Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

An Enzymatic Acetal/Hemiacetal Conversion for the Activation of the C—ON bond Homolysis

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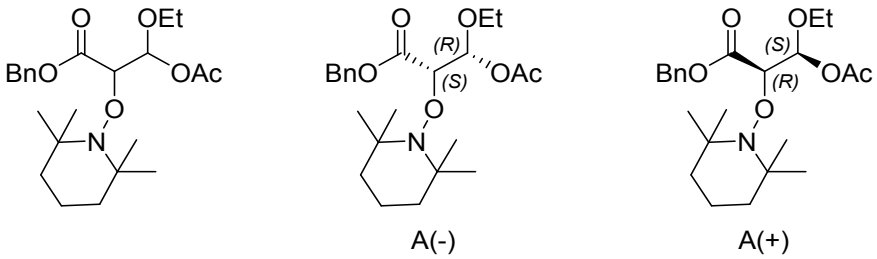
1. Experimental Procedures

Materials. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded with an internal deuterium lock system at room temperature using: Bruker AC400 (400 MHz) and Bruker AC300 (300 MHz) spectrometers. ^{13}C NMR spectra were recorded using Bruker AC400 (162 MHz) and Bruker AC300 (121 MHz) spectrometers with complete proton decoupling. Data were presented as: chemical shift (in ppm) using residual non-deuterated solvents as internal references, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad signal, dd = doublet of doublets, quint. = quintuplet), integration, coupling constant (J in Hz).

When reported, carbons were attributed using the DEPT 135 and HSQC methods. High-resolution mass spectra (HRMS) were recorded using a SYNAPT G2 HDMS (Waters) spectrometer equipped with a pneumatically assisted atmospheric pressure ionization (API) source. Samples underwent electrospray ionized in positive mode: electrospray tension (ISV): 2800 V; opening tension (OR): 20 V; nebulization gas pressure (nitrogen): 800 L h^{-1}. The parent ion ([M + H]+, [M + Na]+, [M + NH_4]+) was quoted. All reagents were weighted and handled in air at room temperature. All the solvents and reactants for the preparation of the alkoxyamines were used as received from Sigma Aldrich or TCI. Routine reaction monitoring was performed using silica gel 60 F254 TLC plates; the spots were visualized upon exposure to UV light and a p-anisaldehyde solution in EtOH followed by heating. Purifications were performed on chromatography columns with silica gel grade 60 (230–400 mesh). Ozonolyse was performed with a Fisher “Ozone generator Model 500”. For EPR measurements, samples with 0.1 mM concentration of nitroxide were prepared in non-degassed solvents



A(-) A(+)

benzyl 3-acetoxy-3-ethoxy-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propanoate **1**[3]

To a suspension of copper (0.056 g ; 0.88 mmol ; 1.1 eq.) and copper bromide (0.063 g ; 0.44 ; 0.55 eq.) in degassed benzene (7 mL) under argon at room temperature was added PMDETA (0.09 mL ; 0.44mmol ; 0.55 eq.), after 5 minutes of stirring a solution of the previous bromide **12** (0,278 g ; 0,8 mmol ; 1.0 eq.) and TEMPO (0,126 g ; 0,88 mmol ; 1.1 eq.) in degassed benzene (8 mL) was canulated into the first flask. The deep green mixture was stirred overnight. The reaction is monitored by TLC, at the end, the solution is dissolved in EtOAc (50 mL) and washed by a solution of NH_4Cl (50 mL), $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried under $MgSO_4$, filtred and evaporated to dryness. Then the compound is purified by silica gel column chromatography with EtOAc / PE (1/9 : v/v) to get the desired alcoxyamine and some remaining TEMPO, a second silica gel chromatography was performed (DCM / MeOH : 98/2 : v/v) to obtain the pure desired product **1** (0.176 g ; 52 %) as a colorless oil. A laboratory specialized in chiral purification separated the 4 isomers. TLC : AcOEt/EP : 2/8 : v/v – Rf = 0.38 (mixture of isomers). HRMS (ESI) calc. for C23H36NO6+ : 422.2537 [M + H]+ ; found: 422.2538.

Dia A+/- : white solid

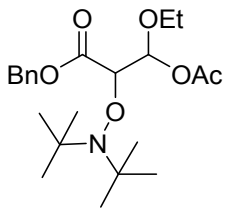
A(-) cristals were obtained from ditethyl ether slow evaporation (4°C)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.29 (m, 5H, H aromatic), 6.05 (d, *J* = 6.8 Hz, 1H, H5), 5.24 – 5.04 (m, 2H, H7), 4.53 (d, *J* = 6.8 Hz, 1H, H3), 3.78 (dd, *J* = 20.6, 7.1 Hz, 2H, H19), 1.81 (s, 3H, H16), 1.65 – 0.93 (m, 21H, H20,23,24,25,27,28,29,30). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.27 (C2), 169.82 (C14), 135.69 (C8), 128.83 (C10,12), 128.62 (C11), 128.38 (C9,13), 95.30 (C5), 85.47 (C3), 66.80 (C19), 66.39 (C7), 61.32 (C22), 59.83 (C26), 40.72 (C23), 40.59 (C25), 33.21 (C29), 32.90 (C30), 20.79 (C16), 20.30 (C28), 20.01 (C27), 17.15 (C24), 15.17 (C20).

Dia B+/- : colorless oil

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.30 (m, 5H, H aromatic), 6.05 (d, *J* = 7.6 Hz, 1H, H5), 5.23 – 5.06 (m, 2H, H7), 4.49 (d, *J* = 7.6 Hz, 1H, H3), 3.81 – 3.37 (m, 2H, H19), 2.11 (s, 3H, H16), 1.67 – 0.92 (m, 21H, H20,23,24,25,27,28,29,30). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.53 (C2), 169.94 (C14), 135.64 (C8), 128.65 (C10,12), 128.58 (C11), 128.36 (C9,13), 95.35 (C5), 84.81 (C3), 66.51 (C19), 66.46 (C7), 61.20

(C22), 59.82 (C26), 40.65 (C23), 40.49 (C25), 33.26 (C29), 32.78 (C30), 21.32 (C16), 20.24 (C28), 19.99 (C27), 17.07 (C24), 14.83 (C20).



benzyl 3-acetoxy-2-((di-tert-butylamino)oxy)-3-ethoxypropanoate **2**[3]

To a suspension of copper (0.174 g ; 2.74 mmol ; 1.1 eq.) and copper bromide (0,197 g ; 2,74 ; 0.55 eq.) in degassed benzene (10 mL) under argon at room temperature was added PMDETA (0,29 mL ; 1,37 mmol ; 0.55 eq.), after 5 minutes of stirring a solution of the previous bromide **12** (0.860 g ; 2.49 mmol ; 1.0 eq.) and DBNO (0,395 g ; 2,74 mmol ; 1.1 eq.) in degassed benzene (10 mL) was canulated into the first flask. The deep green mixture was stirred overnight. The reaction is monitored by TLC, at the end, the solution is dissolved in EtOAc (50 mL) and washed by a solution of NH_4Cl (50 mL), $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried under $MgSO_4$, filtred and evaporated to dryness. Then the compound was purified by silica gel column chromatography with EtOAc / PE (1/9 : v/v) to obtain the pure desired product **2** with some nitroxyde. The remaining DBNO was removed under vacuum at 40°C to get the pure alkoxyamine (0,530 g ; 52%) as a colorless oil. TLC : EtOAc/PE : 2/8 : v/v. Rf = 0.38. HRMS (ESI) calc. for C23H36NO6+ : 410.2537 [M + H]+ ; found: 410.2531.

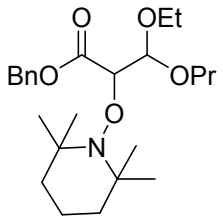
Dia A+/- : colorless oil

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.24 (m, 5H, H aromatic), 6.11 (d, *J* = 6.6 Hz, 1H, H4), 5.13 (s, 2H, H22), 4.58 (d, *J* = 6.6 Hz, 1H, H2), 3.90 – 3.61 (m, 2H, H29), 1.84 (s, 3H, H26), 1.29 (s, 9H, H9,13,14), 1.20 (t, *J* = 7.1 Hz, 3H, H28), 1.17 (s, 9H, H8,11,12). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.28 (C1), 169.55 (C25), 135.60 (C16), 128.78 (C18,20), 128.56 (C19), 128.34 (C17,21), 95.09 (C4), 85.71 (C2), 66.54 (C29), 66.36 (C22), 63.45 (C7), 62.14 (C10), 30.22 (C9,13,14), 30.14 (C8,11,12), 20.79 (C26), 15.11 (C28).

Dia B+/- : colorless oil

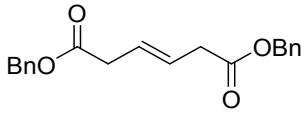
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.31 (m, 5H, H aromatic), 6.11 (d, *J* = 7.3 Hz, 1H, H4), 5.17 (d, *J* = 3.5 Hz, 2H, H22), 4.53 (d, *J* = 7.3 Hz, 1H, H2), δ 3.71 (m, 1H, H29), 3.49 (m, 1H, H29), 2.08 (s, 3H, H26), 1.28 (s, 9H, H9,13,14), 1.16 (s, 9H, H8,11,12), 1.03 (t, *J* = 7.1 Hz, 3H, H28). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.53 (C1), 169.54 (C25), 135.63 (C16), 128.67 (C18,20), 128.57 (C19), 128.36 (C17,21), 95.40 (C4),

85.05 (C2), 66.53 (C29), 66.43 (C22), 63.36 (C7), 62.26 (C10), 30.24 (C9,13,14), 30.19 (C8,11,12), 21.30 (C26), 14.88 (C28).



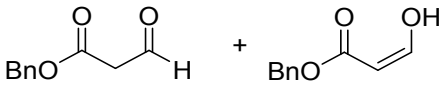
benzyl 3-ethoxy-3-propoxy-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propanoate **6**[3]

To a suspension of copper (0.169 g ; 2.67 mmol ; 1.1 eq.) and copper bromide (0.191 g ; 1.34 ; 0.55 eq.) in degassed benzene (10 mL) under argon at room temperature was added PMDETA (0.27 mL ; 1.34 mmol ; 0.55 eq.), after 5 minutes of stirring a solution of the previous bromide **20** (0,837 g ; 2.4 mmol ; 1.0 eq.) and TEMPO (0.417 g ; 2.67 mmol ; 1.1 eq.) in degassed benzene (10 mL) was canulated into the first flask. The deep green mixture was stirred overnight. The reaction is monitored by TLC, at the end, the solution is dissolved in EtOAc (50 mL) and washed by a solution of saturated NH_4Cl (50 mL), $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried under $MgSO_4$, filtred and evaporated to dryness. Then the compound is purified by silica gel column chromatography with EtOAc/PE (1/9 : v/v) to get the desired alcoxyamine and some remaining TEMPO, a second silica gel chromatography was performed (DCM / MeOH : 98/2 : v/v) to obtain the pure desired product **6** (0.837 g ; 83 %) as a colorless oil. A laboratory specialized in chiral purification separated the 4 isomers. TLC : AcOEt/PE : 2/8 : v/v – Rf = 0.53. HRMS (ESI) calc. for $C_{24}H_{40}NO_5^+$: 422.2901 [M + H]+ ; found: 422.2896. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.29 (m, 5H, H aromatic), 5.13 (d, *J* = 7.0 Hz, 2H, H20), 4.66 (dd, *J* = 7.3, 4.4 Hz, 1H, H5), 4.45 (dd, *J* = 7.3, 4.6 Hz, 1H, H3), 3.83 – 3.25 (m, 4H, H8,10), 1.70 – 0.76 (m, 26H, H9,11,12,16,17,18,27,28,29,30). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.16 (C2), 135.88 (C22), 128.50 (C24), 128.17 (C22,23,25,26), 102.95 (C5majo), 102.91 (C5mino), 86.22 (C3), 71.61 (C10mino), 70.31 (C10majo), 66.26 (C20majo), 66.20 (C20mino), 65.45 (C8majo), 63.98 (C8mino), 61.29 (C15), 59.58 (C19), 40.77 (C16), 40.68 (C18), 33.18 (C30), 33.04 (C29), 23.24 (C11majo), 22.94 (C11mino), 20.38 (C27), 20.11 (C28), 17.16 (C17), 15.40 (C9majo), 15.16 (C9mino), 10.78 (C12mino), 10.60 (C12majo).



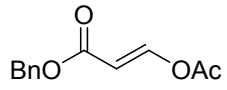
dibenzyl (E)-hex-3-enedioate **9**[1]

To a suspension of trans-beta-hydromucanic acid **8** (3.593 g ; 24.5 mmol ; 1.0 eq.) in DCM (50 mL) under Argon at 0°C was added oxalyl chloride (3.6 mL ; 49.0 mmol ; 2 eq.), and one drop of DMF. After one hour, the solution was heated to 35°C overnight. The mixture was redisolved in DCM (50 mL) and evaporated under vacuo twice to give a red slurry oil. The di-acyl chloride was dissolved in DCM (50 mL) and added drop by drop over 2 hours to a solution of DCM (100 mL), Et_3N (10.2 mL ; 73.5 mmol ; 3 eq.) and Benzyl alcohol (7.5 mL ; 73.5 mmol ; 3 eq.) at 0°C under Argon, then the solution was stirred overnight at room temperature. The mixture was diluted in Et_2O (250 mL) and washed by distilled water (150 mL), HCl 1M (150 mL), $NHCO_3$ sat. (150 mL) and brine (150 mL). The organic layer was dried by $MgSO_4$, filtered and evaporated to dryness. The crude was directly purified by silica gel column chromatography (EtOAc / PE : 1/9 : v/v) to afford the pure compound **9** as a colorless oil (5.2708 g, 66 %) TLC : EtOAc / PE : 2/8 : v/v - Rf : 0.45. 1H NMR (400 MHz, CDCl3) δ 7.33 (s, 10H, H aromatic), 5.71 (m, 2H, H5,6), 5.10 (s, 4H, H11,13), 3.12 (d, J = 5.4 Hz, 4H, H3,7).



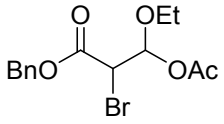
benzyl 3-oxopropanoate **10** ; benzyl (Z)-3-hydroxyacrylate **10'**[1]

The di-ester **9** (1.700 g ; 5.24 mmol ; 1 eq.) was dissolved in DCM (100 mL) and cooled at -78°C, then a small amount of red Soudan was added and Ozone was bubbled inside. When the solution became blue, Argon was bubbled in the solution, and dimethylsulfide (0.9 mL ; 13.1 mmol ; 2.5 eq.) was added. After 3 hours, the reaction was over, and the solution was washed by water (100 mL). The organic layer was dried by $MgSO_4$, filtered and evaporated to dryness and afford 1.675 g of curde as a colorless oil. The aldehyde is directly used in the next reaction without further purification. TLC : AcOEt/PE : 2/8 : v/v – Drag (from 0 to 0.3). 1H NMR (300 MHz, CDCl3) δ 11.34 (d, J = 12.9 Hz, 0.4H, H6), 9.83 (t, J = 2.4 Hz, 0.6H, H19), 7.45 – 7.31 (m, 10H, H aromatic, H_{BnOH} aromatic), 7.13 (dd, J = 12.9, 6.0 Hz, 0.4H, H5), 5.24 – 5.16 (m, 4H, H7,20, H_{BnOH}), 5.15 (d, J = 6.0 Hz, 0.4H, H3), 3.44 (d, J = 2.4 Hz, 1.3H, H16).



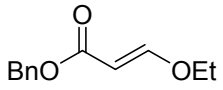
benzyl (E)-3-acetoxyacrylate **11**[1]

To a stirred solution of **10** and **10'** (2.200 g ; 12.4 mmol ; 1.0 eq.) in THF (40 mL) at 0°C under argon was added DIPEA (3.2 mL, 18.5 mmol, 1.5 eq.) and acetic anhydride (2.1 mL, 18.5 mmol, 1.5 eq) in one portion. The mixture was stirring and monitored by TLC, after 6 hours the mixture was disolved in Et_2O and quenched with a solution of NH_4Cl 1M (50 mL), the aqueous phase was extracted with Et_2O (2*100 mL). The combined organic layers were mixed and dried under MgSO4, filtered and evaporated to dryness. The crude was directly purified by silica gel column chromatography (Et_2O / PE : 1 / 9 : v/v) to get the purified compound **11** (1.107 g ; 41 %) as a colorless oil. Isomers were not separated. TLC : AcOEt/PE : 2/8 : v/v – Rf = 0.35. HRMS (ESI) calc. for C12H12O4Na + : 243.0628 [M + Na]+ ; found: 243.0627. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, *J* = 12.5 Hz, 1H, H4), 7.37 (m, 5H, H aromatic), 5.77 (d, *J* = 12.5 Hz, 1H, H2), 5.20 (s, 2H, H12), 2.21 (s, 3H, H16). ^{13}C NMR (75 MHz, CDCl3) δ 166.82 (C15), 166.16 (C1), 149.96 (C4), 135.93 (C6), 128.69 (C8,10), 128.40 (C9), 128.37 (C7,11), 105.72 (C2), 66.41 (C12), 20.61 (C16).



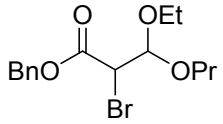
benzyl 3-acetoxy-2-bromo-3-ethoxypropanoate **12**[2]

To a solution of **11** (0.500 g, 2.27 mmol, 1.0 eq.) in absolute ethanol (15 mL) under argon at room temperature is added in 3 equal portion NBS (0.445 g, 2.5 mmol, 1.1 eq) in 30 minutes, after each addition the mixture is turning yellow and orange, when the solution turned colorless a new portion of NBS was added, after the last addition it stayed deep orange. The solution was stirred 2 hours. At the end, the reaction was dissolved in Et_2O (60 mL) and quenched with water (60 mL). The organic layer was dried with $MgSO_4$, filtered, and evaporated to dryness to get a crude product. The crude was directly purified by silica gel chromatography (Et_2O / PE : 1 / 9 : v/v) to get the purified compound **12** (0.352 g, 45 %) as a colorless oil. Isomers was not separated. TLC : AcOEt/PE : 2/8 : v/v – Rf = 0.43. HRMS (ESI) calc. for C14H21NO5Br+ : 362.0598 [M + NH_4]+ ; found: 362.0596. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 5H, H aromatic), 6.17 (d, *J* = 7.9 Hz, 1H, H4), 5.22 (m, 2H, H12), 4.31 (d, *J* = 7.9 Hz, 1H, H2), 3.68 (m, 2H, H19), 2.11 (s, 3H, H16), 1.07 (t, *J* = 7.1 Hz, 3H, H20). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.37(C1), 166.71 (C15), 135.00 (C6), 128.67 (C8,10), 128.63 (C9), 128.41 (C7,11), 95.39 (C4), 67.80 (C12), 66.99 (C19), 44.49 (C2), 20.87 (C16), 14.83 C(20).



benzyl (E)-3-ethoxyacrylate **19**[4]

To a solution of Benzyl acetate **17** (1.500 g ; 10 mmol ; 1 eq) in dichloromethane (40 mL) under argon at -15°C is added successively ethyl formiate **18** (2.66 mL ; 33mmol, 3.3 eq), triethylamine (3.62 mL ; 26 mmol ; 2.6 eq) in one portion. Then $TiCl_4$ (3,74 mL ; 34 mmol ; 3,4 eq) is added drop by drop. After 3 hours at -15°C, the reaction is complete and the mixture is dissolved in EtOAc (100 mL) and quenched with water (100 mL). The aqueous layer is extracted by EtOAc (2*50 mL) and the combined organic layers are washed by brine (150 mL). The organic layer is dryed by $MgSO_4$, filtered and evaporated to afford a crude oil. After a purification by silica gel chromatography column (EtOAc/PE : 1/9 : v/v) **19** is obtained as a colorless oil (1.509 g ; 72%). TLC : EtOAc/PE : 2/8 : v/v. Rf = 0.6. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 12.7 Hz, 1H, H4), 7.43 – 7.27 (m, 4H, H aromatic), 5.25 (d, *J* = 12.6 Hz, 1H, H2), 5.16 (s, 2H, H12), 3.91 (q, *J* = 7.1 Hz, 2H, H15), 1.34 (t, *J* = 7.1 Hz, 3H, H14).



benzyl 2-bromo-3-ethoxy-3-propoxypropanoate **20**[2]

To a solution of **19** (0.100 g, 0.49 mmol, 1.0 eq.) in n-propanol (8 mL) under argon at room temperature is added in 2 equal portion NBS (0.094 g, 0.54 mmol, 1.1 eq) in 10 minutes, and the solution was allowed to stir 2 hours. At the end, the reaction was dissolved in Et_2O (20 mL) and quenched with water (20 mL). The organic layer was dried with $MgSO_4$, filtered, and evaporated to dryness to get a crude product. The crude was directly purified by silica gel chromatography (Et_2O / Petroleum ether : 1 / 9 : v/v) to get the purified compound **20** (0.160 g, 96 %) as a colorless oil. Isomers was not separated. TLC : AcOEt/PE : 2/8 : v/v – Rf = 0.65. HRMS (ESI) calc. for $C_{15}H_{22}O_4Br^+$: 345.0696 [M + H]+ ; found: 345.0695.^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.31 (m, 5H, H aromatic), 5.21 (d, *J* = 1.2 Hz, 2H, H13), 4.88 (d, *J* = 8.3 Hz, 1H, H4), 4.29 (d, *J* = 8.3 Hz, 1H, H2), 3.80 – 3.34 (m, 4H, H17,20), 1.49 (m, 2H, H16), 1.24 (t, *J* = 7.0 Hz, 3H, H19), 0.85 (d, *J* = 7.4 Hz, 3H, H15). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.65 (C1), 135.14 (C7), 128.57 (C9,11), 128.44 (C10), 128.23 (C8,12), 102.01 (C4), 70.27 (C17), 67.49 (C13), 62.71 (C20), 44.86 (C2), 22.80 (C16), 15.12 (C19), 10.43 (C15).

HPLC separation :

Analytical and preparative HPLC experiments were performed on an Agilent 1260 Infinity unit (pump G1311B, autosampler G1329B, DAD G1315D), with a Jasco CD-1595 circular dichroism chiral detector. The analytical (250 x 4.6 mm, 5 µm) and preparative (250 x 10 mm, 5 µm) chiral columns, Chiralpak ID, Chiralpak IE and (*S*,*S*)-Whelk-O1 were purchased from Chiral Technologies Europe (Illkirch, France) and Regis Technologies (Morton Grove, USA).

The four isomers of **1** were separated by preparative HPLC on chiral supports (analytical conditions: 95:5 heptane: 2-PrOH at 1 mL/min flow rate, Chiralpak IE, **1A-**, R_t = 5.59 min, **1A+**, R_t = 5.83 min, **1B+**, R_t = 6.77 min, **1B-**, R_t = 9.04 min, and (*S*,*S*)-Whelk-O1, **1A-**, R_t = 6.52 min, **1A+**, R_t = 7.12 min).

Optical rotations were measured on a Jasco P-2000 polarimeter with a sodium lamp (589 nm), a halogen lamp (578, 546, 436, 405, 365 and 325 nm), in a 10 cm cell, thermostated at 25°C with a Peltier controlled cell holder.

λ (nm)	Dia A ; first eluted on Chiralpak IE $[\alpha]_\lambda^{25}$ (CH_2Cl_2, c =1.06)	Dia A ; second eluted on Chiralpak IE $[\alpha]_\lambda^{25}$ (CH_2Cl_2, c =0.32)
589	- 77	+ 77
578	- 80	+ 80
546	- 92	+ 92
436	- 159	+ 159
405	- 195	+ 195
365	- 268	+ 269
325	- 353	+ 356

λ (nm)	Dia B ; first eluted on Chiralpak IE $[\alpha]_\lambda^{25}$ (CH_2Cl_2, c =0.29)	Dia B ; second eluted on Chiralpak IE $[\alpha]_\lambda^{25}$ (CH_2Cl_2, c =0.33)
589	+ 71	- 71
578	+ 73	- 75
546	+ 85	- 87
436	+ 148	- 149
405	+ 182	- 182

365	+ 253	- 252
325	+ 337	- 335

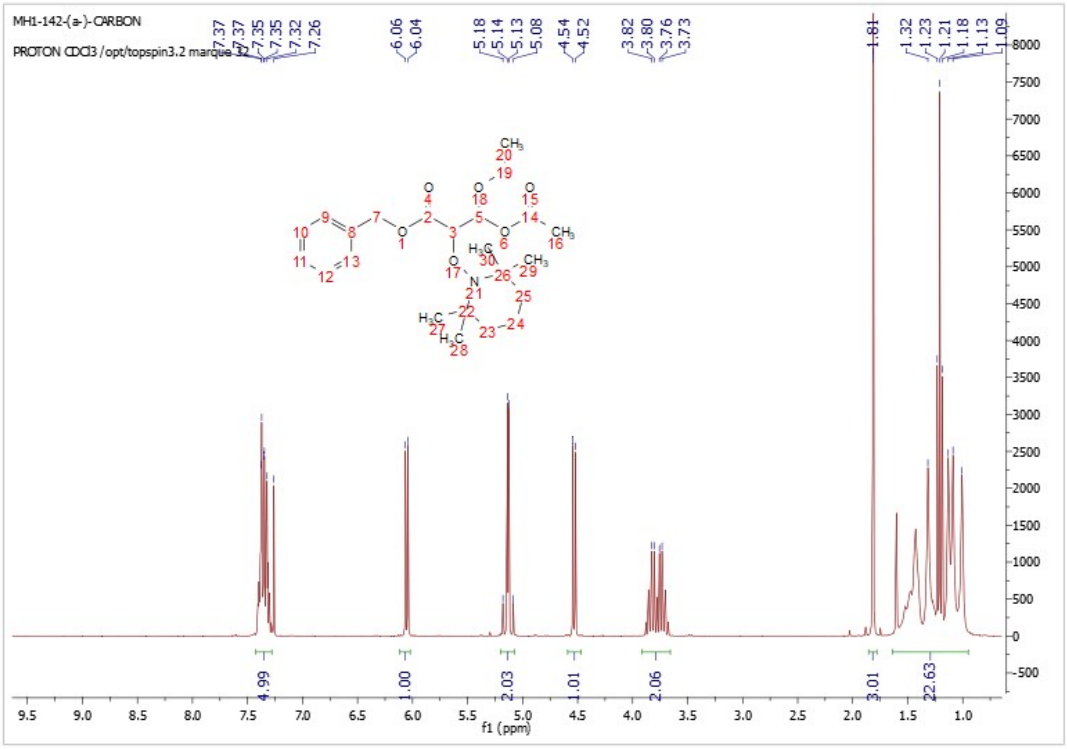
The four isomers of **2** were separated by preparative HPLC on chiral supports (analytical conditions: 95:5 heptane: 2-PrOH at 1 mL/min flow rate, Chiralpak IE, **2A-**, R_t = 5.25 min, **2A+**, R_t = 5.42 min, **2B+**, R_t = 5.92 min, **2B-**, R_t = 7.22 min, and Chiralpak ID, **2A-**, R_t = 4.83 min, **2A+**, R_t = 5.47 min).

Optical rotations were measured on a Jasco P-2000 polarimeter with a sodium lamp (589 nm), a halogen lamp (578 and 546 nm), in a 10 cm cell, thermostated at 25°C with a Peltier controlled cell holder.

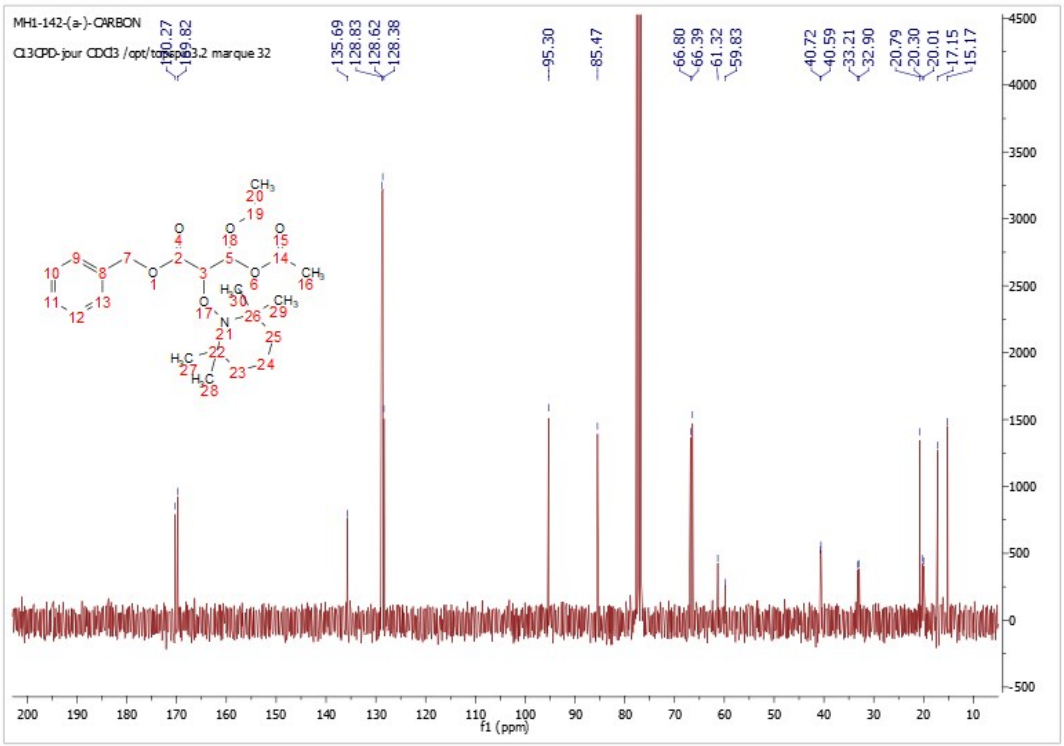
λ (nm)	Dia A ; first eluted on Chiralpak IE $[\alpha]_\lambda^{25}$ (CH_2Cl_2, c = 0.19)	Dia A ; second eluted on Chiralpak IE $[\alpha]_\lambda^{25}$ (CH_2Cl_2, c = 0.165)
589	+ 62	- 62
578	+ 62.5	- 62.5
546	+ 72	- 73
436	+ 126	- 127
405	+ 155	- 155
365	+ 218	- 218
325	+ 300	- 299

λ (nm)	Dia B ; first eluted on Chiralpak ID $[\alpha]_\lambda^{25}$ (CH_2Cl_2, c = 0.196)	Dia B ; second eluted on Chiralpak ID $[\alpha]_\lambda^{25}$ (CH_2Cl_2, c = 0.224)
589	- 80	+ 80
578	- 84	+ 84
546	- 97	+ 97
436	- 165	+ 166
405	- 202	+ 203
365	- 279	+ 279
325	- 374	+ 375

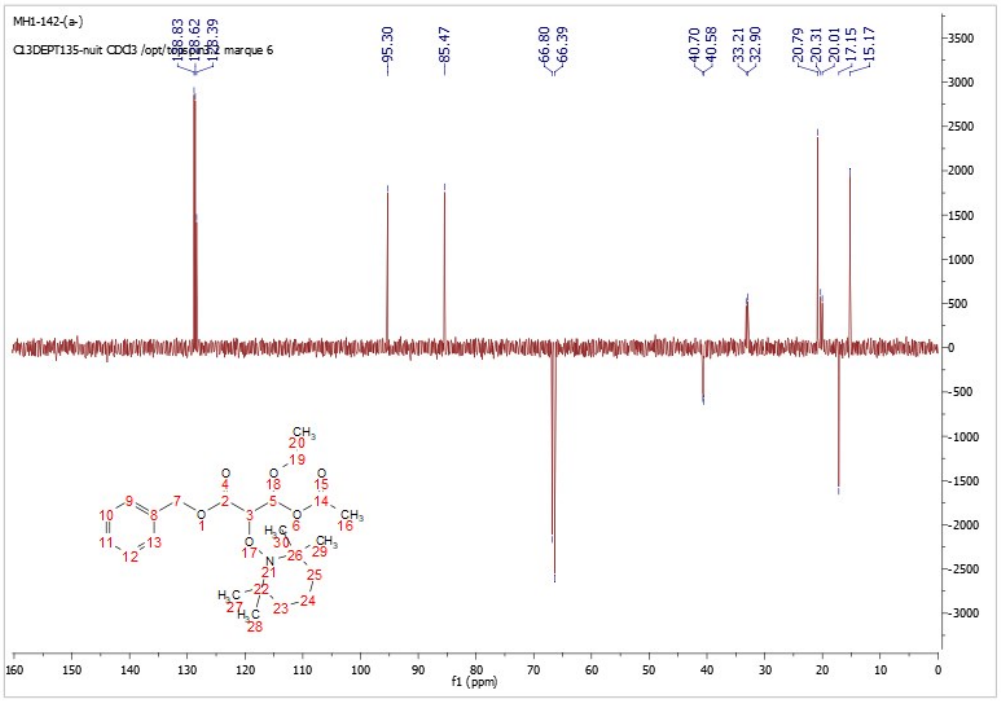
1. NMR (^{1}H ; ^{13}C ; DEPT135 ; HSQC) and HRMS spectra



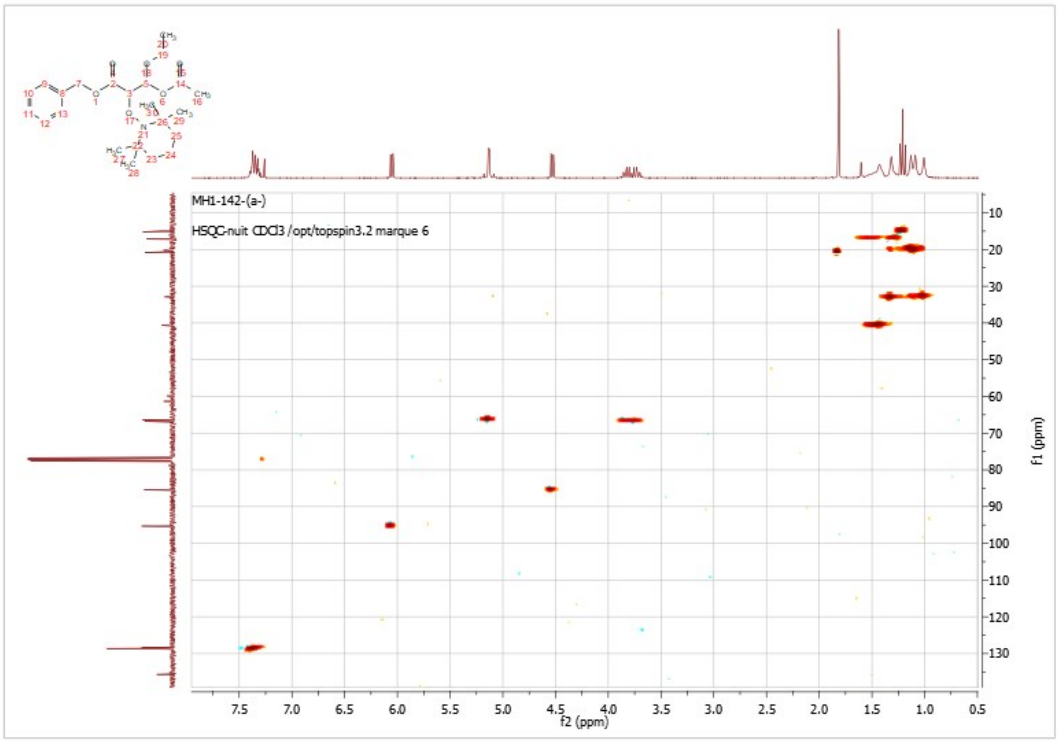
^{1}H : benzyl 3-acetoxy-3-ethoxy-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propanoate **1** (DiaA+/-)



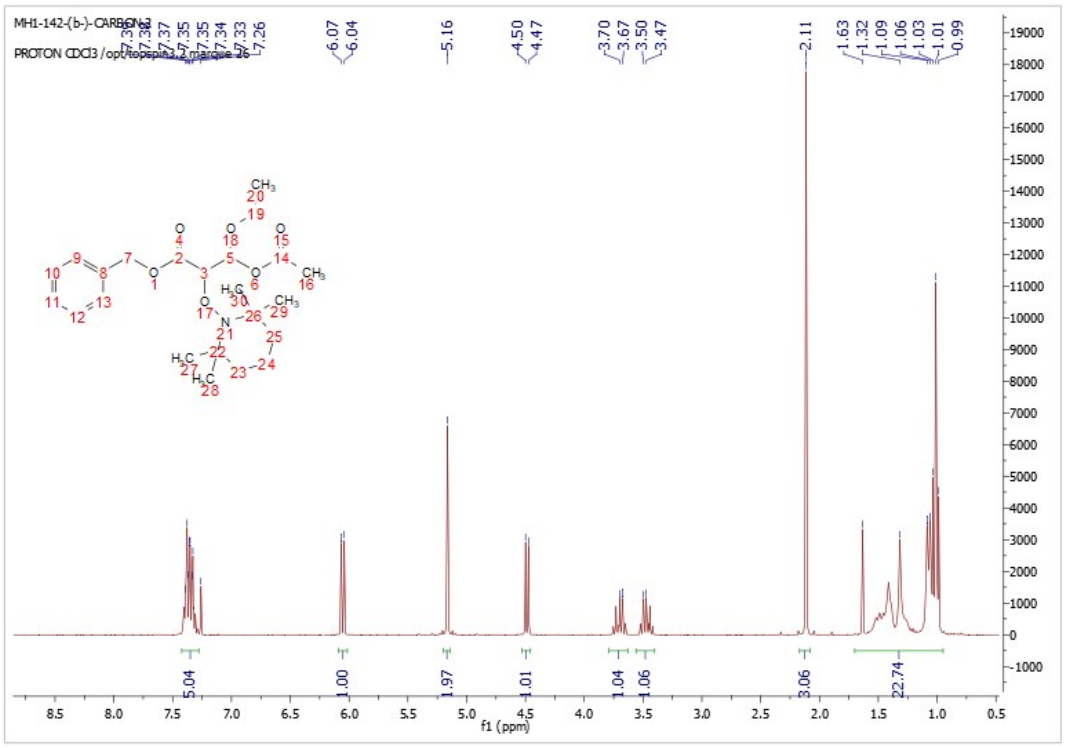
^{13}C : benzyl 3-acetoxy-3-ethoxy-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propanoate **1** (DiaA+/-)



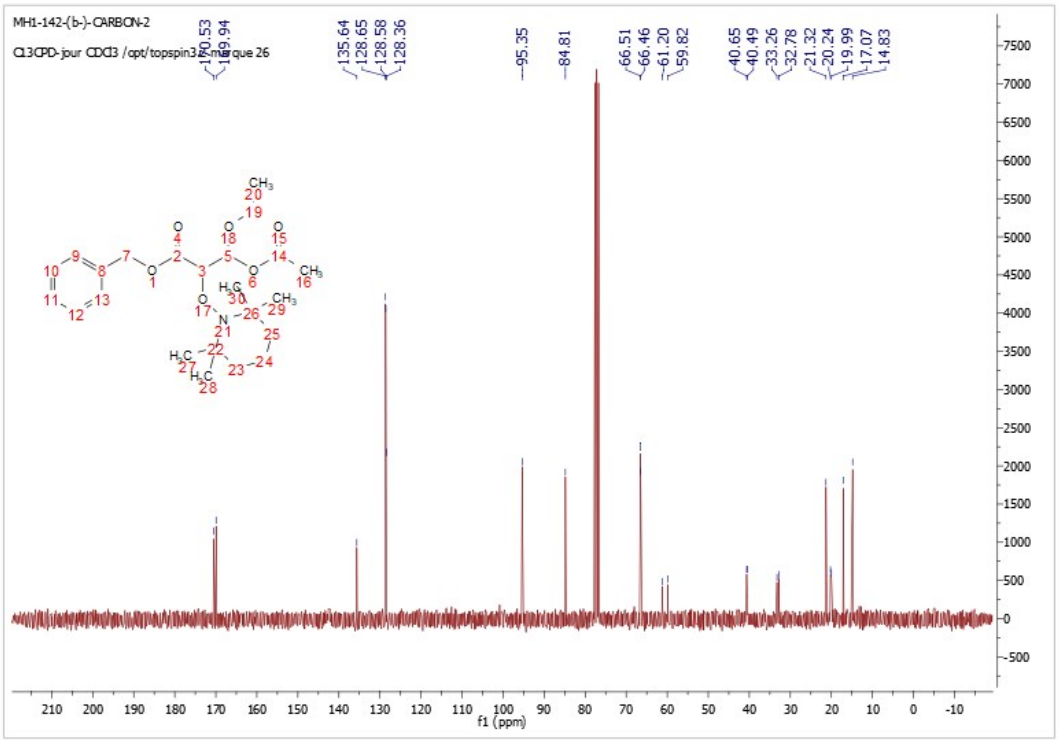
DEPT 135 : benzyl 3-acetoxy-3-ethoxy-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propanoate **1** (DiaA+/-)



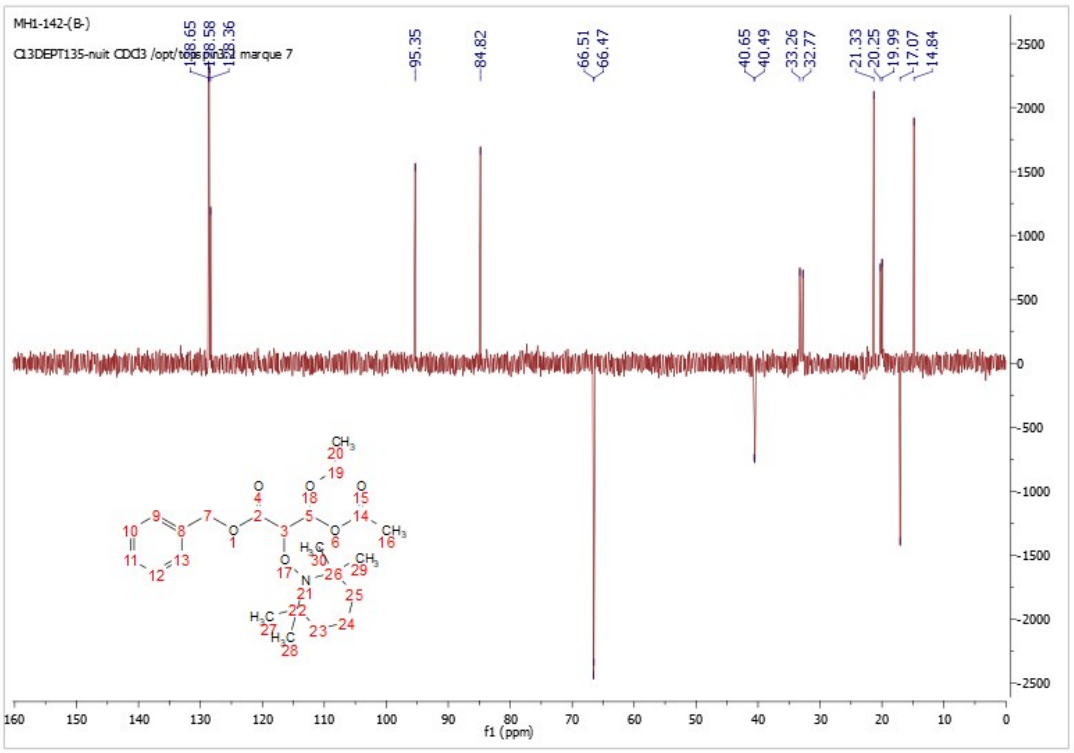
HSQC : benzyl 3-acetoxy-3-ethoxy-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propanoate **1** (DiaA+/-)



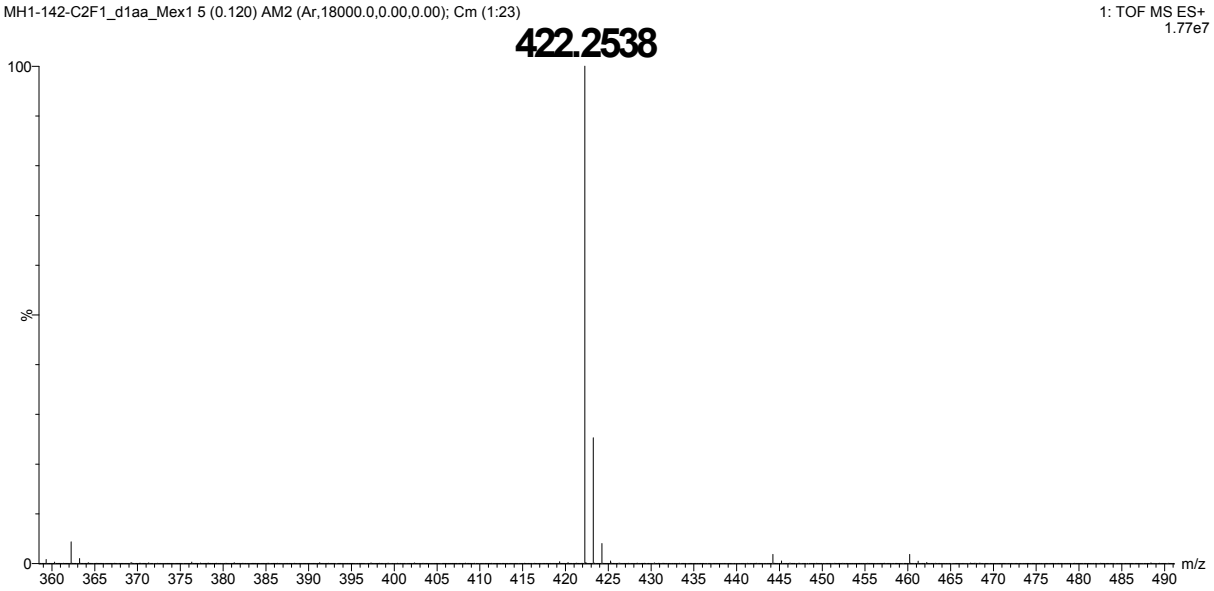
^{1}H : benzyl 3-acetoxy-3-ethoxy-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propanoate **1** (DiaB+/-)



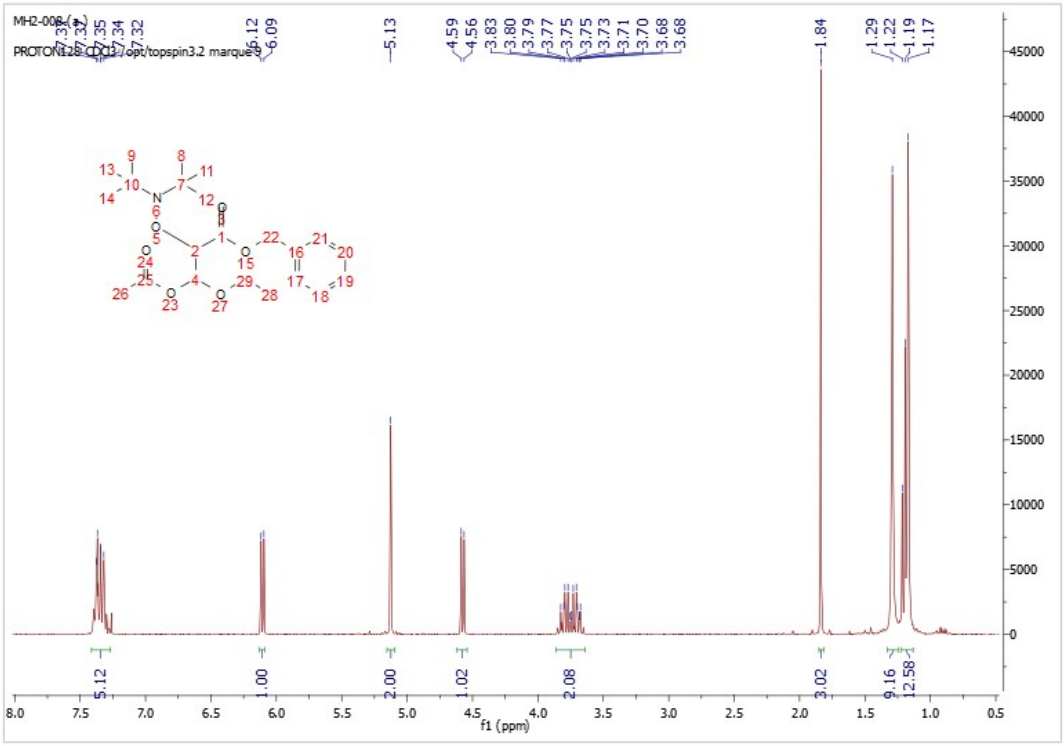
^{13}C : benzyl 3-acetoxy-3-ethoxy-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propanoate **1** (DiaB+/-)



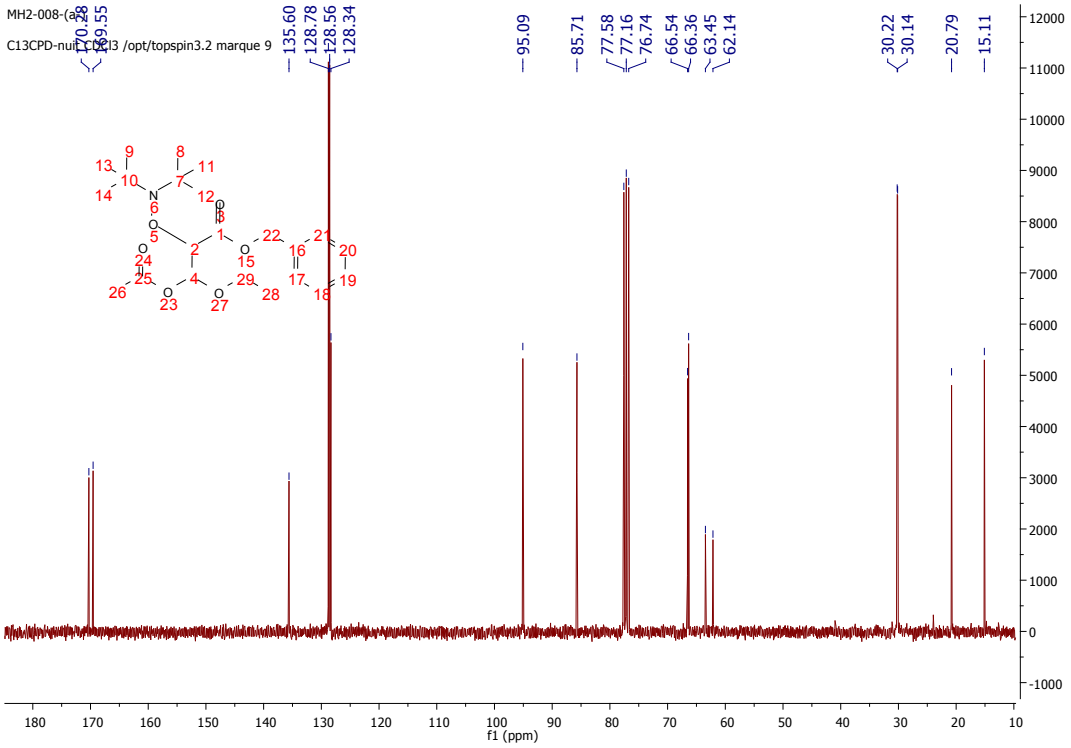
DEPT 135 : benzyl 3-acetoxy-3-ethoxy-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propanoate **1** (DiaB+/-)



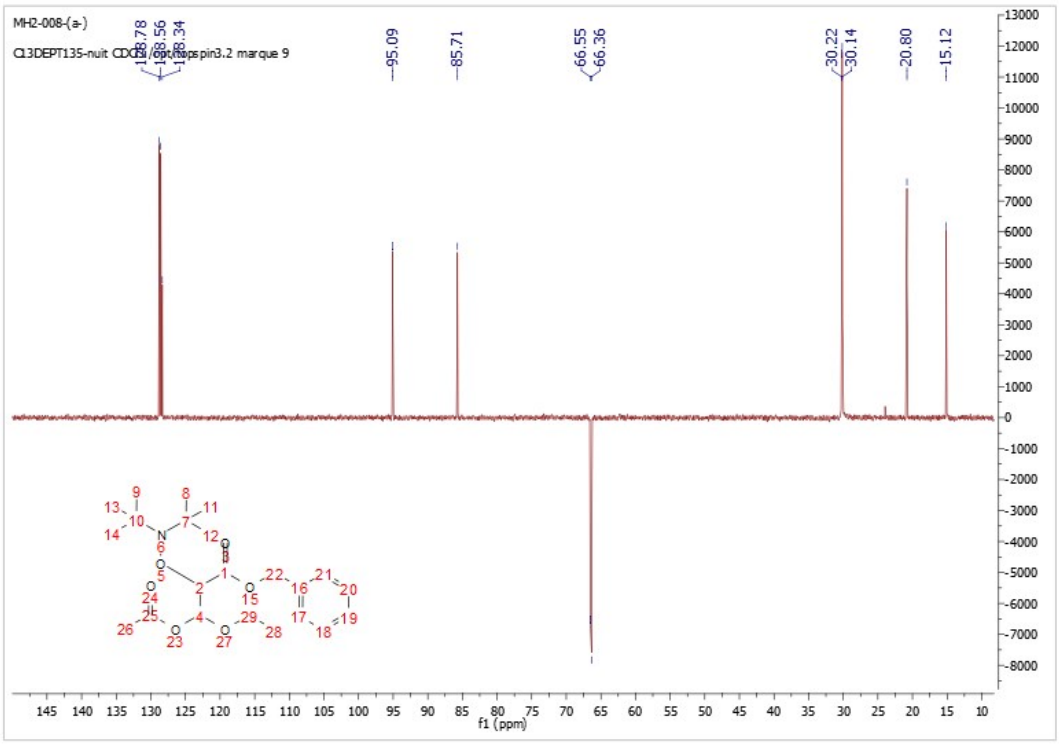
HRMS : benzyl 3-acetoxy-3-ethoxy-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propanoate **1**



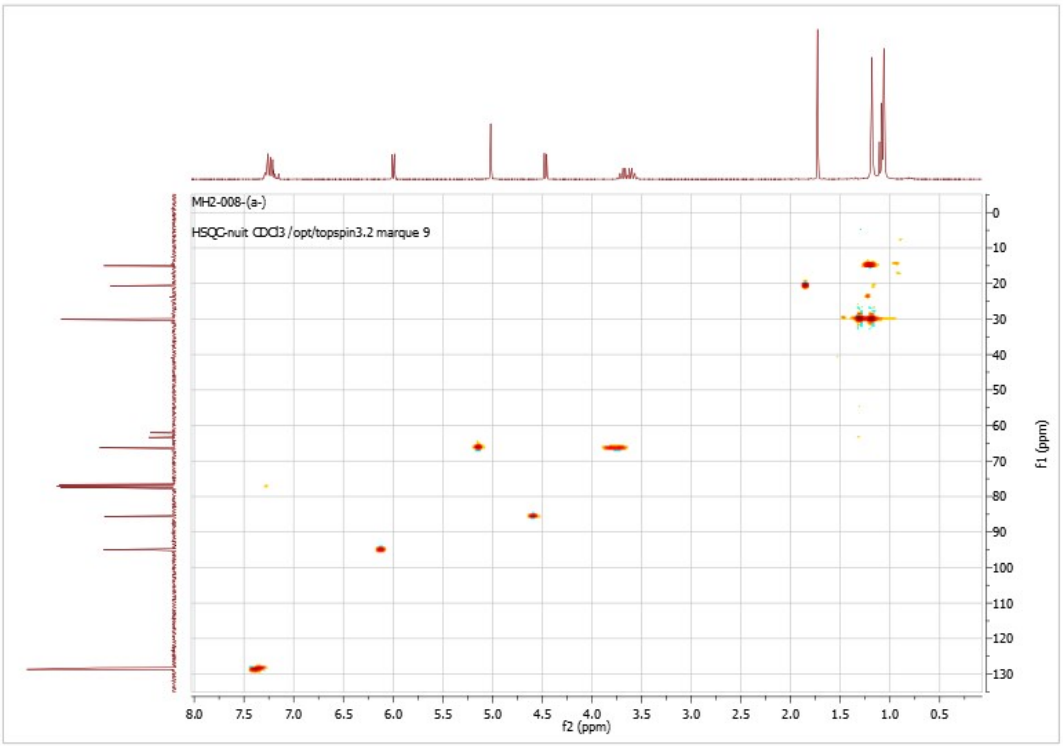
^{1}H : benzyl 3-acetoxy-2-((di-tert-butylamino)oxy)-3-ethoxypropanoate **2** (DiaA+/-)



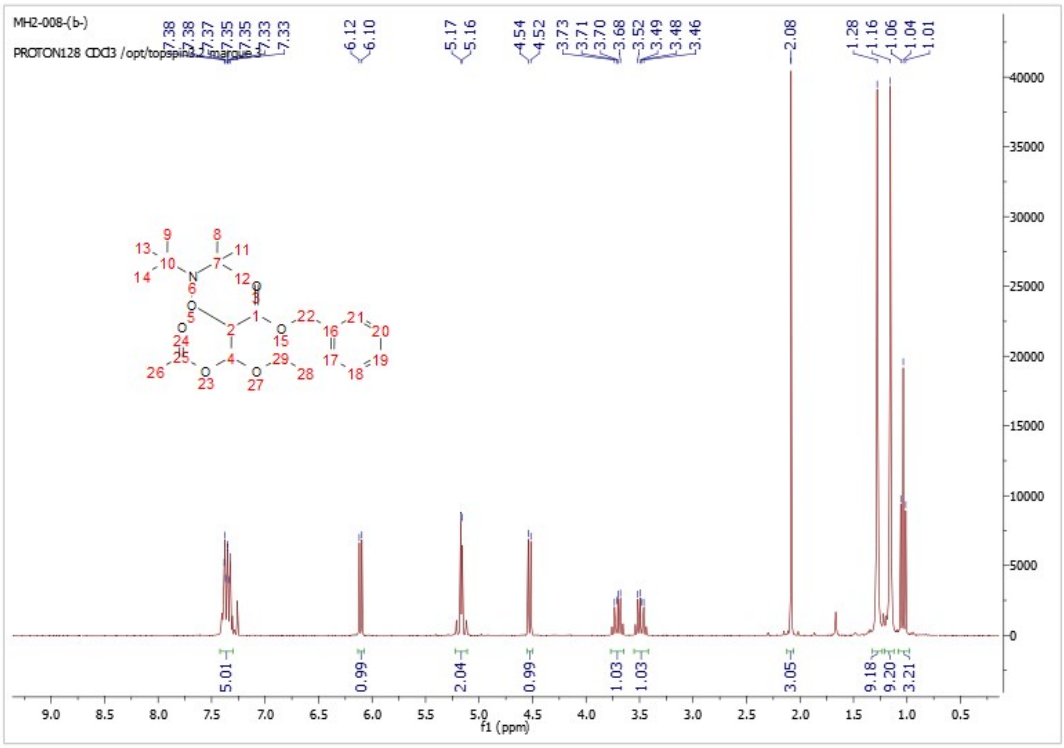
^{13}C : benzyl 3-acetoxy-2-((di-tert-butylamino)oxy)-3-ethoxypropanoate **2** (DiaA+/-)



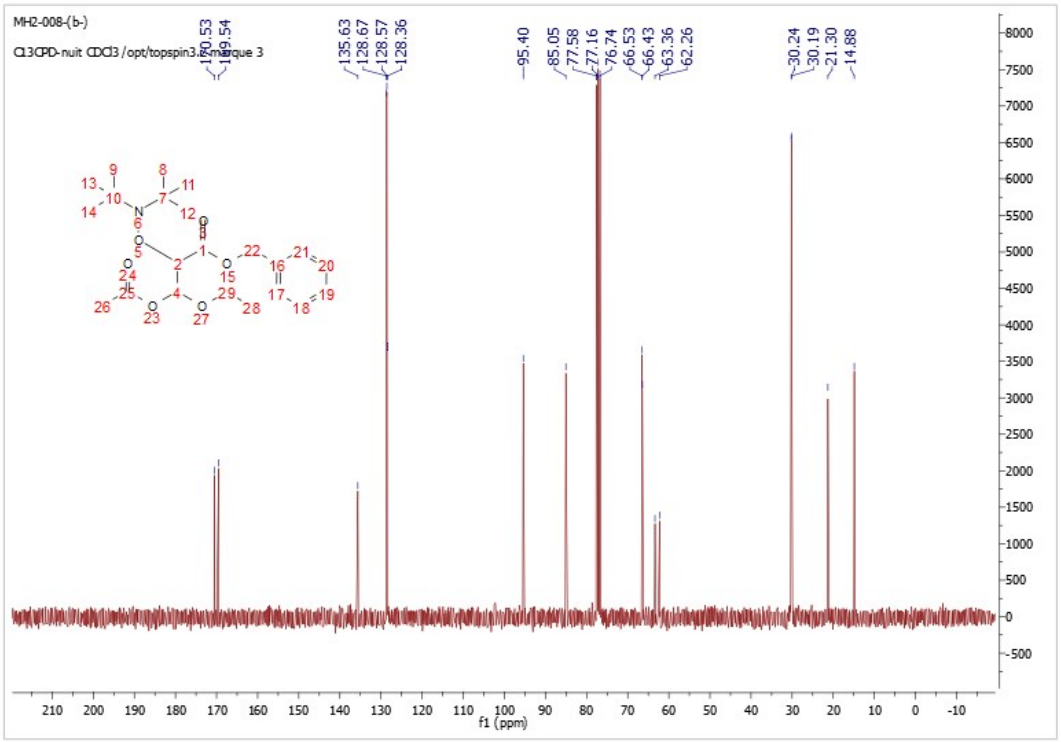
DEPT 135 : benzyl 3-acetoxy-2-((di-tert-butylamino)oxy)-3-ethoxypropanoate **2** (DiaA+/-)



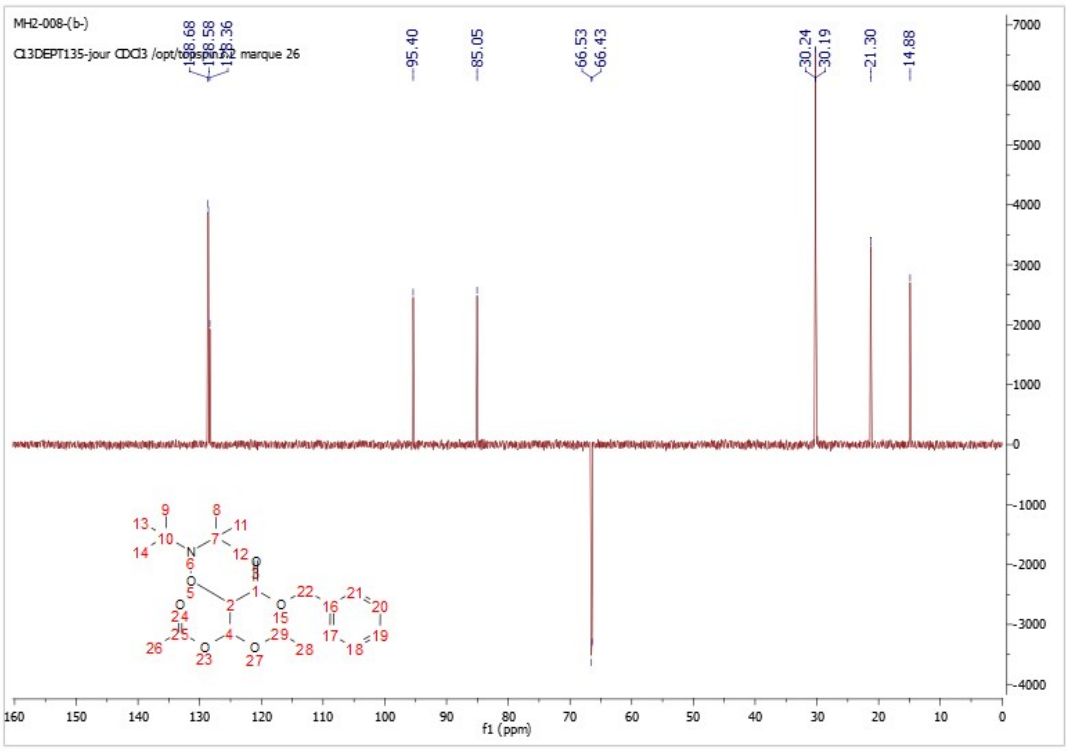
HSQC : benzyl 3-acetoxy-2-((di-tert-butylamino)oxy)-3-ethoxypropanoate **2** (DiaA+/-)



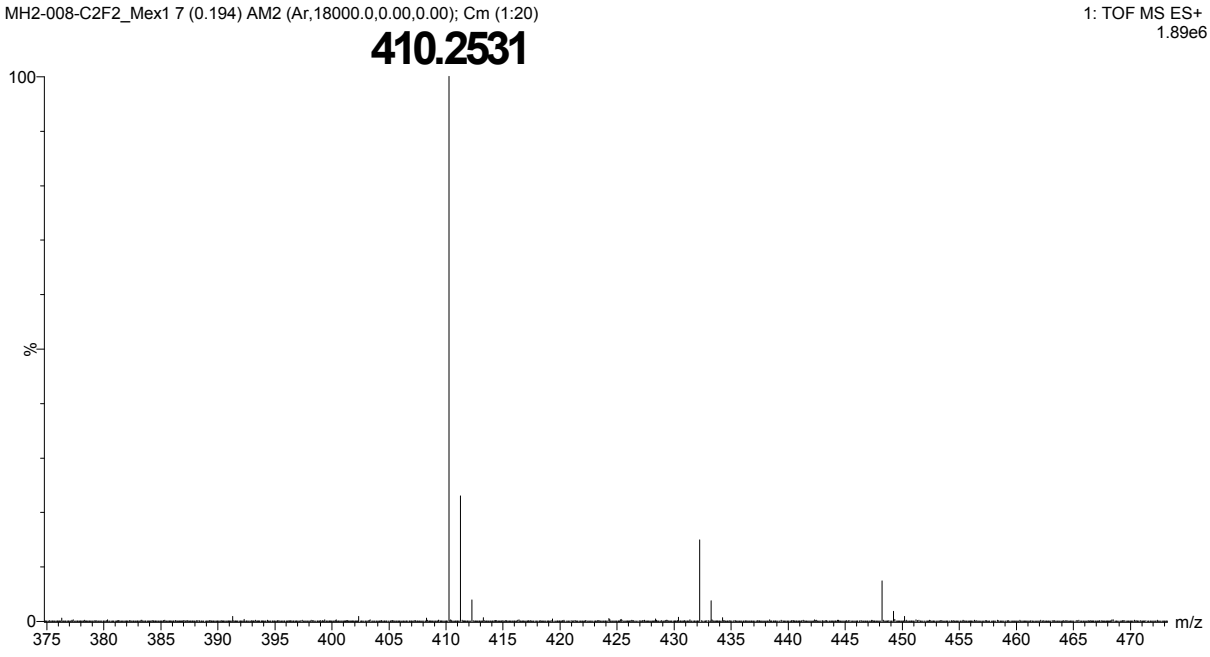
^{1}H : benzyl 3-acetoxy-2-((di-tert-butylamino)oxy)-3-ethoxypropanoate **2** (DiaB+/-)



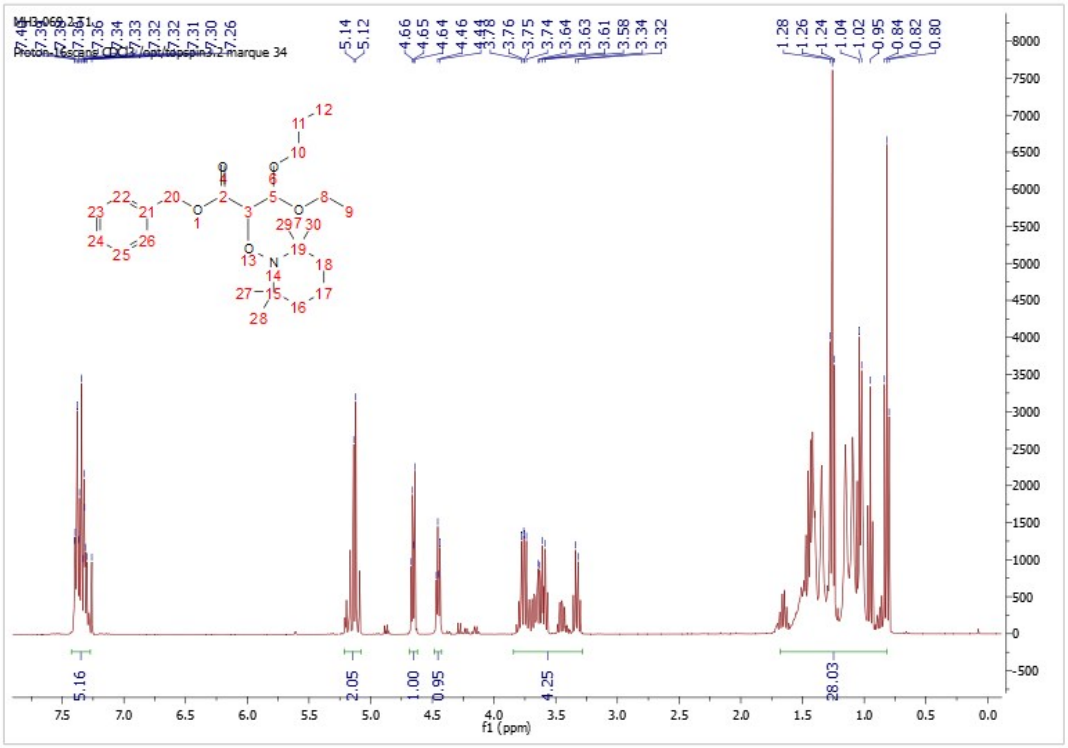
^{13}C : benzyl 3-acetoxy-2-((di-tert-butylamino)oxy)-3-ethoxypropanoate **2** (DiaB+/-)



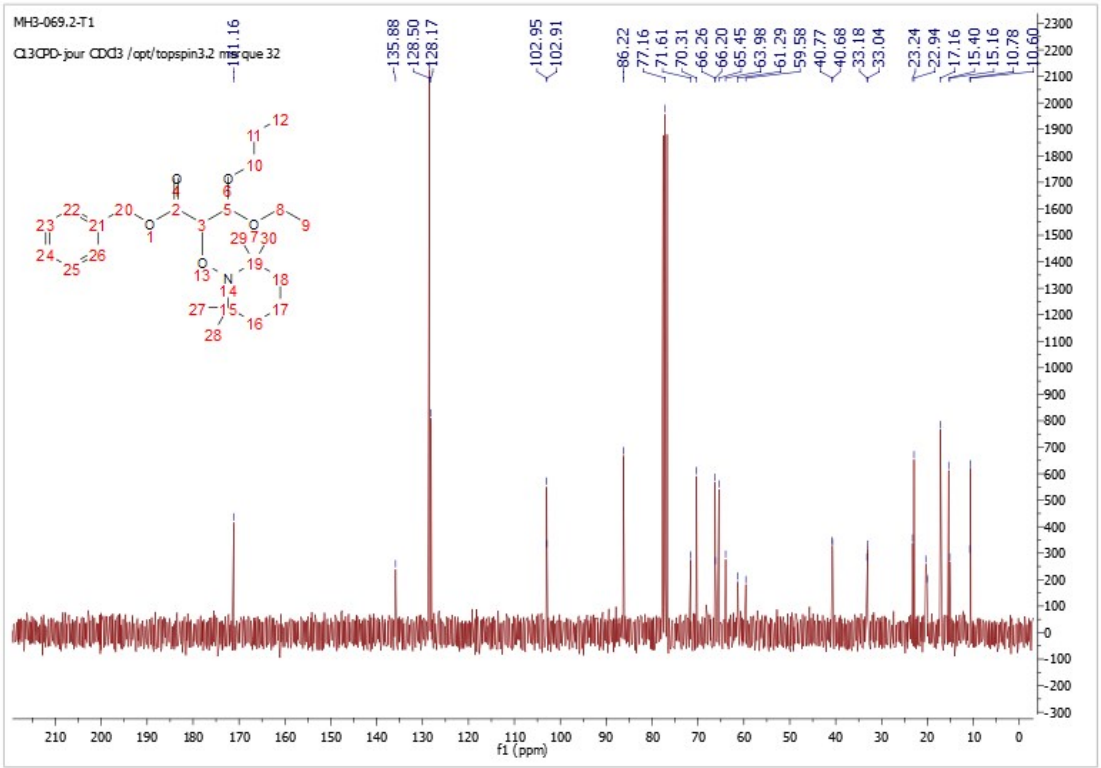
DEPT 135 : benzyl 3-acetoxy-2-((di-tert-butylamino)oxy)-3-ethoxypropanoate **2** (DiaB+/-)



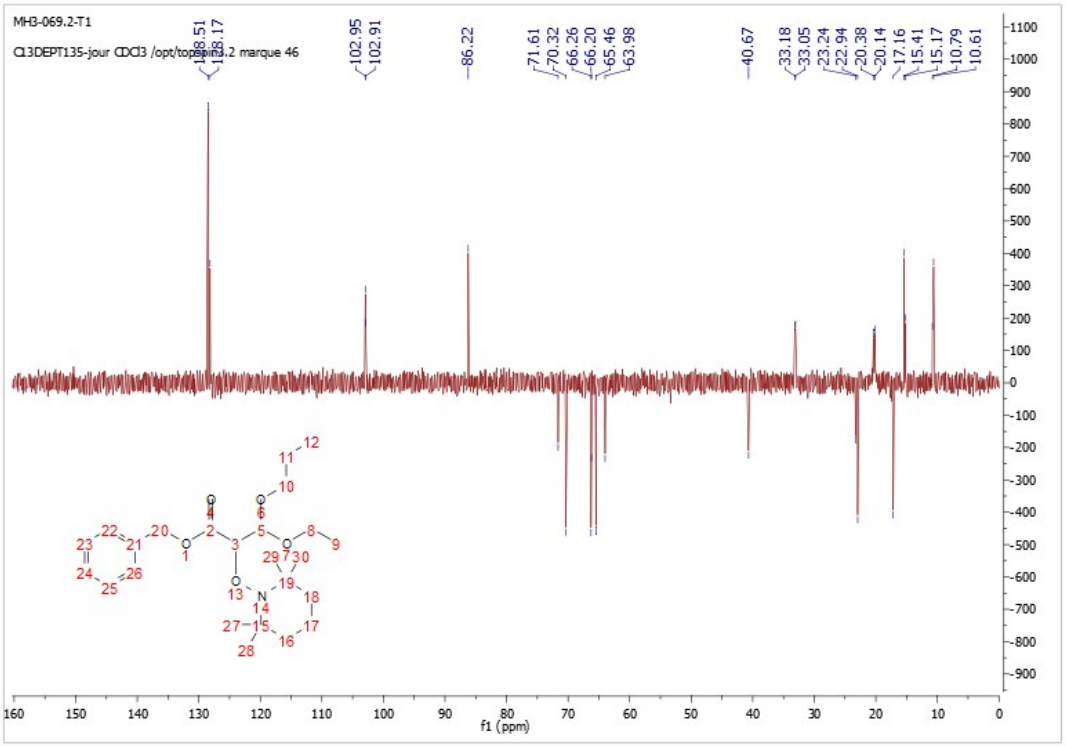
HRMS : benzyl 3-acetoxy-2-((di-tert-butylamino)oxy)-3-ethoxypropanoate **2**



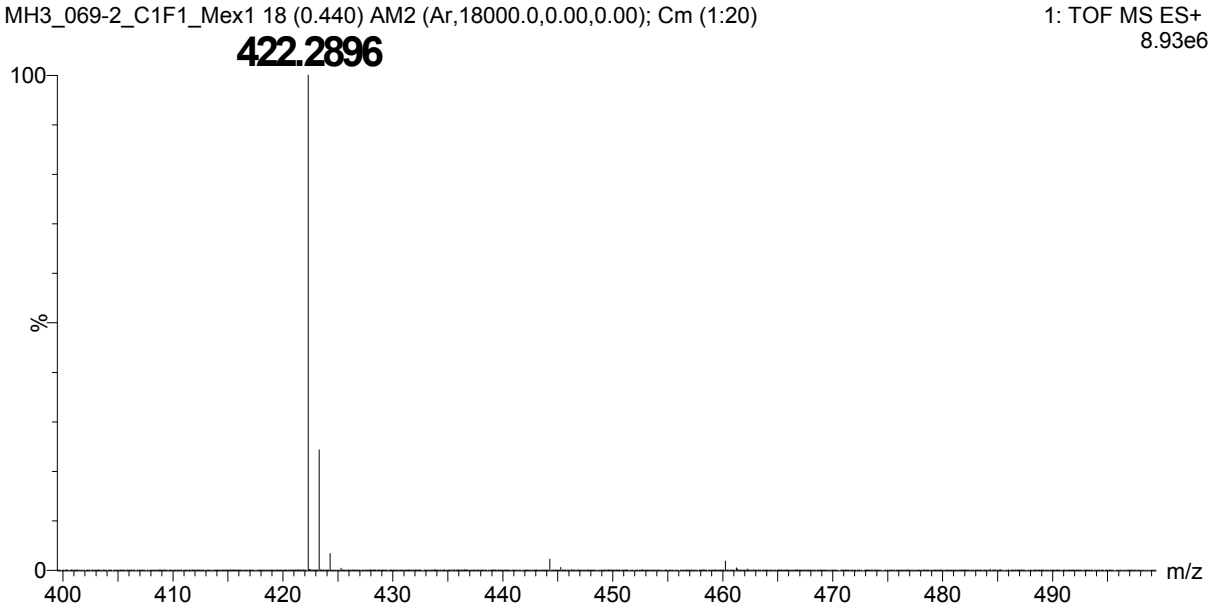
^{1}H : benzyl 3-ethoxy-3-propoxy-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propanoate **6**



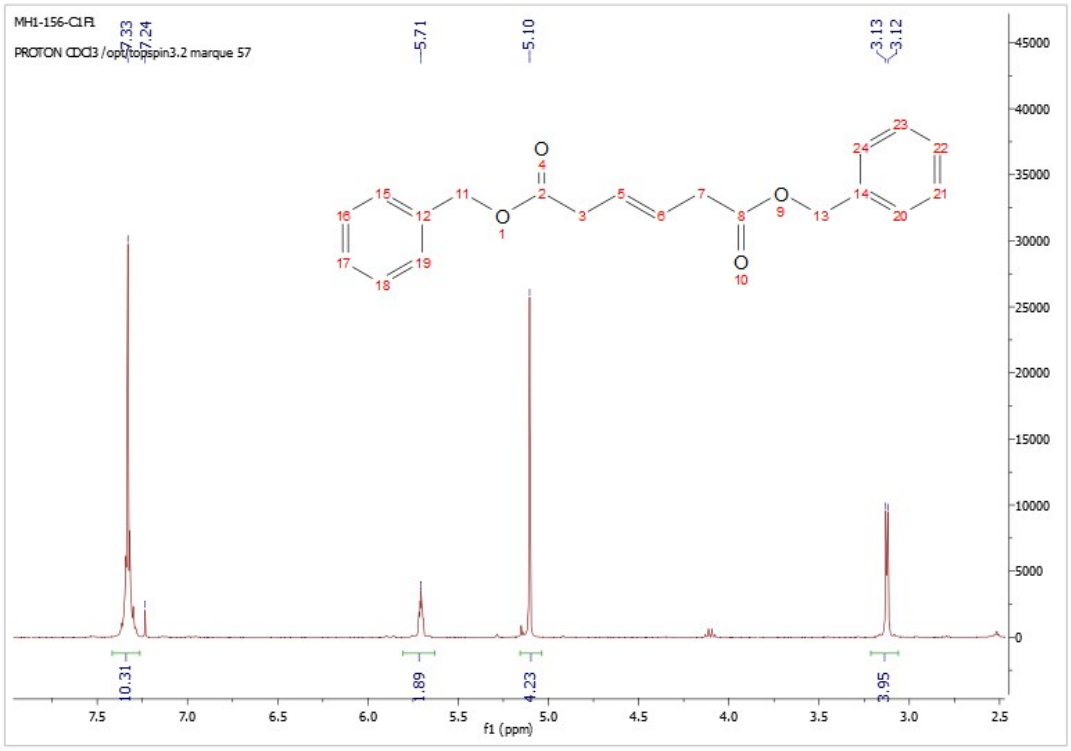
^{13}C : benzyl 3-ethoxy-3-propoxy-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propanoate **6**



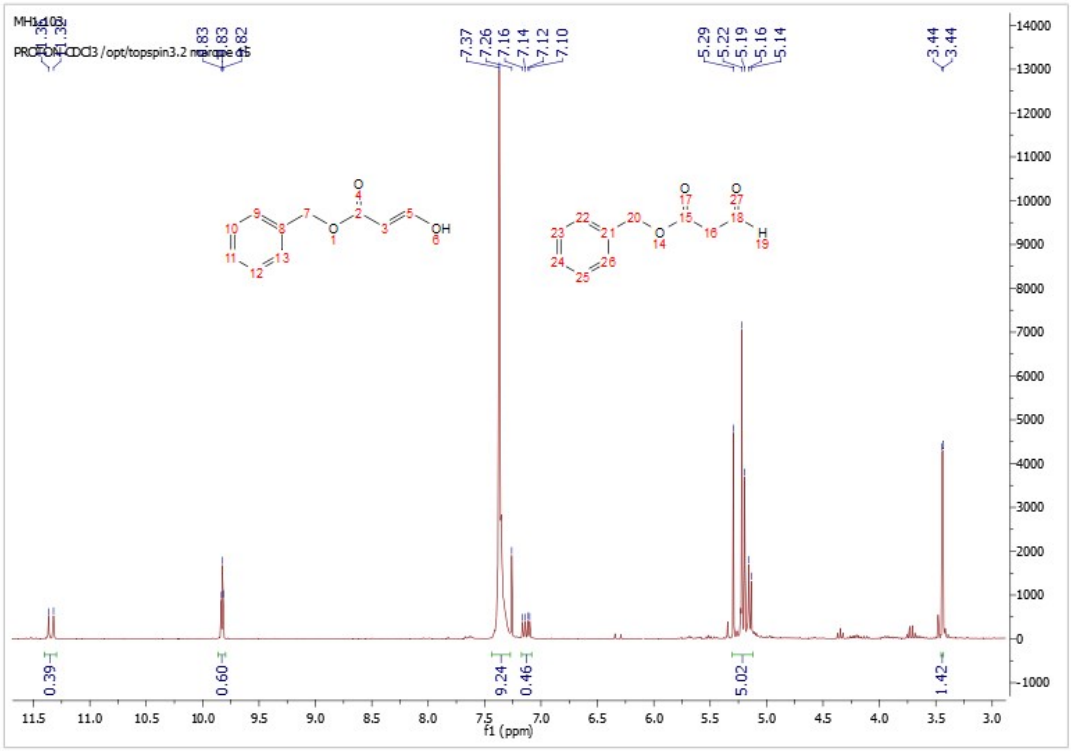
DEPT 135 : benzyl 3-ethoxy-3-propoxy-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propanoate **6**



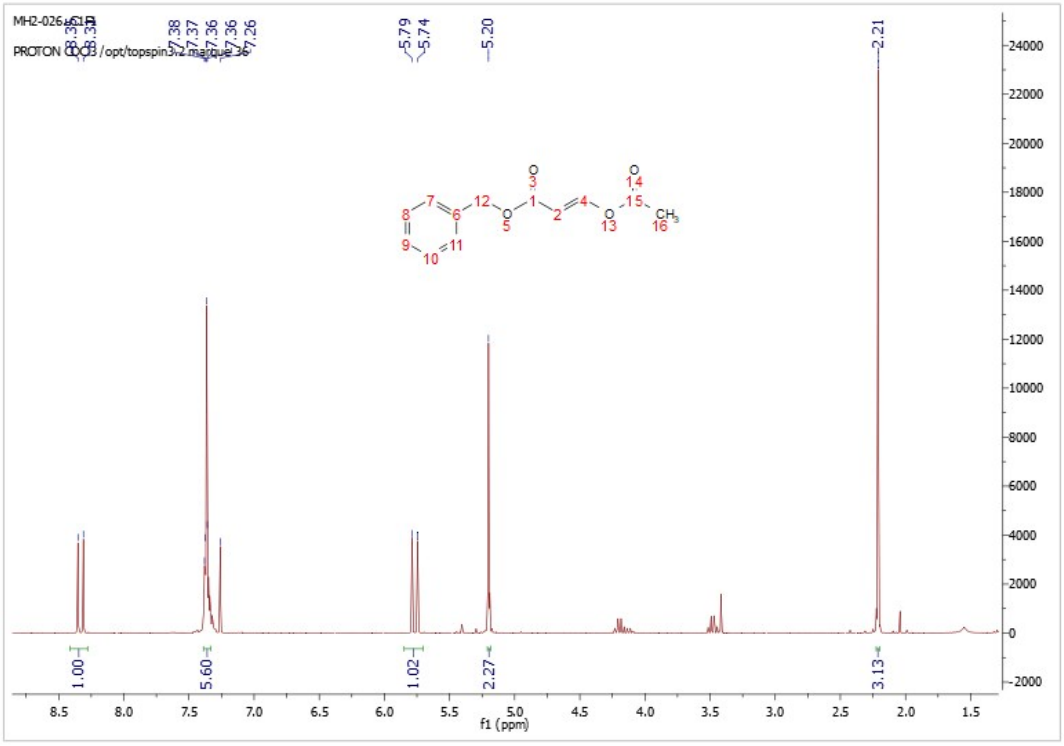
HRMS : benzyl 3-ethoxy-3-propoxy-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propanoate **6**



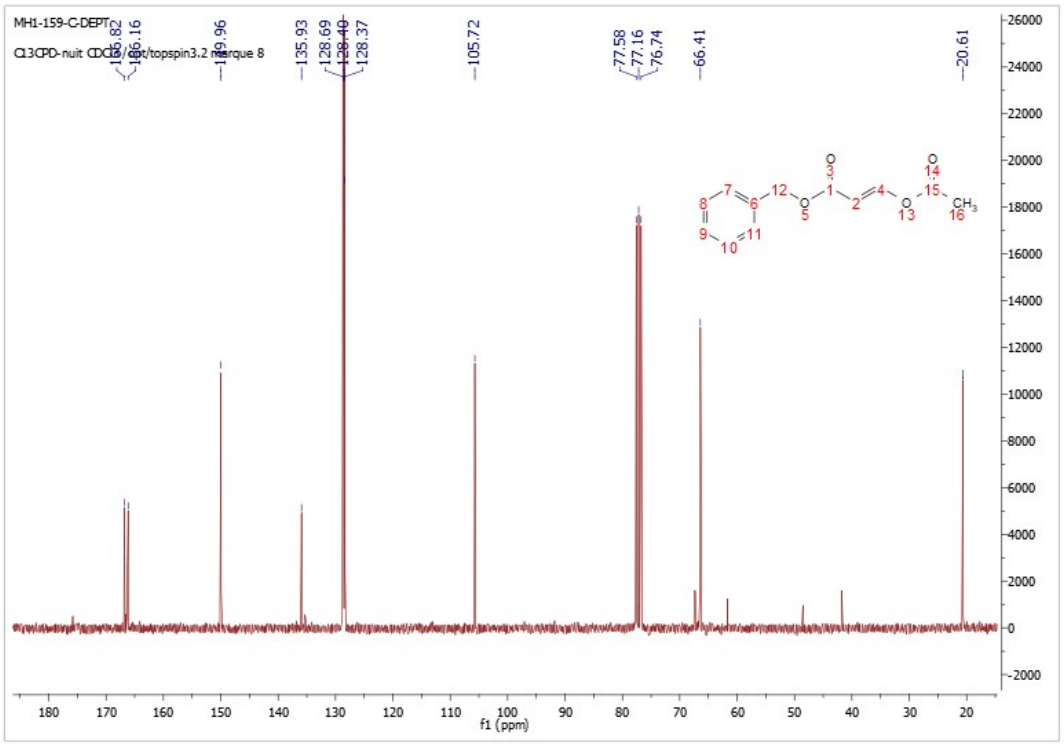
^{1}H : dibenzyl (E)-hex-3-enedioate **9**



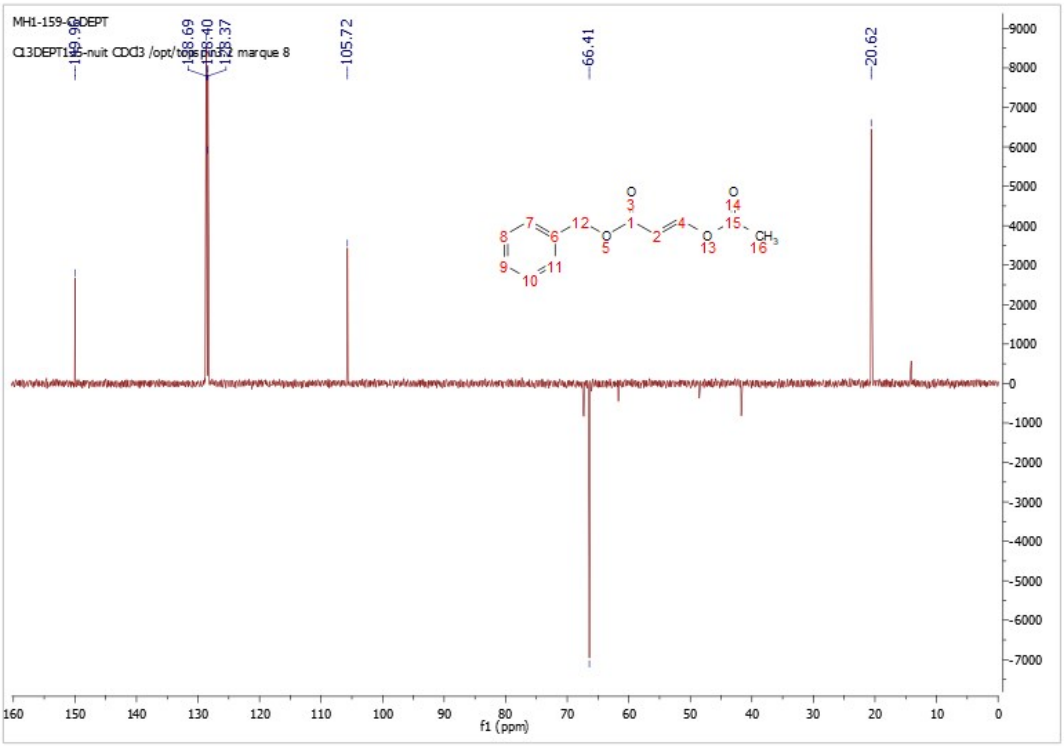
^{1}H : benzyl 3-oxopropanoate **10** and **10'**



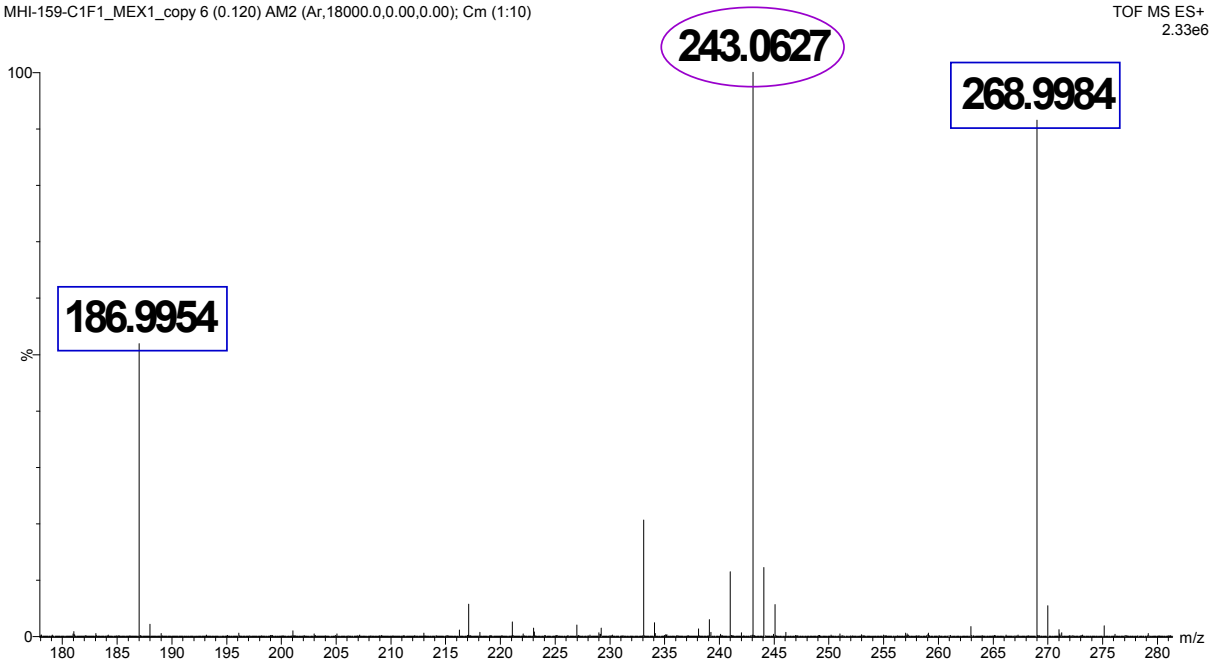
^{1}H : benzyl (E)-3-acetoxyacrylate **11**



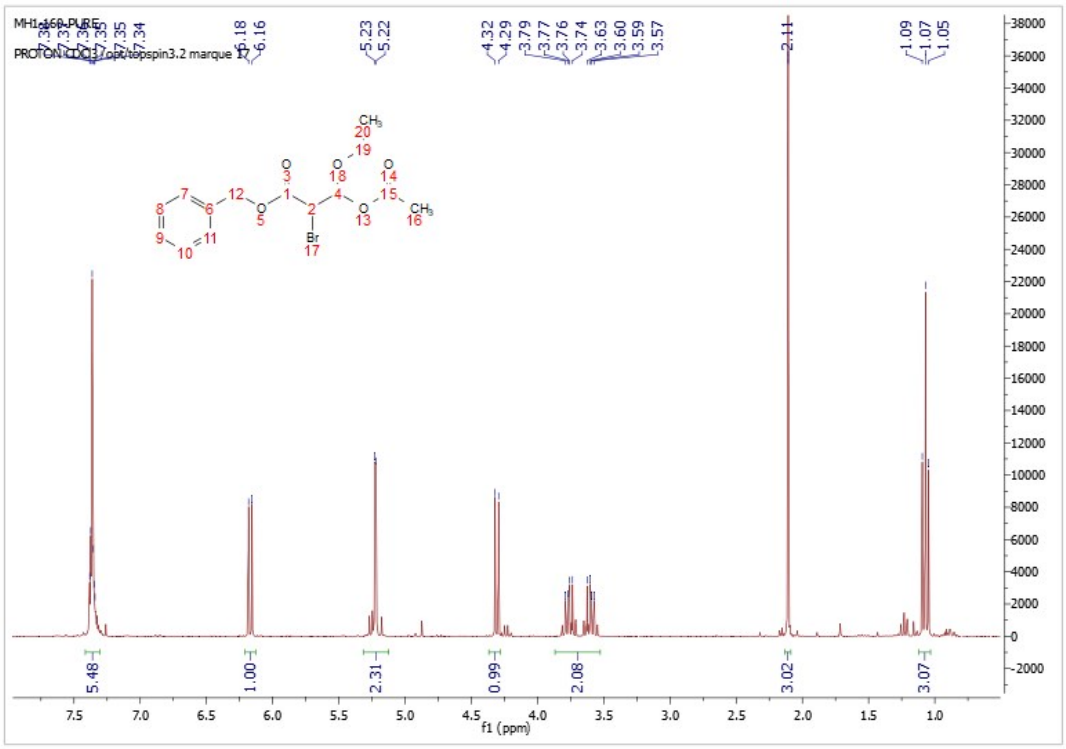
^{13}C : benzyl (E)-3-acetoxyacrylate **11**



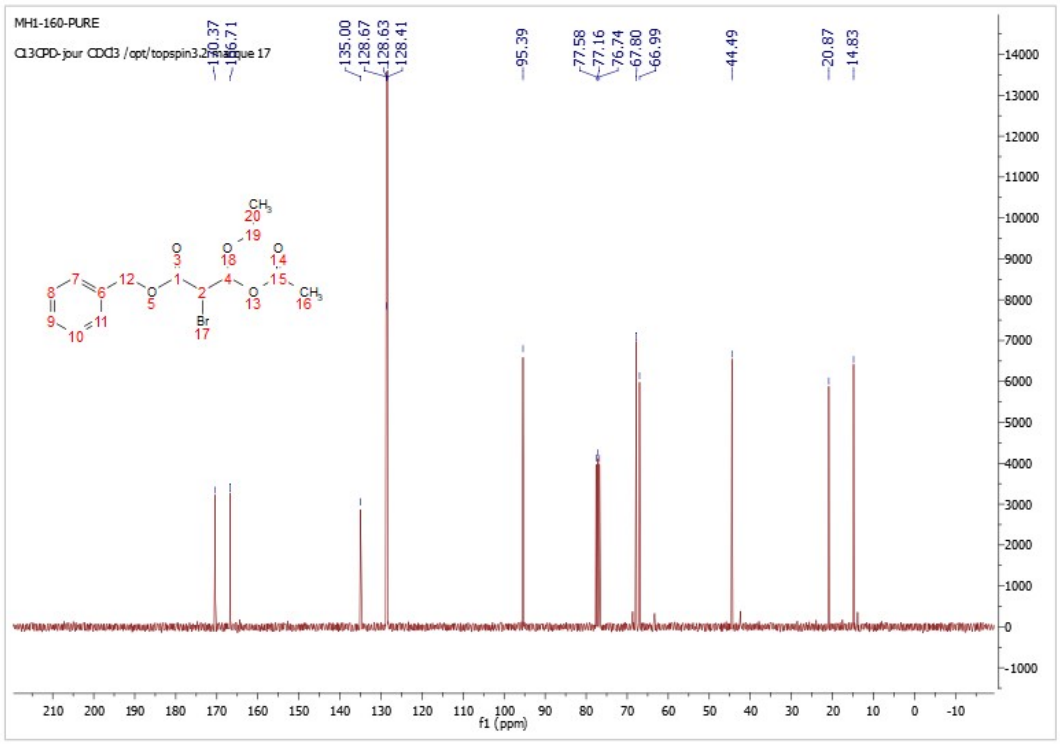
DEPT135 : benzyl (E)-3-acetoxyacrylate **11**



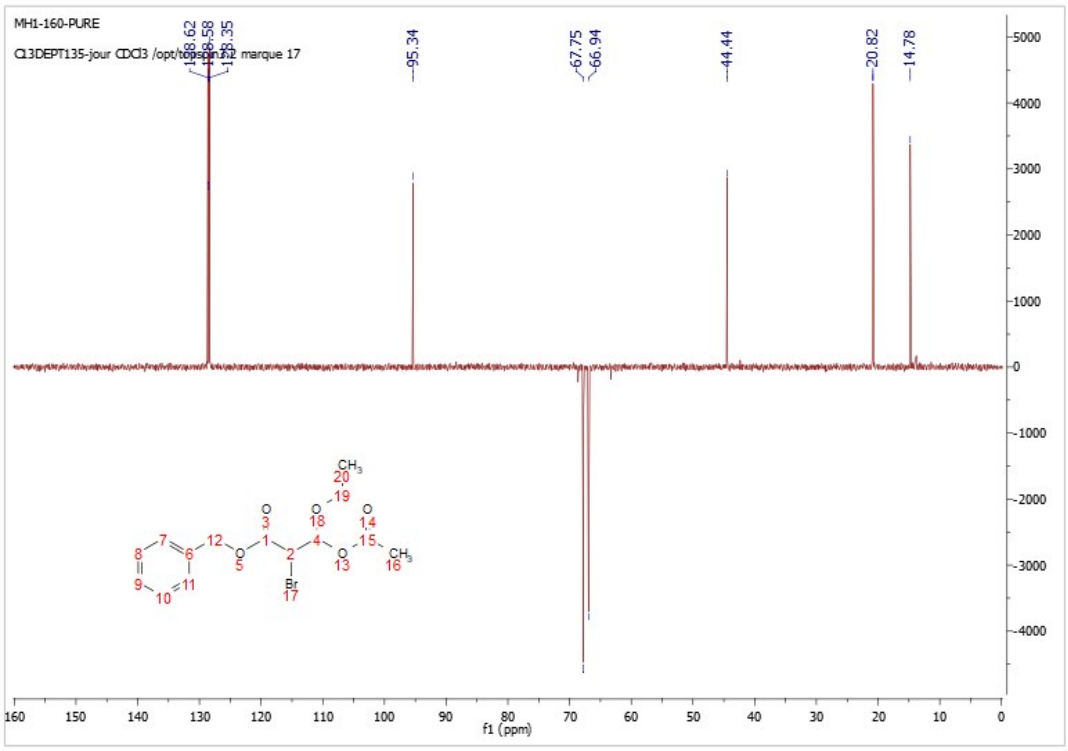
HRMS : benzyl (E)-3-acetoxyacrylate 11



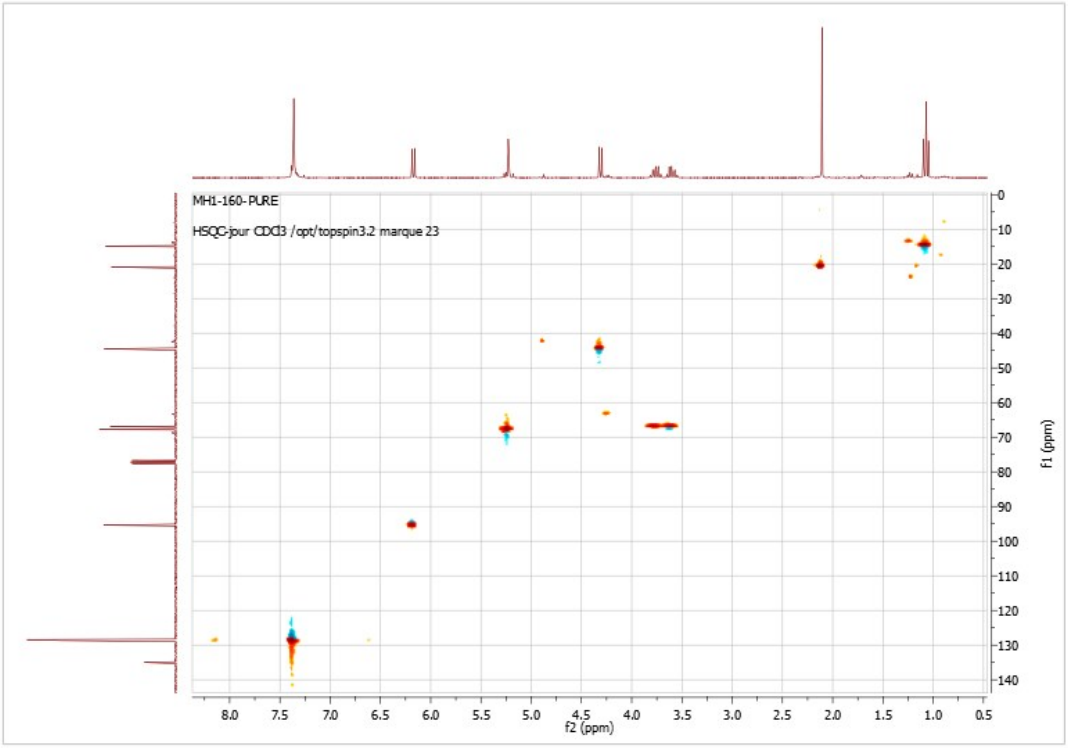
^{1}H : benzyl 3-acetoxy-2-bromo-3-ethoxypropanoate **12**



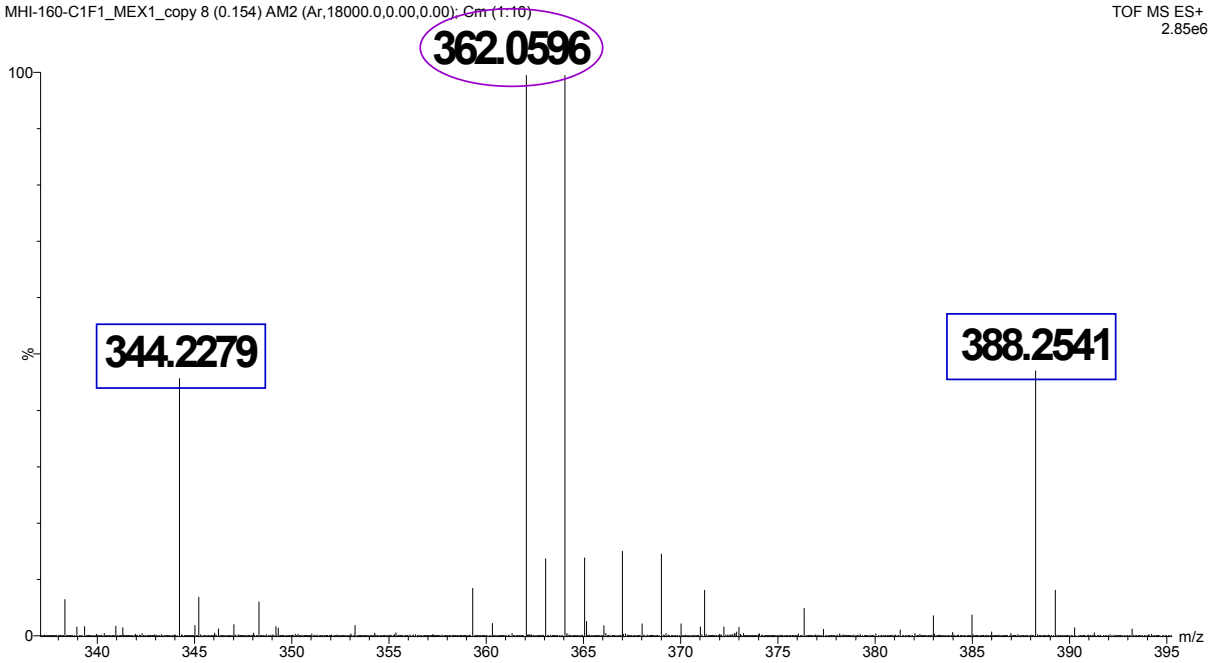
^{13}C : benzyl 3-acetoxy-2-bromo-3-ethoxypropanoate **12**



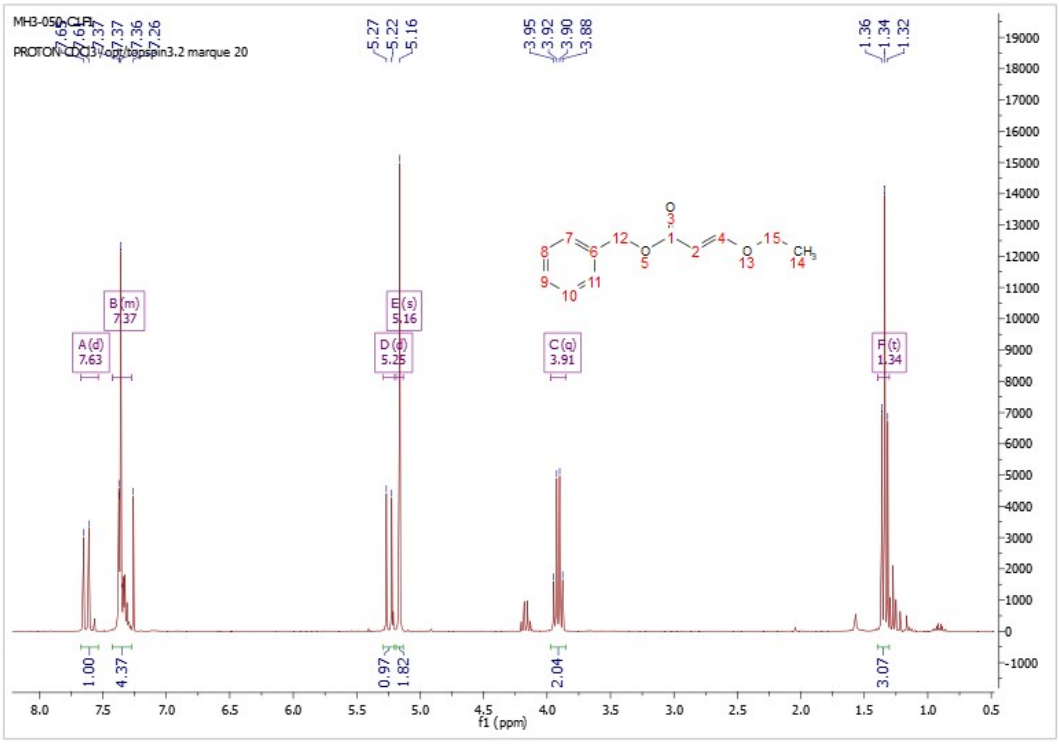
DEPT 135 : benzyl 3-acetoxy-2-bromo-3-ethoxypropanoate **12**



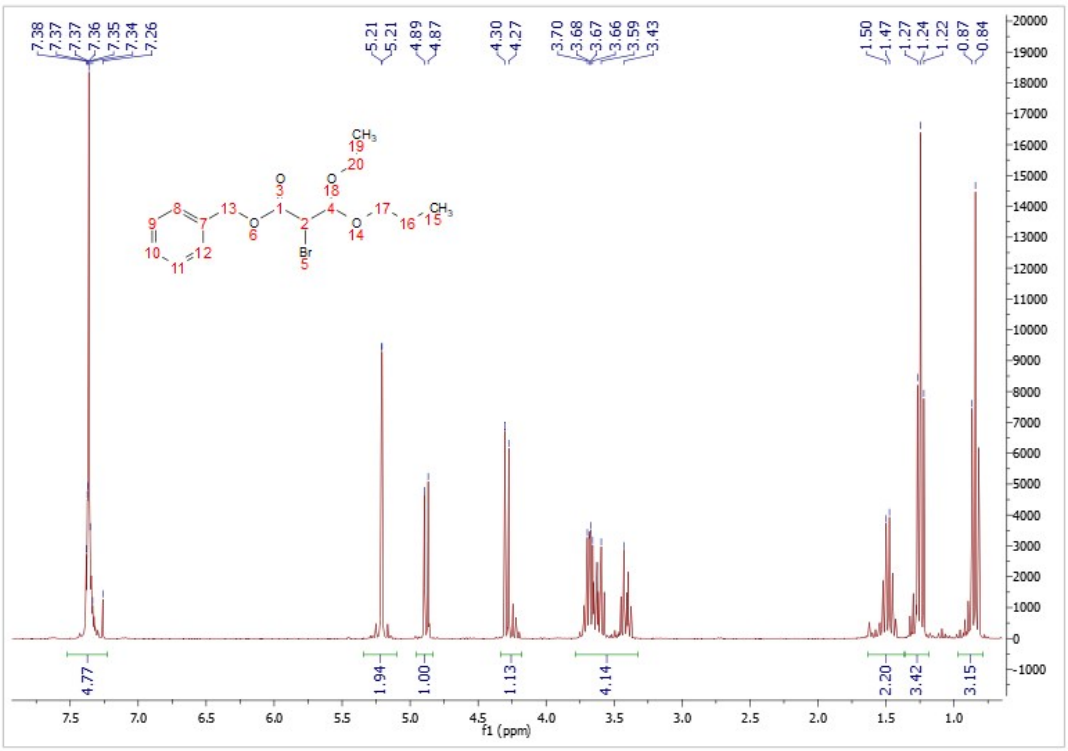
DEPT 135 : benzyl 3-acetoxy-2-bromo-3-ethoxypropanoate **12**



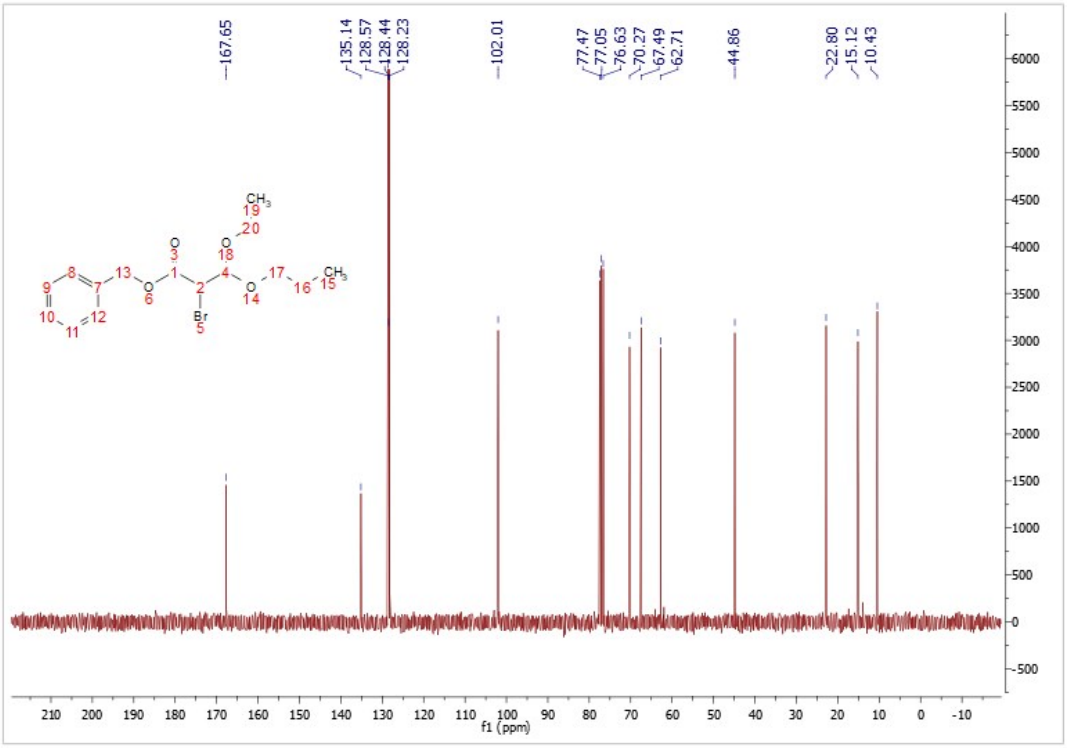
HRMS : benzyl 3-acetoxy-2-bromo-3-ethoxypropanoate **12**



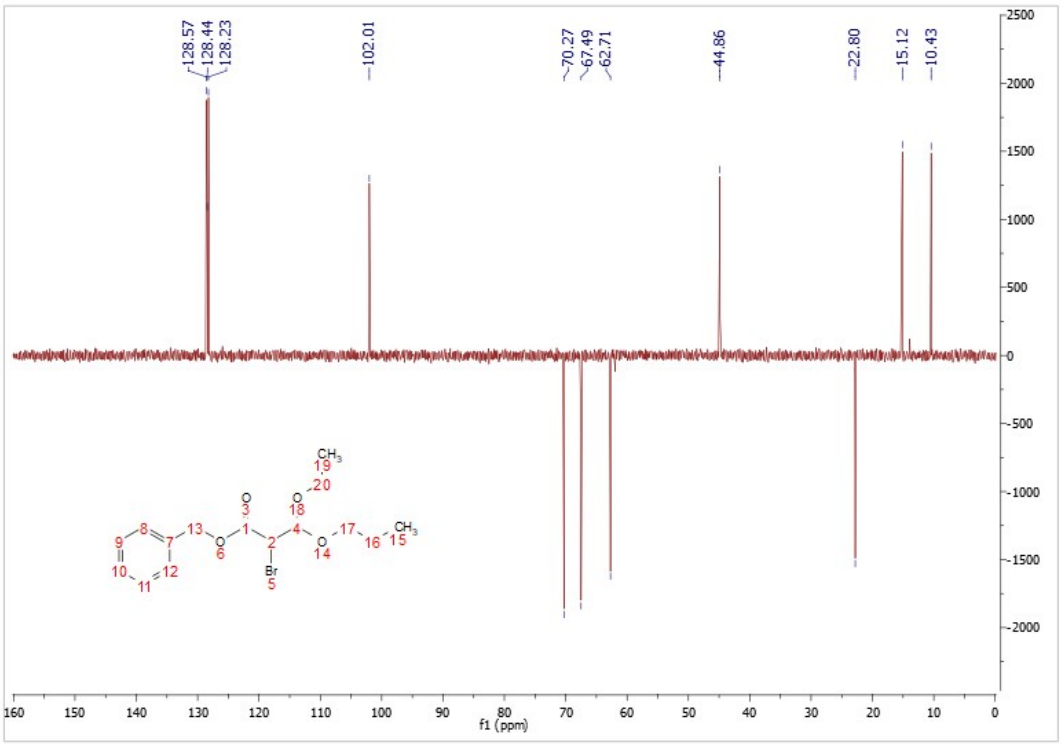
^{1}H : benzyl (E)-3-ethoxyacrylate **19**



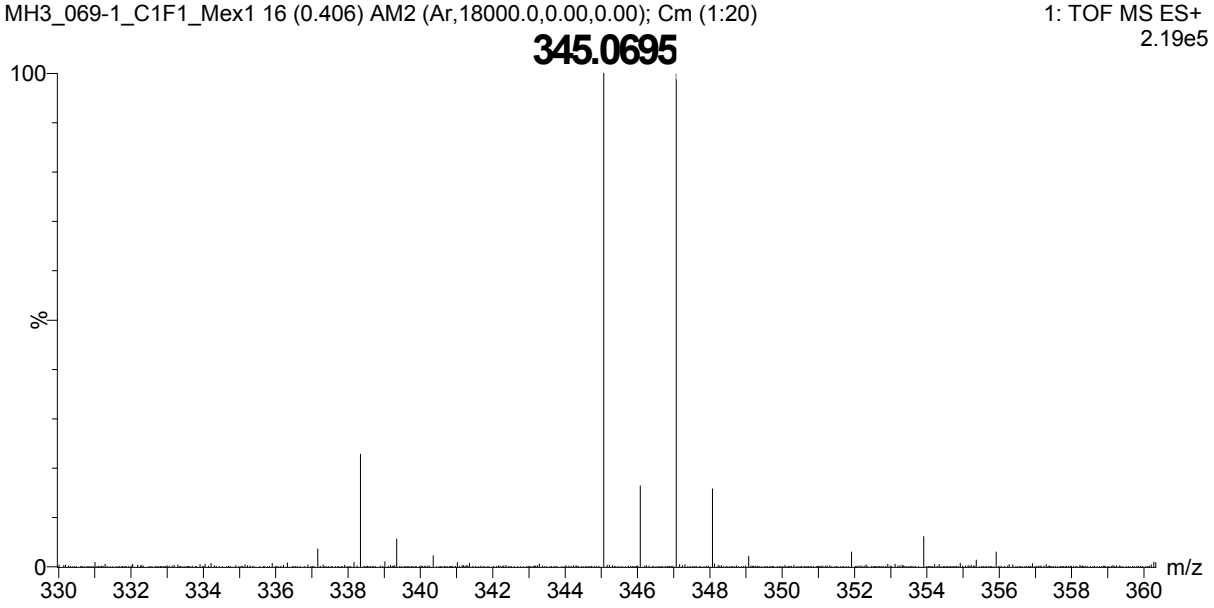
^{1}H : benzyl 2-bromo-3-ethoxy-3-propoxypropanoate **20**



^{13}C : benzyl 2-bromo-3-ethoxy-3-propoxypropanoate **20**



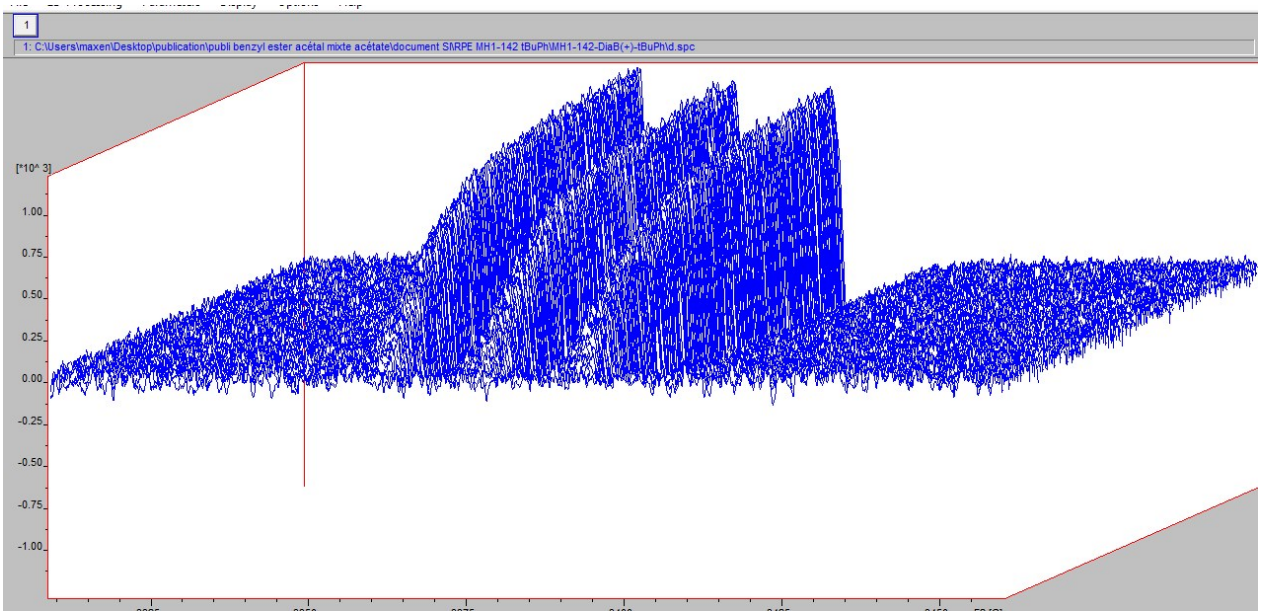
DEPT 135 : benzyl 2-bromo-3-ethoxy-3-propoxypropanoate **20**



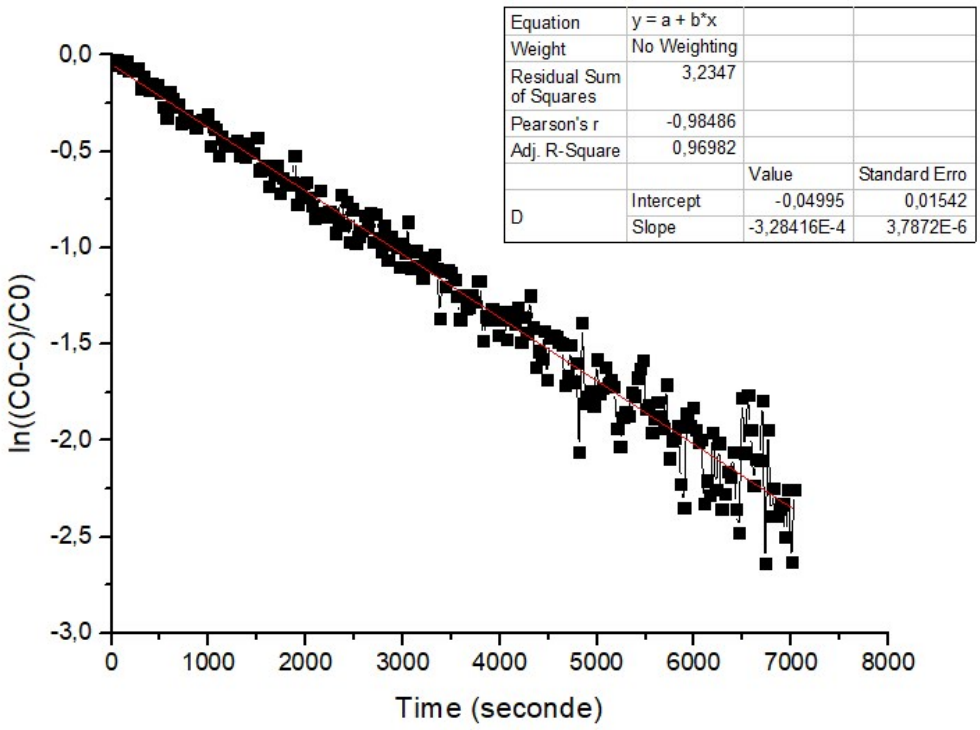
HRMS : benzyl 2-bromo-3-ethoxy-3-propoxypropanoate **20**

2. Kinetic EPR spectra :

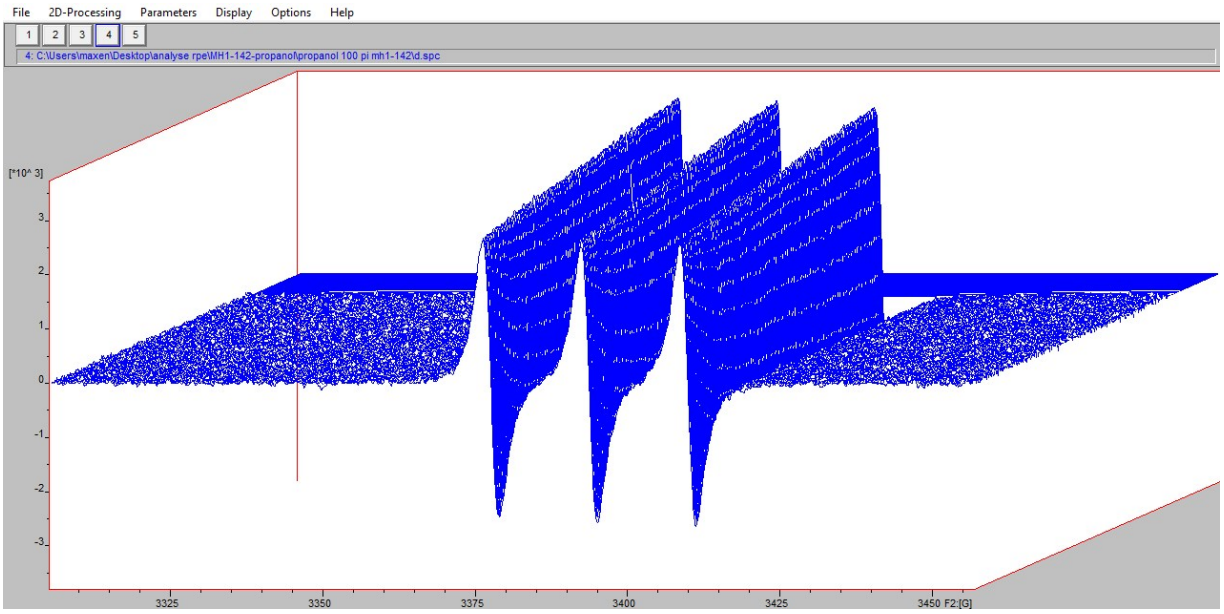
Concentrations in released nitroxides were monitored by EPR (modulation amplitude: 1G, sweep width: 120 G, time constant: 21 s, gain: 10^4) on an EMX Bruker machine equipped with a BVT device to control the temperature. For the plateau method, the initial concentration in alkoxyamine was 0.1 mM and for the initial slope method of 0.01 M or 0.1 M.



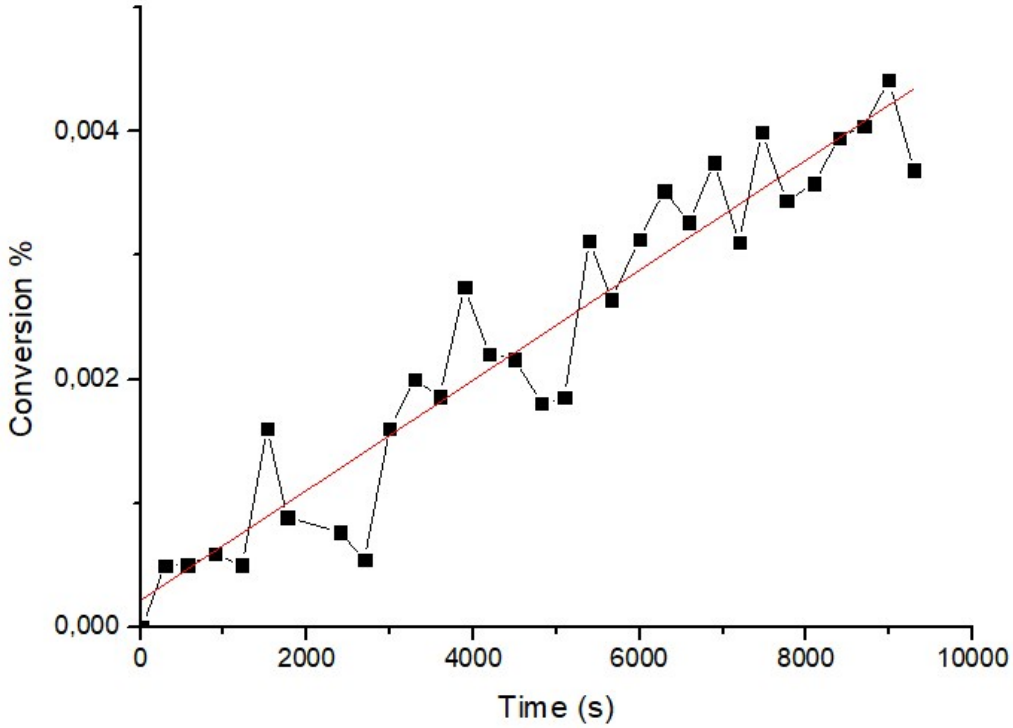
Kinetic of Alkoxyamine **1** DiaB(+) in tBuPh stacked mode



Kinetic of Alkoxyamine **1** DiaB(+) in tBuPh



Kinetic of Alkoxyamine **1** (4 isomers mixture) in PrOH stacked mode



Kinetic of Alkoxyamine **1** (4 isomers mixture) in PrOH

Enzymatic activity :

All enzyme-triggered experiments were done in HEPES buffer, 50 mM, pH 7.4, 0.15 M NaCl. Subtilisin A was purchased from Sigma. Kinetics were monitored by measuring the generation of the stable nitroxides TEMPO or DBNO; revealing the homolysis of the alkoxyamine. TEMPO or DBNO concentrations versus time were recorded using a calibrated EPR EMXnano spectrometer (Bruker). Concentrations were calculated using the Xenon's Spincounting module. Temperature in the probe was kept at 37 °C using a Noxygen temperature controller.

3. Linear Free Energy Relationship :

The effects ruling the C—ON bond homolyses of alkoxyamines are described by several multiparameter relationships corresponding to the nitrosyl fragments investigated, eq. 1 for TEMPO-based alkoxyamines

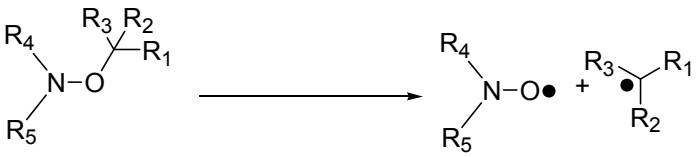
$$\log\left(k_d / s^{-1}\right) = -14.8(\pm 0.7) + 13.9(\pm 0.9)\cdot\sigma_{RS} + 13.6(\pm 3.2)\cdot\sigma_I + 6.6(\pm 0.7)\cdot\upsilon \qquad \text{eq. 1}$$

Parameters σ_{RS}, σ_I and υ are estimated as previously reported[5]. As the various substituents were directly bound to the reactive center (Scheme 1), the value of the electrical Hammett constant σ_I for the alkyl fragment CR1R2R3 is given by eqs. 2-4 for primary, secondary, and tertiary alkyl groups, respectively.

$$\sigma_{I,CH2R} = 0.416\cdot\sigma_{I,R} - 0.0103 \qquad \text{eq. 2}$$

$$\sigma_{I,CHR1R2} = 0.297\cdot\sum\sigma_{I,R} + 0.00482 \qquad \text{eq. 3}$$

$$\sigma_{I,CR1R2R3} = 0.248\cdot\sum\sigma_{I,R} + 0.00398 \qquad \text{eq. 4}$$



Scheme 1

Then, bulkiness of the alkyl fragment is given by eq. 5 assuming υ_1 the saturation of the reactive center, i.e., primary, secondary or tertiary carbon atom, υ_2 for the largest substituent attached to the radical center, and υ_3 is used for the group involved as penultimate unit.

$$\upsilon = 0.866\cdot\upsilon_1 + 0.436\cdot\upsilon_2 + 0.348\cdot\upsilon_3 - 0.0455 \qquad \text{eq. 5}$$

σ_{RS} are estimated using the RSE values given by Rüchardt et al. which are first reported in eqs. 6-8 to give the corrected radical stabilization energy (RSE^{corr}), RSE(CH3•) = 0.0 kJ mol-1 being the reference.

RSE^{corr}(tertiary) = RSE - 18.0 kJ mol^{-1} eq. 6

RSE^{corr}(secondary) = RSE - 14.2 kJ mol^{-1} eq. 7

RSE^{corr}(primary) = RSE - 9.6 kJ mol^{-1} eq. 8

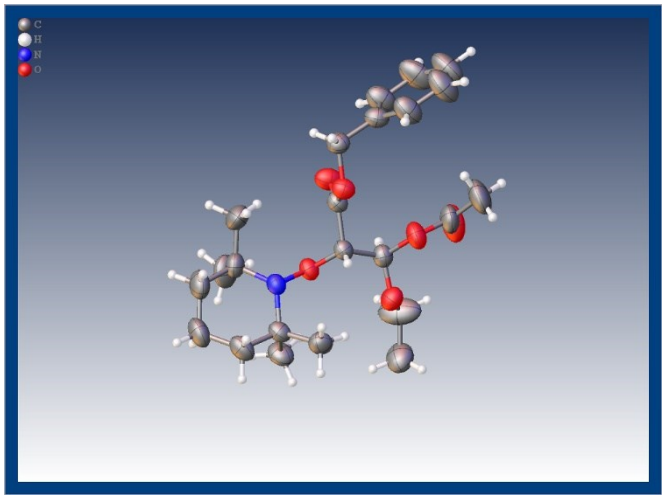
To normalize the RSE^{corr} values, the formation enthalpy of the methyl radical (ΔHf(CH3•)) -146.3 kJ mol-1) was used as it should contain a minimum of effects due to the saturated ground state of the molecule. The values of σ_{RS} are given by eq. 9. The larger σ_{RS} is, the more stabilized the alkyl radical is.

$$\sigma_{\mathrm{RS}} = \frac{RSE^{corr}}{\Delta H_{\mathrm{f}}\left(\mathrm{CH_3^{\bullet}}\right)}$$ eq. 9

4. Analyse XRD[6] :

Alkoxyamine **1** Dia A(-) :

Identification code	MH1-142-a(-)
Empirical formula	$C_{23}H_{35}NO_6$
Formula weight	421.52
Temperature/K	295
Crystal system	monoclinic
Space group	$P2_1$
a/Å	6.11280(10)
b/Å	16.4599(3)
c/Å	12.1815(3)
α/°	90
β/°	99.377(2)
γ/°	90
Volume/Å^3	1209.28(4)
Z	2
ρ_{calc}g/cm^3	1.158
μ/mm^{-1}	0.676
F(000)	456.0
Crystal size/mm^3	0.2 × 0.12 × 0.08
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.356 to 142.36
Index ranges	$-7 \leq h \leq 7$, $-20 \leq k \leq 20$, $-14 \leq l \leq 14$
Reflections collected	16331
Independent reflections	4598 [R_{int} = 0.0575, R_{sigma} = 0.0354]
Data/restraints/parameters	4598/1/277
Goodness-of-fit on F^2	1.059
Final R indexes [I>=2σ (I)]	R_1 = 0.0448, wR_2 = 0.1125
Final R indexes [all data]	R_1 = 0.0461, wR_2 = 0.1138
Largest diff. peak/hole / e Å^{-3}	0.16/-0.21
Flack parameter	-0.05(6)



5. References

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