Tandem Allylic Isomerization – IMDAF Reactions and Other Isomerizations

by

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The first section of this thesis describes a novel allylic isomerization, followed by an intramolecular Diels-Alder furan cycloaddition, fragmentation, aromatization, and *N*-Boc deprotection cascade that leads to the formation of synthetically and biologically useful 5,6,7-substituted indoles. Various 5,6,7-substituted indoles are synthesized in moderate to good yield using this convergent method. Nonthermal microwave effects also prove to be essential in this transformation.

The second section describes the extension of our indole synthesis methodology through a microwave assisted intramolecular Diels-Alder furan cycloaddition to a 5-hydroxyindole synthesis from readily available alkynals and alkynones. This convergent procedure is compatible with multiple-functionalities in the 4-position of the indole, including electron-withdrawing and electron-donating groups. Yields range from 44 to 64%.

The third section describes a methodology study of the alkyne isomerization reaction using a non-nucleophilic base. After screening of reaction conditions, optimal conditions were achieved by the use of 2.2 equiv of LiTMP in THF (1.0 M substrate concentration) at r.t. for 1 h.

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LIST OF ABBREVIATIONS

AAA	asymmetric allylic alkylation
Ac	acetyl
AIBN	azobisisobutyronitrile
Boc	*tert*-butoxycarbonyl
Bn	benzyl
*n*Bu	*n*-butyl
*t*Bu	*tert*-butyl
Bz	benzoyl
Calcd	calculated
DHP	3,4-dihydro-2*H*-pyran
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide (diphenylphosphorazidate)
dppb	1,4-*bis*(diphenylphosphino)butane
dppe	1,2-*bis*(diphenylphosphino)ethane
dppp	1,3-*bis*(diphenylphosphino)propane

EA	ethyl acetate
ee	enantiomeric excess
EI	electron ionization
ESI	electrospray ionization
Et	ethyl
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
HWE	Horner–Wadsworth–Emmons
IMDAF	intramolecular Diels-Alder furan cycloaddition
imid	imidazole
KAPA	potassium 3-aminopropylamide
KHMDS	potassium bis(trimethylsilyl)amide
IR	infrared
LAH	lithium aluminum hydride
LCMS	liquid chromatography–mass spectrometry
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
Me	methyl
Mp	melting point
Ms	methanesulfonyl
NaHMDS	sodium bis(trimethylsilyl)amid
MW	microwave
NBS	*N*-bromosuccinimide

NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
Nuc	nucleophile
Ph	phenyl
PMA	phosphomolybdic acid
PPTS	pyridinium *p*-toluenesulfonate
*i*Pr	isopropyl
pyr	pyridine
rt	room temperature
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*t*-butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	2-tetrahydropyranyl
TLC	thin layer chromatography
TMG	1,1,3,3-tetramethylguanidine
LiTMP	lithium tetramethylpiperidide
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl

1.0 TANDEM ALLYLIC ISOMERIZATION – IMDAF REACTION IN THE SYNTHESIS OF 5,6,7-SUBSTITUTED INDOLES

1.1 INTRODUCTION

1.1.1 Significance of indoles

The indole nucleus is probably one of the most important structural components among a wide array of natural and unnatural compounds.[1] Tryptophan **1**, one of the essential amino acids, is a constituent of many proteins and the precursor of most indole alkaloids. The neurotransmitters serotonin **2** and melatonin **3** are involved in many biochemical pathways.[1] The discovery of the plant hormone auxin **4** further increased the interest in indole chemistry (**Figure 1**).[1]

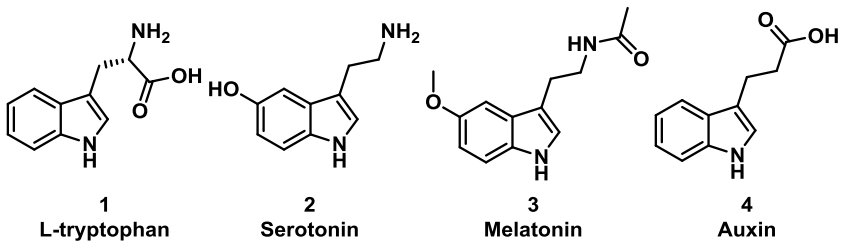


Figure 1. Representative bioactive indoles

In addition, many indole alkaloids exhibit CNS activities, such as ergoline **5**, yohimbine **6** and the iboga alkaloids **7** (**Figure 2**).[2-5] Indole or indoline containing-compounds are also among 4 of the top 200 brand name drugs in 2009 (cialis **8**, zeldox **9**, sutent **10** and maxalt **11**).[6]

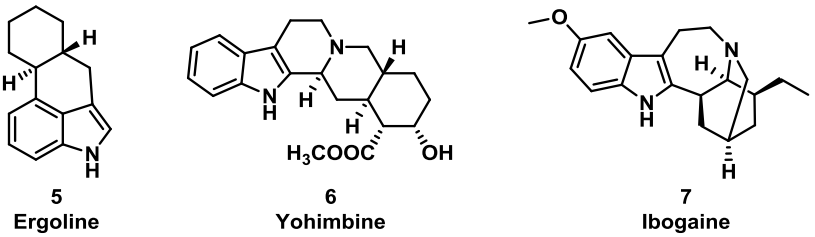


Figure 2. Representative natural indole alkaloids

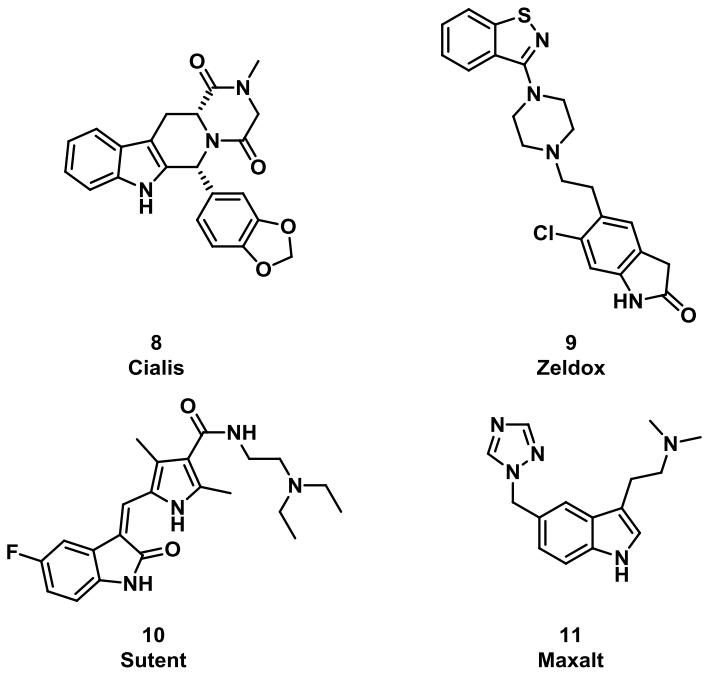


Figure 3. The top 200 brand-name drugs with indole or indoline cores in 2009

As a result of the importance of these heterocycles, huge efforts have been spent toward the synthesis and functionalization of indoles. Some well-established protocols include sigmatropic rearrangements (Fischer and Gassman syntheses), cyclizations (Madelung synthesis, Bischler synthesis) and transition metal catalyzed reactions (Larock synthesis, Fürstner synthesis and Castro synthesis).[7-16]

1.1.2 The Diels-Alder reaction of furans

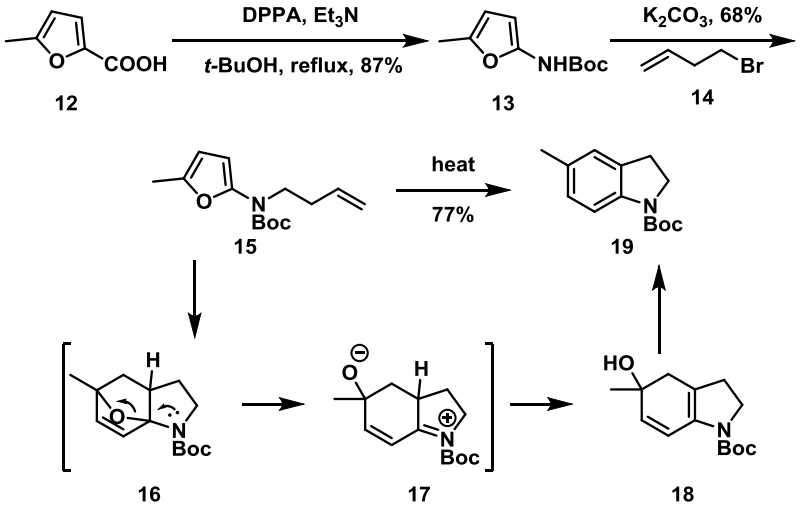
The Diels-Alder cycloaddition is one of the most widely used reactions in the construction of complex natural products.[17] This pericyclic reaction has proven to be broadly applicable and efficient in total synthesis and cascade sequences. The regio- and stereoselectivities of these [4+2] cycloadditions have been improved further by employing chiral auxiliaries or chiral Lewis acids.[18]

The use of furans as diene components in the Diels-Alder reaction can be traced back to its discovery almost eighty-five years ago.[19] The Diels-Alder reaction between dienophiles and furans gives rise to a substituted 7-oxabicyclo[2.2.1]hept-5-ene, which has been further converted into interesting synthetic products.[20]

1.1.3 Amino-furan cycloaddition

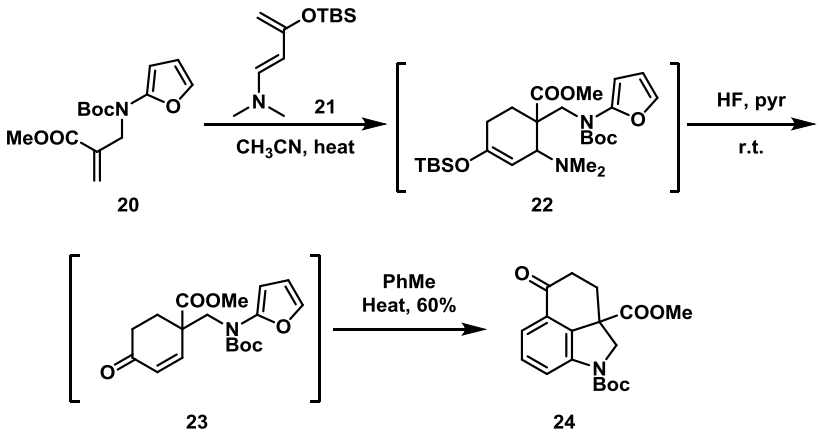
A variety of indolines have been prepared by Padwa and co-workers using the intramolecular Diels-Alder furan cycloaddition (IMDAF) of 2-amino furans with different dienophiles.[21-24]

The *N*-Boc-2-amino furan **13**, prepared by a Curtius rearrangement from furoic acid **12**, was converted to cycloaddition precursor **15** by *N*-alkylation with bromide **14**. The IMDAF reaction occurred at 165 ^{o}C in toluene or at 100 ^{o}C when 4 M ethereal $LiClO_4$ was used in 77% yield. Under these conditions, the initial cycloadduct was converted into indoline **19** with a series of ring openings and deprotonations (**Scheme 1**).[25]



Scheme 1. Intramolecular Diels-Alder reaction of 2-aminofurans

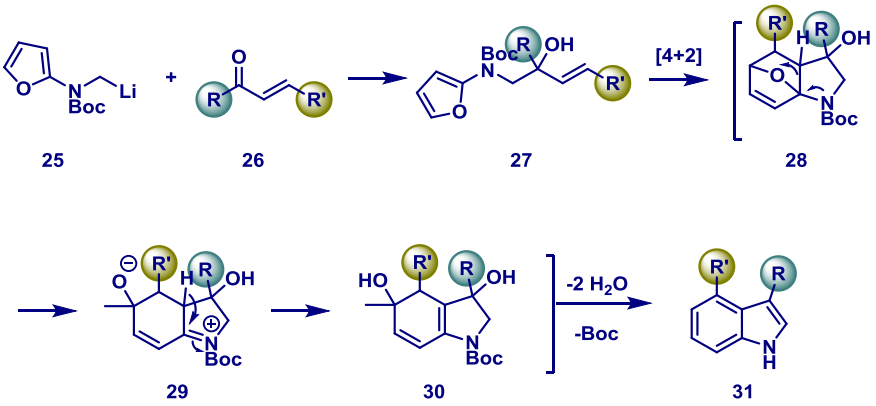
The Padwa group has successfully applied this methodology to the synthesis of several ergoline alkaloids.[26] The 2-amino furan intermediate **23** with pendant enone functionality was generated *in situ* from a TBS deprotection of **22**. Furan **23** was transformed into the desired tricyclic ketone system **24** through the IMDAF reaction under thermal conditions (165 ℃ in toluene) (**Scheme 2**).[26]



Scheme 2. Application of amino-furan cycloaddition in the synthesis of ergoline alkaloids

1.1.4 IMDAF in the synthesis of 3,4-substituted indoles

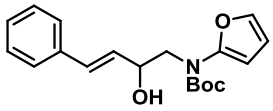
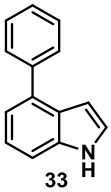
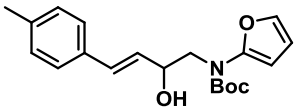
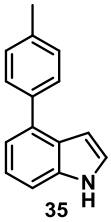
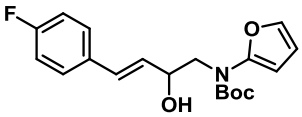
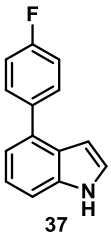
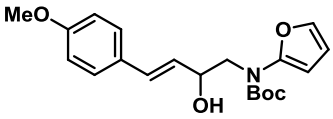
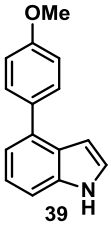
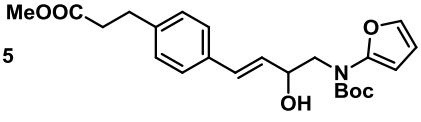
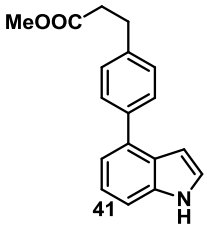
In our group's previous work, efforts were focusing on extending the amino-furan cycloaddition to an indole synthesis. It was envisioned that addition of lithiated reagent **25** to various α,β-unsaturated carbonyl compounds **26**, followed by cycloaddition, dehydration aromatization and deprotection would give different 3,4-substituted indoles **31** (**Scheme 3**).[27]

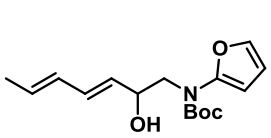
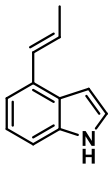
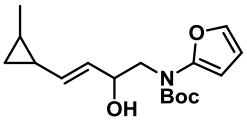
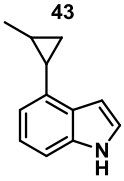
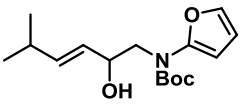
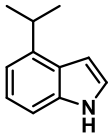


Scheme 3. Proposed indole synthesis

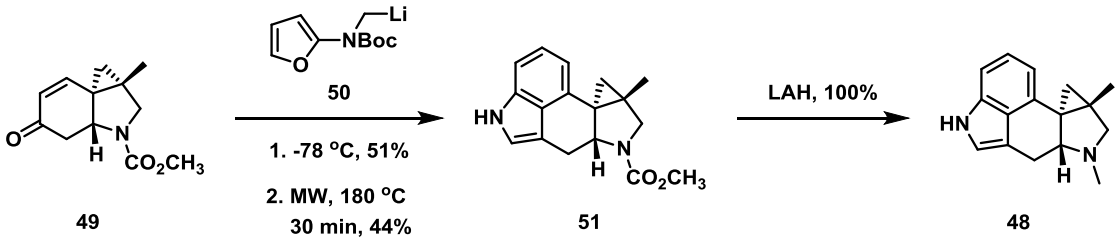
The preparation of several 4-substituted indoles was reported in good yields by subjecting furan-substrates to microwave irradiation (**Table 1**).[27]

Table 1. IMDAF in the synthesis of 4-substituted indoles

Entry	Substrate	Time/min	Product	Yield(%)
1	 **32**	20	 **33**	79
2	 **34**	20	 **35**	76
3	 **36**	20	 **37**	83
4	 **38**	20	 **39**	69
5	 **40**	20	 **41**	77

Entry	Substrate	Time/min	Product	Yield(%)
6		25		69
	42		43	
7		30		48
	44		45	
8		30		36
	46		47	

This methodology was successfully applied for the total synthesis of (±)-cycloclavine **48** (**Scheme 4**).[28] Alkylation of **49** with lithiated reagent **50** afforded the cycloaddition precursor in 51% yield. The indole **51** was obtained by microwave irradiation in 44% isolated yield. Finally, reduction of indole **51** with LAH gave (±)-cycloclavine **48** in quantitative yield.



Scheme 4. Total synthesis of (±)-cycloclavine

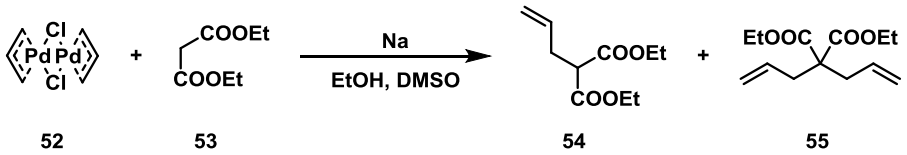
1.1.5 π-Allyl palladium complex

1.1.5.1 Introduction

Palladium catalyzed allylic reactions such as esterifications, aminations and alkylations have been an important area of research.[29] The versatile π-allyl palladium intermediates can easily be formed by treatment of allyl compounds containing leaving groups with various palladium catalysts. This palladium complex intermediate can react with different nucleophiles, such as enamines and the anions derived from diethyl malonate or ethyl acetoacetate. The Tsuji-Trost reaction[30,31] and Saegusa–Ito oxidation[32] are two examples that utilize π-allyl palladium complexes. The White group has recently developed a catalytic method to generate these complexes *via* C-H allylic activation.[33]

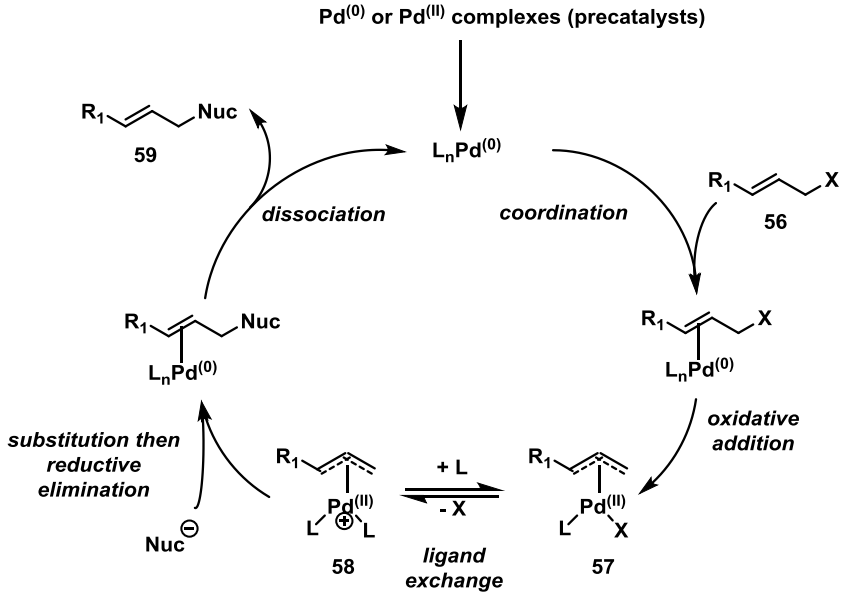
1.1.5.2 Tsuji-Trost reaction

The Pd-catalyzed allylation of carbon nucleophiles with an allylic compound *via* a π-allyl palladium complex is known as the Tsuji-Trost reaction. Tsuji first reported that a π-allyl palladium complex could be substituted with ethyl malonate anion (**Scheme 5**) in 1965.[30] Trost has developed an asymmetric variant of this reaction through the use of chiral phosphine ligands.[31]



Scheme 5. Tsuji's allylic alkylation process

The accepted mechanism (**Scheme 6**) of the Tsuji-Trost reaction begins through coordination of palladium catalyst with allylic substrate **56** followed by oxidative addition and ligand exchange to generate the π-allyl palladium complex **58**. Nucleophilic substitution followed by reductive elimination generates the desired product and the catalyst.[34,35]

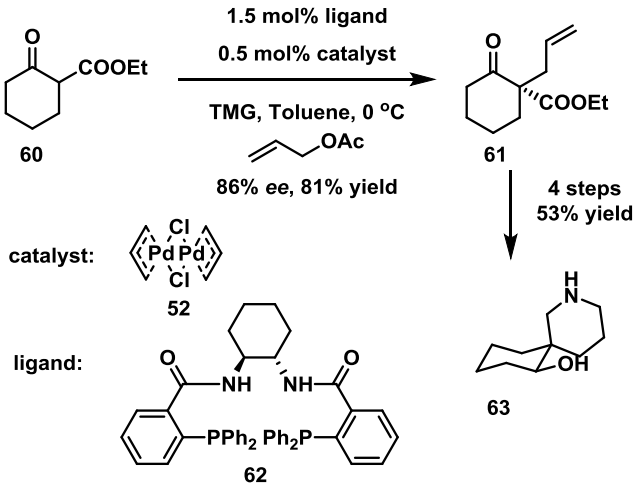


Scheme 6. Mechanism of Tsuji-Trost reaction

Since its discovery, the Tsuji-Trost reaction has been a vibrant area of study. The asymmetric allylic alkylation (AAA) is tolerant of various carbon and heteroatom based nucleophiles and has been used as a key strategy in over 50 total syntheses.[36]

The total synthesis of the spirocyclic alkaloid (-)-nitramine **63** is an example for an asymmetric allylic alkylation reaction.[37] The allyl containing adduct **61** was afforded by the

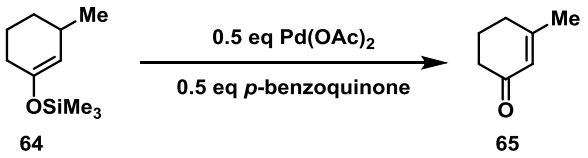
reaction of allyl acetate with ketoester nucleophile **60** in the presence of palladium catalyst **52** and phosphine ligand **62** in 81% yield (86% *ee*) (**Scheme 7**).



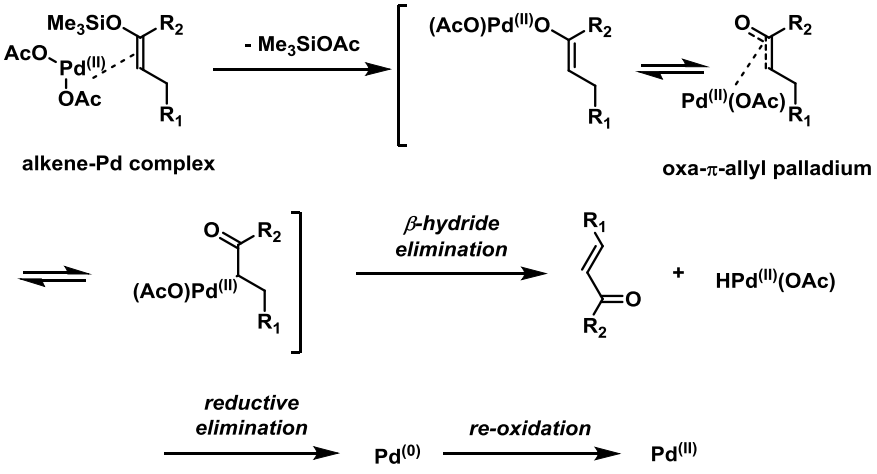
Scheme 7. Asymmetric synthesis of (-)-nitramine

1.1.5.3 Saegusa–Ito oxidation

The Saegusa–Ito oxidation is another reaction that involves π-allyl palladium complexes. It was discovered by Saegusa in 1978 (**Scheme 8**).[32] The catalytic version was developed by Larock in 1995 by using 10 mol% of $Pd(OAc)_2$ and an oxygen atmosphere in DMSO.[38] The mechanism of this process features the formation of an oxa-π-allyl palladium complex followed by β-hydride elimination to give the enone products. The catalyst is regenerated through re-oxidation by oxygen (**Scheme 9**).[39,40]



Scheme 8. Saegusa–Ito oxidation

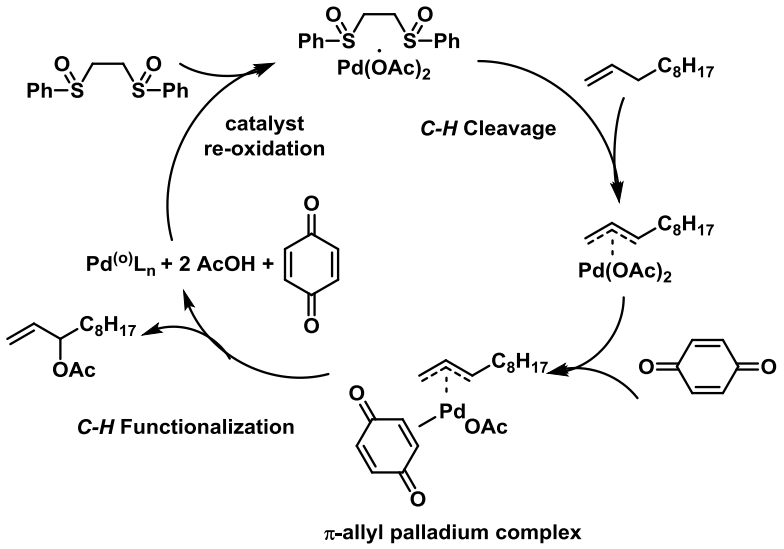


Scheme 9. Mechanism of the Saegusa–Ito oxidation

1.1.5.4 π-Allyl palladium complexes in C-H allylic oxidation

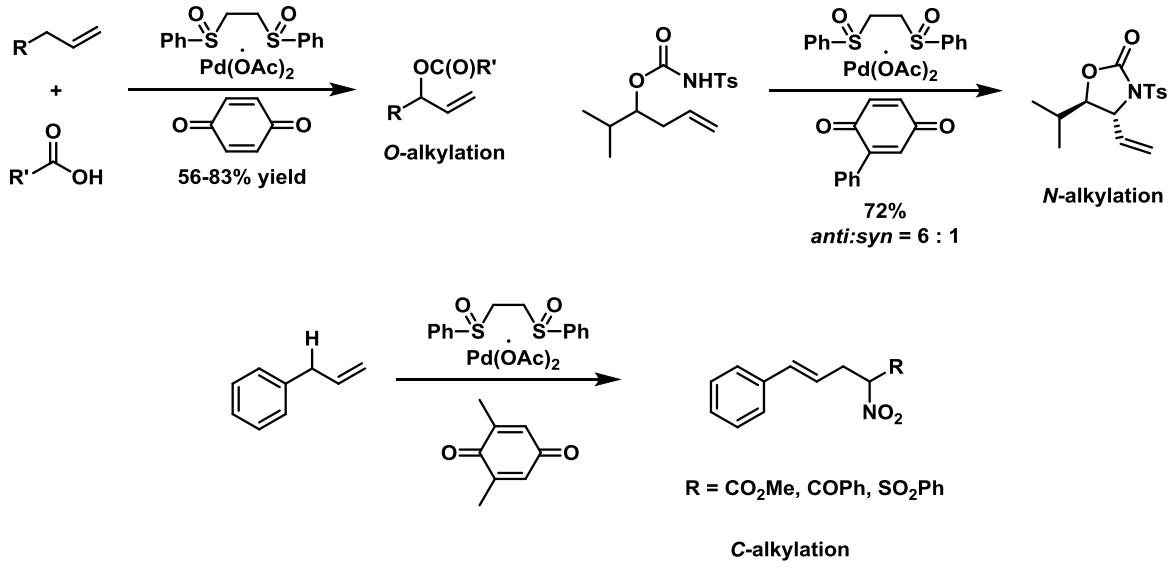
The White group has described an electrophilic Pd(II)/sulfoxide catalyst for allylic C-H activation to generate the π-allyl palladium complex which can be further transformed *via* esterification,[41] amination[42] and alkylation.[43]

The mechanistic pathway begins with the sulfoxide promoted C-H cleavage followed by benzoquinone promoted C-H functionalization. The catalyst is regenerated through oxidation by benzoquinone (**Scheme 10**).[33]



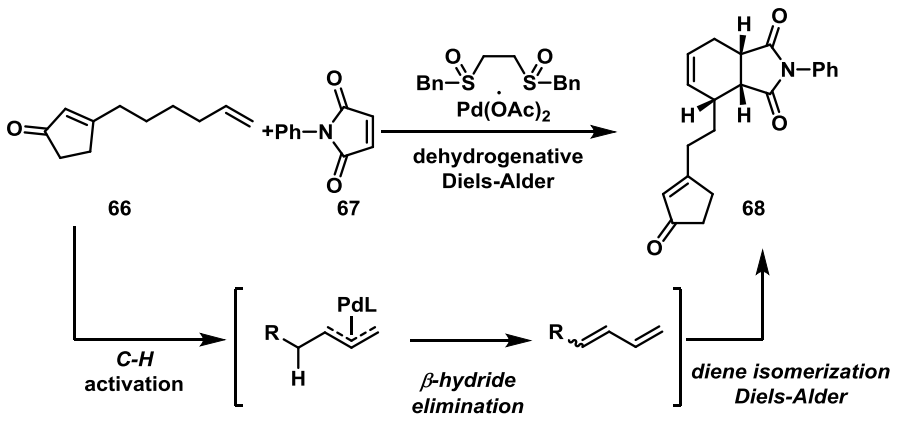
Scheme 10. General mechanism of allylic C-H oxidations

The π-allyl palladium complex *via* allylic C-H activation can undergo substitution with various nucleophiles such as *O*-alkylation,[41] *N*-alkylation[42] and *C*-alkylation[43] (**Scheme 11**).



Scheme 11. Alkylation of a π-allyl palladium complex through allylic C-H oxidation

Active diene intermediates useful for cycloaddition can be generated from π -allyl palladium complexes *via* β-hydride elimination (**Scheme 12**).[44]



Scheme 12. Dehydrogenative Diels-Alder reaction through allylic C-H oxidation

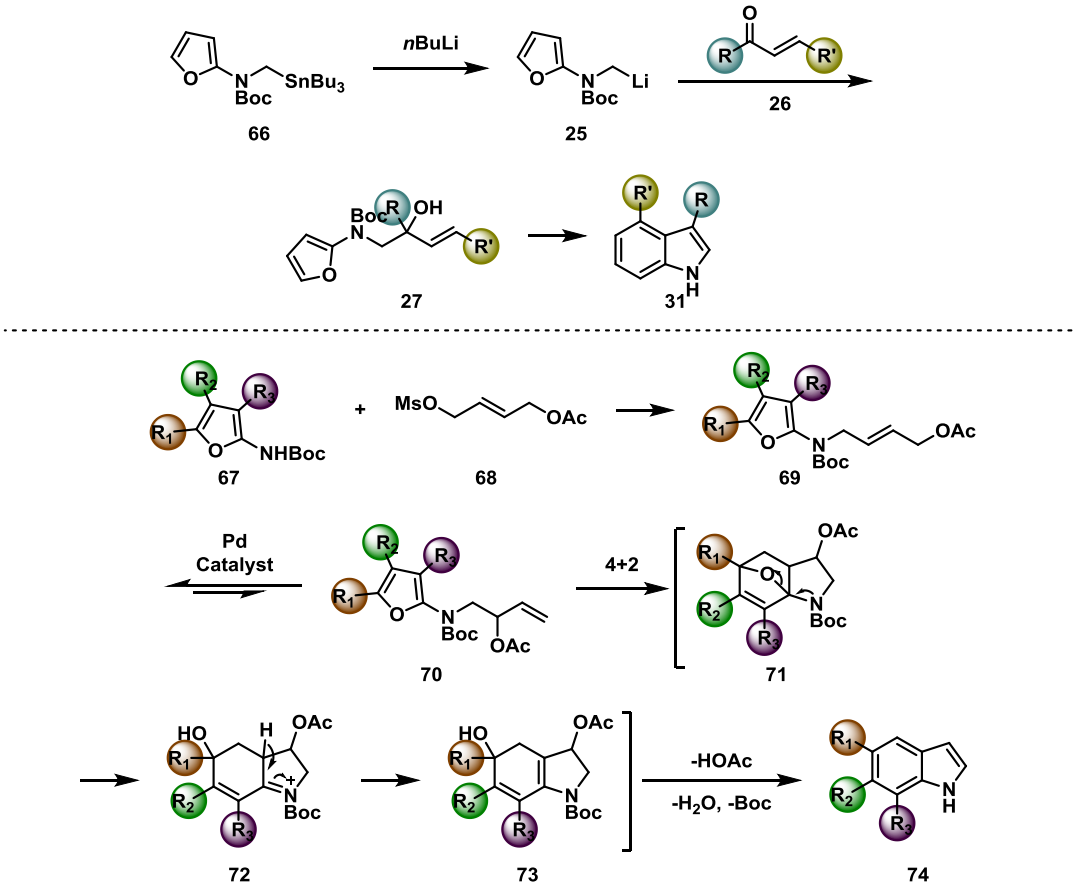
1.2 RESULTS AND DISCUSSION

1.2.1 Introduction

We have recently reported a strategy for a convergent synthesis of 3,4-substituted indoles that uses an intramolecular Diels-Alder furan (IMDAF) cycloaddition.[27,28,45] However, the limited stability and presumed toxicity of stannane reagent **66** prompted an alternative procedure to access the IMDAF intermediates. Furthermore, we were trying to avoid the high temperatures required for the indole cyclization reactions. Therefore, we have developed a tandem palladium catalyzed allylic isomerization-IMDAF process (**Scheme 13**) for the synthesis of indoles

including the 5,6- and 7- substitutions that are present in many pharmaceutical agents (**Figure 4**).[1,3-5]

This procedure begins with coupling of mesylate **68** and variously substituted *N*-Boc-2-aminofurans **67** to afford the allylic acetates **69**. Treatment of **69** with suitable palladium catalysts (*vide infra*) establishes an equilibrium between the thermodynamically less favored acetates **70** which are aligned to undergo the initial IMDAF reaction to cycloadducts **71** which proceed to indoles **74** *via* dehydrative aromatization and deprotection.



Scheme 13. Proposed indole synthesis

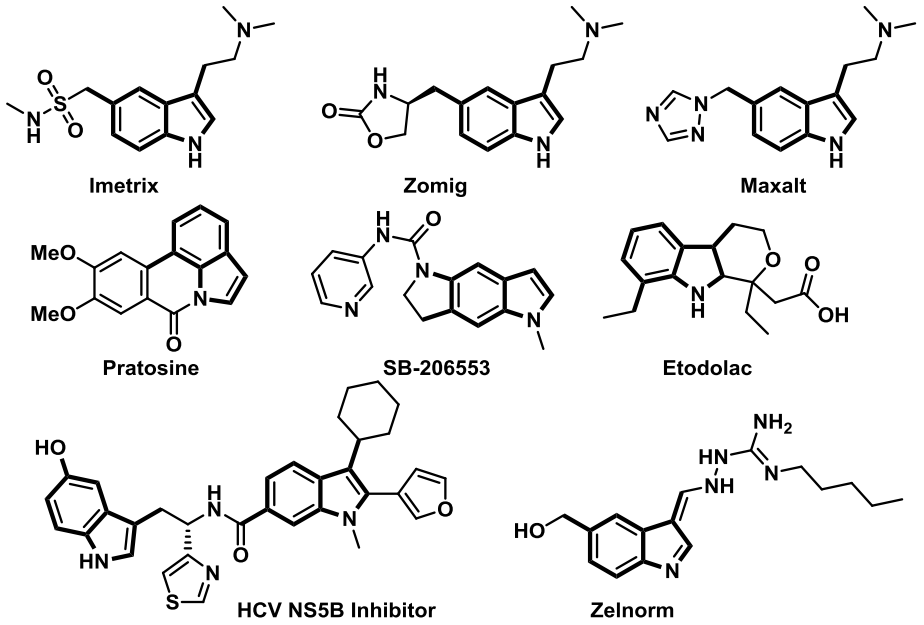


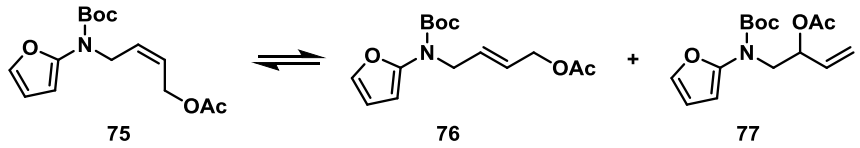
Figure 4. Representative biologically active 5,6,7-substituted indoles (outlined bold)

1.2.2 Screening of reaction conditions

1.2.2.1 Screening of catalysts

Various palladium catalysts, including $Pd(OAc)_2$, $Pd(CH_3CN)_2Cl_2$, and $Pd(PPh_3)_4$ have been used in allylic isomerization reactions.[31] However, there are few examples of allylic isomerization reactions that participate in cascade processes.[46] Initial attempts to isomerize the internal alkene **75** to the terminal alkene **77** using $Pd(OAc)_2$ or $Pd(CH_3CN)_2Cl_2$ failed. However, addition of the Pd(0) catalyst, $Pd(PPh_3)_4$, provided small amounts of the desired alkene **77** as determined by ^{1}H NMR analysis of the crude reaction mixtures (**Table 2**).

Table 2. Catalysts screening for allylic isomerization[a]



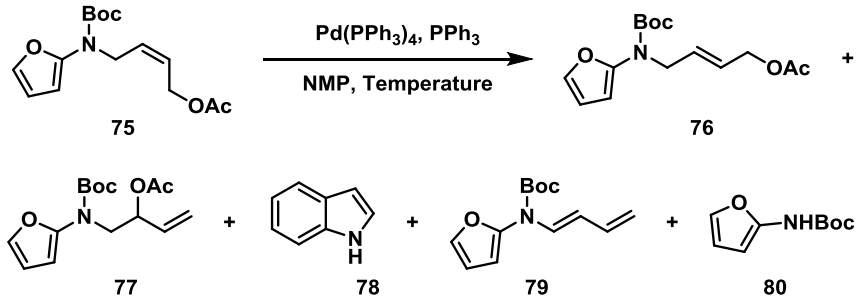
Entry	Catalyst[b]	mol%	Temperature	Results[c]
1	$Pd(OAc)_2$	3	70 °C	**75** (66%) + **76** (34%)
2	$Pd(CH_3CN)_2Cl_2$	20	100 °C	**75** (80%) + **76** (20%)
3	$Pd(PPh_3)_4$	5	70 °C	**75** (63%) + **76** (27%) + **77** (10%)

[a]Reactions were usually carried out in a 1.0 M concentration (80 mg in 0.3 mL of THF) for 4 h. [b]Percentage refers to the ratio determined by crude ^{1}H NMR analysis.

1.2.2.2 Screening of temperature

With these encouraging preliminary results, we decided to investigate the reaction temperatures necessary to promote the IMDAF process. In our previous report[27], microwave irradiation at temperatures exceeding 180 °C was required for the IMDAF reaction in the synthesis of 4-substituted indoles. Efforts to lower the reaction temperatures in the palladium catalyzed process failed to give cycloaddition products. A modest yield of indole **78** was obtained when allylic acetate was subjected to 180 °C for 20 min under microwave conditions (**Entry 5, Table 3**).

Table 3. Temperature screening[a]



Entry	Temperature	Time	Results[c]
1[b]	70 °C	4 h	**75** (50%) + **76** (22%) + **77** (8%)
2[b]	100 °C	18 h	**75** (6%) + **76** (27%) + **77** (9%) + **79** (33%)
3	130 °C	1 h	**76** (22%) + **79** (43%) + **80** (21%)
4	150 °C	1 h	**79** (59%) + **80** (29%)
5	180 °C	20 min	**78** (19%)

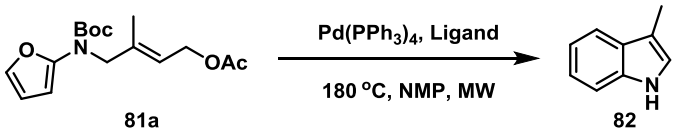
[a]All reactions were carried out with 5 mol% $Pd(PPh_3)_4$ and 20 mol% PPh_3 under microwave irradiation in a concentration of 1.0 M (80 mg in 0.3 mL NMP). [b]Conventional heating. [c]Isolated yields.

1.2.2.3 Screening of ligands

Due to the instability of indole under these elevated temperatures, we changed the allylic acetate substrate to **81a** which would provide the more stable 3-methyl indole **82.**

The evaluation of various ligands revealed that strong electron donating ligands like $P(OR)_3$ (**Entry 5, 9, Table 4**) significantly improved the formation of the desired 3-methyl indole **82**. It was also demonstrated that microwave heating was preferred as conventional heating was unsuccessful which suggests that nonthermal microwave effects[47-49] are essential for this transformation.

Table 4. Ligand screening for cyclization[a]



81a 82

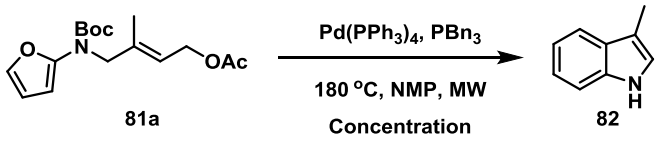
Entry	Ligand	Yield[b]	Entry	Ligand	Yield[b]
1	dppb	59%	**7**	PPh_3	45%
2	dppe	48%	**8**	$P(t\text{Bu})_3$	0
3	dppp	40%	**9**	$P(OEt)_3$	71%
4	PBn_3	74%	**10**	$PH(t\text{Bu})_2O$	21%
5	$P(Oi\text{Pr})_3$	83%	**11**	$P(OPh)_3$	27%
6	$P(n\text{Bu})_3$	25%	**12**[c]	$P(Oi\text{Pr})_3$	0

[a]All reactions were carried out with 5 mol% $Pd(PPh_3)_4$ and 20 mol% ligand under microwave irradiation in a concentration of 0.1 M in NMP at 180 ^oC for 20 min. [b]Isolated yields.

1.2.2.4 Variation of concentration

The optimal reaction concentrations were at 0.1-0.2 M which provided indole **82** in 74 and 72% yield, respectively. More dilute conditions gave <10% conversion of starting material (**Table 5**).

Table 5. Concentration variation for cyclization[a]



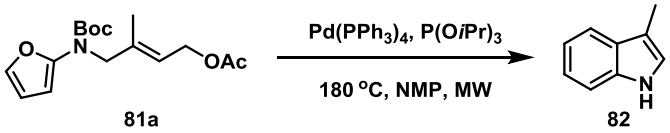
Entry	Concentration	Yield[b]	Entry	Concentration	Yield[b]
1	1.0 M	49%	**4**	0.2 M	72%
2	0.5 M	48%	**5**	0.1 M	74%
3	0.3 M	52%	**6**	0.04 M	<10%

[a]All reactions were carried out with 5 mol% $Pd(PPh_3)_4$ and 20 mol% PBn_3 under microwave irradiation in NMP at 180 °C for 20 min. [b]Isolated yields.

1.2.2.5 Variation of catalyst loading

These initial investigations used 5 mol% catalyst loadings, and efforts to decrease the catalyst (1-2 mol%) were unproductive and resulted only in recovery of starting materials. Slightly lower yields of the indole products were obtained by increasing the catalyst loading (10 and 20 mol%) which could be attributed to palladium-mediated indole oxidations (**Table 6**).

Table 6. Catalyst loading variation for cyclization[a]



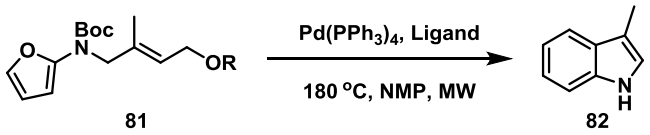
Entry	Catalyst Loading	Ligand Loading	Yields[b]
1	0	0	0
2	1 mol%	4 mol%	0
3	2 mol%	8 mol%	0
4	5 mol%	20 mol%	83%
5	10 mol%	40 mol%	75%
6	20 mol%	80 mol%	71%

[a]All reactions were carried out with $Pd(PPh_3)_4$ as catalyst and $P(OiPr)_3$ as ligand under microwave irradiation in a concentration of 0.2 M in NMP at 180 °C for 20 min. [b]Isolated yields.

1.2.2.6 Screening of leaving groups

The Tsuji-Trost reaction displays marked differences in the substrate reactivities containing various leaving groups.[29] However, the palladium mediated conversion of **81** to indole **82** using the acetyl and benzoate esters as well as methyl carbonates provided comparable results (**Table 7**).

Table 7. Leaving group screening for cyclization[a]

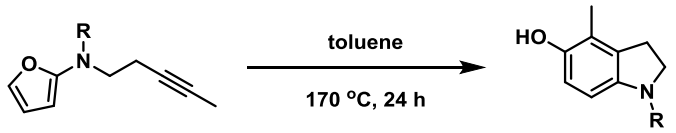


Entry	R	Ligand	Yield[b]
1	**81a**, Ac	PPh_3	40%
2	**81b**, Bz	PPh_3	49%
3	**81c**, COOMe	PPh_3	37%
4	**81a**, Ac	PBn_3	50%
5	**81b**, Bz	PBn_3	48%
6	**81c**, COOMe	PBn_3	46%

[a]All reactions were usually carried out with 5 mol% $Pd(PPh_3)_4$ and 20 mol% PPh_3 under microwave irradiation in a concentration of 1.0 M (80 mg in 0.3 mL NMP) at 180 ^{o}C for 20 min. [b]Isolated yields.

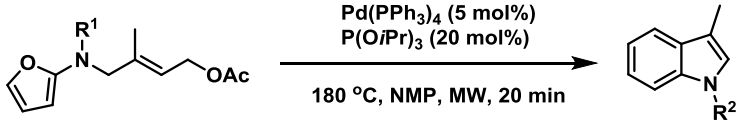
1.2.2.7 Screening of protecting groups

Padwa has reported that an ethyl carbamate group gives a higher yield for indoline formation compared to the *N*-Boc group due to enhanced thermal stability (**Scheme 14, above**).[25] However, the use of the ethyl carbamate derivative under our reaction conditions gave the carbamate-substituted indole **23** in lower yield (**Scheme 14, below**).



83a, R = Boc **84a**, R = Boc, 25%

83b, R = COOEt **84b**, R = COOEt, 82%



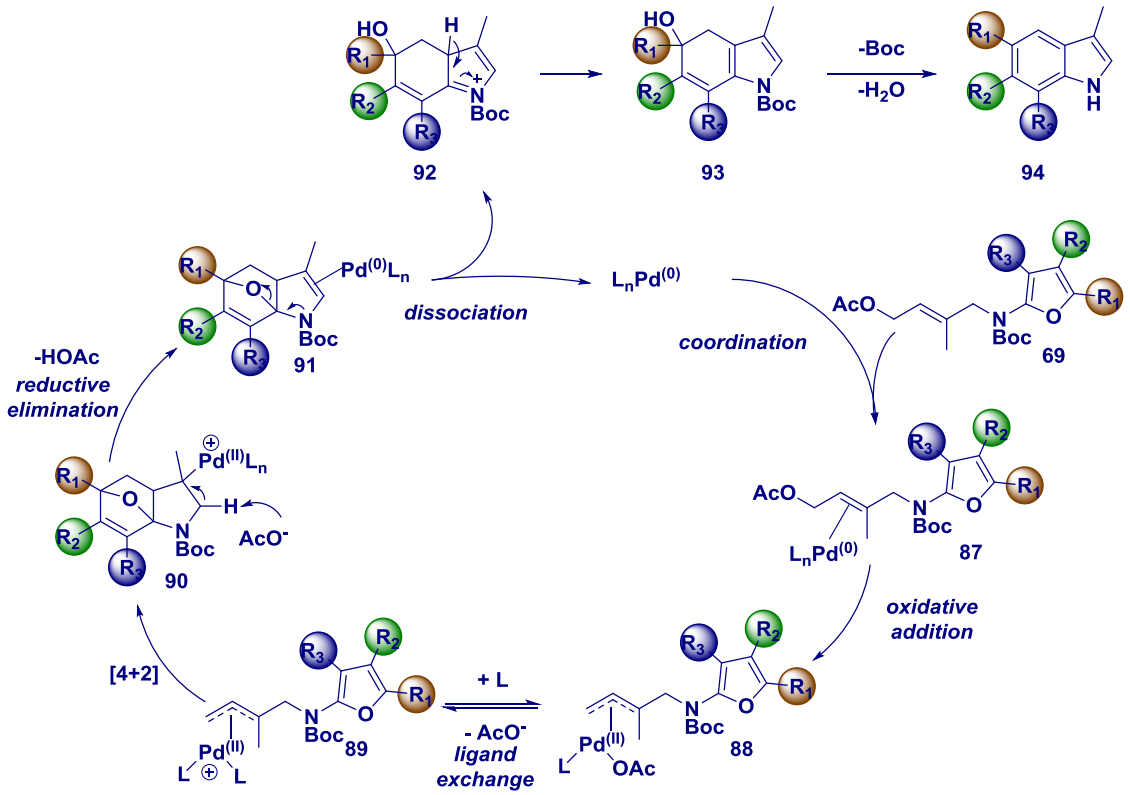
81a, R^1 = Boc **82**, R^2 = H, 83%

85, R^1 = COOEt **86**, R^2 = COOEt, 65%

Scheme 14. Protecting group screening for cyclization

1.2.3 Proposed mechanism

A proposed mechanism is outlined in **Scheme 15** with presumed coordination of palladium catalyst with allylic acetate **69** followed by oxidative addition to give intermediate **88**. After ligand exchange, the π-allyl palladium complex **89** is formed which undergoes an intra-molecular Diels-Alder reaction to form the tricyclic adduct **90**. Reductive elimination with catalyst dissociation affords **91** which proceeds to indole **94** *via* iminium isomerization and dehydration.

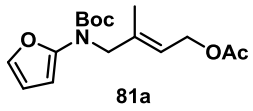
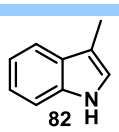
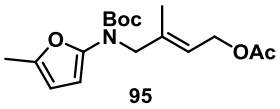
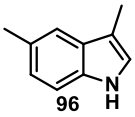
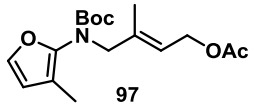
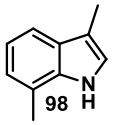
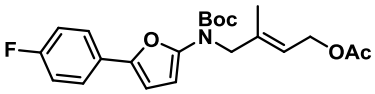
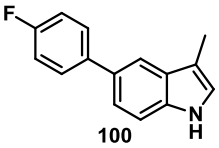
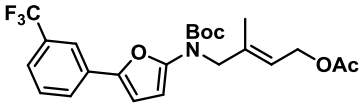
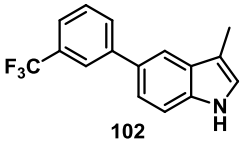
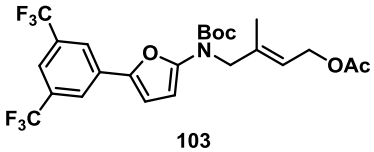
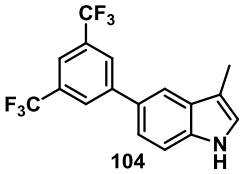
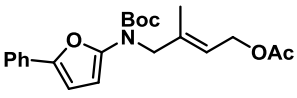
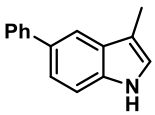
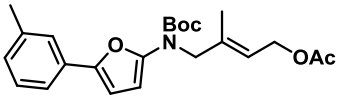
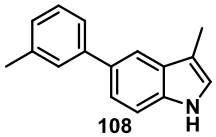
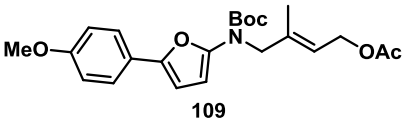
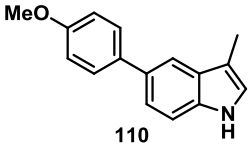


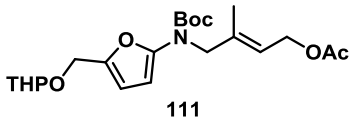
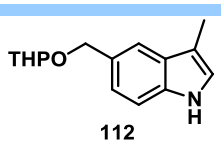
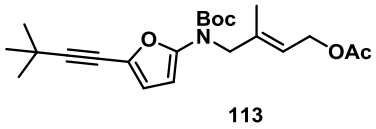
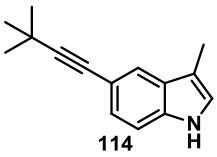
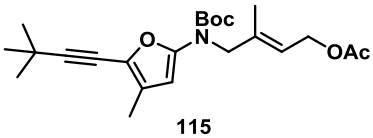
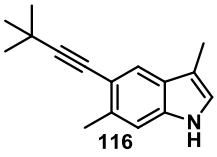
Scheme 15. Proposed mechanism

1.2.4 Examples of the IMDAF reaction for the synthesis of 5,6,7-substituted indoles

With optimal reaction conditions determined (5 mol% $Pd(PPh_3)_4$, 20 mol% $P(OiPr)_3$, microwave irradiation at 180 ^oC for 20 min in 0.2 M substrate concentration), the scope and generality of the reaction was evaluated. This process was compatible with 5-furyl substitutions to give the 3-methyl-5-substituted indoles with the best yields arising from electron-donating functionalities (**Entries 7-9, Table 8**). In general, indoles with 3-, 3,5-, and 3,7- substitutions were obtained in moderate to good yields. An attempt to prepare trisubstituted indoles (3,5,6-substitutions, **Entry 12, Table 8**) gave a significantly lower yield.

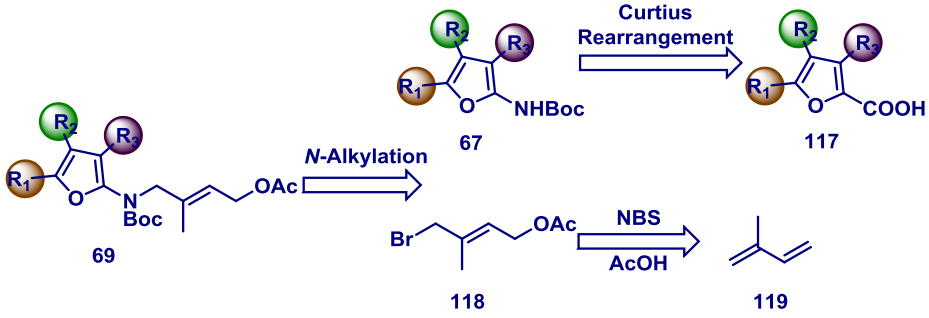
Table 8. Scope of the tandem allylic isomerization – IMDAF reaction in the synthesis of indoles

Entry	Precursor	Product	Yield
1	 81a	 82	83%
2	 95	 96	84%
3	 97	 98	86%
4	 99	 100	66%
5	 101	 102	41%
6	 103	 104	48%
7	 105	 106	77%
8	 107	 108	87%
9	 109	 110	64%

Entry	Precursor	Product	Yield
10	 111	 112	59%
11	 113	 114	52%
12	 115	 116	27%

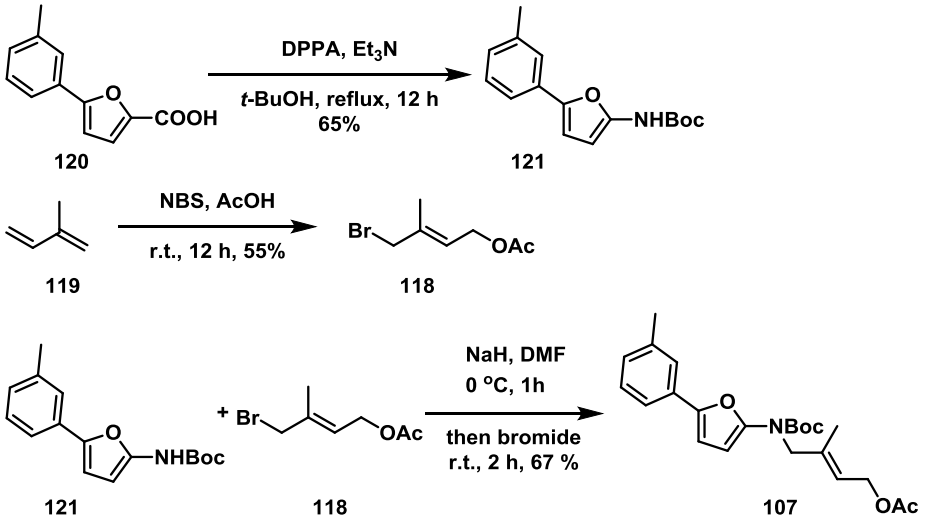
1.2.5 Synthesis of precursors

The precursors for the tandem allylic isomerization – IMDAF reaction were derived from the *N*-alkylation of the substituted *N*-Boc-protected 2-aminofuran **67** with bromide **118**. The Curtius rearrangement of furoic acid **117** was expected to produce **67** (**Scheme 16**).



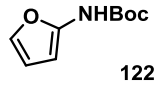
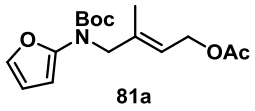
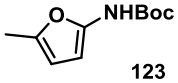
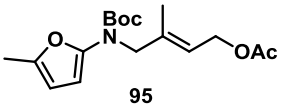
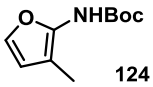
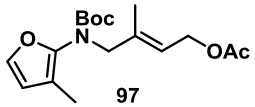
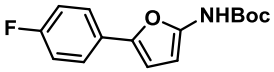
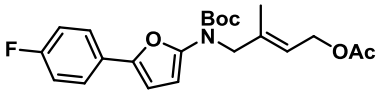
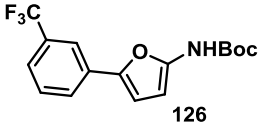
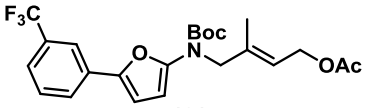
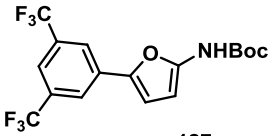
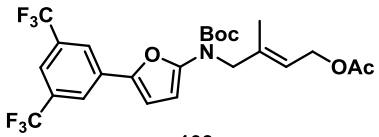
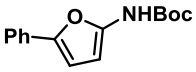
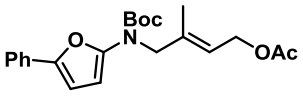
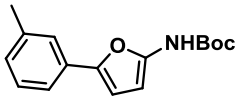
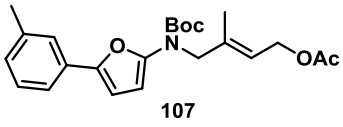
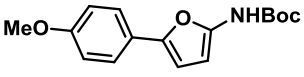
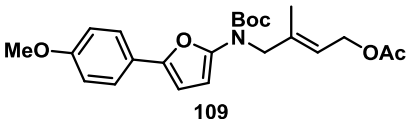
Scheme 16. Retrosynthetic analysis of the precursors for the tandem tandem palladium-catalyzed allylic isomerization – IMDAF reaction

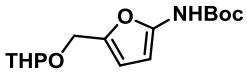
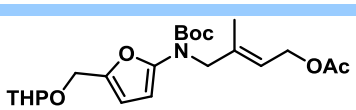
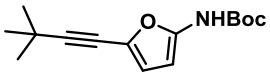
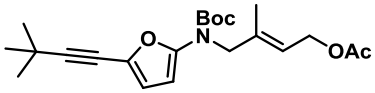
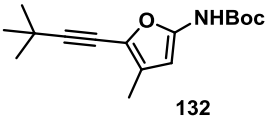
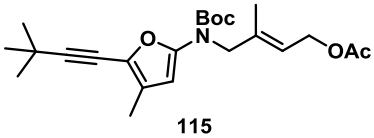
A general example of this sequence is represented by the conversion of acid **120** into 2-aminofuran **121** by treatment with DPPA in *t*-BuOH. Alkylation of **121** with bromide **118** gave precursor **107** in good yield (67%) (**Scheme 17**). Additional substrates were also prepared using this reaction sequence (**Table 9**).



Scheme 17. Representative synthesis of the precursor for the tandem tandem palladium-catalyzed allylic isomerization – IMDAF reaction

Table 9. Preparation of *N*-Boc-protected 2-aminofurans

Entry	2-Aminofuran	Yield	Indole Precursors	Yield
1	 **122**	67%	 **81a**	77%
2	 **123**	86%	 **95**	51%
3	 **124**	75%	 **97**	54%
4	 **125**	64%	 **99**	72%
5	 **126**	81%	 **101**	66%
6	 **127**	68%	 **103**	87%
7	 **128**	64%	 **105**	69%
8	 **121**	65%	 **107**	67%
9	 **129**	64%	 **109**	67%

Entry	2-Aminofuran	Yield	Indole Precursors	Yield
10	 130	43%	 111	80%
11	 131	49%	 113	54%
12	 132	40%	 115	71%

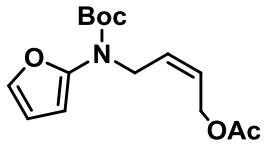
1.2.6 Conclusions

In summary, we have extended our indole synthesis methodology to 5,6,7-substituted indoles *via* the IMDAF reaction. This new protocol avoids the use of tin-containing intermediates and features a microwave assisted allylic-isomerization IMDAF reaction. This convergent procedure is tolerant of multiple-functionalities and generates indole products with substitution patterns that are difficult to access using previously established methods.

1.3 EXPERIMENTAL SECTION

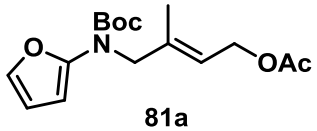
General Information: All reactions were performed under an N_2 or argon atmosphere and all glassware was dried in an oven at 140 ℃ for 2 h prior to use. Reactions carried out at -78 ℃

employed a CO_2/acetone bath. THF was distilled over sodium/benzophenone ketyl, and CH_2Cl_2 was purified using an alumina column filtration system. DMF were dried from 4 Å molecule sieves. Pyridine and Et_3N were dried from KOH. Reactions were monitored by TLC analysis (EM Science pre-coated silica gel 60 F_{254} plates, 250 mM layer thickness) a PMA solution (5 g of phosphomolybdic acid in 100 mL of 95% EtOH), *p*-anisaldehyde solution (2.5 mL of *p*-anisaldehyde, 2 mL of AcOH, and 3.5 mL of conc. H_2SO_4 in 100 mL of 95% EtOH), Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}$•4 H_2O and 0.2 g of $Ce(SO_4)_2$ in 100 mL of a 3.5 N H_2SO_4 solution) or a $KMnO_4$ solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1% NaOH solution). Purifications by chromatography were performed using SiO_2 (SiliaFlash® F60, Silicycle) or using an ISCO- Companion flash chromatography system. $^1H/^{13}C$ NMR spectra were recorded on Bruker Avance 300/75 MHz, Bruker Avance 400/100 MHz or Bruker Avance 500/125 MHz instrument. Chemical shifts were reported in parts per million with the residual solvent peak used as the internal standard. Chemical shifts were tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quarter, dd = doublet of doublet, dt = doublet of triplet, m = multiplet, br = broad, app = apparent), coupling constants, and integration. Mass spectra were obtained on a Micromass Autospec double focusing instrument. IR spectra were obtained on an Identity IR-ATR spectrometer. Microwave reactions were performed using a Biotage Initiator in glass microwave vials (cap sealed) with continuous magnetic stirring and an external surface temperature sensor. LCMS analyses were completed on a Waters MicroMass ZQ with 2525 Binary Gradient Module, 2420 ELSD, 2996 PDA using MeCN/H_2O with 0.1% TFA. Melting points (uncorrected) were determined using a Mel-Temp instrument.



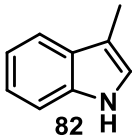
75

(*Z*)-4-((*tert*-Butoxycarbonyl)(furan-2-yl)amino)but-2-en-1-yl acetate (75). To a solution of **2-*N*-Boc-furyl amine**[27] (971.3 mg, 5.302 mmol) in dry DMF (7.0 mL) at 0 ^{o}C was added NaH (318.1 mg, 7.953 mmol, 60 % in mineral oil) in 4 portions. The reaction mixture was stirred at 0 ^{o}C for 2 h. Then, **(*Z*)-4-((methylsulfonyl)oxy)but-2-en-1-yl acetate**[50] (498.6 mg, 3.355 mmol) was added dropwise over 5 min. The resulting solution was stirred at 0 ^{o}C for 2 h and r.t. for 2 h, diluted with Et_2O (5 mL), quenched with saturated aqueous NH_4Cl (5 mL), extracted with Et_2O (3 x 15 mL), washed with water and brine, dried and concentrated under reduced pressure. The crude product was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **75** (939.2 mg, 60%) as a pale yellow liquid: ATR-IR (neat) 2954, 2922, 2852, 1713, 1685, 1368, 1236, 1206, 1150, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.17 (dd, 1 H, *J* = 0.8, 2.0 Hz), 6.32 (dd, 1 H, *J* = 2.4, 3.2 Hz), 6.00 (br, 1 H), 5.74 (ttd, 1 H, *J* = 1.2, 6.8, 10.8 Hz), 5.66 (ttd, 1 H, *J* = 1.2, 6.8, 11.2 Hz), 4.59 (d, 2 H, *J* = 6.4 Hz), 4.27 (d, 2 H, *J* = 6.8 Hz), 2.04 (s, 3 H), 1.45 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2, 153.1, 147.8, 137.8, 129.4, 126.2, 110.6, 100.8, 81.0, 59.5, 45.0, 27.8, 20.4; MS (ESI) *m*/z (%) 318 ($[M+Na]^+$, 27), 259 (56), 218 (100), 203 (50), 136 (29); HRMS (EI) *m*/z calcd for $C_{15}H_{21}NO_5Na$ ($[M+Na]^+$) 318.1317, found 318.1328.



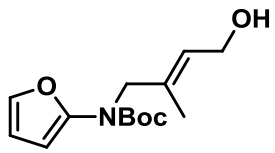
81a

(*E*)-4-((*tert*-Butoxycarbonyl)(furan-2-yl)amino)-3-methylbut-2-en-1-yl acetate (81a). To a solution of **2-*N*-Boc-furyl amine**[27] (413.1 mg, 2.255 mmol) in dry DMF (5.0 mL) at 0 ^{o}C was added NaH (135.2 mg, 3.382 mmol, 60 % in mineral oil) in 4 portions. The reaction mixture was stirred at 0 ^{o}C for 1 h. Then, **(*E*)-4-bromo-3-methylbut-2-en-1-yl acetate**[51] (490.3 mg, 2.368 mmol) was added dropwise over 5 min. The resulting solution was stirred at 0 ^{o}C for 4 h, diluted with Et_2O (5 mL), quenched with saturated aqueous NH_4Cl (5 mL), extracted with Et_2O (3 x 15 mL), washed with water and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give the product **81a** (539.3 mg, 77%) as a pale yellow liquid: ATR-IR (neat) 2973, 2932, 1735, 1709, 1610, 1506, 1504, 1364, 1228, 1158, 1051, 1021, 1003, 857, 766, 736 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.15 (dd, 1 H, *J* = 1.0, 2.0 Hz), 6.31 (dd, 1 H, *J* = 2.0, 3.0 Hz), 5.98 (br, 1 H), 5.43 (qt, 1 H, *J* = 1.0, 7.0 Hz), 4.58 (d, 2 H, *J* = 7.0 Hz), 4.11 (s, 2 H), 2.02 (s, 3 H), 1.71 (s, 3 H, *J* = 1.2 Hz), 1.44 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.9, 153.9, 148.3, 138.1, 137.2, 120.2, 110.8, 101.1, 81.3, 60.8, 55.3, 28.1, 20.9, 14.3. MS (ESI) *m*/z (%) 332 ([M+23]$^{+}$, 100), 276 (42), 232 (90); HRMS (ESI) *m*/z calcd for $C_{16}H_{23}NO_5Na$ ([M+Na]$^{+}$) 332.1474, found 332.1465.



82

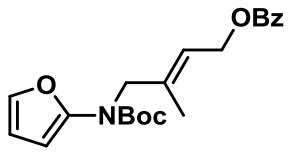
3-Methyl-1*H*-indole (82). To a solution of **81a** (55.5 mg, 0.179 mmol) and $P(OiPr)_3$ (8.90 μL, 0.0359 mmol) in NMP (1.8 mL) was added $Pd(PPh_3)_4$ (10.4 mg, 0.00897 mmol). The reaction mixture was stirred under microwave irradiation at 180 ^oC for 20 min, quenched with ether and water, extracted with ether, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (hexanes : EA = 16 : 1) to give **82** (19.5 mg, 83%) as a yellow solid: Mp 89.2–90.6 ^oC; ATR-IR (neat) 3413, 2921, 736 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.87 (br, 1 H), 7.60 (d, 1 H, *J* = 7.6 Hz), 7.36 (d, 1 H, *J* = 8.0 Hz), 7.20 (dt, 1 H, *J* = 0.8, 8.0 Hz), 7.14 (dt, 1 H, *J* = 1.2, 8.0 Hz), 6.98 (d, 1 H, *J* = 1.2 Hz), 2.35 (d, 3 H, 0.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.2, 128.3, 121.8, 121.5, 119.1, 118.8, 111.7, 110.9, 9.6; MS (EI) *m*/z (%) 131 ($[M]^+$, 57), 130 (100), 86 (55), 84 (82); HRMS (EI) *m*/z calcd for C_9H_9N 131.0735, found 131.0703. The spectral data were consistent with those reported in the literature.[52]



133

(*E*)-*tert*-Butyl furan-2-yl(4-hydroxy-2-methylbut-2-en-1-yl)carbamate (133). To a solution of **81a** (222.0 mg, 0.7176 mmol) in methanol (2.5 mL) was added dropwise an aqueous solution of 20% K_2CO_3 (0.6 mL). The reaction mixture was stirred at r.t. for 2 h, quenched with dilute HCl, concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (hexanes : EA = 2 : 1) to give **133** (185.2 mg, 97%) as a pale yellow liquid: ATR-IR

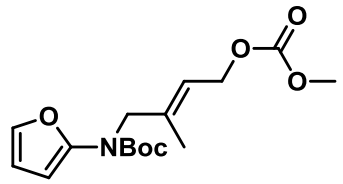
(neat) 3502, 3008, 2982, 2969, 2932, 2880, 1700, 1610, 1389, 1364, 1288, 1252, 1234, 1212, 1158, 1146, 1055, 1010, 999, 852, 762, 736, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.09 (dd, 1 H, *J* = 0.8, 2.0 Hz), 6.24 (dd, 1 H, *J* = 2.4, 3.2 Hz), 5.93 (br, 1 H), 5.41 (qt, 1 H, *J* = 0.8, 6.4 Hz), 4.05 (d, 2 H, *J* = 7.2 Hz), 4.05 (s, 2 H), 2.39 (br, 1 H), 1.61 (s, 3 H), 1.39 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.9, 148.1, 137.9, 133.8, 125.5, 110.6, 101.0, 81.1, 58.6, 55.3, 27.9, 14.0; MS (EI) *m*/z (%) 267 ($[M]^+$, 16), 167 (59), 149 (83), 83 (100), 68 (98); HRMS (EI) *m*/z calcd for $C_{14}H_{21}NO_4Na$ ($[M+Na]^+$) 290.1368, found 290.1358.



81b

(*E*)-4-((*tert*-Butoxycarbonyl)(furan-2-yl)amino)-3-methylbut-2-en-1-yl benzoate (81b). To a solution of **2-*N*-Boc-furyl amine**[27] (265 mg, 1.45 mmol) in dry DMF (2.5 mL) at 0 ^oC was added NaH (86.8 mg, 2.17 mmol, 60 % in mineral oil) in 4 portions. The reaction mixture was stirred at 0 ^oC for 1 h. Then, **(*E*)-4-bromo-3-methylbut-2-en-1-yl benzoate**[53] (409 mg, 1.52 mmol) was added dropwise over 5 min. The resulting solution was stirred at 0 ^oC for 2 h, diluted with Et_2O (5 mL), quenched with saturated aqueous NH_4Cl (5 mL), extracted with Et_2O (3 x 15 mL), washed with water and brine, dried, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **81b** (329 mg, 61%) as a colorless liquid: ATR-IR (neat) 2980, 2971, 2930, 2880, 1705, 1610, 1504, 1450, 1390, 1366, 1269, 1158, 1146, 1072, 1057, 1012, 945, 913, 854, 744, 712 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.02 (td, 2 H, *J* = 1.6, 7.6 Hz), 7.55 (tt, 1 H, *J* = 1.2, 7.2 Hz),

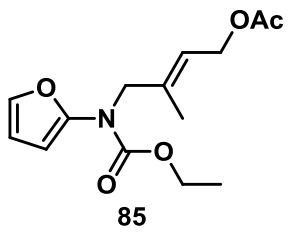
7.43 (t, 2 H, *J* = 1.6, 8.0 Hz), 7.14 (dd, 1 H, *J* = 0.8, 2.0 Hz), 6.28 (dd, 1 H, *J* = 2.4, 2.8 Hz), 5.99 (br, 1 H), 5.57 (qt, 1 H, *J* = 1.2, 6.8 Hz), 4.84 (d, 2 H, *J* = 7.2 Hz), 4.15 (s, 2 H), 1.79 (s, 3 H), 1.44 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.4, 153.9, 148.3, 138.1, 137.5, 132.8, 130.3, 129.6, 128.3, 120.4, 110.8, 101.2, 81.4, 61.3, 55.4, 28.1, 14.5; MS (EI) *m*/z (%) 371 ($[M]^+$, 56), 271 (60), 149 (82), 105 (100), 77 (79), 68 (93); HRMS (ESI) *m*/z calcd for $C_{21}H_{25}NO_5Na$ ($[M+Na]^+$) 394.1630, found 394.1643.



81c

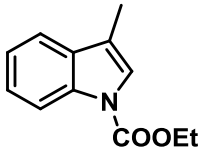
(*E*)-*tert*-Butylfuran-2-yl(4-((methoxycarbonyl)oxy)-2-methylbut-2-en-1-yl)carbamate (81c). To a solution of **133** (276 mg, 1.03 mmol) in dry CH_2Cl_2 (2 mL) and pyridine (0.420 mL, 5.20 mmol) was added methyl chloroformate (0.120 mL, 1.50 mmol) at 0 ^oC. The reaction mixture was stirred at 0 ^oC for 15 min, quenched with CH_2Cl_2 (5 mL) and 1 N HCl solution (5 mL), washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (hexanes : EA = 8 : 1) to give **81c** (193 mg, 58%) as a pale yellow liquid: ATR-IR (neat) 3004, 2977, 2975, 2861, 1746, 1709, 1444, 1441, 1366, 1333, 1256, 1156, 1057, 1008, 941, 859, 790 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.15 (dd, 1 H, *J* = 0.8, 2.0 Hz), 6.30 (dd, 1 H, *J* = 2.0, 2.8 Hz), 5.98 (br, 1 H), 5.46 (qt, 1 H, *J* = 1.6, 7.2 Hz), 4.66 (d, 2 H, *J* = 7.2 Hz), 4.12 (s, 3 H), 3.76 (s, 3 H), 1.73 (s, 3 H), 1.44 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.6, 153.7, 148.1, 138.0, 138.0, 119.5, 110.7, 101.0, 81.2,

64.0, 55.1, 54.6, 28.0, 14.3. HRMS (ESI) *m*/z calcd for $C_{16}H_{23}NO_6Na$ ($[M+Na]^+$) 348.1423, found 348.1448.



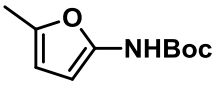
85

(*E*)-4-((Ethoxycarbonyl)(furan-2-yl)amino)-3-methylbut-2-en-1-yl acetate (85). To a solution of **ethyl furan-2-ylcarbamate** (445 mg, 2.87 mmol) in dry DMF (5 mL) at 0 ^oC was added NaH (172 mg, 4.30 mmol, 60 % in mineral oil) in 1 portion. The reaction mixture was stirred at 0 ^oC for 1 h. Then, **(*E*)-4-bromo-3-methylbut-2-en-1-yl acetate**[51] (623 mg, 3.01 mmol) was added dropwise over 5 min. The resulting solution was stirred at r.t. for 2 h, diluted with Et_2O (5 mL), quenched with saturated aqueous NH_4Cl (5 mL), extracted with Et_2O (3 x 10 mL), washed with water and brine, dried and concentrated under reduced pressure. The crude product was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **85** (435 mg, 54 %) as a pale yellow liquid: ATR-IR (neat) 2978, 2932, 2915, 2848, 1713, 1612, 1504, 1444, 1402, 1370, 1348, 1271, 1230, 1156, 1144, 1055, 1021, 738, 770, 714 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.17 (dd, 1 H, *J* = 1.0, 2.0 Hz), 6.32 (dd, 1 H, *J* = 2.0, 3.0 Hz), 6.01 (br, 1 H), 5.43 (qt, 1 H, *J* = 1.0, 6.5 Hz), 4.57 (d, 2 H, *J* = 6.5 Hz), 4.20-4.16 (m, 4 H), 2.02 (s, 3 H), 1.71 (s, 3 H), 1.23 (t, 3 H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8, 155.1, 147.5, 138.5, 136.7, 120.8, 110.8, 101.9, 62.3, 60.7, 55.6, 20.9, 14.4, 14.3; HRMS (ESI) *m*/z calcd for $C_{14}H_{19}NO_5$ ($[M]^+$) 281.1251, found 281.1263.



86

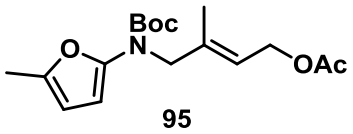
Ethyl 3-methyl-1*H*-indole-1-carboxylate (86). To a solution of **85** (74.0 mg, 0.263 mmol) and P(O*i*Pr)$_3$ (11.0 mg, 0.0526 mmol) in NMP (1.40 mL) was added Pd(PPh$_3$)$_4$ (15.2 mg, 0.0131 mmol). The reaction mixture was stirred under microwave radiation at 180 ^{o}C for 20 min, quenched with ether and water, extracted with ether, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (hexanes : EA = 50 : 1) to give **86** (34.8 mg, 65%) as a colorless liquid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.15 (br, 1 H), 7.50 (ddd, 1 H, *J* = 1.0, 1.0, 7.5 Hz), 7.38 (br, 1 H), 7.33 (dt, 1 H, *J* = 1.0, 8.0 Hz), 7.26 (dt, 1 H, *J* = 1.0, 8.0 Hz), 4.46 (q, 2 H, *J* = 7.0 Hz), 2.26 (d, 3 H, *J* = 1.0 Hz), 1.45 (t, 3 H, *J* = 7.0 Hz). The spectral data were consistent with those reported in the literature.[54]



134

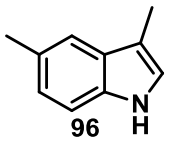
***tert*-Butyl (5-methylfuran-2-yl)carbamate (134).** To a stirred solution of **5-methyl-2-furoic acid** (667 mg, 5.29 mmol) in *t*-BuOH (2.0 mL) was added DPPA (1.14 mL, 5.29 mmol) and TEA (1.49 mL, 10.6 mmol). The reaction mixture was refluxed behind the protective shield and under constant flow of argon for 11 h. The reaction was quenched by NaOH solution (1.0 M), extracted with ethyl acetate, washed with brine, dried (Na_2SO_4) and concentrated to give a

residue that was purified by chromatography on SiO_2 (Hexane : EA = 15 : 1) to give **134** (903 mg, 87%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.45 (s, 1 H), 5.90 (brs, 2 H), 2.21 (s, 3 H), 1.49 (s, 9 H). The spectral data were consistent with those reported in the literature.[55]



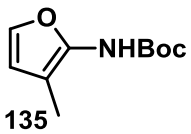
95

(*E*)-4-((*tert*-Butoxycarbonyl)(5-methylfuran-2-yl)amino)-3-methylbut-2-en-1-yl acetate (95). To a solution of **134** (126 mg, 0.640 mmol) in dry DMF (2.0 mL) at 0 ^oC was added NaH (38.4 mg, 0.960 mmol, 60 % in mineral oil) in 4 portions. The reaction mixture was stirred at 0 ^oC for 1 h. Then, **(*E*)-4-bromo-3-methylbut-2-en-1-yl acetate**[51] (139 mg, 0.672 mmol) was added dropwise over 5 min. The resulting solution was stirred at r.t. for 2 h, diluted with Et_2O (10 mL), quenched with saturated aqueous NH_4Cl (10 mL), extracted with Et_2O (3 x 10 mL), washed with water and brine, dried and concentrated under reduced pressure. The crude product was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **95** (105 mg, 51%) as a pale yellow liquid: ATR-IR (neat) 2977, 2928, 1737, 1709, 1616, 1571, 1364, 1228, 1159, 1057, 1020, 956, 859, 775, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.88 (s, 1 H), 5.84 (br, 1 H), 5.44 (t, 1 H, *J* = 7.0 Hz), 4.59 (d, 2 H, *J* = 6.5 Hz), 4.08 (s, 2 H), 2.22 (s, 3 H), 2.03 (s, 3 H), 1.71 (s, 3 H), 1.44 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.0, 154.2, 147.8, 146.3, 137.4, 120.2, 106.4, 102.4, 81.1, 60.9, 60.4, 28.1, 21.0, 14.4, 13.6; HRMS (ESI) *m*/z calcd for $C_{17}H_{25}NO_5Na$ ($[M+Na]^+$) 346.1630, found 346.1613.



96

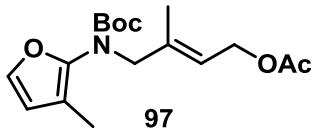
3,5-Dimethyl-1*H*-indole (96). To a solution of **95** (33 mg, 0.10 mmol) and $P(OiPr)_3$ (4.3 mg, 0.021 mmol) in NMP (0.51 mL) was added $Pd(PPh_3)_4$ (5.9 mg, 0.0051 mmol). The reaction mixture was stirred under microwave radiation at 180 ^oC for 20 min, quenched with ether and water, extracted with ether, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (hexanes : EA = 16 : 1) to give **96** (13 mg, 84%) as a yellow solid: Mp 70.9–72.6 ^oC; ATR-IR (neat) 3409, 2919, 742 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.78 (br, 1 H), 7.37 (d, 1 H, *J* = 1.0 Hz), 7.24 (d, 1 H, *J* = 8.5 Hz), 7.02 (dd, 1 H, *J* = 1.0, 8.5 Hz), 6.94 (d, 1 H, *J* = 1.0 Hz), 2.47 (s, 3 H), 2.31 (d, 3 H, *J* = 1.0 Hz); ^{13}C NMR (CDCl3, 125 MHz) δ 134.5, 128.5, 128.3, 123.4, 121.7, 118.5, 111.2, 110.6, 21.5, 9.6; HRMS (EI) *m*/z calcd for $C_{10}H_{10}N$ ($[M-H]^+$) 144.0813, found 144.0798. The spectral data were consistent with those reported in the literature.[56]



135

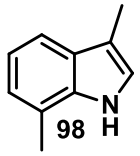
***tert*-Butyl (3-methylfuran-2-yl)carbamate (135).** To a stirred solution of **3-methyl-2-furoic acid** (309 mg, 2.45 mmol) in *t*-BuOH (5 mL) was added DPPA (0.529 mL, 2.45 mmol) and Et_3N (0.689 mL, 4.91 mmol). The reaction mixture was refluxed behind the protective shield and under constant flow of argon for 12 h. The reaction was quenched by NaOH solution (1.0 M), extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), filtered and concentrated to

give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **135** (361 mg, 75%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.13 (d, 1 H, *J* =2.0 Hz), 6.21 (d, 1 H, *J* = 2.0 Hz), 6.05 (br, 1 H), 1.93 (s, 3 H), 1.47 (s, 9 H). The spectral data were consistent with those reported in the literature.[57]



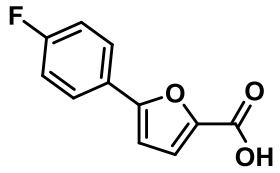
97

(*E*)-4-((*tert*-Butoxycarbonyl)(3-methylfuran-2-yl)amino)-3-methylbut-2-en-1-yl acetate (97). To a solution of **135** (361 mg, 1.83 mmol) in dry DMF (5.0 mL) at 0 ^{o}C was added NaH (110 mg, 2.74 mmol, 60 % in mineral oil) in 4 portions. The reaction mixture was stirred at 0 ^{o}C for 1 h. Then, **(*E*)-4-bromo-3-methylbut-2-en-1-yl acetate**[51] (398 mg, 1.92 mmol) was added dropwise over 5 min. The resulting solution was stirred at r.t. for 2 h, diluted with Et_2O (10 mL), quenched with saturated aqueous NH_4Cl (10 mL), extracted with Et_2O (3 x 10 mL), washed with water and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **97** (320 mg, 54%) as a colorless liquid: ATR-IR (neat) 2977, 2928, 1737, 1709, 1646, 1508, 1364, 1228, 1159, 1094, 1053, 1021, 887, 861, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.09 (s, 1 H), 6.16 (s, 1 H), 5.42 (t, 1 H, *J* = 6.5 Hz), 4.55 (d, 2 H, *J* = 6.5 Hz), 4.05 (s, 2 H), 2.01 (s, 3 H), 1.85 (s, 3 H), 1.72 (s, 3 H), 1.39 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8, 154.5, 144.0, 138.2, 137.6, 137.2, 121.1, 112.9, 80.8, 60.8, 55.2, 28.1, 20.9, 14.5, 9.5; HRMS (ESI) *m*/z calcd for $C_{17}H_{25}NO_5Na$ ($[M+Na]^+$) 346.1630, found 346.1616.



98

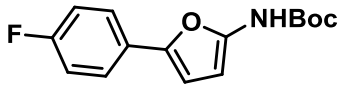
3,7-Dimethyl-1*H*-indole (98). To a solution of **97** (46 mg, 0.14 mmol) and $P(OiPr)_3$ (5.9 mg, 0.028 mmol) in NMP (0.70 mL) was added $Pd(PPh_3)_4$ (8.1 mg, 0.0081 mmol). The reaction mixture was stirred under microwave irradiation at 180 ^oC for 20 min, quenched with ether and water, extracted with ether, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (hexanes : EA = 16 : 1) to give **98** (18 mg, 86%) as a yellow solid: Mp 57.3–59.1 ^oC; ATR-IR (neat) 3417, 2921, 742 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.81 (br, 1 H), 7.46 (d, 1 H, *J* = 7.6 Hz), 7.07 (t, 1 H, *J* = 7.6 Hz), 7.02–6.98 (m, 2 H), 2.49 (s, 3 H), 2.35 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.8, 127.8, 122.4, 121.2, 120.0, 119.3, 116.5, 112.2, 16.5, 9.8; HRMS (EI) *m*/z calcd for $C_{10}H_{11}N$ 145.0891, found 145.0909. The spectral data were consistent with those reported in the literature.[58]



136

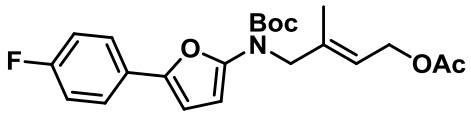
5-(4-Fluorophenyl)furan-2-carboxylic acid (136). To a solution of **5-bromofuroic acid** (405 mg, 2.12 mmol), **(4-fluorophenyl)boronic acid** (594 mg, 4.25 mmol) in DMF (2.8 mL) and K_3PO_4 (aq) (2.1 mL, 4.25 mmol) was added $Pd(PPh_3)_4$ (49.1 mg, 0.0425 mmol). The

reaction mixture was stirred under microwave irradiation at 150 ^{o}C for 30 min, quenched with 1 M HCl (10 mL), extracted with ether, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 4 : 1) to give **136** (350 mg, 80%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.50 (br, 1 H), 7.79 (ddd, 2 H, *J* =2.0, 5.0, 7.0 Hz), 7.39 (d, 1 H, *J* = 3.5 Hz), 7.13 (tt, 2 H, *J* = 2.5, 8.5 Hz), 6.72 (d, 1 H, *J* = 4.0 Hz).



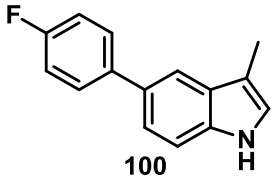
137

***tert*-Butyl (5-(4-fluorophenyl)furan-2-yl)carbamate (137).** To a stirred solution of **136** (270 mg, 1.31 mmol) in *t*-BuOH (3 mL) was added DPPA (0.282 mL, 1.31 mmol) and Et_3N (0.368 mL, 2.62 mmol). The reaction mixture was refluxed behind the protective shield and under constant flow of argon for 10 h. The reaction was quenched by NaOH solution (1.0 M), extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **137** (231 mg, 64%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54-7.49 (m, 2 H), 7.06-7.00 (m, 2 H), 6.68 (br, 1 H), 6.53 (d, 1 H, *J* = 3.2 Hz), 6.12 (br, 1 H), 1.52 (s, 9 H).



99

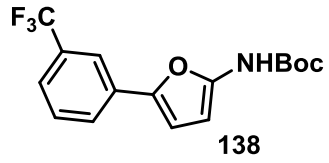
(*E*)-4-((*tert*-Butoxycarbonyl)(5-(4-fluorophenyl)furan-2-yl)amino)-3-methylbut-2-en-1-yl acetate (99). To a solution of **137** (231 mg, 0.833 mmol) in dry DMF (3.0 mL) at 0 ^{o}C was added NaH (50.0 mg, 1.25 mmol, 60 % in mineral oil) in 4 portions. The reaction mixture was stirred at 0 ^{o}C for 1 h. Then, **(*E*)-4-bromo-3-methylbut-2-en-1-yl acetate**[51] (181 mg, 0.875 mmol) was added dropwise over 5 min. The resulting solution was stirred at r.t. for 2 h, diluted with Et_2O (10 mL), quenched with saturated aqueous NH_4Cl (10 mL), extracted with Et_2O (3 x 10 mL), washed with water and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **99** (240 mg, 72%) as a yellow liquid: ATR-IR (neat) 2977, 2928, 1737, 1711, 1618, 1594, 1553, 1497, 1392, 1366, 1228, 1156, 1057, 1020, 835, 779 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55-7.52 (m, 2 H), 7.05 (tt, 2 H, *J* =2.0, 9.0 Hz), 6.50 (d, 1 H, *J* = 3.5 Hz), 6.06 (br, 1 H), 5.52-5.48 (m, 1 H), 4.60 (d, 2 H, *J* = 7.0 Hz), 4.21 (s, 2 H), 1.98 (s, 3 H), 1.75 (s, 3 H), 1.47 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.7, 162.3 (d, J_{CF} = 245.0 Hz), 153.5, 147.7, 137.1, 127.0 (d, J_{CF} = 3.8 Hz), 124.8 (d, J_{CF} = 7.5 Hz), 120.3, 115.5 (d, J_{CF} = 22.5 Hz), 105.6, 102.6, 81.4, 60.6, 55.0, 28.0, 20.7, 14.2; HRMS (ESI) *m*/z calcd for $C_{22}H_{26}NO_5FNa$ ([M+Na]$^{+}$) 426.1693, found 426.1703.



100

5-(4-Fluorophenyl)-3-methyl-1*H*-indole (100). To a solution of **99** (48 mg, 0.12 mmol) and P(O*i*Pr)$_3$ (4.9 mg, 0.024 mmol) in NMP (0.60 mL) was added $Pd(PPh_3)_4$ (6.8 mg, 0.0059

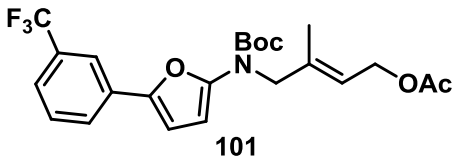
mmol). The reaction mixture was stirred under microwave irradiation at 180 ^{o}C for 20 min, quenched with ether and water, extracted with ether, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (hexanes : EA = 16 : 1) to give **100** (18 mg, 66%) as a yellow solid: Mp 82.9–84.1 ^{o}C; ATR-IR (neat) 3413, 2923, 839, 814 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.93 (br, 1 H), 7.72 (s, 1 H), 7.61 (dd, 2 H, *J* = 5.5, 8.5 Hz), 7.39 (dd, 2 H, *J* = 8.0, 11.0 Hz), 7.13 (dd, 2 H, *J* = 8.5, 8.5 Hz), 7.02 (s, 1 H), 2.37 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.9 (d, J_{CF} = 243.0 Hz), 138.8 (d, J_{CF} = 3.0 Hz), 135.7, 131.8, 128.8 (d, J_{CF} = 7.7 Hz), 128.8, 122.4, 121.6, 117.3, 115.4 (d, J_{CF} = 21.1 Hz), 112.2, 111.2, 9.7; HRMS (ESI) *m*/z calcd for $C_{15}H_{13}NF$ ($[M+H]^+$) 226.1032, found 226.1018.



138

***tert*-Butyl (5-(3-(trifluoromethyl)phenyl)furan-2-yl)carbamate (138).** To a stirred solution of **5-(3-(trifluoromethyl)phenyl)furan-2-carboxylic acid** (397 mg, 1.55 mmol) in *t*-BuOH (3 mL) was added DPPA (0.334 mL, 1.55 mmol) and Et_3N (0.435 mL, 3.10 mmol). The reaction mixture was refluxed behind the protective shield and under constant flow of argon for 10 h. The reaction was quenched by NaOH solution (1.0 M), extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **138** (410

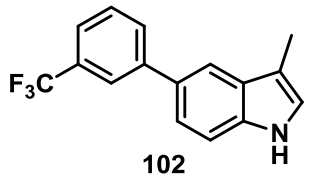
mg, 81%) as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.77 (s, 1 H), 7.70-7.66 (m, 1 H), 7.44-7.42 (m, 2 H), 6.92 (br, 1 H), 6.69 (d, 1 H, *J* = 3.3 Hz), 6.16 (br, 1 H), 1.54 (s, 9 H).



101

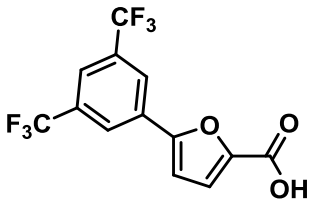
((*E*)-4-((*tert*-Butoxycarbonyl)(5-(3-(trifluoromethyl)phenyl)furan-2-yl)amino)-3-methylbut-2-en-1-yl acetate (101). To a solution of **138** (362 mg, 1.11 mmol) in dry DMF (4.0 mL) at 0 ^{o}C was added NaH (66.3 mg, 1.66 mmol, 60 % in mineral oil) in 4 portions. The reaction mixture was stirred at 0 ^{o}C for 1 h. Then, **(*E*)-4-bromo-3-methylbut-2-en-1-yl acetate**[51] (240 mg, 1.16 mmol) was added dropwise over 5 min. The resulting solution was stirred at r.t. for 2 h, diluted with Et_2O (10 mL), quenched with saturated aqueous NH_4Cl (10 mL), extracted with Et_2O (3 x 10 mL), washed with water and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **101** (333 mg, 66%) as a yellow liquid: ATR-IR (neat) 2978, 2930, 1737, 1713, 1610, 1592, 1551, 1452, 1392, 1366, 1333, 1267, 1230, 1159, 1124, 1098, 1075, 1060, 1021, 857, 796, 783, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (s, 1 H), 7.74-7.72 (m, 1 H), 7.48-7.46 (m, 2 H), 6.68 (d, 1 H, *J* = 3.6 Hz), 6.12 (br, 1 H), 5.51 (qt, 1 H, *J* = 1.2, 6.8 Hz), 4.60 (d, 2 H, *J* = 6.8 Hz), 4.24 (s, 2 H), 1.98 (s, 3 H), 1.76 (s, 3 H), 1.48 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6, 153.2, 148.5, 147.0, 136.9, 131.3, 131.0 (q, J_{CF} = 32.2 Hz), 129.0, 126.0, 124.9 (q, J_{CF} = 271.0 Hz), 123.2 (q, J_{CF} = 3.6 Hz), 120.5, 119.6 (q, J_{CF} = 3.8 Hz),

107.6, 102.4, 81.6, 60.6, 54.7, 27.9, 20.6, 14.2; HRMS (ESI) *m*/z calcd for $C_{23}H_{26}NO_5F_3Na$ ($[M+Na]^+$) 476.1661, found 476.1679.



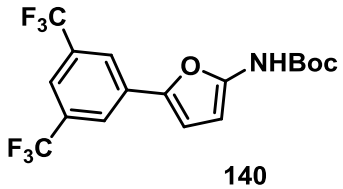
102

3-Methyl-5-(3-(trifluoromethyl)phenyl)-1*H*-indole (102). To a solution of **101** (47 mg, 0.10 mmol) and P(O*i*Pr)$_3$ (4.3 mg, 0.021 mmol) in NMP (0.51 mL) was added $Pd(PPh_3)_4$ (6.0 mg, 0.0051 mmol). The reaction mixture was stirred under microwave irradiation at 180 ^oC for 20 min, quenched with ether and water, extracted with ether, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (hexanes : EA = 16 : 1) to give **102** (12 mg, 41%) as a yellow liquid: ATR-IR (neat) 3418, 2921, 1331, 1070, 792 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.96 (br, 1 H), 7.91 (s, 1 H), 7.85 (dd, 1 H, *J* = 1.5, 4.0 Hz), 7.78 (s, 1 H), 7.56-7.55 (m, 2 H), 7.44 (s, 2 H), 7.04 (d, 1 H, *J* = 1.0 Hz), 2.39 (d, 3 H, *J* = 1.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.5, 136,1, 132,3, 131.0 (q, J_{CF} = 31.0 Hz), 130.6, 129.0, 128.9, 124.4 (q, J_{CF} = 271.0 Hz), 124.0 (q, J_{CF} = 3.8 Hz), 122.9 (q, J_{CF} = 3.8 Hz), 122.6, 121.5, 117.6, 112.3, 111.4, 9.7; HRMS (EI) *m*/z calcd for $C_{16}H_{12}NF_3$ 275.0922, found 275.0900.



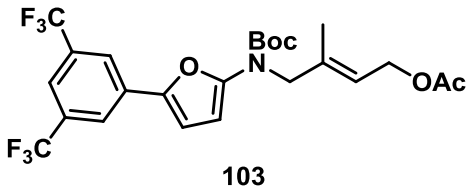
139

5-(3,5-Bis(trifluoromethyl)phenyl)furan-2-carboxylic acid (139). To a solution of **5-bromofuroic acid** (108 mg, 0.567 mmol), **(3,5-bis(trifluoromethyl)phenyl)boronic acid** (293 mg, 1.13 mmol) in DMF (1.0 mL) and K_3PO_4 (aq) (0.6 mL, 1.13 mmol) was added $Pd(PPh_3)_4$ (13.1 mg, 0.0113 mmol). The reaction mixture was stirred under microwave irradiation at 150 ^oC for 30 min, quenched with 1 M HCl (10 mL), extracted with ether, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 4 : 1) to give **139** (177 mg, 96%) as a white solid: ^1H NMR ($CDCl_3$, 500 MHz) δ 11.65 (br, 1 H), 8.19 (s, 2 H), 7.85 (s, 1 H), 7.42 (d, 1 H, *J* = 3.5 Hz), 6.98 (d, 1 H, *J* = 3.5 Hz).



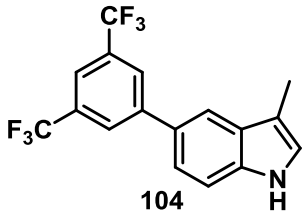
140

***tert*-Butyl (5-(3,5-bis(trifluoromethyl)phenyl)furan-2-yl)carbamate (140).** To a stirred solution of **139** (177 mg, 5.46 mmol) in *t*-BuOH (2 mL) was added DPPA (0.118 mL, 5.47 mmol) and Et_3N (0.154 mL, 1.09 mmol). The reaction mixture was refluxed behind the protective shield and under constant flow of argon for 10 h. The reaction was quenched by NaOH solution (1.0 M), extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **140** (148 mg, 68%) as a white solid: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.85 (s, 2 H), 7.60 (s, 1 H), 7.48 (br, 1 H), 6.75 (d, 1 H, *J* = 3.5 Hz), 6.19 (br, 1 H), 1.54 (s, 9 H).



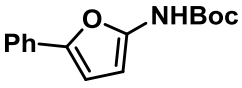
103

(*E*)-4-((5-(3,5-Bis(trifluoromethyl)phenyl)furan-2-yl)(*tert*-butoxycarbonyl)amino)-3-methylbut-2-en-1-yl acetate (103). To a solution of **139** (148 mg, 0.374 mmol) in dry DMF (2.0 mL) at 0 ^{o}C was added NaH (22.4 mg, 0.561 mmol, 60 % in mineral oil) in 4 portions. The reaction mixture was stirred at 0 ^{o}C for 1 h. Then, **(*E*)-4-bromo-3-methylbut-2-en-1-yl acetate**[51] (81.3 mg, 0.393 mmol) was added dropwise over 5 min. The resulting solution was stirred at r.t. for 2 h, diluted with Et_2O (10 mL), quenched with saturated aqueous NH_4Cl (10 mL), extracted with Et_2O (3 x 10 mL), washed with water and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **103** (170 mg, 87%) as a yellow solid: Mp 70.3–71.8 ^{o}C; ATR-IR (neat) 2980, 2928, 2855, 1743, 1720, 1622, 1607, 1549, 1454, 1377, 1370, 1279, 1232, 1172, 1135, 1023, 952, 891, 856, 844, 788, 703, 682 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.92 (s, 2 H), 7.66 (s, 1 H), 6.79 (d, 1 H, J = 3.5 Hz), 6.17 (br, 1 H), 5.50 (qt, 1 H, J = 1.0, 7.0 Hz), 4.60 (d, 2 H, J = 7.0 Hz), 4.26 (s, 2 H), 1.96 (s, 3 H), 1.75 (s, 3 H), 1.48 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8, 153.0, 149.4, 145.4, 136.8, 132.4, 132.1 (q, J_{CF} = 33.0 Hz), 123.2 (q, J_{CF} = 270.0 Hz), 122.6 (q, J_{CF} = 3.8 Hz), 120.6, 119.8 (sp, J_{CF} = 3.8 Hz), 109.4, 102.4, 82.0, 60.6, 54.6, 28.0, 20.7, 14.3; HRMS (ESI) *m*/z calcd for $C_{24}H_{26}NO_5F_6$ ($[M+H]^+$) 522.1715, found 522.1694.



104

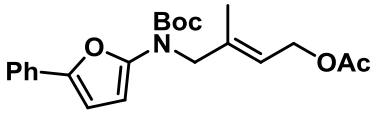
5-(3,3-Dimethylbut-1-yn-1-yl)-3-methyl-1*H*-indole (104). To a solution of **103** (88 mg, 0.17 mmol) and P(O*i*Pr)$_3$ (7.1 mg, 0.034 mmol) in NMP (0.85 mL) was added Pd(PPh$_3$)$_4$ (9.8 mg, 0.0085 mmol). The reaction mixture was stirred under microwave irradiation at 180 ^{o}C for 20 min, quenched with ether and water, extracted with ether, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (hexanes : EA = 16 : 1) to give **104** (28 mg, 48%) as a yellow solid: 109.2–110.8 ^{o}C; ATR-IR (neat) 3420, 2926, 1376, 1277, 1172, 1131, 798, 684 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.08 (s, 1 H), 8.02 (br, 1 H), 7.80 (s, 1 H), 7.79 (d, 1 H, *J* = 0.5 Hz), 7.46 (d, 1 H, *J* = 8.0 Hz), 7.44 (dd, 1 H, *J* = 1.5, 8.5 Hz), 7.06 (d, 1 H, *J* = 1.0 Hz), 2.41 (d, 3 H, *J* = 1.0 Hz); ^{13}C NMR ($CDCl_3$,125 MHz) δ 144.8, 136.4, 131.8 (q, J_{CF} = 32.5 Hz), 129.7, 129.0, 127.3(q, J_{CF} = 2.9 Hz), 123.6 (q, J_{CF} = 270.0 Hz), 122.9, 121.3, 119.7 (sp, J_{CF} = 3.8 Hz); 117.8, 112.5, 111.7, 9.7; HRMS (EI) *m*/z calcd for $C_{17}H_{11}NF_6$ 343.0796, found 343.0815.



141

***tert*-Butyl (5-phenylfuran-2-yl)carbamate (141).** To a stirred solution of **5-phenylfuran-2-carboxylic acid** (366 mg, 1.94 mmol) in *t*-BuOH (3 mL) was added DPPA (0.418 mL, 1.94 mmol) and Et_3N (0.546 mL, 3.89 mmol). The reaction mixture was refluxed

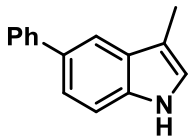
behind the protective shield and under constant flow of argon for 10 h. The reaction was quenched by NaOH solution (1.0 M), extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **141** (320 mg, 64%) as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.54 (d, 2 H, *J* =7.5 Hz), 7.42-7.32 (m, 3 H), 6.72 (br, 1 H), 6.60 (d, 1 H, *J* = 3.3 Hz), 6.13 (br, 1 H), 1.53 (s, 9 H).



105

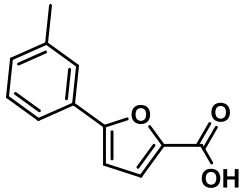
(*E*)-4-((*tert*-Butoxycarbonyl)(5-phenylfuran-2-yl)amino)-3-methylbut-2-en-1-yl acetate (105). To a solution of **141** (320 mg, 1.24 mmol) in dry DMF (3.0 mL) at 0 ^{o}C was added NaH (74.2 mg, 1.85 mmol, 60 % in mineral oil) in 4 portions. The reaction mixture was stirred at 0 ^{o}C for 1 h. Then, **(*E*)-4-bromo-3-methylbut-2-en-1-yl acetate**[51] (269 mg, 1.30 mmol) was added dropwise over 5 min. The resulting solution was stirred at r.t. for 2 h, diluted with Et_2O (10 mL), quenched with saturated aqueous NH_4Cl (10 mL), extracted with Et_2O (3 x 10 mL), washed with water and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **105** (328 mg, 69%) as a pale yellow liquid: ATR-IR (neat) 2977, 2930, 1735, 1709, 1597, 1549, 1446, 1390, 1366, 1228, 1156, 1060, 1020, 857, 759, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56 (d, 2 H, *J* = 7.5 Hz), 7.33 (t, 2 H, *J* = 7.5 Hz), 7.19 (t, 1 H, *J* = 7.5 Hz), 6.57 (d, 1 H, *J* = 3.5 Hz), 6.07 (br, 1 H), 5.51 (qt, 1 H, *J* = 1.0, 7.0 Hz), 4.59 (d, 2 H, *J* = 7.0 Hz), 4.22 (s, 2

H), 1.95 (s, 3 H), 1.74 (s, 3 H), 1.46 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8, 153.4, 147.6, 137.0, 130.5, 129.2, 128.4, 126.8, 123.0, 120.3, 114.6, 106.0, 81.3, 60.6, 54.8, 28.0, 20.6, 14.2; HRMS (ESI) *m*/z calcd for $C_{22}H_{27}NO_5Na$ ($[M+Na]^+$) 408.1787, found 408.1776.



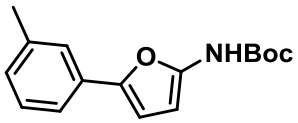
106

3-Methyl-5-phenyl-1*H*-indole (106). To a solution of **105** (57 mg, 0.15 mmol) and P(O*i*Pr)$_3$ (6.1 mg, 0.029 mmol) in NMP (0.73 mL) was added $Pd(PPh_3)_4$ (8.5 mg, 0.0073 mmol). The reaction mixture was stirred under microwave irradiation at 180 ^{o}C for 20 min, quenched with ether and water, extracted with ether, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (hexanes : EA = 16 : 1) to give **106** (24 mg, 77%) as a yellow liquid: ATR-IR (neat) 3416, 3062, 2921, 762 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.92 (br, 1 H), 7.78 (dd, 1 H, *J* = 1.0, 1.5 Hz), 7.68 (d, 1 H, *J* = 1.5 Hz), 7.67 (d, 1 H, *J* = 1.0 Hz), 7.46-7.40 (m, 4 H), 7.32 (tt, 1 H, *J* = 1.0, 7.5 Hz), 7.01 (d, 1 H, *J* = 1.0 Hz), 2.38 (d, 3 H, *J* = 1.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.7, 135.7, 132.8, 128.8, 128.6, 127.4, 126.2, 122.2, 121.7, 117.4, 112.2, 111.1, 9.7; HRMS (EI) *m*/z calcd for $C_{15}H_{13}N$ 207.1048, found 207.1065.



120

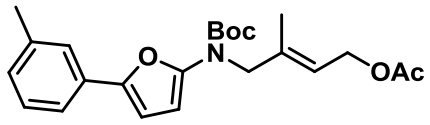
5-(*m*-Tolyl)furan-2-carboxylic acid (120). To a solution of **5-bromofuroic acid** (210 mg, 1.10 mmol), ***m*-tolylboronic acid** (299 mg, 2.20 mmol) in DMF (1.8 mL) and K_3PO_4 (aq) (1.0 mL, 2.20 mmol) was added $Pd(PPh_3)_4$ (22.0 mg, 0.0254 mmol). The reaction mixture was stirred under microwave irradiation at 150 ^oC for 30 min, quenched with 1 M HCl (10 mL), extracted with ether, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 4 : 1) to give **120** (222 mg, 99%) as a white solid: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.65 (s, 1 H), 7.61 (d, 1 H, *J* = 7.8 Hz), 7.41 (d, 1 H, *J* = 3.6 Hz), 7.33 (t, 1 H, *J* = 7.8 Hz), 7.19 (d, 1 H, *J* = 7.5 Hz), 6.78 (d, 1 H, *J* = 4.8 Hz).



121

***tert*-Butyl (5-(*m*-tolyl)furan-2-yl)carbamate (121).** To a stirred solution of **120** (222 mg, 1.10 mmol) in *t*-BuOH (3 mL) was added DPPA (0.237 mL, 1.10 mmol) and Et_3N (0.309 mL, 2.20 mmol). The reaction mixture was refluxed behind the protective shield and under constant flow of argon for 10 h. The reaction was quenched by NaOH solution (1.0 M), extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced

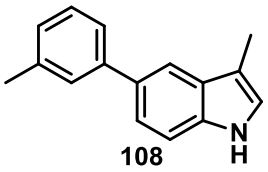
pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **121** (194 mg, 65%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (d, 1 H, *J* = 4.4 Hz), 7.34 (s, 1 H), 7.22 (d, 1 H, *J* = 7.6 Hz), 7.02 (d, 1 H, *J* = 7.6 Hz), 6.72 (br, 1 H), 6.58 (d, 1 H, *J* = 3.2 Hz), 6.12 (br, 1 H), 2.36 (s, 3 H), 1.52 (s, 9 H).



107

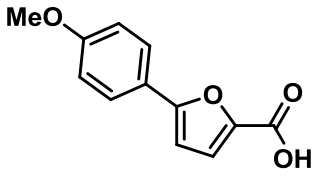
(*E*)-4-((*tert*-Butoxycarbonyl)(5-(*m*-tolyl)furan-2-yl)amino)-3-methylbut-2-en-1-yl acetate (107). To a solution of **121** (170 mg, 0.622 mmol) in dry DMF (2.0 mL) at 0 ^{o}C was added NaH (37.3 mg, 1.25 mmol, 60 % in mineral oil) in 4 portions. The reaction mixture was stirred at 0 ^{o}C for 1 h. Then, **(*E*)-4-bromo-3-methylbut-2-en-1-yl acetate**[51] (135 mg, 0.653 mmol) was added dropwise over 5 min. The resulting solution was stirred at r.t. for 2 h, diluted with Et_2O (10 mL), quenched with saturated aqueous NH_4Cl (10 mL), extracted with Et_2O (3 x 10 mL), washed with water and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **107** (167 mg, 67%) as a yellow liquid: ATR-IR (neat) 2975, 2926, 1735, 1709, 1603, 1549, 1366, 1390, 1228, 1158, 1021, 1060, 949, 857, 779, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38-7.36 (m, 2 H), 7.22 (t, 1 H, *J* = 7.6 Hz), 7.02 (d, 1 H, *J* =7.2 Hz), 6.55 (d, 1 H, *J* = 3.6 Hz), 6.07 (br, 1 H), 5.50 (qt, 1 H, *J* = 1.6, 7.2 Hz), 4.59 (d, 2 H, *J* = 7.2 Hz), 4.22 (s, 2 H); 2.35 (s, 3 H), 1.95 (s, 3 H), 1.75 (s, 3 H), 1.46 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6, 153.4, 148.8,

147.4, 138.0, 137.0, 128.4, 127.6, 123.6, 120.3, 120.2, 105.8, 102.5, 81.3, 60.6, 54.8, 27.9, 21.3, 20.6, 14.2; HRMS (ESI) *m*/z calcd for $C_{23}H_{29}NO_5Na$ ($[M+Na]^+$) 422.1943, found 422.1951.



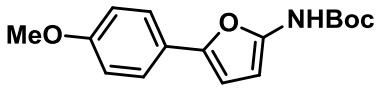
108

3-Methyl-5-(*m*-tolyl)-1*H*-indole (108). To a solution of **107** (34 mg, 0.085 mmol) and $P(OiPr)_3$ (3.5 mg, 0.017 mmol) in NMP (0.43 mL) was added $Pd(PPh_3)_4$ (4.9 mg, 0.0043 mmol). The reaction mixture was stirred under microwave irradiation at 180 ^oC for 20 min, quenched with ether and water, extracted with ether, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (hexanes : EA = 16 : 1) to give **108** (16 mg, 87%) as a yellow liquid: ATR-IR (neat) 3417, 3025, 2921, 785 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.91 (br, 1 H), 7.77 (s, 1 H), 7.49-7.39 (m, 4 H), 7.34 (t, 1 H, *J* = 8.0 Hz), 7.14 (d, 1 H, *J* = 8.0 Hz), 7.00 (s, 1 H), 2.44 (s, 3 H), 2.38 (d, 3 H, *J* = 0.5 Hz); ^{13}C NMR ($CDCl_3$,125 MHz) δ 142.7, 138.1, 135.7, 132.9, 128.7, 128.5, 128.2, 127.0, 124.5, 122.2, 121.8, 117.4, 112.1, 111.1, 21.6, 9.7; HRMS (EI) *m*/z calcd for $C_{16}H_{15}N$ 221.1204, found 221.1216.



142

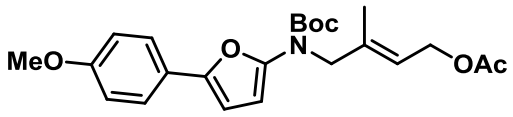
5-(4-Methoxyphenyl)furan-2-carboxylic acid (142). To a solution of **5-bromofuroic acid** (309 mg, 1.62 mmol), **(4-methoxyphenyl)boronic acid** (492 mg, 3.24 mmol) in DMF (1.8 mL) and K_3PO_4 (aq) (1.2 mL, 3.24 mmol) was added $Pd(PPh_3)_4$ (37.4 mg, 0.0324 mmol). The reaction mixture was stirred under microwave irradiation at 150 ^oC for 30 min, quenched with 1 M HCl (10 mL), extracted with ether, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 4 : 1) to give **142** (350 mg, 99%) as a white solid: ^1H NMR ($CDCl_3$, 300 MHz) δ 11.29 (br, 1 H), 7.73 (d, 2 H, *J* = 9.0 Hz), 7.35 (d, 1 H, *J* = 3.6 Hz), 6.94 (d, 2 H, *J* = 9.0 Hz), 6.63 (d, 1 H, *J* = 3.6 Hz), 3.84 (s, 3 H). The spectral data were consistent with those reported in the literature.[59]



143

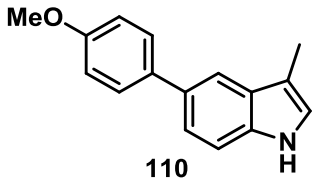
***tert*-Butyl (5-(4-methoxyphenyl)furan-2-yl)carbamate (143).** To a stirred solution of **142** (350 mg, 1.60 mmol) in *t*-BuOH (3 mL) was added DPPA (0.346 mL, 1.60 mmol) and Et_3N (0.451 mL, 3.21 mmol). The reaction mixture was refluxed behind the protective shield and under constant flow of argon for 10 h. The reaction was quenched by NaOH solution (1.0 M), extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **143** (305 mg, 66%) as a white solid: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.48 (td, 2 H,

J = 2.4, 8.8 Hz), 6.89 (td, 2 H, *J* = 2.4, 8.8 Hz), 6.80 (br, 1 H), 6.46 (d, 1 H, *J* = 3.2 Hz), 6.11 (br, 1 H), 3.81 (s, 3 H), 1.51 (s, 9 H).



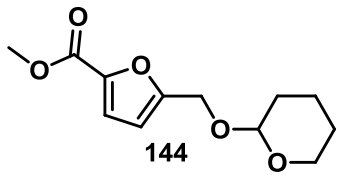
109

(*E*)-4-((*tert*-Butoxycarbonyl)(5-(4-methoxyphenyl)furan-2-yl)amino)-3-methylbut-2-en-1-yl acetate (109). To a solution of **143** (371 mg, 1.28 mmol) in dry DMF (3.0 mL) at 0 ^{o}C was added NaH (76.8 mg, 1.92 mmol, 60 % in mineral oil) in 4 portions. The reaction mixture was stirred at 0 ^{o}C for 1 h. Then, **(*E*)-4-bromo-3-methylbut-2-en-1-yl acetate**[51] (279 mg, 1.34 mmol) was added dropwise over 5 min. The resulting solution was stirred at r.t. for 2 h, diluted with Et_2O (10 mL), quenched with saturated aqueous NH_4Cl (10 mL), extracted with Et_2O (3 x 10 mL), washed with water and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **109** (356 mg, 67%) as a yellow liquid: ATR-IR (neat) 2973, 2928, 1735, 1711, 1620, 1605, 1581, 1554, 1498, 1456, 1441, 1392, 1366, 1292, 1273, 1247, 1230, 1159, 1060, 1021, 951, 831, 779 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.51 (td, 2 H, *J* = 2.5, 9.5 Hz), 6.90 (td, 2 H, *J* = 2.5, 9.5 Hz), 6.43 (d, 1 H, *J* = 3.0 Hz), 6.04 (br, 1 H), 5.50 (qt, 1 H, *J* = 1.5, 7.0 Hz), 4.60 (d, 2 H, *J* = 7.0 Hz), 4.20 (s, 2 H), 3.82 (s, 3 H), 1.99 (s, 3 H), 1.75 (s, 3 H), 1.47 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.9, 158.8, 153.8, 149.1, 147.1, 137.3, 124.7, 123.9, 120.4, 114.1, 104.4, 102.8, 81.4, 60.8, 55.3, 55.2, 28.2, 20.9, 14.4; HRMS (ESI) *m*/z calcd for $C_{23}H_{29}NO_6Na$ ($[M+Na]^+$)438.1893, found 438.1895.



110

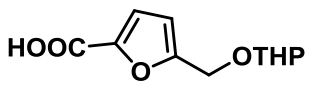
5-(4-Methoxyphenyl)-3-methyl-1*H*-indole (110). To a solution of **109** (53 mg, 0.13 mmol) and P(O*i*Pr)$_3$ (5.3 mg, 0.025 mmol) in NMP (0.64 mL) was added Pd(PPh$_3$)$_4$ (7.4 mg, 0.0063 mmol). The reaction mixture was stirred under microwave irradiation at 180 ^{o}C for 20 min, quenched with ether and water, extracted with ether, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (hexanes : EA = 16 : 1) to give **110** (19 mg, 64%) as a yellow solid: Mp 130.2–133.0 ^{o}C; ATR-IR (neat) 3410, 2919, 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.89 (br, 1 H), 7.73-7.72 (m, 1 H), 7.60 (td, 2 H, *J* = 2.5, 9.0 Hz), 7.40 (dd, 1 H, *J* = 2.0, 8.0 Hz), 7.38 (dd, 1 H, *J* = 0.5, 8.5 Hz), 7.01–6.98 (m, 3 H), 3.86 (s, 3 H), 2.37 (d, 3 H, *J* = 1.0 Hz); ^{13}C NMR ($CDCl_3$,100 MHz) δ 158.4, 135.5, 135.4, 132.5, 128.8, 128.3, 122.2, 121.5, 116.9, 114.1, 112.0, 111.1, 53.4, 9.7; HRMS (ESI) *m*/z calcd for $C_{16}H_{16}NO$ ([M+H]$^{+}$) 238.1232, found 238.1257.



144

Methyl 5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)furan-2-carboxylate (144). To a solution of **methyl 5-(hydroxymethyl)furan-2-carboxylate**[60] (18 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) was added DHP (0.016 mL, 0.17 mmol) and PPTS (2.9 mg, 0.012 mmol). The reaction

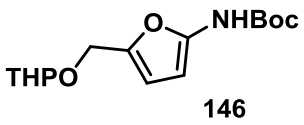
mixture was stirred at r.t. for 4 h, quenched with 1 N HCl (10 mL) and extracted with ethyl acetate, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 to give **144** (25.3 mg, 91%) as a colorless liquid: ATR-IR (neat) 3006, 2930, 2855, 2807, 1720, 1618, 1603, 1526, 1409, 1389, 1288, 1208, 1135, 1072, 1020, 902, 872, 760, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.14(d, 1 H, *J* = 3.6 Hz), 6.44 (d, 1 H, *J* = 3.6 Hz), 4.72 (t, 1 H, *J* = 3.2 Hz), 4.71 (d, 1 H, *J* = 13.2 Hz), 4.53 (d, 1 H, *J* = 13.2 Hz), 3.89 (s, 3 H), 3.87 (ddd, 1 H, *J* = 3.2, 8.8, 12.0 Hz), 3.57-3.52 (m, 1 H), 1.87-1.78 (m, 1 H), 1.76-1.69 (m, 1 H), 1.66-1.59 (m, 2 H), 1.55-1.51 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.1, 156.3, 144.3, 118.8, 110.8, 97.9, 62.0, 60.9, 51.9, 30.3, 25.3, 19.0; HRMS (ESI) *m*/z calcd for $C_{12}H_{16}O_5Na$ ($[M+Na]^+$) 263.0895, found 263.0880.



145

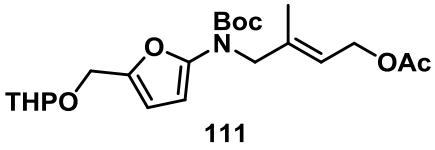
5-(((Tetrahydro-2*H*-pyran-2-yl)oxy)methyl)furan-2-carboxylic acid (145). To a solution of **144** (204 mg, 0.849 mmol) in THF (2 mL) was added LiOH (71.3 mg, 1.70 mmol). The reaction mixture was stirred at r.t. for 4 h, quenched with 1 N HCl (10 mL) and extracted with ethyl acetate, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give **145** (165 mg, 86%) as a white semi-solid: ATR-IR (neat) 3055, 2934, 2855, 1689, 1594, 1526, 1266, 1200, 1120, 1018, 964, 902, 811, 734 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.83 (br, 1 H), 7.27 (d, 1 H, *J* = 3.0 Hz), 6.48 (d, 1 H, *J* = 3.5 Hz), 4.75 (t, 1 H, *J* = 3.2 Hz), 4.74 (d, 1 H, *J* = 13.5 Hz), 4.59 (d, 1 H, *J* = 13.5 Hz), 3.88 (ddd, 1 H, *J* = 3.2, 9.0, 12.0 Hz), 3.57-3.55 (m, 1 H), 1.86-

1.64 (m, 6 H).; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.0, 157.4, 143.5, 120.8, 111.0, 97.9, 62.0, 60.9, 30.2, 25.3, 18.9; HRMS (ESI) *m*/z calcd for $C_{11}H_{13}O_5$ ($[M]^+$) 225.0763, found 225.0773.



146

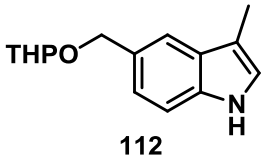
***tert*-Butyl (5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)furan-2-yl)carbamate (146).** To a stirred solution of **145** (124 mg, 0.549 mmol) in *t*-BuOH (5 mL) was added DPPA (0.118 mL, 0.549 mmol) and Et_3N (0.154 mL, 1.10 mmol). The reaction mixture was refluxed behind the protective shield and under constant flow of argon for 12 h. The reaction was quenched by NaOH solution (1.0 M), extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **146** (70.1 mg, 43%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.78 (br, 1 H), 6.27 (d, 1 H, *J* = 3.2 Hz), 5.97 (br, 1 H), 4.69 (t, 1 H, *J* = 3.6 Hz), 4.55 (d, 1 H, *J* = 12.8 Hz), 4.39 (d, 1 H, *J* = 12.8 Hz), 3.87 (ddd, 1 H, *J* = 3.2, 9.2, 12.0 Hz), 3.51 (td, 1 H, *J* = 5.2, 11.2 Hz), 1.85-1.52 (m, 6 H), 1.49 (s, 9 H).



111

(*E*)-4-((*tert*-Butoxycarbonyl)(5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)furan-2-yl)amino)-3-methylbut-2-en-1-yl acetate (111). To a solution of **146** (298 mg, 1.00 mmol) in dry DMF (2.0 mL) at 0 ^{o}C was added NaH (60.0 mg, 1.50 mmol, 60 % in mineral oil) in 4

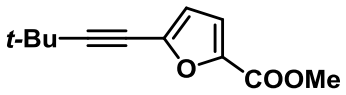
portions. The reaction mixture was stirred at 0 ^{o}C for 1 h. Then, **(*E*)-4-bromo-3-methylbut-2-en-1-yl acetate**[51] (218 mg, 1.05 mmol) was added dropwise over 5 min. The resulting solution was stirred at r.t. for 2 h, diluted with Et_2O (10 mL), quenched with saturated aqueous NH_4Cl (10 mL), extracted with Et_2O (3 x 10 mL), washed with water and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **111** (340 mg, 80%) as a yellow liquid: ATR-IR (neat) 2973, 2939, 2868, 1737, 1713, 1620, 1562, 1454, 1441, 1390, 1366, 1228, 1200, 1159, 1133, 1116, 1016, 964, 904, 869, 816, 785 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.25 (d, 1 H, *J* = 3.2 Hz), 5.93 (br, 1 H), 5.43 (qt, 1 H, *J* = 0.8, 6.4 Hz), 4.69 (t, 1 H, *J* = 3.2 Hz), 4.57 (d, 1 H, *J* = 13.2 Hz), 4.56 (d, 2 H, *J* = 6.8 Hz), 4.42 (d, 1 H, *J* = 13.2 Hz), 4.13 (s, 2 H), 3.88 (ddd, 1 H, *J* = 2.8, 8.4, 11.2 Hz), 3.53 (td, 1 H, *J* = 4.4, 10.8 Hz), 2.02 (s, 3 H), 1.86-1.49 (m, 9 H), 1.44 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 153.5, 148.0,146.7, 137.0, 120.2, 110.4, 101.4, 96.6, 81.1, 61.6, 60.6, 60.4, 54.8, 30.2, 27.9, 25.2, 20.7, 18.9, 14.2; HRMS (ESI) *m*/z calcd for $C_{22}H_{33}NO_7Na$ ($[M+Na]^+$) 446.2155, found 446.2133.



112

3-Methyl-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-1*H*-indole (112). To a solution of **111** (63 mg, 0.15 mmol) and P(O*i*Pr)$_3$ (6.2 mg, 0.030 mmol) in NMP (0.75 mL) was added $Pd(PPh_3)_4$ (8.6 mg, 0.0074 mmol). The reaction mixture was stirred under microwave irradiation at 180 ^{o}C for 20 min, quenched with ether and water, extracted with ether, washed with brine,

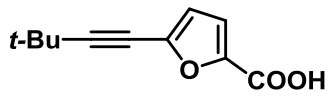
dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (hexanes : EA = 16 : 1) to give **112** (22 mg, 59%) as a pale yellow liquid: ATR-IR (neat) 3411, 2930, 1116, 1074, 1023, 794 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.91 (br, 1 H), 7.58 (s, 1 H), 7.32 (d, 1 H, *J* = 8.0 Hz), 7.22 (dd, 1 H, *J* = 1.0, 8.5 Hz), 6.97 (s, 1 H), 4.90 (d, 1 H, *J* = 11.0 Hz), 4.75 (t, 1 H, *J* = 3.5 Hz), 4.62 (d, 1 H, 11.5 Hz), 3.99 (ddd, 1 H, *J* = 3.0, 9.0, 12.0 Hz), 3.58 (td, 1 H, *J* = 5.0 , 11.0 Hz), 2.33 (d, 3 H, *J* = 0.5 Hz), 1.90-1.84 (m, 1 H), 1.76-1.70 (m, 1 H), 1.67-1.51 (m, 4 H); ^{13}C NMR ($CDCl_3$,125 MHz) δ 135.9, 128.8, 128.3, 122.8, 122.0, 119.0, 111.8, 110.8, 97.2, 62.2, 30.7, 25.6, 19.5, 9.6; HRMS (ESI) *m*/z calcd for $C_{15}H_{19}NO_2Na$ ($[M+Na]^+$) 268.1313, found 268.1335.



147

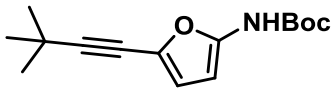
Methyl 5-(3,3-dimethylbut-1-yn-1-yl)furan-2-carboxylate (147). To a stirred solution of **methyl 5-bromofuran-2-carboxylate** (370 mg, 1.80 mmol), CuI (34.4 mg, 0.180 mmol) and $Pd(PPh_3)_2Cl_2$ (27.7 mg, 0.0902 mmol) in 3 mL triethylamine at room temperature was slowly added 3,3-dimethylbutyne (0.445 mL, 3.61 mmol) at r.t.. The reaction mixture was stirred at r.t. for 24 h, filtered by celite and concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 12 : 1) to give **147** (369 mg, 99%) as a white solid.: Mp 72.7–74.3 ^oC; ATR-IR (neat) 2964, 2220, 1713, 1582, 1508, 1439, 1364, 1297, 1212, 1129, 1023, 1021, 986, 923, 811, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.12 (d, 1 H, *J* = 3.6 Hz), 6.50 (d, 1 H, *J* = 3.6 Hz), 3.88 (s, 3 H), 1.30 (s, 9 H);); ^{13}C NMR ($CDCl_3$, 125 MHz)

δ 158.5, 143.5, 141.0, 118.8, 115.2, 104.6, 69.0, 52.0, 30.4, 28.1; HRMS (ESI) *m*/z calcd for $C_{12}H_{15}O_3$ ($[M+H]^+$) 207.1021, found 207.1026.



148

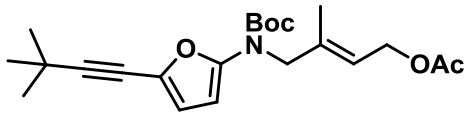
5-(3,3-Dimethylbut-1-yn-1-yl)furan-2-carboxylic acid (148). To a solution of **147** (124 mg, 0.601 mmol) in THF (2 mL) and H_2O (0.5 mL)was added LiOH (50.5 mg, 1.20 mmol). The reaction mixture was stirred at r.t. for 4 h, quenched with 1 N HCl (5 mL), extracted with ethyl acetate, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give **148** (90.0 mg, 78%) as a white solid: Mp 213.0–215.2 ^oC; ATR-IR (neat) 3118, 2967, 2922, 2865, 2222, 1668, 1506, 1418, 1288, 1212, 1159, 1033, 980, 958, 902, 818, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.87 (br, 1 H), 7.25 (d, 1 H, *J* = 4.0 Hz), 6.54 (d, 1 H, *J* = 3.2 Hz), 1.31 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.8, 142.7, 142.1, 120.9, 115.4, 105.2, 69.0, 30.4, 28.2; HRMS (ESI) *m*/z calcd for $C_{11}H_{13}O_3$ ($[M+H]^+$) 193.0865, found 193.0847.



149

***tert*-Butyl (5-(3,3-dimethylbut-1-yn-1-yl)furan-2-yl)carbamate (149).** To a stirred solution of **148** (176 mg, 0.918 mmol) in *t*-BuOH (5 mL) was added DPPA (0.198 mL, 0.918 mmol) and Et_3N (0.258 mL, 1.83 mmol). The reaction mixture was refluxed behind the protective shield and under constant flow of argon for 12 h. The reaction was quenched by

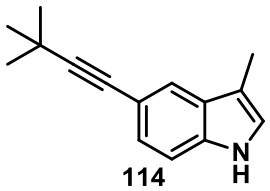
NaOH solution (1.0 M), extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **149** (118 mg, 49%) as a pale yellow solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.65 (br, 1 H), 6.41 (d, 1 H, *J* = 3.2 Hz), 5.99 (br, 1 H), 1.50 (s, 9 H), 1.30 (s, 9 H).



113

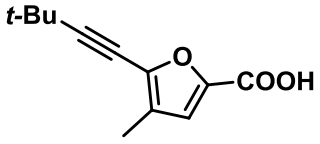
(*E*)-4-((*tert*-Butoxycarbonyl)(5-(3,3-dimethylbut-1-yn-1-yl)furan-2-yl)amino)-3-methylbut-2-en-1-yl acetate (113). To a solution of **149** (119 mg, 0.451 mmol) in dry DMF (2.0 mL) at 0 ^{o}C was added NaH (27.1 mg, 0.677 mmol, 60 % in mineral oil) in 4 portions. The reaction mixture was stirred at 0 ^{o}C for 1 h. Then, **(*E*)-4-bromo-3-methylbut-2-en-1-yl acetate**[51] (98.1 mg, 0.474 mmol) was added dropwise over 5 min. The resulting solution was stirred at r.t. for 2 h, diluted with Et_2O (10 mL), quenched with saturated aqueous NH_4Cl (10 mL), extracted with Et_2O (3 x 10 mL), washed with water and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **113** (95.0 mg, 54%) as a yellow liquid: ATR-IR (neat) 2969, 2928, 2865, 1737, 1715, 1607, 1541, 1448, 1472, 1392, 1364, 1271, 1228, 1158, 1062, 1020, 980, 857, 779 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.38 (d, 1 H, *J* =3.5 Hz), 5.95 (br, 1 H), 5.42 (qt, 1 H, *J* = 1.0, 6.5 Hz), 4.59 (d, 2 H, *J* = 7.0 Hz), 4.14 (s, 2 H), 2.03 (s, 3 H), 1.70 (s, 3 H), 1.44 (s, 9 H), 1.30 (s, 9 H); ^{13}C NMR($CDCl_3$, 125 MHz)) δ 170.9, 153.4, 147.4, 137.0, 132.7,

120.2, 115.2, 102.0, 101.9, 81.6, 69.5, 60.8, 54.5, 30.7, 28.1, 28.1, 20.9, 14.4; HRMS (ESI) *m*/z calcd for $C_{22}H_{31}NO_5Na$ ($[M+Na]^+$) 412.2100, found 412.2094.



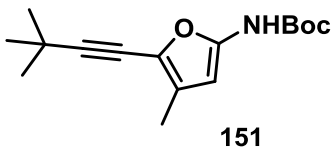
114

5-(3,3-Dimethylbut-1-yn-1-yl)-3-methyl-1*H*-indole (114). To a solution of **113** (51 mg, 0.13 mmol) and P(O*i*Pr)$_3$ (5.5 mg, 0.026 mmol) in NMP (0.65 mL) was added Pd(PPh$_3$)$_4$ (7.6 mg, 0.0065 mmol). The reaction mixture was stirred under microwave irradiation at 180 ^oC for 20 min, quenched with ether and water, extracted with ether, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (hexanes : EA = 16 : 1) to give **114** (15 mg, 52%) as a pale yellow liquid: ATR-IR (neat) 3415, 2922, 2166, 796 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.88 (br, 1 H), 7.65 (s, 1 H), 7.22 (br, 2 H), 6.95 (s, 1 H), 2.30 (s, 3 H), 1.34 (s, 9 H); ^{13}C NMR ($CDCl_3$,125 MHz) δ 135.5, 128.2, 125.6, 122.5, 122.1, 114.5, 111.9, 110.7, 95.6, 80.2, 31.3, 27.9, 9.6; HRMS (EI) *m*/z calcd for $C_{15}H_{17}N$ 211.1360, found 211.1350.



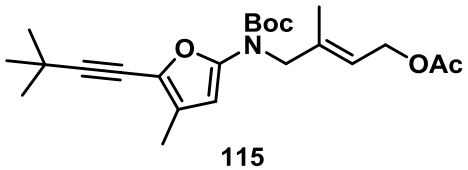
150

5-(3,3-Dimethylbut-1-yn-1-yl)-4-methylfuran-2-carboxylic acid (150). To a solution of **methyl 5-(3,3-dimethylbut-1-yn-1-yl)-4-methylfuran-2-carboxylate**[61] (157 mg, 0.713 mmol) in THF (2 mL) and H_2O (0.5 mL) was added LiOH (59.8 mg, 1.43 mmol). The reaction mixture was stirred at r.t. for 4 h, quenched with 1 N HCl (10 mL) and extracted with ethyl acetate, dried (Na_2SO_4), filtered and concentrated under reduced pressure to **150** (139 mg, 95%) as a white solid: Mp 200.0–202.2 ^oC; ATR-IR (neat) 3360, 3120, 3025, 2965, 2924, 2231, 1678, 1620, 1514, 1422, 1379, 1361, 1323, 1202, 1131, 896, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.65 (br, 1 H), 7.15 (s, 1 H), 2.09 (s, 3 H), 1.32 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.0, 141.8, 139.8, 125.9, 122.4, 107.5, 68.3, 30.6, 28.3, 10.3. HRMS (ESI) *m*/z calcd for $C_{12}H_{15}O_3$ ($[M+H]^+$) 207.1021, found 207.0985.



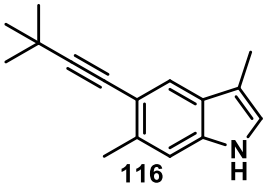
151

***tert*-Butyl (5-(3,3-dimethylbut-1-yn-1-yl)-4-methylfuran-2-yl)carbamate (151).** To a stirred solution of **150** (140 mg, 0.679 mmol) in *t*-BuOH (5 mL) was added DPPA (0.146 mL, 0.678 mmol) and Et_3N (0.191 mL, 1.36 mmol). The reaction mixture was refluxed behind the protective shield and under constant flow of argon for 12 h. The reaction was quenched by NaOH solution (1.0 M), extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **151** (76.0 mg, 40%) as a pale yellow solid: ^1H NMR ($CDCl_3$, 500 MHz) δ 6.61 (br, 1 H), 5.92 (br, 1 H), 2.02 (s, 3 H), 1.49 (s, 9 H), 1.31 (s, 9 H).



115

(*E*)-4-((*tert*-Butoxycarbonyl)(5-(3,3-dimethylbut-1-yn-1-yl)-4-methylfuran-2-yl)amino)-3-methylbut-2-en-1-yl acetate (115). To a solution of **151** (76.0 mg, 0.274 mmol) in dry DMF (0.5 mL) at 0 ^{o}C was added NaH (16.4 mg, 0.411 mmol, 60 % in mineral oil) in 4 portions. The reaction mixture was stirred at 0 ^{o}C for 1 h. Then, **(*E*)-4-bromo-3-methylbut-2-en-1-yl acetate**[51] (59.6 mg, 0.288 mmol) was added dropwise over 5 min. The resulting solution was stirred at r.t. for 2 h, diluted with Et_2O (10 mL), quenched with saturated aqueous NH_4Cl (10 mL), extracted with Et_2O (3 x 10 mL), washed with water and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **115** (78.0 mg, 71%) as a yellow liquid: ATR-IR (neat) 2971, 2932, 2158, 1737, 1713, 1618, 1581, 1554, 1500, 1456, 1443, 1392, 1364, 1230, 1159, 1060, 1023, 951, 857, 831, 777 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.88 (br, 1 H), 5.41 (qt, 1 H, *J* = 1.2, 6.8 Hz), 4.59 (d, 2 H, *J* = 6.8 Hz), 4.13 (s, 2 H), 2.03 (s, 3 H), 2.01 (s, 3 H), 1.69 (s, 3 H), 1.45 (s, 9 H), 1.31 (s, 9 H); HRMS (ESI) *m*/z calcd for $C_{23}H_{33}NO_5Na$ ($[M+Na]^+$) 426.2256, found 426.2253.



116

5-(3,3-Dimethylbut-1-yn-1-yl)-3,6-dimethyl-1*H*-indole (116). To a solution of **115** (54 mg, 0.13 mmol) and P(O*i*Pr)$_3$ (5.6 mg, 0.027 mmol) in NMP (0.67 mL) was added Pd(PPh$_3$)$_4$ (7.8 mg, 0.0067 mmol). The reaction mixture was stirred under microwave irradiation at 180 ^{o}C for 20 min, quenched with ether and water, extracted with ether, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (hexanes : EA = 16 : 1) to give **116** (8.3 mg, 27%) as a pale yellow liquid: ATR-IR (neat) 3396, 2922, 2166, 1277, 1124, 1072, 796 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72 (br, 1 H), 7.61 (s, 1 H), 7.13 (s, 1 H), 6.87 (s, 1 H), 2.49 (s, 3 H), 2.28 (d, 3 H, *J* = 1.0 Hz), 1.36 (s, 9 H); HRMS (EI) *m*/z calcd for $C_{16}H_{19}N$ 225.2517, found 225.1503.

2.0 5‑HYDROXYINDOLES BY INTRAMOLECULAR ALKYNOL−FURAN DIELS−ALDER CYCLOADDITION

2.1 INTRODUCTION

2.1.1 Significance of 5-hydroxyindoles

5-Hydroxyindoles are found in a vast array of pharmacologically active agents and natural products (**Figure 5**). Furthermore, the hydroxy group can be readily converted to derivatives that allow scaffold extensions, cross-coupling or nucleophilic addition reactions of the indole nucleus. [62,63]

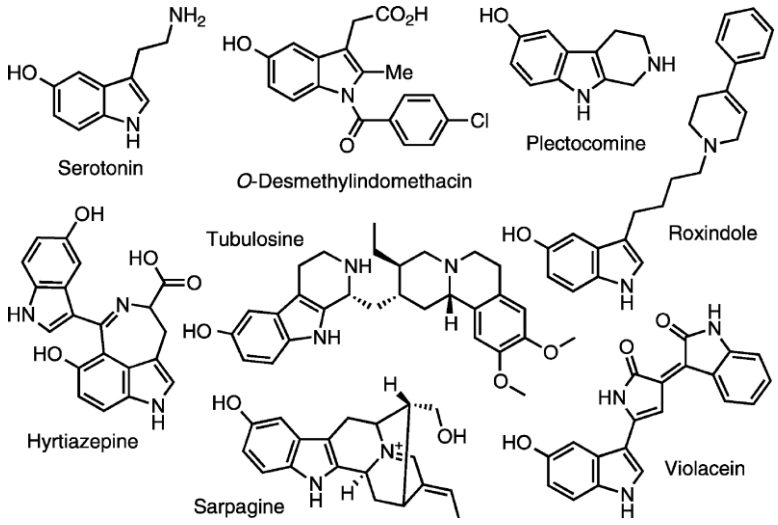
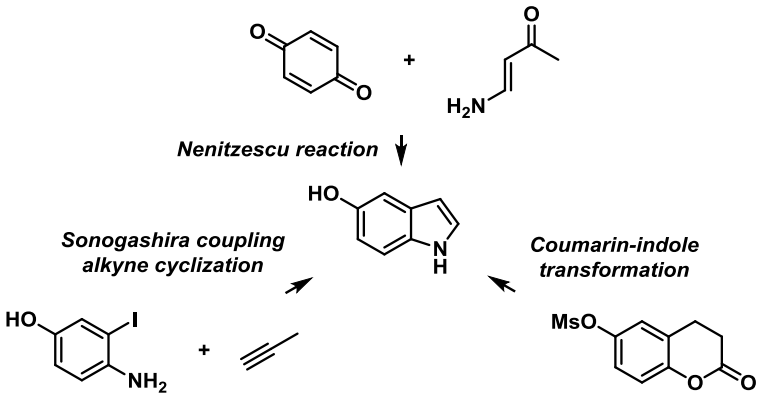


Figure 5. Representative biologically active 5-hydroxyindoles

2.1.2 Methods of 5-hydroxyindole synthesis

General approaches to construct 5-hydroxyindoles include the Nenitzescu reaction,[8] the coumarin−indole transformation,[64] and the Pd-catalyzed coupling of 2-iodoanilines with alkynes[65] (**Scheme 18**). All of these methods feature a linear sequence start from a functionalized 6-membered ring, then the pyrrole moiety is added to form the indole rings.



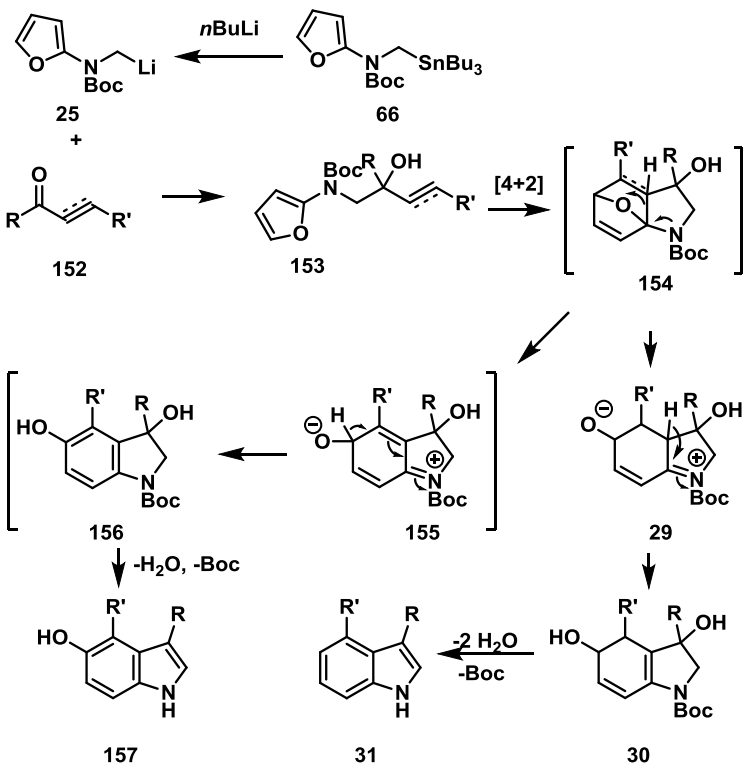
Scheme 18. Methods for formation of 5-hydroxyindoles

2.2 RESULTS AND DISCUSSION

2.2.1 Introduction

In our previous reaction sequence,[27] transmetallation of stannane **66** gives lithiated **25**. Addition of **25** to enones **152** provided the cycloaddition precursors **153**. Subjecting these allylic alcohols **153** to microwave irradiation led to the intitial IMDAF products which underwent aromatizations/dehydration and deprotections to provide indoles **30**.

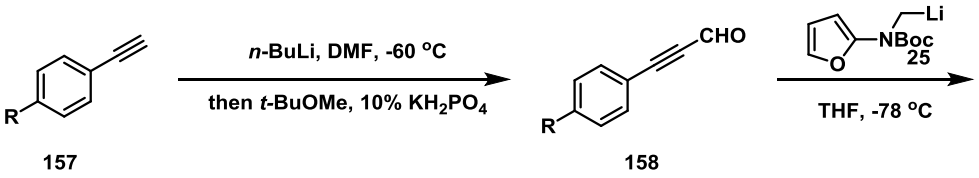
It was envisioned that replacing the enone with alkynone would give us the opportunity to branch out from this reaction pathway, eliminate the bridging oxygen atom in **154** to give **155**, aromatize the intermediate at an earlier stage to give phenol **156**, and finally only eliminate a single molecule of water and, concomitantly, the *N*-protective group[66-68] to yield 5-hydroxyindole **157**.



Scheme 19. Proposed IMDAF reaction pathways for indole and 5-hydroxyindole formation

2.2.2 Examples of the IMDAF reaction for the synthesis of 5-hydroxyindoles

The synthesis of 5-hydroxyindole begins with formylation of commercial available alkyne **157** to afford the alkynal **158**. Treatment of **158** to lithiated **25** gives secondary alcohol **159** in unoptimized 20−52% yields. Microwave heating to 180 ℃ for 30 min effected the desired IMDAF process and aromatization to give 5-hydroxyindoles **160** after chromatographic purification of the reaction mixture on SiO_2.

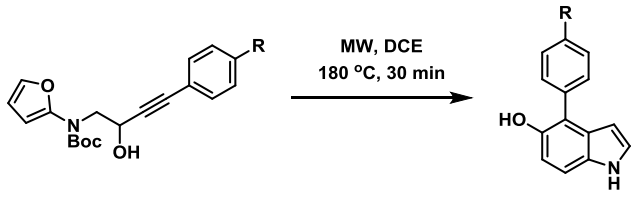


157 158

157a, R = CH_3 **158a**, R = CH_3, 78%

157b, R = F **158b**, R = F, 46%

157c, R = CF_3 **158c**, R = CF_3, 54%



159 160

159a, R = CH_3, 52% **160a**, R = CH_3, 47%

159b, R = F, 20% **160b**, R = F, 44%

159c, R = CF_3, 26% **160c**, R = CF_3, 64%

Scheme 20. Synthesis of 5-hydroxyindoles from secondary alkynols

The reaction tolerated both electron-withdrawing groups and electron-donating groups in the 4-position of indole. No obvious trend for electron-withdrawing or-donating substituents was observed for this transformation. Other substrates with 4-alkyl substitutions gave lower yields (15-23%) due to the lack of extended conjugation.[45]

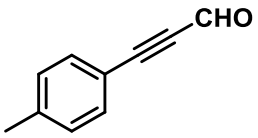
2.2.3 Conclusions

In summary, we have extended our indole synthesis methodology to give synthetically and biologically valuable 5-hydroxy indoles by the use of alkynals as starting materials. The starting materials are readily available from different substituted alkynes. This convergent procedure is compatible with multiple functionalities in the 4-position of the indole, including electron-withdrawing groups and electron-donating groups. Yields range from 44 to 64% due to the high reaction temperature.

2.3 EXPERIMENTAL SECTION

General Information: All reactions were performed under an N_2 or argon atmosphere and all glassware was dried in an oven at 140 ℃ for 2 h prior to use. Reactions carried out at -78 ℃ employed a CO_2/acetone bath. THF was distilled over sodium/benzophenone ketyl, and CH_2Cl_2 was purified using an alumina column filtration system. DMF were dried from 4 Å molecule sieves. Pyridine and Et_3N were dried from KOH. Reactions were monitored by TLC analysis (EM Science pre-coated silica gel 60 F_{254} plates, 250 mM layer thickness) a PMA solution (5 g of phosphomolybdic acid in 100 mL of 95% EtOH), *p*-anisaldehyde solution (2.5 mL of *p*-anisaldehyde, 2 mL of AcOH, and 3.5 mL of conc. H_2SO_4 in 100 mL of 95% EtOH), Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}$•4 H_2O and 0.2 g of $Ce(SO_4)_2$ in 100 mL of a 3.5 N H_2SO_4 solution) or a $KMnO_4$ solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1% NaOH

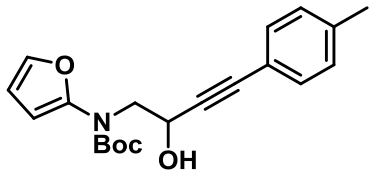
solution). Purifications by chromatography were performed using SiO_2 (SiliaFlash® F60, Silicycle) or using an ISCO- Companion flash chromatography system. $^{1}H/^{13}C$ NMR spectra were recorded on Bruker Avance 300/75 MHz, Bruker Avance 400/100 MHz or Bruker Avance 500/125 MHz instrument. Chemical shifts were reported in parts per million with the residual solvent peak used as the internal standard. Chemical shifts were tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quarter, dd = doublet of doublet, dt = doublet of triplet, m = multiplet, br = broad, app = apparent), coupling constants, and integration. Mass spectra were obtained on a Micromass Autospec double focusing instrument. IR spectra were obtained on an Identity IR-ATR spectrometer. Microwave reactions were performed using a Biotage Initiator in glass microwave vials (cap sealed) with continuous magnetic stirring and an external surface temperature sensor. LCMS analyses were completed on a Waters MicroMass ZQ with 2525 Binary Gradient Module, 2420 ELSD, 2996 PDA using MeCN/H_2O with 0.1% TFA. Melting points (uncorrected) were determined using a Mel-Temp instrument.



158a

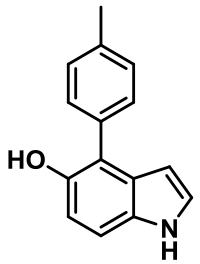
3-(*p*-Tolyl)propiolaldehyde (158a). To a cooled (-60 ^{o}C) solution of 4-methylphenylacetylene (286 mg, 2.46 mmol) in THF (5 mL) was added *n*-BuLi (2.46 mL, 1.1 M in hexanes) with stirring. To this solution was added DMF (0.383 mL, 4.92 mmol) dropwise over 2 min. The reaction mixture was stirred at r.t. for 20 min, and poured into a mixture of *tert*-butyl methyl ether (10 mL) and 10% KH_2PO_4 solution (20 mL) at 0 ^{o}C. The solution was stirred at 0

^{o}C for 30 min, extracted with ethyl acetate, washed with brine, dried, filtered and concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **158a** (276 mg, 78%) as a pale yellow liquid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.40 (s, 1 H), 7.49 (d, 2 H, *J* = 8.4 Hz), 7.20 (d, 2 H, *J* =8.0 Hz), 2.39 (s, 3 H). The spectral data were consistent with those reported in the literature.[69]



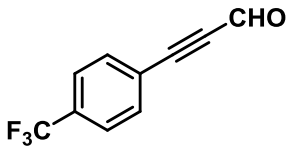
159a

***tert*-Butyl furan-2-yl(2-hydroxy-4-(*p*-tolyl)but-3-yn-1-yl)carbamate (159a).** To a cooled (-78 ^{o}C) solution of **66** (787 mg, 1.62 mmol) in dry THF (4.0 mL) was added *n*-BuLi (1.62 mL, 1.1 M in hexanes). After 15 min, **158a** (117 mg, 0.809 mmol) in THF (1.0 mL) was added into the reaction mixture. The solution was stirred at -78 ^{o}C for 1 h, quenched with ether and NH_4Cl solution, extracted with EtOAc, washed with brine, dried(Na_2SO_4) filtered and concentrated. The residue was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **159a** (144 mg, 52%) as a pale yellow liquid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (d, 2 H, *J* = 8.0 Hz), 7.19 (dd, 1 H, *J* = 0.8, 2.0 Hz), 7.10 (d, 2 H, *J* = 7.6 Hz), 6.34 (dd, 1 H, *J* = 2.0, 3.2 Hz), 6.08 (br, 1 H), 4.81 (dt, 1 H, *J* = 2.0, 8.0 Hz), 3.97 (dd, 1 H, *J* = 8.0, 14.4 Hz), 3.85 (dd, 1 H, *J* = 4.0, 14.4 Hz), 2.34 (s, 3 H), 1.61 (br, 1 H), 1.45 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.0, 148.2, 138.4, 138.2, 131.6, 128.9, 119.3, 110.9, 101.8, 86.9, 85.8, 81.9, 62.0, 54.7, 28.0, 21.3; HRMS (ESI) *m*/z calcd for $C_{20}H_{23}NO_4Na$ ($[M+Na]^+$) 365.1525, found 364.1494.



160a

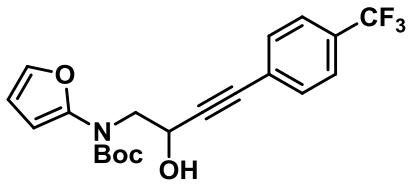
4-(*p*-Tolyl)-1*H*-indol-5-ol (160a). A solution of **159a** (35.0 mg, 0.103 mmol) in 1,2-dichloroethane (1.40 mL) was subjected to microwave irraditation at 180 ^{o}C for 30 min. The reaction mixture was concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 8 : 1) to give **160a** (10.8 mg, 47%) as a pale yellow solid: Mp 112.0-113.8 ^{o}C; ATR-IR (neat) 3523, 3409, 3021, 2917, 2857, 1165, 731 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.10 (br, 1 H), 7.47 (d, 2 H, *J* = 8.5 Hz), 7.35 (d, 2 H, *J* = 8.0 Hz), 7.27 (dd, 1 H, *J* = 0.5, 8.5 Hz), 7.17 (app t, 1 H, *J* = 3.0 Hz), 6.94 (d, 1 H, *J* = 9.0 Hz), 6.32 (ddd, 1 H, *J* = 1.0, 2.0, 3.0 Hz), 5.00 (br, 1 H), 2.45 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.0, 137.4, 132.5, 130.9, 130.0, 129.8, 127.9, 125.0, 117.8, 111.9, 111.1, 101.7, 21.3; HRMS (ESI) *m*/z calcd for $C_{15}H_{14}NO$ ($[M+H]^+$) 224.1075, found 224.1074.



158c

3-(4-(Trifluoromethyl)phenyl)propiolaldehyde (158c). To a cooled (-60 ^{o}C) solution of 1-ethynyl-4-(trifluoromethyl)benzene (225 mg, 1.32 mmol) in THF (4 mL) was added *n*-BuLi

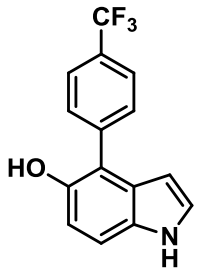
(1.20 mL, 1.1 M in hexanes) with stirring. To this solution was added DMF (0.205 mL, 2.64 mmol) dropwise over 2 min. The reaction mixture was stirred at r.t. for 20 min, and poured into a mixture of tert-butyl methyl ether (10 mL) and 10% KH_2PO_4 solution (20 mL) at 0 ^oC. The solution was stirred at 0 ^oC for 30 min, extracted with ethyl acetate, washed with brine, dried, filtered and concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **158c** (141 mg, 54%) as a pale yellow solid: ^1H NMR ($CDCl_3$, 300 MHz) δ 9.44 (s, 1 H), 7.72 (d, 2 H, *J* = 8.4 Hz), 7.67 (d, 2 H, *J* =8.4 Hz). The spectral data were consistent with those reported in the literature.[70]



159c

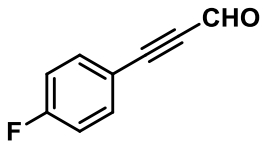
***tert*-Butylfuran-2-yl(2-hydroxy-4-(4-(trifluoromethyl)phenyl)but-3-yn-1-yl)carbamate (159c).** To a cooled (-78 ^oC) solution of **66** (565 mg, 1.16 mmol) in dry THF (4.0 mL) was added *n*-BuLi (1.19 mL, 1.1 M in hexanes). After 15 min, **159b** (130 mg, 0.656 mmol) in THF (1.0 mL) was added into the reaction mixture. The solution was stirred at -78 ^oC for 1 h, quenched with ether and NH_4Cl solution, extracted with EtOAc, washed with brine, dried(Na_2SO_4) filtered and concentrated. The residue was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **159c** (66.7 mg, 26%) as a pale yellow liquid: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.54 (d, 2 H, *J* = 8.5 Hz), 7.49 (d, 2 H, *J* = 8.5 Hz), 7.18 (dd, 1 H, *J* = 1.0, 2.0 Hz), 6.34 (dd, 1 H, *J* = 2.0, 3.0 Hz), 6.07 (br, 1 H), 4.84 (dd, 1 H, *J* = 4.0, 8.0 Hz), 3.98 (dd, 1 H, *J* =

8.0, 14.5 Hz), 3.89 (dd, 1 H, *J* = 4.0, 14.5 Hz), 1.44 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.1, 148.2, 138.4, 132.0, 130.2 (q, *J* = 32.5 Hz), 126.2, 125.2(q, *J* = 3.8 Hz), 123.8 (d, *J* = 270.5 Hz), 111.1, 101.8, 90.1, 84.4, 82.2, 62.2, 54.6, 28.1; HRMS (ESI) *m*/z calcd for $C_{20}H_{20}F_3NO_4$ 396.1423, found 396.1404.



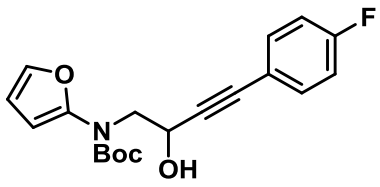
160c

4-(4-(Trifluoromethyl)phenyl)-1*H*-indol-5-ol (160c). A solution of **159c** (29.4 mg, 0.0744 mmol) in 1,2-dichloroethane (1.40 mL) was subjected to microwave irraditation at 180 ^{o}C for 30 min. The reaction mixture was concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 8 : 1) to **160c** (13.1 mg, 64%) as a pale yellow solid: Mp 140.1-142.4 ^{o}C; ATR-IR (neat) 3491, 3407, 2922, 2850, 1322, 1165, 1120, 841 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.17 (br, 1 H), 7.79 (d, 2 H, *J* = 8.0 Hz), 7.73 (d, 2 H, *J* = 8.0 Hz), 7.32 (dd, 1 H, *J* = 0.5, 8.5 Hz), 7.21 (app t, 1 H, *J* = 3.0 Hz), 6.92 (d, 1 H, *J* = 9.0 Hz), 6.31 (ddd, 1 H, *J* = 1.0, 2.5, 3.0 Hz), 4.76 (br, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.9, 139.9, 131.0, 130.4, 129.5 (q, *J* = 32.2 Hz), 127.7, 126.0 (q, *J* = 3.6 Hz), 125.5, 124.2 (q, *J* = 270.1 Hz), 116.7, 112.3, 112.0, 101.4; HRMS (ESI) *m*/z calcd for $C_{15}H_{11}NOF_3$ ($[M+H]^+$) 278.0793, found 278.0794.



158b

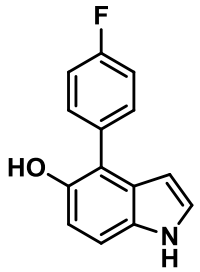
3-(4-Fluorophenyl)propiolaldehyde (158b). To a cooled (-60 ^{o}C) solution of 4-fluorophenylacetylene (157 mg, 1.31 mmol) in THF (3 mL) was added *n*-BuLi (1.19 mL, 1.1 M in hexanes) with stirring. To this solution was added DMF (0.203 mL, 2.61 mmol) dropwise over 2 min. The reaction mixture was stirred at r.t. for 20 min, and poured into a mixture of *tert*-butyl methyl ether (10 mL) and 10% KH_2PO_4 solution (20 mL) at 0 ^{o}C. The solution was stirred at 0 ^{o}C for 30 min, extracted with ethyl acetate, washed with brine, dried, filtered and concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **158b** (89.0 mg, 46%) as a pale yellow liquid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.41 (s, 1 H), 7.64-7.59 (m, 2 H), 7.11 (tt, 2 H, *J* =2.4, 8.4 Hz).[71]



159b

***tert*-Butyl (4-(4-fluorophenyl)-2-hydroxybut-3-yn-1-yl)(furan-2-yl)carbamate (159b)**. To a cooled (-78 ^{o}C) solution of **66** (584 mg, 1.20 mmol) in dry THF (3.0 mL) was added *n*-BuLi (1.20 mL, 1.1 M in hexanes). After 15 min, **158b** (89.0 mg, 0.601 mmol) in THF (1.0 mL) was added into the reaction mixture. The solution was stirred at -78 ^{o}C for 1 h, quenched with ether and NH_4Cl solution, extracted with EtOAc, washed with brine, dried (Na_2SO_4) filtered and

concentrated. The residue was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **159b** (42.0 mg, 20%) as a pale yellow liquid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40-7.36 (m, 2 H), 7.19 (dd, 1 H, *J* = 0.8, 2.0 Hz), 6.99 (tt, 2 H, *J* = 2.0, 8.4 Hz), 6.34 (dd, 1 H, *J* = 2.0, 4.0 Hz), 6.07 (br, 1 H), 4.80 (dd, 1 H, *J* = 4.0, 8.0 Hz), 3.97 (dd, 1 H, *J* = 8.0, 14.4 Hz), 3.86 (dd, 1 H, *J* = 4.0, 14.4 Hz), 3.22 (br, 1 H), 1.45 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.6 (d, *J* = 248.8 Hz); 155.4, 148.2, 138.4, 133.7 (d, *J* = 8.8 Hz), 118.4, 115.5 (d, *J* = 21.2 Hz), 111.0, 101.8, 87.1, 84.8, 82.2, 62.3, 54.8, 28.1; HRMS (ESI) *m*/z calcd for $C_{19}H_{20}FNO_4$ 368.1274, found 368.1258.



160b

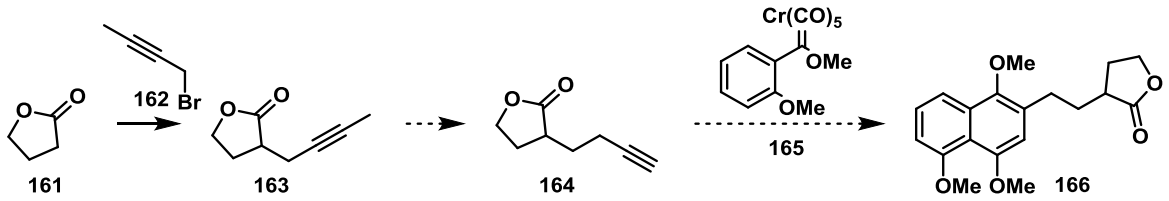
4-(4-Fluorophenyl)-1*H*-indol-5-ol (160b). A solution of **159b** (19 mg, 0.056 mmol) in 1,2-dichloroethane (1.4 mL) was subjected to microwave irraditation at 180 ^{o}C for 30 min. The reaction mixture was concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 8 : 1) to **160b** (5.6 mg, 44%) as a pale yellow solid: Mp 145.6-148.2 ^{o}C; ATR-IR (neat) 3491, 3409, 2919, 1491, 1353, 1223, 1158, 839 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.13 (br, 1 H), 7.57-7.53 (m, 2 H), 7.29 (dd, 1 H, *J* = 1.0, 9.0 Hz), 7.23 (tt, 2 H, *J* = 2.0, 9.0 Hz), 7.18 (app t, 1 H, *J* = 3.0 Hz), 6.93 (d, 1 H, *J* = 8.5 Hz), 6.28 (ddd, 1 H, *J* = 1.0, 2.0, 3.0 Hz), 4.80 (br, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.3 (d, *J* =245.0 Hz),

146.0, 131.8 (d, J = 7.5 Hz), 131.5 (d, J = 2.5 Hz), 130.9, 128.0, 125.2, 116.9, 116.2 (d, J = 24.2 Hz), 112.1, 111.4, 101.5; HRMS (ESI) m/z calcd for $C_{14}H_{10}NOF$ 228.0825, found 228.0827.

3.0 ALKYNE ISOMERIZATION BY NON-NUCLEOPHILIC BASE

3.1 INTRODUCTION

In a planned total synthesis of 9-desmethylpleurotin, a promising strategy was to synthesize lactone **164** from intermediate **163**. The formation of **164** requires an alkyne isomerization reaction[72] (**Scheme 21**). However, the traditional alkyne isomerization method uses an excess of nucleophilic base, which is not compatible with many functional groups, including the lactone group in **163**. Thus, new reaction conditions using non-nucleophilic base were required for this reaction.

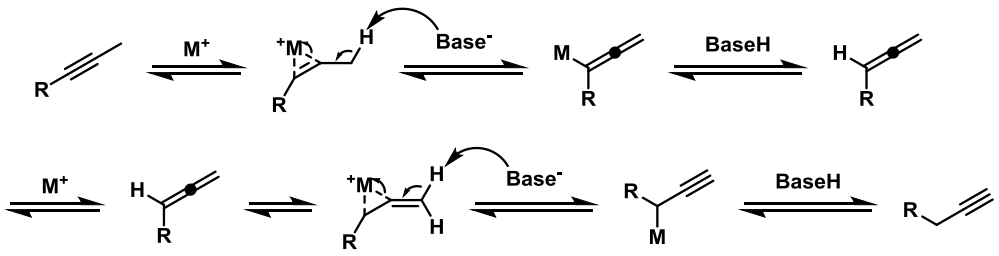


Scheme 21. Alkyne isomerization in the synthesis of a key intermediate **166** of 9-desmethylpleurotin

3.2 RESULTS AND DISCUSSION

3.2.1 Introduction

In 1975, Charles Allen Brown and Ayako Yamashita reported the first alkyne zipper reaction using potassium 1,3-diaminopropanide generated *in situ* by adding potassium hydride to the solvent 1,3-diaminopropane.[72] Since its discovery, the alkyne zipper reaction has been widely used in organic synthesis. However, the nucleophilic nature of 1,3-diaminopropane limited the scope of the reaction. We propose that certain metal catalysts (*vide infra*) could activate the internal alkyne and isomerize it to the terminal alkyne under non-nucleophilic condition as shown in **Scheme 22**.



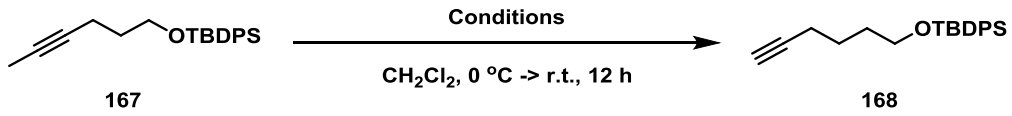
Scheme 22. Proposed mechanism of metal-catalyzed alkyne isomerization

3.2.2 Screening of reaction conditions

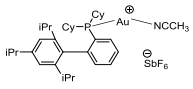
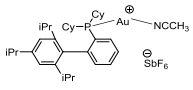
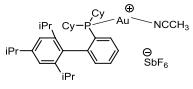
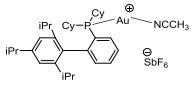
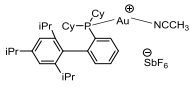
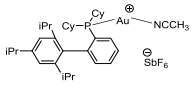
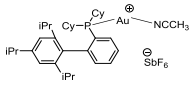
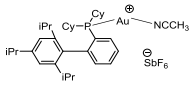
3.2.2.1 Screening of bases

Initial attempts to isomerize the internal alkyne **167** to the terminal alkyne **168** using bases like LiHMDS, NaHMDS, KHMDS, *t*BuOK, DIPEA did not give any detectable product **168** by GC analysis. However, the much stronger base LiTMP provided a trace of the desired alkyne **168** (**Table 10**).

Table 10. Base variation for the alkyne isomerization reaction[a]



Entry	Catalyst	Base (2.2 equiv)	Conversion[b]
1	$Au(PPh_3)Cl$ (5 mol%) + $AgSbF_6$ (5 mol%)	LiHMDS	0
2	$Au(PPh_3)Cl$ (5 mol%) + $AgSbF_6$ (5 mol%)	NaHMDS	0
3	$Au(PPh_3)Cl$ (5 mol%) + $AgSbF_6$ (5 mol%)	KHMDS	0
4	$Au(PPh_3)Cl$ (5 mol%) + $AgSbF_6$ (5 mol%)	*t*-BuOK	0
5	$Au(PPh_3)Cl$ (5 mol%) + $AgSbF_6$ (5 mol%)	LiTMP	trace
6	$Au(PPh_3)Cl$ (5 mol%) + $AgSbF_6$ (5 mol%)	DIPEA	0
7	$Au(PPh_3)Cl$ (5 mol%) + $AgSbF_6$ (5 mol%)		0
8	$Au(PPh_3)Cl$ (5 mol%) + $AgSbF_6$ (5 mol%)		0
9	$(Au(PPh_3)_3)_3OBF_4$ (2 mol%)	LiHMDS	0

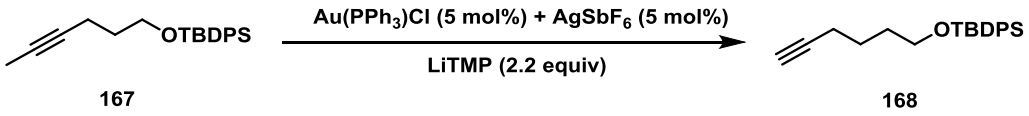
10	$(Au(PPh_3)_3)_3OBF_4$ (2 mol%)	NaHMDS	0
11	$(Au(PPh_3)_3)_3OBF_4$ (2 mol%)	KHMDS	0
12	$(Au(PPh_3)_3)_3OBF_4$ (2 mol%)	*t*-BuOK	0
13	$(Au(PPh_3)_3)_3OBF_4$ (2 mol%)	LiTMP	0
14	$(Au(PPh_3)_3)_3OBF_4$ (2 mol%)	DIPEA	0
15	$(Au(PPh_3)_3)_3OBF_4$ (2 mol%)		0
16	$(Au(PPh_3)_3)_3OBF_4$ (2 mol%)		0
17	 (5 mol%)	LiHMDS	0
18	 (5 mol%)	NaHMDS	0
19	 (5 mol%)	KHMDS	0
20	 (5 mol%)	*t*-BuOK	0
21	 (5 mol%)	LiTMP	0
22	 (5 mol%)	DIPEA	0
23	 (5 mol%)		0
24	 (5 mol%)		0

[a]All reactions were carried out at a concentration of 0.15 M. [b]GC Conversion.

3.2.2.2 Screening of temperature

With these preliminary results, we decided to investigate which reaction temperatures were necessary to promote the isomerization reaction. A 2.7% conversion was obtained after heating the reaction mixture at 90 ^{o}C for 60 h (**Entry 3, Table 11**). Additional efforts to increase the conversion by higher reaction temperature under microwave irradiation only gave trace amounts of the desired terminal alkyne **168**.

Table 11. Temperature variation for the alkyne isomerization reaction[a]



167 168

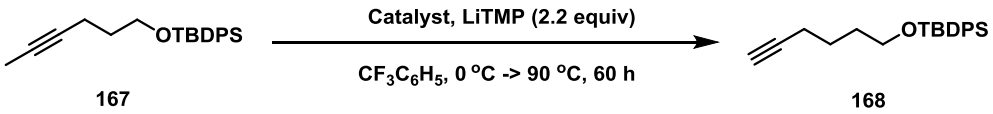
Entry	Solvent	Temperature	Time	Conversion[b]
1	CH_2Cl_2	r.t.	12 h	trace
2	$CF_3C_6H_5$	60 ^{o}C	12 h	trace
3	$CF_3C_6H_5$	90 ^{o}C	60 h	2.7%
4[c]	$CF_3C_6H_5$	120 ^{o}C	1 h	trace
5[c]	$CF_3C_6H_5$	150 ^{o}C	1 h	trace
6[c]	$CF_3C_6H_5$	180 ^{o}C	1 h	trace

[a]All reactions were carried out at a concentration of 0.15 M. [b]GC Conversion. [c]Reactions were carried out under microwave irradiation.

3.2.2.3 Catalyst loading

These initial investigations used 5 mol% catalyst loadings, and control experiment without catalyst gave a similar conversion (**Entry 2, Table 12**). An increase in the reaction concentration from 0.15 M to 1.0 M improved the conversion to 74% in the absence of catalyst (**Entry 4, Table 12**). The isomerization reaction almost stopped when excessive $AgSbF_6$ catalyst was added (**Entry 5, 6, Table 12**).

Table 12. Catalyst loading variation for the alkyne isomerization reaction



167 168

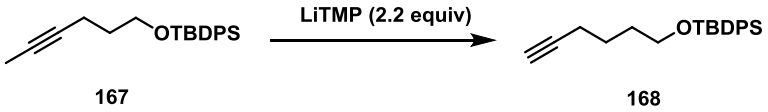
Entry	Catalyst	Concentration	Conversion[a]
1	$Au(PPh_3)Cl$ (5 mol%) + $AgSbF_6$ (5 mol%)	0.15 M	2.7 %
2	$Au(PPh_3)Cl$ (0 mol%) + $AgSbF_6$ (0 mol%)	0.15 M	2.9 %
3	$Au(PPh_3)Cl$ (5 mol%) + $AgSbF_6$ (5 mol%)	1 M	50 %
4	$Au(PPh_3)Cl$ (0 mol%) + $AgSbF_6$ (0 mol%)	1 M	74 %
5	$Au(PPh_3)Cl$ (5 mol%) + $AgSbF_6$ (25 mol%)	1 M	1.0 %
6	$Au(PPh_3)Cl$ (0 mol%) + $AgSbF_6$ (20 mol%)	1 M	1.0 %
7	$PtCl_2$ (5 mol%)	1 M	23 %

[a]GC Conversion.

3.2.2.4 Solvent variation

The evaluation of the solvent effect revealed that solvents with strong coordination properties significantly improved the conversion in the alkyne isomerization (**Entry 3, 7, 8, Table 13**). Full conversion was achieved when THF was used as solvent at room temperature for 1 h (**Entry 7, Table 13**).

Table 13. Solvent variation for the alkyne isomerization reaction



167 168

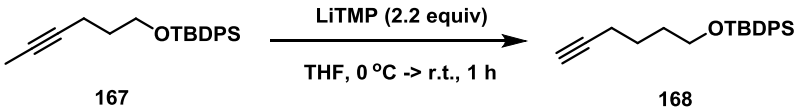
Entry	Solvent	Temperature	Time	Conversion[a]
1	$CF_3C_6H_5$	60 °C	6 h	86%
2	$CF_3C_6H_5$	40 °C	6 h	36%
3	$CF_3C_6H_5$	r.t.	6 h	2%
4	THF	40 °C	6 h	99%
5	THF	r.t.	6 h	99%
6	THF	r.t.	3 h	99%
7	THF	r.t.	1 h	99%
8	Ether	r.t.	1 h	68%

[a]GC Conversion.

3.2.2.5 Concentration variation

These initial investigations used 2.2 eq LiTMP at 1.0 M, and efforts to decrease the concentration (0.25 M, 0.5 M) resulted in slightly lower conversion (**Table 14**). Full conversion was obtained after a longer reaction time at lower concentration (0.5 M, 3 h).

Table 14. Concentration variation for the alkyne isomerization reaction



167 168

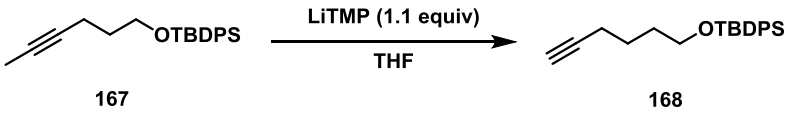
Entry	Concentration	Conversion[a]
1	1 M	99%
2	0.5 M	80%
3	0.25 M	73%

[a]GC Conversion.

3.2.3 Efforts to reduce LiTMP loading

To further expand the functional groups compatibility with this methodology, a lower loading of LiTMP was desired. However, 1.1 eq of LiTMP failed to give full conversion at higher temperature (**Entry 2, Table 15**) or extended reaction time (**Entry 1, Table 15**).

Table 15. Alkyne isomerization reaction with 1.1 eq LiTMP



167 168

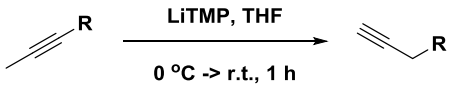
Entry	Conditions	Conversion[a]
1	0 ^{o}C -> r.t., 12 h	33%
2	0 ^{o}C -> reflulx, 3 h	62%

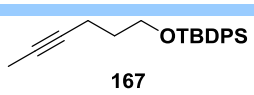
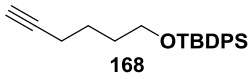
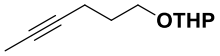
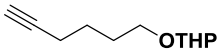
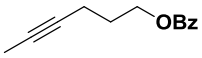
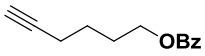
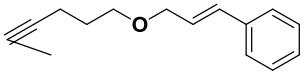
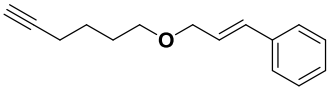
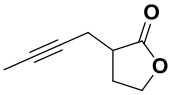
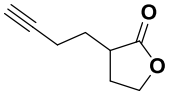
[a]GC Conversion.

3.2.4 Examples of alkyne isomerizations using LiTMP

With optimal reaction conditions determined (2.2 eq LiTMP as base, room temperature for 1 h, and 1.0 M substrate concentration in THF), the scope and generality of the reaction was evaluated. In general, due to the strongly basic nature of LiTMP, the scope of this methodology is limited. THP ether and TBDPS silyl ether give the desired terminal alkyne in 45% and 75% yield (**Entry 1, 2, Table 16**). Benzoyl groups, lactone groups, and cinnamyl ether groups suffered from decomposition.

Table 16. Scope of the alkyne isomerization reaction with LiTMP



Entry	Precursor	Product	Yield[a]
1	 167	 168	75%
2	 169	 170	45%
3	 171	 172	0
4	 173	 174	0
5	 175	 176	0

[a]Isolated yields.

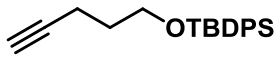
3.2.5 Conclusions

After the screening combinations of eight non-nucleophilic bases, four solvents, four catalysts, and a series of substrate concentrations, we found that 2.2 equiv of LiTMP in THF (1.0 M substrate concentration) at r.t. for 1 h could fully convert an internal to the terminal alkyne. However, the strongly basic LiTMP limited the scope of the reaction. In the future, efforts to explore milder reaction conditions would be necessary. Potentially, this methodology would enable a better route for the total synthesis of 9-desmethylpleurotin.

3.3 EXPERIMENTAL SECTION

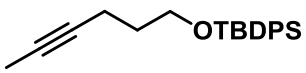
General Information: All reactions were performed under an N_2 or argon atmosphere and all glassware was dried in an oven at 140 ℃ for 2 h prior to use. Reactions carried out at -78 ℃ employed a CO_2/acetone bath. THF was distilled over sodium/benzophenone ketyl, and CH_2Cl_2 was purified using an alumina column filtration system. DMF were dried from 4 Å molecule sieves. Pyridine and Et_3N were dried from KOH. Reactions were monitored by TLC analysis (EM Science pre-coated silica gel 60 F_{254} plates, 250 mM layer thickness) a PMA solution (5 g of phosphomolybdic acid in 100 mL of 95% EtOH), *p*-anisaldehyde solution (2.5 mL of *p*-anisaldehyde, 2 mL of AcOH, and 3.5 mL of conc. H_2SO_4 in 100 mL of 95% EtOH), Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}$•4 H_2O and 0.2 g of $Ce(SO_4)_2$ in 100 mL of a 3.5 N H_2SO_4 solution) or a $KMnO_4$ solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1% NaOH solution). Purifications by chromatography were performed using SiO_2 (SiliaFlash® F60, Silicycle) or using an ISCO- Companion flash chromatography system. $^1H/^{13}C$ NMR spectra were recorded on Bruker Avance 300/75 MHz, Bruker Avance 400/100 MHz or Bruker Avance 500/125 MHz instrument. Chemical shifts were reported in parts per million with the residual solvent peak used as the internal standard. Chemical shifts were tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quarter, dd = doublet of doublet, dt = doublet of triplet, m = multiplet, br = broad, app = apparent), coupling constants, and integration. Mass spectra were obtained on a Micromass Autospec double focusing instrument. IR spectra were obtained on an Identity IR-ATR spectrometer. Microwave reactions were performed using a Biotage Initiator in glass microwave vials (cap sealed) with continuous magnetic stirring and

an external surface temperature sensor. LCMS analyses were completed on a Waters MicroMass ZQ with 2525 Binary Gradient Module, 2420 ELSD, 2996 PDA using MeCN/H_2O with 0.1% TFA. Melting points (uncorrected) were determined using a Mel-Temp instrument.



177

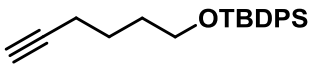
***tert*-Butyl(pent-4-yn-1-yloxy)diphenylsilane (177).** To a cold (0 ^oC) solution of 4-pentyl-1-ol (2.06 g, 24.5 mmol) and imidazole (5.53 g, 36.7 mmol) in CH_2Cl_2 was added TBDPSCl (7.00 mL, 26.9 mmol) dropwise at 0 ^oC. The solution was stirred at r.t. for 12 h, quenched with water, extracted with CH_2Cl_2 (50 mL), washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 50 : 1) to give **177** (7.13 g, 90%) as a colorless liquid: ATR-IR (neat) 3301, 3070, 2950, 2930, 2855, 2155, 1471, 1426, 1105, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.72 (d, 4 H, *J* = 8.0 Hz), 7.48-7.40 (m, 6 H), 3.80 (t, 2 H, *J* = 7.0 Hz), 2.39 (t, 2 H, *J* = 8.5 Hz), 1.95 (d, 1 H, *J* = 1.0 Hz), 1.82 (tt, 2 H, *J* = 8.0, 8.0 Hz), 1.11 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.6, 133.8, 129.6, 127.6, 84.2, 68.3, 62.2, 31.4, 26.8, 19.2, 15.0; HRMS (ESI) *m*/z calcd for $C_{21}H_{27}OSi$ ($[M+H]^+$) 323.1831, found 323.1856.



167

***tert*-Butyl(hex-4-yn-1-yloxy)diphenylsilane (167).** To a solution of **167** (6.34 g, 19.7 mmol) in THF (200 mL) was added *n*-BuLi (8.65 mL, 2.5 M, 21.6 mmol) dropwise at -78 ^oC.

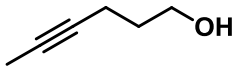
The solution was stirred at -78 ^{o}C for 2 h. Then, MeI (2.45 mL, 39.3 mmol) was added into the solution dropwise at -78 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 1 h, quenched with saturated NH_4Cl, extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 50 : 1) to give **167** as a plae yellow liquid (6.36 g, 96%): ATR-IR (neat) 3070, 3049, 2950, 2930, 2855, 1739, 1588, 1471, 1426, 1103, 1070, 822, 738, 699, 688 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.69-7.67 (m, 4 H), 7.44-7.36 (m, 6 H), 3.74 (t, 2 H, *J* = 6.0 Hz), 2.29-2.26 (m, 2 H), 1.76 (t, 3 H, *J* = 2.5 Hz), 1.73 (tt, 2 H, *J* = 7.0, 8.0 Hz), 1.05 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.6, 134.0, 129.5, 127.6, 78.8, 75.6, 62.6, 32.0, 26.8, 19.2, 15.0, 3.4; HRMS (ESI) *m*/z calcd for $C_{22}H_{29}OSi$ ($[M+H]^+$) 337.1988, found 337.1961.



168

***tert*-Butyl(hex-5-yn-1-yloxy)diphenylsilane (168). Method A.** To a cold (0 ^{o}C) solution of 4-hexnyl-1-ol (96.0 mg, 0.978 mmol) and imidazole (221 mg, 1.47 mmol) in CH_2Cl_2 (3 mL) was added TBDPSCl (0.280 mL, 1.08 mmol) dropwise at 0 ^{o}C. The solution was stirred at r.t. for 12 h, quenched with water, extracted with CH_2Cl_2, washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 50 : 1) to give **168** (295 mg, 90%) as a colorless liquid: ATR-IR (neat) 3304, 3070, 3049, 2930, 2857, 2117, 1588, 1471, 1428, 1389, 1361, 1105, 1090, 822, 740, 699, 686 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.78 (d, 4 H, *J* = 7.0 Hz), 7.52-7.46 (m, 6 H), 3.79 (t, 2 H, *J* = 6.0 Hz), 2.28 (dt, 2 H, *J* = 2.5, 7.0 Hz), 2.01 (t, 1 H, *J* = 2.5 Hz), 1.80-1.72 (m, 4 H), 1.06

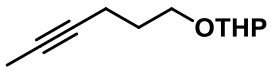
(s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.5, 133.9, 129.5, 127.6, 84.4, 68.3, 64.3, 31.5, 26.8, 24.9, 19.2, 18.1; HRMS (ESI) *m*/z calcd for $C_{22}H_{29}OSi$ ($[M+H]^+$) 337.1988, found 337.1972. **Method B.** To a degassed stirred solution of **167** (101 mg, 0.299 mmol) in THF (0.3 mL) was added LiTMP (96.8 mg, 0.658 mmol) in one portion at 0 ^oC. The solution was stirred at room temperature for 15 min, quenched with CH_2Cl_2 and water, extracted with CH_2Cl_2, washed with brined, dried (Na_2SO_4) and concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 50 : 1) to give **168** (75.2 mg, 75%) as a pale yellow liquid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (d, 4 H, *J* = 7.6 Hz), 7.45-7.39 (m, 6 H), 3.71 (t, 2 H, *J* = 5.6 Hz), 2.22 (dt, 2 H, *J* = 2.4, 6.8 Hz), 1.96 (t, 1 H, *J* = 2.4 Hz), 1.69-1.65 (m, 4 H), 1.08 (s, 9 H). The spectral data were consistent with those from **Method A**.



178

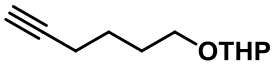
Hex-4-yn-1-ol (178). To **167** (2.30 g, 6.83 mmol) was added TBAF (20.5 mL, 1 M in THF) dropwise at 0 ^oC. The reaction mixture was stirred at r.t. for 3 h, quenched with water, extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 4 : 1) to give **178** as a pale yellow liquid (500 mg, 75%): ATR-IR (neat) 3433, 2947, 2919, 2865, 1700, 1653, 1625, 1463, 1431, 1411, 1383, 1355, 1305, 1275, 1260, 1202, 1187, 1150, 1120, 1060, 1020, 829, 759, 751, 721, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.58 (t, 2 H, *J* = 6.0

Hz), 3.03 (br, 1 H), 2.12 (tt, 2 H, *J* = 2.5, 7.0 Hz), 1.66 (t, 3 H, *J* = 2.5 Hz), 1.60 (app dt, 2 H, *J* = 7.0, 13.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 78.3, 75.7, 61.2, 31.4, 15.0, 3.1. The spectral data were consistent with those reported in the literature.[73]



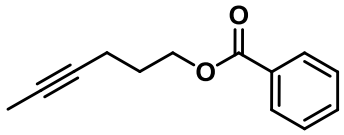
169

2-(Hex-4-yn-1-yloxy)tetrahydro-2*H*-pyran (169). To a solution of **178** (89.5 mg, 0.895 mmol) in CH_2Cl_2 (5 mL) was added DHP (0.122 mL, 1.34 mmol) and PPTS (22.5 mg, 0.0895 mmol) at room temperature. The reaction mixture was stirred at room temperature for 4 h, quenched with 1 N HCl (10 mL) and extracted with ethyl acetate, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give the **169** (163 mg, 96%) as a colorless liquid: ATR-IR (neat) 2932, 2929, 2865, 2857, 2850, 1711, 1692, 1640, 1463, 1450, 1439, 1426, 1273, 1135, 1118, 1033, 988, 902 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.50 (t, 1 H, *J* = 3.6 Hz), 3.79 (tt, 1 H, *J* = 2.8, 10.8 Hz), 3.71 (td, 1 H, *J* = 6.4, 9.6 Hz), 3.37 (tt, 2 H, *J* = 6.0, 13.6 Hz), 2.14 (dt, 2 H, *J* = 2.4, 6.8 Hz), 1.76-1.58 (m, 7 H), 1.51-1.41 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 98.5, 78.3, 75.4, 65.8, 61.8, 30.5, 29.0, 25.3, 19.3, 15.4, 3.2.



170

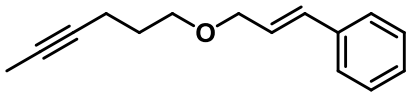
2-(Hex-5-yn-1-yloxy)tetrahydro-2*H*-pyran (170). To a degassed stirred solution of **169** (61.7 mg, 0.339 mmol) in THF (0.35 mL) was added LiTMP (110 mg, 0.745 mmol) in one portion at 0 ^{o}C. The solution was stirred at r.t. for 1 h, quenched with water, extracted with CH_2Cl_2, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **170** (27.5 mg, 45 %) as a pale yellow liquid: ATR-IR (neat) 3301, 2937, 2865, 1452, 1437, 1351, 1135, 1118, 1074, 1062, 1033, 1020, 988, 971, 904, 867, 736 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.57 (t, 1 H, *J* = 4.0 Hz), 3.85 (tt, 1 H, *J* = 3.2, 11.2 Hz), 3.75 (td, 1 H, *J* = 6.4 10.0 Hz), 3.49 (td, 1 H, *J* =4.8, 10.8 Hz), 3.40 (td, 1 H, *J* = 4.8, 10.8 Hz), 2.22 (dt, 2 H, *J* = 2.4, 6.8 Hz), 1.94 (t, 1 H, *J* = 2.8 Hz), 1.84-1.77 (m, 1 H), 1.75-1.49 (m, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 98.7, 84.3, 68.3, 66.8, 66.2, 30.7, 28.8, 25.4, 25.3, 19.6, 18.2. The spectral data were consistent with those reported in the literature.[74]



171

Hex-4-yn-1-yl benzoate (171). To a stirred solution of **178** (95.0 mg, 0.968 mmol), DMAP (11.8 mg, 0.0118 mmol) in CH_2Cl_2 (2 mL) was added triethylamine (0.270 mL, 1.94 mmol) and benzoyl chloride (102 mg, 1.06 mmol) at 0 ^{o}C. The resulting solution was stirred at r.t. for 2 h, quenched with water, extracted with ethyl acetate, washed with brined, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 50 : 1) to give **171** as a pale yellow liquid (160 mg,

82%): ATR-IR (neat) 3057, 2956, 2917, 2850, 1715, 1599, 1512, 1497, 1459, 1450, 1405, 1385, 1329, 1312, 1269, 1174, 1113, 1068, 1034, 1025, 952, 749, 708, 688, 673 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.00 (d, 2 H, 7.5 Hz), 7.48 (t, 1 H, *J* = 7.5 Hz), 7.37 (t, 2 H, *J* = 7.5 Hz), 4.36 (t, 2 H, *J* = 6.0 Hz), 2.27 (tt, 2 H, *J* = 3.0, 7.5 Hz), 1.89 (app dt, 2 H, 6.5, 13.5 Hz), 1.71 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.2, 132.6, 130.1, 129.3, 128.0, 77.5, 76.0, 63.5, 28.0, 15.4, 3.1; HRMS (ESI) *m*/z calcd for $C_{13}H_{13}O_2$ ($[M+H]^+$) 201.0916, found 201.0930.



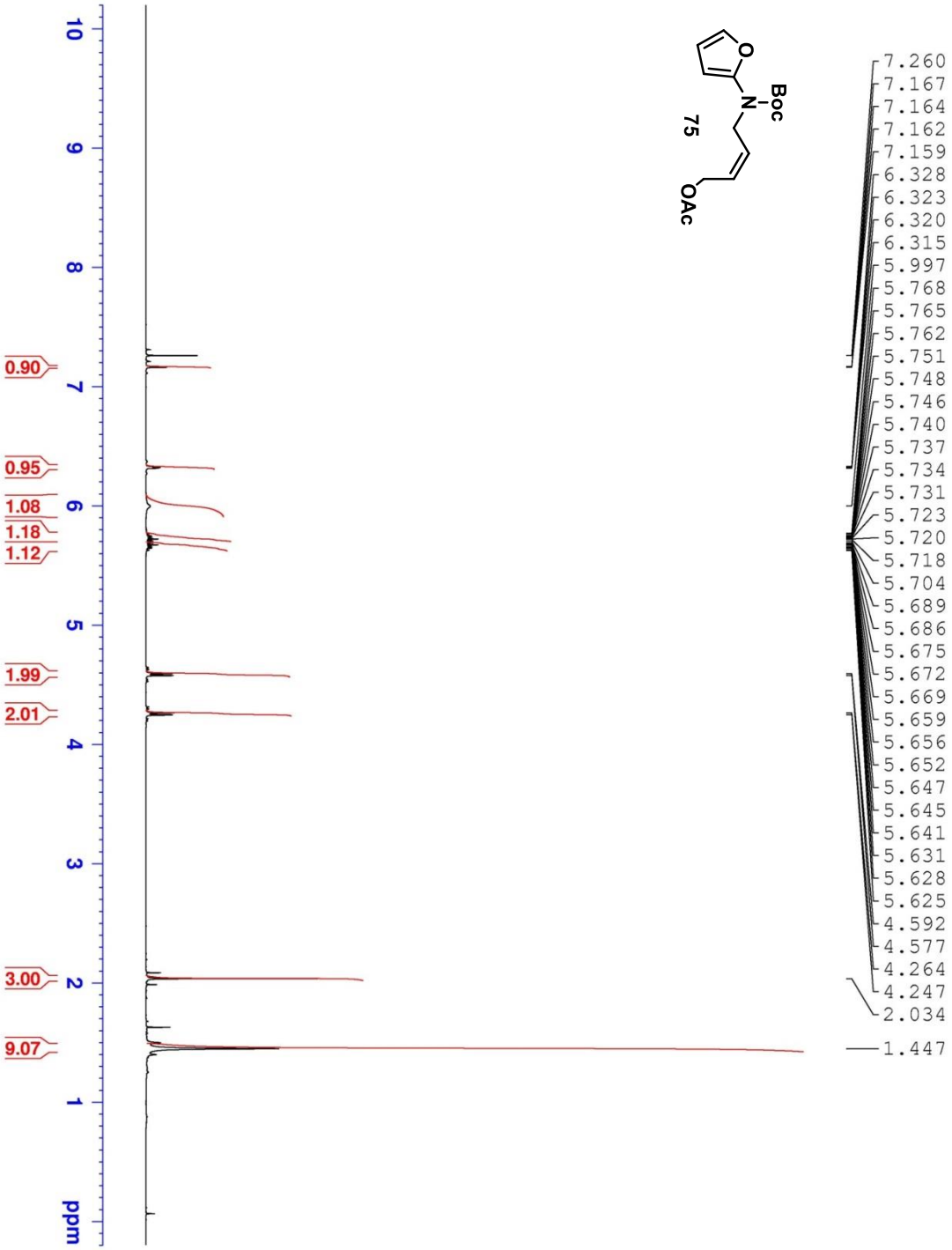
173

(*E*)-(3-(Hex-4-yn-1-yloxy)prop-1-en-1-yl)benzene (173). To a stirred solution of **178** (34.0 mg, 0.346 mmol) in THF (1 mL) was added NaH (34.6 mg, 0.866 mmol, 60% in mineral oil) in one portion. The solution was stirred at 0 ^oC for 30 min. Then, cinamyl bromide (52.6 mg, 0.346 mmol) was added into solution in one portion. The solution was stirred at r.t. for 2 h, quenched with water, extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a residue that was purified by chromatography on SiO_2 (hexanes : EA = 15 : 1) to give **173** (67.0 mg, 90%) as a pale yellow liquid: ATR-IR (neat) 3047, 3025, 2919, 2852, 1446, 1437, 1364, 1264, 1103, 966, 732, 701, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38 (d, 2 H, *J* = 7.2 Hz), 7.30 (t, 2 H, *J* = 7.6 Hz), 7.23 (d, 1 H, *J* = 7.2 Hz), 6.60 (d, 1 H, *J* = 16.0 Hz), 6.29 (dt, 1 H, *J* = 6.0, 16.0 Hz), 4.13 (d, 2 H, *J* = 5.6 Hz), 3.56 (d, 2 H, *J* = 5.6 Hz), 2.27-2.23 (m, 2 H), 1.78 (q, 2 H, *J* = 6.4 Hz), 1.75 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100

MHz) δ 136.8, 132.1, 128.5, 127.5, 126.4, 126.3, 78.5, 75.7, 71.4, 68.9, 29.1, 15.5, 3.4; HRMS (ESI) *m*/z calcd for $C_{15}H_{18}O$ ($[M]^+$) 214.1358, found 214.1361.

APPENDIX A

SELECTED NMR DATA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3.00
9.07
O
N
Boc
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OAc
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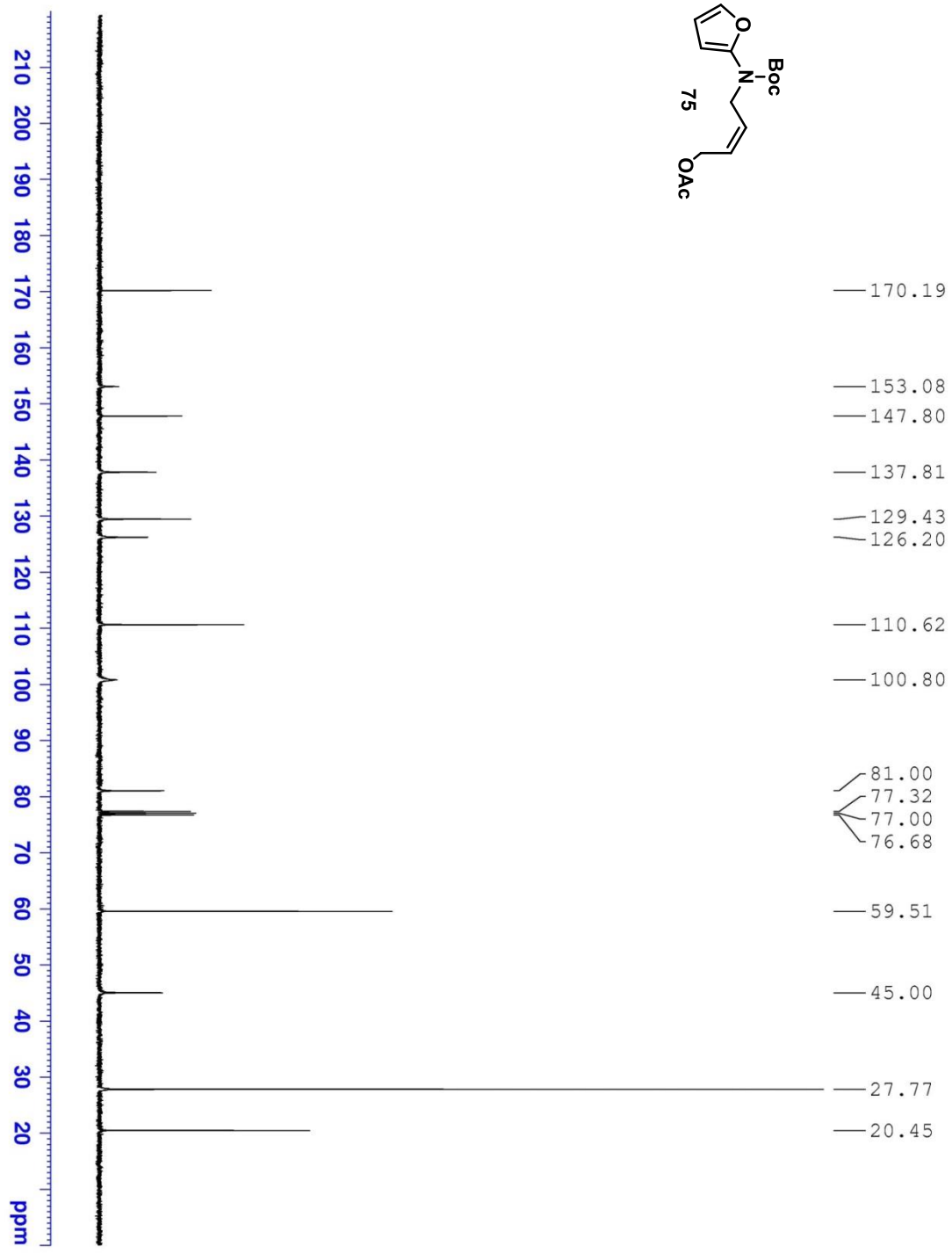
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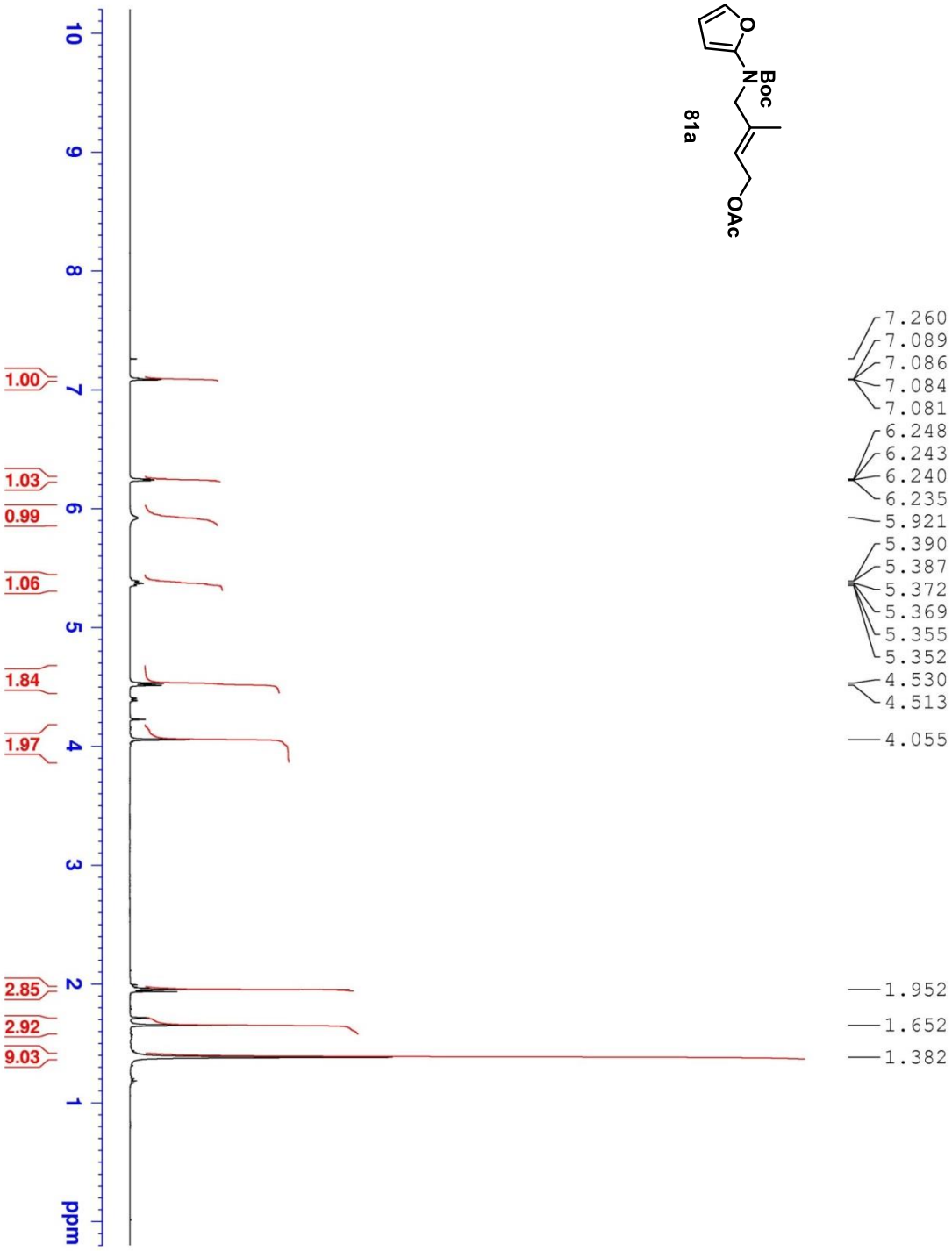
ppm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5.372
5.369
5.355
5.352
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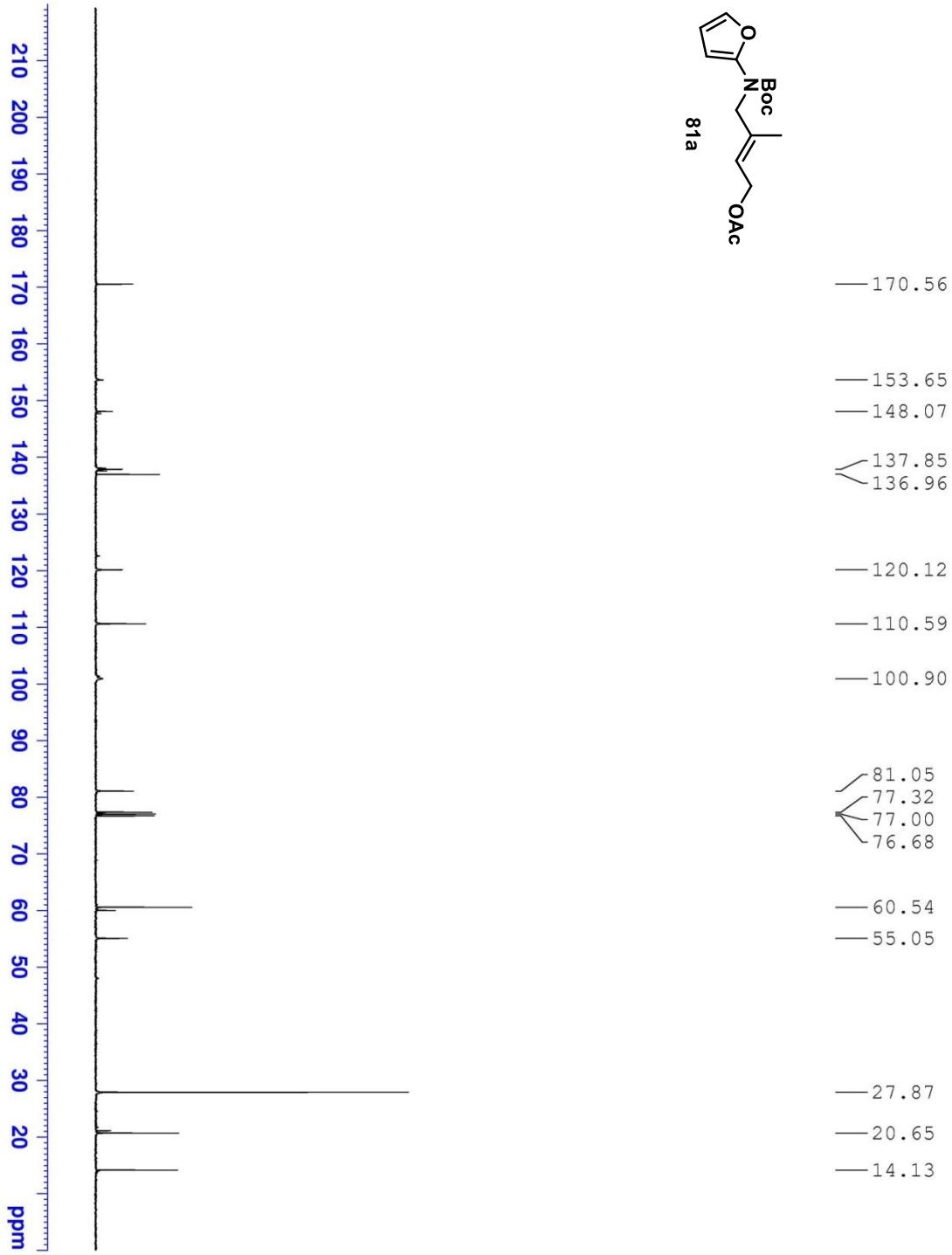
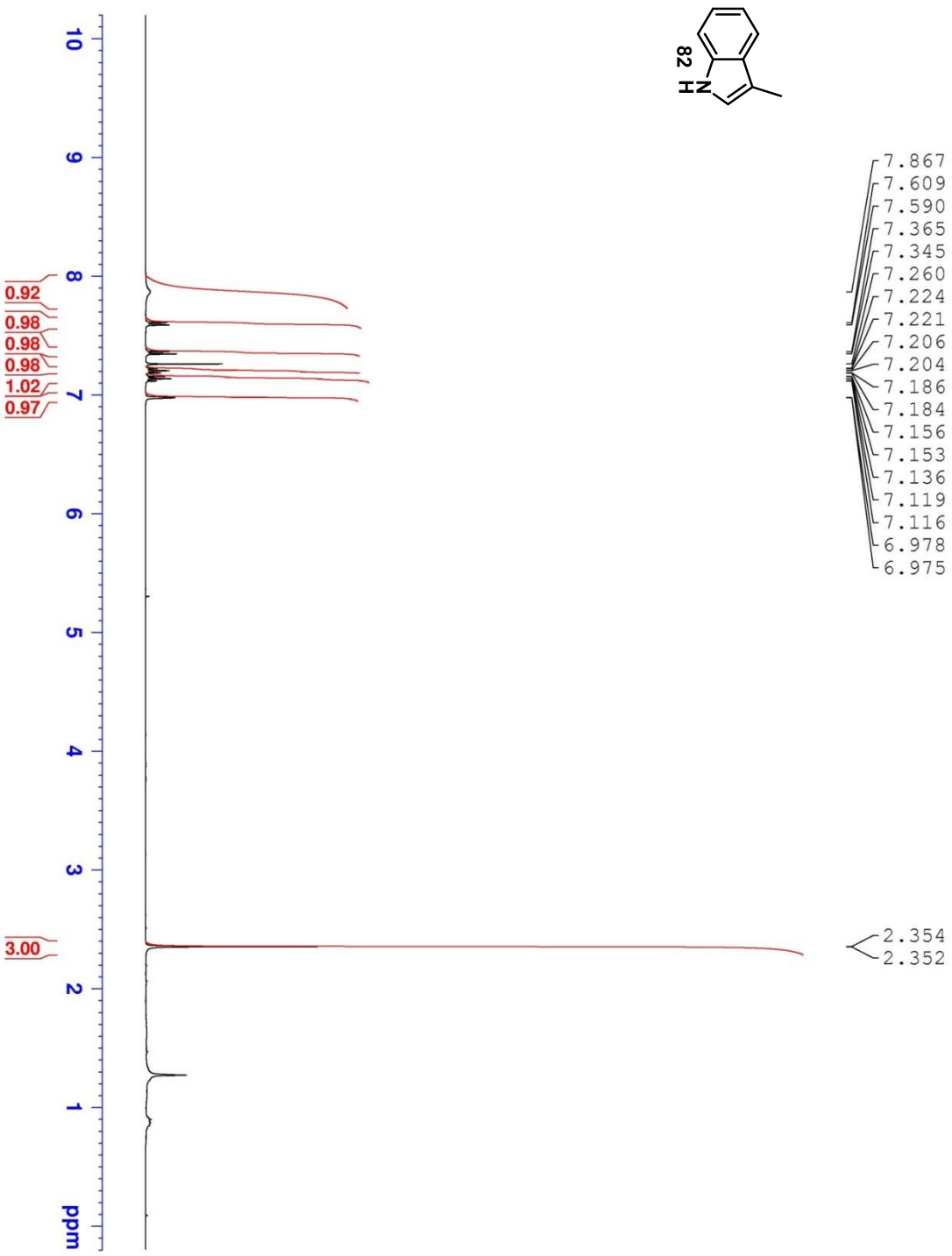
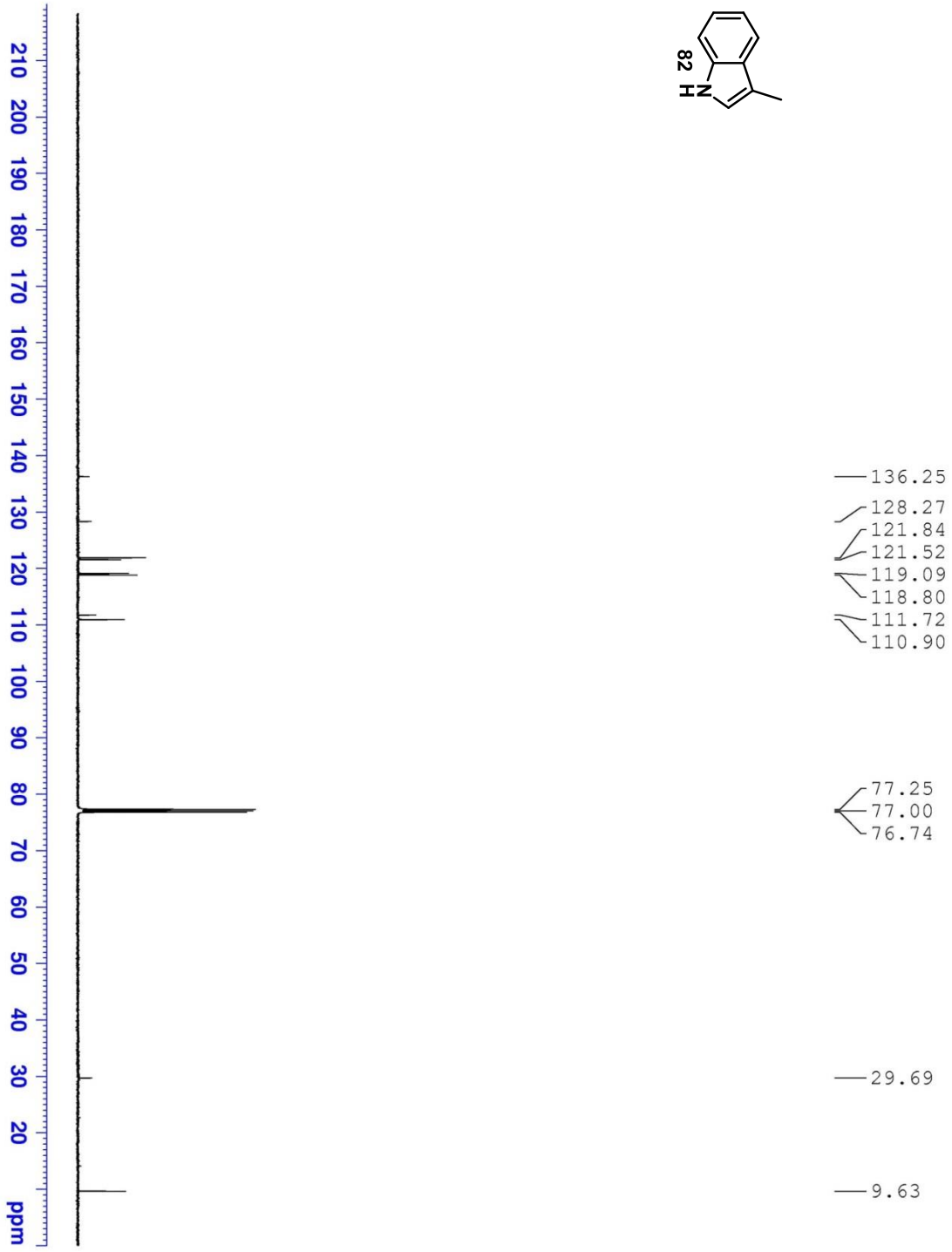
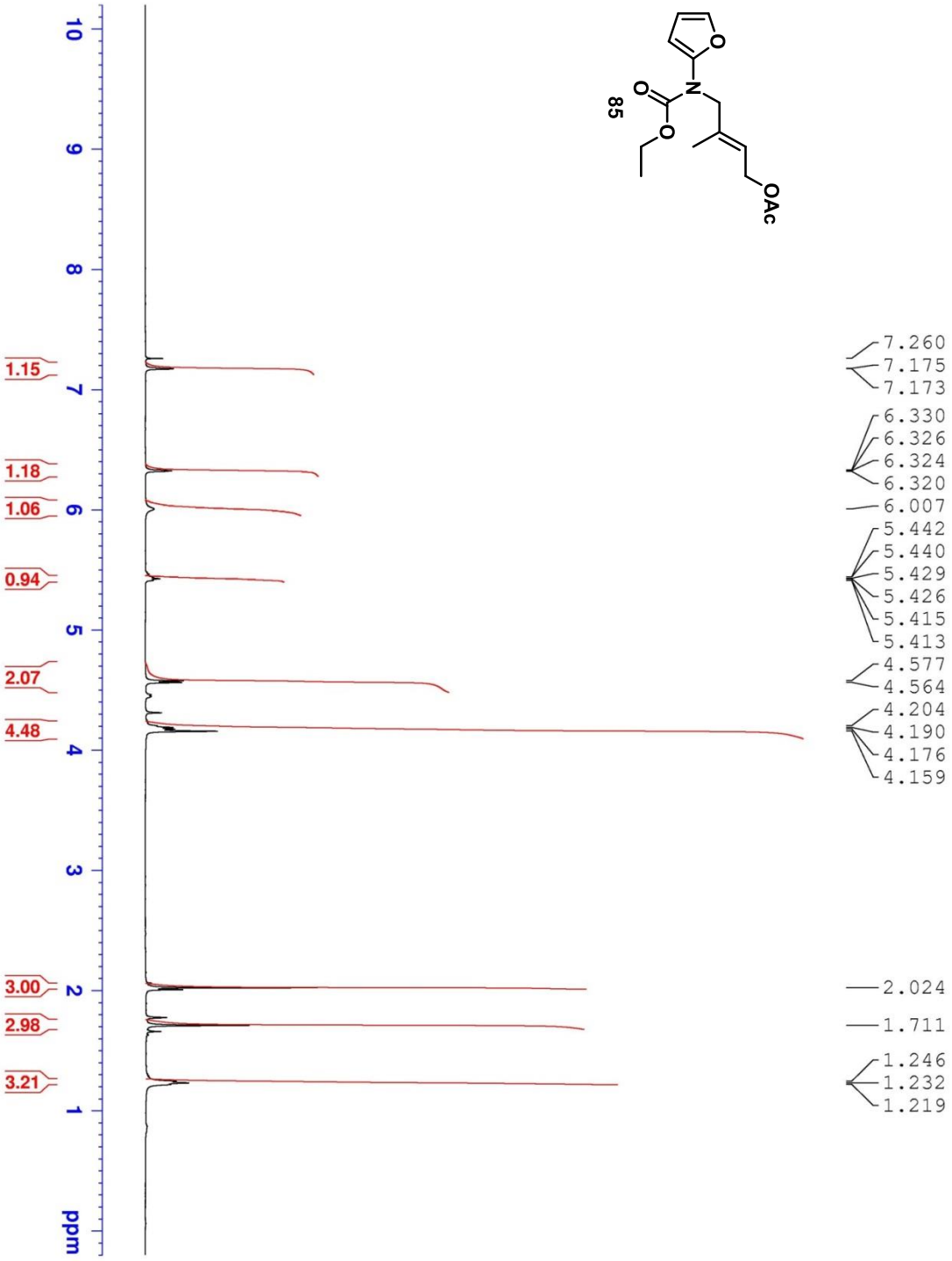
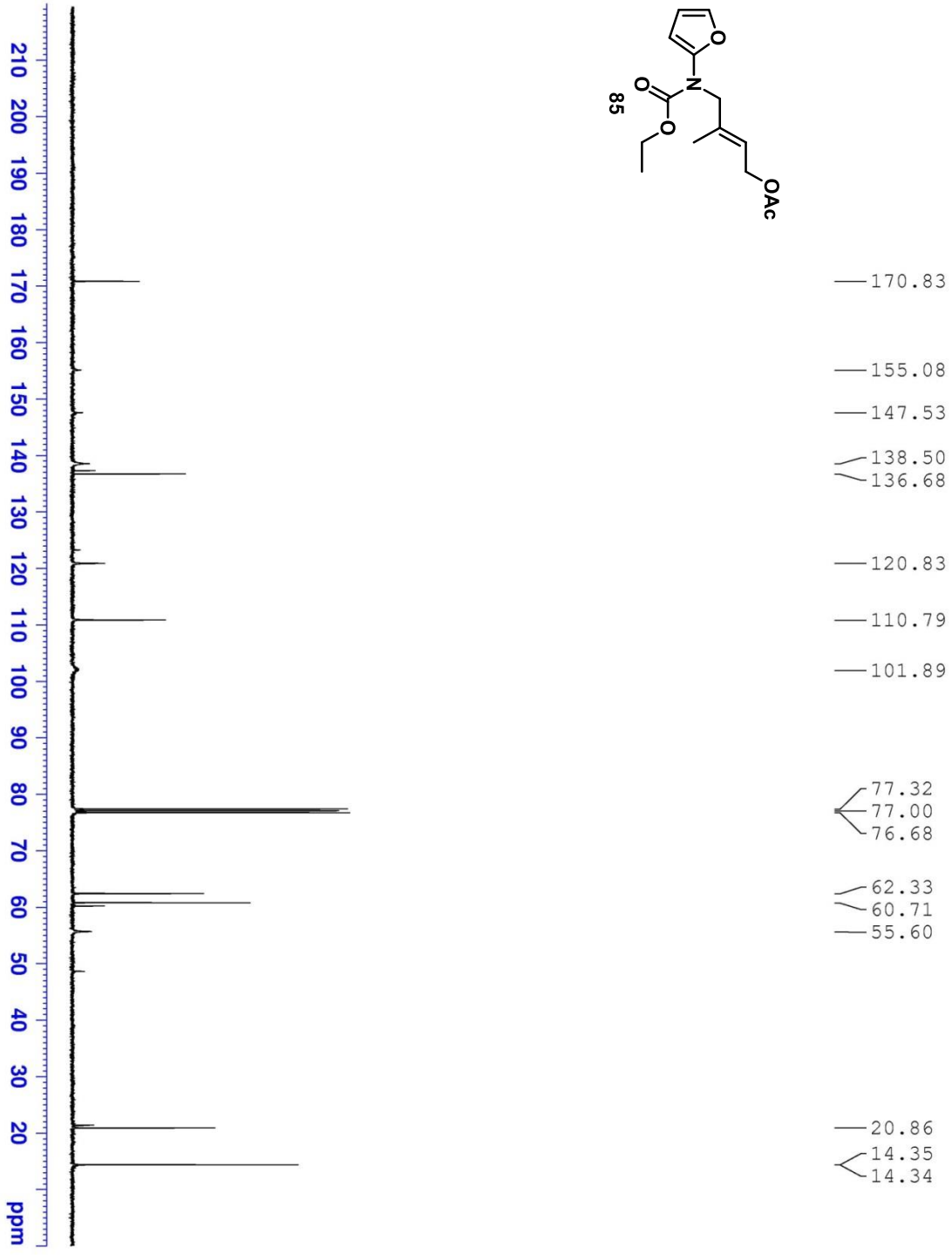
ppm

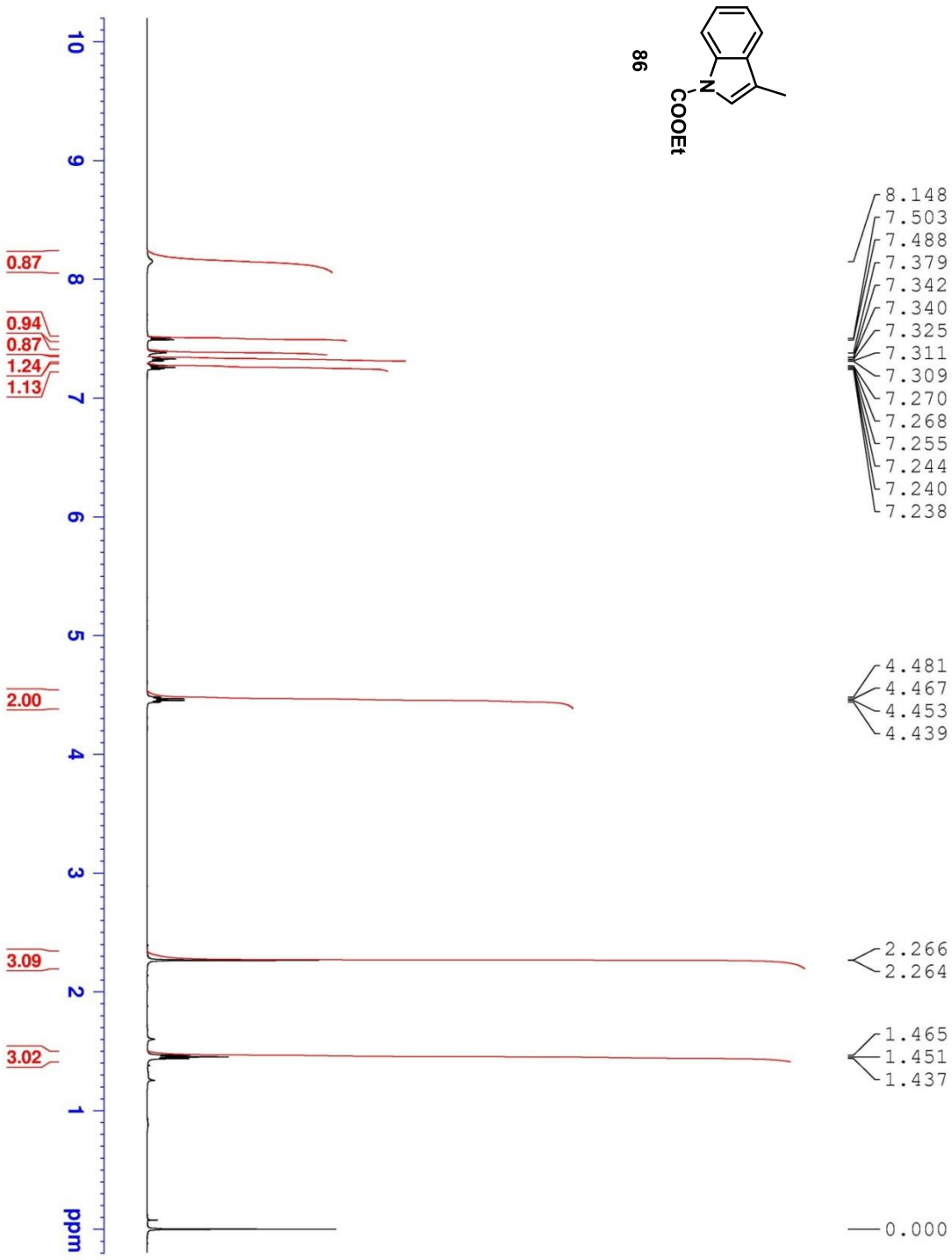

81a
Boc
N
O
OAc
170.56
153.65
148.07
137.85
136.96
120.12
110.59
100.90
81.05
77.32
77.00
76.68
60.54
55.05
27.87
20.65
14.13
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

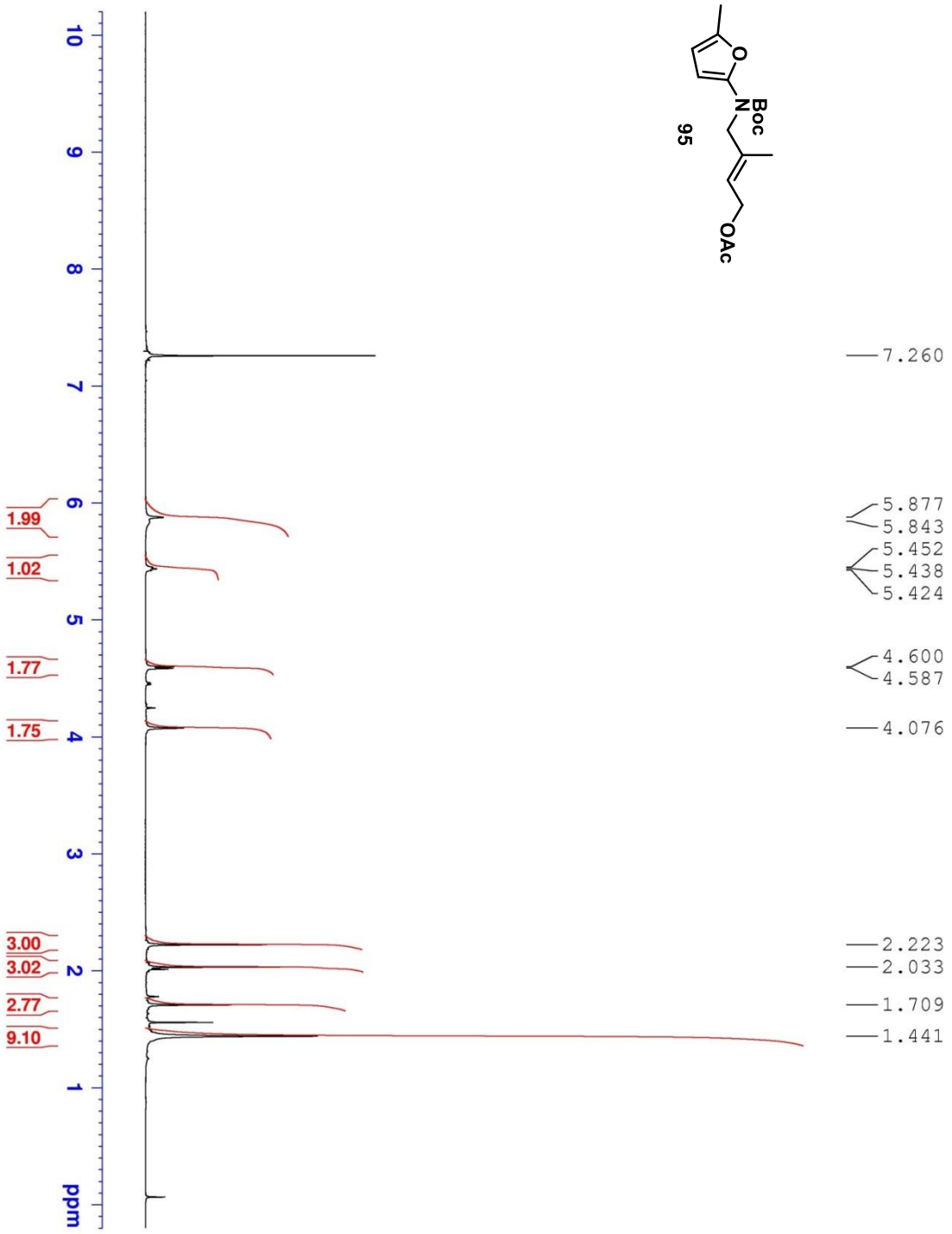

82
H
N
7.867
7.609
7.590
7.365
7.345
7.260
7.224
7.221
7.206
7.204
7.186
7.184
7.156
7.153
7.136
7.119
7.116
6.978
6.975
2.354
2.352
0.92
0.98
0.98
0.98
1.02
0.97
3.00
10
9
8
7
6
5
4
3
2
1
ppm

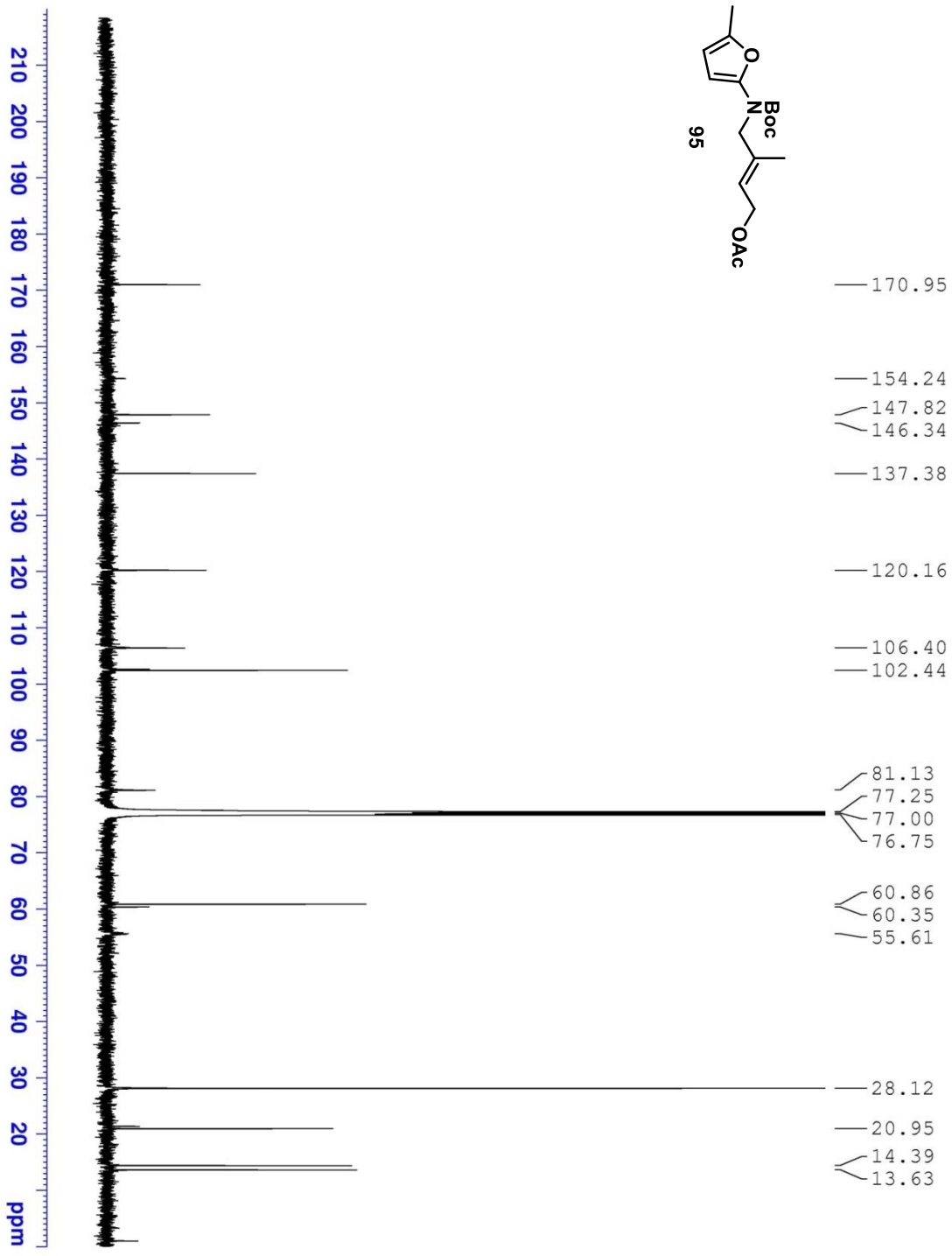

82
H
N
136.25
128.27
121.84
121.52
119.09
118.80
111.72
110.90
77.25
77.00
76.74
29.69
9.63
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

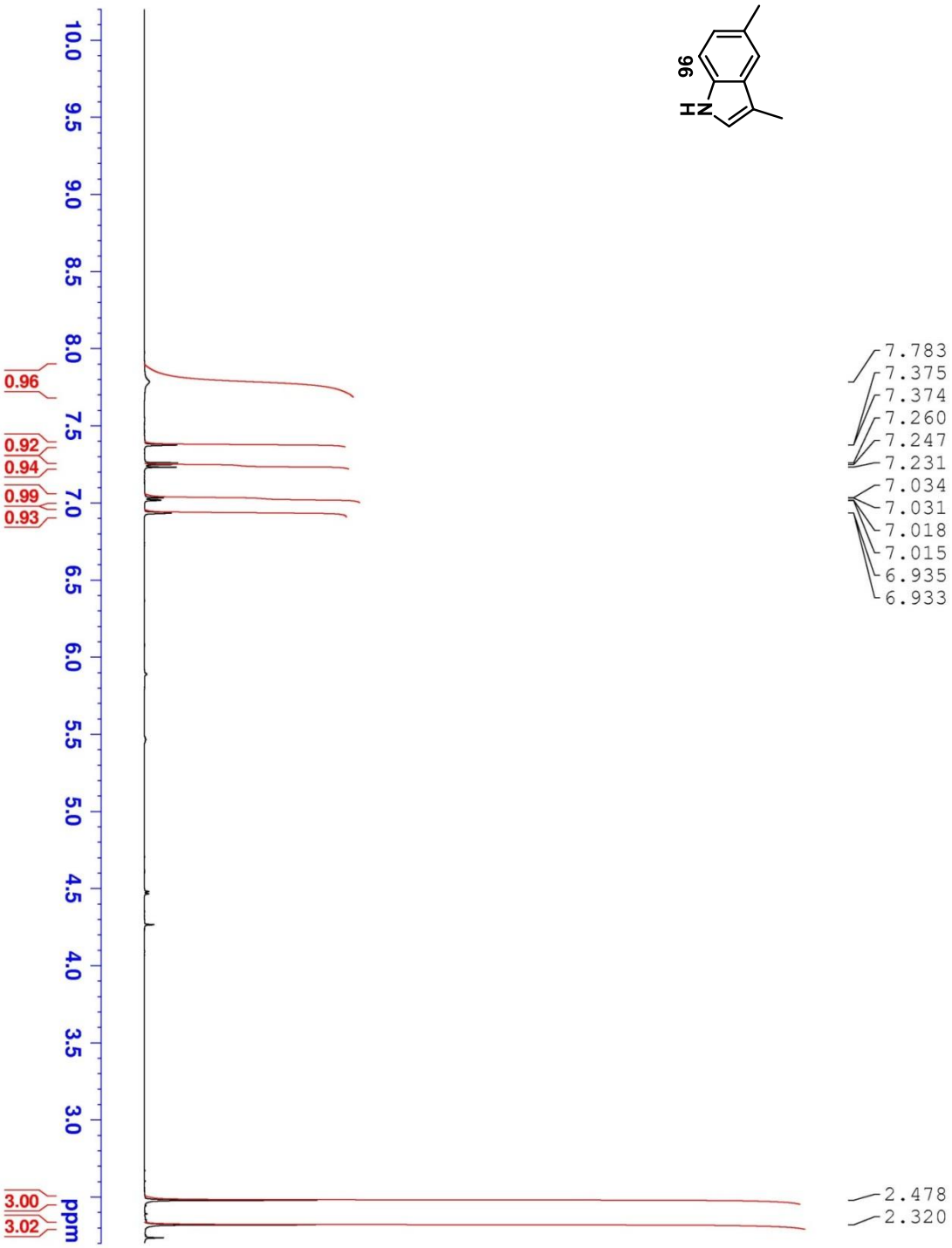

85
OAc
7.260
7.175
7.173
6.330
6.326
6.324
6.320
6.007
5.442
5.440
5.429
5.426
5.415
5.413
4.577
4.564
4.204
4.190
4.176
4.159
2.024
1.711
1.246
1.232
1.219
1.15
1.18
1.06
0.94
2.07
4.48
3.00
2.98
3.21
ppm

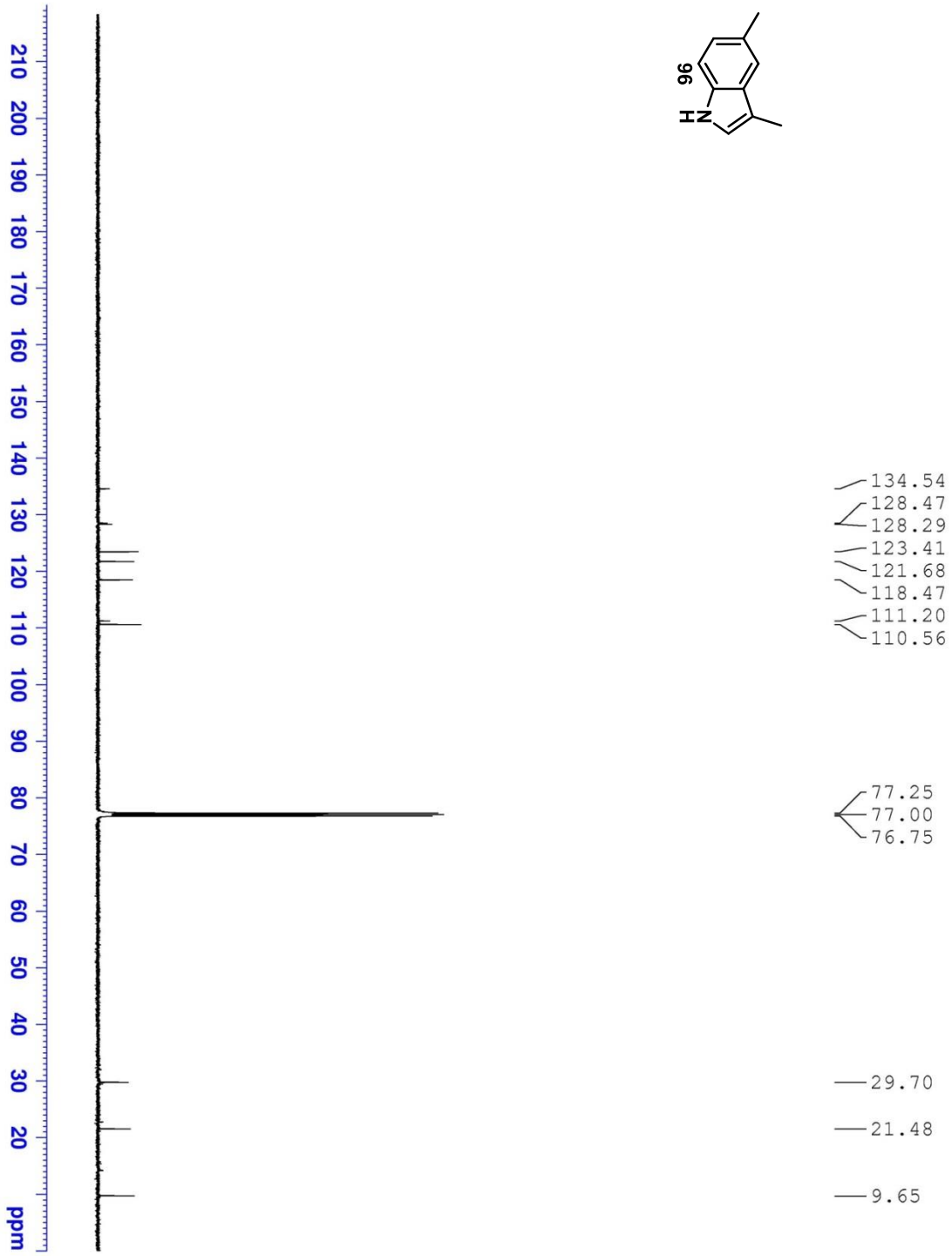

85
170.83
155.08
147.53
138.50
136.68
120.83
110.79
101.89
77.32
77.00
76.68
62.33
60.71
55.60
20.86
14.35
14.34
ppm

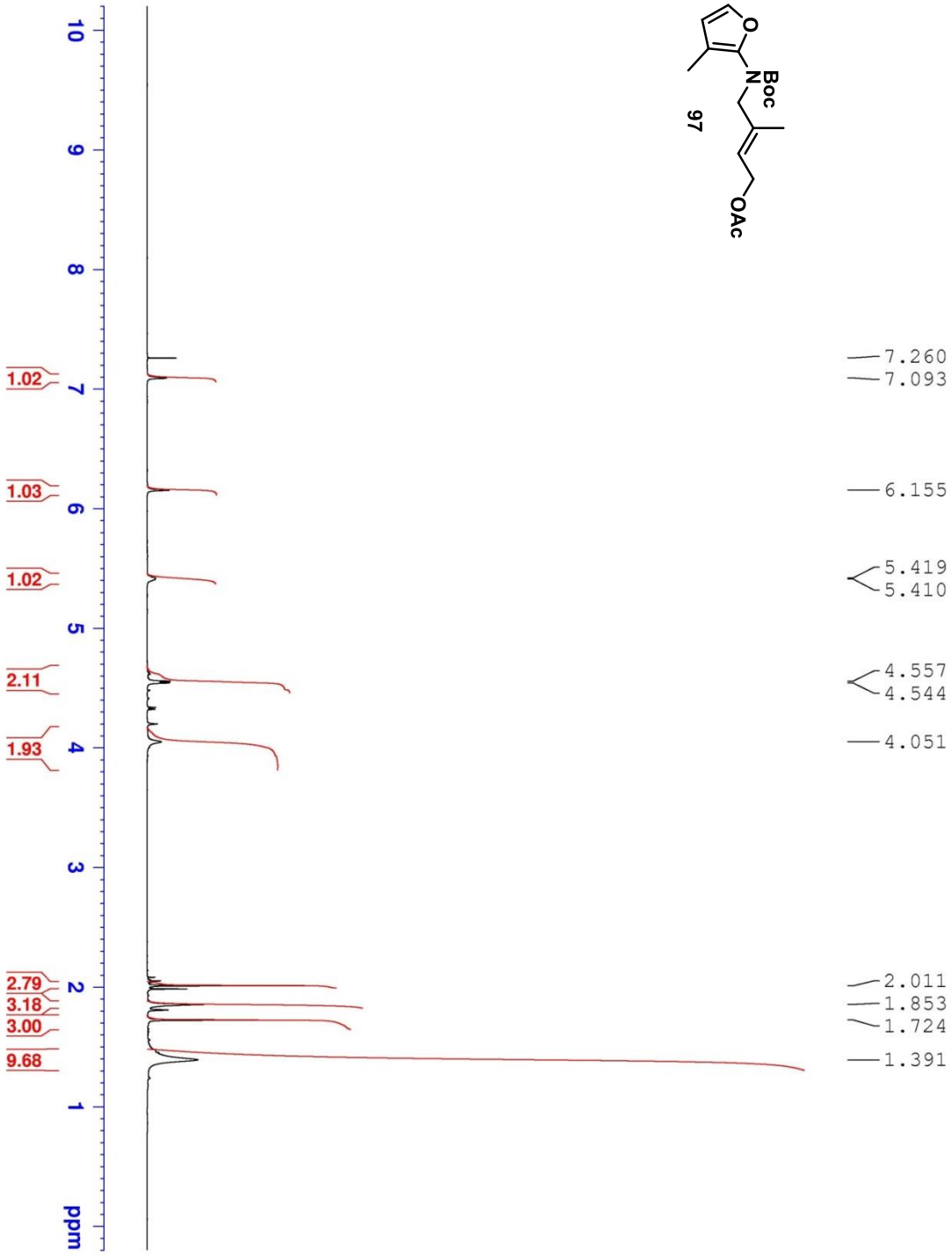

86
N
COOEt
8.148
7.503
7.488
7.379
7.342
7.340
7.325
7.311
7.309
7.270
7.268
7.255
7.244
7.240
7.238
4.481
4.467
4.453
4.439
2.266
2.264
1.465
1.451
1.437
0.000
0.87
0.94
0.87
1.24
1.13
2.00
3.09
3.02
ppm

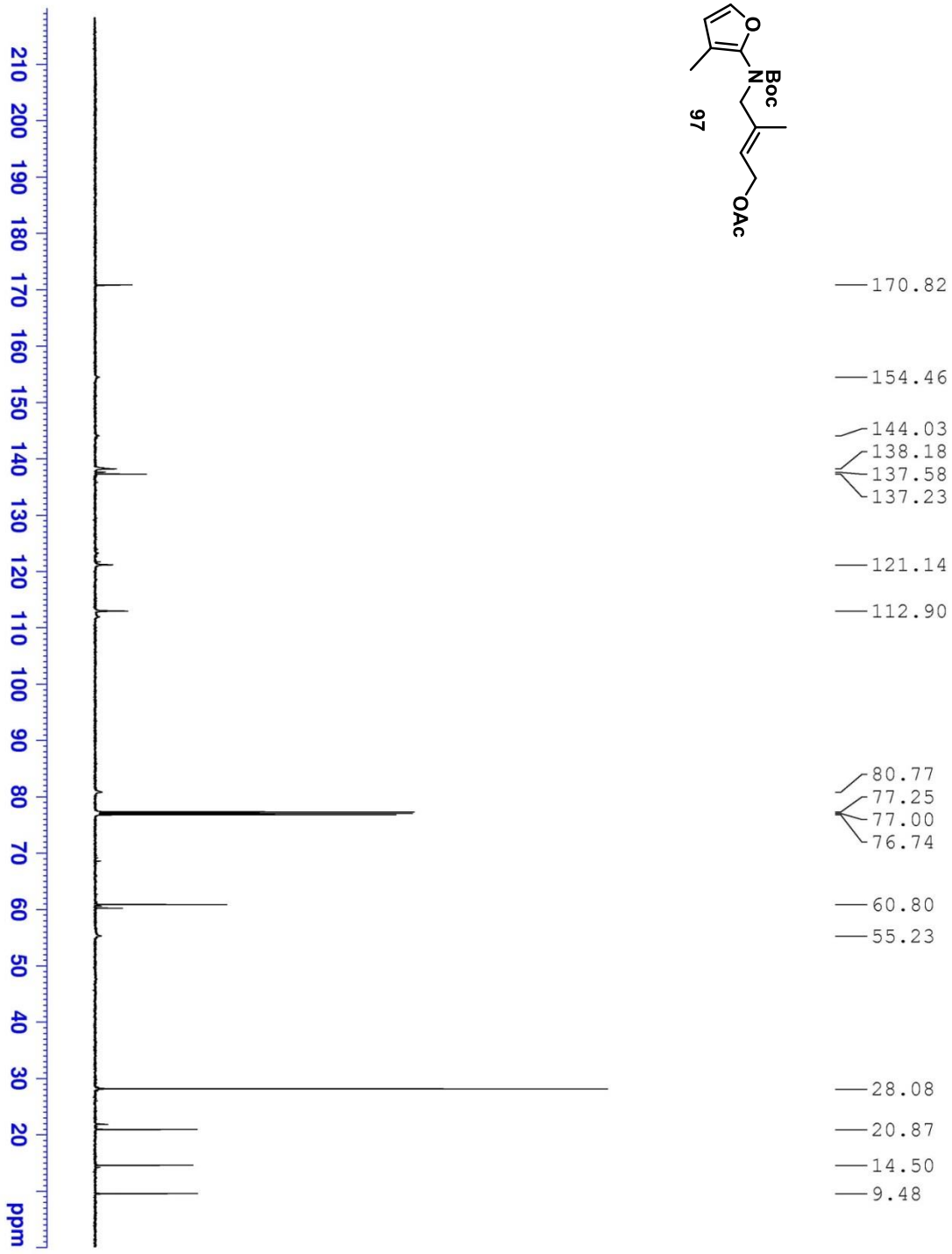

95
Boc
N
O
OAc
7.260
5.877
5.843
5.452
5.438
5.424
4.600
4.587
4.076
2.223
2.033
1.709
1.441
1.99
1.02
1.77
1.75
3.00
3.02
2.77
9.10
ppm

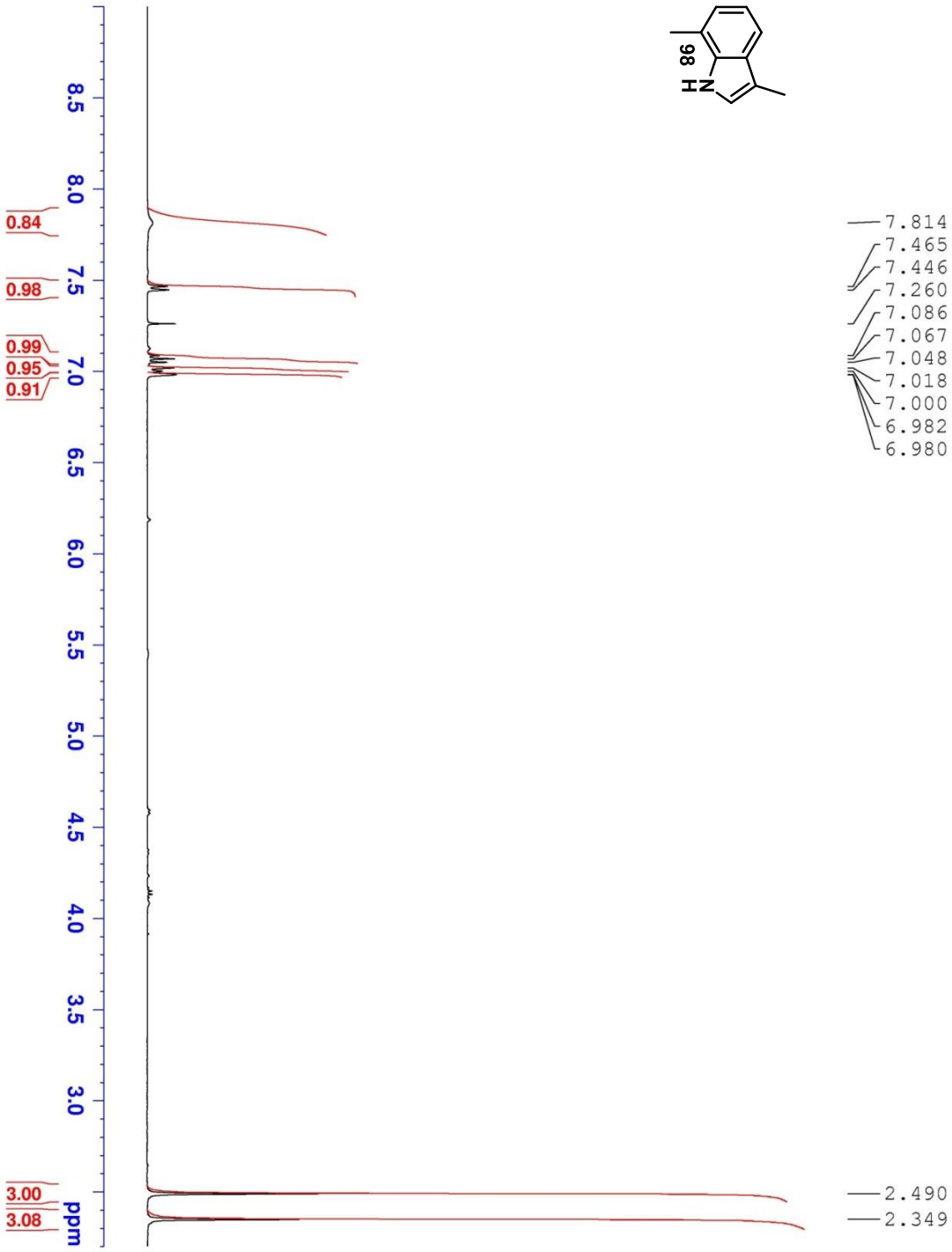

95
Boc
N
O
OAc
170.95
154.24
147.82
146.34
137.38
120.16
106.40
102.44
81.13
77.25
77.00
76.75
60.86
60.35
55.61
28.12
20.95
14.39
13.63
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

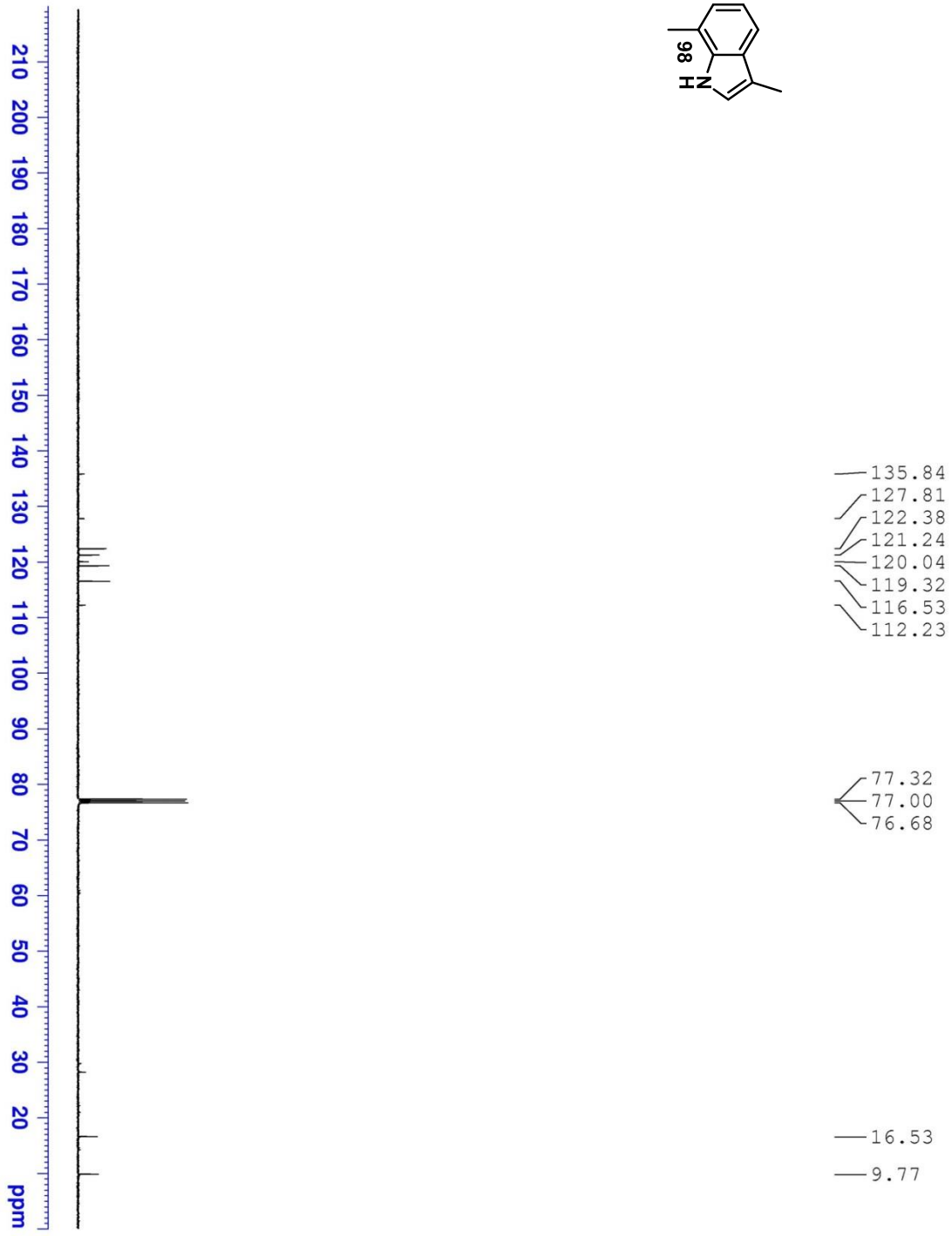

96
H
N
7.783
7.375
7.374
7.260
7.247
7.231
7.034
7.031
7.018
7.015
6.935
6.933
2.478
2.320
0.96
0.92
0.94
0.99
0.93
3.00
3.02
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm

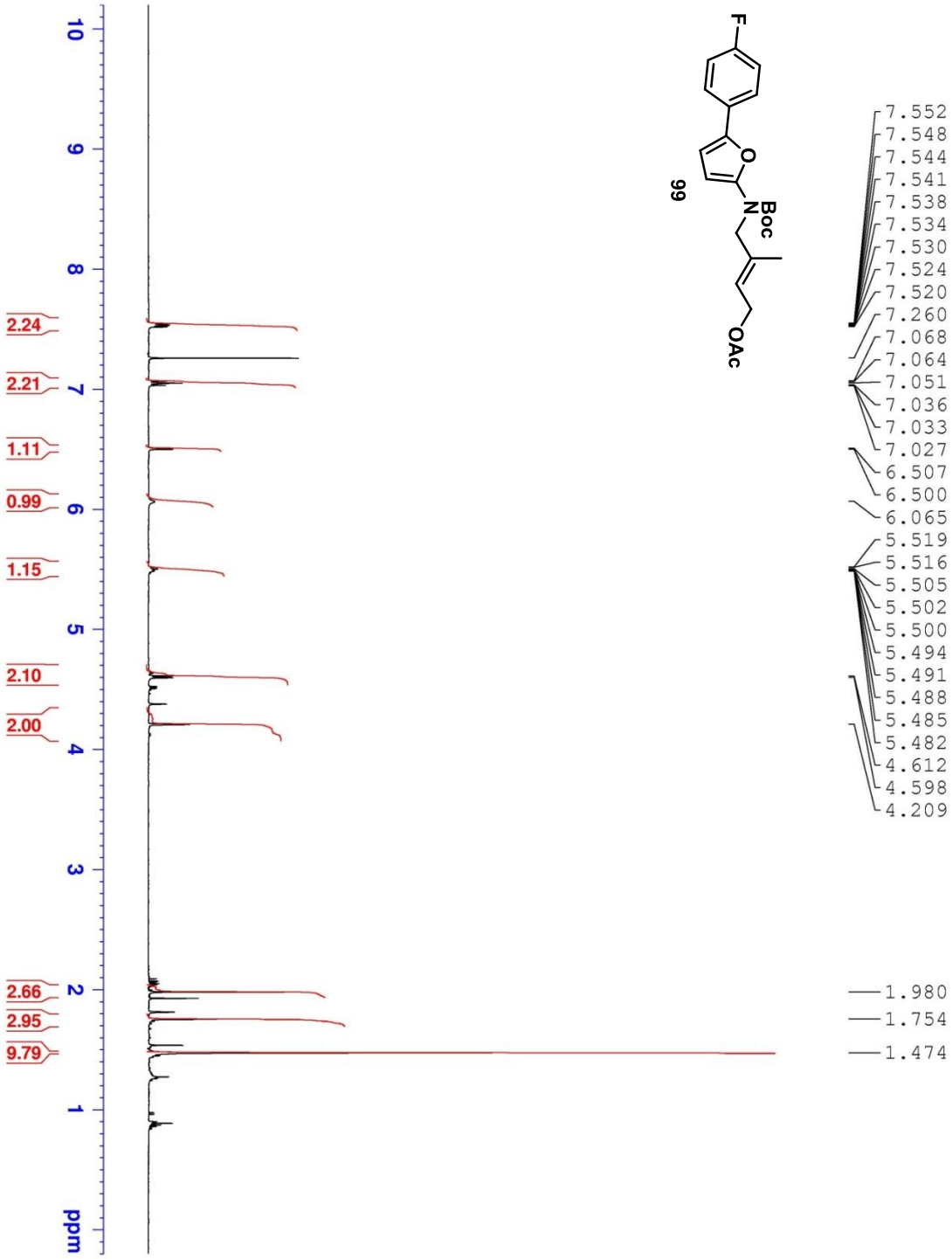

96
H
N
134.54
128.47
128.29
123.41
121.68
118.47
111.20
110.56
77.25
77.00
76.75
29.70
21.48
9.65
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


97
Boc
N
O
OAc
7.260
7.093
6.155
5.419
5.410
4.557
4.544
4.051
2.011
1.853
1.724
1.391
1.02
1.03
1.02
2.11
1.93
2.79
3.18
3.00
9.68
ppm

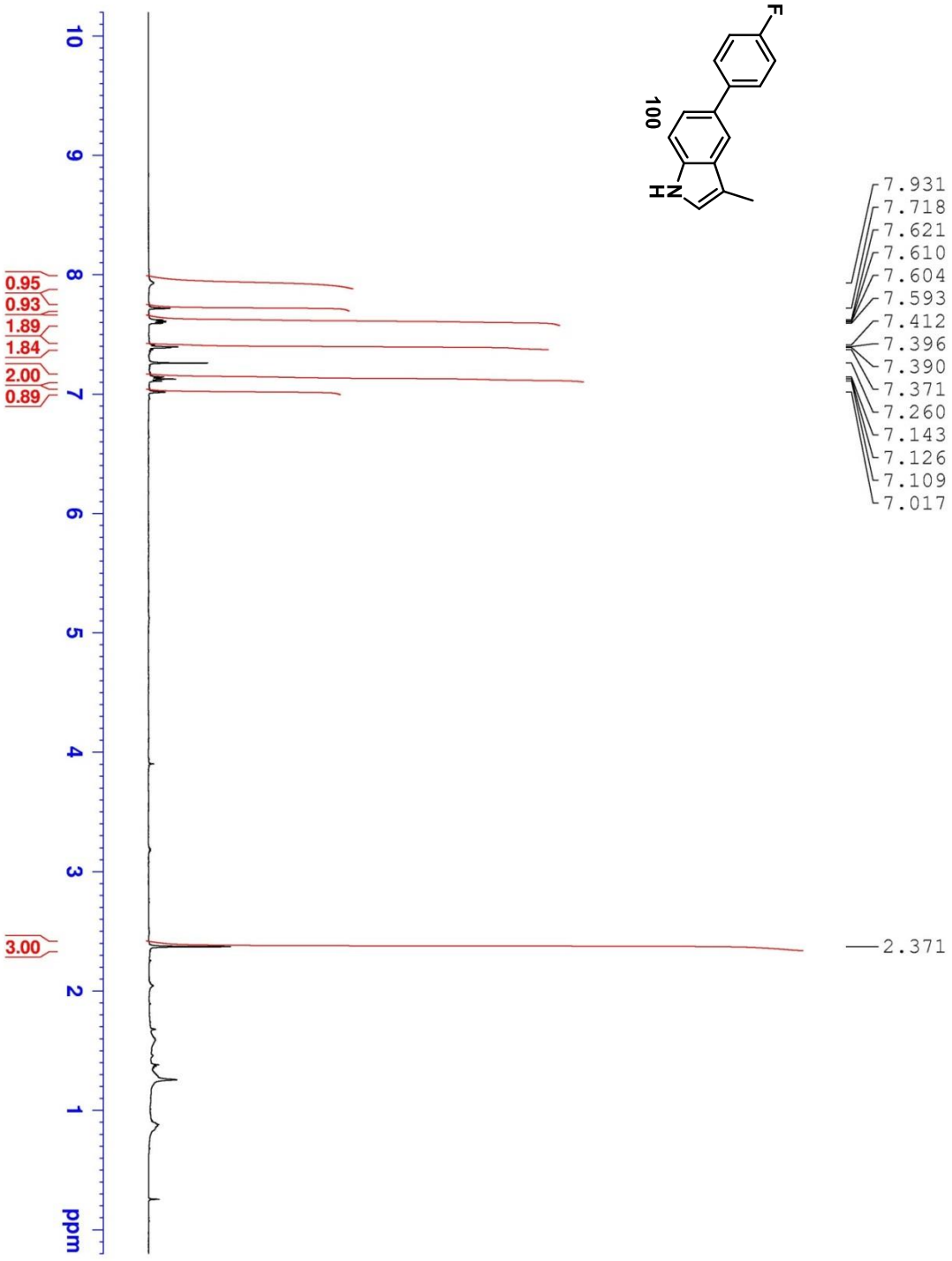

O
N
Boc
OAc
97
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm
170.82
154.46
144.03
138.18
137.58
137.23
121.14
112.90
80.77
77.25
77.00
76.74
60.80
55.23
28.08
20.87
14.50
9.48

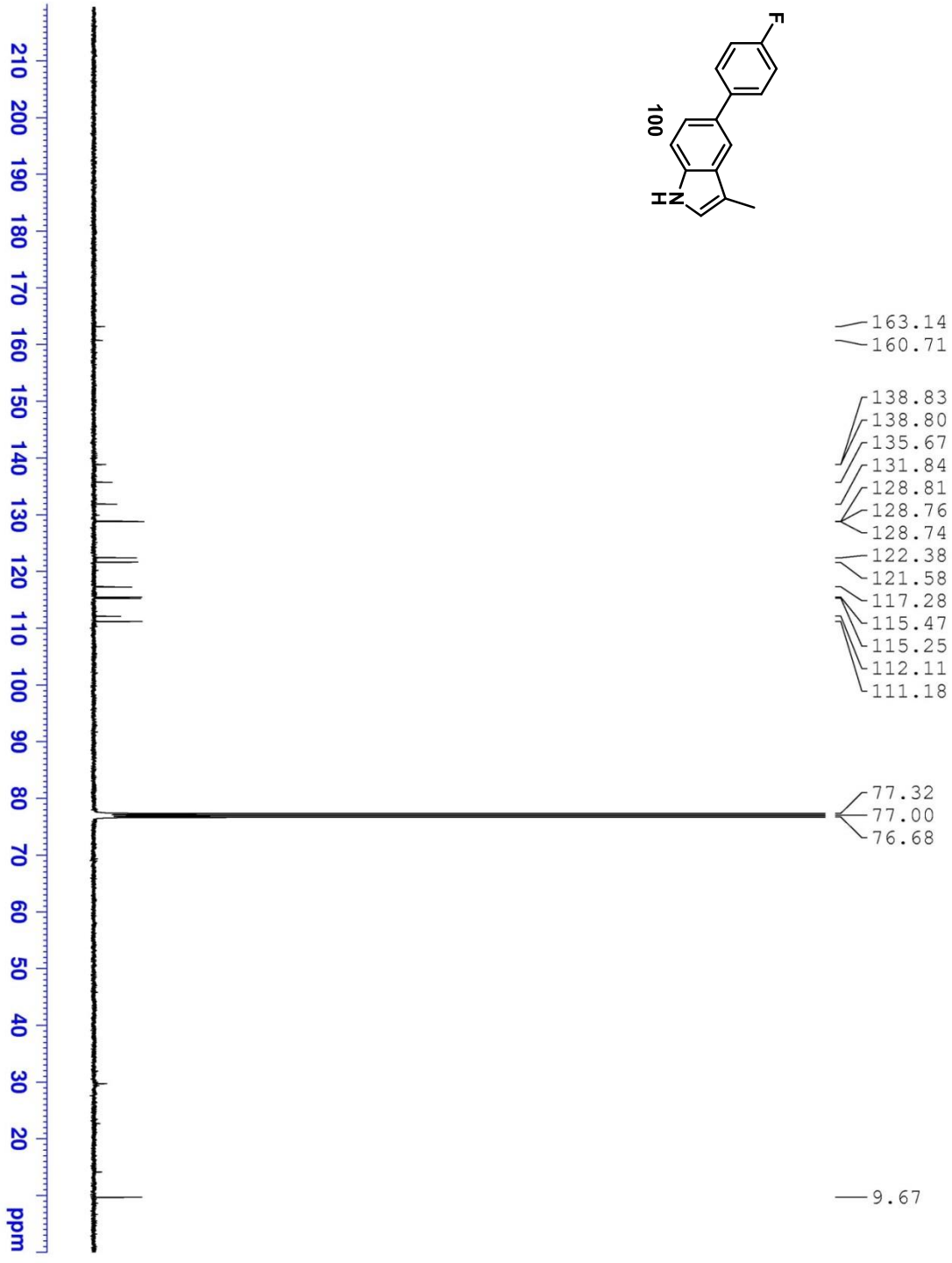

98
H
N
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm
0.84
0.98
0.99
0.95
0.91
3.00
3.08
7.814
7.465
7.446
7.260
7.086
7.067
7.048
7.018
7.000
6.982
6.980
2.490
2.349

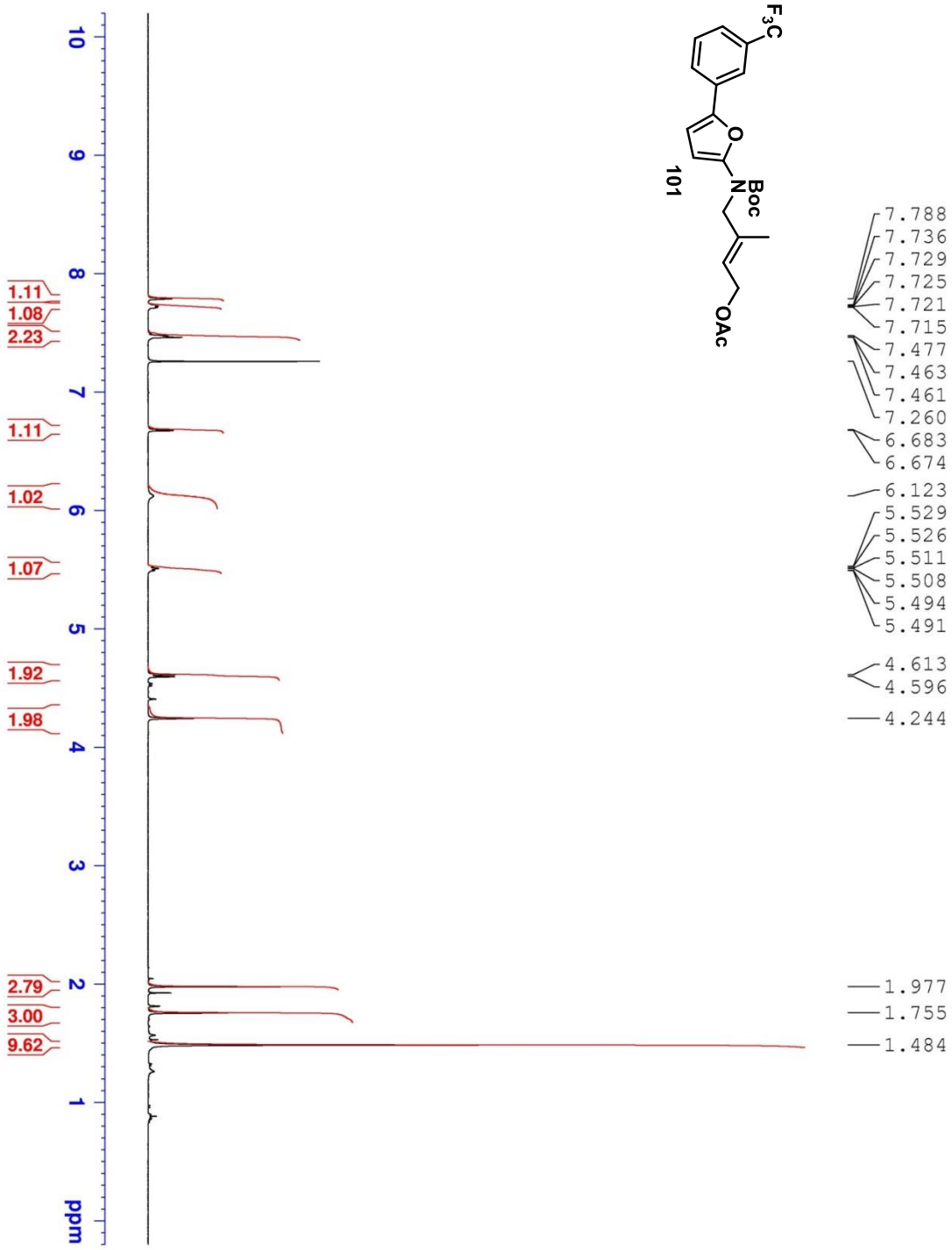

98
H
N
135.84
127.81
122.38
121.24
120.04
119.32
116.53
112.23
77.32
77.00
76.68
16.53
9.77
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

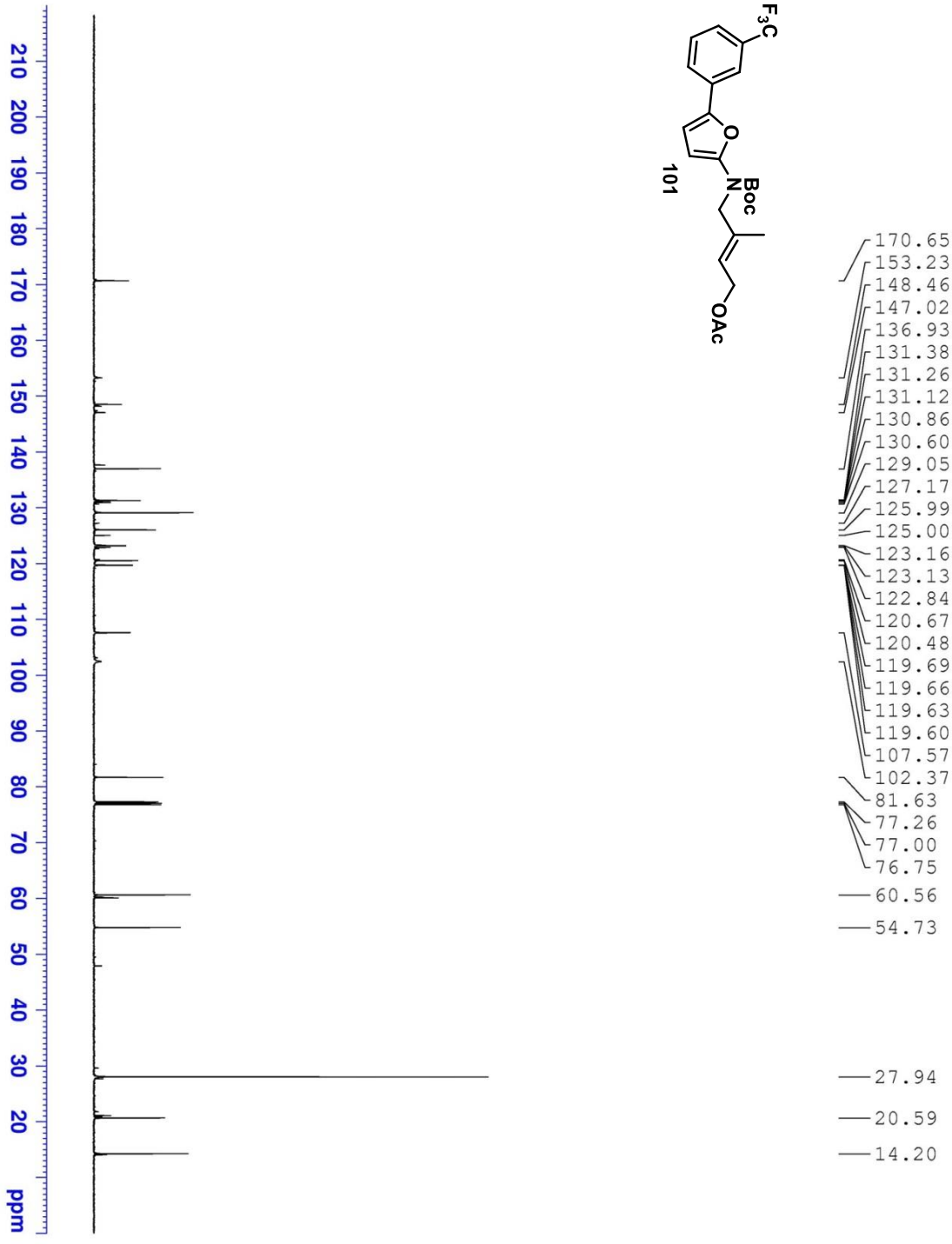

F
O
N
Boc
OAc
99
7.552
7.548
7.544
7.541
7.538
7.534
7.530
7.524
7.520
7.260
7.068
7.064
7.051
7.036
7.033
7.027
6.507
6.500
6.065
5.519
5.516
5.505
5.502
5.500
5.494
5.491
5.488
5.485
5.482
4.612
4.598
4.209
1.980
1.754
1.474
2.24
2.21
1.11
0.99
1.15
2.10
2.00
2.66
2.95
9.79
ppm

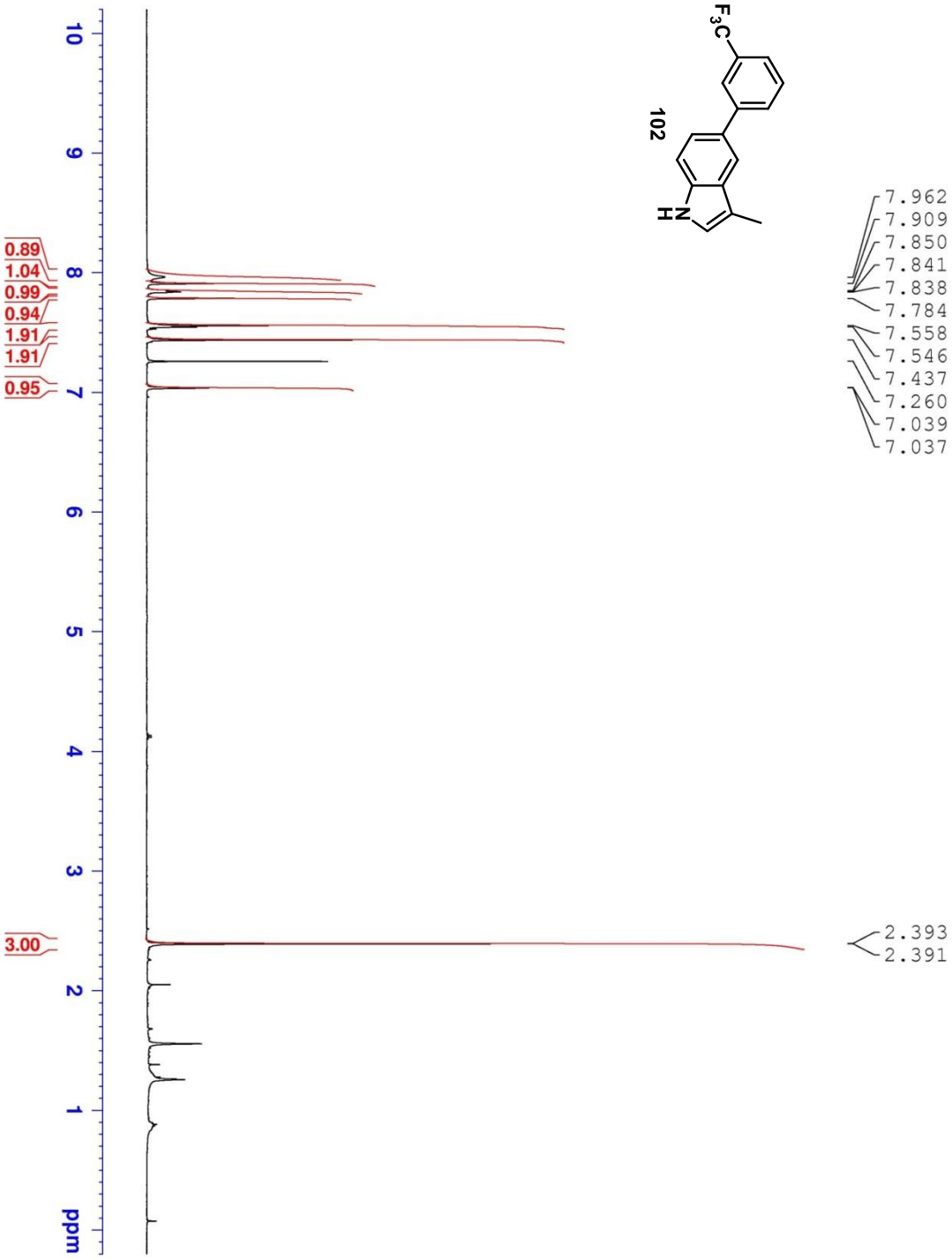
F
O
N
Boc
OAc
99
170.67
162.74
160.78
153.48
147.96
147.66
137.07
126.99
126.96
124.85
124.79
120.34
115.59
115.41
105.64
102.62
81.42
77.25
77.00
76.74
60.61
54.95
27.99
20.69
14.24
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

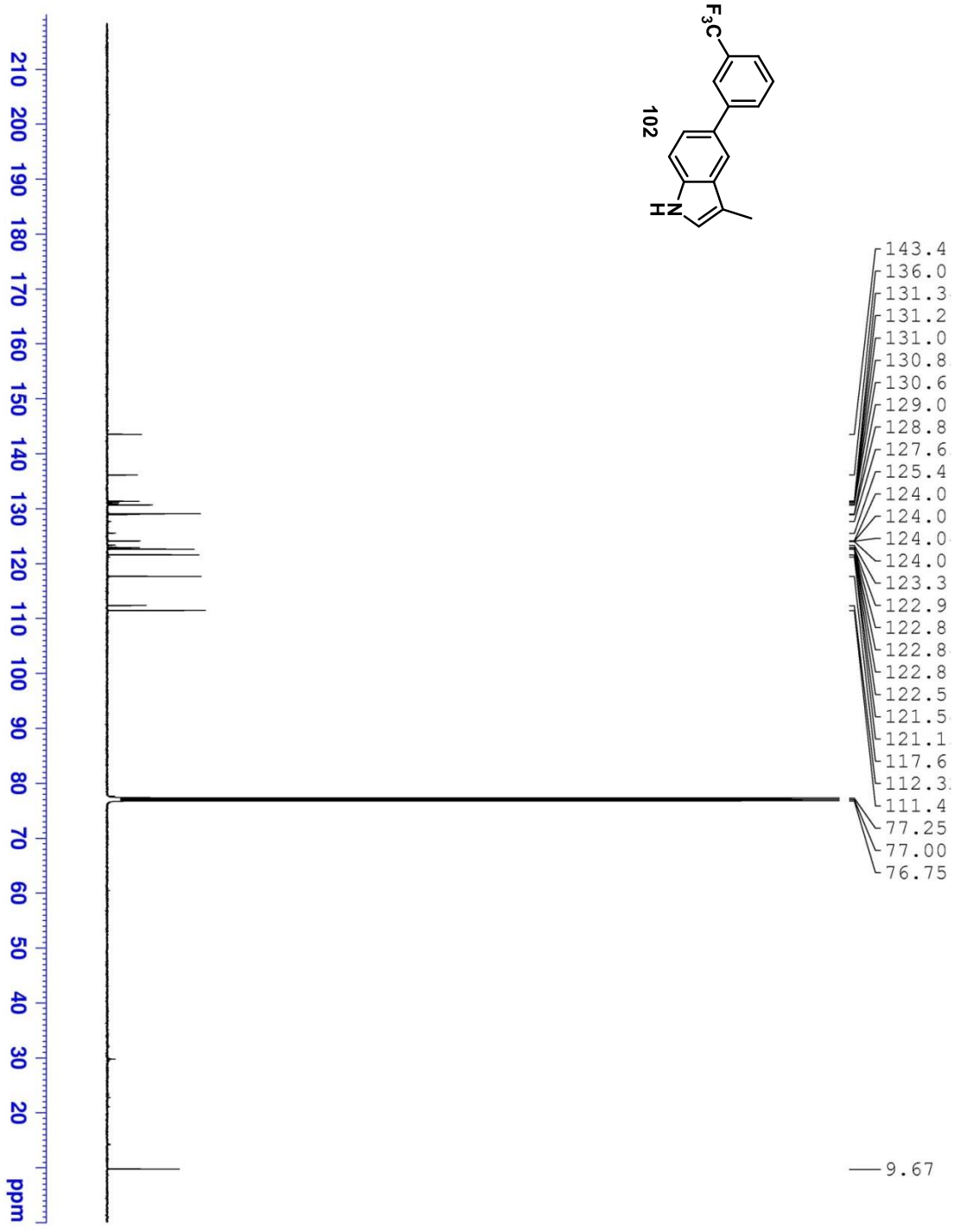

F
100
H
N
7.931
7.718
7.621
7.610
7.604
7.593
7.412
7.396
7.390
7.371
7.260
7.143
7.126
7.109
7.017
2.371
0.95
0.93
1.89
1.84
2.00
0.89
3.00
10
9
8
7
6
5
4
3
2
1
ppm

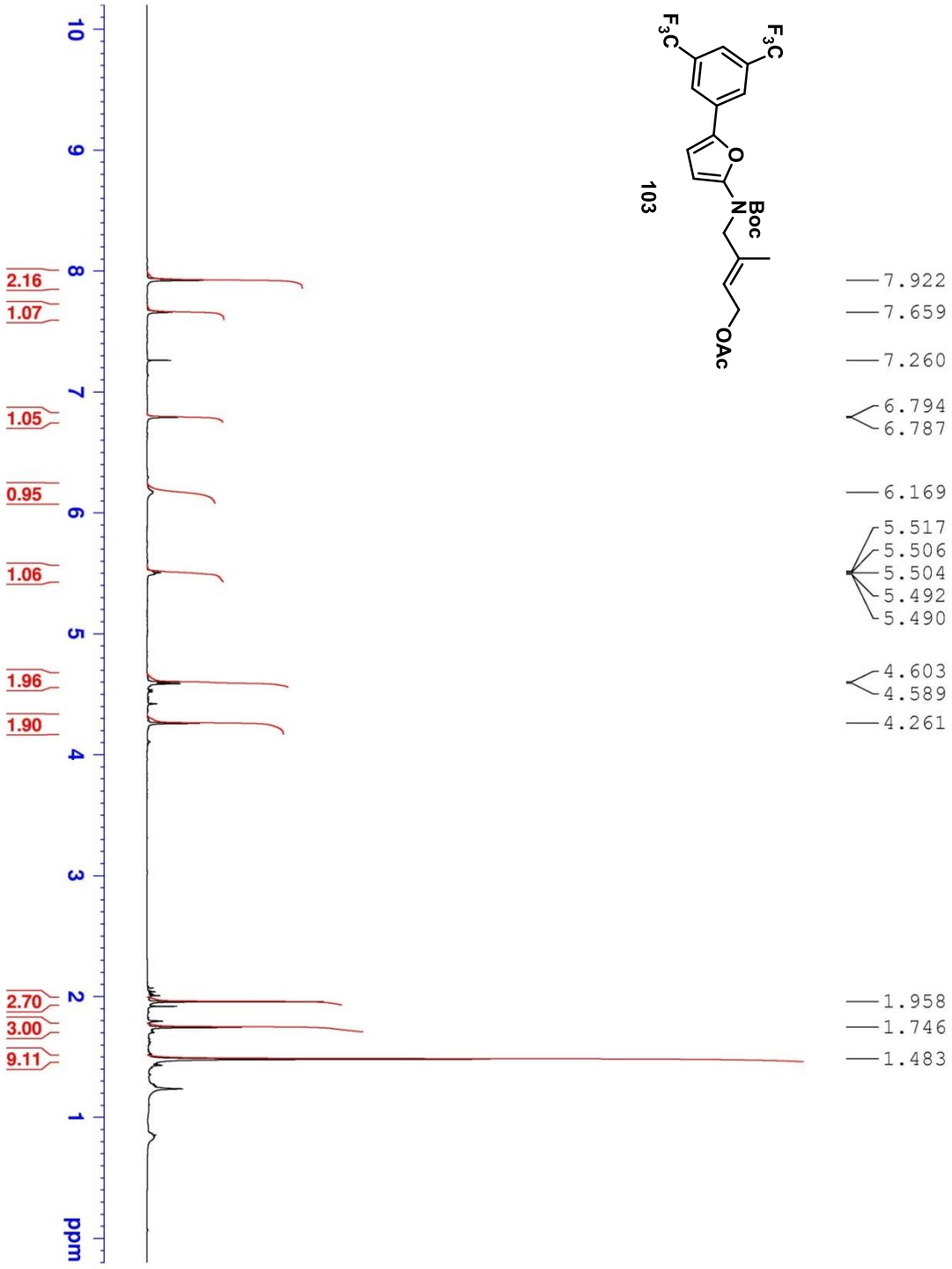

F
100
H
N
163.14
160.71
138.83
138.80
135.67
131.84
128.81
128.76
128.74
122.38
121.58
117.28
115.47
115.25
112.11
111.18
77.32
77.00
76.68
9.67
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

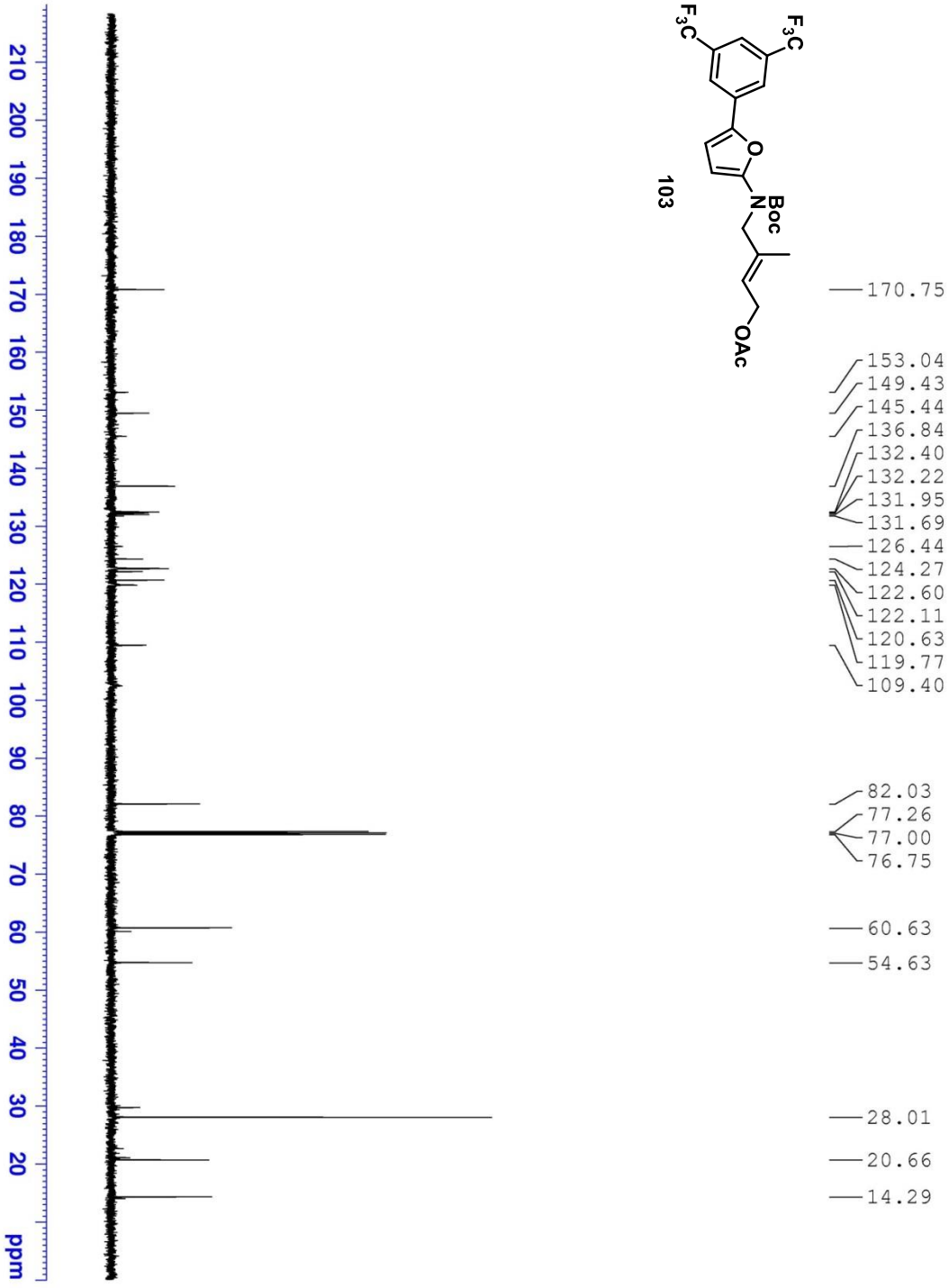

F3C
O
N
Boc
OAc
101
7.788
7.736
7.729
7.725
7.721
7.715
7.477
7.463
7.461
7.260
6.683
6.674
6.123
5.529
5.526
5.511
5.508
5.494
5.491
4.613
4.596
4.244
1.977
1.755
1.484
1.11
1.08
2.23
1.11
1.02
1.07
1.92
1.98
2.79
3.00
9.62
ppm

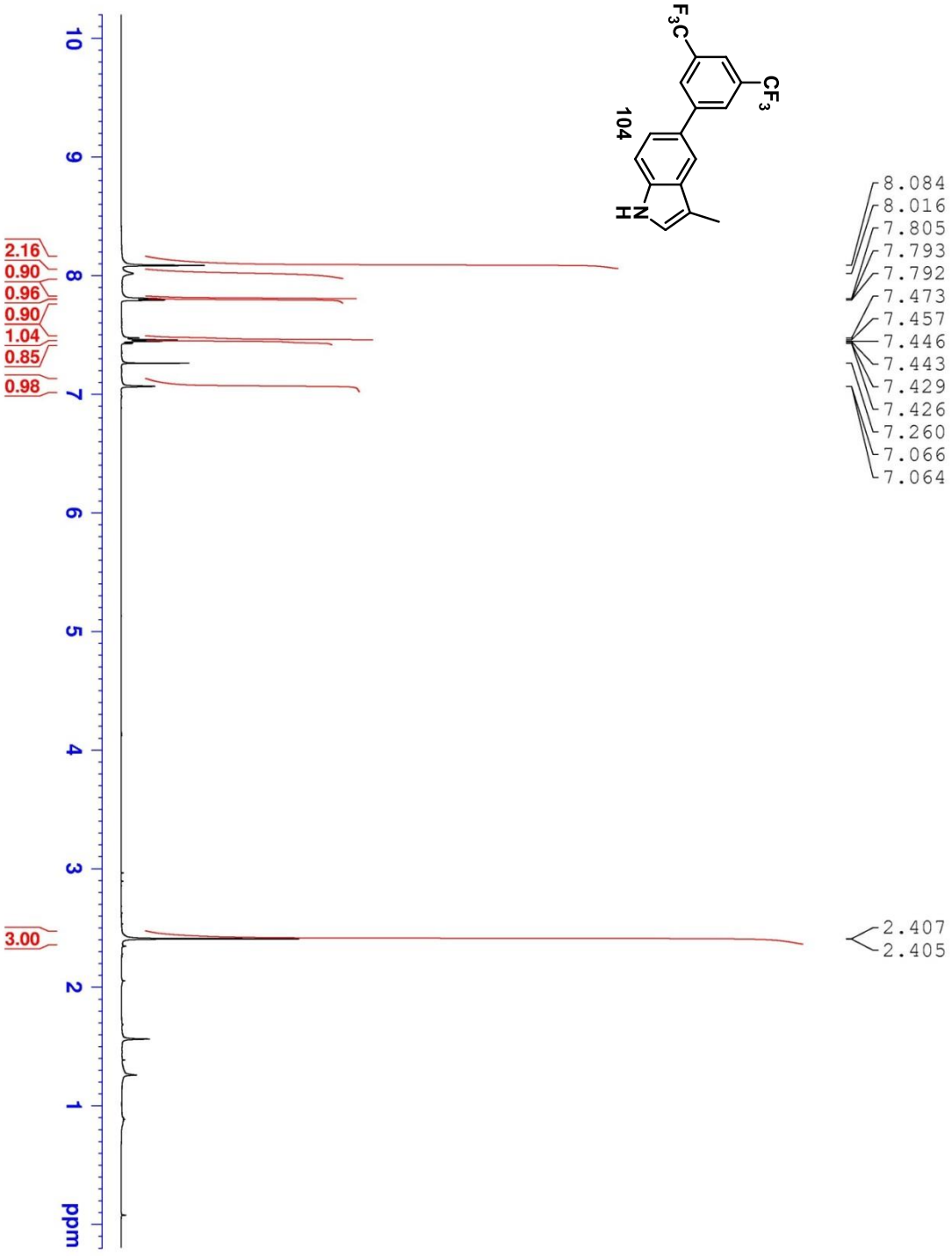

F3C
O
N
Boc
OAc
101
170.65
153.23
148.46
147.02
136.93
131.38
131.26
131.12
130.86
130.60
129.05
127.17
125.99
125.00
123.16
123.13
122.84
120.67
120.48
119.69
119.66
119.63
119.60
107.57
102.37
81.63
77.26
77.00
76.75
60.56
54.73
27.94
20.59
14.20
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

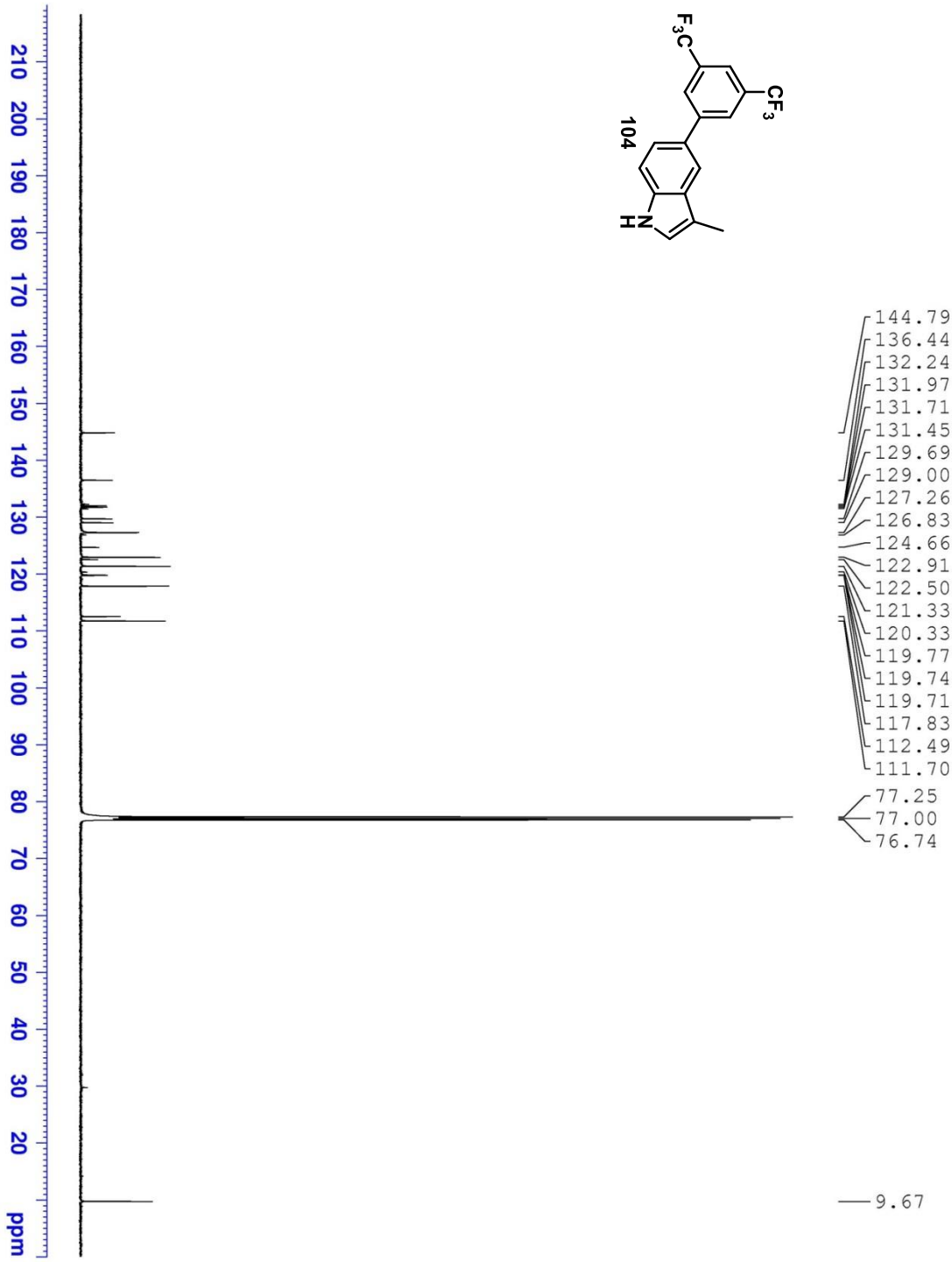

102
F3C
N
H
7.962
7.909
7.850
7.841
7.838
7.784
7.558
7.546
7.437
7.260
7.039
7.037
2.393
2.391
0.89
1.04
0.99
0.94
1.91
1.91
0.95
3.00
10
9
8
7
6
5
4
3
2
1
ppm

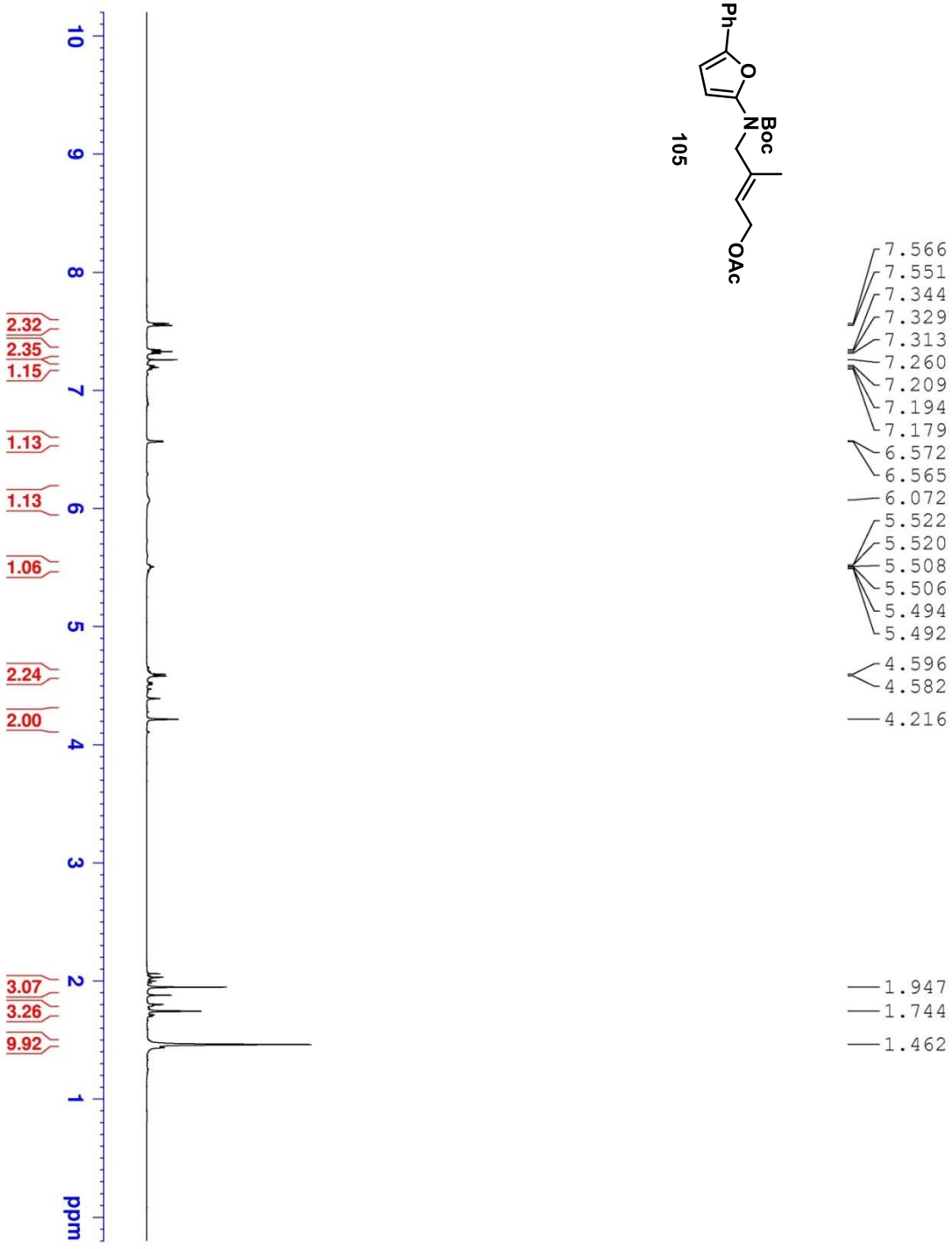

102
143.4
136.0
131.3
131.2
131.0
130.8
130.6
129.0
128.8
127.6
125.4
124.0
124.0
124.0
124.0
123.3
122.9
122.8
122.8
122.8
122.5
121.5
121.1
117.6
112.3
111.4
77.25
77.00
76.75
9.67
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

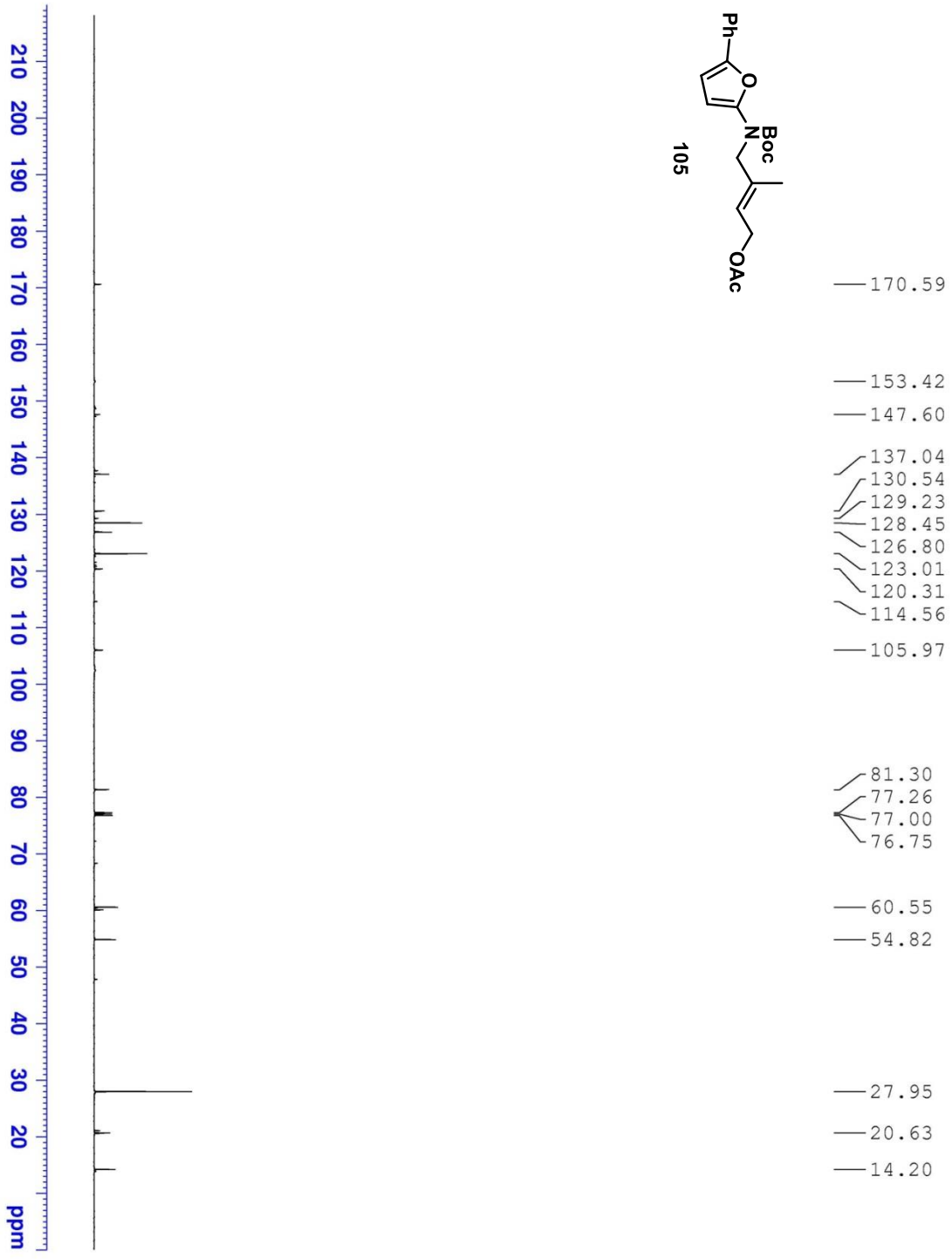

103
F3C
F3C
O
N
Boc
OAc
7.922
7.659
7.260
6.794
6.787
6.169
5.517
5.506
5.504
5.492
5.490
4.603
4.589
4.261
1.958
1.746
1.483
2.16
1.07
1.05
0.95
1.06
1.96
1.90
2.70
3.00
9.11
ppm

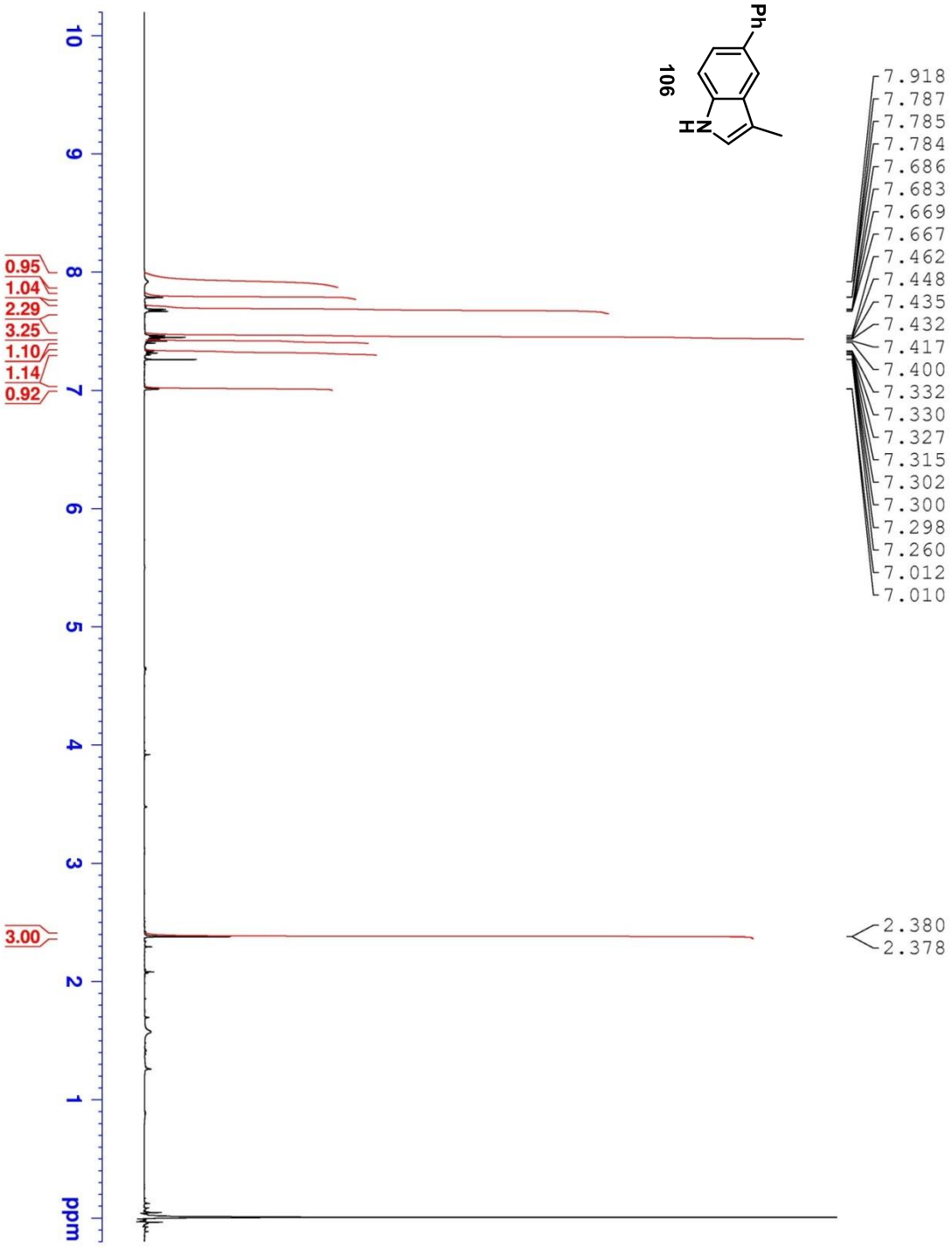

103
170.75
153.04
149.43
145.44
136.84
132.40
132.22
131.95
131.69
126.44
124.27
122.60
122.11
120.63
119.77
109.40
82.03
77.26
77.00
76.75
60.63
54.63
28.01
20.66
14.29
ppm

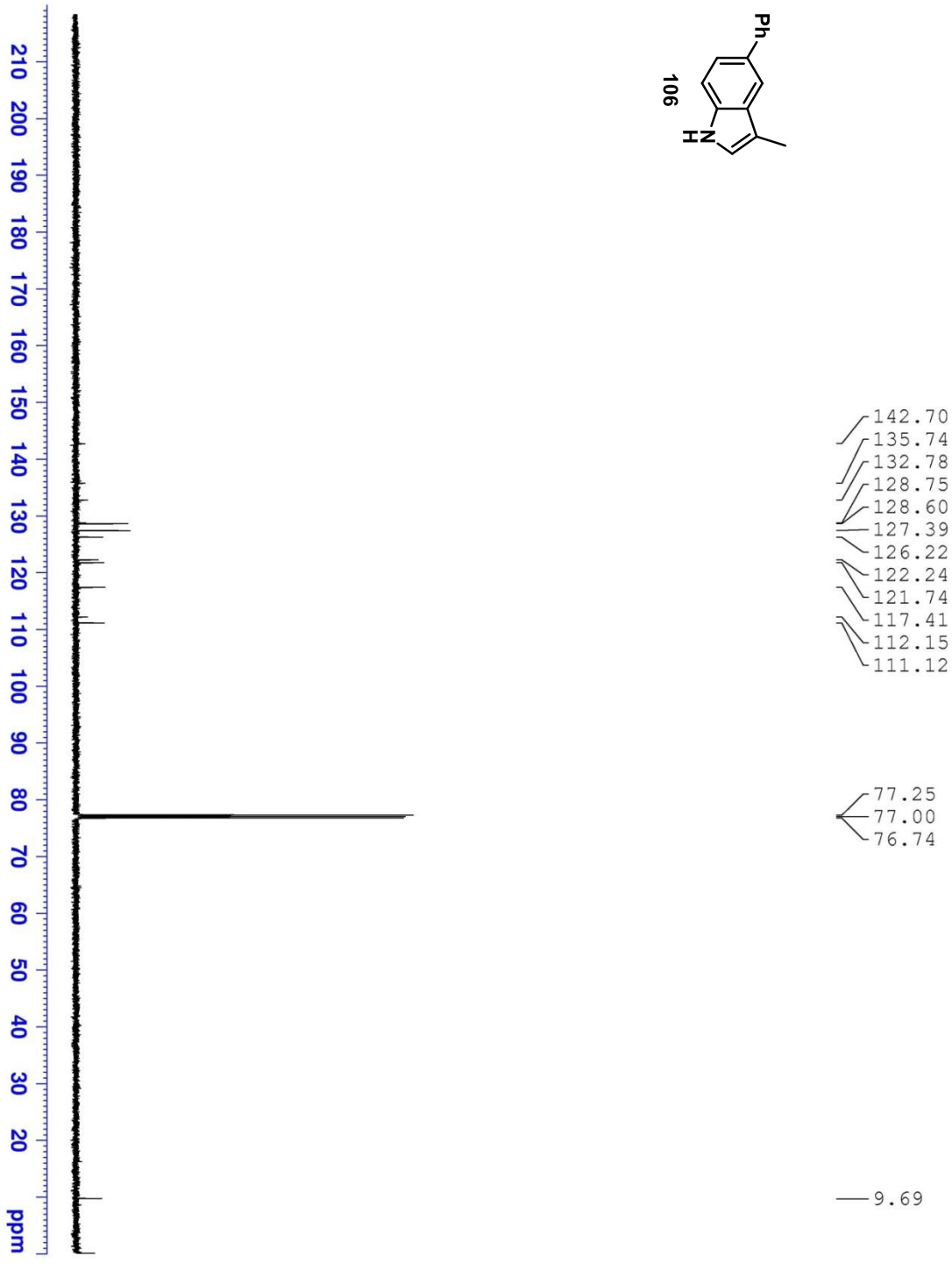

F3C
CF3
104
N
H
8.084
8.016
7.805
7.793
7.792
7.473
7.457
7.446
7.443
7.429
7.426
7.260
7.066
7.064
2.407
2.405
2.16
0.90
0.96
0.90
1.04
0.85
0.98
3.00
10
9
8
7
6
5
4
3
2
1
ppm

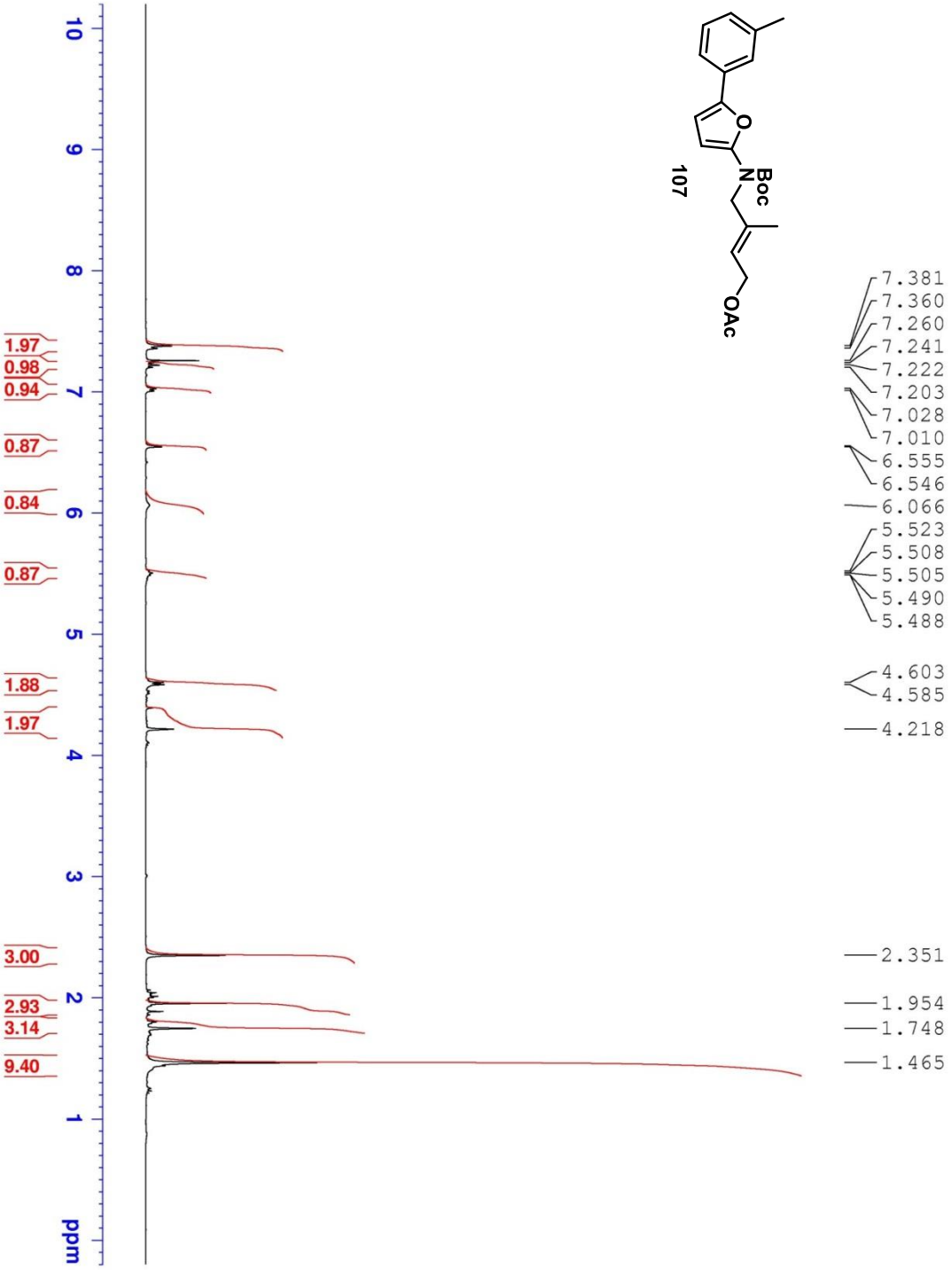

104
144.79
136.44
132.24
131.97
131.71
131.45
129.69
129.00
127.26
126.83
124.66
122.91
122.50
121.33
120.33
119.77
119.74
119.71
117.83
112.49
111.70
77.25
77.00
76.74
9.67
ppm

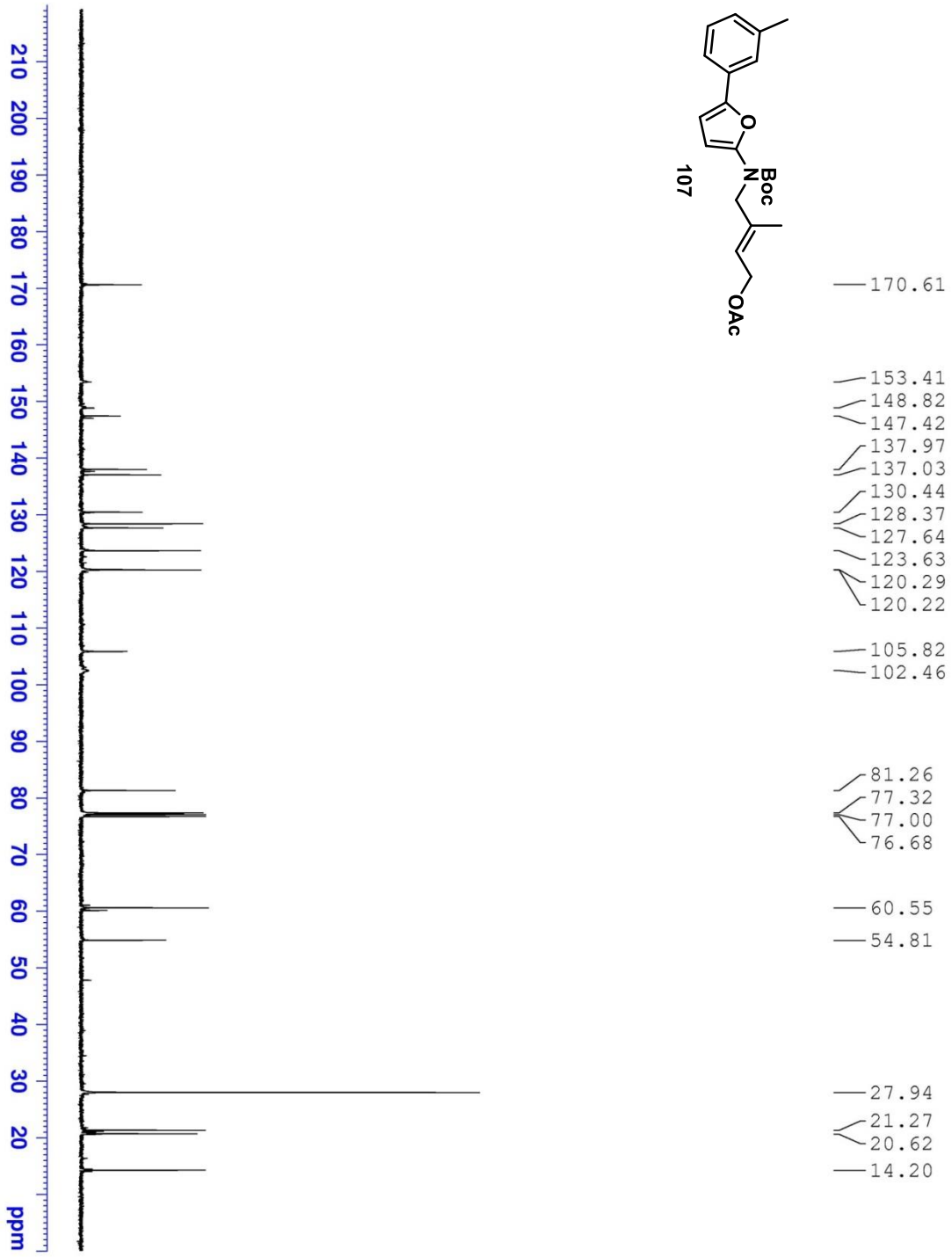

Ph
O
N
Boc
OAc
105
7.566
7.551
7.344
7.329
7.313
7.260
7.209
7.194
7.179
6.572
6.565
6.072
5.522
5.520
5.508
5.506
5.494
5.492
4.596
4.582
4.216
1.947
1.744
1.462
2.32
2.35
1.15
1.13
1.13
1.06
2.24
2.00
3.07
3.26
9.92
10
9
8
7
6
5
4
3
2
1
ppm

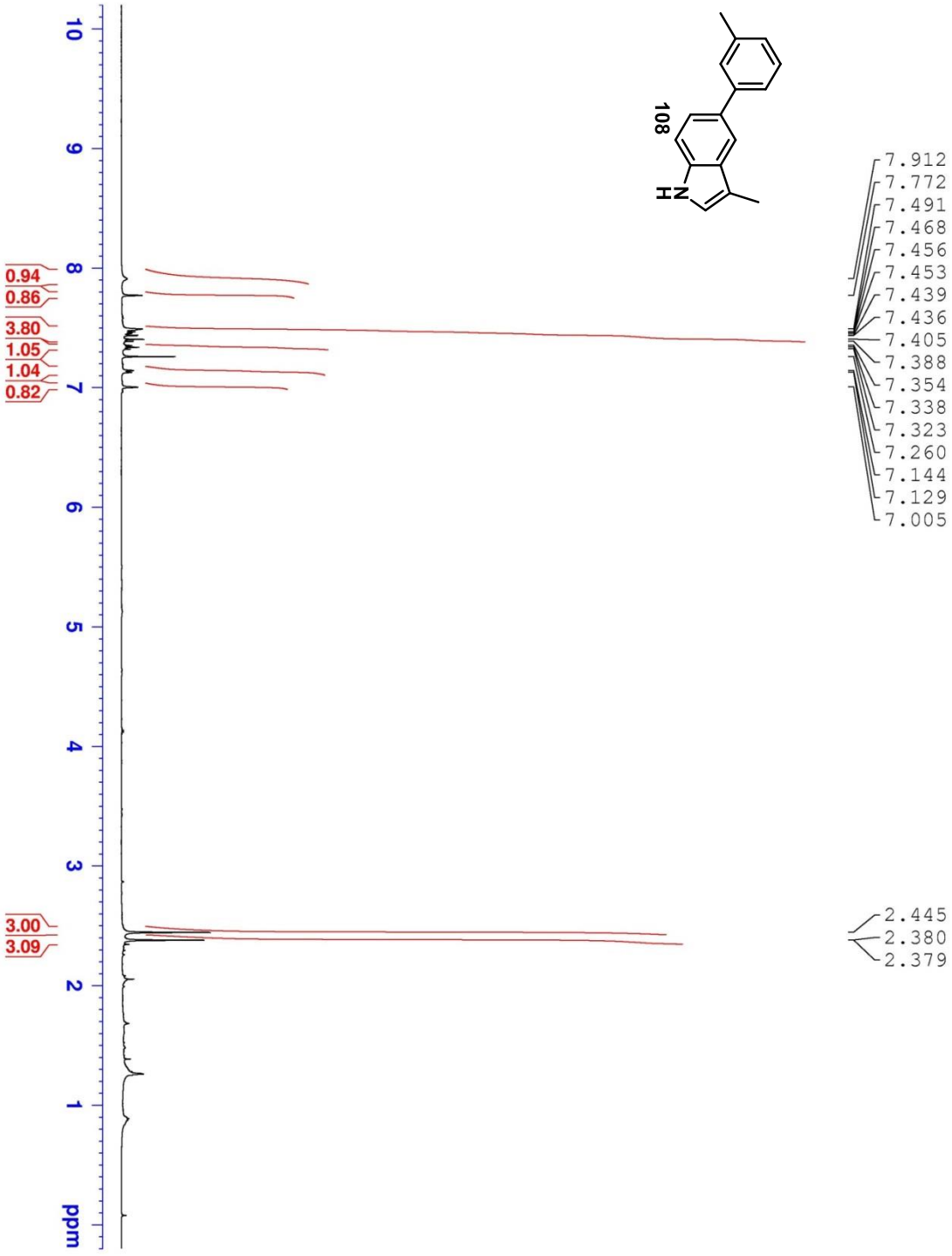

Ph
O
N
Boc
OAc
105
170.59
153.42
147.60
137.04
130.54
129.23
128.45
126.80
123.01
120.31
114.56
105.97
81.30
77.26
77.00
76.75
60.55
54.82
27.95
20.63
14.20
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

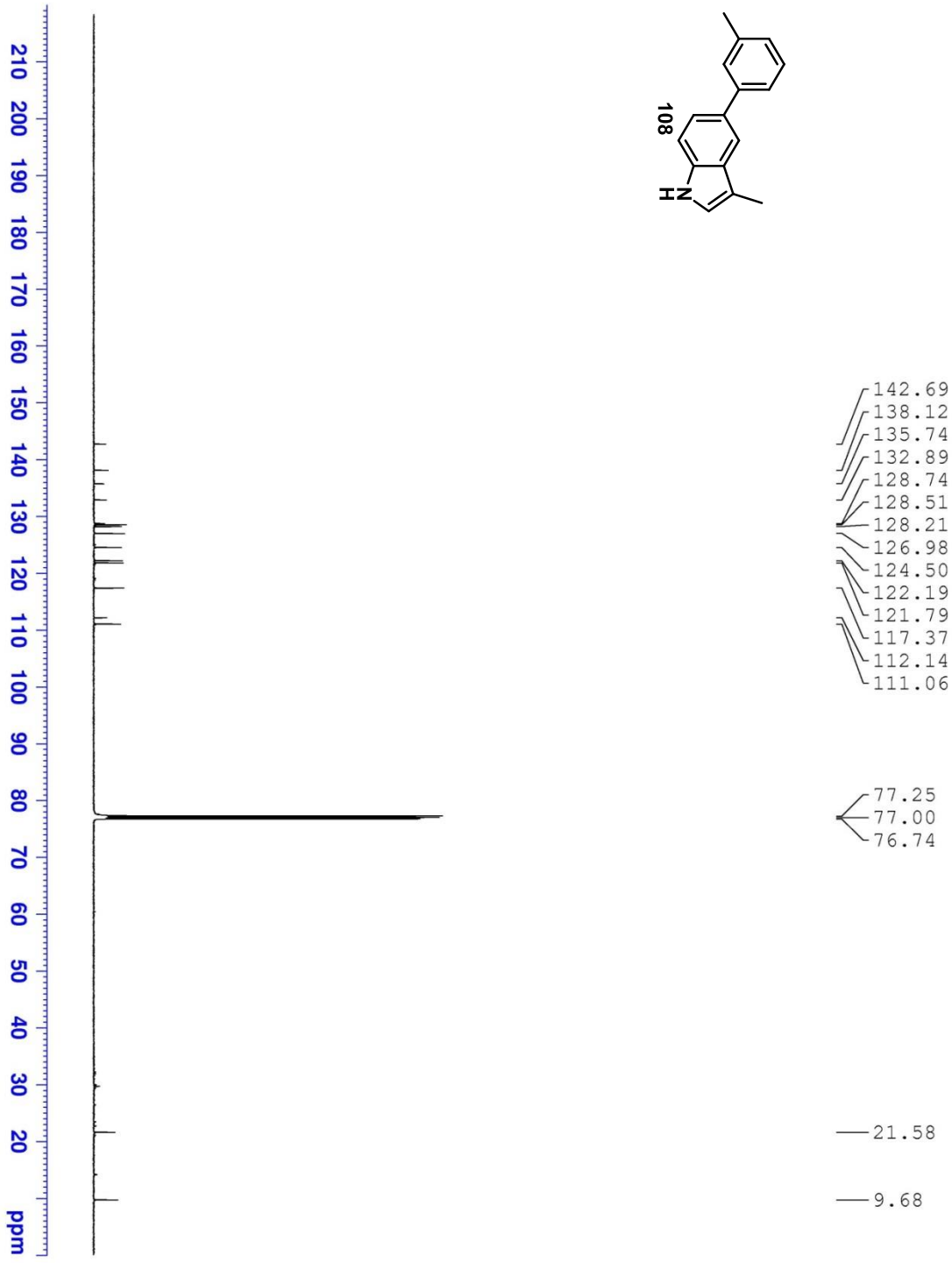

106
Ph
N
H
7.918
7.787
7.785
7.784
7.686
7.683
7.669
7.667
7.462
7.448
7.435
7.432
7.417
7.400
7.332
7.330
7.327
7.315
7.302
7.300
7.298
7.260
7.012
7.010
2.380
2.378
0.95
1.04
2.29
3.25
1.10
1.14
0.92
3.00
10
9
8
7
6
5
4
3
2
1
ppm

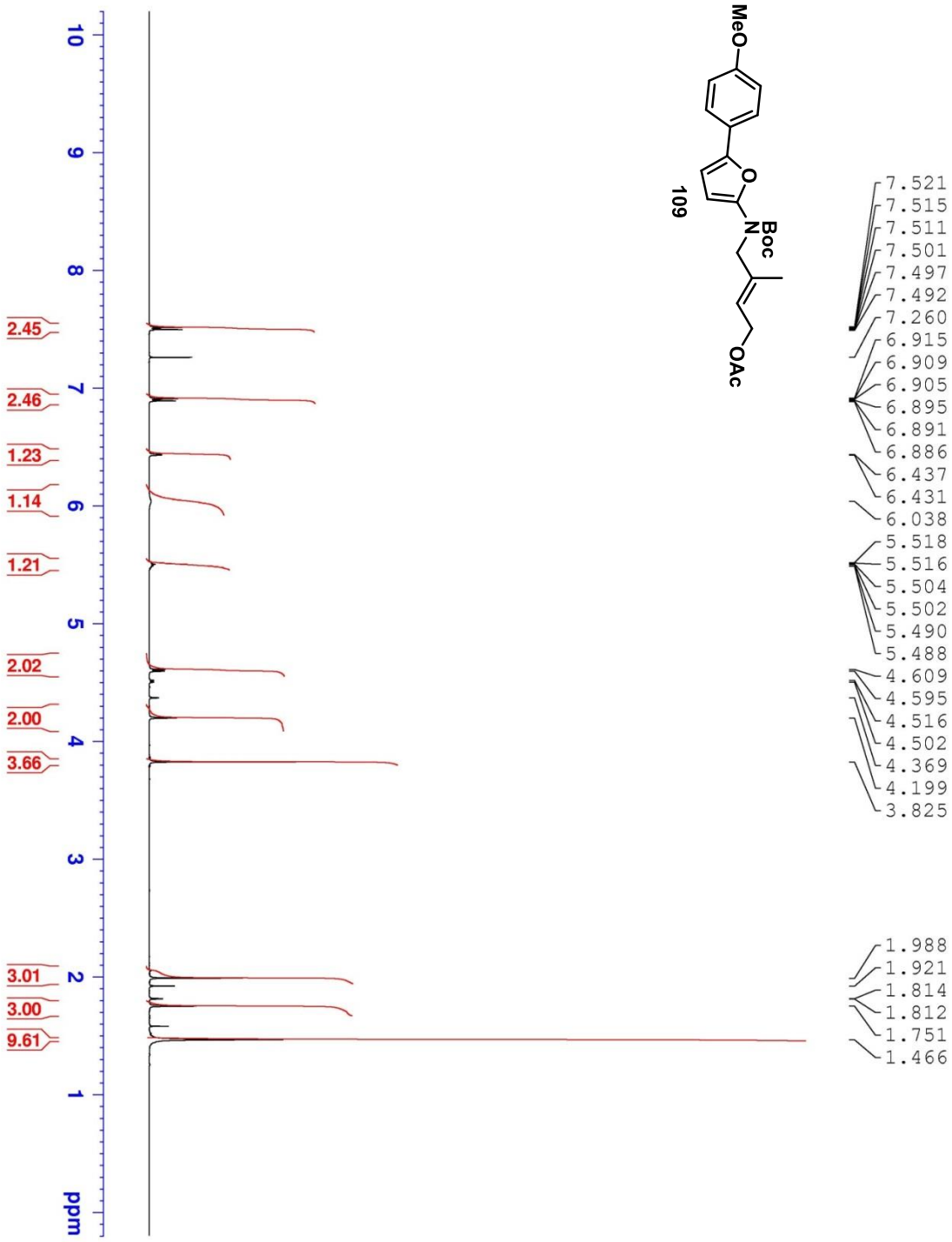

Ph
106
H
N
142.70
135.74
132.78
128.75
128.60
127.39
126.22
122.24
121.74
117.41
112.15
111.12
77.25
77.00
76.74
9.69
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

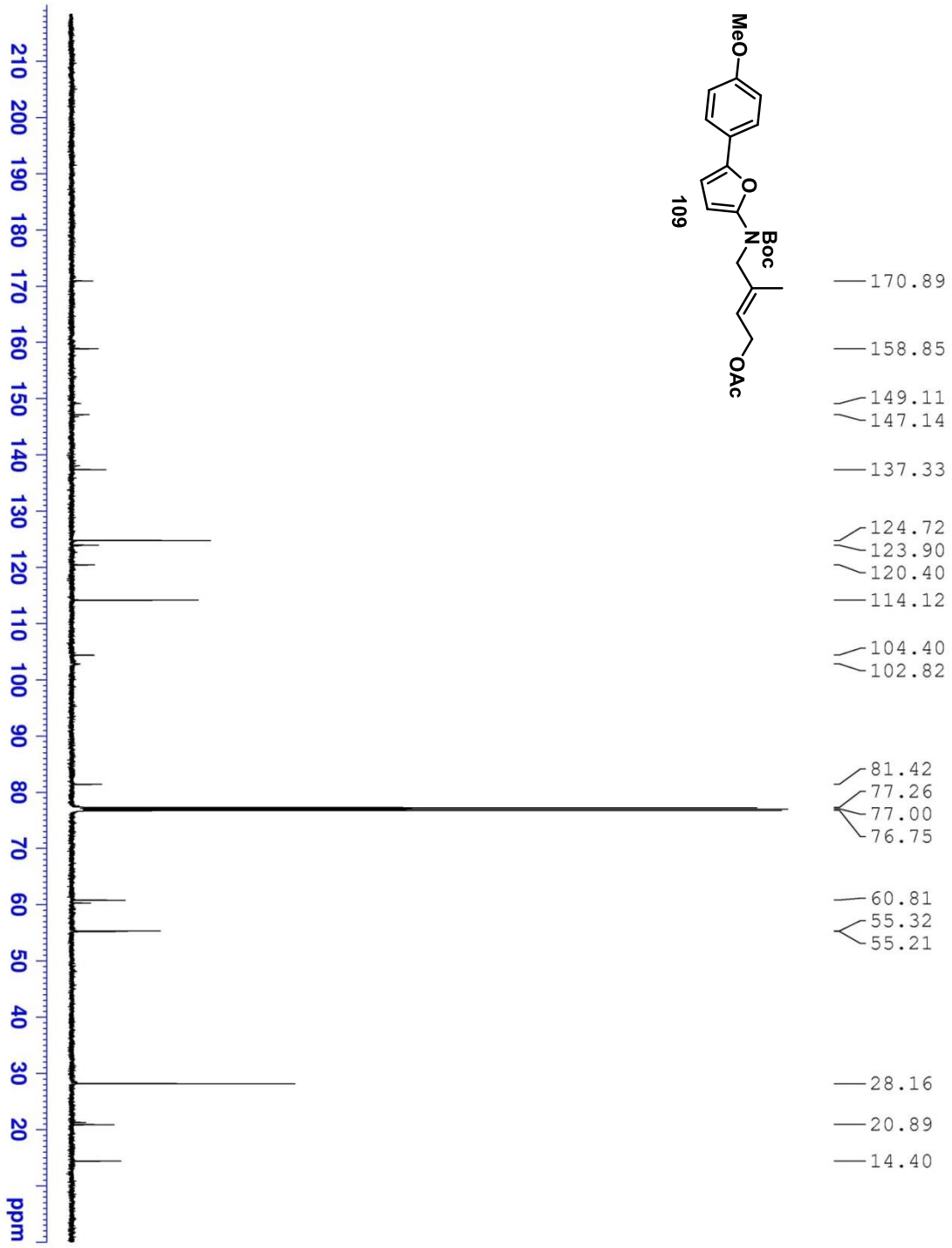

107
Boc
N
O
OAc
7.381
7.360
7.260
7.241
7.222
7.203
7.028
7.010
6.555
6.546
6.066
5.523
5.508
5.505
5.490
5.488
4.603
4.585
4.218
2.351
1.954
1.748
1.465
1.97
0.98
0.94
0.87
0.84
0.87
1.88
1.97
3.00
2.93
3.14
9.40
10
9
8
7
6
5
4
3
2
1
ppm

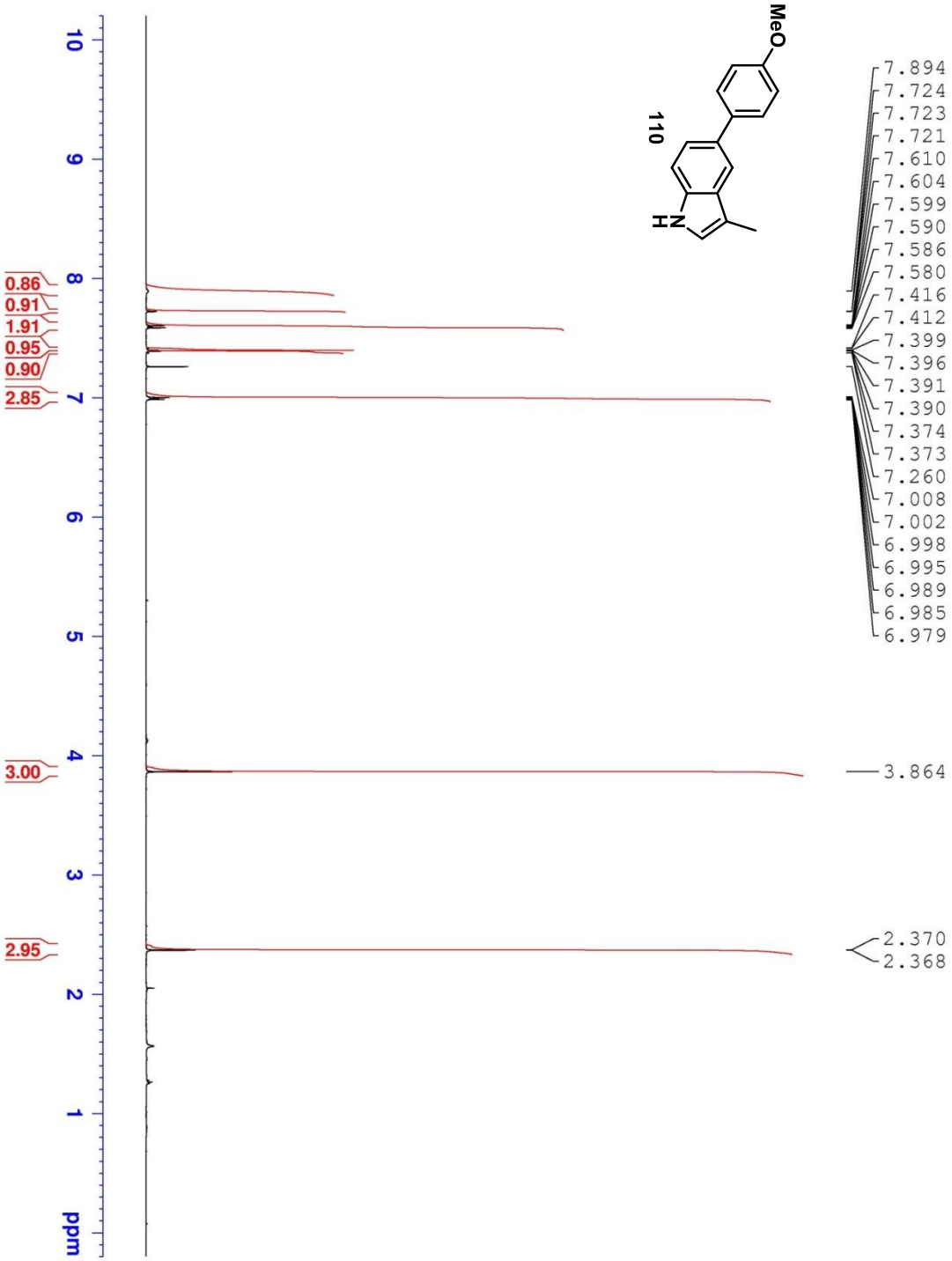

107
Boc
N
O
OAc
170.61
153.41
148.82
147.42
137.97
137.03
130.44
128.37
127.64
123.63
120.29
120.22
105.82
102.46
81.26
77.32
77.00
76.68
60.55
54.81
27.94
21.27
20.62
14.20
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

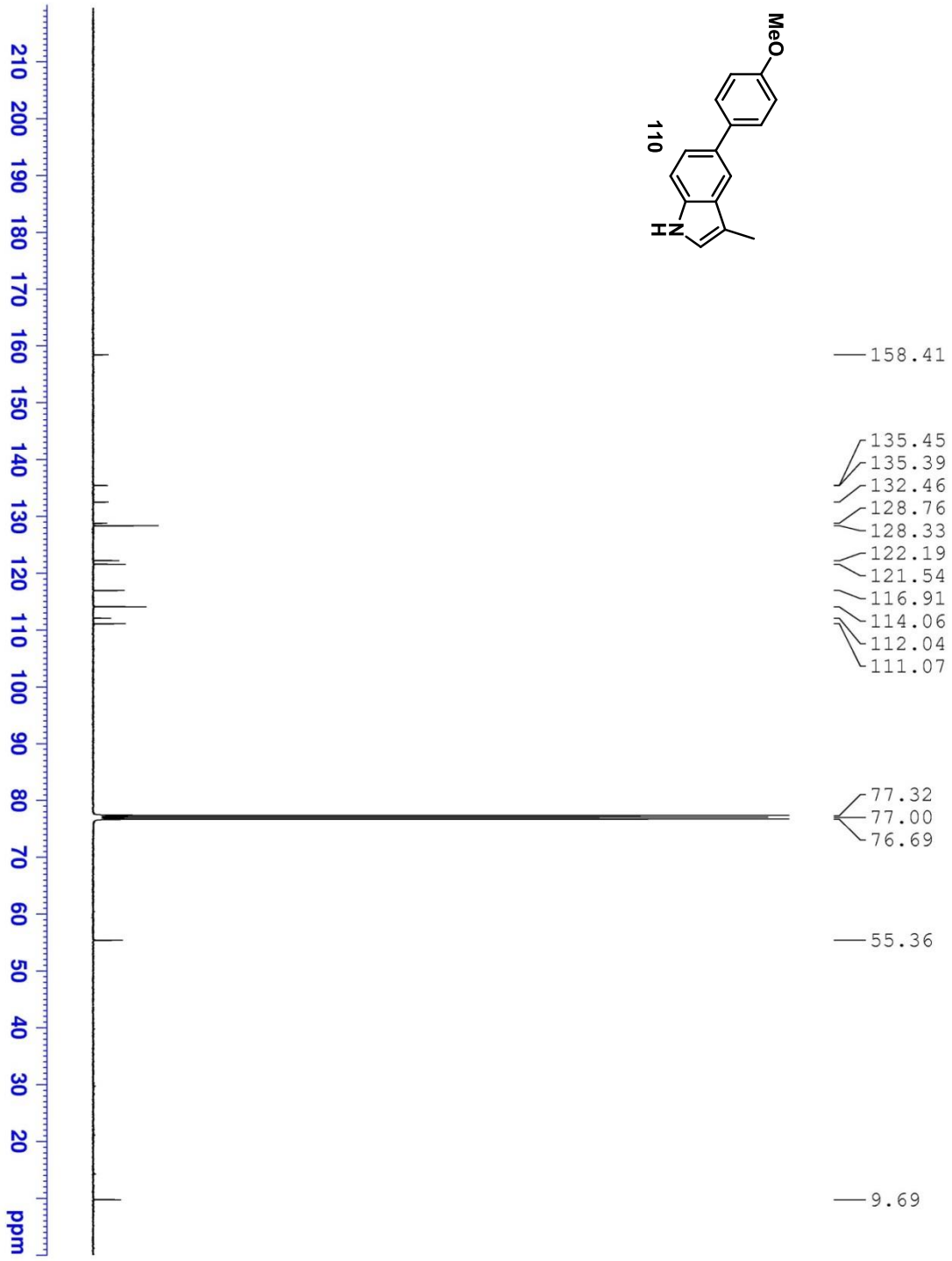

108
H
N
7.912
7.772
7.491
7.468
7.456
7.453
7.439
7.436
7.405
7.388
7.354
7.338
7.323
7.260
7.144
7.129
7.005
2.445
2.380
2.379
0.94
0.86
3.80
1.05
1.04
0.82
3.00
3.09
10
9
8
7
6
5
4
3
2
1
ppm

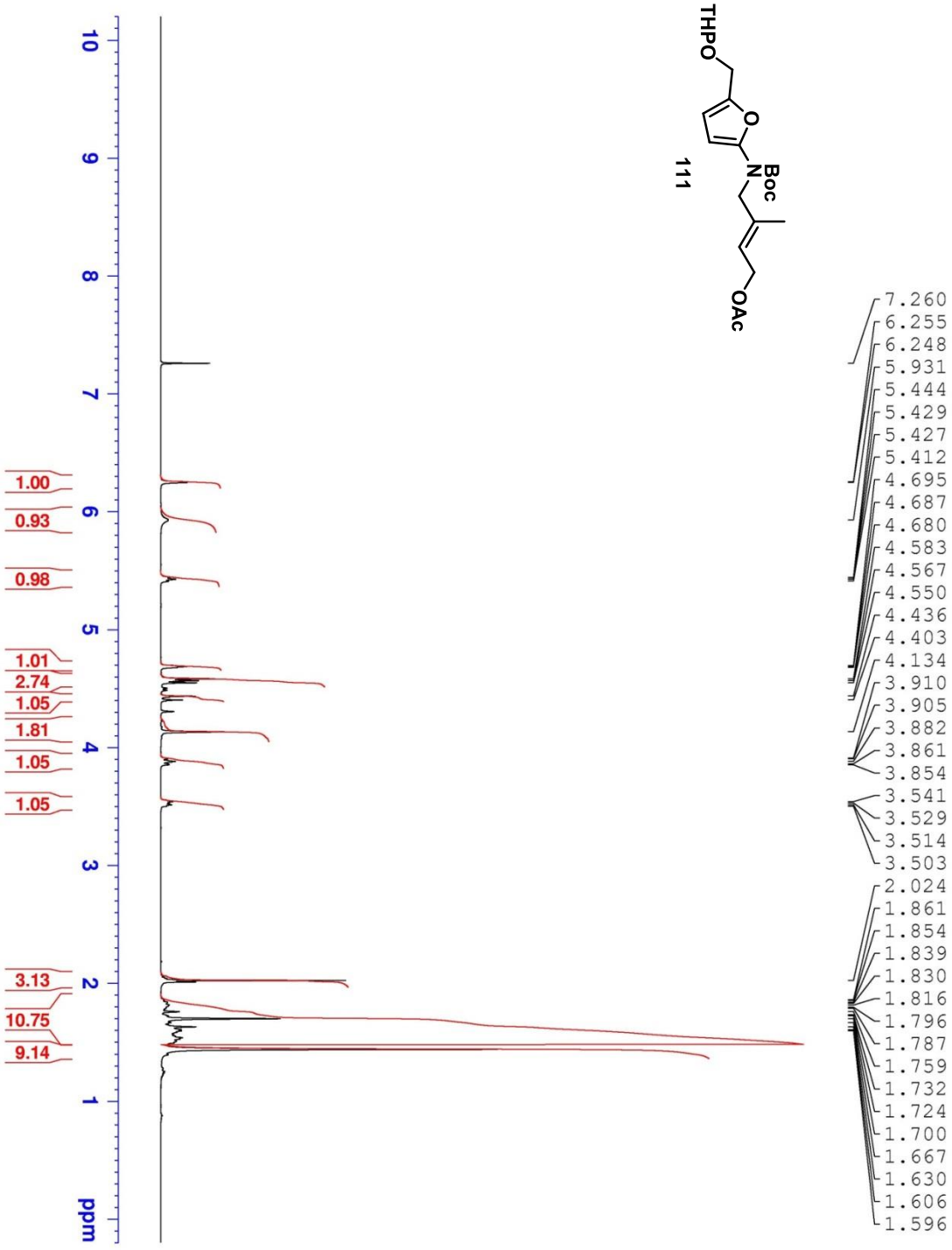

108
H
N
142.69
138.12
135.74
132.89
128.74
128.51
128.21
126.98
124.50
122.19
121.79
117.37
112.14
111.06
77.25
77.00
76.74
21.58
9.68
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

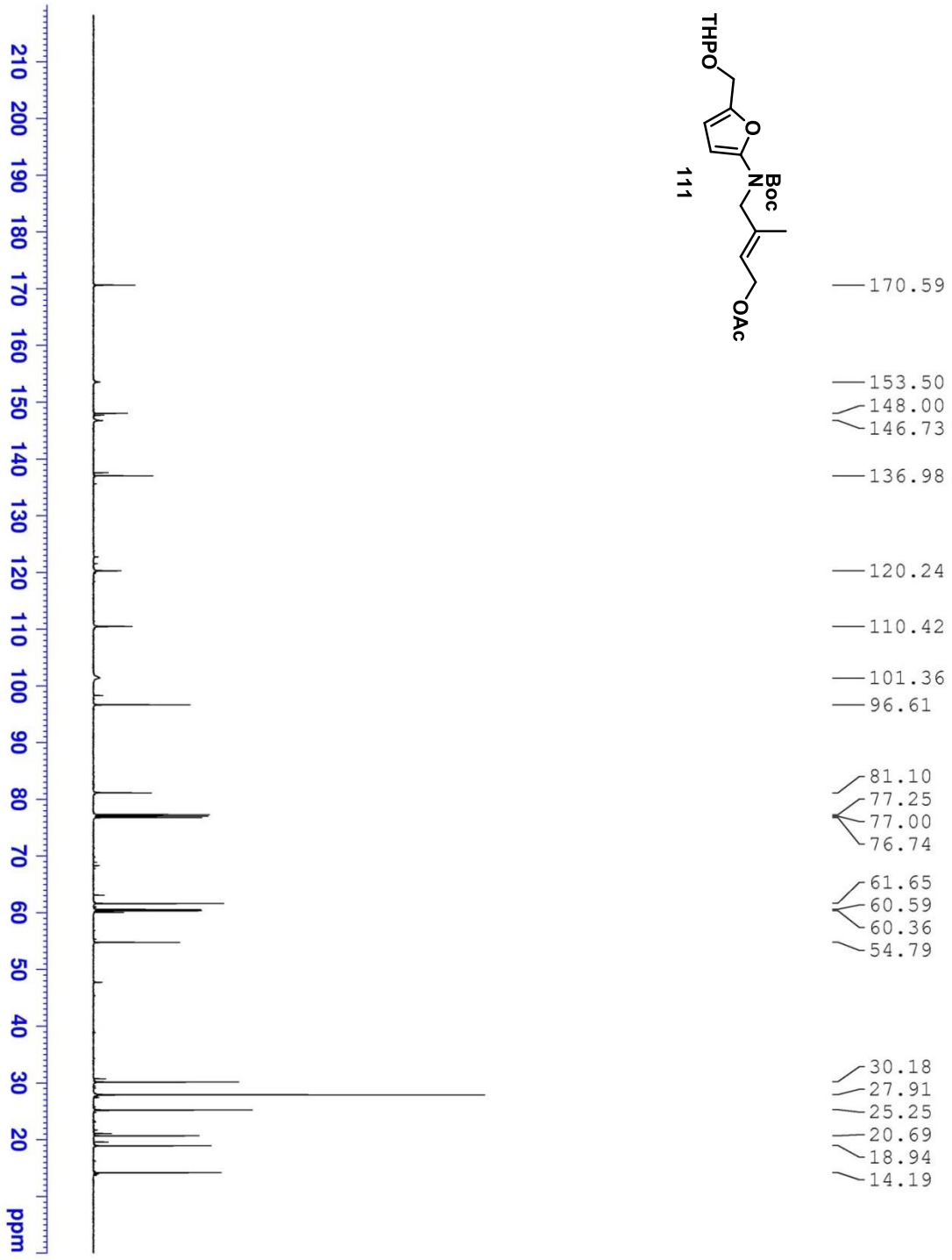

MeO
O
N
Boc
OAc
109
7.521
7.515
7.511
7.501
7.497
7.492
7.260
6.915
6.909
6.905
6.895
6.891
6.886
6.437
6.431
6.038
5.518
5.516
5.504
5.502
5.490
5.488
4.609
4.595
4.516
4.502
4.369
4.199
3.825
1.988
1.921
1.814
1.812
1.751
1.466
2.45
2.46
1.23
1.14
1.21
2.02
2.00
3.66
3.01
3.00
9.61
10
9
8
7
6
5
4
3
2
1
ppm

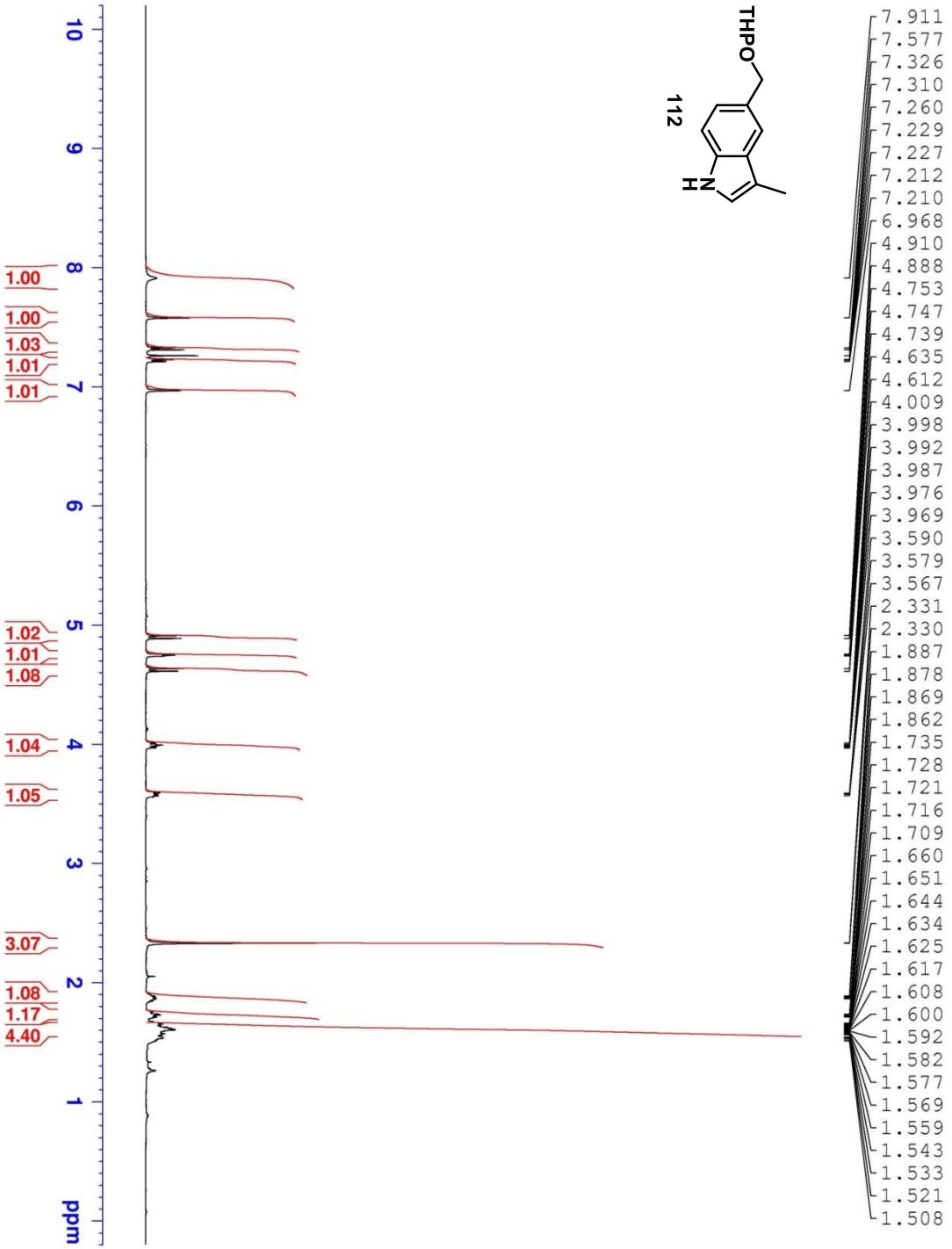

MeO
O
N
Boc
OAc
109
170.89
158.85
149.11
147.14
137.33
124.72
123.90
120.40
114.12
104.40
102.82
81.42
77.26
77.00
76.75
60.81
55.32
55.21
28.16
20.89
14.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

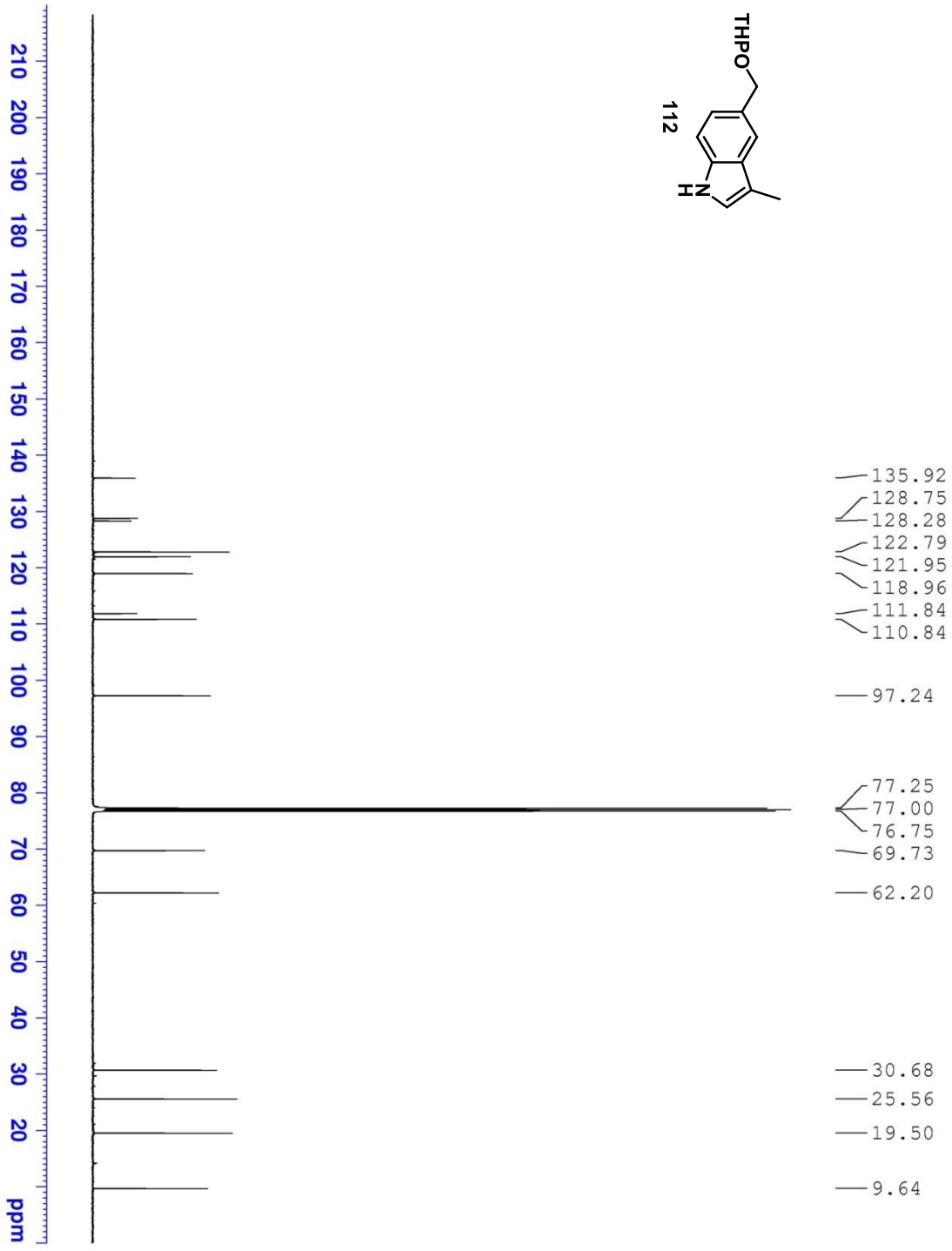

MeO
110
HN
7.894
7.724
7.723
7.721
7.610
7.604
7.599
7.590
7.586
7.580
7.416
7.412
7.399
7.396
7.391
7.390
7.374
7.373
7.260
7.008
7.002
6.998
6.995
6.989
6.985
6.979
3.864
2.370
2.368
0.86
0.91
1.91
0.95
0.90
2.85
3.00
2.95
10
9
8
7
6
5
4
3
2
1
ppm

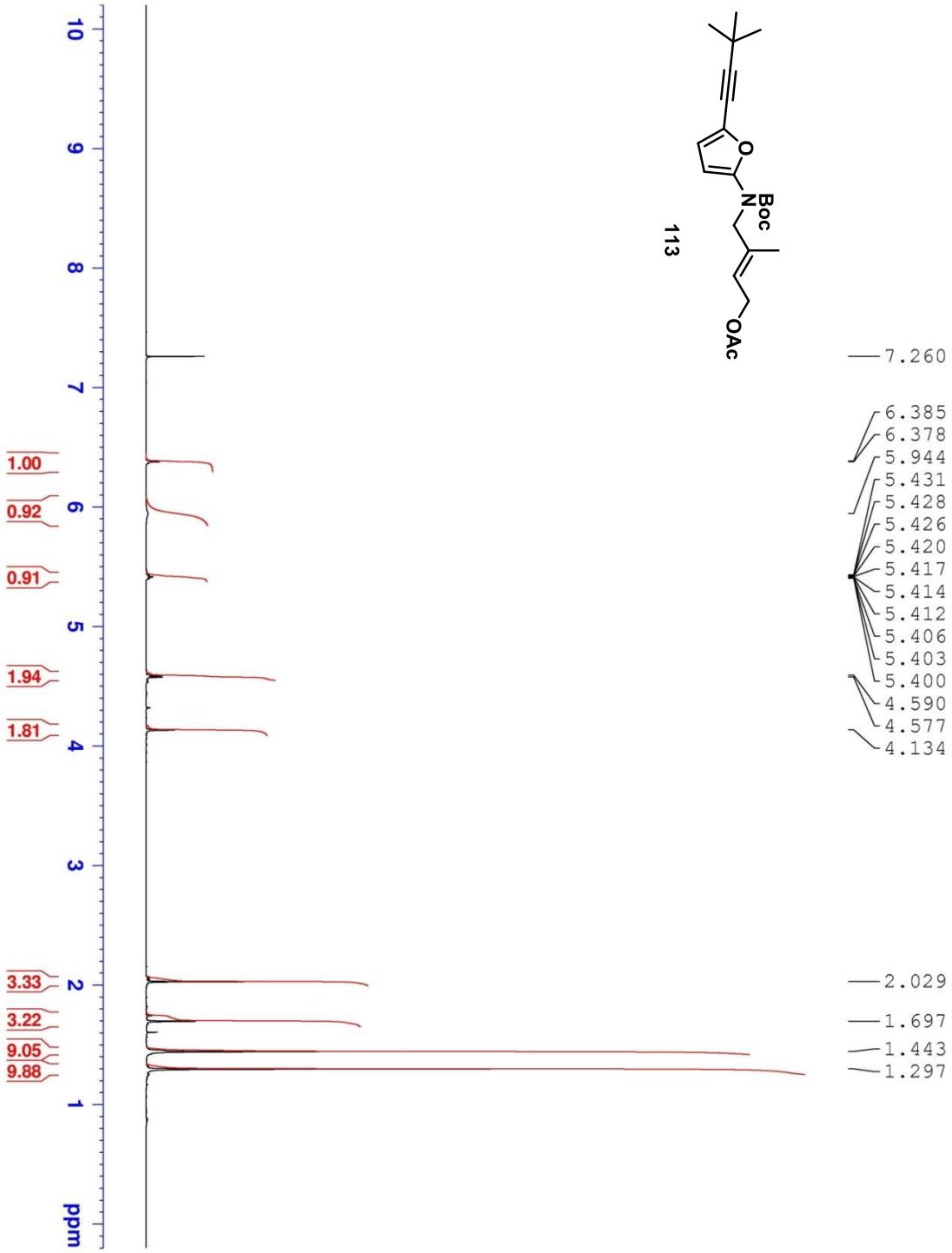

MeO
110
H
N
158.41
135.45
135.39
132.46
128.76
128.33
122.19
121.54
116.91
114.06
112.04
111.07
77.32
77.00
76.69
55.36
9.69
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

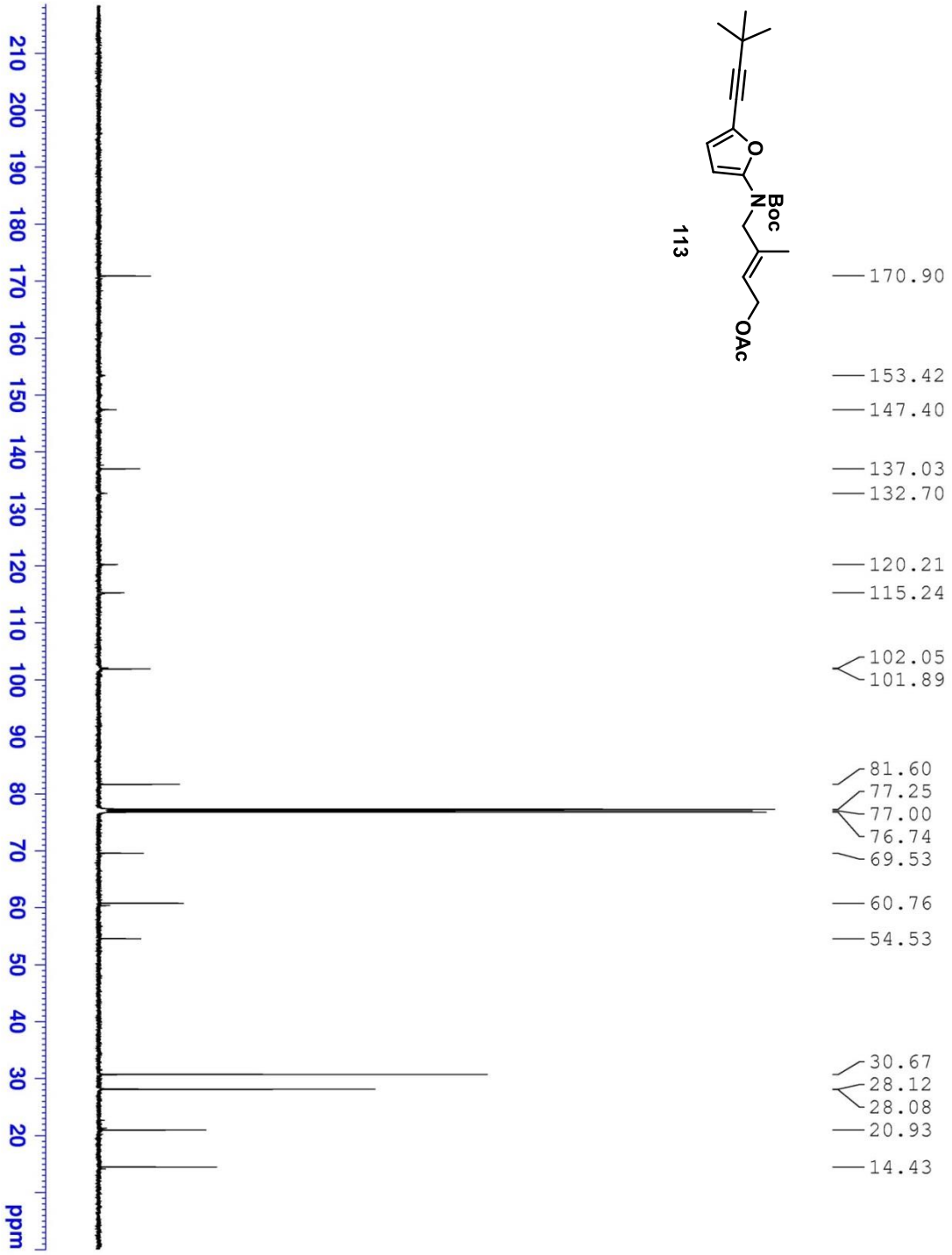

THPO
O
N
Boc
OAc
111
1.00
0.93
0.98
1.01
2.74
1.05
1.81
1.05
1.05
3.13
10.75
9.14
ppm
7.260
6.255
6.248
5.931
5.444
5.429
5.427
5.412
4.695
4.687
4.680
4.583
4.567
4.550
4.436
4.403
4.134
3.910
3.905
3.882
3.861
3.854
3.541
3.529
3.514
3.503
2.024
1.861
1.854
1.839
1.830
1.816
1.796
1.787
1.759
1.732
1.724
1.700
1.667
1.630
1.606
1.596

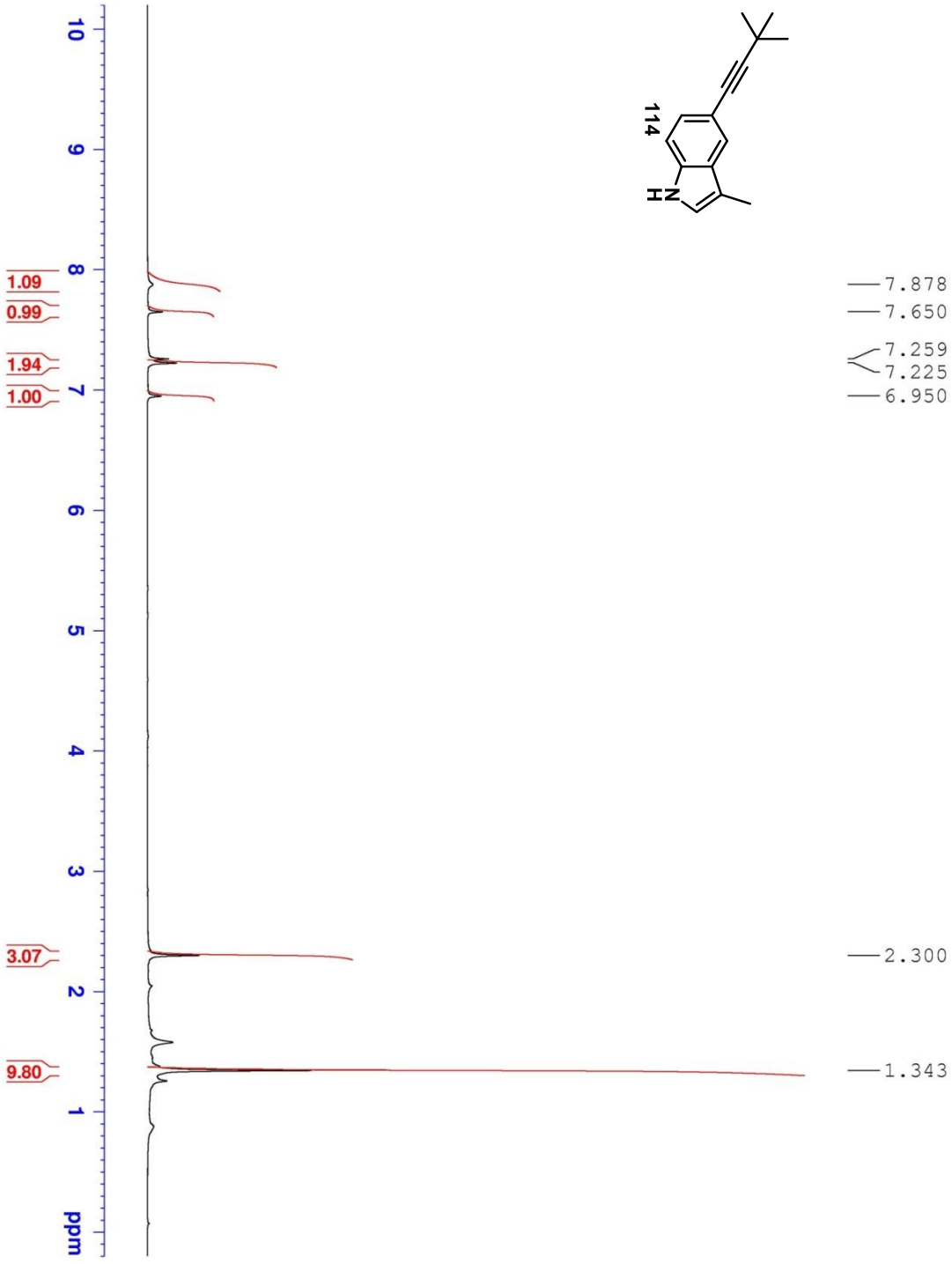

THPO
O
N
Boc
OAc
111
170.59
153.50
148.00
146.73
136.98
120.24
110.42
101.36
96.61
81.10
77.25
77.00
76.74
61.65
60.59
60.36
54.79
30.18
27.91
25.25
20.69
18.94
14.19
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

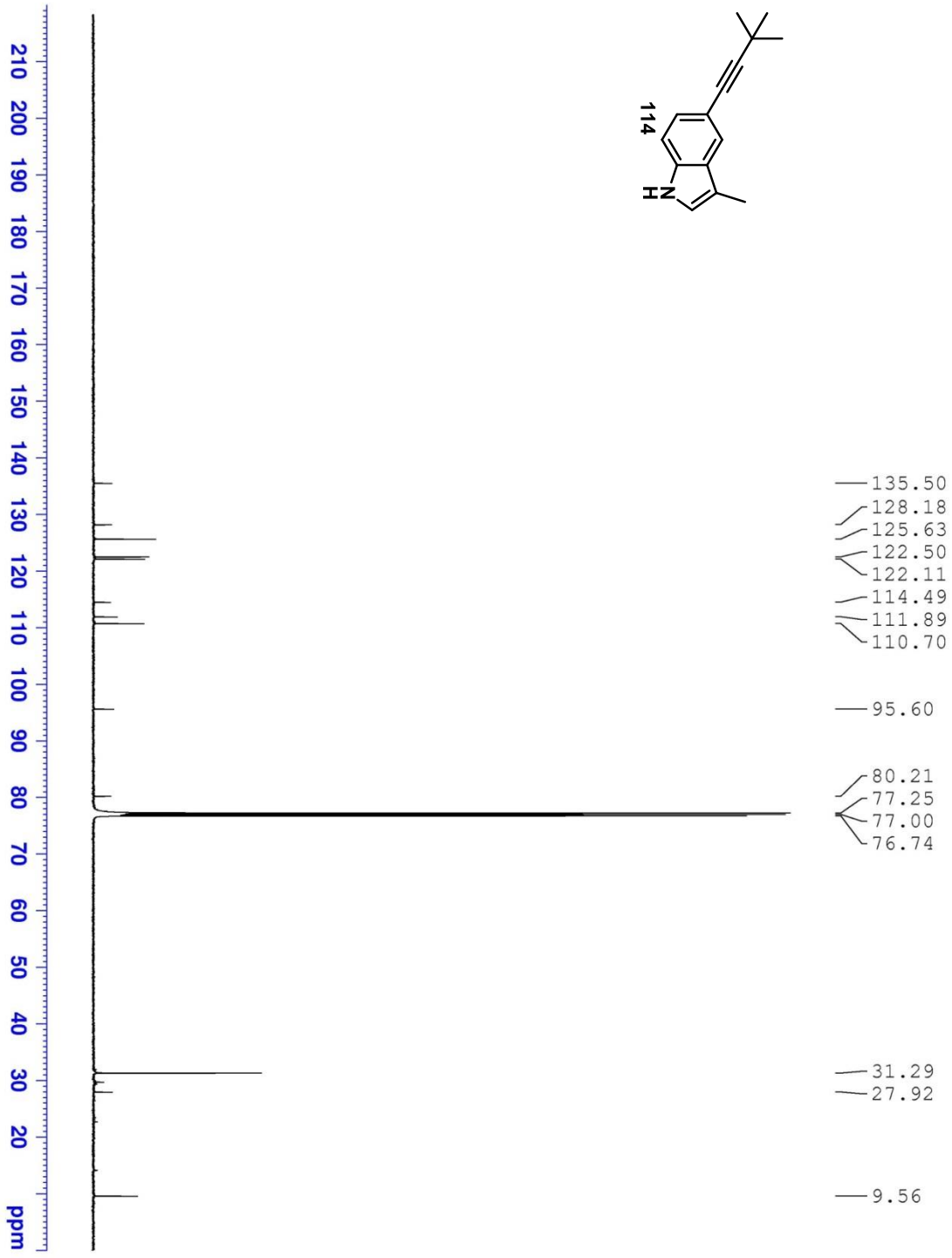

THPO
112
N
H
7.911
7.577
7.326
7.310
7.260
7.229
7.227
7.212
7.210
6.968
4.910
4.888
4.753
4.747
4.739
4.635
4.612
4.009
3.998
3.992
3.987
3.976
3.969
3.590
3.579
3.567
2.331
2.330
1.887
1.878
1.869
1.862
1.735
1.728
1.721
1.716
1.709
1.660
1.651
1.644
1.634
1.625
1.617
1.608
1.600
1.592
1.582
1.577
1.569
1.559
1.543
1.533
1.521
1.508
1.00
1.00
1.03
1.01
1.01
1.02
1.01
1.08
1.04
1.05
3.07
1.08
1.17
4.40
10
9
8
7
6
5
4
3
2
1
ppm

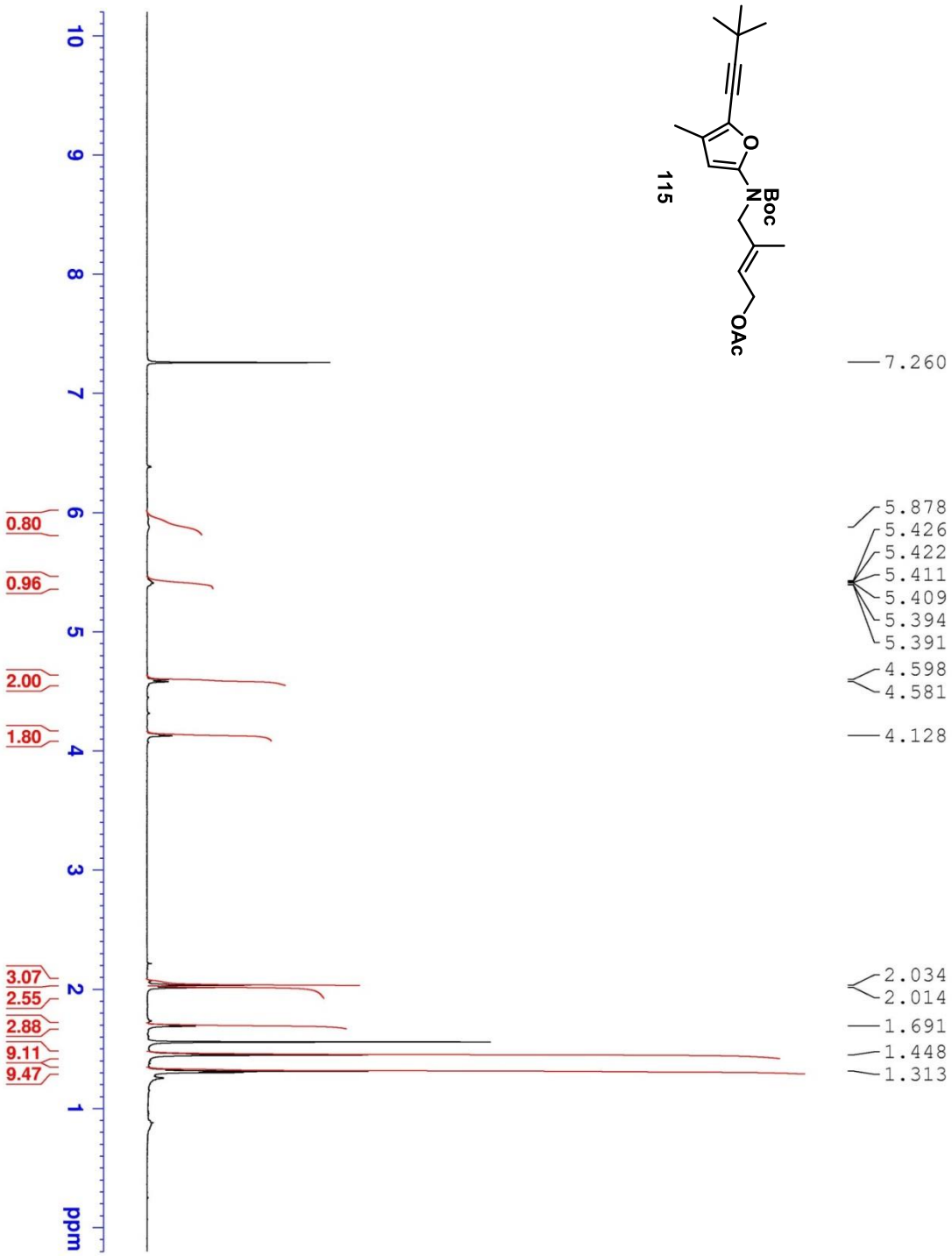

THPO
112
N
H
135.92
128.75
128.28
122.79
121.95
118.96
111.84
110.84
97.24
77.25
77.00
76.75
69.73
62.20
30.68
25.56
19.50
9.64
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

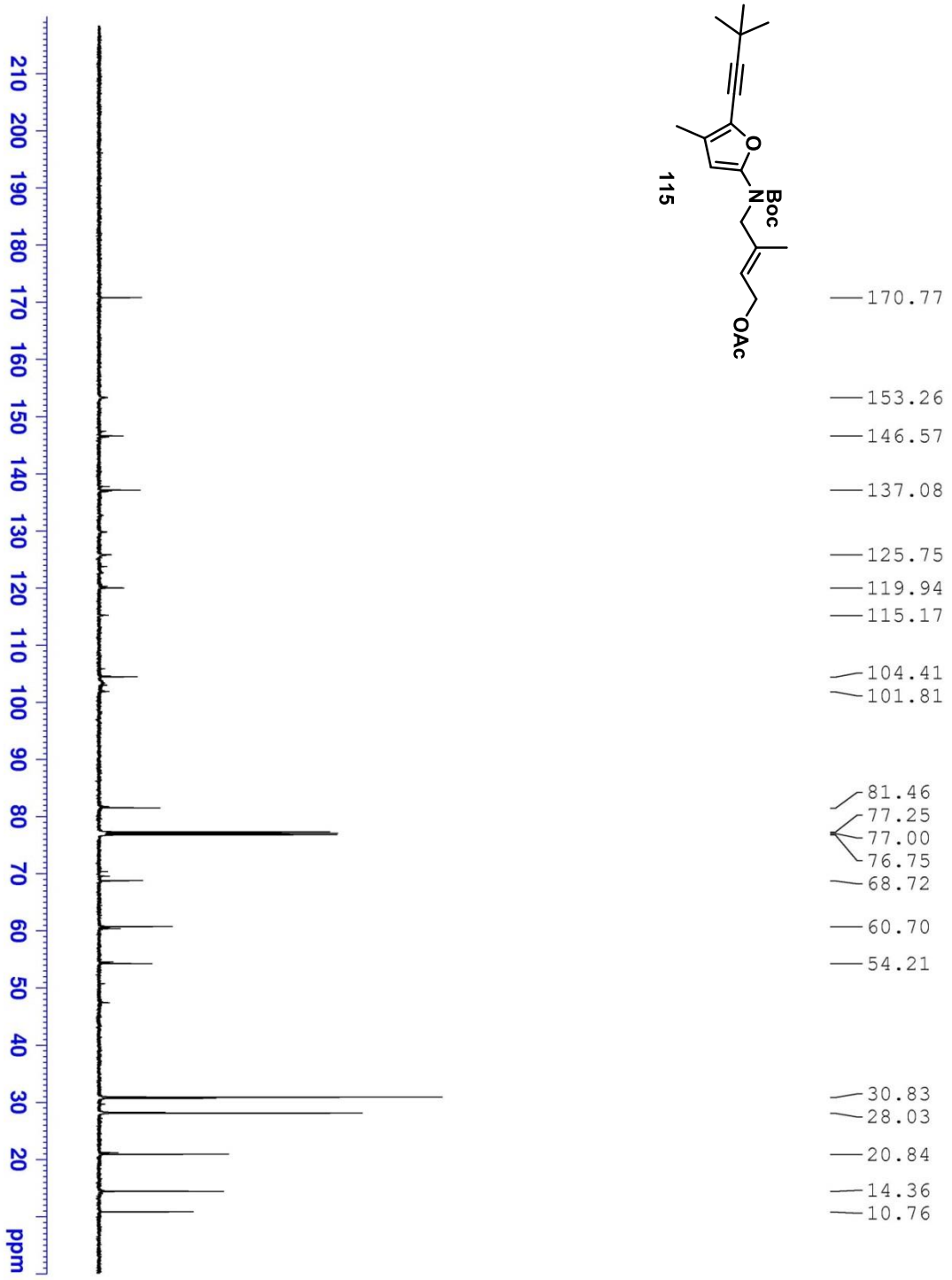

113
Boc
N
O
OAc
7.260
6.385
6.378
5.944
5.431
5.428
5.426
5.420
5.417
5.414
5.412
5.406
5.403
5.400
4.590
4.577
4.134
2.029
1.697
1.443
1.297
1.00
0.92
0.91
1.94
1.81
3.33
3.22
9.05
9.88
ppm

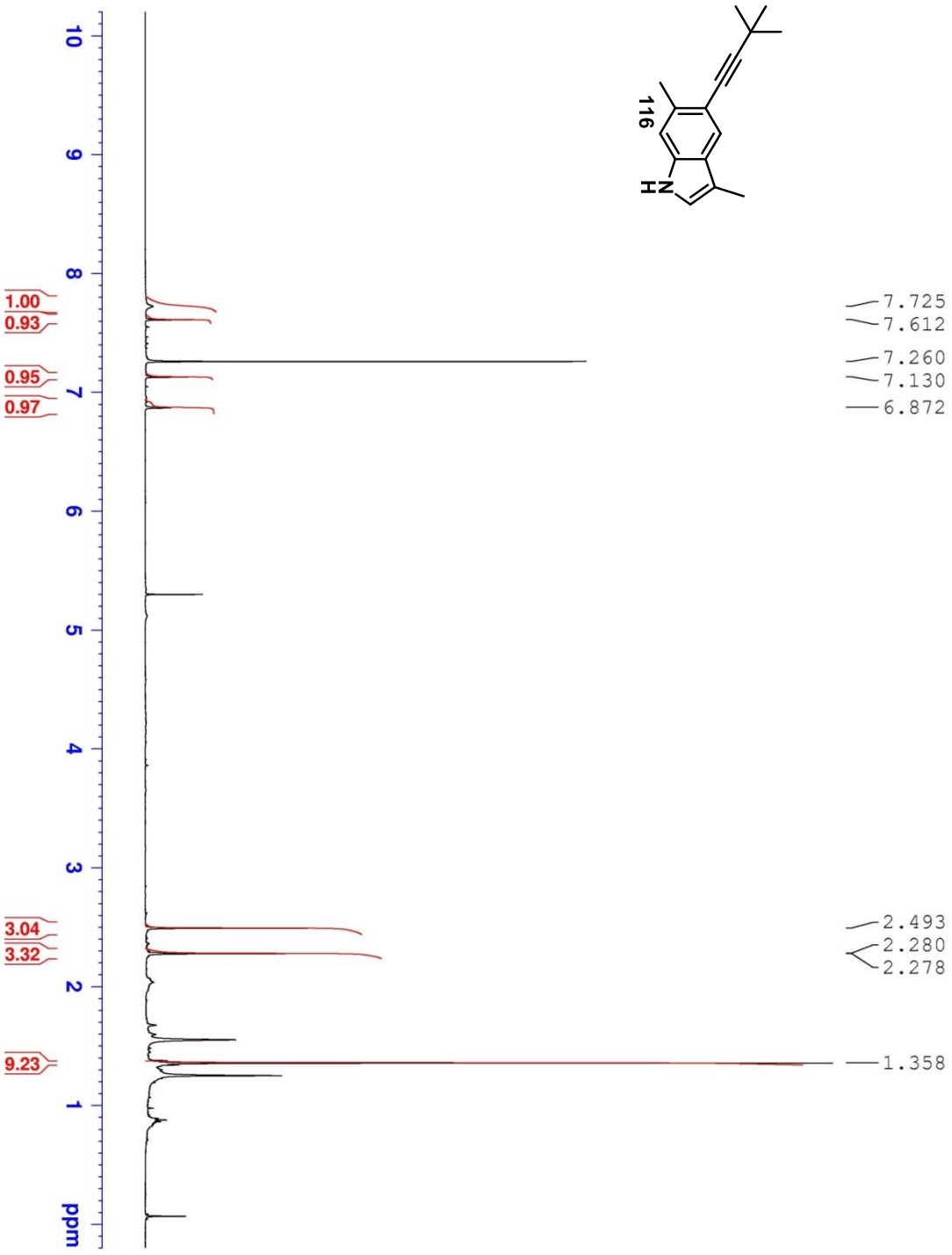

113
Boc
N
O
OAc
170.90
153.42
147.40
137.03
132.70
120.21
115.24
102.05
101.89
81.60
77.25
77.00
76.74
69.53
60.76
54.53
30.67
28.12
28.08
20.93
14.43
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

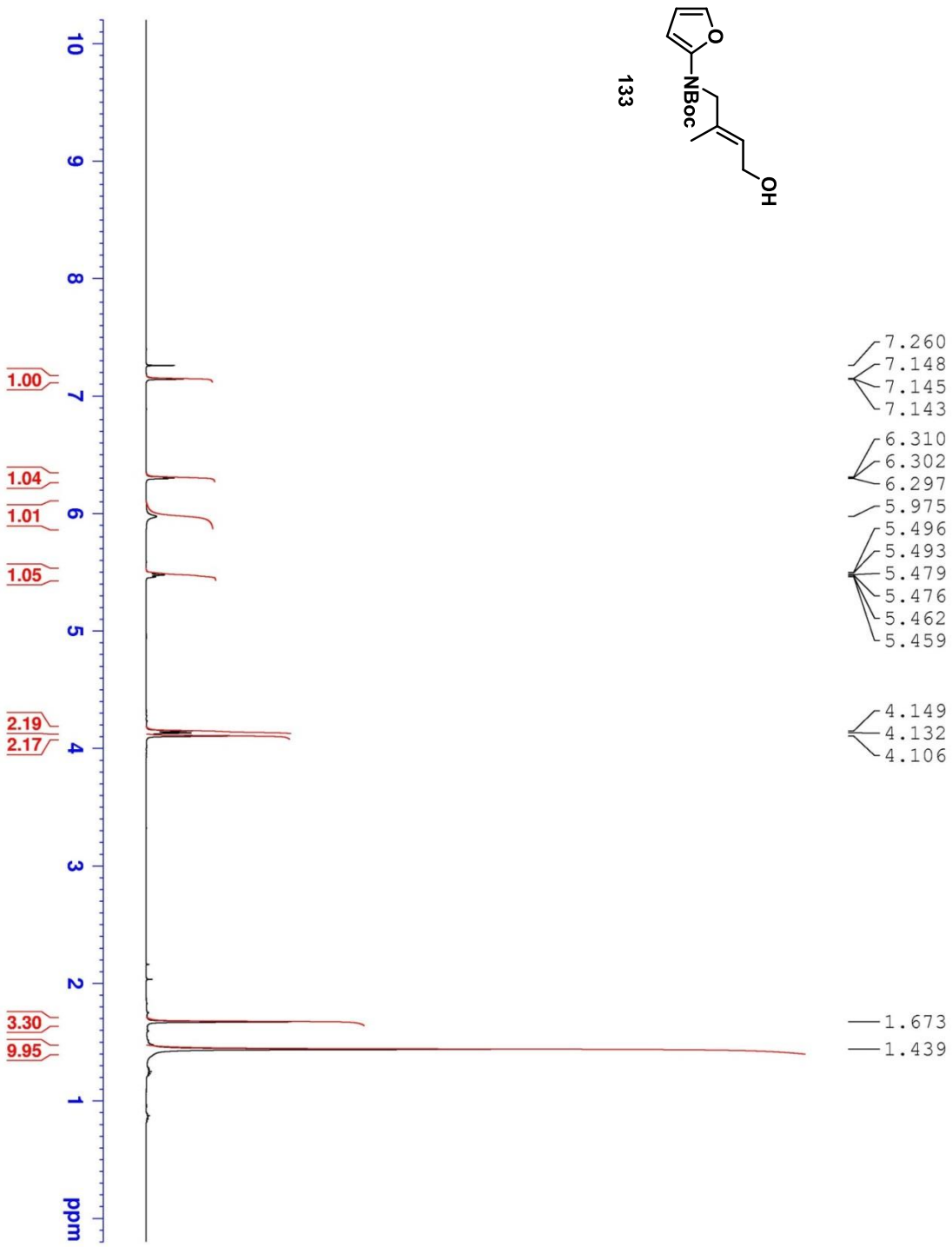

114
1.09
0.99
1.94
1.00
3.07
9.80
7.878
7.650
7.259
7.225
6.950
2.300
1.343
10
9
8
7
6
5
4
3
2
1
ppm

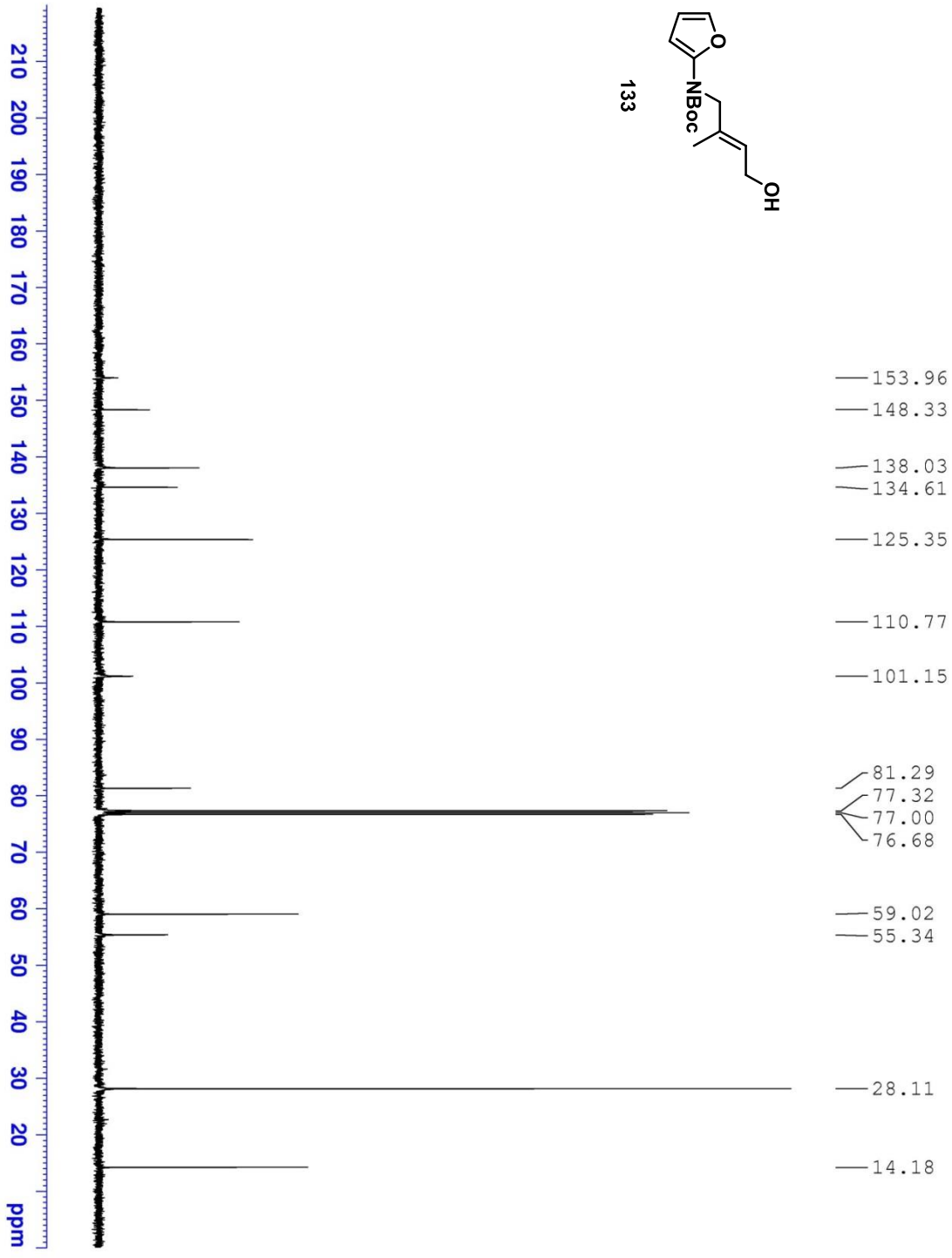

114
H
N
135.50
128.18
125.63
122.50
122.11
114.49
111.89
110.70
95.60
80.21
77.25
77.00
76.74
31.29
27.92
9.56
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

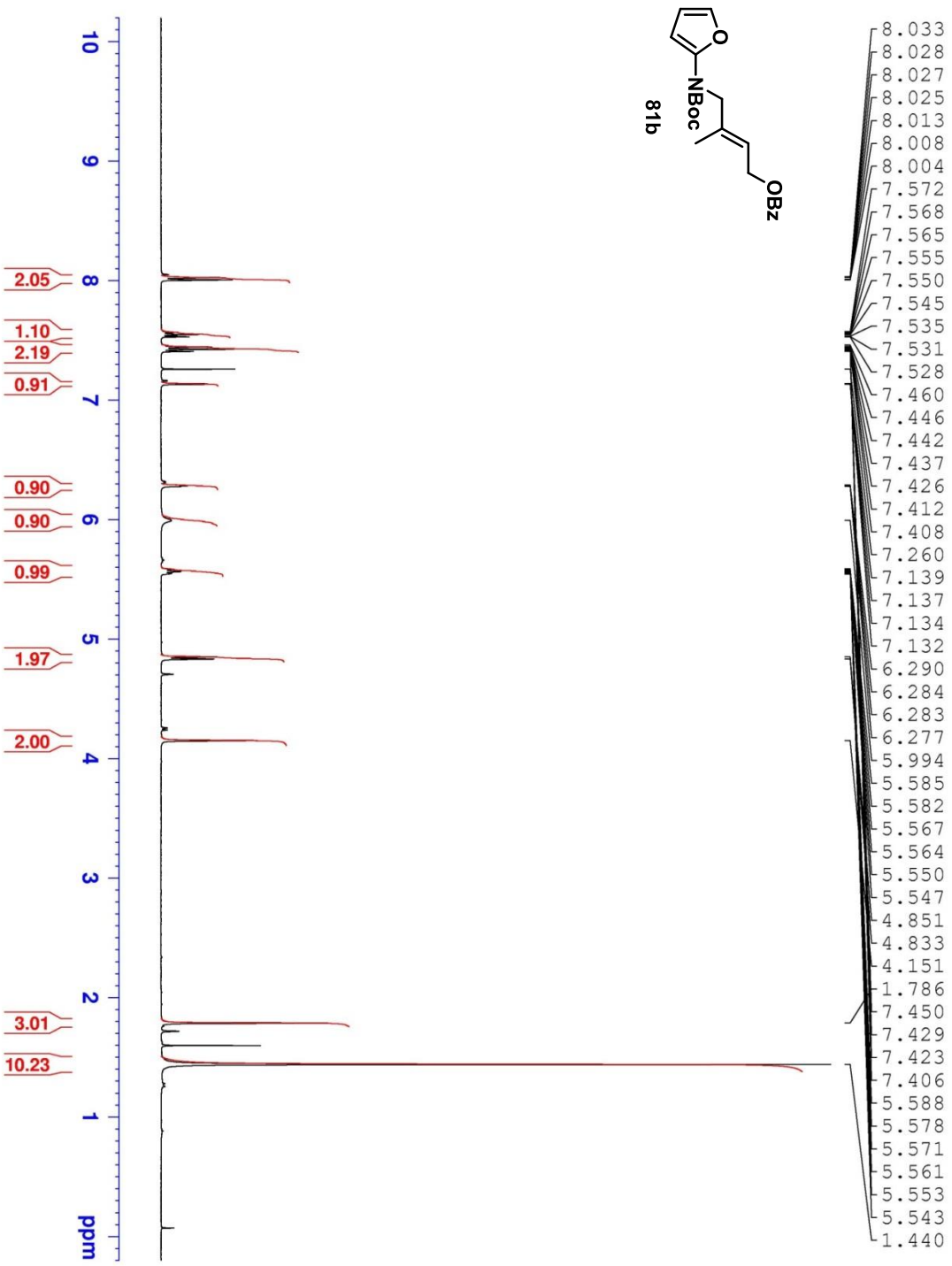

115
Boc
N
O
OAc
7.260
5.878
5.426
5.422
5.411
5.409
5.394
5.391
4.598
4.581
4.128
2.034
2.014
1.691
1.448
1.313
0.80
0.96
2.00
1.80
3.07
2.55
2.88
9.11
9.47
ppm

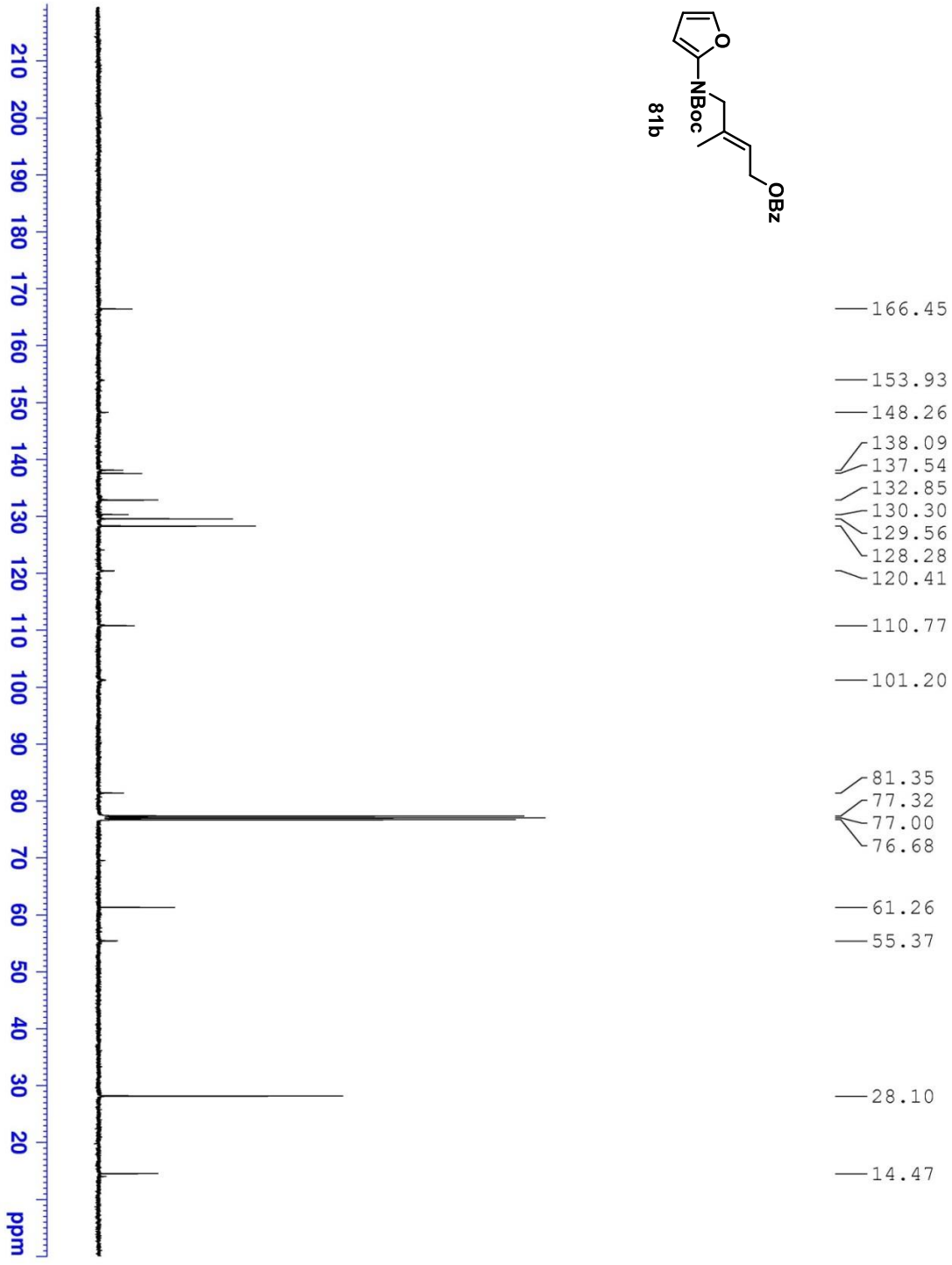

115
Boc
N
O
OAc
170.77
153.26
146.57
137.08
125.75
119.94
115.17
104.41
101.81
81.46
77.25
77.00
76.75
68.72
60.70
54.21
30.83
28.03
20.84
14.36
10.76
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

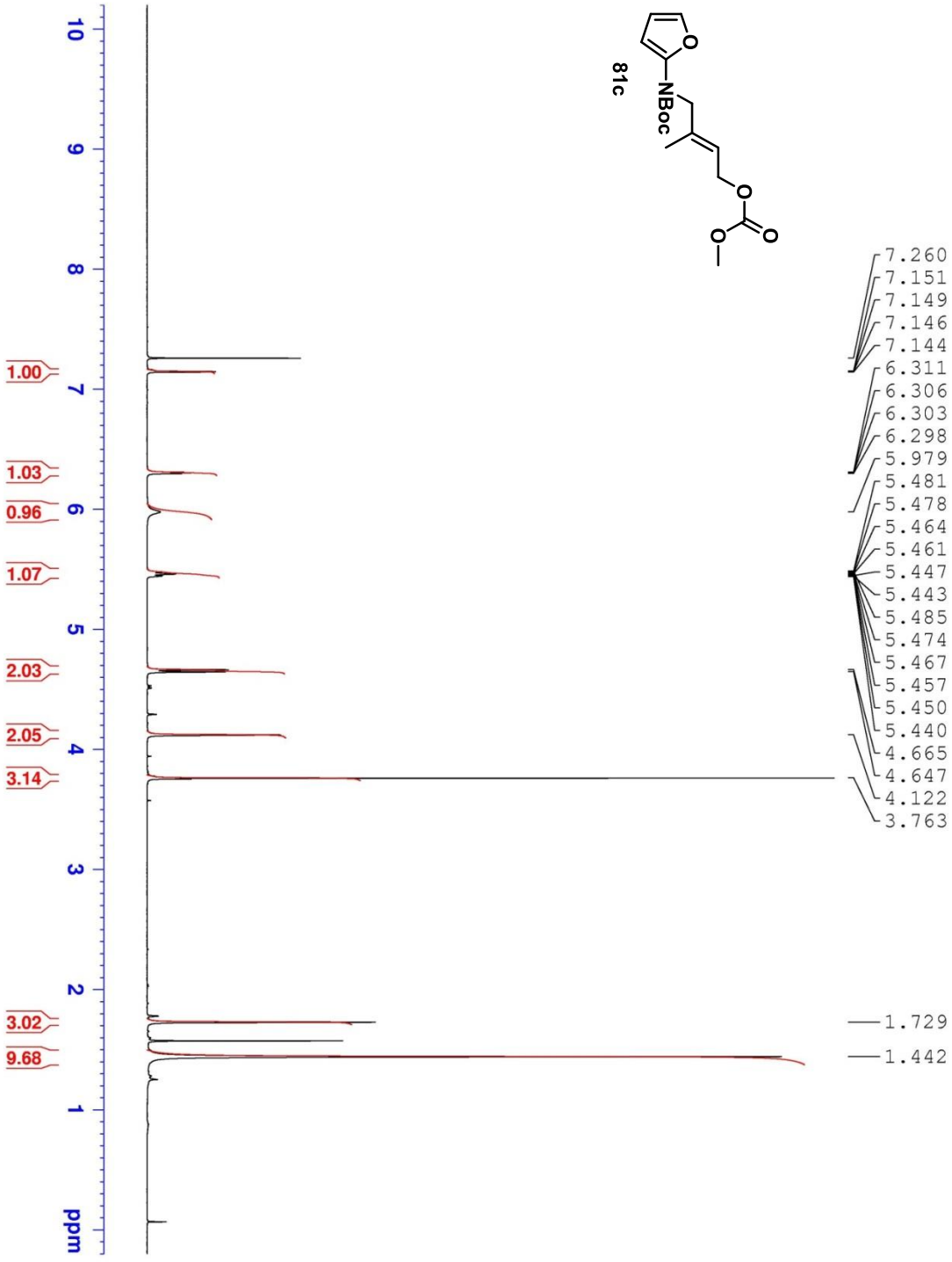

116
H
N
1.00
0.93
0.95
0.97
3.04
3.32
9.23
7.725
7.612
7.260
7.130
6.872
2.493
2.280
2.278
1.358
10
9
8
7
6
5
4
3
2
1
ppm

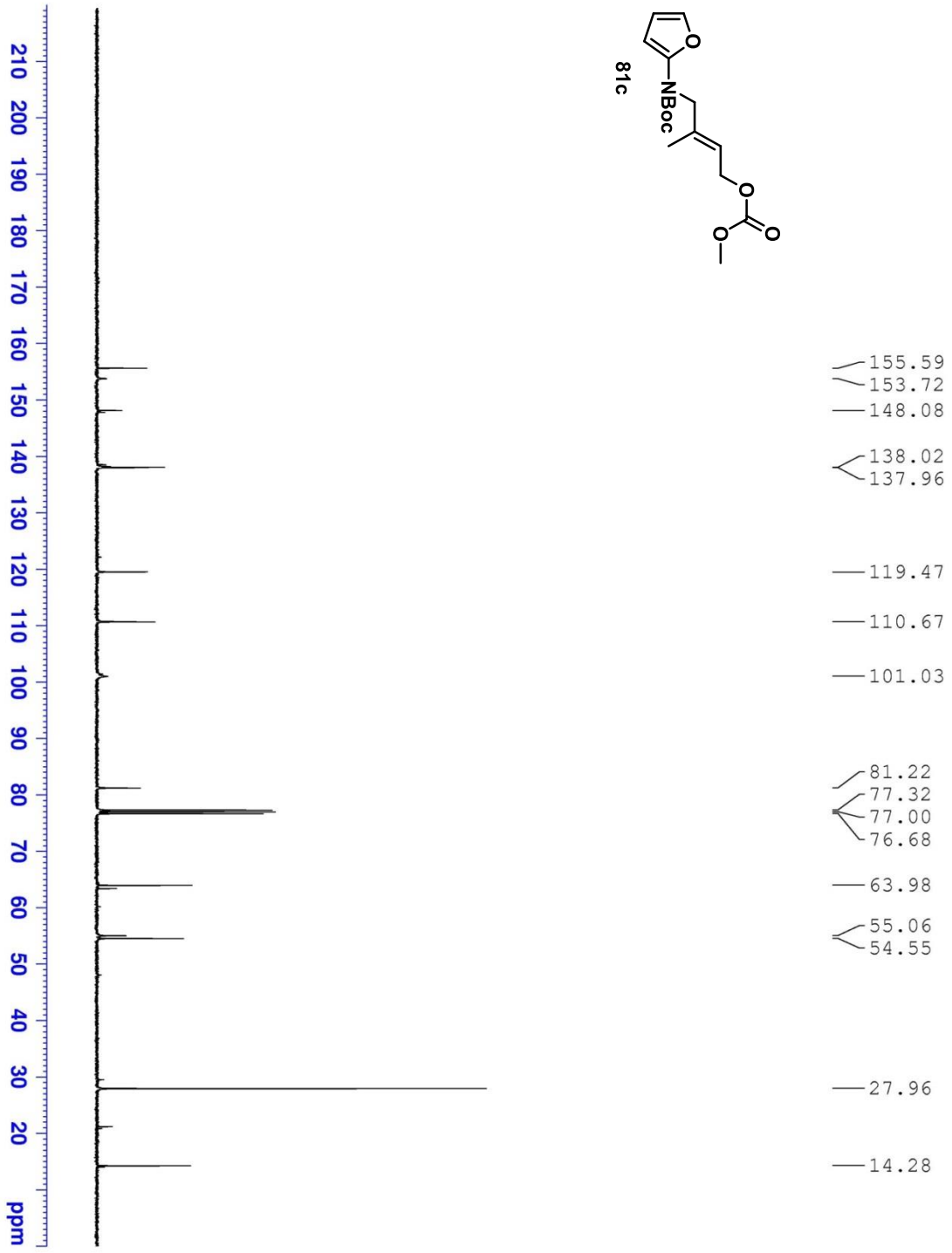

133
NBoc
OH
7.260
7.148
7.145
7.143
6.310
6.302
6.297
5.975
5.496
5.493
5.479
5.476
5.462
5.459
4.149
4.132
4.106
1.673
1.439
1.00
1.04
1.01
1.05
2.19
2.17
3.30
9.95
ppm

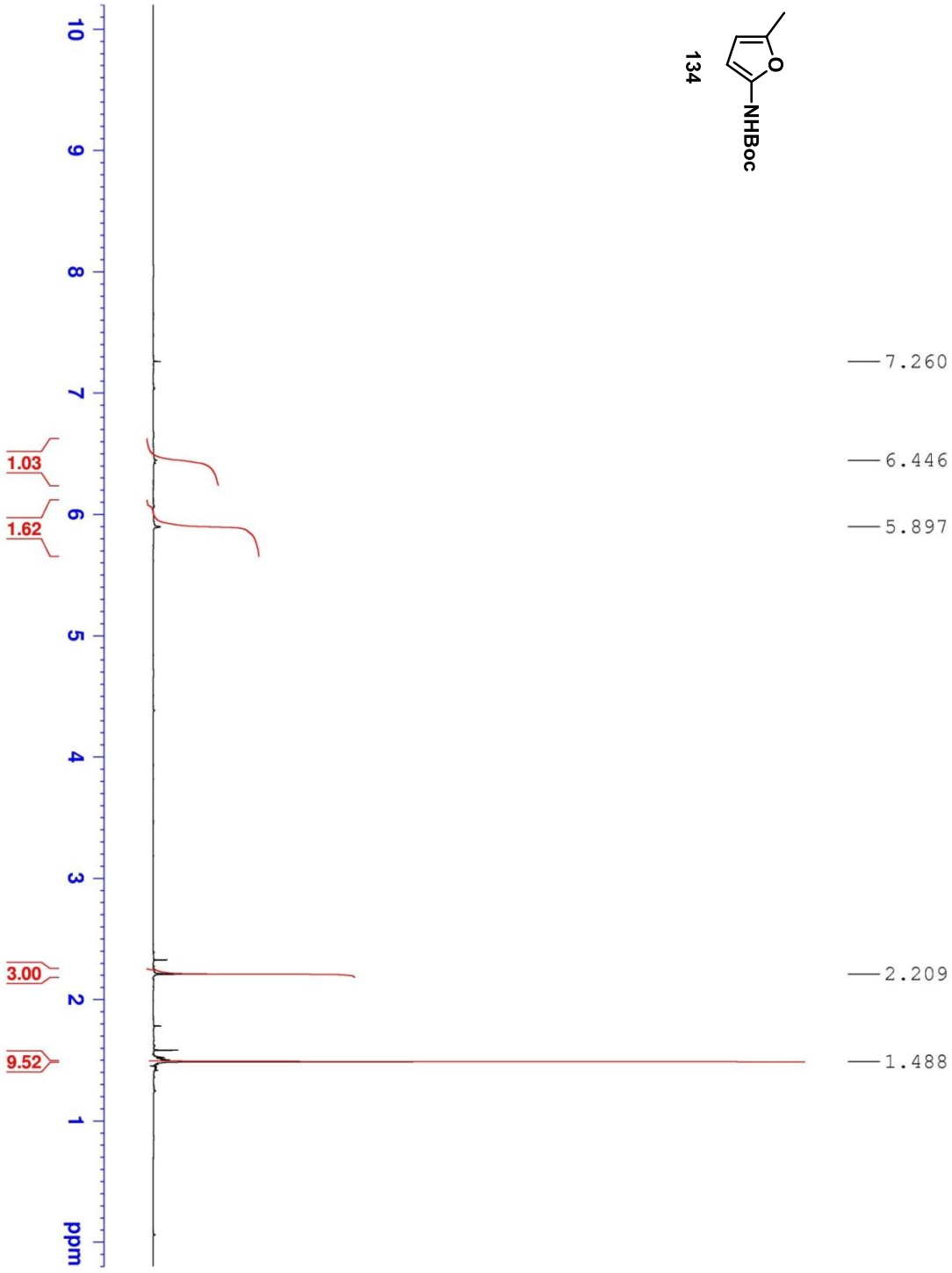

133
NBoc
OH
153.96
148.33
138.03
134.61
125.35
110.77
101.15
81.29
77.32
77.00
76.68
59.02
55.34
28.11
14.18
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

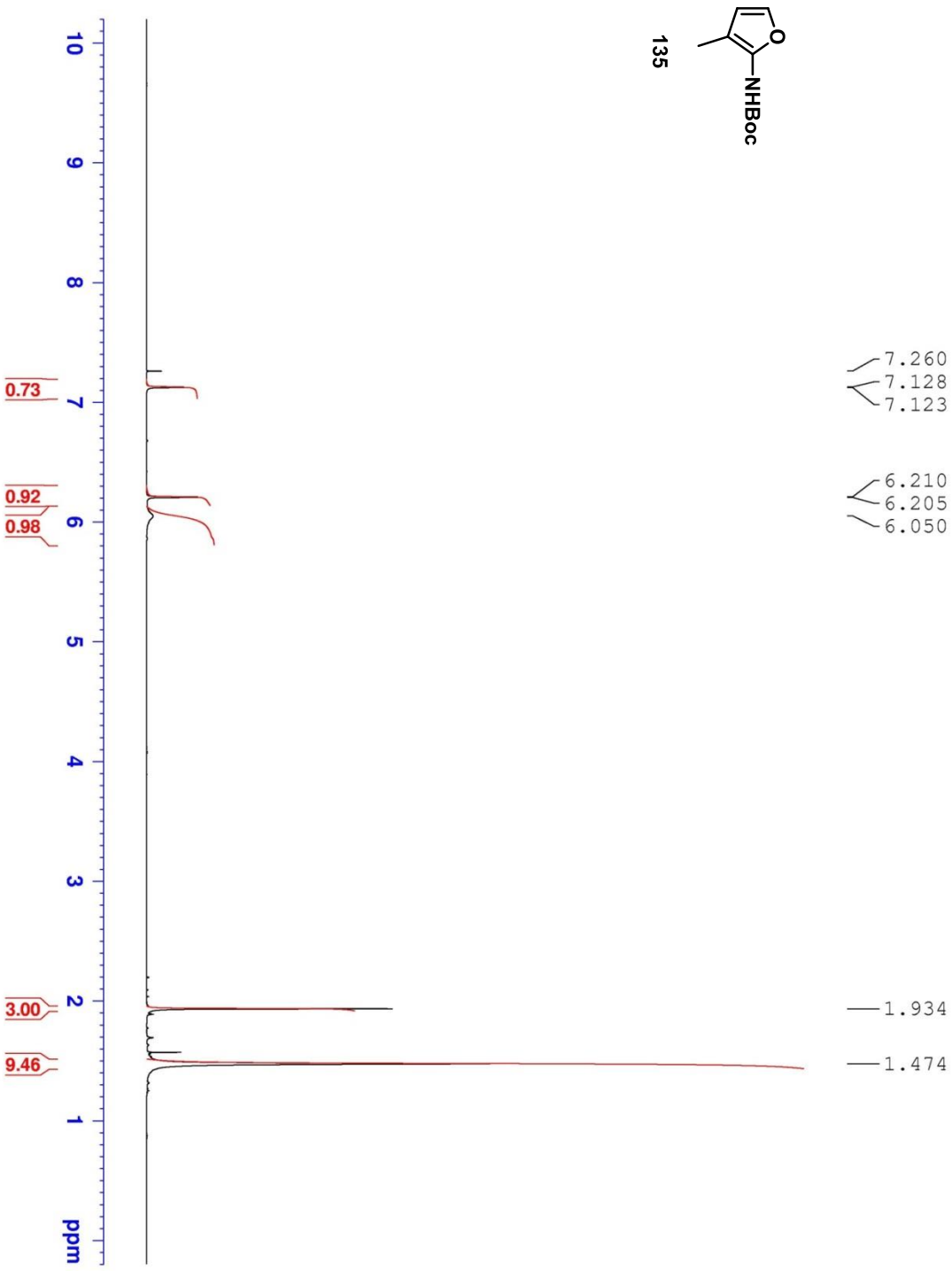

81b
NBoc
OBz
2.05
1.10
2.19
0.91
0.90
0.90
0.99
1.97
2.00
3.01
10.23
ppm
8.033
8.028
8.027
8.025
8.013
8.008
8.004
7.572
7.568
7.565
7.555
7.550
7.545
7.535
7.531
7.528
7.460
7.446
7.442
7.437
7.426
7.412
7.408
7.260
7.139
7.137
7.134
7.132
6.290
6.284
6.283
6.277
5.994
5.585
5.582
5.567
5.564
5.550
5.547
4.851
4.833
4.151
1.786
7.450
7.429
7.423
7.406
5.588
5.578
5.571
5.561
5.553
5.543
1.440

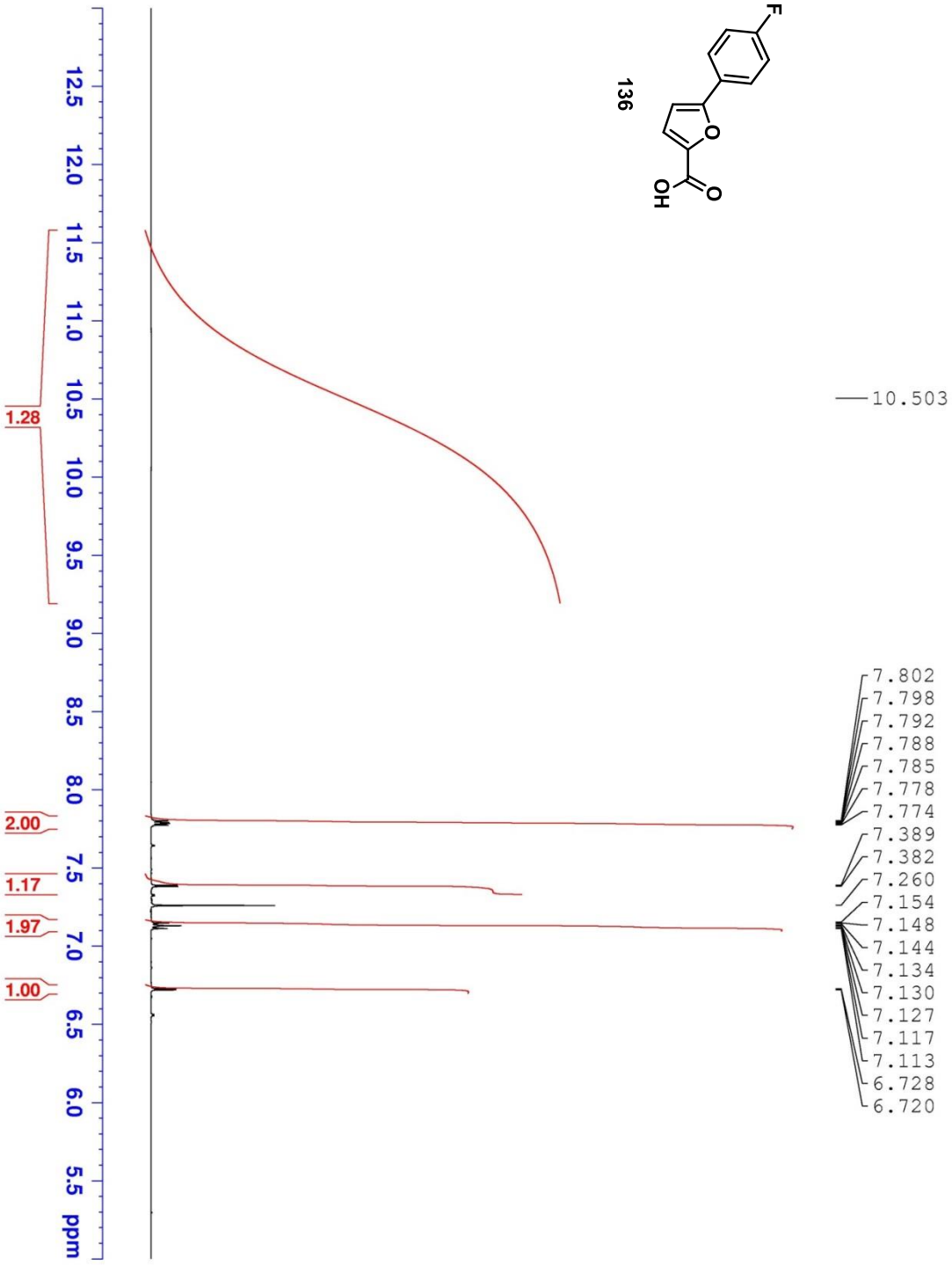

81b
NBoc
OBz
166.45
153.93
148.26
138.09
137.54
132.85
130.30
129.56
128.28
120.41
110.77
101.20
81.35
77.32
77.00
76.68
61.26
55.37
28.10
14.47
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

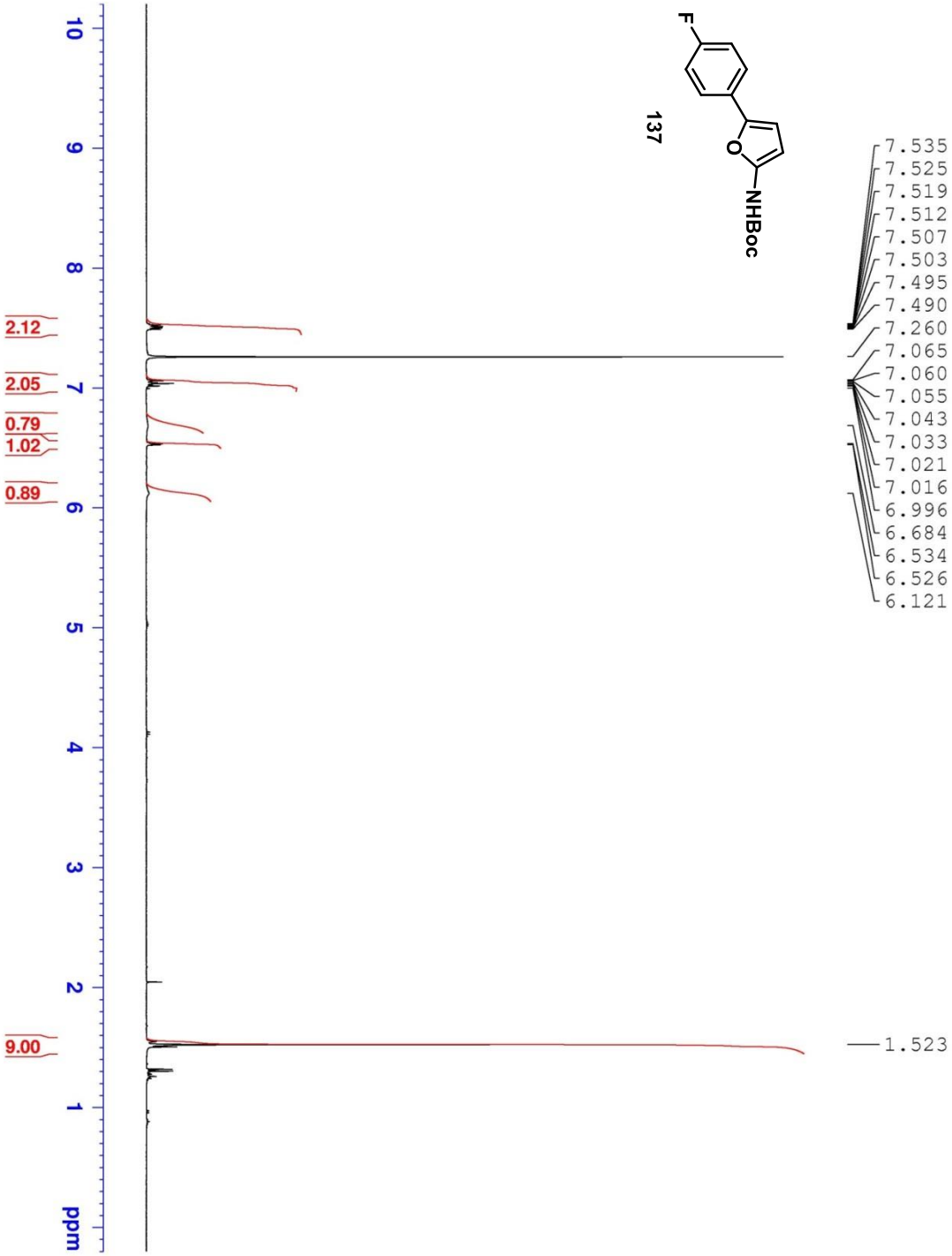

81c
NBoc
O
O
O
O
O
7.260
7.151
7.149
7.146
7.144
6.311
6.306
6.303
6.298
5.979
5.481
5.478
5.464
5.461
5.447
5.443
5.485
5.474
5.467
5.457
5.450
5.440
4.665
4.647
4.122
3.763
1.729
1.442
1.00
1.03
0.96
1.07
2.03
2.05
3.14
3.02
9.68
10
9
8
7
6
5
4
3
2
1
ppm

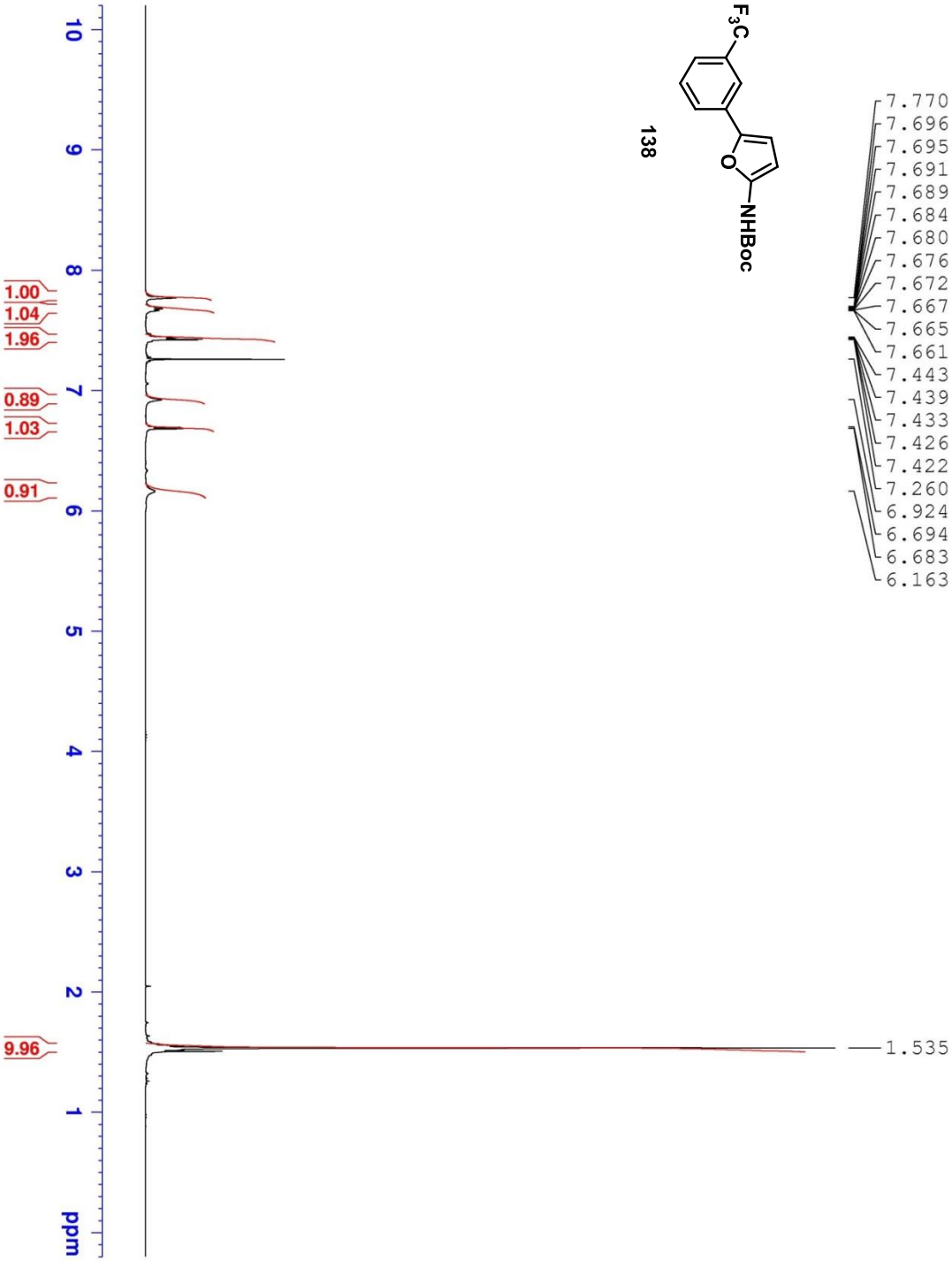

81c
NBoc
155.59
153.72
148.08
138.02
137.96
119.47
110.67
101.03
81.22
77.32
77.00
76.68
63.98
55.06
54.55
27.96
14.28
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

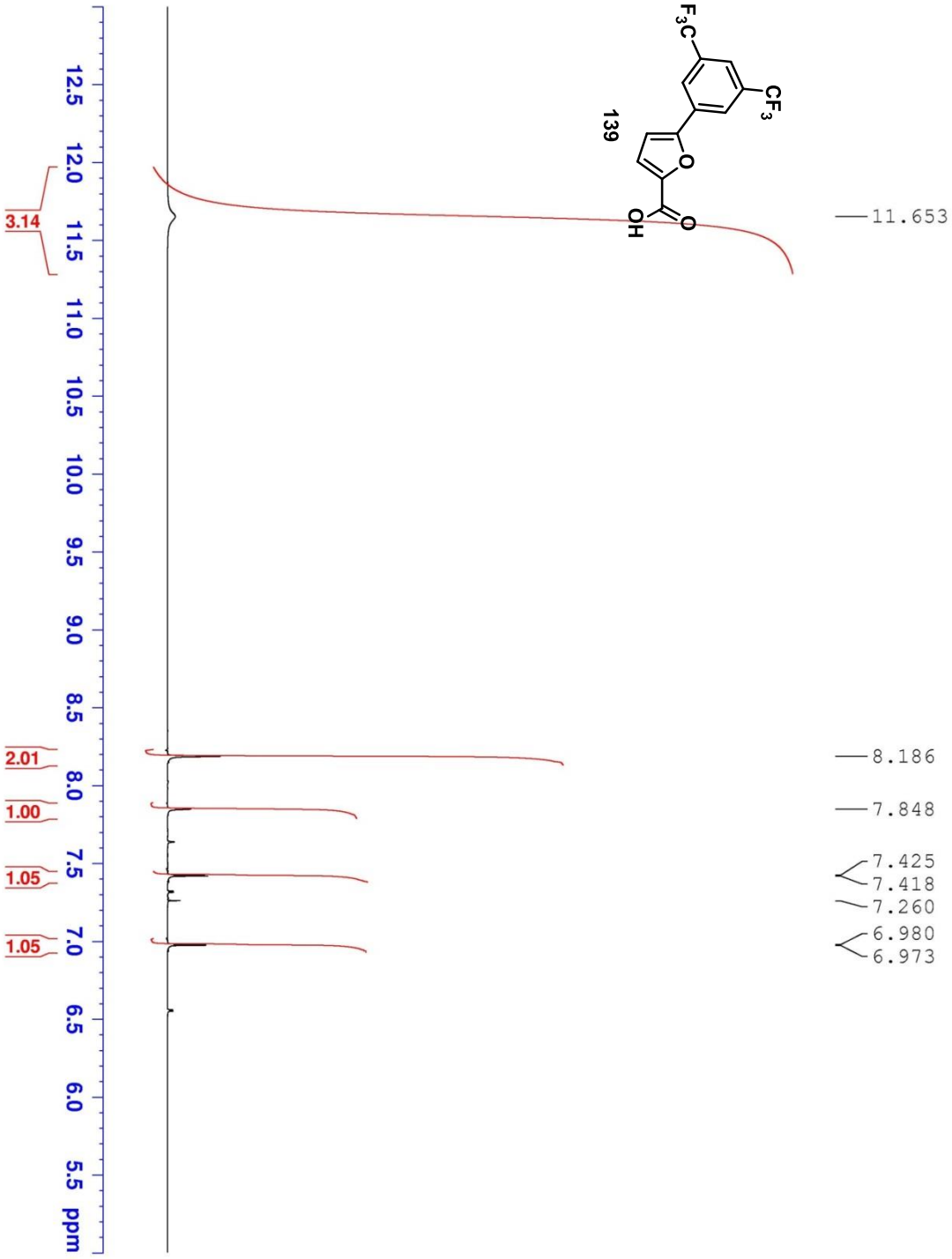

134
NHBoc
O
7.260
6.446
5.897
2.209
1.488
1.03
1.62
3.00
9.52
10
9
8
7
6
5
4
3
2
1
ppm

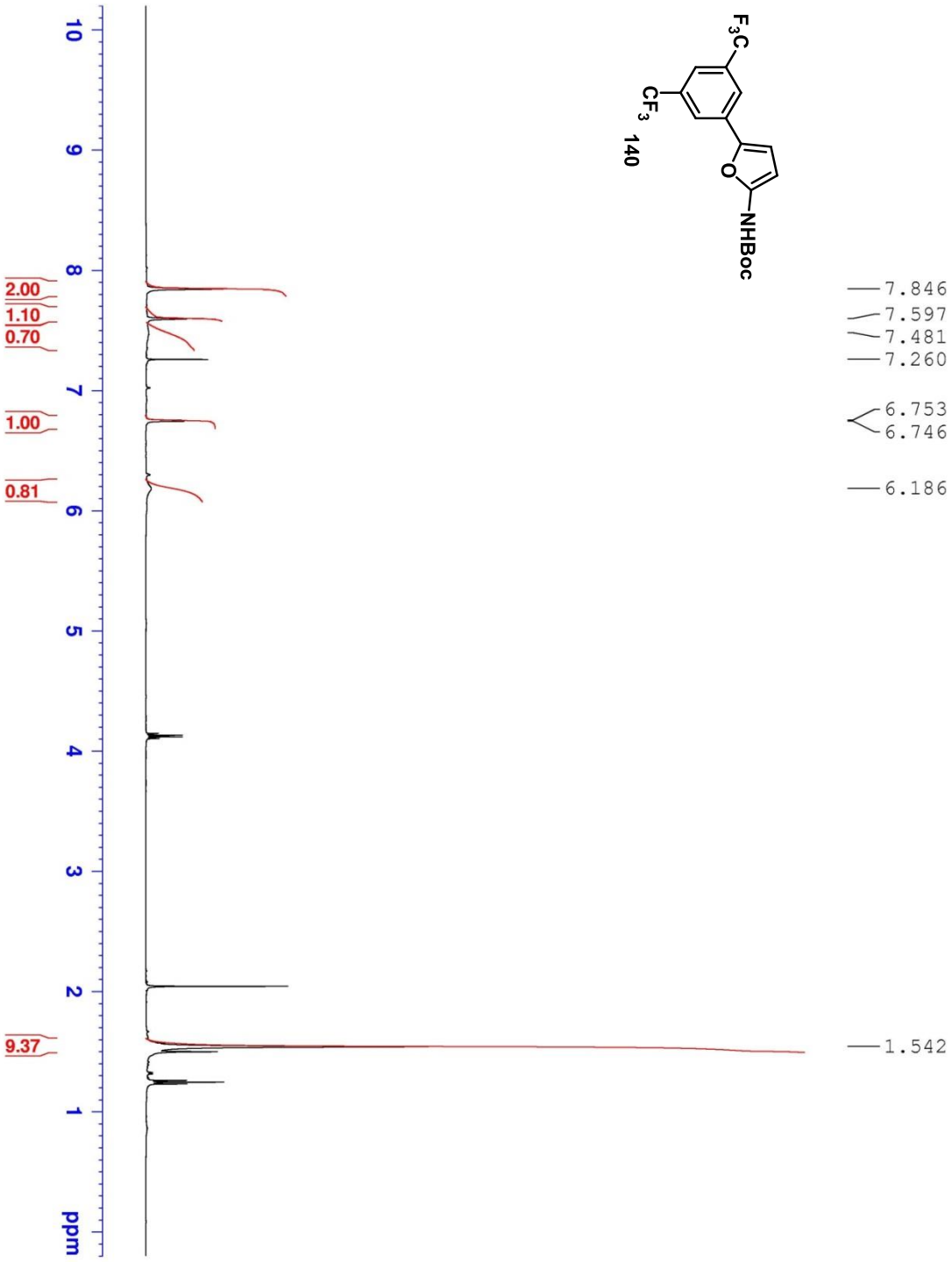

135
NHBoc
7.260
7.128
7.123
6.210
6.205
6.050
1.934
1.474
0.73
0.92
0.98
3.00
9.46
ppm

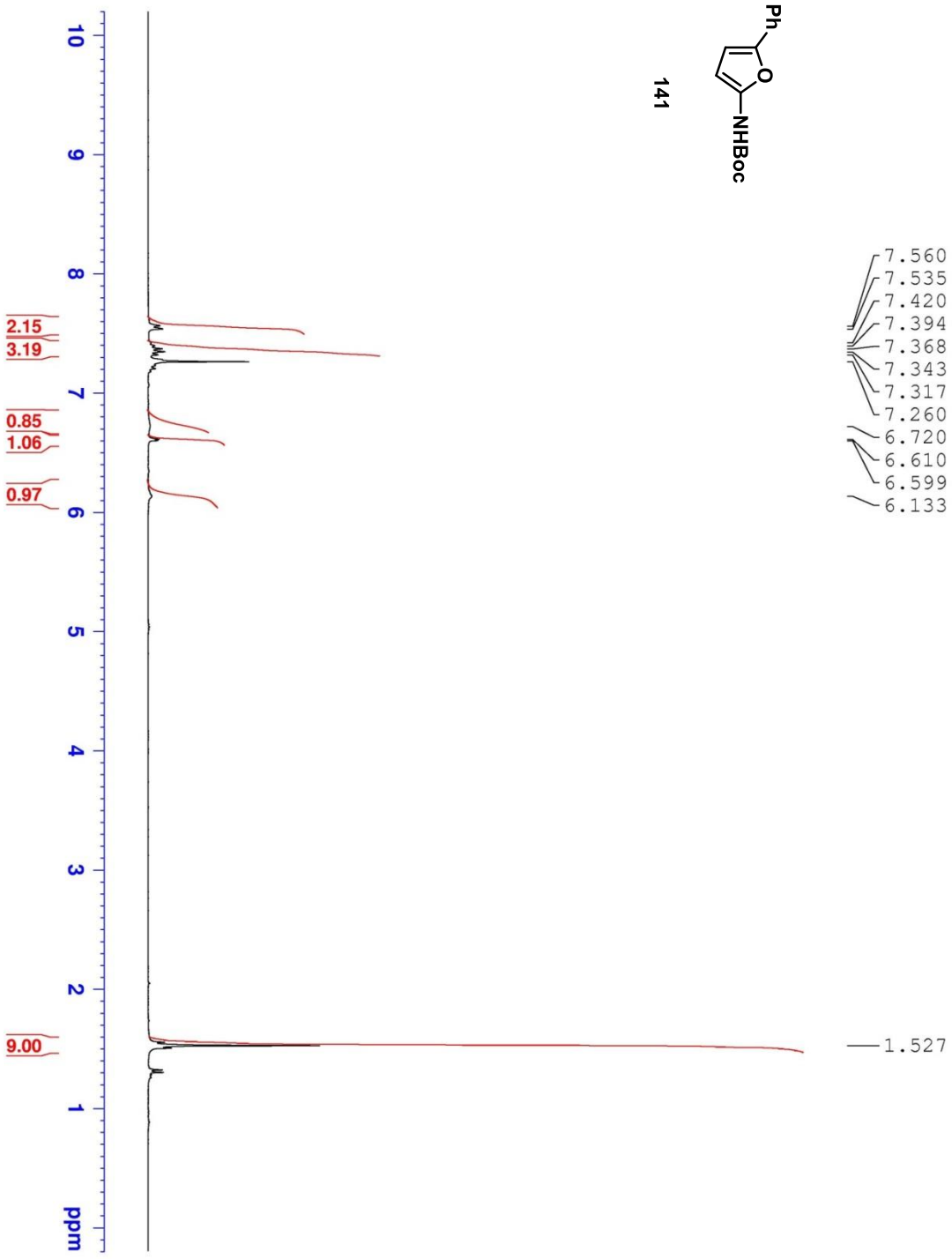

136
F
O
OH
O
10.503
7.802
7.798
7.792
7.788
7.785
7.778
7.774
7.389
7.382
7.260
7.154
7.148
7.144
7.134
7.130
7.127
7.117
7.113
6.728
6.720
1.28
2.00
1.17
1.97
1.00
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
ppm

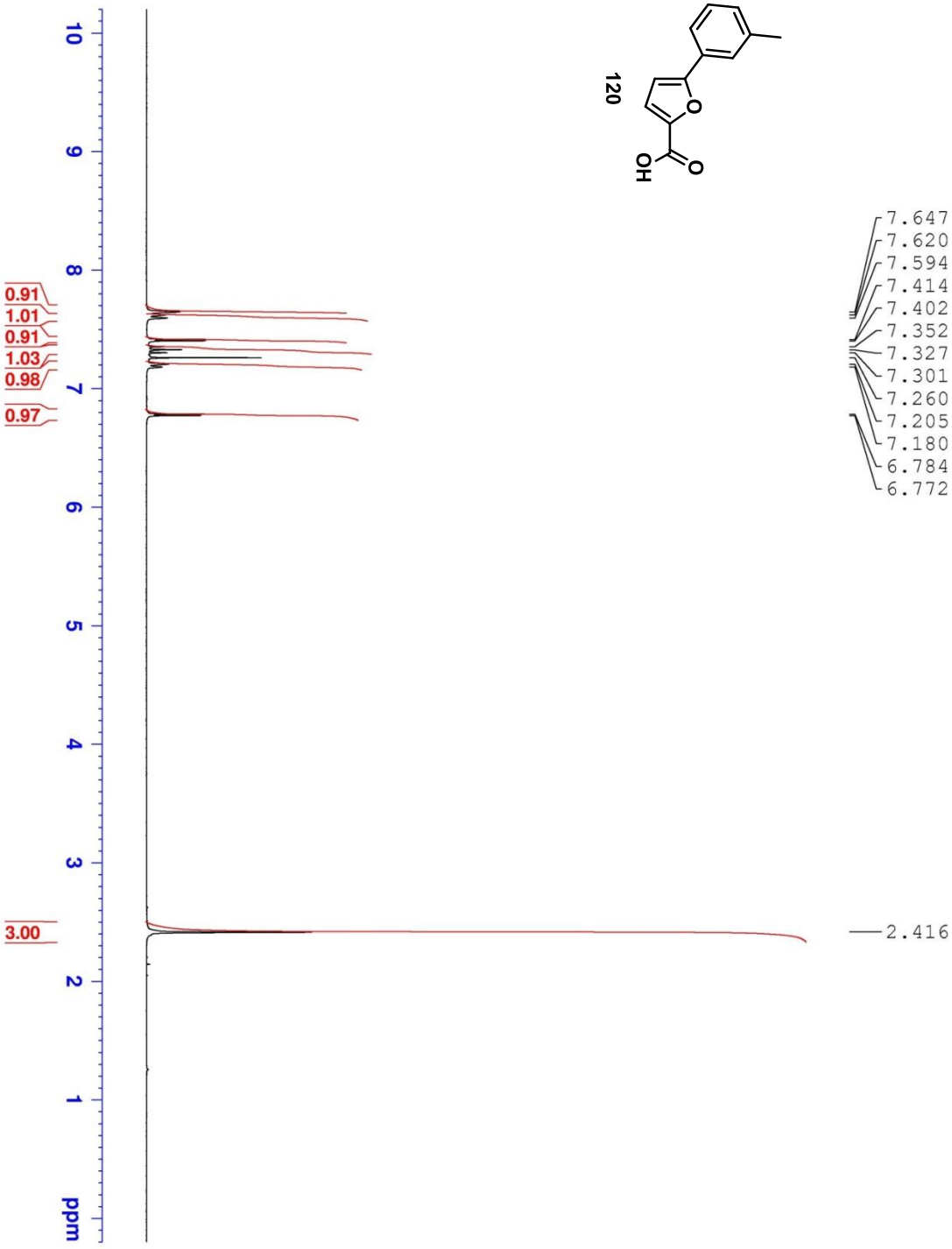

F
O
NHBoc
137
7.535
7.525
7.519
7.512
7.507
7.503
7.495
7.490
7.260
7.065
7.060
7.055
7.043
7.033
7.021
7.016
6.996
6.684
6.534
6.526
6.121
1.523
2.12
2.05
0.79
1.02
0.89
9.00
10
9
8
7
6
5
4
3
2
1
ppm

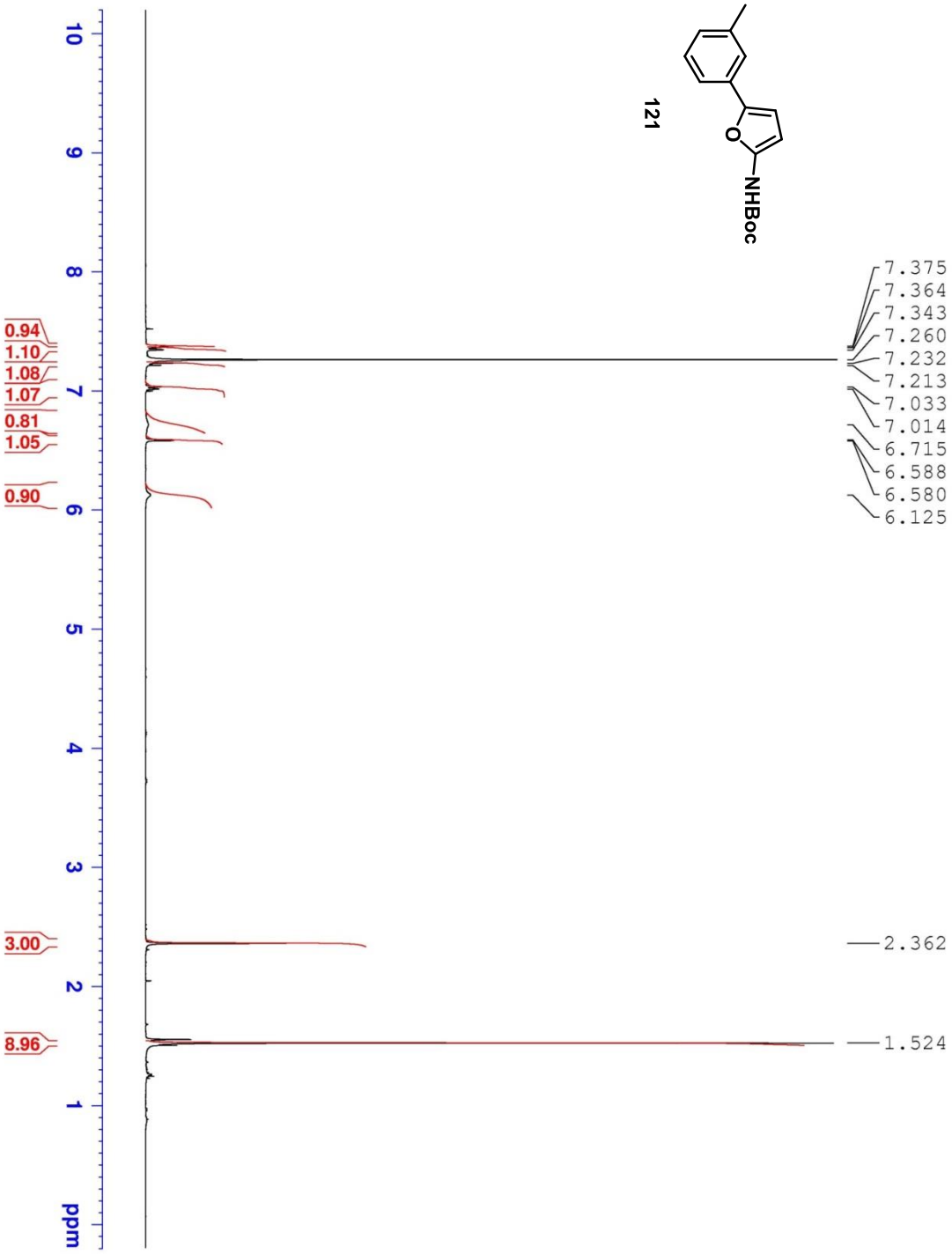

138
F3C
O
NHBoc
7.770
7.696
7.695
7.691
7.689
7.684
7.680
7.676
7.672
7.667
7.665
7.661
7.443
7.439
7.433
7.426
7.422
7.260
6.924
6.694
6.683
6.163
1.535
1.00
1.04
1.96
0.89
1.03
0.91
9.96
10
9
8
7
6
5
4
3
2
1
ppm

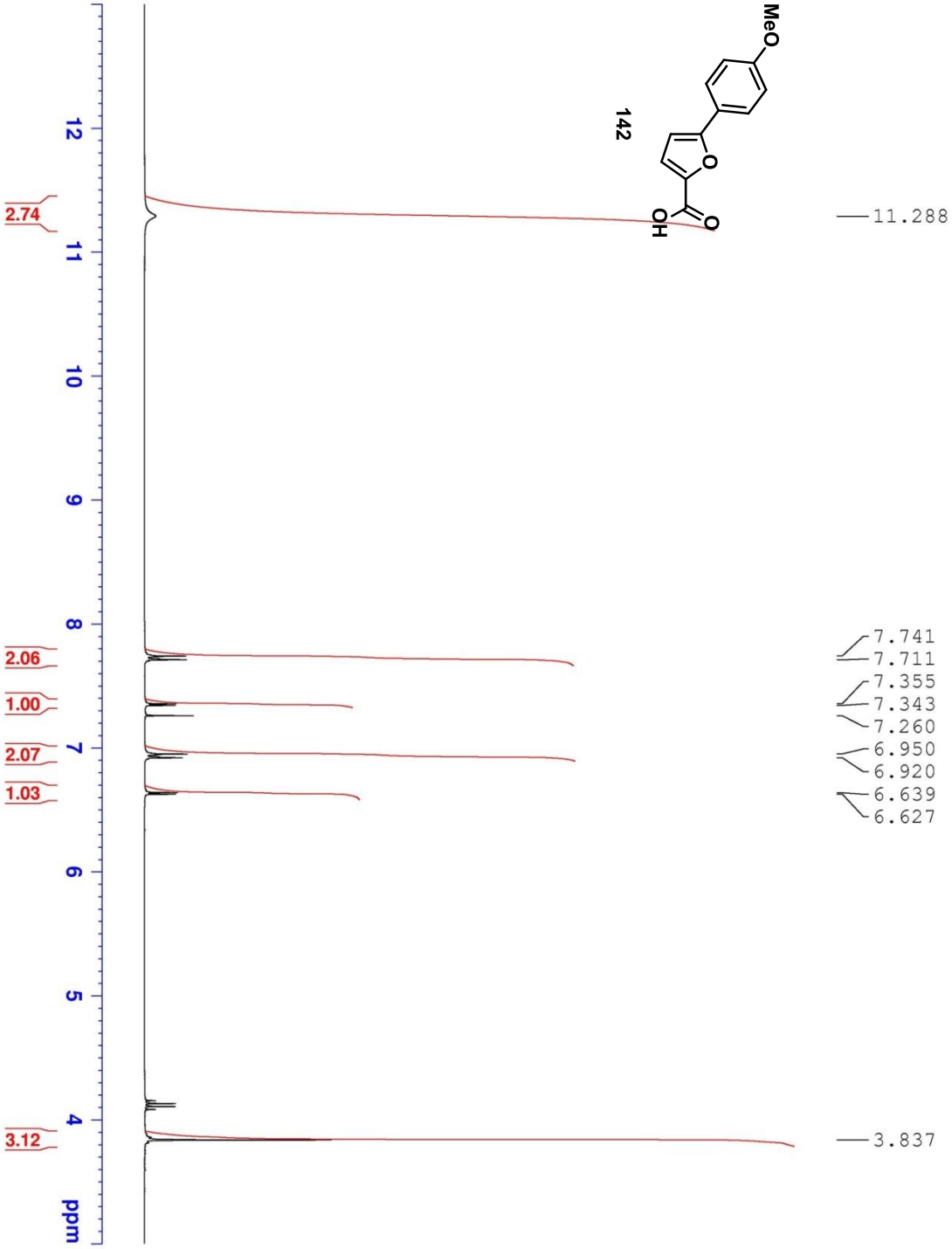

139
F3C
CF3
O
OH
O
11.653
8.186
7.848
7.425
7.418
7.260
6.980
6.973
3.14
2.01
1.00
1.05
1.05
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
ppm

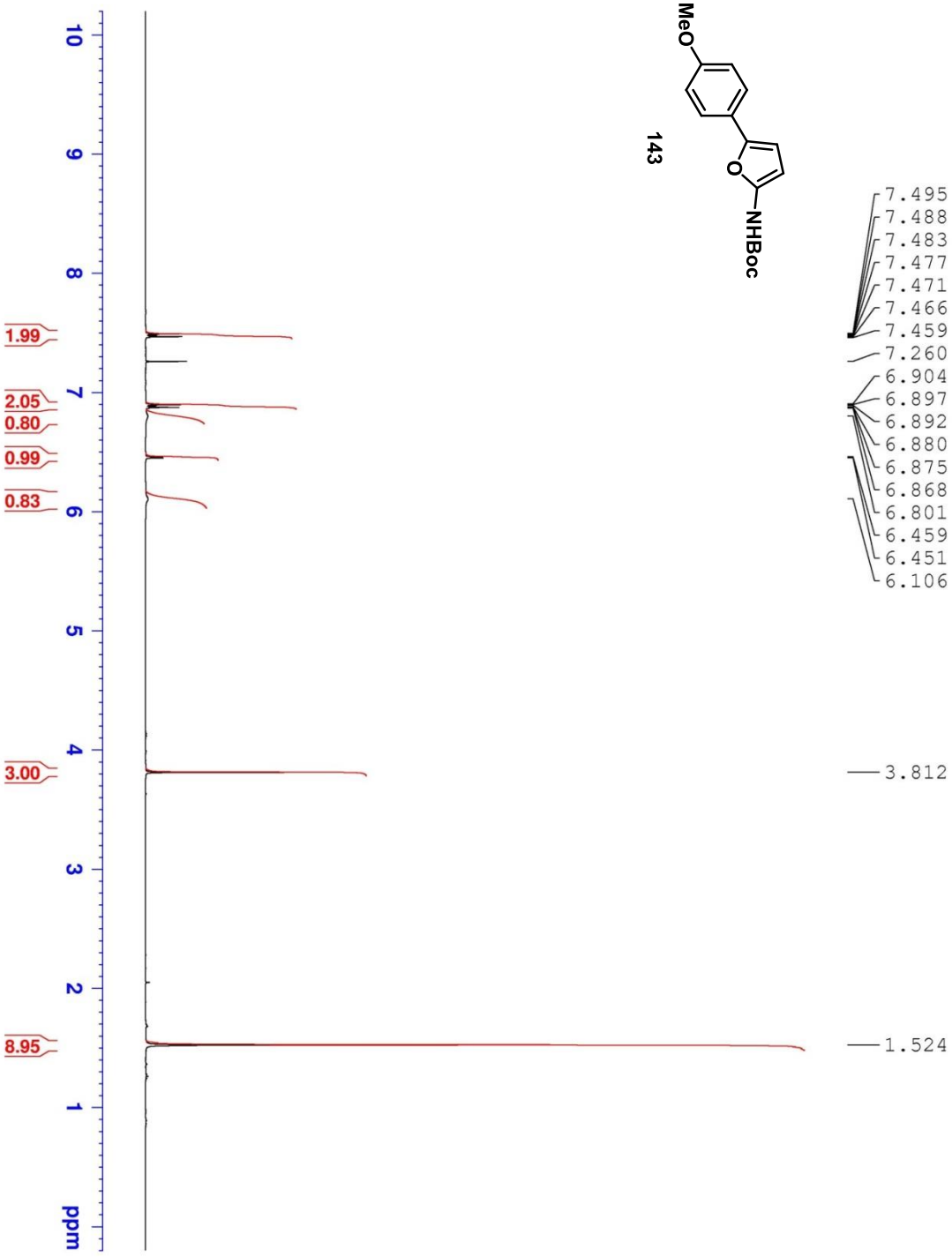

F3C
CF3
140
O
NHBoc
7.846
7.597
7.481
7.260
6.753
6.746
6.186
1.542
2.00
1.10
0.70
1.00
0.81
9.37
10
9
8
7
6
5
4
3
2
1
ppm

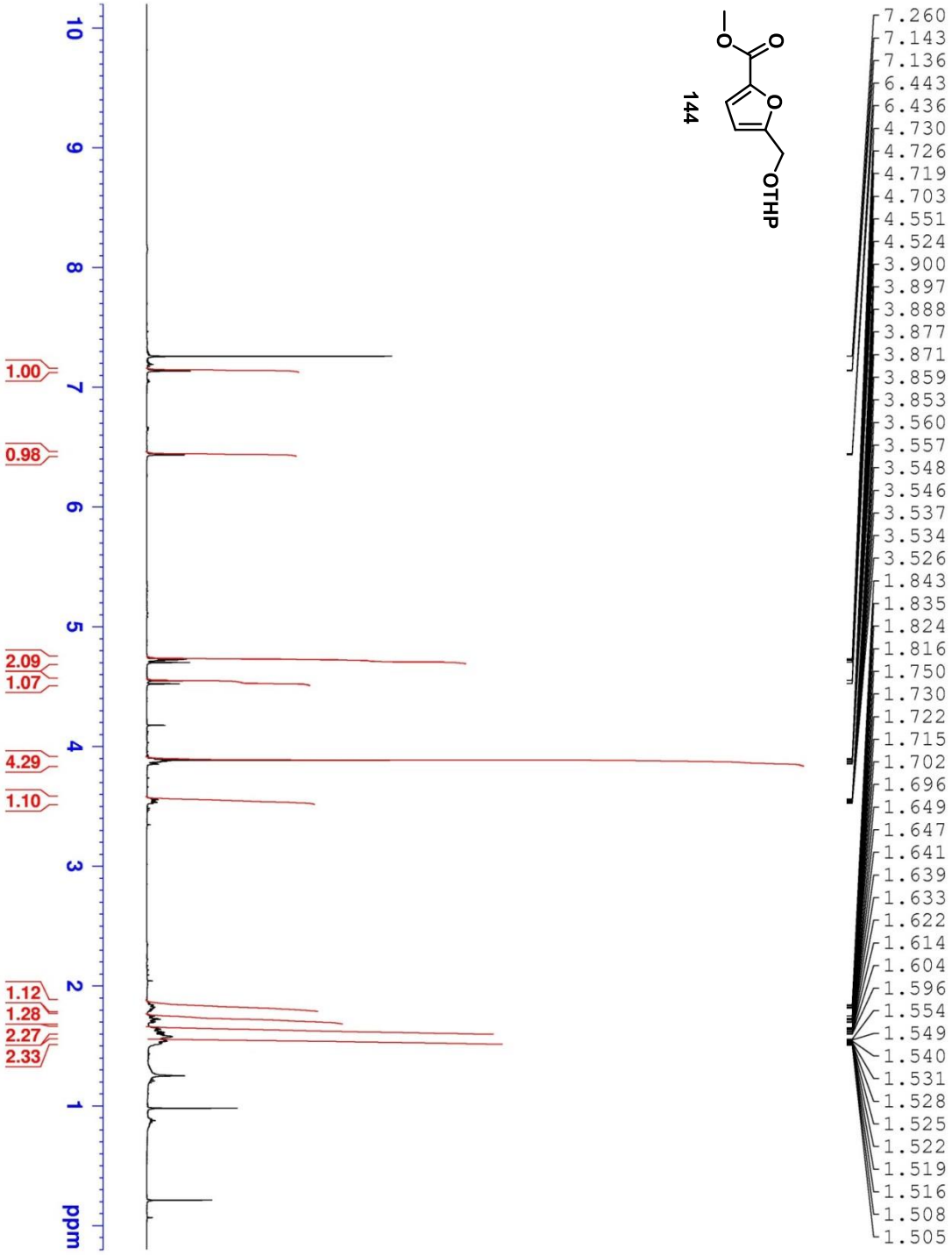

Ph
O
NHBoc
141
7.560
7.535
7.420
7.394
7.368
7.343
7.317
7.260
6.720
6.610
6.599
6.133
1.527
2.15
3.19
0.85
1.06
0.97
9.00
10
9
8
7
6
5
4
3
2
1
ppm

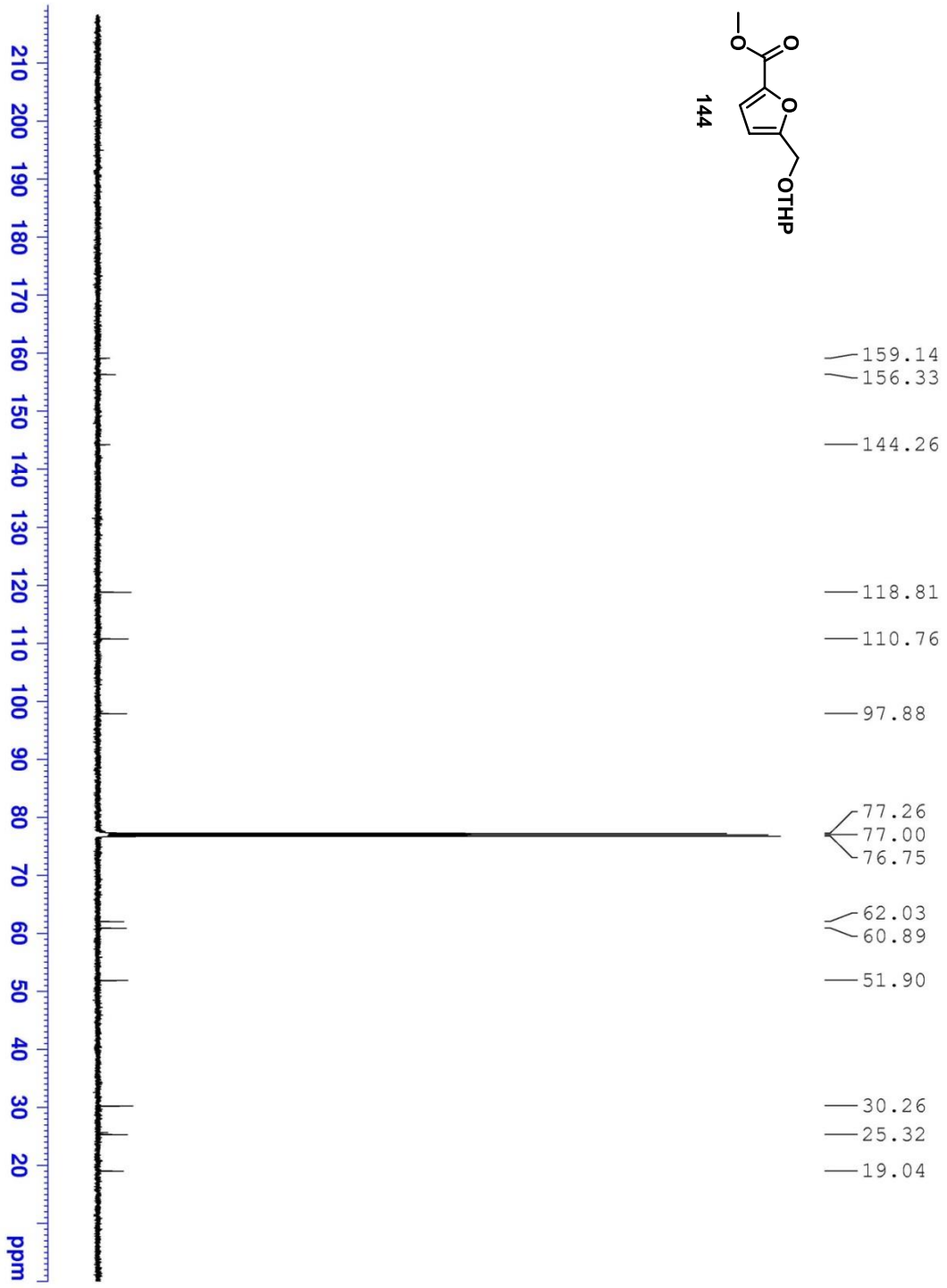

120
OH
O
O
7.647
7.620
7.594
7.414
7.402
7.352
7.327
7.301
7.260
7.205
7.180
6.784
6.772
2.416
0.91
1.01
0.91
1.03
0.98
0.97
3.00
10
9
8
7
6
5
4
3
2
1
ppm

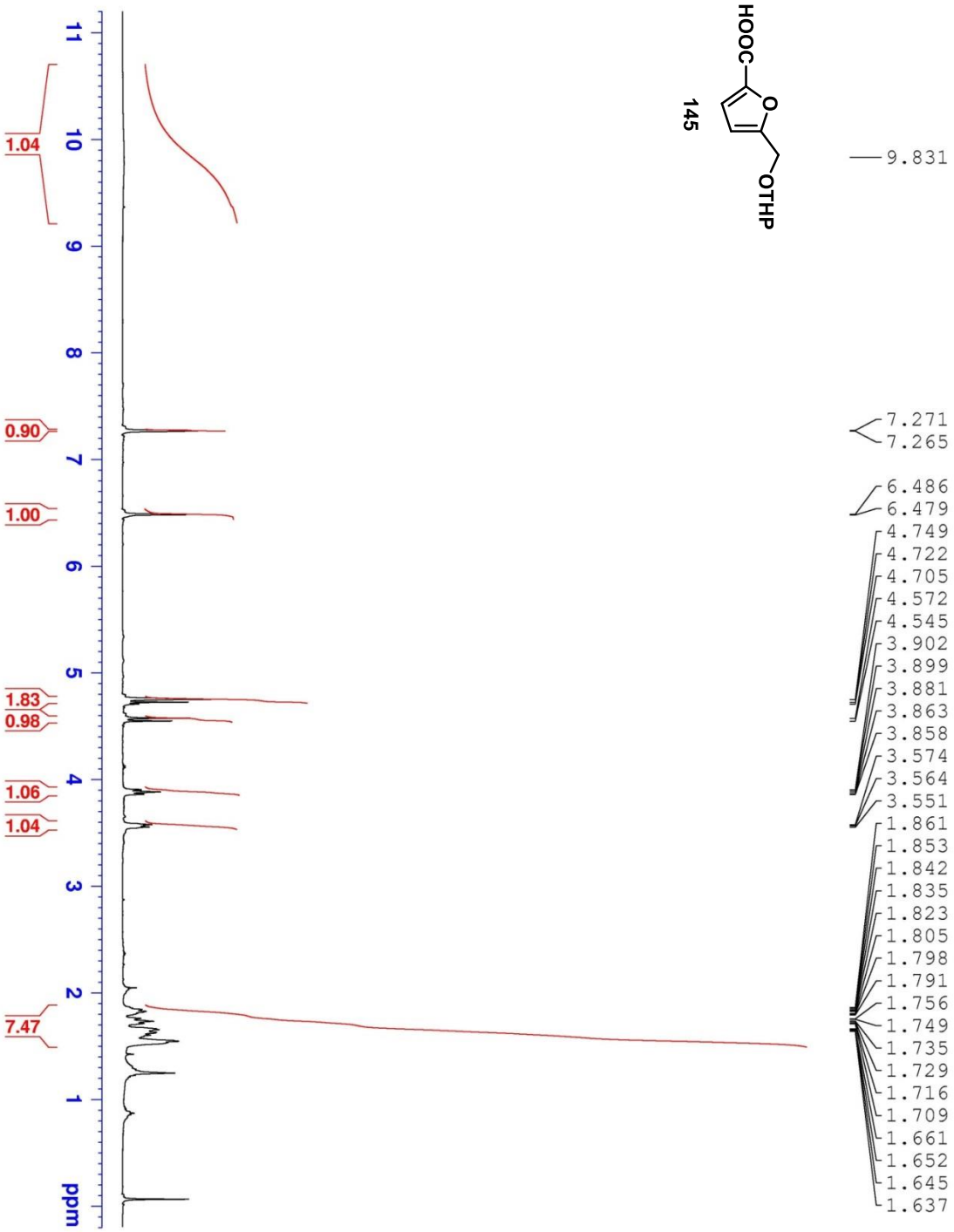

121
NHBoc
7.375
7.364
7.343
7.260
7.232
7.213
7.033
7.014
6.715
6.588
6.580
6.125
2.362
1.524
0.94
1.10
1.08
1.07
0.81
1.05
0.90
3.00
8.96
ppm

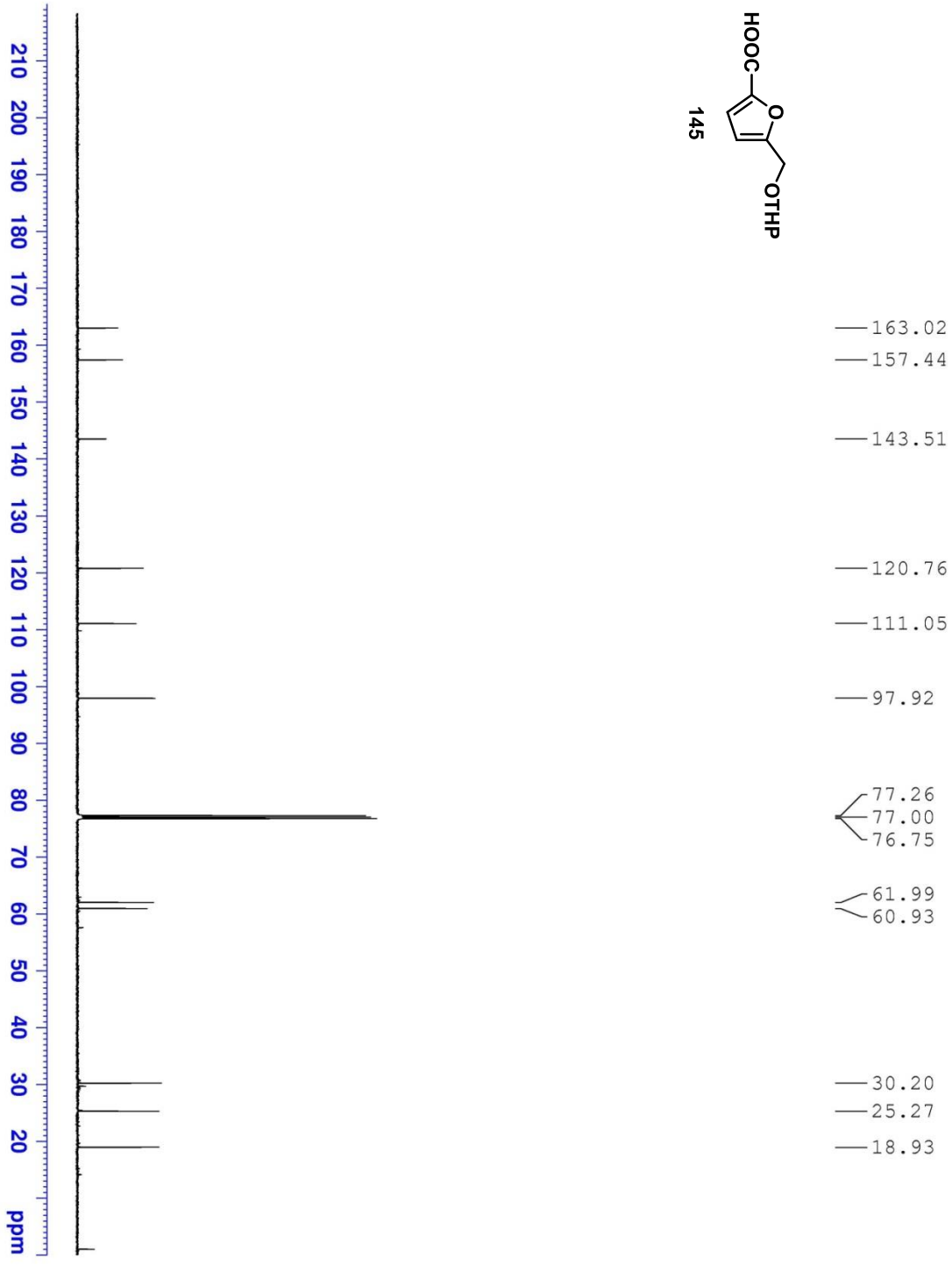

142
MeO
O
OH
O
11.288
7.741
7.711
7.355
7.343
7.260
6.950
6.920
6.639
6.627
3.837
2.74
2.06
1.00
2.07
1.03
3.12
12
11
10
9
8
7
6
5
4
ppm

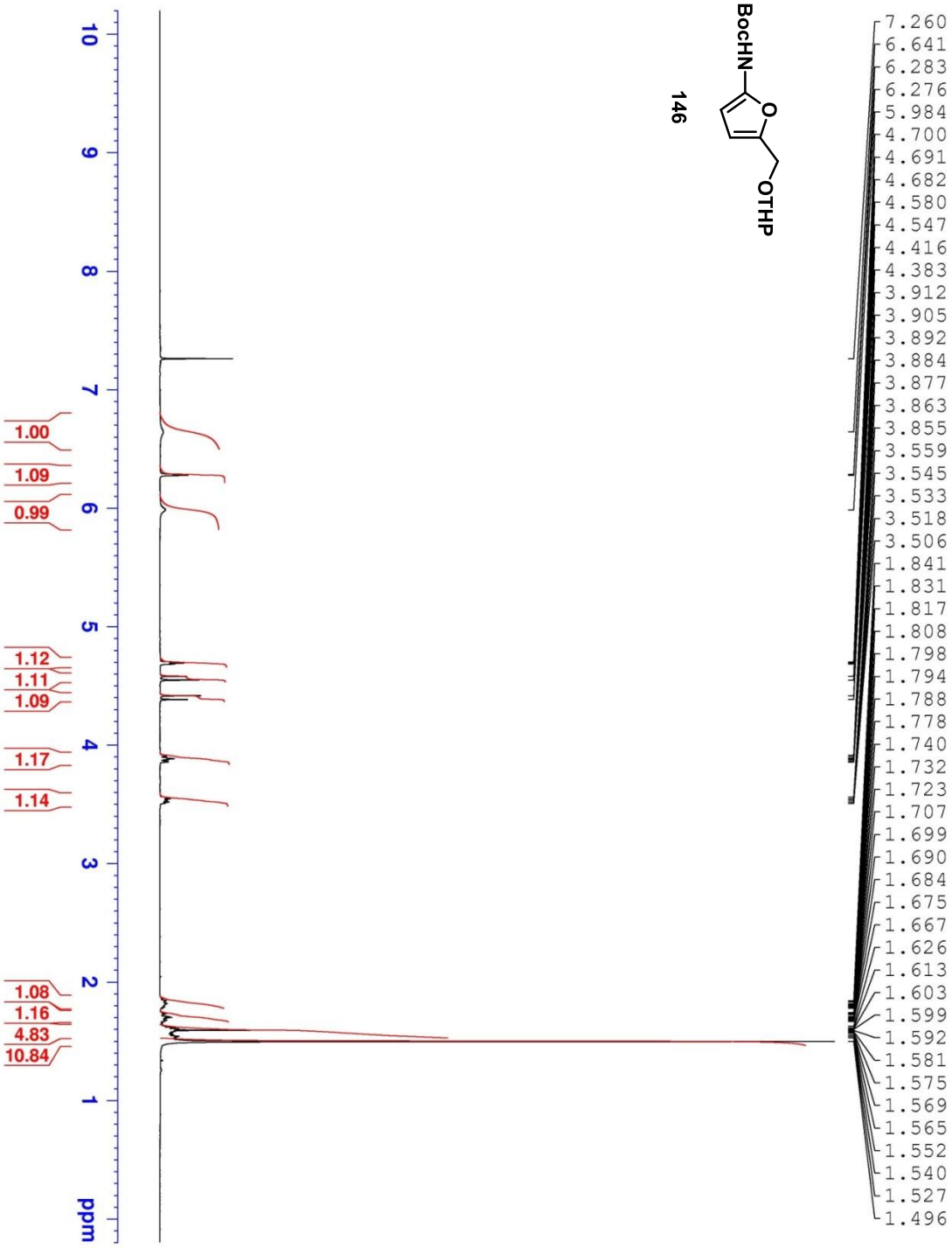

MeO
NHBoc
143
7.495
7.488
7.483
7.477
7.471
7.466
7.459
7.260
6.904
6.897
6.892
6.880
6.875
6.868
6.801
6.459
6.451
6.106
3.812
1.524
1.99
2.05
0.80
0.99
0.83
3.00
8.95
ppm

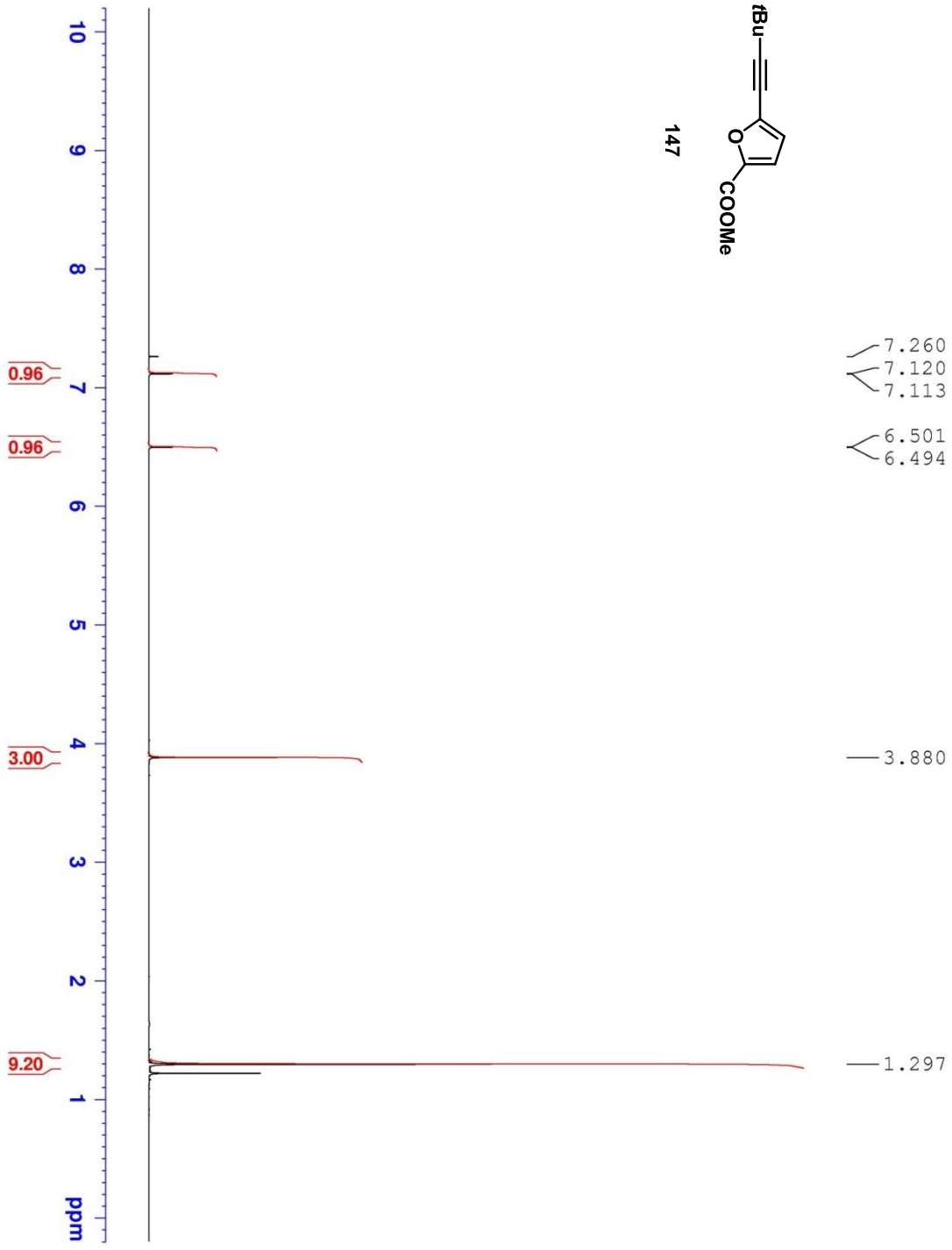

144
OTHP
7.260
7.143
7.136
6.443
6.436
4.730
4.726
4.719
4.703
4.551
4.524
3.900
3.897
3.888
3.877
3.871
3.859
3.853
3.560
3.557
3.548
3.546
3.537
3.534
3.526
1.843
1.835
1.824
1.816
1.750
1.730
1.722
1.715
1.702
1.696
1.649
1.647
1.641
1.639
1.633
1.622
1.614
1.604
1.596
1.554
1.549
1.540
1.531
1.528
1.525
1.522
1.519
1.516
1.508
1.505
1.00
0.98
2.09
1.07
4.29
1.10
1.12
1.28
2.27
2.33
ppm

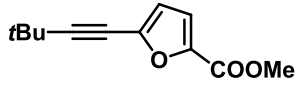

144
OTHP
159.14
156.33
144.26
118.81
110.76
97.88
77.26
77.00
76.75
62.03
60.89
51.90
30.26
25.32
19.04
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


HOOC
O
OTHP
145
9.831
7.271
7.265
6.486
6.479
4.749
4.722
4.705
4.572
4.545
3.902
3.899
3.881
3.863
3.858
3.574
3.564
3.551
1.861
1.853
1.842
1.835
1.823
1.805
1.798
1.791
1.756
1.749
1.735
1.729
1.716
1.709
1.661
1.652
1.645
1.637
1.04
0.90
1.00
1.83
0.98
1.06
1.04
7.47
ppm


HOOC
O
OTHP
145
163.02
157.44
143.51
120.76
111.05
97.92
77.26
77.00
76.75
61.99
60.93
30.20
25.27
18.93
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

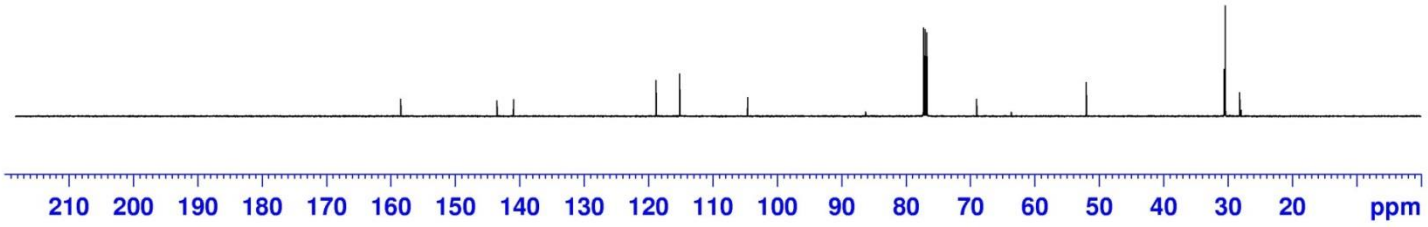

BocHN
O
OTHP
146
7.260
6.641
6.283
6.276
5.984
4.700
4.691
4.682
4.580
4.547
4.416
4.383
3.912
3.905
3.892
3.884
3.877
3.863
3.855
3.559
3.545
3.533
3.518
3.506
1.841
1.831
1.817
1.808
1.798
1.794
1.788
1.778
1.740
1.732
1.723
1.707
1.699
1.690
1.684
1.675
1.667
1.626
1.613
1.603
1.599
1.592
1.581
1.575
1.569
1.565
1.552
1.540
1.527
1.496
1.00
1.09
0.99
1.12
1.11
1.09
1.17
1.14
1.08
1.16
4.83
10.84
10
9
8
7
6
5
4
3
2
1
ppm

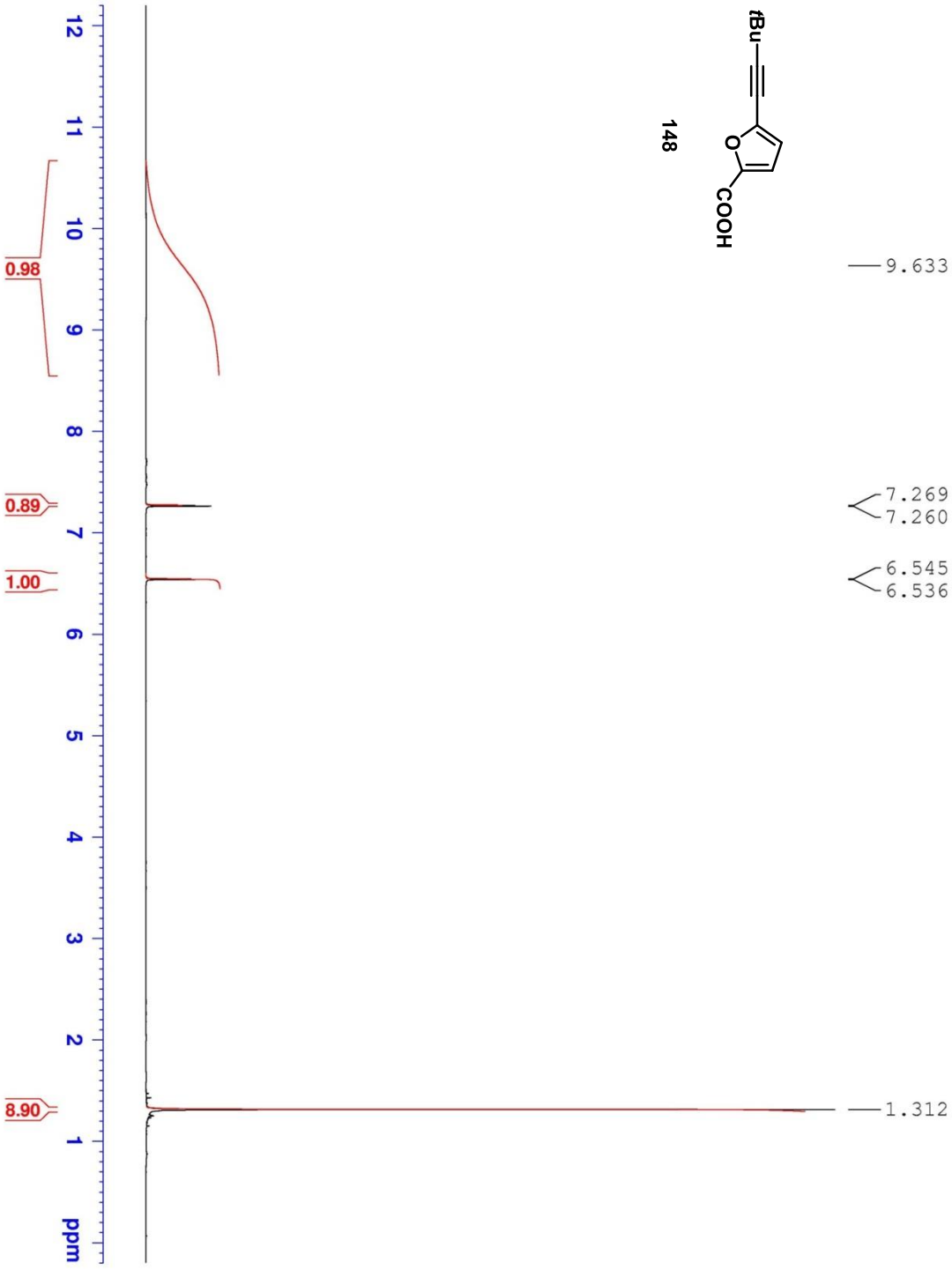

tBu
O
COOMe
147
7.260
7.120
7.113
6.501
6.494
3.880
1.297
0.96
0.96
3.00
9.20
10
9
8
7
6
5
4
3
2
1
ppm

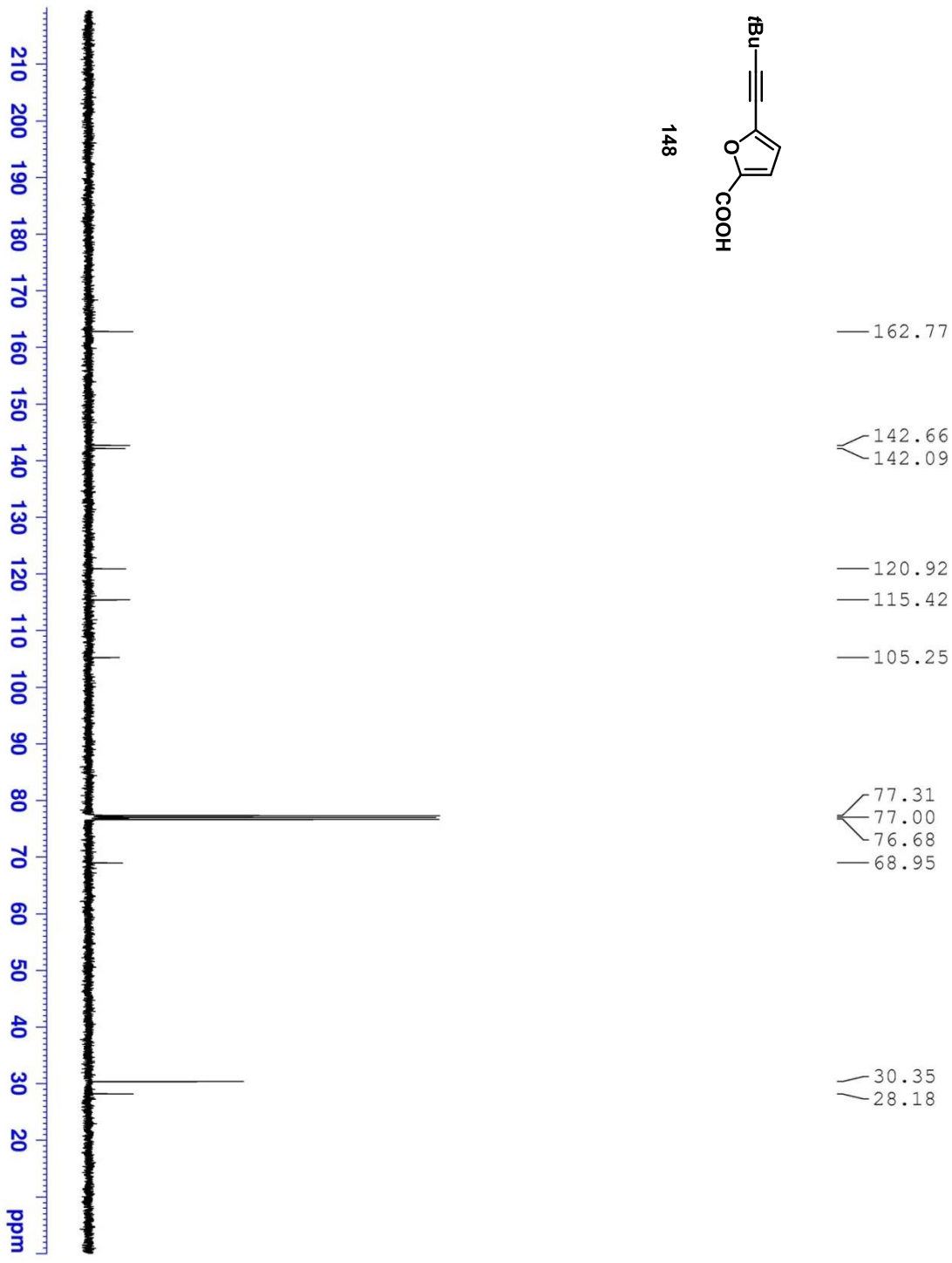


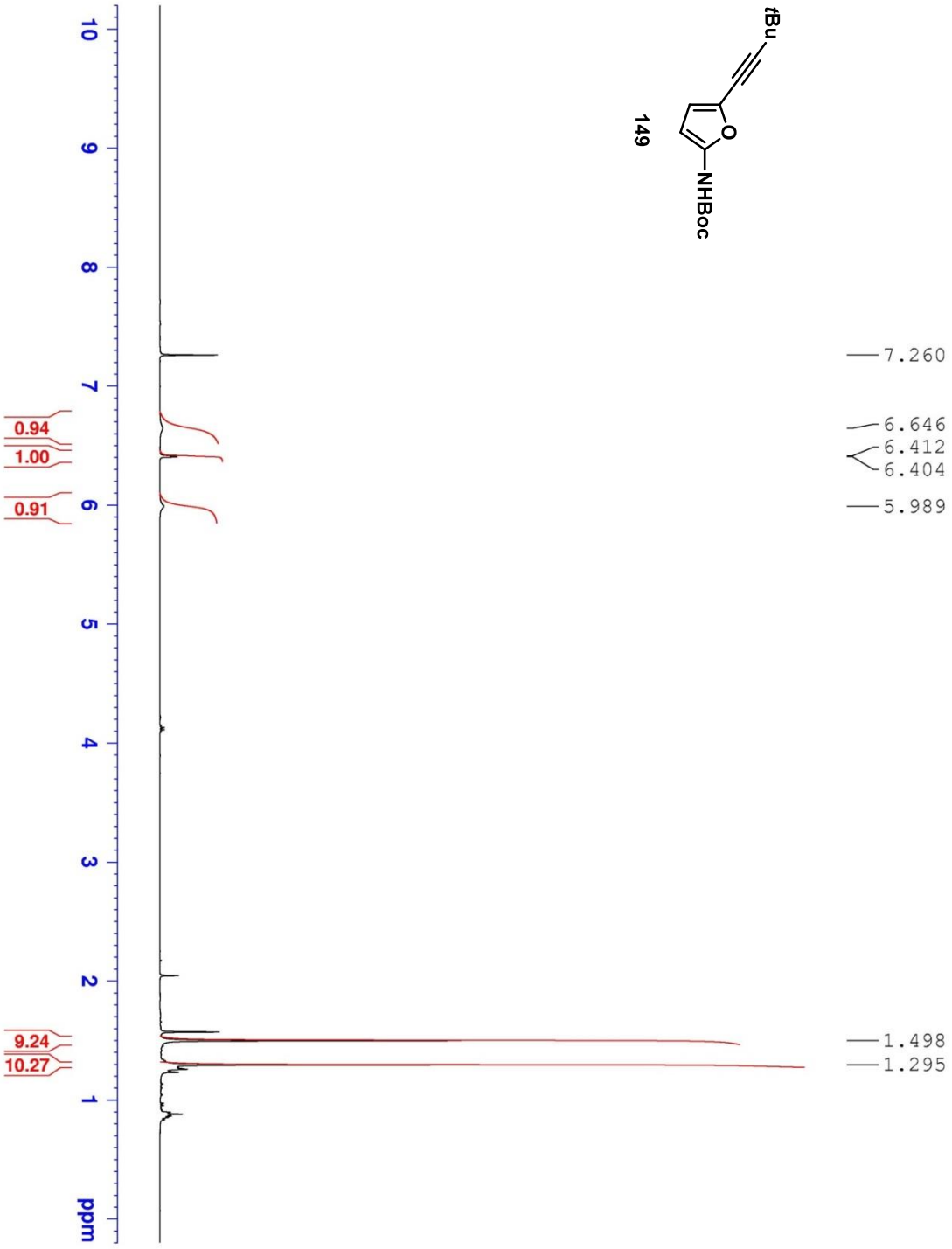
147

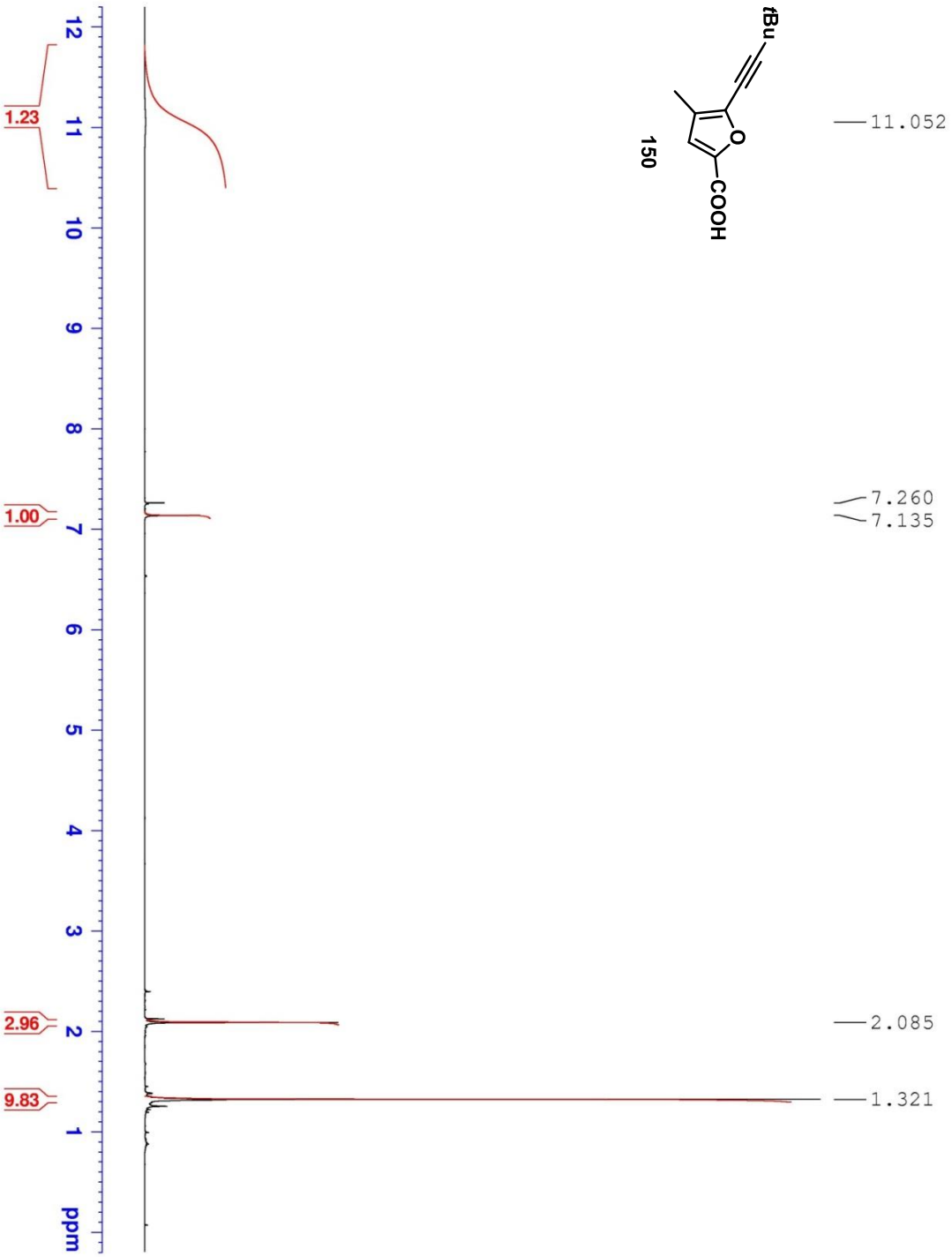
158.49
143.53
140.96
118.81
115.15
104.58
77.25
77.00
76.74
69.01
51.98
30.38
28.13

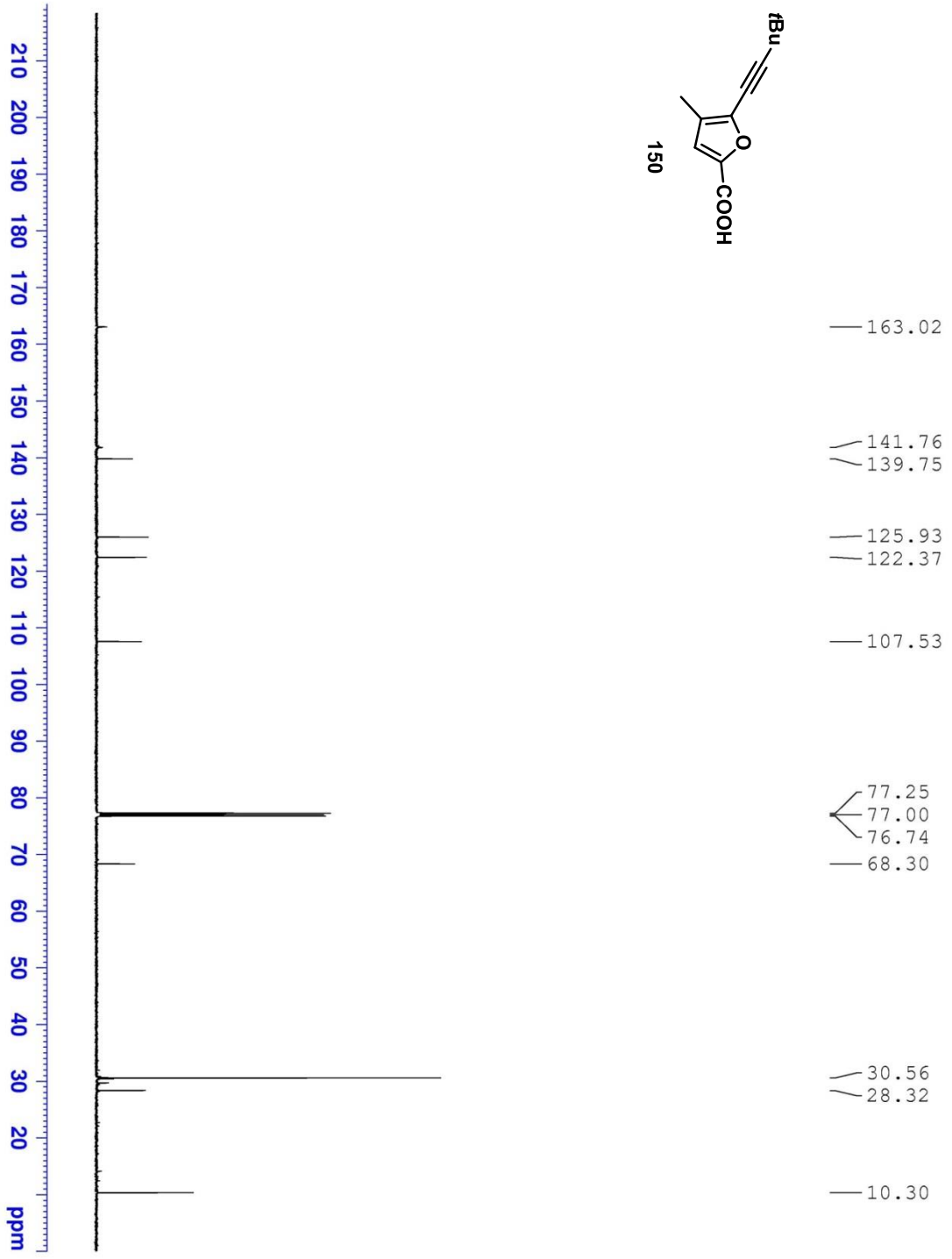


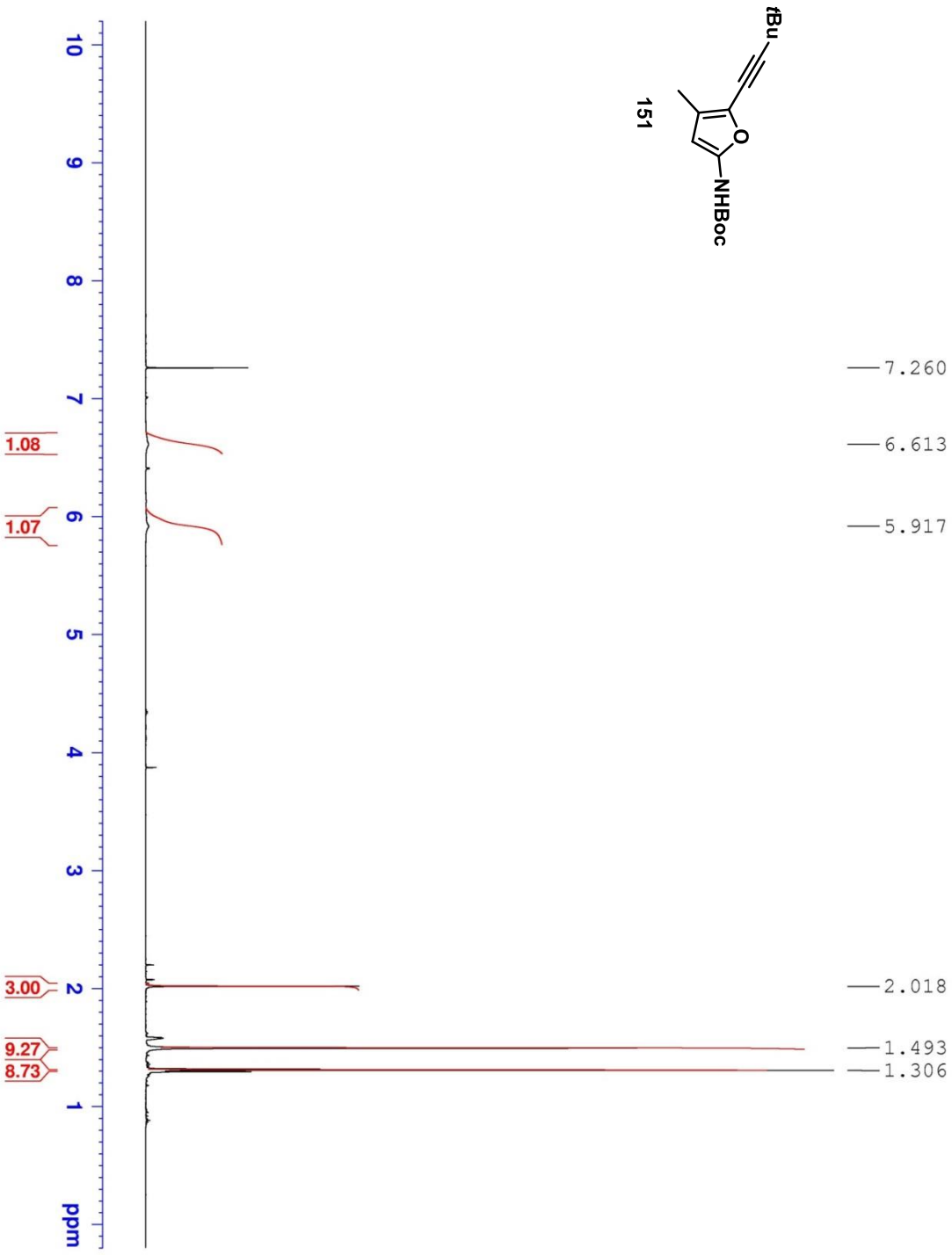

148
tBu
O
COOH
9.633
7.269
7.260
6.545
6.536
1.312
0.98
0.89
1.00
8.90
12
11
10
9
8
7
6
5
4
3
2
1
ppm

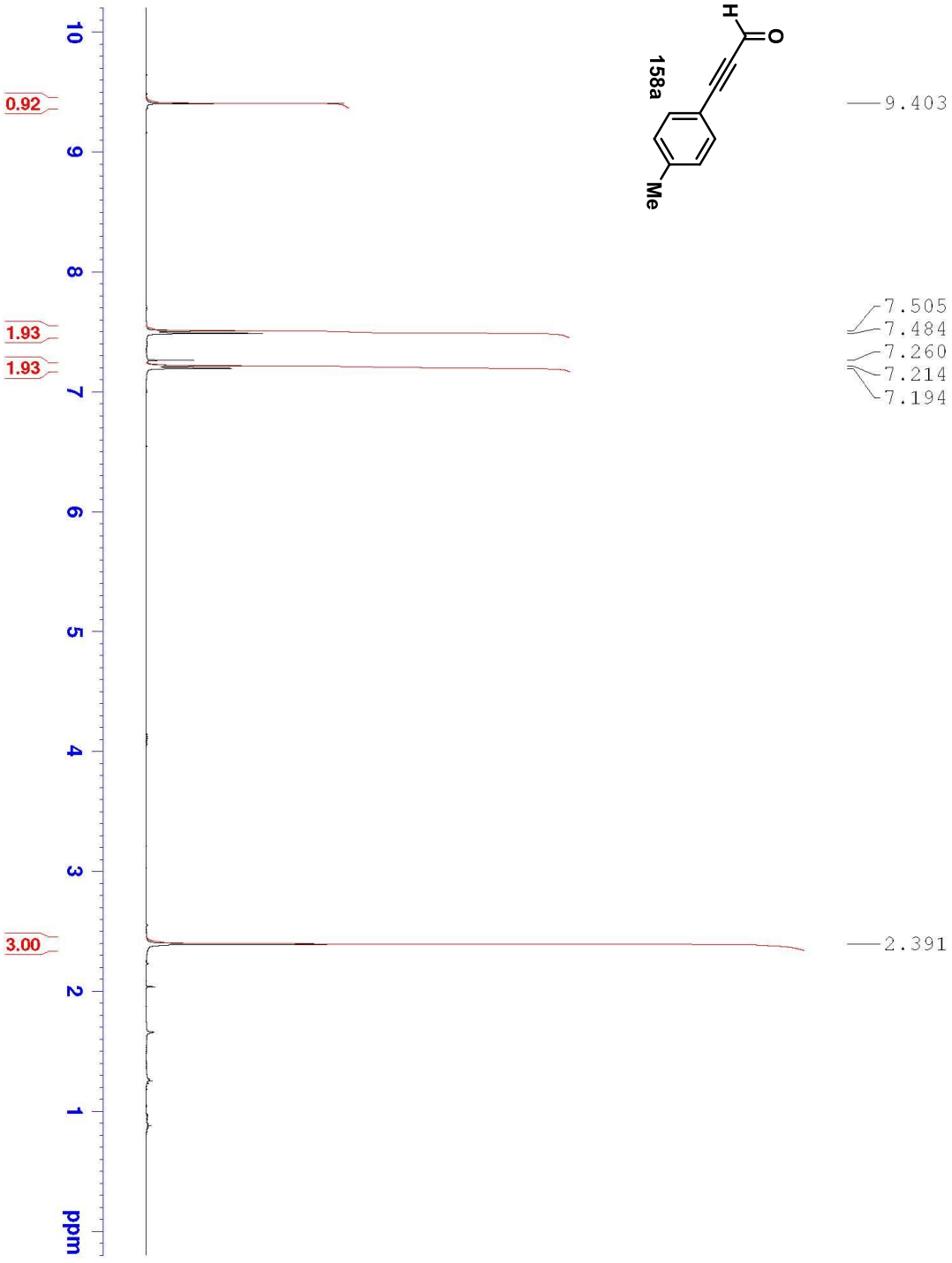

148
tBu
O
COOH
162.77
142.66
142.09
120.92
115.42
105.25
77.31
77.00
76.68
68.95
30.35
28.18
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

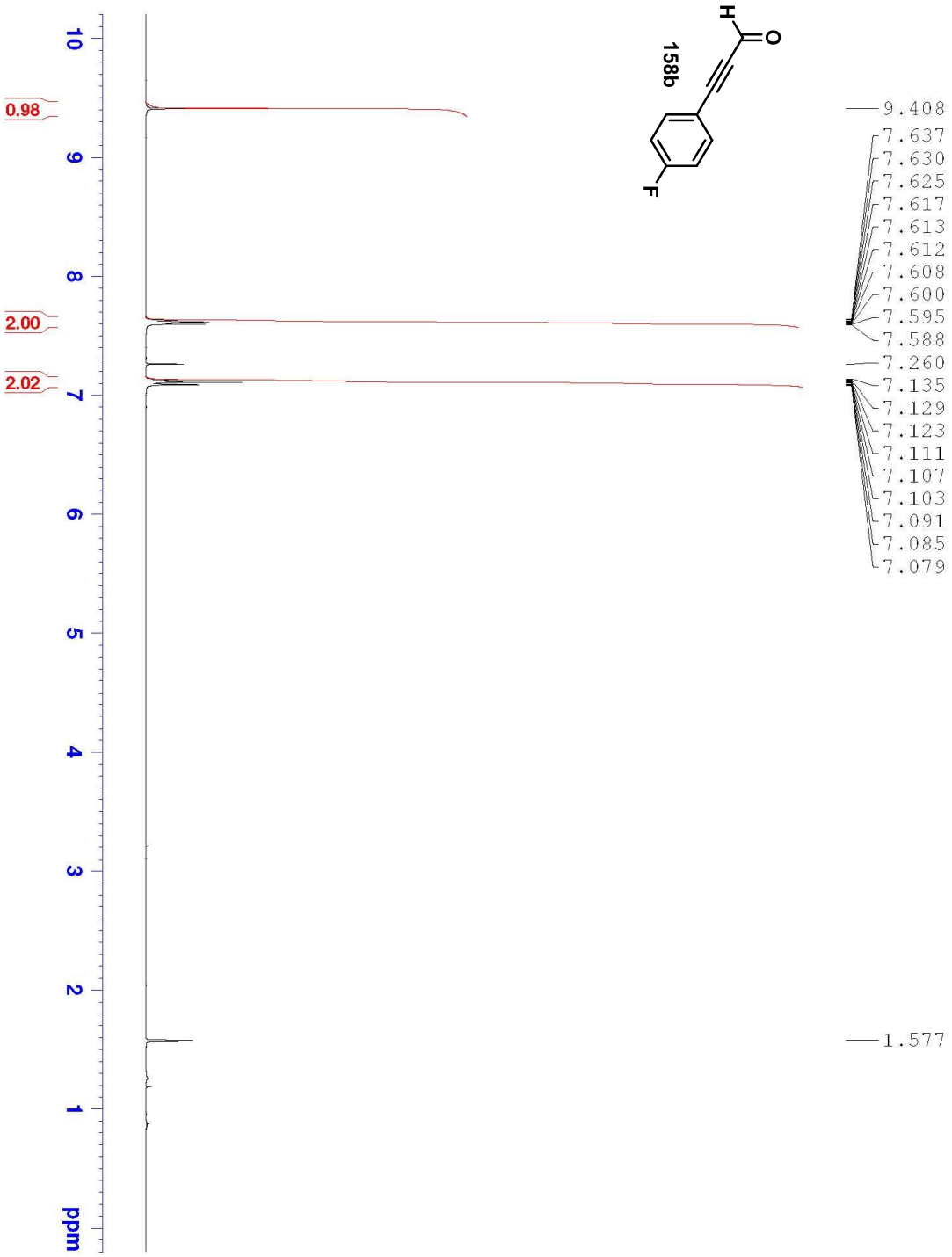

tBu
O
NHBoc
149
7.260
6.646
6.412
6.404
5.989
1.498
1.295
0.94
1.00
0.91
9.24
10.27
10
9
8
7
6
5
4
3
2
1
ppm

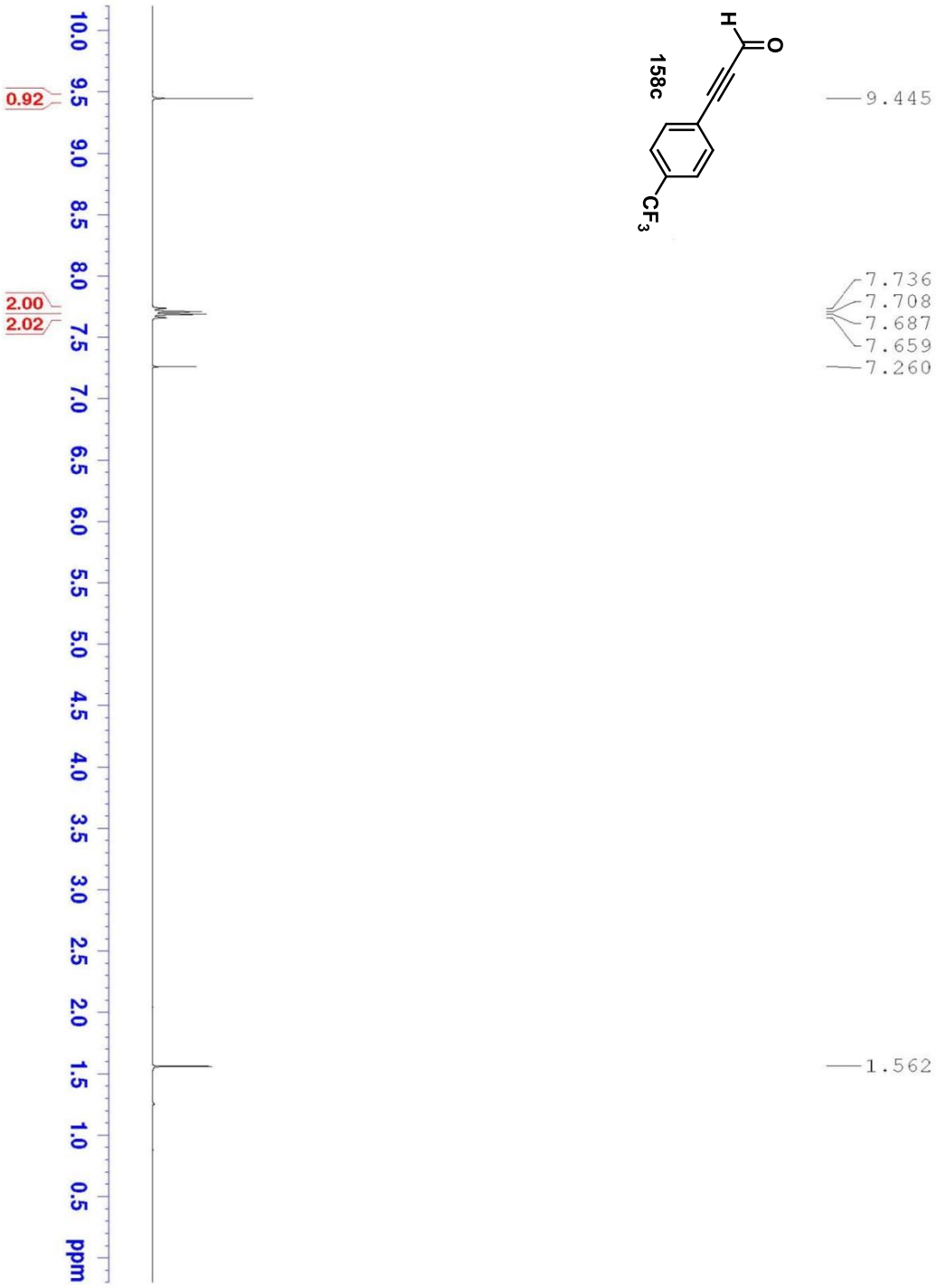

tBu
O
COOH
150
11.052
7.260
7.135
2.085
1.321
1.23
1.00
2.96
9.83
12
11
10
9
8
7
6
5
4
3
2
1
ppm

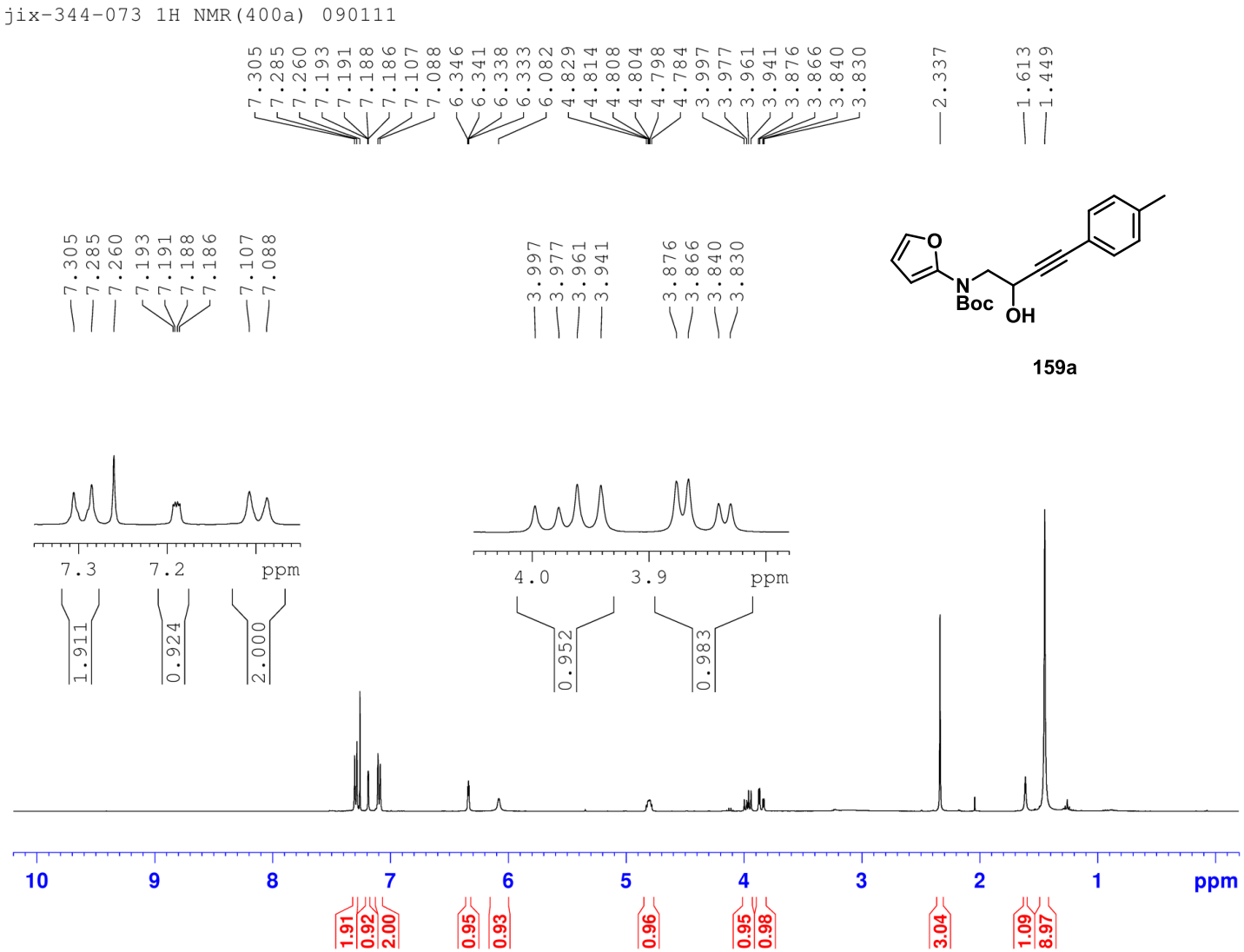

tBu
O
COOH
150
163.02
141.76
139.75
125.93
122.37
107.53
77.25
77.00
76.74
68.30
30.56
28.32
10.30
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


151
tBu
O
NHBoc
7.260
6.613
5.917
2.018
1.493
1.306
1.08
1.07
3.00
9.27
8.73
ppm

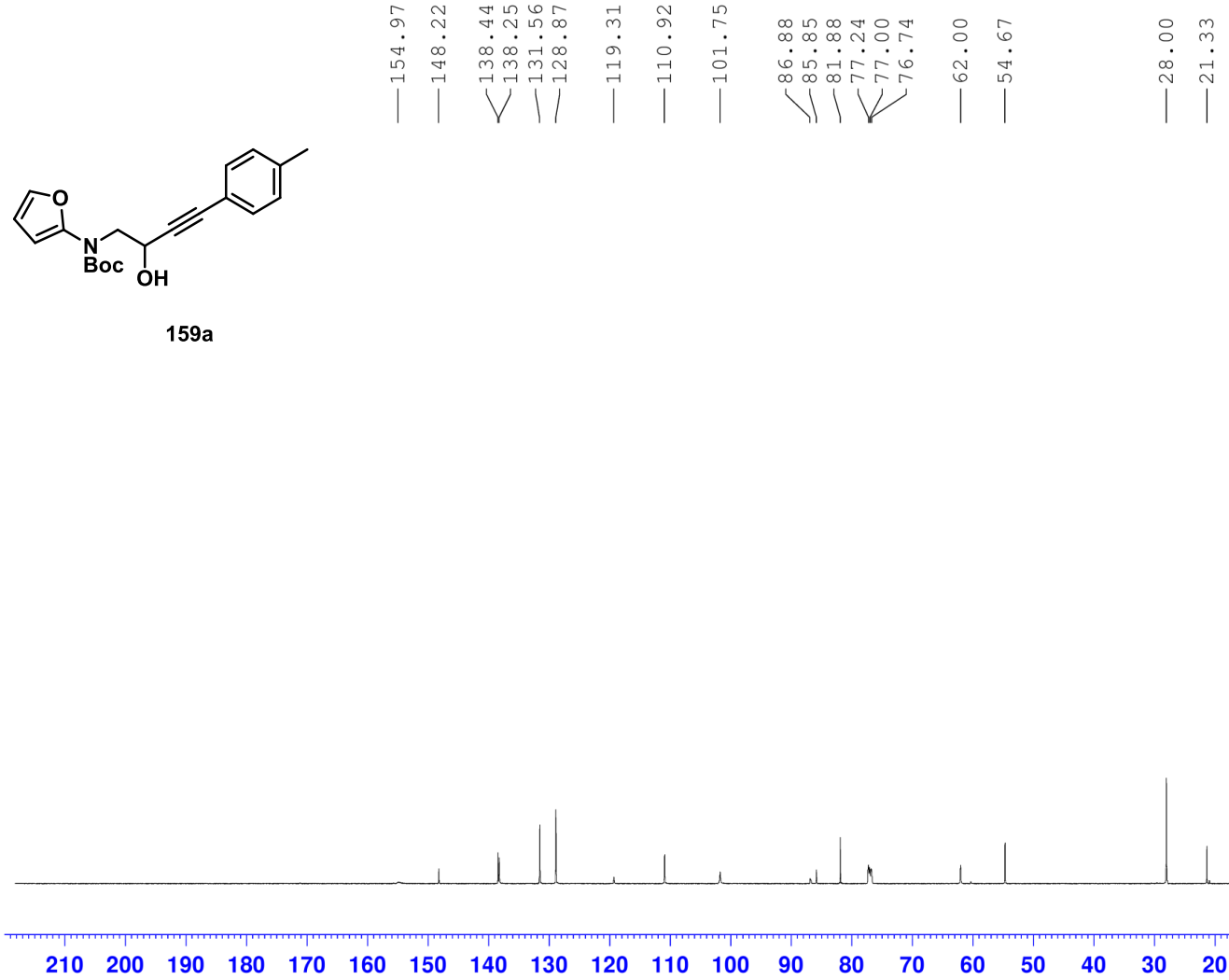

158a
H
O
Me
9.403
7.505
7.484
7.260
7.214
7.194
2.391
0.92
1.93
1.93
3.00
10
9
8
7
6
5
4
3
2
1
ppm


158b
H
O
F
0.98
2.00
2.02
9.408
7.637
7.630
7.625
7.617
7.613
7.612
7.608
7.600
7.595
7.588
7.260
7.135
7.129
7.123
7.111
7.107
7.103
7.091
7.085
7.079
1.577
10
9
8
7
6
5
4
3
2
1
ppm


158c
H
O
CF3
9.445
7.736
7.708
7.687
7.659
7.260
1.562
0.92
2.00
2.02
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


jix-344-073 1H NMR(400a) 090111
7.305
7.285
7.260
7.193
7.191
7.188
7.186
7.107
7.088
6.346
6.341
6.338
6.333
6.082
4.829
4.814
4.808
4.804
4.798
4.784
3.997
3.977
3.961
3.941
3.876
3.866
3.840
3.830
2.337
1.613
1.449
O
N
Boc
OH
159a
7.3
7.2
ppm
1.911
0.924
2.000
4.0
3.9
ppm
0.952
0.983
10
9
8
7
6
5
4
3
2
1
ppm
1.91
0.92
2.00
0.95
0.93
0.96
0.95
0.98
3.04
1.09
8.97

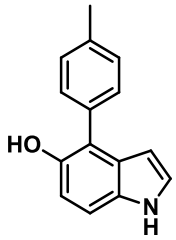
jix-344-073 13C NMR(500) 090111



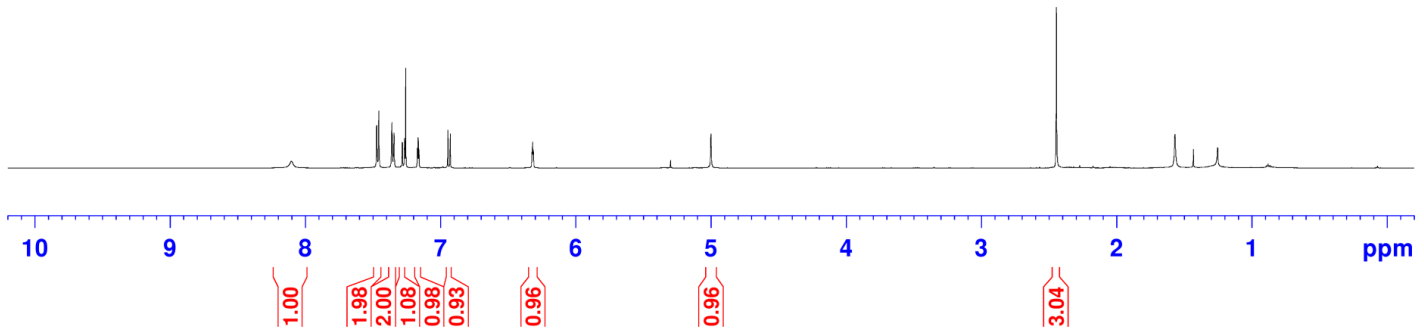
159a

jix-344-079 1H NMR(500) 091411

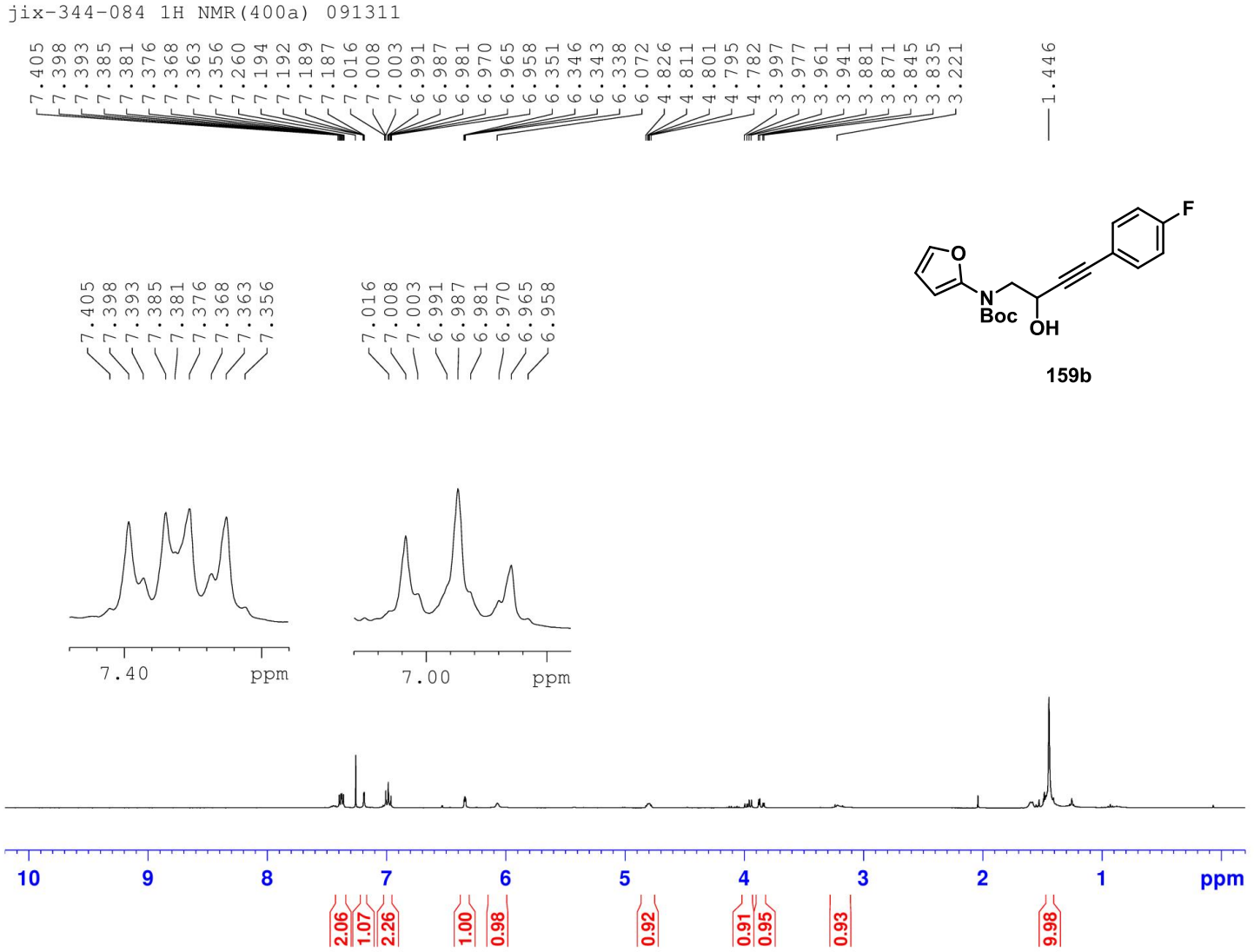
8.106
7.475
7.458
7.362
7.346
7.286
7.285
7.269
7.267
7.260
7.173
7.168
7.162
6.948
6.930
6.326
6.324
6.322
6.320
6.316
6.314
5.002
2.447
1.570



160a

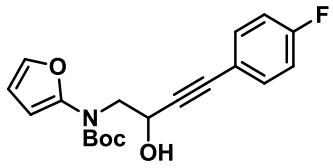


jix-344-079 13C NMR(500) 091311
160a
HO
N
H
146.01
137.45
132.47
130.88
130.04
129.79
127.92
124.99
117.76
111.90
111.08
101.69
77.26
77.00
76.75
21.29
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

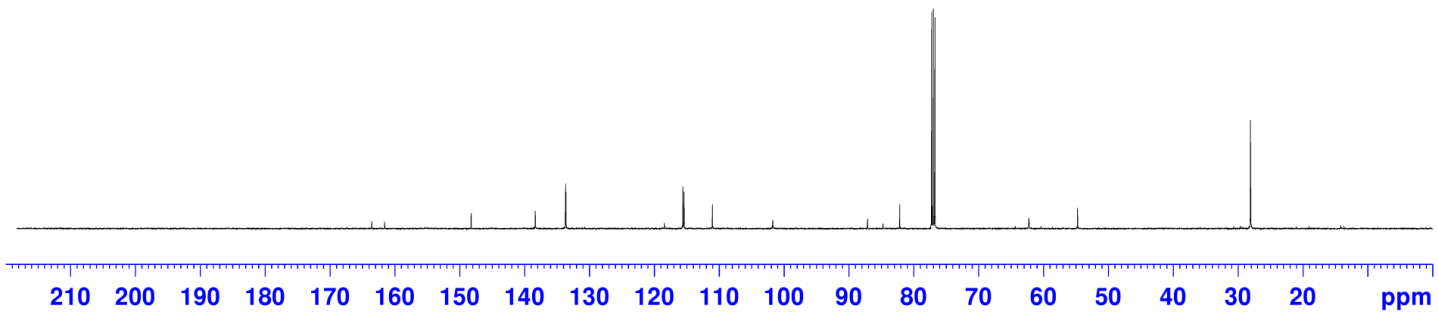

jix-344-084 1H NMR(400a) 091311
7.405
7.398
7.393
7.385
7.381
7.376
7.368
7.363
7.356
7.260
7.194
7.192
7.189
7.187
7.016
7.008
7.003
6.991
6.987
6.981
6.970
6.965
6.958
6.351
6.346
6.343
6.338
6.072
4.826
4.811
4.801
4.795
4.782
3.997
3.977
3.961
3.941
3.881
3.871
3.845
3.835
3.221
1.446
F
O
N
Boc
OH
159b
7.40
ppm
7.00
ppm
10
9
8
7
6
5
4
3
2
1
ppm
2.06
1.07
2.26
1.00
0.98
0.92
0.91
0.95
0.93
9.98

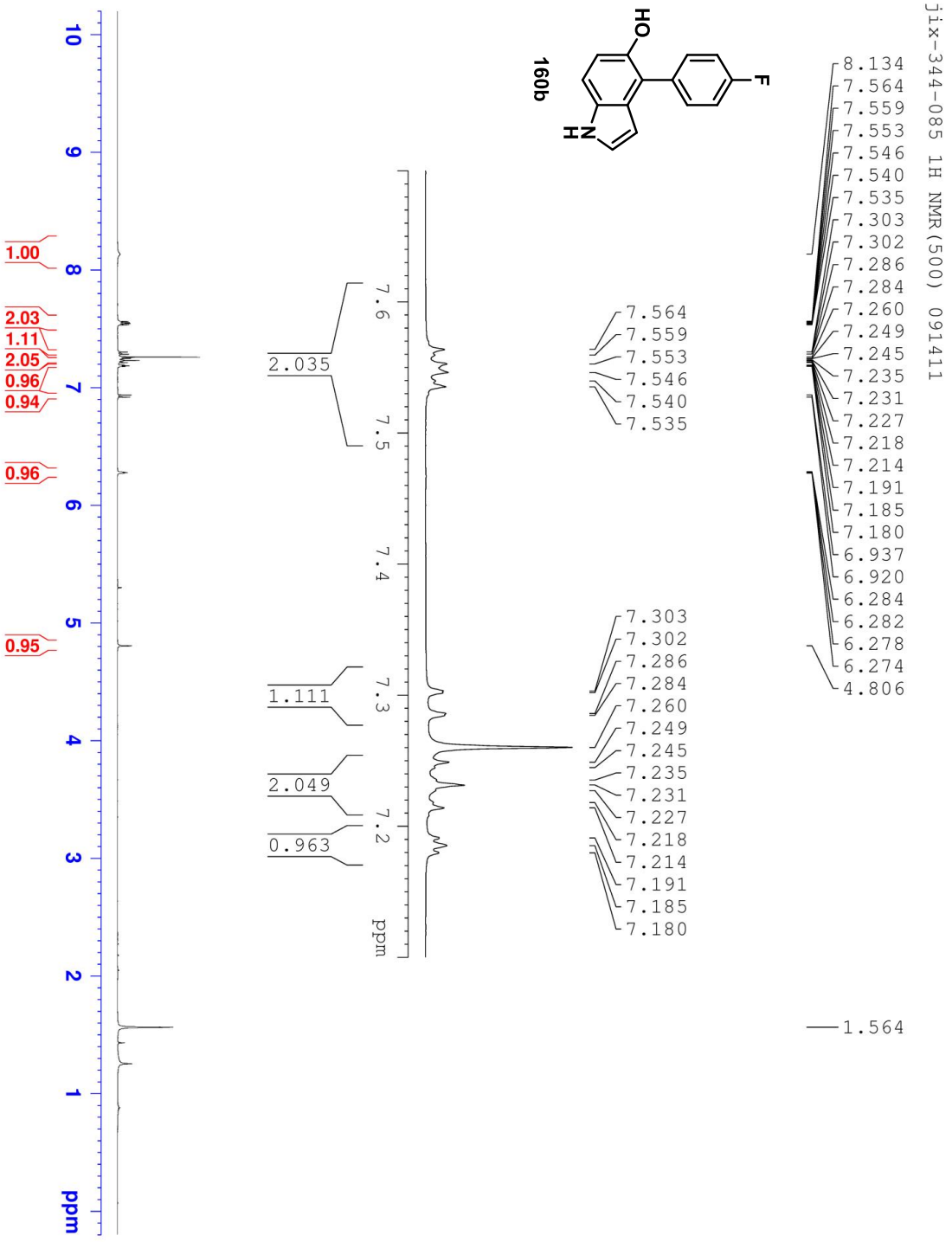
jix-344-084 13C NMR(500) 091311

163.58
161.59
155.35
148.25
138.38
133.69
133.62
118.44
115.60
115.43
111.04
101.76
87.13
84.77
82.16
77.25
77.00
76.75
62.26
54.76
28.07

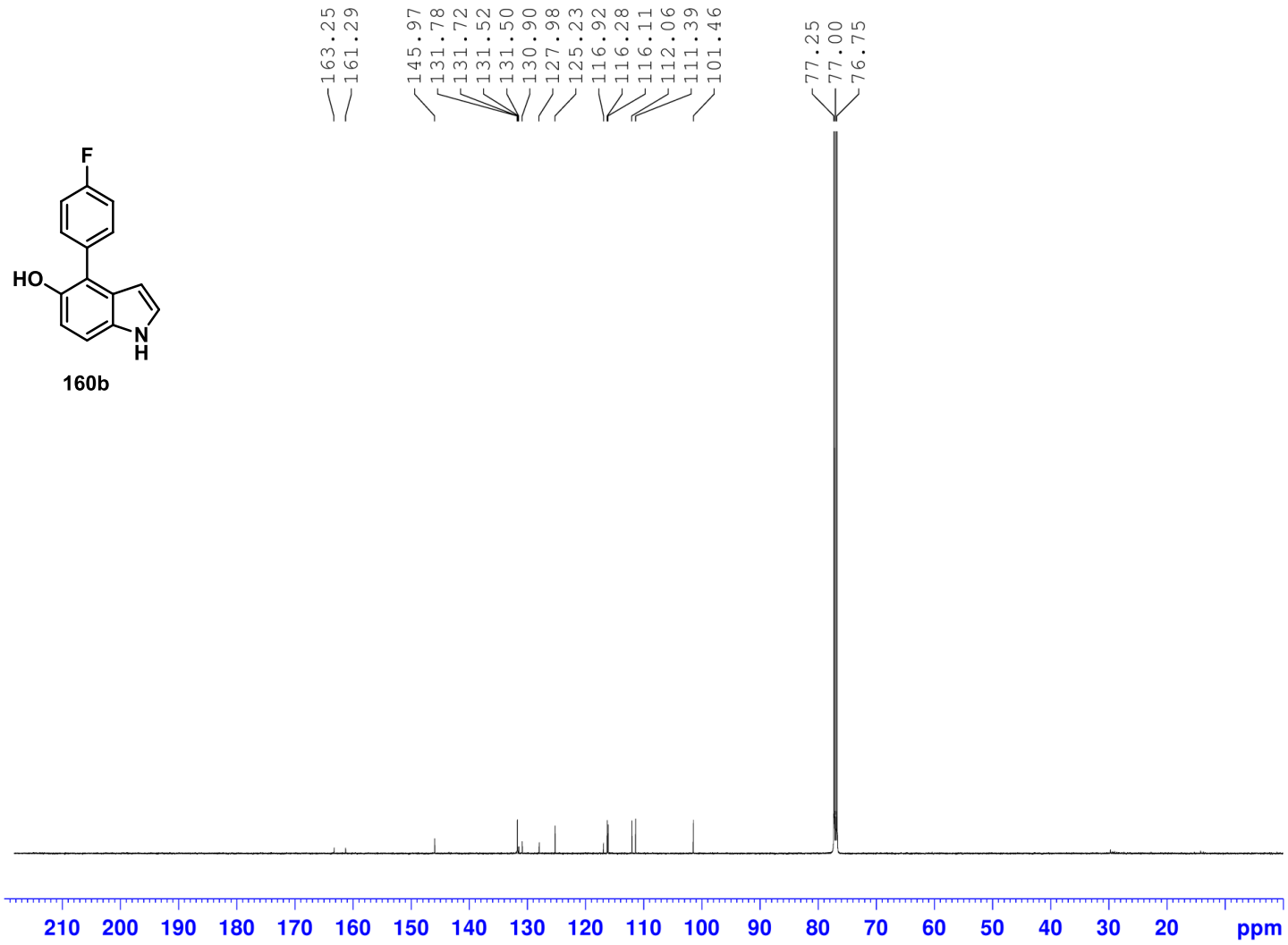


159b

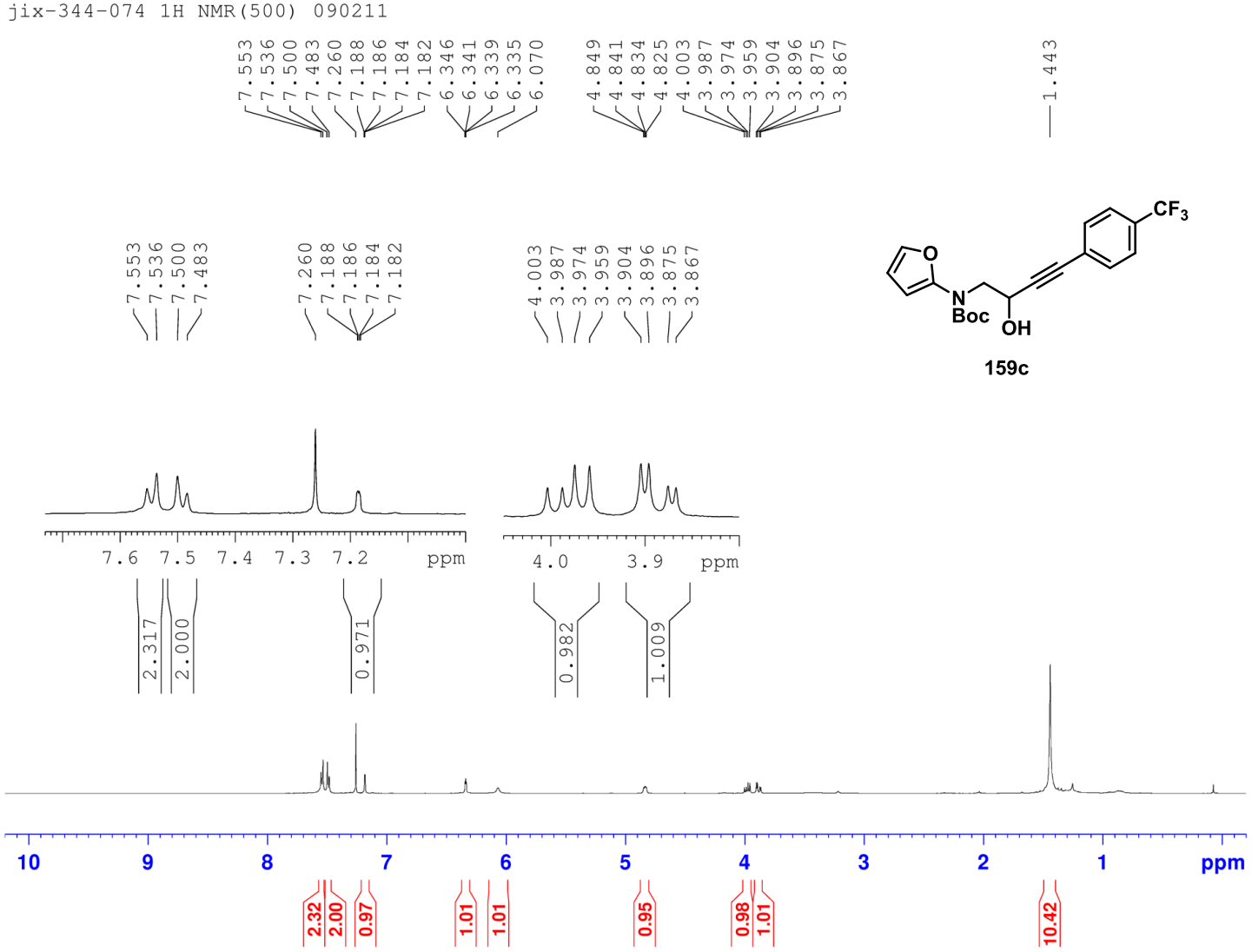



jix-344-085 1H NMR(500) 091411
160b
HO
F
H
N
8.134
7.564
7.559
7.553
7.546
7.540
7.535
7.303
7.302
7.286
7.284
7.260
7.249
7.245
7.235
7.231
7.227
7.218
7.214
7.191
7.185
7.180
6.937
6.920
6.284
6.282
6.278
6.274
4.806
1.564
2.035
1.111
2.049
0.963
1.00
2.03
1.11
2.05
0.96
0.94
0.96
0.95
ppm

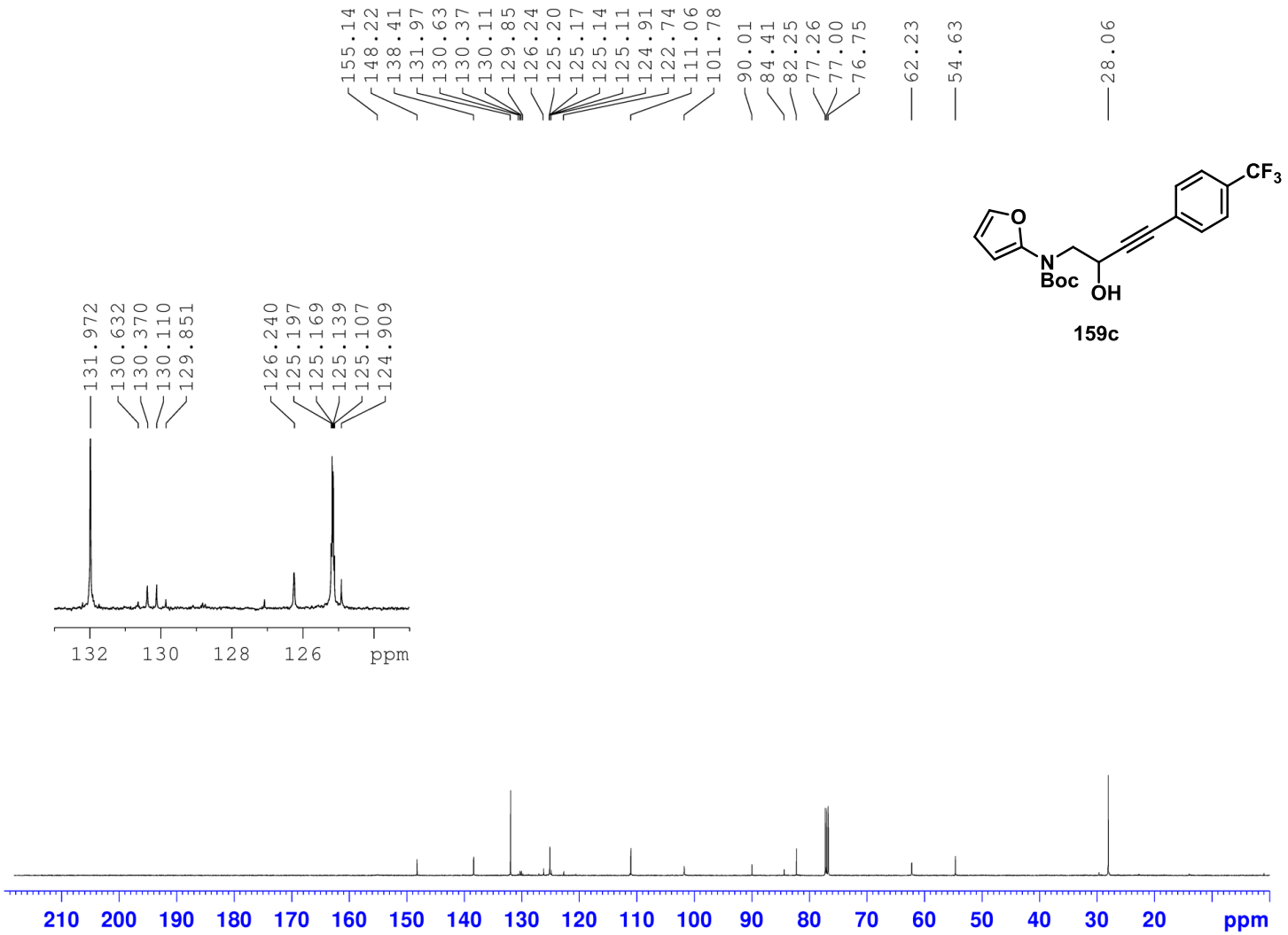
jix-344-085 13C NMR(500) 091411

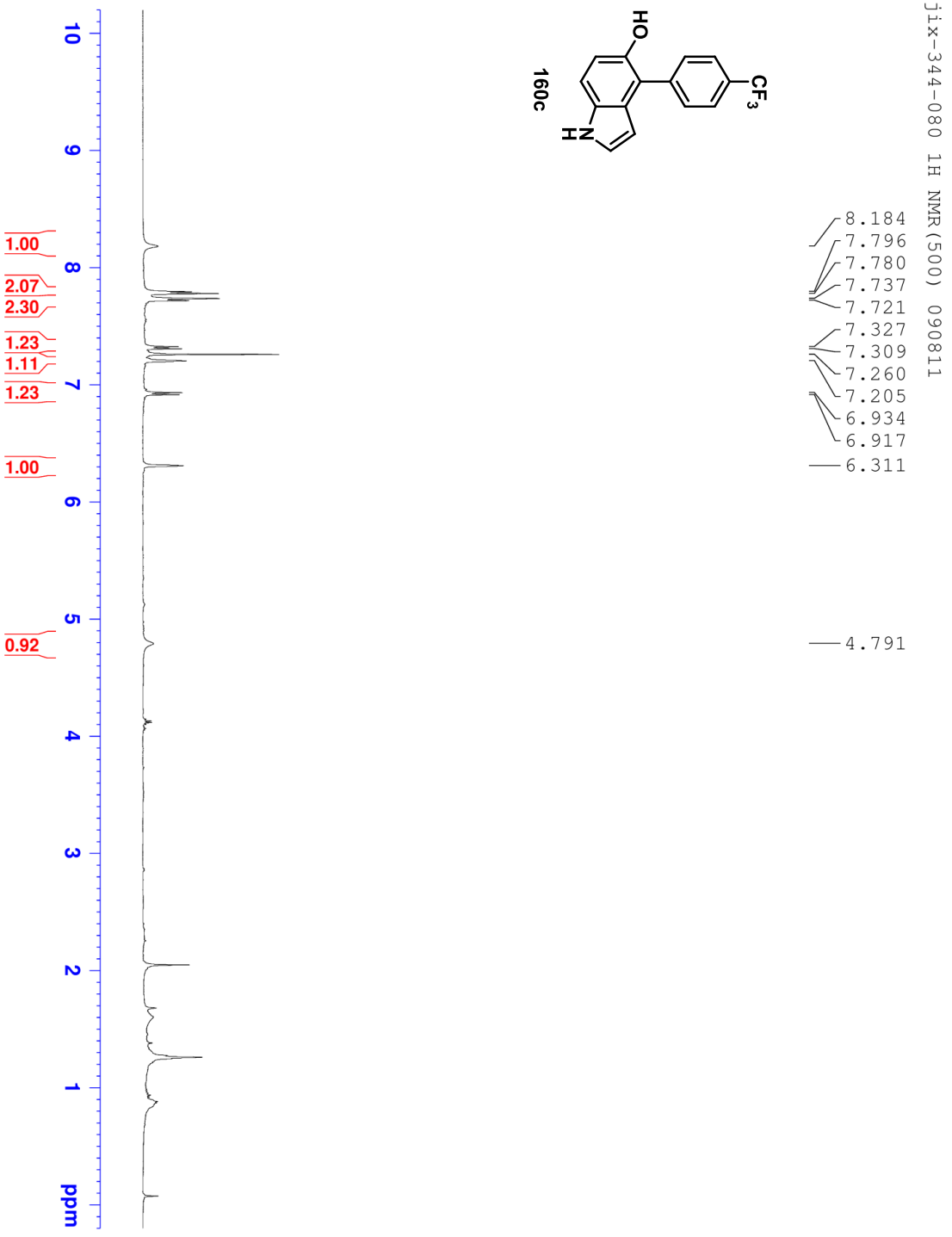


160b

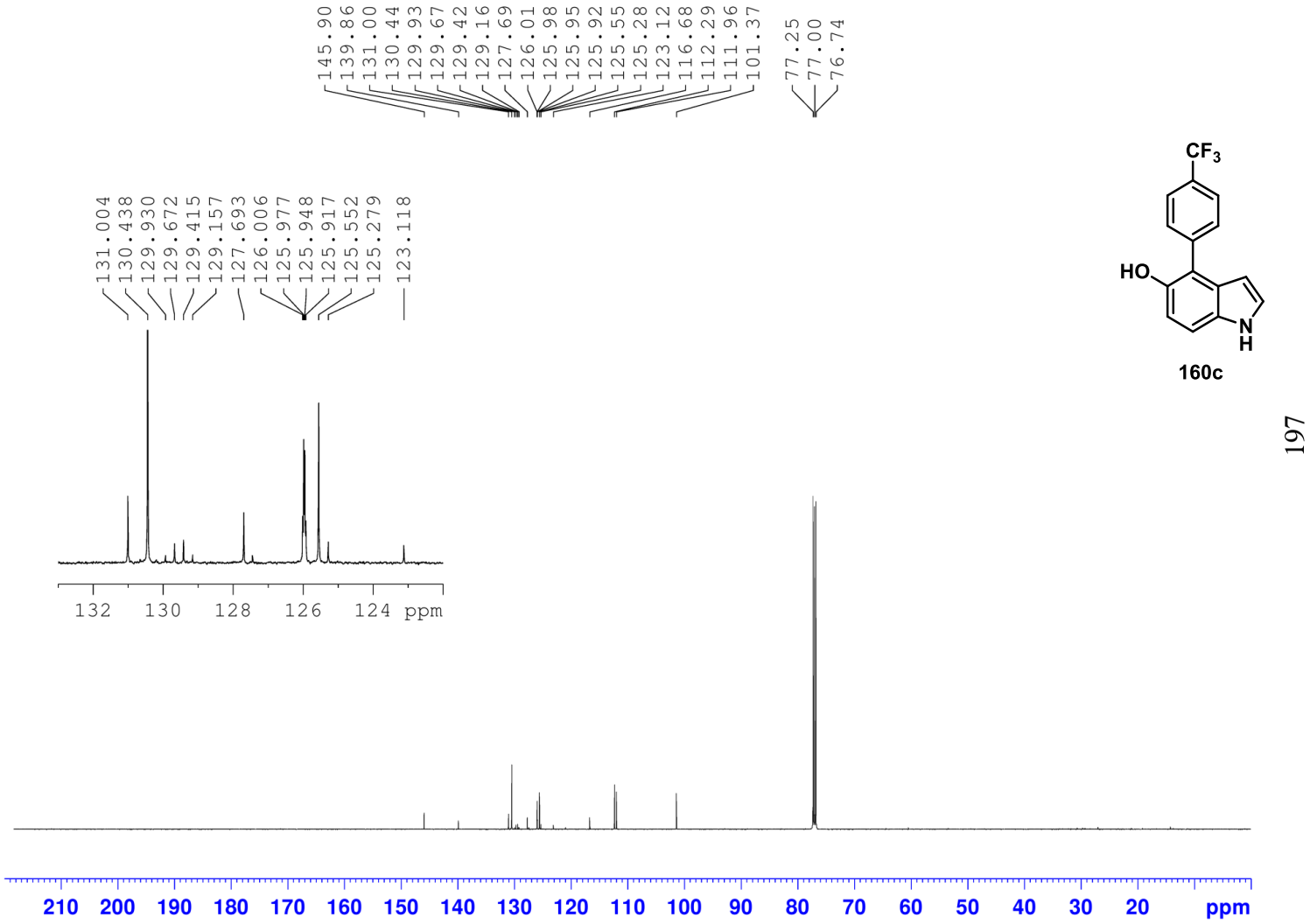

jix-344-074 1H NMR(500) 090211
7.553
7.536
7.500
7.483
7.260
7.188
7.186
7.184
7.182
6.346
6.341
6.339
6.335
6.070
4.849
4.841
4.834
4.825
4.003
3.987
3.974
3.959
3.904
3.896
3.875
3.867
1.443
CF3
O
N
Boc
OH
159c
7.6
7.5
7.4
7.3
7.2
ppm
4.0
3.9
ppm
2.317
2.000
0.971
0.982
1.009
10
9
8
7
6
5
4
3
2
1
ppm
2.32
2.00
0.97
1.01
1.01
0.95
0.98
1.01
10.42

jix-344-074 13C NMR(500) 090211



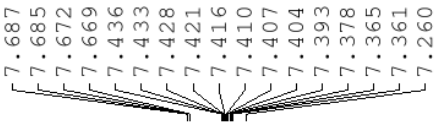

jix-344-080 1H NMR(500) 090811
8.184
7.796
7.780
7.737
7.721
7.327
7.309
7.260
7.205
6.934
6.917
6.311
4.791
HO
CF3
N
H
160c
1.00
2.07
2.30
1.23
1.11
1.23
1.00
0.92
10
9
8
7
6
5
4
3
2
1
ppm

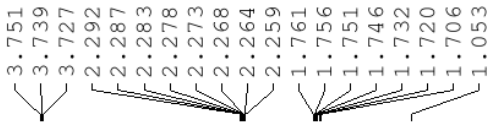
jix-344-080 13C NMR(500) 091311

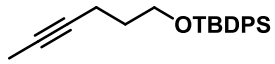


160c

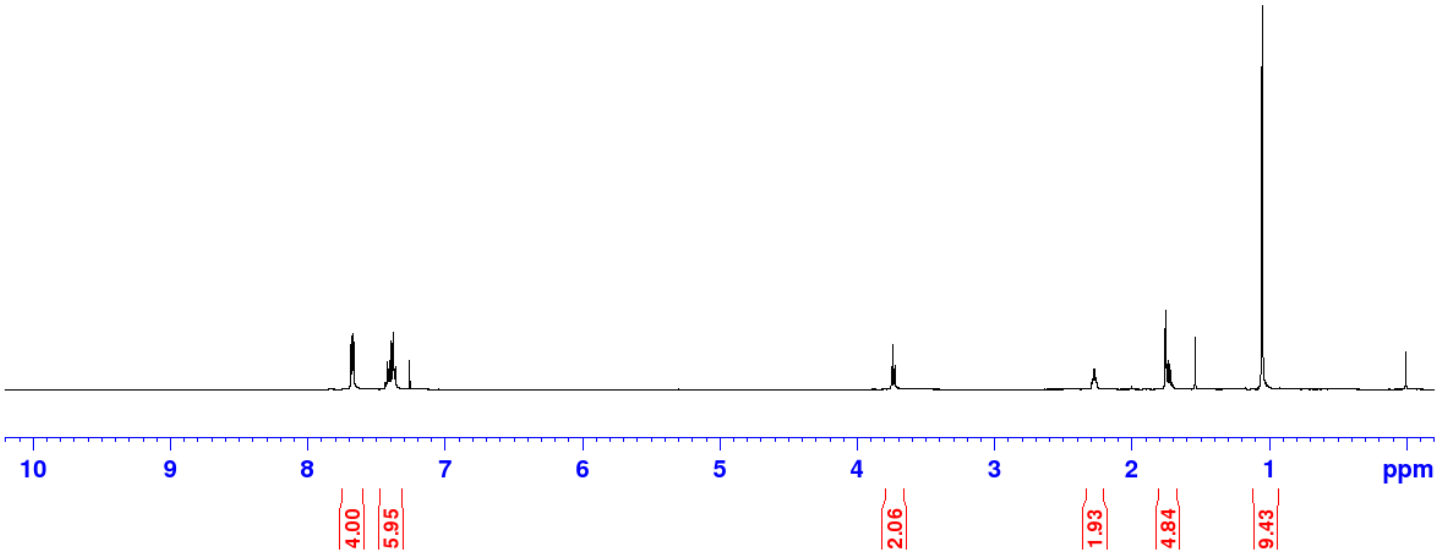
jix-406-080 1H NMR(500) 082912





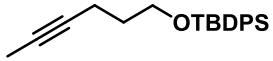


167

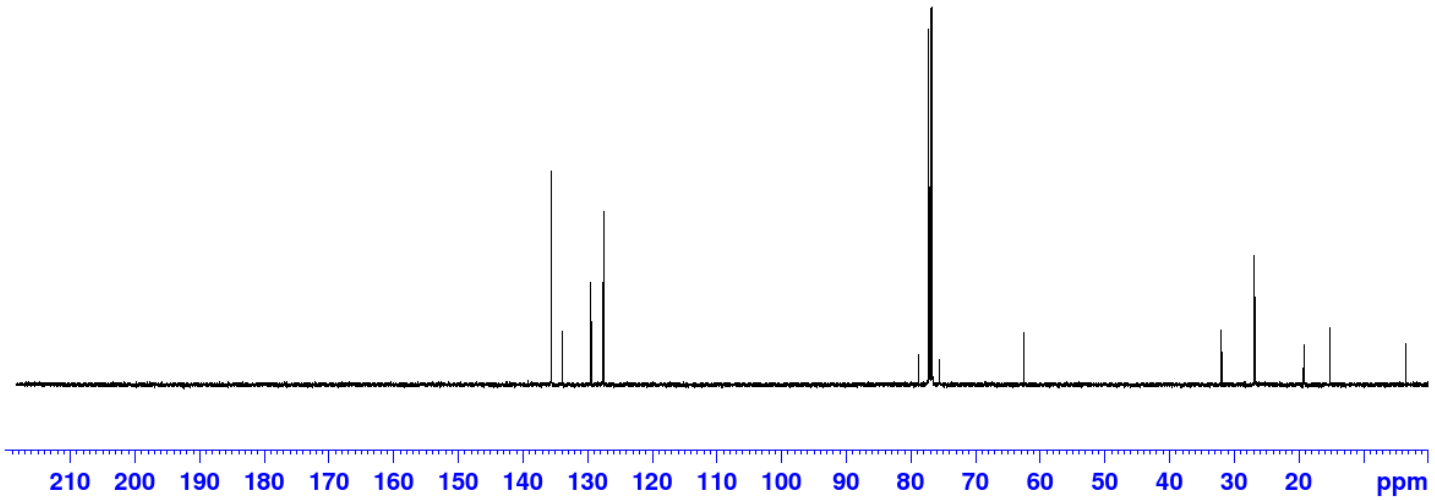


jix-406-080 13C NMR(500) 082912

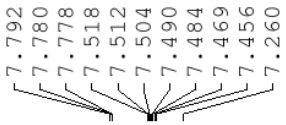
135.60
133.98
129.51
127.59
78.83
77.26
77.00
76.75
75.55
62.55
31.97
26.84
19.24
15.25
3.44

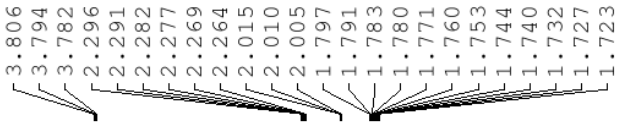


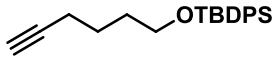
167



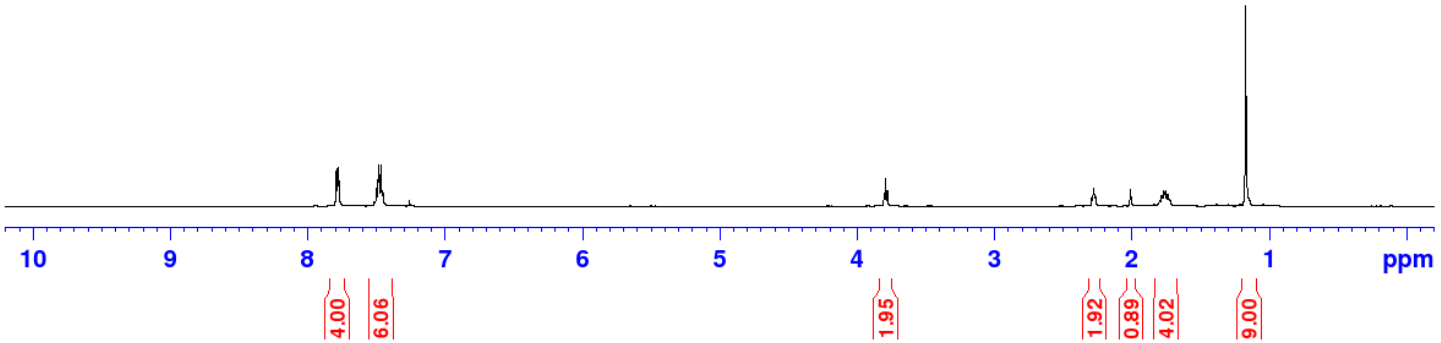
jix-406-081 1H NMR(500) 083112





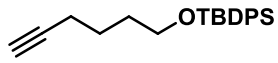


168

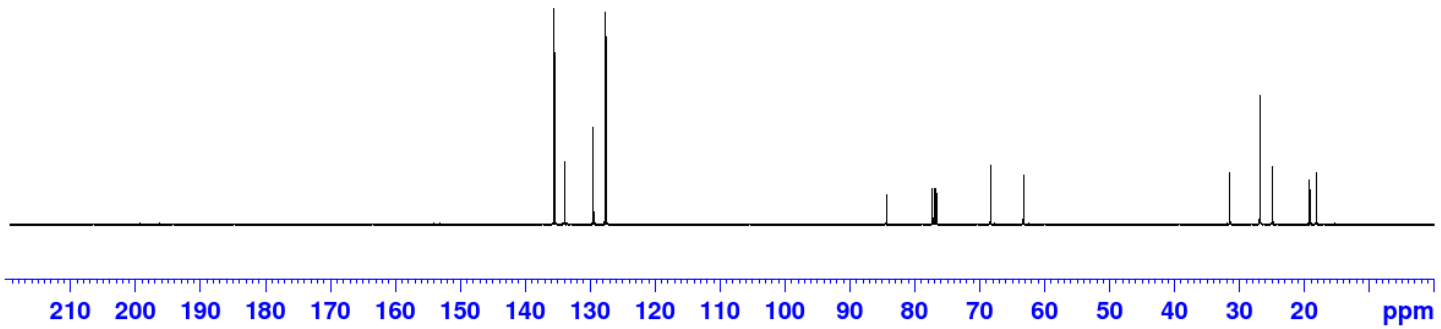


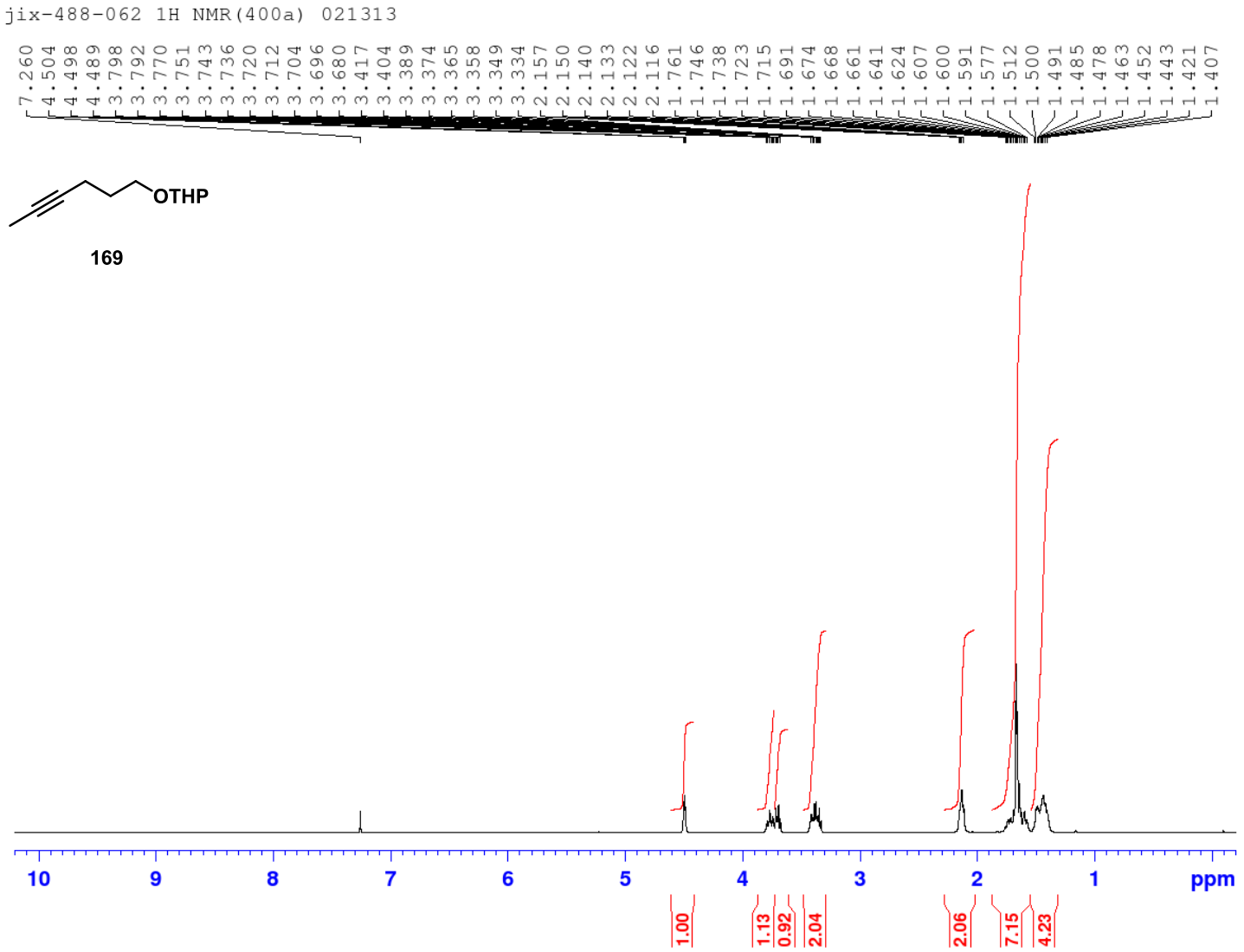
jix-406-081 1H NMR(400a) 083112

135.51
133.91
129.52
127.59
84.38
77.32
77.00
76.68
68.33
63.26
31.50
26.84
24.90
19.17
18.13



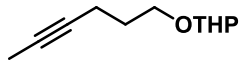
168



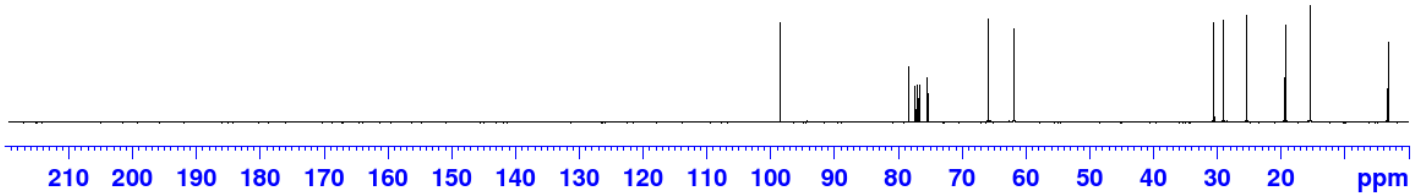

jix-488-062 1H NMR(400a) 021313
7.260
4.504
4.498
4.489
3.798
3.792
3.770
3.751
3.743
3.736
3.720
3.712
3.704
3.696
3.680
3.417
3.404
3.389
3.374
3.365
3.358
3.349
3.334
2.157
2.150
2.140
2.133
2.122
2.116
1.761
1.746
1.738
1.723
1.715
1.691
1.674
1.668
1.661
1.641
1.624
1.607
1.600
1.591
1.577
1.512
1.500
1.491
1.485
1.478
1.463
1.452
1.443
1.421
1.407
OTHP
169
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.13
0.92
2.04
2.06
7.15
4.23

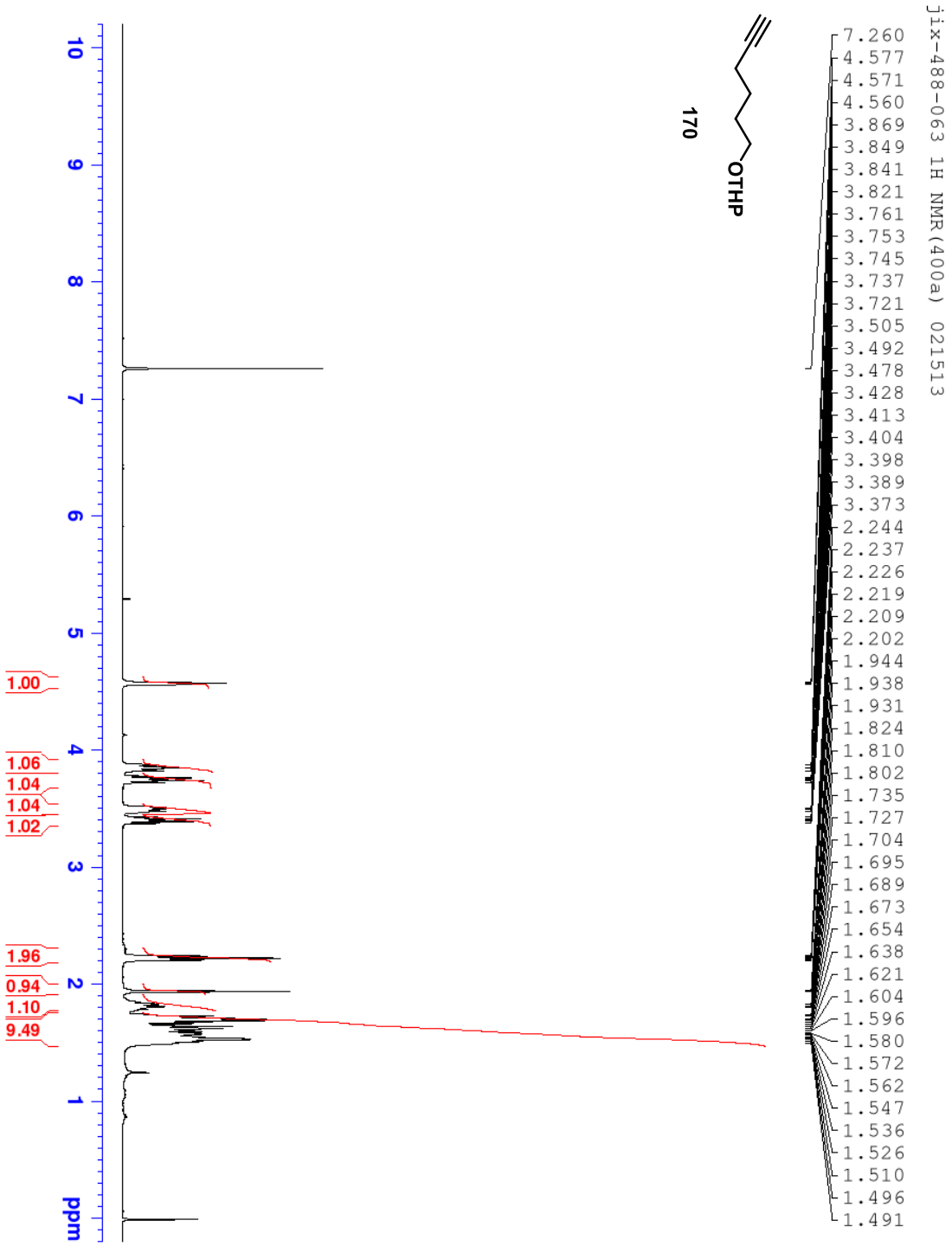
jix-488-062 1H NMR(400a) 021313

98.47
78.30
77.32
77.00
76.68
75.36
65.82
61.80
30.48
29.02
25.32
19.29
15.39
3.16

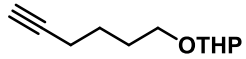


169

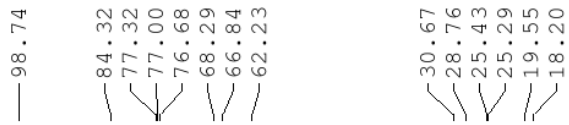


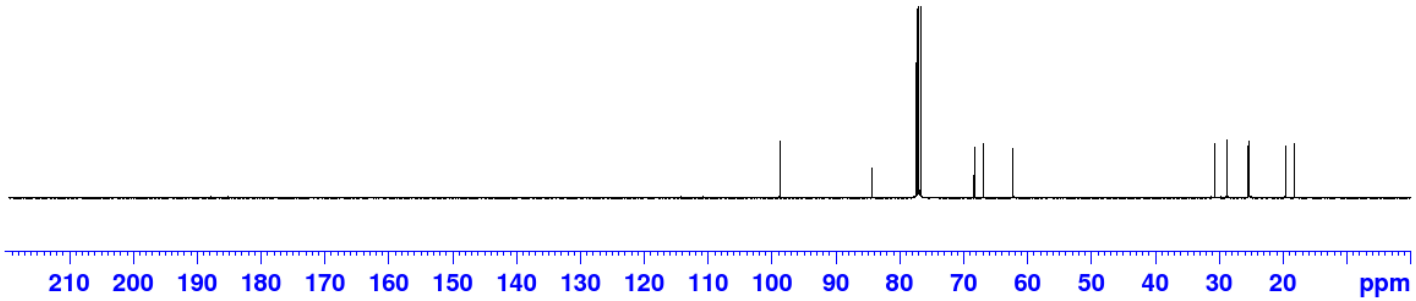

jix-488-063 1H NMR(400a) 021513
7.260
4.577
4.571
4.560
3.869
3.849
3.841
3.821
3.761
3.753
3.745
3.737
3.721
3.505
3.492
3.478
3.428
3.413
3.404
3.398
3.389
3.373
2.244
2.237
2.226
2.219
2.209
2.202
1.944
1.938
1.931
1.824
1.810
1.802
1.735
1.727
1.704
1.695
1.689
1.673
1.654
1.638
1.621
1.604
1.596
1.580
1.572
1.562
1.547
1.536
1.526
1.510
1.496
1.491
170
OTHP
1.00
1.06
1.04
1.04
1.02
1.96
0.94
1.10
9.49
10
9
8
7
6
5
4
3
2
1
ppm

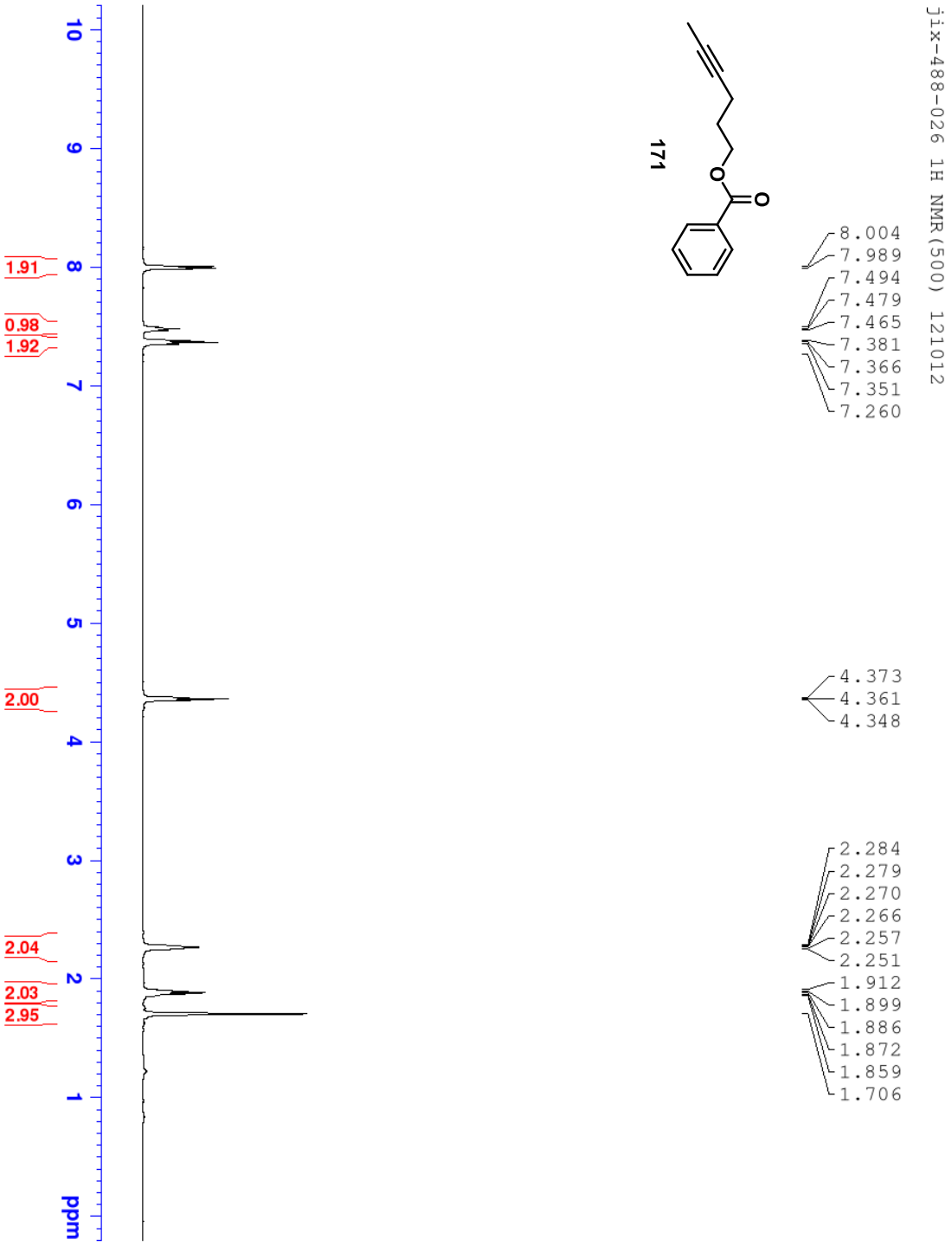
jix-488-063 13C NMR(400a) 021513

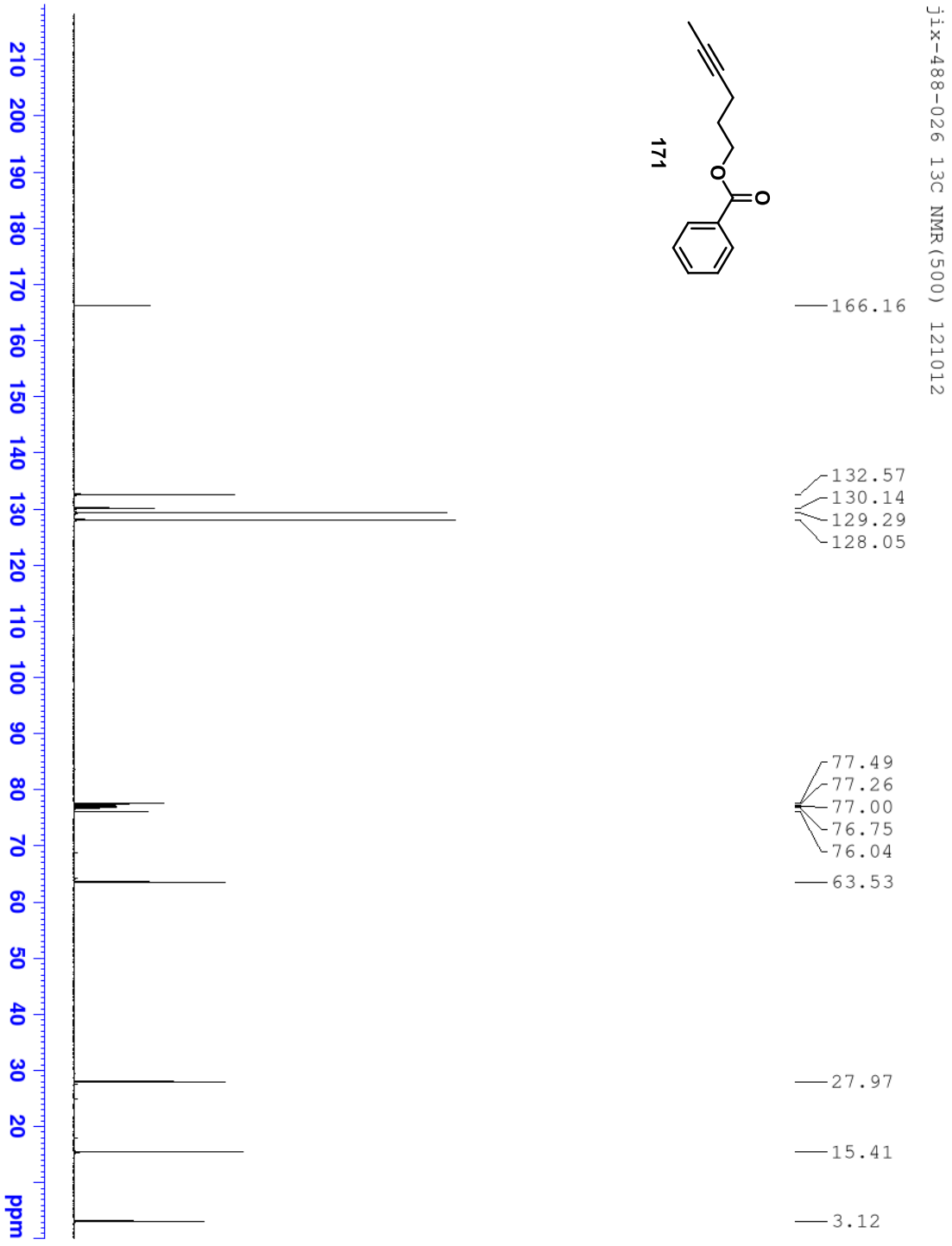


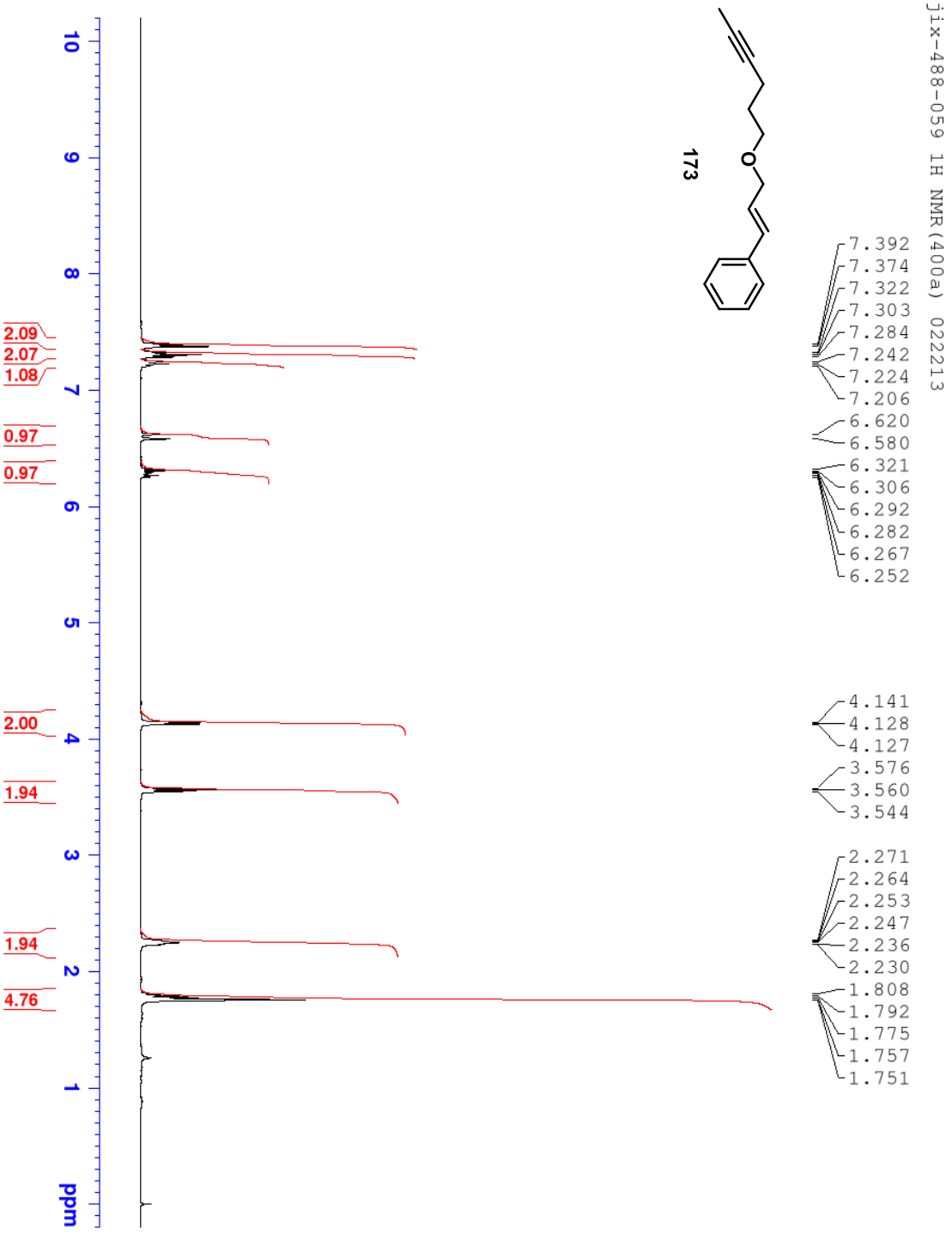
170



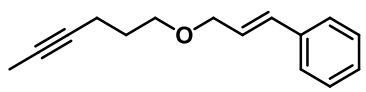



jix-488-026 1H NMR(500) 121012
171
8.004
7.989
7.494
7.479
7.465
7.381
7.366
7.351
7.260
4.373
4.361
4.348
2.284
2.279
2.270
2.266
2.257
2.251
1.912
1.899
1.886
1.872
1.859
1.706
1.91
0.98
1.92
2.00
2.04
2.03
2.95
10
9
8
7
6
5
4
3
2
1
ppm


jix-488-026 13C NMR(500) 121012
171
166.16
132.57
130.14
129.29
128.05
77.49
77.26
77.00
76.75
76.04
63.53
27.97
15.41
3.12
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

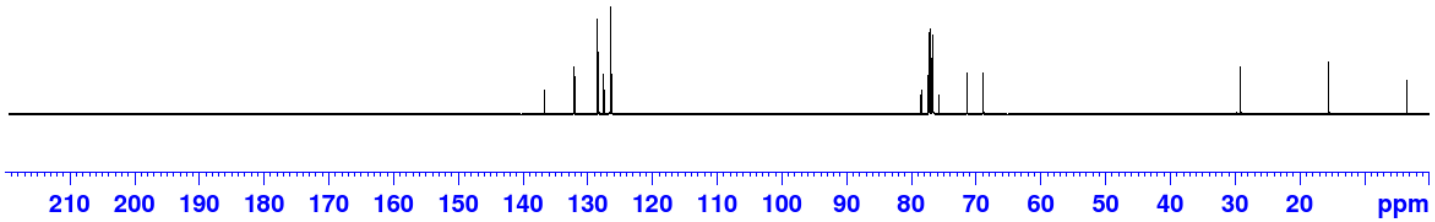

jix-488-059 1H NMR(400a) 022213
173
7.392
7.374
7.322
7.303
7.284
7.242
7.224
7.206
6.620
6.580
6.321
6.306
6.292
6.282
6.267
6.252
4.141
4.128
4.127
3.576
3.560
3.544
2.271
2.264
2.253
2.247
2.236
2.230
1.808
1.792
1.775
1.757
1.751
2.09
2.07
1.08
0.97
0.97
2.00
1.94
1.94
4.76
10
9
8
7
6
5
4
3
2
1
ppm

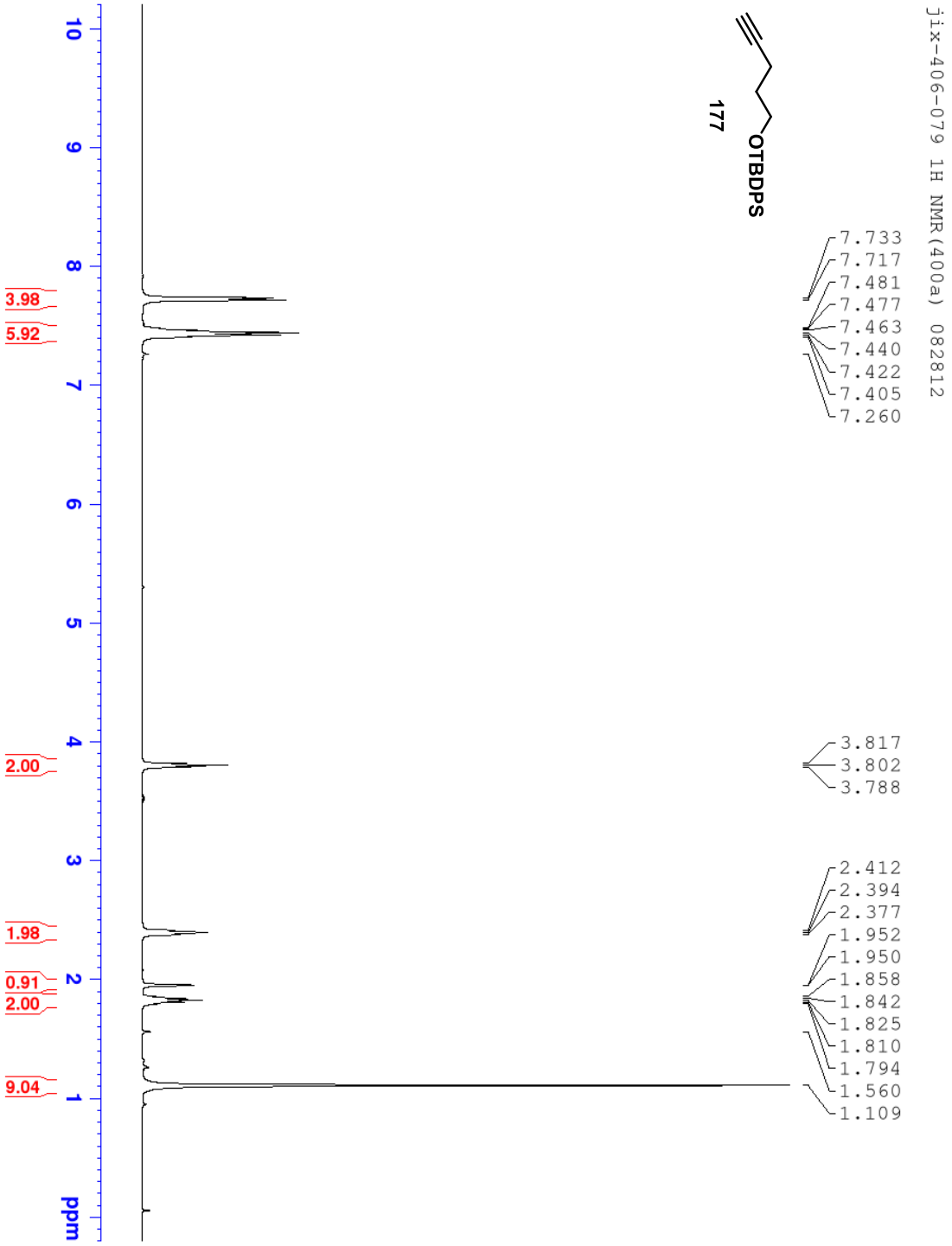
jix-488-059 1H NMR(400a) 022213



173

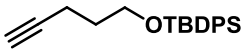
136.75
132.06
128.47
127.54
126.41
126.30
78.48
77.32
77.00
76.68
75.70
71.36
68.87
29.13
15.51
3.40




jix-406-079 1H NMR(400a) 082812
OTBDPS
177
7.733
7.717
7.481
7.477
7.463
7.440
7.422
7.405
7.260
3.817
3.802
3.788
2.412
2.394
2.377
1.952
1.950
1.858
1.842
1.825
1.810
1.794
1.560
1.109
3.98
5.92
2.00
1.98
0.91
2.00
9.04
ppm

jix-406-079 13C NMR(400a) 082812

135.55
133.79
129.57
127.61
84.18
77.32
77.00
76.68
68.29
62.24
31.41
26.82
19.22
14.95



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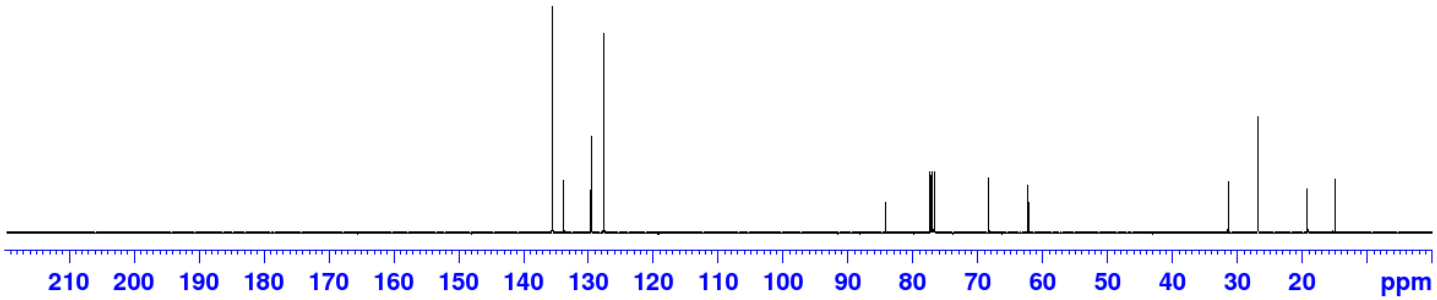
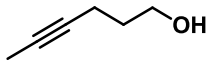


jix-488-024 1H NMR(500) 120612

7.260

3.598
3.585
3.573
3.031
2.139
2.134
2.129
2.125
2.120
2.115
2.111
2.106
1.670
1.664
1.659
1.629
1.615
1.602
1.589
1.575



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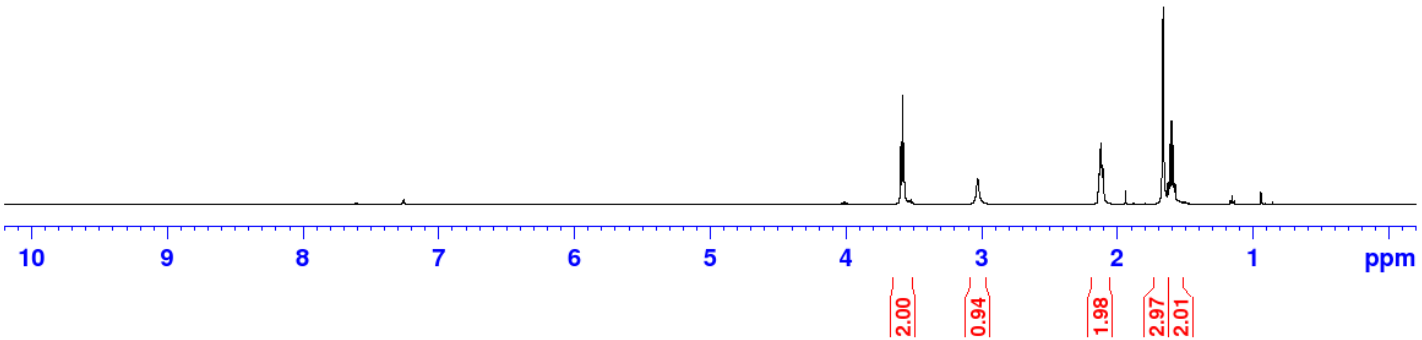
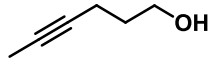


jix-488-024 13C NMR(500) 120612



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