SUPPORTING INFORMATION

Xavier Companyo[a], Andrea Mazzanti[b], Albert Moyano[a], Anna Janecka[c],
Ramon Rios[ad]*

CONTENTS

General methods:

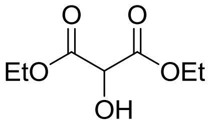
Chemicals and solvents were either purchased *puriss p.A.* from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), conc. H_2SO_4 (60 mL), and H_2O (940 mL) followed by heating or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040-0.063 mm), ^{1}H NMR, ^{19}F NMR and ^{13}C NMR spectra were recorded on Varian AS 400. Chemical shifts are given in ppm relative to tetramethylsilane (TMS) and the coupling constants *J* are given in Hz. The spectra were recorded in $CDCl_3$ as solvent at room temperature. TMS served as internal standard ($\delta = 0$ ppm) for ^{1}H NMR, $CDCl_3$ was used as internal standard ($\delta = 77.0$ ppm) for ^{13}C NMR and TFA was used as external standard for ^{19}F NMR. High-resolution mass spectra were recorded on a Bruker MicrOTOF spectrometer.

SYNTHESIS OF STARTING METERIALS

Procedure for the preparation of the MBH-alcohols: To a round bottom flask charged with MeOH (0.75 eq.) was added the arylaldehyde (1 eq.) and methyl acrylate (1.2 eq.). To the solution was then added 1,4-diaza-bicyclo[2.2.2]octane (50 mol %) and the solution was stirred for 48-96 h. The crude reaction mixture directly was purified by flash column chromatography.(Hexane/EtOAc mixtures).

Procedure for the preparation of MBH-carbonates: To a solution of the Morita-Baylis-Hillman alcohol (1eq.) in CH_2Cl_2 (0.5 M) was added $(Boc)_2O$ (1.05 eq.) and 4-dimethylaminopyridine (10 mol %). The solution was stirred until consumption of starting material and subsequently the solvent was removed by rotary evaporation. The reaction mixture was purified by flash column chromatography (Hexane/EtOAc mixtures).

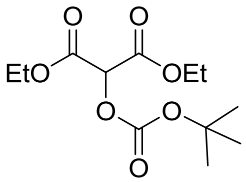
Diethyl 2-hydroxymalonate



To a solution of diethyl 2-oxomalonate (5g, 28.7 mmol, 1 equiv.) in 30 mL of THF under Ar atmosphere, 29 mL of a solution of PMe_3 in THF 1.0M (1.0 equiv.) were added drop wise and reacted 2h at room temperature. After total consumption of the starting material, the crude product was directly purified by flash column chromatography to afford the desired product as colourless oil in 32% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ= 4.69 (bs, 1H), 4.36-4.22 (m, 4H), 3.42 (bs, 1H), 1.31 (t, J= 7.3Hz, 6H).

Diethyl 2-(tert-butoxycarbonyloxy)malonate

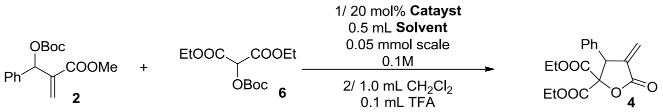


To a solution of Diethyl 2-hydroxymalonate (530 mg, 3.01 mmol, 1.0 equiv.) in 15 mL of CH_2Cl_2, 790 mg of $(Boc)_2O$ (1.2 equiv., 3.61 mmol) and 75mg of DMAP (0.2 equiv., 0.6 mmol) were added sequentially. After total consumption of the starting material (monitored by TLC) the crude product was directly purified by flash column chromatography (Hexane/EtOAc 3:1) to afford the desired product as colourless oil in 73% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ= 5.36 (s, 1H), 4.36-4.23 (m, 4H), 1.51 (s, 9H), 1.30 (t, J=7.3Hz, 6H)

Screening Conditions:

Table 1: Reaction screening[a]



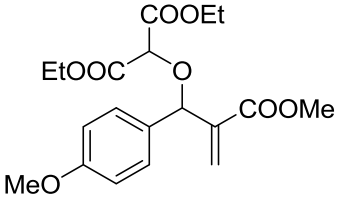
Entry	Catalyst	Solvent	Conv. (14h)[b]	Crude ee[c]
1	β-ICPD (I)	Toluene	100%	-90%
2	Quinine (II)	Toluene	36%	nd[d]
3	Cinchonine (III)	Toluene	traces	nd
4	$(DHQD)_2$AQN (IV)	Toluene	38%	Nd
5	$(DHQD)_2$PHAL(V)	Toluene	79%	90%
6	β-ICPD (I)	CF_3-C_6H_5	100%	-88%
7	β-ICPD (I)	$CHCl_3$	100%	-82%
8	β-ICPD (I)	MeCN	100%	-30%
9	β-ICPD (I)	TBME	Traces	Nd
10	$(DHQD)_2$PHAL(V)	CF_3-C_6H_5	48%	86%
11	$(DHQD)_2$PHAL(V)	$CHCl_3$	82%	86%
12	$(DHQD)_2$PHAL(V)	MeCN	85%	80%
13	$(DHQ)_2$PHAL (VI)	Toluene	36%	nd

a) In a vial equipped with a magnetic stirring bar, the corresponding MBH carbonate (0.05 mmol, 2 equiv.), O-Boc-hydroximalonate (0.025 mmol, 1 equiv.) and catalyst (0.005 mmol, 20 mol%) were added in 0.5 mL of toluene (C=0.1M) and the reaction was stirred at room temperature for 14h. Next, the reaction crude was diluted with 1.0 mL of CH_2Cl_2, 0.1 mL of TFA was added in one portion and the mixture was stirred overnight. Then, 1.0 mL H_2O was added at the reaction crude and neutralized until PH=7 with Na_2CO_3, extracted 3 times with EtOAc. b) Determined by ^{1}H NMR analysis of the reaction crude. c) Enantiomeric excess determined by chiral HPLC; d) not determined

A. **LACTONES**

General procedure for the synthesis of α-methylenelactones from O-Boc Hydroximalonate: In a vial equipped with a magnetic stirring bar, the corresponding MBH carbonate (0.2 mmol, 2 equiv.), O-Boc-hydroximalonate (0.1 mmol, 1 equiv.) and catalyst (0.02 mmol, 20 mol%) were added in 1.0 mL of toluene (C=0.1M) and the reaction was stirred at room temperature over 1-5 days. After consumption of starting material (monitored by ^{1}H-NMR) the reaction crude was diluted with 1.0 mL of CH_2Cl_2, 0.1 mL of TFA was added in one portion and the mixture was stirred overnight. Then, 1.0 mL H_2O was added at the reaction crude and neutralized until PH=7 with Na_2CO_3, extracted 3 times with EtOAc. The combined organic layers were dried with $MgSO_4$ and the organic solvent eliminated to afford the crude product that was purified by flash column chromatography to afford the desired α-methylene-lactone.

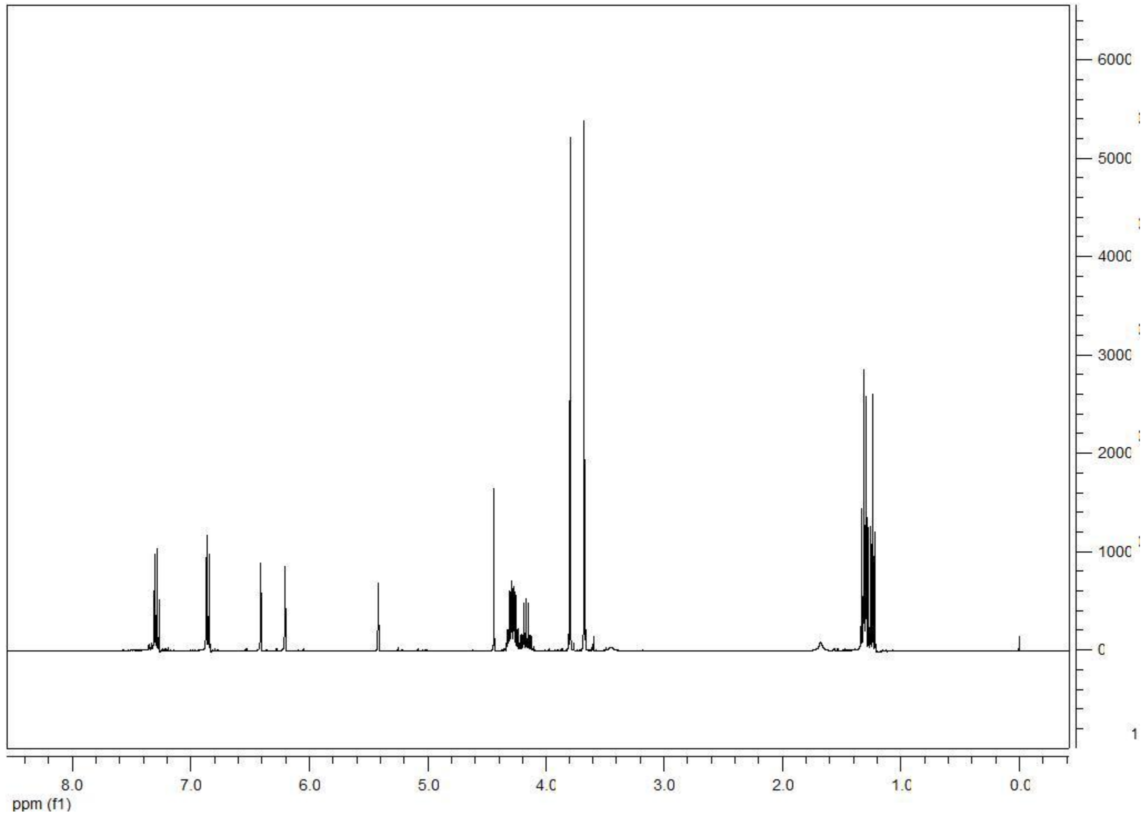
Diethyl 2-(2-(methoxycarbonyl)-1-(4-methoxyphenyl)allyloxy)malonate

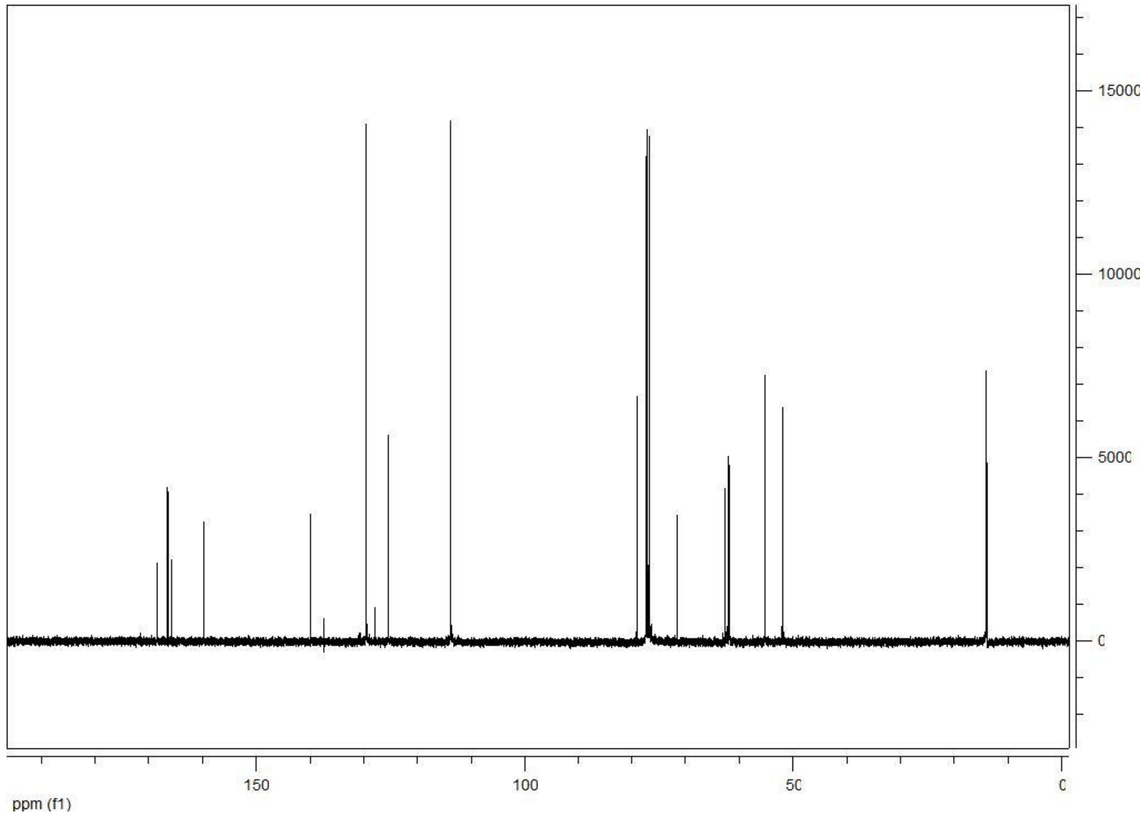


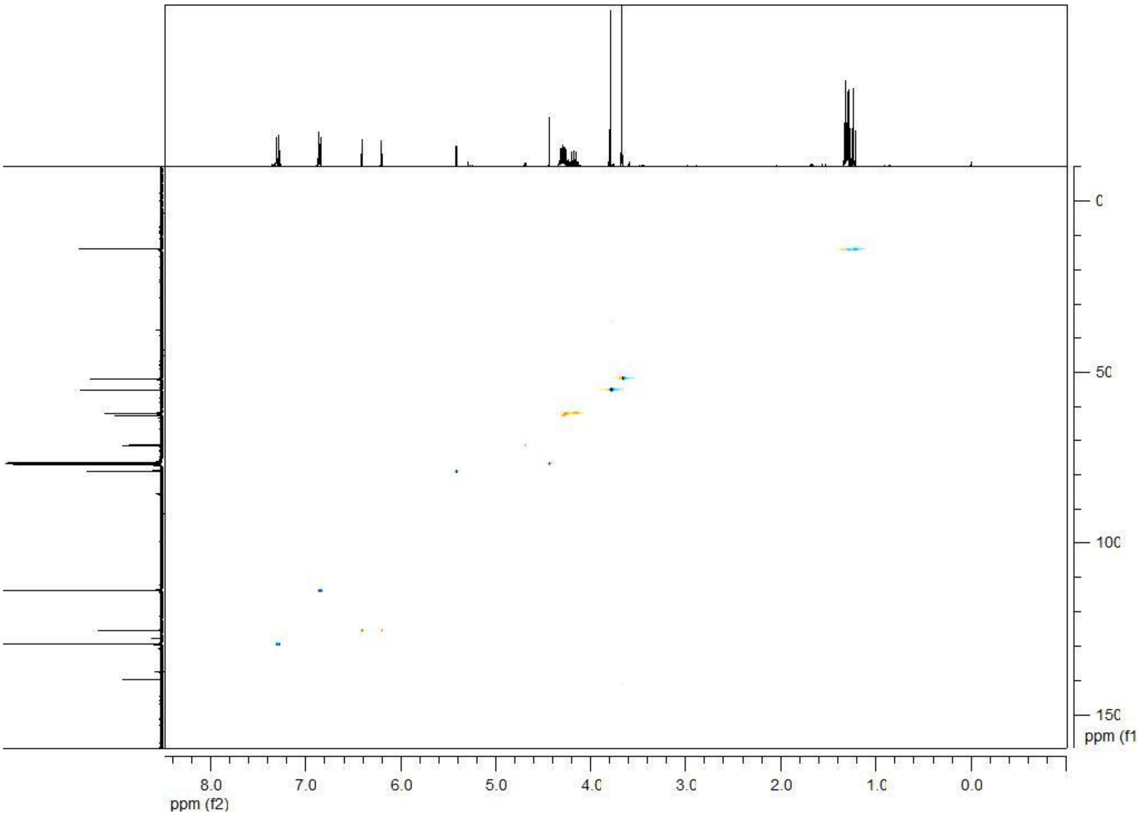
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J=8.7Hz, 2H), 6.84 (d, J= 8.8Hz, 2H), 6.40 (s 1H), 6.19 (s, 1H), 5.41 (s, 1H), 4.43 (s, 1H), 4.34-4.23 (m, 2H), 4.21-4.13 (m, 2H), 3.78 (s, 3H), 3.66 (s, 3H), 1.30 (t, J=7.3Hz, 3H), 1.22 (t, J= 7.2Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 166.4, 166.4, 165.8, 159.7, 139.8, 129.5, 129.4, 125.4, 113.8, 78.9, 71.5, 61.9, 61.8, 55.2, 14.0, 51.8, 13.9.

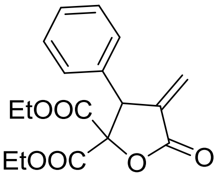
HRMS (ESI) calcd. for $C_{19}H_{25}O_8$ $(M+H)^+$ 381.1544, found 381.1547.


6000
5000
4000
3000
2000
1000
0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)


15000
10000
5000
0
150
100
50
0
ppm (f1)


0
50
100
150
ppm (f1
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f2)

diethyl 4-methylene-5-oxo-3-phenyldihydrofuran-2,2(3H)-dicarboxylate



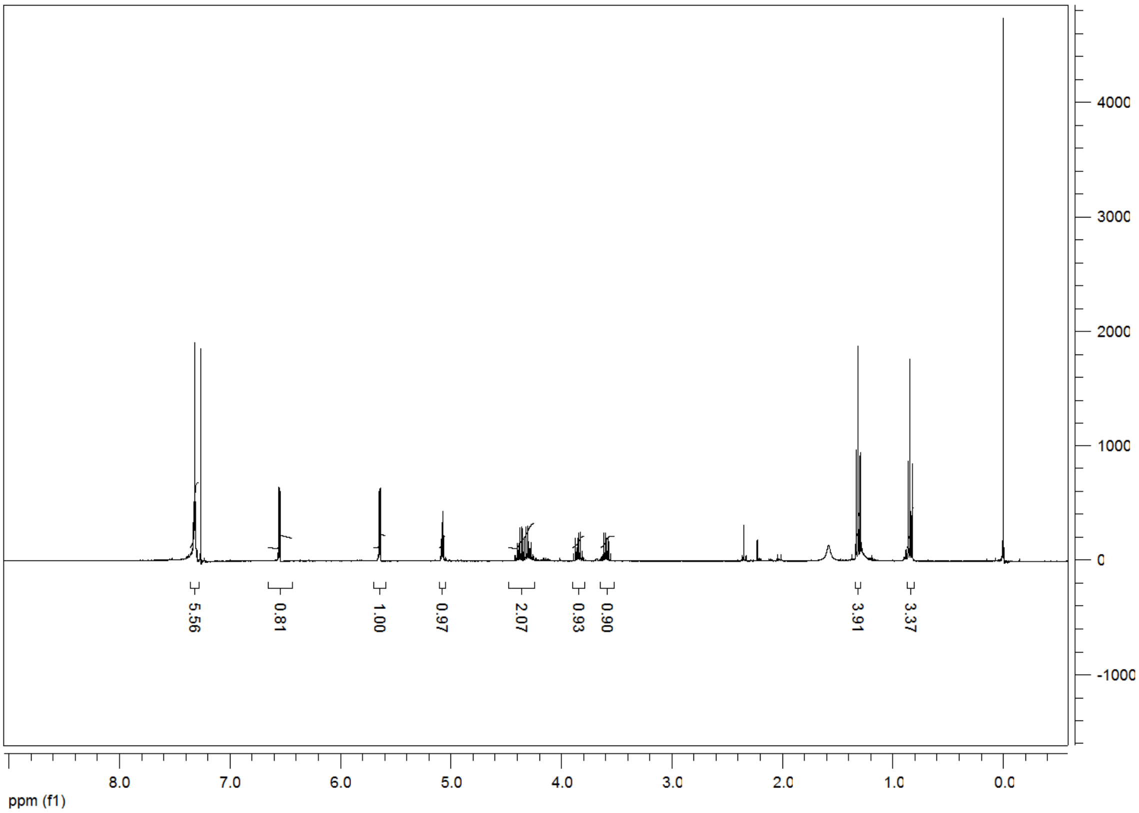
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.30 (m, 5H), 6.55 (d, J=3.3Hz, 1H), 5.64 (d, J=3.1Hz, 1H), 5.07 (t, 3.1Hz, 1H), 4.45-4.25 (m, 2H), 3.90-3.80 (m, 1H), 3.65-3.55 (m, 1H), 1.31 (t, J=7.2Hz, 3H), 0.84 (t, J=7.2Hz, 3H).

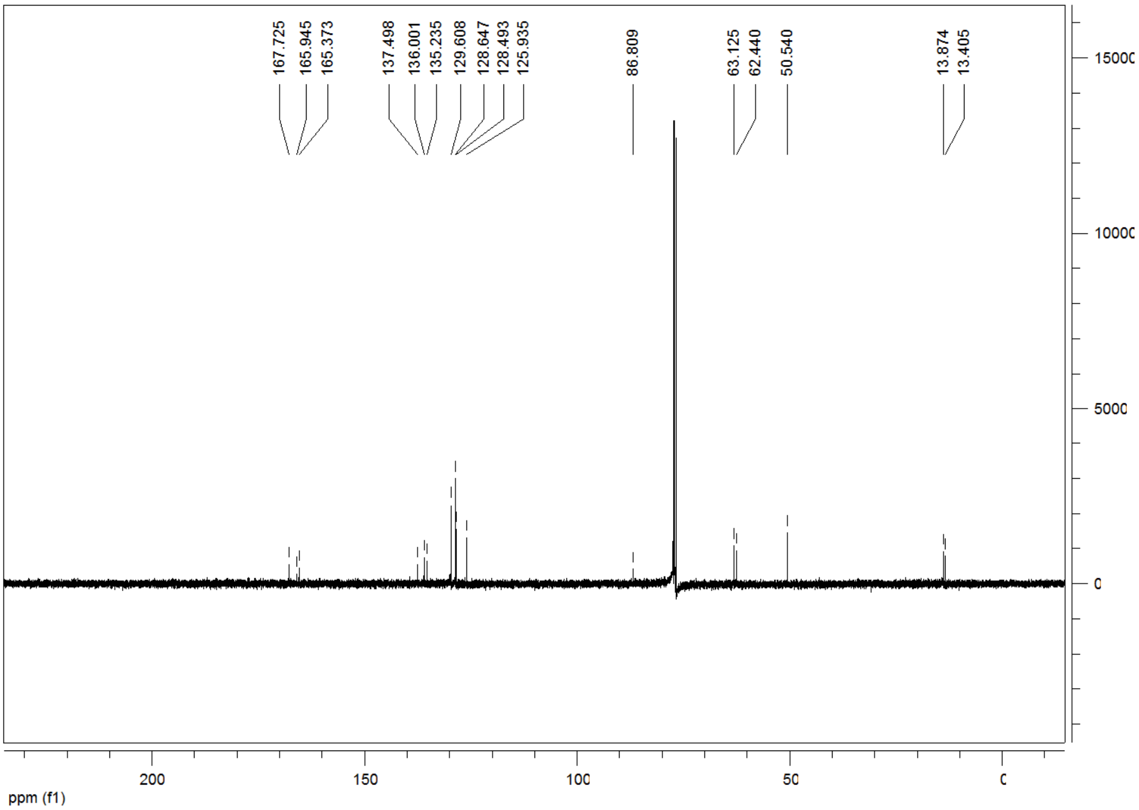
^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 165.9, 165.4, 137.5, 136.0, 135.2, 129.6, 128.6, 128.5, 125.9, 86.8, 63.1, 62.4, 50.5, 13.9, 13.4.

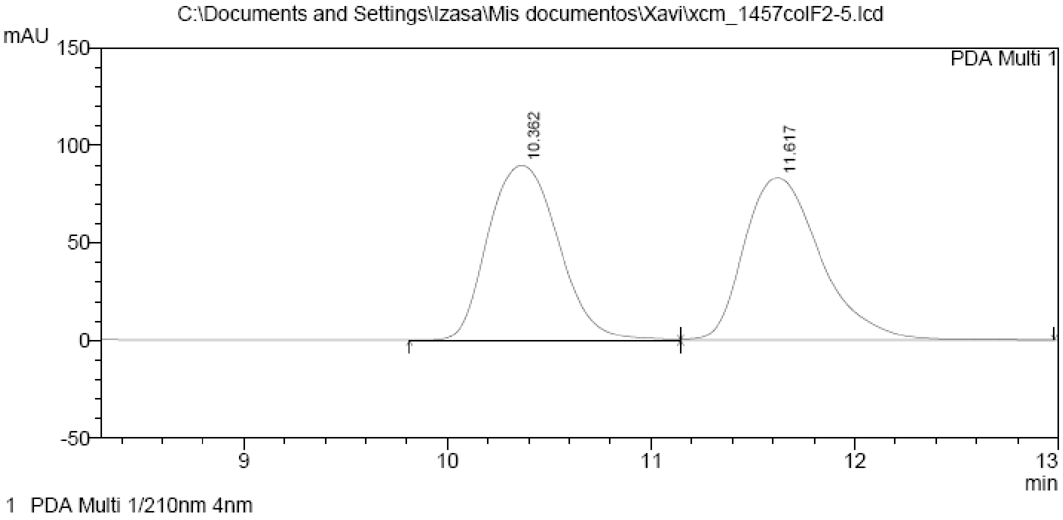
HRMS (ESI) calcd. for $C_{17}H_{19}O_6$ $(M+H)^+$ 319.1176, found 319.1182.

Enantiomeric excess: -91% (b-ICPD)/ +91% ($(DHQD)_2$PHAL), determined by HPLC (Daicel Chiralpak IB, Hexane/i-PrOH 95:5), UV 210 nm, flow rate 1 mL/min, t_R= 10.3, 11.6

$[\alpha]_D^{25}$= +14 (c=0.3, $CHCl_3$, -91% ee)



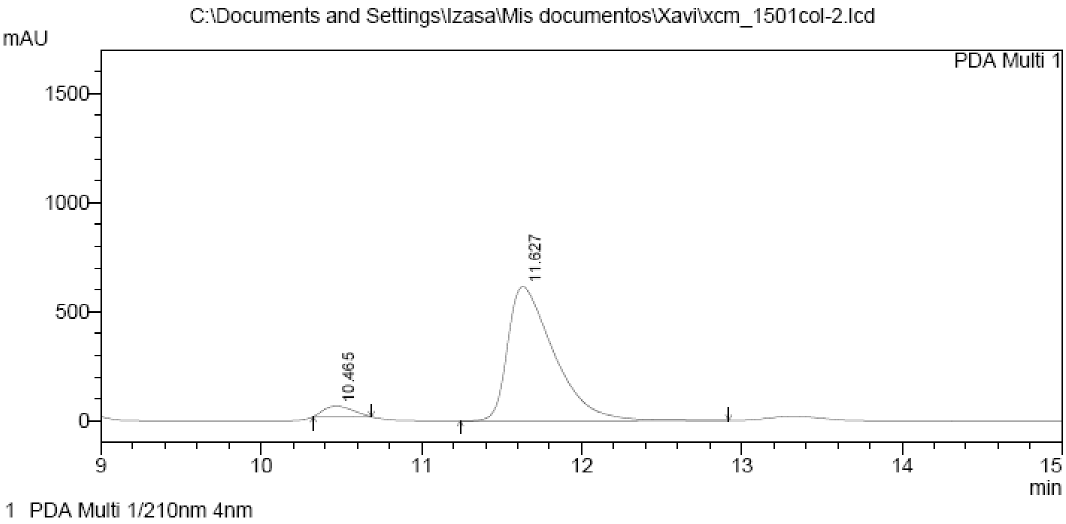




PeakTable

PDA Ch1 210nm 4nm

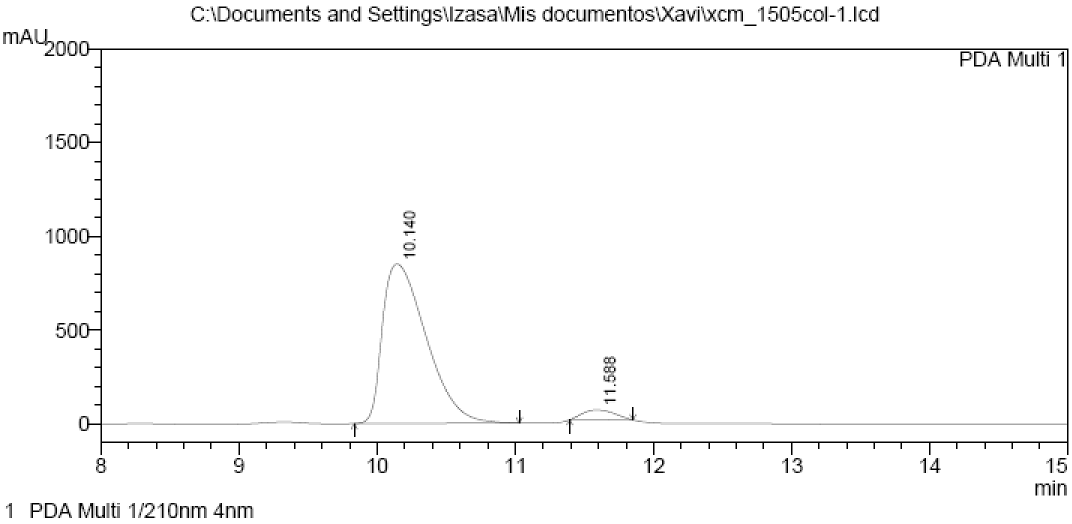
Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.362	2156825	89602	49.786	51.870
2	11.617	2175373	83142	50.214	48.130
Total		4332198		100.000	



PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.465	597305	47751	4.622	7.219
2	11.627	12325669	613751	95.378	92.781
Total		12922974	661502	100.000	100.000

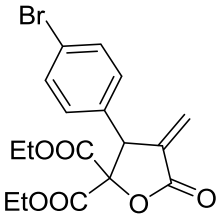


PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.140	18734231	848789	95.617	94.119
2	11.588	858840	53034	4.383	5.881
Total		19593071	901823	100.000	100.000

diethyl 3-(4-bromophenyl)-4-methylene-5-oxodihydrofuran-2,2(3H)-dicarboxylate



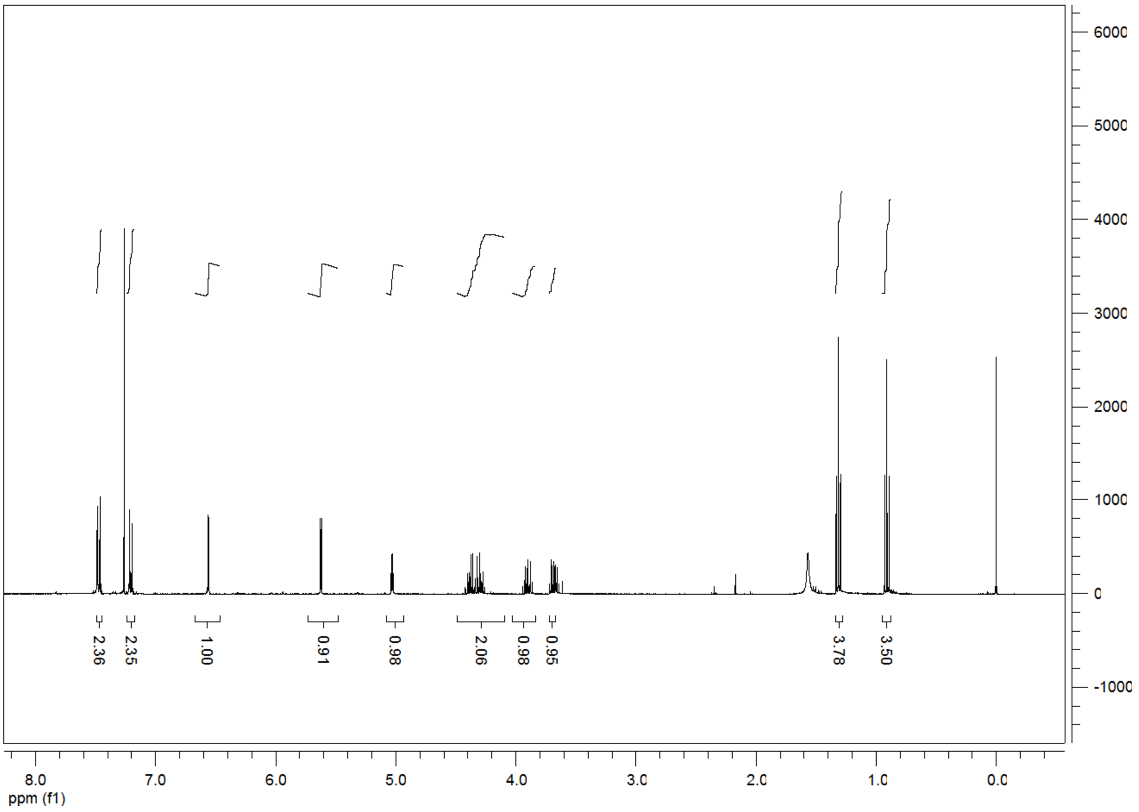
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.47 (d, J=8.7Hz, 2H), 7.20 (d, J=8.7Hz, 2H), 6.56 (d, J=3.5Hz, 1H), 5.62 (d, J=3.5Hz, 1H), 5.03 (t, 3.5Hz, 1H), 4.40-4.28 (m, 2H), 3.93-3.86 (m, 1H), 3.72-3.64 (m, 1H), 1.32 (t, J=7.6Hz, 3H), 0.91 (t, J=7.2Hz, 3H).

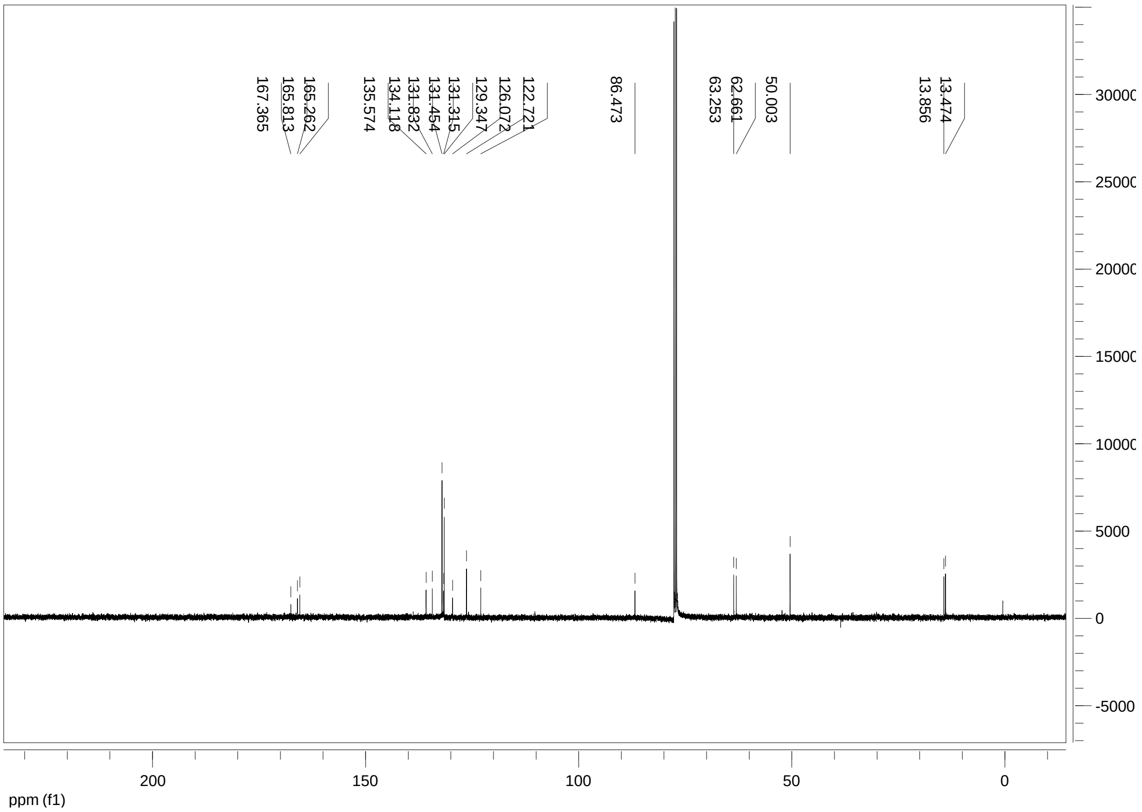
^{13}C NMR (100 MHz, CDCl$_3$) δ 167.4, 165.8, 165.3, 135.6, 134.1, 131.8, 131.5, 131.3,129.3, 126.1, 122.7, 86.5, 63.3, 62.7, 50.0, 13.9, 13.5.

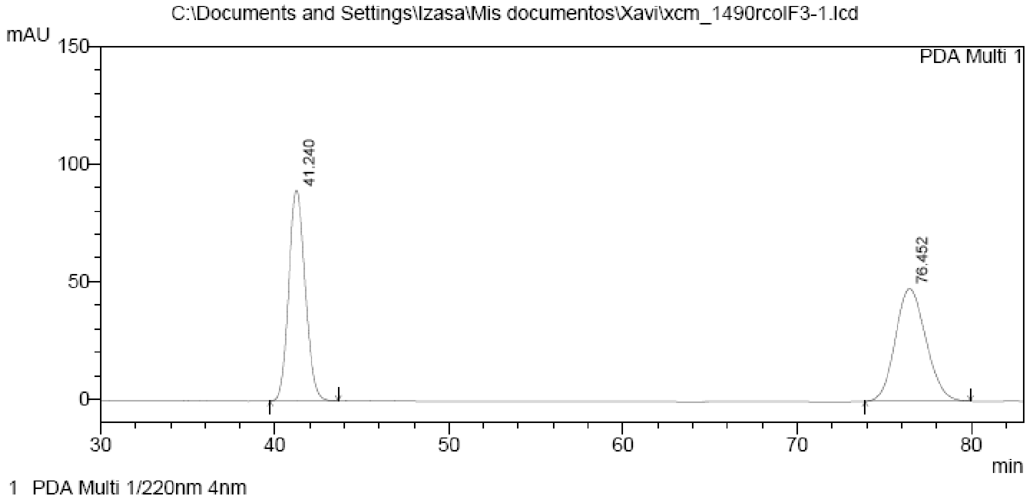
HRMS (ESI) calcd. for $C_{17}H_{21}BrNO_6$ $(M+NH_4)^+$ 414.0547, found 414.0543.

Enantiomeric excess: 91%, determined by HPLC (Daicel Chiralpak IC, i-PrOH/Hexane=10/90), UV 220 nm, flow rate 1 mL/min, t_R= 41.2 min, 76.4 min.

$[\alpha]_D^{25}$= +54 (c=0.4, $CHCl_3$, 91% ee)



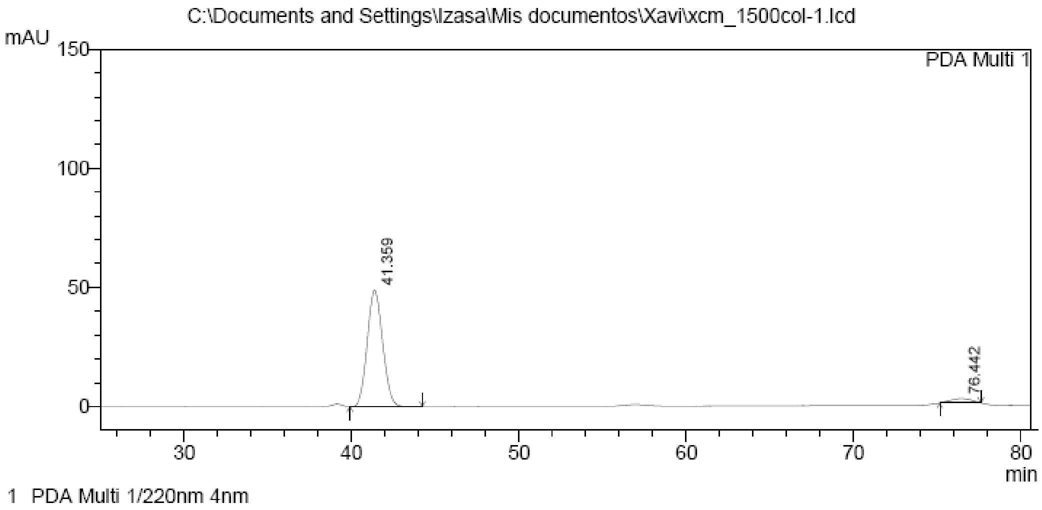




PeakTable

PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	41.240	5868186	89476	50.147	65.195
2	76.452	5833835	47768	49.853	34.805
Total		11702020	137244	100.000	100.000

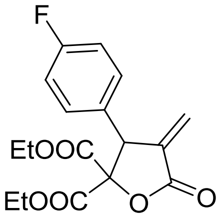


PeakTable

PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	41.359	3144231	49071	95.462	96.622
2	76.442	149477	1715	4.538	3.378
Total		3293708	50786	100.000	100.000

diethyl 3-(4-fluorophenyl)-4-methylene-5-oxodihydrofuran-2,2(3H)-dicarboxylate



^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39-7.25 (m, 2H), 7.02 (t, J=8.6Hz, 2H), 6.55 (d, J= 3.3Hz, 1H), 5.62 (d, J=3.2Hz, 1H), 5.05 (t, J=3.2Hz, 1H), 4.43-4.24 (m, 2H), 3.94-3.84 (m ,1H), 3.71-3.60 (m, 1H), 1.31 (t, J= 7.1Hz, 3H), 0.90 (t, J=7.1Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 167.4, 165.9, 165.3, 162.6 (d, JC-F=248Hz), 135.9, 131.4, 131.3, 130.8, 130.8, 125.9, 115.7, 115.5, 86.6, 63.2, 62.5, 49.8, 13.8, 13.5.

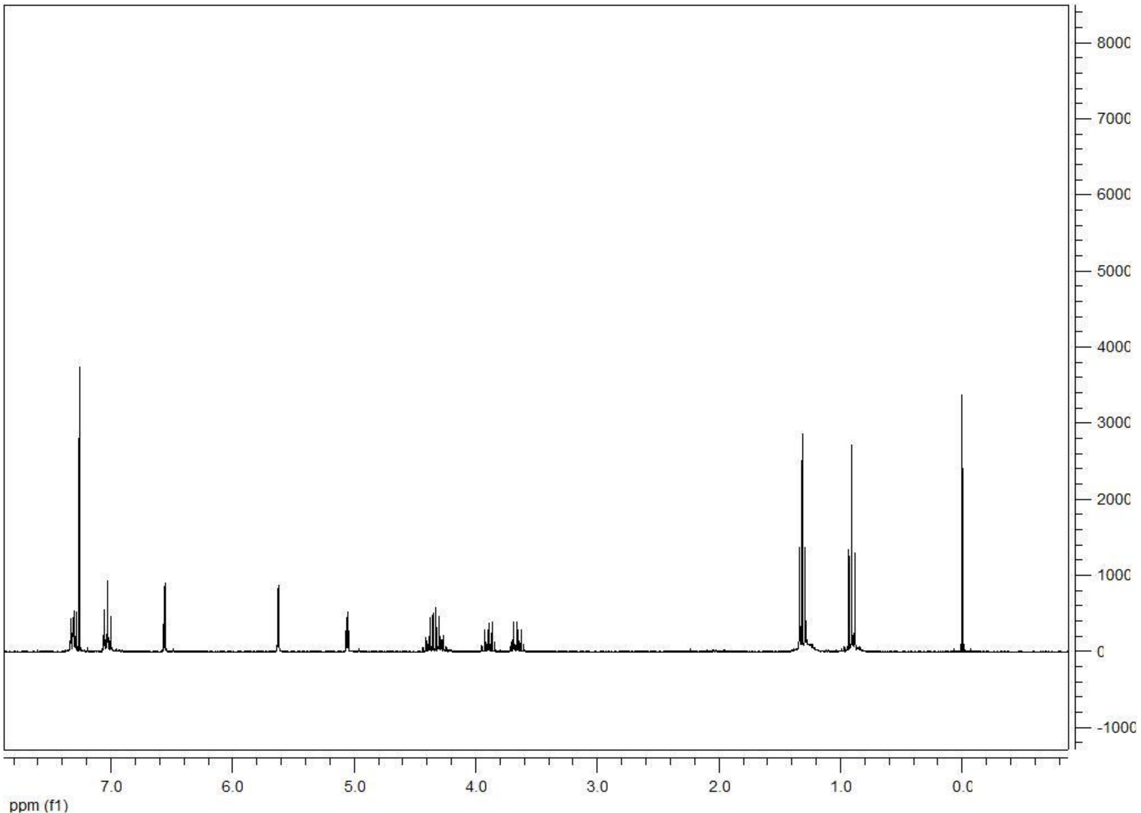
^{19}F NMR (376 MHz, CDCl$_3$) δ -112.9.

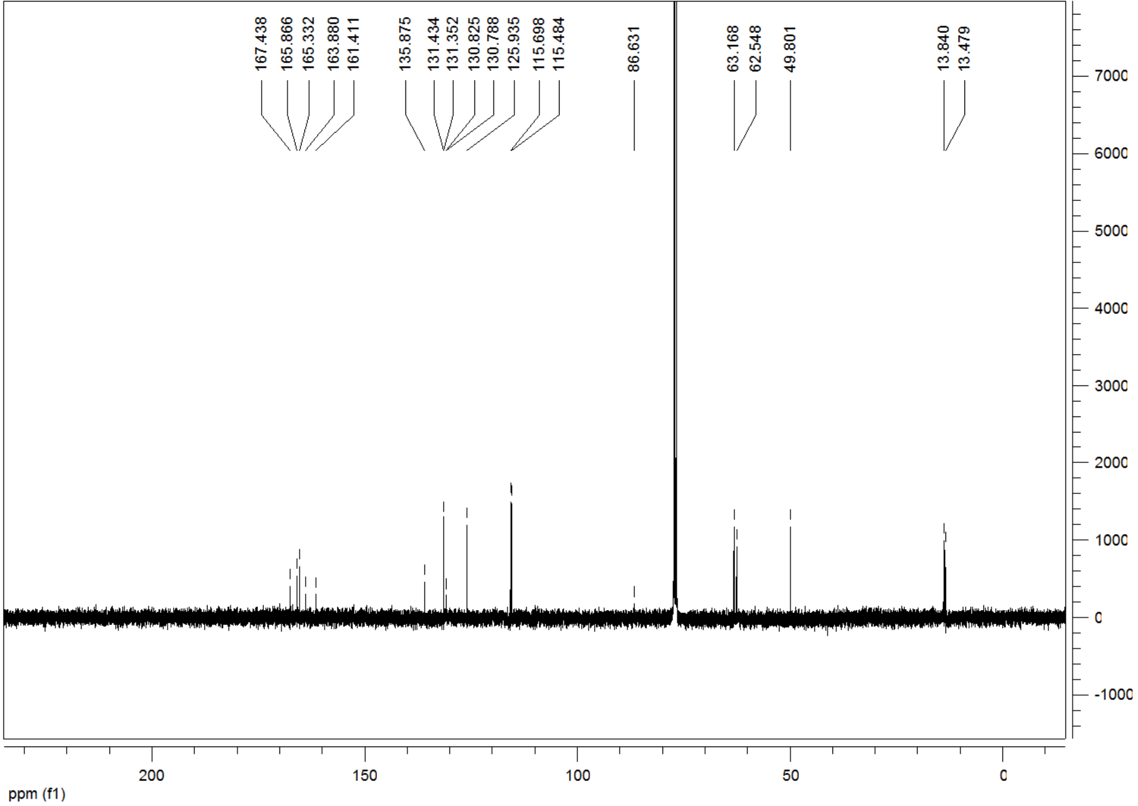
HRMS (ESI) calcd. for $C_{17}H_{18}FO_6$ $(M+H)^+$ 337.1082, found 337.1081.

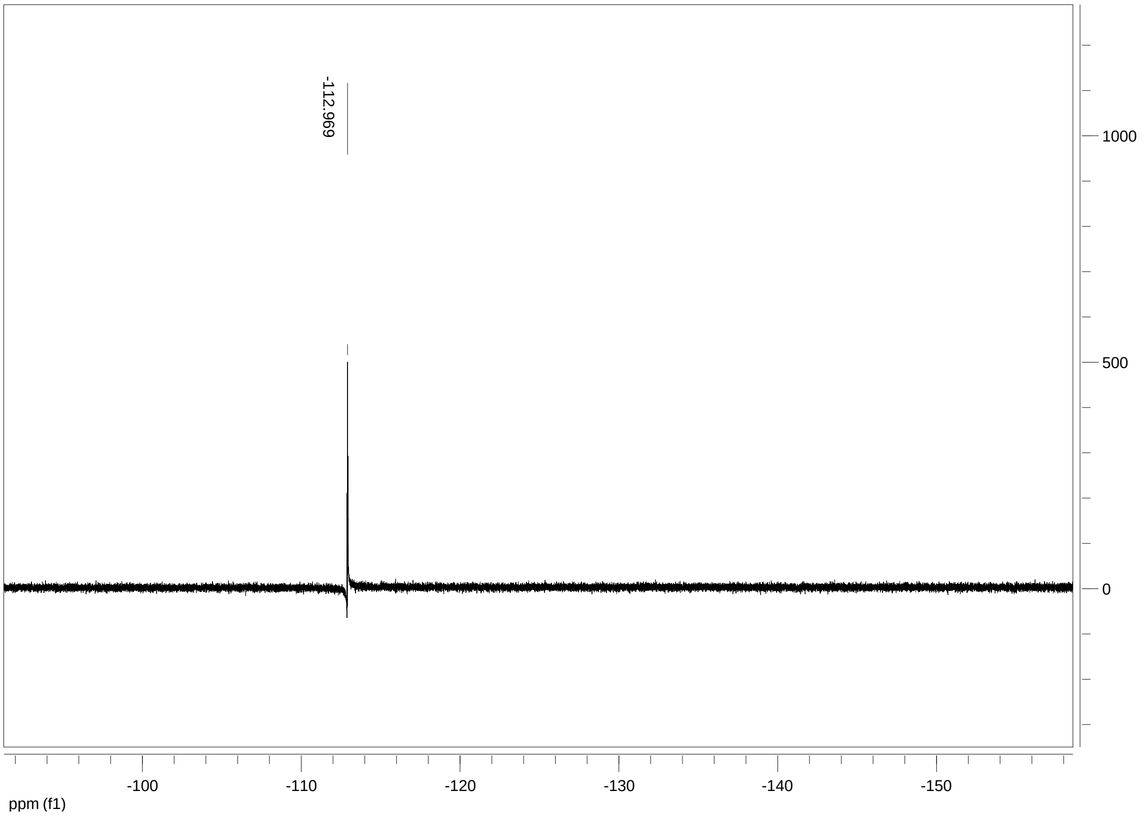
Enantiomeric excess: 84% (β-ICPN) / 96% ((DHQD)$_2$PHAL), determined by HPLC (Daicel Chiralpak IC)

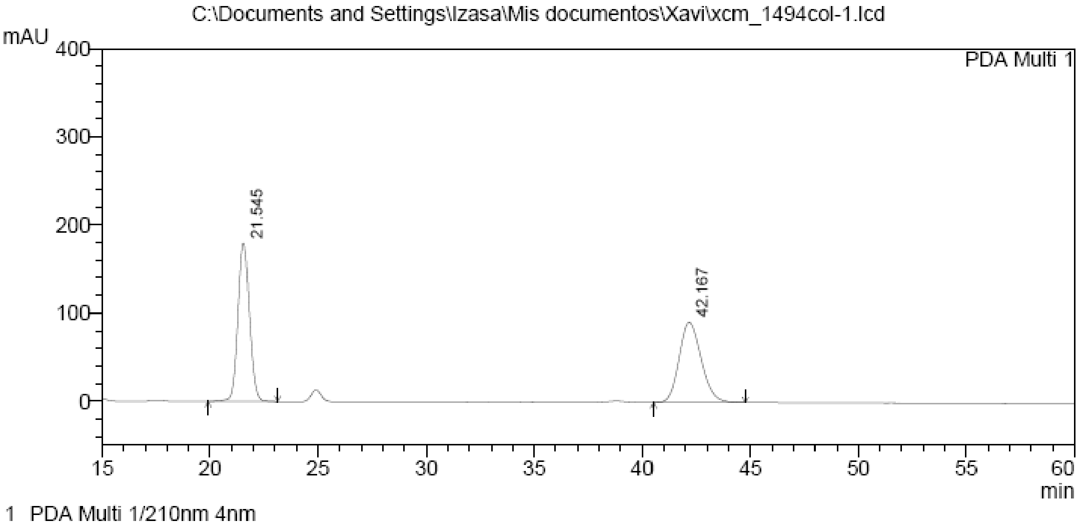
i-PrOH/Hexane=20/80), UV 210 nm, flow rate 1 mL/min, t_R= 21.5min, 42.1 min.

$[\alpha]_D^{25}$= +63 (c=0.6, CHCl$_3$, 84% ee) S-Catalyst


8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)


167.438
165.866
165.332
163.880
161.411
135.875
131.434
131.352
130.825
130.788
125.935
115.698
115.484
86.631
63.168
62.548
49.801
13.840
13.479
7000
6000
5000
4000
3000
2000
1000
0
-1000
200
150
100
50
0
ppm (f1)

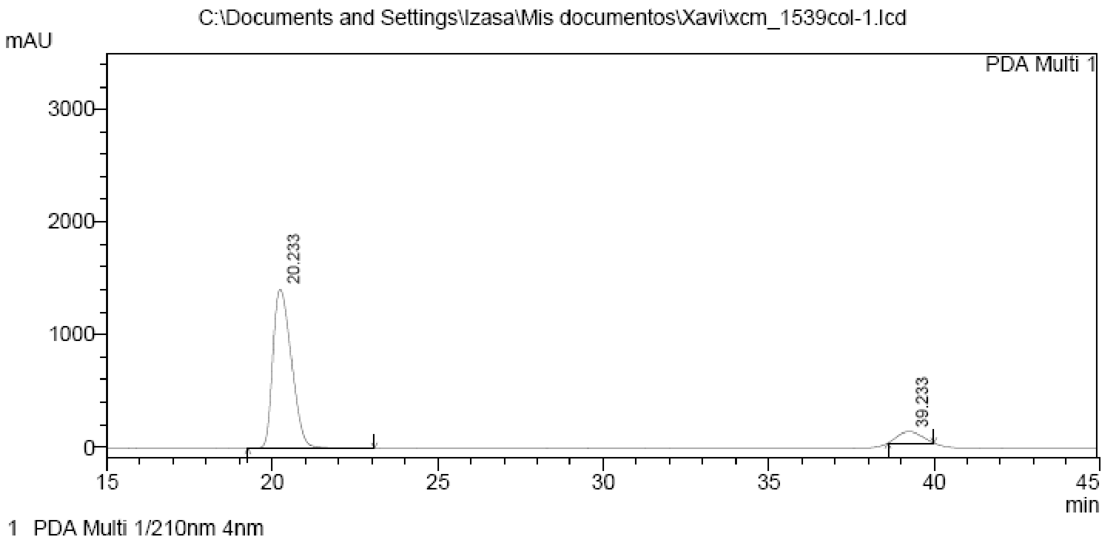




PeakTable

PDA Ch1 210nm 4nm

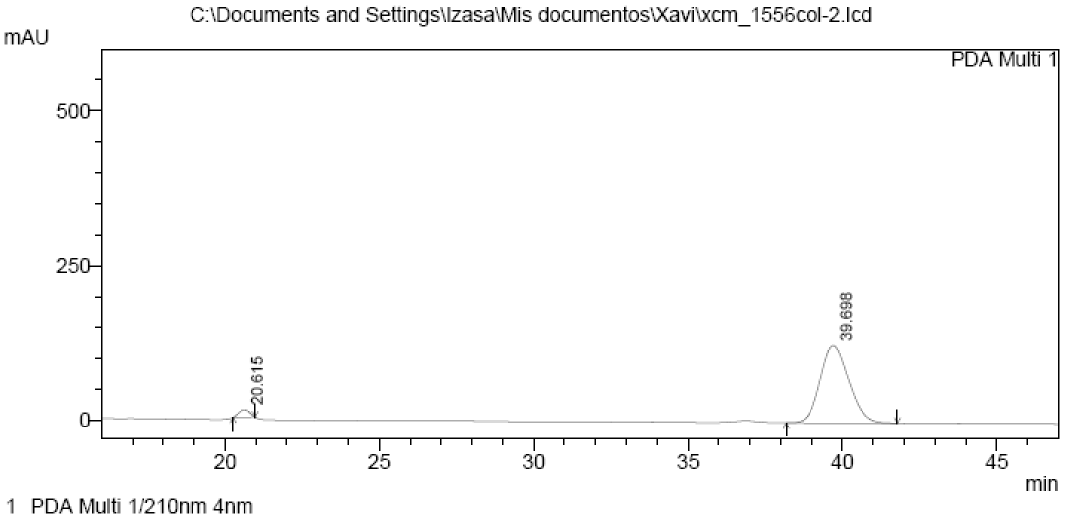
Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.545	6571229	180130	50.065	66.347
2	42.167	6554070	91369	49.935	33.653
Total		13125298	271499	100.000	100.000



PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.233	55123690	1411861	91.774	93.281
2	39.233	4940900	101689	8.226	6.719
Total		60064590	1513551	100.000	100.000

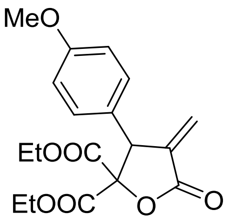


PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.615	293022	12054	3.495	8.795
2	39.698	8092152	125006	96.505	91.205
Total		8385174	137061	100.000	100.000

diethyl 3-(4-methoxyphenyl)-4-methylene-5-oxodihydrofuran-2,2(3H)-dicarboxylate



^{1}H NMR (400 MHz, CDCl$_3$) δ 7.23 (d, J=8.7Hz, 2H), 6.85 (d, J=8.9Hz, 2H), 6.53 (d, J=3.5Hz, 1H), 5.62 (d, J=3.0Hz, 1H), 5.01 (t, 3.0Hz, 1H), 4.42-4.24 (m, 2H), 3.95-3.84 (m, 1H), 3.79 (s, 3H), 3.74-3.60 (m, 1H), 1.31 (t, J=7.3Hz, 3H), 0.90 (t, J=7.3Hz, 3H).

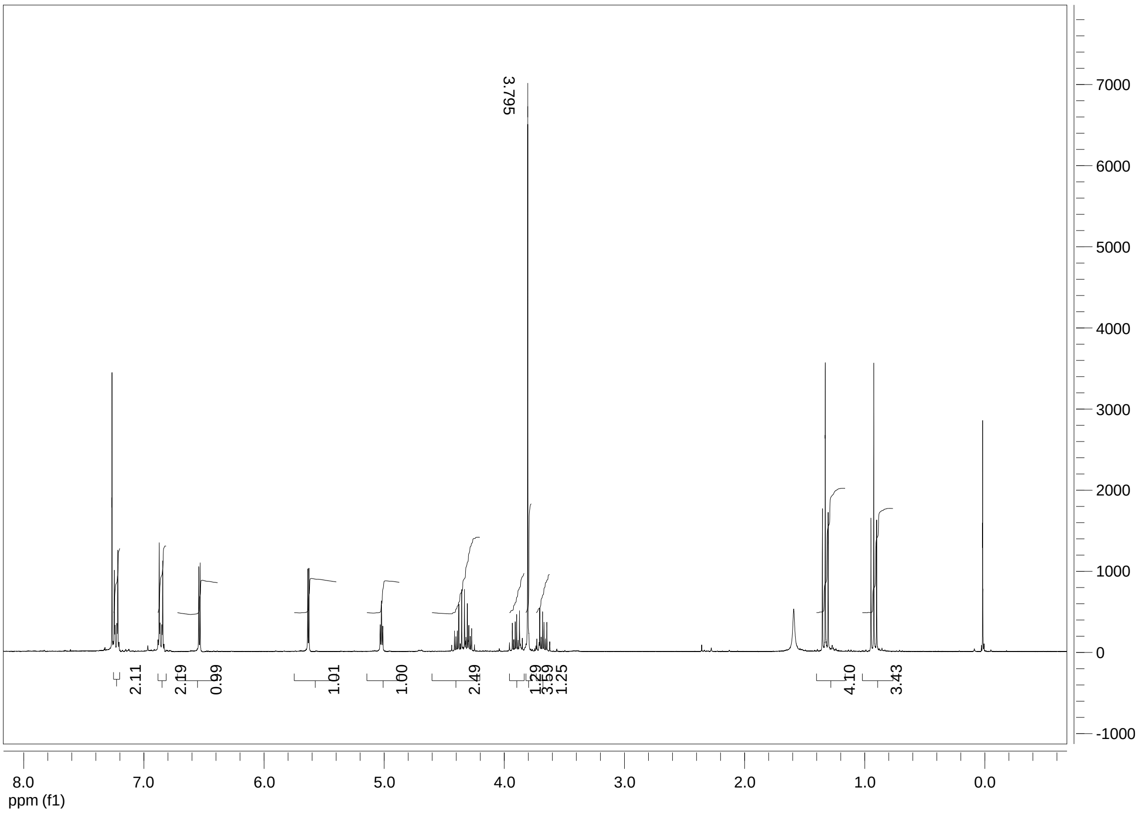
^{13}C NMR (100 MHz, CDCl$_3$) δ 167.8, 166.0, 165.5, 159.6, 136.2, 130.7, 126.9, 125.7, 113.9, 86.9, 63.0, 62.4, 55.3, 49.9, 13.8, 13.5.

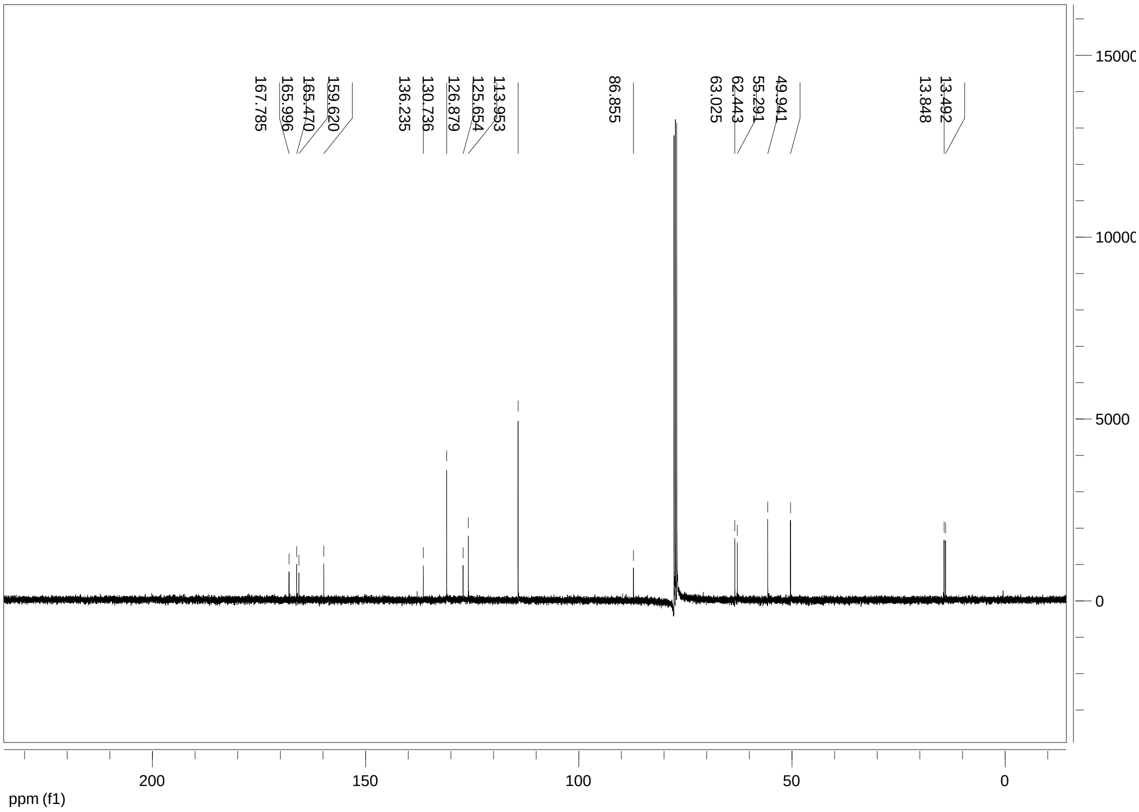
HRMS (ESI) calcd. for $C_{18}H_{21}O_7$ $(M+H)^+$ 349.1282, found 349.1288.

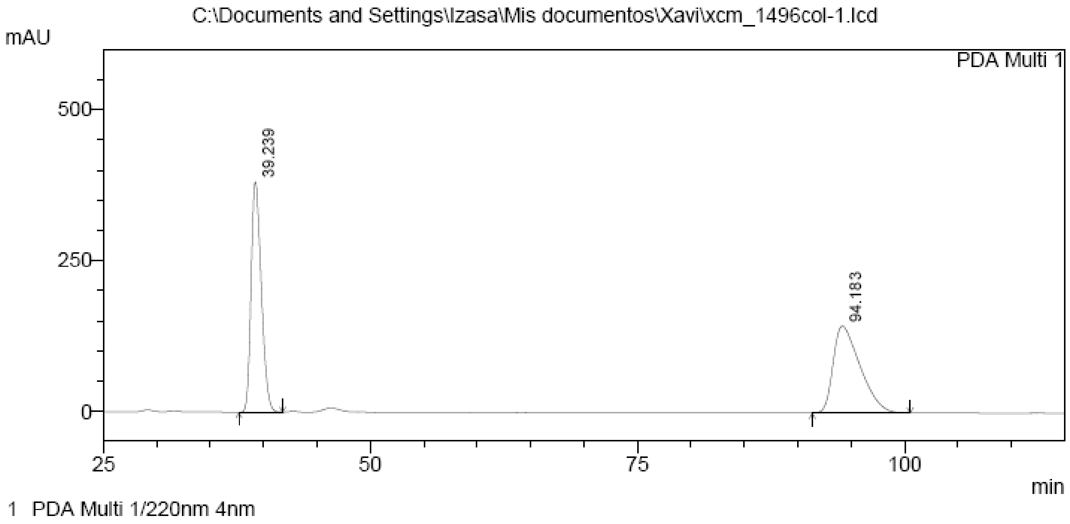
Enantiomeric excess: 93% (β-ICPN) / -88% ((DHQD)$_2$PHAL) determined by HPLC (Daicel Chiralpak IA,

i-PrOH/Hexane= 20:80), UV 210 nm, flow rate 1 mL/min, t_R= 39.2 min, 94.1 min.

$[\alpha]_D^{25}$= +44 (c=0.5, CHCl$_3$, 93% ee)



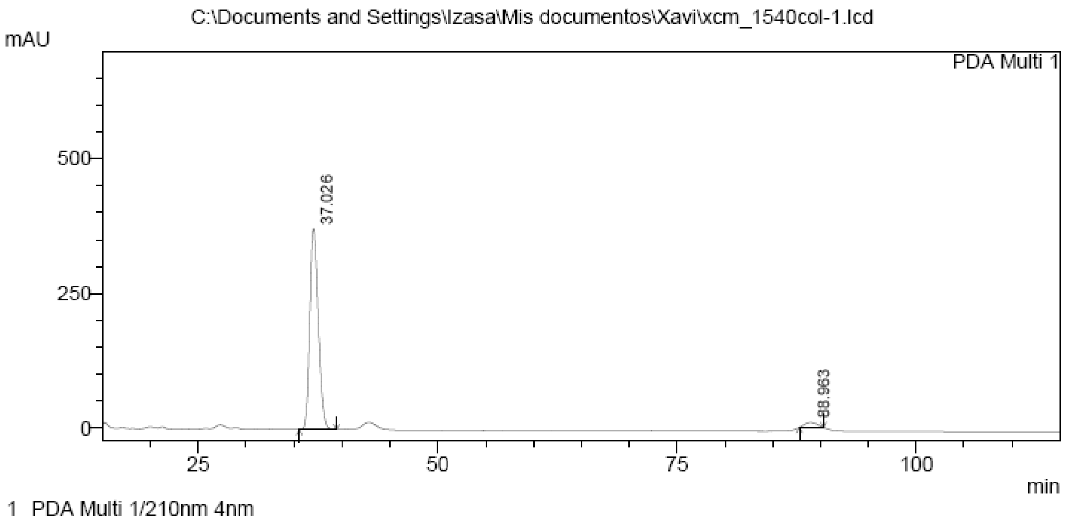




PeakTable

PDA Ch1 220nm 4nm

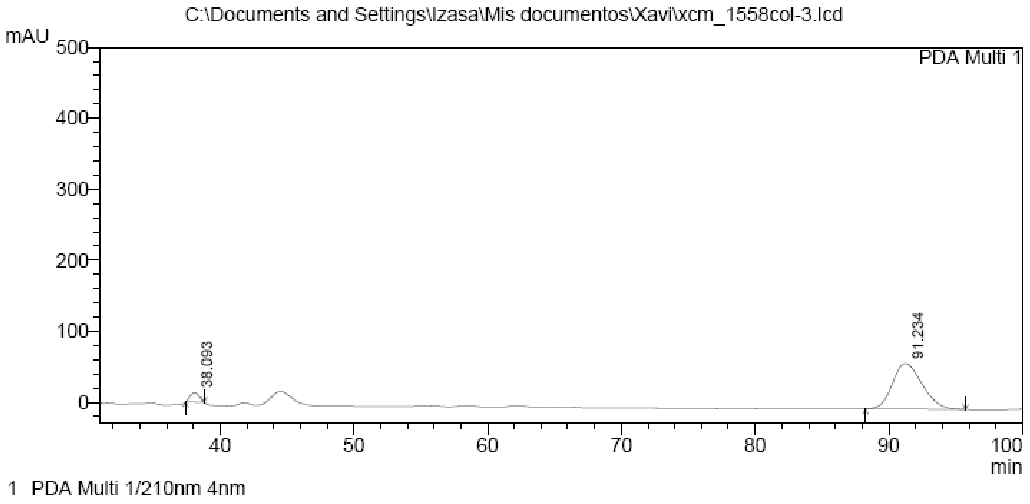
Peak#	Ret. Time	Area	Height	Area %	Height %
1	39.239	25219497	381921	50.000	72.607
2	94.183	25219931	144090	50.000	27.393
Total		50439428	526011	100.000	100.000



PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	37.026	22816833	373116	96.515	97.670
2	88.963	823981	8901	3.485	2.330
Total		23640814	382016	100.000	100.000

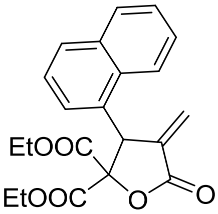


PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	38.093	614398	13145	5.838	16.966
2	91.234	9908909	64330	94.162	83.034
Total		10523307	77474	100.000	100.000

diethyl 4-methylene-3-(naphthalen-1-yl)-5-oxodihydrofuran-2,2(3H)-dicarboxylate



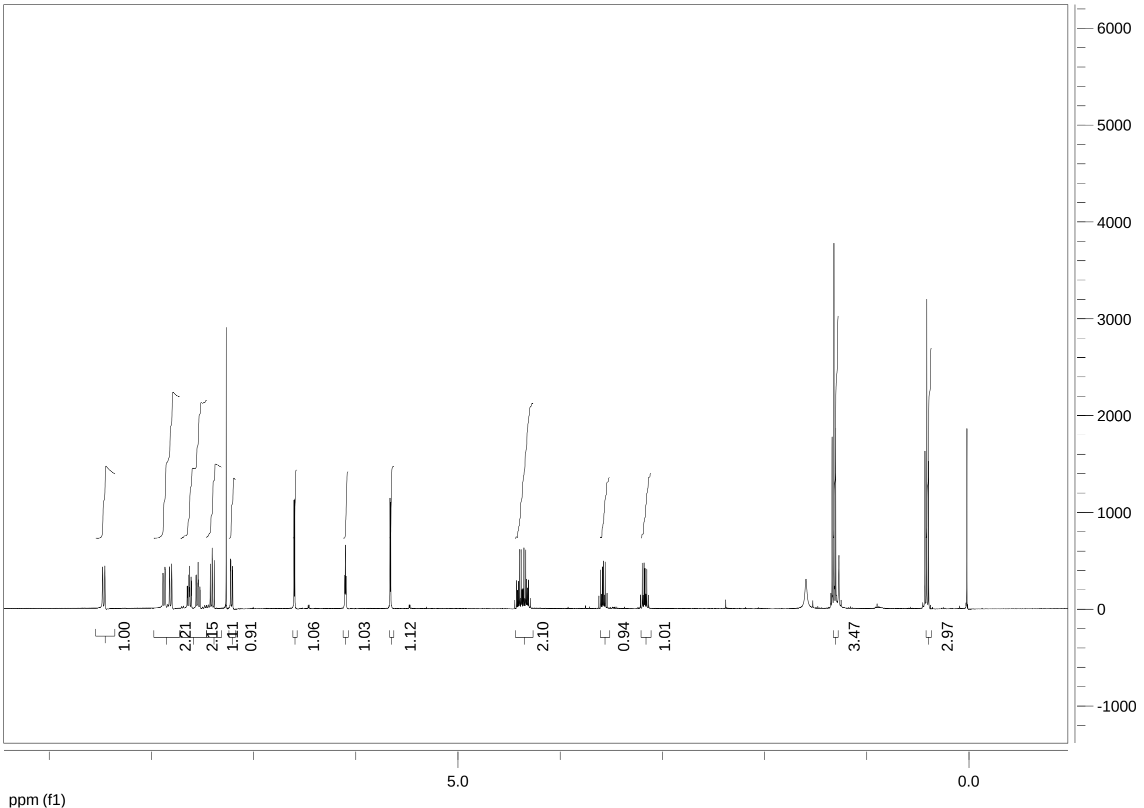
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.46 (d, J=8.7Hz, 1H), 7.87 (d, J=8.4Hz, 1H), 7.80 (d, J=8.2Hz, 1H), 7.65-7.50 (m, 2H), 7.40 (t, J=7.4Hz, 1H), 6.85 (dd, J=7.4Hz, J=1.3Hz, 1H), 6.59 (d, J=2.5Hz, 1H), 6.09 (t, 2.7Hz, 1H), 5.65 (d, J=2.7Hz, 1H), 4.44-4.27 (m, 2H), 3.61-3.51 (m, 1H), 3.20-3.10 (m, 1H), 1.30 (t, J=7.0Hz, 3H), 0.39 (t, J=7.2Hz, 3H).

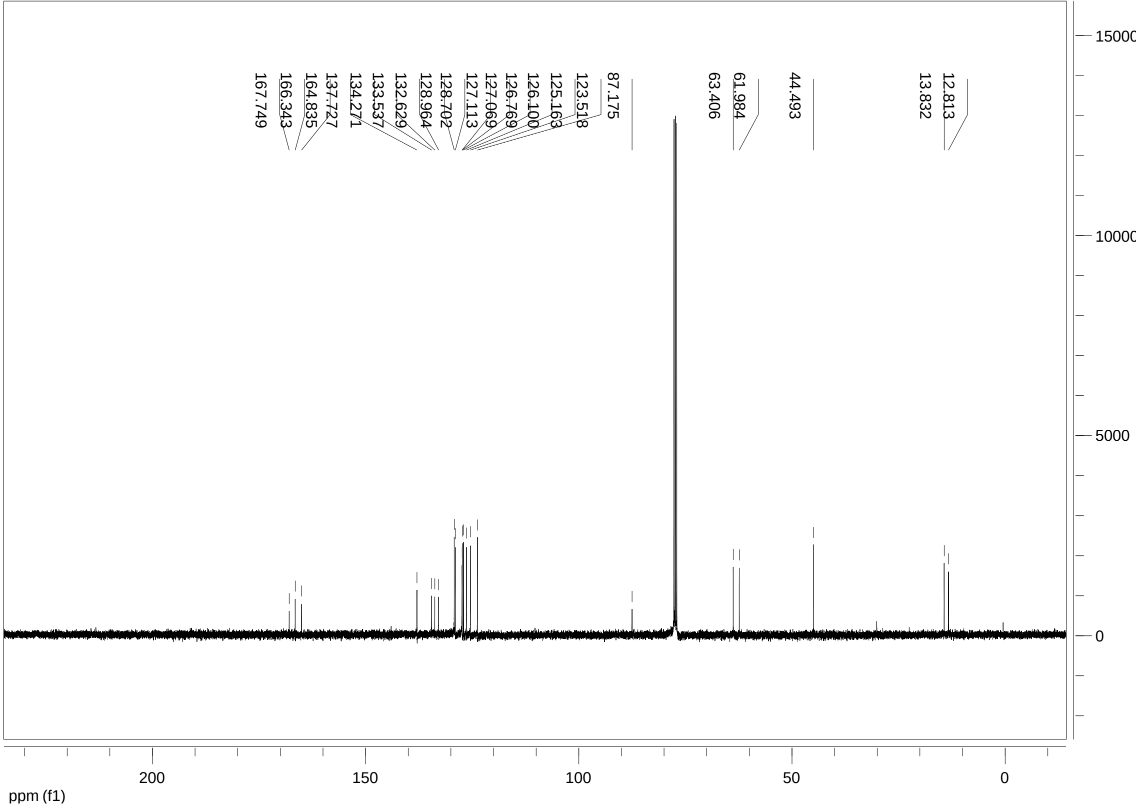
^{13}C NMR (100 MHz, CDCl$_3$) δ 167.7, 166.3, 164.8, 137.7, 134.3, 133.5, 132.6, 129.0, 127.1, 127.0, 126.8, 126.1, 125.2, 123.5, 87.2, 63.4, 62.0, 44.5, 13.8, 12.8.

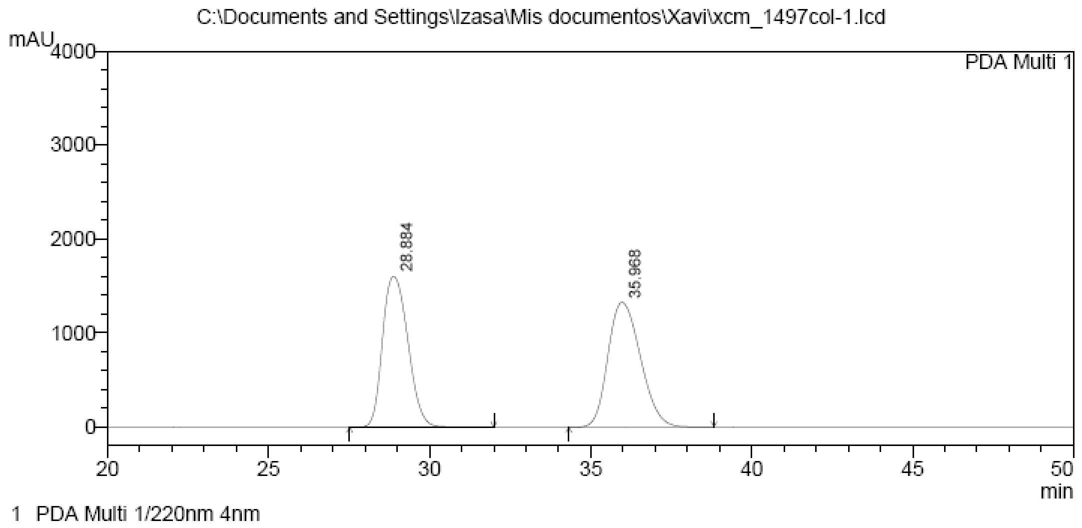
HRMS (ESI) calcd. for $C_{21}H_{21}O_6$ $(M+H)^+$ 369.1333 found 369.1350.

Enantiomeric excess: 68%(β-ICPN) / -71 % ((DHQD)$_2$PHAL) determined by HPLC (Daicel Chiralpak IC, i-PrOH/Hexane=20/80), UV 220 nm, flow rate 1 mL/min, t_R= 28.8 min, 35.9 min.

$[\alpha]_D^{25}$= +52 (c=0.4, CHCl$_3$, 68% ee)


1.00
2.21
2.15
1.11
0.91
1.06
1.03
1.12
2.10
0.94
1.01
3.47
2.97
6000
5000
4000
3000
2000
1000
0
-1000
5.0
0.0
ppm (f1)

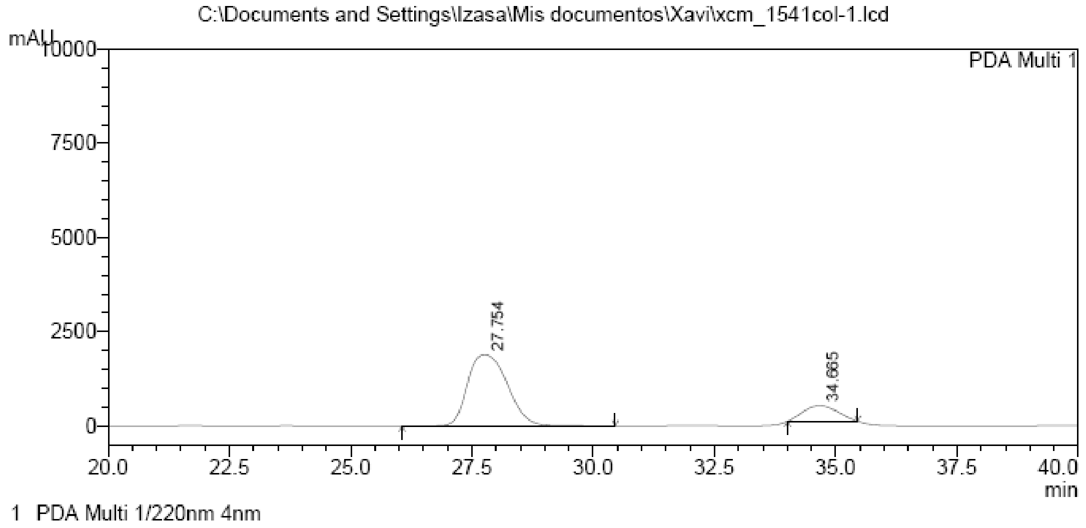

167.749
166.343
164.835
137.727
134.271
133.537
132.629
128.964
128.702
127.113
127.069
126.769
126.100
125.163
123.518
87.175
63.406
61.984
44.493
13.832
12.813
15000
10000
5000
0
200
150
100
50
0
ppm (f1)



PeakTable

PDA Ch1 220nm 4nm

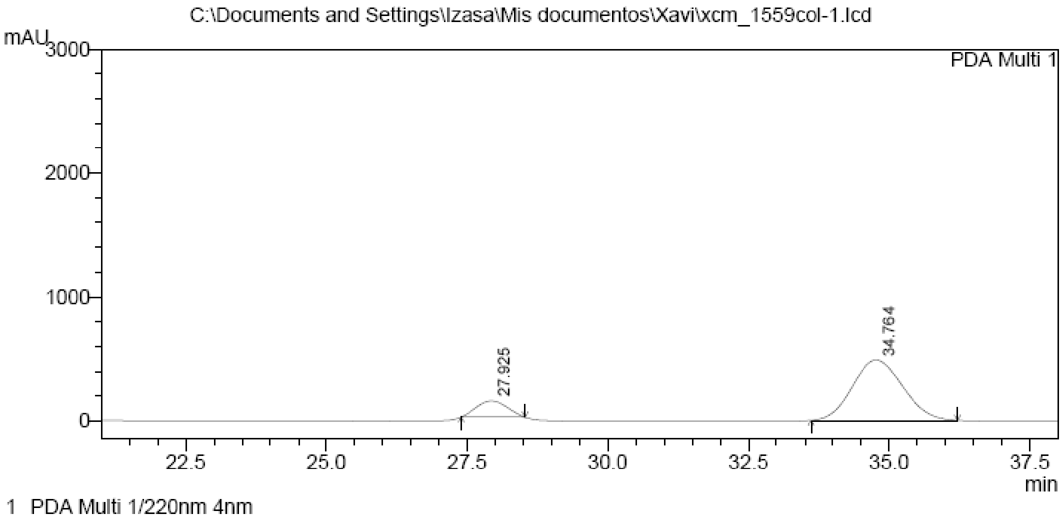
Peak#	Ret. Time	Area	Height	Area %	Height %
1	28.884	87896990	1602887	48.573	54.789
2	35.968	93063407	1322694	51.427	45.211
Total		180960397	2925581	100.000	100.000



PeakTable

PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	27.754	107692494	1892486	84.021	81.995
2	34.665	20480628	415574	15.979	18.005
Total		128173122	2308060	100.000	100.000

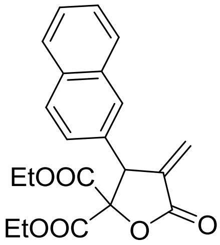


PeakTable

PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	27.925	4900167	129656	14.015	21.084
2	34.764	30062937	485281	85.985	78.916
Total		34963104	614937	100.000	100.000

diethyl 4-methylene-3-(naphthalen-2-yl)-5-oxodihydrofuran-2,2(3H)-dicarboxylate



^{1}H NMR (400 MHz, CDCl$_3$) δ 7.84-7.78 (m, 4H), 7.52-7.47 (m, 2H), 7.38 (dd, J=8.8Hz, J=1.7Hz, 1H), 6.60 (d, J=3.1Hz, 1H), 5.67 (d, J=2.7Hz, 1H), 5.25 (t, 2.7Hz, 1H), 4.44-4.26 (m, 2H), 3.81-3.71 (m, 1H), 3.52-3.43 (m, 1H), 1.32 (t, J=7.0Hz, 3H), 0.65 (t, J=7.4Hz, 3H).

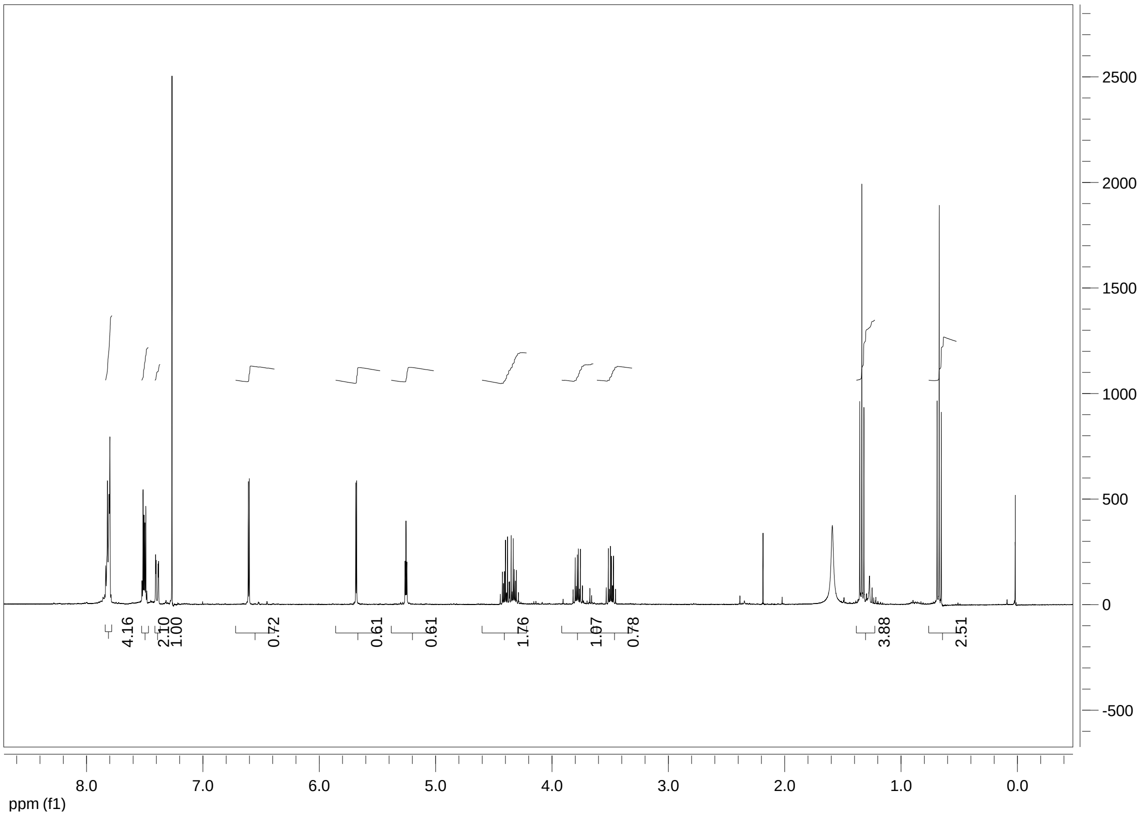
^{13}C NMR (100 MHz, CDCl$_3$) δ 167.7, 166.0, 165.4, 136.1, 133.1, 133.0, 132.5, 129.1, 128.3, 127.9, 127.6, 126.7, 126.6, 126.5, 126.1, 86.8, 63.2, 62.4, 50.7, 13.9, 13.2.

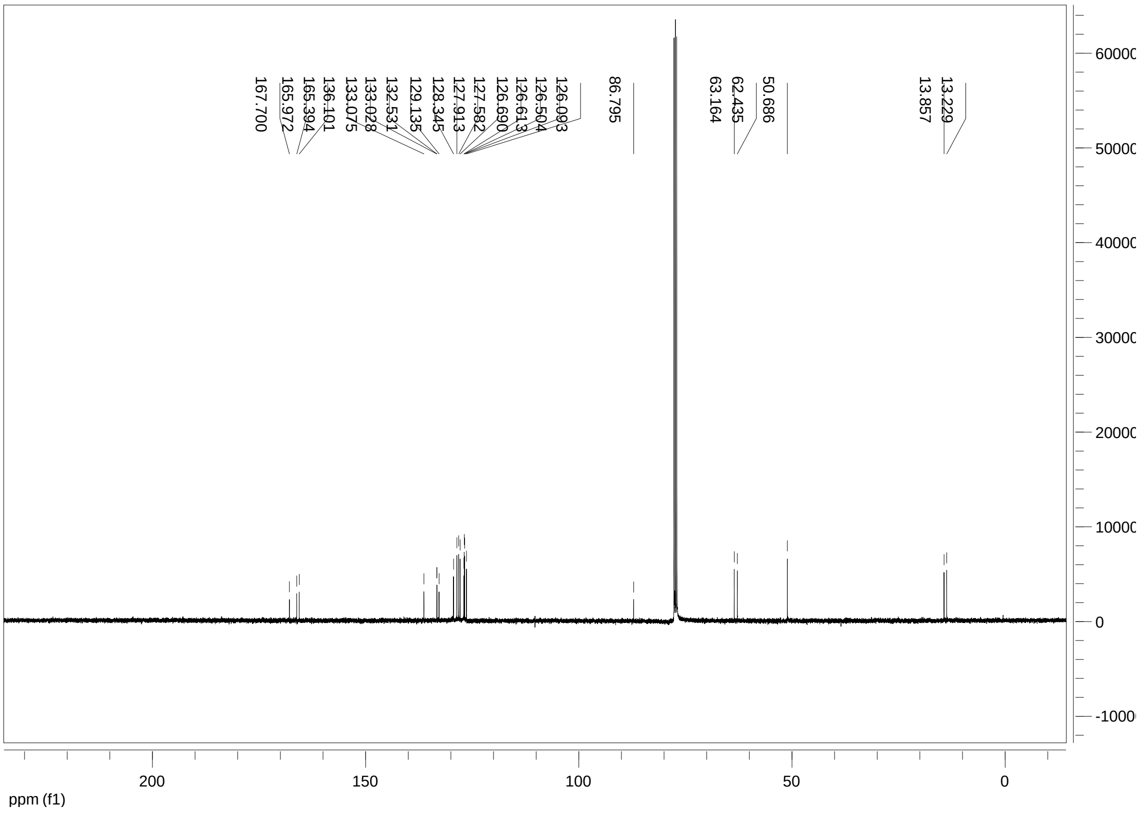
HRMS (ESI) calcd. for $C_{21}H_{21}O_6$ $(M+H)^+$ 369.1333, found 369.1344.

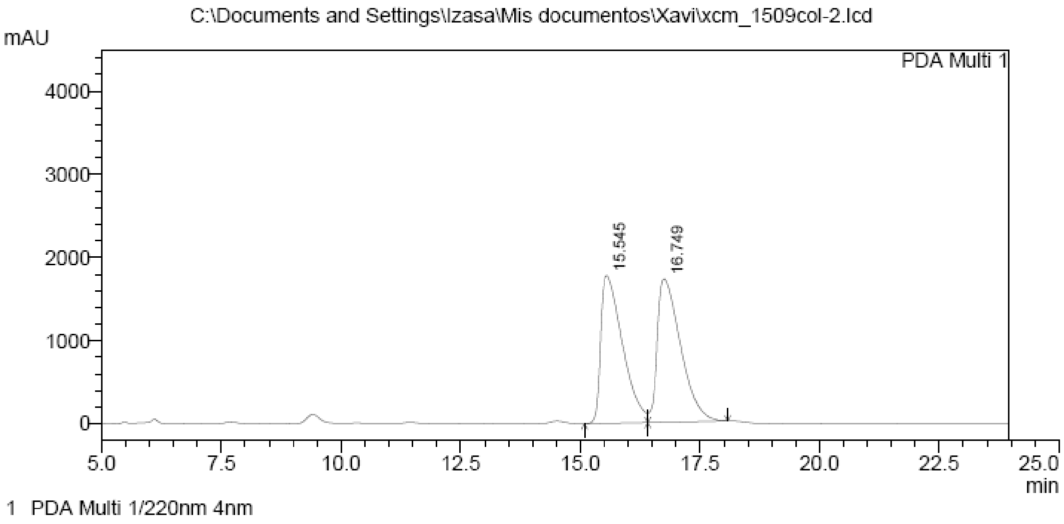
Enantiomeric excess: -93%(β-ICPN) / 84% ((DHQD)$_2$PHAL), determined by HPLC (Daicel Chiralpak IB,

i-PrOH/Hexane=5/95), UV 220 nm, flow rate 1 mL/min, t_R= 15.5 min, 16.6 min.

$[\alpha]_D^{25}$**=** +48 (c=0.6, CHCl$_3$, -93% ee)


4.16
2.10
1.00
0.72
0.61
0.61
1.76
1.07
0.78
3.88
2.51
2500
2000
1500
1000
500
0
-500
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

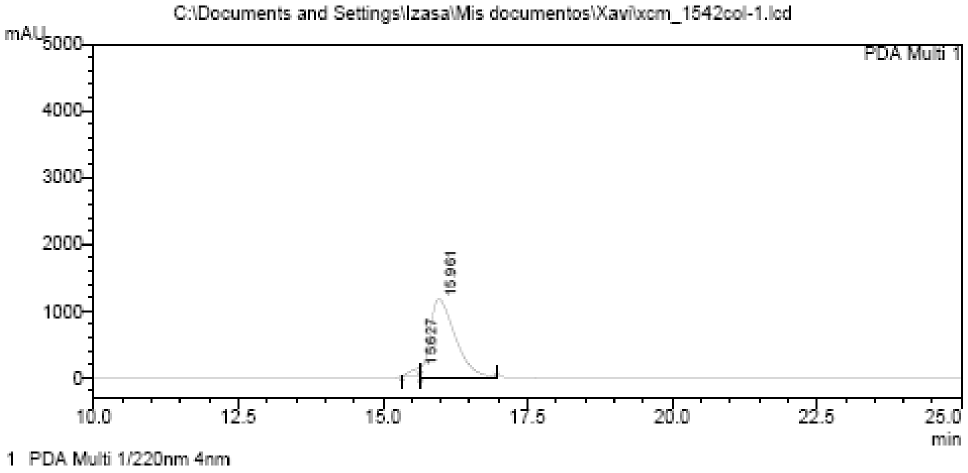

167.700
165.972
165.394
136.101
133.075
133.028
132.531
129.135
128.345
127.913
127.582
126.690
126.613
126.504
126.093
86.795
63.164
62.435
50.686
13.857
13.229
60000
50000
40000
30000
20000
10000
0
-1000
200
150
100
50
0
ppm (f1)



PeakTable

PDA Ch1 220nm 4nm

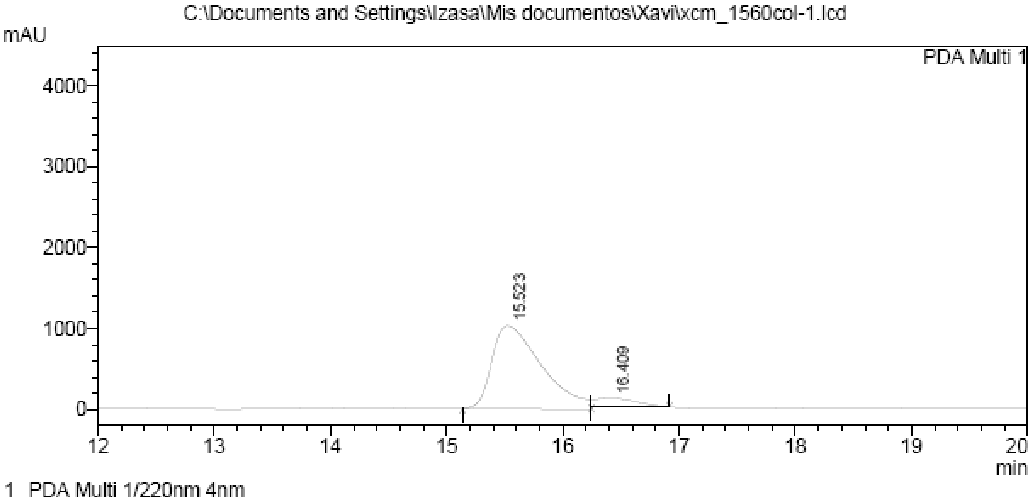
Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.545	56405260	1777742	49.196	50.766
2	16.749	58249541	1724128	50.804	49.234
Total		114654802	3501870	100.000	100.000



PeakTable

PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.627	1335125	124346	3.597	9.580
2	15.961	35777622	1173564	96.403	90.420
Total		37112747	1297909	100.000	100.000

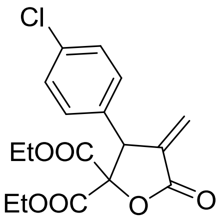


PeakTable

PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.523	30687003	1029076	91.484	90.088
2	16.409	2856539	113223	8.516	9.912
Total		33543542	1142299	100.000	100.000

diethyl 3-(4-chlorophenyl)-4-methylene-5-oxodihydrofuran-2,2(3H)-dicarboxylate



^{1}**H NMR (400 MHz, CDCl$_3$) δ** 7.34-7.25 (m, 4H), 6.56 (d, J=3.3Hz, 1H), 5.62 (d, J=2.9Hz, 1H), 5.04 (t, 3.0Hz, 1H), 4.45-4.25 (m, 2H), 3.94-3.85 (m, 1H), 3.71-3.63 (m, 1H), 1.31 (t, J=7.0Hz, 3H), 0.90 (t, J=7.2Hz, 3H).

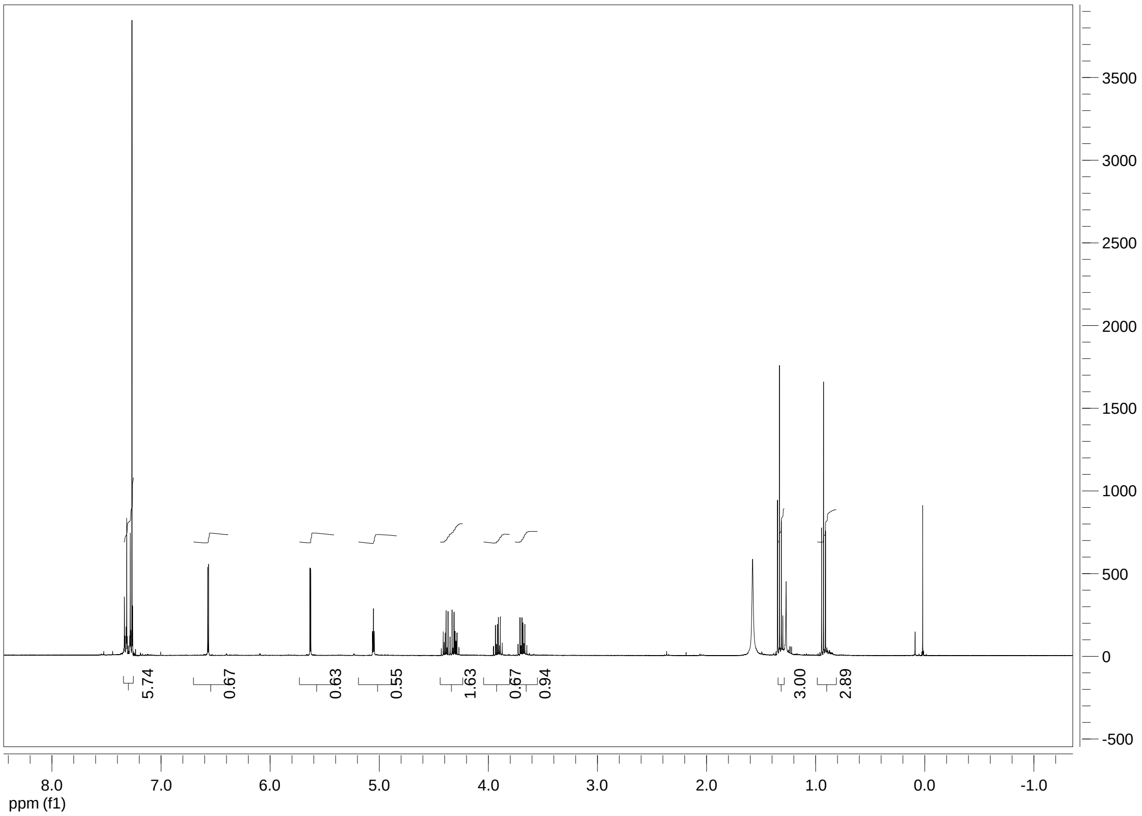
^{13}**C NMR (100 MHz, CDCl$_3$) δ** 167.4, 165.8, 165.3, 135.6, 134.6, 133.6, 131.0, 128.8, 126.0, 86.5, 63.2, 62.6, 49.9, 13.8, 13.4.

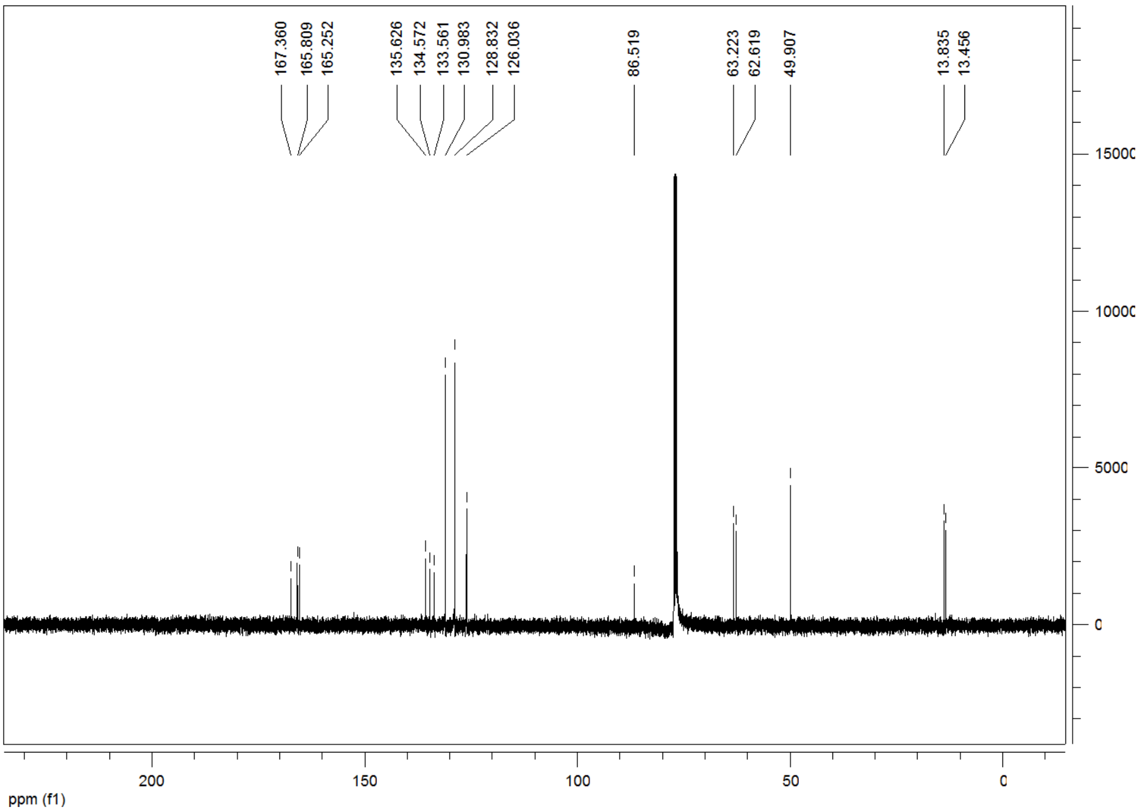
HRMS (ESI) calcd. for $C_{17}H_{18}ClO_6$ $(M+H)^+$ 353.0786, found 353.0783.

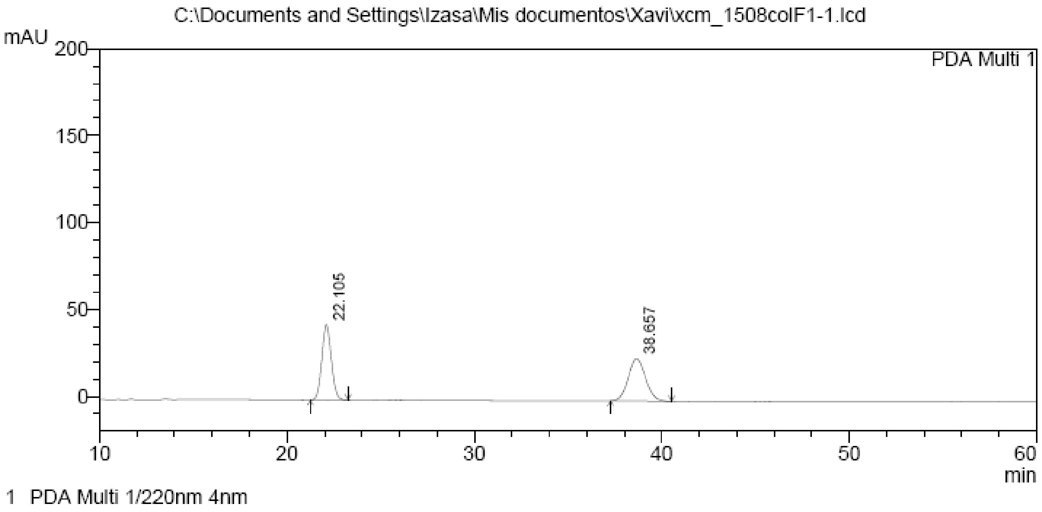
Enantiomeric excess: 86%(β-ICPN) / -92% ((DHQD)$_2$PHAL) determined by HPLC (Daicel Chiralpak IC,

i-PrOH/Hexane=20/80), UV 220 nm, flow rate 1 mL/min, t_R= 22.1min 38.6 min.

$[\alpha]_D^{25}$= +36 (c=0.8, $CHCl_3$, 86% ee)



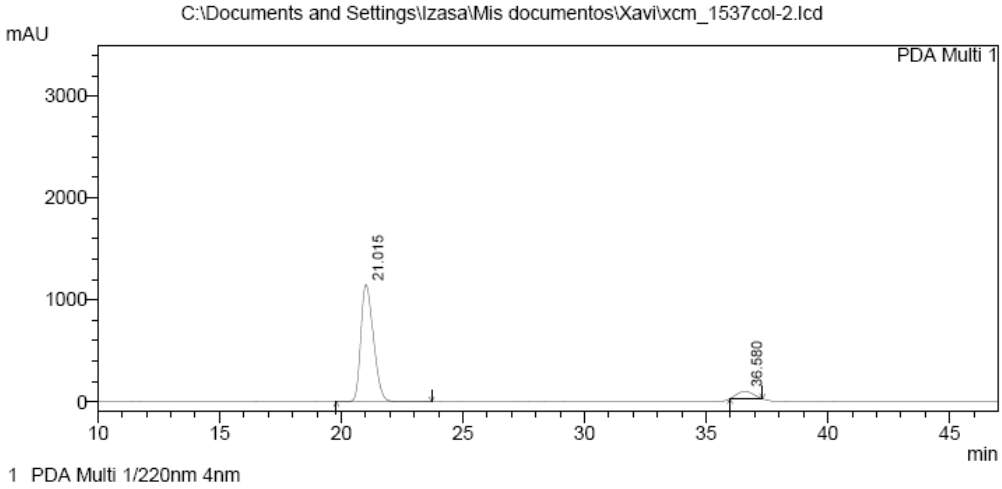




PeakTable

PDA Ch1 220nm 4nm

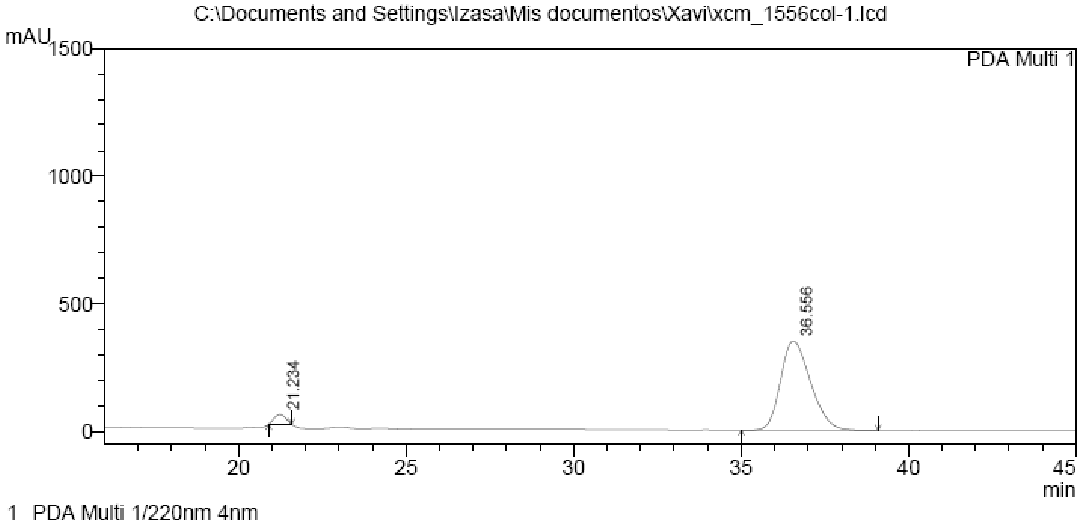
Peak#	Ret. Time	Area	Height	Area %	Height %
1	22.105	1532716	43358	49.829	64.362
2	38.657	1543249	24008	50.171	35.638
Total		3075966	67366	100.000	100.000



PeakTable

PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.015	41558288	1148728	92.578	94.118
2	36.580	3331655	71785	7.422	5.882
Total		44889943	1220513	100.000	100.000

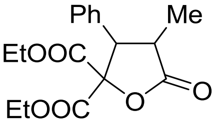


PeakTable

PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.234	867735	36074	3.868	9.372
2	36.556	21566727	348819	96.132	90.628
Total		22434462	384892	100.000	100.000

diethyl 4-methyl-5-oxo-3-phenyldihydrofuran-2,2(3H)-dicarboxylate

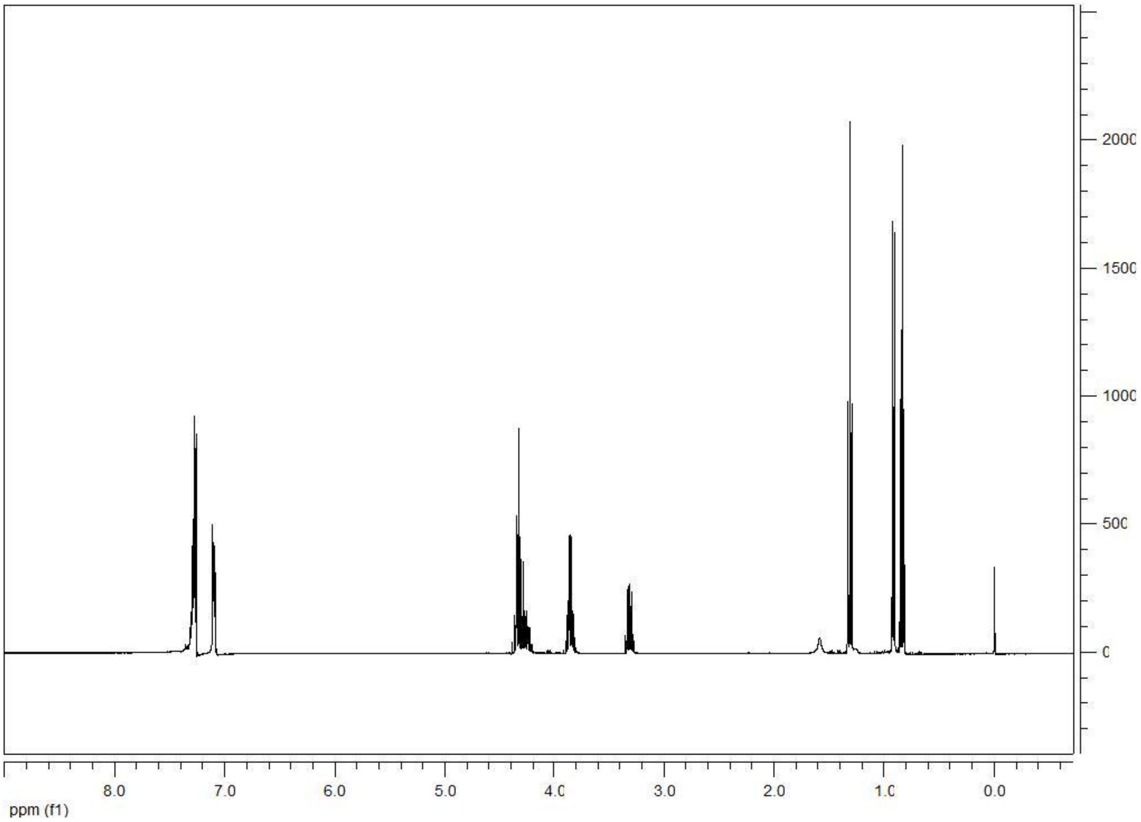


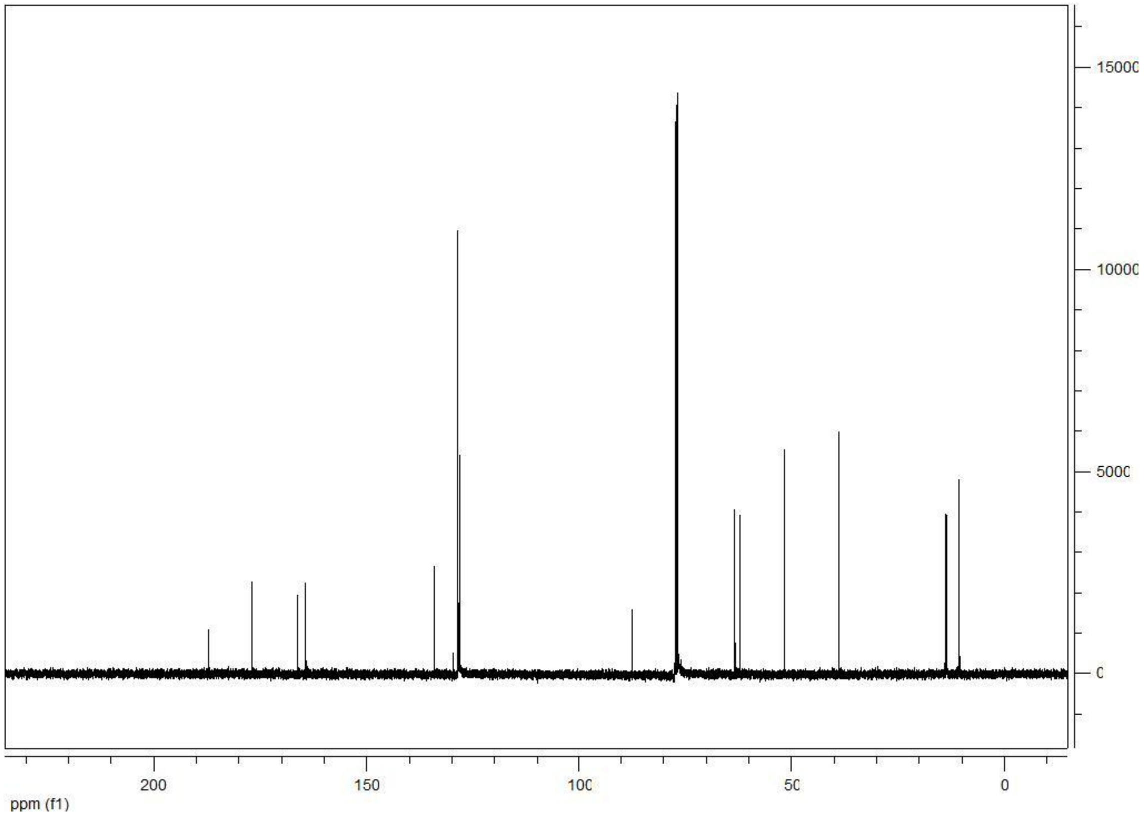
To a solution of compound xx (0.2 mmol) in EtOAc (2 mL) was added 10mol% Pd/C (0.1 equiv.). Hydrogenation was carried out under hydrogen atmosphere at room temperature and atmospheric pressur for 12h. After completation of the reaction (monitored by TLC), the reaction mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. Purification of the residue by flash column chromatograohy (Hexane/EtOAC 3:1) afforded the desired reduced product (93% yield, >25:1 *d.r.*).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.30-7.24 (m, 3H), 7.12-7.06 (m, 2H), 4.39-4.18 (m, 3H), 3.88-3.80 (m, 2H), 3.31 (m, 1H), 1.31 (t, J=7.2Hz, 3H), 0.91 (d, J=7.4Hz, 3H), 0.83 (t, J=7.2Hz, 3H).

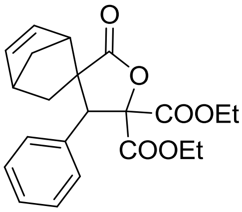
^{13}C NMR (100 MHz, CDCl$_3$) δ 187.2, 176.8, 166.3, 164.4, 134.1, 128.7, 128.6, 128.2, 87.4, 63.3, 62.1, 38.9, 13.8, 13.4, 10.6.

HRMS (ESI) calcd. for $C_{17}H_{21}O_6$ $(M+H)^+$ 321.1333, found 321.1341.




15000
10000
5000
0
200
150
100
50
0
ppm (f1)

diethyl 2'-oxo-4'-phenyl-2'H-spiro[bicyclo[2.2.1]hept[5]ene-2,3'-furan]-5',5'(4'H)-dicarboxylate

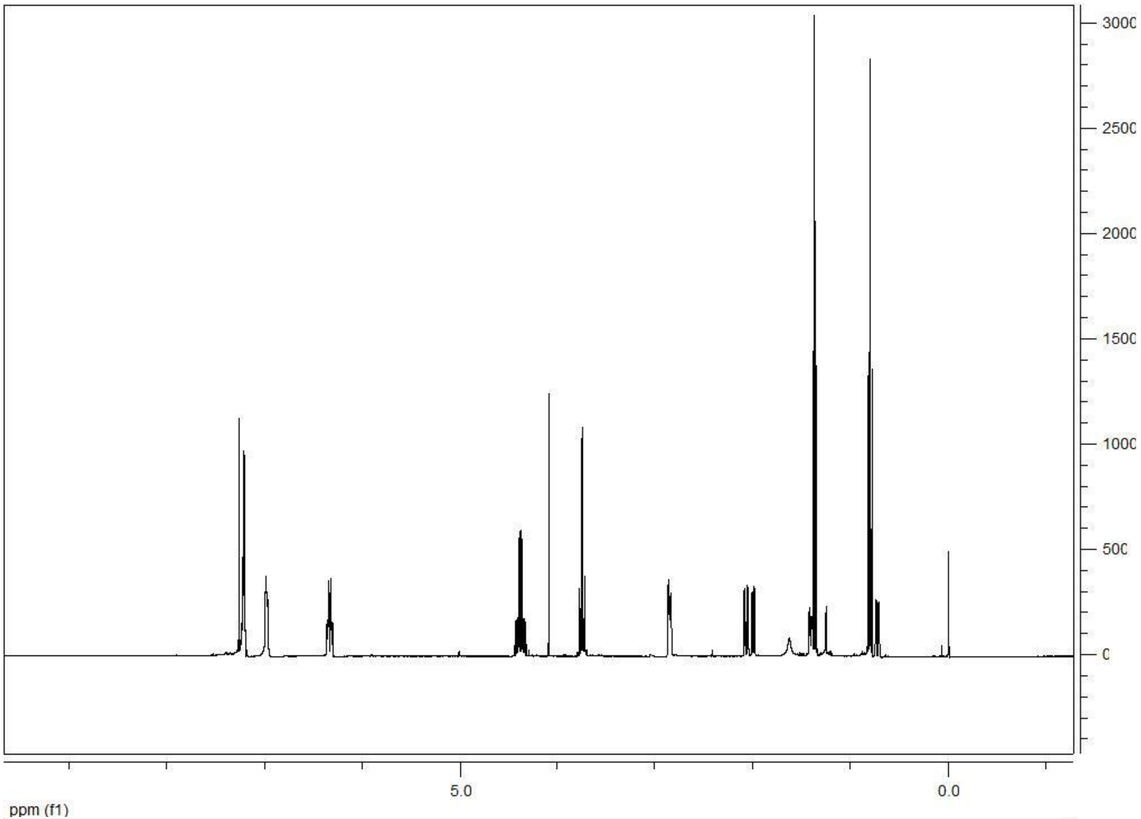


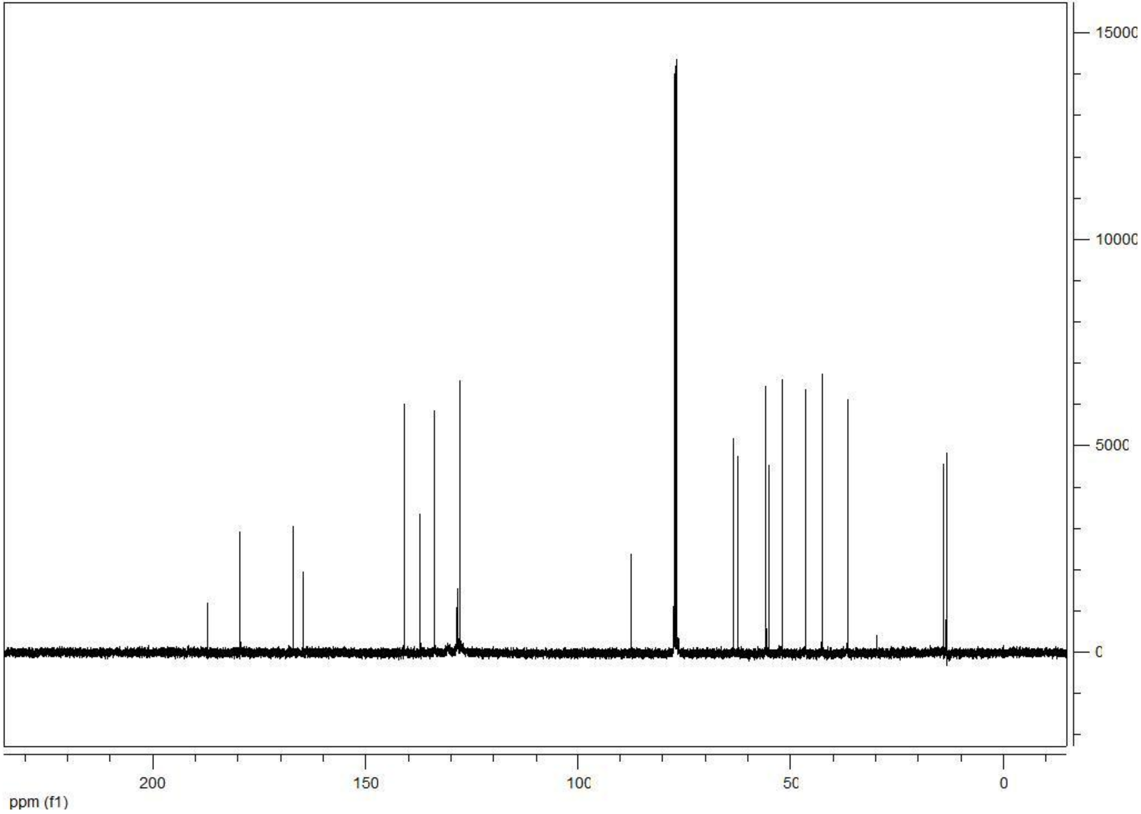
A solution of 50 mg of compound X (0.16 mmol, 1 equiv.) and 100 mg of freshly distilled ciclopentadiene (1.6 mmol, 10 equiv.) in 5 mL of toluene was refluxed overnight. Then, the organic solvent was evaporated and the crude product was directly purified by flash column chromatography (Hexane: EtOAc 3:1) to afford the desired product(91% of yield, >25:1 *dr*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.17 (m, 3H), 7.01-6.94 (m, 2H), 6.37-6.28 (m, 2H), 4.46-4.29 (m, 2H), 4.02 (s, 1H), 3.74 (q, J=7.1Hz, 2H), 2.87-2.81 (bs, 2H), 2.06 (dd, J_1=12.3Hz, J_2=3.7Hz, 1H), 1.99 (d, J= 9.1Hz, 1H), 1.43-1.39 (m, 1H), 1.36 (t, J=7.3Hz, 3H), 0.79 (t, J=7.0Hz, 3H), 0.72 (dd, J_1=12.5Hz, J_2=3.3Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 187.1, 179.4, 167.0, 164.6, 137.2, 141.0, 133.8, 128.4, 127.8, 87.4, 63.3, 62.2, 55.7, 55.1, 51.9, 46.3, 42.4, 36.5, 13.9, 13.3.

HRMS (ESI) calcd. for $C_{22}H_{28}NO_6$ $(M+NH_4)^+$ 402.1911, found 402.1916.


3000
2500
2000
1500
1000
500
0
5.0
0.0
ppm (f1)


15000
10000
5000
0
200
150
100
50
0
ppm (f1)

Conformational analysis and absolute configuration determination of 4b

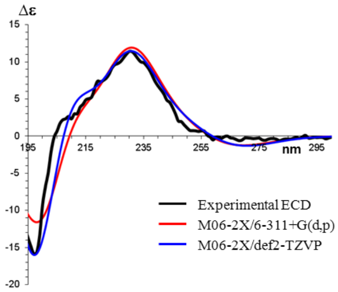
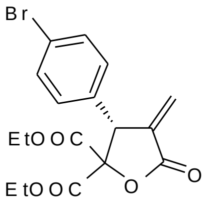


Figure 1. Simulations of the ECD spectrum of **4b** (red and blue traces). The experimental spectrum (black trace) was obtained of acetonitrile solution (1.0 10^{-4} M, 0.2 cm path length). Δε are expressed in Mol L^{-1} cm^{-1}.

All the attempts to obtain good crystals of the prepared compounds were not successful. Moreover, with the exception of **3b**, a suitable heavy atom (Z > Si using standard Mo-Kα radiation[1]) was not available for the assignment of the absolute configuration by the anomalous dispersion X-ray method.[2] For this reason the configuration was determined by a combination of conformational analysis and theoretical simulations of chiro-optical spectra. Compound **4b** was selected as representative compound.



4b

The determination of the absolute configuration (AC) of chiral molecules using chiroptical techniques like optical rotation (OR), electronic circular dichroism (ECD), and vibrational circular dichroism (VCD) has gained feasibility and reliability because of the development of methods for the prediction of these properties based on density functional theory (DFT) and on its Time-Dependent formalism (TD-DFT).[3] In the present case the theoretical calculation of the electronic circular dichroism spectra (ECD) was selected for the absolute configuration assignment. Although the rigidity of

---

[1] Hooft, R. W. W.; Stravera, L. H.; Spek, A. L. *J. Appl. Cryst.*, **2008**, *41*, 96–103

[2] Bijvoet, J. M.; Peerdeman, A.F.; Van Bommel, A.J. *Nature*, **1951**, *168*, 271.

[3] For reviews see: a) Bringmann, G.; Bruhn, T.; Maksimenka, K.; Hemberger, Y. *Eur. J. Org. Chem*. **2009**, 2717-2727.b) Crawford, T.D.; Tam, M.C.; Abrams, M.L. *J. Chem. Phys. A* **2007**, *111*, 12057–12068. c) Pescitelli, G.; Di Bari, L.; Berova, N. *Chem. Soc. Rev.* **2011**, *40*, 4603-4625. d) Mazzanti, A.; Casarini, D. WIREs *Comput. Mol. Sci.* **2012**, *2*, 613-641

the lactone core of **4b** helps in the reduction of the number of conformations to be considered,[4] the conformational freedom of the carboxyethyl moieties represent a challenging issue for the conformational analysis step. A survey on the conformational preferences of this fragment of the molecule was performed using the CSD database.[5] The analysis of two similar structures[6] showed that the terminal methyl groups adopts either anti or *gauche* relationship with the carbonyl group and the preferred relative disposition is largely variable depending on the remaining geometry of the molecule. Being the ethyl groups a non-chromophoric part of **4b**, their contribution to the ECD spectrum can be considered marginal. For this reason the two ethyl groups were substituted by two methyl groups to reduce the conformational space to be explored. The following discussion refers to the model compound **4b$_{\mathbf{Me}}$.**

A full conformational search was performed by Molecular Mechanics (Monte Carlo searching together with the MMFF94 molecular mechanics force field[7]). After the elimination of duplicate or enantiomeric structures, the remaining conformers were then optimized using DFT at the B3LYP/6-311+G(d,p) level[8]. To confirm their stability and to evaluate the free energy of each conformation the harmonic vibrational frequencies were calculated at the same level and no imaginary frequencies were observed. After DFT minimization, four conformations were found to be enclosed in a 3.5 kcal/mol window (conformation **a-d** as in Table S1). They exhibit the very same conformation of the lactone core, and they differ in the relative dispositions of the two carboxymethyl groups (Figure 1). The calculated energy differences suggest that only conformations **a** and **b** should be appreciably populated.

---

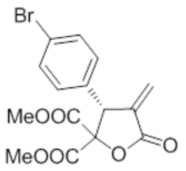
[4] Polavarapu, P.L.; Donahue, E.A.; Shanmugam, G.; Scalmani, G.; Hawkins, E.K.; Rizzo, C.; Ibnusaud, I.; Thomas, G.; Habel, D.; Sebastian, D. *J. Phys. Chem. A* **2011**, *115*, 5665–5673.

[5] CSD database rev 5.33, November 2011.

[6] A) Lu, J-M.; Shi, M. *J. Org. Chem.* **2008**, *73*, 2206-2210. b) Kano,T.; Yamamoto, A.; Song, S.; Maruoka, K. *Chem. Commun.* **2012**, *47*, 4358-4360

[7] Titan 1.0.5, Wavefunction inc.

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



$4b_{Me}$

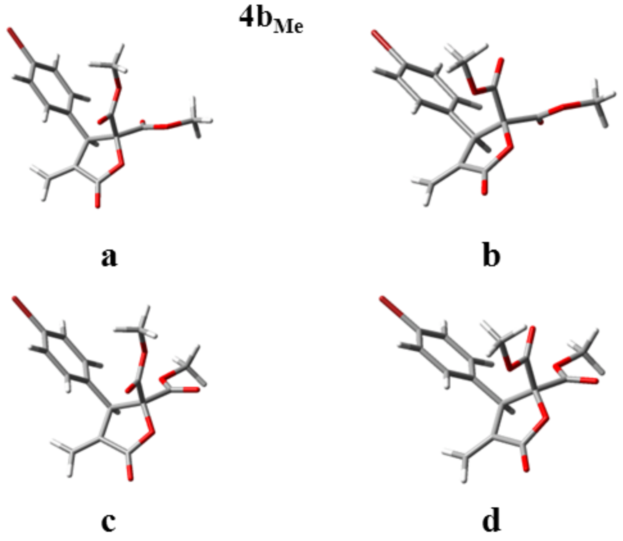


Figure S1. The four available conformations of **$4b_{Me}$**. Geometry optimization at the B3LYP/6-311+G(d,p) level.

Table S1. Calculated energies for the four conformations of **$4b_{Me}$** [B3LYP/6-311+G(d,p) level, in kcal/mol].

Conformation	ΔE	ΔG°	Pop % (ΔG°)
a	0.00	0.00	58
b	0.61	0.22	40
c	2.88	2.18	1.5
d	3.50	2.98	0.5

The electronic excitation energies and rotational strengths have been calculated for the *R* enantiomer as isolated molecule in the gas phase using TD-DFT with four different methods (functionals) and two different basis sets, to monitor if different theoretical levels of calculation provide different shapes of the simulated spectra.[9] Simulations were performed with the hybrid functionals BH&HLYP[10] and M06-2X,[11] the long-range correlated LC-ωB97XD that includes empirical dispersion,[12] and CAM-

---

[9] Check, C.E.; Gilbert, T.M. *J.Org.Chem.* **2005**, *70*, 9828-9834

[10] In Gaussian 09 the BH&HLYP functional has the form: $0.5*E_X^{HF} + 0.5*E_X^{LSDA} + 0.5*\Delta E_X^{Becke88} + E_C^{LYP}$

[11] Zhao, Y.; Truhlar, D.G. *Theor. Chem. Acc.* **2008**, *120*, 215-241.

[12] Chai, J-D.; Head-Gordon,M. *Phys. Chem. Chem. Phys.*, **2008**, *10*, 6615-6620.

B3LYP that includes long range correction using the Coulomb Attenuating Method.[13]. The calculations employed either the 6-311++G(2d,p) or the def2-TZVP[14] basis sets, that proved to be accurate at a reasonable computational cost.[15][16] Rotational strengths were calculated in both length and velocity representation, the resulting values being very similar (RMS differences < 5%). For this reason the errors due to basis set incompleteness should be very small, or negligible.[17]

As shown in Figure S2, the simulated spectra are similar on varying either the functional or the basis set. This implies that different populations of the conformers does not heavily influence the averaged spectrum. In addition to that, it is secured that any conformational modification caused by the presence of the ethyl group in **4b** do not influence the simulated spectra. All the calculations were performed supposing the *R* Absolute Configuration of **4b**$_{\mathbf{Me}}$.

---

[13] Yanai, T.; Tew, D.; Handy, N. *Chem. Phys. Lett.* **2004**, *393*, 51-57.

[14] Weigend, F.; Ahlrichs, R. *Phys. Chem. Chem. Phys.*,**2005**, *7*, 3297-305

[15] a) Cera, G.; Chiarucci,M.; Mazzanti, A.; Mancinelli, M.; Bandini, M. *Org. Lett.* **2012**, *14*, 1350-1353; b) Pesciaioli, F.; Righi, P.; Mazzanti, A.; Bartoli, G.; Bencivenni, G. *Chem. Eur. J.* **2011**, *17*, 2482-2485; c) Duce, S.; Pesciaioli, F.; Gramigna, L.; Bernardi, L.; Mazzanti, A.; Ricci, A.; Bartoli, G.; Bencivenni, G. *Adv. Synt. Catal.* **2011**, *353*, 860-864; d) Bernardi, L.; Comes-Franchini, M.; Fochi, M.; Leo, V.; Mazzanti, A.; Ricci, A. *Adv. Synt. Catal.* **2010**, *352*, 3399-3406.

[16]. Woźnica, M.; Butkiewicz, A.; Grzywacz, A.; Kowalska, P.; Masnyk, M.; Michalak, K.; Luboradzki, R.; Furche, F.; Kruse, H.; Grimme, S.; Frelek J. *J. Org. Chem.* **2011**, *76*, 3306-3319

[17] Stephens, P.J.; McCann, D.M.; Devlin, F.J.; Cheeseman, J.R.; Frisch, M.J. *J. Am. Chem. Soc.* **2004**, *126*, 7514-7521

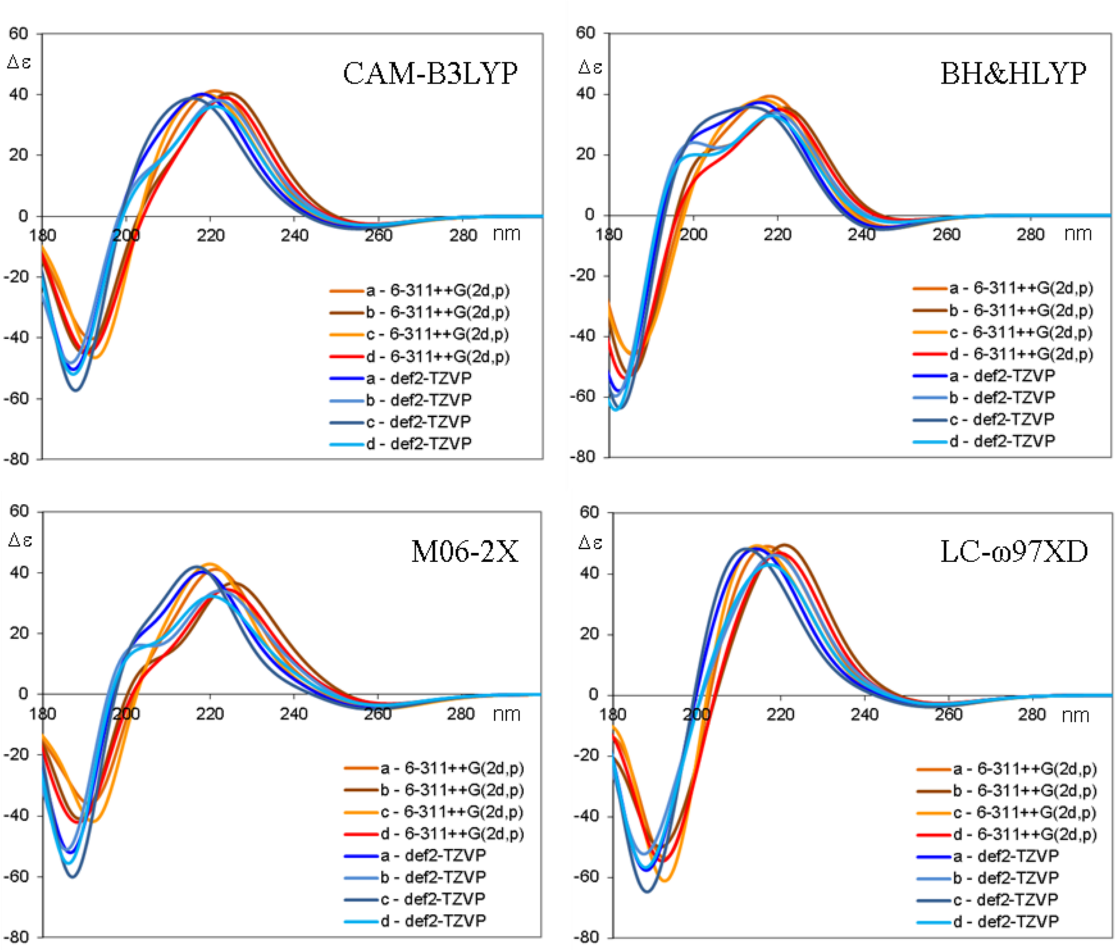


Figure S2. TD-DFT simulated spectra calculated for **4b$_{\mathbf{Me}}$** with the four different methods of calculation. Within the same box, the eight lines correspond to the spectra of the four conformations calculated with the two different basis sets [reddish lines: 6-311++G(2d,p). Bluish lines: def2-TZVP]. The spectra were generated as the sum of Gaussian lines (0.5 eV line width) centered on the calculated discrete transitions.

The conformationally averaged spectra were then obtained using a 58:40:1.5:0.5 ratio, corresponding to a Boltzmann distribution based on the ZPE-corrected free energies at +25°C (Figure S3).

The best simulation was obtained by the M06-2X/def2-TZVP combination, but all the simulated spectra consistently reproduce well the experimental one. The good agreement with the experimental spectrum also confirms that the initial assumption about the feasibility to replace the ethyl groups with two methyl groups was correct. The absolute configuration of **4b** could be thus reliably assigned as *R*.

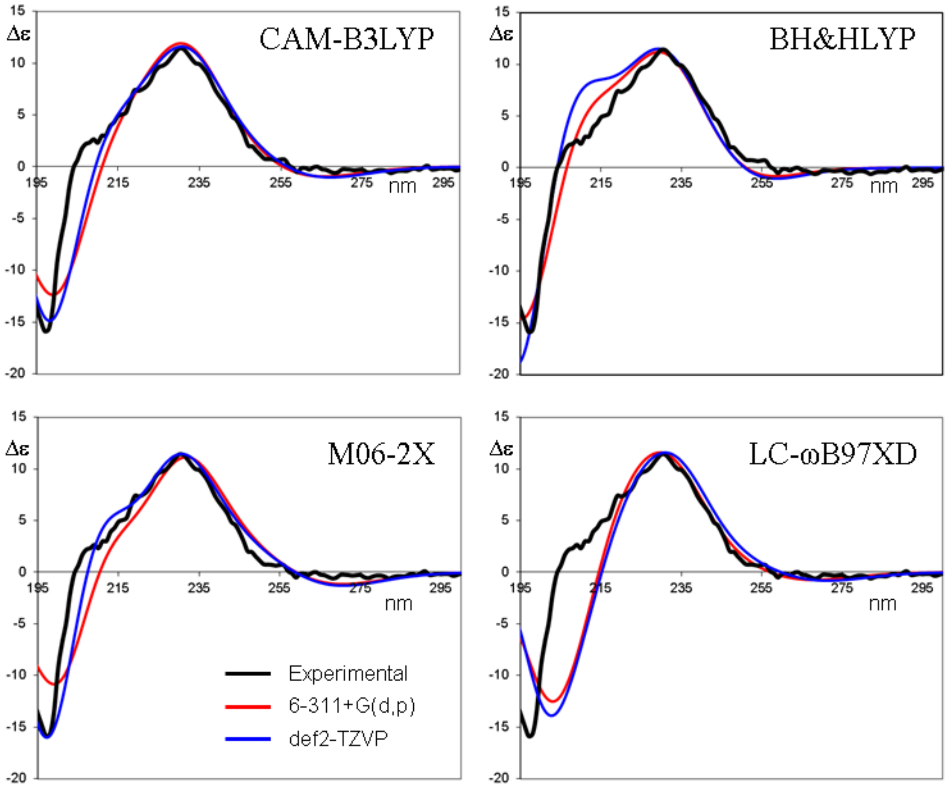


Figure S3: Simulations of the ECD spectrum of **4b**. Each simulated spectrum [calculated for **4b**$_{\mathbf{Me}}$. Red lines: 6-311+G(2d,p) basis set; blue lines: def2-TZVP basis set] was obtained starting from the spectra obtained for the four conformations weighted by Boltzmann distribution using free energies of table S1. The experimental spectrum of **4b** (black trace) was obtained of acetonitrile solutions (1.0 10^{-4} M, 0.2 cm path length). Δε are expressed in Mol L^{-1} cm^{-1}. The simulated spectra were vertically scaled and red-shifted to match the experimental maximum at 229 nm (8-15 nm depending on the functional/basis set combination).