Multiple approaches to enantiopure spirocyclic benzofuranones using organocatalytic cascade reactions

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Supplementary Information

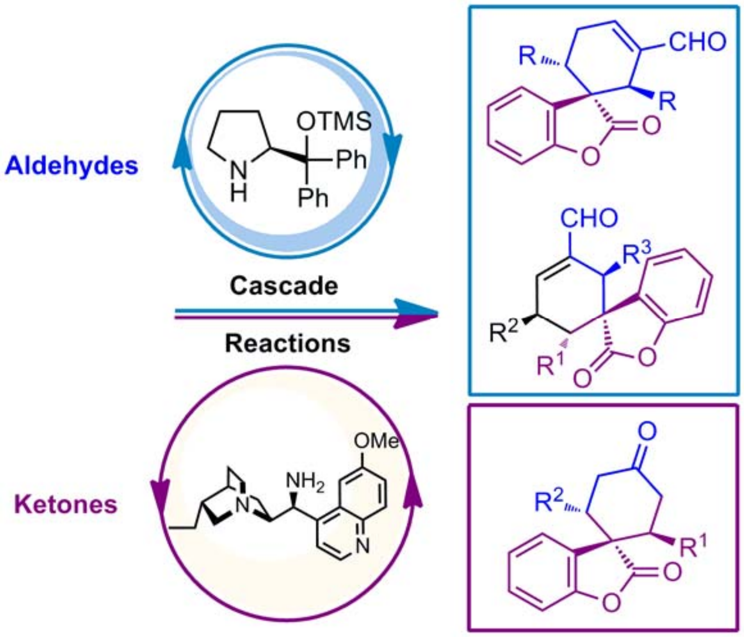

Table of Contents

General Methods. The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents ($CHCl_3$ @ 7.26 ppm ^{1}H NMR, 77.0 ppm ^{13}C NMR). Coupling constants are given in Hz. Carbon types were determined from DEPT ^{13}C NMR experiments. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. Chromatographic purification of products was accomplished using force-flow chromatography (FC) on silica gel (230-400 mesh) according to the method of Still.[1] For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used, using UV light as the visualizing agent and an acidic mixture of ceric ammonium molybdate or basic aqueous potassium permangante ($KMnO_4$), and heat as developing agents. High-resolution mass spectra (HRMS) were obtained from the ICIQ High Resolution Mass Spectrometry Unit on Waters GCT gas chromatograph coupled time-of-flight mass spectrometer (GC/MS-TOF) with electron ionisation (EI). X-ray data were obtained from the ICIQ X-Ray Unit using a Bruker-Nonius diffractometer equipped with an APPEX 2 4K CCD area detector. Optical rotations are reported as follows: $[\alpha]^{rt}_D$ (*c* in g per 100 mL, solvent). All reactions were set up in the air and using undistilled solvent, without any precautions to exclude moisture unless otherwise noted.

Materials. Commercial grade reagents and solvents were used without further purification; otherwise, where necessary, they were purified as recommended.[2] Catalysts (*S*) and (*R*)-**A** were purchased from Aldrich and used as received. Chiral primary amine catalysts, 9-Amino(9-deoxy)*epi*-hydroquinine **B** and its *pseudo*-enantiomer 9-Amino(9-deoxy)*epi*-hydroquinidine were prepared from commercially available hydroquinine and hydroquinidine, respectively, following the literature procedure.[3]

α,β-unsaturated enones (*E*)-4-(4-chlorophenyl)but-3-en-2-one **7b** and (*E*)-4-(thiophen-3-yl)but-3-en-2-one **7g**, were prepared according to the literature procedure,[4] whereas the enal (*E*)-3-(4-chlorophenyl)acrylaldehyde **2d** was prepared using the Wittig olefination reaction from commercially available 4-chloro benzaldehyde and (triphenylphosphoranylidene)acetaldehyde.

All the other enals **2**, aldehydes **5** and unsaturated ketones **7** were purchased from Aldrich or Alfa Aesar and used as received. 1-benzofuran-2(3H)-one **1** is commercially available.

All the Michael acceptors bearing a benzofuranone moiety (**4**) were prepared according to literature procedures.[5] 3-benzylidenebenzofuran-2(3H)-one **4a** was obtained as a 3:1 mixture of *E*/*Z* isomer; isolation of the pure *E* isomer has been accomplished by standard chromatography on silica gel.

(*E*)-3-(4-chlorobenzylidene)benzofuran-2(3H)-one, (E)-3-(4-nitrobenzylidene)benzofuran-2(3H)-one, and (E)-3-butylidenebenzofuran-2(3H)-one were all synthesized as a mixture *E*/*Z* isomers, and used without further purification.

(E)-ethyl 2-(2-oxobenzofuran-3(2H)-ylidene)acetate was synthesized as a single *E* isomer.

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[1] W. C. Still, M. Kahn, A. J. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.

[2] W. L. F. Armarengo, D. D. Perrin, In *Purification of Laboratory Chemicals*, 4th ed.; Butterworth Heinemann: Oxford, 1996.

[3] S. H. McCooey, S. J. Connon. *Org. Lett.* **2007**, *9*, 599-602.

[4] K. Zumbansen, A. Döhring, B. List, *Adv. Syn. Cat.* **2010**, *352*, 1135-1138.

[5] M. Msaddek, M. Rammah, K. Ciamala, J. Vebrel, B. Laude, *Synthesis*, **1997**, 1495-1498.

Determination of Enantiomeric Purity. HPLC analysis on chiral stationary phase was performed on an Agilent 1200-series instrumentation. Daicel Chiralpak IA or IC columns with i-PrOH/hexane as the eluent were used. HPLC traces were compared to racemic samples prepared by performing the reactions using a 1:1 mixture of (*S*)- and (*R*)-**A** as the catalyst for the synthesis of compounds **3** & **6.** Racemic mixtures for compounds **8** were obtained by mixing the two antipodes obtained performing distinct reactions with catalyst 9-Amino(9-deoxy)*epi*-hydroquinine **B** and the *pseudo*-enantiomer 9-Amino(9-deoxy)*epi*-hydroquinidine.

Determination of Diastereomeric Ratios

The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture, and confirmed by HPLC analysis on chiral stationary phase columns.

Absolute and Relative Configuration Determination

X-Ray Structure Analysis.

The absolute and relative configurations of compound **3d, 6b,** and **8b** (Scheme 1) were assigned by X-ray crystallographic analysis. CCDC 780474, 781708, 781524, respectively, contain the supplementary crystallographic data for those compounds. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

Single Crystal X-ray Diffraction Data for compound 3d (table 1, entry 5):

X-ray structure determinations: Crystals of compound **3d** were obtained by slow evaporation in a mixture of Hexane and Diethyl-ether in a 1:1 portion at room temperature. The measured crystals were stable under atmosphere conditions; nevertheless they were prepared under inert conditions immersed in perfluoropoly-ether as protecting oil for manipulation.

Data Collection. Measurements were made on a Bruker-Nonius diffractometer equipped with an APPEX 2 4K CCD area detector, a FR591 rotating anode with $Mo_{K\alpha}$ radiation, Montel mirrors and a Kryoflex low temperature device (T = -173 °C). Full-sphere data collection was used with ω and φ scans.

Programs used: Data collection Apex2 V2009 1.0 (Bruker-Nonius 2008), data reduction Saint + Version 7.60A (Bruker AXS 2008) and absorption correctionTWINABS.[6]

Structure Solution. SIR2007 program was used.[7]

Structure Refinement. SHELXTL-97-UNIX VERSION.

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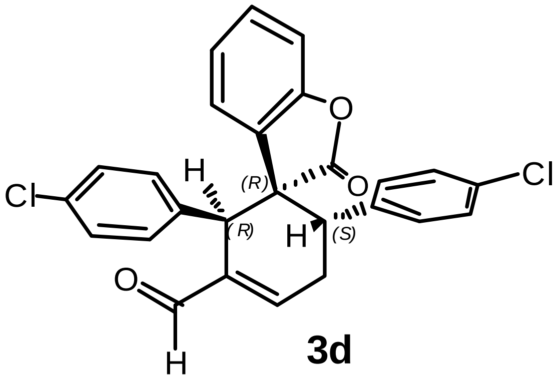
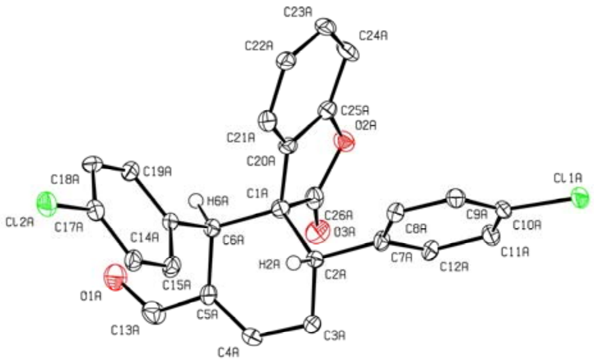
[6] *TWINABS Version 2008/4 Bruker AXS Blessing, Acta Cryst. (1995) A51 33-38*

[7] R.Caliandro, B. Carrozzini, G.L.Cascarano, L. De Caro, C. Giacovazzo and D. Siliqi (2007) Advances in ab initio protein phasing by Patterson deconvolution techniques *J. Appl. Cryst. 40,883-890.*



3d



Crystal data for **3d** at 100 K: **CCDC 780474**

Empirical formula	C_{26} H_{18} Cl_2 O_3	
Formula weight	449.30	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 9.3195(10) Å	α= 82.514(4) °.
	b = 9.3688(10) Å	β = 88.091(4) °.
	c = 26.301(3) Å	γ = 69.752(5) °.
Volume	2136.0(4) Å^3	
Z	4	
Density (calculated)	1.397 Mg/m^3	
Absorption coefficient	0.330 mm^{-1}	
F(000)	928	
Crystal size	0.30 x 0.30 x 0.10 mm^3	
Theta range for data collection	0.78 to0.78 °.	
Index ranges	-13 <=h<=14 ,-13 <=k<=14 ,-41 <=l<=41	
Reflections collected	29711	
Independent reflections	24733 [R(int) = 0.0000]	
Completeness to theta =34.63 °	0.846 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9781 and 0.8102	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	29711 / 3 / 1118	
Goodness-of-fit on F^2	1.052	
Final R indices [I>2sigma(I)]	R1 = 0.0845 , wR2 = 0.2361	
R indices (all data)	R1 = 0.0976 , wR2 = 0.2513	
Absolute Structure Flack parameter	x =0.03(	
Largest diff. peak and hole	1.627 and -0.747 e.Å^{-3}	

The structure refines as a twin made up of two crystal domains with a ratio 71:29. The diffraction measured fraction is low, 0.89, since the reflections of belonging to both crystal domains have been omitted

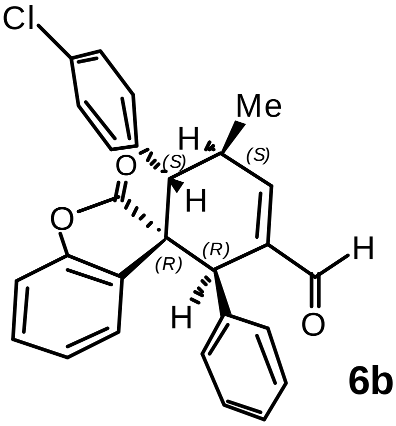
Single Crystal X-ray Diffraction Data for compound 6b (table 2, entry 3):

X-ray structure determinations: Crystals of compound **6b** were obtained by slow evaporation in isopropyl alcohol at 60ºC. The measured crystals were stable under atmosphere conditions; nevertheless they were prepared under inert conditions immersed in perfluoropoly-ether as protecting oil for manipulation.

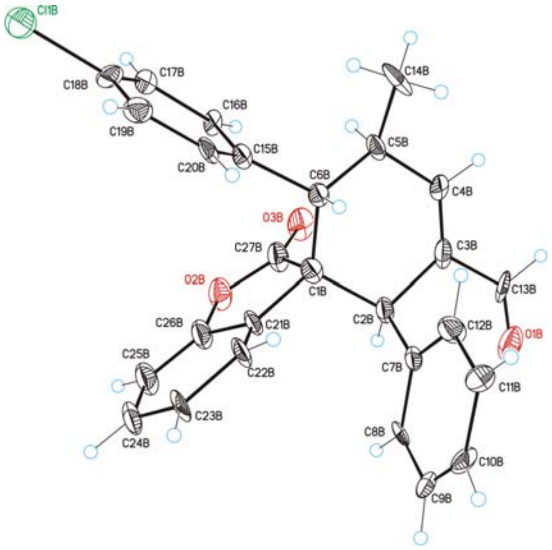
The measured sample is a perfect merohedral twin (twin law 0 1 0 1 0 0 0 0 -1, basf 0.5).

Programs used: Data collection Apex2 V2009 1.0 (Bruker-Nonius 2008), data reduction Saint + Version 7.60A (Bruker AXS 2008) and absorption correctionTWINABS.[6]

Structure Solution. SIR2007 program was used.[7]



6b



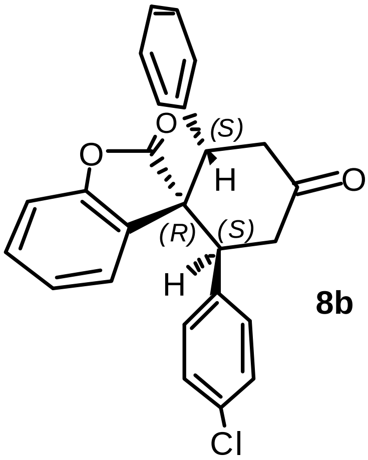
Crystal data for **6b** at 100 K: **CCDC 781708**

Empirical formula	C27 H21 Cl O3	
Formula weight	428.89	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Tetragonal	
Space group	P4(1)	
Unit cell dimensions	a = 9.3547(11) Å	α= 90.00 °.
	b = 9.3547(11) Å	β = 90.00 °.
	c = 51.084(6) Å	γ = 90.00 °.
Volume	4470.4(9) Å^3	
Z	8	
Density (calculated)	1.274 Mg/m^3	
Absorption coefficient	0.197 mm^{-1}	
F(000)	1792	
Crystal size	0.40 x 0.30 x 0.15 mm^3	
Theta range for data collection	0.80 to 28.23 °.	
Index ranges	-12 <=h<=9 ,-7 <=k<=12 ,-63 <=l<=67	

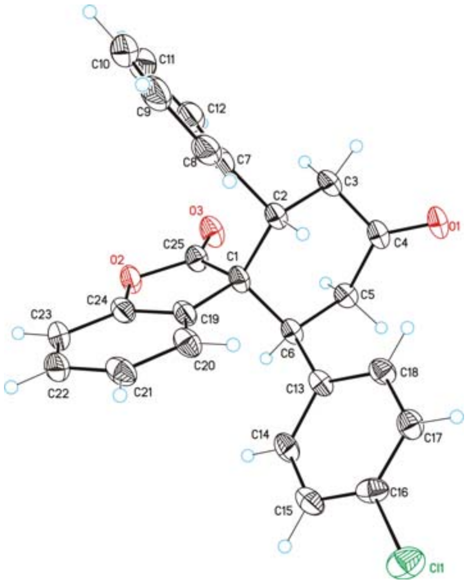
Reflections collected	10668
Independent reflections	9044 [R(int) = 0.0714]
Completeness to theta =28.23 °	0.989 %
Absorption correction	Empirical
Max. and min. transmission	0.9711 and 0.9255
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	10668 / 631 / 562
Goodness-of-fit on F^2	1.112
Final R indices [I>2sigma(I)]	R1 = 0.1074 , wR2 = 0.2585
R indices (all data)	R1 = 0.1222 , wR2 = 0.2669
Absolute Structure Flack parameter	x =0.08(17)
Largest diff. peak and hole	0.564 and -0.795 e.Å^{-3}

Single Crystal X-ray Diffraction Data for compound 8b (table 3, entry 3):

X-ray structure determinations: Crystals of compound **8b** were obtained by slow evaporation in methanol at room temperature. The measured crystals were stable under atmosphere conditions; nevertheless they were prepared under inert conditions immersed in perfluoropoly-ether as protecting oil for manipulation.



8b



Crystal data for **8b** at 100 K: **CCDC 781524**

Crystallized from Methanol	
Empirical formula	$C_{25} H_{19} Cl O_3$
Formula weight	402.85
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)

Unit cell dimensions	a = 9.3490(9) Å	α= 90.00 °.
	b = 6.8640(6) Å	β = 100.578(4) °.
	c = 15.7148(15) Å	γ = 90.00 °.
Volume	991.31(16) Å^3	
Z	2	
Density (calculated)	1.350 Mg/m^3	
Absorption coefficient	0.217 mm^{-1}	
F(000)	420	
Crystal size	0.40 x 0.30 x 0.15 mm^3	
Theta range for data collection	1.32 to 28.41 °.	
Index ranges	-12 <=h<=11 ,-8 <=k<=7 ,-20 <=l<=20	
Reflections collected	4166	
Independent reflections	2922 [R(int) = 0.0658]	
Completeness to theta =28.41 °	0.924 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9682 and 0.9183	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4166 / 1 / 262	
Goodness-of-fit on F^2	0.921	
Final R indices [I>2sigma(I)]	R1 = 0.0552 , wR2 = 0.1372	
R indices (all data)	R1 = 0.0958 , wR2 = 0.1601	
Absolute Structure Flack parameter	x =-0.06(10)	
Largest diff. peak and hole	0.378 and -0.327 e.Å^{-3}	

Influence of the compound 4 geometry on the stereochemical outcome of the cascade reactions.

Partial equilibration of the double-bond geometry of 3-benzylidenebenzofuran-2(3H)-one **4a** (bearing a β-phenyl group) has been observed under the catalytic reaction conditions of the cascade processes reported in table 2 and 3 (Figure S1).

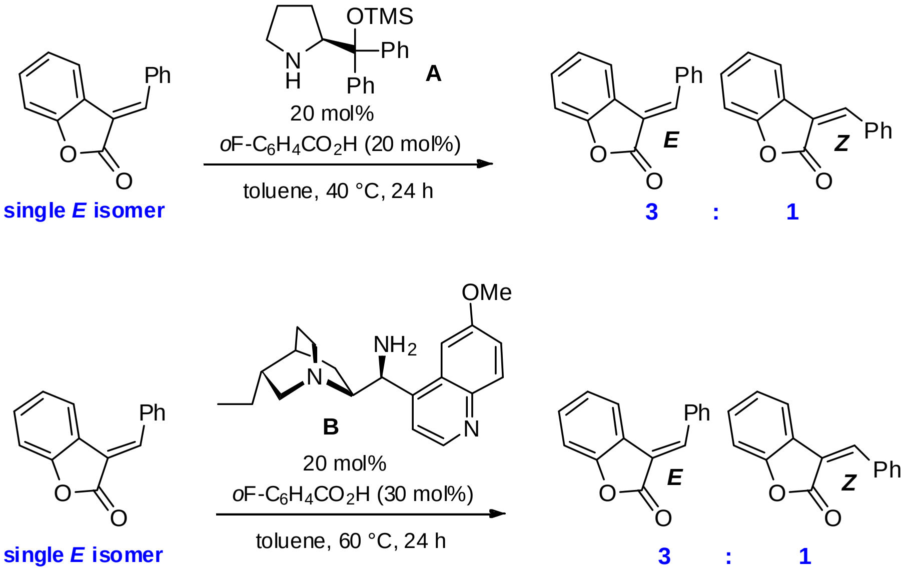


Figure S1. Scrambling Experiments

Notably, using a 3:1 mixture of *E*/Z isomers of compound **4** leads to the same stereochemical outcome as employing geometrically pure *E* isomer (compare entries 1 & 2, Table 2, a single stereoisomer, de and ee >99%).

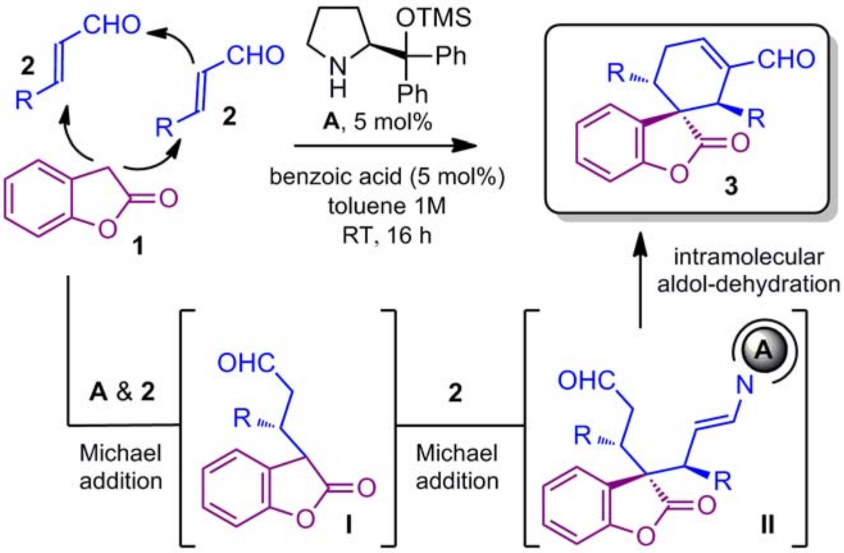
At the same extent, the stereochemical outcome of cascade reactions depicted in Table 3 is not dependent on the geometry of the starting compound **4.**

The stereo-convergence of the triple cascade depicted in Table 2 might be rationalized on the basis of a reversible first enamine-catalysed Michael addition step between aldehyde **5** and **4**, leading to intermediate **III**: a rapid equilibrium may account for a dynamic kinetic resolution process driven by the perfectly suited matched-pair combination of the chiral iminium ion (generated by condensation of catalyst **B** and enals **2**) and only one out of the possible eight stereoisomers of intermediate **III.** Unfortunately, to date we were not able to isolate this key intermediate.

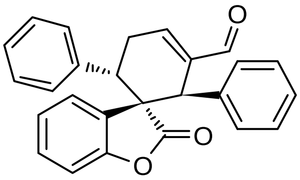
At present, we cannot rule out a stereo-convergence path driven by a different reactivity of the *E* and *Z* isomers of 4, where the double-bond geometry scrambling continuously regenerates the fast reacting isomer.

Form a synthetic standpoint, the fact that the geometry of the starting material **4** is not reflected into the stereochemistry of the final compounds accounts for a more practical synthetic protocol (a mixture of **4** can be used).

General Procedure for the Organocatalytic Triple Cascade of Aldehydes proceeding via an Iminium-Iminium-Enamine Sequence (Table 1)



All the reactions were carried out with no precautions to exclude moisture in undistilled toluene. In an ordinary vial equipped with a Teflon-coated stir bar, (*S*)-(–)-α,α-Diphenyl-2-pyrrolidinemethanol trimethylsilyl ether **A** (0.01 mmol, 20 µL of a 0.5 M toluene stock solution, 5 mol%) was added to 180 µL of toluene. After the addition of benzoic acid (0.01 mmol, 1.2 mg, 5 mol%), the solution was stirred for 5 minutes at room temperature before adding the aldehyde **2** (0.6 mmol, 3 equiv). The mixture was then allowed to stir for 5 minutes further at room temperature before the addition of 2-Cumarone **1** (26.8 mg, 0.2 mmol). The vial was sealed, and the stirring continued at room temperature for 16h. The crude reaction was then flushed through a short plug of silica, using CH_2Cl_2/Et_2O 1/1 as the eluent. Solvent was removed *in vacuo* and, after NMR analysis to determine the diastereomeric ratio of the process, the residue was purified by flash column chromatography (silica gel) to yield the desired product **3.**



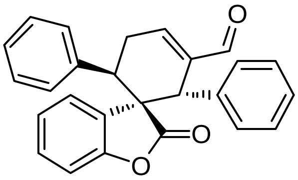
(1''R,2''R,3''S)-2-oxo-1'',3''-diphenyl-2H-spiro[benzofuran-3,2''-cyclohex[5']ene]-6''-carbaldehyde (**3a** – Table 1, entry 1)

The reaction was carried out following the general procedure to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a white solid by column chromatography (hexane/diethyl ether = 8/2) in 75% yield and >99% de and ee. HPLC analysis on a Daicel Chiralpak IC column: 80/20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 12.9 min, τ_{minor} = 23.1 min; HRMS *calcd* for ($C_{26}H_{20}O_3$+Na): 403.1310, *found* 403.1318. $[\alpha]_{25}^{D}$= -167.7 (*c* = 1.00, $CHCl_3$, >99% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.01 (td, 1H, J_d = 20.5 Hz, J_t = 5.7 Hz), 3.38-3.49 (m, 1H), 3.65 (dd, 1H, J_1 = 11.4 Hz, J_2 = 5.8 Hz), 4.09 (s, 1H), 5.44 (dd, 1H, J_1 = 7.7 Hz, J_2 = 0.9 Hz), 6.58 (dt, 1H, J_t = 7.6 Hz, J_d = 0.9 Hz), 6.63-6.79 (m, 2H), 6.87-7.06 (m, 6H), 7.08-7.48 (m, 5H), 9.55 (s, 1H). ^{13}C NMR (400 MHz,

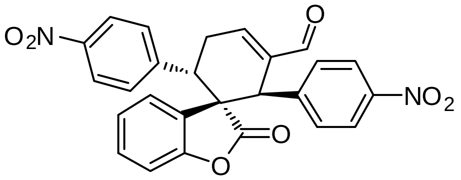
$CDCl_3$): δ 31.3 (CH_2), 42.4 (CH), 46.0 (CH), 53.5 (C), 109.9 (CH), 122.9 (CH), 126.7 (CH), 127.3 (C), 127.4 (CH), 128.1 (CH), 128.2 (C), 128.2 (CH), 128.4 (CH), 128.7 (CH), 137.7 (CH), 138.8 (CH), 139.3 (C), 150.6 (CH), 152.5 (C), 177.0 (C), 192.2 (CH).

Carrying out the reaction in the presence of 1 mol% of the catalyst A at 40 degrees afforded similar results: full conversion, 68% isolated yield, de & ee >99%



(1''S,2''S,3''R)-2-oxo-1'',3''-diphenyl-2H-spiro[benzofuran-3,2''-cyclohex[5']ene]-6''-carbaldehyde.

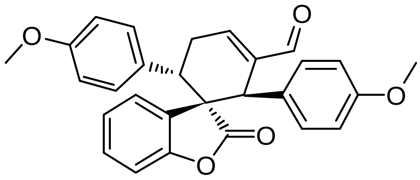
The reaction was carried out following the general procedure using (*R*)-(+)-α,α-Diphenyl-2-pyrrolidinemethanol trimethylsilyl ether as catalyst to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a white solid by column chromatography (hexane/diethyl ether = 8/2) in 72% yield and >99% ee. HPLC analysis on a Daicel Chiralpak IC column: 80/20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: $\tau =_{minor}$ 12.9 min, τ_{major} = 23.1 min;. $[\alpha]_{25}^{D}$= +132.9 (*c* = 1.06, $CHCl_3$, >99% ee).



(1''R,2''R,3''S)-1'',3''-bis(4-nitrophenyl)-2-oxo-2H-spiro[benzofuran-3,2''-cyclohex[5']ene]-6''-carbaldehyde (**3b** – Table 1, entry 3).

The reaction was carried out following the general procedure to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a yellow solid by column chromatography (hexane/diethyl ether = 6/4) in 59% yield and >99% de and ee. HPLC analysis on a Daicel Chiralpak IC column: 70/30 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 45.3 min, τ_{minor} = 54.1 min; HRMS *calcd* for ($C_{26}H_{17}N_2O_7$): 469.1036, *found* 469.1048. $[\alpha]_{26}^{D}$= -258.5 (*c* = 1.07, $CHCl_3$, >99% ee).

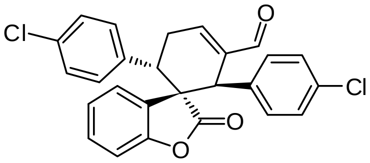
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.08 (td, 1H, J_d = 20.5 Hz, J_t = 5.4 Hz), 3.45-3.53 (m, 1H), 3.66 (dd, 1H, J_1 = 11.3 Hz), 4.21 (s, 1H), 5.50 (dd, 1H, J_1 = 7.6 Hz, J_2 = 0.9 Hz), 6.67 (dt, 1H, J_t = 7.5 Hz, J_d 0.9= Hz), 6.83-6.95 (m, 2H), 7.04-7.13 (m, 3H), 7.37-7.50 (m, 2H), 7.88-7.92 (m, 2H), 8.00-8.11 (m, 1H), 8.24-8.36 (m, 1H), 9.57 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 30.8 (CH_2), 42.5 (CH), 45.6 (CH), 52.6 (C), 111.0 (CH), 123.4 (CH), 123.5 (C), 123.8 (CH), 125.6 (C), 125.8 (CH), 129.2 (CH), 130.0 (CH), 138.6 (C), 144.7 (C), 145.6 (C), 147.4 (C), 147.8 (C), 150.3 (CH), 152.4 (C), 175.8 (C), 191.5 (CH).



(1"R,2"R,3"S)-1",3"-bis(4-methoxyphenyl)-2-oxo-2H-spiro[benzofuran-3,2"-cyclohex[5']ene]-6"-carbaldehyde (**3c** – Table 1, entry 4).

The reaction was carried out following the general procedure to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a pale yellow solid by column chromatography (hexane/diethyl ether = 7/3) in 54% yield and >99% de and ee. HPLC analysis on a Daicel Chiralpak IC column: 70/30 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 18.0 min, τ_{minor} = 38.1 min; HRMS *calcd* for ($C_{28}H_{24}O_5$+Na): 463.1521, *found* 463.1533. $[\alpha]_{26}^{D}$= -215.1 (*c* = 1.08, $CHCl_3$, >99% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.98 (td, 1H, J_d = 20.7 Hz, J_t 5.6= Hz), 3.32-3.44 (m, 1H), 3.58 (dd, 1H, J_1 = 11.4 Hz, J_2 = 5.8 Hz), 3.65 (s, 3H), 3.84 (s, 3H), 4.05 (s, 1H), 5.58 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.0 Hz), 6.54-6.58 (m, 2H), 6.59-6.78 (m, 3H), 6.80 (d, 1H, *J* = 8.0), 6.83-6.87 (m, 2H), 6.91-6.99 (m, 1H),7.02 (dt, 1H, J_d = 1.3 Hz, J_t = 7.7 Hz), 7.11-7.22 (m, 1H), 7.34-7.37 (m, 1H), 9.55 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 31.4 (CH_2), 41.4 (CH), 45.0 (CH), 53.7 (C), 55.0(CH_3), 55.3 (CH_3), 109.8 (CH), 113.4 (C), 113.6 (CH), 122.5 (CH), 126.7 (CH), 127.4 (C), 128.5 (CH), 129.1 (CH), 129.7 (C), 130.7 (C), 139.4 (C), 150.3 (CH), 152.4 (C), 158.5 (C), 159.2 (C), 177.0 (C), 192.2 (CH).

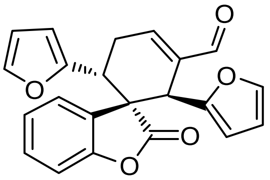


(1"R,2"R,3"S)-1",3"-bis(4-chlorophenyl)-2-oxo-2H-spiro[benzofuran-3,2"-cyclohex[5']ene]-6"-carbaldehyde (**3d** – Table 1, entry 5).

The reaction was carried out following the general procedure to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a white solid by column chromatography (hexane/diethyl ether = 7/3) in 80% yield and 99% ee. HPLC analysis on a Daicel Chiralpak IC column: 70/30 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 10.4 min, τ_{minor} = 17.8 min; HRMS *calcd* for ($C_{26}H_{18}Cl_2O_3$+Na): 471.0531, *found* 471.0535. $[\alpha]_{25}^{D}$= -198.1 (*c* = 1.32, $CHCl_3$, 99% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.01 (td, 1H, J_d = 20.4 Hz, J_t 5.2= Hz), 3.35-3.46 (m, 1H), 3.52 (dd, 1H, J_1 = 11.4 Hz, J_2 = 5.7 Hz), 4.07 (s, 1H), 5.57 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.2 Hz), 6.55-6.74 (m, 2H), 6.82-6.90 (m, 3H), 7.00-7.04 (m, 3H), 7.07(dt, 1H, J_d = 1.4 Hz, J_t = 8.0 Hz), 7.12-7.26 (m, 2H), 7.38-7.46 (m, 2H), 9.55 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 31.2 (CH_2), 41.8 (CH), 45.3 (CH), 53.1 (C), 110.4 (CH), 122.9 (CH), 126.4 (CH), 126.6 (C), 128.5 (CH), 128.7 (CH), 129.2 (CH), 129.5 (CH), 133.4 (C), 134.2 (C), 136.1 (C), 137.1 (C), 139.1 (C), 150.4 (CH), 152.5 (C), 195.5 (CH).

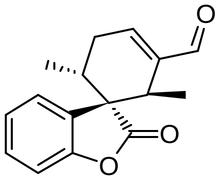
The absolute configuration of 3d was unambiguously determined by single crystal X-ray analysis, see page S4.



(1'R,2'R,6'R)-2',6'-di(furan-2-yl)-2-oxo-2H-spiro[benzofuran-3,1'-cyclohex[3]ene]-3'-carbaldehyde (**3e** – Table 1, entry 6).

The reaction was carried out following the general procedure to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a white solid by column chromatography (hexane/ diethyl ether = 7/3) in 49% yield and 99% ee. HPLC analysis on a Daicel Chiralpak IC column: 80/20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 15.3 min, τ_{minor} = 24.9 min; HRMS *calcd* for ($C_{22}H_{16}O_5$+Na): 383.0895, *found* 383.0913. $[\alpha]_{26}^{D}$= -163.9 c = 0.84, $CHCl_3$, 99% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.96 (td, 1H, J_d = 20.9 Hz, J_t = 5.4 Hz), 3.31-3.42 (m, 1H), 4.06 (dd, 1H, J_1 = 11.2 Hz, J_2 = 5.8 Hz), 4.21 (s, 1H), 5.84 (d, 1H, J = 3.2 Hz), 5.86-5.90 (m, 1H), 6.01 (dd, 1H, J_1 = 3.2 Hz, J_2 = 1.8 Hz), 6.08 (d, 1H, J = 3.2 Hz), 6.35 (dd, 1H, J_1 = 3.2 Hz, J_2 = 1.9 Hz), 6.83 (dt, 1 H, J_t = 7.6 Hz, J_d = 0.9 Hz), 6.89 (d, 1H, J= 7.9 Hz), 7.02-7.04 (m, 1H), 7.13 (dt, 1H, J_t = 7.6 Hz, J_d = 1.0 Hz), 7.20-7.24 (m, 1H), 7.37-7.39 (m, 1H), 9.51(s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): ·· 29.6 (CH_2), 37.0 (CH), 38.9 (CH), 52.0 (C), 107.2 (CH), 110.1(CH), 110.2 (CH), 110.8 (CH), 110.9 (CH), 123.4 (CH), 125.2 (CH), 127.6 (C), 129.2 (CH), 137.2 (C), 141.9 (CH), 142.1 (CH), 150.2 (CH), 151.4 (C), 152.6 (C), 152.7 (C), 191.7 (CH).

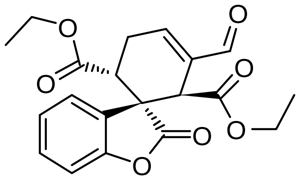


(1'R,2'R,6'R)-2',6'-dimethyl-2-oxo-2H-spiro[benzofuran-3,1'-cyclohex[3]ene]-3'-carbaldehyde (**3f**– Table 1, entry 7).

The reaction was carried out following the general procedure to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a yellowish oil by column chromatography (hexane/diethyl ether = 8/2) in 51% yield and 99% ee. HPLC analysis on a Daicel Chiralpak IC column: 80/20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 13.3 min, τ_{minor} = 17.5 min; HRMS *calcd* for ($C_{16}H_{16}O_3$+Na): 279.0997, *found* 297.0994. $[\alpha]_{26}^{D}$= -21.8 (c = 1.40, $CHCl_3$, 99% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.74 (d, 3H, J = 6.8 Hz), 1.21 (d, 3H, J = 6.9 Hz), 2.43-2.68 (m, 3H), 2.90 (q, 1H, J = 6.9 Hz), 6.92-6.96 (m, 1H), 7.10-7.22 (m, 3H), 7.30-7.35 (m, 1H), 9.48 (s, 1H).

^{13}C NMR (400 MHz, $CDCl_3$): δ 16.9 (CH_3), 17.2 (CH_3), 29.3 (CH), 32.1 (CH_2), 33.5 (CH), 52.7 (C), 111.0 (CH), 123.7 (CH), 125.7 (CH), 128.9 (C), 129.0 (CH), 142.3 (C), 150.4 (CH), 153.4 (C), 176.6 (C), 193.1 (CH).



(1'R,2'R,6'R) - diethyl 3'-formyl-2-oxo-2H-spiro [benzofuran-3,1'-cyclohex[3]ene] -2',6'-dicarboxylate (**3g** – Table 1, entry 8).

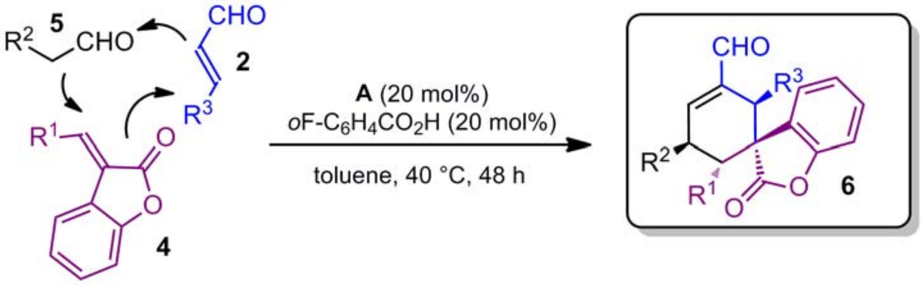
The reaction was carried out following the general procedure to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a colourless oil by column chromatography (hexane/acetone = 8/2) in 38% yield and 99% ee. HPLC analysis on a Daicel Chiralpak IA column: 80/20 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 10.9 min, τ_{minor} = 13.5 min; HRMS *calcd* for ($C_{20}H_{20}O_7$+Na): 395.1107, *found* 395.1111. $[\alpha]_{25}{}^{D}$= -75.5 (*c* = 1.23, $CHCl_3$, 99% ee).

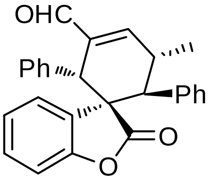
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (t, 3, *J* = 7.2 Hz), 1.10 (t, 3H, *J* = 7.2 Hz), 3.02 (td, 1H, J_d = 20.0 Hz, J_t = 5.7 Hz), 3.12-3.23 (m, 1H), 3.71 (s, 1H), 3.85-4.04 (m, 4H), 4.08-4.17 (m, 1H), 7.02-7.18 (m, 3H), 7.24-7.27 (m, 1H), 7.37 (dt, 1H, J_t = 7.8 Hz, J_d 1.3 = Hz), 9.54 (s, 1H).

^{13}C NMR (400 MHz, $CDCl_3$): δ 13.8 (CH_3), 13.9 (CH_3), 27.2 (CH_2), 42.6 (CH), 45.2 (CH), 46.25 (C), 61.5 (CH_2), 61.7 (CH_2), 111.2 (CH), 123.9 (CH), 124.0 (CH), 127.1 (C), 130.2 (CH), 135.7 (C), 150.7 (CH), 153.6 (C), 170.2 (C), 171.4 (C), 174.78 (C),191.7 (CH).

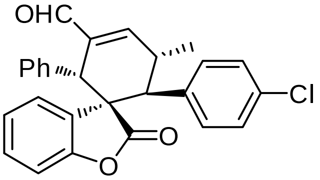
General Procedure for the Organocatalytic Triple Cascade proceeding via enamine – iminium – enamine activation of aldehydes (Table 2)

All the reactions were carried out in an ordinary vial equipped with a Teflon-coated stir bar, with no precautions to exclude moisture in undistilled toluene. Catalyst **A** (0.02 mmol, 20 mol %), aldehyde **5** (0.2 mmol) and *o*-fluoro-benzoic acid (20 mol %) were stirred in toluene (0.2 mL) at room temperature for 10 minutes. The cascade was started by adding a solution of benzofuranone derivative **4** (0.15 mmol) and aldehyde **2** (0.1 mmol), dissolved in 0.3 mL of toluene. The vial was sealed and heated up to 40 degree, and stirring was continued till completion of the reaction, as monitored by TLC (generally 48 hours). The crude reaction was then flushed through a short plug of silica, using CH_2Cl_2/Et_2O 1/1 as the eluent. Solvent was removed *in vacuo* and, after NMR analysis to determine the diastereomeric ratio of the process, the residue was purified by flash column chromatography (silica gel) to yield the desired spiro-compounds **6**.



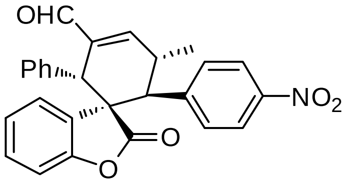


(**6a** - Table 2, entry 1). The reaction was carried out at 40°C following the general procedure to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 20/1) in 56% yield and >99% ee. HPLC analysis on a Daicel Chiralpak IA column: 90/10 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: τ_{major} = 7.56 min, τ_{minor} = 11.2 min. HRMS *calcd* for ($C_{27}H_{22}O_3$+Na): 417.1467, *found* 417.1483. $[\alpha]_{rt}^{D}$= -180.9 (*c* = 0.57, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (d, *J* = 7.2, 3H), 3.15 (d, *J* = 11.2, 1H), 3.53-3.57 (m, 1H), 4.07 (s, 1H), 5.41 (d, *J* = 7.2, 1H), 6.57 (t, *J* = 7.2, 1H), 6.68 (bs, 1H), 6.74 (d, *J* = 8.4, 1H), 6.88-7.02 (m, 6H), 7.17-7.24 (m, 3H), 7.32 (t, *J* = 7.2, 1H), 7.42 (bs, 1H), 9.56 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$): δ 18.7, 34.9, 46.0, 50.0, 54.3, 109.8, 122.5, 126.7, 127.41, 127.46, 128.1, 128.4, 128.6, 137.9, 138.0, 152.4, 156.1, 177.3, 192.4.



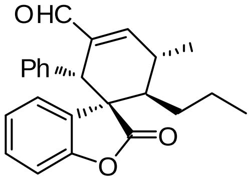
(**6b** - Table 2, entry 3). The reaction was carried out at 40°C following the general procedure to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 20/1) in 57% yield and 99% ee. HPLC analysis on a Daicel Chiralpak IA column: 95/5 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: τ_{major} = 10.23 min, τ_{minor} = 19.75 min. HRMS *calcd* for ($C_{27}H_{21}ClO_3$+Na): 451.1077, *found* 451.1089. $[\alpha]_{rt}^{D}$= -148.5 (*c* = 0.76, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (d, *J* = 7.2, 3H), 3.13 (d, *J* = 10.4, 1H), 3.45-3.53 (m, 1H), 4.06 (s, 1H), 5.38 (d, *J* = 8, 1H), 6.59 (t, *J* = 7.6, 1H), 6.67 (bs, 1H), 6.77-7.02 (m, 6H), 7.16-7.22 (m, 3H), 7.32 (t, *J* = 7.2, 1H), 7.40 (bs, 1H), 9.55 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$): δ 18.7, 34.9, 45.9, 49.4, 54.2, 110.1, 122.7, 126.5, 127.1, 127.5, 128.6, 128.9, 133.2, 136.6, 137.4, 137.9, 152.3, 155.5, 177.0, 192.3.

The absolute configuration of 6b was unambiguously determined by single crystal X-ray analysis, see page S6.

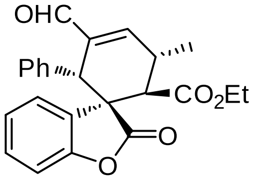


(**6c** - Table 2, entry 4). The reaction was carried out at 40°C following the general procedure to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 7/1) in 52% yield and >99% ee. HPLC analysis on a Daicel Chiralpak IA column: 80/20 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: τ_{major} = 7.37 min, τ_{minor} = 13.6 min. HRMS *calcd* for ($C_{27}H_{21}NO_5$+Na): 462.1317, *found* 462.1331. $[\alpha]_{rt}^{D}$= -199.9 (*c* = 0.61, $CHCl_3$).

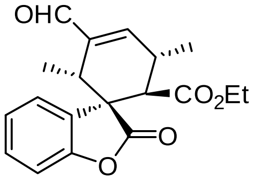
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (d, *J* = 7.2, 3H), 3.30 (d, *J* = 10.4, 1H), 3.54-3.59 (m, 1H), 4.09 (s, 1H), 5.40 (d, *J* = 8.4, 1H), 6.60 (t, *J* = 8, 1H), 6.68 (bs, 1H), 6.77 (d, *J* = 8, 1H), 6.98-7.23 (m, 6H), 7.34 (t, *J* = 7.2, 1H), 7.41(bs, 1H), 7.88 (d, *J* = 9.6, 2H), 9.56 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$): δ 18.7, 34.7, 45.9, 50.0, 54.0, 110.3, 122.9, 123.6, 123.7, 126.4, 126.5, 128.3, 129.3, 137.0, 138.0, 145.9, 147.2, 152.2, 154.6, 176.6, 192.1.



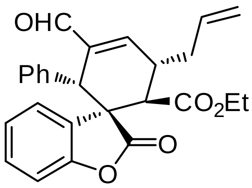
(**6d** - Table 2, entry 5). The reaction was carried out at 40°C following the general procedure to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 20/1) in 56% yield and >99% ee. HPLC analysis on a Daicel Chiralpak IA column: 80/20 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: τ_{major} = 5.06 min, τ_{minor} = 6.3 min. HRMS *calcd* for ($C_{24}H_{24}O_{3}$+Na): 383.1623, *found* 383.1605. $[\alpha]_{rt}^{D}$= -148.2 (*c* = 0.55, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.57 (t, *J* = 8, 3H), 0.88-1.14 (m, 4H), 1.46 (d, *J* = 7.6, 3H), 2.01-2,06 (m, 1H), 2.96-3.05 (m, 1H), 3.89 (s, 1H), 5.46 (d, *J* = 7.6, 1H), 6.73 (t, *J* = 8, 1H), 7.05-7.28 (m, 8H), 9.47 (s, 1H).^{13}C NMR (100 MHz, CDCl$_3$): δ 14.5, 19.2, 21.2, 33.0, 34.7, 41.3, 45.8, 53.4, 110.2, 122.8, 126.4, 127.8, 128.0, 128.1, 128.9, 137.5, 153.0, 156.7, 177.1, 192.4.



(**6e** - Table 2, entry 6). The reaction was carried out at 40°C following the general procedure to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 10/1) in 54% yield and >99% ee. HPLC analysis on a Daicel Chiralpak IA column: 95/5 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: τ_{major} = 21.48 min, τ_{minor} = 22.9 min. HRMS *calcd* for ($C_{24}H_{22}O_{5}$+Na): 413.1365, *found* 413.1366. $[\alpha]_{rt}^{D}$= -97.6 (*c* = 0.55, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.81 (t, *J* = 7.2, 3H), 1.44 (d, *J* = 8, 3H), 3.01 (d, *J* = 11.2, 1H), 3.43-3.48 (m, 1H), 3.75-3.83 (m, 2H), 3.99 (s, 1H), 5.50 (d, *J* = 8, 1H), 6.71 (t, *J* = 8, 1H), 7.05-7.09 (m, 3H), 7.19-7.31 (m, 5H), 9.50 (s, 1H).^{13}C NMR (100 MHz, CDCl$_3$): δ 13.6, 18.5, 32.2, 45.1, 50.4, 50.6, 61.3, 110.3, 122.9, 126.2, 126.6, 128.22, 128.29, 129.5, 136.7,137.8, 154.4, 171.2, 192.0.



(**6f** - Table 2, entry 7). The reaction was carried out at 40°C following the general procedure to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a colorless oil by column chromatography (hexane/AcOEt = 10/1) in 70% yield and 95% ee. HPLC analysis on a Daicel Chiralpak IC column: 80/20 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: τ_{minor} = 6.55 min, τ_{major} = 7.12 min. HRMS *calcd* for ($C_{19}H_{20}O_{5}$+Na): 351.1208, *found* 351.1215.$[\alpha]_{rt}^{D}$= +69.3 (*c* = 0.61, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.86 (t, *J* = 7.6, 3H), 1.21 (d, *J* = 7.2, 3H), 1.30 (d, *J* = 7.2, 3H), 2.88 (q, *J* = 7.2, 1H), 2.99 (d, *J* = 10.8, 1H), 3.32-3.37 (m, 1H), 3.79-3.89 (m, 2H), 6.78 (d, *J* = 3.2, 1H), 7.08-7.34 (m, 4H), 9.50 (s, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 13.6, 17.3, 18.5, 32.4, 33.7, 49.9, 50.0, 61.4, 111.0, 123.5, 125.8, 127.5, 129.6, 140.9, 154.1, 171.3, 192.9.

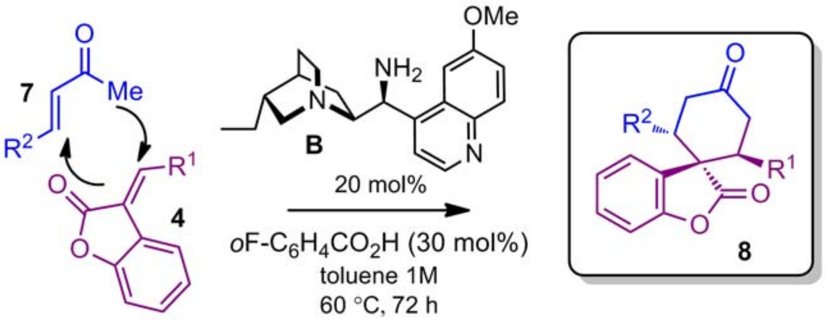


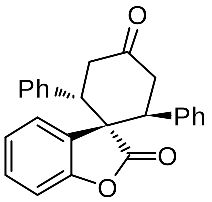
(**6g** - Table 2, entry 8). The reaction was carried out at 40°C following the general procedure to furnish the crude product (d.r. >19:1 determined by ^{1}H NMR analysis of the crude mixture). The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 10/1) in 57% yield and >99% ee. HPLC analysis on a Daicel Chiralpak IA column: 90/10 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm : τ_{minor} = 12.7 min, τ_{major} = 13.22 min. HRMS *calcd* for ($C_{26}H_{24}O_5$+Na): 439.1521, *found* 439.1507. $[\alpha]_{rt}^{D}$= -99.5 (*c* = 0.77, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 0.8 (t, *J* = 7.2, 3H), 2.33-2.41 (m, 1H), 2.65-2.71 (m, 1H), 3.16 (d, *J* = 12, 1H), 3.50-3.56 (m, 1H), 3.78 (q, *J* = 7.2, 2H), 3.97 (s, 1H), 5.30-5.35 (m, 2H), 5.51 (d, *J* = 8.4, 1H), 5.93-6.03 (m, 1H), 6.7(t, *J* = 8, 1H), 7.06 (d, *J* = 7.2, 2H), 7.18-7.31 (m, 6H), 9.50 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$): *δ* 13.5, 36.5, 36.6, 45.1, 48.0, 50.5, 61.3, 110.3, 119.7, 122.9, 126.4, 126.5, 128.20, 128.23, 129.5, 133.6, 136.9, 138.8, 152.2, 153.0, 171.2, 191.9.

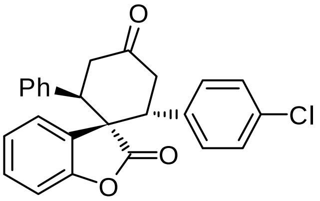
General Procedure for the Organocatalytic Tandem double Michael additions (enamine – iminium activation sequence) (Table 3)

All the reactions were carried out in an ordinary vial equipped with a Teflon-coated stir bar, with no precautions to exclude moisture in undistilled toluene. Catalyst **A** (0.02 mmol, 20 mol %), aldehyde **5** (0.2 mmol) and *o*-fluoro-benzoic acid (20 mol %) were stirred in toluene (0.2 mL) at room temperature for 10 minutes. Catalyst **B** (0.02 mmol, 20 mol %), enone **7** (0.2 mmol) and *o*-fluoro-benzoic acid (30 mol %) were stirred in toluene (0.1 mL) at room temperature for 10 minutes. The cascade was started by adding a solution of benzofuranone derivative **4** (0.15 mmol) dissolved in 1 mL of toluene. The vial was sealed and heated up to 60 degrees, and stirring was continued till completion of the reaction, as monitored by TLC (generally 72 hours). The crude reaction was then flushed through a short plug of silica, using CH_2Cl_2/Et_2O 1/1 as the eluent. Solvent was removed *in vacuo* and, after NMR analysis to determine the diastereomeric ratio of the process, the residue was purified by flash column chromatography (silica gel) to yield the desired spiro-compounds **8**.





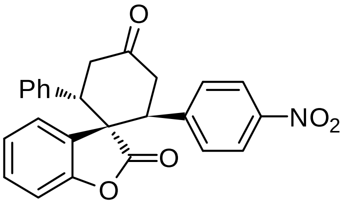
(**8a** - Table 3, entry 1).The reaction was carried out at 60°C following the general procedure to furnish the crude product as a 6.3/1 mixture of diastereoisomers (dr. 6.3:1 determined by integration of ^{1}H NMR signal: δ_{minor} 6.45 d, δ_{major} 6.06 ppm, d). The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 90/10) in 70% yield (as a single of diastereoisomer) and >99% ee. HPLC analysis on a Daicel Chiralpak IC column: 80/20 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: τ_{minor} = 12.8 min, τ_{major} = 15.13 min. HRMS *calcd* for ($C_{25}H_{20}NO_3$+Na): 391.1310, *found* 391.1329. $[\alpha]_{rt}^{D}$= -195.8 (*c* = 0.76, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$): δ 2.76 (d, *J* =13.2, 1H), 2.95 (dd, *J* = 5.2, 16, 1H), 3.61 (dd, *J* = 6, 15.6, 1H), 3.68-3.71 (m, 1H), 3.76-3.87 (m, 1H), 6.04 (d, *J* = 7.2, 1H), 6.73-6.86 (m, 4H), 6.93-6.96 (m, 2H), 7.03-7.07 (m, 4H), 7.24-7.29 (m, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 41.8, 42.6, 45.9, 47.5, 110.2, 123.1,126.0, 127.7, 127.9, 128.0, 128.41, 128.49, 129.0, 129.5, 137.3, 139.0, 152.5, 177.9, 209.7.



(**8b** - Table 3, entry 3). The reaction was carried out at 60°C following the general procedure to furnish the crude product as a 3.5/1 mixture of diastereoisomers (d.r. 3.5:1 determined by integration of ^{1}H NMR signal: δ_{major} 6.25 d, δ_{minor} 6.05 ppm. d). The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 90/10) in 75% yield (as a 3:1 mixture of diastereoisomers) and 97% ee. HPLC analysis on a Daicel Chiralpak IC column: 80/20 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: Major diastereomer (97% ee): τ_{minor} = 13.91 min, τ_{major} = 14.86 min; Minor diastereomer (>99% ee): τ_{minor} = 13.20 min, τ_{major} = 16.29 min. HRMS *calcd* for ($C_{25}H_{19}ClO_3$+Na): 425.0920, *found* 425.0937. $[\alpha]_{rt}^{D}$= -155.7 (*c* = 0.78, $CHCl_3$, dr 3.5:1, 97% ee_{major}, >99% ee_{minor}).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.73-2.79 (m, 1H), 2.91-2.97 (m, 1H), 2.53-2.67 (m, 3H), 3.54 (dd, *J* = 6.12, 16.2, 1H), 3.67-3.85 (m, 4H), 6.03 (d, *J* = 7.6, 1H minor), 6.23 (d, *J* = 8, 1H major), 6.74-6.93 (m, 8H), 7.0-7.10 (m, 5H), 7.21-7.27 (m, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 41.6, 41.7, 42.4, 42.5, 45.3, 46.0, 46.7, 47.4, 55.2, 55.3, 110.45, 110.46, 123.3, 123.4, 125.7, 125.8, 127.62, 127.69, 127.8, 128.0, 128.1, 128.4, 128.5, 128.62, 128.65, 129.27, 129.29, 129.3, 129.4, 130.7, 133.9, 135.8, 136.9, 137.4, 152.5, 177.6, 177.7, 209.1, 209.3.

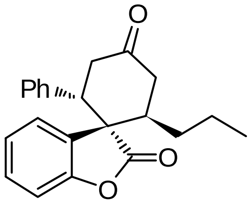
The absolute configuration of 8b was unambiguously determined by single crystal X-ray analysis, see page S7.



(**8c** - Table 3, entry 4).The reaction was carried out at 60°C following the general procedure to furnish the crude product as a 2/1 mixture of diastereoisomers (d.r. 2:1 determined by integration of ^{1}H-NMR signal: δ_{major} 6.46 d, δ_{minor} 6.08 ppm. d). The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 7/1) in 82% yield (as a 2:1 mixture of diastereoisomers) and 98% ee. HPLC analysis on a Daicel Chiralpak IA column: 80/20 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: Major diastereomer (98% ee): τ_{major} = 13.29 min, τ_{minor} = 16.33

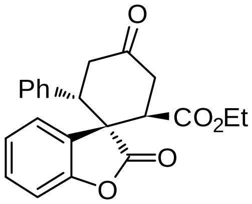
min; Minor diastereomer can't be separated. HRMS *calcd* for ($C_{25}H_{19}NO_5$+Na): 436.1161, *found* 436.1173. $[\alpha]_{rt}^{D}$= -240.2 (*c* = 0.8, $CHCl_3$, dr 2:1, 98% ee_{major}).

^1H NMR (400 MHz, $CDCl_3$): δ 2.75-2.82 (m, 1H), 2.97 (dd, *J* = 4.76, 16.2, 1H, minor), 3.07 (dd, *J* = 7.76, 16.56, 1H, major), 3.62 (dd, *J* = 6.4, 16, 1H, major), 3.45 (dd, *J* = 5.6, 16.32, 1H, minor), 3.69-3.73 (m, 2H), 3.78-3.96 (m, 4H), 6.05 (d, *J* = 8, 1H, minor), 6.42 (d, *J* = 8, 1H, major), 6.73-6.93 (m, 7H), 7.02-7.05(m, 8H), 7.24-7.30 (m, 3H), 7.90 (d, *J* = 8.4, 2H, minor), 8.09 (d, *J* = 8.8, 2H, major).^{13}C NMR (100 MHz, $CDCl_3$): δ 41.1, 41.6, 42.0, 42.1, 45.6, 46.3, 46.7, 47.5, 54.9, 55.6, 110.6, 110.8, 123.5, 123.62, 123.64, 123.8, 125.0, 125.8, 127.0, 127.3, 128.0, 128.1, 128.3, 128.5, 128.6, 129.1, 129.5, 129.6, 129.7, 130.1, 138.4, 144.7, 145.9, 152.4, 152.5, 177.4, 208.3, 208.6.



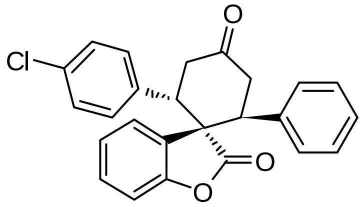
(**8d** - Table 3, entry 5).The reaction was carried out at 60°C following the general procedure to furnish the crude product as a single diastereoisomer. The title compound was isolated as a white solid by preparative TLC (toluene/AcOEt = 100/1) in 40% yield (as a single diastereoisomer) and 91% ee. HPLC analysis on a Daicel Chiralpak IA column: 80/20 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: τ_{minor} = 5.67 min, τ_{major} = 6.23 min; HRMS *calcd* for ($C_{22}H_{22}O_3$+Na): 357.1467, *found* 357.1456. $[\alpha]_{rt}^{D}$= -118.2 (*c* = 0.55, $CHCl_3$, dr 1.5:1, 98% ee_{major}, 88% ee_{minor}).

^1H NMR (400 MHz, $CDCl_3$): δ 0.78 (t, *J* = 7.2, 3H), 1.03-1.12 (m, 1H), 1.25-1.43 (m, 3H), 2.53-2.67 (m, 3H), 3.07 (dd, *J* = 4, 15.6, 1H), 3.55-3.65 (m, 2H), 6.78-6.81 (m, 2H), 6.89 (d, *J* = 8, 1H), 7.07-7.28 (m, 5H), 7.39 (d, *J* = 8, 1H).^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 20.4, 33.3, 40.5, 42.0, 47.2, 55.8, 110.9, 124.0, 124.9, 127.8, 128.0, 128.3, 128.4, 129.0, 129.3, 137.0, 153.0, 178.1, 209.9.



(**8e** - Table 3, entry 6).The reaction was carried out at 60°C following the general procedure to furnish the crude product as a 2.2/1 mixture of diastereoisomers (d.r. 2.2:1 determined by HPLC). The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 10/1) in 77% yield (as a 2.2:1 mixture of diastereoisomers) and 85% ee. HPLC analysis on a Daicel Chiralpak IA column: 90/10 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: Major diastereomer (85% ee): τ_{major} = 16.35 min, τ_{minor} = 17.45 min; Minor diastereomer (>99% ee): τ_{major} = 14.7 min, HRMS *calcd* for ($C_{22}H_{20}O_5$+Na): 387.1208, *found* 428.1225. $[\alpha]_{rt}^{D}$= -57.2 (*c* = 0.58, $CHCl_3$,).

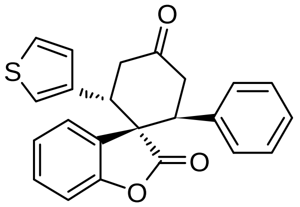
^1H NMR (400 MHz, $CDCl_3$): δ 1.0 (t, *J* = 7.2, 3H), 2.63-2.68 (m, 1H), 2.80-2.86 (m, 1H), 3.32 (dd, *J* = 5.6, 16, 1H), 3.42-3.63 (m, 2H), 6.75-6,91 (m, 3H), 7.06-7.29 (m, 6H).^{13}C NMR (100 MHz, $CDCl_3$): δ 13.73, 13.76, 38.3, 39.6, 41.9, 42.2, 46.4, 46.6, 50.60, 50.61, 52.3, 52.5, 61.6, 61.8, 110.6, 110.7, 122.2, 123.9, 124.1, 124.4, 127.9, 128.0, 128.2, 128.40, 128.44, 129.4, 129.8, 136.2, 136.3, 153.0, 153.2, 170.0, 170.8, 175.7, 176.7, 206.2, 207.2.



(**8f** - Table 3, entry 7).The reaction was carried out at 60°C following the general procedure to furnish the crude product as a 4/1 mixture of diastereoisomers (d.r. 3.5:1 determined by integration of ^{1}H NMR signal: δ_{major} 6.05 d, δ_{minor} 6.24 ppm. d). The title compound was isolated as a white solid by column chromatography (hexane/AcOEt = 85/15) in 85% yield (as a 3.4:1 mixture of diastereoisomers) and 97% ee. HPLC analysis on a Daicel Chiralpak IC column: 8/2 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: Major diastereomer (97% ee): τ_{minor} = 12.9 min, τ_{major} = 15.9 min; Minor diastereomer (96% ee): τ_{minor} = 13.5 min, τ_{major} = 14.5 min. HRMS *calcd* for ($C_{25}H_{19}Cl\ O_3$+Na): 425.0920, *found* 425.0938. $[\alpha]_{rt}^{D}$= -130.6 (*c* = 1.07, $CHCl_3$, dr 4:1, 97% ee$_{major}$, 96% ee$_{minor}$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.71-2.84 (m, 1H), 2.91-3.01 (m, 1H), 3.53.3.88 (m, 4H), 6.05 (d, 1H, *J* = 7.5 Hz major), 6.24 (d, 1H, *J* = 7.5 Hz minor), 6.75.-6.98 (m, 6H), 7.01-7.13 (m, 3H), 7.22-7.34 (m, 3H) ppm.

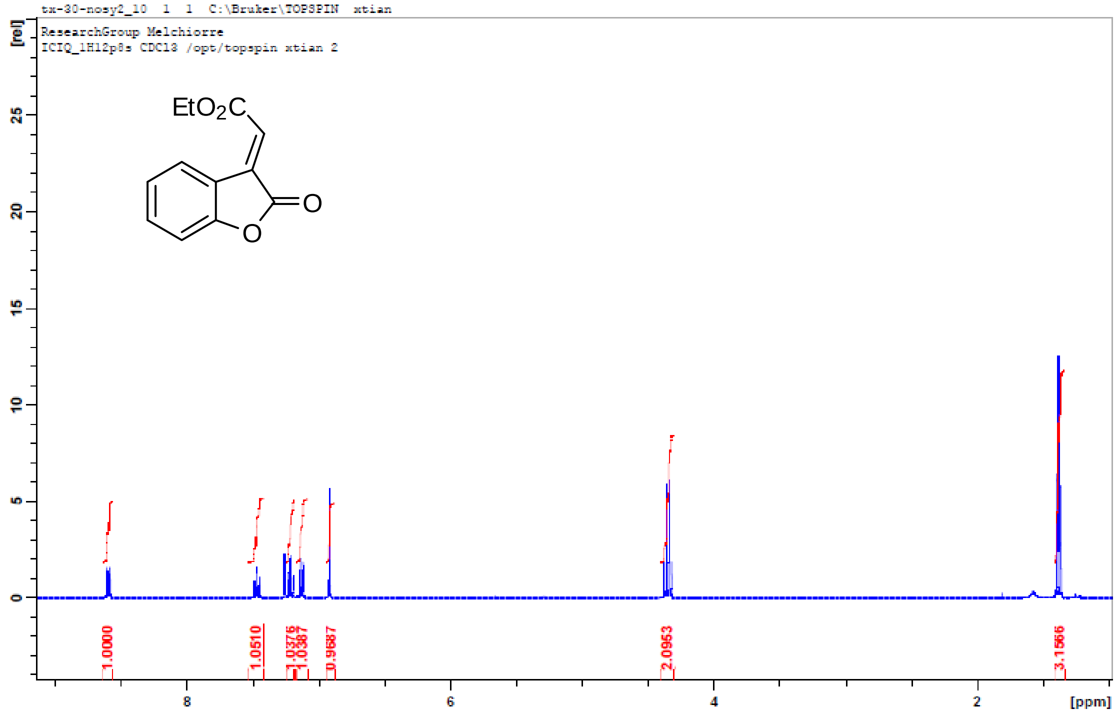
^{13}C NMR (100 MHz, $CDCl_3$): δ 41.7 (CH_2), 42.5 (CH_2), 45.3 (CH), 47.5 (CH), 55.3 (C), 110.5 (CH), 123.3 (CH), 125.8 (CH), 127.6 (C), 128.0 (CH), 128.1 (CH), 128.5 (CH), 128.6 (C), 128.6 (C), 128.7 (C), 129.3 (CH), 129.4 (CH), 129.5 (CH), 130.8 (C), 133.7 (C), 135.9 (C), 138.8 (C), 152.5 (C), 177.7 (C), 209.2 (C) ppm.



(**8g** - Table 3, entry 8).The reaction was carried out at 60°C following the general procedure to furnish the crude product as a 4/1 mixture of diastereoisomers (d.r. 4:1 determined by integration of ^{1}H-NMR signal: δ_{major} 6.02 d, δ_{minor} 6.07 ppm. d). The title compound was isolated as a white solid by column chromatography (hexane/Acetone = 95/5) in 91% yield (as a 4:1 mixture of diastereoisomers) and 96% ee. HPLC analysis on a Daicel Chiralpak IA column: 95/5 hexane/*i*-PrOH, flow rate 1.0 mL/min, λ = 254 nm: Major diastereomer (96% ee): τ_{minor} = 18.7 min, τ_{major} = 24.4 min; Minor diastereomer (93% ee): τ_{minor} = 17.3 min, τ_{major} = 19.6 min. $[\alpha]_{rt}^{D}$= -99.1 (*c* = 0.78, $CHCl_3$, dr 4:1, 96% ee$_{major}$, 93% ee$_{minor}$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.72-2.95 (m, 2H), 3.54.3.84 (m, 4H), 3.94 (dd, 1H, J_1 = 13.7, J_2= 4.2 Hz), 6.02 (d, 1H, *J* = 7.5 Hz major), 6.07 (d, 1H, *J* = 7.5 Hz minor), 6.47 (dd, 1H, J_1= 5.2, J_2= 1.4 Hz), 6.70-6.73 (m, 1H), 6.75-6.88 (m, 2H), 6.91-6.94 (m, 2H), 6.99 (dd, 1H, J_1= 4.9, J_2= 2.9 Hz), 7.02-7.16 (m, 2H), 7.26-7.30 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 41.5 (CH), 41.8 (CH_2), 42.9 (CH_2), 47.3 (CH), 55.1 (C), 110.4 (CH), 122.9 (CH), 123.3 (CH), 125.7 (C), 125.8 (CH), 125.9 (CH), 126.8 (CH), 128.0 (C), 128.1 (CH), 128.5 (CH), 128.6 (CH), 129.1 (CH), 129.5 (CH), 138.2 (C), 139.1 (C), 139.7 (C), 152.8 (C), 177.9 (C), 209.3 (C) ppm.



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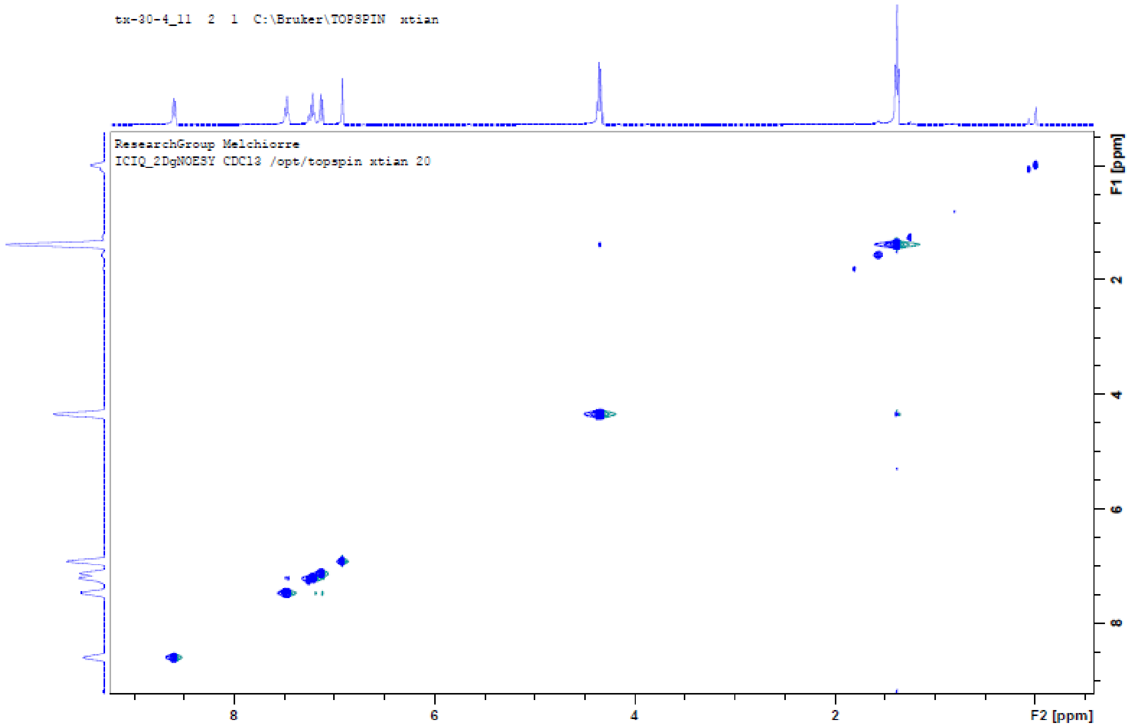

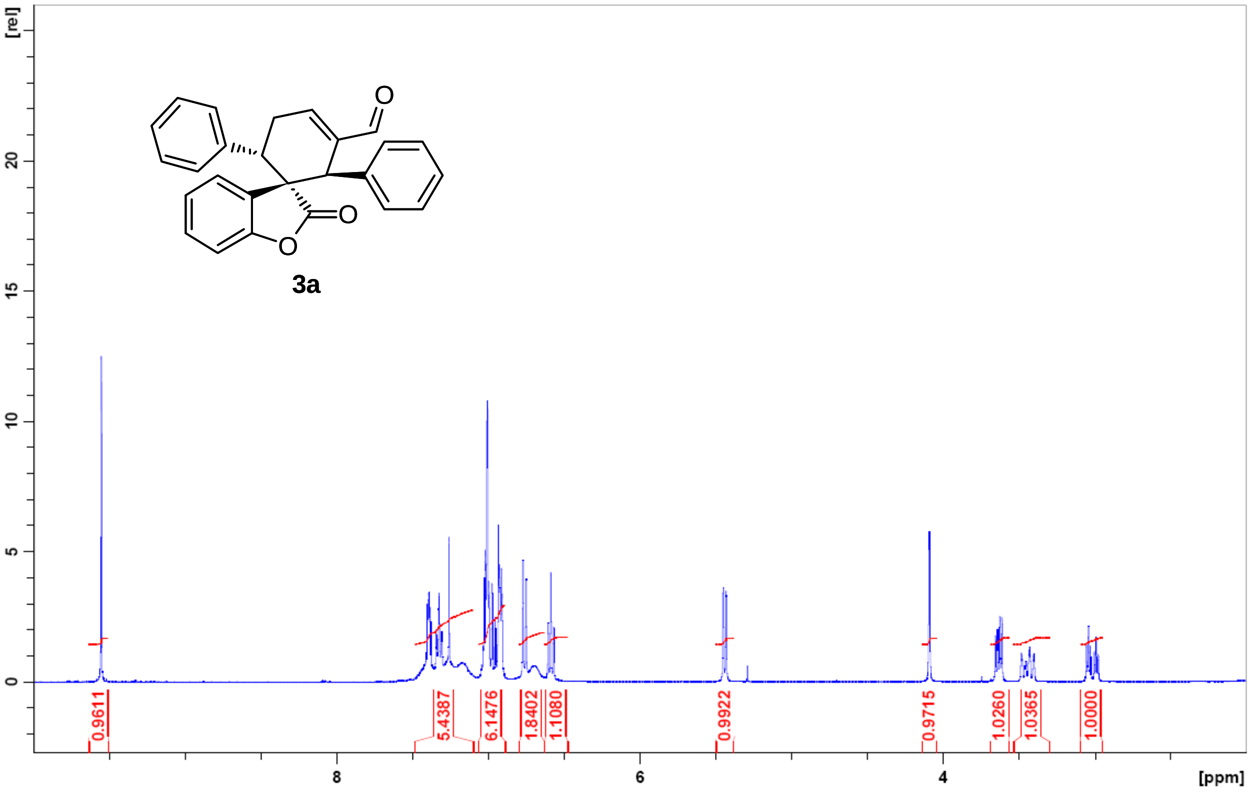
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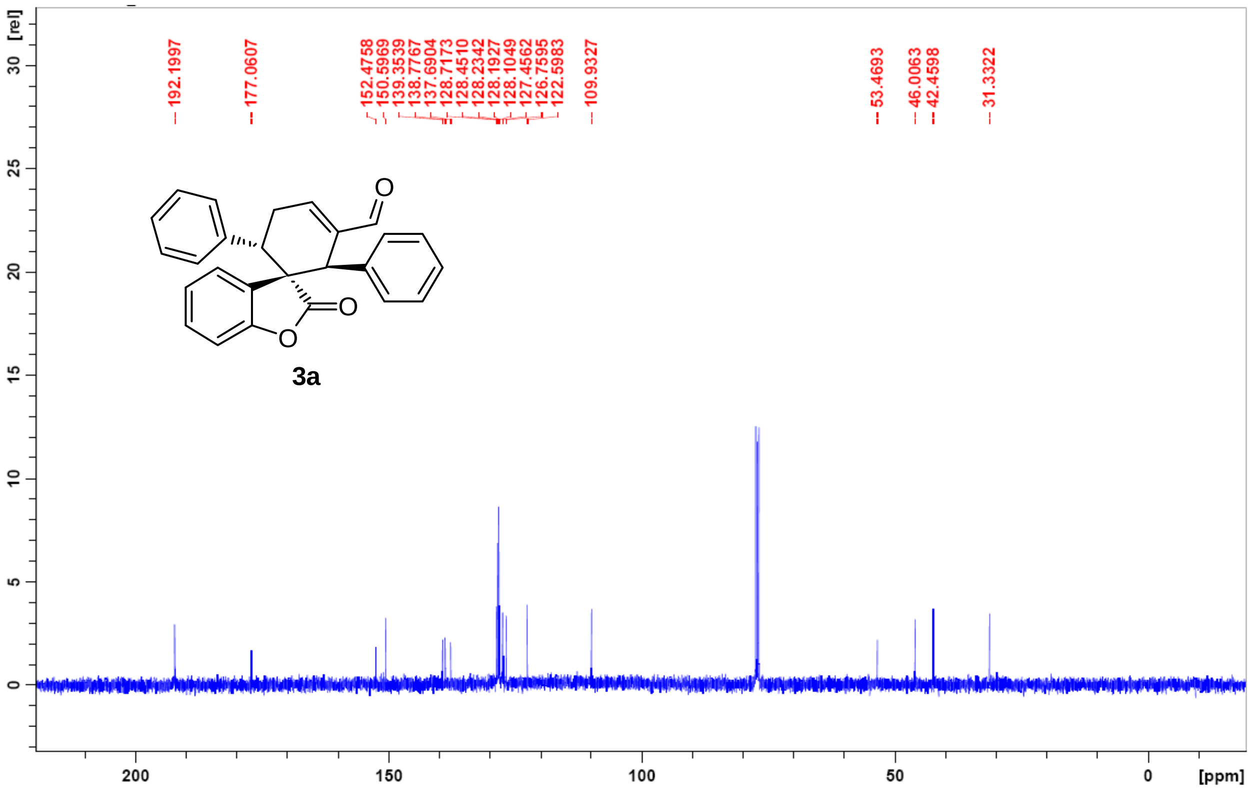
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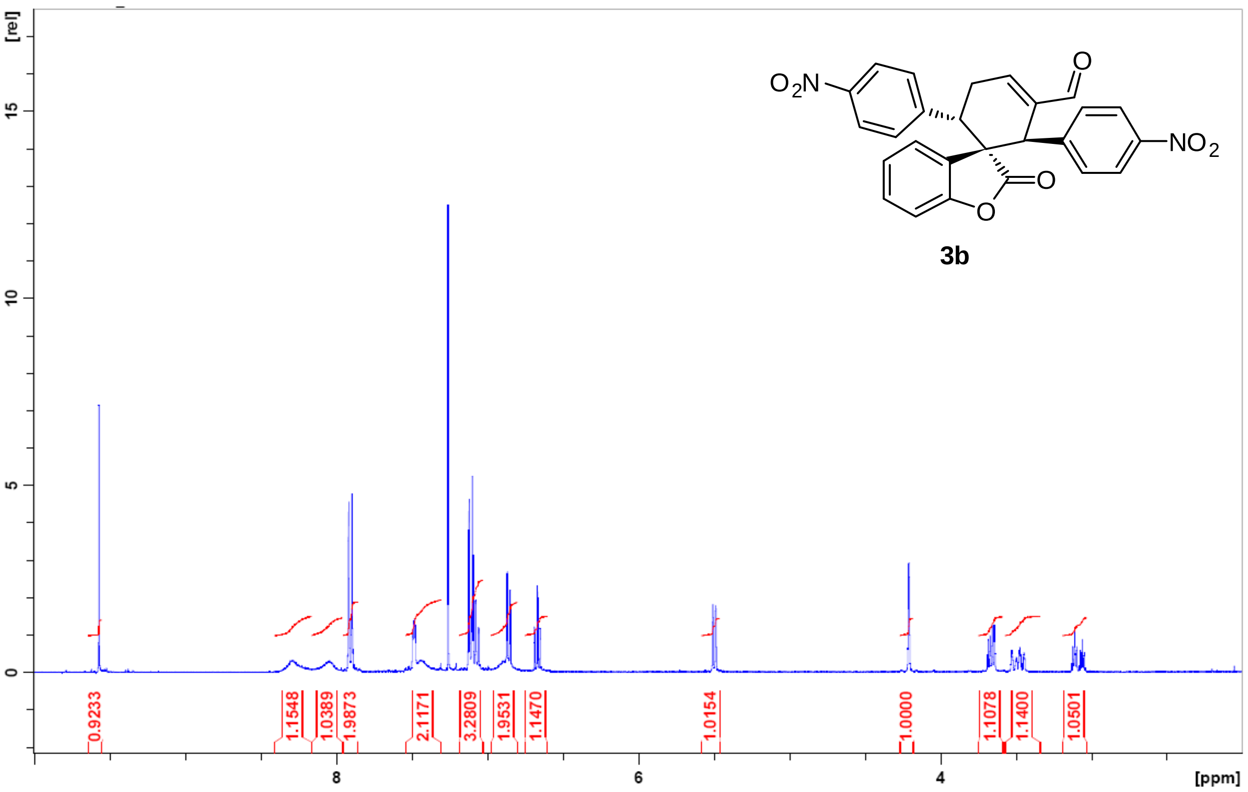
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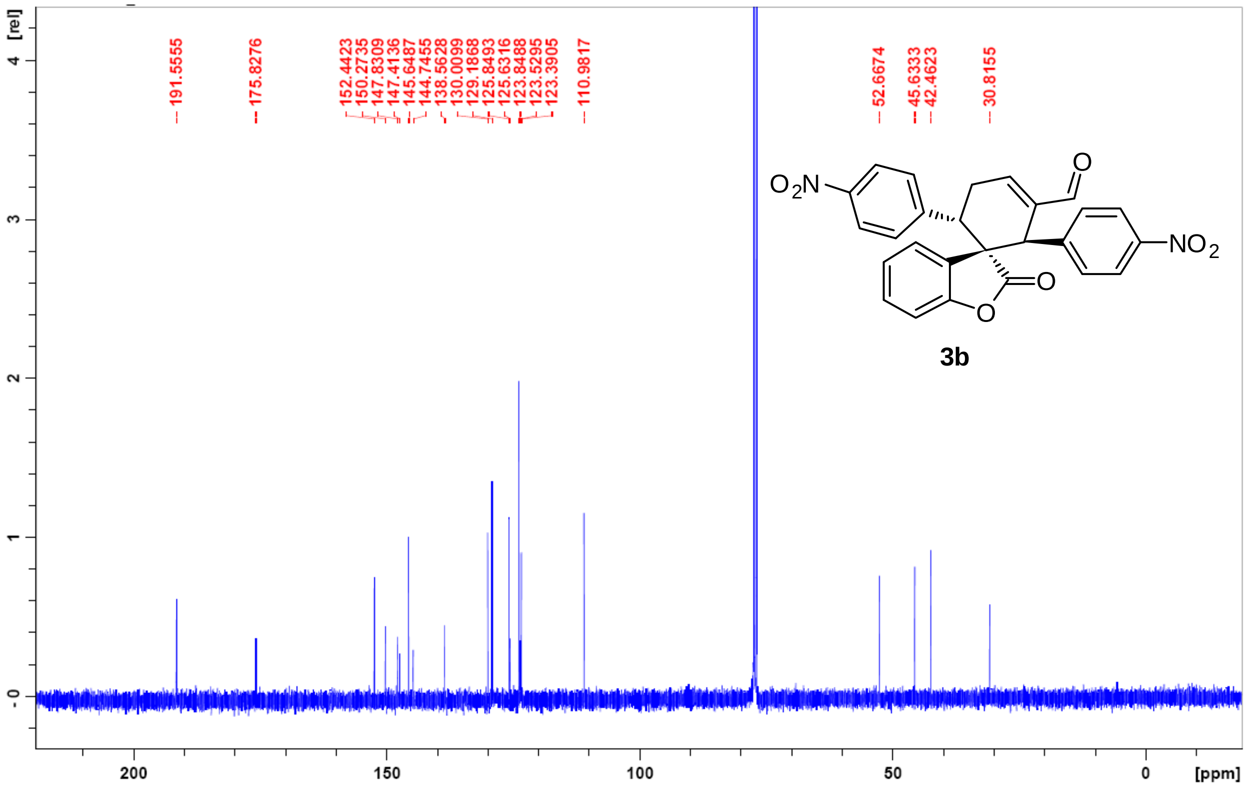
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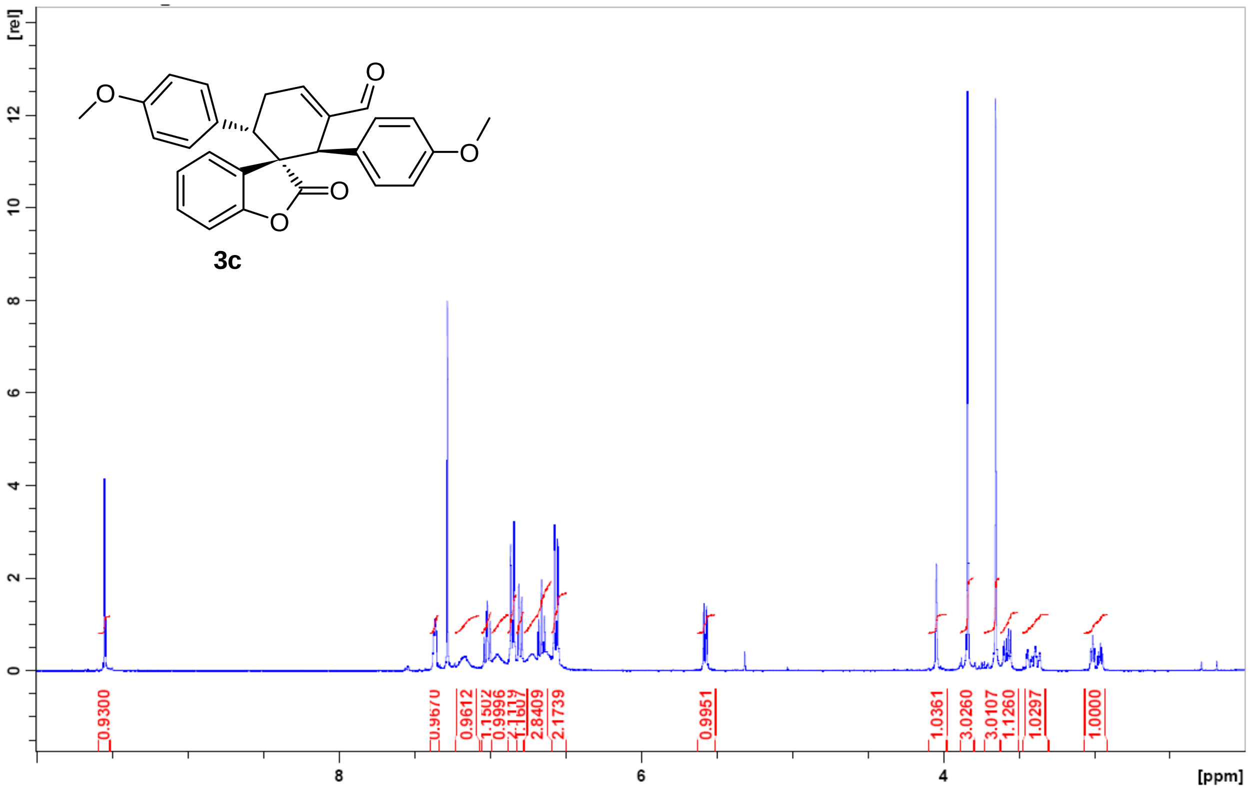
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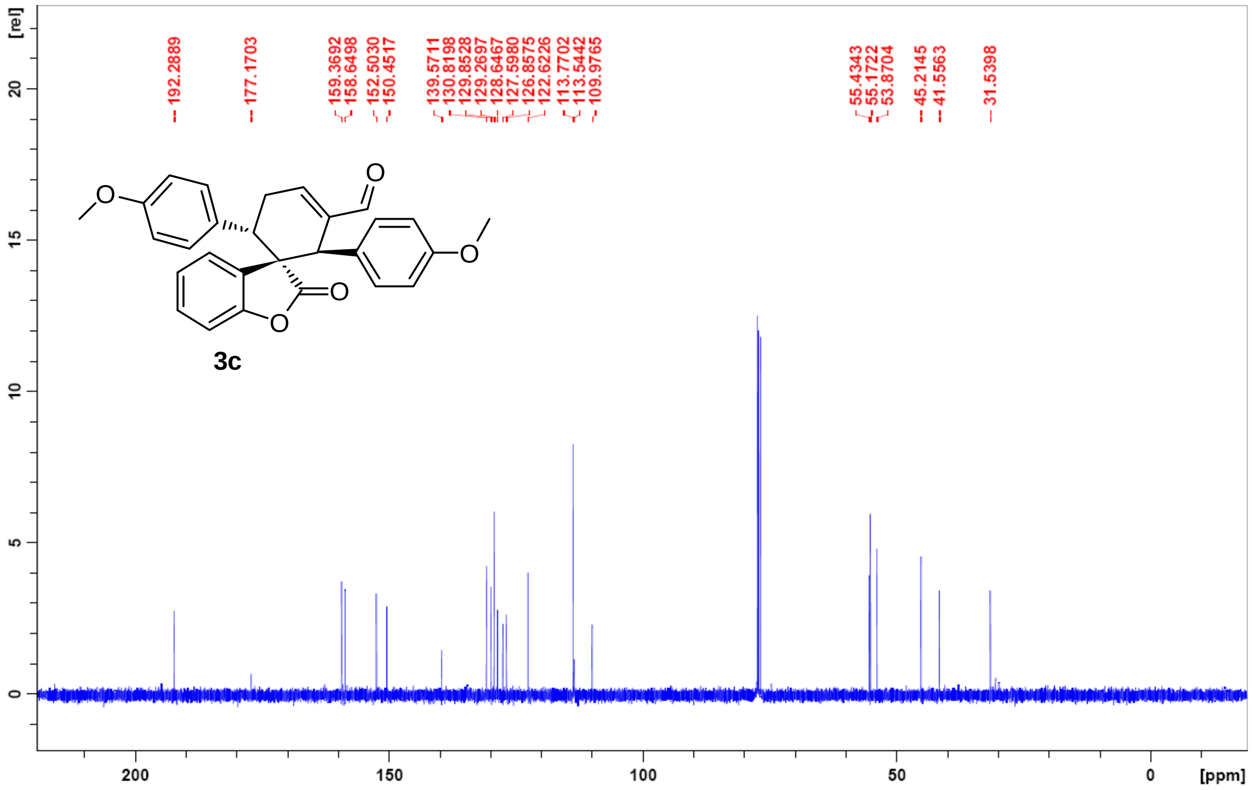
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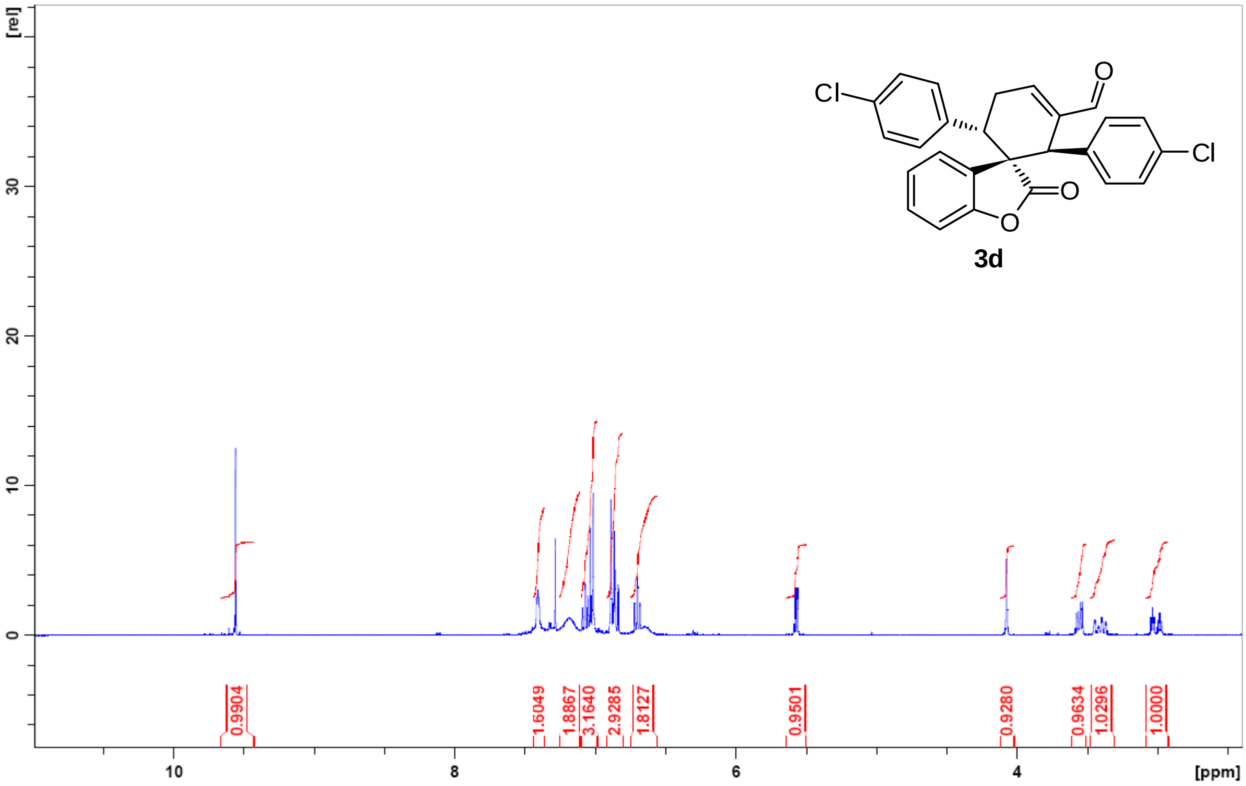
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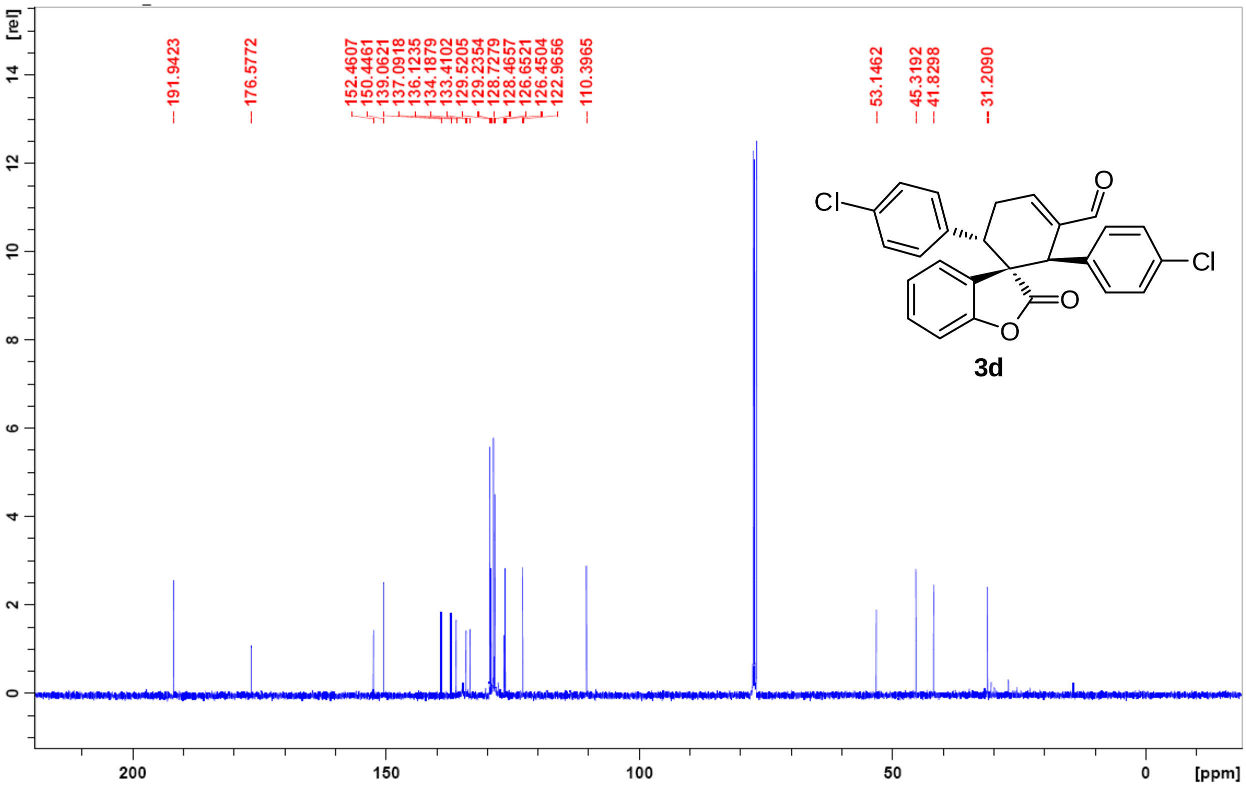
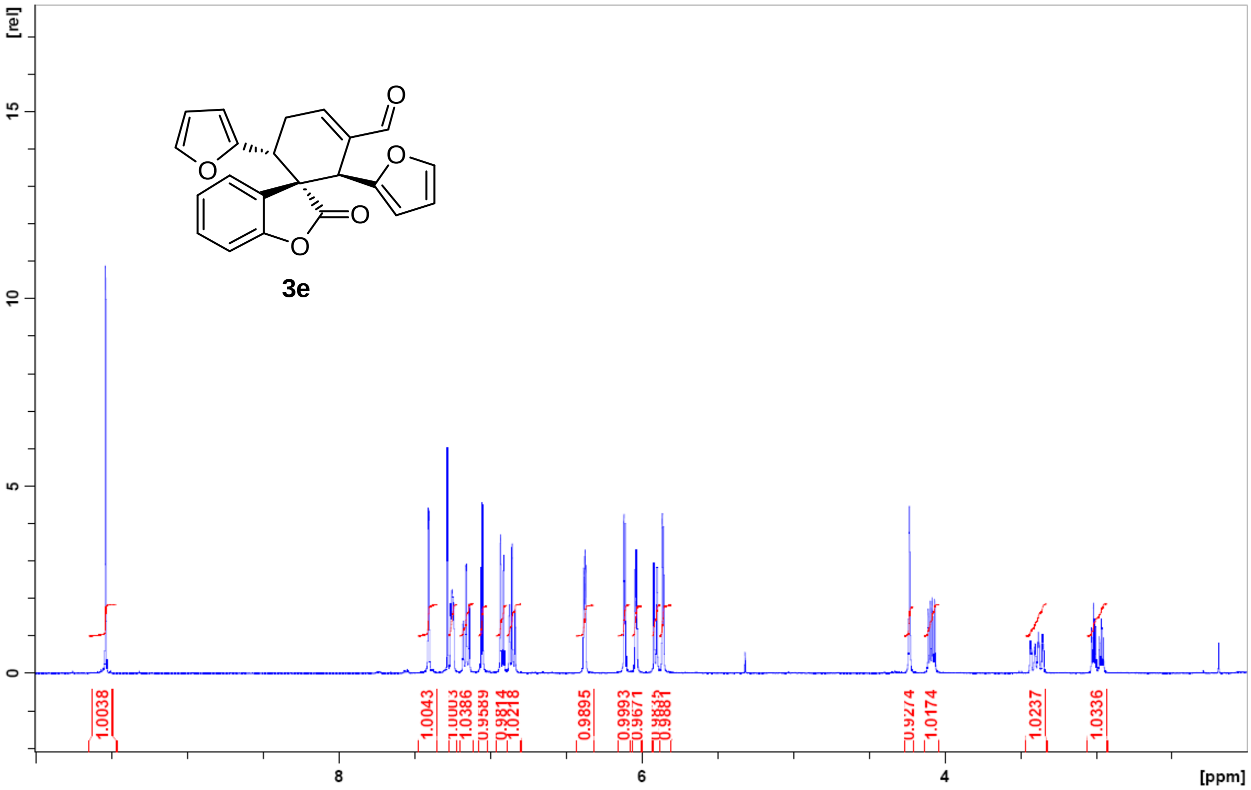
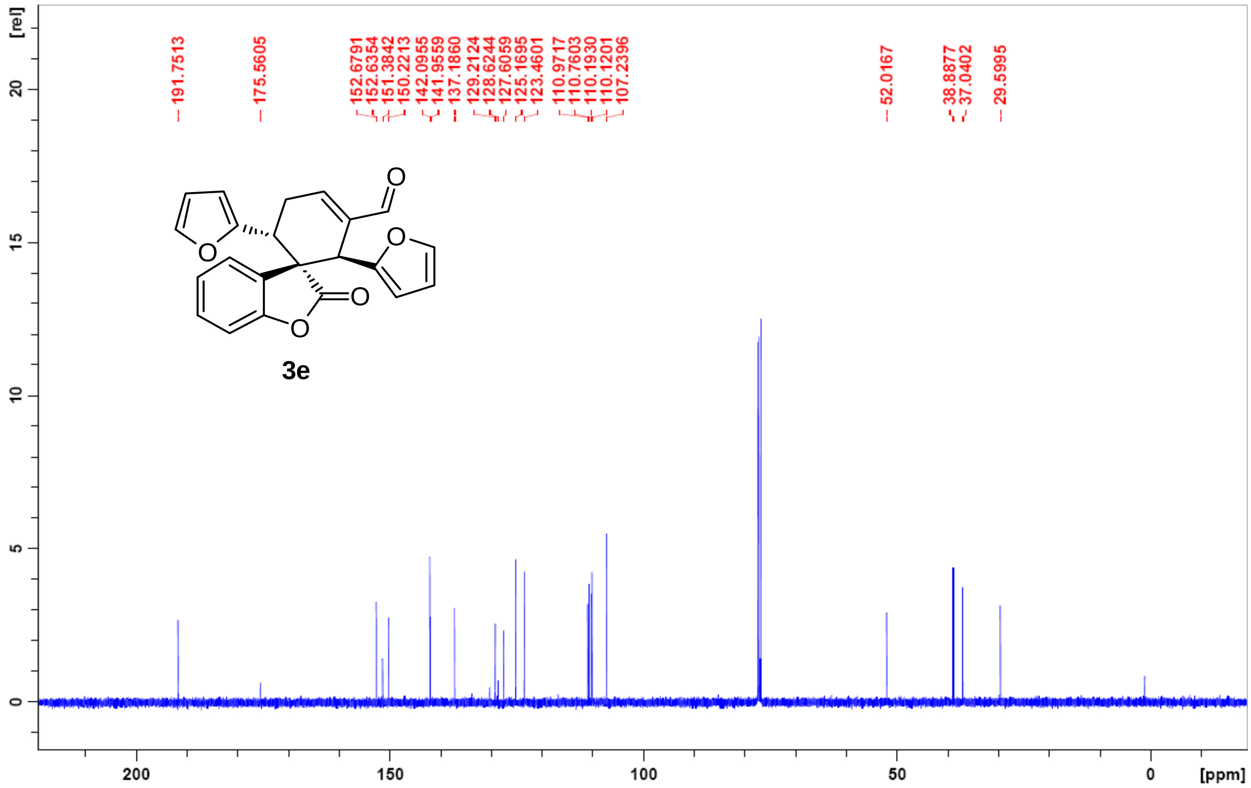

[rel]
14
12
10
8
6
4
2
0
191.9423
176.5772
152.4607
150.4461
139.0621
137.0918
136.1235
134.1879
133.4102
129.5205
129.2354
128.7279
128.4657
126.6521
126.4504
122.9656
110.3965
53.1462
45.3192
41.8298
31.2090
Cl
Cl
O
O
O
3d
200
150
100
50
0
[ppm]


[rel]
15
10
5
0
3e
1.0038
1.0043
1.0003
1.0386
0.9589
0.9814
1.0218
0.9895
0.9993
0.9671
0.9881
0.9274
1.0174
1.0237
1.0336
8
6
4
[ppm]


[rel]
20
15
10
5
0
191.7513
175.5605
152.6791
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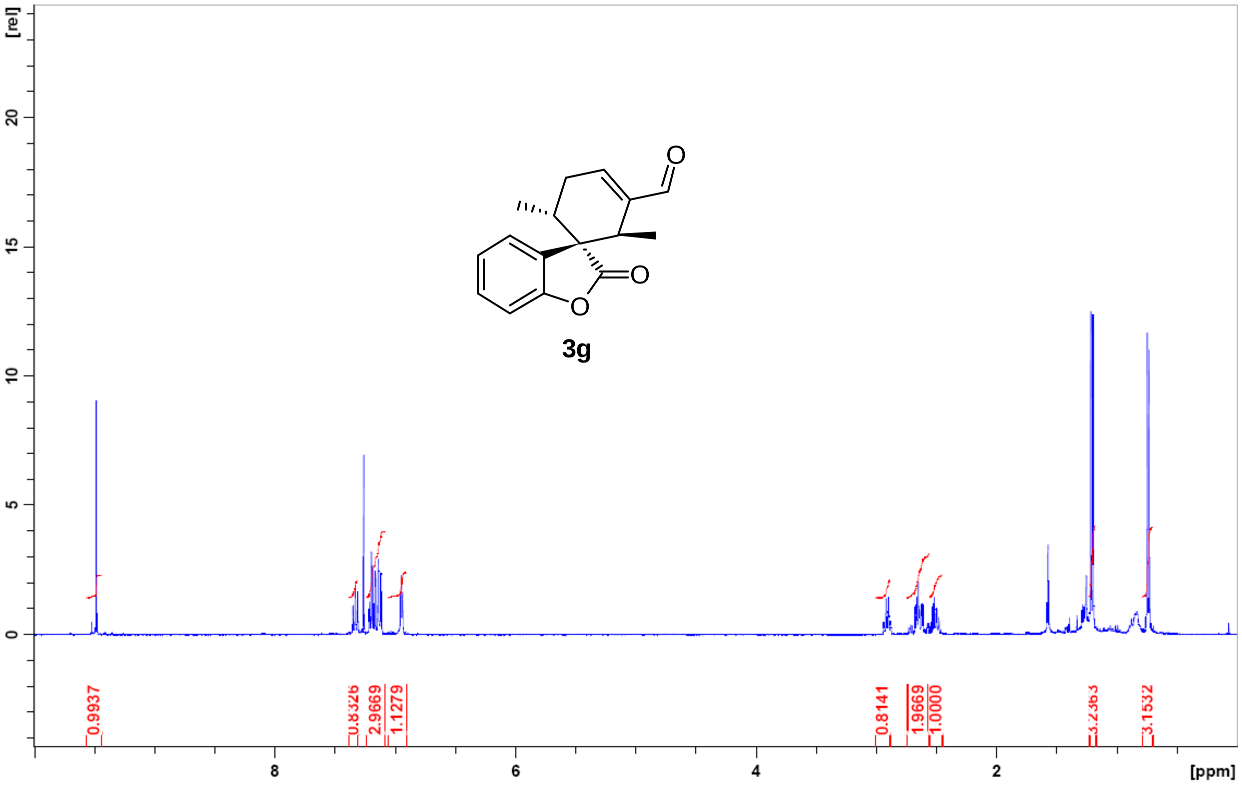
151.3842
150.2213
142.0955
141.9559
137.1860
129.2124
128.6244
127.6059
125.1695
123.4601
110.9717
110.7603
110.1930
110.1201
107.2396
52.0167
38.8877
37.0402
29.5995
3e
200
150
100
50
0
[ppm]


[rel]
20
15
10
5
0
O
O
O
3g
0.9937
0.8326
2.9669
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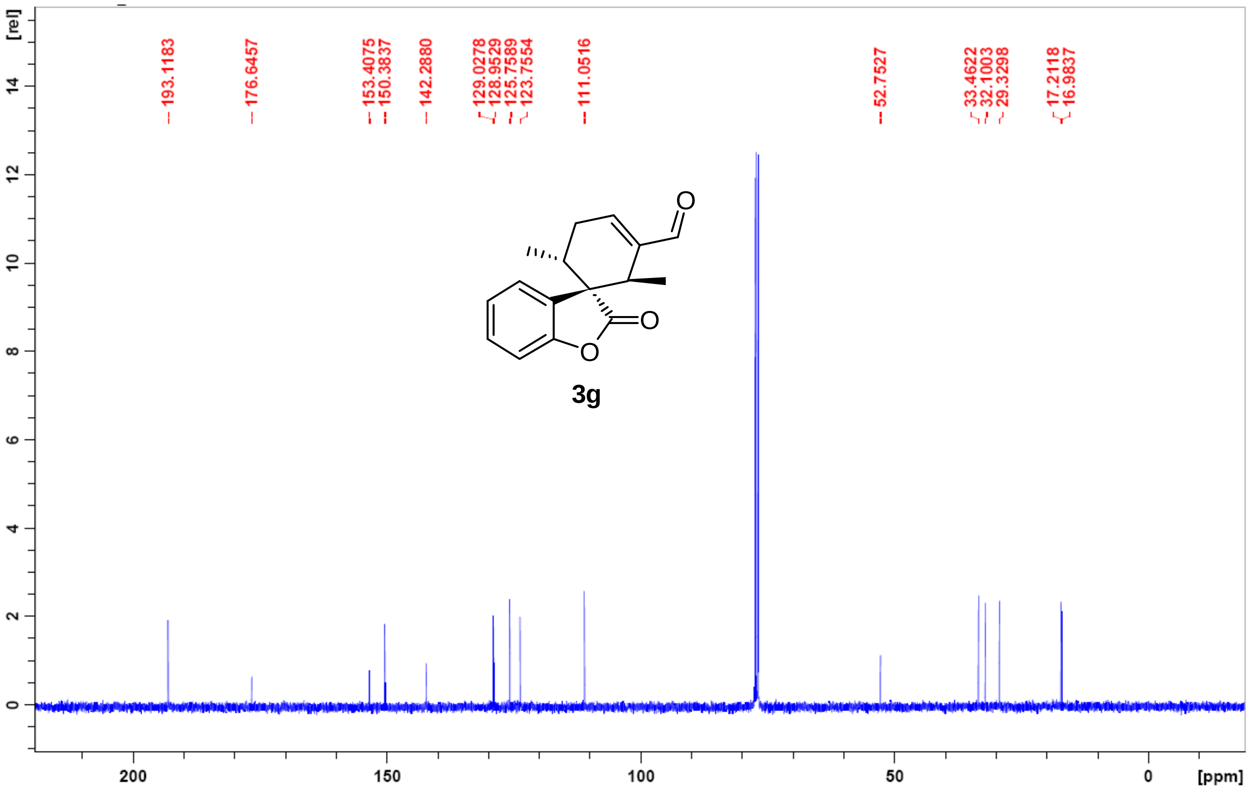
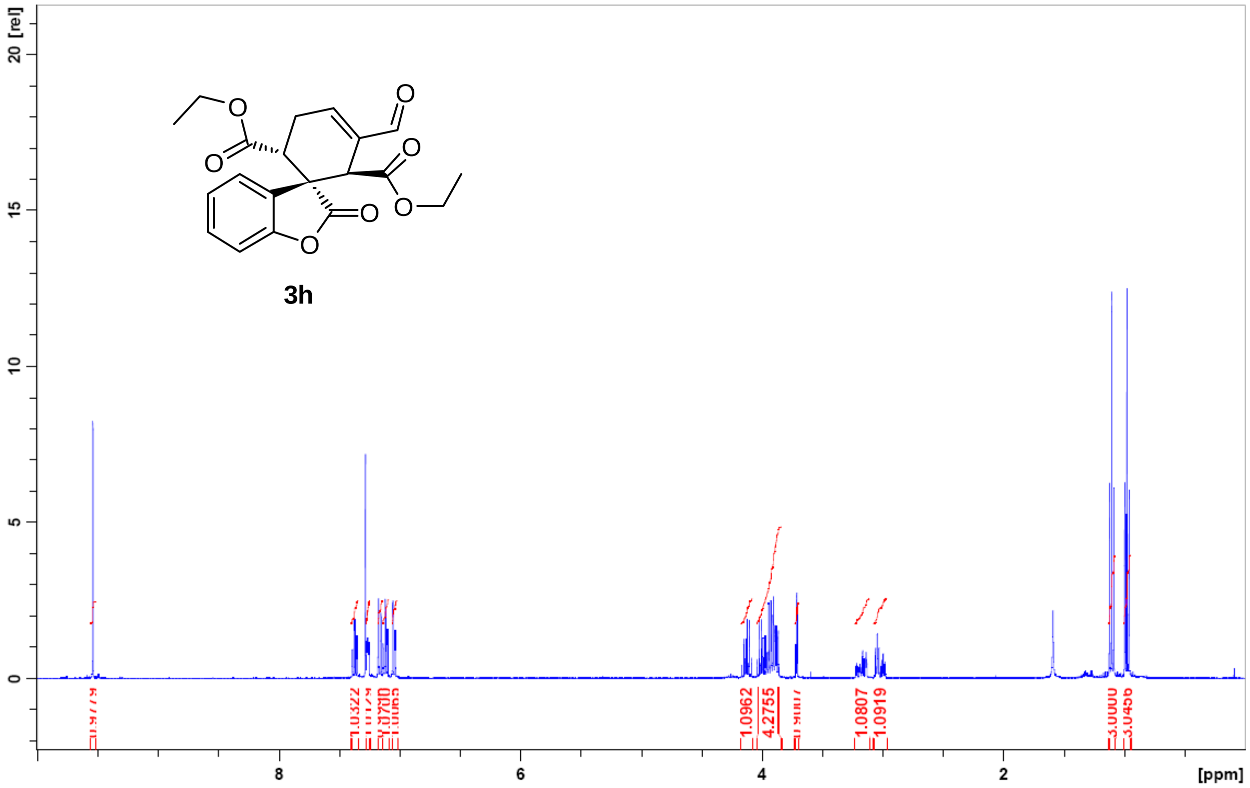
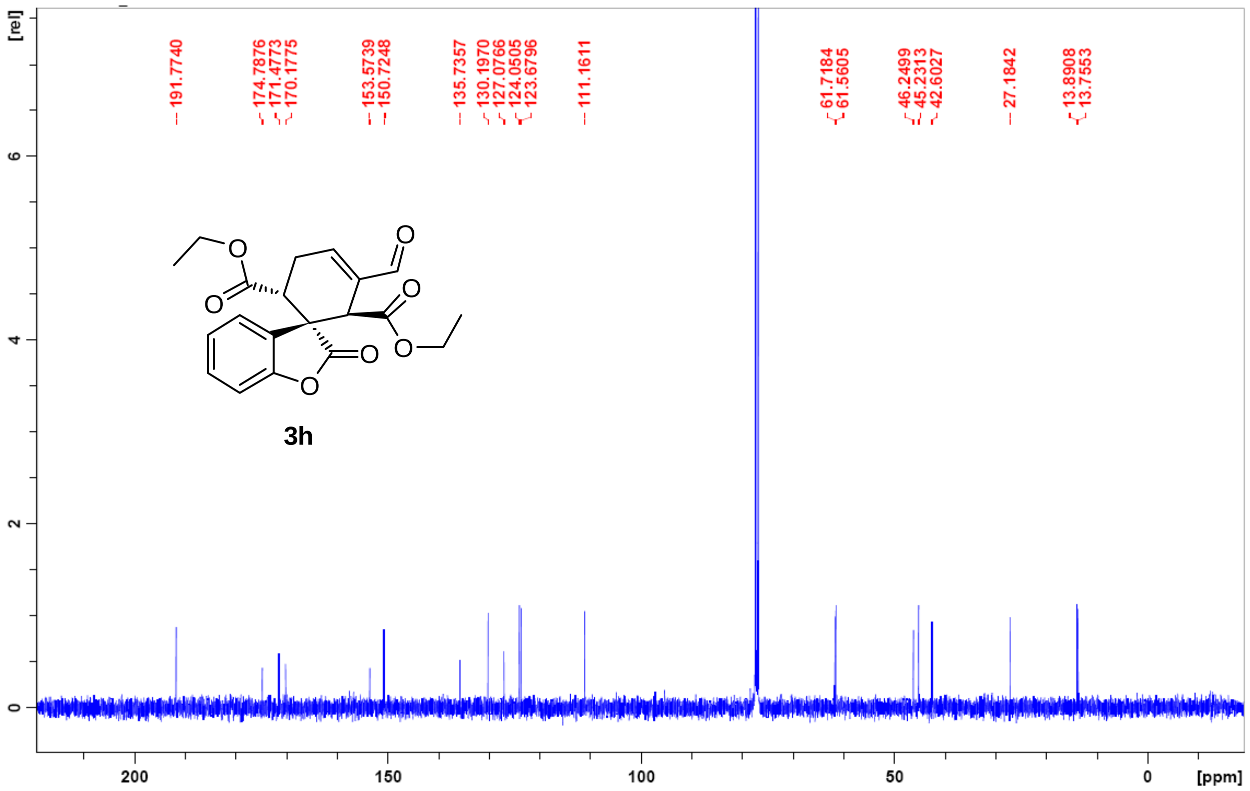
0.8141
1.9669
1.0000
3.2363
3.1532
8
6
4
2
[ppm]


[rel]
14
12
10
8
6
4
2
0
193.1183
176.6457
153.4075
150.3837
142.2880
129.0278
128.9529
125.7589
123.7554
111.0516
52.7527
33.4622
32.1003
29.3298
17.2118
16.9837
O
O
O
3g
200
150
100
50
0
[ppm]



3h

20 [rel]
15
10
5
0
1.0322
1.0962
4.2755
1.0807
1.0919
3.0000
3.0456
8
6
4
2
[ppm]



3h

[rel]
6
4
2
0
191.7740
174.7876
171.4773
170.1775
153.5739
150.7248
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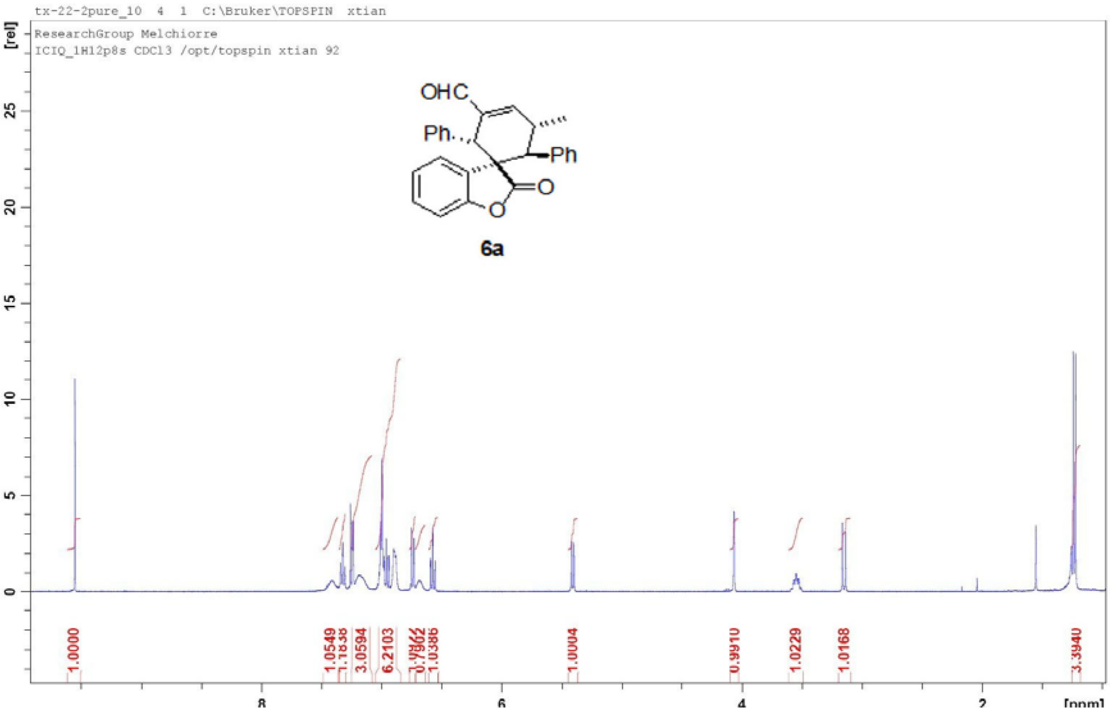
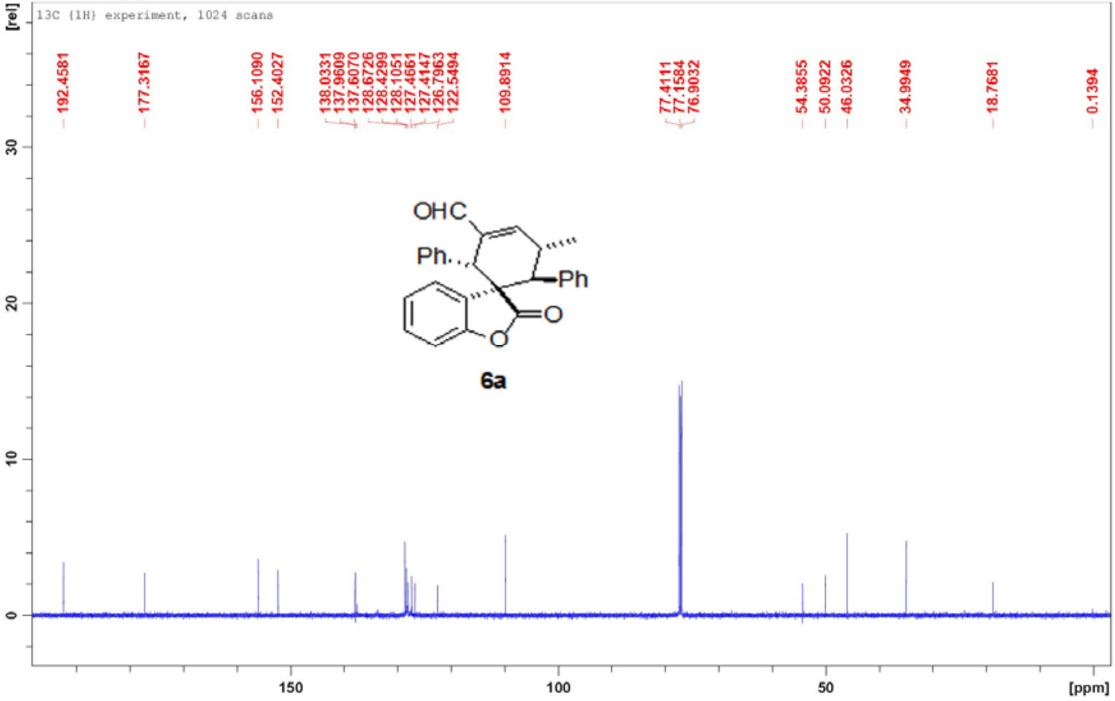
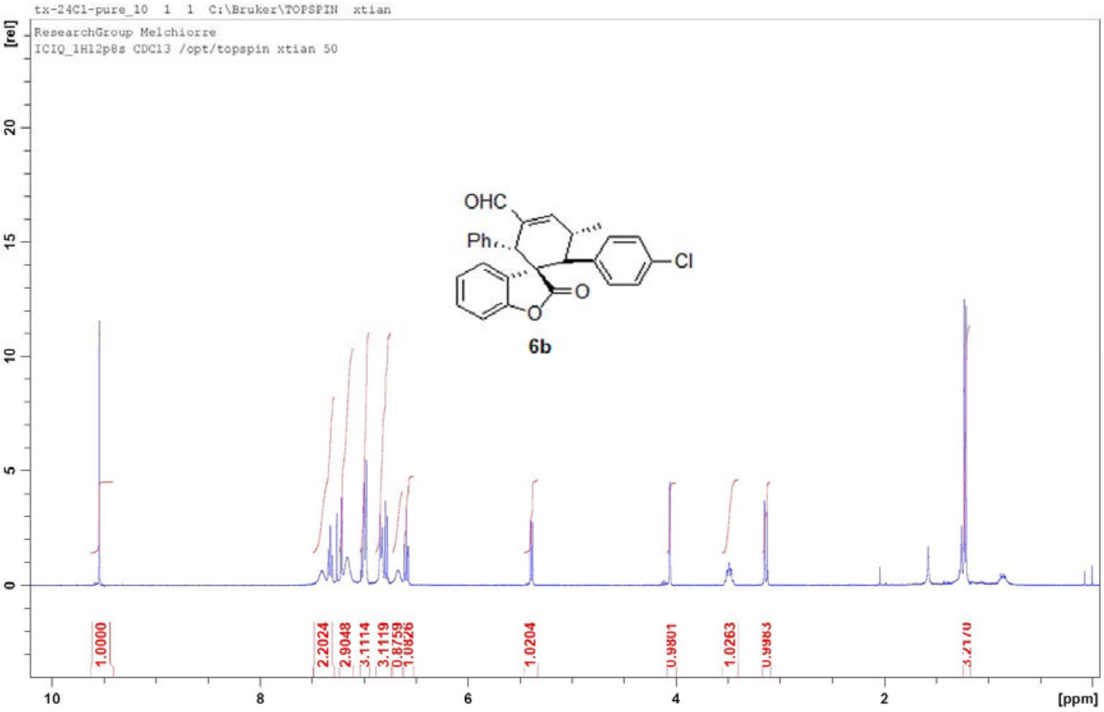
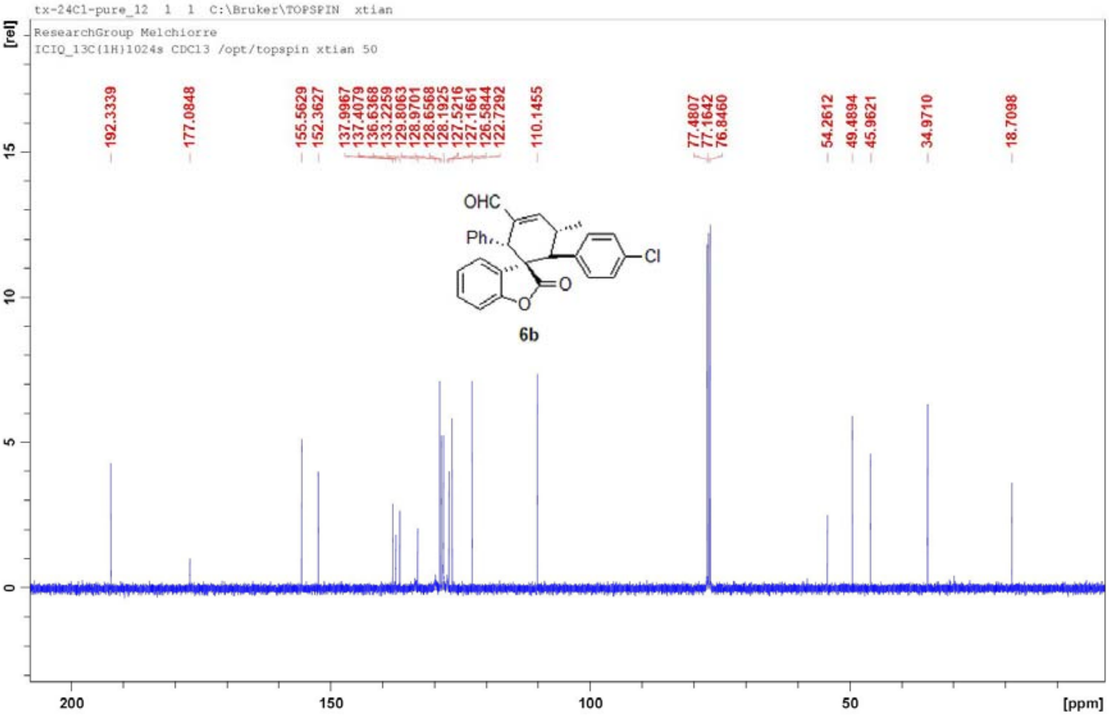
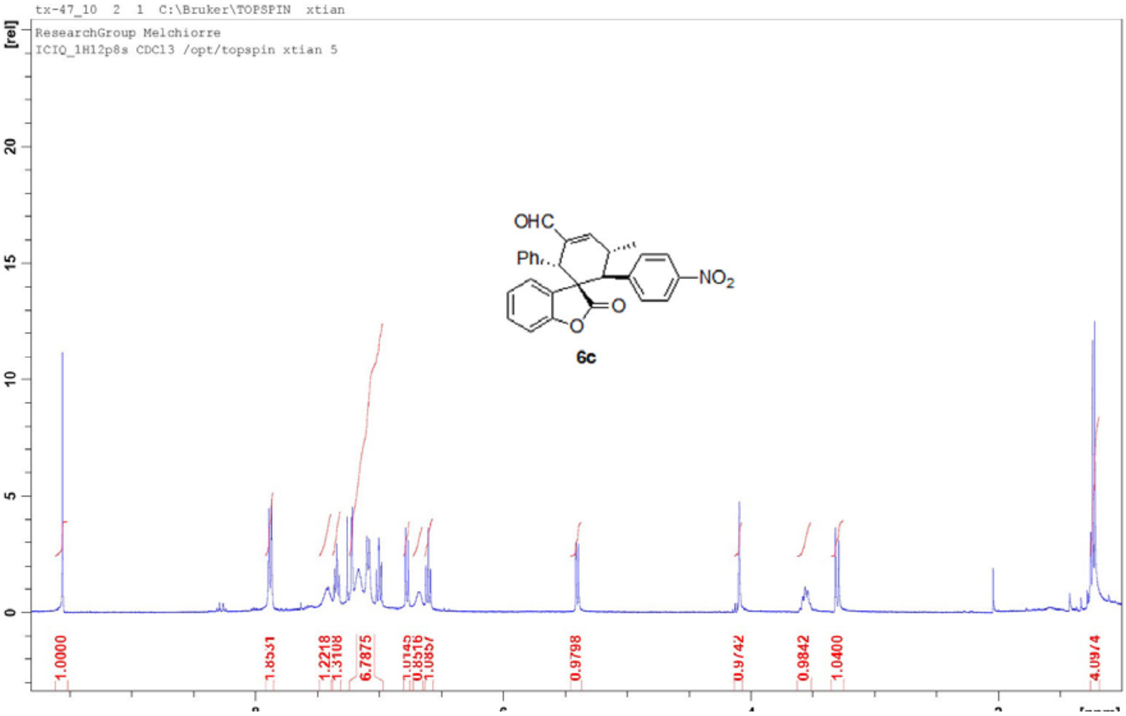
130.1970
127.0766
124.0505
123.6796
111.1611
61.7184
61.5605
46.2499
45.2313
42.6027
27.1842
13.8908
13.7553
200
150
100
50
0
[ppm]

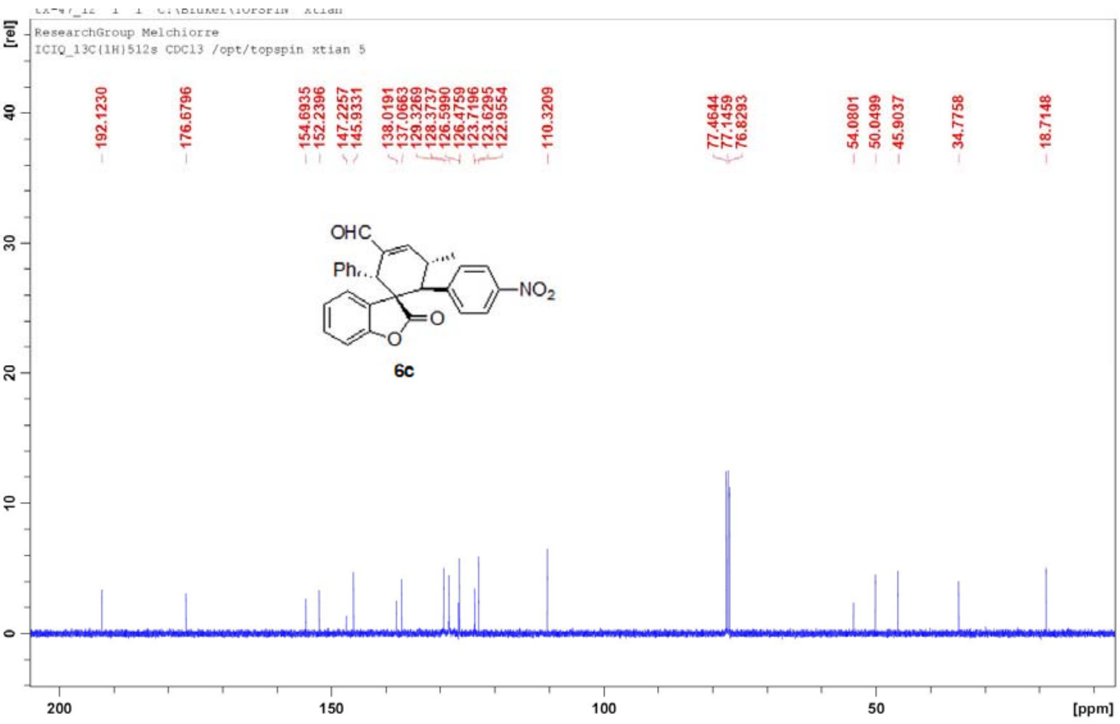

tx-22-2pure_10 4 1 C:\Bruker\TOPSPIN xtian
ResearchGroup Melchiorre
ICIQ_1H12p8s CDCl3 /opt/topspin xtian 92
OHC
Ph
Ph
O
O
6a
[rel]
25
20
15
10
5
0
1.0000
1.0549
3.0594
6.2103
1.0386
1.0004
0.9910
1.0229
1.0168
3.3940
8
6
4
2
[ppm]

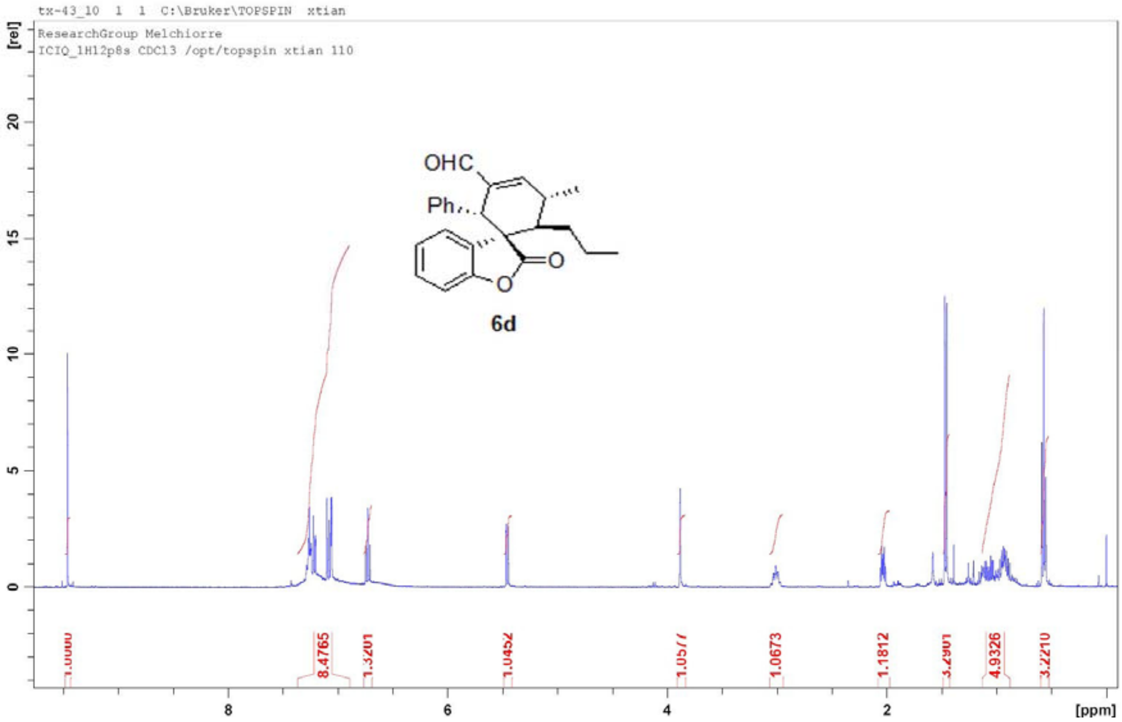

13C {1H} experiment, 1024 scans
[rel]
192.4581
177.3167
156.1090
152.4027
138.0331
137.9609
137.6070
128.6726
128.4299
128.1051
127.4661
127.4147
126.7963
122.5494
109.8914
77.4111
77.1584
76.9032
54.3855
50.0922
46.0326
34.9949
18.7681
0.1394
OHC
Ph
Ph
O
O
6a
30
20
10
0
150
100
50
[ppm]

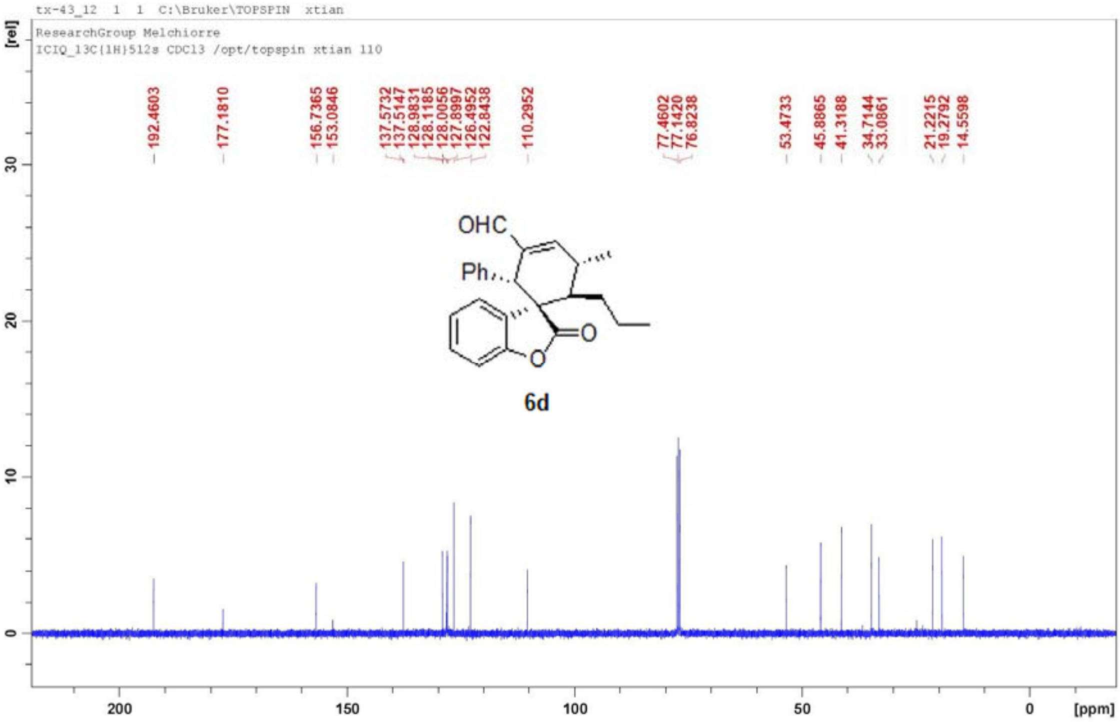

tx-24Cl-pure_10 1 1 C:\Bruker\TOPSPIN xtian
ResearchGroup Melchiorre
ICIQ_1H12p8s CDCl3 /opt/topspin xtian 50
[rel]
20
15
10
5
0
OHC
Ph
Cl
O
O
6b
1.0000
2.2024
2.9048
3.1114
3.1119
0.8759
1.0826
1.0204
0.9801
1.0263
0.9983
3.2170
10
8
6
4
2
[ppm]

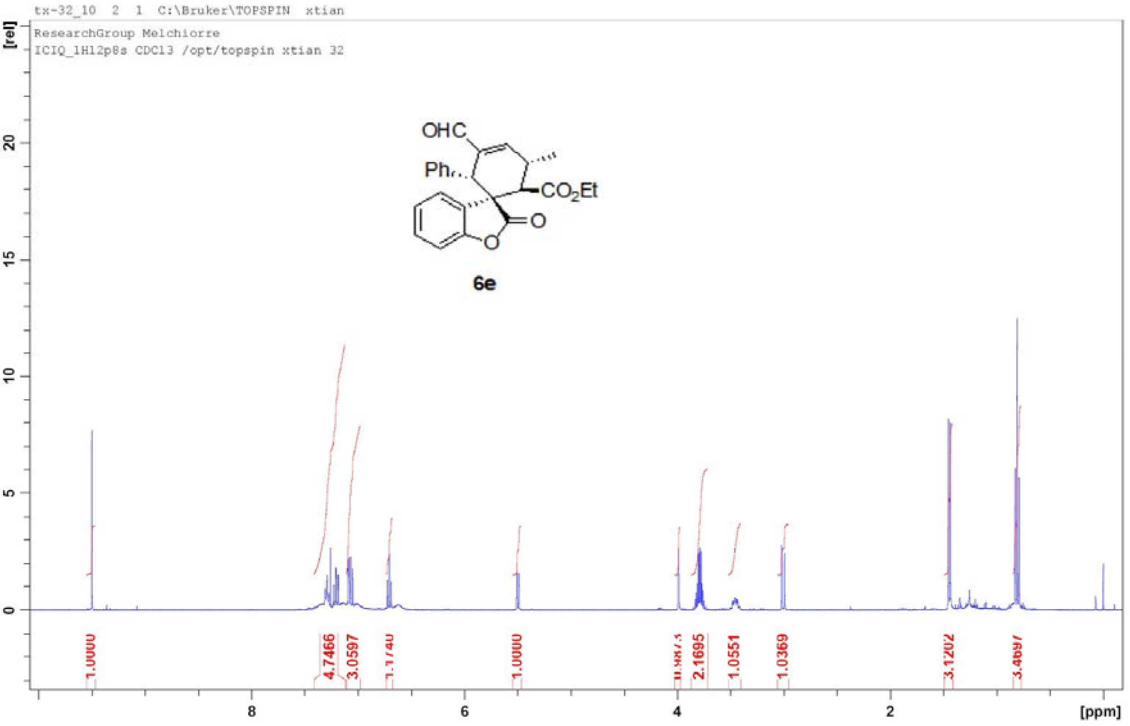

tx-24Cl-pure_12 1 1 C:\Bruker\TOPSPIN xtian
ResearchGroup Melchiorre
ICIQ_13C{1H}1024s CDCl3 /opt/topspin xtian 50
[rel]
192.3339
177.0848
155.5629
152.3627
137.9967
137.4079
136.6368
133.2259
129.8063
128.9701
128.6568
128.1925
127.5216
127.1661
126.5844
122.7292
110.1455
77.4807
77.1642
76.8460
54.2612
49.4894
45.9621
34.9710
18.7098
OHC
Ph
Cl
O
O
6b
15
10
5
0
200
150
100
50
[ppm]

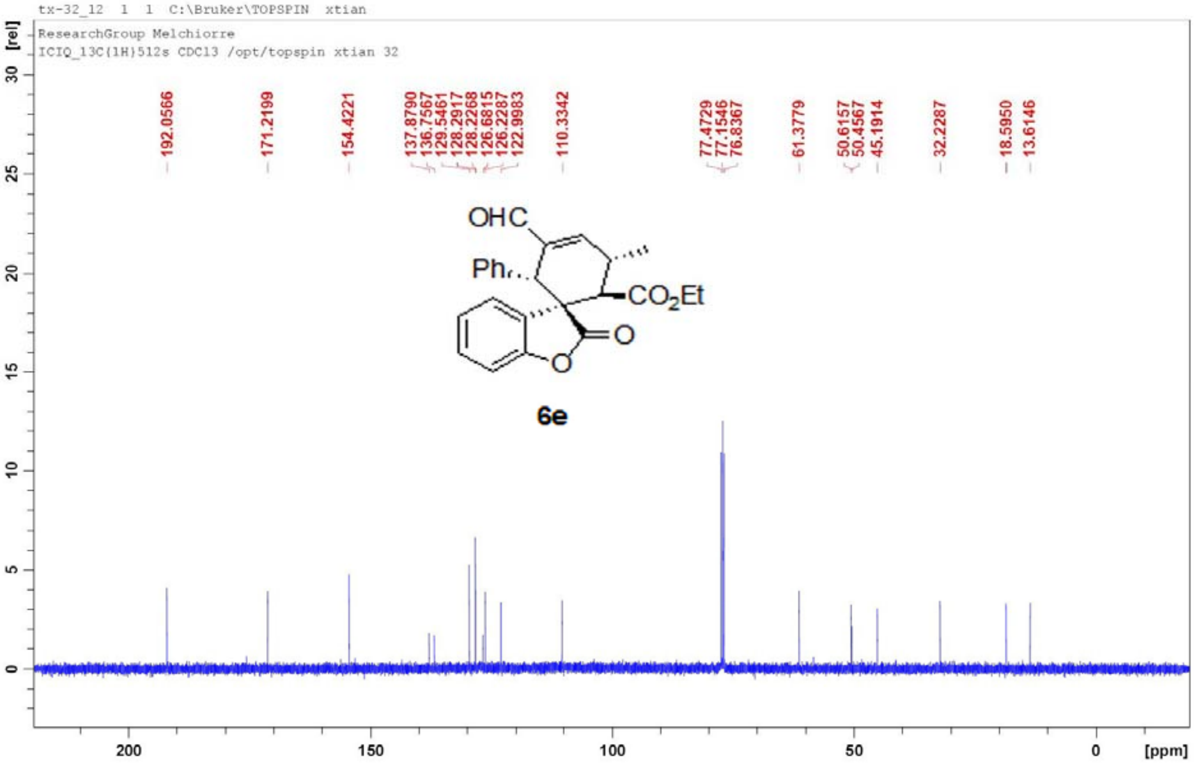

tx-47_10 2 1 C:\Bruker\TOPSPIN xtian
ResearchGroup Melchiorre
ICIQ_1H12p8s CDCl3 /opt/topspin xtian 5
[rel]
20
15
10
5
0
OHC
Ph
NO2
O
O
6c
1.0000
1.8531
1.2218
1.3108
6.7875
1.0145
0.8516
1.0857
0.9798
0.9742
0.9842
1.0400
4.0974
8
6
4
2
[ppm]

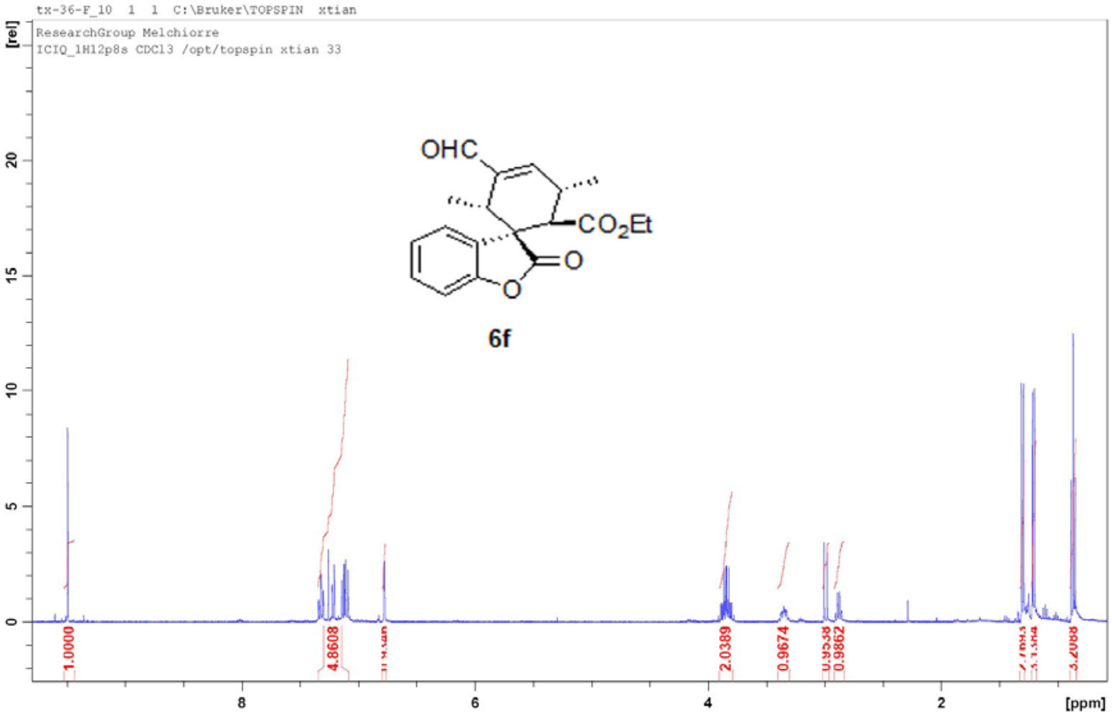

tx-47_12 1 1 C:\Bruker\TOPSPIN xtian
ResearchGroup Melchiorre
ICIQ_13C{1H}512s CDCl3 /opt/topspin xtian 5
[rel]
192.1230
176.6796
154.6935
152.2396
147.2257
145.9331
138.0191
137.0663
129.3269
128.3737
126.5990
126.4759
123.7196
123.6295
122.9554
110.3209
77.4644
77.1459
76.8293
54.0801
50.0499
45.9037
34.7758
18.7148
OHC
Ph
NO2
O
O
6c
40
30
20
10
0
200
150
100
50
[ppm]

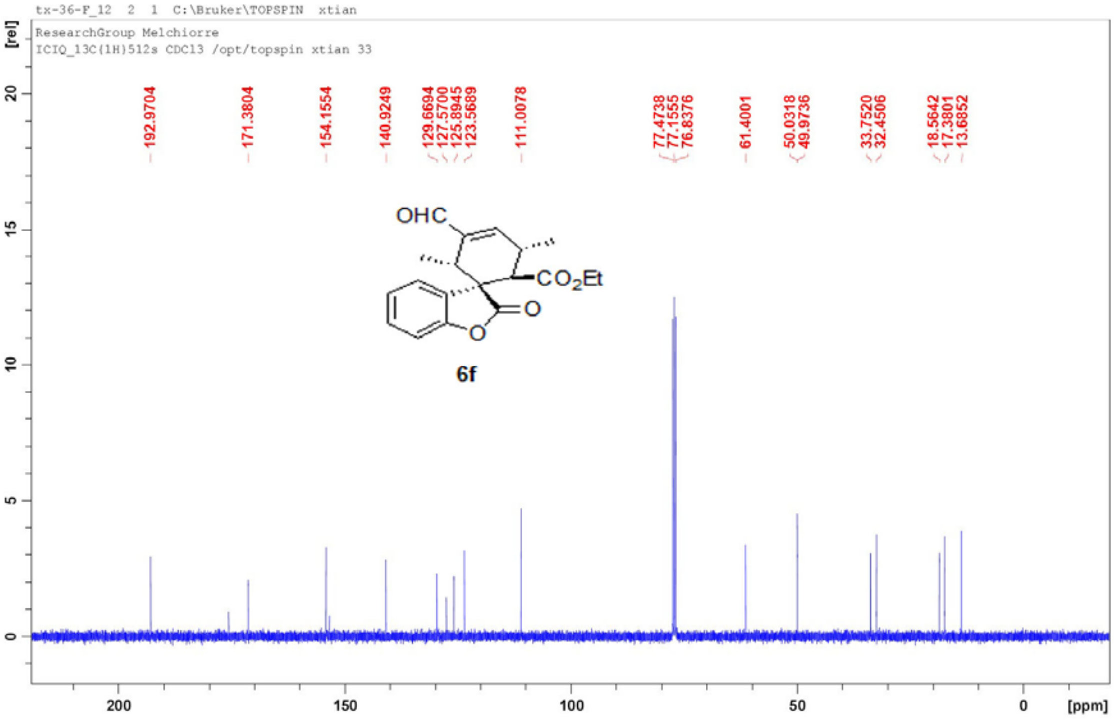

tx-43_10 1 1 C:\Bruker\TOPSPIN xtian
ResearchGroup Melchiorre
ICIQ_1H12p8s CDCl3 /opt/topspin xtian 110
[rel]
20
15
10
5
0
OHC
Ph
O
O
6d
1.0000
8.4765
1.3201
1.0452
1.0577
1.0673
1.1812
3.2901
4.9326
3.2210
8
6
4
2
[ppm]

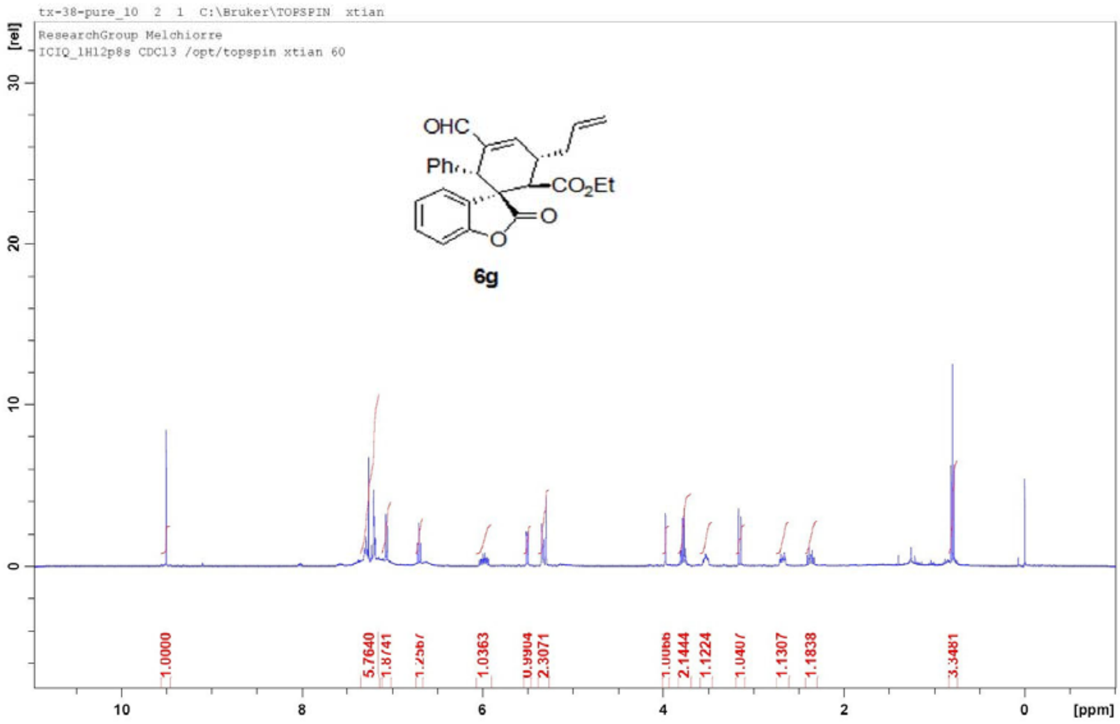

tx-43_12 1 1 C:\Bruker\TOPSPIN xtian
ResearchGroup Melchiorre
ICIQ_13C{1H}512s CDCl3 /opt/topspin xtian 110
[rel]
192.4603
177.1810
156.7365
153.0846
137.5732
137.5147
128.9831
128.1185
128.0056
127.8997
126.4952
122.8438
110.2952
77.4602
77.1420
76.8238
53.4733
45.8865
41.3188
34.7144
33.0861
21.2215
19.2792
14.5598
OHC
Ph
O
O
6d
30
20
10
0
200
150
100
50
0
[ppm]

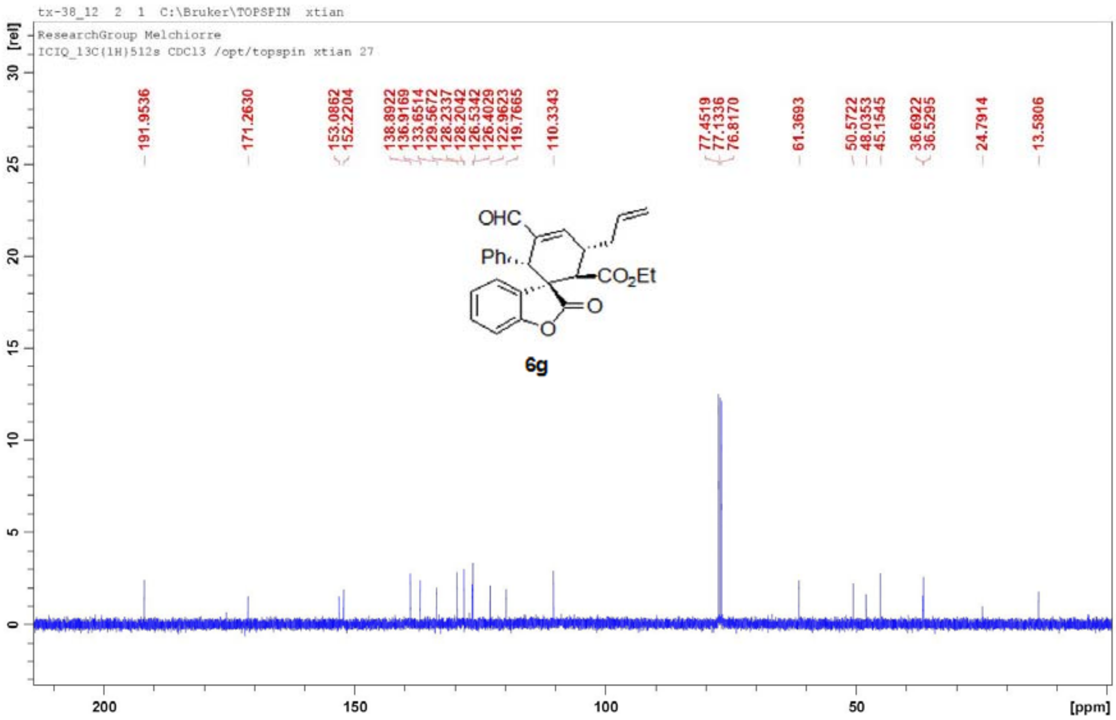

tx-32_10 2 1 C:\Bruker\TOPSPIN xtian
ResearchGroup Melchiorre
ICIQ_1H12p8s CDCl3 /opt/topspin xtian 32
[rel]
OHC
Ph
CO2Et
O
O
6e
1.0000
4.7466
3.0597
1.1740
1.0000
2.1695
1.0551
1.0369
3.1202
3.4697
0
5
10
15
20
8
6
4
2
[ppm]

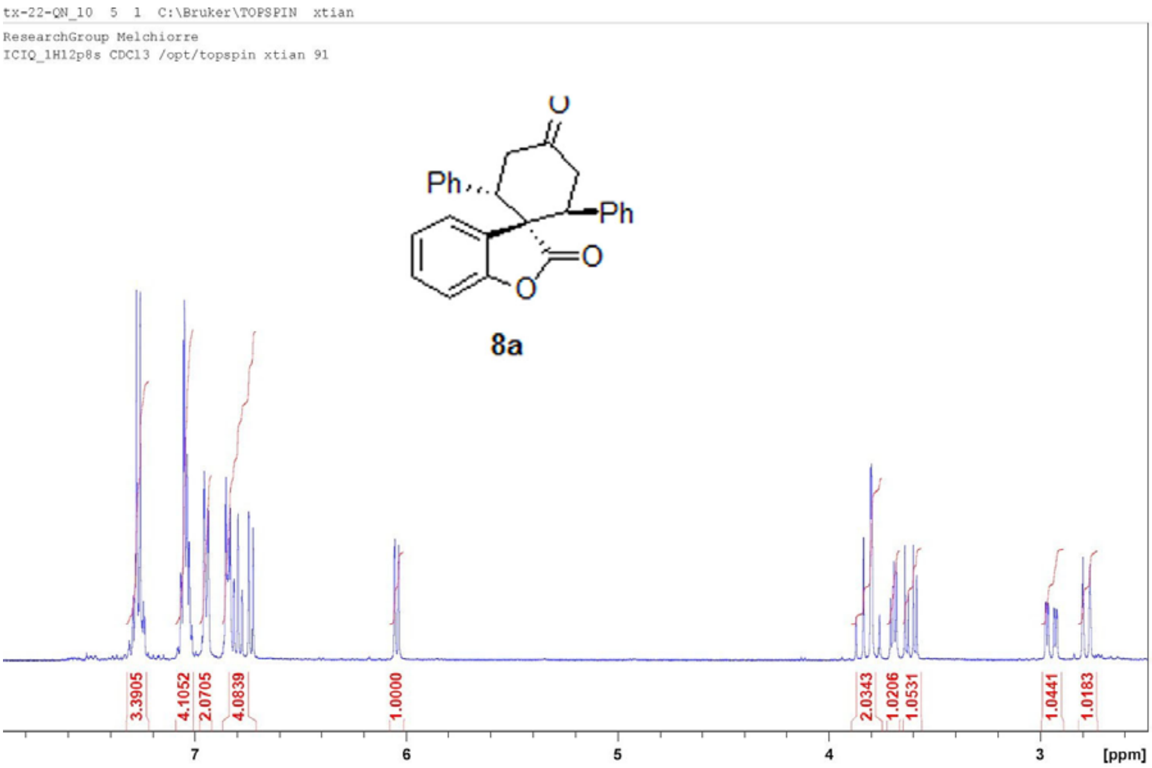

tx-32_12 1 1 C:\Bruker\TOPSPIN xtian
ResearchGroup Melchiorre
ICIQ_13C{1H}512s CDCl3 /opt/topspin xtian 32
[rel]
192.0566
171.2199
154.4221
137.8790
136.7567
129.5461
128.2917
128.2268
126.6815
126.2287
122.9983
110.3342
77.4729
77.1546
76.8367
61.3779
50.6157
50.4567
45.1914
32.2287
18.5950
13.6146
OHC
Ph
CO2Et
O
O
6e
0
5
10
15
20
25
30
200
150
100
50
0
[ppm]

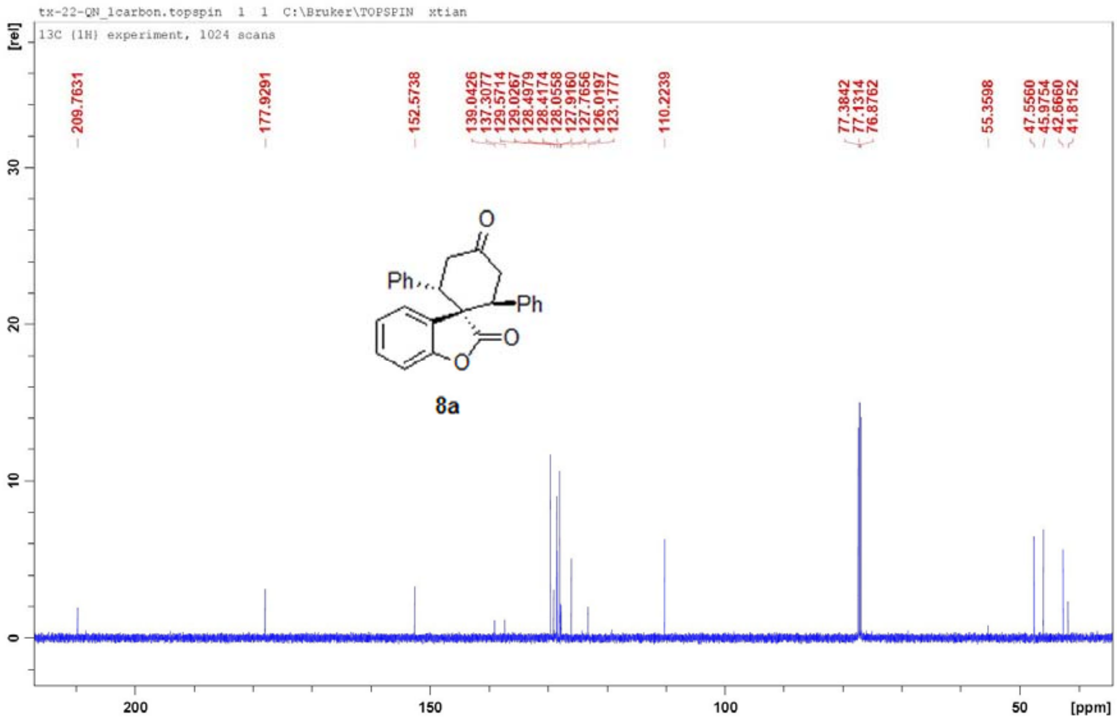

tx-36-F_10 1 1 C:\Bruker\TOPSPIN xtian
ResearchGroup Melchiorre
ICIQ_1H12p8s CDCl3 /opt/topspin xtian 33
[rel]
OHC
CO2Et
O
O
6f
1.0000
4.8608
2.0389
0.9674
0.9862
8
6
4
2
[ppm]
0
5
10
15
20

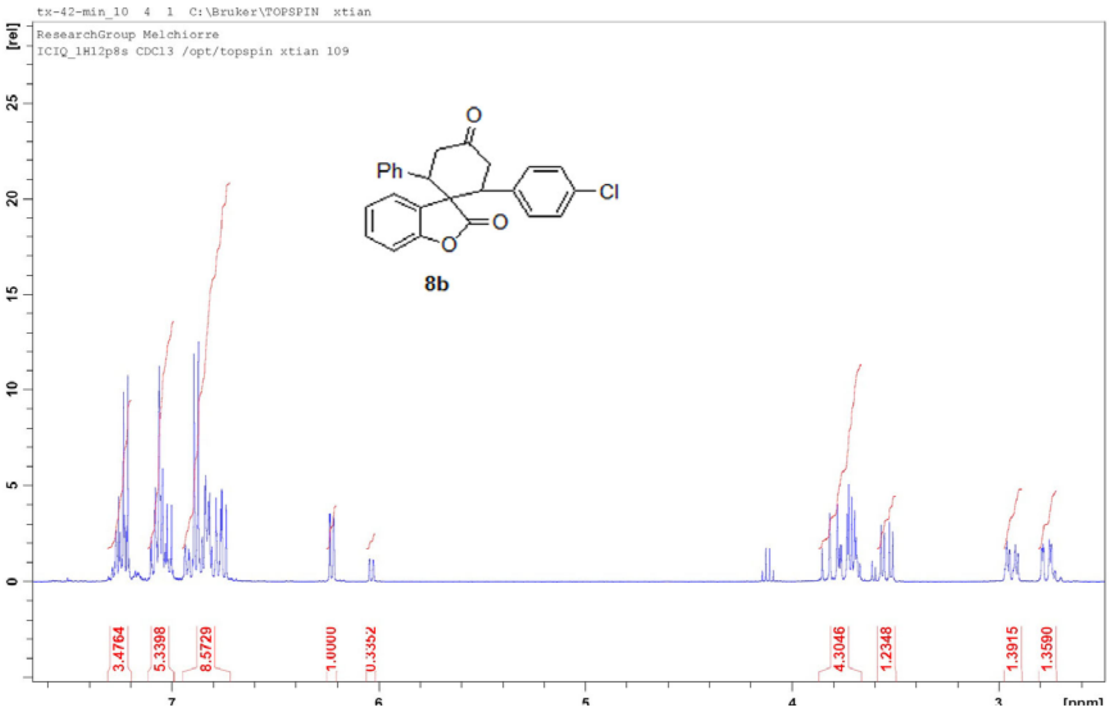

tx-36-F_12 2 1 C:\Bruker\TOPSPIN xtian
ResearchGroup Melchiorre
ICIQ_13C{1H}512s CDCl3 /opt/topspin xtian 33
[rel]
192.9704
171.3804
154.1554
140.9249
129.6694
127.5700
125.8945
123.5689
111.0078
77.4738
77.1555
76.8376
61.4001
50.0318
49.9736
33.7520
32.4506
18.5642
17.3801
13.6852
OHC
CO2Et
O
O
6f
200
150
100
50
0
[ppm]
0
5
10
15
20

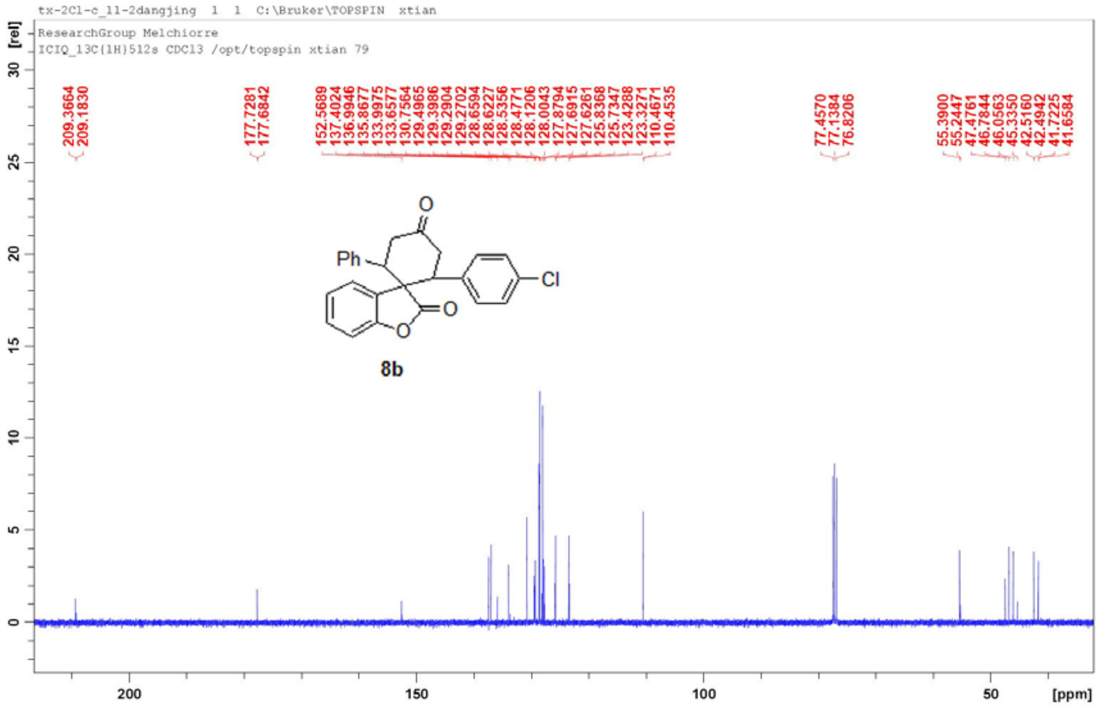

tx-38-pure_10 2 1 C:\Bruker\TOPSPIN xtian
ResearchGroup Melchiorre
ICIQ_1H12p8s CDCl3 /opt/topspin xtian 60
[rel]
30
20
10
0
OHC
Ph
CO2Et
O
O
6g
1.0000
5.7640
1.8741
1.2567
1.0363
0.9904
2.3071
1.0066
2.1444
1.1224
1.0407
1.1307
1.1838
3.3481
10
8
6
4
2
0
[ppm]


tx-38_12 2 1 C:\Bruker\TOPSPIN xtian
ResearchGroup Melchiorre
ICIQ_13C(1H)512s CDCl3 /opt/topspin xtian 27
[rel]
30
25
20
15
10
5
0
191.9536
171.2630
153.0862
152.2204
138.8922
136.9169
133.6514
129.5672
128.2337
128.2042
126.5342
126.4029
122.9623
119.7665
110.3343
77.4519
77.1336
76.8170
61.3693
50.5722
48.0353
45.1545
36.6922
36.5295
24.7914
13.5806
OHC
Ph
CO2Et
O
O
6g
200
150
100
50
[ppm]


tx-22-QN_10 5 1 C:\Bruker\TOPSPIN xtian
ResearchGroup Melchiorre
ICIQ_1H12p8s CDCl3 /opt/topspin xtian 91
O
Ph
Ph
O
O
8a
3.3905
4.1052
2.0705
4.0839
1.0000
2.0343
1.0206
1.0531
1.0441
1.0183
7
6
5
4
3
[ppm]


tx-22-QN_1carbon.topspin 1 1 C:\Bruker\TOPSPIN xtian
13C {1H} experiment, 1024 scans
[rel]
209.7631
177.9291
152.5738
139.0426
137.3077
129.5714
129.0267
128.4979
128.4174
128.0558
127.9160
127.7656
126.0197
123.1777
110.2239
77.3842
77.1314
76.8762
55.3598
47.5560
45.9754
42.6660
41.8152
O
Ph
Ph
O
O
8a
30
20
10
0
200
150
100
50
[ppm]


tx-42-min_10 4 1 C:\Bruker\TOPSPIN xtian
ResearchGroup Melchiorre
ICIQ_1H12p8s CDCl3 /opt/topspin xtian 109
[rel]
0
5
10
15
20
25
Ph
O
O
O
Cl
8b
3.4764
5.3398
8.5729
1.0000
0.3352
4.3046
1.2348
1.3915
1.3590
7
6
5
4
3
[ppm]


tx-2Cl-c_11-2dangjing 1 1 C:\Bruker\TOPSPIN xtian
ResearchGroup Melchiorre
ICIQ_13C{1H}512s CDCl3 /opt/topspin xtian 79
[rel]
0
5
10
15
20
25
30
209.3664
209.1830
177.7281
177.6842
152.5689
137.4024
136.9946
135.8677
133.9975
133.6577
130.7564
129.4965
129.3986
129.2904
129.2702
128.6594
128.6227
128.5356
128.4771
128.1206
128.0043
127.8794
127.6915
127.6261
125.8368
125.7347
123.4288
123.3271
110.4671
110.4535
77.4570
77.1384
76.8206
55.3900
55.2447
47.4761
46.7844
46.0563
45.3350
42.5160
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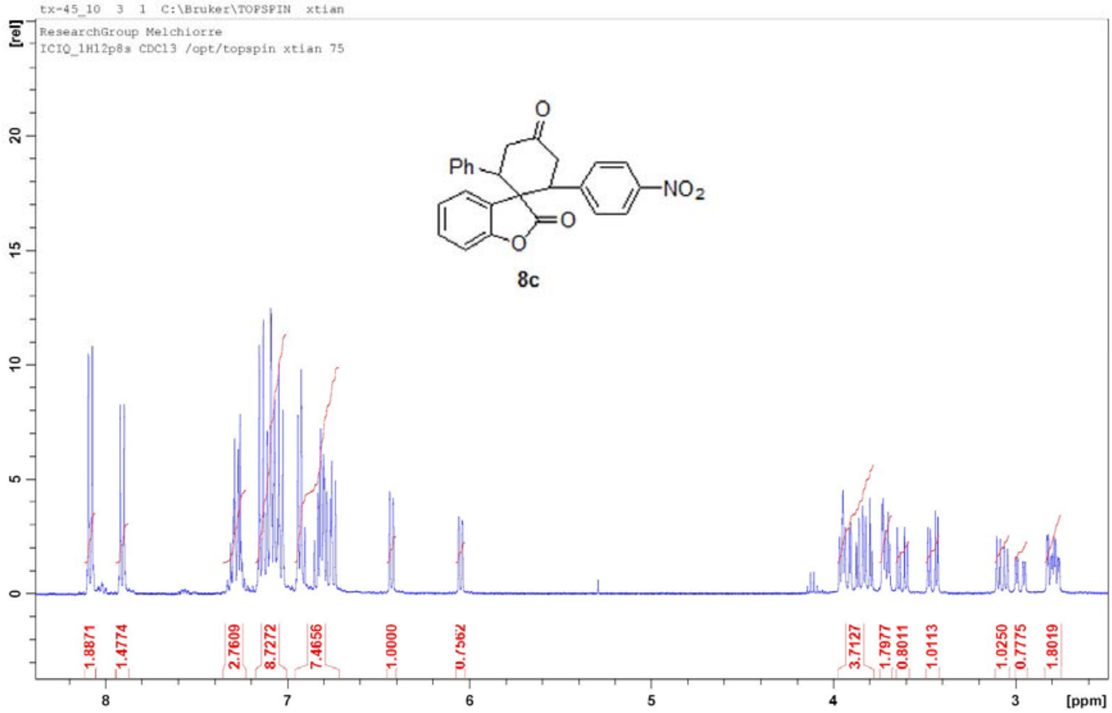
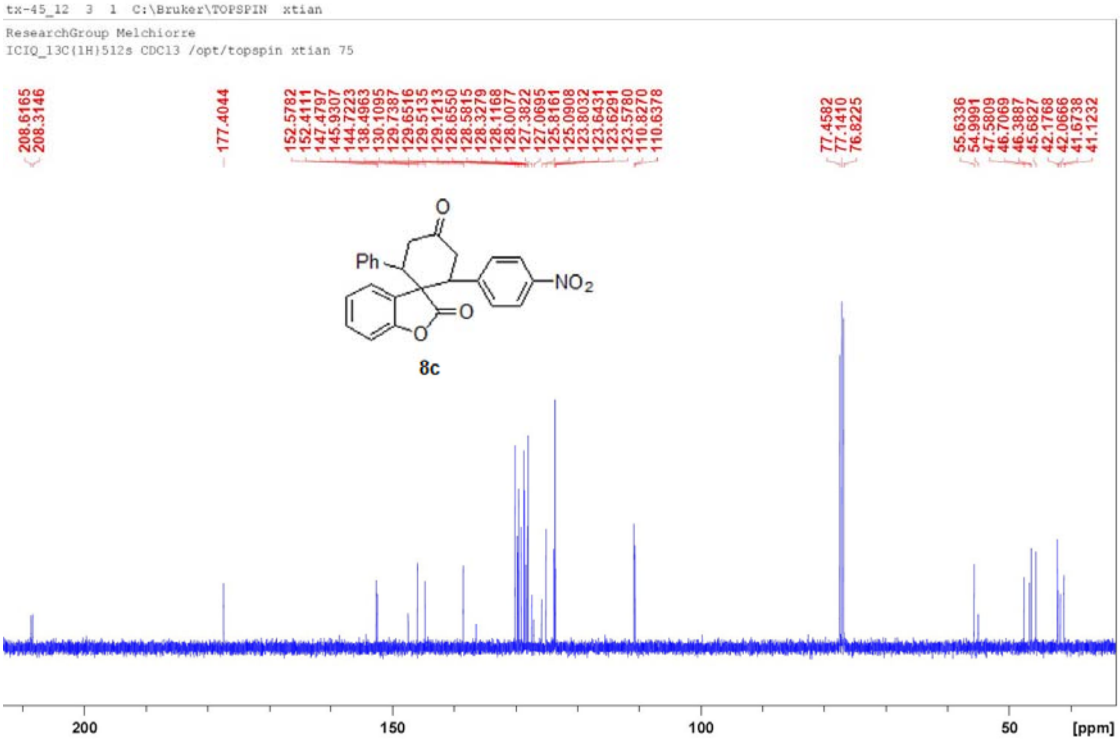
41.7225
41.6584
Ph
O
O
O
Cl
8b
200
150
100
50
[ppm]


tx-45_10 3 1 C:\Bruker\TOPSPIN xtian
ResearchGroup Melchiorre
ICIQ_1H12p8s CDCl3 /opt/topspin xtian 75
[rel]
20
15
10
5
0
Ph
O
NO2
O
O
8c
1.8871
1.4774
2.7609
8.7272
7.4656
1.0000
0.7562
3.7127
1.7977
0.8011
1.0113
1.0250
0.7775
1.8019
8
7
6
5
4
3
[ppm]


tx-45_12 3 1 C:\Bruker\TOPSPIN xtian
ResearchGroup Melchiorre
ICIQ_13C{1H}512s CDCl3 /opt/topspin xtian 75
208.6165
208.3146
177.4044
152.5782
152.4111
147.4797
145.9307
144.7223
138.4963
130.1095
129.7387
129.6516
129.5135
129.1213
128.6550
128.5815
128.3279
128.1168
128.0077
127.3822
127.0695
125.8161
125.0908
123.8032
123.6431
123.6291
123.5780
110.8270
110.6378
77.4582
77.1410
76.8225
55.6336
54.9991
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41.1232
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NO2
O
O
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100
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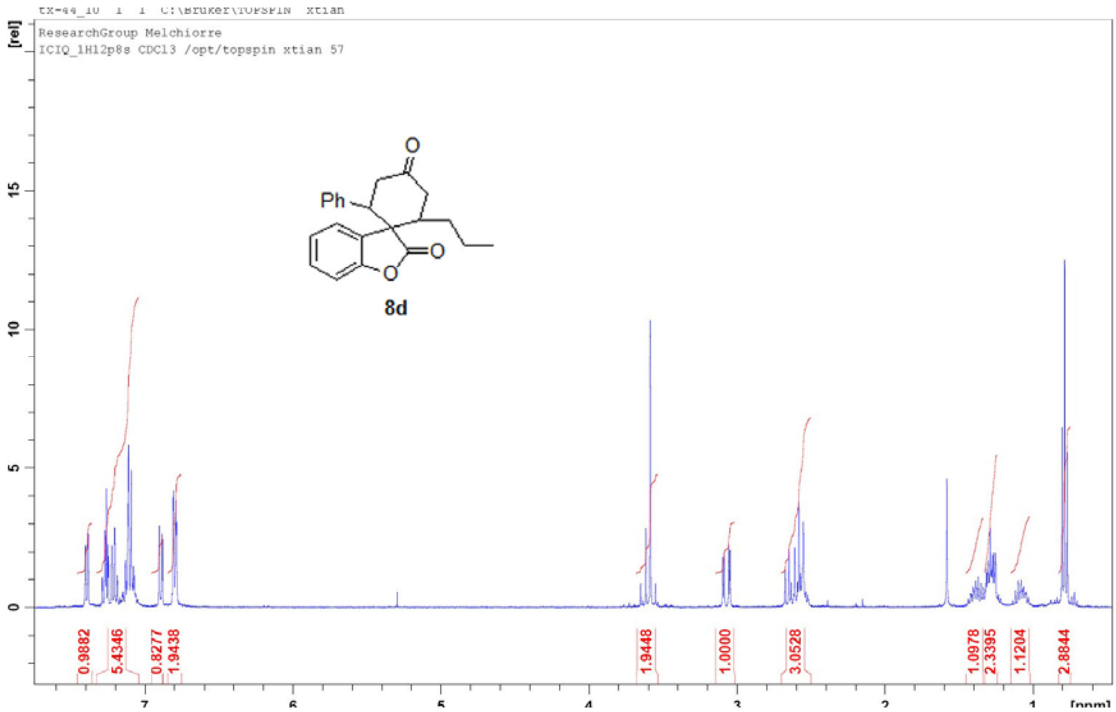
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ResearchGroup Melchiorre
ICIQ_1H12p8s CDCl3 /opt/topspin xtian 57
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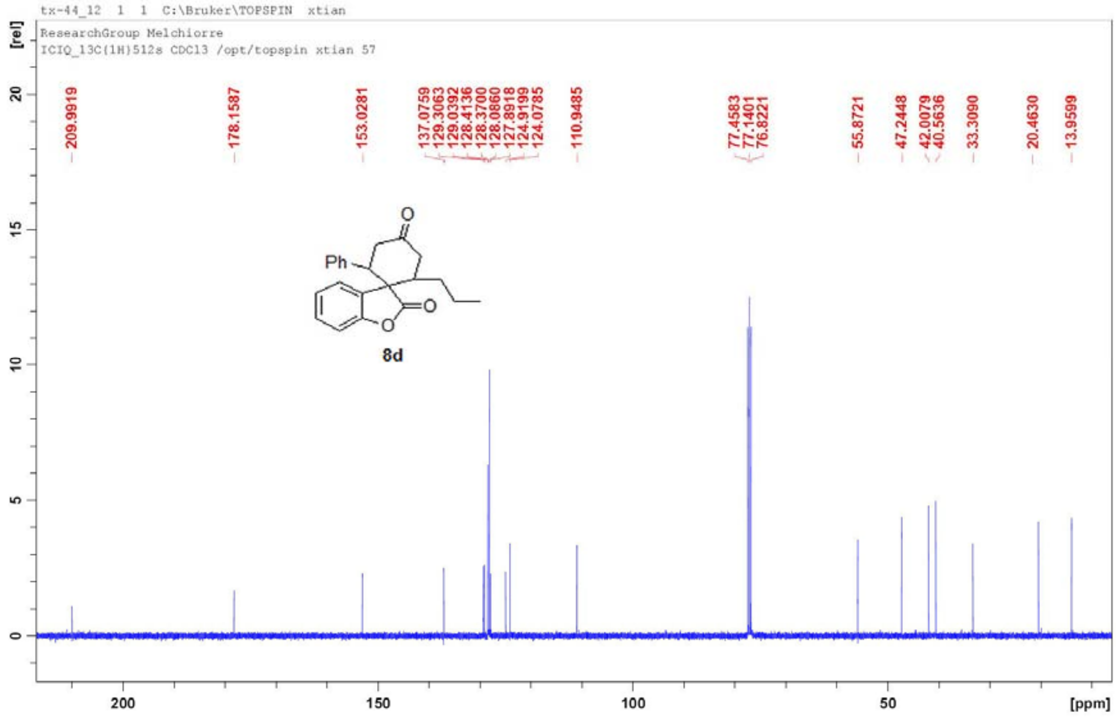
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O
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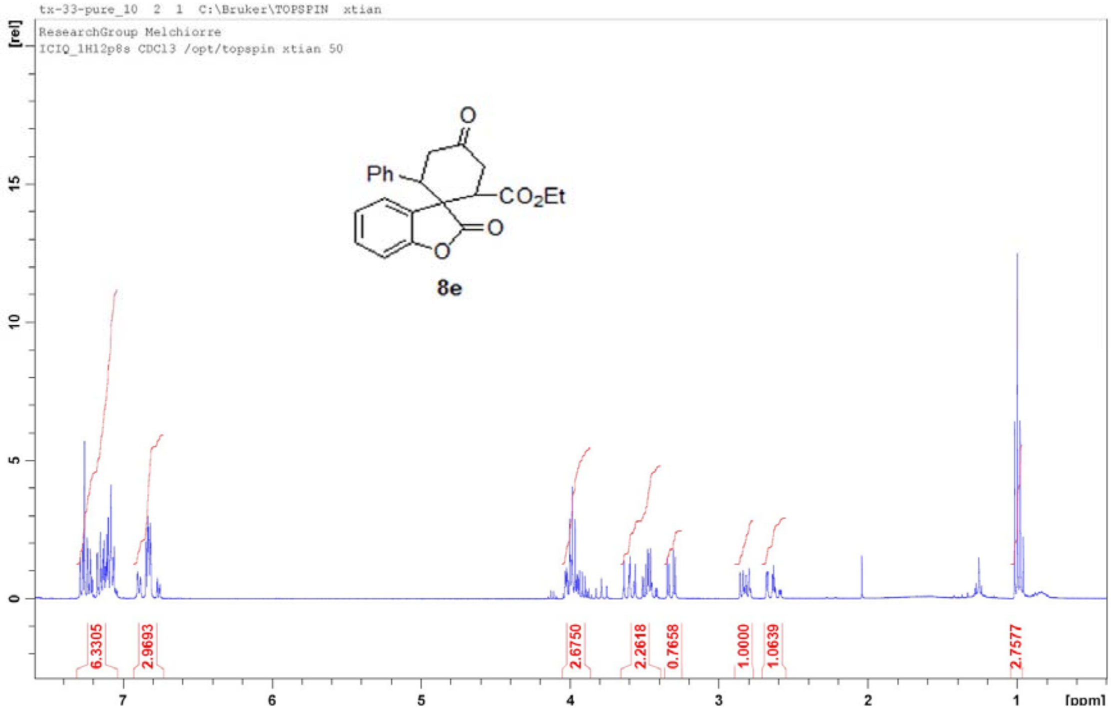
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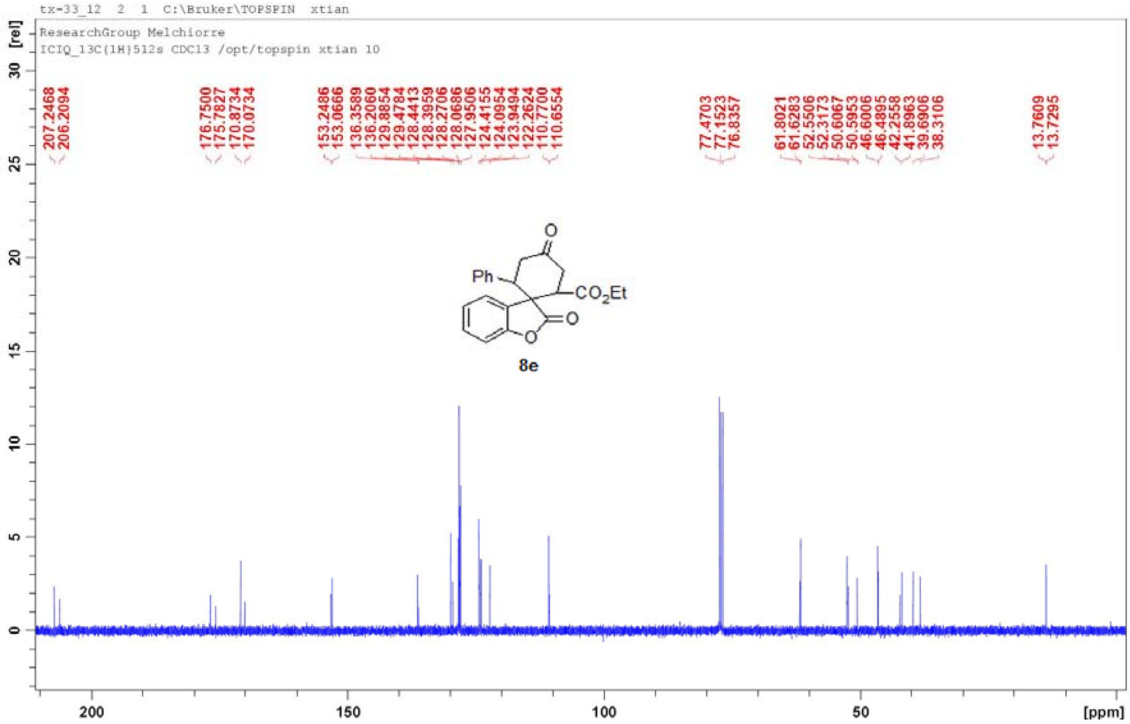
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ResearchGroup Melchiorre
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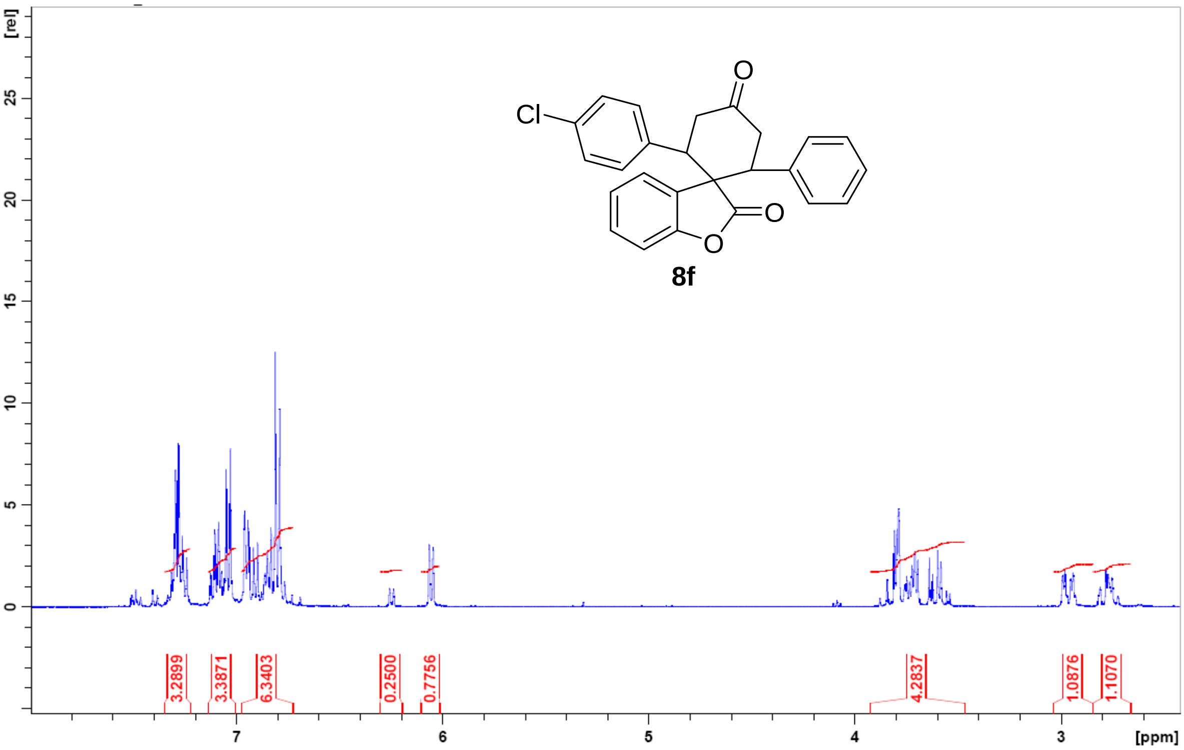
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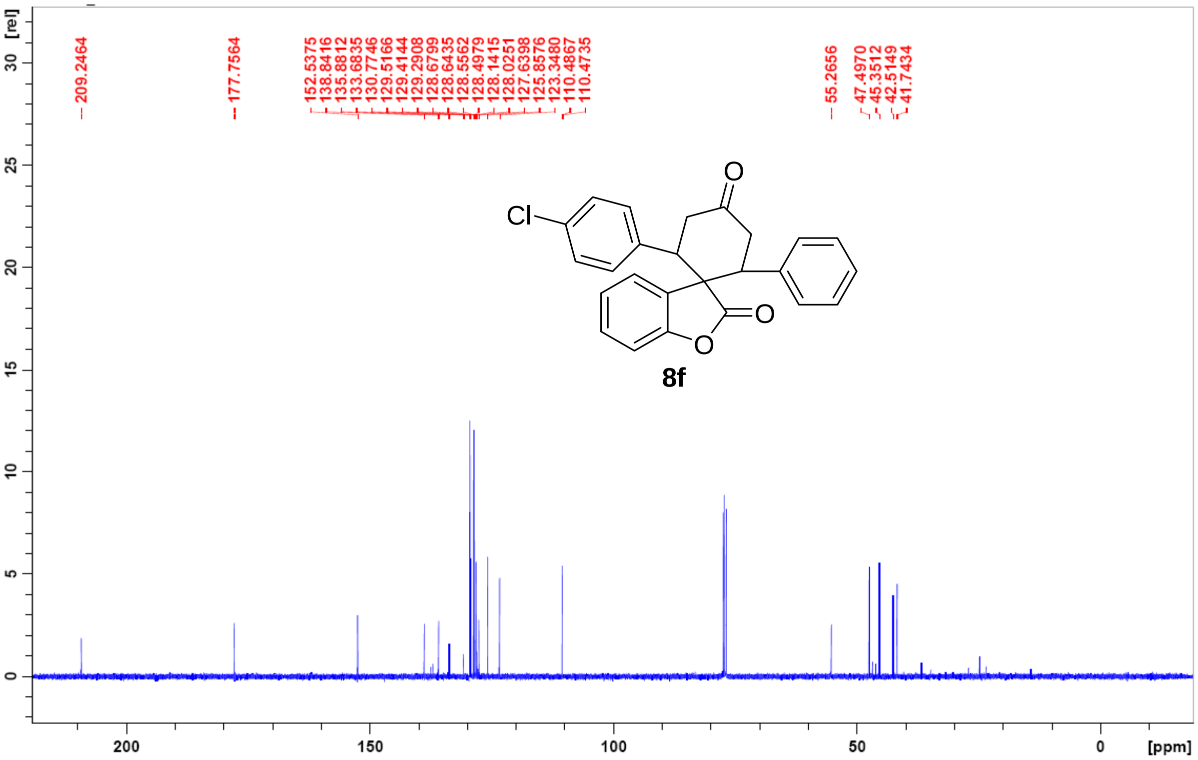
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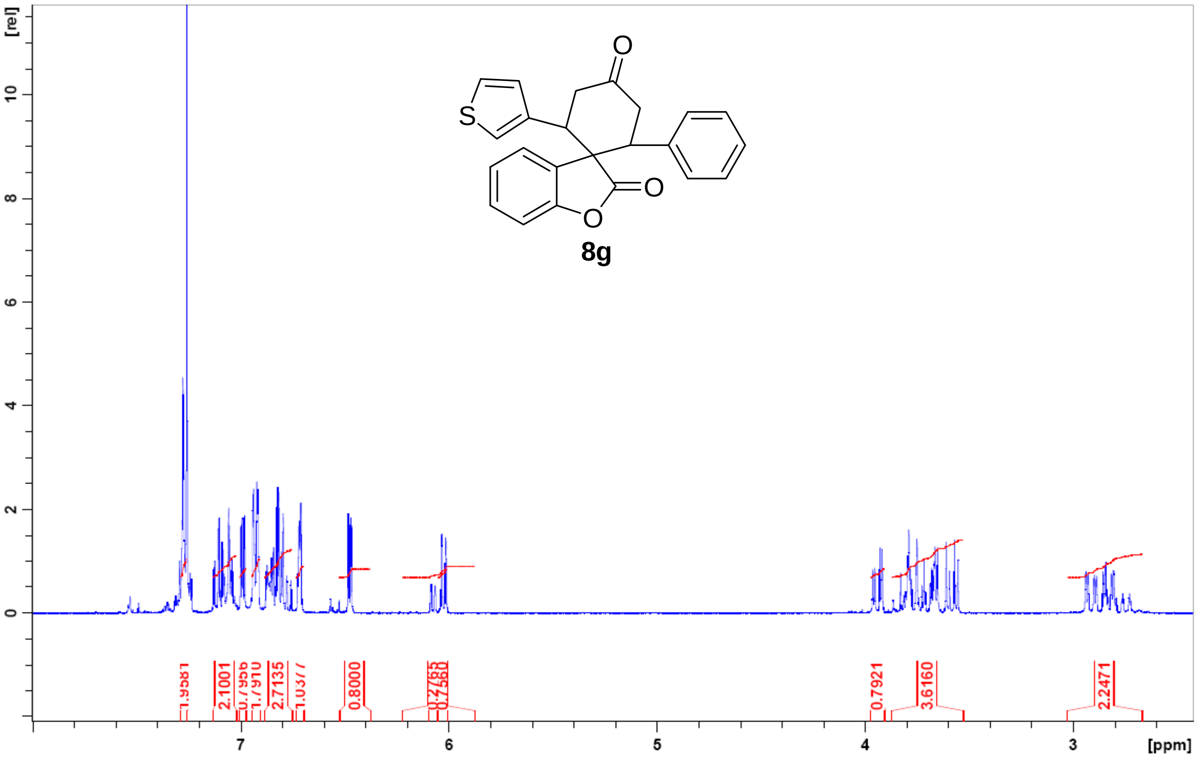
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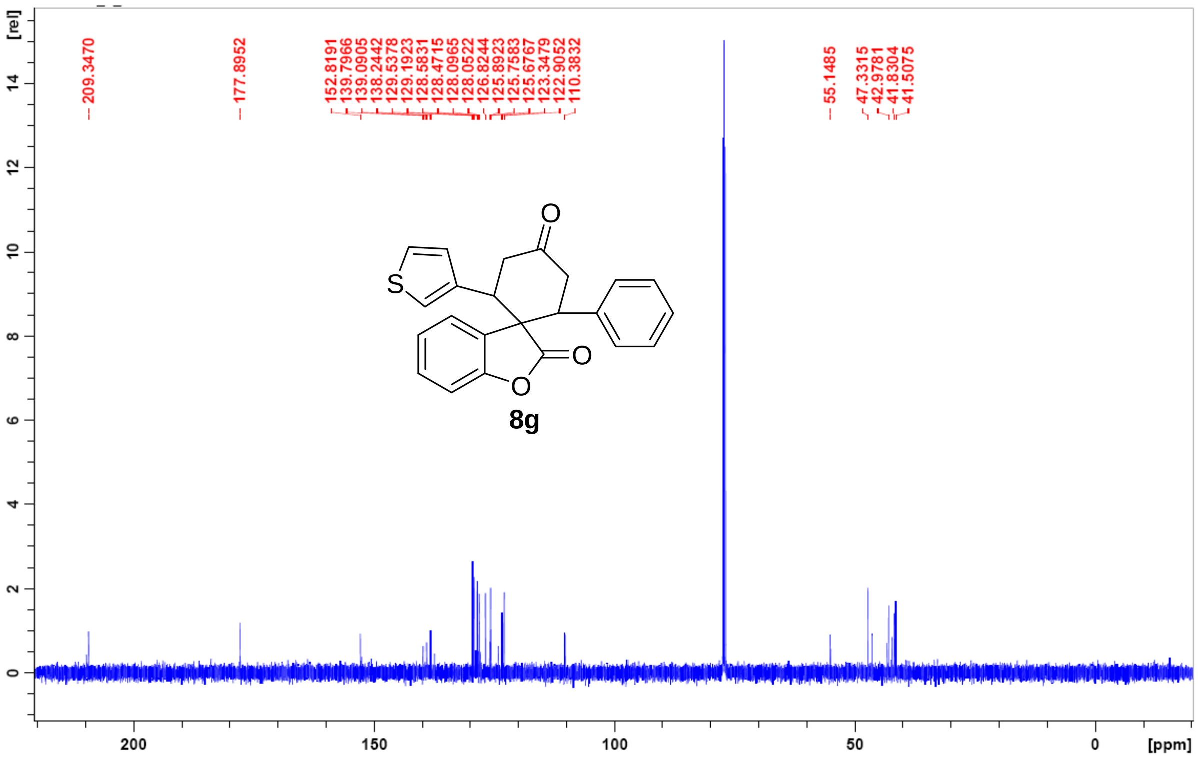
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128.0522
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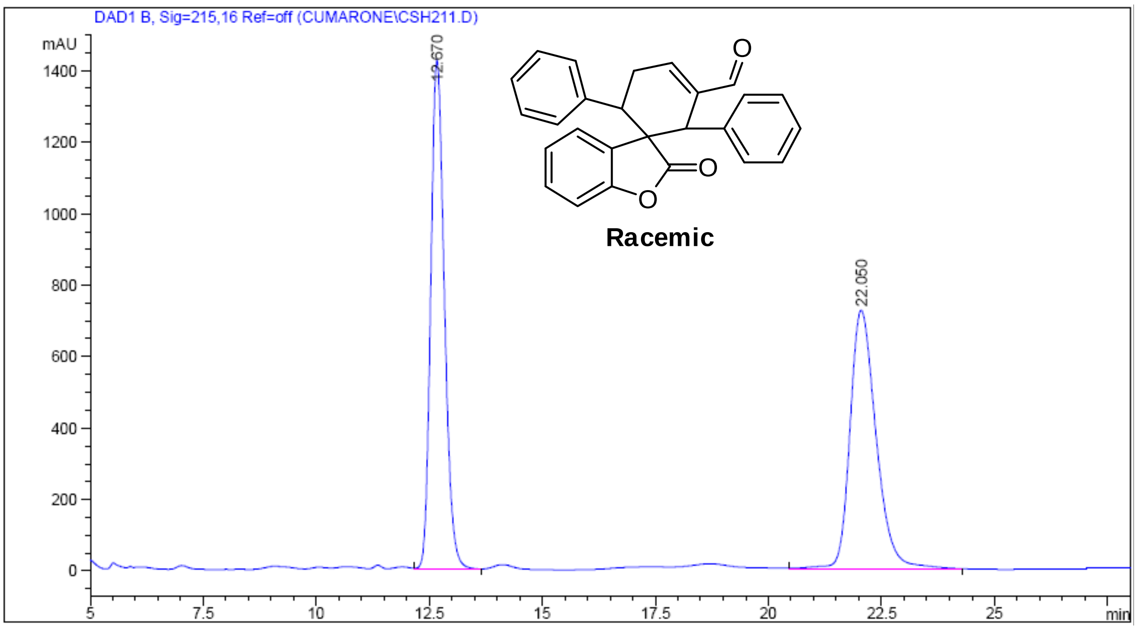
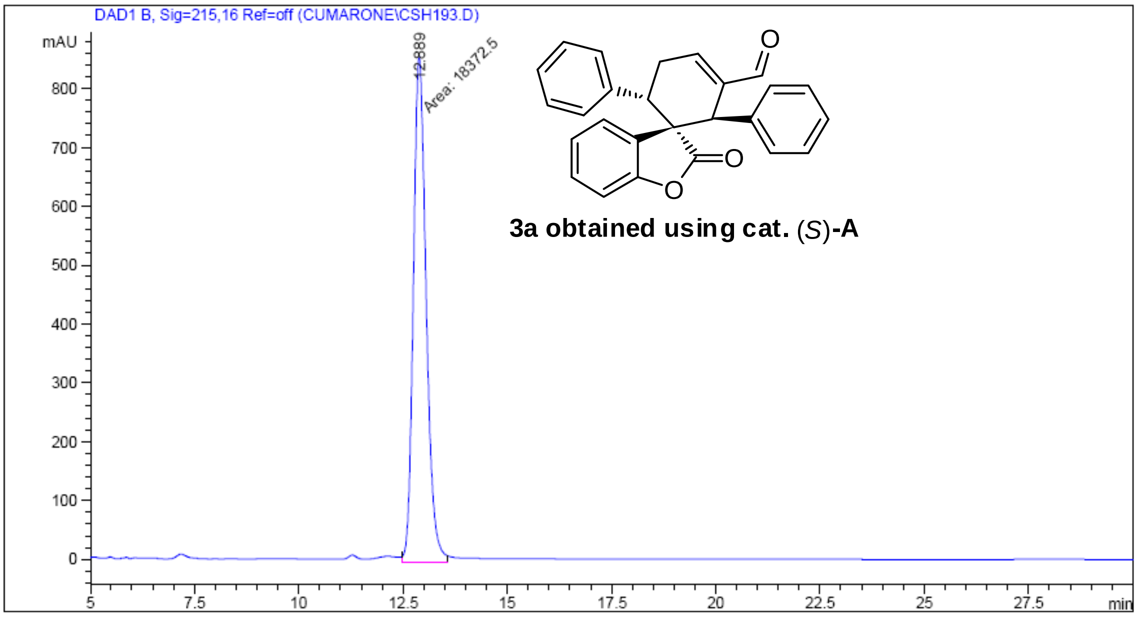


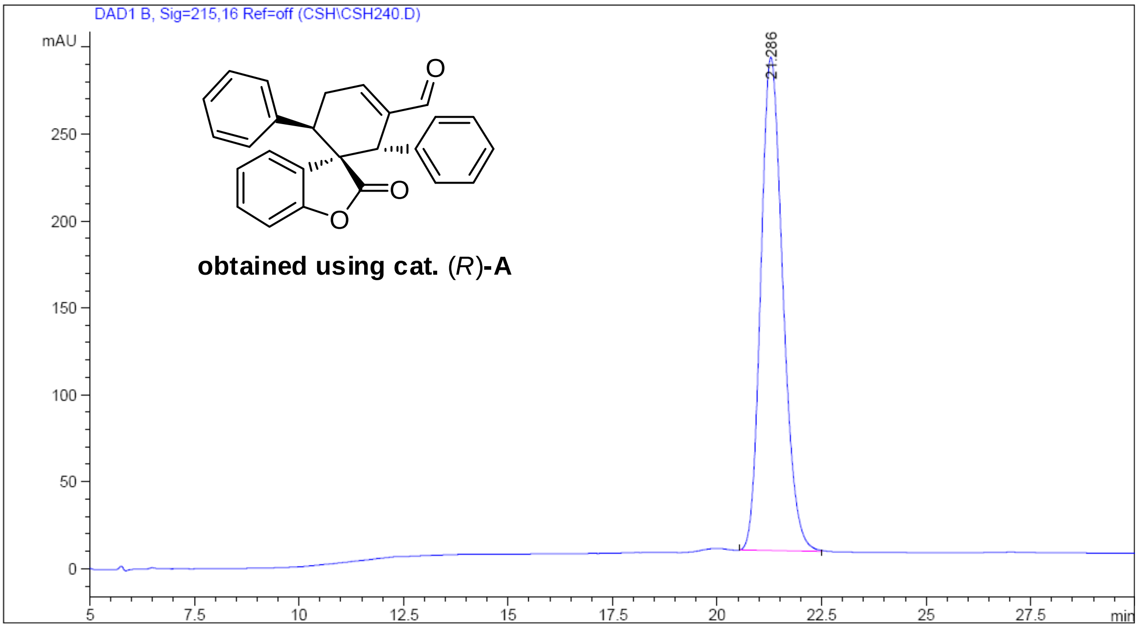
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  12.670 VB    0.3280 3.00631e4 1425.75720  50.6164
   2  22.050 VB    0.6201 2.93308e4  724.75903  49.3836

Totals :                  5.93939e4 2150.51624
```



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  12.889 MM    0.3574 1.83725e4  856.83191 100.0000

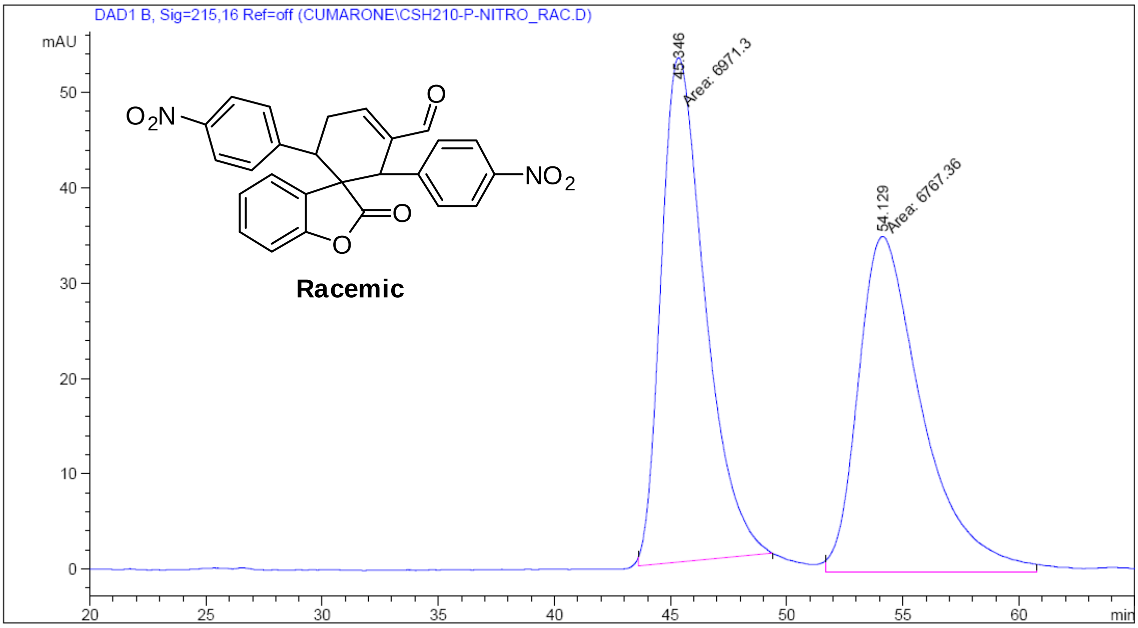
Totals :                  1.83725e4  856.83191
```



obtained using cat. (*R*)-A

```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  21.286 BB    0.5680 1.04068e4  283.69678 100.0000

Totals :                  1.04068e4  283.69678
```



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  45.346 MM     2.1949 6971.30371   52.93671  50.7422
   2  54.129 MM     3.1970 6767.35645   35.27945  49.2578

Totals :                   1.37387e4   88.21616
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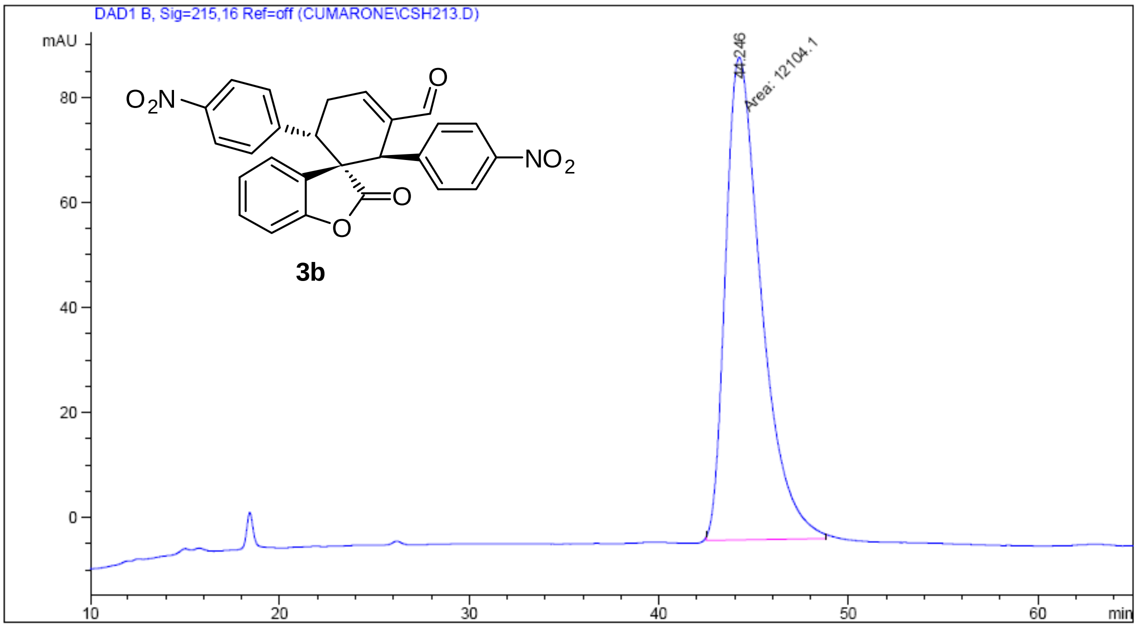
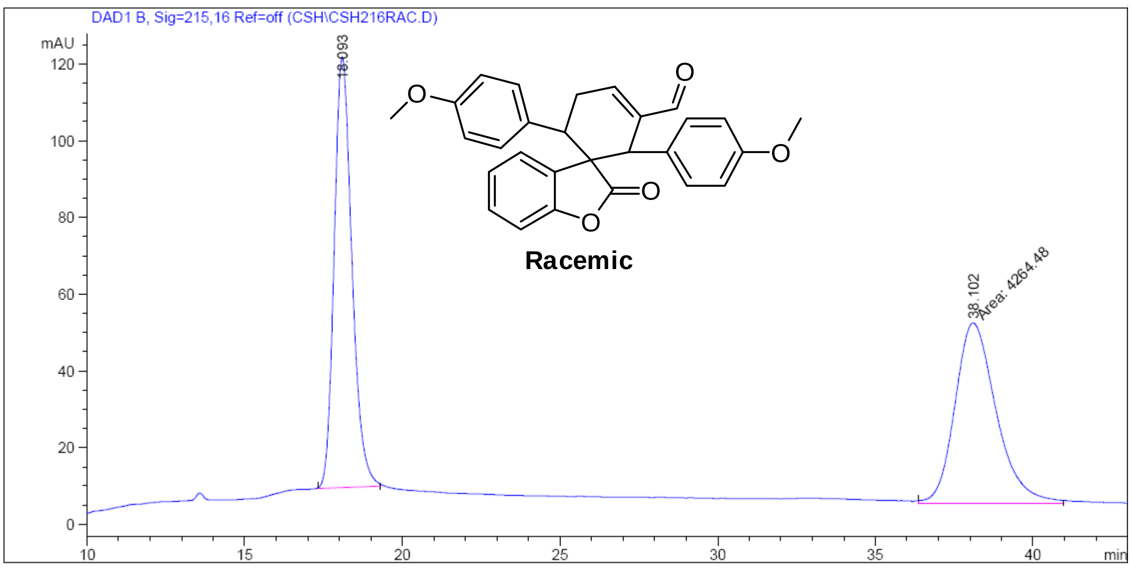


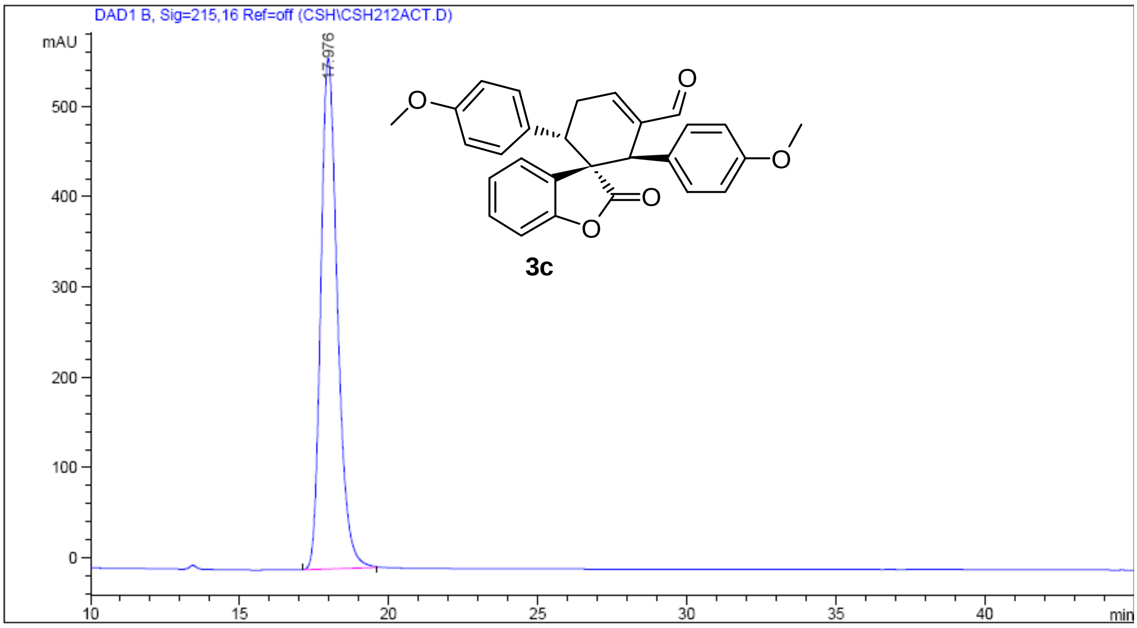
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  44.246 MM     2.1959 1.21041e4   91.86876 100.0000

Totals :                   1.21041e4   91.86876
```



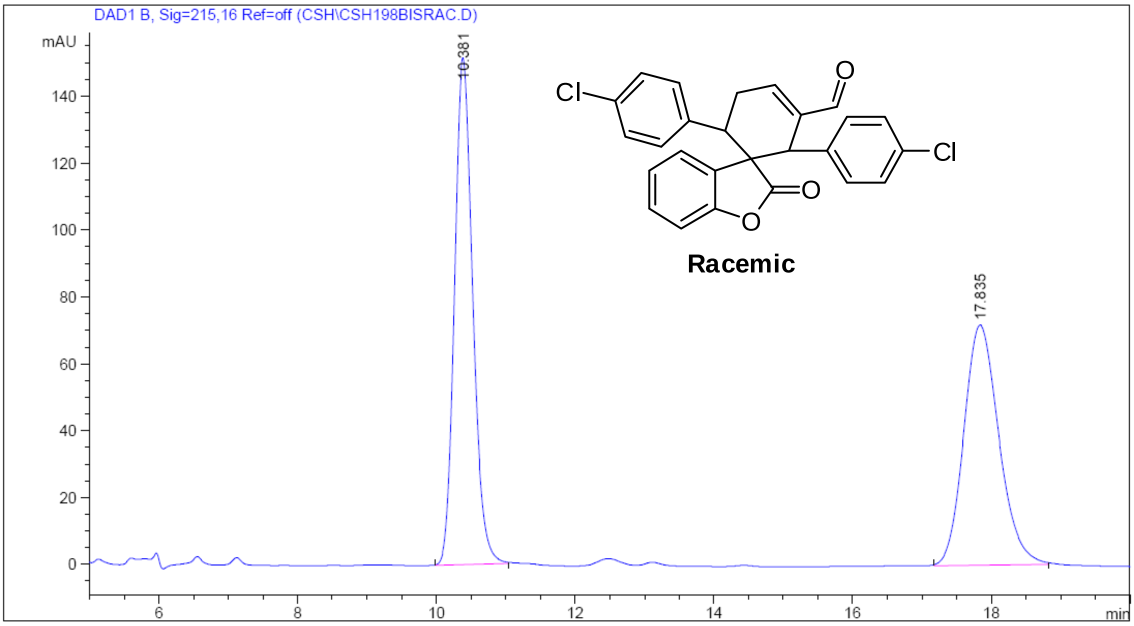
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  18.093 BB    0.6027 4397.37793  112.34100  50.7672
   2  38.102 MM    1.5126 4264.47656   46.98909  49.2328

Totals :                  8661.85449  159.33009
```



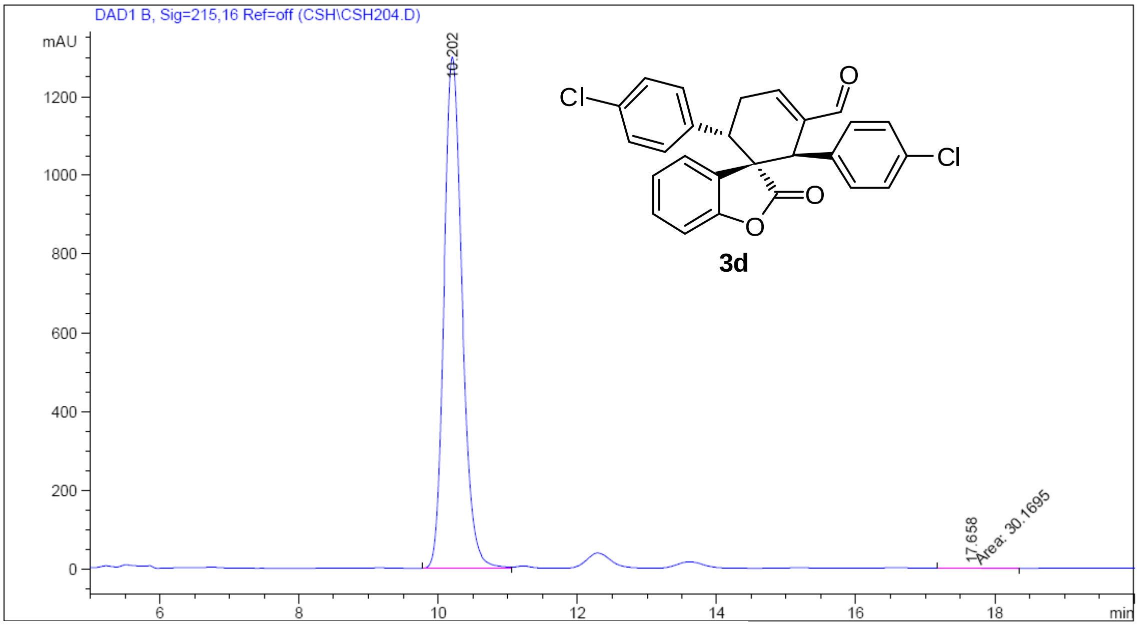
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  17.976 BB    0.5964 2.19693e4  566.55658 100.0000

Totals :                  2.19693e4  566.55658
```



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.381 BB    0.2806 2761.79541  151.53151  52.3209
   2  17.835 BB    0.5407 2516.77246   71.83670  47.6791

Totals :                  5278.56787  223.36821
```



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.202 BV    0.2789 2.34725e4 1298.76355  99.8716
   2  17.658 MM    0.7654   30.16950 6.56904e-1   0.1284

Totals :                  2.35027e4  1299.42045
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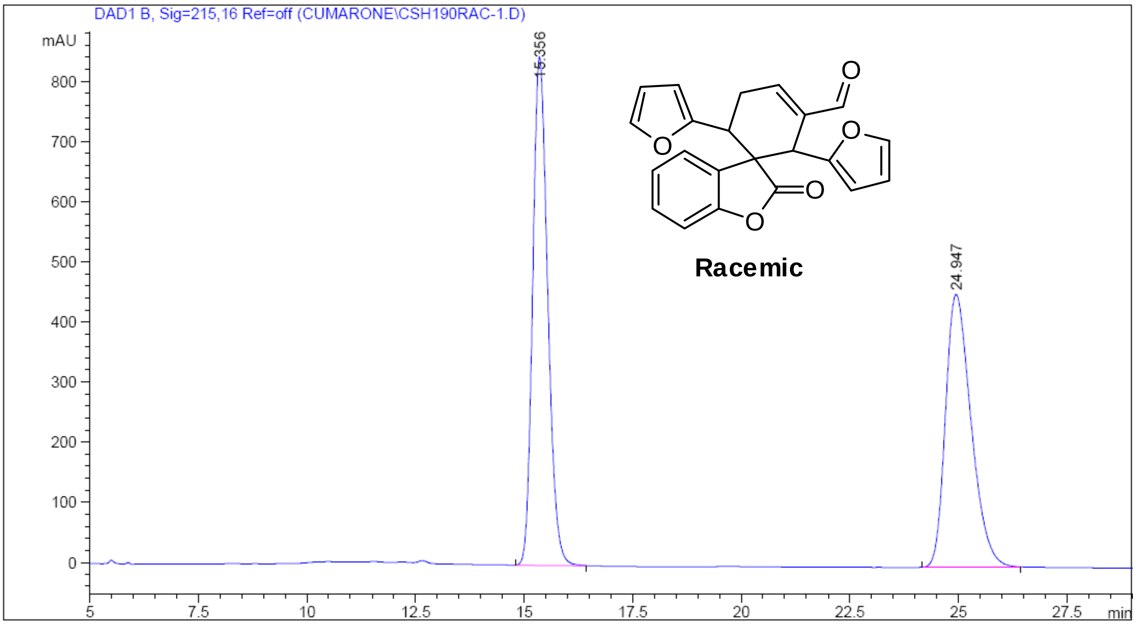
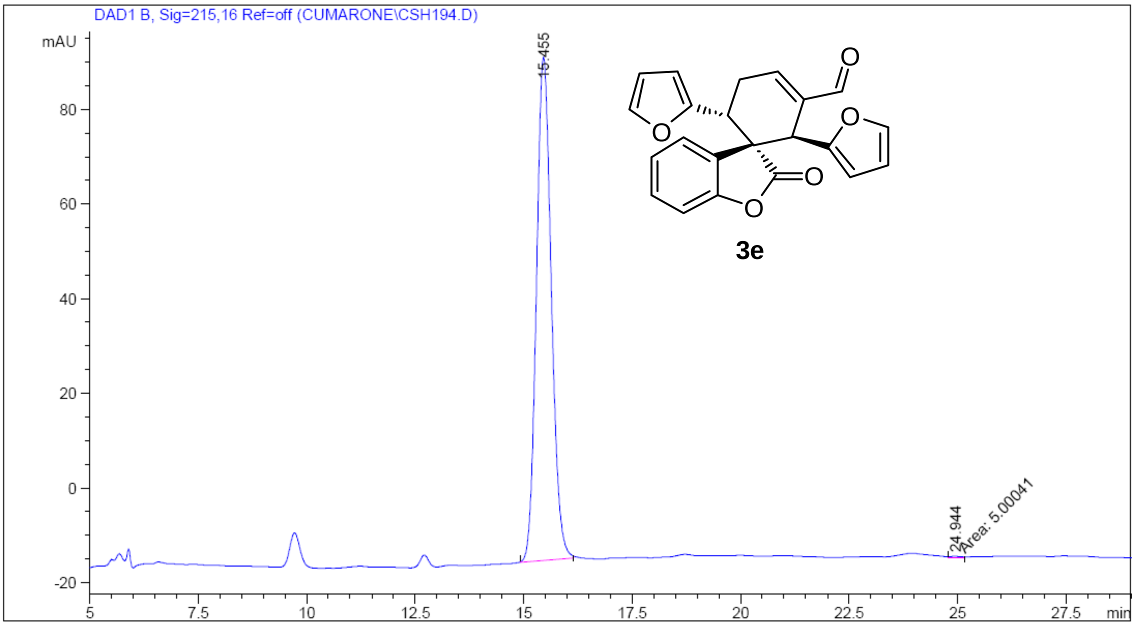


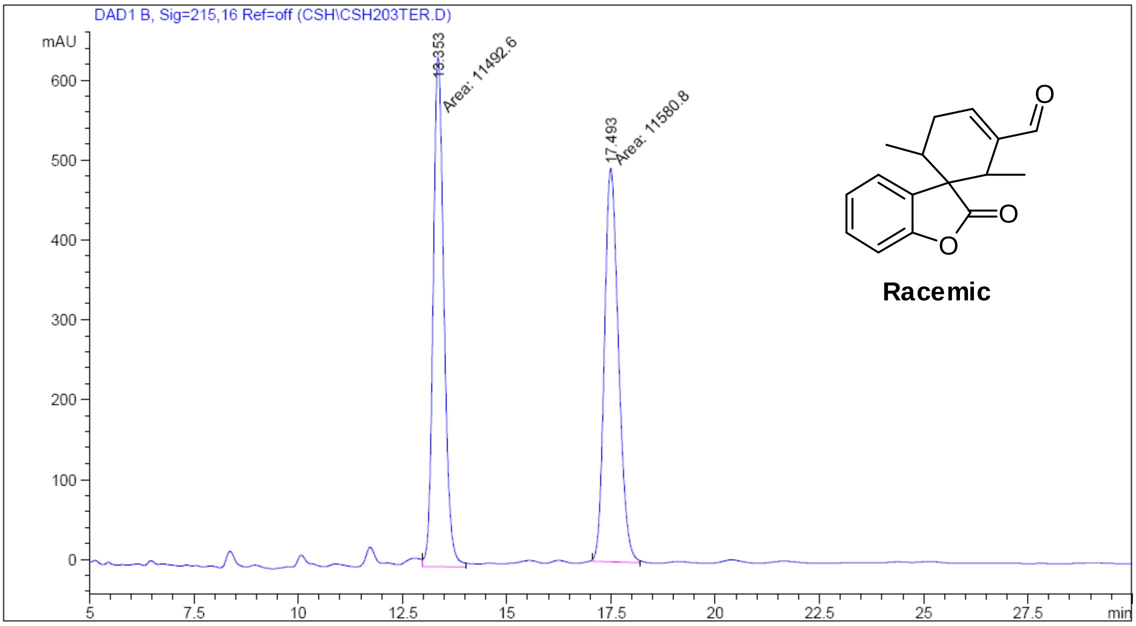
```
Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  15.356 BB    0.3718 2.02829e4  845.85413  52.1302
   2  24.947 BB    0.6307 1.86252e4  453.93668  47.8698

Totals :                  3.89081e4 1299.79080
```



```
Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  15.455 BB    0.3681 2534.28735  106.31599  99.8031
   2  24.944 MM    0.3252    5.00041 2.56305e-1   0.1969

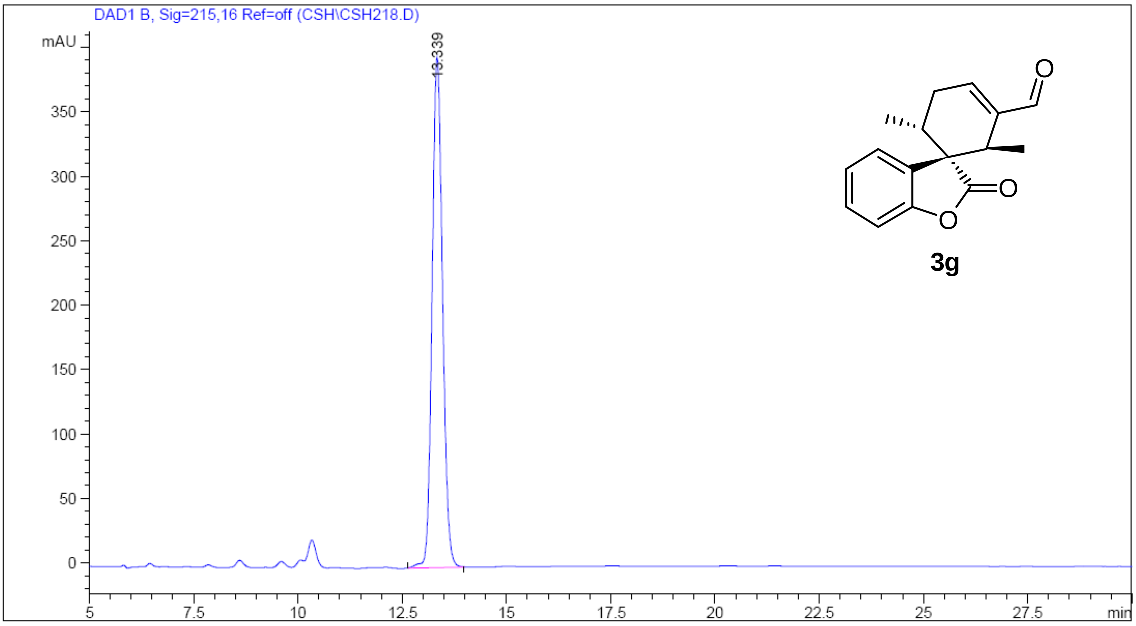
Totals :                  2539.28776  106.57230
```



Racemic

```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  13.353 MM    0.3005 1.14926e4  637.48785  49.8089
   2  17.493 MM    0.3920 1.15808e4  492.41885  50.1911

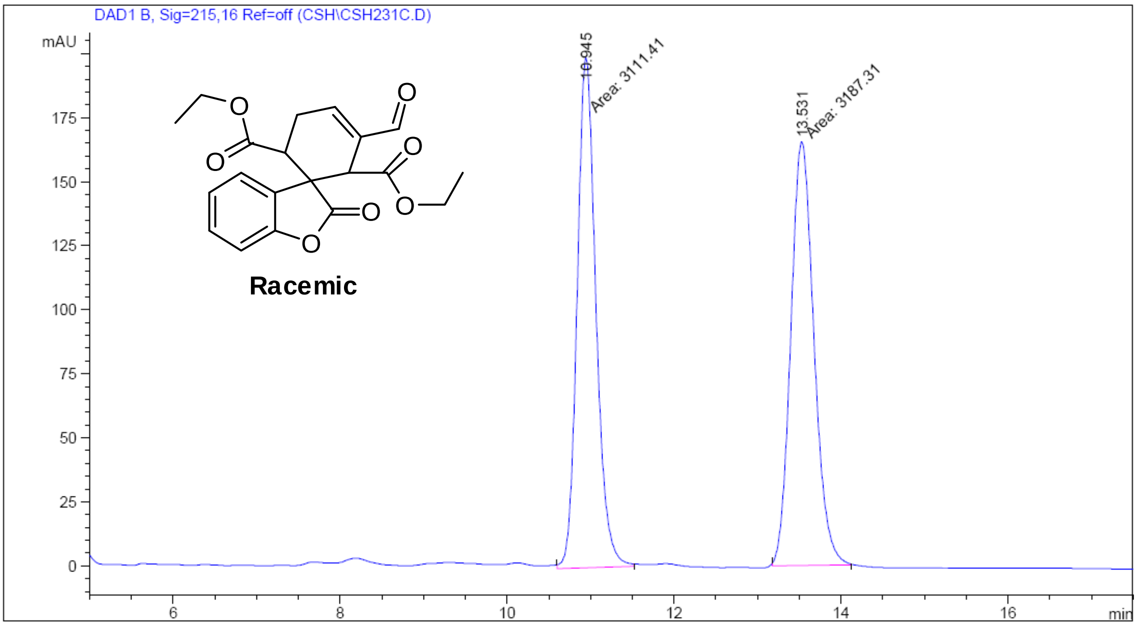
Totals :                  2.30733e4  1129.90671
```



3g

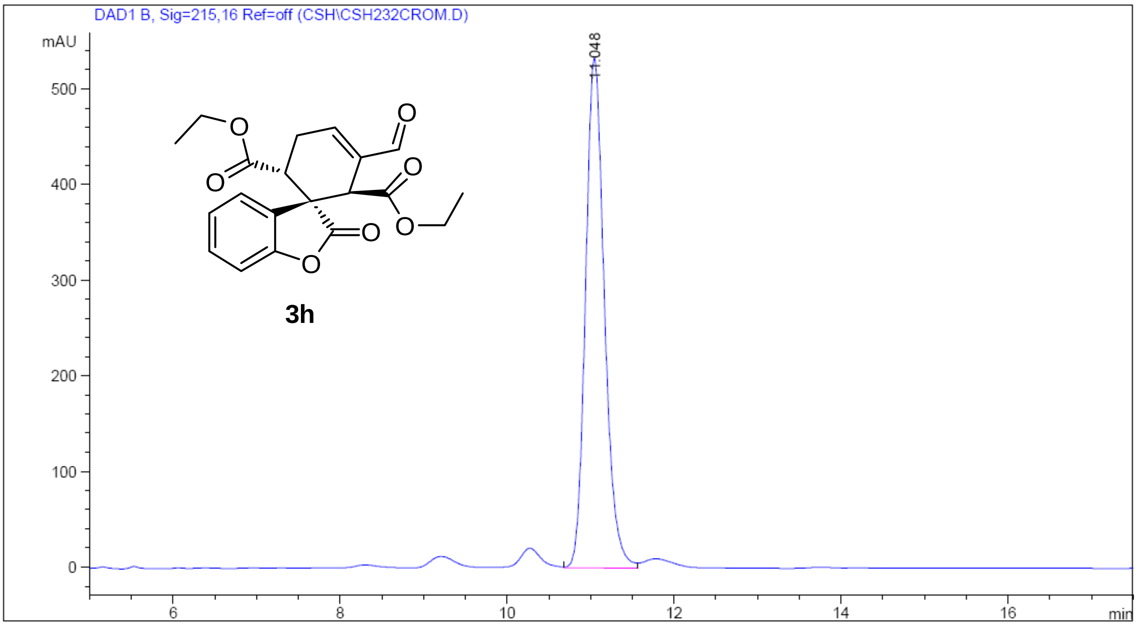
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  13.339 BB    0.2689 6886.70850  395.95444 100.0000

Totals :                  6886.70850  395.95444
```



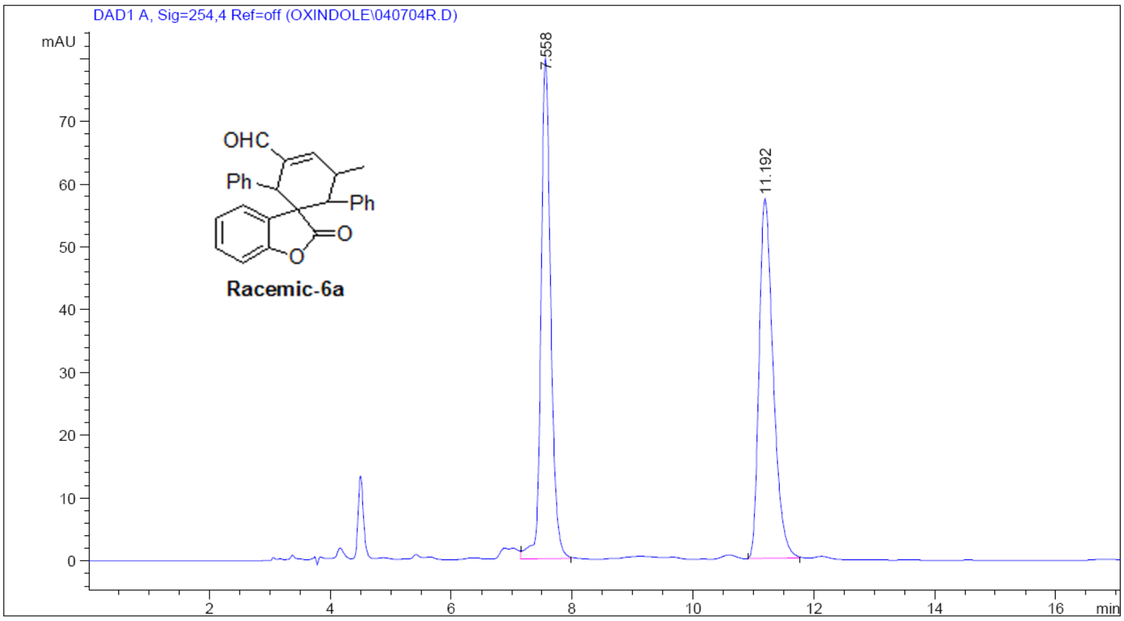
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  10.945 MM    0.2604 3111.40918  199.17015  49.3975
   2  13.531 MM    0.3212 3187.31494  165.39786  50.6025

Totals :                  6298.72412  364.56801
```



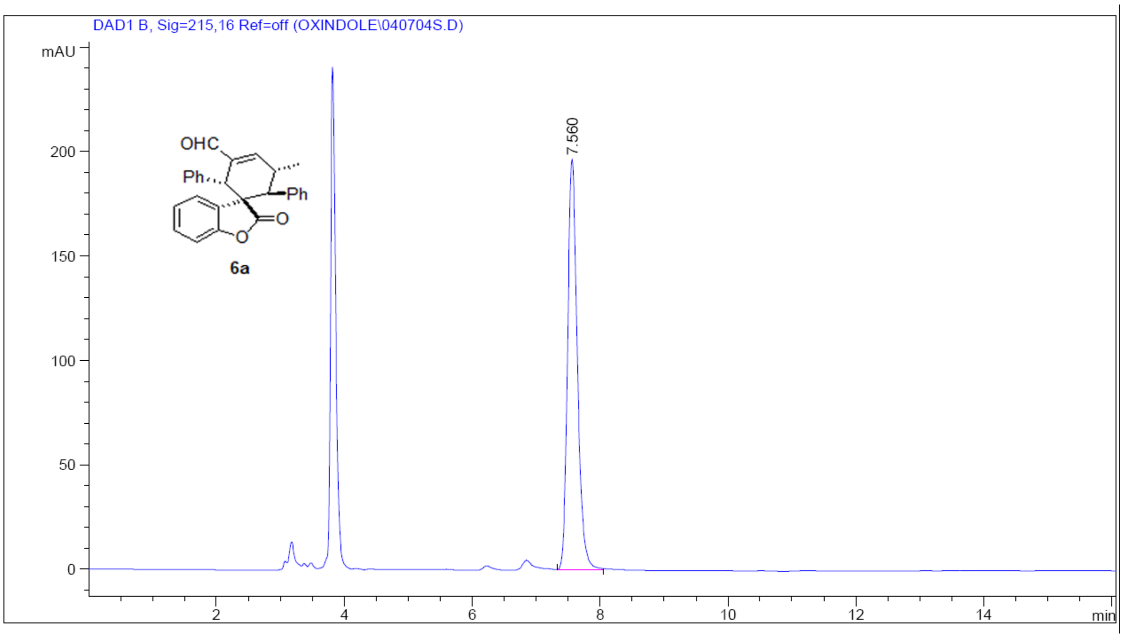
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  11.048 VV    0.2412 8376.80273  533.57141 100.0000

Totals :                  8376.80273  533.57141
```



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   7.558 VB    0.1685  893.03986   79.82891  49.0211
  2  11.192 BB    0.2493  928.70636   57.24773  50.9789

Totals :                 1821.74622  137.07664
```



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   7.560 BB    0.1609 2070.22314  196.46526 100.0000

Totals :                 2070.22314  196.46526
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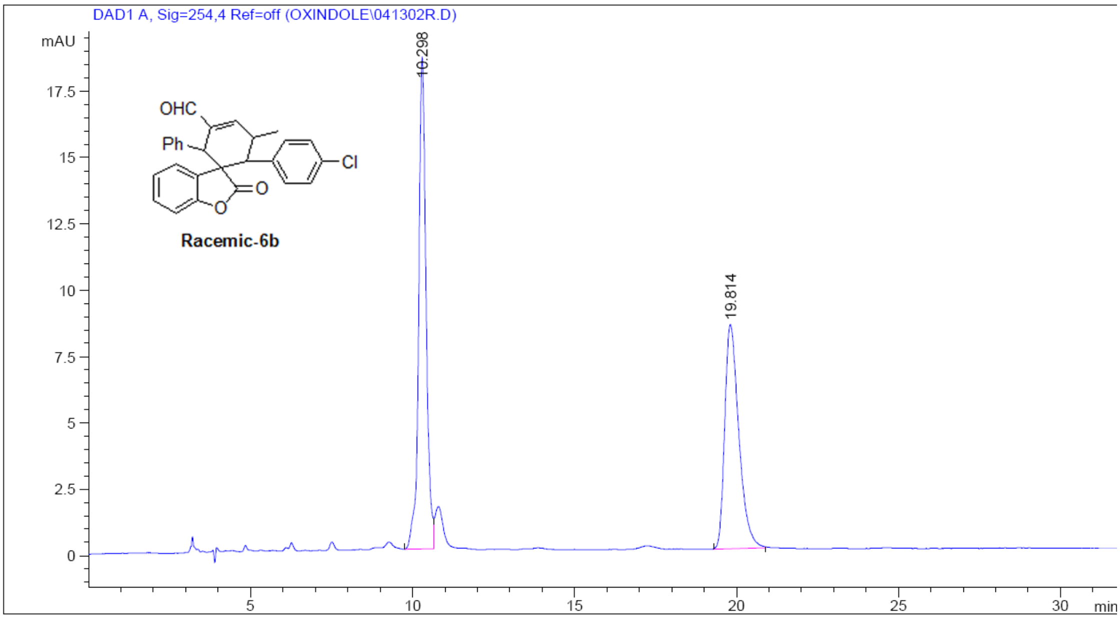

```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  10.298 VV    0.2396  295.30478   18.56240  53.6445
   2  19.814 BB    0.4605  255.17995    8.44560  46.3555

Totals :                   550.48473   27.00800
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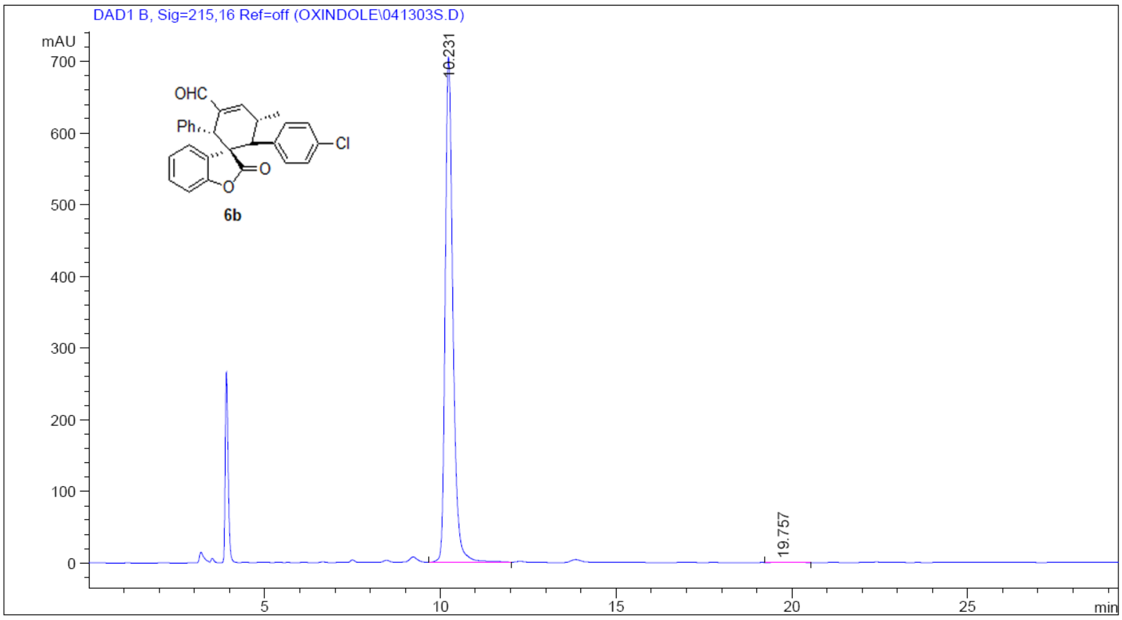
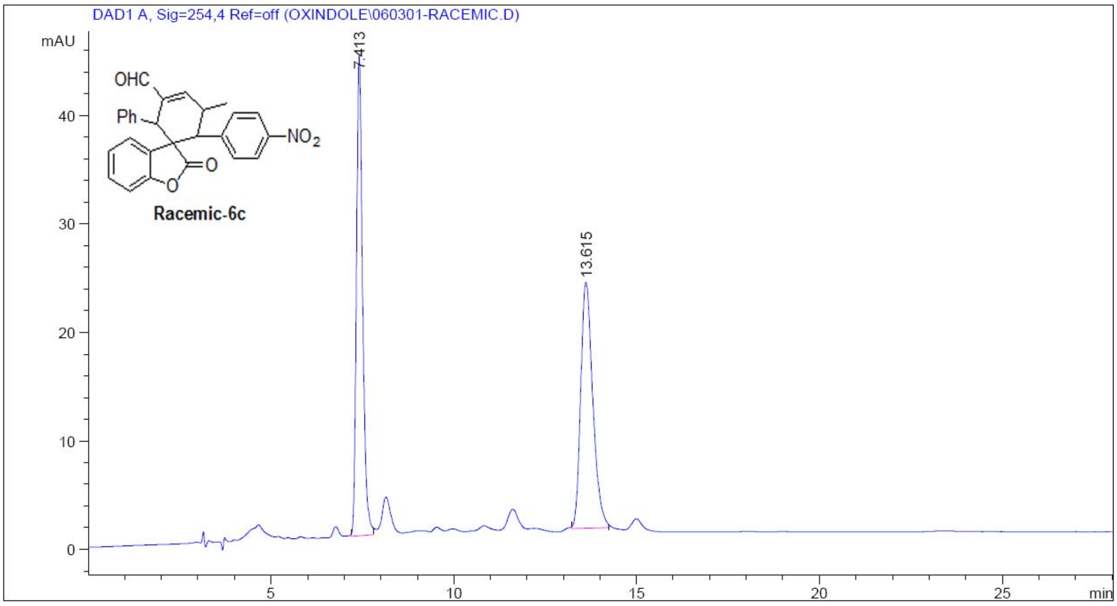


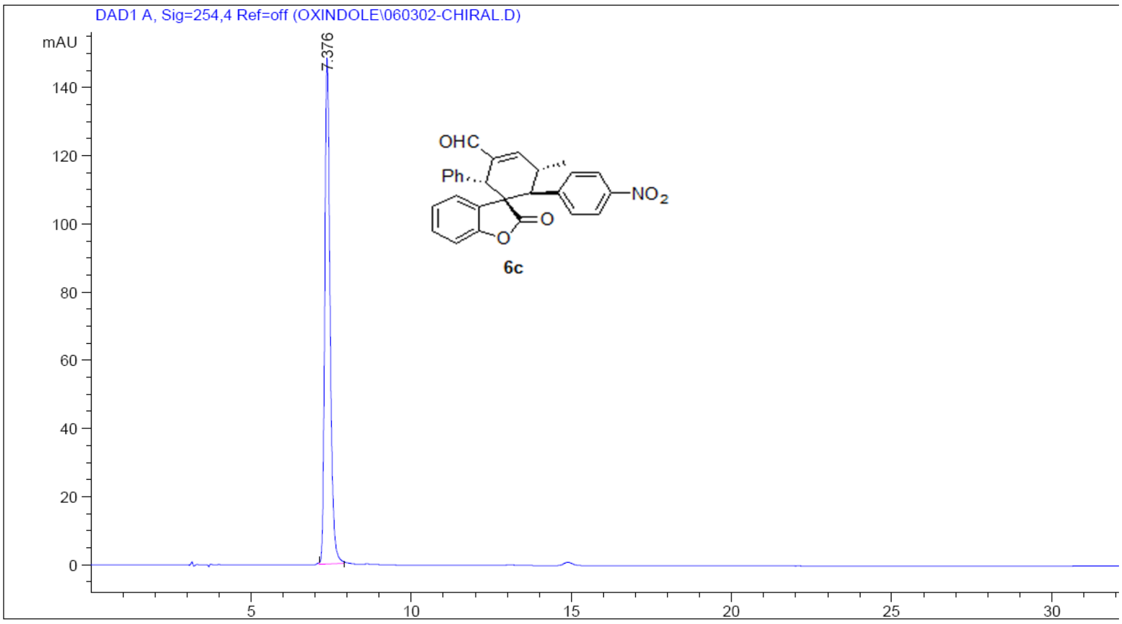
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  10.231 VV    0.2332 1.08471e4   706.24823  99.7885
   2  19.757 BB    0.5324   22.98749 6.50257e-1   0.2115

Totals :                  1.08701e4   706.89849
```



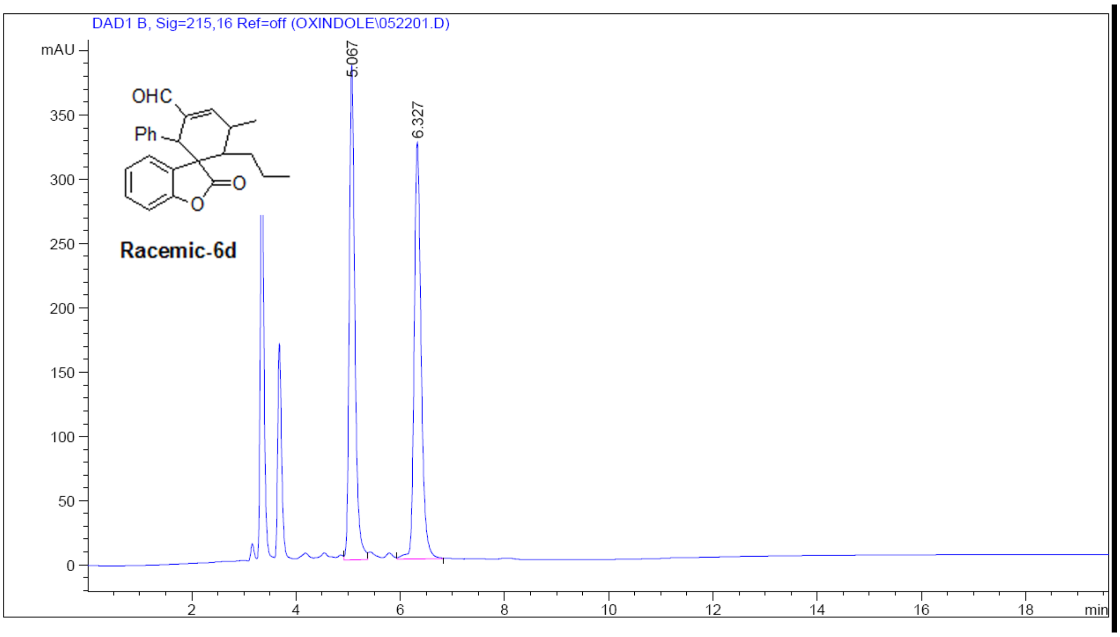
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.413 BB    0.1785  517.09528   44.21056  49.8833
   2  13.615 BB    0.3514  519.51532   22.66383  50.1167

Totals :                  1036.61060   66.87438
```



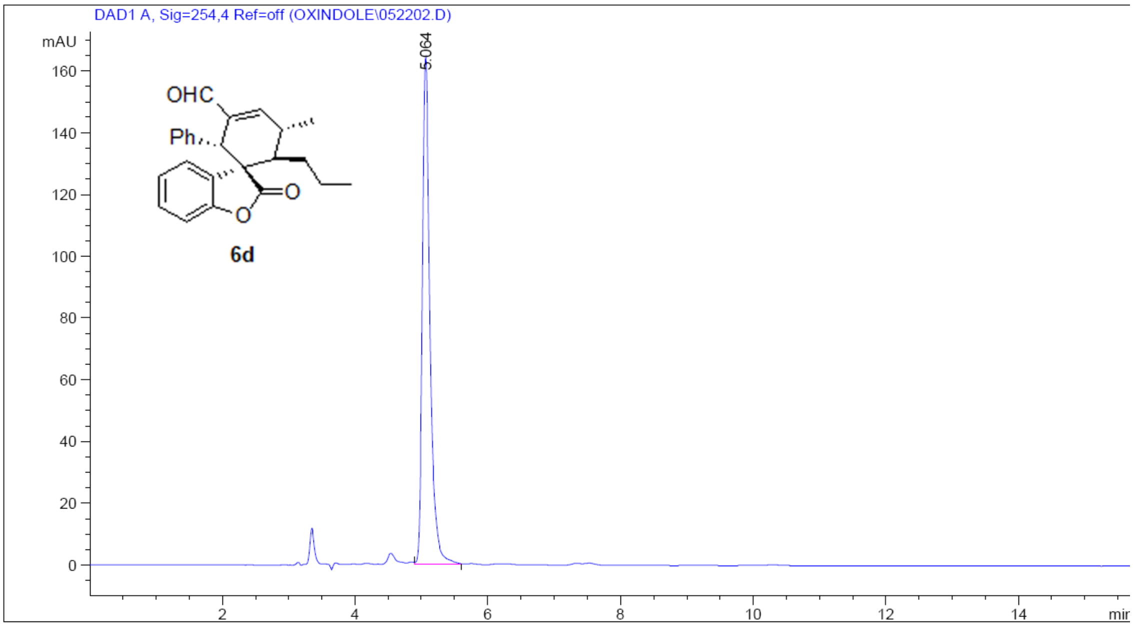
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.376 BB    0.1764 1709.62134  148.41934 100.0000

Totals :                  1709.62134  148.41934
```

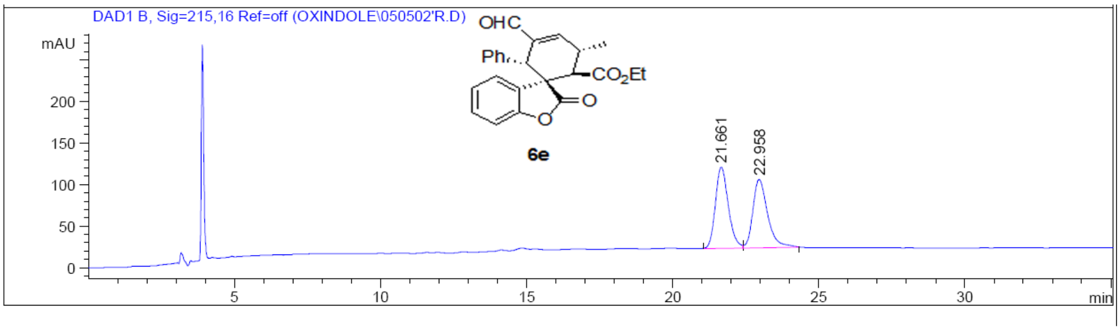


```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   5.067 VV    0.1128 2863.28296  384.98648  48.8830
   2   6.327 VB    0.1398 2994.13232  323.98511  51.1170

Totals :                  5857.41528  708.97159
```

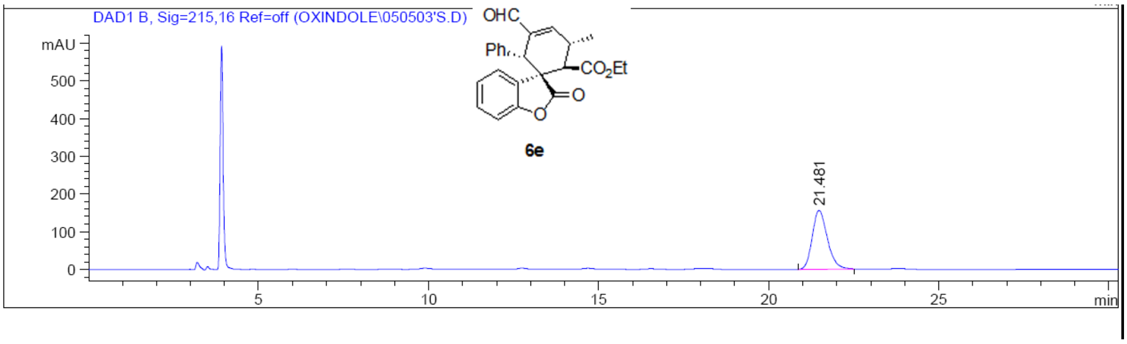


```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   5.064 VB    0.1207 1304.41675  164.21667 100.0000
```



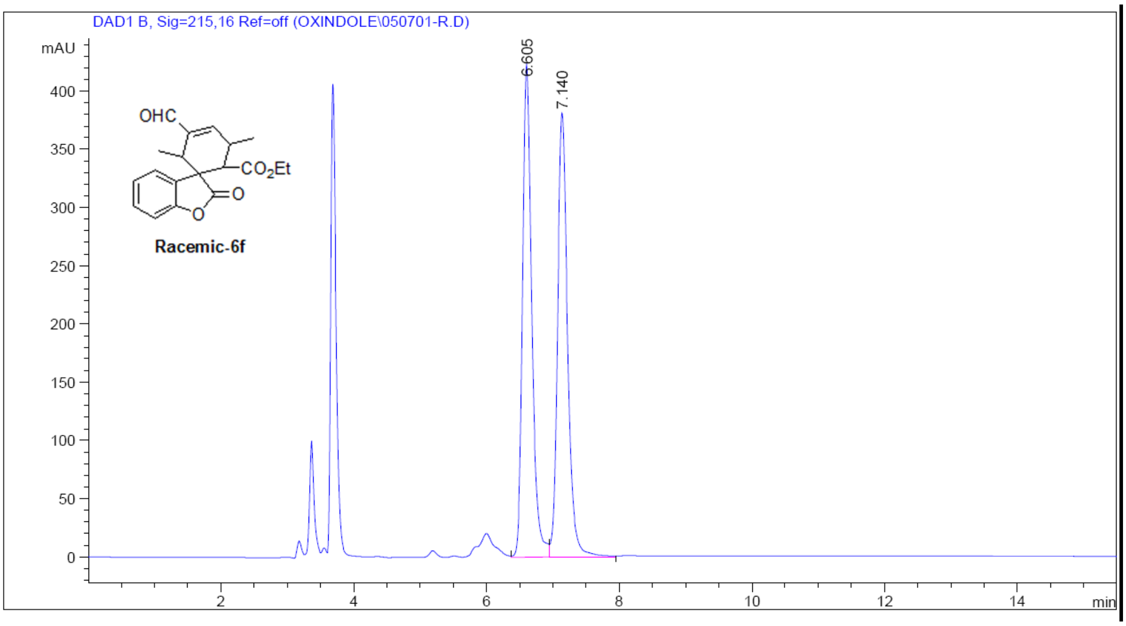
```
Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  21.661 BV    0.4717 2996.48315   97.72817  50.9459
   2  22.958 VB    0.5330 2885.21094   82.30801  49.0541

Totals :                  5881.69409  180.03618
```

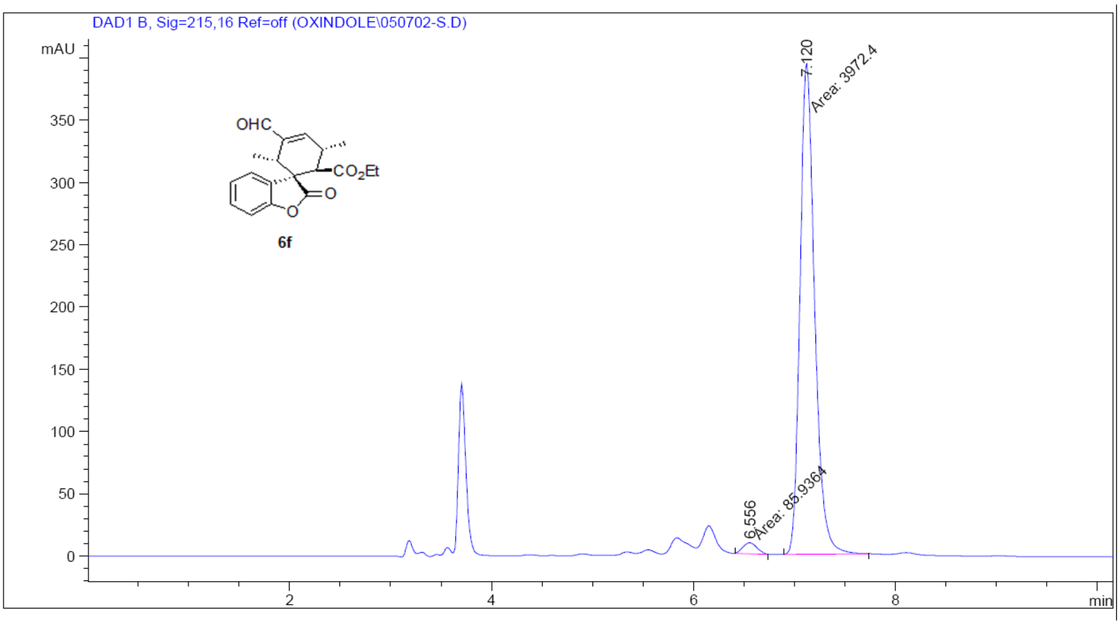


```
Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------
   1  21.481 BB    0.4745 4815.64795  155.86356 100.0000

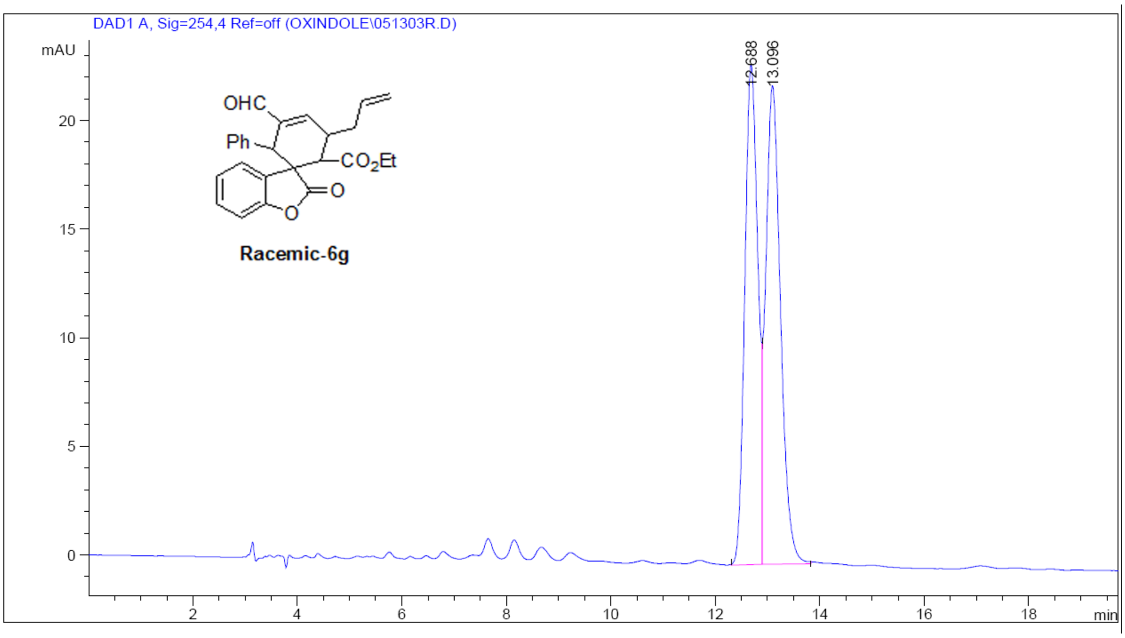
Totals :                  4815.64795  155.86356
```



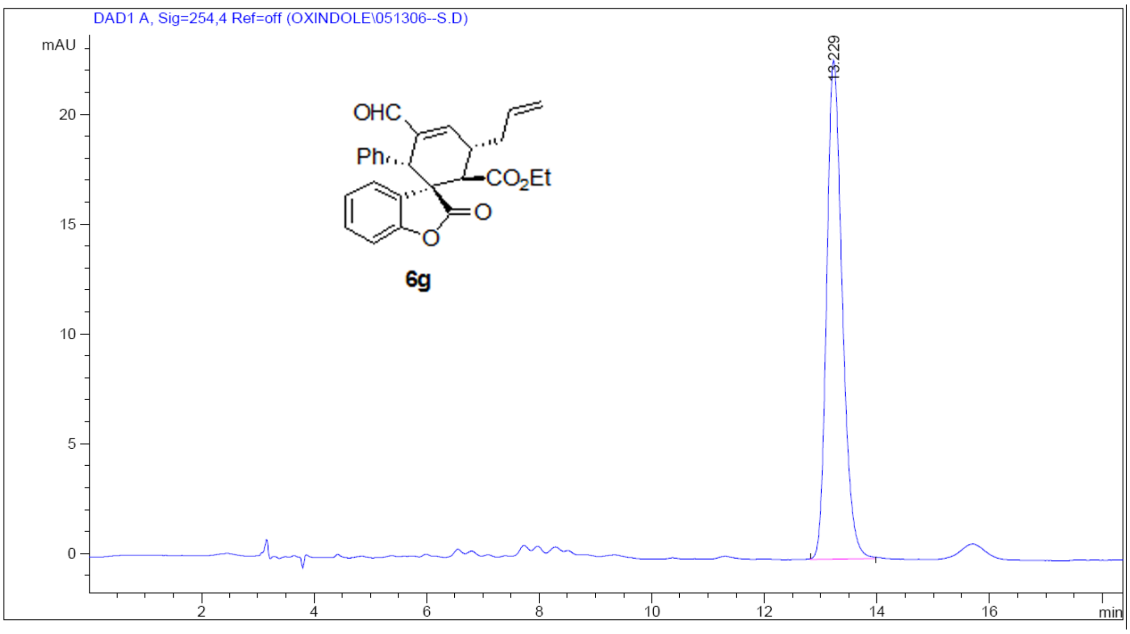
```
Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------
   1   6.605 VV    0.1473 4122.35059  424.40817  50.7078
   2   7.140 VV    0.1586 4007.27393  381.41028  49.2922
```



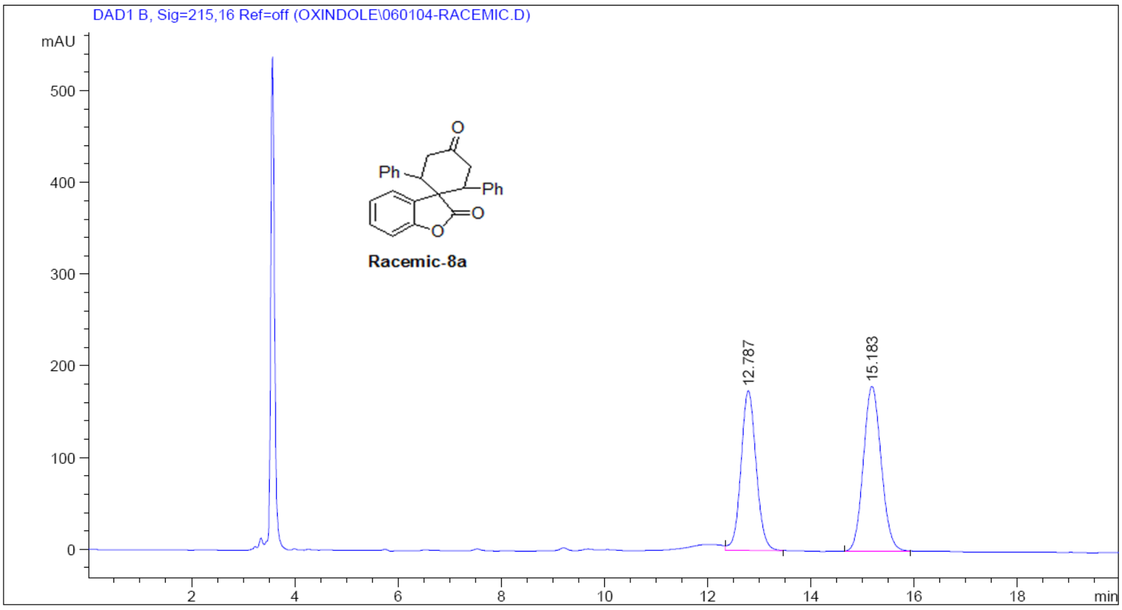
```
Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   6.556 MM    0.1627   85.93645    8.80227   2.1175
   2   7.120 MM    0.1678 3972.39990  394.46863  97.8825
```



```
Peak RetTime Type  Width      Area       Height      Area
  #   [min]        [min]    [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  12.688 BV     0.2673  396.86142   22.99793  47.6897
   2  13.096 VB     0.2964  435.31317   22.04634  52.3103
```

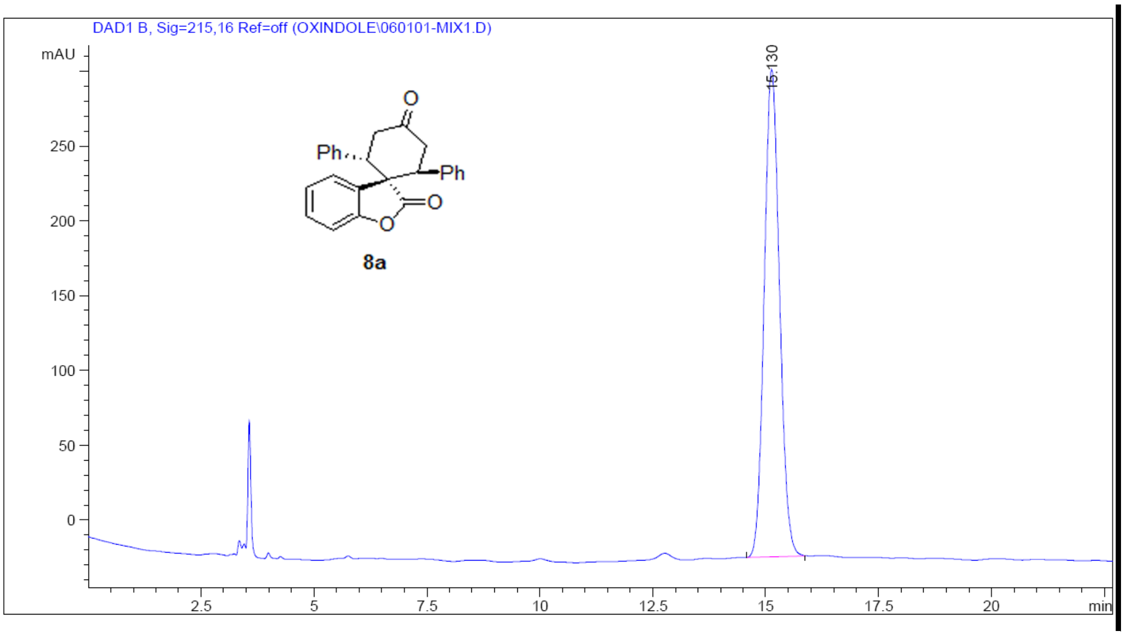


```
Peak RetTime Type  Width      Area       Height      Area
  #   [min]        [min]    [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  13.229 BB     0.2949  438.18790   22.73048 100.0000
```



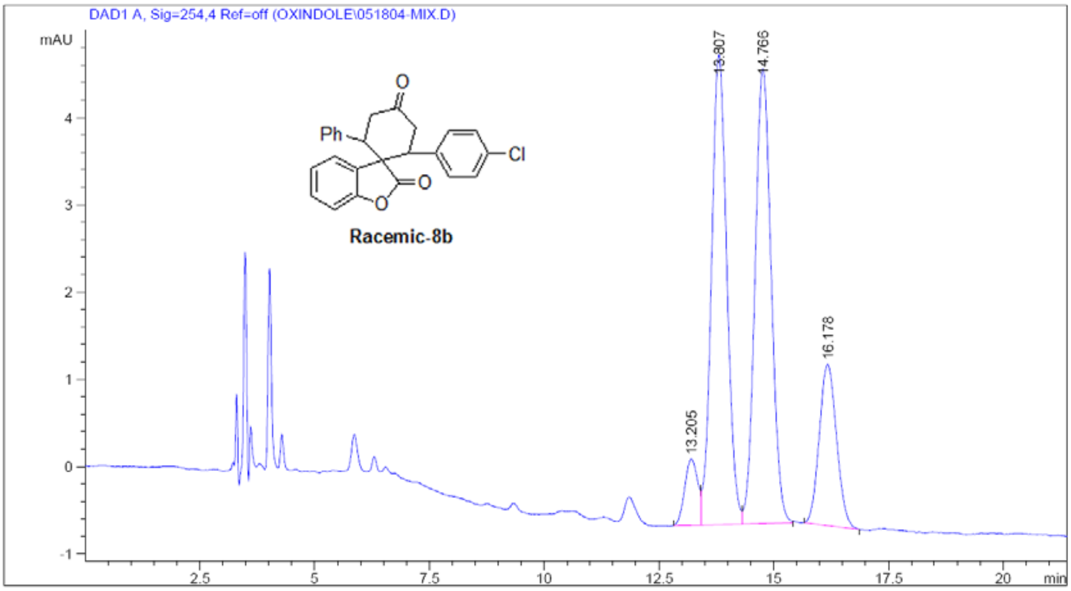
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  12.787 VB    0.3144 3557.84595  174.12607  45.1816
   2  15.183 BB    0.3721 4316.69287  179.77072  54.8184

Totals :                  7874.53882  353.89679
```

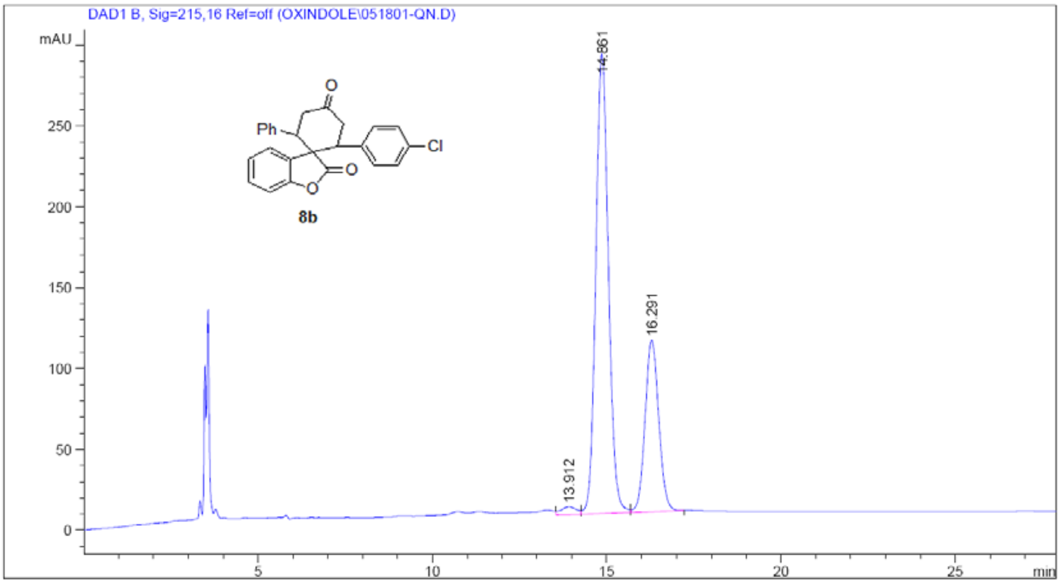


```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  15.130 BB    0.3665 7662.42773  325.67902 100.0000

Totals :                  7662.42773  325.67902
```

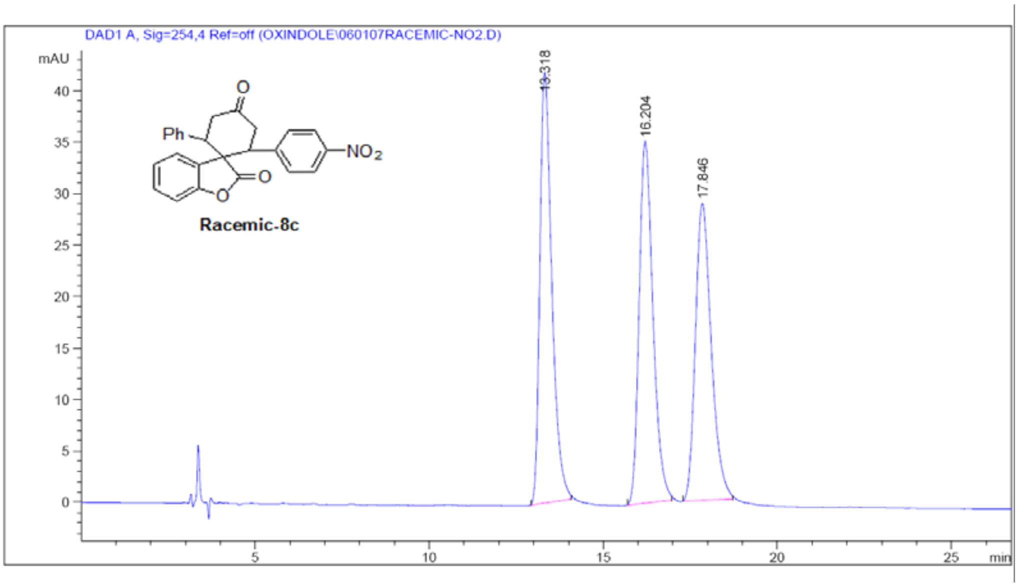


```
Peak RetTime Type  Width      Area       Height      Area
  #   [min]        [min]    [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  13.205 BV    0.2982   15.02096 7.61356e-1   4.7541
   2  13.807 VV    0.3613  125.19480    5.38422  39.6236
   3  14.766 VB    0.3832  127.39693    5.21051  40.3205
   4  16.178 BB    0.4090   48.34781    1.84911  15.3019
```



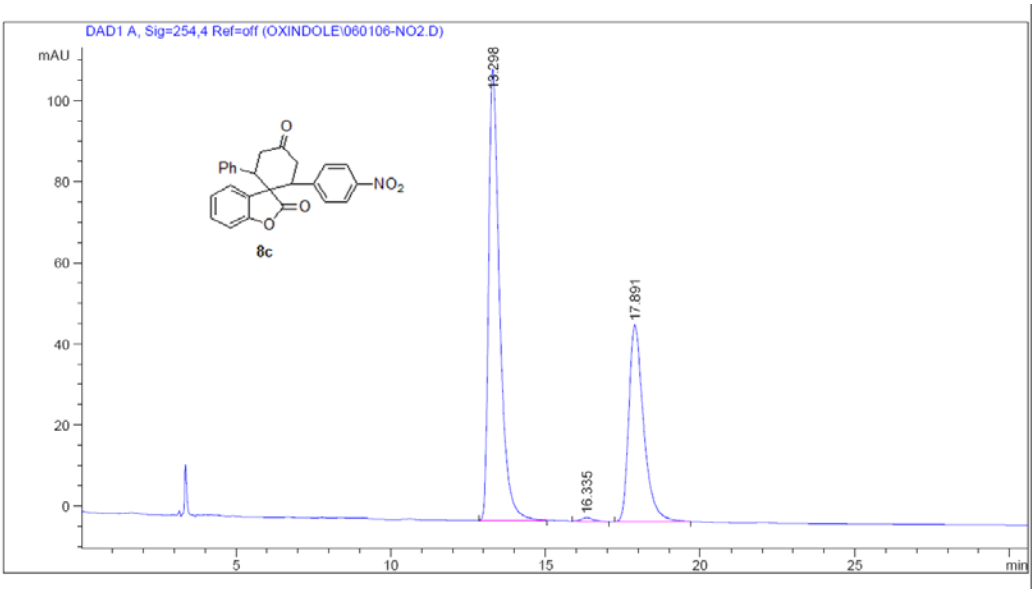
```
Peak RetTime Type  Width      Area       Height      Area
  #   [min]        [min]    [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  13.912 VV    0.4350  141.54593    4.73223   1.3900
   2  14.861 VV    0.3896 7146.10107  283.94275  70.1754
   3  16.291 VB    0.4244 2895.55713  106.08842  28.4346


----|-------|----|-------|----------|----------|
Totals :                  1.01832e4  394.76339
```



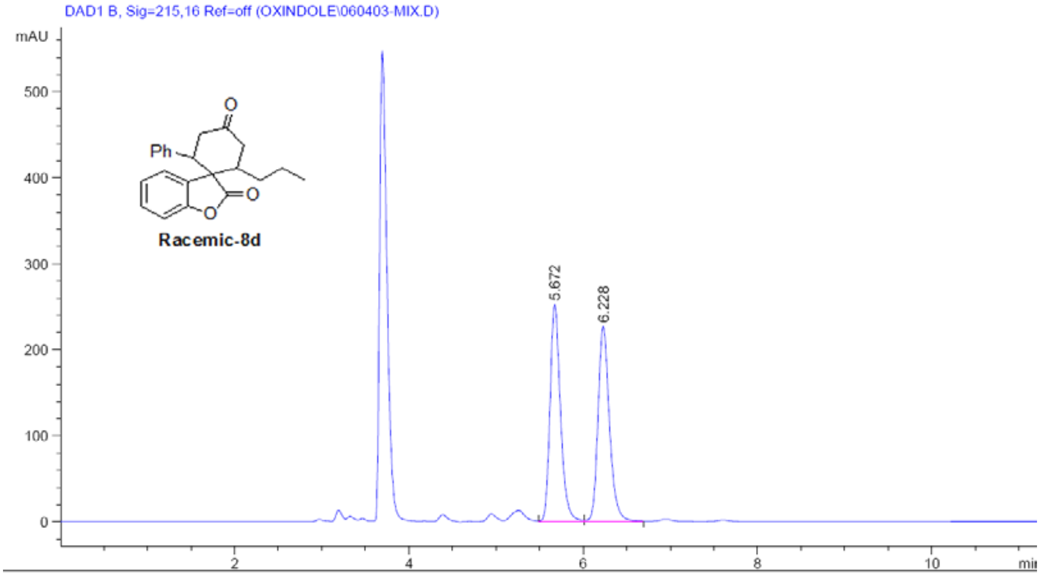
```
Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [mAU*s]     [mAU]         %
----|-------|----|-------|----------|----------|--------
   1  13.318 BB    0.3622  996.94922   41.81077  34.6261
   2  16.204 BB    0.4238  969.32153   35.14362  33.6665
   3  17.846 BB    0.4852  912.91486   28.84921  31.7074

Totals :                  2879.18561  105.80360
```



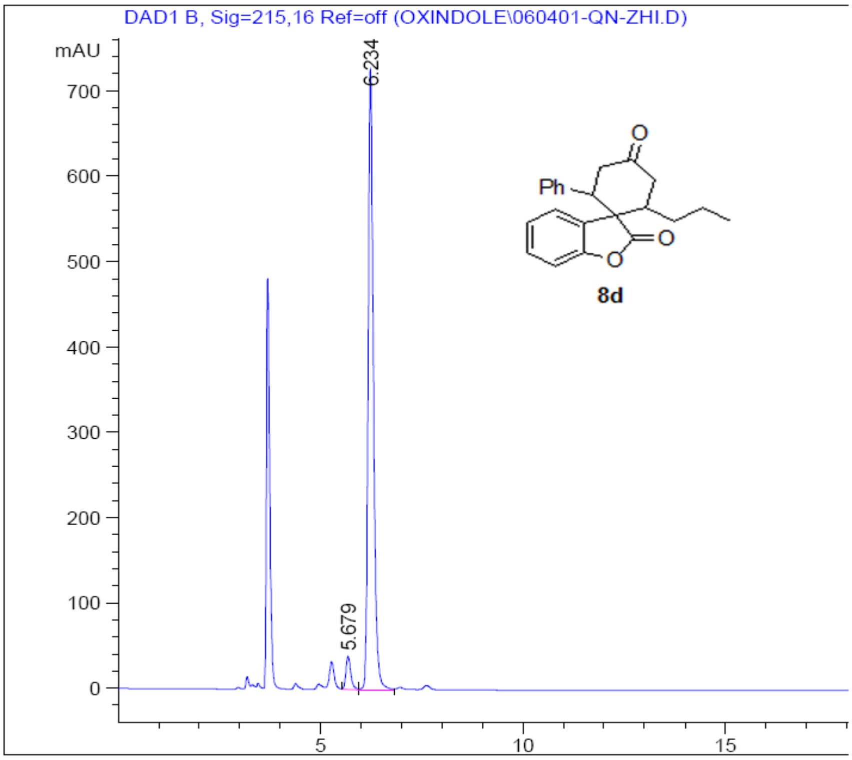
```
Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [mAU*s]     [mAU]         %
----|-------|----|-------|----------|----------|--------
   1  13.298 BB    0.3735 2759.95361  111.21998  62.7875
   2  16.335 BB    0.3966   22.43440 8.21449e-1   0.5104
   3  17.891 BB    0.5020 1613.31628   48.50914  36.7021

Totals :                  4395.70429  160.55057
```



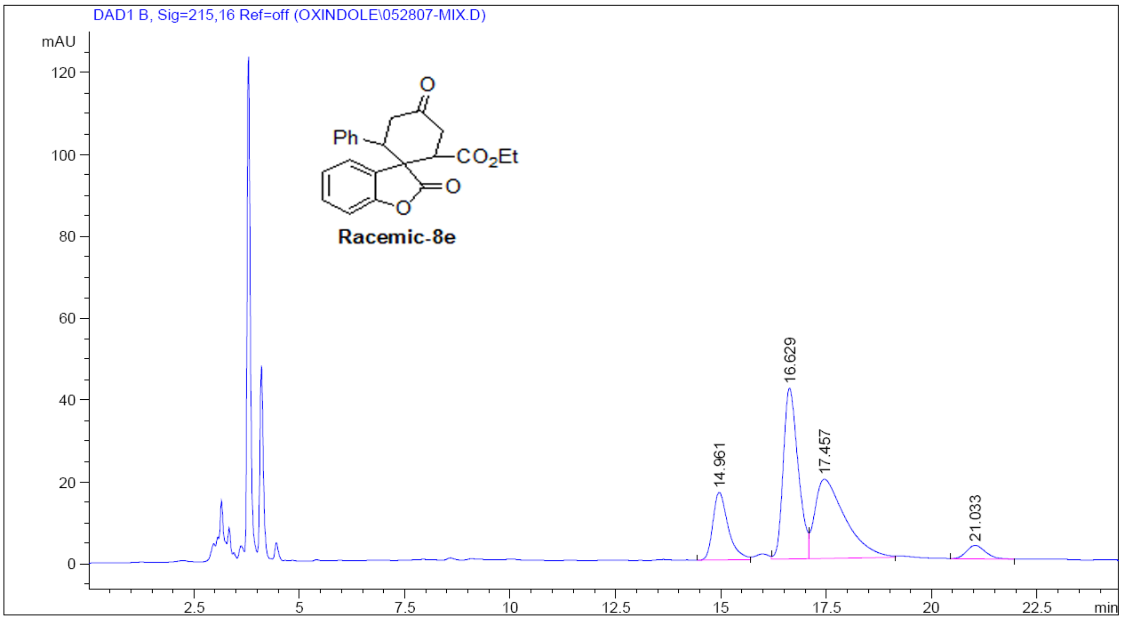
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   5.672 VV    0.1254 2109.42700  252.73001  50.3026
   2   6.228 VB    0.1411 2084.04736  227.09576  49.6974

Totals :                  4193.47437  479.82578
```



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------
   1   5.679 VV    0.1284  328.50851   38.95597   4.6957
   2   6.234 VB    0.1390 6667.37256  726.91235  95.3043

Totals :                  6995.88107  765.86832
```



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  14.961 VV    0.3804  417.68616   16.55015  16.5353
   2  16.629 VV    0.3788 1032.48853   41.70578  40.8739
   3  17.457 VB    0.7327  973.63269   19.36196  38.5439
   4  21.033 BB    0.4824  102.22626    3.27292   4.0469

Totals :                  2526.03364   80.89081
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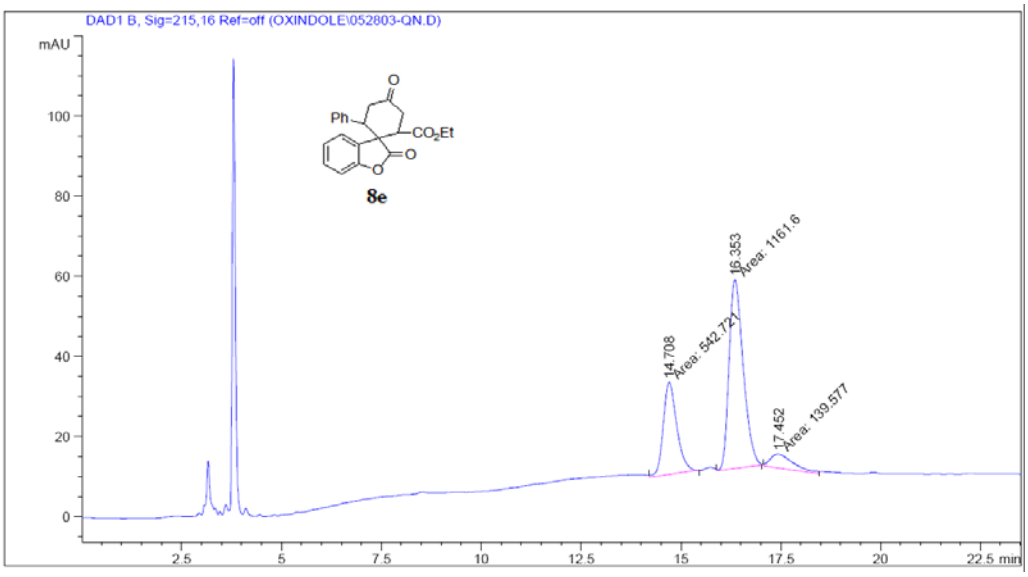
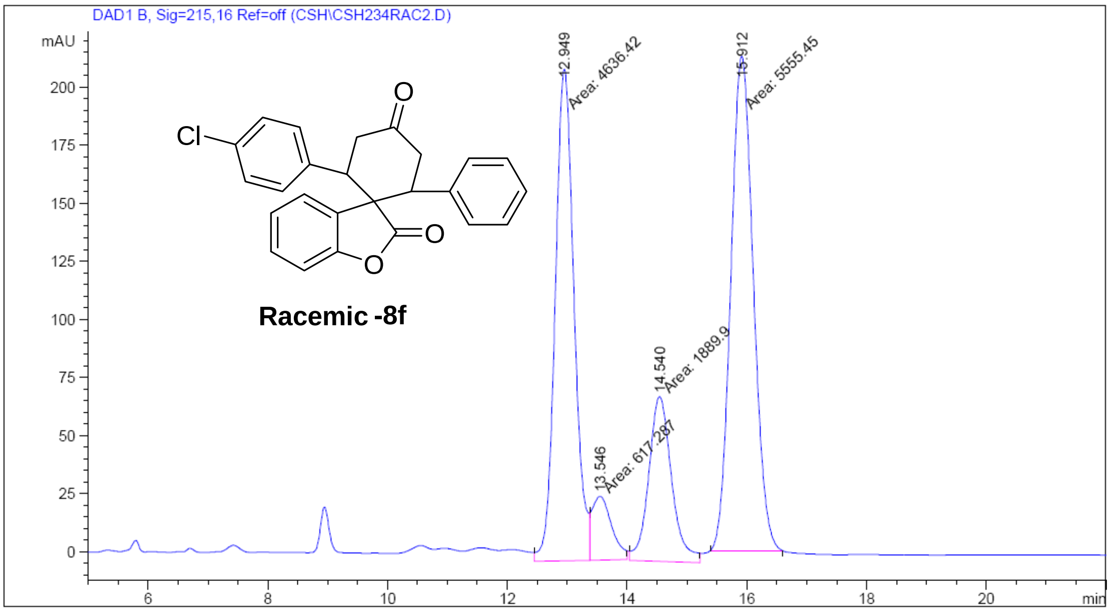


```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  14.708 MM    0.3935  542.72095   22.98631  29.4333
   2  16.353 MM    0.4109 1161.60205   47.11982  62.9970
   3  17.452 MM    0.6689  139.57697    3.47776   7.5697

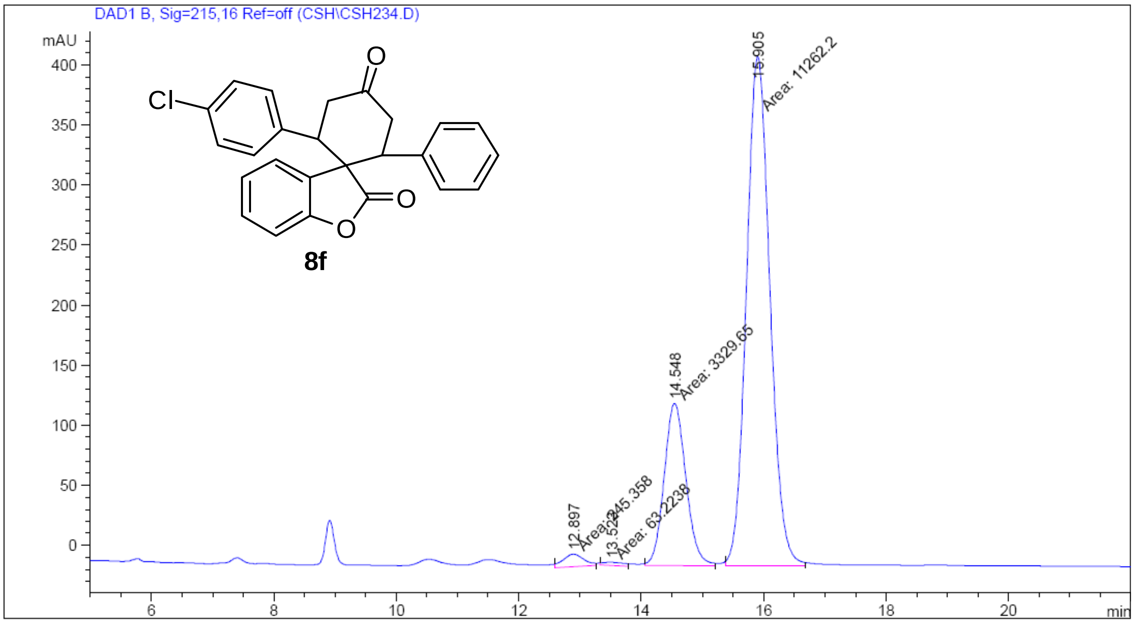
Totals :                  1843.89996   73.58389
```



Racemic -8f

```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  12.949 MF    0.3653 4636.42383  211.54099  36.5100
   2  13.546 FM    0.3742  617.28735   27.49318   4.8609
   3  14.540 MM    0.4438 1889.90161   70.97491  14.8822
   4  15.912 MM    0.4351 5555.44873  212.78580  43.7469

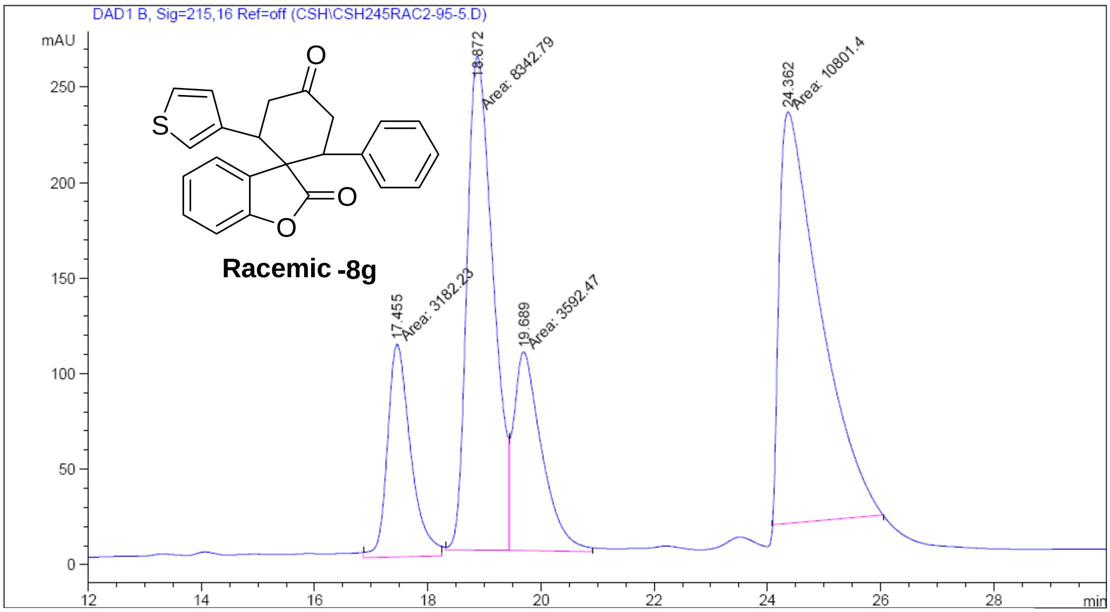
Totals :                  1.26991e4   522.79487
```



8f

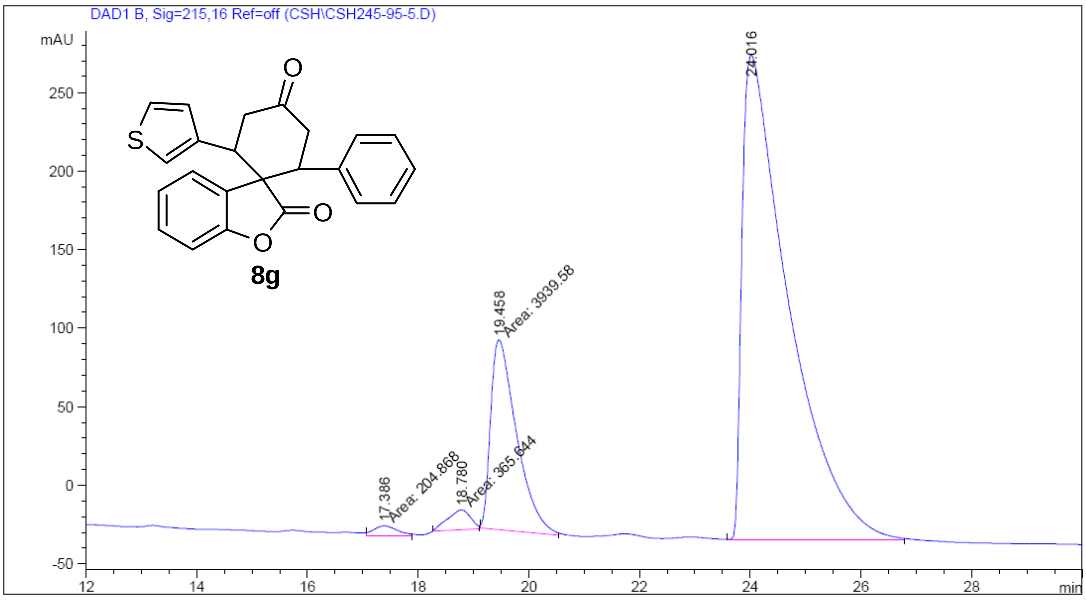
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  12.897 MM    0.3962  245.35780   10.32174   1.6466
   2  13.523 MM    0.3919   63.22379    2.68895   0.4243
   3  14.548 MM    0.4109 3329.65063  135.03899  22.3460
   4  15.905 MM    0.4432 1.12622e4   423.48660  75.5831

Totals :                  1.49004e4   571.53629
```



```
Peak RetTime Type  Width      Area       Height      Area
 #    [min]        [min]    [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|---------|
  1  17.455 MM    0.4772 3182.22583  111.13631  12.2776
  2  18.872 MF    0.5384 8342.79004  258.24600  32.1881
  3  19.689 FM    0.5752 3592.47461  104.10073  13.8604
  4  24.362 MM    0.8370 1.08014e4   215.08942  41.6739

Totals :                 2.59189e4   688.57246
```



```
Peak RetTime Type  Width      Area       Height      Area
 #    [min]        [min]    [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|---------|
  1  17.386 MM    0.5106  204.86830    6.68758    0.9099
  2  18.780 MM    0.4828  365.64371   12.62217    1.6239
  3  19.458 MM    0.5430 3939.58154  120.93026   17.4968
  4  24.016 BB    0.8339 1.80060e4   308.08212   79.9695

Totals :                 2.25161e4   448.32213
```