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Enantioselective vinylogous Mukaiyama aldol reaction of α-ketoesters under bifunctional organocatalysis

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1. General methods and starting materials

All dry solvents were dried using activated 4Å molecular sieves and stored under nitrogen. 4Å molecular sieves, 1.6-2.5 mm of particle size, were activated by microwave (700W) (3 x 60 sec) and subsequent cycles of vacuum/nitrogen. Substrates **1a-g, 1i, 1l, 1m, 1p-q,** as well as catalyst **3a** and **3b**, were acquired from commercial sources. Catalysts **3c-f** and α-ketoesters **1h**, **1j**, **1k**, **1n** were synthesized following a procedure described in the literature.[1] (Buta-1,3-dien-1-yloxy)trimethylsilane (**2a**) was acquired from commercial sources as a 70:30 *E:Z* mixture. (*Z*)-trimethyl((3-methylbuta-1,3-dien-1-yl)oxy)silane (**2b**) was synthesized following a procedure described in the literature.[2] For thin layer chromatography (TLC), silica gel plates with fluorescence indicator 254 nm were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of potassium permanganate in water followed by heating. Flash column chromatography was performed using Geduran® Silica Gel 60 (0.040-0.063 nm). Cyclohexane and ethyl acetate for flash chromatography were acquired from commercial sources and were used without previous purification. Optical rotation was recorded in cells with 10 cm path length; the specific solvents and concentrations (in g/100 mL) are indicated. NMR spectra were acquired on a *Bruker Avance 300 MHz spectrometer*, running at 300 and 75 MHz for ^{1}H and ^{13}C, respectively. ^{19}F-NMR spectra was acquired on a *Bruker Avance 500 MHz spectrometer*, running at 471 MHz. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$, 7.26 ppm for ^{1}H-NMR and 77.2 ppm for ^{13}C-NMR). ^{13}C-NMR was acquired on a broad band decoupled mode. The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), bs (broad singlet). Electrospray ionization has been used for measuring the exact mass (indicated for each case): MS (ESI) (Electrospray ionization mass spectroscopy) was acquired with an *Agilent Technologies 6120 Quadrupole LC/MS*. In this technique, *MassWorks software ver. 4.0.0.0 (Cerno Bioscience*) was used for the formula identification. *MassWorks* is a MS calibration software which calibrates for isotope profile as well as for mass accuracy, allowing highly accurate comparisons between calibrated and theoretical spectra.[3]

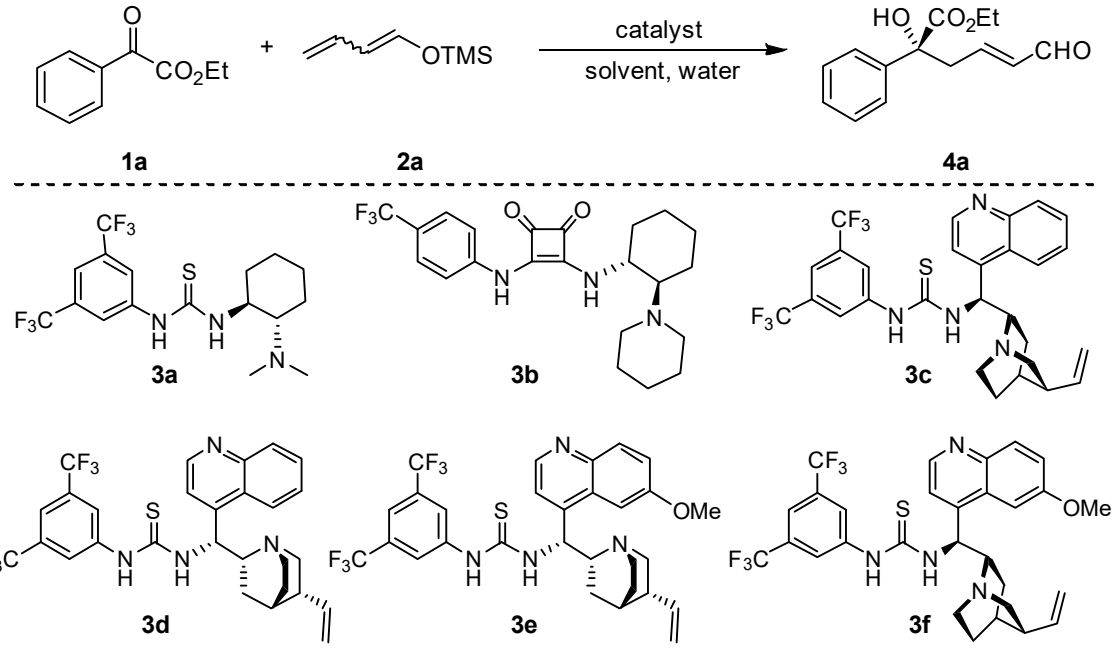
[1] Catalyst synthesis: a) C. Cassani, R. Martín-Rapún, E. Arceo, F. Bravo and P. Melchiorre, *Nature Protocols* 2013, **8**, 325-344; α-ketoester synthesis: b) J. Zhuang, C. Wang, F. Xie, W. Zhang, *Tetrahedron* 2009, **65**, 9797-9800.

[2] M. Frías, R. Mas-Ballesté, S. Arias, C. Alvarado, J. Alemán, *J. Am. Chem. Soc.* 2017, **139**, 672-679.

[3] a) Y. Wang and M. Gu, *Anal. Chem.* 2010, **82**, 7055-7062; b) Y. Wang, Methods for Operating MS Instrument Systems, United States Patent No. 6,983,213, **2006**; c) N. Ochiaia, K. Sasamoto, K. MacNamara *Journal of Chromatography A* 2012, **1270**, 296-304; d) H. Ho, R. Lee, C. Chen, S. Wang, Z. Li and M. Lee, *Rapid Commun. Mass Spectrom.* 2011, **25**, 25-32.

Enantiomeric excess was determined in a Supercritical Fluid Chromatography (SFC) with chiral columns. The chromatograms were acquired with an *Agilent Technologies 1260 Infinity* with a *SFC module* and a UV-vis detector. The chiral columns used were: Chiralpak IA, IB-3, IC, ID-3, IG-3 (see in each case).

2. Optimization table

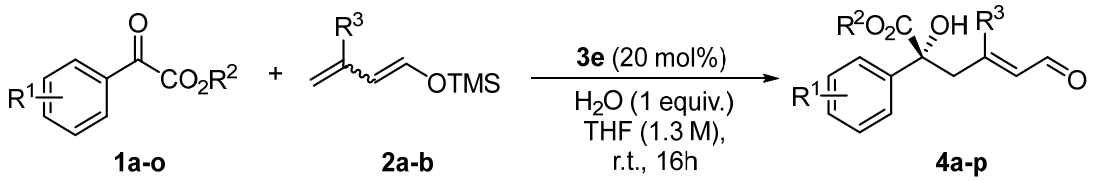


Entry[a]	*Catalyst*	*Solvent*	*Solvent amount (mL)*	*H_2O (equiv.)*	*Yield (%)*	*ee (%)*[b]
1	**3a**	DCM	0.3	3	30	-78
2	**3b**	DCM	0.3	3	26	23
3	**3c**	DCM	0.3	3	19	-79
4	**3d**	DCM	0.3	3	29	89
5	**3e**	DCM	0.3	3	36	93
6	**3f**	DCM	0.3	3	27	-91
7	**3e**	DCE	0.3	3	21	91
8	**3e**	Toluene	0.3	3	25	91
9	**3e**	Xylene	0.3	3	25	90
10	**3e**	Dioxane	0.3	3	33	91
11	**3e**	THF	0.3	3	53	95
12	**3e**	^{t}BuOMe	0.3	3	46	93
13	**3e**	THF	0.3	0	-	-
14	**3e**	THF	0.3	1	57	95

15	**3e**	THF	0.3	6	45	93
16	**3e**	THF	0.15	1	67	95
17	**3e**	THF	0.075	1	70	95
18	**3e**	THF	-	1	64	94
19[c]	**3e**	THF	0.075	1	66	96
20[d]	**3e**	**THF**	**0.075**	**1**	**79**	**95**
21[e]	**3e**	THF	0.075	1	53	93
22[f]	**3e**	THF	0.075	1	63	93
22[g]	**3e**	THF	0.075	1	76	94

[a] Standard conditions: 0.1 mmol of **1a**, 0.5 mmol of a 70:30 *E:Z* mixture of **2a**, 0.3 mmol of H_2O and 0.01 mmol of catalyst **3** in 0.3 mL of solvent (0.3 M) were stirred at room temperature (25 °C) overnight (16 h). [b] Enantiomeric excess was measured by Supercritical Fluid Chromatography (SFC) using chiral columns. [c] 0.005 mmol of catalyst was used. [d] 0.02 mmol of catalyst was used. [e] 0.30 mmol of a 70:30 *E:Z* mixture of **2a** was used. [f] Reaction time was 64 hours. [g] **1o** was used instead of **1a**.

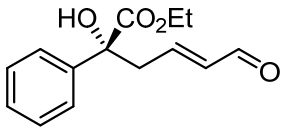
3. General procedure A: Addition of silyl dienol ethers to α-ketoesters



1a-o **2a-b** **4a-p**

Catalyst **3e** (11.9 mg, 0.02 mmol, 0.2 equiv.) was added to a vial provided with a stir bar and it was dissolved in THF (75 µL, 1.3 M). Then, α-ketoester **1a-o** (0.1 mmol, 1.0 equiv.) was added to the vial, followed by the corresponding silyl dienol ether **2a-b** (0.5 mmol, 5.0 equiv.) and water (2 µL, 0.1 mmol, 1.0 equiv.). The solution was stirred overnight at room temperature. After that, the crude was concentrated *in vacuo* and purified by flash column chromatography as described in each case.

Ethyl (*R,E*)-2-hydroxy-6-oxo-2-phenylhex-4-enoate (4a)



Following the general procedure A; reaction between ethyl 2-oxo-2-phenylacetate **1a** (15.9 µL, 0.1 mmol) and 70:30 *E:Z* mixture of (buta-1,3-dien-1-yloxy)trimethylsilane **2a** (87.7 µL, 0.5 mmol) gave product **4a** (79% yield, 95% *ee*) as a colorless oil. Eluent: cyclohexane: ethyl acetate from 97:3 to 80:20. **$[\alpha]^{25}_D$** = -13.1 (*c* 0.62, $CHCl_3$).

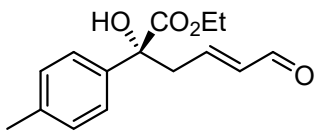
^{1}H-NMR: δ 9.45 (d, *J* = 7.9 Hz, 1H), 7.63 – 7.54 (m, 2H), 7.42 – 7.29 (m, 3H), 6.80 (ddd, *J* = 15.7, 7.6, 6.7 Hz, 1H), 6.17 (ddd, *J* = 15.7, 7.9, 1.2 Hz, 1H), 4.35 – 4.16 (m, 2H), 3.92 (s, 1H), 3.17 (ddd, *J* = 14.6, 7.6, 1.2 Hz, 1H), 3.07 (ddd, *J* = 14.6, 6.7, 1.2 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C-NMR: δ 193.8, 174.1, 151.8, 140.8, 136.1, 128.7 (2C), 128.4, 125.4 (2C), 77.7, 63.2, 42.8, 14.3 ppm.

HRMS (ESI$^+$): calculated for $C_{14}H_{15}O_3$ $[M\text{-}OH]^+$: 231.1016; found: 231.1001.

The enantiomeric excess was determined by SFC using a Chiralpak IG-3 column [CO_2/MeOH from 95:5 to 60:40 in 8 min, flow rate 2.0 mL/min], τ_{minor} = 4.41 min, τ_{major} = 4.61 min (2.5:97.5 *er*).

Ethyl (*R,E*)-2-hydroxy-6-oxo-2-(*p*-tolyl)hex-4-enoate (4b)



Following the general procedure A; reaction between ethyl 2-oxo-2-(*p*-tolyl)acetate **1b** (22.2 µL, 0.1 mmol) and 70:30 *E:Z* mixture of (buta-1,3-dien-1-yloxy)trimethylsilane **2a** (87.7 µL, 0.5 mmol) gave

product **4b** (58% yield, 92% *ee*) as a colorless oil. Eluent: cyclohexane: ethyl acetate from 97:3 to 80:20. $[\alpha]^{25}_{D}$ = -19.5 (*c* 0.60, $CHCl_3$).

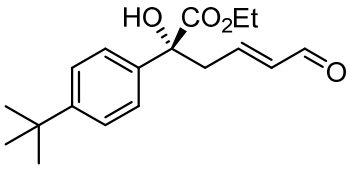
^{1}H-NMR: δ 9.45 (d, *J* = 7.9 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 6.86 – 6.73 (m, 1H), 6.17 (dd, *J* = 15.7, 7.9 Hz, 1H), 4.35 – 4.15 (m, 2H), 3.86 (bs, 1H), 3.15 (dd, *J* = 14.7, 7.7 Hz, 1H), 3.05 (dd, *J* = 14.7, 6.6 Hz, 1H), 2.35 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C-NMR: δ 193.9, 174.3, 152.1, 138.3, 137.9, 136.1, 129.4 (2C), 125.4 (2C), 77.6, 63.1, 42.8, 21.12, 14.3 ppm.

HRMS (ESI$^+$): calculated for $C_{15}H_{17}O_3$ $[M\text{-}OH]^+$: 245.1172; found: 244.1192.

The enantiomeric excess was determined by SFC using a Chiralpak IC column [CO_2/MeOH from 95:5 to 60:40 in 8 min, flow rate 3.0 mL/min], τ_{minor} = 2.81 min, τ_{major} = 3.11 min (96:4 *er*).

Ethyl (*R,E*)-2-(4-(*tert*-butyl)phenyl)-2-hydroxy-6-oxohex-4-enoate (4c)



Following the general procedure A; reaction between ethyl 2-(4-(*tert*-butyl)phenyl)2-oxoacetate **1c** (28.1 µL, 0.1 mmol) and 70:30 *E:Z* mixture of (buta-1,3-dien-1-yloxy)trimethylsilane **2a** (87.7 µL, 0.5 mmol) gave product **4c** (68% yield, 94% *ee*) as a slightly yellow oil. Eluent: cyclohexane: ethyl acetate from 97:3 to 80:20. $[\alpha]^{25}_{D}$ = -12.8 (*c* 0.80, $CHCl_3$).

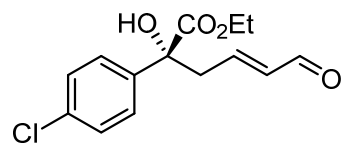
^{1}H-NMR: δ 9.46 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 6.88 – 6.74 (m, 1H), 6.18 (dd, *J* = 15.7, 7.9 Hz, 1H), 4.36 – 4.15 (m, 2H), 3.85 (s, 1H), 3.16 (dd, *J* = 14.7, 7.9 Hz, 1H), 3.05 (dd, *J* = 14.7, 6.5 Hz, 1H), 1.32 (s, 9H), 1.28 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C-NMR: δ 193.9, 174.2, 152.1, 151.4, 137.9, 136.0, 125.6 (2C), 125.1 (2C), 77.6, 63.1, 42.8, 34.7, 31.4 (3C), 14.3 ppm.

HRMS (ESI$^+$): calculated for $C_{18}H_{23}O_3$ $[M\text{-}OH]^+$: 287.1642; found: 287.1670.

The enantiomeric excess was determined by SFC using a Chiralpak IC column [CO_2/MeOH from 95:5 to 60:40 in 8 min, flow rate 3.0 mL/min], τ_{minor} = 2.67 min, τ_{major} = 3.00 min (97:3 *er*).

Ethyl (*R,E*)-2-(4-chlorophenyl)-2-hydroxy-6-oxohex-4-enoate (4d)



Following the general procedure A; reaction between ethyl 2-(4-chlorophenyl)2-oxoacetate **1d** (17.5 µL, 0.1 mmol) and 70:30 *E:Z* mixture of (buta-1,3-dien-1-yloxy)trimethylsilane **2a** (87.7 µL, 0.5 mmol) gave product **4d** (80% yield, 95% *ee*) as a colorless oil. Eluent: cyclohexane: ethyl acetate from 97:3 to 80:20. $[\alpha]^{25}_{D}$ = -16.7 (*c* 0.88, $CHCl_3$).

^{1}H-NMR: δ 9.45 (d, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 8.6 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 6.76 (ddd, *J* = 15.6, 7.7, 6.6 Hz, 1H), 6.16 (dd, *J* = 15.6, 7.8 Hz, 1H), 4.35 – 4.17 (m, 2H), 3.96 (bs, 1H), 3.13 (ddd, *J* = 14.7, 7.7, 1.3 Hz, 1H), 3.03 (ddd, *J* = 14.7, 6.6, 1.3 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H) ppm.

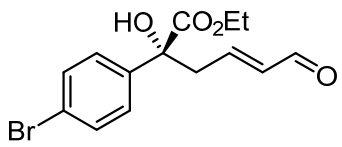
^{13}C-NMR: δ 193.7, 173.8, 151.2, 139.2, 136.3, 134.5, 128.9 (2C), 127.1 (2C), 77.3, 63.4, 42.8, 14.3 ppm.

HRMS (ESI$^+$): calculated for $C_{14}H_{14}ClO_3$ [M-OH]$^+$: 265.0626; found: 265.0653.

The enantiomeric excess was determined by SFC using a Chiralpak IC column [CO_2/MeOH from 95:5 to 60:40 in 8 min, flow rate 3.0 mL/min], τ_{minor} = 2.83 min, τ_{major} = 3.01 min (97.5:2.5 *er*).

The reaction was scaled up to 0.5 mmol scale. General procedure A was followed and product **4d** (102 mg, 72% yield, 96% *ee*) was obtained as a colorless oil. Eluent: cyclohexane: ethyl acetate from 97:3 to 80:20. The enantiomeric excess was determined by SFC using a Chiralpak IC column [CO_2/MeOH from 95:5 to 60:40 in 8 min, flow rate 3.0 mL/min], τ_{minor} = 2.74 min, τ_{major} = 2.91 min (98:2 *er*).

Ethyl (*R,E*)-2-(4-bromophenyl)-2-hydroxy-6-oxohex-4-enoate (4e)



Following the general procedure A; reaction between ethyl 2-(4-bromophenyl)2-oxoacetate **1e** (16.5 µL, 0.1 mmol) and 70:30 *E:Z* mixture of (buta-1,3-dien-1-yloxy)trimethylsilane **2a** (87.7 µL, 0.5 mmol) gave product **4e** (66% yield, 96% *ee*) as a colorless oil. Eluent: cyclohexane: ethyl acetate from 97:3 to 80:20. **$[\alpha]^{25}_D$** = -14.3 (*c* 0.84, $CHCl_3$).

^{1}H-NMR: δ 9.45 (d, *J* = 7.9 Hz, 1H), 7.54 – 7.43 (m, 4H), 6.75 (ddd, *J* = 15.7, 7.9, 6.7 Hz, 1H), 6.16 (ddd, *J* = 15.7, 7.9, 1.2 Hz, 1H), 4.36 – 4.16 (m, 2H), 3.96 (bs, 1H), 3.13 (ddd, *J* = 14.6, 7.9, 1.2 Hz, 1H), 3.02 (ddd, *J* = 14.6, 6.7, 1.2 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C-NMR: δ 193.5, 173.5, 150.9, 139.6, 136.1, 131.7 (2C), 127.2 (2C), 122.5, 77.2, 63.3, 42.6, 14.1 ppm.

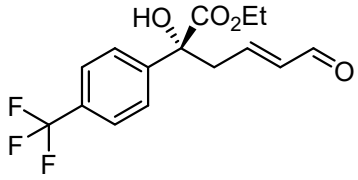
HRMS (ESI$^+$): calculated for $C_{14}H_{14}BrO_3$ [M-OH]$^+$: 309.0121; found: 309.0155.

The enantiomeric excess was determined by SFC using a Chiralpak IB-3 column [CO_2/MeOH from 95:5 to 60:40 in 8 min, flow rate 2.0 mL/min], τ_{minor} = 1.33 min, τ_{major} = 1.52 min (98:2 *er*).

The reaction was scaled up to 0.5 mmol scale. General procedure A was followed and product **4e** (95 mg, 58% yield, 96% *ee*) was obtained as a colorless oil. Eluent: cyclohexane: ethyl acetate from 97:3 to 80:20. The enantiomeric excess was determined by SFC using a Chiralpak IB-3

column [CO_2/MeOH from 95:5 to 60:40 in 8 min, flow rate 2.0 mL/min], τ_{minor} = 1.36 min, τ_{major} = 1.54 min (98:2 *er*).

Ethyl (*R,E*)-2-hydroxy-6-oxo-2-(4-(trifluoromethyl)phenyl)hex-4-enoate (4f)



Following the general procedure A; reaction between ethyl 2-oxo-2-(4-(trifluoromethyl)phenyl)acetate **1f** (20.0 µL, 0.1 mmol) and 70:30 *E:Z* mixture of (buta-1,3-dien-1-yloxy)trimethylsilane **2a** (87.7 µL, 0.5 mmol) gave product **4f** (72% yield, 95% *ee*) as a colorless oil. Eluent: cyclohexane: ethyl acetate from 97:3 to 80:20. **$[\alpha]^{25}_D$** = -15.2 (*c* 0.88, $CHCl_3$).

^{1}H-NMR: δ 9.46 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.64 (d, *J* = 8.3 Hz, 2H), 6.76 (ddd, *J* = 15.7, 7.6, 6.7 Hz, 1H), 6.17 (ddt, *J* = 15.7, 7.8, 1.2 Hz, 1H), 4.37 – 4.17 (m, 2H), 4.01 (bs, 1H), 3.18 (ddd, *J* = 14.7, 7.6, 1.2 Hz, 1H), 3.05 (ddd, *J* = 14.7, 6.7, 1.2 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H) ppm.

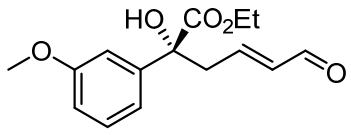
^{13}C-NMR: δ 193.6, 173.5, 150.8, 144.6, 136.4, 130.7 (q, *J* = 32.6 Hz), 126.1 (2C), 125.7 (q, *J* = 3.8 Hz, 2C), 124.1 (q, *J* = 272.3 Hz), 77.5, 63.6, 42.9, 14.2 ppm.

^{19}F-NMR: δ -62.7 ppm.

HRMS (ESI$^+$): calculated for $C_{15}H_{14}F_3O_3$ $[M\text{-}OH]^+$: 299.0890; found: 299.0882.

The enantiomeric excess was determined by SFC using a Chiralpak IA column [CO_2/MeOH from 95:5 to 60:40 in 8 min, flow rate 3.0 mL/min], τ_{minor} = 2.06 min, τ_{major} = 2.27 min (97.5:2.5 *er*).

Ethyl (*R,E*)-2-hydroxy-2-(3-methoxyphenyl)-6-oxohex-4-enoate (4g)



Following the general procedure A; reaction between ethyl 2-(3-methoxyphenyl)-2-oxoacetate **1g** (15.7 µL, 0.1 mmol) and 70:30 *E:Z* mixture of (buta-1,3-dien-1-yloxy)trimethylsilane **2a** (87.7 µL, 0.5 mmol) gave product **4g** (56% yield, 96% *ee*) as a slightly yellow oil. Eluent: cyclohexane: ethyl acetate from 97:3 to 80:20. **$[\alpha]^{25}_D$** = -10.2 (*c* 0.60, $CHCl_3$).

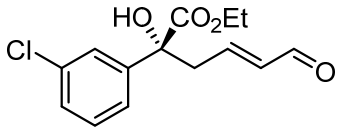
^{1}H-NMR: δ 9.45 (d, *J* = 7.9 Hz, 1H), 7.34 – 7.24 (m, 1H), 7.19 – 7.11 (m, 2H), 6.88 – 6.72 (m, 2H), 6.17 (ddt, *J* = 15.7, 7.9, 1.2 Hz, 1H), 4.35 – 4.17 (m, 2H), 3.88 (bs, 1H), 3.81 (s, 3H), 3.15 (ddd, *J* = 14.7, 7.7, 1.2 Hz, 1H), 3.05 (ddd, *J* = 14.7, 6.6, 1.2 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C-NMR: δ 193.8, 174.0, 160.0, 151.8, 142.5, 136.1, 129.8, 117.7, 113.7, 111.5, 77.7, 63.2, 55.5, 42.8, 14.3 ppm.

HRMS (ESI$^+$): calculated for $C_{15}H_{17}O_4$ $[M\text{-}OH]^+$: 261.1121; found: 261.1132.

The enantiomeric excess was determined by SFC using a Chiralpak IC column [CO_2/MeOH from 95:5 to 60:40 in 8 min, flow rate 3.0 mL/min], τ_{minor} = 2.99 min, τ_{major} = 3.42 min (98:2 *er*).

Ethyl (*R,E*)-2-(3-chlorophenyl)-2-hydroxy-6-oxohex-4-enoate (4h)



Following the general procedure A; reaction between ethyl 2-(3-chlorophenyl)-2-oxoacetate **1h** (22.6 µL, 0.1 mmol) and 70:30 *E:Z* mixture of (buta-1,3-dien-1-yloxy)trimethylsilane **2a** (87.7 µL, 0.5 mmol) gave product **4h** (82% yield, 95% *ee*) as a slightly yellow oil. Eluent: cyclohexane: ethyl acetate from 97:3 to 80:20. **$[\alpha]^{25}_D$** = -16.7 (*c* 0.86, $CHCl_3$).

^{1}H-NMR: δ 9.46 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 0.7 Hz, 1H), 7.53 – 7.42 (m, 1H), 7.36 – 7.26 (m, 2H), 6.83 – 6.69 (m, 1H), 6.16 (ddt, *J* = 15.7, 7.8, 1.2 Hz, 1H), 4.37 – 4.18 (m, 2H), 3.96 (bs, 1H), 3.14 (ddd, *J* = 14.7, 7.6, 1.2 Hz, 1H), 3.03 (ddd, *J* = 14.7, 6.6, 1.2 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H) ppm.

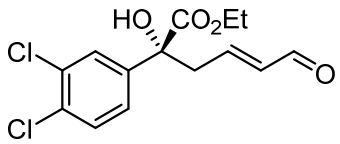
^{13}C-NMR: δ 193.7, 173.6, 151.1, 142.8, 136.3, 134.8, 130.0, 128.6, 125.9, 123.8, 77.3, 63.5, 42.8, 14.3 ppm.

HRMS (ESI$^+$): calculated for $C_{14}H_{14}ClO_3$ $[M\text{-}OH]^+$: 265.0626; found: 265.0649.

The enantiomeric excess was determined by SFC using a Chiralpak IC column [CO_2/MeOH from 95:5 to 60:40 in 8 min, flow rate 3.0 mL/min], τ_{minor} = 2.61 min, τ_{major} = 2.85 min (97:3 *er*).

The reaction was scaled up and performed on a 1.0 mmol scale. General procedure A was followed and product **4h** (226 mg, 79% yield, 96% *ee*) was obtained as a colorless oil. Eluent: cyclohexane: ethyl acetate from 97:3 to 80:20. The enantiomeric excess was determined by SFC using a Chiralpak IC column [CO_2/MeOH from 95:5 to 60:40 in 8 min, flow rate 3.0 mL/min], τ_{minor} = 2.56 min, τ_{major} = 2.80 min (98:2 *er*).

Ethyl (*R,E*)-2-(3,4-dichlorophenyl)-2-hydroxy-6-oxohex-4-enoate (4i)



Following the general procedure A; reaction between ethyl 2-(3,4-dichlorophenyl)-2-oxoacetate **1i** (18.2 µL, 0.1 mmol) and 70:30 *E:Z* mixture of (buta-1,3-dien-1-yloxy)trimethylsilane **2a** (87.7 µL, 0.5 mmol) gave product **4i** (73% yield, 95% *ee*) as a slightly yellow oil. Eluent: cyclohexane: ethyl acetate from 97:3 to 80:20. **$[\alpha]^{25}_D$** = -13.8 (*c* 0.93, $CHCl_3$).

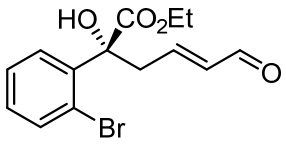
^{1}H-NMR: δ 9.46 (d, *J* = 7.8 Hz, 1H), 7.75 – 7.69 (m, 1H), 7.49 – 7.39 (m, 2H), 6.74 (ddd, *J* = 15.7, 7.5, 6.7 Hz, 1H), 6.16 (ddt, *J* = 15.7, 7.8, 1.2 Hz, 1H), 4.38 – 4.18 (m, 2H), 3.99 (bs, 1H), 3.12 (ddd, *J* = 14.6, 7.5, 1.2 Hz, 1H), 3.00 (ddd, *J* = 14.7, 6.7, 1.2 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C-NMR: δ 193.4, 173.2, 150.4, 140.8, 136.3, 132.9, 132.6, 130.5, 127.8, 125.0, 76.8, 63.5, 42.7, 14.1 ppm.

HRMS (ESI$^+$): calculated for $C_{14}H_{13}Cl_2O_3$ [M-OH]$^+$: 299.0236; found: 299.0240.

The enantiomeric excess was determined by SFC using a Chiralpak IB-3 column [CO_2/MeOH from 95:5 to 60:40 in 8 min, flow rate 2.0 mL/min], τ_{minor} = 1.35 min, τ_{major} = 1.55 min (97.3:2.7 *er*).

Ethyl (*R,E*)-2-(2-bromophenyl)-2-hydroxy-6-oxohex-4-enoate (4j)



Following the general procedure A; reaction between ethyl 2-(2-bromophenyl)-2-oxoacetate **1j** (21.5 µL, 0.1 mmol) and 70:30 *E:Z* mixture of (buta-1,3-dien-1-yloxy)trimethylsilane **2a** (87.7 µL, 0.5 mmol) gave product **4j** (66% yield, 82% *ee*) as a slightly yellow oil. Eluent: cyclohexane: ethyl acetate from 97:3 to 80:20. **$[\alpha]^{25}_D$** = +10.3 (*c* 0.86, $CHCl_3$).

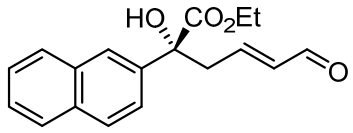
^{1}H-NMR: δ 9.48 (d, *J* = 7.9 Hz, 1H), 7.63 – 7.54 (m, 2H), 7.36 (td, *J* = 7.7, 1.3 Hz, 1H), 7.20 (td, *J* = 7.7, 1.6 Hz, 1H), 6.88 (ddd, *J* = 15.7, 7.4, 6.7 Hz, 1H), 6.16 (dd, *J* = 15.7, 7.9 Hz, 1H), 4.32 – 4.15 (m, 2H), 3.82 (bs, 1H), 3.34 (ddd, *J* = 14.7, 6.7, 1.2 Hz, 1H), 3.22 (ddd, *J* = 14.7, 7.4, 1.2 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C-NMR: δ 193.7, 173.1, 151.7, 139.7, 136.0, 134.9, 130.1, 128.1, 127.7, 122.0, 78.3, 62.9, 40.5, 14.2 ppm.

HRMS (ESI$^+$): calculated for $C_{14}H_{14}ClO_3$ [M-OH]$^+$: 309.0121; found: 309.0063.

The enantiomeric excess was determined by SFC using a Chiralpak ID-3 column [CO_2/MeOH from 95:5 to 60:40 in 8 min, flow rate 2.0 mL/min], τ_{minor} = 1.51 min, τ_{major} = 1.69 min (91:9 *er*).

Ethyl (*R,E*)-2-hydroxy-2-(napthalen-2-yl)-6-oxohex-4-enoate (4k)



Following the general procedure A; reaction between ethyl 2-(napthalen-2-yl)-2-oxoacetate **1k** (18 mg, 0.08 mmol) and 70:30 *E:Z* mixture of (buta-1,3-dien-1-yloxy)trimethylsilane **2a** (70.2 µL, 0.4 mmol) gave product **4k** (66% yield, 92% *ee*) as a slightly yellow oil. Eluent: cyclohexane: ethyl acetate from 97:3 to 80:20. **$[\alpha]^{25}_D$** = -10.2 (*c* 0.60, $CHCl_3$).

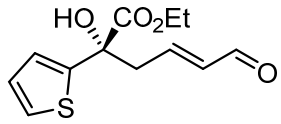
^{1}H-NMR: δ 9.45 (d, *J* = 7.9 Hz, 1H), 8.17 – 8.04 (m, 1H), 7.95 – 7.79 (m, 3H), 7.72 – 7.62 (m, 1H), 7.60 – 7.46 (m, 2H), 6.83 (ddd, *J* = 15.7, 7.7, 6.6 Hz, 1H), 6.21 (dd, *J* = 15.7, 7.9 Hz, 1H), 4.45 – 4.17 (m, 2H), 4.05 (bs, 1H), 3.28 (ddd, *J* = 14.6, 7.7, 1.1 Hz, 1H), 3.19 (ddd, *J* = 14.6, 6.6, 1.1 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C-NMR: δ 193.8, 174.1, 151.7, 138.0, 136.2, 133.2, 133.1, 128.6 (2C), 127.7, 126.8, 126.7, 124.8, 123.2, 77.9, 63.3, 42.7, 14.3 ppm.

HRMS (ESI$^+$): calculated for $C_{18}H_{17}O_3$ [M-OH]$^+$: 281.1172; found: 281.1202.

The enantiomeric excess was determined by SFC using a Chiralpak IB-3 column [CO_2/MeOH from 95:5 to 60:40 in 8 min, flow rate 2.0 mL/min], τ_{minor} = 1.90 min, τ_{major} = 2.80 min (96:4 *er*).

Ethyl (*R,E*)-2-hydroxy-6-oxo-2-(thiophene-2-yl)hex-4-enoate (4l)



Following the general procedure A; reaction between ethyl 2-oxo-2-(thiophen-2yl)acetate **1l** (14.4 µL, 0.1 mmol) and 70:30 *E:Z* mixture of (buta-1,3-dien-1-yloxy)trimethylsilane **2a** (87.7 µL, 0.5 mmol) gave product **4l** (83% yield, 94% *ee*) as a slightly yellow oil. Eluent: cyclohexane: ethyl acetate from 97:3 to 80:20. **[α]$^{25}_D$** = -32.5 (*c* 0.56, $CHCl_3$).

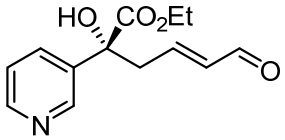
^{1}H-NMR: δ 9.47 (d, *J* = 7.9 Hz, 1H), 7.30 – 7.23 (m, 1H), 7.11 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.99 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.80 (dt, *J* = 15.7, 7.2 Hz, 1H), 6.17 (ddt, *J* = 15.7, 7.9, 1.2 Hz, 1H), 4.38 – 4.24 (m, 2H), 4.18 (bs, 1H), 3.13 (bs, 1H), 3.11 (bs, 1H), 1.31 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C-NMR: δ 193.7, 173.2, 150.8, 145.5, 136.3, 127.4, 125.8, 124.6, 76.5, 63.5, 44.0, 14.2 ppm.

HRMS (ESI$^+$): calculated for $C_{12}H_{13}O_3S$ [M-OH]$^+$: 237.0580; found: 237.0628.

The enantiomeric excess was determined by SFC using a Chiralpak IC column [CO_2/MeOH from 95:5 to 60:40 in 8 min, flow rate 3.0 mL/min], τ_{minor} = 2.91 min, τ_{major} = 3.09 min (97:3 *er*).

Ethyl (*R,E*)-2-hydroxy-6-oxo-2-(pyridine-3-yl)hex-4-enoate (4m)



Following the general procedure A; reaction between ethyl 2-oxo-2-(pyridin-3-yl)acetate **1m** (17.9 mg, 0.1 mmol) and 70:30 *E:Z* mixture of (buta-1,3-dien-1-yloxy)trimethylsilane **2a** (87.7 µL, 0.5 mmol) gave product **4m** (68% yield, 96% *ee*) as a slightly yellow oil. Eluent: cyclohexane: ethyl acetate from 97:3 to 80:20. **[α]$^{25}_D$** = -13.6 (*c* 0.57, $CHCl_3$).

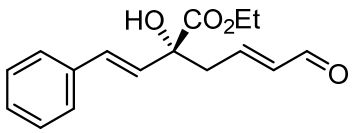
^{1}H-NMR: δ 9.45 (d, *J* = 7.8 Hz, 1H), 8.86 (d, *J* = 2.2 Hz, 1H), 8.56 (dt, *J* = 4.8, 1.6 Hz, 1H), 7.93 (ddd, *J* = 7.9, 2.2, 1.6 Hz, 1H), 7.31 (dd, *J* = 7.9, 4.8 Hz, 1H), 6.83 – 6.70 (ddd, *J* = 15.8, 7.6, 6.7 Hz, 1H), 6.23 – 6.11 (ddt, *J* = 15.8, 7.8, 1.2 Hz, 1H), 4.37 – 4.16 (m, 2H), 3.17 (ddd, *J* = 14.6, 7.6, 1.2 Hz, 1H), 3.06 (ddd, *J* = 14.6, 6.7, 1.2 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C-NMR: δ 193.5, 173.5, 150.5, 149.5, 147.4, 136.5, 136.5, 133.7, 123.5, 76.5, 63.7, 43.0, 14.2 ppm.

HRMS (ESI$^+$): calculated for $C_{13}H_{16}NO_4$ $[M+H]^+$: 250.1074; found: 250.1116.

The enantiomeric excess was determined by SFC using a Chiralpak IC column [CO_2/MeOH from 95:5 to 60:40 in 8 min, flow rate 2.0 mL/min], τ_{minor} = 4.09 min, τ_{major} = 5.06 min (2:98 *er*).

Ethyl (*R,E*)-2-hydroxy-6-oxo-2-((*E*)-styryl)hex-4-enoate (4n)



Following the general procedure A; reaction between ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **1n** (20.6 µL, 0.1 mmol) and 70:30 *E:Z* mixture of (buta-1,3-dien-1-yloxy)trimethylsilane **2a** (87.7 µL, 0.5 mmol) gave product **4n** (73% yield, 90% *ee*) as a slightly yellow oil. Eluent: cyclohexane: ethyl acetate from 97:3 to 80:20. **$[\alpha]^{25}_D$** = +11.0 (*c* 1.00, $CHCl_3$).

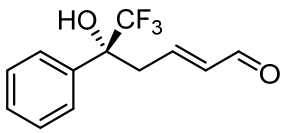
^{1}H-NMR: δ 9.50 (d, *J* = 7.9 Hz, 1H), 7.44 – 7.23 (m, 5H), 6.93 – 6.78 (m, 2H), 6.30 (d, *J* = 15.8 Hz, 1H), 6.19 (dd, *J* = 15.8, 7.9 Hz, 1H), 4.40 – 4.18 (m, 2H), 3.66 (s, 1H), 3.00 – 2.79 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C-NMR: δ 193.7, 174.1, 151.3, 136.1, 136.0, 131.4, 128.9 (2C), 128.7, 128.4, 127.0 (2C), 76.7, 63.1, 42.4, 14.4 ppm.

HRMS (ESI$^+$): calculated for $C_{16}H_{17}O_3$ $[M-OH]^+$: 257.1172; found: 257.1151.

The enantiomeric excess was determined by SFC using a Chiralpak IG-3 column [CO_2/MeOH from 95:5 to 60:40 in 8 min, flow rate 2.0 mL/min], τ_{minor} = 4.76 min, τ_{major} = 6.17 min (95:5 *er*).

(R,E)-6,6,6-trifluoro-5-hydroxy-5-phenylhex-2-enal (4o)



Following the general procedure A; reaction between 2,2,2-trifluoro-1-phenylethan-1-one **1o** (14 µL, 0.1 mmol) and 70:30 *E:Z* mixture of (buta-1,3-dien-1-yloxy)trimethylsilane **2a** (87.7 µL, 0.5 mmol) gave product **4o** (37% yield, 57% *ee*) as a colorless oil. Eluent: cyclohexane: ethyl acetate from 97:3 to 80:20. **$[\alpha]^{25}_D$** = -24.5 (*c* 0.188, $CHCl_3$).

^{1}H-NMR: δ 9.36 (d, *J* = 7.8 Hz, 1H), 7.58 – 7.51 (m, 2H), 7.48 – 7.37 (m, 3H), 6.64 – 6.49 (m, 1H), 6.23 – 6.10 (m, 1H), 3.24 (dd, *J* = 15.3, 7.1 Hz, 1H), 3.09 (dd, *J* = 15.3, 7.3 Hz, 1H), 2.79 (s, 1H) ppm.

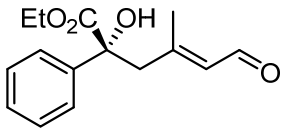
^{13}C-NMR: δ 193.3, 149.3, 137.0, 135.6, 129.3 (2C), 128.9 (2C), 126.3 (q, *J* = 0.9 Hz), 125.3 (q, *J* = 285.9 Hz), 76.8 (q, *J* = 28.7 Hz), 39.1 ppm.

^{19}F-NMR: δ -79.7 ppm.

HRMS (ESI$^+$): calculated for $C_{12}H_{10}F_3O$ $[M-OH]^+$: 227.0678; found: 227.0648.

The enantiomeric excess was determined by SFC using a Chiralpak IA column [CO_2/MeOH from 95:5 to 60:40 in 8 min, flow rate 3.0 mL/min], τ_{minor} = 2.21 min, τ_{major} = 2.41min (21.6:78.4 *er*).

Ethyl (*R,E*)-2-hydroxy-4-methyl-6-oxo-2-phenylhex-4-enoate (4p)



Following the general procedure A; reaction between ethyl 2-oxo-2-phenylacetate **1a** (15.9 µL, 0.1 mmol) and (*Z*)-trimethyl((3-methylbuta-1,3-dien-1-yl)oxy)silane **2b** (128.1 µL, 0.5 mmol) gave product **4p** (65% yield, 90% *ee*) as a colorless oil. Eluent: cyclohexane: ethyl acetate from 97:3 to 80:20. $[\alpha]^{25}_D$ = -4.0 (*c* 0.68, $CHCl_3$).

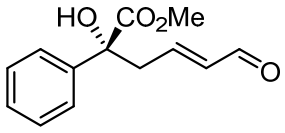
^{1}H-NMR: δ 9.96 (d, *J* = 8.0 Hz, 1H), 7.63 – 7.57 (m, 2H), 7.41 – 7.29 (m, 3H), 5.89 (d, *J* = 8.0 Hz, 1H), 4.32 – 4.20 (m, 2H), 3.87 (s, 1H), 3.12 (d, *J* = 13.7 Hz, 1H), 2.89 (d, *J* = 13.7 Hz, 1H), 2.19 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C-NMR: δ 191.1, 174.3, 158.7, 141.4, 131.1, 128.6 (2C), 128.3, 125.5 (2C), 78.5, 63.2, 49.6, 19.5, 14.2 ppm.

HRMS (ESI$^+$): calculated for $C_{15}H_{17}O_3$ $[M\text{-}OH]^+$: 245.1172 found: 245.1201.

The enantiomeric excess was determined by SFC using a Chiralpak IC column [CO_2/MeOH 95:5, flow rate 2.0 mL/min], τ_{minor} = 9.43 min, τ_{major} = 10.10 min (95:5 *er*).

Methyl (*R,E*)-2-hydroxy-6-oxo-2-phenylhex-4-enoate (4q)



Following the general procedure A; reaction between methyl 2-oxo-2-phenylacetate **1q** (14.2 µL, 0.1 mmol) and 70:30 *E:Z* mixture of (buta-1,3-dien-1-yloxy)trimethylsilane **2a** (87.7 µL, 0.5 mmol) gave product **4q** (76% yield, 94% *ee*) as a colorless oil. Eluent: cyclohexane: ethyl acetate from 97:3 to 80:20. $[\alpha]^{25}_D$ = -4.7 (*c* 0.74, $CHCl_3$).

^{1}H-NMR: δ 9.45 (d, *J* = 7.9 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.44 – 7.31 (m, 3H), 6.78 (ddd, *J* = 15.6, 7.3, 6.7 Hz, 1H), 6.17 (dd, *J* = 15.7, 7.9 Hz, 1H), 3.84 (bs, 1H), 3.81 (s, 3H), 3.18 (dd, *J* = 14.6, 7.3 Hz, 1H), 3.08 (dd, *J* = 14.6, 6.7 Hz, 1H) ppm.

^{13}C-NMR: δ 193.8, 174.6, 151.7, 140.6, 136.1, 128.8 (2C), 128.5 (2C), 125.4, 78.0, 53.8, 42.8 ppm.

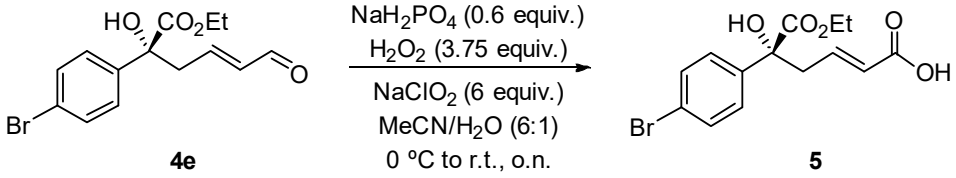
HRMS (ESI$^+$): calculated for $C_{13}H_{13}O_3$ $[M\text{-}OH]^+$: 217.0859; found: 217.0877.

The enantiomeric excess was determined by SFC using a Chiralpak IG-3 column [CO_2/MeOH from 95:5 to 60:40 in 8 min, flow rate 2.0 mL/min], τ_{minor} = 4.61 min, τ_{major} = 5.06 min (3:97 *er*).

4. General procedure B: Synthesis of biologically active derivatives

4.1. Antifungal δ-lactone analog (7)

(*R,E*)-5-(4-bromophenyl)-6-ethoxy-5-hydroxy-6-oxohex-2-enoic acid (5)



4e **5**

To a solution of **4e** in MeCN/H_2O (6:1) at 0°C was added $NaH_2PO_4 \cdot 2H_2O$ (0.6 equiv.) followed by H_2O_2 (3.75 equiv.) and $NaClO_2$ (6.0 equiv.). It was stirred at room temperature overnight. Then, water was added to the reaction, phases were separated, and aqueous phase was extracted with ethyl acetate three times. Combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (cyclohexane: ethyl acetate/EtOH/AcOH (3/1/2%), gradient from 100:0 to 50:50) to give product **5** (84% yield, 95% *ee*) as a colorless oil. $[\alpha]^{25}_D$ = -19.0 (*c* 1.23, $CHCl_3$).

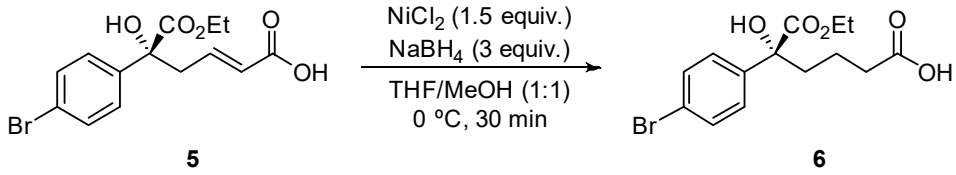
^{1}H-NMR: δ 7.56 – 7.42 (m, 4H), 7.03 – 6.89 (m, 1H), 5.91 (d, *J* = 15.7 Hz, 1H), 4.37 – 4.15 (m, 2H), 3.05 (ddd, *J* = 14.5, 7.6, 1.0 Hz, 1H), 2.90 (ddd, *J* = 14.5, 6.9, 1.3 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C-NMR: δ 173.8, 170.9, 145.1, 140.0, 131.8 (2C), 127.4 (2C), 124.8, 122.6, 77.4, 63.4, 42.6, 14.3 ppm.

HRMS (ESI$^+$): calculated for $C_{14}H_{19}BrNO_5$ $[M+NH_4]^+$: 360.0441; found: 360.0395.

The enantiomeric excess was determined by SFC using a Chiralpak IA column [CO_2/MeOH from 95:5 to 60:40 in 8 min, flow rate 3.0 mL/min], τ_{minor} = 3.87 min, τ_{major} = 6.52 min (97.5:2.5 *er*).

(*R*)-5-(4-bromophenyl)-6-ethoxy-5-hydroxy-6-oxohexanoic acid (6)



5 **6**

To a solution of **5** in THF/MeOH (1:1, 0.1 M) at 0°C was added $NiCl_2 \cdot 6H_2O$ (1.5 equiv.) followed by $NaBH_4$ (3.0 equiv.). It was stirred at the same temperature for 30 min, then the reaction was quenched with ammonium chloride (saturated aqueous solution). Organic solvents were evaporated under reduced pressure and the aqueous phase was extracted with ethyl acetate three times. Combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column

chromatography (cyclohexane: ethyl acetate/EtOH/AcOH (3/1/2%), gradient from 100:0 to 50:50) to give product **6** (79% yield, 95% *ee*) as a colorless oil. **$[\alpha]^{25}_D$** = -3.3 (*c* 0.72, $CHCl_3$).

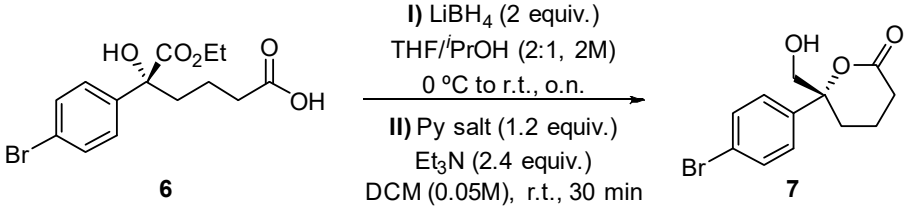
^{1}H-NMR: δ 7.54 – 6.40 (m, 4H), 4.34 – 4.14 (m, 2H), 2.37 (t, *J* = 7.3 Hz, 2H), 2.25 – 2.12 (m, 1H), 2.11 – 1.97 (m, 1H), 1.80 – 1.52 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C-NMR: δ 179.6, 174.8, 140.7, 131.5 (2C), 127.6 (2C), 122.1, 77.9, 63.0, 38.9, 33.8, 19.1, 14.2 ppm.

HRMS (ESI$^+$): calculated for $C_{14}H_{16}BrO_4$ $[M\text{-}OH]^+$: 327.0226; found: 327.0172.

The enantiomeric excess was determined by SFC using a Chiralpak ID-3 column [CO_2/MeOH from 95:5 to 60:40 in 8 min, flow rate 2.0 mL/min], τ_{minor} = 1.75 min, τ_{major} = 3.35 min (97.5:2.5 *er*).

(*R*)-6-(4-bromophenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-one (7)



To a solution of **6** in THF:^{i}PrOH (2:1, 2 M) at 0ºC was added $LiBH_4$ (2.0 equiv.). It was stirred at room temperature overnight. Then, the reaction was quenched with HCl (1M aqueous solution). Organic solvent was evaporated under reduced pressure and the aqueous phase was extracted with ethyl acetate three times. Combined organic layers was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Then, the residue was dissolved in dichloromethane (0.05M) with triethylamine (2.4 equiv.). It was slowly added to a solution of 2-chloro-1-methylpyridinium iodide (1.2 equiv.) in dichloromethane (0.2M). The reaction mixture was stirred at room temperature for 30 minutes. Water was added to the reaction, and it was extracted with dichloromethane four times. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (cyclohexane: ethyl acetate/EtOH/CH_3CO_2H (3/1/2%), gradient from 100:0 to 80:20) to give product **7** (45% yield, 96% ee) as a colorless solid. **$[\alpha]^{25}_D$** = -7.4 (*c* 1.09, $CHCl_3$).

^{1}H-NMR: δ 7.51 (d, *J* = 8.6 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 3.75 (d, *J* = 12.2 Hz, 1H), 3.65 (d, *J* = 12.2 Hz, 1H), 2.52 – 2.43 (m, 2H), 2.36 (ddd, *J* = 14.3, 12.5, 4.4 Hz, 1H), 2.18 (dt, *J* = 14.3, 4.3 Hz, 1H), 1.91 – 1.78 (m, 1H), 1.68 – 1.51 (m, 1H) ppm.

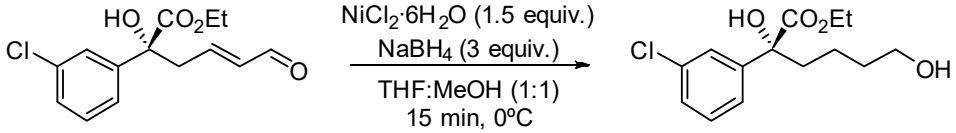
^{13}C-NMR: δ 171.3, 139.7, 132.2 (2C), 127.3 (2C), 122.5, 88.1, 70.1, 29.5, 28.1, 16.1 ppm.

HRMS (ESI$^+$): calculated for $C_{12}H_{14}BrO_3$ $[M\text{-}H]^+$: 285.0121; found: 285.0100.

The enantiomeric excess was determined by SFC using a Chiralpak ID-3 column [CO_2/MeOH from 95:5 to 60:40 in 8 min, flow rate 2.0 mL/min], τ_{minor} = 2.24 min, τ_{major} = 2.42 min (98:2 *er*).

4.2. Inhibitor of neuropatic pain (10)

Ethyl (*R*)-(3-chlorophenyl)-2,6-dihydroxyhexanoate (8)



4h **8**

To a solution of **4h** in THF/MeOH (1:1, 0.1 M) at 0ºC was added $NiCl_2 \cdot 6H_2O$ (1.5 equiv.) followed by $NaBH_4$ (3.0 equiv.). It was stirred at the same temperature for 15 min, then the reaction was quenched with ammonium chloride (saturated aqueous solution). Organic solvents were evaporated under reduced pressure and the aqueous phase was extracted with ethyl acetate three times. Combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (cyclohexane: ethyl acetate, gradient from 100:0 to 50:50) to give product **8** (60% yield, >98% *ee*) as a colorless oil. $[\alpha]^{25}_D$ = -23.9 (*c* 1.0 0, $CHCl_3$).

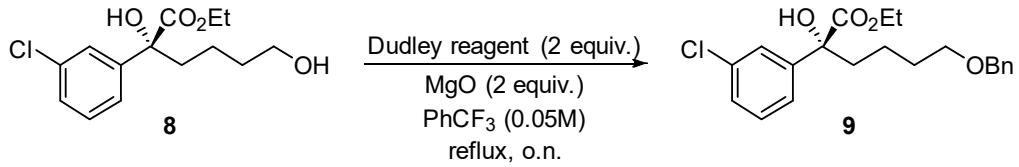
^{1}H-NMR: δ 7.63 – 7.60 (m, 1H), 7.50 – 7.45 (m, 1H), 7.28 – 7.25 (m, 2H), 4.35 – 4.16 (m, 2H), 3.63 (t, *J* = 6.4 Hz, 2H), 2.23 – 2.10 (m, 1H), 2.06 – 1.93 (m, 1H), 1.63 – 1.52 (m, 2H), 1.52 – 1.32 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C-NMR: δ 174.9, 144.1, 134.5, 129.7, 128.0, 126.1, 124.0, 78.1, 63.0, 62.8, 39.7, 32.7, 20.1, 14.3 ppm.

HRMS (ESI$^+$): calculated for $C_{14}H_{18}ClO_3$ $[M\text{-}OH]^+$: 269.0939; found: 269.0991.

The enantiomeric excess was determined by SFC using a Chiralpak IA column [CO_2/MeOH from 95:5 to 60:40 in 8 min, flow rate 3.0 mL/min], τ_{minor} = 2.95 min, τ_{major} = 3.07 min (<2:>98 *er*).

Ethyl (*R*)-6-(benzyloxy)-2-(3-chlorophenyl)-2-hydroxyhexanoate (9)



8 **9**

A stirred suspension of **8** (0.1 mmol), MgO (2 equiv.) and 2-benzyloxy-1-methylpyridinium triflate (2 equiv.) in trifluorotoluene (0.05 M) was heated al 85ºC overnight. Afterwards, the mixture was cooled to room temperature and concentrated under reduced pressure. The crude was purified by silica gel chromatography (cyclohexane: ethyl acetate, gradient from 100:0 to 50:50) and product **9** was obtained as a colorless oil (62% yield, 95% *ee*). $[\alpha]^{25}_D$ = -18.2 (*c* 1.12, $CHCl_3$).

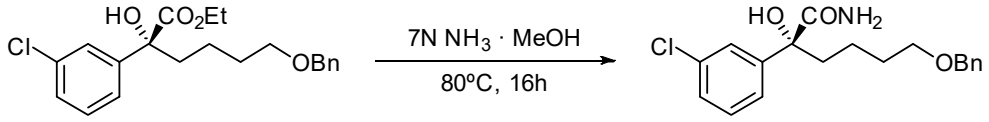
^{1}H-NMR: δ 7.64 – 7.59 (m, 1H), 7.51 – 7.45 (m, 1H), 7.38 – 7.24 (m, 7H), 4.48 (s, 2H), 4.33 – 4.15 (m, 2H), 3.82 (s, 1H), 3.45 (t, *J* = 6.4 Hz, 2H), 2.25 – 2.08 (m, 1H), 2.07 – 1.92 (m, 1H), 1.70 – 1.56 (m, 2H), 1.52 – 1.33 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C-NMR: δ 174.9, 144.2, 138.7, 134.4, 129.6, 128.5 (2C), 128.0, 127.8 (2C), 127.7, 126.2, 124.0, 78.1, 73.1, 70.3, 62.9, 39.8, 29.8, 20.6, 14.3 ppm.

HRMS (ESI$^+$): calculated for $C_{21}H_{24}ClO_3$ $[M\text{-}OH]^+$: 359.1408; found: 359.1458.

The enantiomeric excess was determined by SFC using a Chiralpak IB-3 column [CO_2/MeOH from 95:5 to 60:40 in 8 min, flow rate 2.0 mL/min], τ_{minor} = 1.60 min, τ_{major} = 2.68 min (97:3 *er*).

(*R*)-6-(benzyloxy)-2-(3-chlorophenyl)-2-hydroxyhexanamide (10)



9 **10**

7N ammonia solution in methanol (1 mL) was added to product **9** (0.07 mmol) and the reaction was stirred at 80ºC overnight. Then, reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (cyclohexane: ethyl acetate, gradient from 100:0 to 25:75) to give product **10** (68% yield, >98% *ee*) as a colorless oil. **$[\alpha]^{25}_D$** = -3.7 (*c* 0.27, $CHCl_3$).

^{1}H-NMR: δ 7.63 – 7.58 (m, 1H), 7.50 – 7.43 (m, 1H), 7.38 – 7.28 (m, 5H), 7.26 – 7.24 (m, 2H), 6.54 (bs, 1H), 5.39 (bs, 1H), 4.49 (s, 2H), 3.85 (s, 1H), 3.53 (t, *J* = 5.9 Hz, 2H), 2.33 – 2.20 (m, 1H), 2.14 – 2.02 (m, 1H), 1.74 – 1.63 (m, 2H), 1.56 – 1.37 (m, 2H) ppm.

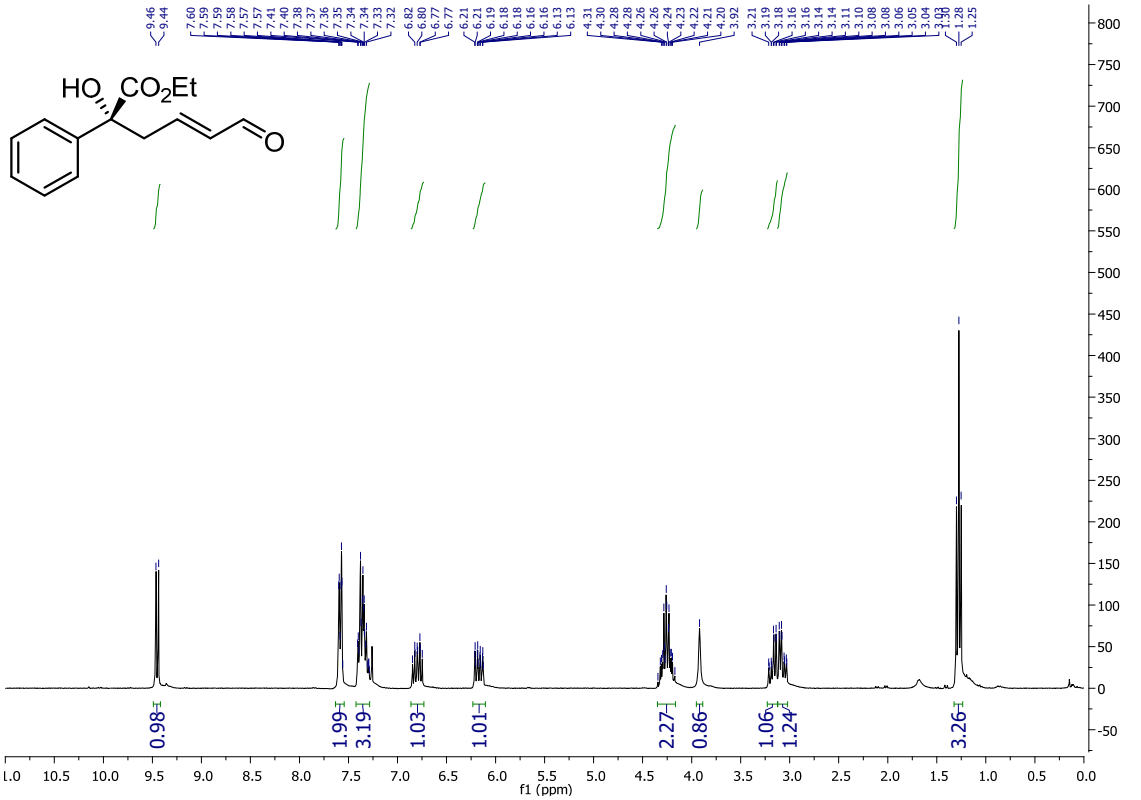
^{13}C-NMR: δ 176.4, 144.7, 138.1, 134.5, 129.7, 128.7 (2C), 128.1 (2C), 128.0, 127.9, 125.9, 123.9, 78.9, 73.4, 70.5, 38.6, 29.1, 21.1 ppm.

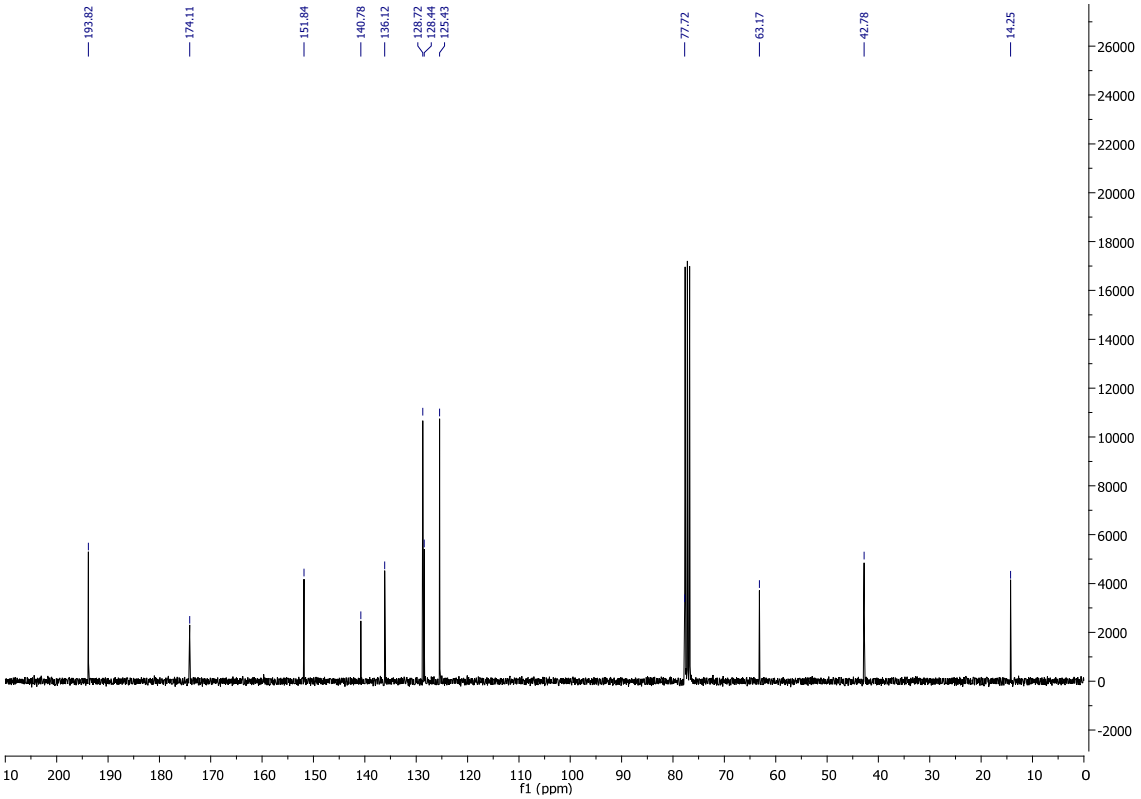
HRMS (ESI$^+$): calculated for $C_{19}H_{23}ClNO_3$ $[M+H]^+$: 348.1361; found: 348.1330.

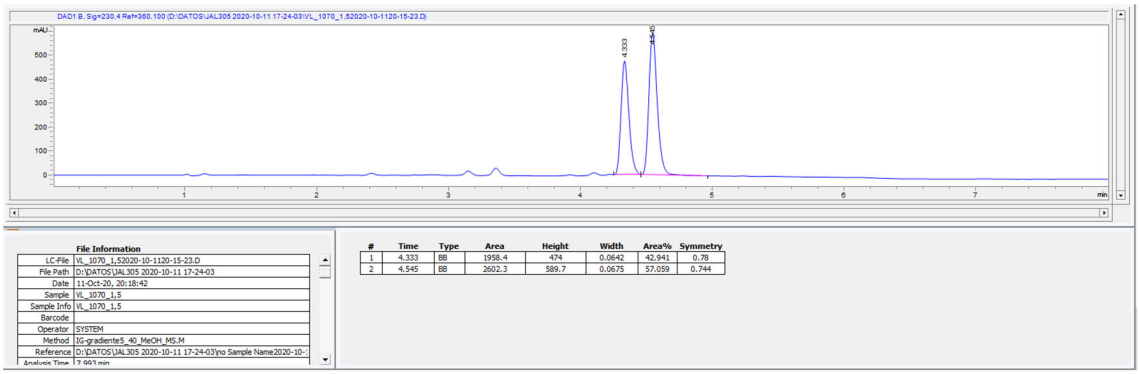
The enantiomeric excess was determined by SFC using a Chiralpak IB-3 column [CO_2/MeOH from 95:5 to 60:40 in 8 min, flow rate 2.0 mL/min], τ_{minor} = 3.50 min, τ_{major} = 6.52 min (>98:<2 *er*).

5. NMR spectra and SFC chromatograms

Ethyl (*R,E*)-2-hydroxy-6-oxo-2-phenylhex-4-enoate (4a)







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Sample Info	VL_1070_1,5
Barcode	
Operator	SYSTEM
Method	IG-gradiente5_40_MeOH_MS.M
Reference	D:\DATOS\JAL305 2020-10-11 17-24-03\no Sample Name2020-10-1
Analysis Time	7.00 min

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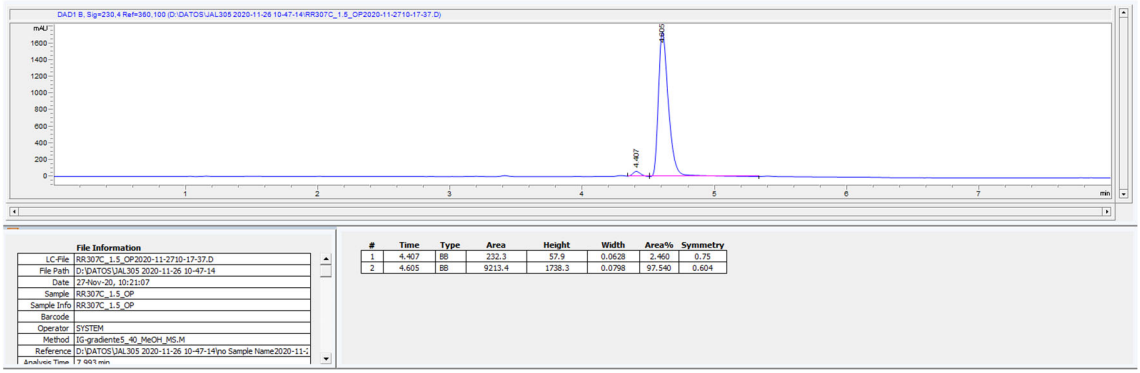

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Date	27-Nov-20, 10:21:07
Sample	RR307C_1.5_OP
Sample Info	RR307C_1.5_OP
Barcode	
Operator	SYSTEM
Method	IG-gradiente5_40_MeOH_MS.M
Reference	D:\DATOS\JAL305 2020-11-26 10-47-14\no Sample Name2020-11-2
Analysis Time	7.00 min

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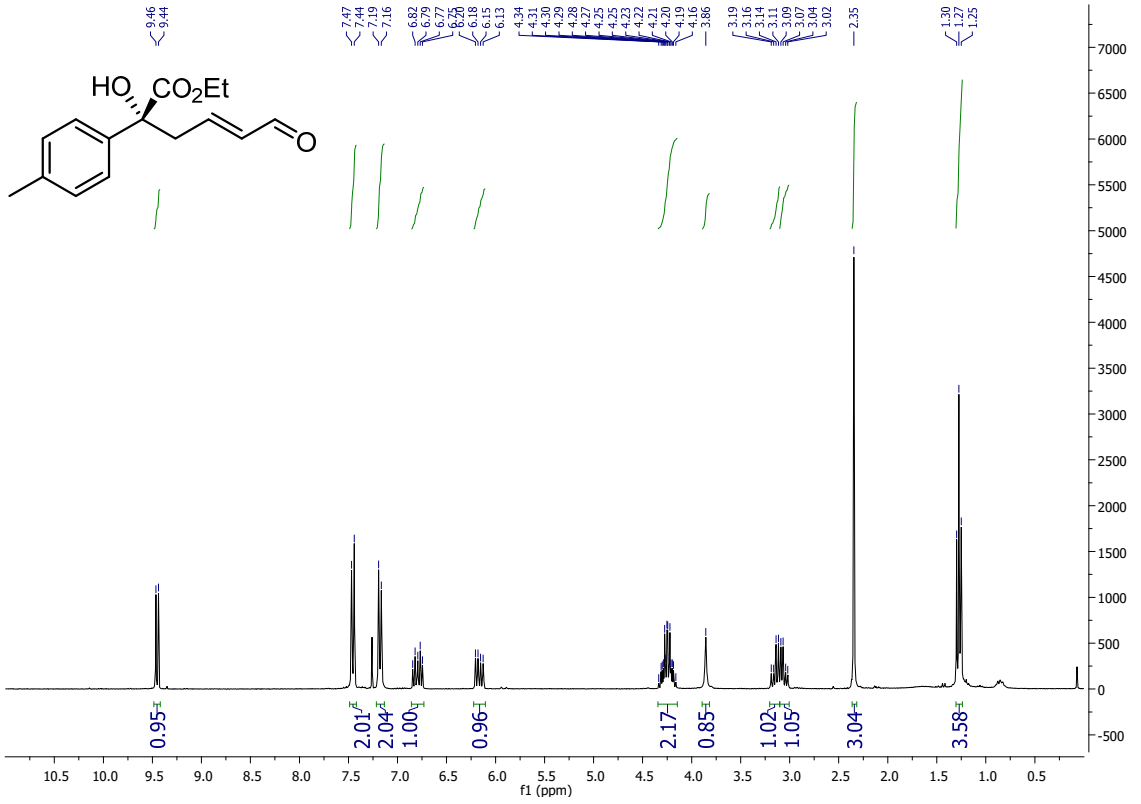
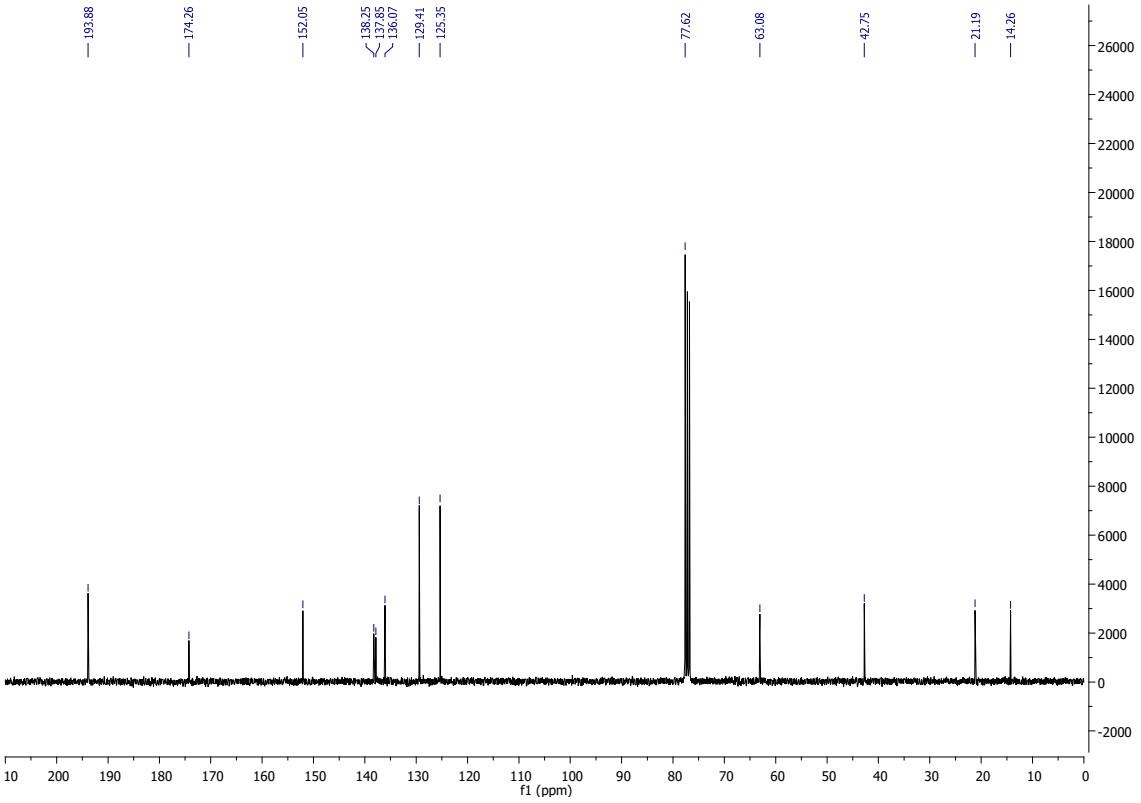
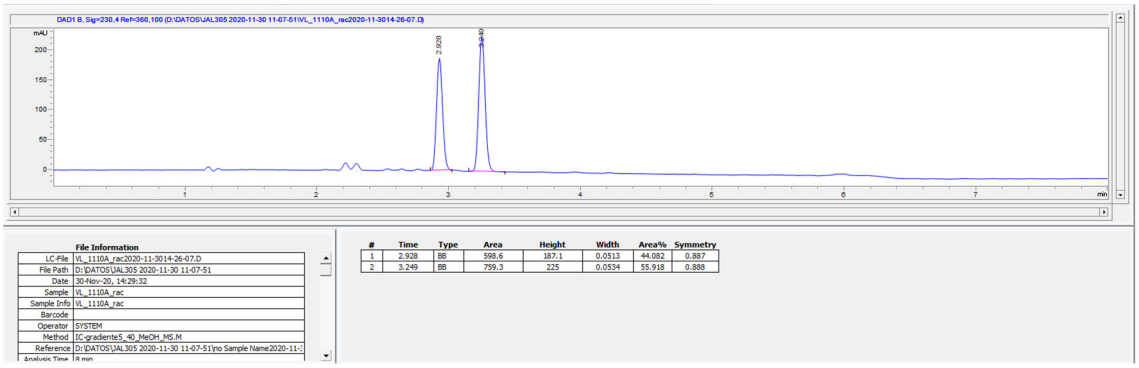
Ethyl (*R,E*)-2-hydroxy-6-oxo-2-(*p*-tolyl)hex-4-enoate (4b)







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Date	30-Nov-20, 14:29:32
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Sample Info	VL_1110A_rac
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Operator	SYSTEM
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Reference	D:\DATOS\JAL305 2020-11-30 11-07-51\no Sample Name2020-11-3
Analysis Time	8 min

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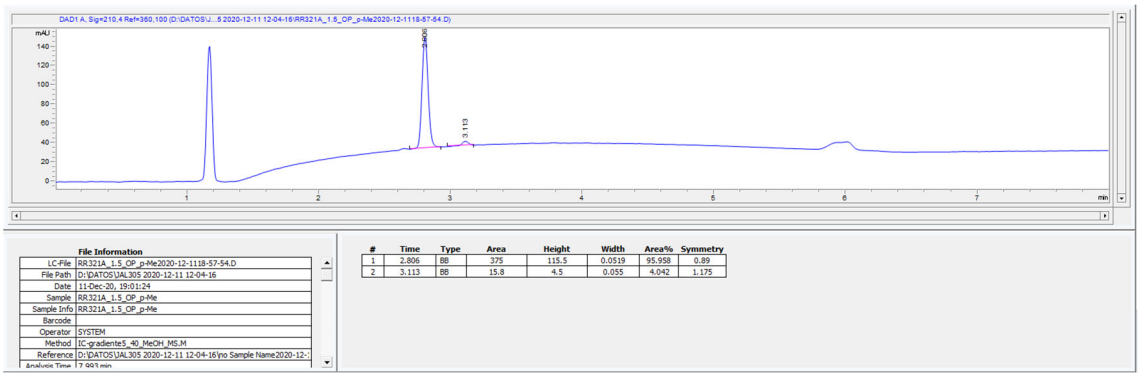

File Information

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Date	11-Dec-20, 19:01:24
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Sample Info	RR321A_1.5_OP_p-Me
Barcode	
Operator	SYSTEM
Method	IC-gradiente5_40_MeOH_MS.M
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Analysis Time	7.991 min

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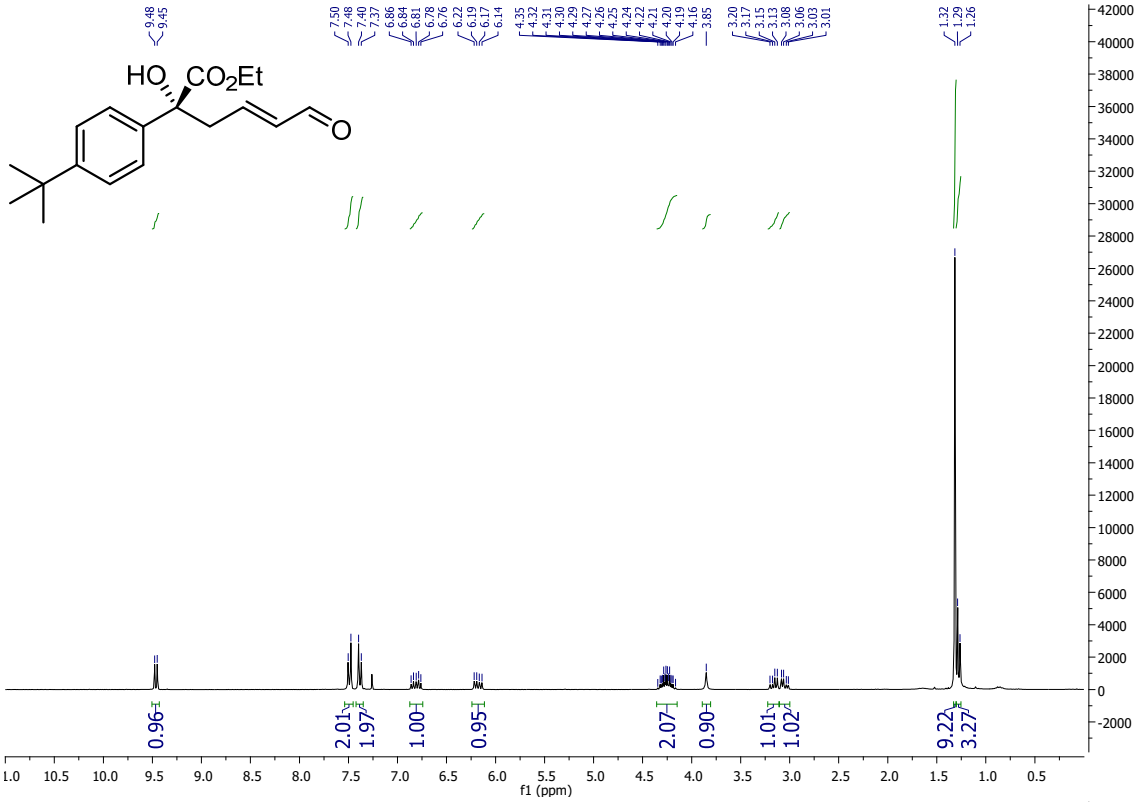
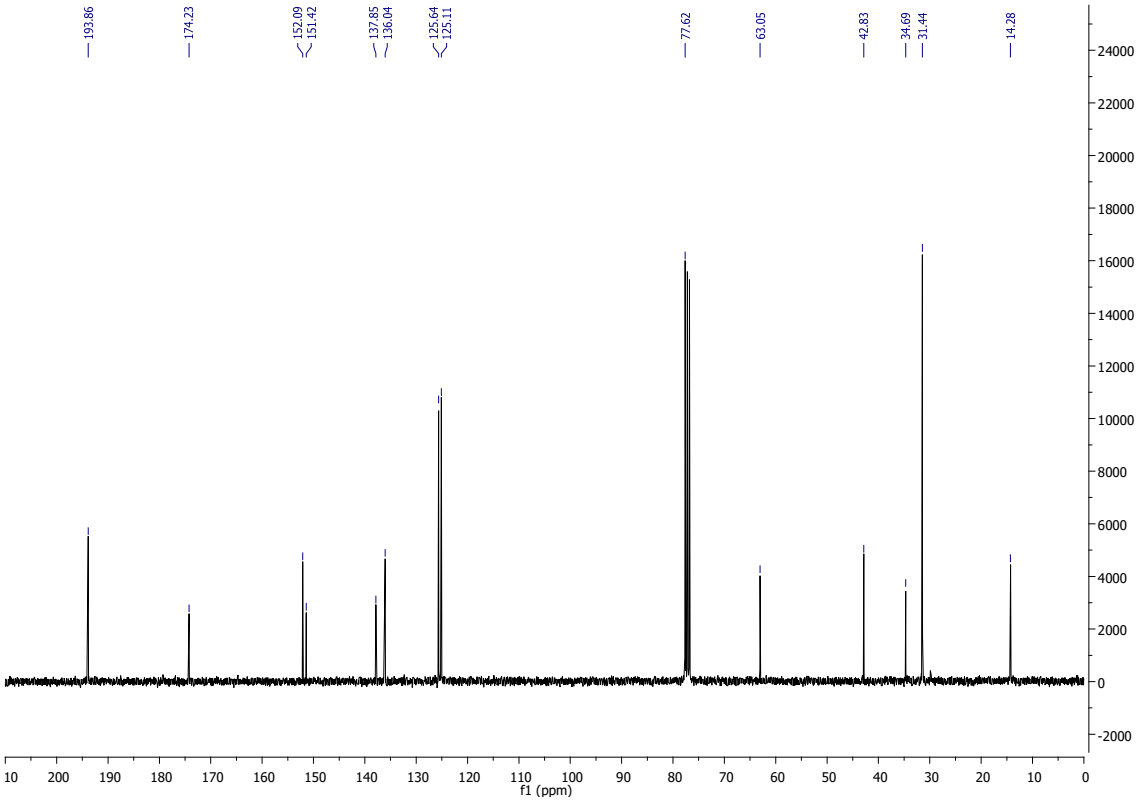
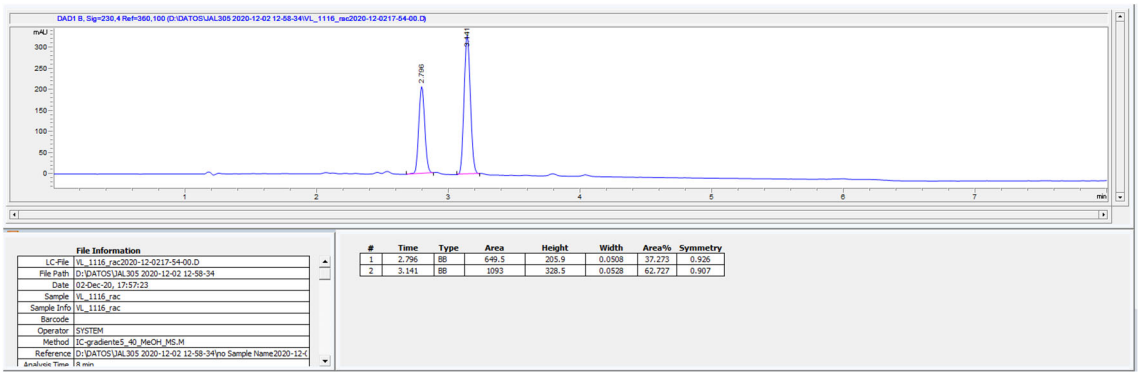
Ethyl (*R,E*)-2-(4-(*tert*-butyl)phenyl)-2-hydroxy-6-oxohex-4-enoate (4c)







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Date	02-Dec-20, 17:57:23
Sample	VL_1116_rac
Sample Info	VL_1116_rac
Barcode	
Operator	SYSTEM
Method	IC-gradiente5_40_MeOH_MS.M
Reference	D:\DATOS\JAL305 2020-12-02 12-58-34\no Sample Name2020-12-(
Analysis Time	8 min

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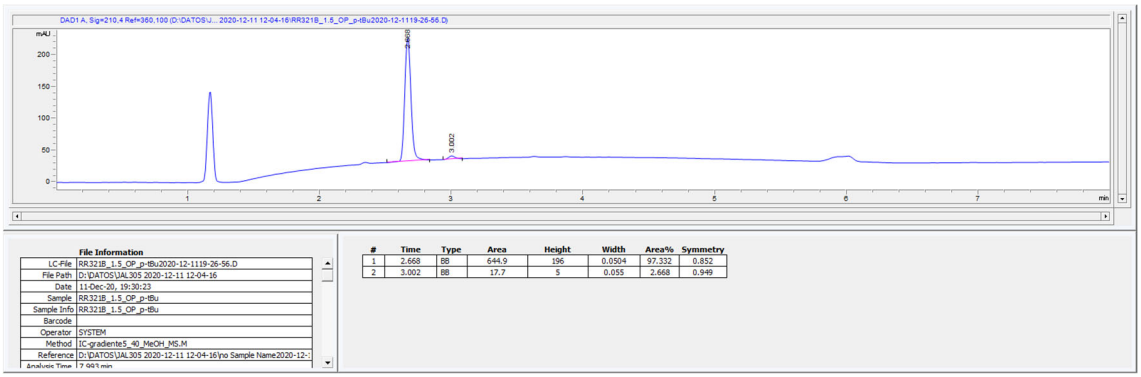

File Information

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Sample Info	RR321B_1.5_OP_p-tBu
Barcode	
Operator	SYSTEM
Method	IC-gradiente5_40_MeOH_MS.M
Reference	D:\DATOS\JAL305 2020-12-11 12-04-16\no Sample Name2020-12-(
Analysis Time	7.98 min

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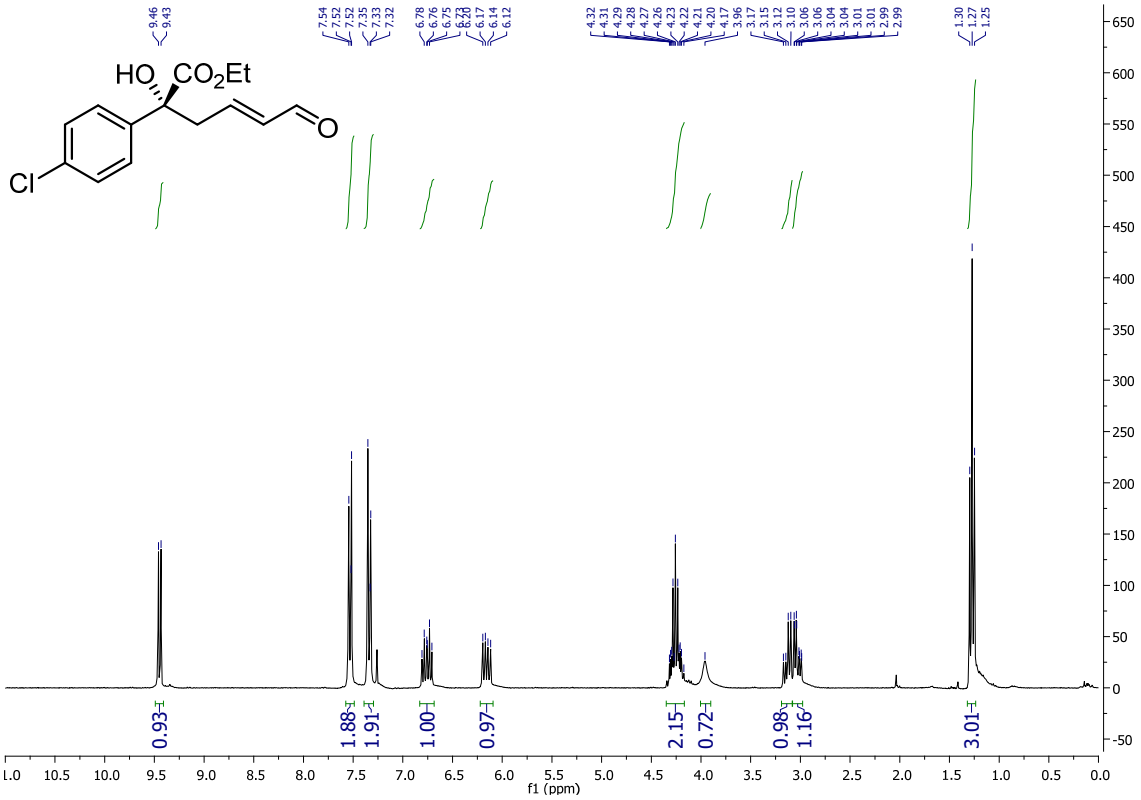
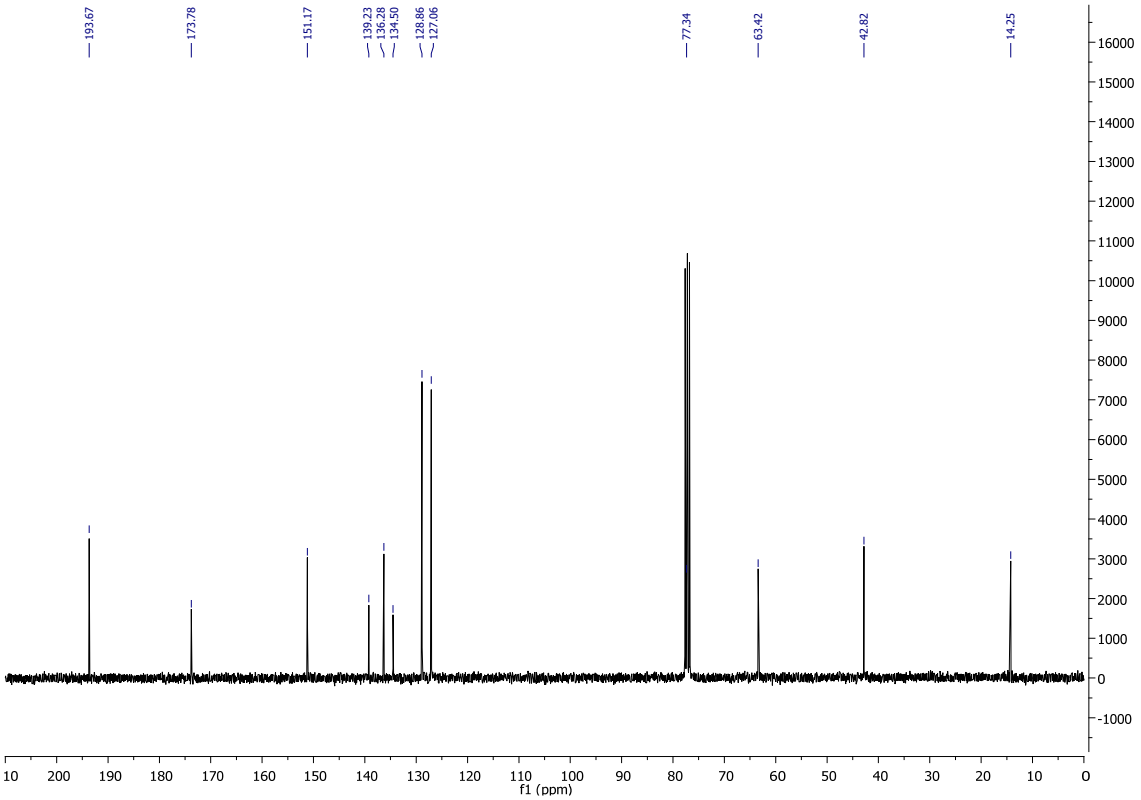
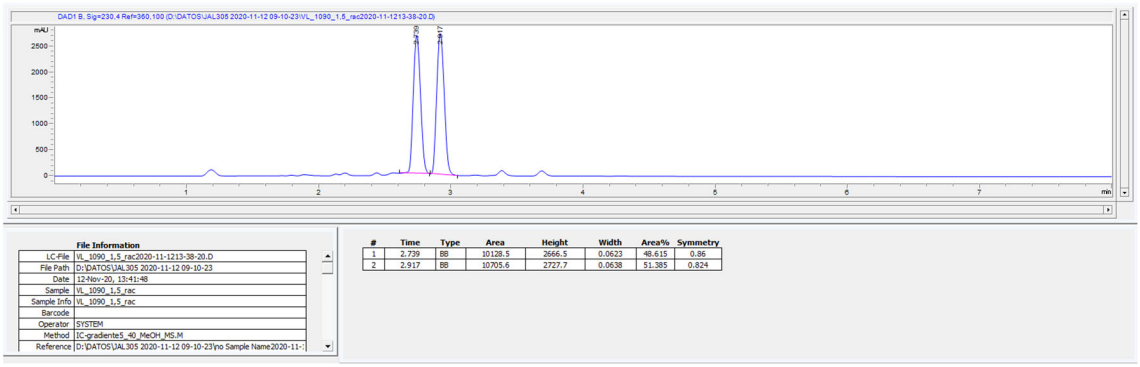
Ethyl (*R,E*)-2-(4-chlorophenyl)-2-hydroxy-6-oxohex-4-enoate (4d)







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Sample Info	VL_1090_1,5_rac
Barcode	
Operator	SYSTEM
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Reference	D:\DATOS\JAL305 2020-11-12 09-10-23\no Sample Name2020-11-1

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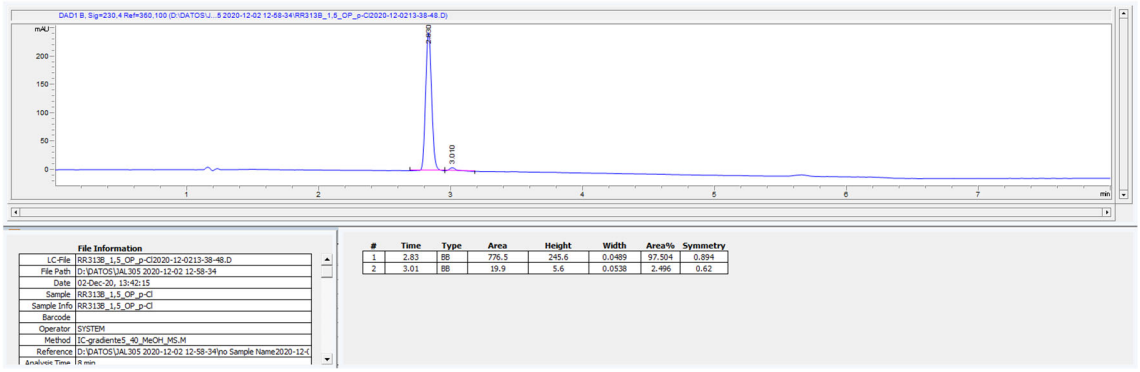

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Sample Info	RR313B_1,5_OP_p-Cl
Barcode	
Operator	SYSTEM
Method	IC-gradiente5_40_MeOH_MS.M
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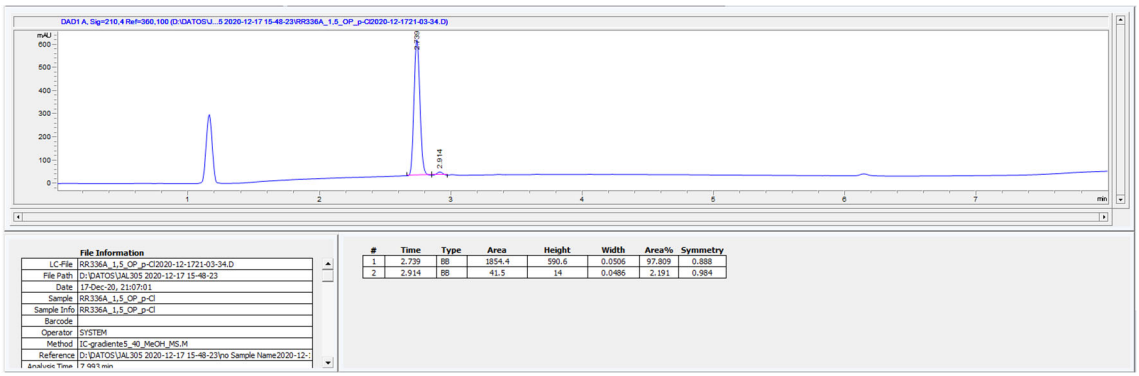

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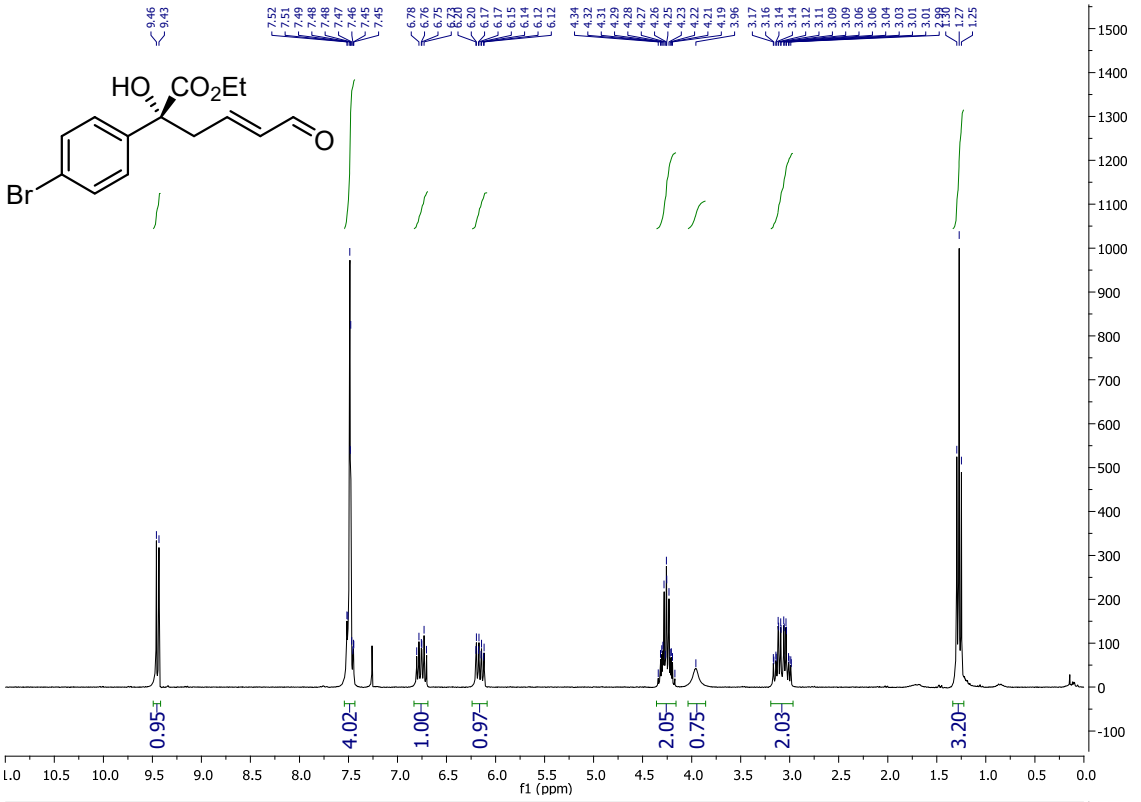
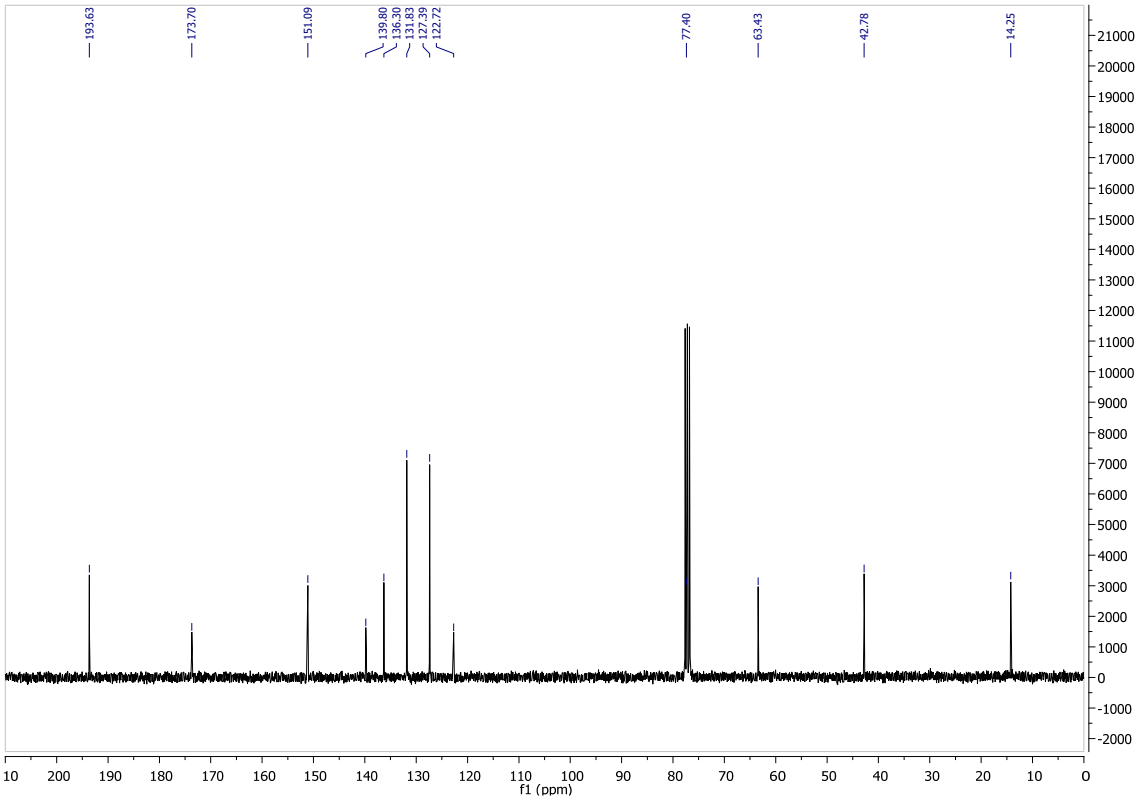
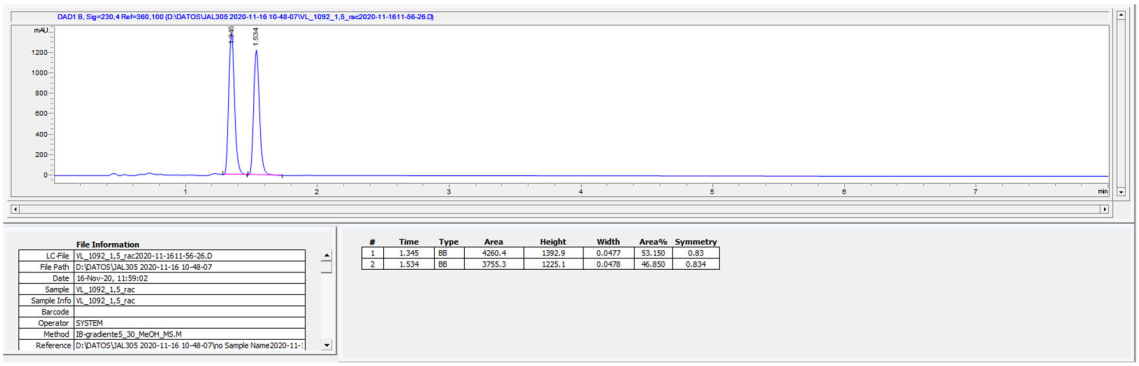
Sample Info	RR336A_1,5_OP_p-Cl
Barcode	
Operator	SYSTEM
Method	IC-gradiente5_40_MeOH_MS.M
Reference	D:\DATOS\JAL305 2020-12-17 15-48-23\no Sample Name2020-12-1

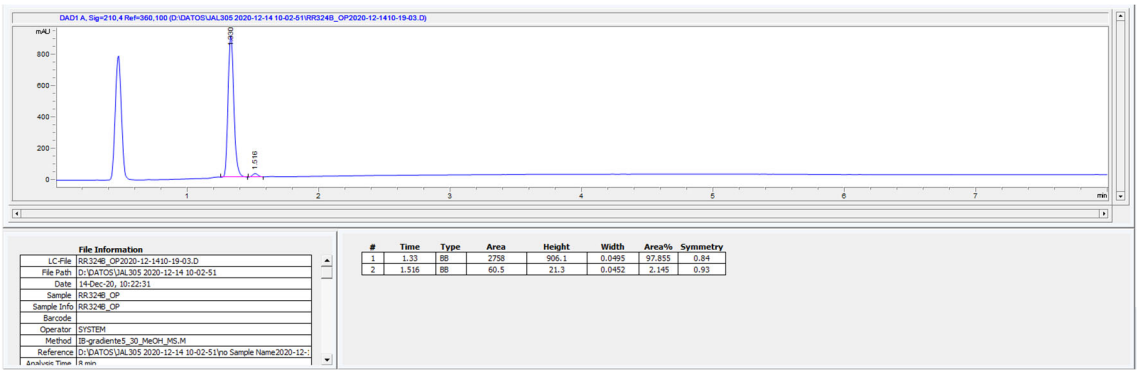
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	2.739	BB	1854.4	590.6	0.0506	97.809	0.888
2	2.914	BB	41.5	14	0.0486	2.191	0.984

Ethyl (*R,E*)-2-(4-bromophenyl)-2-hydroxy-6-oxohex-4-enoate (4e)

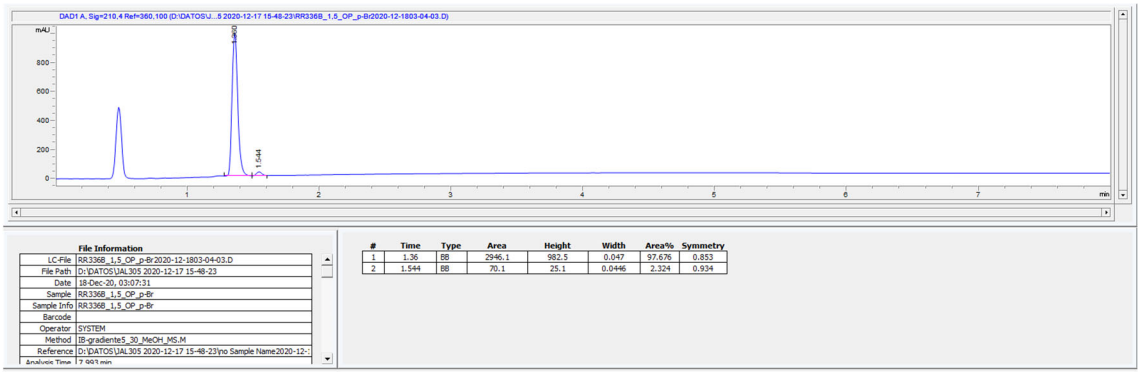




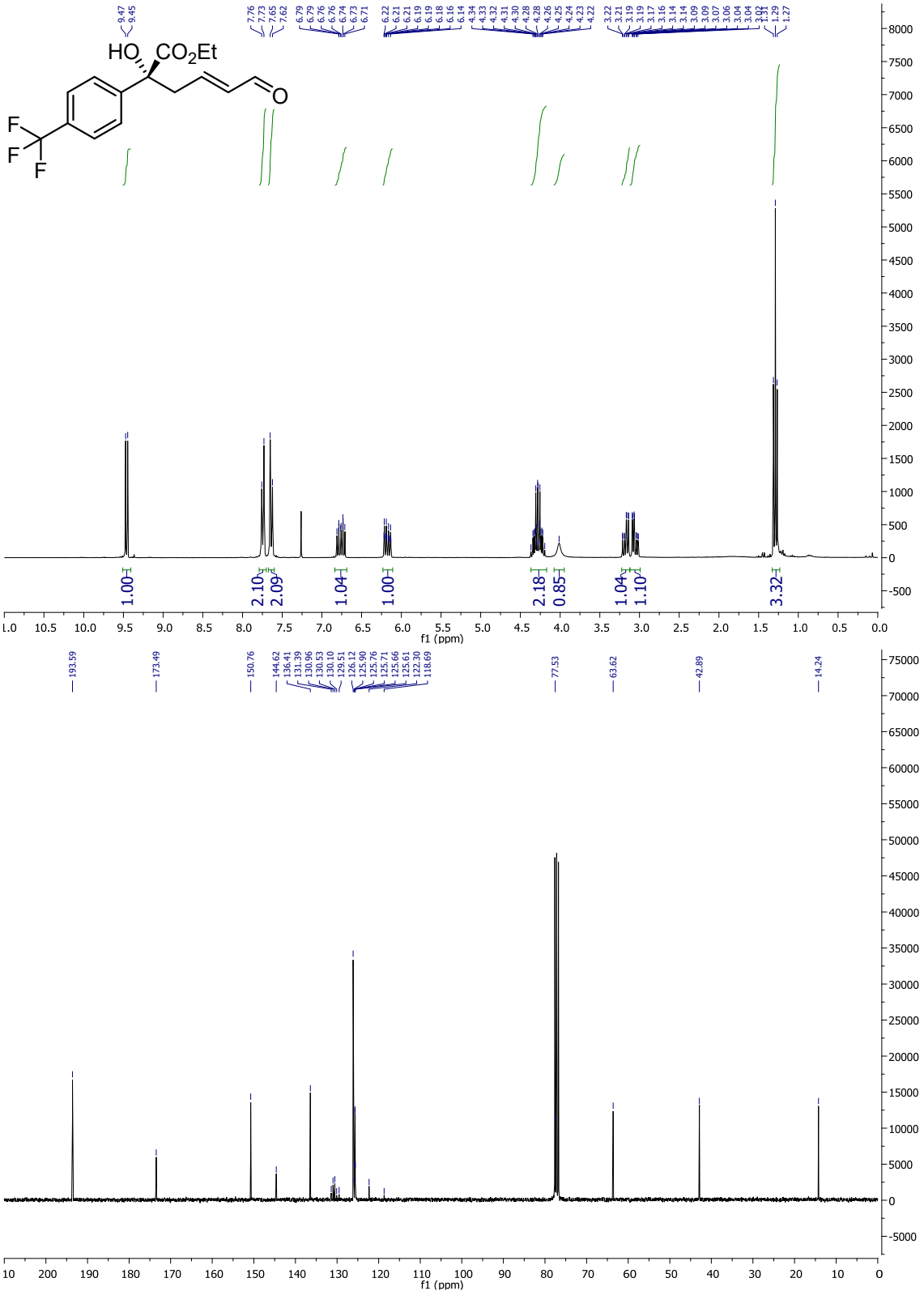


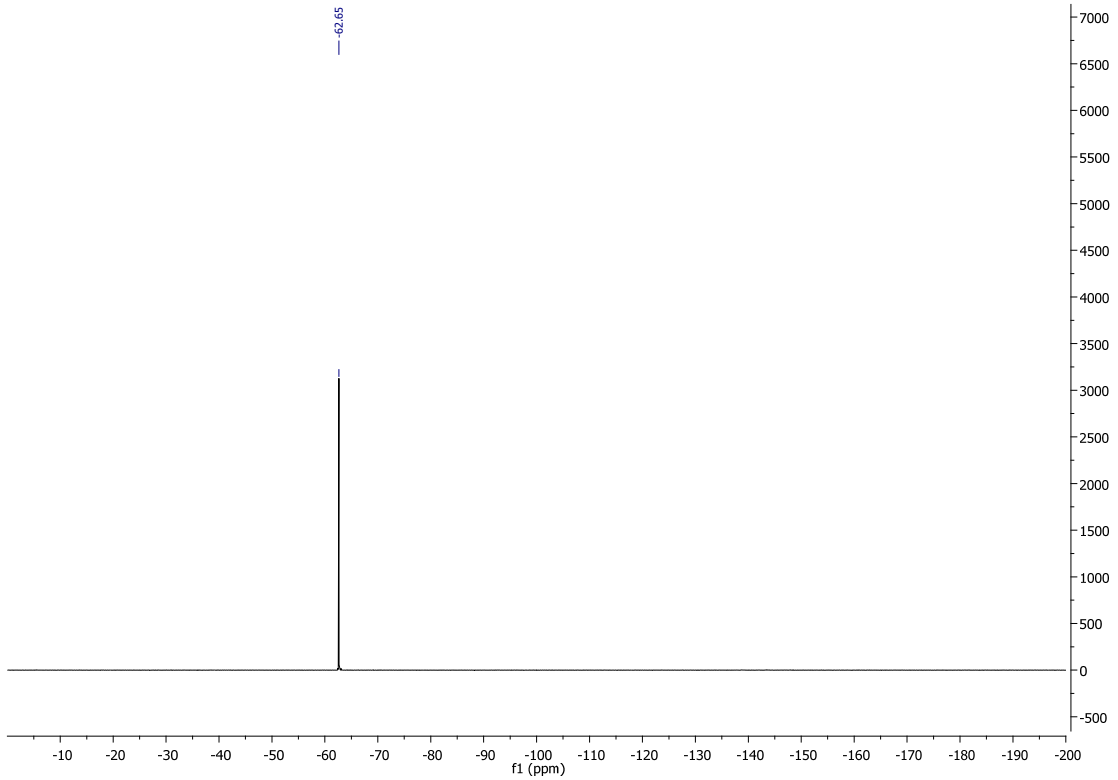


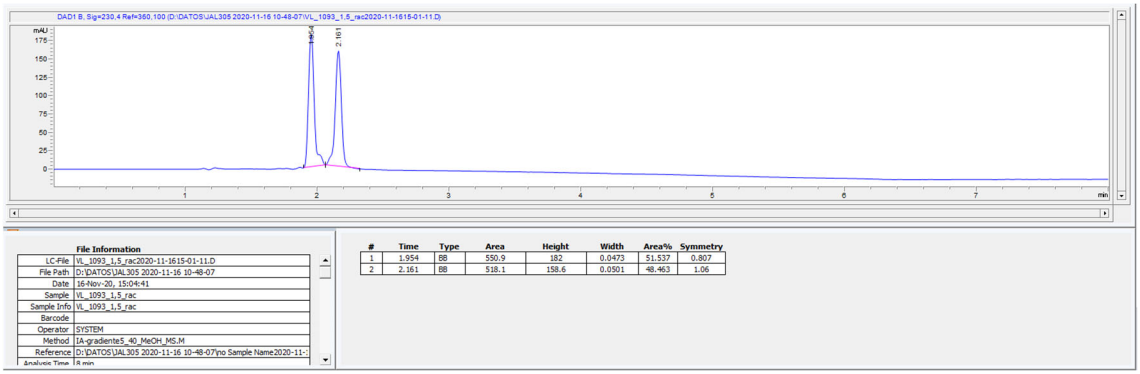
- 0.5 mmol scale chromatogram:



Ethyl (*R,E*)-2-hydroxy-6-oxo-2-(4-(trifluoromethyl)phenyl)hex-4-enoate (4f)



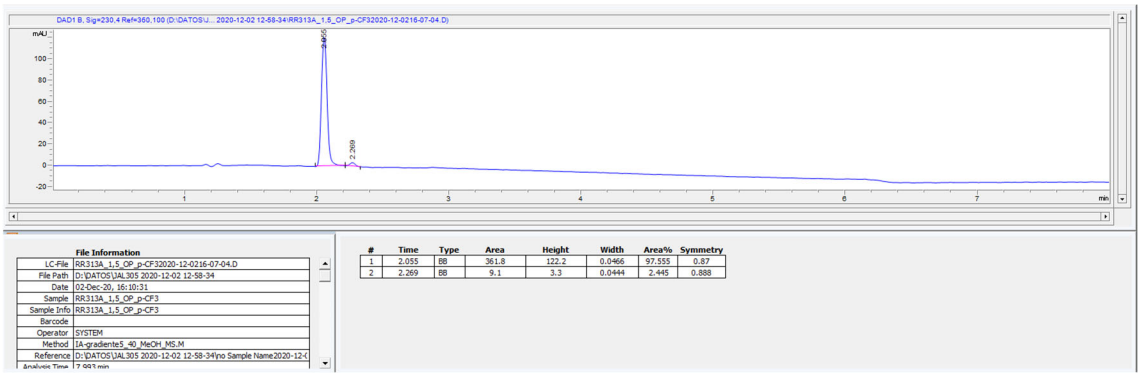




File Information

LC-File	VL_1093_1,5_rac2020-11-1615-01-11.D
File Path	D:\DATOS\JAL305 2020-11-16 10-48-07
Date	16-Nov-20, 15:04:41
Sample	VL_1093_1,5_rac
Sample Info	VL_1093_1,5_rac
Barcode	
Operator	SYSTEM
Method	IA-gradiente5_40_MeOH_MS.M
Reference	D:\DATOS\JAL305 2020-11-16 10-48-07\no Sample Name2020-11-
Analysis Time	8 min

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	1.954	BB	550.9	182	0.0473	51.537	0.807
2	2.161	BB	518.1	158.6	0.0501	48.463	1.06

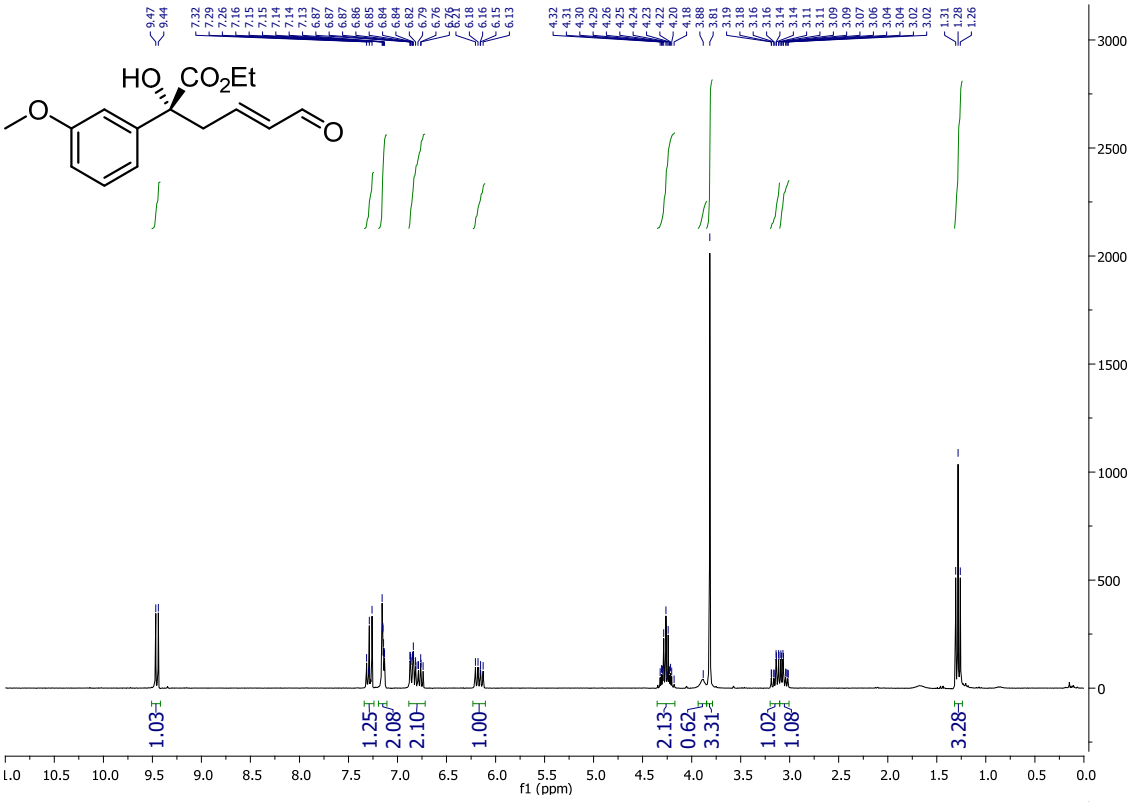


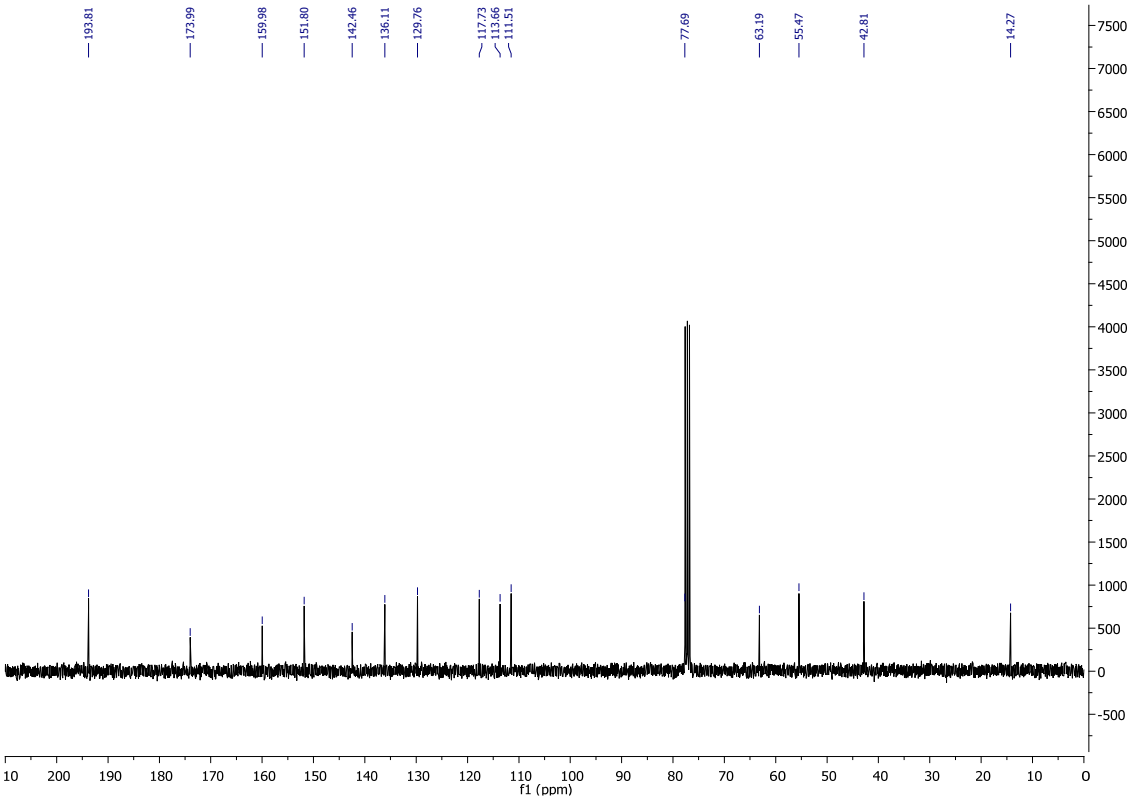
File Information

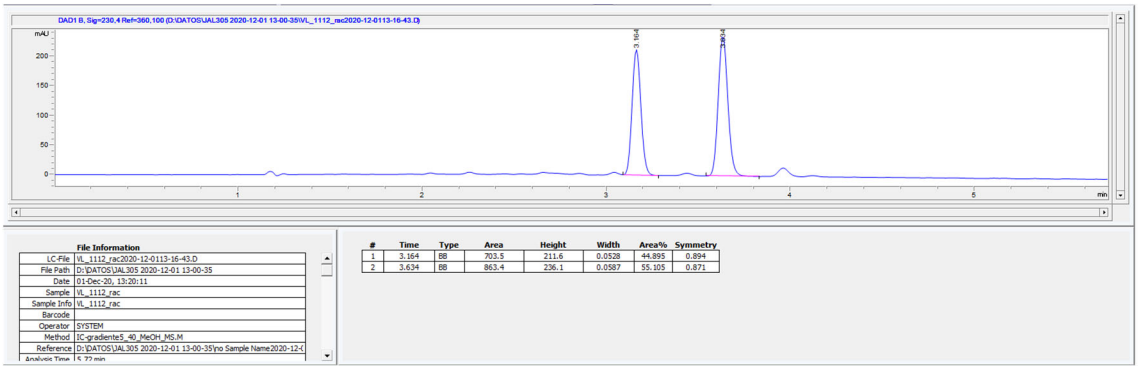
LC-File	RR313A_1,5_OP_p-CF32020-12-0216-07-04.D
File Path	D:\DATOS\JAL305 2020-12-02 12-58-34
Date	02-Dec-20, 16:10:31
Sample	RR313A_1,5_OP_p-CF3
Sample Info	RR313A_1,5_OP_p-CF3
Barcode	
Operator	SYSTEM
Method	IA-gradiente5_40_MeOH_MS.M
Reference	D:\DATOS\JAL305 2020-12-02 12-58-34\no Sample Name2020-12-(
Analysis Time	7.983 min

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	2.055	BB	361.8	122.2	0.0466	97.555	0.87
2	2.269	BB	9.1	3.3	0.0444	2.445	0.888

Ethyl (*R,E*)-2-hydroxy-2-(3-methoxyphenyl)-6-oxohex-4-enoate (4g)



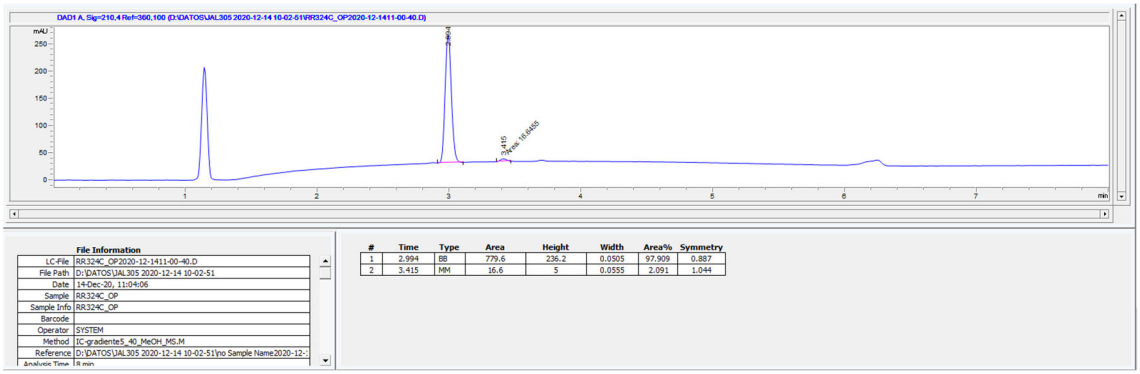




File Information

LC-File	VL_1112_rac2020-12-0113-16-43.D
File Path	D:\DATOS\JAL305 2020-12-01 13-00-35
Date	01-Dec-20, 13:20:11
Sample	VL_1112_rac
Sample Info	VL_1112_rac
Barcode	
Operator	SYSTEM
Method	IC-gradiente5_40_MeOH_MS.M
Reference	D:\DATOS\JAL305 2020-12-01 13-00-35\no Sample Name2020-12-(
Analysis Time	5.73 min

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	3.164	BB	703.5	211.6	0.0528	44.895	0.894
2	3.634	BB	863.4	236.1	0.0587	55.105	0.871

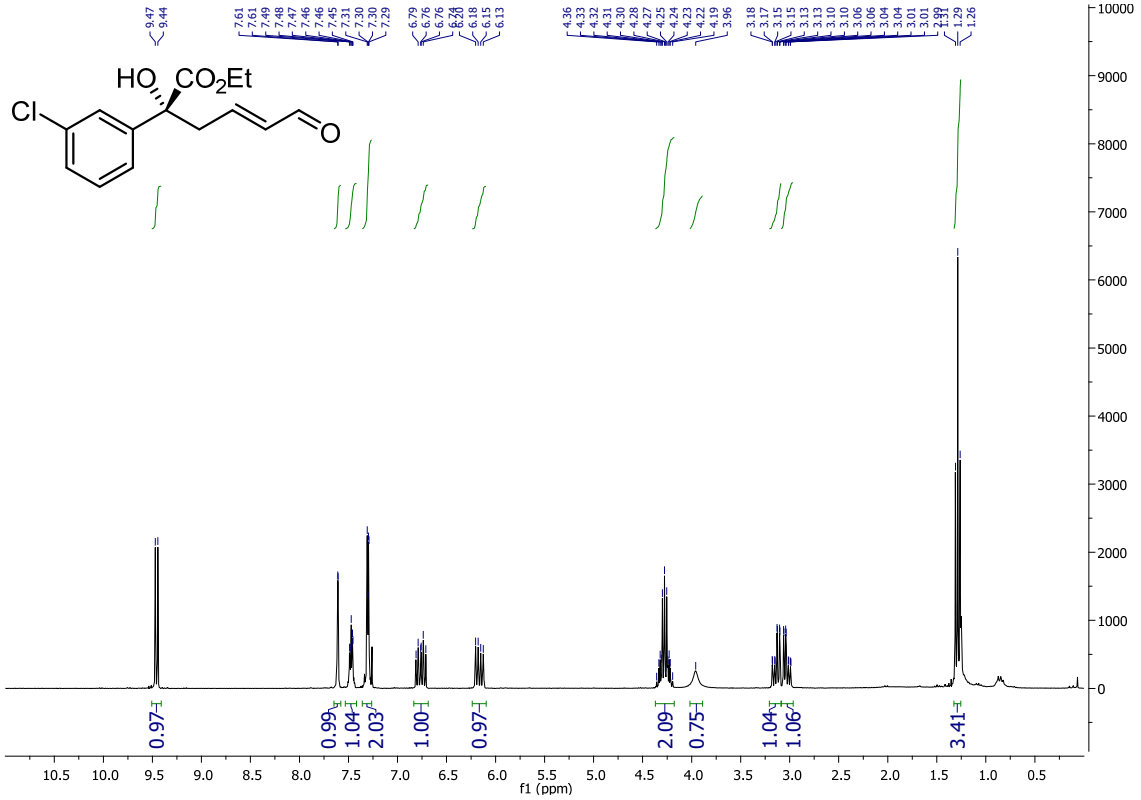


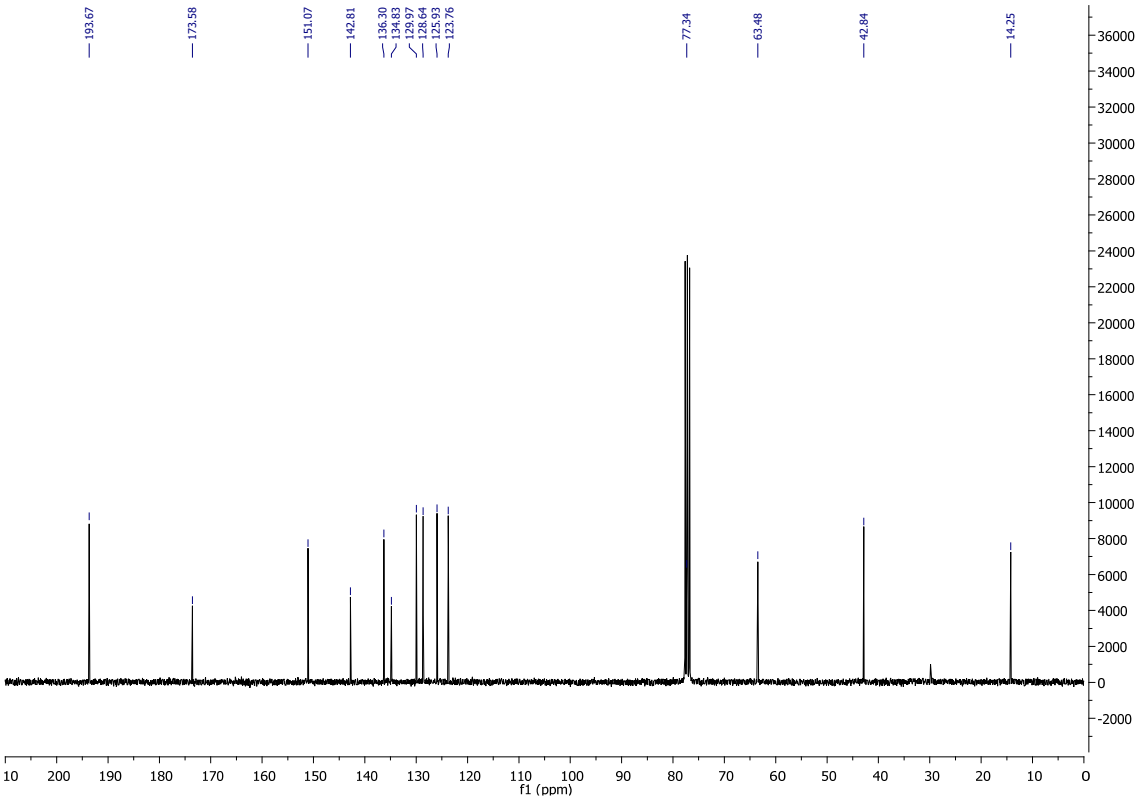
File Information

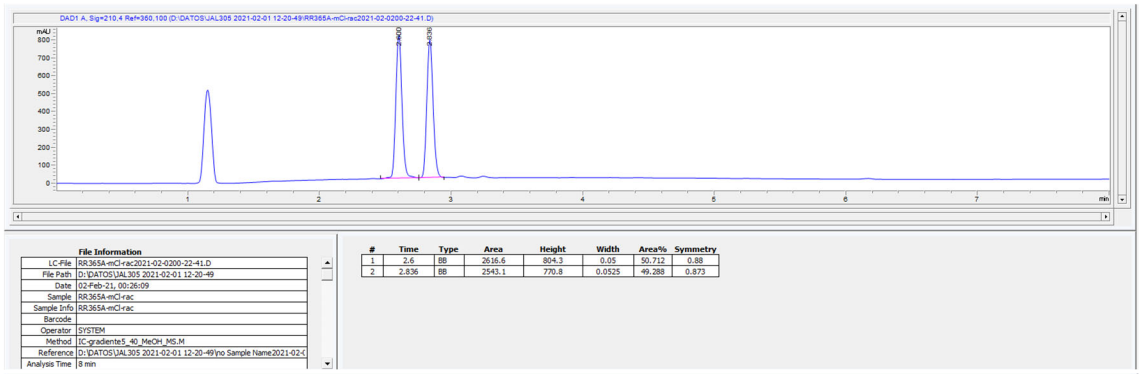
LC-File	RR324C_OP2020-12-1411-00-40.D
File Path	D:\DATOS\JAL305 2020-12-14 10-02-51
Date	14-Dec-20, 11:04:06
Sample	RR324C_OP
Sample Info	RR324C_OP
Barcode	
Operator	SYSTEM
Method	IC-gradiente5_40_MeOH_MS.M
Reference	D:\DATOS\JAL305 2020-12-14 10-02-51\no Sample Name2020-12-:
Analysis Time	8 min

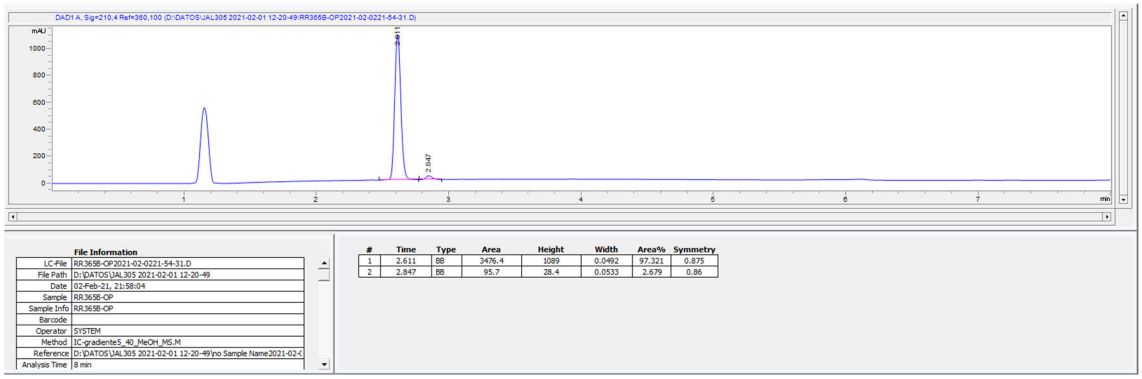
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	2.994	BB	779.6	236.2	0.0505	97.909	0.887
2	3.415	MM	16.6	5	0.0555	2.091	1.044

Ethyl (*R,E*)-2-(3-chlorophenyl)-2-hydroxy-6-oxohex-4-enoate (4h)

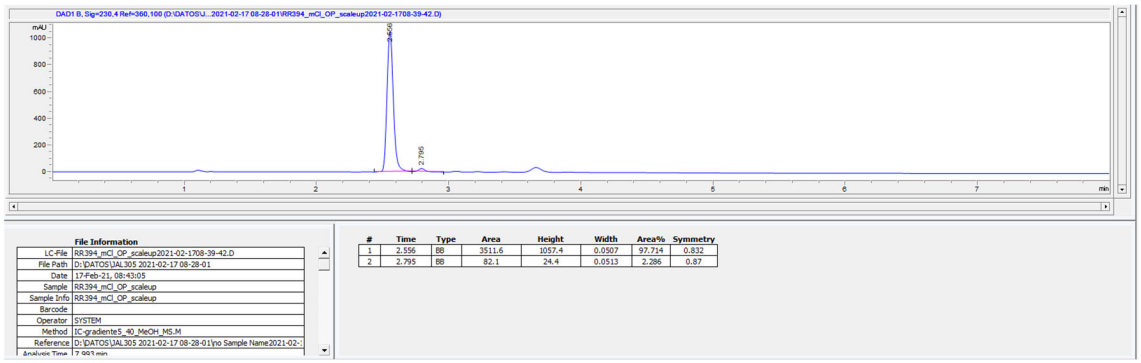




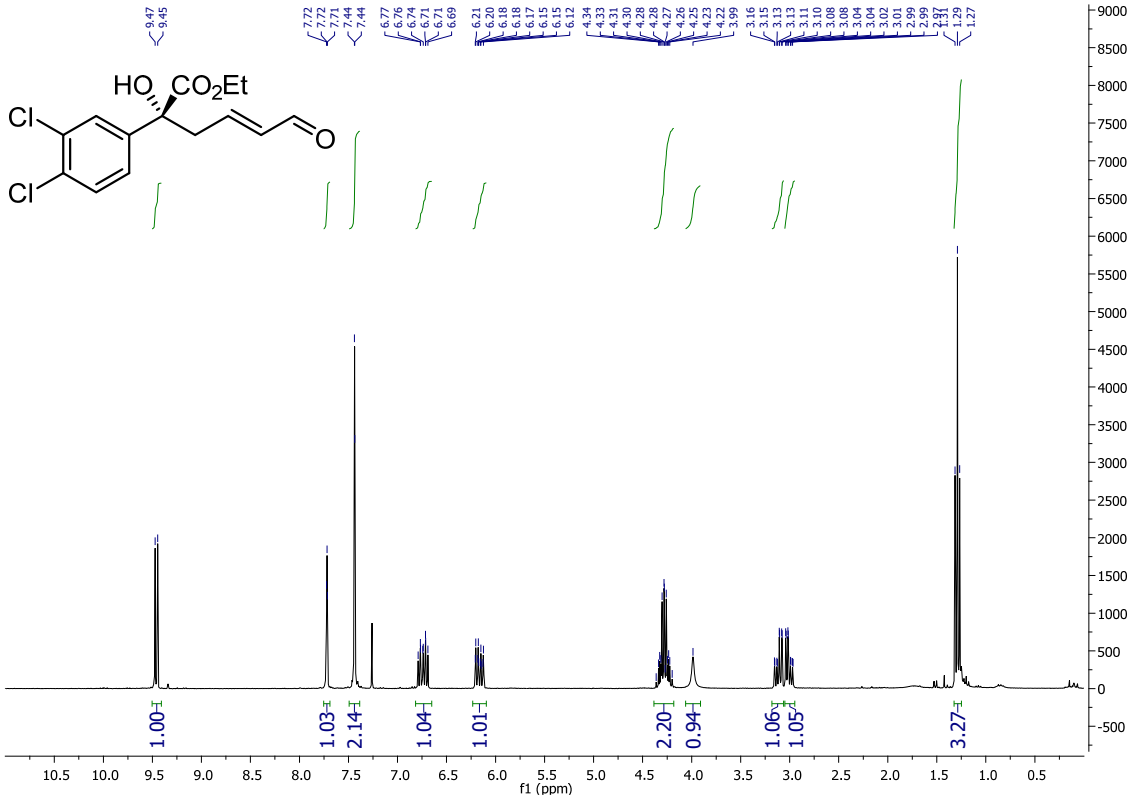


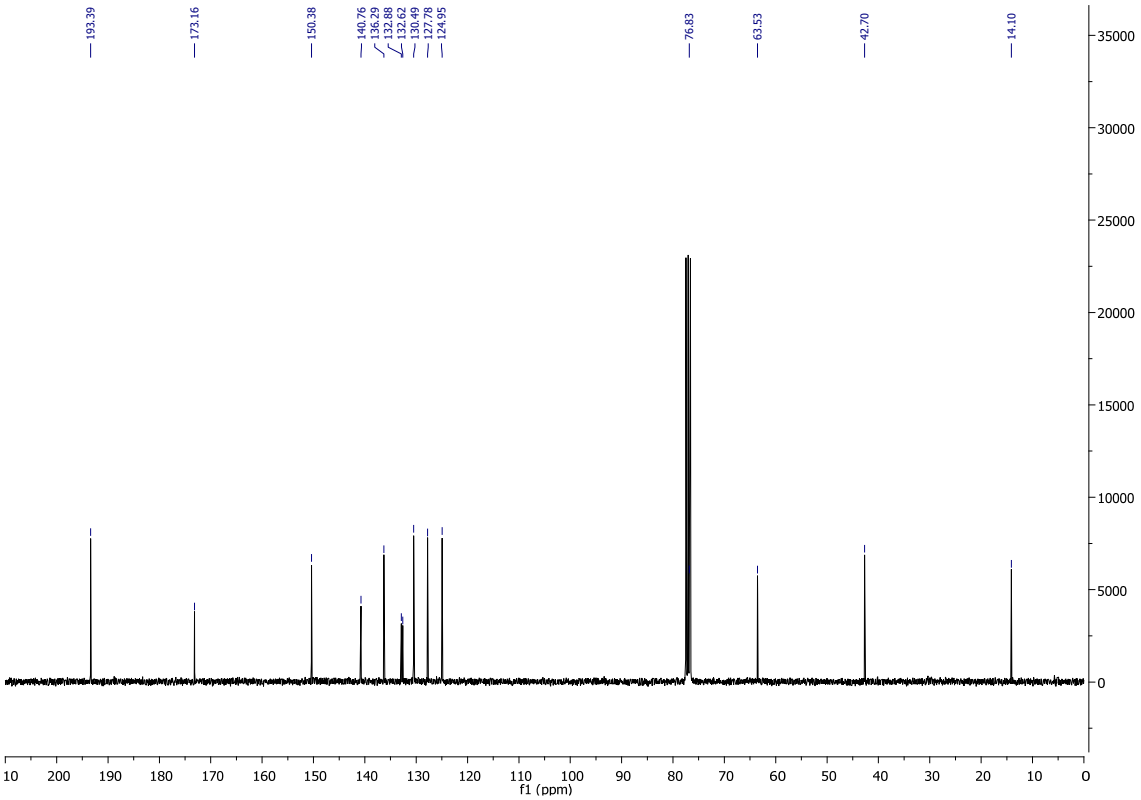


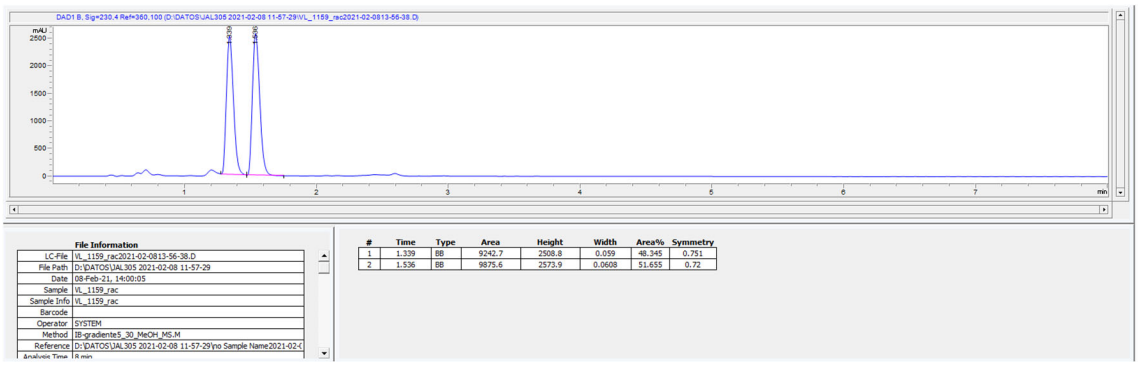
- 1.0 mmol scale chromatogram:



Ethyl (*R,E*)-2-(3,4-dichlorophenyl)-2-hydroxy-6-oxohex-4-enoate (4i)



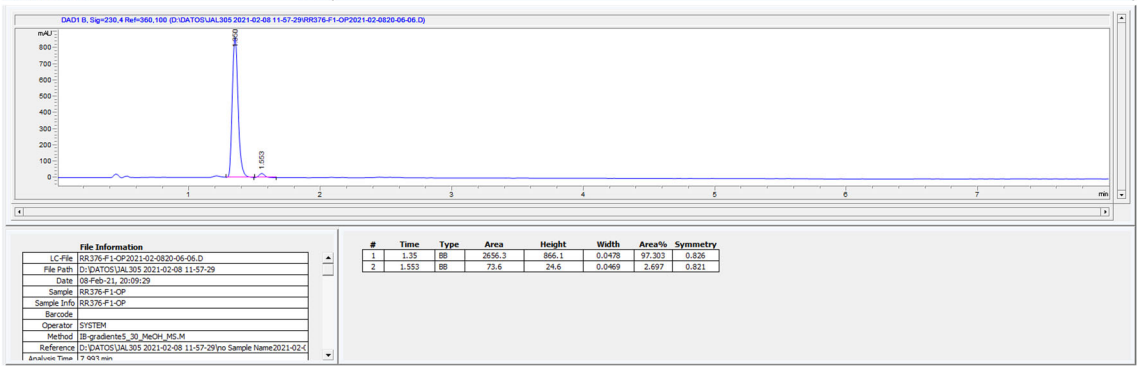




File Information

LC-File	VL_1159_rac2021-02-0813-56-38.D
File Path	D:\DATOS\JAL305 2021-02-08 11-57-29
Date	08-Feb-21, 14:00:05
Sample	VL_1159_rac
Sample Info	VL_1159_rac
Barcode	
Operator	SYSTEM
Method	IB-gradiente5_30_MeOH_MS.M
Reference	D:\DATOS\JAL305 2021-02-08 11-57-29\no Sample Name2021-02-(
Analysis Time	8 min

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	1.339	BB	9242.7	2508.8	0.059	48.345	0.751
2	1.536	BB	9875.6	2573.9	0.0608	51.655	0.72

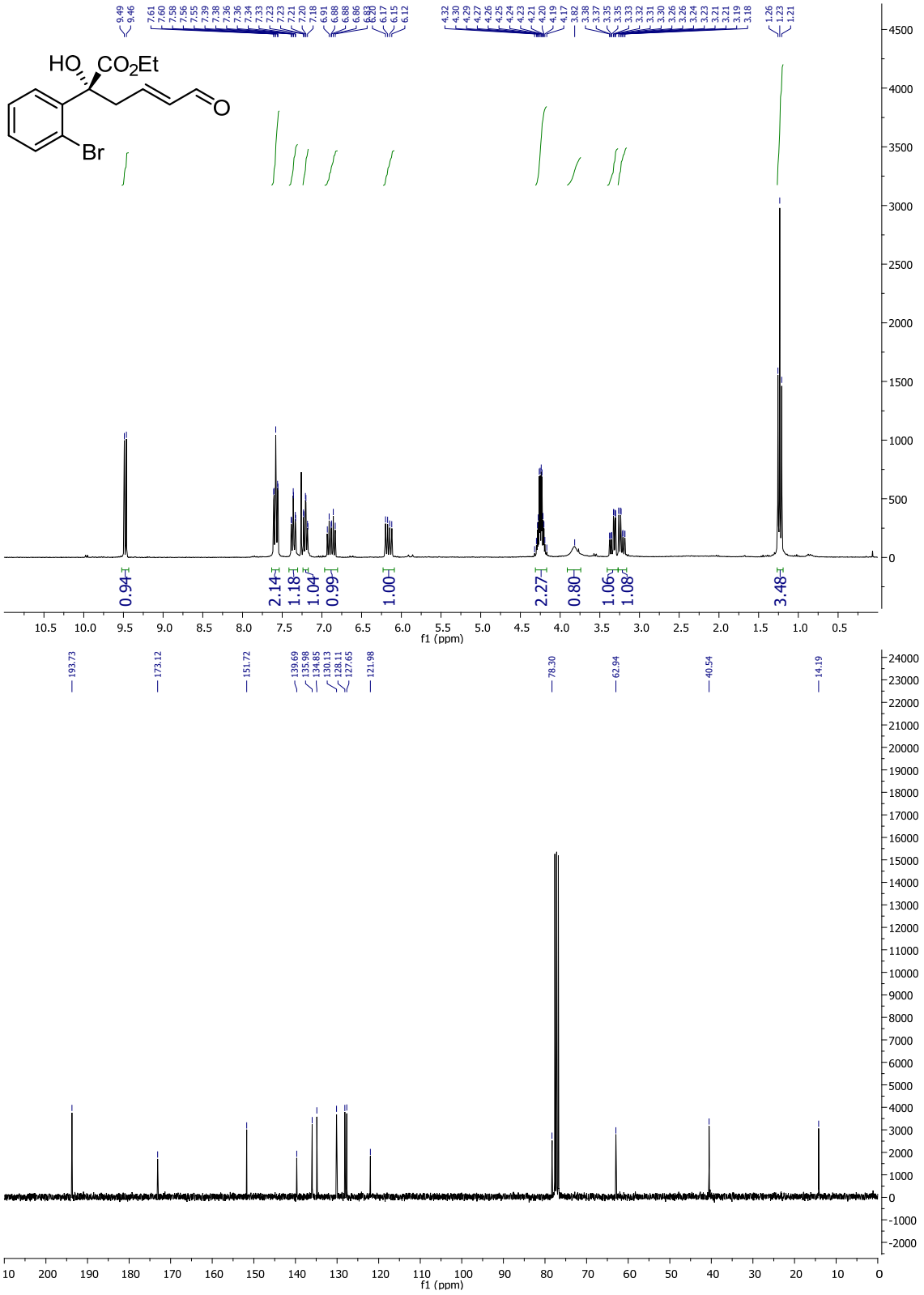


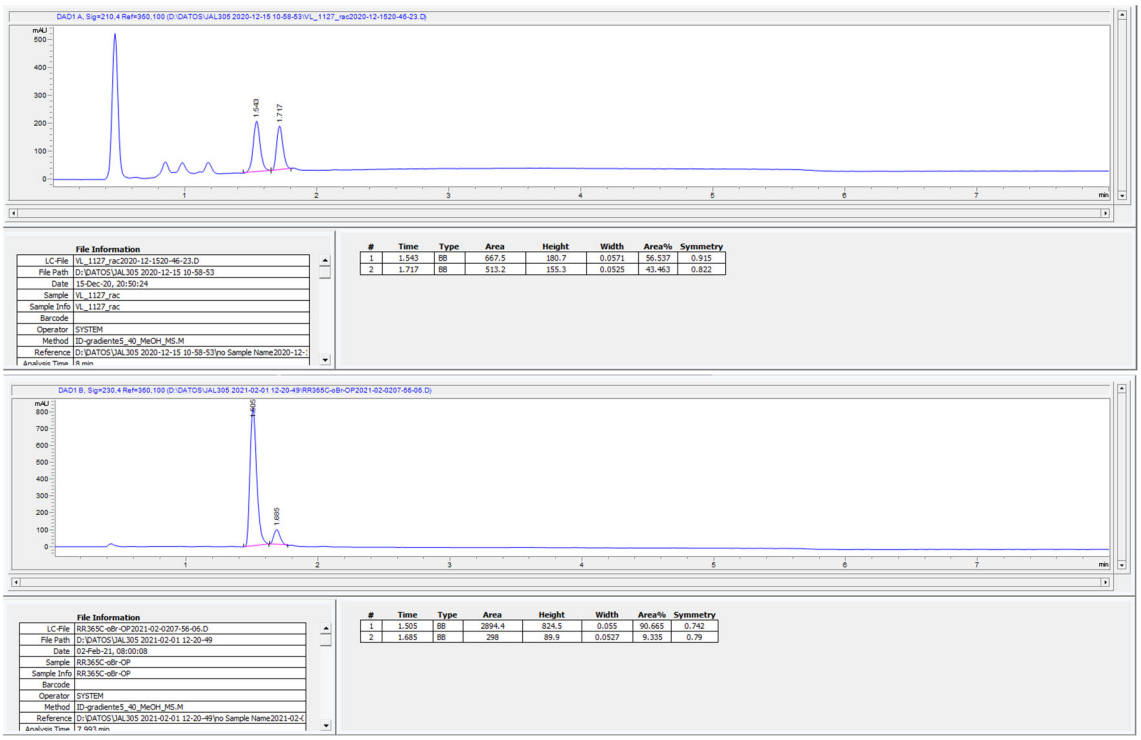
File Information

LC-File	RR376-F1-OP2021-02-0820-06-06.D
File Path	D:\DATOS\JAL305 2021-02-08 11-57-29
Date	08-Feb-21, 20:09:29
Sample	RR376-F1-OP
Sample Info	RR376-F1-OP
Barcode	
Operator	SYSTEM
Method	IB-gradiente5_30_MeOH_MS.M
Reference	D:\DATOS\JAL305 2021-02-08 11-57-29\no Sample Name2021-02-(
Analysis Time	7.992 min

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	1.35	BB	2656.3	866.1	0.0478	97.303	0.826
2	1.553	BB	73.6	24.6	0.0469	2.697	0.821

Ethyl (*R,E*)-2-(2-bromophenyl)-2-hydroxy-6-oxohex-4-enoate (4j)





File Information

LC-File	VL_1127_rac2020-12-1520-46-23.D
File Path	D:\DATOS\IAL305 2020-12-15 10-58-53
Date	15-Dec-20, 20:50:24
Sample	VL_1127_rac
Sample Info	VL_1127_rac
Barcode	
Operator	SYSTEM
Method	ID-gradiente5_40_MeOH_MS.M
Reference	D:\DATOS\IAL305 2020-12-15 10-58-53\no Sample Name2020-12-1
Analysis Time	8 min

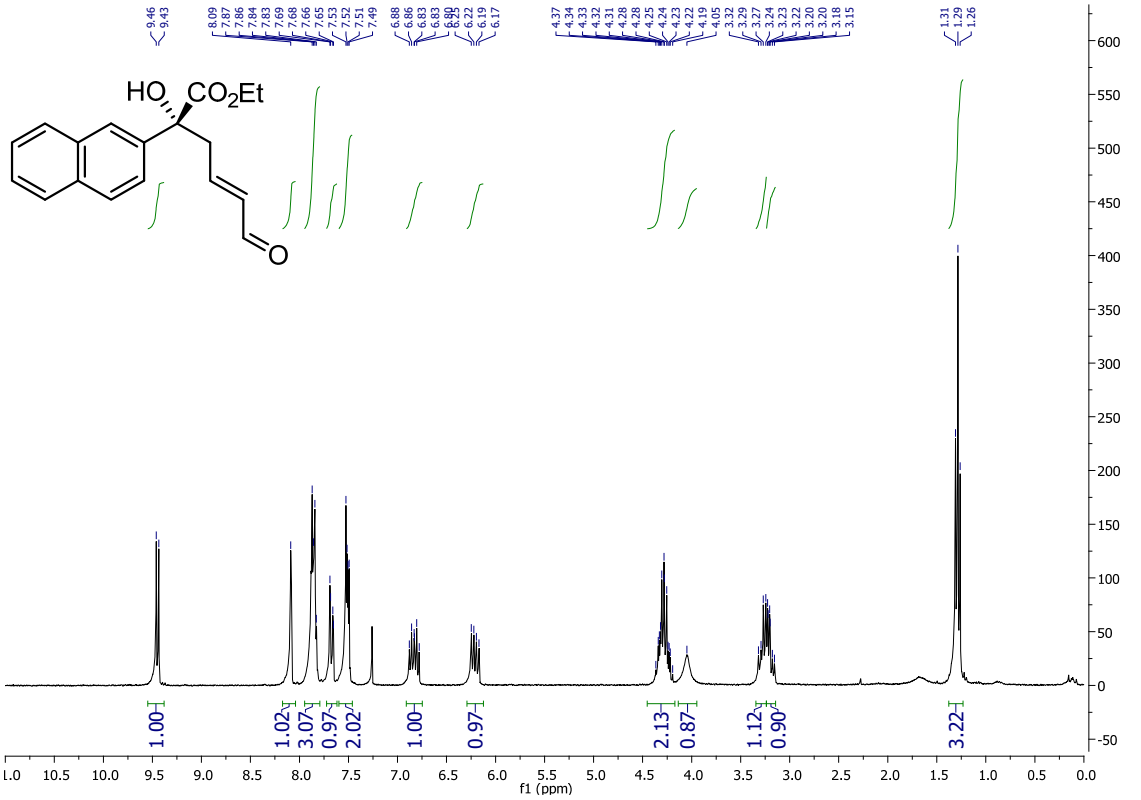
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	1.543	BB	667.5	180.7	0.0571	56.537	0.915
2	1.717	BB	513.2	155.3	0.0525	43.463	0.822

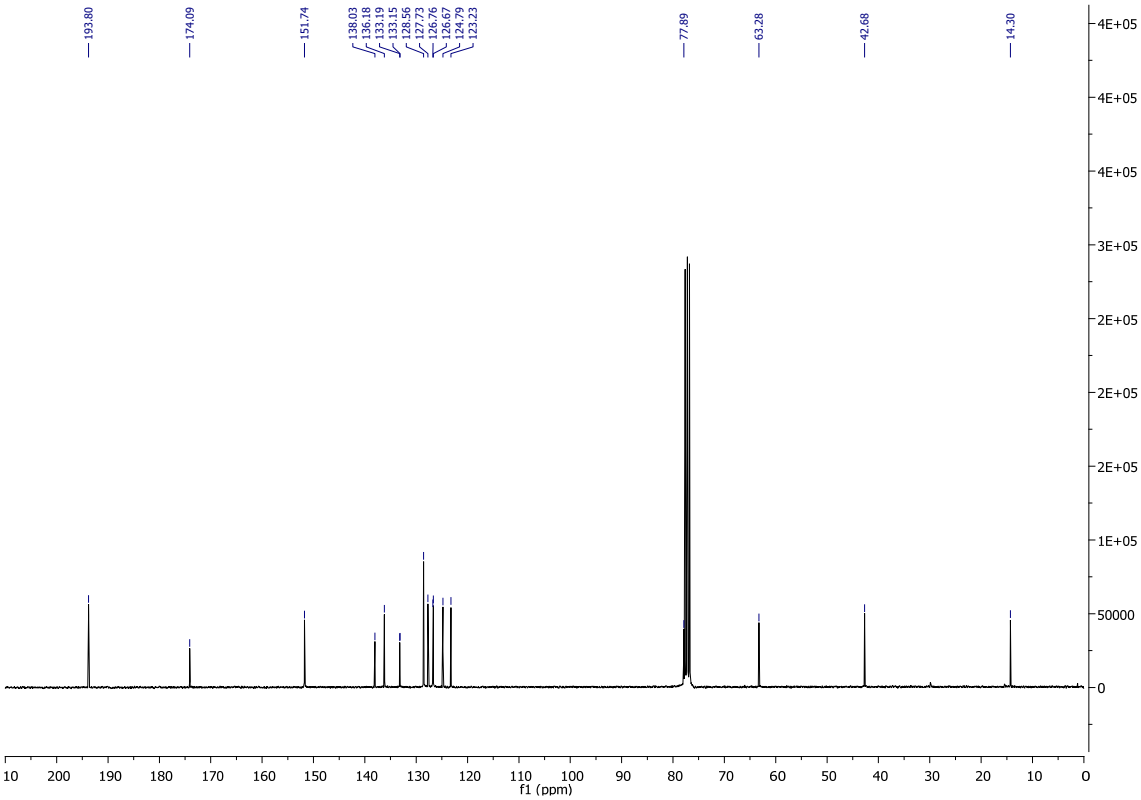
File Information

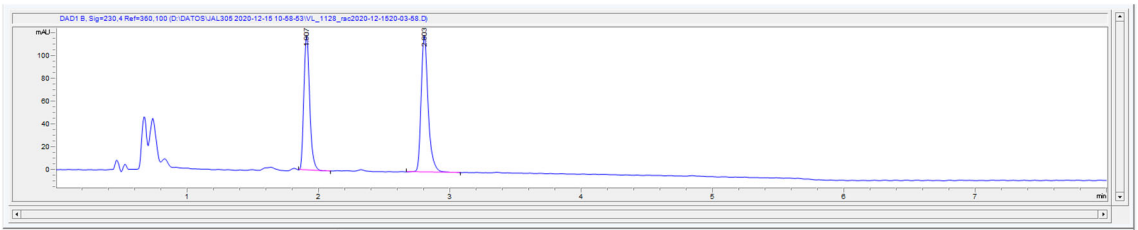
LC-File	RR365C-oBr-OP2021-02-0207-56-06.D
File Path	D:\DATOS\IAL305 2021-02-01 12-20-49
Date	02-Feb-21, 08:00:08
Sample	RR365C-oBr-OP
Sample Info	RR365C-oBr-OP
Barcode	
Operator	SYSTEM
Method	ID-gradiente5_40_MeOH_MS.M
Reference	D:\DATOS\IAL305 2021-02-01 12-20-49\no Sample Name2021-02-(
Analysis Time	7.991 min

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	1.505	BB	2894.4	824.5	0.055	90.665	0.742
2	1.685	BB	298	89.9	0.0527	9.335	0.79

Ethyl (*R,E*)-2-hydroxy-2-(napthalen-2-yl)-6-oxohex-4-enoate (4k)



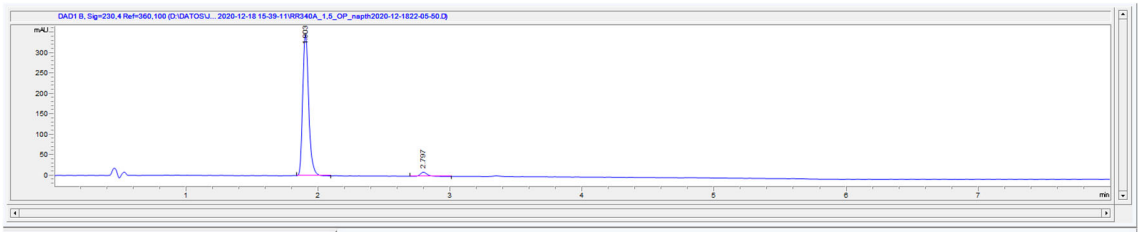




File Information

LC-File	VL_1128_rac2020-12-1520-03-58.D
File Path	D:\DATOS\JAL305 2020-12-15 10-58-53
Date	15-Dec-20, 20:07:27
Sample	VL_1128_rac
Sample Info	VL_1128_rac
Barcode	
Operator	SYSTEM
Method	IB-gradiente5_30_MeOH_MS.M
Reference	D:\DATOS\JAL305 2020-12-15 10-58-53\no Sample Name2020-12-
Analysis Time	8 min

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	1.907	BB	365.3	118.4	0.048	45.095	0.823
2	2.803	BB	444.8	120.6	0.057	54.905	0.74

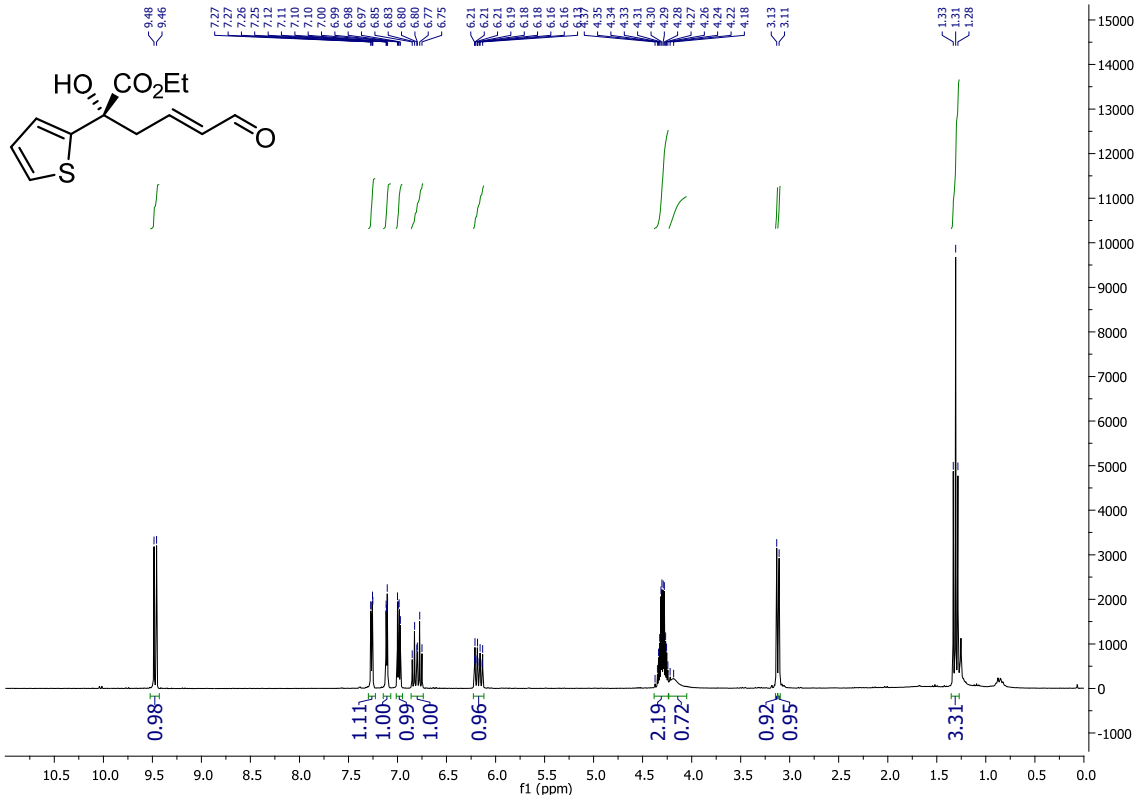


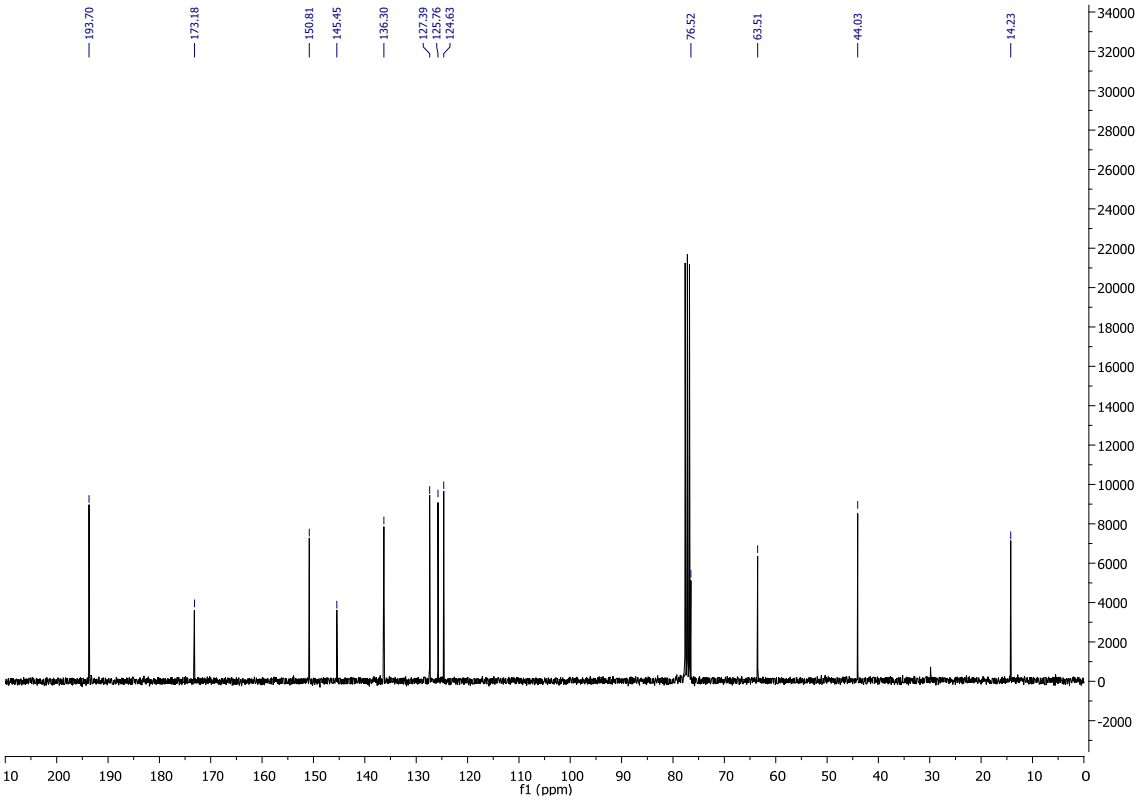
File Information

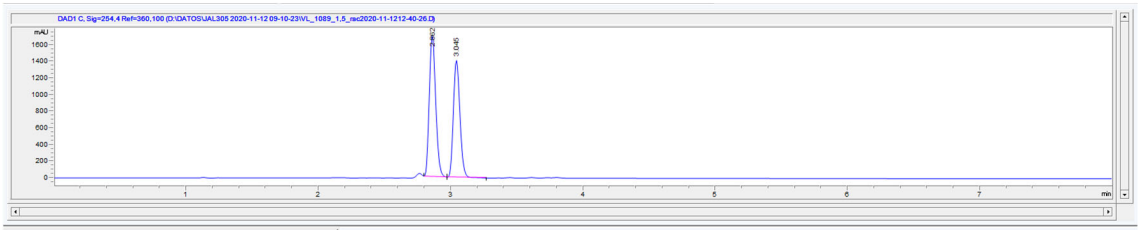
LC-File	RR340A_1,5_OP_napth2020-12-1822-05-50.D
File Path	D:\DATOS\JAL305 2020-12-18 15-39-11
Date	18-Dec-20, 22:09:20
Sample	RR340A_1,5_OP_napth
Sample Info	RR340A_1,5_OP_napth
Barcode	
Operator	SYSTEM
Method	IB-gradiente5_30_MeOH_MS.M
Reference	D:\DATOS\JAL305 2020-12-18 15-39-11\no Sample Name2020-12-
Analysis Time	7.992 min

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	1.903	BB	1094.8	349	0.0486	96.521	0.806
2	2.797	BB	39.5	10.2	0.0571	3.479	0.712

Ethyl (*R,E*)-2-hydroxy-6-oxo-2-(thiophene-2-yl)hex-4-enoate (4l)

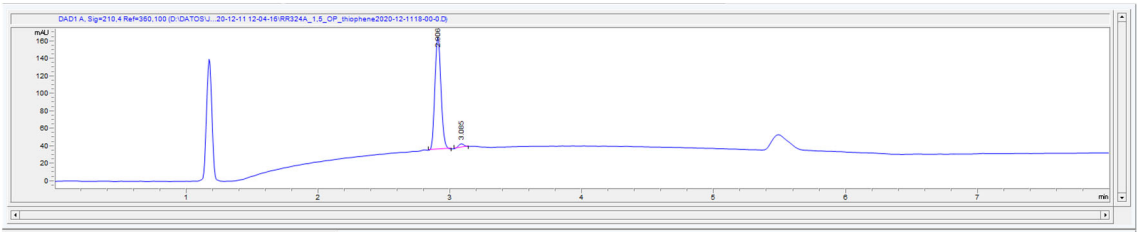






File Information	
LC-File	VL_1089_1,5_rac2020-11-1212-40-26.D
File Path	D:\DATOS\JAL305 2020-11-12 09-10-23
Date	12-Nov-20, 12:43:54
Sample	VL_1089_1,5_rac
Sample Info	VL_1089_1,5_rac
Barcode	
Operator	SYSTEM
Method	IC-gradiente5_40_MeOH_MS.M
Reference	D:\DATOS\JAL305 2020-11-12 09-10-23\no Sample Name2020-11-:

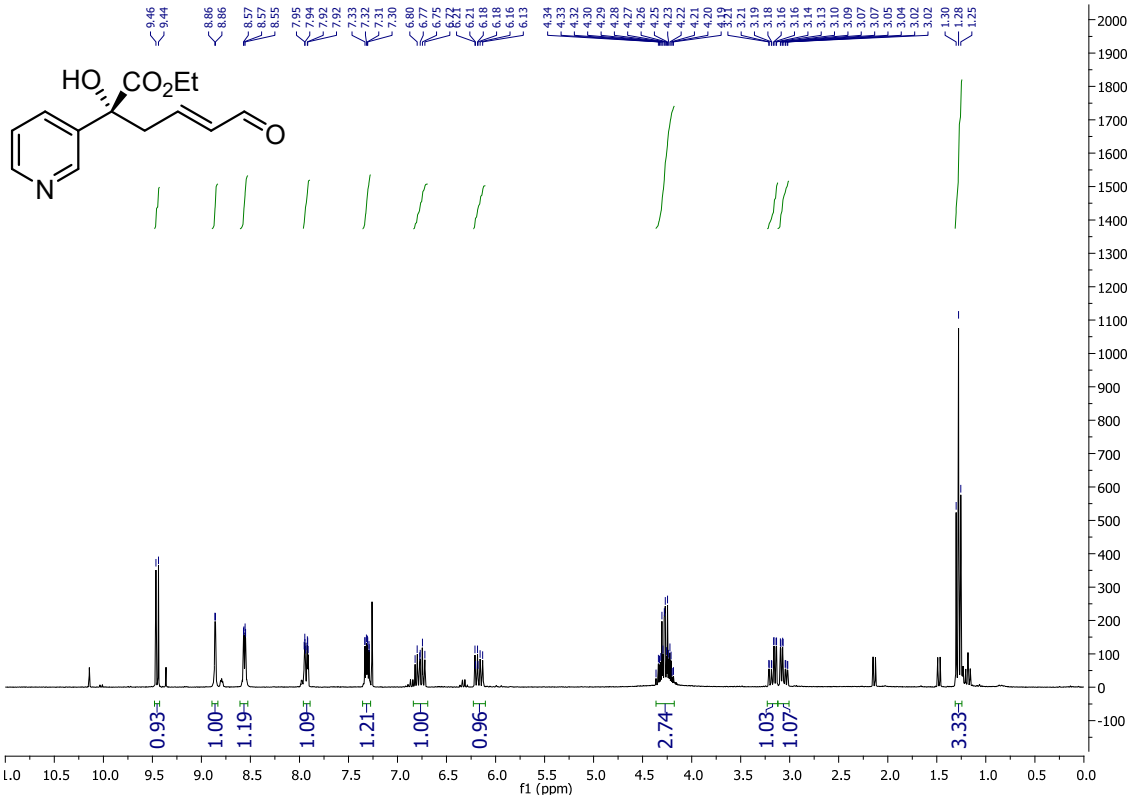
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	2.862	BB	5736.9	1707.3	0.0532	54.180	0.826
2	3.045	BB	4851.6	1411.2	0.0541	45.820	0.823

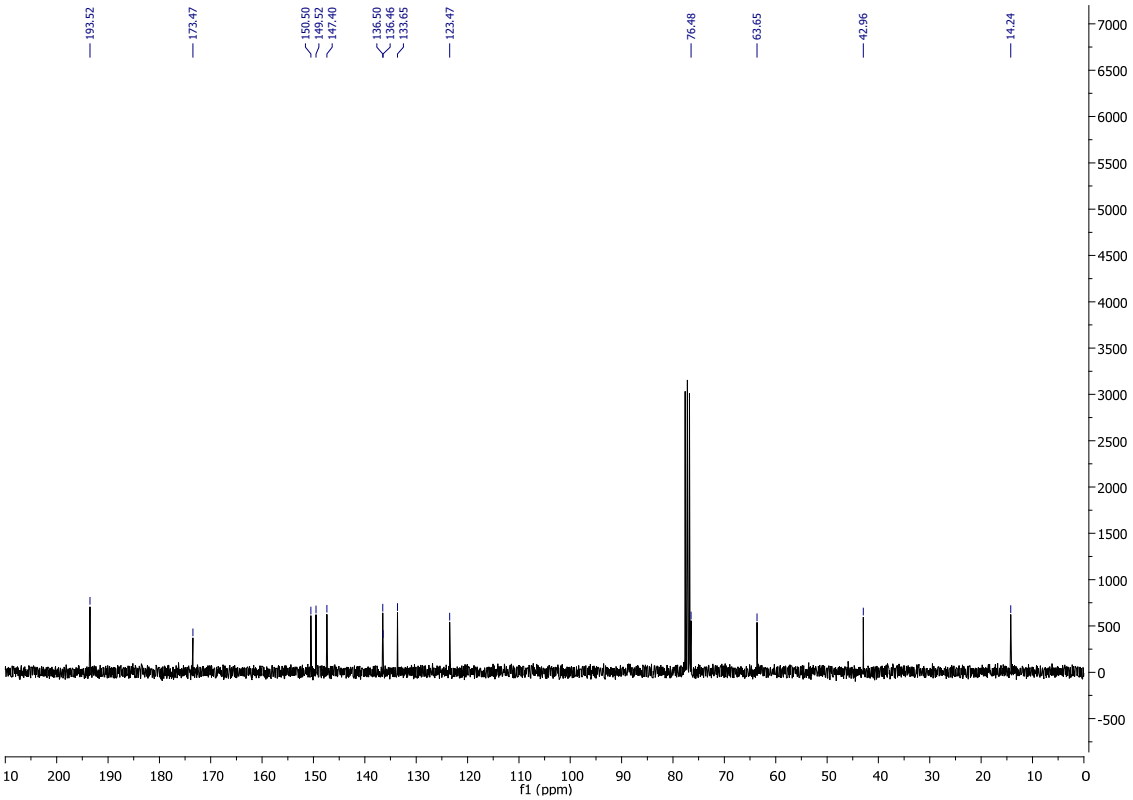


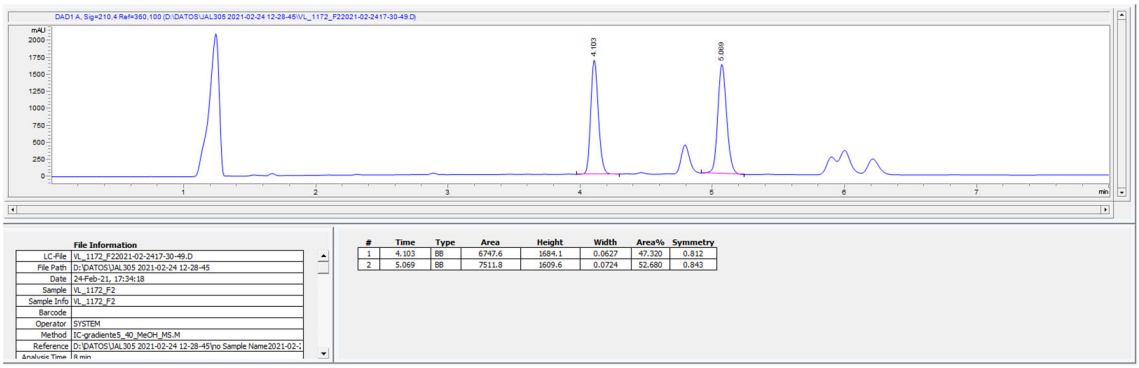
File Information	
LC-File	RR324A_1,5_OP_thiophene2020-12-1118-00-0.D
File Path	D:\DATOS\JAL305 2020-12-11 12-04-16
Date	11-Dec-20, 18:03:29
Sample	RR324A_1,5_OP_thiophene
Sample Info	RR324A_1,5_OP_thiophene
Barcode	
Operator	SYSTEM
Method	IC-gradiente5_40_MeOH_MS.M
Reference	D:\DATOS\JAL305 2020-12-11 12-04-16\no Sample Name2020-12-:

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	2.906	BB	417.6	130	0.0515	97.040	0.879
2	3.085	BB	12.7	4.3	0.0469	2.960	1.146

Ethyl (*R,E*)-2-hydroxy-6-oxo-2-(pyridine-3-yl)hex-4-enoate (4m)

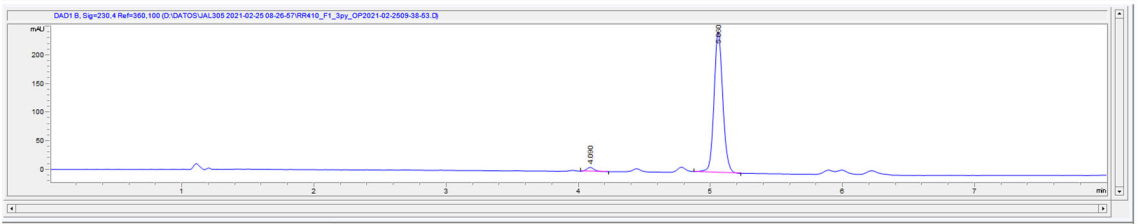






File Information	
LC-File	VL_1172_F22021-02-2417-30-49.D
File Path	D:\DATOS\IAL305 2021-02-24 12-28-45
Date	24-Feb-21, 17:34:18
Sample	VL_1172_F2
Sample Info	VL_1172_F2
Barcode	
Operator	SYSTEM
Method	IC-gradienteS_40_MeOH_MS.M
Reference	D:\DATOS\IAL305 2021-02-24 12-28-45\no Sample Name2021-02-2
Analysis Time	8 min

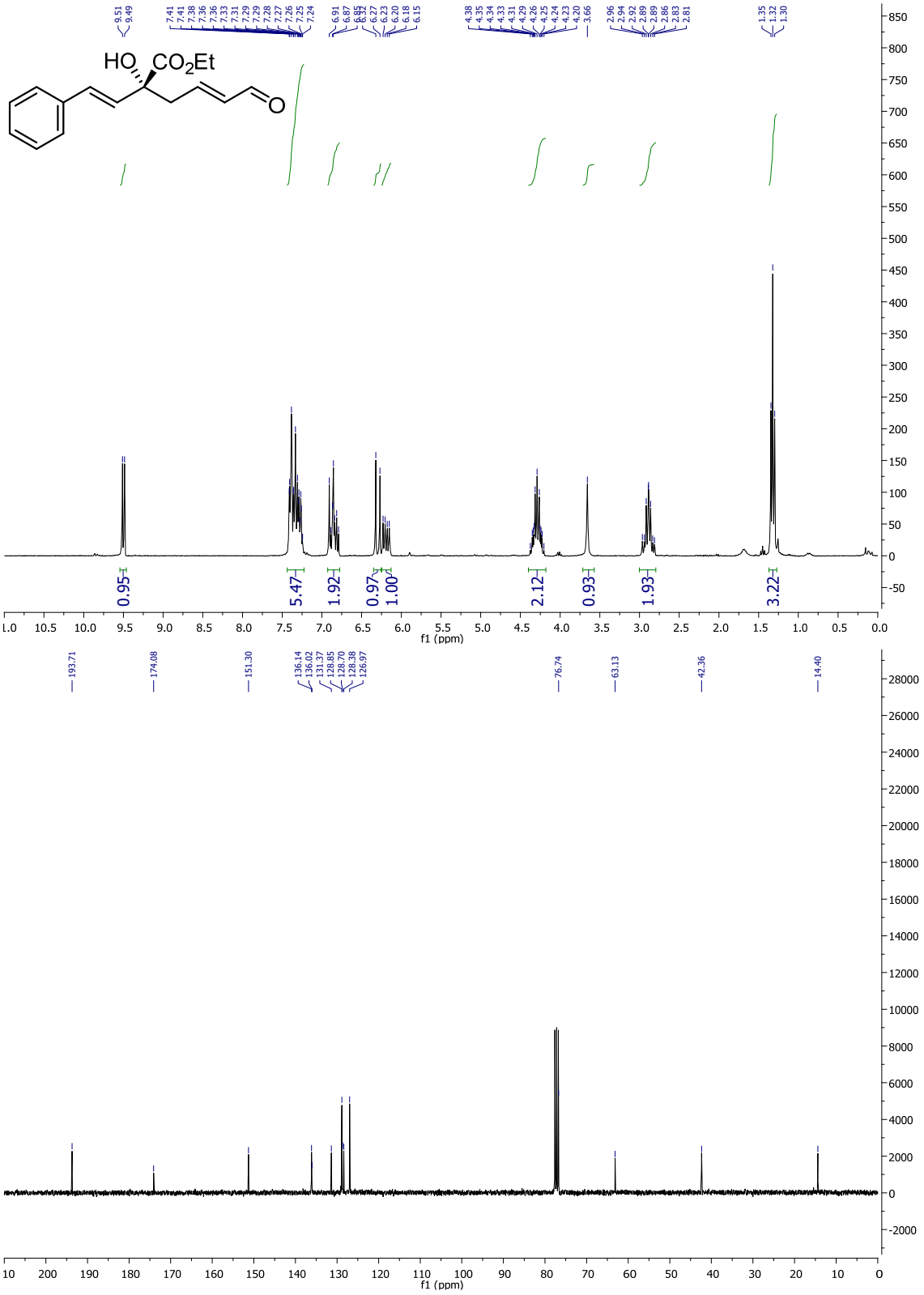
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	4.103	BB	6747.6	1684.1	0.0627	47.320	0.812
2	5.069	BB	7511.8	1609.6	0.0724	52.680	0.843

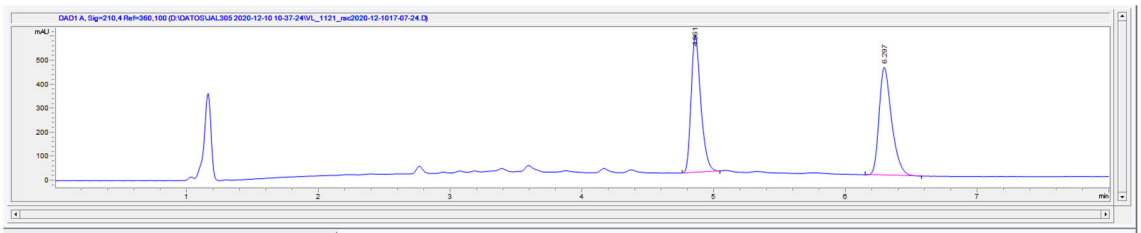


File Information	
LC-File	RR410_F1_3py_OP2021-02-2509-38-53.D
File Path	D:\DATOS\IAL305 2021-02-25 08-26-57
Date	25-Feb-21, 09:42:21
Sample	RR410_F1_3py_OP
Sample Info	RR410_F1_3py_OP
Barcode	
Operator	SYSTEM
Method	IC-gradienteS_40_MeOH_MS.M
Reference	D:\DATOS\IAL305 2021-02-25 08-26-57\no Sample Name2021-02-2
Analysis Time	7.983 min

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	4.09	BB	26.6	6.9	0.0612	2.308	0.838
2	5.06	BB	1127.9	245	0.0717	97.692	0.879

Ethyl (*R*,*E*)-2-hydroxy-6-oxo-2-((*E*)-styryl)hex-4-enoate (4n)

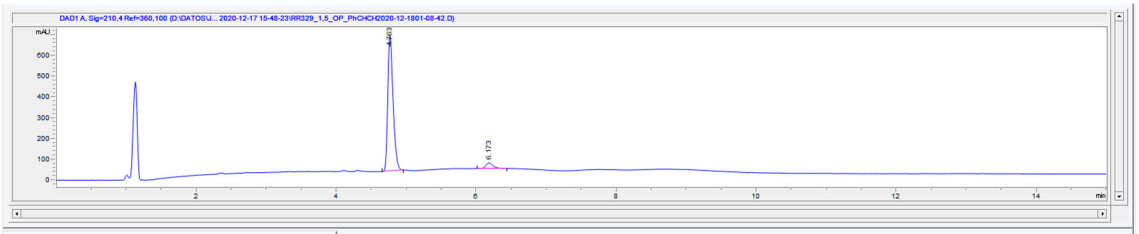




File Information

LC-File	VL_1121_rac2020-12-1017-07-24.D
File Path	D:\DATOS\JAL305 2020-12-10 10-37-24
Date	10-Dec-20, 17:10:48
Sample	VL_1121_rac
Sample Info	VL_1121_rac
Barcode	
Operator	SYSTEM
Method	IG-gradiente5_40_MeOH_MS.M
Reference	D:\DATOS\JAL305 2020-12-10 10-37-24\no Sample Name2020-12-
Analysis Time	8 min

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	4.861	BB	2909.7	570.9	0.0775	49.315	0.695
2	6.297	BB	2990.5	450.6	0.0994	50.685	0.667

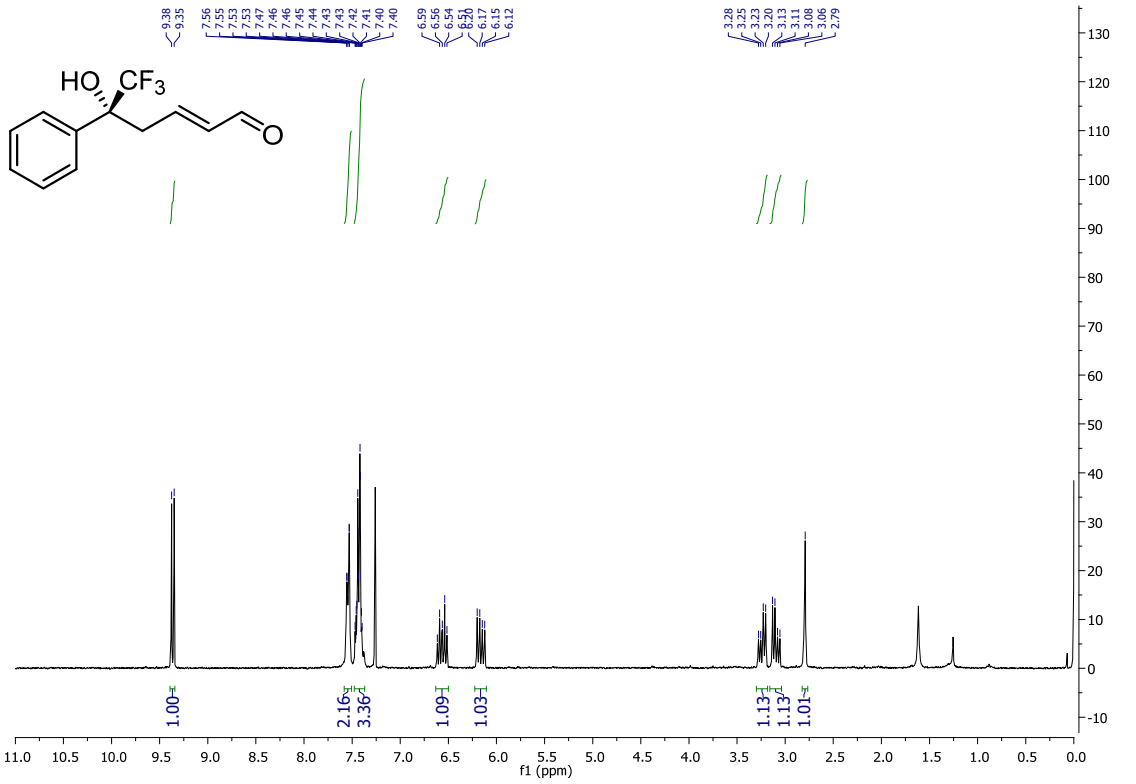


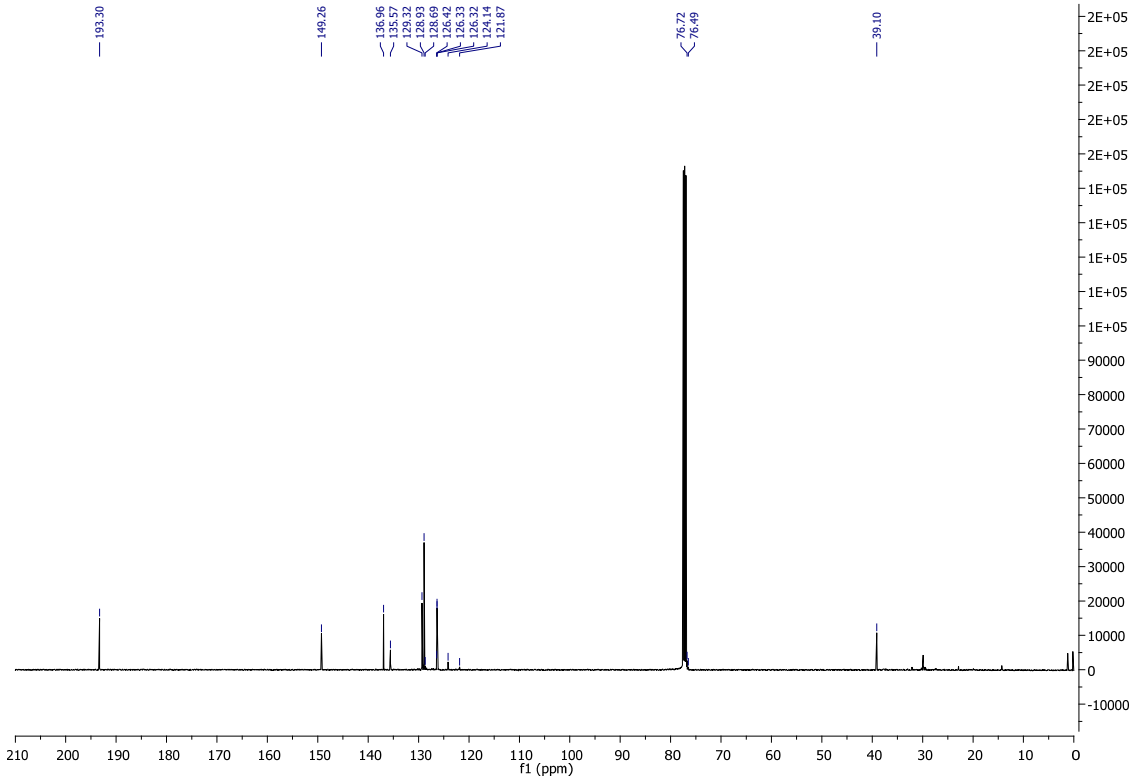
File Information

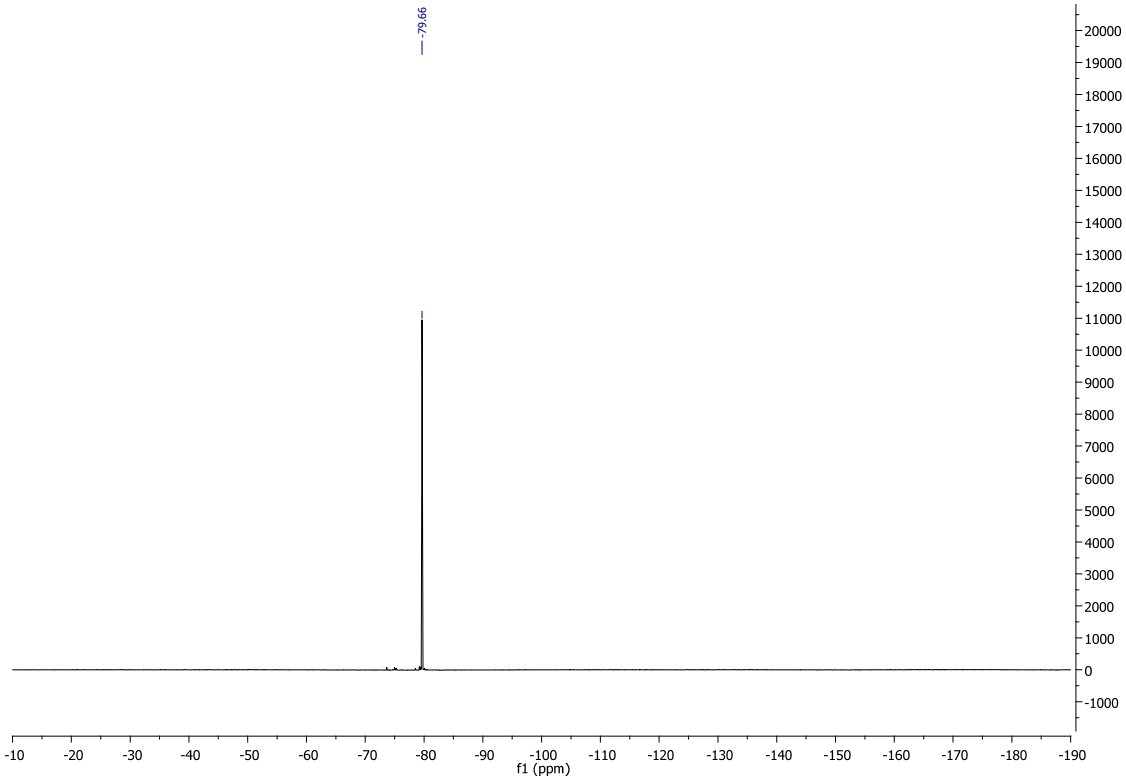
LC-File	RR329_1,5_OP_PhCHCH2020-12-1801-08-42.D
File Path	D:\DATOS\JAL305 2020-12-17 15-48-23
Date	18-Dec-20, 01:12:08
Sample	RR329_1,5_OP_PhCHCH
Sample Info	RR329_1,5_OP_PhCHCH
Barcode	
Operator	SYSTEM
Method	IG-gradiente5_40_MeOH_15min_MS.M
Reference	D:\DATOS\JAL305 2020-12-17 15-48-23\no Sample Name2020-12-
Analysis Time	15 min

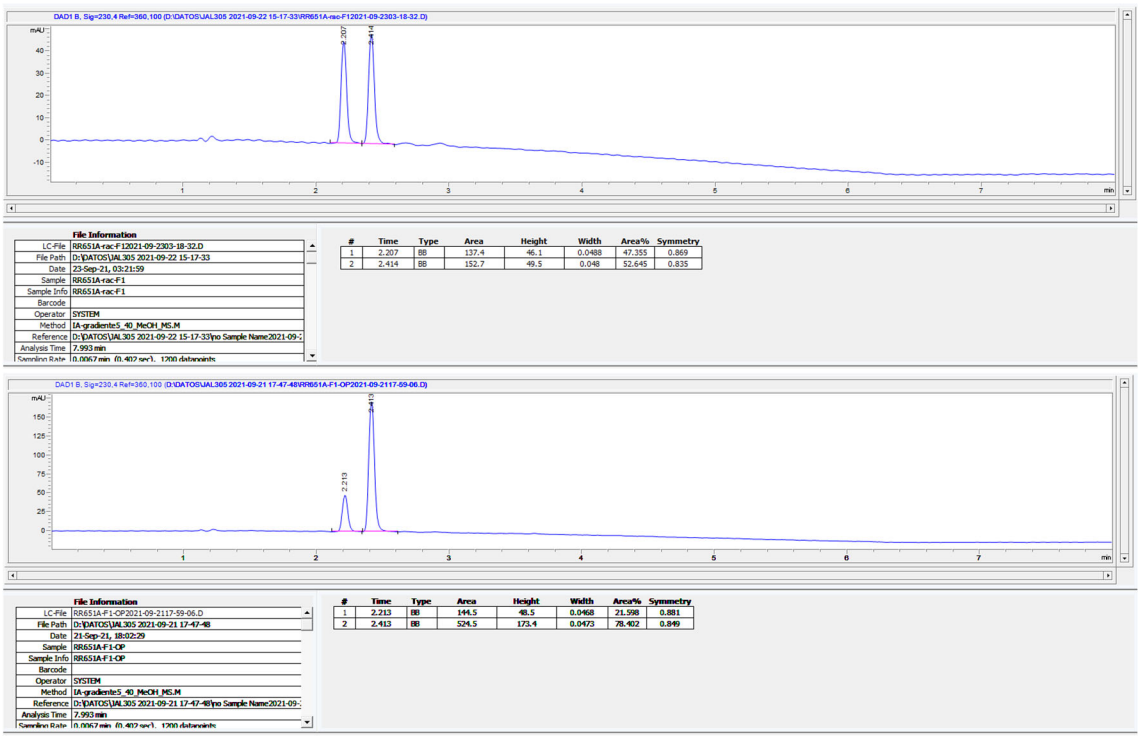
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	4.763	BB	3430	654	0.0792	94.604	0.678
2	6.173	BB	195.6	27.7	0.1085	5.396	0.674

(R,E)-6,6,6-trifluoro-5-hydroxy-5-phenylhex-2-enal (4o)









File Information

LC-File	RR651A-rac-F12021-09-2303-18-32.D
File Path	D:\DATOS\IAL305 2021-09-22 15-17-33
Date	23-Sep-21, 03:21:59
Sample	RR651A-rac-F1
Sample Info	RR651A-rac-F1
Barcode	
Operator	SYSTEM
Method	IA-gradiente5_40_MeOH_MS.M
Reference	D:\DATOS\IAL305 2021-09-22 15-17-33\no Sample Name2021-09-2
Analysis Time	7.993 min
Sampling Rate	0.0067 min (0.402 sec), 1200 datapoints

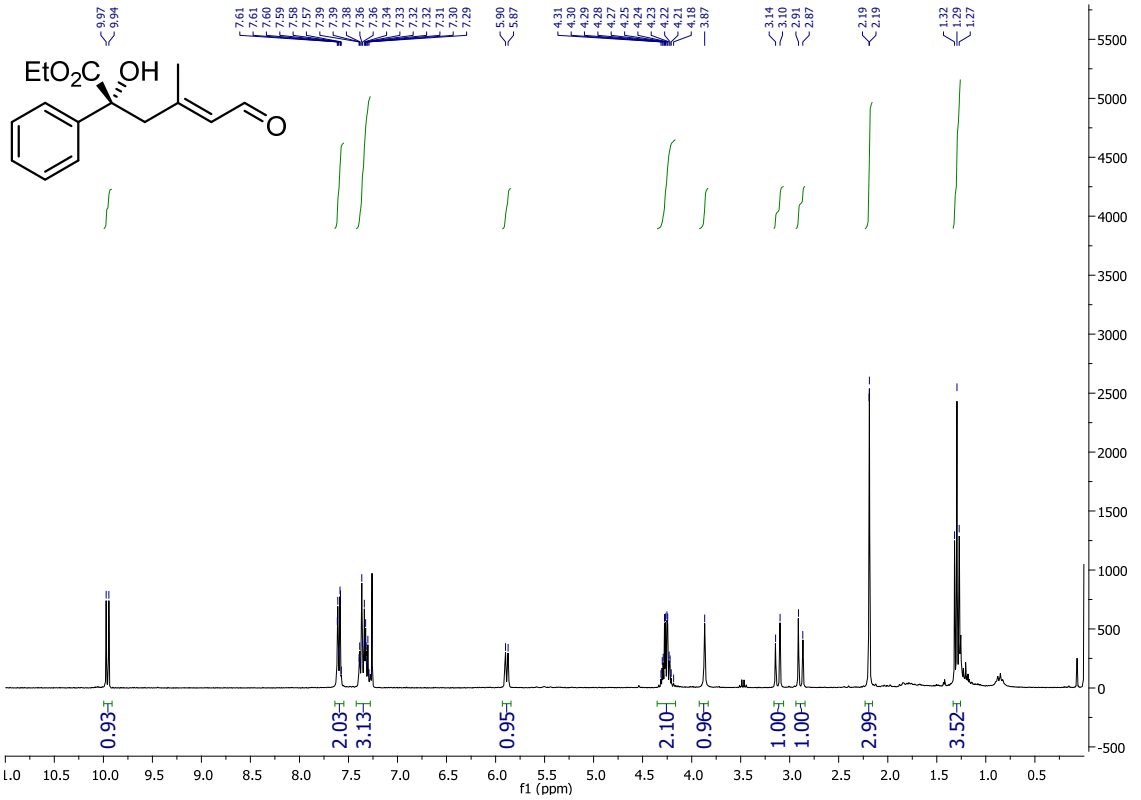
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	2.207	BB	137.4	46.1	0.0488	47.355	0.869
2	2.414	BB	152.7	49.5	0.048	52.645	0.835

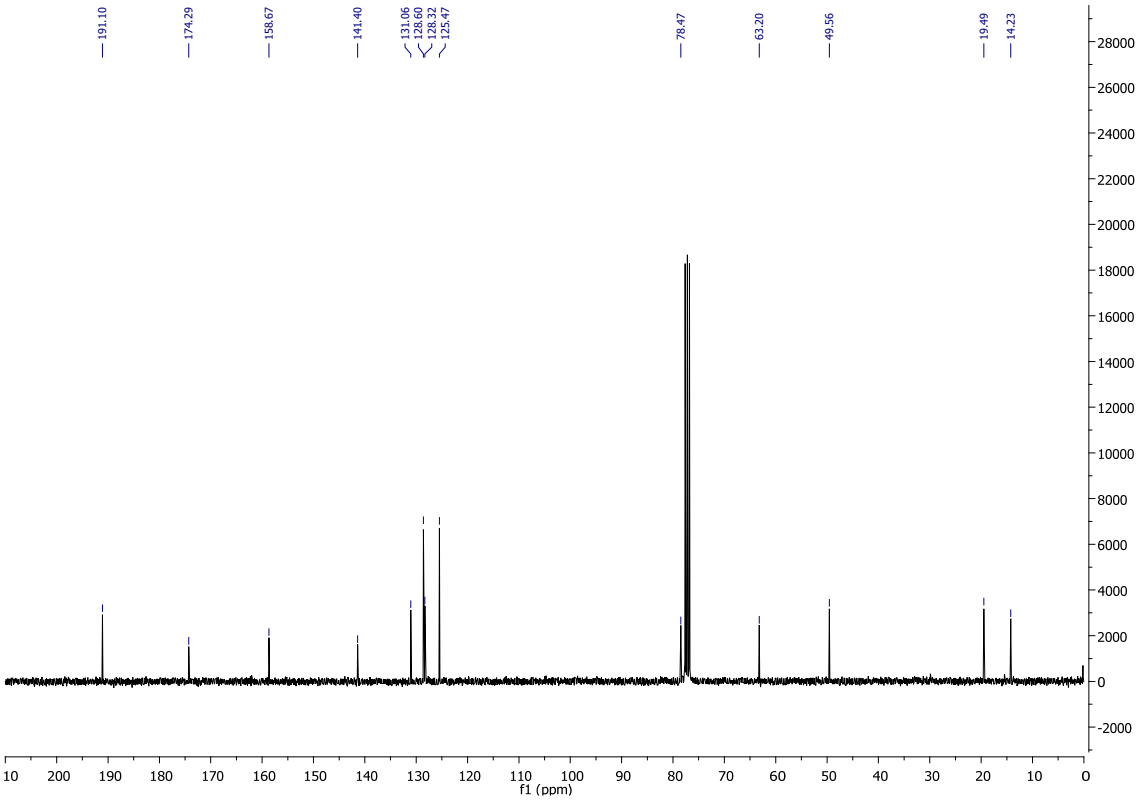
File Information

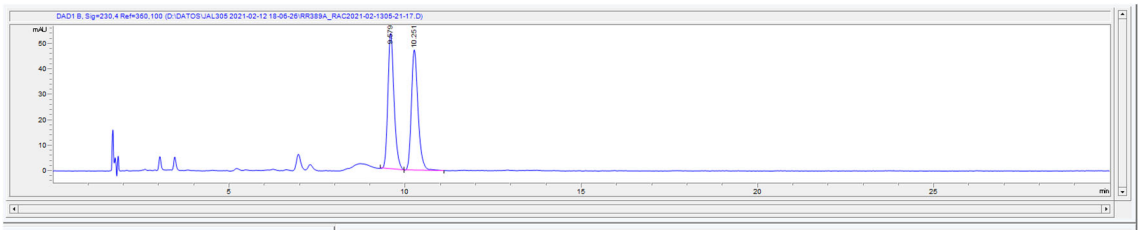
LC-File	RR651A-F1-OP2021-09-2117-59-06.D
File Path	D:\DATOS\IAL305 2021-09-21 17-47-48
Date	21-Sep-21, 18:02:29
Sample	RR651A-F1-OP
Sample Info	RR651A-F1-OP
Barcode	
Operator	SYSTEM
Method	IA-gradiente5_40_MeOH_MS.M
Reference	D:\DATOS\IAL305 2021-09-21 17-47-48\no Sample Name2021-09-2
Analysis Time	7.993 min
Sampling Rate	0.0067 min (0.402 sec), 1200 datapoints

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	2.213	BB	144.5	48.5	0.0468	21.598	0.881
2	2.413	BB	524.5	173.4	0.0473	78.402	0.849

Ethyl (*R,E*)-2-hydroxy-4-methyl-6-oxo-2-phenylhex-4-enoate (4p)

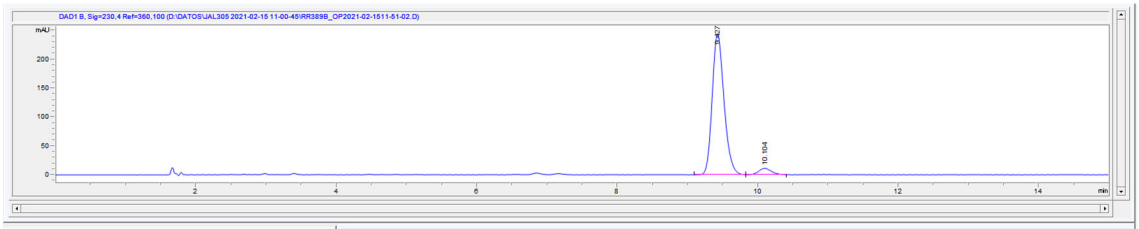






File Information	
LC-File	RR389A_RAC2021-02-1305-21-17.D
File Path	D:\DATOS\JAL305 2021-02-12 18-06-26
Date	13-Feb-21, 05:23:49
Sample	RR389A_RAC
Sample Info	RR389A_RAC
Barcode	
Operator	SYSTEM
Method	IC-2-5-30_MeOH_NO_MS.M
Reference	D:\DATOS\JAL305 2021-02-12 18-06-26\no Sample Name2021-02-
Analysis Time	29.993 min

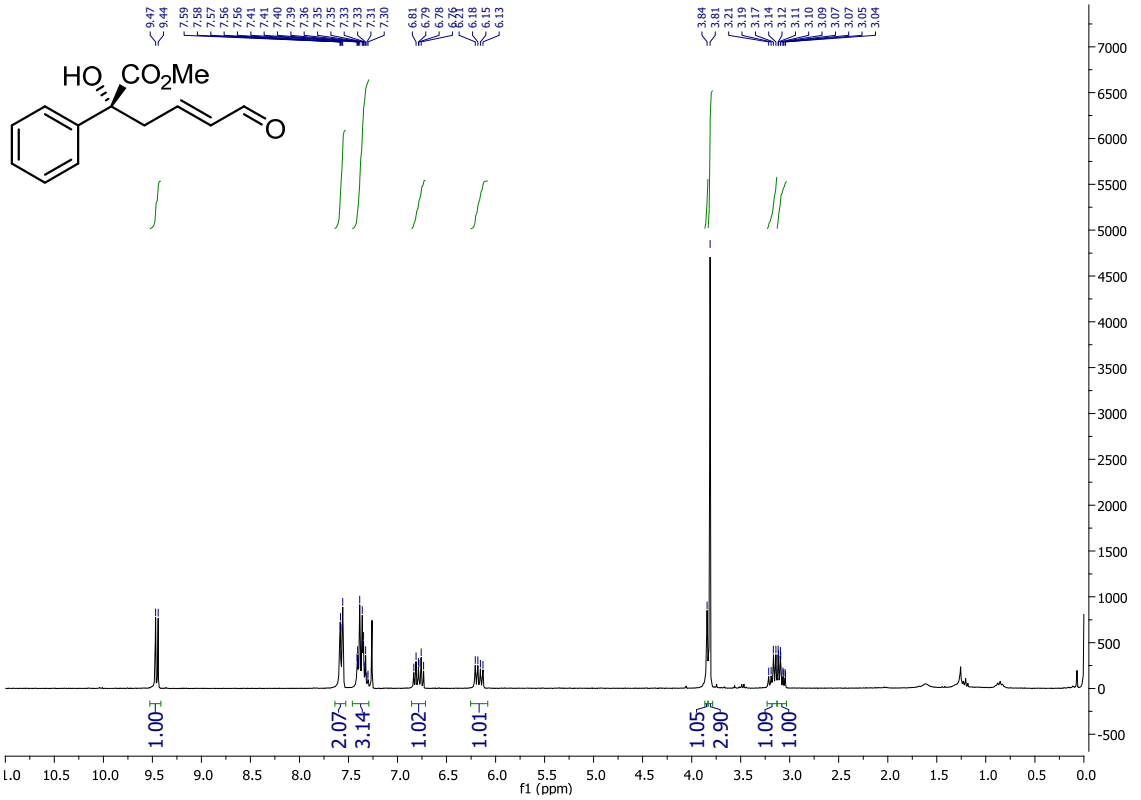
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.579	BB	650.6	53.5	0.1838	51.004	0.772
2	10.251	BB	625	47.4	0.1998	48.996	0.736

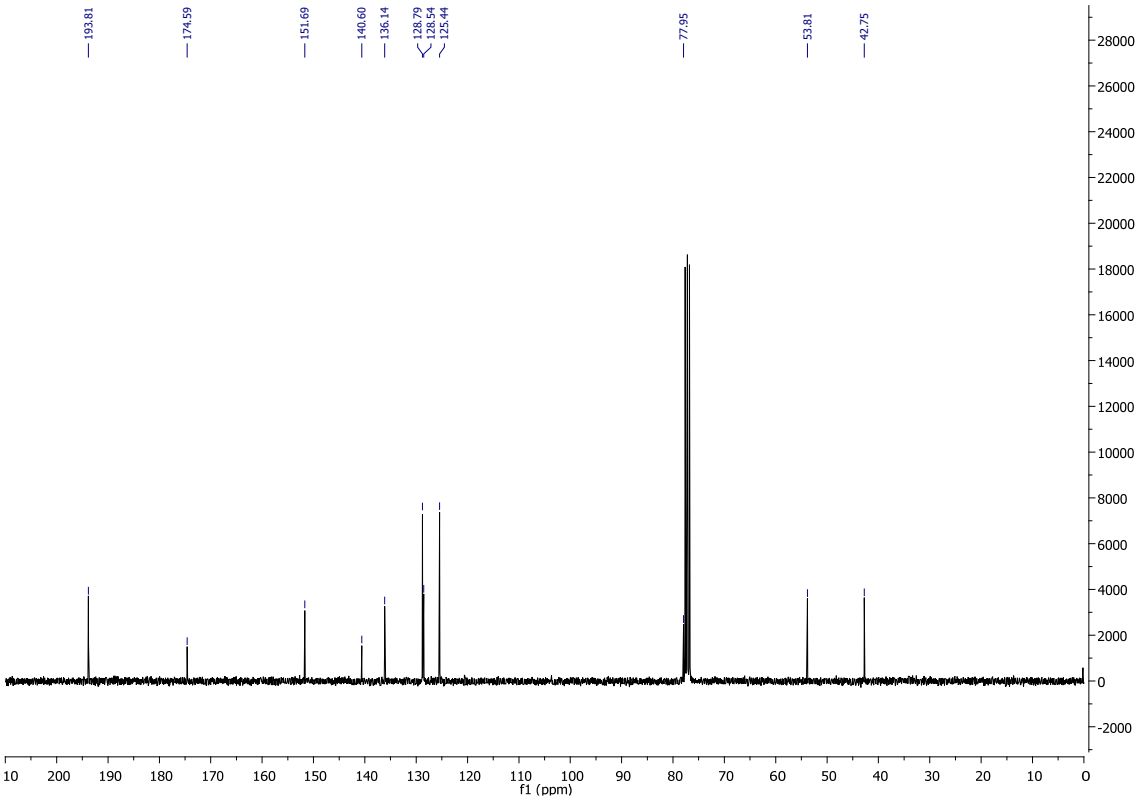


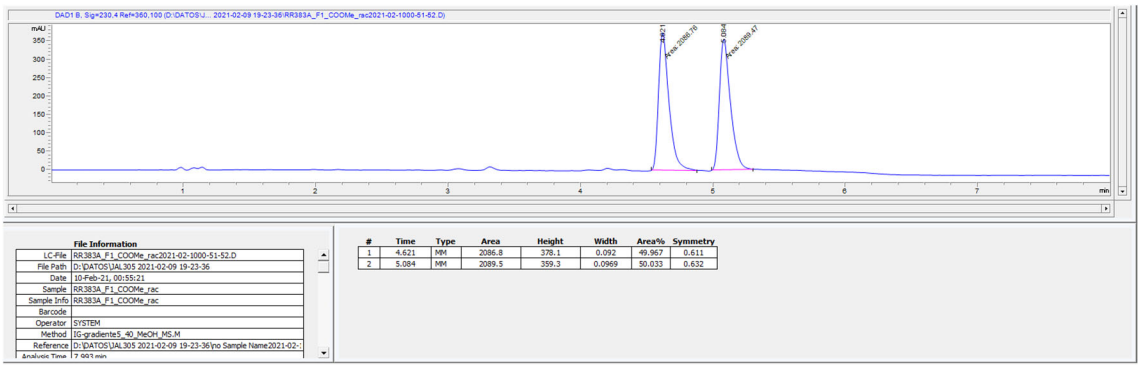
File Information	
LC-File	RR389B_OP2021-02-1511-51-02.D
File Path	D:\DATOS\JAL305 2021-02-15 11-00-45
Date	15-Feb-21, 11:53:23
Sample	RR389B_OP
Sample Info	RR389B_OP
Barcode	
Operator	SYSTEM
Method	IC-2-5-15_MeOH_MS.M
Reference	D:\DATOS\JAL305 2021-02-15 11-00-45\no Sample Name2021-02-
Analysis Time	14.993 min

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.427	BB	2862.1	244.8	0.1804	95.317	0.782
2	10.104	BB	140.6	11.1	0.1852	4.683	0.925

Methyl (*R,E*)-2-hydroxy-6-oxo-2-phenylhex-4-enoate (4q)

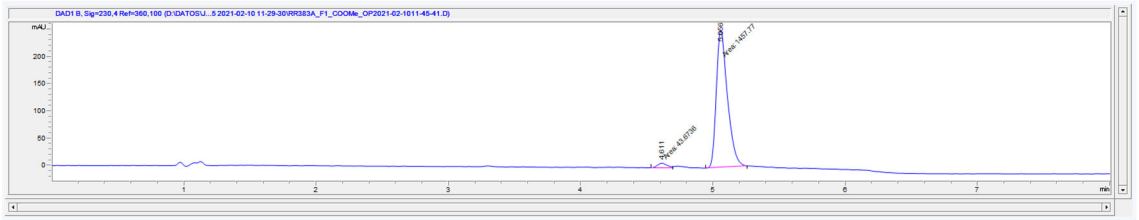






File Information	
LC-File	RR383A_F1_COOMe_rac2021-02-1000-51-52.D
File Path	D:\DATOS\JAL305 2021-02-09 19-23-36
Date	10-Feb-21, 00:55:21
Sample	RR383A_F1_COOMe_rac
Sample Info	RR383A_F1_COOMe_rac
Barcode	
Operator	SYSTEM
Method	IG-gradiente5_40_MeOH_MS.M
Reference	D:\DATOS\JAL305 2021-02-09 19-23-36\no Sample Name2021-02-
Analysis Time	7.997 min

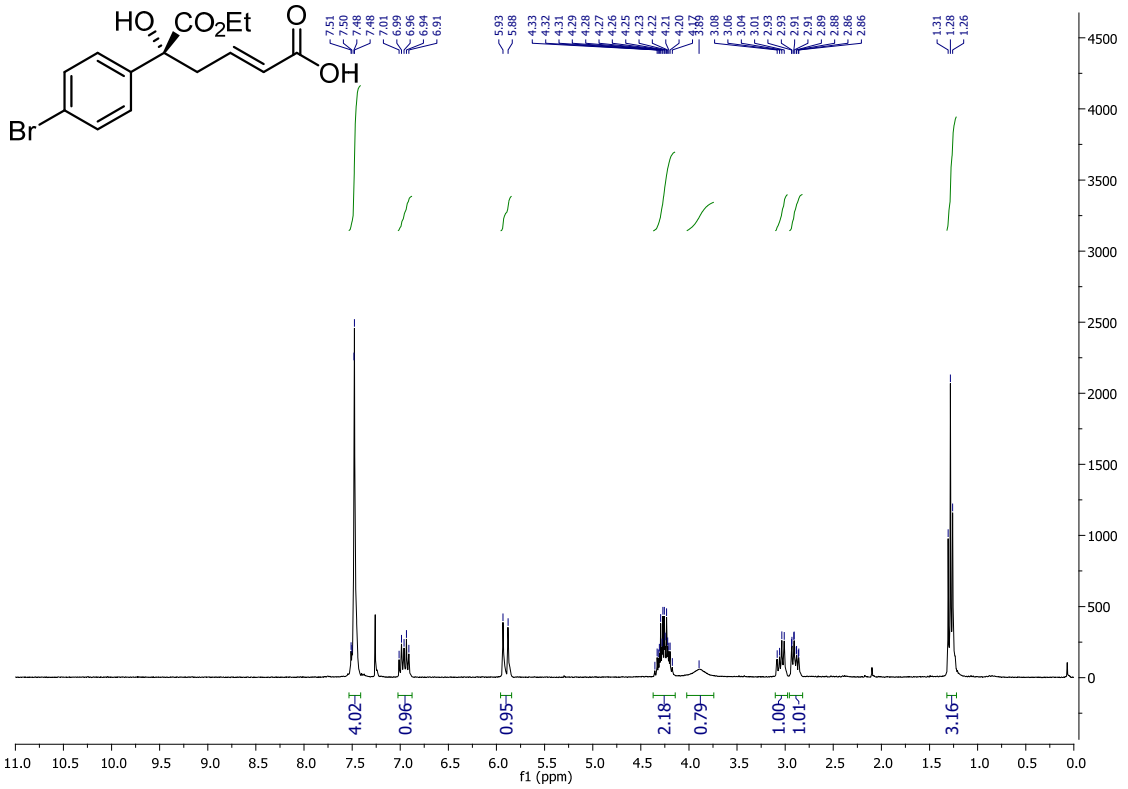
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	4.621	MM	2086.8	378.1	0.092	49.967	0.611
2	5.084	MM	2089.5	359.3	0.0969	50.033	0.632

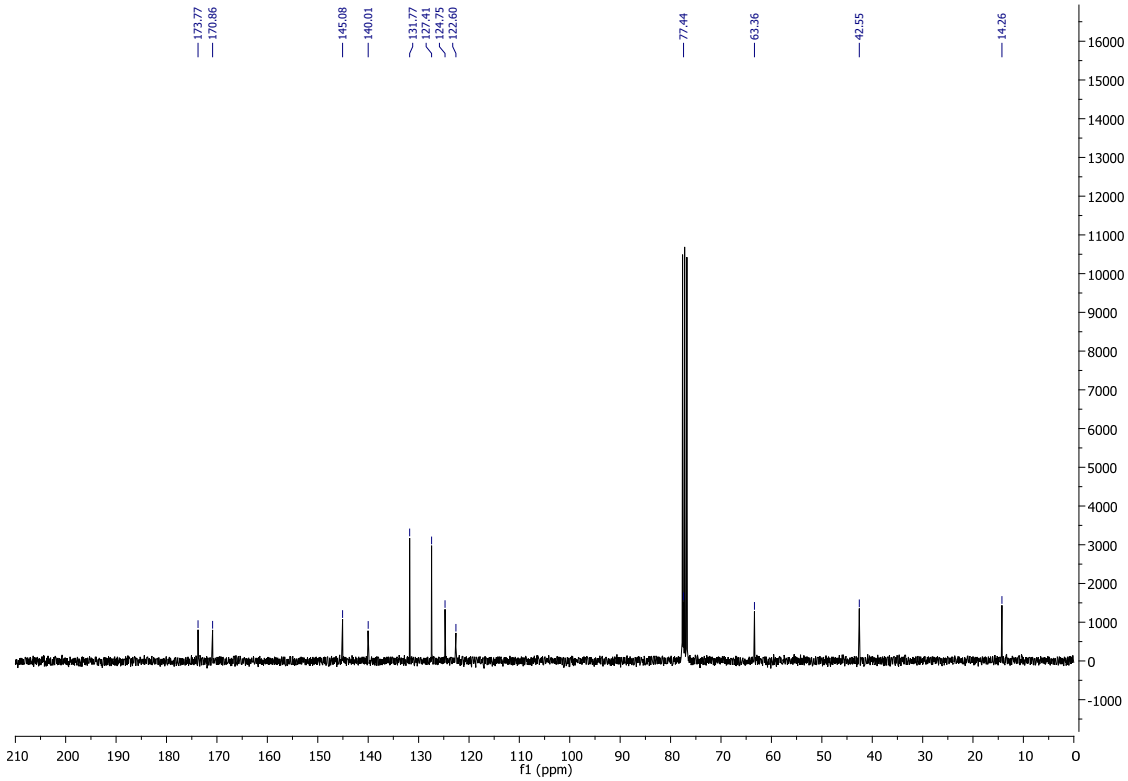


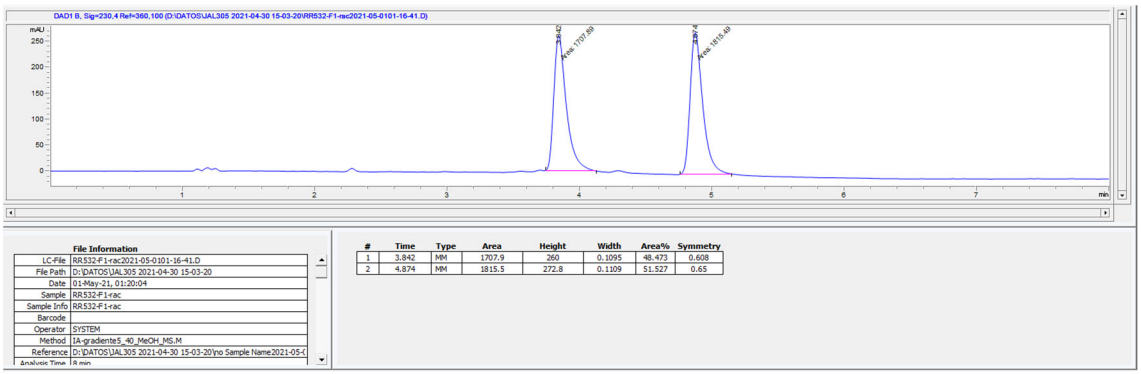
File Information	
LC-File	RR383A_F1_COOMe_OP2021-02-1011-45-41.D
File Path	D:\DATOS\JAL305 2021-02-10 11-29-30
Date	10-Feb-21, 11:49:07
Sample	RR383A_F1_COOMe_OP
Sample Info	RR383A_F1_COOMe_OP
Barcode	
Operator	SYSTEM
Method	IG-gradiente5_40_MeOH_MS.M
Reference	D:\DATOS\JAL305 2021-02-10 11-29-30\no Sample Name2021-02-
Analysis Time	8 min

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	4.611	MF	43.7	8.3	0.0875	2.909	0.748
2	5.056	MM	1457.8	251.2	0.0967	97.091	0.646

(*R,E*)-5-(4-bromophenyl)-6-ethoxy-5-hydroxy-6-oxohex-2-enoic acid (5)

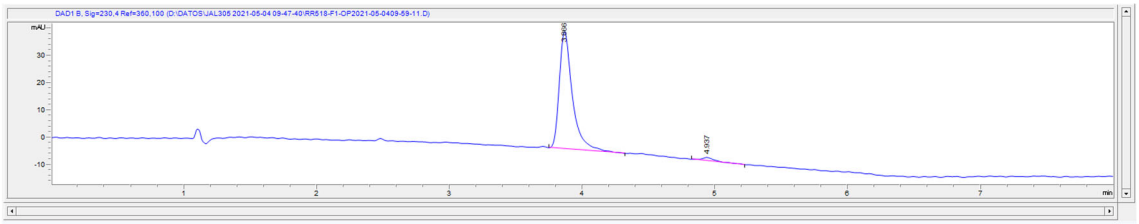






File Information	
LC-File	RR532-F1-rac2021-05-0101-16-41.D
File Path	D:\DATOS\IAL305 2021-04-30 15-03-20
Date	01-May-21, 01:20:04
Sample	RR532-F1-rac
Sample Info	RR532-F1-rac
Barcode	
Operator	SYSTEM
Method	IA-gradiente5_40_MeOH_MS.M
Reference	D:\DATOS\IAL305 2021-04-30 15-03-20\no Sample Name2021-05-(

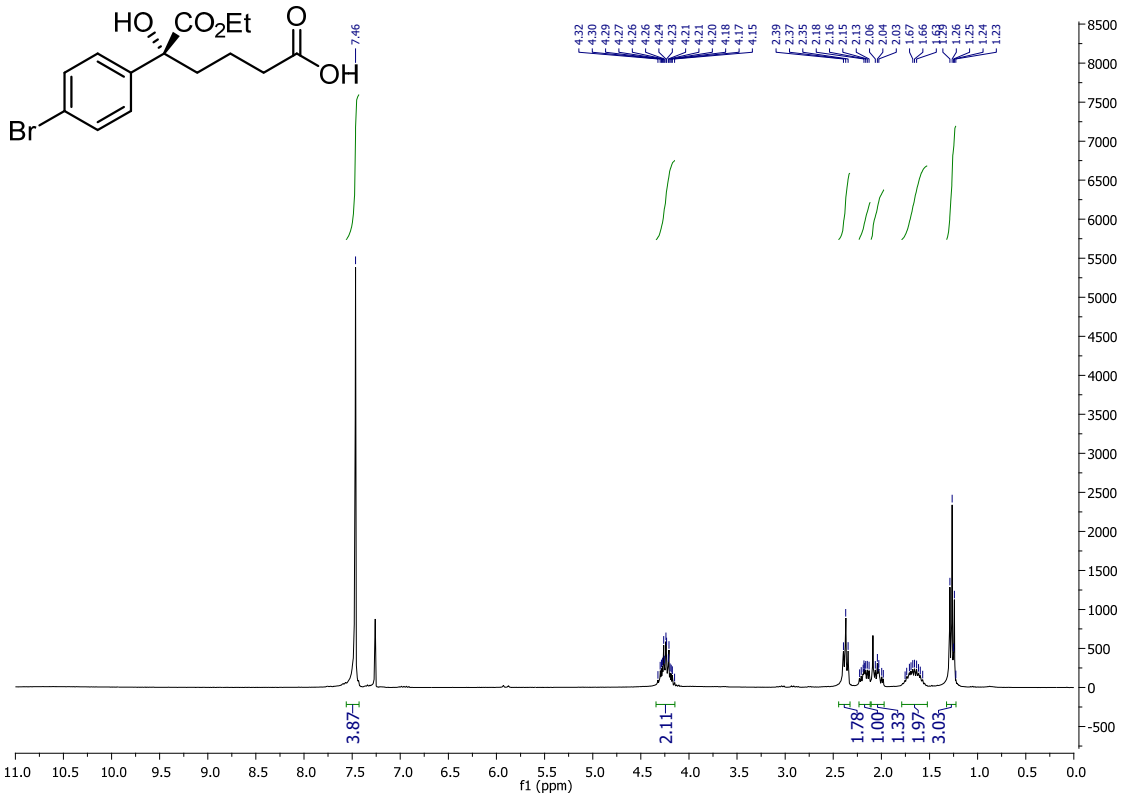
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	3.842	MM	1707.9	260	0.1095	48.473	0.608
2	4.874	MM	1815.5	272.8	0.1109	51.527	0.65

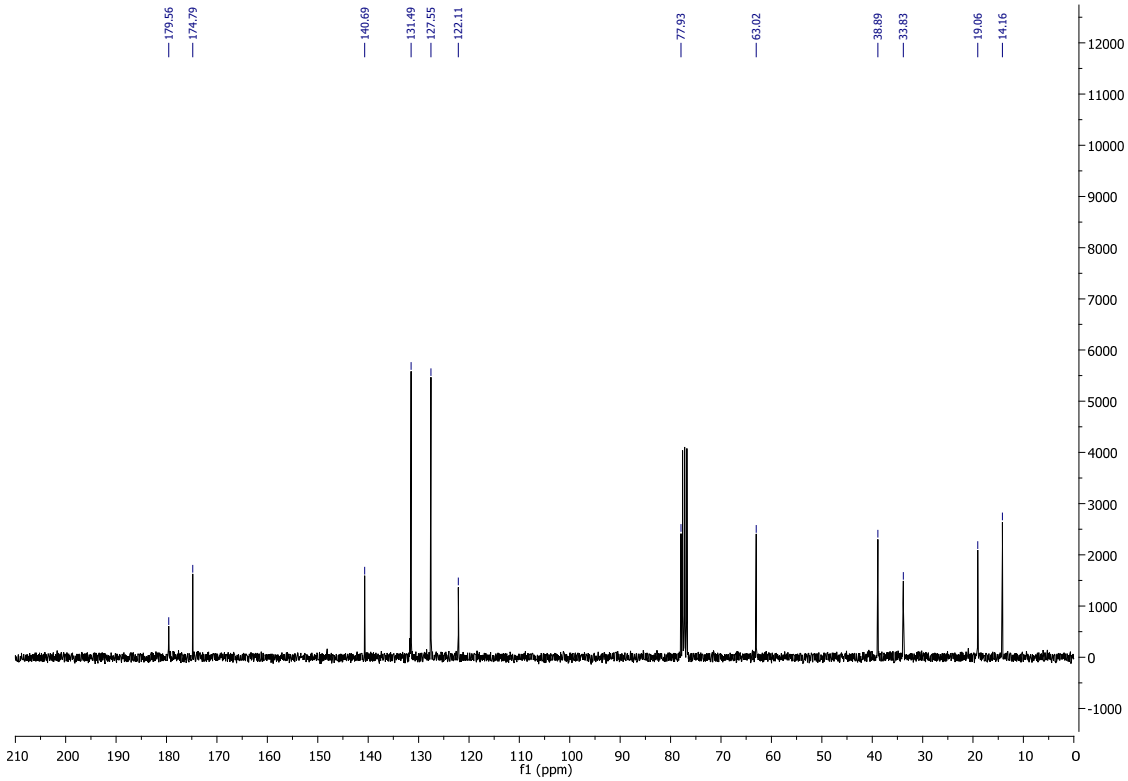


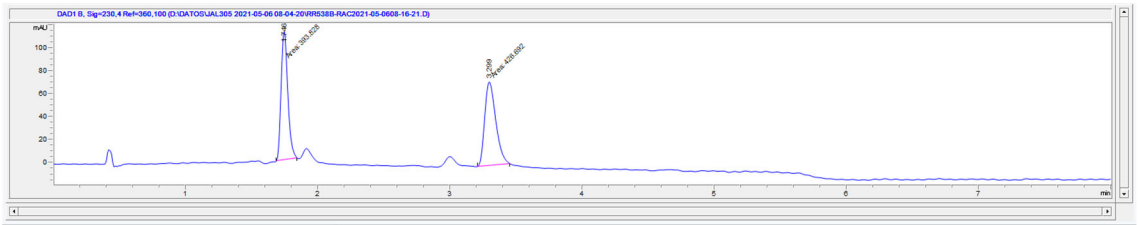
File Information	
LC-File	RR518-F1-OP2021-05-0409-59-11.D
File Path	D:\DATOS\IAL305 2021-05-04 09-47-40
Date	04-May-21, 10:02:37
Sample	RR518-F1-OP
Sample Info	RR518-F1-OP
Barcode	
Operator	SYSTEM
Method	IA-gradiente5_40_MeOH_MS.M
Reference	D:\DATOS\IAL305 2021-05-04 09-47-40\no Sample Name2021-05-(

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	3.866	BB	297.6	43.2	0.1023	97.309	0.596
2	4.937	BB	8.2	1.2	0.0932	2.691	0.567

(*R*)-5-(4-bromophenyl)-6-ethoxy-5-hydroxy-6-oxohexanoic acid (6)

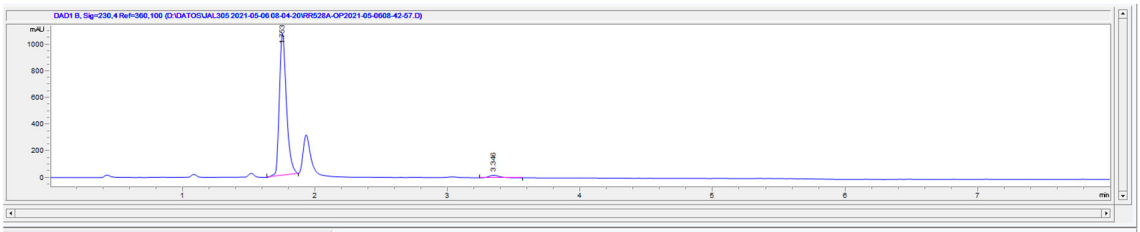






File Information	
LC-File	RR538B-RAC2021-05-0608-16-21.D
File Path	D:\DATOS\JAL305 2021-05-06 08-04-20
Date	06-May-21, 08:20:19
Sample	RR538B-RAC
Sample Info	
Barcode	
Operator	SYSTEM
Method	ID-gradiente5_40_MeOH_MS.M
Reference	D:\DATOS\JAL305 2021-05-06 08-04-20\no Sample Name2021-05-(

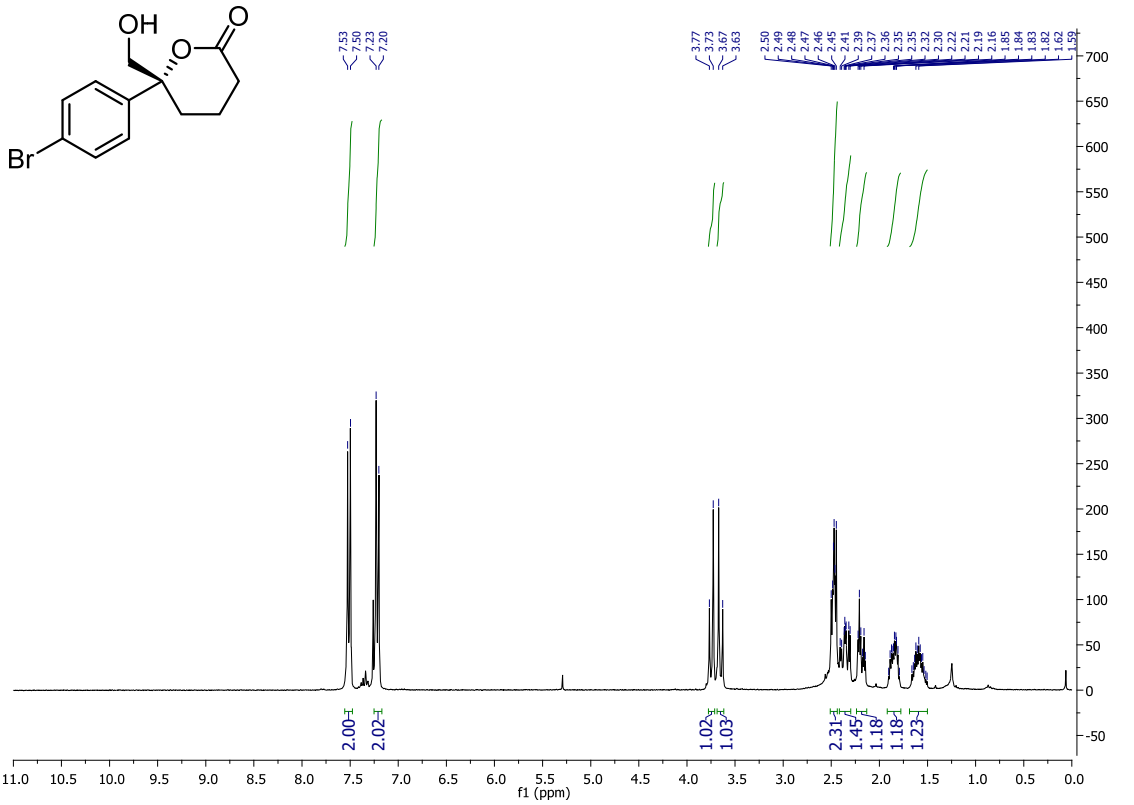
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	1.746	MM	393.8	113.3	0.0579	47.997	0.809
2	3.299	MM	426.7	73.2	0.0971	52.003	0.68

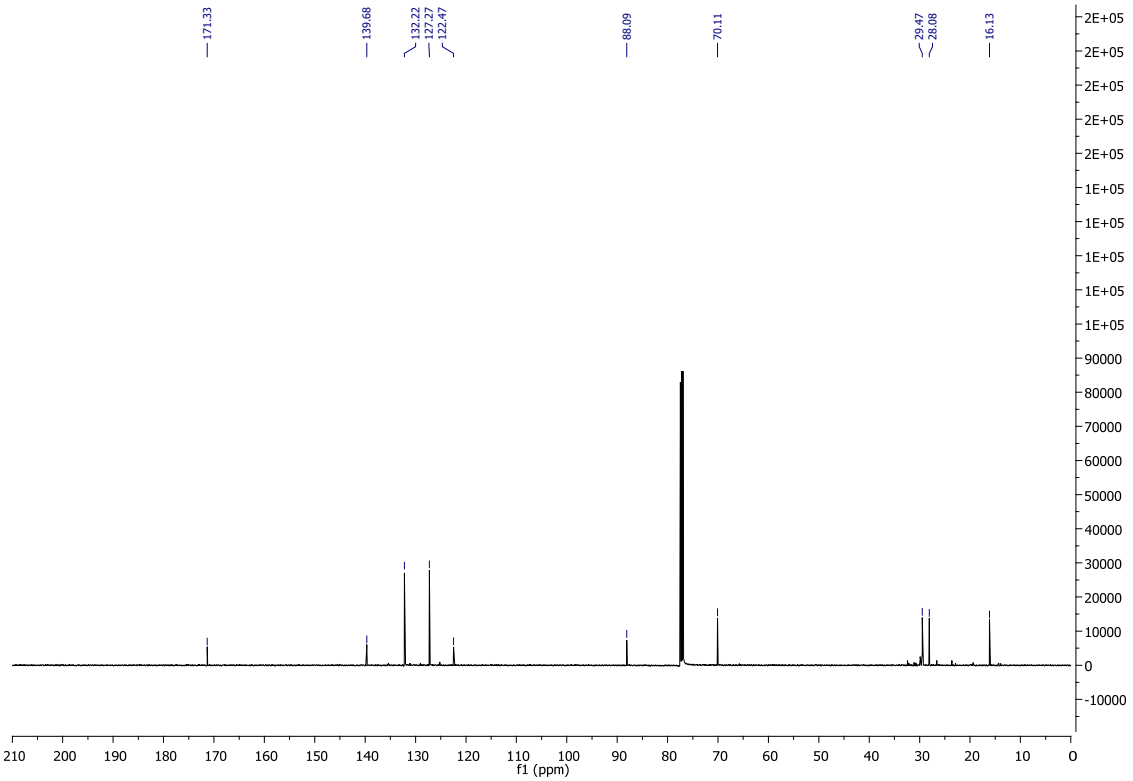


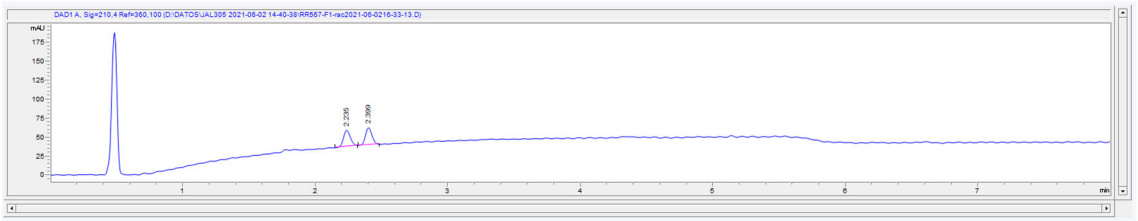
File Information	
LC-File	RR528A-OP2021-05-0608-42-57.D
File Path	D:\DATOS\JAL305 2021-05-06 08-04-20
Date	06-May-21, 08:46:58
Sample	RR528A-OP
Sample Info	
Barcode	
Operator	SYSTEM
Method	ID-gradiente5_40_MeOH_MS.M
Reference	D:\DATOS\JAL305 2021-05-06 08-04-20\no Sample Name2021-05-(

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	1.753	BB	3940.8	1071.4	0.0569	97.315	0.732
2	3.346	BB	108.7	19.2	0.0881	2.685	0.714

(*R*)-6-(4-bromophenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-one (7)

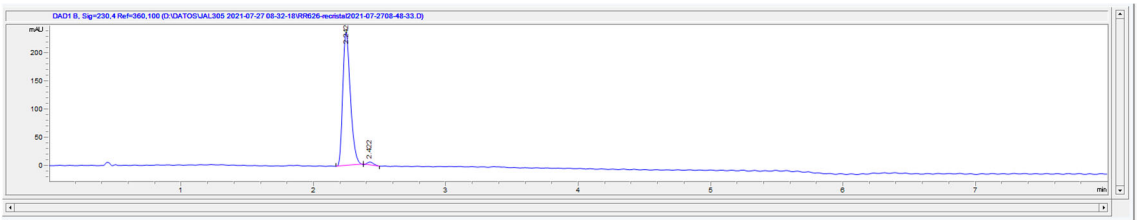






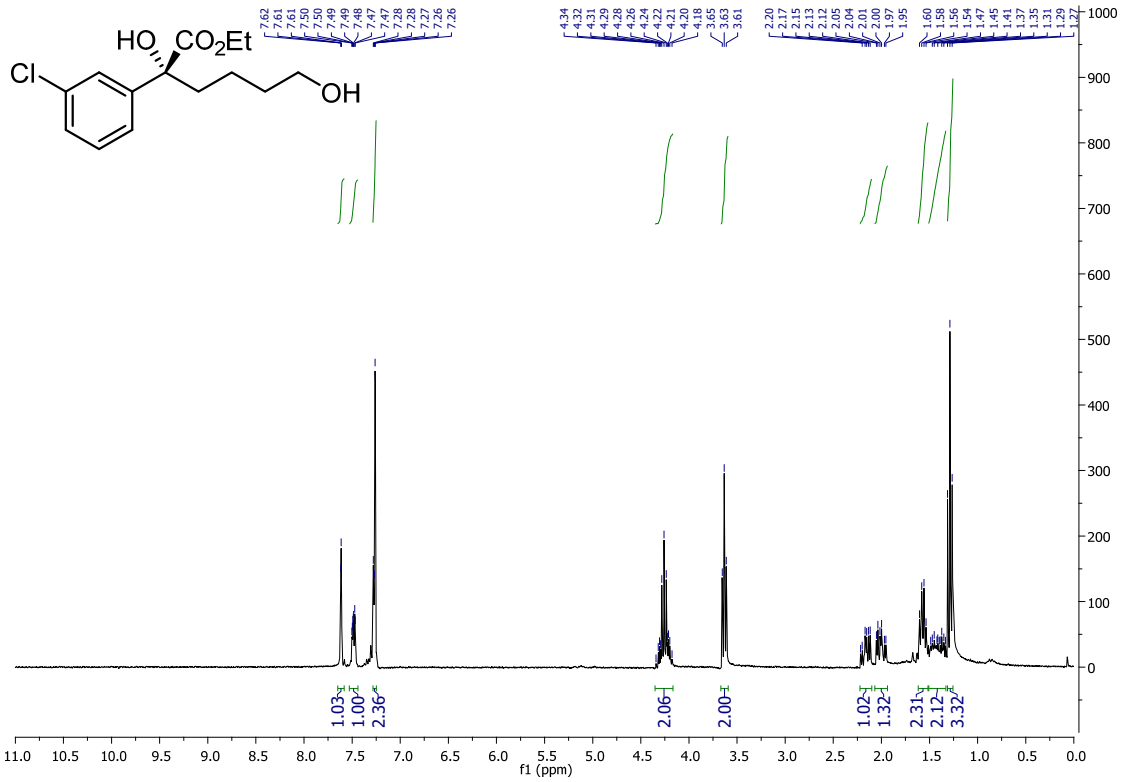
File Information	
LC-File	RR567-F1-rac2021-06-0216-33-13.D
File Path	D:\DATOS\JAL305 2021-06-02 14-40-38
Date	02-Jun-21, 16:37:03
Sample	RR567-F1-rac
Sample Info	RR567-F1-rac
Barcode	
Operator	SYSTEM
Method	ID-gradiente5_40_MeOH_MS.M
Reference	D:\DATOS\JAL305 2021-06-02 14-40-38\no Sample Name2021-06-(
Analysis Time	7.987 min

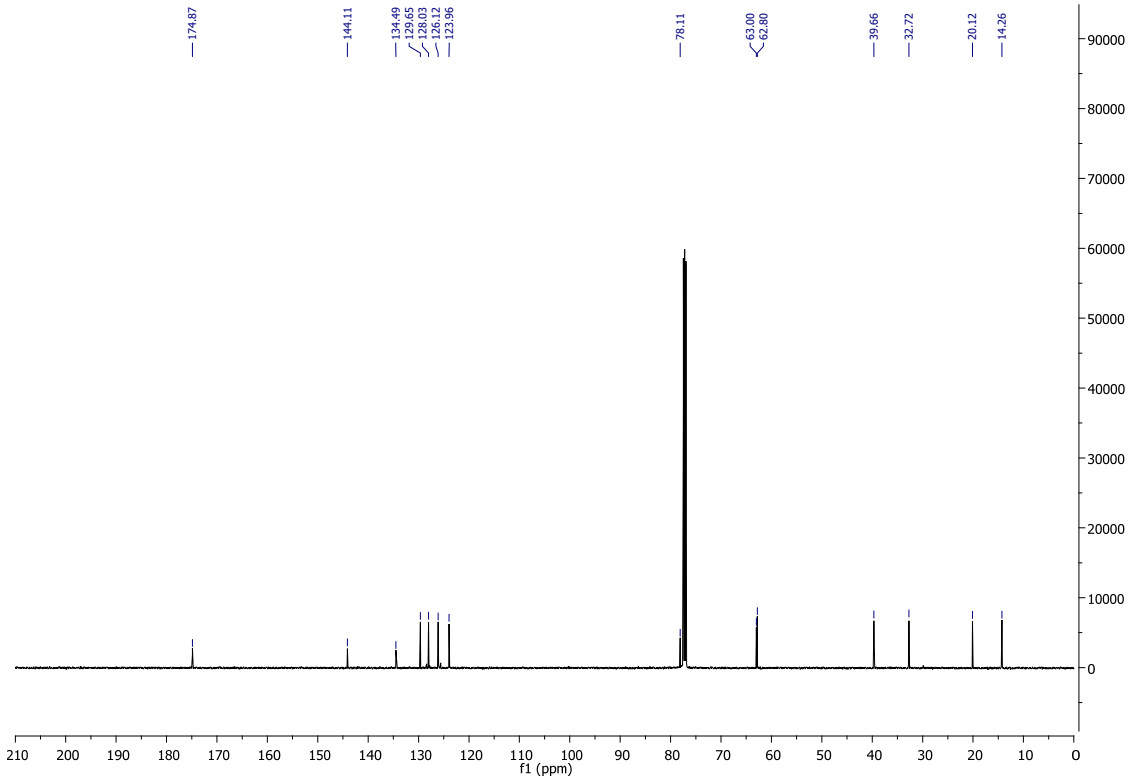
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	2.235	BB	77.1	21.6	0.0557	49.873	0.865
2	2.399	BB	77.5	22.6	0.0539	50.127	0.843

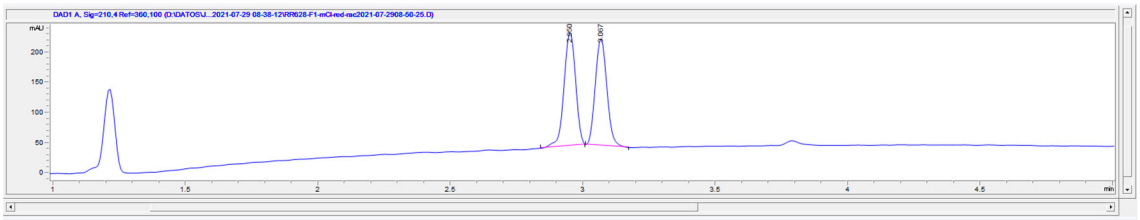


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	2.242	BB	944.5	236.8	0.0625	98.069	0.703
2	2.422	BB	18.6	5.6	0.0527	1.931	0.688

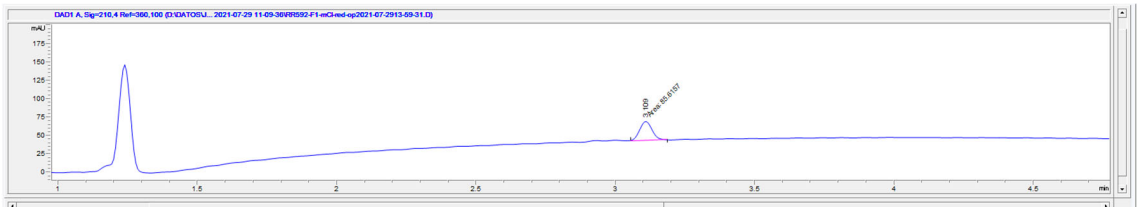
Ethyl (*R*)-(3-chlorophenyl)-2,6-dihydroxyhexanoate (8)





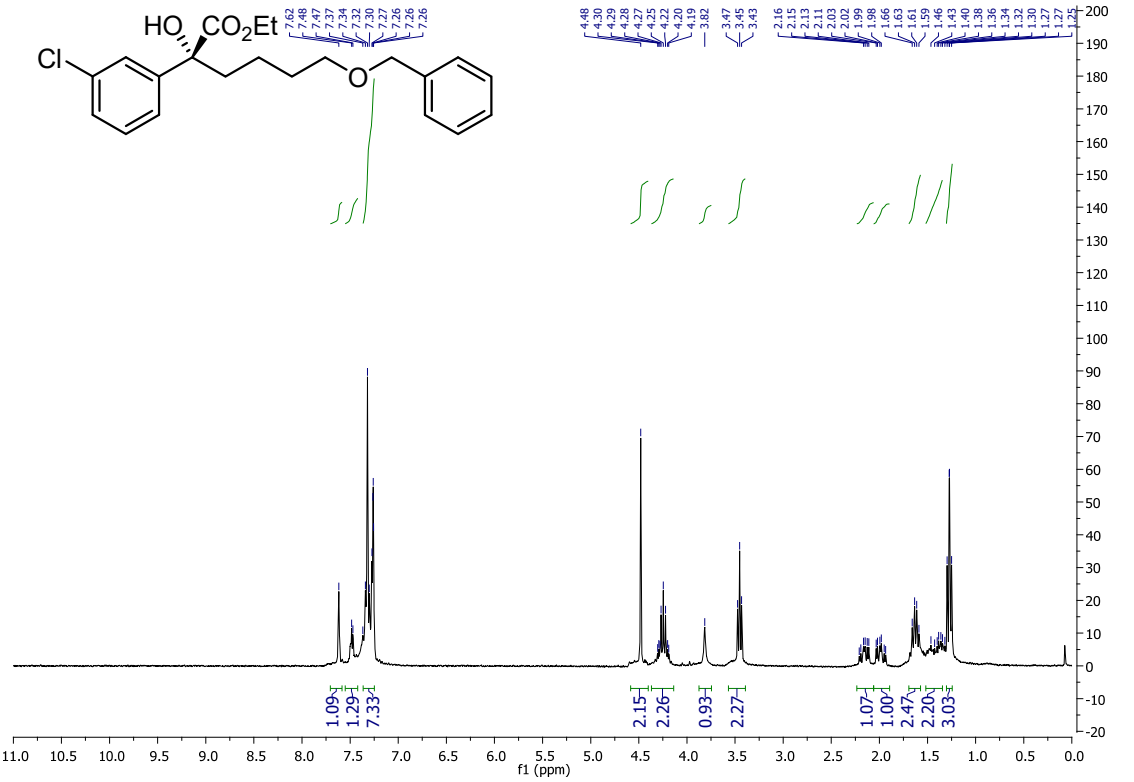


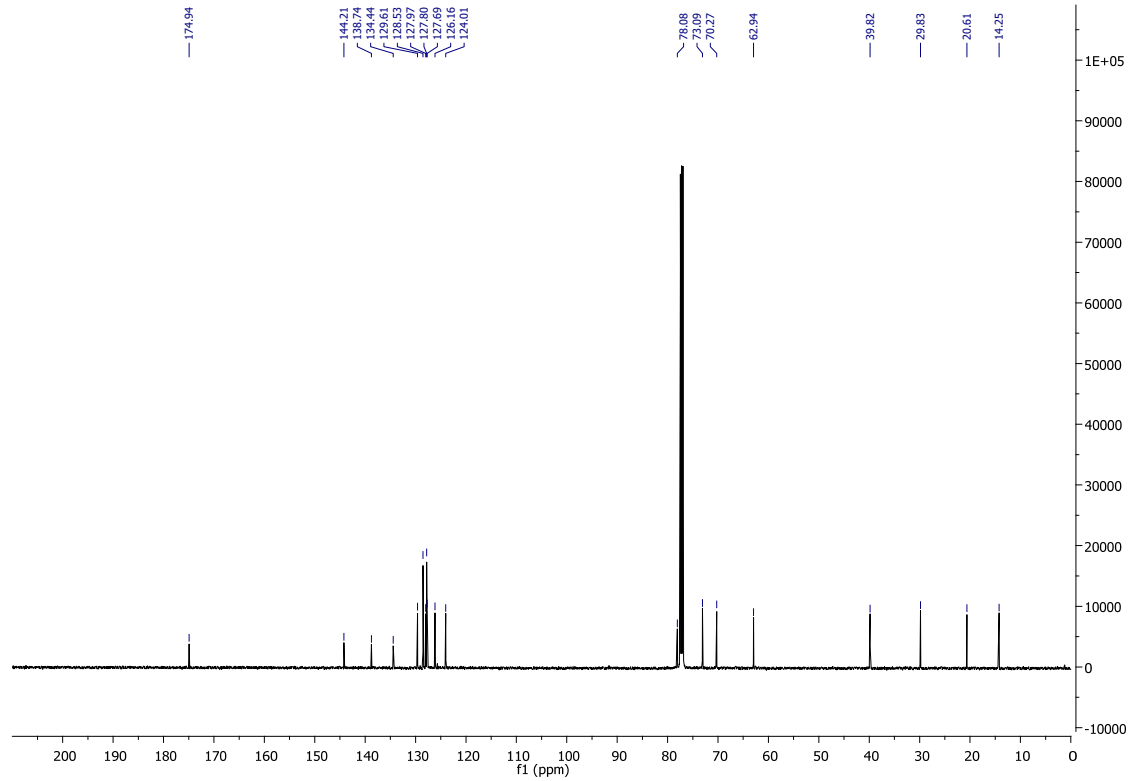
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	2.95	BB	575.8	190.3	0.0473	51.591	1.062
2	3.067	BB	540.3	178.4	0.0473	48.409	0.89



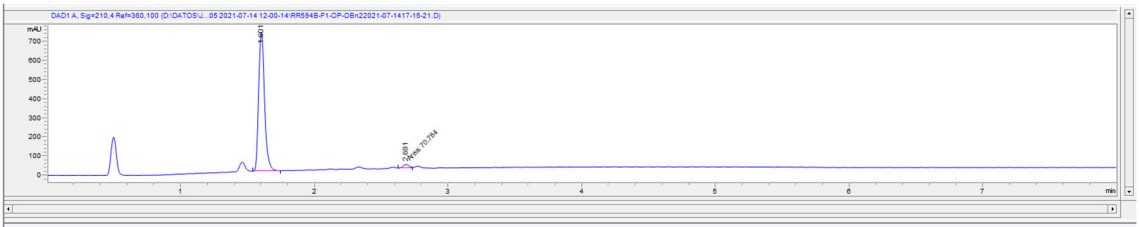
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	3.109	MM	85.6	26.8	0.0533	100.000	0.944

Ethyl (*R*)-6-(benzyloxy)-2-(3-chlorophenyl)-2-hydroxyhexanoate (9)



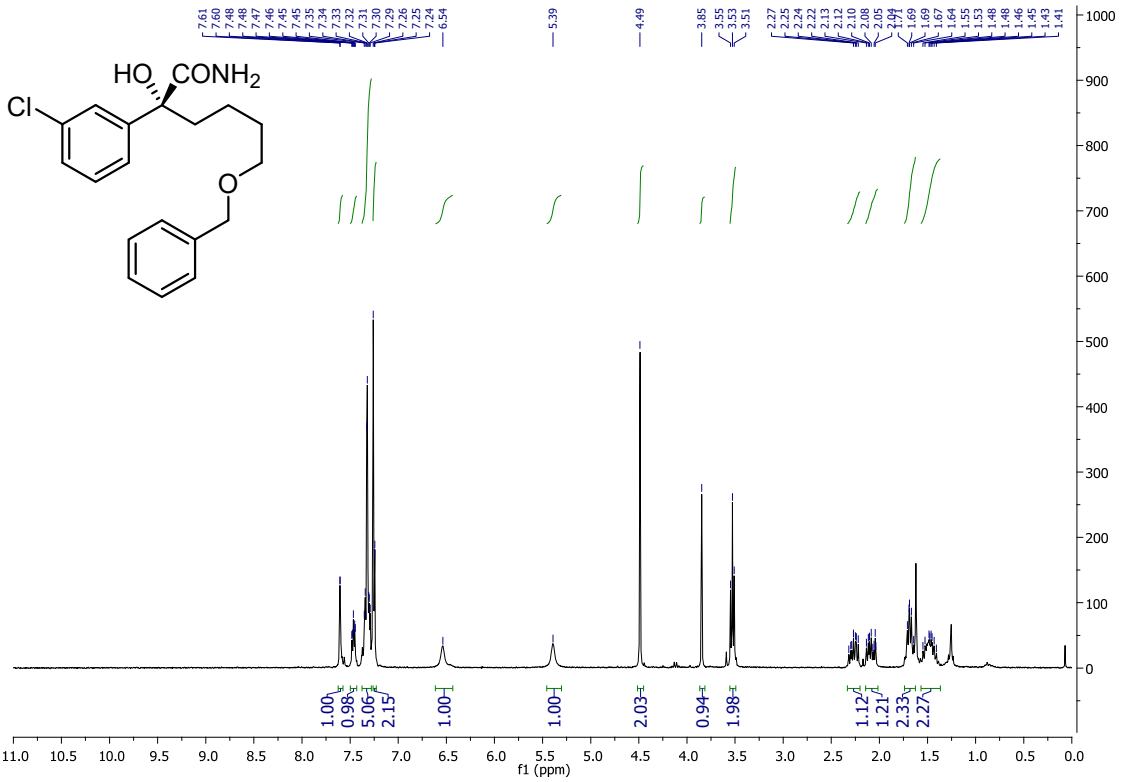


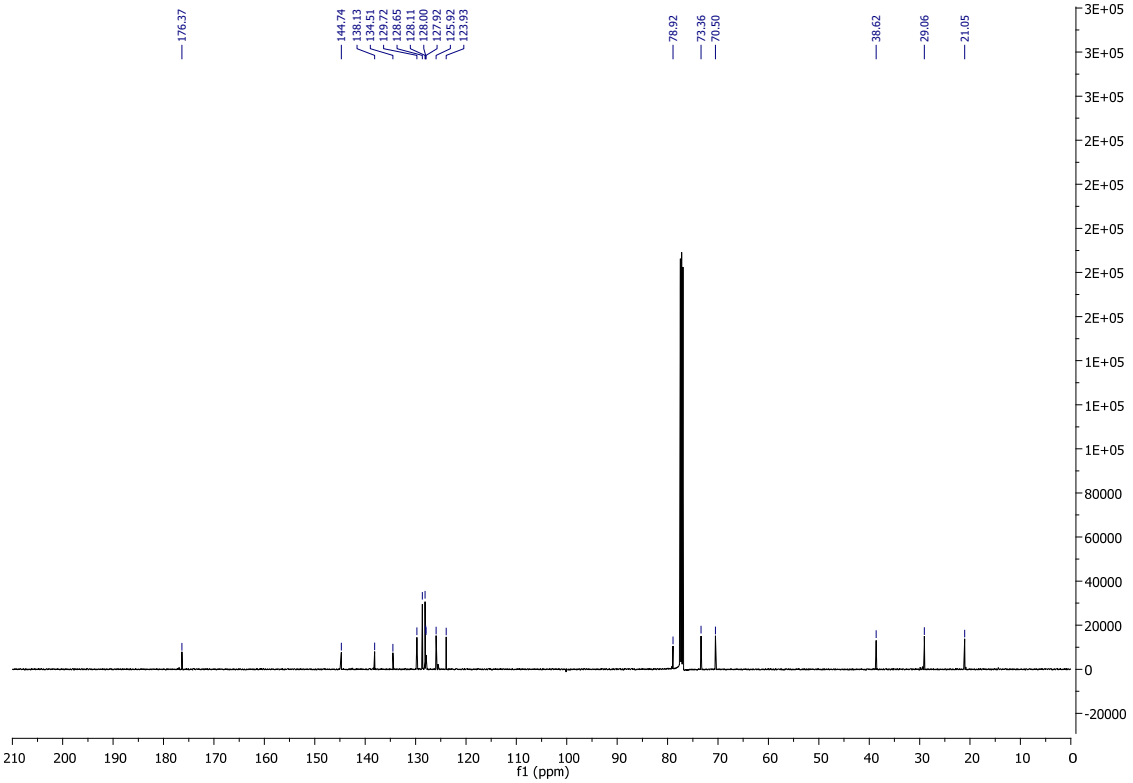
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	1.591	MM	529.1	166.2	0.0531	49.546	0.893
2	2.775	MM	538.8	129.5	0.0693	50.454	0.725

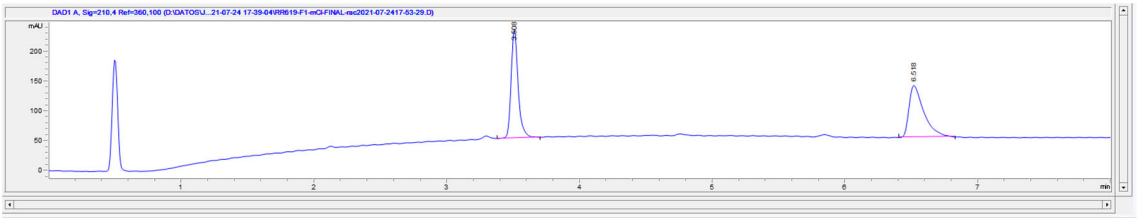


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	1.601	BB	2235.8	730.4	0.0477	96.931	0.801
2	2.681	MF	70.8	20.1	0.0588	3.069	0.83

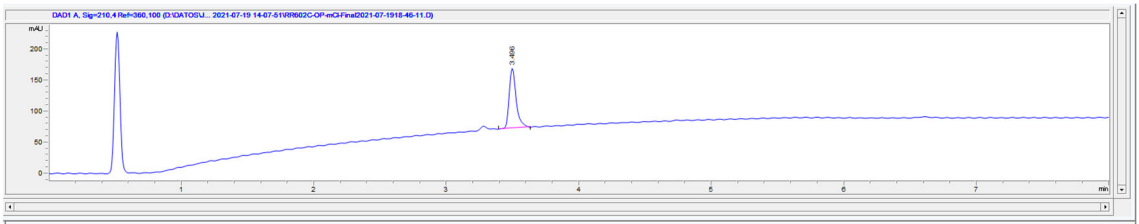
(*R*)-6-(benzyloxy)-2-(3-chlorophenyl)-2-hydroxyhexanamide (10)





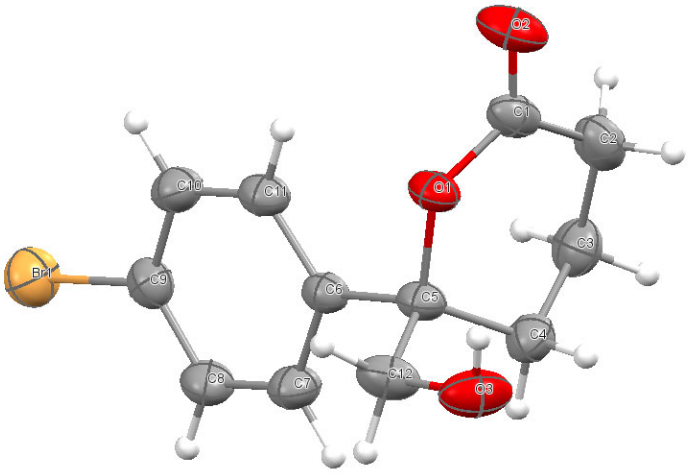


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	3.508	BB	672	182	0.0551	49.516	0.772
2	6.518	BB	685.1	87.3	0.1155	50.484	0.45



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	3.496	BB	353.1	96.4	0.0567	100.000	0.722

6. Single Crystal X-Ray Structure of δ-lactone 7



CCDC 2101111

A clear colourless prismatic-like specimen of $C_{12}H_{13}BrO_3$, approximate dimensions 0.065 mm x 0.192 mm x 0.218 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured on a Bruker Kappa Apex II Bruker APEX-II CCD system (Mo K_α, λ = 0.71073 Å).

The total exposure time was 20.28 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 22324 reflections to a maximum θ angle of 25.35° (0.83 Å resolution), of which 2111 were independent (average redundancy 10.575, completeness = 99.8%, R_{int} = 3.09%, R_{sig} = 1.92%) and 2051 (97.16%) were greater than $2\sigma(F^2)$. The final cell constants of a = 8.3815(2) Å, b = 7.13240(10) Å, c = 10.0251(2) Å, β = 103.8320(10)°, volume = 581.92(2) $Å^3$, are based upon the refinement of the XYZ-centroids of 9956 reflections above 20 σ(I) with 5.005° < 2θ < 52.29°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.819. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.5140 and 0.8030.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P 1 21 1, with Z = 2 for the formula unit, $C_{12}H_{13}BrO_3$. The final anisotropic full-matrix least-squares refinement on F^2 with 146 variables converged at R1 = 1.83%, for the observed data and wR2 = 5.47% for all data. The goodness-of-fit was 1.183. The largest peak in the final difference electron density synthesis was 0.317 $e^-/Å^3$ and the largest hole was -0.295 $e^-/Å^3$ with an RMS deviation of 0.052 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.627 g/cm^3 and F(000), 288 e^-.

Table 1. Sample and crystal data.

Identification code	03363
Chemical formula	$C_{12}H_{13}BrO_3$
Formula weight	285.13 g/mol
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal size	0.065 x 0.192 x 0.218 mm
Crystal habit	clear colourless prismatic
Crystal system	monoclinic
Space group	P 1 21 1
Unit cell dimensions	a = 8.3815(2) Å α = 90°
	b = 7.13240(10) Å β = 103.8320(10)°
	c = 10.0251(2) Å γ = 90°
Volume	581.92(2) $Å^3$
Z	2
Density (calculated)	1.627 g/cm^3
Absorption coefficient	3.521 mm^{-1}
F(000)	288

Table 2. Data collection and structure refinement.

Diffractometer	Bruker Kappa Apex II Bruker APEX-II CCD
Theta range for data collection	2.09 to 25.35°
Index ranges	-10<=h<=10, -8<=k<=8, -12<=l<=12
Reflections collected	22324
Independent reflections	2111 [R(int) = 0.0309]
Coverage of independent reflections	99.8%
Absorption correction	multi-scan
Max. and min. transmission	0.8030 and 0.5140
Structure solution technique	direct methods
Structure solution program	SHELXS-97 (Sheldrick 2008)
Refinement method	Full-matrix least-squares on F^2
Refinement program	SHELXL-2018/3 (Sheldrick, 2018)
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	2111 / 1 / 146
Goodness-of-fit on F^2	1.183
Final R indices	2051 data; I>2σ(I) R1 = 0.0183, wR2 = 0.0462
	all data R1 = 0.0195, wR2 = 0.0547
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0223P)^2+0.1857P]$ where $P=(F_o^2+2F_c^2)/3$
Absolute structure parameter	0.016(4)
Largest diff. peak and hole	0.317 and -0.295 $eÅ^{-3}$
R.M.S. deviation from mean	0.052 $eÅ^{-3}$

Table 3. Atomic coordinates and equivalent isotropic atomic displacement parameters (Å^2).

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U(eq)
Br1	0.87779(4)	0.01906(8)	0.76130(4)	0.05028(14)
C1	0.5415(5)	0.5982(5)	0.5775(4)	0.0352(8)
C2	0.6765(4)	0.4976(8)	0.6758(4)	0.0452(9)
C3	0.6415(5)	0.4464(6)	0.8137(4)	0.0440(9)
C4	0.5517(5)	0.6081(6)	0.8614(4)	0.0389(8)
C5	0.3895(4)	0.6466(5)	0.7595(3)	0.0314(7)
C6	0.2634(4)	0.4928(6)	0.7566(3)	0.0290(7)
C7	0.2164(5)	0.4458(5)	0.8772(4)	0.0396(9)
C8	0.1021(5)	0.3060(6)	0.8787(4)	0.0405(9)
C9	0.0334(4)	0.2123(5)	0.7586(4)	0.0347(8)
C10	0.0741(5)	0.2565(5)	0.6380(4)	0.0384(8)
C11	0.1887(5)	0.3964(5)	0.6375(3)	0.0344(8)
C12	0.3177(5)	0.8357(5)	0.7864(4)	0.0416(9)
O1	0.4132(3)	0.6681(4)	0.6196(2)	0.0338(5)
O2	0.5421(4)	0.6257(5)	0.4588(3)	0.0554(8)
O3	0.4306(4)	0.9853(4)	0.7963(3)	0.0520(8)

Table 4. Bond lengths (Å).

Br1-C9	1.902(4)	C1-O2	1.208(5)
C1-O1	1.341(4)	C1-C2	1.495(6)
C2-C3	1.525(6)	C3-C4	1.516(5)
C4-C5	1.517(5)	C5-O1	1.471(4)
C5-C6	1.519(5)	C5-C12	1.527(5)
C6-C11	1.390(5)	C6-C7	1.400(5)
C7-C8	1.385(5)	C8-C9	1.377(5)
C9-C10	1.370(5)	C10-C11	1.386(5)
C12-O3	1.414(5)		

Table 5. Bond angles (°).

O2-C1-O1	116.3(4)	O2-C1-C2	123.1(3)
O1-C1-C2	120.6(3)	C1-C2-C3	115.7(3)
C4-C3-C2	108.7(3)	C3-C4-C5	111.0(3)
O1-C5-C4	110.9(3)	O1-C5-C6	108.0(3)
C4-C5-C6	112.9(3)	O1-C5-C12	103.0(3)
C4-C5-C12	111.6(3)	C6-C5-C12	109.9(3)
C11-C6-C7	117.5(3)	C11-C6-C5	122.8(3)
C7-C6-C5	119.7(3)	C8-C7-C6	121.3(3)
C9-C8-C7	119.0(3)	C10-C9-C8	121.3(4)

C10-C9-Br1	119.7(3)	C8-C9-Br1	119.0(3)
C9-C10-C11	119.2(3)	C10-C11-C6	121.5(3)
O3-C12-C5	113.2(3)	C1-O1-C5	124.2(3)

Table 6. Torsion angles (°).

O2-C1-C2-C3	-169.8(4)	O1-C1-C2-C3	12.0(6)
C1-C2-C3-C4	-40.2(5)	C2-C3-C4-C5	60.7(4)
C3-C4-C5-O1	-51.8(4)	C3-C4-C5-C6	69.6(4)
C3-C4-C5-C12	-166.0(3)	O1-C5-C6-C11	-0.3(4)
C4-C5-C6-C11	-123.3(4)	C12-C5-C6-C11	111.4(4)
O1-C5-C6-C7	-179.1(3)	C4-C5-C6-C7	57.9(4)
C12-C5-C6-C7	-67.4(4)	C11-C6-C7-C8	1.3(6)
C5-C6-C7-C8	-179.8(3)	C6-C7-C8-C9	-0.2(6)
C7-C8-C9-C10	-1.0(6)	C7-C8-C9-Br1	179.5(3)
C8-C9-C10-C11	1.1(6)	Br1-C9-C10-C11	-179.5(3)
C9-C10-C11-C6	0.1(5)	C7-C6-C11-C10	-1.2(5)
C5-C6-C11-C10	180.0(3)	O1-C5-C12-O3	-67.6(4)
C4-C5-C12-O3	51.5(4)	C6-C5-C12-O3	177.5(3)
O2-C1-O1-C5	179.0(3)	C2-C1-O1-C5	-2.7(5)
C4-C5-O1-C1	22.6(5)	C6-C5-O1-C1	-101.6(3)
C12-C5-O1-C1	142.2(3)		

Table 7. Anisotropic atomic displacement parameters (Å^2).

The anisotropic atomic displacement factor exponent takes the form:
$-2\pi^2[\, h^2\, a^{*2}\, U_{11} + \ldots + 2\, h\, k\, a^{*}\, b^{*}\, U_{12}\,]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Br1	0.0513(2)	0.0494(2)	0.0521(2)	0.0025(3)	0.01619(15)	-0.0112(2)
C1	0.044(2)	0.0279(16)	0.039(2)	-0.0066(14)	0.0189(16)	-0.0050(15)
C2	0.0401(18)	0.041(3)	0.057(2)	-0.005(2)	0.0174(15)	0.005(2)
C3	0.039(2)	0.045(2)	0.044(2)	0.0061(16)	0.0013(17)	0.0060(17)
C4	0.037(2)	0.046(2)	0.0316(19)	0.0013(16)	0.0039(16)	-0.0019(17)
C5	0.0374(19)	0.0349(19)	0.0238(16)	0.0002(14)	0.0110(14)	0.0026(15)
C6	0.0324(14)	0.030(2)	0.0253(13)	0.0022(15)	0.0082(11)	0.0050(15)
C7	0.045(2)	0.047(2)	0.0274(17)	-0.0024(14)	0.0098(15)	-0.0045(16)
C8	0.044(2)	0.050(2)	0.0292(18)	0.0028(16)	0.0130(16)	-0.0021(18)
C9	0.0331(18)	0.0336(19)	0.0379(19)	0.0042(15)	0.0094(15)	0.0036(15)
C10	0.042(2)	0.042(2)	0.0304(18)	-0.0036(16)	0.0067(15)	-0.0014(17)
C11	0.0403(19)	0.0374(19)	0.0269(16)	0.0026(15)	0.0107(14)	0.0038(16)
C12	0.058(2)	0.035(2)	0.037(2)	-0.0006(16)	0.0218(18)	0.0056(18)
O1	0.0397(13)	0.0391(14)	0.0258(12)	0.0041(10)	0.0140(10)	0.0051(11)
O2	0.074(2)	0.0593(18)	0.0430(17)	0.0029(14)	0.0347(15)	0.0073(16)
O3	0.0842(19)	0.035(2)	0.0406(13)	-0.0050(13)	0.0234(13)	-0.0090(15)

Table 8. Hydrogen atomic coordinates and isotropic atomic displacement parameters (Å^2).

	x/a	y/b	z/c	U(eq)
H2A	0.7762	0.5771	0.6932	0.054
H2B	0.7015	0.3809	0.6313	0.054
H3A	0.5732	0.3316	0.8040	0.053
H3B	0.7458	0.4215	0.8821	0.053
H4A	0.6212	0.7219	0.8718	0.047
H4B	0.5310	0.5778	0.9522	0.047
H7	0.2637	0.5112	0.9597	0.048
H8	0.0716	0.2752	0.9614	0.049
H10	0.0243	0.1920	0.5556	0.046
H11	0.2169	0.4272	0.5538	0.041
H12A	0.2202	0.8626	0.7111	0.05
H12B	0.2808	0.8280	0.8729	0.05
H3O	0.4352	1.0194	0.7171	0.078

Table 9. Hydrogen bond distances (Å) and angles (°).

	Donor-H	Acceptor-H	Donor-Acceptor	Angle
C2-H2B···Br1#1	0.99	3.10	3.813(5)	129.8
C4-H4B···O3#2	0.99	2.55	3.510(5)	163.0
O3-H3O···O2#3	0.84	1.97	2.806(4)	173.5