Supplementary Material

Enantioselective synthesis of a new styryl lactone 9-deoxygoniopypyrone derivative and its antiproliferative activity

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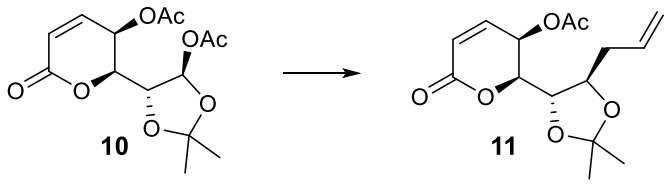
General Information

Dichloromethane (CH_2Cl_2) was freshly distilled over CaH_2 before use. Tetrahydrofuran (THF) was newly distilled over sodium/benzophenone before use. Thin Layer Chromatography (TLC) was performed on aluminum plates pre-coated with silica gel (MERCK, $60F_{254}$), which were visualized by UV fluorescence (λ_{max} 254 nm) and/or by staining with 10% w/v $(NH_4)_2MoO_4$ in 1.8M aqueous H_2SO_4; or 1% v/v *p*-anisaldehyde in EtOH/AcOH/H_2SO_4 (85:10:5). Nuclear Magnetic Resonance (NMR) spectra were acquired on a BRUKER 500 spectrometer 500 MHz for ^1H and 125 MHz for ^{13}C, respectively. Unequivocal ^1H and ^{13}C assignments were made using two-dimensional HH-COSY and CH-HSQC experiments. All ^1H NMR spectra are reported in parts per million (ppm) downfield of TMS and were measured relative to the signals at 7.26 ppm ($CDCl_3$), All ^{13}C NMR spectra were reported in ppm relative to 77.16 ppm ($CDCl_3$) and were obtained with ^1H-decoupling. Data for ^1H NMR are described as follows: chemical shift (δ in ppm), multiplicity (σ, singlet; d, doublet; t, triplet; m, multiple; br, broad signal), coupling constant *J* (Hz), integration. Data for ^{13}C NMR spectra are described in terms of chemical shift (δ in ppm).

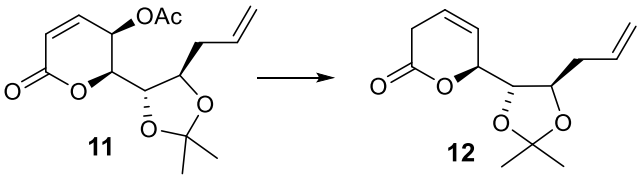
Experimental procedure and analytical data

(2*S*,3*R*)-2-[(4*S*,5*R*)-5-Allyl-2,2-dimethyl-1,3-dioxolan-4-yl]-6-oxo-3,6-dihydro-2*H*-pyran-3-yl acetate (11).



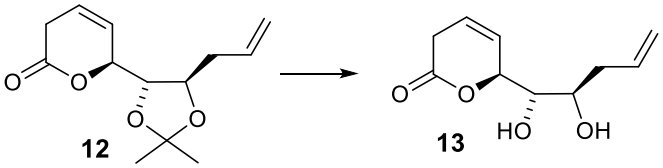
To a stirred solution of diacetoxylated **10** (1.0 g, 3.2 mmol) in anhydrous CH_2Cl_2 (12 mL), allyltrimethylsilane (1.01 mL, 6.4 mmol) was added, the mixture was cooled to -40 °C, then $BF_3{\cdot}OEt_2$ (0.79 mL, 6.4 mmol) was added dropwise, after 10 min the reaction mixture was stirred at room temperature for 1.5 h. Finally, it was neutralized with $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude reaction was purified by flash chromatography (EtOAc/Hexane, 2:8), obtaining the allylated **11**, (0.8 g, 85%) as a colorless oil: R_f 0.64 (Hexane/EtOAc, 1:1); FT-IR (cm^{-1}) □: 3057, 2992, 1740, 1375, 1265, 1224; $[\alpha]_D^{22}$ -99.2° (*c* 1.0, $CHCl_3$); HRMS-FAB (*m/z*): $[M+1]^+$ calculated to $C_{15}H_{20}O_6$ 297.1338 found 297.1332; ^1H NMR (500 MHz, $CDCl_3$): δ_H 6.85 (dd, *J* 10.0, 5.0, 1H), 6.20 (dd, *J* 9.5, 0.5, 1H), 5.88-5.79 (m, 1H), 5.54-5.52 (m, 1H), 5.16-5.12 (m, 1H), 4.24 (dt, *J* 12.0, 6.0, 2.0, 1H), 3.96 (dd, *J* 8.5, 3.5, 1H), 2.37 (t, *J* 6.3, 6.1, 2H), 2.10 (s, 3H), 1.39 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 170.1, 162.0, 140.1, 133.1, 124.6, 118.2, 109.7, 78.1, 75.9, 75.4, 62.4, 37.0, 27.2, 26.6, 20.7.

(*S*)-6-[(4*S*,5*R*)-5-Allyl-2,2-dimethyl-1,3-dioxolan-4-yl]-3,6-dihydro-2*H*-pyran-2-one (12).



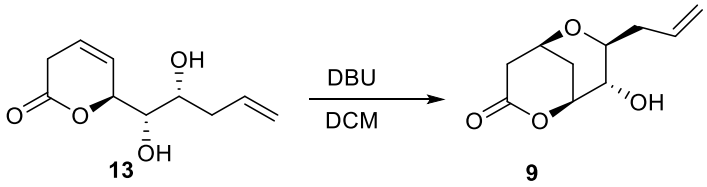
To a stirred solution of the allylated **11** (0.7 g, 2.2 mmol) in THF (10 mL) was added Zn powder (0.77 g, 11.82 mmol), followed by a supersaturated solution of NH_4Cl (10 mL) and the mixture was allowed to stir for 1 h. In the end, the solids were decanted, and the phases were separated by extractions with EtOAc (3 × 5 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude reaction mixture was purified by flash chromatography (Hexane/EtOAc, 4:1) obtaining the deacetoxylated compound **12** (0.51 g, 90%) as a colorless oil: R_f 0.65 (Hexane/EtOAc, 1:1); FT-IR (cm^{-1}) v: 3327, 2856, 1720, 1644, 1528, 1452, 1377; $[\alpha]_D^{22}$ -44.43 (*c* 1.0, $CHCl_3$), FAB-HRMS: $[M+1]^+$ *m/z* calculated to $C_{13}H_{18}O_4$ 239.1287, found 239.1283; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 5.92-5.88 (m, 1H), 5.84-5.77 (m, 2H), 5.13-5.07 (m, 2H), 4.87 (s, 1H), 4.25 (dd, *J* 14.2, 6.2, 1H), 3.70 (d, *J* 8.4, 1H), 3.02-3.12 (m, 2H), 2.36 (dtd, *J* 20.9, 14.1, 6.5, 2H), 1.34 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 168.8, 133.1, 123.5, 123.0, 118.1, 109.3, 81.7, 76.5, 74.4, 36.9, 30.4, 27.4, 26.2.

(*S*)-6-[(1*S*,2*R*)-1,2-Dihydroxypent-4-en-1-yl]-3,6-dihydro-2*H*-pyran-2-one (13).

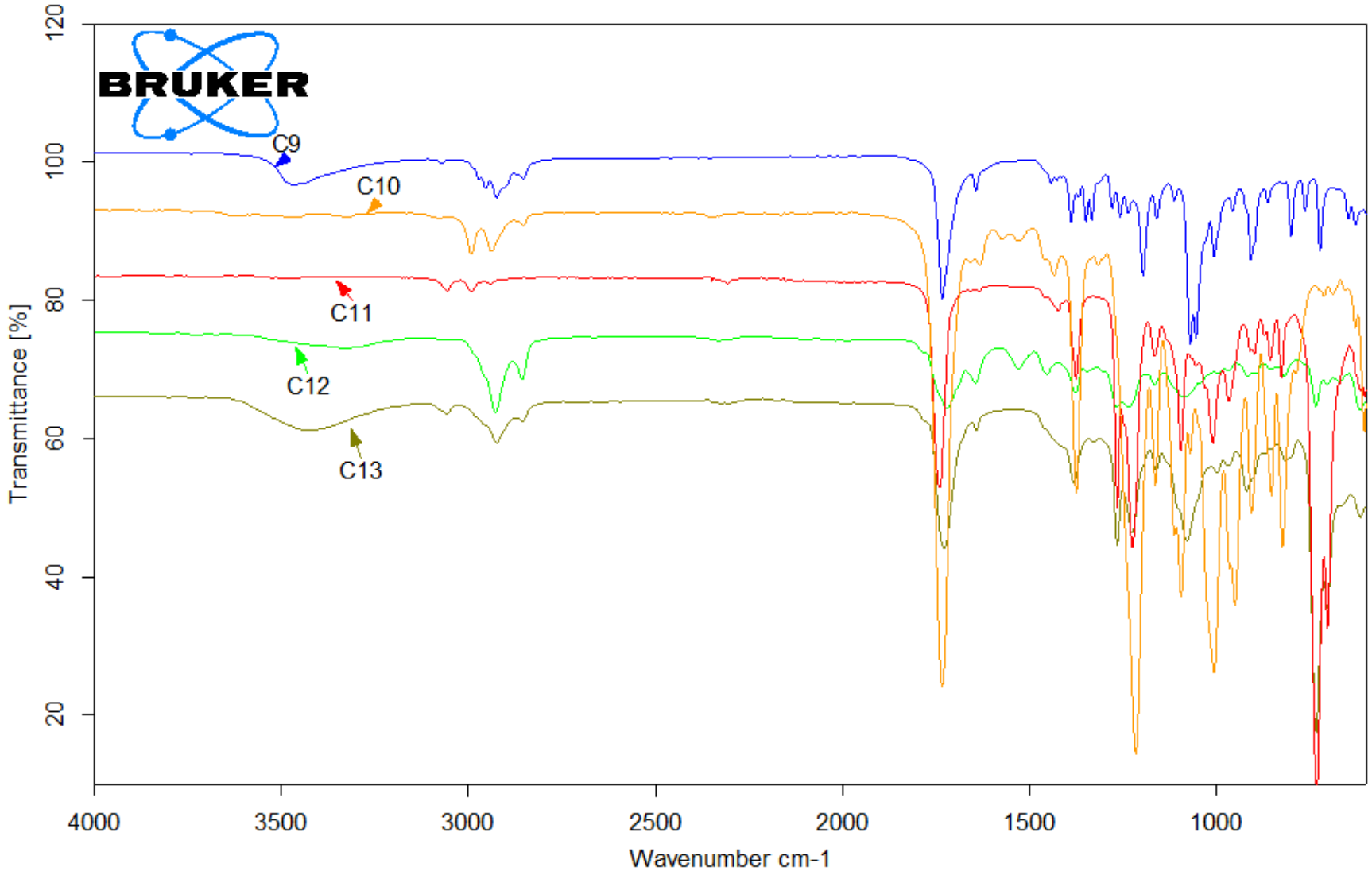


Trifluoroacetic acid (0.38 mL, 5 mmol) was added to a solution of **12** (0.3 g, 1.25 mmol) in dichloromethane (4 mL). The mixture was kept stirring at room temperature for 2 h. The reaction was treated with a saturated $NaHCO_3$ solution until pH 7. The layers were separated, and the aqueous layer was extracted (EtOAc, 3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography (Hexanes/EtOAc, 7:3) of the raw product yielded **13** (207 mg, 83%) as a colorless oil as the only isolable product: R_f 0.15 (Hexane/EtOAc, 1:2 ratio); FT-IR (cm^{-1}) v: 3418, 3057, 2924, 1728, 1642, 1381, 1365, 1225; $[\alpha]_D^{20}$ -49.3 (*c* 1.0, $CHCl_3$). FAB-HRMS: $[M+1]^+$ *m/z* calculated to $C_{10}H_{14}O_4$ 199.0985, found 199.0970; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 5.98-5.88 (m, 1H), 5.84 (ddd, *J* 10.5, 5.2, 3.2, 2H), 5.17-5.12 (m, 2H), 5.05 (s, 1H), 3.87 (dt, *J* 5.35, 5.2, 4.9 1H), 3.57 (dd, *J* 3.5, 3.6, 1H), 3.14 (dd, *J* 48.6, 22.0, 2H), 2.31-2.43 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 169.7, 133.9, 123.3, 123.0, 118.2, 81.1, 74.7, 70.4, 38.1, 30.1.

(1*S*,5*S*,7*S*,8*S*)-7-Allyl-8-hydroxy-2,6-dioxabicyclo[3.3.1]nonan-3-one (9).



To a solution of **13** (0.3 g, 1.51 mmol) in anhydrous dichloromethane (4 mL), the temperature was lowered to 0 °C, and DBU (0.537 mL, 3.6 mmol) was added slowly. After stirring for 8 h, the mixture was neutralized with a 10% HCl solution. The layers were separated, and the aqueous layer was extracted (EtOAc, 3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography of the residue (Hexanes/EtOAc, 7:3) yielded compound **9** (0.27 g, 90%) as a colorless crystals, which was the only isolable product: R_f 0.27 (Hexane/EtOAc, 1:2), mp: 93-94 °C; FT-IR (cm^{-1}) ν: 2925, 2854, 3469, 1733, 1642, 1388, 1348, 1333, 1195, 1070; $[\alpha]_D^{20}$ +40.3(*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 5.78 (ddt, *J* 11.7, 7.1, 4.1, 1H), 5.17 (dq, *J* 17.2, 3.3, 1.7, 1.65, 1H), 5.11 (dq, *J* 10.2, 3.2, 1.7, 1.4, 1H), 4.72-4.75 (m, 1H), 4.35-4.33 (m, 1H), 3.79-3.75 (m, 2H), 2.87 (dt, *J* 19.4, 2.1, 2.0, 1H), 2.81 (d, *J* 5.2, 1H), 2.77 (d, *J* 5.1, 1H), 2.73 (d, 6.5, 1H) 2.49 -2.32 (m, 3H), 1.79 (dd, *J* 14.2, 4.2, 4.1, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 169.8 (C-2), 133.4 (C-4′), 118.1 (C-5′), 75.1 (C-6), 68.0 (C-2′), 66.4 (C-1′), 65.8 (C-4), 36.4 (C-3), 35.3 (C-3′), 24.3 (C-5).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C10
C11
C12
C13
Transmittance [%]
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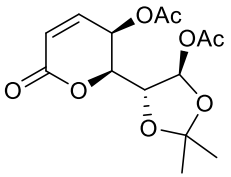
60
40
20
4000
3500
3000
2500
2000
1500
1000
Wavenumber cm-1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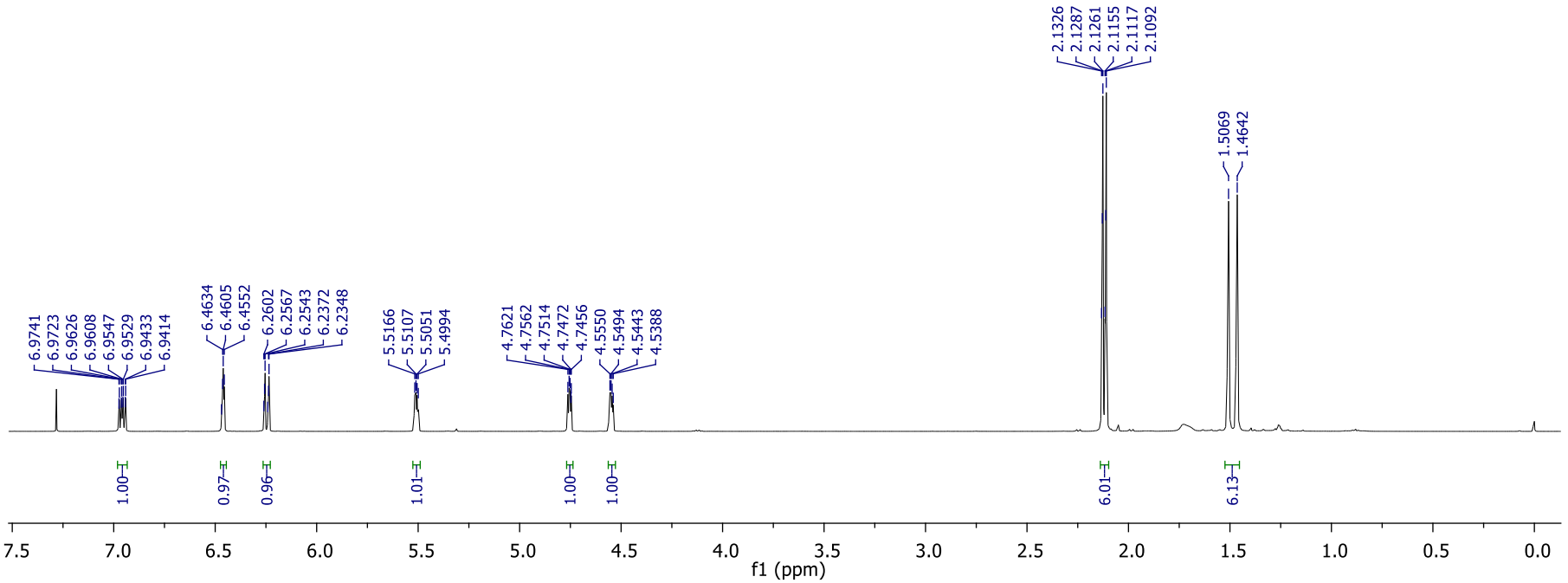
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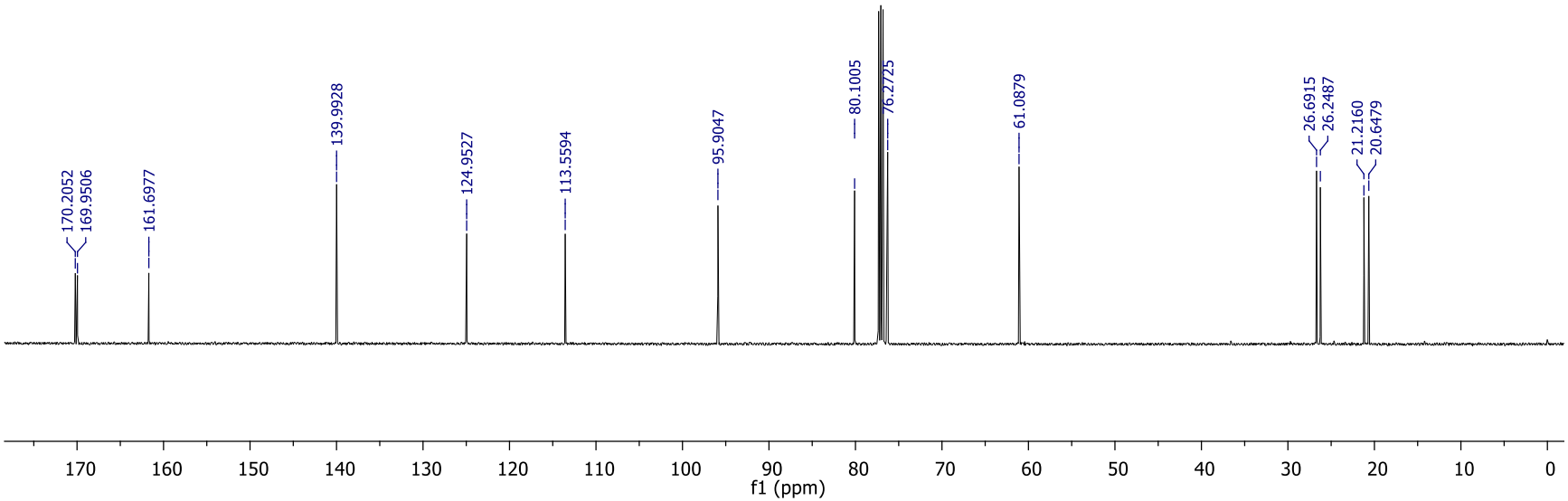
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20.6479
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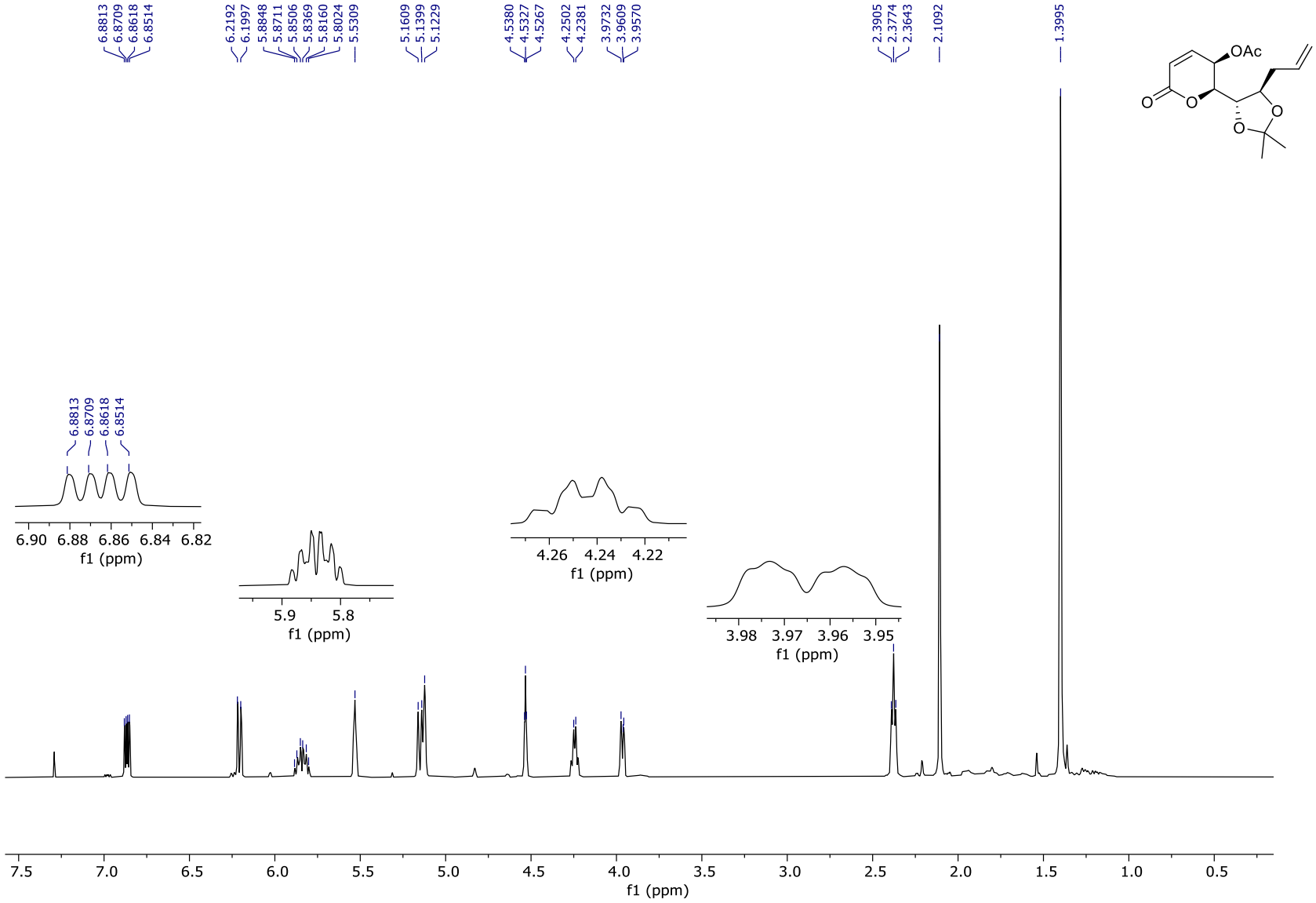
f1 (ppm)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f1 (ppm)
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f1 (ppm)
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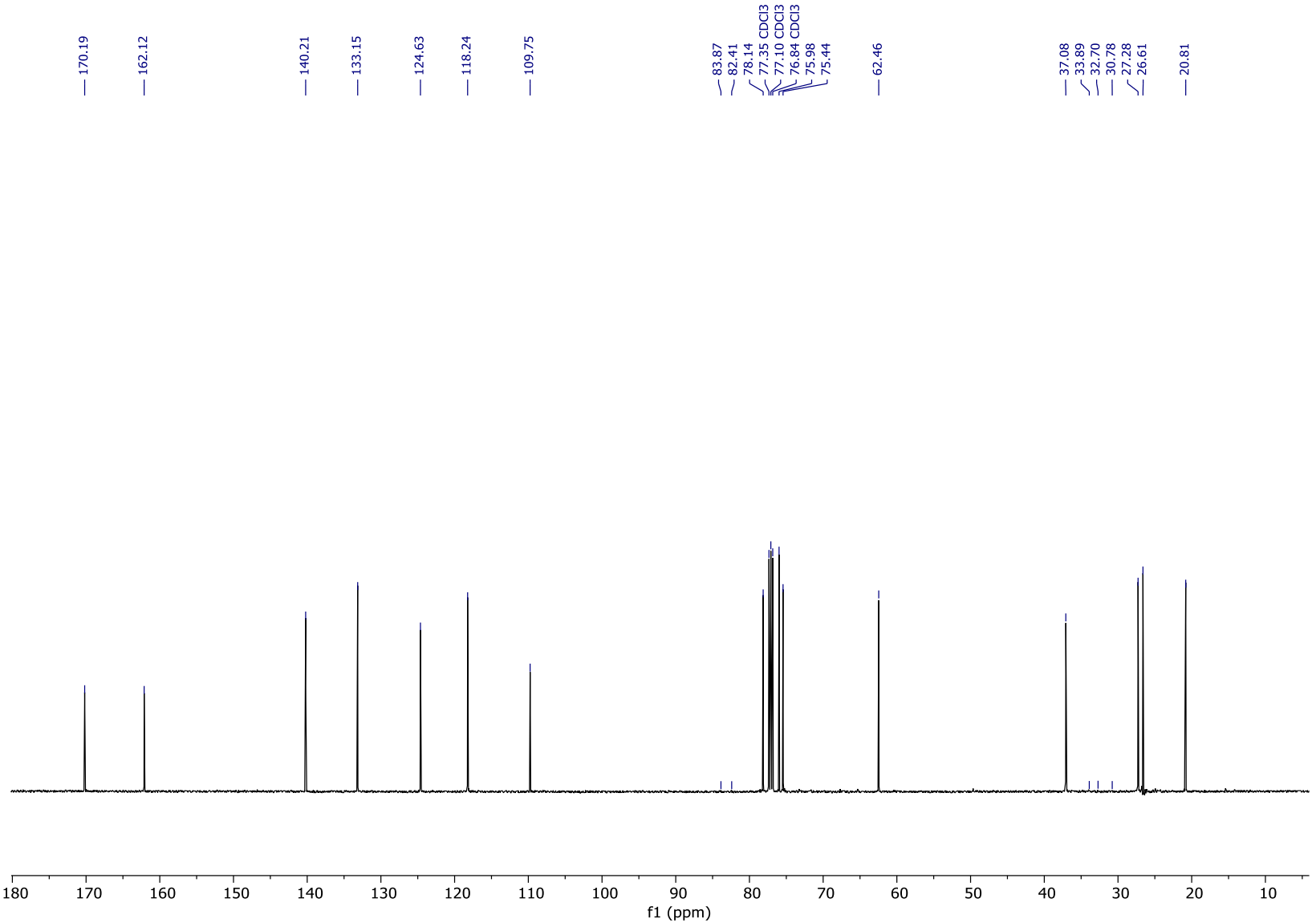
f1 (ppm)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30.78
27.28
26.61
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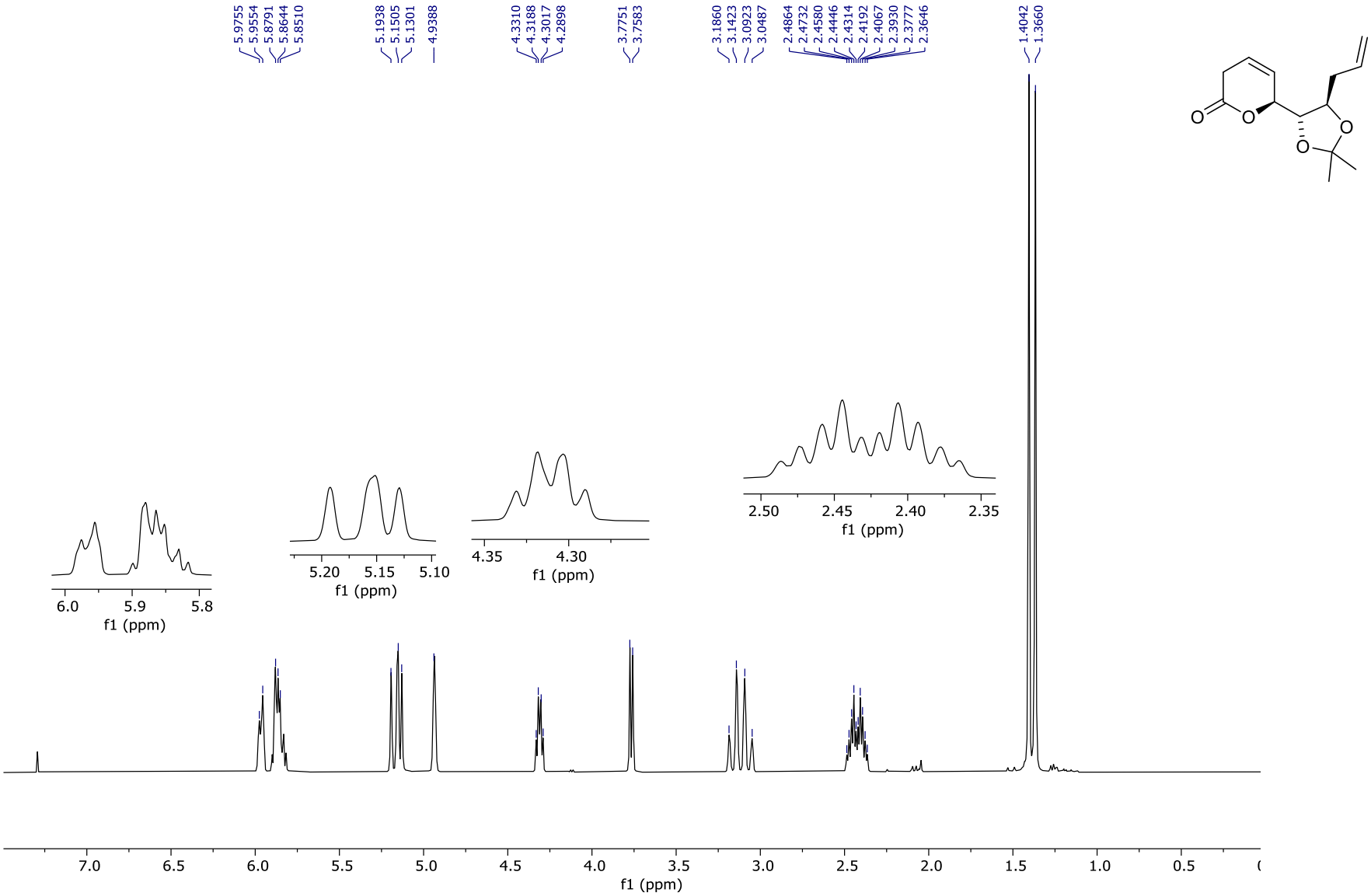
f1 (ppm)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f1 (ppm)
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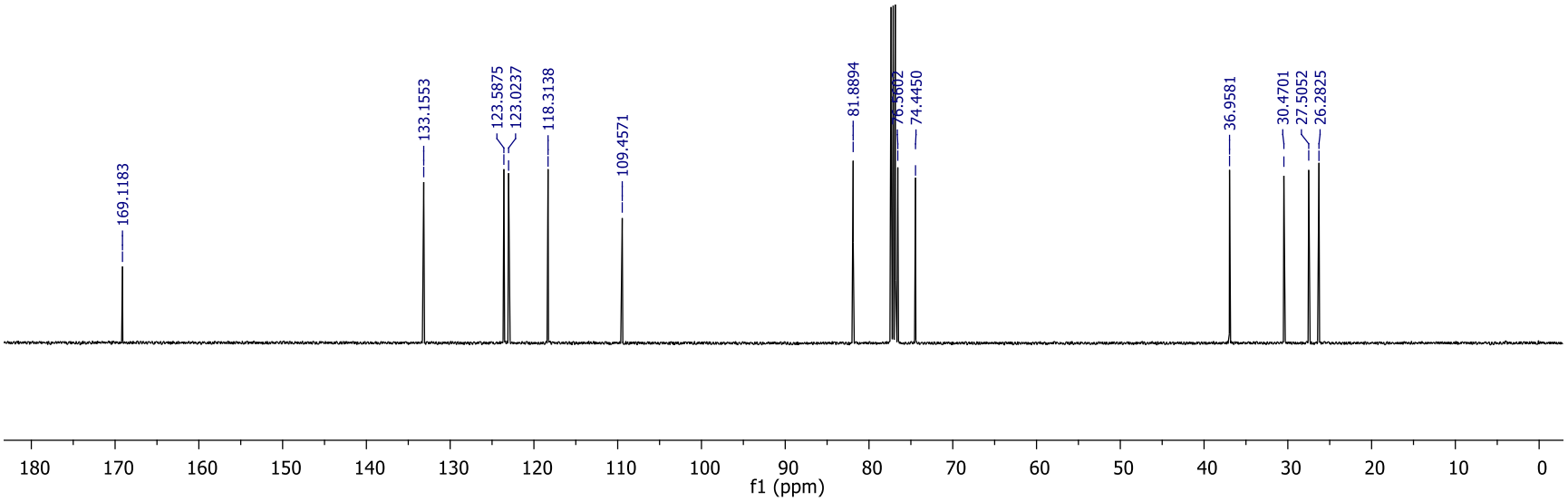
f1 (ppm)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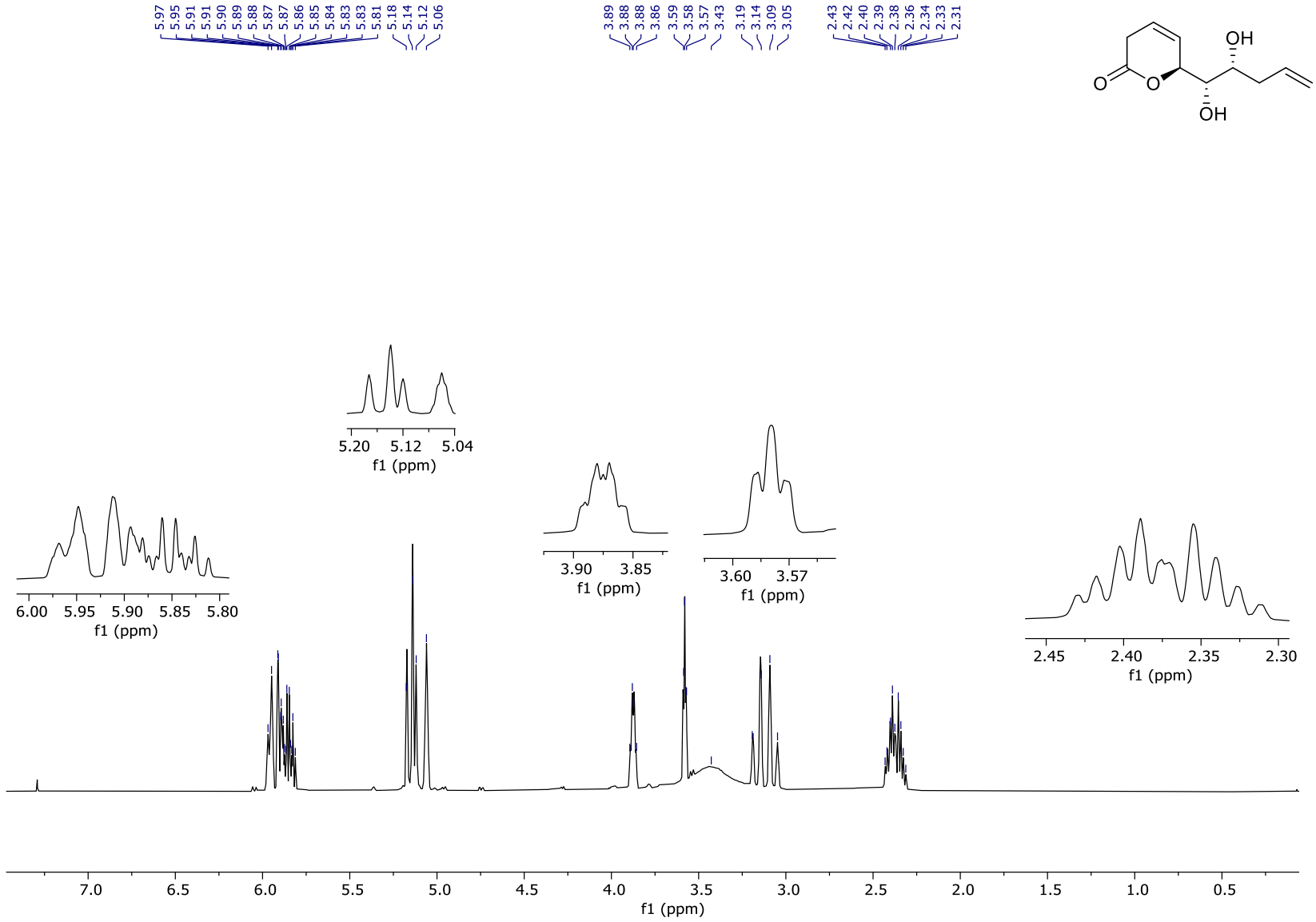
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OH
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f1 (ppm)
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f1 (ppm)
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f1 (ppm)
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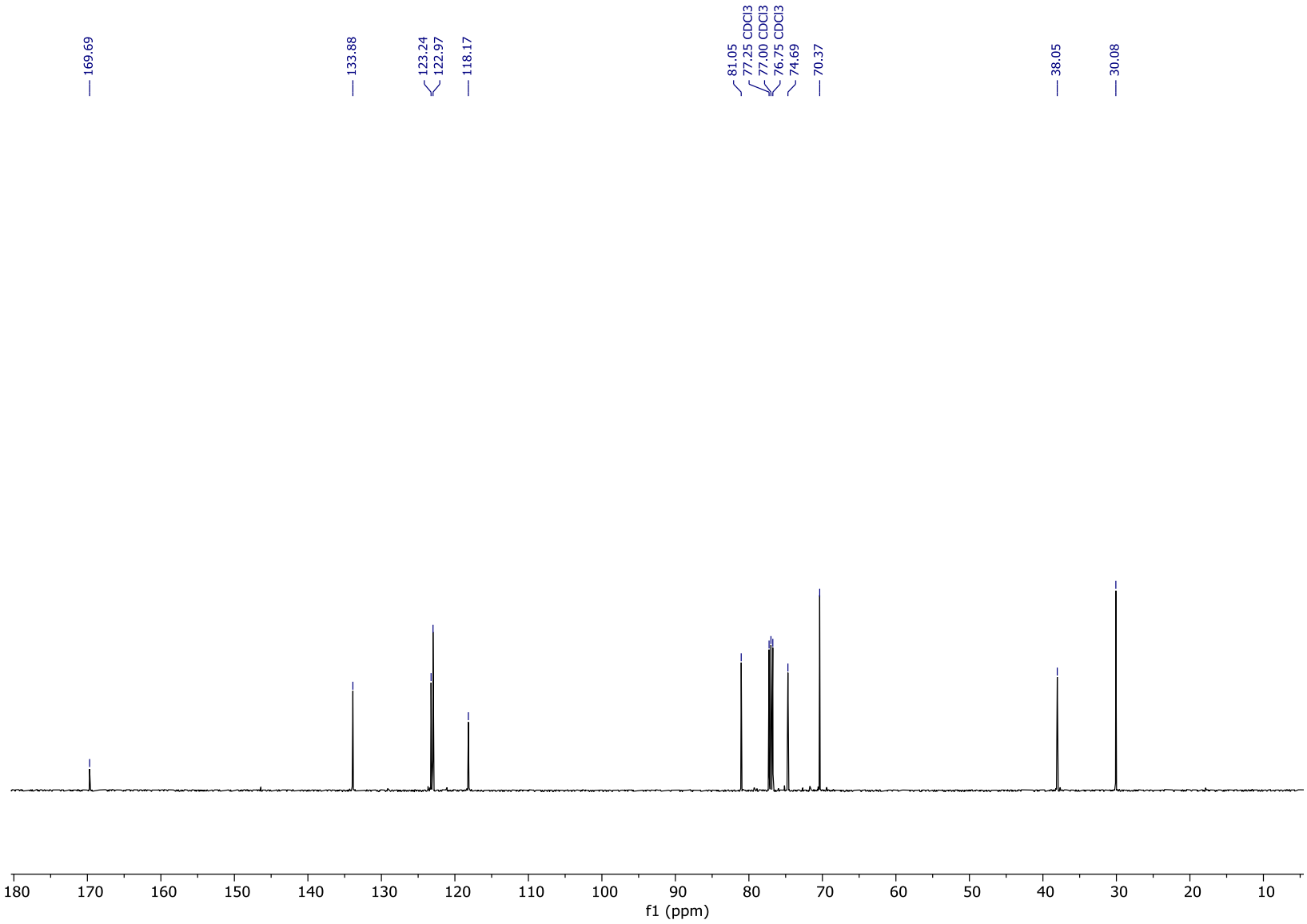
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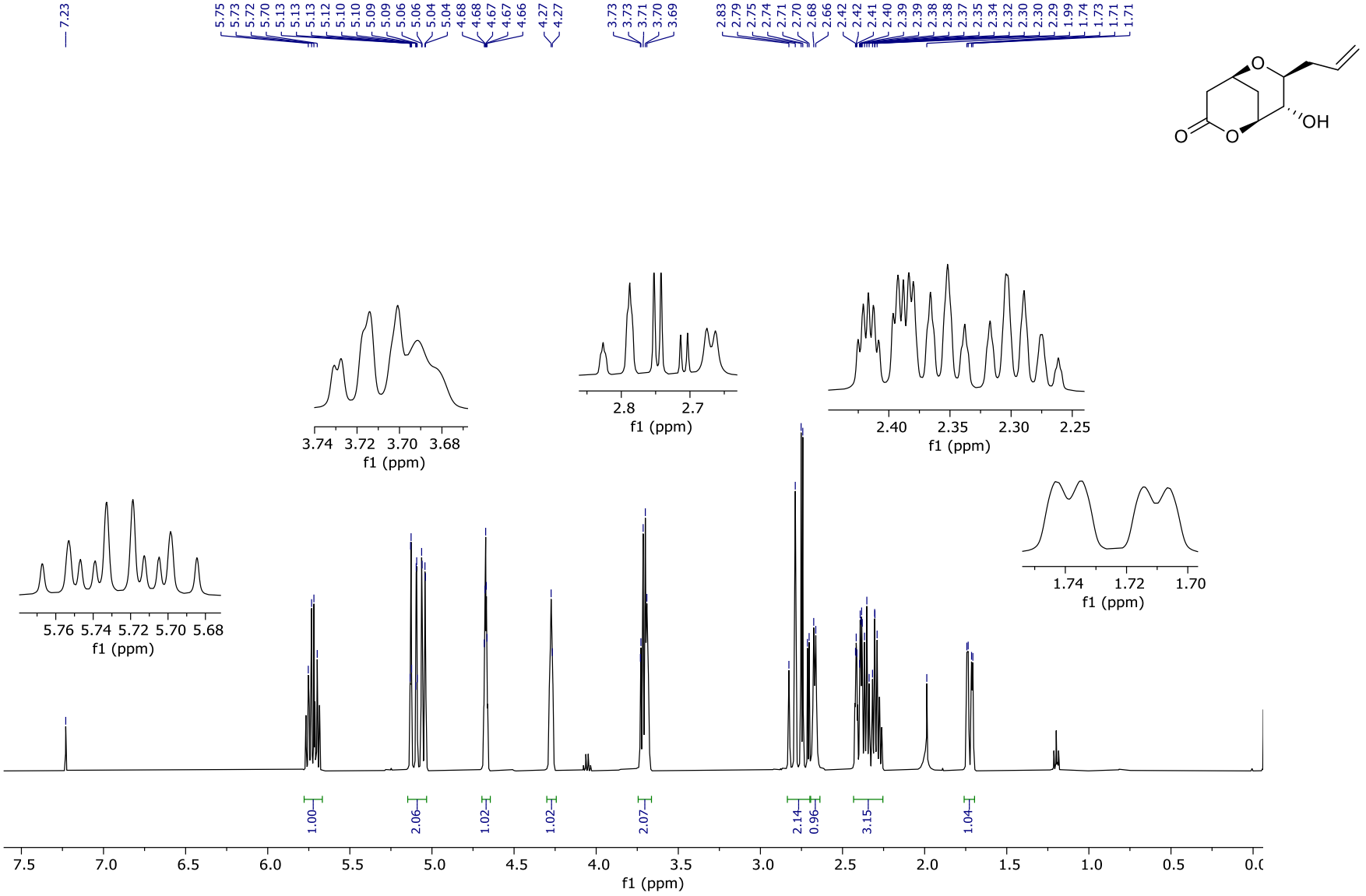
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O
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OH
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f1 (ppm)
2.40 2.35 2.30 2.25
f1 (ppm)
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f1 (ppm)
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f1 (ppm)
1.00 2.06 1.02 1.02 2.07 2.14 0.96 3.15 1.04
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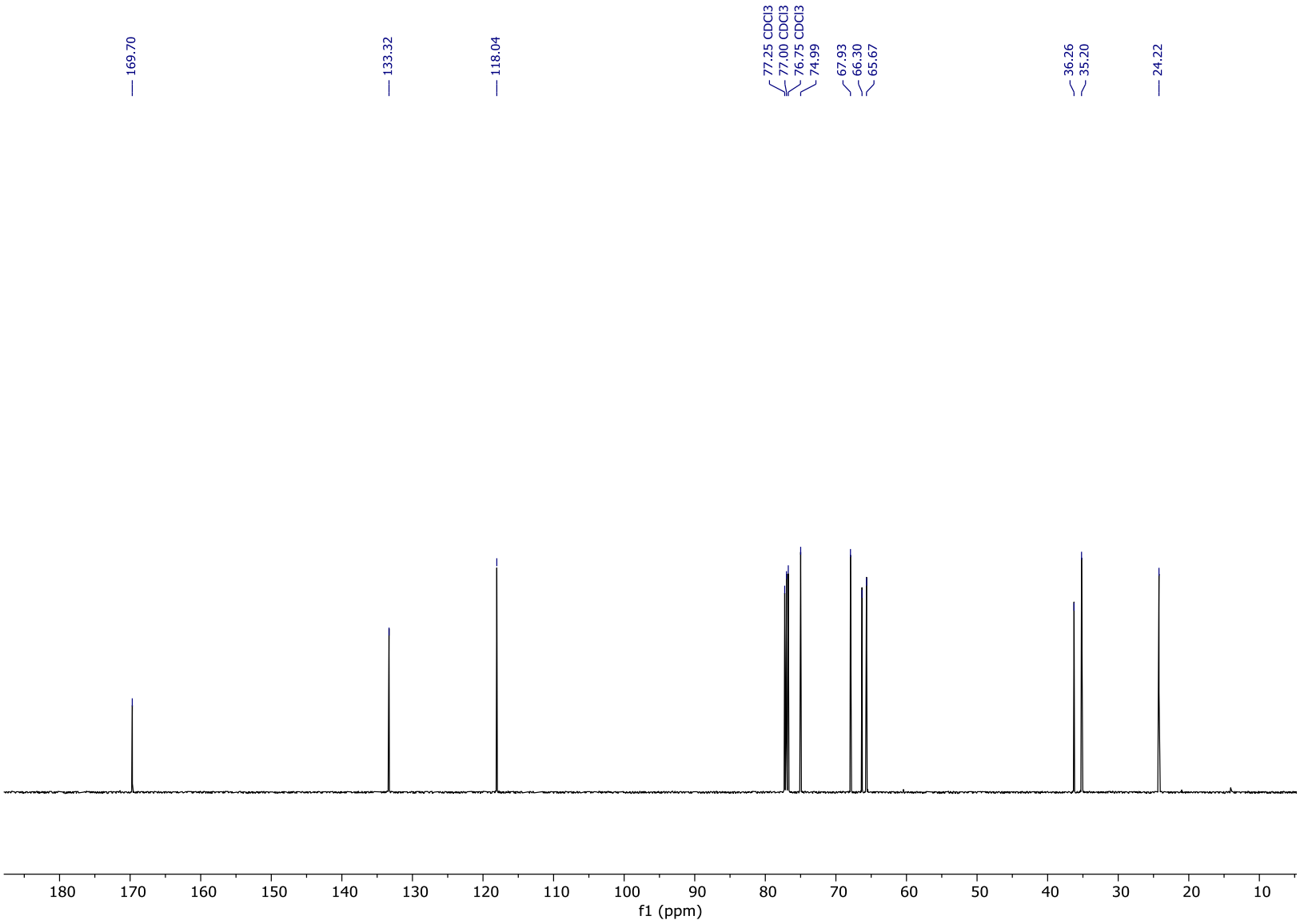
f1 (ppm)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180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

Table S1. Crystallographic data for compound **9**

	Polymorph I	Polymorph II
CCDC deposition	**2381690**	**2381691**
Formula	C_{10} H_{14} O_4	C_{10} H_{14} O_4
fw	198.21	198.21
Crystal size (mm^3)	0.54 × 0.27 × 0.24	0.27 × 0.09 × 0.08
Colour	colourless	colourless
Space group	$P2_1$	$P2_12_12_1$
a, *b*, *c* (Å)	6.2588(6), 8.3428(5), 9.9421(8)	6.0654(3), 7.9436(4), 20.7057(16)
α, β, γ (°)	90, 106.501(7), 90	90,90,90
V ($Å^3$)	497.76(7)	997.62(10)
Z, *Z*'	2, 1	4, 1
Diffractometer	Stoe Stadivari	Stoe Stadivari
Radiation	Ag Kα (λ = 0.56083 Å)	Ag Kα (λ = 0.56083 Å)
T (K)	295(1)	295(1)
Density ($g.cm^{-3}$)	1.322	1.320
Absorption coef. (mm^{-1})	0.063	0.063
Transmission factors	0.5293-1.000	0.3671-1.000
Refl. collected	10200	24084
Indep. Refl. (R_{int})	2196 (0.023)	2316 (0.071)
Senθ/λ ($Å^{-1}$)	0.67	0.65
Data /parameter/restraints	2196 / 131 / 1	2316 / 130 / 0
R_1, wR_2 [$I > 2\sigma(I)$]	0.0298, 0.0765	0.0362, 0.0733
R_1, wR_2 [all data]	0.0374, 0.0791	0.0580, 0.0809
GOF on F^2	1.051	0.901

check CIF/PLATON report

Structure factors have been supplied for datablock(s) 9_polymorph_I, 9_polymorph_II

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors were found. CIF dictionary Interpreting this report

Datablock: 9_polymorph_I

Bond precision: C-C = 0.0030 A Wavelength=0.56083

Cell:	a=6.2588(6)	b=8.3428(5)	c=9.9421(8)
	alpha=90	beta=106.501(7)	gamma=90
Temperature:	295 K		

	Calculated	Reported
Volume	497.76(7)	497.76(7)
Space group	P 21	P 21
Hall Group	P 2yb	P 2yb
Moiety formula	C10 H14 O4	C10 H14 O4
Sum formula	C10 H14 O4	C10 H14 O4
Mr	198.21	198.21
Dx,g cm-3	1.322	1.322
Z	2	2
Mu (mm-1)	0.063	0.063
F000	212.0	212.0
F000’	212.05	
h,k,lmax	8,11,13	8,11,13
Nref	2487[1328]	2196
Tmin,Tmax	0.980,0.985	0.529,1.000
Tmin’	0.966	

Correction method= # Reported T Limits: Tmin=0.529 Tmax=1.000AbsCorr = MULTI-SCAN

Data completeness= 1.65/0.88 Theta(max)= 21.998

R(reflections)= 0.0298(1848) wR2(reflections)= 0.0791(2196)

S = 1.051 Npar= 131

The following ALERTS were generated. Each ALERT has the format

test-name_ALERT_alert-type_alert-level.

Click on the hyperlinks for more details of the test.

Alert level C

PLAT915_ALERT_3_C No Flack x Check Done: Low Friedel Pair Coverage 75 %

Alert level G

PLAT791_ALERT_4_G Model has Chirality at C1 (Sohncke SpGr) S VerifyPLAT791_ALERT_4_G Model has Chirality at C5 (Sohncke SpGr) S VerifyPLAT791_ALERT_4_G Model has Chirality

at C7 (Sohncke SpGr) R VerifyPLAT791_ALERT_4_G Model has Chirality at C8 (Sohncke SpGr)
S VerifyPLAT910_ALERT_3_G Missing # of FCF Reflection(s) Below Theta(Min). 1 Note

0 0 1,

PLAT969_ALERT_5_G The 'Henn et al.' R-Factor-gap value ..... 4.404 NotePredicted wR2: Based on SigI**2 1.80 or SHELX Weight 7.52

PLAT978_ALERT_2_G Number C-C Bonds with Positive Residual Density. 4 Info

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0 **ALERT level A** = Most likely a serious problem - resolve or explain

0 **ALERT level B** = A potentially serious problem, consider carefully
1 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight
7 **ALERT level G** = General information/check it is not something unexpected

0 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
1 ALERT type 2 Indicator that the structure model may be wrong or deficient
2 ALERT type 3 Indicator that the structure quality may be low
4 ALERT type 4 Improvement, methodology, query, or suggestion

1 ALERT type 5 Informative message, check

Datablock: 9_polymorph_II

Bond precision: C-C = 0.0032 A Wavelength=0.56083

Cell: a=6.0654(3) b=7.9436(4) c=20.7057(16)
alpha=90 beta=90 gamma=90
Temperature: 295 K

	Calculated	Reported
Volume	997.62(10)	997.62(10)
Space group	P 21 21 21	P 21 21 21
Hall group	P 2ac 2ab	P 2ac 2ab
Moiety formula	C10 H14 O4	C10 H14 O4
Sum formula	C10 H14 O4	C10 H14 O4
Mr	198.21	198.21
Dx,g cm-3	1.320	1.320
Z	4	4
Mu (mm-1)	0.063	0.063
F000	424.0	424.0
F000'	424.11	
h,k,lmax	7,10,27	7,10,27

Nref	2318[1373]	2316
Tmin,Tmax	0.993,0.995	0.367,1.000
Tmin'	0.983	

Correction method= # Reported T Limits: Tmin=0.367 Tmax=1.000AbsCorr = MULTI-SCAN

Data completeness= 1.69/1.00 Theta(max)= 21.500

R(reflections)= 0.0362(1563) wR2(reflections)= 0.0809(2316)

S = 0.901 Npar= 130

The following ALERTS were generated. Each ALERT has the format

test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level G

PLAT791_ALERT_4_G has Chirality at C1 (Sohncke SpGr) S Verify Model
PLAT791_ALERT_4_G has Chirality at C5 (Sohncke SpGr) S Verify Model
PLAT791_ALERT_4_G has Chirality at C7 (Sohncke SpGr) R Verify Model
PLAT791_ALERT_4_G has Chirality at C8 (Sohncke SpGr) S Verify Model
PLAT910_ALERT_3_G Missing # of FCF Reflection(s) Below Theta(Min). 2 Note
0 1 1, 0 0 2,
PLAT955_ALERT_1_G Reported (CIF) and Actual (FCF) Lmax Differ by . 1 Units
PLAT969_ALERT_5_G The 'Henn et al.' R-Factor-gap value ..... 2.661 Note
Predicted wR2: Based on SigI**2 3.04 or SHELX Weight 8.97
PLAT978_ALERT_2_G Number C-C Bonds with Positive Residual Density. 0 Info

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0 **ALERT level A** = Most likely a serious problem - resolve or explain

0 **ALERT level B** = A potentially serious problem, consider carefully

0 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight

8 **ALERT level G** = General information/check it is not something unexpected

1 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
1 ALERT type 2 Indicator that the structure model may be wrong or deficient
1 ALERT type 3 Indicator that the structure quality may be low

T
4 ALER type 4 Improvement, methodology, query or suggestion
T
1 ALER type 5 Informative message, check
T

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors, and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. To resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations, and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needingattention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

Publication of your CIF in IUCr journals

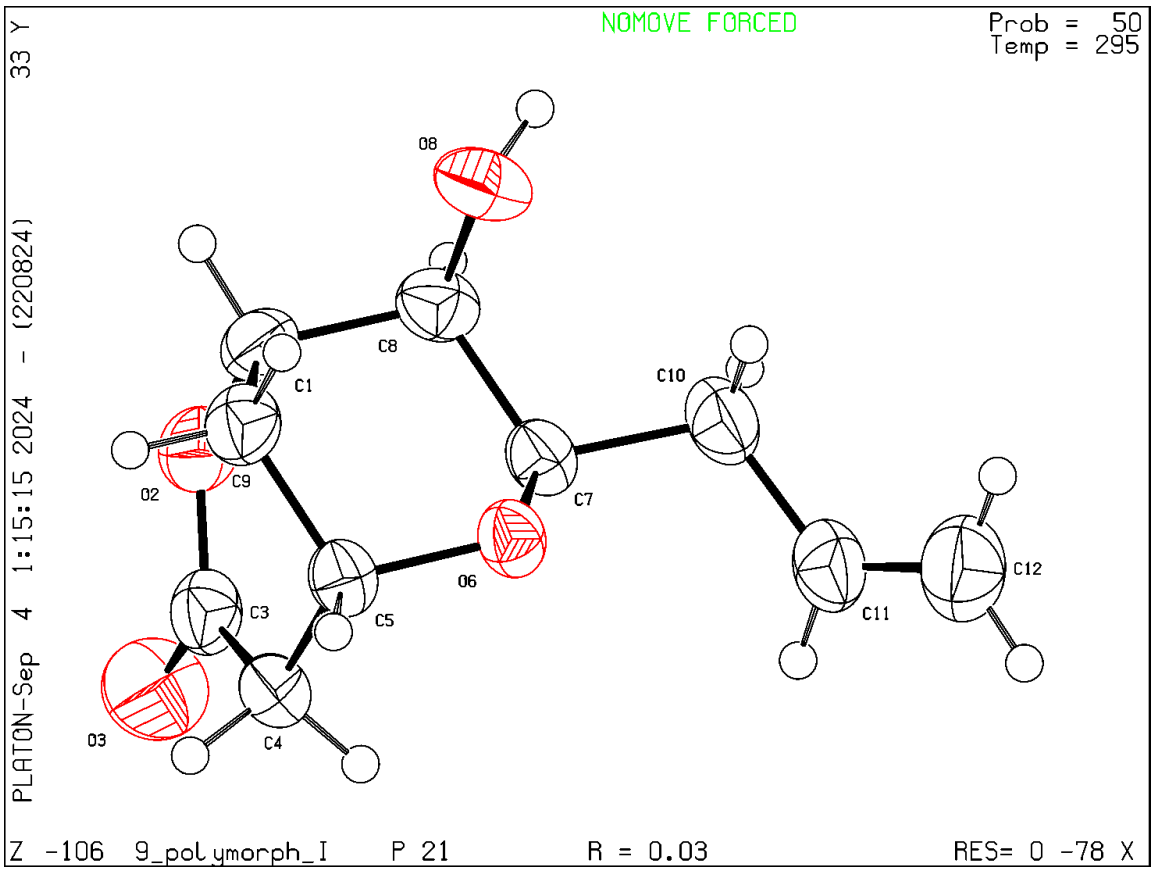
A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica*, *Journal of Applied Crystallography*, *Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E* or *IUCrData*, you should make sure that full publication checks arerun on the final version of your CIF before submission.

Publication of your CIF in other journals

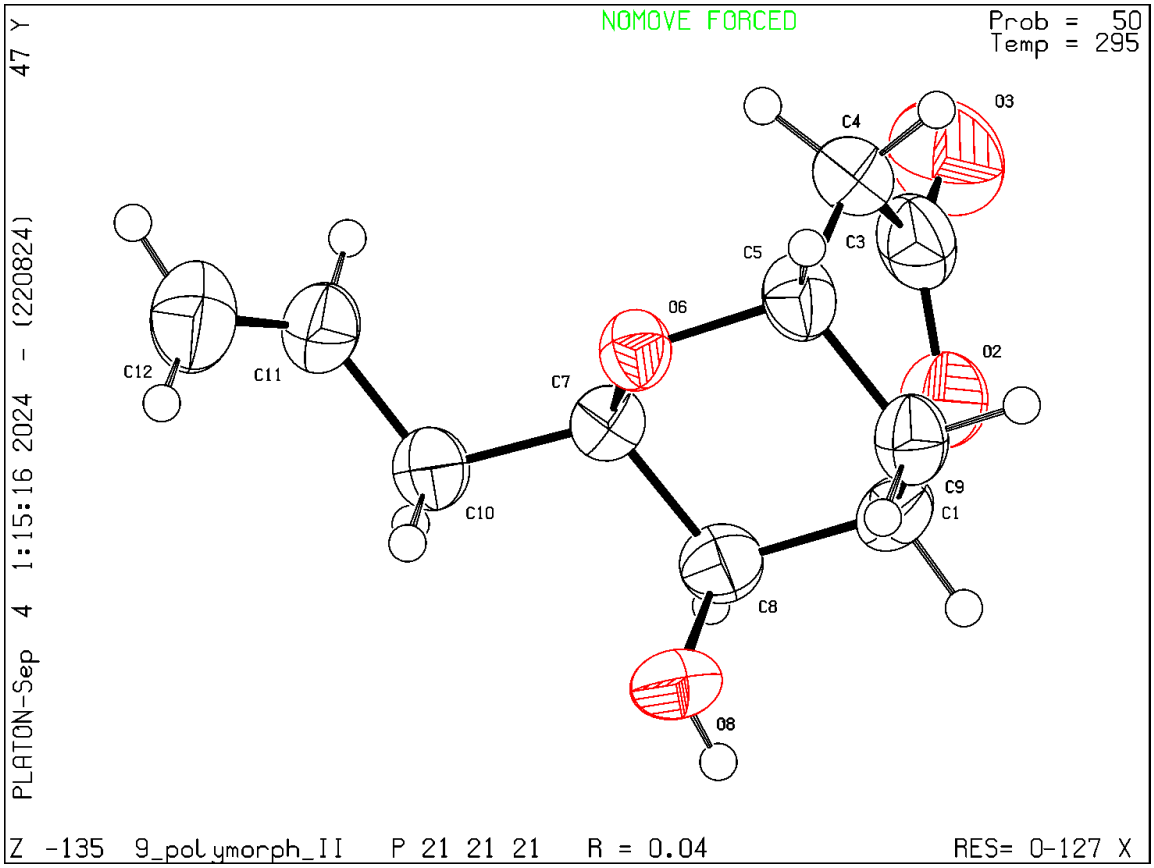
Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIFsubmission.

PLATON version of 22/08/2024; check.def file version of 21/08/2024

Datablock 9_polymorph_I - ellipsoid plot



Datablock 9_polymorph_II - ellipsoid plot



Cytotoxicity tests of 9 with human cells

Table S2. Growth inhibition percentage by cell line.[a]

Sample (9)	U251	PC-3	K562	HCT-15	MCF-7	SKLU-1	COS7
10 mM EtOH	NC	NC	17.5	NC	PD	1.0	NC
25 mM DMSO	NC	3.3	1.4	NC	NC	7.8	NC
25 mM EtOH	NC	5.8	NC	NC	13.14	NC	NC
5-FU	34.0	83.0	46.9	70.3	49.1	72.0	37.5

[a] Protocol: Sulforhodamine B; Assay: Cytotoxicity in human cancer cell lines; Trial type: Primary screening. Concentration: 25 µM Vehicle: DMSO and ethanol; U251= central nervous system glia, PC-3= prostate, K562= leukemia, HCT-15= colon, MCF-7= breast, SKLU= lung. COS-7: monkey kidney cell line (non-cancerous): NC: non-cytotoxic PD pending.