

Stereospecific Asymmetric N-Heterocyclic Carbene (NHC)- Catalyzed Redox Synthesis of Trifluoromethyl Dihydropyranones and Mechanistic Insights

Alyn T. Davies,[†] James E. Taylor,[†] James Douglas,[†] Christopher J. Collett,[†]
Louis C. Morrill,[†] Charlene Fallan,[†] Alexandra M. Z. Slawin,[†] Gwydion Churchill,[‡] and
Andrew D. Smith^{*,†}

[†]*EaStCHEM, School of Chemistry, University of St Andrews, North Haugh, St Andrews, KY16 9ST, United Kingdom*

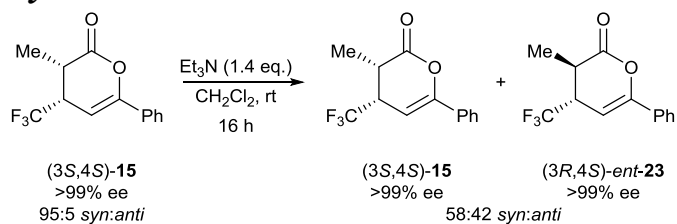
[‡]*AstraZeneca, Process Research and Development, Macclesfield, Cheshire, SK10 2NA, United Kingdom*

E-mail: ads10@st-andrews.ac.uk

Contents

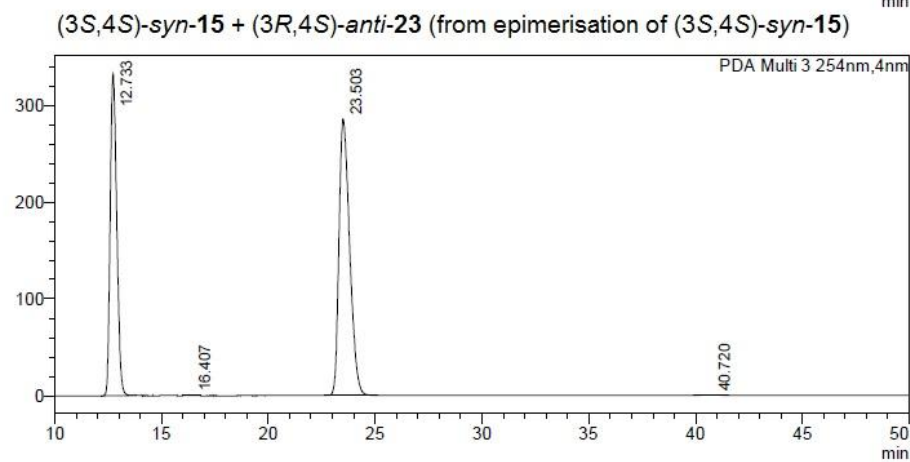
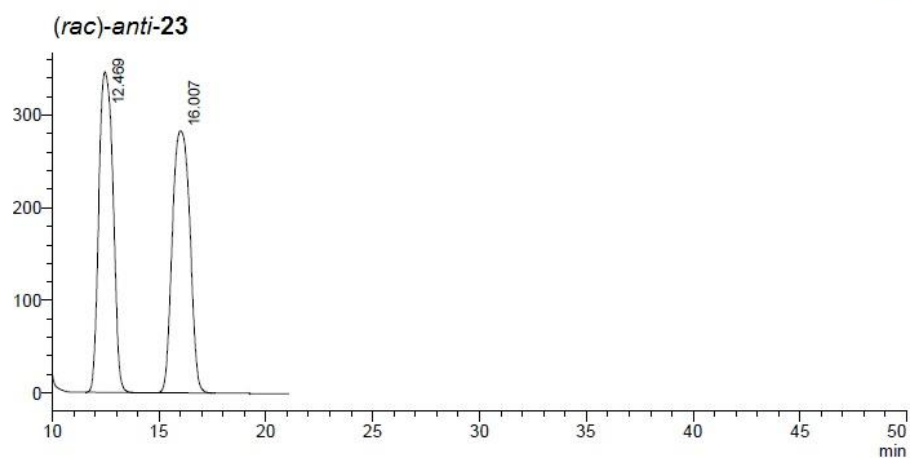
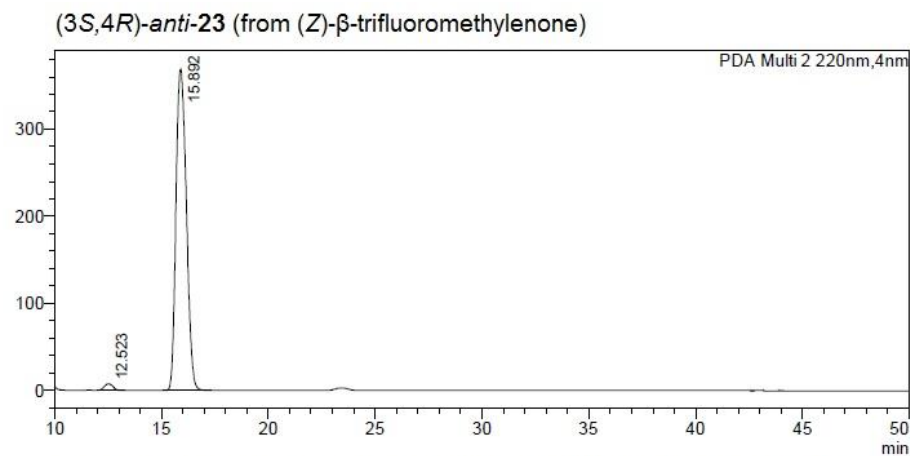
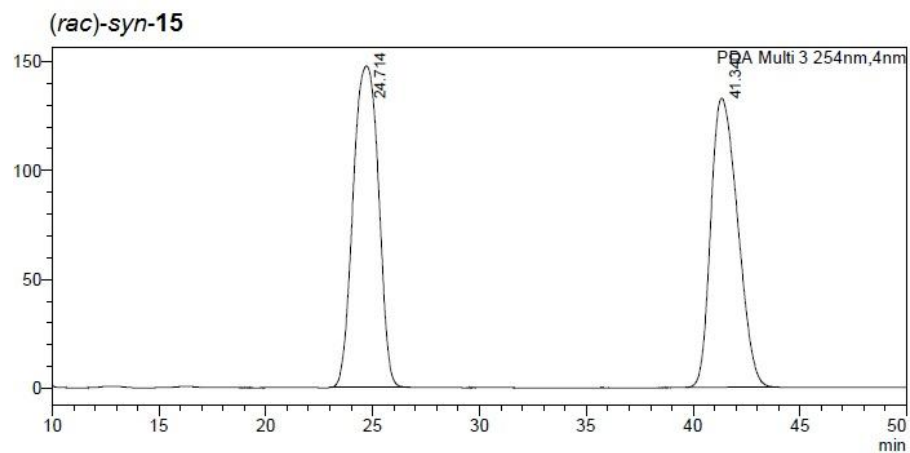
Epimerisation of <i>syn</i>-15	S2
Kinetic Profiles	S4
<i>Reaction profiles with achiral NHC 7</i>	S4
<i>Reaction profiles with chiral NHC 1</i>	S7
<i>Studies on isolated adduct 29</i>	S10
<i>Studies on O-acylated enolate 30</i>	S12
Kinetic Isotope Effect	S13
NMR Data	S16
<i>Compounds from Table 2</i>	S16
<i>Compounds from Table 3</i>	S40
<i>Derivatisations</i>	S50
<i>Adduct 29</i>	S58
<i>O-Acylated enolate 30</i>	S60
HPLC Data	S62
<i>Compounds from Table 2</i>	S62
<i>Compounds from Table 3</i>	S74
<i>Derivatisations</i>	S79
X-Ray Crystal Structure of <i>syn</i>-12	S81

Epimerisation of *syn*-**15**



(3*S*,4*S*)-3-Methyl-6-phenyl-4-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one **15** (51.2 mg, 0.200 mmol, 1.0 eq.) was dissolved in CH₂Cl₂ (4 mL), followed by addition for Et₃N (39.0 μ L, 0.280 mmol, 1.4 eq.) and the reaction was left stirring for 16 hours at RT. The mixture was diluted with CH₂Cl₂, washed with 1M HCl, dried over Na₂SO₄, filtered and concentrated *in vacuo* to leave a white crystalline solid (49.3 mg, 0.192 mmol, 96%). Chiral HPLC analysis; Chiralcel OD-H (99:1 hexane : IPA, flow rate 1 mLmin⁻¹, 254 nm, 30 °C) *t_R*(3*R*,4*S*): 12.7 min, *t_R*(3*S*,4*R*): 16.4 min, *t_R*(3*S*,4*S*): 24.0 min, *t_R*(3*R*,4*R*): 41.3 min, >99% ee (*syn*), >99% ee (*anti*).

See overleaf for relevant HPLC traces.

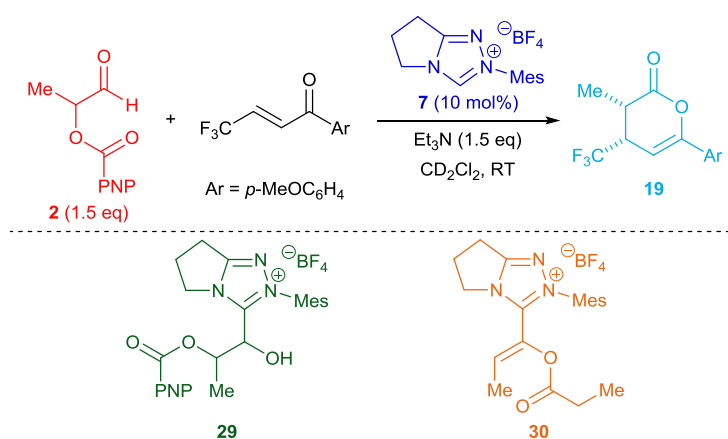


Kinetic Profiles

Reaction Monitoring via ^1H NMR

The concentrations of reactants, intermediates and products were determined from the integral of the species itself, relative to the integral of the internal standard tetramethylsilane (TMS). The concentration of the internal standard was set relative to the integral corresponding to the major substrate at $t=0$, which corresponded to a known starting concentration.

Reaction Profiles with Achiral NHC **7**



In an NMR tube, aldehyde **2** (12.6 mg, 0.0563 mmol), β -trifluoromethyl enone (8.6 mg 0.0375 mmol) and NHC precatalyst **7** (1.2 mg, 0.00375 mmol) were dissolved in CD₂Cl₂ (0.75 mL, ~3 mM TMS). The reaction was initiated by the addition of NEt₃ (7.8 μ L, 0.0563 mmol) and monitored by ^1H NMR spectroscopy (400 MHz) at ambient temperature. Representative ^1H NMR spectra taken at intervals over the course of the reaction are shown in Figure S1. Spectra of isolated starting materials, intermediates and product are shown in Figure S3.

Figure S1: Representative ^1H NMR spectra for the reaction with achiral NHC precatalyst **7**.

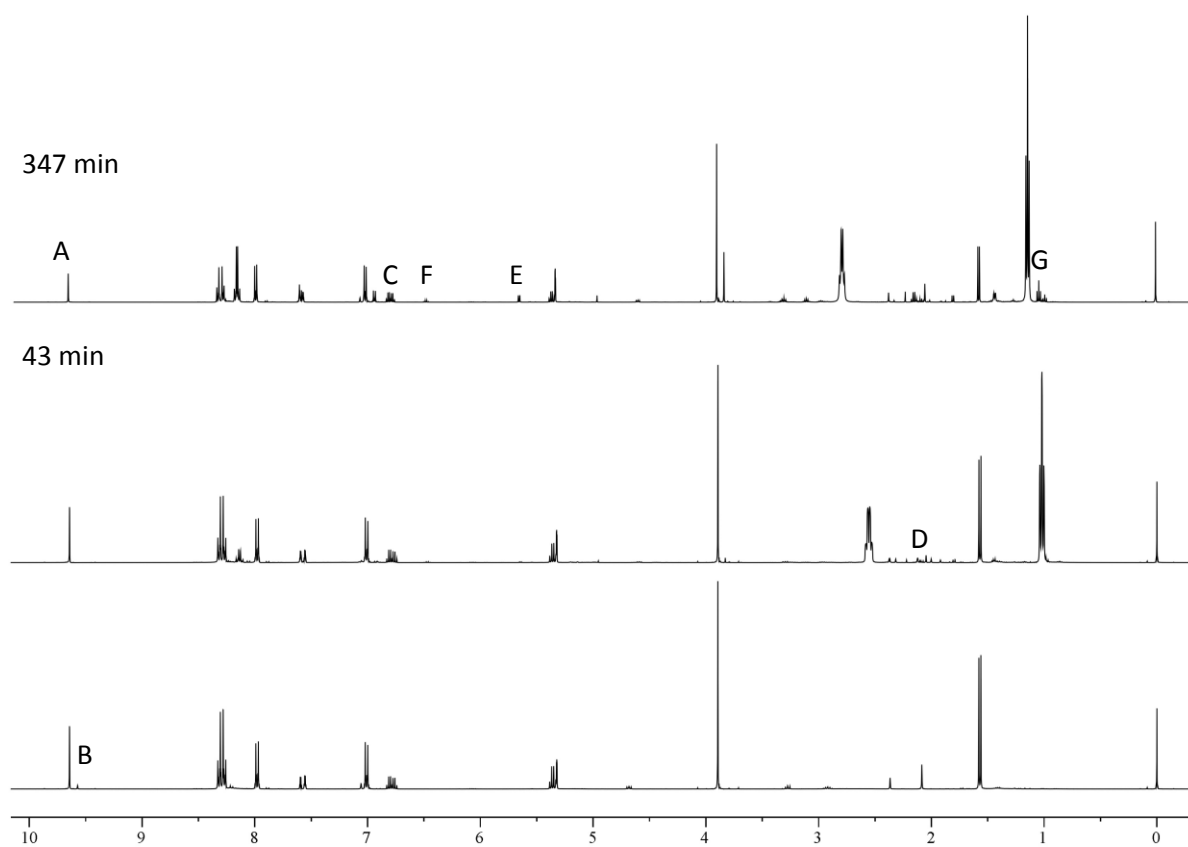


Figure S2: Reaction profile for the reaction with achiral NHC precatalyst **7**.

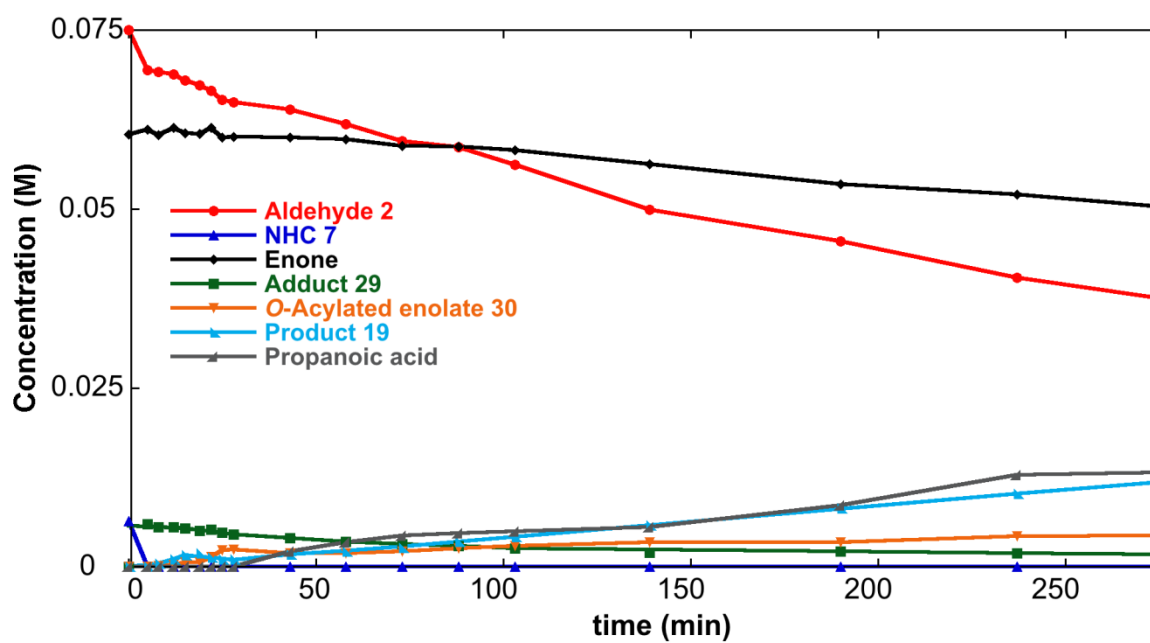
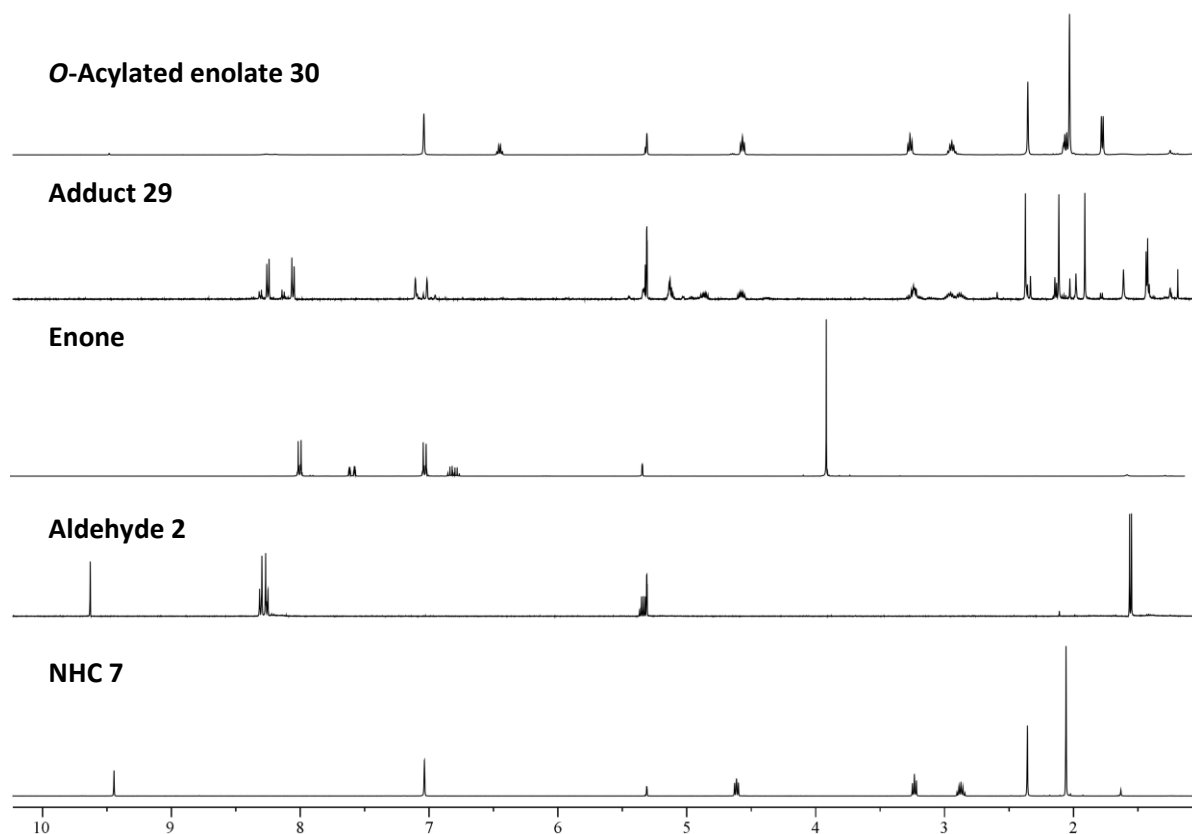
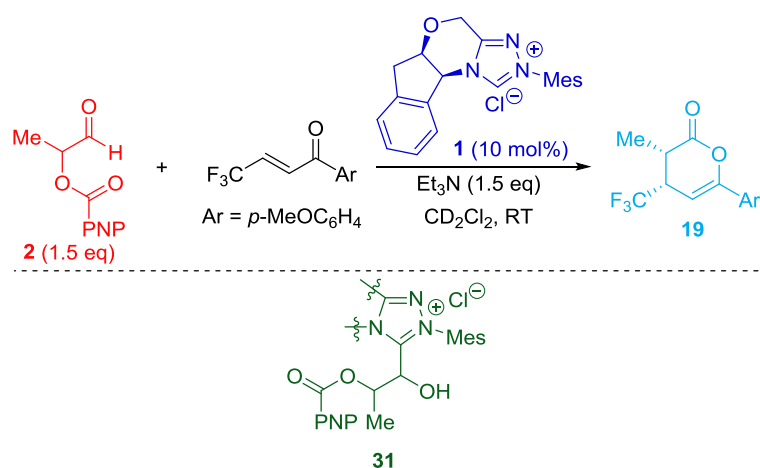


Figure S3: ^1H NMR spectra of starting materials, intermediates and product in CD_2Cl_2 .



The concentration of aldehyde **2** was determined using the singlet at 9.64 ppm (A), corresponding to the aldehyde $\text{C}=\text{O}(\text{H})$. The singlet at 9.57 ppm (B) was used to determine the concentration of NHC precursor **7**, which was assigned to the triazole CH. The concentration of enone was determined using the multiplet at 6.78 ppm. Initially a new set of peaks was observed which was assigned to the intermediate **29**, the concentration of both diastereoisomers was calculated sum of the singlets at 2.00 and 1.92 ppm (D), corresponding to the $\text{Ar}-\text{CH}_3$ groups. Over time the formation of product **19** was seen and the concentration was determined using the doublet at 4.28 ppm (E). Additionally, the formation of **30** was observed, the concentration of which was determined from the quartet at 6.47 ppm (F). Propanoic acid was also seen and the triplet at 1.07 ppm was used to determine the concentration. The presence of propanoic acid was also confirmed by doping of the experiment with a pure sample.

Reaction Profiles with Chiral NHC **1**



In an NMR tube, aldehyde **2** (12.6 mg, 0.0563 mmol), β -trifluoromethyl enone (8.6 mg 0.0375 mmol) and NHC precatalyst **1** (1.4 mg, 0.00375 mmol) were dissolved in CD₂Cl₂ (0.75 mL, ~3 mM TMS). The reaction was initiated by the addition of NEt₃ (7.8 μ L, 0.0563 mmol) and monitored by ¹H NMR spectroscopy (400 MHz) at ambient temperature. Representative ¹H NMR spectra taken at intervals over the course of the reaction are shown in Figure S4. A spectrum of NHC precatalyst **1** is also shown.

Figure S4: Representative ^1H NMR spectra for the reaction with chiral NHC precatalyst **1**.

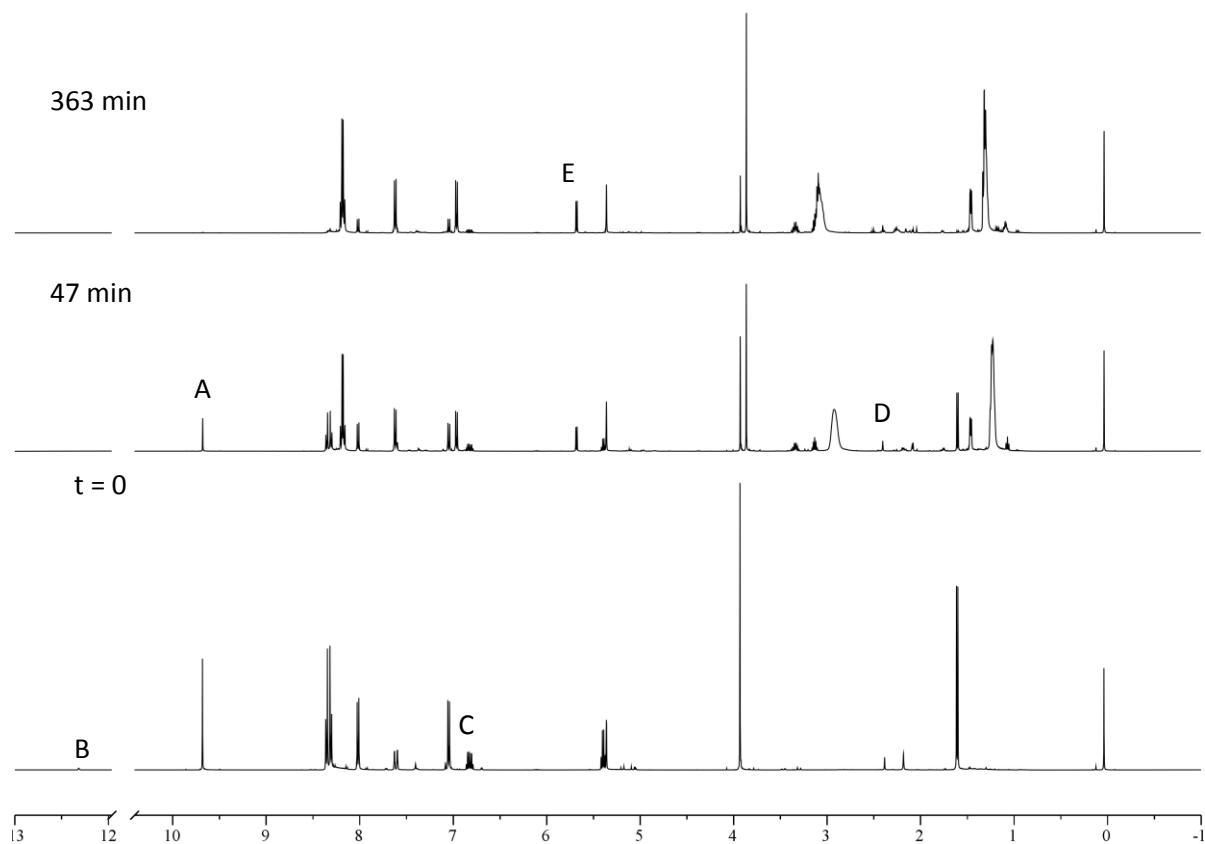
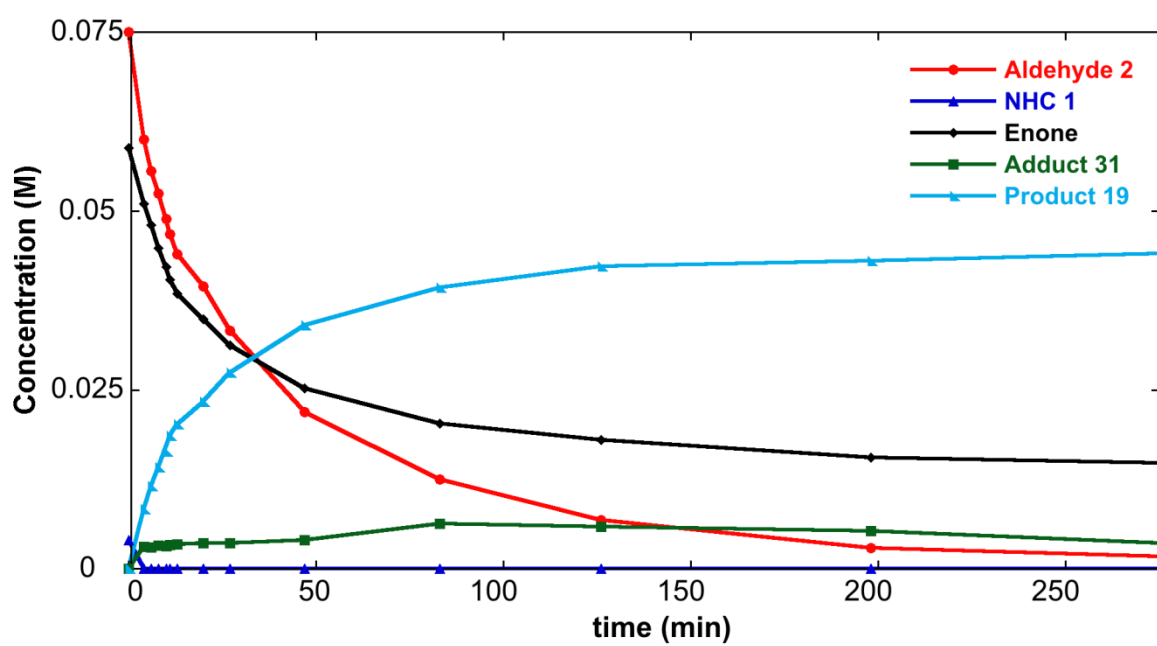
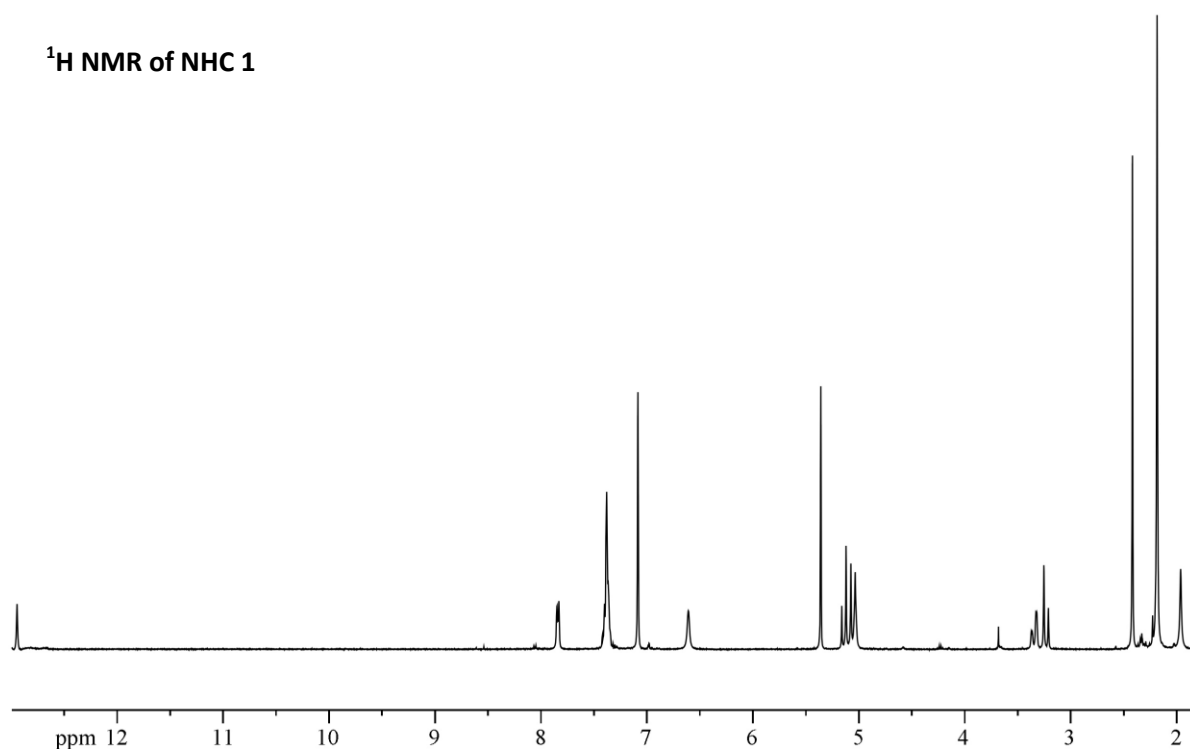


Figure S5: Reaction profile for the reaction with chiral NHC precatalyst **1**.

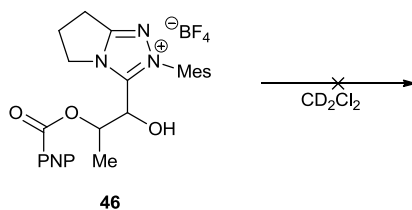


¹H NMR of NHC **1**



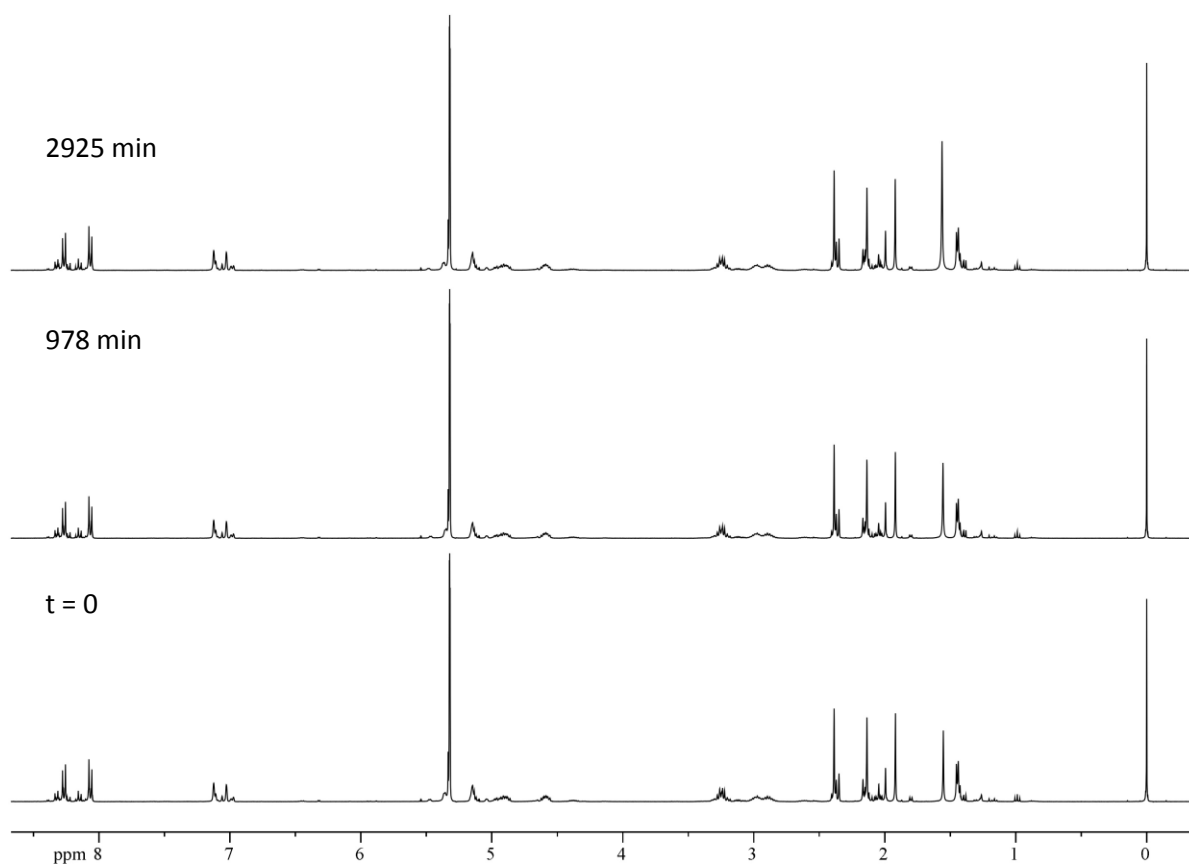
Concentrations of aldehyde **2** (A), enone (C) and product **19** (E) were determined as previously described. In this system, the concentration of NHC precursor was determined using the singlet at 12.32 ppm which was assigned to the triazole CH of **1**. The signals for the initially formed NHC-aldehyde addition product were assigned by analogy to **31**. The concentration was determined using the singlet at 2.41 ppm, corresponding to the Ar-CH₃ group.

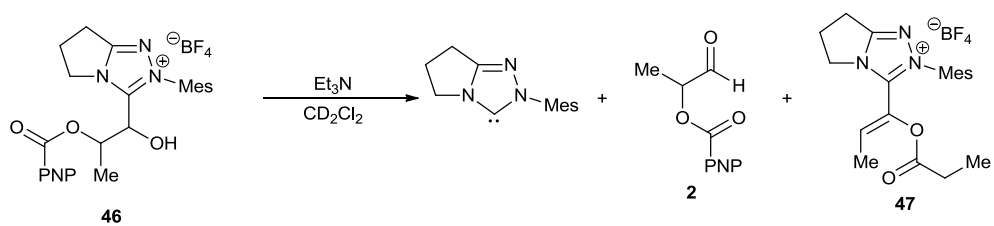
Studies on isolated adduct 29



A 0.01 M solution of **29** was monitored *via* ¹H NMR spectroscopy at r.t. over 2d. Over the course of the experiment no change in the integrals of any of the signals was observed relative to the internal standard. Representative NMR spectra are shown in Figure S6.

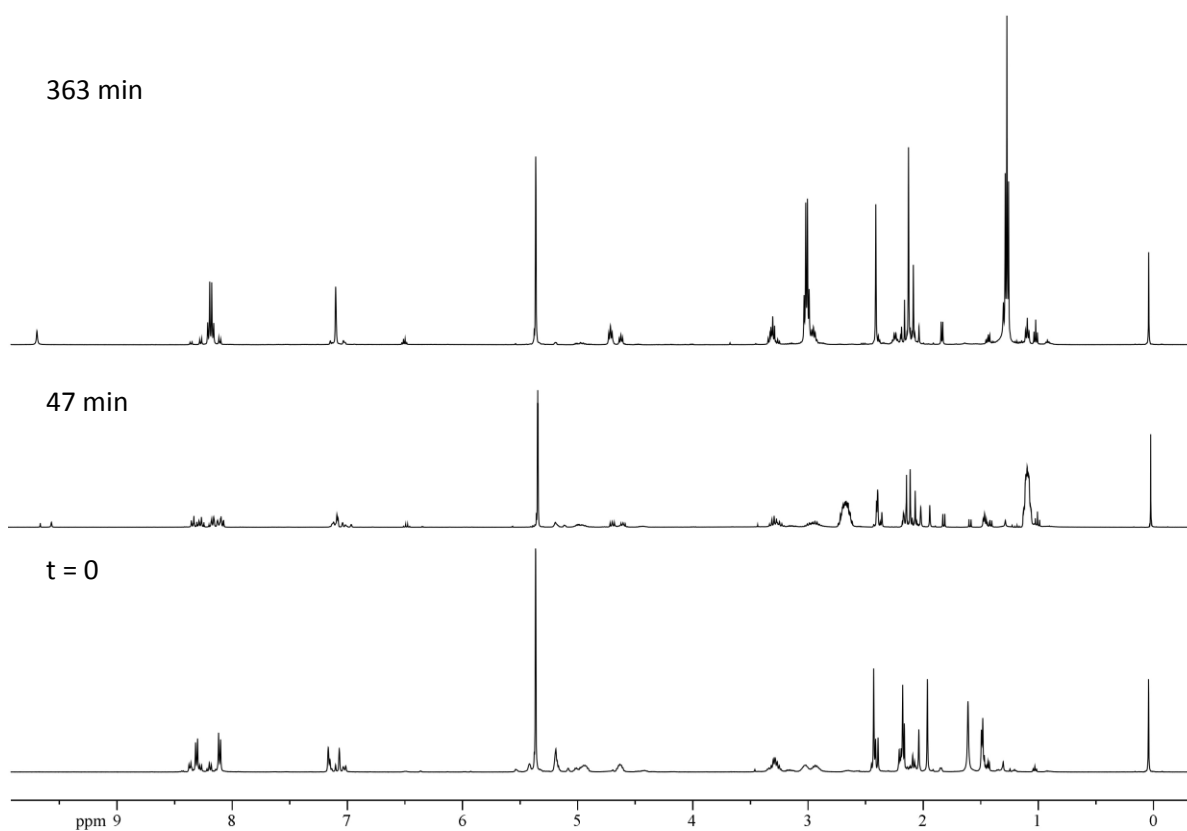
Figure S6: ¹H NMR spectra showing the stability of intermediate **29** in CD₂Cl₂.



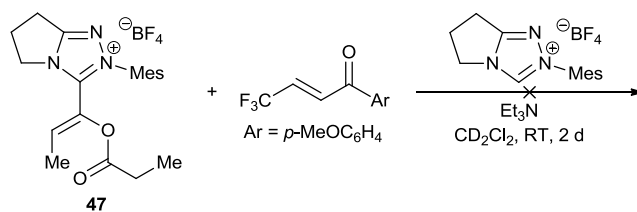


To a 0.01 M solution of **29** was added NEt_3 (1.1 μL 0.01 M) and the solution was monitored *via* ^1H NMR spectroscopy at r.t. over eight hours. Representative ^1H NMR spectra are shown in Figure S7.

Figure S7: ^1H NMR spectra showing the reaction of intermediate **29** with Et_3N in CD_2Cl_2 .

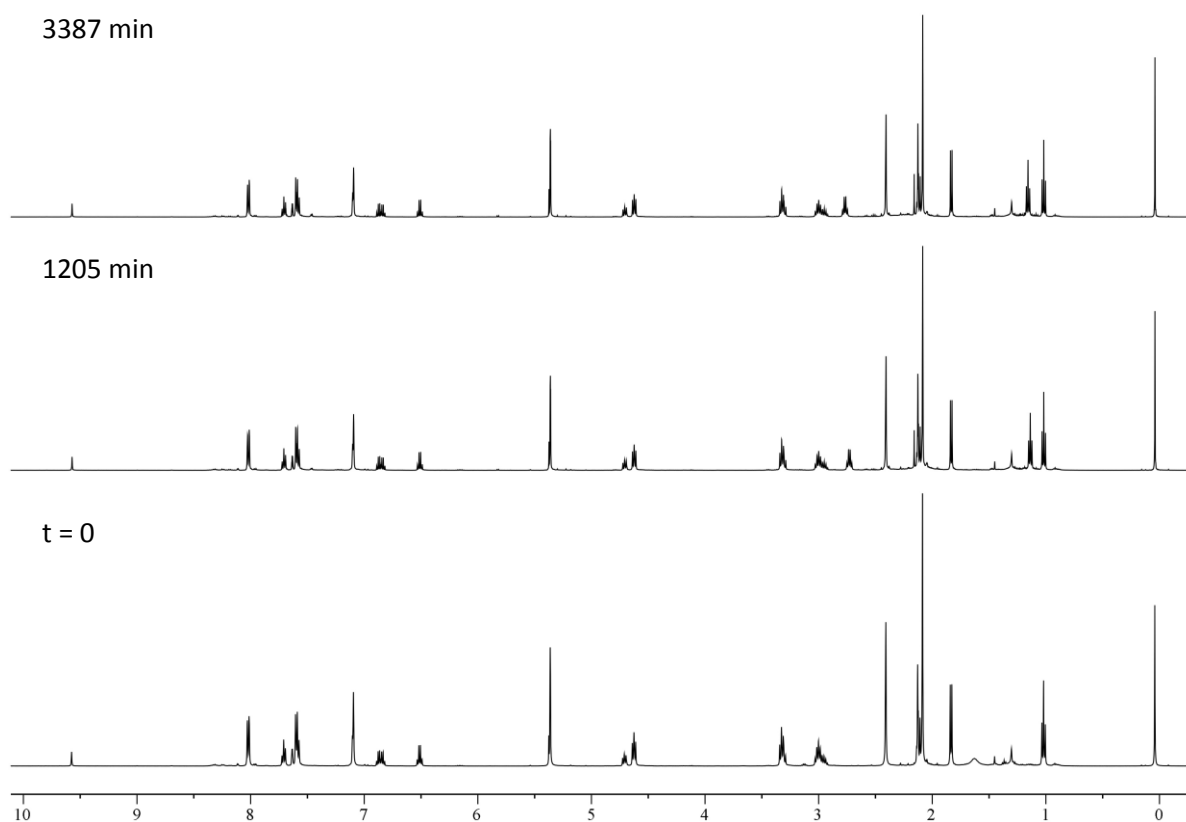


Studies on *O*-Acylated Enolate **30**



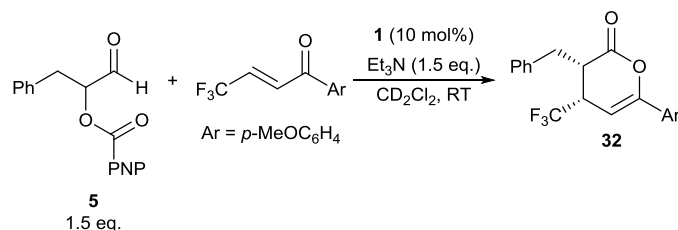
To a 0.02 M solution of **30**, containing 4 mM triazolium salt **7** and 0.02 M enone was added NEt₃ (0.4 μ L 4 mM) and the solution was monitored *via* ¹H NMR spectroscopy at r.t. over 2d. Over the course of the experiment no change in the integrals of any of the signals was observed relative to the internal standard. Representative ¹H NMR spectra are shown in Figure S8.

Figure S8: ¹H NMR spectra showing the stability of *O*-acylated enolate **30** in CD₂Cl₂.



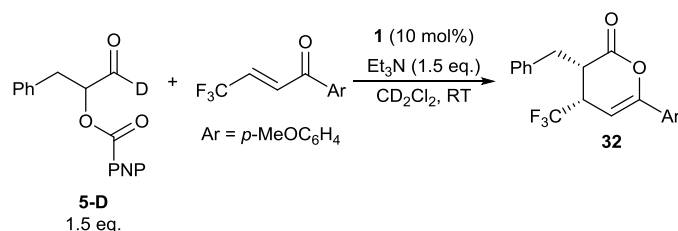
Kinetic Isotope Effect

Kinetics with α -aroyloxyaldehyde **5**



Aldehyde **5** (300 μ L of a 0.0938 M solution in CD₂Cl₂), β -trifluoromethyl enone (300 μ L of a 0.0625 M solution in CD₂Cl₂) and NHC precatalyst **1** (150 μ L of a 0.0125 M solution in CD₂Cl₂) were added to an NMR tube. The reaction was initiated by the addition of Et₃N (3.9 μ L, 0.028 mmol) and monitored by ¹H NMR spectroscopy (500 MHz). Representative ¹H NMR spectra are shown in Figure S9. Concentrations of aldehyde **5**, enone and product **32** were monitored over time relative to an internal standard of TMS. A plot of enone concentration versus time is shown in Figure S11.

Kinetics with α -aroyloxyaldehyde **5-D**



Aldehyde **5-D** (300 μ L of a 0.0938 M solution in CD₂Cl₂), β -trifluoromethyl enone (300 μ L of a 0.0625 M solution in CD₂Cl₂) and NHC precatalyst **1** (150 μ L of a 0.0125 M solution in CD₂Cl₂) were added to an NMR tube. The reaction was initiated by the addition of Et₃N (3.9 μ L, 0.028 mmol) and monitored by ¹H NMR spectroscopy (500 MHz). Representative ¹H NMR spectra are shown in Figure S10. Concentrations of aldehyde **5-D**, enone and product **32** were monitored over time relative to an internal standard of TMS. A plot of enone concentration versus time is shown in Figure S11.

Figure S9: Representative ^1H NMR spectra for kinetics with aldehyde **5**.

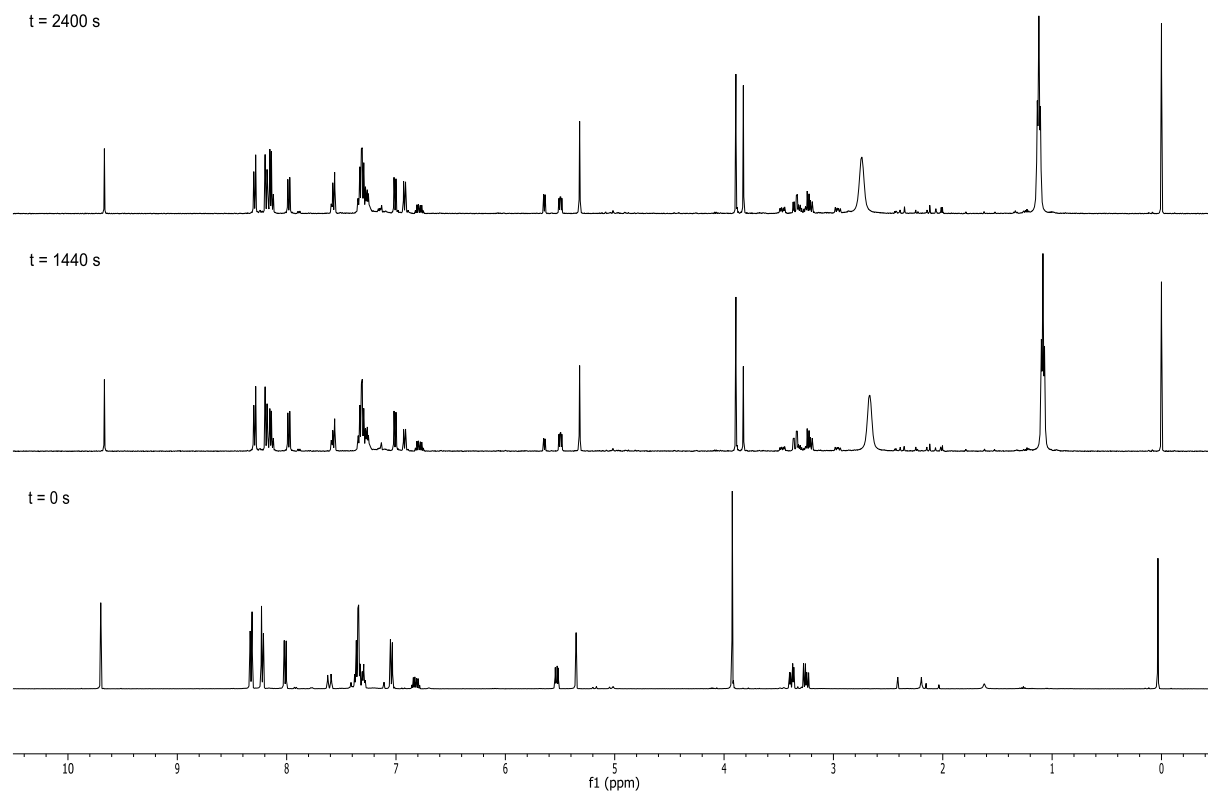


Figure S10: Representative ^1H NMR spectra for kinetics with aldehyde **5-D**.

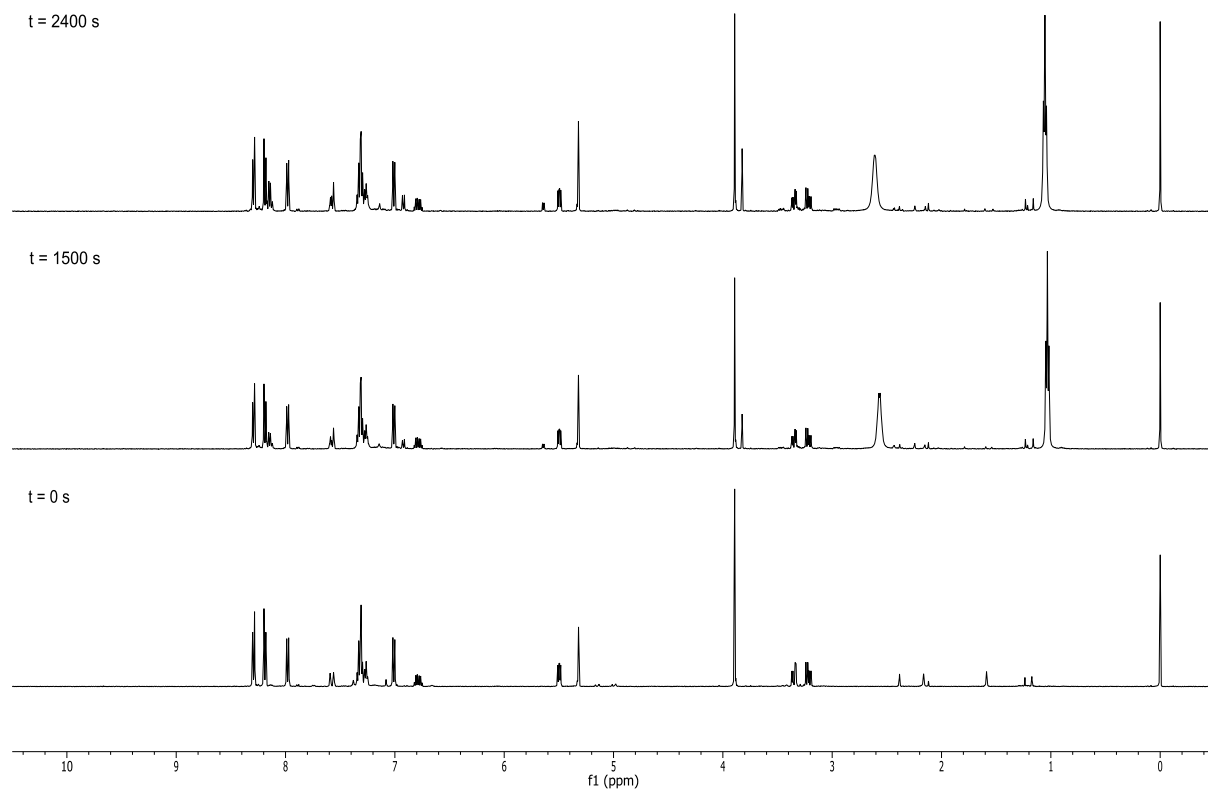
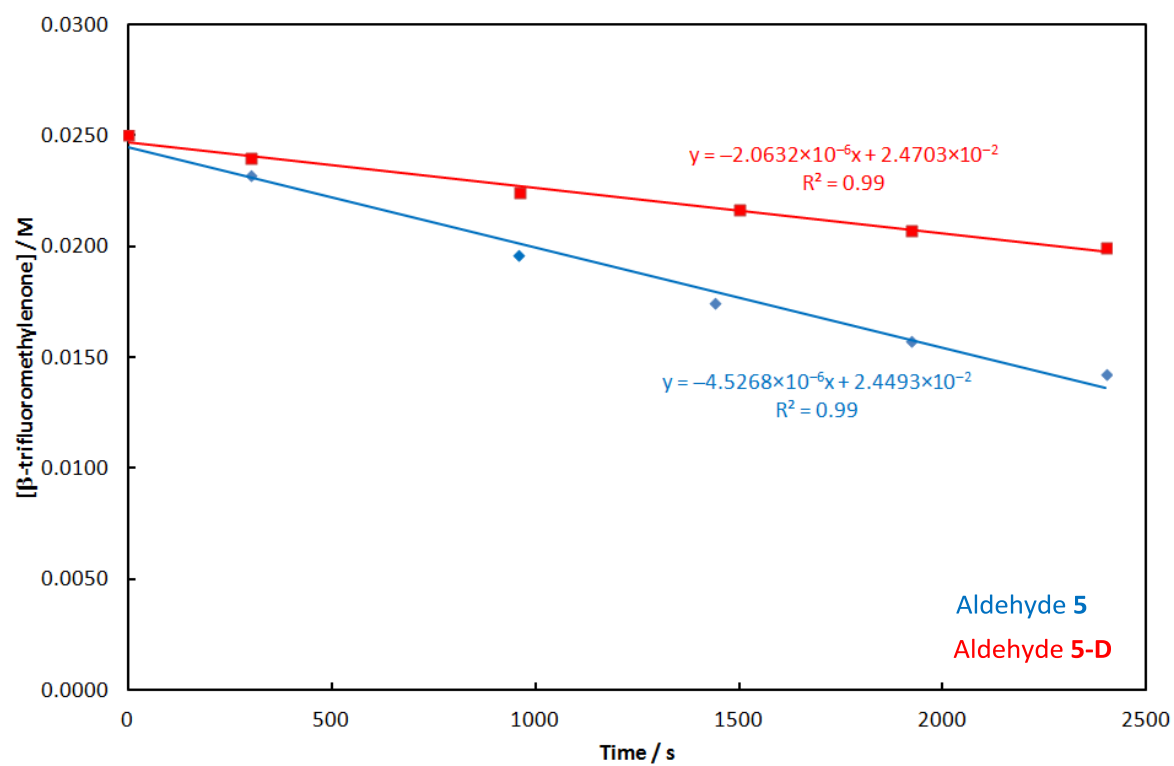
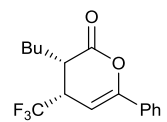


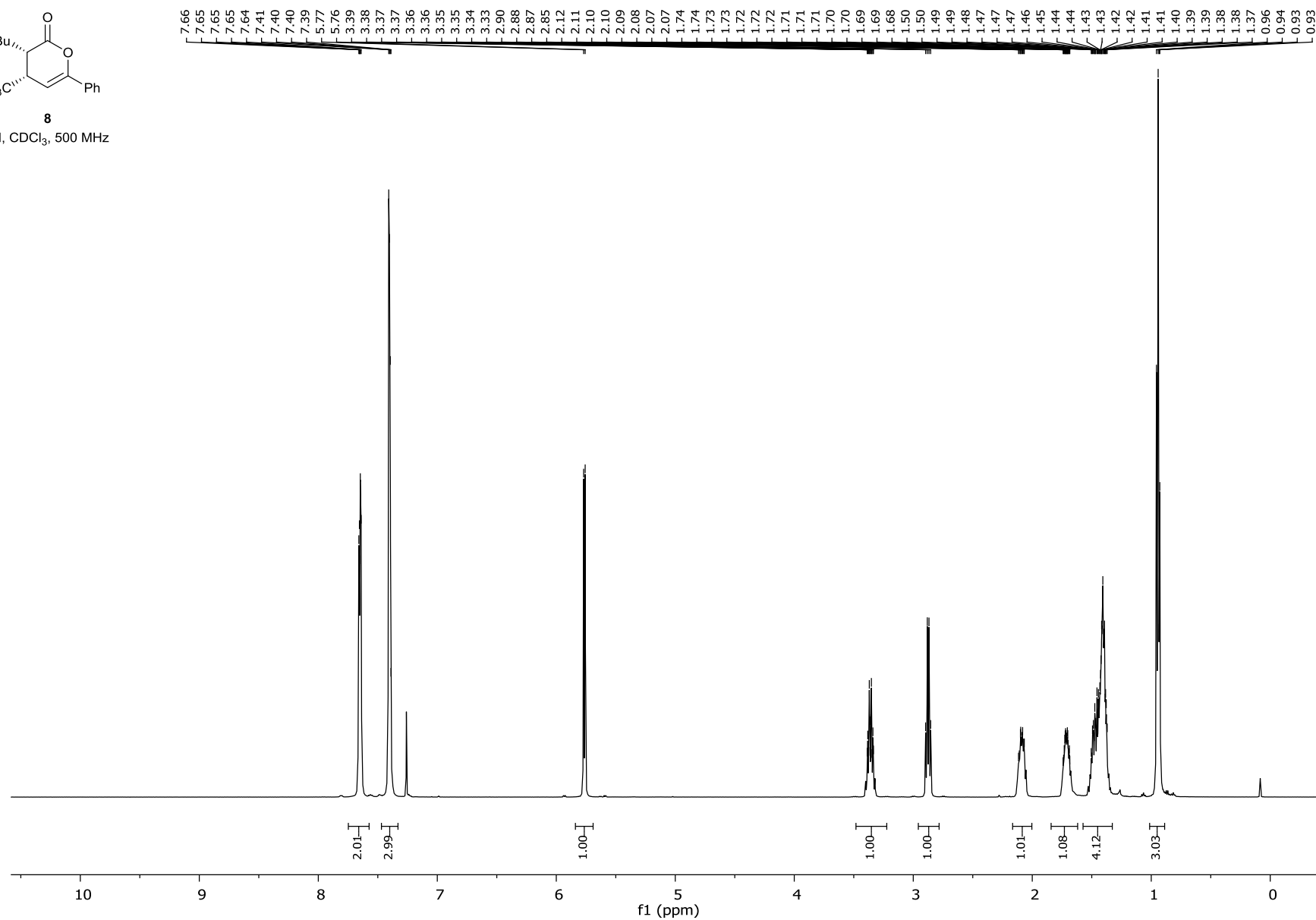
Figure S11: Plot of β -trifluoromethyl enone concentration over time

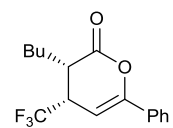




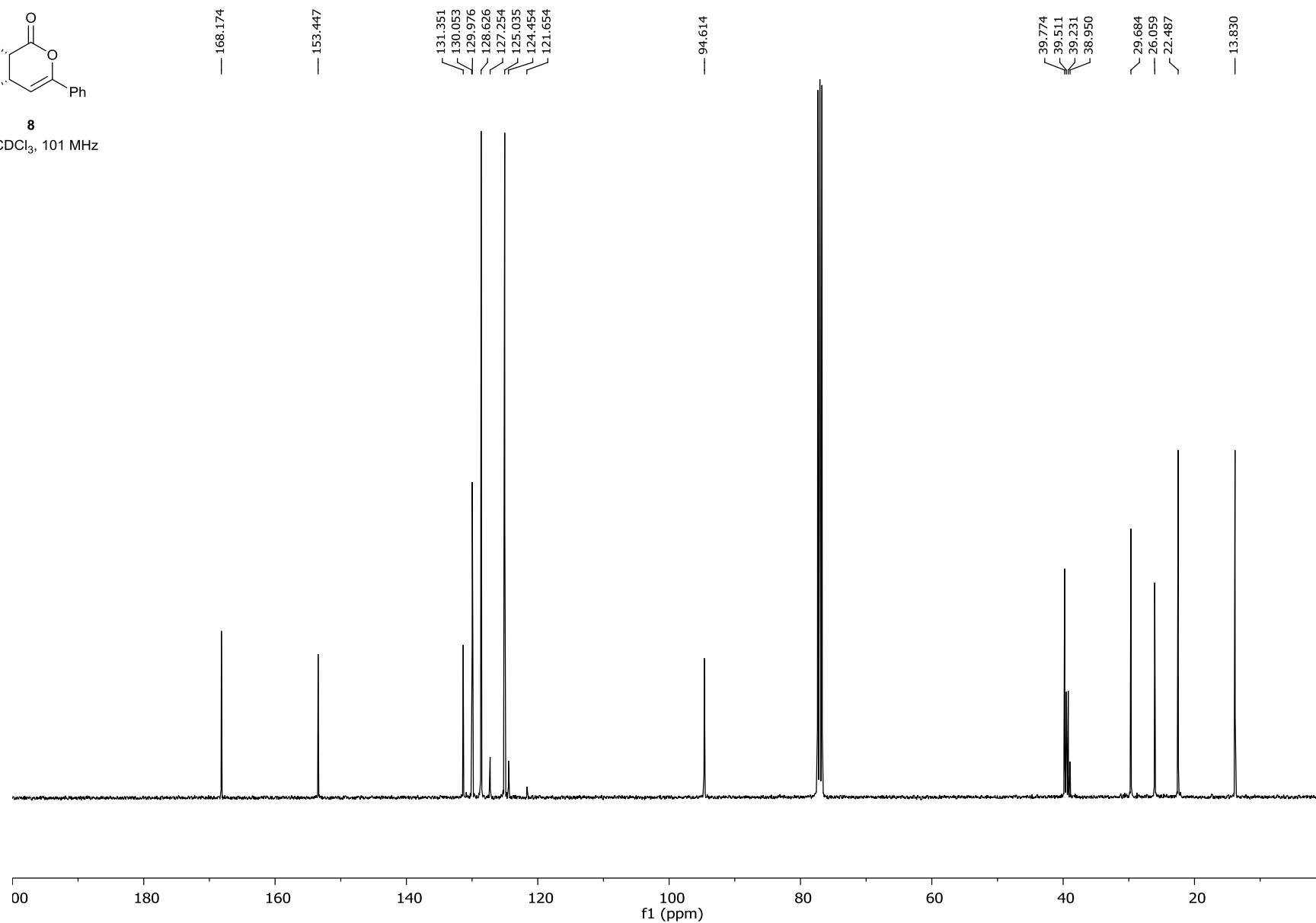
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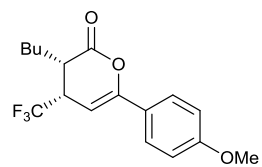
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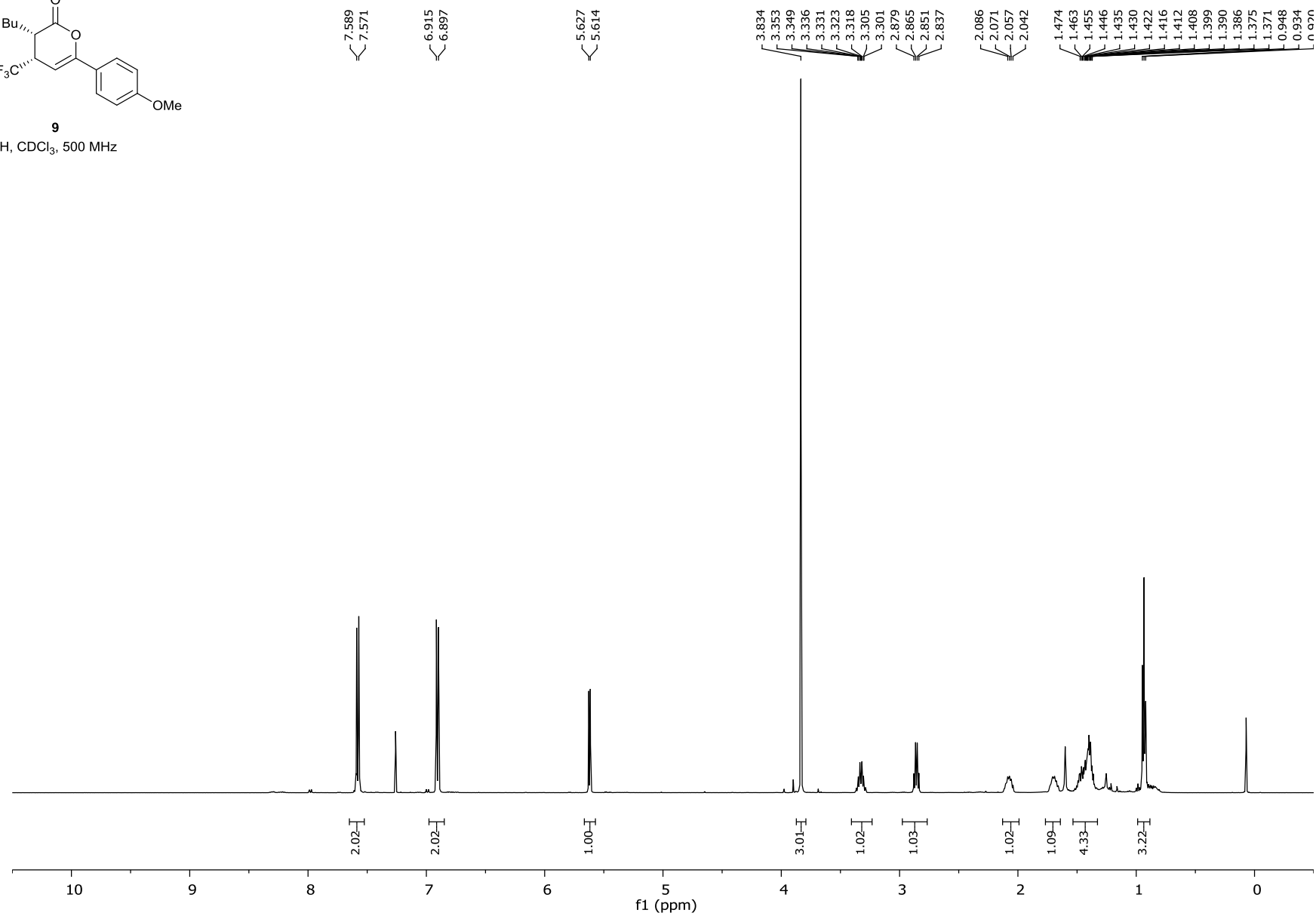


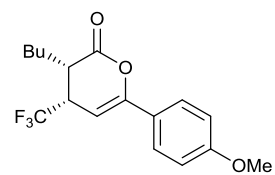
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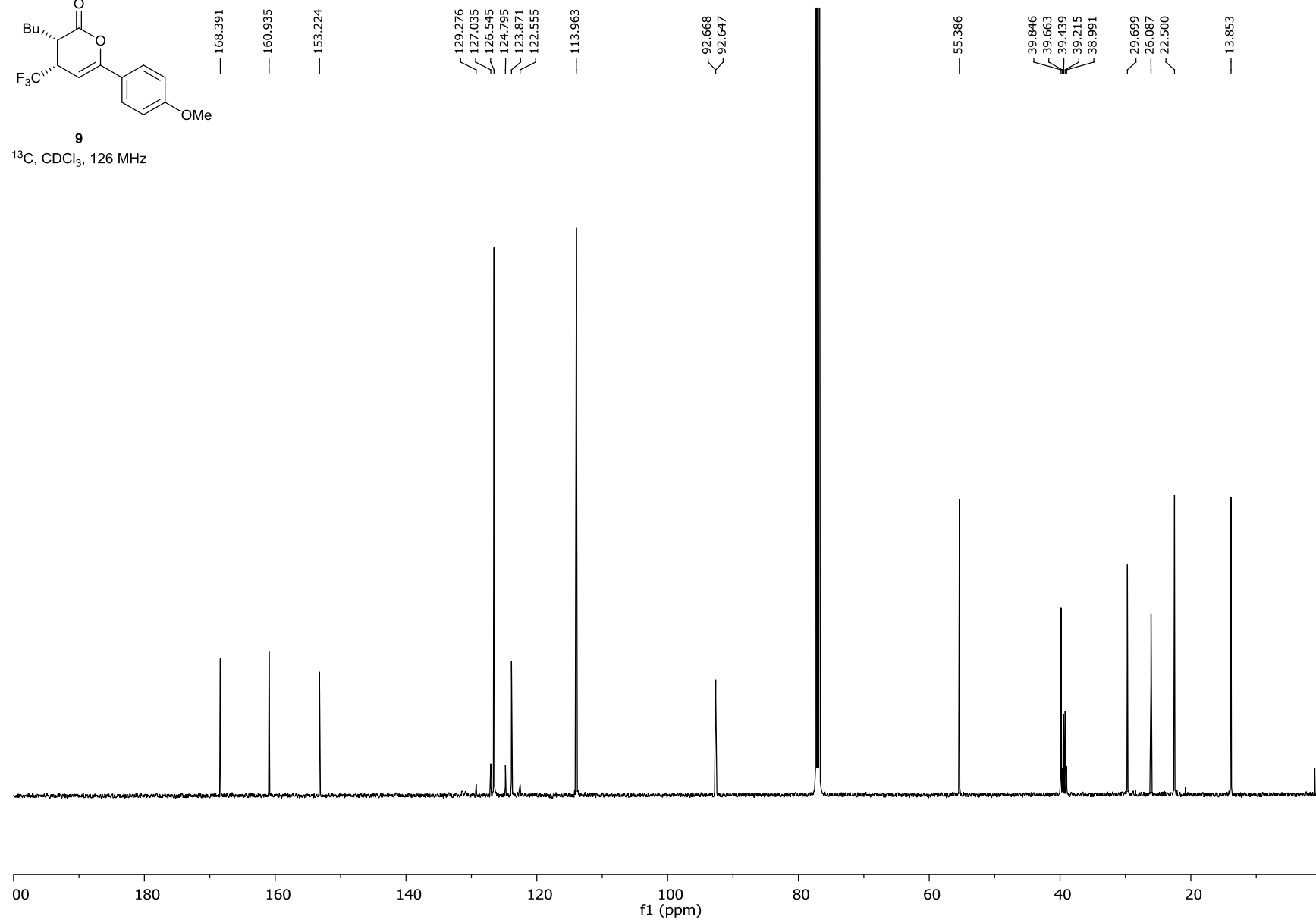
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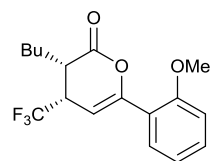




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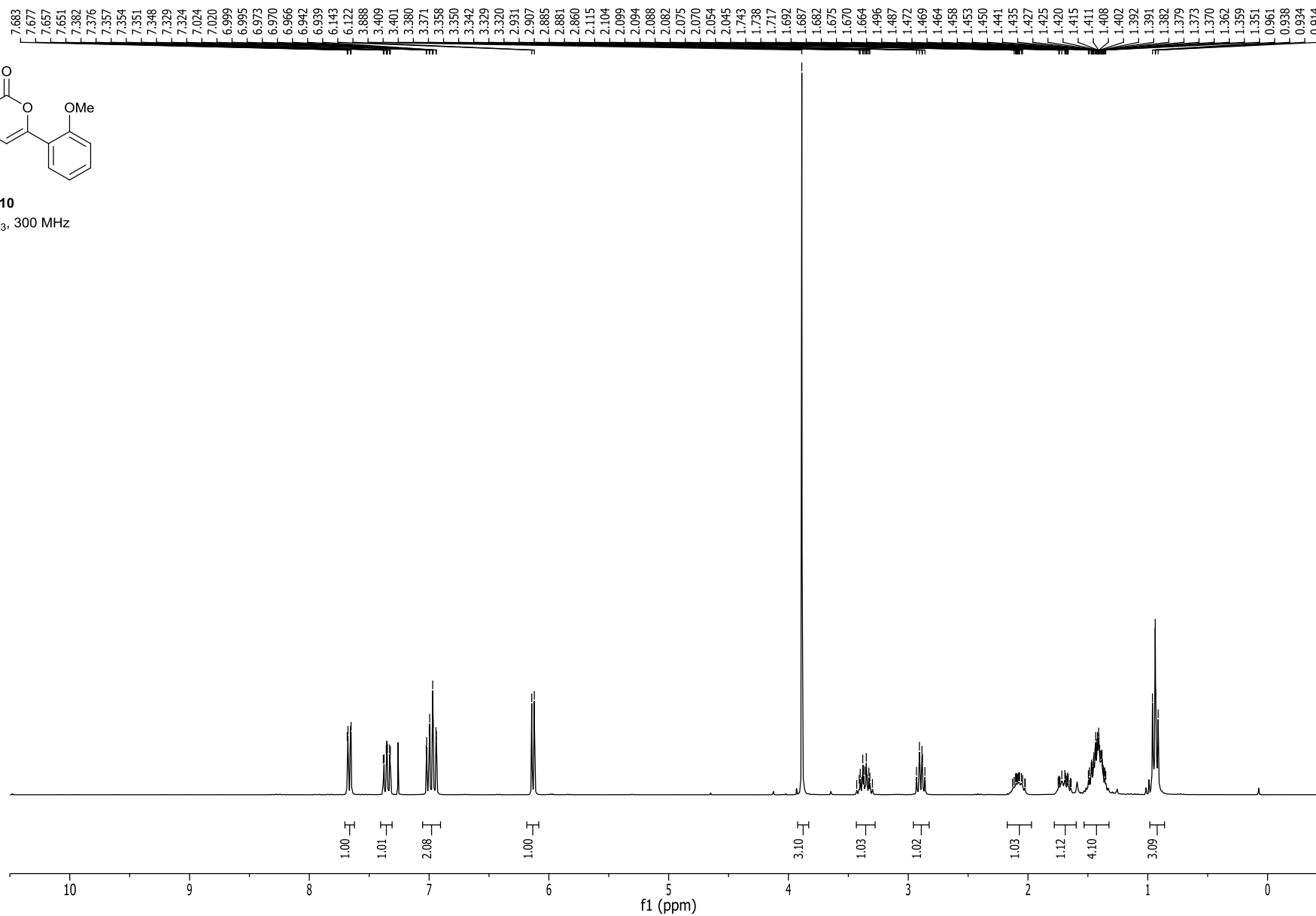
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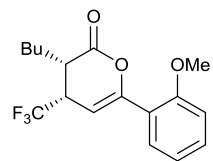




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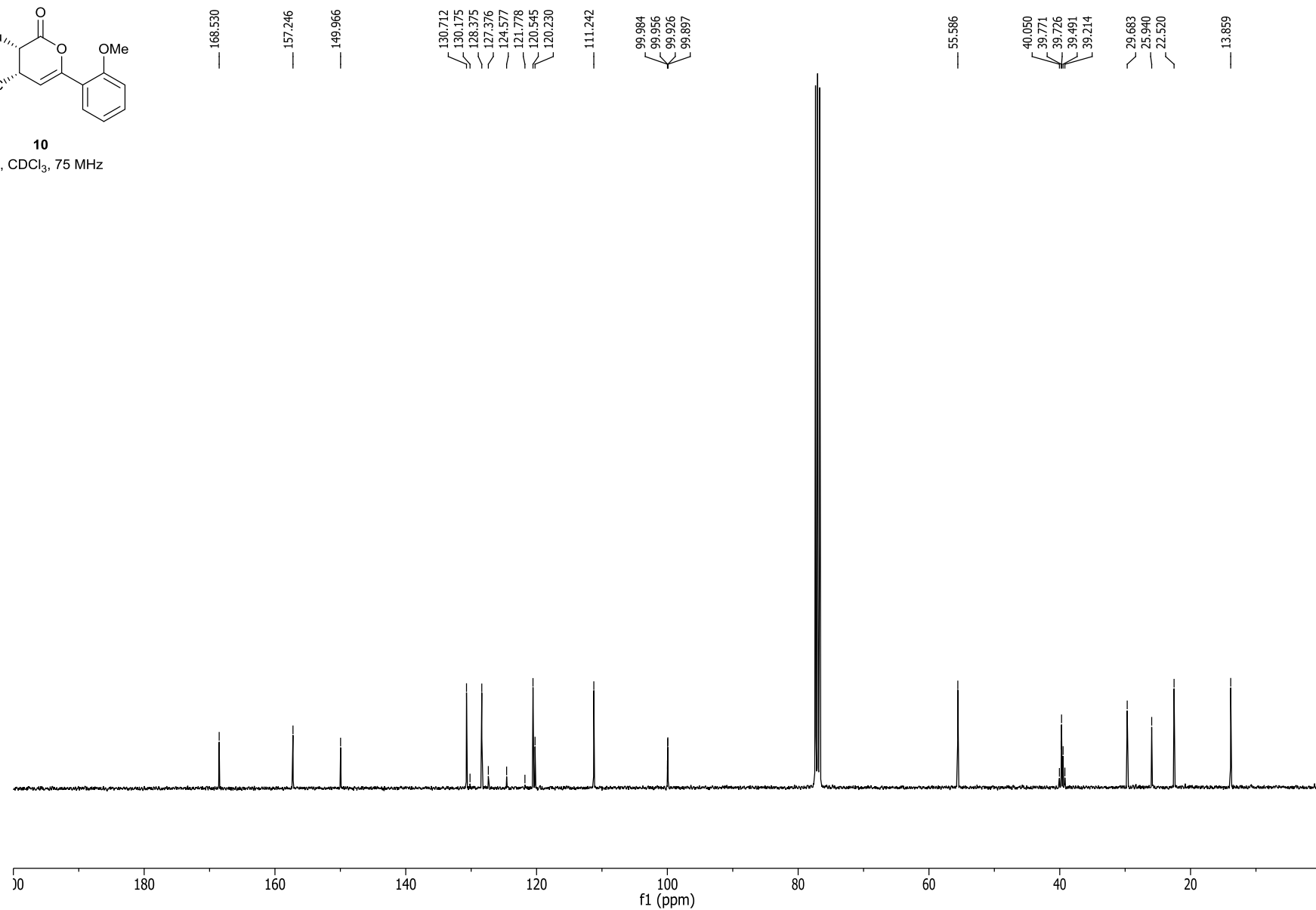
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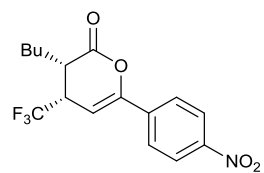




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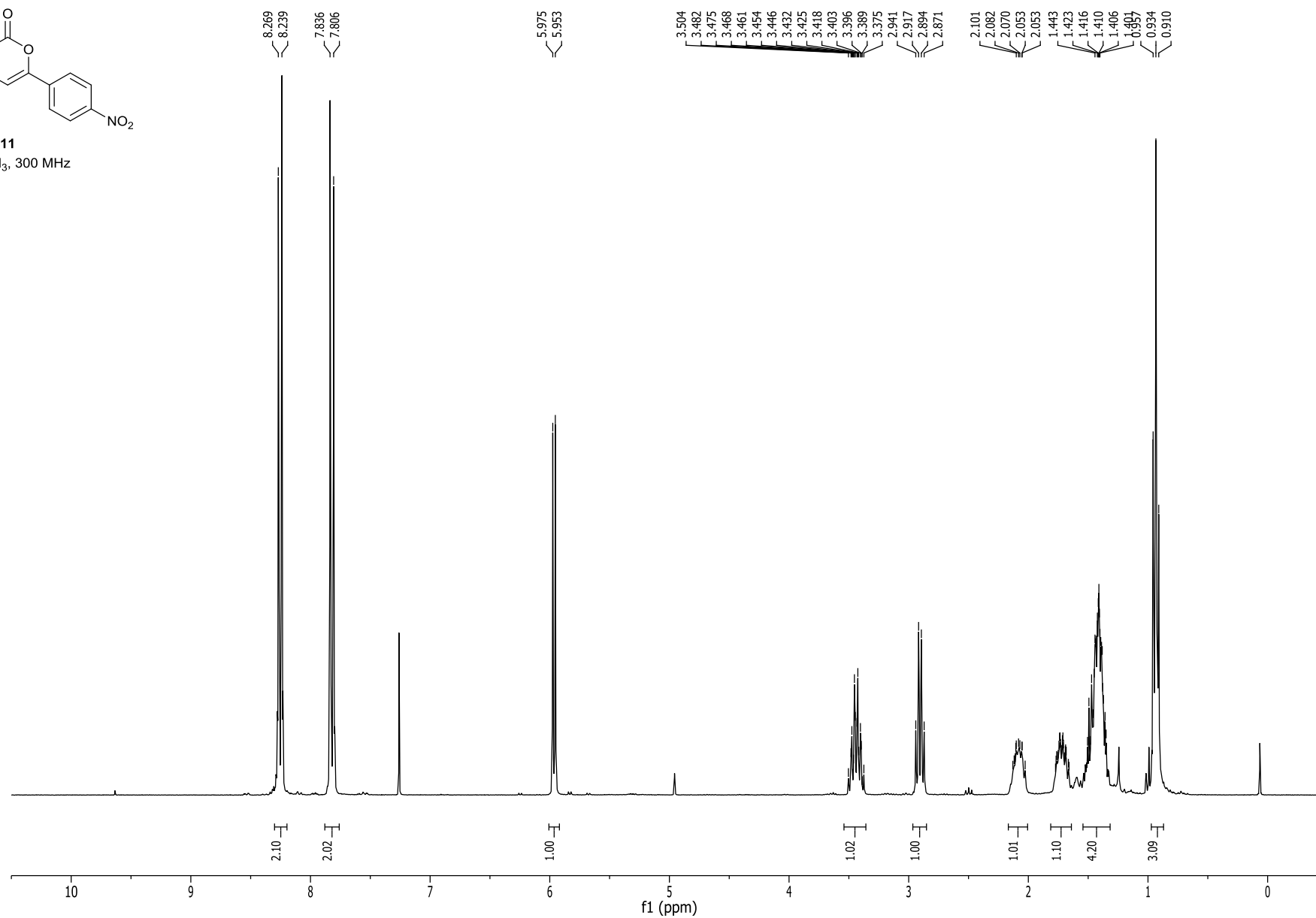
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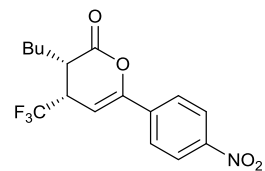




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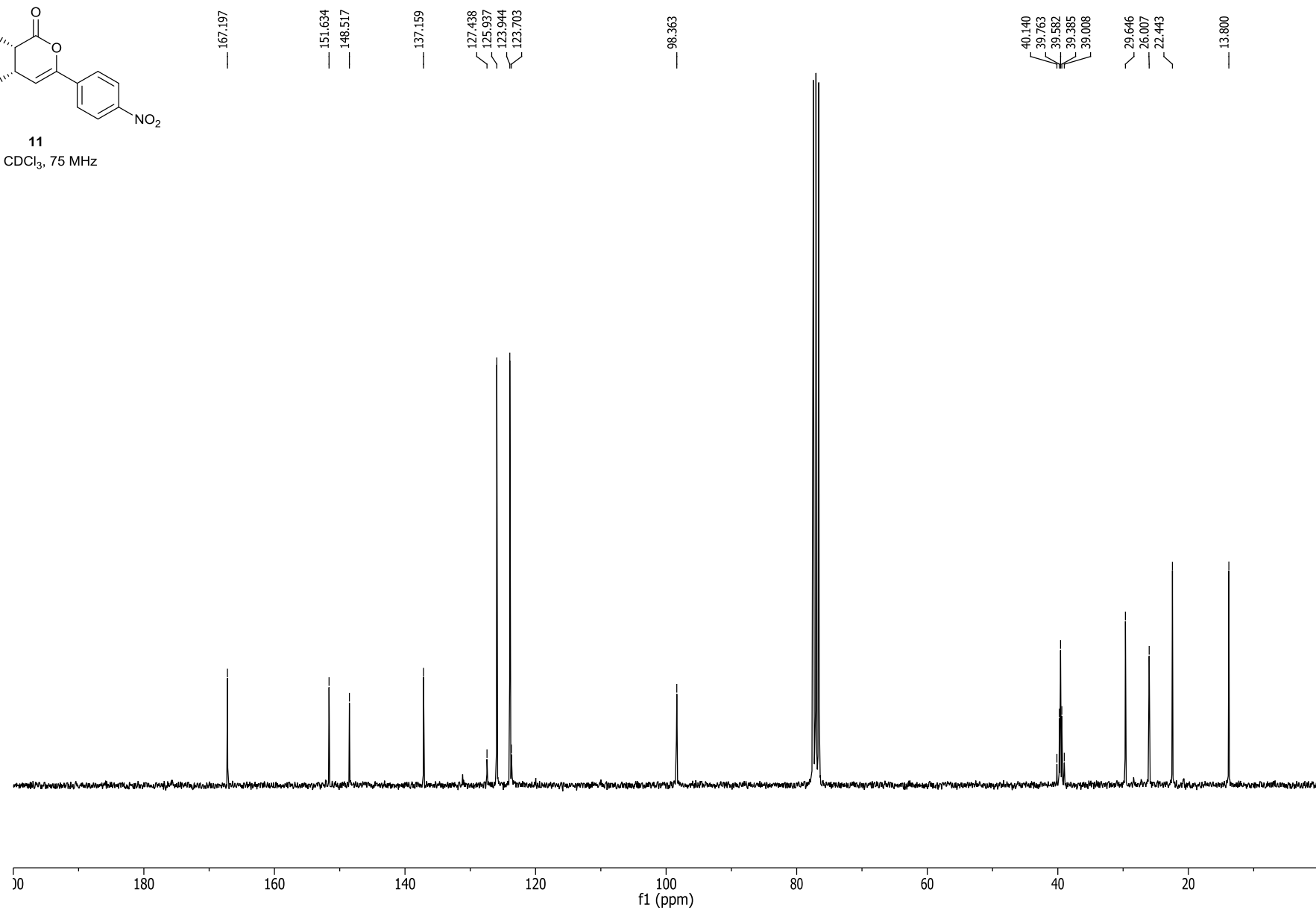
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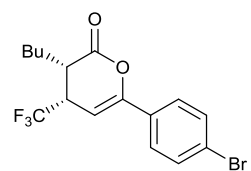




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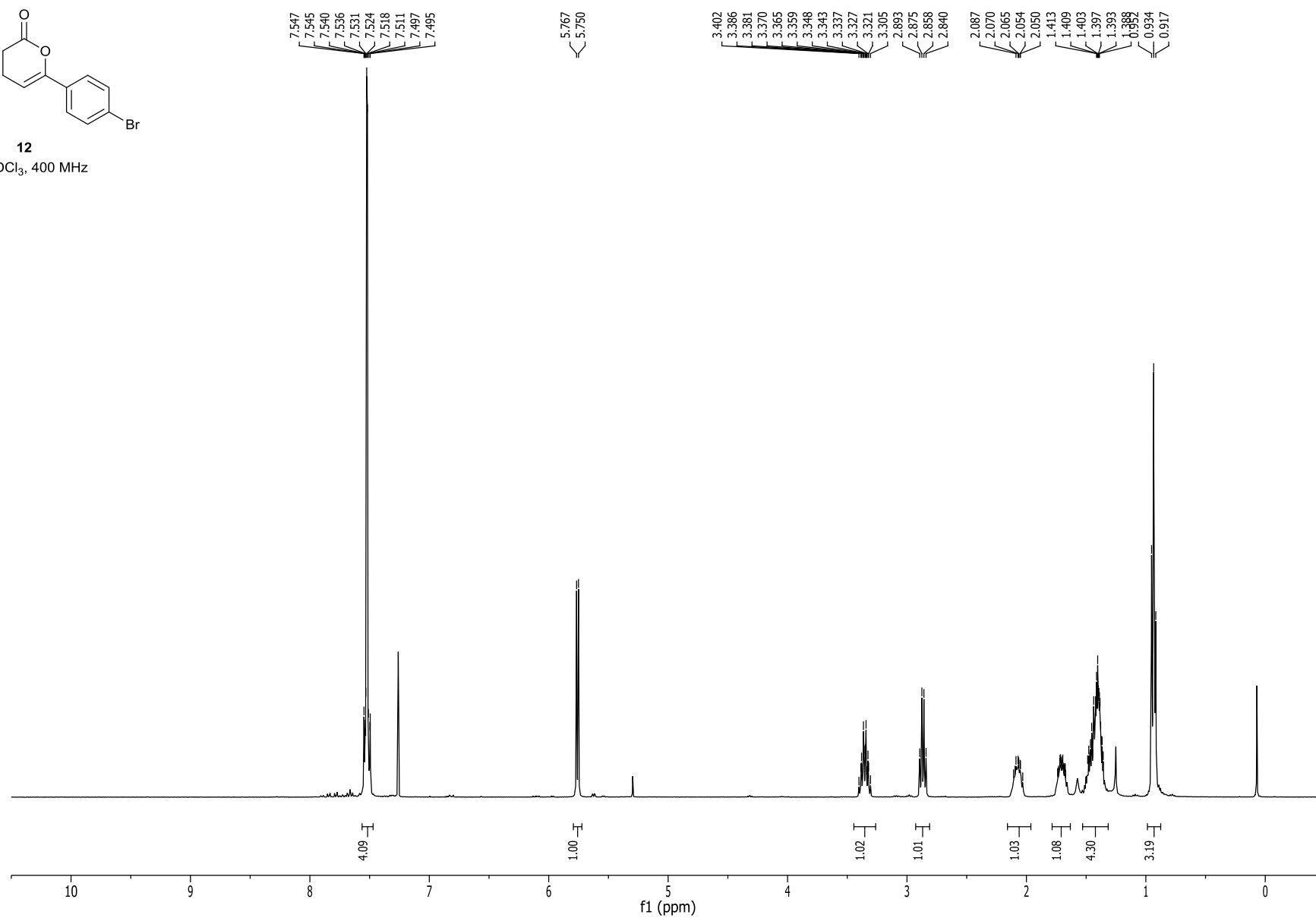
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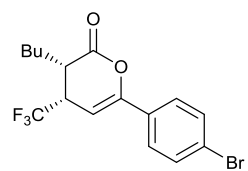




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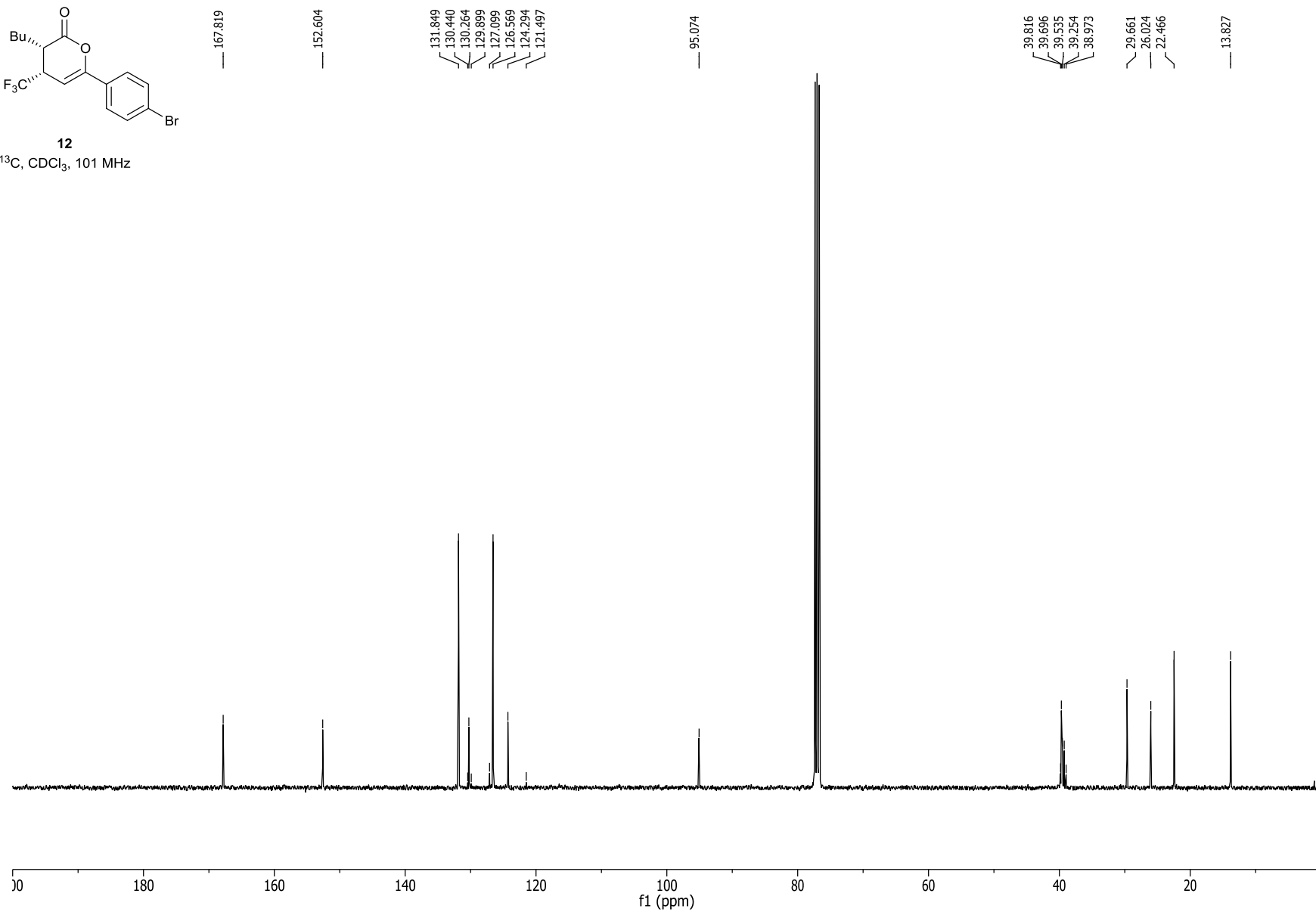
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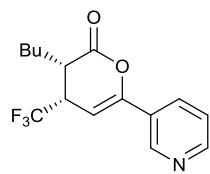




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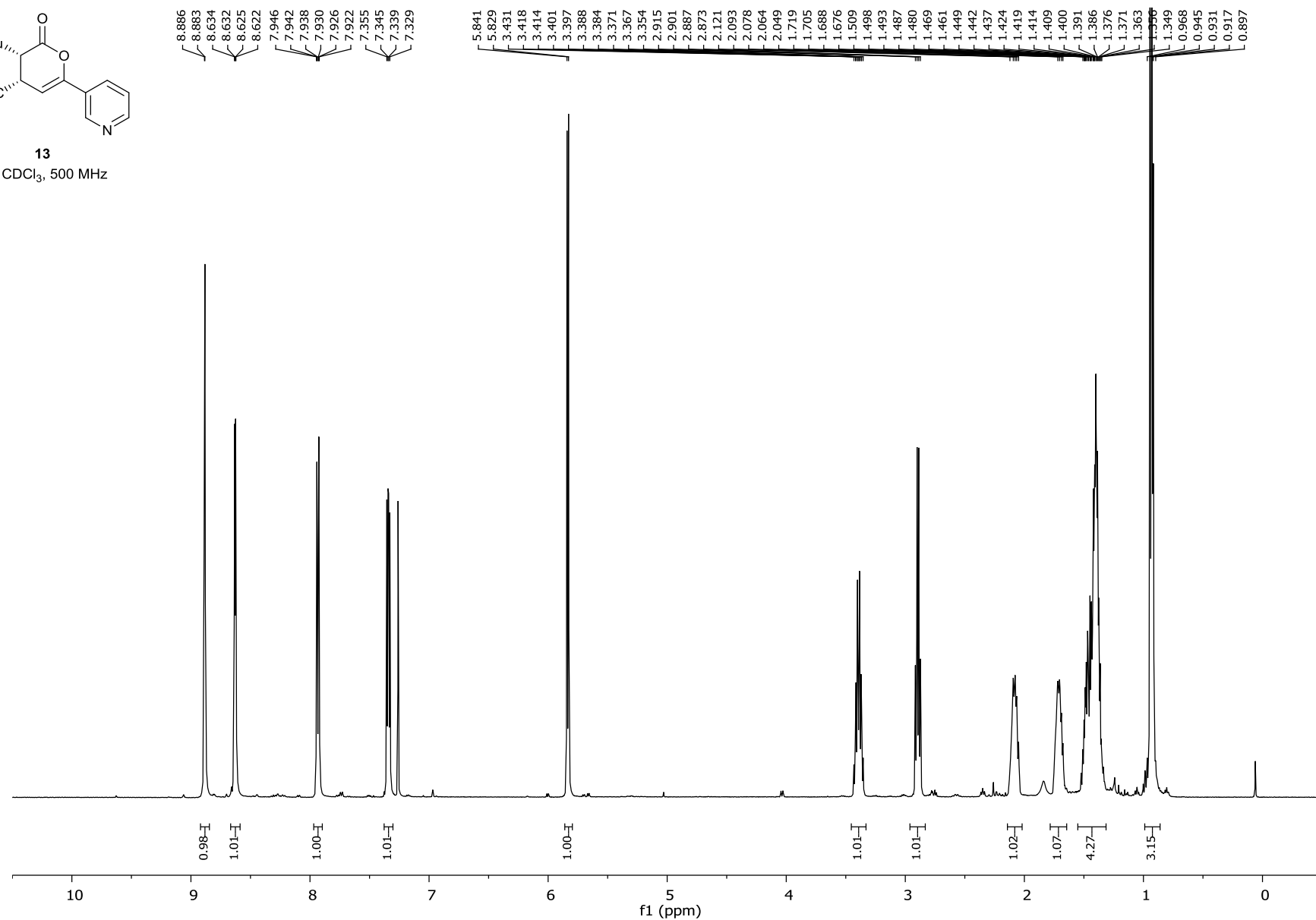
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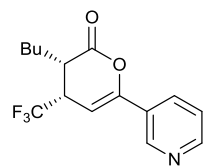




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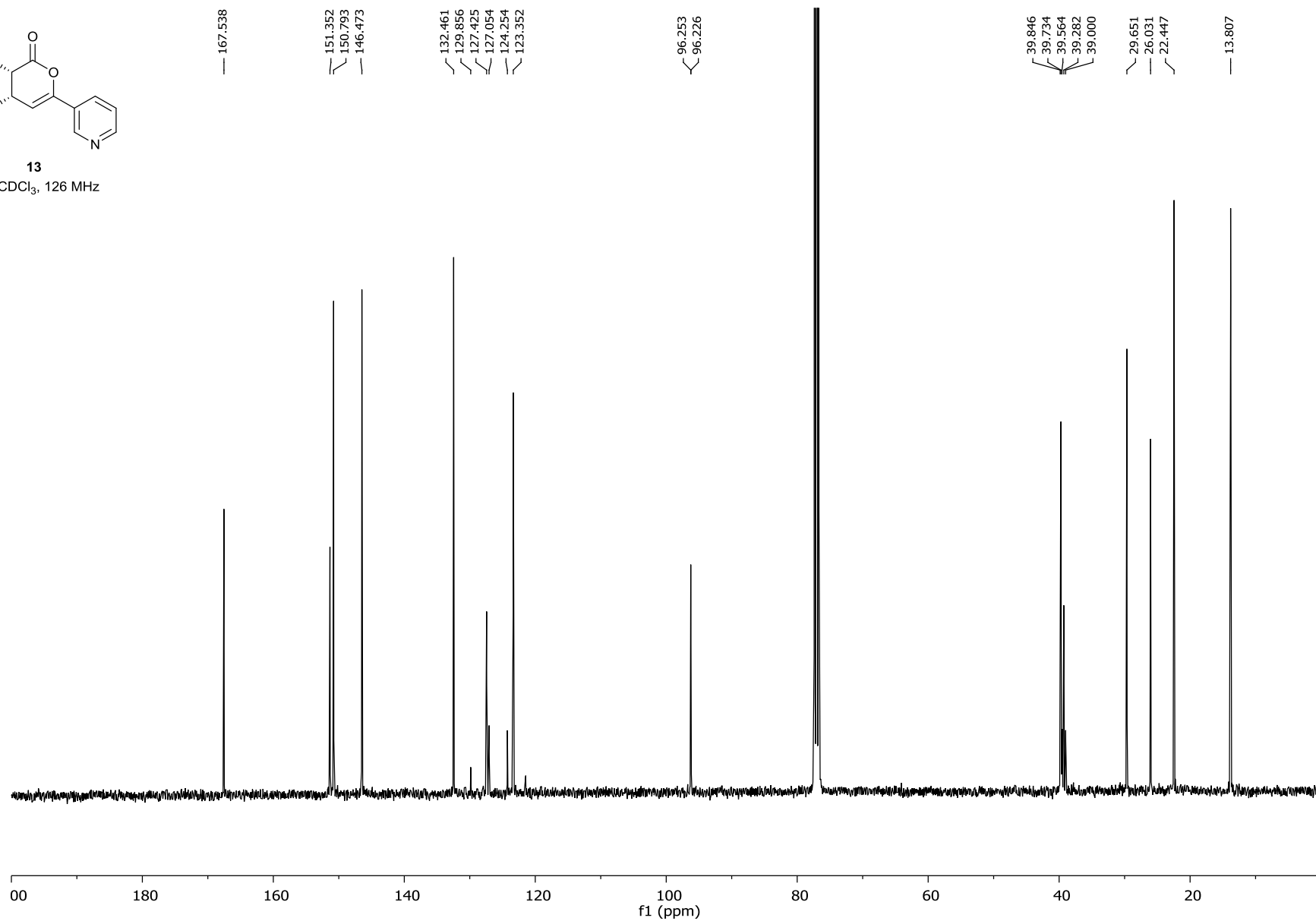
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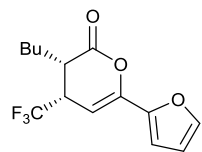




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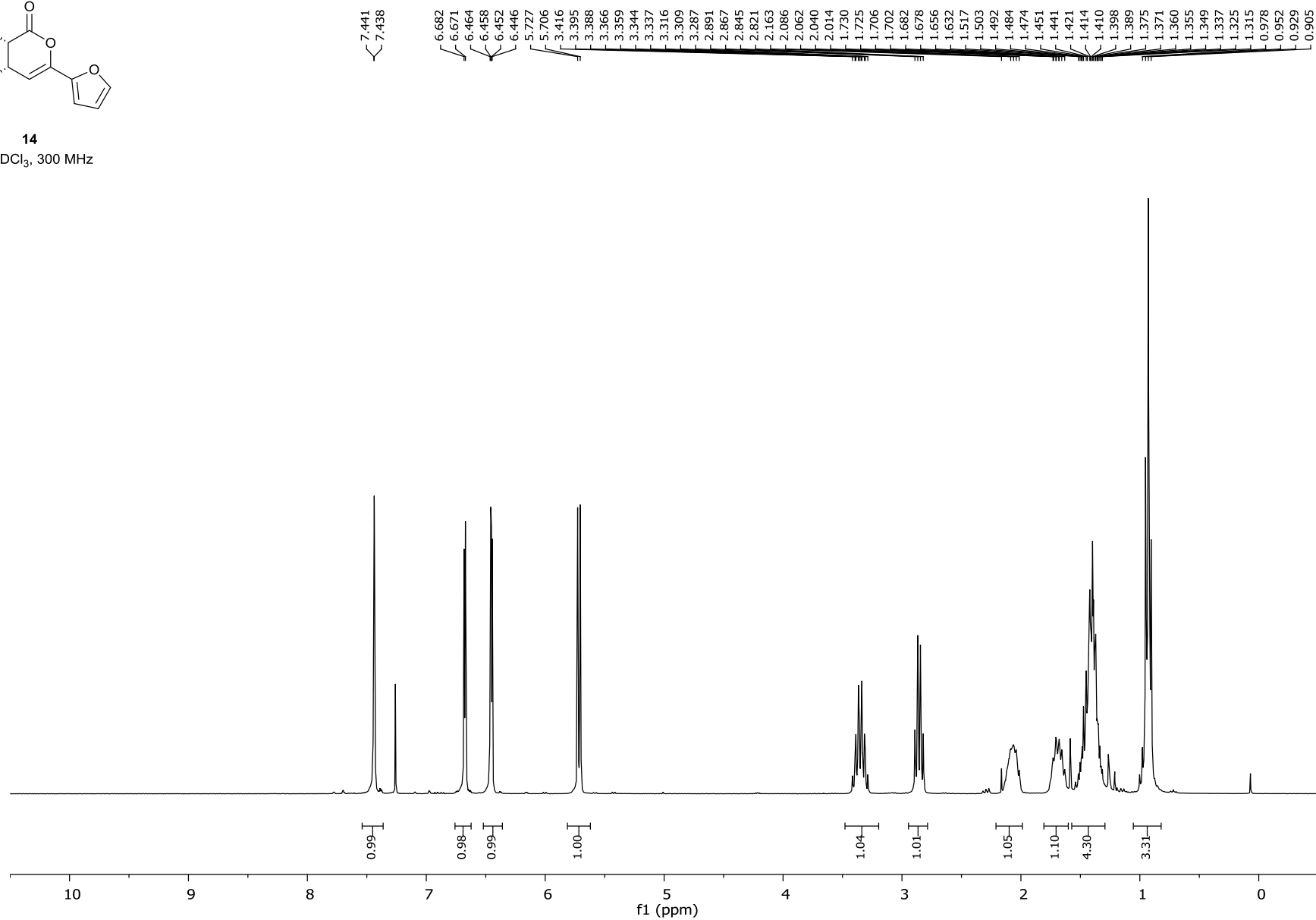
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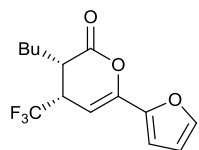




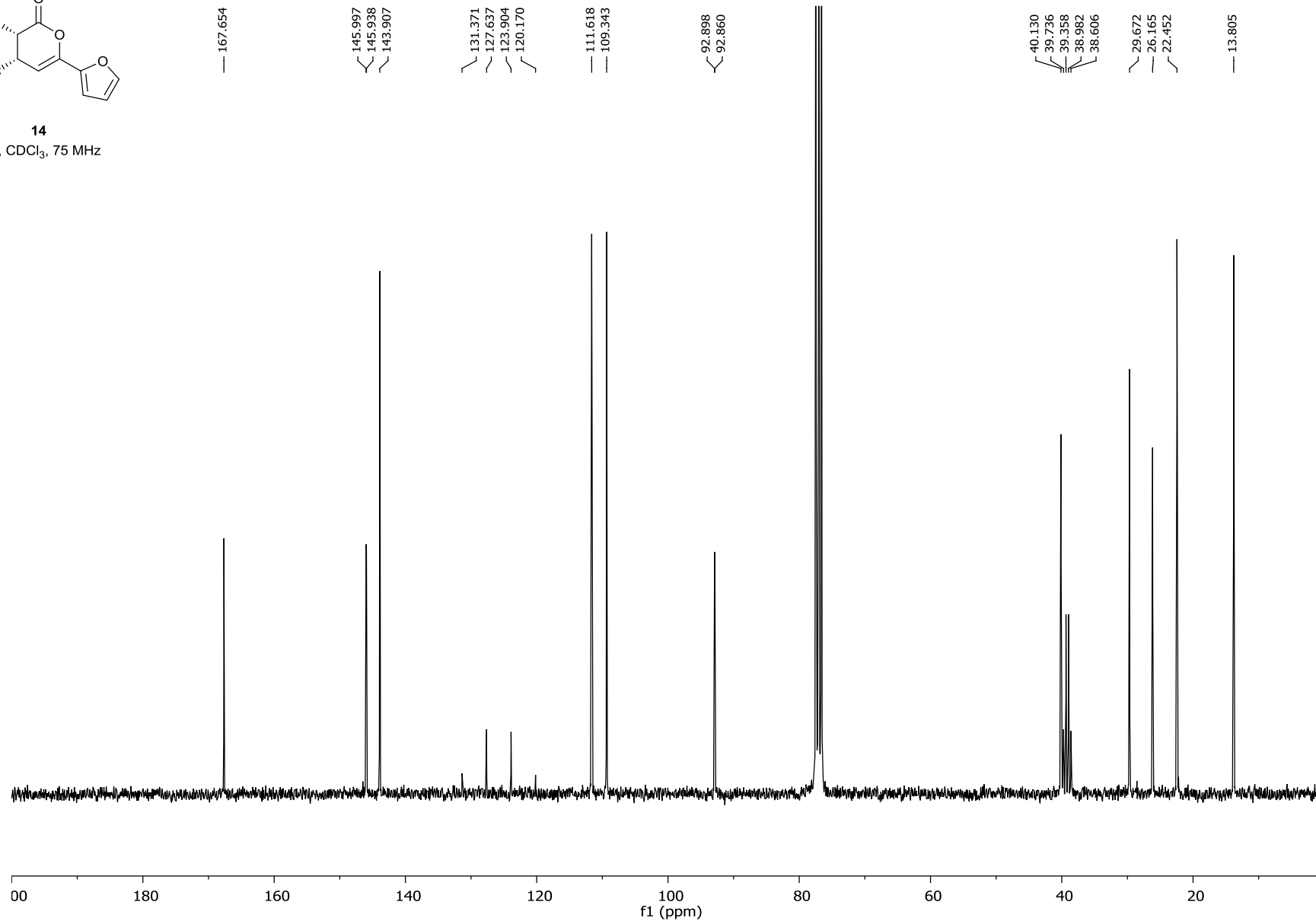
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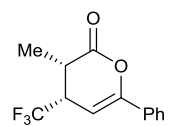
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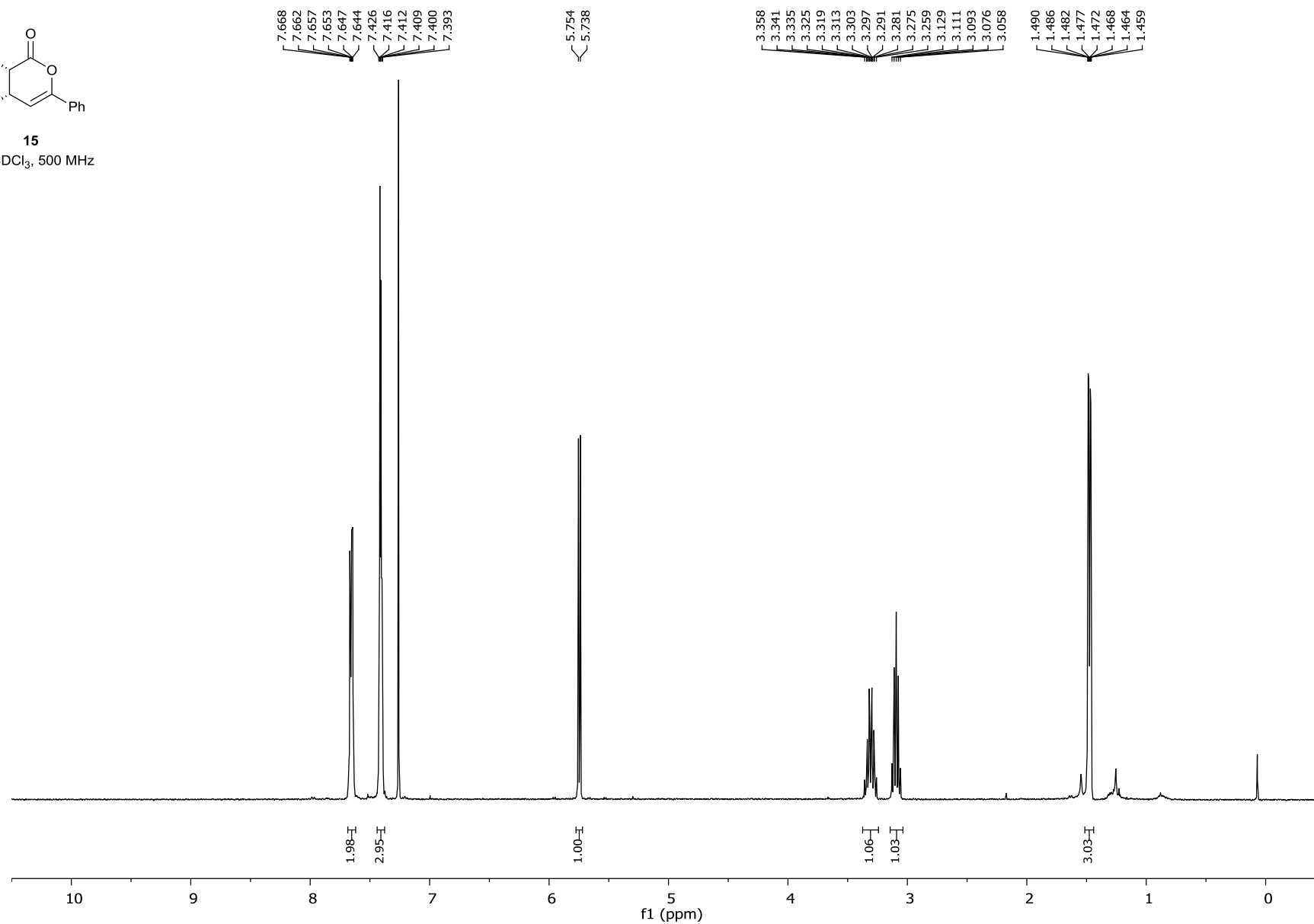
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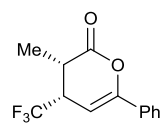




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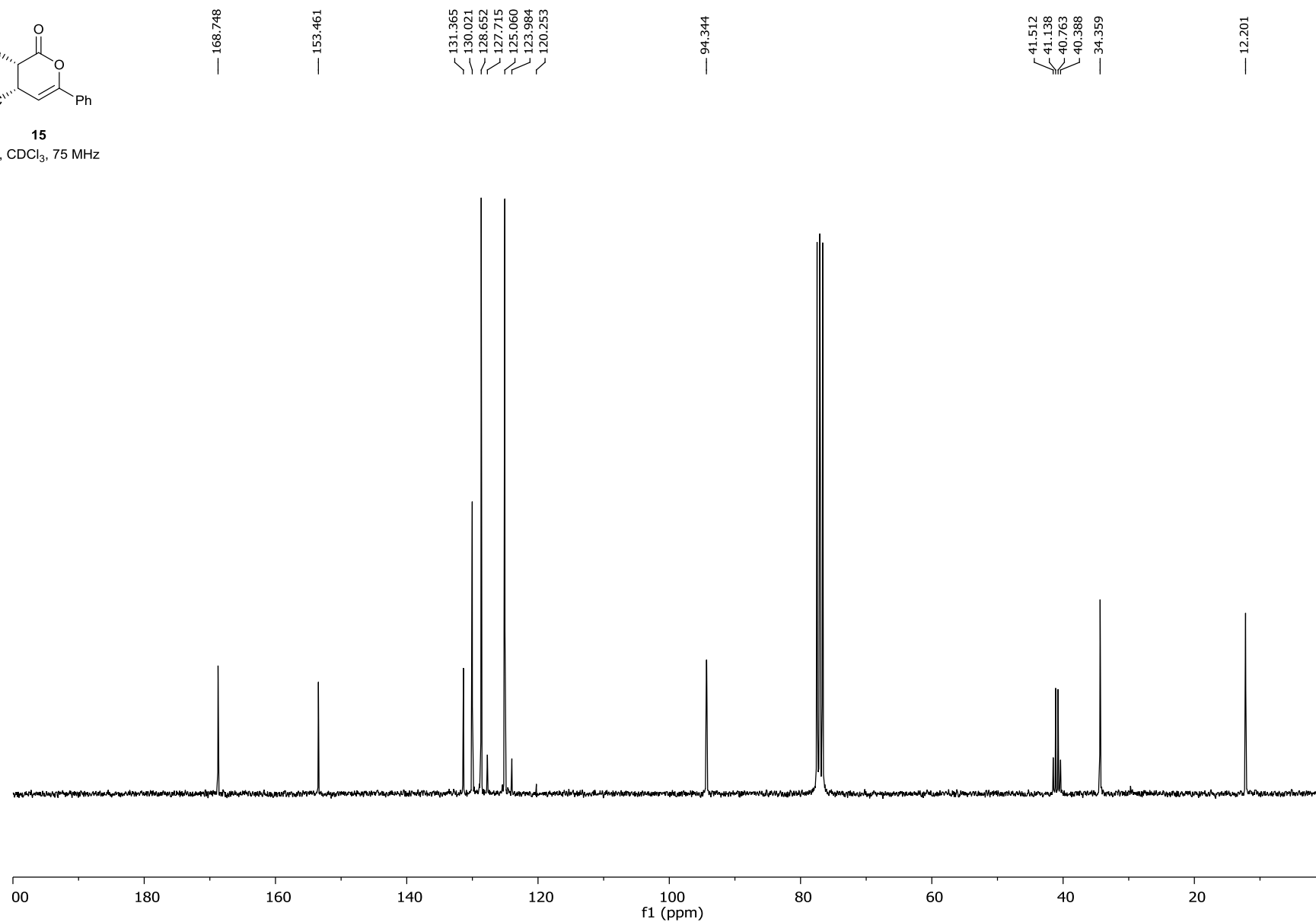
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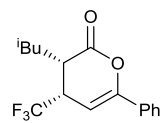




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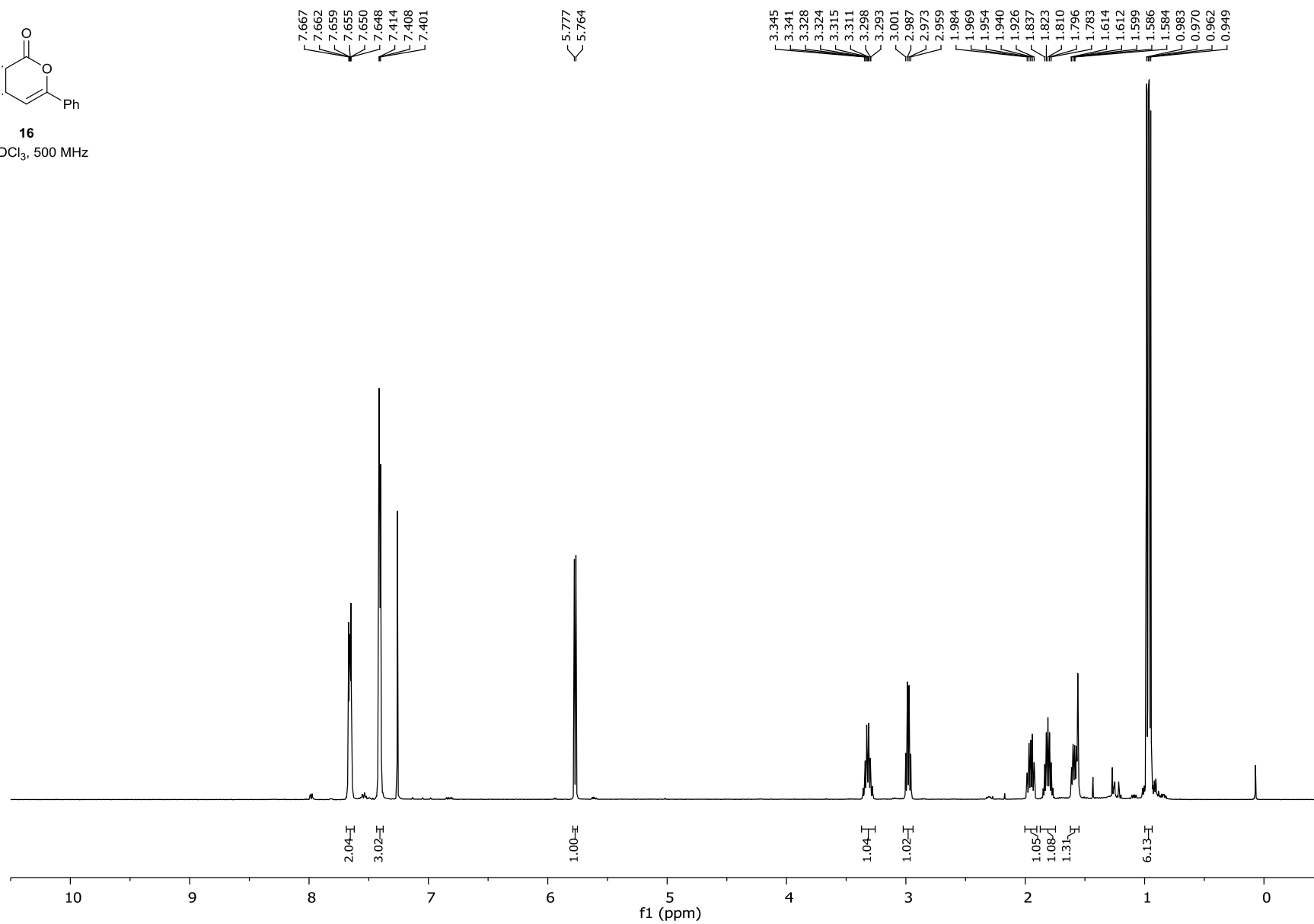
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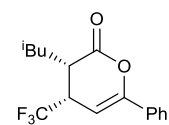




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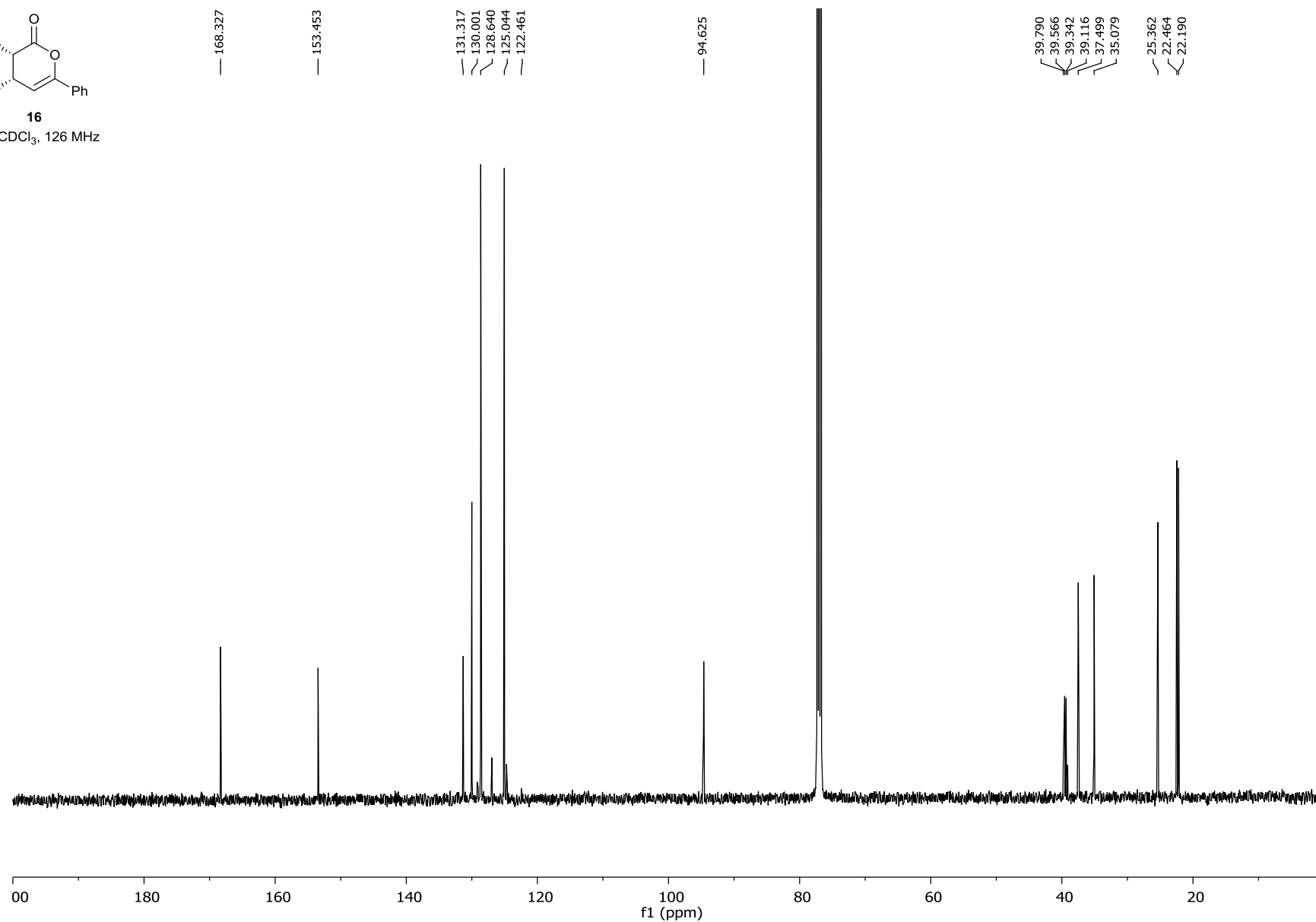
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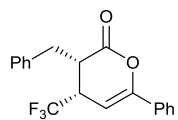




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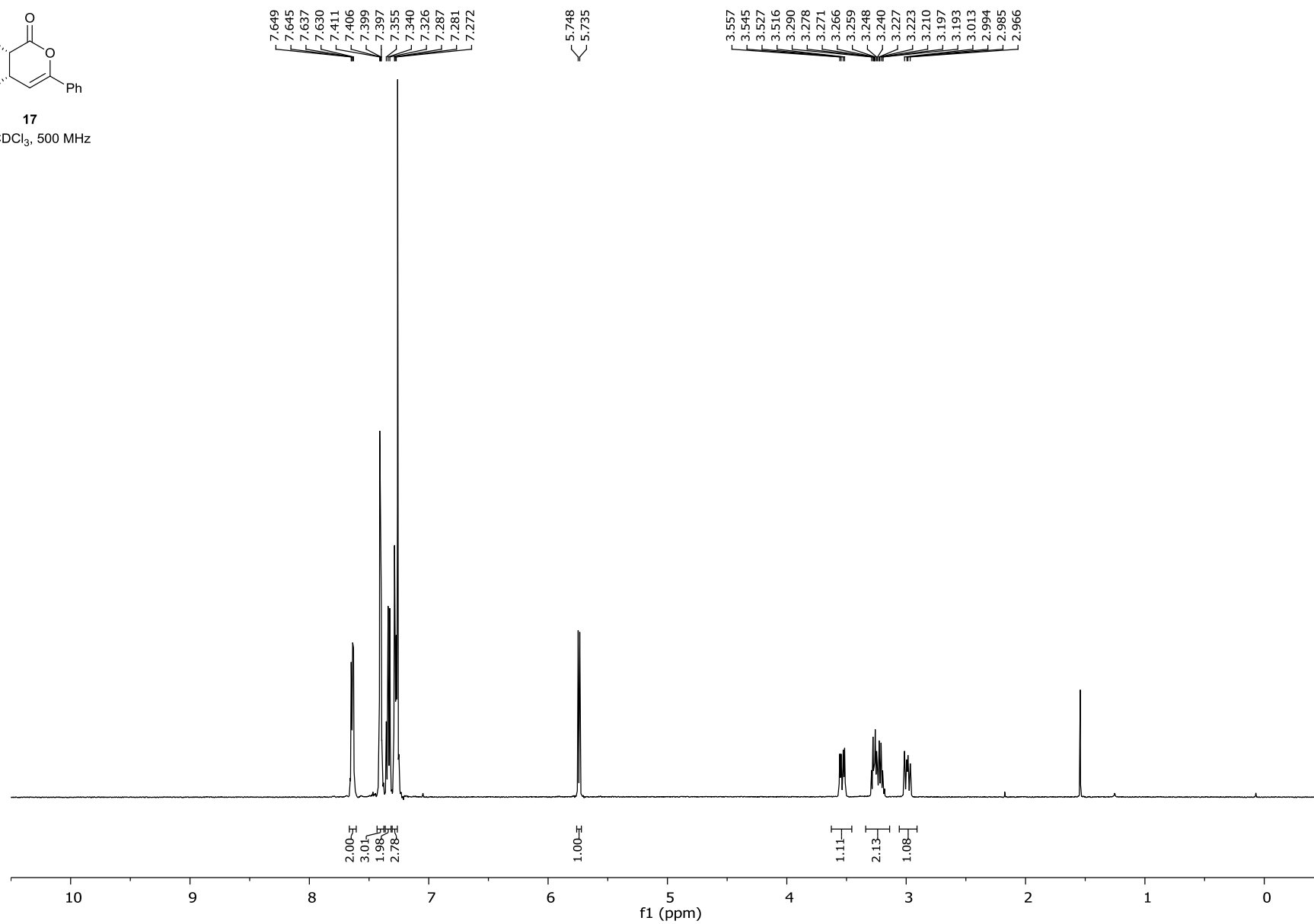
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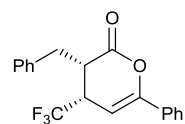




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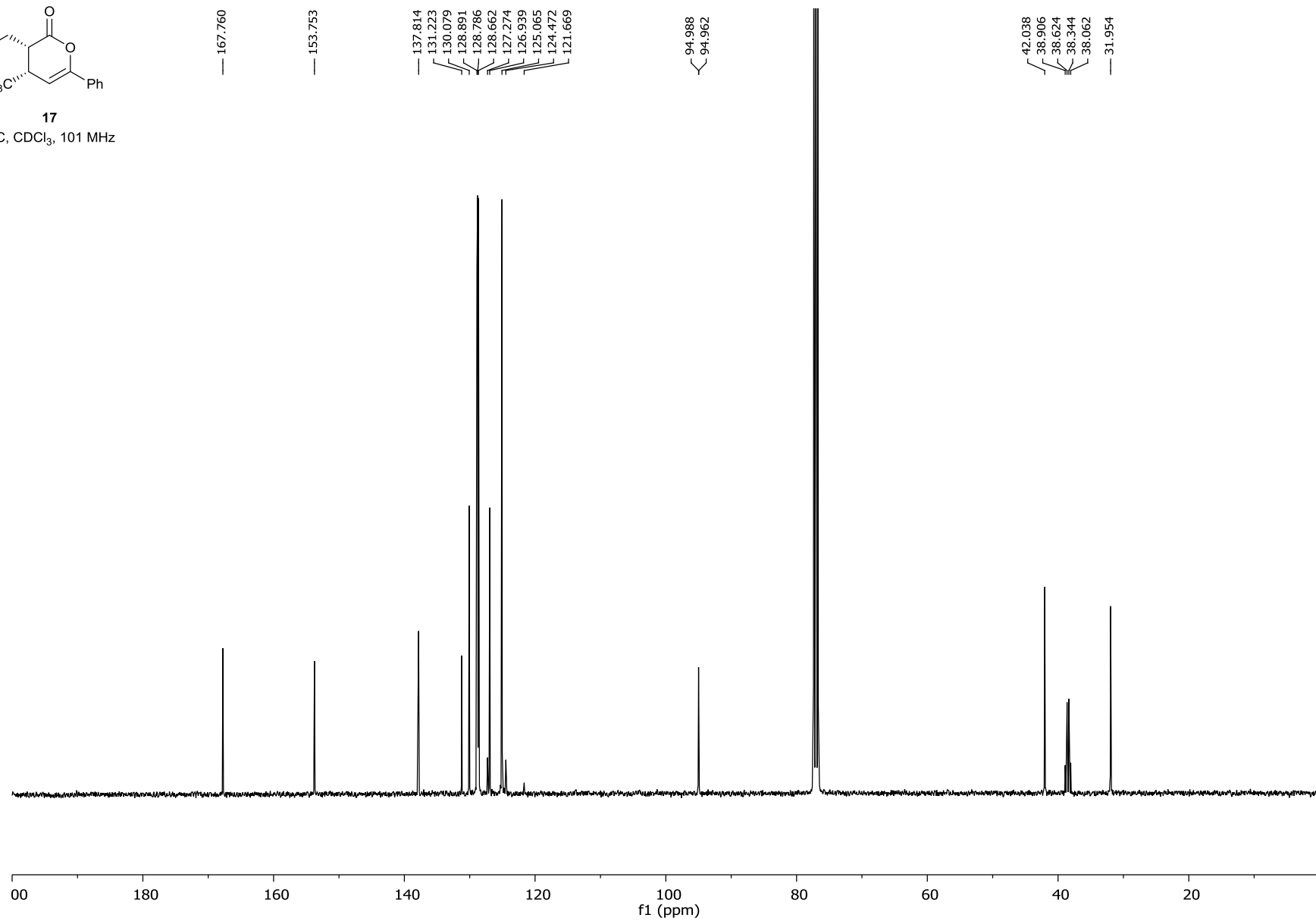
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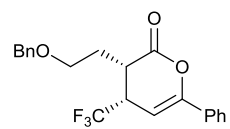




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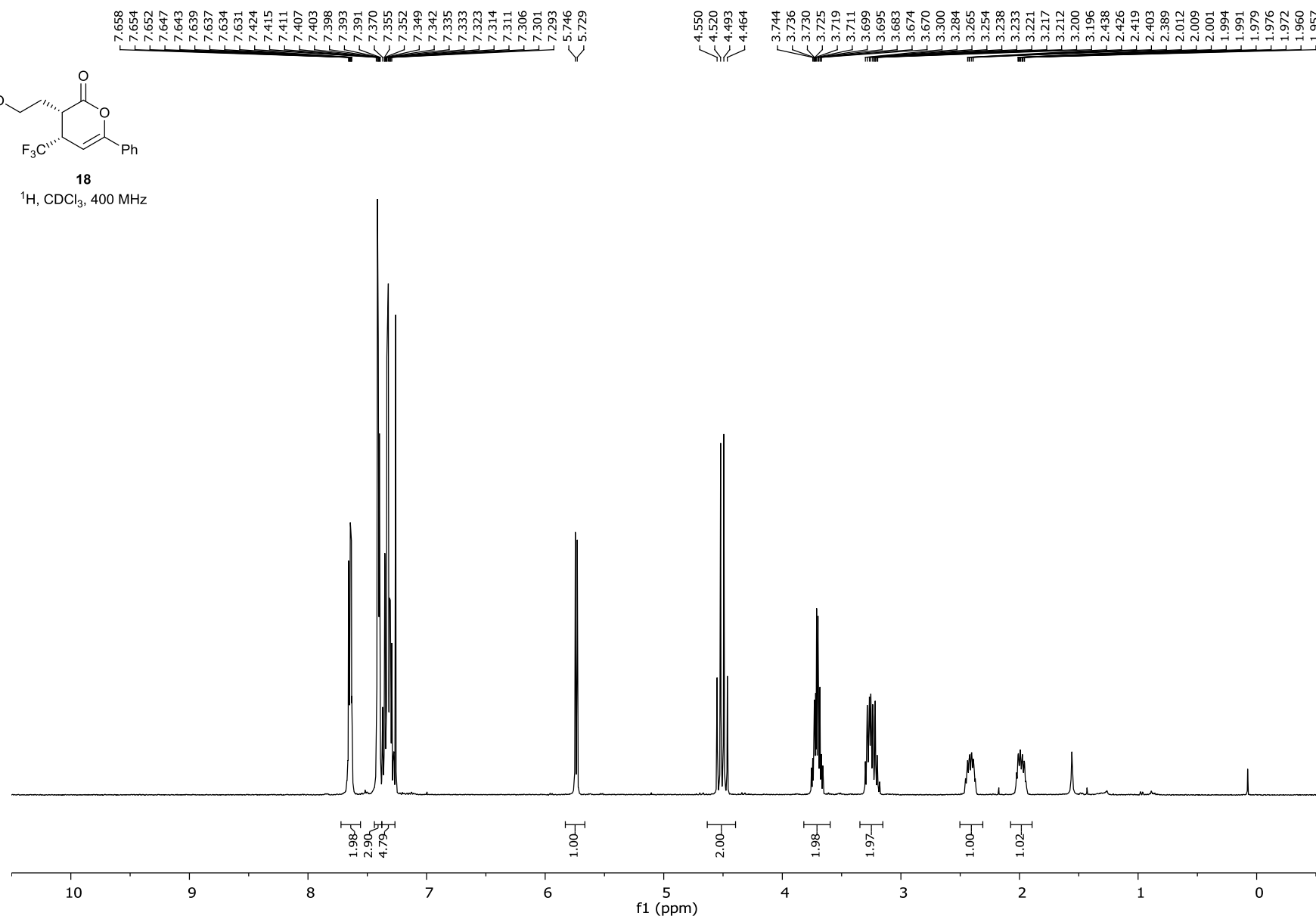
^{13}C , CDCl_3 , 101 MHz

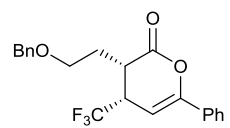




18

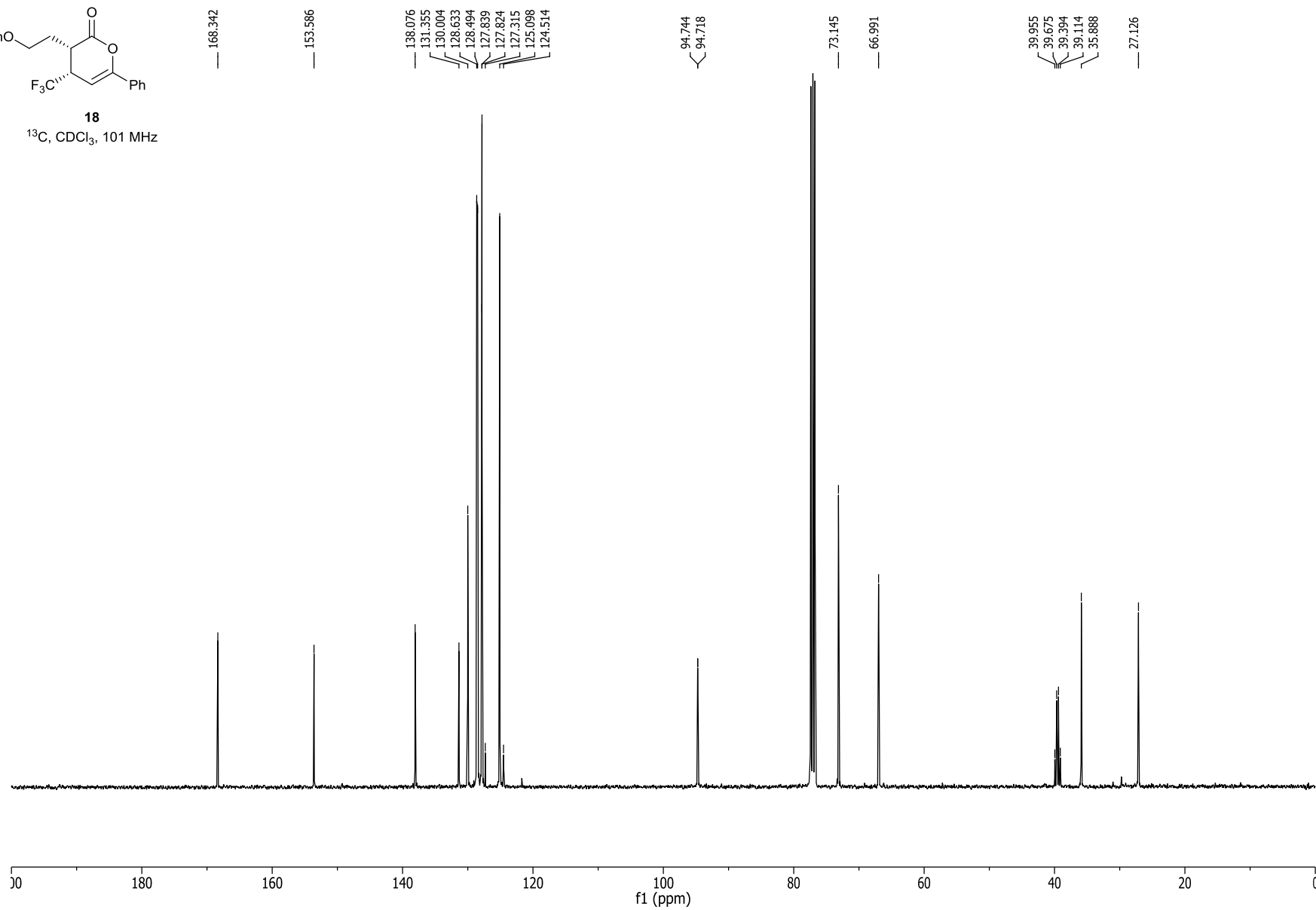
^1H , CDCl_3 , 400 MHz

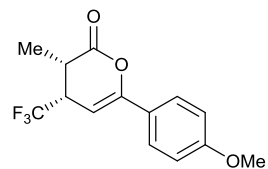




18

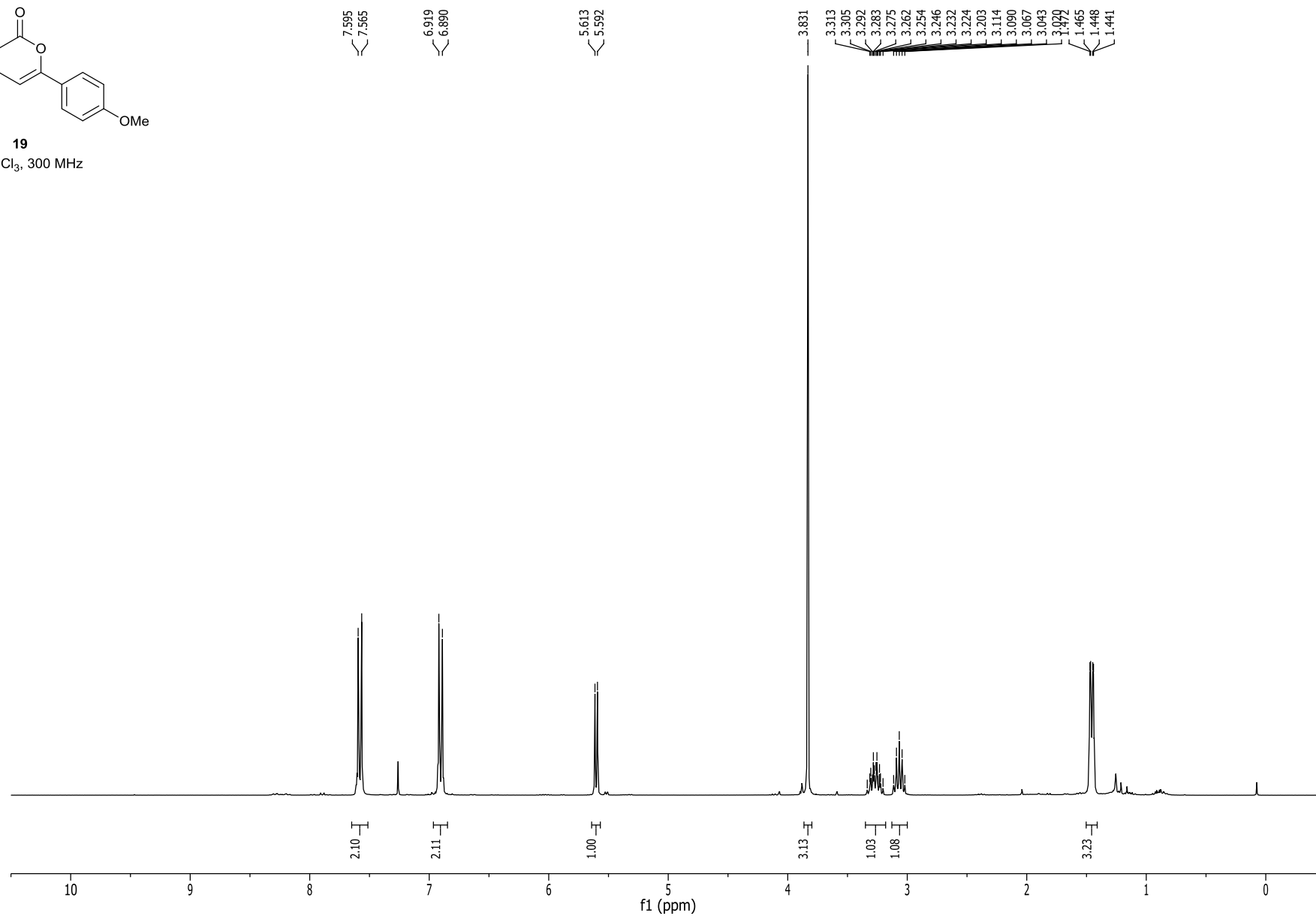
^{13}C , CDCl_3 , 101 MHz

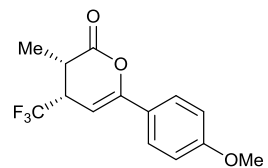




19

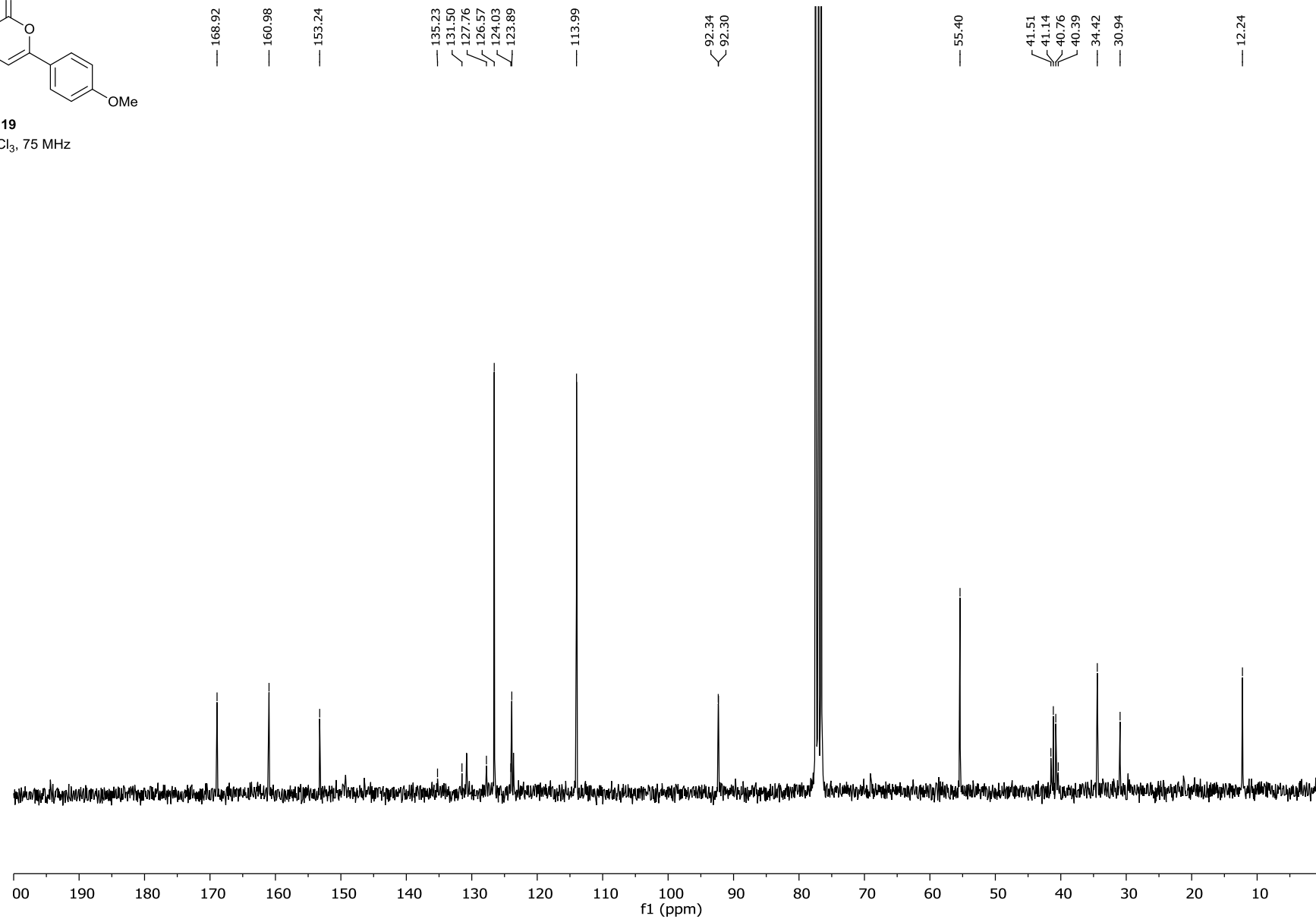
¹H, CDCl₃, 300 MHz

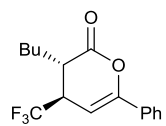




19

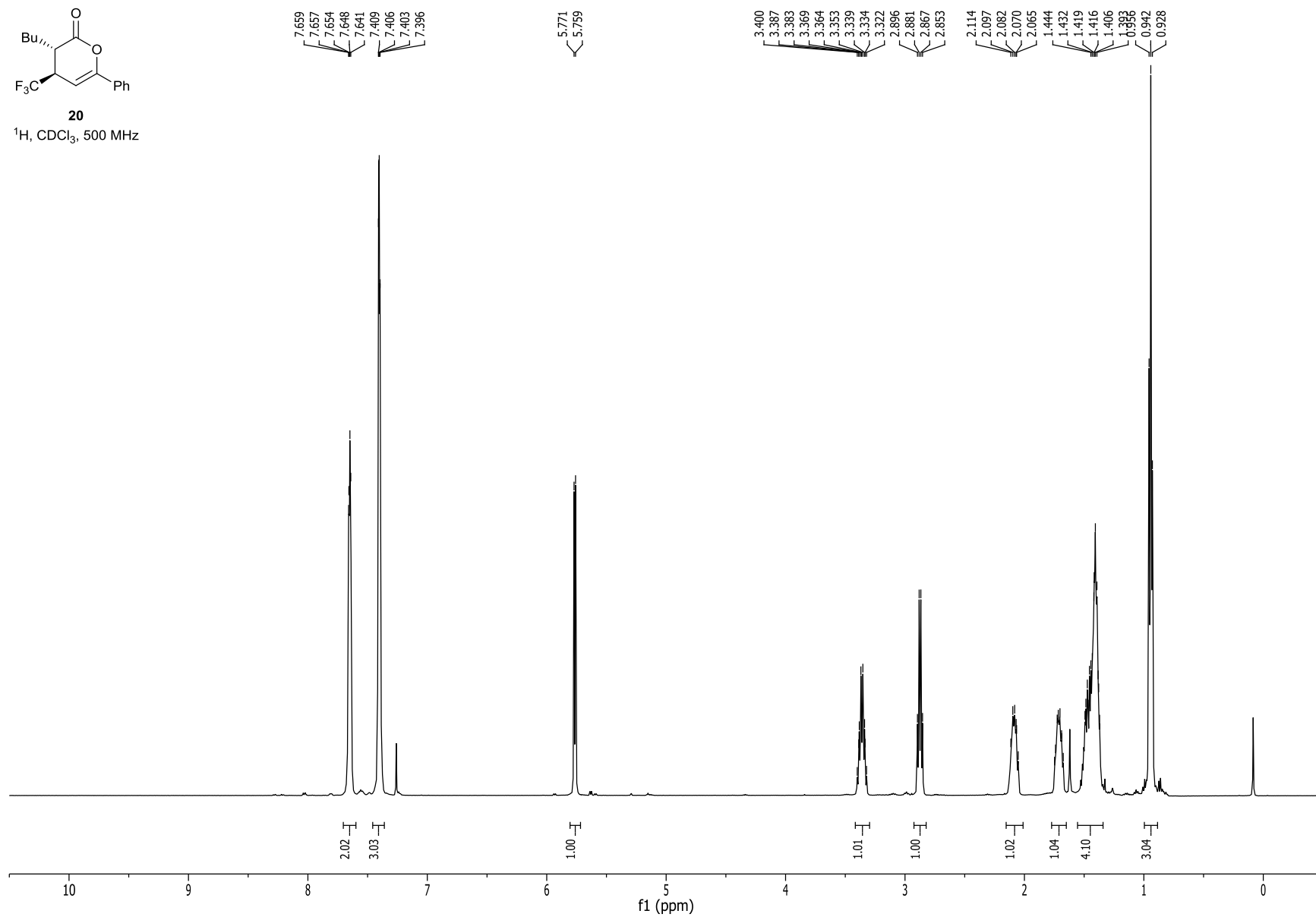
^{13}C , CDCl_3 , 75 MHz

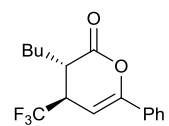




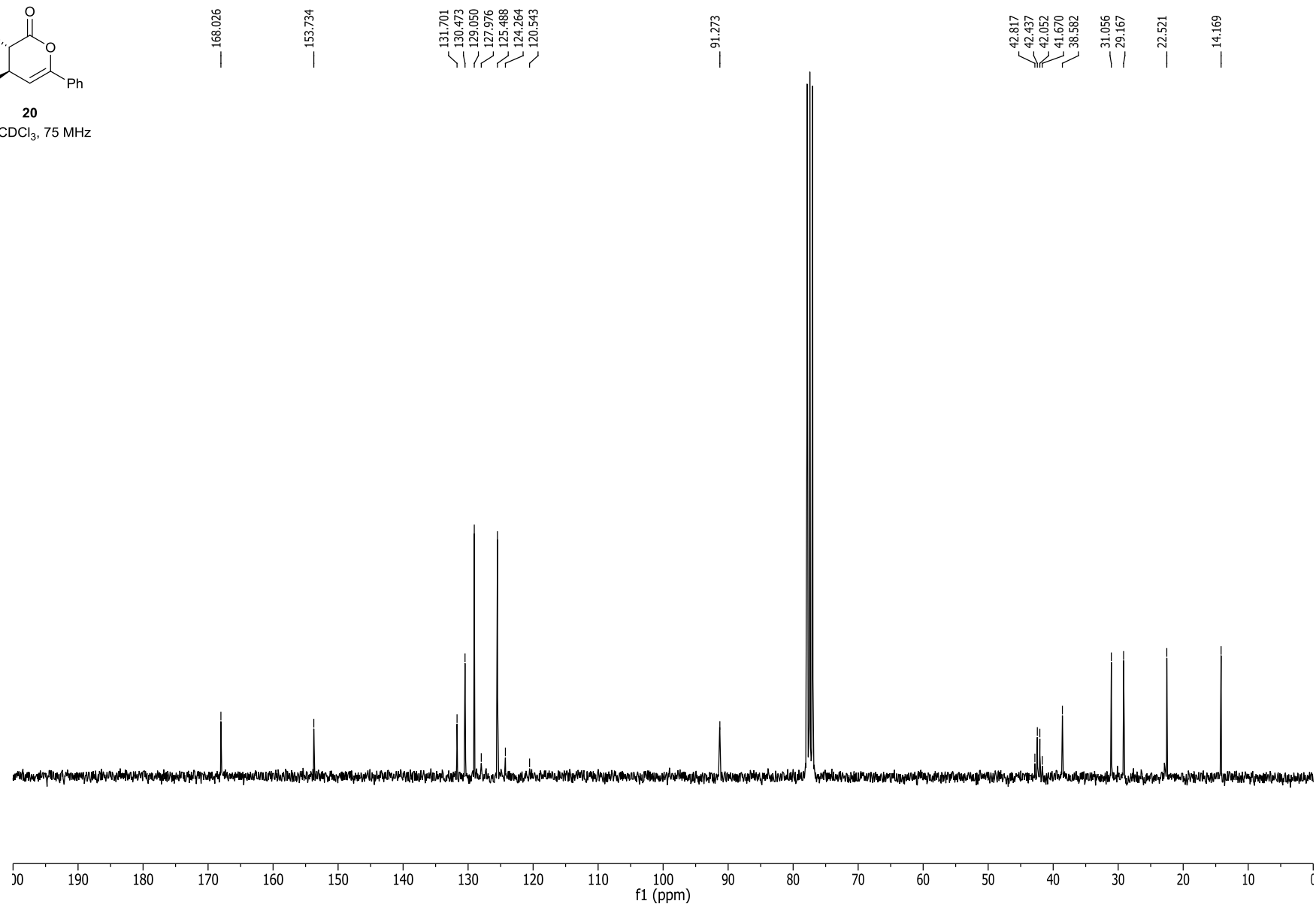
20

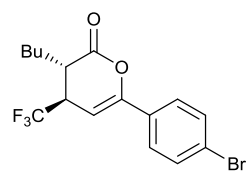
¹H, CDCl₃, 500 MHz





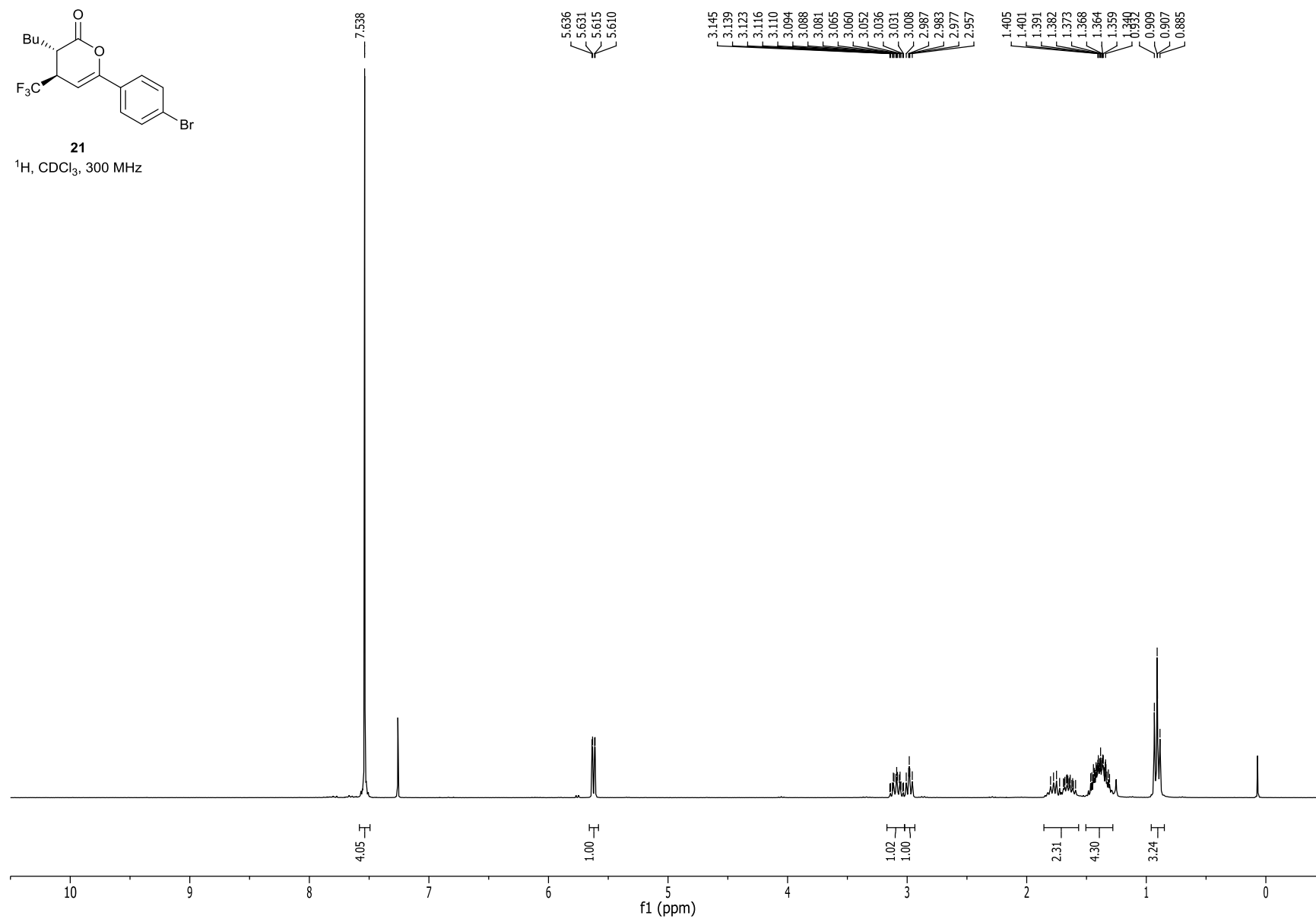
20
 ^{13}C , CDCl_3 , 75 MHz

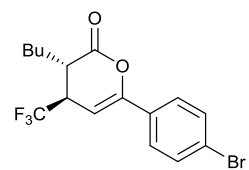




21

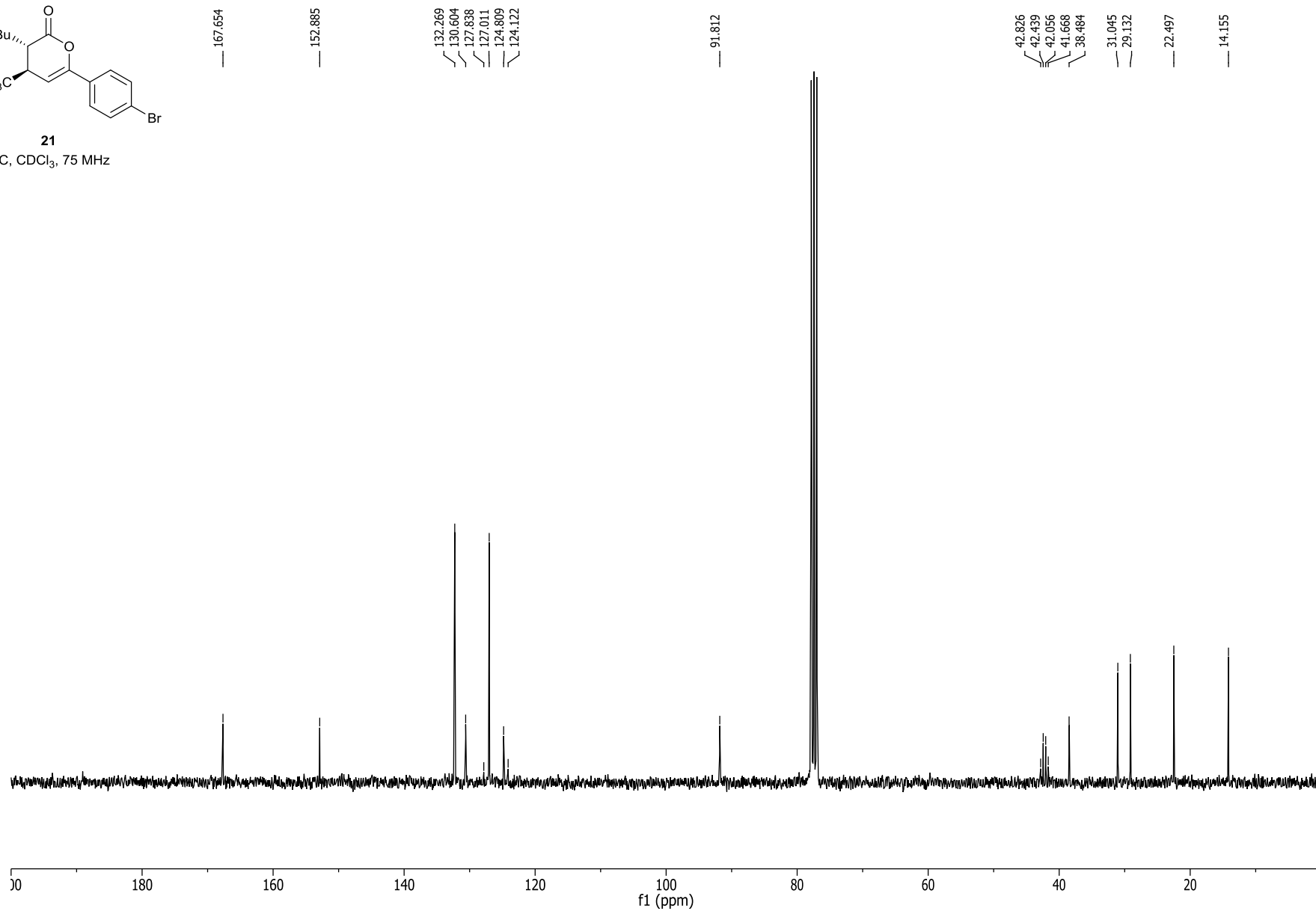
^1H , CDCl_3 , 300 MHz

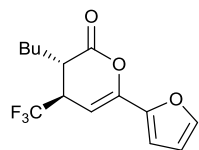




21

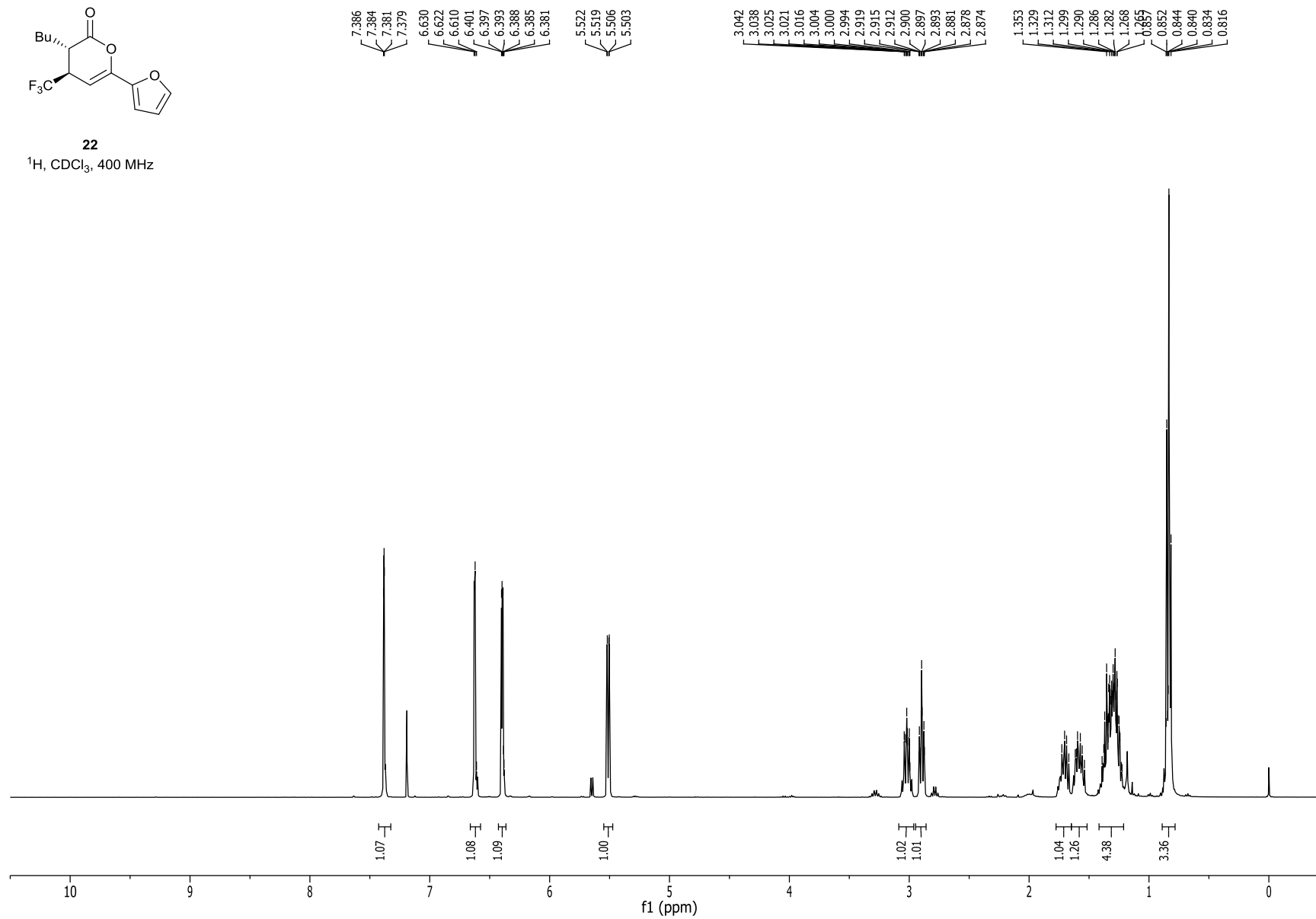
^{13}C , CDCl_3 , 75 MHz

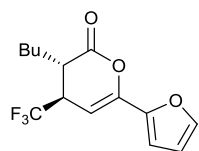




22

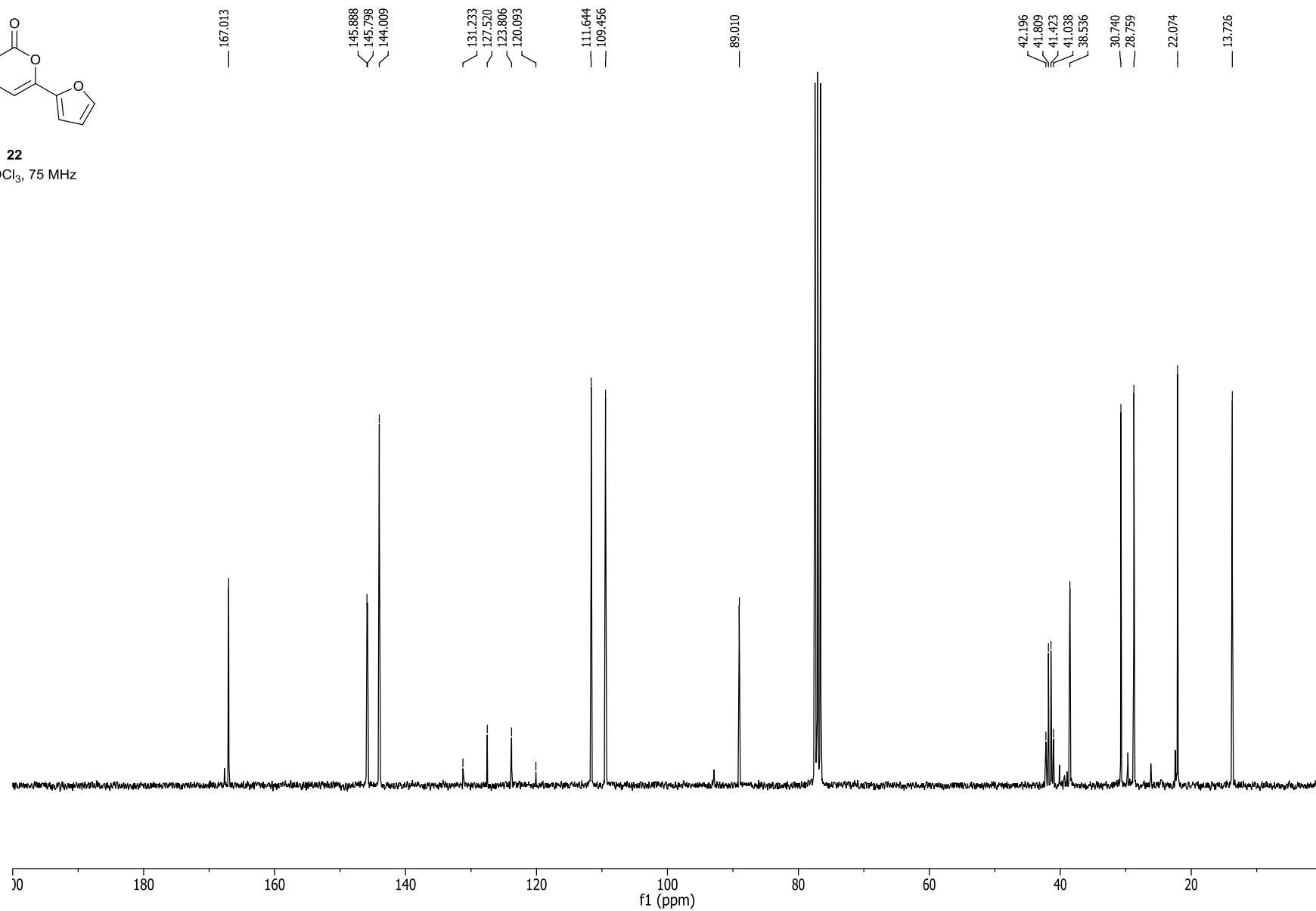
^1H , CDCl_3 , 400 MHz

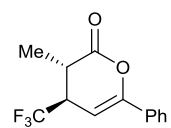




22

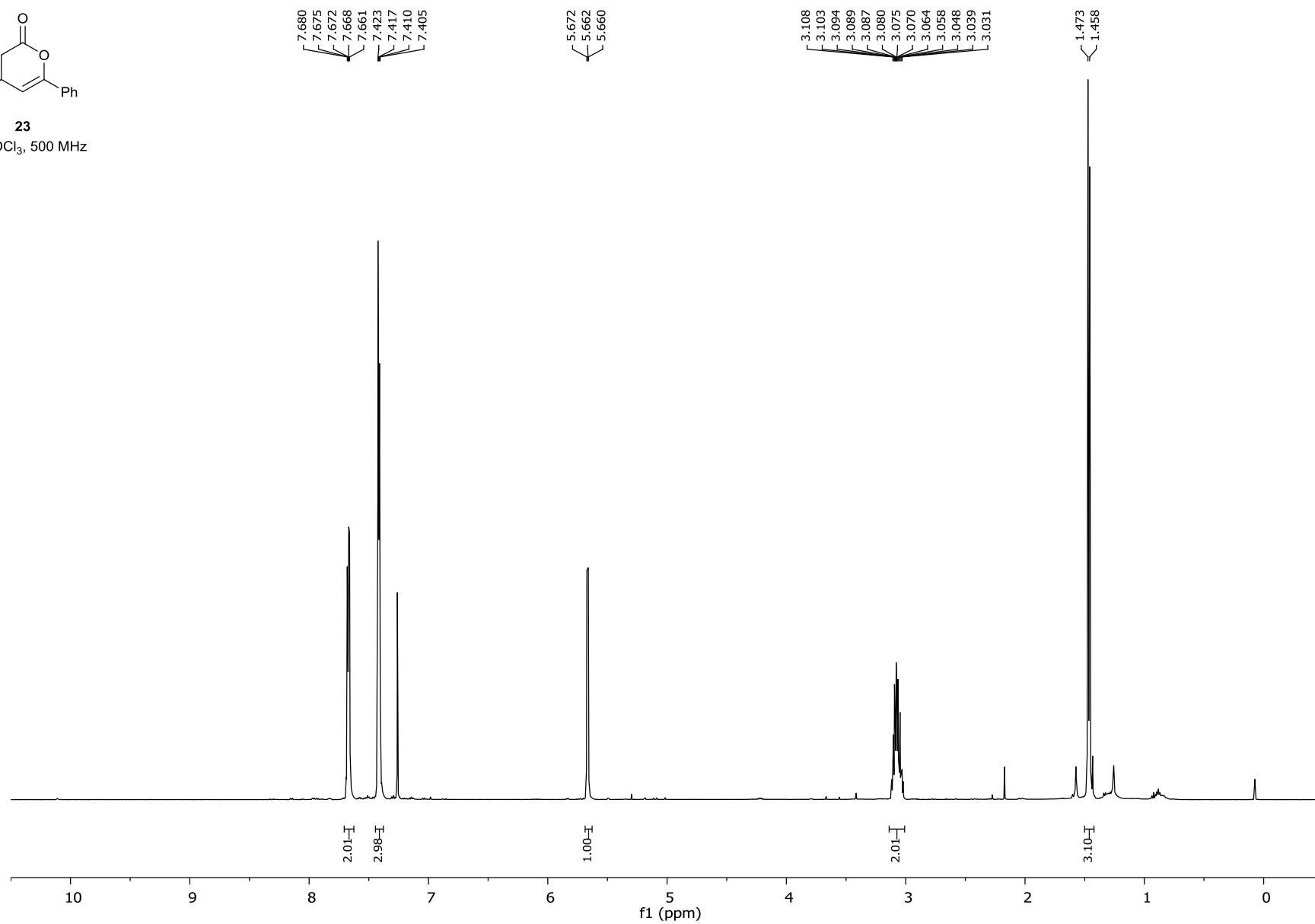
^{13}C , CDCl_3 , 75 MHz

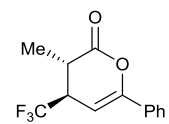




23

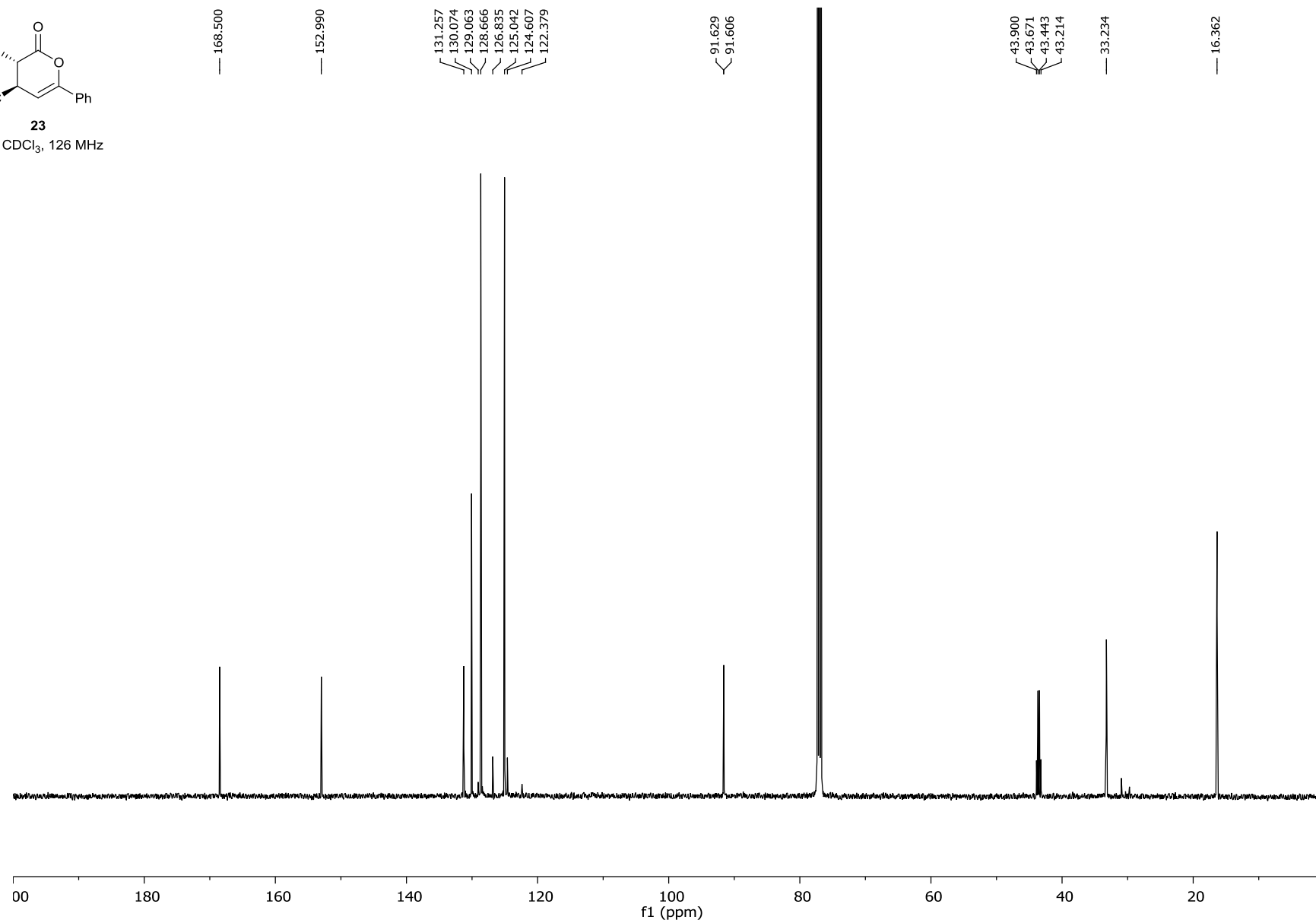
¹H, CDCl₃, 500 MHz

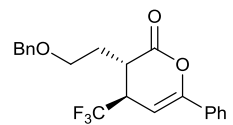




23

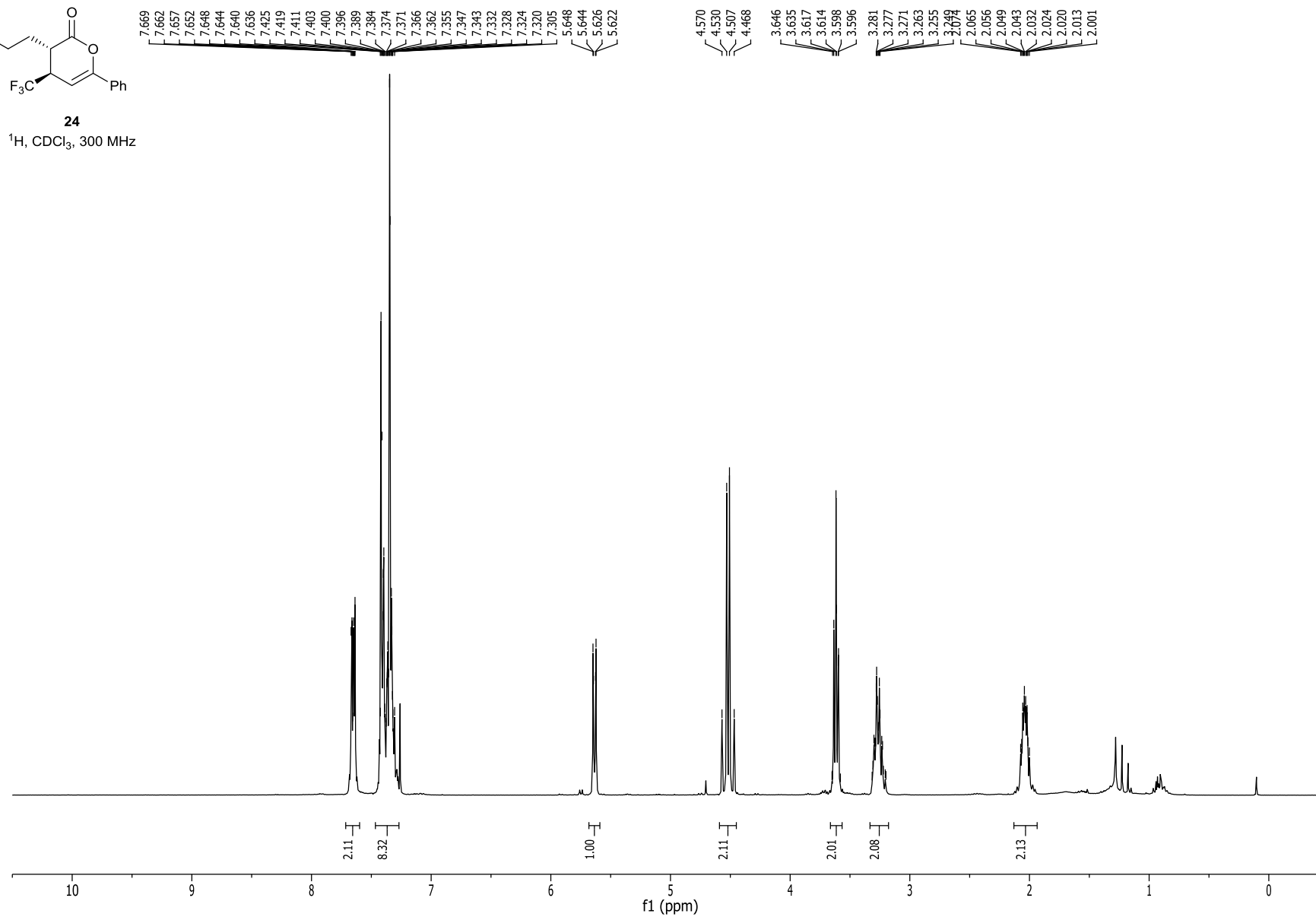
¹³C, CDCl₃, 126 MHz

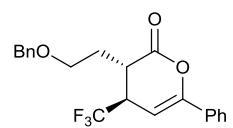




24

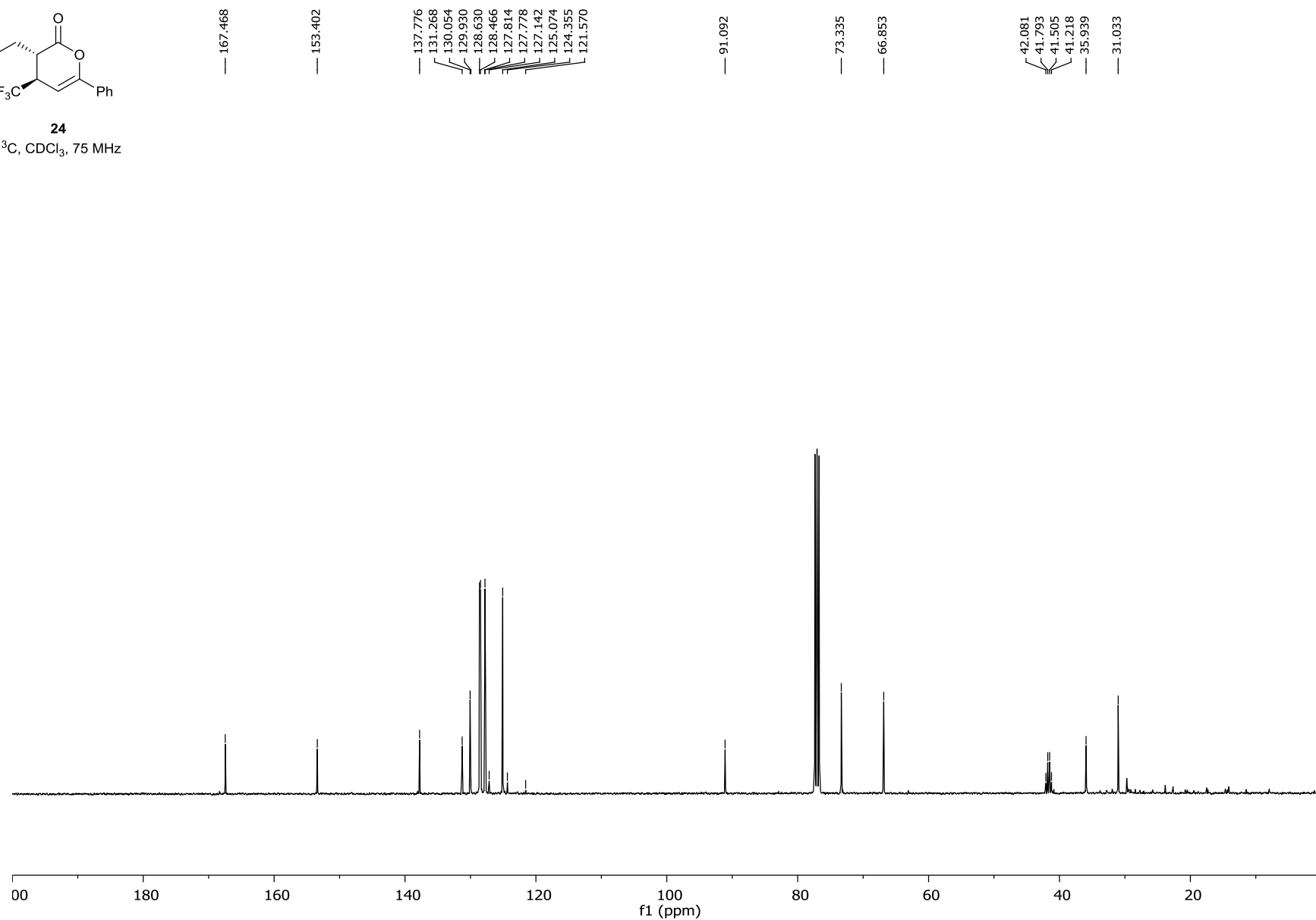
^1H , CDCl_3 , 300 MHz

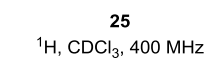


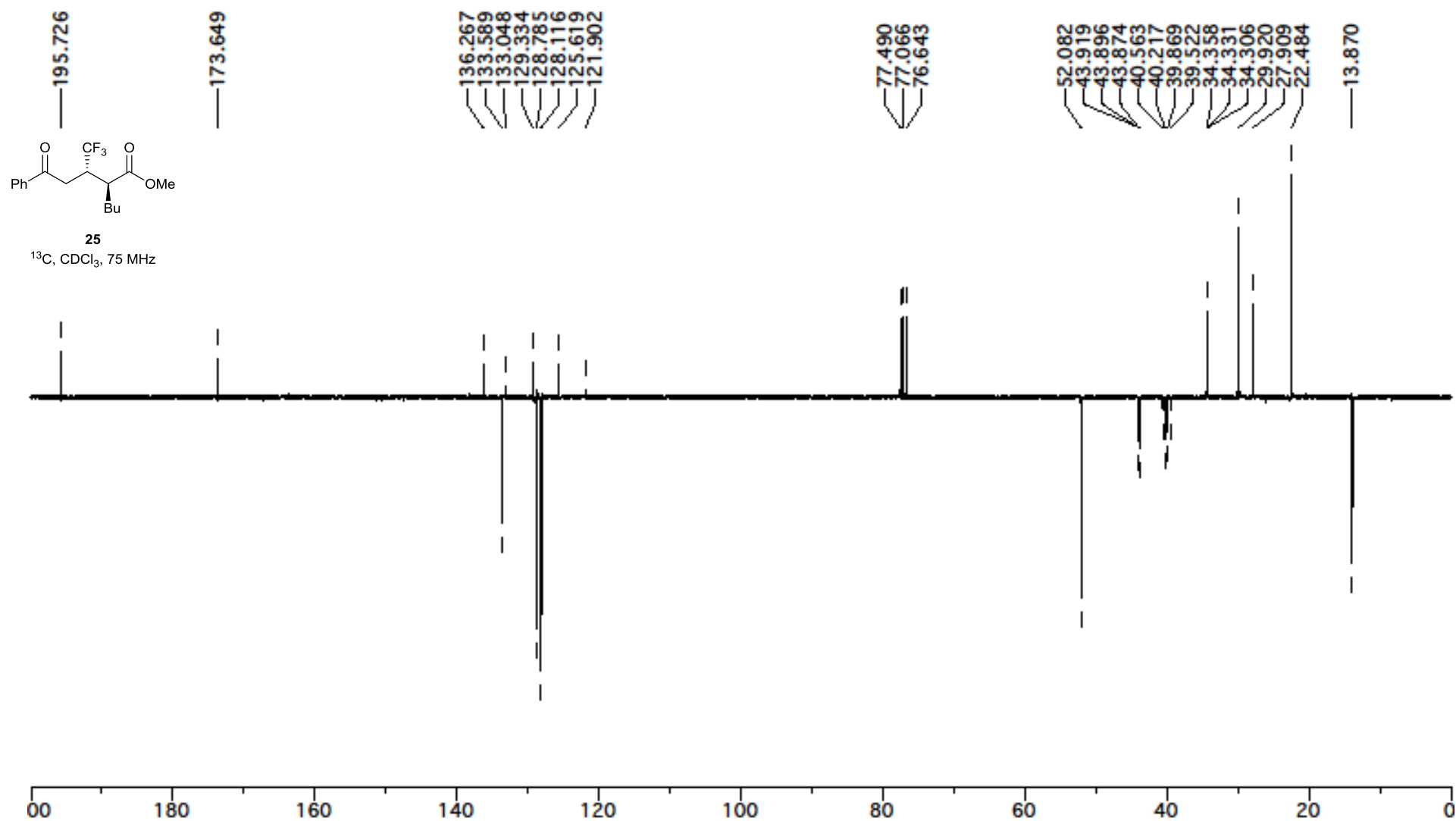


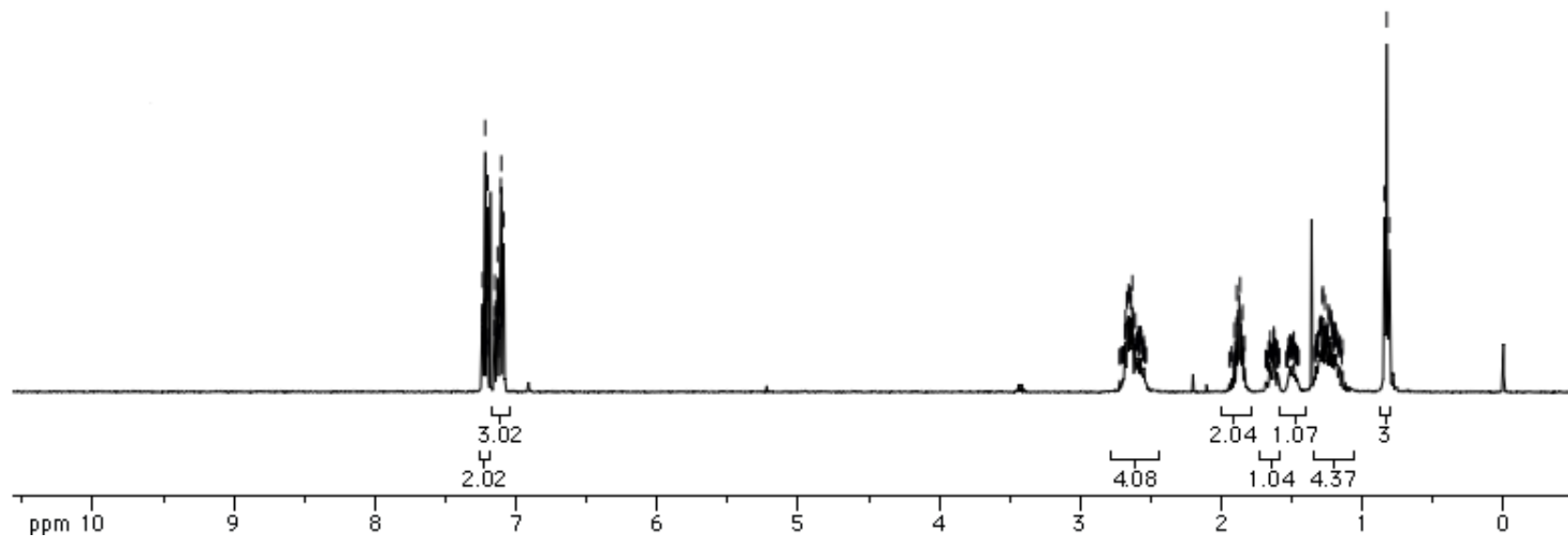
24

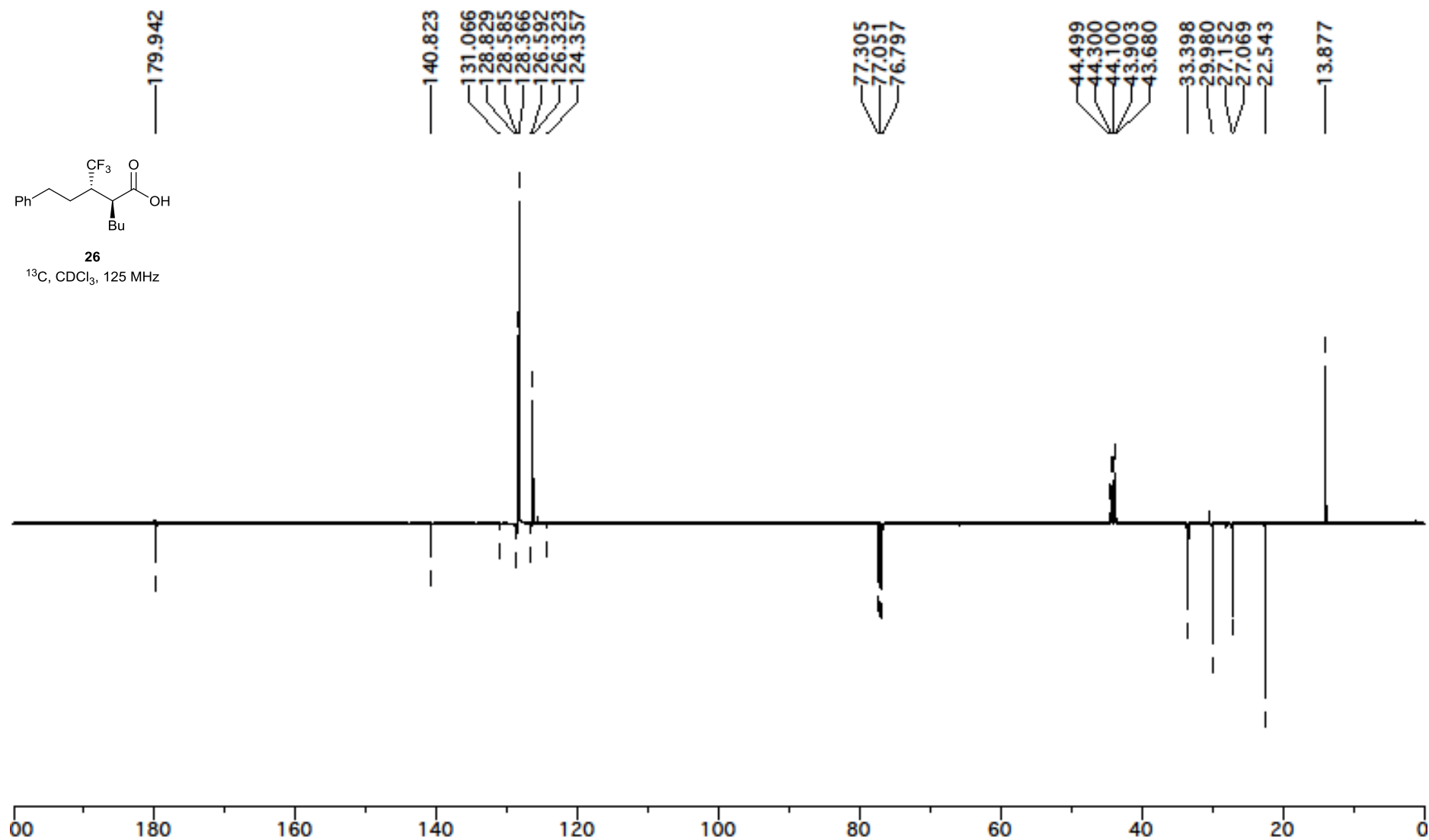
^{13}C , CDCl_3 , 75 MHz

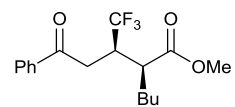






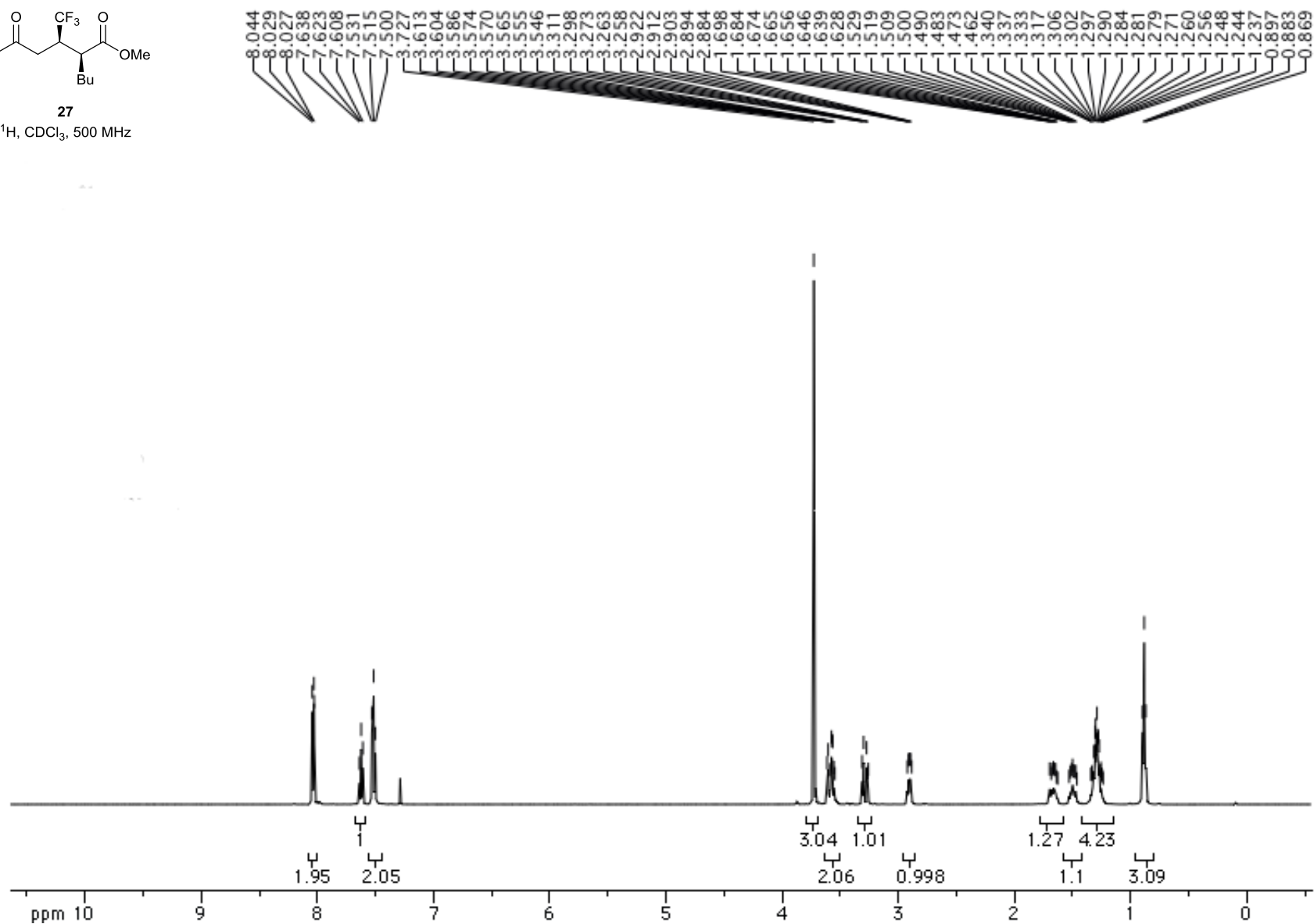
¹H, CDCl₃, 400 MHz

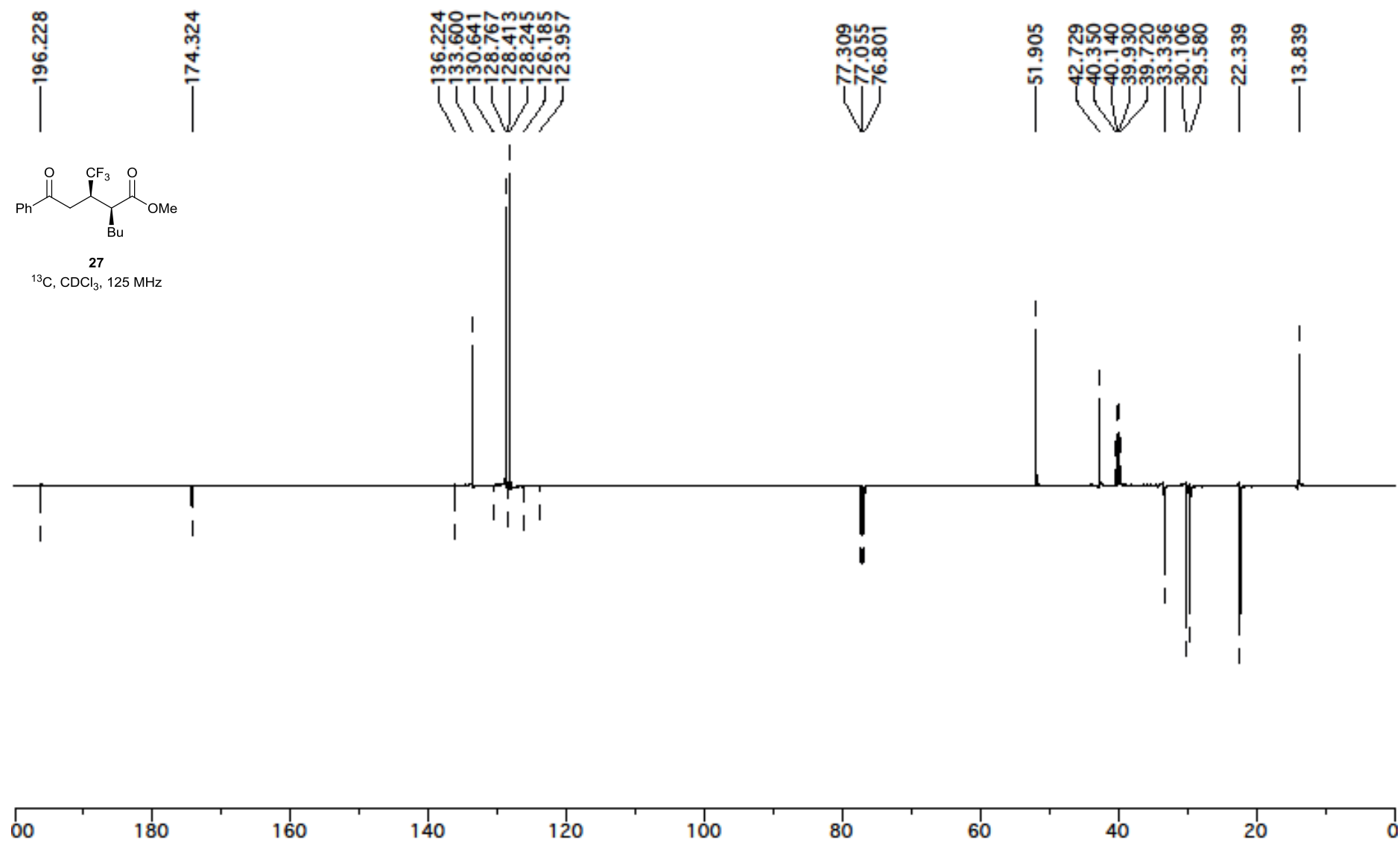


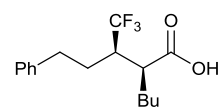


27

¹H, CDCl₃, 500 MHz

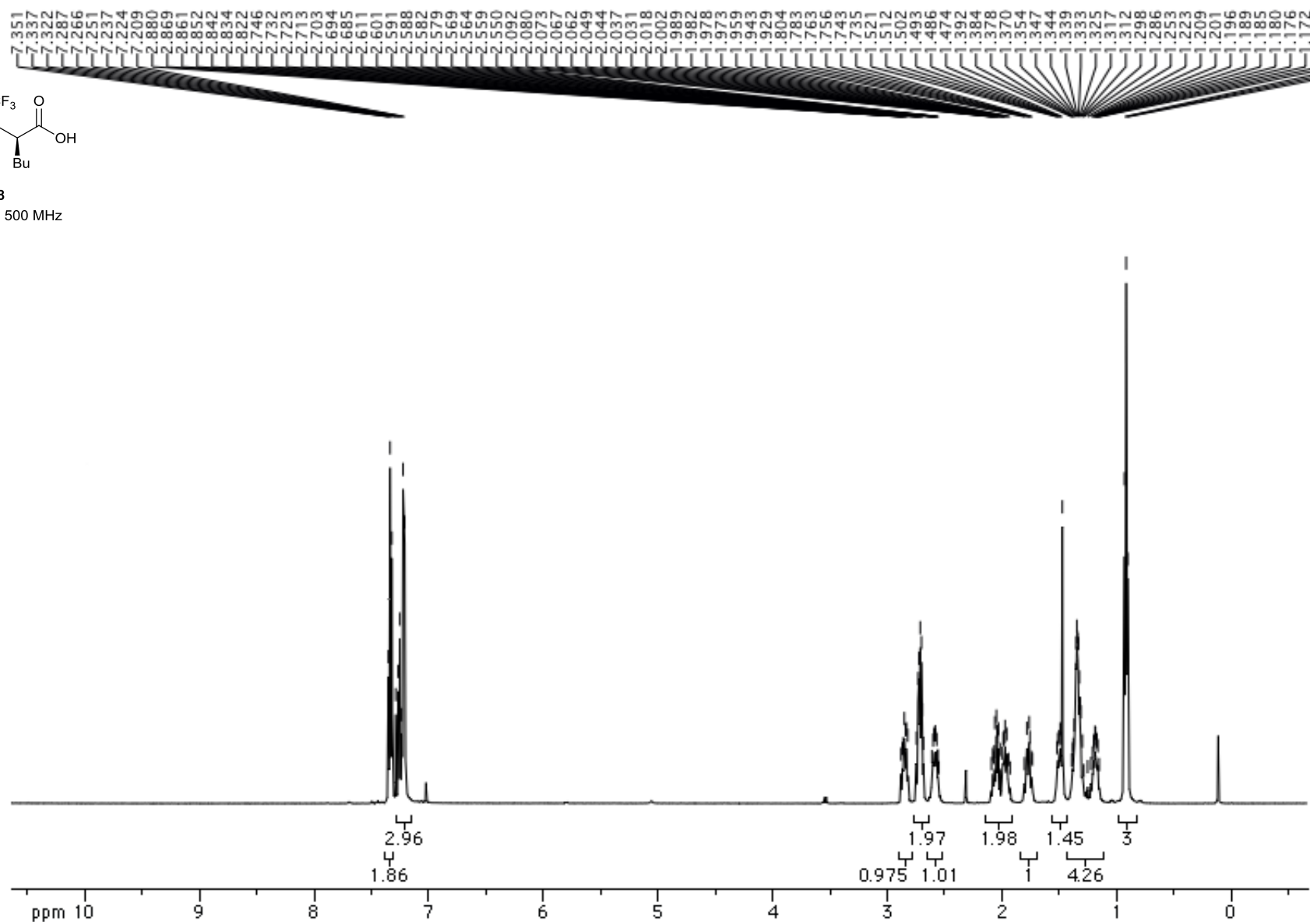


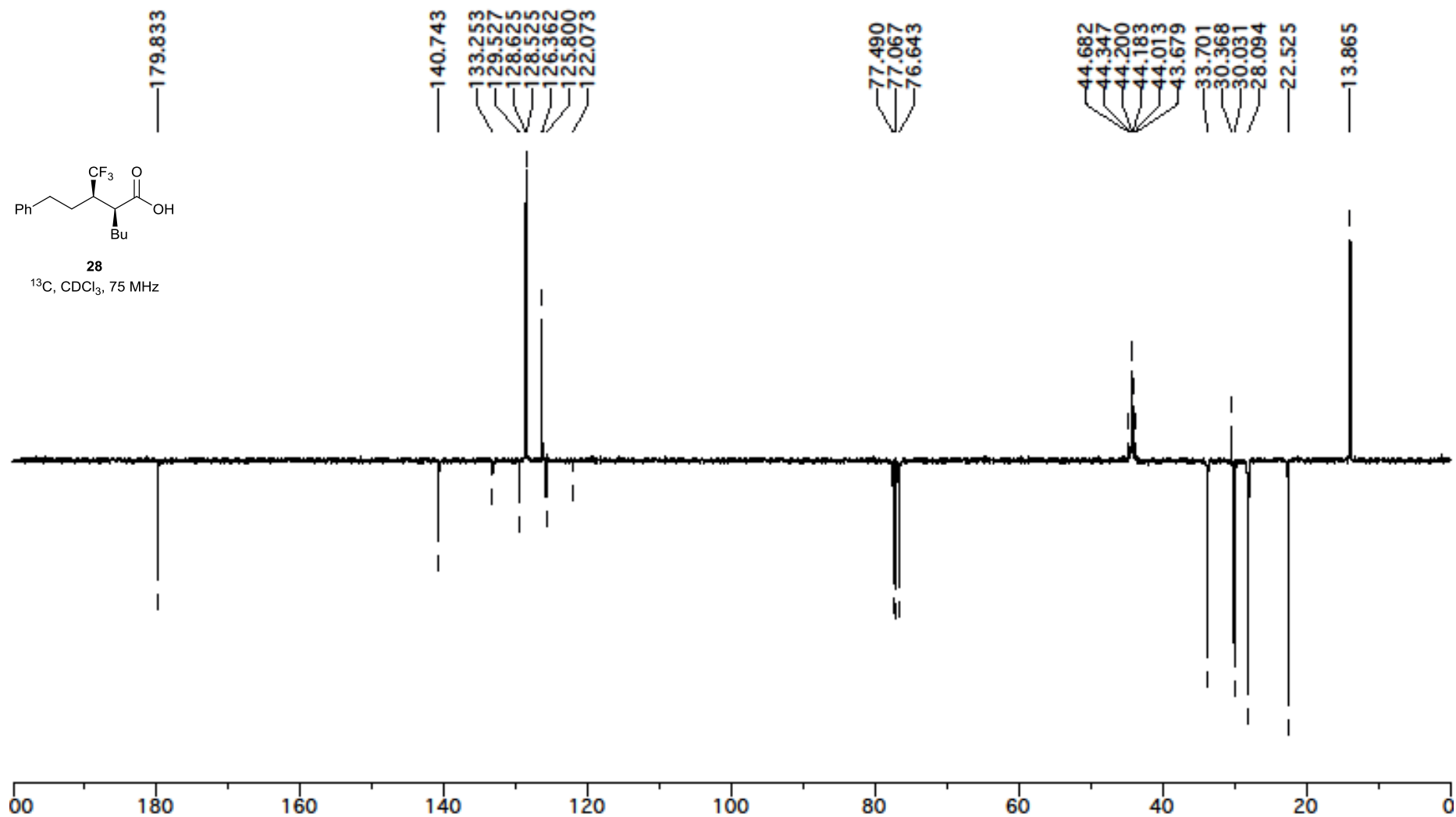


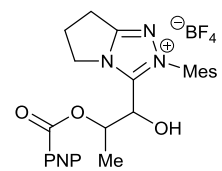


28

^1H , CDCl_3 , 500 MHz

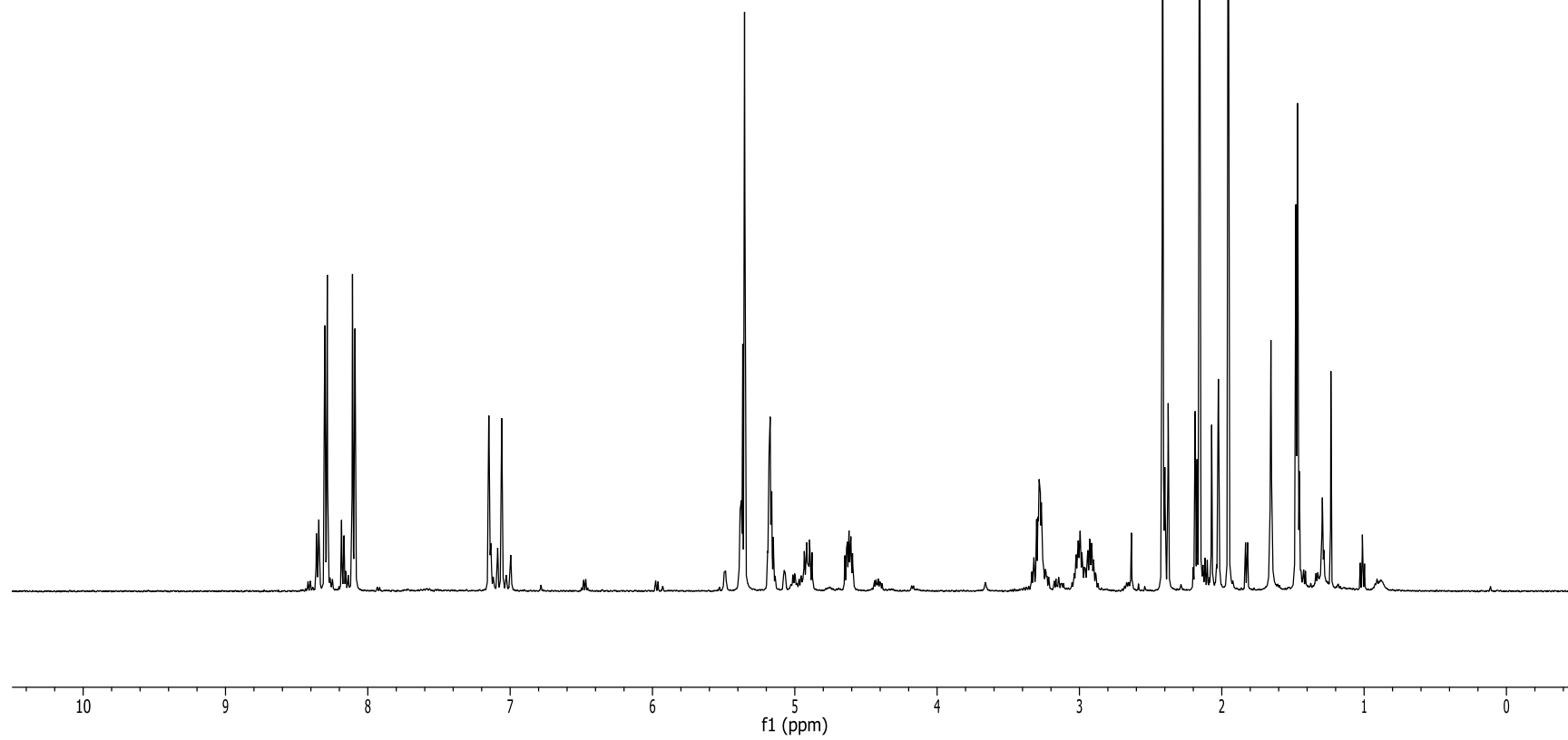


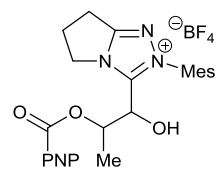




29

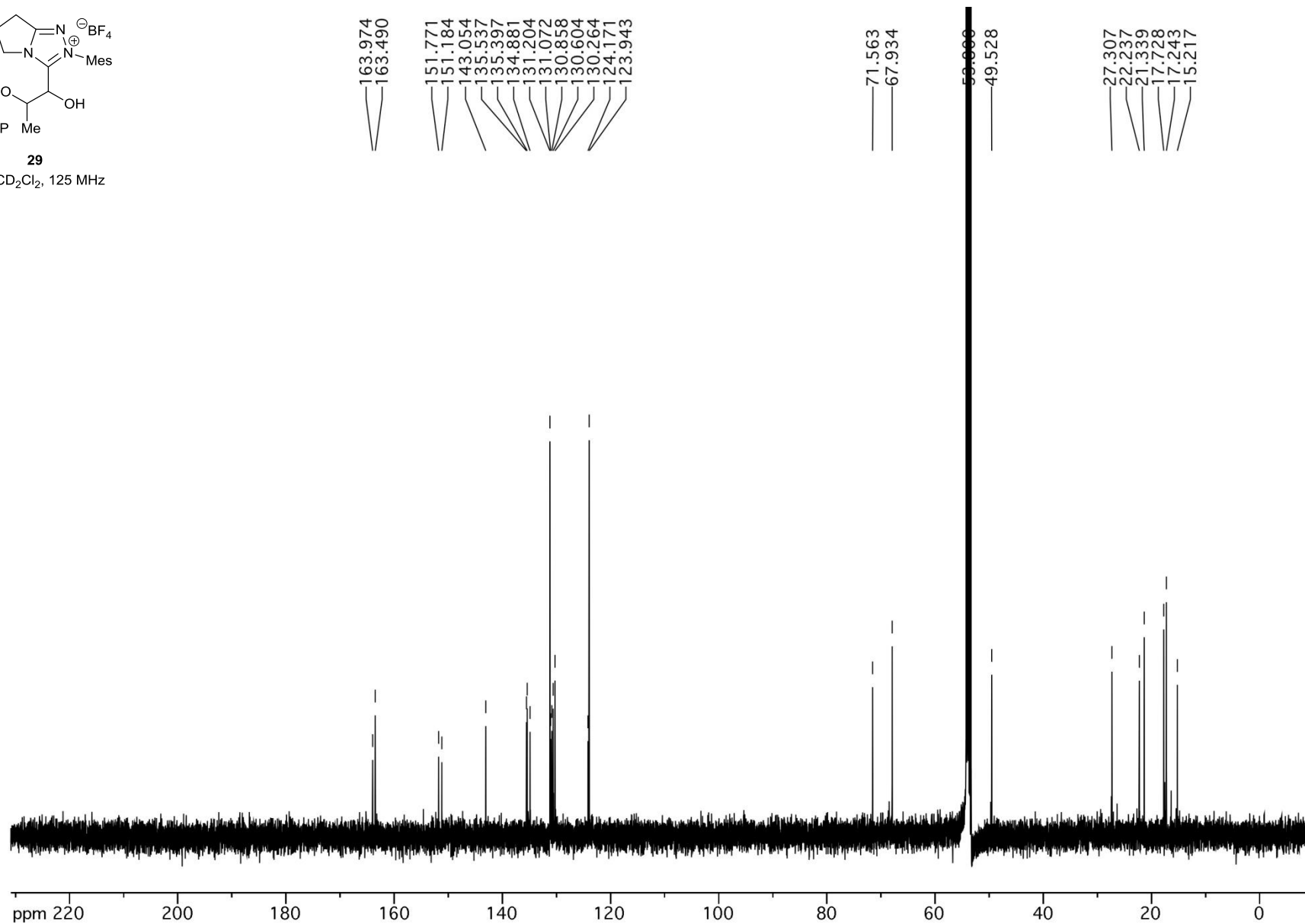
¹H, CD₂Cl₂, 500 MHz

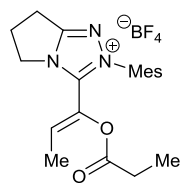




29

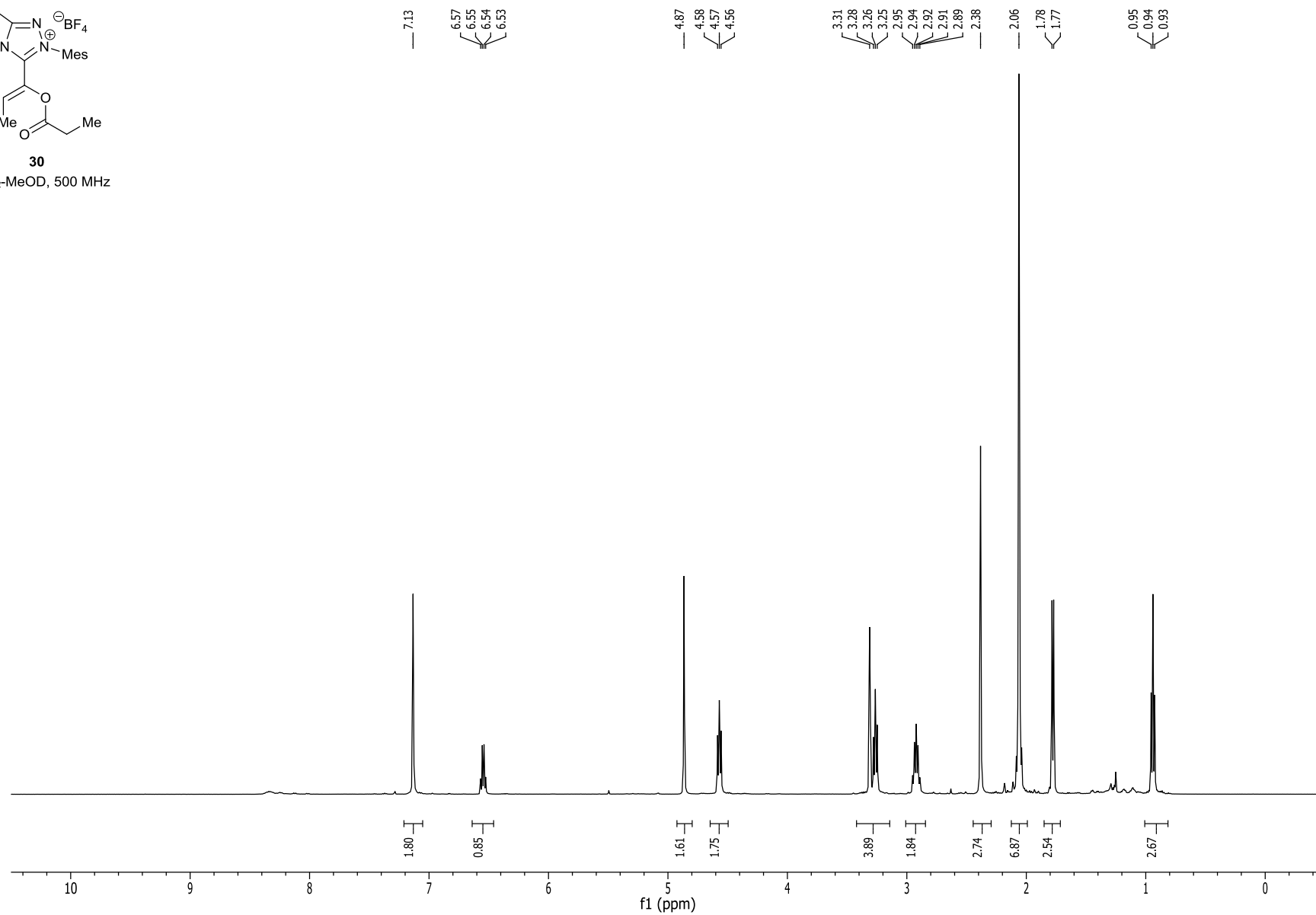
^{13}C , CD_2Cl_2 , 125 MHz

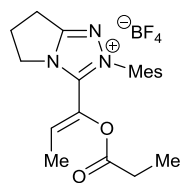




30

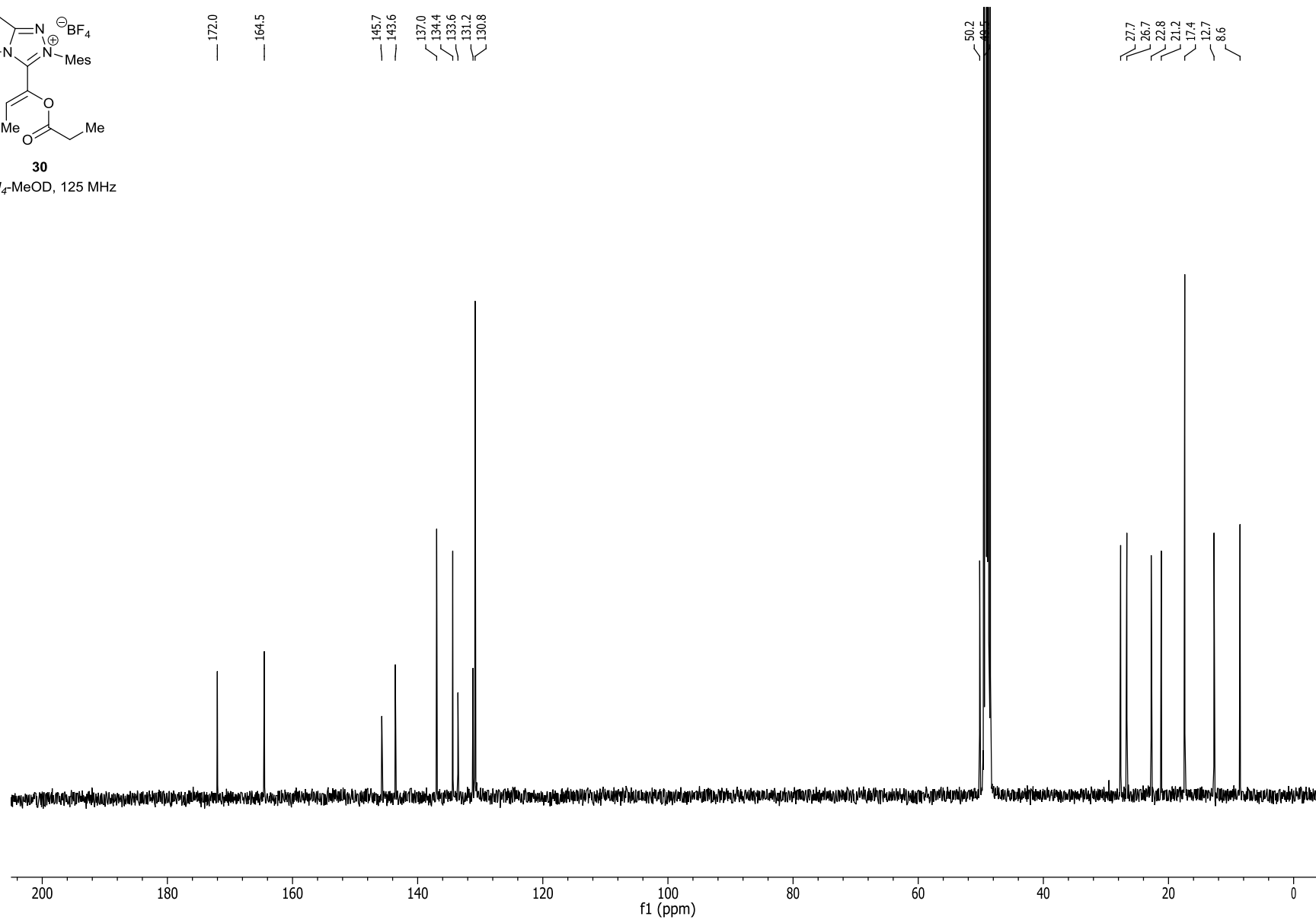
^1H , d_4 -MeOD, 500 MHz



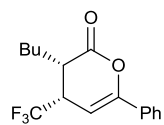


30

^{13}C , d_4 -MeOD, 125 MHz

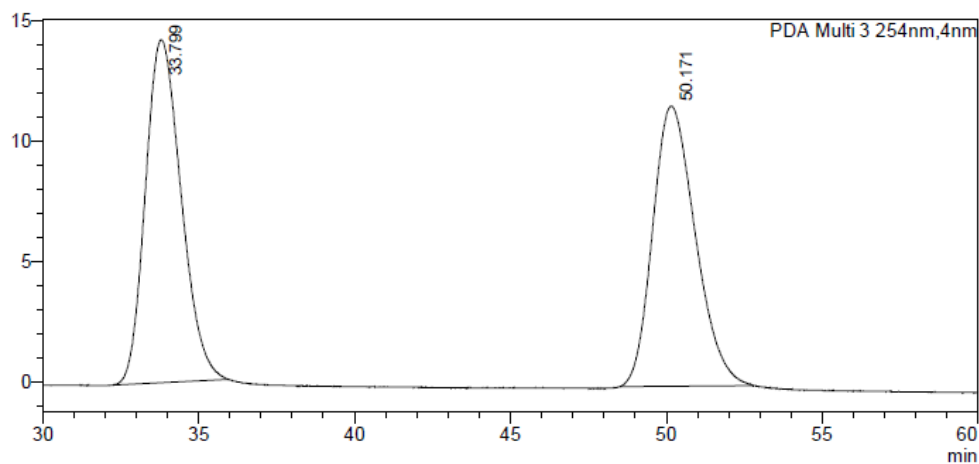


HPLC data compound **8**: Chiralcel OJ-H, 99.8:0.2 hexane : IPA, flow rate 1 mLmin⁻¹, 254 nm, 30 °C, >99% ee.



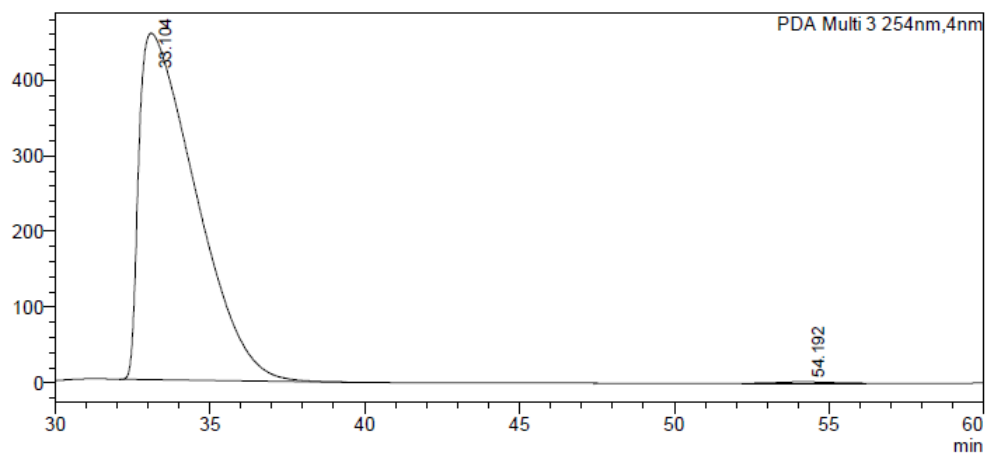
PDA Ch3 254nm

Peak#	Ret. Time	Area	Area%
1	33.799	1139062	50.668
2	50.171	1109033	49.332
Total		2248095	100.000

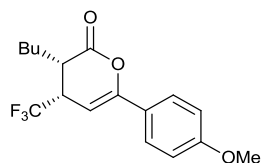


PDA Ch3 254nm

Peak#	Ret. Time	Area	Area%
1	33.104	58274239	99.693
2	54.192	179380	0.307
Total		58453619	100.000

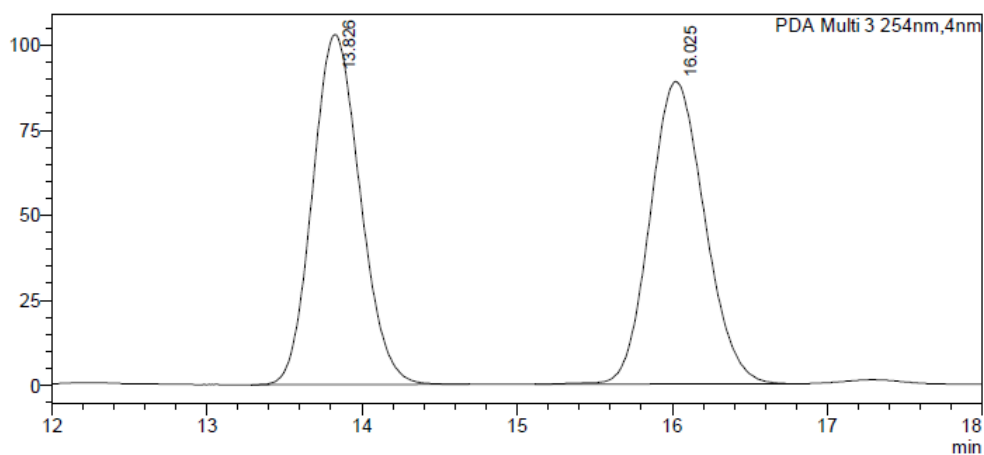


HPLC data compound **9**: Chiralpak AD-H, 95:5 hexane : IPA, flow rate 1 mLmin⁻¹, 254 nm, 30 °C, >99% ee.



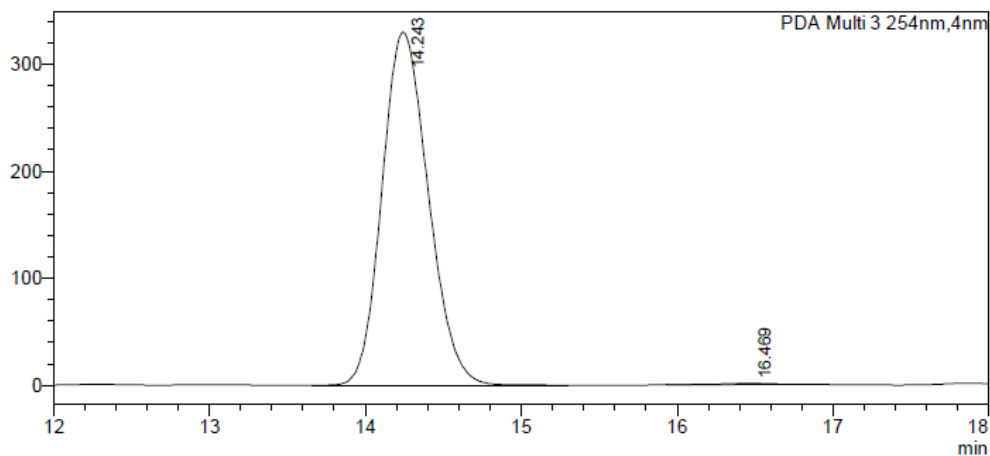
PDA Ch3 254nm

Peak#	Ret. Time	Area	Area%
1	13.826	2198880	50.180
2	16.025	2183084	49.820
Total		4381964	100.000

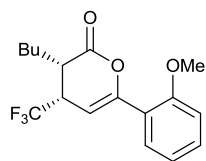


PDA Ch3 254nm

Peak#	Ret. Time	Area	Area%
1	14.243	6808811	99.560
2	16.469	30082	0.440
Total		6838893	100.000

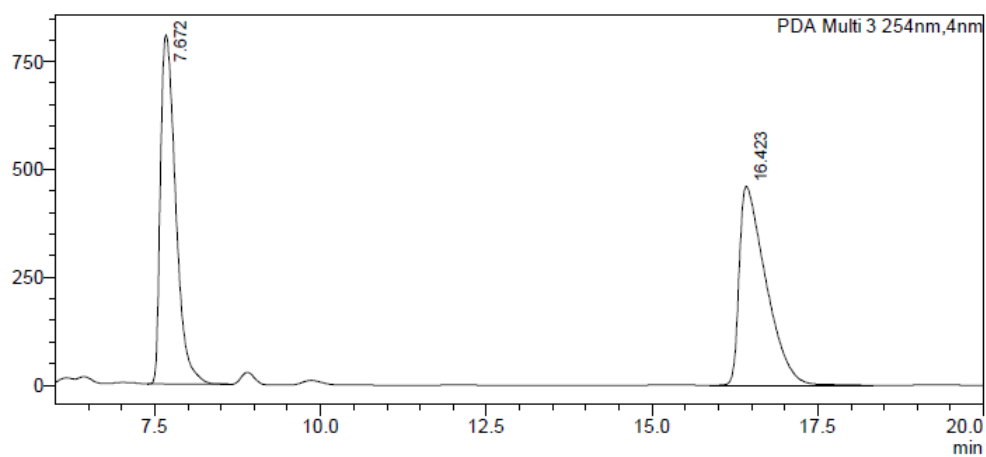


HPLC data compound **10**: Chiralpak IA, 98:2 hexane : IPA, flow rate 1 mLmin⁻¹, 254 nm, 30 °C, 99% ee.



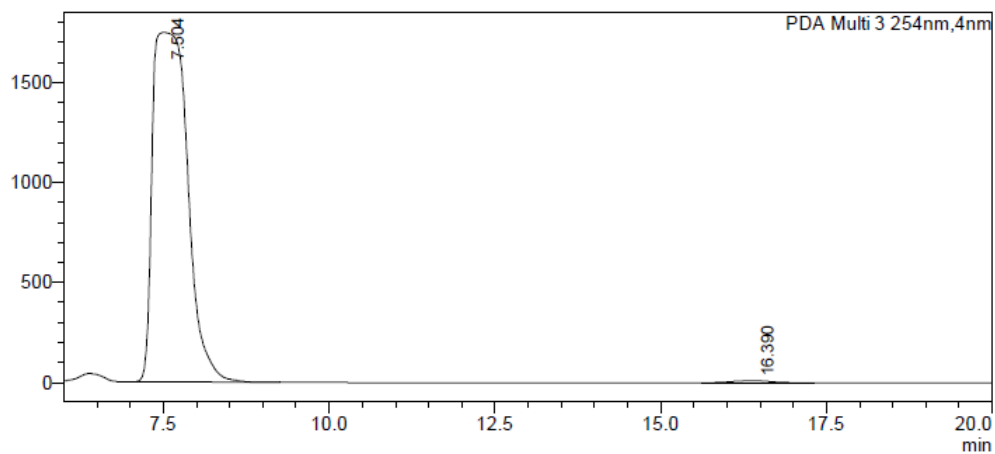
PDA Ch3 254nm

Peak#	Ret. Time	Area	Area%
1	7.672	12954521	50.132
2	16.423	12886296	49.868
Total		25840818	100.000

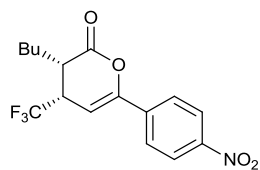


PDA Ch3 254nm

Peak#	Ret. Time	Area	Area%
1	7.504	64466475	99.464
2	16.390	347554	0.536
Total		64814029	100.000

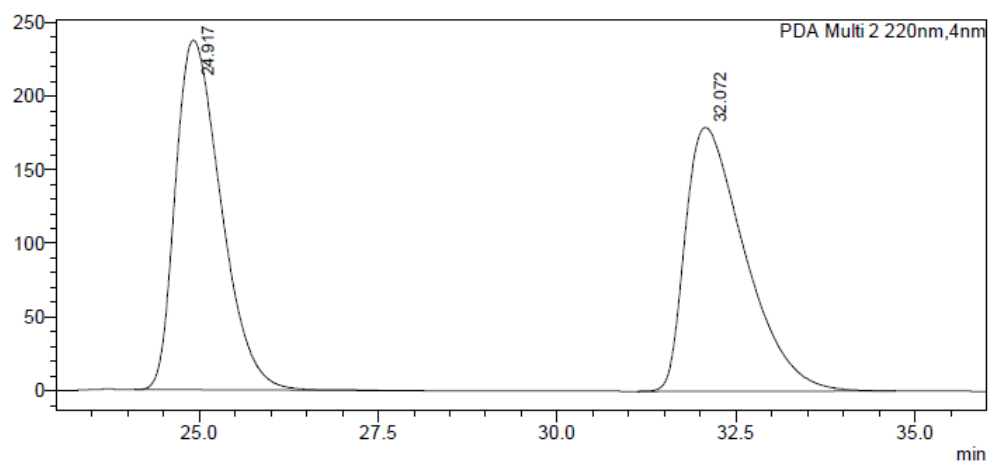


HPLC data compound **11**: Chiralpak IA, 95:5 hexane : IPA, flow rate 1 mLmin⁻¹, 220 nm, 30 °C, >99% ee.



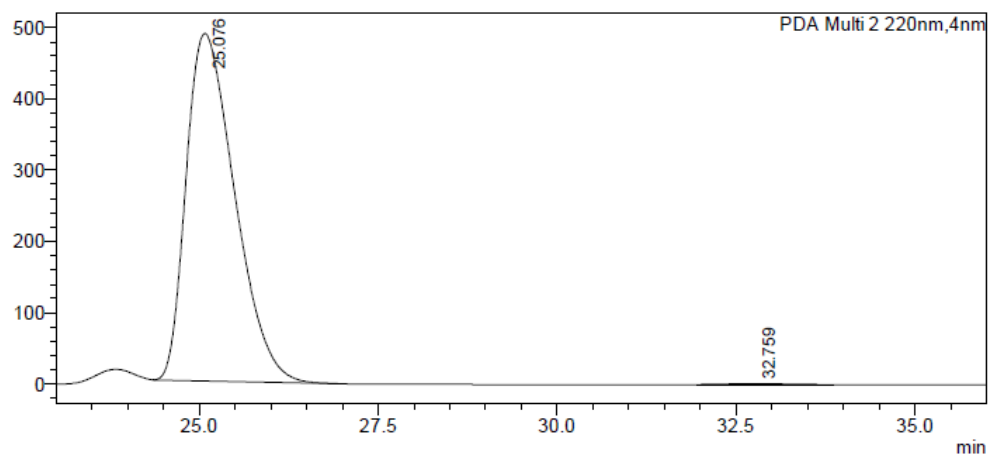
PDA Ch2 220nm

Peak#	Ret. Time	Area	Area%
1	24.917	10538177	50.356
2	32.072	10389317	49.644
Total		20927495	100.000

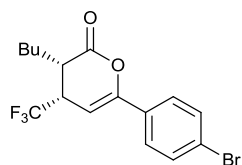


PDA Ch2 220nm

Peak#	Ret. Time	Area	Area%
1	25.076	23027091	99.685
2	32.759	72715	0.315
Total		23099806	100.000

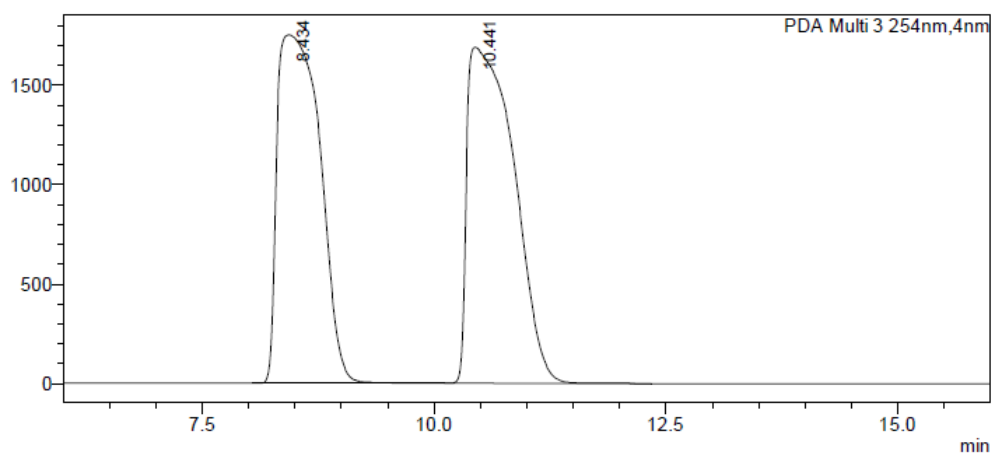


HPLC data compound **12**: Chiralpak IB, 99.1 hexane : IPA, flow rate 1 mLmin⁻¹, 254 nm, 40 °C, >99% ee.



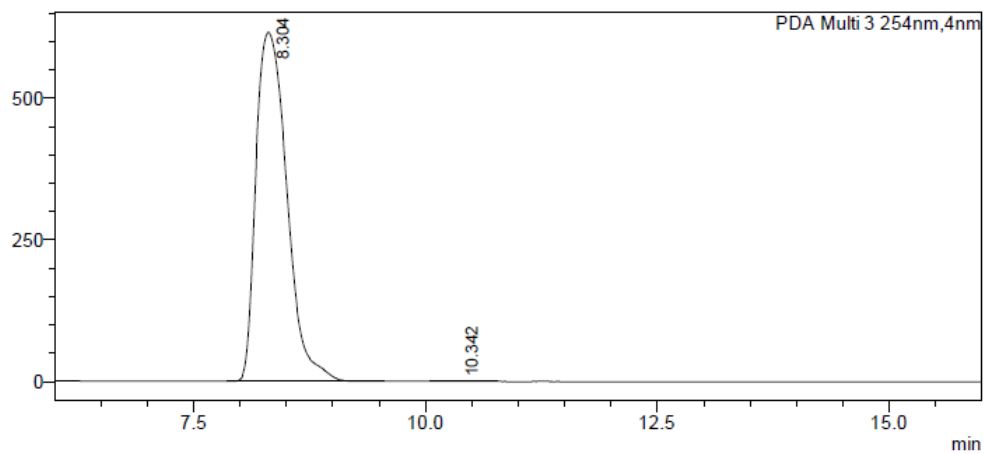
PDA Ch3 254nm

Peak#	Ret. Time	Area	Area%
1	8.434	56533784	48.641
2	10.441	59693008	51.359
Total		116226792	100.000

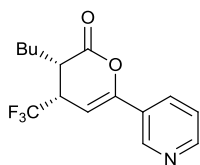


PDA Ch3 254nm

Peak#	Ret. Time	Area	Area%
1	8.304	14315138	99.940
2	10.342	8648	0.060
Total		14323787	100.000

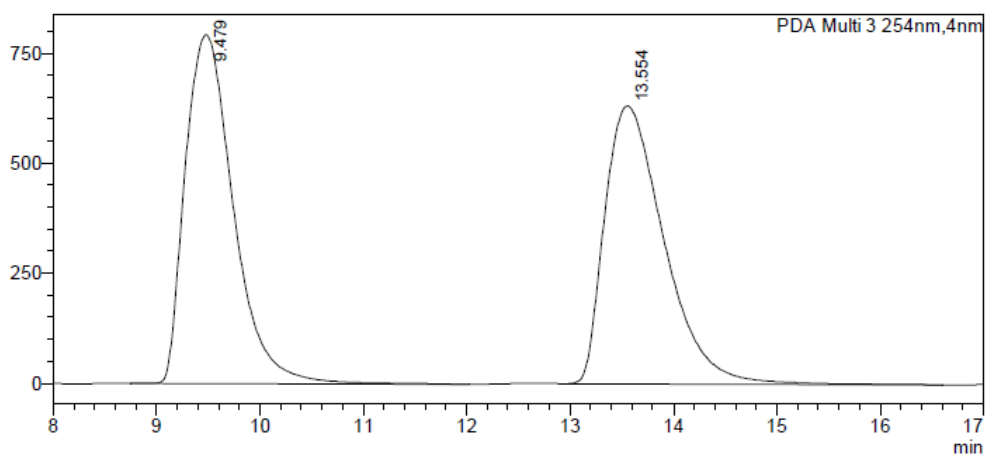


HPLC data compound **13**: Chiralpak IA, 90:10 hexane : IPA, flow rate 1 mLmin⁻¹, 254 nm, 30 °C, >99% ee.



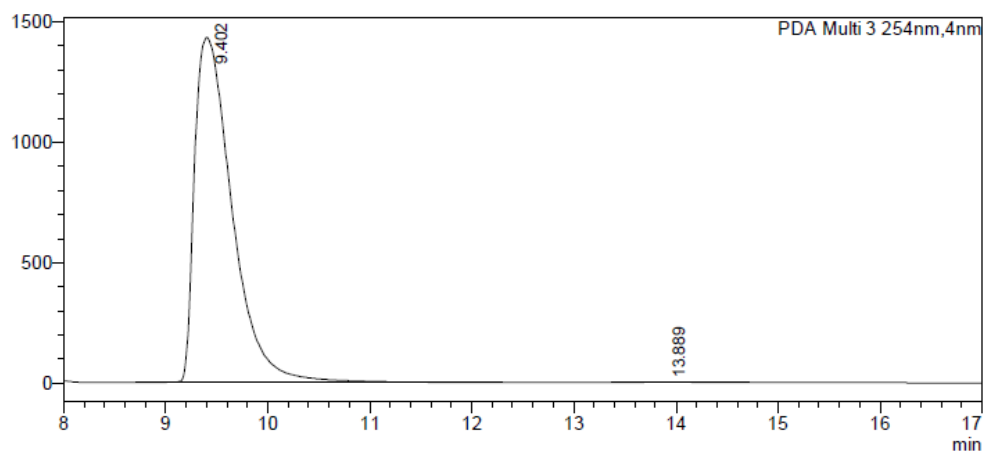
PDA Ch3 254nm

Peak#	Ret. Time	Area	Area%
1	9.479	25807644	50.489
2	13.554	25308145	49.511
Total		51115789	100.000

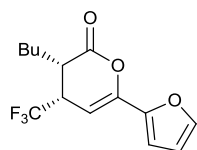


PDA Ch3 254nm

Peak#	Ret. Time	Area	Area%
1	9.402	36878709	99.708
2	13.889	107885	0.292
Total		36986594	100.000

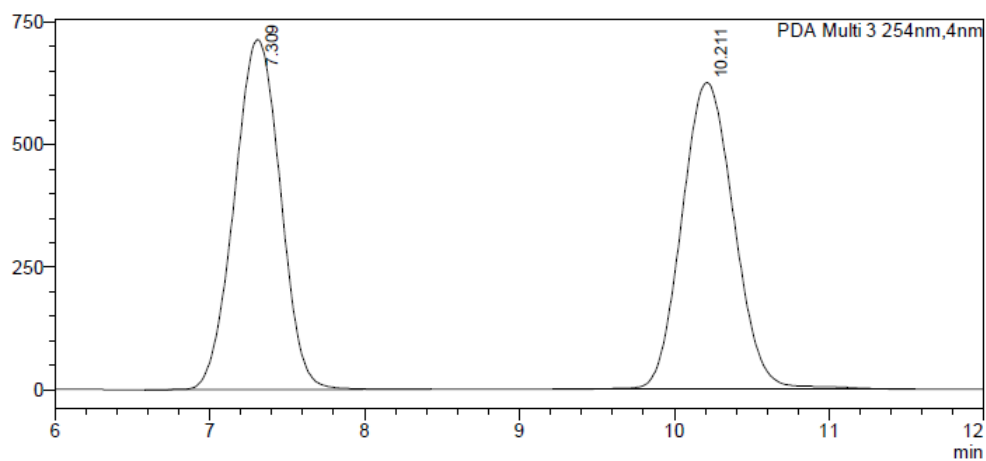


HPLC data compound **14**: Chiralpak AD-H, 98:2 hexane : IPA, flow rate 1 mLmin⁻¹, 254 nm, 30 °C, >99% ee.



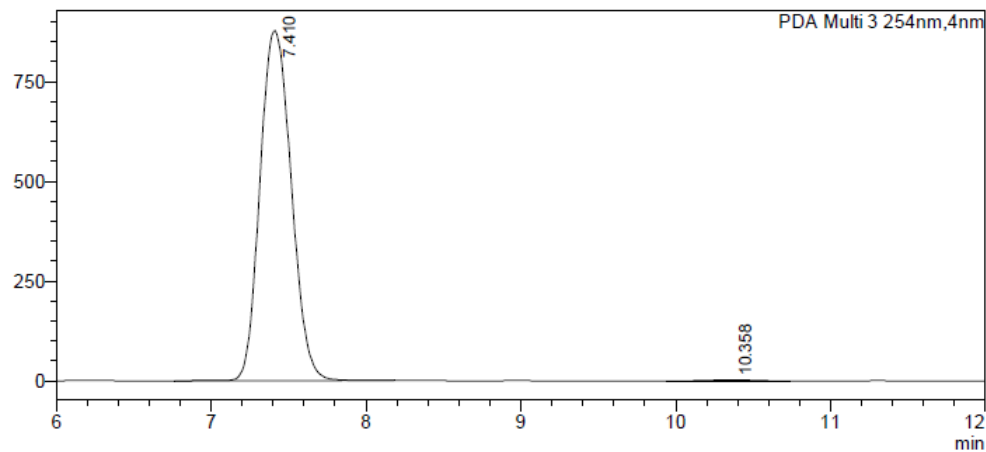
PDA Ch3 254nm

Peak#	Ret. Time	Area	Area%
1	7.309	14793145	50.108
2	10.211	14729204	49.892
Total		29522349	100.000

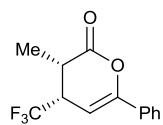


PDA Ch3 254nm

Peak#	Ret. Time	Area	Area%
1	7.410	12357140	99.621
2	10.358	47049	0.379
Total		12404189	100.000

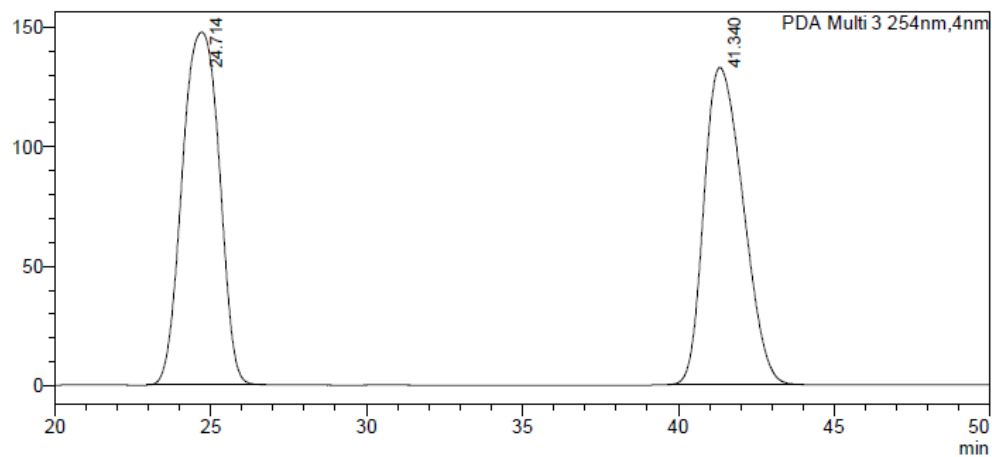


HPLC data compound **15**: Chiralcel OD-H, 99:1 hexane : IPA, flow rate 1 mLmin⁻¹, 254 nm, 30 °C, >99% ee.



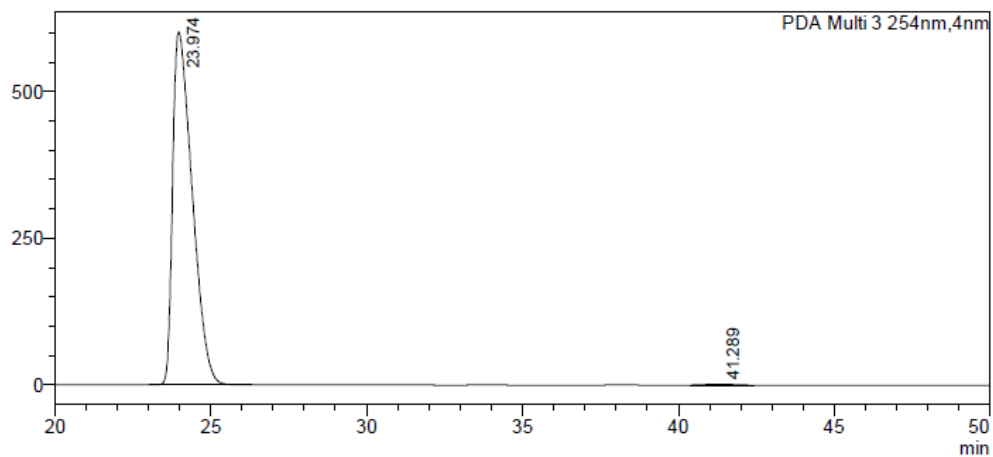
PDA Ch3 254nm

Peak#	Ret. Time	Area	Area%
1	24.714	12216498	51.292
2	41.340	11601118	48.708
Total		23817616	100.000

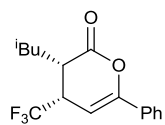


PDA Ch3 254nm

Peak#	Ret. Time	Area	Area%
1	23.974	26199388	99.622
2	41.289	99427	0.378
Total		26298815	100.000

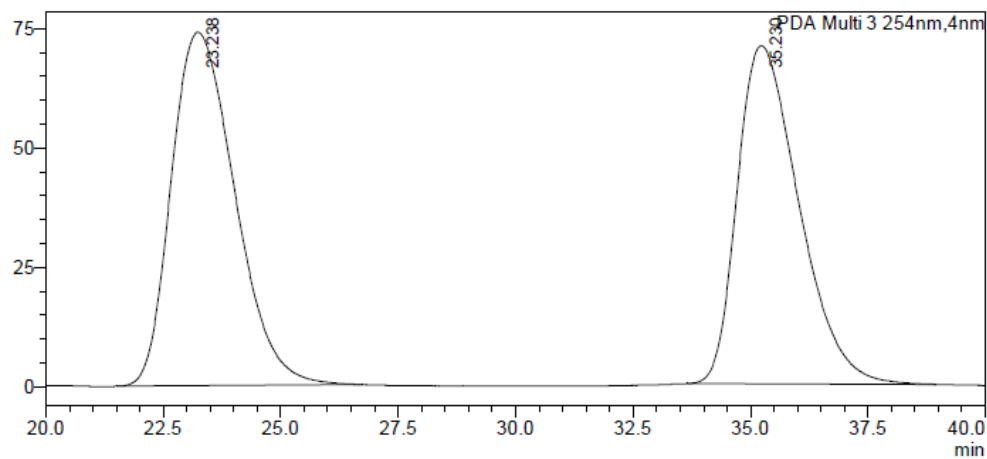


HPLC data compound **16**: Chiralcel OJ-H, 99.8:0.2 hexane : IPA, flow rate 1 mLmin⁻¹, 254 nm, 30 °C, >99% ee.



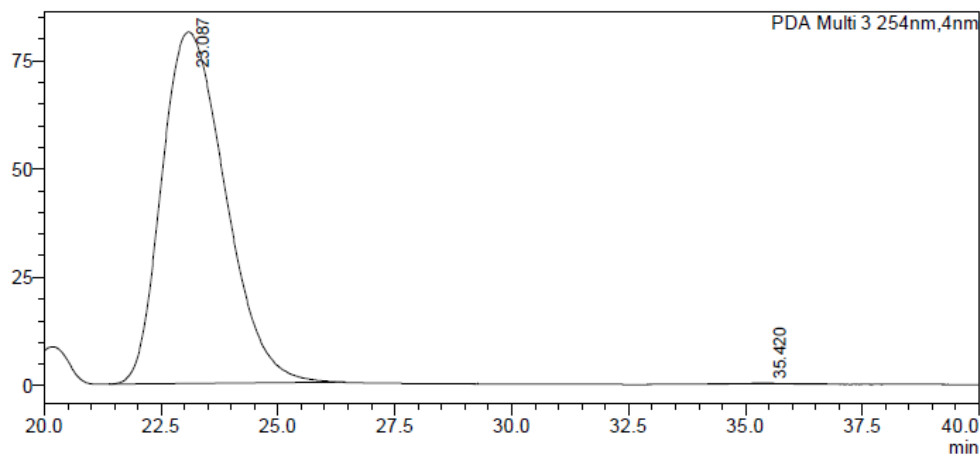
PDA Ch3 254nm

Peak#	Ret. Time	Area	Area%
1	23.238	6966812	51.851
2	35.230	6469286	48.149
Total		13436098	100.000

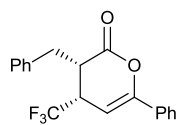


PDA Ch3 254nm

Peak#	Ret. Time	Area	Area%
1	23.087	7700496	99.791
2	35.420	16110	0.209
Total		7716605	100.000

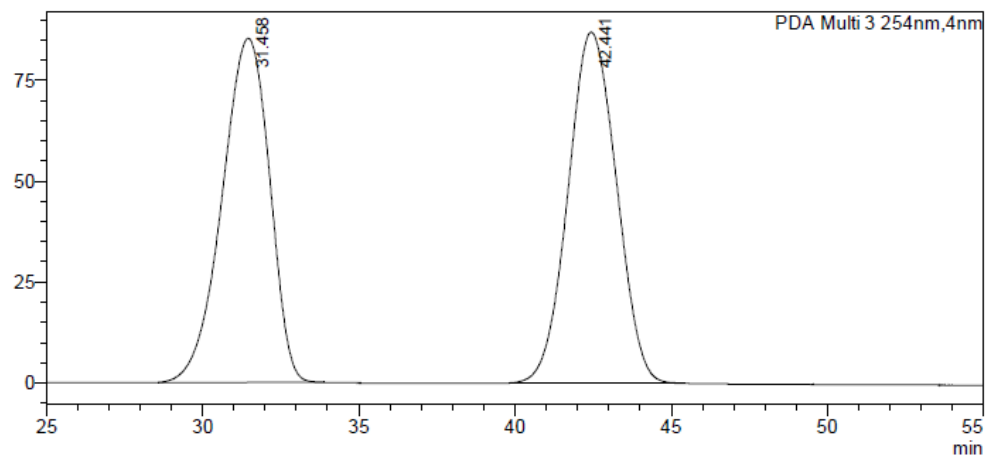


HPLC data compound **17**: Chiralpak AD-H, 99:1 hexane : IPA, flow rate 1 mLmin⁻¹, 254 nm, 30 °C, >99% ee.



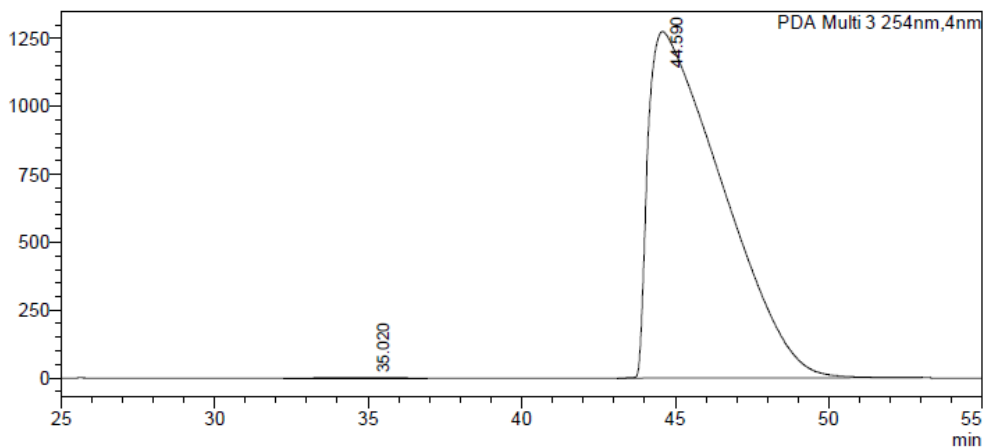
PDA Ch3 254nm

Peak#	Ret. Time	Area	Area%
1	31.458	9051189	49.104
2	42.441	9381549	50.896
Total		18432738	100.000

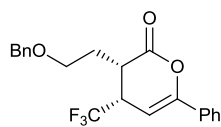


PDA Ch3 254nm

Peak#	Ret. Time	Area	Area%
1	35.020	173322	0.081
2	44.590	213929552	99.919
Total		214102874	100.000

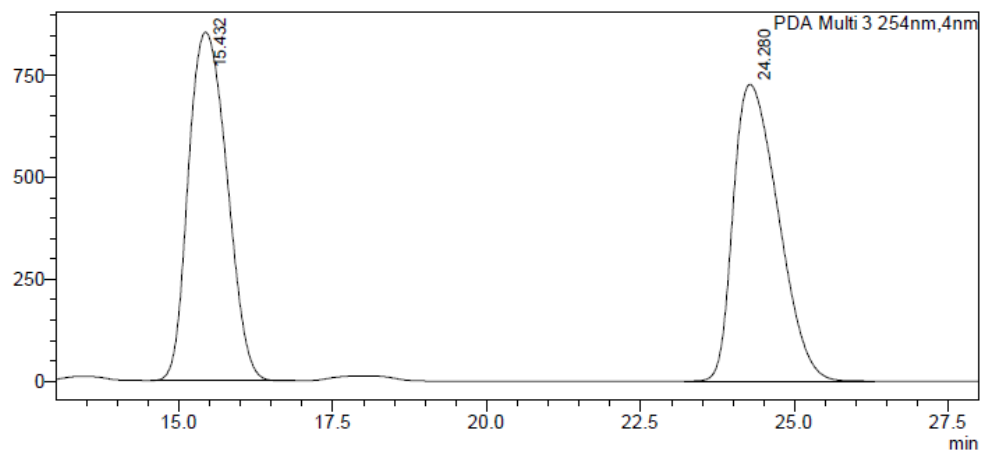


HPLC data compound **18**: Chiralpak AD-H, 98:2 hexane : IPA, flow rate 1 mLmin⁻¹, 254 nm, 30 °C, >99% ee.



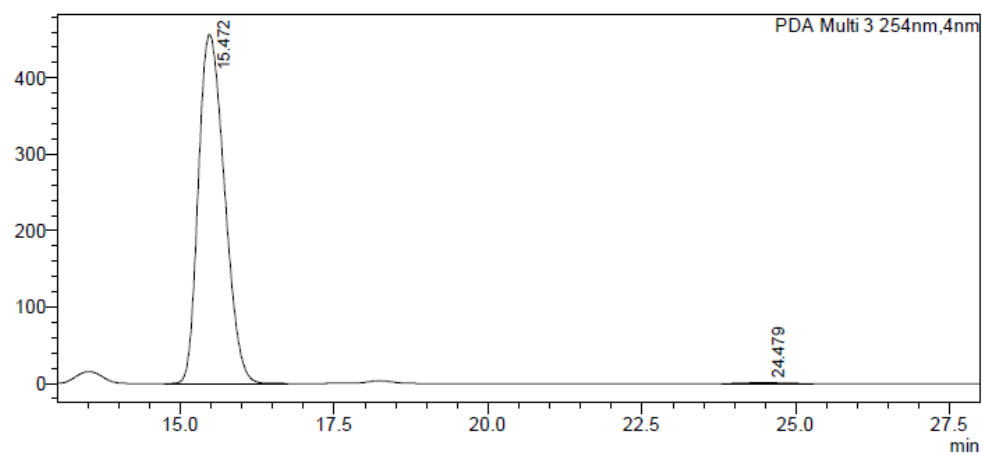
PDA Ch3 254nm

Peak#	Ret. Time	Area	Area%
1	15.432	37400182	50.280
2	24.280	36984348	49.720
Total		74384530	100.000

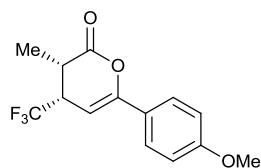


PDA Ch3 254nm

Peak#	Ret. Time	Area	Area%
1	15.472	13489135	99.679
2	24.479	43477	0.321
Total		13532613	100.000

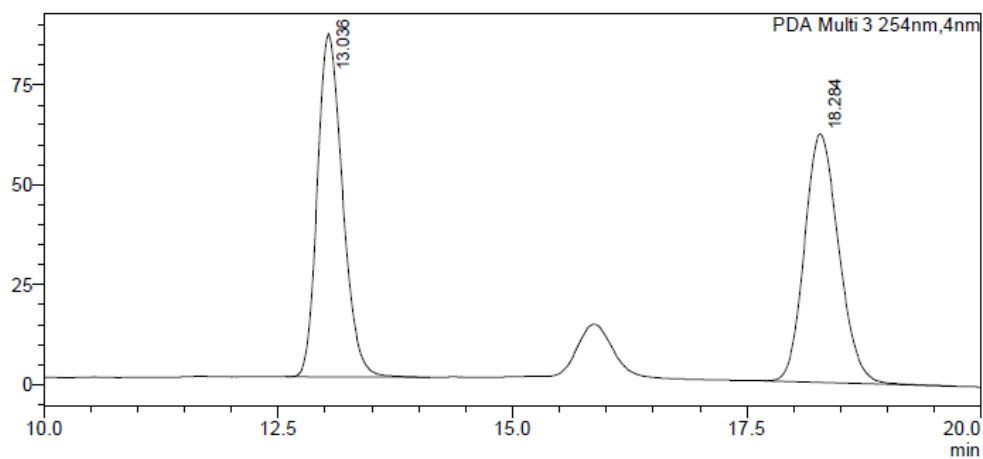


HPLC data compound **19**: Chiralcel OD-H, 95:5 hexane : IPA, flow rate 1 mLmin⁻¹, 254 nm, 30 °C, 99% ee.



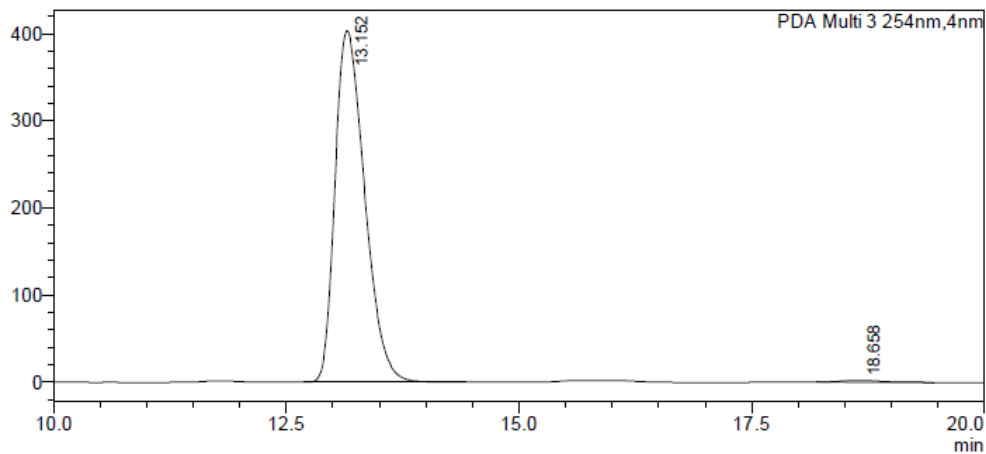
PDA Ch3 254nm

Peak#	Ret. Time	Area	Area%
1	13.036	1607853	50.407
2	18.284	1581910	49.593
Total		3189763	100.000

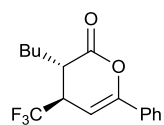


PDA Ch3 254nm

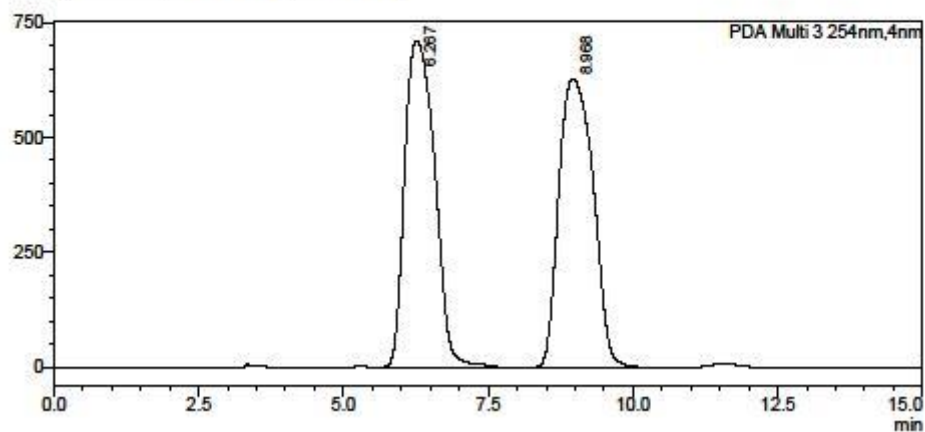
Peak#	Ret. Time	Area	Area%
1	13.152	8948409	99.329
2	18.658	60411	0.671
Total		9008820	100.000



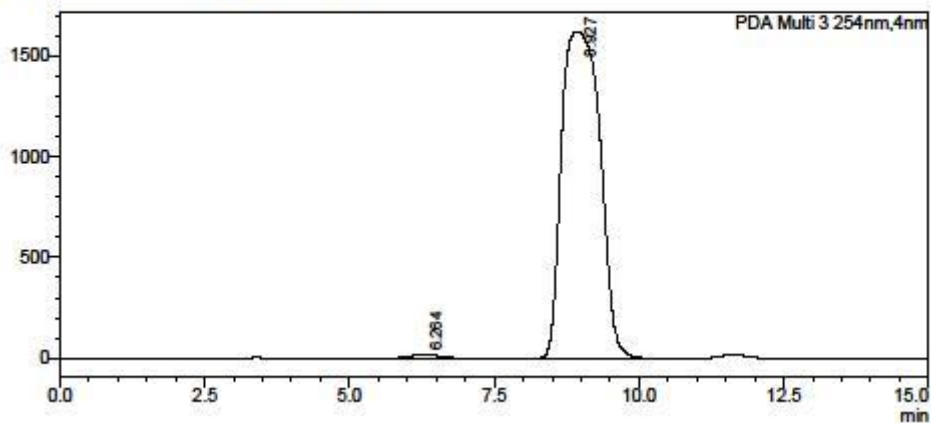
HPLC data compound **20**: Chiralcel OD-H 99:1 hexane : IPA, 1 mLmin⁻¹, 254 nm, 30 °C, 99% ee.



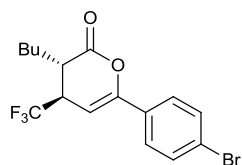
PDA Ch3 254nm			
Peak#	Ret. Time	Area	Area%
1	6.267	25613088	49.760
2	8.968	25860200	50.240
Total		51473288	100.000



PDA Ch3 254nm			
Peak#	Ret. Time	Area	Area%
1	6.264	530860	0.707
2	8.927	74578107	99.293
Total		75108967	100.000

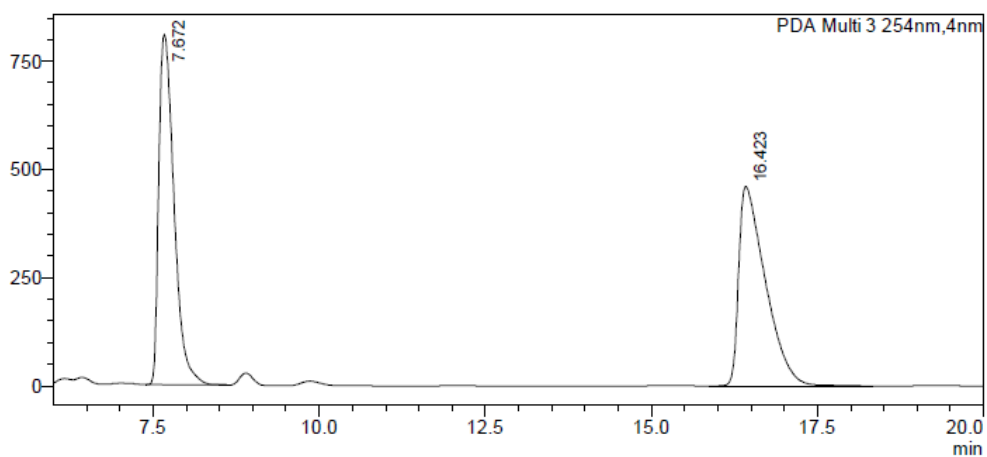


HPLC data compound **21**: Chiralpak IA, 99:1 hexane : IPA, flow rate 1 mLmin⁻¹, 30 °C, 254 nm, 96% ee.



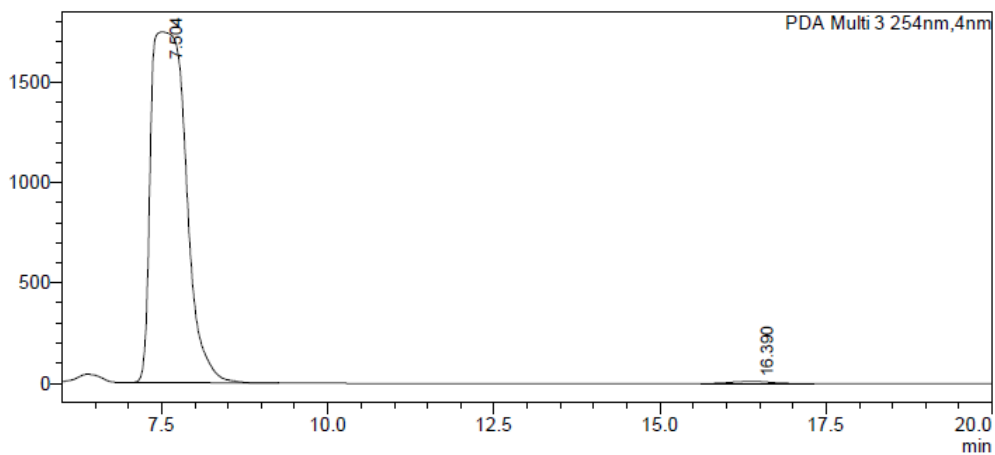
PDA Ch3 254nm

Peak#	Ret. Time	Area	Area%
1	7.672	12954521	50.132
2	16.423	12886296	49.868
Total		25840818	100.000

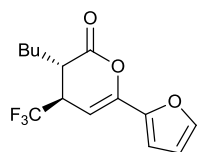


PDA Ch3 254nm

Peak#	Ret. Time	Area	Area%
1	7.504	64466475	99.464
2	16.390	347554	0.536
Total		64814029	100.000

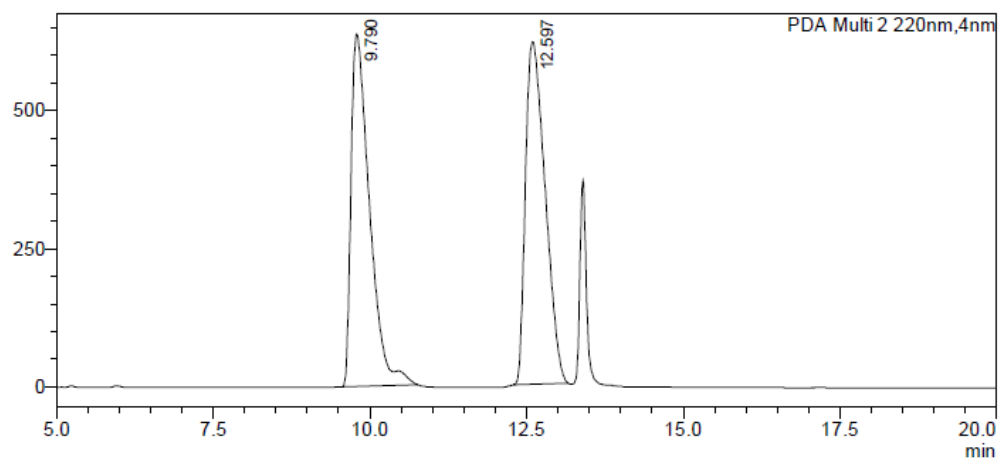


HPLC data compound **22**: Chiralpak IA, 99.8:0.2 hexane : IPA, flow rate 1 mLmin⁻¹, 30 °C, 220 nm, 995:5 ee.



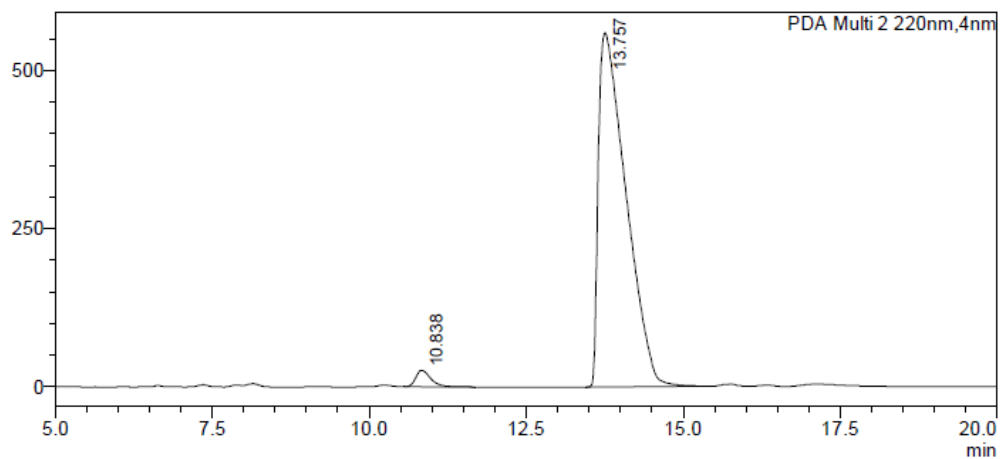
PDA Ch2 220nm

Peak#	Ret. Time	Area	Area%
1	9.790	13076984	49.114
2	12.597	13548957	50.886
Total		26625941	100.000

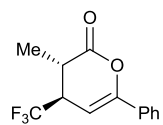


PDA Ch2 220nm

Peak#	Ret. Time	Area	Area%
1	10.838	430605	2.449
2	13.757	17154545	97.551
Total		17585150	100.000

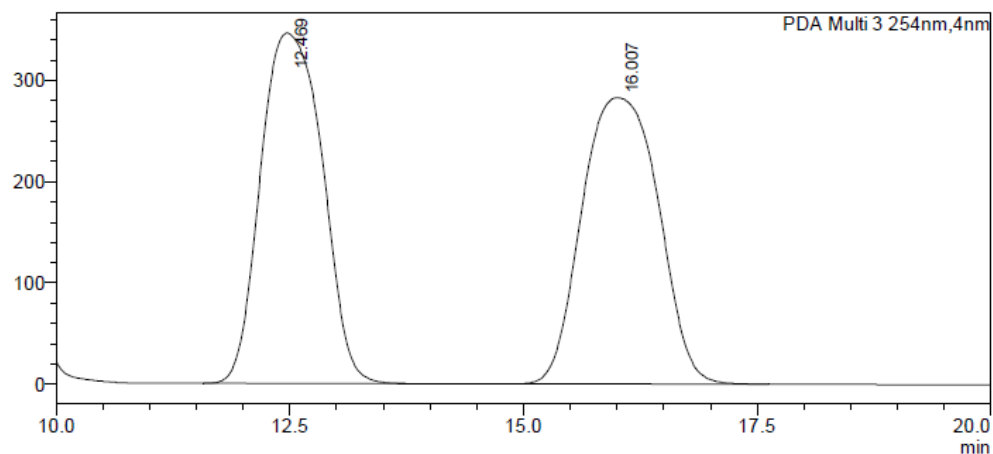


HPLC data compound **23**: Chiralcel OD-H, 99:1 hexane : IPA, flow rate 1 mLmin⁻¹, 30 °C, 254 nm, 99% ee.



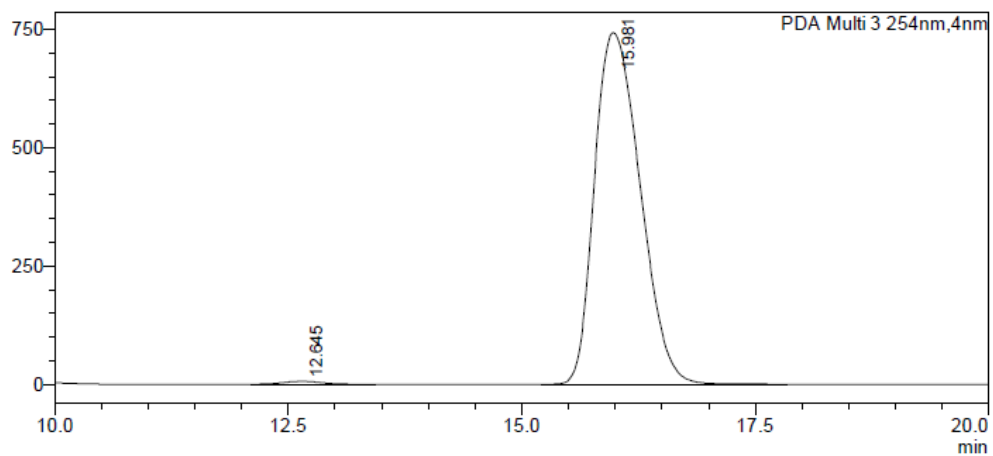
PDA Ch3 254nm

Peak#	Ret. Time	Area	Area%
1	12.469	15966359	49.698
2	16.007	16160193	50.302
Total		32126552	100.000

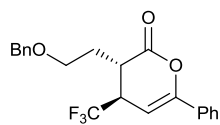


PDA Ch3 254nm

Peak#	Ret. Time	Area	Area%
1	12.645	160654	0.632
2	15.981	25263535	99.368
Total		25424189	100.000

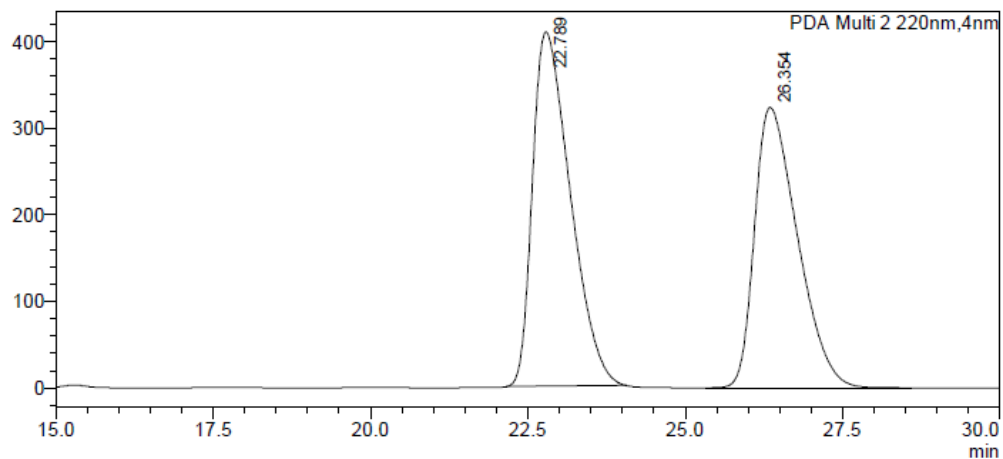


HPLC data compound **24**: Chiralcel OD-H, 98:2 hexane : IPA, flow rate 1 mLmin⁻¹, 30 °C, 254 nm, 96% ee.



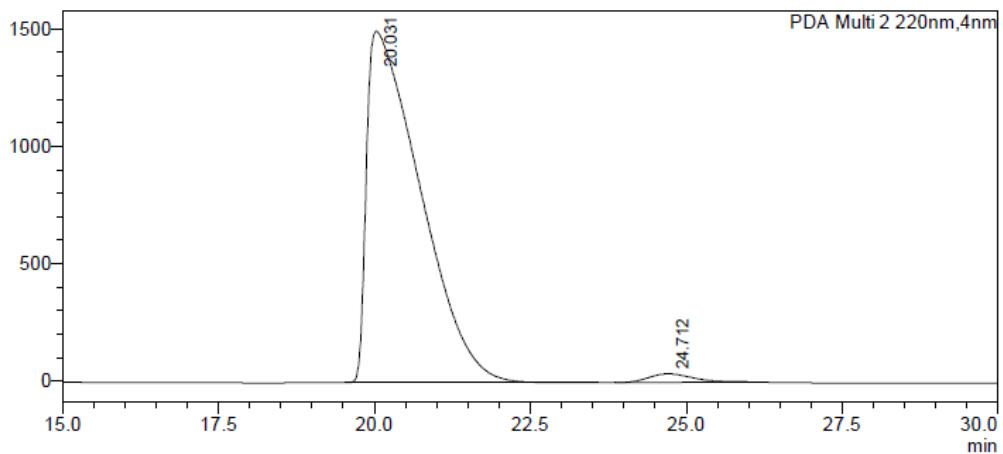
PDA Ch2 220nm

Peak#	Ret. Time	Area	Area%
1	22.789	17139246	52.747
2	26.354	15353879	47.253
Total		32493125	100.000

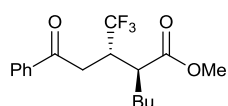


PDA Ch2 220nm

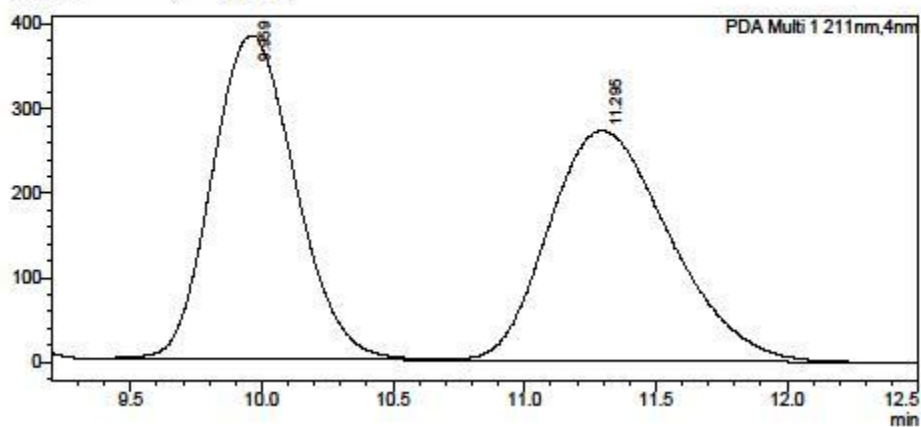
Peak#	Ret. Time	Area	Area%
1	20.031	89895368	97.901
2	24.712	1927570	2.099
Total		91822938	100.000



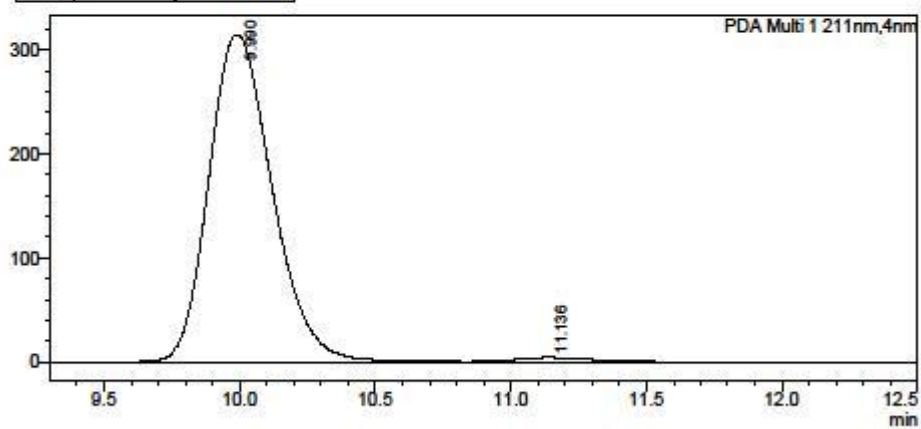
HPLC data compound **25**: Chiralcel OJ-H 95:5 hexane : IPA, 0.5 mLmin⁻¹, 211 nm, 30 °C, 97% ee



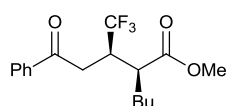
PDA Ch1 211nm		
Peak#	Ret. Time	Area%
1	9.959	49.225
2	11.295	50.775
Total		100.000



PDA Ch1 211nm		
Peak#	Ret. Time	Area%
1	9.990	98.231
2	11.136	1.769
Total		100.000

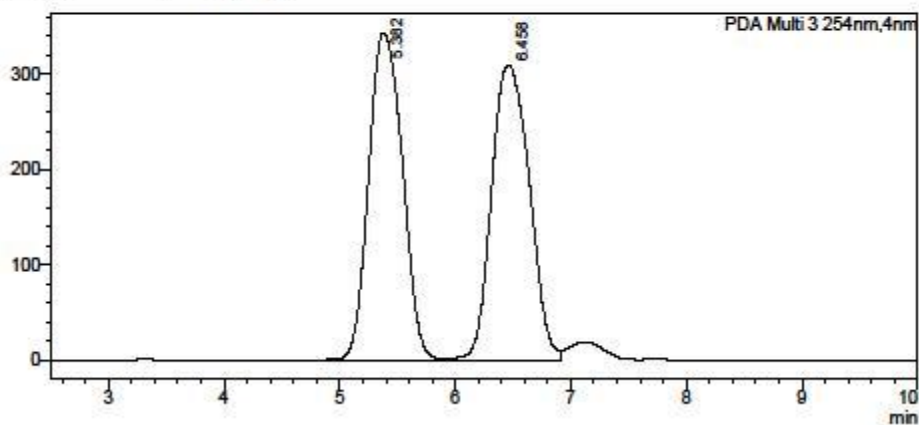


HPLC data compound **27**: Chiralpak AD-H 98:2 hexane : IPA, 1 mLmin⁻¹, 254 nm, 30 °C, >995:5 ee



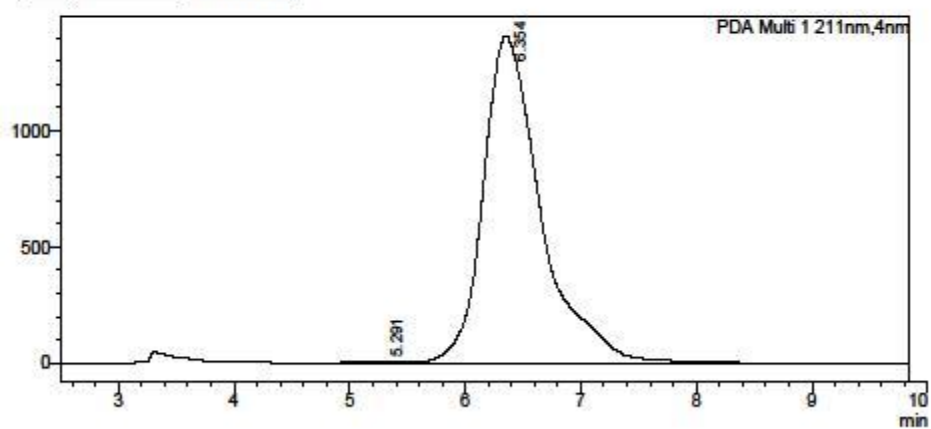
PDA Ch3 254nm

Peak#	Ret. Time	Area%
1	5.382	49.740
2	6.458	50.260
Total		100.000



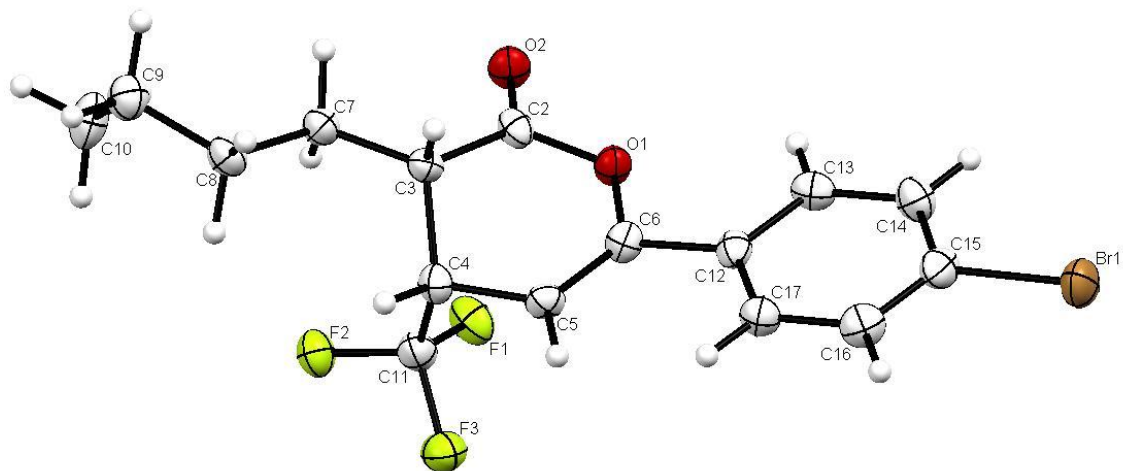
PDA Ch1 211nm

Peak#	Ret. Time	Area%
1	5.291	0.437
2	6.354	99.563
Total		100.000



X-Ray Crystal Structure of *syn*-12

See CIF file for full crystallographic details.



Thermal ellipsoid contours shown at 50% probability level