SUPPORTING INFORMATION

Organocatalytic Enantioselective Alkylation of Aldehydes with $[Fe(bpy)_3]Br_2$ Catalyst and Visible Light

Andrea Gualandi,[a] Marianna Marchini,[a] Luca Mengozzi,[a] Mirco Natali,[b,c] Marco Lucarini [a] Paola Ceroni,[,a] and Pier Giorgio Cozzi*[,a]*

[a] Dipartimento di Chimica "G. Ciamician", ALMA MATER STUDIORUM, Università di Bologna; Via Selmi 2, 40126, Bologna, Italy

[b] Dipartimento di Scienze Chimiche e Farmaceutiche, Università di Ferrara, Ferrara, Italy

[c] Centro Interuniversitario per la Conversione Chimica dell'Energia Solare (SOLAR-CHEM)

emails: paola.ceroni@unibo.it piergiorgio.cozzi@unibo.it

Table of contents:

General methods. ^{1}H NMR spectra were recorded on Varian Gemini 200, Varian Mercury 400 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (deuterochloroform: δ = 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = duplet, t = triplet, q = quartet, dd = double duplet, dt = double triplet, bs = broad signal, pd = pseudo duplet, pt = pseudo triplet, m = multiplet), coupling constants (Hz). ^{13}C NMR spectra were recorded on Varian Gemini 200, Varian MR400 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard (deuterochloroform: δ= 77.0 ppm).GC-MS spectra were taken by EI ionization at 70 eV on a Hewlett-Packard 5971 with GC injection. LC-electrospray ionization mass spectra (ESI-MS) were obtained with Agilent Technologies MSD1100 single-quadrupole mass spectrometer. They are reported as: *m/z* (rel. intense). Chromatographic purification was done with 240-400 mesh silica gel. Purification on preparative thin layer chromatography was done on Merck TLC silica gel 60 F_{254} and on Merck TLC aluminum oxide 60 F_{254} neutral. Determination of diastereomeric ratio and of enantiomeric excess was performed on Agilent Technologies 1200 instrument equipped with a variable wave-length UV detector (reference 420 nm), using Daicel Chiralpak® columns (0.46 cm I.D. x 25 cm) and HPLC grade isopropanol and *n*-hexane as eluting solvents. Optical rotations were determined in a 1 mL cell with a path length of 1 dm (Na_D line).

Materials. Anhydrous solvents were supplied by Aldrich in Sureseal® bottles and were used as received avoiding further purification. Reagents were purchased from Aldrich and used without further purification unless otherwise stated. The aldehydes and 2,6-lutidine were supplied by Aldrich and used after distillation.

2-Cyclohexylacetaldehyde (**1d**),[S1] *tert*-butyl 4-(2-oxoethyl)piperidine-1-carboxylate (**1e**),[S2] 2-bromo-1-(4-nitrophenyl)ethan-1-one (**2d**),[S3] 2',2',2'-trifluoroethyl 2-bromoacetate (**2e**),[S4] (2*R*,5*S*)-2-*t*-butyl-3,5-dimethylimidazolin-4-one hydrochloride[S5] and iron complexes[S6] were prepared according to literature procedures.

Optimization of the enantioselective photoalkylation of aldehydes

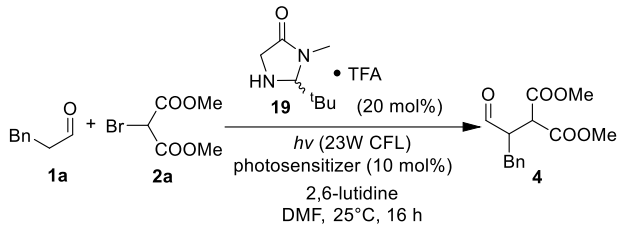


Table S1. Effect of photosensitizer nature.[a]

Photosensitizer	Yield **4** (%)[b]
$FeBr_2$	0
$[Fe(bpy)_3]Br_2$	99
$[(PPh_3)_2Fe(NO_2)_2]$	5
$[Fe(phen)_3]Cl_2$	89
$[Fe(phen)_3](PF_6)_2$	92

[a] The reactions were performed at r.t. with 0.1 mmol of bromomalonate (**2a**), 2 equiv of aldehyde (**1a**) and 2 equiv of 2,6-lutidine, in the presence of 20 mol% of organocatalyst**19** and 10 mol% of photosensitizer in DMF (0.1 M), and stopped after 16 h. [b] Determined by GC-MS analysis.

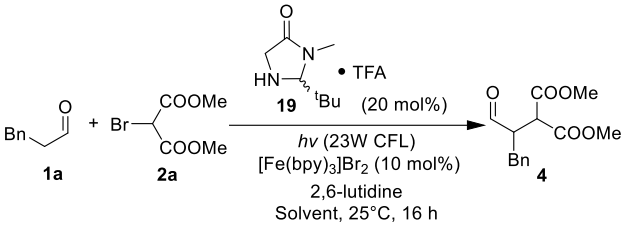


Table S2. Effect of solvent.[a]

Solvent	Yield **4** (%)[b]
DMF	99
DCE	11[c]
CH_3CN	42[c]
DMF/H_2O (9/1)	88

[a] The reactions were performed at r.t. with 0.1 mmol of bromomalonate (**2a**), 2 equiv of aldehyde (**1a**) and 2 equiv of 2,6-lutidine, in the presence of 20 mol% of organocatalyst and 10 mol% of $[Fe(bpy)_3]Br_2$ in the indicated solvent (0.1 M), and stopped after 16 h. [b] Determined by GC-MS analysis. [c] Reaction stopped after 4 h.

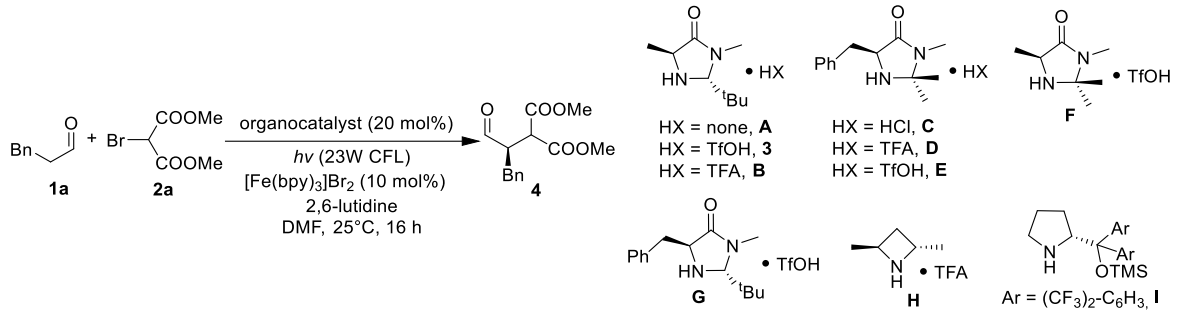


Table S3. Effect of organocatalyst.[a]

Organocatalyst	Yield **4** (%)[b]	ee **4**(%)[c]
A	29	93
3	79	93
B	52	73
A+LutTFA[d]	77	81
A+LutTfOH[e]	65	93
C	32	89
D	63	62
E	73	83
F	76	58
G	54	36
H	28	n.d.
I	20	-70

[a] The reactions were performed at r.t. with 0.1 mmol of bromomalonate (**2a**), 2 equiv of aldehyde (**1a**) and 2 equiv of 2,6-lutidine, in the presence of 20 mol% of organocatalyst and 10 mol% of $[Fe(bpy)_3]Br_2$ in DMF (0.1 M), and stopped after 16 h. [b]Determined by GC-MS analysis. [c] Determined by HPLC analysis on chiral stationary phase. [d] Lutidinium trifluoroacetate. [e]Lutidiniumtriflate.

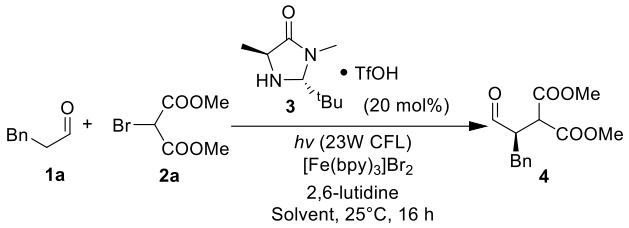


Table S4. Effect of concentration and iron catalyst loading.[a]

Photosensitizer loading (mol%)	Concentration of bromomalonate (**2a**)(M)	Yield **4** (%)[b]	Ee **4** (%)[c]
10	0.1	79	93
10	0.5	81	92
5	0.5	74	93
5	0.2	61	93
2.5	0.5	89	93
1	0.5	70	92

[a] The reactions were performed at r.t with 0.1 mmol of bromomalonate (**2a**), 2 equiv of aldehyde (**1a**) and 2 equiv of 2,6-lutidine, in the presence of 20 mol% of organocatalyst and of the reported percentage of $[Fe(bpy)_3]Br_2$ in DMF. The reaction was stopped after 16 h. [b] Determined by GC-MS analysis. [c] Determined by HPLC analysis on chiral stationary phase.

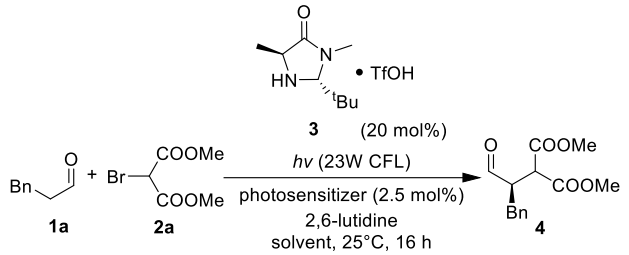


Table S5. Further iron salts and solvents screened under the so far optimized conditions.[a]

Photosensitizer	Solvent	Yield (%)[b]	ee (%)[c]
$[Fe(bpy)_3](PF_6)_2$	DMF	63	92
$[Fe(bpy)_3]Br_2$	**DMF**	**89 (83)** [d]	**93**
$[Fe(bpy)_3]Br_2$	CH_3CN	19	n.d.
$[Fe(bpy)_3]Br_2$	DMSO	27	93

[a] The reactions were performed at r.t with 0.1 mmol of bromomalonate (**2a**), 2 equiv of aldehyde (**1a**) and 2 equiv of 2,6-lutidine, in the presence of 20 mol% of **3** and 2.5 mol% ofiron catalyst in the reported solvent (0.5 M). The reaction was stopped after 16 h. [b] Determined by GC-MS analysis. [c] Determined by HPLC analysis on chiral stationary phase. [d] Isolated yield after chromatographic purification.

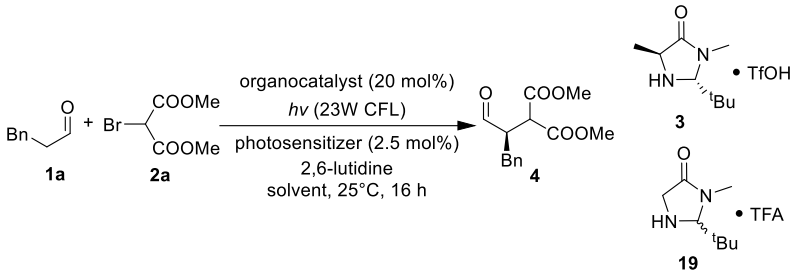


Table S6. Light effect.[a]

Photosensitizer (mol%)	Organocatalyst	Light	Time (h)	Yield **4** (%)[b]	ee **4** (%)[c]
-	**19**	YES (23W CFL)	16	95[d]	-
-	**19**	YES (λ>420, 250W)	6	0	-
$[Fe(bpy)_3]Br_2$ (0.004 mol%)	**19**	YES (λ >420, 250W)	10	82	
$[Fe(bpy)_3]Br_2$ (0.25 mol%)	**19**	YES (λ >420, 250W)	6	87	-
$[Fe(bpy)_3]Br_2$ (0.25 mol%)	**3**	YES (λ >420, 250W)	6	49	93
$[Fe(bpy)_3]Br_2$ (2.5 mol%)	**3**	YES (23W CFL)	16	89	93
$[Fe(bpy)_3]Br_2$ (2.5 mol%)	**3**	NO	16	0	-
-	**3**	YES (λ >420, 23W CFL)	16	0	-
-	**3**	YES (23W CFL)	16	32[d]	93

[a] The reactions were performed at r.t with 0.2 mmol of bromomalonate (**2a**), 2 equiv of aldehyde (**1a**) and 2 equiv of 2,6-lutidine, in the presence of 20 mol% of organocatalyst and of the reported catalytic amount of iron complexes in DMF (0.5 M). The reaction was stopped after the reported time. [b] Determined by GC-MS analysis. [c] Determined by HPLC analysis on chiral stationary phase.[d] As reported by Melchiorre photoexcited state of enamines are able to transfer electron to bromomalonates starting a radical-chain reaction[S7] under not filtered CFL light. Better yields were obtained with the catalyst **19** are due to the less sterical hindrance. The result obtained with the catalyst **3** was also reported by Melchiorre (see supporting information ref. S7).

Light/dark effect

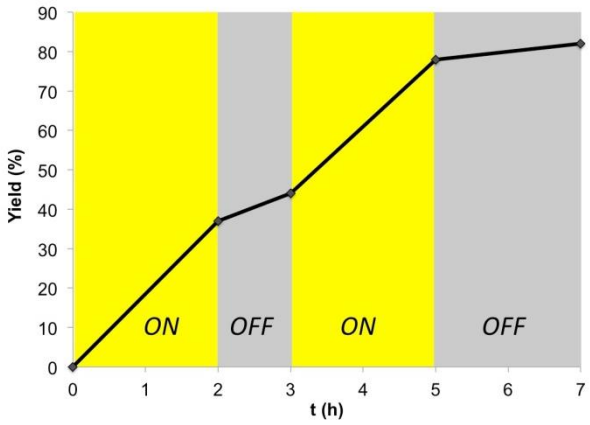


Figure S1. Successive intervals of irradiation and dark periods. The reaction was performed at r.t with 0.2 mmol of bromomalonate (**2a**), 2 equiv of aldehyde (**1a**) and 2 equiv of 2,6-lutidine, in the presence of 20 mol% of **3** and 2.5 mol% of $[Fe(bpy)_3]Br_2$ in DMF (0.5 M). Yield was determined by GC-MS analysis from an aliquot of the reaction mixture.

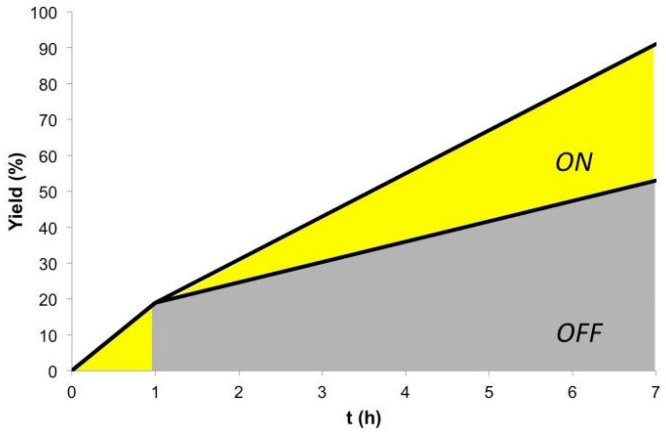


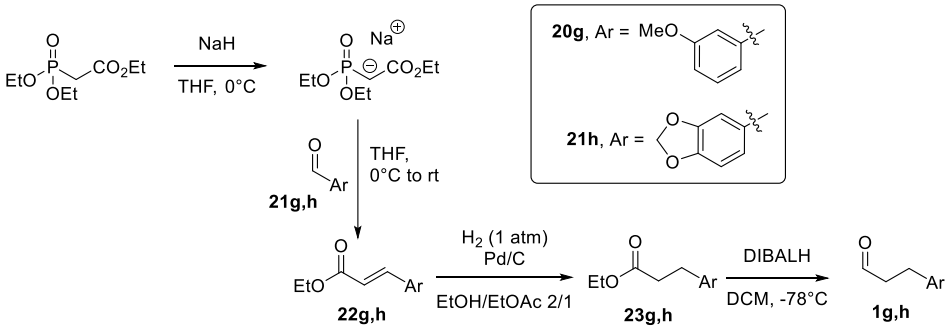
Figure S2. Two separate but identical reaction were simultaneously performed. The first one was irradiated for 1h and it was kept in the dark for 6 hours. The second one was irradiate for 6 hours. The reactions were performed at r.t with 0.2 mmol of bromomalonate (**2a**), 2 equiv of aldehyde (**1a**) and 2 equiv of 2,6-lutidine, in the presence of 20 mol% of **3** and 2.5 mol% of $[Fe(bpy)_3]Br_2$ in DMF (0.5 M). Yield was determined by GC-MS analysis from an aliquot of the reaction mixture.

Synthesis of catalyst 3

Macmillan catalyst (2*R*,5*S*)-2-*t*-butyl-3,5-dimethylimidazolin-4-one monohydrochloride[S5](321 mg, 1.30 mmol) was dissolved in $NaHCO_3$ aq. sat. solution (4 mL) inside a separator funnel and the aqueous layer was extracted with $CHCl_3$ (5x 5 mL). The collected organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting oil was dissolved in dry Et_2O (5 mL) and cooled to 0°C. TfOH (1.9 mmol, 167 μL) was added dropwise under stirring and a white solid precipitated. After 10 min the solution was filtered on a Gooch septum and the solid was washed with Et_2O (2.5 mL) and pentane (10 mL), recovered and dried under vacuum to furnish **3** (358 mg, 1.12 mmol, 86% yield) as white solid.

The same procedure, using TFA instead of TfOH, was used to obtain trifluoroacetic salt of catalyst**.**

Synthesis of aldehydes 1g,h



General procedure for homologation reaction.

22g: To a NaH (60% wt dispersion in mineral oil, 332 mg, 8.3 mmol) suspension in THF (5 mL) at 0°C under nitrogen atmosphere, a solution of triethylphosphonoacetate(1.6 mL, 8.3 mmol) in THF (10 mL) was added dropwise over 10 min. After 30 min a solution of 3-methoxy benzaldehyde (**21g**, 1.0 mL, 8.2 mmol) in THF (10 mL) was added dropwise over 10 min. The mixture is allowed to warm to rt overnight. Water (5 mL) was added and the organic solvent was evaporated under reduced pressure. The residue was extracted with AcOEt (3x25 mL). The collected organic phases are dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford **22g** (1.60 g, 7.8 mmol, 95% yield) as a yellowish sticky solid. The compound was used in the next step without further purification. Spectroscopic properties were according to those reported in literature.[S8]

22h was prepared according the protocol for **22g**, using piperonal **21h**[S9] (998 mg, 6.65 mmol) as starting material. **22h**(1.23 g, 5.6 mmol, 85% yield) was obtained as a white solid and used in the next step without further purification. Spectroscopic properties were according to those reported in literature.[S10]

General procedure for the hydrogenation reaction.

23g: To a solution of **22g** (1.6 g, 7.8 mmol) in EtOH/EtOAc (2/1 ratio, 12 mL), 10% wt Pd/C (5.0% wt, 80 mg) was added. The reaction flask evacuated, filled with hydrogen (1 atm) and stirred for 24 h. Then it was diluted with DCM (10 mL) and filtered through a pad composed by silica (bottom) and Celite® (top), and was washed with further 50 mL of DCM. The organic solution was concentrated under reduced pressure to afford pure **22g** (1.52 g, 7.3 mmol, 93% yield) as a white sticky solid. The compound was used in the next step without further purification. Spectroscopic properties were according to those reported in literature.[S11]

23h was prepared according to the protocol for **23g**, using **22h** (1.23 g, 5.6 mmol) as starting material. **22h**(1.22 g, 5.5 mmol, 98% yield) was obtained as a white solid and used in the next step without further purification. Spectroscopic properties were according to those reported in literature.[S12]

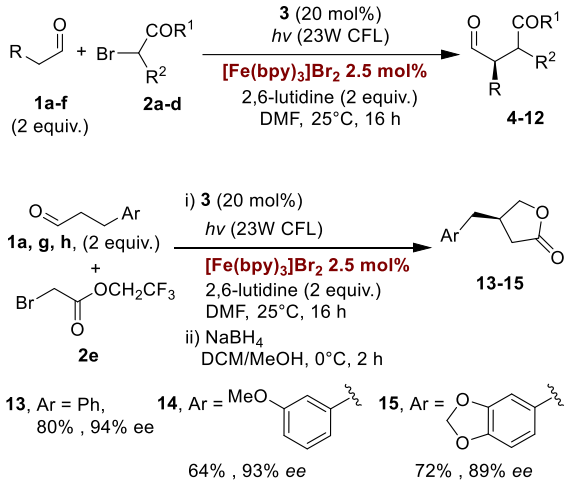
General procedure for the reduction to aldehydes.

1g: To a solution of **23g** (600 mg, 2.88 mmol) in DCM (6 mL) at -78°C under nitrogen atmosphere, a solution of DIBAL-H (1M in DCM, 3.17 mL, 3.17 mmol) in DCM (6 mL) was added dropwise over 15 min. After 2hours complete conversion was observed by TLC and GC-MS analysis. The reaction mixture was diluted with non-anhydrous diethyl ether and warmed to 0°C. Then H_2O(127

µL), 15% aq. NaOH (127 µL), H_2O (317 µL) were sequentially added at 10 min intervals, and a white solid precipitated. After 15 min, $MgSO_4$ was added and the mixture was stirred for further 15 min at rt. Then it was filtered through a Celite® pad and washed with AcOEt (20 mL). The solution was concentrated and the crude product was purified by column chromatography (SiO_2, cyclohexane/EtOAc 9/1) to afford pure **1g** (382 mg, 2.33 mmol, 81% yield) as a colorless oil. Spectroscopic properties were according to those reported in literature.[S13]

1h was prepared according the protocol for **1g**, using **23ch** (473 mg, 2.1 mmol) as starting material. Column chromatography (SiO_2, cyclohexane/EtOAc 7/3) of the crude mixture gave **1h** (276 mg, 1.56 mmol, 74% yield) as a colorless oil. Spectroscopic properties were according to those reported in literature.[S14]

General procedure for enantioselective photoalkylation of aldehydes



In a Schlenk tube with rotaflo stopcock under argon atmosphere at r.t., $[Fe(bpy)_3]Br_2$ (3.4 mg, 0.005 mmol) and the Macmillan catalyst **3** (12 mg, 0.04 mmol) were dissolved in 400 µL DMF. Aldehydes **1a-h**(2 eq, 0.4 mmol), bromo derivatives **2a-e** (1 equiv, 0.2 mmol) and 2,6-lutidine (48 µL, 0.4 mmol) were then added.

The reaction mixture was carefully degassed via freeze-pump thaw (three times), and the vessel refilled with argon. The Schlelk tube was stirred and irradiated with a 23 W CFL bulb positioned approximately at 10 cm distance from the reaction vessel. After 16 h of irradiation, aq. HCl 1M (2 mL) was added and the mixture was extracted with AcOEt (4x5 mL). The collected organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure.

Products **4-12** were purified by column flash chromatography on SiO_2.

Lactones **13-15**: The crude mixture was dissolved in DCM/MeOH (1/1 ratio, 4 mL), cooled to 0°C and $NaBH_4$ (30 mg, 0.8 mmol) was added. After 2 hours of stirring, complete conversion was

observed by TLC analysis and the mixture was concentrated under reduced pressure. Aq. HCl 1M (5 mL) was added to the residue and the mixture was extracted with EtOAc (3 x 8 mL). The collected organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Title compounds were purified by column chromatography on SiO_2 to afford lactones **13-15**.

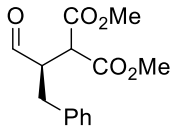
Racemic compounds were synthesized according to general procedure using racemic imidazolinone catalyst **16** instead of **3**.

General procedure for determination of enantiomeric excesses of compounds 6-9.

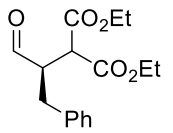
Products **6-9** were transformed in their corresponding diastereomeric acetals according to the literature protocol[S15] in order to determine their enantiomeric excess.

To a solution of **6-9** (0.05 mmol) in DCM (1.0 mL), (2*S*,4*S*)-(+)-pentanediol (>99% ee, 12.5 mg, 0.12mmol) and *p*-toluenesulfonic acid monohydrate (1.9 mg, 0.01 mmol) were added. The solution was stirred at rt until complete conversion was observed by TLC analysis. The mixture was concentrated under reduced pressure. Enantiomeric excesses were calculated from diastereomeric ratios of the resulting acetals, determined either by ^{1}H NMR or GC-MS analysis.

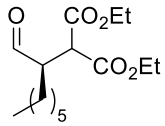
Characterization data of compounds 4-15



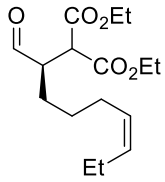
(**4**):The title compound was isolated by flash column chromatography (SiO_2,cyclohexane/EtOAc 95/5)as colourless oil (44 mg, 0.17 mmol, 83% yield, 92% ee).Ee was determined by chiral HPLC analysis using Daicel Chiralpak®IC column: hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min, 30°C, λ = 210 nm: τ_{major}= 22.67 min., τ_{minor} = 18.05 min.;$[\alpha]_D^{20}$=+30.5 (*c*=0.6 in CH_2Cl_2).^{1}H NMR and ^{13}C NMR were according to those reported in literature.[S16]



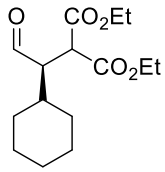
(**5**):The title compound was isolated by flash column chromatography(SiO_2, cyclohexane/EtOAc 95/5) as colourless oil (46 mg, 0.16 mmol, 78% yield, 92% ee). Ee was determined by chiral HPLC analysis using Daicel Chiralpak®IC column: hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min, 30°C, λ = 210 nm: τ_{major}= 19.48 min., τ_{minor} = 15.17 min.; ^{1}H NMR and ^{13}C NMR were according to those reported in literature.[S15]



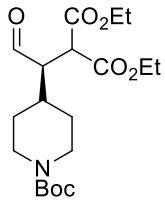
(**6**): The title compound was isolated by flash column chromatography(SiO_2, cyclohexane/EtOAc 95/5) as colourless oil (47 mg, 0.16 mmol, 82% yield, 92% ee). Ee was determined after derivatization of 29 mg of the title compound to its corresponding diastereomeric acetal following general procedure. Ee was determined by integration of the two ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) signals at 3.63 ppm (*major*, doublet) and 3.67ppm (*minor*, doublet) corresponding to the two diastereomeric acetals.^{1}H NMR and ^{13}C NMR were according to those reported in literature.[S15]



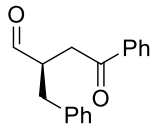
(**7**): The title compound was isolated by flash column chromatography (SiO_2, cyclohexane/EtOAc 95/5) as colourless oil (46 mg, 0.16 mmol,78% yield, 97% ee). Ee was determined after derivatization of 30 mg of the title compound to its corresponding diastereomeric acetal following general procedure. Ee wasdetermined by integration of the two ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) signals 3.68 (*major*, doublet) and 3.72 ppm (*minor*, doublet) corresponding to the two diastereomeric acetals. The same ee was determined by integration of the signals at 22.98 min (*major*) and 22.85 min (*minor*) corresponding to the two diastereomeric acetals after injection in GC-MS analysis. (Agilent 122-553ui, 5% phenyl 10% dimethylarylenesiloxane column, 1.7 mL/min helium flow rate, 150°C for 2 min, then temperature ramp to 280°C at 2.5°C/min rate). ^{1}H NMR and ^{13}C NMR were according to those reported in literature.[S15]



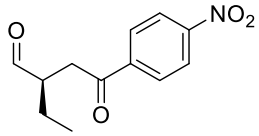
(**8**): The title compound was isolated by flash column chromatography (SiO_2, cyclohexane/EtOAc from 100/0 to 90/10) as colourless oil (43 mg, 0.15 mmol, 75% yield, 97% ee). Ee was determined after derivatization of 28 mg of the title compound to its corresponding diastereomeric acetal following general procedure B. Ee was determined by integration of the two ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) signals 3.73 (*major*, doublet) and 3.81 ppm (*minor*, doublet) corresponding to the two diastereomeric acetals. The same ee was determined by integration of the signals at 20.47 min (*major*) and 20.39 min (*minor*) corresponding to the two diastereomeric acetals after injection in GC-MS analysis. (GC-MS program: Agilent 122-553ui, 5% phenyl 10% dimethylarylenesiloxane column, 1.7 mL/min helium flow rate, 50°C for 2 min, then temperature ramp to 280°C at 10°C/min rate). ^{1}H NMR and ^{13}C NMR were according to those reported in literature.[S15]



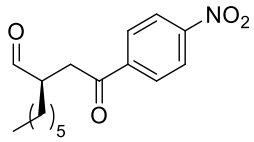
(**9**):The title compound was isolated by flash column chromatography (SiO_2, cyclohexane/EtOAc from 9/1 to 7/3) as colourless oil (46 mg, 0.12 mmol, 60% yield, 89% ee). Ee was determined after derivatization of 39 mg of the title compound to its corresponding diastereomeric acetal following general procedure B. Ee was determined by integration of the signals at 38.32 min (*major*) and 38.10 min (*minor*) corresponding to the two diastereomeric acetals after injection in GC-MS analysis. (GC-MS analysis: Agilent 122-553ui, 5% phenyl 10% dimethylarylenesiloxane column, 1.7 mL/min helium flow rate, 150°C for 2 min, then temperature ramp to 280°C at 2.5°C/min rate).^{1}H NMR and ^{13}C NMR were according to those reported in literature.[S15]



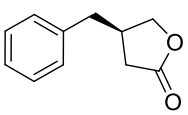
(**10**): The title compound was isolated by flash column chromatography(SiO_2, cyclohexane/EtOAc 9/1) as a colourless oil (20 mg, 0.08 mmol, 40% yield, 92% ee). Ee was determined by chiral HPLC analysis using Daicel Chiralpak®IC column, hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min, 30°C, λ = 210 nm: τ_{major}= 18.75 min., τ_{minor} = 15.65 min.; ^{1}H NMR and ^{13}C NMR were according to those reported in literature.[S16]



(**11**): The title compound was isolated by flash column chromatography(cyclohexane/EtOAc from 9/1 to 8/2) as colourless oil (26 mg, 0.11 mmol, 55% yield, 81% ee). Ee was determined by chiral HPLC analysis using Daicel Chiralpak®IA column: hexane/*i*-PrOH 80:20, flow rate 1.00 mL/min, 30°C, λ = 260 nm: τ_{major}= 21.93 min., τ_{minor} = 17.82 min.; ^{1}H NMR and ^{13}C NMR were according to those reported in literature.[S17]

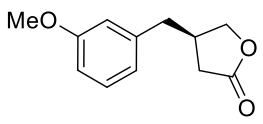


(**12**):The title compound was purified by preparative TLC on silica (cyclohexane/EtOAc 8/2) as colourless oil (31 mg, 0.11 mmol, 53% yield, 87% ee). Ee was determined by chiral HPLC analysis using Daicel Chiralpak®IA column: hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min, 30°C, λ = 260 nm: τ_{major}= 10.91 min., τ_{minor} = 9.62 min.; ^{1}H NMR and ^{13}C NMR were according to those reported in literature.[S15]

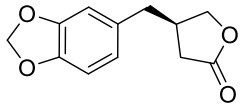


(**13**):The title compound was isolated by flash column chromatography(SiO_2, cyclohexane/EtOAc 9/1)as colourless oil (28 mg, 0.16 mmol, 80% yield, 94% ee).Ee was determined by chiral HPLC analysis using Daicel Chiralpak®AD column: hexane/*i*-PrOH 95:5, flow rate 0.70 mL/min, 40°C, λ = 210 nm: τ_{major}= 17.53 min., τ_{minor} = 18.79 min.;

$[\alpha]_D^{20}$=+15.3 (*c*=0.3 in $CHCl_3$).^{1}H NMR and ^{13}C NMR were according to those reported in literature.[S18]

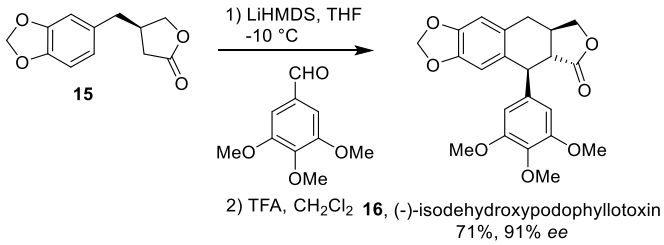


(**14**):The title compound was purified by preparative TLC on silica (cyclohexane/EtOAc 7/3) as colourless oil (26 mg, 0.13 mmol, 64% yield, 93% ee). Ee was determined by chiral HPLC analysis using Daicel Chiralpak®AD column: hexane/*i*-PrOH from 85:15, flow rate 0.70 mL/min, 30°C, λ = 285 nm: τ_{major}= 13.29 min., τ_{minor} = 14.40 min.; ^{1}H NMR and ^{13}C NMR were according to those reported in literature.[S18]



(**15**): The title compound was isolated by flash column chromatography (SiO_2, DCM/EtOAc from 100/0 to 95/5)as colourless oil (32 mg, 0.14 mmol, 72% yield, 89% ee). Ee was determined by chiral HPLC analysis using Daicel Chiralpak®IC column: hexane/*i*-PrOH 60:40, flow rate 1.00 mL/min, 30°C, λ = 287 nm: τ_{major}= 25.94 min., τ_{minor} = 24.80 min.; ^{1}H NMR and ^{13}C NMR were according to those reported in literature.[S18]

Synthesis of (-)-isodeoxypodophyllotoxin



To a solution of LiHMDS (1 M in hexanes, 1.2 mL, 1.2 mmol) in THF (1 mL), a solution of lactone **15** (66 mg, 0.3 mmol) and 3,4,5-trimethoxybenzaldehyde (60 mg, 0.3 mmol) in THF (3 mL) was added dropwise at -10 °C. The reaction was stirred at -10°C for 30 minutes and was allowed to raise at 0 °C in 30 min. After complete conversion of the starting lactone (determined by TLC analysis) a solution of aqueous 15% of HCl pre-cooled at -10 °C was added at -10°C and the reaction mixture was extracted with EtOAc (3x8 mL). The collected organic layers were washed with saturated solution of $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated under reduced pressure.

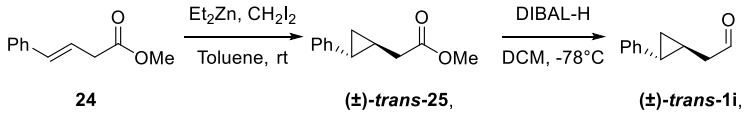
The crude product was dissolved in anhydrous CH_2Cl_2 (2.5 mL) and TFA (2.5 mL) was added dropwise. The reaction mixture was stirred overnight and the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc (25 mL), washed with saturated solution of $NaHCO_3$, and brine. The collected organic layers were dried over Na_2SO_4, filtered and concentrated under

reduced pressure to give a white solid. The title compound was isolated by flash column chromatography(SiO_2, cyclohexane/EtOAc 6/4)as white solid(84 mg, 0.21 mmol, 71% yield, 89% ee). After crystallization from boiling EtOH the ee increase to 91%.

Ee was determined by chiral HPLC analysis using Daicel Chiralpak®IA column: hexane/*i*-PrOH 50:50, flow rate 1.00 mL/min, 40°C, λ = 295 nm: τ_{major}= 8.5 min., τ_{minor} = 7.8 min.; ^{1}H NMR and ^{13}C NMR were according to those reported in literature.[S19] $[\alpha]_D^{20}$ = -79.8 (*c*=1.4 in $CHCl_3$). Lit: $[\alpha]_D^{20}$ = -81.2 (*c*=1.0 in $CHCl_3$).[S20]

Mechanistic insight

Synthesis of aldehyde(±)-*trans*1i



24 **(±)-*trans*-25**, **(±)-*trans*-1i**,

Methyl ester **24** was prepared according to literature procedure.[S21]

Procedure for the cyclopropanation reaction.

(±)-*trans*-25. In a Schlenk tube under nitrogen atmosphere, **24** (497 μL, 3.00mmol, d = 1.063 g/mL) was dissolved in 2 mL of toluene. Then Et_2Zn (1.1 M in toluene, 10.9 mL, 12 mmol) and CH_2I_2 (1.9 mL, 24 mmol) were added. The reaction was stirred for 24 h and during this time a white precipitate was formed. After complete conversion was determined by GC-MS analysis, the mixture was cooled to 0°C and carefully quenched by addition of 1M aq. HCl until acid pH. After addition of EtOAc (15 mL), the organic phase was separated and the aqueous layer extracted with EtOAc (2x15 mL). The collected organic phases were filtered thought a Celite® pad, the solution was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, cyclohexane/EtOAc from 100/0 to 95/5) to afford**(±)-*trans*-25** as colourless oil (455 mg, 2.39 mmol, 80% yield).

^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ= 0.88 (dt, J_1 = 8.6 Hz, J_2 = 5.3 Hz, 1H), 1.03 (dt, J_1 = 8.6 Hz, J_2 = 5.3 Hz, 1H), 1.36-1.45 (m, 1H), 1.74-1.82 (m, 1H), 2.37 (dd, J_1 = 15.7 Hz, J_2 = 7.0 Hz, 1H), 2.48 (dd, J_1 = 15.7 Hz, J_2 = 7.0 Hz, 1H), 3.72 (s, 3H), 7.10 (pd, J = 7.7 Hz, 2H), 7.17 (pt, J = 7.2 Hz, 1H), 7.68 (pt, J = 7.2 Hz, 2H); ^{13}CNMR (100 MHz, $CDCl_3$, 25°C): δ= 15.3, 18.4, 22.8, 38.7, 51.6, 125.6, 126.0 (2C), 128.2 (2C), 142.5, 173.1; ESI-MS *m/z*: 191.1 $[M+H]^+$, 213.1 $[M+Na]^+$.

Procedure for the reduction to aldehyde.

(±)-*trans*-1i:To a solution of **(±)-*trans*-25** (650 μL, 3.64 mmol, d = 1.063 g/mL) in DCM (8 mL) at -78°C under nitrogen atmosphere, a solution of DIBAL-H (1M in DCM, 4.00 mL, 4.00 mmol) in DCM (8 mL) was added dropwise over 20 min. After 2 hours complete conversion was observed by TLC and GC-MS analysis. The reaction mixture was diluted with non-anhydrous diethyl ether and warmed to 0°C. Then H_2O (146 μL), 15% aq. NaOH (146 μL), H_2O (364 μL) were sequentially added at 10 min intervals, and a white solid precipitated. After 15 min, $MgSO_4$ was added and the mixture was stirred for further 15 min at rt. Then it was filtered through a Celite® pad and washed with AcOEt (20 mL). The solution was concentrated and the crude product was purified by column chromatography (SiO_2, cyclohexane/EtOAc from 97/3 to 90/10) to afford **(±)-*trans*-1i** (380 mg, 2.38 mmol, 65% yield) as a colourless oil. Spectroscopic properties were according to those reported in literature.[S17]

Synthesis of aldehyde (±)-*cis*-1i

Alkyne **26** was synthesized according to literature procedure.[S22]

Stereoselective reduction of alkyne 26

27: To a solution of $Ni(OAc)_2·4H_2O$ (50 mg, 0.2 mmol) in EtOH (1mL) under nitrogen atmosphere, a solution of $NaBH_4$(67 mg, 1.8 mmol) in EtOH (3mL) was added at rt. The resulting mixture turned immediately black and was stirred for 1 hour, during which a dark precipitate formed. Then a solution of **23**(485 mg, 2.1 mmol) and ethylenediamine (103μL, 1.5 mmol) in EtOH (3 mL) was added and the resulting mixture was stirred for 16hours at rt under nitrogen atmosphere, until complete conversion was observed by GC-MS. The mixture was concentrated and title compound was purified by column chromatography (SiO_2, cyclohexane/EtOAc 8/2) to afford **27**as colorless oil (464 mg, 2.0 mmol, 95% yield).

^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ= 1.31-1.66 (m, 4H), 1.67-1.78 (m, 1H), 1.79-1.97 (m, 1H), 2.54-2.78 (m, 2H), 3.37-3.62 (m, 2H), 3.72-3.98 (m, 2H), 4.20 (dd, J_1 = 4.8 Hz, J_2 = 3.3 Hz, 1H), 5.65-5.80 (m, 1H), 6.52 (dt, J_1 = 11.8 Hz, J_2 = 2.0 Hz, 1H), 7.18-7.26 (m, 1H), 7.29-7.39 (m, 4H); ^{13}CNMR (50 MHz, $CDCl_3$, 25°C): δ= 19.4, 25.4, 29.1, 30.5, 62.0, 66.8, 98.6, 126.5, 128.0 (2C), 128.6 (2C), 128.7, 130.4, 137.3; ESI-MS *m/z*: 233.1 $[M+H]^+$, 255.1 $[M+Na]^+$.

Cyclopropanation reaction and removal of THP protecting group

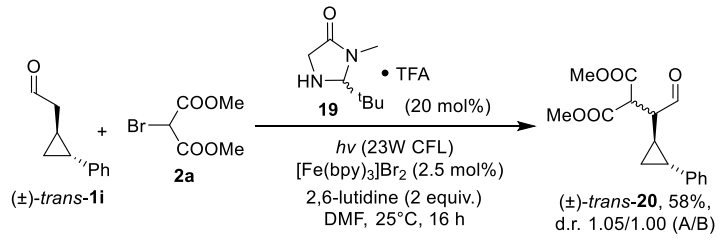
(±)-*cis*-28: Compound **27** (464 mg, 2.00mmol) was subjected to the same protocol described for **25** to obtain protected cyclopropane alcohol**.** The crude was dissolved in DCM/MeOH (1/1 ratio, 20 mL) and *p*-toluenesulfonic acid monohydrate (38 mg, 0.2 mmol) was added. The reaction mixture was stirred for 3 hours at rt, and concentrated under reduced pressure. The residue was subjected to flash column chromatography on $SiO_2$to afford **(±)-*cis*-28** (239 mg, 1.48 mmol, 74 % yield) as colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ= 0.72 (q, J = 5.6 Hz, 1H), 0.96-1.04 (m, 1H), 1.09-1.23 (m, 2H), 1.33-1.45 (m, 1H), 1.53 (d, J = 4.7 Hz, 1H), 2.11-2.18 (pq, 1H), 3.51-3.57 (m, 2H), 7.13-7.20 (m, 3H), 7.23-7.30 (m, 2H);^{13}CNMR (100 MHz, $CDCl_3$, 25°C): δ= 9.1, 15.6, 20.4, 31.6, 62.7, 125.7, 127.9 (2C), 128.9 (2C), 139.1; ESI-MS *m/z*: 163.2 $[M+H]^+$, 185.1 $[M+Na]^+$.

Oxidation of (±)-*cis*-28 to aldehyde (±)-*cis*-1i.

(±)-*cis*-1i:To a solution of**(±)-*cis*-28** (170 mg, 1.05 mmol) in DCM (5 mL) at 0°C, Dess-Martin periodinane (535 mg, 1.26 mmol) was added. After 30 minutes, the solution was allowed to warm to rt. TLC analysis after 2hours revealed partial conversion, thus further Dess-Martin periodinane (200 mg, 0.47 mmol) was added to achieve complete conversion. The reaction was quenched by addition of $NaHCO_3$ aq. sat. solution (5 mL) and $Na_2S_2O_3$ aq. sat. solution (5 mL). The organic layer was separated and the aqueous one was extracted with DCM (3 x10 mL). The collected organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. After purification by flash column chromatography (SiO_2, cyclohexane/EtOAc 9/1),**(±)-*cis*-1i**(128 mg, 0.80 mmol, 76% yield) was obtained as colourless oil. Spectroscopic properties were according to those reported in literature.[S17]

Photoalkylation of aldehyde (±)-*trans* 1i.



(±)-*trans*-17 was prepared according to the general procedure for photoalkylation of aldehydes on 0.5 mmol scale, using **(±)-*trans*-2i** as aldehyde and **19** as Macmillan catalyst. The crude product was purified by column chromatography (cyclohexane/EtOAc from 9/1 to 8/2) to afford pure **(±)-**

***trans*-20** as a yellowish oil (84 mg, 0.29 mmol, 58% yield) as an inseparable mixture of diastereoisomers (**A:B**, 1.05:1.00 ratio).

^{1}H NMR (400 MHz, $CDCl_3$, 25°C) (two diastereoisomers A:B, 1.05:1.00 ratio):δ = 0.91-0.97 (m, $1H_A$), 1.05-1.21 (m, $2H_A$ +$2H_B$), 1.23-1.30 (m, $1H_B$), 1.81-1.89 (m, $1H_B$), 2.09-2.18 (m, $1H_A$), 2.59 (t, J = 10.1 Hz, $1H_A$), 2.61 (t, J = 9.8 Hz, $1H_B$), 3.46 (s, $3H_B$), 3.70 (s, $3H_B$), 3.77 (s, $3H_A$), 3.79 (s, $3H_A$), 3.89 (d, J = 8.7 Hz, $1H_A$), 3.90 (d, J = 9.2 Hz, $1H_B$), 7.02 (d, J = 7.5 Hz, $1H_A$ +$1H_B$), 7.08 (d, J = 7.4 Hz, $1H_A$ +$1H_B$), 7.14-7.21 (m, $1H_A$ +$1H_B$), 7.22-7.30 (m, $2H_A$ +$2H_B$), 9.85 (s, $1H_A$), 9.87 (s, $1H_B$); ^{13}CNMR (100 MHz, $CDCl_3$, 25°C) (two diastereoisomers A:B, 1.05:1.00 ratio): δ= 14.3 ($1C_A$), 14.5 ($1C_B$), 19.2 ($1C_B$), 19.7 ($1C_A$), 21.6 ($1C_A$), 23.2 ($1C_B$), 51.3 ($1C_B$), 51.4 ($1C_A$), 52.6 ($1C_B$), 52.7 ($1C_A$), 52.8 ($1C_B$), 52.9 ($1C_A$), 54.9 ($1C_A$), 55.0 ($1C_B$), 125.6 ($1C_A$+$1C_B$), 126.0 ($2C_A$+$1C_B$), 126.1 ($1C_B$), 128.3 ($2C_A$), 128.4 ($2C_B$), 140.9 ($1C_A$), 141.2 ($1C_B$), 168.3 ($2C_A$), 168.43 ($1C_B$), 168.44 ($1C_B$), 199.6 ($1C_A$), 199.7 ($1C_B$);ESI-MS *m/z*: 291.2 $[M+H]^+$.

^{1}H NMR signals were assigned by COSY experiment (Figures S3-5). The *trans* stereochemistry of the substituents on cyclopropane ring was established by performing n.O.e. experiments on pure **(±)-*trans*-20** as mixture of diastereoisomers. Selective excitation ^{1}H NMR spectra were recorded on Varian Mercury 400 in a mixture of $CDCl_3$ and TFA (10%), using a DPFGSE-NOE sequence with a 50 Hz 'rsnob' pulse and a mixing time of 1.5 seconds.

Selective excitation of H^4 signal relative to diastereoisomer **A** (Figure S6) shows a positive n.O.e. on different protons present in the molecule. In particularly it was observed a much more intense positive n.O.e. (0.71 considered 100 the intensity of the irradiated signal) on H^6 proton than on H^3 and H^5 (respectively 0.32 and 0.33 considered 100 the intensity of the irradiated signal).

Similar behaviour was observed in the experiment performed on the diastereoisomer **B** (Figure S7). Also in this case the selective excitation of the proton H^4 gives rise to much more intense positive n.O.e. (1.16 considered 100 the intensity of the irradiated signal) on H^6 proton than on H^3 and H^5 (respectively 0.39 and 0.30 considered 100 the intensity of the irradiated signal).

On the basis of these evidences it is possible to confirm that the two substituents on the cyclopropane ring have *trans* configuration.

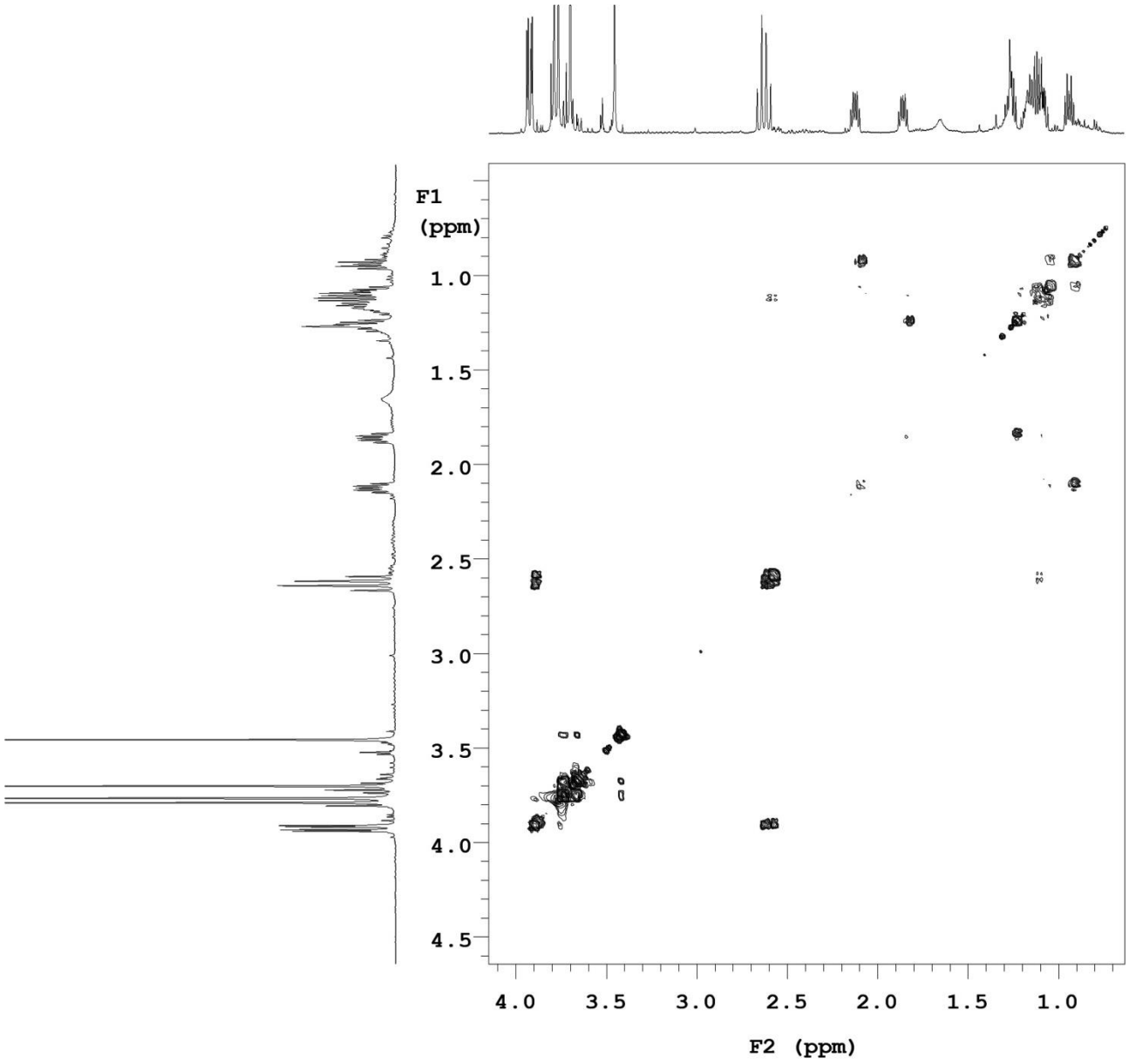


Figure S3. COSY spectra of **(±)-*trans*-20 (A+B).**

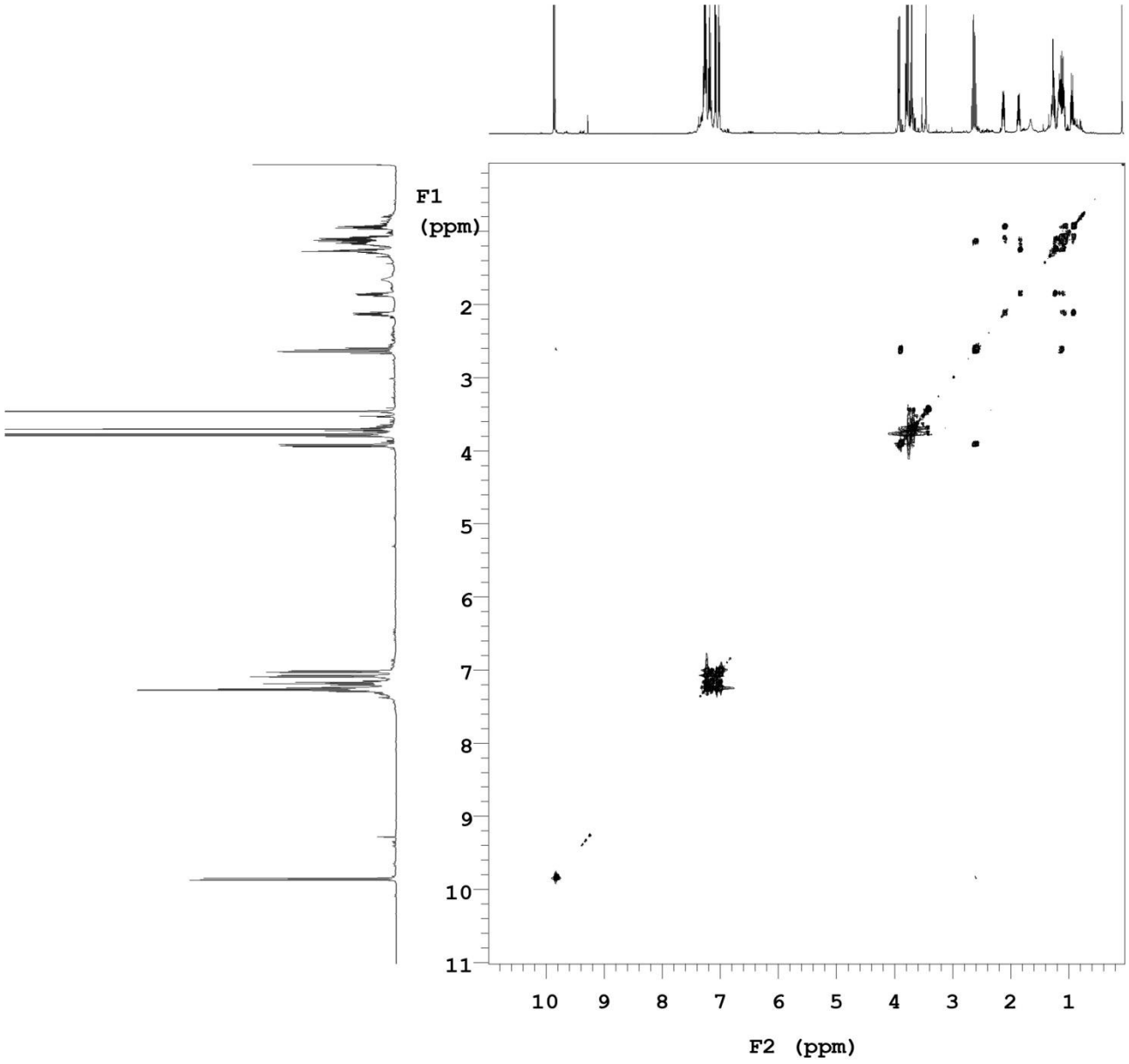


Figure S4. Aliphatic region of COSY spectra of **(±)-*trans*-20 (A+B).**

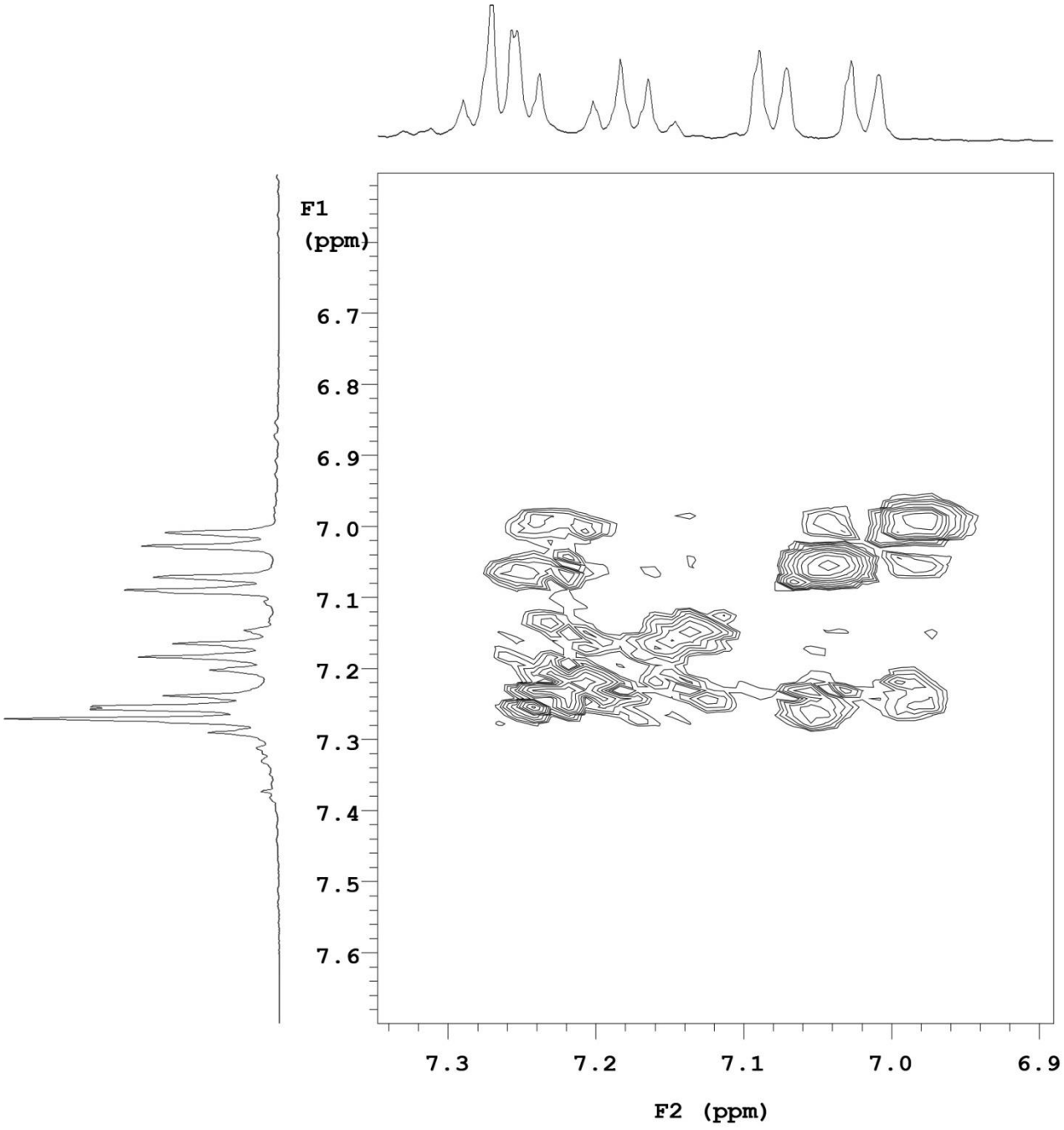


Figure S5. Aromatic region of COSY spectra of **(±)-*trans*-20 (A+B).**

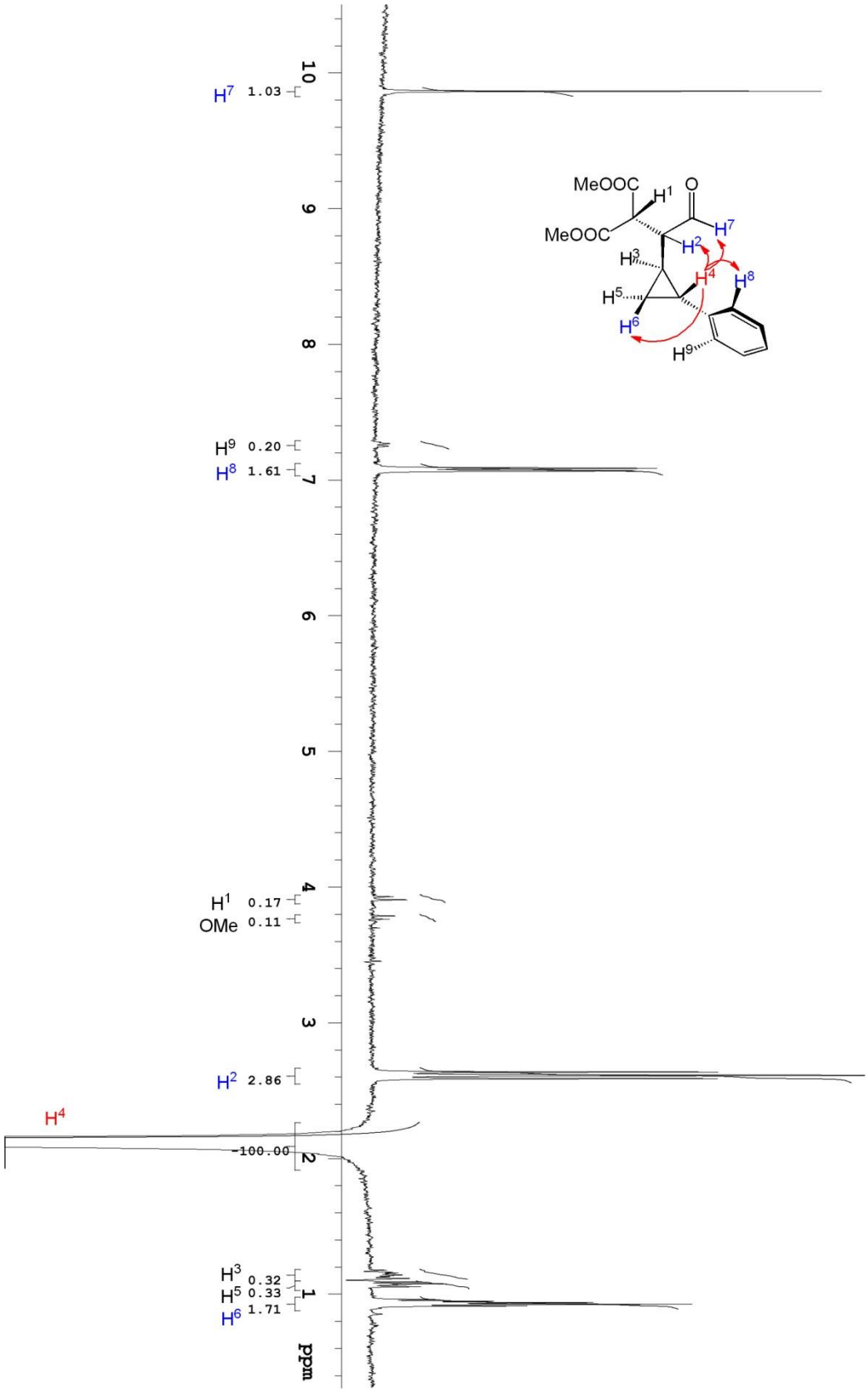


Figure S6. Selective excitation experiment of H^4on compound **(±)-*trans*-20** diastereoisomer **A.**

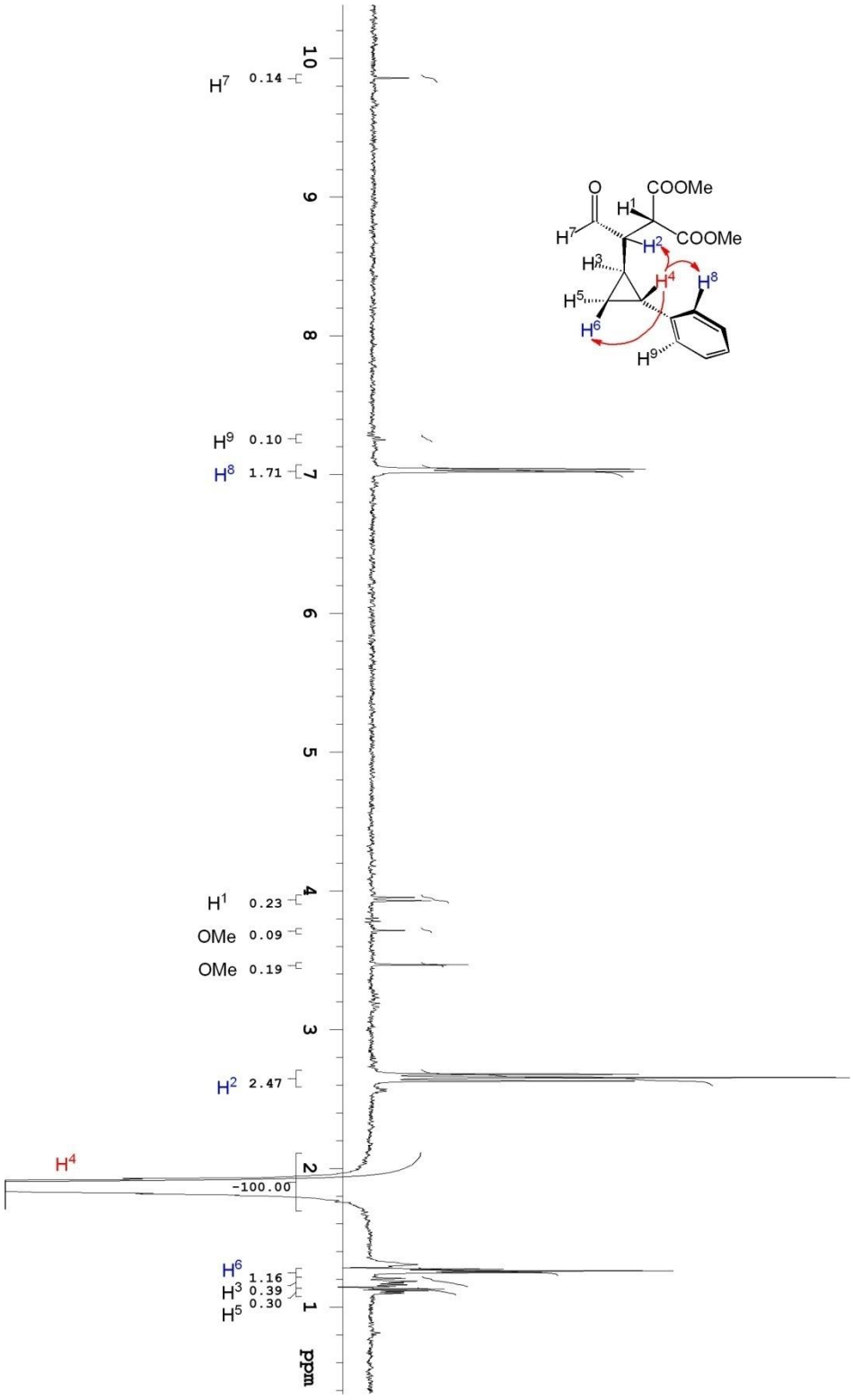
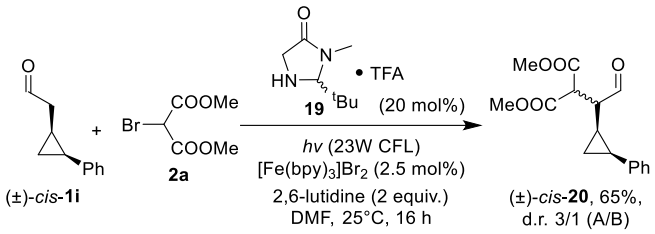


Figure S7. Selective excitation experiment of H^4on compound **(±)-*trans*-20** diastereoisomer **B**.

Photoalkylation of aldehyde (±)-*cis*-1i.



(±)-*cis*-20 was prepared according to general procedure for photoalkylation of aldehydes on 0.3 mmol scale, using **(±)-*cis*-1i** as aldehyde and **19** as Macmillan catalyst. The crude product was a mixture of two diastereoisomers (A/B, 3/1), that presented different retention times in GC-MS analysis and NMR properties compared to those observed for **(±)-*trans*-20**. The crude product was purified by column chromatography (cyclohexane/EtOAc from 9/1 to 8/2) to afford pure **(±)-*cis*-20** as a yellowish oil (54 mg, 0.19 mmol, 62% yield) as single diastereoisomer **A**.

^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 0.97-1.04 (m, 1H), 1.10-1.16 (m, 1H), 1.21-1.31 (m, 1H), 2.37-2.44 (m, 1H), 2.57 (dd, J_1 = 11.4 Hz, J_2 = 8.4 Hz, 1H), 3.72 (3.86 rotamer) (s, 3H), 3.81 (3.87 rotamer) (s, 3H), 3.89 (d, J = 8.4 Hz, 1H), 7.19-7.27 (m, 3H), 7.28-7.36 (m, 2H), 9.28 (s, 1H); ^{13}CNMR (100 MHz, $CDCl_3$, 25°C): δ = 8.9, 17.7, 20.4, 49.2, 51.8, 52.7, 52.6, 126.7, 128.4 (2C), 128.6 (2C), 137.5, 168.4, 168.6, 200.5; ESI-MS *m/z*: 291.2 $[M+H]^+$.

Selective excitation ^{1}H NMR spectra were recorded on Varian Mercury 400 in a mixture of $CDCl_3$ and TFA (10%), using a DPFGSE-NOE sequence with a 50 Hz 'rsnob' pulse and a mixing time of 1.5 seconds.

Selective excitation of H^4 (Figure S8) revealed a positive n.O.e. of comparable intensity of H^3 and H^5 (2.49 and 1.64 respectively considered 100 the intensity of the irradiated signal), while H^6 did not show any n.O.e. effect establishing the *cis* configuration of the cyclopropane ring. This was further confirmed by selective excitation of H^6 signal (Figure S9): a positive n.O.e effect was observed on geminal H^5 (12.62 considered 100 the intensity of the irradiated signal) while no response was observed either for H^3 either for H^4 accordingly with the assigned *cis* configuration. Moreover selective excitation of H^2 (Figure S8) lead to the observation of a positive n.O.e effect on H^6 (2.07 considered 100 the intensity of the irradiated signal), H^8 (2.53 considered 100 the intensity of the irradiated signal), H^7 (2.87 considered 100 the intensity of the irradiated signal) and one of the malonate methyl groups (2.04 considered 100 the intensity of the irradiated signal). No n.O.e. was observed on H^3, H^4 and for H^5 accordingly with the assigned *cis* configuration.

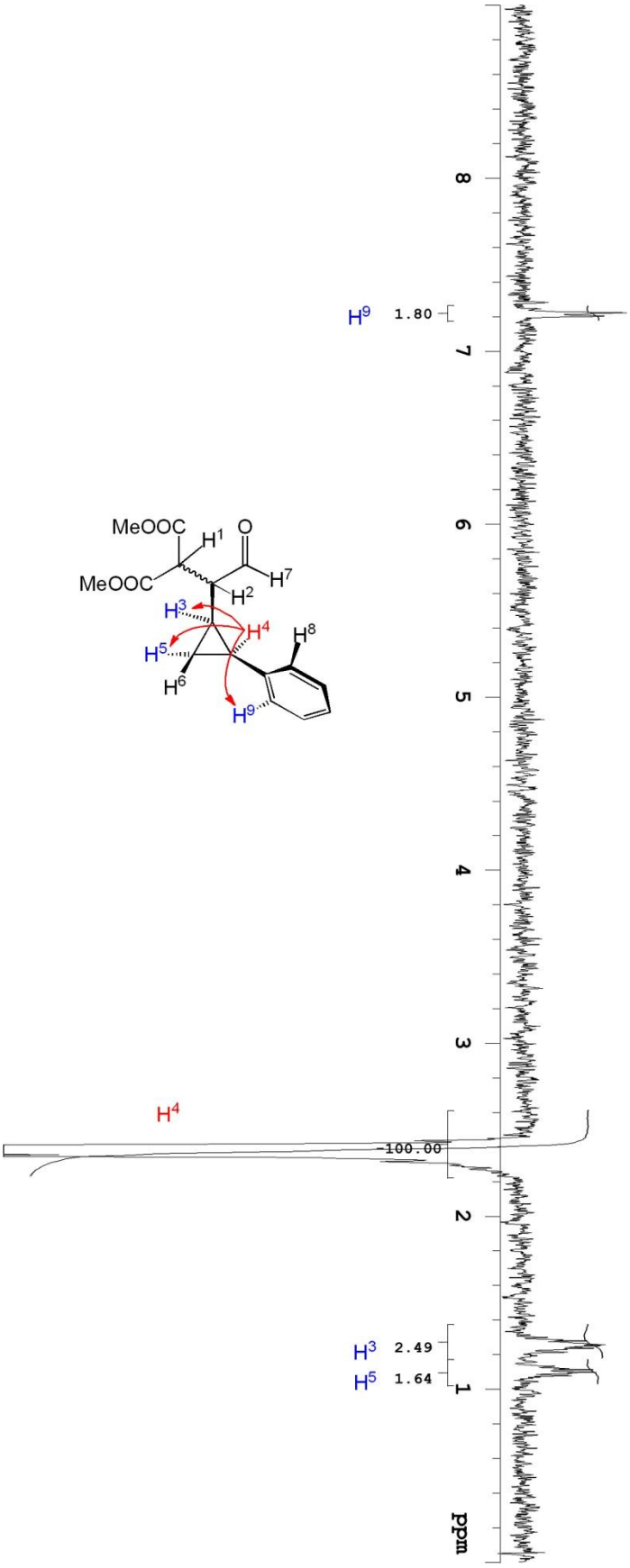


Figure S8. Selective excitation experiment of H^4 on compound**(±)-*cis*-20** major diastereoisomer.

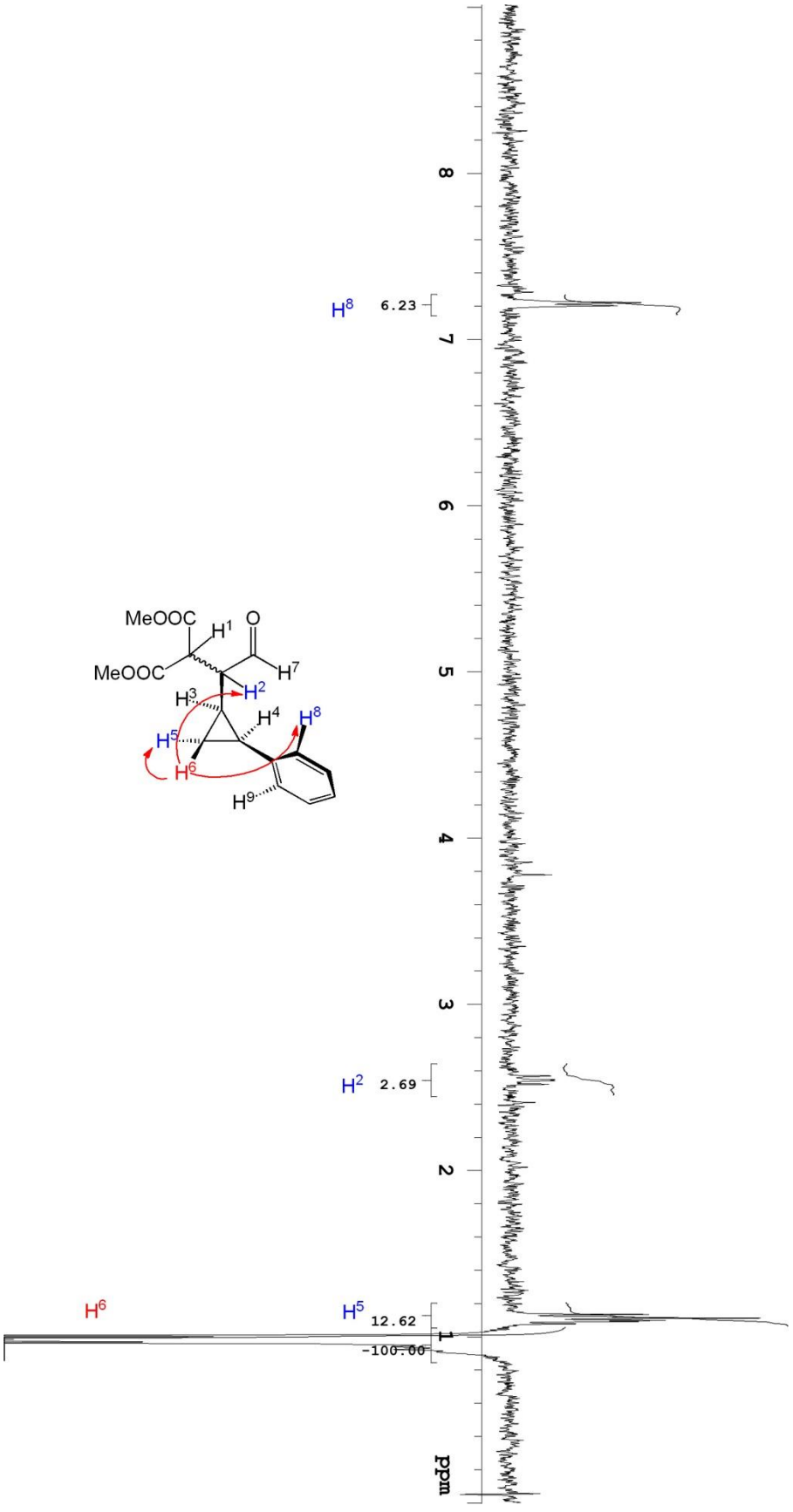


Figure S9. Selective excitation experiment of H^6 on compound**(±)-*cis*-20** major diastereoisomer.

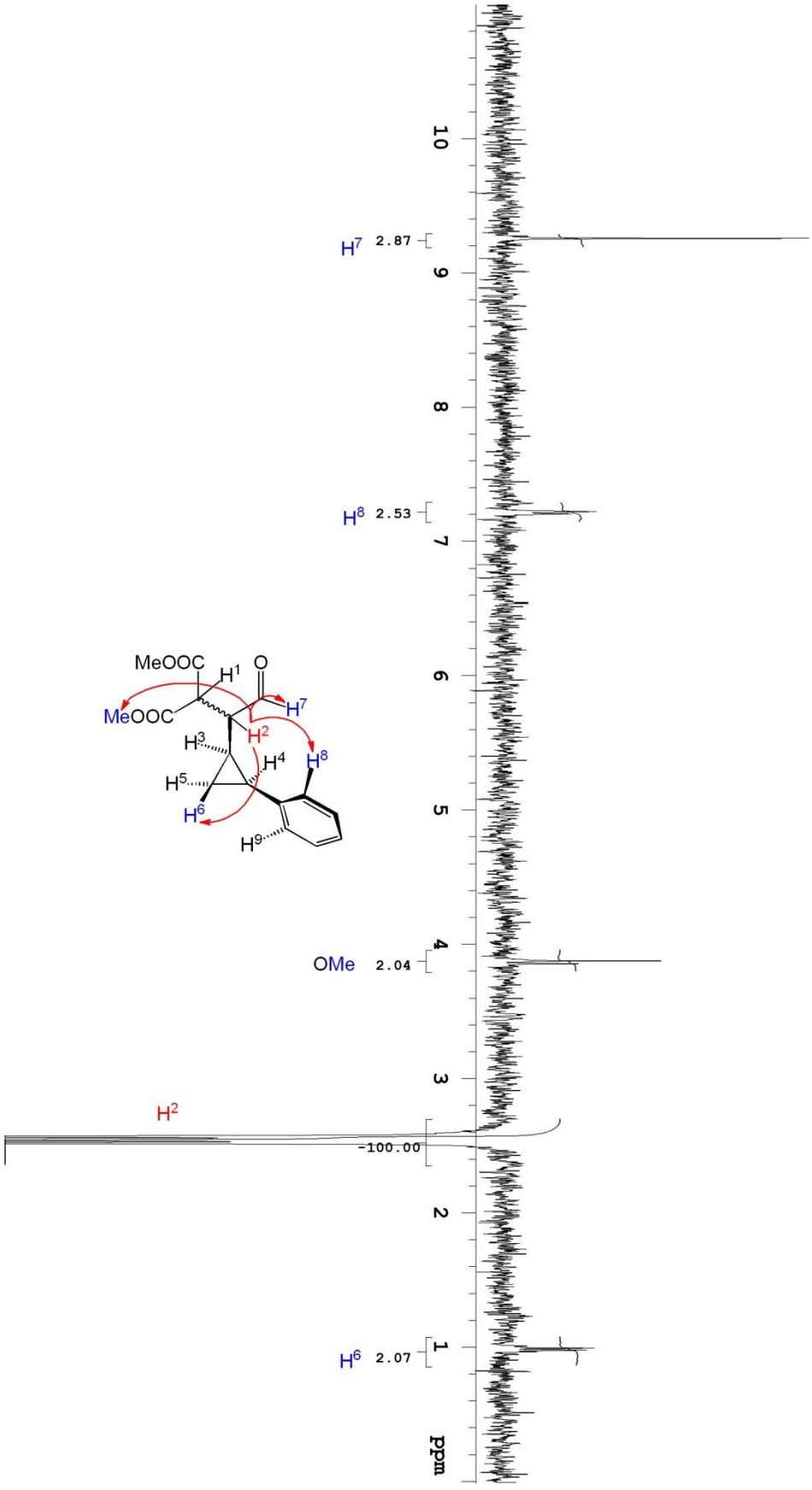
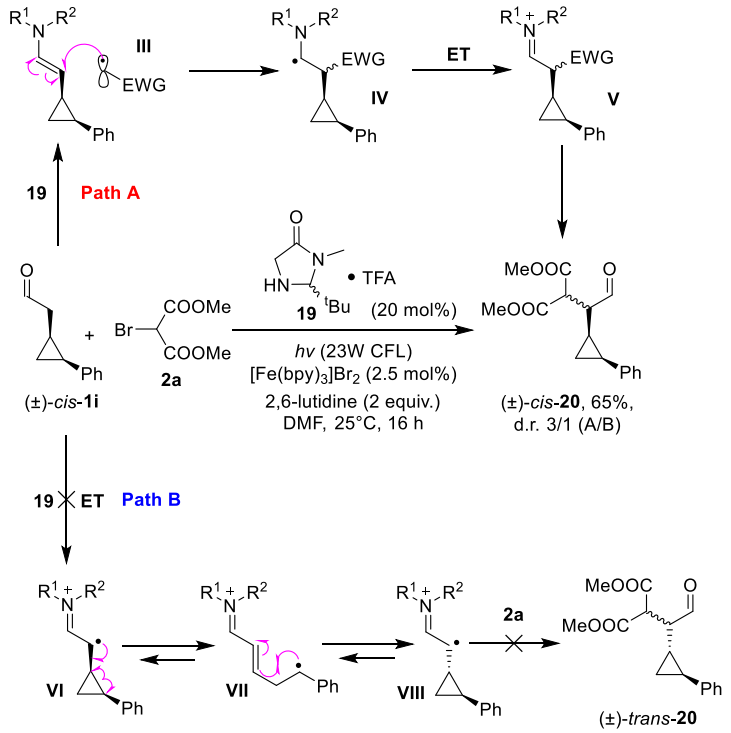


Figure S10. Selective excitation experiment of H^2 on compound**(±)-*cis*-20** major diastereoisomer.

Photoalkylation of *cis*-cyclopropane-substituted aldehyde **(±)-*cis*-1i** with dimethyl bromomalonate (**2a**) was performed to demonstrate that reaction proceeded through a traditional enamine catalysis pathway, with the EWG stabilized carbon-centred radical (**III**) species adding to the generated enamine (**II**) as the propagation step (Path A).

If the reaction proceeded through a radical-cation pathway (Path B), the cyclopropylcarbinyl radical (**VI**) formed after electron transfer process should undergo fast ring-opening (**VII**) and ring closing prior to C-C bond formation leading to the thermodynamically more stable intermediate (**VIII**) and consequentially to the product **(±)-*trans*-20**.

When **(±)-*cis*-1i** was subjected to the photocatalytic alkylation protocol with bromide **2a** the **(±)-*cis*-20** product was exclusively formed, excluding the reaction pathway B and confirming the reaction pathway A.



Photophysical measurements

Photochemical experiments were carried out at room temperature in deaerated solutions. All absorption spectra were recorded in a quartz cuvette (optical pathlength 0.1 cm) with a UV/VIS spectrophotometer Perkin Elmer Lambda 650.

The irradiation was performed with an halogen lamp (24V, 250W), cut-off filter at 420 nm, in a reaction mixture containing $[Fe(bpy)_3]Br_2$ (0.0005mmol), dimethylbromomalonate **2a**(0.2 mmol), 2,6-lutidine (0.4 mmol), 3-phenylpropanal **1a**(0.4 mmol) and MacMillan catalyst **20** (0.04 mmol) in 400 μL DMF Uvasol® stirred solution.

The amount of reagents dissolved in DMF for the spectrophotometric measurement comply with quantities used in reaction mixture excluding $[Fe(bpy)_3]Br_2$ that was used in smaller quantities to register the absorption spectrum.

Ultrafast absorption spectroscopy experiments were carried upon 510 nm excitation using a pump-probe detection system based on the Spectra-Physics Hurricane Ti: sapphire laser source and the Ultrafast Systems Helios spectrometer. 510-nm pump pulses were generated by Spectra Physics OPA. Probe pulses were obtained by continuum generation on a sapphire plate (useful spectral range: 450-800 nm). Effective time resolution ca. 300 fs, temporal chirp over the white-light 450-750 nm range ca. 200 fs, temporal window of the optical delay stage 0-2000 ps.

To get a better insight into the reaction mechanism from the photochemical point of view, we investigated ground- and excited state interactions between the photosensitizer $[Fe(bpy)_3]Br_2$ and each component of the reaction mixture. The absorption band in the visible region of the $[Fe(bpy)_3]Br_2$. complex is not affected by the reagents and, as previously stated, does not change at the end of the irradiation. Due to the very short lifetime of the lowest energy excited state of the iron(II) complex, we used femtosecond laser absorption spectroscopy to monitor the possibility of excited state interactions. Upon irradiation at 510 nm of a 5.7 x 10-4 M solution of $[Fe(bpy)_3]Br_2$ in DMF, the characteristic bleaching of the MLCT absorption band was observed at very short time delay (t = 1.2 ps, Figure S13a). This transient then decays monotonically to the baseline. Plot of the absorbance change (ΔA) at 535 nm as a function of time results in a mono exponential decay with a lifetime of 570 ps (Figure S13b, black line), very similar to the literature reported values for the ligand field excited state (MC). Upon addition of bromomalonate (in the range 0.5-6.8M) or enamine obtained from (5*S*)-2,2,3-trimethyl-5-phenylmethyl-4-imidazolidinone (0.06 M; see SI for details), no appreciable changes in the transient absorption feature were measured (Figure S13), in agreement with the proposed chain reaction mechanism. The excited state of $[Fe(bpy)_3]^{2+}$ is involved only to start the chain reaction, so that the efficiency of quenching is so low that cannot be detected.

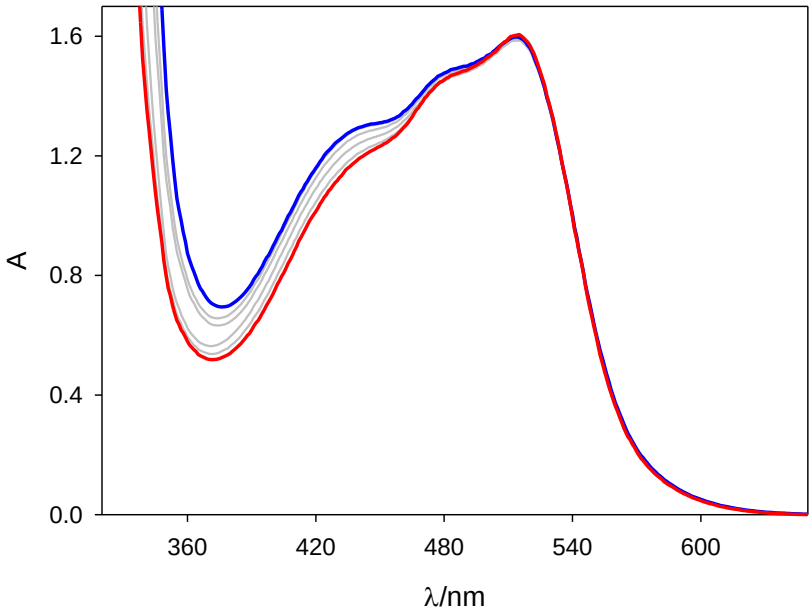


Figure S11. Reaction mixture composed of: $[Fe(bpy)_3]Br_2$ 1.2 × 10^{-3} M, 2,6-lutidine 1 M, dimethyl bromomalonate **2a** 0.5 M, 3-phenylpropanal **1a** 1 M and MacMillan catalyst **20** 0.1 M in DMF solution irradiated for 0 min (red solid line), 30 min, 80 min, 130 min, 240 min (grey solid lines) and 360 min (blue solid line).

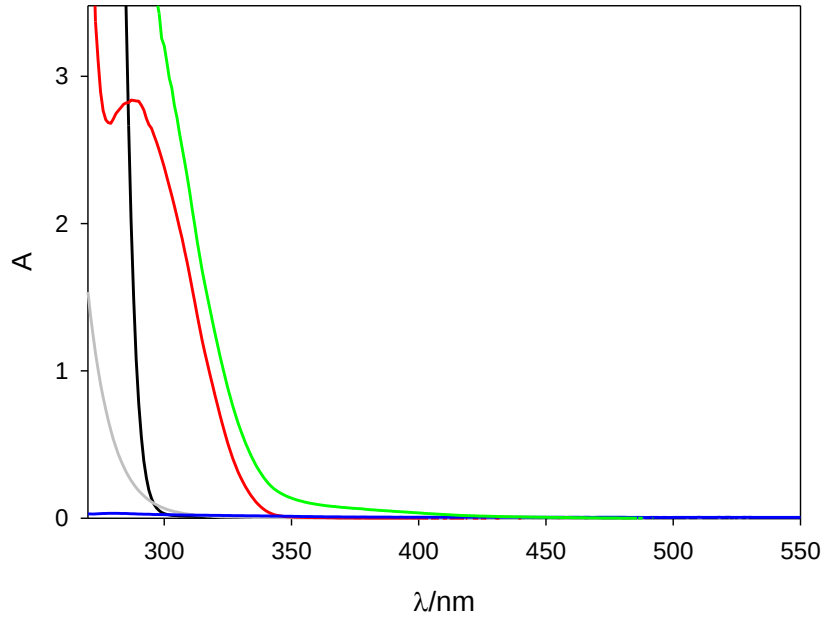


Figure S12. Absorption spectra of 2,6-lutidine 1 M (black solid line), dimethyl bromomalonate**2a** 0.5 M (grey solid line), 3-phenylpropanal **1a**1 M (red solid line), MacMillan catalyst**16** 0.1 M (blue solid line) and complete reaction mixture without $[Fe(bpy)_3]Br_2$ (green solid line) in DMF. The amount of the species in solution is the same used during the photoreaction.

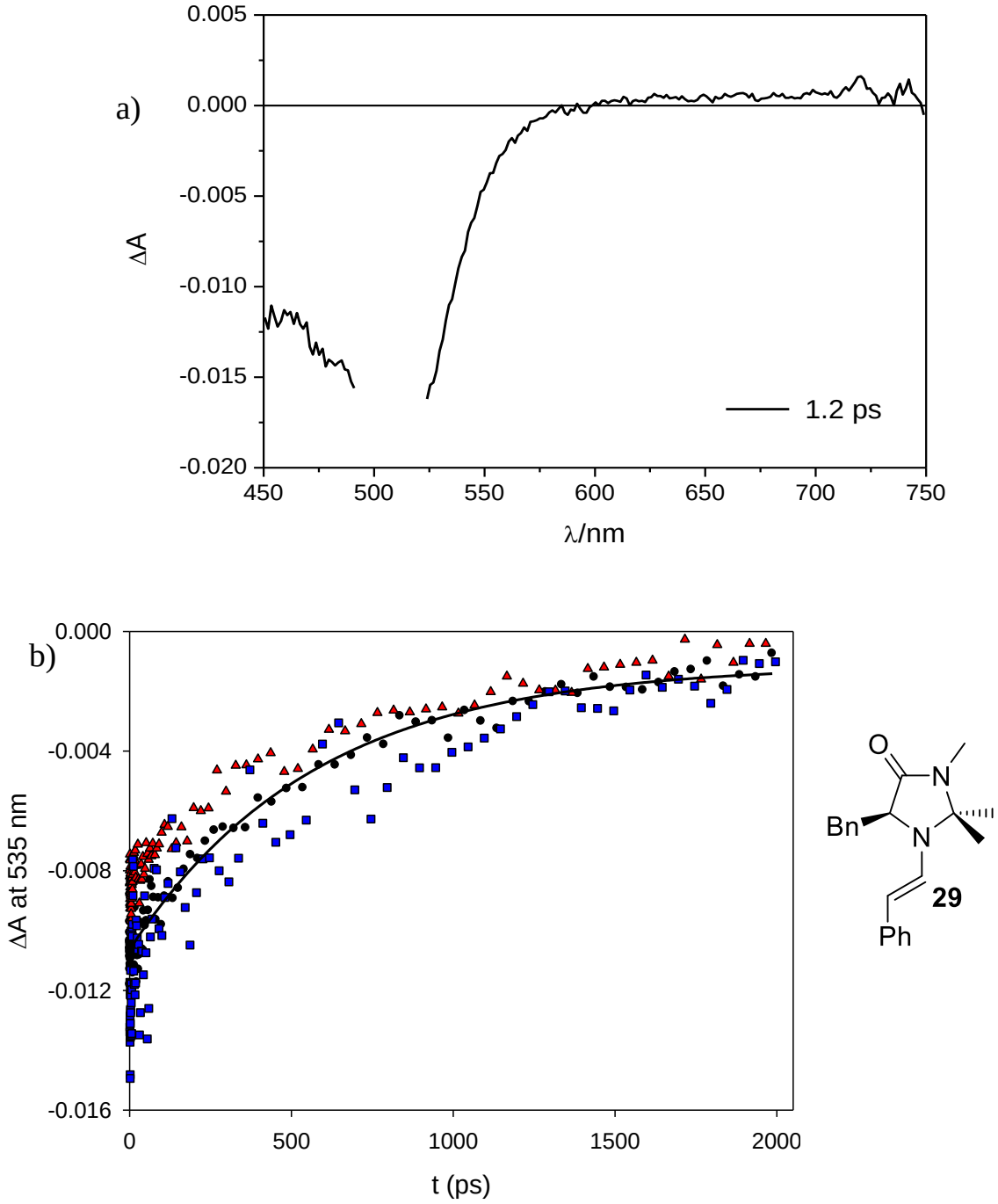


Figure S13. (a)Transient absorption spectrum at 1.2 ps time-delay obtained by ultrafast spectroscopy (excitation at 510 nm) of $[Fe(bpy)_3]Br_2$(concentration 5.7 x 10^{-4} M in DMF); (b)Exponential decay (upon laser excitation at 510 nm) of absorption changes at 535 nm of: $[Fe(bpy)_3]Br_2$(5.7 x 10^{-4} M, black circle), $[Fe(bpy)_3]Br_2^{+}$(5.7 x 10^{-4} M) with dimethyl bromomalonate (**2a**) 0.5 M (red triangle) and $[Fe(bpy)_3]Br_2$ (5.7 x 10^{-4} M) with enamine **29** 0.06 M (blue square) in DMF stirred solution. The amount of dimethyl bromomalonate (**2a**)in solution is the same used to perform the photoreaction. The black solid line is the fitting curve of $[Fe(bpy)_3]Br_2$exponential decay: the lifetime obtained from the fitting in 570 ps.

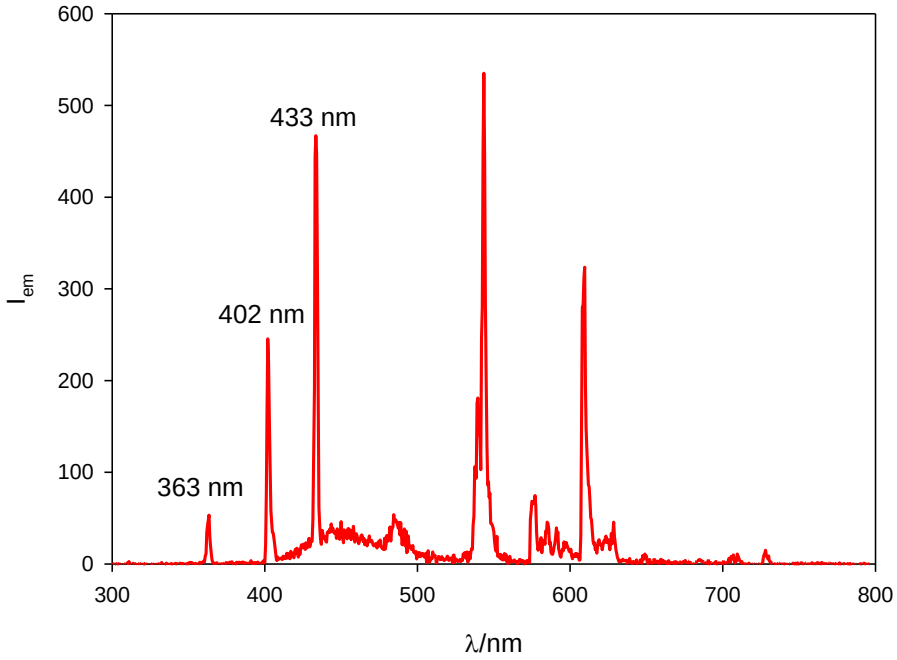


Figure S14. Emission profile of the 23W Compact Fluorescent lamp used to irradiate the solutions.

EPR Studies

EPR measurements. ESR spectra were obtained by photolysing the reaction mixture with a filtered light from a 500 W high pressure mercury lamp directly inside the cavity of a Bruker ELEXYS spectrometer equipped with a ER033M Field Frequency Lock. The instrument settings were as follows: microwave power 5.0 mW, modulation amplitude 0.05 mT, modulation frequency 100 kHz, scan time 180 s. An iterative least squares fitting procedure based on the systematic application of the Monte Carlo method was performed in order to obtain the experimental spectral parameters of the radical species.[23]

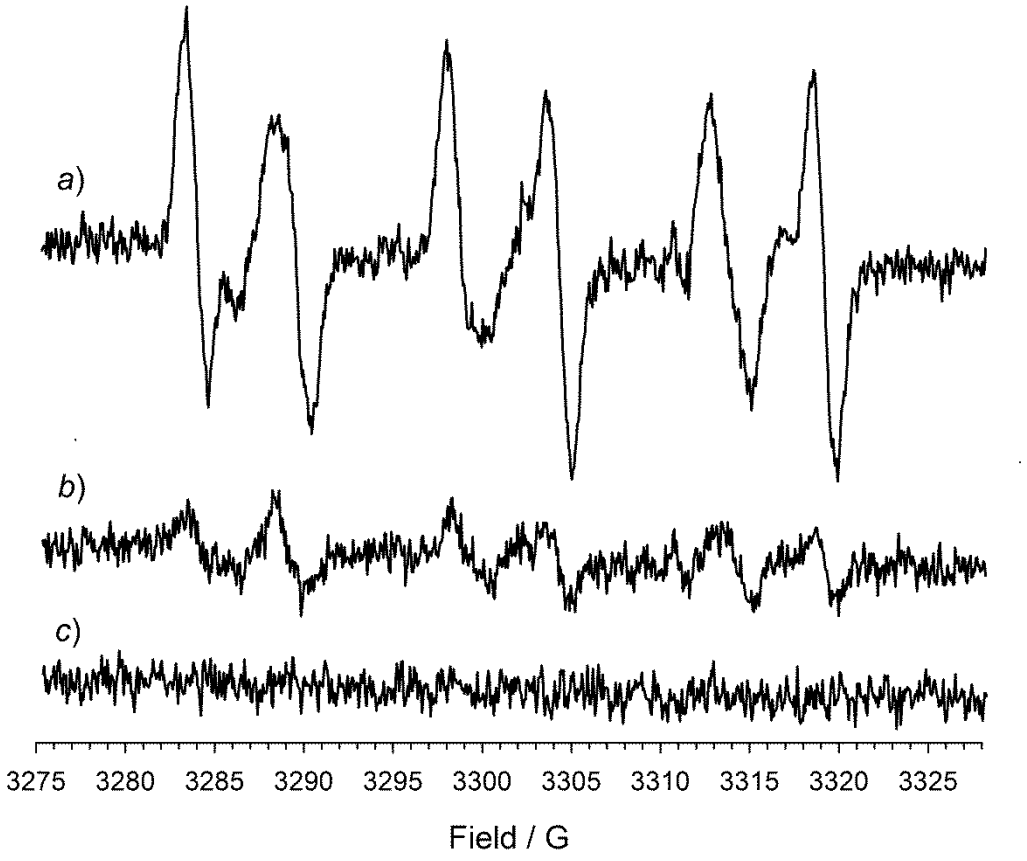


Figure SI15. EPR spectra of spin adduct **18**generated in DMF in the presence of bromo ester **2e** (0.5 M) and PBN (0.1 M) as the spin trap at room temperature (microwave power, 5 mW; modulation frequency, 100 kHz; modulation amplitude, 0.4 G).Reaction conditions: a) $[Fe(bpy)_3]Br_2$ (10 mol %), irradiation with UV-visible light (λ>320 nm); b) $[Fe(bpy)_3]Br_2$ (10 mol%), irradiation with visible light (λ>420 nm); c) $[Fe(bpy)_3]Br_2$ (10 mol%) no irradiation.

References

S1 Righi, G.; Rumboldt, G. *J. Org. Chem.* **1996**, 61, 3557-3560.

S2 Zhao, Y.; Jiang, X.; Yeun, Y-Y *Angew. Chem Int. Ed*. **2013**, 52, 8597-8601.

S3 Cui, M.; Ono, M.; Kimura, H.; Liu, B.; Saji, H. *Bioorg. Med. Chem.* **2011**, 19, 4148–4153.

S4 Morphy, J. R.; Rankovic, Z.; York, M. *Tetrahedron* **2003**, 59, 2137–2145.

S5 Graham, T. H.; Horning, B. D.; MacMillan, D. W. C. *Org. Synth.* **2011**, 88, 42-53.

S6 Bouzaid, J.; Schultz, M.; Lao, Z.; Bartley, J.; Bostrom, T.; McMurtrie, J. *Cryst. Growth Des.* **2012**,12, 3906–3916.

S7 Silvi, M.; Arceo, E.; Jurberg, I. D.; Cassani, C.; Melchiorre, P. *J. Am. Chem. Soc.* **2015**, 137, 6120.

S8 a) Bartels, B.; Schmidt, M.; Pekari, K.; Beckers, T.; Zimmermann, A.; Gekeler, V.; Assignee: Nycomed GmbH, Germany, PCT Int. Appl., 2008020045, 21 Feb 2008; b) Pathania, V.; Sharma, A.; Sinha, A. K. *Helv. Chim. Acta* **2005**, 88, 811-816.

S9 Piperonal was prepared according to literature procedure: Manoni, E.; Gualandi, A.; Mengozzi, L.; Bandini, M.; Cozzi, P. G. *RSC Adv.* **2015**, 5, 10546-10550.

S10 Kona, J. R.; King'ondu, C. K.; Howell, A.R.; Suib, S. L. *ChemCatChem* **2014**, 6, 749–752.

S11 Brown, T. H.; Blakemore, R. C.; Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Parsons, M. E.; Rawlings, D. A.; Walker, T. F. *Eur. J. Med. Chem.* **1988**, 23, 53-62.

S12 Makhey, J. D.; Li, D.; Zhao, B.; Sim, S.-P.; Li, T.-K.; Liu, A.; Liu, L. F.; LaVoie, E. J. *Bioorg. Med. Chem*. **2003**, 11, 1809–1820.

S13 Browder, C. C.; Marmsater, F. P.; West, F. G. *Cand. J. Chem.* **2004**, 82 , 375-385.

S14 Schobert, R., Siegfried, S.; Gordon, G. J.*J. Chem. Soc. Perkin Trans.* **2001**, 1, 2393–2397.

S15 Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, 322, 77–80.

S16 Riente, P.; Adams,A. M.; Albero, J.; Palomares, E.; Pericàs, M. A. *Angew. Chem*. **2014**, 126, 9767-9770; *Angew. Chem. Int. Ed*. **2014**, 53, 9613–9616.

S17 Arceo, E.; Jurberg, I. D.; Álvarez-Fernández, A.; Melchiorre, P. *Nature Chem.* **2013**, 5, 750–756.

S18 Rudroff, F.; Rydz, J.; Ogink, F. H.; Fink, M.; Mihovilovic, M. D. *Adv. Synth. Catal*. **2007**, 349, 1436–1444.

S19 Bode, J. W.; Doyle, M. P.; Protopopova, M. N.; Zhou, Q.-L. *J. Org. Chem.* **1996**, *61*, 9146.

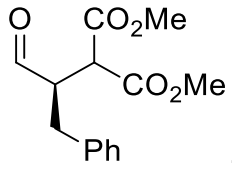
S20 Itoh, T.; Chika, J.; Takagi, Y.; Nishiyama, S. *J. Org. Chem.* **1993**, *58*, 5717.

S21 Izquierdo, J.; Rodríguez, S.; González, F. V. *Org. Lett.* **2011**, 13, 3856-3859.

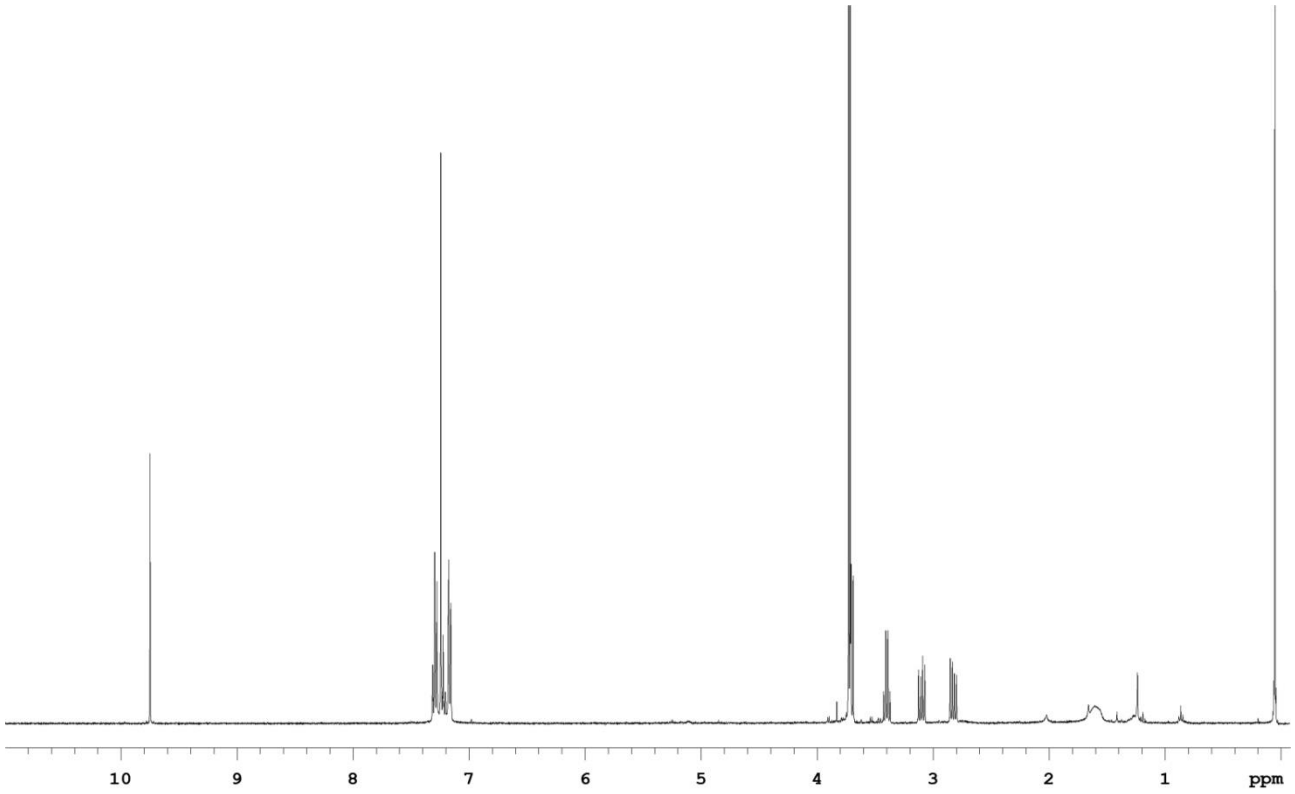
S22 Fuji, K.; Morimoto, T.; Tsutsumi, K.; Kakiuchi, K. *Chem. Commun*. **2005**, 3295–3297.

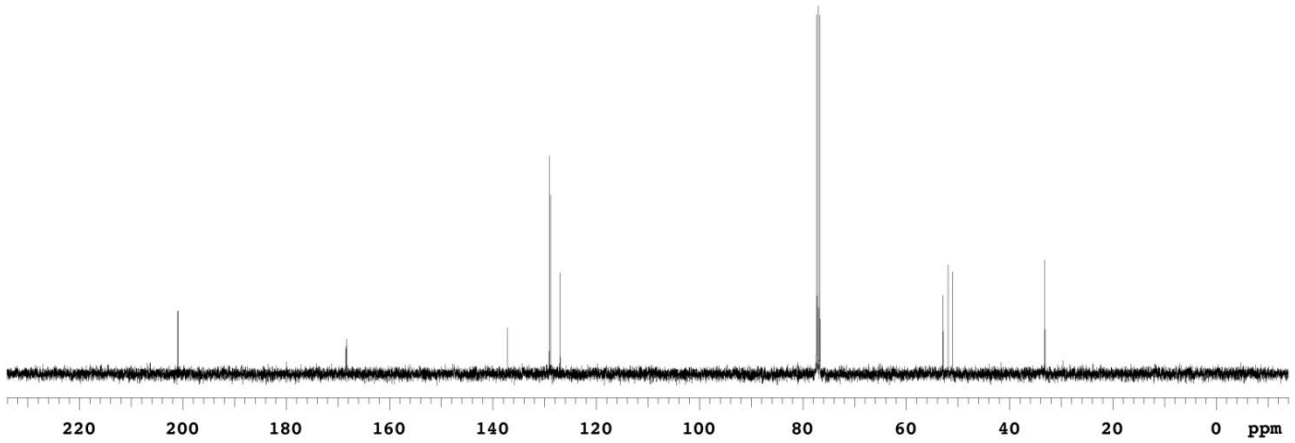
S23 a) Franchi, P.; Mezzina, E.; Lucarini, M. *J. Am. Chem. Soc.* **2014**, 136, 1250; b) Valgimigli, L.; Lucarini, M.; Pedulli, G. F.; Ingold, K. U. *J. Am. Chem. Soc.* **2014**, 119, 8095.

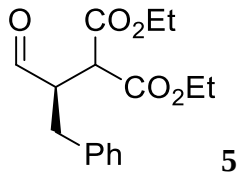
Copies of NMR spectra



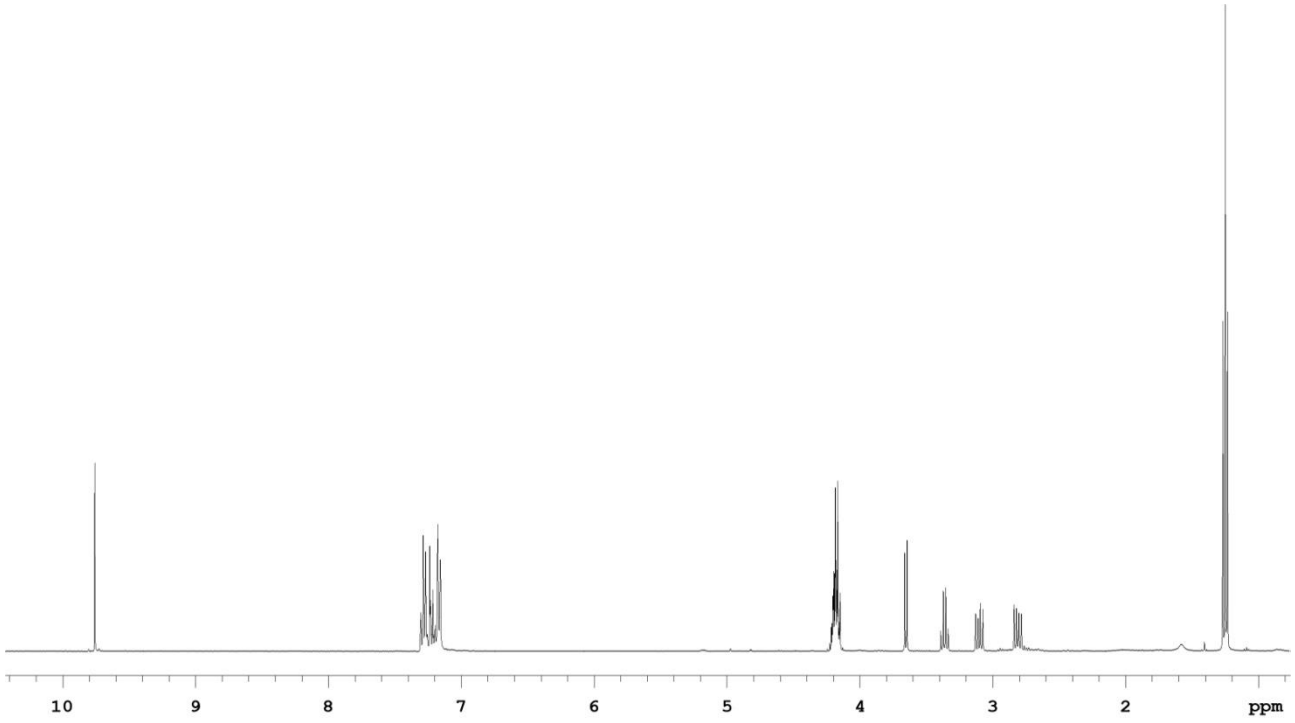
4

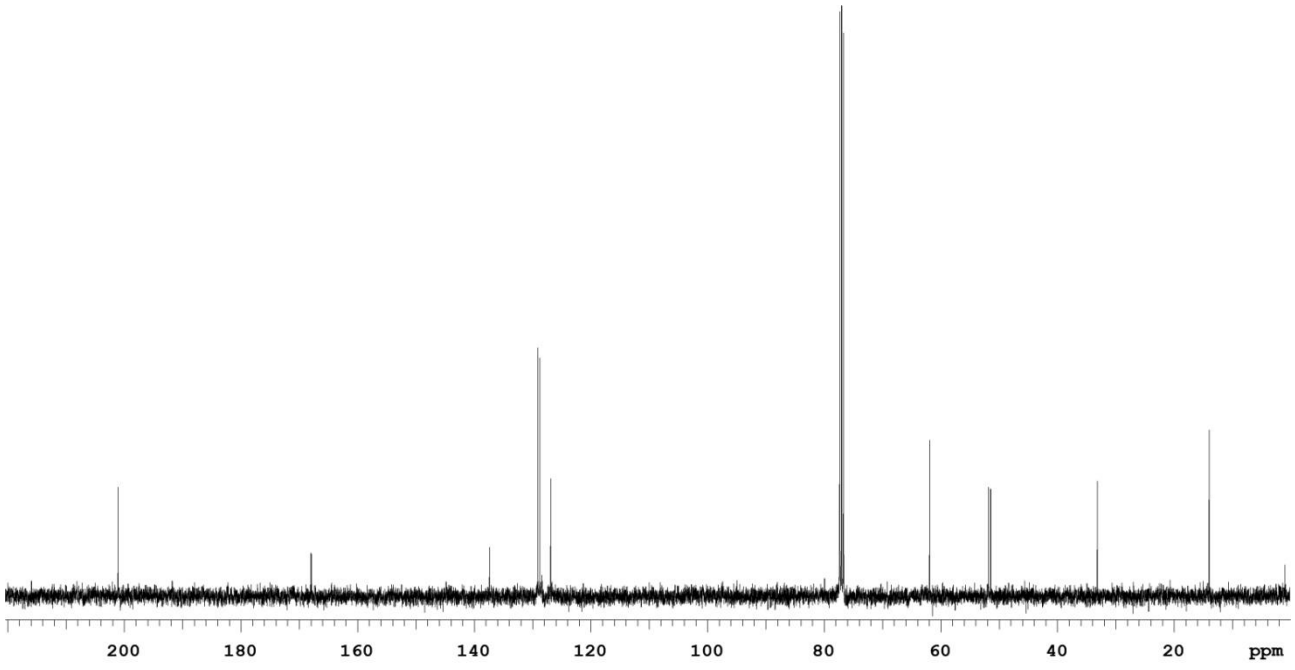


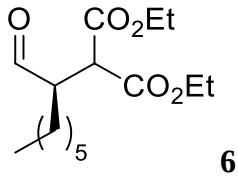



O
CO2Et
CO2Et
Ph

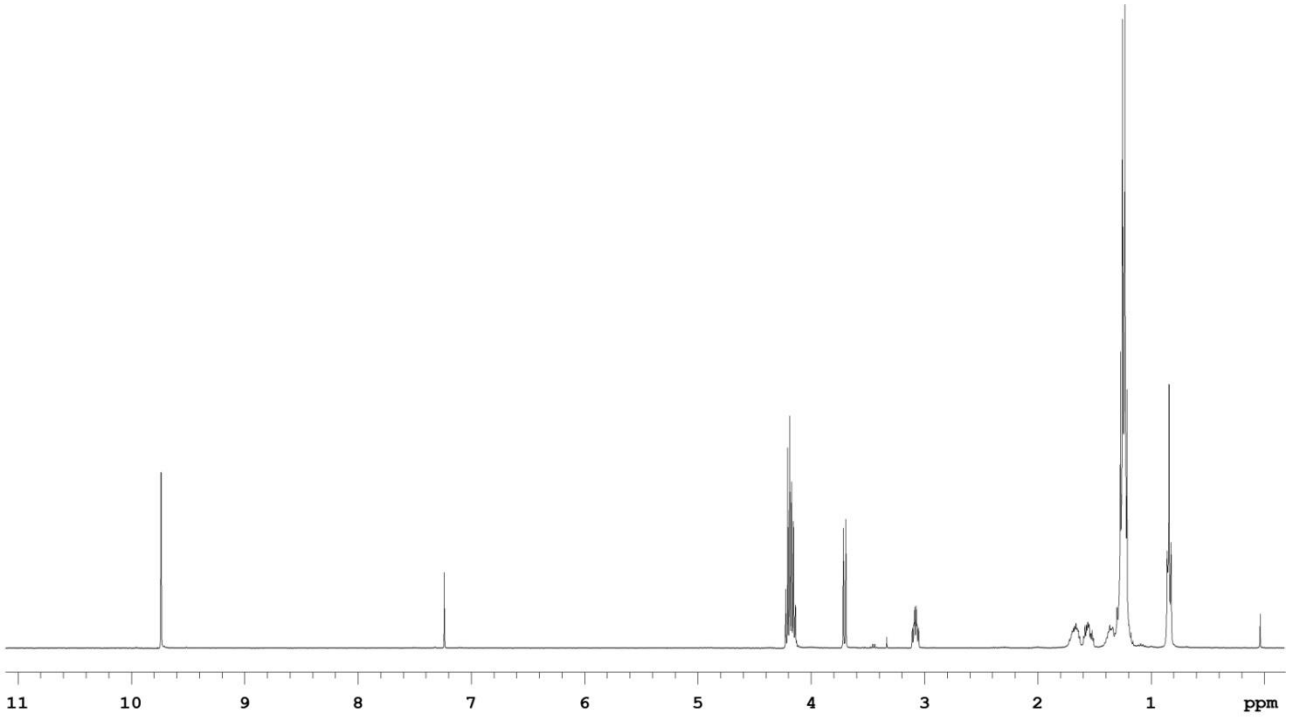
5

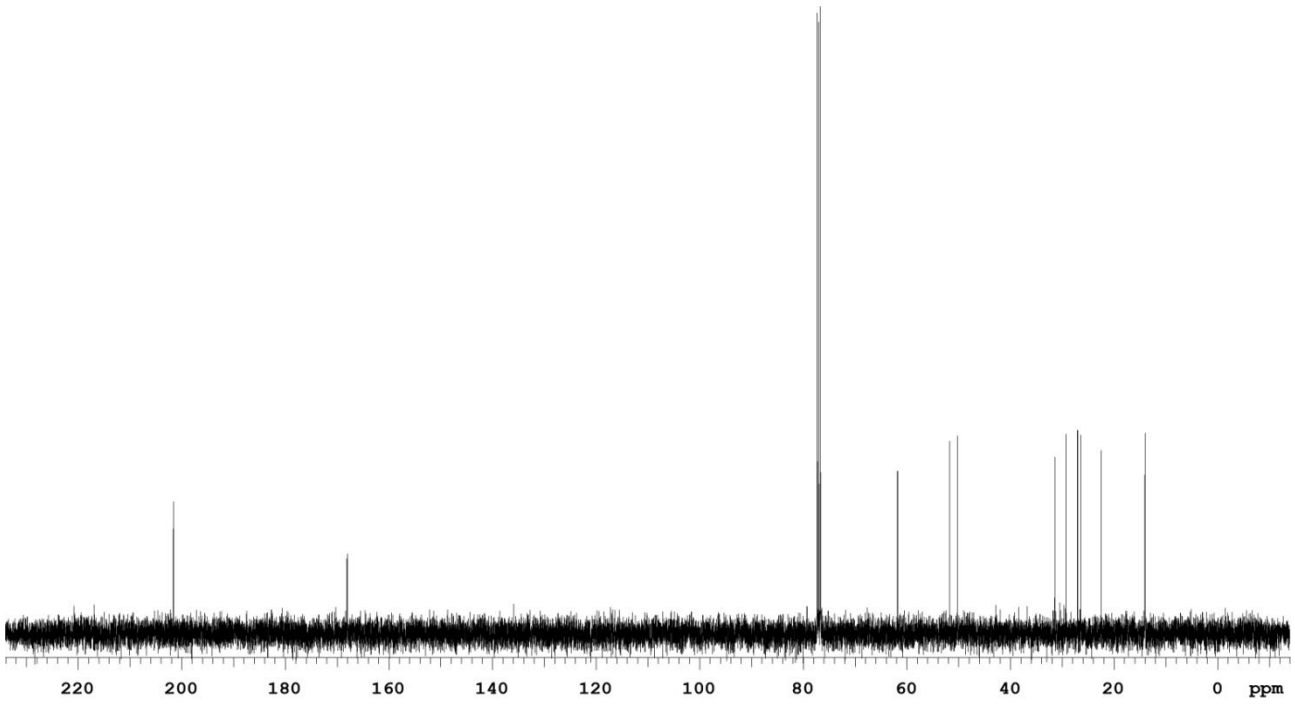

10
9
8
7
6
5
4
3
2
ppm

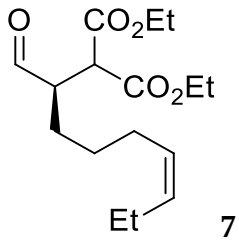

200
180
160
140
120
100
80
60
40
20
ppm


O
CO2Et
CO2Et
5

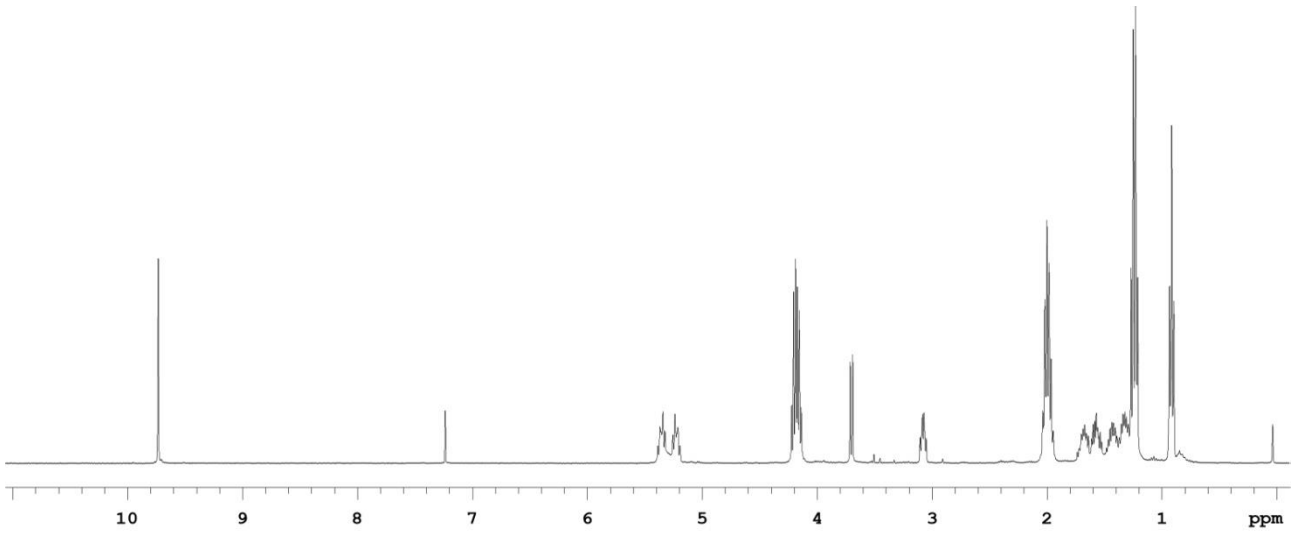
6

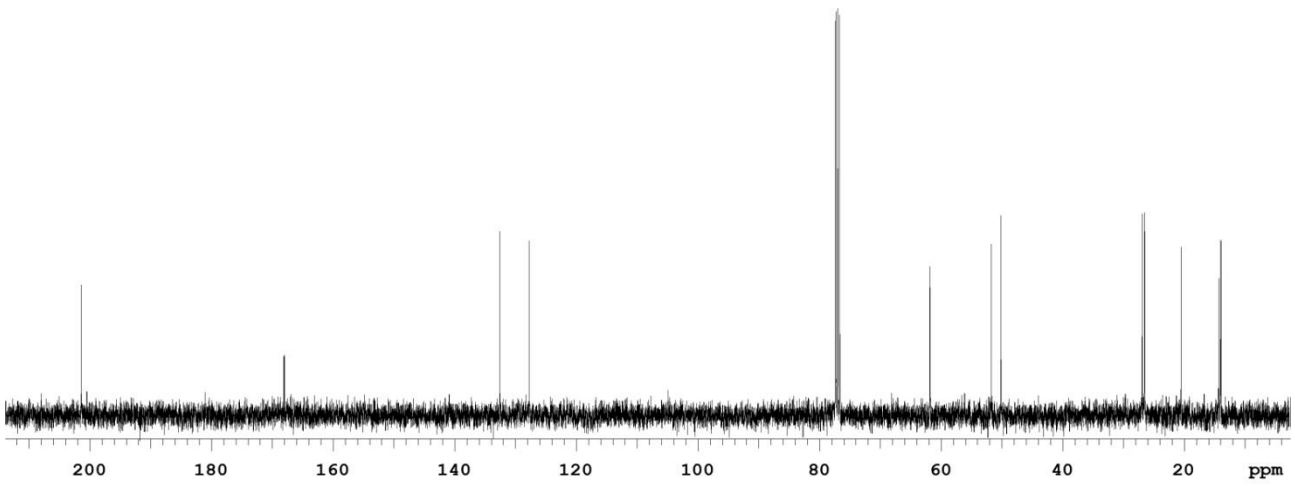

11
10
9
8
7
6
5
4
3
2
1
ppm

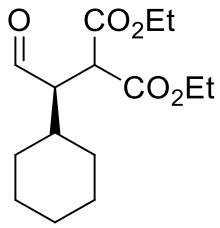

220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
CO2Et
CO2Et
Et

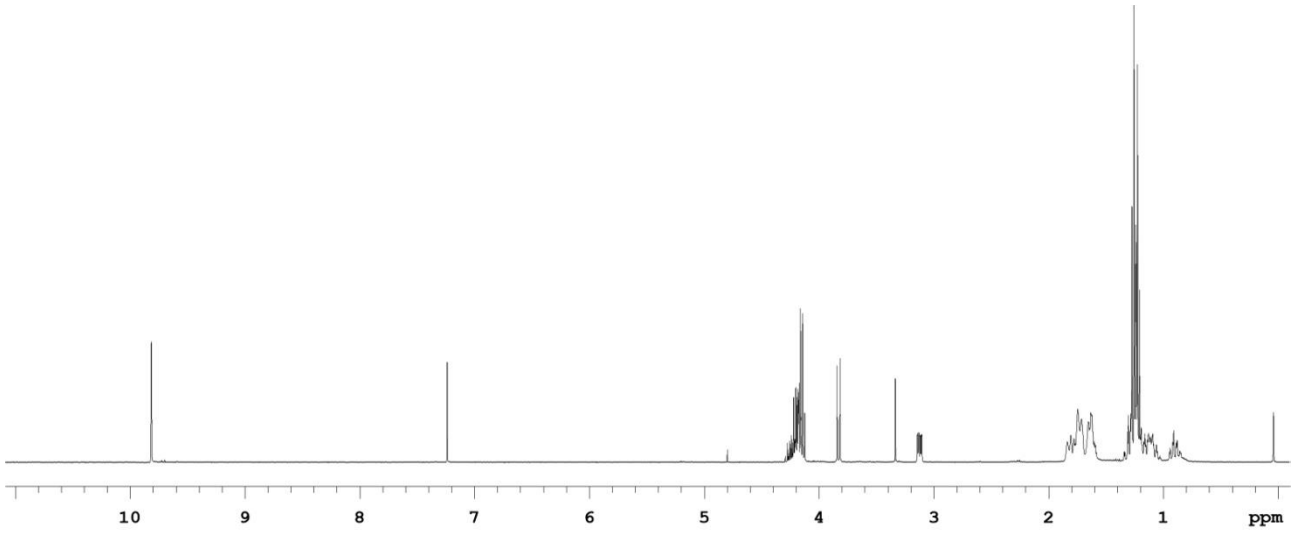
7

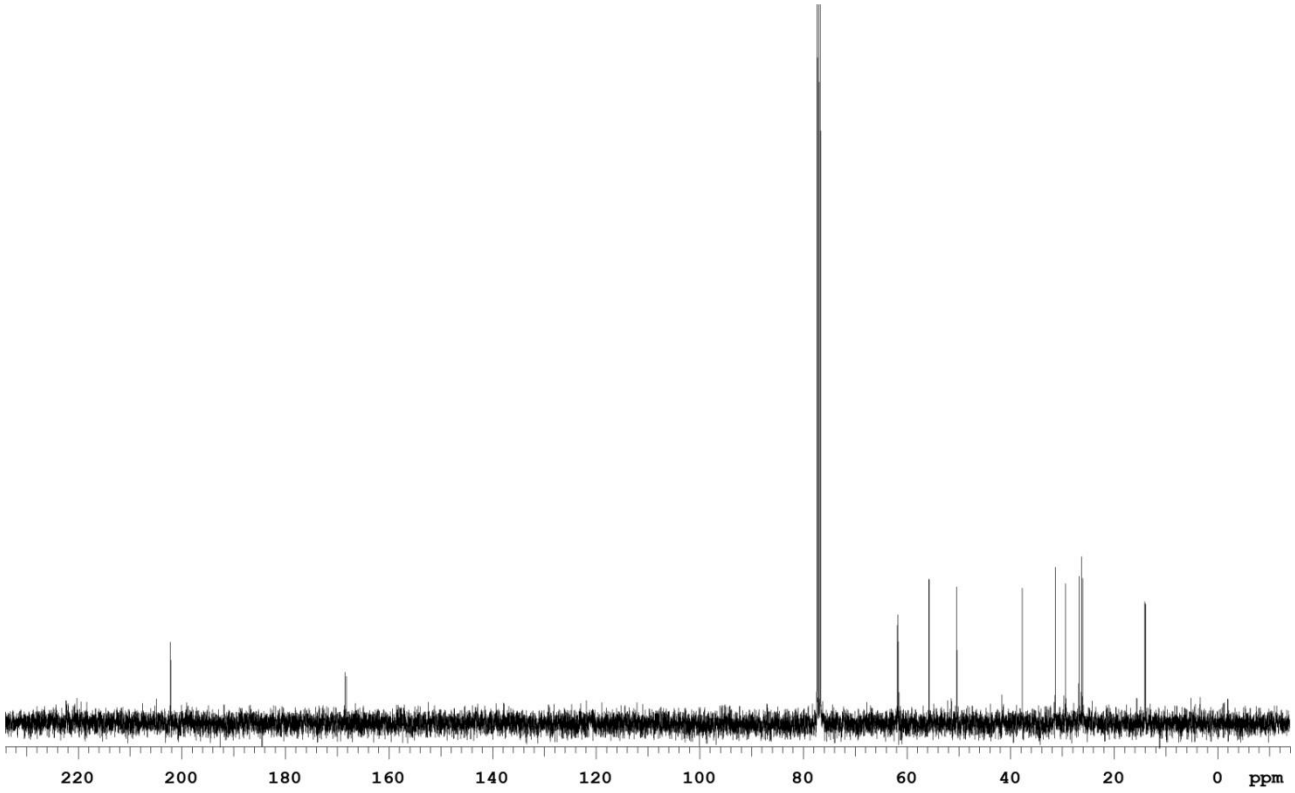

10
9
8
7
6
5
4
3
2
1
ppm

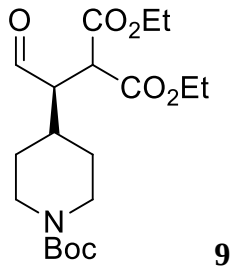

200
180
160
140
120
100
80
60
40
20
ppm


O
CO2Et
CO2Et

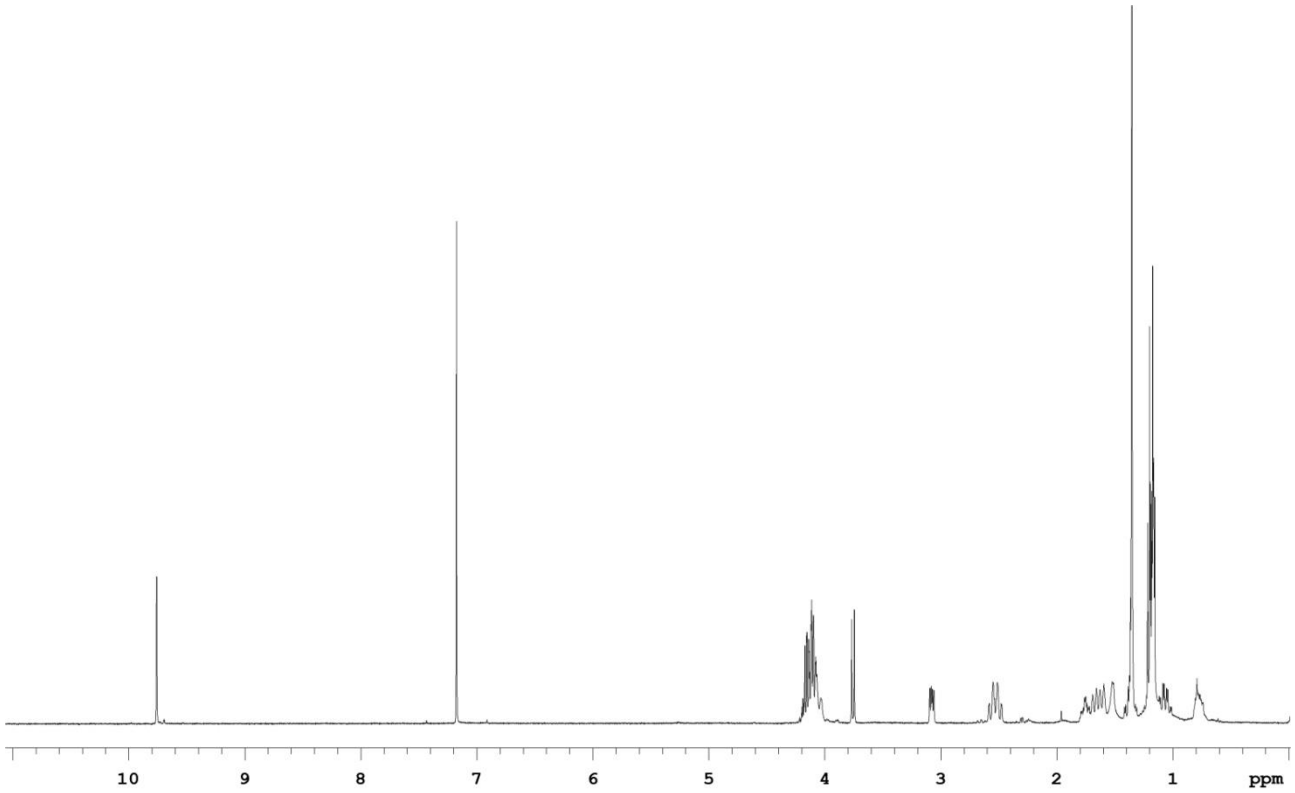
8

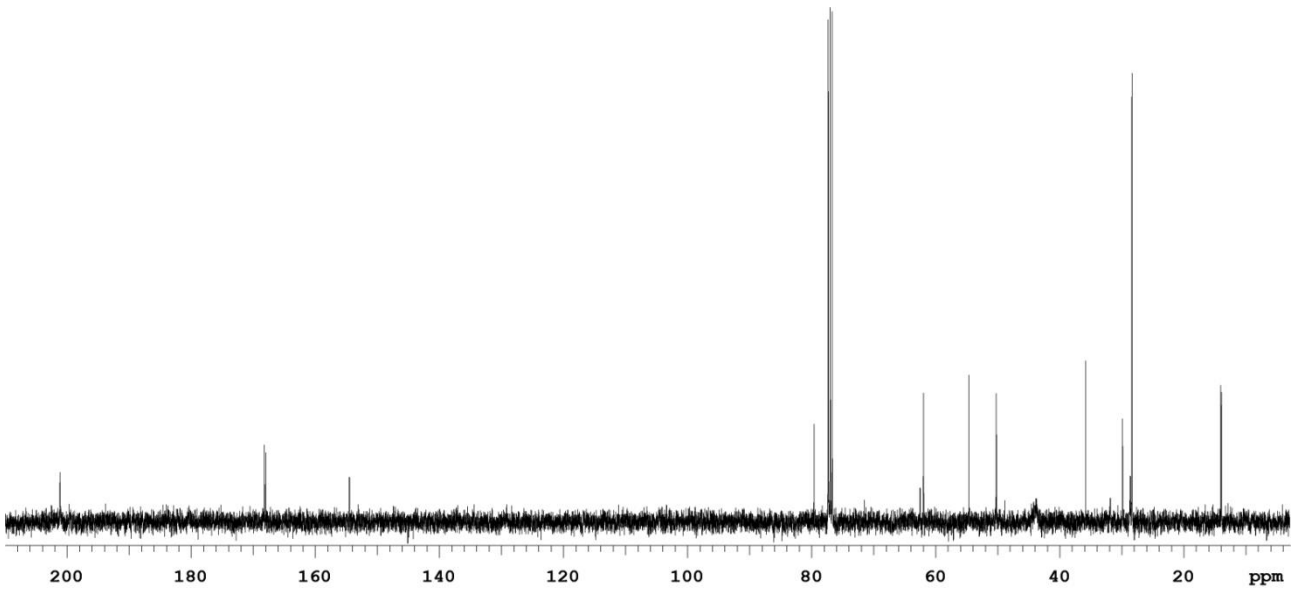

10
9
8
7
6
5
4
3
2
1
ppm

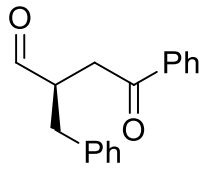

220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
CO2Et
CO2Et
N
Boc

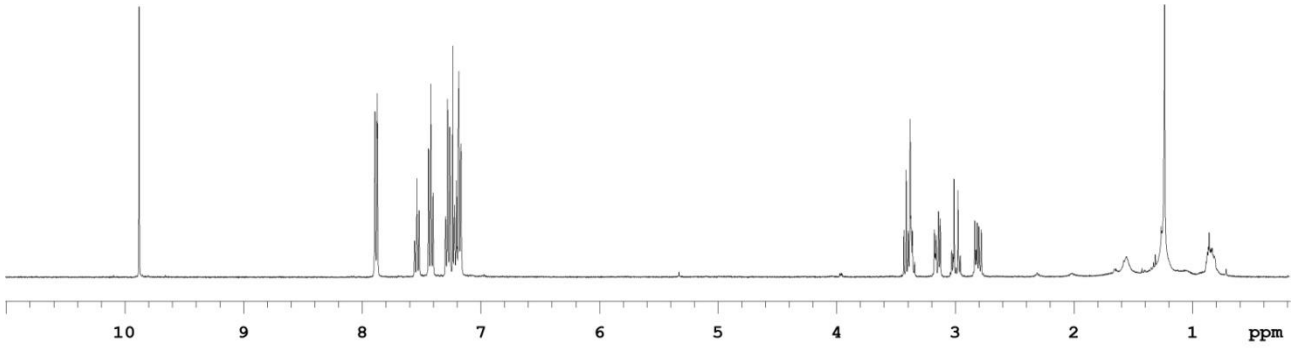
9

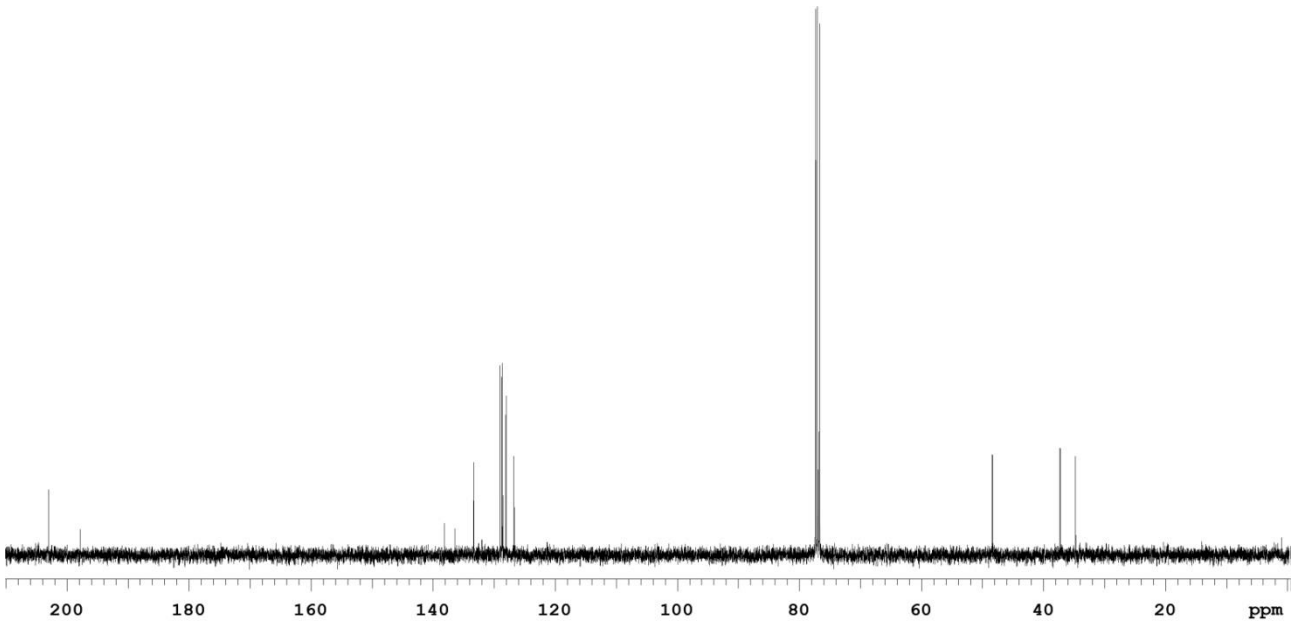

10
9
8
7
6
5
4
3
2
1
ppm

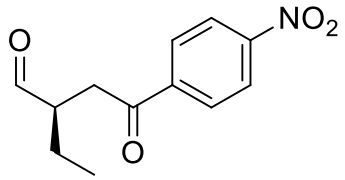

200
180
160
140
120
100
80
60
40
20
ppm



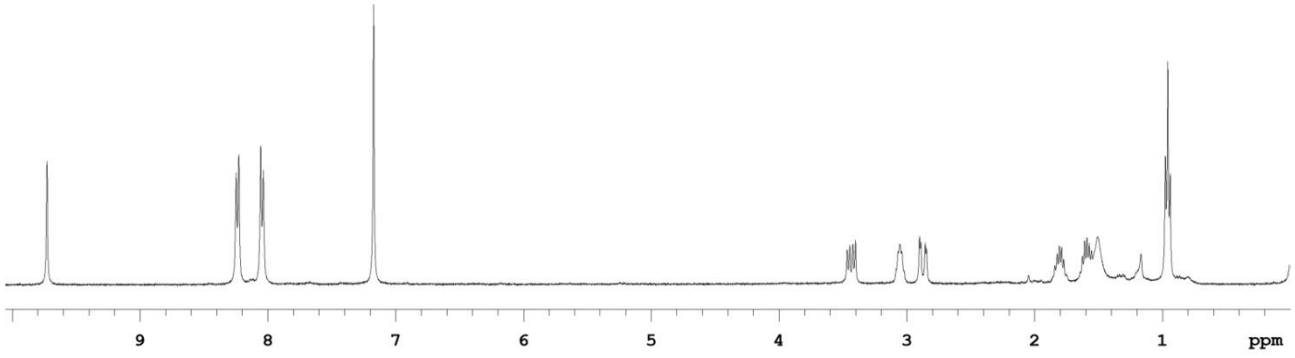
10

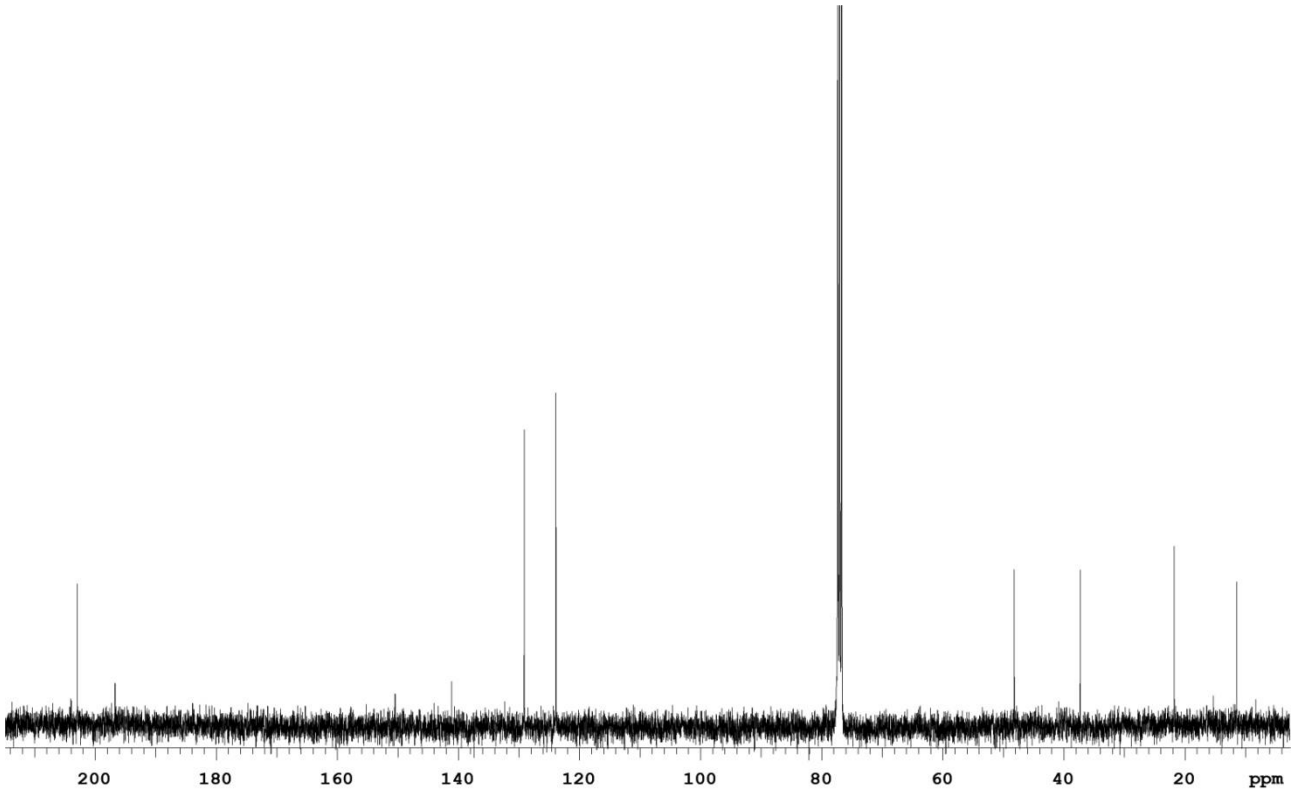


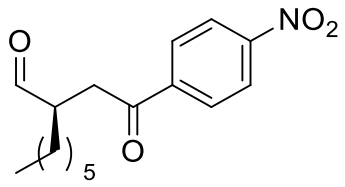




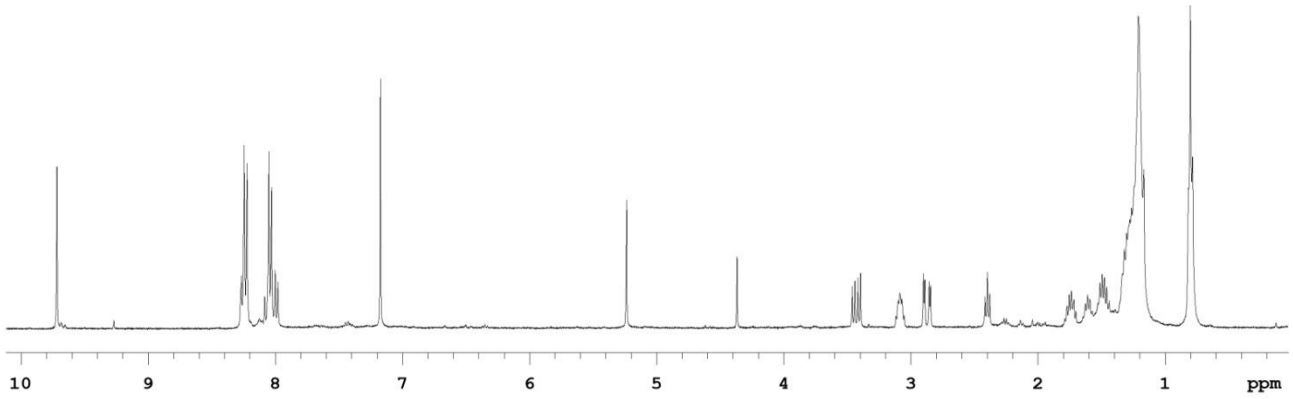
11

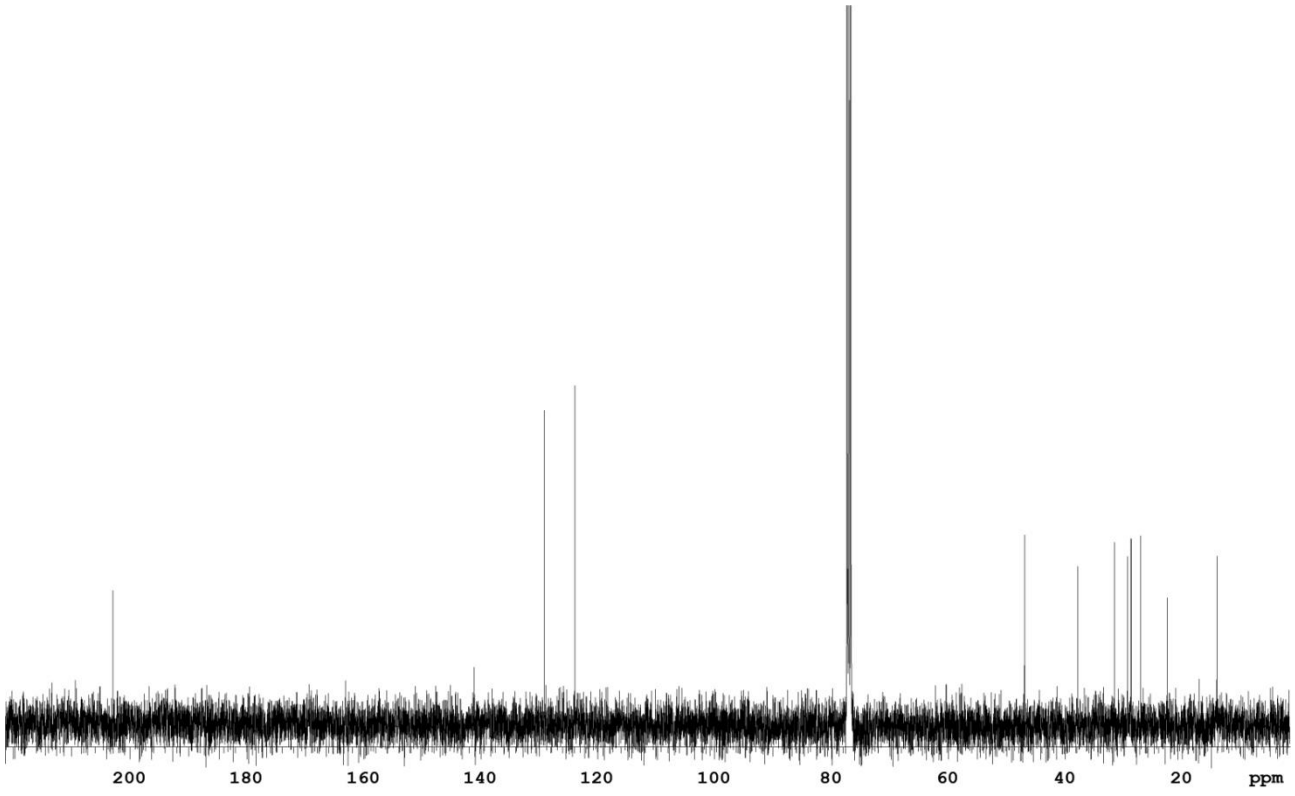


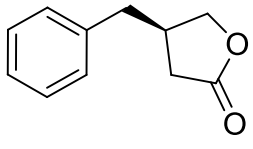




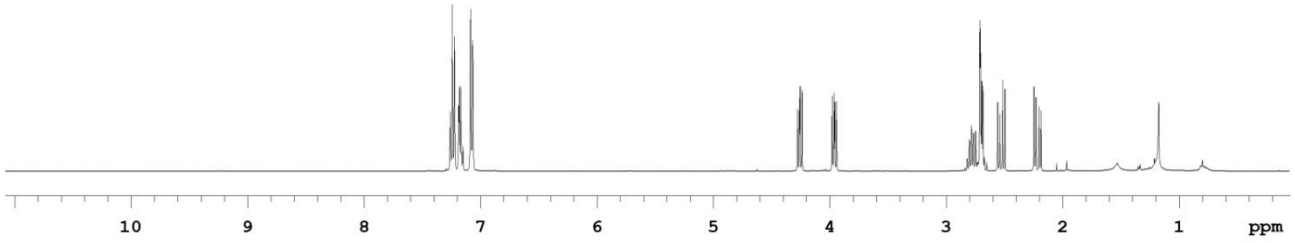
12

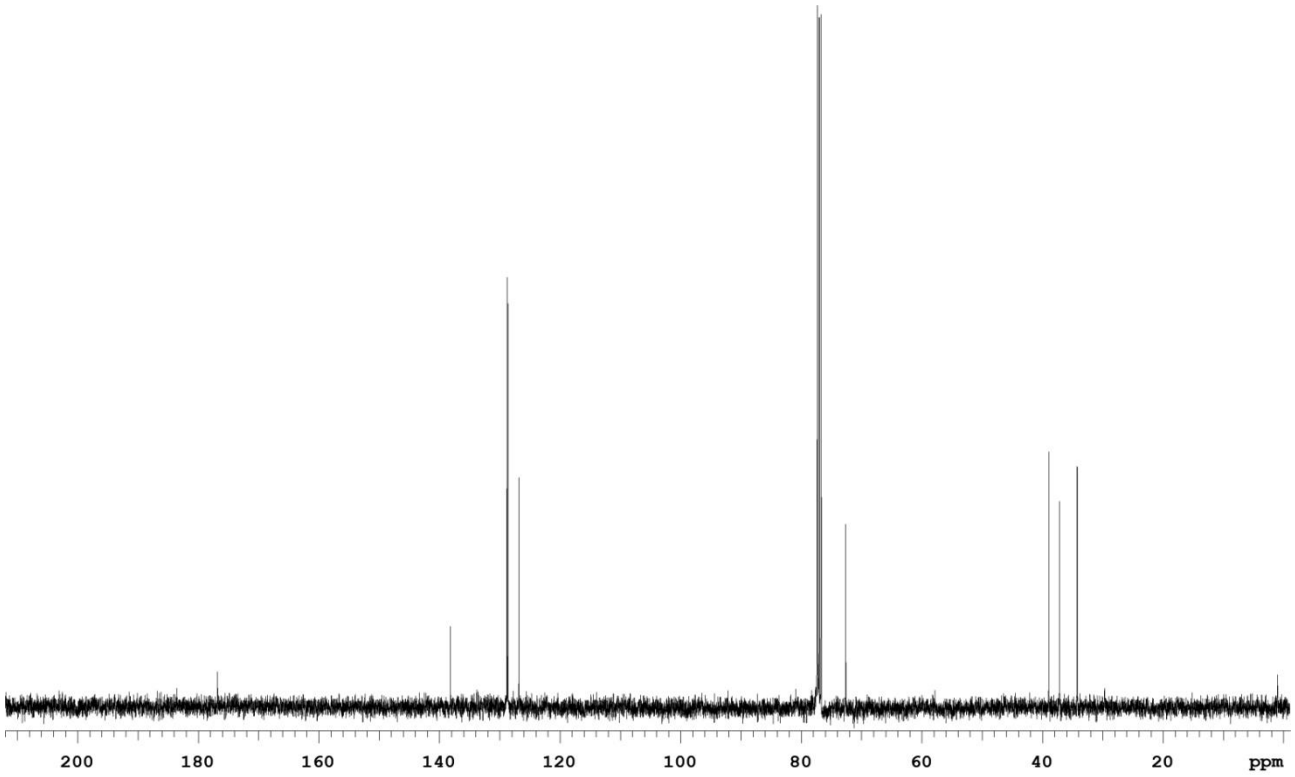


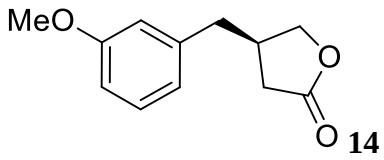




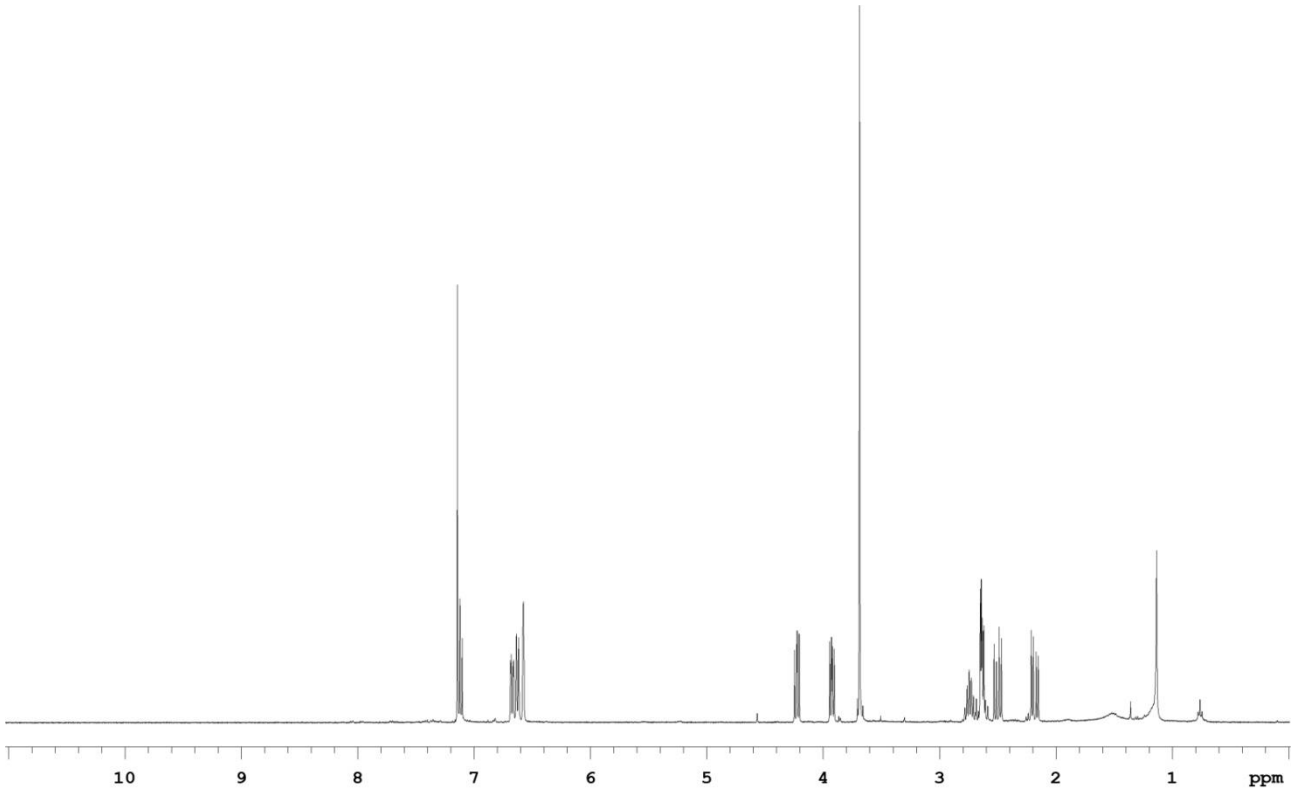
13

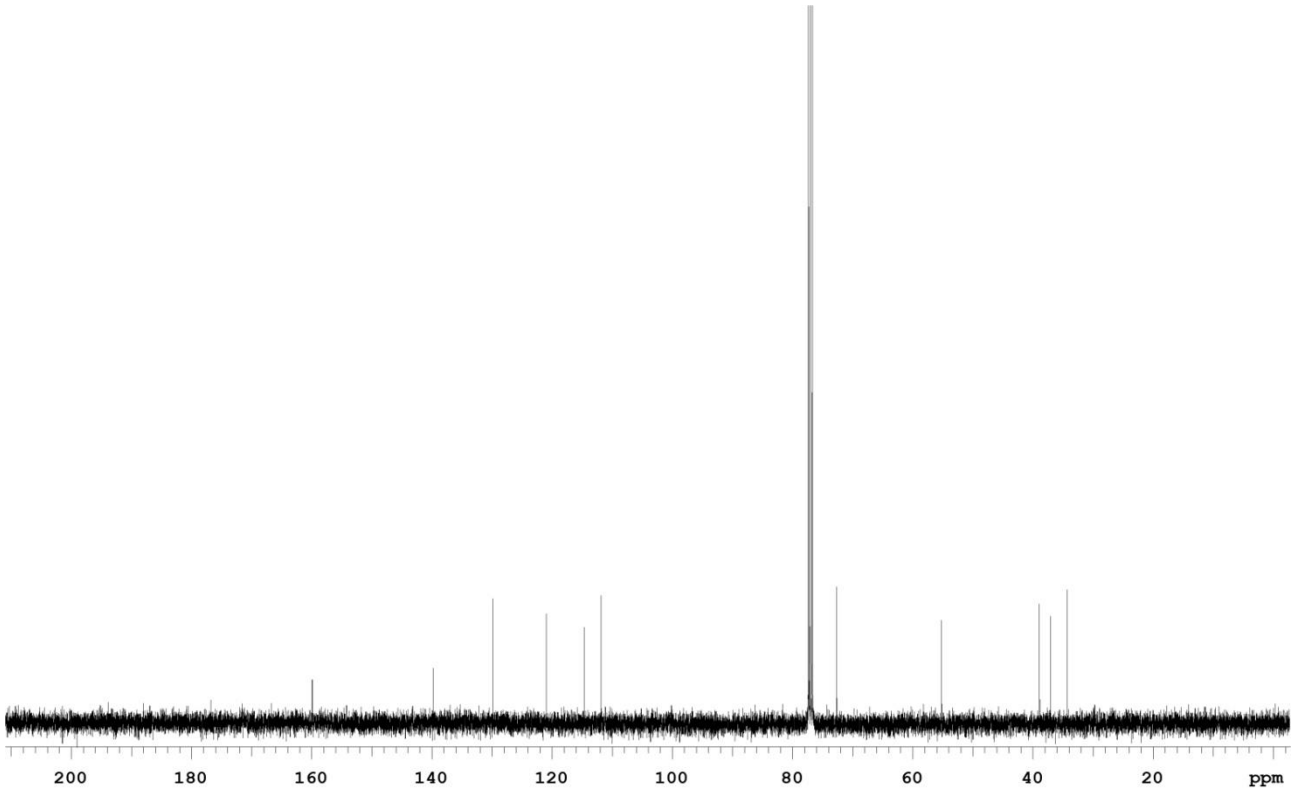


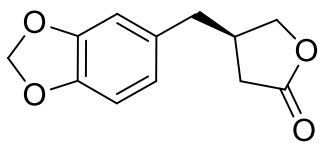




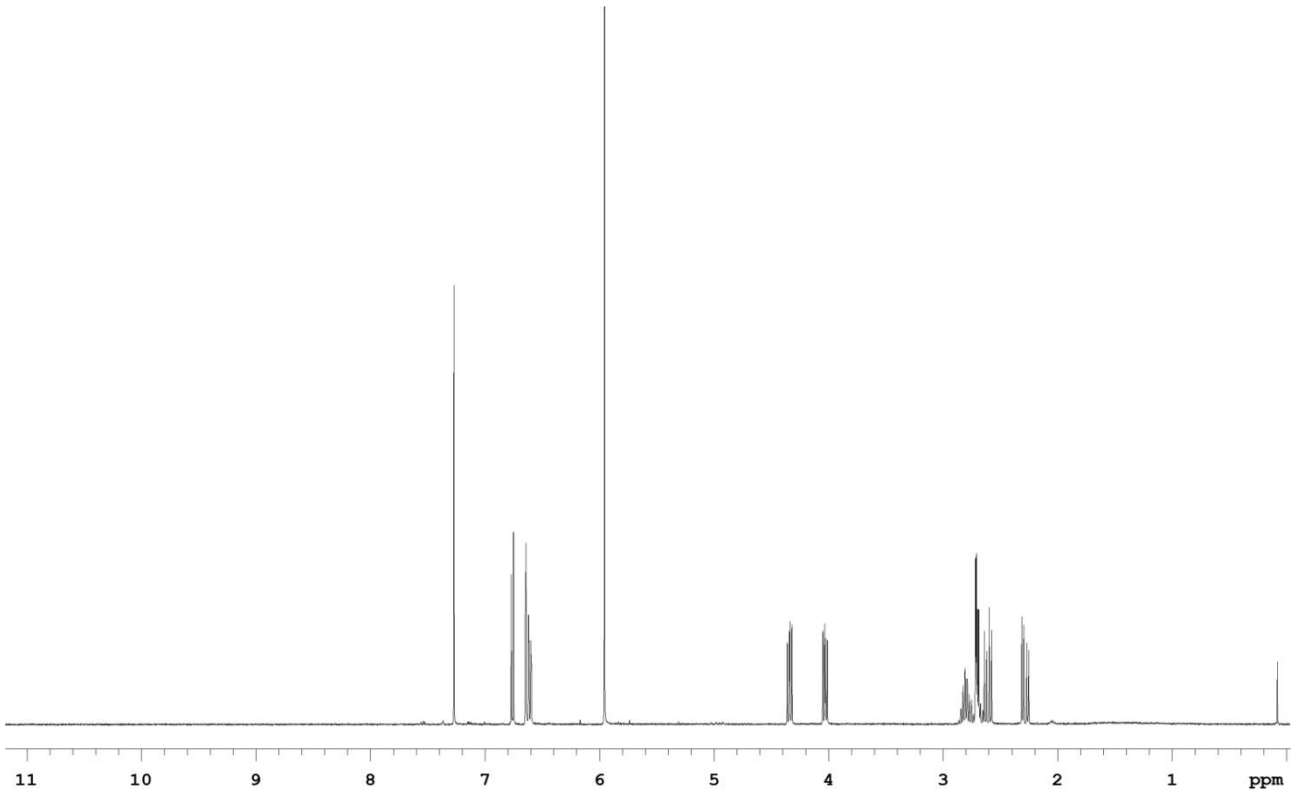
14

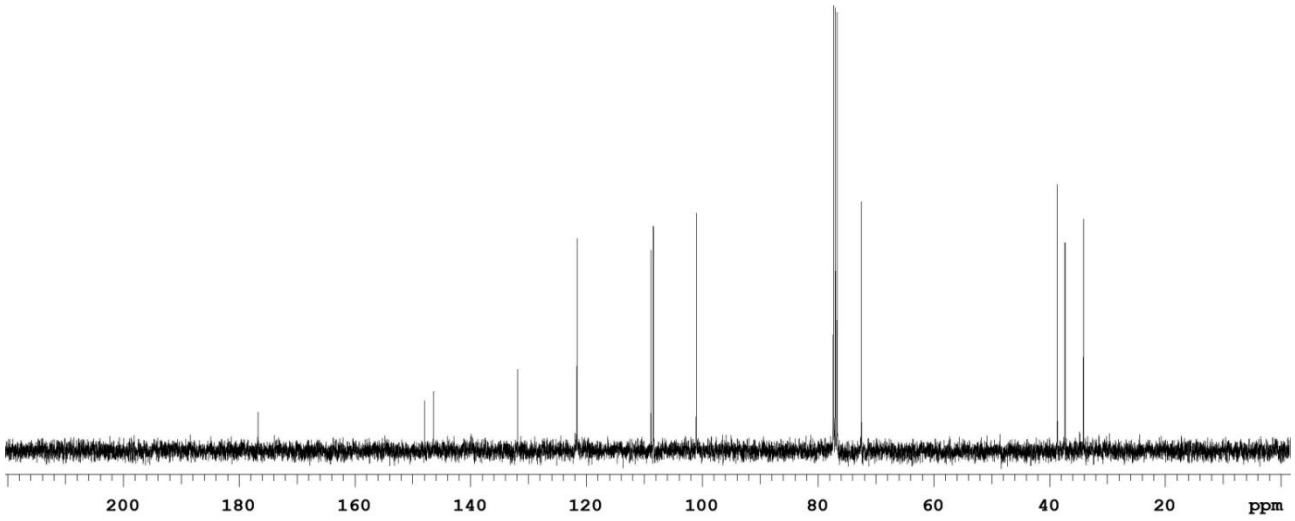


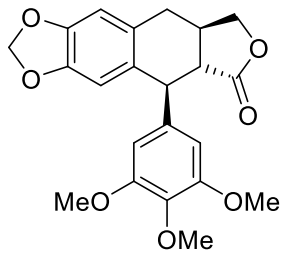




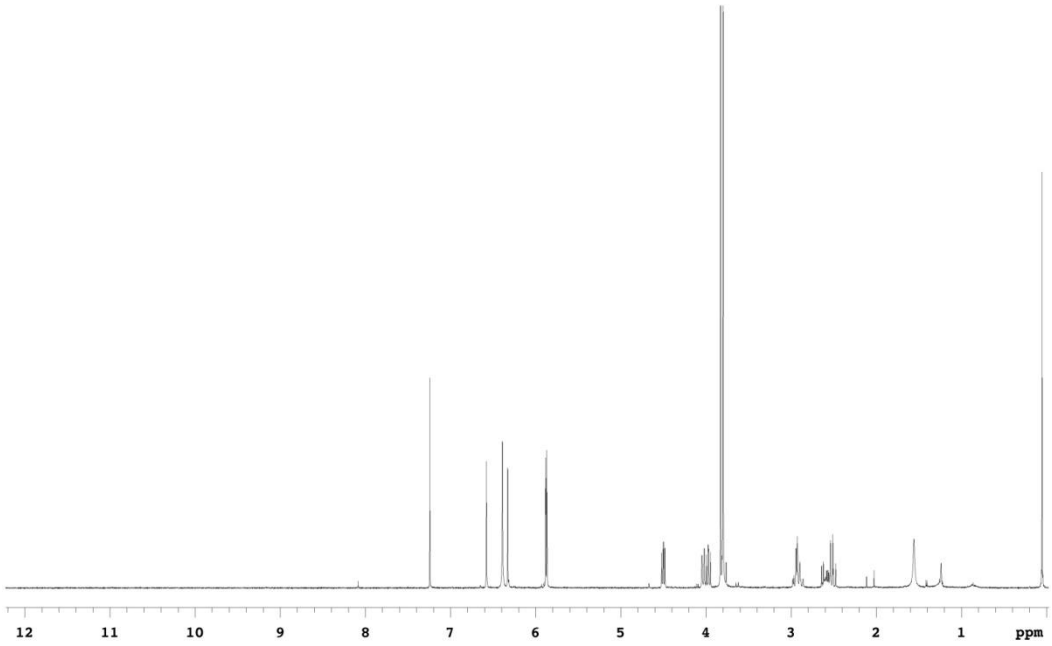
15

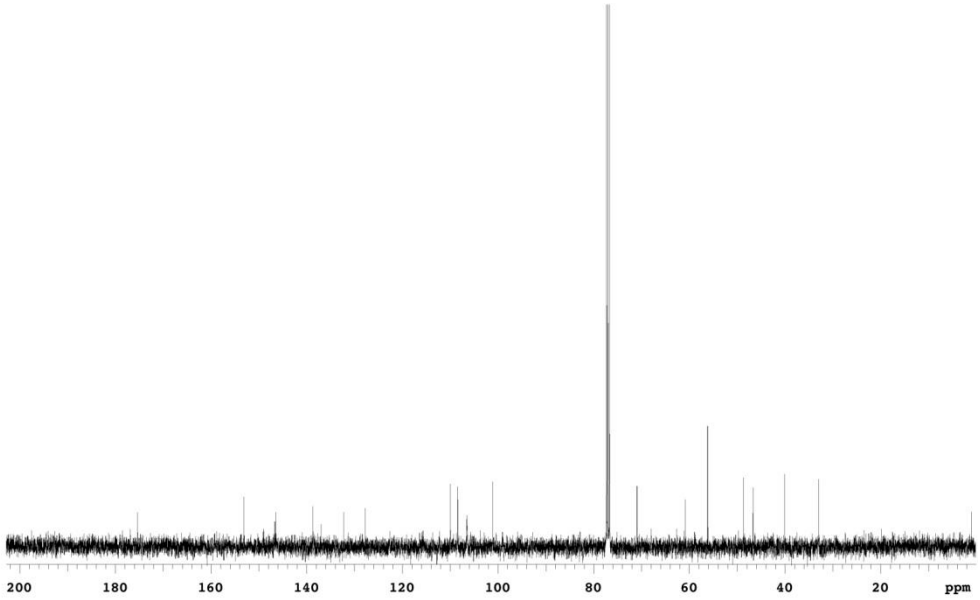


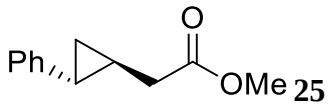



O
O
O
O
O
MeO
OMe
OMe

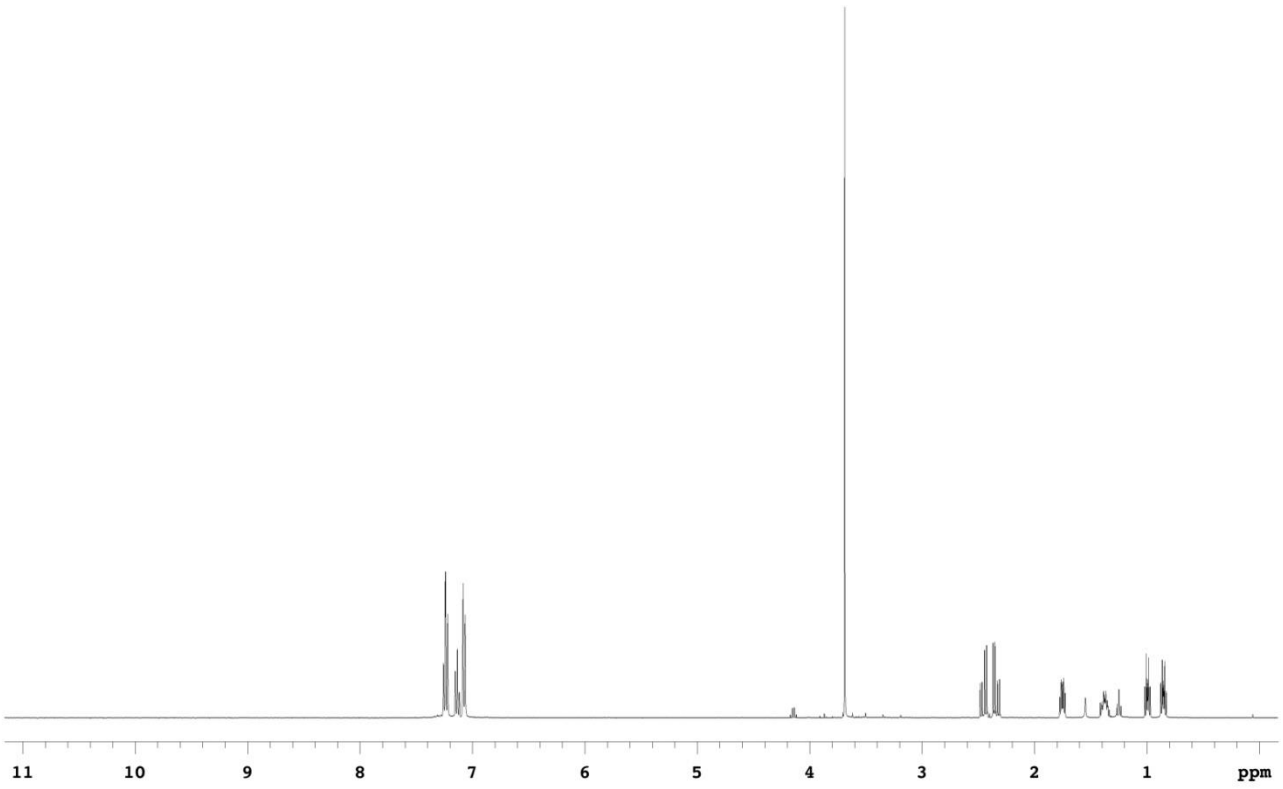
16

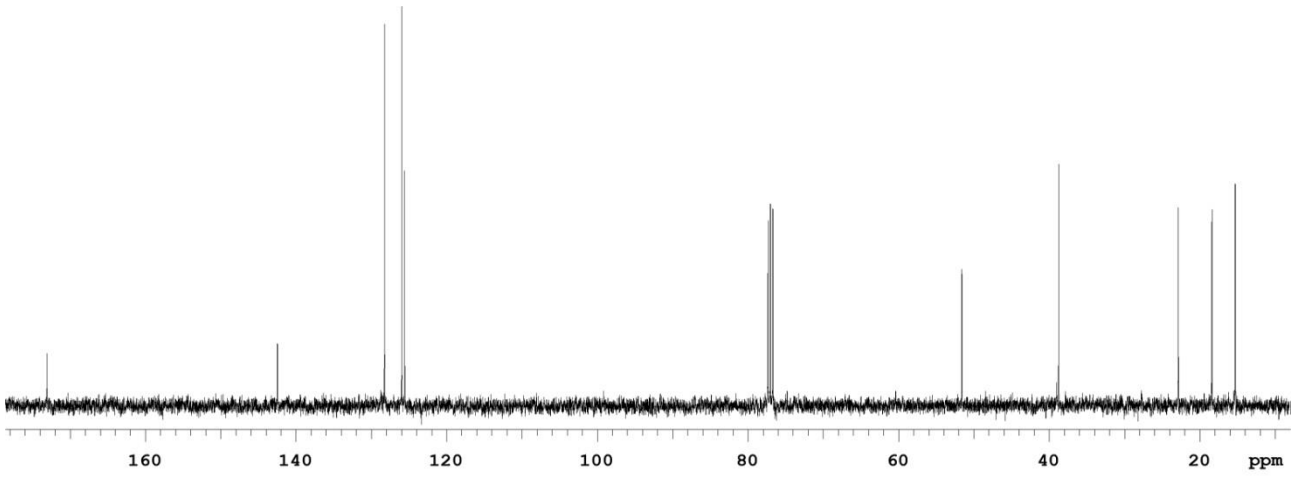

12
11
10
9
8
7
6
5
4
3
2
1
ppm

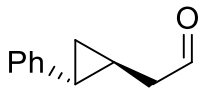

200
180
160
140
120
100
80
60
40
20
ppm



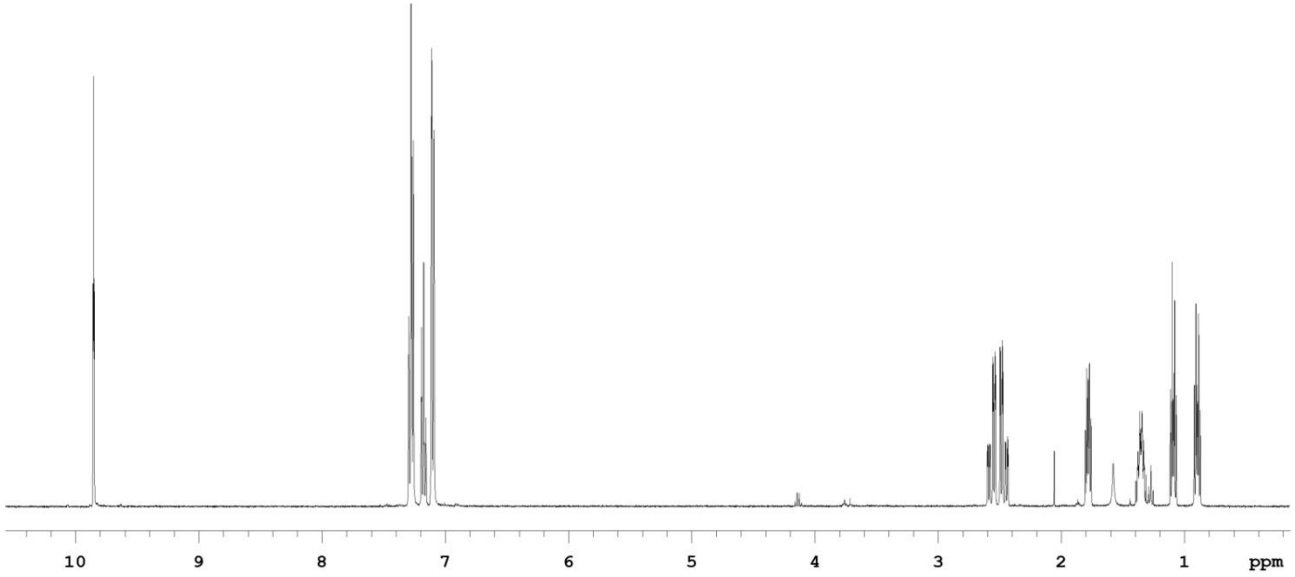
25

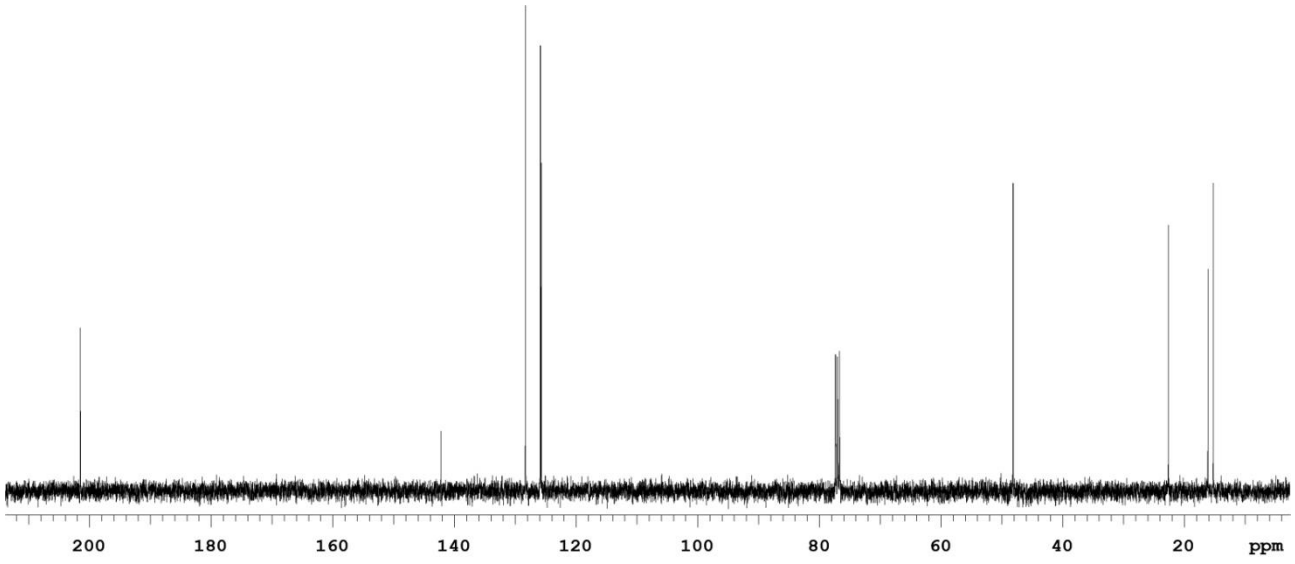


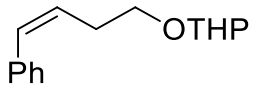




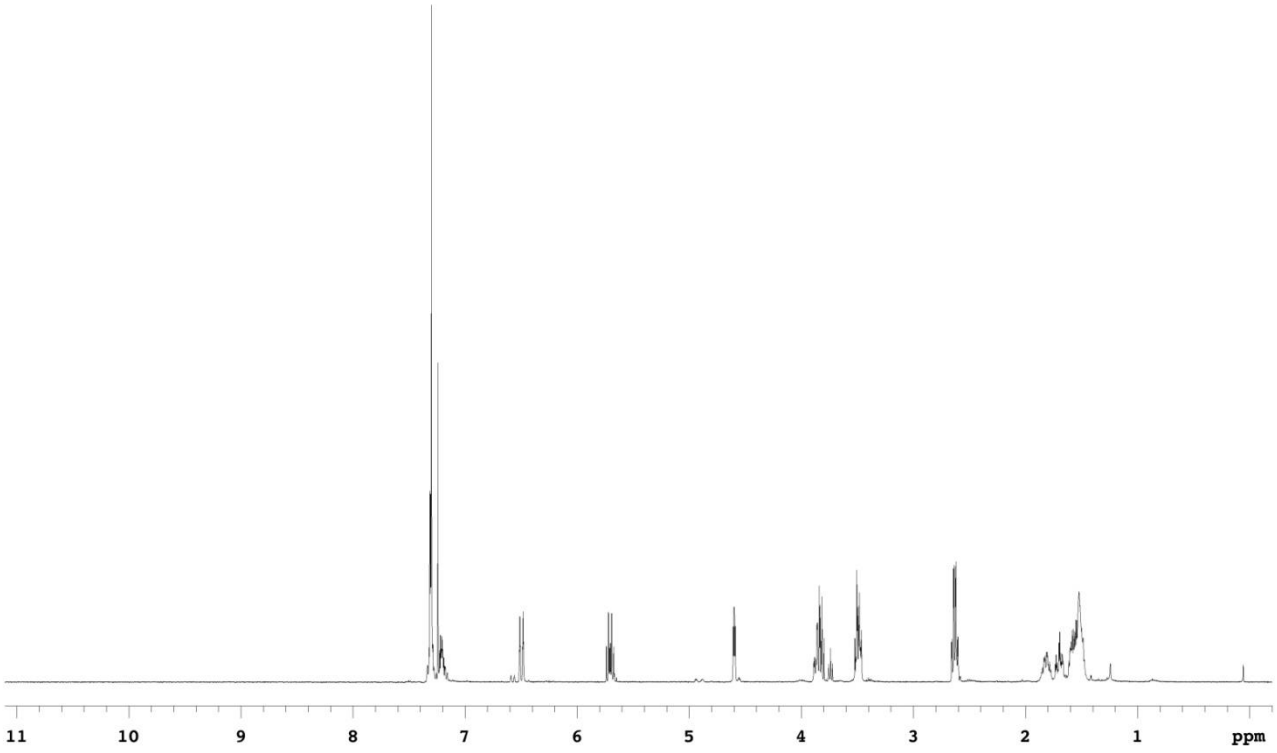
(±)-*trans*-1i

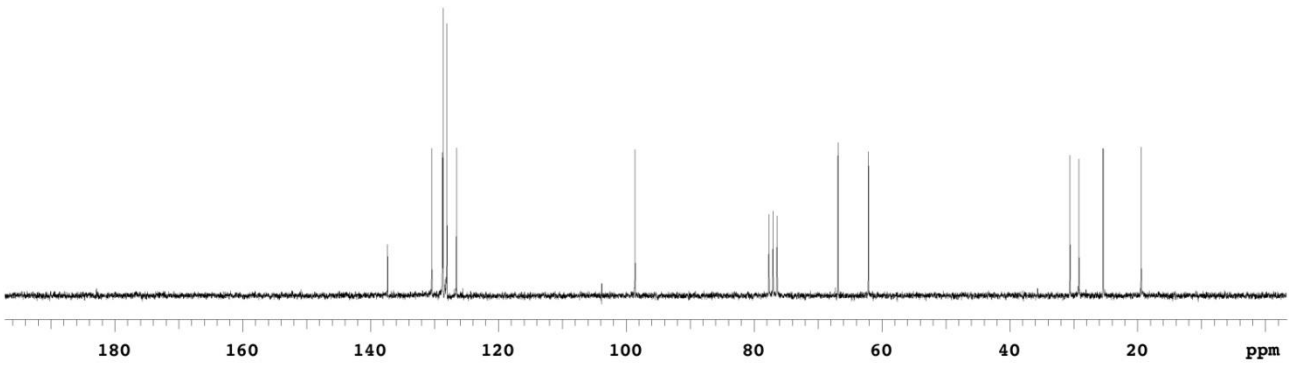


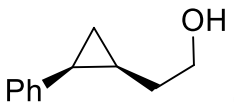




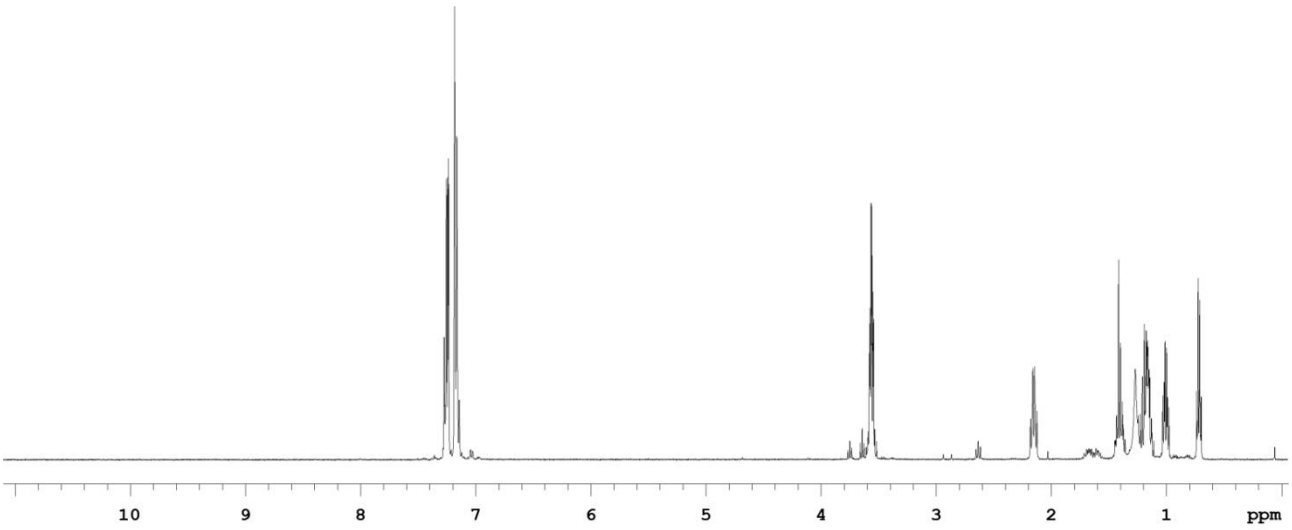
27

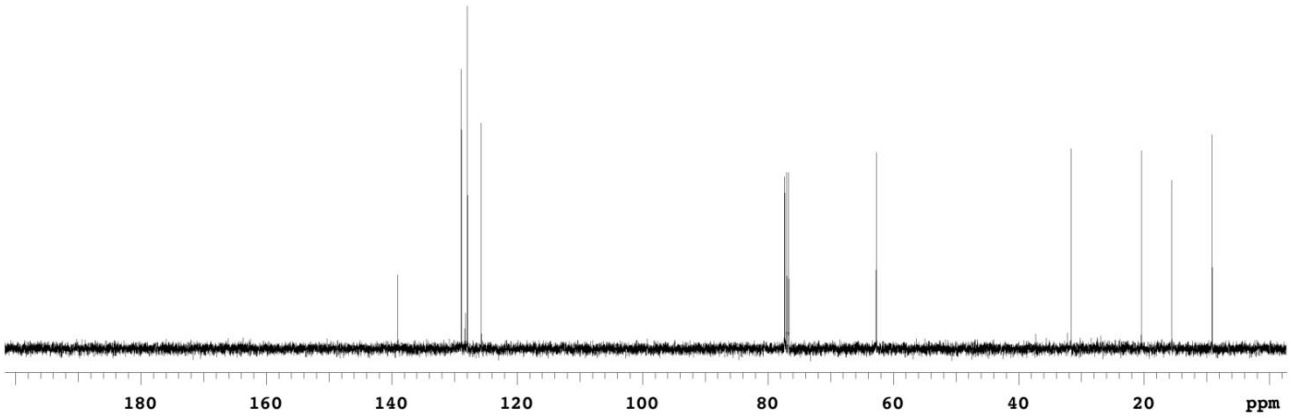


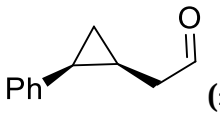




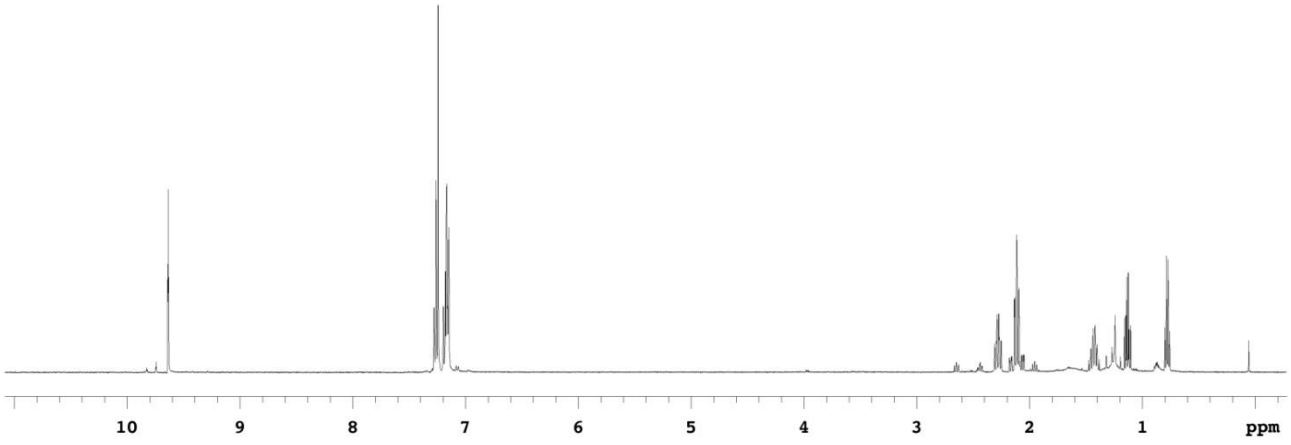
(±)-*cis*-28

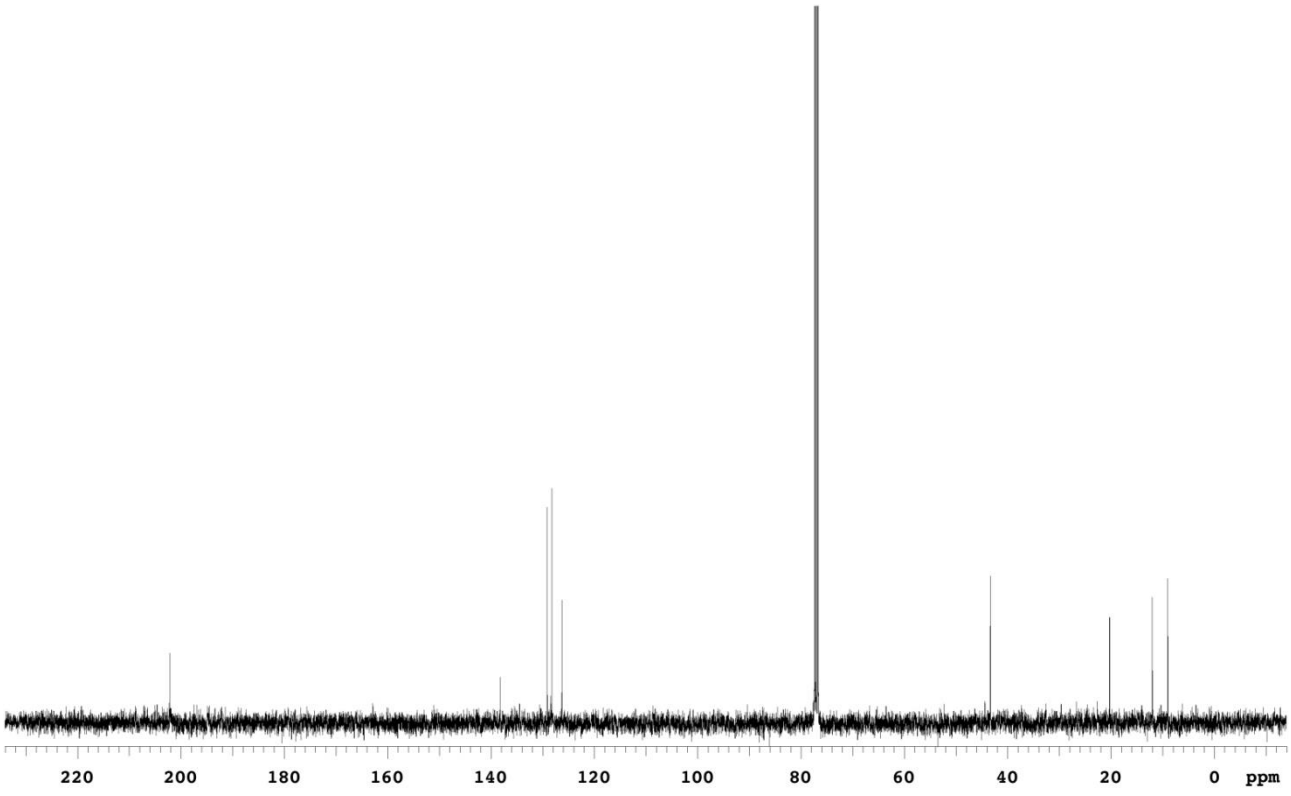


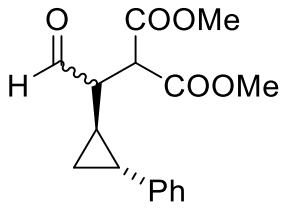



O
Ph

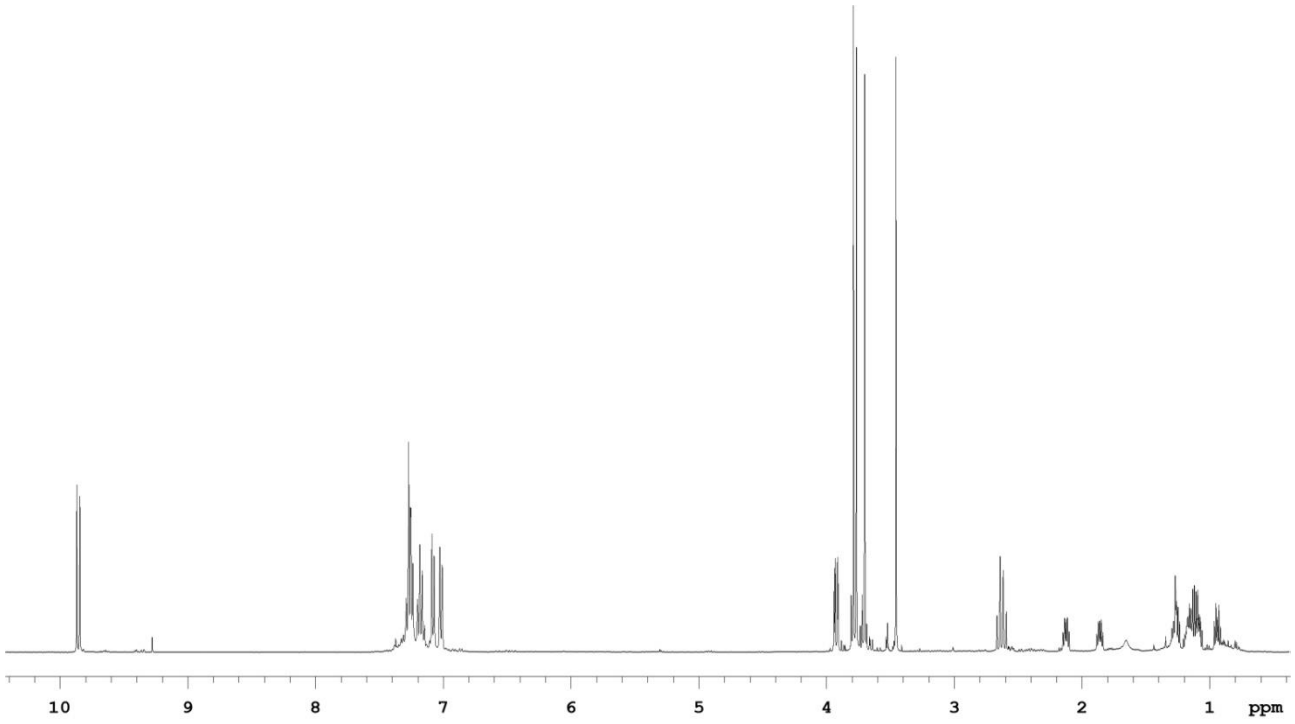
(±)-cis-1i

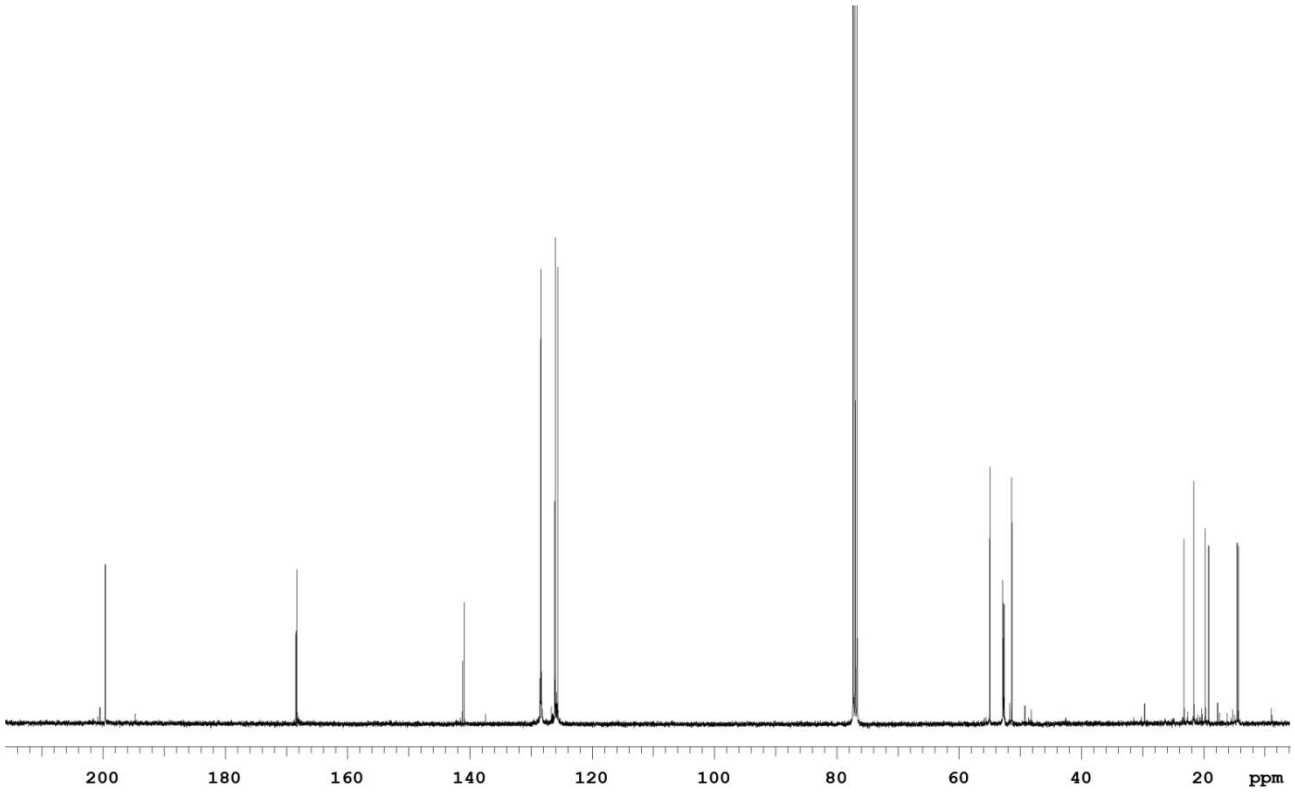

10
9
8
7
6
5
4
3
2
1
ppm

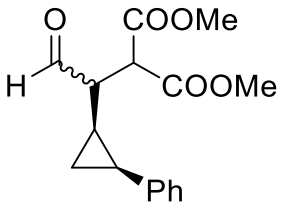

220
200
180
160
140
120
100
80
60
40
20
0
ppm



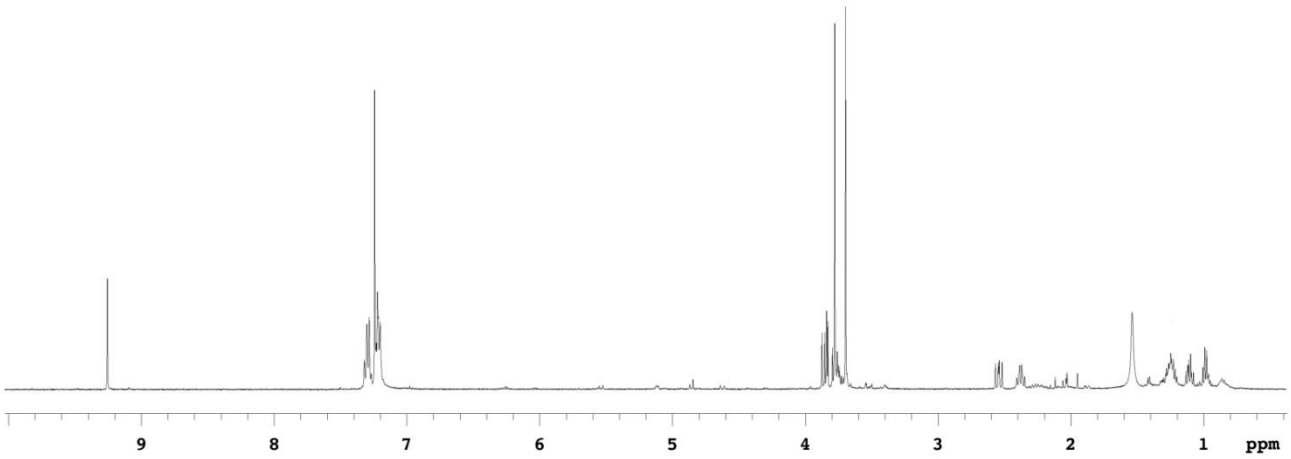
(±)-*trans*-20 d.r. 1.05:1.00 (A/B)

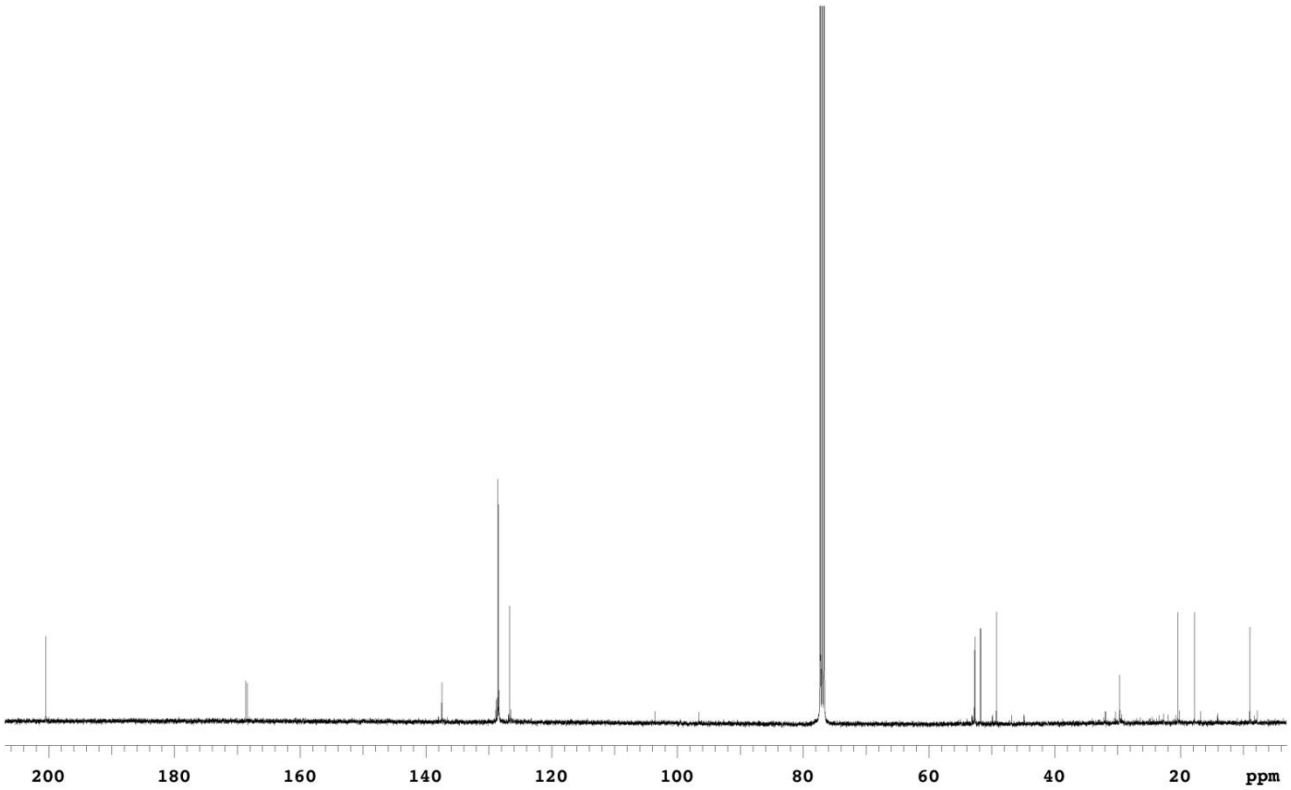




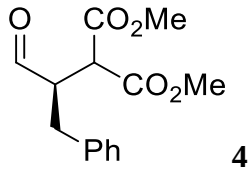


(±)-*cis*-20 diastereoisomer A



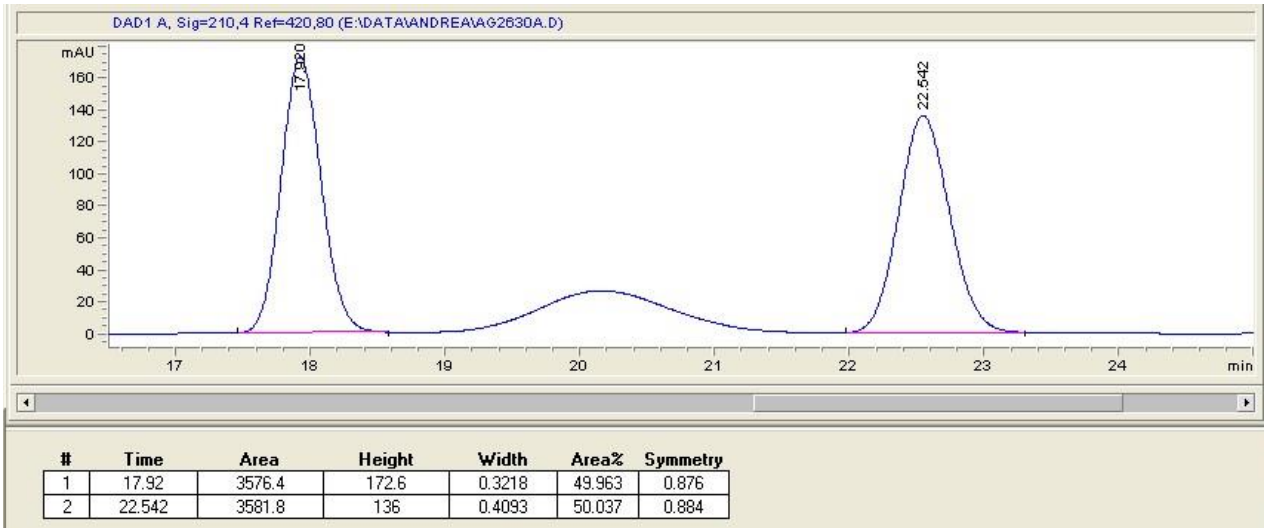


Copies of HPLC, GC traces and NMR spectra for the determination of enantiomeric excess



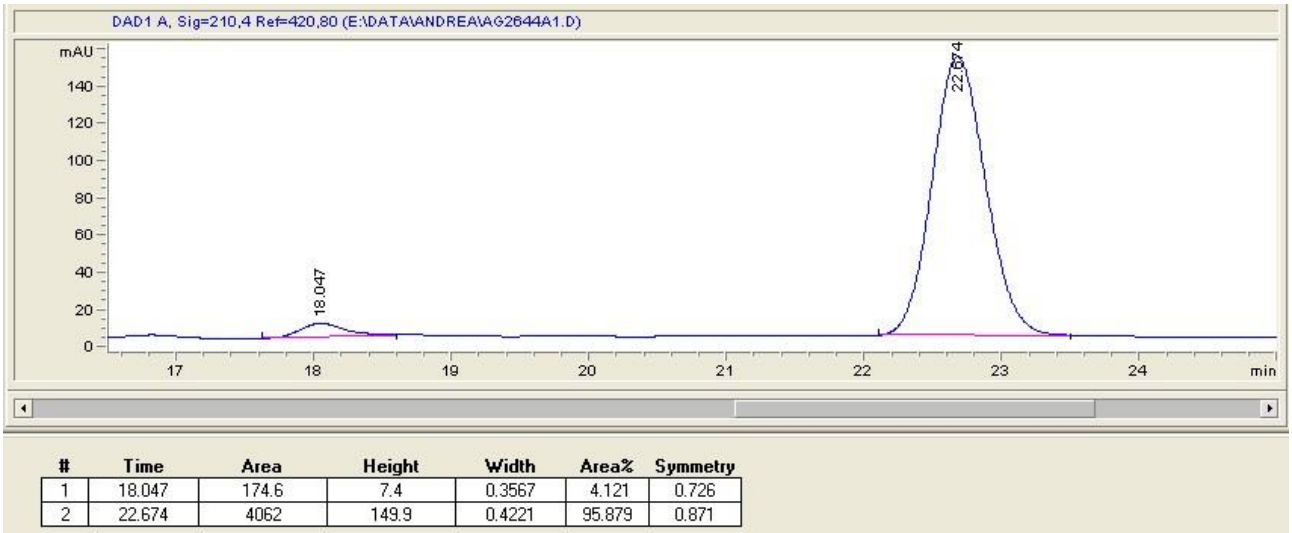
4

racemic

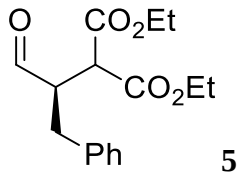


#	Time	Area	Height	Width	Area%	Symmetry
1	17.92	3576.4	172.6	0.3218	49.963	0.876
2	22.542	3581.8	136	0.4093	50.037	0.884

Active

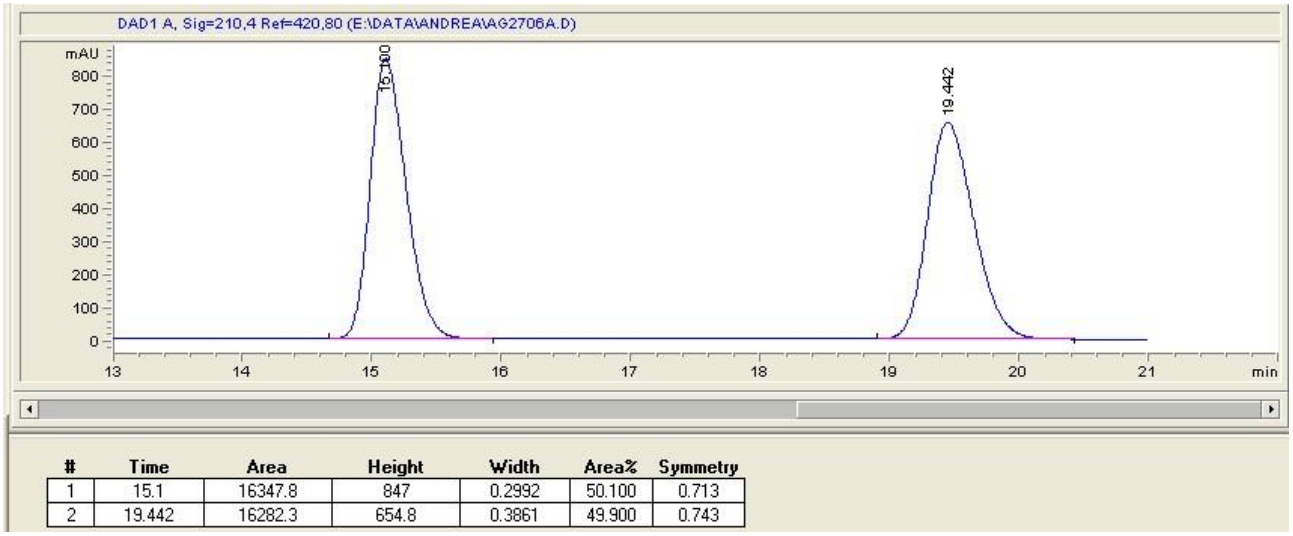


#	Time	Area	Height	Width	Area%	Symmetry
1	18.047	174.6	7.4	0.3567	4.121	0.726
2	22.674	4062	149.9	0.4221	95.879	0.871



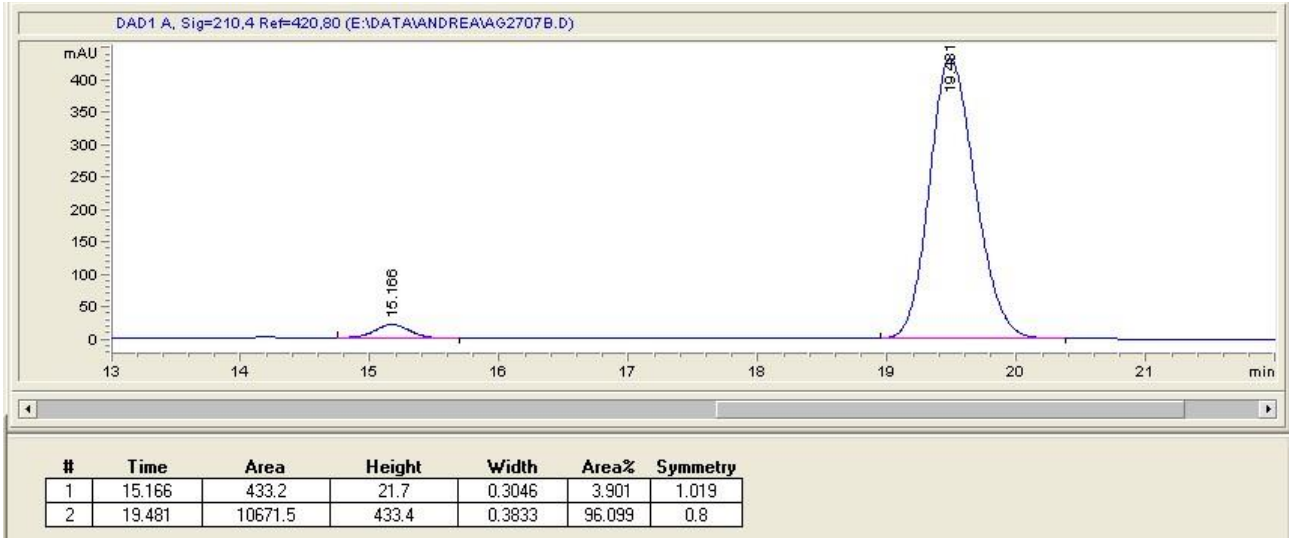
5

racemic

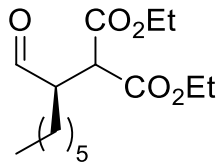


#	Time	Area	Height	Width	Area%	Symmetry
1	15.1	16347.8	847	0.2992	50.100	0.713
2	19.442	16282.3	654.8	0.3861	49.900	0.743

Active

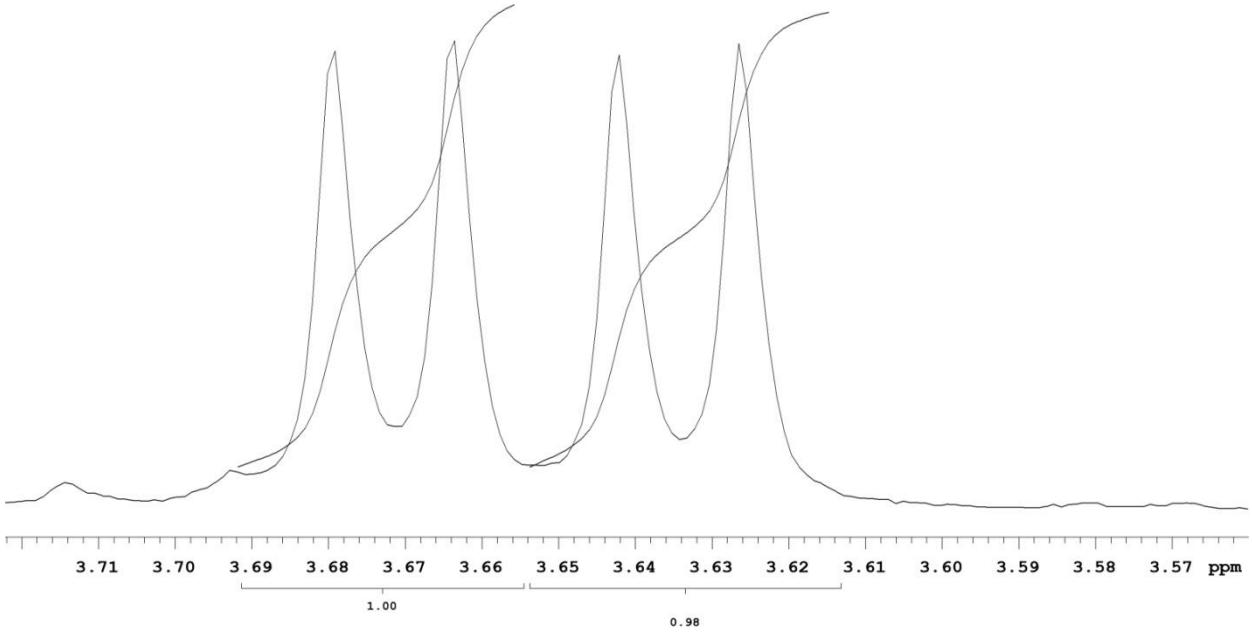


#	Time	Area	Height	Width	Area%	Symmetry
1	15.166	433.2	21.7	0.3046	3.901	1.019
2	19.481	10671.5	433.4	0.3833	96.099	0.8

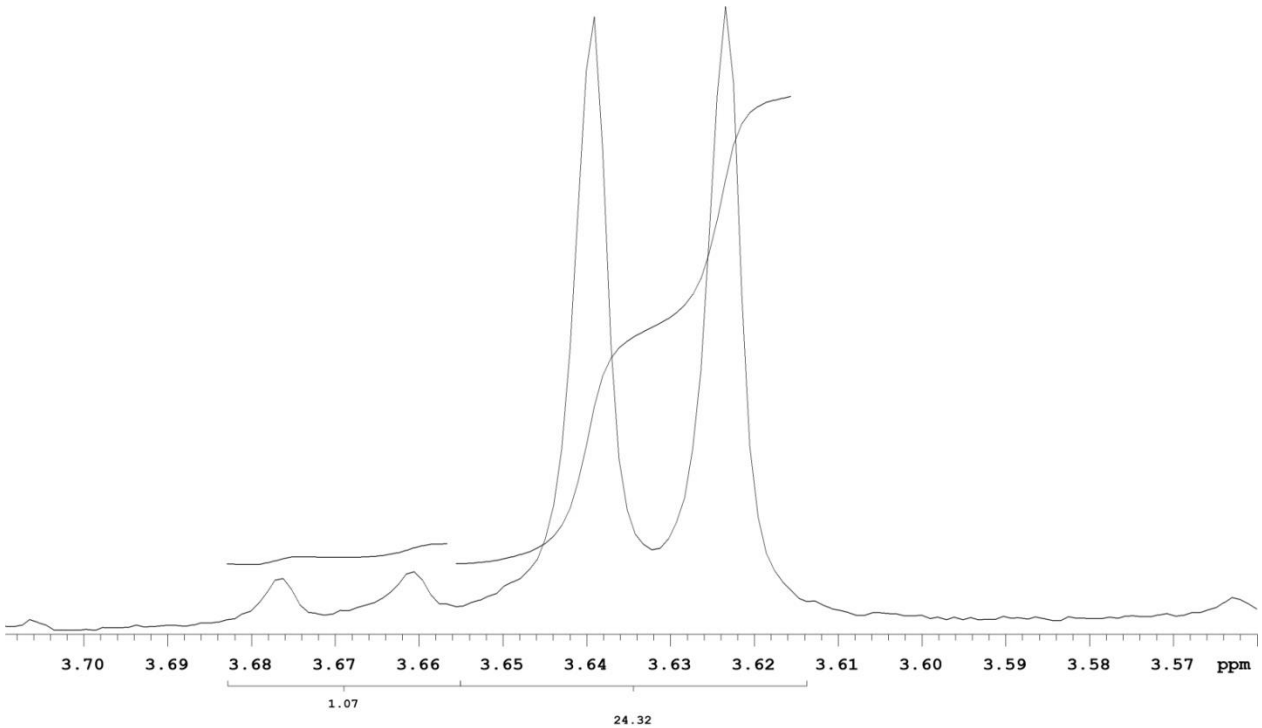


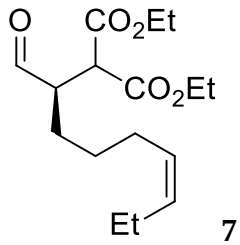
6

Racemic



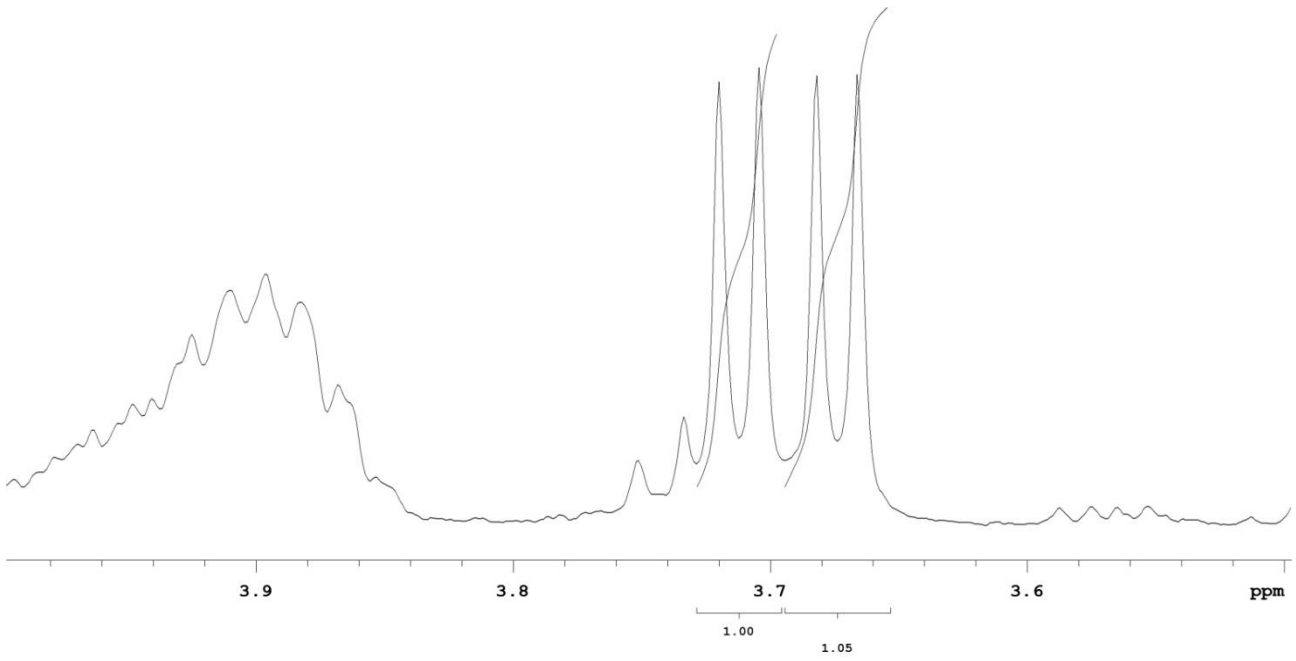
Active



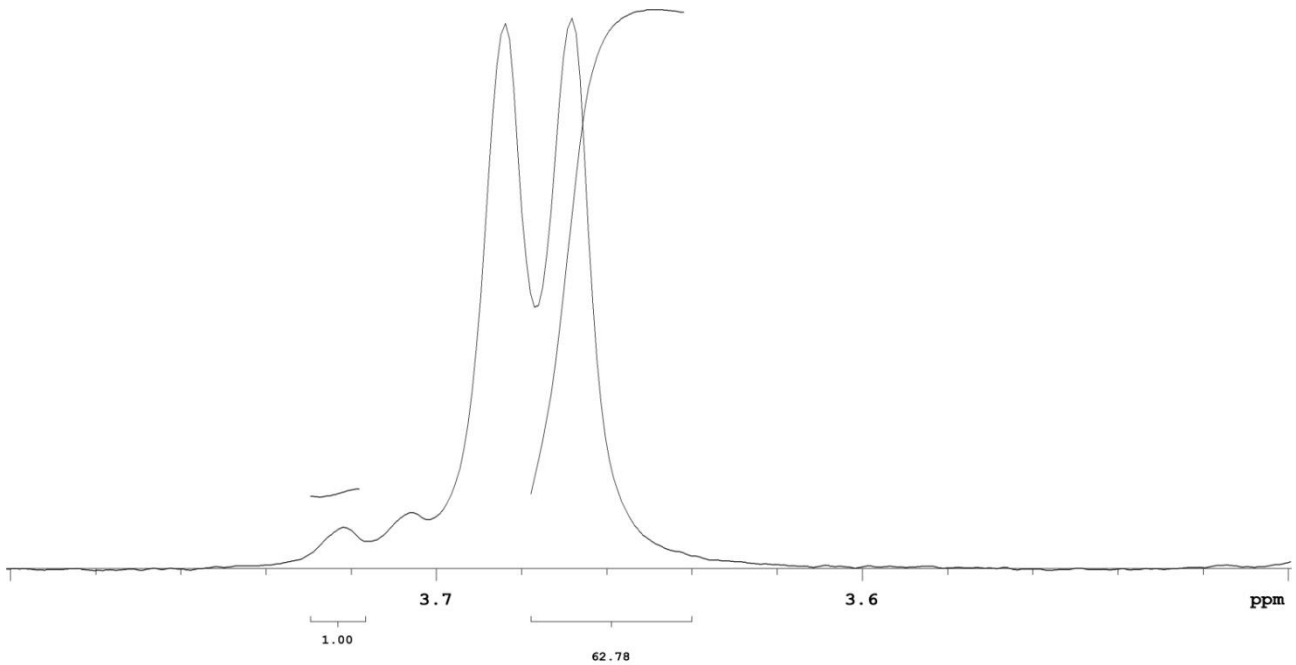


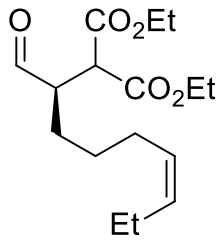
7

Racemic



Active

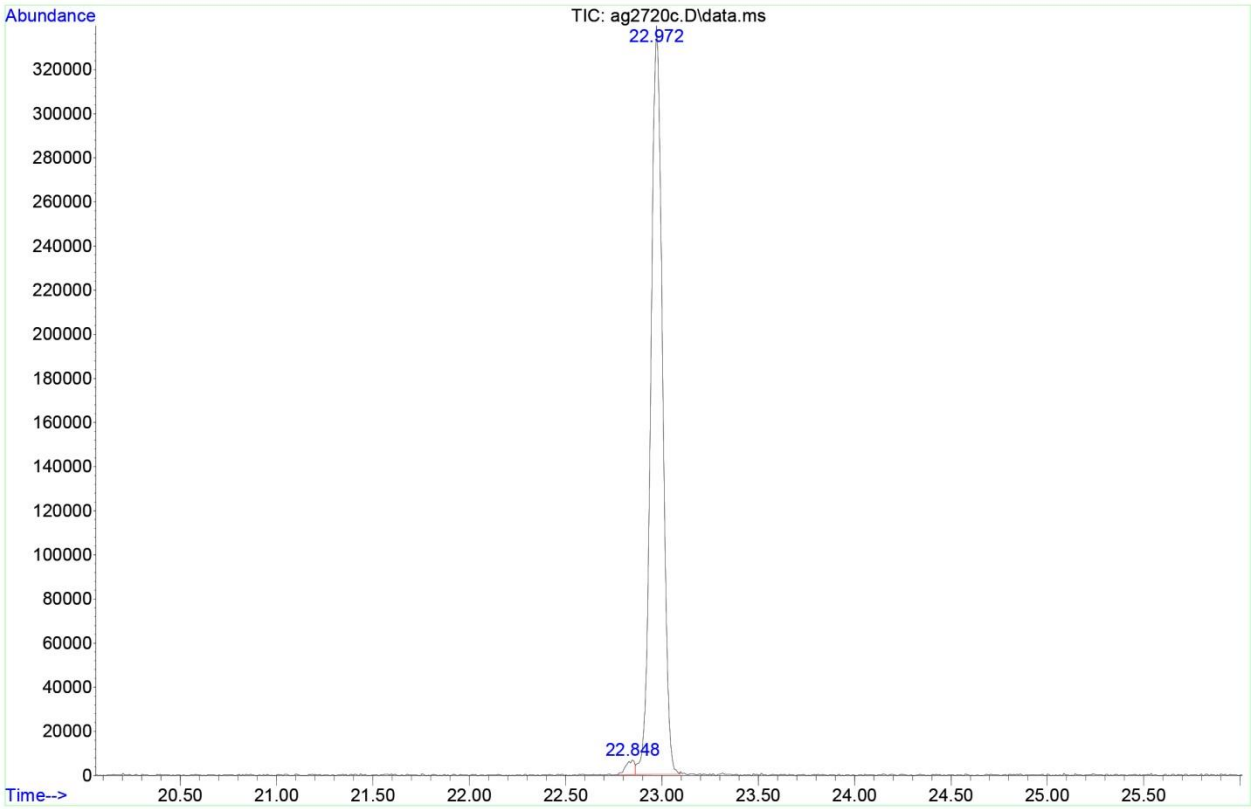




7

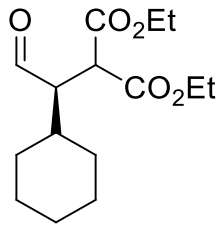
active

```
File       :C:\msdchem\1\DATA\Andrea\ag2720c.D
Operator   : Stefano Grilli
Acquired   : 27 Nov 2014  17:43     using AcqMethod AG3.M
Instrument :    GC-MS
Sample Name: ag2720
Misc Info  :
Vial Number: 4
```



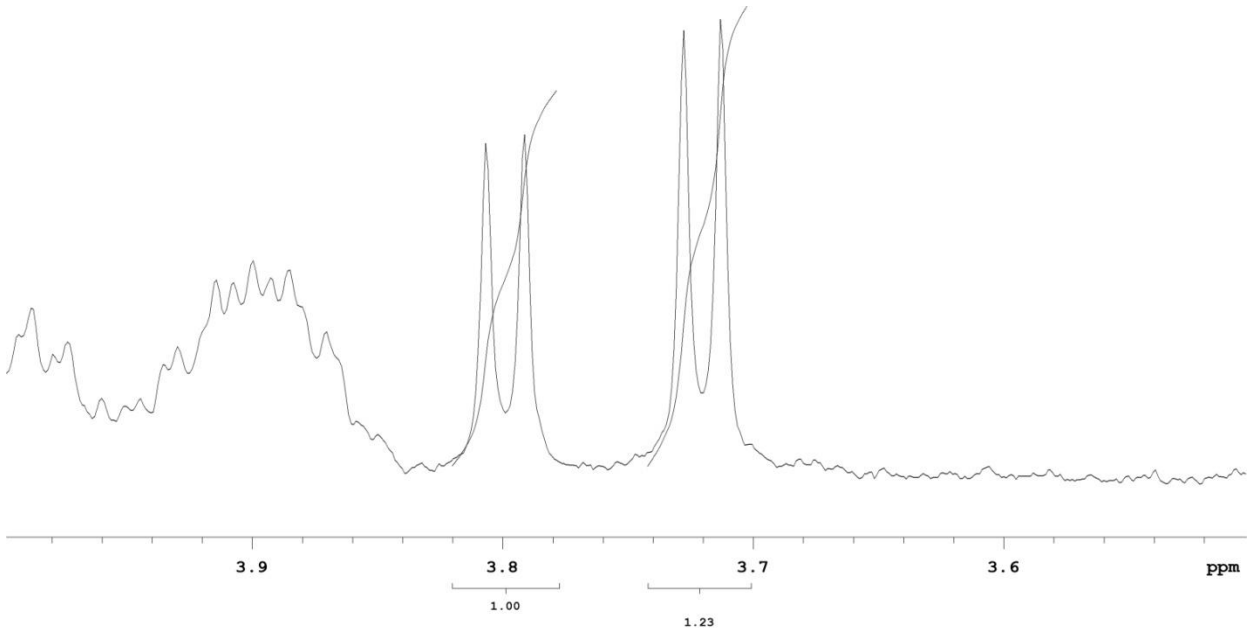

```
  Signal      : TIC: ag2720c.D\data.ms

peak   R.T.  first   max  last   PK   peak      corr.    corr.     % of
  #    min    scan  scan  scan   TY  height     area     % max.    total
---   -----  -----  ----  ----  ---  -------   -------  ------   -------
 1   22.846   2109  2118  2120    M4     6765    187490   1.31%    1.294%
 2   22.971   2120  2133  2152    M2   340261  14298424 100.00%   98.706%
```

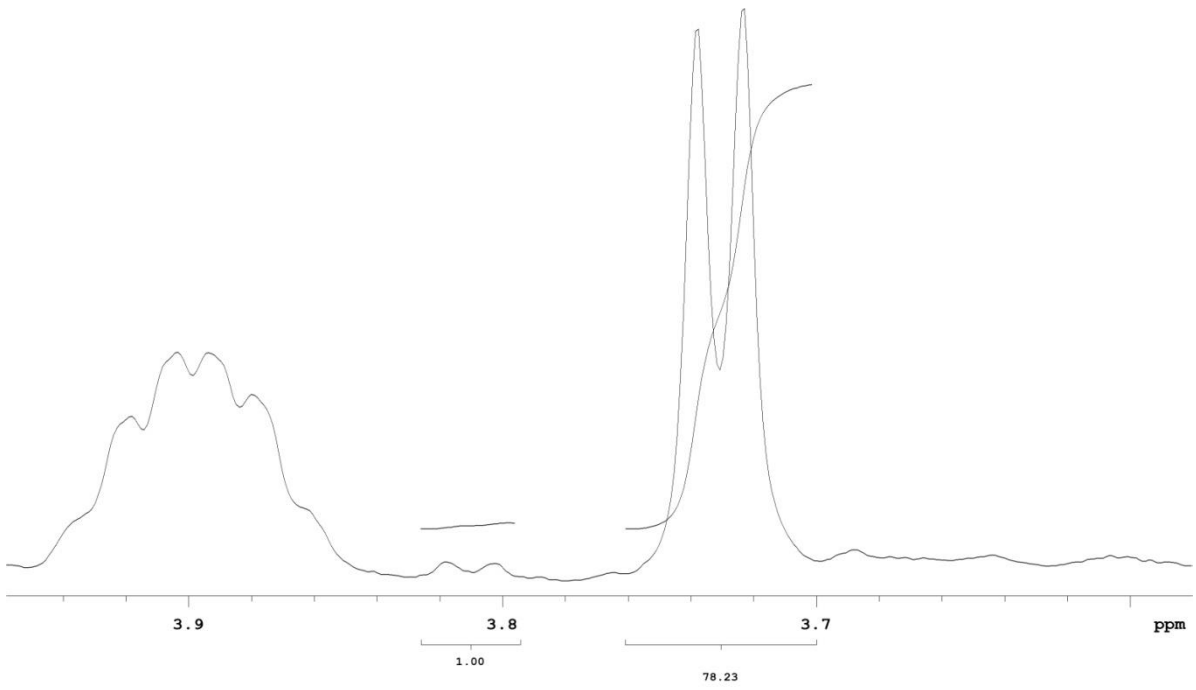


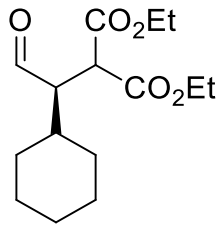
8

Racemic



Active

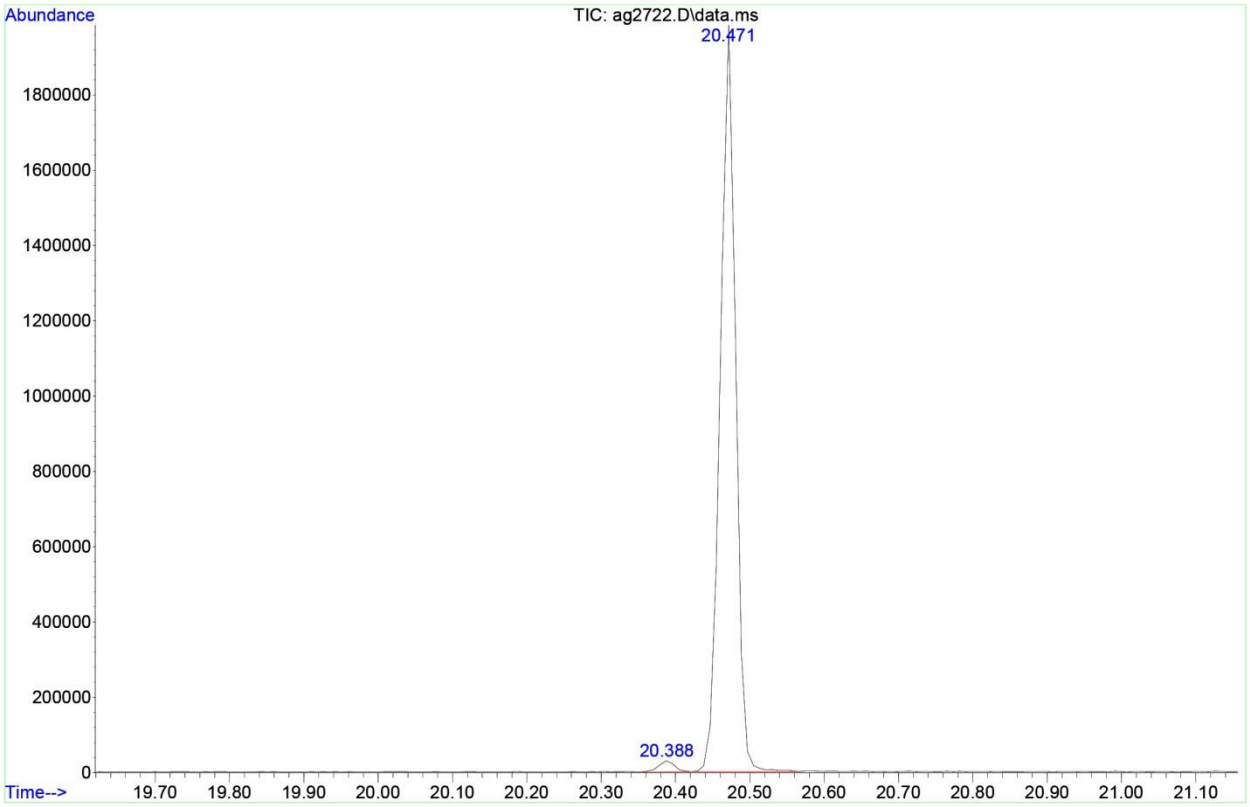




8

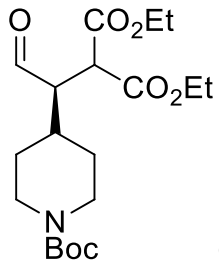
Active

```
File       :C:\msdchem\1\DATA\Andrea\ag2722.D
Operator   : Stefano Grilli
Acquired   : 27 Nov 2014  11:02     using AcqMethod AG.M
Instrument :    GC-MS
Sample Name: ag2722
Misc Info  :
Vial Number: 2
```



Signal : TIC: ag2722.D\data.ms

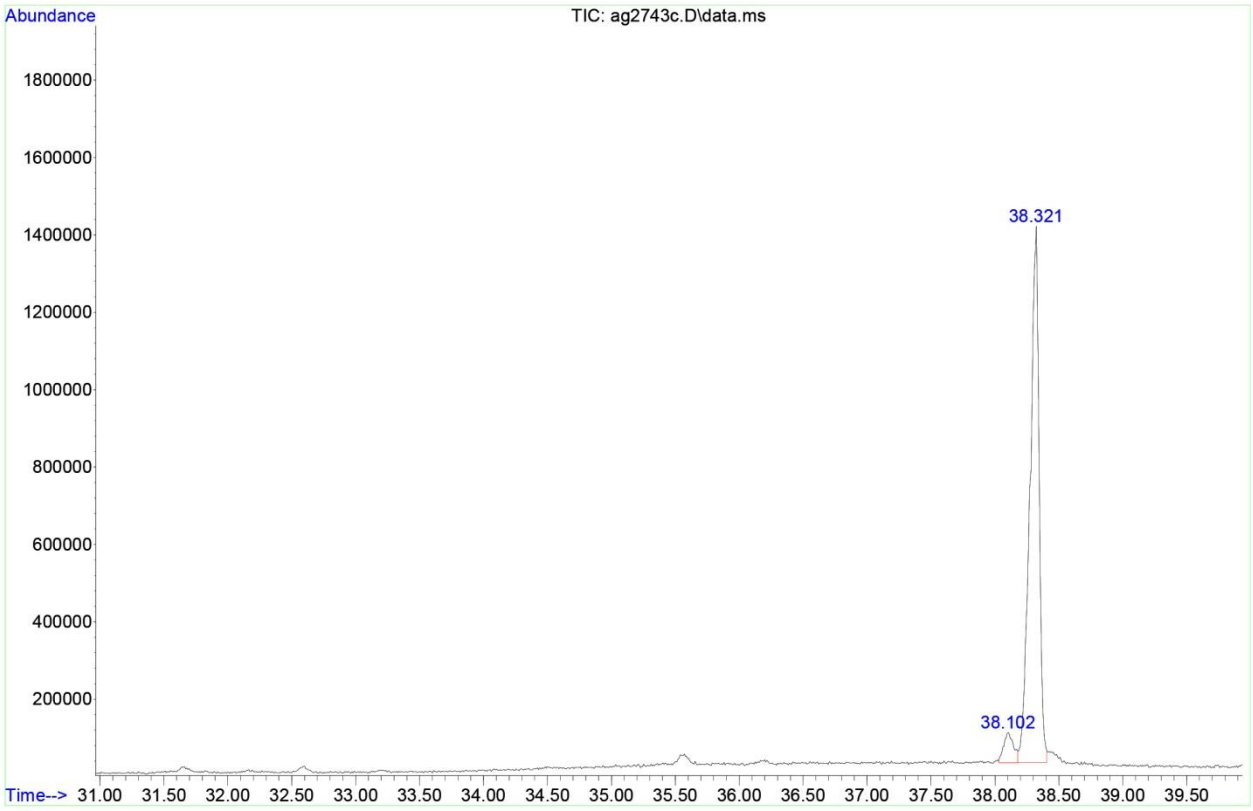
peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	20.388	1820	1825	1829	M	30528	460242	1.60%	1.579%
2	20.472	1829	1835	1846	M	1986114	28684771	100.00%	98.421%



9

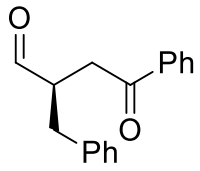
Active

```
File       :C:\msdchem\1\DATA\Andrea\ag2743c.D
Operator   : Stefano Grilli
Acquired   : 18 Dec 2014  14:23     using AcqMethod AG3.M
Instrument :    GC-MS
Sample Name: ag2743b
Misc Info  :
Vial Number: 4
```



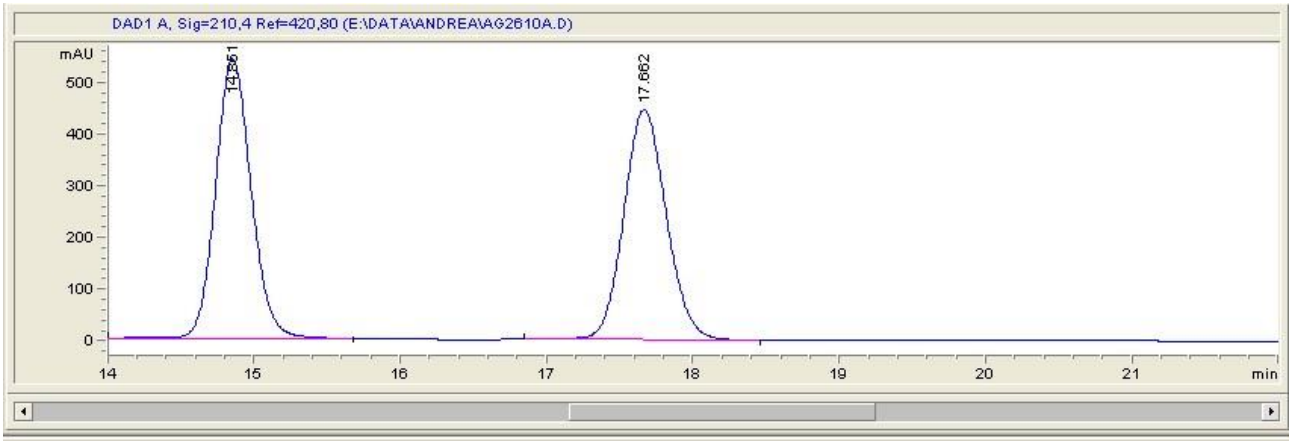
Signal : TIC: ag2743c.D\data.ms

peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	38.104	3928	3937	3946	M9	77263	4023446	5.83%	5.511%
2	38.323	3946	3963	3973	M	1389605	68977584	100.00%	94.489%



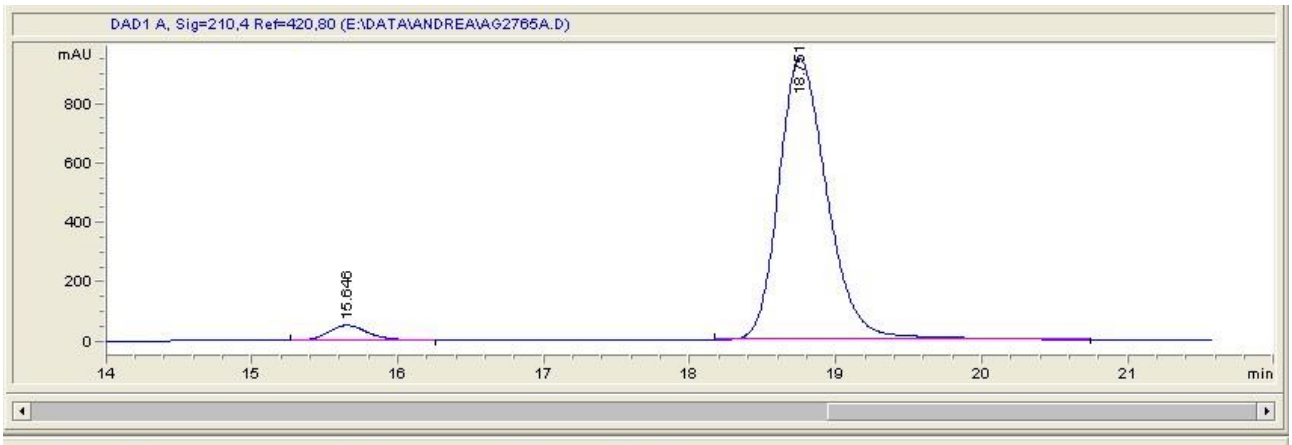
10

racemic

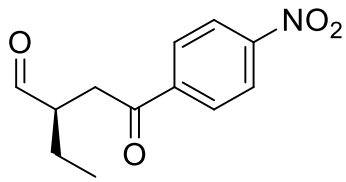


#	Time	Area	Height	Width	Area%	Symmetry
1	14.851	9359.4	543.1	0.265	50.779	0.893
2	17.662	9072.1	445.7	0.3155	49.221	0.885

Active

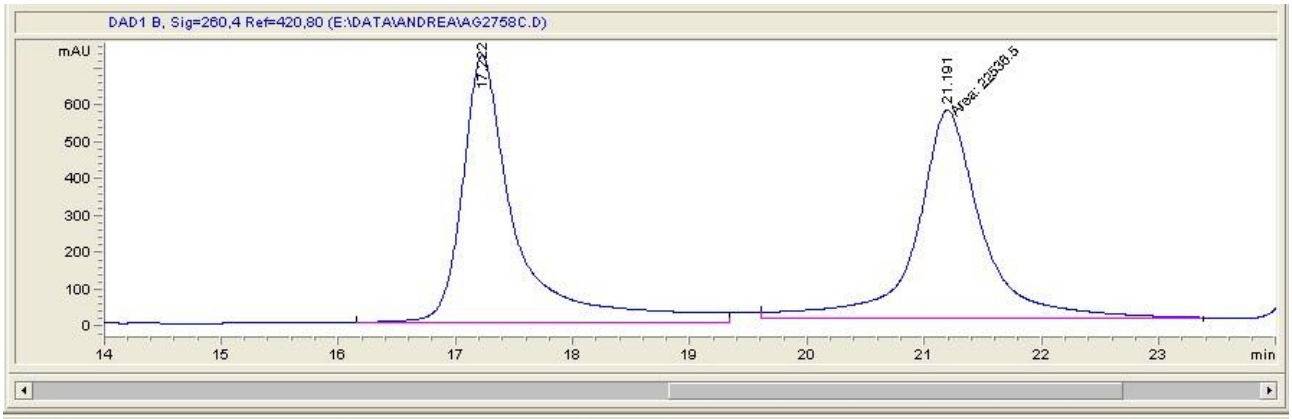


#	Time	Area	Height	Width	Area%	Symmetry
1	15.646	977.8	51	0.2937	4.231	0.808
2	18.751	22131.6	946.9	0.3587	95.769	0.72



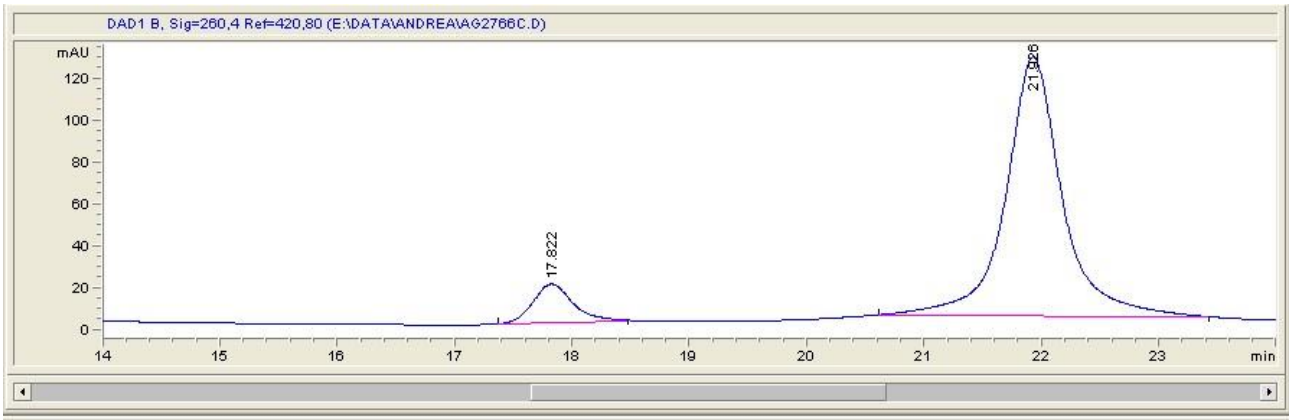
11

racemic

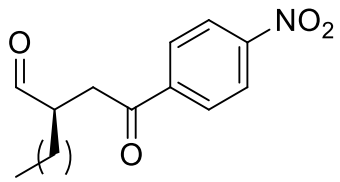


#	Time	Area	Height	Width	Area%	Symmetry
1	17.222	23142.9	724.7	0.4546	50.664	0.529
2	21.191	22536.5	566.2	0.6634	49.336	0.874

Active

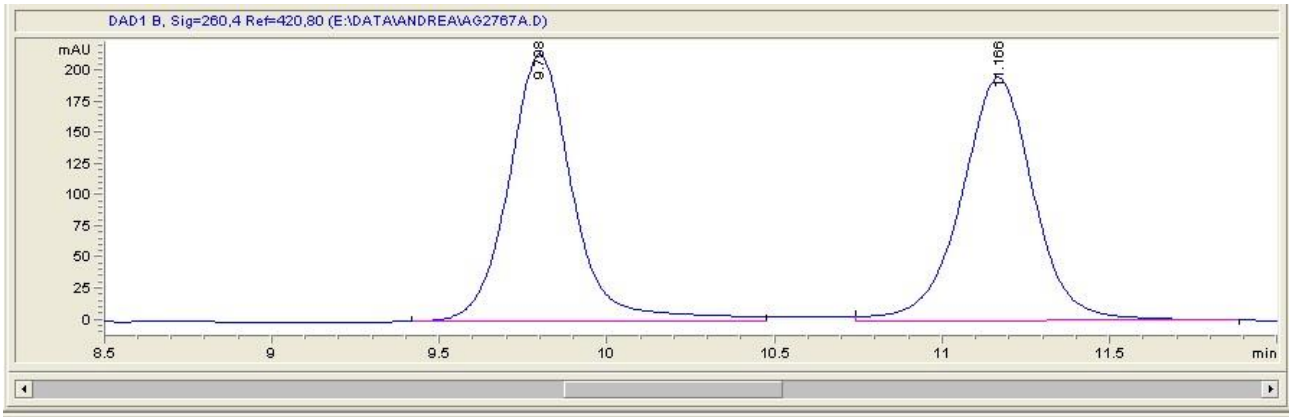


#	Time	Area	Height	Width	Area%	Symmetry
1	17.822	453.6	18.7	0.3634	9.555	0.807
2	21.926	4293	124.3	0.5028	90.445	0.926



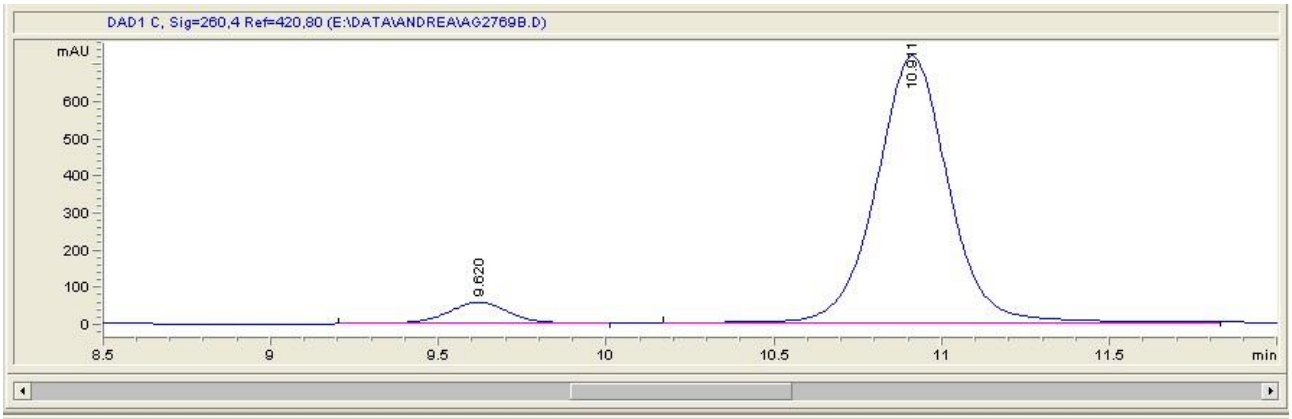
12

Racemic

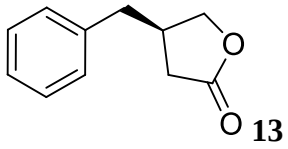


#	Time	Area	Height	Width	Area%	Symmetry
1	9.798	2905.5	215.2	0.2035	49.433	0.856
2	11.166	2972.2	196.2	0.2287	50.567	1.012

Active

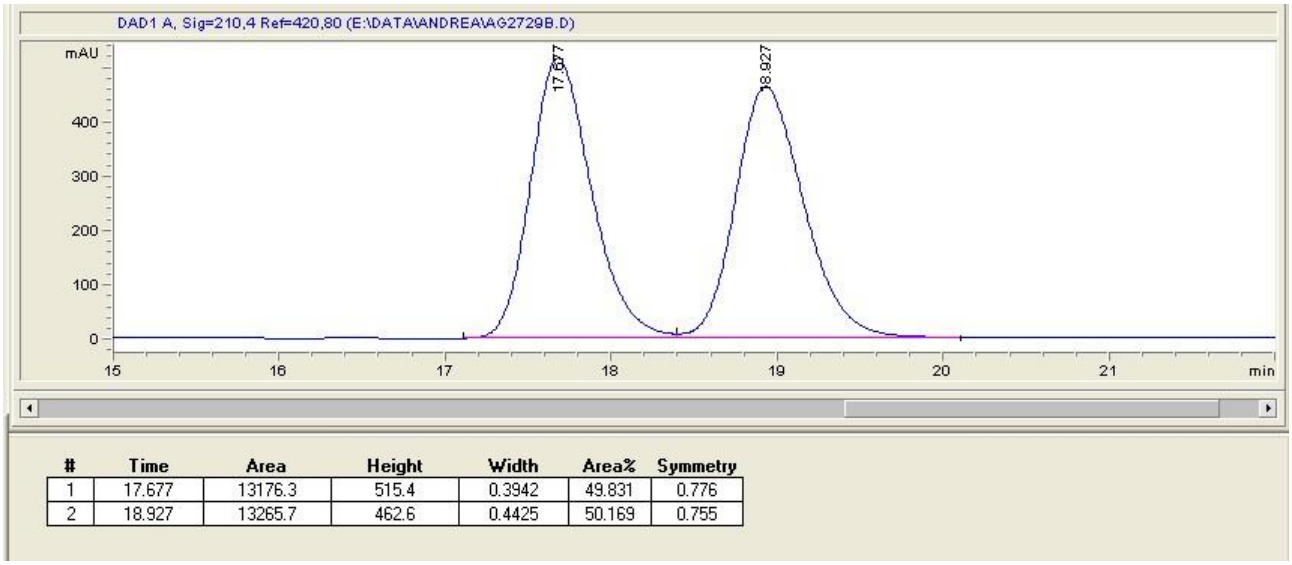


#	Time	Area	Height	Width	Area%	Symmetry
1	9.62	798.7	58.1	0.2044	6.718	0.987
2	10.911	11091.2	722.1	0.2312	93.282	0.949



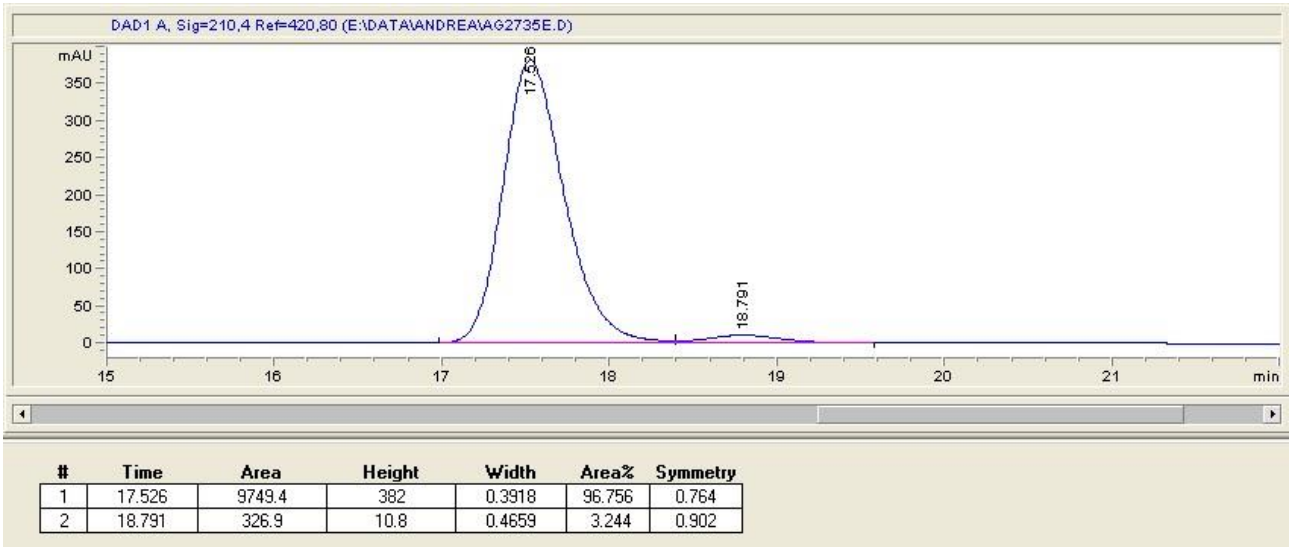
13

racemic

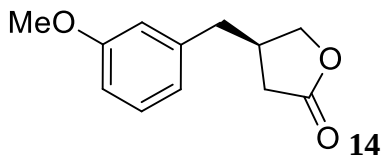


#	Time	Area	Height	Width	Area%	Symmetry
1	17.677	13176.3	515.4	0.3942	49.831	0.776
2	18.927	13265.7	462.6	0.4425	50.169	0.755

Active

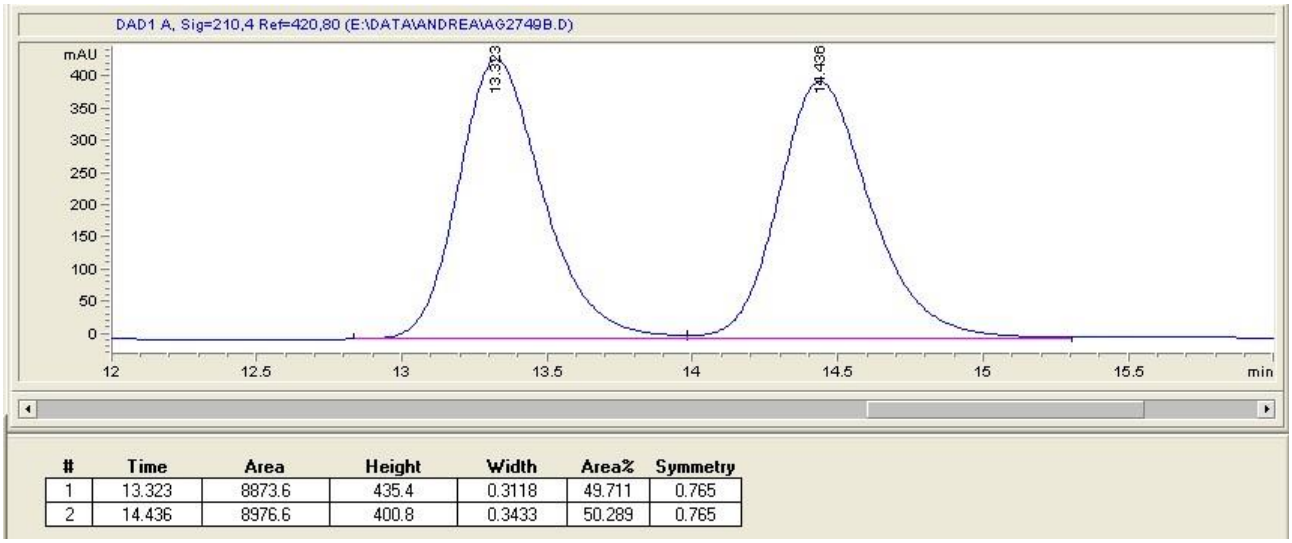


#	Time	Area	Height	Width	Area%	Symmetry
1	17.526	9749.4	382	0.3918	96.756	0.764
2	18.791	326.9	10.8	0.4659	3.244	0.902



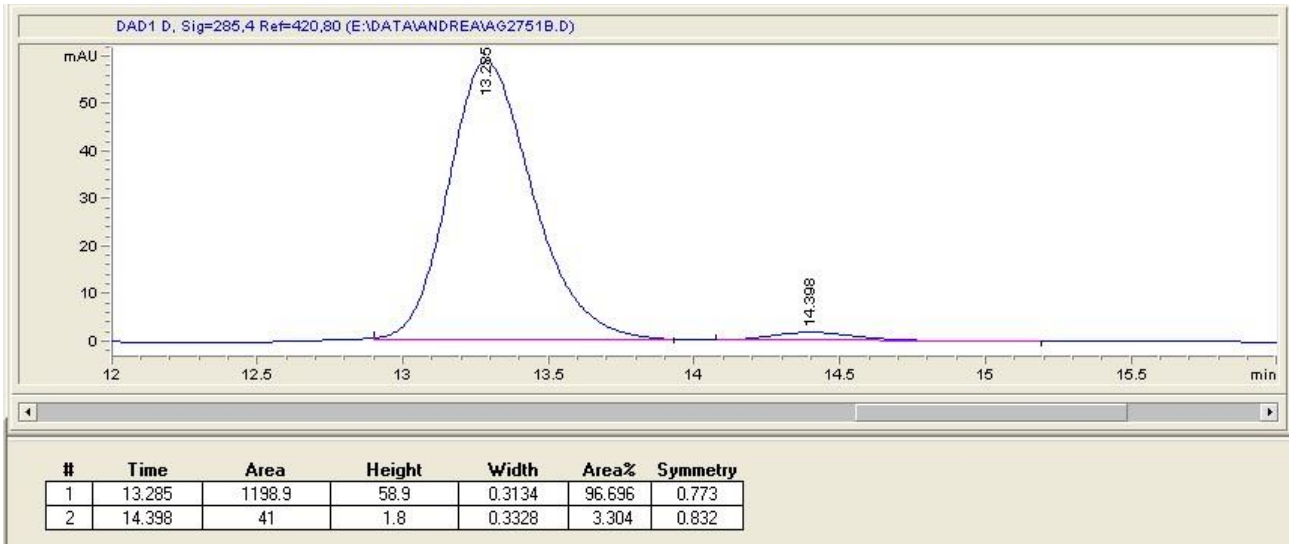
14

Racemic

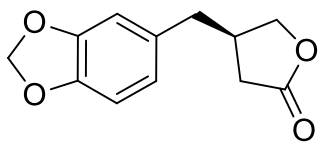


#	Time	Area	Height	Width	Area%	Symmetry
1	13.323	8873.6	435.4	0.3118	49.711	0.765
2	14.436	8976.6	400.8	0.3433	50.289	0.765

Active

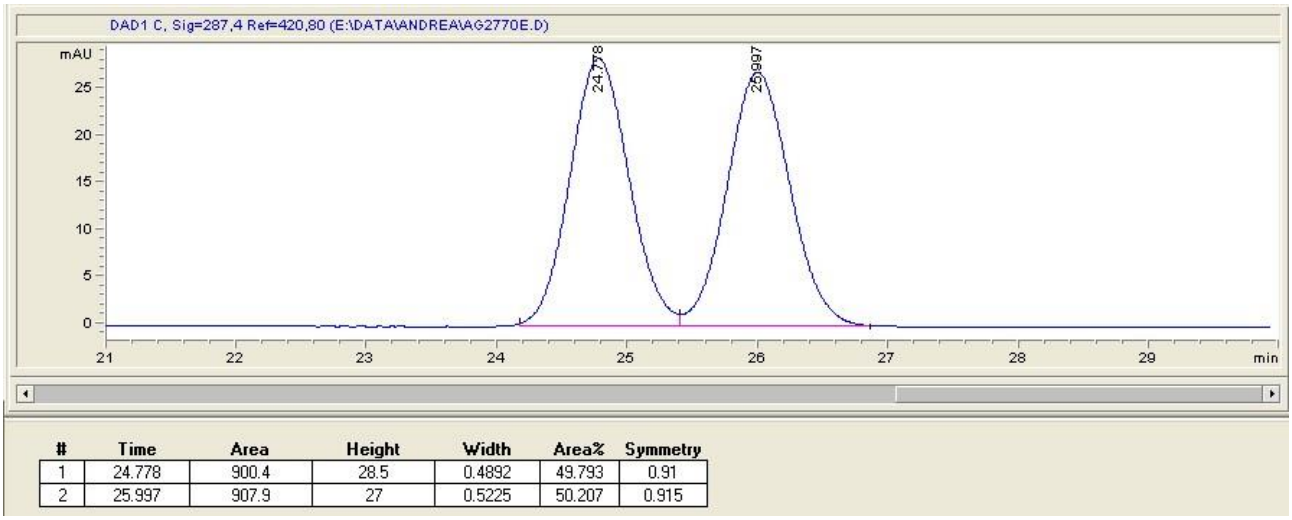


#	Time	Area	Height	Width	Area%	Symmetry
1	13.285	1198.9	58.9	0.3134	96.696	0.773
2	14.398	41	1.8	0.3328	3.304	0.832



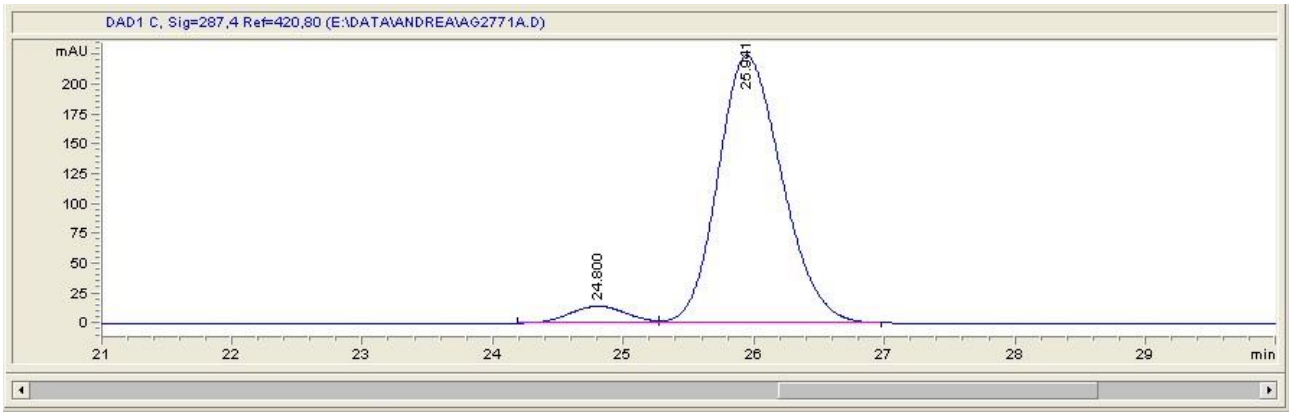
15

Racemic

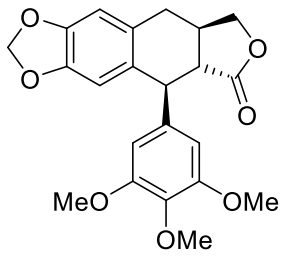


#	Time	Area	Height	Width	Area%	Symmetry
1	24.778	900.4	28.5	0.4892	49.793	0.91
2	25.997	907.9	27	0.5225	50.207	0.915

Active

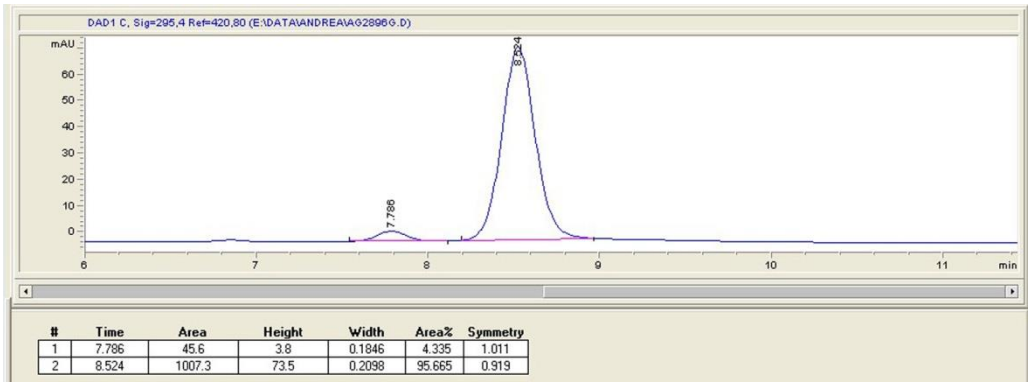


#	Time	Area	Height	Width	Area%	Symmetry
1	24.8	436.6	14.2	0.4815	5.414	0.961
2	25.941	7626.9	224.2	0.5288	94.586	0.786



16

Active



#	Time	Area	Height	Width	Area%	Symmetry
1	7.786	45.6	3.8	0.1846	4.335	1.011
2	8.524	1007.3	73.5	0.2098	95.665	0.919