Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.


# Supporting Information

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**General experimental procedures**

All anhydrous solvents were distilled under argon. Tetrahydrofuran was distilled over sodium and benzophenone; *N*,*N*-dimethylformamide and dichloromethane were distilled over calcium hydride.

All chromatography was performed using distilled solvents. Petroleum spirit refers to the hydrocarbon fraction with boiling range 40 - 60ºC. Thin layer chromatography was performed on Merck 60 $F_{254}$ silica gel plates. Flash column chromatography was performed on 40-63 μm, 60 Å silica gel (Santai Technologies) using an Isolera (Biotage).

$^{1}H$ and $^{13}C$ nuclear magnetic resonance spectroscopy was performed on a Bruker AV300 (300 MHz, 75 MHz), AV500 (500 MHz, 125 MHz) or AS500 (500 MHz, 125 MHz). All NMR experiments were performed in deuterochloroform at 298K. Chemical shifts are reported on the δ scale in parts per million (ppm), and are calibrated to the solvent peak ($CHCl_3$ δ 7.26; $CDCl_3$ δ 77.16). Coupling constants are reported as *J* values in Hertz.

Accurate masses (HRESIMS) were measured on a Bruker MicrOTOF-Q (quadrupole time-of-flight). All observed m/z values deviate no more than 5 ppm from theoretical values.

Specific rotation was measured at 589 nm using a Jasco P-2000 polarimeter with a tungsten-halogen light source.

High-performance liquid chromatography was performed on a Shimadzu LC-20AD with an SIL-20A autosampler, DGU-20A degassing unit, SPD-M20A and ELSD-LT II detectors (UV and light scattering, respectively), CTO-20AC column oven, and FRC-10A fraction collector. The column was a Luna preparative column from Phenomenex (silica, 10 μm, 100 Å, 250x10 mm).

Melting points were measured on an Electrothermal instrument, and are uncorrected.

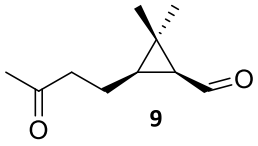
Chemical structure drawings and structural nomenclature were generated using ChemDraw Professional Version 15.1 (Perkin Elmer).

**(1*S*,3*R*)-2,2-Dimethyl-3-(3-oxobutyl)cyclopropane-1-carbaldehyde 9**

The compound was prepared following a procedure published by Nicolaou[1]. To a magnetically-stirred, room-temperature solution of (+)-2-carene (**8**) (128 mg, 0.94 mmol) in acetone/water (8.5 mL acetone, 1 mL water) was added *N*-methylmorpholine *N*-oxide (159 mg, 1.4mmol), 2,6-lutidine (0.25 mL, 2.15 mmol) and osmium tetroxide (5 mg, 0.02 mmol). Once thin layer chromatography indicated complete consumption of starting material (approximately three hours), (diacetoxyiodo)benzene (474 mg, 1.5 mmol) was added. After thin layer chromatography indicated complete consumption of the intermediate diol (approximately 15 minutes), the reaction mixture was quenched with saturated aqueous sodium thiosulfate (10 mL), and then extracted with petroleum ether (5 x 10 mL). The combined organic extracts were washed with saturated aqueous $CuSO_4$ (2 x 10 mL) and saturated aqueous NaCl (10 mL). The organic extracts were dried over $MgSO_4$, filtered, and then concentrated under reduced pressure to yield a light-brown oil. Subjecting this oil to flash silica gel chromatography (elution from 1:19 to 3:2 v/v ethyl acetate / petroleum spirit) furnished the *title compound* ***9*** (77 mg, 49%) as a clear oil. $^1$H NMR data were consistent with those reported by McMurry[2].

Note: Aldehyde **9** was prone to oxidation in the open atmosphere, transforming into the corresponding carboxylic acid. While it is possible to purify the aldehyde *via* chromatography, a higher yield of ketoester **11** (see below) over two steps was achieved if instead of chromatography, the crude aldehyde was subjected immediately to Wittig olefination.

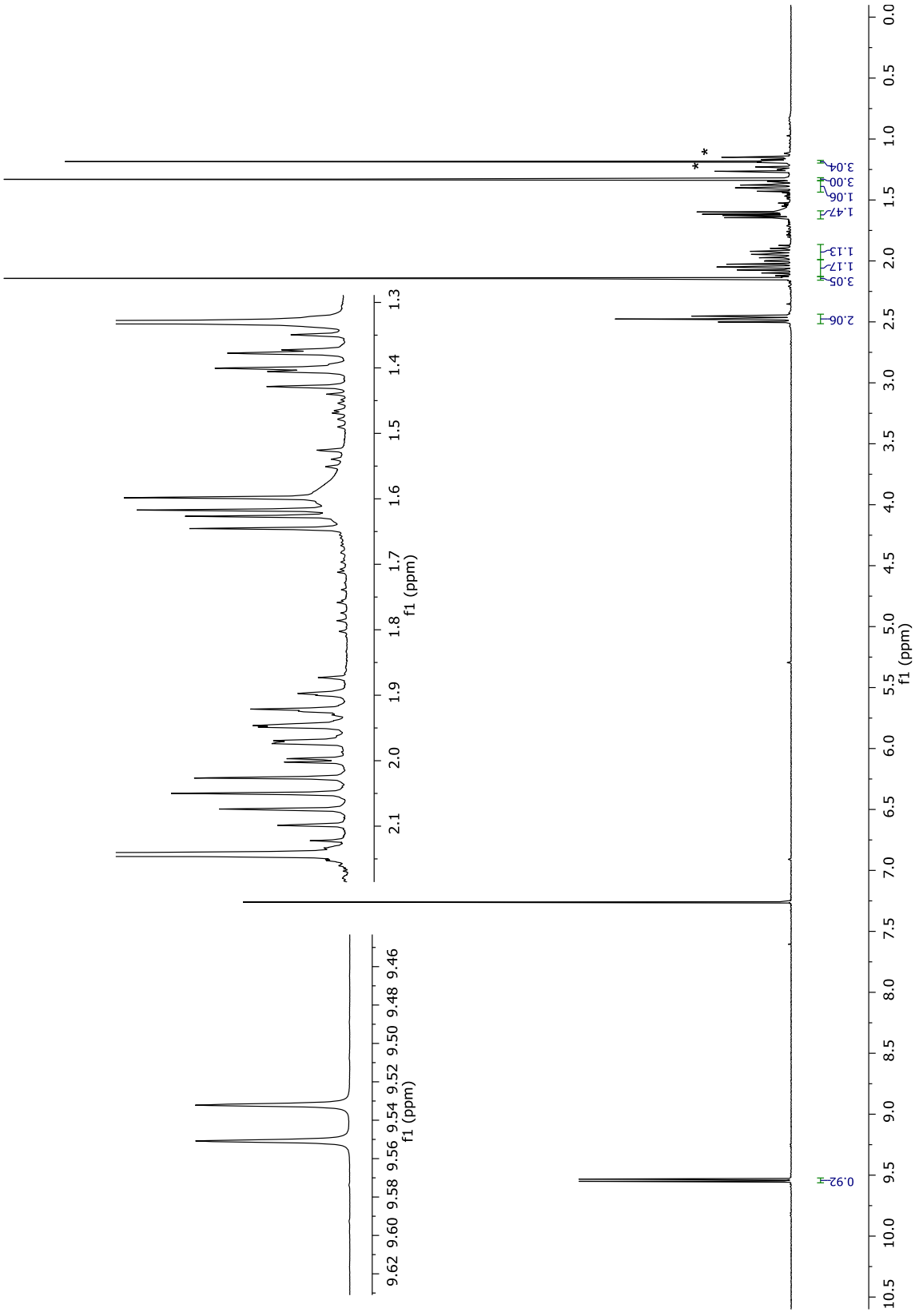
**$^1$H NMR** (300 MHz, $CDCl_3$, 298K): δ 9.54 (d, $J$ = 5.7 Hz, 1H), 2.48 (t, $J$ = 7.2 Hz), 2.14 (s, 3H), 2.05 (m, 1H), 1.94 (m, 1H), 1.62 (dd, $J$ = 8.5, 5.6 Hz, 1H), 1.39 (m, 1H), 1.33 (s, 3H), 1.19 (s, 3H).




**9**

**$^1$H**

**300 MHz, $CDCl_3$, 298K**



**Methyl (*E*)-3-((1*S*,3*R*)-2,2-dimethyl-3-(3-oxobutyl)cyclopropyl)-2-methylacrylate 11**

Methyl 2-(triphenyl-$\lambda^5$-phosphanylidene)propanoate **10** (7.20 g, 20.7 mmol) was dissolved in dichloromethane (50 mL) and added to a magnetically-stirred solution of compound **9** (2.14 g, 12.7 mmol) in dichloromethane (30 mL). After 20 h, the reaction mixture was concentrated and subjected to flash column chromatography (silica, 1:9 → 3:2 v/v ethyl acetate / petroleum spirit elution). Concentration of the appropriate fractions ($R_f$ = 0.31, 1:4 v/v ethyl acetate / petroleum spirit elution) gave the *title compound **11*** (2.42 g, 80%) as a clear oil.

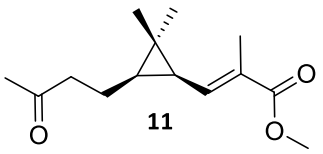
A higher yield of the title compound **11** (see preparation of **9**) over two steps was achieved if instead of chromatography, the crude aldehyde **9** was subjected immediately to Wittig olefination.

**$^1$H NMR** (500 MHz, $CDCl_3$, 298K) δ 6.54 (dq, *J* = 10.3 and 1.5 Hz, 1H), 3.71 (s, 3H), 2.44 (ddd, *J* = 7.2, 7.2 and 1.3 Hz, 2H), 2.18 (s, 3H), 1.90 (d, *J* = 1.5 Hz, 3H), 1.74 (ddt, *J* = 14.5, 8.1 and 7.2 Hz, 1H), 1.59 (ddt, *J* = 14.5, 7.9 and 7.2 Hz, 1H), 1.39 (dd, *J* = 10.4 and 8.7 Hz, 1H), 1.14 (s, 3H), 1.07 (s, 3H), 1.01 (dd, *J* = 16.1 and 7.9 Hz, 1H).

**$^{13}$C NMR** (125 MHz, $CDCl_3$, 298K) δ 208.6, 168.5, 140.1, 128.1, 51.8, 43.6, 32.4, 30.1, 29.0, 27.6, 24.5, 19.8, 15.8, 12.8.

**IR (thin film) $\nu_{max}$** 2951, 1707, 1635, 1436, 1362, 1265, 1251, 1118, 1106, 757 $cm^{-1}$.

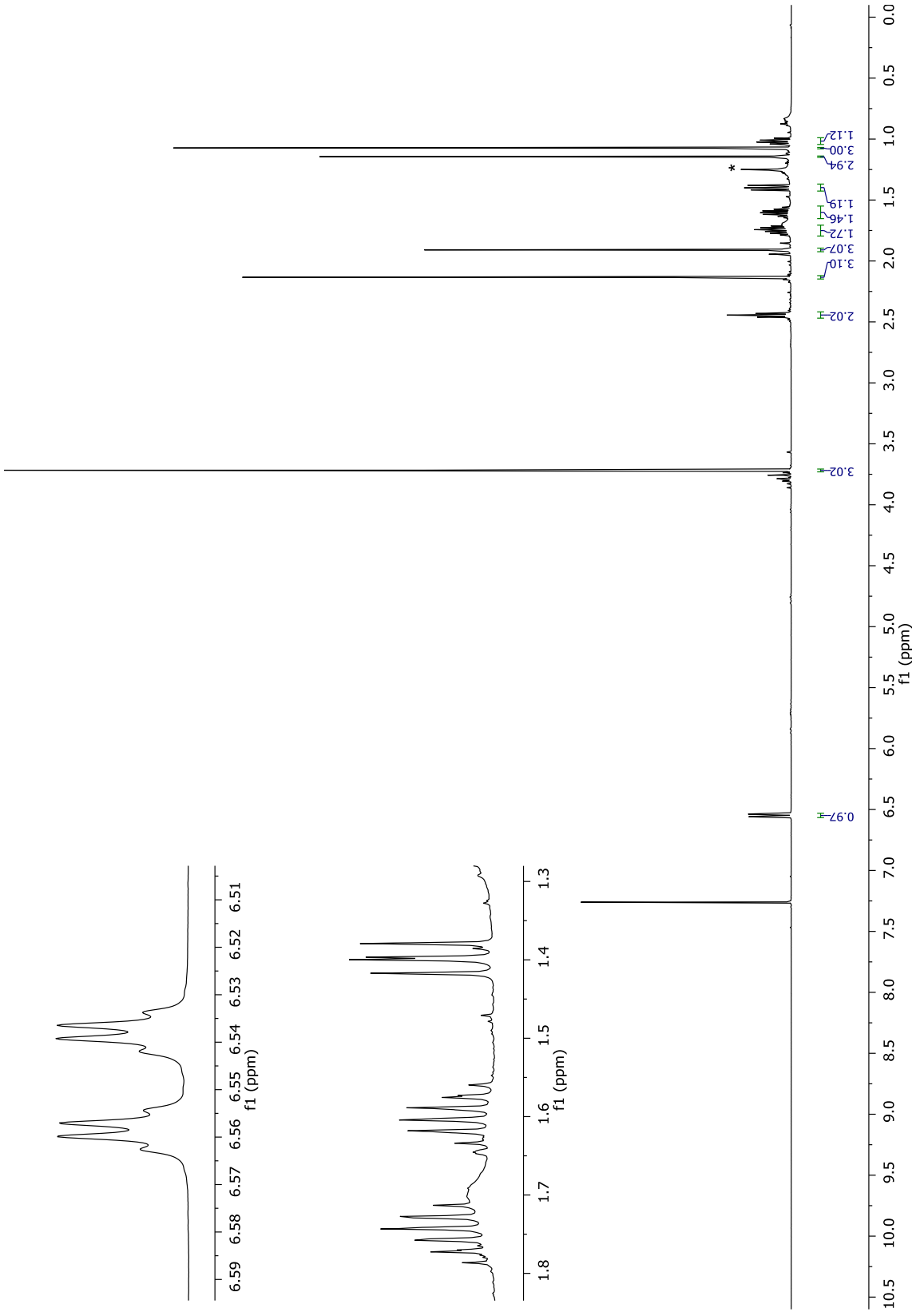
**HRESIMS** Found: 261.1465. $C_{14}H_{22}NaO_3$ requires $[M+Na]^+$, 261.1461.

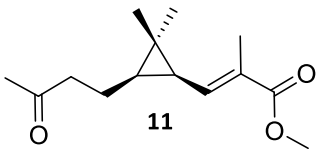



**11**

**$^1$H**

**500 MHz, $CDCl_3$, 298K**

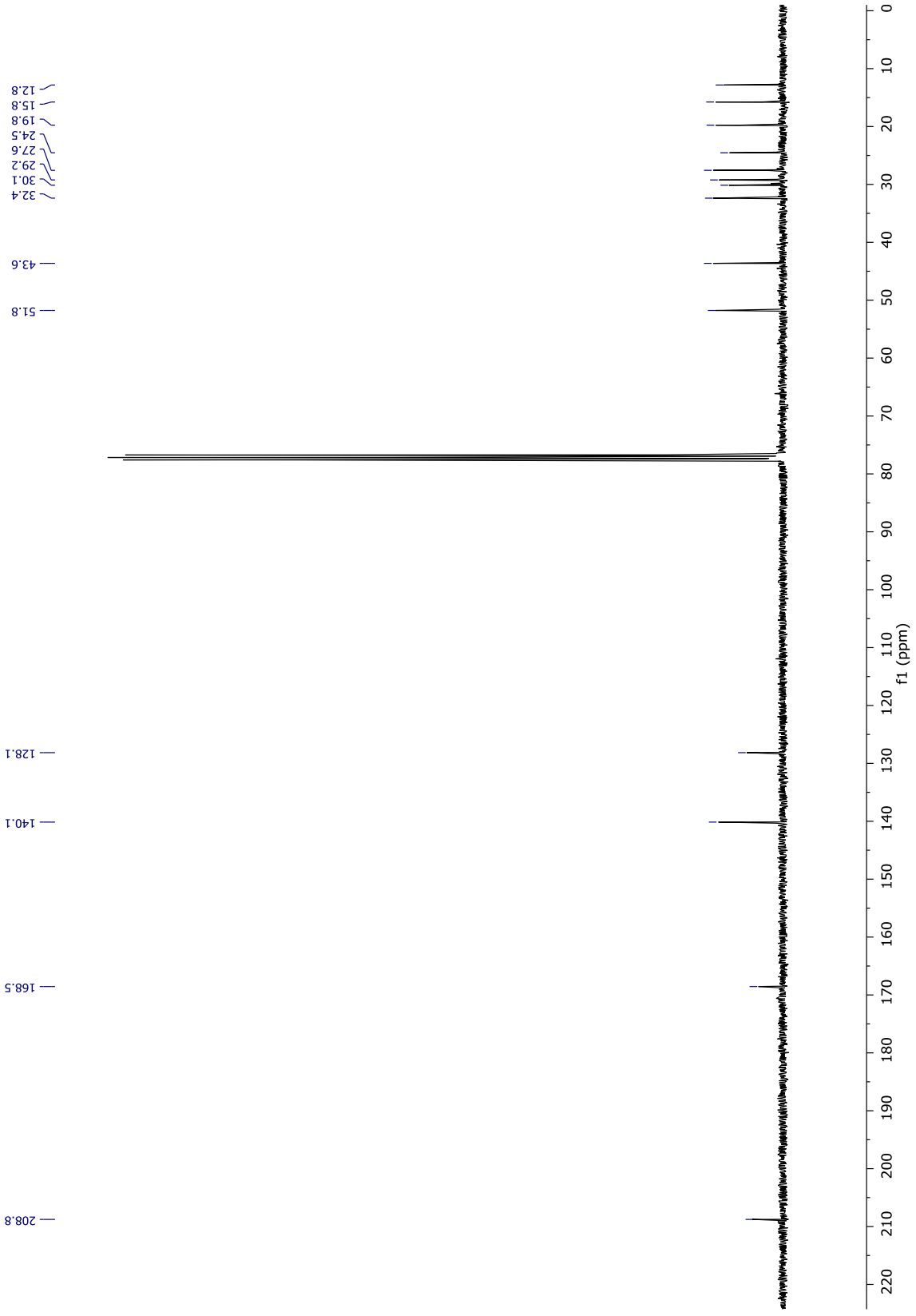


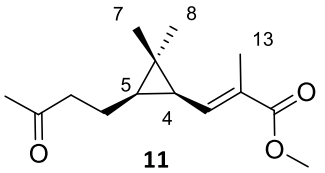



**11**

**$^{13}C\{^{1}H\}$**

**125 MHz, $CDCl_3$, 298K**

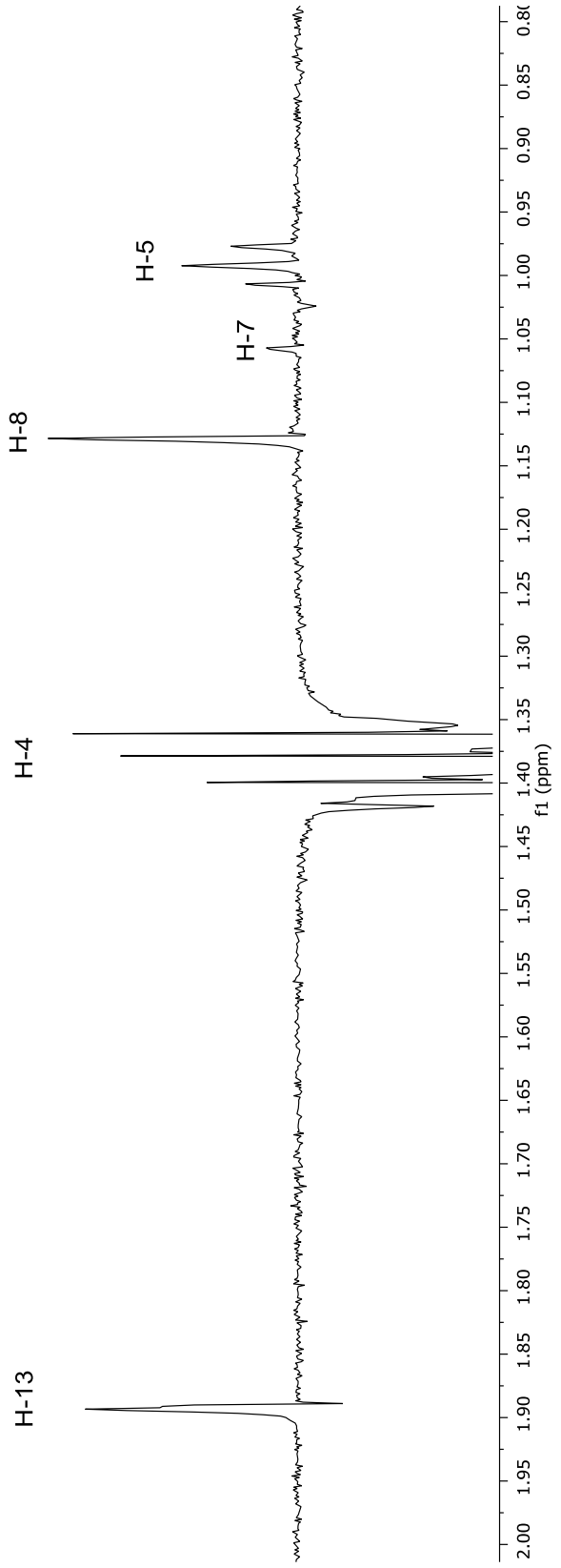





**$^1$H nOe Difference**

**Irradiation of H-4**

**500 MHz, $CDCl_3$, 298K**



**Methyl (*E*)-3-((1*S*,3*R*)-2,2-dimethyl-3-((*E*)-3-methylhex-3-en-5-yn-1-yl)cyclopropyl)-2-methylacrylate (12*E*-14) and methyl (*E*)-3-((1*S*,3*R*)-2,2-dimethyl-3-((*Z*)-3-methylhex-3-en-5-yn-1-yl)cyclopropyl)-2-methylacrylate (12*Z*-14)**

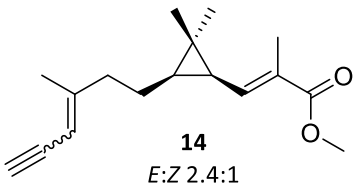
Sodium bis(trimethylsilyl)amide (0.95 mL of a 1.0 M solution in tetrahydrofuran, 950 μmol) was added dropwise to a magnetically stirred solution of compound **13** (269 mg, 1.08 mmol) in tetrahydrofuran (10 mL) at −78 °C under an argon atmosphere. After one hour, this mixture was transferred via cannula to a solution of compound **11** (206 mg, 0.87 mmol) in tetrahydrofuran (5 mL) at -78°C under an argon atmosphere. After 1 h, tetra-*n*-butylammonium fluoride (1.4 mL of a 1.0 M solution in tetrahydrofuran, 950 μmol) and acetic acid (250 μL, 4.37 mmol) were added consecutively. After a further 10 min, the cooling bath was removed and dilute HCl (50 mL of a 2 M aqueous solution) was added. The ensuing mixture was extracted with petroleum ether (3 × 20 mL). The combined organic extracts were rinsed with $NaHCO_3$ (20 mL of a saturated aqueous solution) and brine (20 mL), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale-yellow oil (238 mg). Subjecting this material to flash chromatography (silica, 1:49 → 1:9 v/v ethyl acetate / petroleum spirit elution) and concentration of the appropriate fractions ($R_f$ = 0.29, 1:19 v/v ethyl acetate / petroleum spirit elution) gave the *title compounds 12E-**14*** and *12Z-**14*** (166 mg, 74%) as a clear oil. $^1$H NMR spectrum peak integration indicated that the ratio of 12*E*-**14**:12*Z*-**14** (i.e., the d.r.) was approximately 2.4:1.0. As suitable conditions for the separation of these compounds were not found, they were characterized as a mixture.

**$^1$H NMR** (500 MHz, $CDCl_3$, 298K) δ 6.60 (dq, *J* = 10.3, 1.4 Hz, 1H, 12*Z*-**14**), 6.55 (dq, *J* = 10.3, 1.4 Hz, 1H, 12*E*-**14**), 5.25 (m, 1H, 12*E*-**14** and 12*Z*-**14**), 3.72 (s, 3H, 12*E*-**14**), 3.71 (s, 3H, 12*Z*-**14**), 3.01 (d, *J* = 2.2 Hz, 1H, 12*E*-**14**), 2.96 (d, *J* = 2.4 Hz, 1H, 12*Z*-**14**), 2.39-2.28 (m, 2H, 12*Z*-**14**), 2.10 (m, 2H, 12*E*-**14**), 1.91 (m, 3H, 12*E*-**14** and 12*Z*-**14**), 1.90 (d, *J* = 1.1 Hz, 3H, 12*E*-**14**), 1.78 (d, *J* = 1.6 Hz, 3H, 12*Z*-**14**), 1.60-1.54 (m, 2H, 12*E*-**14** and 12*Z*-**14**), 1.41 (dd, *J* = 10.3, 8.8 Hz, 1H, 12*Z*-**14**), 1.40 (dd, *J* = 10.3, 8.7 Hz, 1H, 12*E*-**14**), 1.16 (s, 3H, 12*Z*-**14**), 1.14 (s, 3H, 12*E*-**14**), 1.09 (s, 3H, 12*Z*-**14**), 1.06 (s, 3H, 12*E*-**14**), 1.04-0.93 (m, 1H, 12*E*-**14** and 12*Z*-**14**).

**$^{13}$C NMR** (125 MHz, $CDCl_3$, 298K) δ 168.5 (quaternary C, 12*Z*-**14**), 168.4 (quaternary C, 12*E*-**14**), 153.9 (quaternary C, 12*Z*-**14**), 153.8 (quaternary C, 12*Z*-**14**), 140.7 (CH, 12*Z*-**14**), 140.3 (CH, 12*E*-**14**), 127.7 (quaternary C, 12*E*-**14**), 127.6 (quaternary C, 12*Z*-**14**), 104.6 (CH, 12*Z*-**14**), 104.1 (CH, 12*E*-**14**), 81.7 (quaternary C, 12*E*-**14**), 81.5 (quaternary C, 12*Z*-**14**), 79.6 (CH, 12*E*-**14**), 79.2 (CH, 12*Z*-**14**), 51.6 ($CH_3$, 12*E*-**14**), 51.5 ($CH_3$, 12*Z*-**14**), 38.6 ($CH_2$, 12*E*-**14**), 34.7 ($CH_2$, 12*Z*-**14**), 32.8 (CH, 12*Z*-**14**), 32.5 (CH, 12*E*-**14**), 29.1(2) ($CH_3$, 12*Z*-**14**), 29.0(6) ($CH_3$, 12*E*-**14**), 27.7 (CH, 12*Z*-**14**), 27.5 (CH, 12*E*-**14**), 24.4 (quaternary C, 12*Z*-**14**), 24.3 (quaternary C, 12*E*-**14**), 23.5 ($CH_2$, 12*E*-**14**), 23.4 ($CH_2$, 12*Z*-**14**), 22.6 ($CH_3$, 12*Z*-**14**), 19.3 ($CH_3$, 12*E*-**14**), 15.7 ($CH_3$, 12*E*-**14**), 15.6 ($CH_3$, 12*Z*-**14**), 12.6 ($CH_3$, 12*E*-**14** and 12*Z*-**14** overlapping).

**IR (thin film) $\nu_{max}$** 3305, 2948, 2098, 1706, 1634, 1435, 1242, 1117, 1105, 756, 637, 594 $cm^{-1}$.

**HRESIMS** Found:283.1670. $C_{17}H_{24}NaO_2$ requires $[M+Na]^+$, 283.1669.

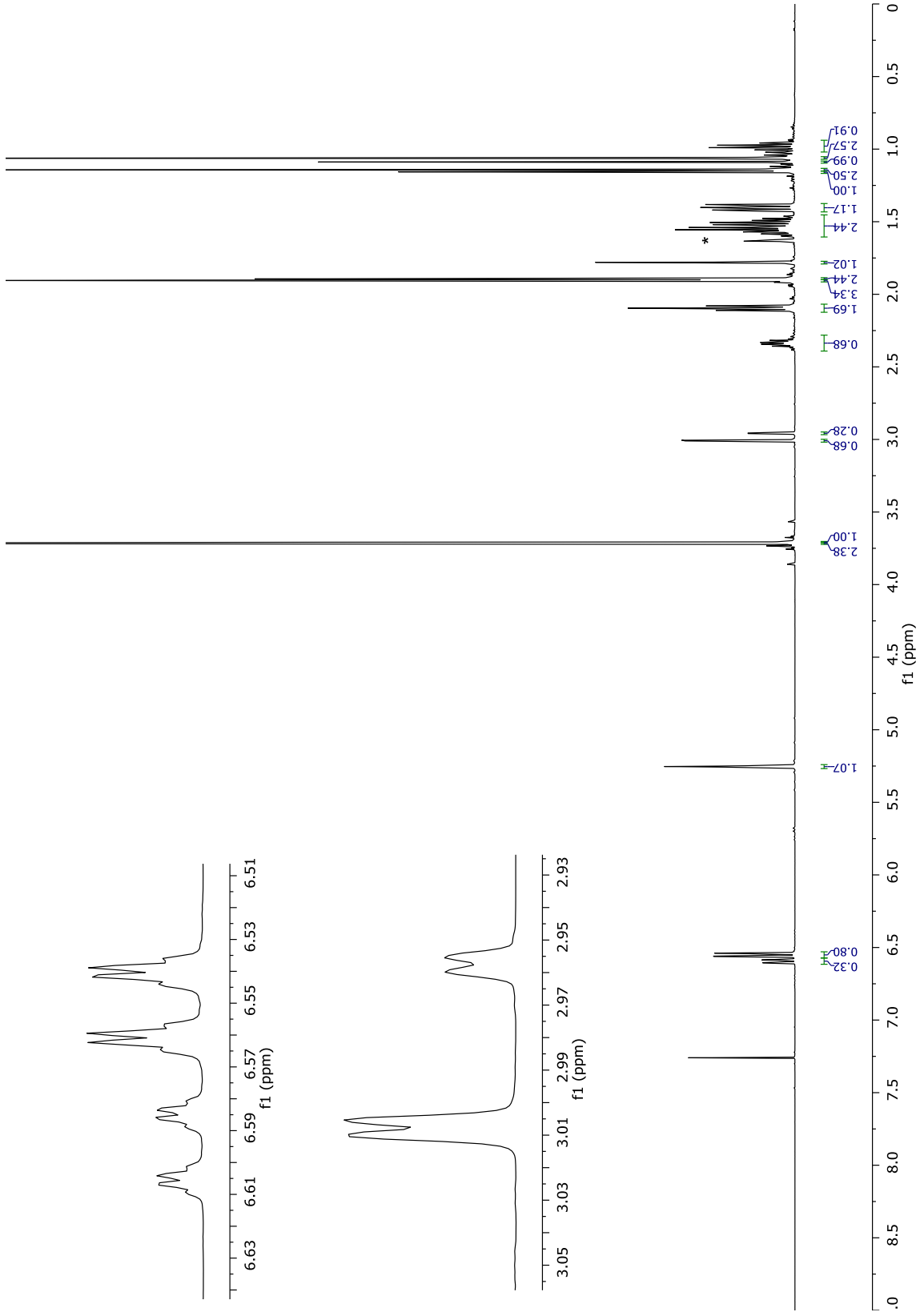


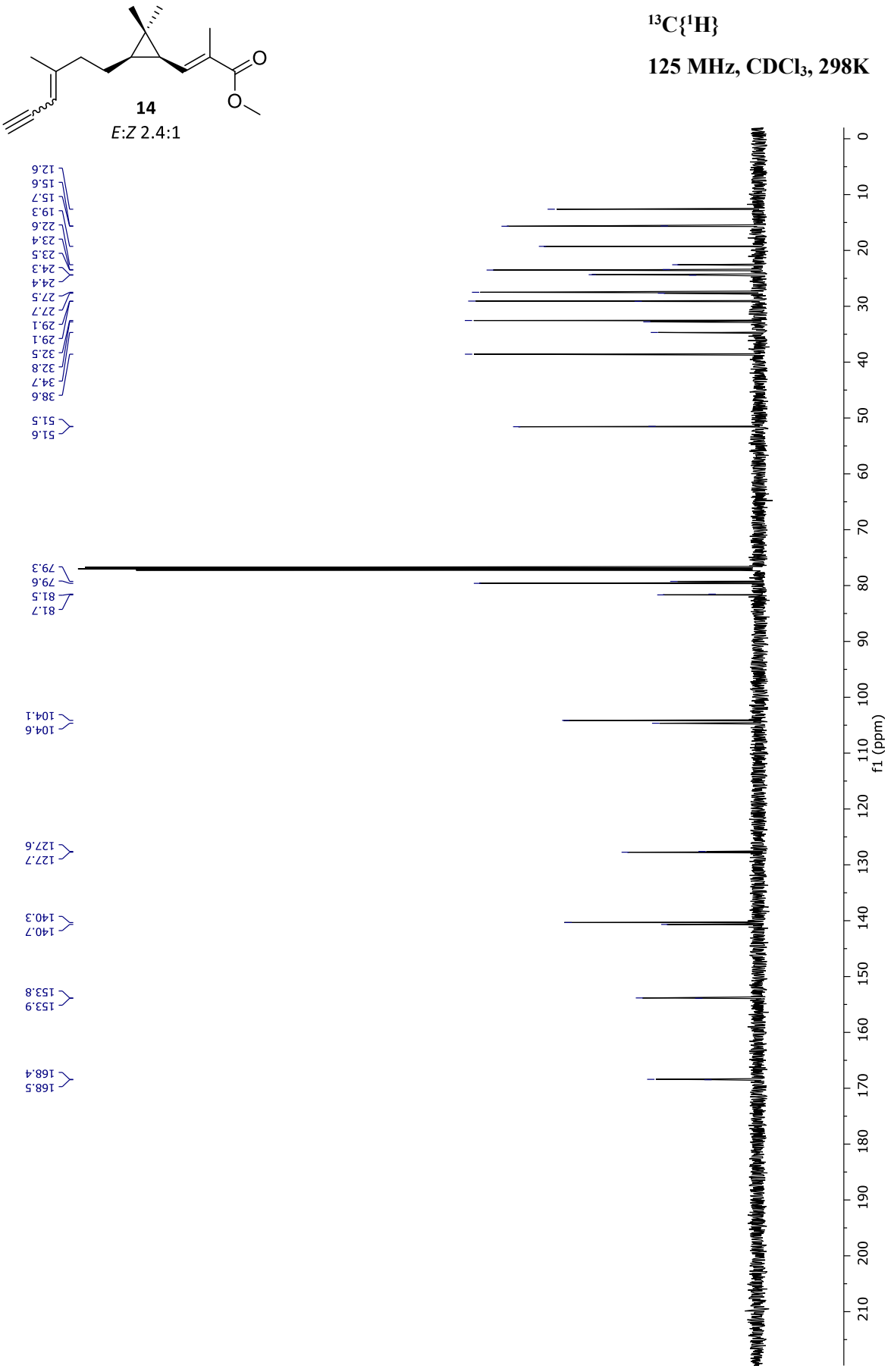
**14**

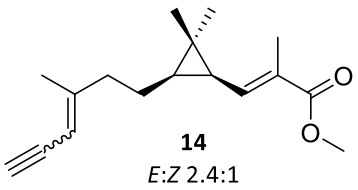
*E*:*Z* 2.4:1

**$^1$H**

**500 MHz, $CDCl_3$, 298K**




14
E:Z 2.4:1
13C{1H}
125 MHz, CDCl3, 298K
12.6
15.6
15.7
19.3
22.6
23.4
23.5
24.3
24.4
27.5
27.7
29.1
29.1
32.5
32.8
34.7
38.6
51.5
51.6
79.3
79.6
81.5
81.7
104.1
104.6
127.6
127.7
140.3
140.7
153.8
153.9
168.4
168.5
f1 (ppm)

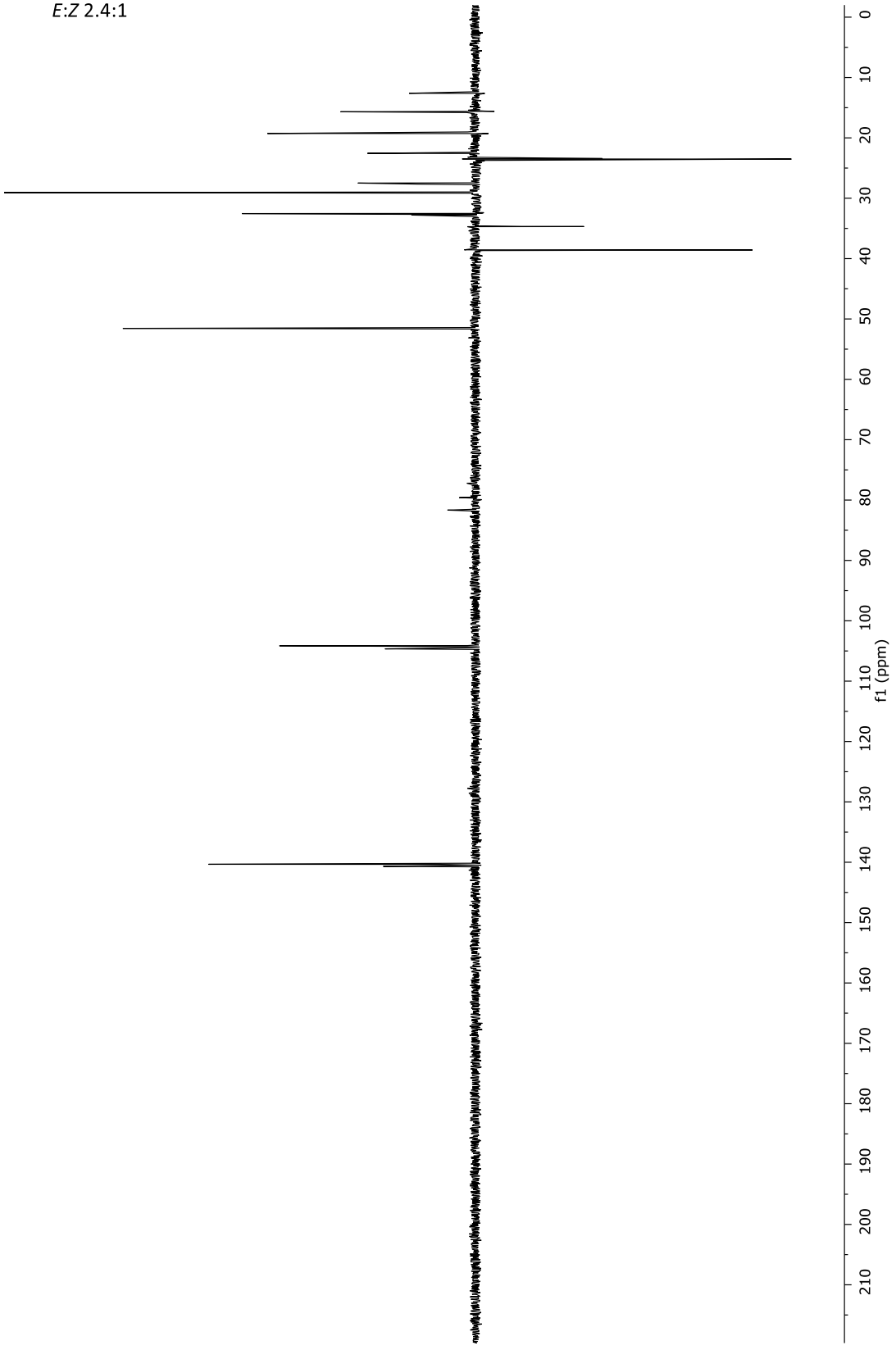


**14**

*E*:*Z* 2.4:1

**$^{13}$C DEPT-135**

**125 MHz, $CDCl_3$, 298K**



**(*E*)-3-((1S,3R)-2,2-dimethyl-3-((*E*)-3-methylhex-3-en-5-yn-1-yl)cyclopropyl)-2-methylacrylic acid (12*E*-15) and (*E*)-3-((1S,3R)-2,2-dimethyl-3-((*Z*)-3-methylhex-3-en-5-yn-1-yl)cyclopropyl)-2-methylacrylic acid (12*Z*-15)**

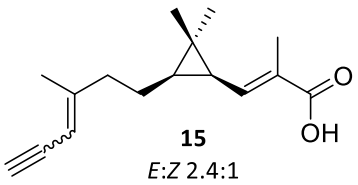
Sodium hydroxide (1.5 mL of a 3.5 M aqueous solution, 5.25 mmol) was added to a magnetically stirred solution of 12*EZ*-**14** (135 mg of a 2.5:1.0 mixture, respectively, 519 µmol) in HPLC-grade tetrahydrofuran (1.5 mL). The reaction mixture was heated at 70 °C for 48 h, then cooled to 20 °C and treated with dilute HCl (10 mL of a 2M aqueous solution). The ensuing mixture was extracted with dichloromethane (3 × 3 mL). The combined organic extracts were rinsed with saturated aqueous NaCl (5 mL), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale-yellow oil (136 mg). Subjecting this material to flash chromatography (silica, 1:99 → 1:4 v/v ethyl acetate / petroleum spirit elution) and concentration of the appropriate fractions ($R_f$ = 0.38, 1:9 v/v ethyl acetate / petroleum spirit elution) gave the *title compounds 12E-**15*** and *12Z-**15*** (108 mg, 85%) as a clear oil. Calculations based on the integration of analogous signals present in the $^1$H NMR spectrum indicated that the ratio of compound 12*E*-**15**:12*Z*-**15** (i.e., the d.r.) was approximately 2.4:1.0, respectively (unchanged from the starting material). As suitable conditions for the separation of these compounds were not found, they were characterized as a mixture.

**$^1$H NMR** (500 MHz, $CDCl_3$, 298K) δ 6.77 (dq, *J* = 10.5 and 1.4 Hz, 1H, 12*Z*-**15**), 6.72 (dq, *J* = 10.5 and 1.3 Hz, 1H, 12*E*-**15**), 5.27 – 5.25 (complex m, 1H, 12*E*-**15** and 12*Z*-**15**), 3.01 (dm, *J* = 2.2 Hz, 1H, 12*E*-**15**), 2.97 (dm, *J* = 2.3 Hz, 1H, 12*Z*-**15**), 2.36 – 2.32 (m, 2H, 12*Z*-**15**), 2.10 (m, 2H, 12*E*-**15**), 1.91(3) (d, *J* = 1.3 Hz, 3H, 12*Z*-**15**), 1.91(0) (d, *J* = 1.3 Hz, 3H, 12*E*-**15**), 1.90 (d, *J* = 0.7 Hz, 3H, 12*E*-**15**), 1.79 (dd, *J* = 1.6 and 0.5 Hz, 3H, 12*Z*-**15**), 1.64 – 1.48 (complex m, 2H, 12*E*-**15** and 12*Z*-**15**), 1.45 (dd, *J* = 10.6 and 8.6 Hz, 1H, 12*Z*-**15**), 1.44 (dd, *J* = 10.6 and 8.8 Hz, 1H, 12*E*-**15**), 1.17 (s, 3H, 12*Z*-**15**), 1.16 (s, 3H, 12*E*-**15**), 1.11 (s, 3H, 12*Z*-**15**), 1.14 – 1.01 (complex m, 1H, 12*E*-**15** and 12*Z*-**15**), 1.08 (s, 3H, 12*E*-**15**).

**$^{13}$C NMR** (125 MHz, $CDCl_3$, 298K) δ 173.2 (quaternary C, 12*E*-1**5** and 12*Z*-**15** overlapping), 153.8 (quaternary C, 12**Z**-**15**), 153.7 (quaternary C, 12*E*-**15**), 143.8 (CH, 12*Z*-**15**), 143.4 (CH, 12*E*-**15**), 126.9 (quaternary C, 12*E*-**15**), 126.8 (quaternary C, 12*Z*-**15**), 104.7 (CH, 12*Z*-**15**), 104.2 (CH, 12*E*-**15**), 81.7 (quaternary C, 12*E*-**15**), 81.5 (quaternary C, 12*Z*-**15**), 79.6 (quaternary C, 12*E*-**15**), 79.3 (quaternary C, 12*Z*-**15**), 38.6 ($CH_2$, 12*E*-**15**), 34.7 ($CH_2$, 12*Z*-**15**), 33.5 (CH, 12*Z*-**15**), 33.3 (CH, 12*E*-**15**), 29.2 (CH, 12*Z*-**15**), 29.1 (CH, 12*E*-**15**), 28.1 ($CH_3$, 12*Z*-**15**), 27.9 ($CH_3$, 12*E*-**15**), 25.3 (quaternary C, 12*Z*-**15**), 25.1 (quaternary C, 12*E*-**15**), 23.5 ($CH_2$, 12*E*-**15**), 23.4 ($CH_2$, 12*Z*-**15**), 22.6 ($CH_3$, 12*Z*-**15**), 19.3 ($CH_3$, 12*E*-**15**), 15.7 ($CH_3$, 12*E*-**15**), 15.6 ($CH_3$, 12*Z*-**15**), 12.1 ($CH_3$, 12*E*-**15** and 12*Z*-**15** overlapping).

**IR (thin film) $\nu_{max}$** 3308, 2925, 2865, 2651, 2098, 1673, 1627, 1417, 1275, 1138, 1123 $cm^{-1}$.

**HRESIMS** Found: 245.1548. $C_{16}H_{21}O_2$ $[M-H]^-$ requires 245.1547.

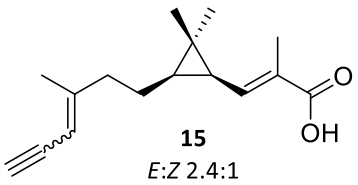



**15**

*E*:*Z* 2.4:1

**$^1$H**

**500 MHz, $CDCl_3$, 298K**

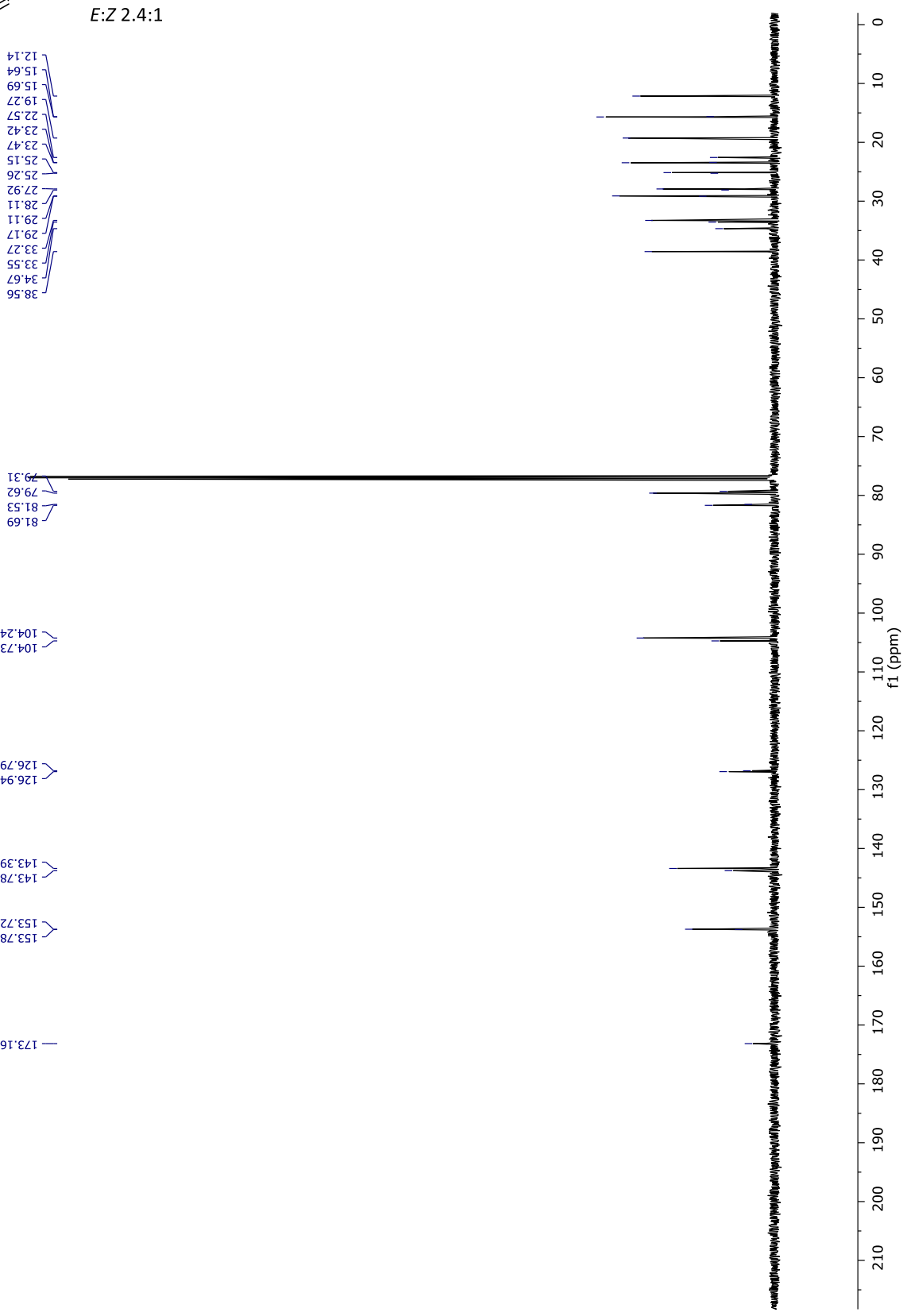


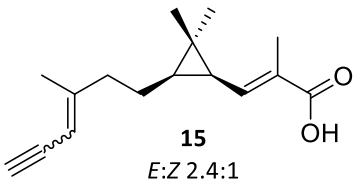

**15**

*E*:*Z* 2.4:1

**$^{13}C\{^{1}H\}$**

**125 MHz, $CDCl_3$, 298K**



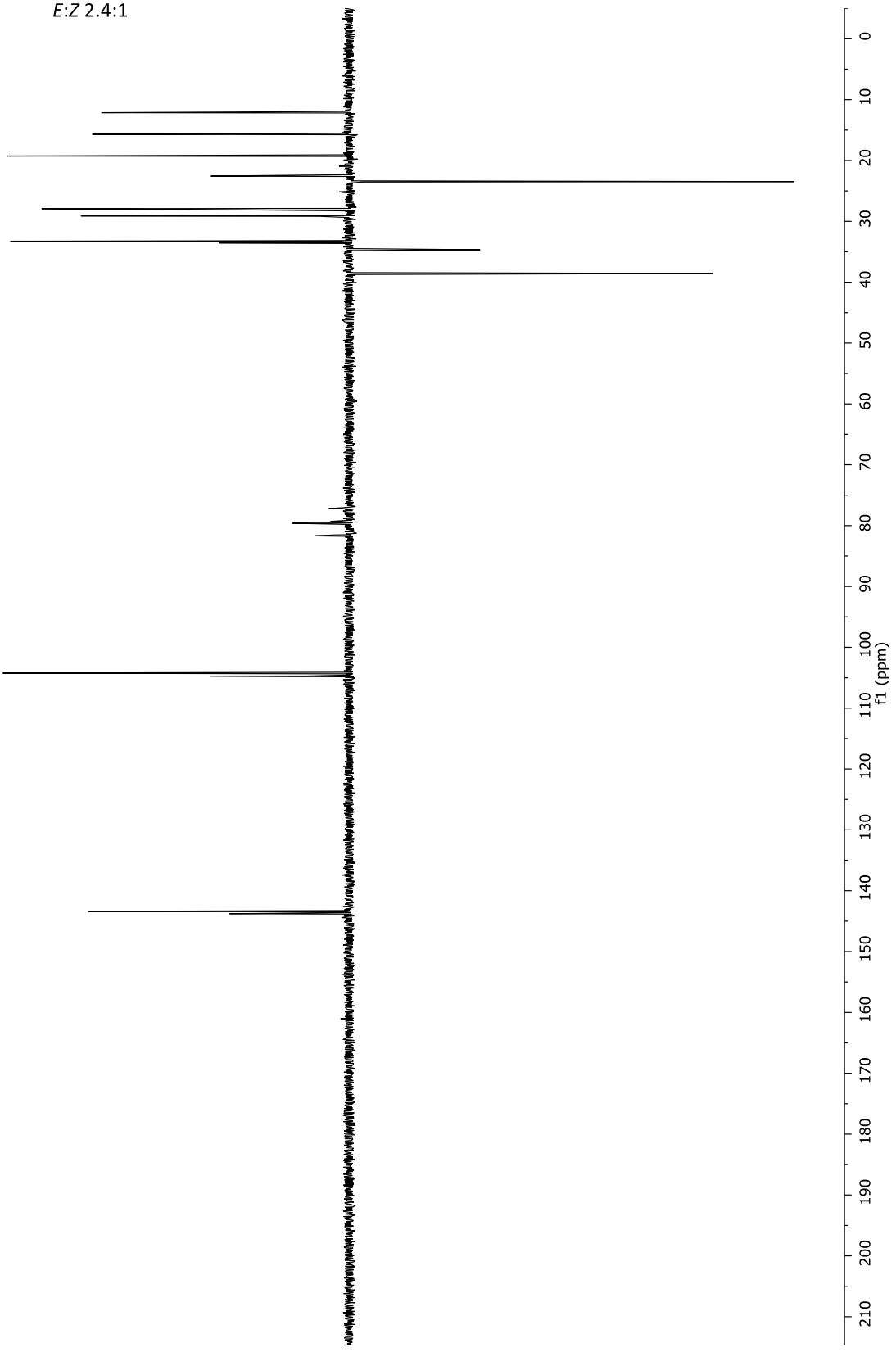



**15**

*E*:*Z* 2.4:1

**$^{13}$C DEPT-135**

**125 MHz, $CDCl_3$, 298K**



**(+)-EBC-329 (6) and 12*Z*-EBC-329 (17)**

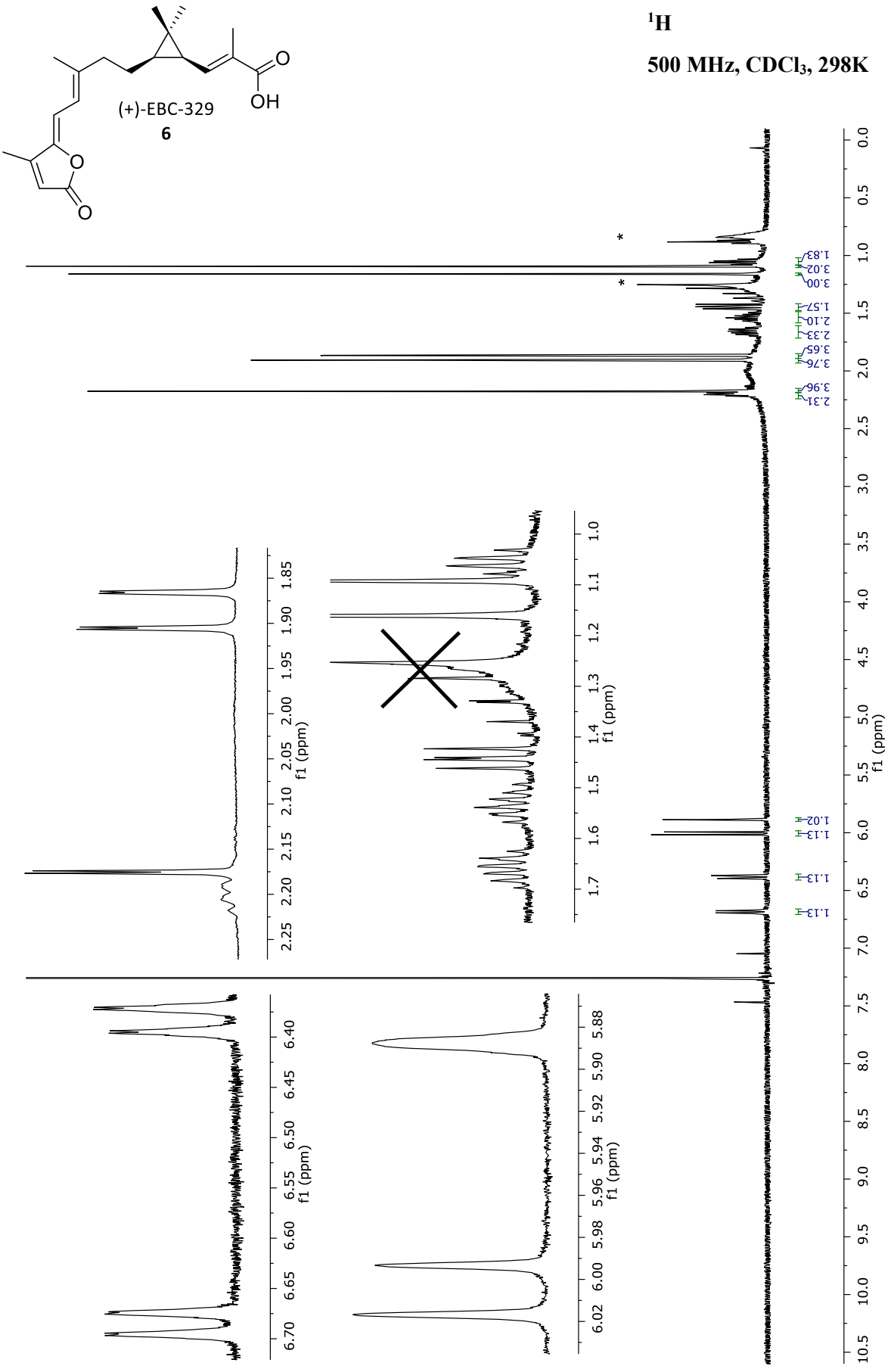
Following a modified procedure by Abarbri and Parrain.[5] A Schlenk tube was charged with a suspension of $K_2CO_3$ (150 mg, 1.1 mmol) and *Z*-3-iodobutenoic acid **16** (55 mg, 0.53 mmol) in *N*,*N*-dimethylformamide (DMF) (1 mL). The suspension was stirred vigorously for 20 minutes before being degassed *via* three freeze-pump-thaw cycles using liquid nitrogen. A solution of 12*EZ*-**15** (70 mg, 0.29 mmol) in *N*,*N*-dimethylformamide (0.9 mL) was prepared and degassed in the same manner. The alkyne solution was then transferred at room temperature *via* cannula to the suspension. Following addition of neat CuI (55 mg, 0.29 mmol), the mixture was heated to 55°C. Once thin layer chromatography indicated complete consumption of starting material (approximately 90 minutes), the mixture was allowed to equilibrate to 20 °C before being quenched with aqueous saturated ammonium chloride (3 mL), followed by water (4 mL). This aqueous phase was extracted with ethyl acetate (5 x 2 mL). The combined organic phases were dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield a yellow-brown residue. $^1$H NMR of the residue showed only the *title compounds* (30 mg, 31%) along with residual DMF (total weight 72 mg). High performance liquid chromatography of a portion of the crude (isocratic 95:5 hexane/isopropanol) yielded pure (+)-EBC-329 (**6**) as a clear oil, and impure 12Z-EBC-329 (**17**), which could not be further purified.

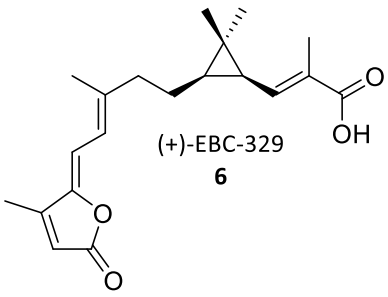
*(+)-EBC-329*

$[\alpha]^{21}_D$ +14.3° (c 0.015, $CDCl_3$).

**$^1$H NMR** (500 MHz, $CDCl_3$, 298K) δ 6.69 (d, *J* = 10.7 Hz, 1H), 6.38 (dd, *J* = 11.8, 1.4 Hz, 1H), 6.00 (dd, *J* = 11.7, 0.6 Hz, 1H), 5.89 (br. s, 1H), 2.24 – 2.19 (m, 2H), 2.18 (d, *J* = 1.3 Hz, 3H), 1.91 (d, *J* = 1.4 Hz, 3H), 1.87 (d, *J* = 1.3 Hz, 3H), 1.66 (m, 1H), 1.53 (m, 1H), 1.44 (dd, *J* = 10.7, 8.7 Hz, 1H), 1.16 (s, 3H), 1.09 (s, 3H), 1.09 – 1.02 (m, 1H).

**$^{13}$C NMR** (125 MHz, $CDCl_3$, 298K) δ 169.7, 154.6, 148.8, 147.3, 143.0, 127.0, 118.9, 115.5, 107.6, 40.7, 33.6, 29.3, 28.1, 25.2, 24.2, 17.5, 15.9, 12.5, 11.8. Resonance of carboxylic acid carbonyl below detection threshold.


(+)-EBC-329
6
OH
O
O
O
O
$^1$H
500 MHz, CDCl$_3$, 298K
f1 (ppm)

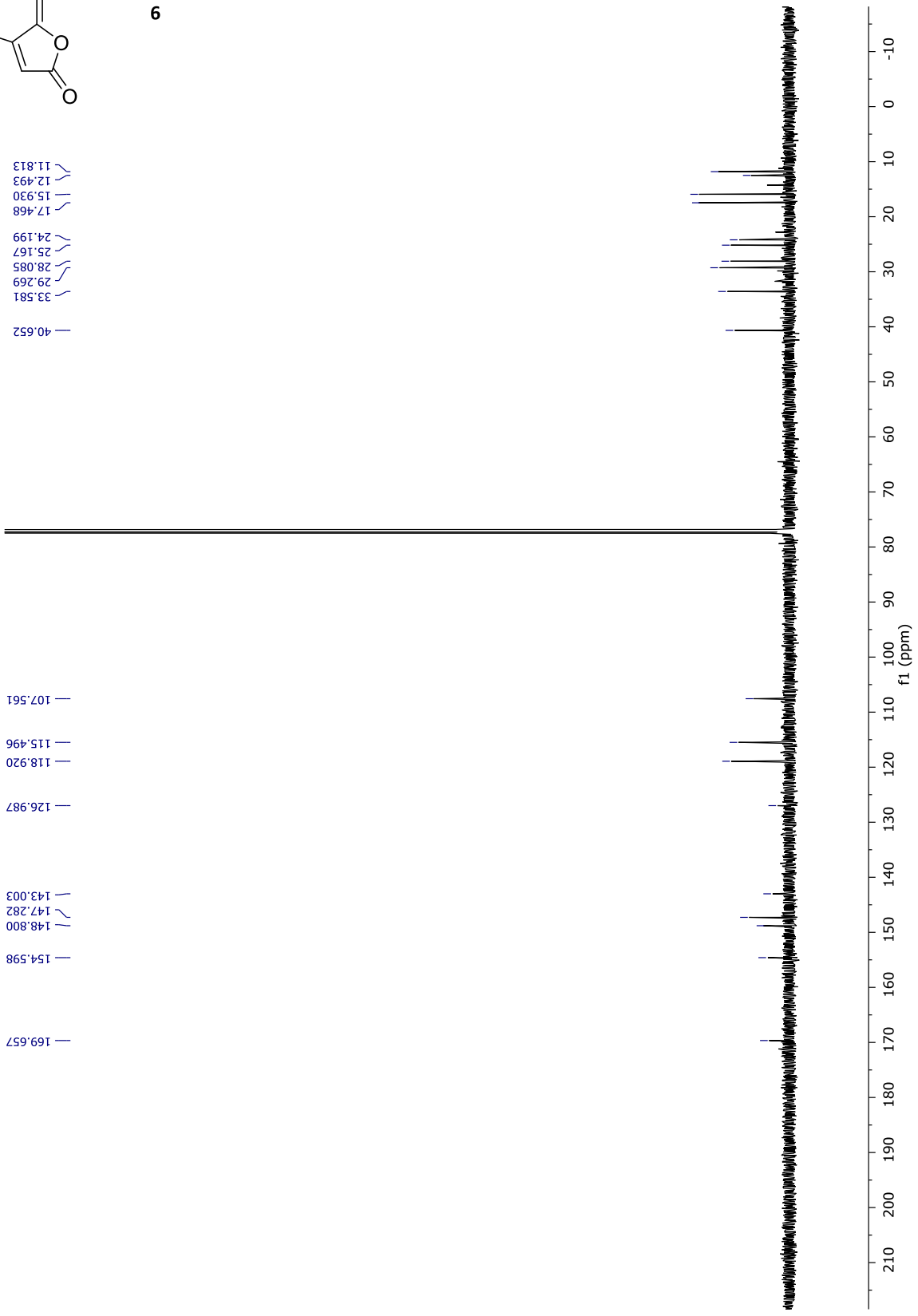


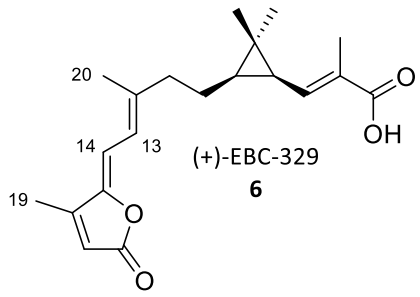

(+)-EBC-329

**6**

**$^{13}C\{^{1}H\}$**

**125 MHz, $CDCl_3$, 298K**





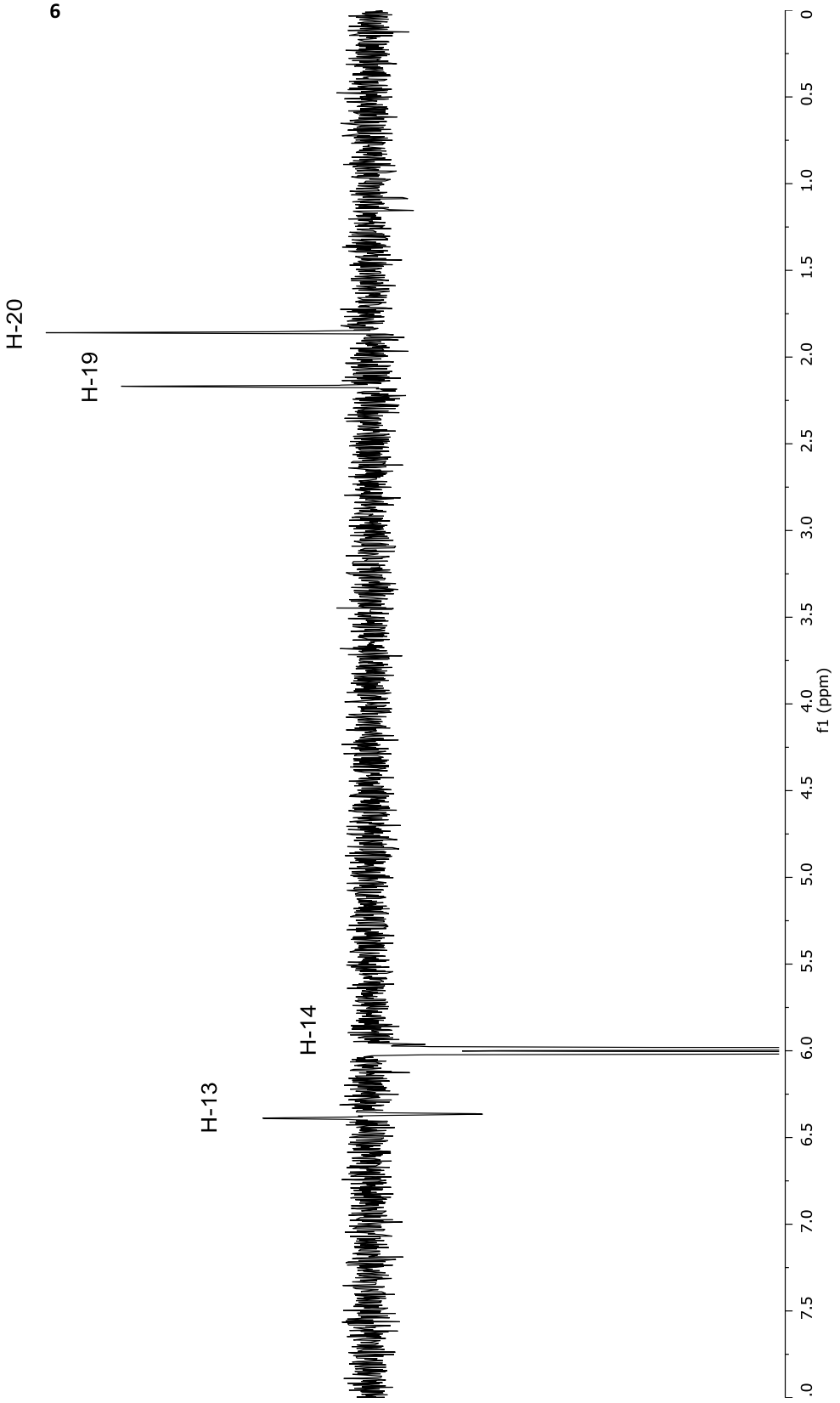

(+)-EBC-329

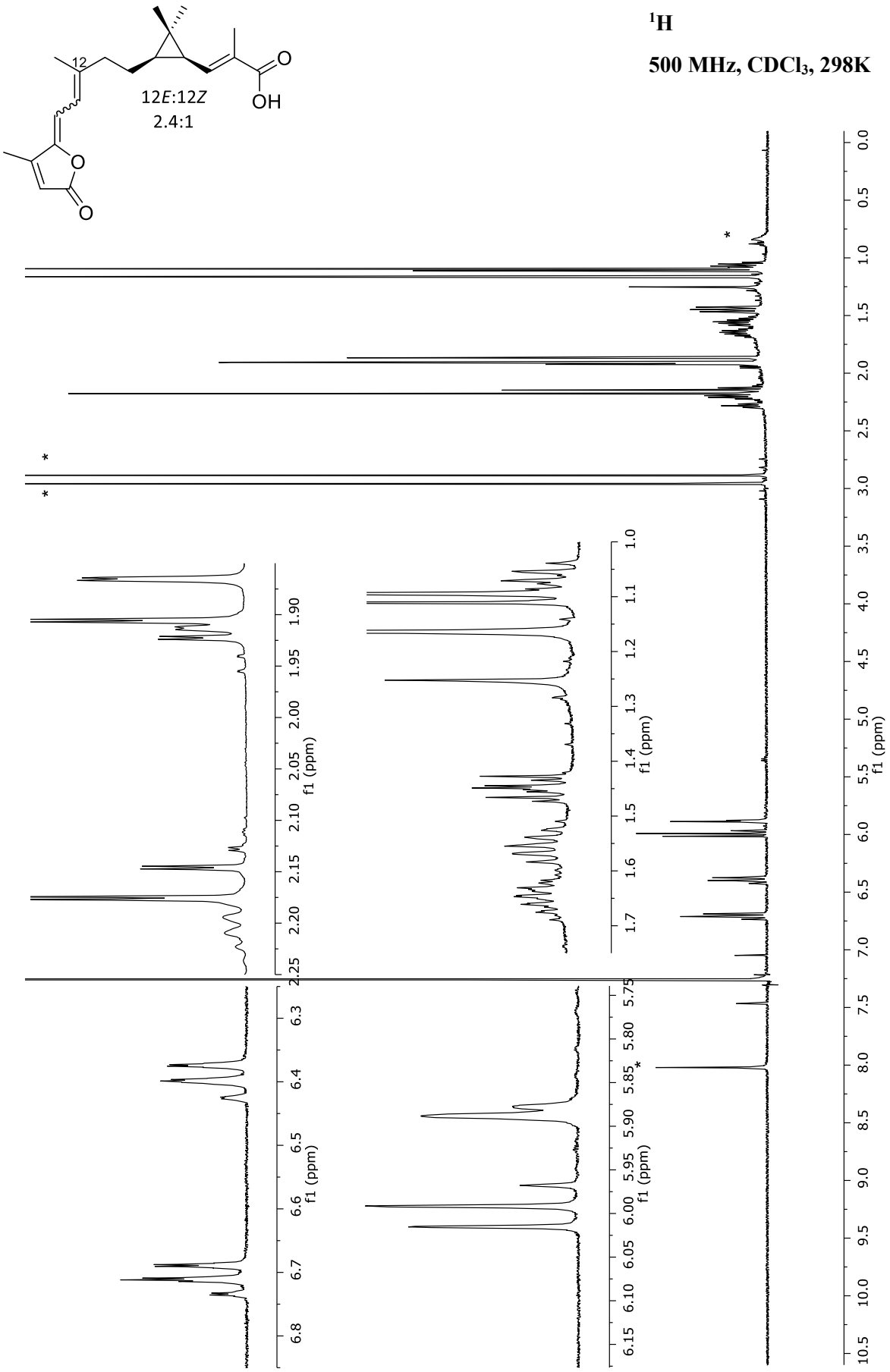
**6**

**$^1$H nOe Difference**

**Irradiation of H-14**

**500 MHz, $CDCl_3$, 298K**

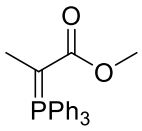



12
12E:12Z
2.4:1
O
OH
O
O
$^1$H
500 MHz, CDCl$_3$, 298K
f1 (ppm)

**Methyl 2-(triphenyl-λ$^5$-phosphanylidene)propanoate 10**

The *titled compound* was prepared according to Roush.[3] Methyl 2-bromopropionate (20.6 g, 123 mmol) was combined with water (300 mL) and triphenylphosphine (29.1 g, 111 mmol). The suspension was allowed to stir overnight at 70°C. After cooling to 20 °C, aqueous sodium hydroxide (2 M, 125 mL, 250 mmol) was added dropwise to the solution with vigorous stirring. Dichloromethane was used to dissolve the precipitate. The two phases were separated, and then the aqueous phase was extracted three times with dichloromethane. The organic phases were combined, washed once with brine, dried over sodium sulfate, and then concentrated under reduced pressure to yield a solid, which was triturated with petroleum spirit to yield the *title compound* ***10*** (34.4 g, 89%) as a yellow solid. $^1$H NMR data were consistent with the cited report.

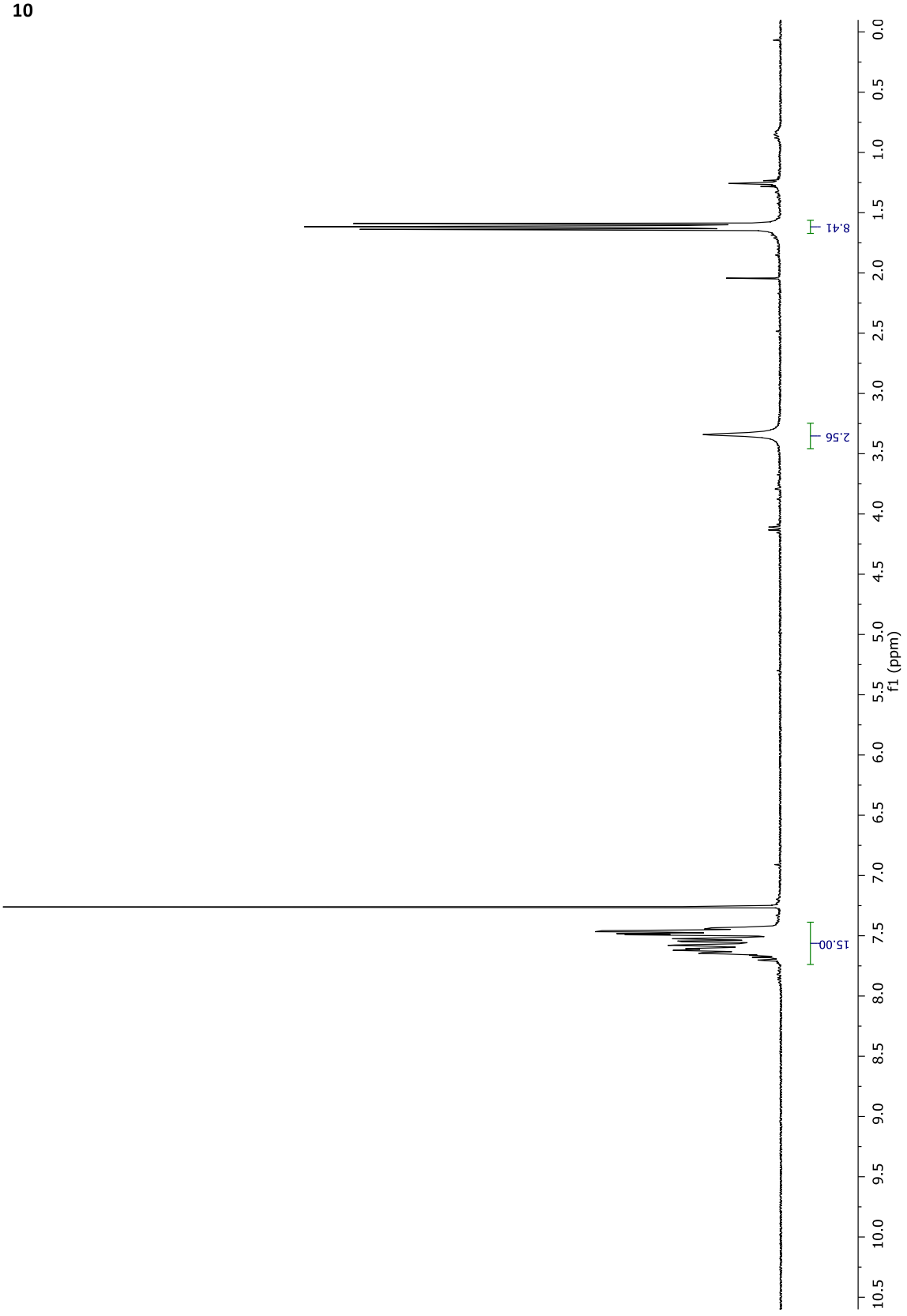
**$^1$H NMR** (300MHz, $CDCl_3$, 298K) δ 7.56 (m, 15H), 3.35 (s, 3H), 1.61 (d, *J* = 13.1 Hz, 3H).




**10**

**$^1$H**

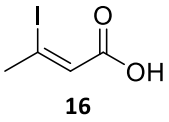
**300 MHz, $CDCl_3$, 298K**



**(*Z*)-3-Iodobut-2-enoic acid 16**

Following the procedure reported by Chen.[4] 2-Butynoic acid (94 mg, 1.1 mmol) was combined with hydroiodic acid (48%, 0.15 mL, 1.5 mmol) and magnetically stirred at 90°C. Reaction progress was monitored using FT-IR. After 4 hours, the reaction was allowed to cool to 20 °C The crude material was collected *via* filtration and washed with water to yield the *title compound* ***16*** (160 mg, 69%) as a solid. Concentration of the *title compound* from deuterochloroform yielded clear crystals (melting point 110°C) suitable for x-ray diffraction (see below). $^{1}$H NMR data were consistent with that reported.

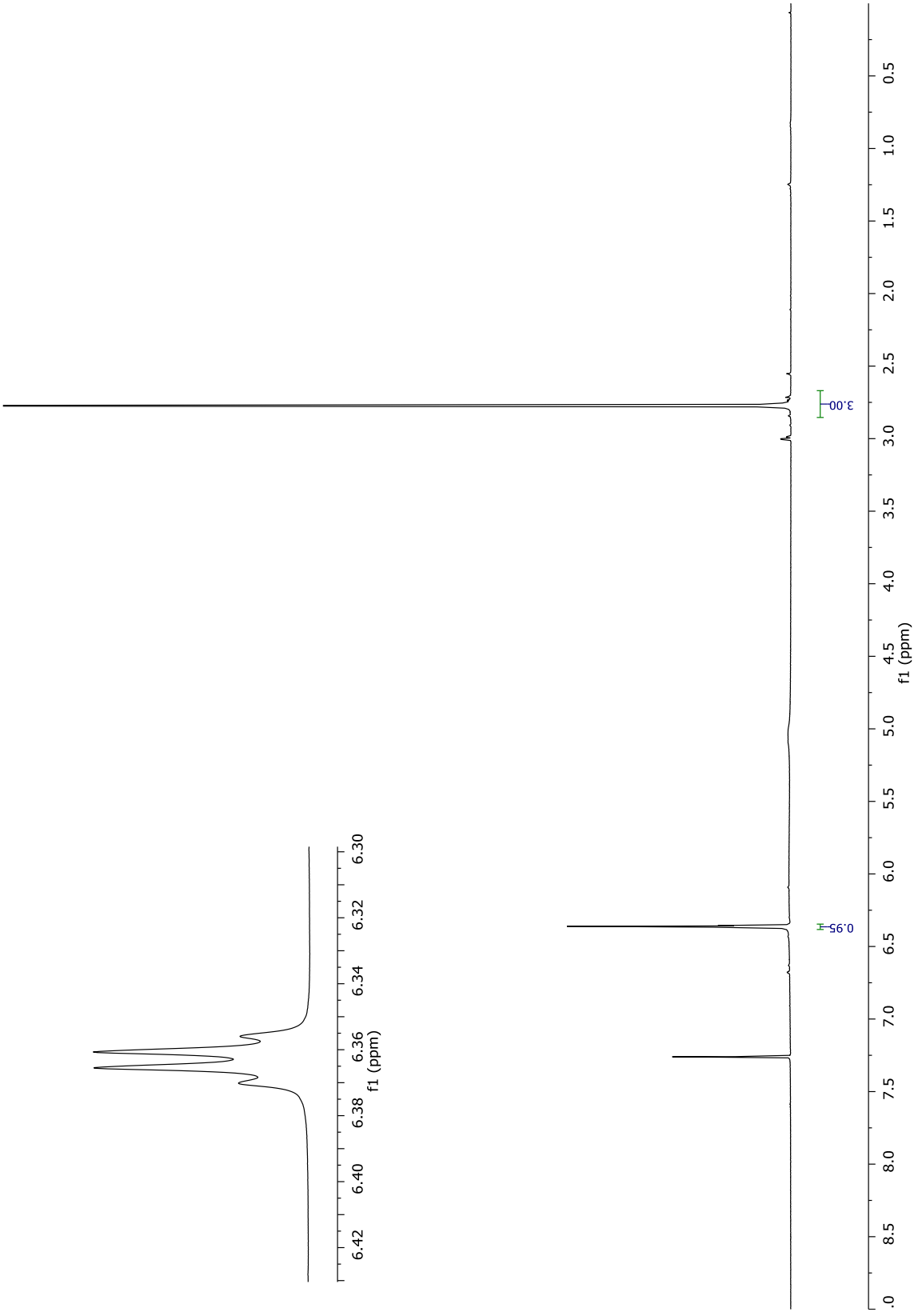
**$^{1}$H NMR** (300 MHz, $CDCl_3$, 298K) δ 6.36 (q, *J* = 1.4 Hz, 1H), 2.77 (d, *J* = 1.4 Hz, 3H).




**16**

**$^1$H**

**300 MHz, $CDCl_3$, 298K**



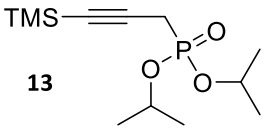
**Diisopropyl (3-(trimethylsilyl)prop-2-yn-1-yl)phosphonate 13**

Triisopropyl phosphite (786 mg, 3.77 mmol) and 3-bromo-1-(trimethylsilyl)-1-propyne (756 mg, 3.95 mmol) were combined neat in a round-bottom flask fitted with a reflux condenser. The mixture was heated to 80°C and stirred magnetically for 16 hours, and then subjected to silica gel chromatography (5:19 → 1:1 v/v ethyl acetate / petroleum ether elution) to yield the *title compound* ***13*** (699 mg, 67%) as a clear mobile oil. The $^{1}$H NMR data of the *title compound* were consistent with those reported by Steliou;[8] the present work is the first report of $^{13}$C NMR data for **13**.

The above procedure was employed specifically for small scale synthesis. Steliou[8] has published a procedure more suitable for large-scale work.

**$^{1}$H NMR** (300 MHz, $CDCl_3$, 298K) δ 4.76 (multiplet, 2H), 2.76 (d, *J* = 22.2 Hz, 2H), 1.35 (dd, *J* = 6.2, 2.2 Hz, 12H), 0.15 (s, 9H).

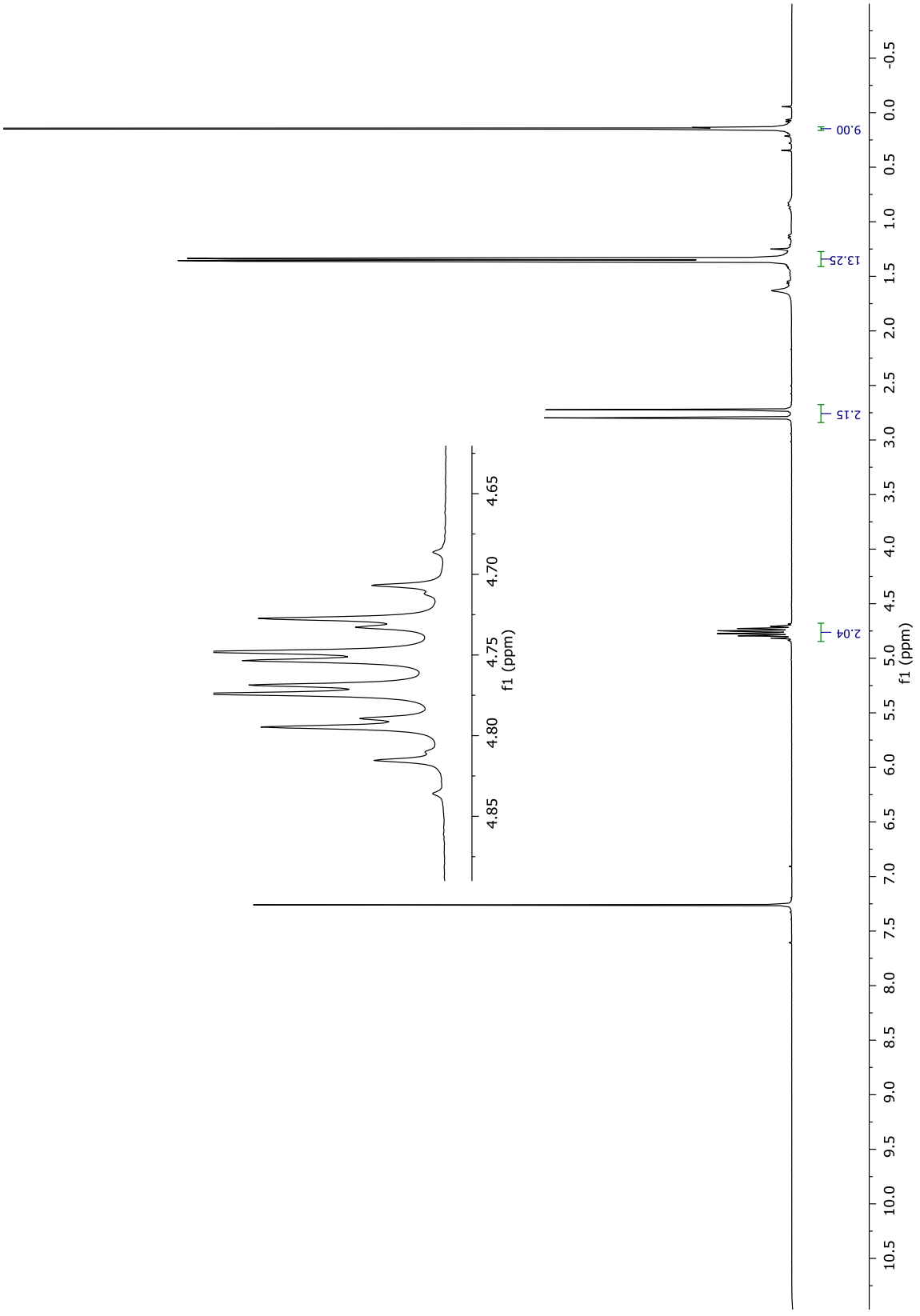
**$^{13}$C NMR** (75 MHz, $CDCl_3$, 298K) δ 96.5 (d, *J* = 13.5 Hz), 87.7 (d, *J* = 8.7 Hz), 71.7 (d, *J* = 6.9 Hz), 24.2 (d, *J* = 3.9 Hz), 24.05 (d, *J* = 5.1 Hz), 20.4 (d, *J* = 145.4 Hz), -0.06 (s).

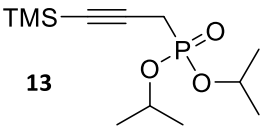



**13**

**$^1$H**

**300 MHz, $CDCl_3$, 298K**

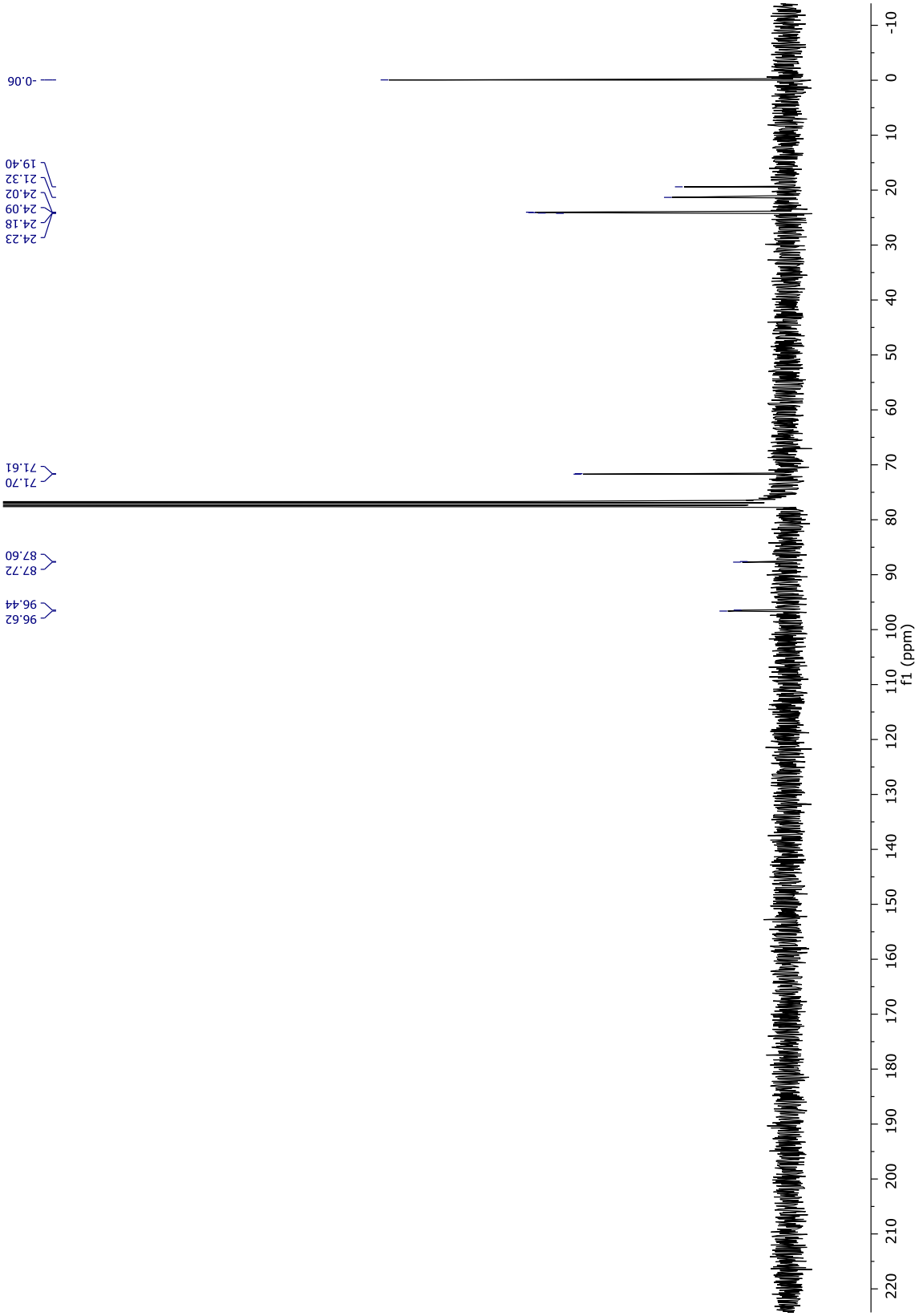





**13**

**$^{13}C\{^{1}H\}$**

**75 MHz, $CDCl_3$, 298K**

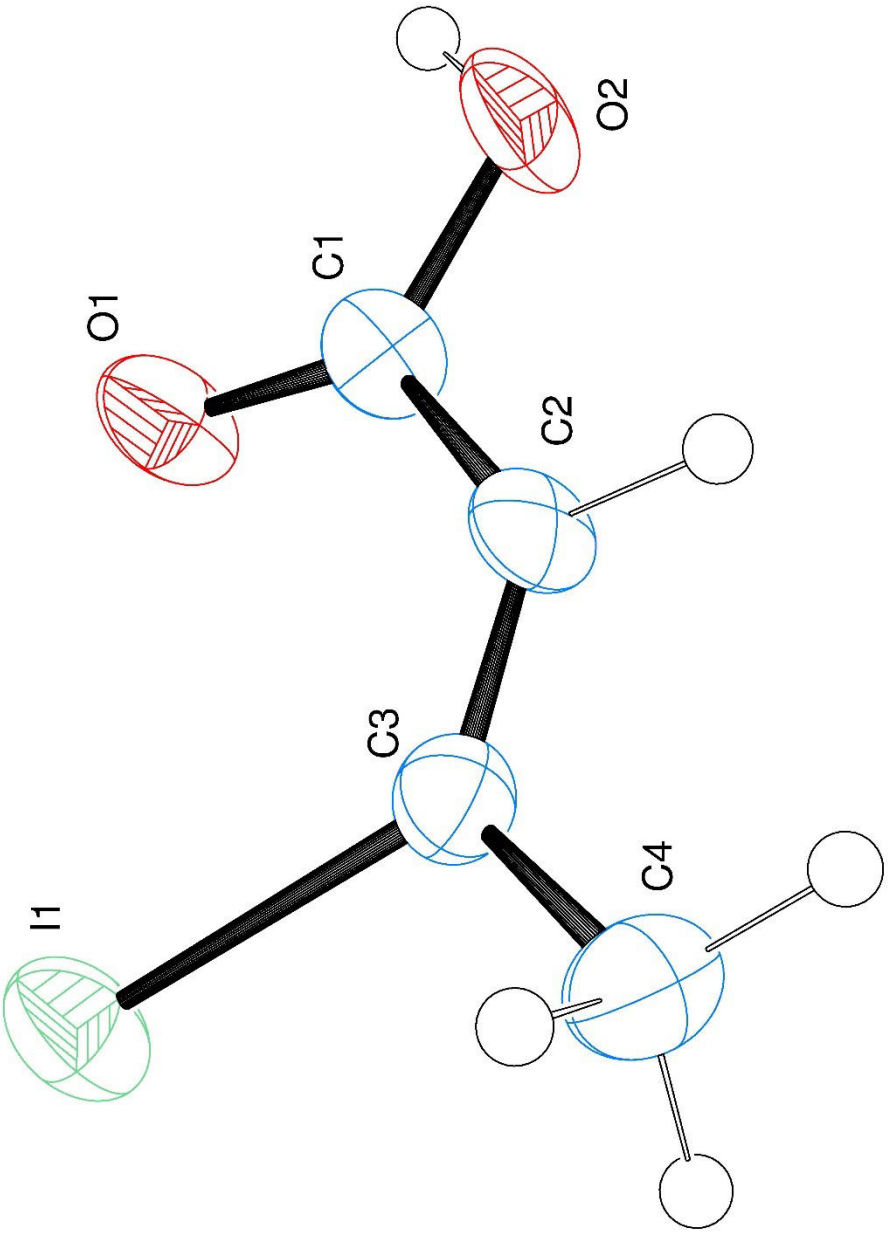


**Single Crystal X-ray Diffraction Analysis of 16**

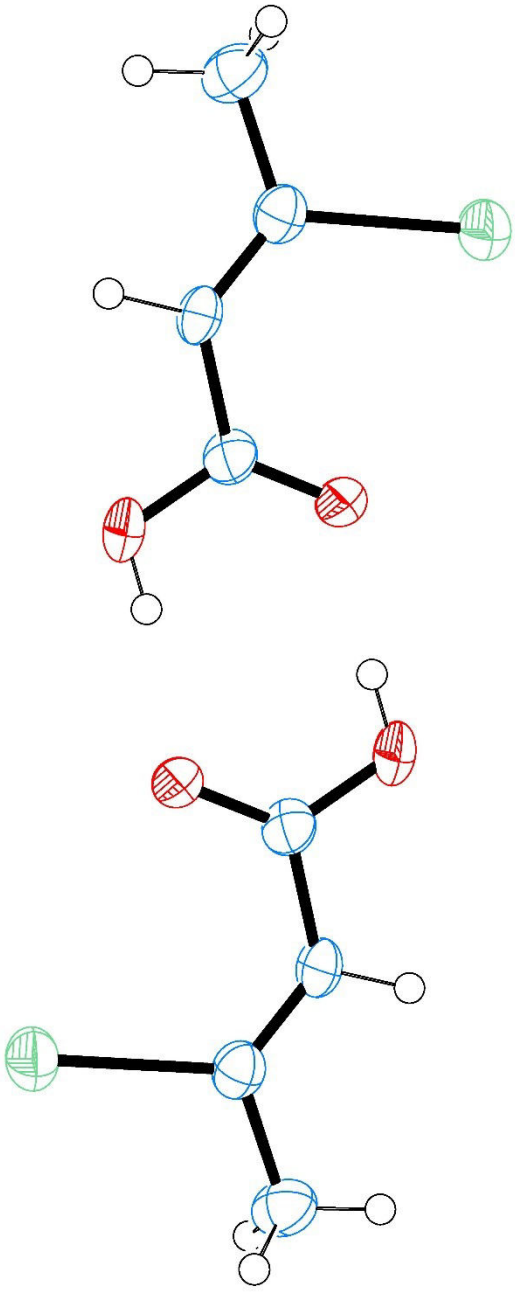
Crystallographic data were collected at 190K on an Oxford Diffraction Gemini Ultra S CCD diffractometer employing graphite monochromated Mo-Kα radiation (0.71073 Å) in the range $2 < 2\theta < 50°$. Data reduction and empirical absorption corrections were performed with CrysAlisPro (Version 1.171.37.35, Agilent Technologies). The structure was solved using dual space methods with SHELXT[2], and refined by full-matrix least-squares analysis against $F^2$ with SHELXL-2014[3] within the WinGX package[4]. H-atoms bound to carbon were included at estimated positions using a riding model, with the torsion angle of the methyl group allowed to refine freely. The $U_{iso}$(H) of the methyl group were constrained to 1.5 times $U_{eq}$ of the parent carbon atom, while $U_{iso}$(H) of the alkene was constrained to 1.2 times $U_{eq}$ of its parent carbon atom. The H-atom of the carboxyl group was located from a difference map, and its coordinates were refined using distance and common plane restraints. $U_{iso}$(H) of the carboxyl group was constrained to 1.5 times that of the parent oxygen atom. Drawings of the molecule were produced with ORTEP-3 (Windows version 2013.1). The structure was deposited with the Cambridge Crystallographic Data Centre (CCDC number 1521107). The crystal data are summarized in the following table:

| | |
|---|---|
| Empirical formula | C4 H5 I O2 |
| Formula weight | 211.98 |
| Temperature | 190(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Monoclinic |
| Space group | P 21/c |
| Unit cell dimensions | a = 7.1646(6) Å |
| | b = 5.8851(4) Å |
| | c = 14.5753(14) Å |
| Volume | 613.69(9) Å$^3$ |
| Z | 4 |
| Density (calculated) | 2.294 Mg/m$^3$ |
| Absorption coefficient | 5.113 mm$^{-1}$ |
| F(000) | 392 |
| Crystal size | 0.4000 x 0.1000 x 0.1000 mm$^3$ |
| Theta range for data collection | 3.735 to 29.280°. |
| Index ranges | -8<=h<=9, -7<=k<=4, -17<=l<=19 |
| Reflections collected | 2796 |
| Independent reflections | 1426 [R(int) = 0.0396] |
| Completeness to theta = 25.242° | 99.8 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 1.00000 and 0.65331 |
| Refinement method | Full-matrix least-squares on F$^2$ |
| Data / restraints / parameters | 1426 / 2 / 68 |
| Goodness-of-fit on F$^2$ | 1.030 |
| Final R indices [I>2sigma(I)] | R1 = 0.0461, wR2 = 0.0772 |
| R indices (all data) | R1 = 0.0782, wR2 = 0.0967 |
| Extinction coefficient | n/a |
| Largest diff. peak and hole | 0.767 and -0.927 e.Å$^{-3}$ |
| CCDC number | 1521107 |

ORTEP illustrations appear on the following pages.



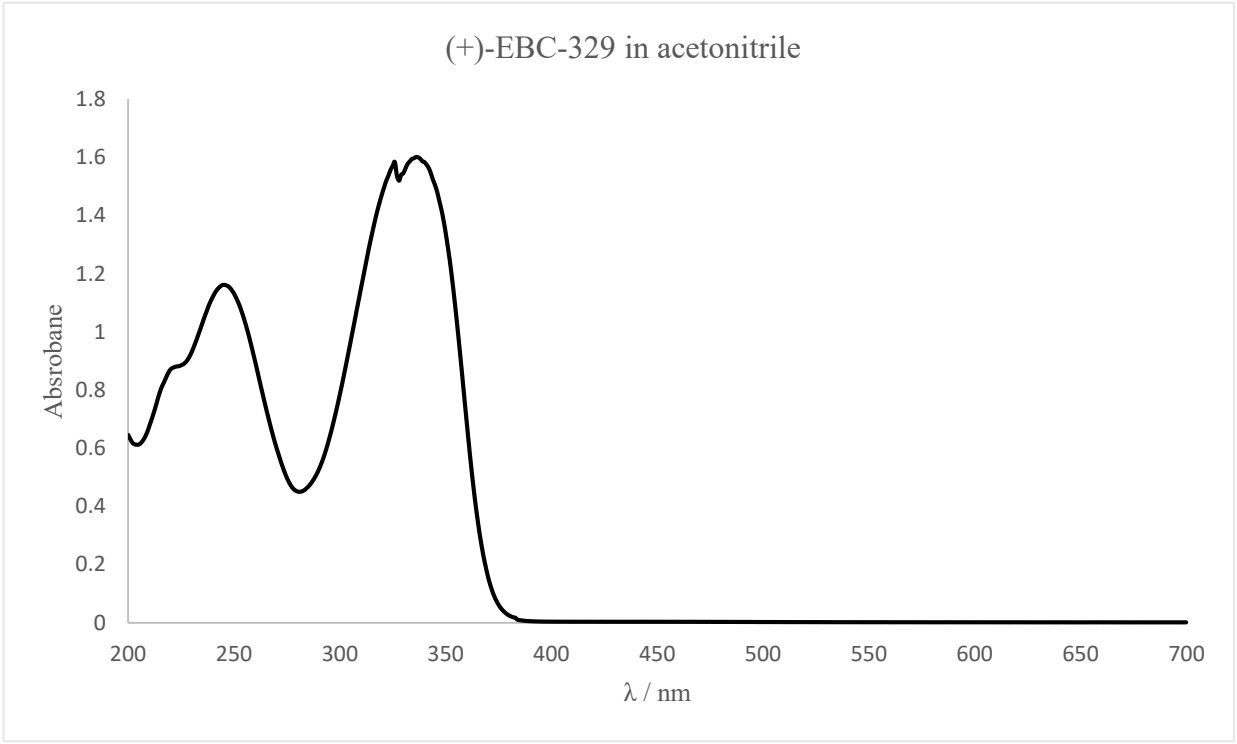

ORTEP illustration of (Z)-3-iodobut-2-enoic acid (**16**). Anisotropic displacement elipsoids display 50% probability levels.

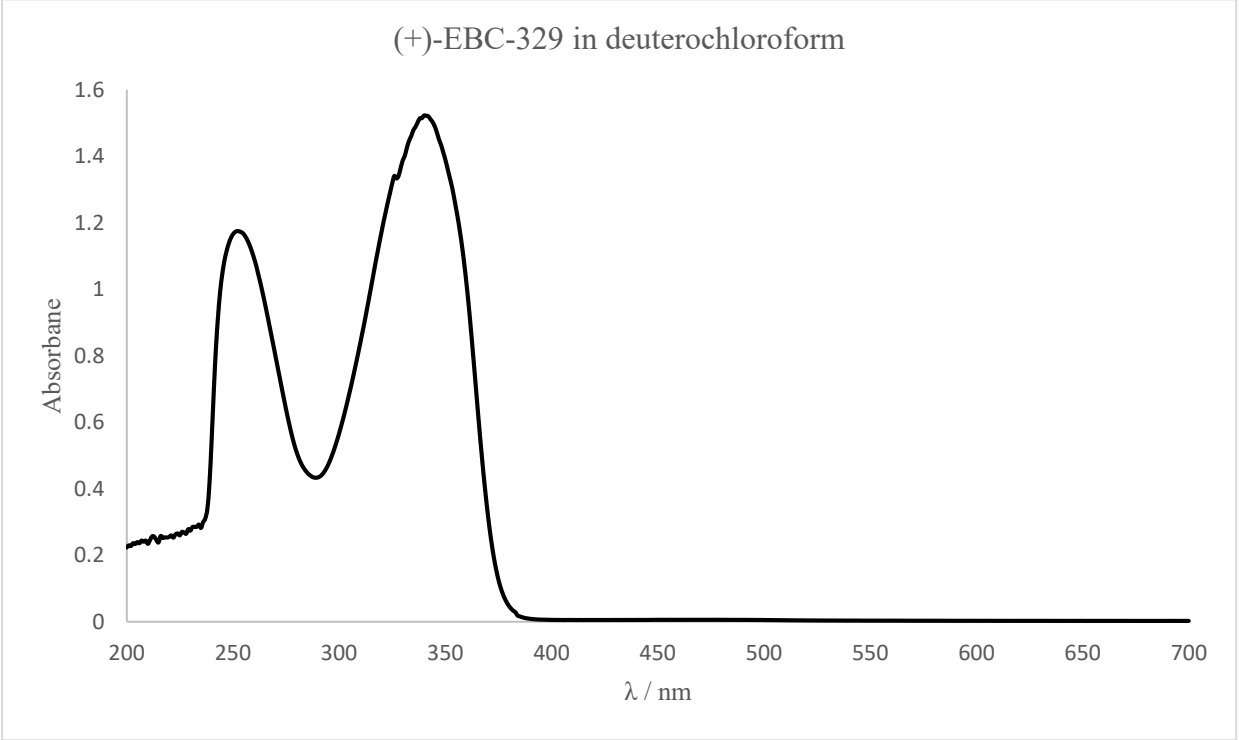


ORTEP illustration of the hydrogen-bonding present in crystals of compound **16**. Anisotropic displacement elipsoids display 50% probability levels.

**Ultraviolet-visible spectroscopy of synthetic (+)-EBC-329 (6)**

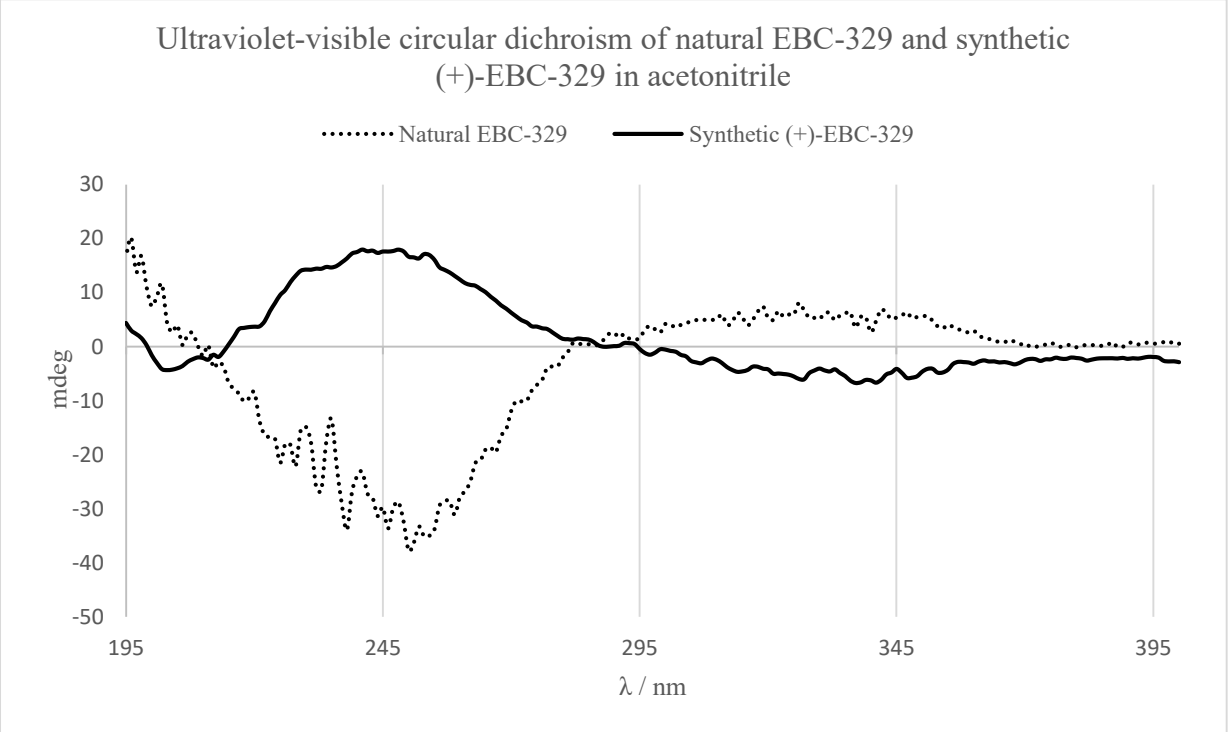
Ultraviolet-visible spectroscopy was performed at 20 °C on a Perkin-Elmer Lambda-35 instrument using quartz cuvettes (1 cm path length, 0.15 mM). Both acquisitions were performed with bandwidth and data intervals set to 1 nm, a scan rate of 480 nm per minute, and a single accumulation lasting 1 second.



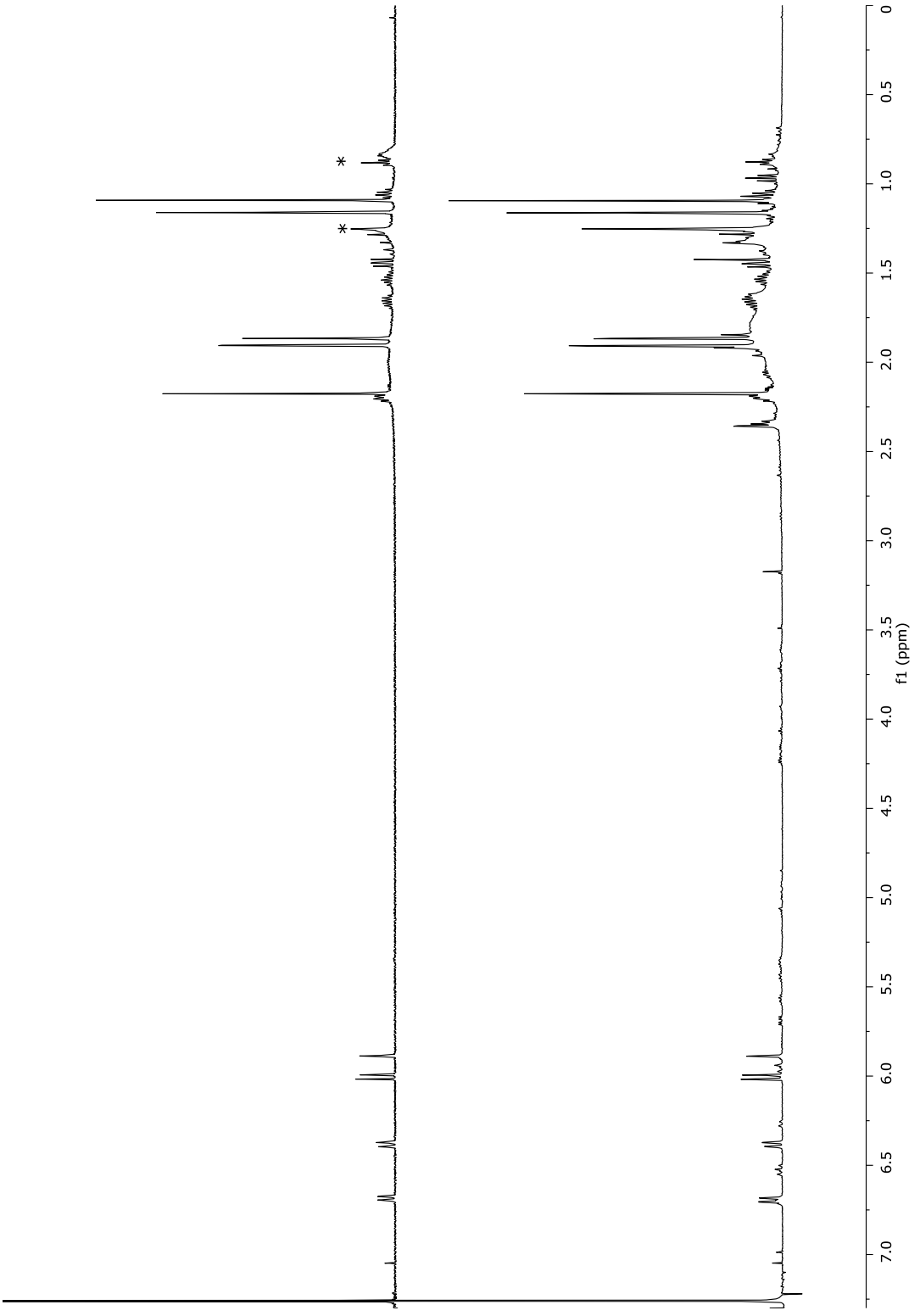
**Ultraviolet-visible circular dichroism spectroscopy of natural (-) and synthetic (+)-EBC-329 (6)**

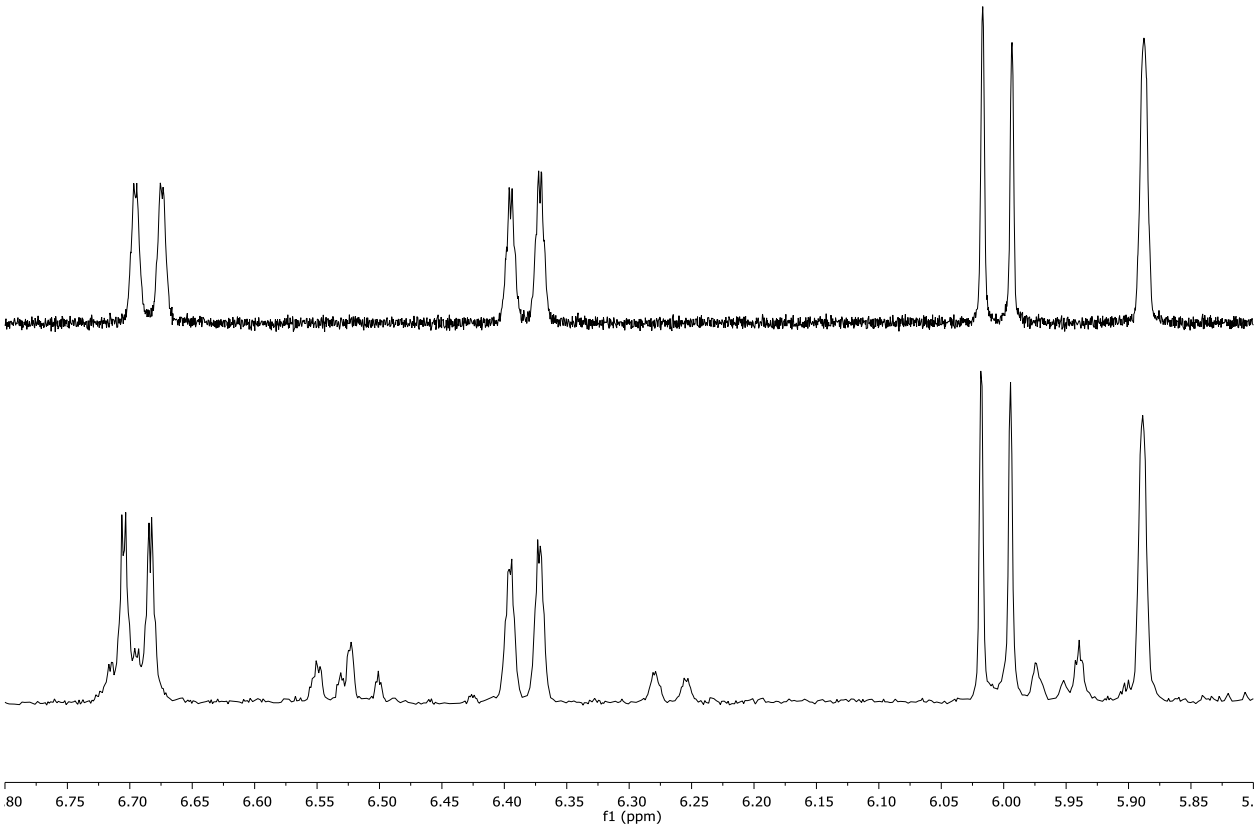
Ultraviolet-visible circular dichroism spectroscopy was performed in acetonitrile at 20 °C on a Jasco J-715 instrument using quartz cuvettes (0.1 cm path length). The natural sample was analysed at a concentration of 0.5 mg $mL^{-1}$; the synthetic sample was analysed at a concentration of 0.25 mg $mL^{-1}$ (0.75 mM). Both spectra were acquired using two accumulations. The spectrum of the natural material was acquired with a 2 nm bandwidth using a 50 nm $min^{-1}$ scan rate. The spectrum of the synthetic material was acquired with a 1 nm bandwidth using a 200 nm $min^{-1}$ scan rate.

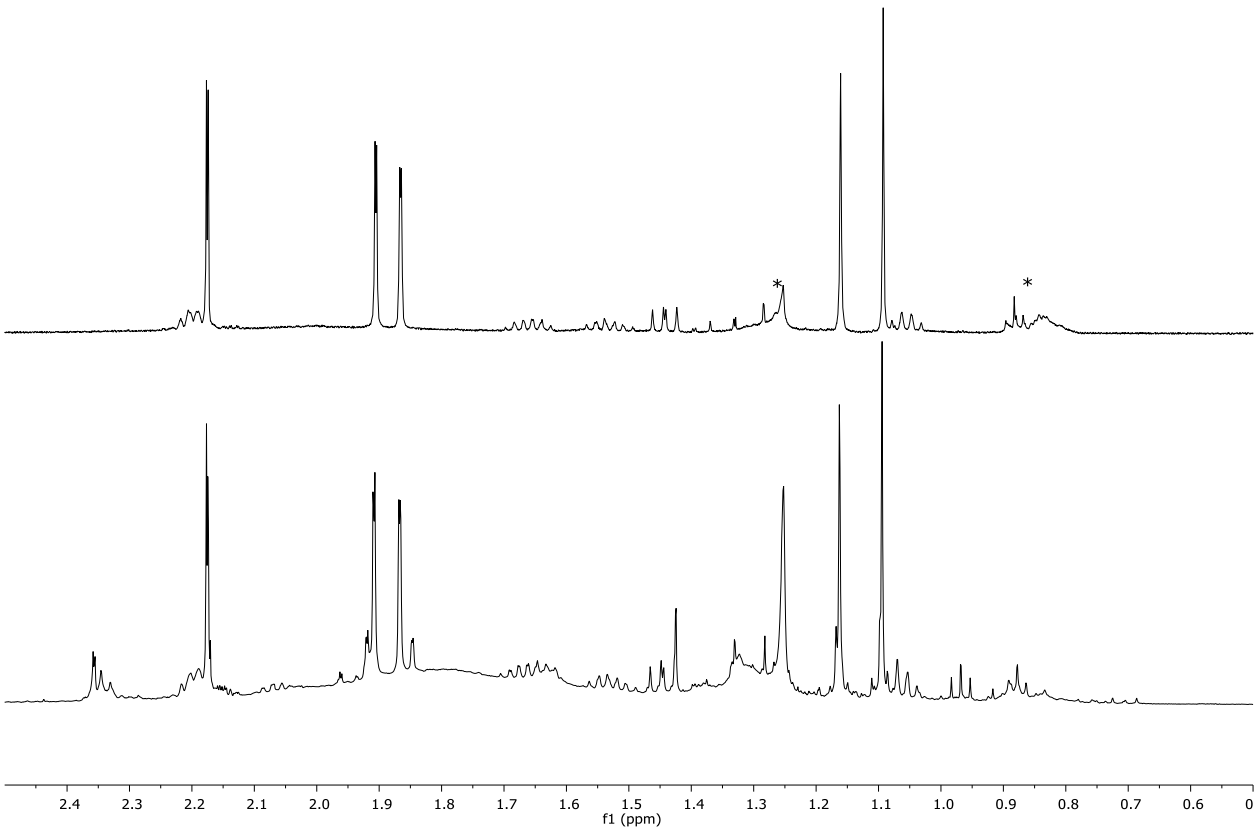


**$^{1}$H NMR comparison between natural and synthetic EBC-329**

In all of the following figures, the $^{1}$H NMR spectrum of synthetic EBC-329 appears on top of the stack. The $^{1}$H NMR spectrum of natural EBC-329 was originally reported by Maslovskaya *et al* in 2014[6].

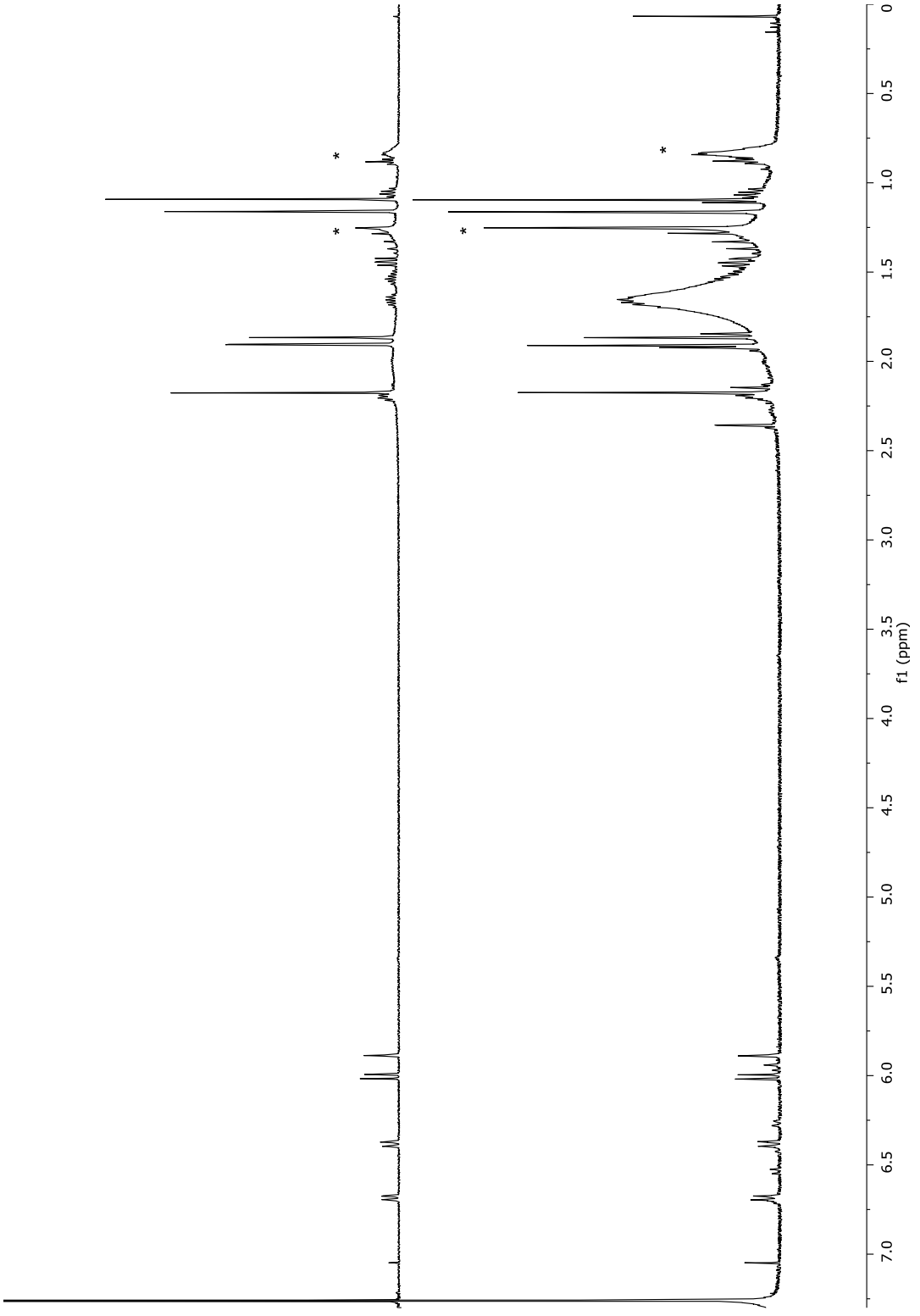


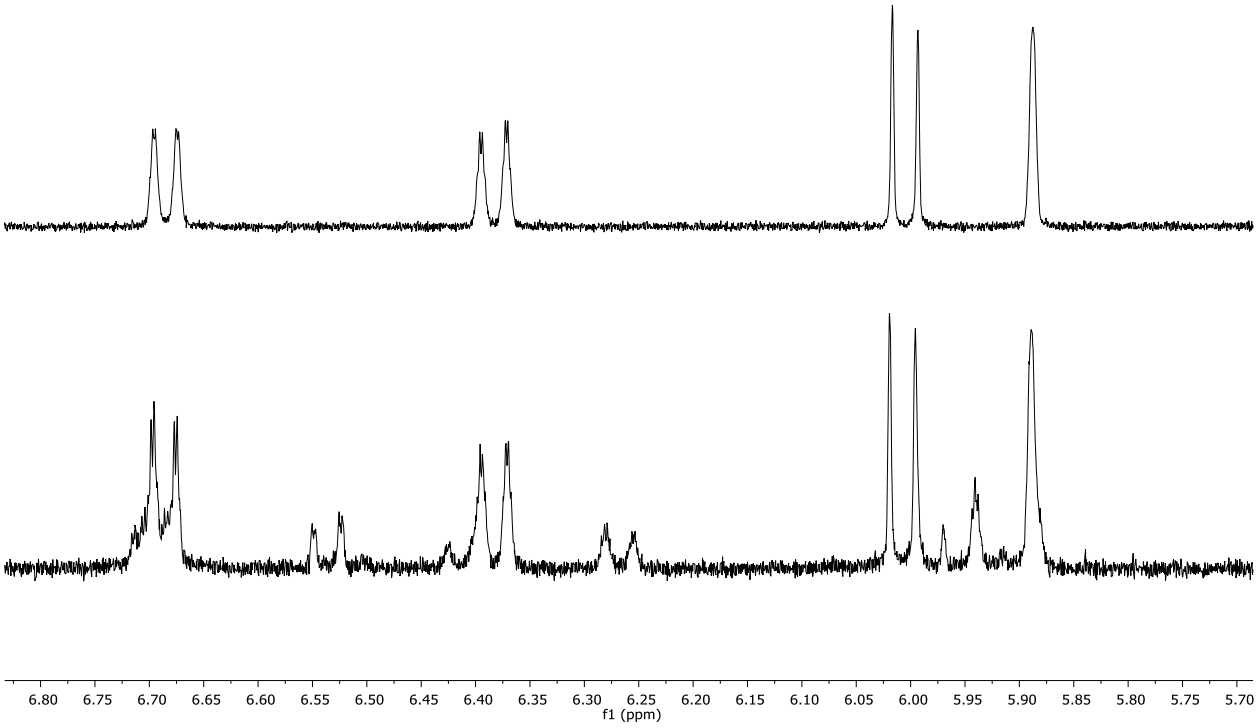

80 6.75 6.70 6.65 6.60 6.55 6.50 6.45 6.40 6.35 6.30 6.25 6.20 6.15 6.10 6.05 6.00 5.95 5.90 5.85 5.
f1 (ppm)

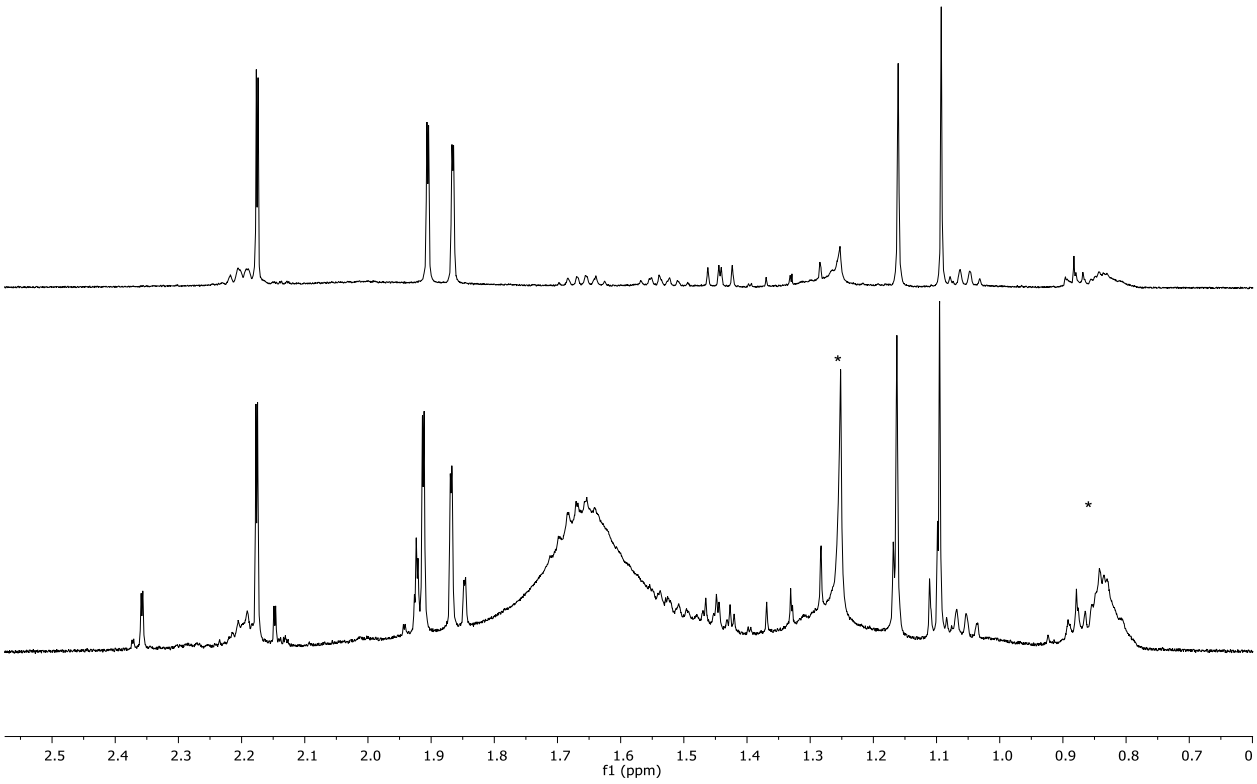

*
*
2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9 0.8 0.7 0.6 0
f1 (ppm)

**Photoisomerisation of (+)-EBC-329 in deuterochloroform**

A sample of (+)-EBC-329 in deuterochloroform was divided between two NMR tubes. One sample was subjected to continuous irradiation from normal fluorescent lighting in a fumehood, while the other sample was kept in the dark. No change was observed in the dark. A comparison between the $^{1}$H NMR spectrum of the irradiated sample (acquired after 60 hours) and the pre-irradiation material appear below. Note that the presence of water in the irradiated sample obscures the resonances of the diastereotpic methylene protons immediately adjacent to the cyclopropyl unit.

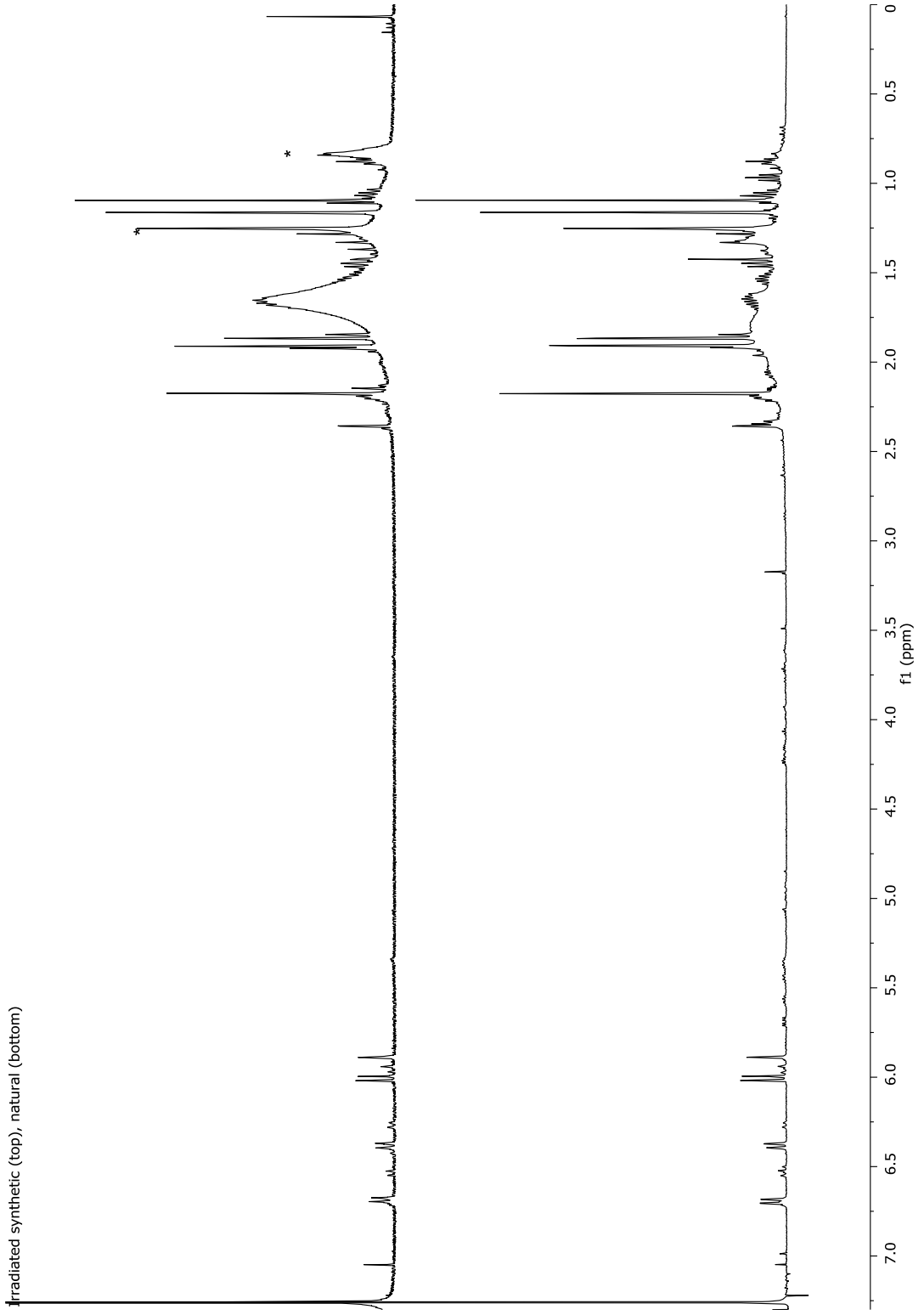



6.80 6.75 6.70 6.65 6.60 6.55 6.50 6.45 6.40 6.35 6.30 6.25 6.20 6.15 6.10 6.05 6.00 5.95 5.90 5.85 5.80 5.75 5.70
f1 (ppm)

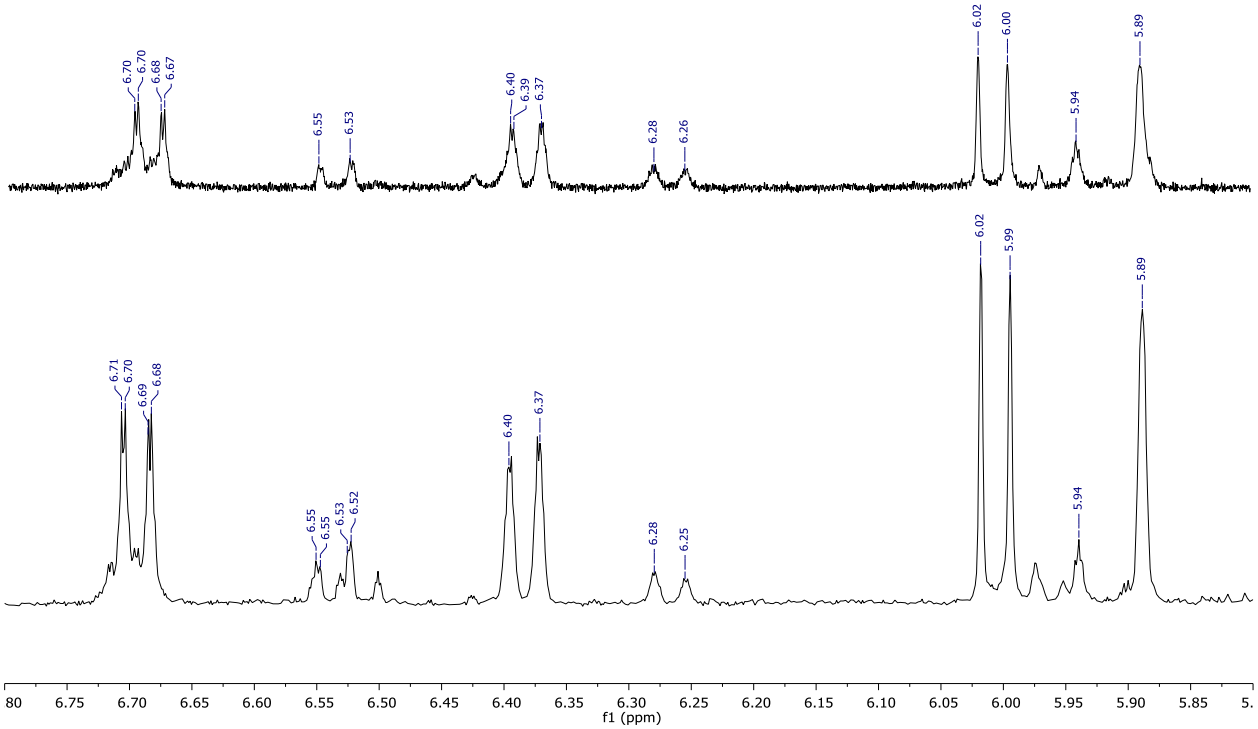

*
*
2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9 0.8 0.7 0
f1 (ppm)

**Comparison between irradiated synthetic (+)-EBC-329 and isolated natural material**

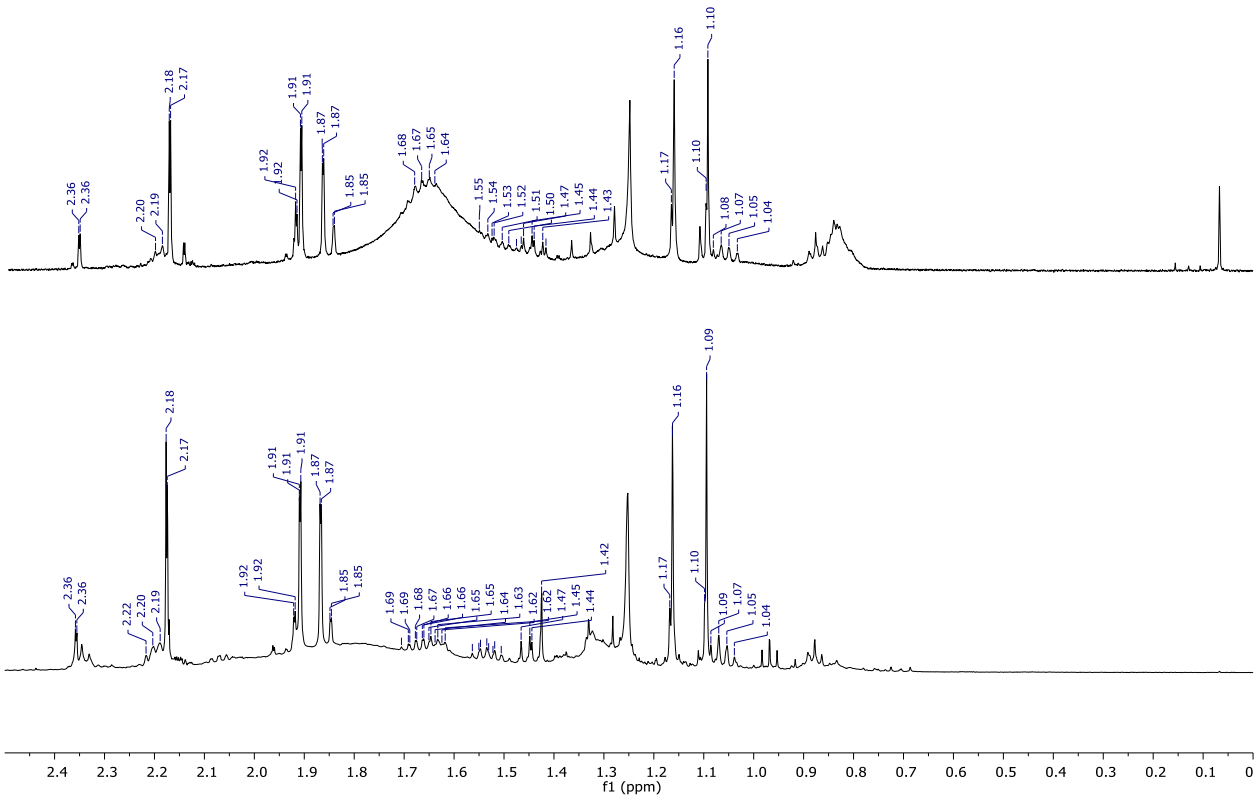
The following stacked plots compare the $^{1}$H NMR spectra of the isolated natural EBC-329 sample and synthetic (+)-EBC-329 following 60 hours of irradiation in deuterochloroform. The spectrum of the natural material was originally reported by Maslovskaya *et al* in 2014[6]. Note: that the presence of water in the irradiated sample obscures the resonances of the diastereotpic methylene protons immediately adjacent to the cyclopropyl unit.



Irradiated synthetic (top), natural (bottom)

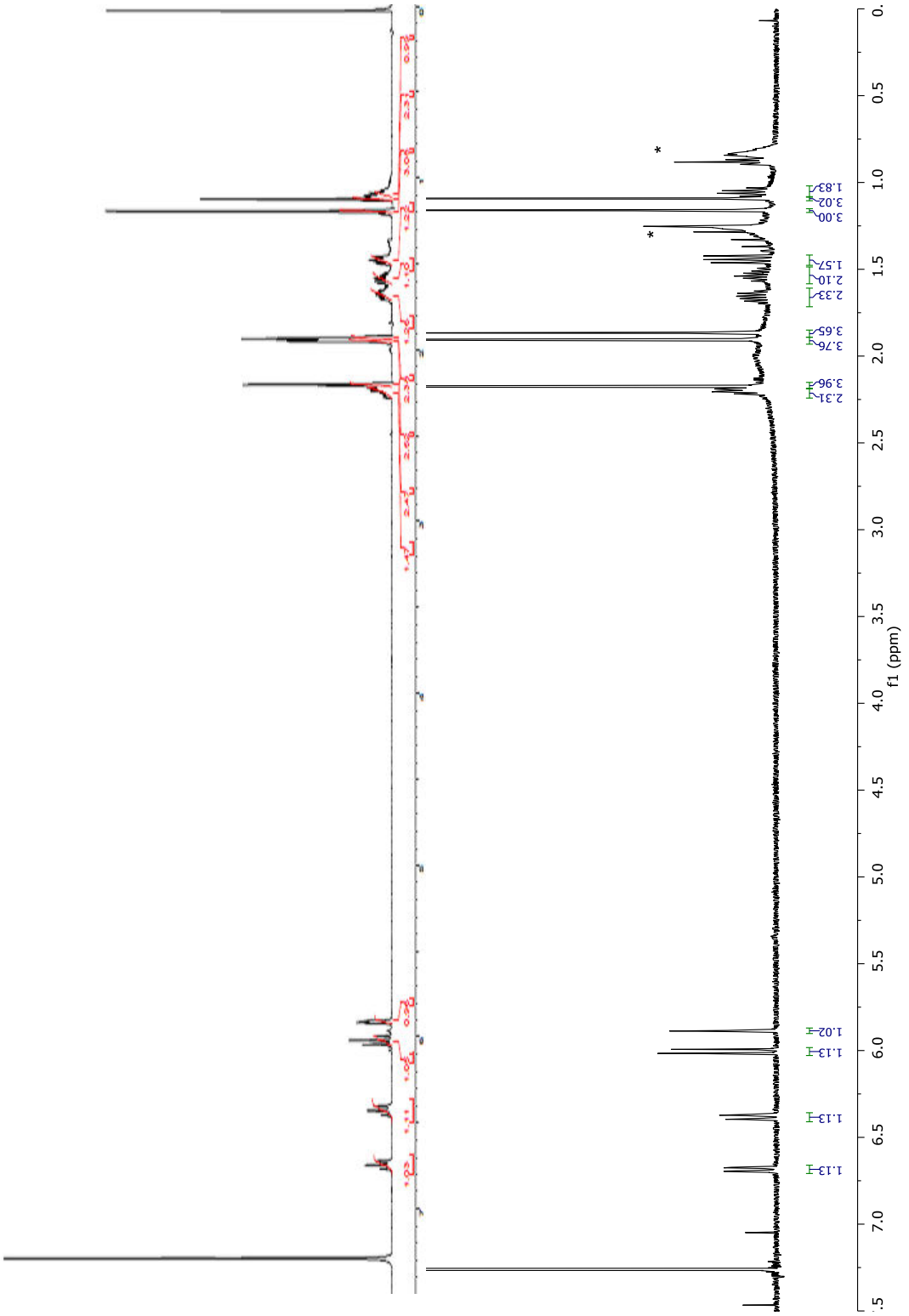


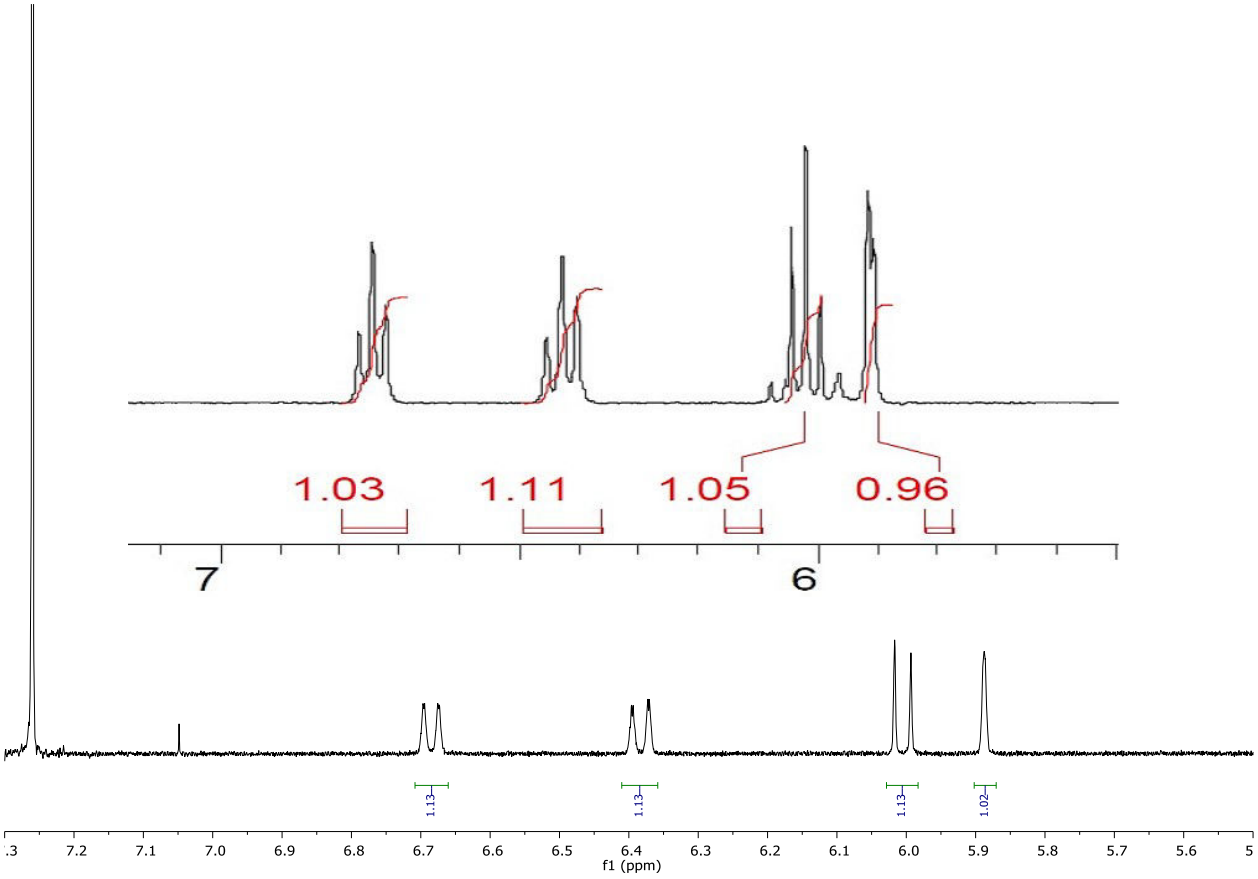

Irradiated synthetic (top), natural (bottom)

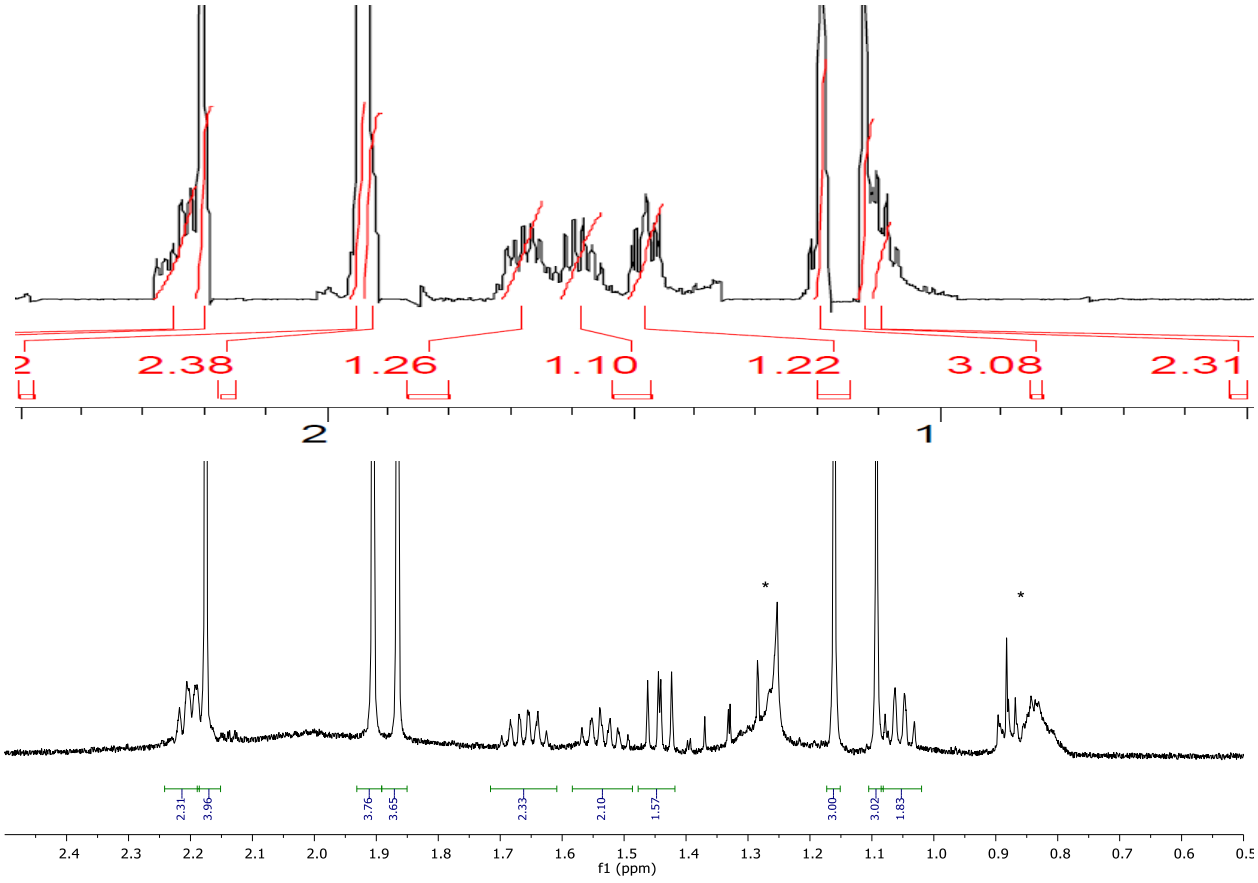


**Comparison between synthetic (+)-EBC-329 and racemic material prepared by Jadhav *et al***

The following figures present $^{1}$H NMR comparisons between synthetic (+)-EBC-329 prepared in the present work to that of synthetic (±)-EBC-329 reported by Jadhav *et al*[7]. In all the following figures, the synthetic (+)-EBC-329 from the present work appears at the bottom of the stack. Asterisks in the synthetic $^{1}$H NMR from the present work indicate minor contaminants.

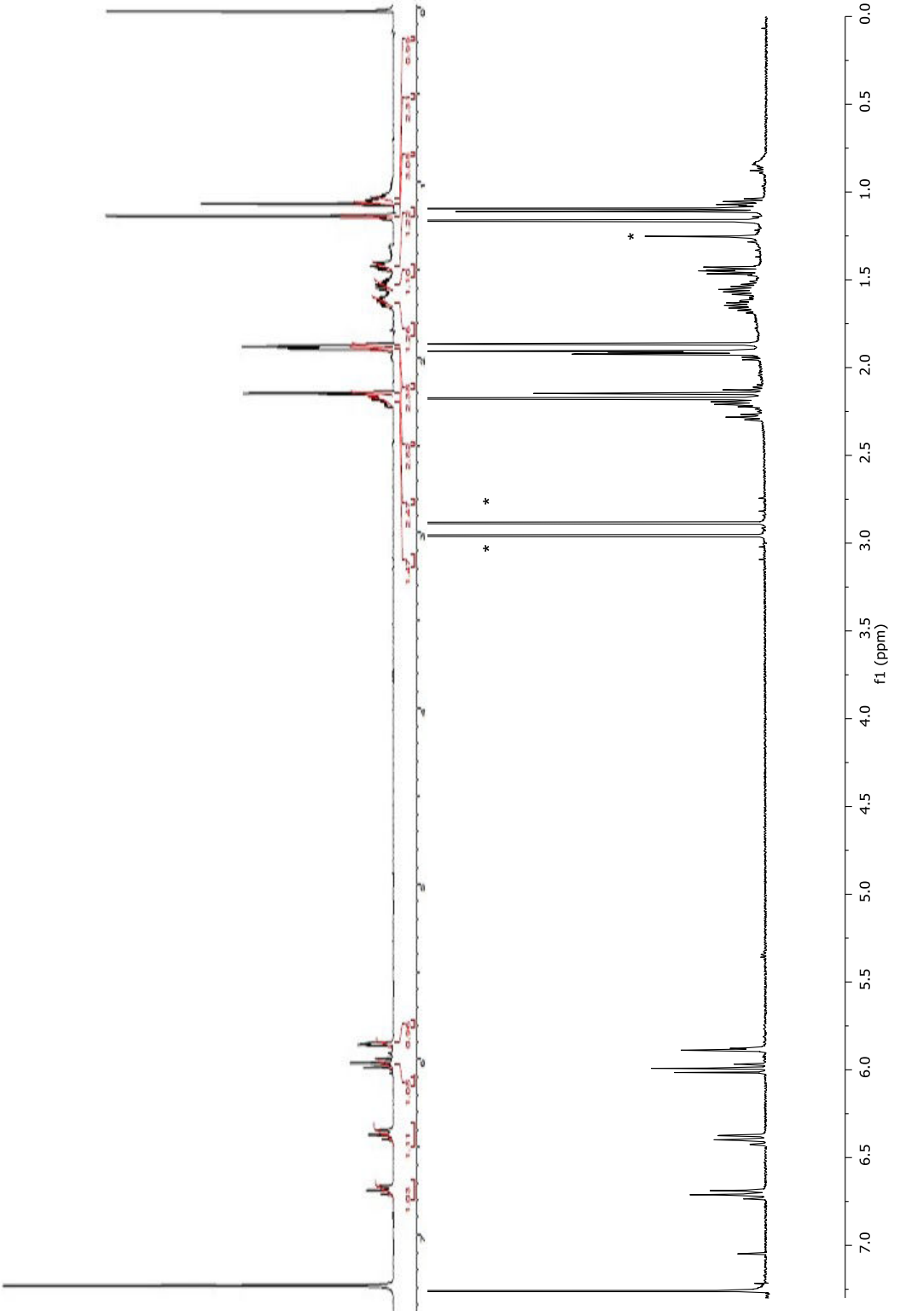


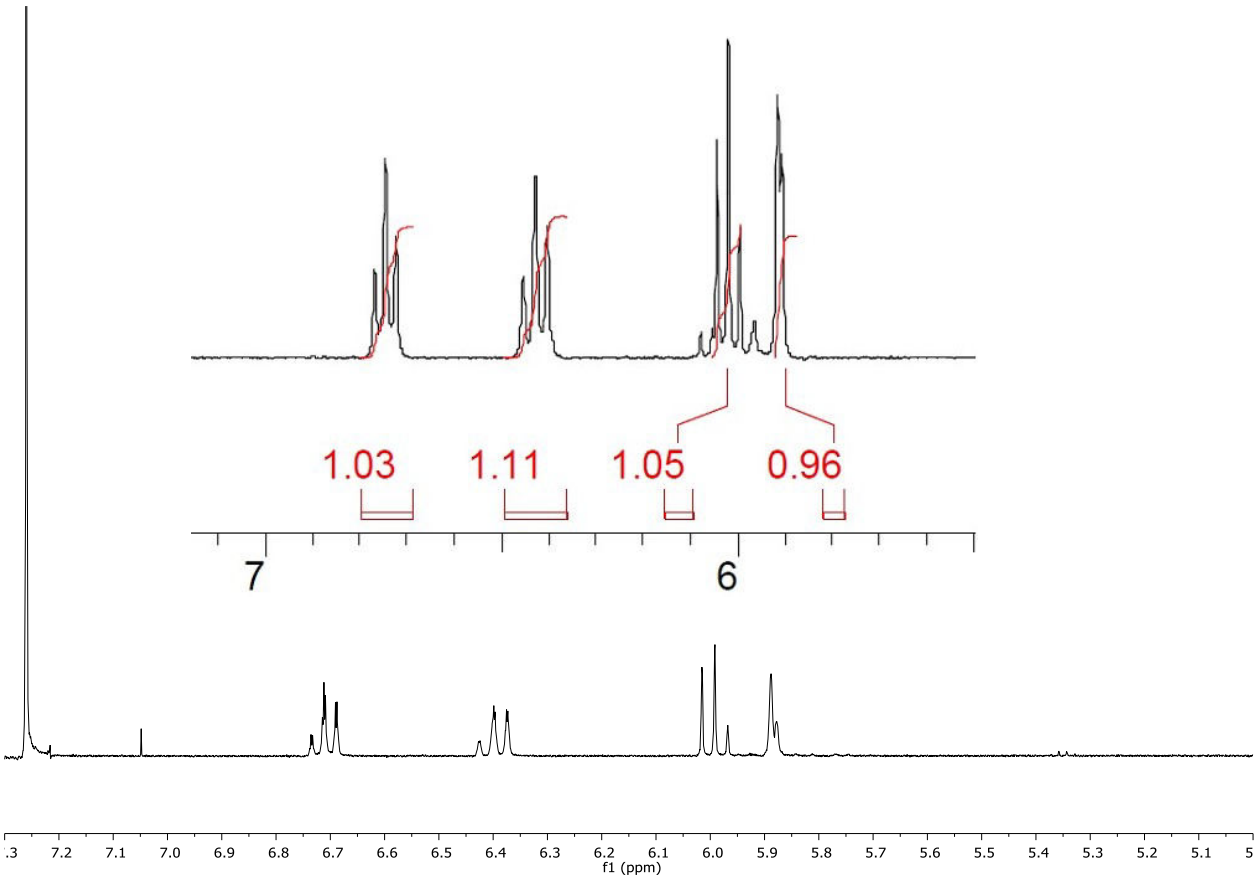

1.03
1.11
1.05
0.96
7
6
1.13
1.13
1.13
1.02
f1 (ppm)

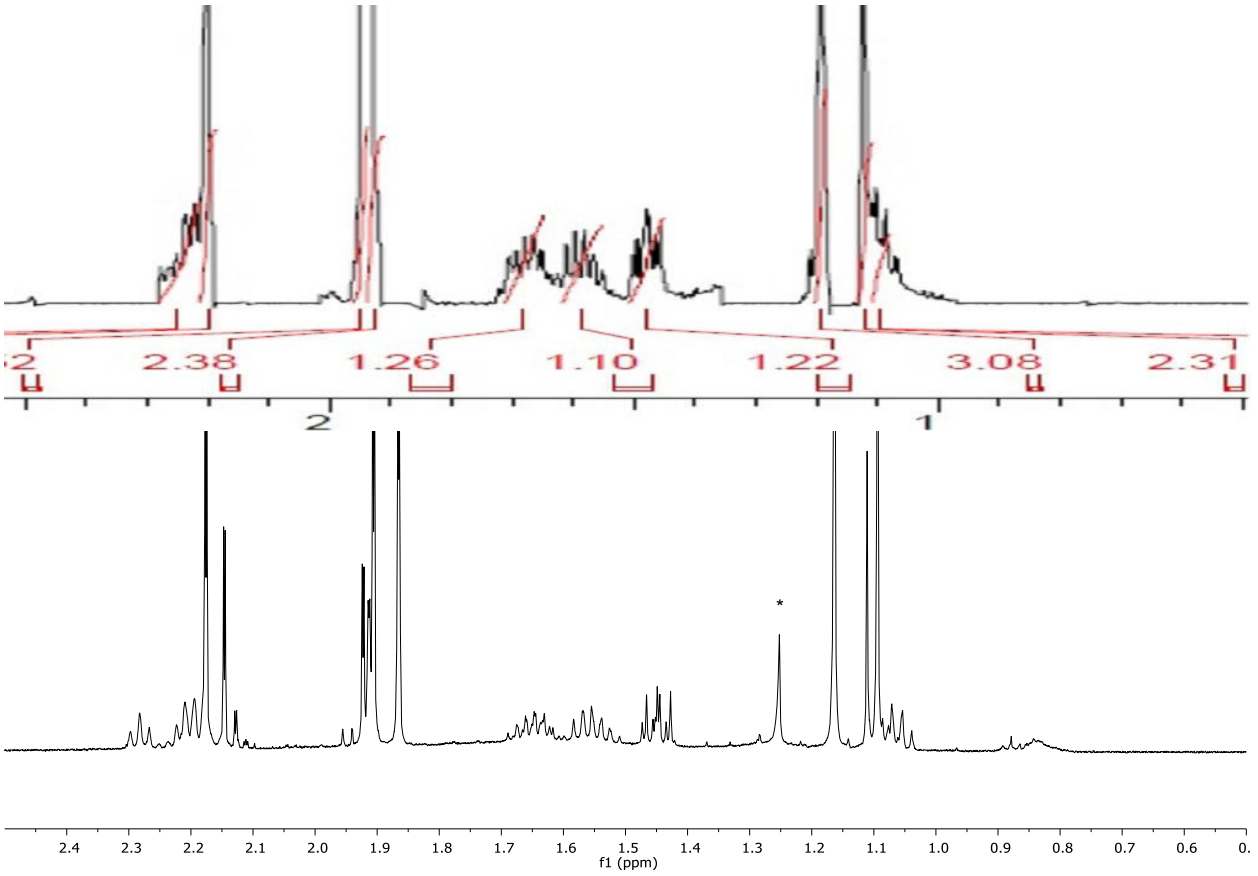

2.38
1.26
1.10
1.22
3.08
2.31
2
1
*
*
2.31
3.96
3.76
3.65
2.33
2.10
1.57
3.00
3.02
1.83
f1 (ppm)

**Comparison between a mixture of synthetic (+)-EBC-329 / 12*Z*-EBC-329, and the synthetic material prepared by Jadhav *et al***

The following figures present $^{1}$H NMR comparisons between the (+)-EBC-329 / 12Z-EBC-329 mixture prepared in the present work to that of EBC-329 reported by Jadhav *et al*[7]. In all the following figures, the $^{1}$H NMR for the (+)-EBC-329 / 12*Z*-EBC-329 mixture appears on the bottom of each stack. Asterisks in the $^{1}$H NMR for the (+)-EBC-329 / 12*Z*-EBC-329 denote signals from minor contaminants, and *N*,*N*-dimethylformamide as a major contaminant.




1.03
1.11
1.05
0.96
7
6
f1 (ppm)


2.38
1.26
1.10
1.22
3.08
2.31
2
1
*
f1 (ppm)

**Tabulated comparison of the different NMR data reported for EBC-329**

The following table presents the NMR data for natural EBC-329[6], the synthetic EBC-329 prepared in the current work, and the synthetic EBC-329 reported by Jadhav *et al*[7]. Entries highlighted in yellow are in significant disagreement with the natural product.

| **Position** | **Natural EBC-329**[6] | | **This work** | | **Jadhav *et al*[7]** | |
|---|---|---|---|---|---|---|
| | $^{1}$H (δ ppm, *J* Hz) | $^{13}$C (δ ppm) | $^{1}$H (δ ppm, *J* Hz) | $^{13}$C (δ ppm) | $^{1}$H (δ ppm, *J* Hz) | $^{13}$C (δ ppm) |
| 1 | - | 148.68 | - | 148.8 | - | 148.62 |
| 2 | - | 154.37 | - | 154.6 | - | 154.32 |
| 3 | 5.87, 1H (br. s) | 115.38 | 5.89, 1H (br. s) | 115.5 | 5.87, 1H (br. s) | 115.34 |
| 4 | - | 169.36 | - | 169.7 | - | 169.44 |
| 5 | - | 171.83 | - | *Below detection threshold* | - | 172.02 |
| 6 | - | 126.68 | - | 127.0 | - | 126.60 |
| 7 | 6.69, 1H (dd, 10.6, 1.2) | 143.37 | 6.69, 1H (d, 10.7) | 143.0 | 6.71, 1H (t, 11.6) | 143.48 |
| 8 | 1.43, 1H (m) | 28.05 | 1.44, 1H (dd, 10.7, 8.7) | 28.1 | 1.42-1.46, 1H (m) | 28.02 |
| 9 | 1.05, 1H (m) | 33.56 | 1.02 – 1.09, 1H (m) | 33.6 | 1.05-1.07, 1H (m) | 33.56 |
| 10a | 1.54, 1H (dd, 14.6, 6.5) | 23.90 | 1.53, 1H (m) | 24.2 | 1.51-1.59, 1H (m) | 23.88 |
| 10b | 1.62, 1H (dt ,14.6, 7.1) | - | 1.66, 1H (m) | - | 1.61-1.68, 1H (m) | See above |
| 11 | 2.15-2.21. 2H (m) | 40.50 | 2.19 – 2.24, 2H (m) | 40.7 | 2.18-2.24, 1H (m) | 40.48 |
| 12 | - | 146.91 | - | 147.3 | - | 147.00 |
| 13 | 6.37, 1H (dd, 11.7, 1.0) | 118.78 | 6.38, 1H (dd, 11.8, 1.4) | 118.9 | 6.41, 1H (t, 11.9) | 118.73 |
| 14 | 5.98, 1H (d, 11.7) | 107.28 | 6.00, 1H (dd, 11.7, 0.6) | 107.6 | 5.98, 1H (t, 11.9) | 107.34 |
| 15 | - | 25.15 | - | 25.2 | - | 25.19 |
| 16 | 1.08, 3H (s) | 15.78 | 1.09, 3H (s) | 15.9 | 1.09, 3H (s) | 15.78 |
| 17 | 1.14, 3H (s) | 29.13 | 1.16, 3H (s) | 29.3 | 1.16, 3H (s) | 29.11 |
| 18 | 1.88, 3H (d, 1.2) | 12.24 | 1.91, 3H (d, 1.4) | 12.5 | 1.90, 3H (d, 1.2) | 12.25 |
| 19 | 2.16, 3H (d, 1.0) | 11.65 | 2.18, 3H (d, 1.3) | 11.8 | 2.16, 3H (d, 1.2) | 11.66 |
| 20 | 1.84, 3H (s) | 17.30 | 1.87, 3H (d, 1.3) | 17.5 | 1.89, 3H (br. s) | 17.30 |

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