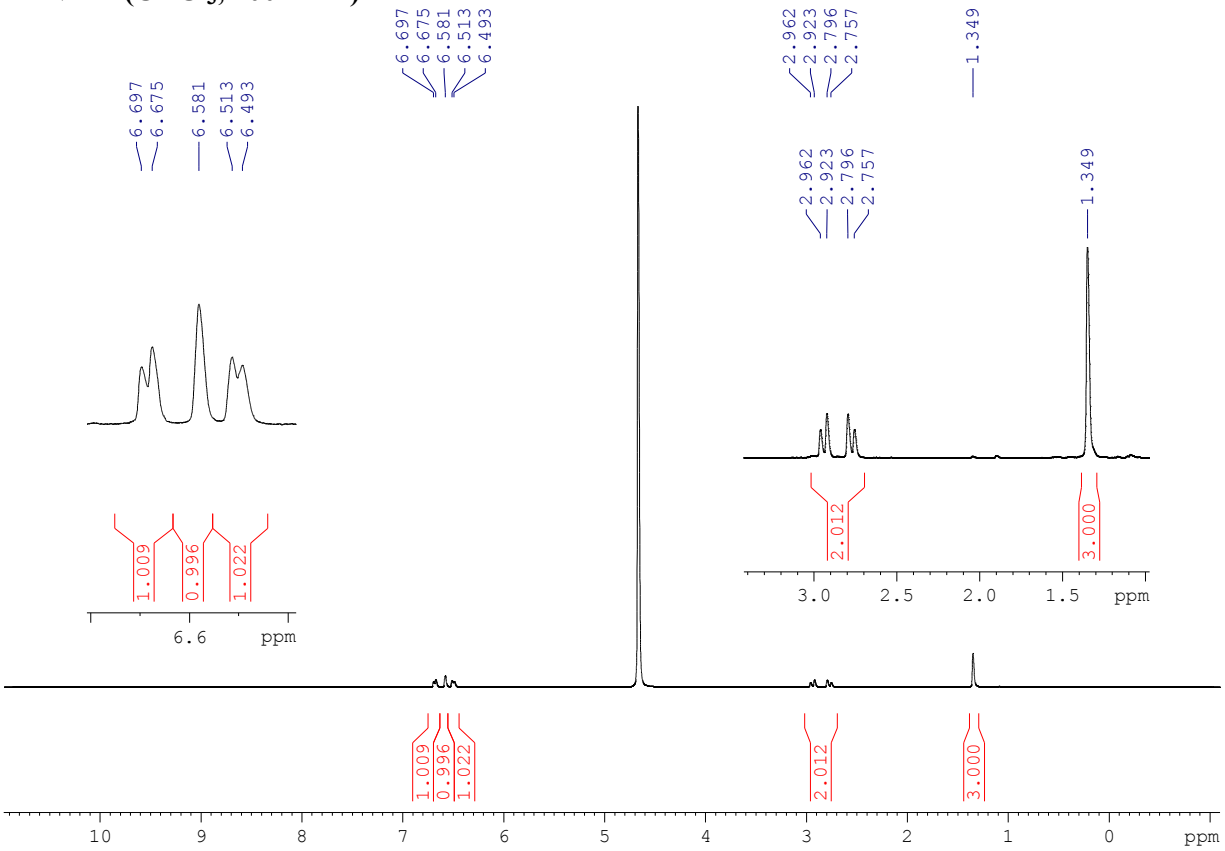
HPLC chromatogram of racemic mixture of 7d.



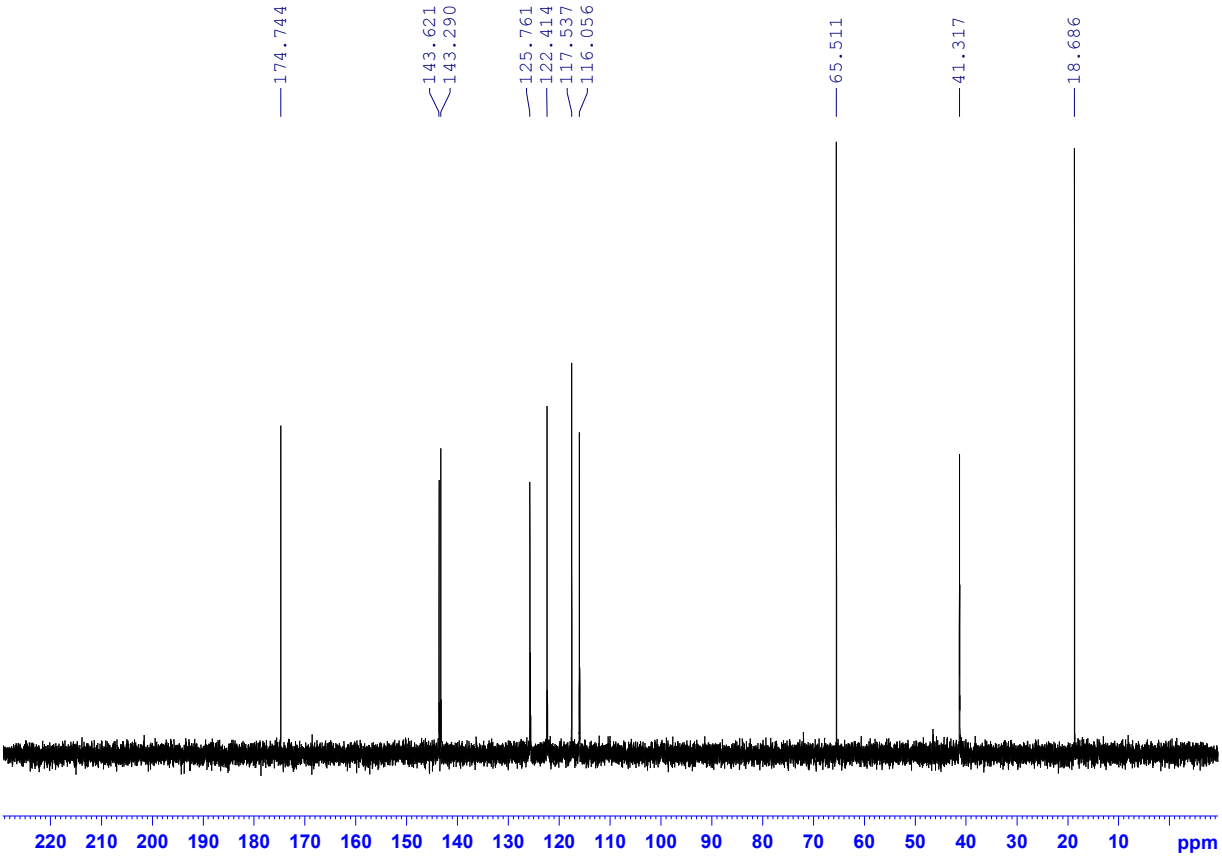
	Name	Retention Time	Area	% Area	Height	Int Type
1		9.180	17600239	49.99	932120	Bb
2		11.011	17610329	50.01	766504	BB



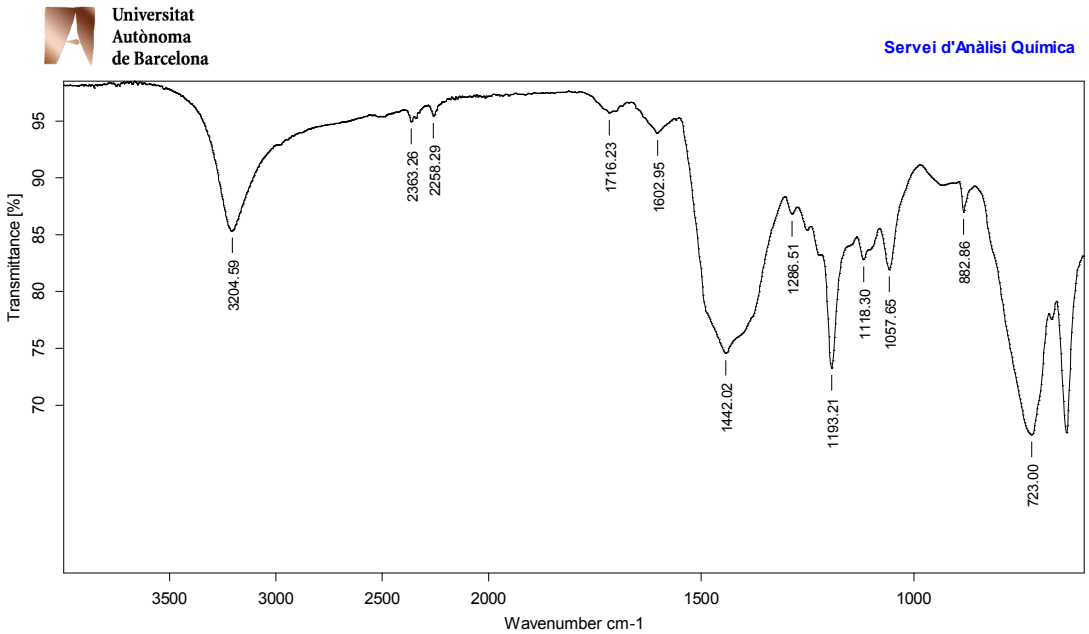
^{1}H NMR ($CDCl_3$, 400 MHz)



^{13}C NMR ($CDCl_3$, 100 MHz)



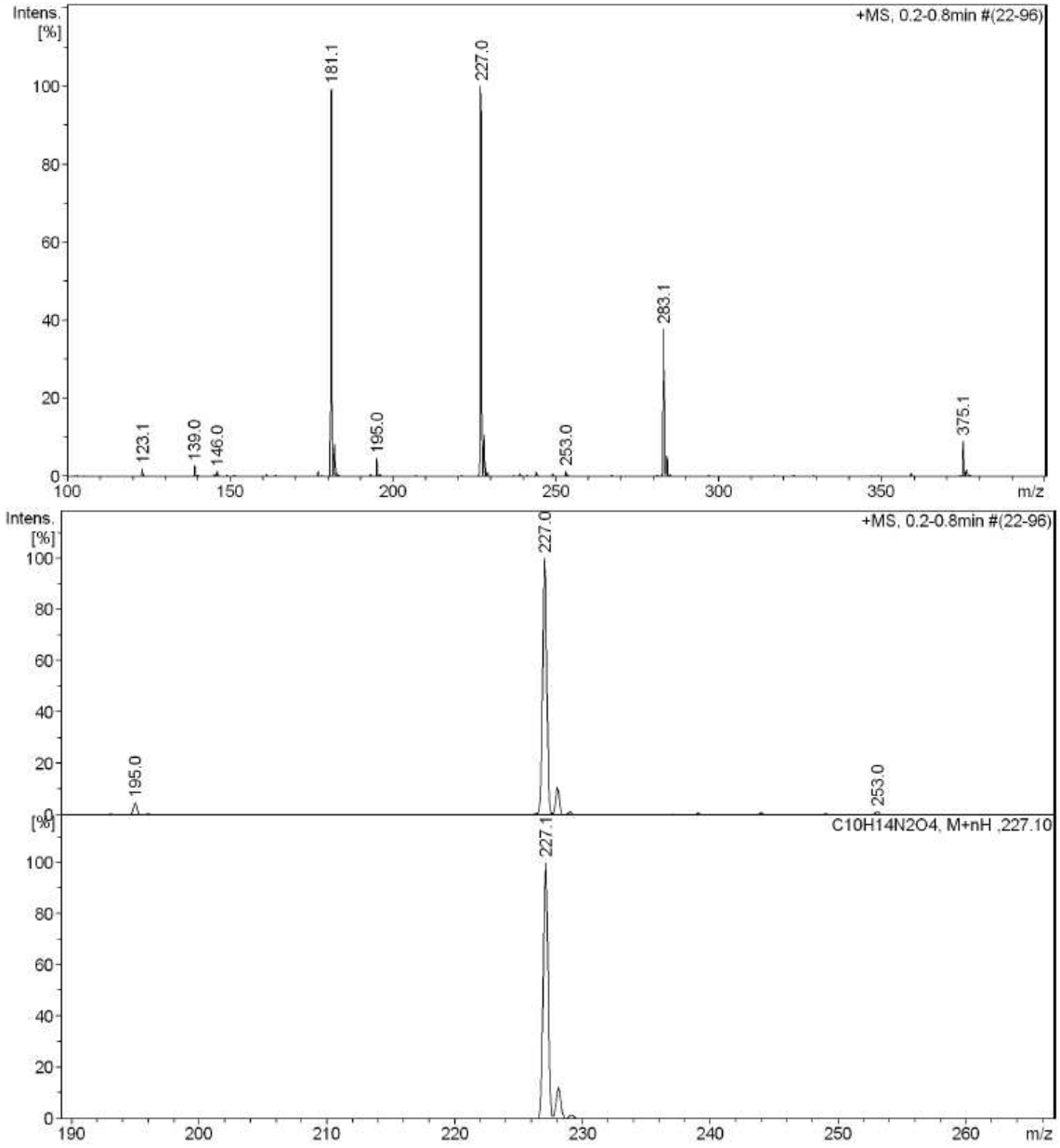
IR (ATR)



ESI$^+$

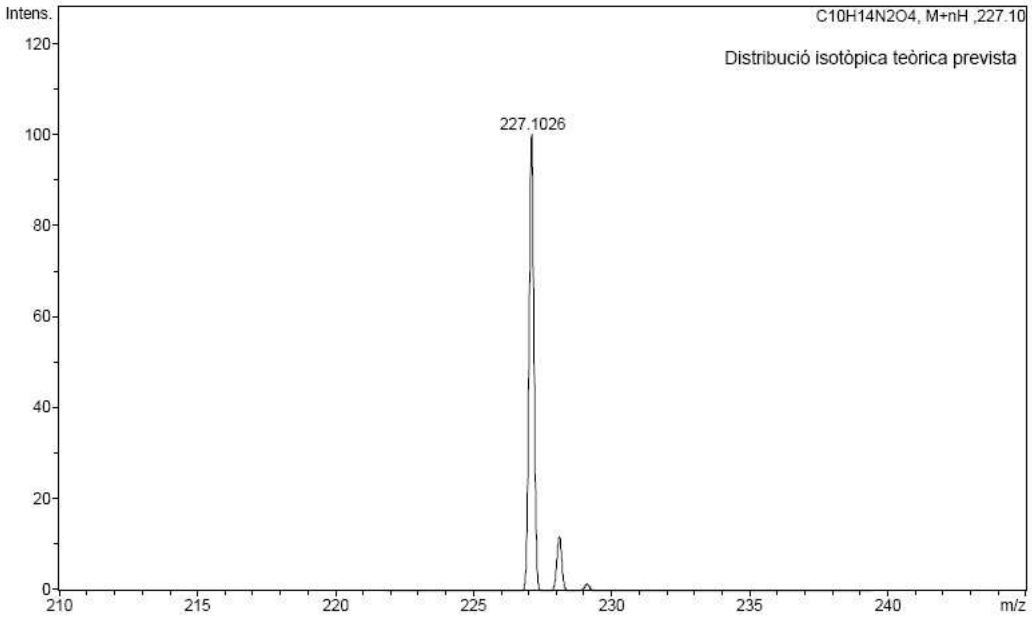
Acquisition Parameter

Ion Source Type	ESI	Ion Polarity	Positive	Alternating Ion Polarity	off
Mass Range Mode	Std/Normal	Scan Begin	100 m/z	Scan End	400 m/z
Capillary Exit	50.0 Volt	Skimmer	15.0 Volt	Trap Drive	43.9
Accumulation Time	364 µs	Averages	7 Spectra	Auto MS/MS	off



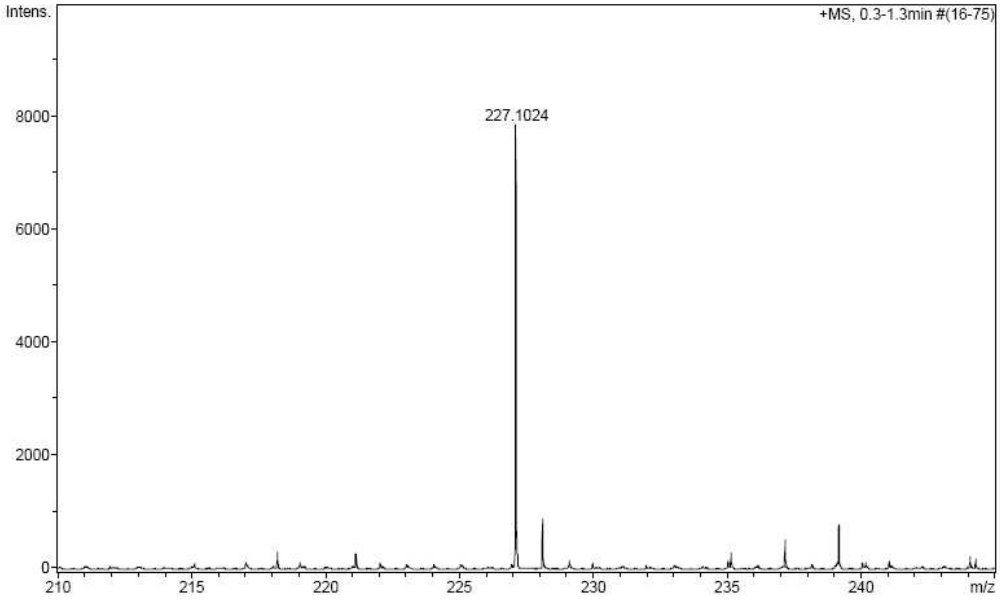
HIGH-RESOLUTION MASS SPECTRA

Theorical

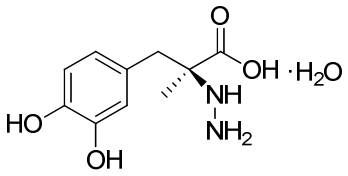


#	m/z	I	I %
1	227.1026	100	100.0
2	228.1060	12	11.9
3	229.1069	1	1.5

Experimental

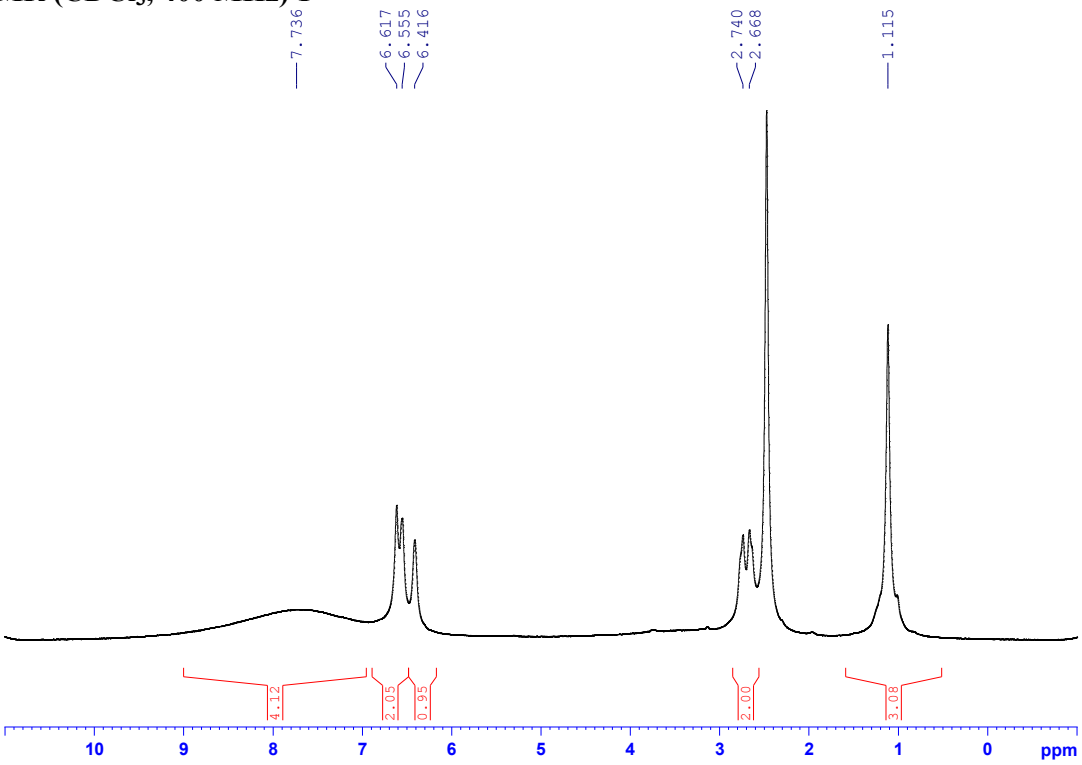


#	m/z	I	I %
1	227.1024	7849	100.0
2	228.1054	882	11.2
3	229.1075	138	1.8

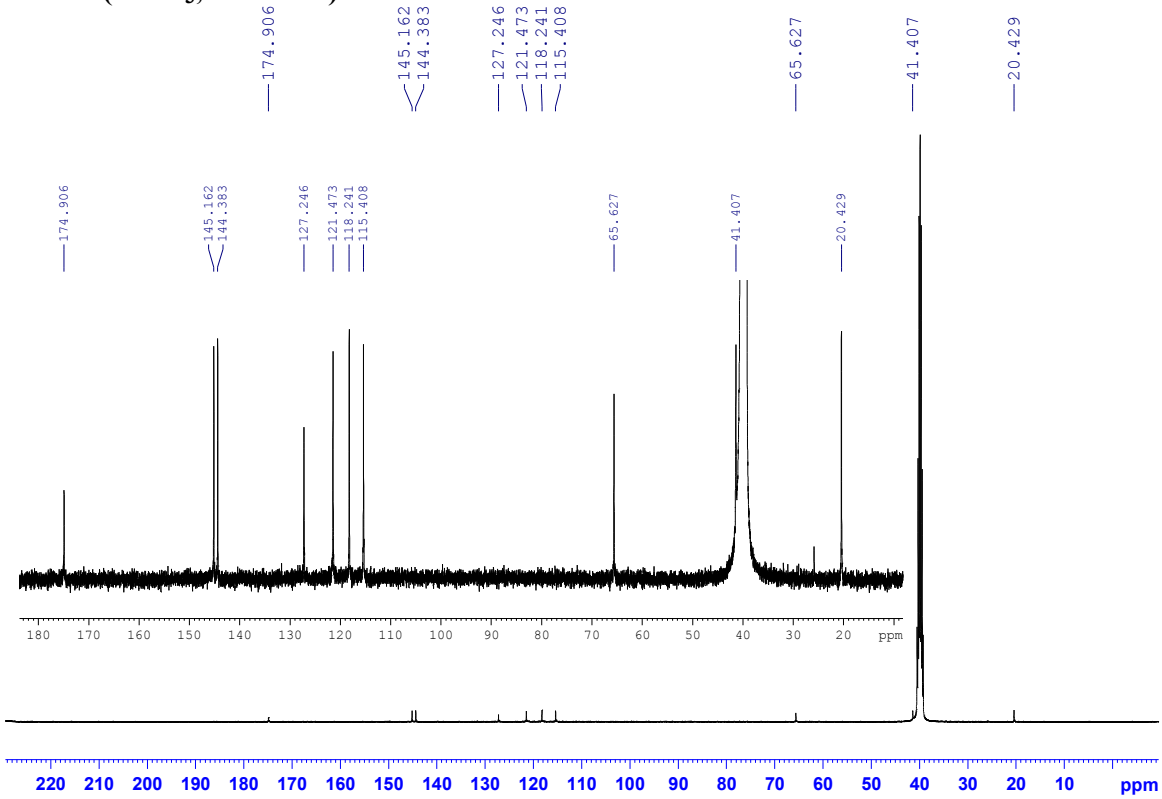


1

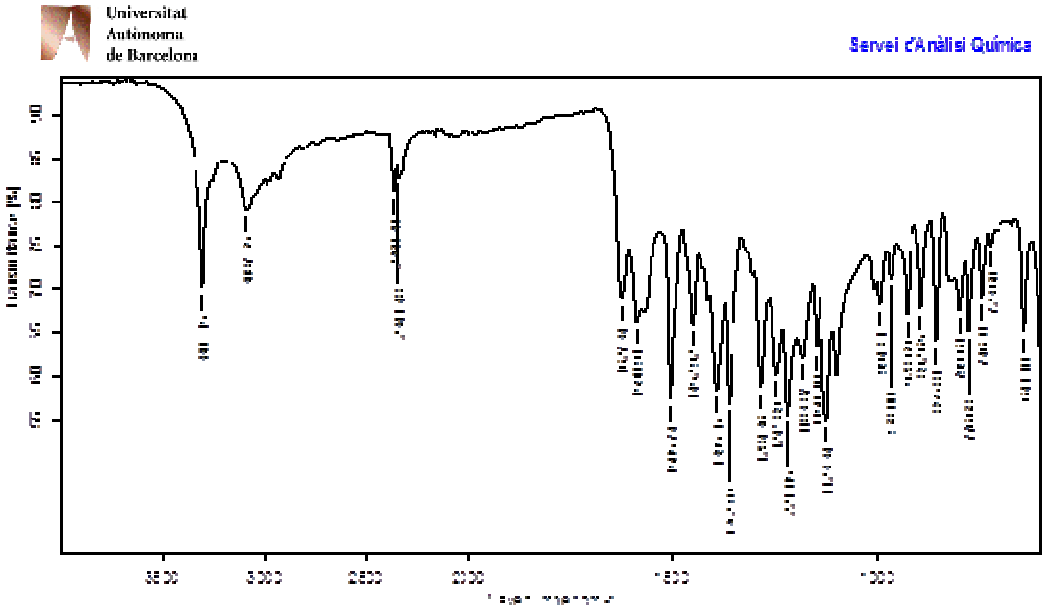
^{1}H NMR ($CDCl_3$, 400 MHz) 1



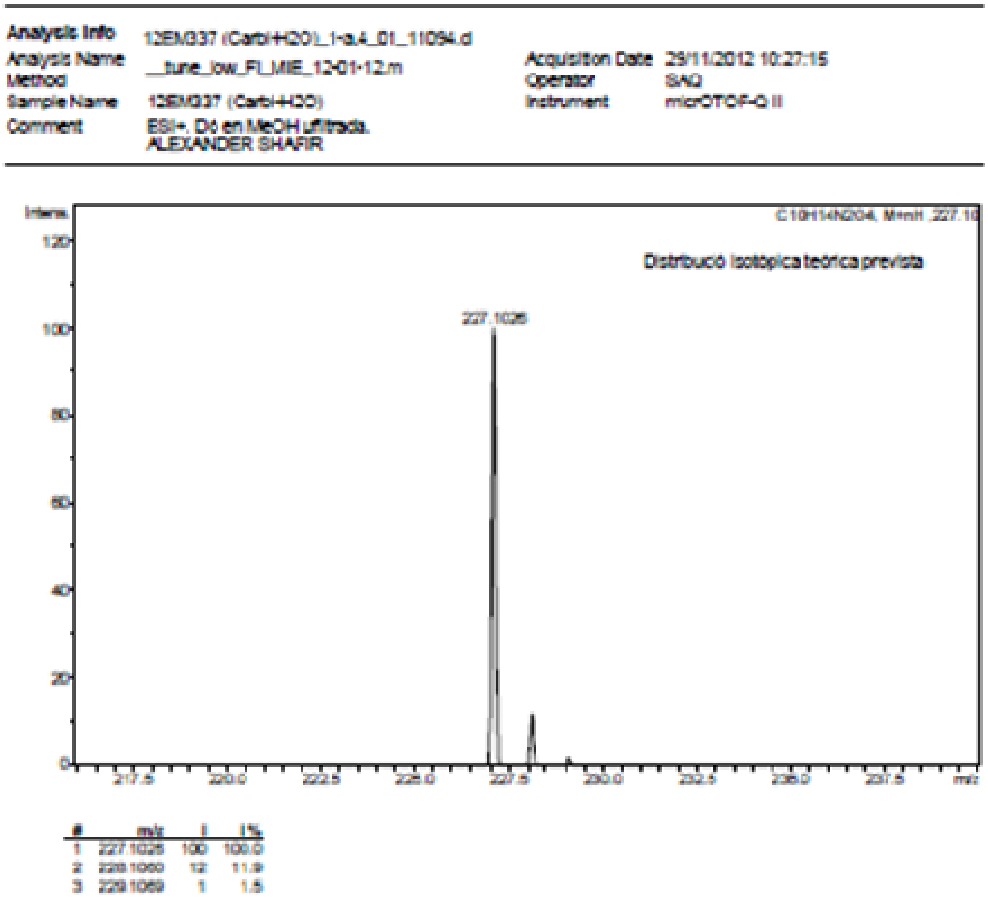
^{13}C NMR ($CDCl_3$, 100 MHz) 1



IR (ATR) 1



HIGH-RESOLUTION MASS SPECTRA 1
Theorical



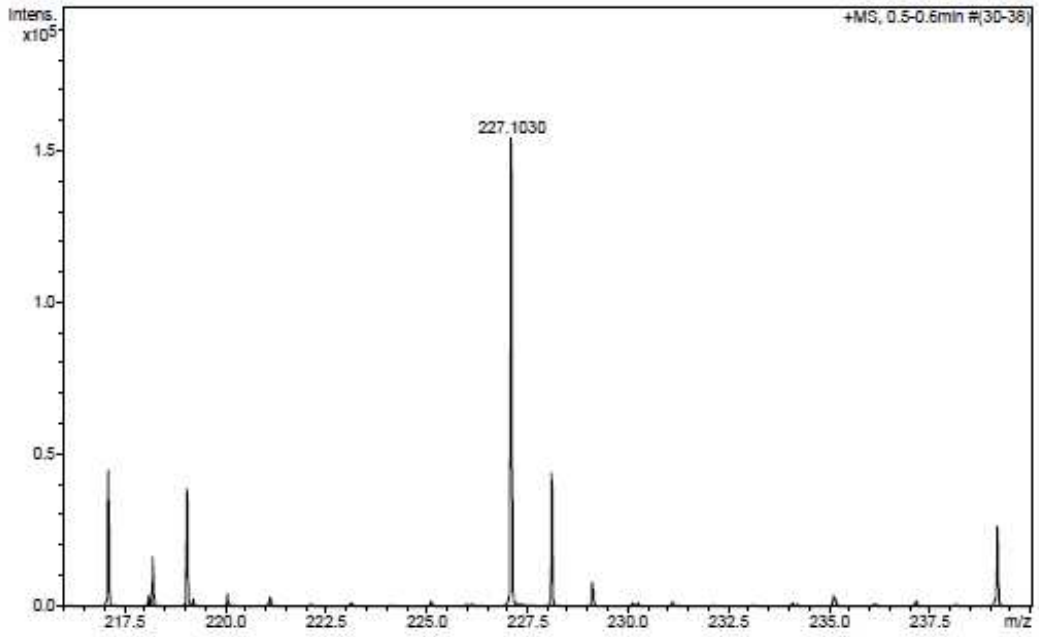
Servei d'Anàlisi Química — **Universitat Autonoma de Barcelona**

Àrea de Cromatografia i Espectrometria de Masses

Registre d'alta resolució

Analysis Info

Analysis Name	12EM337 (Carbi-H2O)_1-a,4_01_11094.d	Acquisition Date	29/11/2012 10:27:15
Method	__tune_low_FI_MIE_12-01-12.m	Operator	SAQ
Sample Name	12EM337 (Carbi-H2O)	Instrument	micrOTOF-Q II
Comment	ESI+. Dó en MeOH µfiltrada. ALEXANDER SHAFIR		



#	m/z	I	I %
1	227.1030	154275	100.0
2	228.1078	43908	28.5
3	229.1153	7846	5.1