University of Nevada, Reno

Annulation and Substitution Reactions Mediated by Cobalt and Scandium Complexes, Respectively

A dissertation submitted in partial fulfilment of the

Requirements for the degree of Doctor of Philosophy in Chemistry

By

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Substitution and Annulation Reactions mediated by Cobalt and Scandium Complexes, Respectively

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ABSTRACT

The following dissertation work is generally divided into five main chapters. Besides chapter one (Background) and chapter five (conclusion and future work) Content in chapter two and three have been published in *Organometallics* and *RSC Advances* in 2018 and 2020, respectively.

Chapter one is a short background of chemistry of ethers and Pauson-Khand reaction. Chapter two mainly focuses on the substitution reactions catalyzed by Scandium and Dimethylaminoprydine for the synthesis of unsymmetrical ethers. In terms of step and atom economy, substitution reactions using catalysts for the synthesis of asymmetrical ethers has been great deal of interest among all research groups. So, we have reported catalytic activation of alcohols using scandium triflate and dimethyl aminopyridine (DMAP) as the ligand for the synthesis of secondary and tertiary alcohols. In chapter four and five the development of the PKR has been reported. Using nitrous oxide as the promoter and arylboronic acid in the reactions enabled us to synthesize new molecular structure from the precursors which have not been reported before in the reaction.

DEDICATION

I dedicate my dissertation work to my dear family

ACKNOWLEDGMENTS

I would like to pay my special regards to my graduate advisor, Dr. Laina Geary who was more than generous with their expertise and precious time. Also, I wish to show my deepest gratitude to my committee members Dr. Thomas Bell, Dr. Sean Casey, Dr. Jonathan Weinstein, and Dr. Behrouz Abbasi for their practical suggestions.

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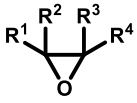
Chapter 1 Background

1.1 Chemistry of ether

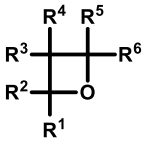
Acyclic or cyclic ethers containing (SP^3) C-O-C (SP^3) functionality have been widely used in organic chemistry as intermediates or targeted molecules. Generally, there are eight product classes of ethers that each class has its own methods of preparation.

- dialkyl ethers

- epoxides (oxiranes)



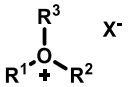
- oxetanes



- five-membered and larger-ring oxacycloalk-3-enes

- five-membered and larger-ring oxacycloalkanes

- oxonium salts



- oligo- and monosaccharide ethers

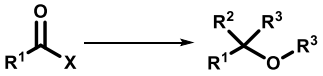
- ethers as protecting groups

R^2= Removable group

Among all these classes dialkyl ethers are produced from various precursors as esters, aldehydes, ketones, and acetals. Also, they have been produced through substitution reactions and, alkene addition. Moreover, these functional group have been synthesized to protect alcohol in organic reactions.[1,2]

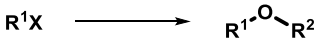
Scheme 1.1 Synthetic methods for synthesis of ethers

- Synthesis from esters, aldehydes, ketones, and acetals

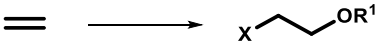


X= H, alkyl, alkoxy

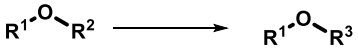
- Synthesis by substitution



- Synthesis by addition to alkenes



- Synthesis from other ethers



1.1.2 Direct catalytic dehydrative substitution of alcohols

In terms of atom/step economy and green chemistry, alcohols are great chemicals for substitution reactions that make water as by-products. Due to the poor leaving group ability of hydroxyl group, these chemicals are transformed to halides or pseudohalides prior to substitution reaction. Therefore, direct catalytic activation of these chemicals which enables the hydroxyl group to leave, have been of great interest of research groups. [3]

Mary and et al. have been pioneered in domain of S_N1 -type dehydrative substitution of alcohol. They have reported the reaction rates of different nucleophiles and electrophiles. Also, they have introduced a formula that predict if a reaction can occur at room temperature. (**equation 1.1**)

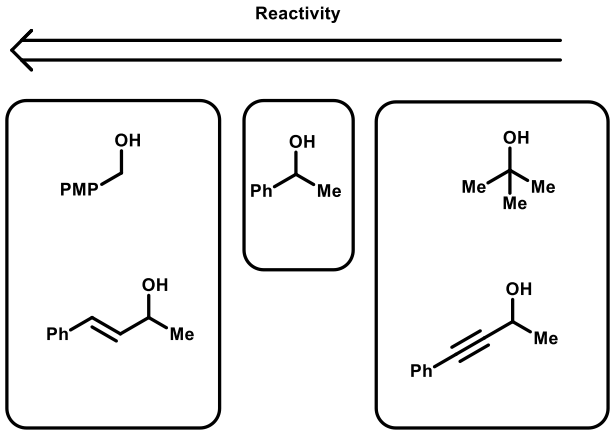
Equation 1.1 prediction of the S_N1 -type dehydrative substitution of alcohol

$E + N > -5$

According to this rule of thumb, if the nucleophilicity parameter (N) plus the electrophilicity parameter of a pair of electrophile/nucleophile is greater than -5, the reaction occurs at room temperature.[4,5,6]

In 2013, Samec and Biswas, reported interesting experimental findings regarding the dehydrative substitution of alcohol. They stated that formation of carbocation determines the completion of the reaction. In other words, formation of the carbocation is more important than the electrophilicity of the carbocation. Also, they observed that the formation of the final product is heavily dependent on the combination of the nucleophile and catalyst. They have reported the following alcohol substrates in the order of reactivity in catalytic dehydrative substitution reactions. As the π-Activated Alcohols do not have β-hydrogen atoms, the substitution reaction does not compete with the elimination reactions, so the probability of the substation reaction increases in the reaction.[7] (**Figure 1.1**)

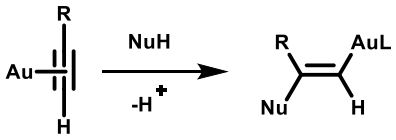
Figure 1.1 Reactivity of alcohols in reactivity in catalytic dehydrative substitution reactions



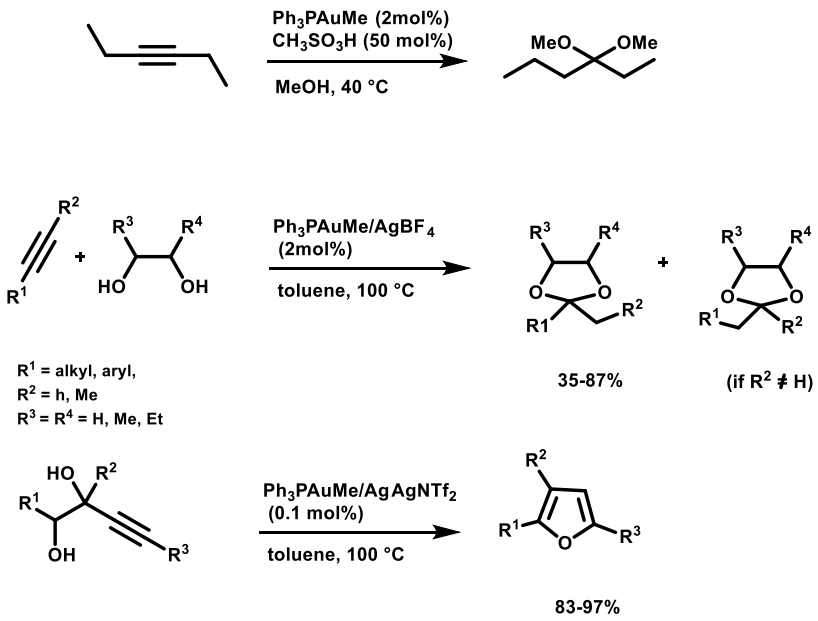
1.1.3 Metal catalyzed reactions for the formation of unsymmetrical ethers

Hight π-bond selectivity of alkynes identifies gold (I) complexes as the most effective catalyst for the activation of alkyne and formation of molecular complexity. Among all gold complexes, gold(I) complexes bearing phosphines or N-heterocyclic carbenes as ligands have been greatly utilized for activation of alkynes. According to the literatures, Markovnikov alkyne coordination into the metal forms trans-alkenyl-gold intermediate. (Scheme 1.1)

Scheme 1.2 Activation of alkynes gold(I) complexes



So far, many studies have been reported nucleophilic activation of alkynes for the formation of asymmetrical ethers using gold complexes in intramolecular and intermolecular fashions.[8,9,10]

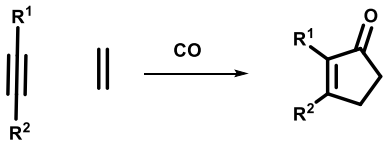


Besides gold (I) complexes, Pt(II), Ag(I) complexes and Ga(III) and In-(III) salts have been used for the formation of asymmetrical ethers in substitution reactions.[11]

1.2 Pauson-Khand reaction

Pauson-Khand reaction as an annulation technique has been used frequently in pharmaceutical industries for the synthesis of cyclopentenone using alkyne, alkene, and carbonyl. Dr. Pauson and his postdoc associate Dr. Khan reported the annulation technique for the first time in 1970. Their results were published in 1971 in Chemical Communication Journal. [12]

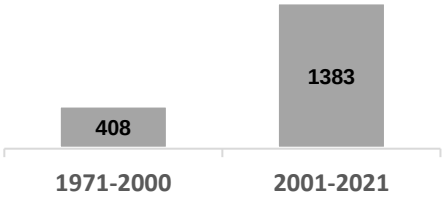
Scheme 1.3 Pauson-Khand reaction



This method was reported stoichiometrically, although many papers have been published regarding the catalytic PKR. Moreover, Non-chiral, diastereoselective, asymmetric and, enantioselective PKR have

been investigated. Also, this annulation method has been widely used for the total synthesis of chemical which is greatly significant in terms of atom economy and cost. PKR reaction has been of great interest of research groups and so far, almost 2000 papers have been published citing this technique. [13]

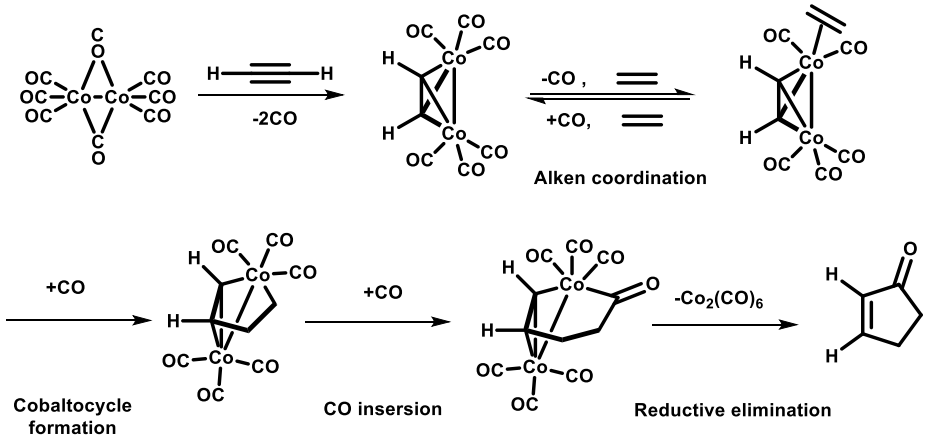
Figure 1.2 Number of papers of the PKR



1.2.1 Mechanism of Pauson-Khand Reaction

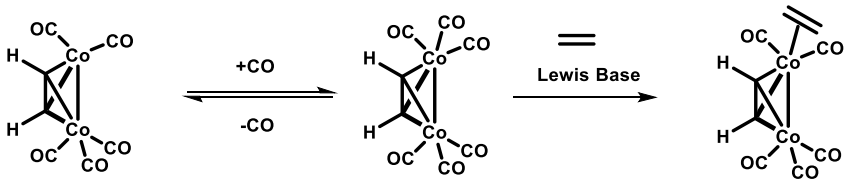
As it was mentioned earlier, PKR is a reaction between and alkyne, alkene and carbonyl which usually comes from cobalt carbonyl complex. Many transition metals have been used as the catalyst in the PKR. According to the mechanistic studies, this reaction is divided into five general steps including alkyne-dicobalt hexacarbonyl formation, alkene coordination, cobaltocycle formation, carbonyl insertion and reductive elimination. (**Scheme 1.2**)

Scheme 1.4 Mechanism of stoichiometric PKR reaction



Alkene-coordination formation is an equilibrium step, so using Lewis base additives as *N*-oxides accelerate the reaction toward the cobaltocycle formation by releasing carbon dioxide. On the other hand, performing the reaction under CO pressure inhibits the reaction. (**Scheme 1.3**)

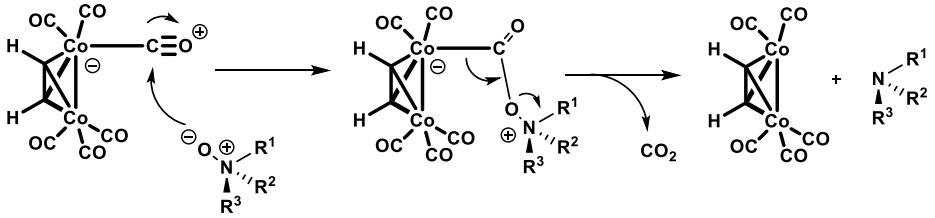
Scheme 1.5 CO pressure and promoter in CO dissociation



1.2.2 *N*-oxides promoted Pauson-Khand reactions

It has been found that the efficiency of the PKR reaction greatly increased by using promoters. In 1990 Schereiber et al. reported promoted PKR using *N*-methyl morpholine oxide (NMO) in an intermolecular fashion.[14] One year later Jeong et al. reported intramolecular PKR using trimethylamine N-oxide (TMAO) in presence of Molybdenum hexacarbonyl ($Mo(CO)_6$).[15] Beside the two above-mentioned promoters other *N*-oxides have been utilized in the PKR reaction. [16] According to the literature *N*-oxides promotes the reaction through the following mechanism. As it is illustrated in scheme 1.4, nucleophilic attack of the *N*-oxide on the carbon carbonyl release carbon dioxide and left the amine as the by product. [16].

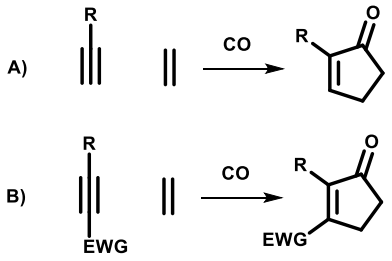
Scheme 1.6 Nucleophilic coordination of the N-oxide



1.2.3 Regioselectivity of Pauson-Khand reaction

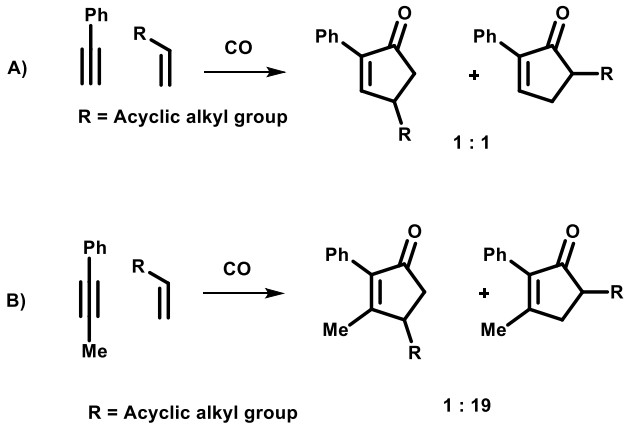
Regioselectivity of the alkyne substrates is more predictable than olefines. Large substituent usually occupied 2-position on the cyclopentenone formed. Orientation of alkene coordination determine the regiochemistry of the final product. (**Scheme 1.5, A**) Also, it has been found that the EWG of a disubstituted alkyne causes the polarizability of the alkyne complex intermediate. As a result, EWG resides in 3-position of the product. [17] (**Scheme 1.5, B**)

Scheme 1.7 Regioselectivity of the PKR



According to the investigations, mixture of regioisomers is formed when acyclic alkenes react with terminal alkynes. (**Scheme 1.6, A**) Also, regioselectivity of acyclic alkenes increase when they react with internal alkynes. [17] (**Scheme 1.6, B**)

Scheme 1.8 Regioselectivity of alkene component



1.2.4 Limitations of Pauson-Khand reaction

Intermolecular Pauson-Khand reaction as well as intramolecular Pauson-Khand reaction have been reported. Despite many advantages of this annulation technique, it is still limited to some alkyne and alkene substrates. Internal alkynes generally deliver lower yield compared to terminal alkynes and acetylene. Also, alkenes bearing electro-withdrawing groups do not tend to participate in the reaction. For the latter case, it has been rationalized that the LUMO energy state of the alkene is not lower enough to accept metal electron donation.[18,19]

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Chapter 2 Metal Catalytic Formation of Unsymmetrical Ethers

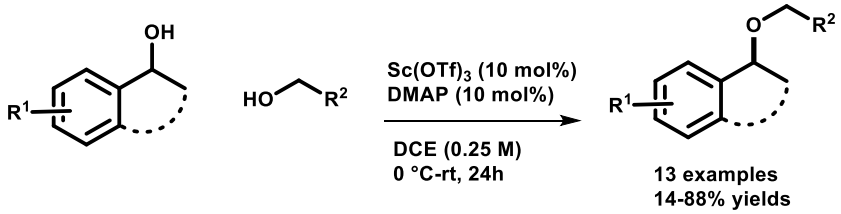
2.1. Abstract

We developed a direct catalytic condensation of benzylic alcohols and primary alcohols to synthesize unsymmetrical ethers in one step, catalyzed by scandium triflate and p dimethylaminopyridine (DMAP). Preliminary experiments give some insight into the mechanism of the reaction, though suggest that the process is quite complex. We suspect the rapid formation of a dimer from a secondary benzylic alcohol via a carbocation intermediate precedes unsymmetrical ether formation.

2.2. Introduction

The direct modification of functional groups is an ongoing challenge in synthetic organic chemistry. Alcohols are abundant and easily accessible via a variety of transformations and are thus attractive substrates for further modification. However, alcohols typically require derivatization or preactivation to enable their use in coupling or substitution reactions. The desire for chemoselective, direct transformation of alcohols into alternate functional groups has been identified as a key goal in the pharmaceutical industry.[1] While there are now a number of protocols to do so,[2] direct condensation of two symmetrical alcohols to form ethers represents a significant challenge. Recent work in the syntheses of unsymmetrical ethers have relied on gold catalysts,[3] solid-phase thiazolium salts,[4] ruthenium catalysts,[5] and boronic acid activation.[6] We discovered that when 3-hydroxydihydrobenzofuran **1a** was exposed to a Lewis acid catalyst and primary alcohol, direct substitution to the unsymmetrical ethers occurred. We report application of this chemistry to a variety of secondary and tertiary benzylic alcohols, as well as some preliminary mechanistic investigations.

Scheme 2.1. The synthesis of unsymmetrical ethers via a direct catalytic substitution.

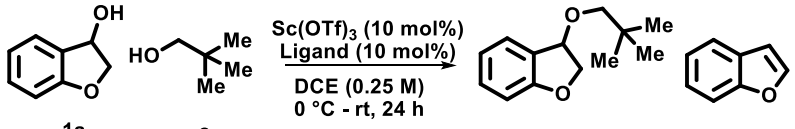


2.3. Results and Discussion

Initial screening studies used 3-hydroxydihydrobenzofuran **1a** as substrate for reactions with prenol. Scandium triflate is a well-known Lewis acid catalyst for dehydrogenation of alcohols in a variety of applications.[7–11] Applying catalytic amounts of scandium triflate led to full consumption of **1a** at room temperature in acetonitrile after 30 minutes; however, only trace amounts of the desired ether substitution product was detected, along with significant amounts of benzofuran from competing elimination chemistry. Copper,[12] ytterbium,[13] and bismuth triflates[14–16] all led to incomplete consumption of **1a** under otherwise identical conditions, and yielded only trace amounts of the substitution product, despite precedence for their ability to enable direct ionization of alcohols. Both zinc triflate, able to catalyze the direct cyanation of benzylic alcohols at 100 °C,[17] and zinc chloride, known for dehydration of alcohols to form ethers at room temperature,[18] were unreactive towards **1a** at room temperature. Similarly, copper catalysts known to ionize allylic alcohols at room[19] or elevated temperatures[20] were ineffective at this dehydrogenative benzylic ether formation from **1a**. As the preliminary reactions performed using scandium triflate as the catalyst led to the complete consumption of the **1a**, albeit with low selectivity for ether formation, we then screened various reaction conditions in the coupling of **3a** with neopentyl alcohol **2a** to optimize for formation of the desired ether. Ultimately, we found that performing the reaction in the polar aprotic dichloroethane (DCE) and initiating the reaction at 0 °C was optimal as increasing the temperature led to complete formation of benzofuran 4, and keeping the reaction at lower temperatures slowed the reaction down

substantially. However, in the absence of an exogenous ligand, that was at the expense of formation of ether **3a** (**Table 2.1**, **entry 1**). We examined amino acids as ligands, which are an inexpensive source of diverse functionality, with **1a** and neopentyl alcohol **2a** as substrates (**entries 2-7**). Heteroaromatic *L*-histidine led to full consumption of **1a** and a modest yield of the desired **3a**. Applying basic amino acids *L*-lysine and *L*-arginine as ligands improved the relative conversion to **3a**, though the isolated yield was slightly diminished (**entry 3, 4**). Other aromatic amino acid ligands, *L*-tryptophan and *L*-phenylalanine performed poorly, and incomplete consumption of **1a** was observed (**entry 5, 6**). Although use of glycine as ligand gave comparable product ratios to *L*-histidine, the yield was poor. We were interested in identifying the particular chemical motif of *L*-histidine that allowed it to function as an effective ligand for selective direct substitution of a benzylic alcohol. Imidazole as a ligand led to poor conversion and selectivity for **3a** (**entry 8**). *N*-Substitution at the 1 or 3 positions of the imidazole ring of *L*-histidine improved selectivity for **3a** and modestly improved yield but did not give full conversion of **1a** (**entries 9, 10**). Converting the carboxylic acid of *L*-histidine to the methyl ester resulted in an improvement in isolated yield of **3a** relative to the parent amino acid (**entry 11 vs 2**), but the yield was still only moderate at 44%.

Table 2.1. Selected optimization experiments in the dehydrative coupling of 3 hydroxydihydrobenzofuran 1a to neopentyl alcohol 2a. [a]



1a (1 equiv) 2a (1.5 equiv) 3a 4

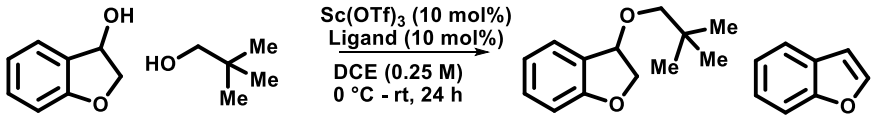
Entry	Ligand	1a:3a:4	Yield% (3a)[a]
1	-	0:0:trace	0[b]
2	L-histidine	0:1.5:1	27
3	L-lysine	2:8.5:1	22
4	L-arginine	0:3:1	25
5	L-tryptophan	1:0:0	NR
6	L-phenylalanine	1.5:1.3:1	6
7	glycine	0:1:1	13
8	imidazole	1.6:1.5:1	32
9	1-methyl-L-histidine	6:11:1	35
⇨ 10	3-methyl-L-histidine	1:6:1	42
11	L-histidine methyl ester	1:6:1.5	44
12	4-(dimethylamino)pyridine	0:2:1	58[c]

[a] Isolated yields of analytically pure material. [b]Intractable mixture. [c]The isolated yield was reduced to 40% if left to run for 48 hours.

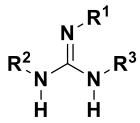
We rationalized that the Lewis basic ligands were modulating the relative Lewis acidity of the scandium catalyst, and were pleased to find that employing 4-dimethylaminopyridine in conjunction with $Sc(OTf)_3$ led to the formation of **3a** in 58% isolated yield (entry 12). Increasing catalyst loading to 20 mol% did not result in a significant increase in isolated yield of **3a** and decreasing the loading to 5 mol% only slowed the reaction down and did not improve selectivity for **3a** over 4. The unusual success of DMAP in combination with $Sc(OTf)_3$[21] promoted us to evaluate other nitrogen bases, both mono- and bidentate (**Table 2.2**). Guanidine·HCl and guanidine derivatives led to exclusive production of benzofuran 4, unless functionalized with an electron donating group (**entries 1-3** versus **entries 4-6**). Bidentate ligands slowed the consumption of **1a** substantially, consistent with decreased reactivity with excess DMAP (vide infra). While the catalyst derived from bipyridines **L7** and **L8** were

able to successfully generate some ether **3a**, the catalysts derived from phenanthrolines **L9** and **L10** led only to formation of benzofuran 4, perhaps due to the increased basicity of the phenanthrolines relative to bypyridines.[22] Most reactions that employed pyridine-derived ligands produced moderate amounts of ether **3a**, with the exception of 2,6-lutidine **L16** and 2,6-di*tert*butylpyridine **L17**, which only produced benzofuran 4. DMAP **L13**, 2-phenylpyridine **L18**, and 2,6-bis(diethylamino)pyridine **L20** were equally effective, and DMAP **L13** was selected for further studies as it is inexpensive, easily handled, and not as susceptible to decomposition as **L20**.

Table 2.2. Screening of Lewis basic ligand in conjunction with scandium triflate.



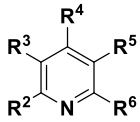
1a (1 equiv) 2a (1.5 equiv) 3a 4

(A)		L1, R^1=R^2=R^3=H[b]	L4, R^1=R^2=Boc, R^3=Bn
		L2, R^1=H, R^2=R^3=Boc[c]	L5, R^1=R^2=Boc, R^3=pyrrolidine
		L3, R^1=Tf,[c] R^2=R^3=Boc	L6, R^1=H, R^2=R^3=Ph

Entry	Ligand	3a:4	Yield% (3a)[a]
1	L1	0:1	0
2	L2	0:1	0
3	L3	0:1	0
4	L4	1:0.67	47%
5	L5	1:0.72	43%
6	L6	1:0.3	41%

(B)		L7, bipyridine (bipy)	L10, neocuproine
		L8, 4,4'-$(tBu)_2$-bipy	L11, TMEDA[d]
N_2		L9, phenanthroline	L12, DABCO[e]

Entry		Ligand	3a:4	Yield% (3a)[a]
7	aryl	L7	1.3:1	39%
8		L8	1:2	29%
9		L9	0:1	0
10		L10	0:1	0
11	alkyl	L11	0:1	0
12		L12	0.4:1	18%

(C)[f]		L13, R^4=NMe_2, DMAP	L17, R^2=R^6=tBu
		L14, R^3=OMe, R^5=Cl	L18, R^2=R^4=Me, R^6=NH_2
N		L15, R^2=Ph	L19, R^2=R^6=NH_2
		L16, R^2=R^6=Me	L20, R^2=R^6=NEt_2

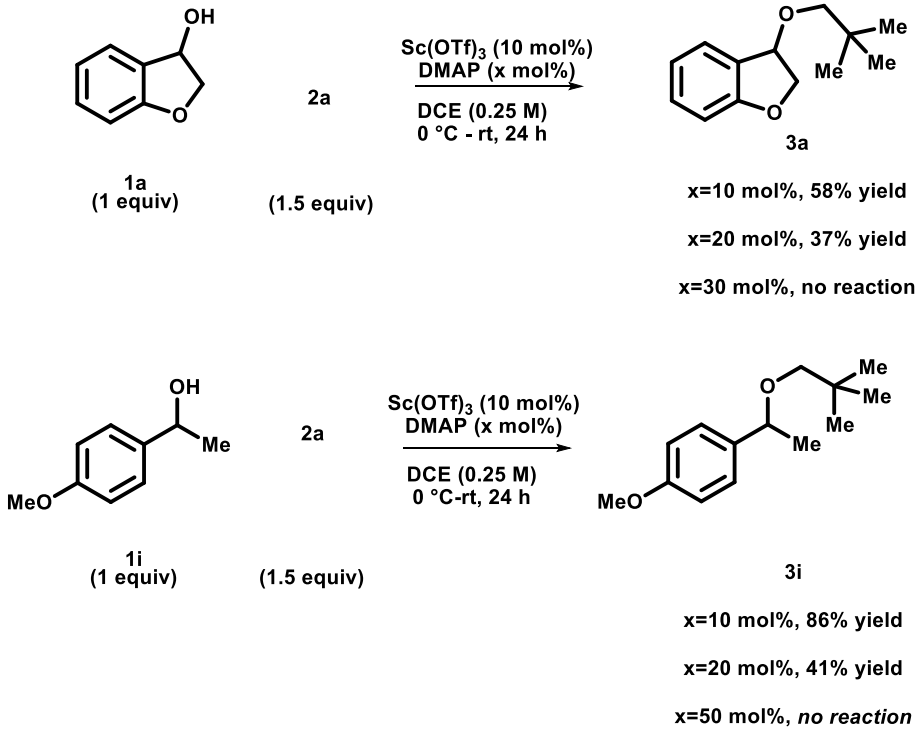
Entry	Ligand	3a:4	Yield% (3a)[a]
13	L13	2:1	58%
14	L14	N.D.[g]	48%
15	L15	N.D.	58%
16	L16	0:1	0
17	L17	JD	JD
18	L18	1.2:1	40%
19	L19	1:0.6	42%
20	L20	N.D	57%

[a]Isolated yield of 3a. [b]Used as the HCl salt. [c]Boc = t-butyl carbonate.
[d]TMEDA = tetramethylethylenediamine. [e]DABCO = 1,4-diazabicyclo[2.2.2]octane.
[f]R=H unless otherwise indicated. [g]N.D.=not determined.

We then finally looked at the effect of DMAP loading relative to scandium (**Scheme 2.2**); unsurprisingly, we found that increasing DMAP to 20 mol% (2 equiv. relative to scandium), the reaction between either **1a** or 1i and neopentyl alcohol **2a** was slowed, and the isolated yields of ethers **3a** and **3i** were reduced. Further increasing the loading of DMAP to 30 mol% (reaction with **1a**) or 50

mol% (reaction with 1l), the reaction was shut down entirely, and no ether or elimination product could be detected. These results are consistent with the reduced ability of catalysts derived from bidentate ligands to promote the reaction, and further supports that the DMAP ligand is tuning the Lewis acidity of scandium to control the reaction and favor substitution reactions.

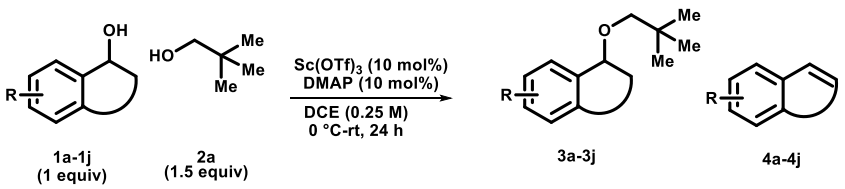
Scheme 2.2. Effect of DMAP loading on conversion to 3a and 3i.



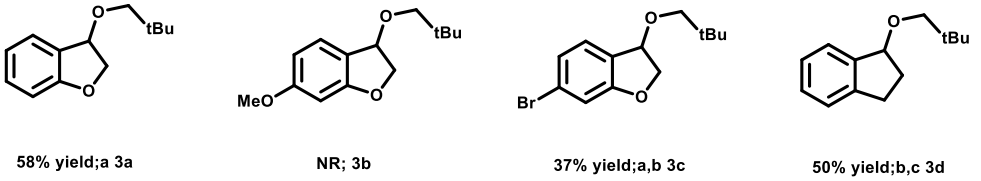
With optimized conditions in hand, we evaluated the scope of the reaction with respect to the nature of the benzylic alcohol component (**Table 2.3**). While the reaction between **2a** and **1a** gave ether **3a** in 58% yield, an analogous 3- hydroxy-5-methoxydihydrobenzofuran **1b** substrate was unreactive under identical conditions. However, 5-bromo-3-hydroxydihydrobenzofuran **1c** as substrate gave a modest 37% yield of the corresponding ether **3c** with incomplete consumption of **1c**. One could predict that a carbocation generated from **1b** would be more stabilized and therefore less reactive than a carbocation generated from either **1a** or **1c**;[23] given that we have evidence of the possibility of carbocation

intermediates (vide infra), that could justify the lack of reactivity of **1b**. The reaction of indanol **1d** with **2a** gave 50% yield of ether **3d** as estimated by the crude ^{1}H NMR spectrum of the reaction mixture, which could not be separated cleanly from the competing elimination product, indene **4d**. We then evaluated the direct substitution of dihydrochromenols and tetrahydronapthalenols in the presence of scandium and DMAP. Dihydrochromenols **1e** and **1f** were suitable substrates, and ethers **3e** and **3f** were formed in 40% and 70% yield, respectively, in high conversion and selectivity. However, tetrahydronaphalenol **3g** was produced in only 26% yield and reaction with the quaternary **1h** led gave exclusive elimination to dihydronaphthalene **4h**.

Table 2.3. Scandium catalyzed substitution of benzylic alcohols 1a -1t.

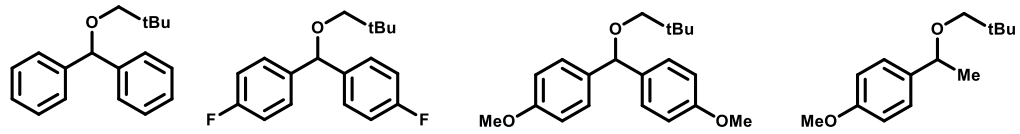


1a-1j (1 equiv) 2a (1.5 equiv) 3a-3j 4a-4j

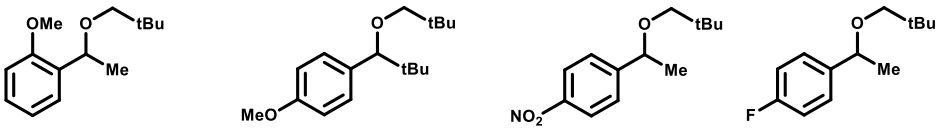


58% yield;a 3a | NR; 3b | 37% yield;a,b 3c | 50% yield;b,c 3d

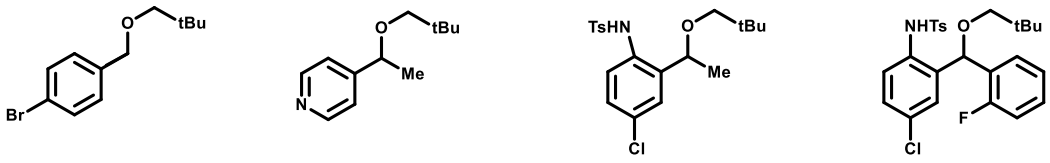
40% yield;a,b 3e | 70% yield;a 3f | 26% yield;b,c 3g | 0% yield;b 3h



20% yield;a 3i | 14% yield;a 3j | 99% yield;a 3k | 88% yield;a,f 3l



88% yield;a 3m | 25% yield;a 3n | NR, 3o | NR, 3p



NR, 3q | NR, 3r | NR, 3s | NR, 3t

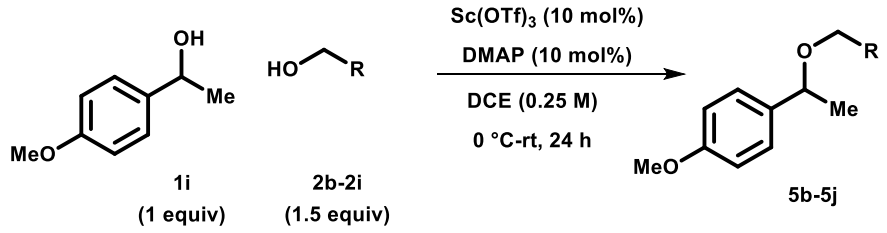
aIsolated yields of pure material. bSubstantial amounts of elmination byproduct 4 detected by analysis of crude 1H NMR spectra. cYield determined by analysis of crude 1H NMR spectra.

We next evaluated the utility of acyclic benzhydrols and secondary benzylic alcohols in the substitution chemistry. The parent benzyhydrol, as well as the di-*p*-fluorosubstituted variant were only

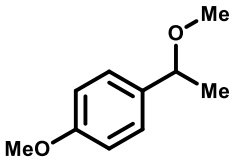
moderately good substrates, and ethers **3i** and **3j** were produced in relatively low yields. In contrast, the bis(*p* methoxyphenyl)methanol was an excellent substrate, and ether **3k** was produced in nearly quantitative yield. With those data in hand, we evaluated several secondary benzylic alcohols with one aryl and one alkyl ligand **(1l-1t**). Unfortunately, but unsurprisingly, only substrates with a methoxy group were reactive (**1l-1n**). The reaction was most successful when the methoxy group was in the *para* position, and ether **3l** was isolated in 86% yield; the more sterically encumbered ethers **3m** and **3n** were isolated in lower yields. Benzylic alcohols with electron withdrawing groups were entirely unreactive under the optimized conditions, consistent with the necessity for generating a cationic intermediate.

As ether **3l** was produced in high yield, we next examined the scope of the reaction of **1l** with various primary alcohol nucleophiles (**Table 1.4**). Most alcohols examined gave moderate to high yields of the unsymmetrical ether (**5b**-**5j**). Simply primary and allylic alcohols were effective coupling partners (**2b**-**2d**) to yield ethers **5b**-**5d**, as were alcohols containing β–substitution (**2e** and **2f** to give **5e** and **5f**). Notably, furfural alcohol **2g** and highly activated benzylic alcohol **2h** could also be employed, and the unsymmetrical ethers **5g** and **5h** were isolated in high yields, with no detection of byproducts arising from ionization of **2g** or **2h**. We then sought to employ amino alcohols as coupling partners for direct ether formation. Though unprotected amino alcohols were unreactive in this process, *N*-tosyl-3-aminopropanol **2i** and *N*-tosyl-(*S*)-valinol **2j** were both able to couple with benzylic alcohol **1i**, and ethers **5i** and **5j** were isolated in high yields, albeit with no diastereoselectivity in the case of **5j** (1:1 dr). An analogous reaction with *N*-Boc valinol was unsuccessful; the consumption of **1i** was incomplete, and the only identifiable products were *p*-methoxystryene and dimer 6.

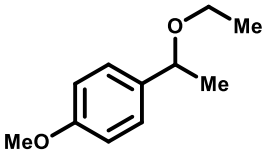
Table 2.4. Scandium catalyzed substitution of 4-methoxyphenyl-1-ethanol 1i with alcohols 2a-1i.



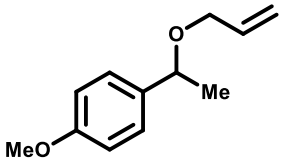
2b, R = H
2c, R = Me
2d, R = $CH_2CH{=}CH2$
2e, R = c-hexyl
2f, R = adamantyl
2g, R = 2-furyl
2h, R = 3,4,5-$(OMe)_3C_6H_2$
2i, Nu = CH_2CH_2NHTs
2j, Nu = (S)-N-Ts-valinol



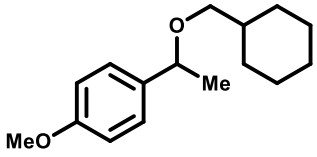
76% yield;a 5b



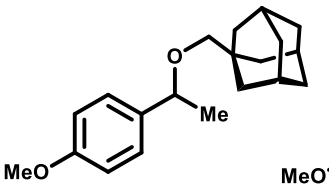
74% yield;a 5c



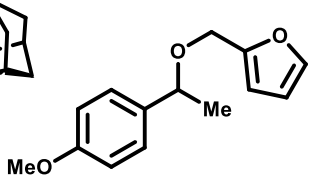
90% yield;a 5d



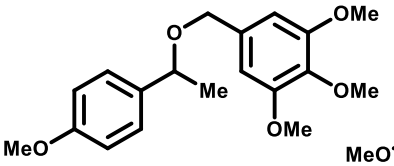
90% yield;a 5e



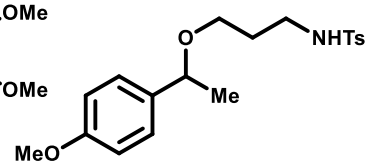
79% yield;a 5f



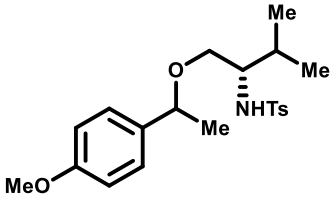
83% yield;a 5g



83% yield;a 5h



79% yield;a 5i



86% yield;a 5j
1:1 dr

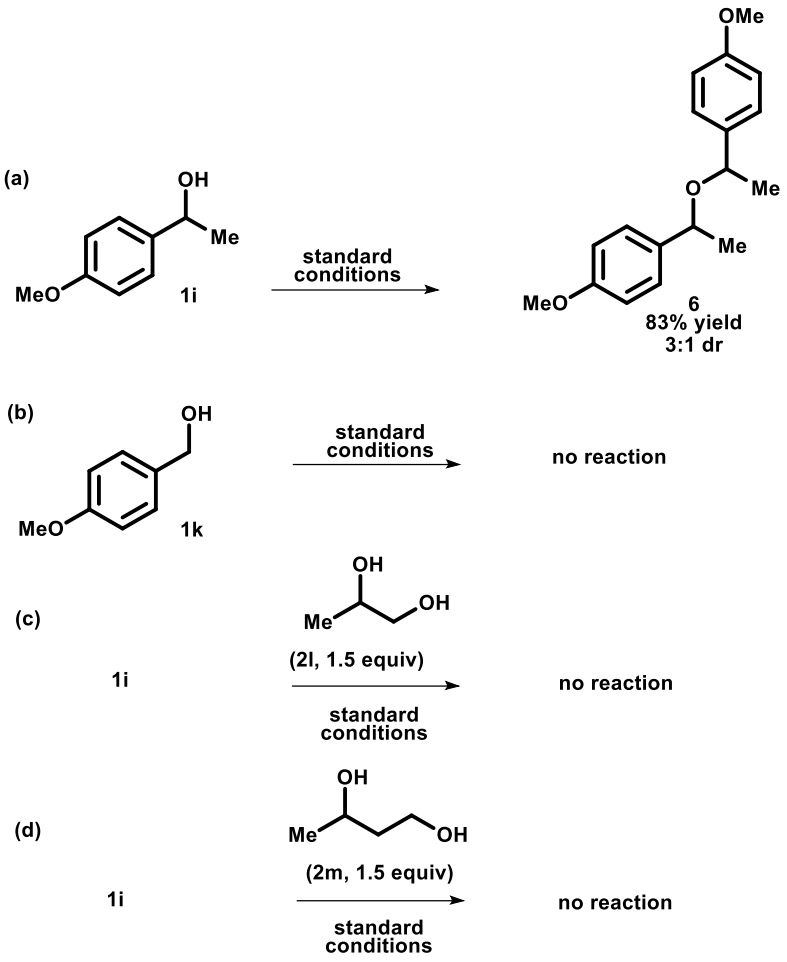
aIsolated yields of pure material.

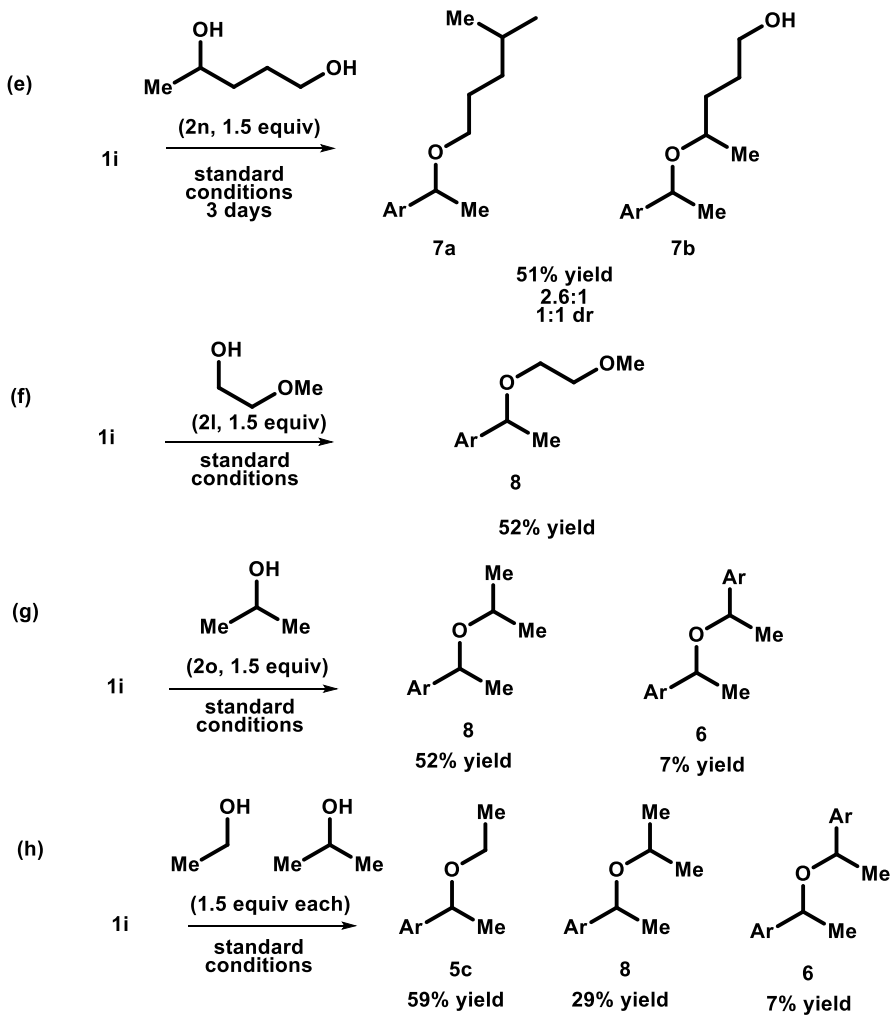
In most experiments in **Table 1.4**, we couldn't detect any significant amount of elimination product to p-methoxystyrene or the product of homodimerization of **1l**. However, when the primary alcohol was

omitted from the reaction, homodimer 6 was isolated in high yields and moderate diasteroselectivity (**Scheme 1.3**, **equation a**). p-Methoxybenzyl alcohol **1k** was unreactive under the standard reaction conditions (equation b). Those results suggested that we should have been able to selectively couple an activated benzylic alcohol with an unprotected diol, and thus we evaluated several diol coupling partners with benzylic alcohol **1l** under our optimized conditions (**Scheme 1.3**, **equations c-e**). We found that both 1,2-propane diol (**Scheme 1.3c**) and 1,3-butanediol (**Scheme 1.3d**) were unreactive under optimized conditions, nor were styrene of dimer 6 detected. We hypothesized that the lack of reactivity was due to the diol chelating the Lewis acid catalyst, rendering it unable to promote any reaction. We reasoned that a longer chain between the secondary and primary alcohols would be less likely to form a chelate with scandium, and exposed **1i** to 1,4-pentanediol under optimized conditions (**Scheme 3e**). Unlike reactions with primary alcohols that generally went to completion within 20 hours (**Table 2.3**), the reaction with 1,4-pentanediol was very slow, and reasonable conversion was observed only after 3 days. We attribute this to some amount of scandium-diol chelate forming; however, this would form a 7-membered chelate, which wasn't as stable as the 5- and 6-membered chelates that would have formed from 1,2-propane and 1,3-butanediols and scandium, respectively. Thus, some active catalyst was present in solution and could promote the reaction between **1l** and pentanediol, yielding 51% yield of a 2.6:1 mixture of **7a** and **7b** as 1:1 mixture of diastereomers.

To further probe that hypothesis, we employed methoxyethanol as a substrate, and ether 8 was isolated in 43% yield (**Scheme 2.3f**). This supports our hypothesis above and, protecting one of the alcohols makes the deoxygenated substrate a poorer ligand for scandium, enabling the catalytic dehydrogenative coupling.

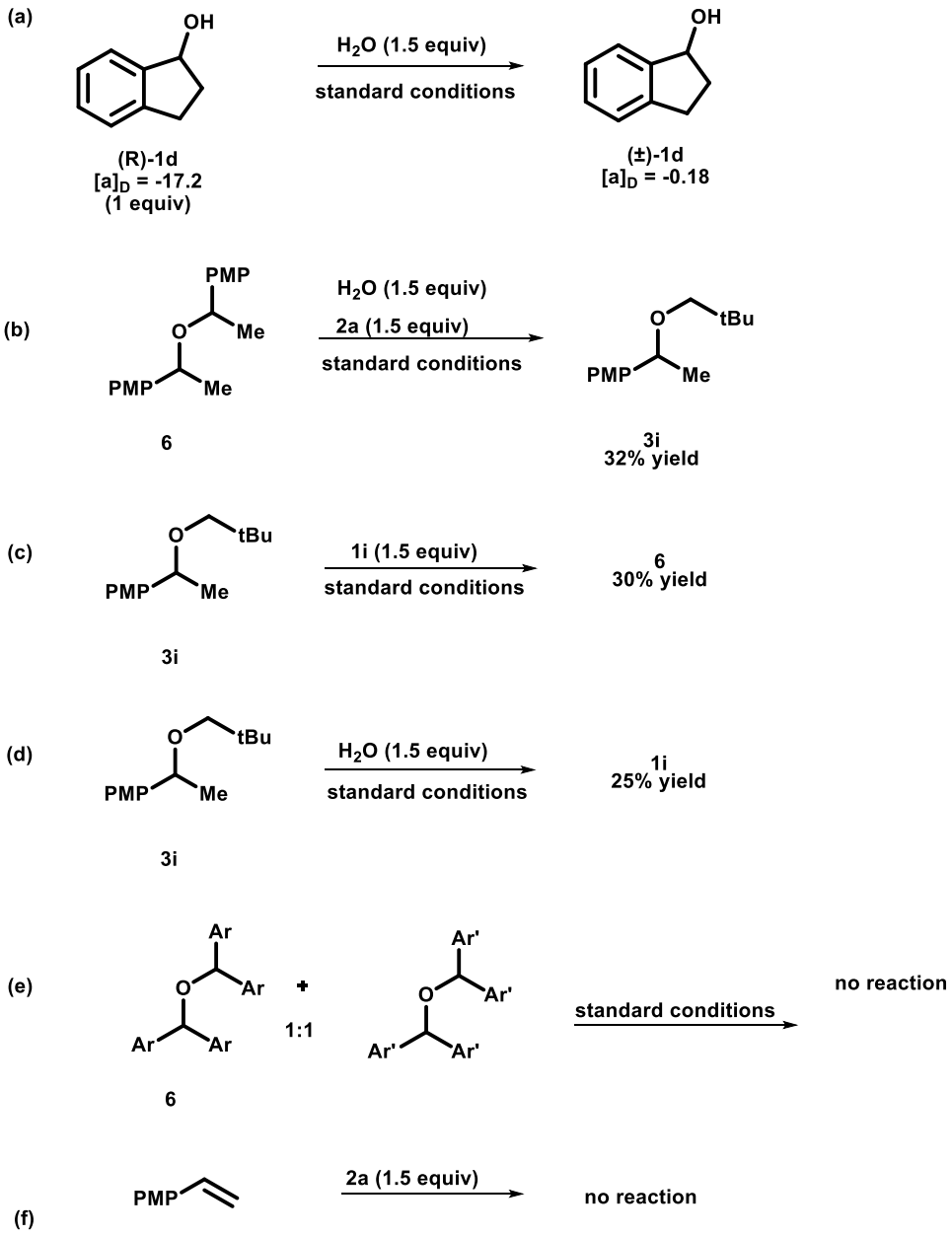
Scheme 2.3. Selectivity for reaction of benzylic alcohol with primary versus secondary alcohols.





An exogenous secondary aliphatic alcohol was able to selectively react with alcohol **1l**, and ether 9 was formed in 52% yield, with only 7% of the benzylic dimer 6 isolated (**Scheme 2.3g**). This could be due to decreased steric encumbrance about isopropanol relative to benzylic alcohol **1l**, increased nucleophilicity of the aliphatic alcohol, or a combination of both factors. In the intramolecular competition experiment between primary and secondary alcohols, the primary alcohol out competed the secondary alcohol in a 2.6:1 ratio (**Scheme 2.3e**); a similar result was observed in an intermolecular competition reaction with alcohol **1l** and an equimolar mixture of ethanol and isopropanol; ether **5c** was favored over ether 9 in a 2:1 ratio, with only a small amount of benzylic dimer isolated (**Scheme 2.3g**).

Scheme 2.4. Control reactions to help elucidate the mechanism**.**

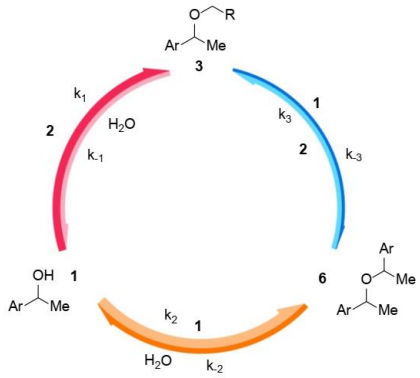


For further mechanistic insight, we subjected enantiopure (*R*)-indanol to the standard reaction conditions in the presence of water as a nucleophile. After approximately 20 hours, the observed optical rotation went from $[\alpha]_{D20}$ = - 17.2 to $[\alpha]_{D20}$ = -0.18 (**Scheme 2.4**, **equation a**), suggestive of a carbocation intermediate. We next subjected both the dimer 6 and elimination product to standard

reaction conditions to evaluate their role within the catalytic cycle. We found that the dimer 6 was consumed under standard reaction conditions and was slowly converted into the unsymmetrical ether **3l** in the presence of neopentyl alcohol **1l** (**equation b**). Hall[24] and Gunanathan[25]recently made similar observations, where the catalytic activation of benzylic alcohols rapidly formed a dimer, which was slowly converted to arylated species via Friedel-Crafts-type reactivity. When ether **3l** was exposed to benzyl alcohol **1l**, the dimer 6 could be isolated in 30% yield (**equation c**); similarly, when ether **3l** was exposed to water, benzyl alcohol was isolated in 25% yield (**equation d**). However, when a mixture of dimers of benzhydrol derivatives were combined in the absence of an alcohol or water nucleophile under otherwise standard reaction conditions, no reaction was observed (**equation e**), consistent with the necessity of an alcohol or water nucleophile to initiate ionization of the ethers. Similarly, the styrene elimination product was unreactive under the standard reaction conditions (**equation f**).

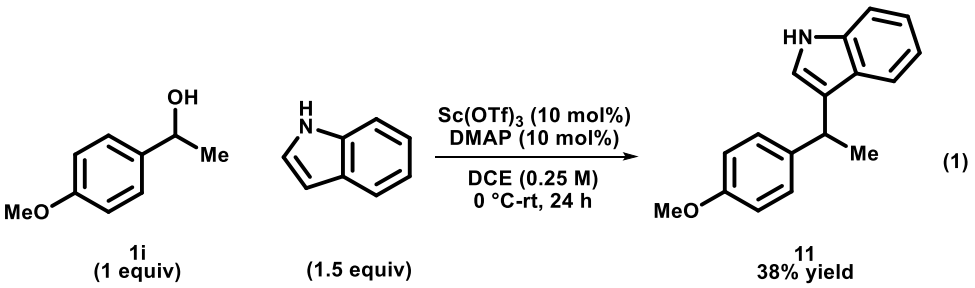
Thus, we have derived a preliminary mechanistic scenario (**Figure 2.1**). The target ether **3** is clearly accessible from dimeric ether **6**, though it is difficult to assess relative rates of formation of **3** from **1** and **6** ($\mathbf{k}_1$ vs $\mathbf{k}_3$) due to the complexity of the reaction. Hydrolysis to starting alcohol **1** occurs from both **3** and **6** ($\mathbf{k}_{-1}$ and $\mathbf{k}_{-2}$, respectively), though those relative rates do not appear to weigh significantly on the overall rate to formation of **3**. The rate of formation of dimer **6** is much faster than direct formation of **3** from **1** ($k_2 >> k_1$). Competing elimination appears to only occur from the starting alcohol **1**, and formation of the styrene is irreversible and off cycle, as it is not reactive under the reaction conditions.

Figure 2.1. Preliminary relative rates of the competing reactions.



Finally, we were also able to demonstrate that this chemistry may employ aromatic nucleophiles in a Friedel-Crafts type alkylation (**Scheme 2.5**).[24,26–28] The reaction between **1a** and indole produced 38% yield of alkylated indole **11**. Further examination of aromatic nucleophiles showed promising results towards development of catalytic electrophilic aromatic substitution chemistry, results for which are forthcoming.

Scheme 2.5. Reaction of indole with a benzylic alcohol via a Friedel-Crafts-like reaction.



2.4. Conclusions

In summary, we have developed a simple and selective method for producing unsymmetrical ethers via catalytic substitution of benzylic alcohols with primary alcohols. Preliminary mechanistic investigations suggest that the reaction is more SN1-like than SN2-like due to racemization of enantiopure starting alcohols, but the dynamics are complex. The relative rates of formation of dimer **6**

and ether **3** are $\mathbf{k_2} > \mathbf{k_1} >> \mathbf{k_3}$, where dimer formation occurs faster than unsymmetrical ether from the alcohol **1**, and the dimer is much more slowly converted to the ether **3**; the overall process has complex kinetics due to competing and reversible side reactions. Further detailed mechanistic studies are warranted to understand both the nature of the catalyst and the origin of selectivity and will be reported in due course.

2.6. Experimental Procedures

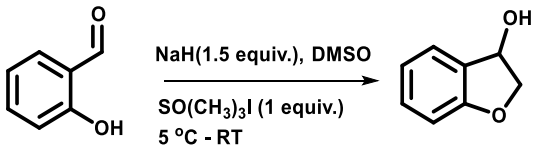
2.6.1 General information

NMR: ^{1}H and ^{13}C NMR spectra were obtained on a 500 MHz Varian VNMRS or a 400 MHz Varian VNMRS instrument in $CDCl_3$ referenced to tetramethylsilane (TMS) internal standard. All chemical shifts for ^{1}H and ^{13}C NMR spectra are reported in parts per million (ppm) downfield from TMS. Mass Spectrometry: High resolution mass spectra were obtained on Agilent model G6230A TOFMass Spectrometer. Low resolution mass spectra were obtained on an Agilent 7890A gas chromatograph coupled to a 5975C quadrupole mass spectrometer.

Solvents: Anhydrous dichloroethane and anhydrous methanol were purchased and used without further purification. All other solvents used were degassed prior to use and obtained over dual purifying alumina columns (101mm OD x 635 mm L) under nitrogen pressure. Glassware: All glassware used was either oven dried or flame dried and flushed with nitrogen prior to use. All reactions were performed under nitrogen atmosphere unless otherwise noted. Reagents: All chemicals were purchased from chemical suppliers and used without further purification unless otherwise noted. Chromatography: 40-63 mm (230-400 mesh) silica gel was used for purification via column chromatography with reagent grade eluent. Aluminum backed TLC silica gel 60 F_{254} analytical plates was used for thin layer chromatography to monitor reaction progress and in tandem with column chromatography.

2.6.2. Synthesis of starting materials for table 1.3

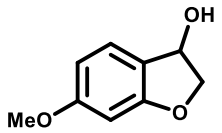
(1a) 2,3-dihydro-1-benzofuran-3-ol



1a

This compound was prepared under standard Corey-Chaykovsky reaction conditions.[29] NaH (3.6 g, 60% dispersion in mineral oil, 90 mmol, 1.5 equiv.) was suspended in anhydrous DMSO (40 ml) and cooled to 5 °C on a salt ice bath. Trimethylsulfoxonium iodide (13.2 g, 60 mmol, 1equiv.) was added portionwise and the mixture stirred for 2 hours at 5 °C. Salicylaldehyde (6.4 ml, 60 mmol, 1 equiv.) was added dropwise and the reaction stirred overnight allowing it to come to ambient room temperature. The reaction was quenched by the slow addition of water (100 ml). The organics were extracted into EtOAc (3 x 100 ml), washed with brine (3 x 50 ml), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The product was isolated via column chromatography over silica gel (20% EtOAc/Hex) as a white solid (1.2871 g, 31% yield). ^{1}HNMR data were consistent with literature values.[30] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 1H), 7.18 (tdd, *J* = 8.0, 1.5, 0.9 Hz, 1H), 6.91 – 6.82 (m,1H), 6.77 (dt, *J* = 8.1, 0.8 Hz, 1H), 5.03 (tt, *J* = 5.7, 2.4 Hz, 1H), 4.29 (dd, *J* = 10.7, 6.6 Hz, 1H), 4.17 (dd, *J* = 10.7, 2.6 Hz, 1H), 3.74 (d, *J* = 5.4 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 130.5, 128.1, 125.5, 120.9, 110.3, 78.8, 71.6 ppm.

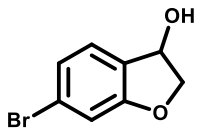
(1b) 6-methoxy-2,3-dihydro-1-benzofuran-3-ol



1b

This compound was prepared via the same method as **1a** at a 30 mmol scale. The product was isolated via column chromatography over silica gel (2.5%EtOH/DCM) to gain a pale yellow solid (1.5264 g, 30% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.3 Hz, 1H), 6.50 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.43 (d, *J* = 1.9 Hz, 1H), 5.28 (broad t, *J* = 5.1, 1H), 4.55 (dd, *J* = 10.6, 6.3 Hz, 1H), 4.46 (dd, *J* = 10.6, 2.3 Hz, 1H), 3.78 (s, 3H), 1.86 (d, *J* = 5.2 Hz, 1H) ppm. ^{13}C NMR (101 MHz $CDCl_3$) δ 162.4, 161.9, 125.7, 120.6, 107.5, 96.2, 80.3, 71.9, 55.5 ppm. HRMS (ESI) m/z (%): calcd. For $C_9H_{11}O_3$ [$(M+H)^+$] 167.0708 ; found 167.0728, 147.0596 [(M+H)- (H_2O)].

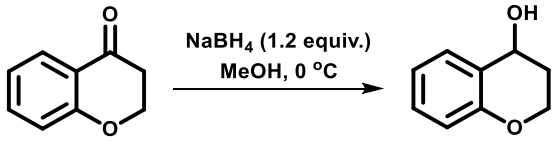
(1c) 6-bromo-2,3-dihydro-1-benzofuran-3-ol



1c

This compound was prepared via the same method as **1a** at a 20 mmol scale. The product was isolated via recrystallization from toluene to gain a yellow solid (1.5185 g, 35% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (dt, *J* = 7.9, 0.6 Hz, 1H), 7.08 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.05 (dt, *J* = 1.7, 0.5 Hz, 1H), 5.32 (td, *J* = 7.1, 2.6 Hz, 1H), 4.57 (dd, *J* = 10.7, 6.5 Hz, 1H), 4.46 (dd, *J* = 10.8, 2.6 Hz, 1H), 1.93 (d, *J* = 7.6 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2, 127.5, 126.4, 124.2, 124.1, 114.2, 79.9, 71.6 ppm. HRMS (APCI) m/z (%): calcd. for C_8H_6OBr [$(M+H)-(H_2O)_+$] 196.9602; found 196.9597.

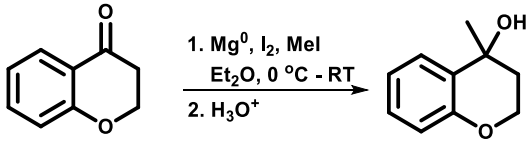
(1e) 3,4-dihydro-2*H*-chromen-4-ol



1e

This compound was prepared via standard sodium borohydride reduction conditions.[31] 4-chromanone (370.4 mg, 2.5 mmol, 1 equiv.) was dissolved in anhydrous MeOH (5 ml) and cooled to 0 °C on an ice bath. NaBH4 (113.5 mg, 3 mmol, 1.2 equiv.) was added portionwise. The reaction was monitored via TLC (30% EtOAc/Hex). After completion (20 minutes), water (5 ml) was slowly added to quench. The organics were extracted into EtOAc (3 x 5 ml), washed with water (5 ml), 3 M HCl (3 ml), and brine (3 ml), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The product was isolated via column chromatography over silica gel (30% EtOAc/Hex) to gain a clear oil (354.6 mg, 94 % yield). ^{1}H and ^{13}C NMR data were consistent with literature values.[32] ^{1}H NMR (400 MHz, CDCl3) δ 7.32 (ddd, J = 7.7, 1.8, 0.5 Hz, 1H), 7.21 (ddd, J = 8.2, 7.3, 1.7 Hz, 1H), 6.93 (td, J = 7.4, 1.2 Hz, 1H), 6.85 (dd, J = 8.3, 1.3 Hz, 1H), 4.80 (q, J = 4.3 Hz, 1H), 4.30 – 4.25 (m, 2H), 2.19 – 1.98 (m, 2H), 1.78 (d, J = 4.7 Hz, 1H) ppm. ^{13}C NMR (101 MHz, CDCl3) δ 154.7, 129.8, 129.8, 124.4, 120.7, 117.2, 63.3, 62.0, 30.9 ppm.

(1f) 4-methyl-3,4-dihydro-2*H*-chromen-4-ol

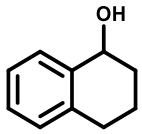


1f

This compound was prepared from 4-chromanone in a similar fashion reported in literature.[33] To a flame dried round bottom flask under nitrogen, Mg0 turnings (364.7 mg, 15 mmol, 1.5 equiv.) and Iodine (2 pieces) were added followed by anhydrous diethyl ether (7 ml) over an ice bath.

Iodomethane (6.9 ml, 11 mmol, 1.1 equiv.) in diethyl ether (5 ml) was added dropwise via syringe. The ice bath was removed, and the mixture allowed to reflux for 30 minutes. The mixture was cooled to 0 °C and a solution of 4-chromanone (1.4816 g, 10 mmol, 1 equiv.) in diethyl ether (3 ml) was added dropwise via syringe. The reaction was stirred overnight allowing it to come to ambient room temperature, then hydrolyzed by the addition of saturated ammonium chloride (10 ml) followed by 1 M HCl (2 ml) and stirred for 30 minutes. The organics were extracted into Et2O (3 x 30 ml), washed with brine (20 ml), dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product was recrystallized from hexanes to gain a white solid (54 mg, 33% yield). ^{1}H and ^{13}C NMR data were consistent with literature values. ^{1}H NMR (400 MHz, CDCl3) δ 7.49 (dd, J = 7.8, 1.6 Hz, 1H), 7.18 (ddd, J = 8.2, 7.2, 1.7 Hz, 1H), 6.94 (ddd, J = 7.8, 7.2, 1.3 Hz, 1H), 6.82 (ddd, J = 8.2, 1.3, 0.4 Hz, 1H), 4.34 – 4.18 (m, 2H), 2.09 – 2.06 (m, 2H), 1.91 (s, 1H), 1.63 (s, 3H) ppm.6 ^{13}C NMR (101 MHz, CDCl3) δ 154.0, 129.3, 128.6, 126.5, 120.9, 117.3, 66.5, 63.5, 38.2, 29.7 ppm.

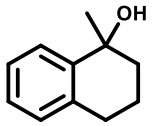
(1g) 1,2,3,4-tetrahydronaphthalen-1-ol



1g

This compound was prepared via the same method as **1e** at a 10 mmol scale. The product was isolated via column chromatography over silica gel (30% EtOAc/Hex) to gain a white solid (280.2 mg, 19 % yield, mp 41-42 ˚C). ^{1}H and ^{13}C NMR data were consistent with literature values.[32] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.38 (m, 1H), 7.24 – 7.15 (m, 2H), 7.14 – 7.04 (m, 1H), 4.78 (d, *J* = 4.8 Hz, 1H), 2.83 (dt, *J* = 16.6, 5.5 Hz, 1H), 2.72 (dt, *J* = 16.5, 5.9 Hz, 1H), 2.08 – 1.85 (m, 3H), 1.85 – 1.73 (m, 1H), 1.70 (d, *J* = 4.5 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 137.3, 129.2, 128.8, 127.7, 126.3, 68.3, 32.4, 29.4, 18.9 ppm.

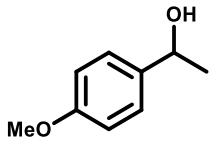
(1h) 1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol



1h

This compound was prepared via the same method as **1f** at a 10 mmol scale. Recrystallization from hexanes yielded a white solid (728 mg, 45% yield). ^{1}H NMR data were consistent with literature values.[34] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.0 Hz, 1H), 7.21 (tdd, *J* = 7.3, 1.8, 0.9 Hz, 1H), 7.16 (tt, *J* = 7.2, 1.4 Hz, 1H), 7.10 – 7.03 (m, 1H), 2.87 – 2.70 (m, 2H), 2.04 – 1.88 (m, 3H), 1.87 – 1.77 (m, 1H), 1.74 (s, 1H), 1.56 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.0, 136.4, 129.0, 127.3, 126.5, 126.4, 70.8, 40.0, 30.9, 30.1, 20.6 ppm.

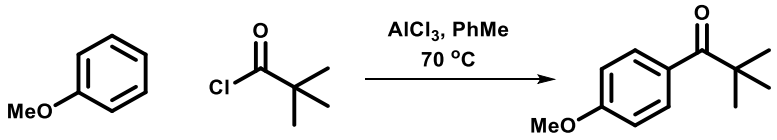
(1l) 1-(4-methoxyphenyl)ethanol



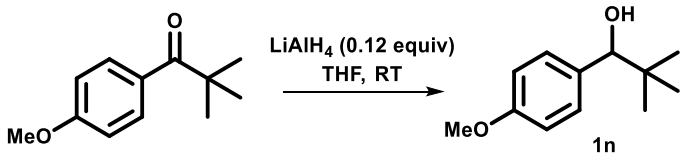
1l

This compound was prepared from 4-methoxyacetophenone via the same method as **1e** at a 10 mmol scale. The product was isolated via column chromatography over silica gel (30% EtOAc/Hex) to gain a colorless oil (1.2605 g, 82 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.84 (q, *J* = 6.5 Hz, 1H), 3.80 (s, 3H), 1.47 (d, *J* = 6.4 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 138.1, 126.8, 114.0, 70.1, 55.4, 25.1 ppm.

(1n) 1-(4-methoxyphenyl)-2,2-dimethylpropan-1-ol



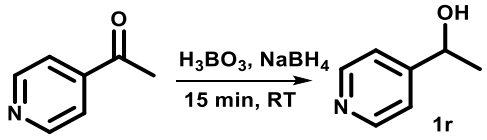
This compound was prepared according to literature procedures.[35] 1-(4-methoxyphenyl)-2,2-dimethylpropan-1-one: Anisole (2.16 g, 20 mmol, 2 equiv.) and pivaloyl chloride (1.21 g, 10 mmol, 1 equiv.) were dissolved in toluene (6 ml) and $AlCl_3$ (1.33 g, 20 mmol, 2 equiv.) was added. The mixture was stirred at 70 °C under nitrogen for 40 minutes. After cooling on an ice bath, 1 M HCl was added to quench. The organics were extracted into Et_2O (3 x 10 ml), washed with saturated $NaHCO_3$ (aq.) (30 ml), dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification via column chromatography (10% EtOAc/Hex) gave a clear oil (1.1824 g, 61% yield). 1H NMR data were consistent with literature values.[36] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 9.1, 1.0 Hz, 1H), 6.90 (dd, *J* = 9.1, 0.9 Hz, 1H), 3.85 (s, 3H), 1.37 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.4, 162.1, 131.1, 130.2, 113.4, 55.5, 44.0, 28.5 ppm.



1-(4-methoxyphenyl)-2,2-dimethylpropan-1-ol: A solution of 1-(4-methoxyphenyl)-2,2 dimethylpropan-1-one (0.9613 g, 5 mmol, 1 equiv.) in dry THF (3 ml) was added dropwise to a slurry of $LiAlH_4$ (23 mg, 0.6 mmol, 0.12 equiv.) in THF (7 ml) at room temperature under nitrogen. The mixture was heated to reflux for 24 hours. After completion, the reaction was quenched by the slow addition of water (10 ml) followed by 15% NaOH (aq.) (5 ml). The organics were extracted into Et_2O (3 x 10 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by column chromatography over silica gel gave a clear oil (237 mg, 24% yield). ^{1}H NMR data were

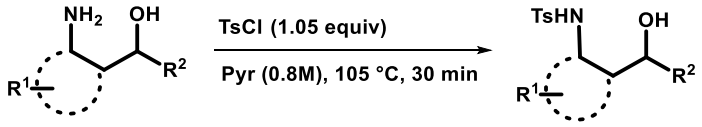
consistent with literature values.[9] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.3 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.35 (d, *J* = 2.7 Hz, 1H), 3.80 (s, 3H), 1.82 (d, *J* = 2.8 Hz, 1H), 0.91 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 134.4, 128.6, 112.9, 82.0, 55.2, 35.7, 25.9 ppm.

(1r) 1-(4-Pyridinyl)ethanol



According to a literature procedure,[37] in a mixture of boric acid (0.1854 g, 3mmol, 3 equiv.) and sodium borohydride (0.1135 g, 3mmol, 3 equiv.), 4-actyl pyridine (0.1211 g, 1mmol, 1 equiv.) was added and the final mixture was ground using mortar and pestle for 15 mins at room temperature. The reaction was quenched with 1M HCl. The product was isolated via column chromatography over silica gel (0.1218 g, 99%). ^{1}H NMR Data were consistent with literature values.[38] $_{1}$H NMR (400 MHz, $CDCl_3$) δ 8.3 (d, J = 6.48 2H), 7.4 (d, J = 6.61, 2H), 4.92 (q, J = 6.59,6.58, 1H), 1.40 (d, J = 6.63, 3H) ppm. ^{13}C NMR (101 MHz, CDCl3) δ 159.24, 147.02, 122.12, 68.03, 24.79 ppm.

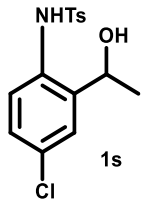
General procedure for protection of amine



The protection of the amine group was carried out according to the literature.[39] The amine compound (1mmol, 1equiv.) was added portionwise to a solution of tosyl chloride (0.2 g, 1.05 mmol, 1.05 equiv) and pyridine (0.8 M) at 105 ˚C for 30 minutes under argon. After completion, the resulting mixture

was diluted with ethyl acetate then washed with 3M HCl and brine, dried over sodium sulfate. The product was isolated via column chromatography over silica gel.

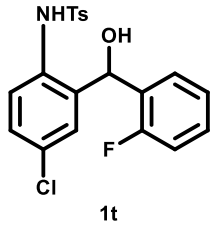
(1s) N-[4-chloro-2-(1-hydroxyethyl) phenyl]-4-methylbenzene-1-sulfonamide



1s

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.59-7.65 (m, 2H), 7.33(d, J = 8.27, 1H), 7.20-7.25 (m, 1H), 712 (dd, *J* = 8.53, 2.45, 1H), 7.05 (d, *J* = 2.54, 1H), 4.72-4.82 (m, 1H), 2.82-2.87 (m, 1H), 2.35 (s, 3H), 1.26 (d, *J* = 6.59, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 136.4, 136.5, 134.2, 130.3, 129.9, 128.4, 127.2, 123.5, 69.2, 22.9, 21.7 ppm. HRMS (ESI) m/z (%): calcd. For $C_{15}H_{16}ClNO_3S$ [(M+H)-(H_2O)$^{+}$] 308.0512; found 308.0502. R_f = 0.35, Hexane/EtOAc (2:1), white solid, 90%, 144 mg.

(1t) N-{4-chloro-2-[(2-fluorophenyl) (hydroxy)methyl]phenyl}-4-methylbenzene-1-sulfonamide.



1t

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 6.63-7.69 (m, 10H), 5.86 (s, 1H), 5.28 (s, 1H), 3.33 (s, 1H), 2.38 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 161.0, 158.6, 144.3, 136.2, 135.6, 134.0, 131.1, 129.9, 129.0, 128.6, 127.9, 127.2, 124,9, 115.7, 110.1, 68.1, 24.8, 21.6 ppm. HRMS (ESI) m/z (%):

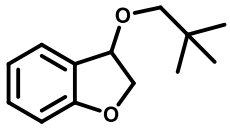
calcd. for $C_{20}H_{17}ClFNO_3S$ [(M+H)-(H_2O)$^+$] 388.0574; found 388.0584. R_f = 0.58, Hexane/EtOAc (2:1), yellow solid, 64%, 0.52 g.

2.6.3 General procedure for synthesis of benzyl ethers

$Sc(OTf)_3$ (12.3 mg, 0.025 mmol) and DMAP (3.1 mg, 0.025 mmol) were stirred in anhydrous DCE (0.5 ml) for 30 minutes at room temperature, then cooled to 0°C on an ice bath. A solution of benzylic alcohol (0.25 mmol, 1 equiv.) and primary alcohol (0.375 mmol) in DCE (0.5 ml) was added dropwise via syringe. The reaction was stirred for 24 hours allowing it to slowly come to ambient room temperature. The crude mixture was filtered through a short pad of celite, the filtrate concentrated under reduced pressure and the residue purified via column chromatography on silica gel (30-50% DCM/Hexanes).

2.6.4 Characterization data for products of table 1.3 (3a-3t)

(3a) 3-(2,2-dimethylpropoxy)-2,3-dihydro-1-benzofuran

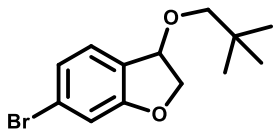


3a

^{1}H NMR (400 MHz, CDCl3) δ 7.38 (ddt, *J* = 7.4, 1.1, 0.6 Hz, 1H), 7.29 – 7.20 (m, 1H), 6.91 (tt, *J* = 7.4, 1.0 Hz, 1H), 6.86 (ddt, *J* = 8.1, 1.1, 0.5 Hz, 1H), 5.09 (dd, *J* = 6.4, 2.7 Hz, 1H), 4.51 (dd, *J* = 10.5, 2.9 Hz, 1H), 4.46 (dd, *J* = 10.5, 6.5 Hz, 1H), 3.19 (d, *J* = 8.4 Hz, 1H), 3.04 (d, *J* = 8.4 Hz, 1H), 0.87 (s, 9H) ppm. ^{13}C NMR (101 MHz, CDCl3) δ 160.7, 130.3, 126.3, 126.1, 120.4, 110.4, 79.1, 78.0, 76.3,

31.9, 26.7ppm. HRMS (APCI) m/z (%): calcd. for C13H18O2Na+ ([M+Na]$^+$) 229.1199; found 229.1172, 119.0509 ([M-C5H11O]$^+$).

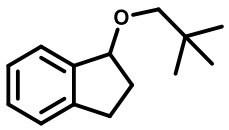
(3c) 6-bromo-3-(2,2-dimethylpropoxy)-2,3-dihydro-1-benzofuran



3c

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (ddd, *J* = 7.6, 1.8, 0.7 Hz, 1H), 7.06 (td, *J* = 1.7, 0.6 Hz, 1H), 7.04 (dd, *J* = 1.7, 0.7 Hz, 1H), 5.07 – 5.00 (m, 1H), 4.56 – 4.45 (m, 2H), 3.16 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.03 (dd, *J* = 8.4, 2.3 Hz, 1H), 0.88 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.8, 127.2, 125.8, 123.9, 123.8, 114.2, 78.6, 78.3, 77.3, 32.1, 26.8 ppm. HRMS (APCI) m/z (%): calcd. For $C_{13}H_{17}BrO_2$ ([M]$^+$) 284.0412; found 284.0417, 196.9597 ([M$C_5H_{11}O$]$^+$).

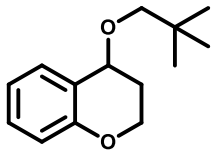
(3d) 2,3-dihydro-1*H*-inden-1-yl 2,2-dimethylpropyl ether



3d

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 7.3, 0.9 Hz, 1H), 7.26 – 7.17 (m, 3H), 4.90 (t, *J* = 6.1 Hz, 1H), 3.23 (d, *J* = 8.6 Hz, 1H), 3.18 (d, *J* = 8.8 Hz, 1H), 3.03 (ddd, *J* = 15.9, 8.7, 4.8 Hz, 1H), 2.87 – 2.73 (m, 1H), 2.43 – 2.31 (m, 1H), 2.06 – 1.95 (m, 1H), 0.93 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5, 127.9, 126.2, 124.9, 124.7, 110.0, 83.7, 79.2, 32.3, 32.1, 30.1, 26.8 ppm. HRMS (APCI) m/z (%): calcd. for $C_{14}H_{21}O$+ ([M+H]$^+$) 205.1587; found 205.1278, 117.0705 ([M$C_5H_{11}O$]+).

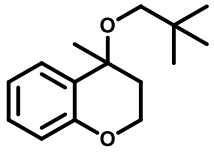
(3e) 4-(2,2-dimethylpropoxy)-3,4-dihydro-2*H*-chromene



3e

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 1H), 7.21 – 7.15 (m, 1H), 6.88 (td, *J* =7.4, 1.3 Hz, 1H), 6.82 (ddd, *J* = 8.3, 1.2, 0.6 Hz, 1H), 4.33 (t, *J* = 4.1 Hz, 1H), 4.28 (dd, *J* = 10.3, 3.2 Hz, 1H), 4.22 (dddt, *J* = 10.7, 4.4, 3.9, 0.7 Hz, 1H), 3.26 (d, *J* = 8.3 Hz, 1H), 3.18 (d, *J* = 8.3 Hz, 1H), 2.16 – 1.96 (m, 2H), 0.92 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9, 130.6, 129.4, 122.8, 120.0, 116.9, 79.0, 71.0, 62.6, 32.3, 27.9, 26.9 ppm. HRMS (APCI) m/z (%): calcd. for $C_{14}H_{21}O_2$ ($[M+H]^+$) 221.1536; found 221.147, 133.0650 ($[MC_5H_{11}O]^+$).

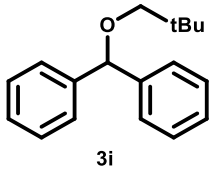
(3f) 4-(2,2-dimethylpropoxy)-4-methyl-3,4-dihydro-2*H*-chromene



3f

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.14 (ddd, *J* = 8.2, 7.2, 1.7 Hz, 1H), 6.92 – 6.82 (m, 1H), 6.79 (dd, *J* = 8.2, 0.9 Hz, 1H), 4.36 (ddd, *J* = 11.0, 8.8, 3.3 Hz, 1H), 4.17 (ddd, *J* = 11.0, 6.8, 3.4 Hz, 1H), 2.89 (d, *J* = 8.1 Hz, 1H), 2.85 (d, *J* = 8.1 Hz, 1H), 2.21 (ddd, *J* = 13.7, 6.8, 3.3 Hz, 1H), 1.85 (ddd, *J* = 13.7, 8.7, 3.5 Hz, 1H), 1.52 (s, 3H), 0.83 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 128.7, 127.7, 125.8, 119.7, 116.8, 71.9, 69.7, 63.5, 34.3, 31.7, 26.8, 26.5 ppm. HRMS (APCI) m/z (%): calcd. for $C_{15}H_{23}O_2$ ($[M+H]^+$) 235.1672; found 235.169, 147.0808 ($[MC_5H_{11}O]^+$).

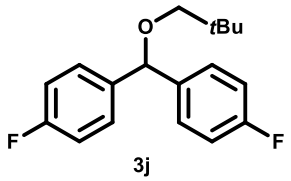
(3i) [(2,2-dimethylpropoxy)(phenyl)methyl]benzene.



3i

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.38 (m, 10H), 5.30 (s, 1H), 3.10 (s, 2H), 0.97 (s,9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 128.4, 127.3, 127.0, 83.8, 79.5, 32.4, 27.1 ppm. HRMS (ESI) m/z (%): calcd. for 2 $C_{18}H_{22}O$ $[(M+H)^+]$ 254.1671; found 254.0471. HRMS (ESI) m/z (%): calcd. for $C_{18}H_{22}O$ $[(M+H)^+]$ 255.1749; found , 255.1739, 167.0849 ($[MC_5H_{11}O]^+$). R_f = 0.85, Hexane/DCM (3:1), colorless liquid, 20%, 50 mg.

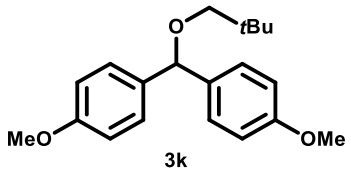
(3j) 1-[(2,2-dimethylpropoxy)(4-fluorophenyl)methyl]-4-fluorobenzene.



3j

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.30 (m, 4H), 6.96-7.04 (m, 4H), 5.24 (s, 1H), 3.05 (s, 2H), 0.94 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (s), 138.7 (d), 128.6 (d), 115.3 (d), 82.5, 79.5, 32.3, 27.0. ^{19}FNMR (376 MHz, $CDCl_3$) δ -113.07 ppm HRMS (ESI) m/z (%): calcd. For $C_{18}H_{20}F_2O$ $[(M+H)^+]$ 291.1560; found 291.1543, 204.0747 ($[MC_5H_{11}O]^+$). R_f = 0.52, Hexane/DCM (2:1), colorless liquid, 14%, 39 mg

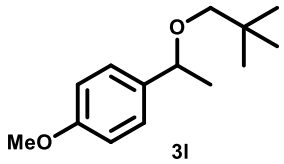
(3k) 1-[(2,2-dimethylpropoxy)(4-methoxyphenyl)methyl]-4-methoxybenzene.



3k

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (td, J =8.76, 2.87, 4H), 6.93 (dt, J = 6.91, 3.14, 4H), 5.29 (s, 1H) , 3.83 (s, 6H), 3.15 (s, 2H), 1.04 (s, 9H) ppm. ^{13}C NMR (400 MHz, CDCl3) δ 158.8, 135.6, 128.2, 113.7, 82.9, 79.2, 55.2, 32.3, 27.0 ppm. HRMS (ESI) m/z (%): calcd. for $C_{20}H_{26}O_3$ [(M+H)$^+$] 315.1960; found 350.2013, 227.1156([$MC_5H_{11}O$]$^+$). R_f = 0.44, Hexane/EtOAc (2:1), colorless liquid, 99%, 0.34 g

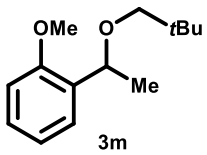
(3l) 1-[1-(2,2-dimethylpropoxy)ethyl]-4-methoxybenzene



3l

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 8.5, 1.4 Hz, 2H), 6.86 (dd, *J* = 8.6, 1.6 Hz, 2H), 4.29 (q, *J* = 6.4 Hz, 1H), 3.80 (s, 3H), 2.94 (d, *J* = 8.7 Hz, 1H), 2.91 (d, *J* = 8.7 Hz, 1H), 1.39 (d, *J* = 6.5 Hz, 2H), 0.89 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 137.0, 127.4, 113.8, 79.1, 77.9, 55.4, 32.1, 26.9, 24.3 ppm. HRMS (APCI) m/z (%): calcd. for $C_{14}H_{23}O_2$ ([M+H]$^+$) 223.1693; found 223.1668, 135.0808 ([$MC_5H_{11}O$]$^+$).

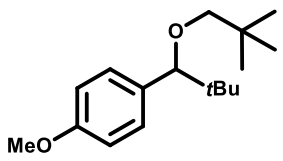
(3m) 1-[1-(2,2-dimethylpropoxy)ethyl]-2-methoxybenzene



3m

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, J =5.73, 1.83, Hz, 1H), 7.23-7.27 (m, 1H), 7.01 (dtd, J = 7.48, J =1.1, 0.43 Hz, 1H), 6.88 (dd, J = 8.23, 1.14, 1H), 4.80 (q, J = 6.39 Hz, 1H), 3.84 (s, 3H), 3.08 (d, *J* = 8.64, 1H), 2.99 (d, J = 8.8 Hz, 1H), 1.39 (d, J = 6.52 Hz, 3H), 0.96 (s, 9H) ppm. ^{13}C NMR (400 MHz, CDCl3) δ 156.55, 133.33, 127.71, 126.22, 120.82, 110.21, 79.54, 72.22, 55.36, 32.22, 26.97, 22.91 ppm. HRMS (ESI) m/z (%): calcd. for $C_{14}H_{22}O_2$ [$(M+H)^+$] 223.1698; found 223.1663, 136.0846 ([$MC_5H_{11}O]^+$). R_f = 0.55, Hexane/DCM (2:1), colorless liquid, 40%, 90 mg

(3n) 1-[1-(2,2-dimethylpropoxy)-2,2-dimethylpropyl]-4-methoxybenzene



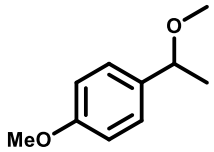
3n

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 3.81 (s, 3H), 3.76 (s, 1H), 2.94 (d, *J* = 8.3 Hz, 1H), 2.76 (d, *J* = 8.3 Hz, 1H), 0.91 (s, 9H), 0.87 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 132.5, 129.5, 112.8, 89.8, 79.8, 55.3, 36.2, 32.5, 27.0, 26.4 ppm. HRMS (APCI) m/z (%): calcd. for $C_{12}H_{17}O$ ([$M-C_5H_{11}O]^+$) 177.1279; found 177.1276.

2.6.5 Characterization data for products of table 1.4

All of these were synthesized according to the general procedure.

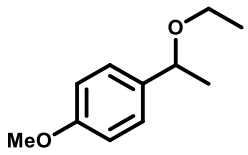
(5b) 1-methoxy-4-(1-methoxyethyl)benzene



5b

^{1}H and ^{13}C NMR data are consistent with literature reports.[40] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.23 (q, *J* = 6.5 Hz, 1H), 3.79 (s, 3H), 3.18 (s, 3H), 1.41 (d, *J* = 6.5 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 135.4, 127.4, 113.8, 79.1, 56.1, 55.2, 23.7 ppm. GC-MS (EI): calcd. for $C_{10}H_{14}O_2$ ($[M]^+$) 166.0994; found 166.1. HRMS (APCI) m/z (%): calcd. for $C_9H_{11}O$ ($[M-CH_3O]^+$) 135.0810; found 135.0824 ($[M-CH_3O]^+$)

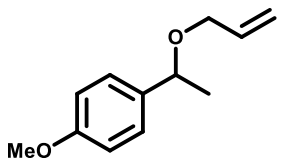
(5c) 1-(1-ethoxyethyl)-4-methoxybenzene



5c

^{1}H and ^{13}C NMR data are consistent with literature reports.[41] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.34 (d, *J* = 6.5 Hz, 1H), 3.78 (s, 3H), 3.31 (q, *J* = 7.0 Hz, 2H), 1.41 (d, *J* = 6.5 Hz, 3H), 1.16 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 136.2, 127.3, 113.7, 77.2, 63.6, 55.2, 24.1, 15.4 ppm. GC-MS (EI): calcd. for $C_{11}H_{16}O_2$ ($[M]^+$) 180.1150; found 180.1. HRMS (APCI) m/z (%): calcd. for $C_9H_{11}O$ ($[M-C_2H_5O]^+$) 135.0810; found 135.0843 ($[M-C_2H_5O]^+$).

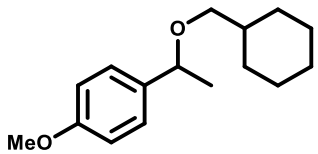
(5d) 1-methoxy-4-[1-(prop-2-en-1-yloxy)ethyl]benzene



5d

^{1}H and ^{13}C NMR data are consistent with literature reports.[42] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.94-5.84 (m, 1H), 5.25-5.19 (m, 1H), 5.15 – 5.13 (m, 1H), 4.41 (q, *J* = 6.5 Hz, 1H), 3.89-3.74 (m, 2H), 3.79 (s, 3H), 1.43 (d, *J* = 6.5 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 135.7, 135.1, 127.4, 116.5, 113.8, 76.7, 69.2, 55.2, 24.0 ppm. GC-MS (EI): calcd. for $C_{12}H_{16}O_2$ ($[M]^+$) 192.1150; 192.1. HRMS (APCI) m/z (%): calcd. for $C_9H_{11}O$ ($[M-C_3H_5O]^+$) 135.0810; found 135.0812 ($[M-C_3H_5O]^+$).

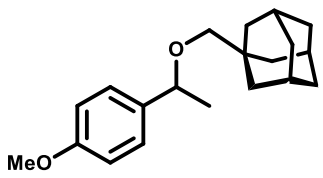
(5e) 1-[1-(cyclohexylmethoxy)ethyl]-4-methoxybenzene



5e

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.30 (q, *J* = 6.5 Hz, 1H), 3.79 (s, 3H), 3.06 (d, *J* = 6.3 Hz, 2H), 1.81-1.51 (m, 6H), 1.40 (d, *J* = 6.5 Hz, 3H), 1.29-1.10 (m, 3H), 0.92-0.78 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 136.5, 127.3, 113.6, 77.4, 74.4, 55.2, 38.2, 30.3, 30.1, 26.7, 25.9, 25.8, 24.2 ppm. GC-MS (EI): calcd. for $C_{16}H_{24}O_2$ ($[M]^+$) 248.1776; found 248.2. HRMS (APCI) m/z (%): calcd. for $C_9H_{11}O$ ($[M-C_7H_{13}O]^+$) 248.1776; found 135.0814 ($[M-C_7H_{13}O]^+$)

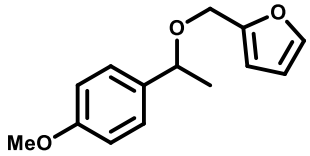
(5f) 1-{[1-(4-methoxyphenyl)ethoxy]methyl}tricyclo[3.3.1.1^{3,7}]decane



5f

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.26 (q, *J* = 6.4 Hz, 1H), 3.80 (s, 3H), 2.85 (q, *J* = 8.9 Hz, 2H), 1.95 (s, 3H), 1.73-1.63 (m, 6H), 1.53 (s, 6H), 1.38 (d, *J* = 6.4 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 136.9, 127.2, 113.6, 79.4, 77.7, 55.2, 39.8, 37.3, 34.0, 28.3, 24.2 ppm. GC-MS (EI): calcd. for $C_{20}H_{28}O_2$ ($[M]^+$) 300.2089; found 300.1. HRMS (APCI) m/z (%): calcd. for $C_9H_{11}O$ ($[M\text{-}C_{11}H_{17}O]^+$) 135.0810; found 135.0811 ($[M\ C_{11}H_{17}O]^+$)

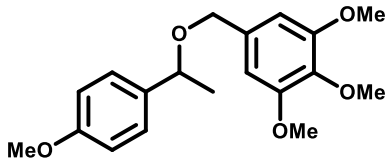
(5g) 2-{[1-(4-methoxyphenyl)ethoxy]methyl}furan



5g

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 -7.38(m, 1H), 7.28 (d, *J* = 8.7 Hz, 2H), 6.90b(d, *J* = 8.7 Hz, 2H), 6.32-6.31 (m, 1H), 6.23-6.22 (m, 1H), 4.46 (q, *J* = 6.5 Hz,b1H), 4.35-4.20 (m, 2H), 3.81 (s, 3H), 1.44 (d, *J* = 6.5 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 152.1, 142.6, 135.2, 127.6,113.9, 110.2, 108.9, 76.5, 62.1, 55.2, 24.0 ppm. GC-MS (EI): $C_{14}H_{16}O_3$ ($[M]^+$) 232.1099; found 232.1. HRMS (APCI) m/z (%): calcd. for $C_9H_{11}O$ ($[M\text{-}C_5H_5O_2]^+$) 135.0810; found 135.0814 ($[M\text{-}C_5H_5O_2]^+$).

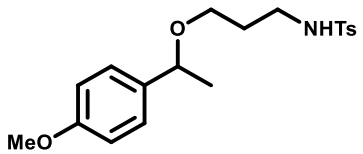
(5h) 1,2,3-trimethoxy-5-{[1-(4-methoxyphenyl)ethoxy]methyl}benzene



5h

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.54 (s, 2H), 4.47 (q, *J* = 6.5 Hz, 1H), 4.38-4.22 (m, 2H), 3.86 (s, 6H), 3.84 (s, 3H), 3.83 (s, 3H), 1.49 (d, *J* = 6.5 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 153.2, 137.3, 135.6, 134.4, 127.6, 113.9, 104.7, 76.8, 70.3, 60.8, 56.0, 55.2, 24.1 ppm. GC-MS (EI): calcd. for $C_{19}H_{24}O_5$ ($[M]^+$) 332.1624; found 332.2. HRMS (APCI) m/z (%): calcd. for $C_9H_{11}O$ ($[M-C_{10}H_{13}O_4]^+$) 135.0810; found 135.0811 ($[M C_{10}H_{13}O_4]^+$).

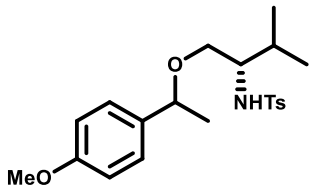
(5i) 1-[1-(4-methoxyphenyl)ethoxy]-3-methylbutan-2-tosylamine



5i

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.65 (m, 2H), 7.37 – 7.24 (m, 2H), 7.20 – 7.06 (m, 2H), 6.92 – 6.77 (m, 2H), 5.27 (t, *J* = 5.8 Hz, 1H), 4.26 (q, *J* = 6.4 Hz, 1H), 3.79 (s, 3H), 3.35 – 3.20 (m, 2H), 3.12 – 2.94 (m, 2H), 2.43 (s, 3H), 1.75 – 1.56 (m, 2H), 1.38 (d, *J* = 6.5 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 143.2, 137.1, 135.3, 129.7, 127.3, 127.1, 113.9, 77.9, 67.0, 55.3, 42.1, 28.9, 23.9, 21.6 ppm. GC-MS (EI): 363.1. HRMS (APCI) m/z (%): calcd. for $C_{19}H_{25}NO_4S$ ($[M]^+$) 363.1504; found 363.1478 ($[M- C_{19}H_{25}NO_4S]^+$)

(5j) (2*S*)-1-[1-(4-methoxyphenyl)ethoxy]-3-methylbutan-2-tosylamine

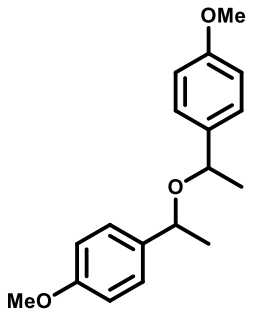


5j

Mixture (dr 1:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (7.61) (d, *J* = 8.2 Hz, 2H), 7.25 (7,14) (d, *J* = 8.2 Hz, 2H), 7.05 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 4.94 (4.88) (d, *J* = 8.8 Hz, 1H), 4.12 (4.00) (q, *J* = 6.4 Hz, 1H), 3.79 (3.76) (s, 3H), 3.17 (3.11) (dd, *J* = 9.5, 3.6 Hz, 1H), 3.03-2.97 (m, 1H), 2.93-2.84 (m, 1H), 2.40 (2.35) (s, 3H), 1.98-1.75 (m, 1H), 1.28 (1.27) (d, *J* = 6.4, 3H), 0.87-0.68 (m, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 143.0, 142.8, 138.4, 138.1, 135.2, 135.2, 129.5, 129.4, 127.3, 127.2, 127.0, 127.0, 113.8, 113.7, 78.1, 77.9, 67.3, 67.2, 59.0, 58.8, 55.2, 55.2, 29.8, 29.8, 23.6, 23.5, 21.5, 21.4, 19.1, 19.0, 18.7, 18.3 ppm. GC-MS (EI): calcd. for $C_{21}H_{29}NO_4S$ ($[M]^+$) 391.1817; found 391.2. HRMS (APCI) m/z (%): calcd. for $C_9H_{11}O$ ([M $C_{12}H_{18}NO_3S]^+$) 135.0810; found 135.0813 ($[MC_{12}H_{18}NO_3S]^+$)

2.6.6 Characterization data for the products of scheme 1.3

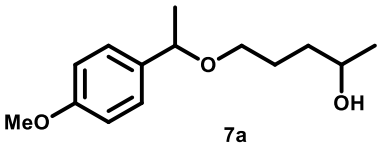
(6) (2*S*)-1-[1-(4-methoxyphenyl)ethoxy]-3-methylbutan-2-tosylamine



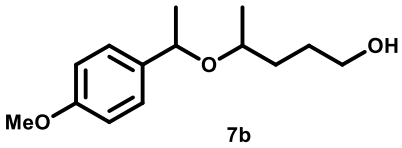
6

Mixture (3:1 dr). ^{1}H and ^{13}C NMR data were consistent with literature values.[43] $_{1}H$ NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.17 (m, 5H), 6.92 – 6.86 (6.85 – 6.80) (m, 3H), 4.18 (4.46) (q, *J* = 6.5 Hz, 2H), 3.81 (3.78) (s, 3H), 1.35 (1.43) (d, *J* = 6.5 Hz, 3H) ppm. $_{13}C$ NMR (101 MHz, $CDCl_3$) δ 158.9, 158.7, 136.4, 136.2, 127.5, 127.4, 113.8, 113.6, 73.7, 73.7, 55.2, 55.2, 24.7, 22.8 ppm. GC-MS (EI): 286.1

(7a) (2*S*)-1-[1-(4-methoxyphenyl)ethoxy]-3-methylbutan-2-tosylamine and (7b)



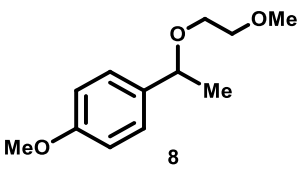
7a



7b

Mixture (2.6:1); each regioisomer dr 1:1 ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.20 (m, 2H), 6.91 – 6.84 (m, 2H), 4.36 (q, *J* = 6.5 Hz, 1H), (4.36) [(4.51) (4.48)], 3.80 (s, 3H), 3.77 (m, 1H), (3.69 – 3.60), 3.36 – 3.23 (m, 2H), 2.88 (s, 1H) (2.75), 1.69 – 1.61 (m, 2H), 1.61 – 1.45 (m, 3H), 1.43 (d, *J* = 6.5, 0.7 Hz, 3H) (1.41), 1.18 (d, *J* = 6.2, 3H), 1.14 (d, *J* = 6.1 Hz, 3H), (1.03) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 135.6, 127.7, 127.3, 113.7, 113.6, 77.7, 75.1, 73.9, 72.6, 71.0, 68.7, 68.5, 67.8, 67.6, 63.0, 62.9, 55.2, 36.9, 36.7, 34.1, 32.5, 28.6, 28.3, 26.7, 26.4, 24.4, 24.0, 23.9, 23.8, 23.4, 20.5, 18.8 ppm. GC-MS (EI): 238.1 HRMS (APCI) m/z (%): calcd. for $C_{14}H_{21}O_3$ ($[M-H]^-$) 237.1491; found 237.1504

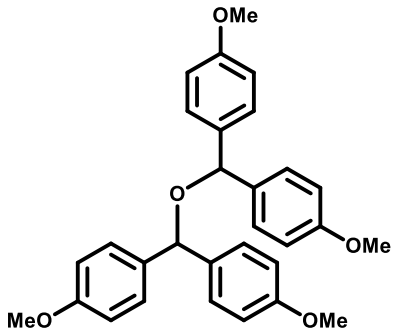
(8) 1-methoxy-4-[1-(2-methoxyethoxy)ethyl]benzene



8

^{1}H NMR (400 MHz, CDCl3) δ 7.22-7.27 (m, 2H), 6.85-6.90 (m, 2H), 4.40 (q, J = 6.46 Hz, 1H), 3.80 (s, 3H), 3.46-3.52 (m, 2H), 3.39-3.45 (m, 2H), 3.36 (s, 3H), 1.43 (d, J = 6.48 Hz, 3H) ppm. ^{13}C NMR (100 MHz, CDCl3) δ 159.1, 135.8, 127.53, 113.87, 78.1, 72.2, 67.6, 59.1, 53.3, 24.1 ppm.

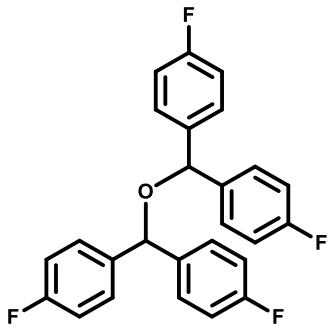
(10a) 1-{[bis(4-methoxyphenyl)methoxy](4-methoxyphenyl)methyl}-4-methoxybenzene



10a

^{1}H NMR (400 MHz, CDCl3) δ 7.24 (d, *J*= 8.66, 2H), 6.82 (d, *J*= 8.66, 2H), 4.40 (s, 1H), 3.69 (s, 3H), ppm. ^{13}C NMR (100 MHz, CDCl3) δ 158.92, 134.92, 128.54, 113.83, 79.06, 55.25 ppm.[44]

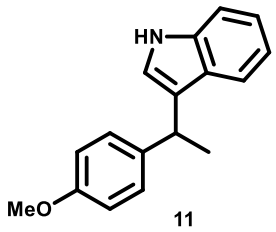
(10b) 1-{[bis(4-fluorophenyl) methoxy](4-fluorophenyl)methyl}-4-fluorobenzene



10b

^{1}H NMR (400 MHz, CDCl3) δ 7.24-7.33 (m, 2H), 6.94-7.03 (m, 2H), 5.33 (s, 1H) ppm. ^{13}C NMR (100 MHz, CDCl3) δ 163.53, 161.06, 137.47,.128.83, 115.35, 78.91 ppm.[45]

(11) 3-[1-(4-methoxyphenyl)ethyl]-1*H*-indole



11

^{1}H and ^{13}C NMR data are consistent with literature reports.[46] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.33 (dd, *J* = 19.1, 7.7 Hz, 1H), 7.19 (d, *J* = 8.8 Hz, 2H), 7.13 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 6.99 (ddt, *J* = 8.0, 7.0, 0.8 Hz, 1H), 6.96 (dd, *J* = 2.4, 1.0 Hz, 1H), 6.81 (d, *J* = 8.6 Hz, 2H), 4.32 (q, *J* = 7.1 Hz, 1H), 3.76 (s, 3H), 1.67 (d, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9, 139.1, 136.8, 128.4, 127.0, 122.1, 122.0, 121.1, 119.9, 119.3, 113.8, 111.1, 55.4, 36.2, 22.7 ppm. HRMS (ESI) m/z (%): calcd. for $C_{17}H_{18}NO$ ($[M+H]^+$) 252.1388; found 252.1402.

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Chapter 3 Nitrous Oxide Promoted Pauson-Khand Reaction

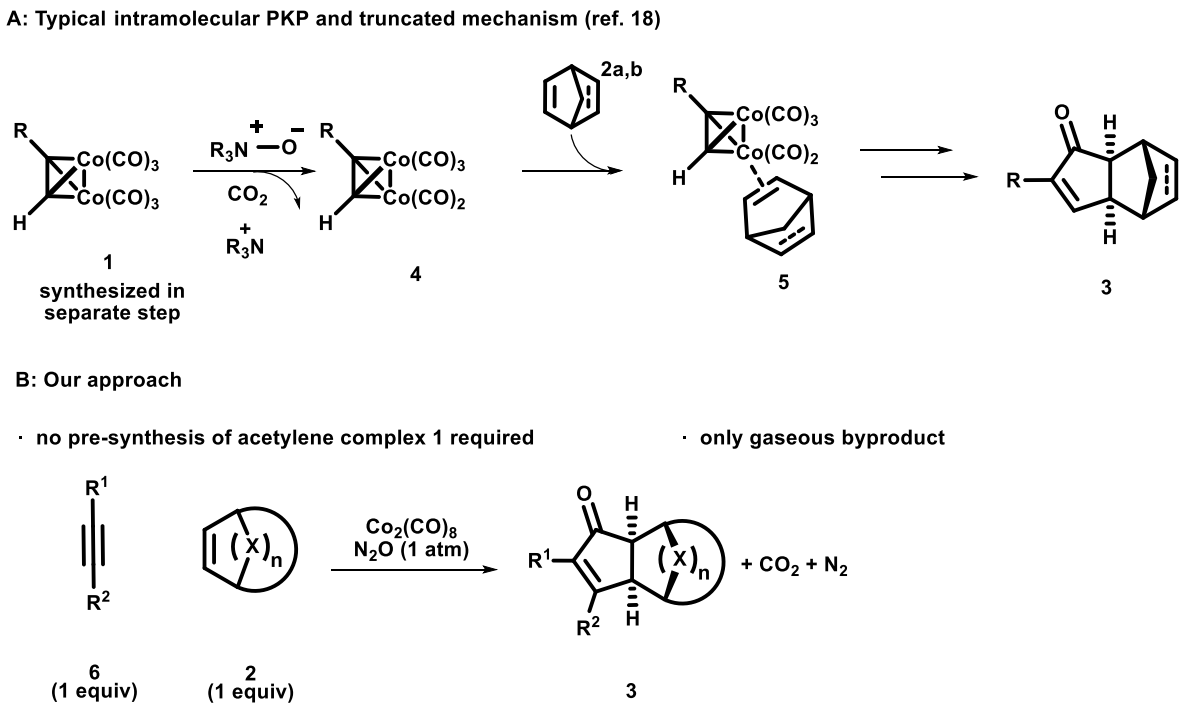
3.1. Abstract

A Pauson-Khand cycladdition of alkynes, alkenes, and carbon monoxide, promoted by cobalt carbonyl and nitrous oxide to furnish cyclopentenones is described. Preliminary mechanistic experiments suggest that nitrous oxide functions in a similar manner to that of the *N*-oxide promoters typically employed in Pauson-Khand reactions Only dinitrogen and carbon dioxide, thus avoiding high molecular weight reagents and the build up of basic byproducts. The chemistry is done using equimolar amounts of alkyne, alkene, and dicobalt octacarbonyl, and is performed directly from the acetylenic component without having to presynthesize a cobalt-alkyne complex. Terminal acetylenes were suitable substrates, as was solid calcium carbide, and the corresponding adducts were isolated in good yields. Furthermore, two sequential [4+3] and [2+2+1] cycloadditions were performed, generating densely functionalized in only two steps from readily available starting materials.

3.2. Introduction

The Pauson-Khand reaction (PKR) is a [2+2+1] cycloaddition between an alkyne, an alkene, and carbon monoxide to yield cyclopentenones.[1-2] It was first discovered in the early 1970s as a stoichiometric reaction between acetylenedicobalthexacarbonyl **1a** (R=H) and norbornene **2a** at elevated temperatures to yield the cycloadduct in moderate yield. The accepted mechanism (**Scheme 3.1, A**)[3–5] was proposed based on observed regiochemistry of **3a**, and has been largely supported by DFT calculations[6] and mass spectrometry.[7–10] After formation of the dicobalt acetylene complex **1**, dissociation of a molecule of CO from **1** to form **4** must occur so that an alkene can coordinate to generate **5**, which goes on to form the cyclopentenone product **3**. The most common method for formation of **4** is the application of a promoter, typically amine *N*-oxides.[11–14] The amine *N*-oxide is required to be used in 5-10 fold excess to get synthetically useful yields of the cyclopentenone adducts, generating substantial amount of waste. Thus, it is somewhat surprising that the simplest *N*-oxide, nitrous oxide (N_2O), has never been used as a promoter in this reaction. Replacing the commonly employed trimethylamine *N*-oxide (TMAO) with N_2O reduce the amount of waste generated. Moreover, nitrous oxide is inexpensive and widely available, yet there are few applications of the gas as a reagent in chemical synthesis.[15,16] Most transition metal catalysed or mediated processes that currently utilize N_2O involve direct transfer of the oxygen atom of N_2O to the transition metal center. [17–22] However, we hypothesized that if N_2O could oxidize the CO ligand rather than cobalt,[23] we could promote the PKR, and avoid the need for large excesses of solid oxide promoters (**Scheme 3.1, B**).

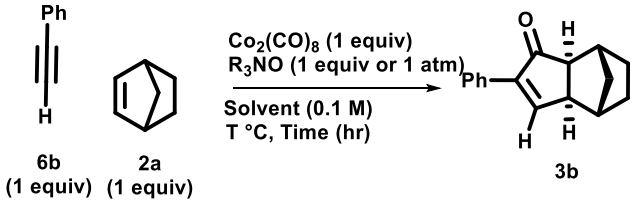
Scheme 3.1. Summary of cobalt-mediated Pauson-Khand cycloadditions.



3.3. Results and Discussion

We began the study by comparing the isolated yields of cyclopentenone **3b** when the cycloaddition was performed in the presence of 1 equivalent of $Co_2(CO)_8$ and either 1 equivalent of a solid *N*-oxide promotors or in the presence of N_2O at 40 ^oC in acetonitrile (**Table 3.1**). We found that at that loading TMAO was an effective promoter of the PKR (**entry 1**), but *N*-methylmorpholine *N*-oxide (NMO) required higher loading in accordance with previously reported studies (**entry 3**) to be effective.

Table 3.1. Selected optimization experiments in the N2O mediated PKR.[a]

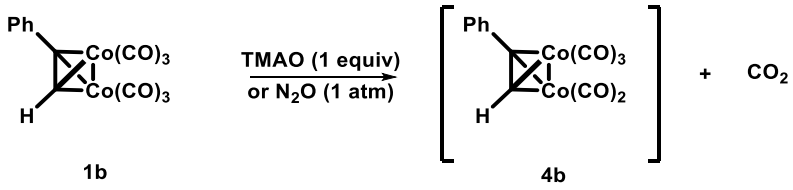


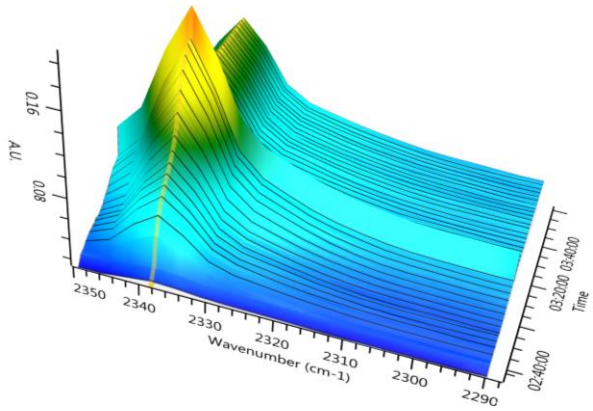
Entry	R_3NO	Solvent (M)	T (°C)	t (h)	Yield% (3a)[a]
1	TMAO	MeCN	40	20	69
2	NMO	MeCN	40	20	29
3	NMO[b]	MeCN	40	20	75
⇨ 4	NNO	MeCN	40	24	Intractable Mixture
5	N_2O	MeCN	40	20	80
6	N_2O	MeCN	40	24	86
7	N_2O	MeCN	20	24	64
8	N_2O	Toluene	40	24	74
9	N_2O	DME	40	24	10
10	N_2O	THF	40	24	77
11	N_2O	DCM	40	24	40
12	N_2O	$CHCl_3$	40	24	52

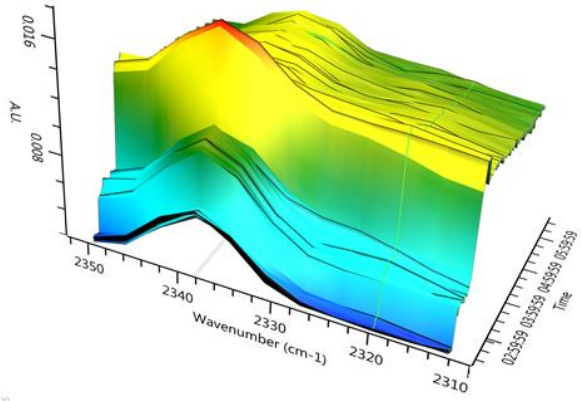
[a]Yields are of material isolated by silica gel chromatography. [b] 6 eqs. of NMO.
See Supporting Information for further details.

Nicotinamide *N*-oxide (NNO) was ineffective, and **3b** was produced in low yields among other unidentifiable materials (**entry 4**). We were pleased to note that performing the PKR in an N_2O-saturated acetonitrile solution gave cyclopentenone **3b** in 80% yield after 20 hours (**entry 5**). Extending the reaction time to 24 h improved the isolated yield of **3b** to 86% (**entry 6**). Performing the reaction at room temperature led to a slight reduction in isolated yield of **3b** (**entry 7**). We attempted to further improve the yield of the cycloadduct by varying the solvent (entries 8-12), but the reaction performed best in MeCN.

Figure 3.1. In situ FTIR data comparing the activation of the cobalt-phenylacetylene complex 1b (top) as promoted by TMAO (middle) and N2O (bottom). The x-axis shows the region of CO2 absorbance, and the z-axis begins at the addition of the N-oxide.





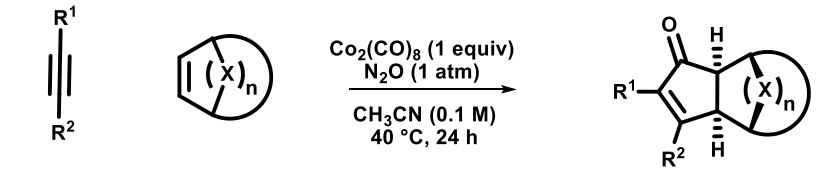


To determine whether N_2O was in fact acting in an analogous manner to other *N*-oxides, we compared in situ FTIR data for the reaction between the phenylacetylene-cobalt hexacarbonyl complex **1b** and both TMAO and N_2O. The generation of CO_2 was observed at 2338 cm^{-1} upon addition of each

promoter, though rapid outgassing of the solution prevented kinetic analysis of the two processes (**Figure 3.1**). While production of CO_2 is consistent with the oxidative extrusion of a CO ligand from the hexacarbonyl intermediate **1b** and formation of the putative pentacarbonyl species **4b**, we cannot rule out a more complex role for N_2O at this time.

We then turned to examining the scope of the alkyne component in the reaction (**Table 3.2**, top). To synthesis the parent cyclopentenone, we opted to use the solid reagent calcium carbide (**6a**) rather than gaseous acetylene to avoid concurrent introduction of two gaseous reagents. Calcium carbide, though exceedingly inexpensive, is not often employed as an acetylene surrogate. We were pleased to note that CaC_2 was an effective substrate when used with 2 equivalents of water, and the cyclopentenone **3a** was isolated in good yield.[24–27] Phenylacetylene **6b** was an excellent substrate, yielding cyclopentenone **3b** in high yield. Electronically different, whether electron-rich (**6c**) or electron-poor (**6d** and **6e**) were somewhat less effective, and products **3c**-**3e** were isolated in somewhat lower yields. The internal alkyne dimethyl acetylenedicarboxylate **6f** was an excellent substrate, and the product **6f** was isolated in good yield. Other functional groups were well-tolerated, and cyclopentenones containing coordinative alcohol and nitrile functional groups, **3h** and **3i** were isolated in good yields. Norbornadiene proved to be a less effective coupling partner with the exception of **3j**.

Table 3.2. Scope of the intermolecular PKR between alkynes 1a-1i and norbornene 2a as promoted by nitrous oxide.[a]



6a-6l (1 equiv) | 2a-b; 8a-c (1 equiv) | 3a-3p 45-90% yields ≥20:1 dr

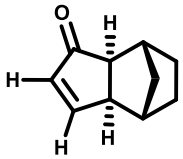
---

with 2a = norbornene.

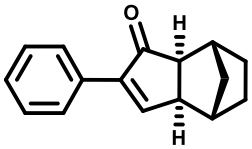
6a = CaC_2 | 6b, R^1 = Ph, R^2 = H | 6c, R^1 = p-MeC_6H_4, R^2 = H

6d, R^1 = m-FC_6H_4, R^2 = H | 6e, R^1 = p-$CF_3C_6H_4$, R^2 = H | 6f, R^1 = R^2 = CO_2Et

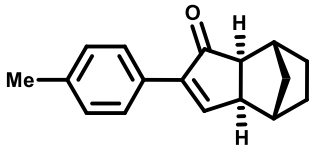
6g, R^1 = $(CH_2)_2CH_3$, R^2 = H | 6h, R^1 = $(CH_2)_2OH$, R^2 = H | 6i, R^1 = $(CH_2)_3CN$, R^2 = H



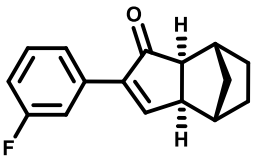
70% Yield, 3a[b]



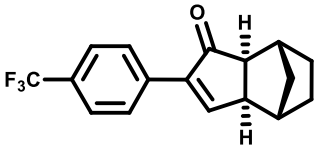
90% Yield, 3b



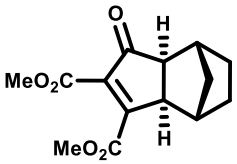
60% Yield, 3c



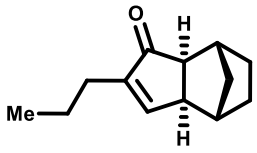
52% Yield, 3d



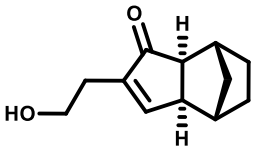
45% Yield, 3e



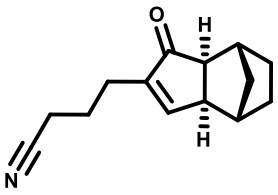
70% Yield, 3f



65% Yield, 3g



58% Yield, 3h



65% Yield, 3i

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with 2b = norbornadiene.

6h, R^1 = $(CH_2)_2OH$, R^2 = H | 6b, R^1 = Ph, R^2 = H | 6f, R^1 = R^2 = CO_2Et

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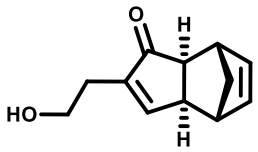
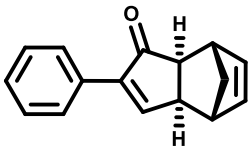
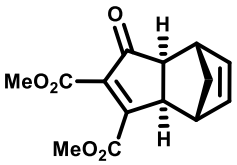


66% Yield, 3j



28% Yield, 3k



48% Yield, 3l

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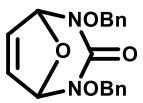
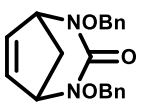
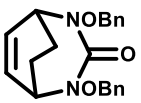
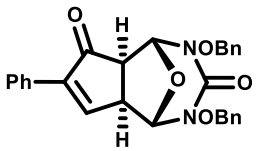
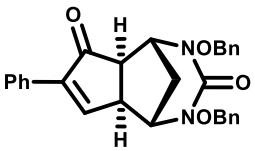
with 6b = phenylacetylene

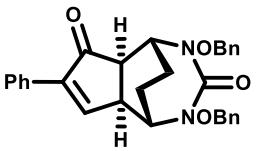
8a 

8b 

8c 



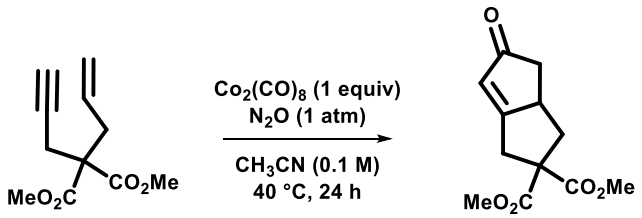




The intermolecular PKR is typically limited to olefins with either a low LUMO or those that possess a pendant Lewis base for secondary coordination to cobalt, but otherwise contain little functionality.[28,29] We were interested in applying more functionalized alkenes to the PKR. The [3.2.1] and [3.2.2] bicyclic olefins **8a-8c** were particularly interesting as they are easily constructed from cyclic butadienes and ureas via [4+3] cycloadditions, and contain many synthetic handles for downstream transformations. We thus subjected bridged bicyclic alkenes **8a-8c** to our standard conditions. Though not as strained as the [2.2.1] bicyclic alkenes,[30] these olefins were ready participants in the PKR, and densely functionalized cyclopentenones **3m-3o** were produced in good yields (**Table 3.2**, **bottom**). All cyclopentenones were isolated as single isomers, and *exo*-selectivity was determined by comparing acquired spectral data to known compounds **3a-b, 3f-h, 3j-l** and extrapolating that to unknown compounds **3c-e, 3i, 3m-o**.

Finally, we demonstrated the applicability of these reaction conditions to the cyclization of a 1,6-enyne (eq 1). The malonate derivative 9 smoothly reacted with $Co_2(CO)_8$ in the presence of N_2O to give the [5,5] bicyclic compound **10** in high yields (89%).

Scheme 3.2. Scope of the reaction



(1 equiv) (eq 1)

9 10

3.4. Conclusion

In conclusion, N_2O has been used for the first time as a promoter in the Pauson-Khand reaction. Its usage avoids the build-up of basic waste in situ that other often used promoters (NMO, TMAO) leave behind. We have preliminary evidence that N_2O oxidatively removes a CO ligand from the cobalt complex, but more detailed mechanistic explorations are warranted. We found that N_2O promoted the cycloaddition between alkynes and bridged bicyclic olefins in moderate to good yields, and could be executed directly from the alkyne with no need to presynthesize the cobalt alkyne complex. Our application of sequential [4+3] and [2+2+1] cycloadditions combines inexpensive and readily available starting materials to complex, densely functionalized tricyclic ring systems in only two steps.

3.5. Experimental Procedures

3.5.1. General information

All glassware were oven dried at 140 °C overnight and cooled in a desiccator before use. DCM, THF, and acetonitrile were purified by passage through an activated alumina column. All reagents were used as received unless otherwise noted below. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates. Visualization was accomplished with UV light followed by dipping in a potassium permanganate solution and heating. Purification of the reaction products were carried out by flash column chromatography using 40-63 μm silica gel.

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded with a Varian spectrometer in $CDCl_3$ solutions. ^{13}C NMR spectra were routinely run with broadband decoupling. Chemical shifts for ^{1}H and ^{13}C are reported in parts per million (ppm) down field from TMS, using residual $CDCl_3$ (7.26 ppm and triplet at 77.0 ppm, respectively) or tetramethylsilane as an internal standard. The following

abbreviations are used: m (multiplet), s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), etc.

3.5.2. Experimental procedure-solvent & promotor screen

To a sealable 5 mL reaction vial, .1 mmol of alkyne, .1 mmol alkene, .1 mmol $Co_2(CO)_8$, .1mmol of promotor and 1 mL of solvent was added. The reaction was then heated to 40 ˚C. After 20 or 24 hours (depending on entry in **Table 2.1**) at that temperature, the vial was removed from the hotplate, and the solvent was removed in vacuo. The product was purified via flash chromatography. *N*-Methylmorpholine *N*-oxide was used in its monohydrate form, and trimethylamine *N*-oxide was used in its dihydrate form.

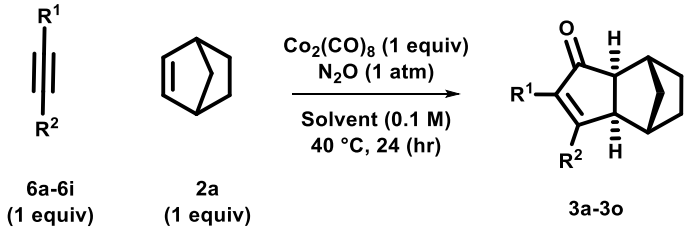
3.5.3. In situ IR spectroscopy

The instrument used was a Mettler Toledo ReactIR 15 with a SiComp AgX FiberConduit probe. TMANO promoted reaction: To a large reaction tube, 5 ml of THF was added. The IR probe was submerged in solvent and care was taken to not move probe after this point. 150 mg of dicobalt octacarbonyl was added via a ground glass side port. Ten minutes was allowed to elapse at which point 50 µL of phenylacetylene was added to the tube. The two reagents were allowed to react completely at which point 55 mg of trimethylamine N-oxide was added to the tube. After 20 minutes norbornene was added to the reaction mixture. A scan interval of 30 seconds was used. N2O promoted reaction: To a large reaction tube, 5 ml of THF was added. The IR probe was submerged in solvent and care was taken to not move probe after this point. 150 mg of dicobalt octacarbonyl was added via a ground glass side port. Ten minutes was allowed to elapse at which point 50 µL of phenylacetylene was added to the tube. The two reagents were allowed to react completely, at which point N2O was bubbled into the mixture. After 20 minutes of bubbling, norbornene was added to the reaction mixture. A scan interval of 30 seconds was used.

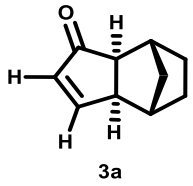
3.5.4. General experimental procedure for PKR with N_2O promoter

To a sealable 5 mL reaction vial, .1 mmol of alkyne, .1 mmol alkene, .1 mmol $Co_2(CO)_8$, and 1 mL of acetonitrile was added. A septum was added to the vial and, while stirring, N_2O from a Schlenk apparatus was gently bubbled through the solution for 5 minutes and then immediately capped while maintaining a positive pressure of N_2O. The reaction was then heated to 40 ˚C. After 24 hours at that temperature, the vial was removed from the hotplate, and the solvent was removed in vacuo. The product was purified via flash chromatography using the solvent systems specified for each product below. Any other modifications for specific substrates will be noted below.

3.5.5. Synthetic details – PKR with alkynes 6a-6i and norbornene



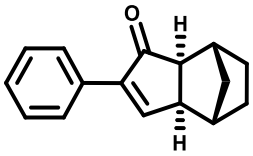
(1*R,2*S**,6*R**,7*S**)-Tricyclo[5.2.1.0^{2,6}]dec-4-en-3-one (3a)**



The general procedure was followed with the following exception, after bubbling N_2O through reaction mixture (.2 mmol) 3.6 µL of H_2O was added immediately prior to capping to hydrolyze calcium carbide.[31] 3.5 mg of CaC_2 and 9.5 mg of norbornene afforded 10.4 mg of **3a** (70% yield) as a clear liquid after evaporating off the solvent and purification via flash chromatography (8:1

Hex:EtOAc) R_f=0.4. The recorded spectra corresponds well to the previously published data.[4] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50 (dd, J = 5.6, 2.7 Hz, 1H), 6.26 (dd, J = 5.6, 1.6 Hz, 1H), 2.72 – 2.68 (m, 1H), 2.40 – 2.37 (m, 1H), 2.19 (d, J = 4.2 Hz, 1H), 2.13 (d, J = 5.2 Hz, 1H), 1.71 – 1.54 (m, 2H), 1.34 – 1.19 (m, 2H), 1.08 – 0.92 (m, 2H).HR-ESIMS calculated for $C_{10}H_{13}O$ $(M+H)^+$ 149.0960, observed 149.0966.

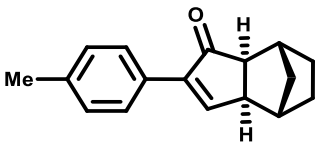
(1*R,2*S**,6*S**,7*S**)-4-Phenyltricyclo[5.2.1.0^{2,6}]dec-4-en-3-one (3b)**



3b

Following the general procedure, 10.5 mg of ethynylbenzene (distilled before use) and 9.4 mg of norbornene yielded 20.2 mg (90% yield) of **3b** as a white solid after purification via flash chromatography (8:1 Hex:EtOAc) R_f=0.45. The recorded spectra corresponds well to the previously published data.[32] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 – 7.68 (m, 2H), 7.64 (d, *J* = 2.9 Hz, 1H), 7.40 – 7.29 (m, 3H), 2.70 (dd, *J* = 5.3, 3.0 Hz, 1H), 2.50 (d, *J* = 4.2 Hz, 1H), 2.37 (d, *J* = 5.1 Hz, 1H), 2.27 (d, *J* = 4.3 Hz, 1H), 1.76 – 1.57 (m, 2H), 1.41 – 1.28 (m, 2H), 1.16 – 0.97 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 208.9, 160.1, 146.1, 131.5, 128.4, 128.4, 127.0, 54.9, 47.7, 39.5, 38.4, 31.3, 29.1, 28.4. HR-ESIMS calculated for $C_{16}H_{16}NaO$ $(M+Na)^+$ 247.1099, observed 247.1096.

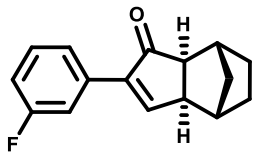
(1*R,2*S**,6*S**,7*S**)-4-(*p*-Tolyl)tricyclo[5.2.1.0^{2,6}]dec-4-en-3-one (3c)**



3c

Following the general procedure, 11 mg of 4-ethynyltoluene and 9.4 mg of norbornene yielded 15.6 mg (60% yield) of 3c as a white solid after purification via flash chromatography(20:1 hexane:EtOAc) Rf=0.4. 1H NMR (500 MHz, CDCl3) δ: 7.65 – 7.59 (m, 3H) 7.19 (d, J = 7.9 Hz, 2H), 2.70 (d, J = 3.2 Hz, 1H), 2.50 (d, J = 3.4 Hz, 1H), 2.36 (app s, 4H), 2.27 (d, J = 3.7 Hz, 1H), 1.77 – 1.69 (m, 1H), 1.66 – 1.59 (m, 1H), 1.41 – 1.29 (m, 2H), 1.13 (d, J = 10.5 Hz, 1H), 1.03 – 0.98 (m, 1H). 13C{1H} NMR (101 MHz, CDCl3) δ: 209.1, 159.3, 145.9, 138.2, 129.0, 128.6, 126.8, 70.9, 54.8, 47.6, 39.4, 38.3, 31.2, 29.6, 29.1, 28.3, 21.2. HR-ESIMS calculated for C17H18NaO (M+Na)+ 261.1255, observed 261.1264. Elemental Analysis(%C/%H/%N)- Calc'd(85.67/7.85/0), Found-(85.28/7.85/0)

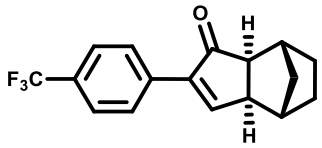
(1*R,2*S**,6*S**,7*S**)-4-(*m*-Fluorophenyl)tricyclo[5.2.1.0^{2,6}]dec-4-en-3-one (3d)**



3d

Following the general procedure, 12 mg of 1-ethynyl-3-fluorobenzene, and 9.4 mg of norbornene yielded 13.8 mg of **3d** (52% yield) as a white solid after purification via flash column chromatography (20:1 hexane:EtOAc) R_f=0.35. ^{1}H NMR(400 MHz, $CDCl_3$) δ: 7.68 (d, *J* = 2.9 Hz, 1H), 7.53 – 7.45 (m, 2H), 7.38 – 7.30 (m, 1H), 7.02 (tdd, *J* = 8.4, 2.6, 1.0 Hz, 1H), 2.75 – 2.70 (m, 1H), 2.51 (d, *J* = 3.8 Hz, 1H), 2.39 (d, *J* = 5.2 Hz, 1H), 2.30 (d, *J* = 4.0 Hz, 1H), 1.78 – 1.70 (m, 1H), 1.67 – 1.60 (m, 1H), 1.43 – 1.31 (m, 2H), 1.13 – 1.08 (m, 1H), 1.05 – 1.00 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 28.4, 29.2, 31.3, 38.4, 39.5, 47.8, 55.0, 114.1 (d, J = 22.7 Hz), 115.3 (d, J = 21.2 Hz), 122.7 (d, J = 2.9 Hz), 129.9 (d, J = 7.8 Hz), 133.6 (d, J = 4.1 Hz), 145.0 (d, J = 2.5 Hz), 160.9, 162.7 (d, J = 245.3 Hz), 208.53.· HR-ESIMS calculated for $C_{16}H_{15}FNaO$ $(M+Na)^+$ 265.1005, observed 265.1018. Elemental Analysis(%C/%H/%N)- Calc'd(79.32/6.24/0), Found-(78.92/6.22/0)

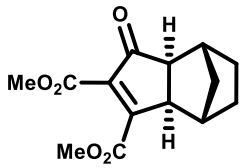
(1*R,2*S**,6*S**,7*S**)-4-[*p*-(Trifluoromethyl)phenyl]tricyclo[5.2.1.0^{2,6}]dec-4-en-3-one (3e)**



3e

Following the general procedure, 18 mg of 4-(trifluoromethoxy)phenylacetylene and 9.4 mg of norbornene yielded 14.1 mg of **3e** (45% yield) as a white solid after purification via flash column chromatography(20:1 hexane:EtOAc) R_f=0.3. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83 (d, *J* = 8.2 Hz, 2H), 7.75 (d, *J* = 2.9 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 2H), 2.76 (dd, *J* = 5.3, 3.0 Hz, 1H), 2.53 (d, *J* = 4.0 Hz, 1H), 2.41 (d, *J* = 5.2 Hz, 1H), 2.32 (d, *J* = 4.3 Hz, 1H), 1.79 – 1.71 (m, 1H), 1.69 – 1.61 (m, 1H), 1.44 – 1.32 (m, 2H), 1.14 – 1.08 (m, 1H), 1.04 (dt, *J* = 10.5, 1.4 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ : 208.4, 161.7, 145.0, 134.9, 130.4, 130.1, 127.3, 125.4, 125.3 (q, *J*=3.8), 123.9 (q, *J*=271.1 Hz), 54.9, 47.9, 39.5, 38.3, 29.1, 28.3. HR-ESIMS calculated for $C_{17}H_{15}F_3NaO$ $(M+Na)^+$ 315.0973, observed 315.0985. Elemental Analysis(%C/%H/%N)- Calc'd(69.85/5.17/0), Found-(69.60/5.18/0)

Dimethyl (1*S,2*R**,6*S**,7*R**)-5-oxotricyclo[5.2.1.0^{2,6}]dec-3-ene-3,4-dicarboxylate (3f)**

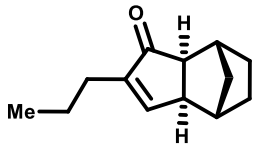


3f

Following the general procedure, 17.8 mg of dimethylacetylene dicarboxylate and 9.4 mg of norbornene yielded 18.5 mg of **3f** as a clear liquid (70% yield). R_f=0.4 (5:1 hex:EtOAc). The recorded spectra correspond well to the previously published data. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.89 (s, 3H),

3.87 (s, 3H), 2.96 (d, *J* = 5.3 Hz, 1H), 2.55 (d, *J* = 4.0 Hz, 1H), 2.51 (d, *J* = 4.0 Hz, 1H), 2.41 (d, *J* = 5.3 Hz, 1H), 1.75 (tt, *J* = 11.8, 4.3 Hz, 1H), 1.66 – 1.59 (m, 1H), 1.44 – 1.37 (m, 1H), 1.37 – 1.29 (m, 1H), 1.19 – 1.13 (m, 1H), 1.12 – 1.07 (m, 1H). $^{13}C\{^{1}H\}$ NMR(126 MHz, $CDCl_3$) δ: 204.6, 164.3, 163.5, 163.1, 142.6, 54.8, 52.9, 52.6, 48.9, 40.0, 38.4, 31.6, 29.0, 28.2.[33]

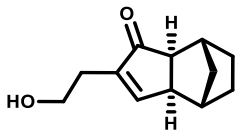
(1*R,2*S**,6*S**,7*S**)-4-Propyltricyclo[5.2.1.0^{2,6}]dec-4-en-3-one (3g)**



3g

Following the general procedure, 17.8 mg of dimethylacetylene dicarboxylate and 9.4 mg of norbornene yielded 18.5 mg of **3g** as a clear liquid (65% yield). The recorded spectra correspond well to the previously published data.[34] R_f=0.5 (15:1 hex:EtOAc). ^{1}H-NMR(400 MHz, $CDCl_3$) δ: 7.10 (1H, m, HC=), 2.56 (1H, m), 2.38 (1H, m), 2.14 (4H, m), 1.73–1.56 (2H, m), 1.49 (2H, h, *J*=7.4 Hz), 1.28 (2H, m), 1.04–0.90 (2H, m), 0.91 (3H, t, *J*=7.4 Hz); $^{13}C\{^{1}H\}$(101 MHz, $CDCl_3$) NMR-δ :211.3, 158.8, 149.3, 53.9, 48.2, 39.0, 38.0, 31.0, 29.1, 28.5, 26.8, 21.1, 13.9.

(1*R,2*S**,6*S**,7*S**)-4-(2-Hydroxyethyl)tricyclo[5.2.1.0^{2,6}]dec-4-en-3-one (3h)**

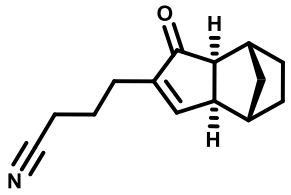


3h

Following the general procedure, 7.1 mg of 3-butyn-1-ol and 9.4 mg of norbornene yielded 11.1 mg of **3h** (58% yield) as a clear liquid (gradient from 4:1 hex:EtOAc to 1:3 hex:EtOAc). The recorded spectra correspond well to the previously published data.[34] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25 (d,

J=1.3 Hz, 1H), 3.78-3.67 (m, 2H), 2.62 (s, 1H) , 2.51-2.48(m,3H), 2.4(d, *J*=3.8 Hz, 1H), 2.23(dd, *J*=5.0,5.0 Hz, 1H), 2.19 (d, *J*=4.1Hz, 1H), 1.73-1.56(m, 2H), 1.35-1.23(m,2H), 1.04-0.95 (m, 2H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ-212.5, 161.8, 146.9, 61.4, 53.9, 48.6, 39.1, 37.9, 31.1, 29.3, 29.0, 28.4. HR-ESIMS calculated for $C_{12}H_{17}O_3$ $(M+H)^+$ 193.1229, observed 193.1225.

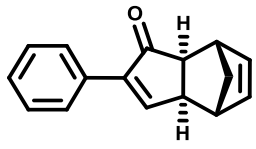
4-{(1*S,2*S**,6*S**,7*R**)-5-Oxotricyclo[5.2.1.0^{2,6}]dec-3-en-4-yl}butyronitrile (3i)**



3i

Following the general procedure, 9.7 mg of 5-hexynenitrile and 9.4 mg of norbornene yielded 15.5 mg of **3i** (65% yield) as a clear liquid. R_f=0.35 (9:1 hex:EtOAc) ^1H NMR δ: 7.22 – 7.19 (m, 1H), 2.63 – 2.59 (br s, 1H), 2.40 (d, *J* = 4.2 Hz, 1H), 2.37 (t, *J* = 1.4 Hz, 1H), 2.35 (t, *J* = 7.1 Hz, 2H), 1.93 – 1.80 (m, 2H), 1.73 – 1.65 (m, 1H), 1.59 (tq, *J* = 11.5, 4.2 Hz, 2H), 1.36 – 1.25 (m, 4H), 1.00 – 0.92 (m, 2H). $^{13}C\{^{1}H\}$ NMR(500 MHz, $CDCl_3$)-δ: 210.8, 160.4, 147.2, 119.4, 54.0, 48.5, 39.2, 38.1, 31.3,29.2, 28.5, 24.2, 23.8, 17.0. HR-ESIMS calculated for $C_{14}H_{17}NNaO$ $(M+Na)^+$ 238.1202, observed 238.1203.

(1*S,2*S**,6*S**,7*R**)-4-Phenyltricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (3j)**

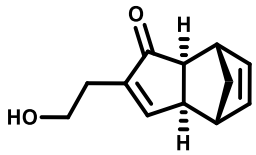


3j

Following the general procedure, 10.2 mg of ethynylbenzene (distilled before use) and 9.2 mg of norboradiene yielded 17.1 mg (77% yield) of **3b** as a white solid after purification via flash

chromatography (9:1 Hex:EtOAc) R_f=0.45. The recorded spectra corresponds well to the previously published data. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72 – 7.68 (m, 2H), 7.64 (d, *J* = 2.9 Hz, 1H), 7.40 – 7.29 (m, 3H), 2.70 (dd, *J* = 5.3, 3.0 Hz, 1H), 2.50 (d, *J* = 4.2 Hz, 1H), 2.37 (d, *J* = 5.1 Hz, 1H), 2.27 (d, *J* = 4.3 Hz, 1H), 1.76 – 1.57 (m, 2H), 1.41 – 1.28 (m, 2H), 1.16 – 0.97 (m, 2H).^{13}C{^{1}H} NMR (101 MHz, cdcl$_3$) δ 207.8, 160.0, 147.4, 138.7, 137.3, 131.8, 128.6, 128.6, 127.2, 53.7, 47.4, 44.3, 43.5, 41.6.[35]

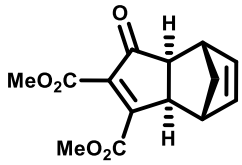
(1*S,2*S**,6*S**,7*R**)-4-(2-Hydroxyethyl)tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (3k)**



3k

Following the general procedure, 14.2mg of 3-butyn-1-ol and 18.8 mg of norbornadiene yielded 25 mg of **3h** (66% yield) as a clear liquid (4:1 hex:EtOAc). The recorded spectra correspond well to the previously published data.[36] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (d, *J* = 2.6 Hz, 1H), 6.28 (dd, *J* = 5.6, 3.1 Hz, 1H), 6.20 (dd, *J* = 5.6, 3.0 Hz, 1H), 3.73 (td, *J* = 6.1, 2.7 Hz, 2H), 2.95-2.88 (m, 1H), 2.74 (t, *J* = 3.6 Hz, 1H), 2.68 (d, *J* = 3.1 Hz, 1H), 2.57 - 2.17 (m, 4 H), 1.48 - 1.10 (m, 2 H) ppm. ^{13}C{^{1}H} NMR (101 MHz, cdcl3) δ 210.4, 161.3, 147.3, 138.1, 136.3, 60.3, 52.2, 47.7, 43.3, 42.5, 40.8, 28.6 ppm.[36]

Dimethyl (1*R,2*R**,6*S**,7*S**)-5-oxotricyclo[5.2.1.0^{2,6}]deca-3,8-diene-3,4-dicarboxylate (3l)**

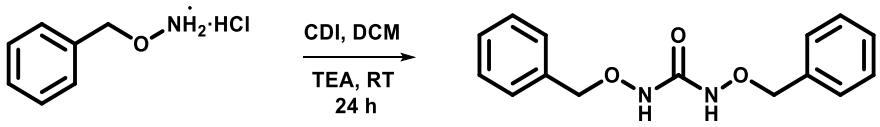


3l

Following the general procedure, 28.1 mg of dimethylacetylene dicarboxylate and 18.4 mg of norbornadiene yielded 26.1 mg of 3f as a white solid (48% yield). Rf=0.4 (5:1 hex:EtOAc). The recorded spectra correspond well to the previously published data. 1H NMR (400 MHz, CDCl3) δ: 6.36 (dd, J=5.6, 3.1 Hz, 1H), 6.25 (dd, J=5.6, 2.0 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.09 (d, J=5.3 Hz, 1H), 3.06 (app. s, 1H), 3.02 (app. s, 1H), 2.54 (d, J=5.1 Hz, 1H), 1.52 (d, J=9.9 Hz, 1H), 1.37 (d, J=9.9 Hz, 1H).. 13C{1H} NMR (101 MHz, cdcl3) δ 41.5, 43.4, 44.6, 48.5, 52.6, 52.9, 53.8, 137.4, 138.7, 143.0, 162.6, 163.0, 164.1, 202.9.8

3.5.6. Synthesis of unsaturated urea derivatives via [4+3] cycloaddition

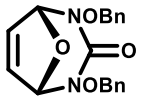
Ureas **8a**-**8c** were synthesized according to literature procedure from commercially available *O*-benzylhydroxylamine HCl in two steps.[29]



To a solution of *O*-benzylhydroxylamine hydrochloride (20.0 g, 125.305 mmol) in dichloromethane (313 mL) was added triethylamine (17.264 mL, 125.305 mmol) at 0 °C and stirred for 10 minutes before the addition of 1,1′-carbonyldiimidazole (9.104 g, 55.76 mmol) over a period of 15 minutes in 3 portions. The reaction mixture was stirred at room temperature for 24 hours. The reaction was quenched with water (100 mL) and extracted with dichloromethane (3 x 400 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified via column chromatography (4:1 to 3:2, hexanes: ethyl acetate) to provide the colorless solid (12.4 g, 44.89 mmol, 72 %). R_f = 0.25 (3:2, hexanes: ethyl acetate); mp = 89.8 – 90.2

°C; 1 H NMR (500 MHz, CDCl3): δ 7.54 (s, 2H), 7.39 – 7.35 (m, 6H), 7.34 – 7.30 (m, 4H), and 4.79 (s, 4H). The recorded spectra correspond well to the previously published data.[29]

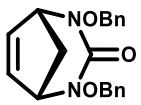
(±)-(1*S*,5*R*)-2,4-Bis(benzyloxy)-8-oxa-2,4-diazabicyclo[3.2.1]oct-6-en-3-one (8a)



8a

8a was synthesized according to the general procedure on a 5 g scale as an off-white solid (3.5 g,70%). The recorded spectra correspond well to the previously published data.[291]H NMR δ: 7.46 – 7.42 (m, 3H), 7.40 – 7.32 (m, 5H), 6.33 (dd, *J*=0.8,0.8 Hz, 2H), 5.24 (dd, *J* = 0.8,0.8 Hz, 2H), 5.02 (d, *J* = 11.1 Hz, 2H), 4.92 (d, *J* = 11.1 Hz, 2H). [13]C NMR δ: 160.2, 135.7, 133.6, 133.6, 129.6, 128.7, 128.5, 92.5, 78.8.

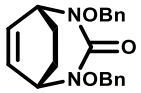
(±)-(1*R*,5*S*)-2,4-Bis(benzyloxy)-2.4-diazabicyclo[3.2.1]oct-6-en-3-one (8b)



8b

8b was synthesized according to the general procedure on a 5 g scale as an off-white solid (3.76 g, 75%). The recorded spectra correspond well to the previously published data.[29] [1]H NMR(400 MHz, $CDCl_3$) δ: 7.47 – 7.43 (m, 4H), 7.38 – 7.30 (m, 6H), 6.32 (dd, *J* = 1.5, 1.5 Hz, 2H), 5.00 (d, *J* = 10.9 Hz, 2H), 4.87 (d, *J* = 10.9 Hz, 2H), 3.97 – 3.92 (m, 2H), 1.99 – 1.94 (m, 1H), 1.75 (dt, *J* = 11.3, 4.4 Hz, 1H).

(±)-(1*R*,5*S*)-2,4-Bis(benzyloxy)-2.4-diazabicyclo[3.2.2]non-6-en-3-one (8c)

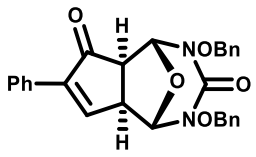


8c

8b was synthesized according to the general procedure on a 3 g scale as an off-white solid (2.05 g, 68%). The recorded spectra correspond well to the previously published data.[29] ^{1}H NMR δ: 7.50 – 7.46 (m, 4H), 7.40 – 7.33 (m, 6H), 6.26 (dd, *J* = 5.0, 3.2 Hz, 2H), 5.04 (d, *J* = 10.6 Hz, 2H), 5.00 (d, *J* = 10.6 Hz, 2H), 3.78 – 3.73 (m, 2H), 2.15 – 1.97 (m, 2H), 1.56 – 1.43 (m, 2H). ^{13}C NMR δ: 158.9, 136.0, 133.0, 129.9, 128.5, 128.4, 128.4, 78.1, 56.1, 55.6, 24.3.

3.5.7. Synthetic details – PKR with cyclic ureas 8a-8c and phenylacetylene

(1*R,2*R**,6*S**,7*S**)-8,10-Bis(benzyloxy)-4-phenyl-11-oxa-8.10-diazatricyclo[5.3.1.0^{2,6}]undec-4-ene-3,9-dione (3m)**

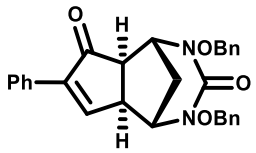


3m

Following the general procedure, 33.8 mg of **8a** and 10.5 mg of ethynylbenzene yielded 28.2 mg of **3j** as an white solid after column chromatography (4:1 to 2:3 hex:EtOAc) (60% yield). Melting point:127-129 ˚C R_f=0.15 (4:1 hex:EtOAc) ^{1}H NMR δ: 7.61 – 7.55 (m, 2H), 7.52 – 7.46 (m, 4H), 7.44 – 7.40 (m, 6H), 7.37 – 7.32 (m, 4H), 5.16 – 5.07 (m, 2H), 5.00 (d, *J* = 6.5 Hz, 1H), 4.98 (d, *J* = 6.6 Hz, 1H), 4.84 (s, 1H), 4.70 (s, 1H), 3.57 (dd, *J* = 5.6, 3.1 Hz, 1H), 3.28 (d, *J* = 5.6 Hz, 1H). ^{13}C{^{1}H}-NMR (126 MHz, cdcl$_3$)δ: 202.4, 158.2, 154.5, 145.9, 135.6, 135.3, 130.0, 129.8, 129.6, 129.3, 129.0, 128.9, 128.70, 128.66, 128.5, 127.6, 127.1, 127.0, 92.7, 91.8, 78.8, 78.8, 65.4, 54.6, 47.6. HR-ESIMS

calculated for $C_{28}H_{25}N_2O_5$ $(M+H)^+$ 469.1763, observed 469.1758. Elemental Analysis(%C/%H/%N)-Calc'd(71.78/5.16/5.98), Found-(71.39/5.27/5.94).

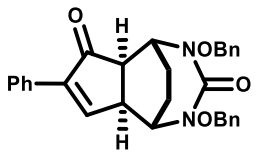
(1*R,2*R**,6*S**,7*S**)-8,10-Bis(benzyloxy)-4-phenyl-8.10-diazatricyclo[5.3.1.0^{2,6}]undec-4-ene-3,9-dione (3n)**



3n

Following the general procedure, 33.6 mg of **8b** and 10.4 mg of ethynylbenzene yielded 25.8 mg of **3k** as an off-white solid after column chromatography (4:1 to 1:2 hex:EtOAc) (55% yield) R_f=0.2 (4:1 hex:EtOAc) Melting point:118-120 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 7.5, 2.2 Hz, 2H), 7.57 (d, *J* = 3.2 Hz, 1H), 7.53 – 7.47 (m, 4H), 7.42 – 7.33 (m, 9H), 5.09 (dd, *J* = 10.8, 5.3 Hz, 2H), 4.97 – 4.86 (m, 2H), 3.78 (d, *J* = 4.2 Hz, 1H), 3.72 (t, *J* = 4.3 Hz, 1H), 3.56 (br. d, *J* = 4.3 Hz, 1H), 3.42 (d, *J* = 5.3 Hz, 1H), 1.91 (d, *J* = 13.1 Hz, 1H), 1.50 (dt, *J* = 13.2, 4.4 Hz, 1H).^{13}C{^{1}H} NMR(cdcl$_3$, 101 MHz): δ = 204.8, 160.6, 156.8, 135.9, 135.7, 130.4, 129.6, 129.5, 129.1, 128.7, 128.6, 128.5, 128.5, 128.4, 127.0, 78.0, 77.9, 63.8, 63.6, 54.5, 47.0, 28.3.HR-ESIMS calculated for $C_{29}H_{27}N_2O_4$ $(M+H)^+$ 467.1971, observed 467.1972.

(1*R,2*R**,6*S**,7*S**)-8,10-Bis(benzyloxy)-4-phenyl-8.10-diazatricyclo[5.3.2.0^{2,6}]dodec-4-ene-3,9-dione (3o)**



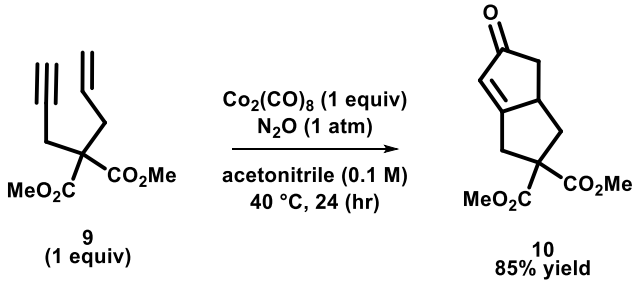
3o

Following the general procedure, 35 mg of **8c** and 10.4 mg of ethynylbenzene yielded 21.8 mg of **3l** as an off-white solid after column chromatography (5:1 to 1:2 hex:EtOAc) (45% yield). Melting point:122-124 ˚C ^{1}H NMR (400 MHz, cdcl3) δ 7.68 – 7.61 (m, 2H), 7.53 – 7.48 (m, 4H), 7.47 (d, *J* = 3.0 Hz, 1H), 7.45 – 7.30 (m, 9H), 5.17 – 5.05 (m, 4H), 3.87 – 3.82 (m, 1H), 3.60 – 3.56 (m, 1H), 3.42 – 3.36 (m, 1H), 3.00 (ddd, *J* = 7.0, 3.2, 1.5 Hz, 1H), 1.77 – 1.66 (m, 2H), 1.51 – 1.31 (m, 2H). ^{13}C{^{1}H} NMR(cdcl3, 101 MHz): δ = 205.1, 158.8, 157.4, 144.8, 136.0, 135.7, 130.4, 130.0, 129.9, 129.1, 128.7, 128.7, 128.5, 128.5, 127.0, 78.0, 77.3, 77.0, 76.7, 59.7, 58.9, 49.2, 42.4, 21.9, 20.9. HR-ESIMS calculated for $C_{30}H_{29}N_2O_4$ $(M+H)^+$ 481.2127, observed 481.2126. Elemental Analysis(%C/%H/%N)-Calc'd(74.98/5.87/5.83), Found-(75.39/6.09/5.50)

3.5.8. Intramolecular N_2O mediated Pauson-Khand reaction

Synthesis of **9** was achieved by subsequent allylation[37] and propargylation[38] of dimethyl malonate as described previously. The recorded spectra corresponded well to the previously published data. ^{1}H-NMR (400 MHz, CDCl3) δ: 5.56-5.65 (m, 1H), 5.11-5.21 (m, 2H), 3.74 (s, 6H), 2.79-2.82 (m, 4H), 2.02 (t, J = 2.8 Hz, 1H).

Dimethyl (*R*)-5-oxo-2,3,3a,4-tetrahydro-1*H*-pentalene-2,2-dicarboxylate (10)



9
(1 equiv)

10
85% yield

21 mg of **7**, 34.1 mg of $Co_2(CO)_8$, and 1 mL of acetonitrile were added to a sealable 5 ml reaction vial. A septa was added to the vial and, while stirring, N_2O from a Schlenk apparatus was bubbled through

the solution for 5 minutes and then capped and allowed to heat to 40 ˚C. After 24 hours, the vial was removed from the hotplate, and the solvent was removed in vacuo. The product was purified via column chromatography (4:1 hexane:EtOAc) and yielded **10** as a clear liquid 20.2 mg (85%). The recorded spectra corresponds well to the previously published data.[39] ^{1}H NMR(400 MHz, $CDCl_3$) δ: 1.72 (t, *J* = 12.7 Hz, 1H), 2.10 (dd, *J* = 17.8, 3.3 Hz, 1H), 2.61 (dd, *J* = 17.9, 6.4 Hz, 1H), 2.79 (dd, *J* = 12.8, 7.6 Hz, 1H), 3.03 – 3.13 (m, 1H), 3.24 (d, *J* = 19.0 Hz, 1H), 3.33 (d, *J* = 19.0 Hz, 1H), 3.73 (s, 3H), 3.77 (s, 3H), 5.91 (q, *J* = 1.9 Hz, 1H). HR-ESIMS calculated for $C_{12}H_{15}O_5$ $(M+H)^+$ 239.0919, observed 239.0910.

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Chapter 4 Activated Pauson-Khand Reaction

4.1. Abstract

Despite the applicability of the Pauson- Khand reaction for the synthesis of cyclopentenone derivatives, this annulation technique is limited to certain types of alkenes. Electron-deficient alkenes such as unsaturated carboxylic acid derivatives, either do not participate in the PKR or generate low-yield products. For the first time in an electrophilic activation strategy catalyzed by 2,3,4-triflouroboronic acid, unsaturated carboxylic acid derivatives were applied directly in the PKR. Results indicated that N_2O compared to classic promoters has better performance. Beside the regular PKR product, reductive products have been detected for some substrates.

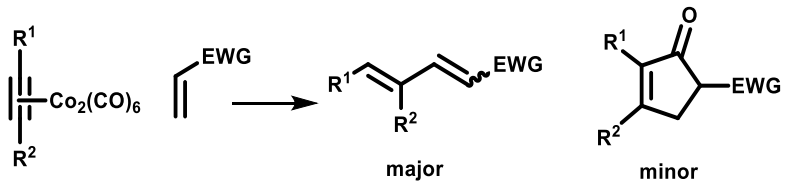
4.2. Introduction

The Pauson-Khand reaction, introduced in 1971, is a [2+2+1] cycloaddition between an alkyne, alkene, and cobalt carbonyl complex for the synthesis of cyclopentenone derivatives.[1] Despite many advances, in the domain of cyclization techniques, it is not a comprehensive method for all types of alkynes and alkenes. Internal alkynes are poor substrates compared to terminal alkynes. Olefins bearing electro-withdrawing groups are poor substrates. strained cyclic alkenes usually deliver more yields than unstrained ones. Therefore, over 40 years, researches have been focused to further develop this method into a general and robust process. [2]

Associated with the reactivity of alkene component, it has been discovered that strained cyclic olefins compared with unstrained and linear olefins generally deliver better yields because in these compounds the C=C-C bond angle is adequately small and consequently, the π^* orbital (LUMO) is

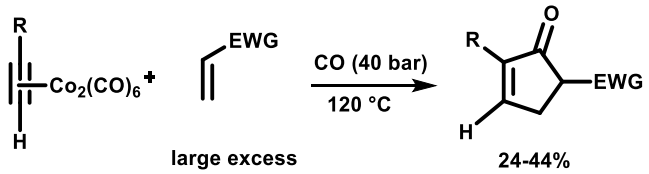
low enough to be filled out by the metal electrons in the back-donation process. [3] Also, electron-deficient olefins such as α, β unsaturated esters, ketones, nitriles, and carboxylic acids, mostly in the intermolecular PKR, are not active compounds. β-hydride elimination is the major conversion rather than carbonyl insertion and the C-C bond formation occurs between the most accessible carbons of both partners, so in a linear reaction, conjugated dienes as the major products are formed (**Scheme 4.1**).[4]

Scheme 4.1. Reactivity of electron-deficient alkenes in the PKR.

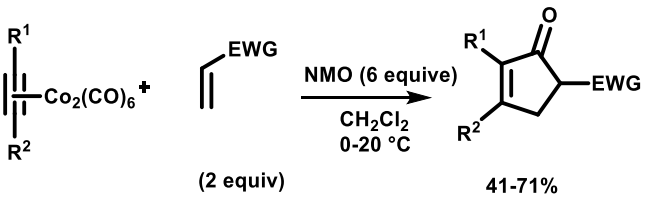


However, a small number of papers have been published in this regard in which electron-deficient olefins, such as alkyl acrylates, acrylonitrile, and phenyl vinyl sulfone under certain circumstances have provided the PKR products in low to moderate yields (**Scheme 4.1**). [5,6]

Scheme 4.2. PKR Reactions using electron-deficient alkynes.



R = nBu, tBu, Ph
EWG = CO_2Me, CO_2Et, CN

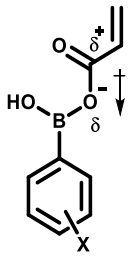


R^1 = Ph, C_3H_7, Me
R^2 = Me, H
EWG = CO_2Me,SO_2Ph

To the best of our knowledge, among electron-deficient olefins unsaturated carboxylic acids have never been used in the PKR. We hypothesized that the poor reactivity of unsaturated carboxylic acids is correlated with its LUMO. So, electrophilic activation of these compounds by LUMO lowering agents would form the cyclopentenones predominantly. To achieve this goal, phenylboronic acid (PBA) was considered a suitable electrophilic activator because PBAs have been applied in numerous Diels-Alder reactions and cyclizations as the activating agent that catalyzes the reactions by lowering the LUMO of the dienophiles. For instance, in 2008, Hall et al. reported the catalytic Diels-Alder reaction of unsaturated carboxylic acids in presence of 2-bromophenylboronic acid in high yields.[7]

Later in 2010, they extended the application of PBAs for the activation of unsaturated carboxylic acids in the dipolar [3+2] cycloadditions. [8] They have rationalized that in the reaction between an unsaturated carboxylic acid and an aryl boronic acid, the monoacrylborate intermediate is formed reversibly, which causes a decrease in the LUMO of the acid. Moreover, when the reaction is catalyzed by the arylboronic acid, no additional synthetic step is required to mask the acidic group.[7,8]

Scheme 4.3. Electrophilic activation of unsaturated carboxylic acids.

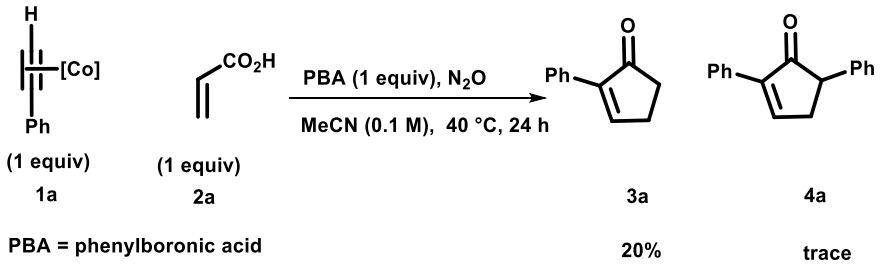


Herein, we report an activated PKR using 2,3,4 tri-fluorophenylboronic acid as the LUMO lowering agent. Following from our previous study, this reaction was promoted by nitrous oxide (N_2O) which avoids massive basic waste generated by a large excess of the classic promoters such as TMAO and NMO. [9]

4.3. Result and Discussion

We started off the study with the model substrate reaction between one equivalent of acrylic acid, pre-synthesized phenylacetylenic dicobalt hexacarbonyl complex and, phenylboronic acid in acetonitrile solvent (0.1 M) at 40 ◦C for 24 h. (**Scheme 4.4**)

Scheme 4.4. The model substrate reaction.



The initial results showed that the cyclization led to the formation of 2-phenylcyclopent-2-en-1-one (**3a**) with a 20 percent yield. Also, trace amount of 2,5-diphenylcyclopent-2-en-1-one (**4a**) as a

reductive product formed. Optimization of the PBA showed that, 20% mole of the PBA deliver 3a with 30% yield. (**entry 7**).

Table 4.1. Optimization table of the PBA.

Entry	PBA [mol%]	Yield% (3a)[a]	Yield% (4a)[a]
1	-	trace[a]	ND[b]
2	5	9	ND
3	10	11	ND
4	20	24	ND
5	30	18	ND
6	30	19	ND
⇨ 7	40	30	ND
8	50	25	ND

[a]detected by GCMS [b] Not Detected

In the continuation of the study, the reaction condition in presence of a variety of phenylboronic acids and, solvents at different reaction time and temperatures were screened. As illustrated in the optimization table (Error! Reference source not found.**, entry 3)**, 2,3,4 triflourophenylboronic acid showed a better impact on the annulation process with 37% yield. Among solvents, DMF increased the efficiency of the reaction up to 47% for **3a** and 6% for **4a**. Finally, when acrylic acid **2a** was doubled cyclopentenones **3a** and **4a** formed with 74 % yield and 10% yield, respectively. (**entry 14)**

Table 4.2. Table of selected optimization experiments.

Entry	PBA	PBA [mol%]	Solvent	m(equiv)	Promoter	t (h)	T(°C)	3a	4a
1	2-Cyanophenylboronic acid	40	MeCN	1	N_2O[b]	24	40	13%	NR
2	2-Methoxyphenylboronic acid	40	MeCN	1	N_2O	24	40	5%	NR
3	2,3,4 Triflourophenylboronic acid	40	MeCN	1	N_2O	24	40	37%	trace
4	2-Chloro$_3$-Bromophenylboronic acid	40	MeCN	1	N_2O	24	40	23%	trace
5	2-Iodophenylboronic acid	40	MeCN	1	N_2O	24	40	14%	NR
6	2-Bromophenylboronic acid	40	MeCN	1	N_2O	24	40	19%	trace
7	2,3,4 Triflourophenylboronic acid	40	Hexane	1	N_2O	24	40	NR%	NR
8	2,3,4 Triflourophenylboronic acid	40	DCM	1	N_2O	24	40	trace	NR
9	2,3,4 Triflourophenylboronic acid	40	DMF	1	N_2O	24	40	47%	6%
10	2,3,4 Triflourophenylboronic acid	40	EtOAc	1	N_2O	24	40	trace	NR
11	2,3,4 Triflourophenylboronic acid	40	DMF	1	N_2O	24	rt	42%	trace
12	2,3,4 Triflourophenylboronic acid	40	DMF	1	N_2O	24	60	36%	15%
13	2,3,4 Triflourophenylboronic acid	40	DMF	1	N_2O	24	120	26%	11%
14	2,3,4 Triflourophenylboronic acid	40	DMF	2	N_2O	24	40	74%	10%
15	2,3,4 Triflourophenylboronic acid	40	DMF	2	N_2O	12	40	50%	5%
16	2,3,4 Triflourophenylboronic acid	40	DMF	2	N_2O	48	40	65%	8%
17	2,3,4 Triflourophenylboronic acid	40	DMF	2	-	48	40	trace	trace
18	2,3,4 Triflourophenylboronic acid	40	DMF	2	NMO[c]	24	40	10%	NR
19	2,3,4 Triflourophenylboronic acid	40	DMF	2	TMAO[c]	24	40	23%	NR
20	2,3,4 Triflourophenylboronic acid	40	DMF	2	N_2O/NMM[d]	24	40	32%	NR

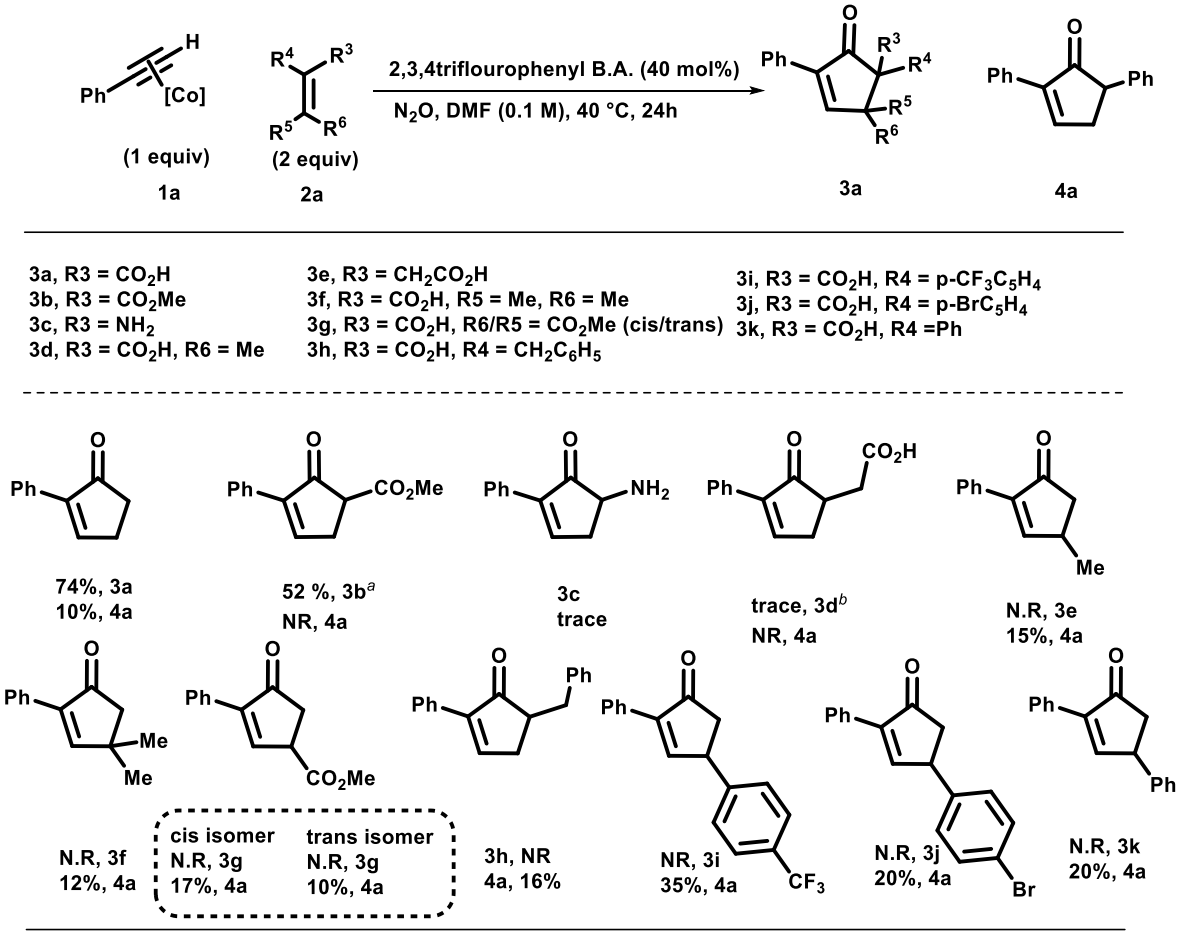
[a] Yields are of product 2a isolated by silica gel chromatography. [b] The reaction solution was purged by N_2O for 5 minutes. [c] 3 equiv of NMO and TMAO . d 1 equiv of NMM.

Neither changing the temperature nor the reaction time improved the yield. Classic promoters such as N-Methylmorpholine N-oxide (NMO) and trimethylamine N-oxide (TMAO) did not increase the efficiency of the reaction. This approves the role of nitrous oxide for the formation of cyclopentenone 2a in comparison to classical promoters.

Moreover, addition of N-methylmorpholine (NMM) decreased the productivity of the reaction. This is due to low reactivity of Nitrous oxide in presence of NMM. (**entry 20**). With the best optimized condition in hand, we began to examine the scope of starting materials. As it is shown in **table 4.3** methyl acrylate and acrylamide yielded **3a** with 52% yield and trace amount of the product respectively. However, **4a** was not formed in any of these reactions. The LUMO of pent-4-enoic acid

was not low enough to deliver the PKR product. (**3d**). Also, no reductive product formed. Then, we examined di/trisubstituted alkenes to find out more about the scope of the method.

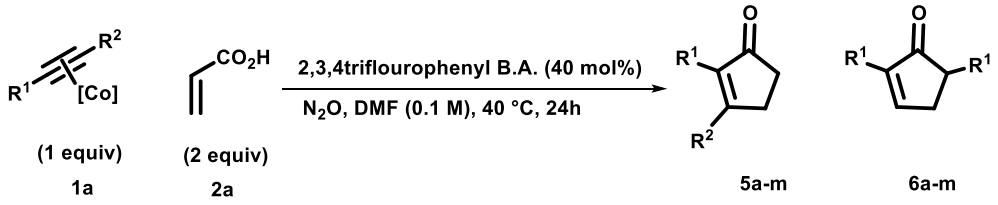
Table 4.1. Substrate scope of the alkene component.



[a] Detected by GCMS. [b] 9% yield was obtained without B.A.

In the PKR reaction increasing steric of the olefins negatively affect the annulation process. [10] Similarly disubstituted acrylic acid derivatives give poor yields even at elevated reaction temperatures. when we applied α, α /α, β disubstituted unsaturated olefins**. (3e-3k**). Cis-isomer of **3g** produced **4a** give higher yield than trans-isomer. (**3g**). P-triflouromethylphenylacetylene (**3i**) and p-bromophenylacetylene yielded **4a** with 35% and 20% yield, respectively.

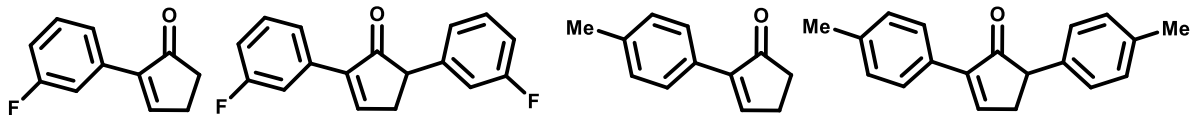
Table 4.4. Substrate scope of the Alkyne component.



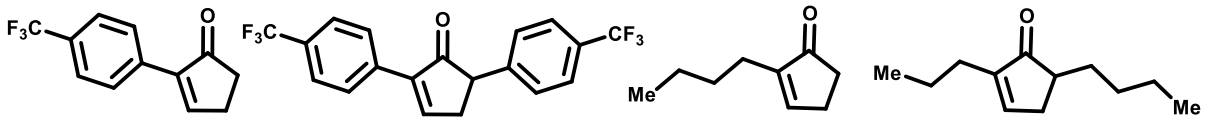
5a/6a, R^1 = m-FC_6H_4
5b/6b, R^1 = p-$CH_3C_6H_4$
5c/6c, R^1 = p-$CF_3C_6H_4$

5d/6d, R^1 = $(CH_2)_2CH_3$
5e/6e, R^1 = C_2H_4OH
5f/6f, R^1 = $(CH_2)_3CN$

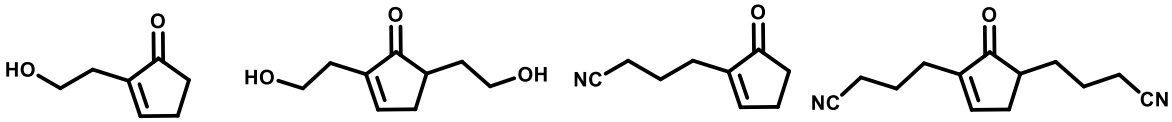
5g/6g, R^1 = C_3H_5
5h/6h, R^1 = Ph, R^2 = Ph
5i/6i, R^1 = CO_2Me, R^2 = CO_2Me



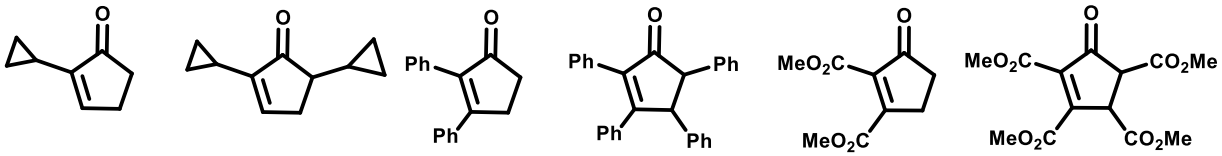
60%, 5a | 36%, 6a | 52%, 5b | Trace, 6b



51%, 5c | 40%, 6c | trace, 5d | trace, 6d



trace, 5e | trace, 6e | 30%, 5f | trace, 6f



trace, 5g | trace, 6g | NR, 5h | NR, 6h | NR, 5i | NR, 6i

All trace amount of the products was detected by GCMS

Substrate scope for alkyne components showed that aromatic alkynes bearing EWGs and EDGs provided regular PKR products in low to moderate yields. (5a-5c). Also, reductive PKR product was produced in higher yield more when aromatic alkynes have EWGs on the phenyl ring. (6a-6c). Applying aliphatic alkynes such as but-3-yn-1-ol (**5d**) and pent-1-yne (**5e**) in the reaction led to the formation of trace amounts of both products. Pent-4-ynenitrile (**5f**) formed 30% of the PKR product in 30%yield. Due to steric interaction, internal alkynes did not deliver the products. This is in accordance with the low reactivity of these components in the PKR reaction. [10] (**5h-5i**).

4.4. Conclusion

In this chapter, activated PKR using a pre-synthesized acetylenic hexacarbonyl complex, unsaturated olefins and, aryl boronic acid as the electrophilic activator has been investigated. According to the results, decarboxylation of the acrylic acid occurs. With the exceptions of except acrylic acid and methyl acrylate, mono/disubstituted alkenes did not successfully participate in the reaction. Moreover, aromatic alkynes showed better compatibility with the reaction conditions compared to aliphatic alkynes.

4.5. Experimental Procedures

4.5.1. General information

All chemicals were purchased from chemical suppler, unless the chemicals which were synthesized in the lab. All solvent except anhydrous dichloromethane hexane and acetonitrile were purchased and used without further purification. Anhydrous dichloromethane hexane and acetonitrile were obtained over dual purifying alumina columns (101mm OD x 635 mm L) under nitrogen pressure. All glassware were oven-dried overnight and flushed with nitrogen prior to use. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates. The reaction products were purified via column chromatography using 40-63 μm silica gel. 1H and 13C NMR spectra were obtained using a 500 MHz Varian VNMRS in CDCl3 referenced to tetramethylsilane (TMS) internal standard. High- and low-resolution mass spectra were obtained on Agilent model G6230A TOF-Mass Spectrometer and Agilent 7890A gas chromatograph coupled to a 5975C quadrupole mass spectrometer, respectively.

4.5.2. General experimental procedure for the synthesis of acetylenic dicobalt hexacarbonyl complex

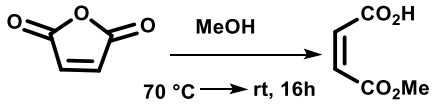
1 equivalent of cobalt carbonyl complex in DCM (0.1M) was cooled down to 0 ◦C under argon. Then 1.2 equivalent of the alkyne was added slowly. Then the ice bath was removed to let the reaction media warm up to the room temperature. After 1.5 hours the solvent was removed in vacuo and the product was isolated via flash chromatography. The brownish product was characterized via ^{1}H and ^{13}C NMR.

4.5.3. General experimental procedure for the Synthesis of activated PKR products

40% mol of 2,3,4-triflourophynylboronic acid was added to 0.2 mmol of acetylenic dicobalt hexacarbonyl complex in 2 ml DMF solvent.0.2g of molecular sieve (4 A˚) for each 0.1 mmol of the pre-synthesized complex was added to the reaction vessel. The reaction mixture was stirred under argon for 5 minutes then degassed with nitrous oxide for 5 minutes, immediately sealed and heated at 40 ˚C for 24h. After 24 hours the solvent was removed in vacuo and the product was isolated via flash chromatography.

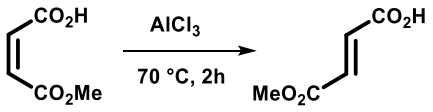
4.5.4. Experimental procedure for the synthesis of starting materials

(2*Z*)-but-2-enedioic acid



In accordance with the literature[11], in a sealed pressure tube, 0.04 ml of methanol (1 equiv) was added drop wise to 0.098 g (1.02 equiv) of melted maleic acid at 70 ◦C. The mixture was stirred for 16 hours. Then, the mixture was dried under vacuum to give the colorless liquid. (0.1 g, 77% yield). R_f = 0.2 (MeOH: DCM, 30:70) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.47 (d, J = 12.3, 1H), 6.39 (d, J = 12.3, 1H), 3.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.19, 166.92, 132.87, 130.15, 53.02.

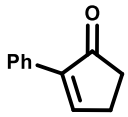
(2*E*)-but-2-enedioic acid



In accordance with the literature,[11] in a reaction vessel of 1.30 g of (Z) monomethyl fumarate, 0.53 g of $AlCl_3$ was added slowly. The mixture was heated at 70 ◦C for 2 hours. Then, the reaction mixture was quenched with 1M HCl, extracted with EtOAc (3×40 ml). The organic layer was washed with brine (2×20 ml) dried over $MgSO_4$, filtered to give a mixture of both isomers. The mixture of isomers was recrystallized to give the E-isomer. R_f = 0.5 (H: DCM, 70:30) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.91 (d, J = 15.5, 1H), 6.87 (d, J = 15.5, 1H), 3.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.07, 165.05, 135.02, 132.67, 52.48.

4.5.5. Experimental procedure for the synthesis of activated PKR products

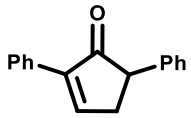
2-phenylcyclopent-2-en-1-one (3a)



3a

Following the general procedure, 77 mg of acetylenic dicobalt hexacarbonyl complex in DMF solvent (0.2 mmol), 29 mg of acrylic acid and, 14 mg of 2,3,4-triflourophynylboronic acid yielded 23 mg (74% yield) of **3a** as a white solid after purification via flash chromatography. (4:1 Hex: EtOAc) R_f=0.37 (distilled before use) and 9.4 mg of norbornene yielded 20.2 mg (90% yield) of **3b** as a white solid after purification via flash chromatography (8:1 Hex: EtOAc) R_f=0.45. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (t, *J* = 2.9 Hz 1H), 7.66-7.71 (m, 2H), 7.42 – 7.30 (m, 4H),2.74-2.69 (m, 2H), 2.59-2.64 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.5, 158.9, 143.5, 131.6, 131.6, 128.4, 127.1, 35.7, 26.2.

2,5-diphenylcyclopent-2-en-1-one (4a)

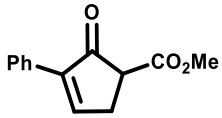


4a

White solid, (8:1 Hex: EtOAc) R_f=0.45.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (t, *J* = 2.9 Hz 1H), 7.66-7.71 (m, 2H), 7.42 – 7.30 (m, 4H),2.74-2.69 (m, 2H), 2.59-2.64 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.5, 158.9, 143.5, 131.6, 131.6, 128.4, 127.1, 35.7, 26.2.

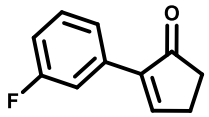
methyl 2-oxo-3-phenylcyclopent-3-ene-1-carboxylate (3b)



3b

Following the general procedure, 77 mg of acetylenic dicobalt hexacarbonyl complex in DMF solvent (0.2 mmol), 34 mg of methyl acrylate and, 14 mg of 2,3,4-triflourophynylboronic acid yielded 24 mg (56% yield) of **3b** as a colorless liquid after purification via flash chromatography. (3:1 Hex: EtOAc) R_f=0.33. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (t, *J* = 2.9 Hz 1H), 7.66-7.71 (m, 2H), 7.42 – 7.30 (m, 4H), 3.8 (s, 3H),3.64(t, *J* = 3 Hz 1H), 3.12 (dd, *J* = 3 Hz 1H) 2.97 (dd, *J* = 3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.3, 169.4, 158.3, 141.9, 131, 128.8, 128.6 127.2, 52.9, 52.5, 30.5.

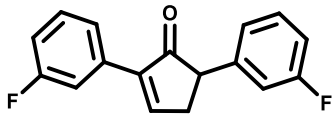
2-(3-fluorophenyl)cyclopent-2-en-1-one (5a)



5a

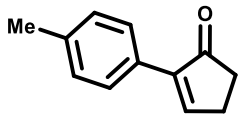
Following the general procedure, 81 mg of acetylenic dicobalt hexacarbonyl complex in DMF solvent (0.2 mmol), 34 mg of acrylic acid and, 14 mg of 2,3,4-triflourophynylboronic acid yielded 21 mg (60% yield) of **5a** as a white solid after purification via flash chromatography. (2:1 Hex: DCM) R_f=0.37. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (t, *J* = 2.9 Hz, 1H), 7.48-7.42 (m, 2H), 7.32-7.34 (m, 1H), 6.98-7 (m, 1H),2.68-2.74 (m, 2H), 2.61-2.58 (m, 2H) 2.97. ^{13}C NMR (101 MHz, $CDCl_3$) δ 207, 159.6, 129.9, 129.8, 122.64, 122.61, 115.3, 115, 114, 113.8, 35.7, 26.19.

2,5-bis(3-fluorophenyl)cyclopent-2-en-1-one (6a)



6a

2-(p-tolyl)cyclopent-2-en-1-one (5b)

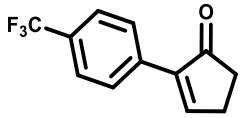


5b

Following the general procedure, 80 mg of acetylenic dicobalt hexacarbonyl complex in DMF solvent (0.2 mmol), 34 mg of acrylic acid and, 14 mg of 2,3,4-triflourophynylboronic acid yielded 17 mg (52% yield) of **5b** as a white solid after purification via flash chromatography. (2:1 Hex: DCM) R_f=0.37. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (t, *J* = 2.9 Hz, 1H), 7.59 (d, *J* = 7.9, 2H), 7.19 (d, *J* = 7.9

2H), 2.73-2.66 (m, 2H), 2.63-2.55 (m, 2H), 2.36 (s,3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.7, 143.3, 138.2, 129, 128.7, 126.8, 35.7, 26.1, 21.2.

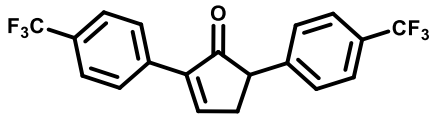
2-(4-(trifluoromethyl)phenyl)cyclopent-2-en-1-one (5c)



5c

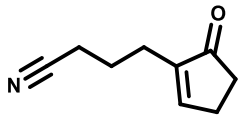
Following the general procedure, 80 mg of acetylenic dicobalt hexacarbonyl complex in DMF solvent (0.2 mmol), 34 mg of acrylic acid and, 14 mg of 2,3,4-triflourophynylboronic acid yielded 22 mg (51% yield) of **5c** as a white solid after purification via flash chromatography. (4:1 Hex: EtOAc) R_f=0.28. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (t, *J* = 3.4 Hz, 1H), 7.81 (d, *J* = 8.4, 2H), 7.64 (d, *J* = 8.4 2H), 2.79-2.74 (m, 2H), 2.65-2.61 (m, 2H. ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.9, 160.4, 127.3, 125.4, 125.38, 125.34, 125.31, 125.2, 35.6, 26.3.

2,5-bis(4-(trifluoromethyl)phenyl)cyclopent-2-en-1-one (6c)



6c

4-(5-oxocyclopent-1-en-1-yl)butanenitrile (5f)



5f

Following the general procedure, 75 mg of hex-5-ynenitrile dicobalt hexacarbonyl complex in DMF solvent (0.2 mmol), 34 mg of acrylic acid and, 14 mg of 2,3,4-triflourophynylboronic acid yielded 8 mg (30% yield) of **3o** as a colorless liquid after purification via flash chromatography. (1:2 Hex: EtOAc) R_f=0.22. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.38 (m, 1H), 2.43-2.30 (m, 6H), 1.81-1.91 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.5, 159.1, 144.2, 119.4, 34.5, 26.7, 24.2, 23.70, 16.97.

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Chapter 5 Conclusion and future work

In summary, the synthesis of unsymmetrical ethers catalyzed by scandium triflate and DMAP between benzylic alcohols and primary alcohols has been discussed in chapter two. The formation of carbocation intermediate showed the reaction is done through an SN1-like pathway. The stability of the carbocation intermediate of benzylic alcohol bearing EWGs is low, so these compounds are not participants in the reaction.

In chapter three, the development of the PKR reaction using nitrous oxide as the promoter has been reported. In a one-pot reaction, various alkynes with norbornene, norbornadiene, and bridged bicyclic alkenes delivered moderate to high yield products. In-suite IR study showed that coordination of nitrous oxide into cobalt led to the formation of carbon dioxide in the reaction media.

Despite the advances, the PKR reaction is still limited to certain alkene components. Unsaturated alkene having EWGs do not participate in the reaction. In chapter four aryl boronic acid as a LUMO lower has been used in the PKR reaction. Different presynthesized alkyne complexes were participants in the PKR with acrylic acid. Either regular PKR product or reductive PKR product were detected. Arylboronic acid is the hydride source for the reductive process and proton exchange occurs during the reaction. Optimization of the reaction as well as performing the reaction at different pH may change the productivity of the reaction. Also, the mechanism of the reaction requires to be more explored.

Appendix

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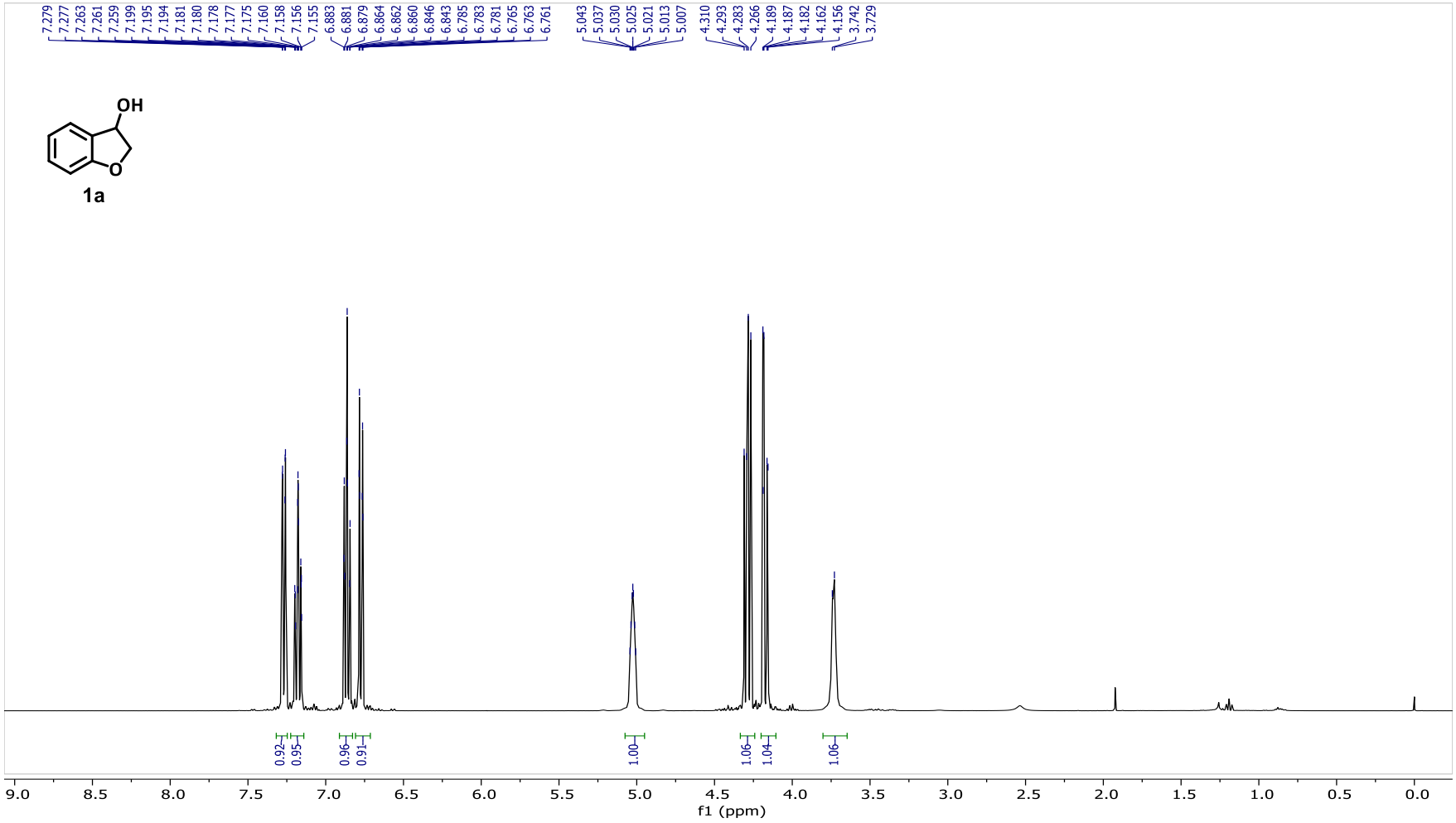
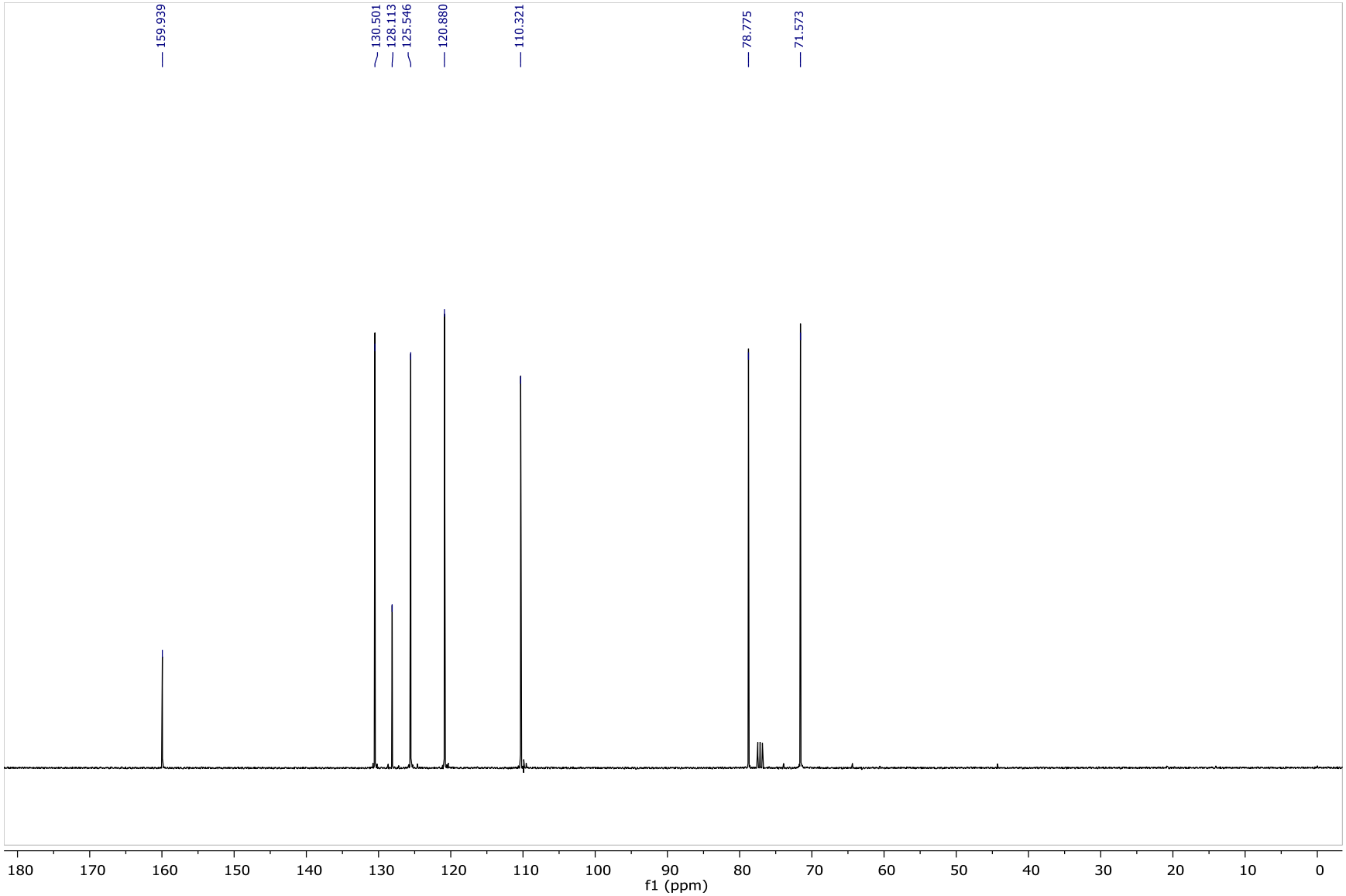
Contents

Chapter 1

(1a) 2,3-dihydro-1-benzofuran-3-o

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170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
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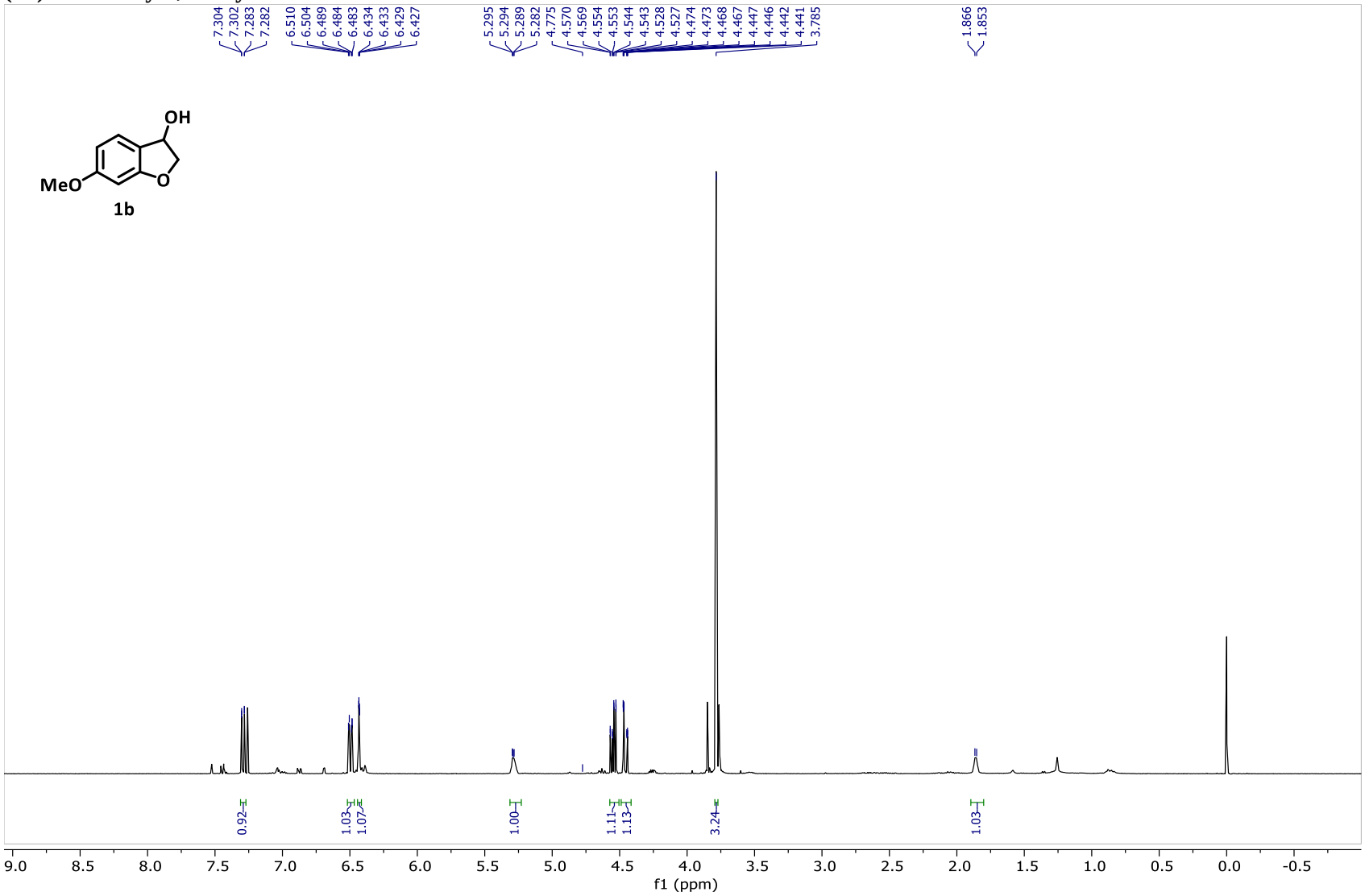

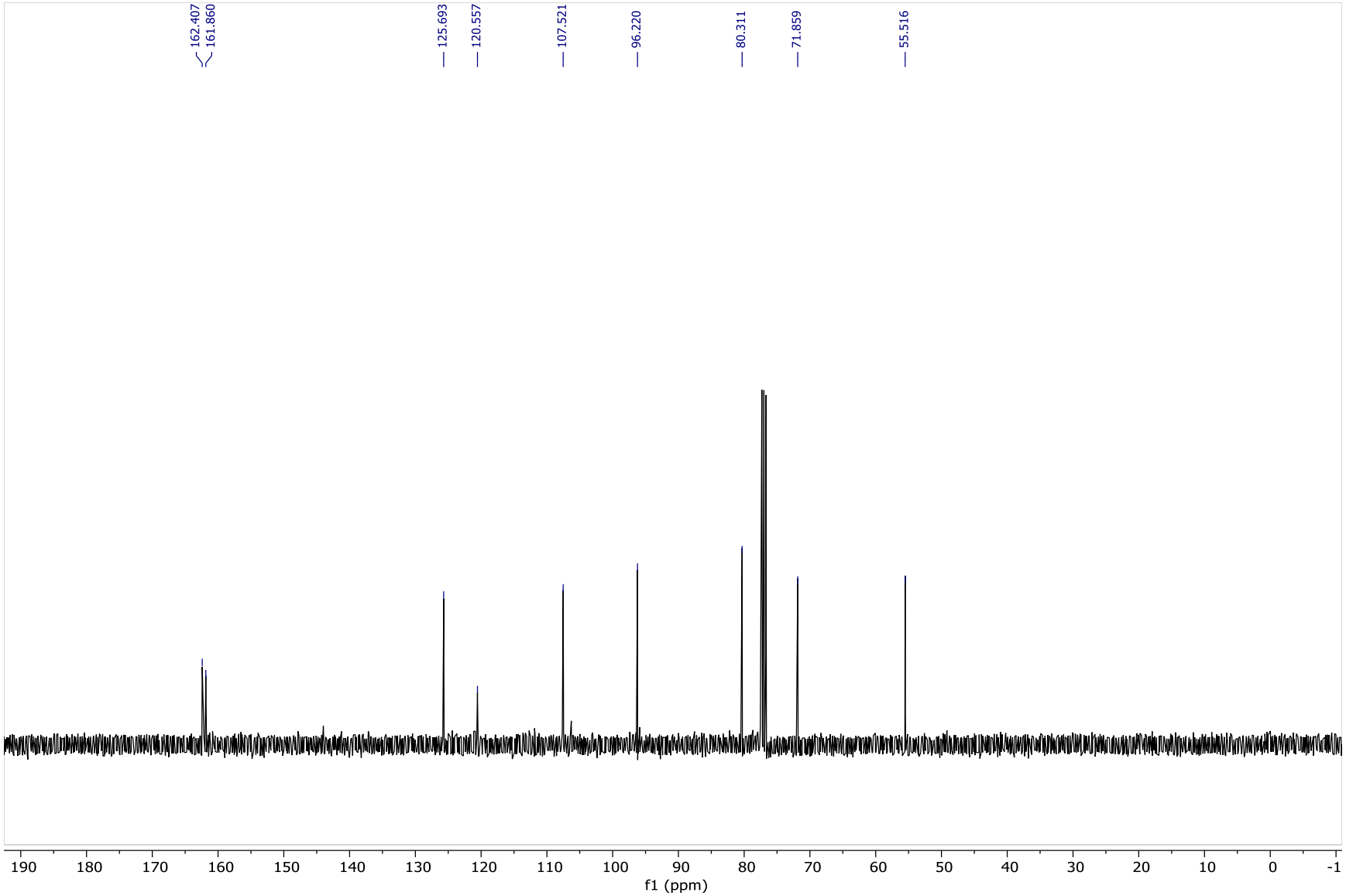
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96.220
80.311
71.859
55.516
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
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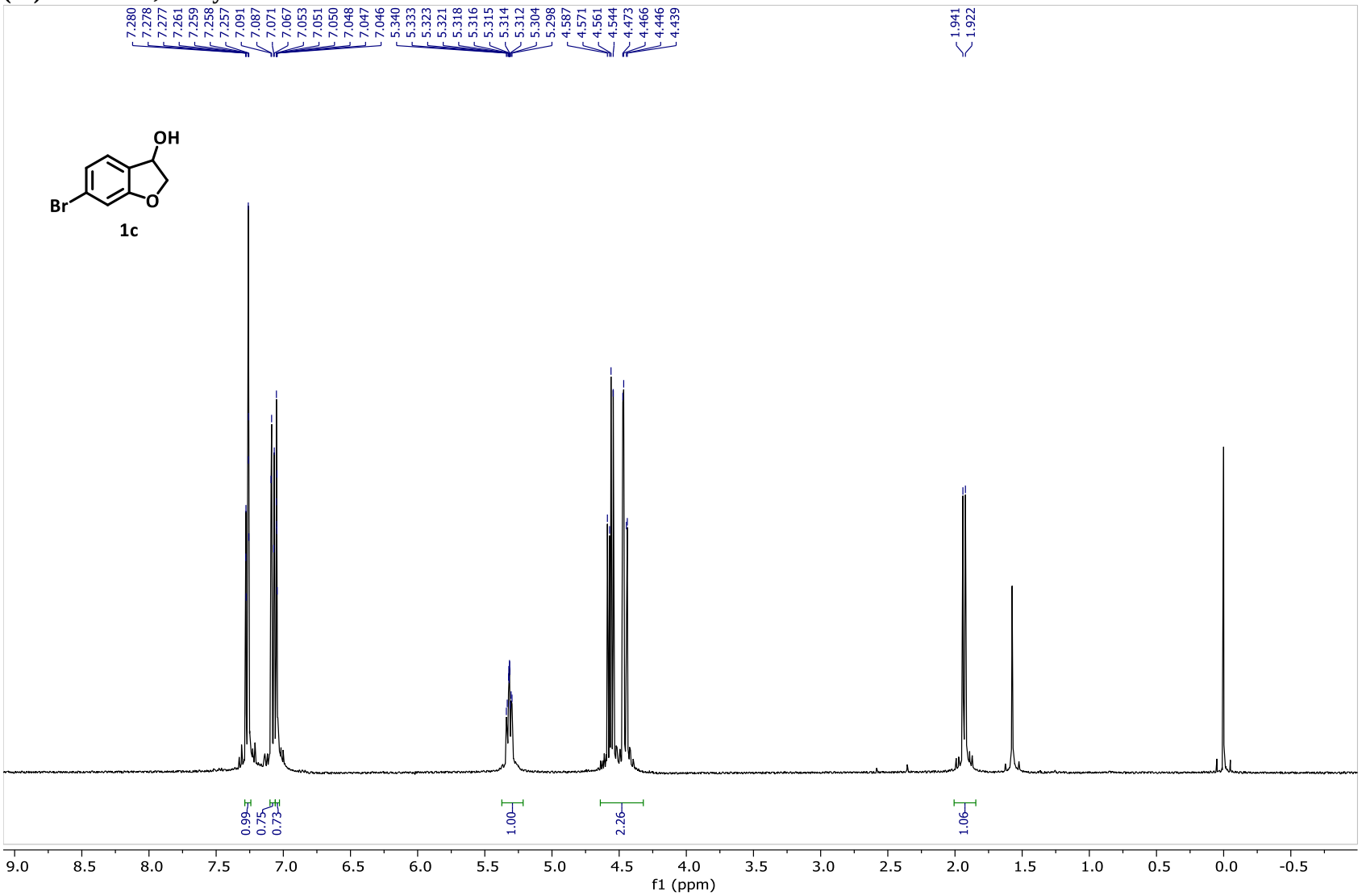
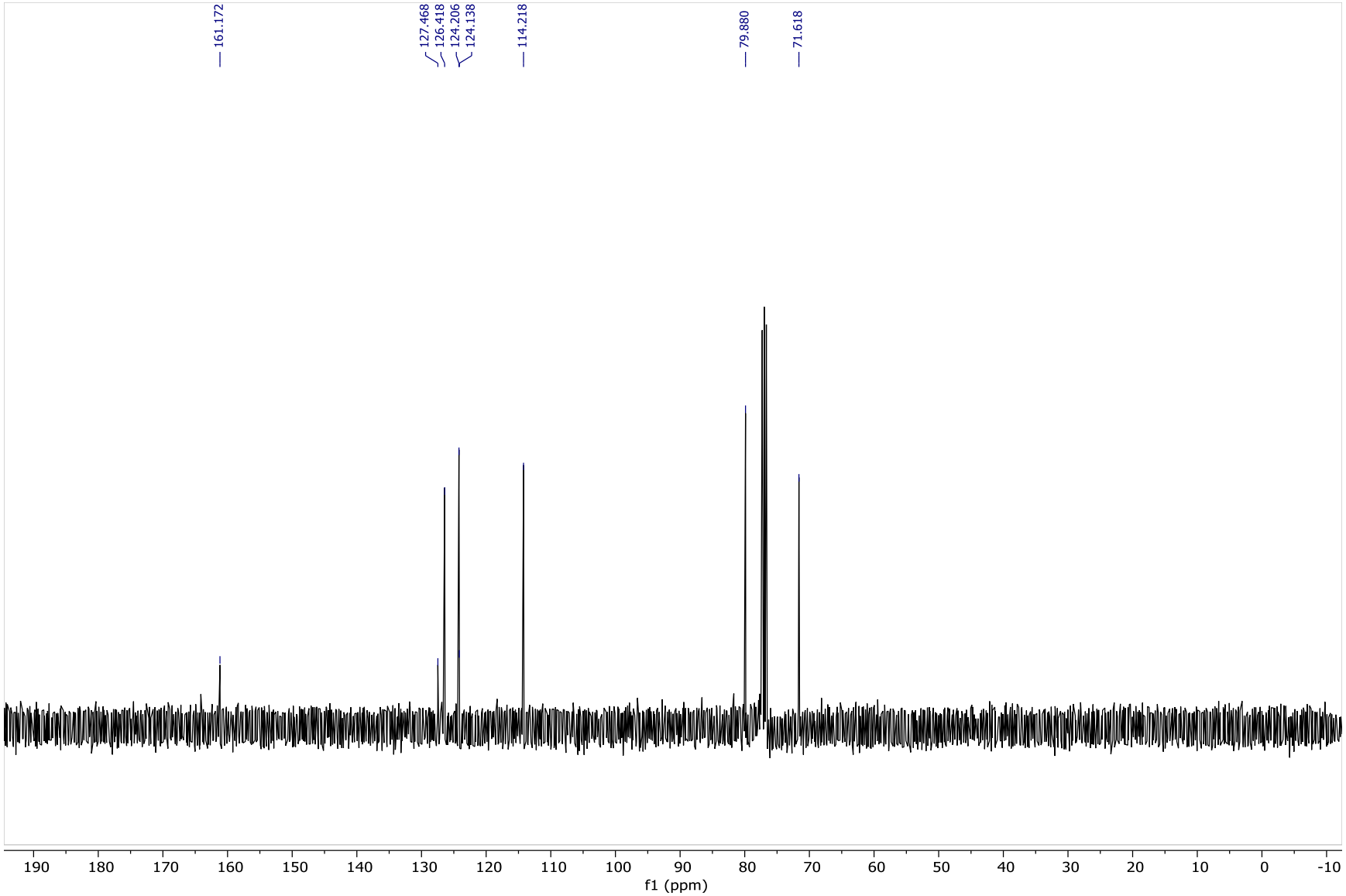
-1
f1 (ppm)

(1c) 6-bromo-2,3-dihydro-1-benzofuran-3-ol




161.172
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126.418
124.206
124.138
114.218
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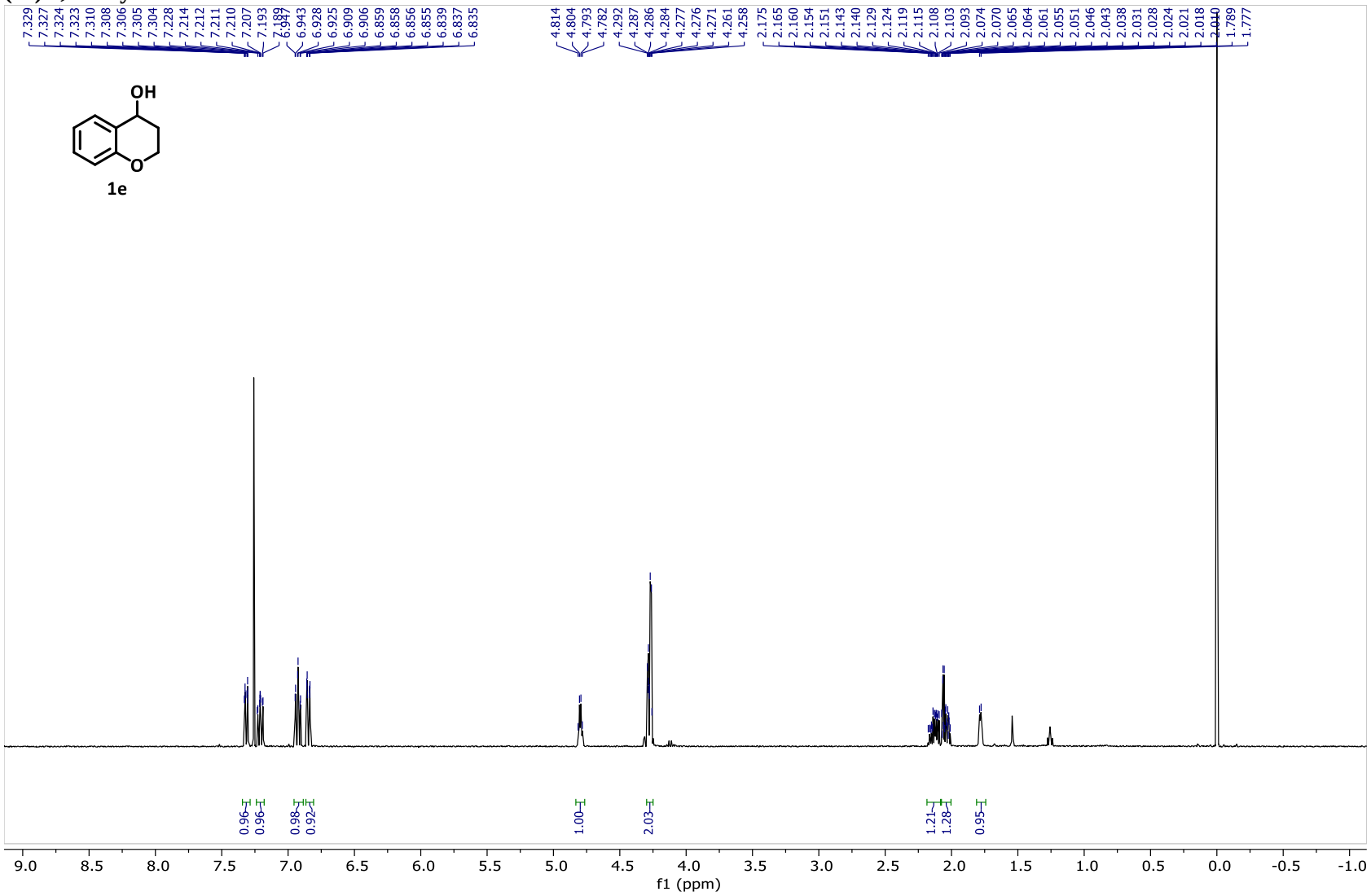
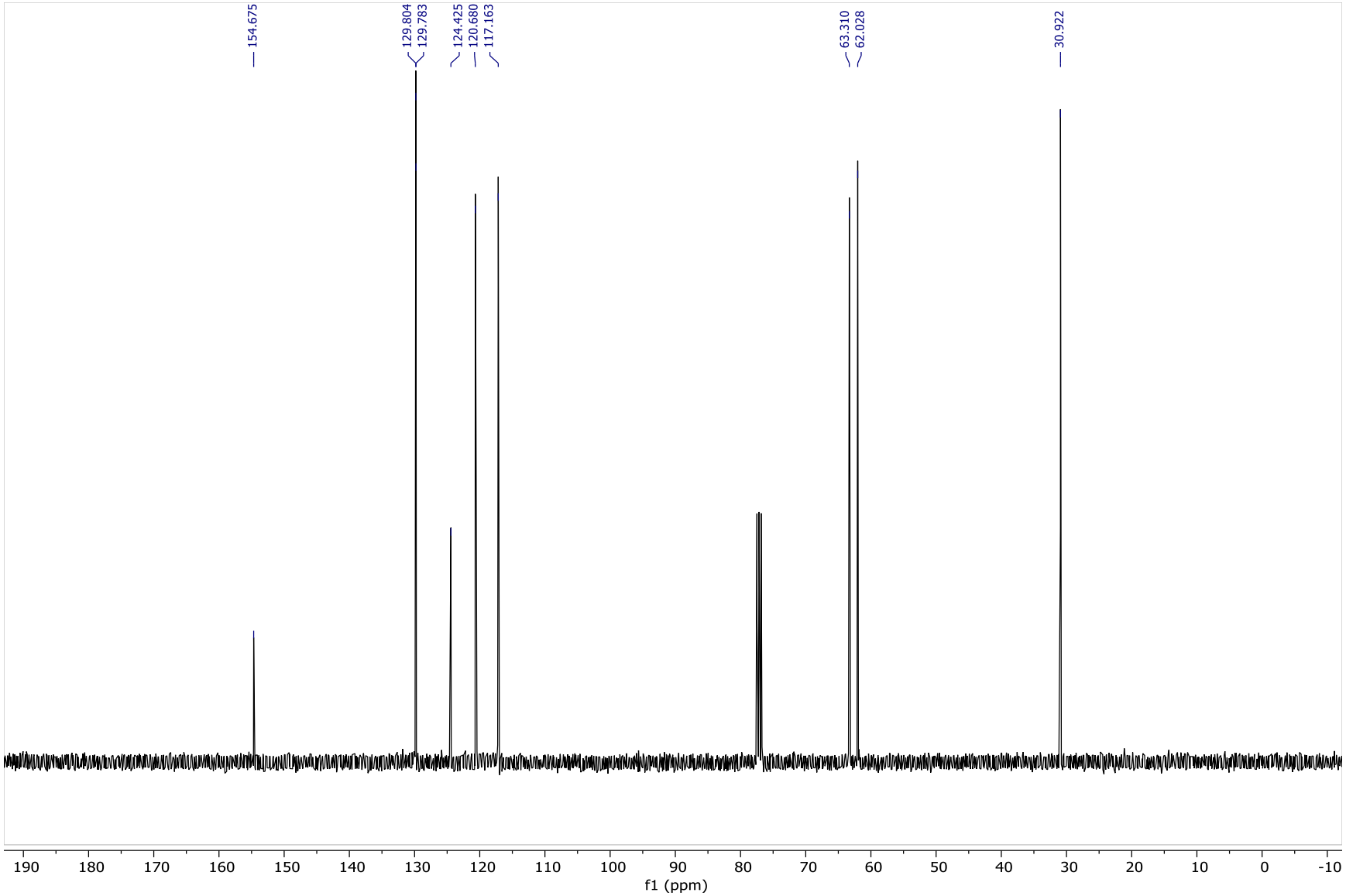
71.618
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

(1e) 3,4-dihydro-2*H*-chromen-4-ol

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180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

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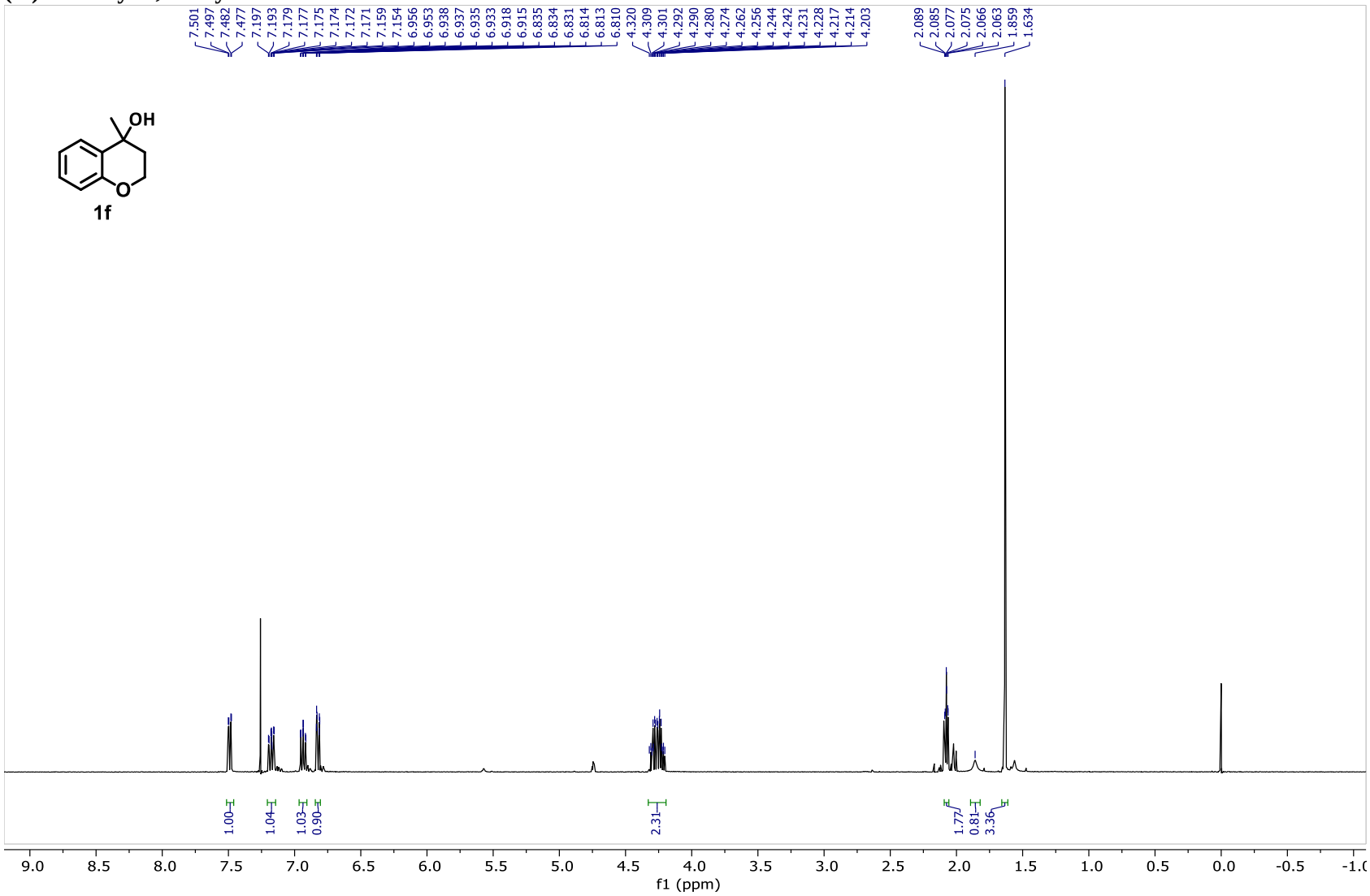

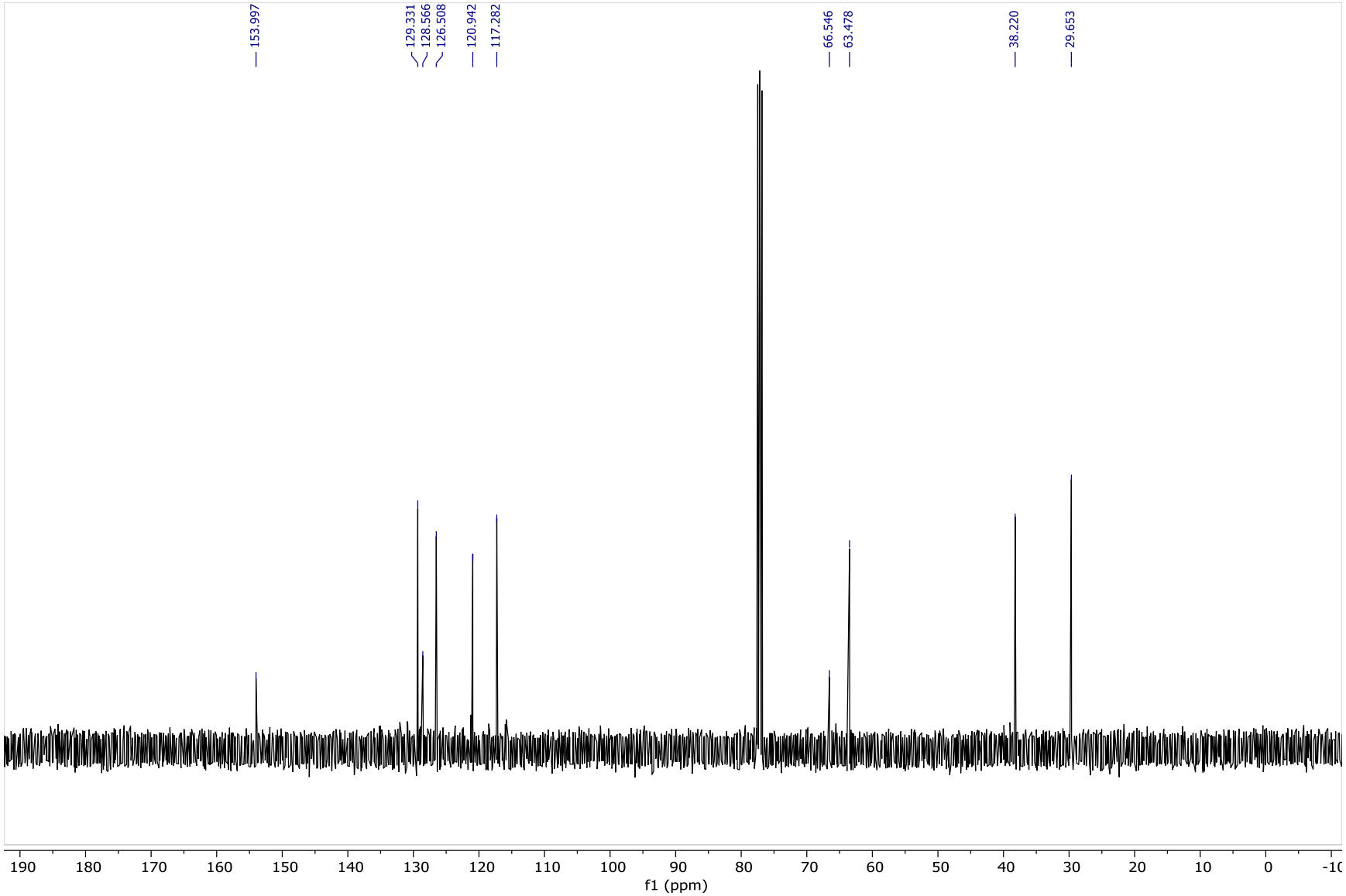
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63.478
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29.653
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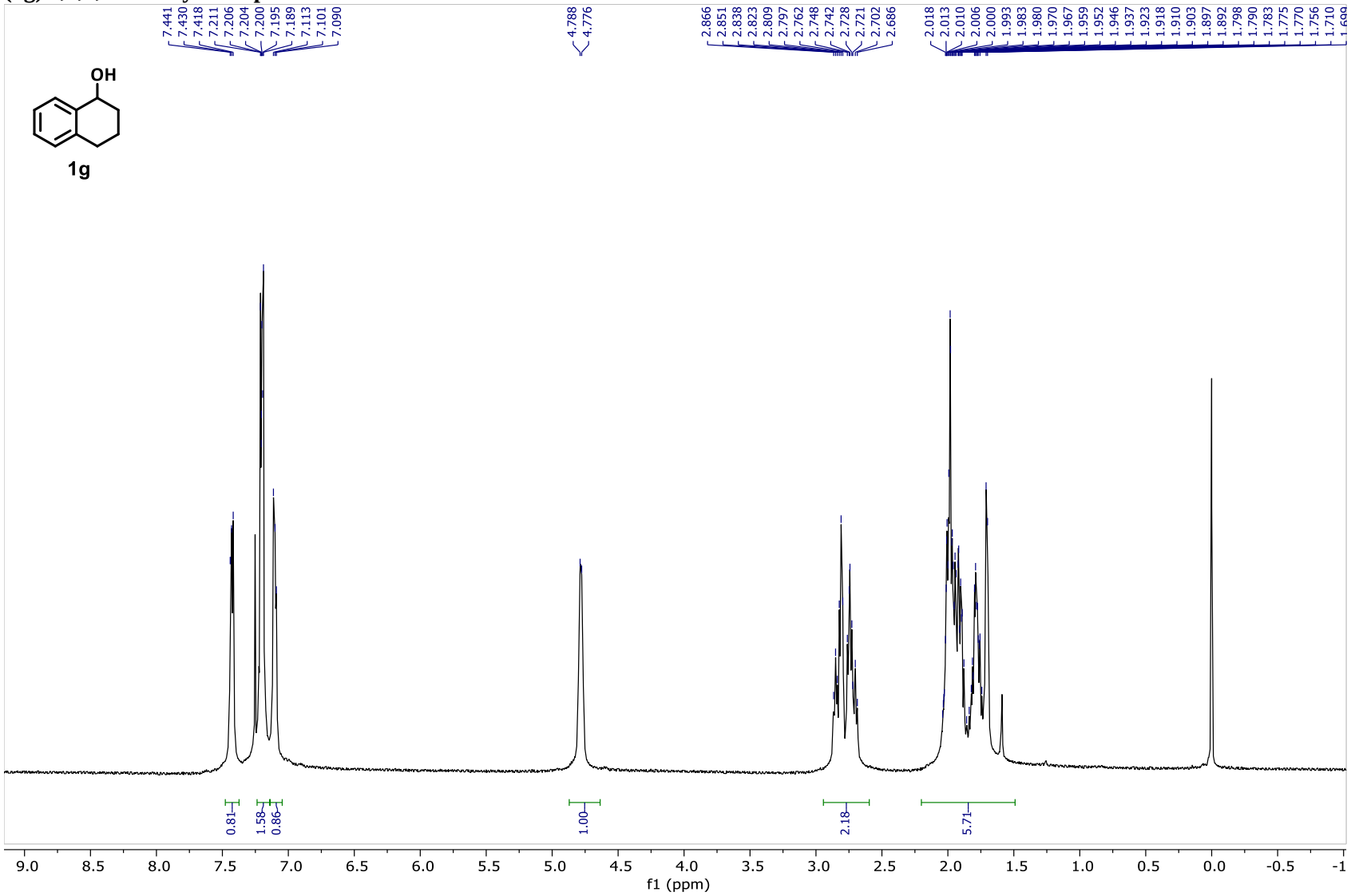
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

(1g) 1,2,3,4-tetrahydronaphthalen-1-ol



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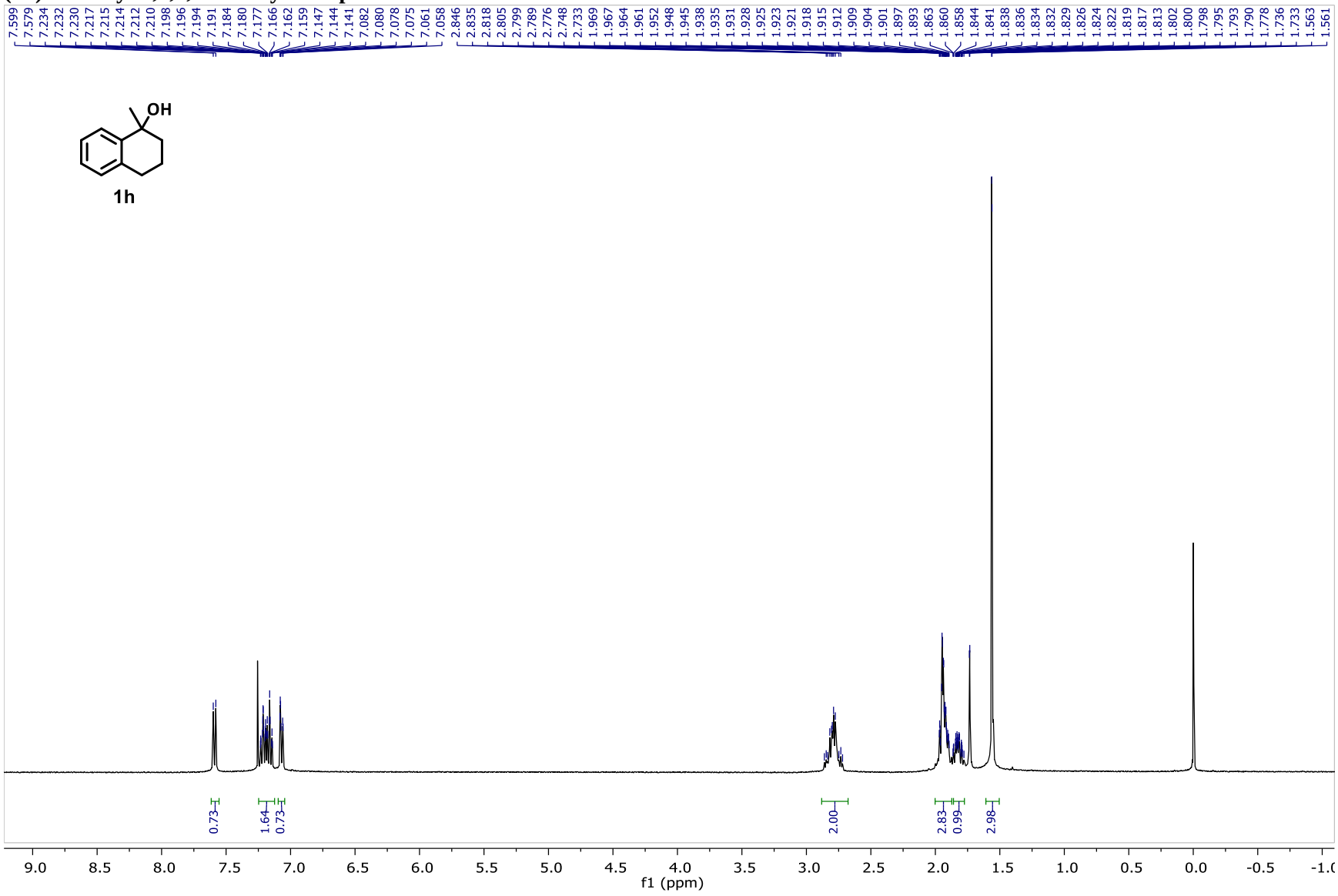

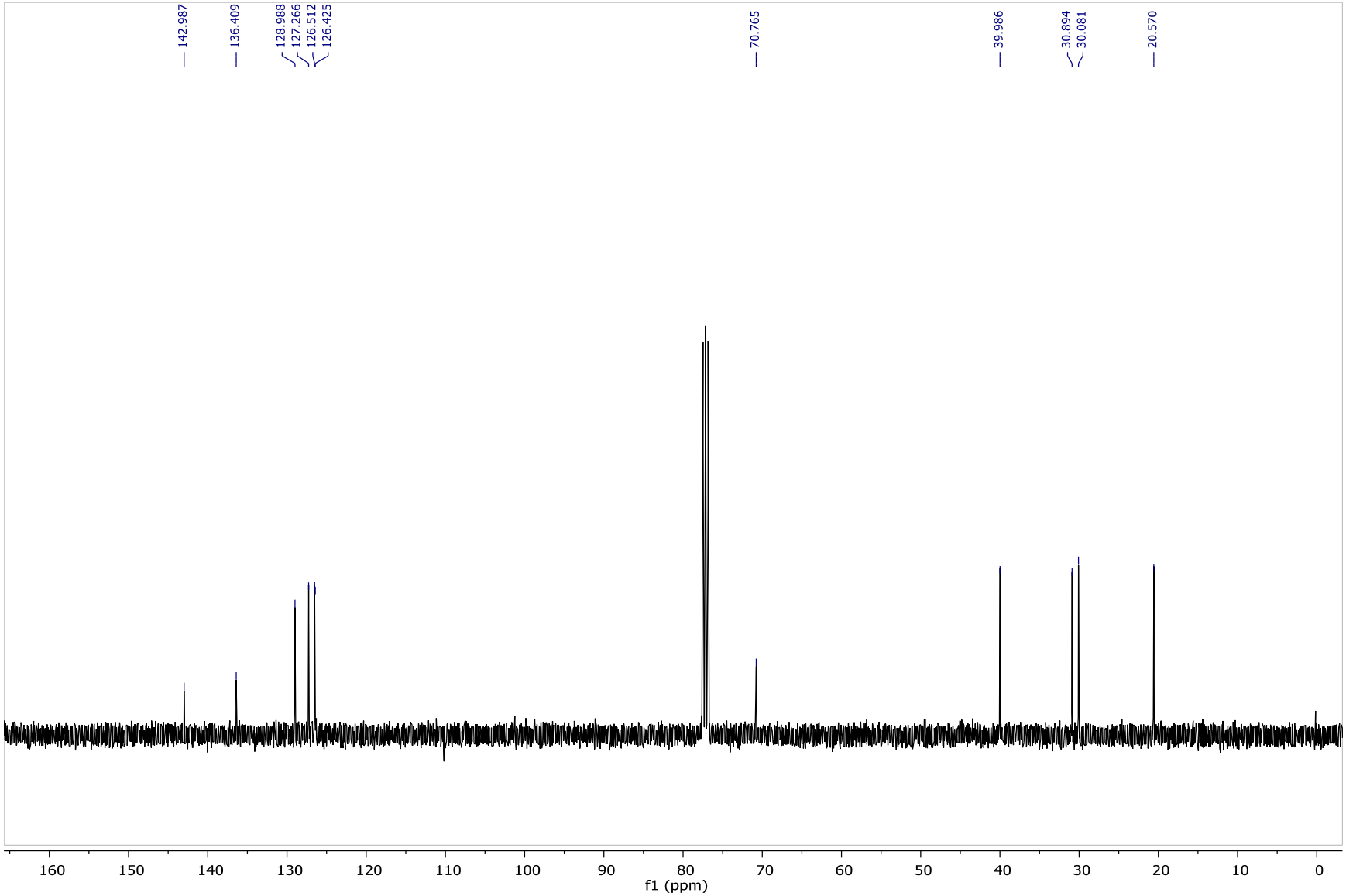
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39.986
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160
150
140
130
120
110
100
90
80
70
60
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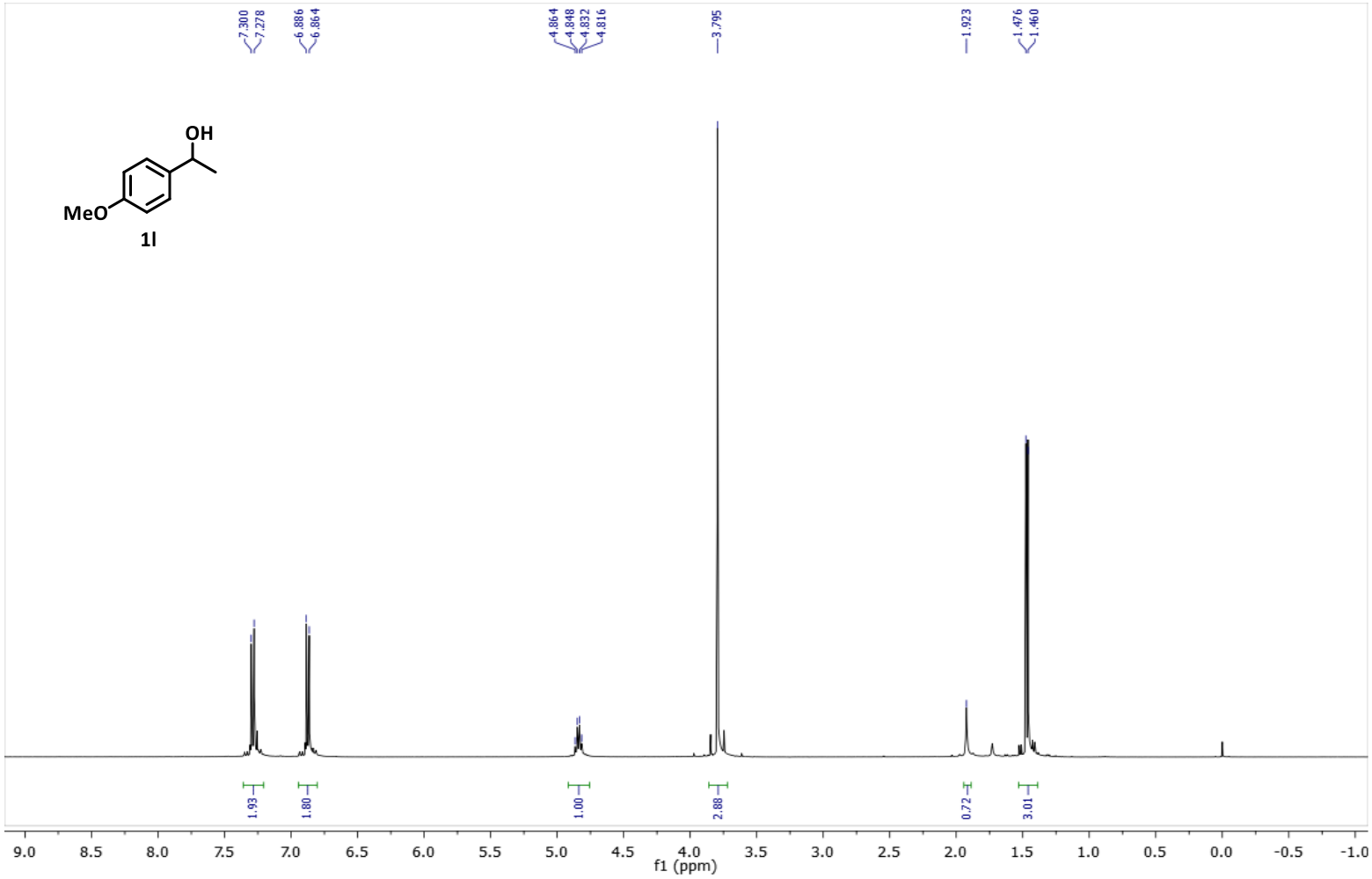
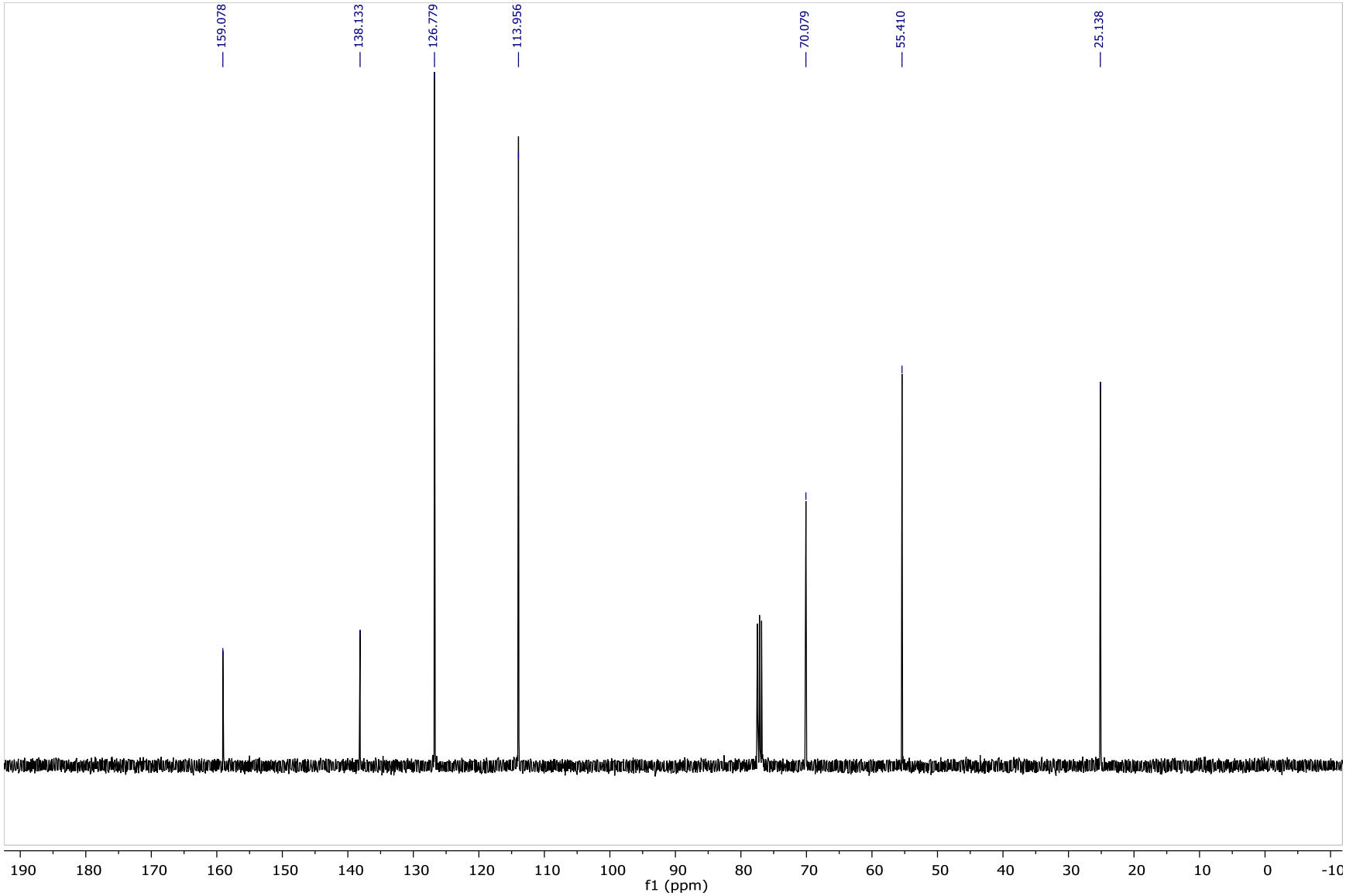
40
30
20
10
0
f1 (ppm)

(1l) 1-(4-methoxyphenyl)ethanol

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190
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130
120
110
100
90
80
70
60
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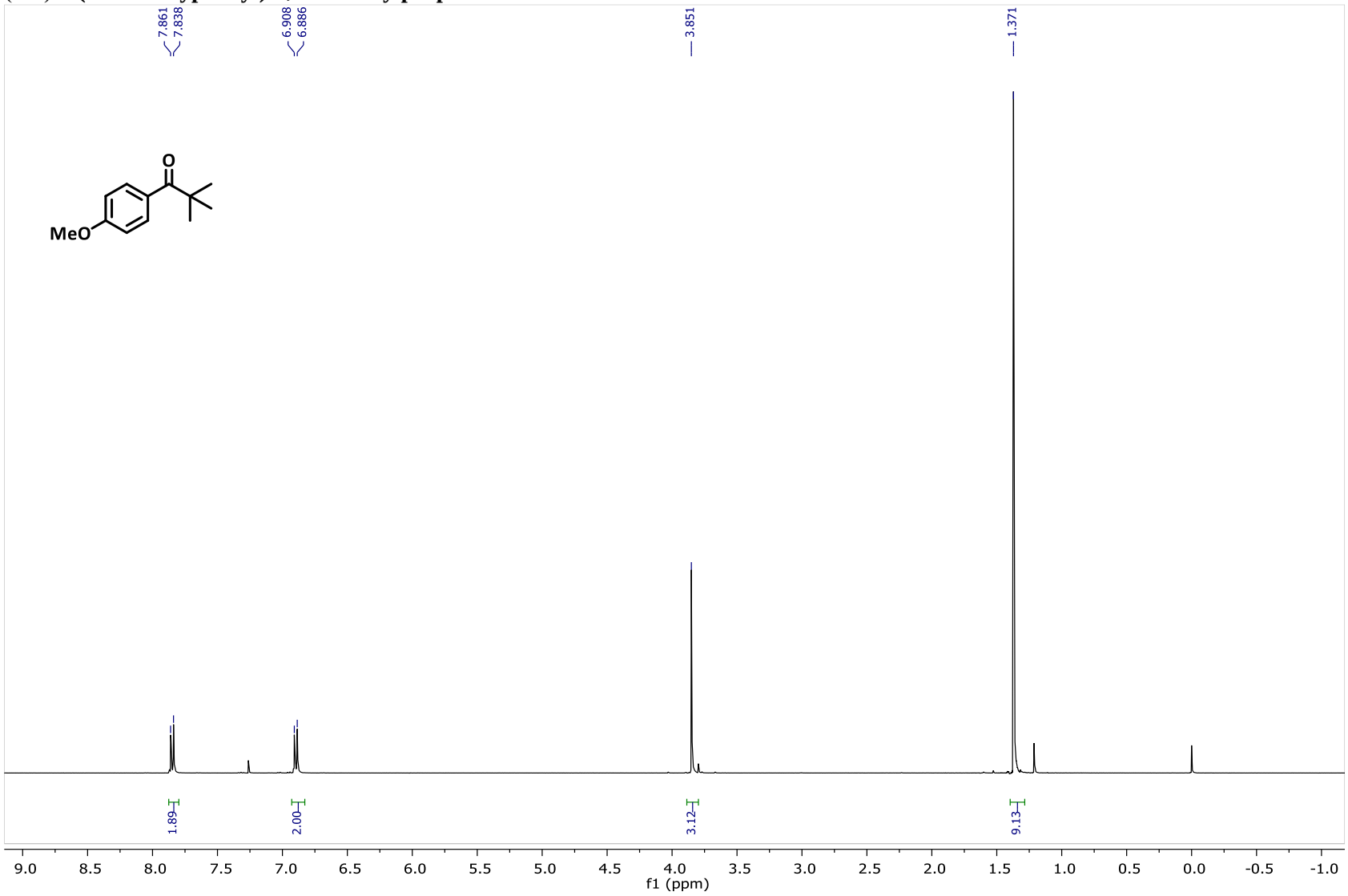
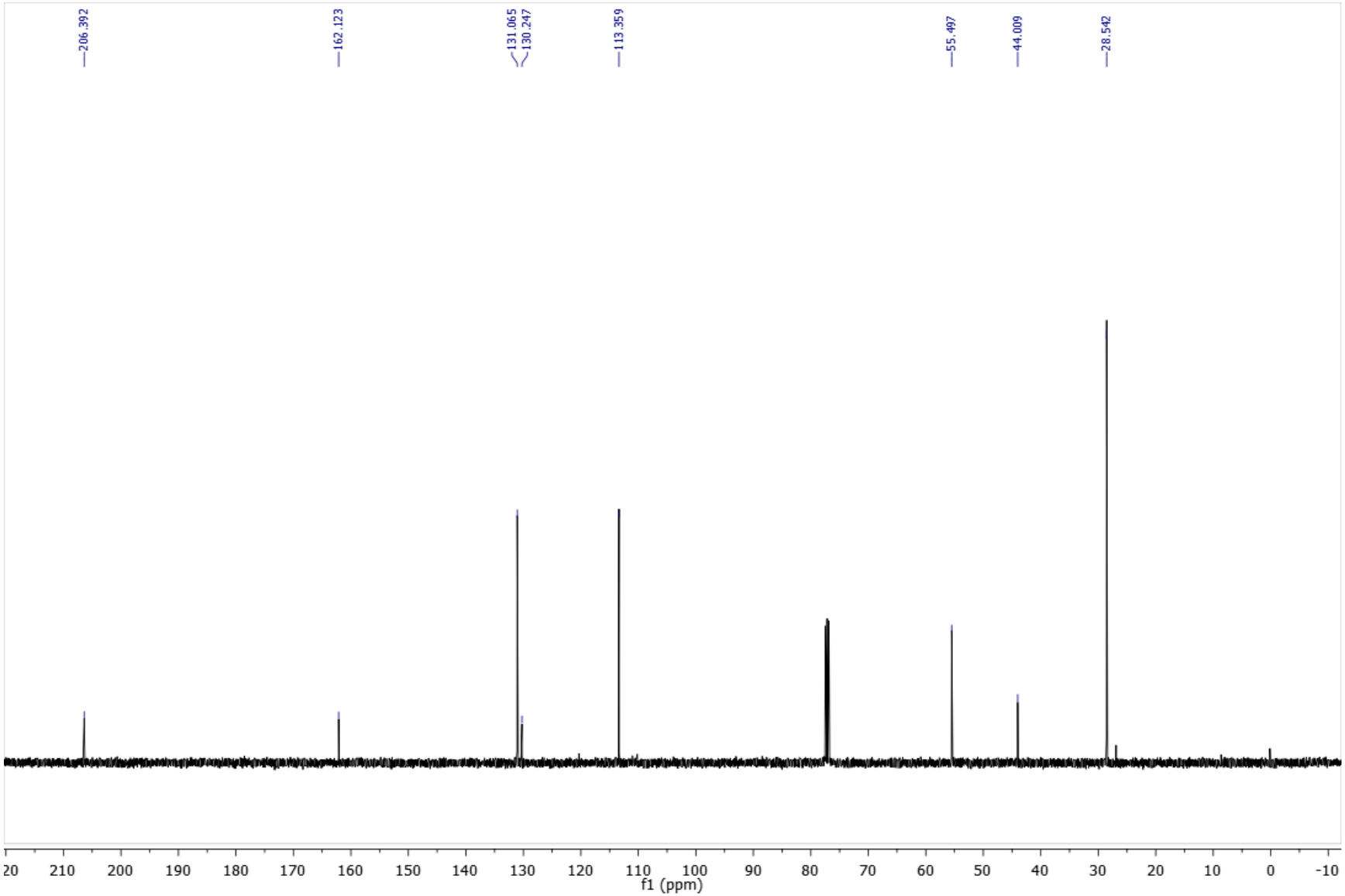
-10
f1 (ppm)

(1n') 1-(4-methoxyphenyl)-2,2-dimethylpropan-1-one

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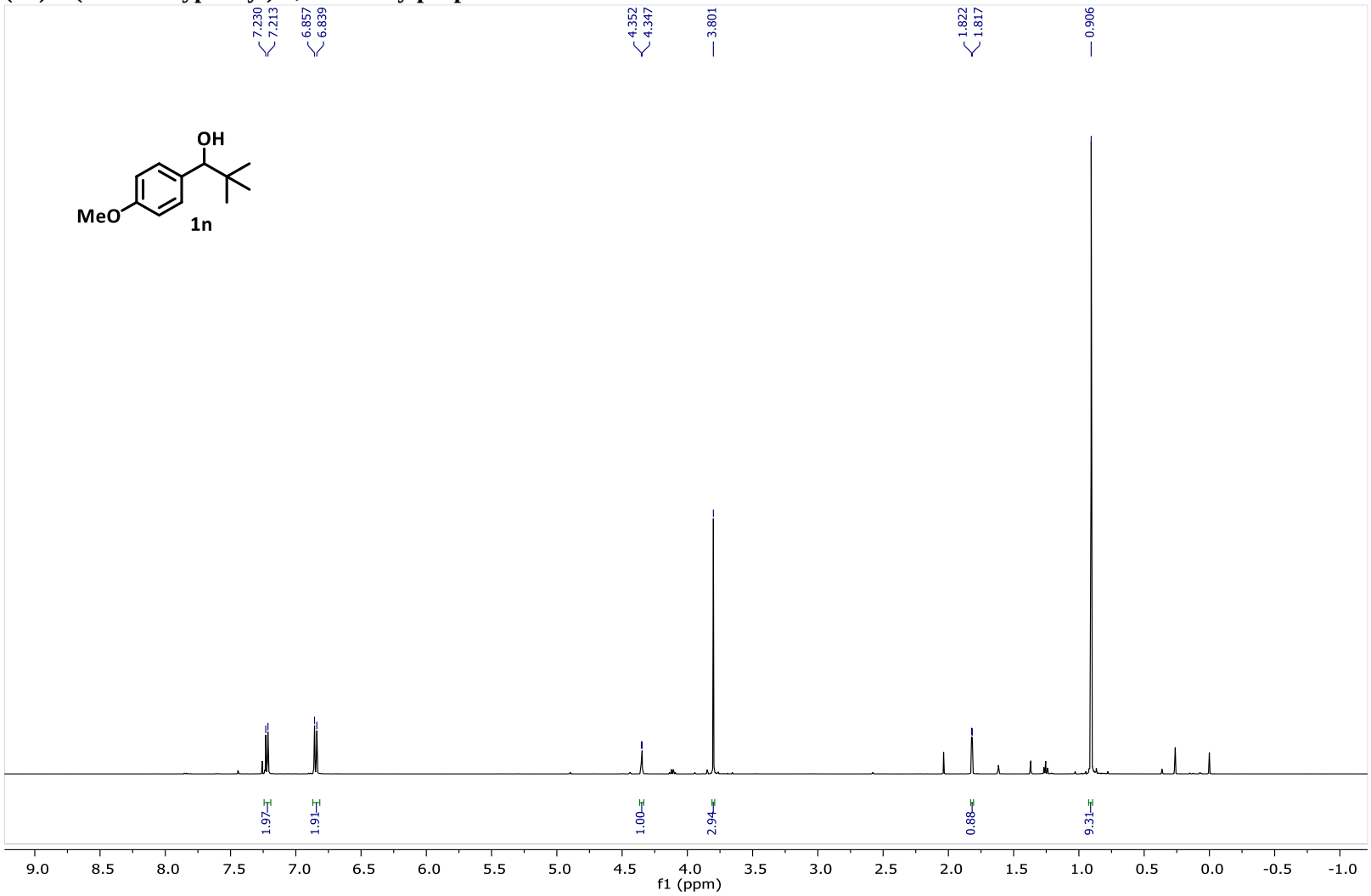
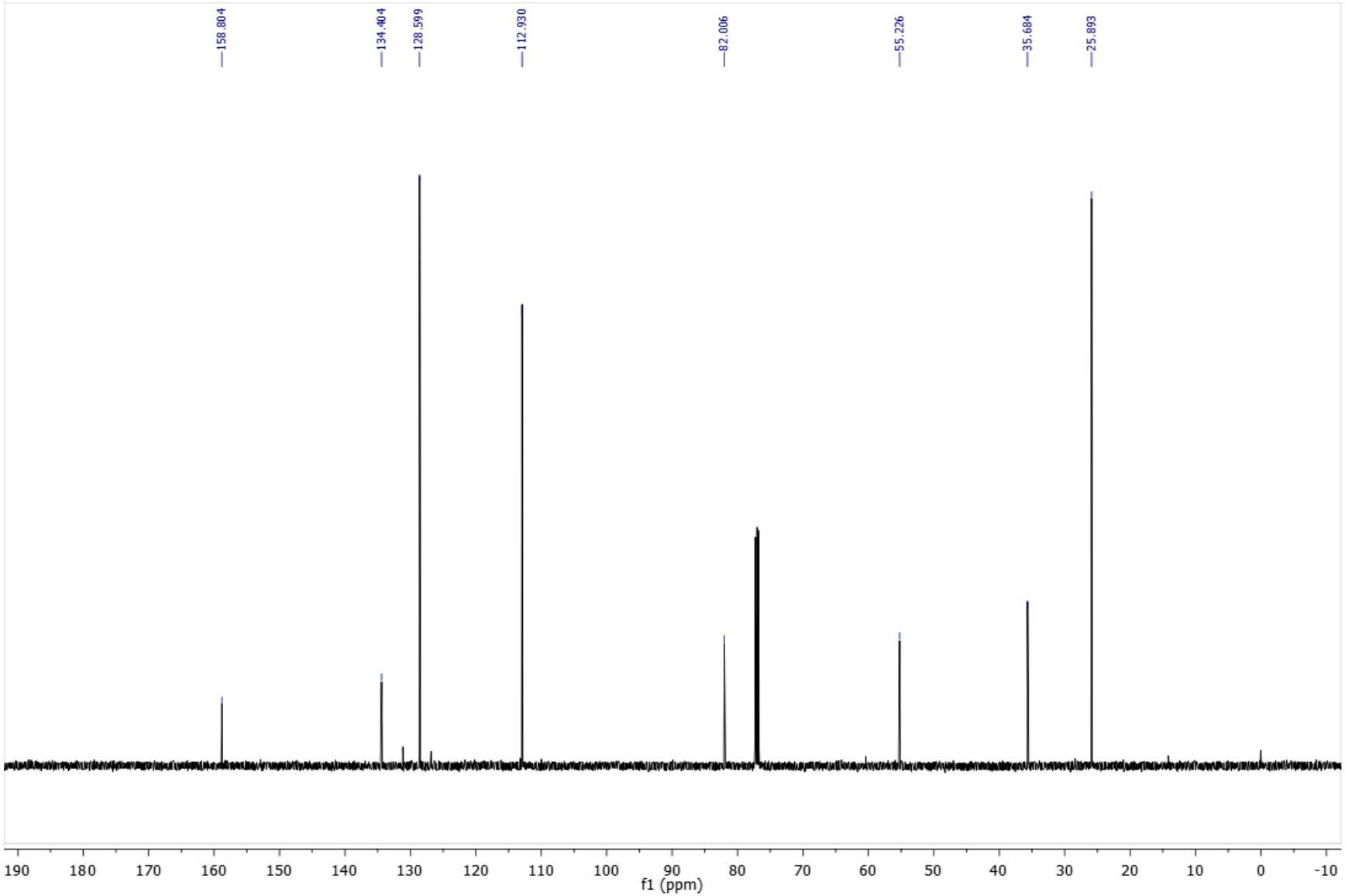
55.497
44.009
28.542
f1 (ppm)

(1n) 1-(4-methoxyphenyl)-2,2-dimethylpropan-1-ol

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150
140
130
120
110
100
90
80
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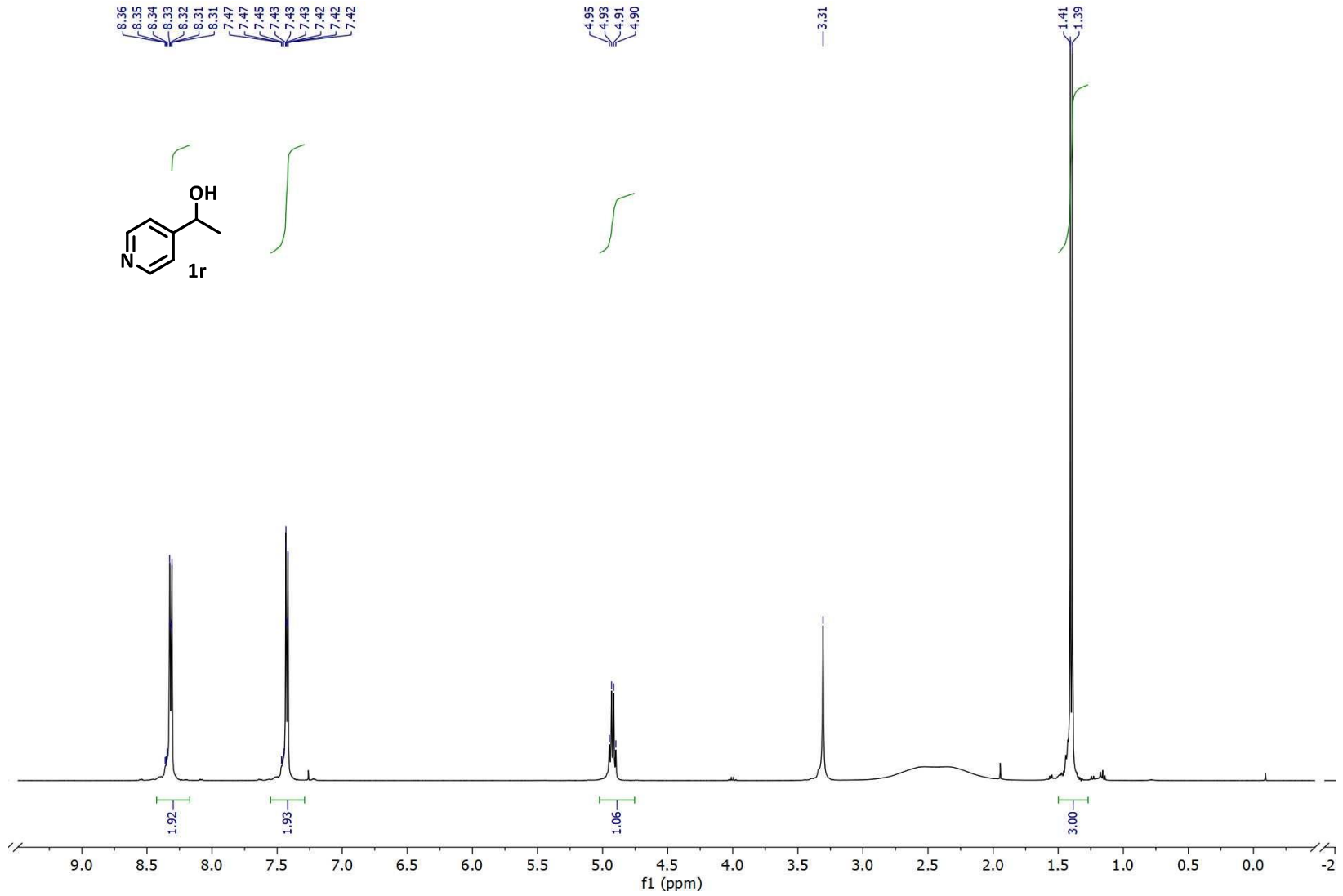
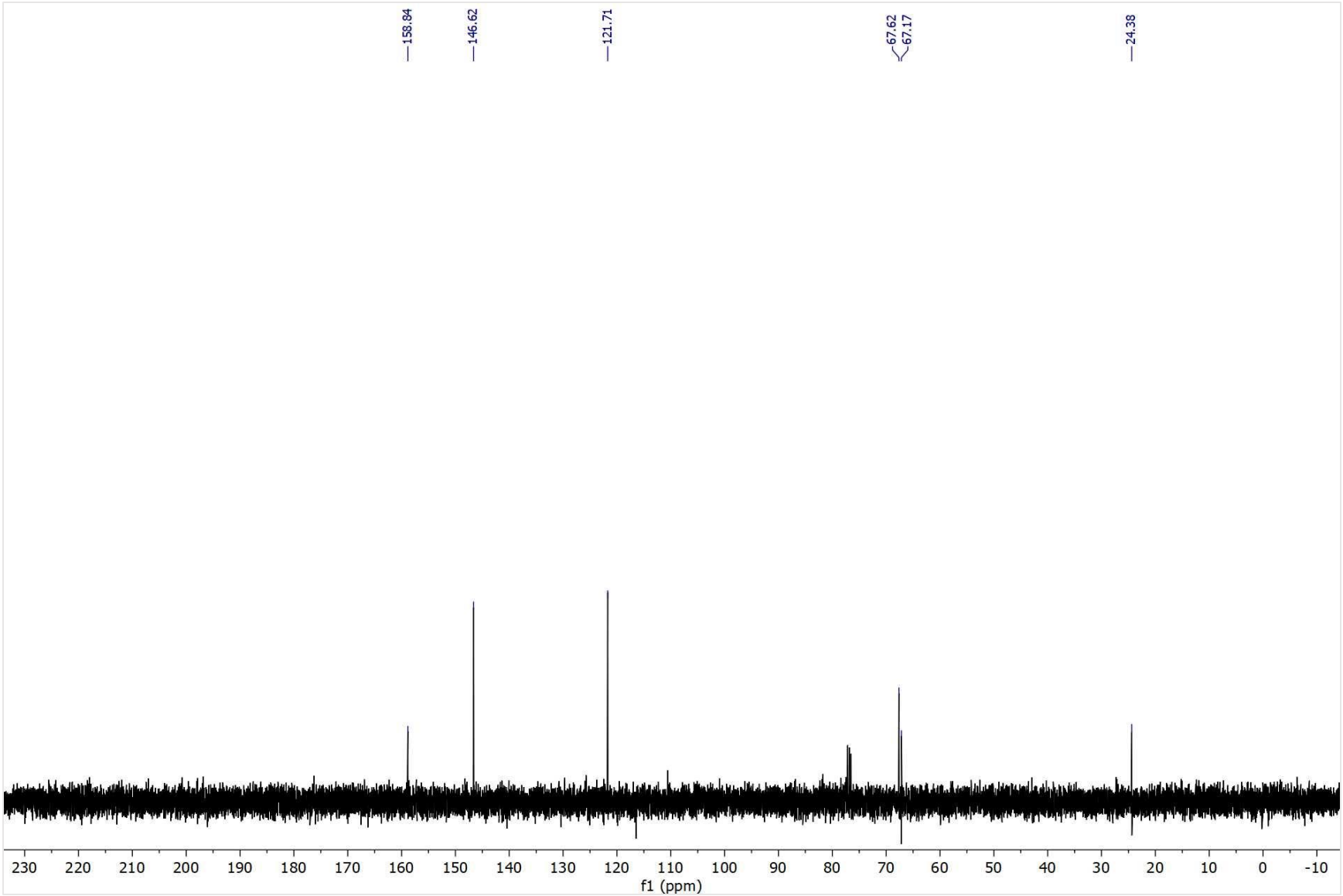
-10
f1 (ppm)

(1r) 1-(4-Pyridinyl)ethanol

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121.71
67.62
67.17
24.38
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

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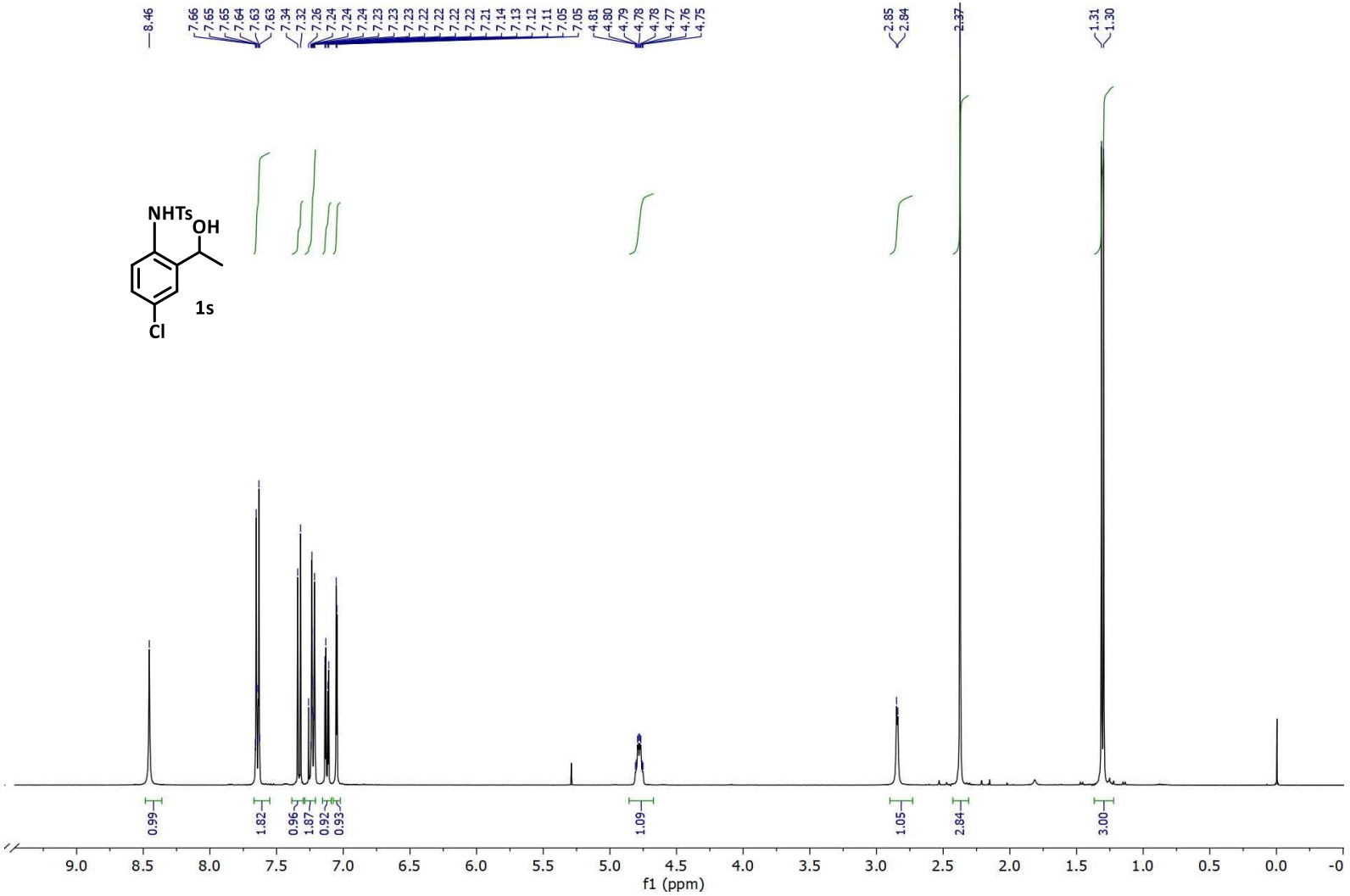
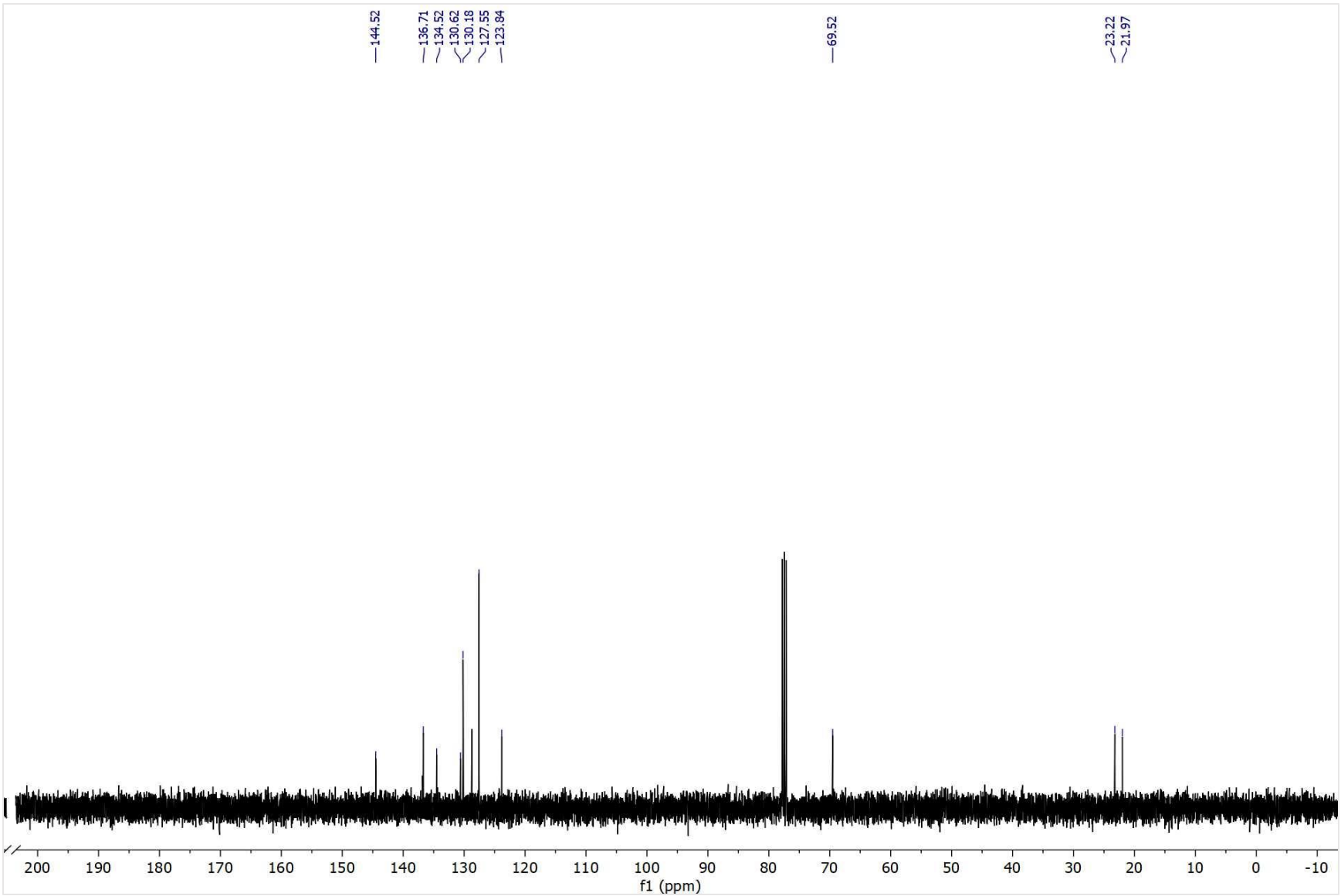
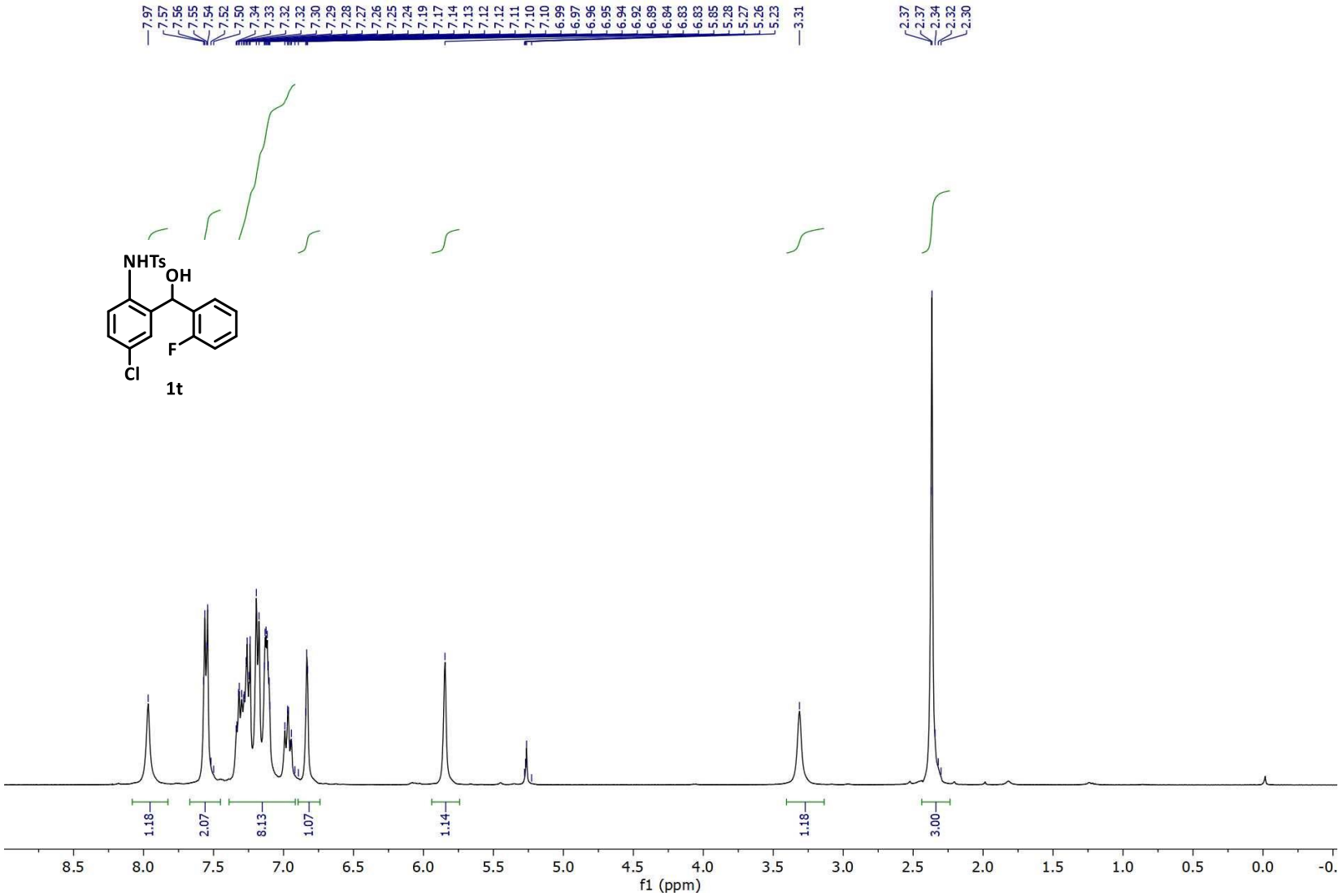
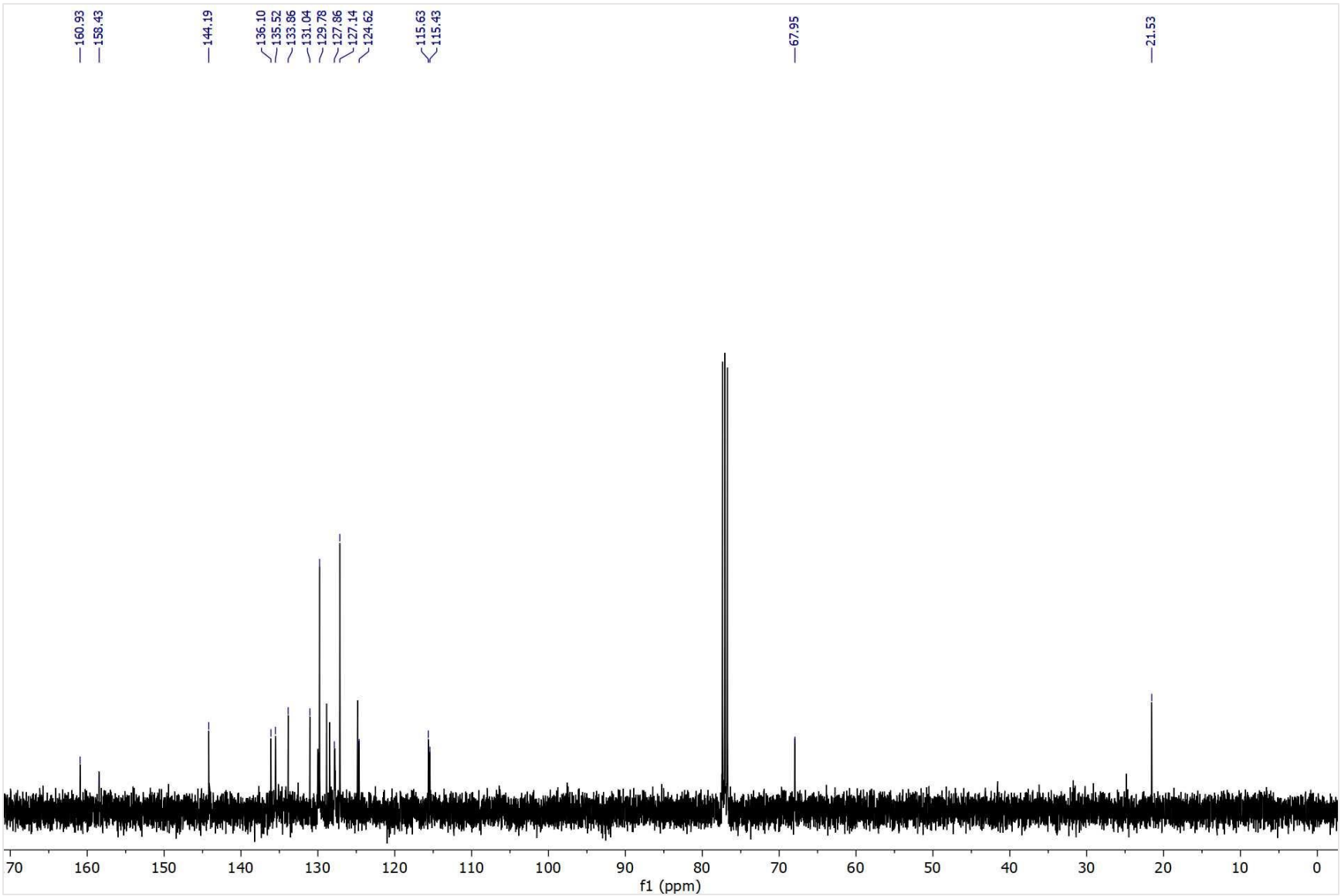


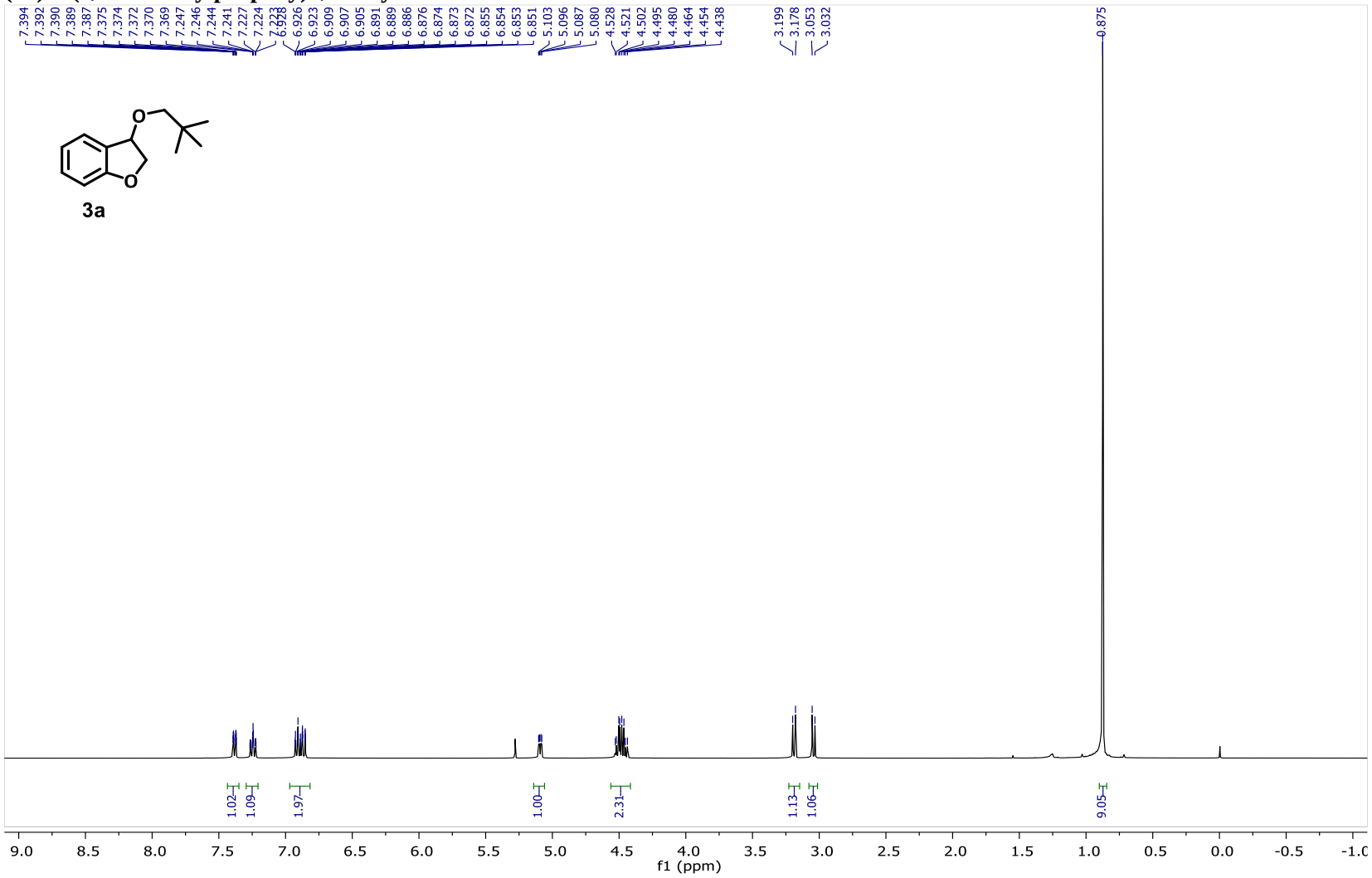

144.52
136.71
134.52
130.62
130.18
127.55
123.84
69.52
23.22
21.97
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

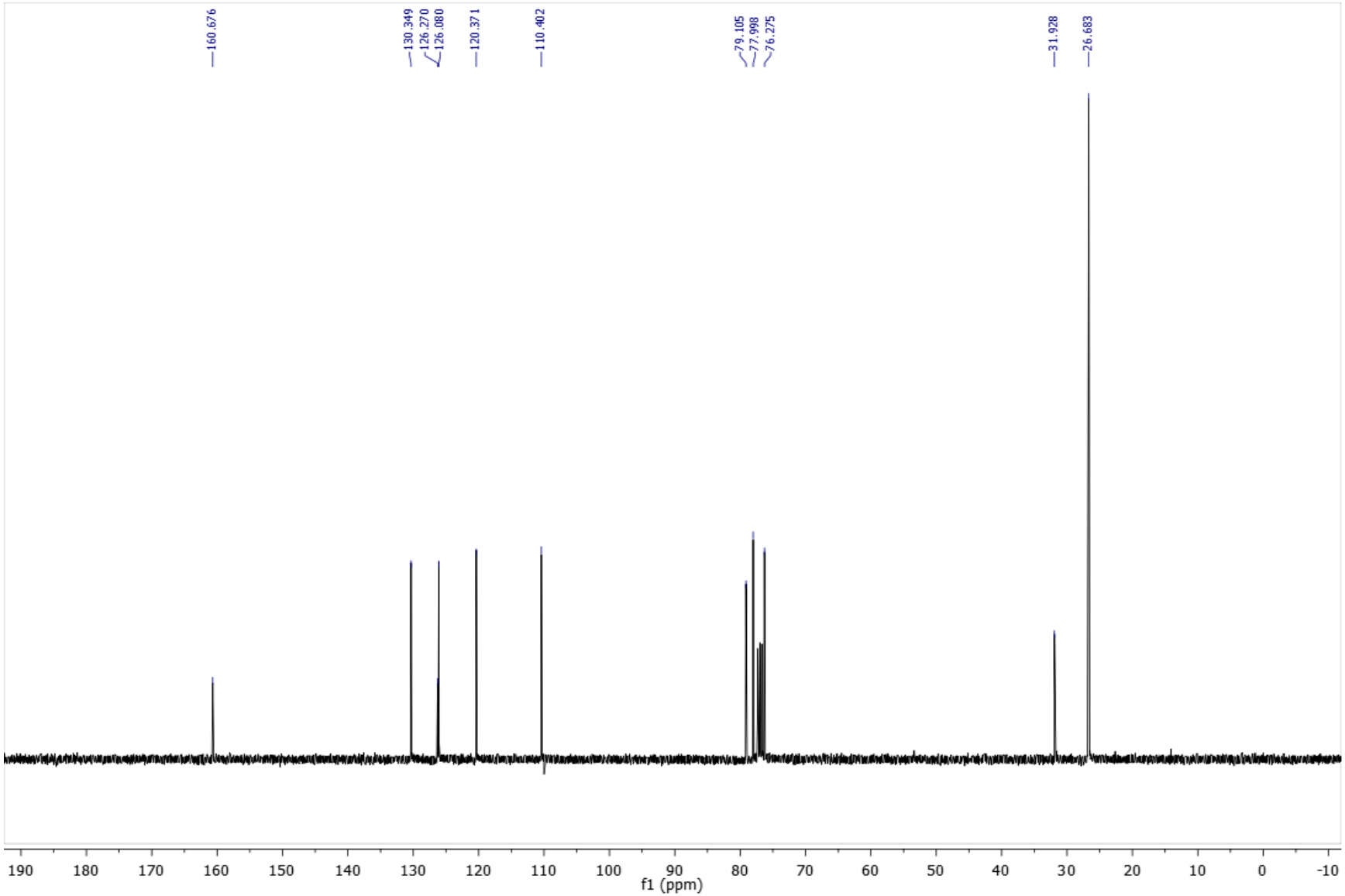
(1t) N-{4-chloro-2-[(2-fluorophenyl) (hydroxy)methyl]phenyl}-4-methylbenzene-1-sulfonamide.



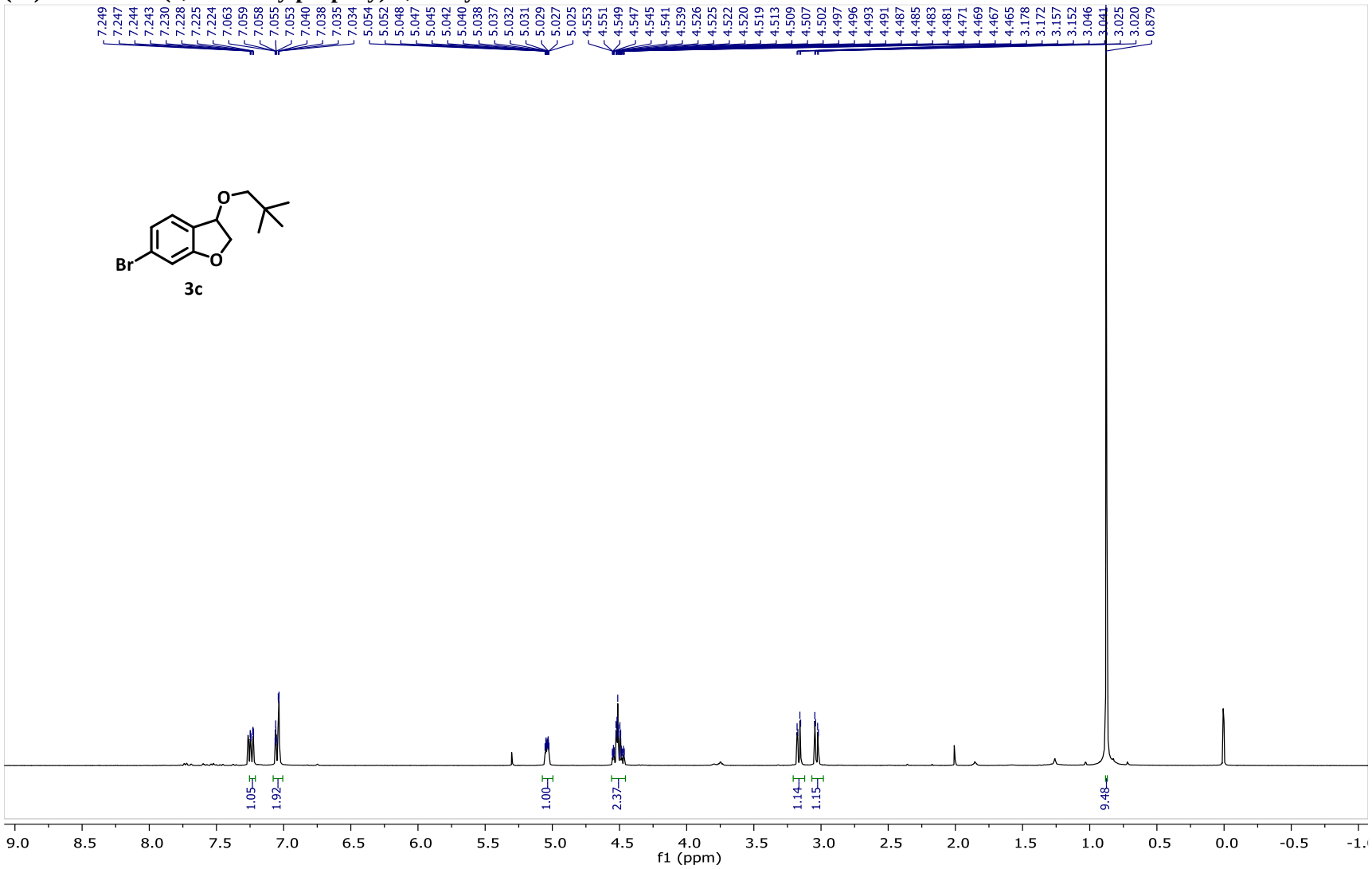

160.93
158.43
144.19
136.10
135.52
133.86
131.04
129.78
127.86
127.14
124.62
115.63
115.43
67.95
21.53
70
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

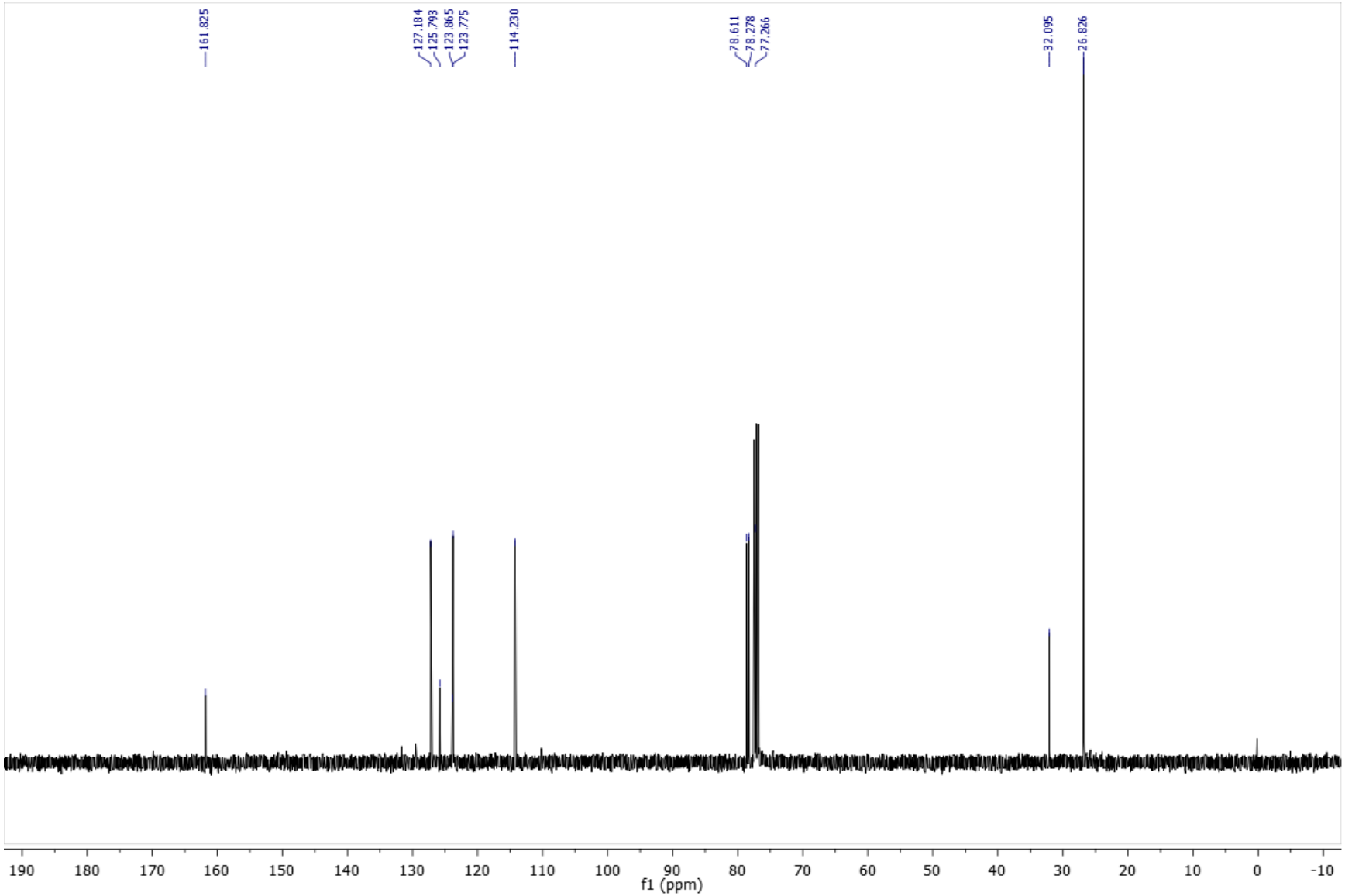
(3a) 3-(2,2-Dimethylpropoxy)2,3-dihydro-1-benzofuran



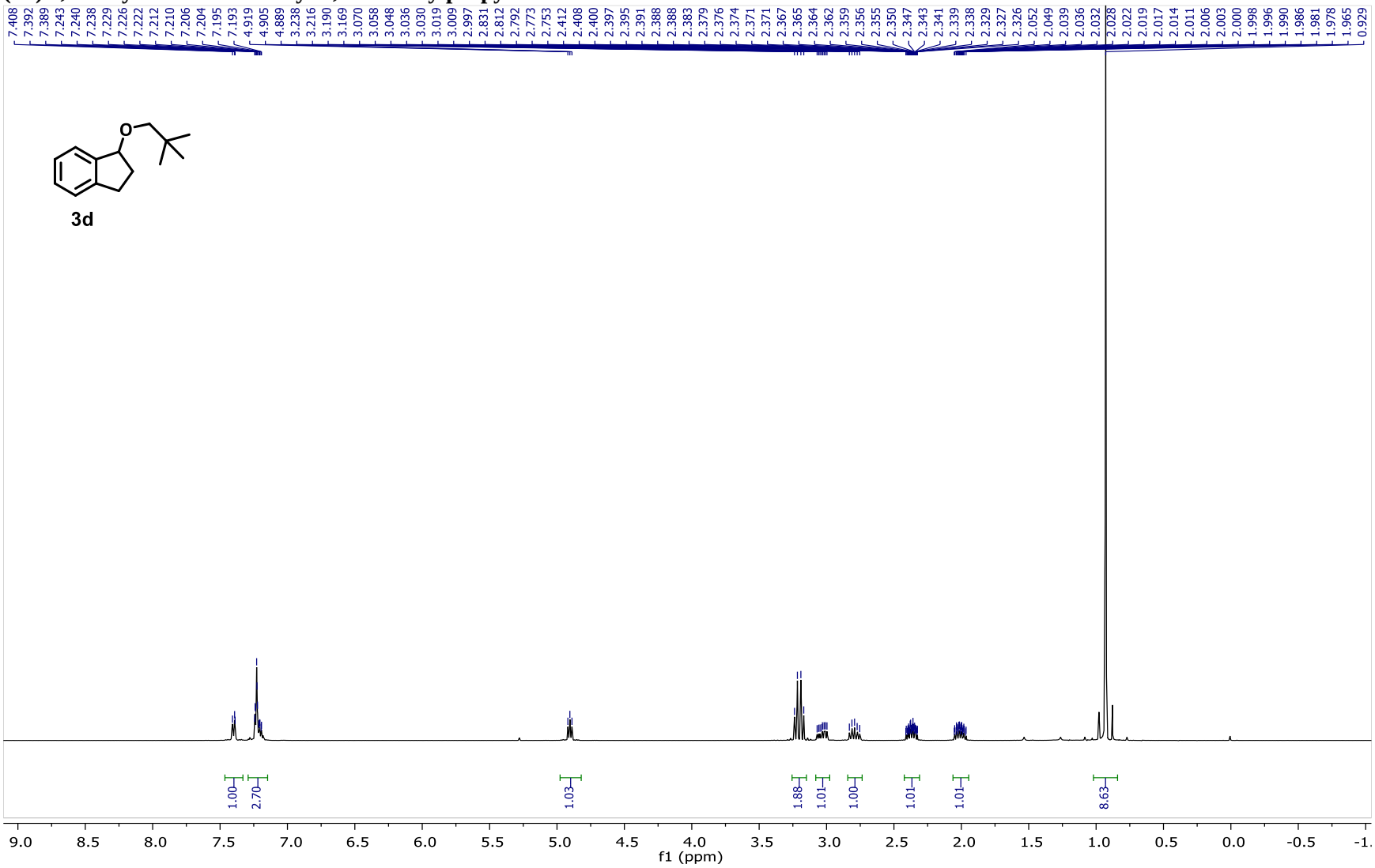

160.676
130.349
126.270
126.080
120.371
110.402
79.105
77.998
76.275
31.928
26.683
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

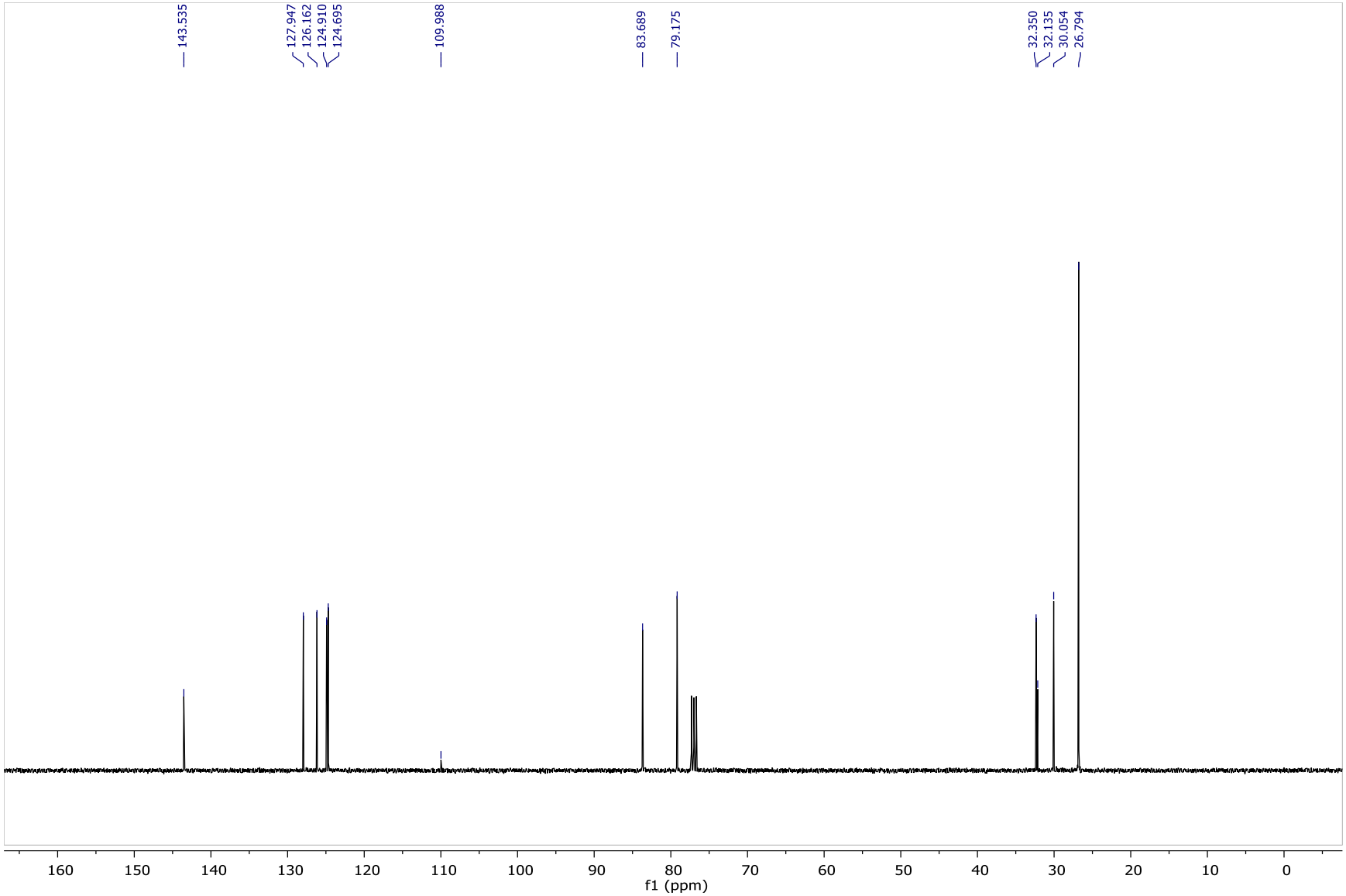
(3c) 6-Bromo-3-(2,2-dimethylpropoxy)-2,3-dihydro-1-benzofuran



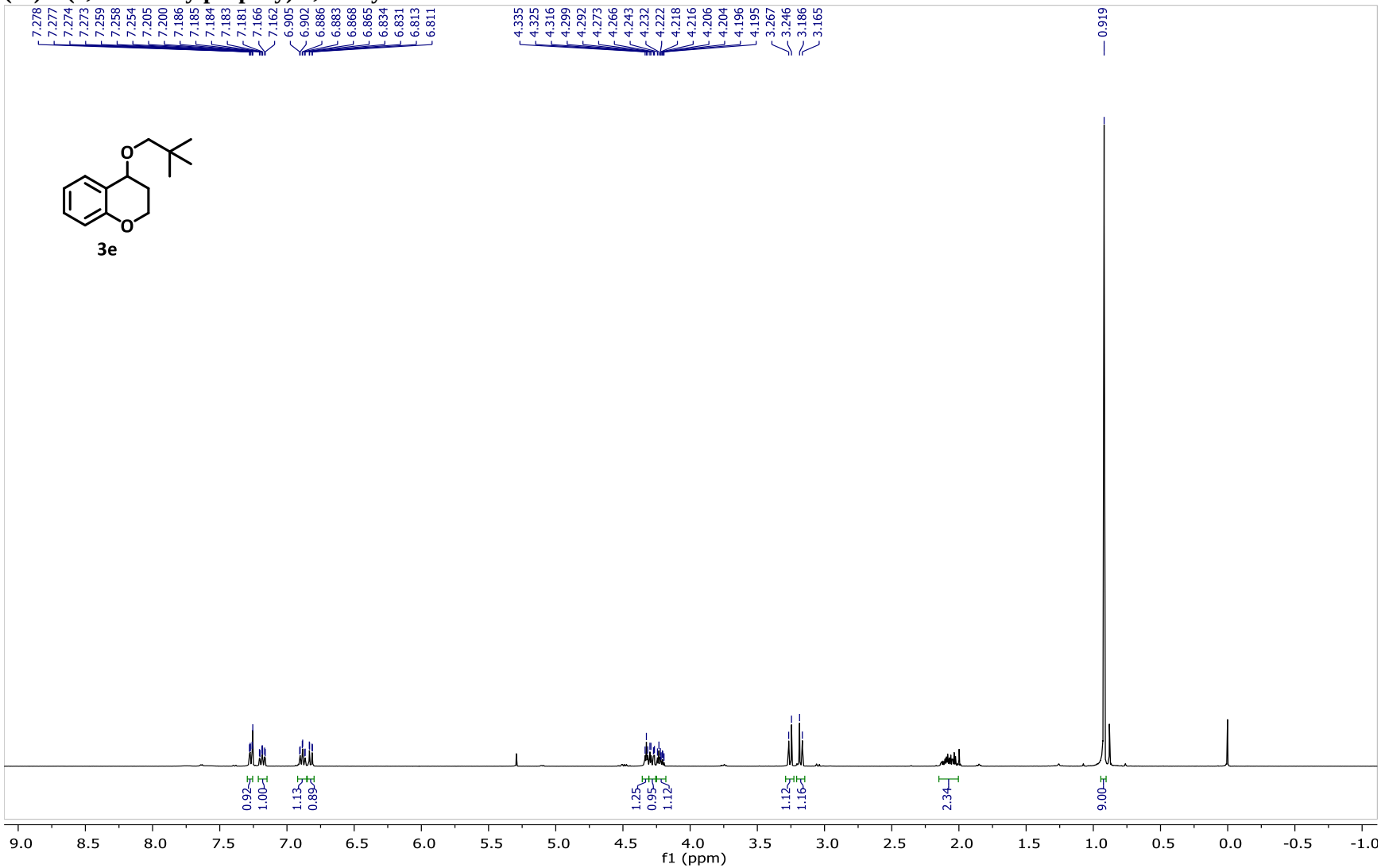

161.825
127.184
125.793
123.865
123.775
114.230
78.611
78.278
77.266
32.095
26.826
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

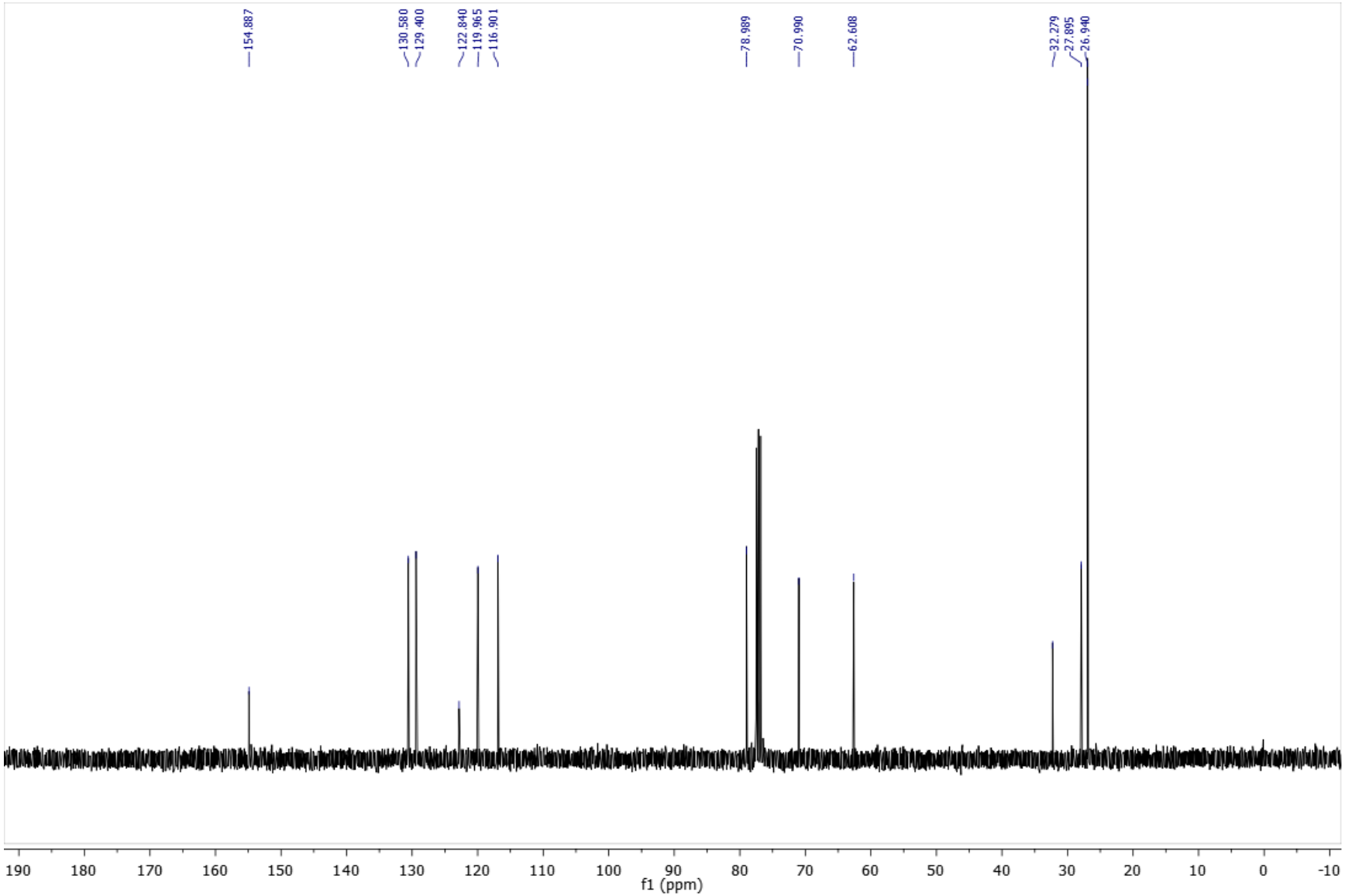
(3d) 2,3-Dihydro-1*H*-inden-1-yl-2,2-dimethylpropyl ether



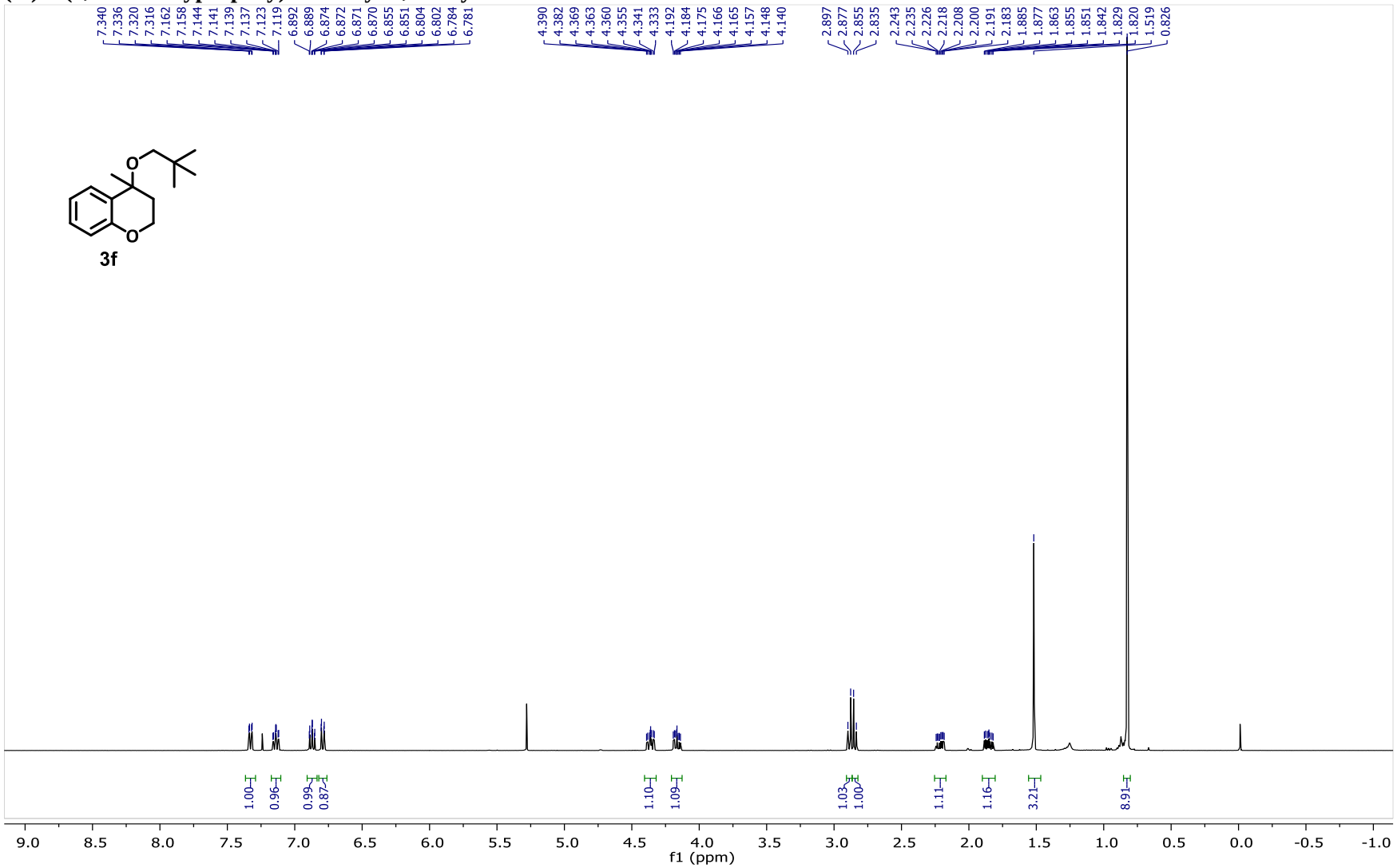

143.535
127.947
126.162
124.910
124.695
109.988
83.689
79.175
32.350
32.135
30.054
26.794
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

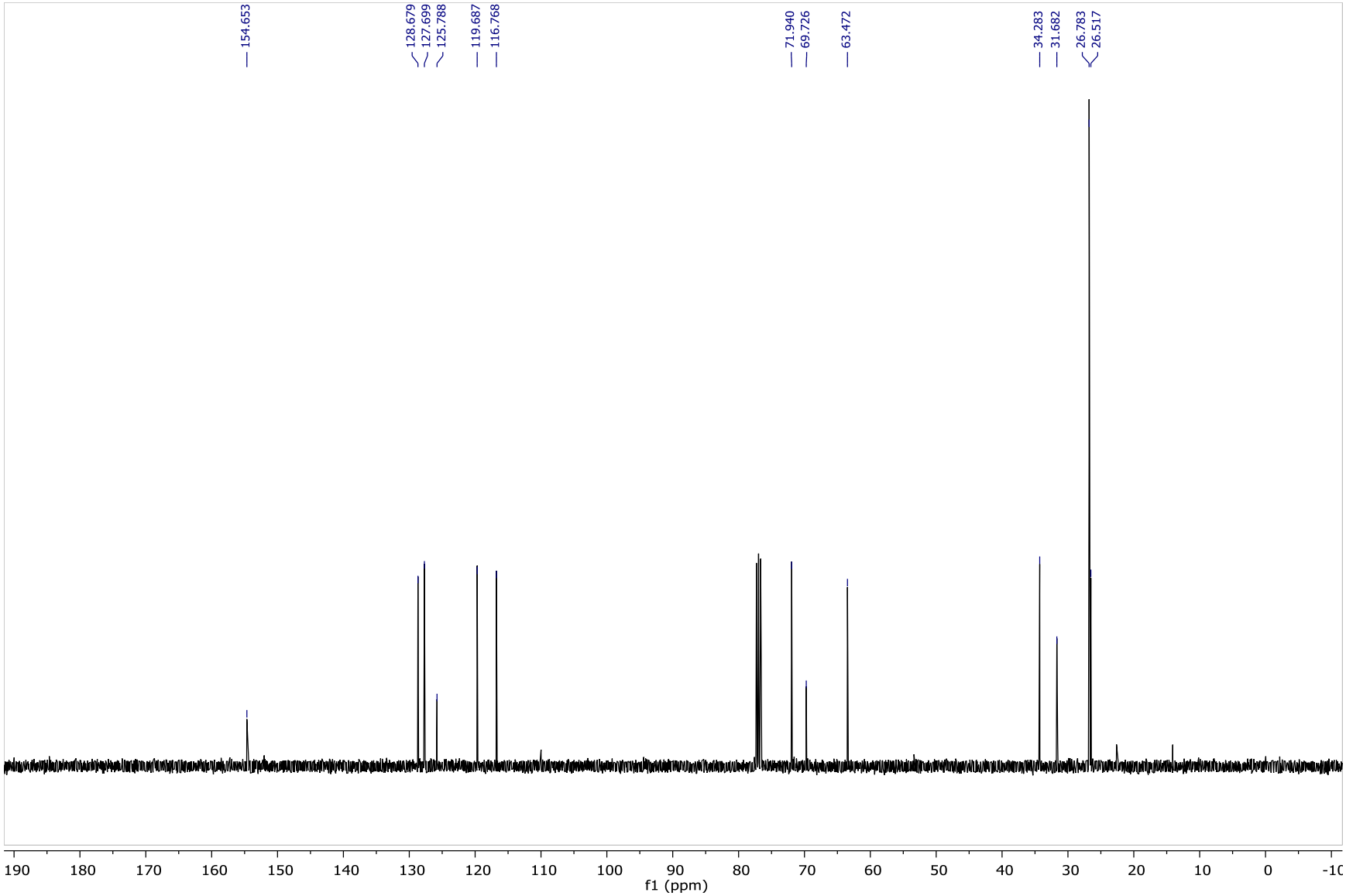
(3e) 4-(2,2-Dimethylpropoxy)-3,4-dihydro-2*H*-chromene



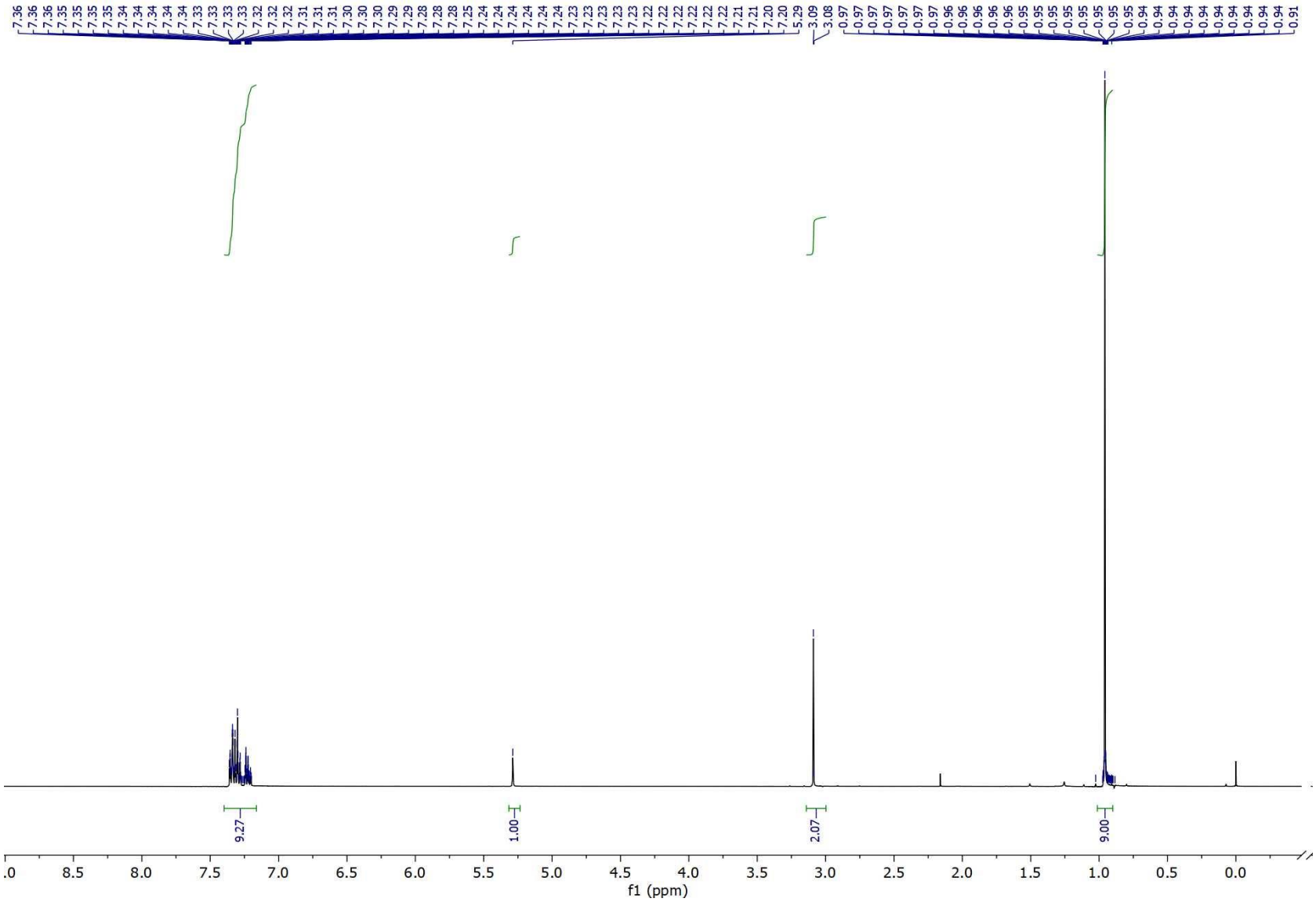

154.887
130.580
129.400
122.840
119.965
116.901
78.989
70.990
62.608
32.279
27.895
26.940
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

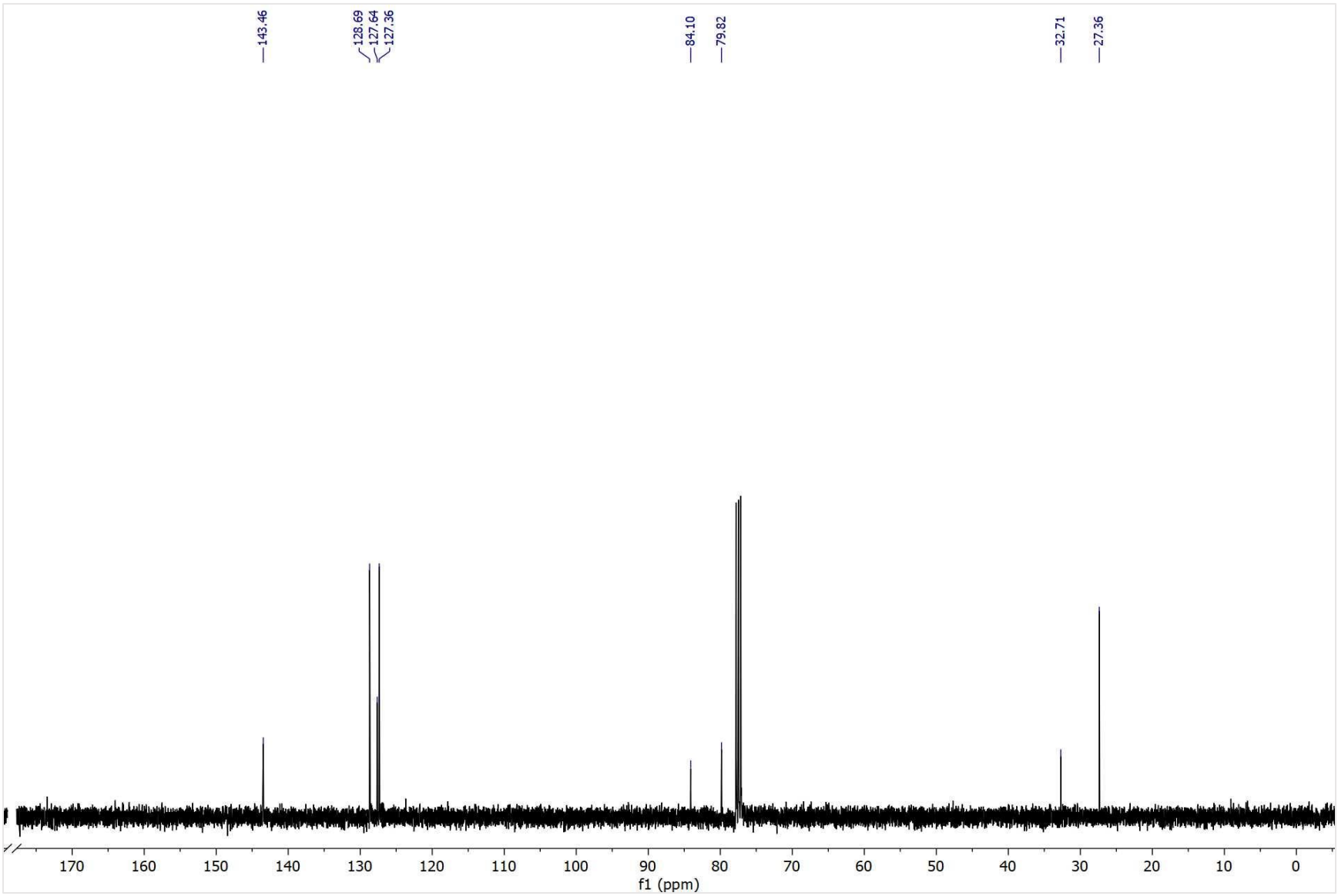
(3f) 4-(2,2-Dimethypropoxy)-4-methyl-3,4-dihydro-2*H*-chromene



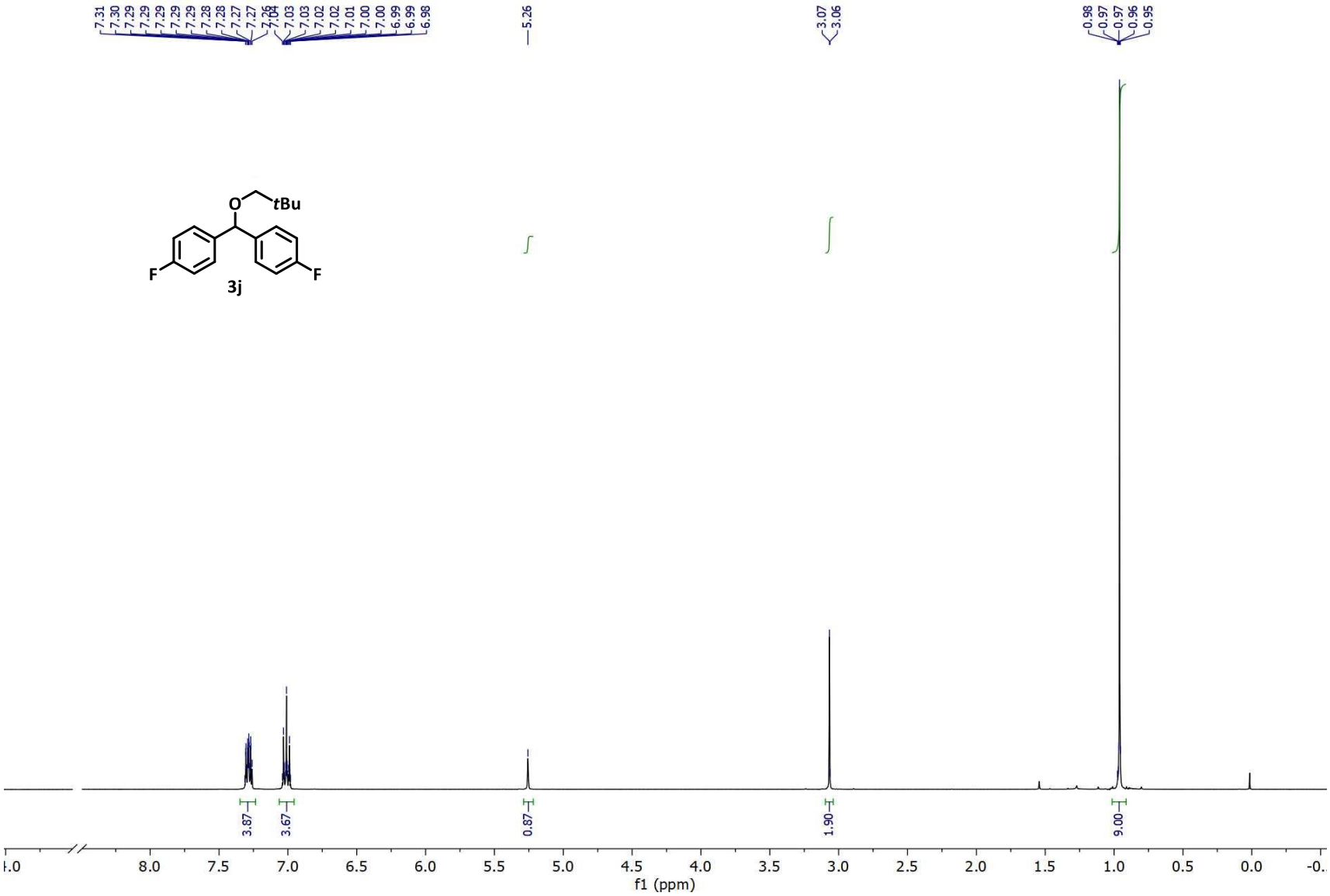

154.653
128.679
127.699
125.788
119.687
116.768
71.940
69.726
63.472
34.283
31.682
26.783
26.517
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

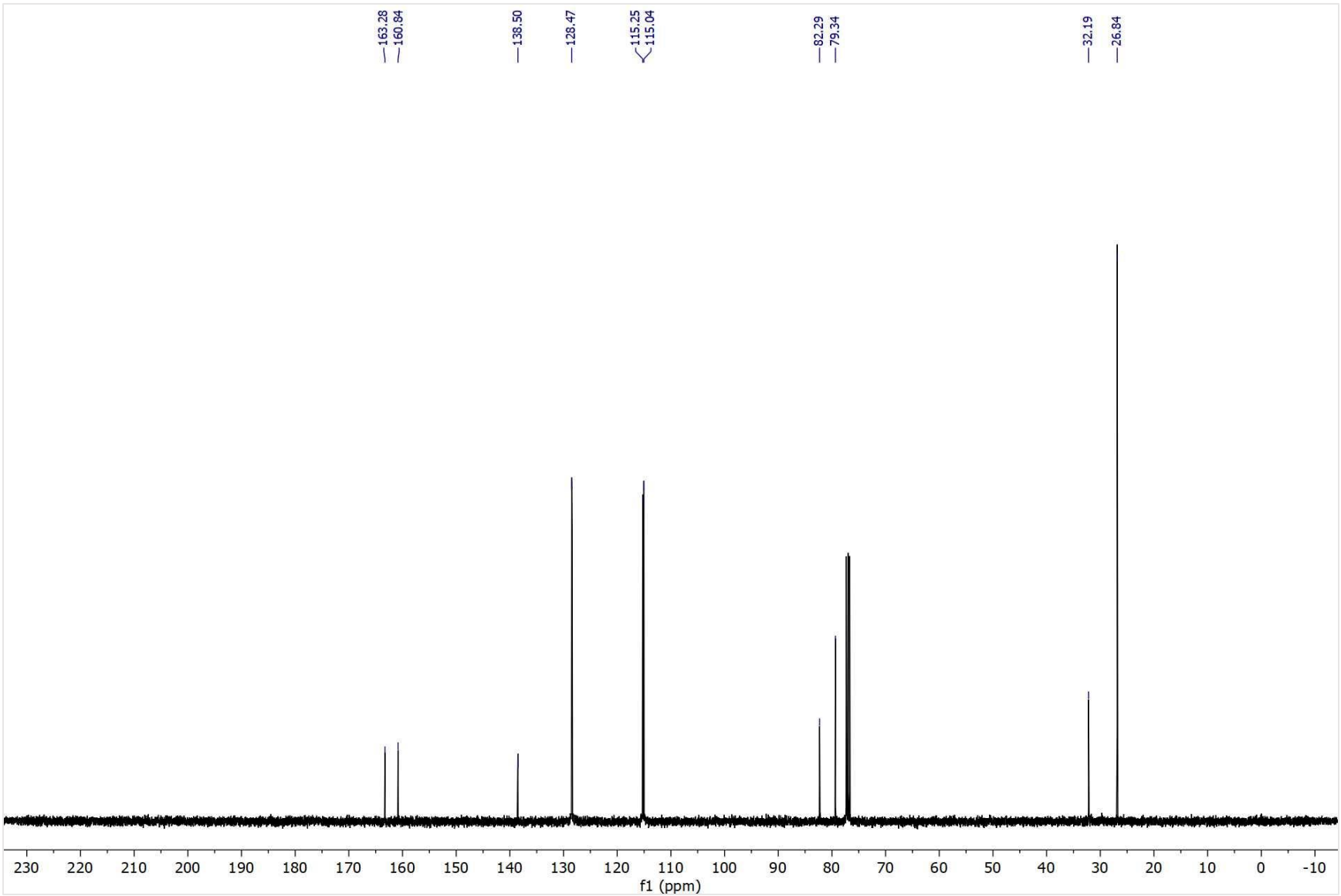
(3i) [(2,2-dimethylpropoxy)(phenyl)methyl]benzene.



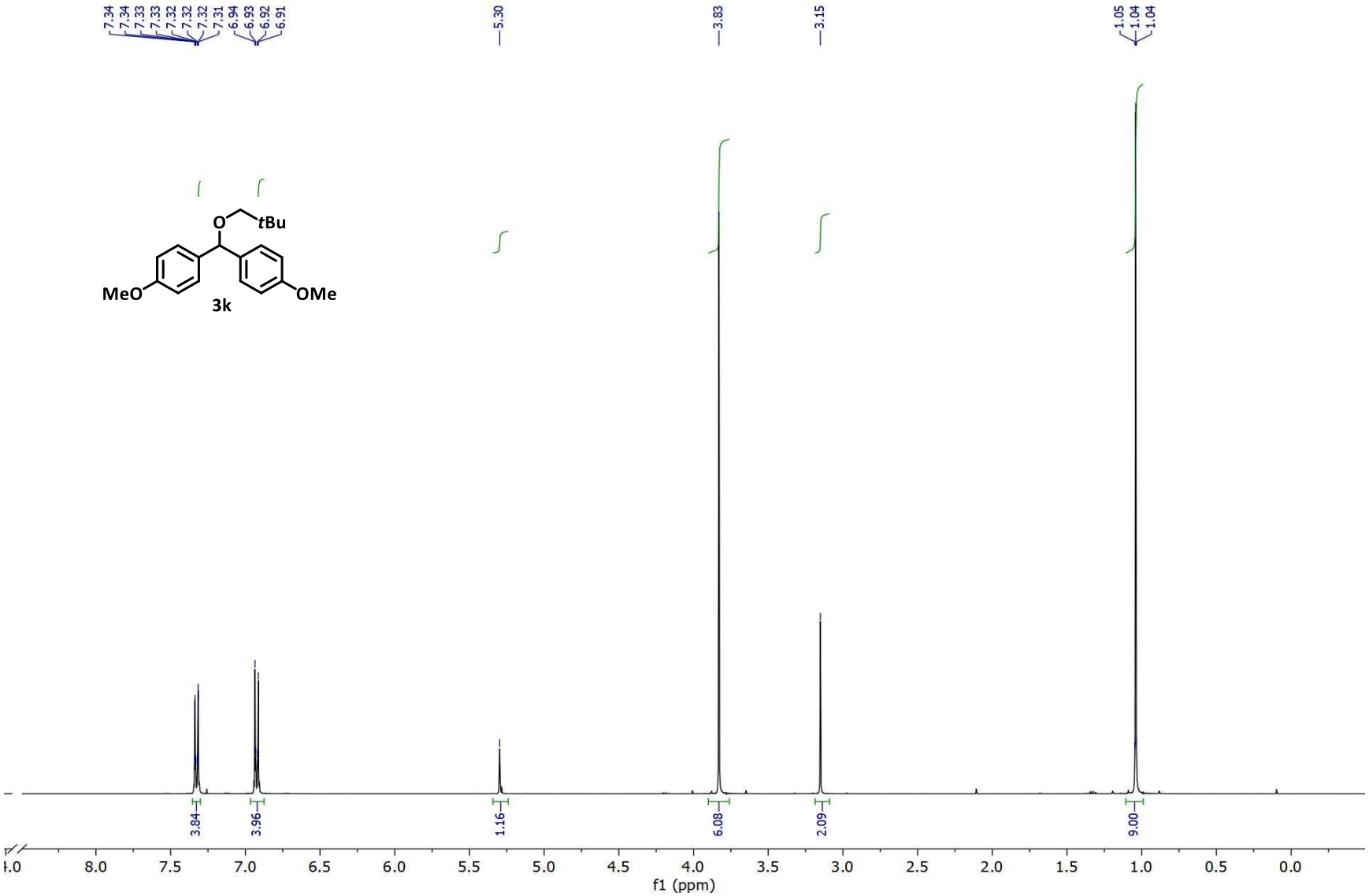

143.46
128.69
127.64
127.36
84.10
79.82
32.71
27.36
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

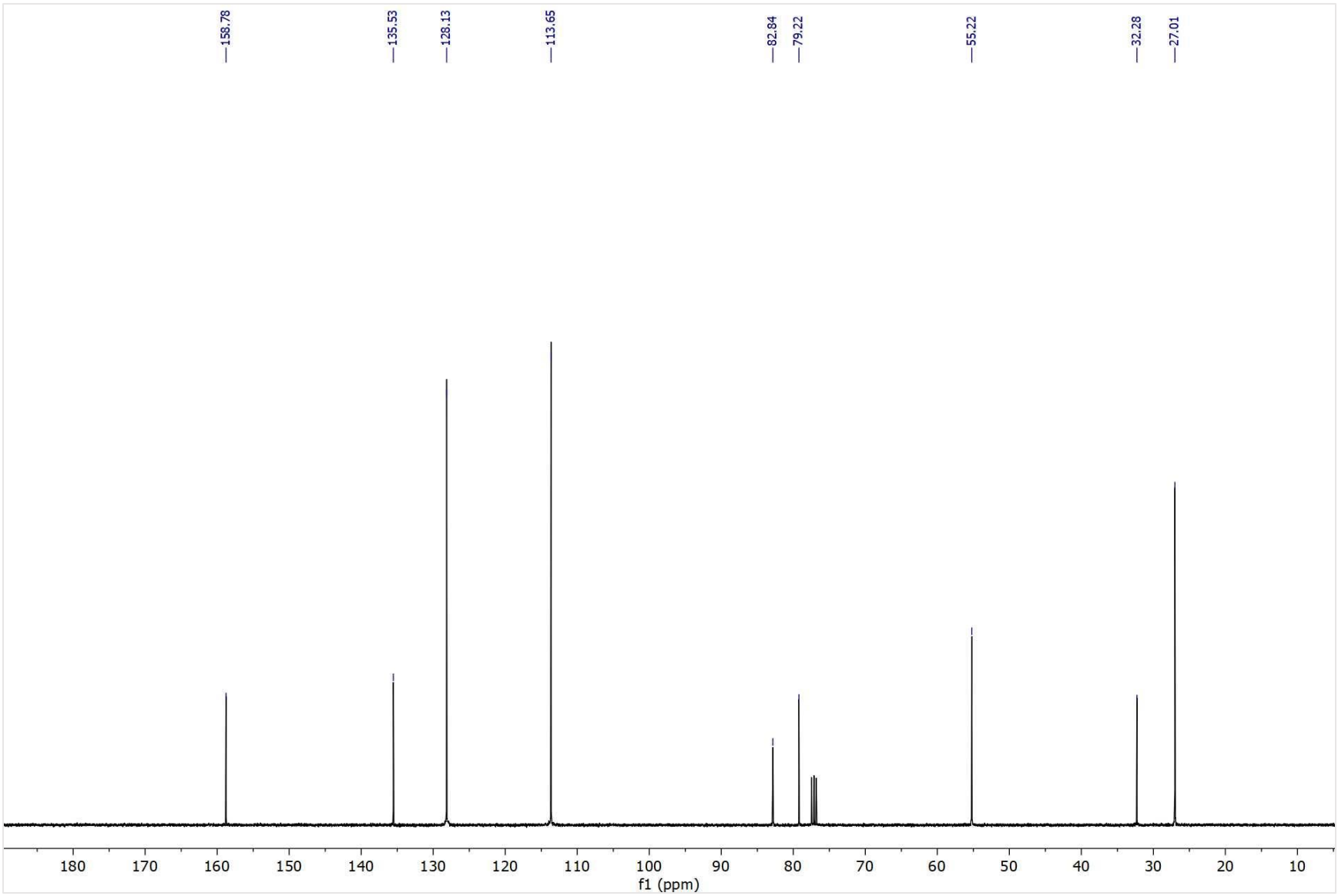
(3j) 1-[(2,2-dimethylpropoxy)(4-fluorophenyl)methyl]-4-fluorobenzene.



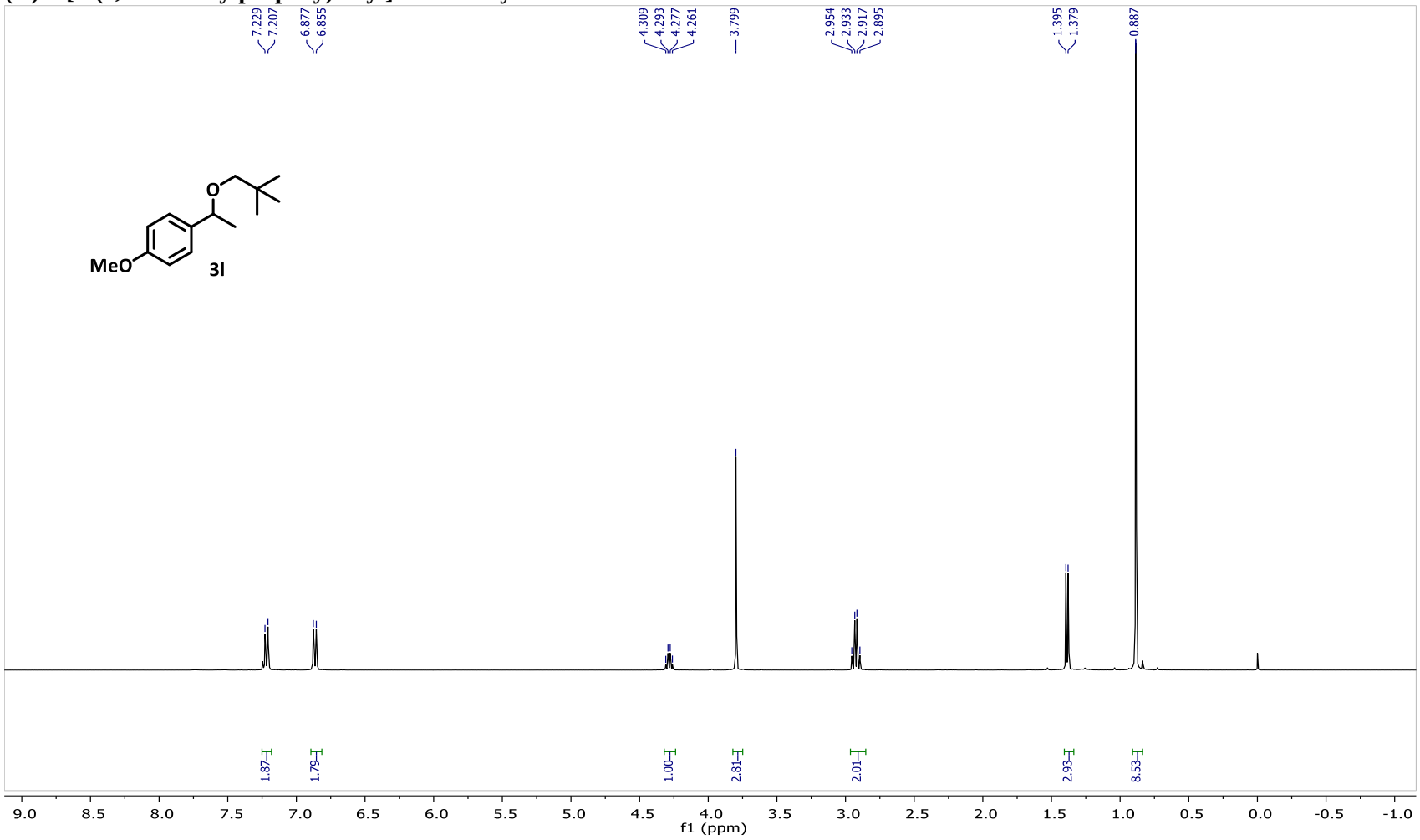

163.28
160.84
138.50
128.47
115.25
115.04
82.29
79.34
32.19
26.84
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

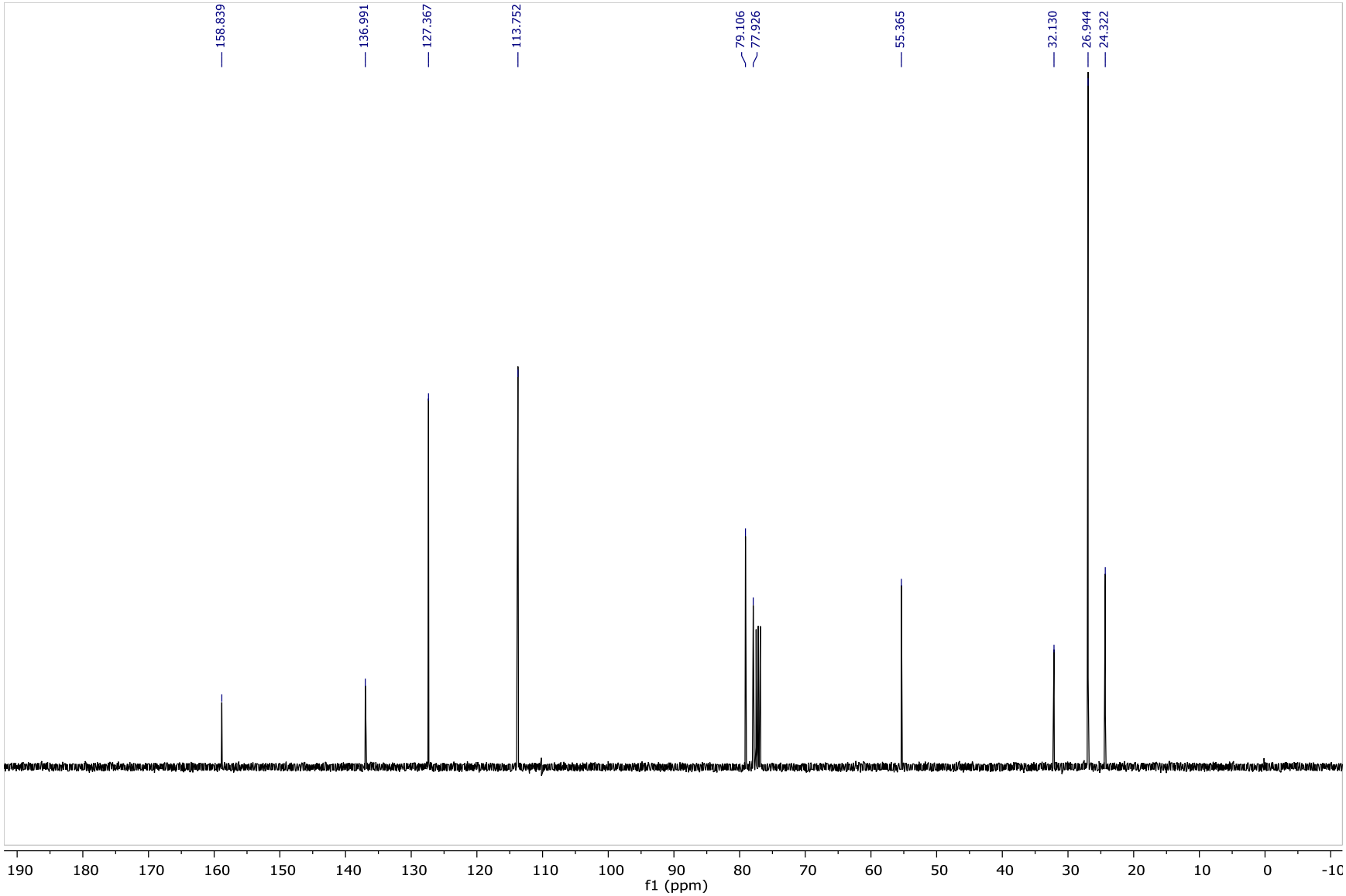
(3k) 1-[(2,2-dimethylpropoxy)(4-methoxyphenyl)methyl]-4-methoxybenzene.



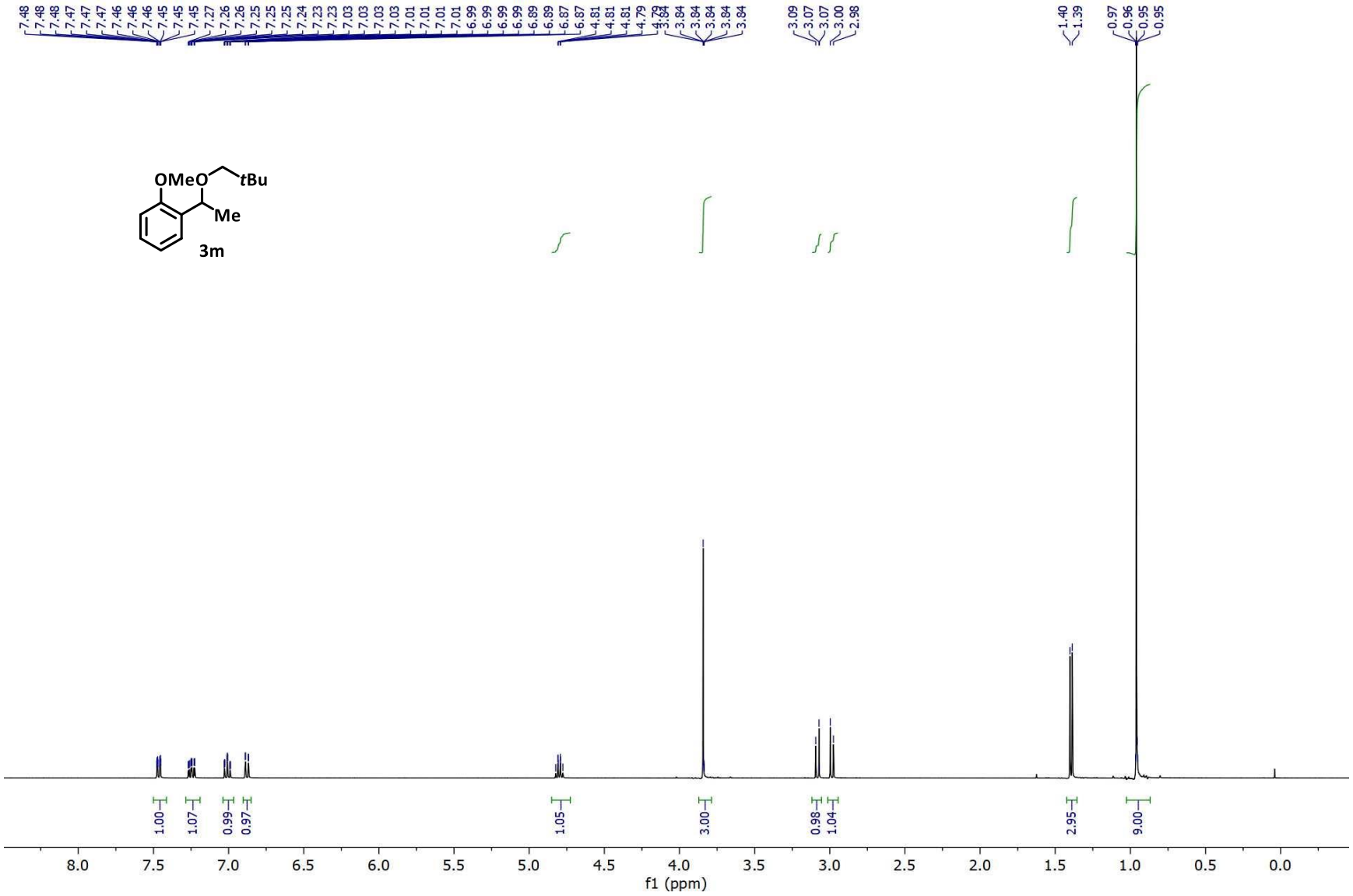

158.78
135.53
128.13
113.65
82.84
79.22
55.22
32.28
27.01
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

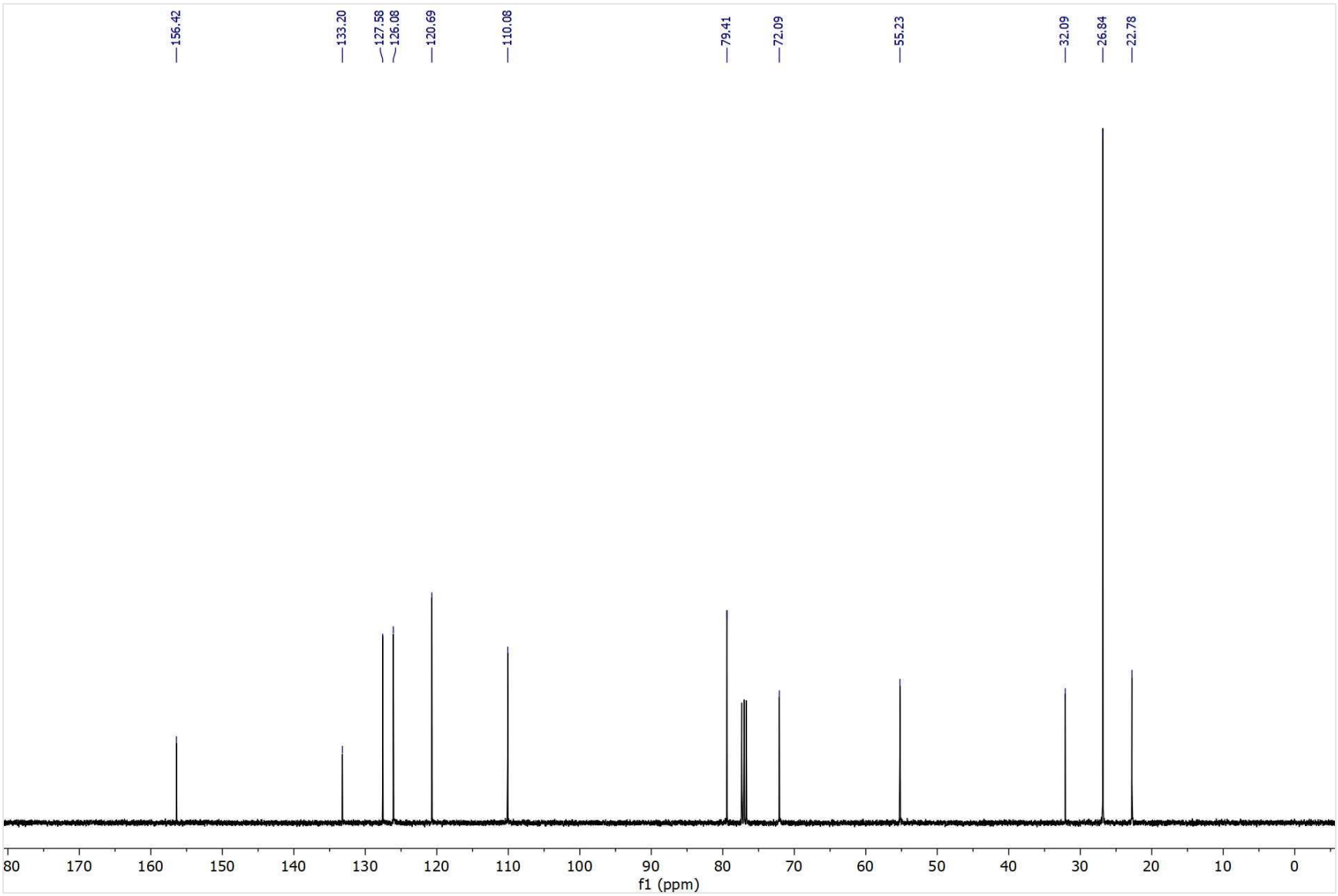
(3l) 1-[1-(2,2-Dimethylpropoxy)ethyl]-4-methoxybenzene



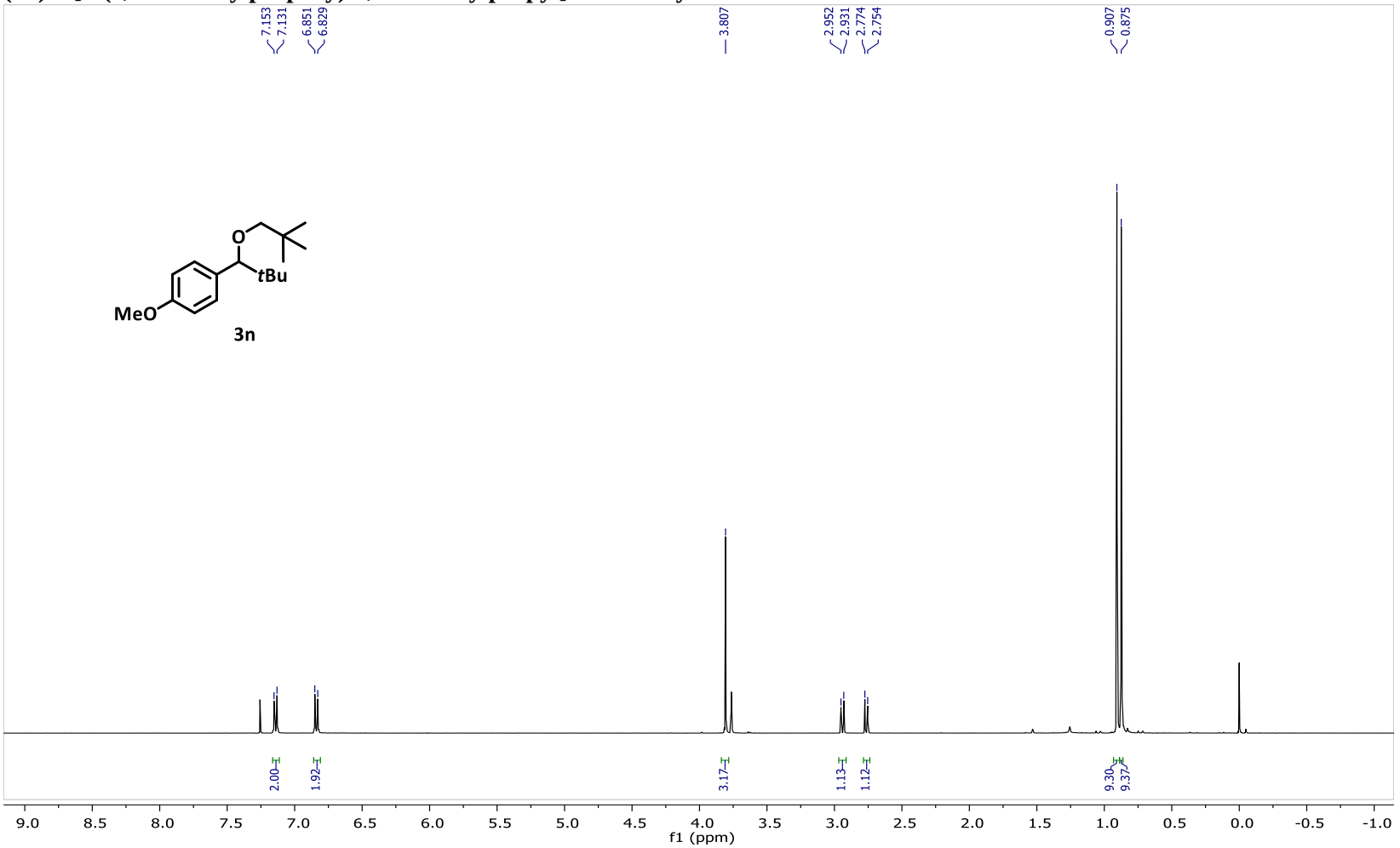

158.839
136.991
127.367
113.752
79.106
77.926
55.365
32.130
26.944
24.322
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

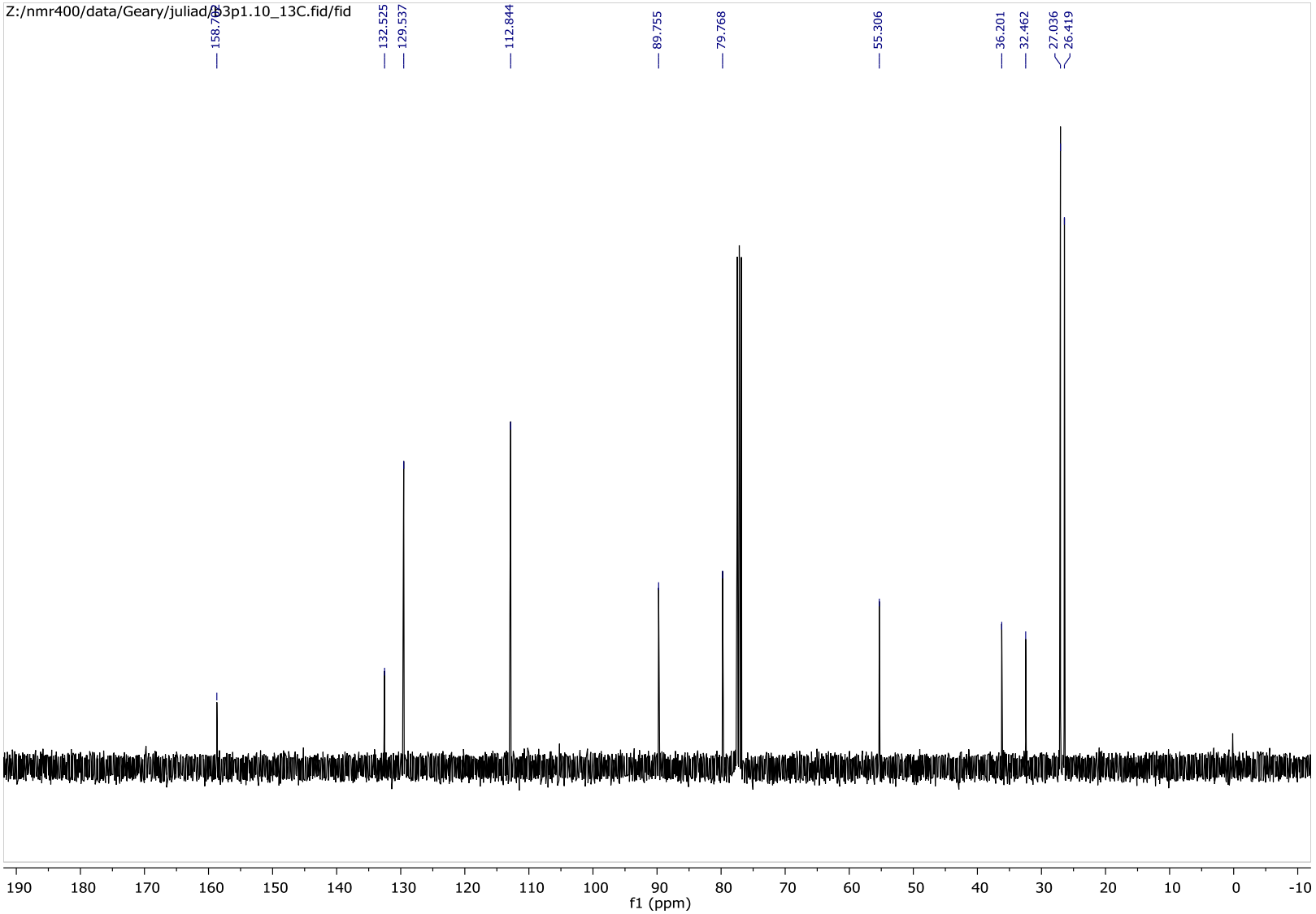
(3m) 1-[1-(2,2-dimethylpropoxy)ethyl]-2-methoxybenzene



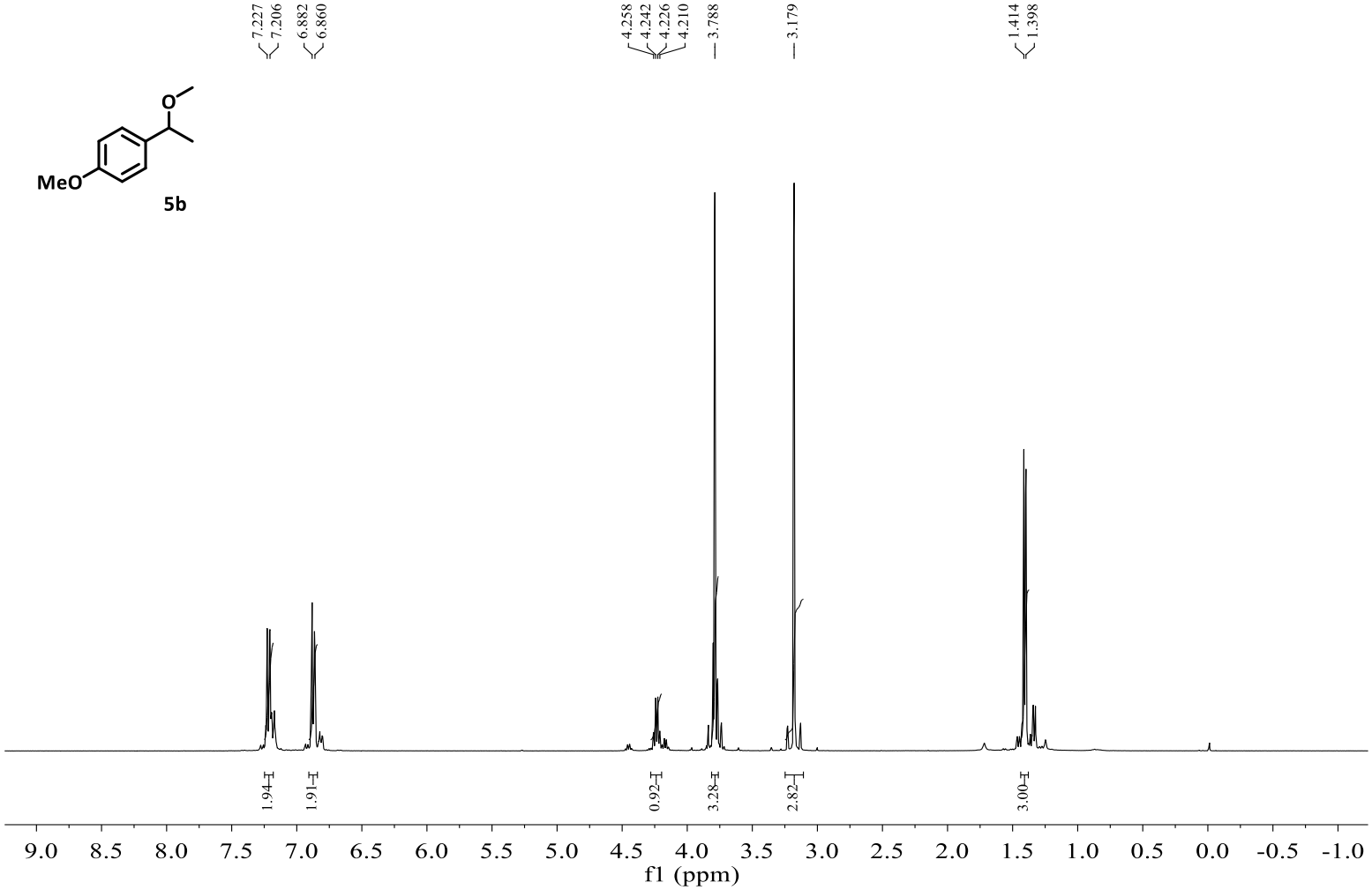

156.42
133.20
127.58
126.08
120.69
110.08
79.41
72.09
55.23
32.09
26.84
22.78
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

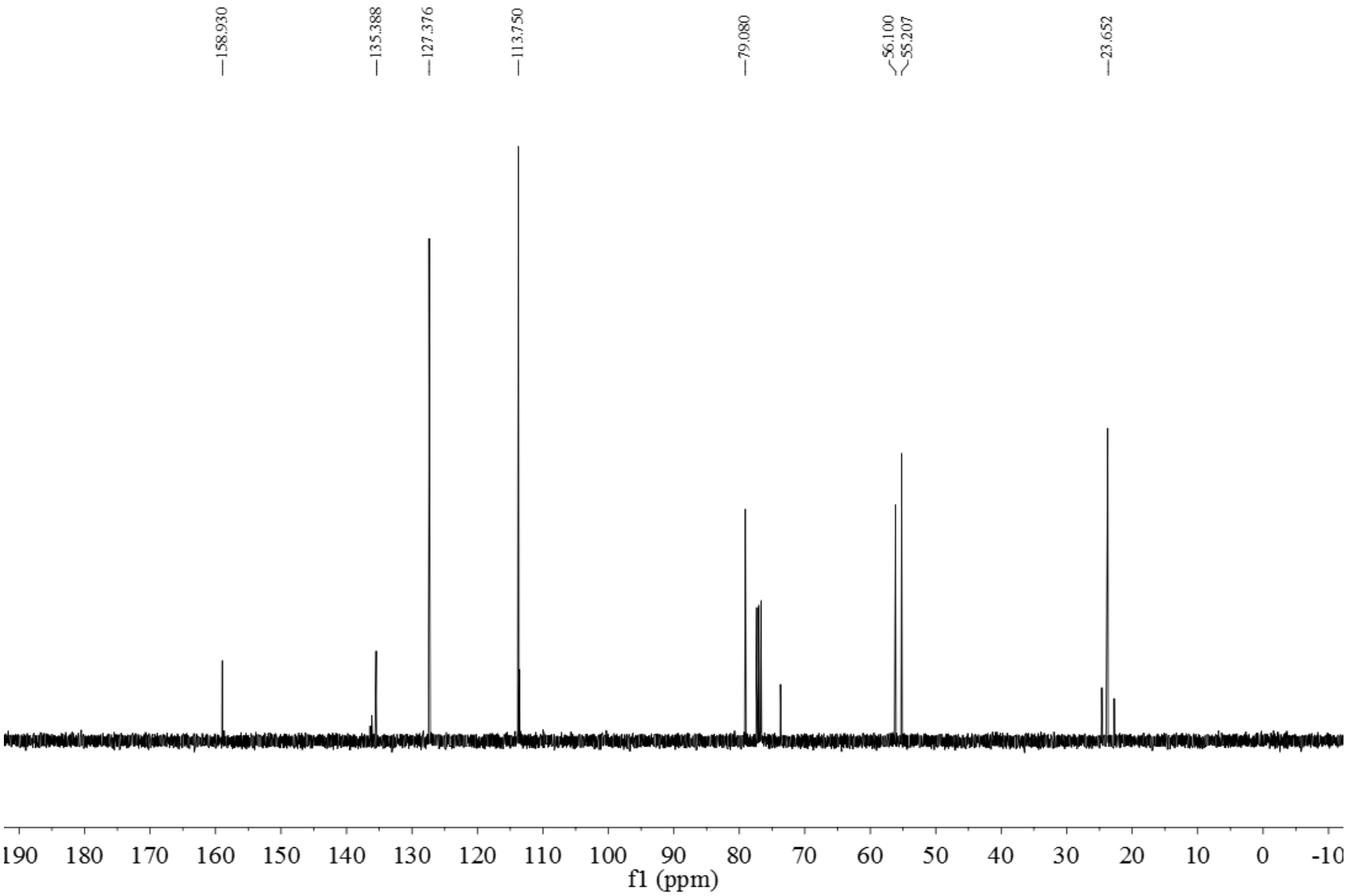
(3n) 1-[1-(2,2-Dimethylpropoxy)-2,2-dimethylpropyl]-4-methoxybenzene



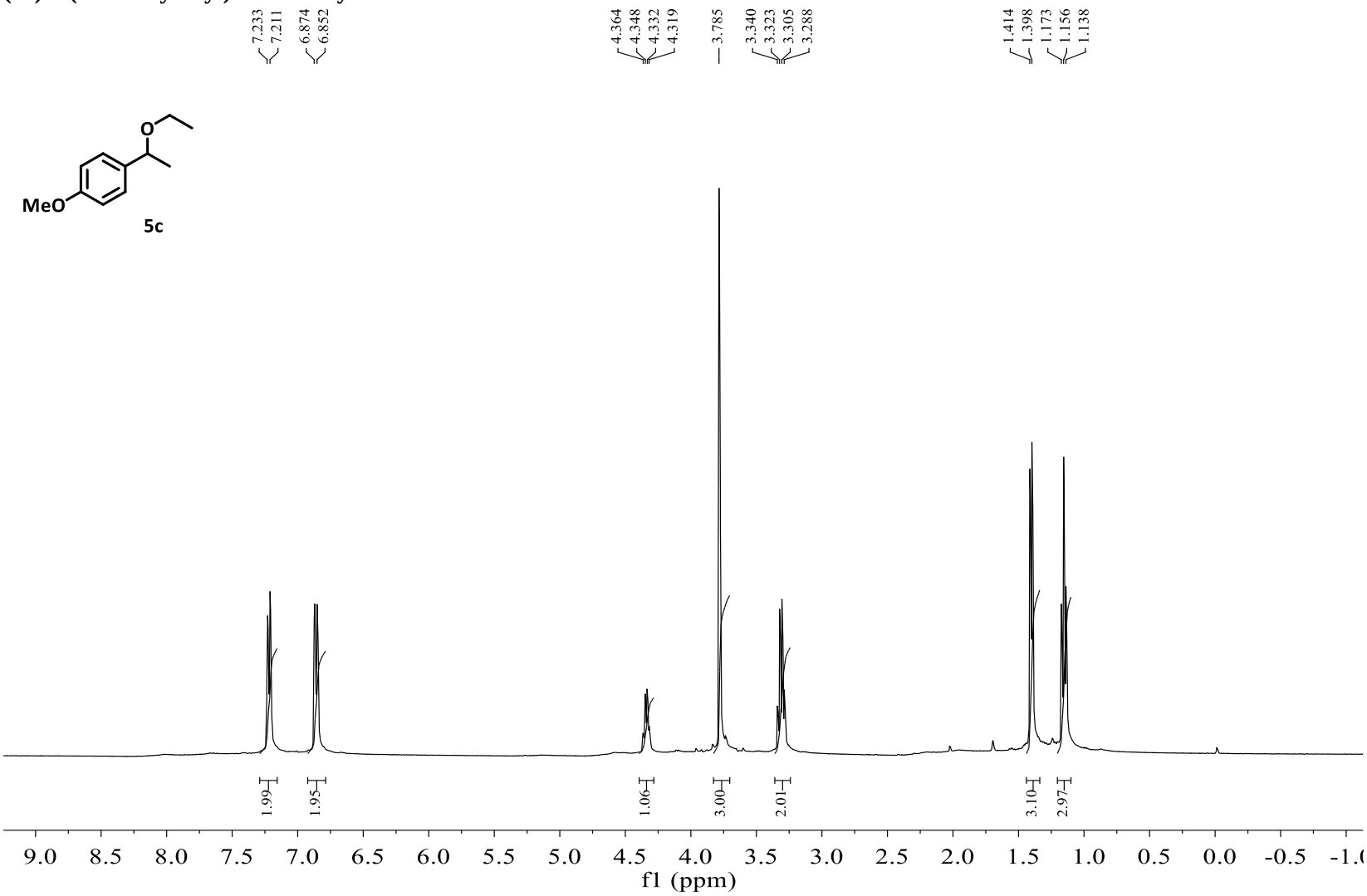

Z:/nmr400/data/Geary/juliad/J3p1.10_13C.fid/fid
158.700
132.525
129.537
112.844
89.755
79.768
55.306
36.201
32.462
27.036
26.419
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

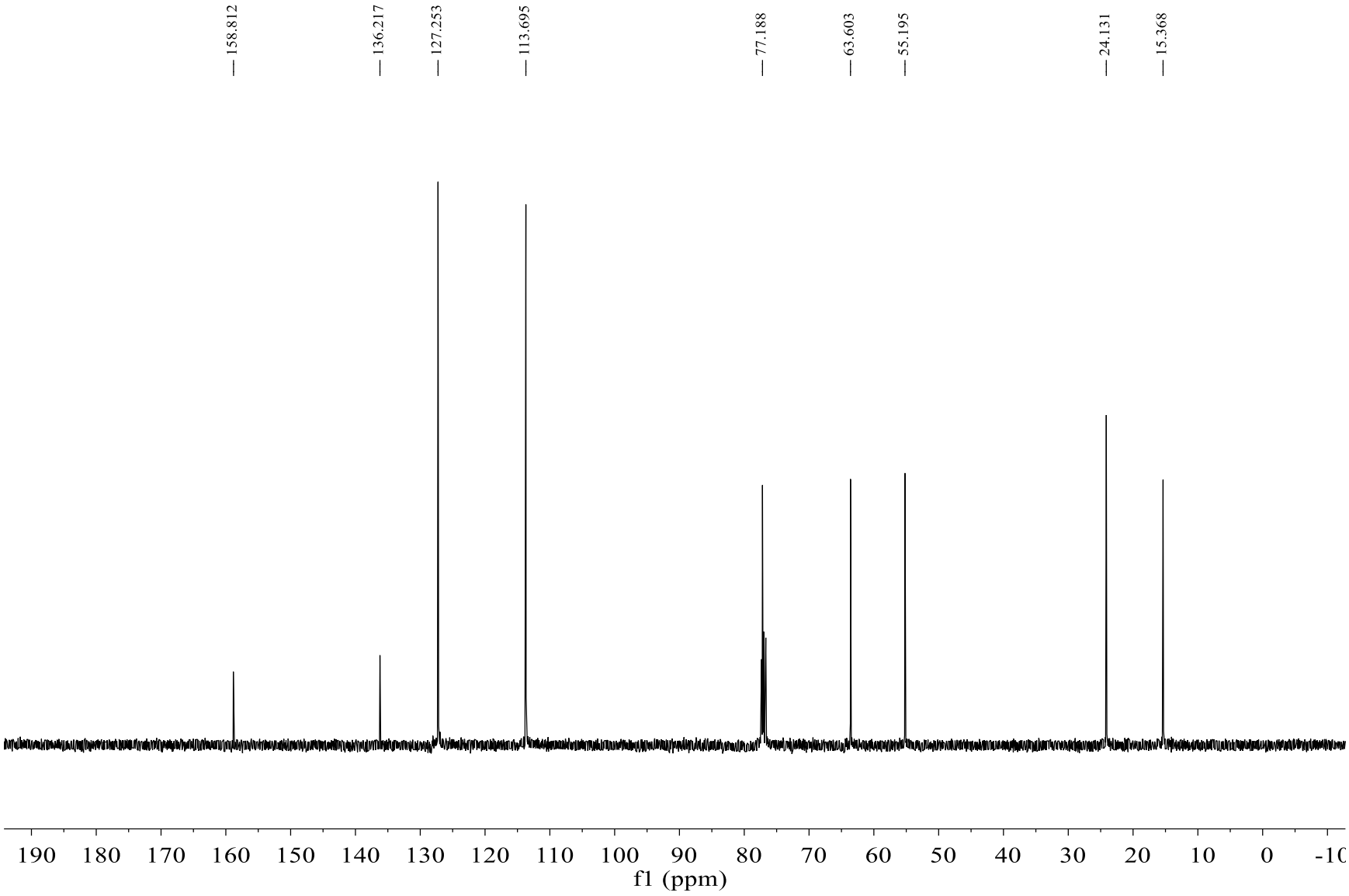
(5b) 1-Methoxy-4-(1-methoxyethyl)benzene



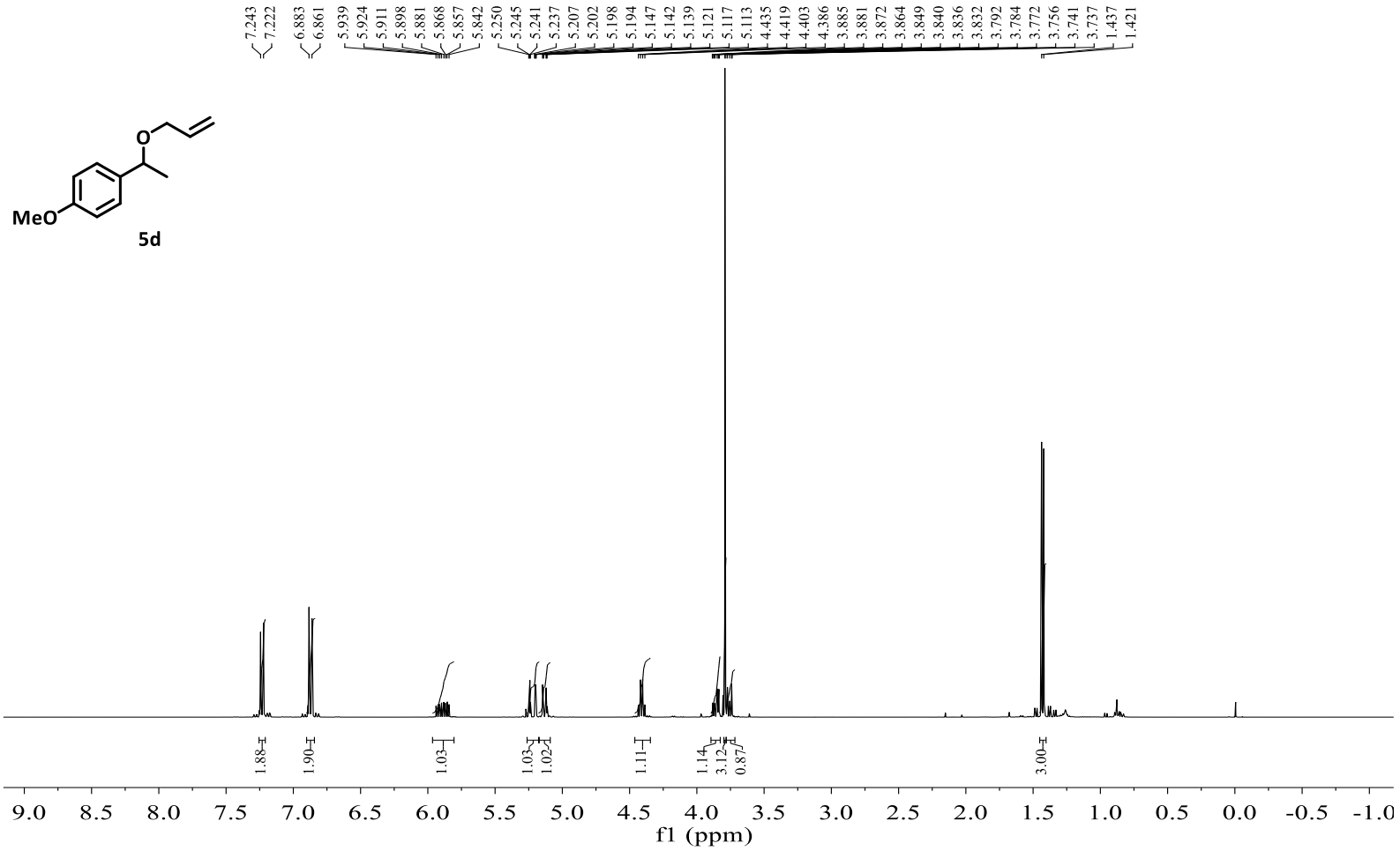

158.930
135.388
127.376
113.750
79.080
56.100
55.207
23.652
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

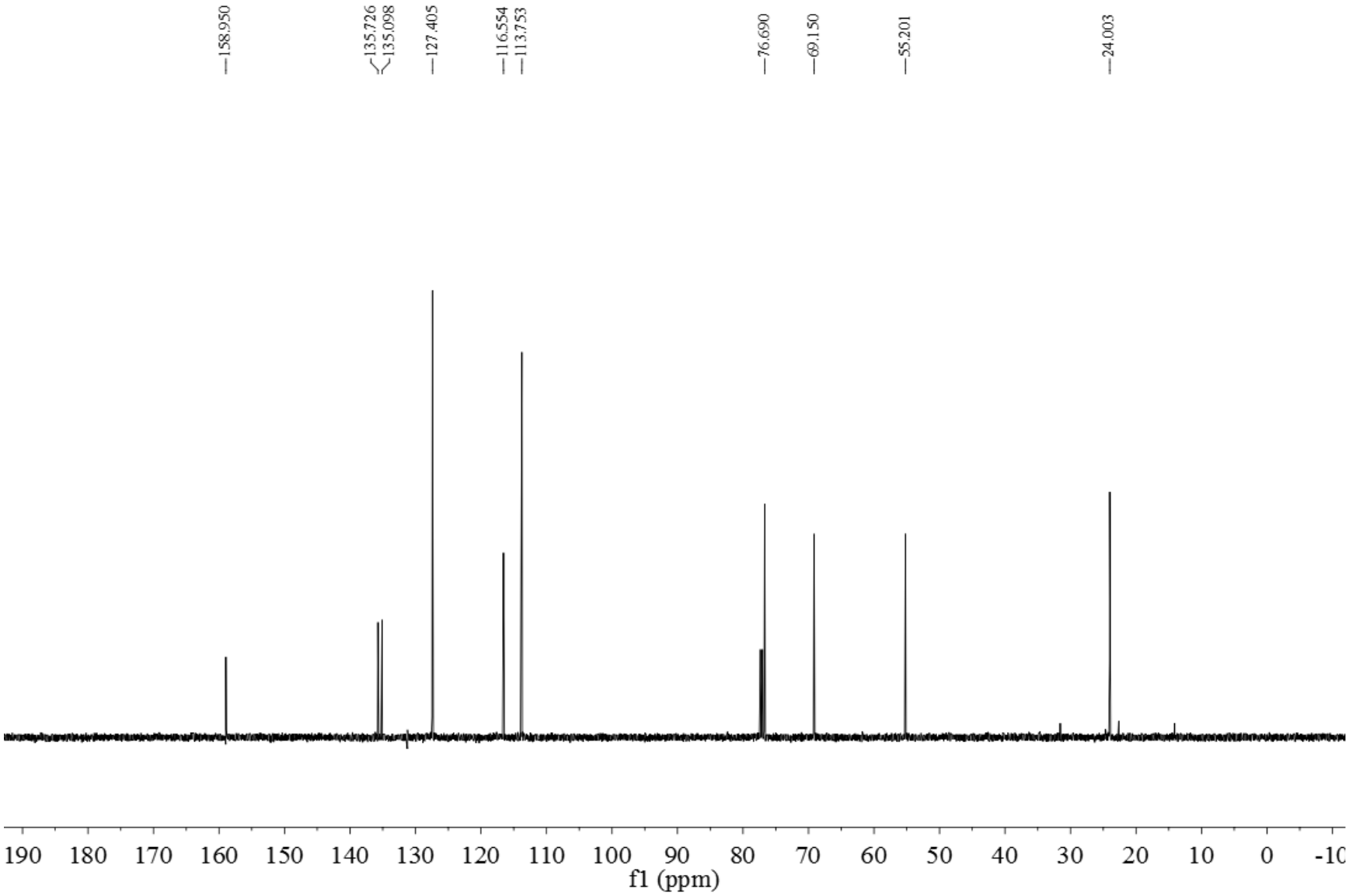
(5c) 1-(1-Ethoxyethyl)-4-methoxybenzene



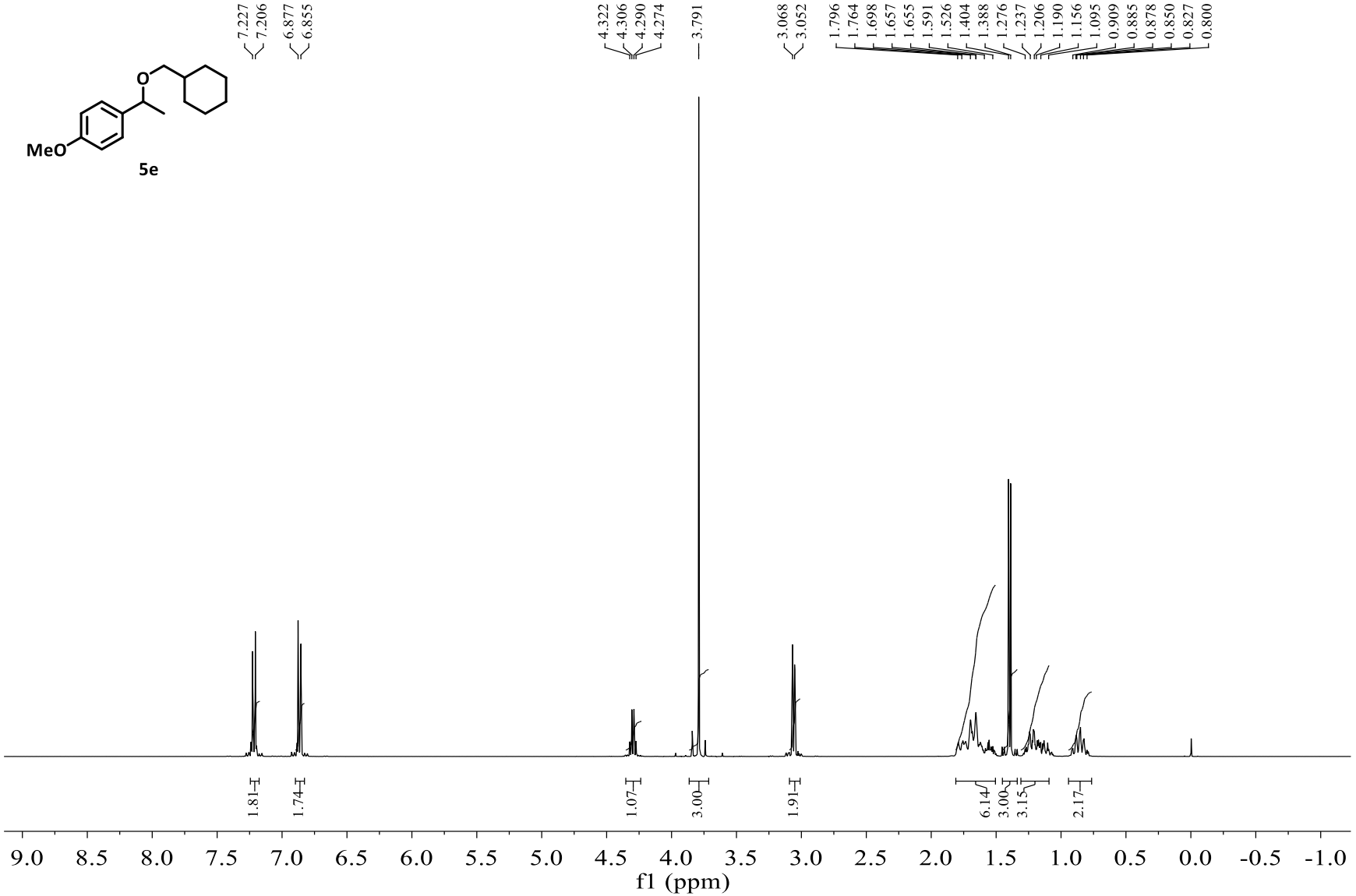

158.812
136.217
127.253
113.695
77.188
63.603
55.195
24.131
15.368
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

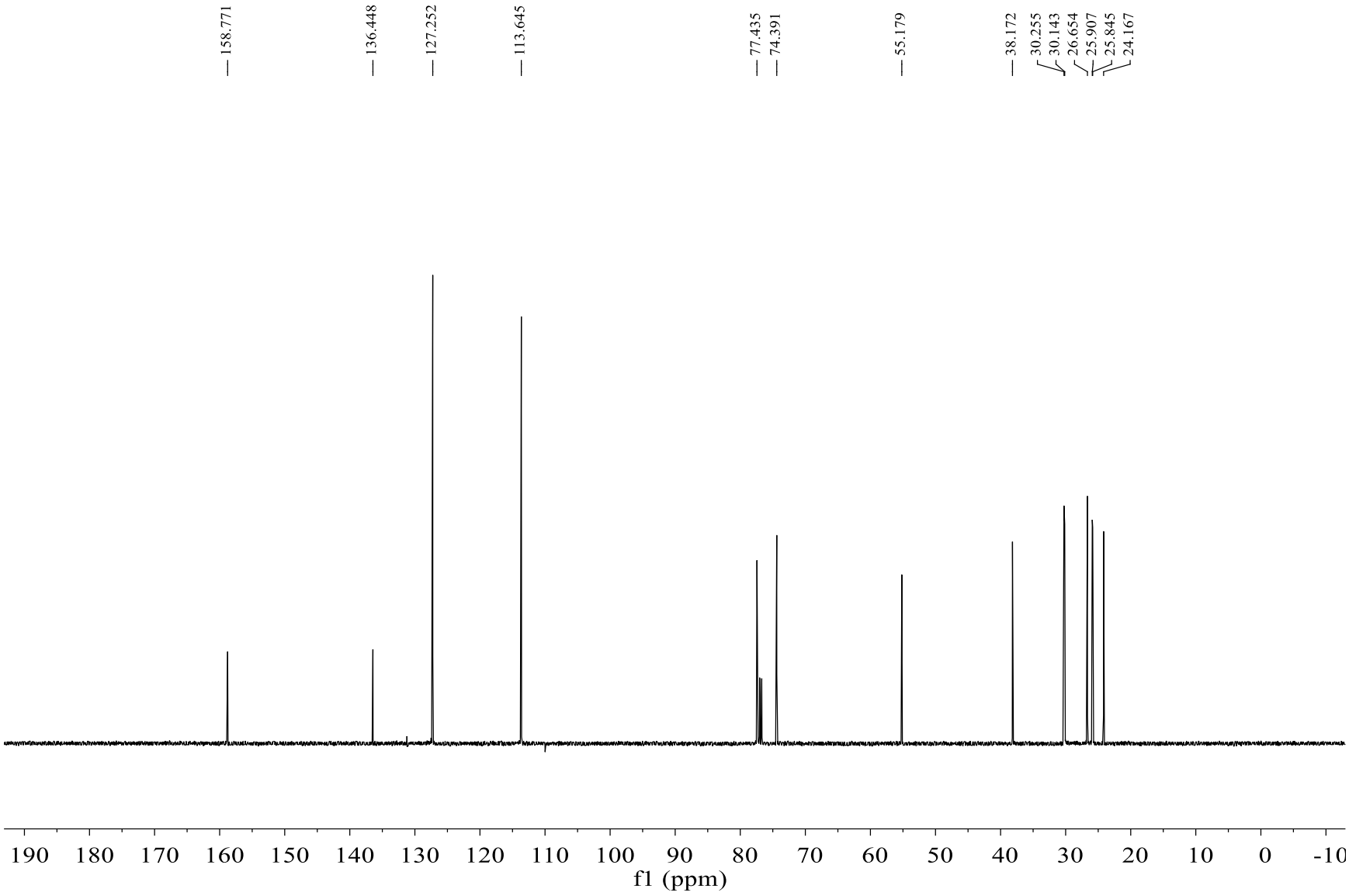
(5d) 1-Methoxy-4-[1-(prop-2-en-1-yloxy)ethyl]benzene



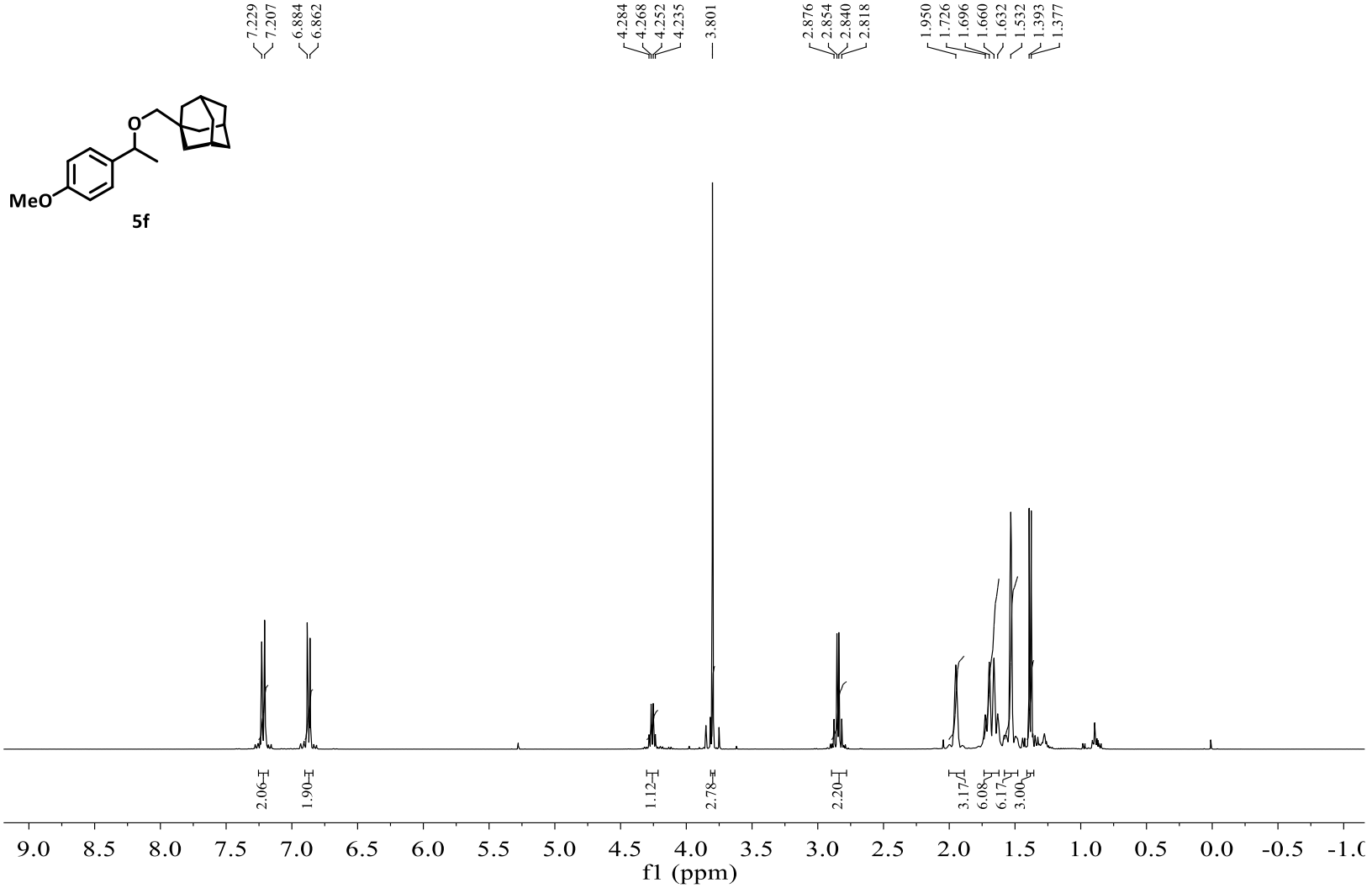

158.950
135.726
135.098
127.405
116.554
113.753
76.690
69.150
55.201
24.003
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

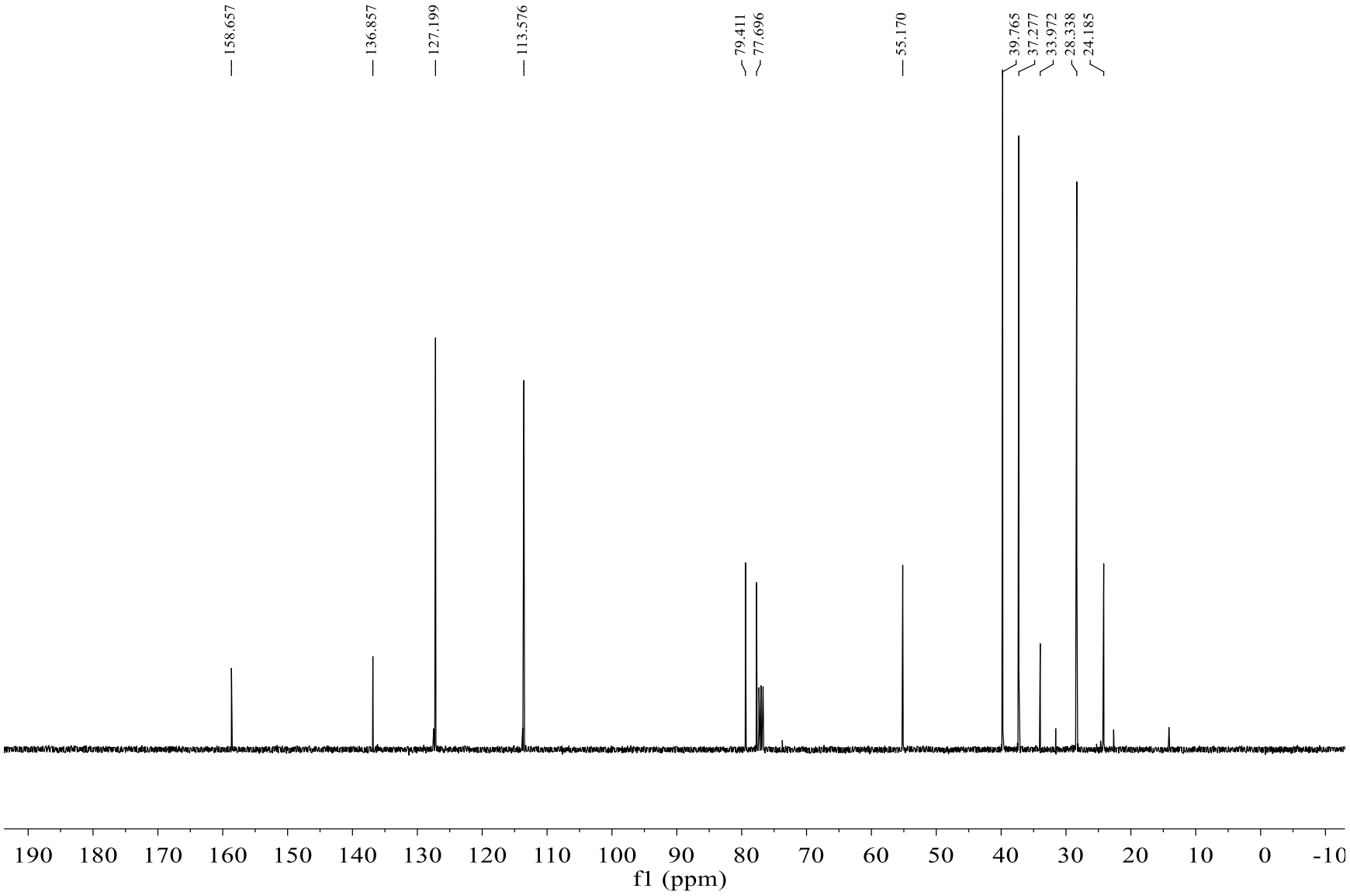
(5e) 1-[1-(Cyclohexylmethoxy)ethyl]-4-methoxybenzene



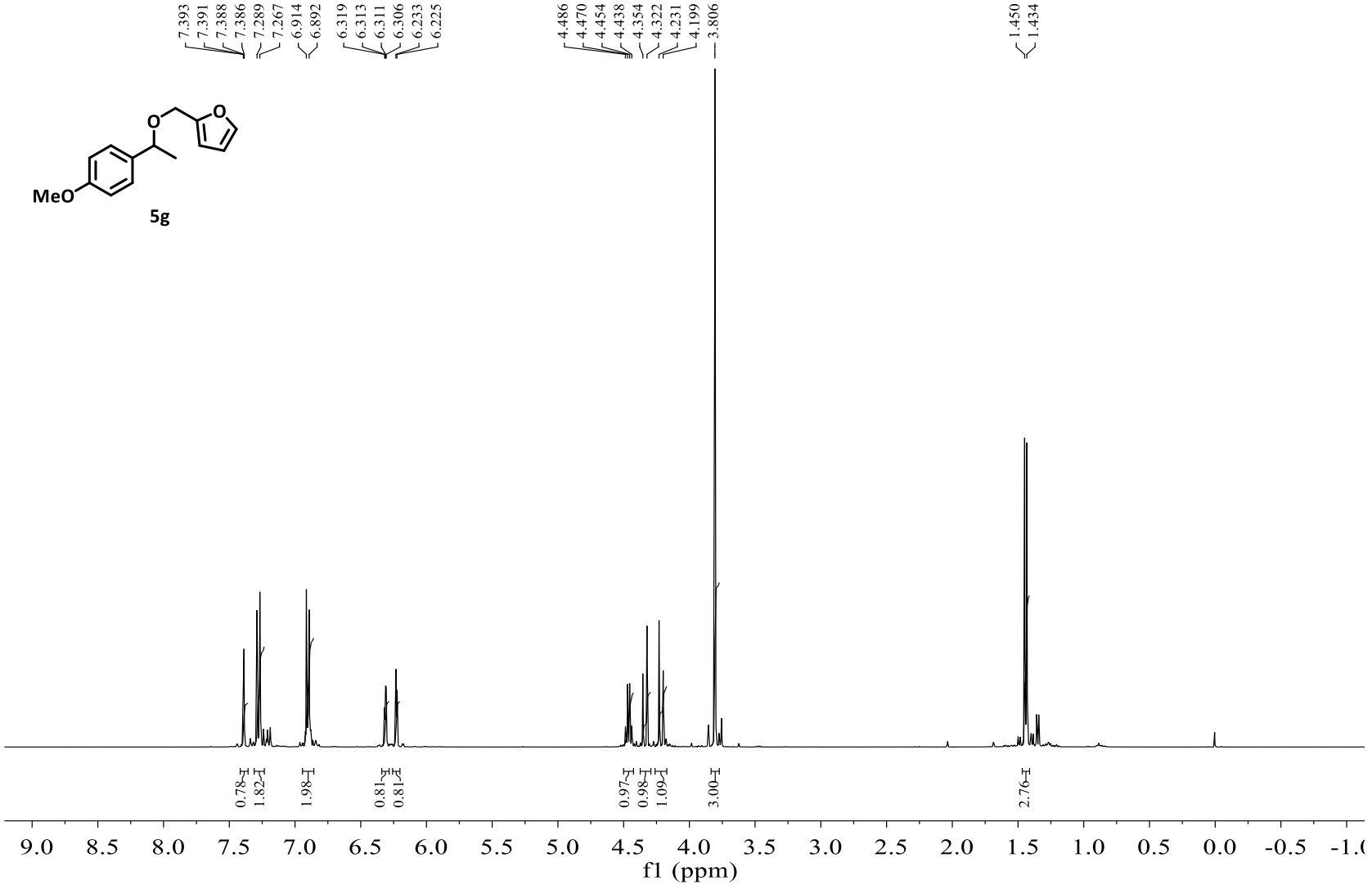

158.771
136.448
127.252
113.645
77.435
74.391
55.179
38.172
30.255
30.143
26.654
25.907
25.845
24.167
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

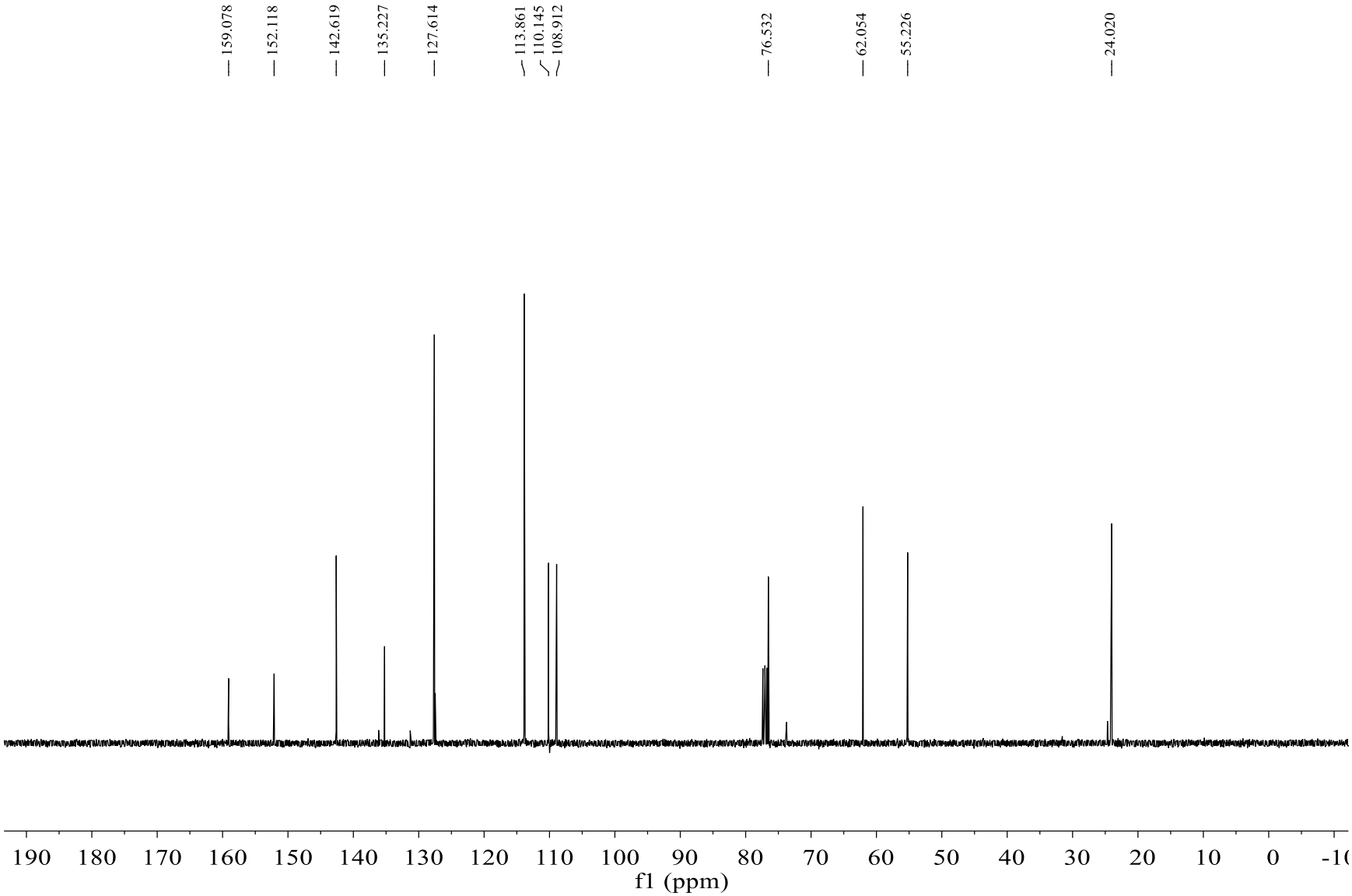
(5f) 1-{[1-(4-Methoxyphenyl)ethoxy]methyl}tricyclo[3.3.1.1^{3,7}]-decane



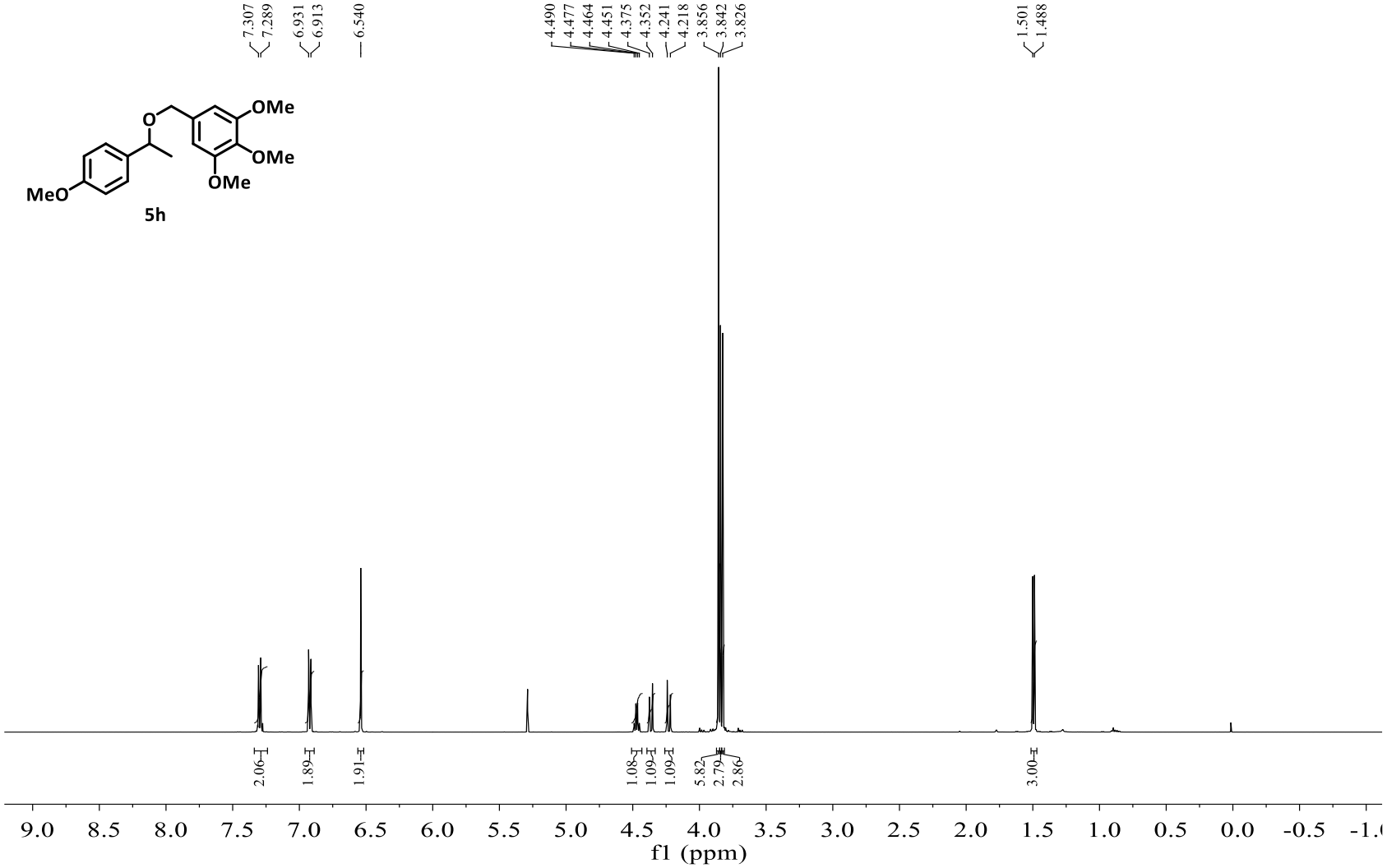

158.657
136.857
127.199
113.576
79.411
77.696
55.170
39.765
37.277
33.972
28.338
24.185
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

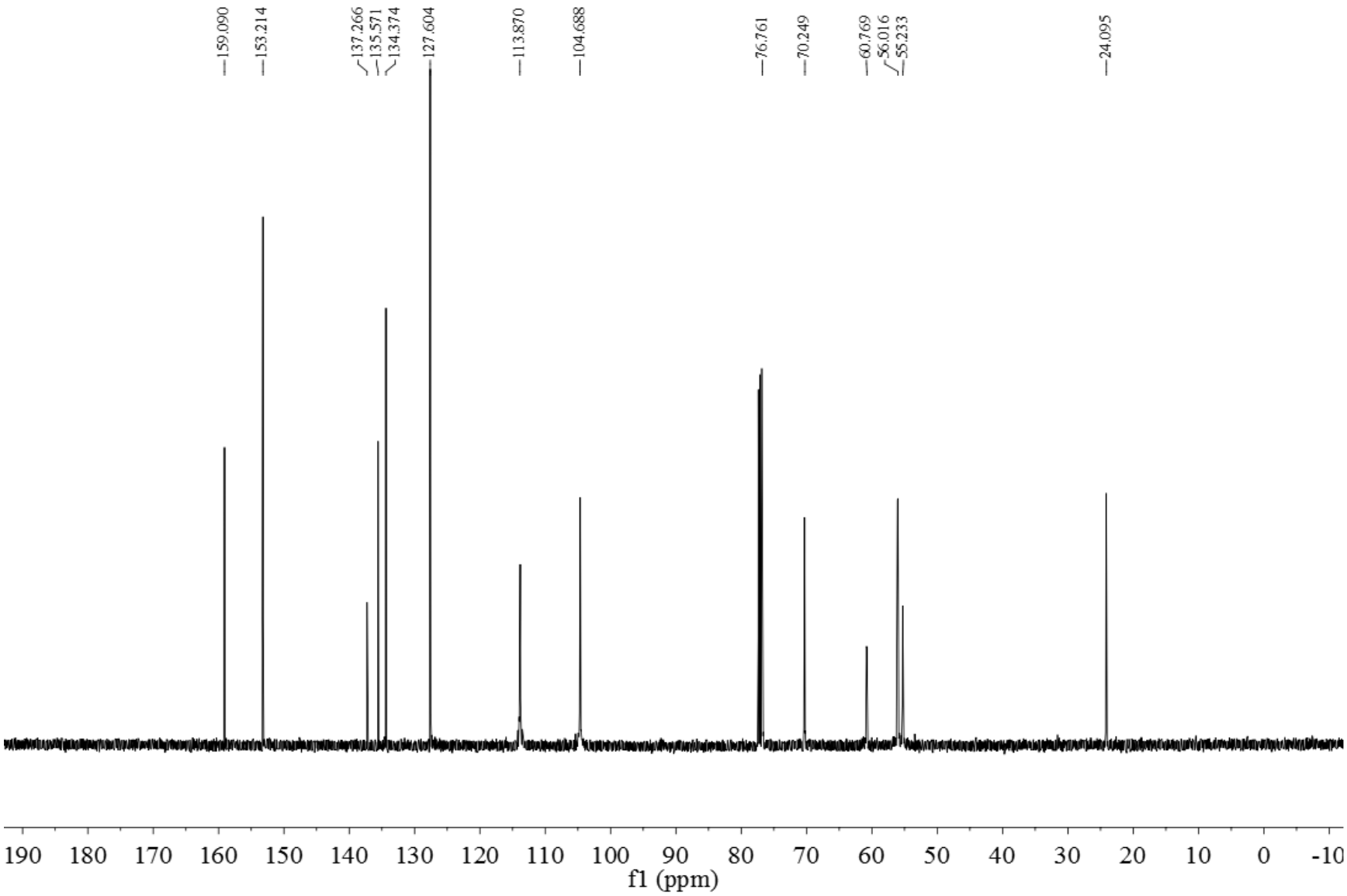
(5g) 2-{[1-(4-Methoxyphenyl)ethoxy]methyl}furan



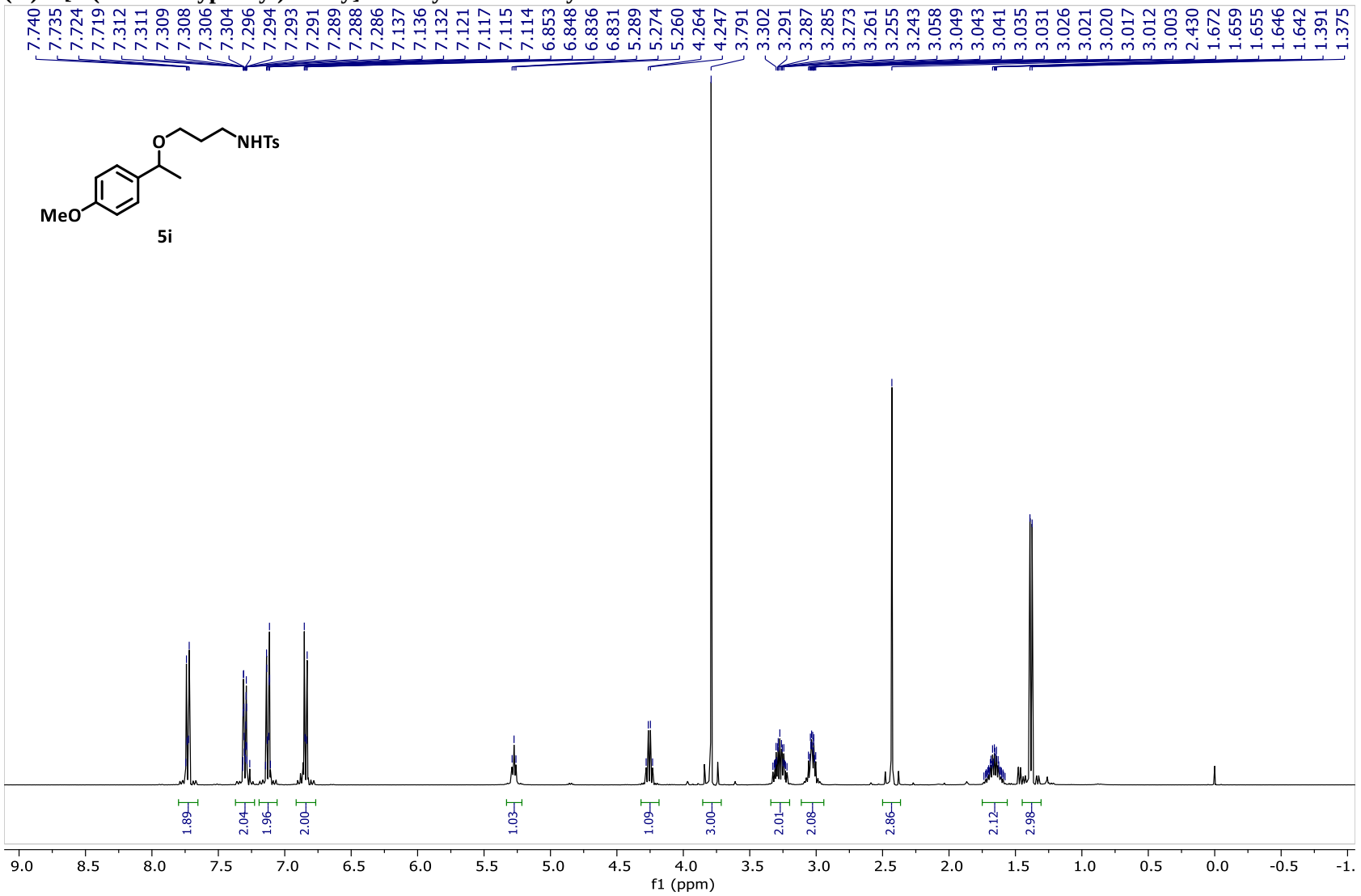

159.078
152.118
142.619
135.227
127.614
113.861
110.145
108.912
76.532
62.054
55.226
24.020
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

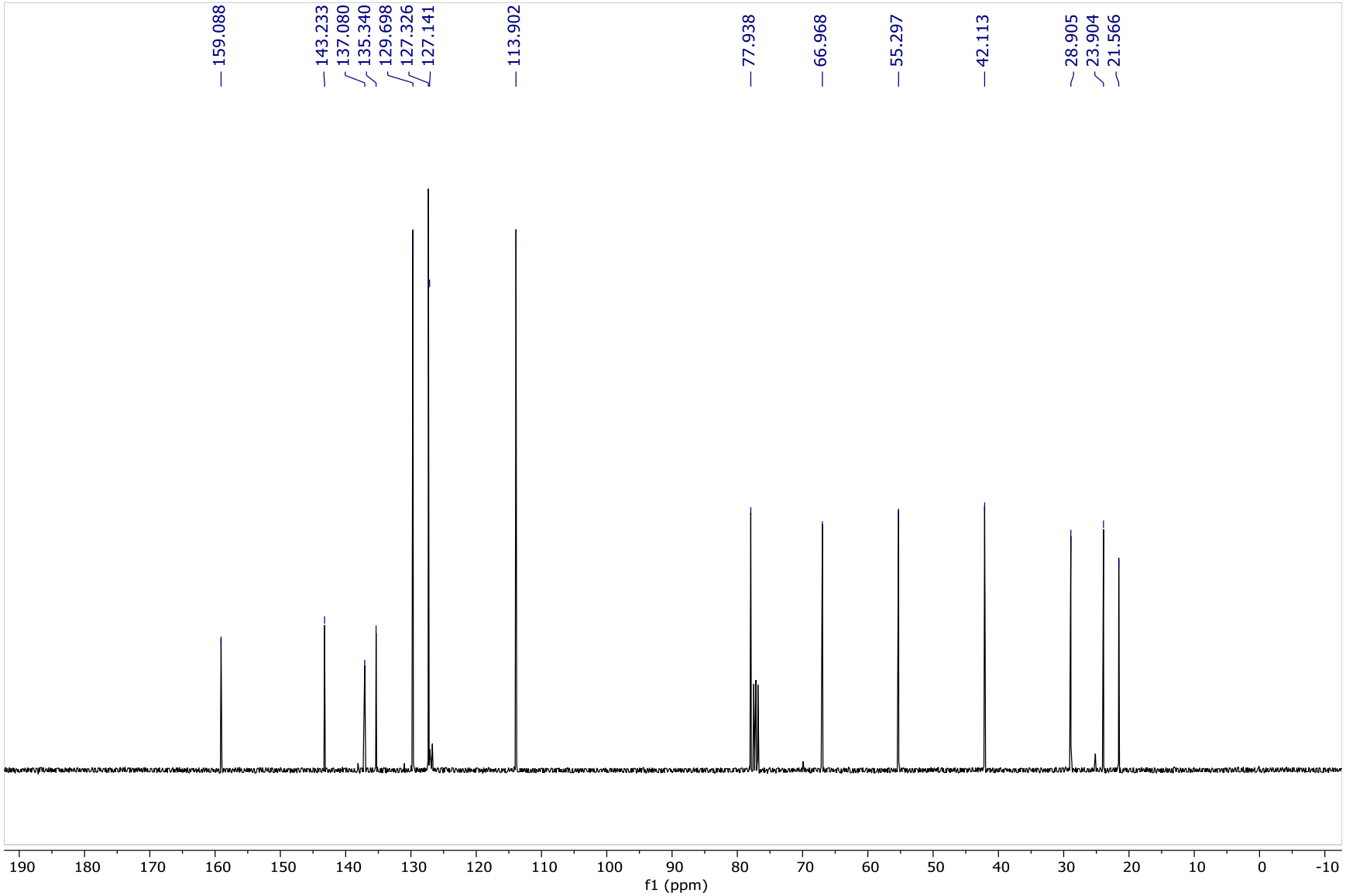
(5h) 1,2,3-Trimethoxy-5-{[1-(4-methoxyphenyl)ethoxy]methyl}benzene



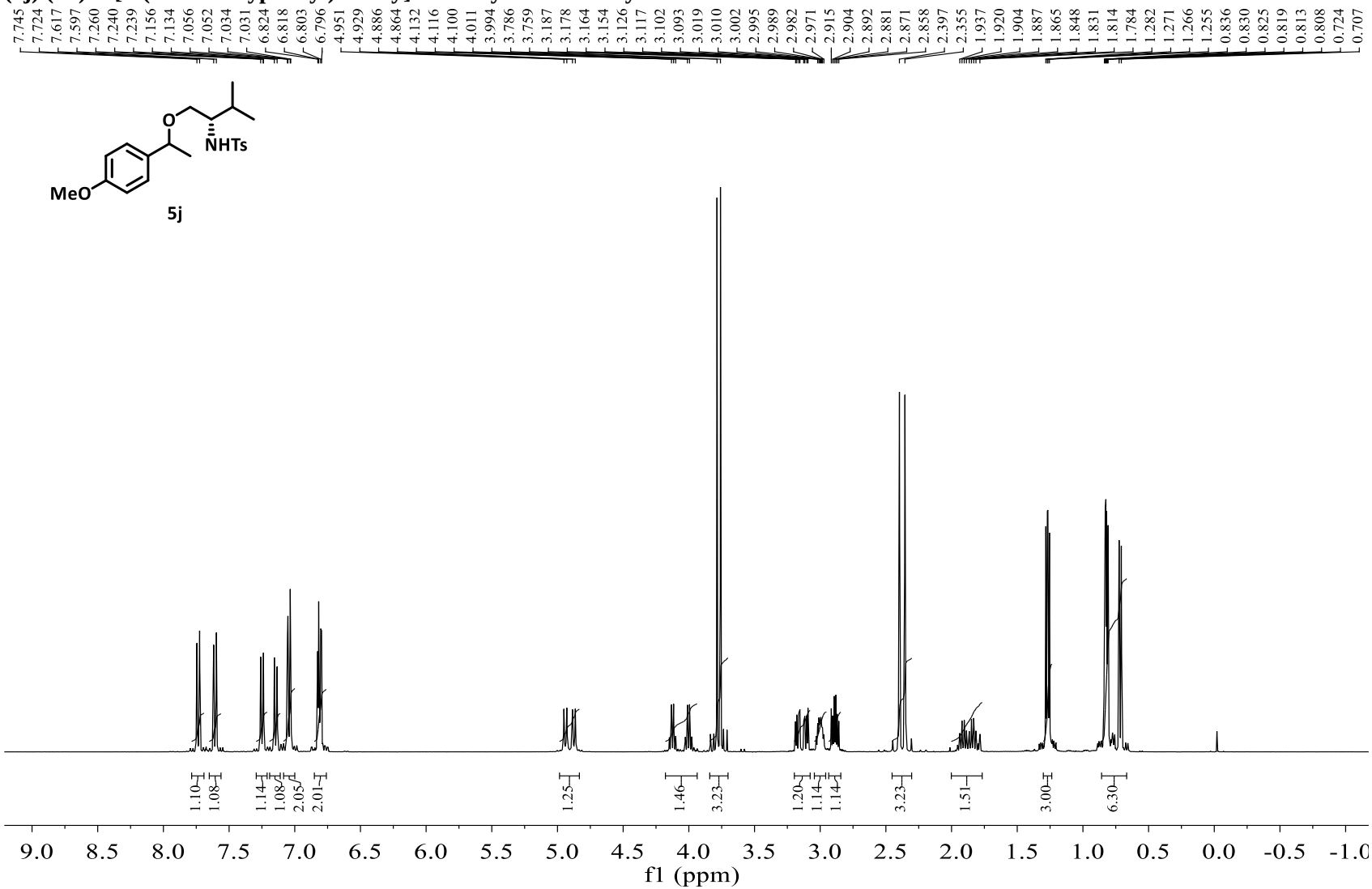

159.090
153.214
137.266
135.571
134.374
127.604
113.870
104.688
76.761
70.249
60.769
56.016
55.233
24.095
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

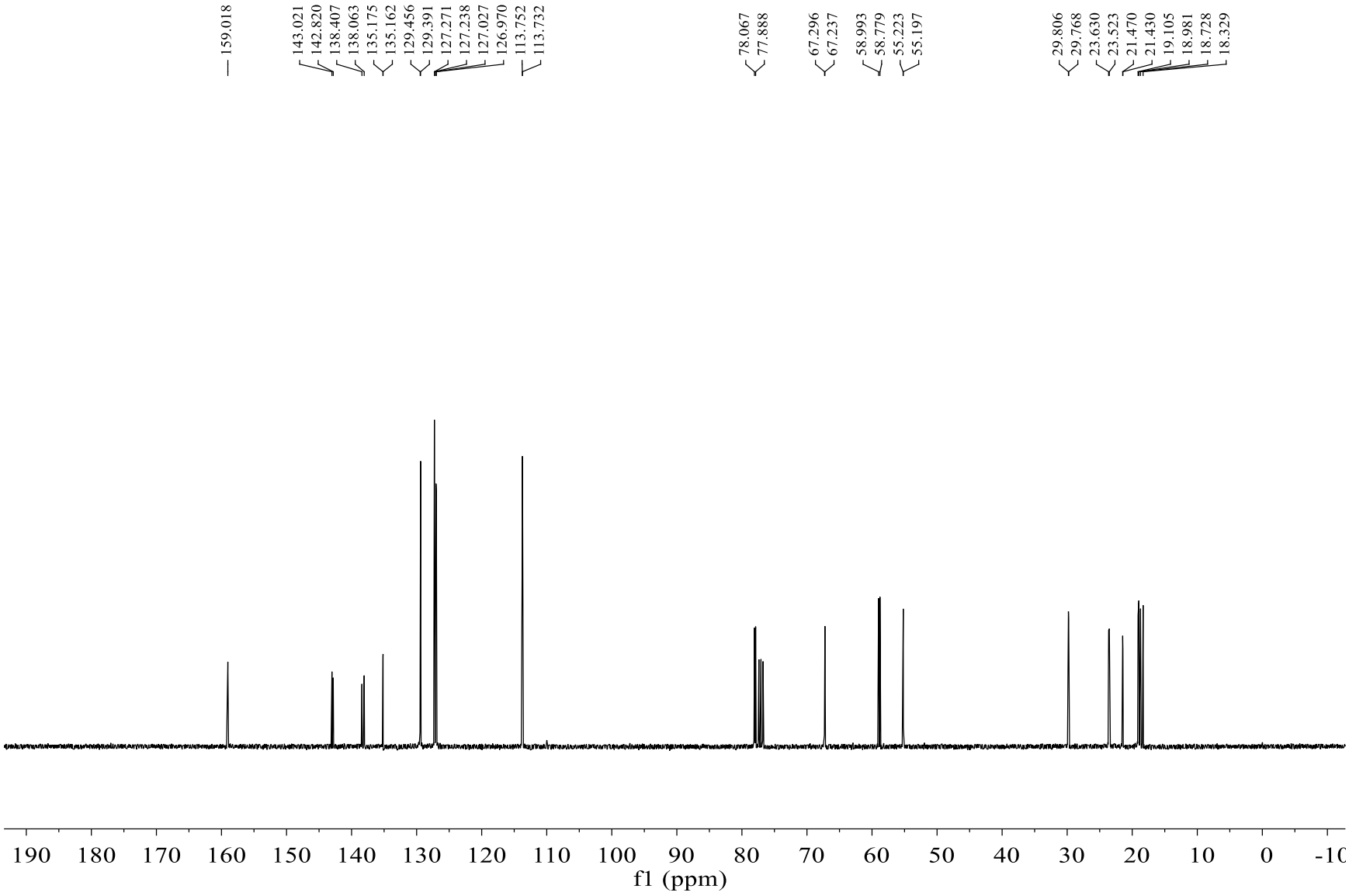
(5i) 1-[1-(4-Methoxyphenyl)ethoxy]3-methylbutan-2-tosylamine



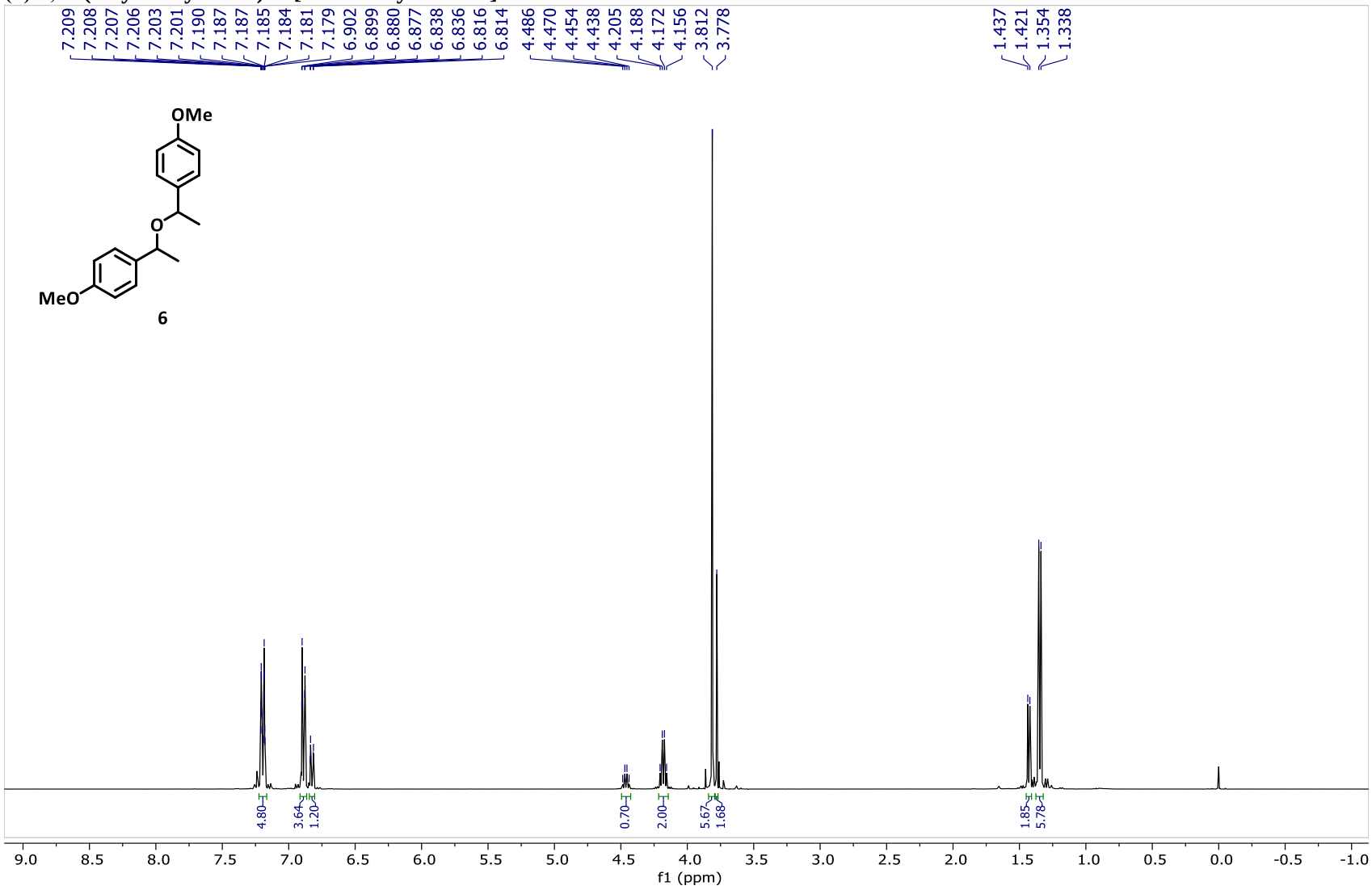

159.088
143.233
137.080
135.340
129.698
127.326
127.141
113.902
77.938
66.968
55.297
42.113
28.905
23.904
21.566
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

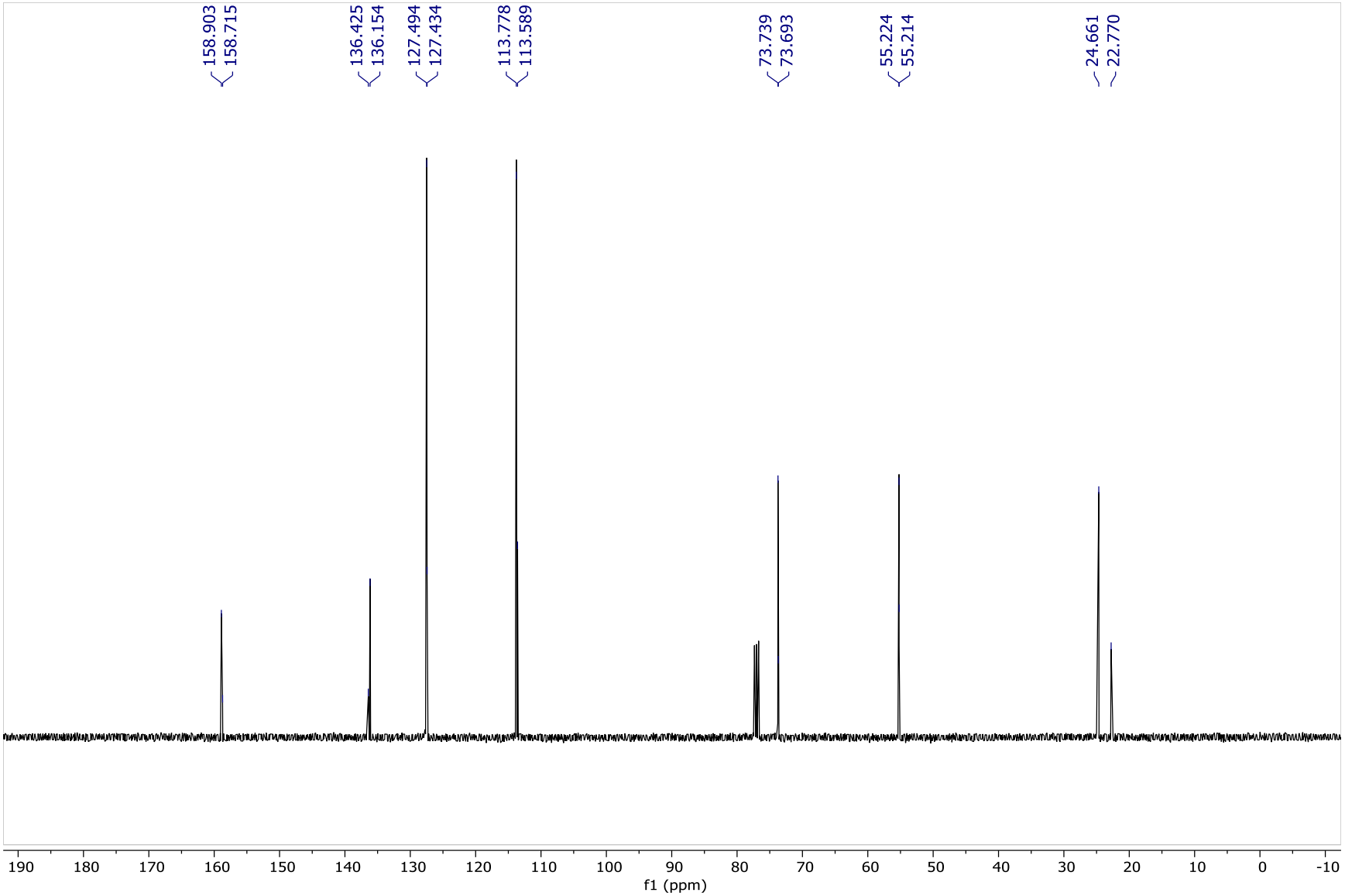
(5j) (2*S*)-1-[1-(4-Methoxyphenyl)ethoxy]-3-methylbutan-2-tosylamine



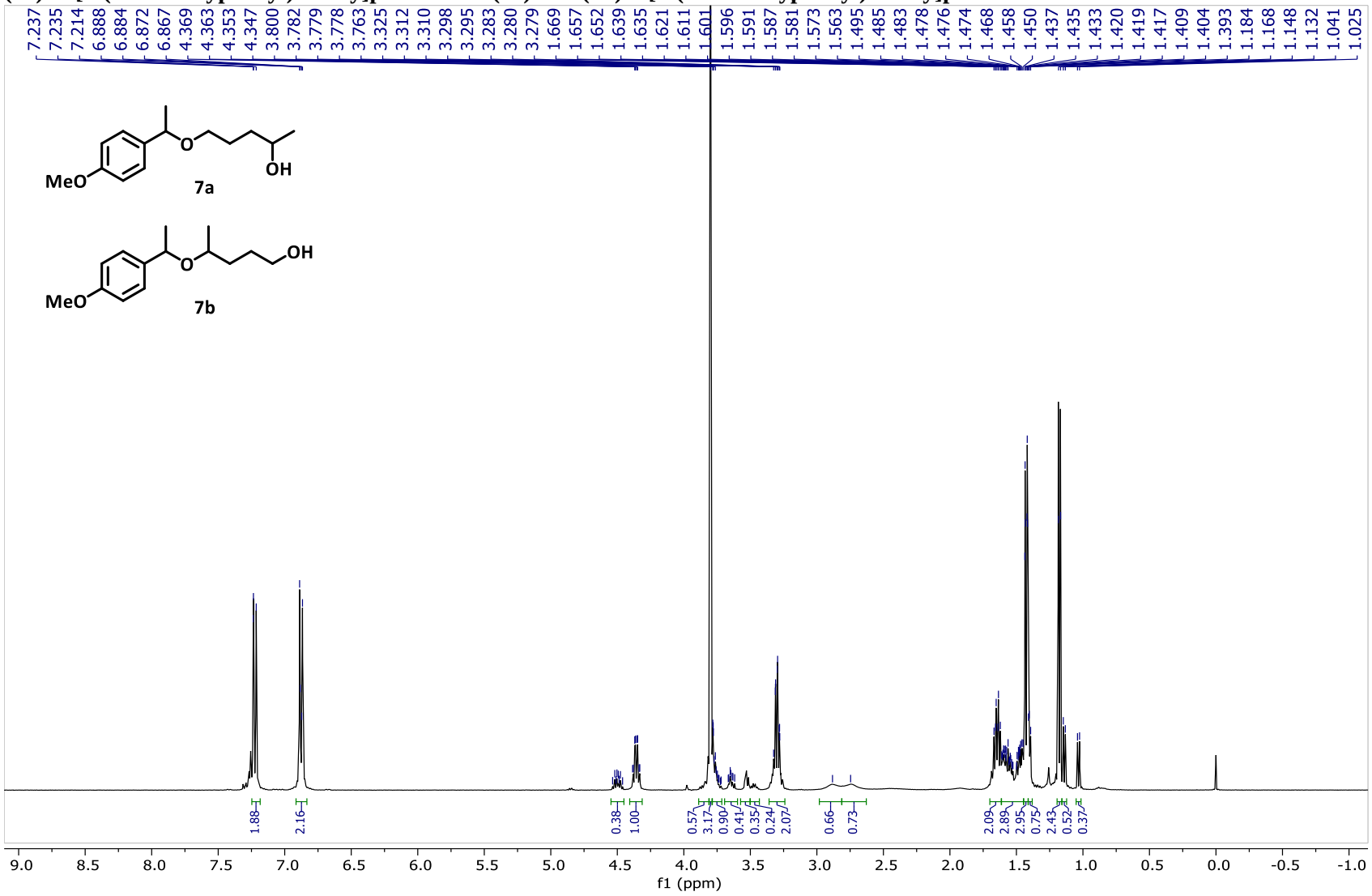

159.018
143.021
142.820
138.407
138.063
135.175
135.162
129.456
129.391
127.271
127.238
127.027
126.970
113.752
113.732
78.067
77.888
67.296
67.237
58.993
58.779
55.223
55.197
29.806
29.768
23.630
23.523
21.470
21.430
19.105
18.981
18.728
18.329
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

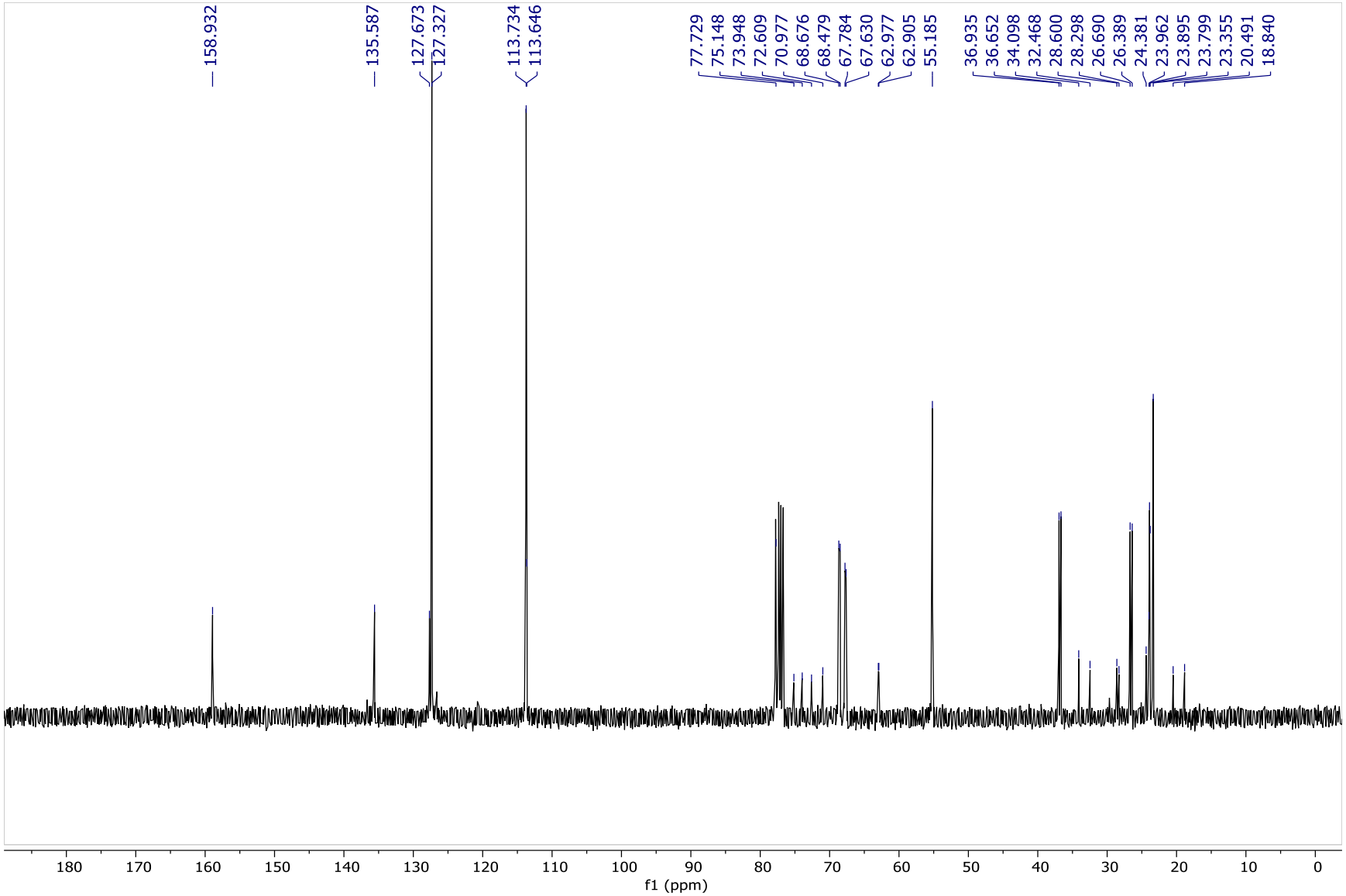
(6) 1,1'-(Oxydiethylidene)bis[4-methoxybenzene]



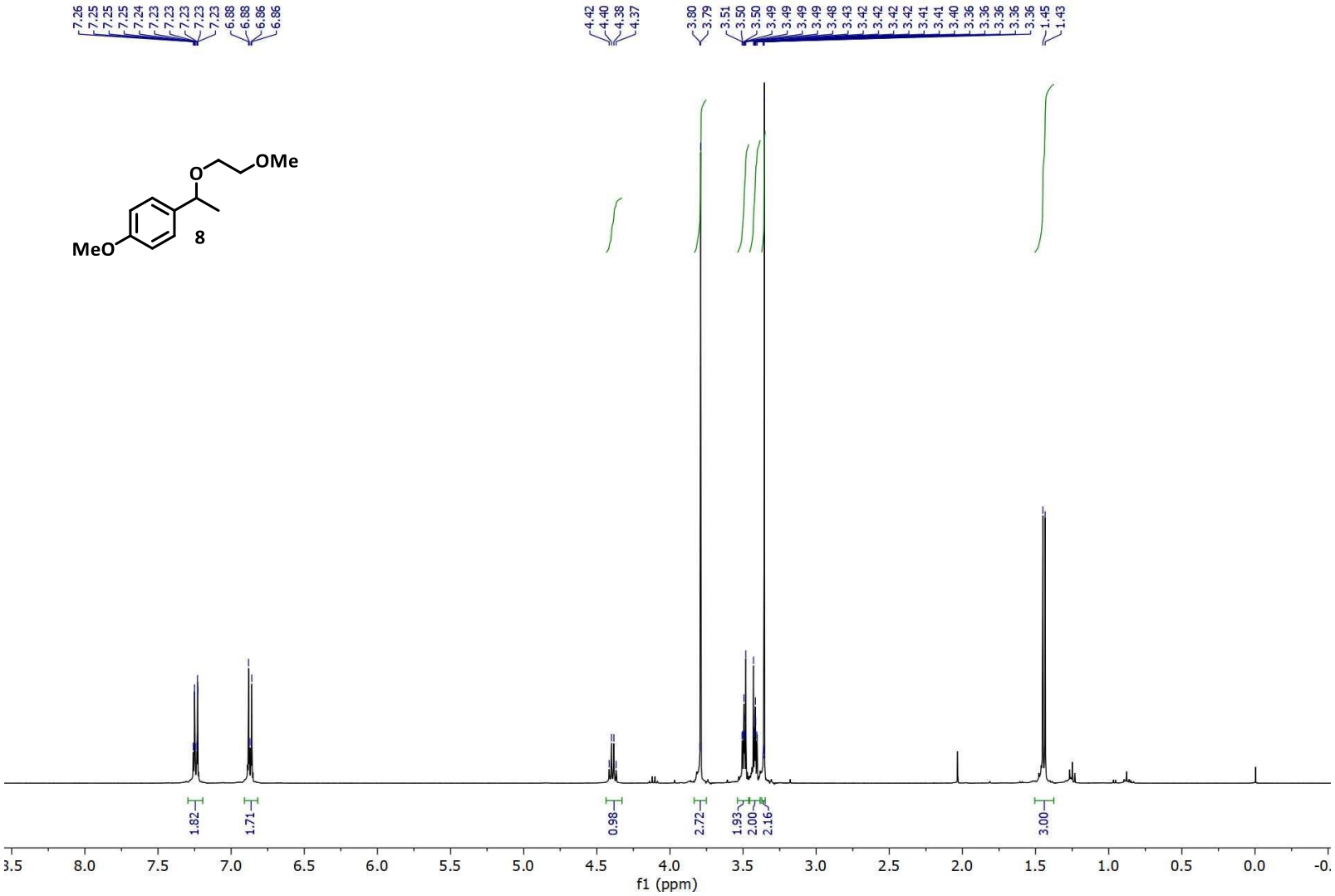

158.903
158.715
136.425
136.154
127.494
127.434
113.778
113.589
73.739
73.693
55.224
55.214
24.661
22.770
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

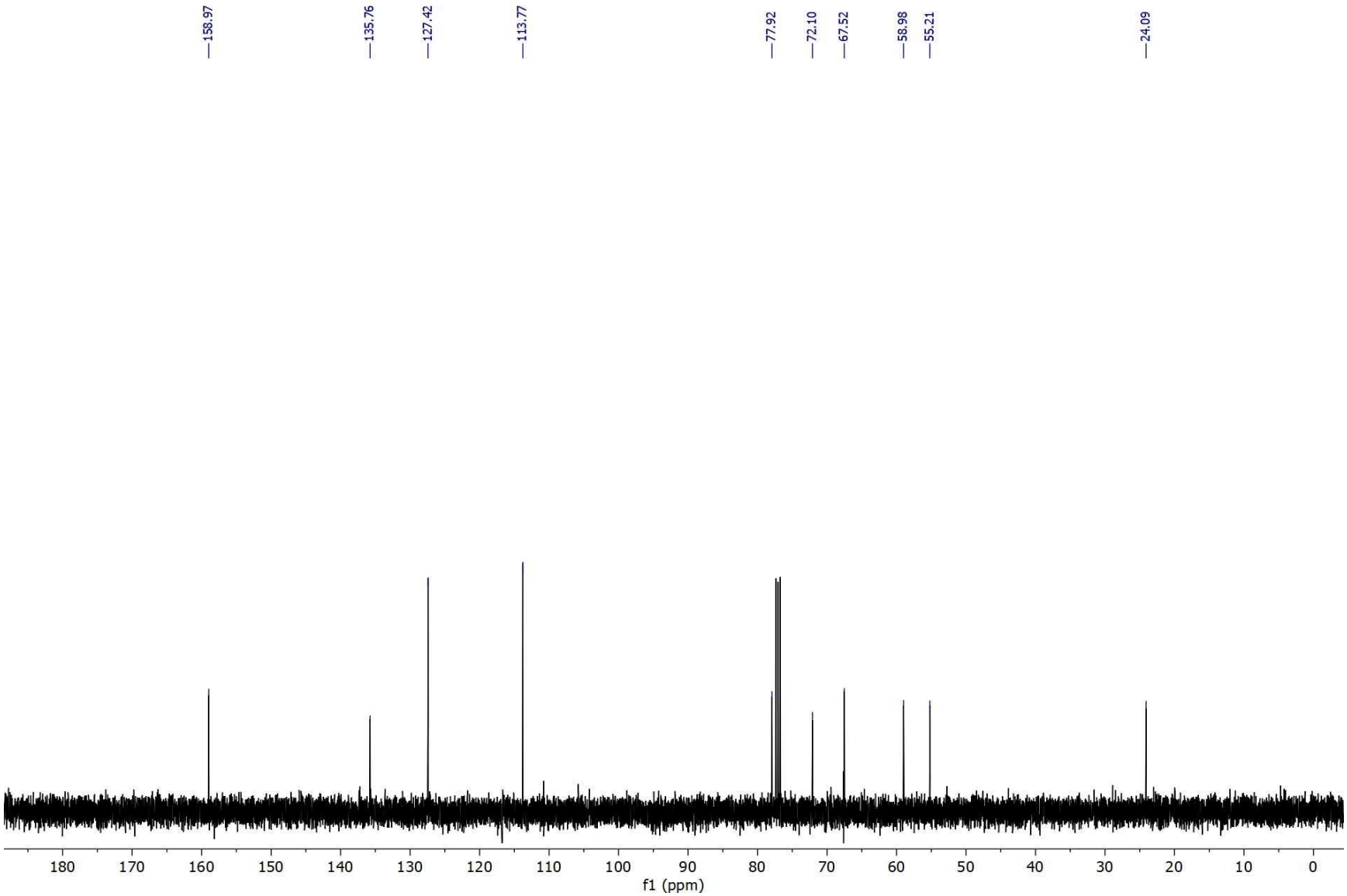
(7a) 5-[1-(4-methoxyphenyl)ethoxy]pentan-2-ol (7a) and (7b) 4-[1-(4-methoxyphenyl)ethoxy]pentan-1-ol



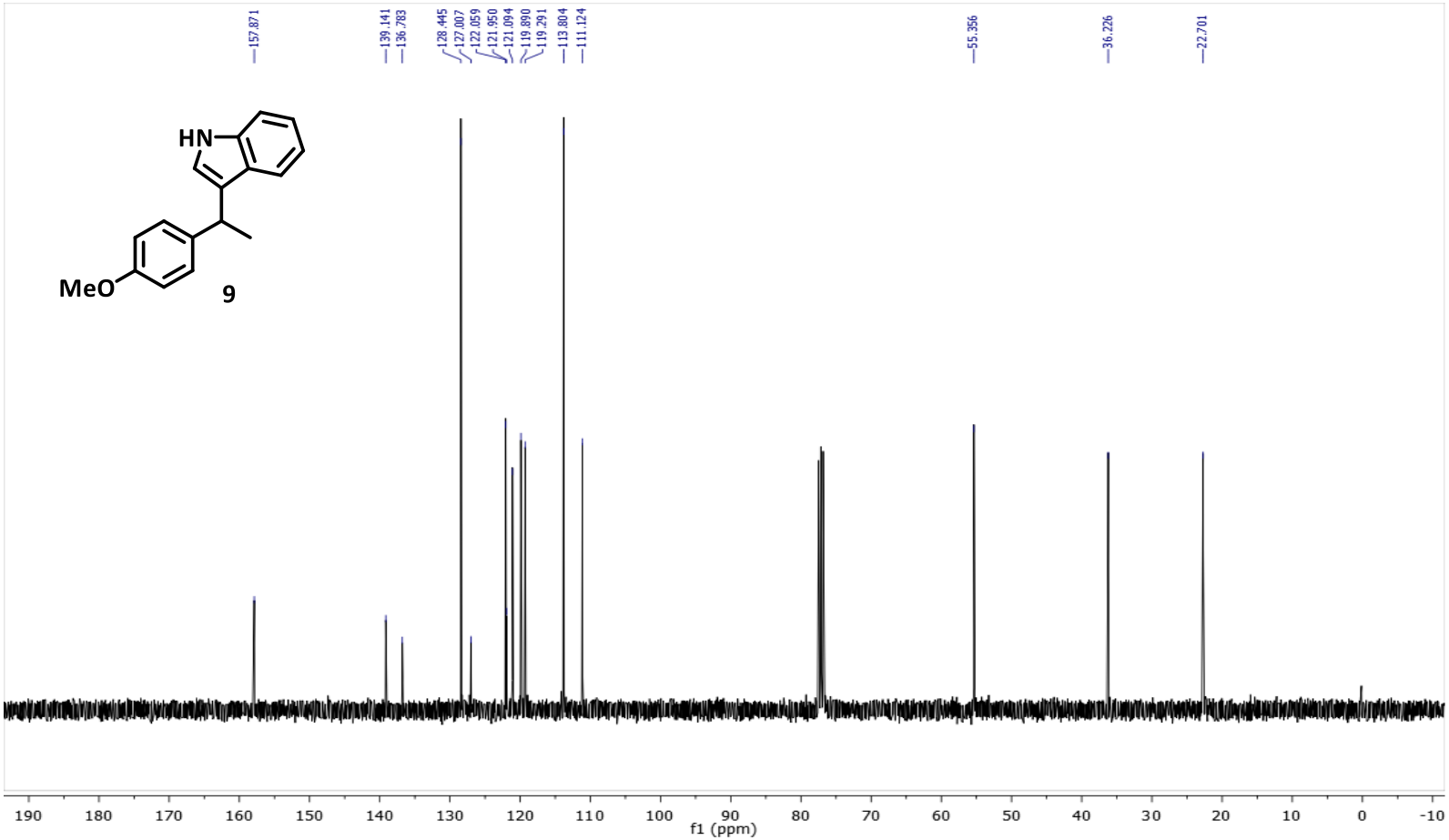

158.932
135.587
127.673
127.327
113.734
113.646
77.729
75.148
73.948
72.609
70.977
68.676
68.479
67.784
67.630
62.977
62.905
55.185
36.935
36.652
34.098
32.468
28.600
28.298
26.690
26.389
24.381
23.962
23.895
23.799
23.355
20.491
18.840
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

(8) 1-methoxy-4-[1-(2-methoxyethoxy)ethyl]benzene

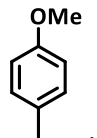


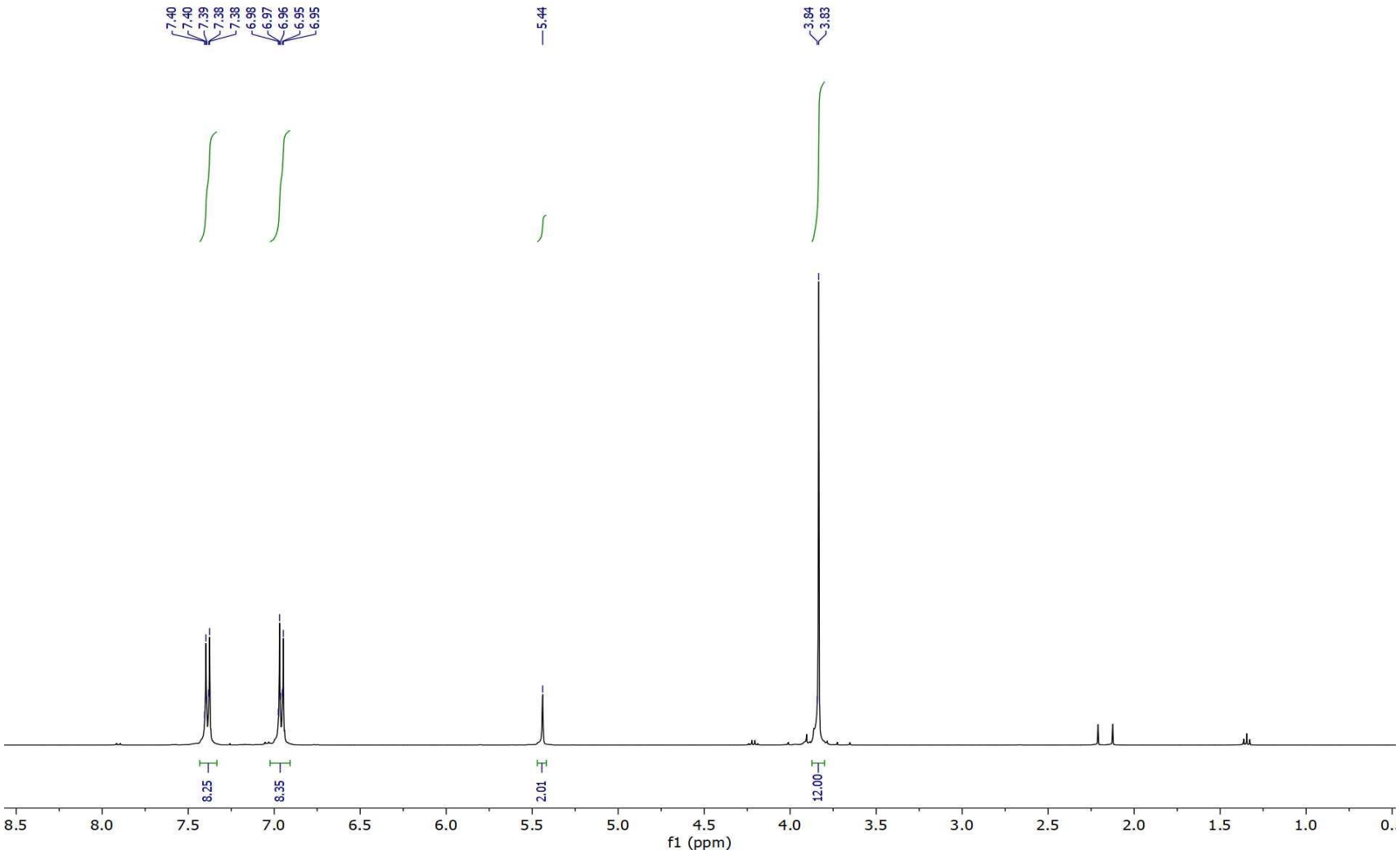

158.97
135.76
127.42
113.77
77.92
72.10
67.52
58.98
55.21
24.09
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

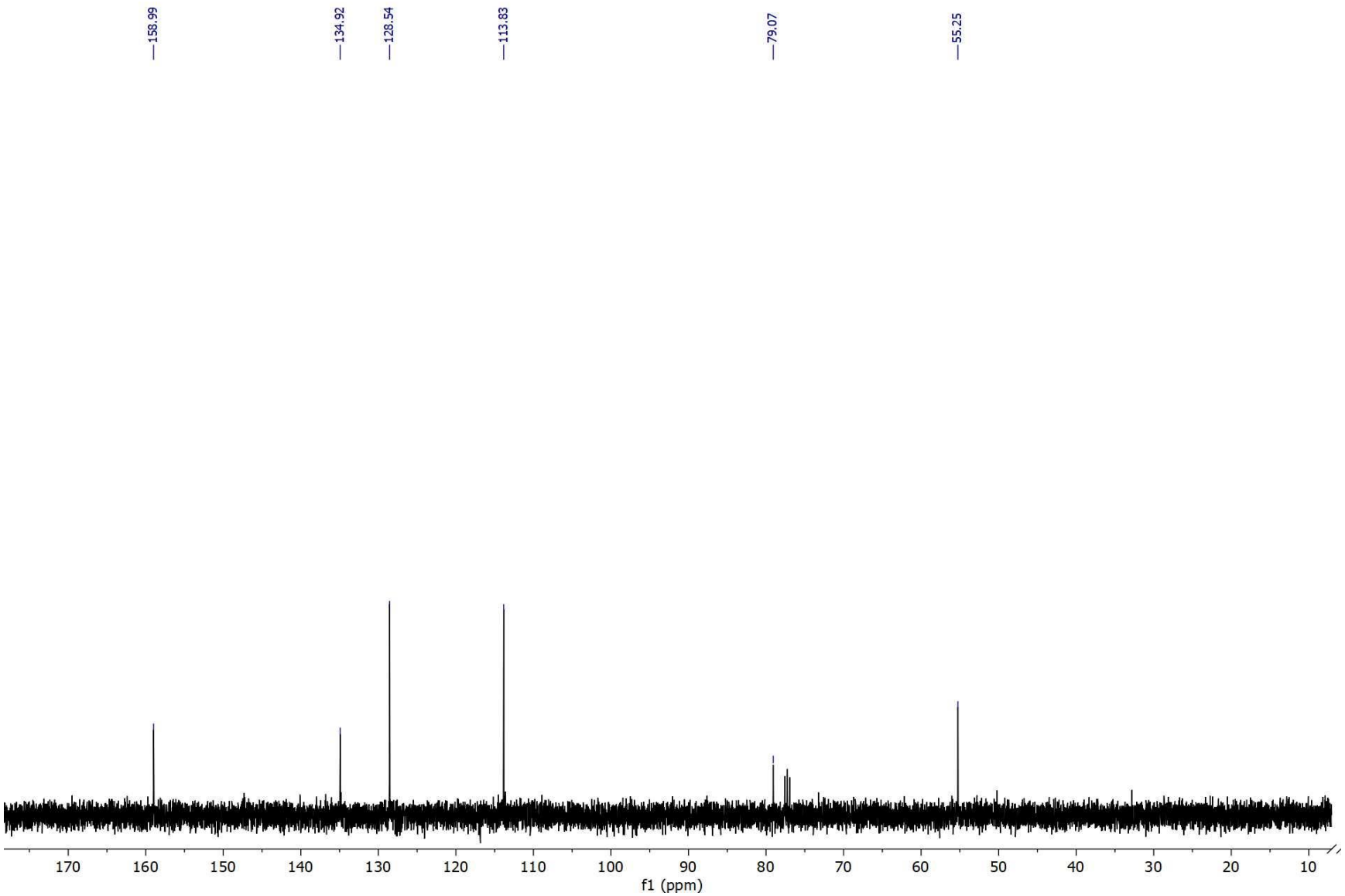
(9) 3-[1-(4-Methoxyphenyl)ethyl]-1*H*-indole



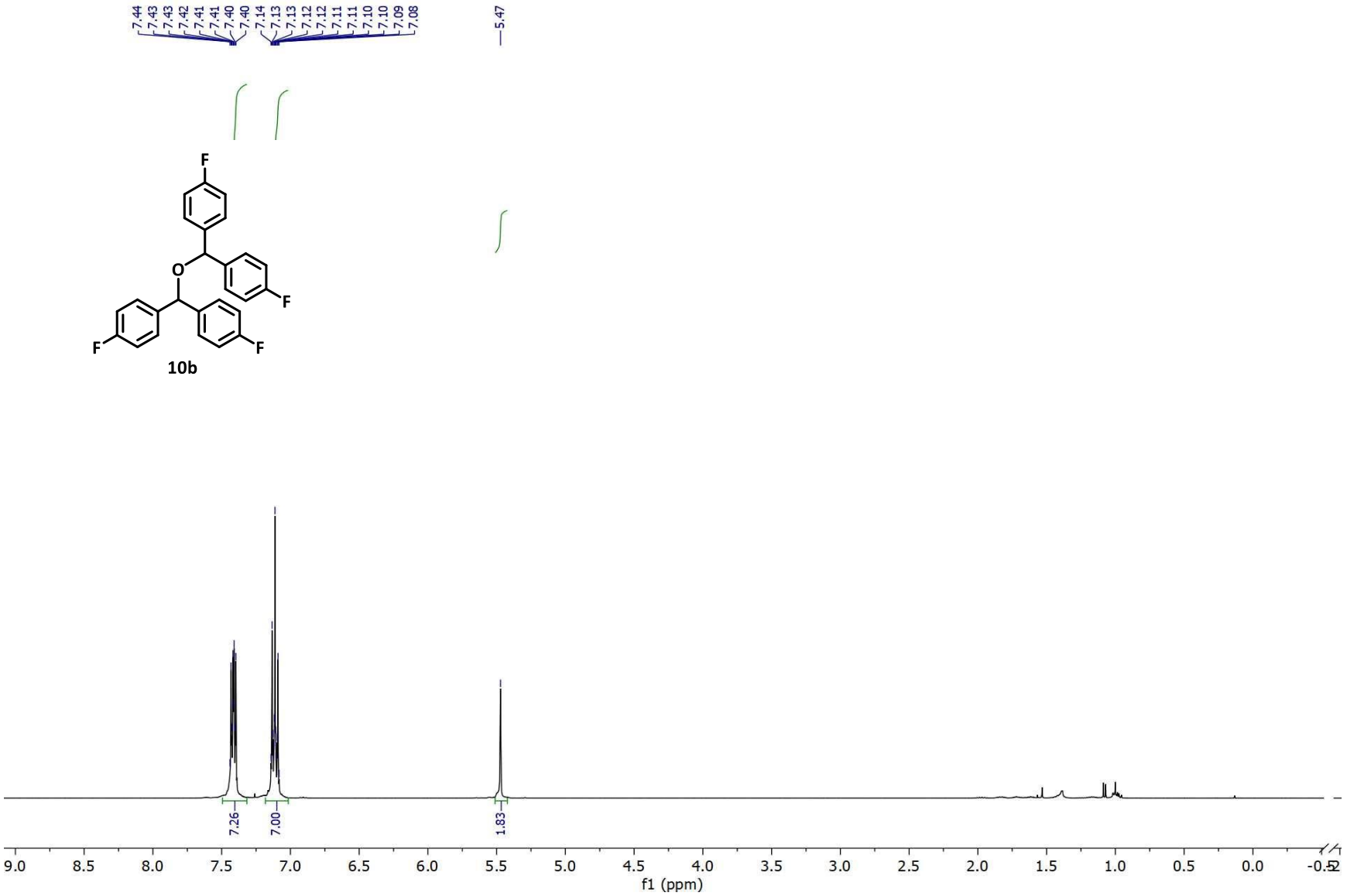
(10a) 1-{[bis(4-methoxyphenyl)methoxy](4-methoxyphenyl)methyl}-4-methoxybenzene

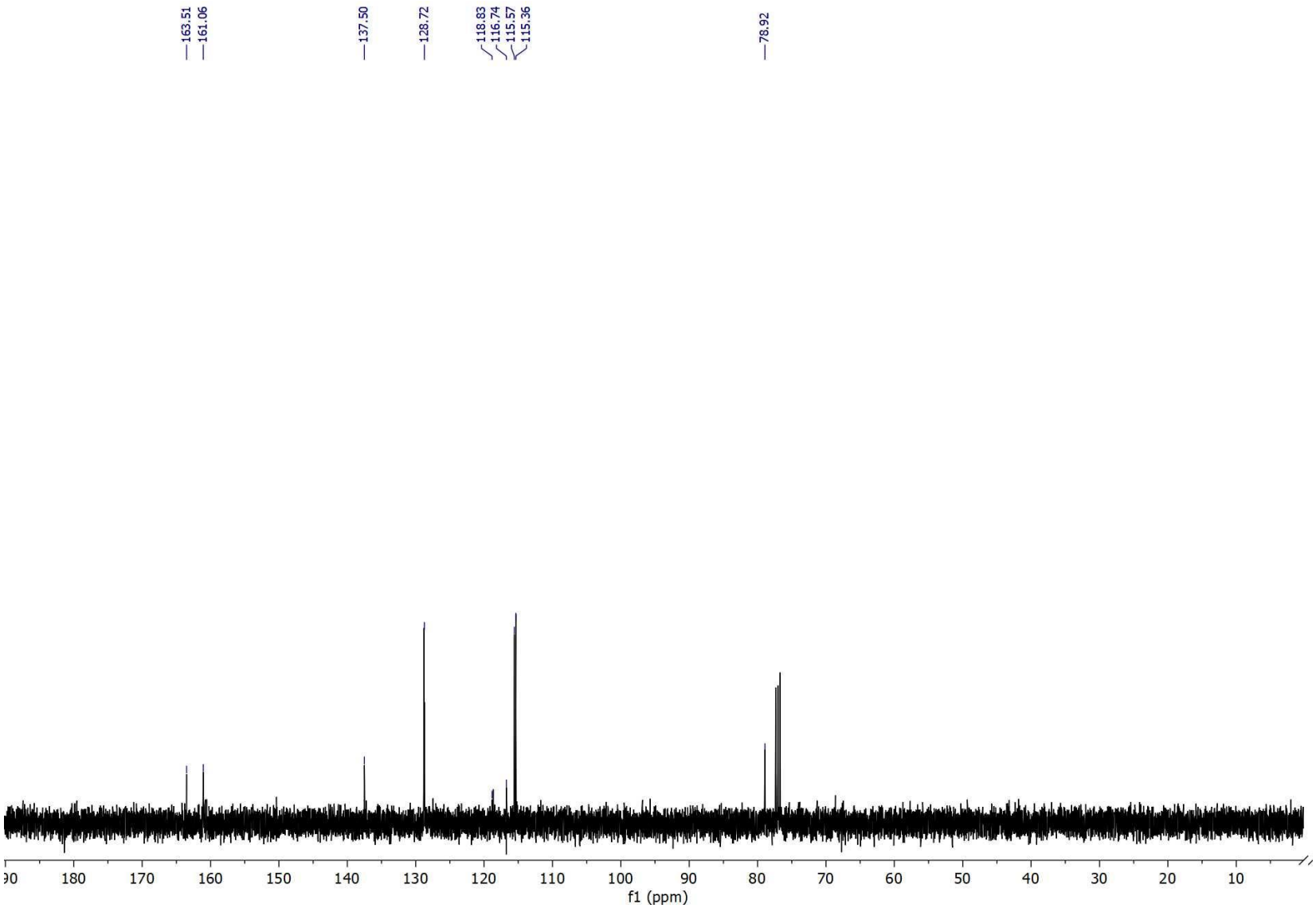



7.40
7.40
7.39
7.38
7.38
6.98
6.97
6.96
6.95
6.95
5.44
3.84
3.83
8.25
8.35
2.01
12.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


158.99
134.92
128.54
113.83
79.07
55.25
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

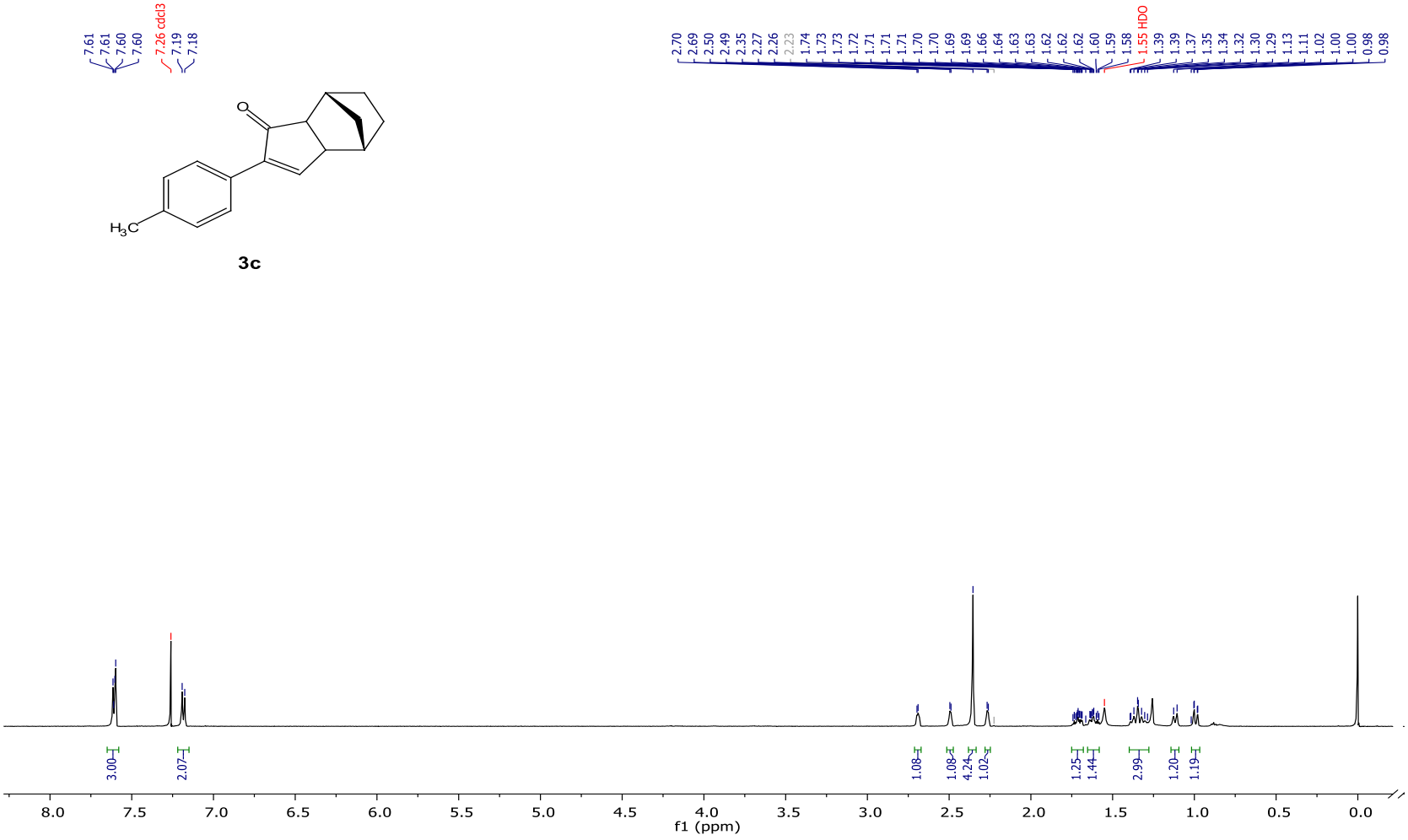
(10b) 1-{[bis(4-fluorophenyl) methoxy](4-fluorophenyl)methyl}-4-fluorobenzene

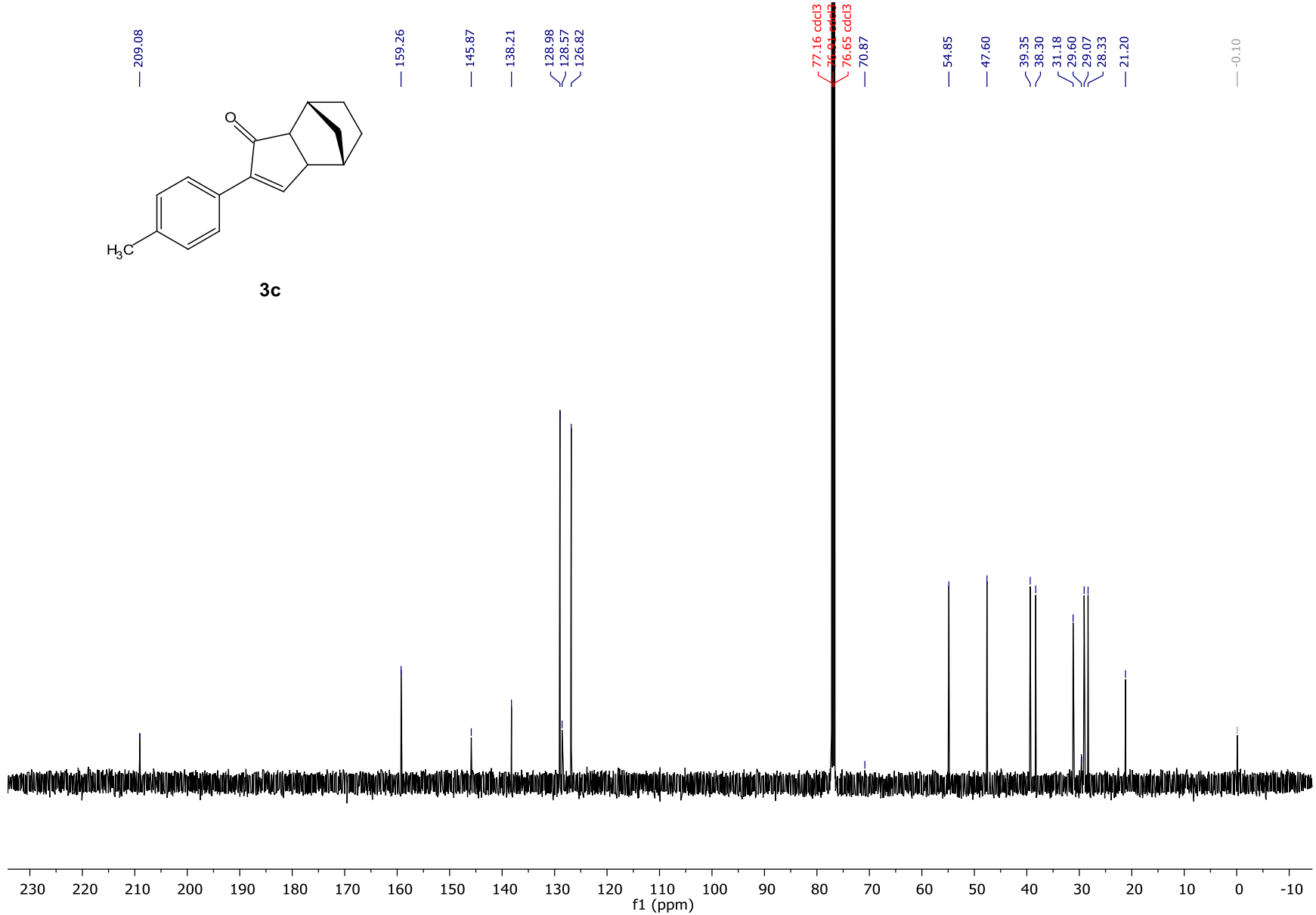



163.51
161.06
137.50
128.72
118.83
116.74
115.57
115.36
78.92
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

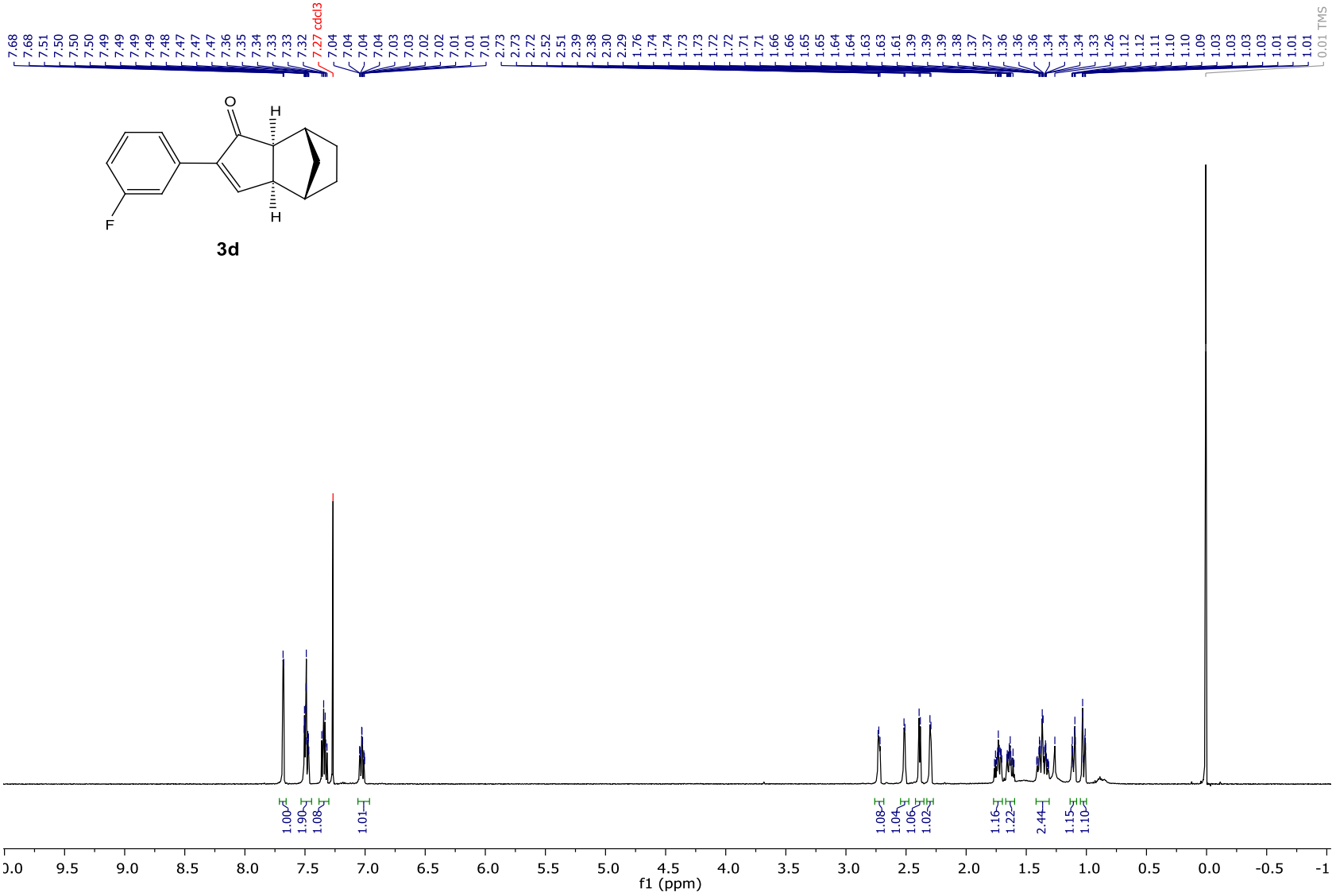
Chapter two

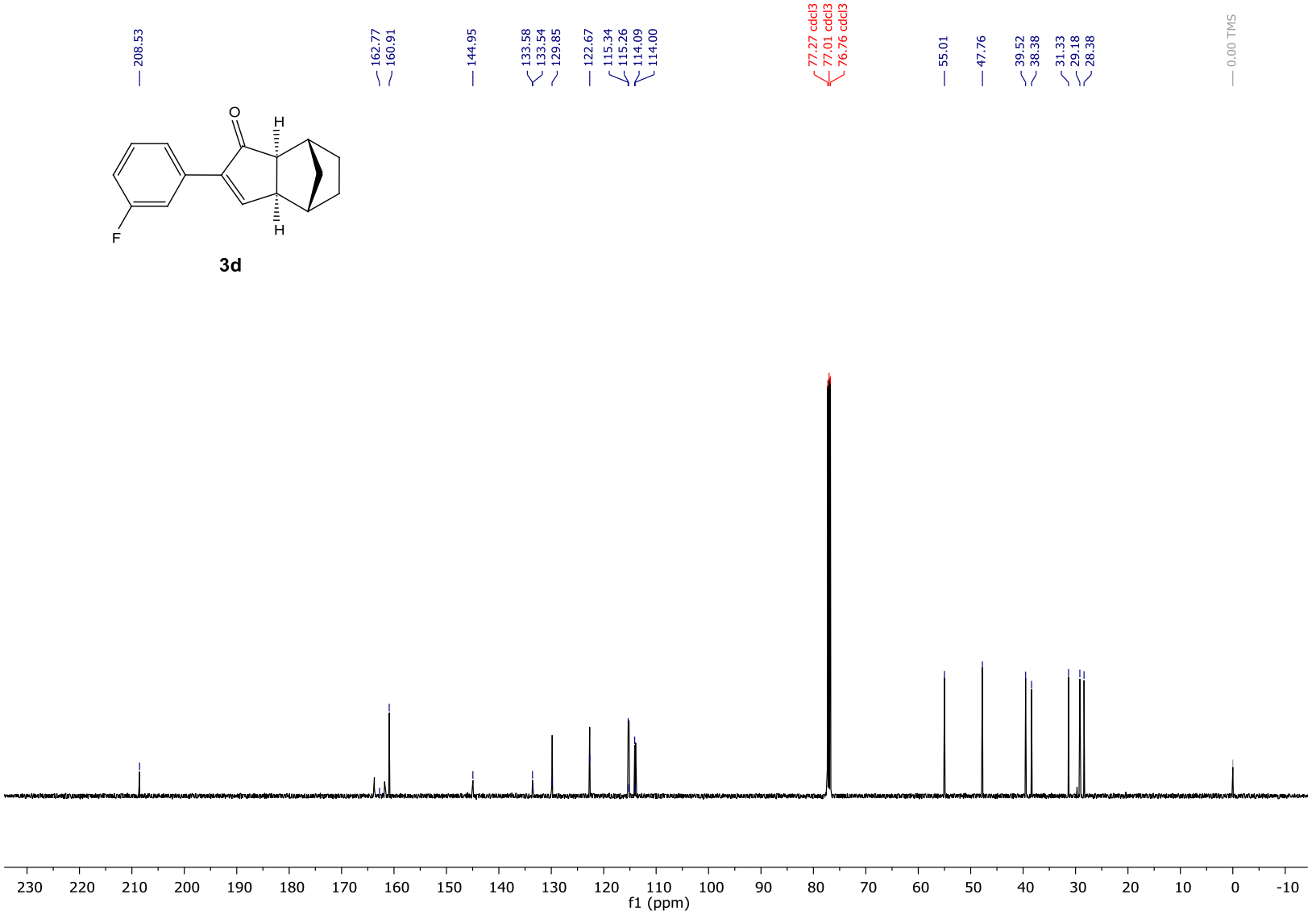
(1*R,2*S**,6*S**,7*S**)-4-(*p*-Tolyl)tricyclo[5.2.1.0^{2,6}]dec-4-en-3-one (3c)**



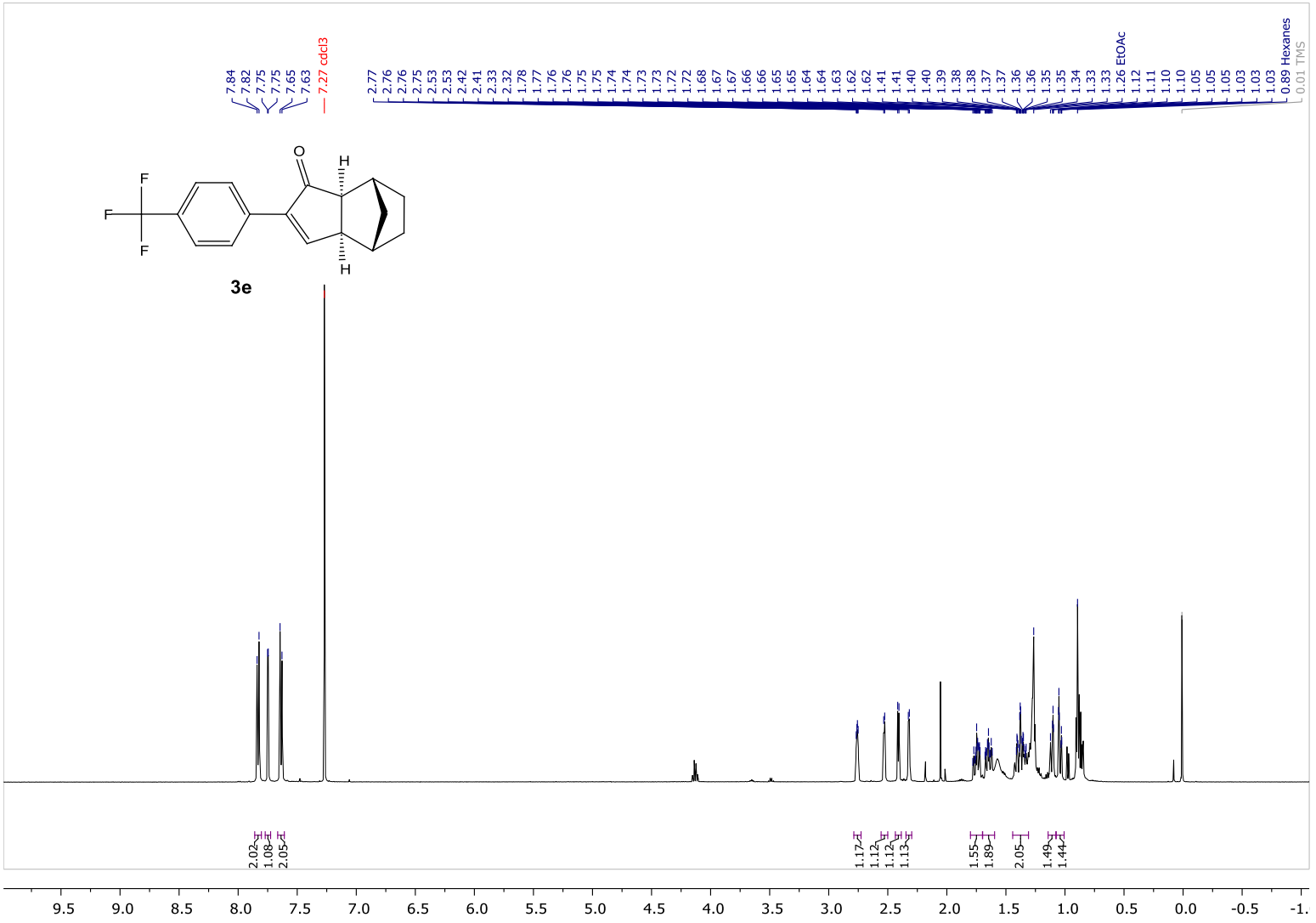

209.08
159.26
145.87
138.21
128.98
128.57
126.82
77.16 cdcl3
76.65 cdcl3
70.87
54.85
47.60
39.35
38.30
31.18
29.60
29.07
28.33
21.20
-0.10
O
H3C
3c
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

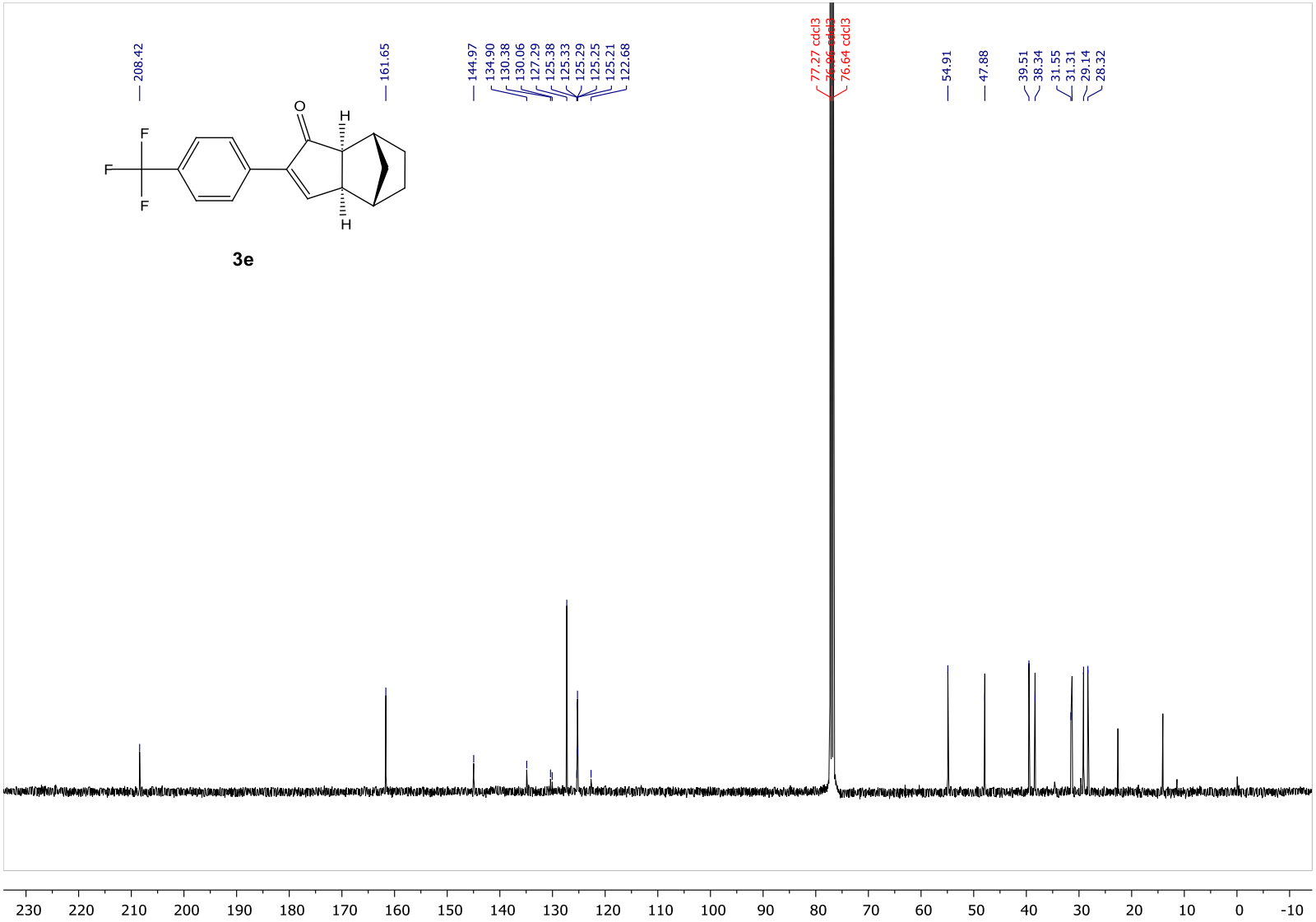
(1*R,2*S**,6*S**,7*S**)-4-(*m*-Fluorophenyl)tricyclo[5.2.1.0^{2,6}]dec-4-en-3-one (3d)**



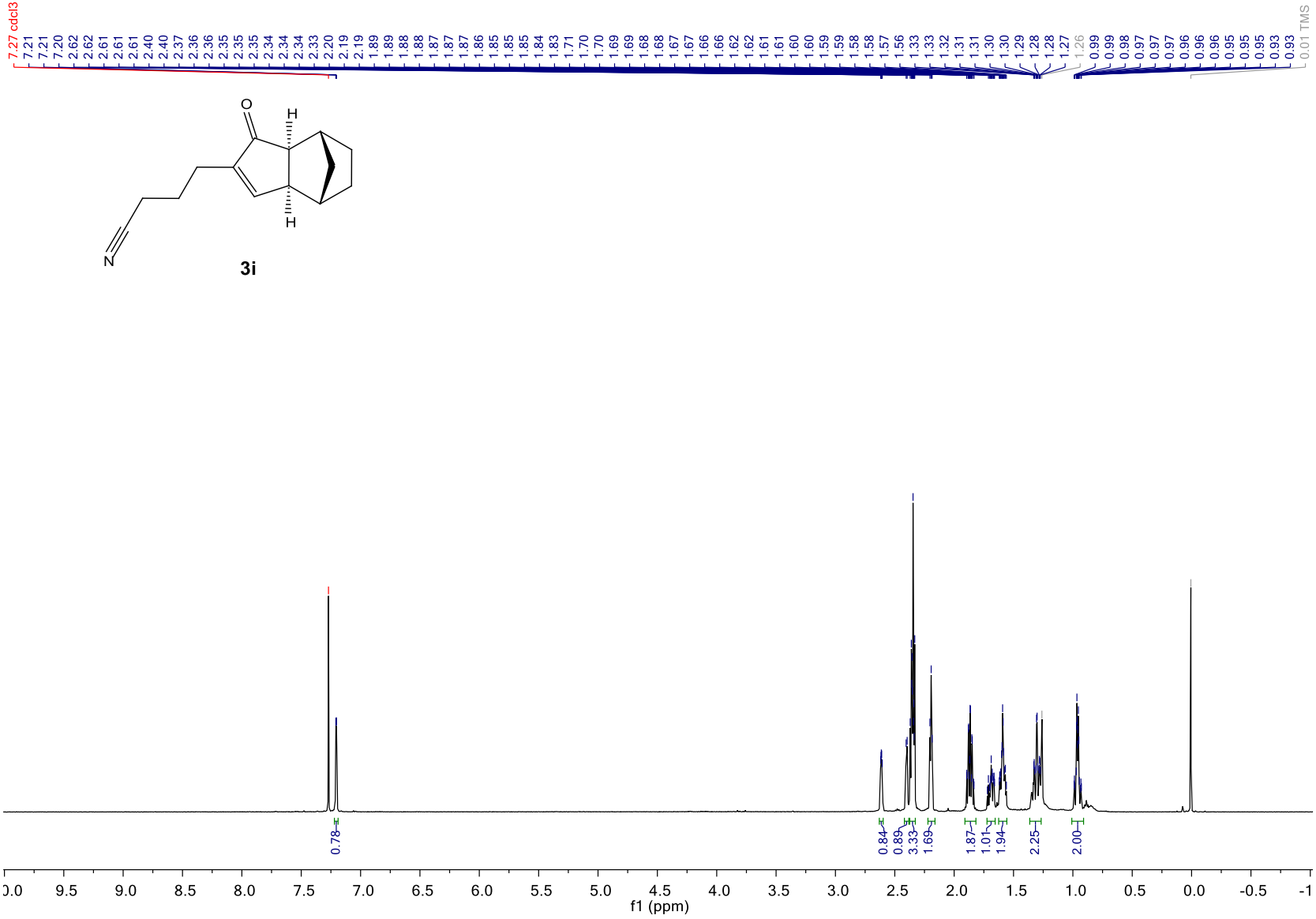

208.53
162.77
160.91
144.95
133.58
133.54
129.85
122.67
115.34
115.26
114.09
114.00
77.27 cdcl3
77.01 cdcl3
76.76 cdcl3
55.01
47.76
39.52
38.38
31.33
29.18
28.38
0.00 TMS
O
H
H
F
3d
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

(1*R,2*S**,6*S**,7*S**)-4-[*p*-(Trifluoromethyl)phenyl]tricyclo[5.2.1.0^{2,6}]dec-4-en-3-one (3e)**

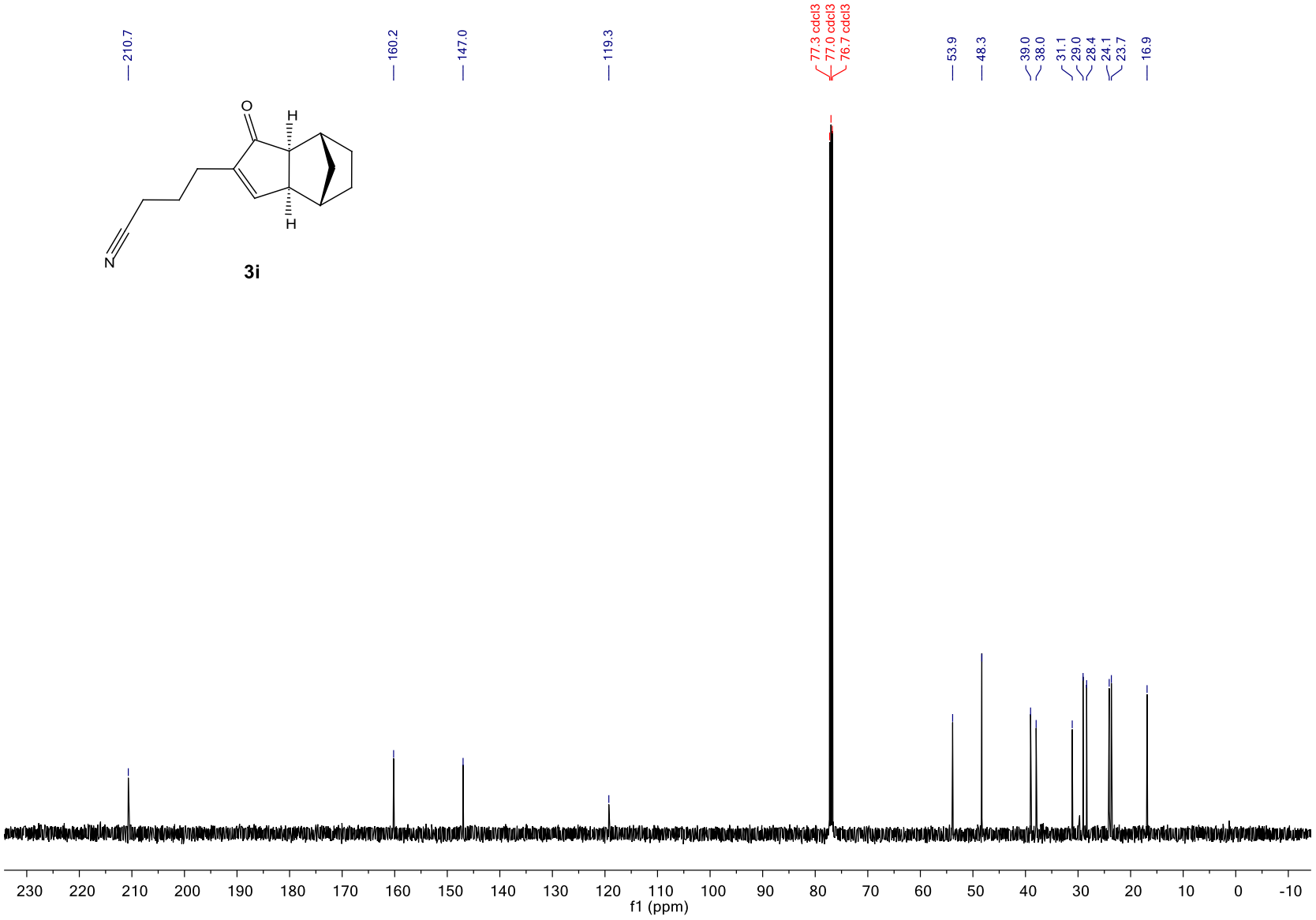



208.42
161.65
144.97
134.90
130.38
130.06
127.29
125.38
125.33
125.29
125.25
125.21
122.68
77.27 cdcl3
76.64 cdcl3
54.91
47.88
39.51
38.34
31.55
31.31
29.14
28.32
O
H
F
F
F
H
3e
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

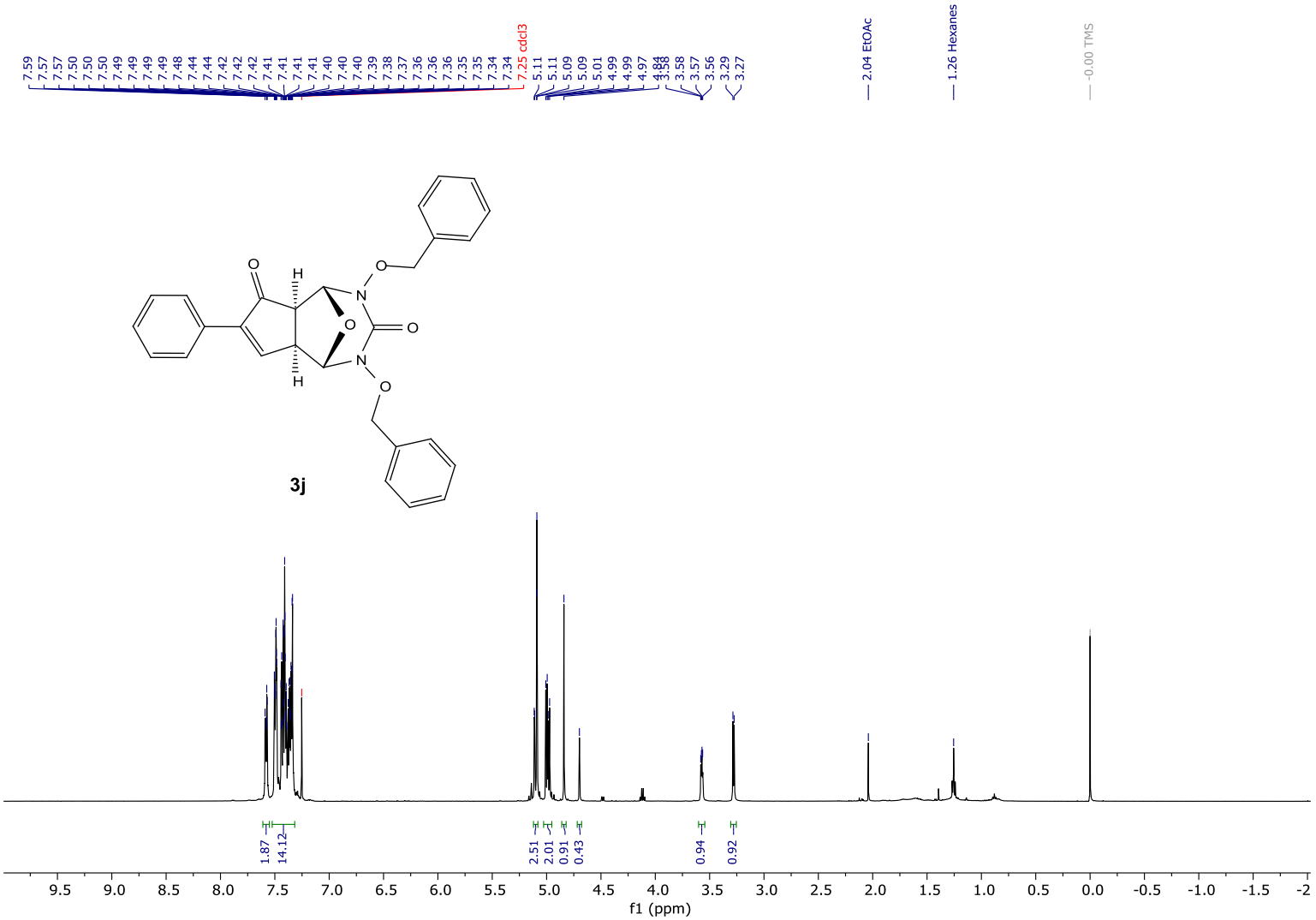
4-{(1*S,2*S**,6*S**,7*R**)-5-Oxotricyclo[5.2.1.0^{2,6}]dec-3-en-4-yl}butyronitrile (3i)**

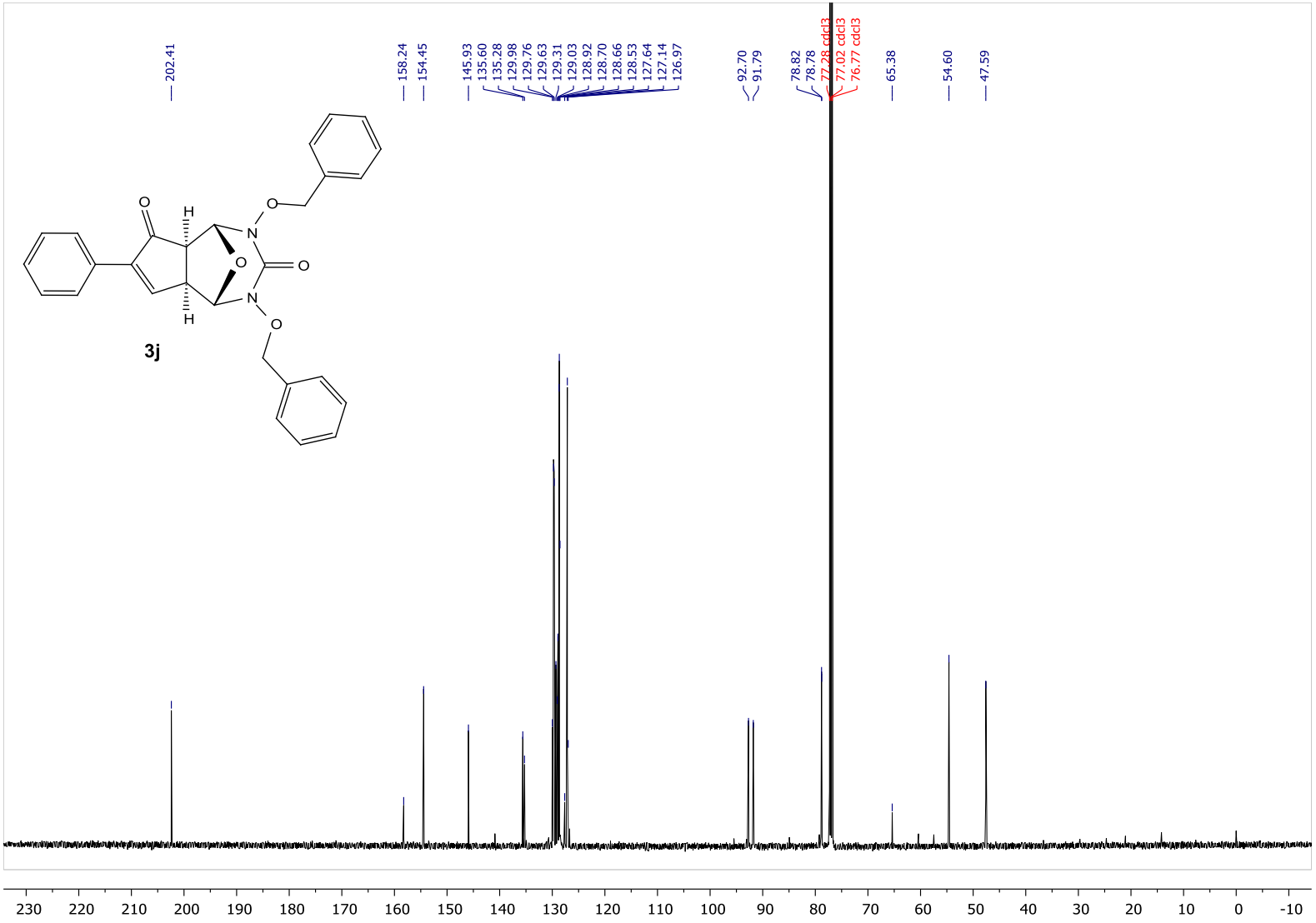


3i

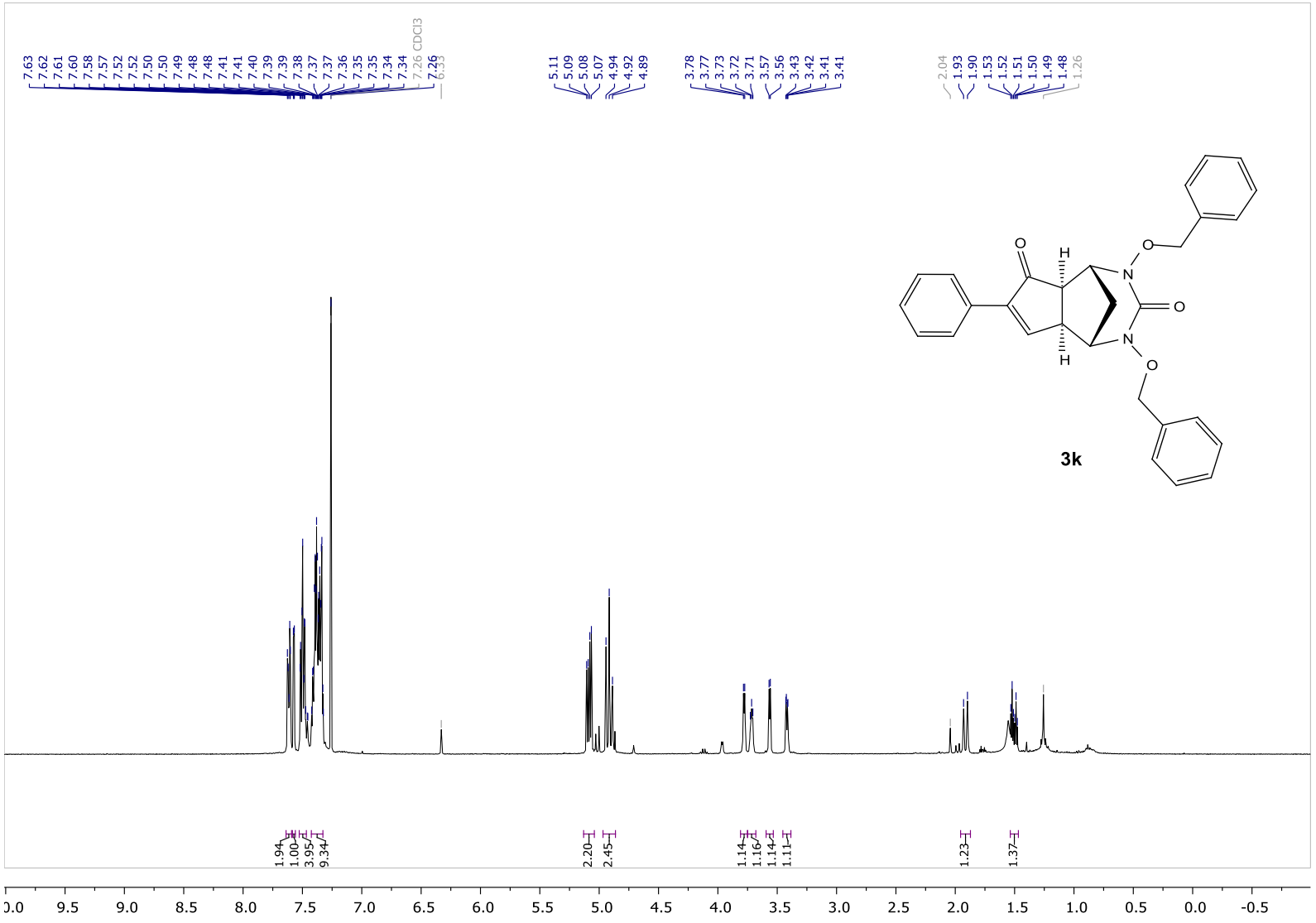

210.7
160.2
147.0
119.3
77.3 cdcl3
77.0 cdcl3
76.7 cdcl3
53.9
48.3
39.0
38.0
31.1
29.0
28.4
24.1
23.7
16.9
O
H
H
N
3i
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

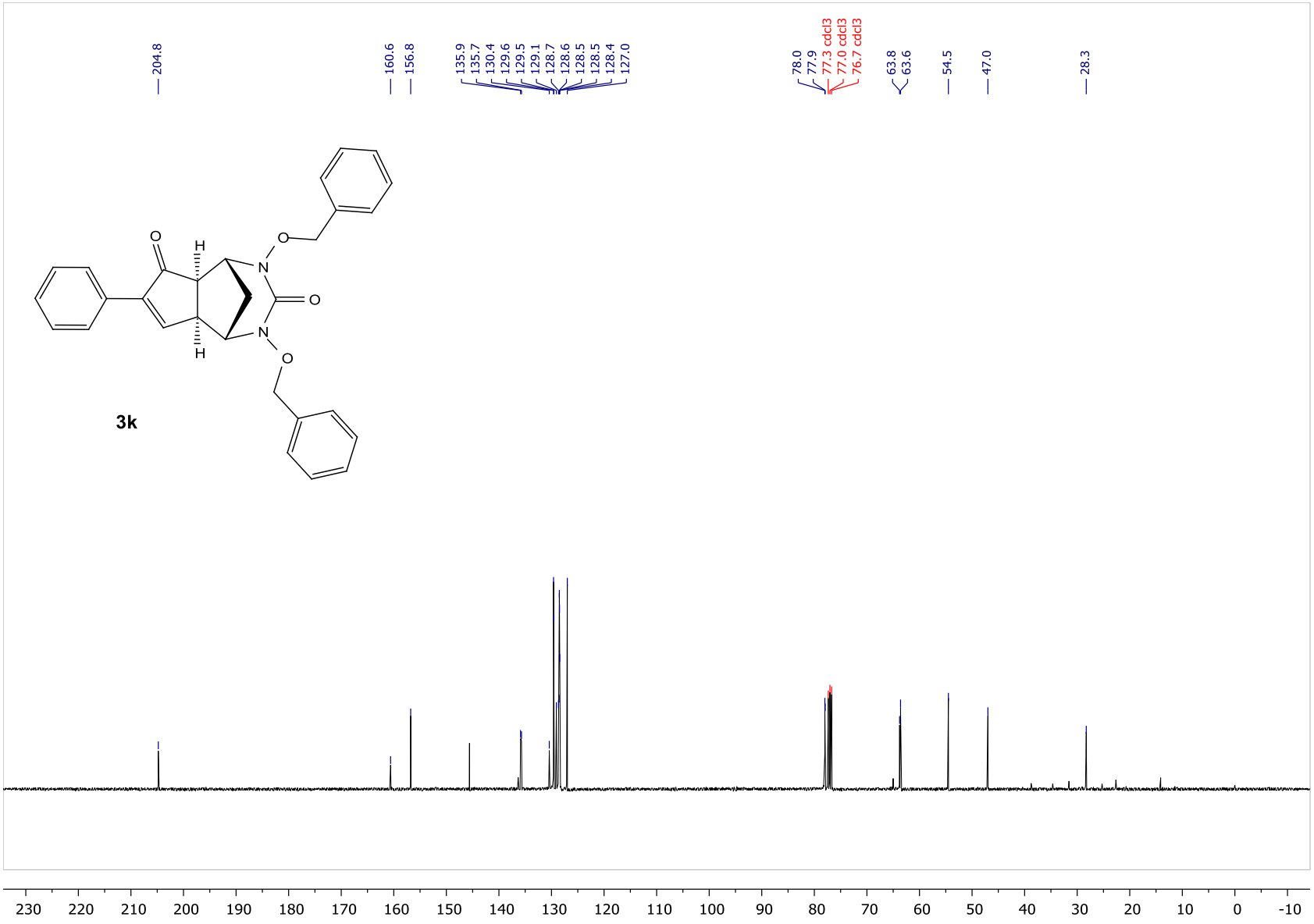
(1*S,2*S**,6*S**,7*R**)-4-Phenyltricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (3j)**



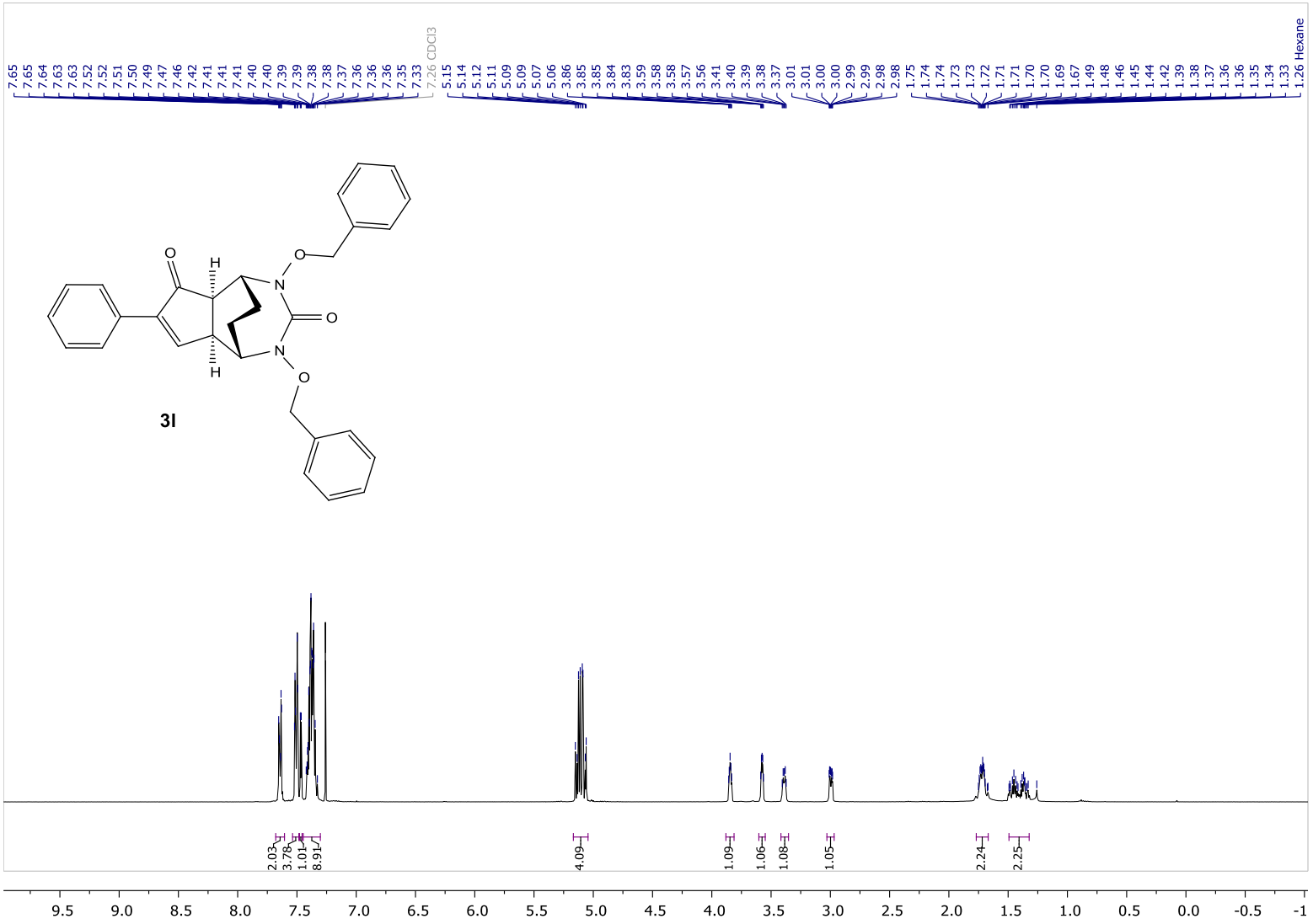

202.41
158.24
154.45
145.93
135.60
135.28
129.98
129.76
129.63
129.31
129.03
128.92
128.70
128.66
128.53
127.64
127.14
126.97
92.70
91.79
78.82
78.78
77.28 cdcl3
77.02 cdcl3
76.77 cdcl3
65.38
54.60
47.59
3j
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

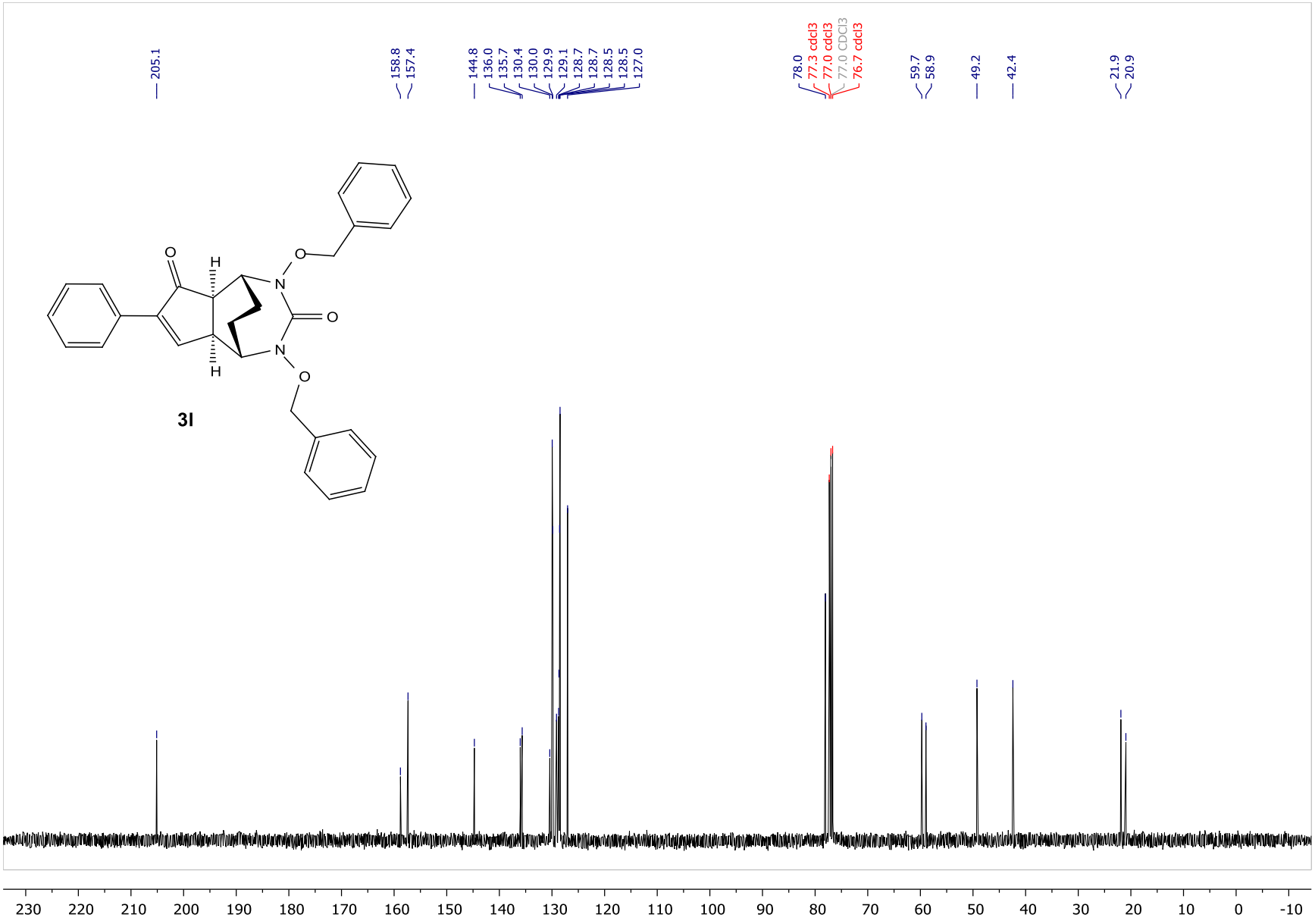
(1*S,2*S**,6*S**,7*R**)-4-(2-Hydroxyethyl)tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (3k)**




204.8
160.6
156.8
135.9
135.7
130.4
129.6
129.5
129.1
128.7
128.6
128.5
128.5
128.4
127.0
78.0
77.9
77.3 cdcl3
77.0 cdcl3
76.7 cdcl3
63.8
63.6
54.5
47.0
28.3
O
H
N
O
O
N
O
H
3k
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

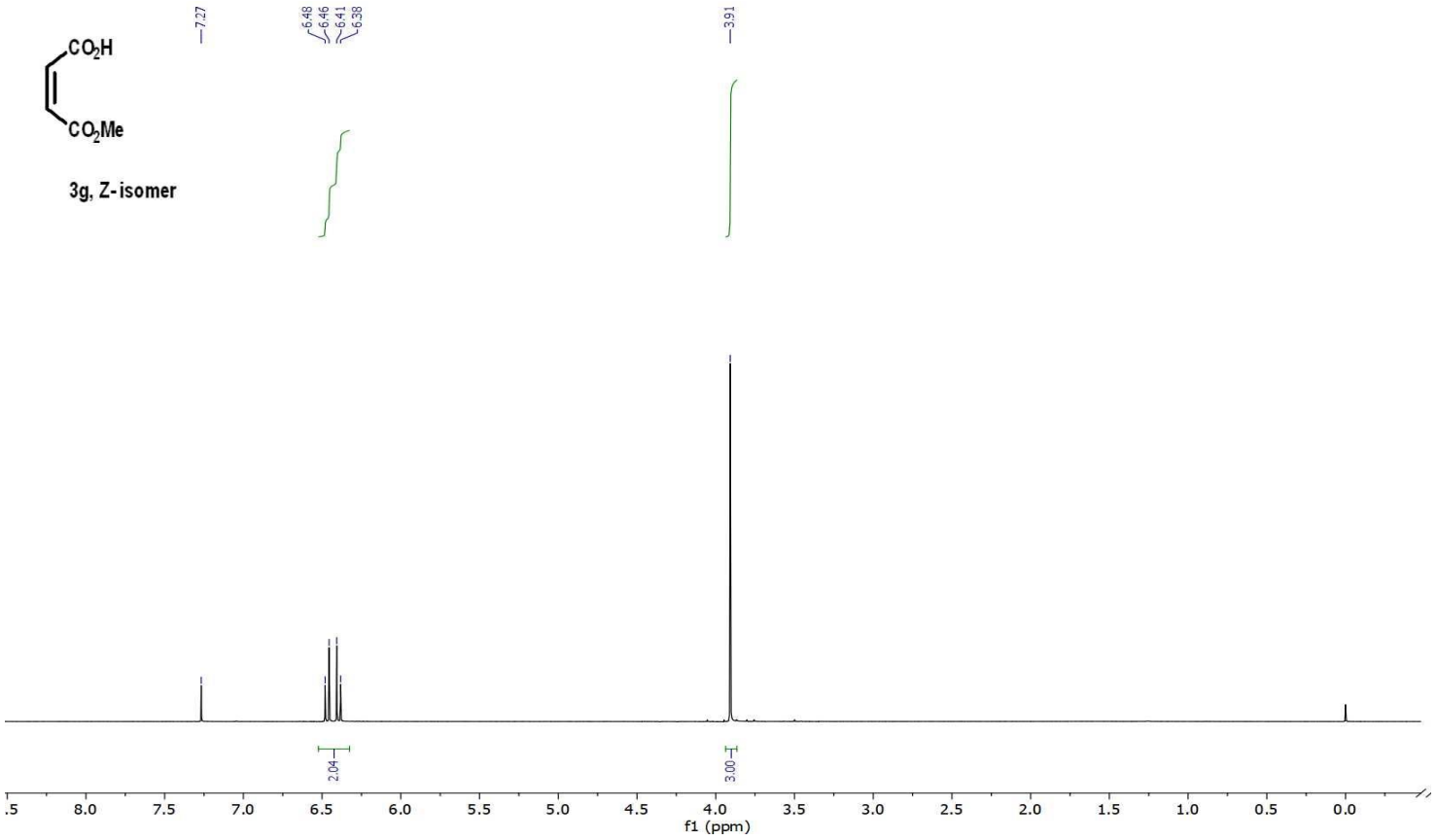
Dimethyl (1*R,2*R**,6*S**,7*S**)-5-oxotricyclo[5.2.1.0^{2,6}]deca-3,8-diene-3,4-dicarboxylate (3l)**

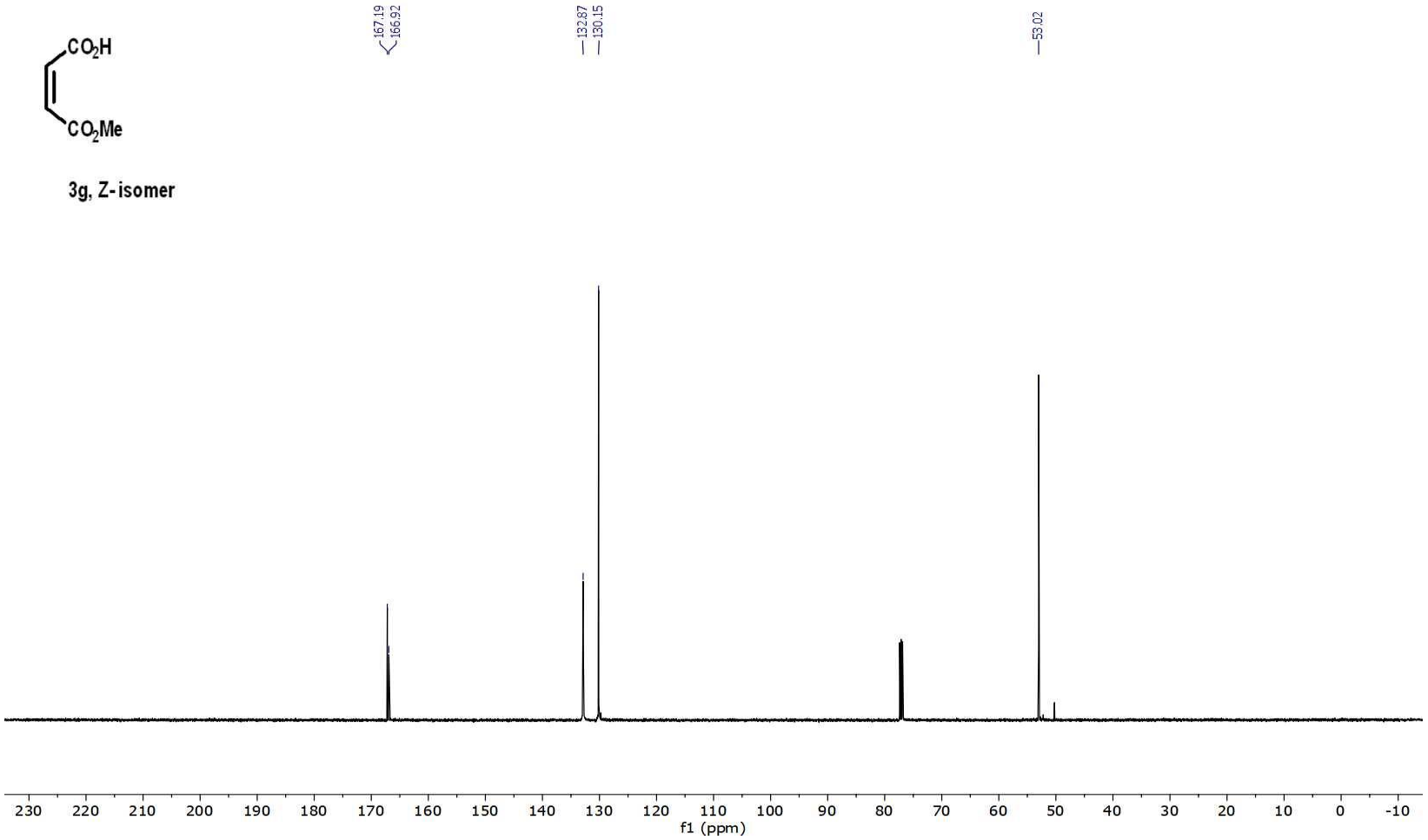



205.1
158.8
157.4
144.8
136.0
135.7
130.4
130.0
129.9
129.1
128.7
128.5
128.5
127.0
78.0
77.3 cdcl3
77.0 cdcl3
77.0 CDCl3
76.7 cdcl3
59.7
58.9
49.2
42.4
21.9
20.9
O
H
N
O
O
N
H
O
3l
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

Chapter three

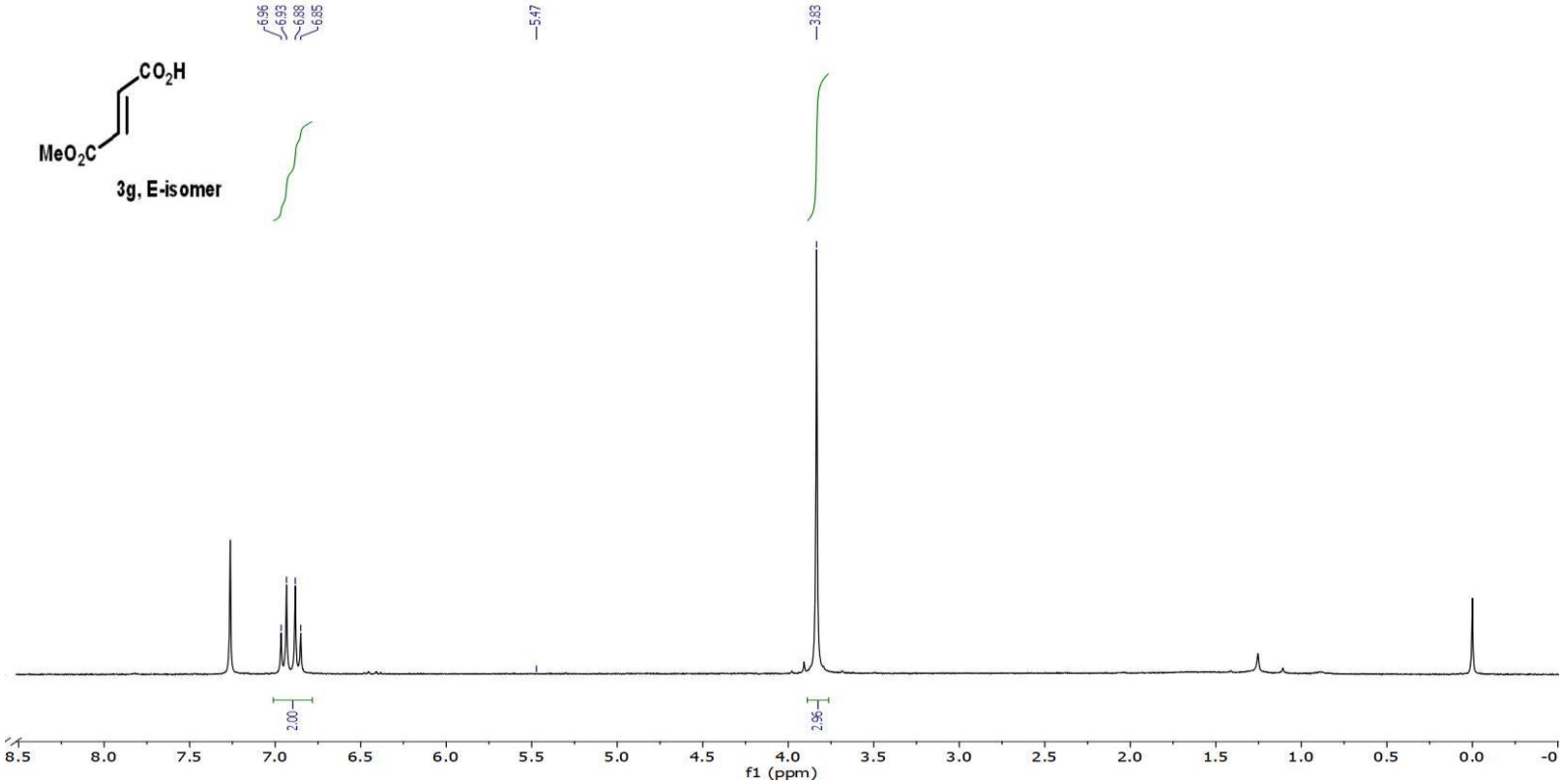
(2Z)-but-2-enedioic acid

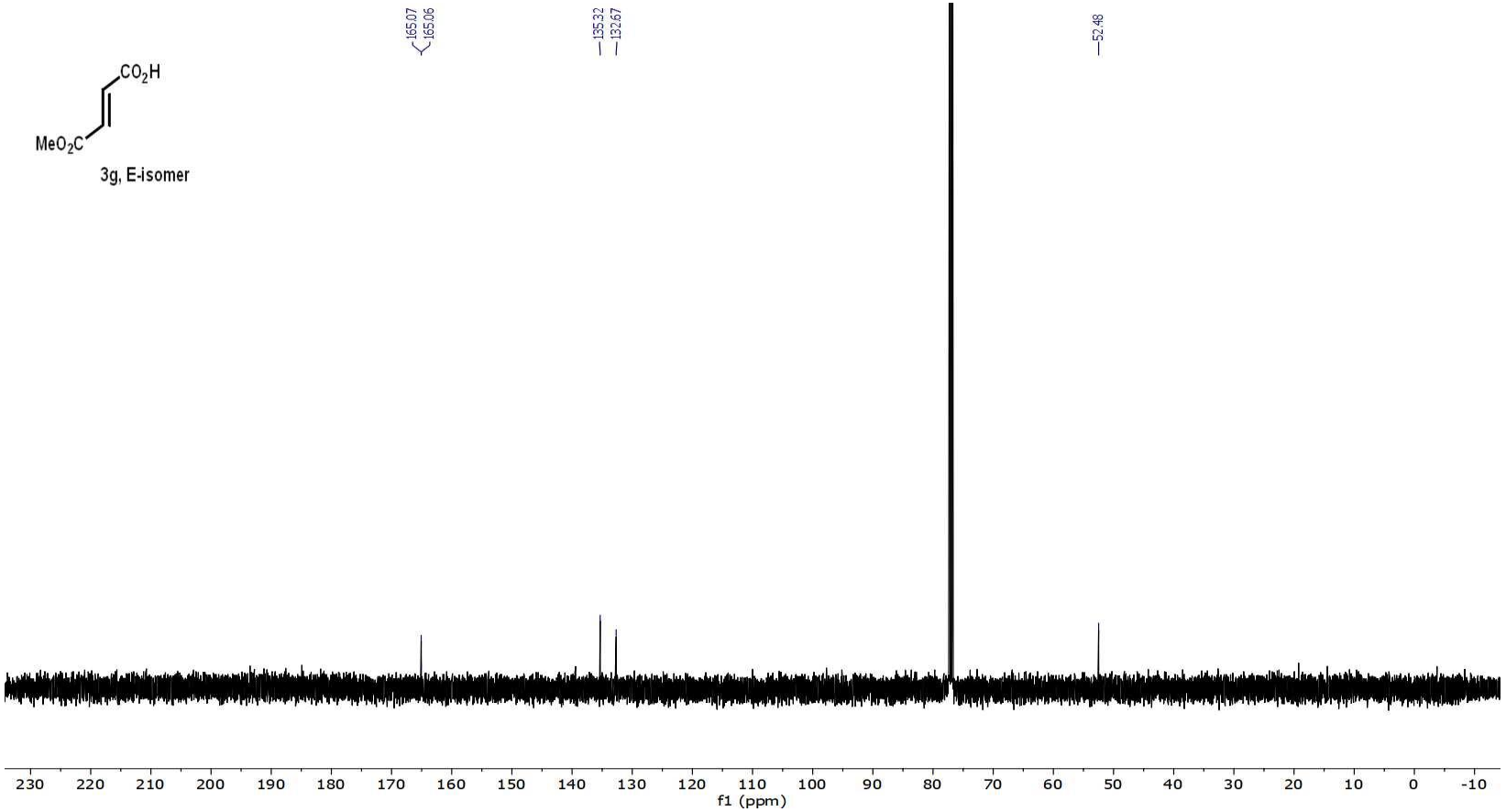



CO2H
CO2Me
167.19
166.92
132.87
130.15
53.02
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

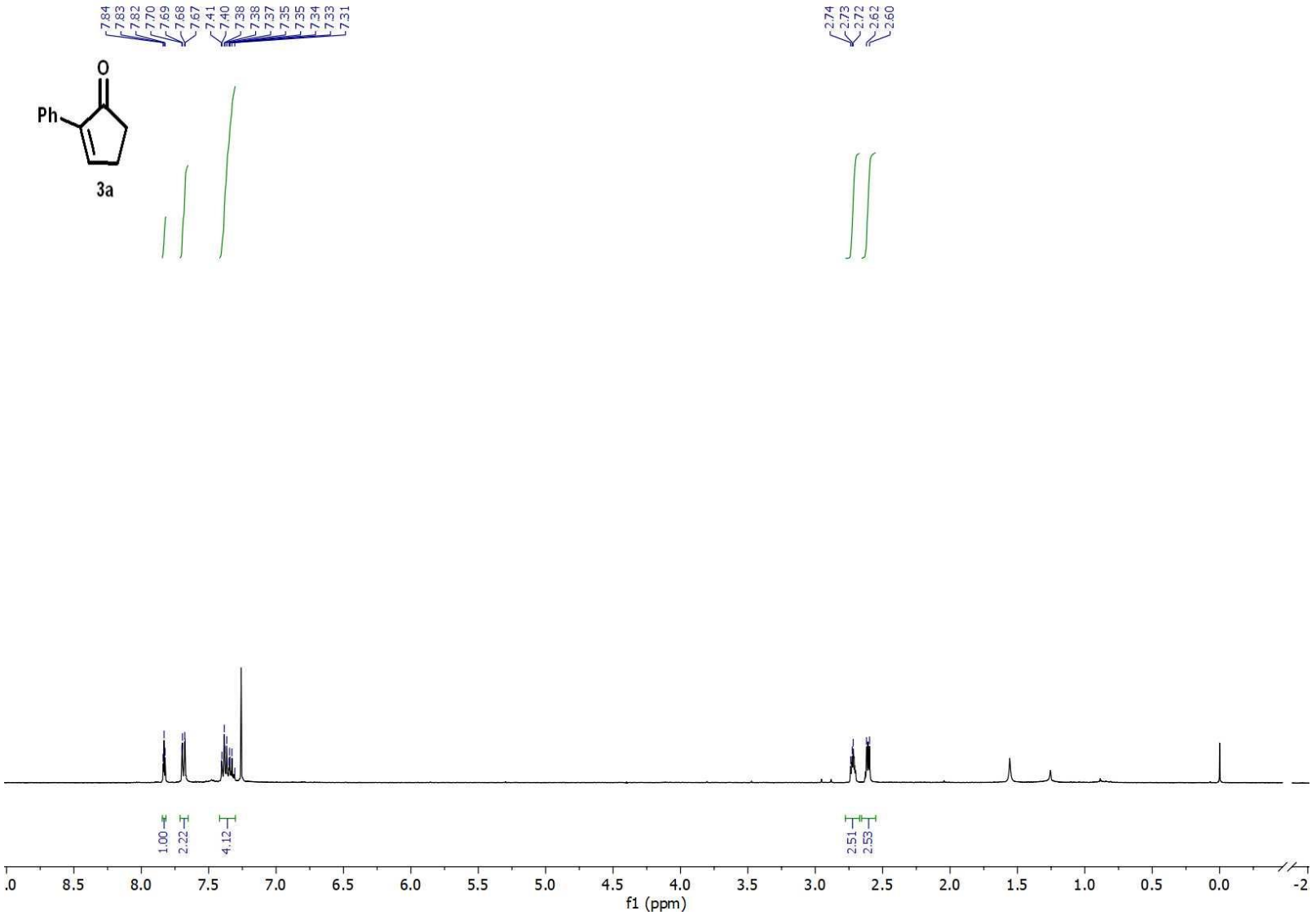
3g, Z-isomer

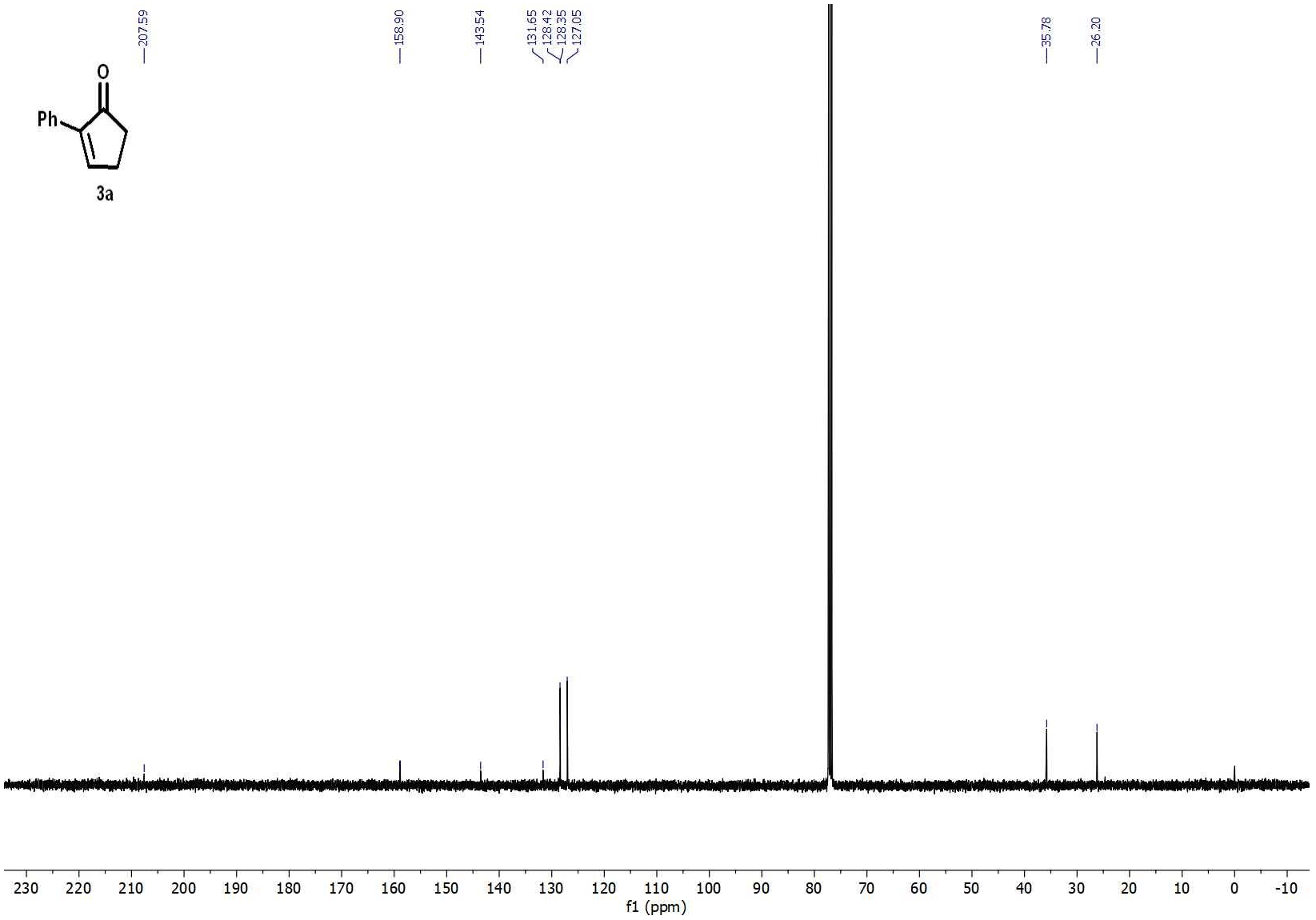
(2*E*)-but-2-enedioic acid



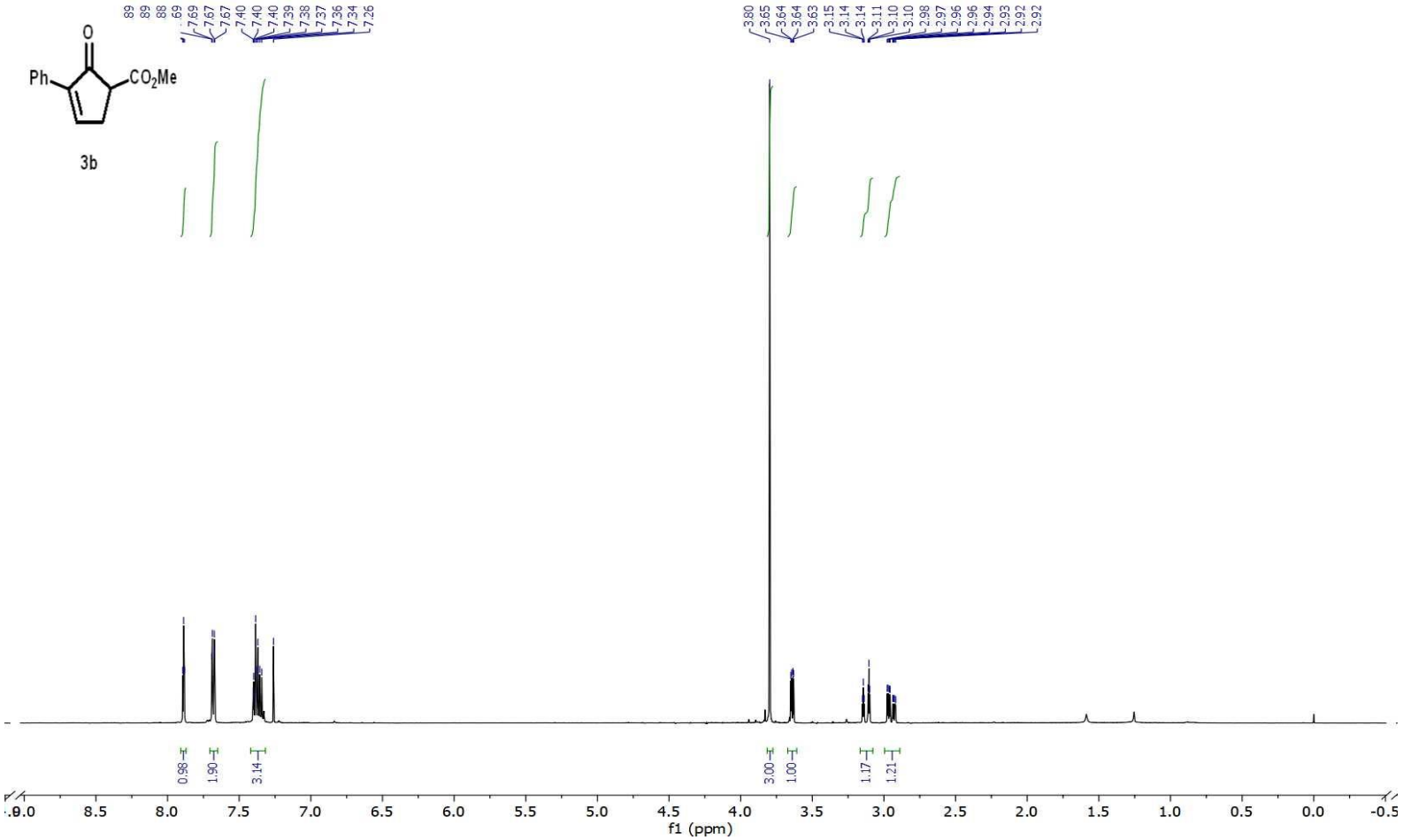

CO2H
MeO2C
3g, E-isomer
165.07
165.06
135.32
132.67
52.48
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

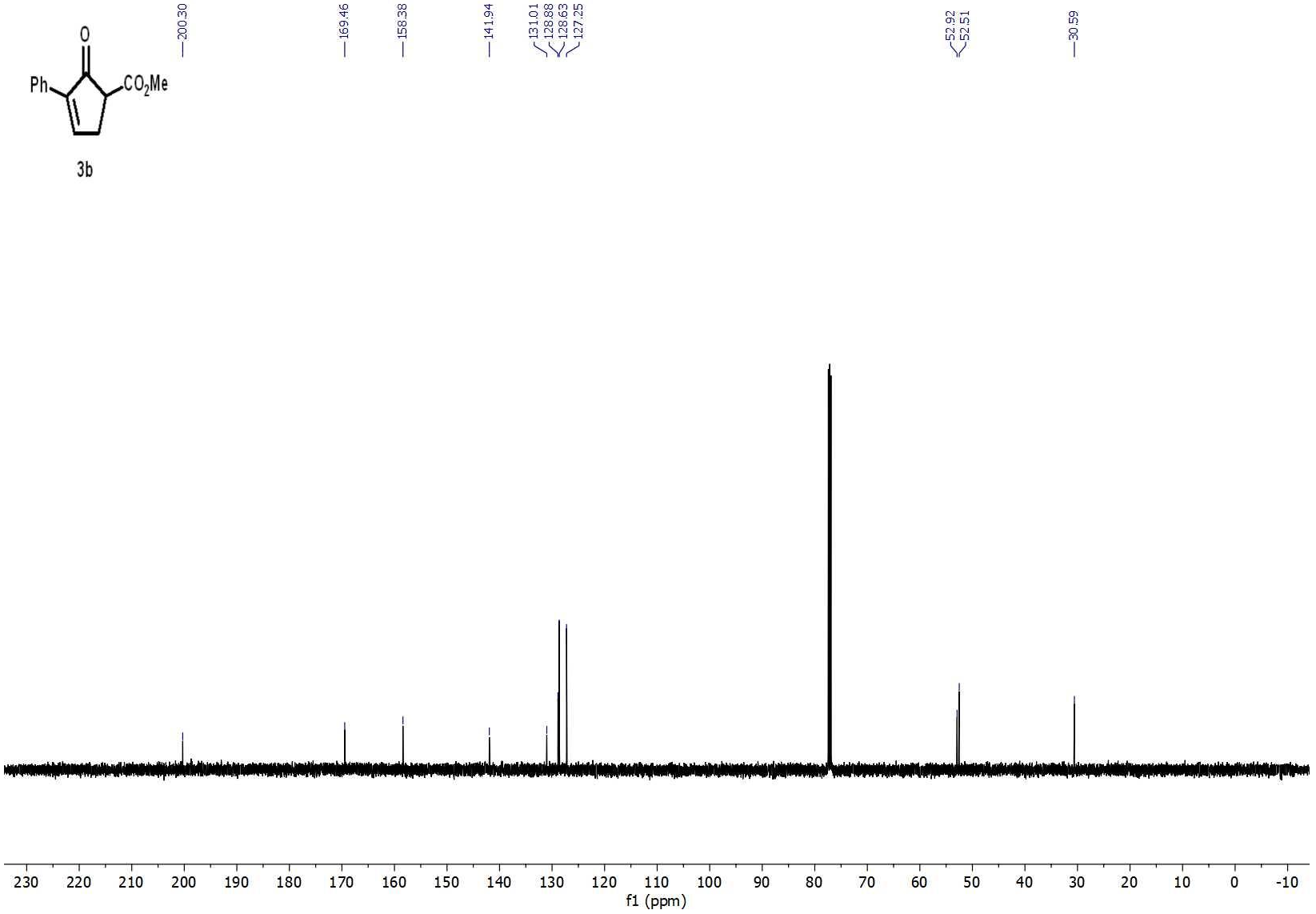
2-phenylcyclopent-2-en-1-one (3a)



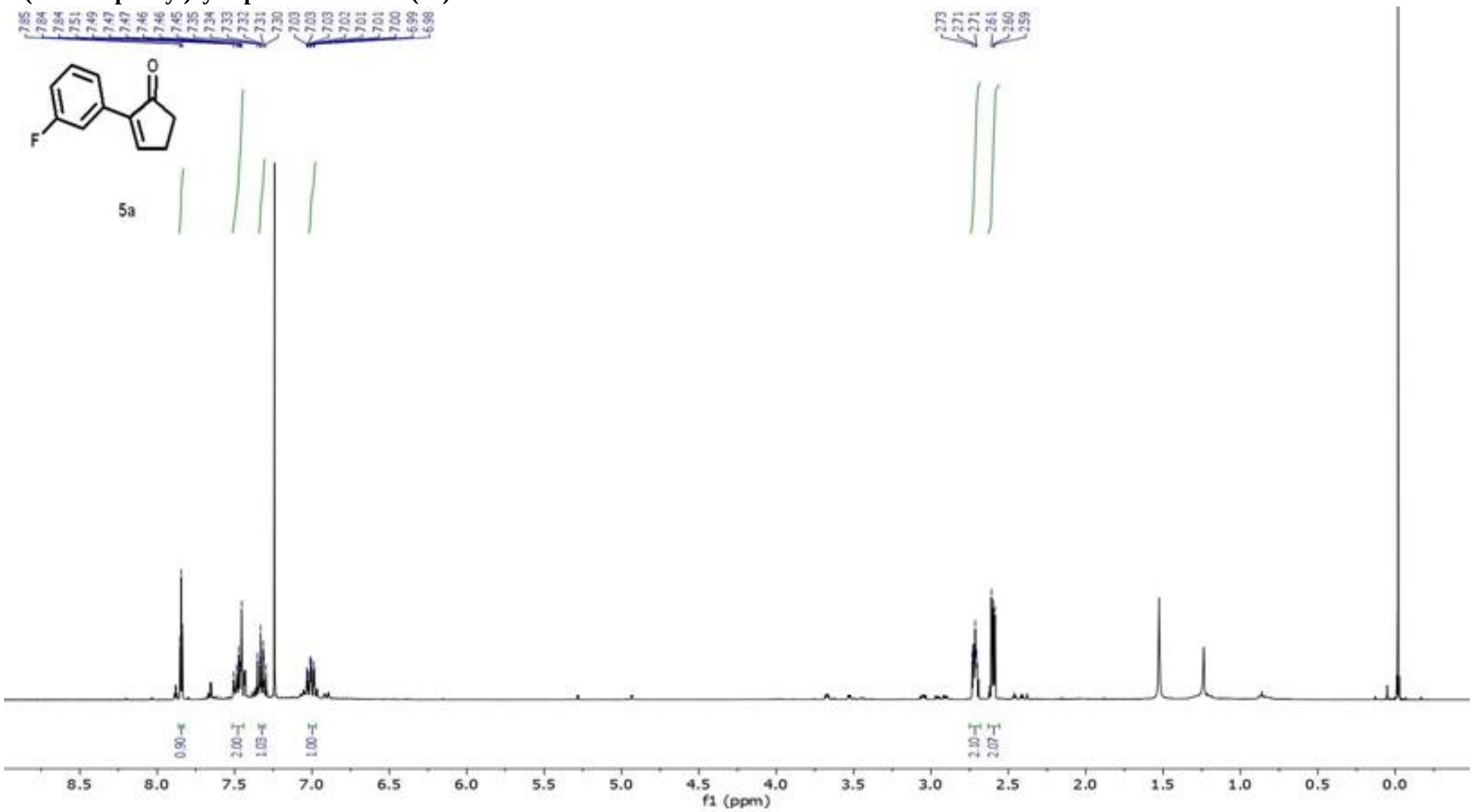

207.59
158.90
143.54
131.65
128.42
128.35
127.05
35.78
26.20
O
Ph
3a
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

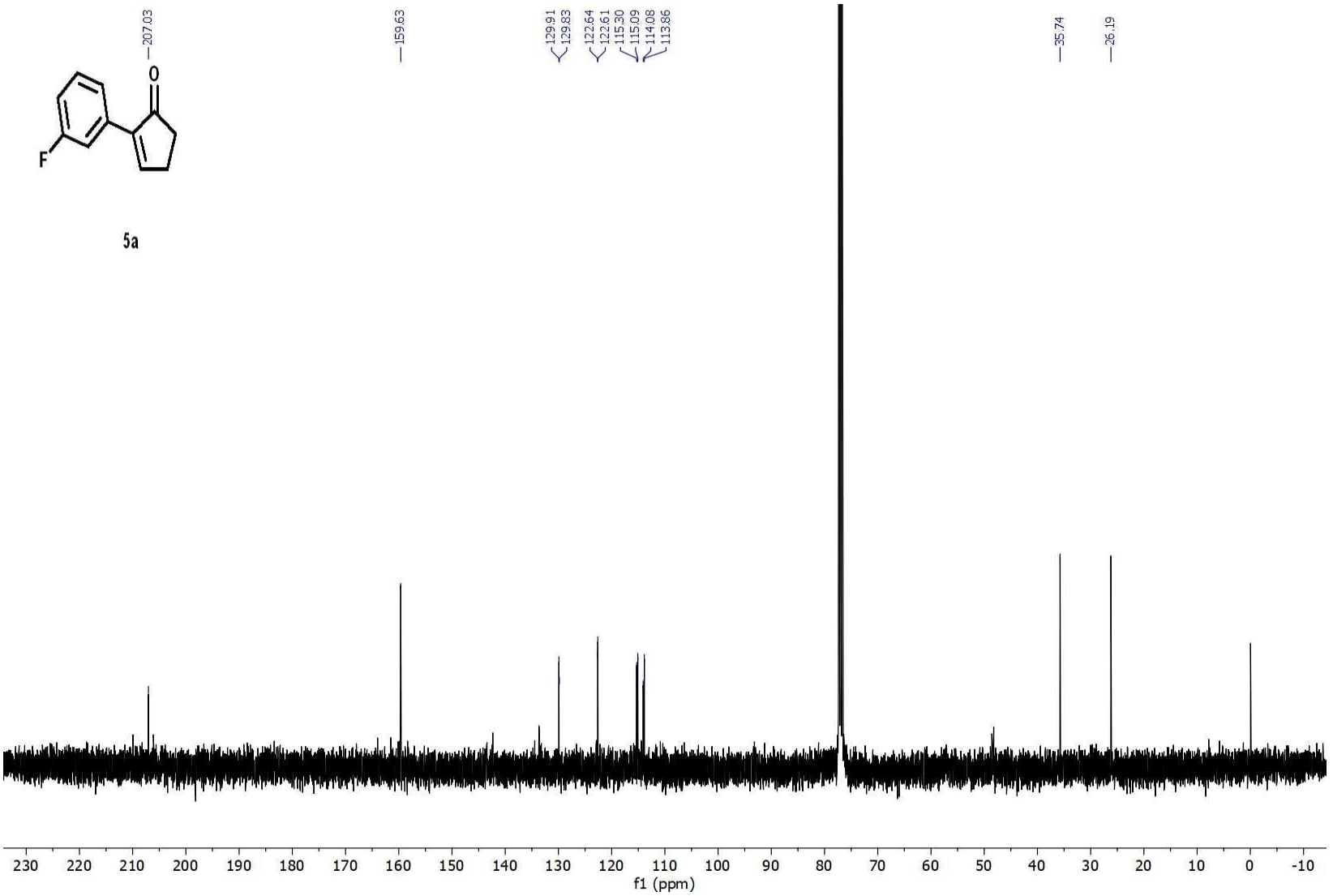
methyl 2-oxo-3-phenylcyclopent-3-ene-1-carboxylate (3b)



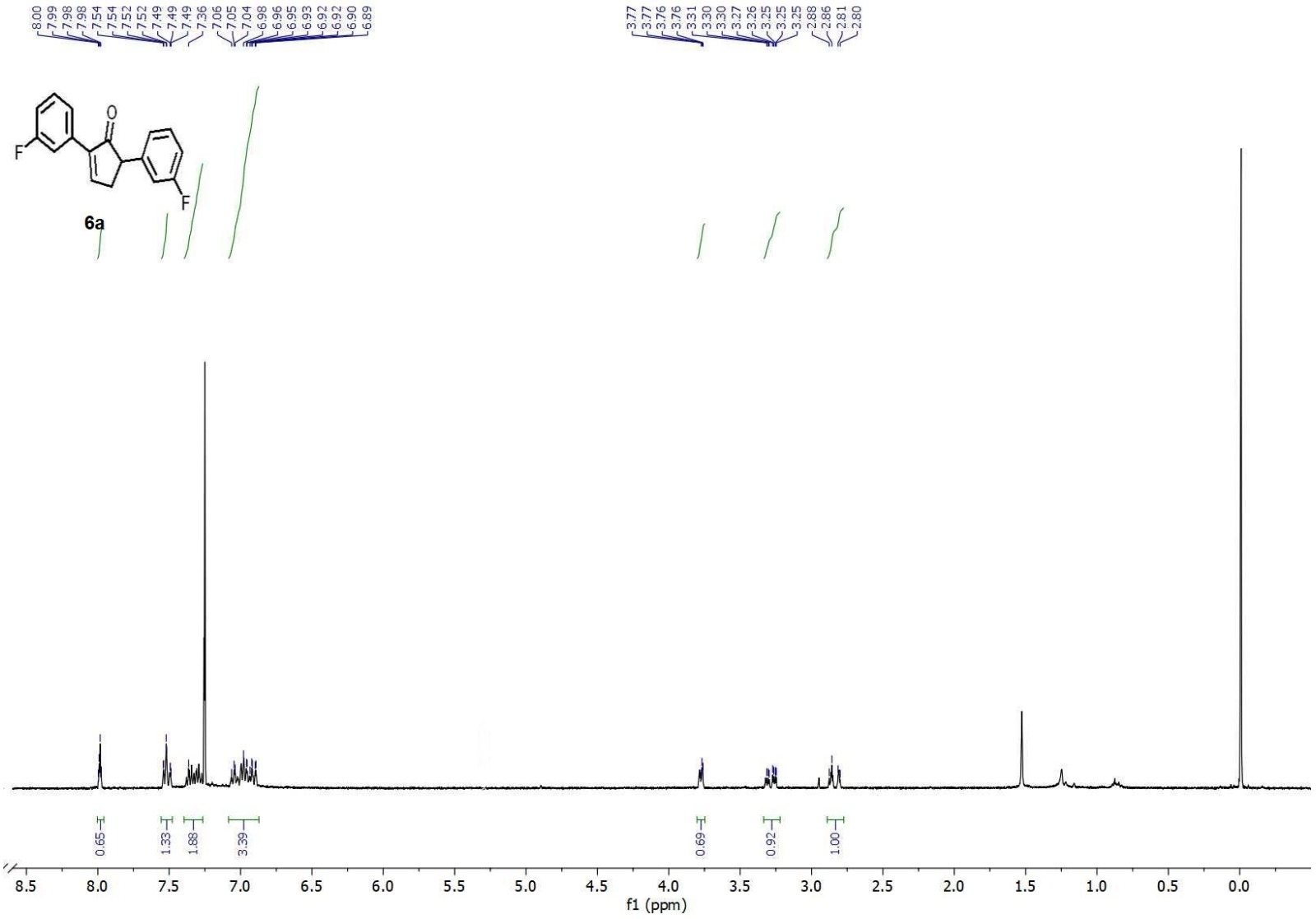

O
Ph
CO2Me
3b
200.30
169.46
158.38
141.94
131.01
128.88
128.63
127.25
52.92
52.51
30.59
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

2-(3-fluorophenyl)cyclopent-2-en-1-one (5a)

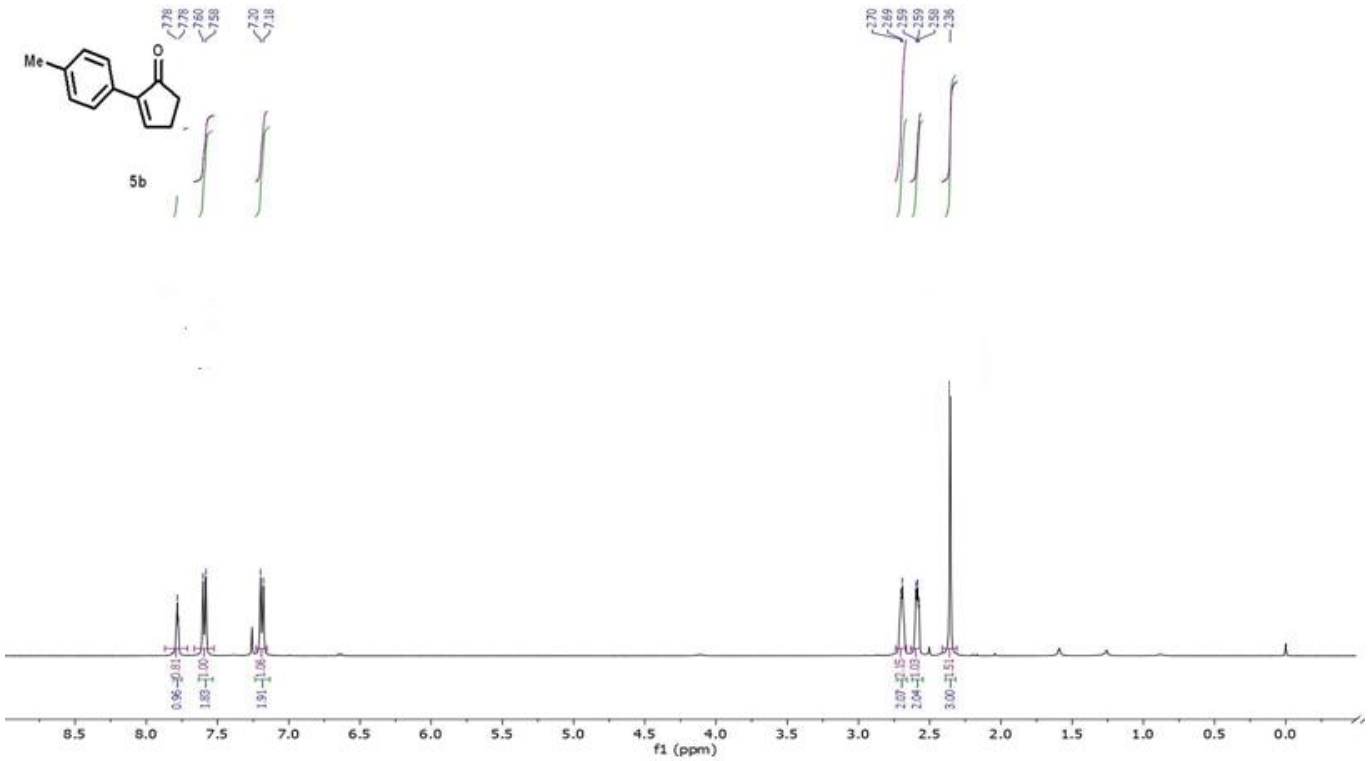


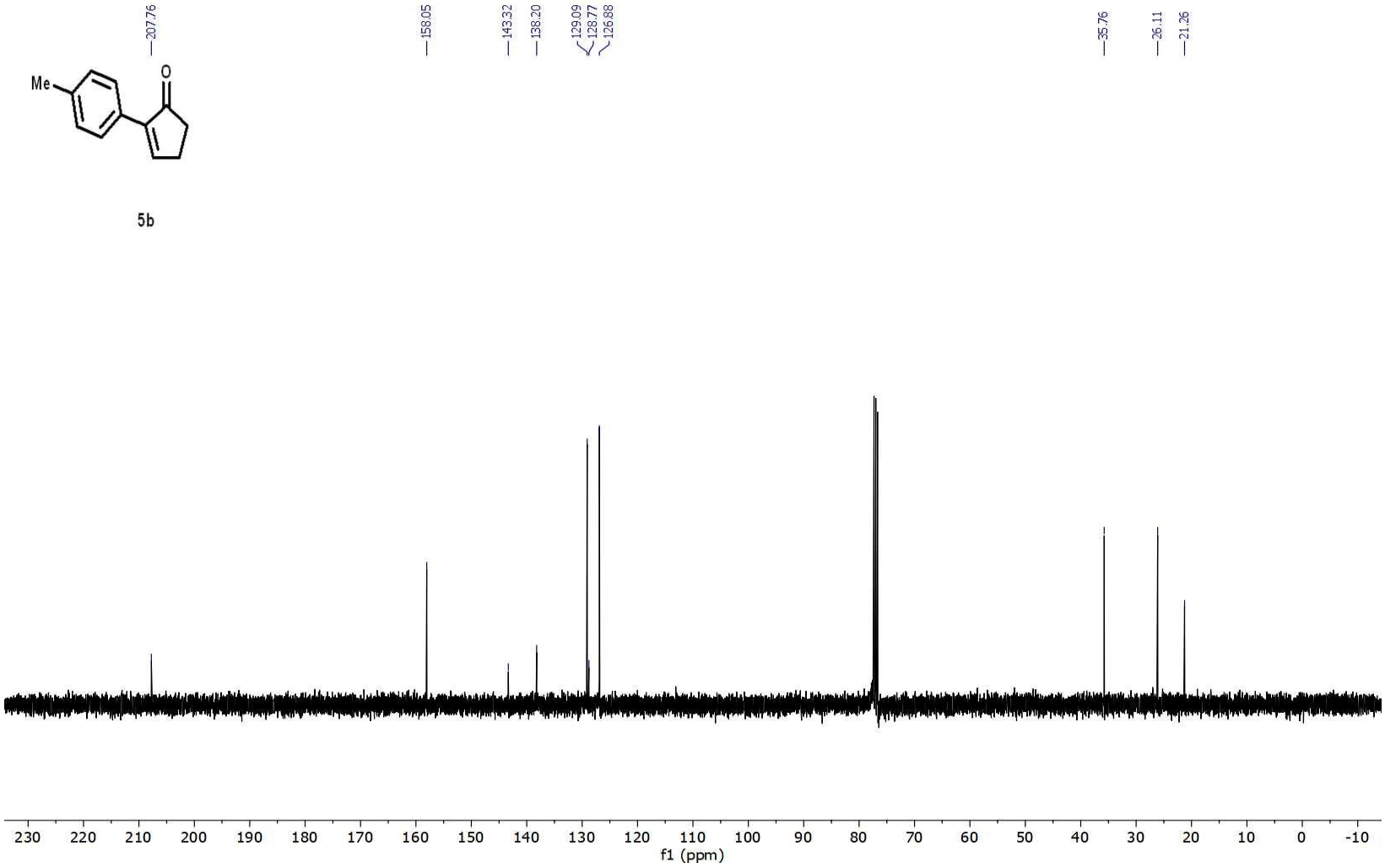

207.03
159.63
129.91
129.83
122.64
122.61
115.30
115.09
114.08
113.86
35.74
26.19
O
F
5a
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

2,5-bis(3-fluorophenyl)cyclopent-2-en-1-one(6a)

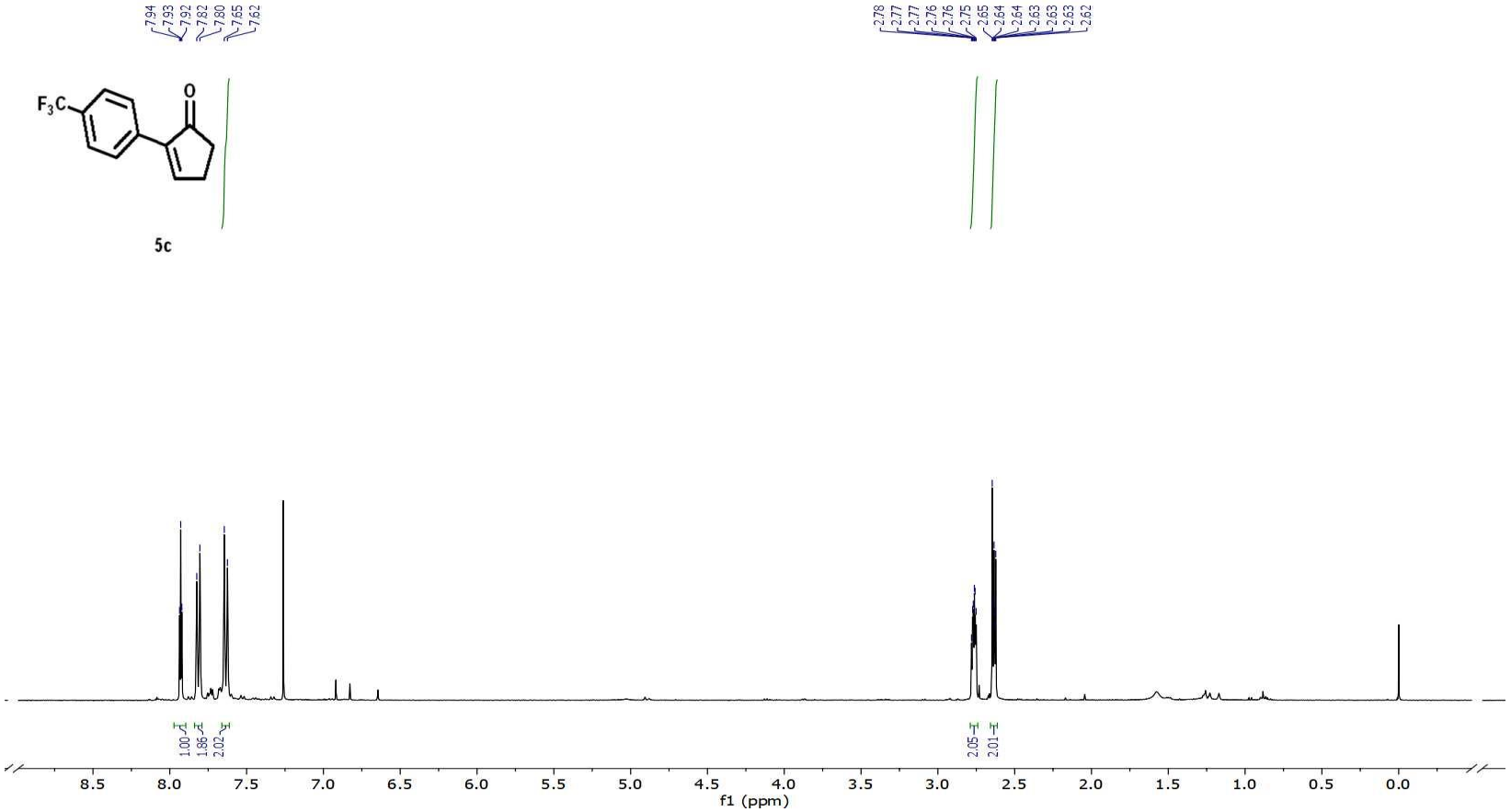


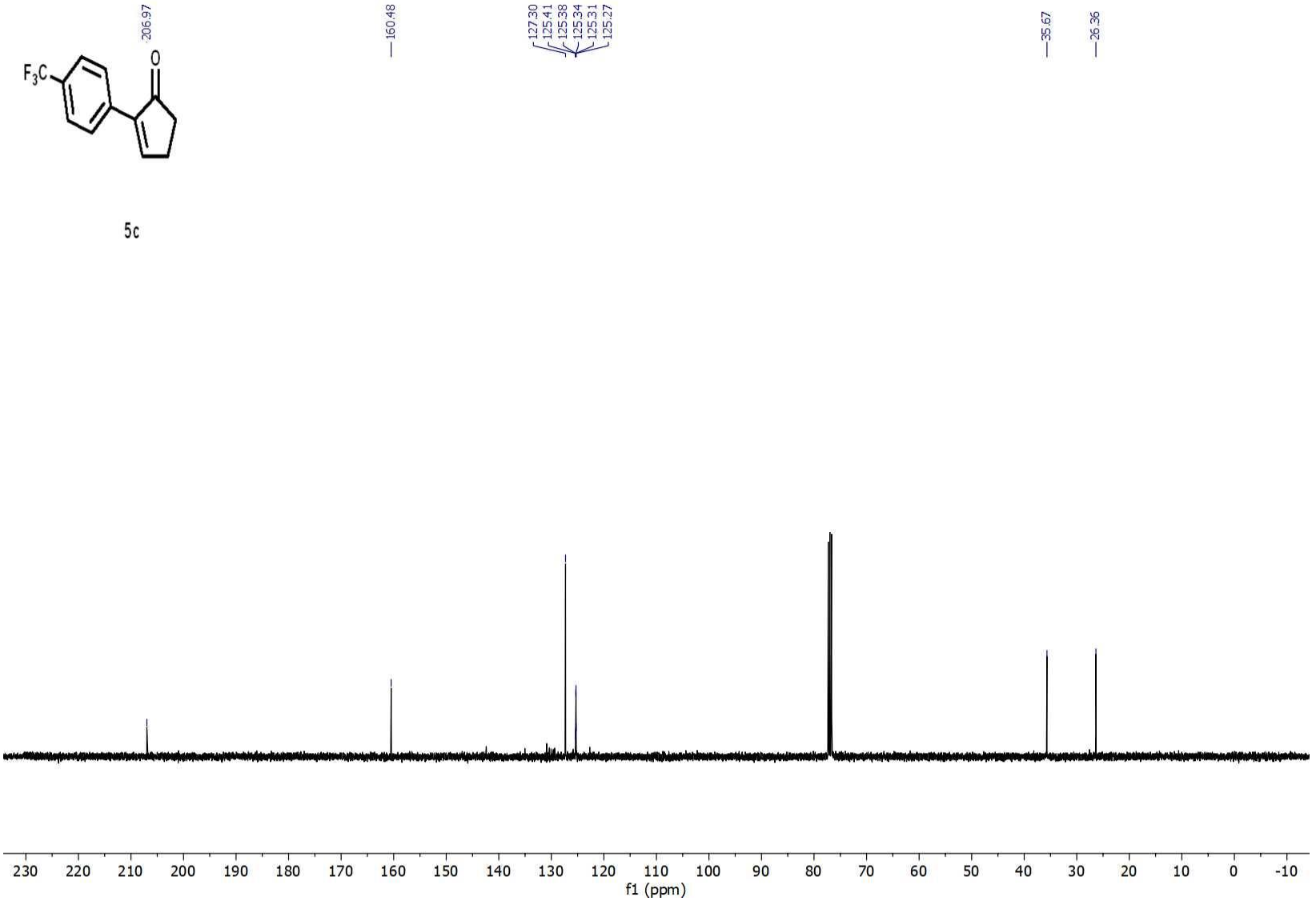
2-(p-tolyl)cyclopent-2-en-1-one (5b)



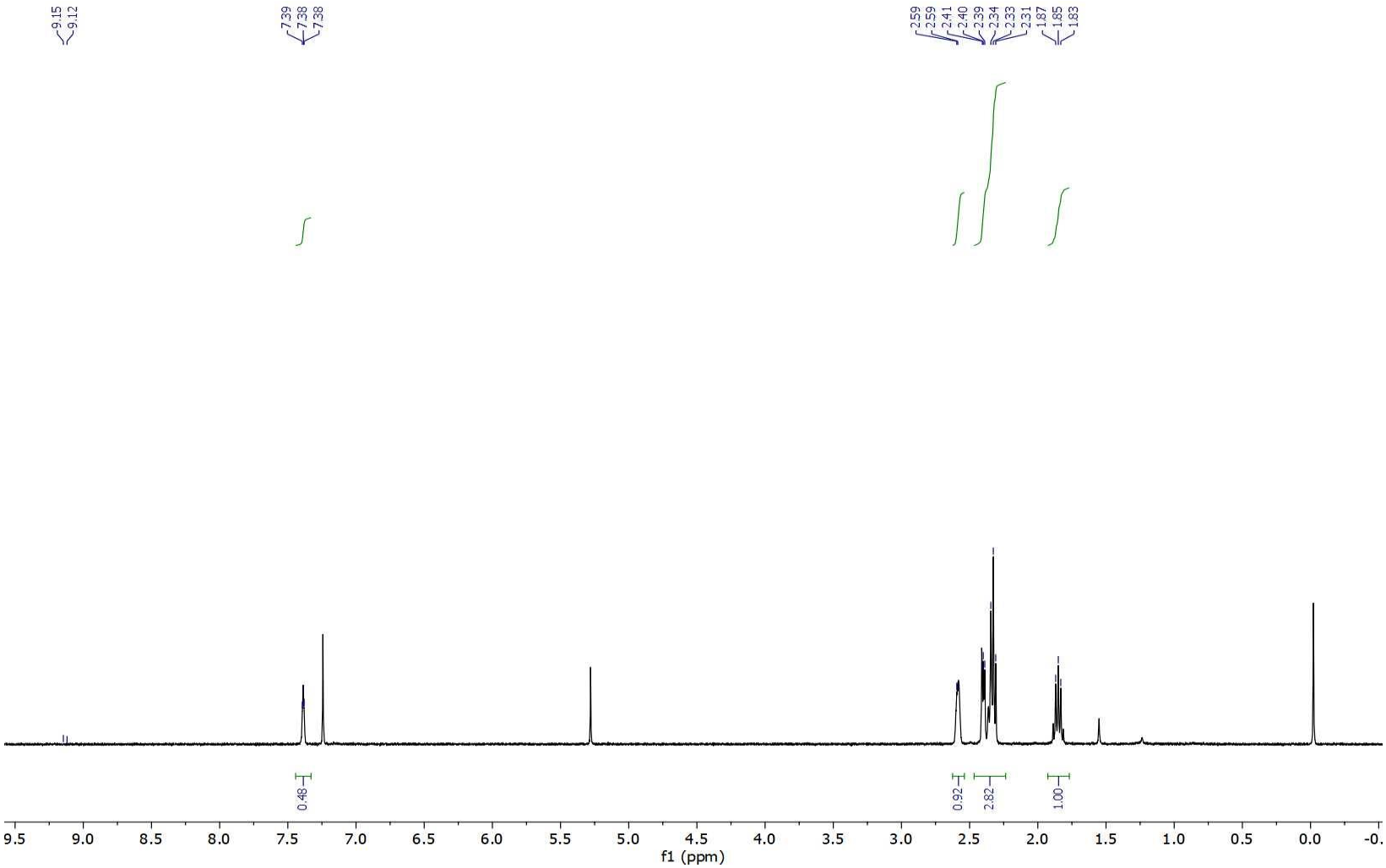

207.76
158.05
143.32
138.20
129.09
128.77
126.88
35.76
26.11
21.26
Me
O
5b
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

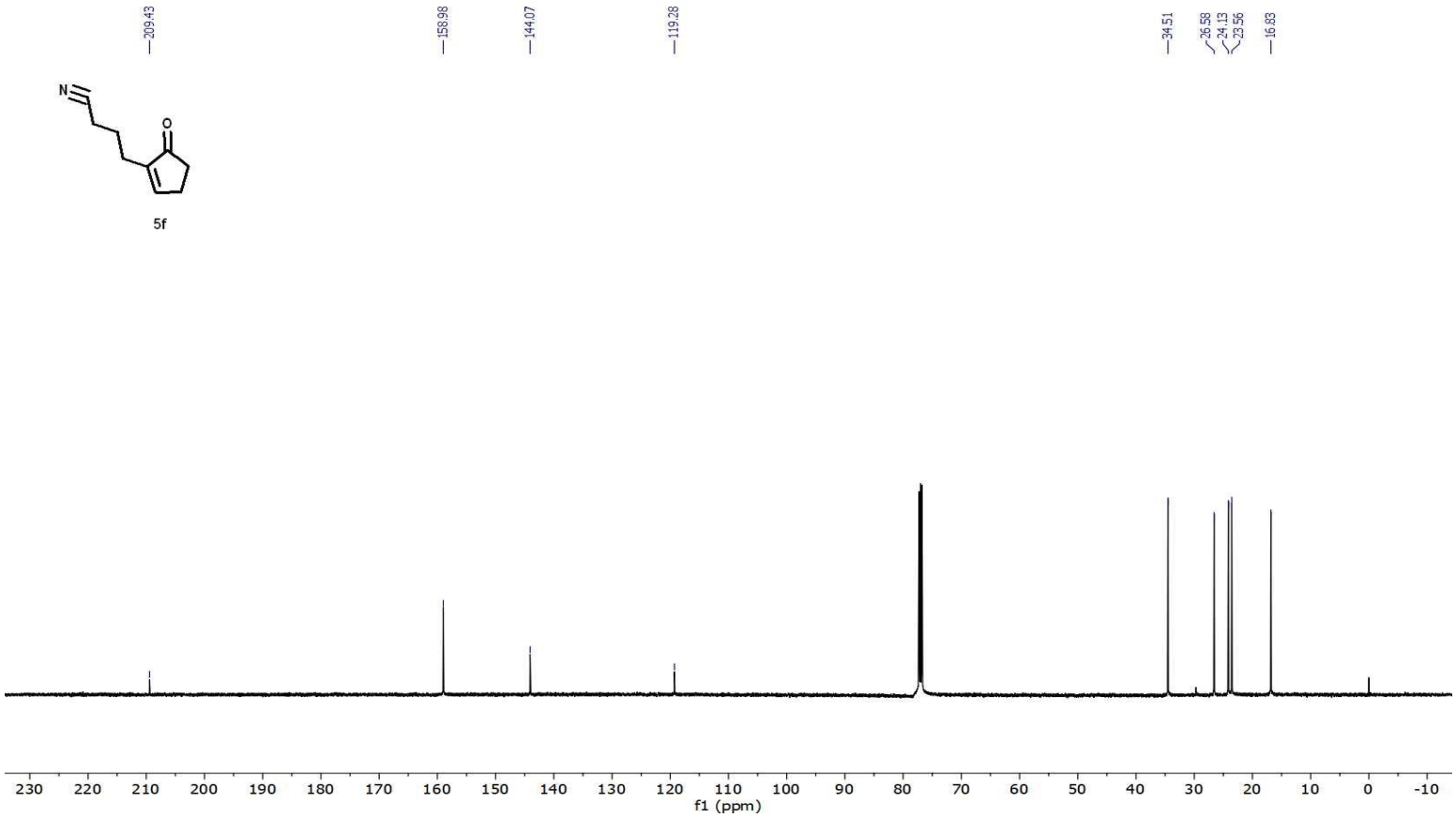
2-(4-(trifluoromethyl)phenyl)cyclopent-2-en-1-one (5c)




206.97
160.48
127.30
125.41
125.38
125.34
125.31
125.27
35.67
26.36
F3C
O
5c
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

4-(5-oxocyclopent-1-en-1-yl) butanenitrile (5f)




209.43
158.98
144.07
119.28
34.51
26.58
24.13
23.56
16.83
N
O
5f
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)