The Diverted Total Synthesis of Carolacton-Inspired Analogs Yields Three Distinct Phenotypes in *Streptococcus mutans* Biofilms

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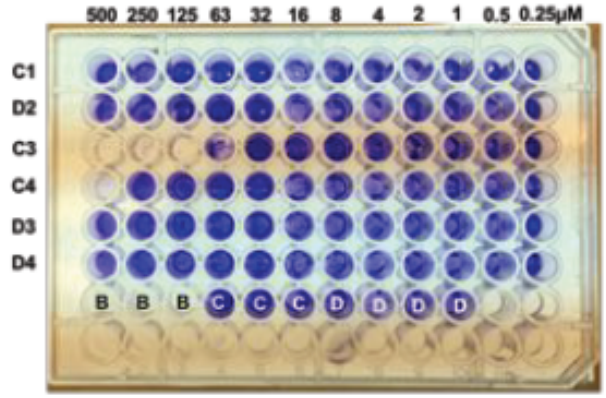
Compound	MIC	$MBIC_{50}$	Phenotype
A1	>500μM	>500μM	NORMAL
A2	>500μM	>500μM	NORMAL
A3	>500μM	500μM	INHIBITED
A4	>500μM	>500μM	NORMAL
B1	>500μM	500μM	INHIBITED
B2	>500μM	>500μM	NORMAL
B3	500μM	500μM	INHIBITED
B4	500μM	500μM	INHIBITED
C1	>500μM	>500μM	1
C2	500μM	500μM	INHIBITED
C3	500μM	63μM	INHIBITED
C4	500μM	500μM	INHIBITED
D1	>500μM	>500μM	NORMAL
D2	>500μM	>500μM	1
D3	>500μM	>500μM	NORMAL
D4	>500μM	>500μM	2
Carolacton	>500μM	>500μM	2
		1 = microcolony	
		2 = carolacton-like	

Figure S1. Summary of observed MIC values, MBIC values and phenotypes observed via confocal imaging. Experiments were completed in triplicate.

Full image of crystal violet plate and controls. OD measurements were taken at 595nm.



	500uM	250	125	63	32	16	8	4	2	1	0.5	0.25
C3	0.09	0.13	0.16	0.31	0.87	0.83	0.56	0.44	1.64	1.22	1.11	1.03
C4	0.17	0.32	1.55	0.85	1.69	0.92	1.35	0.93	1.18	1.13	0.94	0.89
Controls	0.05	0.07	0.10	0.59	0.61	1.00	0.60	0.48	0.58	0.69		
	B	B	B	C	C	C	D	D	D	D		

OD values taken directly from plate reader. B= Blank, only media; C= Cells in media; D= 5% DMSO control. Controls were averaged for normalization below.

Blank Average = 0.07±0.02
Cells Average = 0.73±0.23
DMSO Average = 0.59±0.09

	500uM	250	125	63	32	16	8	4	2	1	0.5	0.25
C3	0.03	0.11	0.17	0.46	1.55	1.47	0.94	0.72	3.03	2.23	2.01	1.86
C4	0.20	0.48	2.86	1.51	3.14	1.64	2.47	1.66	2.14	2.06	1.69	1.58

OD values normalized to the Blank and DMSO controls.

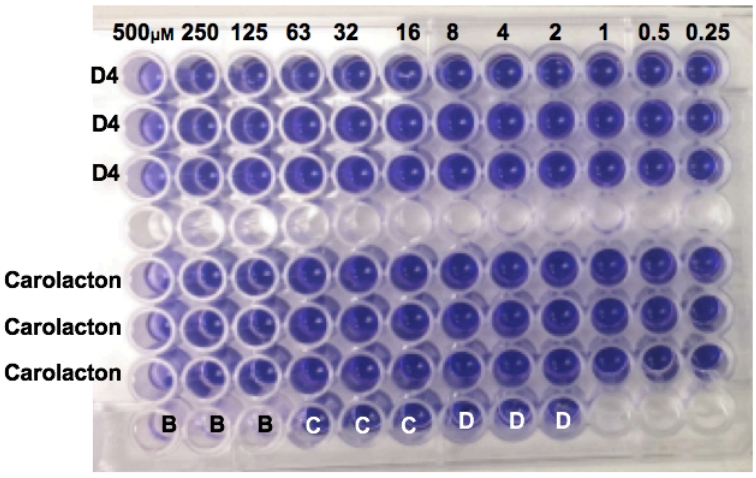


Figure S2. MBIC assay stained with crystal violet and subsequent OD values (normalized to blank and DMSO control)

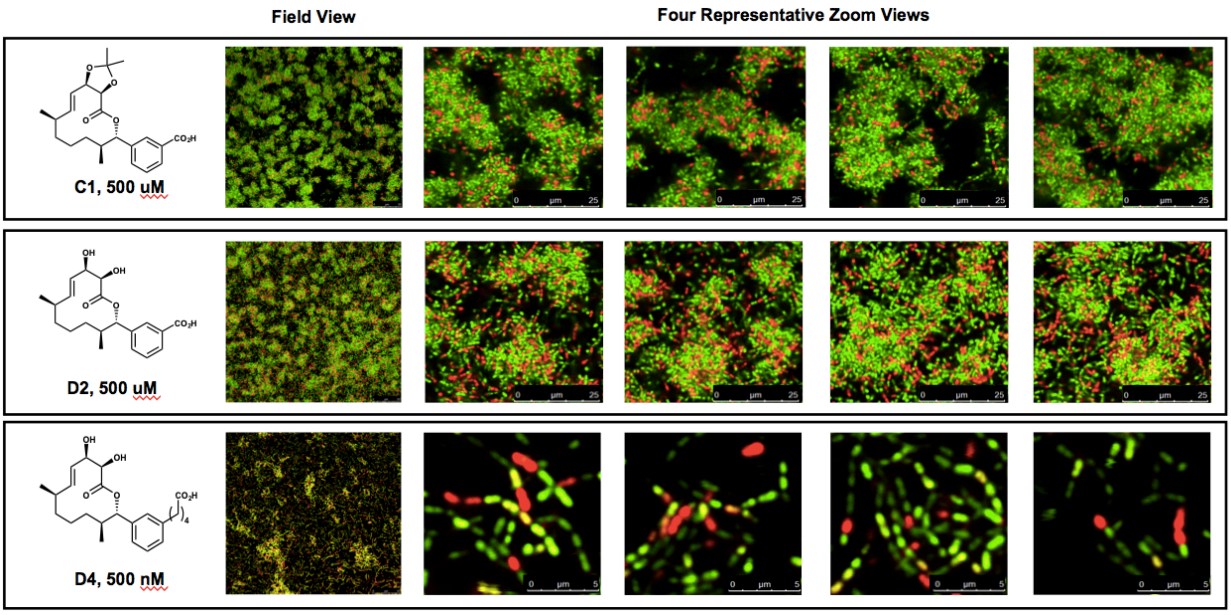


Figure S3. Field and representative zoom views of compounds **C1, D2**, and **D4** under confocal microscope.

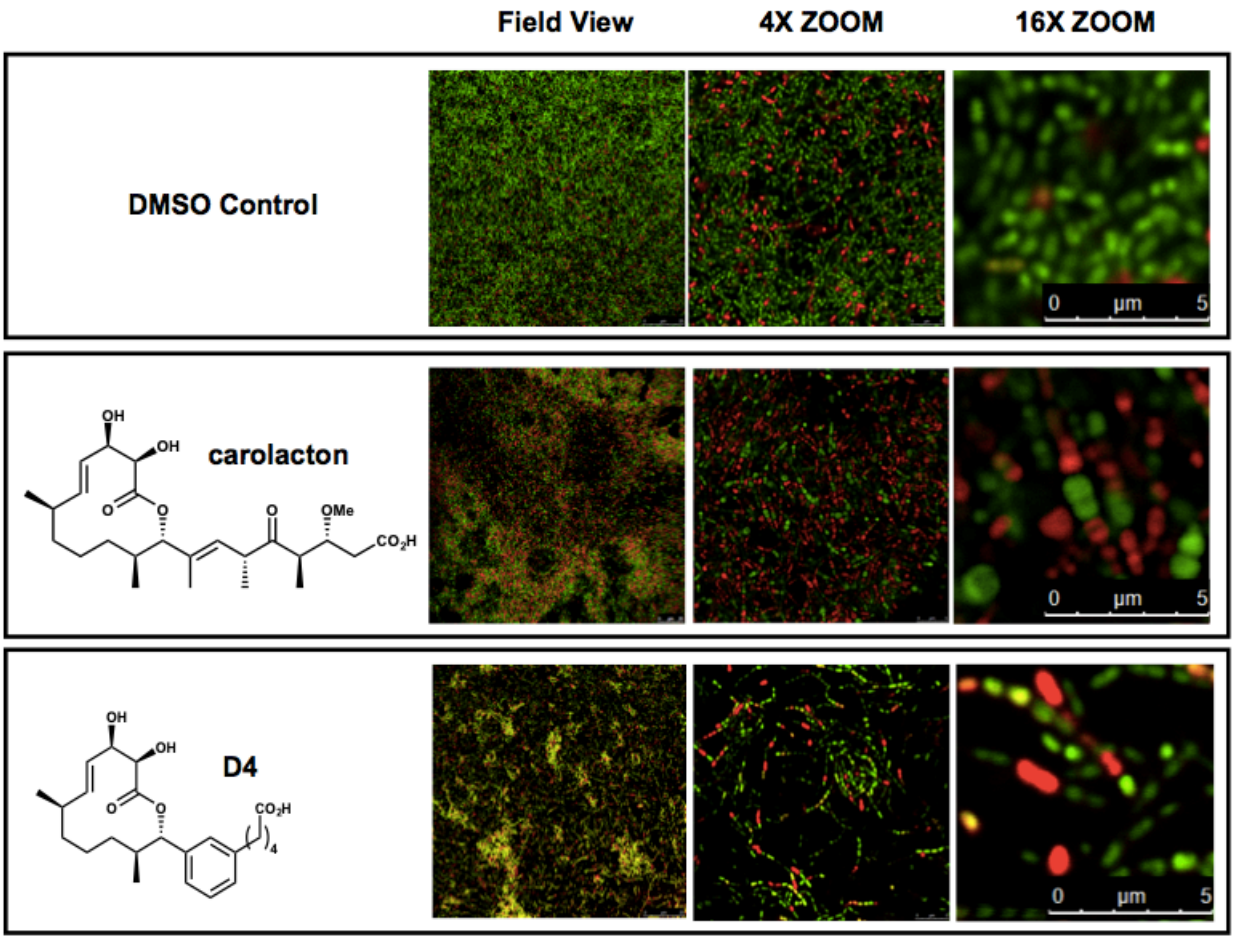


Figure S4. Comparison of DMSO control, carolacton, and compound D4 (both at 500 nM) at various field strengths.

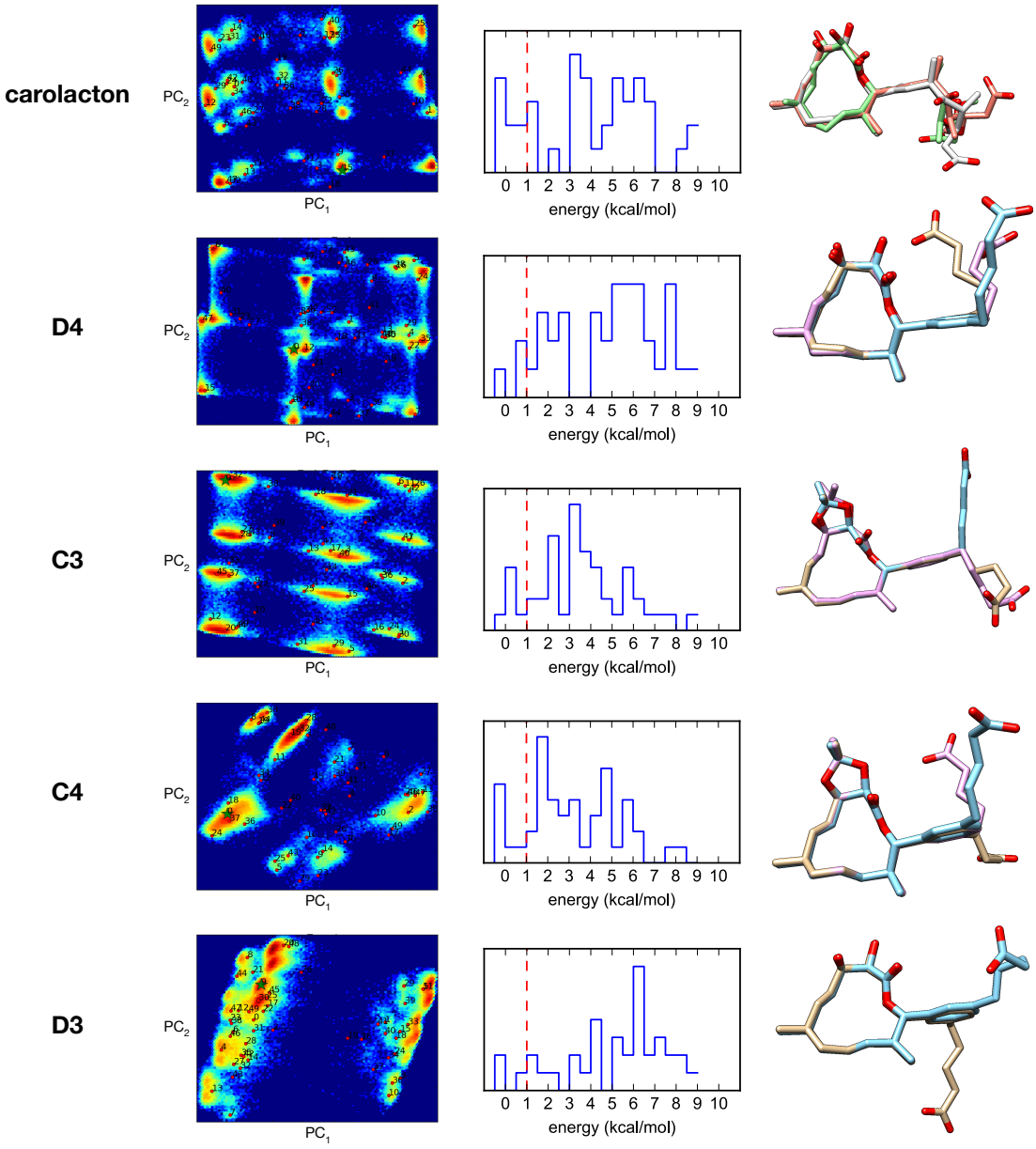


Figure S5. REMD/QM calculations for carolacton, **D4**, **C3**, **C4** and **D3**. Left column: REMD trajectory data projected to the first two principal components (PC_1 and PC_2) of dihedral angle space. Red dots indicate the 50 cluster generators obtained from *k*-centers clustering, which overlap well with regions of sampled density (shows as a log-scaled color gradient). The dispersion of clusters in the principal component subspace can be mainly attributed to variation in the flexible side chain of the carolacton analogs. Center column: Histograms of DFT energies calculated for the 50 QM-refined conformations. Right column: A superposition of the three lowest-energy conformations (within 0.2, 1.2, 0.7, 0.2 and 0.5 kcal/mol of the calculated ground state, respectively for carolacton, **D4**, **C3**, **C4** and **D3).**

2. Methods

General. NMR spectra were recorded using the following spectrometers: Bruker Advance 500 (500/125 MHz) or Bruker Advance 400 (400/100 MHz). Chemical shifts are quoted in ppm relative to tetramethylsilane and with the indicated solvent as an internal reference. The following abbreviations are used to describe signal multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), dd (doublet of doublets), dt (doublet of triplets), etc. Accurate mass spectra were recorded on an Agilent 6520 Accurate-Mass Q-TOF LC/MS, infrared spectra were obtained using a Thermo Nicolet Nexus 670 FTIR spectrophotometer and specific rotation measurements were made with a 1 dm path length using a Perkin Elmer 341 Polarimeter. Non-aqueous reactions were performed under an atmosphere of argon, in flame-dried glassware, with HPLC-grade solvents dried by passage through activated alumina. Amine bases were freshly distilled from CaH_2 prior to use. Brine refers to a saturated aqueous solution of sodium chloride. Products purified via flash chromatography using Biotage Isolera One Automated column. Reactions monitored via thin-layer chromatography (TLC) using EMD Millipore® TLC silica gel glass plates with $KMnO_4$ stain.

Materials. Streptococcus mutans wild-type strain UA159 was used for all bacterial cultures and was provided by Dr. Bettina Buttaro from Temple University Medical School, Philadelphia, PA. Bacteria were routinely maintained on in Bacto™ Todd- Hewitt (TH) agar plates and liquid cultures were grown in in Bacto™ Todd-Hewitt broth (THB). For growth of biofilms, THB was supplemented with 0.1% sucrose. Incubation was stagnant at 37 °C.

S. *mutans* MIC assay. Stock solution of carolacton analogs, 1000 μM, were serial diluted in THB media in flat-bottom 96-well microtiter plates. Then 2 μL of overnight cell culture are added to reach final volume of 200 μL. Plates are incubated at 37 °C in 5% CO_2 for 20-24 hours upon which time wells are evaluated visually for bacterial growth. The MIC is determined as the lowest concentration of compound resulting in no bacterial growth visible to the naked eye. Biological triplicates were performed to confirm results.

***S. mutans* biofilm model.** Stock solution of carolacton analogs, 1000 μM, were serial diluted in THB media with 0.1% sucrose (w/v) in glass flat-bottom 96-well microtiter plates. Then 2 μL of overnight cell culture are added to reach final volume of 200 μL. Plates are incubated at 37 °C in 5% CO_2 for 18-20 hours (early stage biofilm) at which time wells are evaluated visually for bacterial growth.

S. mutans $MBIC_{50}$ assay. Biofilms were prepared with above procedure and evaluated visually and then emptied by inverting carefully, as to not disturb the biofilm. Wells were washed with 200μL of DI H_2O and dried for 6h at 37°C. Once dry, plates were incubated for 10min at room temperature with 50μL of 1% w/v crystal violet (25% ethanol in H_2O). Excess crystal violet was removed by submerging plates in fresh tap water until the run off was colorless. Plates were then inverted and dried at room temperature. Crystal violet was redissolved with 200μL of 95% ethanol, 100μL of which was then transferred to a fresh flat-bottom 96-well plate for absorbance measurements at 595nm. DMSO controls corresponding to each test concentration were performed. Three biological replicates were performed.

Confocal Imaging. Biofilms were grown with method described above. To note, the glass flat-bottom microtiter plates allowed for more efficient imaging compared to method using glass slips. After incubation, media was removed and each well was rinsed twice with PBS to remove planktonic cells. Subsequently, 10 μL of BacLight LIVE/DEAD stain was added to each well. Images of biofilms were then obtained using the Leica DM IRE2 confocal microscope at Temple University Medical School.

Molecular Modeling. To model the structures of carolacton analogs in aqueous solution, a two-step REMD/QM approach was used, similar to previous work.[37] In the first step, replica-exchange molecular dynamics (REMD) was used for exhaustive conformational sampling. Selected structures from populated conformational basins were then further refined using DFT geometry optimization and energy calculation.

3. Biology

3.1 Procedures and General Notes

3.1.1 Bacterial Strains and Culture Conditions

Streptococcus mutans wild-type strain UA159 was obtained from Prof. Bettina Buttaro, Philadelphia, Pennsylvania.

3.1.2 MIC Assay

Stock solution of carolacton analogs, 1000 μM, were serial diluted in THB media in flat-bottom 96-well microtiter plates. Then 2 μL of overnight cell culture are added to reach final volume of 200 μL. Plates are incubated at 37°C in 5% CO_2 for 20-24 hours upon which time wells are evaluated visually for bacterial growth. The MIC is determined as the lowest concentration of compound resulting in no bacterial growth visible to the naked eye. Biological triplicates were performed to confirm results.

3.1.3 *S. mutans* biofilm model.

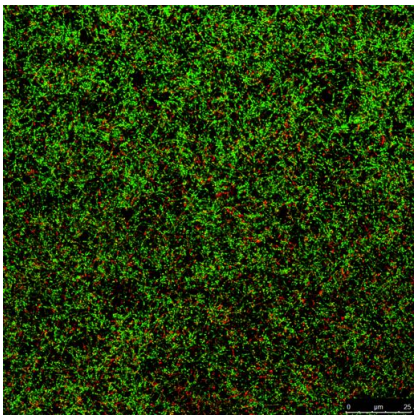
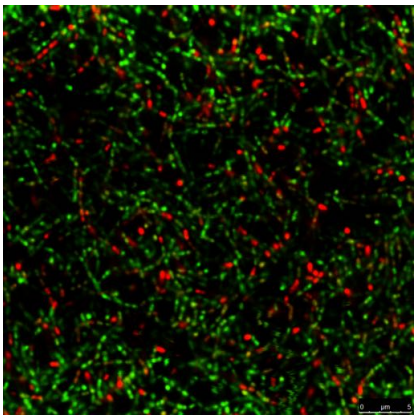
Stock solution of carolacton analogs, 1000 μM, were serial diluted in THB media with 0.1% sucrose (w/v) in glass flat-bottom 96-well microtiter plates. Then 2 μL of overnight cell culture are added to reach final volume of 200 μL. Plates are incubated at 37 °C in 5% CO_2 for 18-20 hours (early stage biofilm) at which time wells are evaluated visually for bacterial growth. After incubation, the media was removed from each desired well and the biofilm was rinsed with phosphate buffered saline (PBS) and then stained with Propidium Iodide/ Syto9.

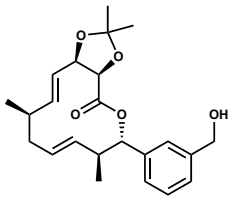
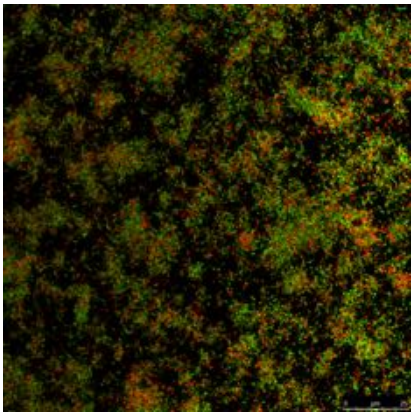
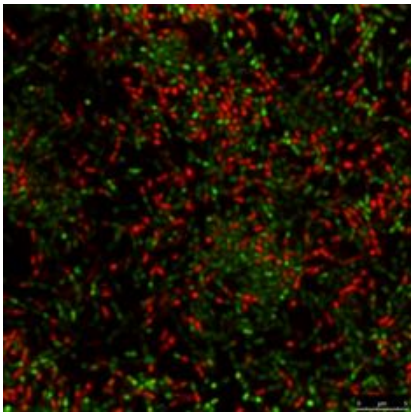
3.1.4 Biofilm Inhibition Assay ($MBIC_{50}$)

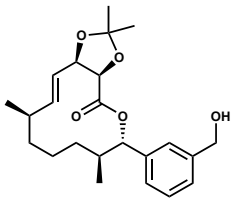
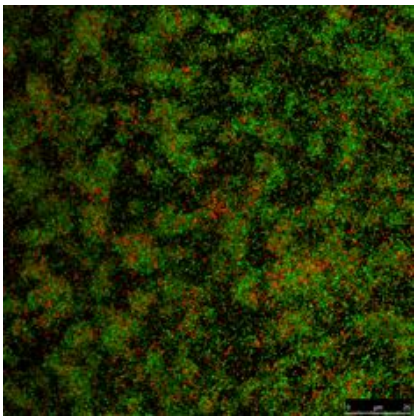
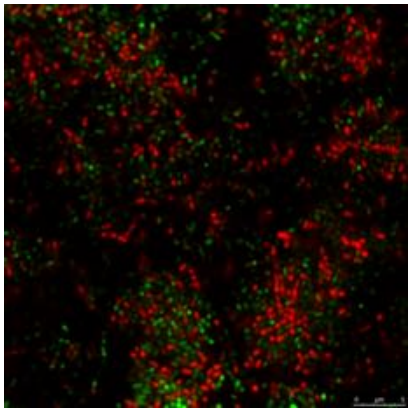
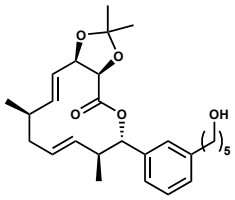
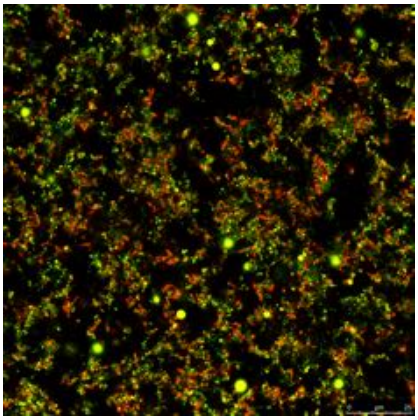
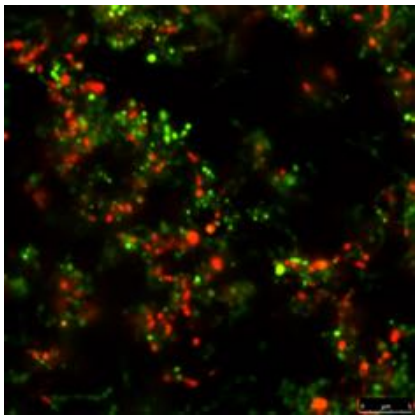
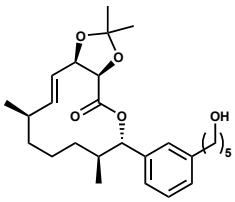
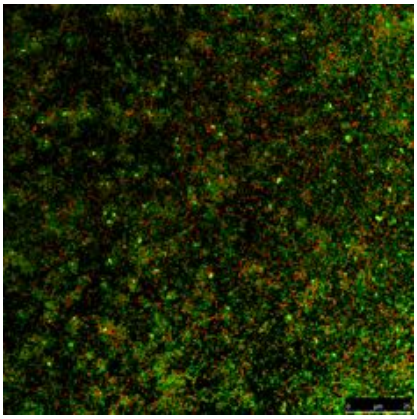
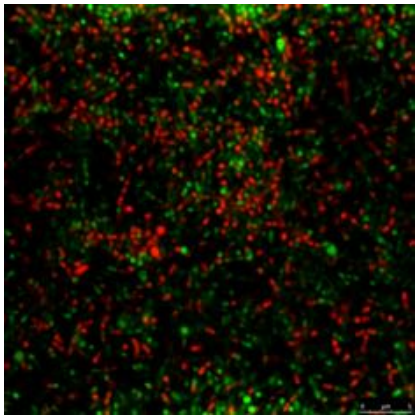
Biofilms were prepared with above procedure and evaluated visually and then emptied by inverting carefully, as to not disturb the biofilm. Wells were washed with 200μL of DI H_2O and dried for 6h at 37°C. Once dry, plates were incubated for 10min at room temperature with 50μL of 1% w/v crystal violet (25% ethanol in H_2O). Excess crystal violet was removed by submerging plates in fresh tap water until the run off was colorless. Plates were then inverted and dried at room temperature. Crystal violet was redissolved with 200μL of 95% ethanol, 100μL of which was then transferred to a fresh flat-bottom 96-well plate for absorbance measurements at 595nm. DMSO controls corresponding to each test concentration were performed. Three biological replicates were performed.

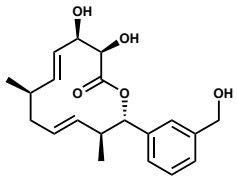
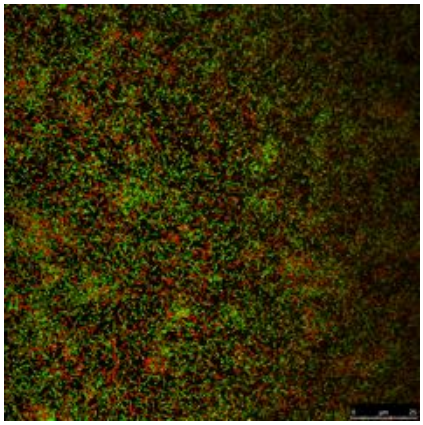
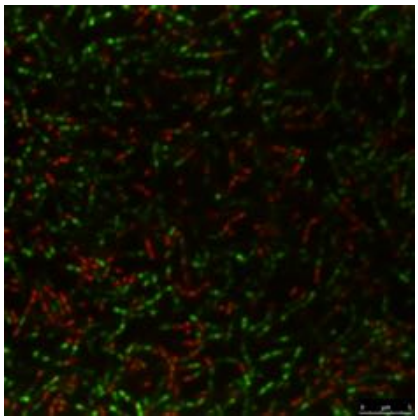
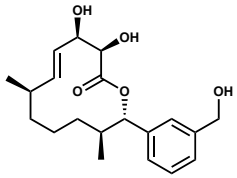
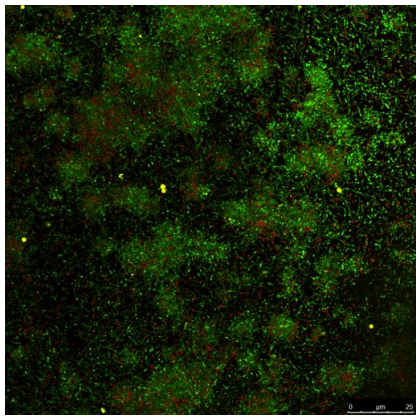
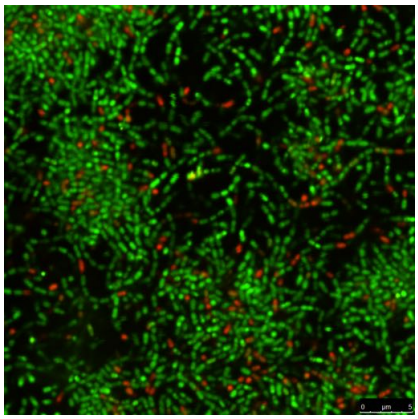
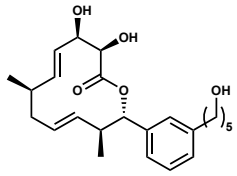
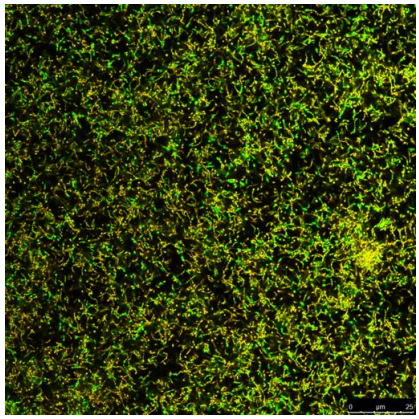
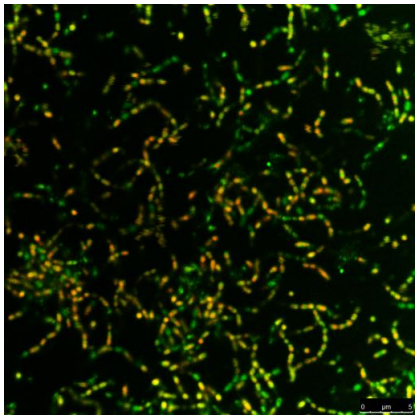
3.2 Biofilm Confocal Images

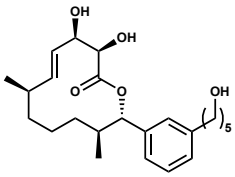
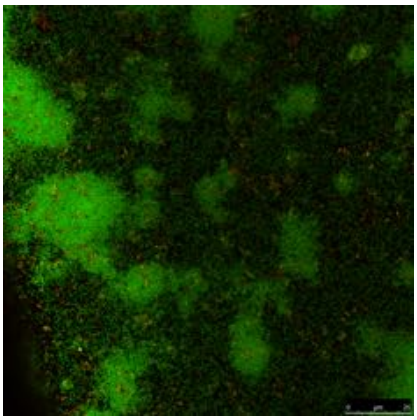
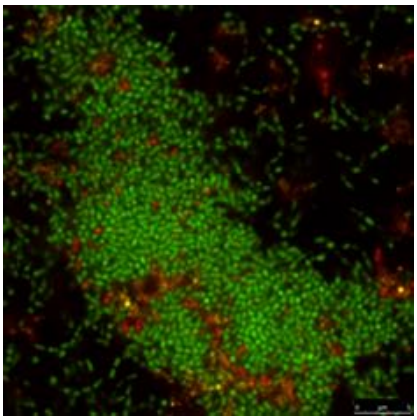
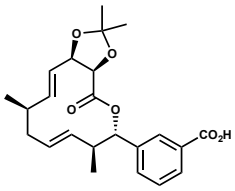
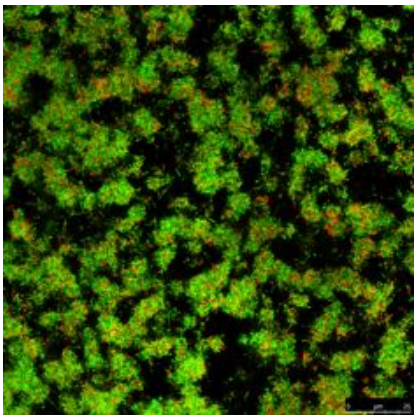
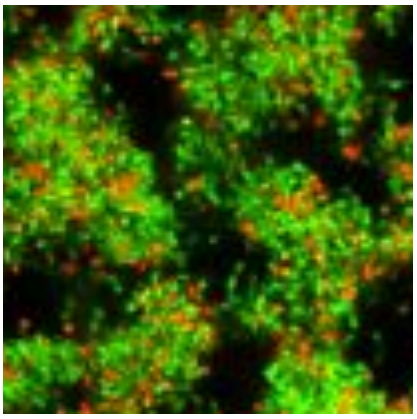
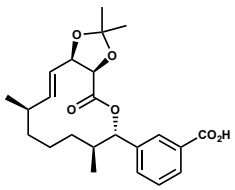
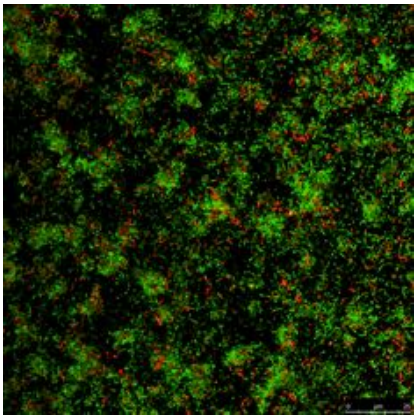
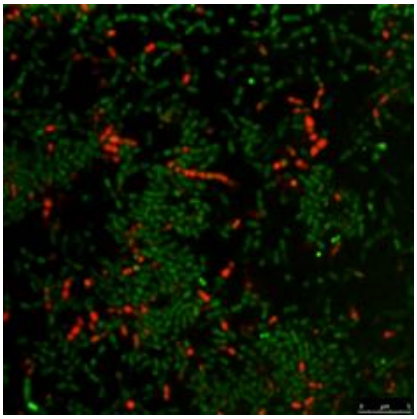
DMSO Control

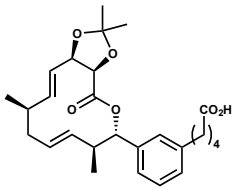
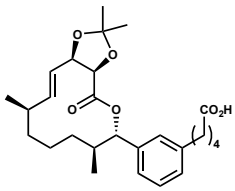
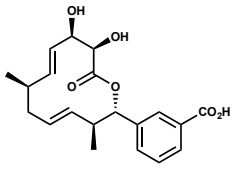
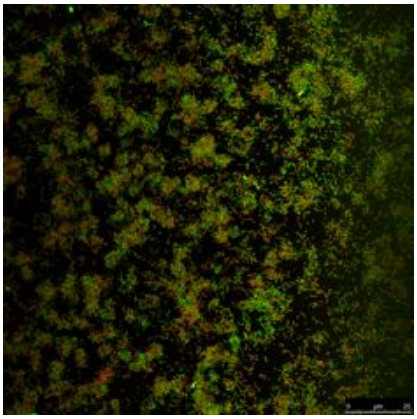
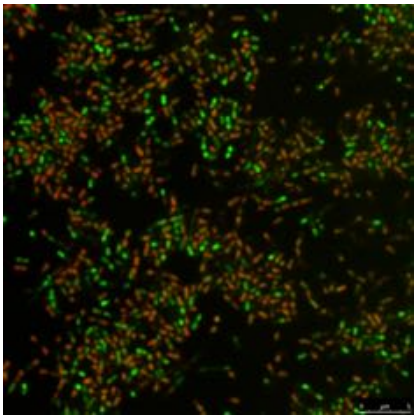
	Full	Zoom
DMSO		

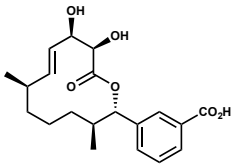
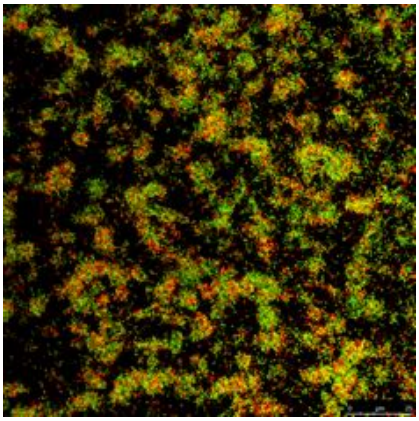
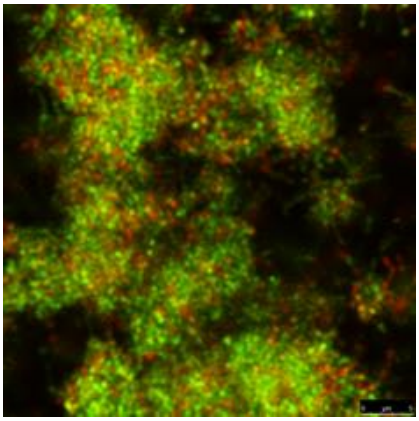
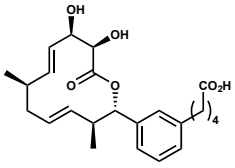
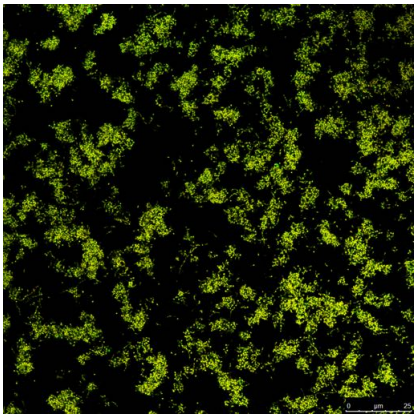
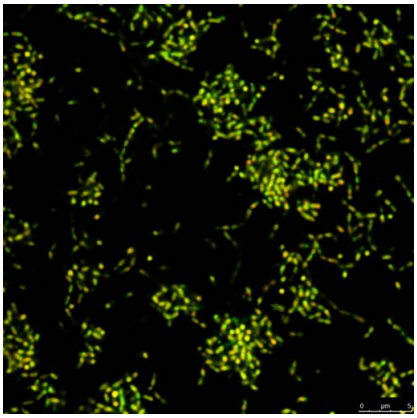
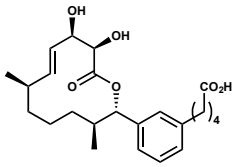
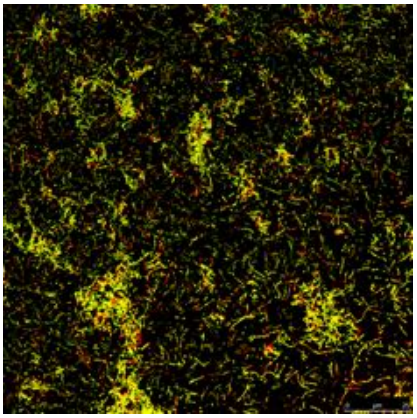
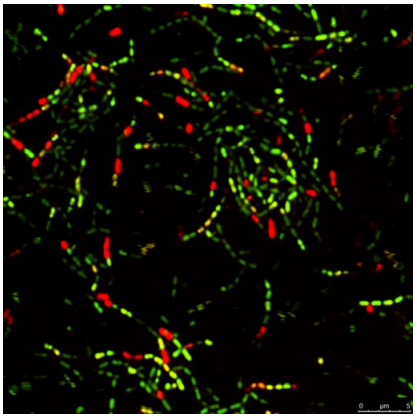
Compound	Full (500 μM)	Zoom (500 μM)
 **A1**		

 A2		
 A3		
 A4		

 B1		
 B2		
 B3		

 B4		
 C1		
 C2		

 C3		
 C4		
 D1		

 D2		
 D3		
 D4		

4. Computational Methods

To model the structures of carolacton analogs in aqueous solution, a two-step REMD/QM approach was used, similar to previous work.[2] In the first step, replica-exchange molecular dynamics (REMD) was used for exhaustive conformational sampling. Selected structures from populated conformational basins were then further refined using DFT geometry optimization and energy calculation.

REMD simulation. Molecular topologies for carolacton, D4, C3, C4 and D3 were built in UCSF Chimera, and parameterized using the General Amber Force Field (GAFF)[3] with partial changes from AM1-BCC.[4] Molecular simulations were performed using the GROMACS 4.6 dynamics package.[5] The OBC Generalized Born implicit solvation model was used in all simulations.[6] Twenty-four replicas were used with exponentially-spaced temperatures ranging from 300 K to 450 K. Swaps between adjacent replicas were attempted every 10 ps, with acceptance ratios around 90%. REMD trajectories were simulated for 1.2 μs (× 24 replicas) for carolacton, and 1.6 μs (× 24 replicas) for D4, C3, C4 and D3 using stochastic integration (Langevin dynamics) with a 2 fs time step and water-like viscosity. Trajectory snapshots and energies were written every 10 ps.

For each analog, principal component analysis (PCA) of all rotatable dihedral angles (both in the macrolide ring and side chain) was used to project the trajectory data to a low-dimensional subspace, facilitating conformational clustering into 50 conformational basins using the *k*-centers clustering algorithm (Figure S2). The 50 conformations corresponding to each cluster generator were then selected for further refinement using *ab initio* QM.

***Ab initio* QM calculations for carolacton analogs**. DFT calculations were performed using Gaussian09.[7] Structures were geometry-optimized using HF/6-31+G(d) with the PCM (polarizable continuum solvent model), following by single point energy calculation using B3LYP/6-311+G(2d,p) with PCM.

5. Synthesis

5.1 Instrumentation and General Notes

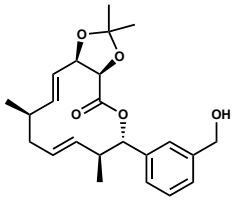
NMR spectra were recorded using the following spectrometers: Bruker Advance 500 (500/125 MHz) or Bruker Advance 400 (400/100 MHz). Chemical shifts are quoted in ppm relative to tetramethylsilane and with the indicated solvent as an internal reference. The following abbreviations are used to describe signal multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), dd (doublet of doublets), dt (doublet of triplets), etc. Accurate mass spectra were recorded on an Agilent 6520 Accurate-Mass Q-TOF LC/MS,

infrared spectra were obtained using a Thermo Nicolet Nexus 670 FTIR spectrophotometer, and specific rotation measurements were made with a 1 dm path length using a Perkin Elmer 341 Polarimeter.

Non-aqueous reactions were performed under an atmosphere of argon, in oven and flame-dried glassware, with HPLC-grade solvents (dichloromethane (DCM), tetrahydrofuran (THF), toluene (PhMe), acetonitrile (ACN)) dried by passage through activated alumina. Amine bases were freshly distilled from CaH2 prior to use. Brine refers to a saturated aqueous solution of sodium chloride.

All reported yields are based upon purity by ^{1}HNMR and therefore some yields are based upon samples containing residual amounts of solvent, as

5.2 Experimental procedures



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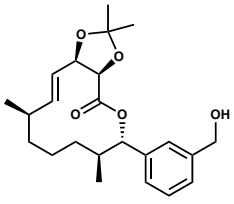

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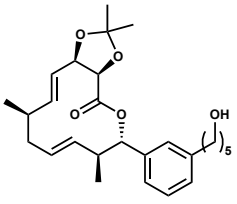

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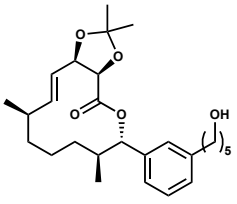

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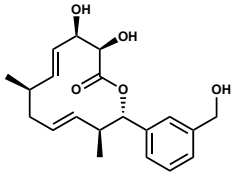

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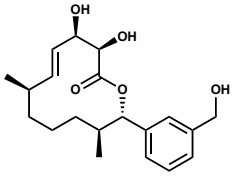

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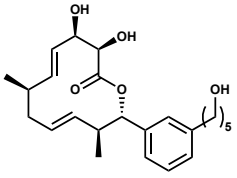

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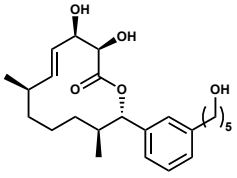

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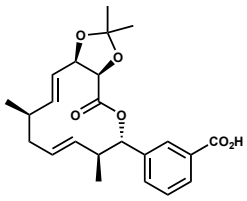

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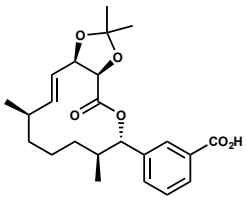

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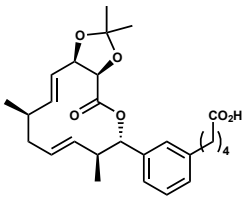

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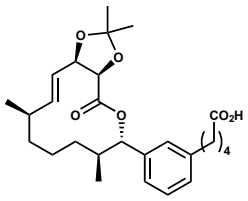

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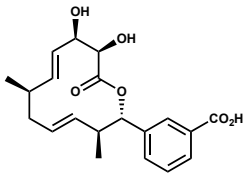

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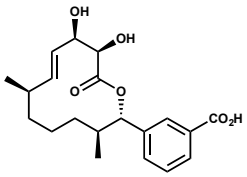

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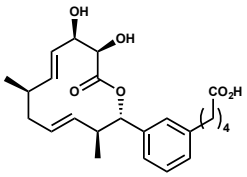

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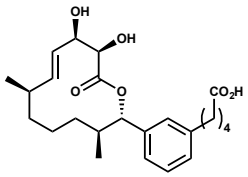

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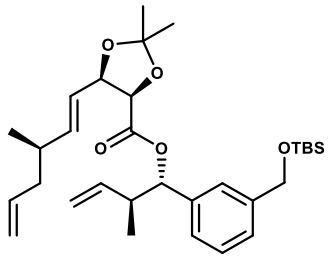
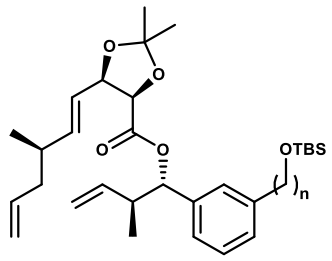


Representative Procedure A: EDC Esterification

(4*R*,5*R*)-(1*S*,2*S*)-1-(3-(((*tert*-Butyldimethylsilyl)oxy)methyl)phenyl)-2-methyl but-3-en-1-yl-2,2-dimethyl-5-((*R*,*E*)-3-methylhexa-1,5-dien-1-yl)-1,3-dioxolane-4-carboxylate ((−)-9a) A flame dried flask was charged with argon and **(−)-3** (100 mg, 0.416 mmol) and DCM (4.2 mL) and subsequently cooled to 0 ^{o}C. Once cool, DMAP (34 mg, 0.027 mmol) and EDCI (106 mg, 0.555 mmol) were added consecutively followed by a solution of **(−)-5a** (85 mg, 0.277 mmol) in DCM (2.8 mL) added via syringe pump. The reaction was stirred 18 hours whereupon it was added to a separatory funnel containing H_2O (15 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 x 15 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated.

Purification by flash column chromatography (0 to 20% EtOAc in hexanes) afforded the product as a clear oil (130 mg, 89%).

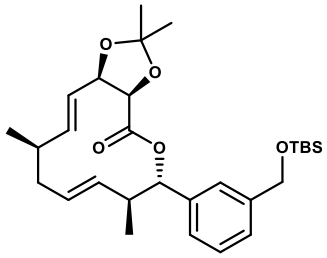
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 3H), 7.22 – 7.17 (m, 1H), 5.85 – 5.64 (m, 3H), 5.61 (d, *J* = 7.5 Hz, 1H), 5.19 – 5.10 (m, 1H), 5.10 – 5.03 (m, 2H), 5.01 – 4.92 (m, 2H), 4.79 – 4.71 (m, 3H), 4.61 (d, *J* = 7.0 Hz, 1H), 2.74 – 2.64 (m, 1H), 2.08 – 1.95 (m, 2H), 1.89 – 1.83 (m, 1H), 1.66 (s, 3H), 1.40 (s, 3H), 0.95 (s, 9H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.10 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.12, 142.70, 141.55, 139.54, 138.49, 136.78, 128.24, 126.06, 125.80, 125.13, 122.13, 116.19, 115.96, 110.95, 80.33, 79.37, 78.34, 64.93, 43.04, 40.72, 35.93, 27.18, 26.08, 25.81, 19.16, 18.53, 16.06, -5.09; **IR** (neat): 3076, 2956, 2928, 2856, 1758, 1733, 1641, 1471, 1462, 1379, 1253, 1217, 1183, 1162, 1082, 1042, 1004, 973, 913, 880, 836, 815, 776, 703, 668, 567, 561 cm^{-1}; **$[\alpha]^{25}_D$** -61.6 (c = 0.92 in $CHCl_3$); **HRMS** (ES^+): Found 551.3152 (-1.1 ppm), $C_{31}H_{48}O_5SiNa$ ($M+Na^+$) requires 551.3163



(4*R*,5*R*)-(1*S*,2*S*)-1-(3-(5-((*tert*-Butyldimethylsilyl)oxy)pentyl)phenyl)-2-methyl but-3-en-1-yl-2,2-dimethyl-5-((*R*,*E*)-3-methylhexa-1,5-dien-1-yl)-1,3-dioxolane-4-carboxylate ((−)-9b)

Prepared according to Representative Procedure A: **(−)-3 (**650 mg, 2.71 mmol), in DCM (27 mL), DMAP (826 mg, 6.76 mmol), EDCI (778 mg, 4.06 mmol), and **(−)-5b** (490 mg, 1.35 mmol) in DCM (14 mL) yielded 759 mg (96%) of the ester. Purified by column chromatography (0 to 20% EtOAc in hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.18 (m, 1H), 7.14 – 7.03 (m, 3H), 5.82 – 5.61 (m, 3H), 5.58 (d, *J* = 7.6 Hz, 1H), 5.13 – 5.06 (m, 1H), 5.06 – 5.00 (m, 2H), 4.99 – 4.91 (m, 2H), 4.77 – 4.70 (m, 1H), 4.59 (d, *J* = 7.0 Hz, 1H), 3.60 (t, *J* = 6.6 Hz, 2H), 2.70 – 2.66 (m, 1H), 2.61 – 2.56 (m, 2H), 2.02 – 1.93 (m, 2H), 1.87 – 1.81 (m, 1H), 1.65 (s, 3H), 1.63 – 1.52 (m, 4H), 1.40 – 1.34 (m, 5H), 0.91 – 0.86 (m, 12H), 0.79 (d, *J* = 6.6 Hz, 3H), 0.04 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.17, 142.73, 142.69, 139.65, 138.52, 136.80, 128.20, 127.65, 124.78, 122.10, 116.18, 115.90, 110.96, 80.35, 79.40, 78.40, 63.35, 43.12, 40.73, 36.06, 35.91, 32.87, 31.41, 27.18, 26.14, 25.83, 25.72, 19.15, 18.53, 16.16, -5.11; **IR** (neat): 2929, 2857, 1735, 1641, 1608, 1461, 1372, 1234, 1163, 1091, 1022, 997, 974, 913, 880, 834, 774, 706, 661 cm^{-1}; **$[\alpha]^{25}_D$** -47.3 (c = 0.30 in $CHCl_3$); **HRMS** (ES^+): Found 602.4218 (-2.3 ppm), $C_{35}H_{60}O_5SiN$ ($M+NH_4^+$) requires 602.4241

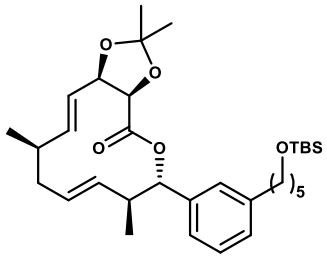


Representative Procedure B: Ring-Closing Metathesis

(3a*R*,6*S*,7*S*,8*E*,11*R*,12*E*,13a*R*)-6-(3-(((*tert*-Butyldimethylsilyl)oxy)methyl)phenyl)-2,2,7,11-tetramethyl-6,7,10,11-tetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*][1]oxacyclo dodecin-4(13a*H*)-one ((−)-6a) A flask was charged with **(−)-9a** (80 mg, 0.150 mmol) and DCM (30 mL). Grubbs 2nd generation catalyst (6.0 mg, 0.0076 mmol, 5 mol%) was added and the reaction was stirred at room temperature for 20 hours. The solvent was removed and the crude residue was purified by flash column chromatography (0 to 3% EtOAc in hexanes) to afford the product as a yellowish

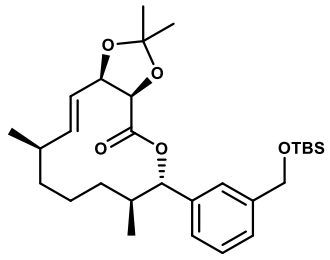
oil (59 mg, 78%). *NOTE: In our experience, degassing solvent prior to use had no noticeable effect on the outcome of the reaction.*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.25 (m, 3H), 7.21 – 7.17 (m, 1H), 5.87 – 5.75 (m, 1H), 5.58 (d, *J* = 10.8 Hz, 1H), 5.38 – 5.22 (m, 3H), 4.77 – 4.69 (m, 3H), 4.45 (d, *J* = 6.6 Hz, 1H), 2.66 – 2.49 (m, 1H), 2.39 – 2.19 (m, 2H), 2.16 – 1.98 (m, 1H), 1.66 (s, 3H), 1.37 (s, 3H), 1.08 (d, *J* = 6.7 Hz, 3H), 0.93 (s, 9H), 0.75 (d, *J* = 6.8 Hz, 3H), 0.08 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.85, 141.81, 139.29, 138.85, 134.70, 130.68, 128.43, 126.56, 126.12, 125.54, 123.65, 111.03, 80.72, 79.11, 78.43, 64.91, 43.29, 38.54, 35.90, 26.90, 26.07, 25.99, 20.99, 17.61, -5.07; **IR** (neat): 2955, 2928, 2856, 1796, 1750, 1472, 1461, 1379, 1252, 1222, 1180, 1161, 1081, 1001, 968, 879, 814, 776, 735, 703, 670 cm^{-1}; **$[\alpha]^{25}_D$** -34.4 (c = 1.00 in $CHCl_3$); **HRMS** (ES^+): Found 523.2869 (+1.3 ppm), $C_{29}H_{44}O_5SiNa$ ($M+Na^+$) requires 523.2856



(3a*R*,6*S*,7*S*,8*E*,11*R*,12*E*,13a*R*)-6-(3-(5-((*tert*-Butyldimethylsilyl)oxy) pentyl)phenyl)-2,2,7,11-tetramethyl-6,7,10,11-tetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*][1]oxacyclo dodecin-4(13a*H*)-one ((−)-6b) Prepared according to Representative Procedure B: **(−)-9b** (750 mg, 1.28 mmol), Grubbs 2nd Generation catalyst (54 mg, 0.064 mmol, 5 mol%), and DCM (128 mL) yielded 710 mg (99%) of the product as a clear oil. Purified by column chromatography (0 to 3% EtOAc in hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.17 (m, 1H), 7.15 – 7.06 (m, 3H), 5.85 – 5.78 (m, 1H), 5.57 (d, *J* = 10.8 Hz, 1H), 5.35 – 5.29 (m, 1H), 5.29 – 5.23 (m, 2H), 4.77 – 4.70 (m, 1H), 4.47 (d, *J* = 6.7 Hz, 1H), 3.60 (t, *J* = 6.6 Hz, 2H), 2.62 – 2.55 (m, 3H), 2.34 – 2.21 (m, 2H), 2.09 – 1.99 (m, 1H), 1.67 (s, 3H), 1.63 – 1.57 (m, 2H), 1.57 – 1.51 (m, 2H), 1.39 – 1.33 (m, 5H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.75 (d, *J* = 6.8 Hz, 3H), 0.04 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.81, 142.99, 139.25, 138.84, 134.79, 130.59, 128.44, 127.93, 125.20, 123.69, 111.00, 80.76, 79.11, 78.42, 63.28, 43.30, 38.53, 35.98, 35.88, 32.79, 31.40, 26.88, 26.10, 25.96, 25.68, 21.00, 18.47, 17.65, -5.15; **IR** (neat): 2954, 2928, 2856, 1751, 1608, 1586, 1459, 1379, 1251, 1222, 1180, 1085, 1002, 968, 880, 834, 813, 775, 705, 662 cm^{-1}; **$[\alpha]^{25}_D$** -69.4 (c = 1.90 in $CHCl_3$); **HRMS** (ES^+): Found 557.3639 (-1.8 ppm), $C_{33}H_{52}O_5Si$ ($M+H^+$) requires 557.3657

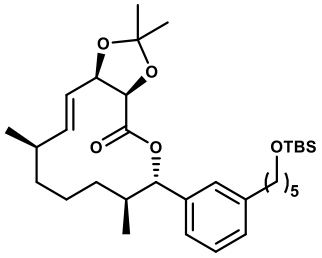


Representative Procedure C: Hydrogenation

(3a*R*,6*S*,7*S*,11*R*,13a*R*,*E*)-6-(3-(((*tert*-Butyldimethylsilyl)oxy)methyl)phenyl)-2,2,7,11-tetramethyl-6,7,8,9,10,11-hexahydro-3a*H*-[1,3]dioxolo[4,5-*c*][1]oxacyclododecin-4(13a*H*)-one ((−)-7a) To a solution of **(−)-6a** (36 mg, 0.072 mmol) in ethanol (7.2 mL) was added palladium on carbon (10% w/w, 6 mg). The reaction was sparged with hydrogen gas 5 times from a balloon and stirred for 1.5 hours. The reaction was passed through a pad of celite with EtOAc (100 mL) and the solvent was removed. The residue was purified by preparative TLC (3% EtOAc in hexanes, eluted twice, to remove a more non-polar impurity) to afford the product

as a clear oil (25 mg, 69%).

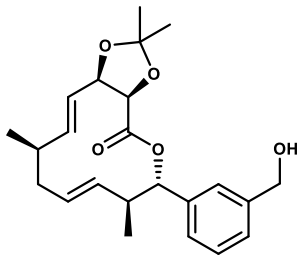
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.20 (m, 3H), 7.19 – 7.14 (m, 1H), 5.72 – 5.59 (m, 2H), 5.51 (d, *J* = 11.3 Hz, 1H), 4.87 – 4.82 (m, 1H), 4.70 (s, 2H), 4.52 (d, *J* = 6.6 Hz, 1H), 2.44 – 2.33 (m, 1H), 2.28 – 2.17 (m, 1H), 2.03 – 1.92 (m, 1H), 1.68 (s, 3H), 1.41 – 1.36 (m, 6H), 1.02 (d, *J* = 6.6 Hz, 2H), 0.93 (s, 9H), 0.68 (d, *J* = 7.0 Hz, 3H), 0.08 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.49, 141.63, 139.92, 135.89, 128.32, 126.56, 125.95, 125.46, 122.37, 110.98, 79.40, 78.66, 65.00, 36.26, 35.81, 33.87, 29.44, 26.95, 26.09, 26.03, 21.06, 18.54, 17.99, 15.91, -5.06; **IR** (neat): 2956, 2928, 2856, 2904, 1752, 1462, 1379, 1250, 1224, 1176, 1123, 1081, 1006, 976, 815, 776, 719, 702, 668, 617 cm^{-1}; **$[\alpha]^{25}_D$** -106 (c = 1.88 in $CHCl_3$); **HRMS** (ES^+): Found 525.3036 (+2.4 ppm), $C_{29}H_{46}O_5SiNa$ ($M+Na^+$) requires 525.3012



(3a*R*,6*S*,7*S*,11*R*,13a*R*,*E*)-6-(3-(5-((*tert*-Butyldimethylsilyl)oxy)pentyl)phenyl)-2,2,7,11-tetramethyl-6,7,8,9,10,11-hexahydro-3a*H*-[1,3]dioxolo[4,5-*c*][1]oxacyclododecin-4(13a*H*)-one ((−)-7b) Prepared according to Representative Procedure C: **(−)-6b** (20 mg, 0.036 mmol), Pd/C (10% w/w, 2 mg), and EtOH (3.6 mL) yielded 11 mg (55%) of the product as a clear oil. Purified by preparative TLC (3% EtOAc in hexanes, eluted twice).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 – 7.15 (m, 1H), 7.11 – 7.08 (m, 2H), 7.07 – 7.03 (m, 1H), 5.71 – 5.60 (m, 2H), 5.49 (d, *J* = 11.5 Hz, 1H), 4.87 – 4.80 (m, 1H), 4.54 (d, *J* = 6.6 Hz, 1H), 3.59 (t, *J* = 6.6 Hz, 1H), 2.58 – 2.54 (m, 2H), 2.42 – 2.36 (m, 1H), 2.28 – 2.17 (m, 1H), 2.01 – 1.94 (m, 1H), 1.68 (s, 3H), 1.63 – 1.50 (m, 6H), 1.39 – 1.37 (m, 3H), 1.37 – 1.32 (m, 3H), 1.08 –

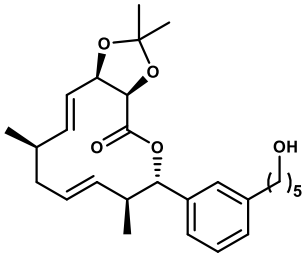
1.04 (m, 2H), 1.02 (d, J = 6.5 Hz, 3H), 0.89 (s, 9H), 0.68 (d, J = 7.0 Hz, 3H), 0.04 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.49, 142.84, 139.98, 135.91, 128.29, 128.24, 127.83, 125.18, 122.37, 110.99, 79.50, 78.69, 63.37, 36.36, 36.02, 35.82, 33.90, 32.85, 31.41, 29.44, 26.96, 26.14, 26.04, 25.73, 21.07, 18.53, 17.97, 15.95, -5.10; **IR** (neat): 2928, 2856, 2360, 1753, 1608, 1460, 1379, 1250, 1223, 1176, 1085, 1005, 977, 874, 834, 775, 705, 667 cm^{-1}; **$[\alpha]^{25}_D$** -63.9 (c = 0.43 in $CHCl_3$); **HRMS** (ES^+): Found 581.3630 (-0.8 ppm), $C_{33}H_{54}O_{5Si}Na$ ($M+Na^+$) requires 581.3638



Representative Procedure D: TBS removal

(3a*R*,6*S*,7*S*,8*E*,11*R*,12*E*,13a*R*)-6-(3-(Hydroxymethyl)phenyl)-2,2,7,11-tetramethyl-6,7,10,11-tetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*][1]oxacyclododecin-4(13a*H*)-one ((−)-A1) To a solution of **(−)-6a** (21 mg, 0.0420 mmol) in THF (0.42 mL) was added *tetra*-butylammonium fluoride (1M in THF, 0.13 mL), and the reaction was stirred for 1 hour. The reaction was quenched with saturated aqueous ammonium chloride and diluted in diethyl ether. The organic layer was separated and the aqueous layer was extracted 4 times with diethyl ether. The combined organic layers were washed with water and brine, dried over sodium sulfate, filtered, and concentrated. The crude product was purified by preparative TLC (3:2 hexanes/EtOAc) to afford the product alcohol as a clear oil (15 mg, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 1H), 7.32 – 7.26 (m, 1H), 7.28 – 7.22 (m, 1H), 5.82 (dd, *J* = 15.7, 6.6 Hz, 1H), 5.58 (d, *J* = 10.8 Hz, 1H), 5.36 – 5.23 (m, 3H), 4.76 – 4.70 (m, 1H), 4.67 (s, 2H), 4.46 (d, *J* = 6.7 Hz, 1H), 2.69 – 2.52 (m, 1H), 2.36 – 2.20 (m, 2H), 2.11 – 1.99 (m, 1H), 1.65 (s, 3H), 1.37 (s, 3H), 1.08 (d, *J* = 6.5 Hz, 3H), 0.76 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.89, 141.29, 139.45, 139.38, 134.63, 130.77, 128.78, 127.33, 127.02, 126.40, 123.67, 111.10, 80.69, 79.22, 78.43, 65.31, 43.15, 38.49, 35.87, 26.91, 25.99, 20.95, 17.61; **IR** (neat): 3467, 2959, 2929, 2872, 1746, 1455, 1378, 1293, 1251, 1221, 1183, 1161, 1082, 1039, 1000, 969, 910, 880, 785, 729, 705, 673, 647 cm^{-1}; **$[\alpha]^{25}_D$** -76.4 (c = 1.40 in $CHCl_3$); **HRMS** (ES^+): Found 387.2169 (+0.3 ppm), $C_{23}H_{30}O_5$ ($M+H^+$) requires 387.2166

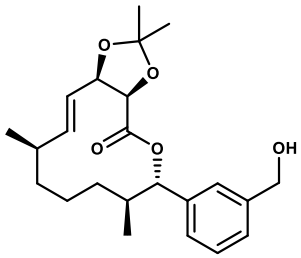


(3a*R*,6*S*,7*S*,8*E*,11*R*,12*E*,13a*R*)-6-(3-(5-Hydroxypentyl)phenyl)-2,2,7,11-tetramethyl-6,7,10,11-tetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*][1]oxacyclododecin-4(13a*H*)-one((−)-A3)

Prepared according to Representative Procedure D: **(−)-6b** (35 mg, 0.063 mmol), TBAF (1M in THF, 0.63 mL), and THF (0.63 mL) yielded 19 mg (68%) of the product as a clear oil. Purified by preparative TLC (1:1 EtOAc/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.20 (m, 1H), 7.16 – 7.08 (m, 3H), 5.82 (dd, *J* = 15.6, 6.6 Hz, 1H), 5.56 (d, *J* = 10.8 Hz, 1H), 5.37 – 5.22 (m, 3H), 4.73 (t, *J* = 7.1 Hz, 1H), 4.47 (d, *J* = 6.6 Hz, 1H), 3.63 (t, *J* = 6.6 Hz, 2H), 2.64 – 2.56 (m, 3H), 2.37 – 2.23 (m, 2H), 2.12 – 2.02 (m, 1H), 1.66 (s, 3H), 1.64 – 1.53 (m, 4H), 1.43 – 1.33 (m, 5H), 1.09 (d, *J* = 6.7 Hz, 3H), 0.76 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.88, 142.83, 139.44, 138.90, 134.81, 130.65,

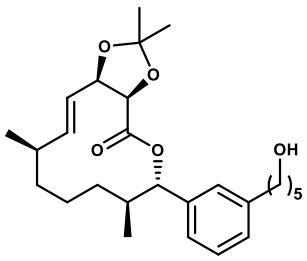
128.50, 128.12, 125.24, 123.70, 111.09, 80.88, 79.21, 78.44, 63.05, 43.20, 38.52, 35.91, 32.73, 31.28, 26.92, 25.99, 25.51, 20.99, 17.65; **IR** (neat): 3313, 2927, 2855, 1748, 1608, 1456, 1379, 1221, 1182, 1083, 969, 880, 786, 753, 705, 667 cm^{-1}; **[α]$^{25}_{D}$** -46.2 (c = 0.58 in $CHCl_3$); **HRMS** (ES^+): Found 443.2788 (-0.4 ppm), $C_{27}H_{38}O_5$ ($M+H^+$) requires 443.2792



(3a*R*,6*S*,7*S*,11*R*,13a*R*,*E*)-6-(3-(Hydroxymethyl)phenyl)-2,2,7,11-tetramethyl-6,7,8,9,10,11-hexahydro-3a*H*-[1,3]dioxolo[4,5-*c*][1]oxacyclododecin-4(13a*H*)-one ((−)-A2) Prepared according to Representative Procedure D: **(−)-7a** (28 mg, 0.058 mmol), TBAF (1M in THF, 0.17 mL), and THF (0.56 mL) yielded 19.5 mg (90%) of the product as a clear oil. Purified by preparative TLC (3:2 hexanes/EtOAc).

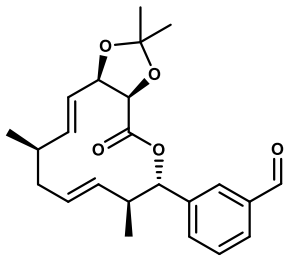
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 3H), 7.24 – 7.21 (m, 1H), 5.70 – 5.59 (m, 2H), 5.52 (d, *J* = 11.5 Hz, 1H), 4.87 – 4.82 (m, 1H), 4.66 (s, 2H), 4.54 (d, *J* = 6.6 Hz, 1H), 2.44 – 2.34 (m, 1H), 2.28 – 2.20 (m, 1H), 2.02 – 1.94 (m, 1H), 1.67 (s, 3H), 1.44 – 1.33 (m, 7H), 1.11 – 1.05 (m, 2H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.69 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.60, 141.08, 140.42, 135.87, 128.70, 127.19, 126.84, 126.42, 122.32, 111.03, 79.32, 78.63, 65.38, 36.23, 35.81, 33.83, 29.34, 26.94, 26.01, 21.07, 17.91, 15.91; **IR** (neat): 3500, 2931, 2360, 2342, 1748, 1455, 1379, 1223, 1182, 1162, 1123, 1083, 974, 909, 873, 837, 738, 729, 704, 648 cm^{-1}; **[α]$^{25}_{D}$** -100 (c = 0.50 in $CHCl_3$); **HRMS** (ES^+): Found 411.2125 (-1.7 ppm), $C_{23}H_{32}O_5Na$

($M+Na^+$) requires 411.2142



(3a*R*,6*S*,7*S*,11*R*,13a*R*,*E*)-6-(3-(5-Hydroxypentyl)phenyl)-2,2,7,11-tetramethyl-6,7,8,9,10,11-hexahydro-3a*H*-[1,3]dioxolo[4,5-*c*][1]oxacyclododecin-4(13a*H*)-one ((−)-A4) Prepared according to representative Procedure D: **(−)-7b** (21 mg, 0.038 mmol), TBAF (1M in THF, 0.11 mL), and THF (0.38 mL) yielded 10.7 mg (64%) of the product as a clear oil. Purified by preparative TLC (3:2 hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.15 (m, 1H), 7.12 – 7.08 (m, 2H), 7.07 – 7.03 (m, 1H), 5.71 – 5.57 (m, 2H), 5.48 (d, *J* = 11.5 Hz, 1H), 4.85 (dd, *J* = 6.5, 3.2 Hz, 1H), 4.54 (d, *J* = 6.6 Hz, 1H), 3.62 (t, *J* = 6.6 Hz, 2H), 2.58 (t, *J* = 7.6 Hz, 2H), 2.43 – 2.35 (m, 1H), 2.28 – 2.18 (m, 1H), 2.04 – 1.93 (m, 1H), 1.68 (s, 3H), 1.65 – 1.52 (m, 6H), 1.42 – 1.32 (m, 7H), 1.13 – 1.05 (m, 2H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.68 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.53, 142.59, 139.95, 135.88, 128.36, 128.27, 128.07, 125.11, 122.34, 111.02, 79.53, 78.64, 63.04, 36.23, 35.88, 35.81, 33.87, 32.73, 31.20, 29.39, 26.94, 26.01, 25.45, 21.07, 17.93, 15.94; **IR** (neat): 3392, 2932, 2859, 2360, 2341, 1748, 1608, 1456, 1380, 1184, 1123, 1083, 976, 874, 836, 785, 752, 705, 667 cm^{-1}; **$[\alpha]^{25}_D$** -100.6 (c = 0.72 in $CHCl_3$); **HRMS** (ES^+): Found 445.2935 (-1.4 ppm), $C_{27}H_{40}O_5$ ($M+H^+$) requires 445.2949

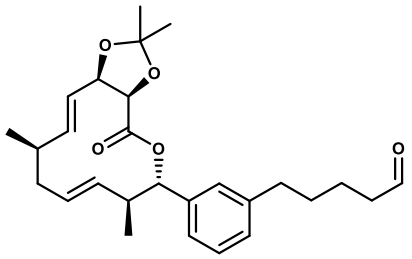


Representative Procedure E: Parikh-Döering Oxidation

3-((3a*R*,6*S*,7*S*,8*E*,11*R*,12*E*,13a*R*)-2,2,7,11-Tetramethyl-4-oxo-4,6,7,10,11,13a-hexahydro-3a*H*-[1,3]dioxolo[4,5-*c*][1]oxacyclododecin-6-yl)benzaldehyde ((−)-10a) To a solution of **(−)-A1** (10 mg, 0.026 mmol) in DCM (0.26 mL) was added DMSO (0.04 mL, 0.52 mmol) and triethylamine (0.04 mL, 0.26 mmol). The solution was cooled to 0 ^{o}C and SO_3-Pyr (33 mg, 0.21 mmol) was added in a single portion. The reaction mixture was removed from the cooling bath and allowed to stir at room temperature for 45 minutes. The reaction was then quenched with saturated aqueous ammonium chloride, diluted in DCM, and poured into a separatory funnel. The organic layer was removed and the aqueous layer was extracted 5x DCM (5 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and reduced. The residue was purified by preparative TLC (4:1 hexanes/EtOAc) to afford the product as a clear oil (8 mg, 80%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.01 (s, 1H), 7.88 (s, 1H), 7.85 – 7.78 (m, 1H), 7.64 – 7.55 (m, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 5.83 (dd, *J* = 15.7, 6.7 Hz, 1H), 5.65 (d, *J* = 10.8 Hz, 1H), 5.36 – 5.21 (m, 3H), 4.78 – 4.72 (m, 1H), 4.48 (d, *J* = 6.6 Hz, 1H), 2.66 – 2.57 (m, 1H), 2.37 – 2.31 (m, 1H), 2.30 – 2.24 (m, 1H), 2.12 – 2.05 (m, 1H), 1.66 (s, 3H), 1.37 (s, 3H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.77 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.15, 169.90, 140.35, 139.60, 136.78, 134.20, 134.07, 131.21, 130.07, 129.32, 128.66, 123.52, 111.19, 79.99, 79.23, 78.34,

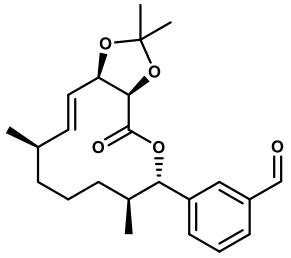
43.20, 38.41, 35.84, 26.88, 25.96, 20.90, 17.45; **IR** (neat): 2958, 2927, 2876, 2851, 2726, 2257, 1821, 1748, 1699, 1604, 1535, 1455, 1379, 1290, 1250, 1220, 1180, 1161, 1040, 1000, 969, 911, 880, 785, 731, 696, 675, 650 cm^{-1}; **$[\alpha]^{25}_{D}$** -65.3 (c = 0.30 in $CHCl_3$); **HRMS** (ES^+): Found 407.1825 (-0.9 ppm), $C_{23}H_{28}O_5Na$ ($M+Na^+$) requires 407.1834



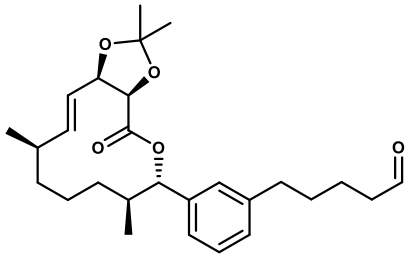
5-(3-((3a*R*,6*S*,7*S*,8*E*,11*R*,12*E*,13a*R*)-2,2,7,11-Tetramethyl-4-oxo-4,6,7,10,11,13a-hexahydro-3a*H*-[1,3]dioxolo[4,5-*c*][1]oxacyclododecin-6-yl)phenyl)pentanal ((−)-11a) Prepared according to Representative Procedure E: **(−)-A3** (10 mg, 0.026 mmol), DMSO (0.03 mL, 0.45 mmol), triethylamine (0.03 mL, 0.23 mmol), SO_3-Pyr (29 mg, 0.18 mmol), and DCM (0.23 mL) yielded 6.2 mg (63%) of the product as a clear oil. Purified by preparative TLC (4:1 hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, *J* = 3.6 Hz, 1H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.16 – 7.07 (m, 3H), 5.82 (dd, *J* = 15.6, 6.6 Hz, 1H), 5.56 (d, *J* = 10.9 Hz, 1H), 5.36 – 5.23 (m, 3H), 4.76 – 4.70 (m, 1H), 4.47 (d, *J* = 6.6 Hz, 1H), 2.64 – 2.52 (m, 3H), 2.49 – 2.42 (m, 2H), 2.36 – 2.21 (m, 2H), 2.11 – 2.01 (m, 1H), 1.70 – 1.62 (m, 7H), 1.37 (s, 3H), 1.08 (d, *J* = 6.7 Hz, 3H), 0.75 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.69, 169.89, 142.25, 139.42, 139.06, 134.77, 130.70, 128.56, 128.47, 125.49, 123.69, 111.08, 80.79, 79.20, 78.46, 43.87, 43.29, 38.54, 35.90, 35.71, 30.97, 26.92, 26.00, 21.86, 21.01, 17.66; **IR** (neat): 3031, 2959, 2024, 2873, 2854, 2720, 2360, 2343, 1748, 1724, 1608, 1559, 1488, 1457, 1379, 1252, 1222, 1183, 1084, 1041, 1000,

970, 880, 786, 706, 667 cm^{-1}; **[α]$^{25}_{D}$** -84 (c = 0.22 in $CHCl_3$); **HRMS** (ES^+): Found 463.2487 (+2.7 ppm), $C_{27}H_{36}O_5Na$ ($M+Na^+$) requires 463.2460

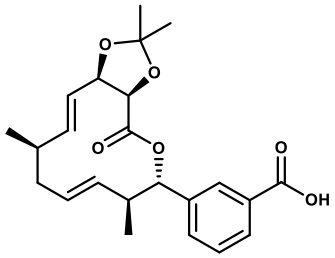


3-((3a*R*,6*S*,7*S*,11*R*,13a*R*,*E*)-2,2,7,11-Tetramethyl-4-oxo-4,6,7,8,9,10,11,13a-octahydro-3a*H*-[1,3]dioxolo[4,5-*c*][1]oxacyclododecin-6-yl)benzaldehyde ((−)-10b) Prepared according to Representative Procedure E: **(−)-A2** (14 mg, 0.036 mmol), DMSO (0.05 mL, 0.72 mmol), triethylamine (0.05 mL, 0.36 mL) SO_3-Pyr (46 mg, 0.29 mmol), and DCM (0.36 mL) yielded 12.5 mg (89%) of the product as a clear oil. Purified by preparative TLC (4:1 hexanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.84 – 7.83 (m, 1H), 7.80 – 7.77 (m, 1H), 7.60 – 7.55 (m, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 5.74 – 5.63 (m, 2H), 5.59 (d, *J* = 11.5 Hz, 1H), 4.86 (dd, *J* = 6.5, 3.3 Hz, 1H), 4.55 (d, *J* = 6.6 Hz, 1H), 2.46 – 2.35 (m, 1H), 2.33 – 2.23 (m, 1H), 2.06 – 1.97 (m, 1H), 1.67 (s, 3H), 1.46 – 1.35 (m, 6H), 1.13 – 1.06 (m, 2H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.69 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 192.19, 169.65, 141.40, 136.72, 135.92, 134.18, 129.80, 129.23, 128.77, 122.31, 111.13, 78.64, 78.58, 36.33, 35.81, 33.77, 29.27, 26.92, 25.99, 21.05, 17.90, 15.79; **IR** (neat): 2959, 2926, 2852, 2729, 2160, 2031, 1974, 1790, 1749, 1698, 1604, 1455, 1379, 1288, 1224, 1178, 1160, 1124, 1082, 977, 908, 873, 837, 789, 728, 696, 650 cm^{-1}; **[α]$^{25}_{D}$** -84.4 (c = 0.50 in $CHCl_3$); **HRMS** (ES^+): Found 409.1999 (+0.8 ppm), $C_{23}H_{30}O_5Na$ ($M+Na^+$) requires 409.1991



5-(3-((3a*R*,6*S*,7*S*,11*R*,13a*R*,*E*)-2,2,7,11-Tetramethyl-4-oxo-4,6,7,8,9,10,11,13a-octahydro-3a*H*-[1,3]dioxolo[4,5-*c*][1]oxacyclododecin-6-yl)phenyl)pentanal ((−)-11b) Prepared according to Representative Procedure E: **(−)A4** (7.0 mg, 0.016 mmol), DMSO (0.02 mL, 0.315 mmol), triethylamine (0.02 mL, 0.157 mmol) SO_3-Pyr (20 mg, 0.126 mmol), and DCM (0.16 mL) yielded 6 mg (86 %) of the product as a clear oil. Purified by preparative TLC (4:1 hexanes/EtOAc) .

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.13 – 7.04 (m, 3H), 5.71 – 5.60 (m, 2H), 5.49 (d, *J* = 11.5 Hz, 1H), 4.86 – 4.84 (m, 1H), 4.54 (d, *J* = 6.6 Hz, 1H), 2.59 (t, *J* = 7.1 Hz, 2H), 2.46 – 2.43 (m, 2H), 2.40 – 2.35 (m, 1H), 2.25 – 2.18 (m, 1H), 2.02 – 1.95 (m, 1H), 1.68 (s, 3H), 1.66 – 1.61 (m, 4H), 1.42 – 1.34 (m, 6H), 1.09 – 1.05 (m, 2H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.68 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.74, 169.52, 142.02, 140.15, 135.91, 128.44, 128.22, 127.87, 125.40, 122.36, 111.01, 79.45, 78.67, 43.87, 36.33, 35.82, 35.68, 33.88, 30.92, 29.41, 26.96, 26.03, 21.85, 21.07, 17.95, 15.94; **IR** (neat): 2926, 2855, 1749, 1724, 1608, 1488, 1456, 1379, 1223, 1180, 1124, 1084, 977, 911, 874, 836, 785, 731, 706, 648 cm^{-1}; **$[\alpha]^{25}_D$** -76.6 (c = 0.60 in $CHCl_3$); **HRMS** (ES^+): Found 443.2757 (-4.0 ppm), $C_{27}H_{39}O_5$ ($M+H^+$) requires 443.2797

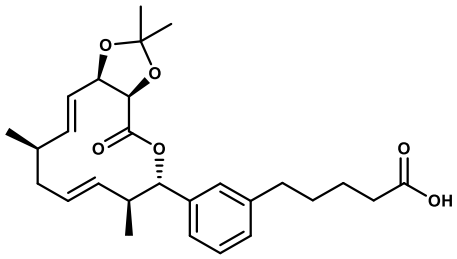


Representative Procedure F: Pinnick Oxidation

3-((3a*R*,6*S*,7*S*,8*E*,11*R*,12*E*,13a*R*)-2,2,7,11-Tetramethyl-4-oxo-4,6,7,10,11,13a-hexahydro-3a*H*-[1,3]dioxolo[4,5-*c*][1]oxacyclododecin-6-yl)benzoic acid ((−)-C1) To a rapidly stirring solution of **(−)-10a** (8.0 mg, 0.021 mmol) in *tert*-butyl alcohol (0.42 mL) and acetonitrile (0.21 mL) was added 2-methyl-2-butene (neat, 0.11mL), and the reaction vessel was sparged with argon. The solution was cooled to 0 °C, and a freshly prepared solution of NaH_2PO_4 (12 mg, 0.10 mmol) and $NaClO_2$ (10 mg, 0.11 mmol) in water (0.62 mL) was added dropwise. The reaction was slowly warmed to room temperature and stirred overnight. The reaction was quenched by addition of a saturated aqueous solution of sodium thiosulfate (1 mL) and diluted in EtOAc. The aqueous layer was separated and acidified to pH 3 with 1N HCl. The acidified aqueous layer was extracted 5x EtOAc (5x 5 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by preparative TLC (1% AcOH, 49% hexanes, 50% EtOAc) to afford the product (6 mg, 75%) as an off white residue.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1H), 8.06 – 8.02 (m, 1H), 7.60 – 7.55 (m, 1H), 7.44 (t, *J* = 7.7 Hz, 1H), 5.87 – 5.79 (m, 1H), 5.65 (d, *J* = 10.8 Hz, 1H), 5.36 – 5.21 (m, 3H), 4.78 – 4.71 (m, 1H), 4.50 (d, *J* = 6.6 Hz, 1H), 2.70 – 2.57 (m, 1H), 2.35 – 2.24 (m, 2H), 2.11 – 2.02 (m, 1H), 1.66 (s, 3H), 1.38 (s, 3H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.77 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.96, 169.90, 139.76, 139.54, 134.21, 133.65, 131.14, 130.31, 129.67, 129.40,

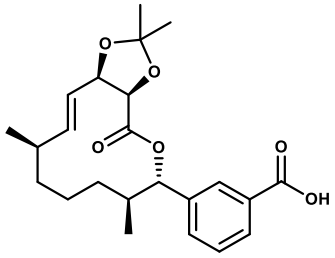
128.81, 123.56, 111.17, 80.09, 79.21, 78.36, 43.28, 38.46, 35.87, 26.89, 25.97, 20.94, 17.50; **IR** (neat): 2957, 2925, 2853, 2360, 1749, 1727, 1693, 1554, 1486, 1455, 1379, 1252, 1222, 1177, 1083, 1039, 970, 913, 880, 814, 784, 758, 696, 668 cm^{-1}; $[\alpha]^{25}_{D}$ -169 (c = 0.40 in $CHCl_3$); **HRMS** (ES^+): Found 423.1777 (-0.1 ppm), $C_{23}H_{28}O_6Na$ ($M+Na^+$) requires 423.1778



5-(3-((3a*R*,6*S*,7*S*,8*E*,11*R*,12*E*,13a*R*)-2,2,7,11-Tetramethyl-4-oxo-4,6,7,10,11,13a-hexahydro-3a*H*-[1,3]dioxolo[4,5-*c*][1]oxacyclododecin-6-yl)phenyl)pentanoic acid ((−)-C3) Prepared according to Representative Procedure F: **(−)-11a** (5.0 mg, 0.011 mmol), *tert*-butyl alcohol (0.23 mL), 2-methyl-2 butene (0.06 mL), acetonitrile (0.11 mL), NaH_2PO_4 (7.0 mg, 0.057 mmol), $NaClO_2$ (6.0 mg, 0.062 mmol), and H_2O (0.34 mL) yielded 3.3 mg (65%) of the product as an off-white residue. Purified by preparative TLC (1% AcOH, 49% hexanes, 50% EtOAc).

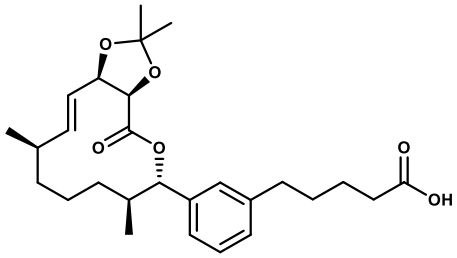
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (t, *J* = 7.5 Hz, 1H), 7.16 – 7.12 (m, 2H), 7.10 – 7.08 (m, 1H), 5.85 – 5.79 (m, 1H), 5.56 (d, *J* = 10.8 Hz, 1H), 5.35 – 5.24 (m, 3H), 4.76 – 4.72 (m, 1H), 4.48 (d, *J* = 6.7 Hz, 1H), 2.65 – 2.55 (m, 3H), 2.39 – 2.34 (m, 2H), 2.34 – 2.30 (m, 1H), 2.28 – 2.24 (m, 1H), 2.10 – 2.02 (m, 1H), 1.69 – 1.63 (m, 7H), 1.38 (s, 3H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.76 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.74, 169.87, 142.32, 139.48, 138.99, 134.78, 130.68, 128.55, 128.52, 125.43, 123.65, 111.12, 80.82, 79.21, 78.40, 43.16, 38.51, 35.88, 35.54, 33.63, 30.76, 26.91, 26.00, 24.37, 21.01, 17.65; **IR** (neat): 2925, 2854, 1747, 1707, 1608, 1488, 1455, 1412, 1378, 1221, 1182, 1162, 1084, 1042, 1000, 969, 880, 786, 755, 705, 667 cm^{-1};

[α]$^{25}_{D}$ -67.2 (c = 0.33 in $CHCl_3$); **HRMS** (ES^+): Found 457.2576 (-0.9 ppm), $C_{27}H_{36}O_6$ ($M+H^+$) requires 457.2585



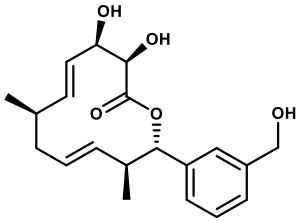
3-((3a*R*,6*S*,7*S*,11*R*,13a*R*,*E*)-2,2,7,11-Tetramethyl-4-oxo-4,6,7,8,9,10,11,13a-octahydro-3a*H*-[1,3]dioxolo[4,5-*c*][1]oxacyclododecin-6-yl)benzoic acid ((−)-C2) Prepared according to Representative Procedure F: **(−)-10b** (5.0 mg, 0.013 mmol), *tert*-butyl alcohol (0.26 mL), 2-methyl-2 butene (0.07 mL), acetonitrile (0.13 mL), NaH_2PO_4 (8.0 mg, 0.065 mmol), $NaClO_2$ (6.0 mg, 0.071 mmol), and H_2O (0.39 mL) yielded 5.0 mg (96%) of the product as an off-white residue. Purified by preparative TLC (1% AcOH, 49% hexanes, 50% EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 8.02 – 7.98 (m, 1H), 7.57 – 7.53 (m, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 5.72 – 5.62 (m, 2H), 5.58 (d, *J* = 11.5 Hz, 1H), 4.87 (dd, *J* = 6.6, 3.6 Hz, 1H), 4.57 (d, *J* = 6.5 Hz, 1H), 2.46 – 2.35 (m, 1H), 2.31 – 2.23 (m, 1H), 2.05 – 1.98 (m, 1H), 1.68 (s, 3H), 1.42 – 1.36 (m, 6H), 1.11 – 1.07 (m, 2H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.70 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.82, 169.60, 140.81, 135.91, 133.64, 130.10, 129.55, 129.30, 128.68, 122.34, 111.09, 78.75, 78.59, 36.38, 35.81, 33.80, 29.31, 26.94, 26.00, 21.06, 17.92, 15.81; **IR** (neat): 2927, 2853, 2553, 1781, 1749, 1681, 1608, 1589, 1454, 1413, 1380, 1283, 1228, 1175, 1123, 1084, 979, 940, 893, 873, 825, 782, 758, 723, 695, 677 cm^{-1}; **[α]$^{25}_{D}$** -130.5 (c = 0.36 in $CHCl_3$); **HRMS** (ES^+): Found 369.1669 (-0.3 ppm), $C_{20}H_{26}O_5Na$ ($M+Na^+$) requires 369.1672



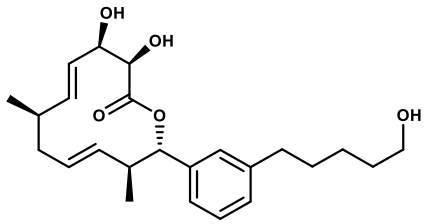
5-(3-((3a*R*,6*S*,7*S*,11*R*,13a*R*,*E*)-2,2,7,11-Tetramethyl-4-oxo-4,6,7,8,9,10,11,13a-octahydro-3a*H*-[1,3]dioxolo[4,5-*c*][1]oxacyclododecin-6-yl)phenyl)pentanoic acid ((−)-C4) Prepared according to Representative Procedure F: **(−)-11b** (6.0 mg, 0.014 mmol), *tert*-butyl alcohol (0.27 mL), 2-methyl-2 butene (0.07 mL), acetonitrile (0.14 mL), NaH_2PO_4 (8.1 mg, 0.068 mmol), $NaClO_2$ (6.7 mg, 0.075 mmol), and H_2O (0.41 mL) yielded 5.7 mg (92%) of the product as an off-white residue. Purified by preparative TLC (1% AcOH, 49% hexanes, 50% EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 – 7.16 (m, 1H), 7.13 – 7.09 (m, 2H), 7.07 – 7.03 (m, 1H), 5.70 – 5.59 (m, 2H), 5.49 (d, J = 11.5 Hz, 1H), 4.85 (ddd, J = 6.5, 3.9, 0.9 Hz, 1H), 4.55 (d, J = 6.5 Hz, 1H), 2.64 – 2.57 (m, 2H), 2.41 – 2.32 (m, 3H), 2.26 – 2.19 (m, 1H), 2.02 – 1.94 (m, 1H), 1.68 (s, 3H), 1.66 – 1.60 (m, 4H), 1.41 – 1.36 (m, 6H), 1.09 – 1.05 (m, 2H), 1.02 (d, J = 6.6 Hz, 3H), 0.68 (d, J = 7.0 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.51, 142.11, 140.09, 135.91, 128.38, 127.90, 125.33, 122.32, 111.08, 79.50, 78.62, 76.91, 36.22, 35.83, 35.51, 33.89, 33.62, 32.08, 30.68, 29.40, 26.94, 26.03, 24.36, 22.85, 21.09, 17.95, 15.94, 14.28; **IR** (neat): 2921, 2852, 1750, 1708, 1607, 1554, 1456, 1377, 1284, 1224, 1178, 1124, 1085, 977, 874, 836, 787, 720, 706 cm-1; **$[\alpha]^{25}_D$** -48.1 (c = 0.54 in $CHCl_3$); **HRMS** (ES+): Found 481.2583 (+ 1.7 ppm), $C_{27}H_{38}O_6Na$ (M+Na+) requires 481.2566



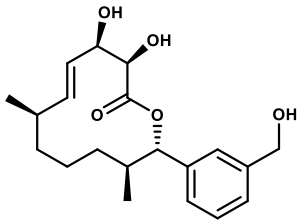
Representative Procedure G: Global Deprotection

(3*R*,4*R*,5*E*,7*R*,9*E*,11*S*,12*S*)-3,4-Dihydroxy-12-(3-(hydroxymethyl)phenyl)-7,11-dimethyloxacyclododeca-5,9-dien-2-one ((−)-B1) To a solution of **(−)-6a** (16 mg, 0.032 mmol) in MeOH (1.4 mL) and THF (0.32 mL) was added 1N HCl (1.4 mL), and the reaction vessel was sparged with argon. The reaction was stirred for 22.5 hours. Water was added, and the mixture was diluted in EtOAc. The organic layer was separated and the aqueous layer was extracted 5 times with EtOAc (5x 5 mL). The combined organic fractions were washed with brine, dried over sodium sulfate, filtered, and concentrated. Purification by preparative TLC to remove less polar impurities (5% MeOH in DCM) afforded the product (9 mg, 82%) as an off-white residue. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.19 (m, 4H), 5.42 – 5.26 (m, 4H), 5.08 – 4.96 (m, 1H), 4.68 (s, 2H), 4.48 – 4.40 (m, 1H), 4.11 – 4.04 (m, 1H), 2.67 – 2.53 (m, 1H), 2.27 – 2.18 (m, 2H), 1.81 – 1.68 (m, 1H), 1.08 (d, *J* = 6.6 Hz, 3H), 0.71 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.01, 141.37, 139.31, 135.26, 134.12, 131.42, 128.81, 127.27, 127.10, 126.49, 126.12, 81.54, 74.04, 73.78, 65.26, 43.51, 40.92, 38.36, 21.41, 17.69; **IR** (neat): 3398, 2956, 2924, 2870, 2848, 2246, 2160, 2029, 1977, 1725, 1616, 1555, 1491, 1453, 1374, 1235, 1195, 1111, 1081, 1018, 966, 907, 840, 791, 705, 673, 646, 591 cm^{-1}; **$[\alpha]^{25}_D$** -62.4 (c = 0.74 in $CHCl_3$); **HRMS** (ES^+): Found 369.1669 (-0.3 ppm), $C_{20}H_{26}O_5Na$ ($M+Na^+$) requires 369.1672



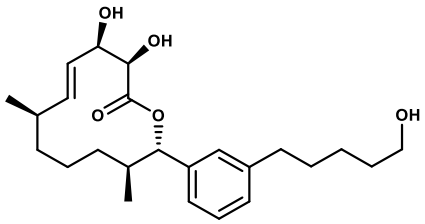
(3*R*,4*R*,5*E*,7*R*,9*E*,11*S*,12*S*)-3,4-Dihydroxy-12-(3-(5-hydroxypentyl)phenyl)-7,11-dimethyloxacyclododeca-5,9-dien-2-one ((−)-B3) Prepared according to Representative Procedure G: **(−)-6b** (19 mg, 0.034 mmol), MeOH (1.7 mL), THF (0.37 mL), and 1N HCl (1.7 mL) yielded 8 mg (57 %) of the product as an off-white residue. Purified by preparative TLC (5% MeOH in DCM).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.22 (m, 1H), 7.15 – 7.09 (m, 3H), 5.41 – 5.35 (m, 2H), 5.35 – 5.29 (m, 2H), 5.07 – 4.97 (m, 1H), 4.45 (d, *J* = 2.8 Hz, 1H), 4.09 (d, *J* = 2.8 Hz, 1H), 3.61 (t, *J* = 6.5 Hz, 2H), 2.67 – 2.54 (m, 4H), 2.25 – 2.18 (m, 2H), 1.80 – 1.70 (m, 1H), 1.69 – 1.52 (m, 6H), 1.41 – 1.32 (m, 2H), 1.08 (d, *J* = 6.5 Hz, 3H), 0.72 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.96, 142.83, 138.81, 135.22, 134.31, 131.26, 128.62, 128.53, 128.05, 126.56, 125.17, 81.67, 74.11, 73.80, 62.99, 43.42, 40.93, 38.36, 35.82, 32.62, 31.10, 25.29, 21.42, 17.69; **IR** (neat): 3409, 2925, 2854, 1729, 1608, 1589, 1488, 1453, 1373, 1235, 1192, 1111, 1080, 1018, 965, 887, 839, 794, 706, 647 cm^{-1}; **$[\alpha]^{25}_{D}$** -36.2 (c = 0.64 in $CHCl_3$); **HRMS** (ES^+): Found 403.2481 (+0.2 ppm), $C_{24}H_{34}O_5$ ($M+H^+$) requires 403.2479



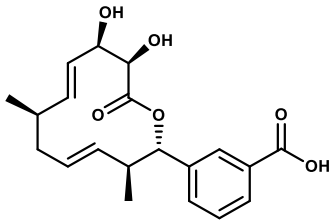
(3*R*,4*R*,7*R*,11*S*,12*S*,*E*)-3,4-Dihydroxy-12-(3-(hydroxymethyl)phenyl)-7,11-dimethyloxacyclododec-5-en-2-one ((−)-B2) Prepared according to Representative Procedure G: **(−)-7a** (14 mg, 0.028 mmol), MeOH (1.4 mL), THF (0.30 mL), and 1N HCl (1.4 mL) yielded 5 mg (50 %) of the product as an off-white residue. Purified by preparative TLC (5% MeOH in DCM).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 3H), 7.24 – 7.21 (m, 1H), 5.61 (dd, *J* = 15.4, 2.3 Hz, 1H), 5.55 – 5.45 (m, 1H), 5.29 (d, *J* = 11.4 Hz, 1H), 4.68 (s, 2H), 4.53 – 4.46 (m, 1H), 4.19 (dd, *J* = 8.8, 3.7 Hz, 1H), 3.25 (d, *J* = 8.8 Hz, 1H), 2.47 – 2.35 (m, 2H), 2.29 – 2.19 (m, 1H), 2.02 – 1.94 (m, 1H), 1.79 (s, 1H), 1.48 – 1.28 (m, 3H), 1.13 – 1.07 (m, 2H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.67 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.98, 141.23, 140.28, 134.54, 128.73, 127.08, 126.93, 126.00, 125.57, 80.86, 73.78, 73.02, 65.32, 36.77, 35.84, 34.60, 28.76, 21.86, 18.96, 15.66; **IR** (neat): 3441, 3413, 3240, 2965, 2936, 2857, 2360, 2342, 1727, 1451, 1373, 1353, 1307, 1247, 1203, 1125, 1096, 1051, 1016, 982, 908, 890, 864, 837, 799, 784, 718, 668, 654 cm^{-1}; **$[\alpha]^{25}_{D}$** -49.8 (c = 0.90 in $CHCl_3$); **HRMS** (ES^+): Found 371.1874 (+4.0 ppm), $C_{20}H_{28}O_5Na$ ($M+Na^+$) requires 371.1834



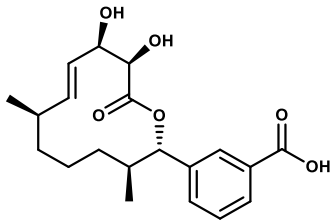
(3*R*,4*R*,7*R*,11*S*,12*S*,*E*)-3,4-Dihydroxy-12-(3-(5-hydroxypentyl)phenyl)-7,11-dimethyloxacyclododec-5-en-2-one ((−)-B4) Prepared according to Representative Procedure G: **(−)-7b** (11 mg, 0.020 mmol), MeOH (1.0 mL), THF (0.22 mL), and 1N HCl (1.0 mL) yielded 5 mg (63 %) of the product as an off-white residue. Purified by preparative TLC (5% MeOH in DCM).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.17 (m, 1H), 7.14 – 7.04 (m, 3H), 5.66 – 5.44 (m, 2H), 5.26 (d, *J* = 11.4 Hz, 1H), 4.50 (s, 1H), 4.19 (d, *J* = 3.6 Hz, 1H), 3.60 (t, *J* = 6.5 Hz, 2H), 2.61 (t, *J* = 7.4 Hz, 2H), 2.54 – 2.46 (m, 1H), 2.42 – 2.33 (m, 1H), 2.27 – 2.17 (m, 1H), 2.01 – 1.93 (m, 1H), 1.67 – 1.51 (m, 7H), 1.38 – 1.31 (m, 4H), 1.11 – 1.04 (m, 2H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.68 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.94, 142.63, 139.77, 134.50, 128.45, 127.97, 125.59, 124.99, 81.00, 73.81, 73.01, 63.02, 36.65, 35.78, 34.63, 32.62, 30.98, 28.77, 25.18, 21.87, 18.92, 15.66, 1.17; **IR** (neat): 3423, 2930, 1732, 1553, 1450, 1373, 1201, 1125, 1055, 1013, 979, 844, 780, 710 cm^{-1}; **$[\alpha]^{25}_{D}$** -52.9 (c = 0.17 in $CHCl_3$); **HRMS** (ES^+): Found 427.2445 (-1.0 ppm), $C_{24}H_{36}O_5Na$ ($M+Na^+$) requires 427.2455



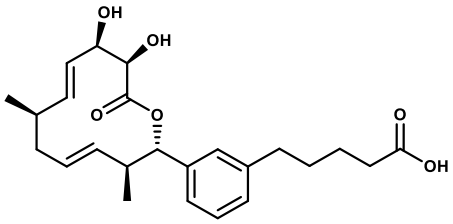
3-((2*S*,3*S*,4*E*,7*R*,8*E*,10*R*,11*R*)-10,11-Dihydroxy-3,7-dimethyl-12-oxooxacyclododeca-4,8-dien-2-yl)benzoic acid ((−)-D1) To a solution of **(−)-C1** (6.0 mg, 0.015 mmol) in H_2O (0.08 mL) at room temperature was added TFA (0.08 mL), and the reaction vessel was sparged with argon. The reaction was allowed to stir for 48 hours. The solvent was removed and the residue was co-evaporated with ethanol twice to remove residual water. If necessary, nonpolar impurities may be removed by taking up the product in acetonitrile, washing 5 x 1mL pentane, and reducing the acetonitrile fraction. In this manner, 4.4 mg (79%) of the product was obtained as an off-white residue.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 8.04 (d, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 5.45 – 5.31 (m, 4H), 5.03 (dd, *J* = 14.9, 9.6 Hz, 1H), 4.49 (s, 1H), 4.16 – 4.11 (m, 1H), 2.68 – 2.57 (m, 1H), 2.24 (d, *J* = 12.6 Hz, 2H), 1.77 (q, *J* = 12.2 Hz, 1H), 1.09 (d, *J* = 6.4 Hz, 3H), 0.72 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.11, 170.57, 139.68, 135.35, 133.69, 133.46, 131.81, 130.41, 129.78, 129.32, 128.89, 126.45, 81.00, 74.10, 73.82, 43.48, 40.91, 38.36, 21.40, 17.55; **IR** (neat): 3409, 2957, 2926, 2871, 1721, 692, 1609, 1591, 1453, 1411, 1375, 1192, 1109, 1080, 1019, 967, 909, 861, 839, 800, 757, 730, 697, 667, 656 cm^{-1}; **$[\alpha]^{25}_D$** -139 (c = 0.50 in $CHCl_3$); **HRMS** (ES^+): Found 383.1503 (+3.2 ppm), $C_{20}H_{24}O_6Na$ ($M+Na^+$) requires 383.1471



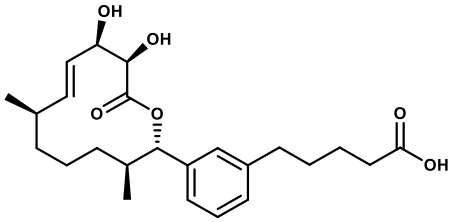
3-((2*S*,3*S*,7*R*,10*R*,*E*)-10,11-dihydroxy-3,7-dimethyl-12-oxooxacyclododec-8-en-2-yl)benzoic acid ((−)-D2) To a solution of **(−)-C2** (11.8 mg, 0.029 mmol) in H_2O (1.45 mL) at room temperature was added TFA (1.45 mL), and the reaction vessel was sparged with argon. The reaction was allowed to stir for 48 hours. The solvent was removed and the residue was co-evaporated with ethanol twice to remove residual water. Crude product was purified via preparative TLC (1:1 hexanes in ethyl acetate with 1% acetic acid) to yield 6.1 mg (58%). If necessary, nonpolar impurities may be removed by taking up the product in acetonitrile, washing 5 x 1mL pentane, and reducing the acetonitrile fraction.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (t, *J* = 24.3 Hz, 1H), 7.56 (d, *J* = 25.4 Hz, 1H), 7.43 (s, 1H), 5.61 (d, *J* = 15.2 Hz, 1H), 5.50 (s, 1H), 5.33 (d, *J* = 10.7 Hz, 1H), 4.52 (s, 1H), 4.23 (s, 1H), 3.34 (s, 1H), 2.38 (s, 1H), 2.24 (s, 1H), 2.00 (s, 1H), 1.29 (d, *J* = 46.8 Hz, 3H), 1.09 (s, 1H), 1.00 (s, 1H), 0.92 (s, 1H), 0.72 (s, 1H), 0.66 (s, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.88, 169.23, 140.53, 134.38, 133.14, 130.08, 128.99, 128.78, 128.65, 125.41, 80.17, 77.60, 73.65, 72.86, 36.68, 35.70, 34.41, 28.48, 21.75, 15.40 ; **IR** (neat): 3335, 2955, 2922, 2853, 1719, 1454, 1377, 1260, 1195, 1084, 1018, 978, 952 cm^{-1}; **$[\alpha]^{25}_D$** -33 (c = 0.0023 in $CHCl_3$); **HRMS** (ES^+): Found 385.1629 (+ 0.2 ppm), $C_{20}H_{25}O_6Na$ ($M+Na^+$) requires 385.1627



5-(3-((2*S*,3*S*,4*E*,7*R*,8*E*,10*R*,11*R*)-10,11-dihydroxy-3,7-dimethyl-12-oxooxacyclododeca-4,8-dien-2-yl)phenyl)pentanoic acid ((−)-D3) To a solution of **C3** (35 mg, 0.077 mmol) in H_2O (0.40 mL) at room temperature was added TFA (0.40 mL), and the reaction vessel was sparged with argon. The reaction was allowed to stir for 48 hours. The solvent was removed and the residue was co-evaporated with ethanol twice to remove residual water. The crude product was purified by preparatory TLC (1:1 hexanes in ethyl acetate with 1% acetic acid). If necessary, nonpolar impurities may be removed by taking up the product in acetonitrile, washing 5 x 1mL pentane, and reducing the acetonitrile fraction. In this manner, 18.8 mg (59%) of the product was obtained as an off-white residue.

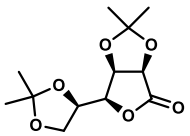
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.22 (m, 1H), 7.16 – 7.12 (m, 2H), 7.10 (d, *J* = 7.6 Hz, 1H), 5.39 (d, *J* = 4.6 Hz, 2H), 5.34 – 5.29 (m, 2H), 5.06 – 4.99 (m, 1H), 4.46 (s, 1H), 4.13 (s, 1H), 2.70 – 2.50 (m, 3H), 2.33 (t, *J* = 6.9 Hz, 2H), 2.22 (d, *J* = 13.6 Hz, 2H), 1.76 (dd, *J* = 24.2, 12.1 Hz, 2H), 1.66 (ddd, *J* = 23.0, 15.9, 8.3 Hz, 5H), 1.27 (d, *J* = 15.7 Hz, 6H), 1.08 (d, *J* = 6.5 Hz, 3H), 0.72 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.33, 172.22, 142.62, 139.09, 135.50, 134.47, 131.54, 128.99, 128.73, 128.03, 126.70, 125.63, 81.87, 74.23, 73.95, 43.59, 41.15, 38.58, 35.68, 33.78, 30.76, 30.06, 24.43, 21.64, 17.90; **IR** (neat): 3434, 2923, 2851, 1707, 1453, 1410, 1193, 1081, 966 cm^{-1} ; **$[\alpha]^{25}_D$** -28 (c = 0.0028 in $CHCl_3$; **HRMS** (ES^+): Found 439.2102 (- 0.5 ppm), $C_{24}H_{32}O_6Na$ ($M+Na^+$) requires 439.2097



5-(3-((2S,3S,7R,10R,11R,E)-10,11-dihydroxy-3,7-dimethyl-12-oxooxacyclododec-8-en-2-yl)phenyl)penanoic acid ((−)-D4) To a solution of **C4** (5 mg, 0.011 mmol) in H_2O (0.60 mL) at room temperature was added TFA (0.60 mL), and the reaction vessel was sparged with argon. The reaction was allowed to stir for 48 hours. The solvent was removed and the residue was co-evaporated with ethanol twice to remove residual water. The crude product was purified by preparatory TLC (1:1 hexanes in ethyl acetate with 1% acetic acid). If necessary, nonpolar impurities may be removed by taking up the product in acetonitrile, washing 5 x 1mL pentane, and reducing the acetonitrile fraction. In this manner, 4.6 mg (59%) of the product was obtained as an off-white residue.

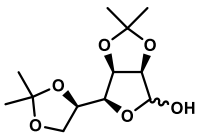
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (t, *J* = 7.5 Hz, 1H), 7.02 (dd, *J* = 12.4, 7.7 Hz, 3H), 5.57 – 5.38 (m, 2H), 5.19 (d, *J* = 11.4 Hz, 1H), 4.45 (dt, *J* = 4.1, 2.1 Hz, 1H), 4.17 (d, *J* = 3.6 Hz, 1H), 2.63 – 2.47 (m, 2H), 2.31 (ddd, *J* = 16.5, 11.6, 4.6 Hz, 1H), 2.24 (t, *J* = 7.0 Hz, 2H), 2.19 – 2.09 (m, 1H), 1.93 (td, *J* = 14.5, 9.4 Hz, 1H), 1.57 (ddd, *J* = 23.2, 15.5, 8.6 Hz, 4H), 1.40 – 1.14 (m, 7H), 1.02 (d, *J* = 9.0 Hz, 2H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.61 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.12, 172.22, 142.46, 140.12, 134.71, 128.83, 128.57, 127.77, 125.79, 125.51, 99.99, 99.86, 81.19, 73.95, 73.14, 36.86, 36.02, 35.62, 34.84, 33.77, 30.62, 28.92, 24.35, 22.11, 19.07, 15.86; **IR** (neat): 3392, 2923, 2852, 2361, 2341, 1735, 1456, 1376, 1241, 1199, 1088 cm^{-}

[1]; **[α]$^{25}_{D}$** -410 (c = 0.002 in $CHCl_3$; **HRMS** (ES^+): Found 419.2408 (- 2.6 ppm), $C_{24}H_{35}O_6$ ($M+H^+$) requires 419.2434



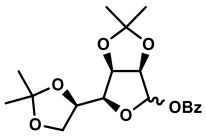
(3a*R*,6*S*,6a*R*)-6-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyldihydrofuro [3,4-*d*][1,3]dioxol-4(3a*H*)-one (12) A round bottom flask was charged with **D-gulonic acid lactone** (40.0 g, 224 mmol), acetone (320 mL), *p*-toluenesulfonic acid monohydrate (2.21 g, 11.6 mmol), and 2,2-dimethoxypropane (67.0 mL, 326 mmol). The mixture was allowed to stir 40 hours, becoming clear as the reaction proceeds. A second portion of 2,2-dimethoxypropane (30 mL, 244 mmol) is added and the reaction was allowed to stir a further 20 hours. Upon completion, sodium bicarbonate (3.00 g, 35.7 mmol) was added to the mixture and allowed to stir for 15 minutes. The newly formed suspension was concentrated and the clumpy solid slurry was dissolved in dichloromethane (200 mL). The solution was added to a separatory funnel and water (200 mL) was added, forming two layers. The aqueous layer was extracted with dichloromethane (2x 200 mL). The combined organic layers were then dried over $MgSO_4$, filtered, and reduced to give a white solid, which was then recrystallized in hot ethyl acetate to afford the bis-protected product as white crystals. The mother liquor was concentrated and dissolved in acetone (200 mL) and another portion of *p*-toluenesulfonic acid monohydrate (2.21 g, 11.6 mmol) is added. The mixture was allowed to stir a further 48 hours, after which the same workup procedure was followed, yielding white crystals (41.69 g, 72%). Experimental data matched that previously described.[1,6,7]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (d, *J* = 5.6 Hz, 1H), 4.74 (dd, *J* = 5.6, 3.5 Hz, 1H), 4.50 – 4.36 (m, 2H), 4.26 – 4.17 (m, 1H), 3.86 – 3.76 (m, 1H), 1.48 (s, 3H), 1.47 (s, 3H), 1.40 (s, 3H), 1.38 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.38, 114.39, 110.28, 80.89, 75.97, 75.74, 75.14, 65.05, 26.57, 25.66, 25.14



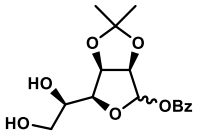
(3a*R*,6*S*,6a*R*)-6-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (13) A flame dried round bottom flask was charged with **12** (4.65 g, 18.0 mmol) and dry dichloromethane (90 mL). The stirring solution was cooled to -78^{o}C and neat DIBAL-H (3.8 mL, 21.6 mmol) was added via syringe. The reaction aws maintained at that temperature for 3 hours, then it was added to a stirring solution of 50% saturated Rochelle's salt (90 mL) at 0^{o}C. The thick white slurry was warmed to room temperature and stirred for 3 hours. The reaction was then poured into a separatory funnel and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3x 90 mL). The organic fractions were combined, washed with brine, dried over sodium sulfate, filtered, and concentrated. The lactol was obtained as a white solid (4.51 g, 96%) and used without further purification. If necessary, the product may be recrystallized from hot ethanol. Experimental data matched that previously described.[1,6,7]

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.44 (d, *J* = 2.5 Hz, 1H), 4.68 (dd, *J* = 5.9, 3.8 Hz, 1H), 4.61 (d, *J* = 5.9 Hz, 1H), 4.34 (dt, *J* = 8.5, 6.9 Hz, 1H), 4.19 (dd, *J* = 8.5, 6.5 Hz, 1H), 4.10 (dd, *J* = 8.5, 3.8 Hz, 1H), 3.71 (dd, *J* = 8.4, 7.1 Hz, 1H), 3.40 (d, *J* = 2.5 Hz, 1H), 1.43 – 1.41 (m, 6H), 1.36 (s, 3H), 1.27 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 112.80, 109.78, 101.24, 85.72, 81.97, 79.85, 75.53, 66.00, 26.72, 25.96, 25.42, 24.73



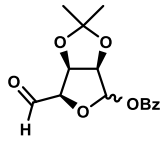
(3a*R*,6*S*,6a*R*)-6-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydro-furo[3,4-*d*][1,3]dioxol-4-yl benzoate (14) A flame dried round bottom flask was charged with **13** (41.9 g, 160 mmol) and dry dichloromethane (1000 mL). The solution was cooled to -78^{o}C, whereupon triethylamine (56 mL, 400 mmol) was added, followed by DMAP (2.0 g, 16 mmol), and freshly distilled benzoyl chloride (28.0 mL, 241 mmol). The reaction was allowed to stir overnight while warming to room temperature. Upon completion, the reaction was added to an equal volume of water at 0 ^{o}C and the layers were separated. The aqueous layer was extracted with dichloromethane (2x 300 mL), and the organic layer was washed with 0.5M HCl (3 x 300 mL), H_2O (2 x 300 mL), $NaHCO_3$ (3 x 300 mL), and brine (400 mL). The organic fractions were then combined and dried over $MgSO_4$, filtered, and reduced, yielding a white solid (58.35 g, >99%). Experimental data matched that previously described.[1,6,7]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 – 7.97 (m, 2H), 7.61 – 7.53 (m, 1H), 7.47 – 7.39 (m, 2H), 6.50 (s, 1H), 4.90 – 4.80 (m, 2H), 4.43 (q, *J* = 7.2 Hz, 1H), 4.29 – 4.20 (m, 2H), 3.76 (t, *J* = 7.8 Hz, 1H), 1.51 (s, 3H), 1.46 (s, 3H), 1.39 (s, 3H), 1.32 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.95, 133.54, 129.94, 129.70, 128.56, 113.70, 110.11, 101.87, 85.55, 84.91, 79.66, 75.66, 66.07, 26.90, 26.14, 25.48, 24.93

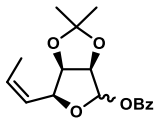


(3a*R*,6*S*,6a*R*)-6-((*R*)-1,2-Dihydroxyethyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl benzoate (15) A flame dried round bottom flask was charged with **14** (10.0 g, 27.4 mmol), H_2O (17 mL), and acetic acid (150 mL). The slurry was heated to 35°C and allowed to stir overnight. The now clear solution was reduced, co-evaporated with toluene (40 mL), reduced, and recrystallized from hot ethanol, yielding white crystals (8.57 g, 96%). Experimental data matched that previously described.[1,6,7]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 – 7.94 (m, 2H), 7.64 – 7.55 (m, 1H), 7.52 – 7.41 (m, 2H), 6.43 (s, 1H), 4.95 – 4.88 (m, 2H), 4.30 – 4.24 (m, 1H), 4.19 – 4.09 (m, 1H), 3.89 – 3.69 (m, 2H), 2.84 (s, 1H), 2.21 (s, 1H), 1.52 (s, 3H), 1.35 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.18, 133.68, 129.93, 129.49, 128.60, 113.56, 101.08, 85.74, 82.56, 79.56, 70.86, 63.15, 26.13, 24.79

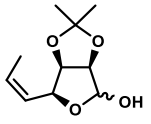


(3a*R*,6*R*,6a*R*)-6-Formyl-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl benzoate (16) A round bottom flask was charged with **15** (3.07 g, 9.47 mmol), 1,4-dioxane (100 mL), and water (100 mL). Sodium metaperiodate (4.05 g, 18.9 mmol) was added and the reaction was allowed to stir for ~90 minutes. The mixture was then filtered over celite, rinsed with ethyl acetate (3 x 100 mL), and added to a separatory funnel. The aqueous layer was extracted with ethyl acetate (3 x 100 mL) and the organic layers were combined, washed with brine (200 mL), dried over $MgSO_4$, filtered, and reduced. The resulting viscous oil was then co-eluted with toluene and once again reduced, yielding the intermediate aldehyde as a cloudy oil which was used for the next reaction without further purification.



(3a*R*,6*S*,6a*R*)-2,2-Dimethyl-6-((*Z*)-prop-1-en-1-yl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl benzoate (1) A flame dried round bottom flask was charged with freshly prepared ethyltriphenylphosphonium iodide[8] (4.59 g, 11.0 mmol) and tetrahydrofuran (82 mL), forming an insoluble white suspension. A solution of 1.0 M KHMDS (10.9 mL) was added, immediately forming an orange solution. The ylide solution was allowed to stir 90 minutes, and was then cooled to -78 ^{o}C, whereupon a solution of **16** (assuming quantitative yield) in THF (60 mL) was added to the ylide. The reaction was then allowed to stir overnight, warming to room temperature. Upon completion, the reaction was quenched with saturated ammonium chloride (100 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 150 mL). The organic layers were combined and washed with brine (200 mL), dried over $MgSO_4$, filtered, and reduced. Purification via column chromatography (7:3 hexanes/ EtOAc) afforded the product olefin (1.96 g, 70% two steps) as a white crystalline solid. Experimental data matched that previously described.[1]

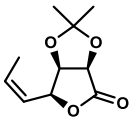
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 8.01 (m, 2H), 7.62 – 7.56 (m, 1H), 7.48 – 7.43 (m, 2H), 6.41 (s, 1H), 5.88 – 5.79 (m, 1H), 5.70 – 5.62 (m, 1H), 5.00 (dd, *J* = 8.2, 3.7 Hz, 1H), 4.90 (d, *J* = 5.7 Hz, 1H), 4.82 (dd, *J* = 5.8, 3.7 Hz, 1H), 1.74 (dd, *J* = 7.0, 1.7 Hz, 3H), 1.54 (s, 3H), 1.36 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.22, 157.74, 133.49, 129.87, 128.56, 123.94, 113.25, 101.53, 99.77, 85.65, 81.06, 77.88, 26.26, 25.07, 14.03



(3a*R*,6*S*,6a*R*)-2,2-Dimethyl-6-((*Z*)-prop-1-en-1-yl)tetrahydrofuro[3,4-*d*]

[1,3]dioxol-4-ol (8) A flame dried round bottom flask was charged with **1** (4.77 g, 15.6 mmol), tetrahydrofuran (44 mL), and methanol (44 mL). K_2CO_3 (2.59 g, 18.8 mmol) was then added to the flask and the reaction was allowed to stir 3 h, at which point the starting material was completely consumed by TLC (if starting material remained, the reaction was allowed to continue stirring until which time TLC shows complete conversion to product). The mixture was then filtered, reduced, and purified by column chromatography (3:1-1:2 hexanes/ EtOAc) to afford the lactol (3.11 g, 99%) as a clear oil. Experimental data matched that previously described.[1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 – 5.77 (m, 1H), 5.68 – 5.59 (m, 1H), 5.41 (d, *J* = 2.2 Hz, 1H), 5.00 (dd, *J* = 8.6, 3.7 Hz, 1H), 4.71 (dd, *J* = 5.8, 3.7 Hz, 1H), 4.65 (d, *J* = 5.8 Hz, 1H), 2.42 (d, *J* = 2.4 Hz, 1H), 1.75 (dd, *J* = 7.0, 1.8 Hz, 3H), 1.48 (s, 3H), 1.33 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 129.84, 124.40, 112.66, 101.14, 85.99, 81.44, 75.58, 26.24, 24.96, 13.92

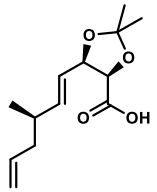


(3a*R*,6*S*,6a*R*)-2,2-Dimethyl-6-((*Z*)-prop-1-en-1-yl)dihydrofuro[3,4-*d*]

[1,3]dioxol-4(3a*H*)-one (2) A flame dried round bottom flask was charged with oxalyl chloride (0.11 mL, 1.3 mmol) and dry dichloromethane (6.5 mL). The stirring solution was cooled to -78 ^{o}C and DMSO (0.37 mL, 5.2 mmol) was added. The solution was maintained at this temperature for 1 hour and 20 minutes at which time a solution of **8** (126 mg, 0.63 mmol) in dry dichloromethane (1.7 mL + 2x 0.4 mL washes) was added via cannula at -78 ^{o}C. The reaction was maintained at this temperature for 2 hours and 30 minutes and then triethylamine (0.50 mL,

3.6 mmol) was added. The reaction was allowed to stir in the presence of the cooling bath for 2 hours, then at room temperature for an additional 1 hour. The reaction was then poured into a separatory funnel and washed with 0.5M HCl (2x 10 mL), saturated sodium bicarbonate (2x 10 mL), and brine. The organic fraction was dried over sodium sulfate, filtered and concentrated. Elution through a short plug of silica gel with dichloromethane (~50 mL) and concentration of the eluate afforded the product lactone as a white solid (117 mg, 94%), which may be used without further purification. Experimental data matched that previously described.[1]

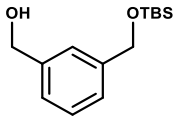
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 – 5.92 (m, 1H), 5.72 – 5.65 (m, 1H), 5.28 (ddd, *J* = 8.8, 3.6, 1.2 Hz, 1H), 4.83 (d, *J* = 5.3 Hz, 1H), 4.77 (dd, *J* = 5.3, 3.6 Hz, 1H), 1.79 (dd, *J* = 7.1, 1.8 Hz, 3H), 1.50 (s, 3H), 1.40 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.26, 132.57, 122.31, 114.15, 77.85, 76.35, 74.64, 65.65, 26.91, 25.97, 13.87



(4*R*,5*R*)-2,2-Dimethyl-5-((*R*,*E*)-3-methylhexa-1,5-dien-1-yl)-1,3-dioxolane-4-carboxylic acid (3) A flame dried round bottom flask (previously rinsed in a base bath and oven dried) was charged with copper (I) cyanide (1.13 g, 12.61 mmol) and dry THF (630 mL). The slurry was cooled to -10 °C in an ice-salt water bath and freshly prepared allylmagnesium bromide[9] (0.61M, 16.6 mL, 10.13 mmol) was added very slowly. The solution was stirred at -10 °C for 30 minutes prior to dropwise addition of a solution of **2** (1.00 g, 5.04 mmol) in THF (10 mL). The reaction was maintained at this temperature for ~ 10 minutes, then allowed to warm to room temperature and stirred an additional 3 hours at which point the staring material has been consumed (by

TLC). The reaction was quenched by addition of a 9:1 solution of saturated aqueous ammonium chloride and 1-M ammonium hydroxide (630 mL total volume). The solution was stirred ~ 1 hour until it reached a deep blue color. The reaction was then poured into a separatory funnel and the aqueous layer was separated and acidified to ~ pH 2 with 1-M HCl. The acidified aqueous layer was extracted with diethyl ether (5x 50 mL). The combined organic layer was washed with saturated aqueous ammonium chloride (2x 50mL) and brine, dried over sodium sulfate, filtered, and concentrated. Purification via column chromatography (9:1 DCM/MeOH) provided the acid as a pale yellow oil (1.07 g, 88%). Experimental data matched that previously described[1]

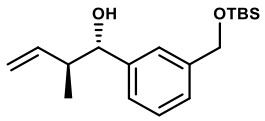
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (dd, *J* = 15.4, 7.1 Hz, 1H), 5.78 – 5.68 (m, 1H), 5.40 – 5.33 (m, 1H), 5.03 – 4.97 (m, 2H), 4.84 (t, *J* = 7.6 Hz, 1H), 4.64 (d, *J* = 7.5 Hz, 1H), 2.31 – 2.24 (m, 1H), 2.15 – 2.09 (m, 1H), 2.06 – 1.98 (m, 1H), 1.63 (s, 3H), 1.42 (s, 3H), 0.98 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.78, 142.58, 136.64, 122.04, 116.33, 111.27, 78.80, 76.91, 40.85, 36.10, 27.05, 25.41, 19.53



(3-(((*tert*-Butyldimethylsilyl)oxy)methyl)phenyl)methanol (17) Prepared according to known procedures:[3] A flask was charged with sodium hydride (60% w/w, 583 mg, 14.6 mmol) and THF (32 mL). The slurry was cooled to 0°C and a solution of 1,3-benzenedimethanol (5.87 g, 42.5 mmol) in THF (9 ml) was added slowly *via* cannula. The mixture is stirred at this temperature for 15 minutes before addition of *tert*-butylammonium iodide (123 mg, 0.332 mmol) and portion-wise addition of *tert*-butyldimethylsilyl chloride (1.0 g, 6.6 mmol). The reaction was allowed to warm to room temperature slowly and stirred 20 hours. The reaction was quenched by addition

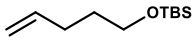
of water. The organic layer was separated and the aqueous layer was extracted 4 times with DCM. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude product was passed through a short column of silica gel (4:1 hexanes/EtOAc). The eluent was concentrated to afford a clear oil (1.13 g, 68%), which was used directly in the next step.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 2H), 7.27 (s, 2H), 4.75 (s, 2H), 4.69 (d, J = 4.4 Hz, 2H), 0.95 (s, 9H), 0.11 (s, 6H)



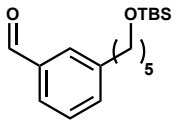
(1*S*,2*S*)-1-(3-(((*tert*-Butyldimethylsilyl)oxy)methyl)phenyl)-2-methylbut-3-en-1-ol ((−)-5a) A flask was charged with a stir bar and powdered 4Å mol sieves (250 mg) and was then flame dried. A solution of *E*-crotylboronate in toluene (prepared *via* known procedure,[4] 1.29M, 8.5 mL) was added, followed by additional toluene (19 mL). The solution was cooled to -78°C. **4a** (922 mg, 3.68 mmol) was then added as a solution in toluene (9 mL + 2 mL wash) slowly *via* syringe pump over ~20 minutes. The reaction was stirred for 3 hours at this temperature. NaOH was then added (2M (aq), 14 mL) and the reaction was transferred to a 0 °C cooling bath and stirred for 20 minutes. The reaction was then filtered through a pad of celite. The organic layer was separated and the aqueous layer was extracted 4 times with diethyl ether. The combined organic layers are washed with water and brine, dried over sodium sulfate, filtered, and concentrated. The crude product was purified by flash column chromatography (4:1 hexanes/EtOAc) to afford the product alcohol as a clear oil (961 mg, 85%). The product was thus obtained as a single diastereomer as determined by ^{1}H NMR.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.18 (m, 4H), 5.88 – 5.75 (m, 1H), 5.25 – 5.14 (m, 2H), 4.75 (s, 2H), 4.36 (d, *J* = 7.8 Hz, 1H), 2.52 – 2.42 (m, 1H), 2.12 (s, 1H), 0.94 (s, 9H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.10 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.50, 141.61, 140.84, 128.30, 125.57, 124.67, 116.91, 78.05, 65.10, 46.39, 26.09, 18.56, 16.68, -5.07; **IR** (neat): 3436, 3078, 3031, 2956, 2928, 2856, 1710, 1639, 1607, 1488, 1472, 1462, 1387, 1360, 1254, 1155, 1097, 1032, 1005, 938, 910, 836, 774, 707, 680, 662 cm^{-1}; **$[\alpha]^{25}_D$** -39 (c = 1.00 in $CHCl_3$); **HRMS** (ES^+): Found 329.1896 (-1.7 ppm), $C_{18}H_{30}O_2SiNa$ ($M+Na^+$) requires 329.1913



tert-**Butyldimethyl(pent-4-en-1-yloxy)silane (18)** Prepared according to known procedures:[5] A flask was charged with 4-penten-1-ol (2.35 mL, 23.2 mmol) and DMF (23 mL). The solution was cooled to 0°C, followed by addition of *tert*-butyldimethylsilyl chloride (4.55 g, 30.2 mmol), imidazole (2.06 g, 30.2 mmol), and DMAP (142 mg, 1.16 mmol). The reaction was allowed to slowly warm to room temperature and was stirred for 19 hours. The reaction was quenched by addition of brine and the organic layer was separated. The aqueous layer was extracted 5 times with EtOAc. The combined organic layers were washed with a saturated aqueous ammonium chloride, sodium bicarbonate, water, and brine, dried over sodium sulfate, filtered, and concentrated. The crude product was purified by flash column chromatography (5% EtOAc in hexanes) to afford the product alkene as a clear oil (3.68 g, 79%). *NOTE: The product is a volatile compound. Care should be taken when removing solvent. Refrain from leaving under vacuum for extended periods.* Experimental data matched that previously described.[5]

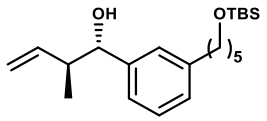
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 – 5.78 (m, 1H), 5.07 – 4.92 (m, 2H), 3.62 (t, *J* = 6.5 Hz, 2H), 2.13 – 2.07 (m, 2H), 1.65 – 1.58 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H)



3-(5-((*tert*-Butyldimethylsilyl)oxy)pentyl) benzaldehyde (4b) A 2-neck flask fitted with a reflux condenser and septum was charged with **18** (1.25 g, 6.24 mmol) and THF (2.8 mL). The solution was cooled to 0 °C followed by slow addition of 9-BBN (0.5M in THF, 12.5 mL). The reaction was allowed to warm to room temperature in the presence of the cooling bath, and was then stirred a further 19 hours at room temperature. DMF (16 mL), $PdCl_2$(dppf)-CH_2Cl_2 (69 mg, 0.094 mmol), *meta*-bromobenzaldehyde (0.36 mL, 3.12 mmol) and potassium carbonate (1.55 g, 11.2 mmol) were added. The mixture was heated to 50°C and stirred a further 24 hours. The reaction was then cooled to room temperature and poured into a separatory funnel containing water (50 mL). Toluene was added (it may be necessary to add additional water for layers to separate) and the organic layer was separated. The aqueous layer was extracted 5 times with toluene (4x 50 mL), and the combined organic layers were washed 4 times with water (4x 25 mL) and one time with brine, dried over sodium sulfate, filtered, and concentrated to afford a viscous brown oil as the crude product. Purification by flash column chromatography (0 to 10% EtOAc in hexanes) afforded the product aldehyde as a clear oil (821 mg, 86%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.00 (s, 1H), 7.72 – 7.61 (m, 2H), 7.54 – 7.40 (m, 2H), 3.60 (t, *J* = 6.5 Hz, 2H), 2.72 – 2.68 (m, 2H), 1.70 – 1.62 (m, 2H), 1.55 – 1.50 (m, 2H), 1.41 – 1.33 (m, 2H), 0.88 (s, 9H), 0.03 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 192.74, 143.91, 136.66, 134.86, 129.52, 129.05, 127.65, 63.17, 35.76, 32.76, 31.21, 26.09, 25.57, 18.49, -5.14; **IR** (neat): 2928, 2856, 2726, 1702, 1603, 1588, 1471, 1462, 1386, 1360, 1301, 1250, 1142, 1096, 1005, 938, 910,

833, 774, 692, 651 cm^{-1}; **HRMS** (ES^+): Found 307.2117 (+2.4 ppm), $C_{18}H_{30}O_2Si$ ($M+H^+$) requires 307.2093



(1*S*,2*S*)-1-(3-(5-((*tert*-Butyldimethylsilyl)oxy)pentyl)phenyl)-2-methylbut-3-en-1-ol ((−)-5b)

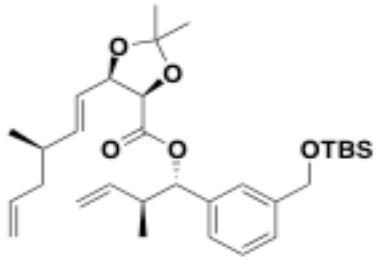
Prepared according to the procedure for **(−)-5a: 4a (**821 mg, 2.68 mmol), *E*-crotylboronate (6.2 mL, 8.0 mmol), toluene (20 mL), and NaOH (2M, 10mL) yielded 810mg (83%) of the product as a clear oil. Purified by column chromatography (10% EtOAc in hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.22 (m, 1H), 7.15 – 7.12 (m, 2H), 7.11 – 7.08 (m, 1H), 5.86 – 5.76 (m, 1H), 5.23 – 5.15 (m, 2H), 4.33 (dd, *J* = 8.0, 2.0 Hz, 1H), 3.60 (t, *J* = 6.6 Hz, 2H), 2.66 – 2.57 (m, 2H), 2.53 – 2.42 (m, 1H), 1.67 – 1.59 (m, 2H), 1.57 – 1.51 (m, 2H), 1.40 – 1.33 (m, 2H), 0.89 (s, 9H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.04 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.84, 142.48, 140.92, 128.24, 127.86, 126.98, 124.31, 116.79, 78.07, 63.31, 46.37, 36.09, 32.83, 31.47, 25.66, 18.49, 16.71, -5.14; **IR** (neat): 3438, 3080, 3022, 2928, 2856, 1639, 1607, 1471, 1462, 1387, 1361, 1254, 1155, 1098, 1005, 911, 833, 813, 774, 707, 679, 661 cm^{-1}; **$[\alpha]^{25}_D$** -24.1 (c = 4.20 in $CHCl_3$); **HRMS** (ES^+): Found 385.2544 (+0.5 ppm), $C_{22}H_{38}O_2SiNa$ ($M+Na^+$) requires 385.2539

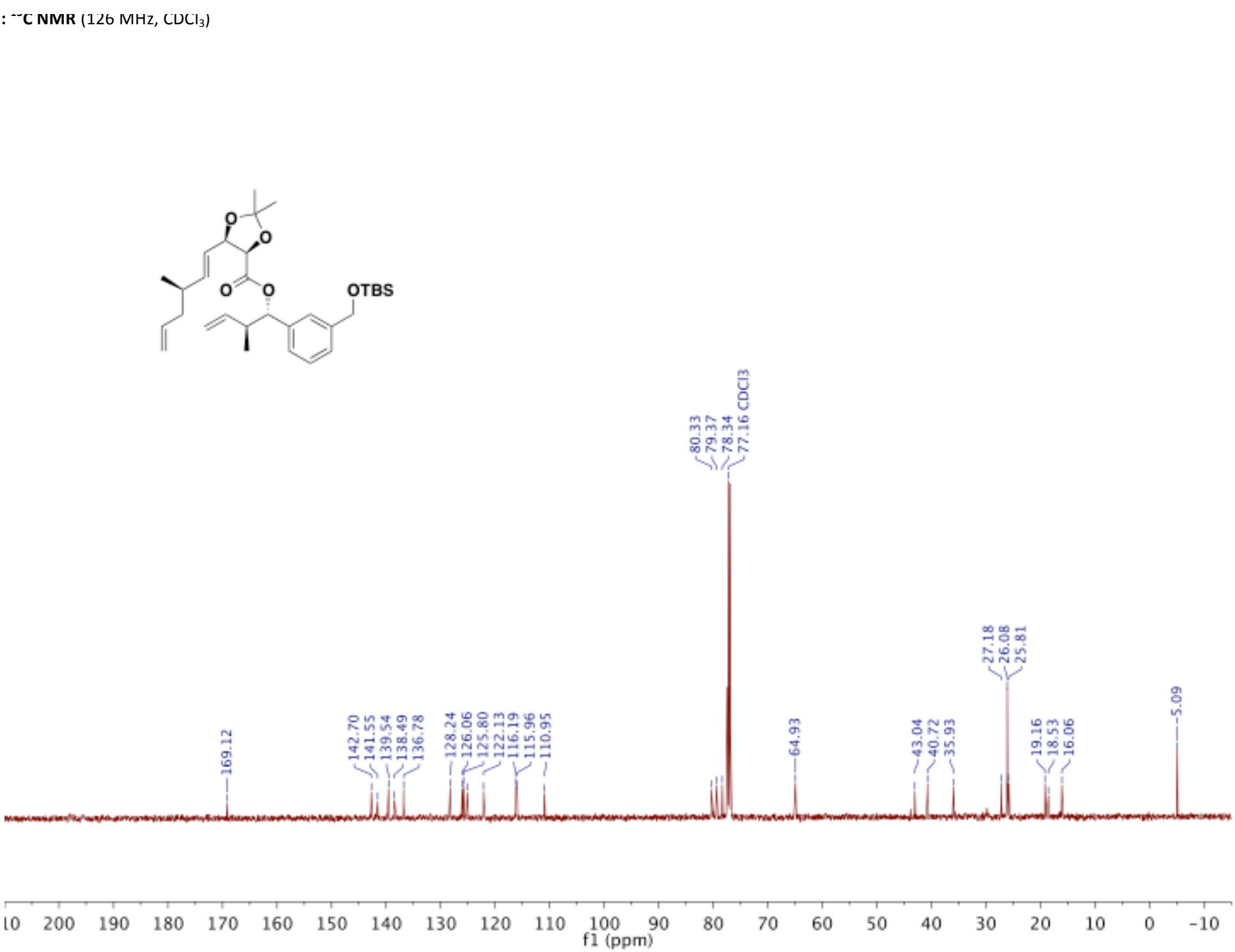
The synthetic route to acid **3** was greatly improved upon compared to lab's previous efforts.[1] In addition to reducing the time it took to accomplish this route, we were also able to make it safer by reducing the use of toxic chemicals. Most importantly, we achieved a 36% overall yield in the route to **3**, a 50% increase from past efforts.

5.3 Experimental Spectra

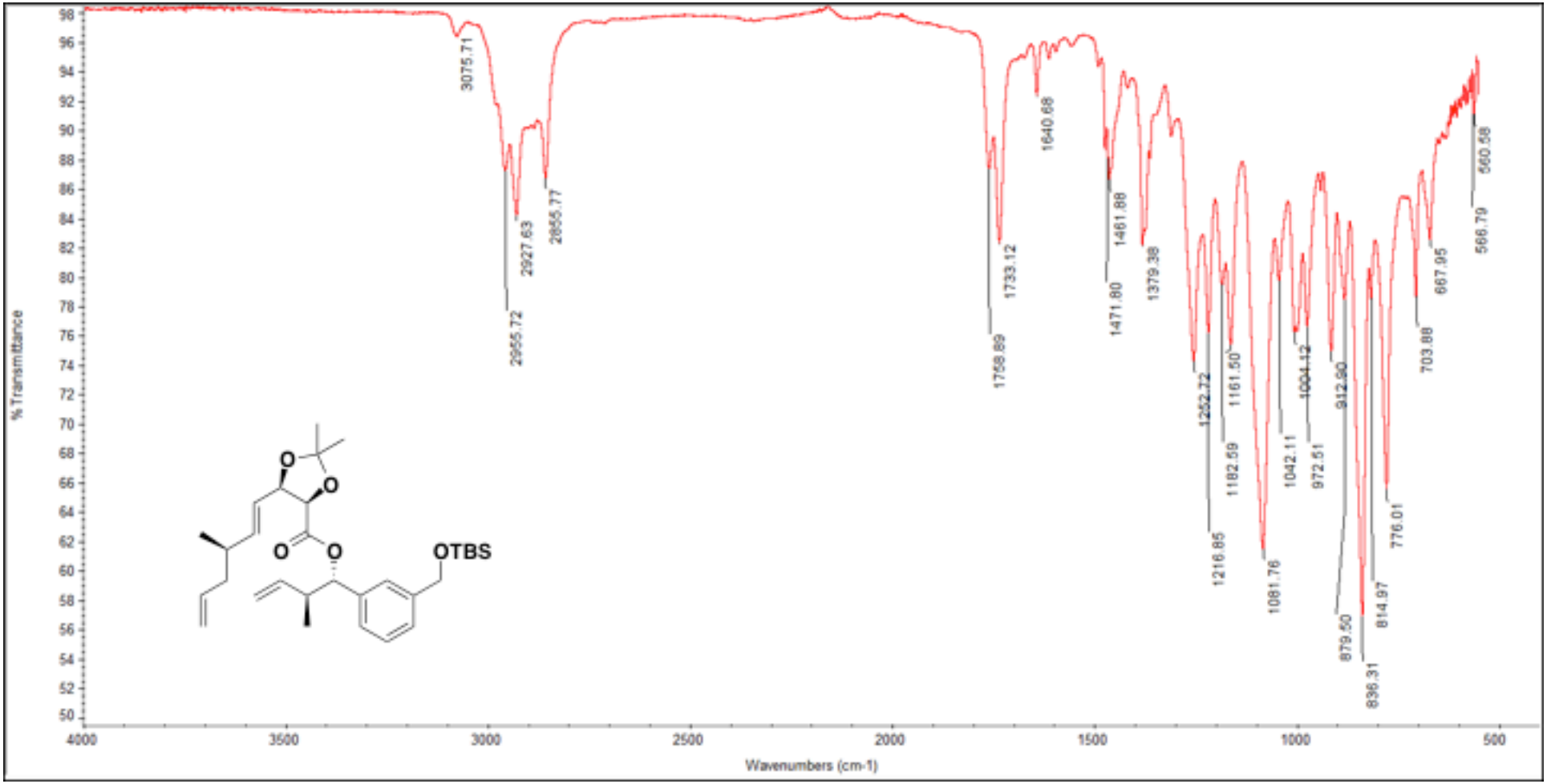
(−)-9a: ^{1}H NMR (500 MHz, $CDCl_3$)



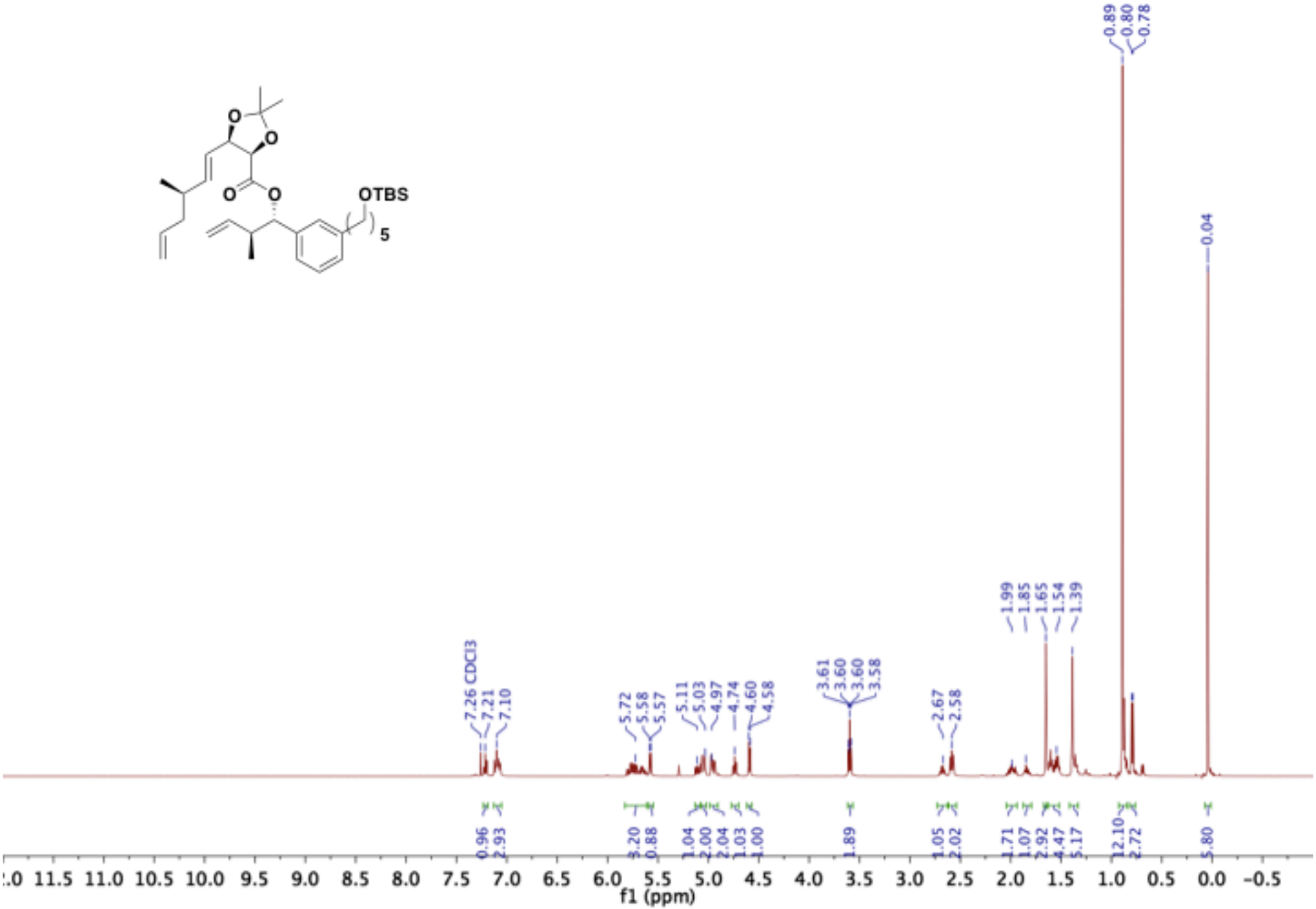
(−)-9a: ^{13}C NMR (126 MHz, $CDCl_3$)



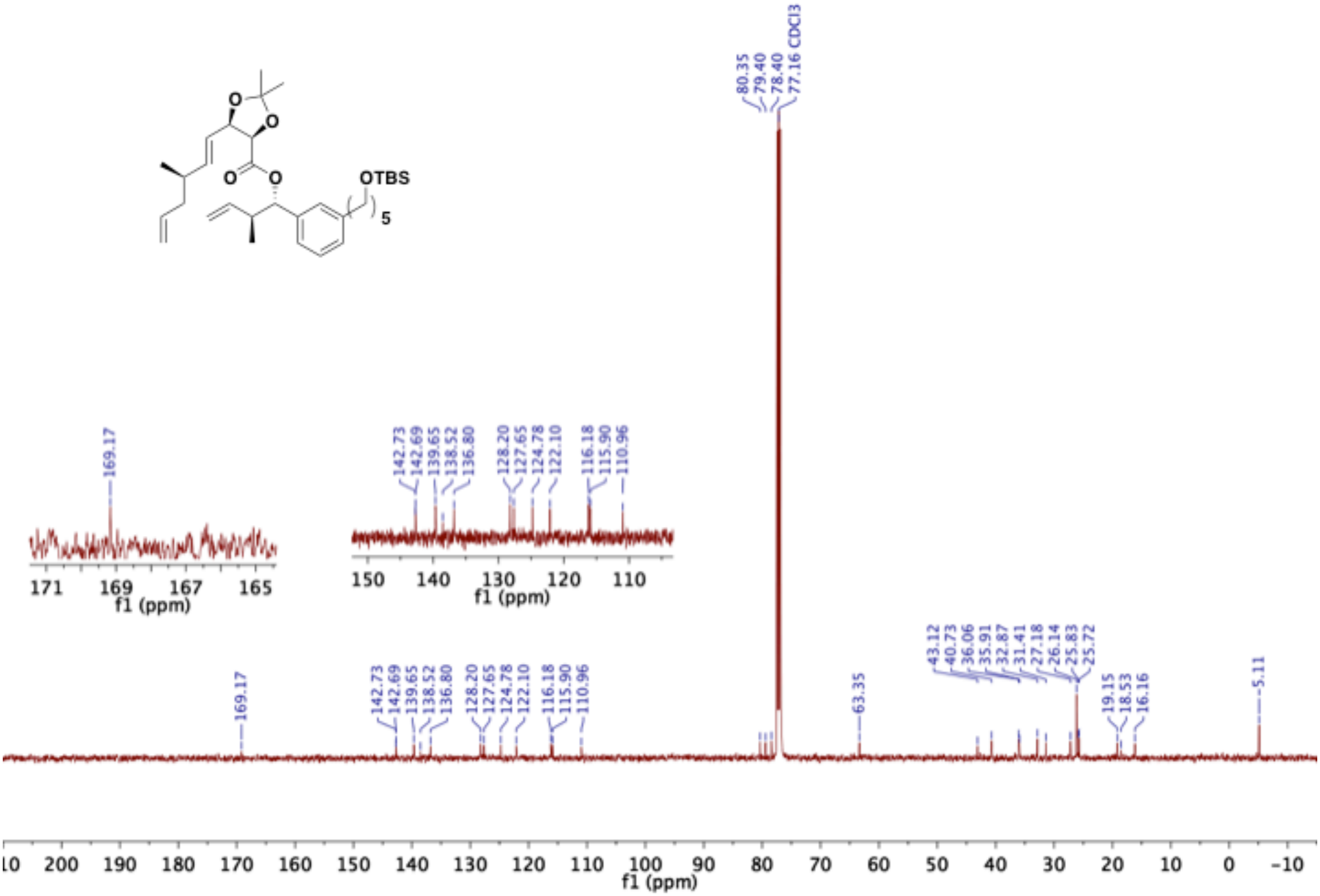
(−)-9a: IR


% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
3075.71
2955.72
2927.63
2855.77
1758.89
1733.12
1640.68
1471.80
1461.88
1379.38
1252.72
1216.85
1182.59
1161.50
1081.76
1042.11
1004.12
972.51
912.90
879.50
836.31
814.97
776.01
703.88
667.95
566.79
560.58
O
O
O
O
OTBS

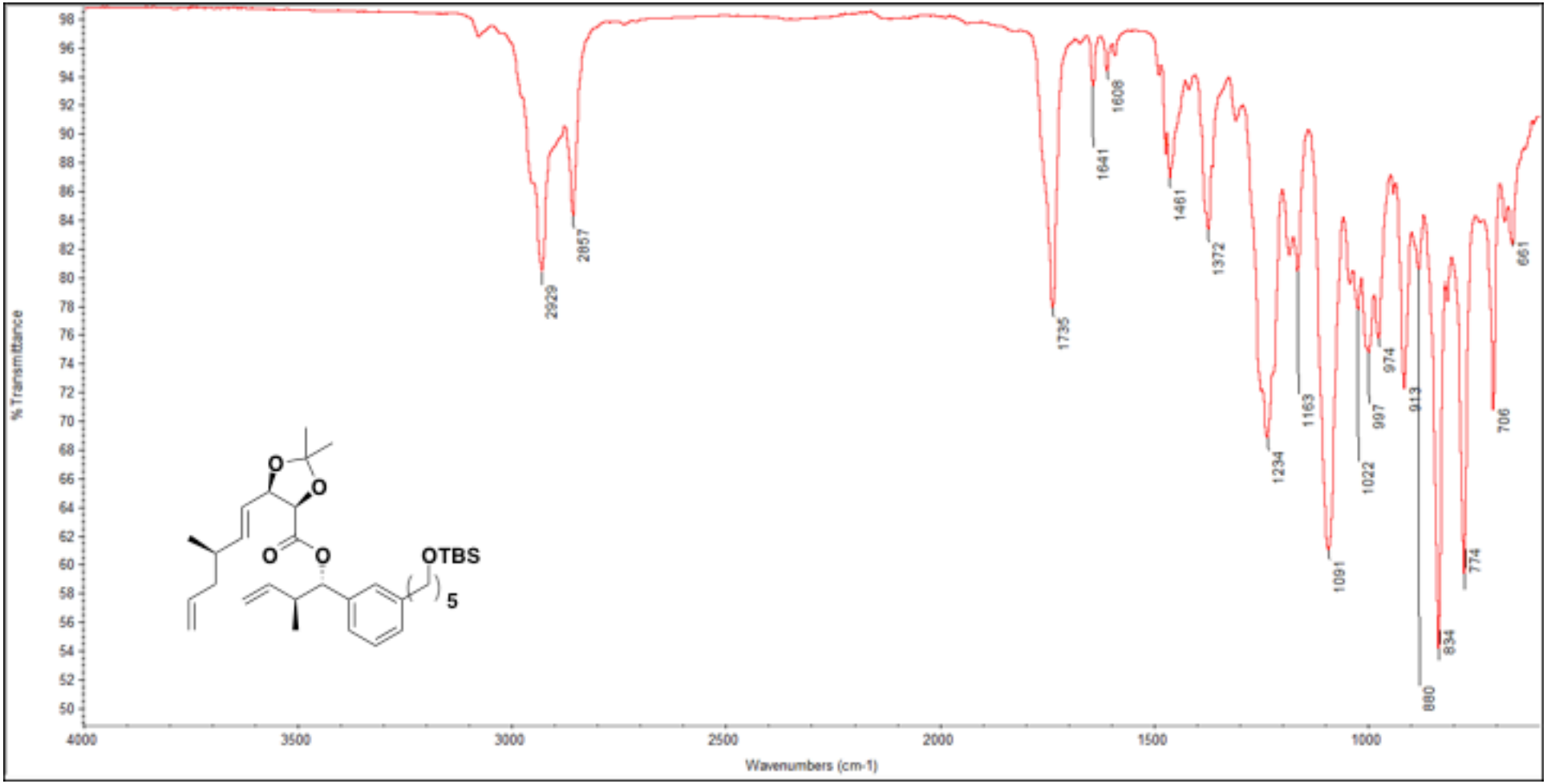
(−)-9b: ^{1}H NMR (500 MHz, $CDCl_3$)



(−)-9b: ^{13}C NMR (126 MHz, $CDCl_3$)



(−)-9b: IR


% Transmittance
Wavenumbers (cm-1)
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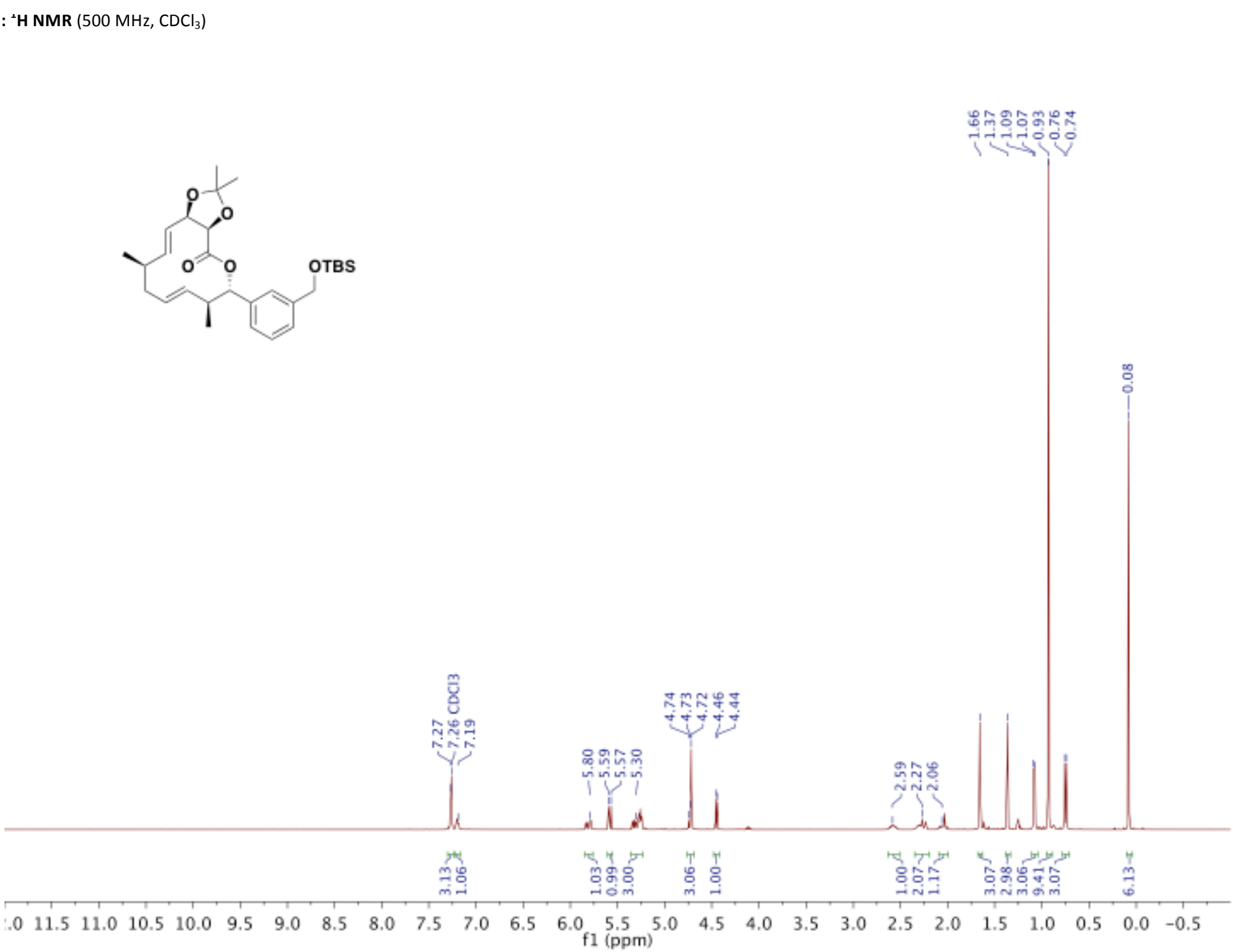
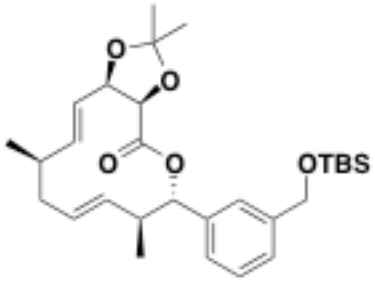
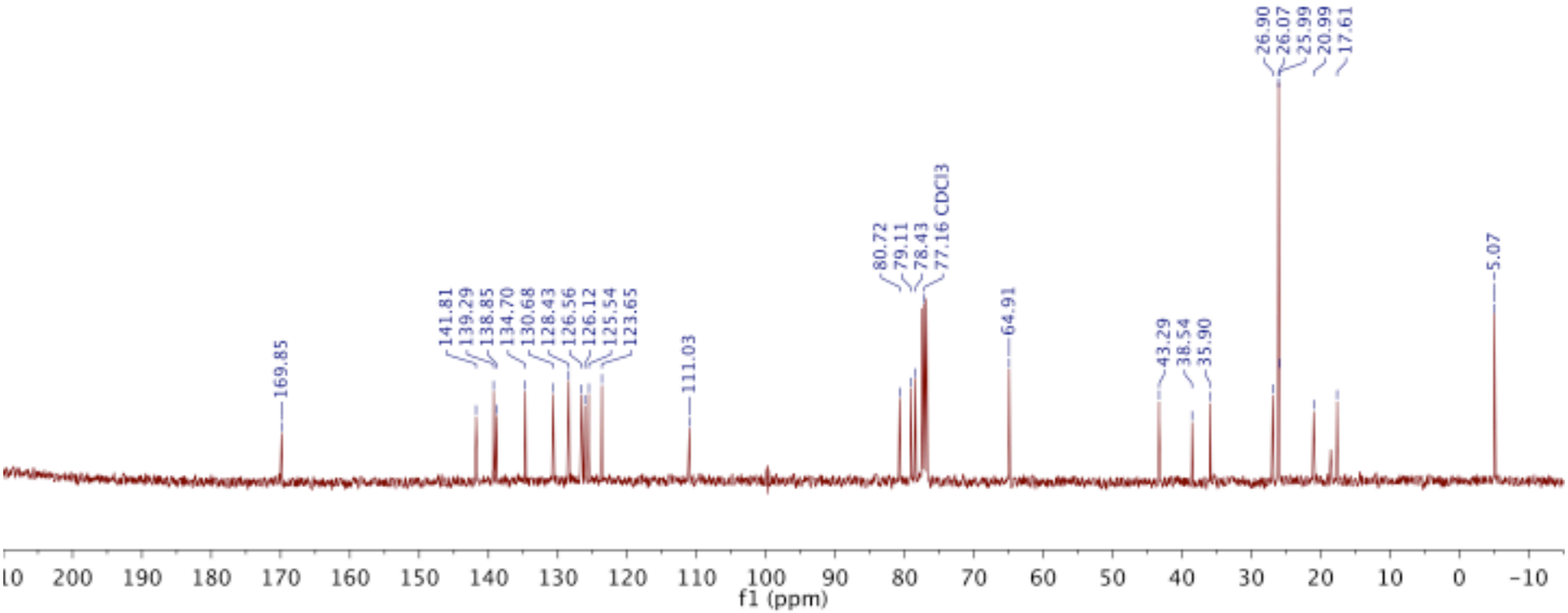
3500
3000
2500
2000
1500
1000
2929
2857
1735
1641
1608
1461
1372
1234
1163
1091
1022
997
974
913
880
834
774
706
661
O
O
O
O
OTBS
5

(−)-6a: ^{1}H NMR (500 MHz, $CDCl_3$)

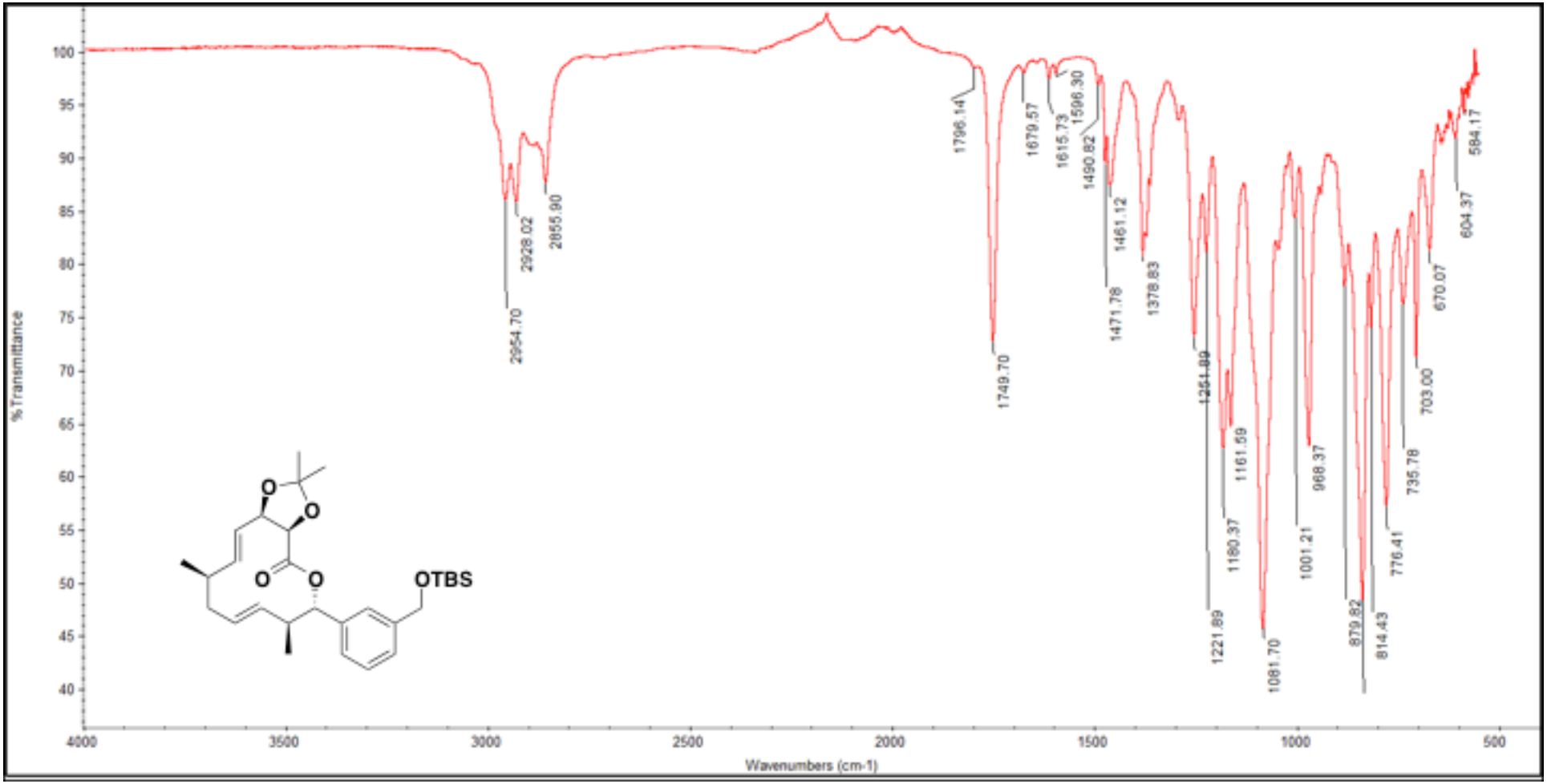


(−)-6a: ^{13}C NMR (126 MHz, $CDCl_3$)

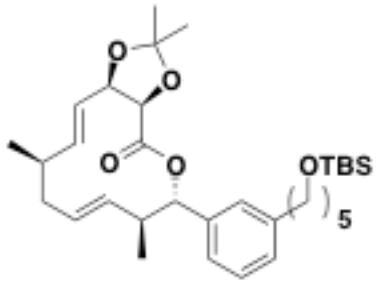




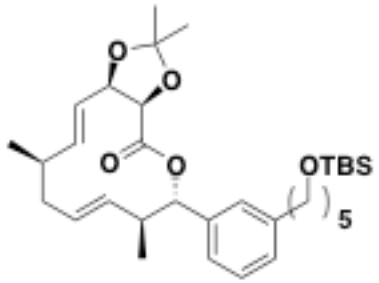
(−)-6a: IR


%Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
100
95
90
85
80
75
70
65
60
55
50
45
40
2954.70
2928.02
2855.90
1796.14
1749.70
1679.57
1615.73
1596.30
1490.82
1471.78
1461.12
1378.83
1251.89
1221.89
1180.37
1161.59
1081.70
1001.21
968.37
879.82
814.43
776.41
735.78
703.00
670.07
604.37
584.17
O
O
O
O
OTBS

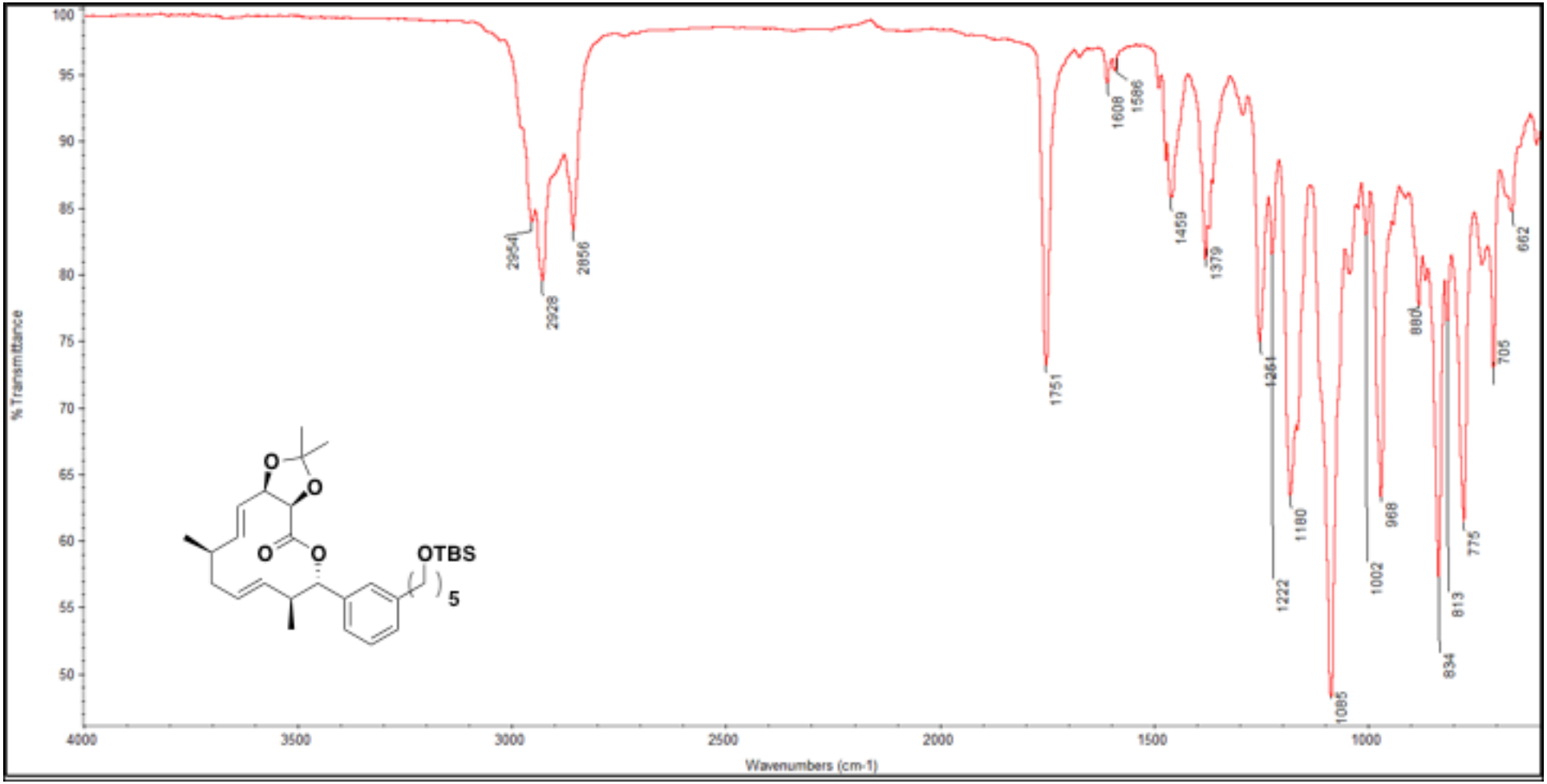
(–)-6b: ^{1}H NMR (500 MHz, $CDCl_3$)



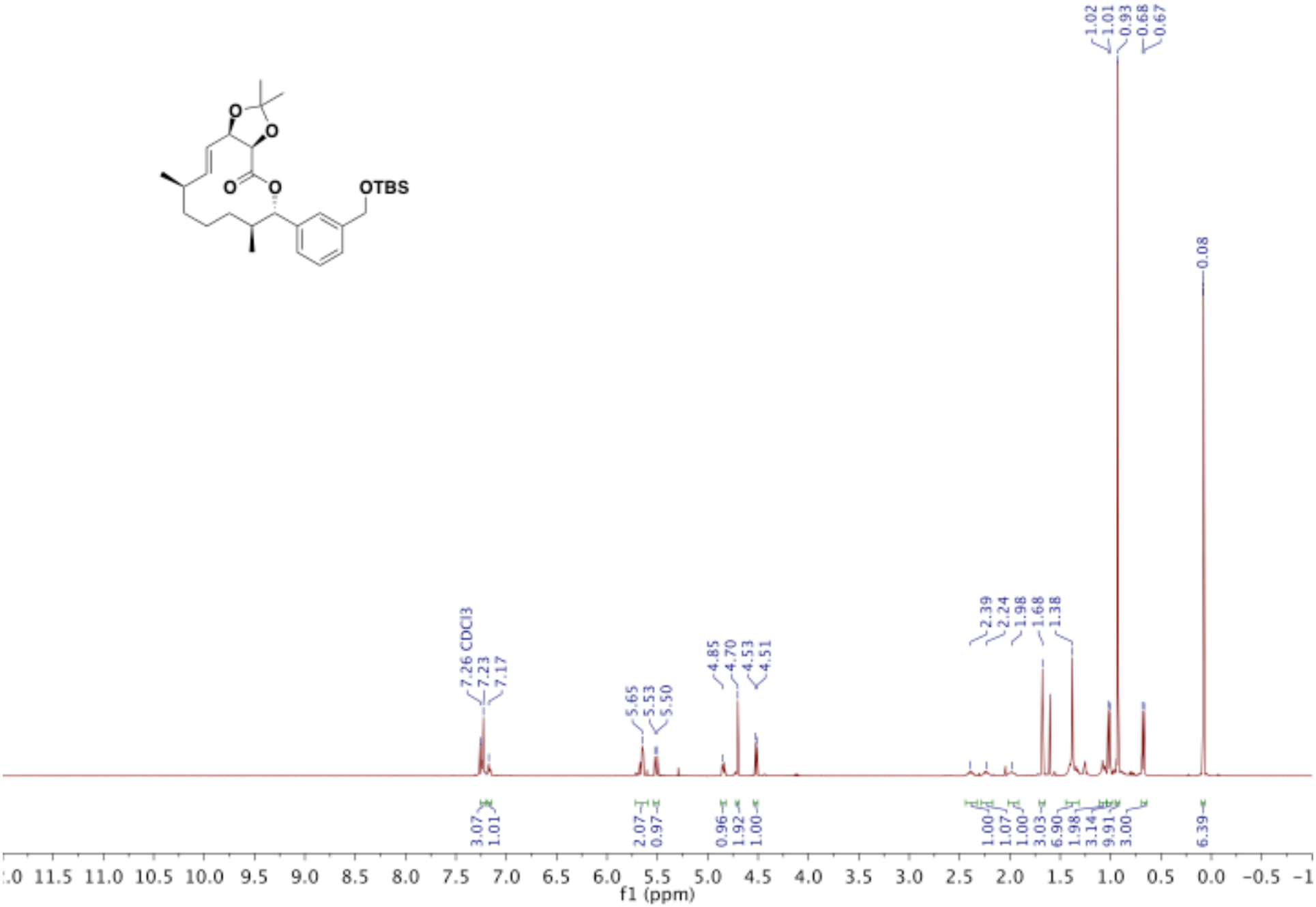
(−)-6b: ^{13}C NMR (126 MHz, $CDCl_3$)



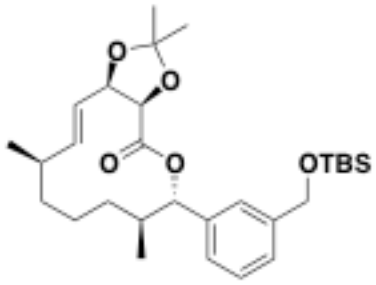
(−)-6b: IR

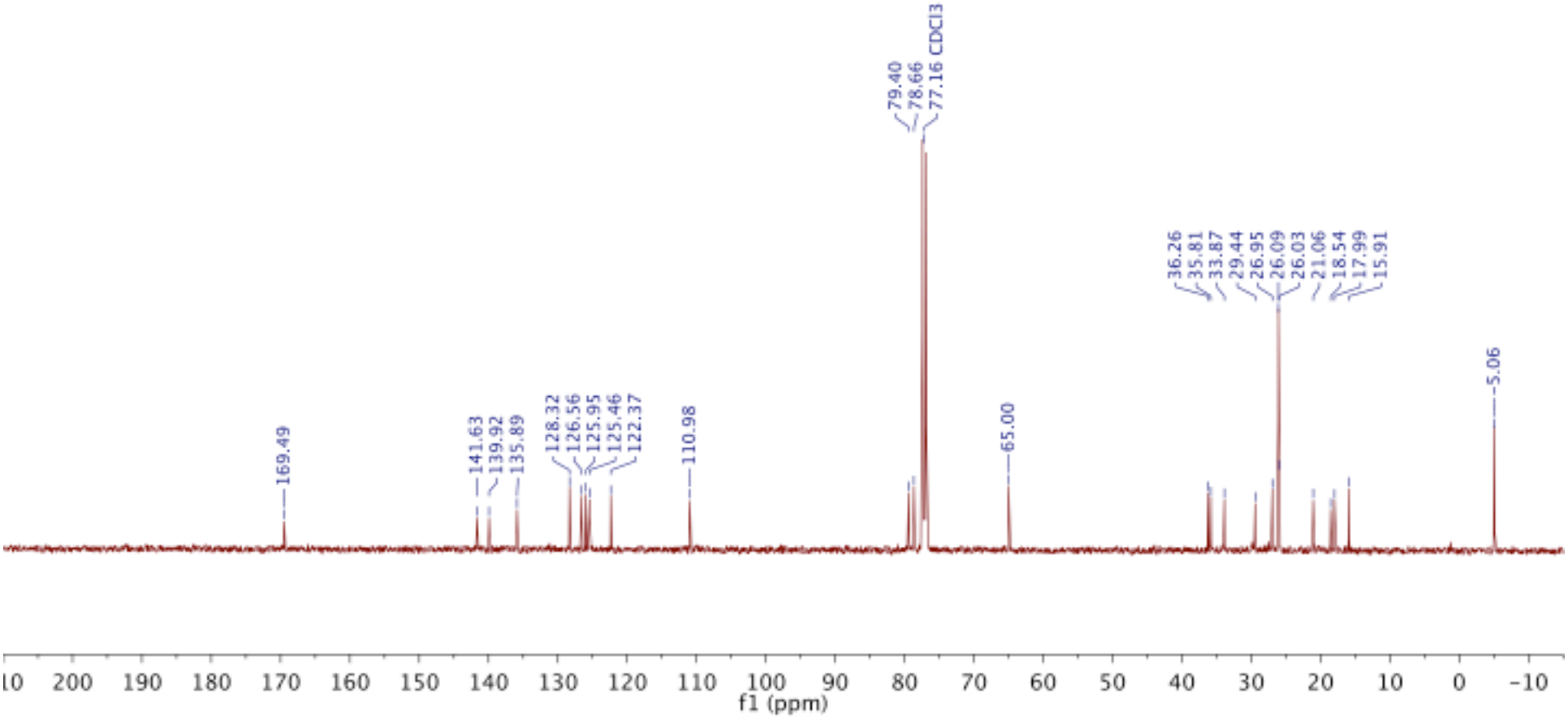

% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
100
95
90
85
80
75
70
65
60
55
50
2954
2928
2856
1751
1608
1586
1459
1379
1361
1222
1180
1085
1002
968
880
834
813
775
705
662
O
O
O
O
OTBS
5

(–)-7a: ^{1}H NMR (500 MHz, $CDCl_3$)

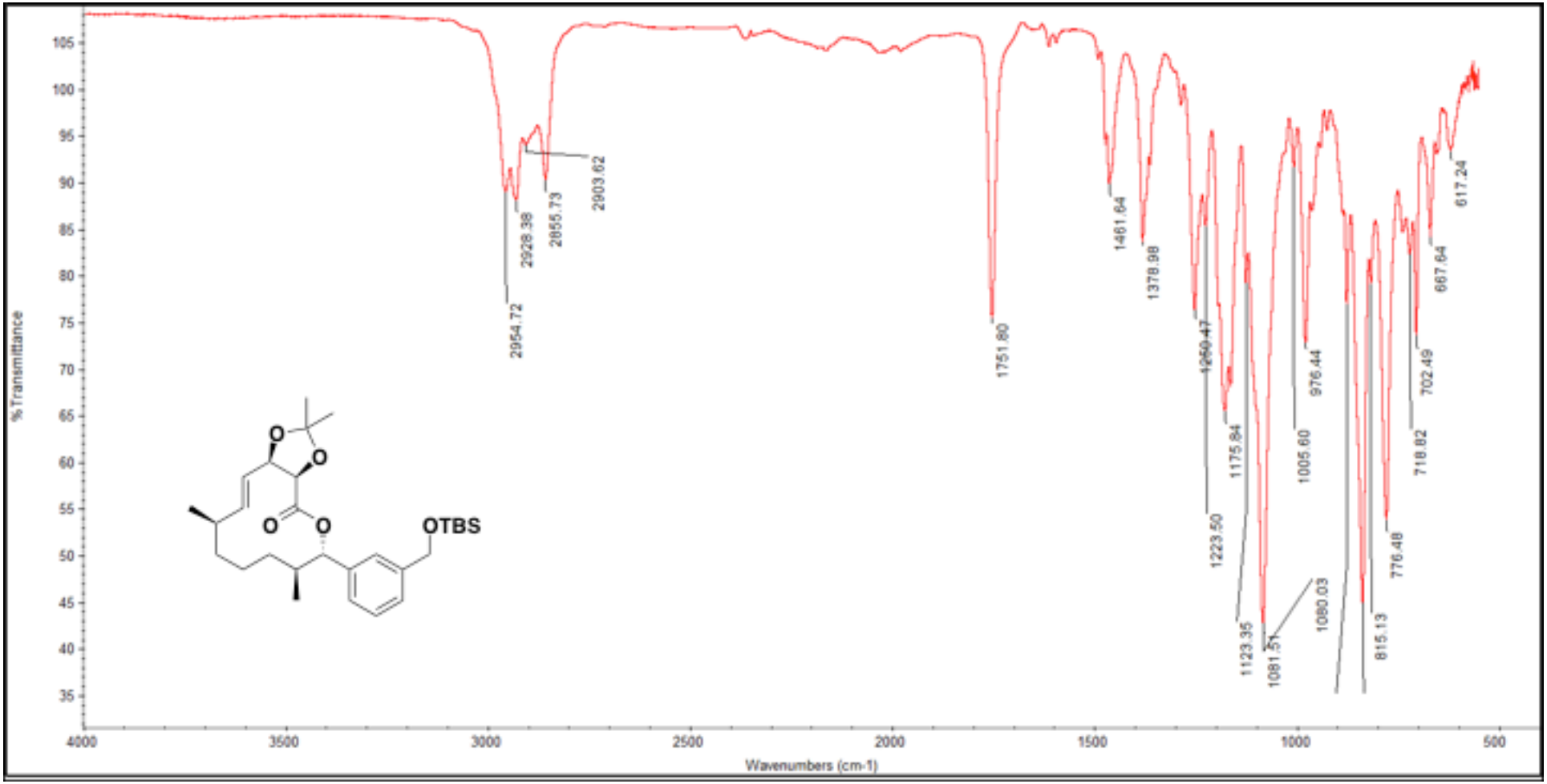


(−)-7a: ^{13}**C NMR** (126 MHz, $CDCl_3$)

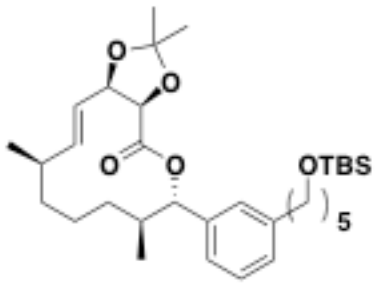




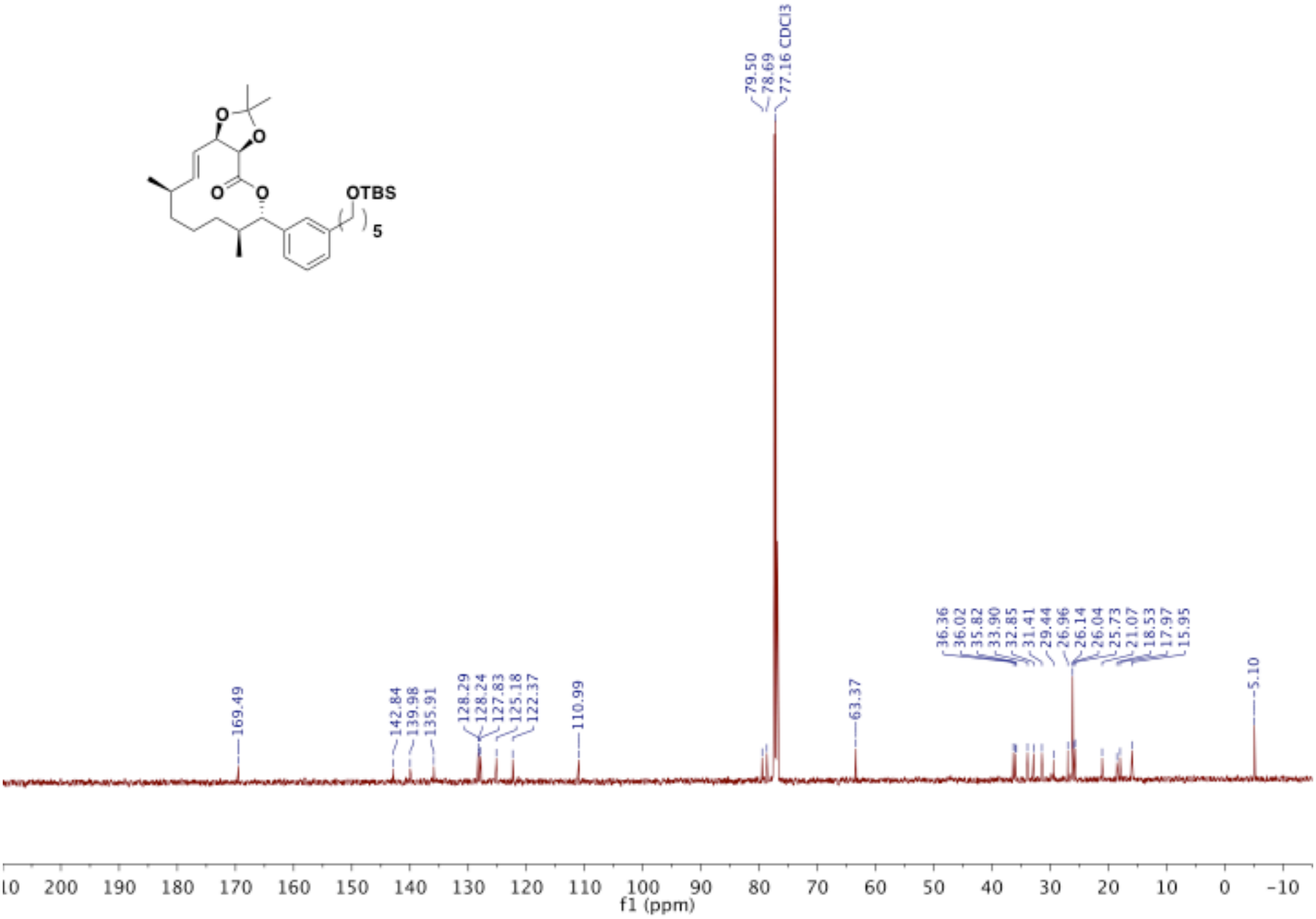
(−)-7a: IR


% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
2954.72
2928.38
2855.73
2903.62
1751.80
1461.64
1378.98
1250.47
1223.50
1175.84
1123.35
1081.51
1080.03
1005.60
976.44
815.13
776.48
718.82
702.49
667.64
617.24
O
O
O
O
OTBS

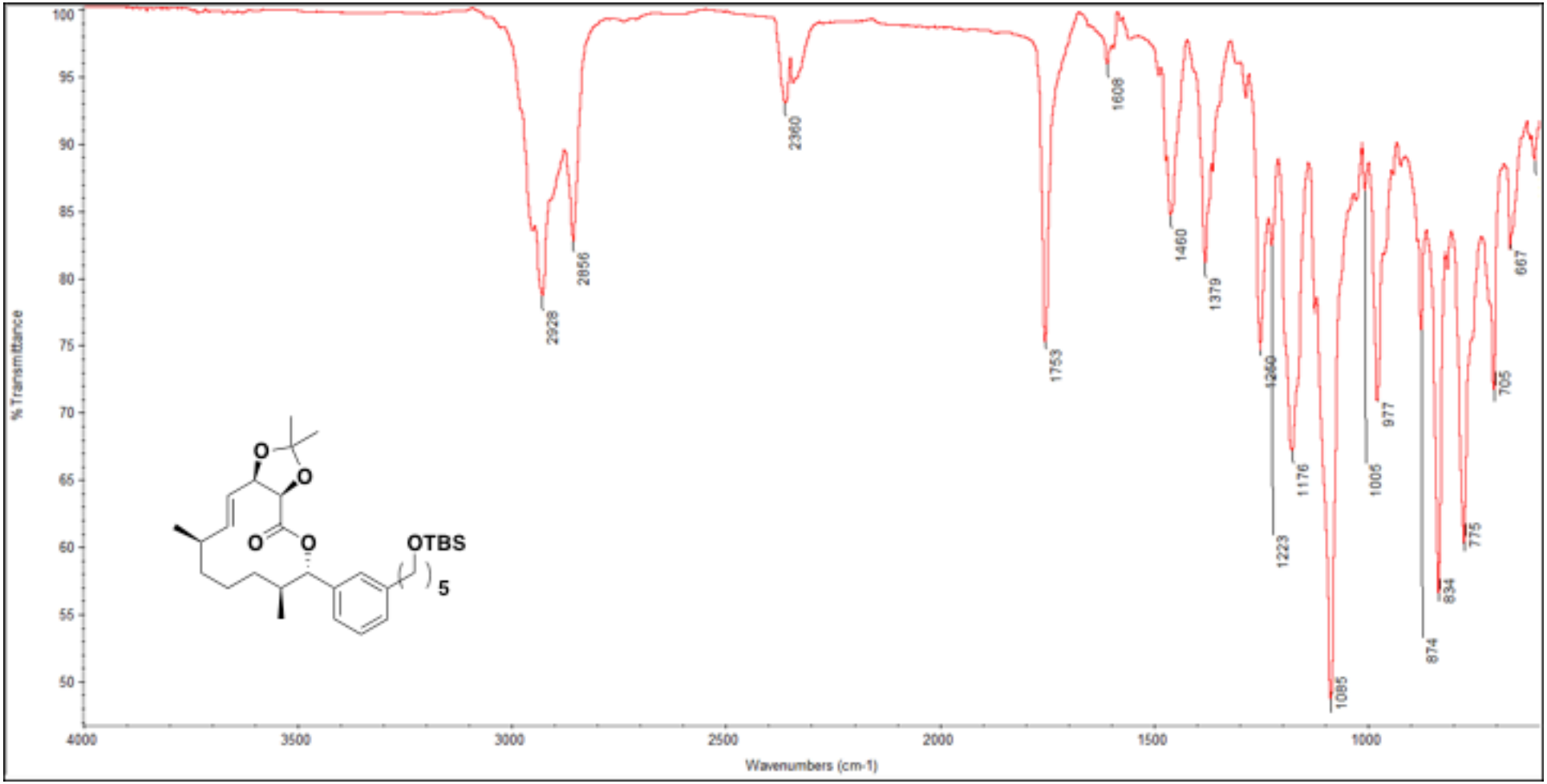
(−)-7b: ^{1}H NMR (500 MHz, $CDCl_3$)



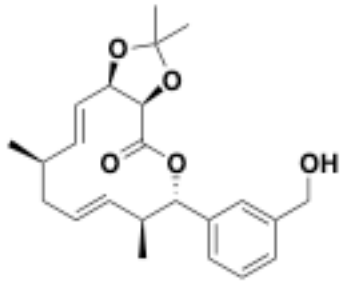
(–)-7b: ^{13}C NMR (126 MHz, $CDCl_3$)

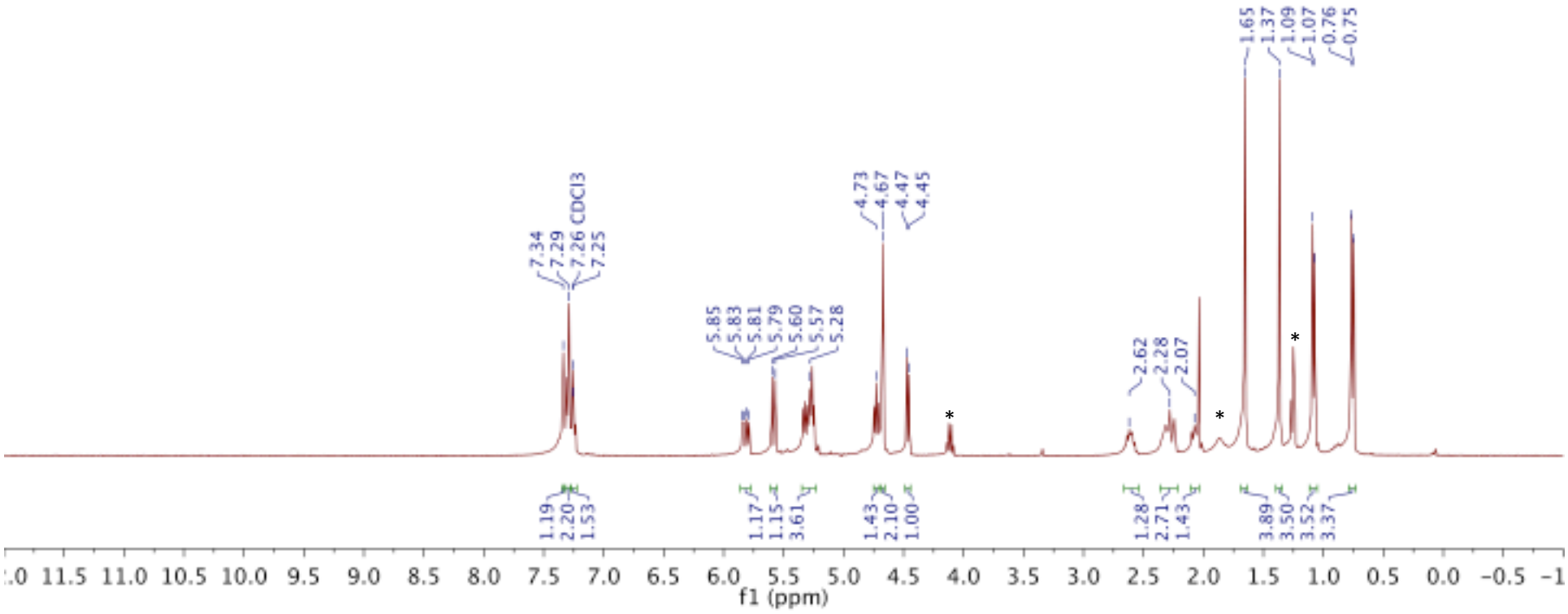


(−)-7b: IR


% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
100
95
90
85
80
75
70
65
60
55
50
2928
2856
2360
1753
1608
1460
1379
1260
1223
1176
1085
1005
977
874
834
775
705
667
O
O
O
O
OTBS
5

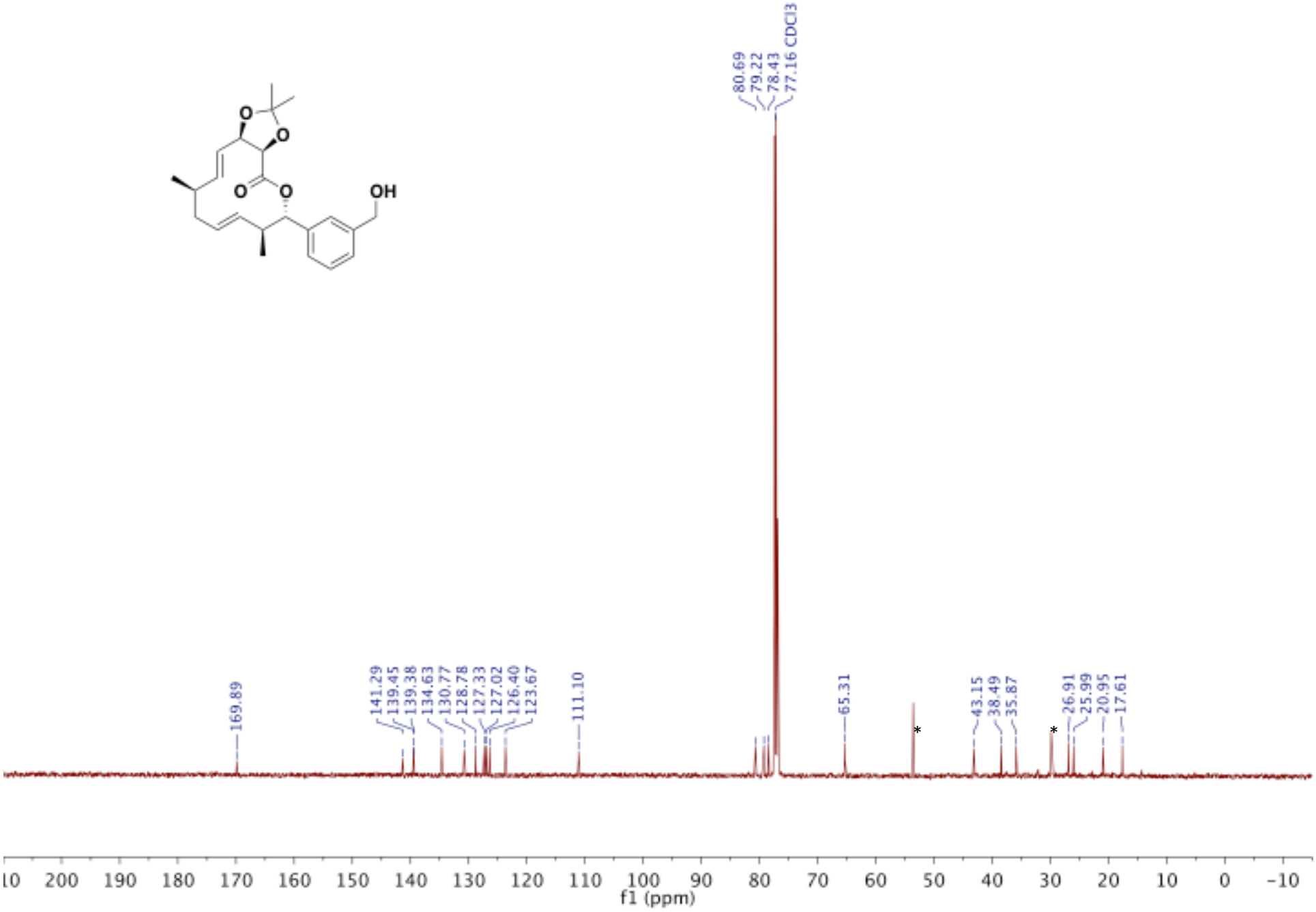
(−)-A1: ^{1}H NMR (500 MHz, $CDCl_3$)





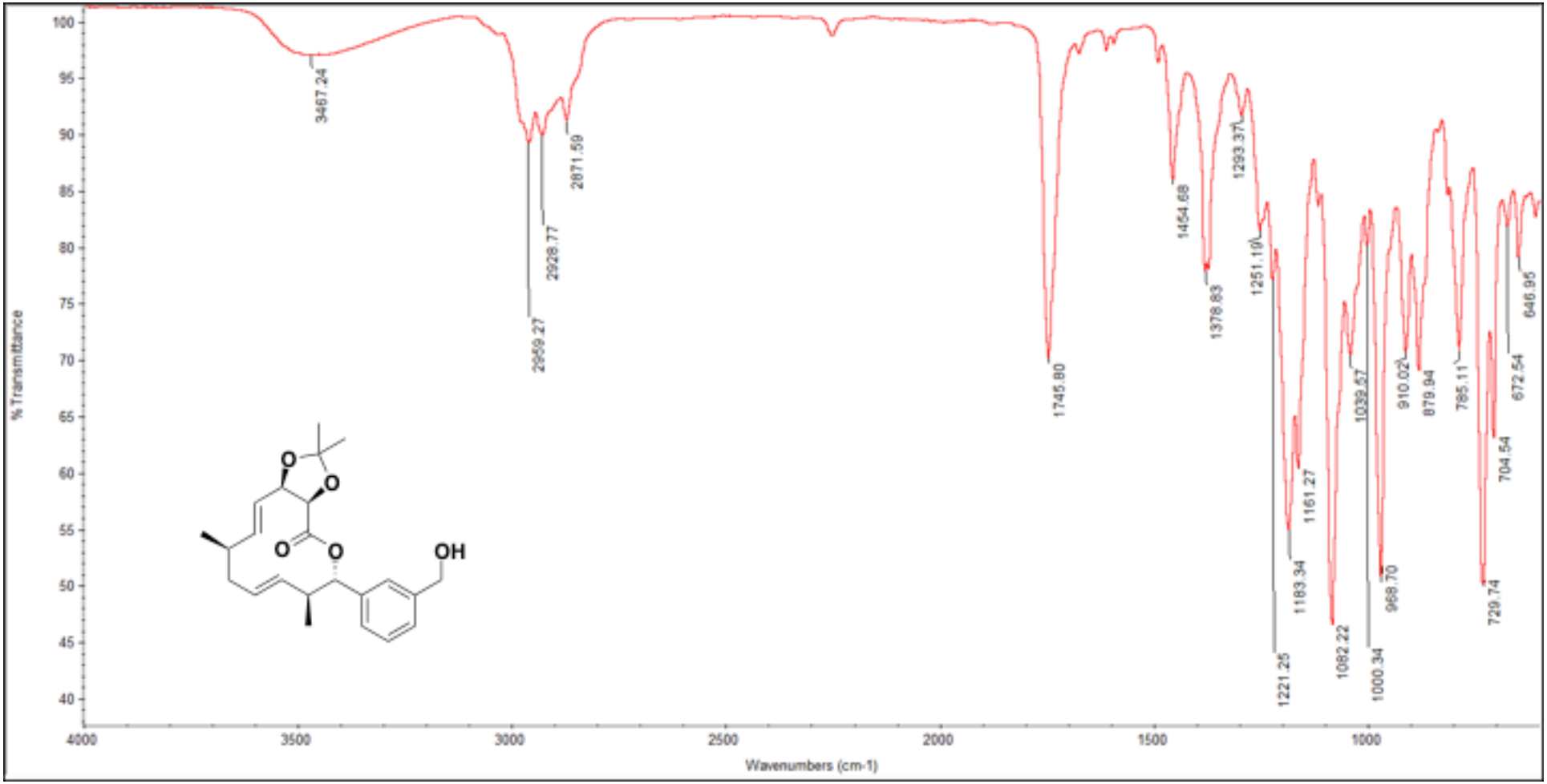
*Impurities present in spectrum

(−)-A1: ^{13}C NMR (126 MHz, $CDCl_3$)

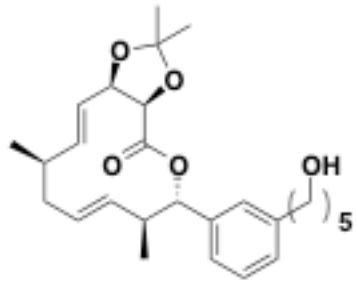


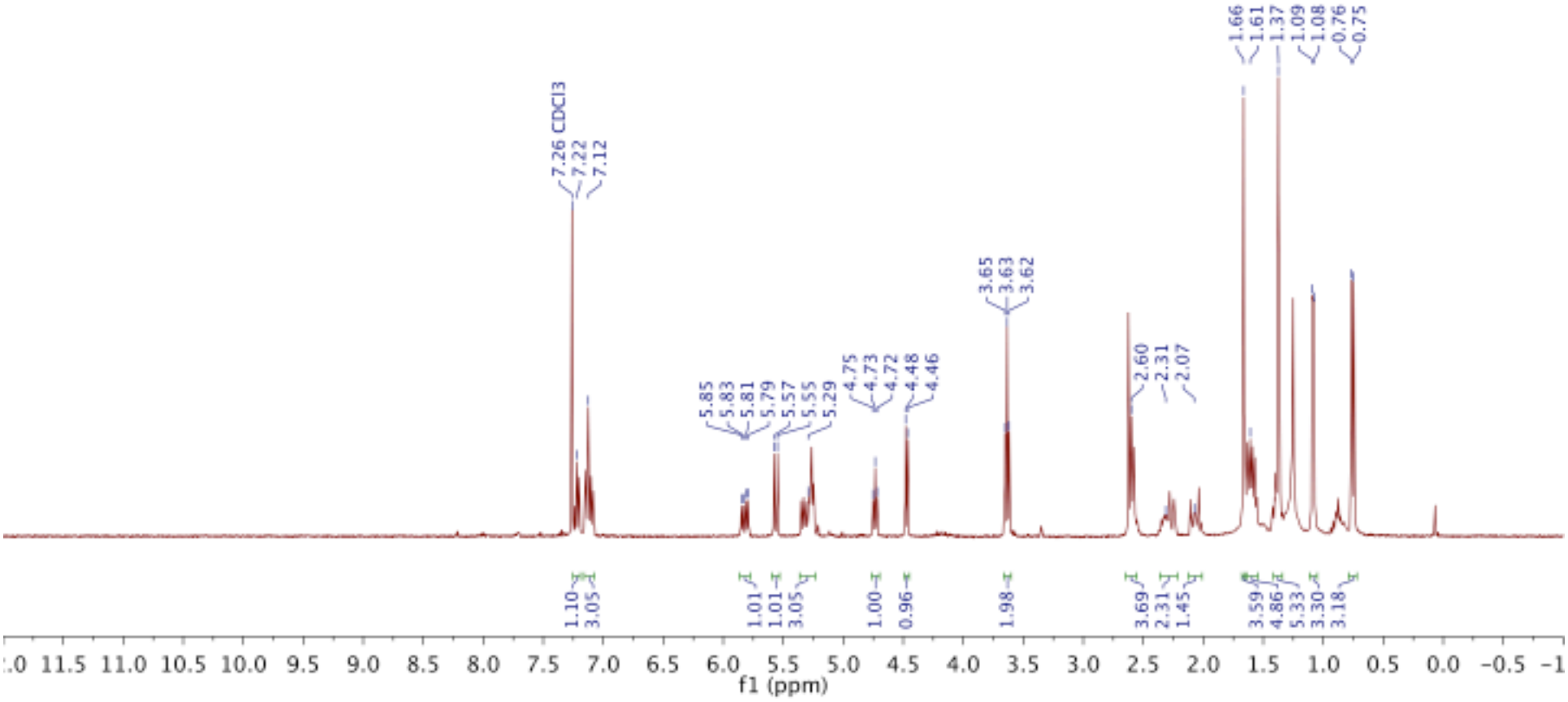
*Impurities present in spectrum

(–)-A1: IR

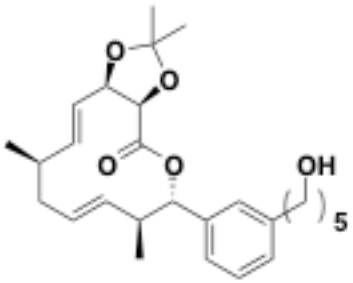

% Transmittance
Wavenumbers (cm-1)
3467.24
2959.27
2928.77
2871.59
1745.80
1454.68
1378.83
1293.37
1251.19
1221.25
1183.34
1161.27
1082.22
1039.57
1000.34
968.70
910.02
879.94
785.11
729.74
704.54
672.54
646.95
OH

(–)-A3: ^{1}H NMR (500 MHz, $CDCl_3$)

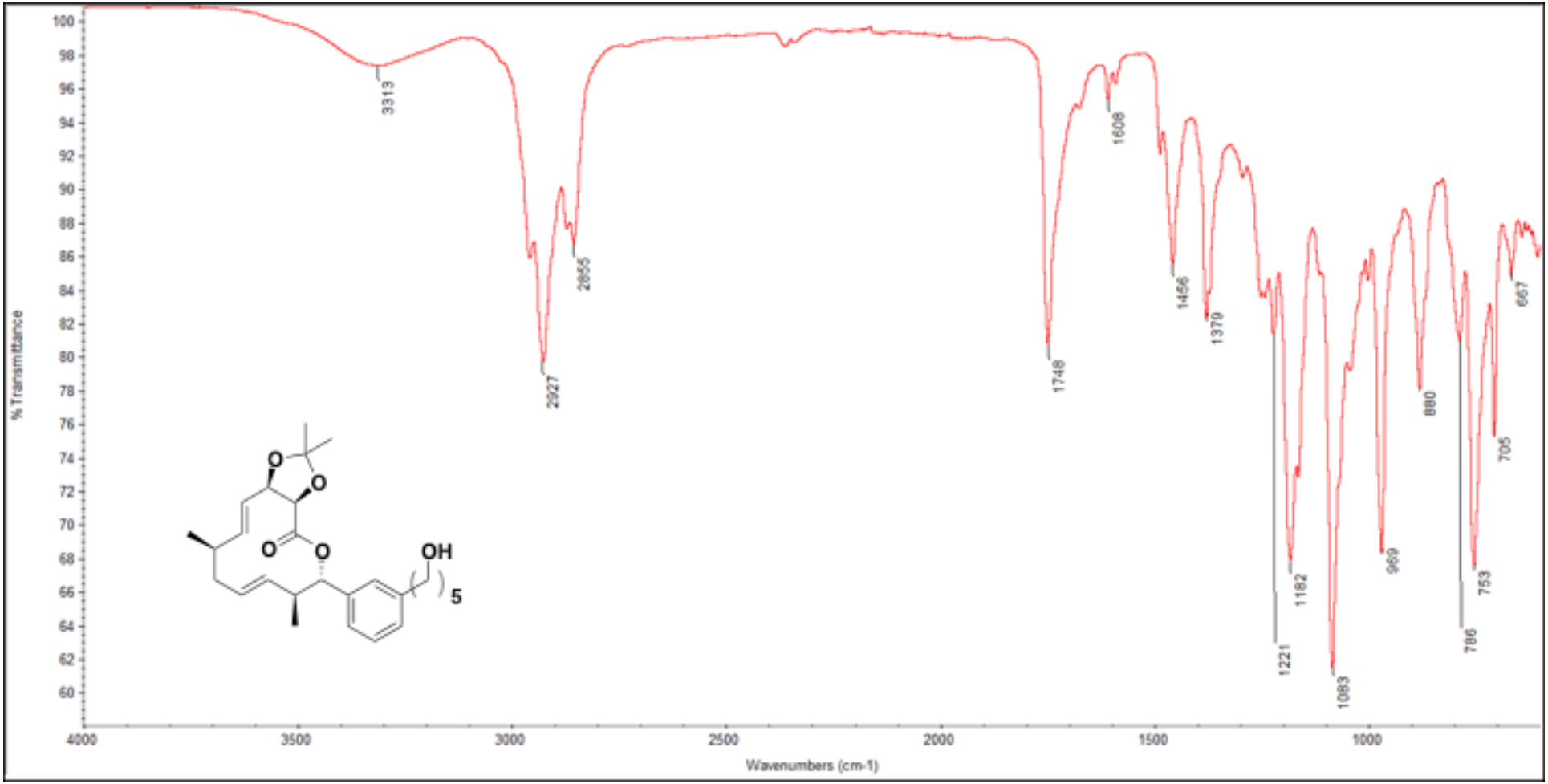




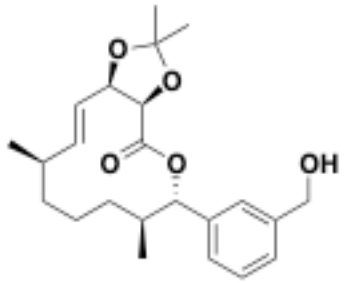
(−)-A3: ^{13}C NMR (126 MHz, $CDCl_3$)

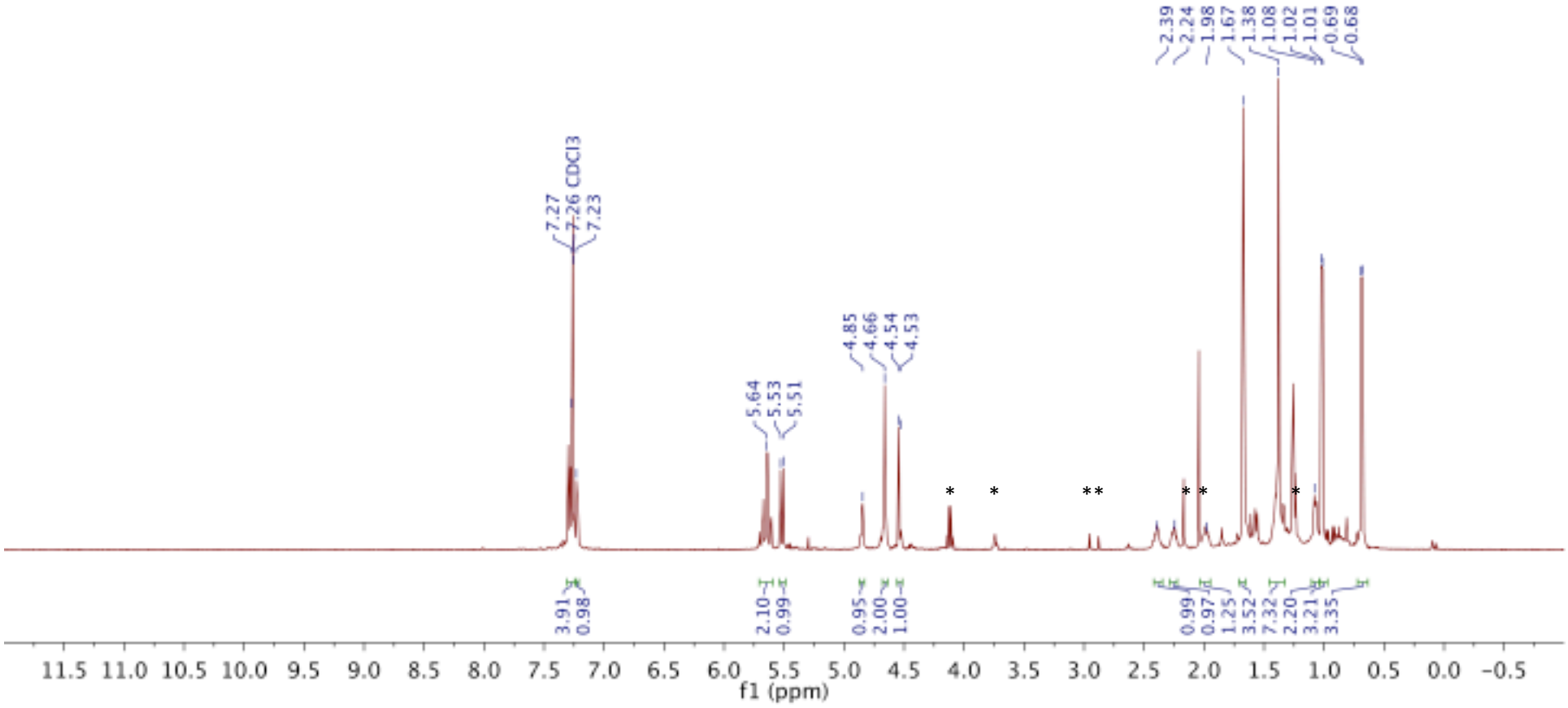


(−)-A3: IR


% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
3313
2927
2855
1748
1608
1456
1379
1221
1182
1083
969
880
786
753
705
667
O
O
O
O
OH
5

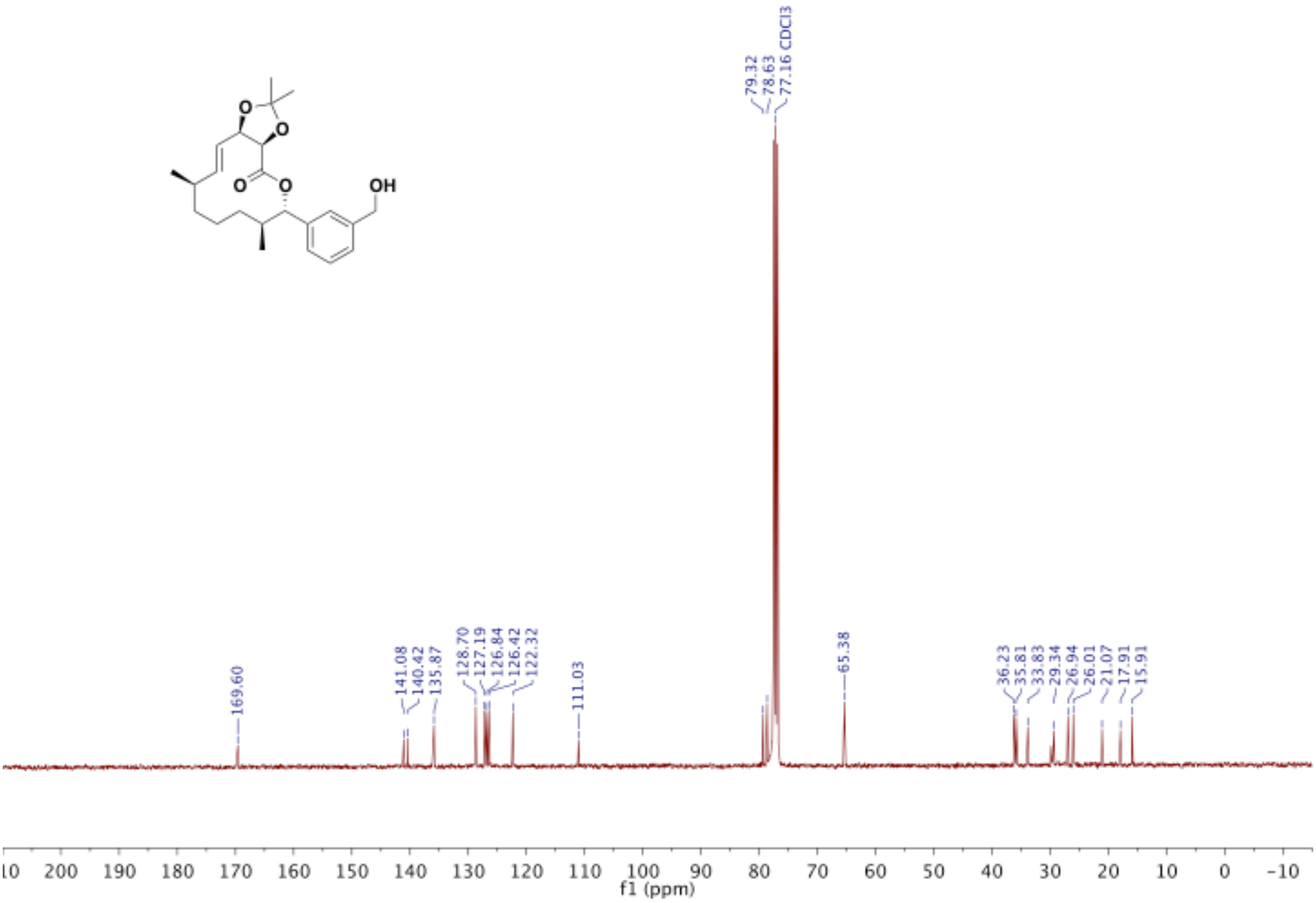
(−)-A2: ^{1}H NMR (500 MHz, $CDCl_3$)



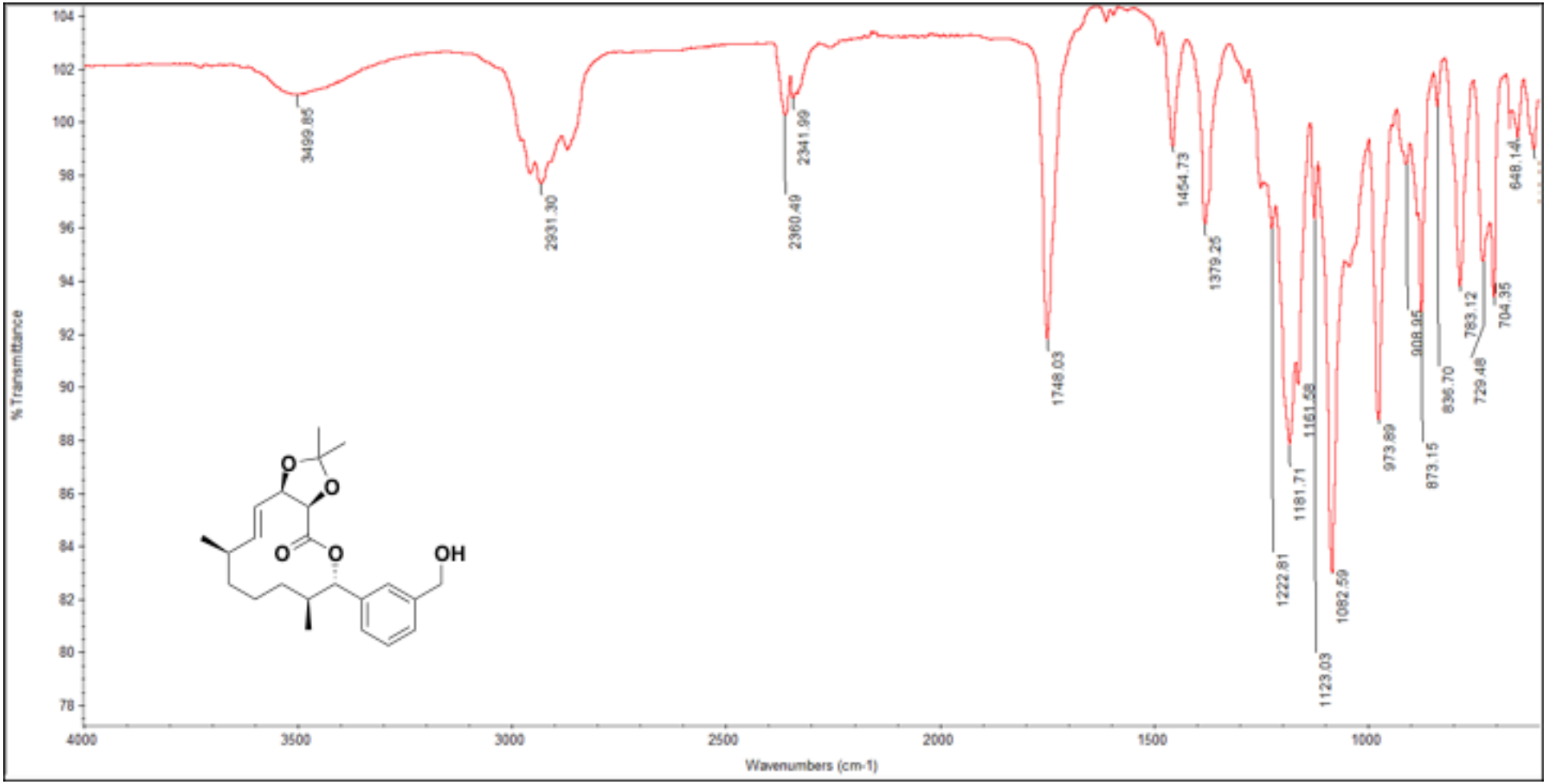


*Impurities present in spectrum

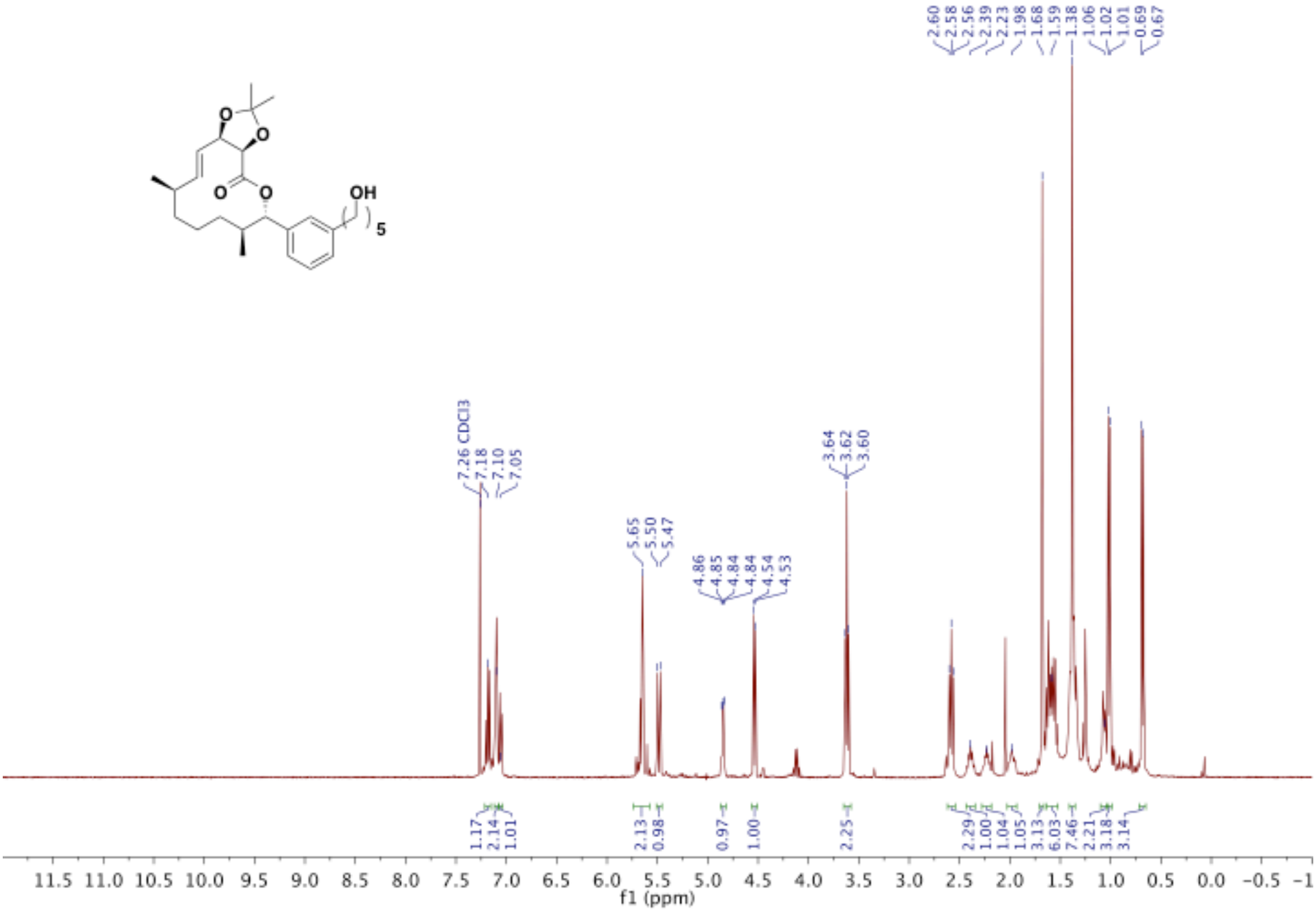
(−)-A2: ^{13}C NMR (126 MHz, $CDCl_3$)



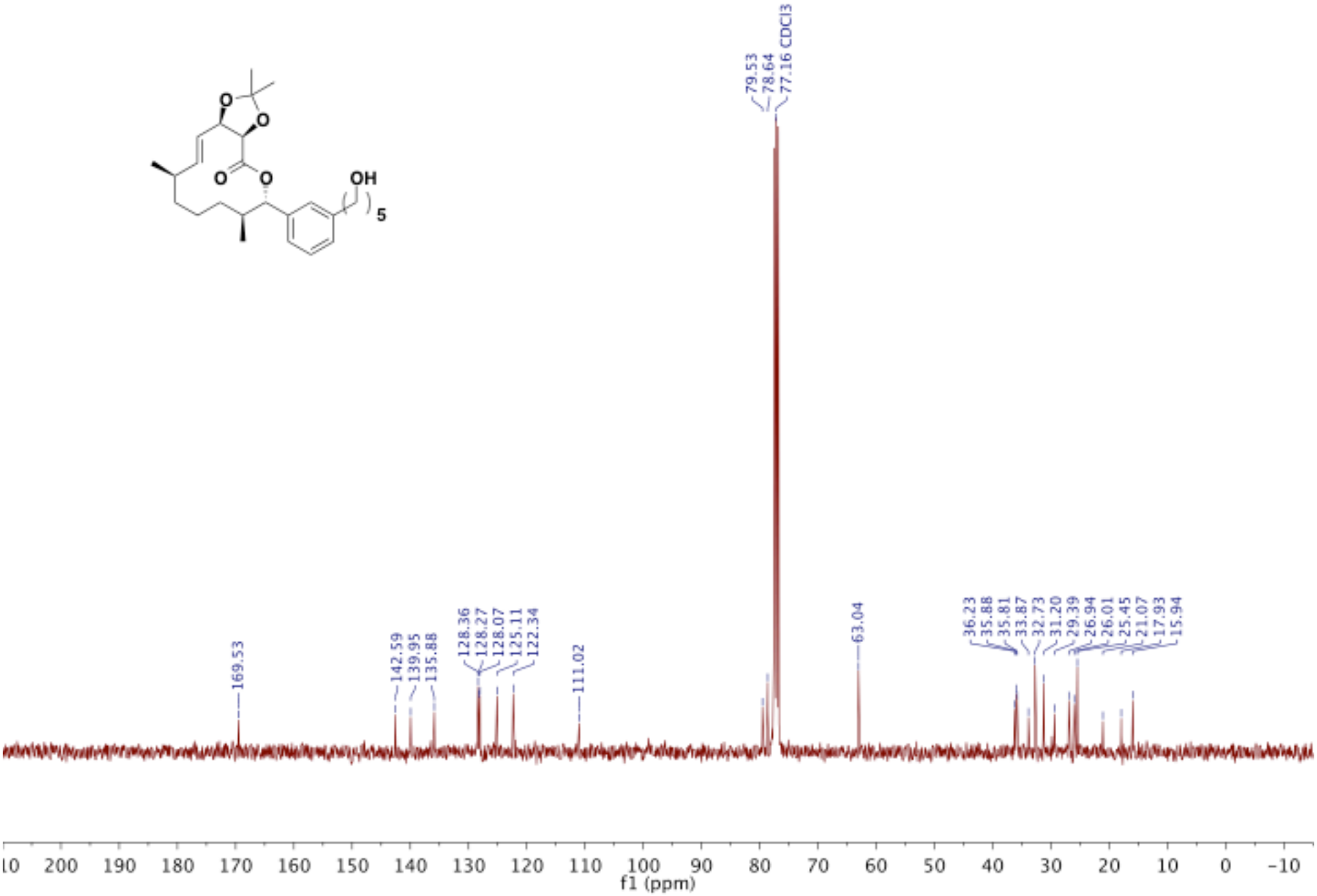
(−)-A2: IR


% Transmittance
Wavenumbers (cm-1)
3499.85
2931.30
2360.49
2341.99
1748.03
1454.73
1379.25
1222.81
1181.71
1161.58
1123.03
1082.59
973.89
908.95
873.15
836.70
783.12
729.48
704.35
648.14
OH

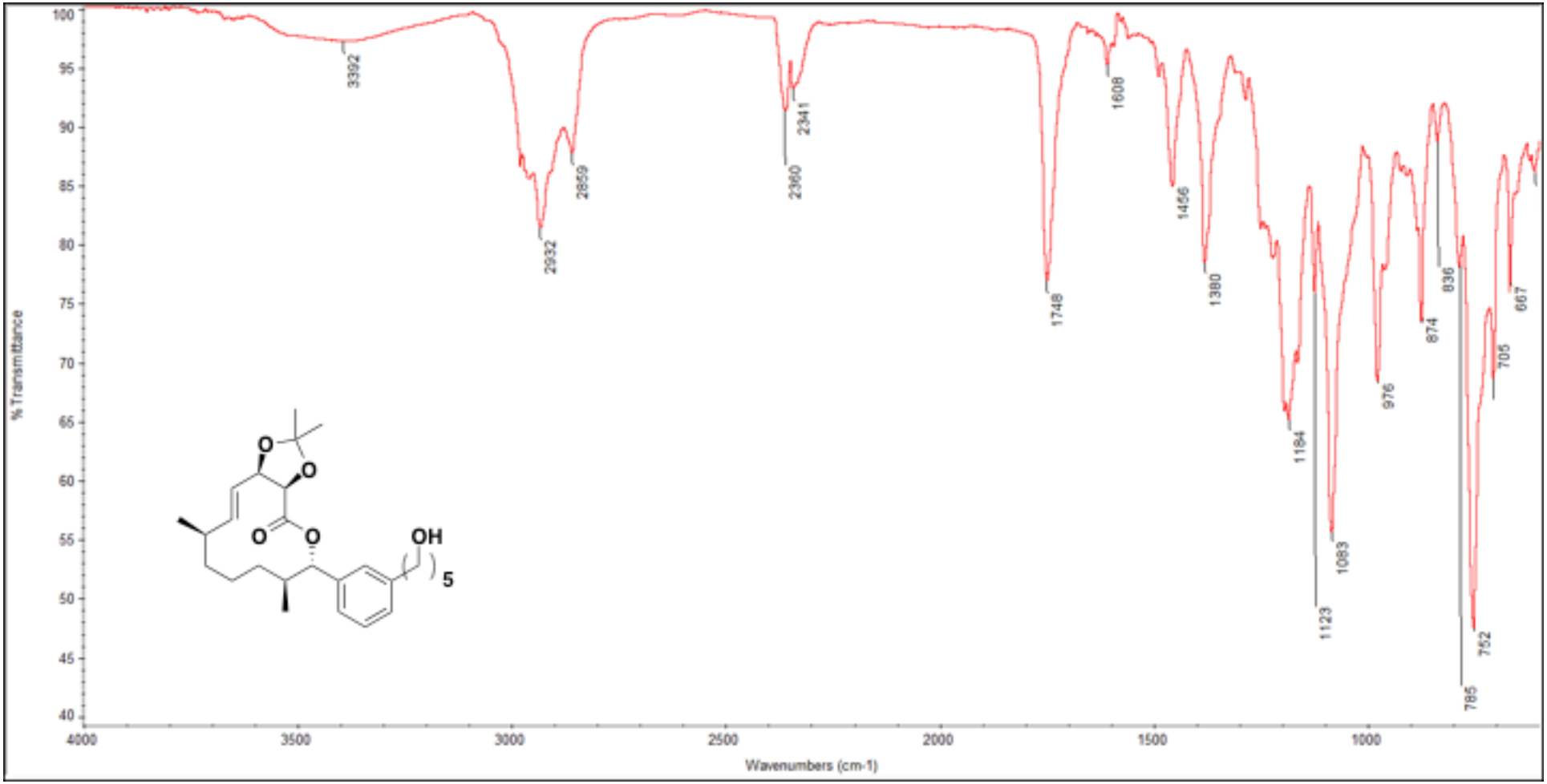
(–)-A4: ^{1}H NMR (500 MHz, $CDCl_3$)



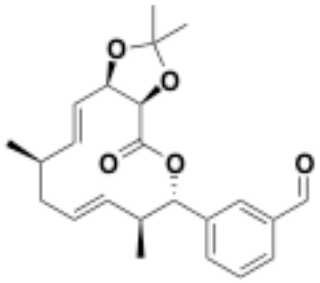
(−)-A4: ^{13}C NMR (126 MHz, $CDCl_3$)

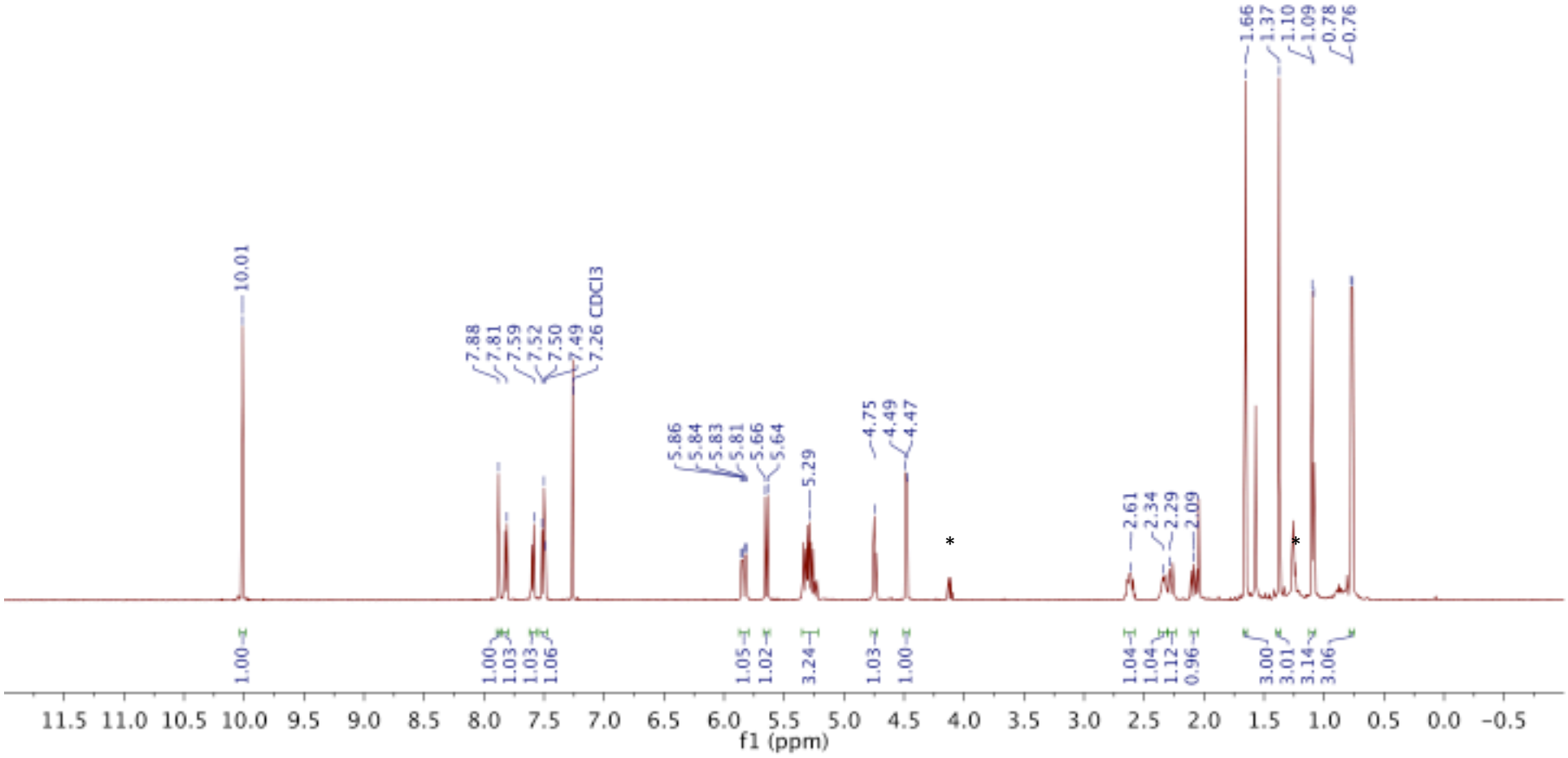


(−)-A4: IR


% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
100
95
90
85
80
75
70
65
60
55
50
45
40
3392
2932
2859
2360
2341
1748
1608
1456
1380
1184
1123
1083
976
874
836
785
752
705
667
O
O
O
O
OH
5

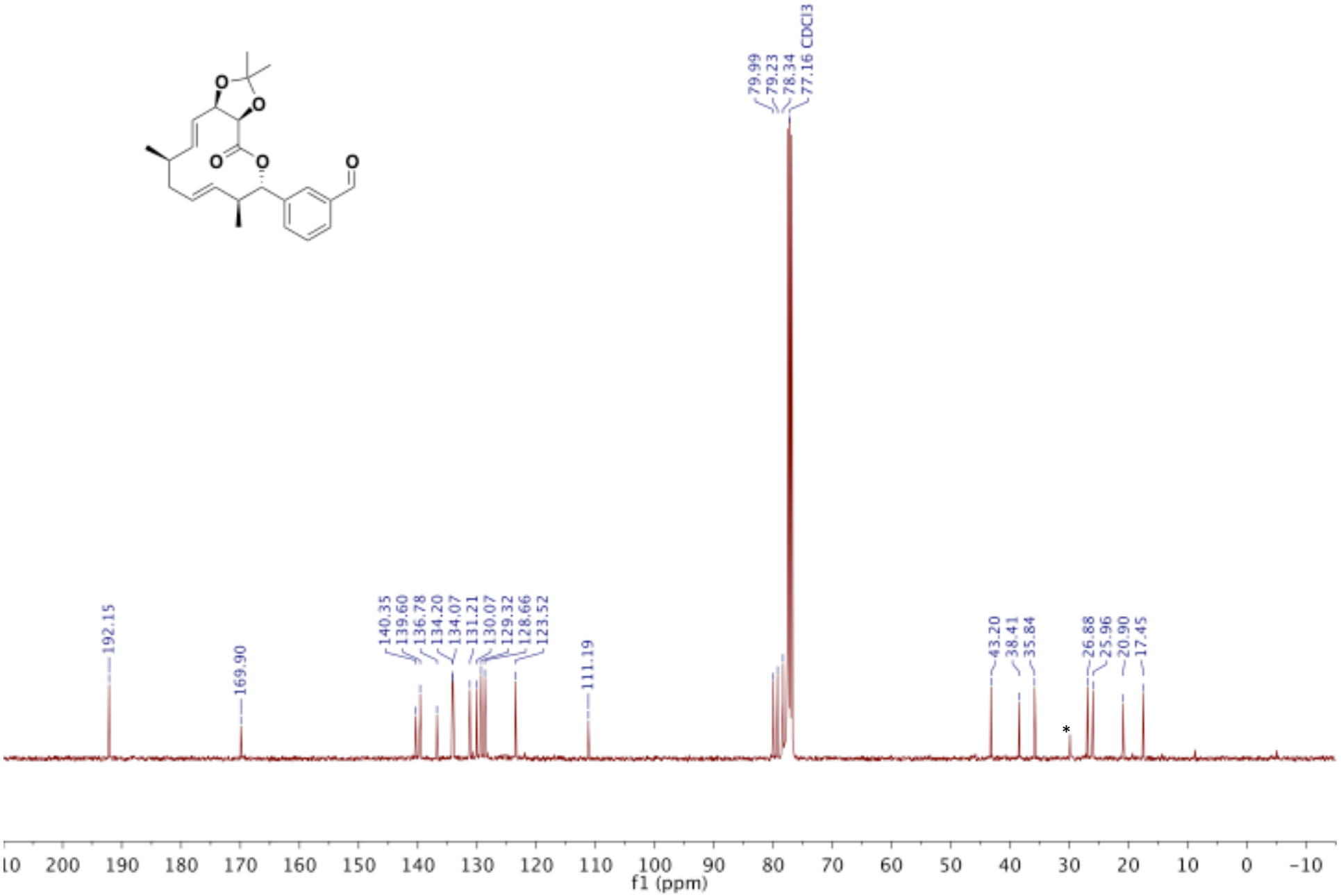
(−)-10a: ^{1}H NMR (500 MHz, $CDCl_3$)





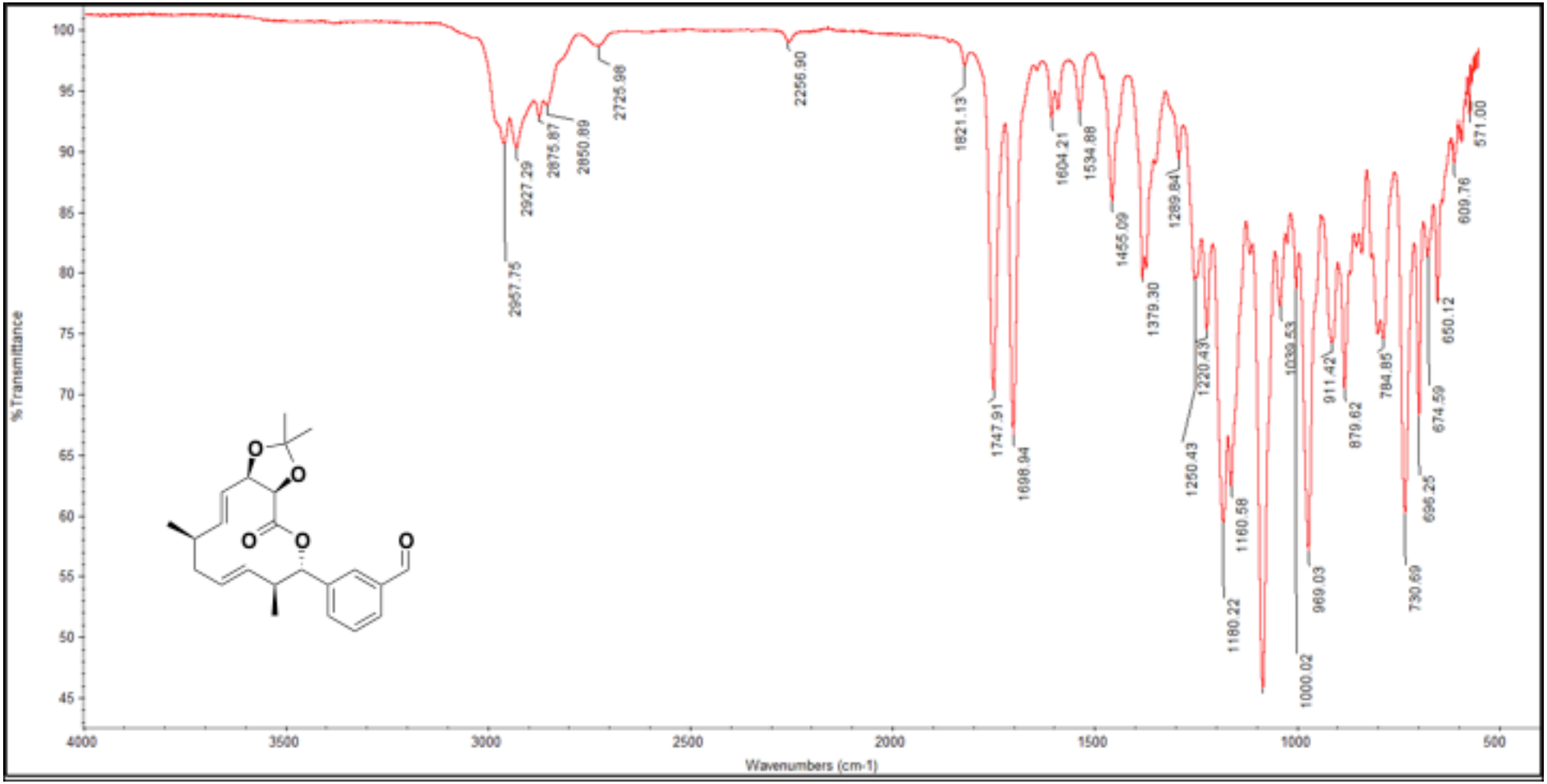
*Impurities present in spectrum

(−)-10a: ^{13}C NMR (126 MHz, $CDCl_3$)

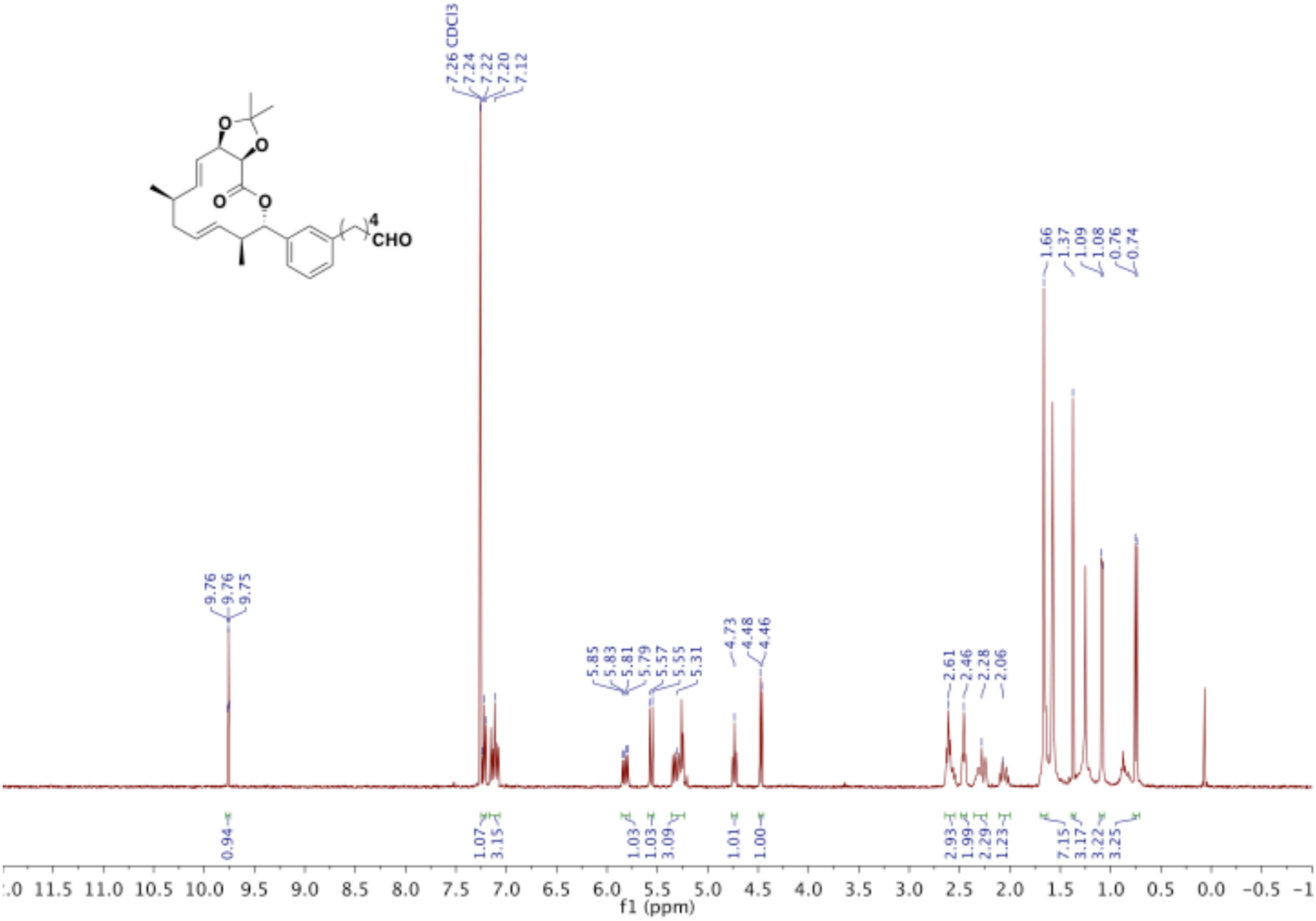


*Impurity present in spectrum

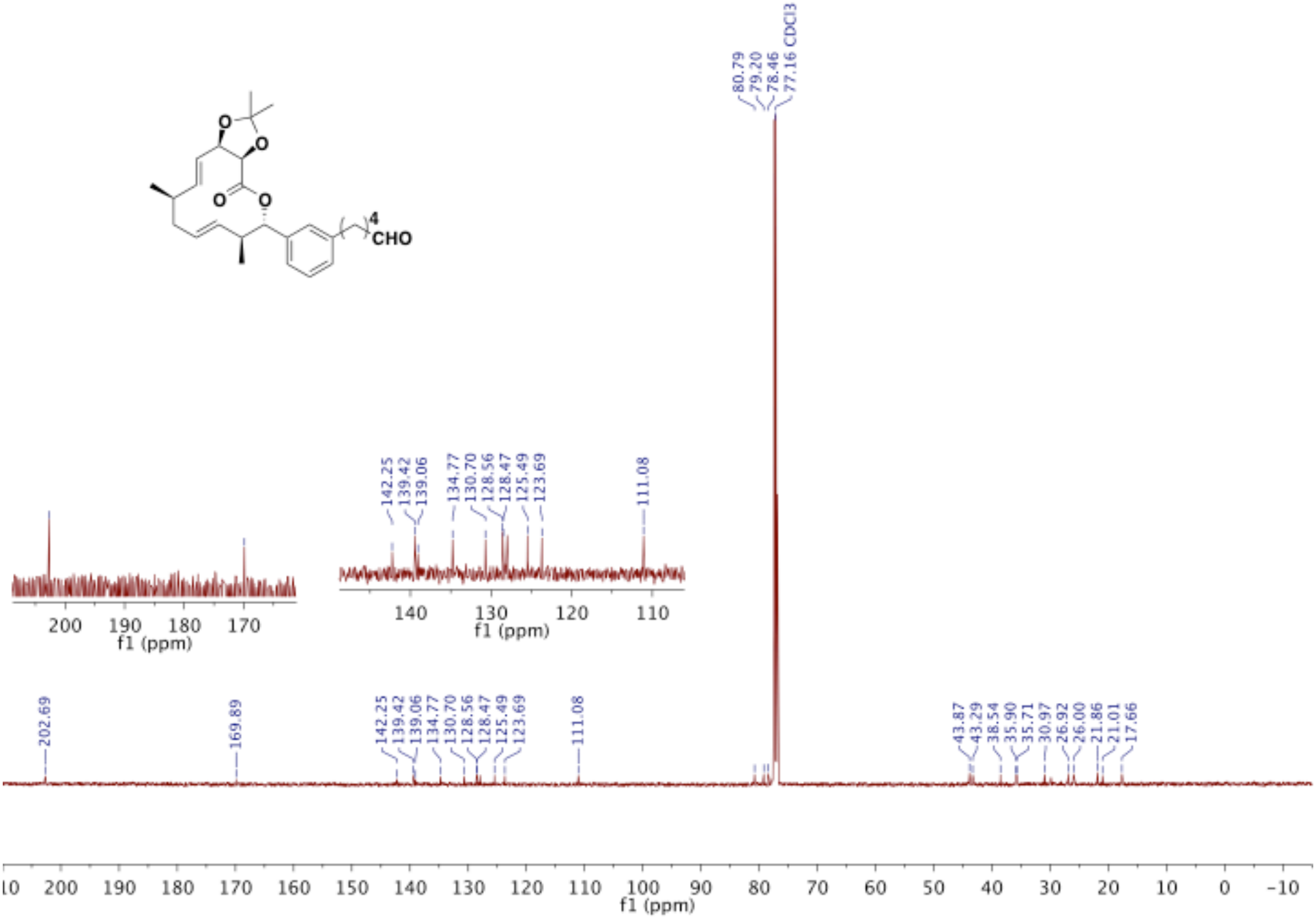
(–)-10a: IR


%Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
100
95
90
85
80
75
70
65
60
55
50
45
2957.75
2927.29
2875.87
2850.89
2725.98
2256.90
1821.13
1747.91
1698.94
1604.21
1534.88
1455.09
1379.30
1289.84
1250.43
1220.43
1180.22
1160.58
1039.53
1000.02
969.03
911.42
879.62
784.85
730.69
696.25
674.59
650.12
609.76
571.00
O
O
O
O
O

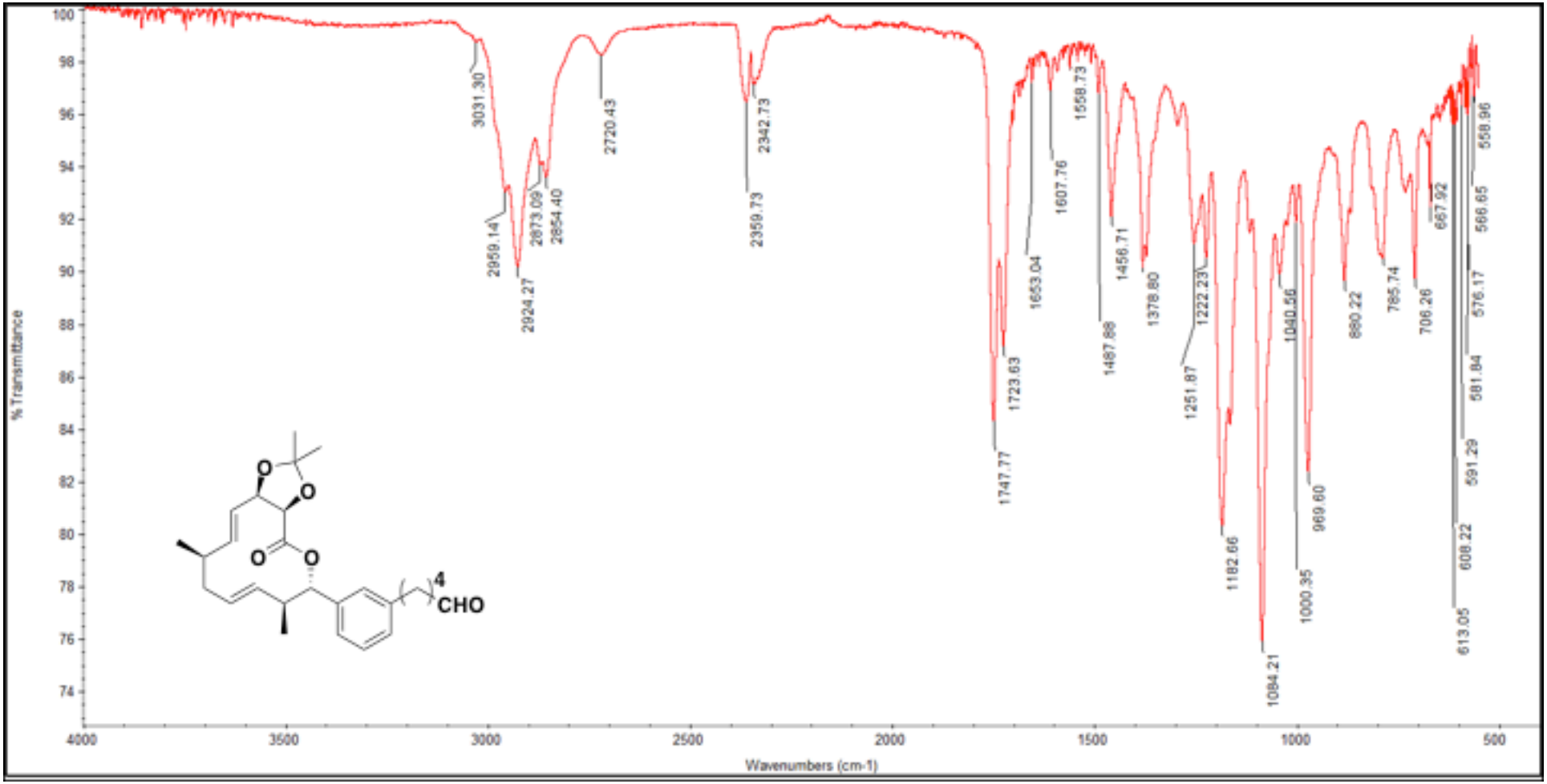
(−)-11a: ^{1}**H NMR** (500 MHz, $CDCl_3$)



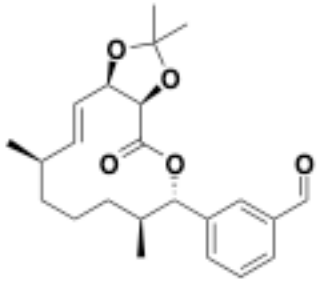
(−)-11a: ^{13}C NMR (126 MHz, $CDCl_3$)

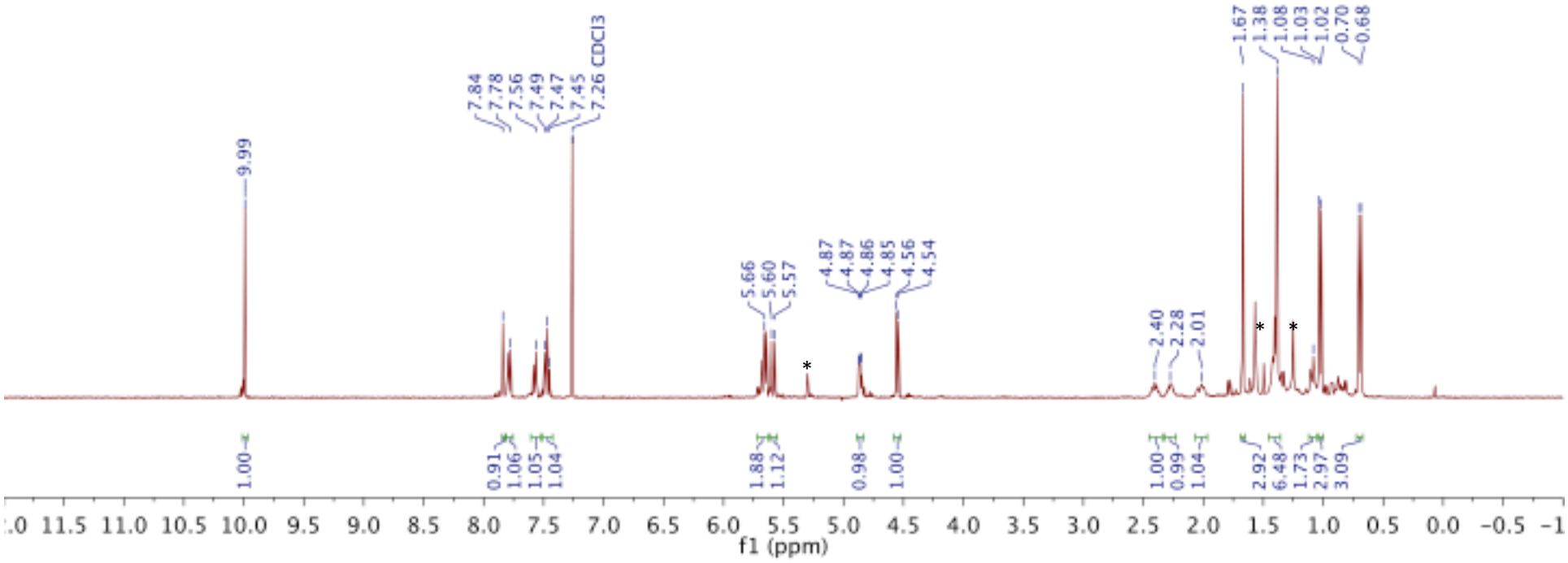


(–)-11a: IR


% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
100
98
96
94
92
90
88
86
84
82
80
78
76
74
3031.30
2959.14
2924.27
2873.09
2854.40
2720.43
2359.73
2342.73
1747.77
1723.63
1653.04
1607.76
1558.73
1487.88
1456.71
1378.80
1251.87
1222.23
1182.66
1084.21
1040.56
1000.35
969.60
880.22
785.74
706.26
667.92
613.05
608.22
591.29
581.84
576.17
566.65
558.96
O
O
O
O
4
CHO

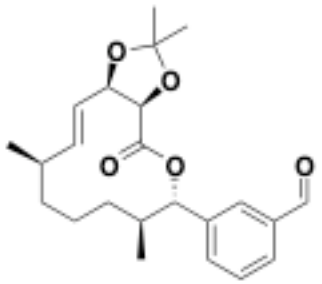
(−)-10b: ^{1}H NMR (500 MHz, $CDCl_3$)



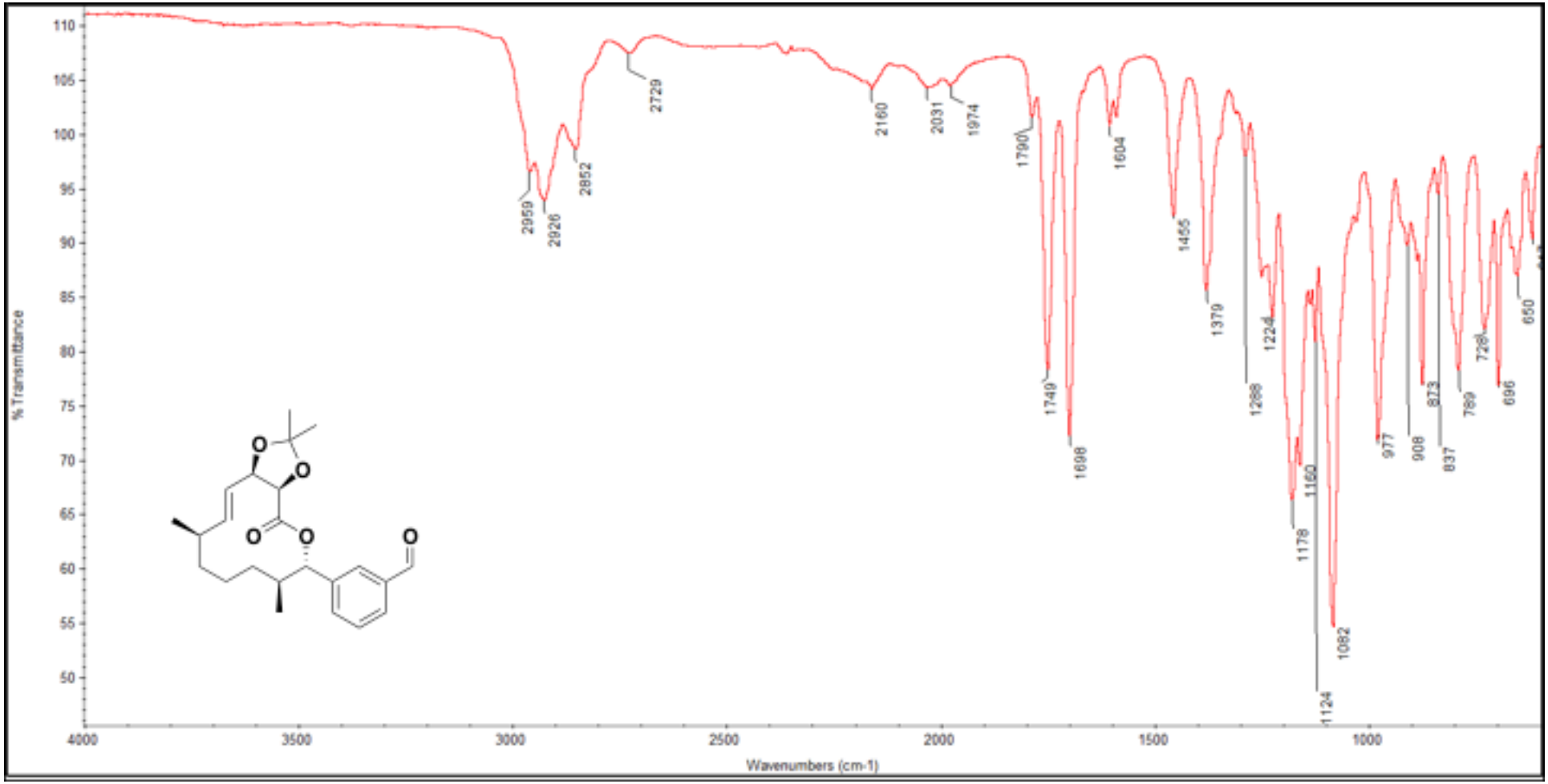


*Impurities present in spectrum

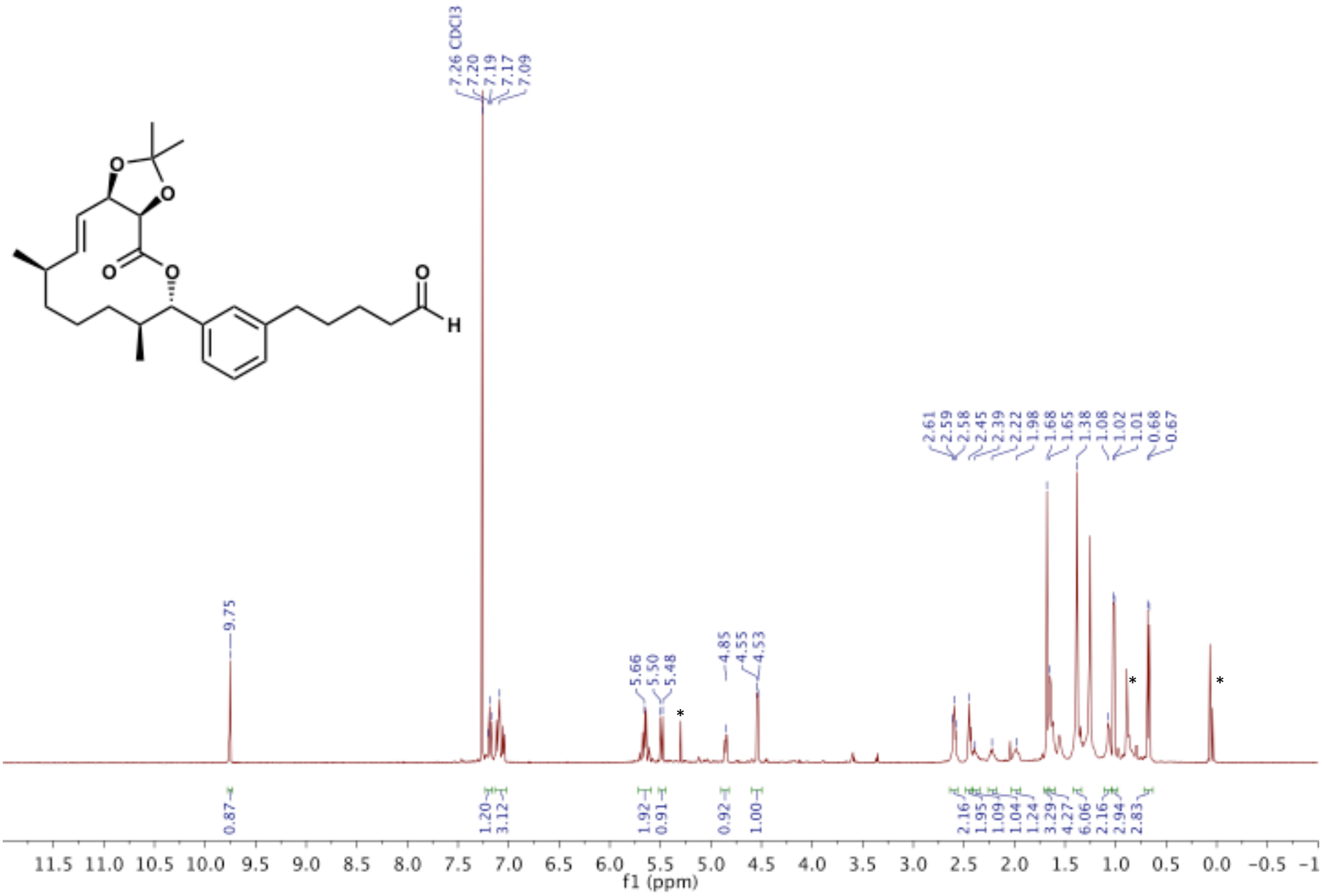
(–)-10b: ^{13}C NMR (126 MHz, $CDCl_3$)



(–)-10b: IR

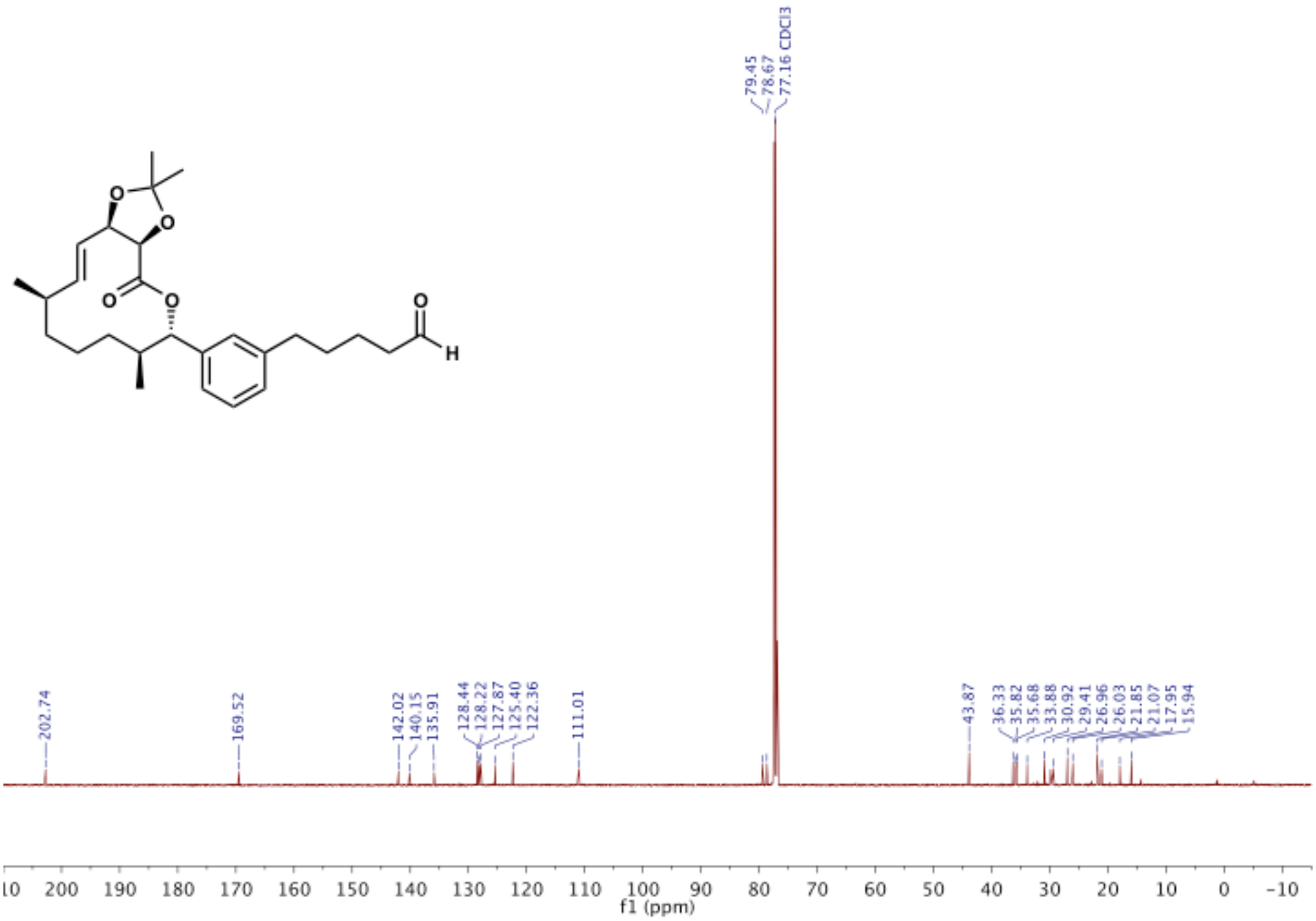

% Transmittance
Wavenumbers (cm-1)
2959
2926
2852
2729
2160
2031
1974
1790
1749
1698
1604
1455
1379
1288
1224
1178
1160
1124
1082
977
908
873
837
789
726
696
650

(−)-11b: ^{1}H NMR (500 MHz, $CDCl_3$)

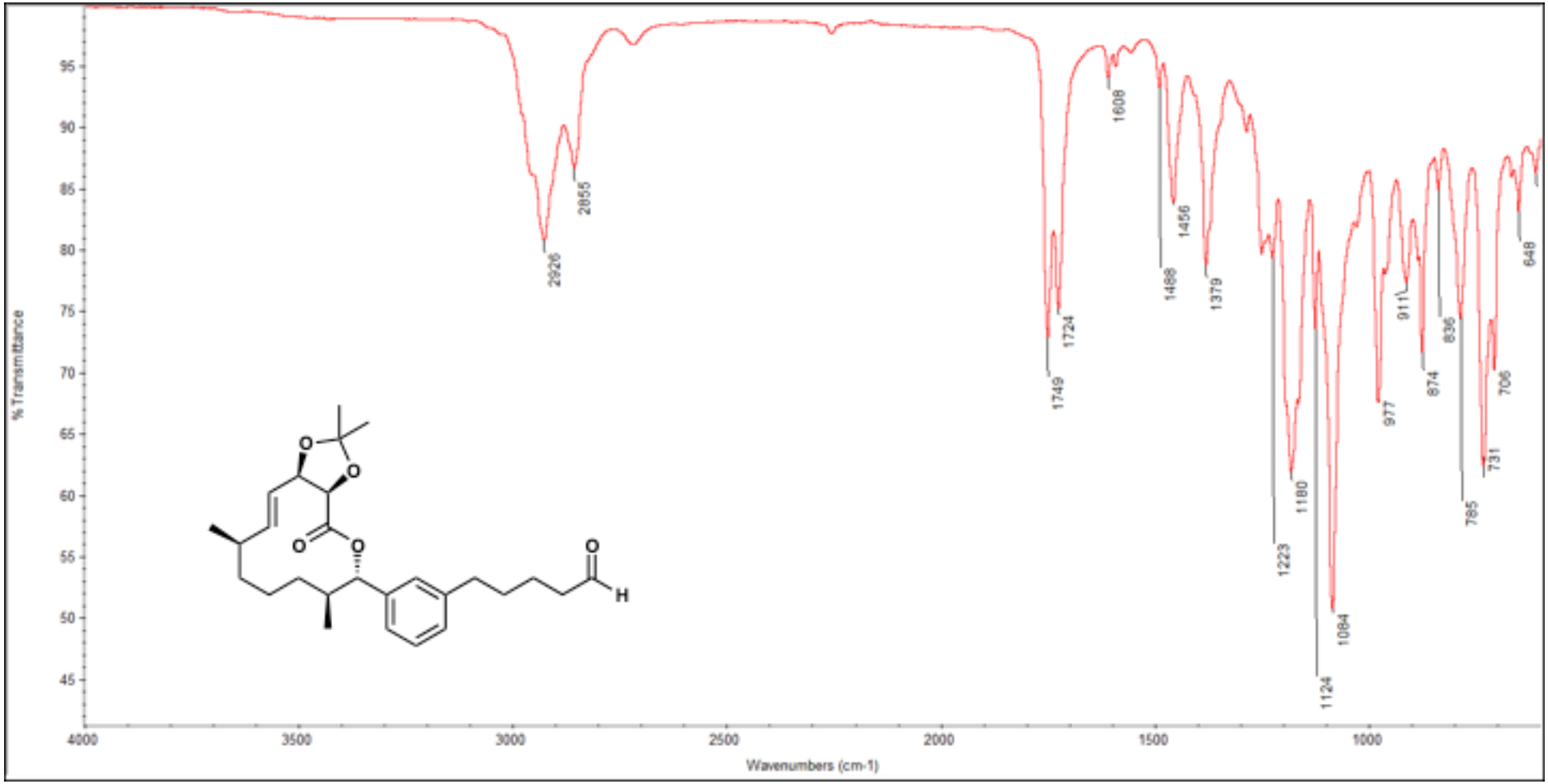


*Impurities present in spectrum

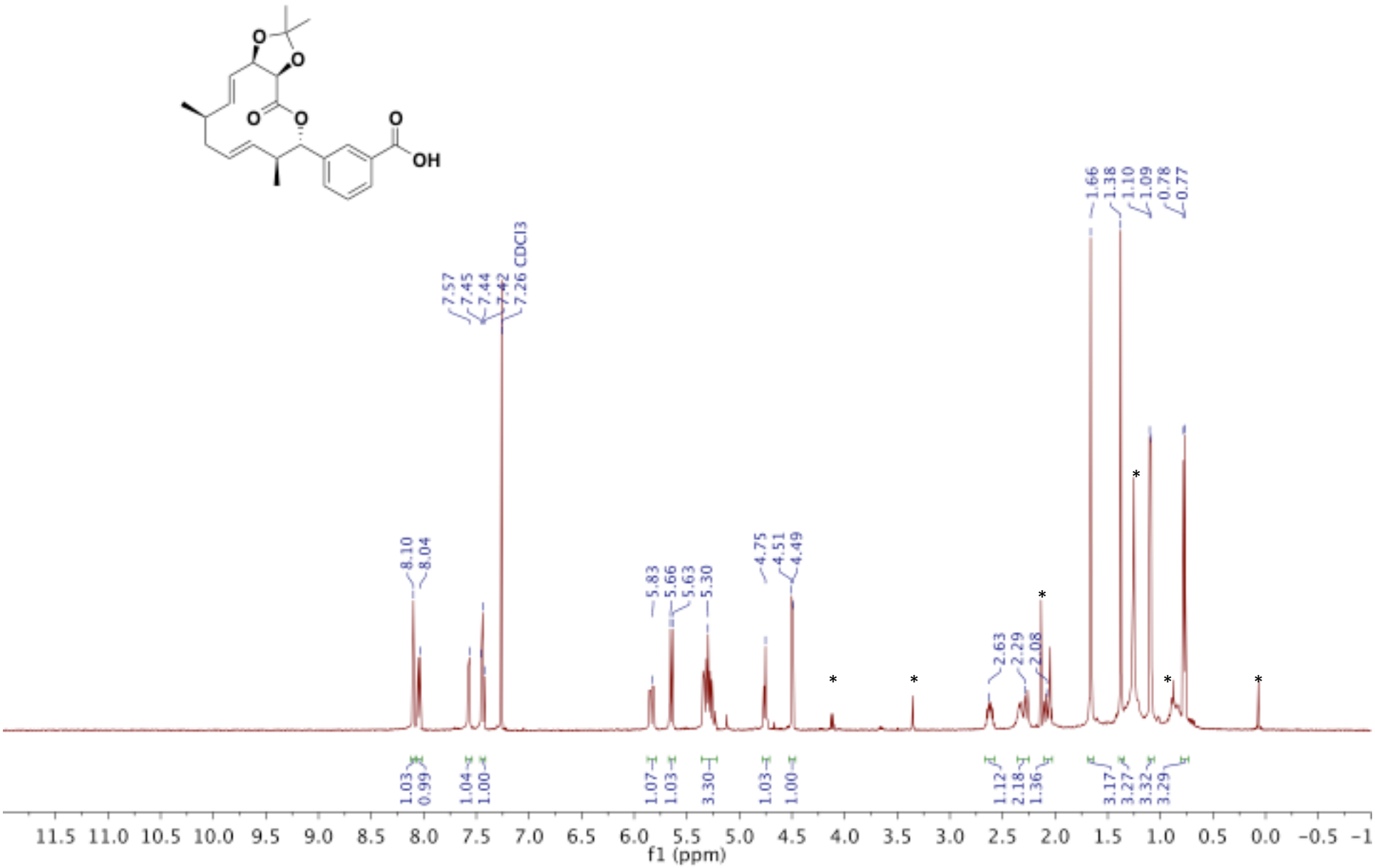
(−)-11b: ^{13}**C NMR** (126 MHz, $CDCl_3$)



(−)-11b: IR

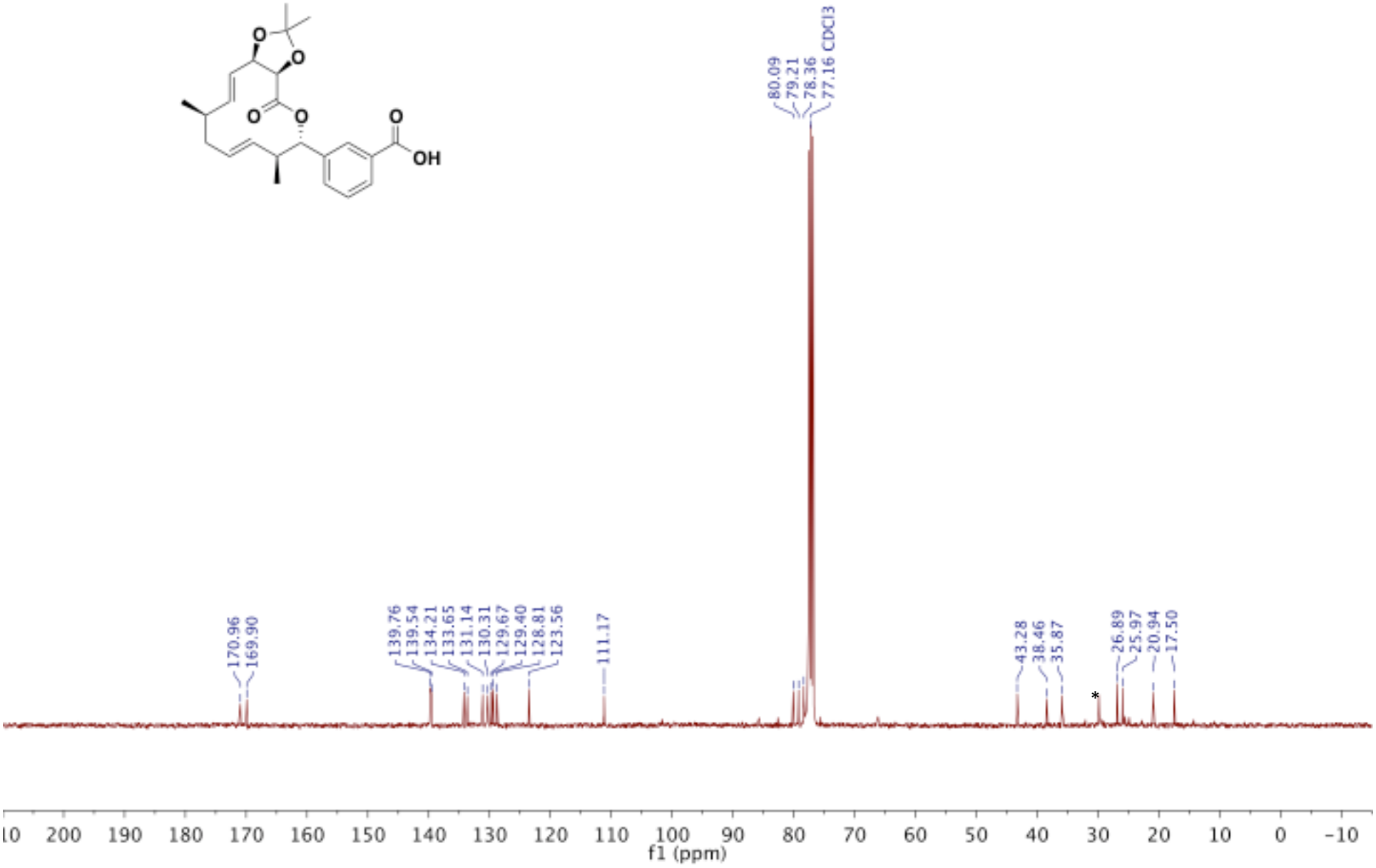

% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
95
90
85
80
75
70
65
60
55
50
45
2926
2855
1749
1724
1608
1488
1456
1379
1223
1180
1124
1084
977
911
874
836
785
731
706
648
O
O
O
O
O
H

(–)-C1: ^{1}**H NMR** (500 MHz, $CDCl_3$)



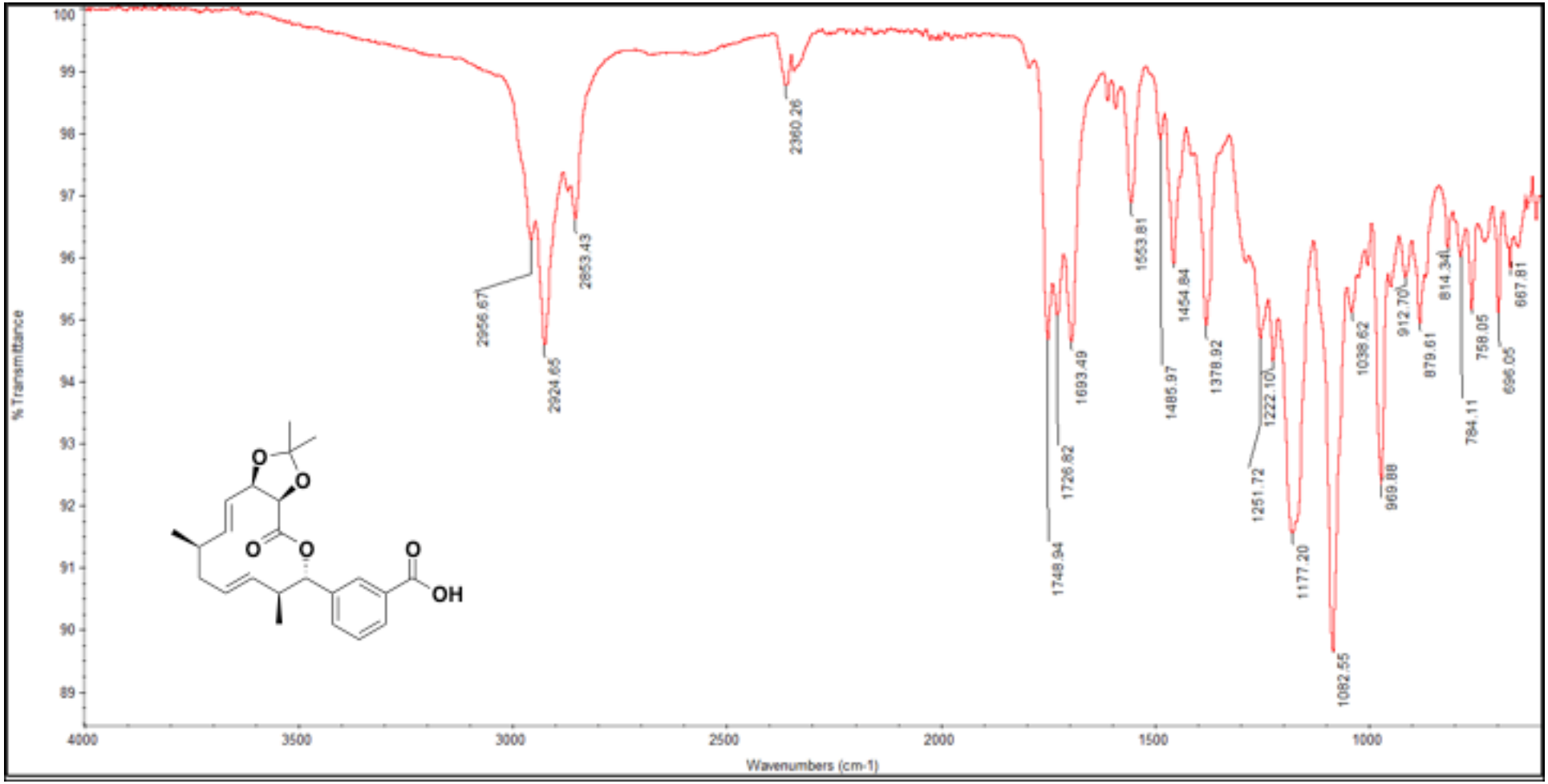
*Impurities present in spectrum

(−)-C1: ^{13}C NMR (126 MHz, $CDCl_3$)

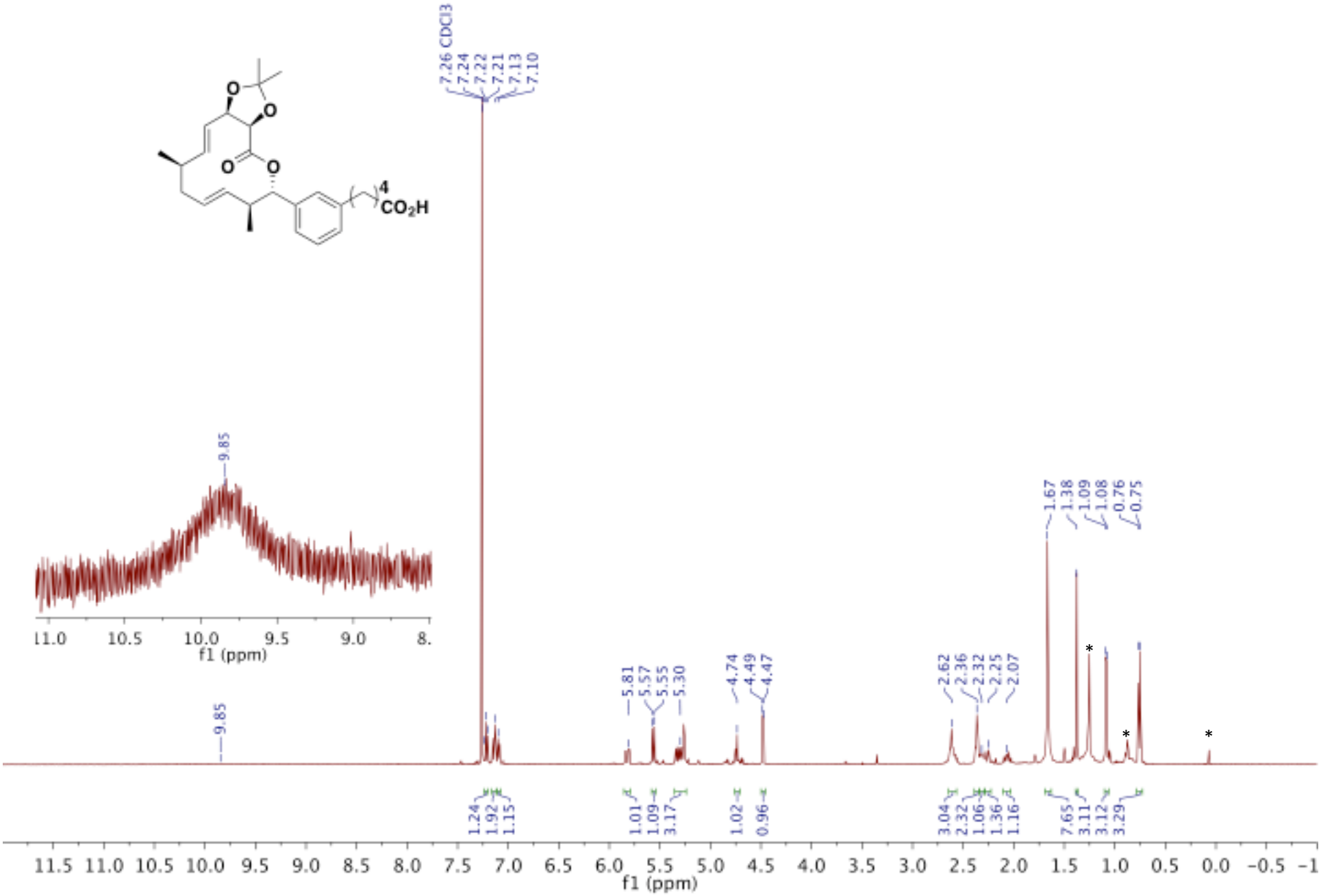


*Impurity present in spectrum

(–)-C1: IR

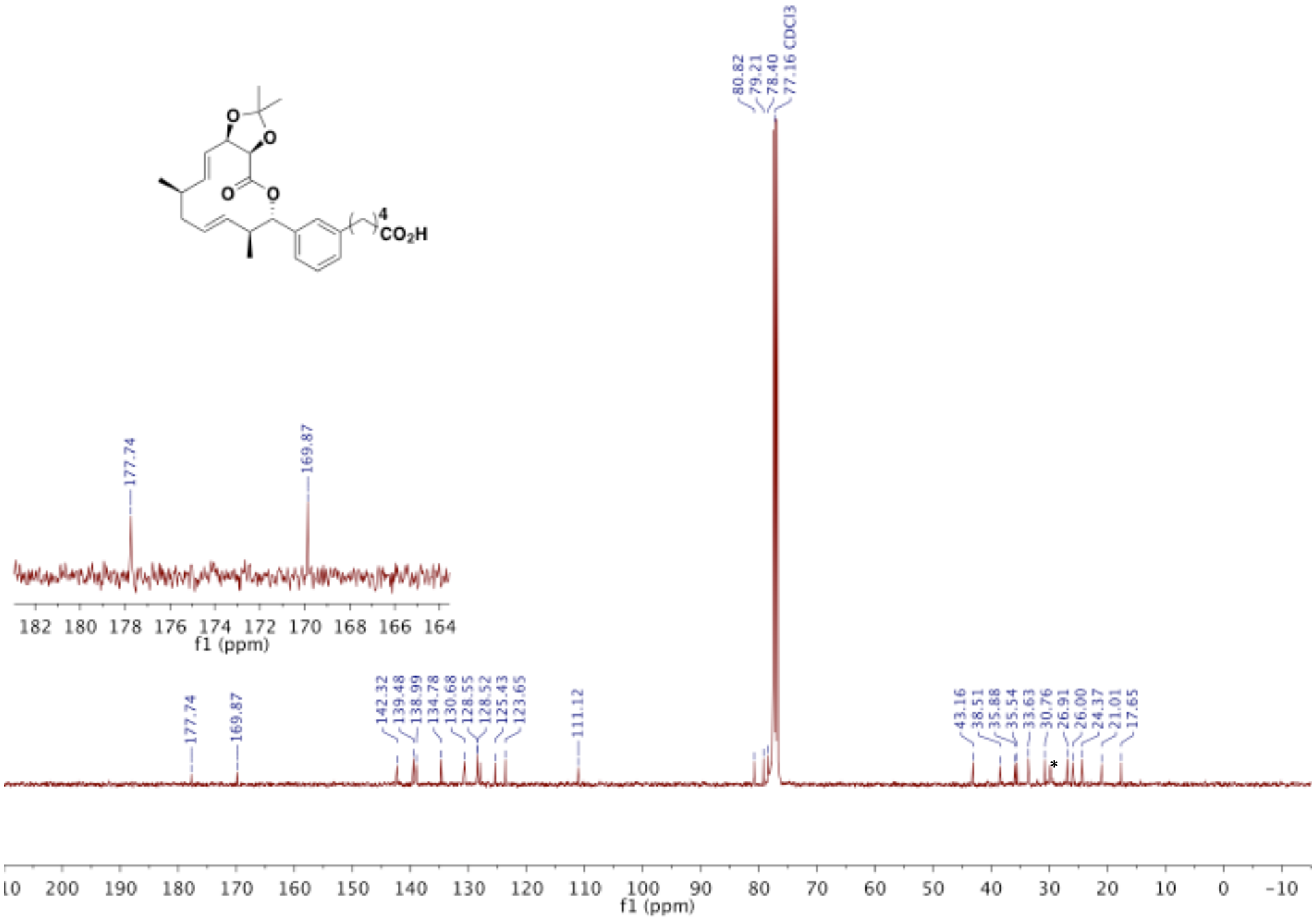

% Transmittance
Wavenumbers (cm-1)
2956.67
2924.65
2853.43
2360.26
1748.94
1726.82
1693.49
1553.81
1485.97
1454.84
1378.92
1251.72
1222.10
1177.20
1082.55
1038.62
969.88
912.70
879.61
814.34
784.11
758.05
696.05
667.81
OH

(−)-C3: ^{1}H NMR (500 MHz, $CDCl_3$)



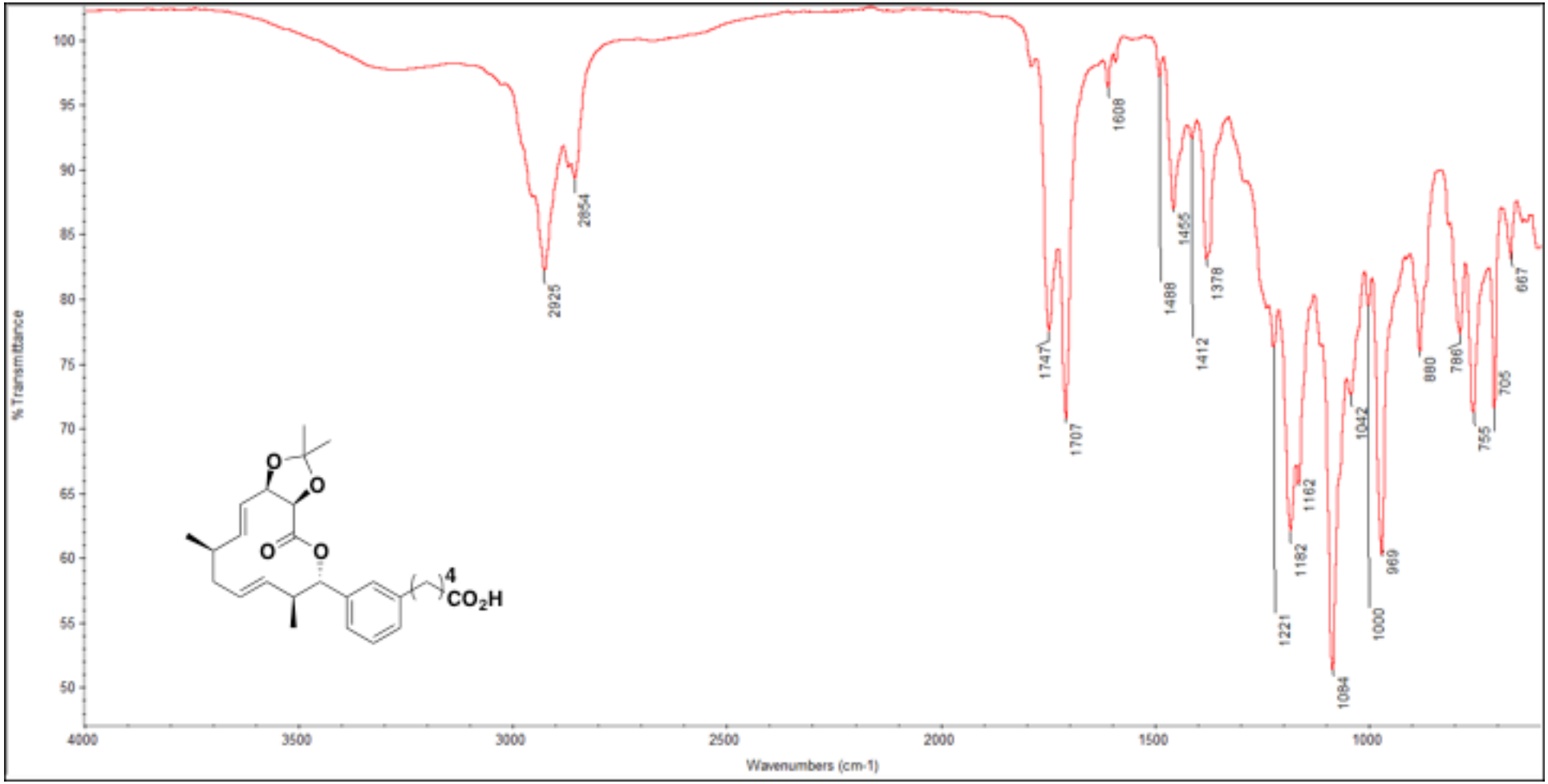
*Impurities present in spectrum

(−)-C3: ^{13}C NMR (126 MHz, $CDCl_3$)

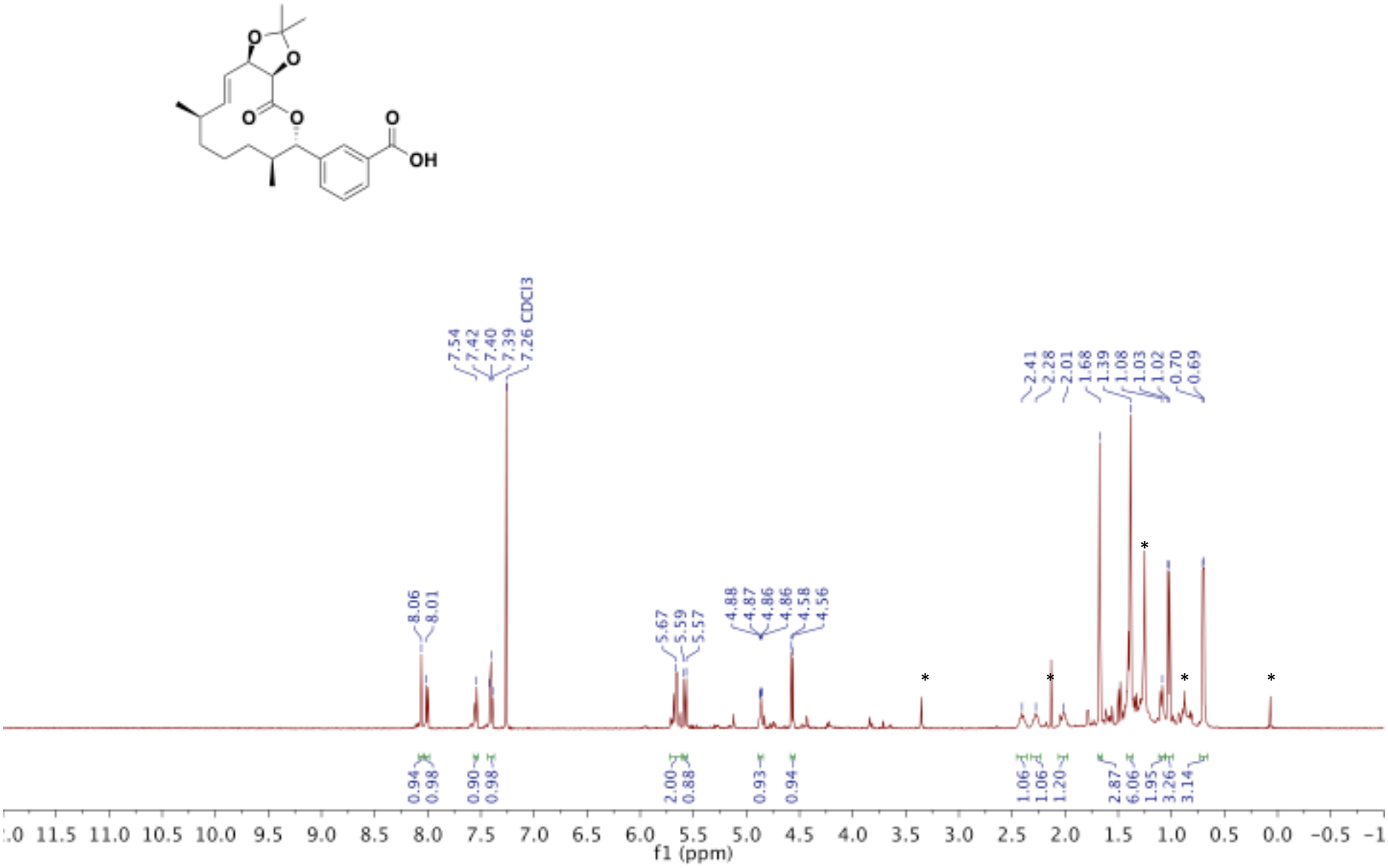


*Impurity present in spectrum

(–)-C3: IR

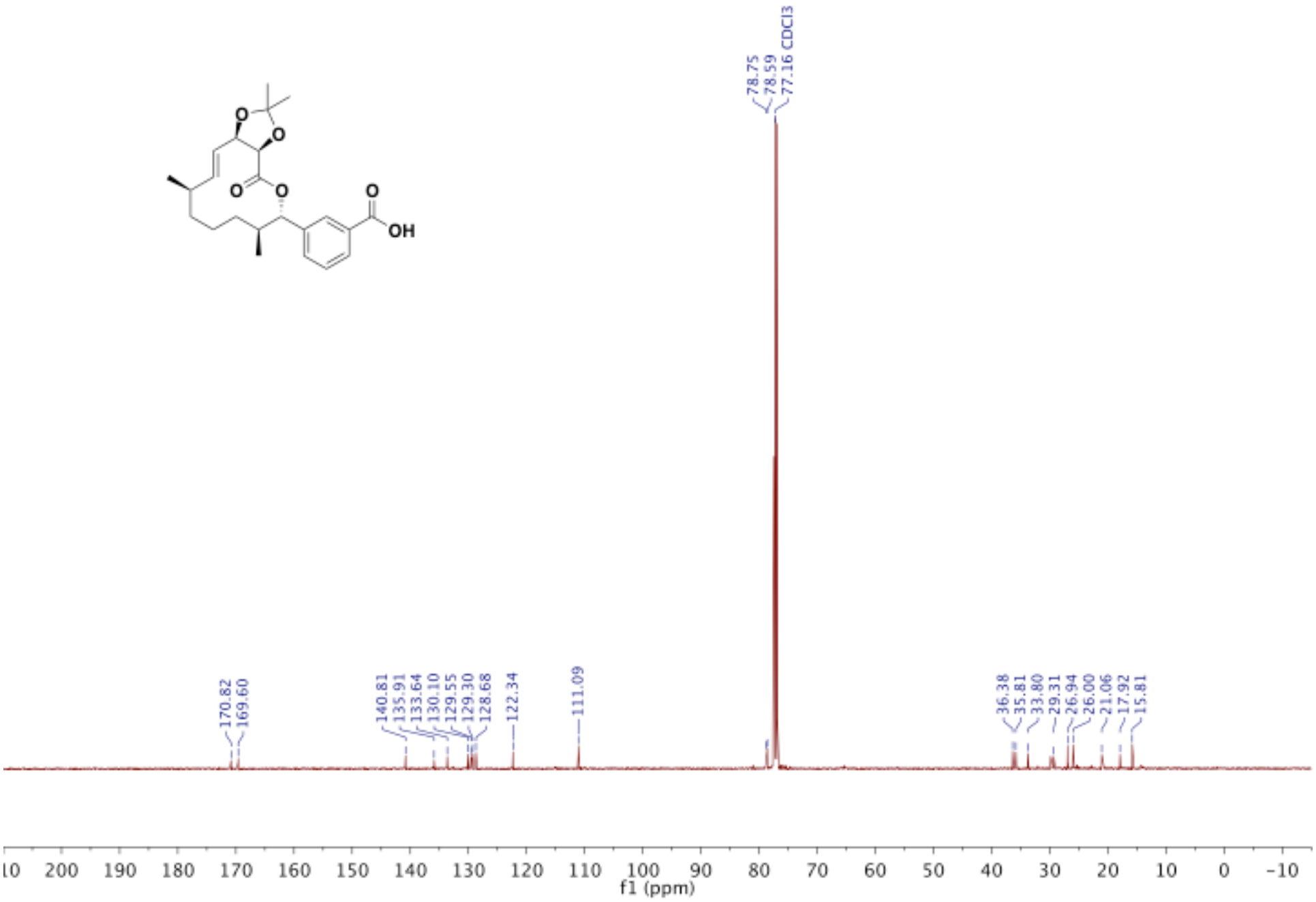

% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
100
95
90
85
80
75
70
65
60
55
50
2925
2854
1747
1707
1608
1488
1455
1412
1378
1221
1182
1162
1084
1042
1000
969
880
786
755
705
667
O
O
O
O
4
CO2H

(–)-C2: ^{1}**H NMR** (500 MHz, $CDCl_3$)

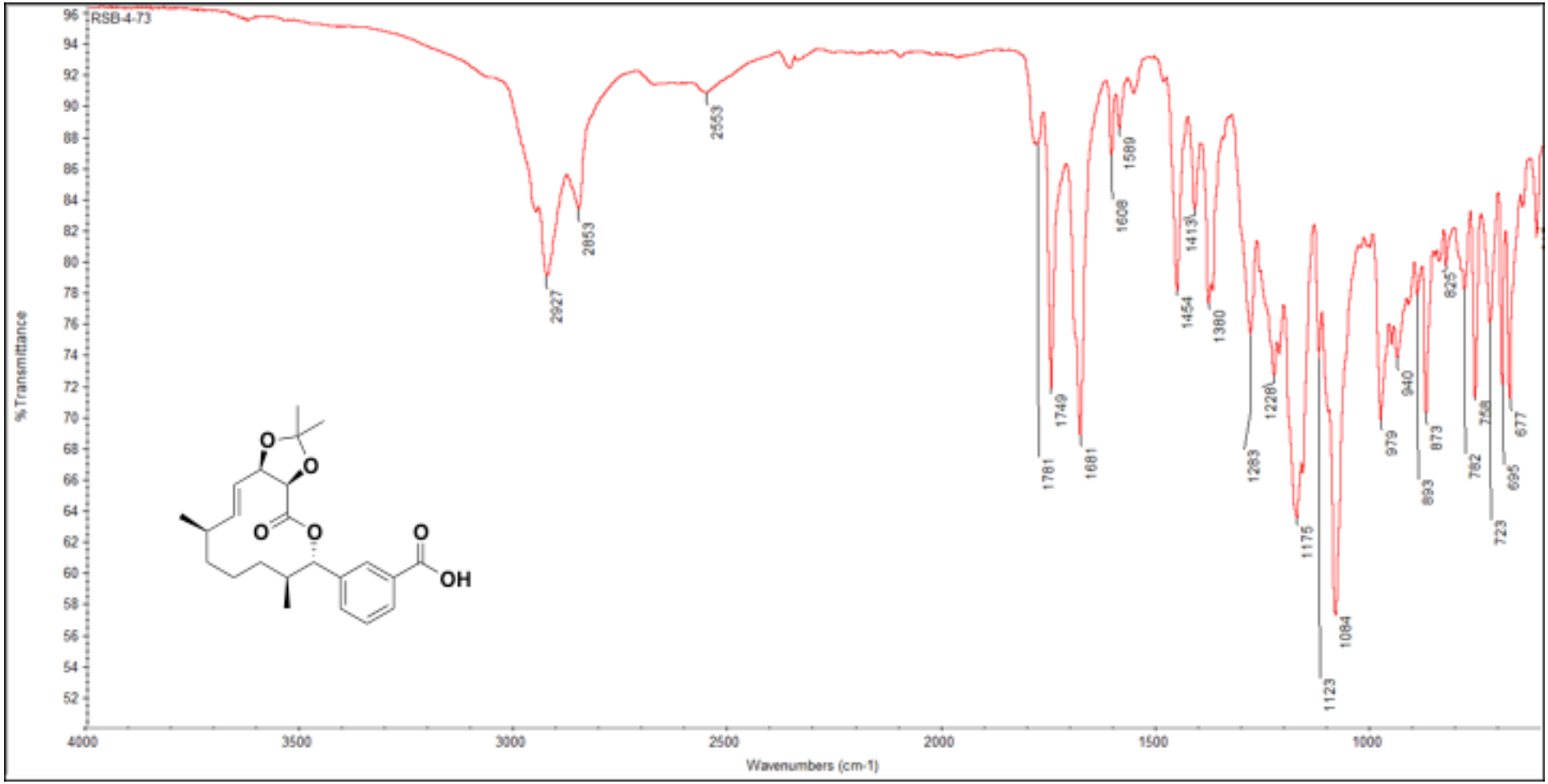


*Impurities present in spectrum

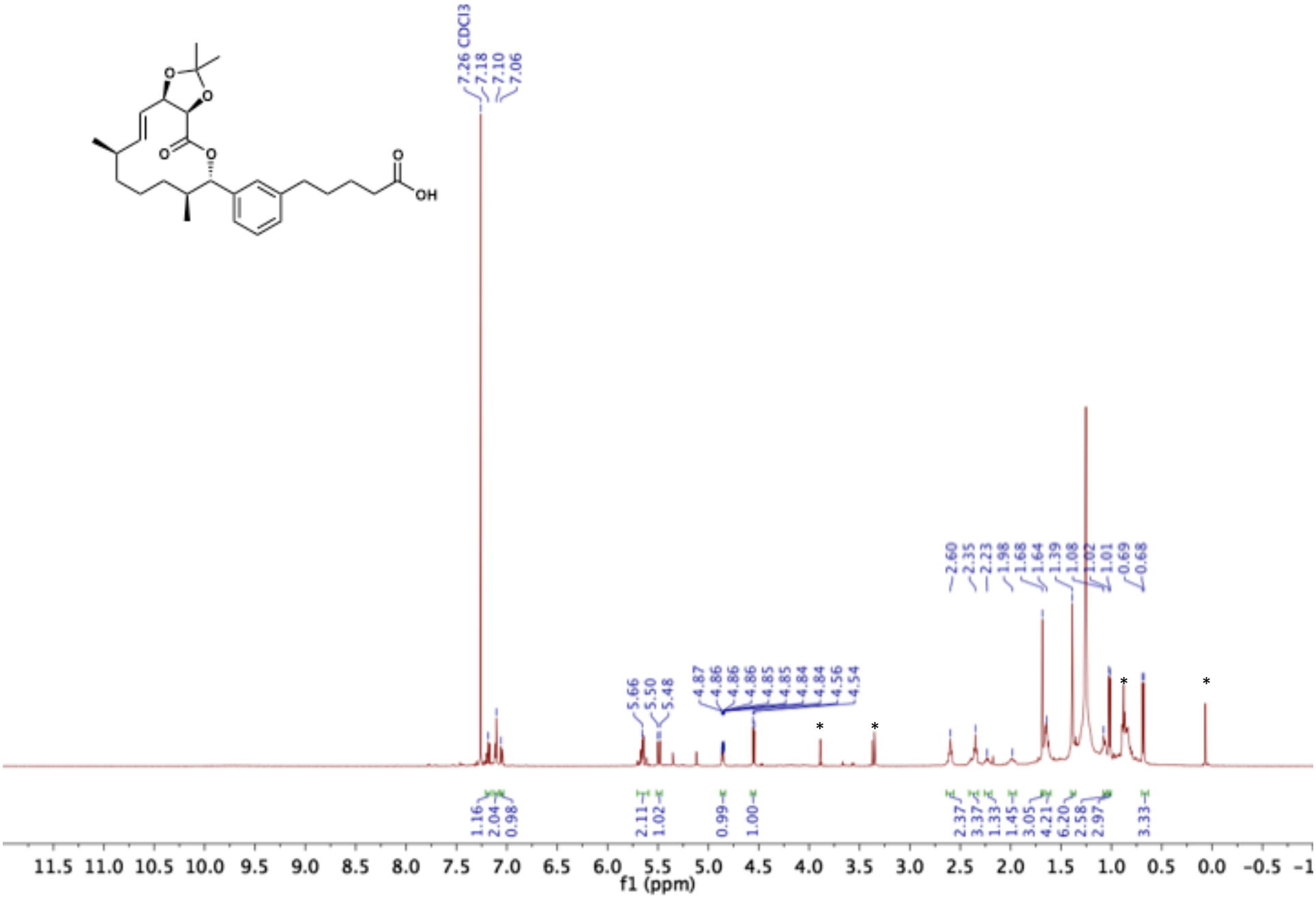
(−)-C2: ^{13}C NMR (126 MHz, $CDCl_3$)



(−)-C2: IR


RSB-4-73
% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
2927
2853
2553
1781
1749
1681
1608
1589
1454
1413
1380
1283
1228
1175
1123
1084
979
940
893
873
825
782
758
723
695
677
OH

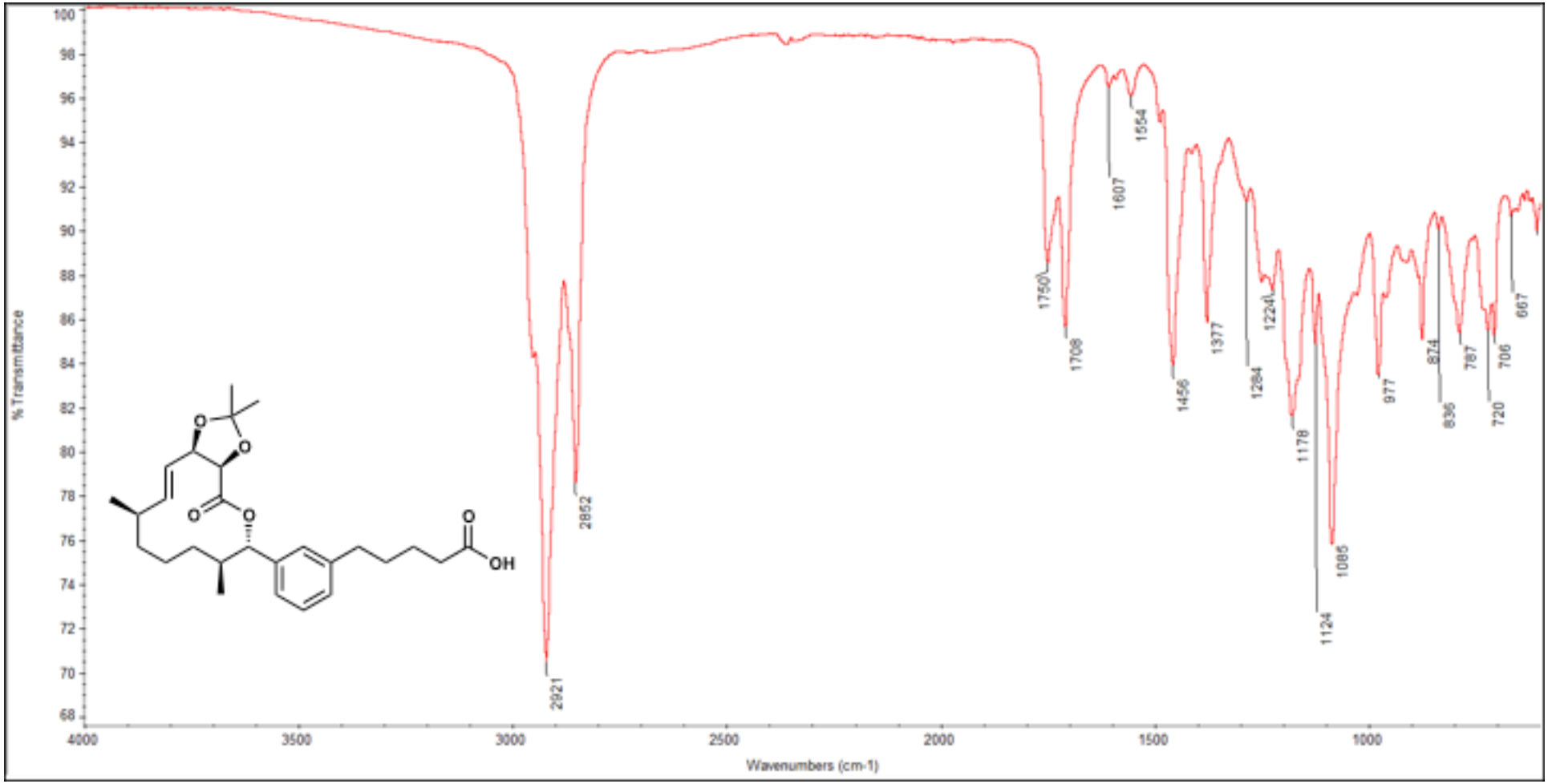
(−)-C4: ^{1}H NMR (500 MHz, $CDCl_3$)



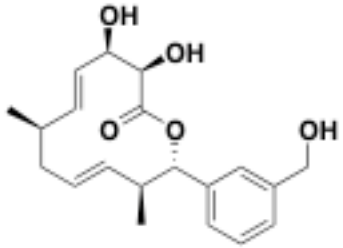
*Impurities present in spectrum

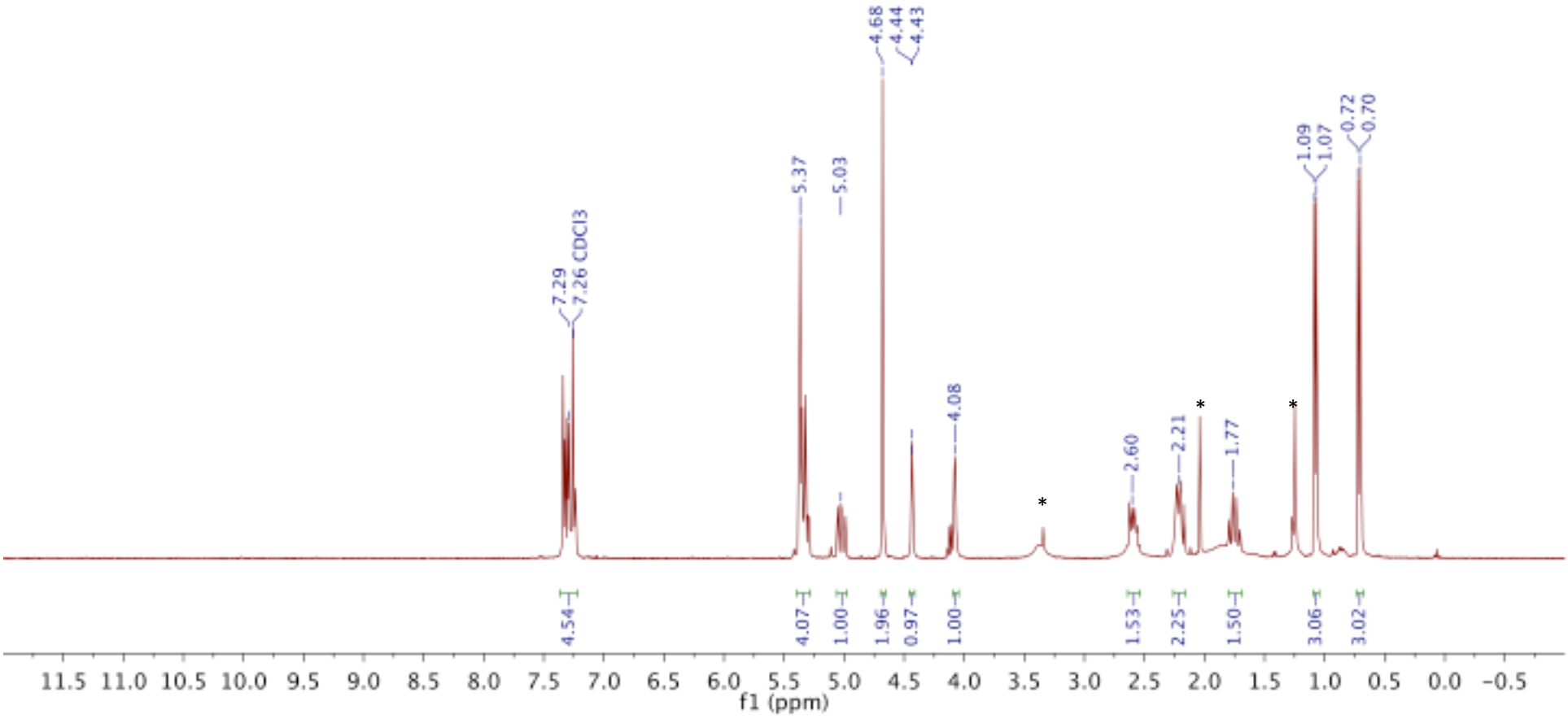
(–)-C4: ^{13}C NMR (126 MHz, $CDCl_3$)

(−)-C4: IR


% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
2921
2852
1750
1708
1607
1554
1456
1377
1284
1224
1178
1124
1085
977
874
836
787
720
706
667
O
O
O
O
O
OH

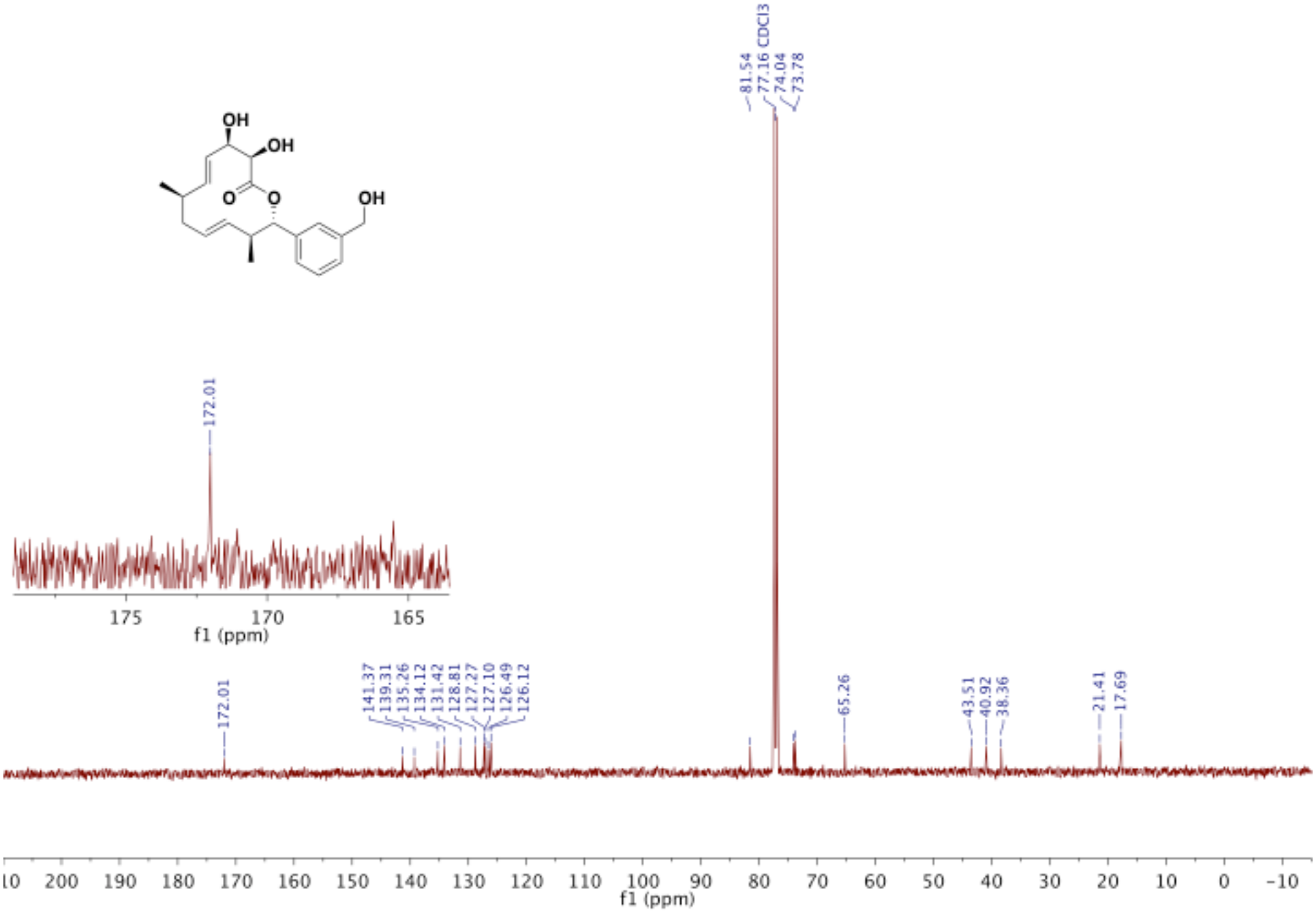
(−)-B1: ^{1}H NMR (500 MHz, $CDCl_3$)



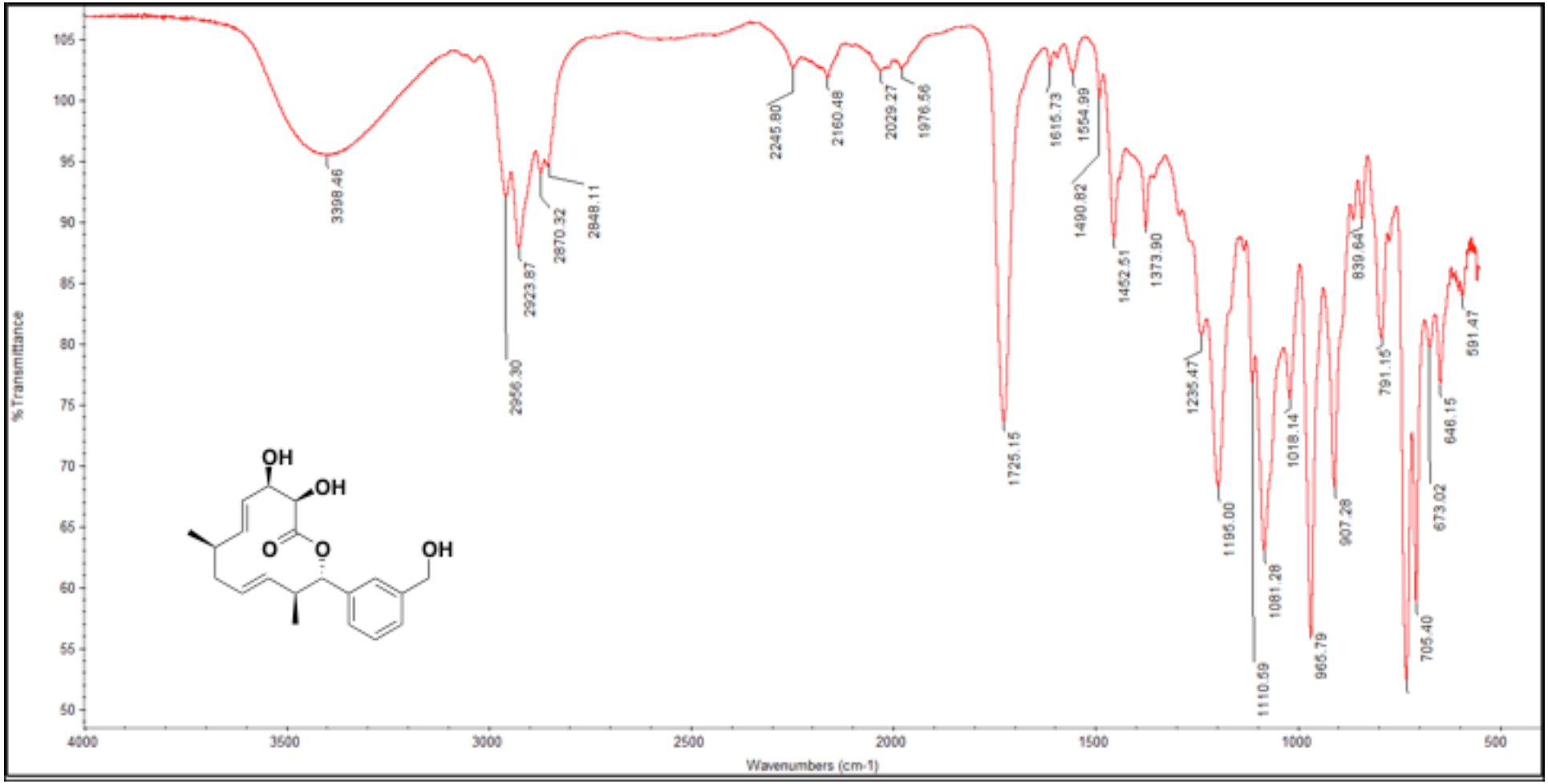


*Impurities present in spectrum

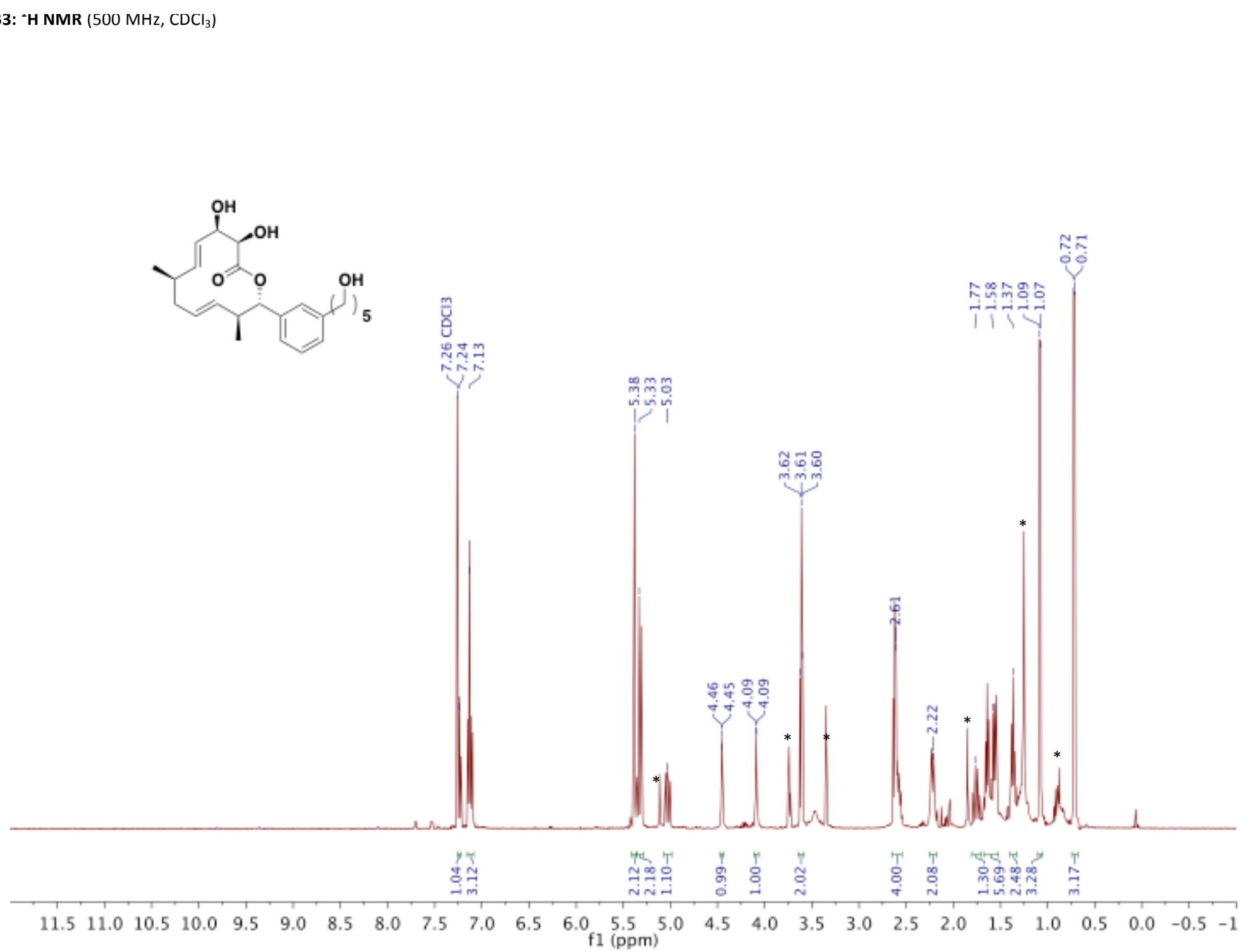
(−)-B1: ^{13}C NMR (126 MHz, $CDCl_3$)



(−)-B1: IR

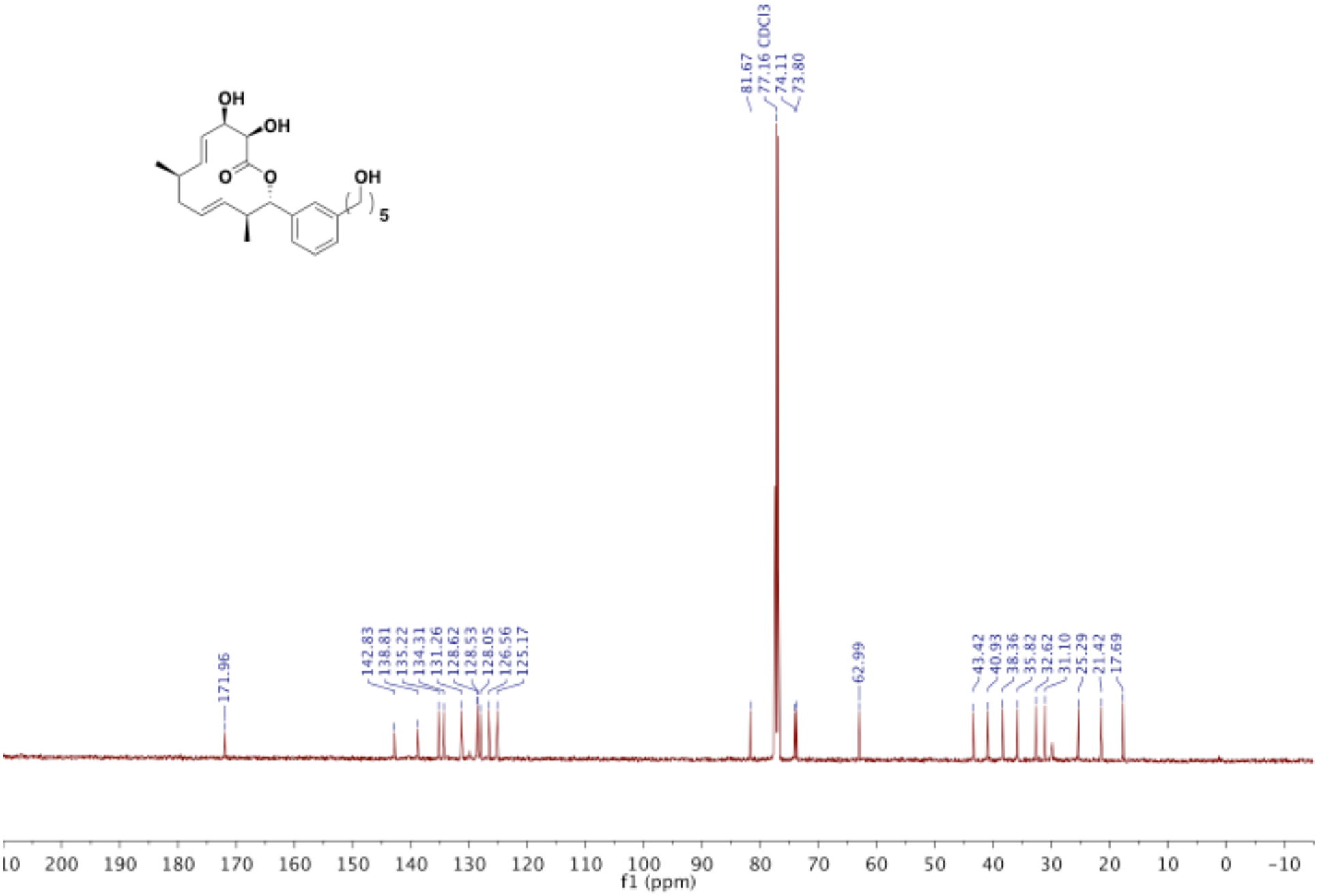

%Transmittance
Wavenumbers (cm-1)
3398.46
2956.30
2923.87
2870.32
2848.11
2245.80
2160.48
2029.27
1976.56
1725.15
1615.73
1554.99
1490.82
1452.51
1373.90
1235.47
1195.00
1110.59
1081.28
1018.14
965.79
907.28
839.64
791.15
705.40
673.02
646.15
591.47
OH
OH
O
O
OH

(−)-B3: ^{1}H NMR (500 MHz, $CDCl_3$)

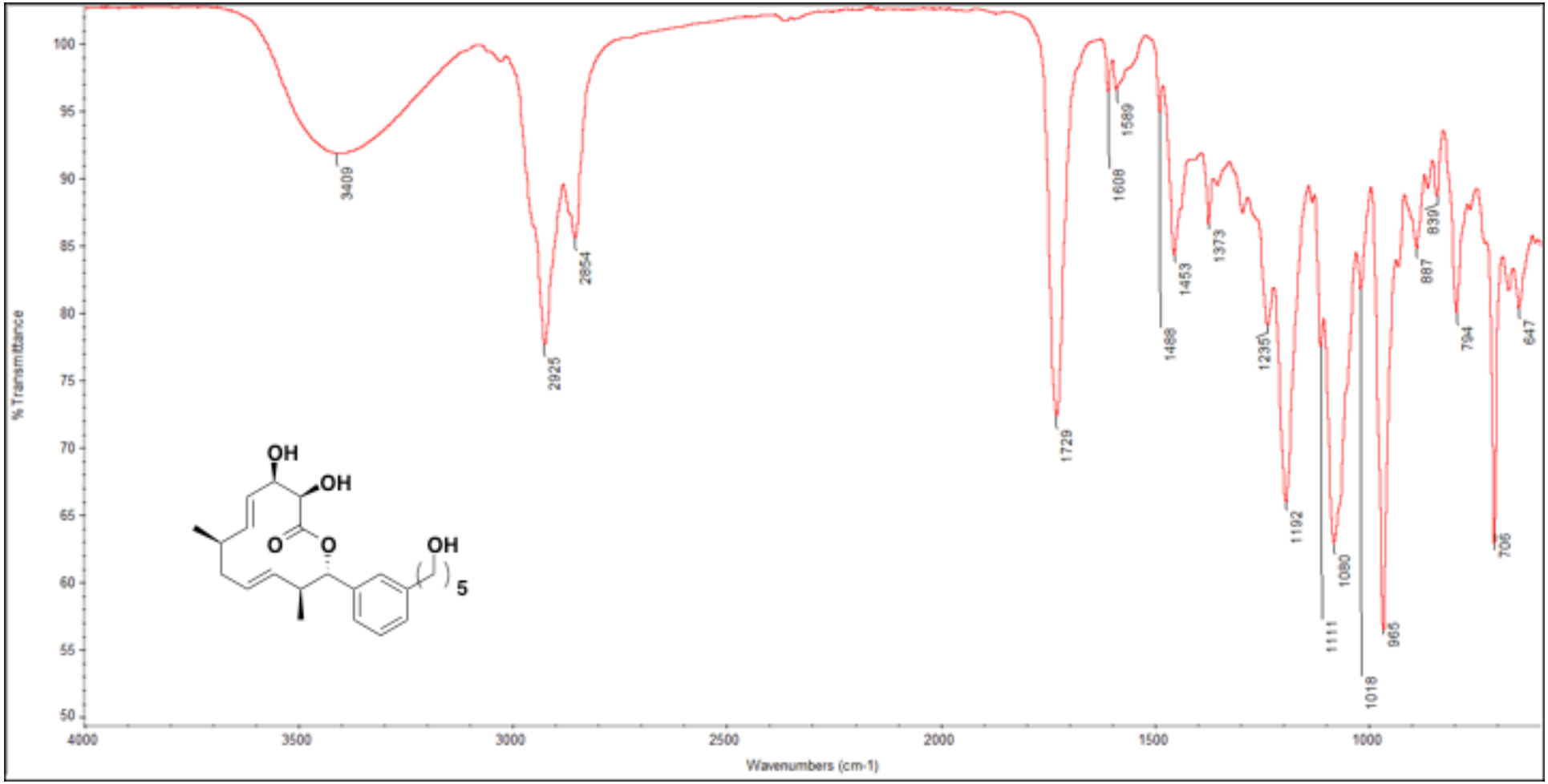


*Impurities present in spectrum

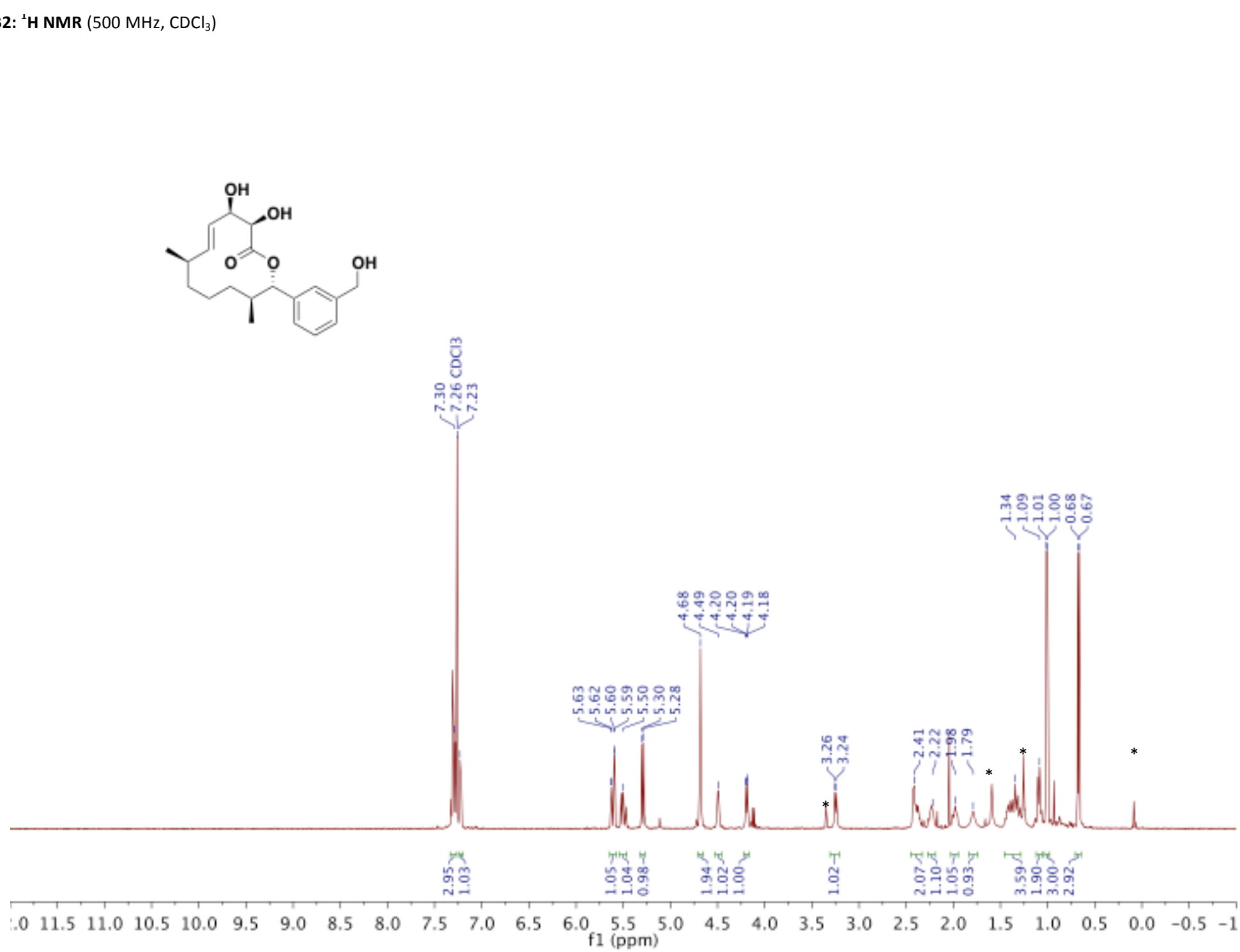
(–)-B3: ^{13}C NMR (126 MHz, $CDCl_3$)



(−)-B3: IR

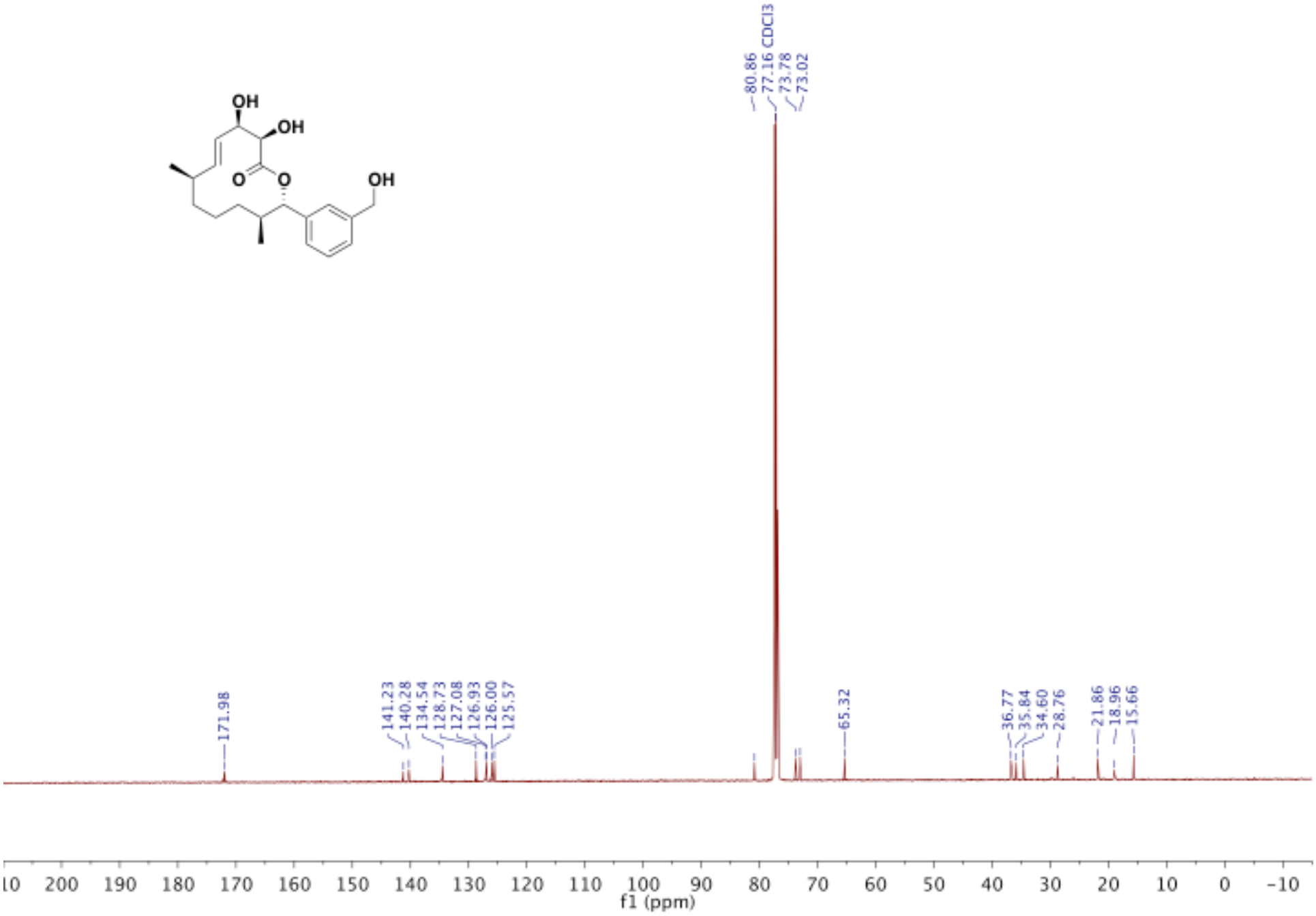

% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
100
95
90
85
80
75
70
65
60
55
50
3409
2925
2854
1729
1608
1589
1488
1453
1373
1235
1192
1111
1080
1018
965
887
839
794
706
647
OH
OH
O
O
OH
5

(–)-B2: ^{1}H NMR (500 MHz, $CDCl_3$)

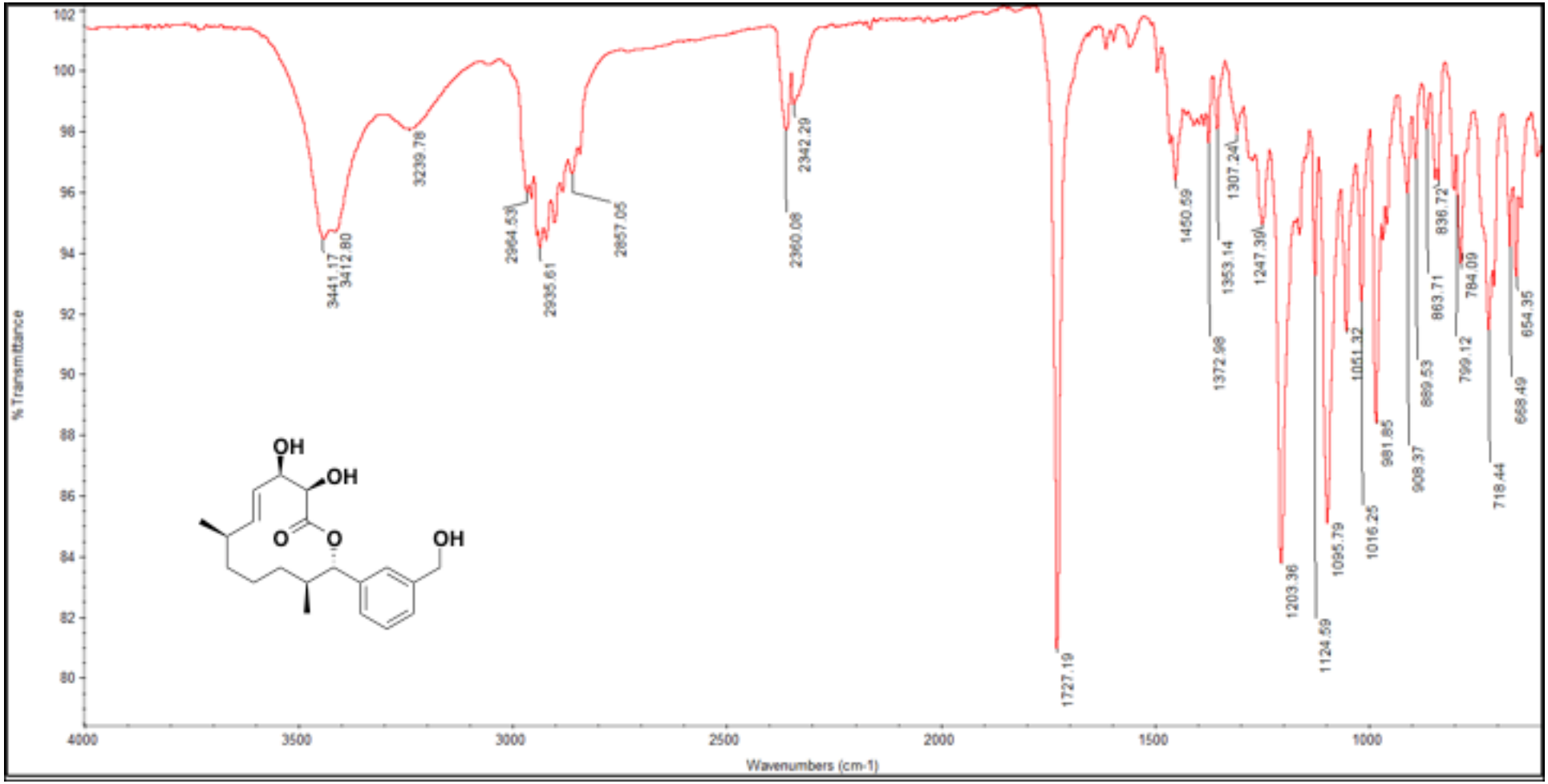


*Impurities present in spectrum

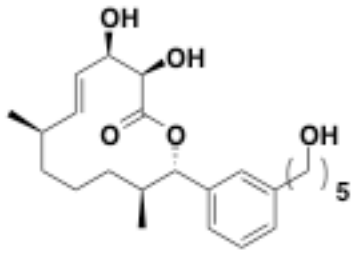
(−)-B2: ^{13}C NMR (126 MHz, $CDCl_3$)

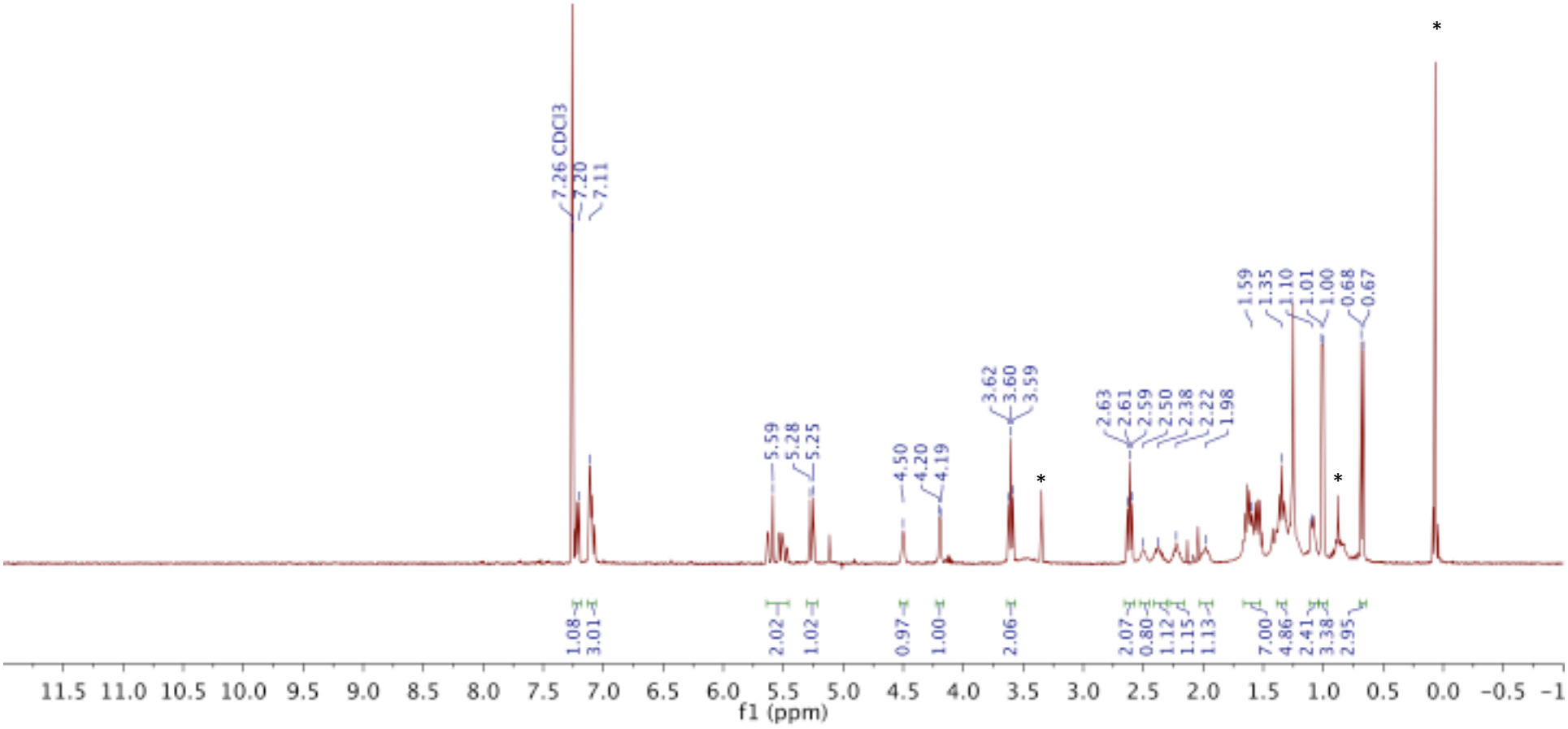


(−)-B2: IR


% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
3441.17
3412.80
3239.78
2964.53
2935.61
2857.05
2360.08
2342.29
1727.19
1450.59
1372.98
1353.14
1307.24
1247.39
1203.36
1124.59
1085.79
1051.32
1016.25
981.85
908.37
889.53
863.71
836.72
799.12
784.09
718.44
668.49
654.35
OH
OH
O
O
OH

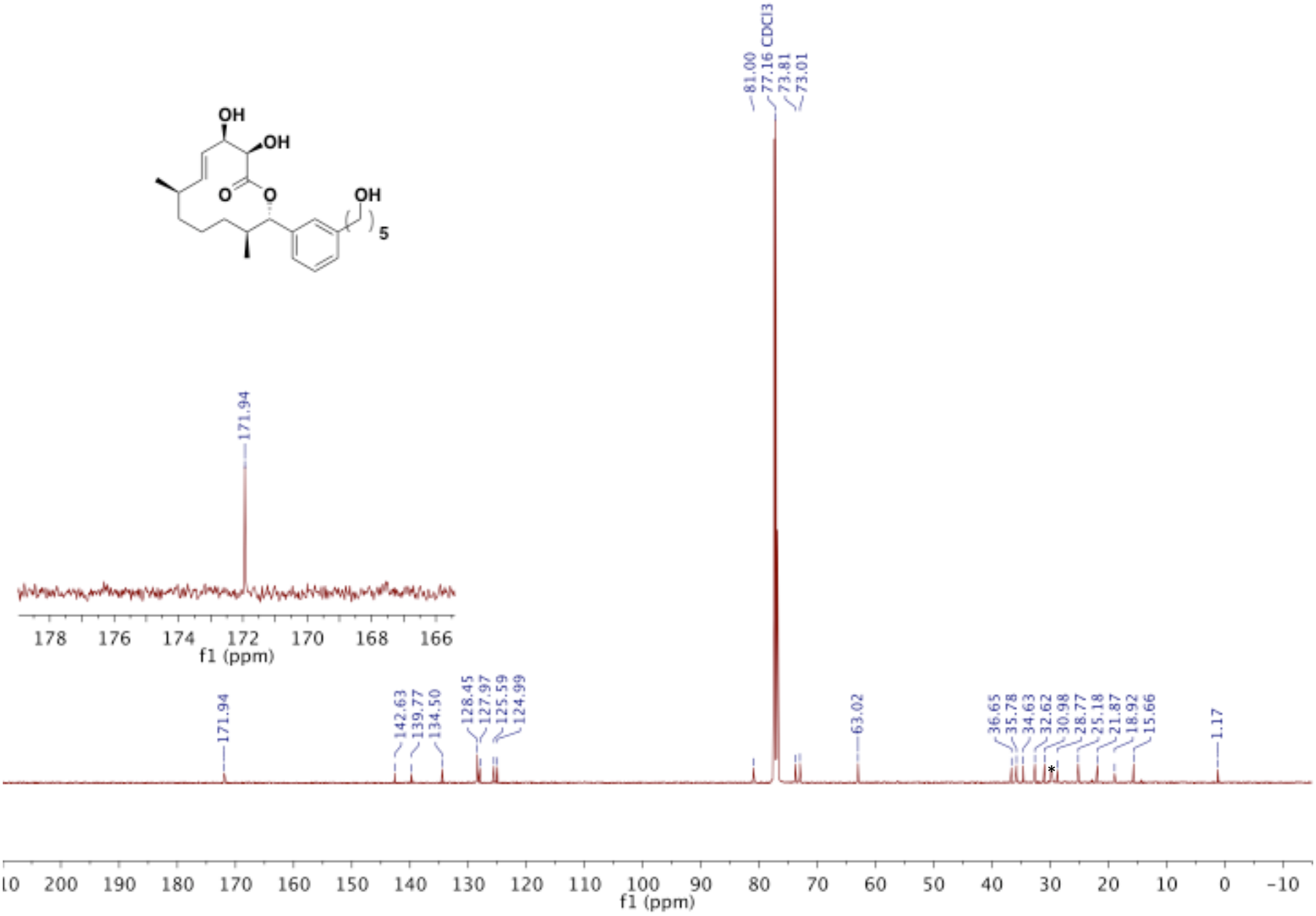
(−)-B4: ^{1}H NMR (500 MHz, $CDCl_3$)





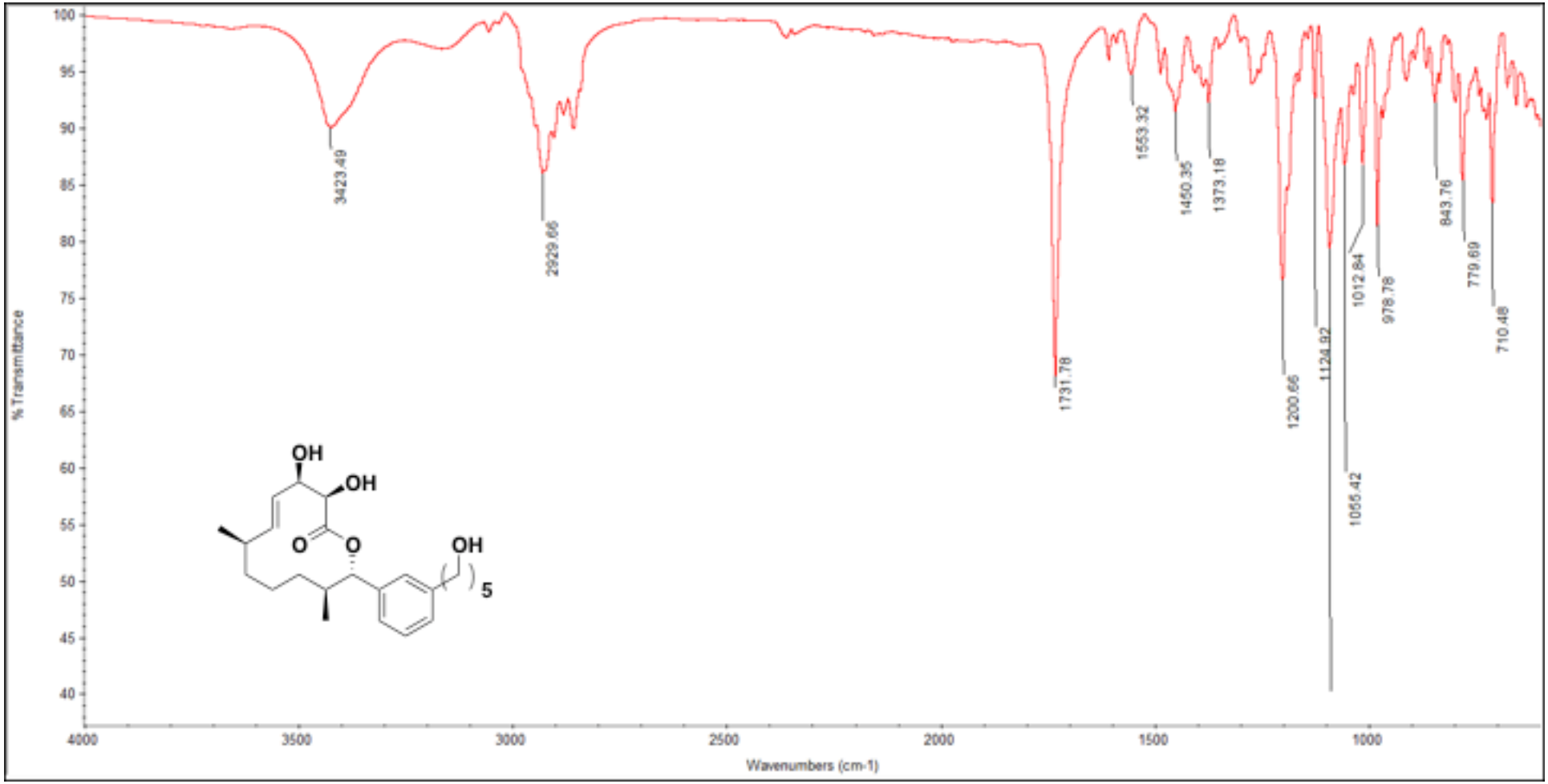
*Impurities present in spectrum

(−)-B4: ^{13}C NMR (126 MHz, $CDCl_3$)

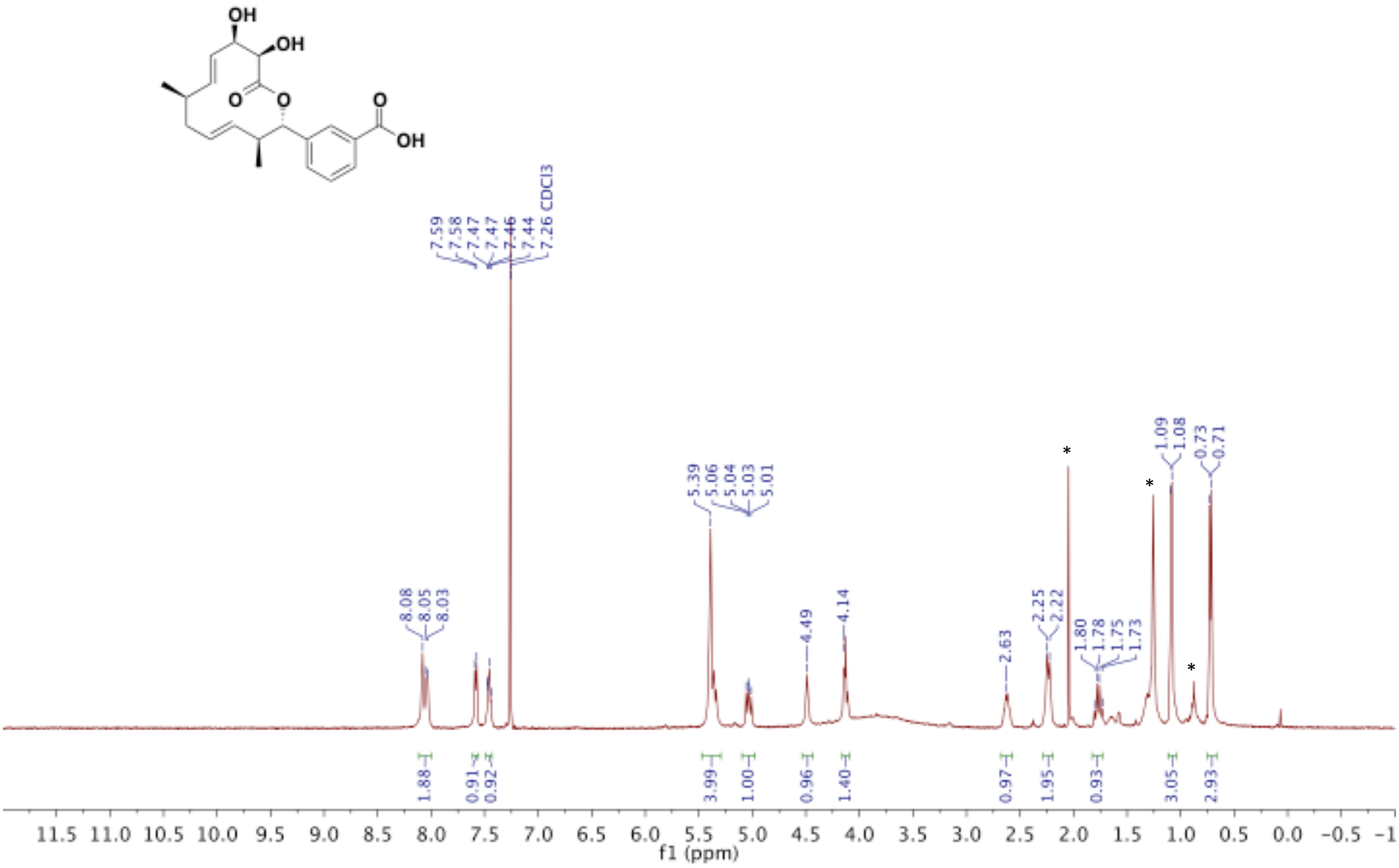


*Impurity present in spectrum

(−)-B4: IR

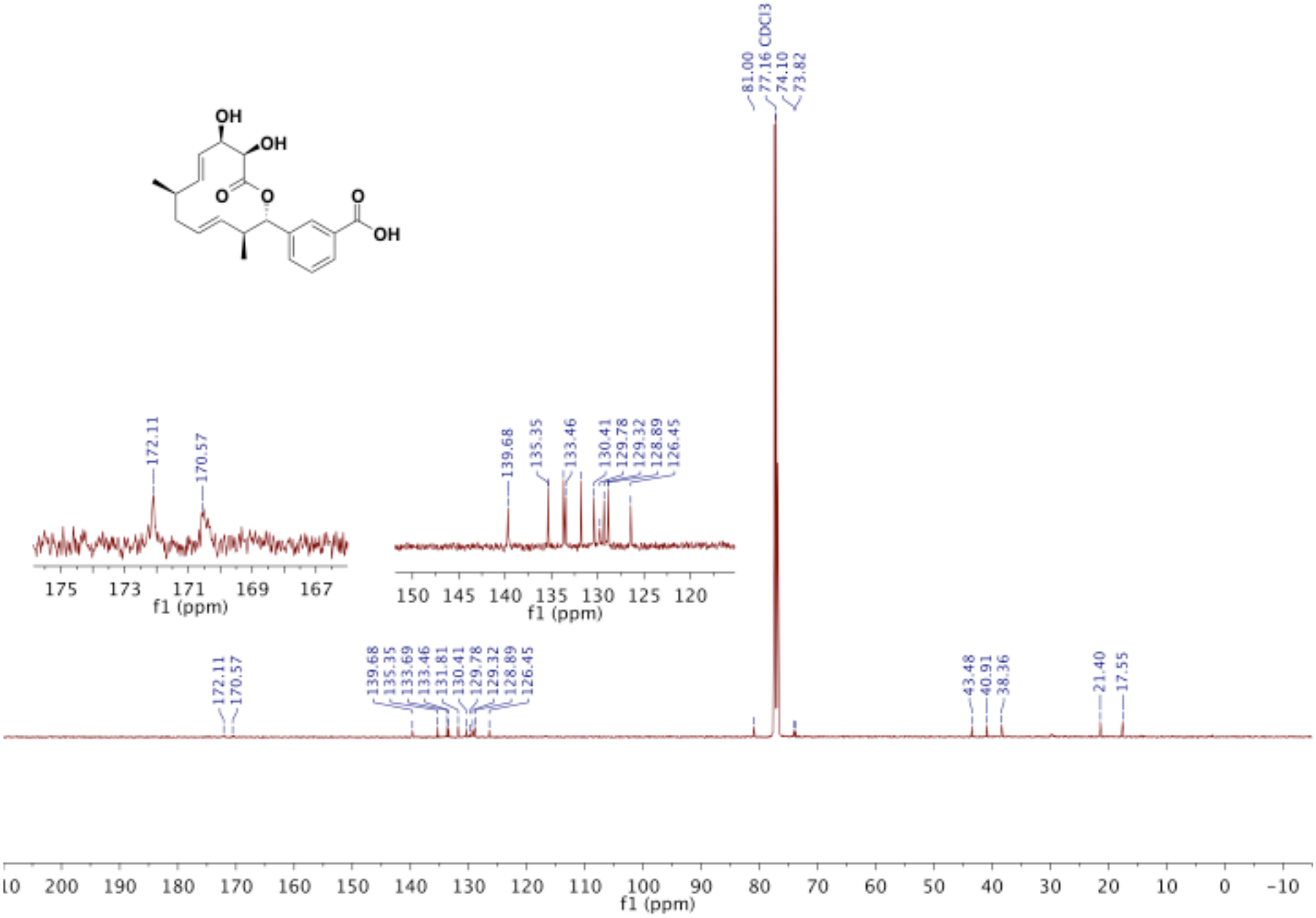

% Transmittance
Wavenumbers (cm-1)
3423.49
2929.66
1731.78
1553.32
1450.35
1373.18
1200.66
1124.92
1055.42
1012.84
978.78
843.76
779.69
710.48
OH
OH
O
O
OH
5

(−)-D1: ^{1}H NMR (500 MHz, $CDCl_3$)

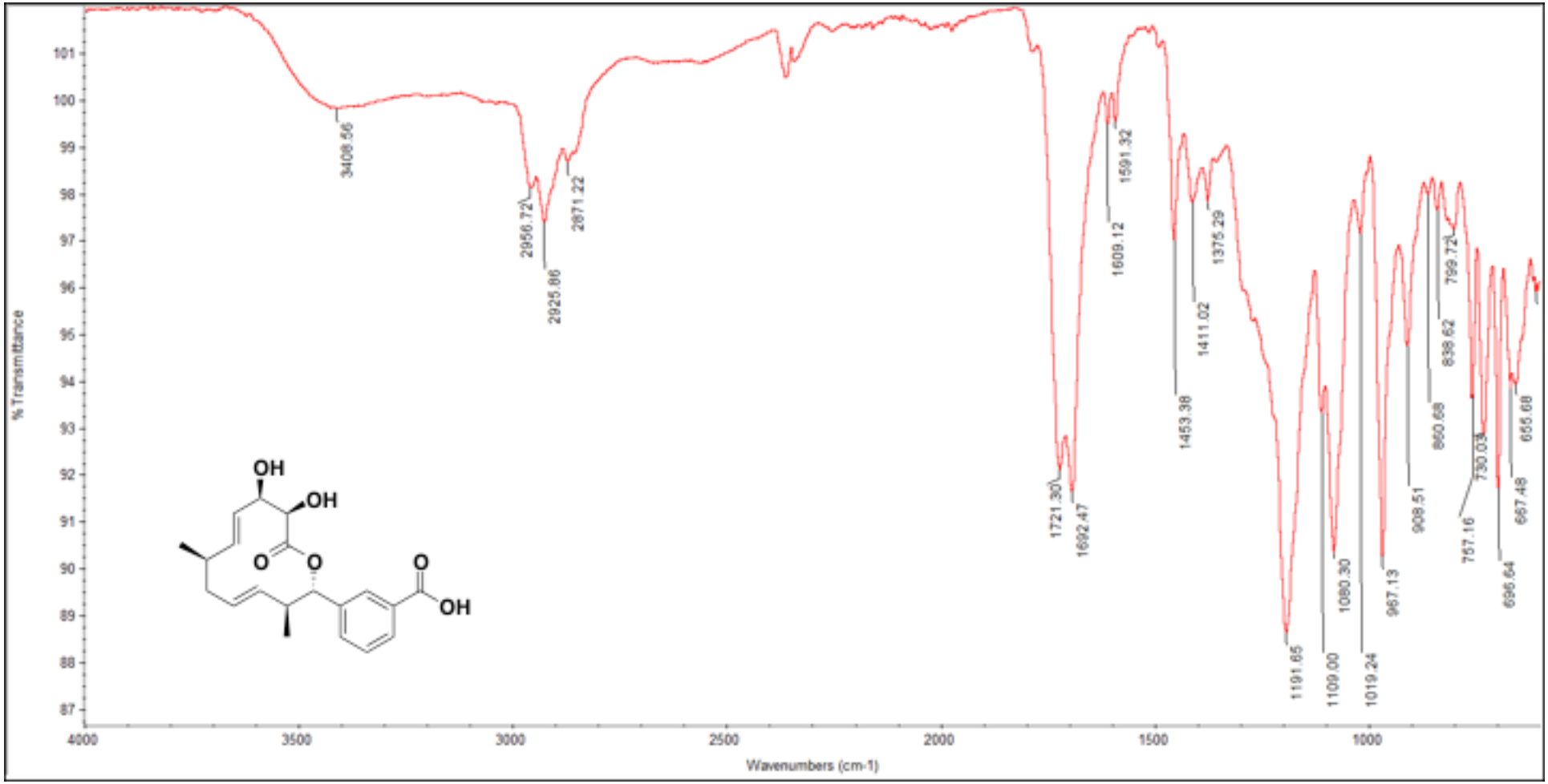


*Impurities present in spectrum

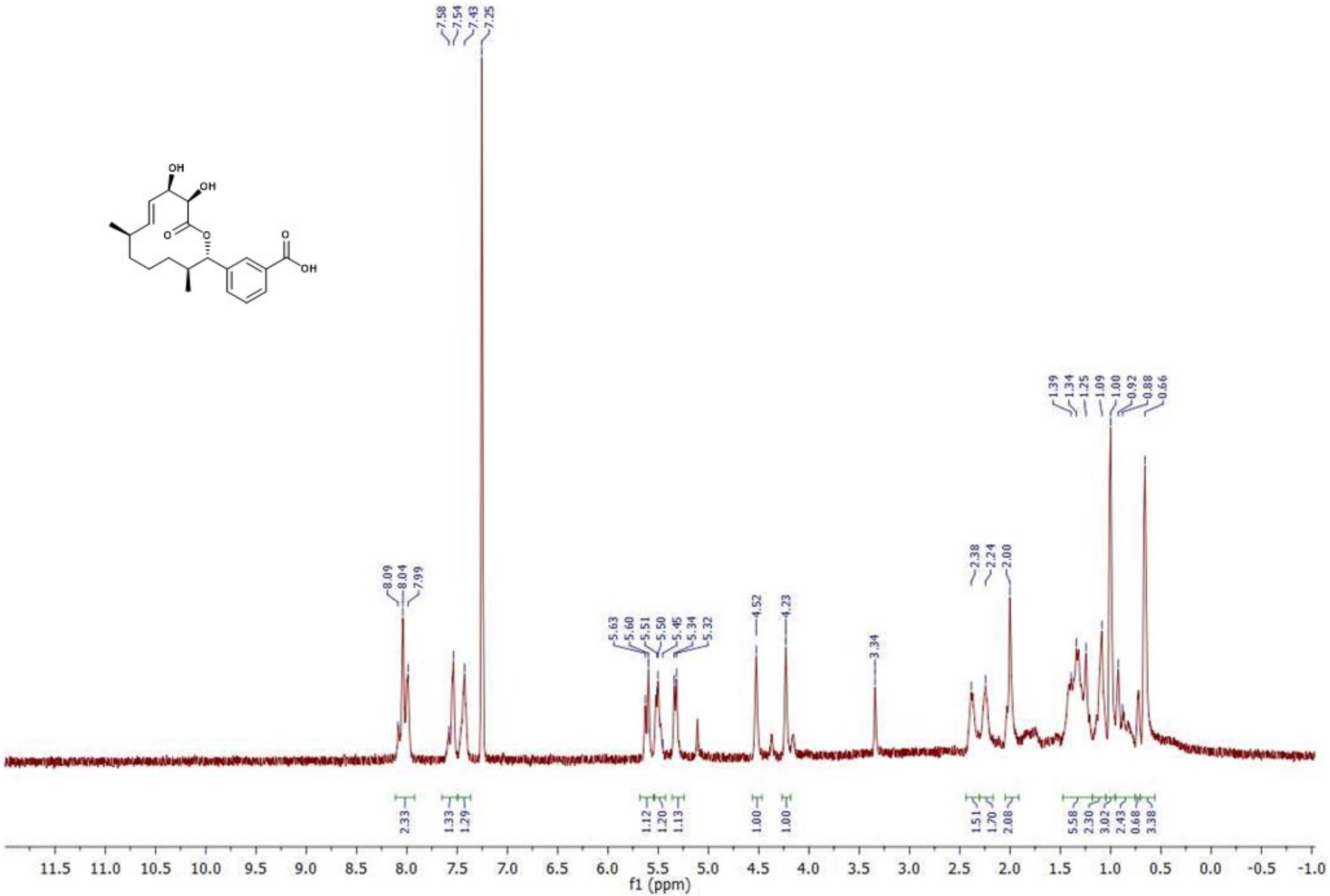
(−)-D1: ^{13}C NMR (126 MHz, $CDCl_3$)



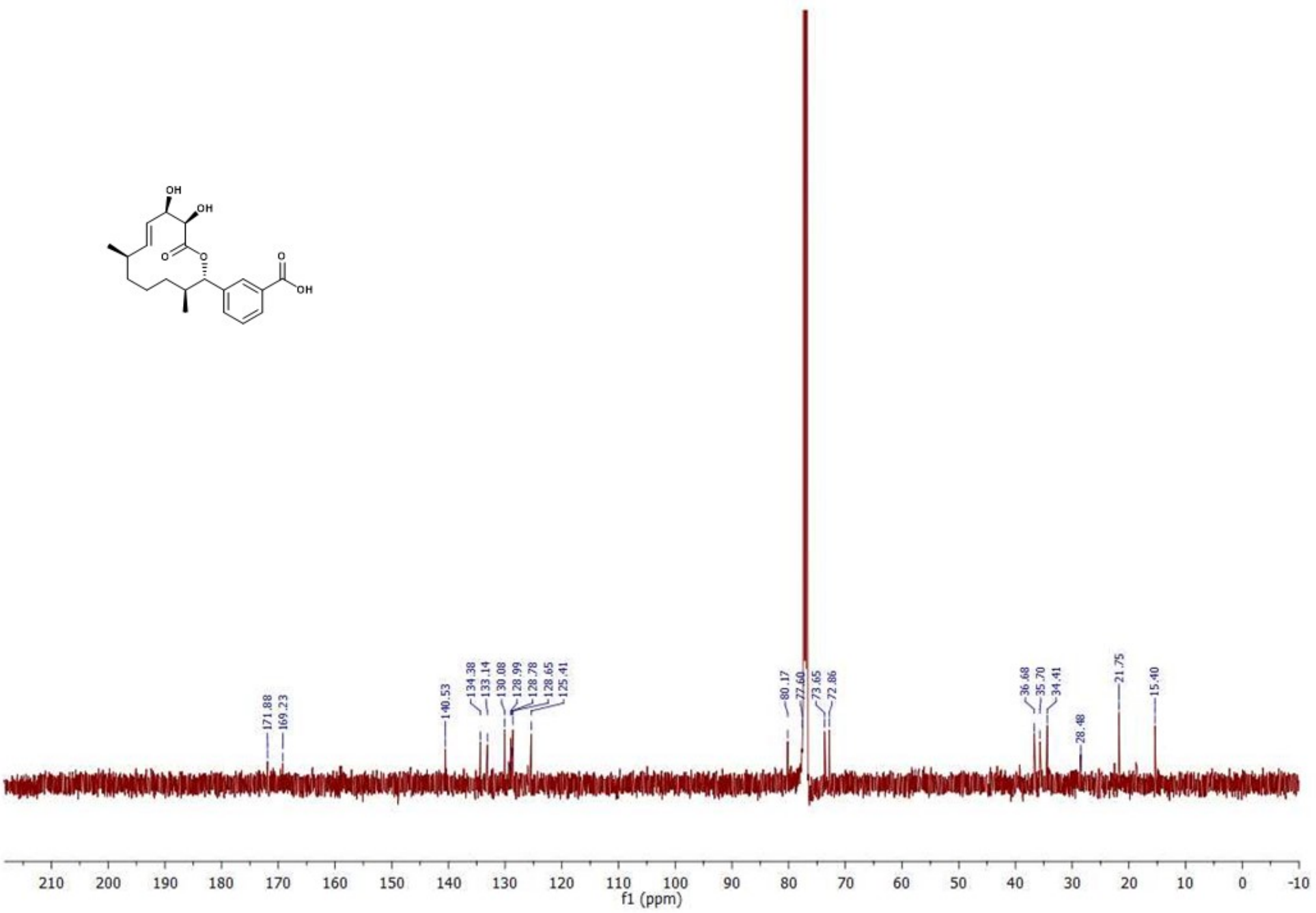
(–)-D1: IR


% Transmittance
Wavenumbers (cm-1)
3408.56
2956.72
2925.86
2871.22
1721.30
1692.47
1609.12
1591.32
1453.38
1411.02
1375.29
1191.65
1109.00
1080.30
1019.24
967.13
909.51
860.68
838.62
799.72
757.16
730.03
696.64
667.48
655.68
OH
OH
O
O
O
OH

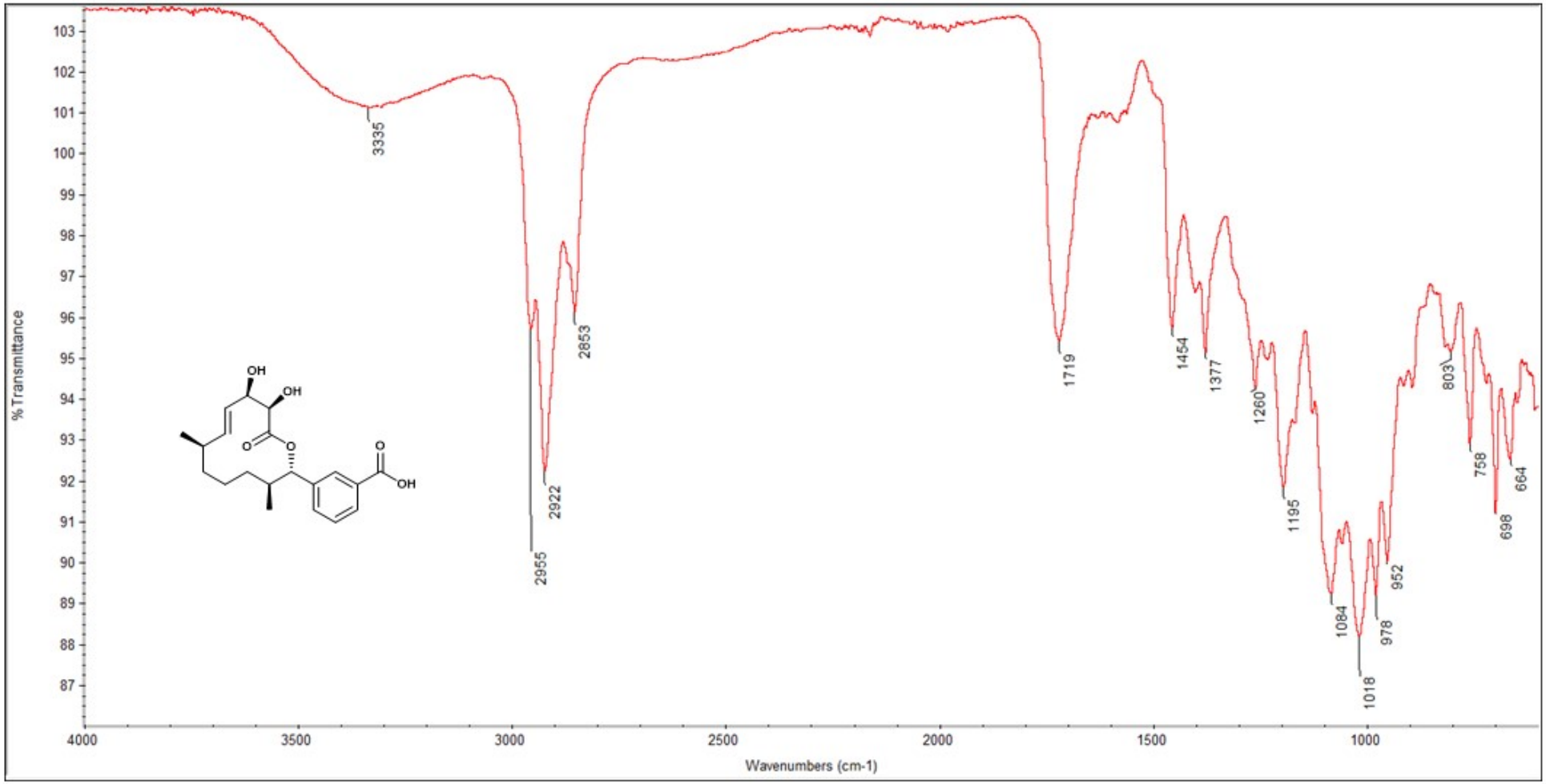
(−)-D2: ^{1}H NMR (500 MHz, $CDCl_3$)



(–)-D2: ^{13}C NMR (126 MHz, $CDCl_3$)

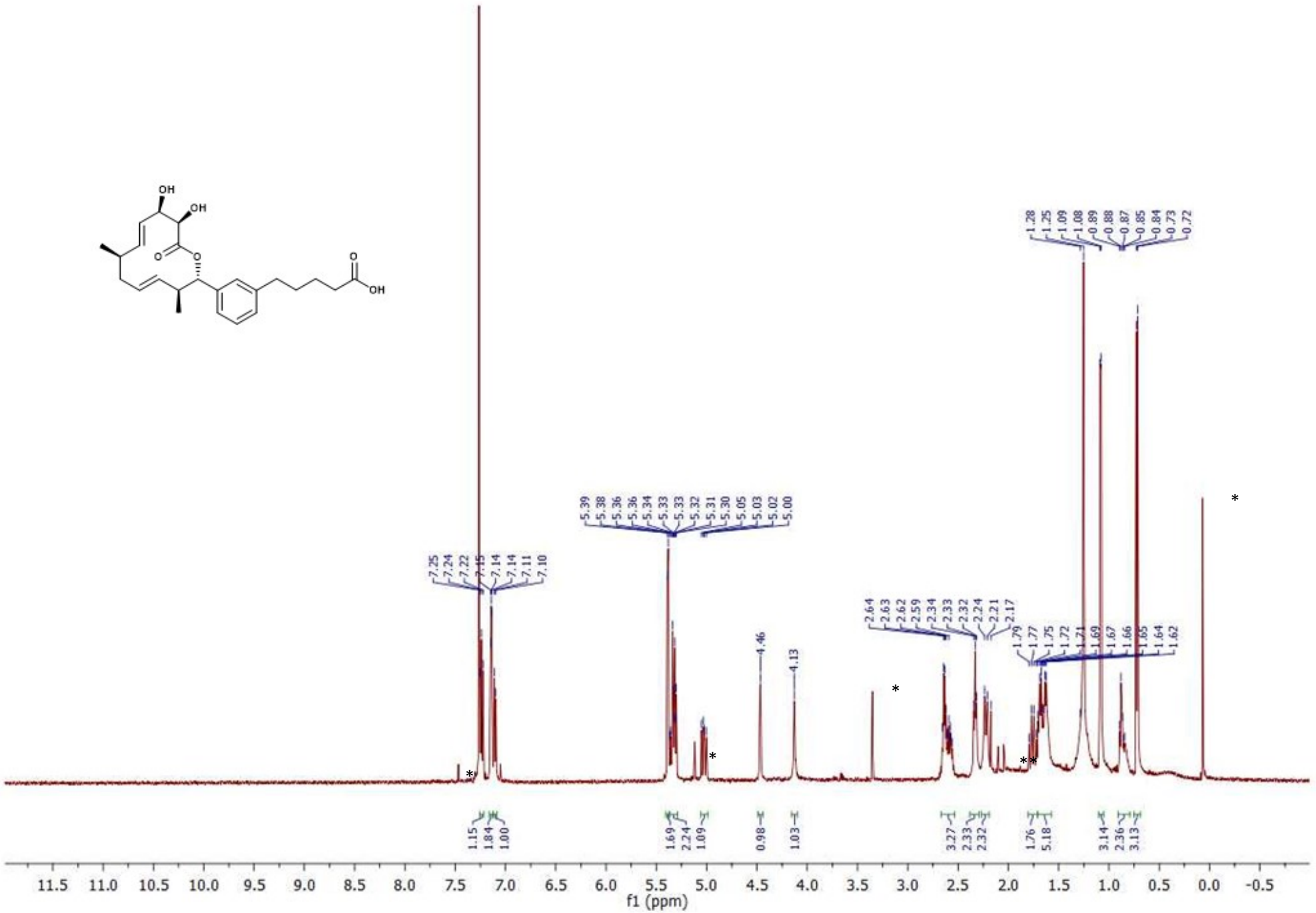


(–)-D2: IR


% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
3335
2955
2922
2853
1719
1454
1377
1260
1195
1084
1018
978
952
803
758
698
664
OH
OH
O
O
O
OH

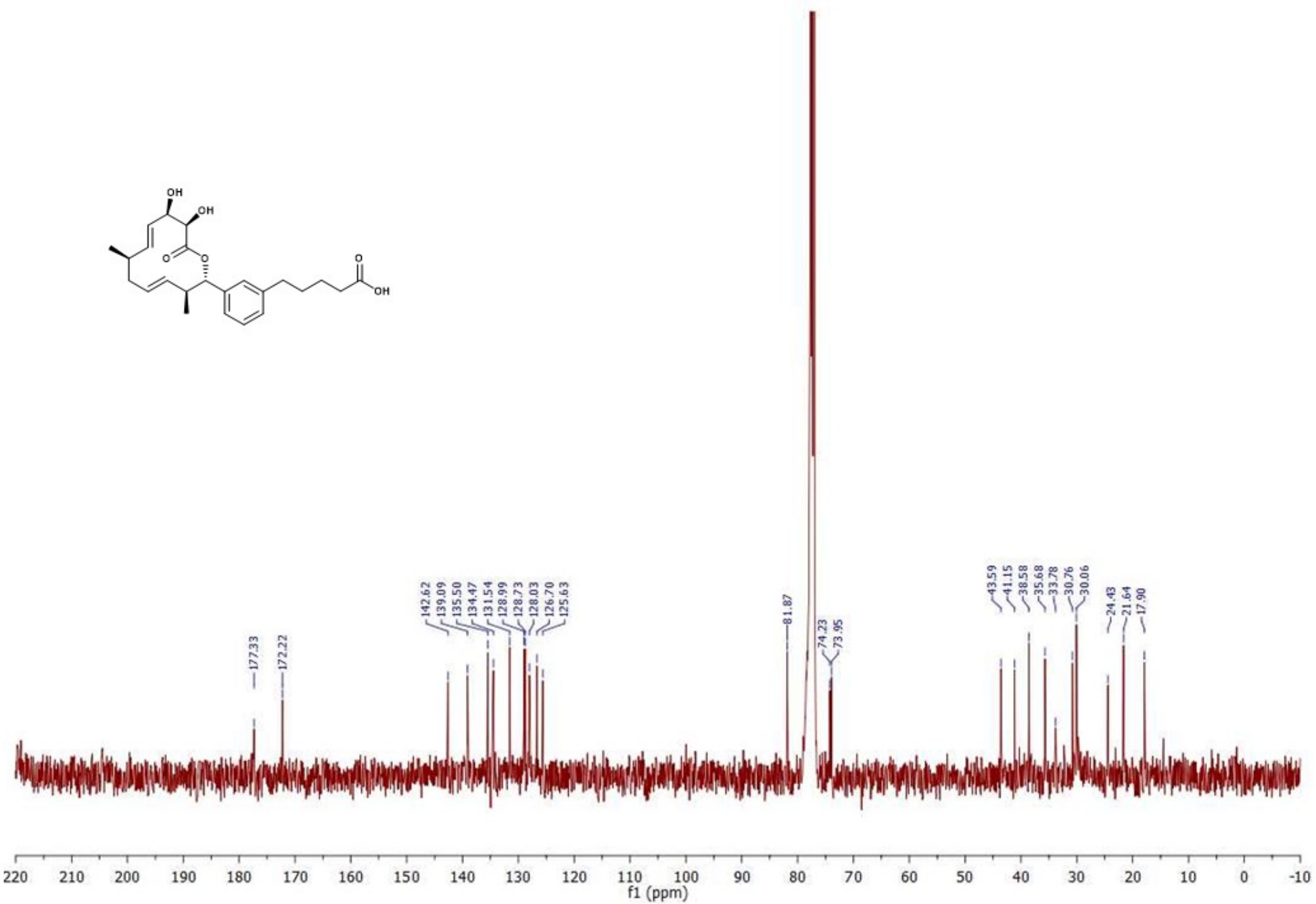
(−)-D3: ^{1}H NMR (500 MHz, $CDCl_3$)

(−)-D3: ^{1}H NMR (500 MHz, $CDCl_3$)

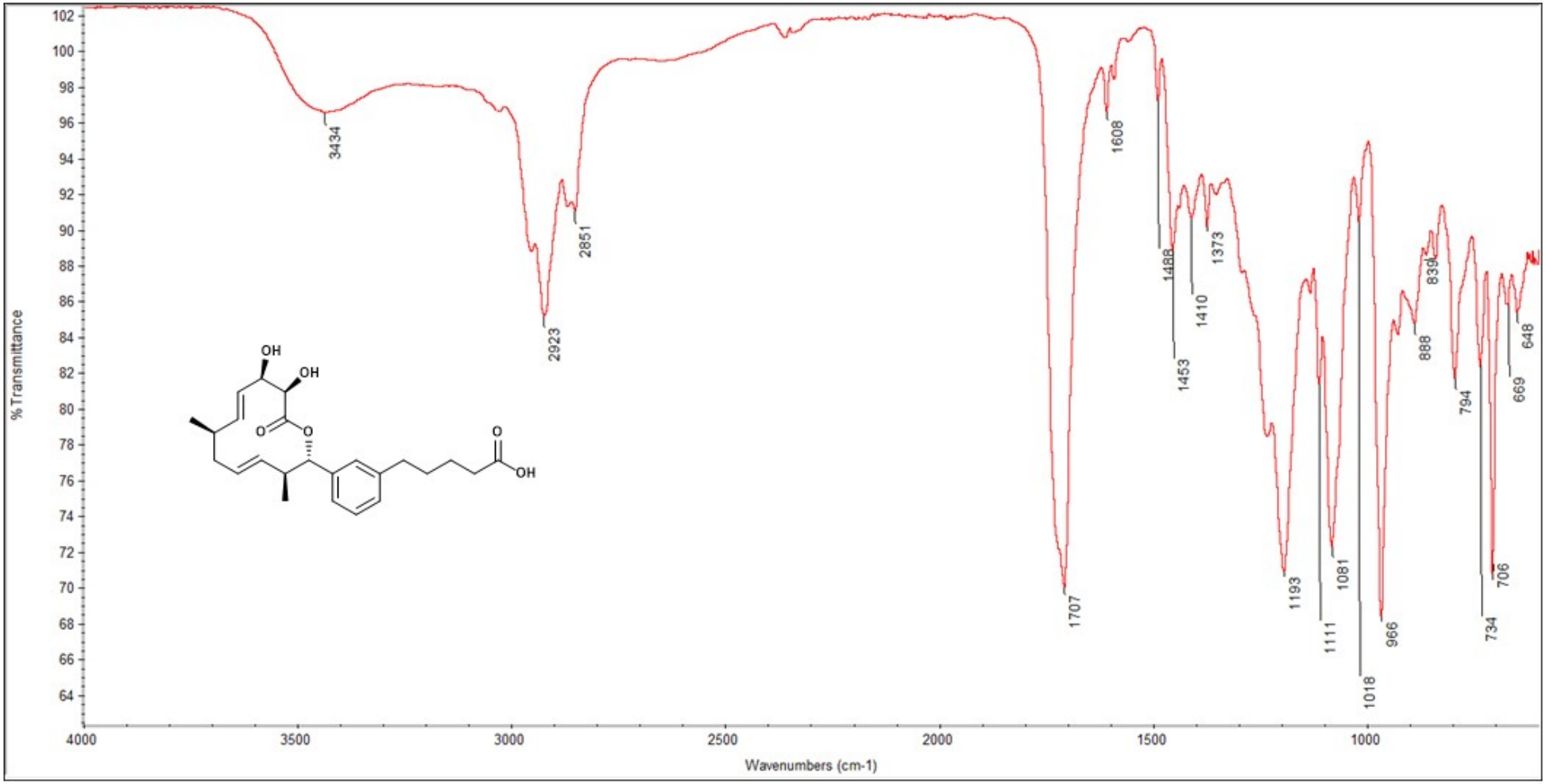


*Impurities present in spectrum

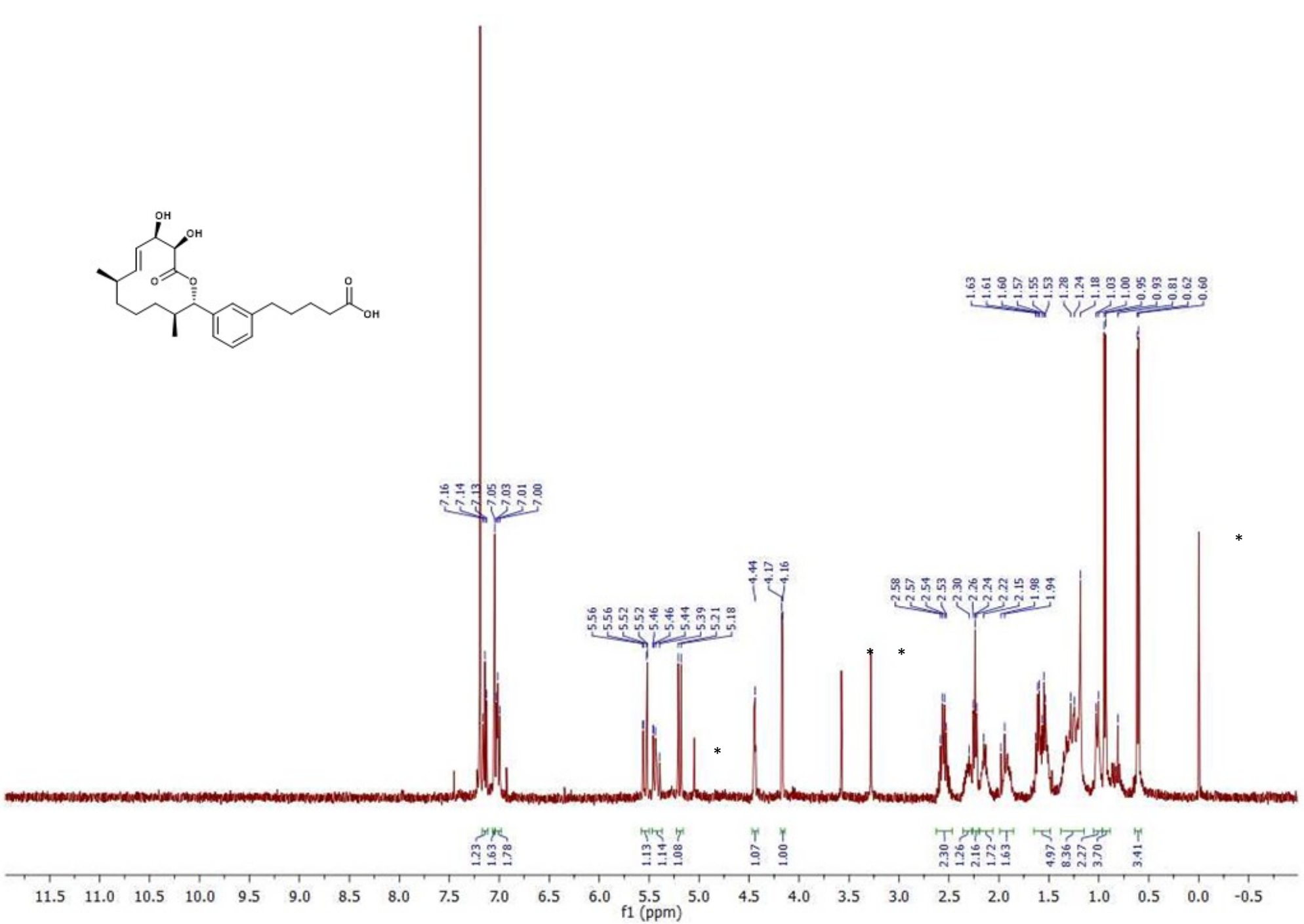
(–)-D3: ^{13}**C NMR** (126 MHz, $CDCl_3$)



(−)-D3: IR

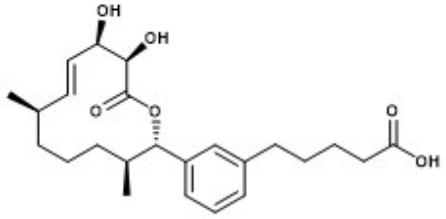

% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
3434
2923
2851
1707
1608
1488
1453
1410
1373
1193
1111
1081
1018
966
888
839
794
734
706
669
648
OH
OH
O
O
O
OH

(−)-D4: ^{1}H NMR (500 MHz, $CDCl_3$)

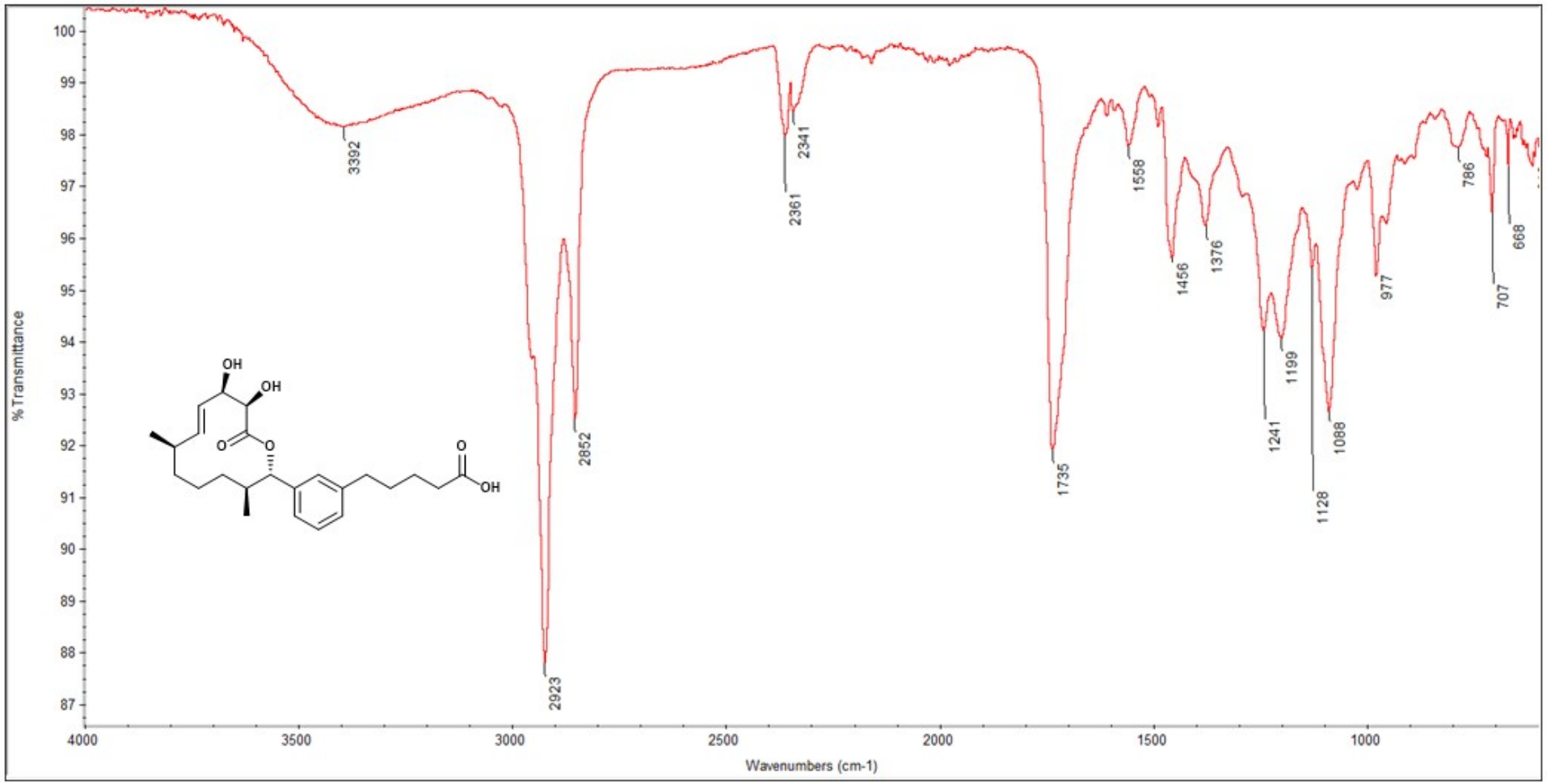


*Impurities present in spectrum

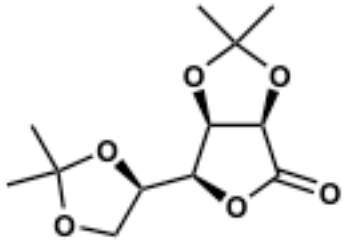
(−)-D4: ^{13}C NMR (126 MHz, $CDCl_3$)

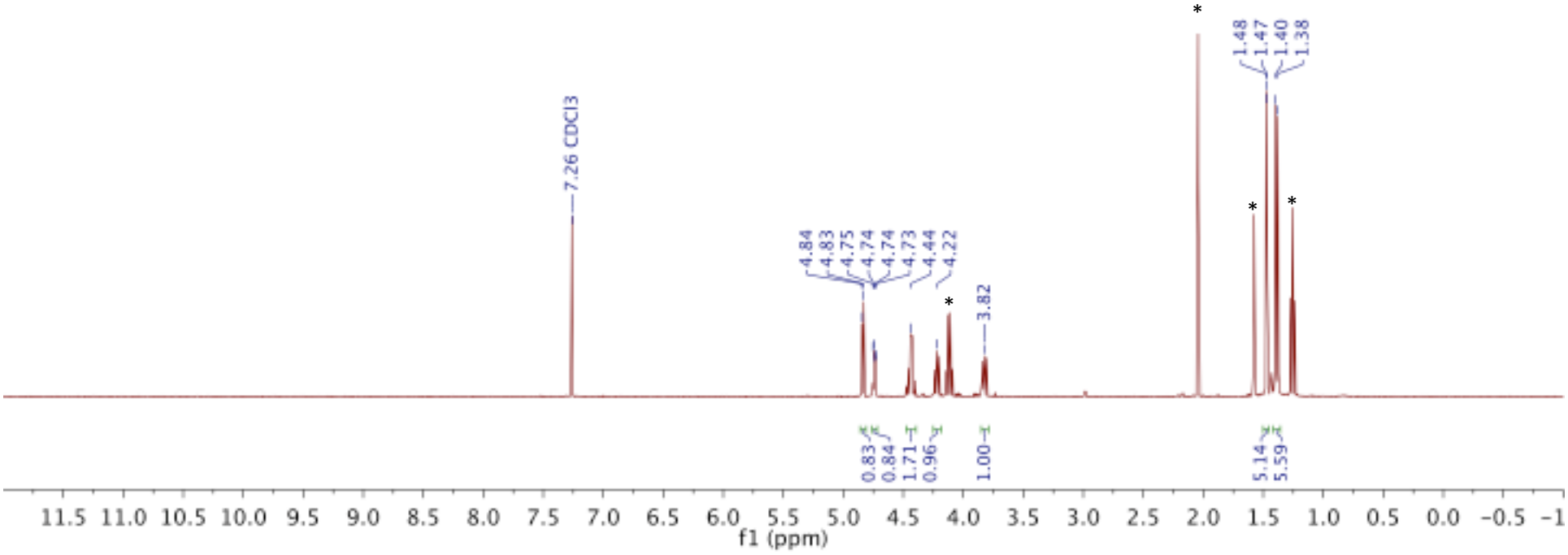


(−)-D4: IR


% Transmittance
Wavenumbers (cm-1)
3392
2923
2852
2361
2341
1735
1558
1456
1376
1241
1199
1128
1088
977
786
707
668
OH
OH
O
O
O
OH

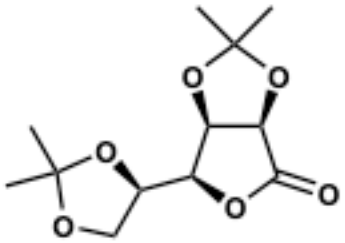
12: ^{1}H NMR (500 MHz, $CDCl_3$)

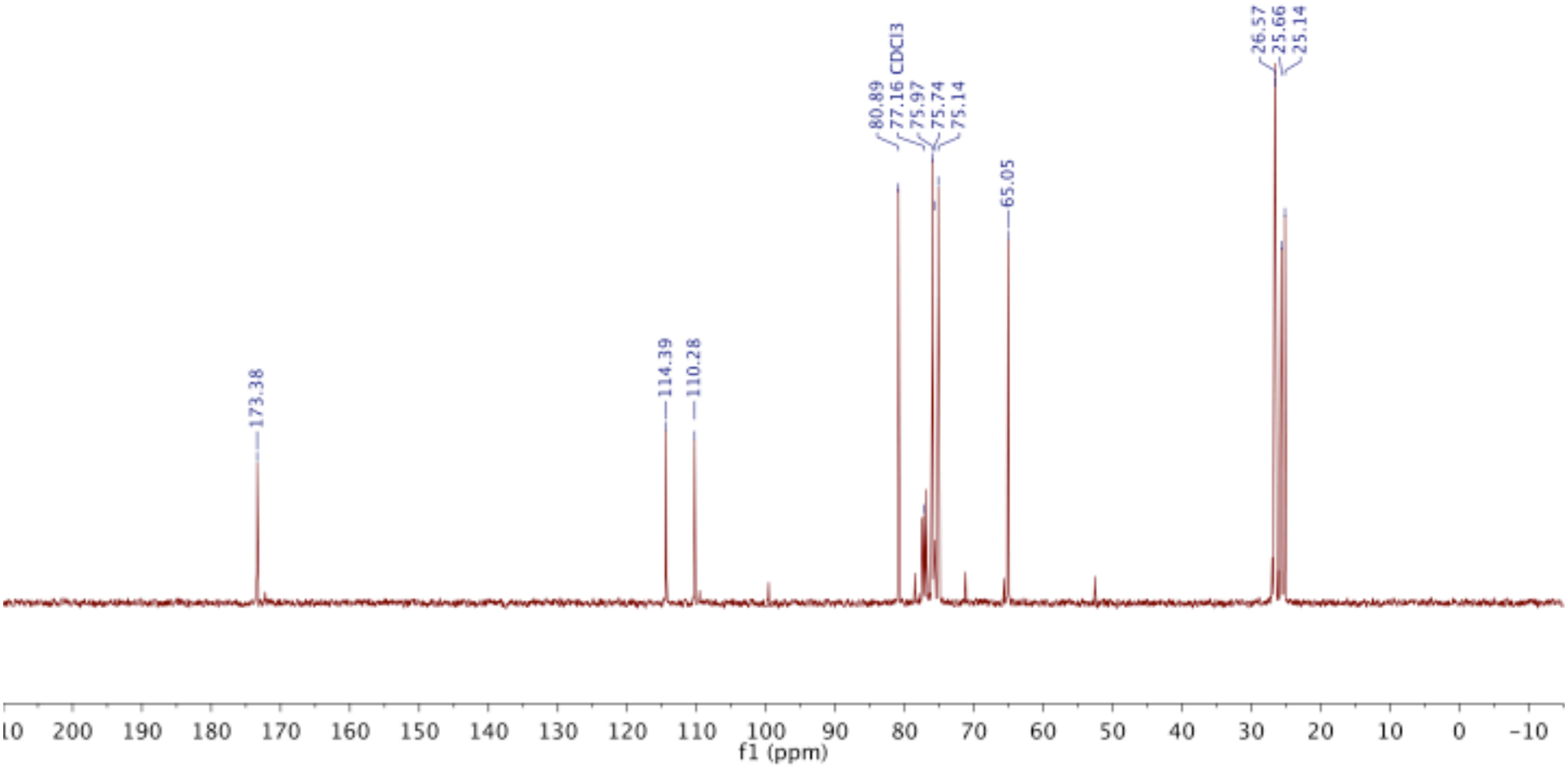




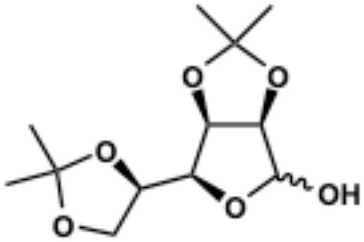
*Impurities present in spectrum

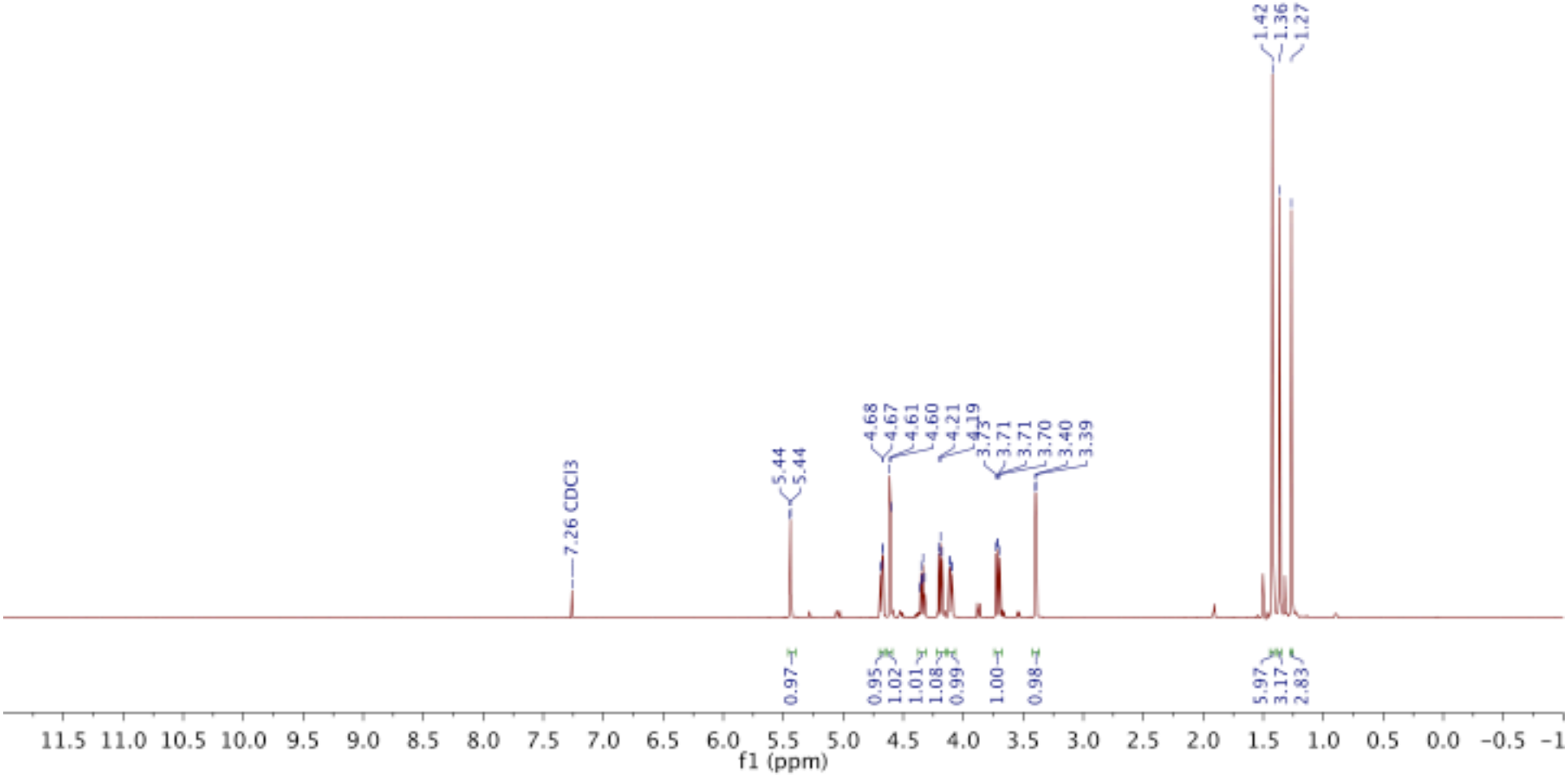
12: ^{13}**C NMR** (126 MHz, $CDCl_3$)



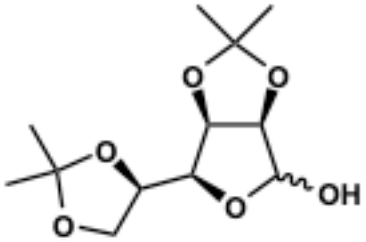


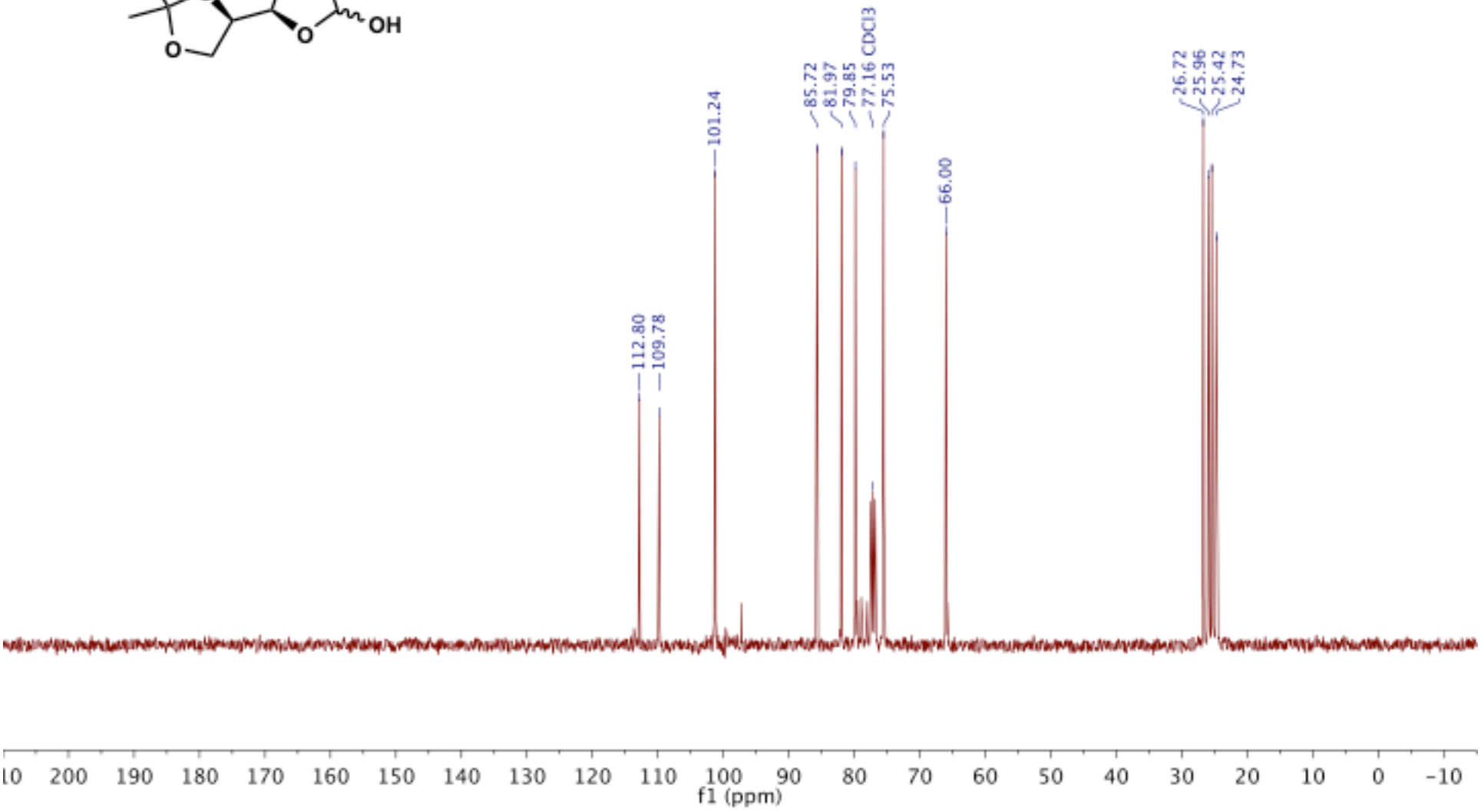
13: ^{1}H NMR (500 MHz, $CDCl_3$)



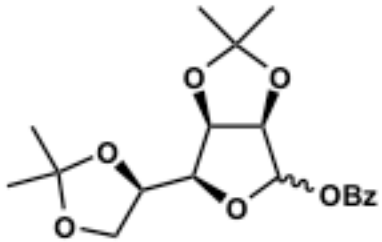


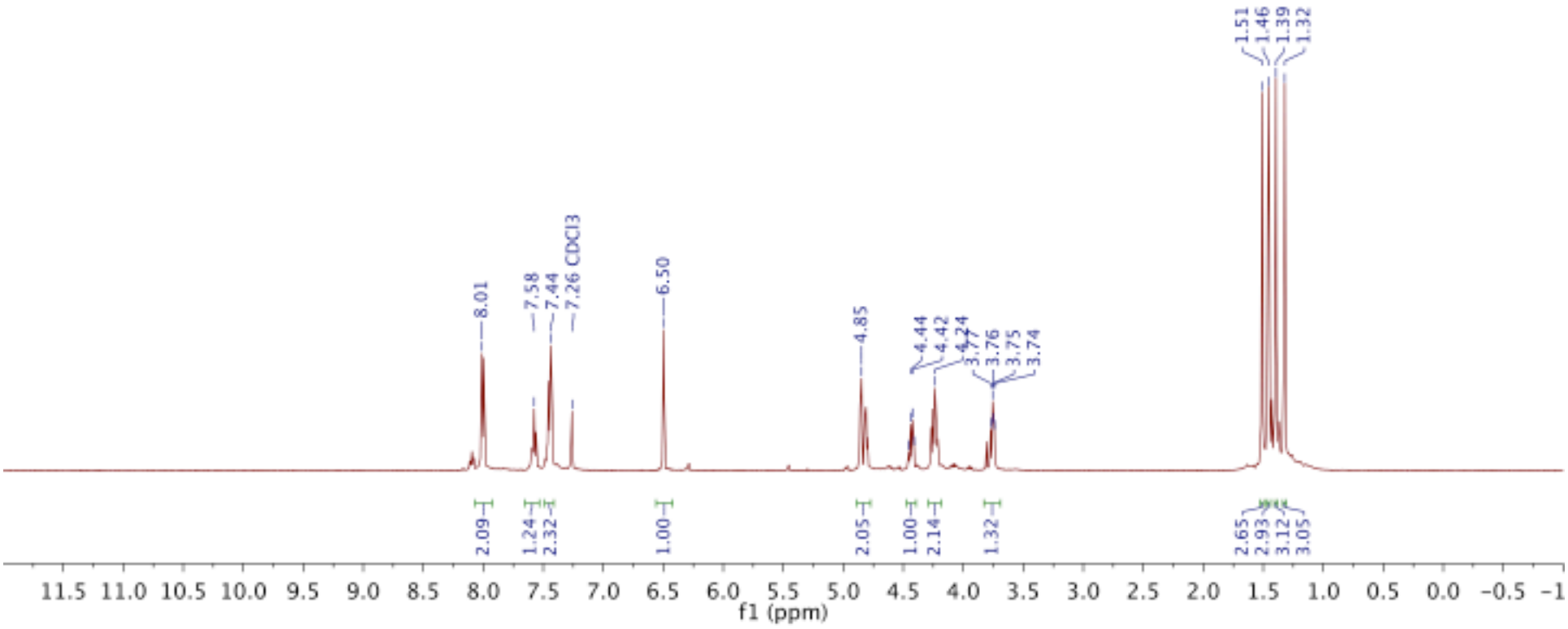
13: ^{13}C NMR (126 MHz, $CDCl_3$)



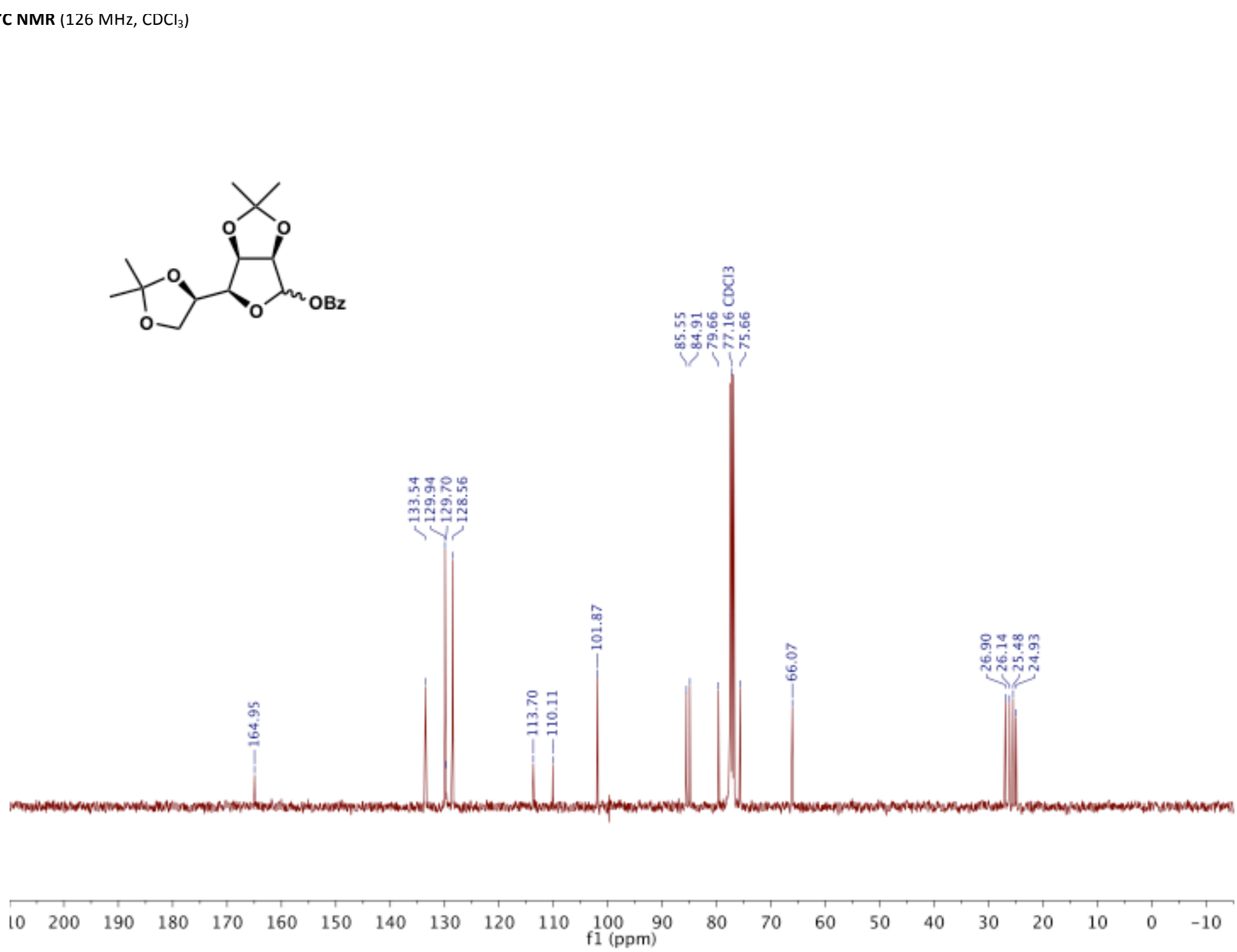


14: ^{1}H NMR (500 MHz, $CDCl_3$)

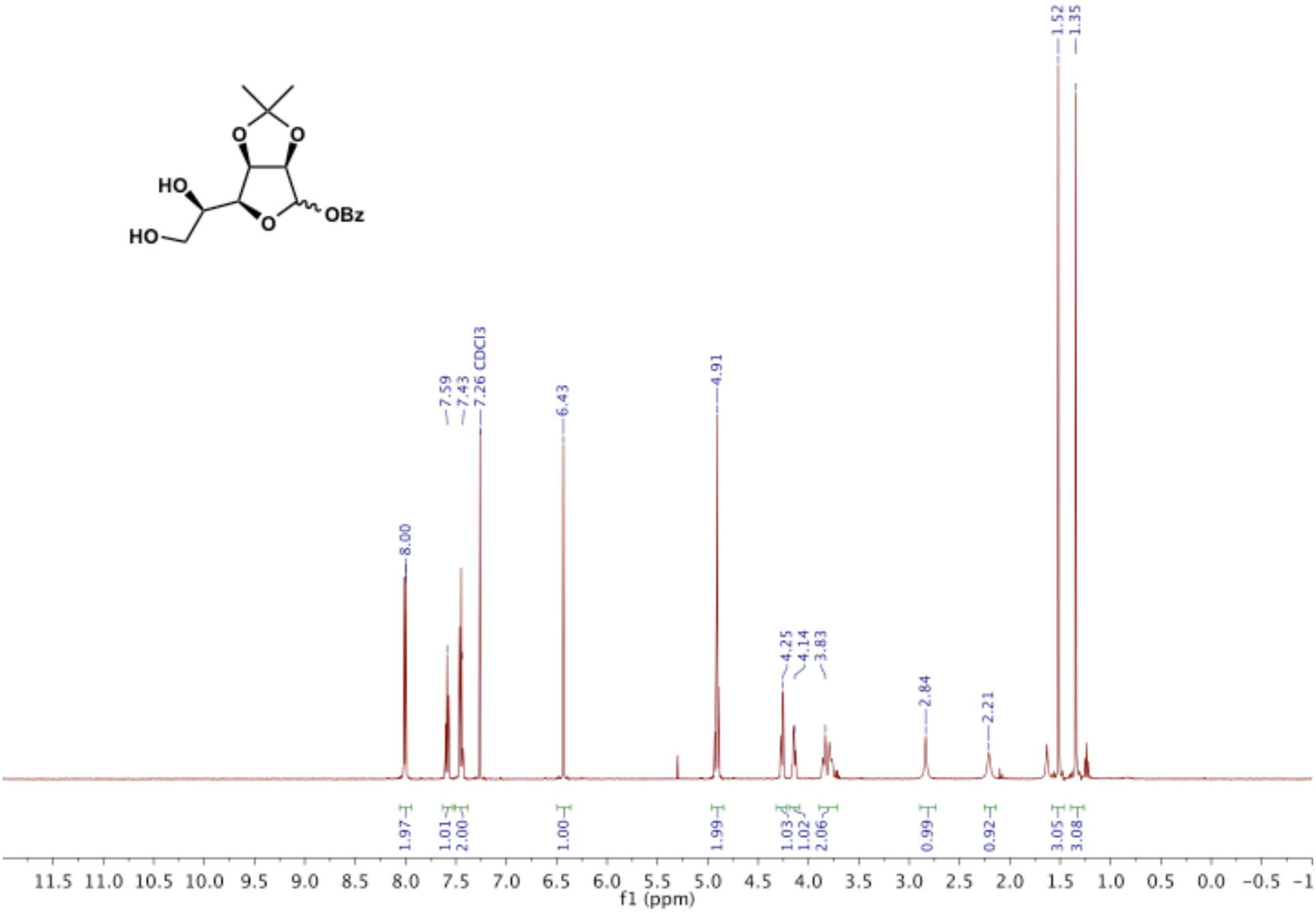




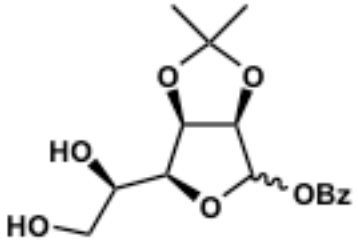
14: ^{13}C NMR (126 MHz, $CDCl_3$)

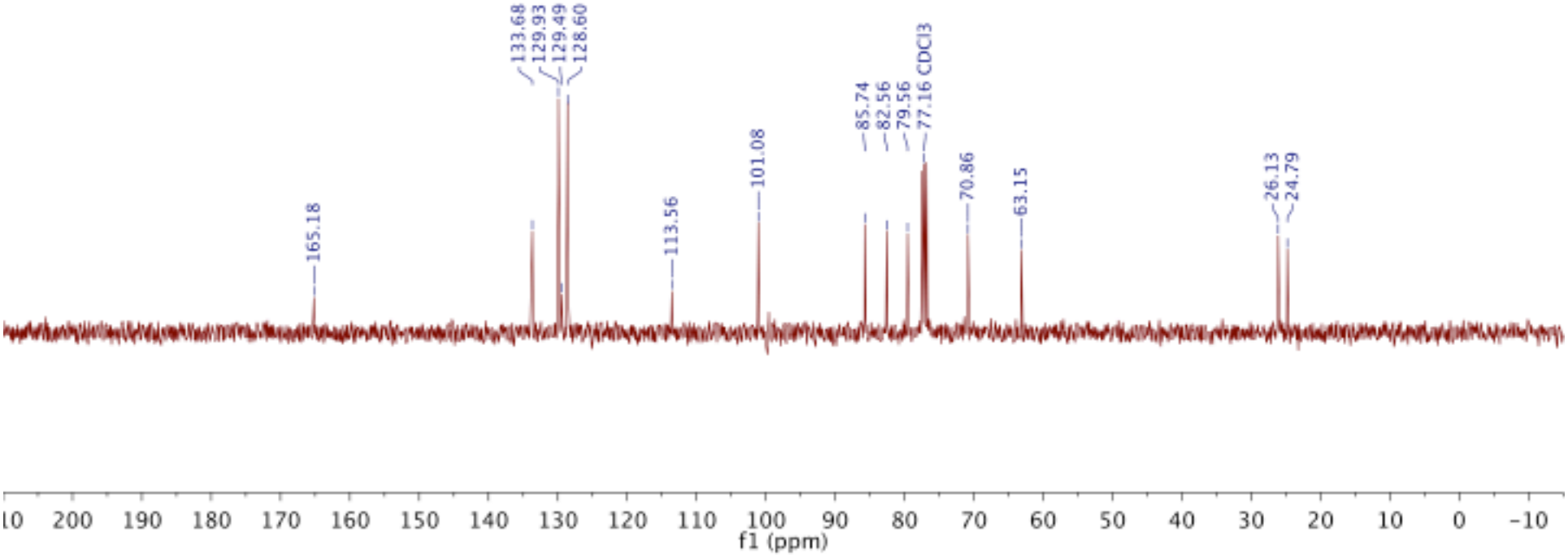


15: ^{1}H NMR (500 MHz, $CDCl_3$)

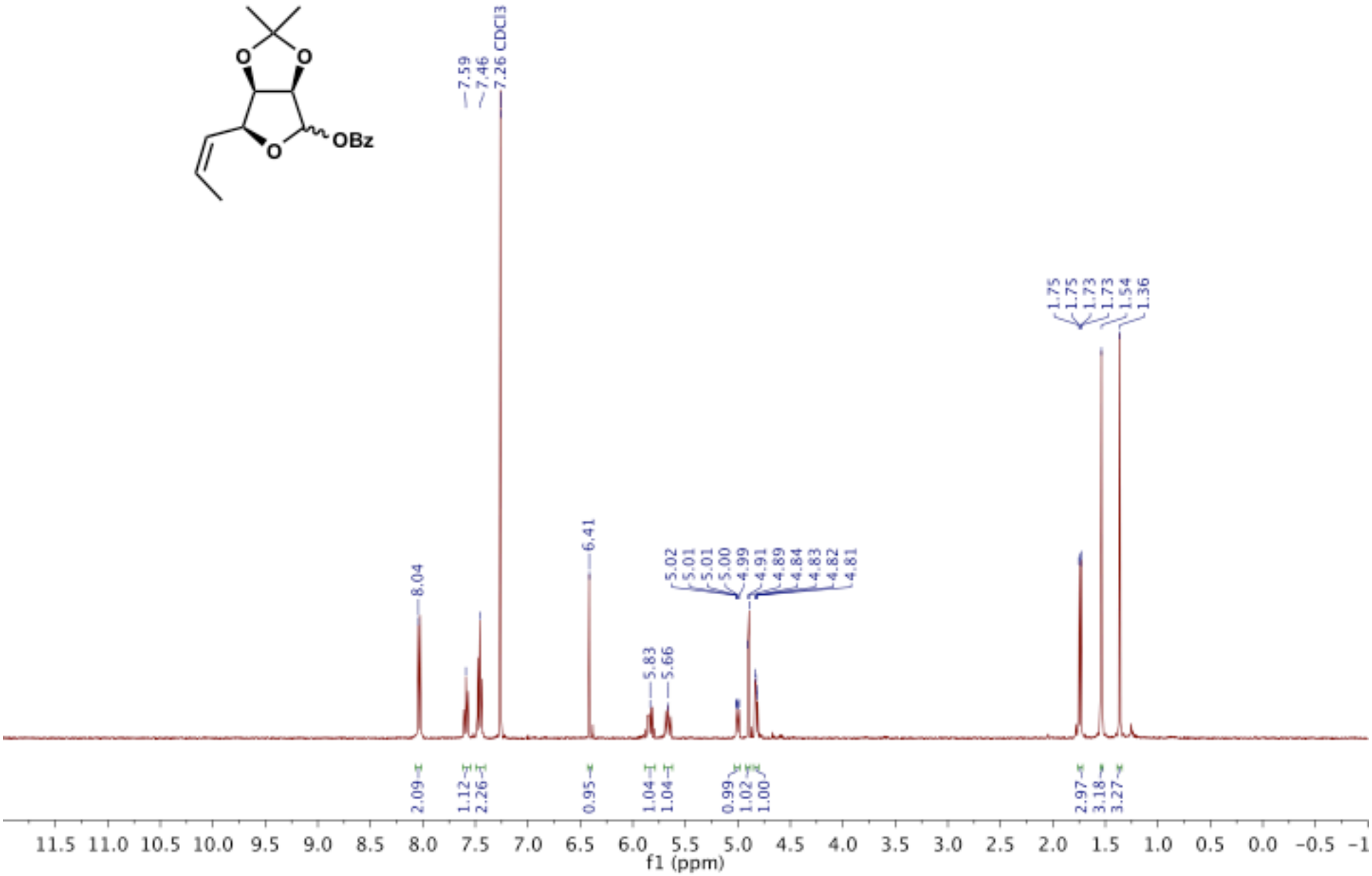


15: ^{13}C NMR (126 MHz, $CDCl_3$)

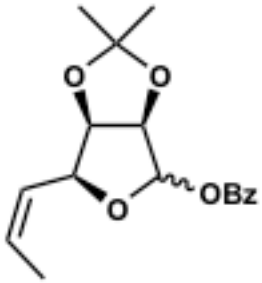


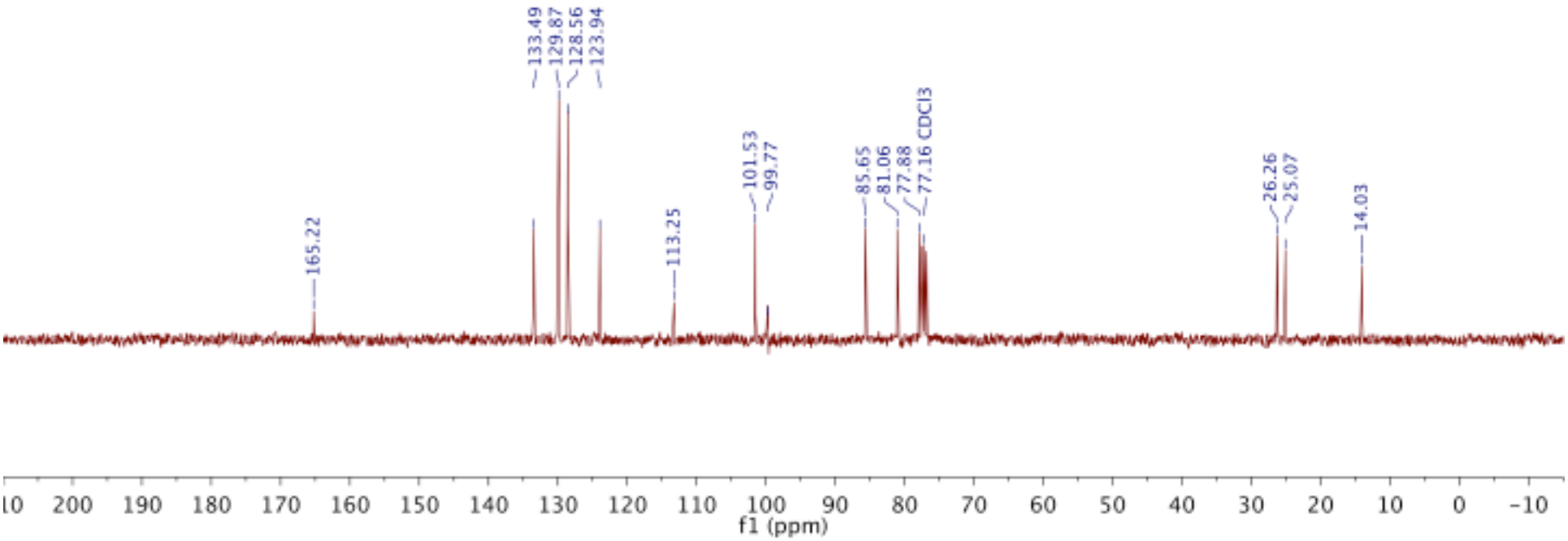


1: ^{1}H NMR (500 MHz, $CDCl_3$)

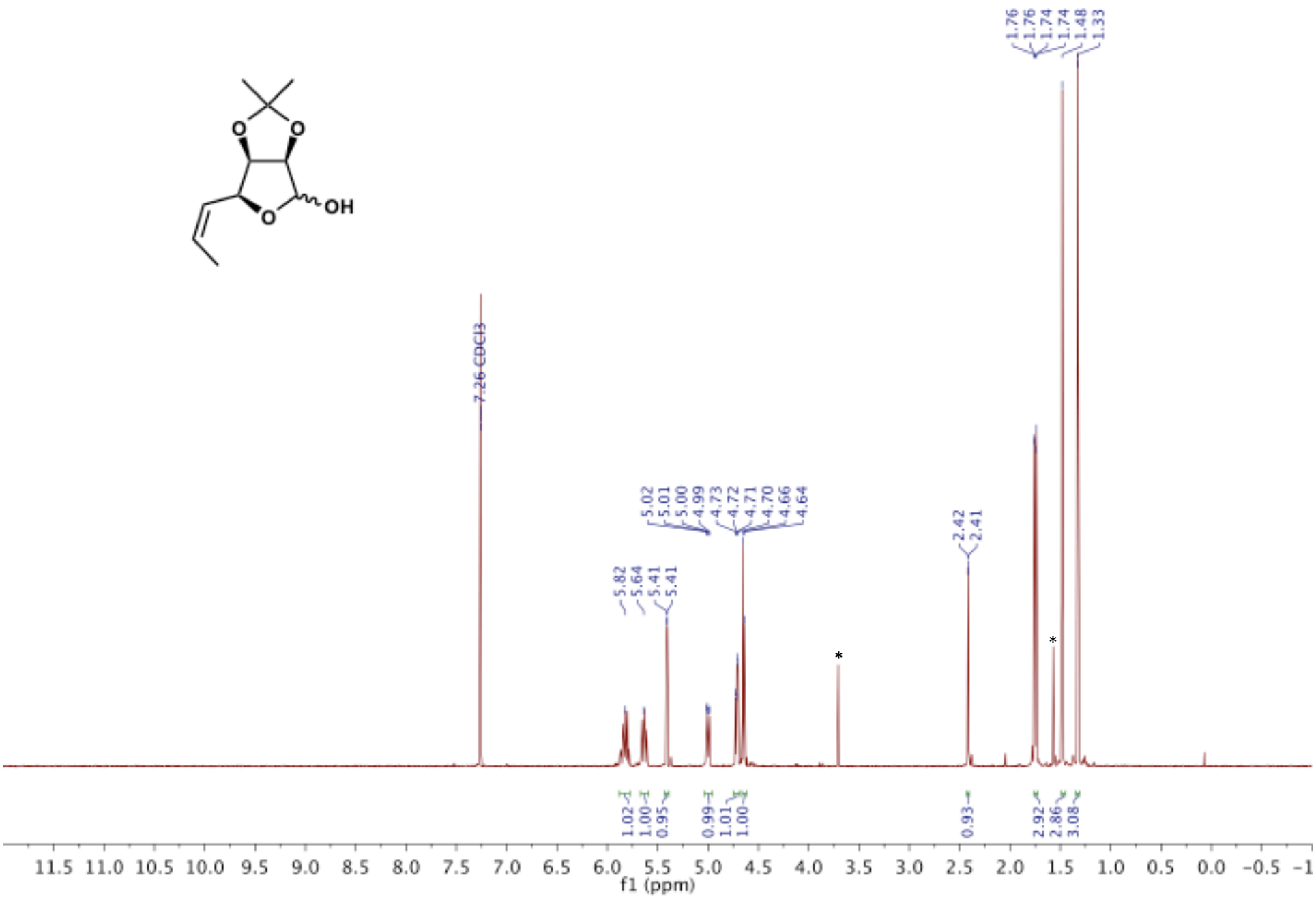


1: ^{13}C NMR (126 MHz, $CDCl_3$)

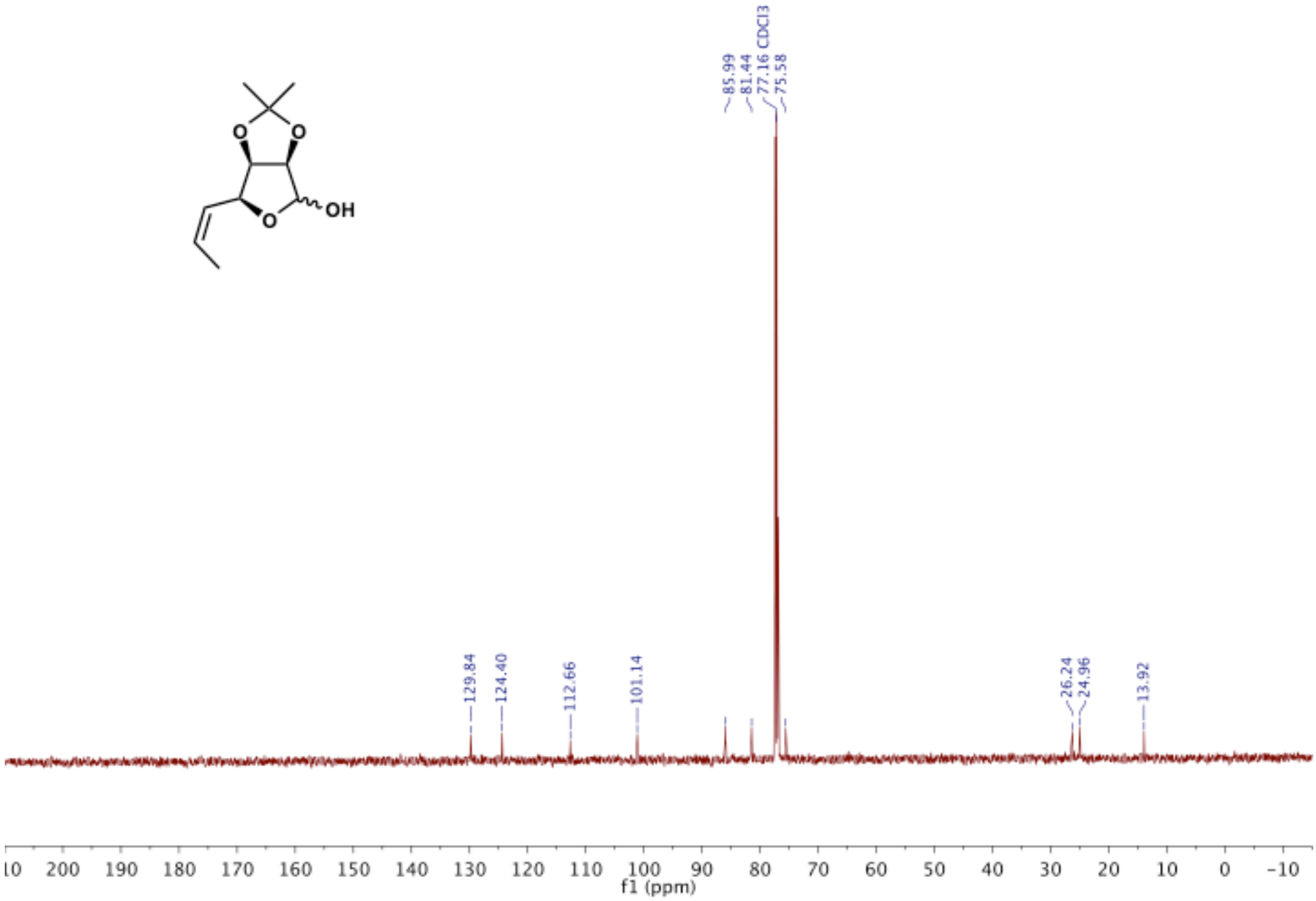




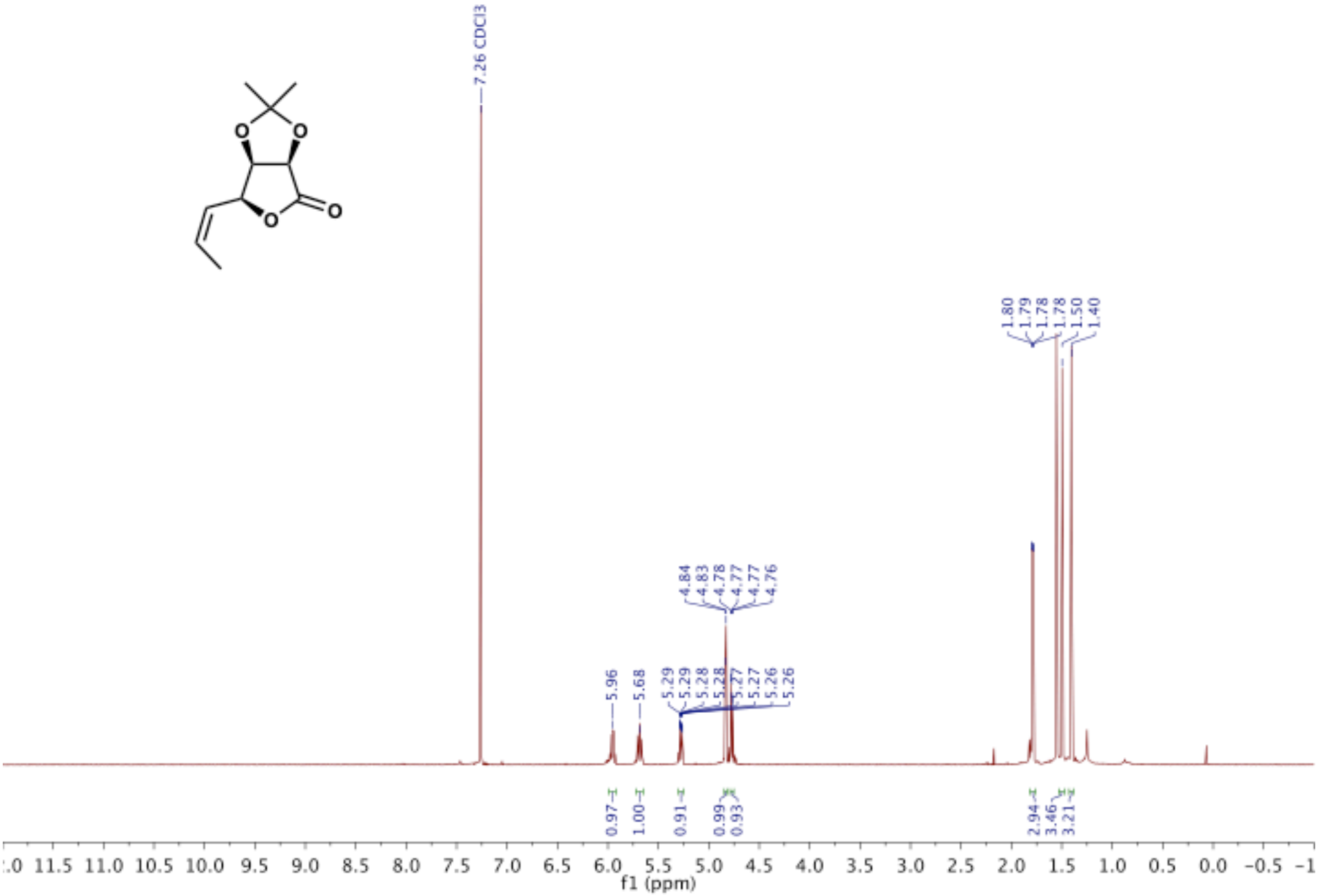
8: ^{1}H NMR (500 MHz, $CDCl_3$)



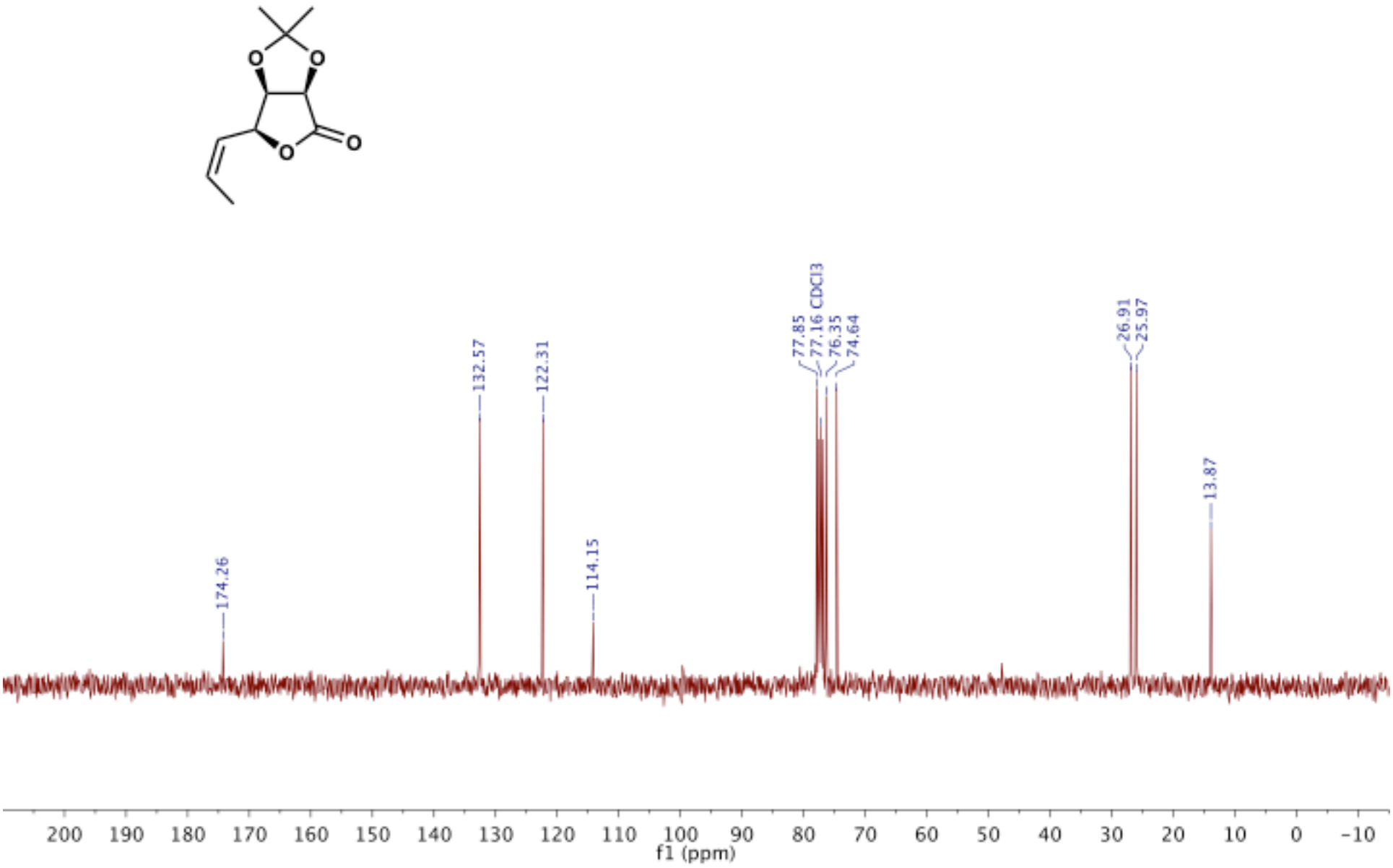
8: ^{13}C NMR (126 MHz, $CDCl_3$)



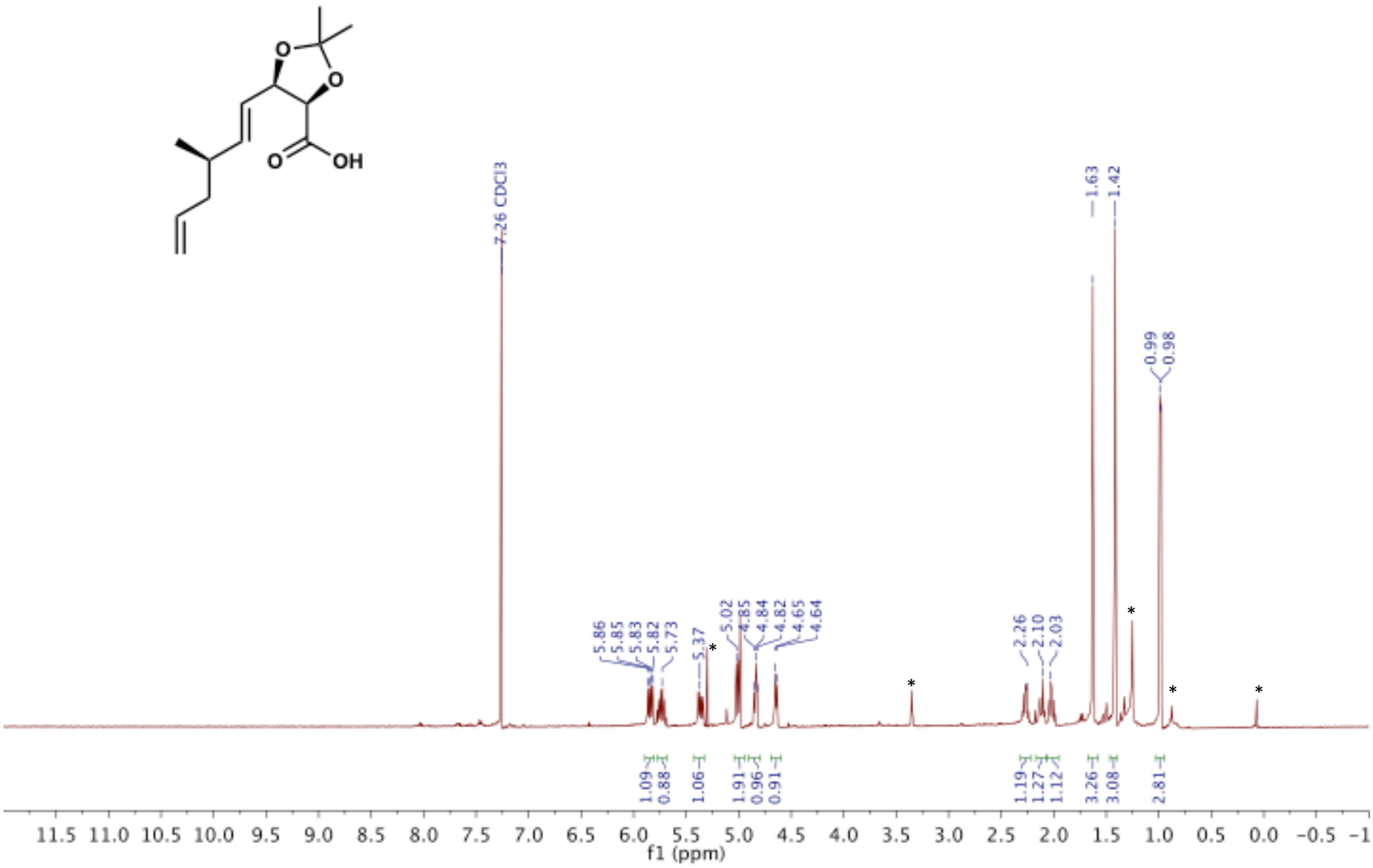
2: ^{1}H NMR (500 MHz, $CDCl_3$)



2: ^{13}C NMR (126 MHz, $CDCl_3$)

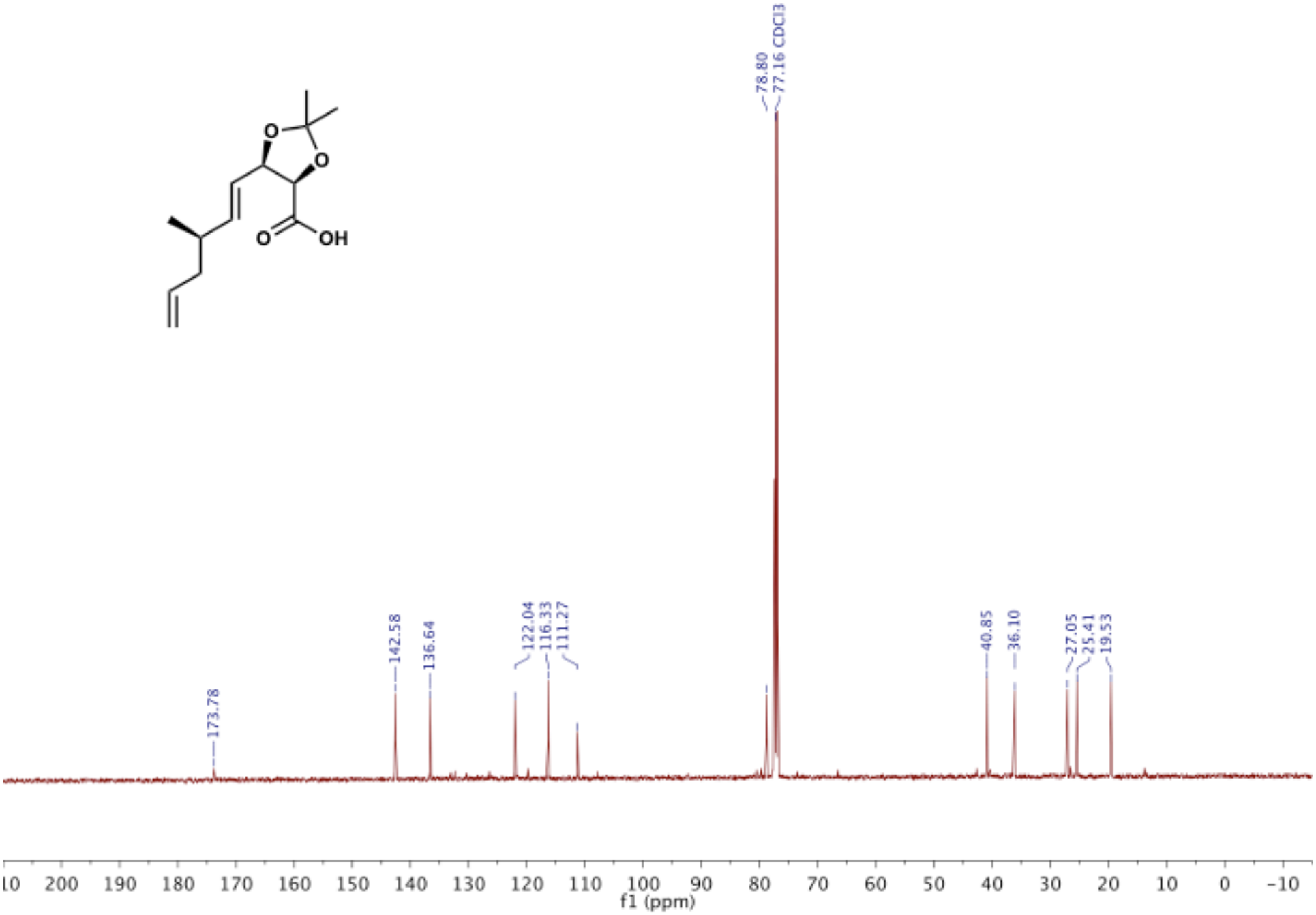


3: ^{1}H NMR (500 MHz, $CDCl_3$)

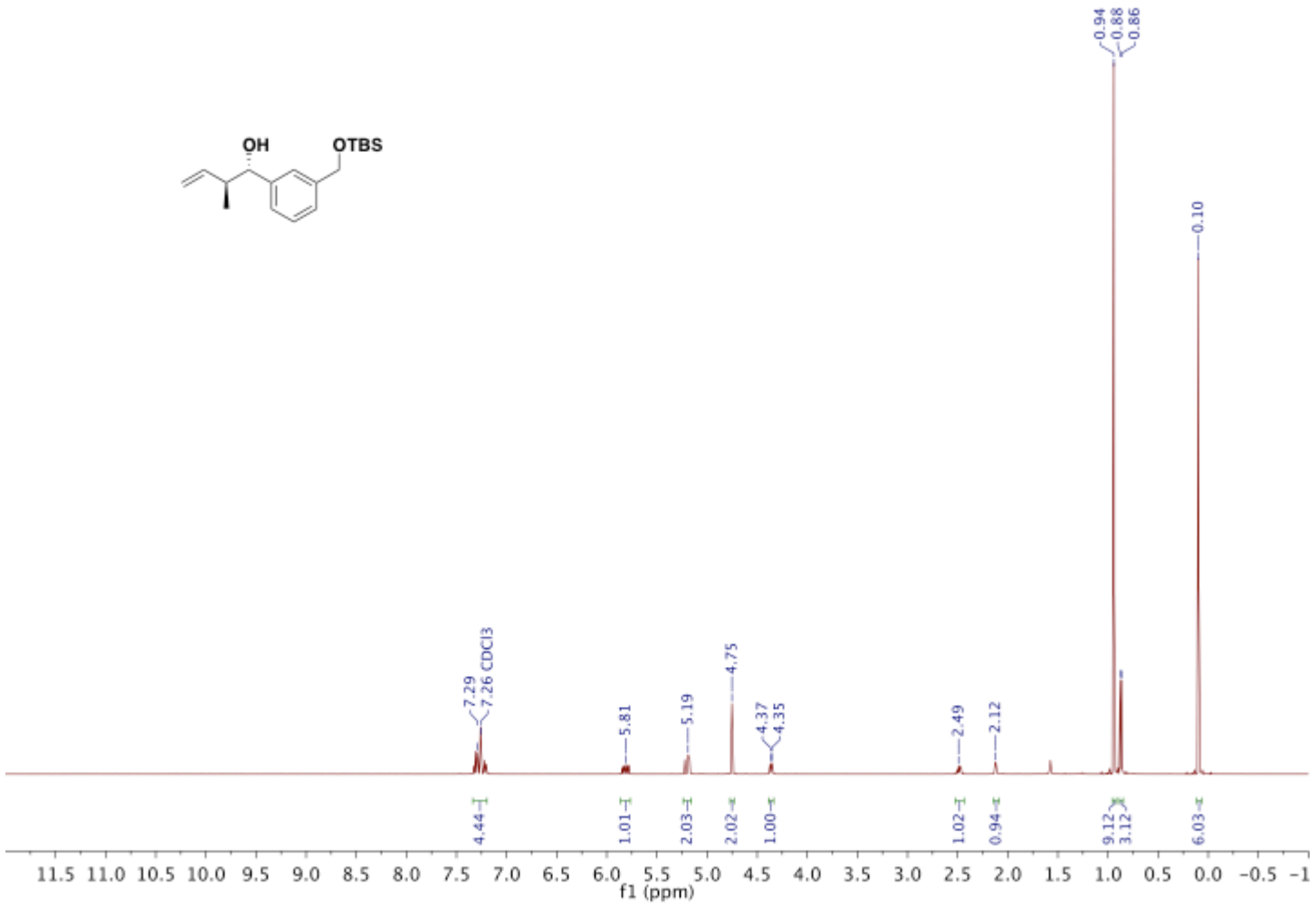


*Impurities present in spectrum

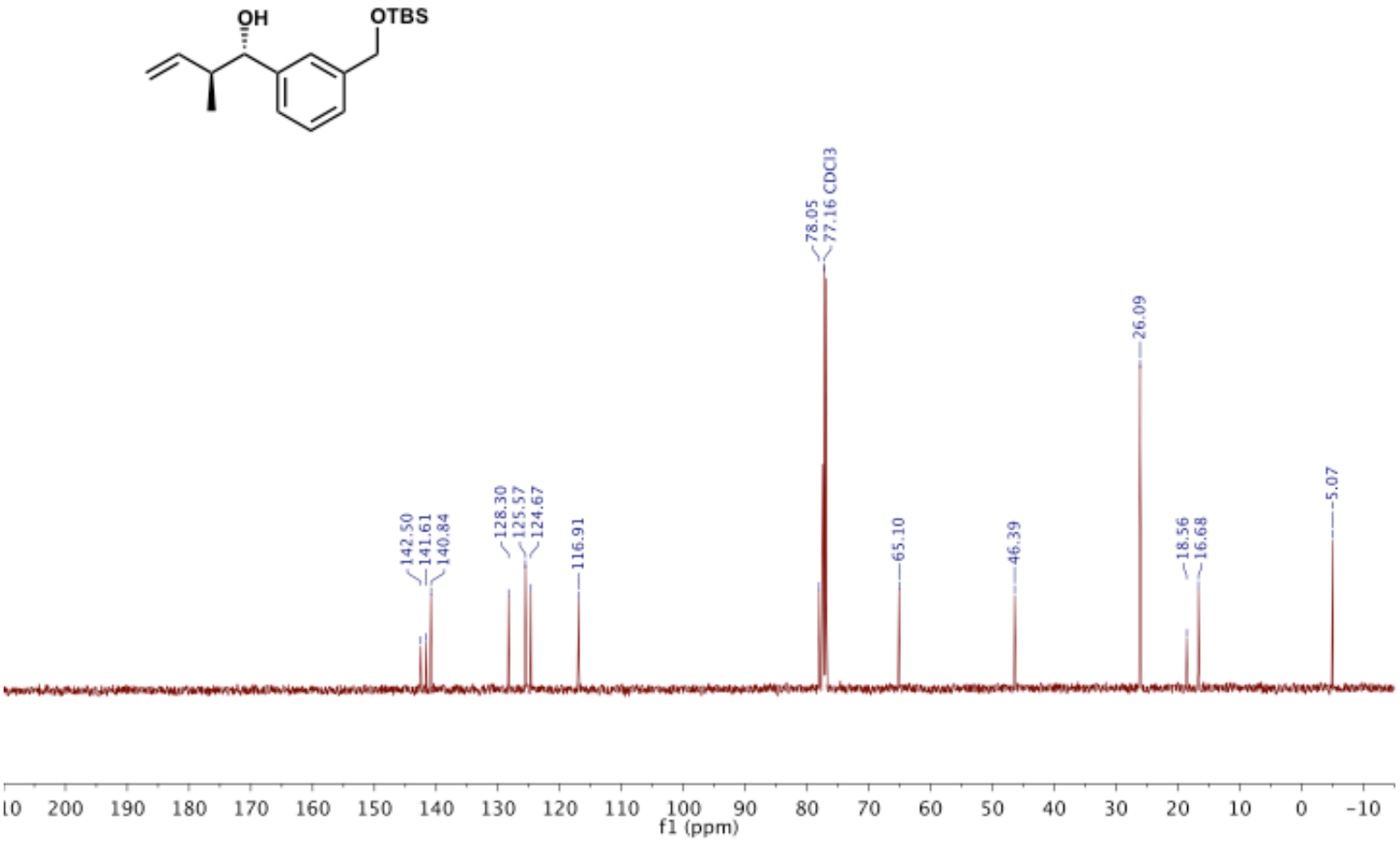
3: ^{13}C NMR (126 MHz, $CDCl_3$)



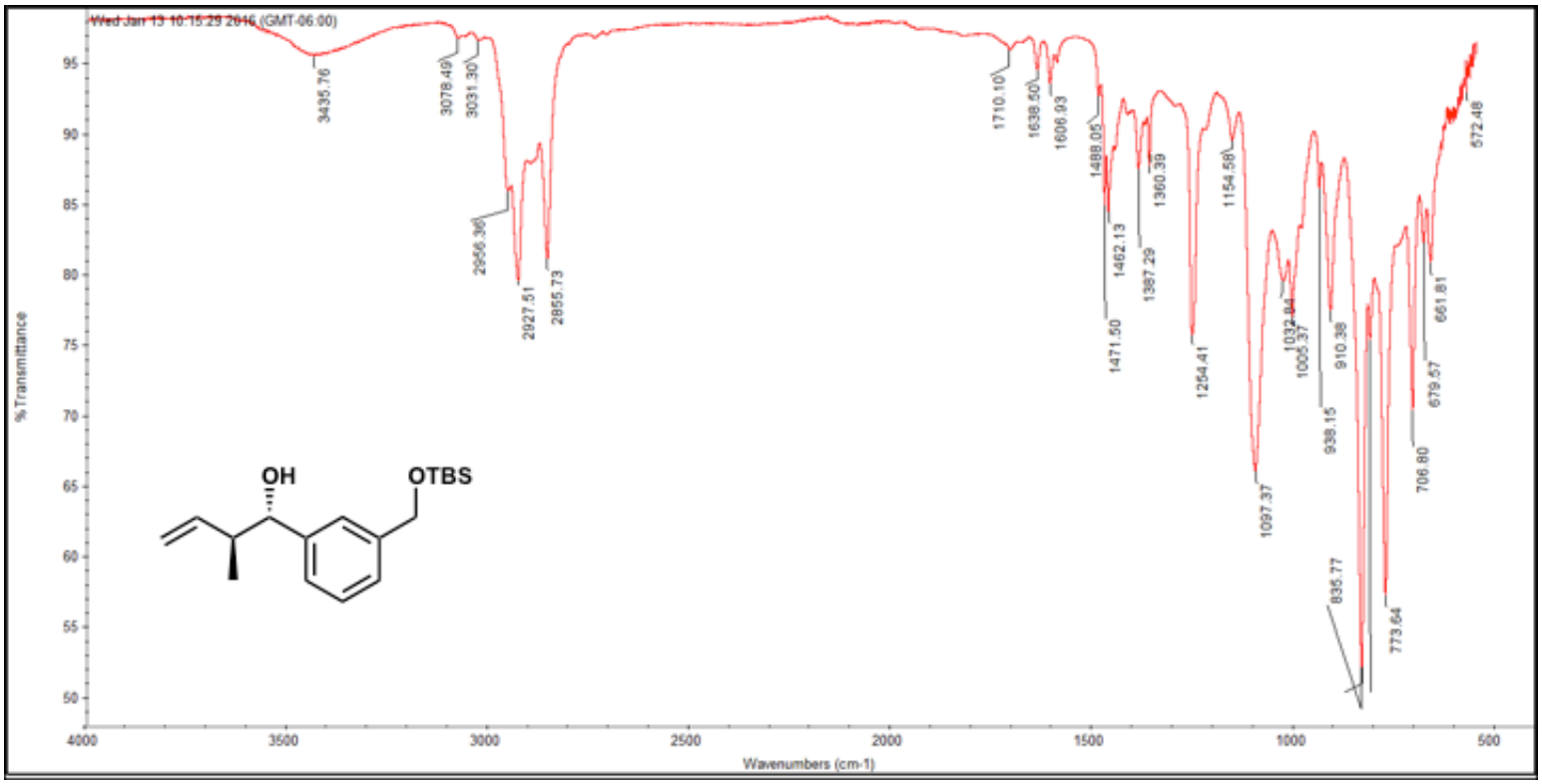
(-)-5a: ^{1}H NMR (500 MHz, $CDCl_3$)



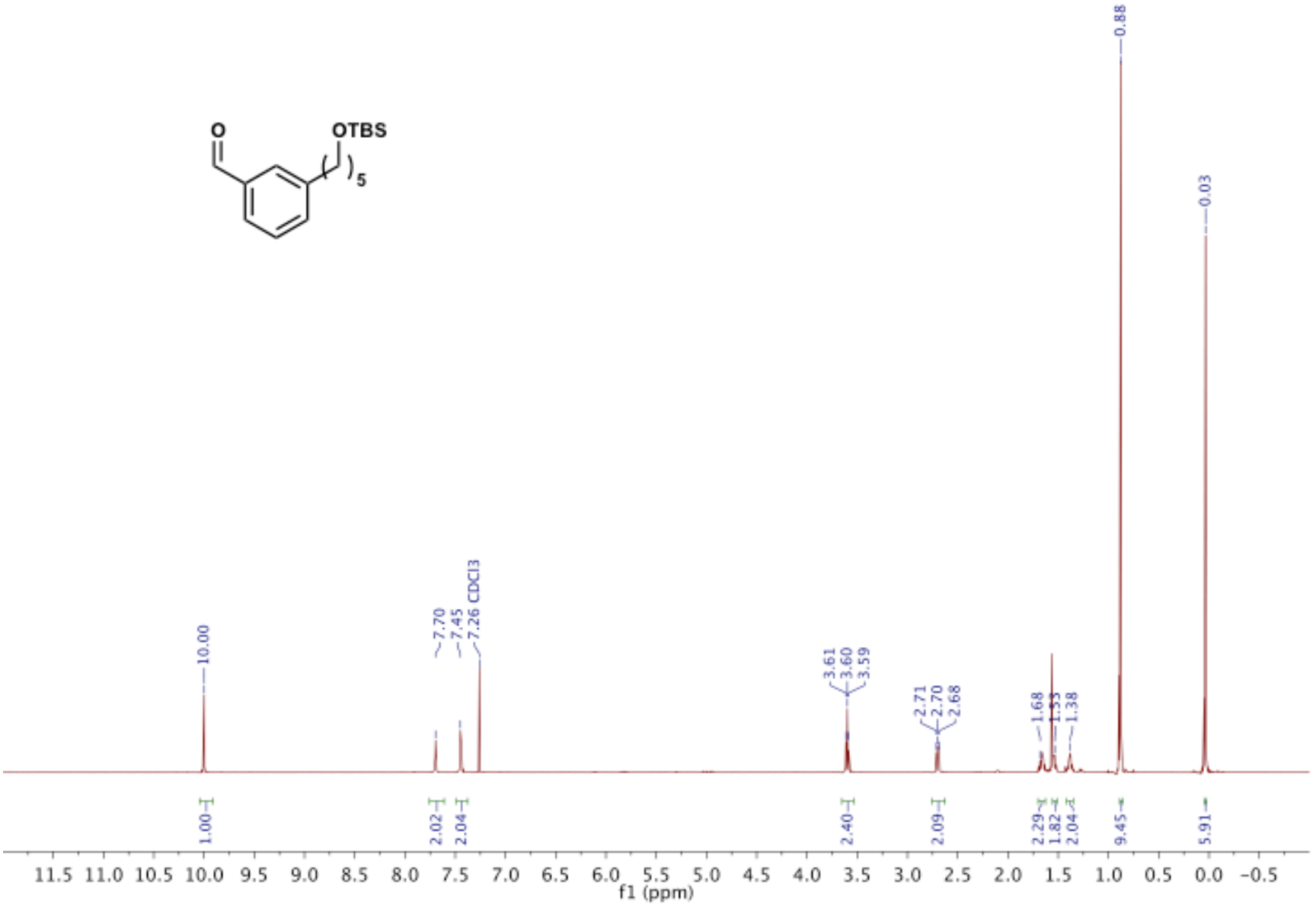
(-)-5a: ^{13}C NMR (126 MHz, $CDCl_3$)



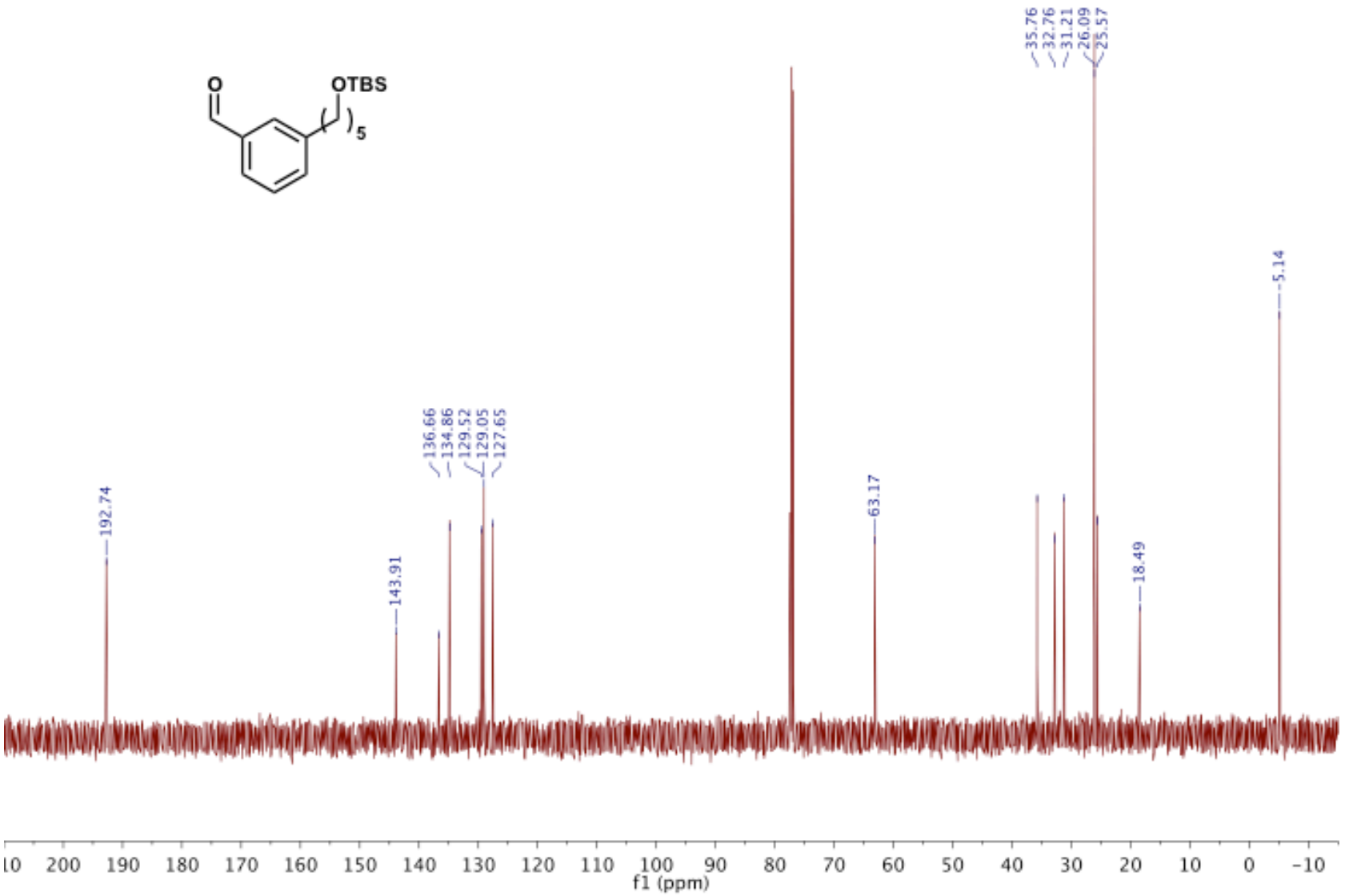
(-)-5a: IR


Wed Jan 13 10:15:29 2016 (GMT-06:00)
% Transmittance
Wavenumbers (cm-1)
3435.76
3078.49
3031.30
2956.36
2927.51
2855.73
1710.10
1638.50
1606.93
1488.05
1471.50
1462.13
1387.29
1360.39
1254.41
1154.58
1097.37
1032.84
1005.37
938.15
910.38
835.77
773.64
706.80
679.57
661.81
572.48
OH
OTBS

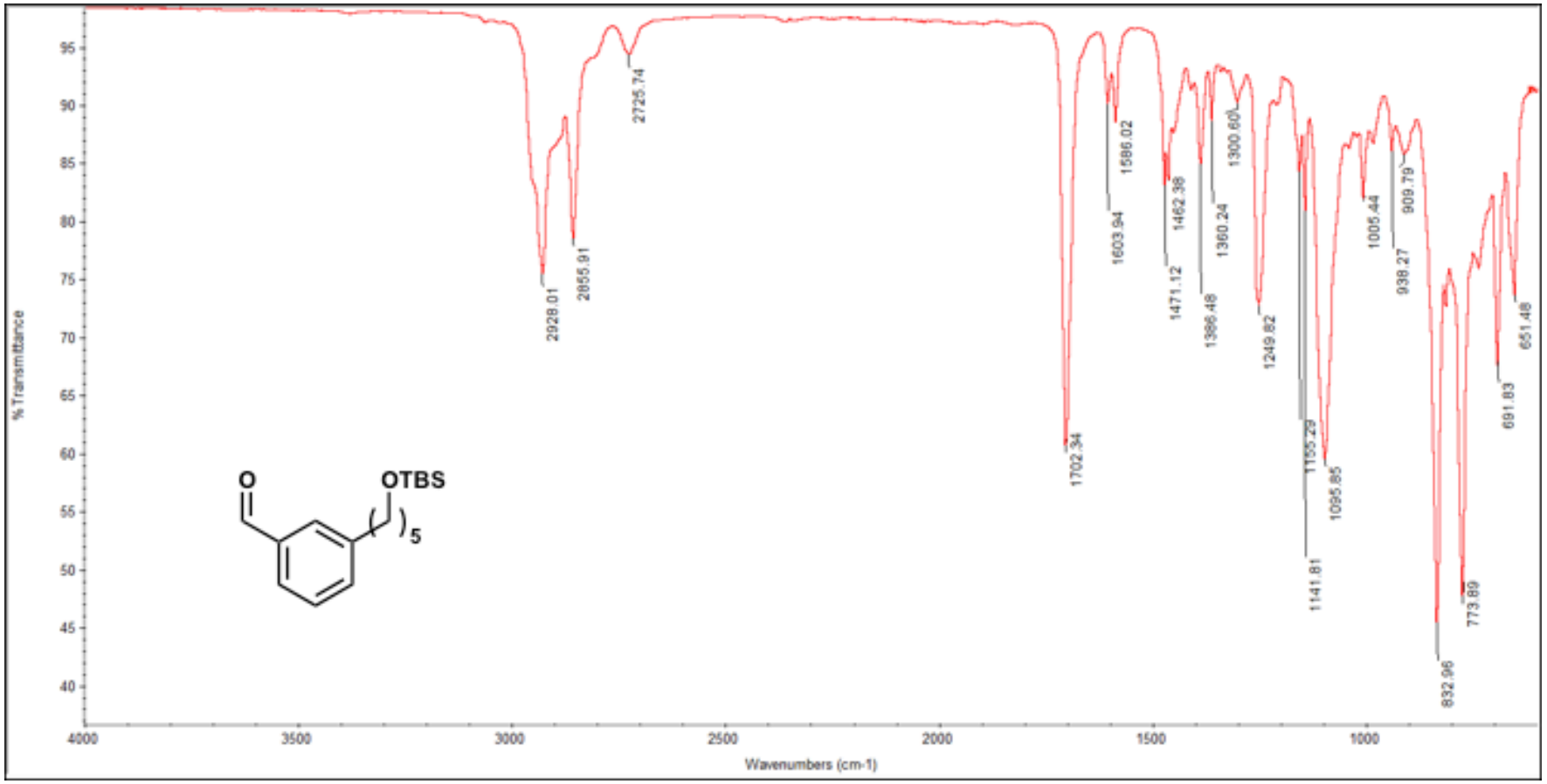
4b: ^{1}**H NMR** (500 MHz, $CDCl_3$)



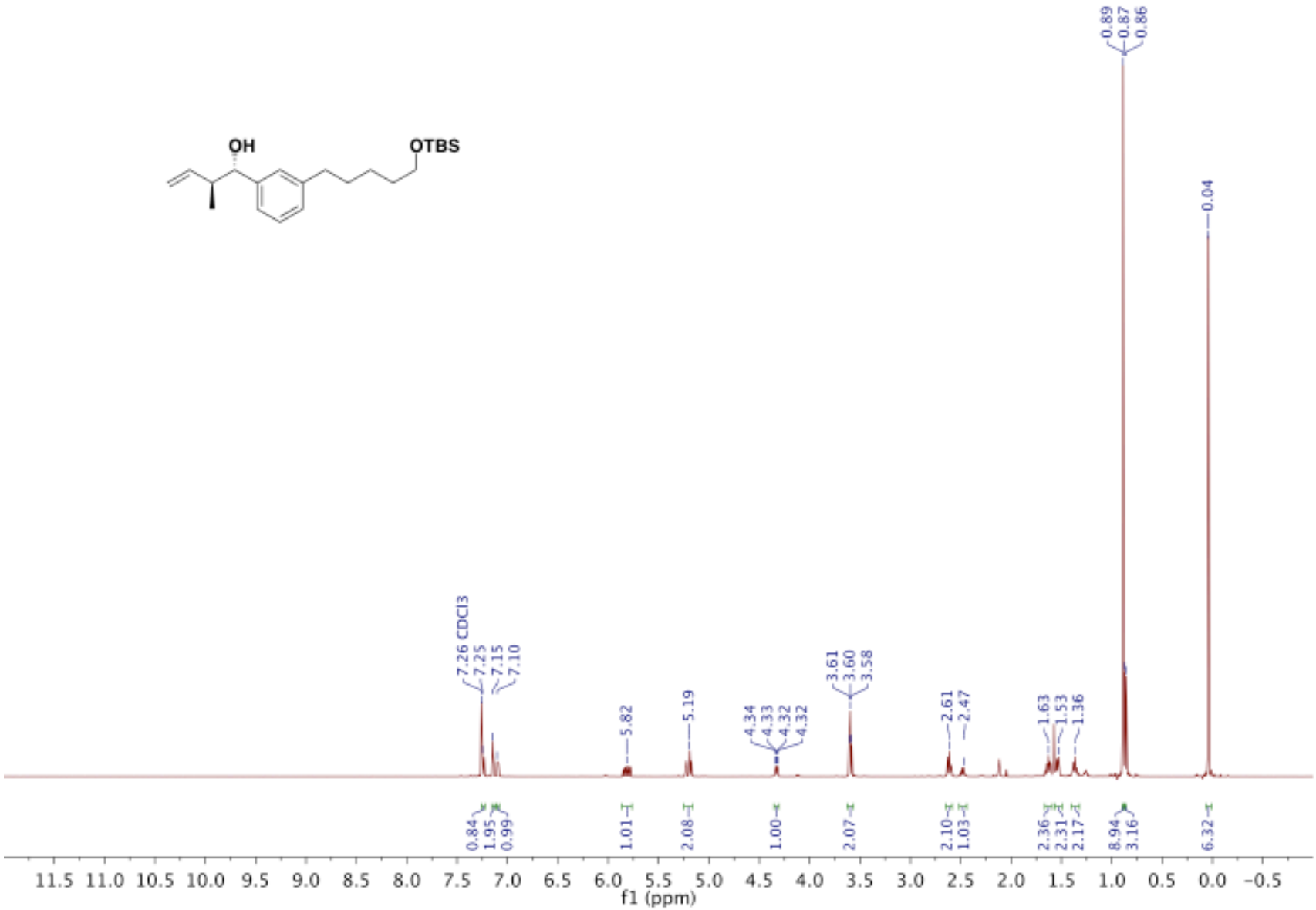
4b: ^{13}C NMR (126 MHz, $CDCl_3$)



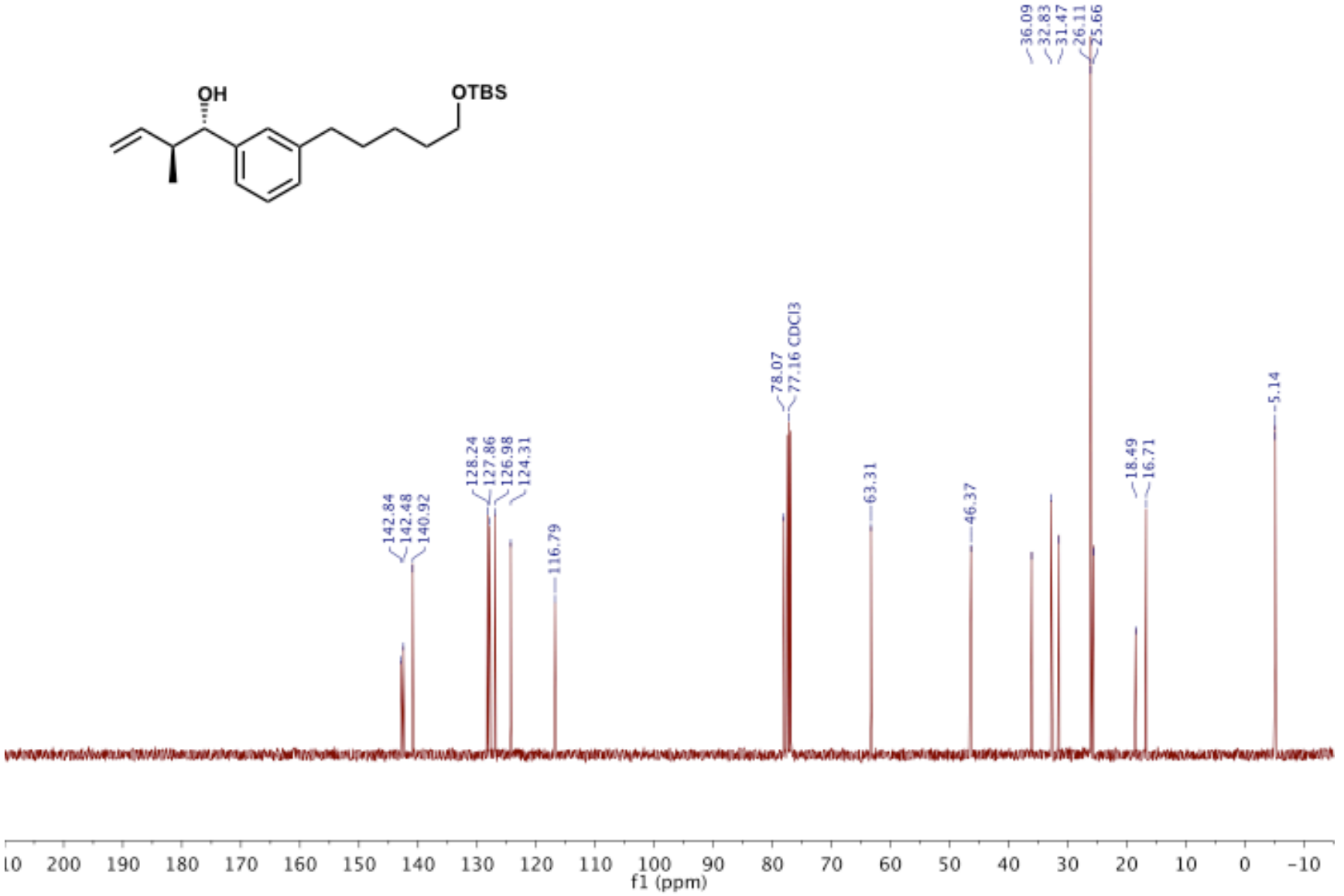
4b: IR


% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
95
90
85
80
75
70
65
60
55
50
45
40
2928.01
2855.91
2725.74
1702.34
1603.94
1586.02
1471.12
1462.38
1386.48
1360.24
1300.60
1249.82
1155.29
1141.81
1095.85
1005.44
938.27
909.79
832.96
773.89
691.83
651.48
O
OTBS
5

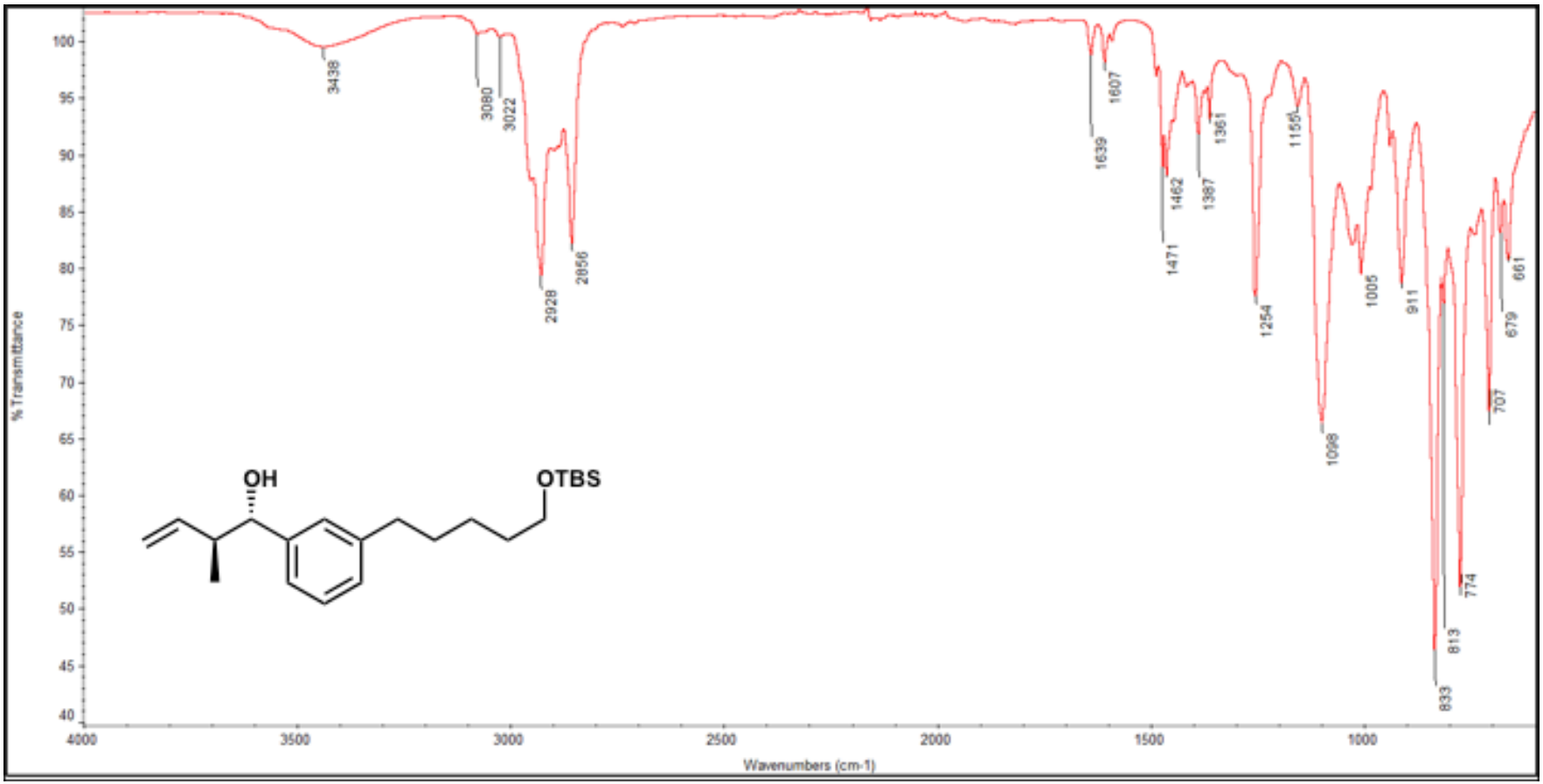
(-)-5b: ^{1}H NMR (500 MHz, $CDCl_3$)



(-)-5b: ^{13}C NMR (126 MHz, $CDCl_3$)



(-)-5b: IR


% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
100
95
90
85
80
75
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65
60
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50
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1639
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1471
1462
1387
1361
1254
1155
1098
1005
911
833
813
774
707
679
661
OH
OTBS

6. References

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