UNIVERSITÉ DU QUÉBEC À MONTRÉAL

DEVELOPMENT OF COPPER-CATALYZED ARYLATION REACTIONS USING TRIARYLBISMUTH REAGENTS

THESIS

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DÉVELOPPEMENT DE RÉACTIONS D'ARYLATION CATALYSÉES PAR LE CUIVRE UTILISANT LES TRIARYLBISMUTHS COMME RÉACTIF

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PRÉSENTÉ

COMME EXIGENCE PARTIELLE

DE LA MAÎTRISE EN CHIMIE

PAR

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DEDICATION

I would like to
dedicate this thesis
to my grandparents,
Masood Alam and Anwar
Jahan Zaidi

TABLE OF CONTENT

LIST OF ABBREVIATIONS

Å	Angstrom
α	Alpha
Abs	Absorbance
Ac	Acetyl
arom.	Aromatic
β	Beta
B	Base
Bz	Benzoyl
c	Concentration
C	Carbon
°C	Degree Celcius
cm	Centimeter
COSY	COrrelation SpectroscopY
d	Doublet
dd	Doublet of doublets
DCM	Dichloromethane
DIC	Diisopropylcarbodiimide
DIPEA	*N,N*-diisopropylethylamine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
e	Electron

eq.	Equivalent
ESI	Electrospray ionization
g	Gram
H	Hydrogen
h	Hour
Hex	Hexanes
HMBC	Heteronuclear Multiple Bond Correlation
Hz	Hertz
IR	Infrared
J	Coupling constant
M	Molar, concentration
m	Multiplet
Me	Methyl
MHz	Mega Hertz
min	Minute
mL	Milliliter
mmol	Millimole
mm	Millimeter
m/z	Mass/charge ratio
NOE	Nuclear overhauser effect
NOESY	Nuclear Overhauser Effect Spectroscopy
ppm	Parts per million
Pyr	Pyridine

Rf	Retention factor
NMR	Nuclear MagneticResonance
s	Singlet
TBAB	Tetrabutylammonium bromide
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
µ	Micro
µL	Microliter
µM	Micromolar

RÉSUMÉ

Le bismuth est un élément présent en faible quantité dans la nature. Cependant le processus de raffinage des métaux nous permet de nous en procurer de manière plus facile. Le bismuth dispose aussi de caractéristiques uniques telles que la non-toxicité et une bonne stabilité, chose qui le rend utile dans l'industrie de la chimie verte. Parmi les composés organobismuth qui sont connus, on trouve les composés alkylbismuth et arylbismuth. Dans ce travail, l'accent sera mis sur l'utilisation de composés de type triarylbismuth. Il est à noter que les composés organobismuths sont présents sous deux formes: les triarylbismuths(III) et les triarylbismuths(V). Dans le passé et durant plusieurs années, les composés organobismuth ont été utilisés dans de nombreuses réactions organiques synthétiques importantes.

Le but de ce travail est d'appliquer les triarylbismuths(III) comme réactifs dans les réactions d'arylation catalysées par le cuivre. Ainsi, la première partie de mon travail consiste à synthétiser les différents composés de bismuth triaryl(III) qui portent des groupes fonctionnels. Les réactifs de type triarylbismuth peuvent être facilement obtenus par l'addition d'un réactif de Grignard sur le chlorure de bismuth et cela afin d'obtenir des réactifs organobismuth fonctionnalisés avec des rendements allant de modérés à bon. Les triarylbismuthanes sont stables dans l'air et peuvent être purifiés par une simple chromatographie sur gel de silice. En outre, les organobismuthanes montrent une remarquable tolérance aux groupes fonctionnels ce qui fait d'eux des candidats idéaux pour le développement de méthodologies orientées vers des applications de chimie médicinale.

La deuxième partie de mon projet consiste à appliquer le triarylbismuth(III) en tant que réactif dans les réactions d'arylation catalysées par le cuivre. Des protocoles efficaces pour la O-arylation catalysée utilisant des phénols, des 1,2 -aminoalcools N-protégés ou du chloramphenicol par du cuivre en utilisant des réactifs de triarylbismuth fonctionnalisés ont été développés. Une quantité catalytique d'acétate de cuivre a favorisé une réaction de couplage croisé C–O dans des conditions douces. Cette réaction tolère une grande diversité de groupes fonctionnels donnant accès à une gamme de ß-aryloxyamines ou aryl éthers qui sont importants pour la synthèse de composés pertinents médicalement ainsi que des motifs structuraux très importants de

nombreux produits et polymères naturels biologiquement actifs dans l'industrie de la science des matériaux

SUMMARY

Bismuth is present in small amount in nature, but can easily be accessed by the refining process of metals. Bismuth has some unique features, such as a low toxicity and high stability. This makes bismuth useful in green chemistry.

Different classes of organobismuth compounds are known such as alkylbismuth and arylbismuth compounds. In this work, the focus lays on the use of triarylbismuth compounds. Organobismuth compounds are present in two forms: triarylbismuth(III) and triarylbismuth(V) compounds. For the past several years, organobismuth compounds have been used in many important synthetic organic reactions.

The aim of this work was to synthesize triarylbismuth(III) compounds and to apply them as reagents in various copper catalyzed arylation reactions.

The first part was to synthesize different triarylbismuth(III) compounds bearing functional groups. Triarylbismuth reagents can be easily accessed via the addition of Grignard reagents onto bismuth chloride to afford functionalized organobismuth reagents in moderate to good yields. Triarylbismuthanes are air and moisture stable and can be purified by simple silica gel chromatography. In addition, organobismuthanes show remarkable functional group tolerance, making them ideal candidates for the development of methodologies oriented towards medicinal chemistry applications.

The second part of the project was to apply triarylbismuth(III) as reagents in copper-catalyzed arylation reactions. fficient protocols for the copper-catalyzed *O*-arylation of phenols, *N*-protected 1,2-aminoalcohols and chloramphenicol using functionalized triarylbismuth reagents were developed. Catalytic amount of copper acetate promoted a C–O cross-coupling reaction under mild conditions. These reactions tolerate a wide diversity of functional groups giving access to a range of β-aryloxyamines or aryl ethers which are important for the synthesis of medicinally relevant compounds and very important structural motifs of numerous biologically active natural products and polymers in the material science industries.

CHAPTER I

TRIARYLBISMUTH REAGENTS: SYNTHESIS, PROPERTIES AND USE IN SYNTHESIS

1. INTRODUCTION

The element bismuth, the 64th most abundant compound in the Earth's crust [1], is a rare element and therefore not very commonly used. Bismuth has many interesting properties [2]: it is the most diamagnetic of all metals, it has the lowest thermal conductivity (in exception of mercury), it has a high electrical resistance, it is the heaviest stable element, it is not toxic or carcinogen (in contradiction to the other heavy metals like arsenic and lead) and it is not radioactive. Bismuth comes as a side product in the process of refining lead, copper, tin, silver and gold ores which is a low cost process. Due to low toxicity of bismuth, it can be use for green chemistry as well. In this century, the development of reactions that follow the principles of green chemistry is a must, because of the environmental principles that the field of research and industry are dealing with.

In bismuth compounds, bismuth is mostly present in the oxidation states +3 and +5. Bismuth(III) compounds can be easily transformed into bismuth(V) compounds using a variety of oxidizing agents such as peroxides, peracids and hypervalent iodine reagents. A few cases of bismuth(I) and bismuth(II) compounds have been reported, but those oxidation states are rare [3, 4]. Compounds where the bismuth center has an oxidation state of +3 have some Lewis acid properties due to the Lanthanide contraction. The electron configuration of bismuth is [Xe]$4f^{14}5d^{10}6s^{2}6p^{3}$, so the $4f$ electrons are weakly shielded.

The concept of organobismuth chemistry (compounds containing a C– Bi bond) started in 1850 with the synthesis of triethylbismuthine by Lowig and Schweizer [5]. The above compound is spontaneously flammable in air. On the contrary,

triphenylbismuthine, first synthesized by Michaelis and Polis in 1887 [6], is air-stable. A large number of derivatives of triphenylbismuthine have since been prepared. The first tetraaryl and pentaarylbismuth compounds were only synthesized in 1952 by Wittig and Clauss [7].

Triarylbismuth compounds are organometallic reagents where the bismuth is at the oxidation state of +3 and exist in the form of $BiAr_3$ or $Ar_{3-n}BiX_n$ (n = 0 to 3) [8-11]. The bismuth-carbon bond is one of the weakest among element-carbon bonds: the mean bond dissociation energy of triphenylbismuthine (Ph_3Bi) is 193.9 ± 10.8 kJ/mol compared to 321 ± 21 kJ/mol for triphenylphosphine (Ph_3P) and 373.7 ± 4.2 kJ/mol for triphenylamine (Ph_3N) [12]. A unique reactivity was hence expected and demonstrated by the arylation reactions of a great array of substrates. The organic derivatives of bismuth compounds were first used for medicinal preparations. In the 1980s, Barton and Finet reported a series of arylation reactions using triphenylbismuth and triphenylbismuth diacetate as the arylating agents [9, 13, 14].

Oganobismuth compounds have come out as an important class of organometallic reagents with many applications in different areas in past several years [15, 16], as organobismuth chemistry has undergone growth rapidly and some novel organobismuth compounds have been reported [17-19]. Many types of organobismuth compounds have proved to be efficient reagents in *C*-, *N*- and *O*-arylation reactions [20], benzoylation reactions [21], cross-coupling reactions [22], etc. However, the organometallic chemistry of bismuth has developed relatively slowly compared to that of other main group metals [23, 24].

1.1 Preparation of Different Types of Triarylbismuth Compounds

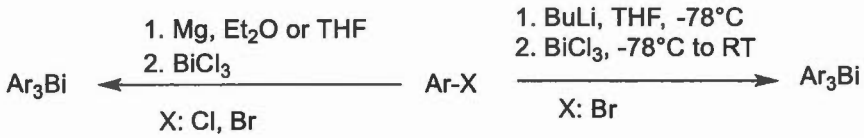
In the past several years, many organobismuth compounds have been discovered along with the development of the chemistry of organobismuth species. This class of compounds can be prepared by several methods including metathesis, oxidative

addition, reduction, transmetallation, thermolysis, disproportionation, electrochemical coupling and others.

1.1.1 Preparation of Triarylbismuth Reagents

The organometallic route, i.e. the addition of an organometallic reagent on bismuth chloride, is the most trivial and frequently used method for the synthesis of triarylbismuthines. A wide variety of symmetrical tertiary bismuthines possessing groups such as alkyl, fluorine, methoxy and chlorine at different positions on the aryl moiety can be prepared using Grignard reagents and organolithium reagents as shown in Scheme 1. Ar_3Bi can also be prepared on large scale using this route [25, 26].

Scheme 1

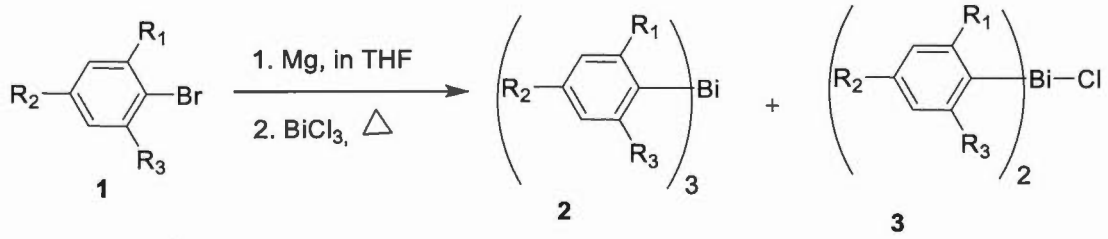


This approach consists of two-step procedure: an organomagnesium reagent is first formed by the reaction of an aryl bromide with magnesium turnings in tetrahydrofuran or diethyl ether as the solvent under inert atmosphere and the thus formed organomagnesium species is then added cautiously over bismuth chloride or bismuth bromide as a bismuth source under controlled temperature. Aryl chlorides can also be used [27]. Triarylbismuth compounds can also be prepared from organolithium reagents obtained via the halogen/metal exchange method as mentioned in scheme 1.

1.1.2 Preparation of Hindered Organobismuth Reagents

The above method can also be used for the preparation of hindered organobismuthines and diarylbismuth halides as shown in Scheme 2.

Scheme 2



R: Me, Et, *i*Pr

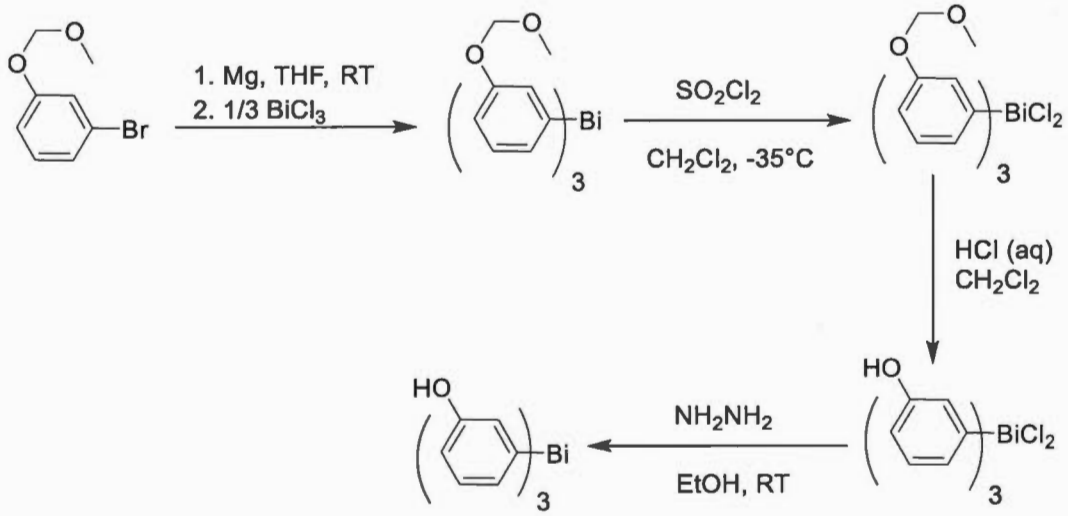
Suzuki and co-workers reported the synthesis of crowded triarylbismuthines where bulky aryl groups were transferred from an organomagnesium or organolithium to bismuth chloride [28]. Compound **2**, where R = Me [*tris*-(2,4,6-trimethylphenyl)bismuthine] and R = Et [*tris*-(2,4,6-triethylphenyl)bismuthine], can be synthesized by heating the reaction mixture at reflux with phenylmagnesium halide at 0°C. When some bulky groups like isopropyl R = *i*-Pr are present, only two aryl groups are transferred to $BiCl_3$ at room temperature, giving chloro-*bis*-(2,4,6-triisopropylphenyl)bismuth (Ar_2BiCl) as an isolated product.

1.1.3 Preparation of Triarylbismuth Reagents Having Acidic Substituents

For the synthesis of triarylbismuth compounds bearing acidic groups, a protecting group is generally required. The selected protecting group should be stable during the formation of the Grignard reagent (which is later added over $BiCl_3$) and the Bi−C bond should not be cleaved during the deprotection step. For example, the synthesis of *tris*-(3-hydroxyphenyl)bismuthine was accomplished by the reaction of Grignard

reagent with $BiCl_3$ followed by oxidative chlorination to give the arylbismuth(V) dichloride on which the MOM protecting group was then removed, affording triarylbismuth bearing a free phenol. The Bi–C bonds in arylbismuth(V) are known to be more stable toward acidic conditions compared to the corresponding bonds in arylbismuths(III). Deprotection was performed using aqueous HCl in DCM. Reduction of the Bi(V) center to Bi(III) by reaction with hydrazine gave phenolic hydroxyl group on triarylbismuth as shown in Scheme 3 [17].

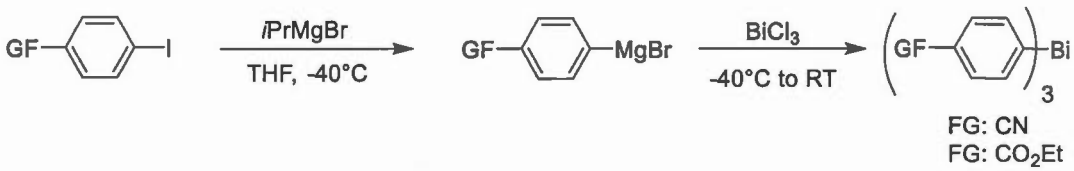
Scheme 3



1.1.4 Preparation of Triarylbismuth Reagents Having Deactivating Groups

Triarylbismuth compounds having electron-withdrawing groups can also be prepared by the traditional Grignard method as proposed by Murafugi and Sugihara [29, 30]. The required functionalized Grignard reagents were prepared using the Knochel method [31, 32] via iodine magnesium exchange in tetrahydrofuran at -40°C or -20°C using aryl iodide and isopropylmagnesium bromide to generate the aryl Grignard reagent followed by dropwise addition over $BiCl_3$ at -40°C as shown in Scheme 4.

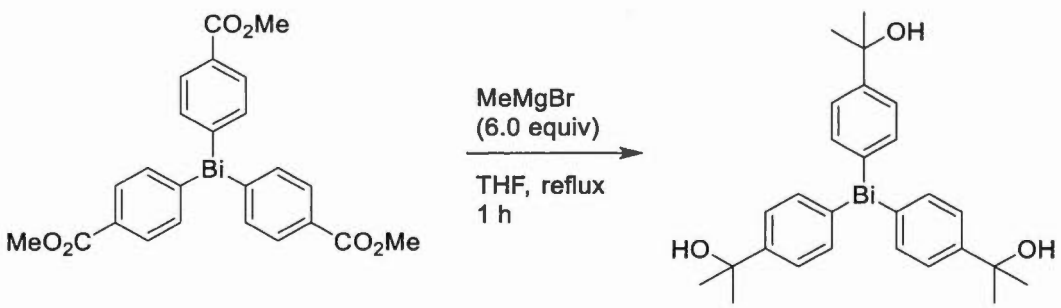
Scheme 4



1.1.5 Preparation of Highly Functionalized Organobismuthanes Reagents by Functional Group Manipulation

Due to robustness of the Bi−C bond, alteration of functional groups can be done directly on selected organobismuthanes. As reported by our group, triarylbismuths carrying an alcohol functional group can be synthesised by refluxing the ester derivative of triarylbismuth with 6 equivalents of methylmagnesium bromide in THF for an hour as shown in Scheme 5 [33].

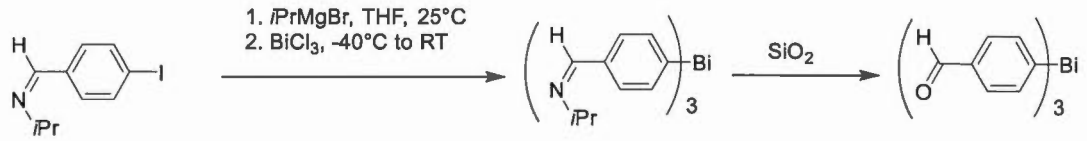
Scheme 5



1.1.6 Preparation of Organobismuth Reagents Having Formyl Groups

The synthesis of *tris*-(4-formylphenyl)bismuthine was done by iodine–exchange method at 25°C [31, 32]. Protection of the formyl group as an imine was required as shown in Scheme 6.

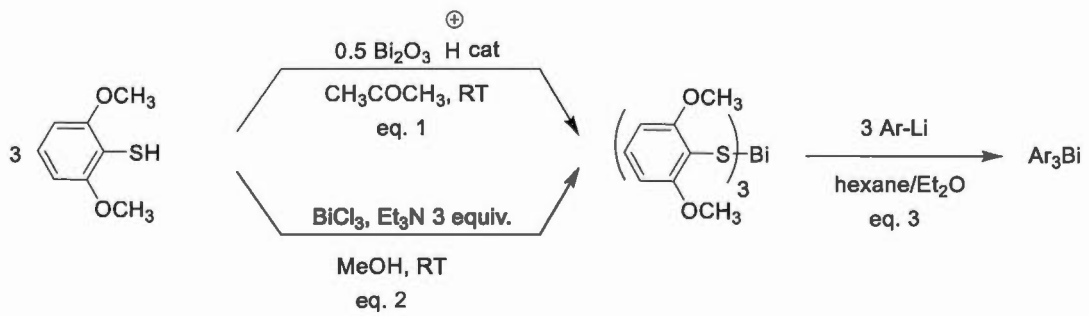
Scheme 6



1.1.7 Preparation of Thiolatobismuth Reagents

Thiolatobismuth reagent [$Bi(SAr)_3$] can be obtained as an intermediate in the process of formation of Ar_3Bi as shown in Scheme 7. It can be synthesized either by reaction of bismuth(III) oxide with 2,6-dimethoxybenzenethiol (ArSH) in $(CH_3)_2CO$ in the presence of catalytic amount of HNO_3 (Scheme 7; Eq 1) or by reaction of bismuth chloride with ArSH in MeOH (Scheme 7; Eq 2), affording $Bi(SAr)_3$ as reported by Wada and co-workers [34], which on further reaction with an organolithium reagent gives Ar_3Bi (Scheme 7; Eq 3).

Scheme 7

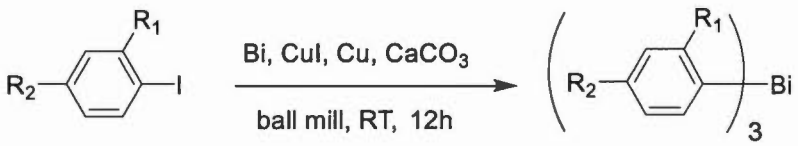


1.1.8 Preparation of *Ortho* Functionalized Triarylbismuth Reagents Having Electron-Withdrawing Groups

This class of reagents can be prepared by the "ball mill" technique [35] which is a one-pot solvent free technique where an aryl iodide is mixed with metallic bismuth,

copper, copper iodide and calcium carbonate at room temperature for about 12 hours in a ball mill apparatus as shown in Scheme 8. This procedure has some limitations due to the interaction between the *ortho* functional group (cyano, nitro) and reactive metal intermediates. A combination of Bi and Cu or CuI is essential for the present reaction and the combined use of Cu powder and CuI gave better results than the separate use of either one of these. Without copper, no triarylbismuthanes were formed. Commercial bismuth powder proved to be less satisfactory for the present purpose. This observation demonstrates a crucial role of the nascent bismuth surface in the formation of organobismuth compounds. Thus, with an idea to modulate the milling rate of bismuth shots, about 0.5–0.7 molar equivalents of calcite grains were added to the reaction mixture, since both bismuth and calcite are located at grade 3 on the Mohs hardness scale.

Scheme 8



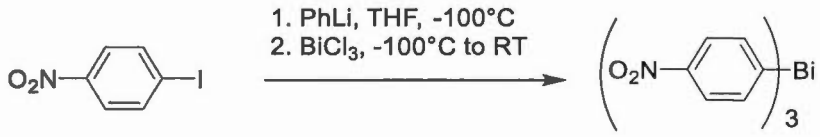
R_1: H, F, Cl, Br, CF_3, $N{=}CHC_6H_5$, OMe, CO_2Et
R_2: H, F, CF_3

1.1.9 Preparation of *Tris*-(*p*-nitrophenyl)bismuth Reagents

Various methods that have already been illustrated above can be used to prepare triarylbismuth compounds bearing a nitro group. For example, the iodine-lithium exchange starting from 4-iodonitrobenzene and phenyllithium to generate the corresponding lithium reagent and its subsequent addition over $BiCl_3$ in THF was

utilized to afford *tris*-(*p*-nitrophenyl)bismuth, as shown in Scheme 9 [29].

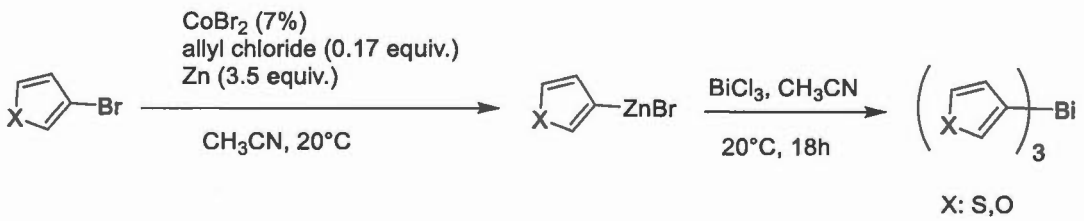
Scheme 9



1.1.10 Preparation of *Tris*-(heteroaryl)bismuth Reagents

These reagents can be prepared via addition of Grignard or organo-lithium reagents over bismuth salts. For example, *tris*-(3-methyl-2-thienyl)bismuthine was prepared from the corresponding organomagnesium reagent [36] whereas *tris*-(N-methyl-5-indolyl)bismuthine [37] and *tris*-(1-methyl-2-pyrrolyl)bismuthine [38] were synthesized by lithium-halogen exchange followed by addition of bismuth chloride. A more recent method involving the formation of an organozinc reagent was developed by Condon *et al.* for the synthesis of *tris*-(heteroaryl)bismuth reagent [39] as shown in Scheme 10. In this approach, heteroarylzinc reagents were prepared by cobalt-catalyzed bromine/zinc exchange by reduction of aryl halide with zinc dust [40]. In the next step, the *in situ* formed organozinc reagent was added over bismuth chloride.

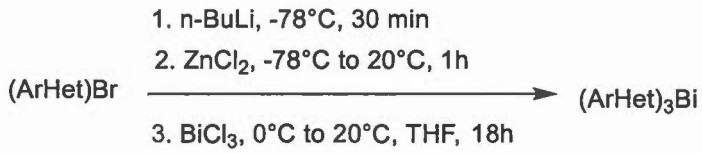
Scheme 10



Another protocol, where heteroarylzinc reagents [39] are obtained by bromine-lithium exchange in THF followed by two subsequent transmetallation steps, one

with $ZnCl_2$ and a second transmetallation with $BiCl_3$, was developed to afford tris-(heteroaryl)bismuth reagents as shown in Scheme 11.

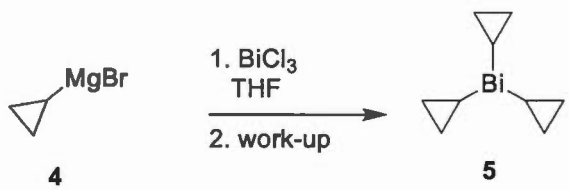
Scheme 11



1.1.11 Preparation of Tricyclopropylbismuth

Tricyclobismuth can be prepared by the addition of cyclopropylmagnesium bromide over $BiCl_3$ as shown in Scheme 12 by our group. It was found that tricyclopropylbismuth is not pyrophoric [41]. Therefore, a simple work-up and trituration in hexanes provided the desired compound as a white solid [42].

Scheme 12



1.2 Objectives of the Project

The objective of this project was to synthesize organobismuthines which are an attractive class of organometallic reagents that can be accessed from inexpensive and non-toxic bismuth salts. Triarylbismuthines are particularly interesting due to their air and moisture stability and high functional group tolerance. The strategy that we explored consists of introducing the incompatible functional group by performing a functional group transformation directly on the organobismuth species. In the course of our studies, we found that the C–Bi bond of organobismuthines is resistant to acidic, reductive, and even oxidative conditions, thus enabling the transformation of the functional group into a more elaborated functional group. We report herein a detailed study on the preparation of highly functionalized triarylbismuth reagents by functional group manipulation. To further gain insight into the structure of triarylbismuthines, we crystallized and analyzed by X-ray diffraction several derivatives of triarylbismuth reagents bearing different functional groups at different positions; we published these results in *JOC* **2016** p5401.

1.3 RESULTS AND DISCUSSION

The synthesis of organobimuth reagents was performed in two steps as shown in Scheme 13. First, reagent **7** was obtained by reaction of magnesium with organic halide **6** as shown in equation 1 of scheme 13. The usual route for the synthesis of Grignard reagents is the oxidative addition of magnesium metal to organic halides in a polar and aprotic solvent such as THF. However, since organomagnesium reagents are highly sensitive to moisture, an inert atmosphere was maintained to avoid the hydrolysis of the Grignard reagent. In the second step, the organomagnesium reagent was slowly added dropwise to the solution of bismuth chloride in THF at a controlled temperature of -10°C to afford the corresponding triarylbismuth reagent **8** as shown in equation 2 of scheme 13.

Scheme 13

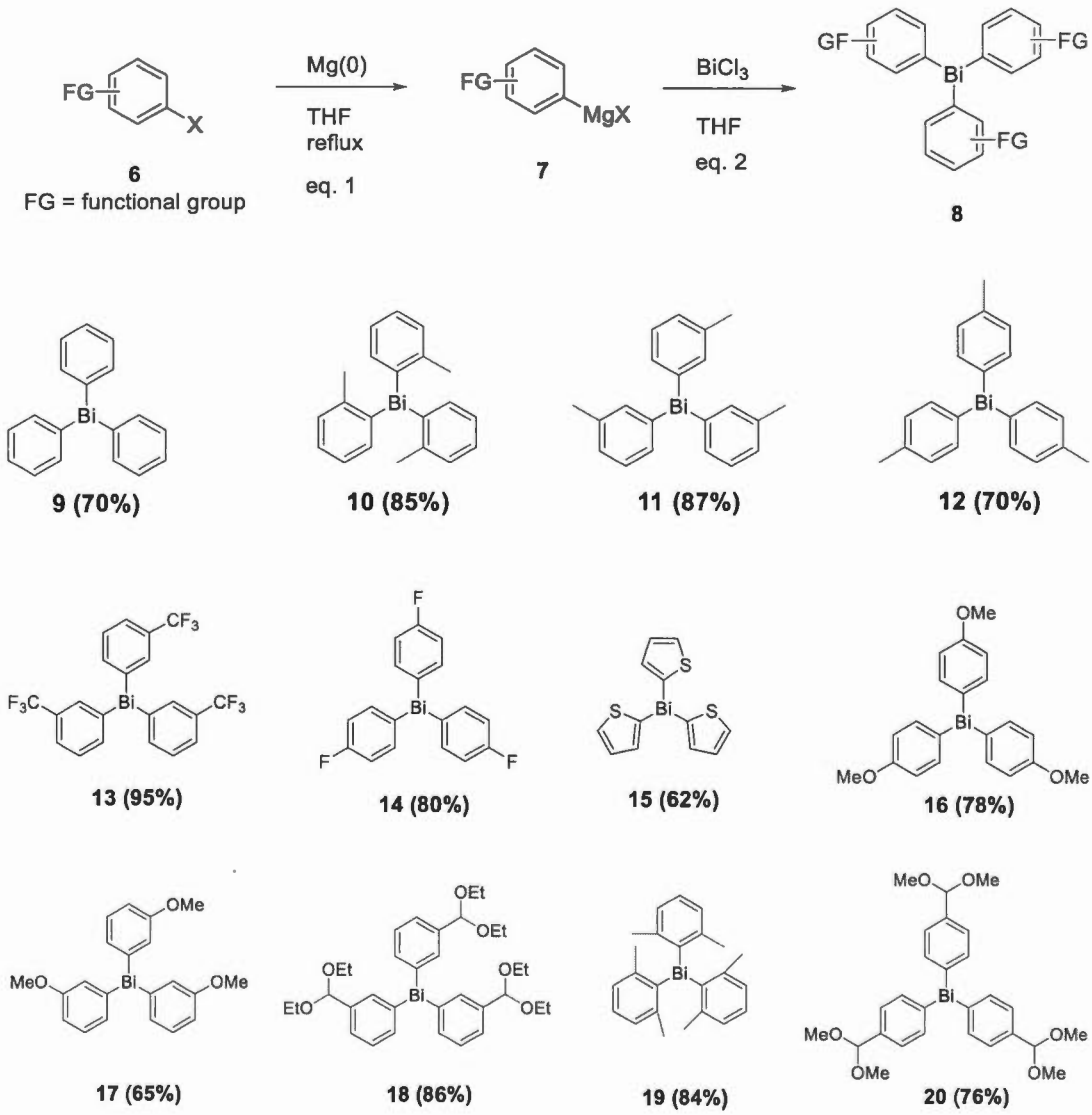


Figure 1: Functionalized Organobismuth Reagents

Using this protocol, we were able to synthesize a broad range of triarylbismuth reagents containing alkyl, methoxy, fluorine, acetal and heteroaryl groups at different positions of the aryl moiety in moderate to good yields as shown in Figure 1.Here, the ^{1}H-NMR spectra of compound **12**, **14**, **15**, **16** and **20** are analyzed and discussed.

The ^{1}H-NMR spectrum of compound **12** shows characteristic signals for the *p*-methyl group at 2.3 ppm (Figure 2), which confirms the obtention of the desired product. Two doublets are also indicative of a *para*-disubstituted phenyl ring.

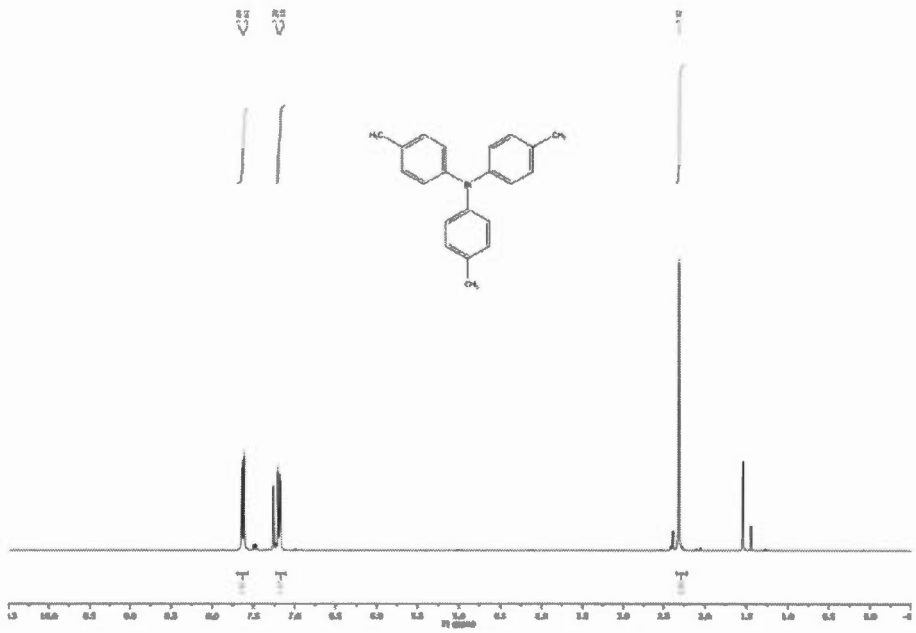


Figure 2: ^{1}H-NMR Spectrum of Compound 12

Compound **14** was characterized by ^{1}H-NMR. The spectra shows the formation of the desired product as shown in Figure 3.

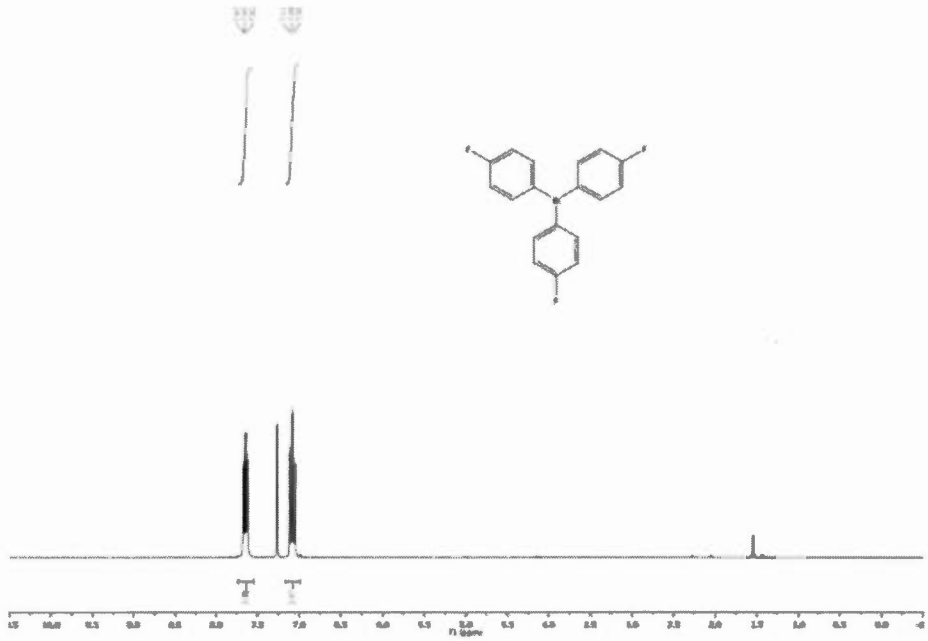


Figure 3: ^{1}H-NMR Spectrum of Compound 14

The ^{1}H-NMR spectrum of isolated compound **15** shows the characteristic signals for the thiophene protons, confirming the formation of the desired compound without any presence of starting material as shown in Figure 4.

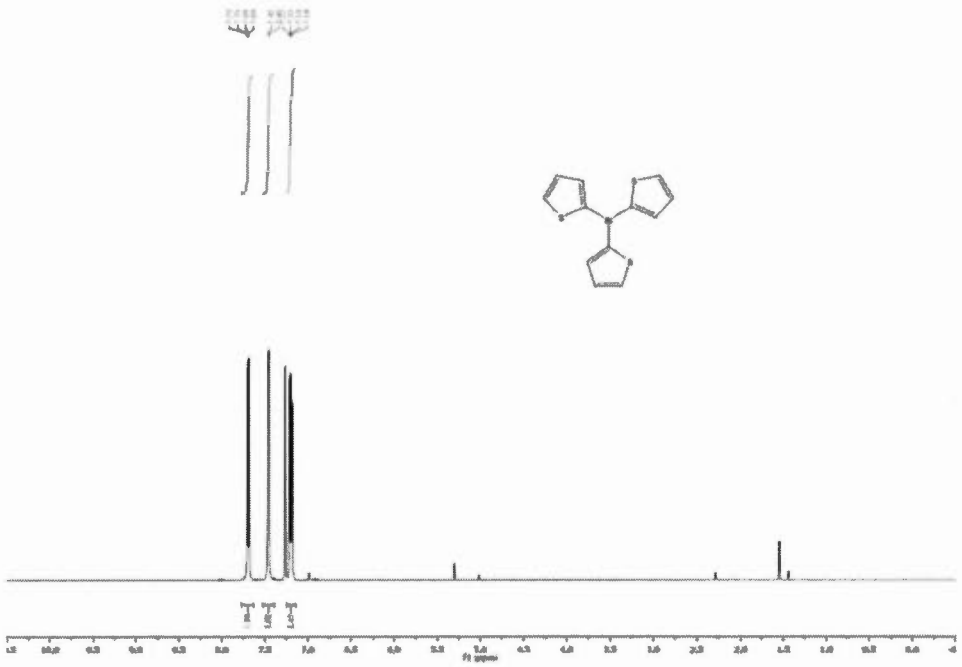


Figure 4: ^{1}H-NMR Spectrum of Compound 15

The ^{1}H-NMR spectrum of compound **16** shows the presence of a methoxy group on the aromatic ring which is activating because the oxygen atom of the methoxy group donates its lone pair into the aromatic ring via resonance, making it more electron rich. As a consequence, an upfield shift is observed for the aromatic protons compared to the *para*-tolyl derivative 12. The resonace of the OMe in phenyl ring affects the δ of H on the phenyl ring, not the H of the OMe. Since it is a Csp^3–H, the OMe comes out at the lower ppm as shown in Figure 5.

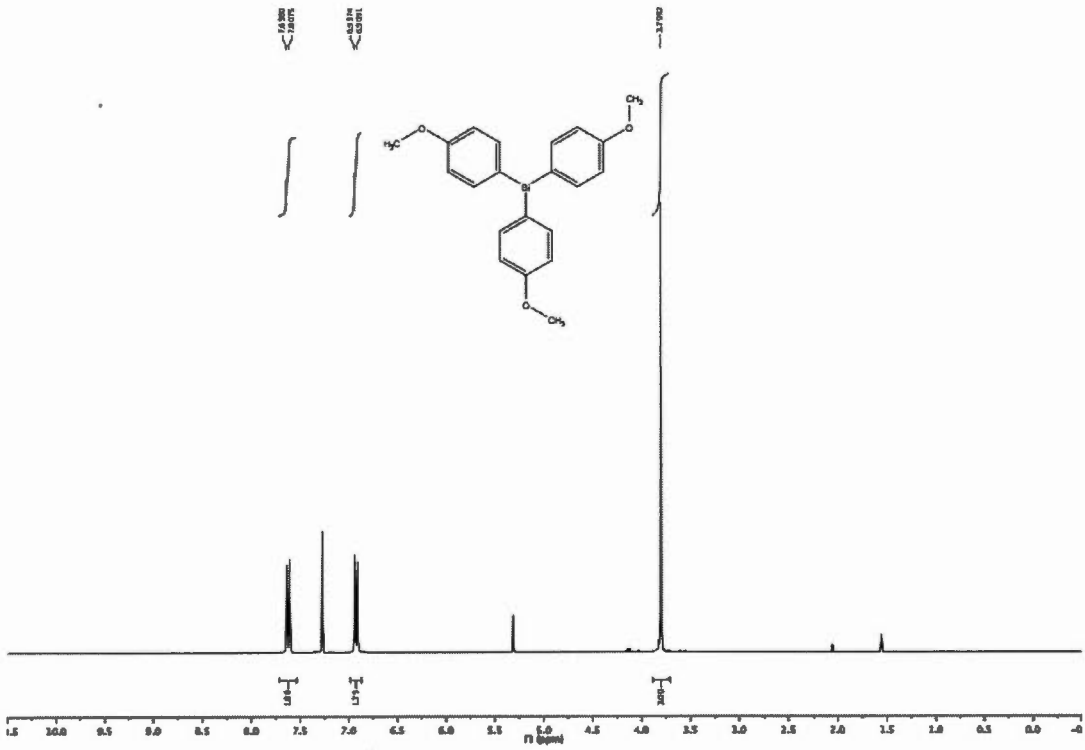


Figure 5: ^{1}H-NMR Spectrum of Compound 16

The ^{1}H-NMR spectrum of isolated compound **20** shows the characteristic signals for the acetal group as a 3H triplet at 1 ppm, 2H quartet at 3.56 ppm and 1H singlet at 5.5 ppm. Aromatic protons at around 7 ppm are also observed in the form of two doublets, confirming the presence of a *para*-substitued phenyl ring as shown in Figure 6.

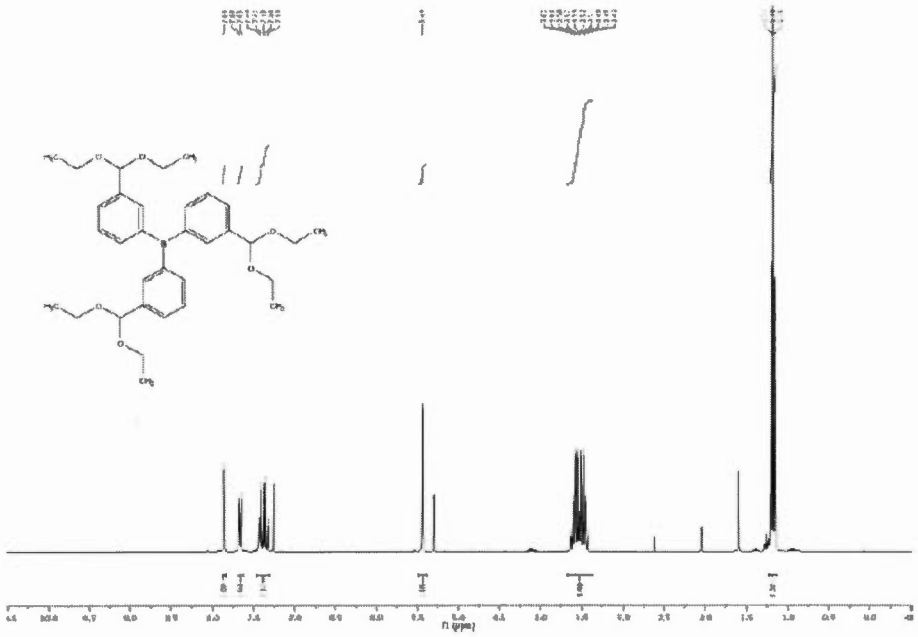


Figure 6: ^{1}H-NMR Spectrum of Compound 20

1.4 Structural Characterization of Selected Triarylbismuthines

To understand more deeply the structure of the triarylbismuthines, compound **21, 22, 23, 24, 25, 26** and **27** in figure 7 were crystallized and analyzed by X-ray diffraction. The results show that the organobismuthines have a distorded pyramidal structure and that the C–Bi bond lengths vary from 2.24Å to 2.27Å whereas the C–Bi–C bond angles vary between 91° and 98°. Interestingly, the nature and position of the substituent appears to have little impact on the structure of the organobismuthine. It should be noted that the small bond angle is due to the relativistic effect of the lone pair of 6s orbital of bismuth which leads to formation of C–Bi bonds with the p_x, p_y, and p_z orbitals of the bismuth.

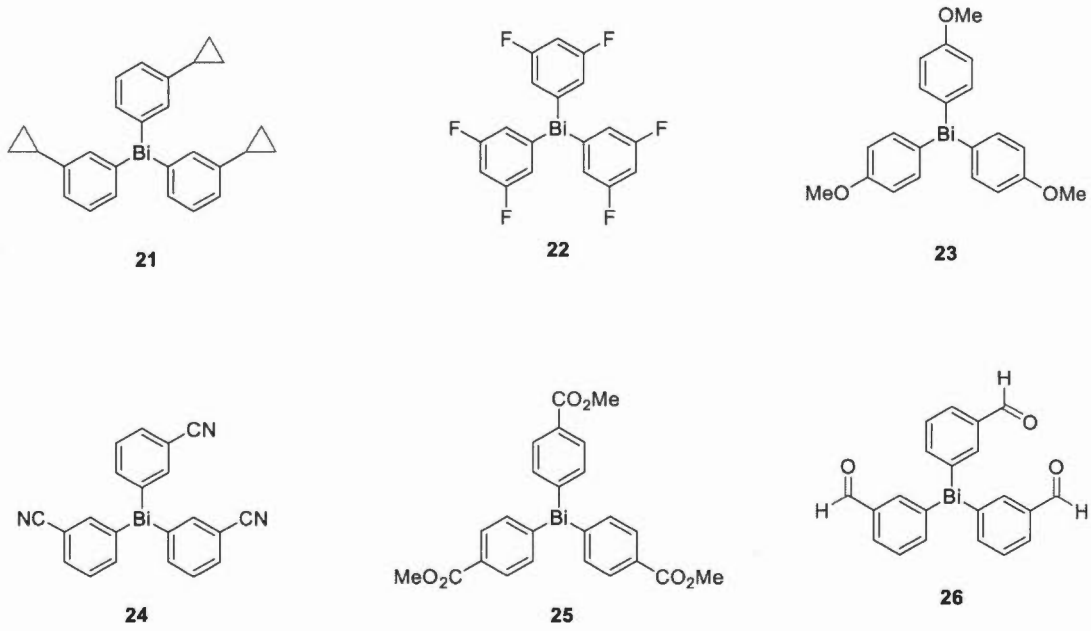
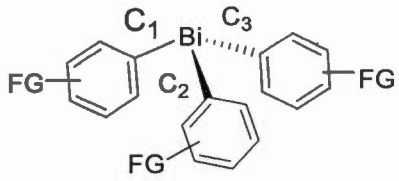
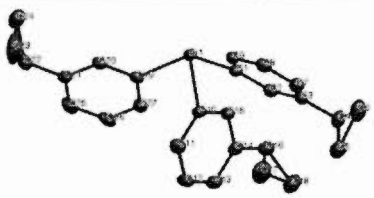
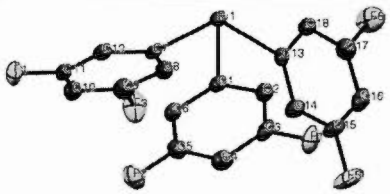
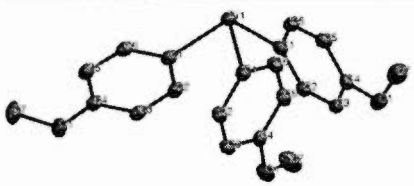
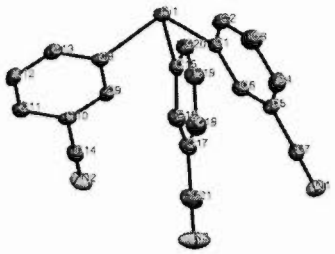
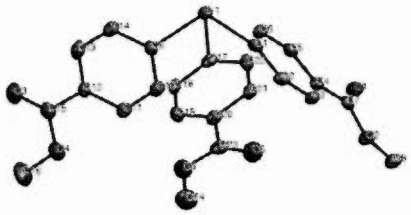
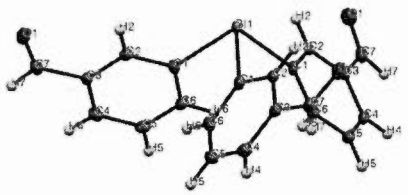
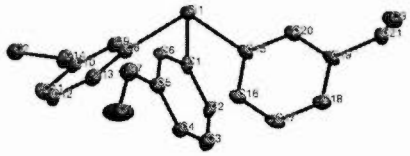


Figure 7: Crystallized Organobismuth Reagents

Table 1: X-Ray Structures of Some Organobismuth Reagents



FG	Ortep diagram	C–Bi bond length			C–Bi–C bond angle		
		C_1–Bi (Å)	C_2–Bi (Å)	C_3–Bi (Å)	C_1–Bi–C_2 (°)	C_2–Bi–C_3 (°)	C_1–Bi–C_3 (°)
21 3-*c*-Pr		2.254	2.256	2.253	95.73	94.94	92.47
22 3,5-diF_2		2.264	2.263	2.255	92.93	93.09	96.20
23 4-MeO		2.250	2.251	2.251	93.80	93.78	93.81

24 3-CN		2.273	2.263	2.269	93.07	98.04	91.77
25 4-CO_2Me		2.262	2.260	2.255	93.33	94.81	92.11
26 3-CHO		2.266	2.266	2.266	92.02	92.02	92.02
27 3-(CH_2OH)		2.254	2.264	2.2541	91.50	94.58	95.61

CHAPTER II

TRIARYLBISMUTH COMPOUNDS AS ARYLATING REAGENTS IN ORGANIC SYNTHESIS

2.1 INTRODUCTION

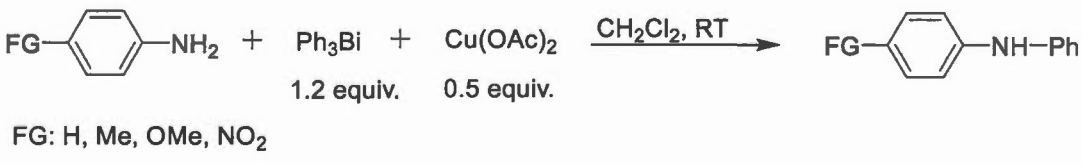
Organobismuth reagents, like other organometallic reagents, have been well studied and frequently used as a reagents in organic synthesis [43, 44]. Due to environmental factors, the use of non-toxic reagents represents the ideal approach in organic synthesis. Thus, this class of reagent is ideal for arylation reactions [20, 45, 46].

Organobismuth reagents undergo different major types of arylation reactions: (a) *C*- and *O*-arylation; (b) *O*-arylation; (c) *O*- and *N*-arylation (d) C-*S* arylation [20, 46].

2.1.1 *N*-Arylation Reactions of Aliphatic and Aromatic Amines Using Triarylbismuth Reagents

N-Arylation of aliphatic and aromatic amines with $Ar_3Bi(OAc)_2$ under neutral conditions catalyzed by copper powder was reported by Barton and co-workers [47]. In a subsequent study, they reported a $Cu(OAc)_2$ mediated *N*-arylation of aliphatic and aromatic amines with Ar_3Bi under mild conditions as shown in Scheme 14. These reactions are sensitive to steric hindrance on the amine and dependent on its basicity [48].

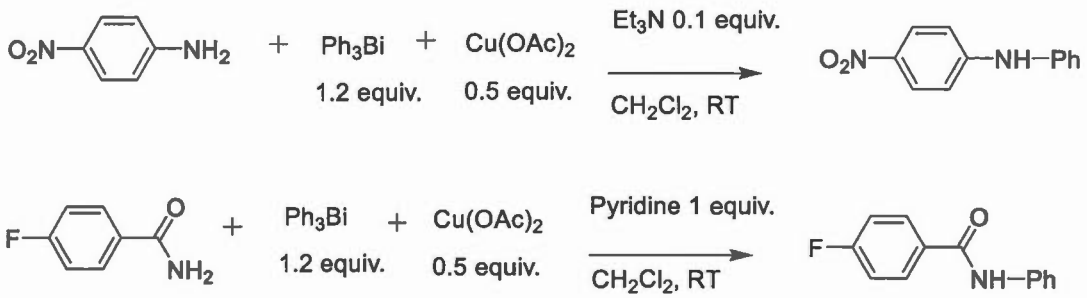
Scheme 14



2.1.2 N–H Bond Formation Using Triarylbismuth Reagents

Later, Barton's work was modified by Chan where a tertiary amine was introduced as a promoter [49]. By addition of triethylamine or pyridine, the scope of the arylation reaction of N–H compounds was extended to other substrates such as amides, imides, ureas, carbamates and sulfonamides with the yield ranging from 6 to 82% as shown in Scheme 15.

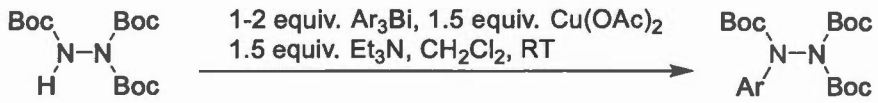
Scheme 15



2.1.3 *N*-Arylation of Diversely Substituted Hydrazines Using Triarylbismuth Reagents

The arylation of substituted hydrazines such as $Boc_2N-NHBoc$ and Cbz(Boc)N–NHBoc was reported by Mäeorg and Ragnarsson *et al* (Scheme 16) [50-52].

Scheme 16

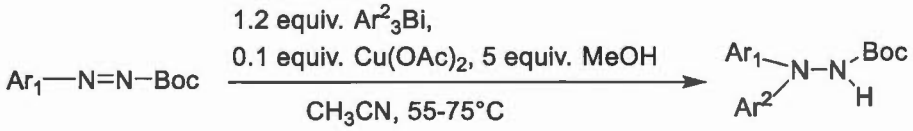


Ar: Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$

2.1.4 *N*-Arylation of Azo Compounds Using Triarylbismuth Reagents

The copper-catalyzed arylation of azo compounds using triarylbismuth reagents is a reaction which is conducted in methanol. In this transformation, the methanol serves as a source of proton rather than a solvent. The reaction is performed in acetonitrile and was found to be regioselective, delivering the aryl group on the nitrogen which is connected to the aryl group already in place rather than on the nitrogen which is connected to the BOC protecting group (Scheme 17) [53].

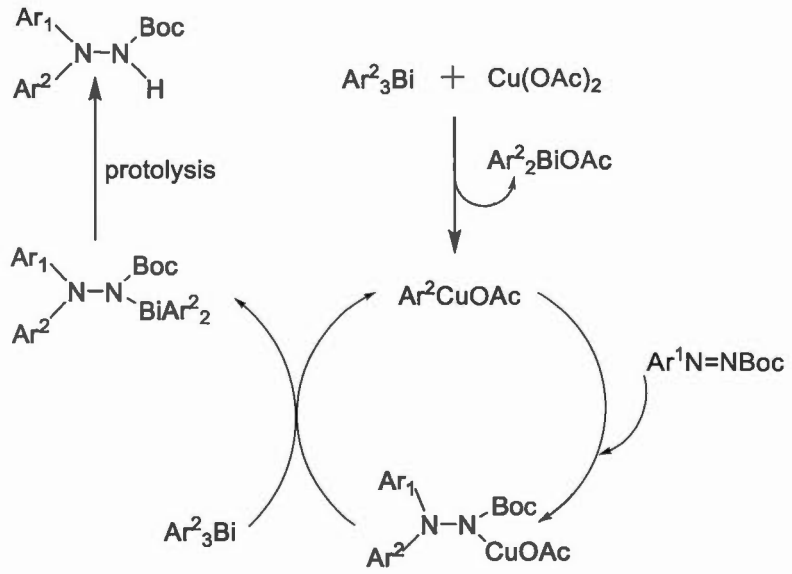
Scheme 17



Ar^1: Ph, *o*-Tol, 2,4-$(NO_2)_2C_6H_3$, 4-$NO_2C_6H_4$
Ar^2: Ph, 1-Np, *o*-Tol

These types of reactions can be performed under mild conditions by using different solvents such as acetonitrile, methanol, *N*-Methyl-2-Pyrrolidone (NMP) and different copper salts such as copper(II) chloride, copper(II) chloride hydrate or copper(II) acetate. The presence of slightly electron donating groups (for example methyl) or electron withdrawing groups (for example nitro) on the aryl moiety of the azo compound does not have any significant impact on the efficiency of the reaction. The proposed mechanism is illustrated in Scheme 18.

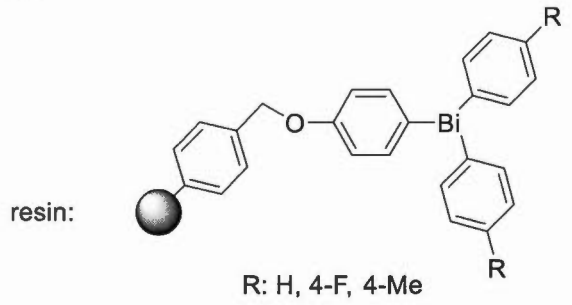
Scheme 18



2.1.5 Resin-Bound Bismuthanes as *N*- and *O*-Arylating Reagents

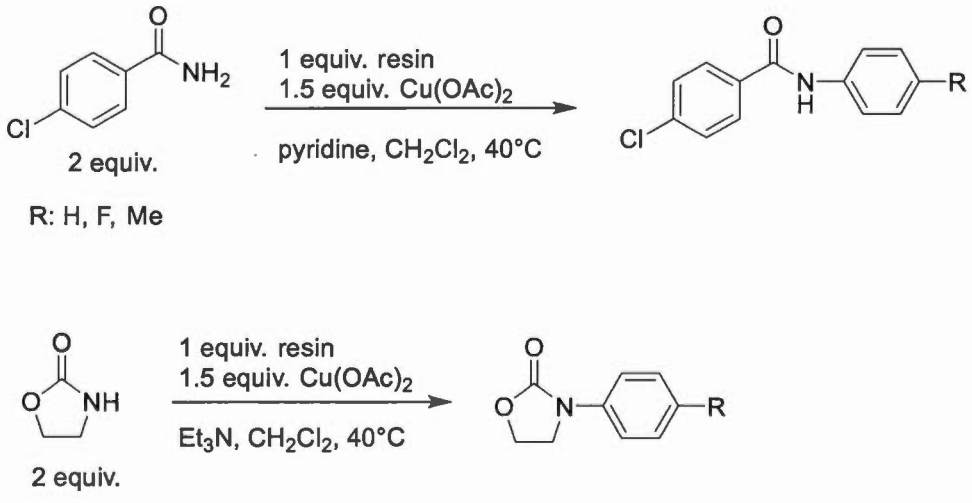
Resin-bound bismuthanes were used in *N*- and *O*- arylation reactions [54] and in Suzuki cross-coupling reactions in solid-phase organic synthesis [55]. These reagents can be prepared from commercially available chloromethyl polystyrene, *p*-iodophenol as linker precursor and diarylbismuth triflate HMPA complex. These arylating reagents are designed in a way that there is a sufficient distance between two types of aryl groups, which is important to protect the carbon–bismuth bond and to allow the selective split of two aryl transfer groups during the chemical process. Accordingly, the phenoxy group has been selected as a spacer since most electron poor aryl groups are known to be selectively transferred in arylation reactions (Scheme 19) [56].

Scheme 19



In Scheme 20, *p*-chlorobenzanilide and oxazolidin-2-one were arylated using resin-bound bismuth as the arylating reagent in the presence of copper(II) acetate, pyridine as a base in methylene dichloride as the solvent, providing mild conditions for this reaction. This method is less attractive than Chan's method due to its low productivity which could be due to possible indigent diffusion of poorly soluble copper(II) acetate into the resin [49].

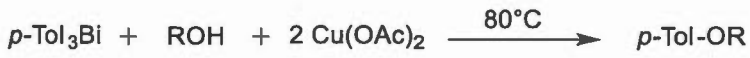
Scheme 20



2.1.6 *O*-Arylation of Aliphatic Alcohols Using Triarylbismuth Reagents

The use of arylbismuth(III) as O-phenylating reagents is less common relative to arylbismuth(V). Dononov and co-workers reported the O-arylation of aliphatic phenols under mild conditions using copper(II) acetate as the catalyst (Scheme 21) [57].

Scheme 21

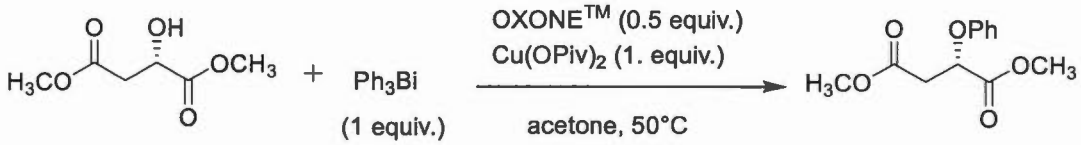


R: Bu, Me

2.1.7 *In-situ* Oxidation of Arylbismuth(III) to Arylbismuth(V)

Pentavalent arylbismuth reagents can be obtained via oxidation of trivalent arylbismuths using iodobenzene-diacetate [58], benzoyl peroxide [59] or potassium peroxymonosulfate (OXONE®) [60]. In the presence of copper(II) pivalate and potassium peroxymonosulfate, bismuth(V) species were formed during aryl transfer reactions as reported by Sheppard (Scheme 22) [61].

Scheme 22

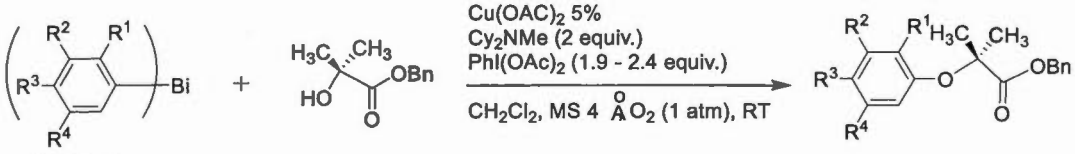


2.1.8 *O*-Arylation of Tertiary Alcohols Under Anhydrous Conditions

The one-pot arylation reaction of α-hydroxy benzyl propionates in the presence of stoichiometric amount of copper(II) acetate under anhydrous conditions and using trivalent arylbismuthines was reported by Sato and co-workers (Scheme 23) [60]. The

oxidation of electron-rich triarylbismuthines was assured by (diacetoxyiodo)benzene in the presence of *N*-methyldicyclohexylamine under O_2 atmosphere. The steric hindrance at the *ortho*-position on the aryl moiety was found to be sensitive during the aryl transfer.

Scheme 23

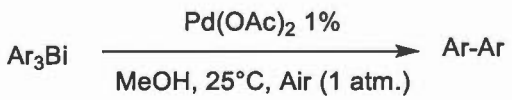


R^1, R^4: Me, OMOM; R^2, R^3: H vice-versa

2.1.9 Conversion of Triarylbismuth Reagents into Symmetrical Biaryl Products

The first conversion of Ar_3Bi into symmetrical biaryls and Bi(0) mediated by Pd(0) generated *in situ* from a stoichiometric amount of $Pd(OAc)_2$ and triethylamine as base in either THF, MeCN or HMPA as solvent was reported by Barton *et al.* in 1988 [62]. Later, Uemura and co-workers reported the synthesis of biaryl compounds mediated by $Pd(OAc)_2$ in methanol under oxidative conditions as shown in Scheme 24 [63].

Scheme 24

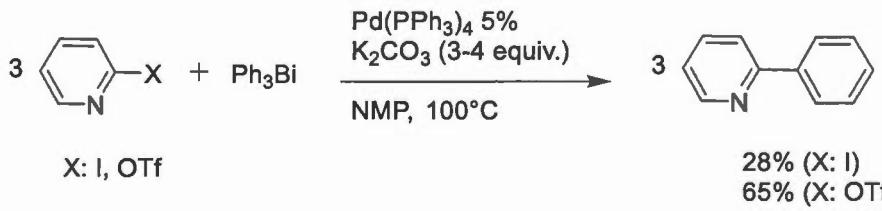


Ar: 4-$MeOC_6H_4$, 3-MeC_6H_4, 4-MeC_6H_4, 4-FC_6H_4, 4-ClC_6H_4

2.1.10 Cross-Coupling Reaction of Triarylbismuth Reagents with Aryl Halides and Aryl Triflates

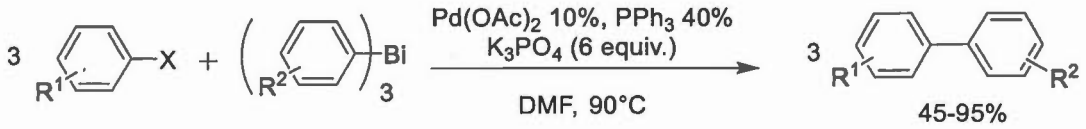
Shimada and co-workers demonstrated that the cross-coupling reaction of triarylbismuth reagents with organic electrophiles such as aryl bromides, iodides and triflates is possible via catalysis using palladium(0) complexes. Organobismuth compounds can be efficiently coupled with electron deficient, electron neutral and even electron rich aryl bromides in the presence of commercially available $Pd(PPh_3)_4$ at 100°C in NMP or 1,2 dimethoxyethane. Additives such as K_2CO_3, Cs_2CO_3 and CsF considerably improved the efficiency of the reaction [64]. The reaction can also be performed on 2-iodopyridine and 2-pyridinyltrifluoromethanesulfonate as shown in Scheme 25.

Scheme 25



Later studies were done to evaluate the solvent and catalyst effect [65, 66] and it was found that $Pd(OAc)_2/PPh_3$ at 90°C in DMF provides better yields than $Pd(PPh_3)_4$ as shown in Scheme 26.

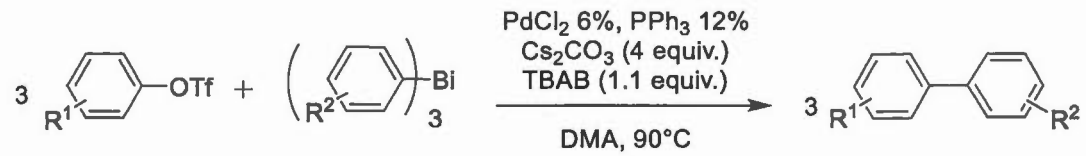
Scheme 26



X: Br, I, Tf
R^1: COMe, Cl, NO_2, F, CN, CF_3, CO_2Et, COPh, Me
R^2: H, OMe, Me, F, Cl

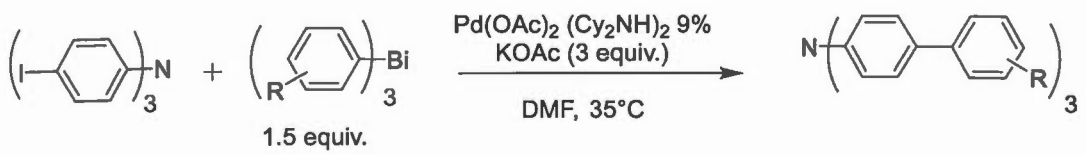
Another set of conditions consisting of $PdCl_2/PPh_3$ in DMA along with Cs_2CO_3 provided good yields of the desired cross-coupling products as shown in Scheme 27 [43]. The addition of TBAB or TBAI in the cross-coupling reaction of aryl triflates was found to be beneficial (Scheme 27).

Scheme 27



Later, Rao and co-workers developed a protocol for the synthesis of structural motifs which can be used in photochemistry, as illustrated in Scheme 28.

Scheme 28

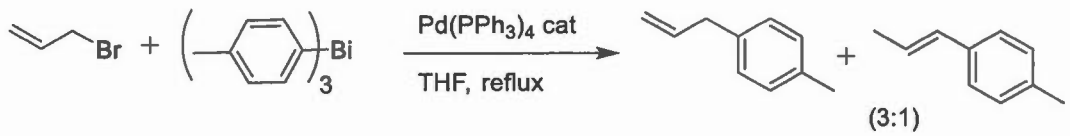


R: 3-Me, 4-Me, 3-CF_3, 4-CF_3, 4-OEt, 3-OMe

2.1.11 Cross-Coupling Reaction of Allylic Bromides with Triarylbismuth Reagents

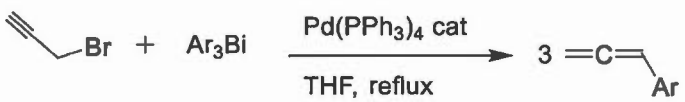
Palladium mediated cross-coupling of allylic bromides with Ar_3Bi at reflux of THF was reported by Wada and Ohki (Scheme 29) [67]. Two different regioisomers were obtained.

Scheme 29



Arylallenes can also be synthesized from propargyl bromide via palladium-catalyzed cross-coupling reaction using triarylbismuthines using the above protocol as exemplified in Scheme 30 [68].

Scheme 30

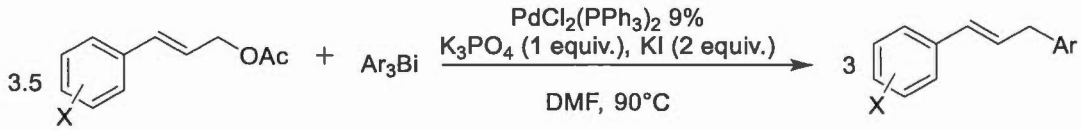


Ar: Ph, *p*-Tol, 4-ClPh

2.1.12 Arylation of Allylic Acetates with Triarylbismuth Reagents

The regioselective arylation of allylic acetates with Ar_3Bi was reported by Rao and co-workers (Scheme 31) [69]. The reaction tolerates a wide diversity of functional groups on the allyl acetate and provides the desired products in good to excellent yields with high regioselectivity. The key factors for efficient coupling are the addition of KI, which probably promotes the stability of η3-Pd intermediates *via* an acetate/iodide exchange and the addition of a small excess of allylic acetate to counteract the unwanted partial hydrolysis of the allylic acetate.

Scheme 31

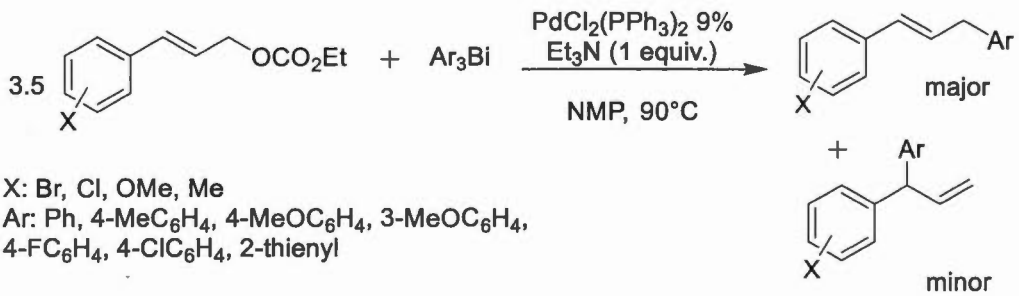


X: H, 3-OMe, 4-Me, 2-Cl, 3-Cl, 4-Cl, 3-Br, 4-Br
Ar: Ph, *p*-Tol, *p*-An, *m*-An, 4-FC_6H_4, 4-ClC_6H_4, 2-thienyl

2.1.13 Arylation of Allylic Carbonates with Triarylbismuth Reagents

1,3-Disubstitued propenes can be synthesized as a major product via arylation of allylic carbonates with triarylbismuth reagents. Due to decomposition of Ar_3Bi, some branched isomers were formed as a minor product, as illustrated in Scheme 32 [70].

Scheme 32

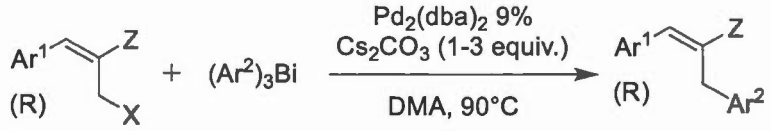


X: Br, Cl, OMe, Me
Ar: Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 2-thienyl

2.1.14 Coupling of Baylis-Hillman Adducts with Triarylbismuth Reagents

Bromo and chloro derivatives of Baylis-Hillman adducts react with Ar_3Bi in the presence of $Pd_2(dba)_2$ as a catalyst along with Cs_2CO_3 in DMA at 90°C as shown in Scheme 33 [71].

Scheme 33

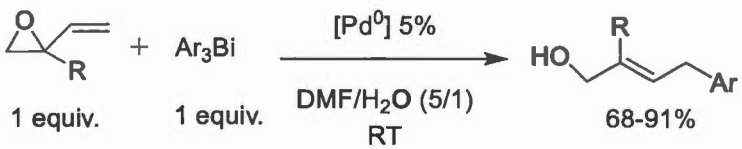


Ar^1: Ph, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 2-furanyl
R: *n*Bu
Ar^2: Ph, *p*-Tol, -An, F-C_6H_4, Cl-C_6H_4
X: Cl, Br Z: CO_2Me, CN

2.1.15 Arylation of Vinyl Epoxides with Triarylbismuth Reagents

(*E*)-Allylic alcohols can be synthesized via ring opening and arylation of vinyl epoxides in the presence of Pd^0 at room temperature as shown in Scheme 34 [72, 73].

Scheme 34

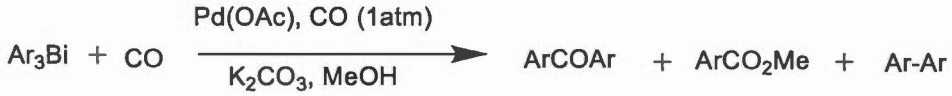


R: H, Me
Ar: Ph, *o*-An, *p*-Tol
[Pd]: $PdCl_2$, $PdCl_2$(dppf), $PdCl_2(dba)_2.CHCl_3$

2.1.16 Reaction of Carbon Monoxide with Triarylbismuth Reagents

Carbonylated aryl compounds can be prepared by reacting Ar_3Bi with carbon monoxide (Scheme 35). The reaction conditions involve Pd(II) acetate as the catalyst, CO (1 atm) and K_2CO_3 in MeOH to afford methylbenzoates as the major products and biaryl compounds as a minor product. Such reactions can also performed in MeOH using rhodium catalyst such as ($RhCl_3.3H_2O$, $[RhCl(CO)_2]_2$, $[RhCl(COD)]_2$) to afford a mixture of diaryl ketones and methylbenzoate [74].

Scheme 35



2.2 Objective of the Project

One important aspect of triarylbismuth reagents is their ability to deliver three aryl groups per equivalent of organometallic reagent in cross-coupling reactions, making them more atom-economical than other conventional Ar–M reagents. However, in most cases, a limited array of functional groups was present on the organobismuth partner. We recently reported a copper-catalyzed reaction to cross-couple triarylbismuthines with phenols and aminoalcohols. Therefore, with our functionalized organobismuthines in hand, we next explored their reactivity in copper-catalyzed cross-coupling reactions with diversely substituted phenols and alcohols in order to probe the breadth and functional group tolerance of this transformation. A few reports on *O*-arylation of alcohols and phenols using organobismuth reagents have been disclosed in various literatures. However, most of these methods rely on pentavalent organobismuth compounds, which must be prepared from their corresponding trivalent analogues. Therefore, the development of *O*-arylation reactions directly from trivalent organobismuthines is of high interest as it can reduce the number of steps required to obtain the desired *O*-arylated product. We recently reported an efficient and general method to prepare diarylethers and β-aryloxyamine skeleton via a copper-catalyzed *O*-arylation of phenols and aminoalcohols using highly functionalized triarylbismuthines, which we published in *CEJ* **2014** p2755 and *OBC* **2015** p1322 where I am the co-author. Using the protocol where phenols and aminoalcohols were coupled in presence of stoichiometric amount of copper-acetate, pyridine or triethylamine in DCM at 50°C under oxygen for overnight, we seeked to evaluate the applicability of the highly functionalized organobismuthines in the *O*-arylation of diversely substituted phenols, methyl 3-

hydroxybenzoate and 1,2-aminoalcohols. Two sets of conditions were tested: in Method A, the reaction was run at 50 °C for 3 h under air using 1.0 equivalent of triarylbismuthine, pyridine or triethylamine as the base and a stoichiometric amount of copper acetate; in Method B, the catalyst loading was lowered to 0.3 equivalents by performing the reaction under oxygen for 16 hours.

2.3 RESULTS AND DISCUSSION

2.4 Synthesis of Highly Functionalized Diaryl Ethers by Copper-Mediated O-Arylation of Phenols using Trivalent Arylbismuth Reagents

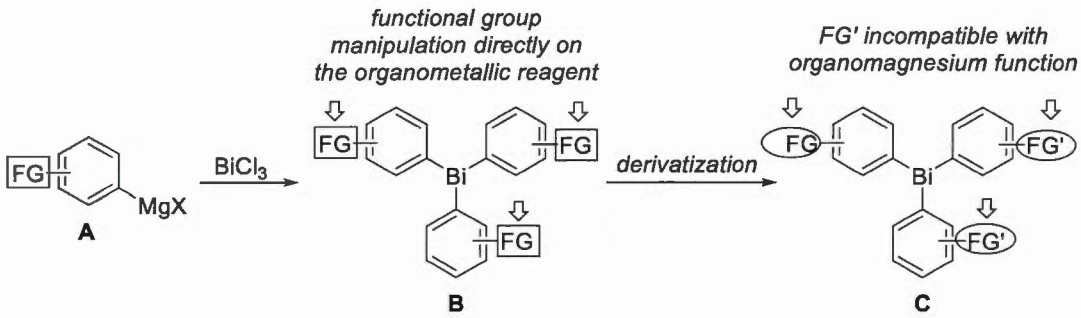
Diaryl ethers are a class of compounds that are important in medicinal chemistry [75] and natural products [76]. The macrocyclic diaryl ethers in the antibiotic vancomycin [77] are an important structural motif of heptapeptide backbone. The first method for the synthesis of diaryl ethers was reported by Ullmann and consisted in the coupling of phenols with aryl halides in presence of copper as a catalyst [78]. Ullmann ether synthesis requires high temperatures (>100°C) and the presence of a base and affords inconsistent results for functionalized products. Later, Chan and co-workers reported the coupling of arylboronic acids with phenols to give access to the corresponding diaryl ethers [79-81]. Even though this protocol constitues a mild method for the construction of diaryl ethers, it often requires a large quantity of the boronic acid to afford good yields.

The Ullmann ether synthesis reaction was later modified by Buchwald by using catalytic amounts of copper(I) salts with a ligand [82, 83]. Olofsson also reported the *O*-arylation of phenols using aryliodonium reagents in presence of a strong base [84, 85]. *O*-Arylation of phenols to afford functionalized diaryl ethers can be done using boronic acids [79, 81]. It can also be performed using potassium trifluoroborates [86], organolead [87] and organotin [88] reagents. *O*-Arylation of phenols can also be achieved using triphenylbismuth diacetate reagents as reported by Barton [89]. After

further studies, it was found that it can also be achieved via pentavalent and trivalent organobismuth reagents. Extensive reports on the use of trivalent organobismuth reagents was disclosed using hydroxyl benzyl acetates which require $PhI(OAc)_2$ in catalytic amount as a co-oxidant [60].

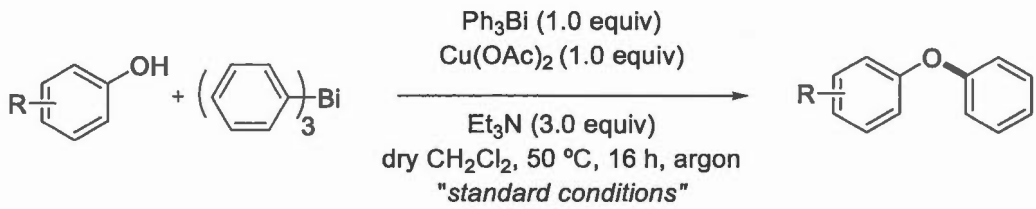
Triarylbismuth reagent **B** represents a useful class of reagents in organic synthesis because of its low toxicity and unique reactivity [90]. These reagents can easily be accessed via addition of Grignard reagent **A** onto bismuth chloride under inert atmosphere, which on further derivatization leads to highly functionalized organobismuth reagent **C** as illustrated in Scheme 36.

Scheme 36



The goal of this project is to develop a copper-catalyzed O-arylation of phenols using highly functionalized organobismuth reagents that would allow the use of substoichiometric amount of catalyst and would tolerate a wide range of functional groups on both coupling partners. Keeping these objectives in mind, the O-arylation of phenols was performed. The reaction was performed directly with trivalent organobismuth reagents (1 equiv.) in the presence of stoichiometric amount of copper (II) acetate (1 equiv.) in anhydrous dichloromethane along with triethylamine (3 equiv.) as a base, under argon atmosphere at 50°C for 16 hours, as shown in Scheme 37.

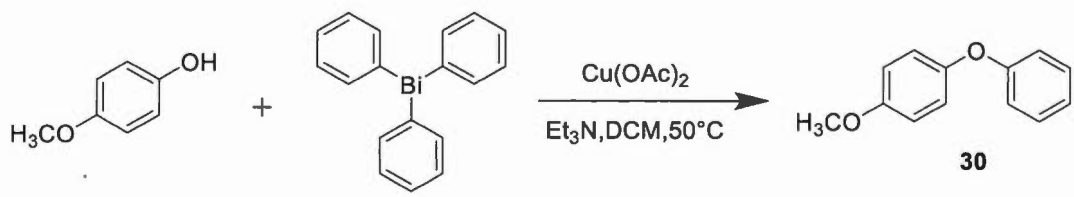
Scheme 37



Using the above standard reaction conditions, we studied the *O*-phenylation of diversely substituted phenols with various trivalent organobismuth reagents. To observe better results, the reactions was done with two different methods which are illustrated here: **Method A:** Ph_3Bi (1.0 equiv.), $Cu(OAc)_2$ (1.0 equiv.), Et_3N (3.0 equiv.), DCM, 50°C, air, 3h; **Method B:** Ph_3Bi (1.0 equiv.), $Cu(OAc)_2$ (0.3 equiv.), Et_3N (3.0 equiv.), DCM, 50°C, O_2, 16h. These studies are part of a publication from our group where I was a coauthor [91].

The synthesis of **compound 30** was done using Method A by treating commercially available 4-methoxyphenol **28** with triphenylbismuth reagent **29** to afford the desired product **30** (Scheme 38). Due to the presence of the electron donating group on the phenol, the protocol leads to a modest reduction in the yield of reaction.

Scheme 38

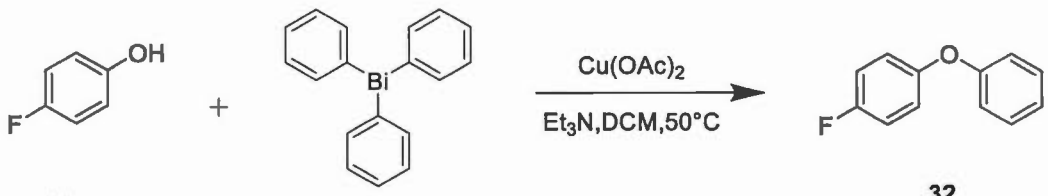


28 **29** **Method A: 62%**

Compound 32 was obtained by using Method A: triphenylbismuth reagent **29** reacted with 4-fluorophenol **31** to give access to the final product **32**. High yield was

obtained for the *O*-arylation of phenols possessing electron withdrawing group as in Scheme 39.

Scheme 39

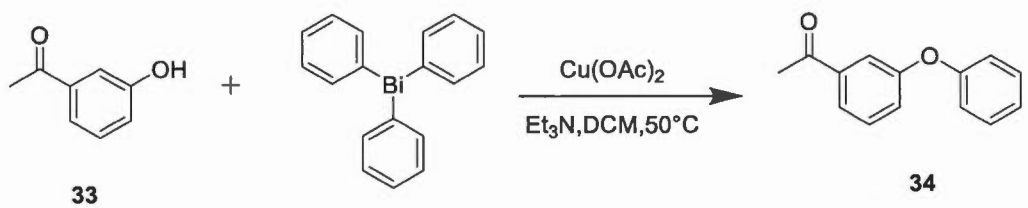


31 **29** **32**

Method A: 81%

The synthesis of **compound 34**was done using Method B. Triarylbismuth reagent **29**reacted with commercially available 3-acetylphenol **33** to afford the desired product **34**. Theresult showed that the presence of ketones on phenols is well tolerated and provides good to excellent yield of the desired biphenyl ether as shown in Scheme 40.

Scheme 40

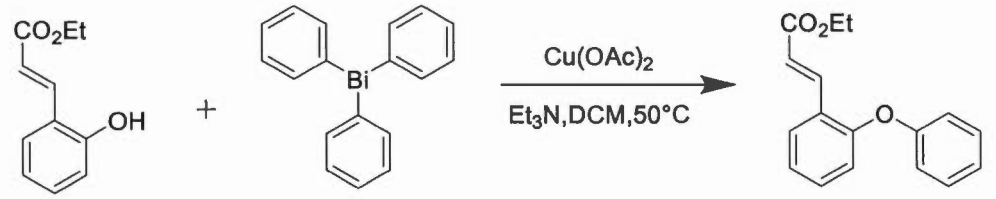


33 **29** **34**

Method B: 86%

Compound 36 was prepared using Method A and B. Phenol **35**was treated with Organobismuth reagent **29**having an α,β-unsaturated estersat the *ortho* position as a functional group, affording the final product **36**in good yield. It was found that similar yields were generally obtained using the method involving stoichiometric or substoichiometric amounts of copper acetate, as in Scheme 41.

Scheme 41

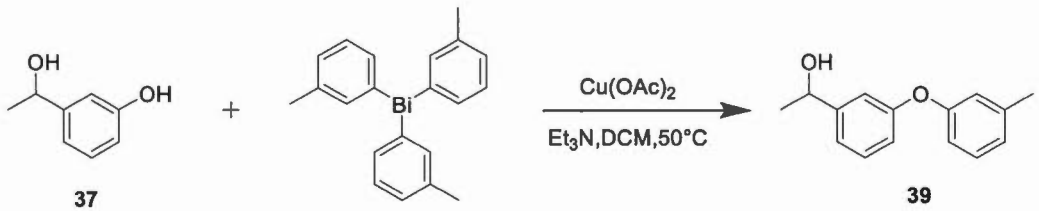


35 **29** **36**

Method A: 90%
Method B: 92%

Diaryl ether **39**was conveniently prepared in excellent yield from 3-(1-hydroxyethyl)phenol **37** by reacting it with *meta* tolyl bismuth reagent **38**usingMethod B as in Scheme 42.

Scheme 42

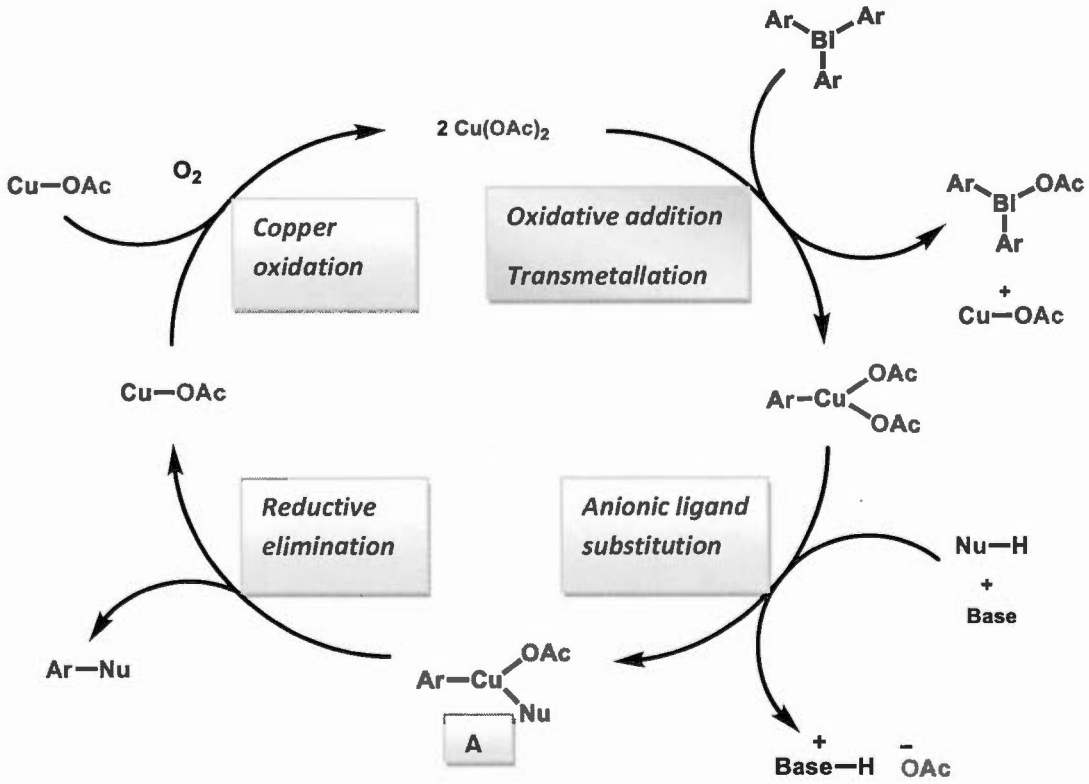


37 **38** **39**

Method B: 94%

Proposed Mechanism for the *O*-Arylation of Phenols, Indoles and Amino Alcohols Using Trivalent Organobismuthines

Scheme 43



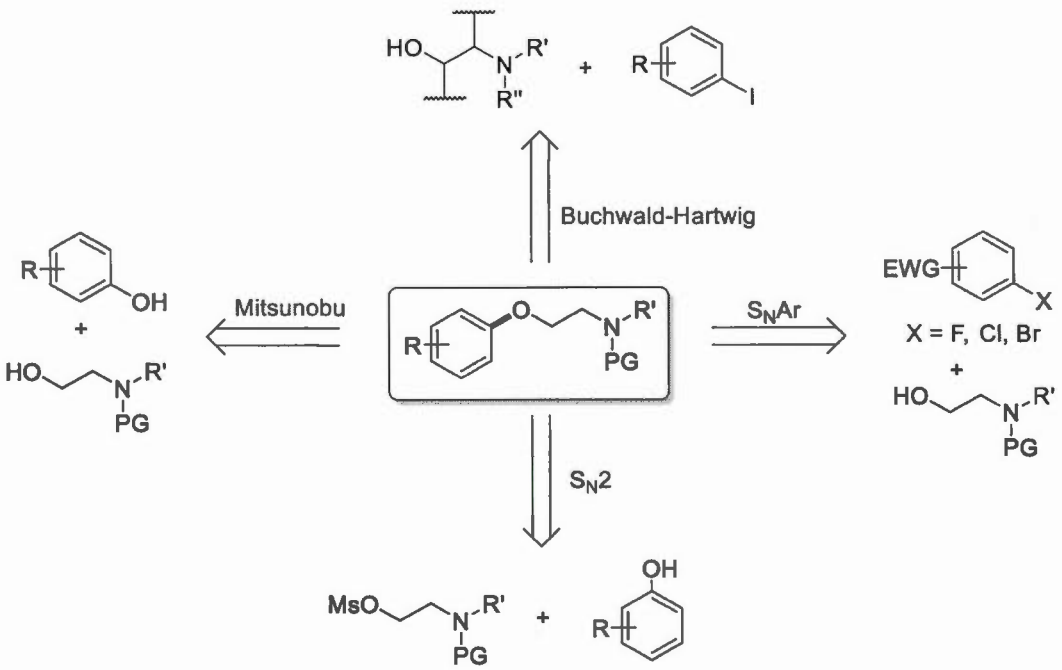
The mechanism for the copper-catalyzed *O*-arylation of phenols, indoles and amino alcohols (summarized by Nu–H) using triarylbismuthines involves the formation of an organocopper(III) species **A** where the deprotonated nucleophile, the aryl group, and one acetate are simultaneously ligated to the metal. This species would be formed by the reaction of triarylbismuthine Ar_3Bi and copper acetate, concomitantly with the deprotonation of the nucleophile Nu–H by the base (either triethylamine or pyridine), leading to copper(III) intermediate copper(I) acetate, and diarylbismuth acetate ($Ar_2Bi(OAc)$). Reductive elimination from species **A** would then provide the arylated nucleophile Nu–Ar.

2.5 Copper-Catalyzed *O*-Arylation of N-Protected 1,2-aminoalcohols Using Functionalized Trivalent Organobismuth Reagents

β-Aryloxyamines are the backbone of many natural products and medicinal compounds. These compounds can be prepared through various methods as shown in Scheme44such as S_NAr reaction between 1,2 aminoalcohols and electron deficient aryl halides [92]. They can also be accessed from the same precursor by addition of phenols via Mitsunobu conditions[93] or by using SN_2 approaches on the corresponding mesylates or tosylates [94]. These methods are widely used in the pharma industry but they have some limitations such as the need for an electron withdrawing group on the aryl moiety (for S_NAr reaction) and the requirement for derivatization of the alcohol into an activated form such as a mesylate or tosylate(SN_2reaction),the formation of unwanted side products that can jeopardize the isolation of desired product (for the Mitsunobu reaction, i.e. generation of triphenylphosphine oxide).

Buchwald [95] reported a highly productive approach for the synthesis of β-aryloxyamines via copper-catalyzed *O*-arylation of 1,2 aminoalcohols using aryl halides.

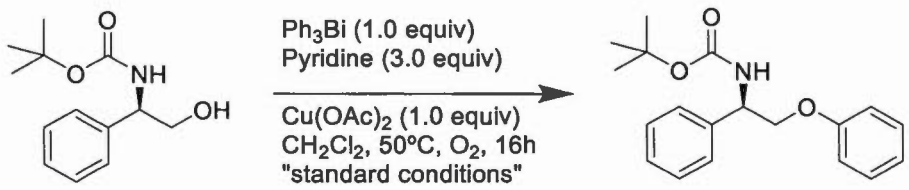
Scheme 44: Access to β-Aryloxyamines



Studies on the *O*-arylation of 1,2 aminoalcohols using functionalized organobismuth reagents are reported here. These studies are part of a publication from our group where I was a coauthor [96].The *O*-arylation reaction of (–)-*N*-BOC-D-α-phenylglycinol**40**was done by using standard reaction conditions i.e. Phenylbismuth1.0 eqiv., Pyridine 3.0 equiv., copper acetate 1.0 equiv., in DCM at

50°C for 16 hours under oxygen to afford *O*-phenyl product **41** (73% yield) shown in Scheme 45.

Scheme 45



40 **41**

Table 2: Optimization of Scheme 45

Entry	Change from "standard conditions"	Yield (%)
1	**No change**	**73**
2	Ambient air instead of oxygen	49
3	0.7 equiv Ph_3Bi instead of 1.0	51
4	Et_3N instead of pyridine	73
5	K_2CO_3 instead of pyridine	31
6	1.2 equiv pyridine instead of 3.0	67
7	Toluene instead of CH_2Cl_2	76
8[x]	0.3 equiv $Cu(OAc)_2$ instead of 1.0	62
9[x]	0.3 equiv $Cu(OAc)_2$ and 6h instead of o.n.	58
10[x]	**0.3 equiv $Cu(OAc)_2$ in toluene at 80°C**	**71**

x: 1.2 equivalents of pyridine

The first step consisted in optimizing the reaction conditions, as shown in **Table 2.** Performing the reaction under air had a negative impact on the yield of the reaction,suggesting that the presence of oxygen is important for the process of O-arylation reaction (**Entry 2).** Reducing the number of equivalents of triarylbismuth reagent from 1.0 to 0.7 gave a considerable drop in the yield of compound **41**, confirming the transfer of only one aryl group from the triarylbismuth reagent (**Entry 3**).

Entry 4 and **5** show the screening of bases by replacingpyridine with triethylamine and potassium carbonate. By using potassium carbonate, the yield of the reaction dropped to 31%, showing that an organic base is essential for the process. This was confirmed with triethylamine in which case the yield remained essentially the same (**Entry 4**).

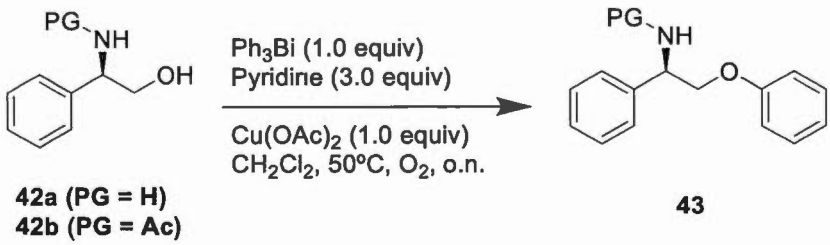
Further studies showed that the reduction in the number of equivalents of pyridine from 3.0 to 1.2 as in **Entry 6** had not much overall impact on the yield of the reaction. The effect of solvent (**Entry 7**) showed that toluene provides a similar yield of the desired product as DCM (76% for toluene compared to 73% in DCM).

Next, the catalyst loading was reduced to substoichiometric amounts and 1.2 equivalent of pyridine were used, affording the arylated product in 62%(**Entry 8**). In addition, instead of doing the reaction overnight, the reaction time was reduced to 6 hours (**Entry 9**). In this case, a 4% drop in the yield was observed for the arylation process. Performing the reaction with 0.3 equivalents of copper acetate in toluene at 80°C had a remarkable effect on the yield of reaction as shown in **Entry 10.**

Impact of Protecting Group on the Arylation of *N*-Protected Phenylglycinol:The effect of the amine protecting group on the *O*-arylation reaction is shown in Scheme 46

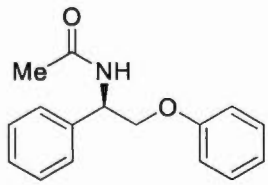
Arylation of unprotected phenylglycinol gave the*N*,*O*-diaryl product **43a** which means that the amino group must essentially be protected to avoid unwanted *N*-arylation reaction. **Compound 43b** was synthesized by protecting the amine group of phenylglycinol **42b** by acetyl as a protecting group which has slightly good effect on the yield of the reaction. **PG = Protecting Group**

Scheme 46



42a (PG = H)
42b (PG = Ac)

43

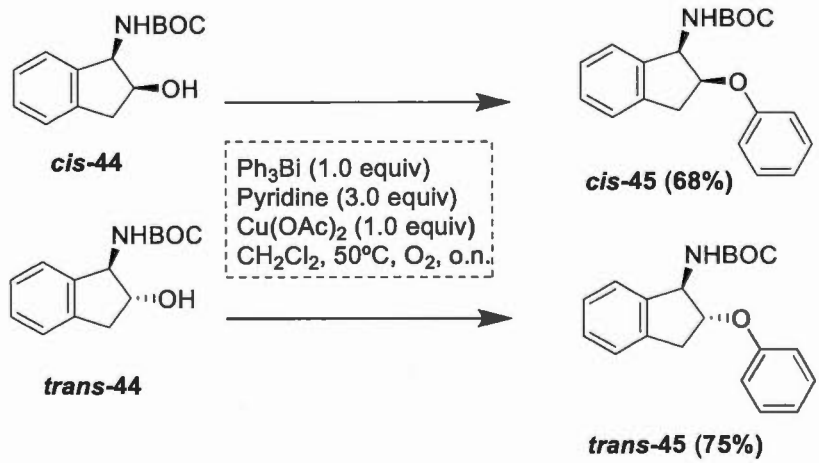


43a (62%) **43b (71%)**

Impact of the Conformational Effects on *O*-Arylation of *N*-BOC-1-amino-2-indanol: Geometrical and functional modifications were done to assess the role of the amino group in the*O*-arylation process. We first hypothesizedthat the NHBOC group was acceleratingthe *O*-arylation reaction via complexation of copper species through the carbonyl group present on the carbamate. To evaluate this hypothesis, a

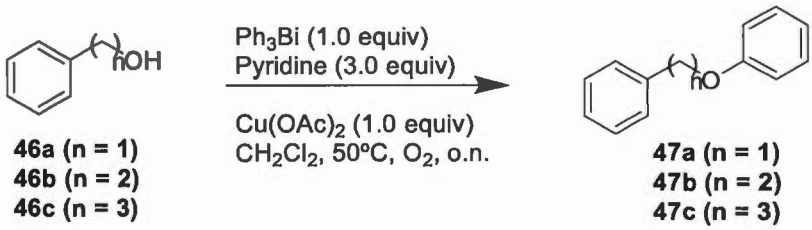
comparative study of reactivities of **compound *cis*-44** and **compound *trans*-45** was done by using standard reaction conditions as illustrated in Scheme 47. To our surprise,the *trans* isomer of indanol gave a better overall yield of the *O*-arylation product than its*cis*stereoisomer, suggesting that the accelerating effect provided by the amino group is not a result of a complexation by the carbonyl group.

Scheme 47



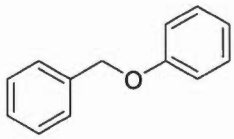
***O*-Arylation of Benzyl Alcohol 46a, Phenylethyl Alcohol 46b and 3-Phenyl-1-propanol 46c**: Further studies were done to assess the relevance of the amino group by performing the arylation reaction on phenylethyl alcohol **46b**. This simple alcohol with no amine group showed a drop in the yield of reaction to 30% compared to phenylglycinol **40**as illustrated in Scheme 48. These results indicate that the presence of the β-amino group has a significant effect on the *O*-arylation process and the difference in reactivity between 1,2-aminoalcohols (pKa=15.8) and simple alcohols (pKa=17.3) could derive from an inductive effect generated by the β-amino group, effectively lowering the pKa of the alcohol moiety.

Scheme 48

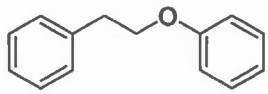


46a (n = 1)
46b (n = 2)
46c (n = 3)

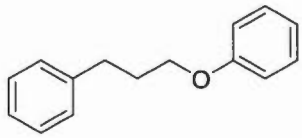
47a (n = 1)
47b (n = 2)
47c (n = 3)



47a (n = 1)
34%



47b (n = 2)
43%

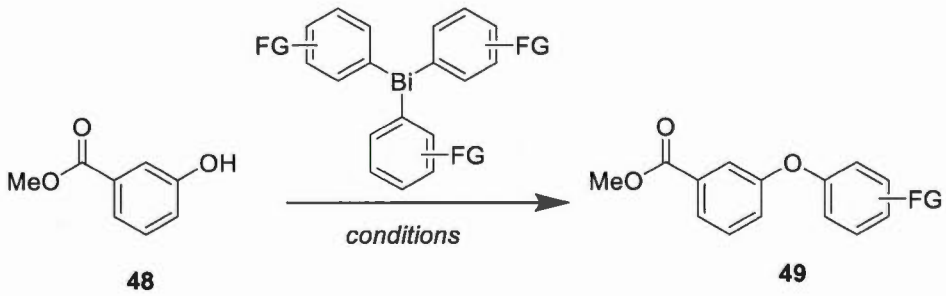


47c (n = 3)
43%

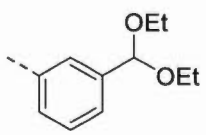
2.6Formation of C–O Bonds via Copper-Catalyzed *O*-Arylation of Phenols

***O*-Arylationof3-hydroxymethylbenzoate 48 Using Highly Functionalized Organobismuth Reagents**: In Scheme 49, the *O*-arylation of 3-hydroxymethylbenzoate **48**is reported to afford the desired diaryl ether product. The*O*-arylation can be achieved successfully by using two sets of conditions:**Condition A**: Ar_3Bi (1.0 equiv.), $Cu(OAc)_2$ (1.0 equiv.), Et_3N (3.0 equiv.), CH_2Cl_2, 50°C, air, 3h; **Condition B**: Ar_3Bi (1.0 equiv.), $Cu(OAc)_2$ (0.3 equiv.), Et_3N (3.0 equiv.), CH_2Cl_2, 50°C, O_2, 16h. The above protocols to form diaryl ether allow the transfer of aryl groups carrying an array of functional groups such as an acetal **49a**,**49b** and anα-β unsaturated ester **49c**.

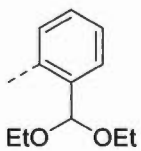
Scheme 49



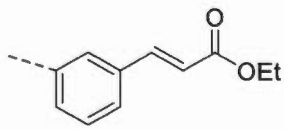
48 **49**



49a
87% (A)
60% (B)



49b
50% (A)
74% (B)



49c
53% (A)
42% (B)

CHAPTER III

Preparation of 3-*O*-Aryl Chloramphenicol Derivatives via Chemoselective Copper-Catalyzed *O*-Arylation of (1*R*,2*R*)-(–)-*N*-BOC-2-Amino-1-(4-nitrophenyl)-1,3-propanediol Using Triarylbismuthines

3.1INTRODUCTION

Chloramphenicol (CAM) was the first of the clinically useful antibiotics to be synthesized and the only one which is marketed in synthetic form today. It was first isolated from *Streptomyces venezuelae* in 1947. Because of its relatively simple structure, a large number of modifications of this antibiotic have been prepared and tested. A number of chemists, biochemists and physiologists have viewed its simple structure and have been encouraged to work on it, possibly with the feeling that what looks simple must have a simple mode of action. This view has proved to be erroneous, but has led to a large number of interesting studies. CAM is the first example of an antibiotic discovered through screening of soil microorganisms and is also the only example of this class of therapeutical compound which wascommercialized. The structure of CAM consists of two chiral centers and only the*R,R* is active.Furthermore, there must be a group on the aromatic ring that can resonates with the ring. The propanediol chain is essential for the activity of CAM molecule, but the dichloroacetamide group can be replaced by any other electronegative group. Chloramphenicol binds to the 50S subunit of ribosomes. It inhibits the movement of ribosomes along mRNA. It has both bacteriostatic and bactericidal effect; in the usual therapeutic concentrations it is bacteriostatic. Chloramphenicol is used for the treatment of serious gram-negative, gram-positive,

and anaerobic infections. It is especially useful in the treatment of meningitis, typhoid fever, and cystic fibrosis.

Human Toxicity: Chloramphenicol can be toxic and even fatal at acute overdose. Symptoms of poisoning have been associated with nausea and vomiting (especially with oral exposure), metabolic acidosis (an early sign, more common with chronic toxicity), hypotension, hypothermia, abdominal distention, heart failure, cardiovascular collapse, and coma. Signs of toxicity may be delayed 5 to 12 h after overdose.

In neonates and toddlers, who develop excessive serum concentrations of the drug, chloramphenicol can cause "gray baby syndrome" consisting of progressive cyanosis, metabolic acidosis, vasomotor collapse, respiratory difficulties, and death.

Both oral and intravenous therapeutic doses of chloramphenicol range from 25 to 100 mg/kg/day in an adult. Doses should be adjusted to result in serum levels of 10 to 30 mg/L (31 to 93 μM) to avoid toxicity, especially in newborns, premature infants, and patients with hepatic disease.

Dose-related effects indicating toxicity of chloramphenicol are generally observed with plasma/serum levels greater than 25 to 30 mg/L. Critical values causing serious toxicity exceed 60 mg/L. The minimum lethal serum concentration, based on the data was 70 mg/L. The mean lethal concentration, based on two acute poisoning cases, was 190 mg/L.

Metabolism and Excretion: Chloramphenicol is extensively metabolized in the liver, primarily by the glucuronide conjugation and to a lesser extent, by hydrolysis of the amide linkage. Main metabolites found in the urine 8 hours after a single 500 mg oral dose were 48% as chloramphenicol glucuronide and 4.3% as *p*-nitrophenyl-2-amino-1,3-propanediol. Another minor metabolite, *p*-nitrophenyl-2-hydroxyacetamido-1,3-propanediol, was found in the urine of newborns in an

unstated amount. A total of 93% of a dose is excreted in the 24 h urine, largely as inactive metabolites. 5 to 10 percent is excreted in the parentform. About 3% of chloramphenicol and 5% of its glucuronide metabolite are excreted in the bile.

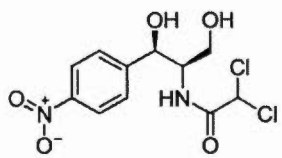
Pharmacological Mechanisms: Only the D-stereoisomer of chloramphenicol is biologically active. Chloramphenicol interferes with bacterial mitochondrial protein synthesis by binding to the 50S subunit of bacterial ribosomes. It blocks protein synthesis in bacteria and in mitochondria by interfering with the peptidyl transferase function (peptidyl transferase is a function of the 50S or 60S subunit; synthesis of the peptide bond is catalyzed by a peptidyl transferase activity). Also other mitochondrial enzymes, such as cytochrome oxidase and ATPase are inhibited. Consequently, oxidative phosphorylation is inhibited and cellular energy is depleted.

Toxicological Mechanisms: Some of the known effects of chloramphenicol include interference of attachment of messenger RNA to the ribosomes, which leads to inhibition of protein synthesis.
Chloramphenicol binds to mitochondrial ribosomes and inhibits enzyme synthesis, for example, enzymes necessary for oxidative phosphorylation. Among the enzymes that are affected by chloramphenicol are cytochrome oxidase and ATPase, mentioned above, as well as an enzyme ferrochelatase which is also localized in the mitochondria and is a final enzyme in heme biosynthesis (catalyzing the incorporation of iron in hemoglobin).

Chloramphenicol has weak negative inotropic effect. Inotropic effects are ones that change the strength of contraction of the heart muscle. High serum concentrations (> 25 mg/l) of chloramphenicol at chronic exposure are associated with a reversible bone marrow suppression expressed as a reticulocytopenia, anemia, leucopenia, thrombocytopenia, or any combination of these abnormalities. Most serious

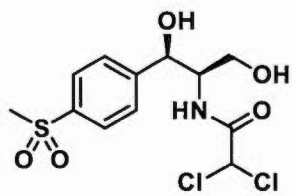
hematological toxicity, which is irreversible complication and often fatal, is associated with aplastic anemia (failure of bone marrow to produce blood cells).

SAR of Chloramphenicol: The replacement of the nitro group by other electron withdrawing groups gives active compounds; examples include CH_3SO_2-(Thiamphenicol) and$CH_3C(=O)$-(Cetophenicol). Replacement of *p*-nitrophenylby other aryl structures gives active compounds but can lead to reduced activity. For instance,shiftingthenitro group from *para* position to other positions reduces the activity. Replacement of phenyl group by alicyclic (saturated rings) also reduces the activity.



50

Chloramphenicol



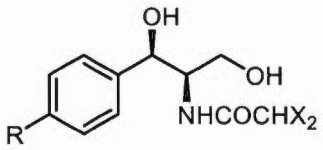
51

Thiamphenicol

1.7x more active than chloramphenicol

Low incidence of aplastic anemia

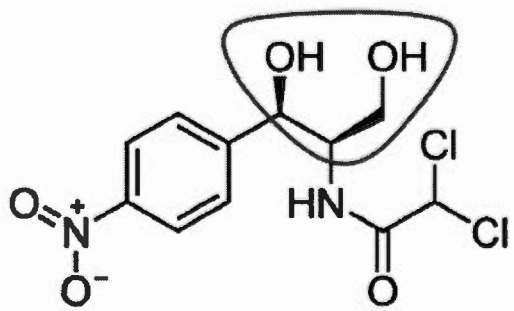
The dichloroacetamide group is important for the activity of Chloramphenicol. Other dihaloderivatives of the side chain are slightly less active whereas trihaloderivatives (e.g. $NHCOCF_3$) are slightly more active. The chlorine atoms in the dichloracetamide group can be replaced with other electronegative groups like fluorine with no appreciable loss of activity called as Fluoramphenicol.



1. R= NO_2 X= Cl - Chloramphenicol
2. R= NO_2 X= F - Flouramphenicol
3. R= SO_2CH_3 X= Cl - Thiamphenicol

52

The 1,3-propanediol side chain is also needed for the activity. The primary alcohol at C1 is important for activity whereas conversion of C1–OH to C=O causes loss of activity.



53

A large number of structural analogues of **chloramphenicol** has been prepared on the basis of the following themes:

1. Removal of the chlorine atom, transference of chlorine atom to the aromatic nucleus;

2. Transference of the nitro moiety to the *ortho*or *meta*-position;

3. Esterification of the hydroxyl functional group;

4. Replacement of the phenyl ring with furyl, naphthyland xenyl rings respectively;

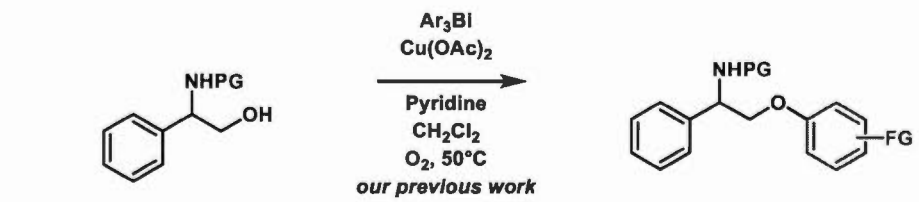
5. Addition of alkyl or alkoxysubstituents to the aryl ring;

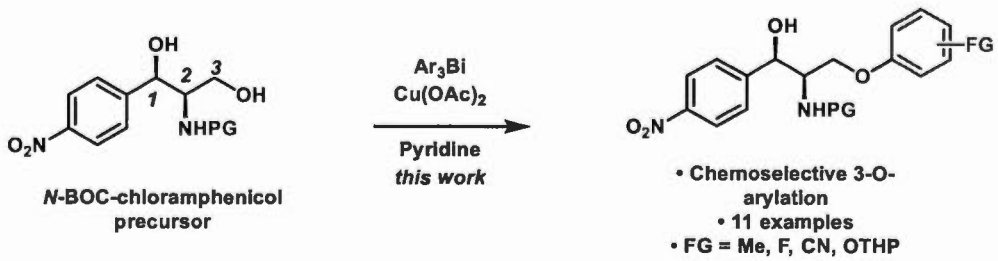
6. Replacement of the inherent nitro group by a halogen atom.

However, none of these provide analogues of activity even similar to **chloramphenicol** towards *Shigella paradysenteriae.*

3.2 Objective of the reaserch project: To explore the impact of arylation of the 3-OH group of CAM for the generation of new antibiotics. Previously we reported a protocol for the *O*-arylation of 1,2-aminoalcohol using triarlybismuth reagent in presence of stechiometric amount of copper acetate, pyridine in DCM at 50°C under oxygen which we published in *OBC* **2014** p1322. Using the same protocol we tried chemoselective *O*-arylation of primary alcohol of chloramphenicol for the generation of new lead compounds, which we published in Tetrahedron Letters, 2016.

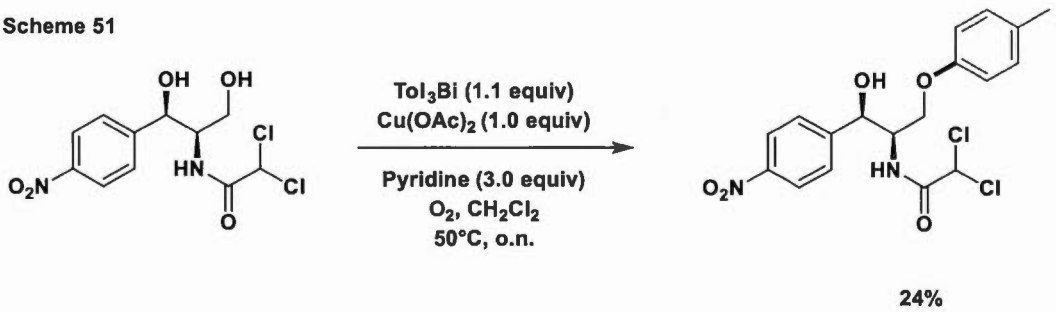
Scheme 50





3.3 Challenges of the project: First, we tried the direct copper-catalyzed *O*-arylation of the primary alcohol of chloramphenicol drug using *tolyl*-bismuth reagent Tol_3Bi in presence of copper-acetate, pyridine in DCM at 50°C under oxygen for overnight with 24% isolated yield. The low yield shows thatthe biggest challenge of this project was to improve the isolated yield of the product by finding a more efficientroute which would give access to different 3-*O*-aryl derivatives of chloramphenicol. To overcome this problem we tried different methods such as palladium and copper-catalyzed arylation reactions using aryliodides or arylboronic acids to directly arylate chloramphenicol but these methods did nowork for such type of reagents. We thensuspected that the dichloroacetamide group was responsible for the low yield in the arylation of chloramphenicol. Consequently,we decided toexplored the BOC derivatives of chloramphenicol.

Scheme 51



24%

3.4 Contributions of authors: The manuscript of this paper was written by Professor Alexandre Gagnon. Entry 4 in Table 1 was done by Julien Dansereau whoalso did a few entries in Scheme 2. Martin Hébert also completed a few entries in Scheme 2.

NOTE: This work has been published in *Tetrahedron Lett. 57*, 4284-4287, **2016** and is attached at the end of the thesis.

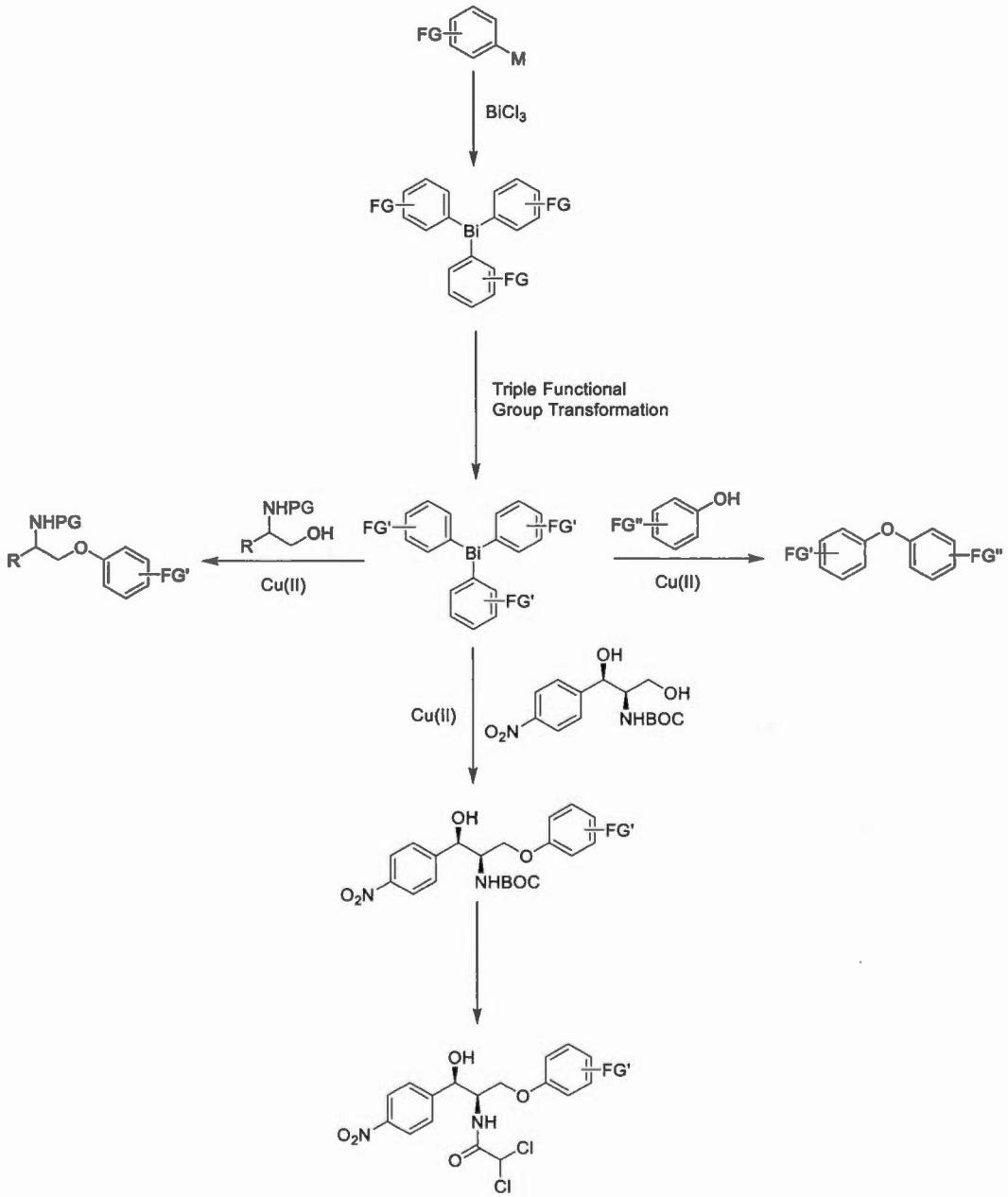
CHAPTER IV

CONCLUSION

In summary, we demonstrated that highly functionalized triarylbismuthines can be prepared by triple functional group manipulation using acidic, nucleophilic, and reducing conditions or involving organometallic reagents or ylides. Using this approach, triarylbismuthines bearing different substitution at different positions like methyl, methoxy, aldehydes, α,β-unsaturated esters, vinyl groups were prepared. These triarylbismuthines represent a class of highly functionalized and versatile organometallic reagents that are in high demand. We then developed a copper-catalyzed process to successfully *O*-arylatediversely substituted phenols. Preliminary mechanistic studies demonstrate that copper acetate is essential for the reaction to proceed and that the order of reactivity between the trivalent and pentavalent species depends on the nature of the substrate. Our copper-catalyzed arylation reactions are simple to operate and show high functional group tolerance. The *O*-arylation procedures developed in this work constitute an efficient and general portfolio of methods for the preparation of medicinally relevant scaffolds. We have also developed a copper-catalyzed *O*-arylation reaction of 1,2-aminoalcohols using functionalized triarylbismuthanes. The reaction is promoted by catalytic amounts of copper acetate and tolerates a variety of substituents on the organobismuthane, giving access to functionalized β-aryloxyamines. Finally, we demonstrated that the presence of an amino group in β relative to the alcohol provides an increase in reactivity, probably through inductive effect. The application of this protocol to the arylation of other hydroxy-containing substrates is in progress in our group and results will be reported in due course. Finally we developed a chemoselective coppercatalyzed *O*-arylation reaction of (1*R*,2*R*)-(–)-*N*-BOC-2-amino-1-(4-nitrophenyl)-1,3-propanediol

using triarylbismuthines. The method allows the transfer of *ortho*-, *meta*-, and *para*-substituted aryl groups, shows good functional group tolerance and leads to arylation of the primary alcohol. The arylated products were expeditively transformed into the corresponding 3-*O*arylchloramphenicol derivatives in two simple steps. The activity and metabolic stability of the prepared chloramphenicol derivatives against a panel of gram-negative and gram-positive bacteria will be investigated and the results will be reported in due course.

Scheme 52


FG
M
BiCl3
FG
Bi
FG
FG
Triple Functional
Group Transformation
NHPG
R
OH
Cu(II)
FG'
FG'
Bi
FG'
FG"
OH
Cu(II)
FG'
O
FG"
Cu(II)
OH
OH
NHBOC
O2N
OH
FG'
O
NHBOC
O2N
OH
FG'
O
NH
O
Cl
Cl
O2N

CHAPTER V

EXPERIMENTAL PART

General Information

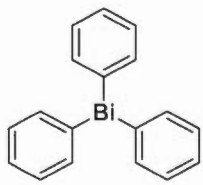
All reactions were run under argon atmosphere in non flame dried glassware. Unless otherwise stated, commercial reagents were used without further purification. Grignard reagents were purchased from Aldrich or prepared using conventional methods with metallic magnesium or via Knochel's procedure and were titrated prior use. Triphenylbismuth and anhydrous bismuth chloride 99.999% were purchased from Strem Chemicals. Anhydrous solvents were obtained using a MBRAUN (model MB-SPS 800) encapsulated solvent purification system. The evolution of reactions was monitored by analytical thin layer chromatography using silica gel 60 F254 precoated plates. Flash chromatography was performed employing 230-400 mesh silica (Silicycle) using the indicated solvent system according to standard techniques. Microwave irradiation was conducted using a Biotage Initiator microwave system. Melting points were taken on an Electrothermal Mel-TEMP and are uncorrected. Nuclear magnetic resonance spectra (^{1}H, 13C) were recorded on a Bruker Avance-III 300MHz spectrometer. Chemical shifts for ^{1}H-NMR spectra are recorded in parts per millon from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ 7.27 ppm, DMSO δ 2.54 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant *J* in Hz and integration. Chemical shifts for 13C spectra are recorded in parts per million from tetramethylsilane using the central peak of deuterochloroform (77.00 ppm) as the internal standard. All 13C spectra were obtained with complete proton decoupling. IR spectra were recorded on a Thermo Scientific Nicolet 6700 PT-IR from thin films and are reported in reciprocal

centimeters (cm^{-1}). HRMS were performed at Université du Québec à Montréal on Agilent Technologies, LC 1200 Series / 6210 TOF LCMS analyzer using the electrospray (ESI) mode.

General Procedure for the Preparation of Triarylbismuthanes

Bismuth chloride (x mg, y mmol) was dissolved in anhydrous THF (x mL) and was cooled to –10°C (ice-acetone bath). The organomagnesium reagent (x mmol) was slowly added drop wise under argon (Organomagnesium reagents were prepared via standard Grignard reaction). The reaction mixture was stirred at room temperature (r.t.) for one hour and heated at 65°C for 30 minutes. After cooling to r.t., the solution was diluted with sat. aq. sodium bicarbonate (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic phases were washed with sat. aq. sodium bicarbonate (2 x 100 mL), brine (2 x 100 mL), dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using the indicated solvent system to afford the desired triarylbismuth.

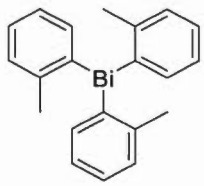
Triphenylbismuth (9)



The general procedure was followed by 5.6g (17.8 mmol) of $BiCl_3$ was dissolved in 40 mL of THF. Phenylmagnesium bromide 69.4 mmol was slowly added dropwise. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford 9 as a white solid (5.21g, 70%);m.p.76°C. Spectral data: ^1H NMR (300 MHz, $CDCl_3$)δ7.83-7.81 (t, 6H), 7.48-7.44 (t, 6H), 7.40-7.36 (d, 3H); 13C NMR (300 MHz, CD_2Cl_2)137.52, 130.48, 127.75; IR υ3056, 3044, 3034, 3015, 2976, 1980, 1645,

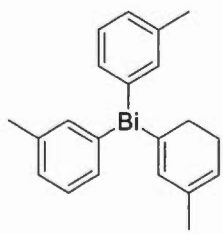
1876, 1812, 1759, 1692, 1659, 1631, 1581,1566, 1502, 1472, 1424, 1326, 1299, 1259, 1182, 1153, 1055, 1013, 995, 965, 900, 851, 721, 691, 644, 615, 448, 435.

Tris(2-methylphenyl)bismuthine (10)



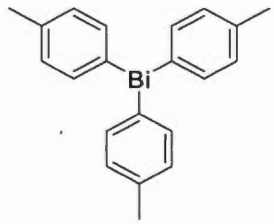
The general procedure was followed by 210 mg (1.45 mmol) of $BiCl_3$ was dissolved in 23mL of THF. *o*–tolylmagnesium bromide 4.8 mmol was slowly added dropwise. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford 10 as a white solid (500 mg, 85%); m.p. 130-131°C. Spectral data: ^{1}H-NMR (300 MHz, $CDCl_3$) 7.59 (dd, J = 7.3, 1.0 Hz, 1H), 7.39-7.28 (m, 2H), 7.10 (t, J = 7.3 Hz, 1H), 2.47 (s, 3H).

Tris(3-methylphenyl)bismuthine (11)



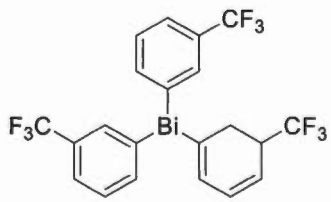
The general procedure was followed on a 2.4 mmol scale starting from bismuth chloride and 3-tolylmagnesium bromide. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford tris(3-methylphenyl)bismuthine (11) as a white solid (1.0 g, 87%); m.p. 64-66°C. Spectral data: ^{1}H-NMR (300 MHz, CDCl3) δ 7.61 (s, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.31-7.29 (m, 1H), 7.13 (d, J = 7.4 Hz, 1H), 2.31 (s, 3H).

Tris(4-methylphenyl)bismuthine (12)



The general procedure was followed by 788 mg (2.54 mmol) of $BiCl_3$ was dissolved in 25 mL of THF. *p*-tolylmagnesium bromide 8.4 mmol was slowly added dropwise. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford 12as a white solid (2.37g, 70%); m.p. 119-120°C. Spectral data: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.64 (d, J = 7.8 Hz, 2H), 7.20 (d, J = 7.4 Hz, 2H), 2.32 (s, 3H).

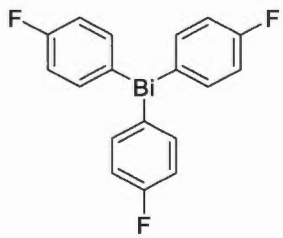
Tris(3-trifluoromethylphenyl)bismuthine (13)



The general procedure was followed on a 4.4 mmol scale starting from bismuth chloride and 3-trifluoromethylphenylmagnesium bromide. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford tris(3-trifluoromethylphenyl)bismuthine (13) as a yellow oil (2.7 g, 95%): R*f* 0.56 (20% EtOAc/hexanes); Spectral data: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.90 (d, J = 7.3 Hz, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.58-7.53 (m, 1H); 13C-NMR (75 MHz, $CDCl_3$) δ 156.2, 140.8 (d, J = 1.2 Hz), 133.9 (q, J = 3.8 Hz), 132.8 (q, J = 31.8 Hz),

131.2, 125.3 (q, J = 3.8 Hz), 122.5; IR (neat) 3051, 2959, 1592, 1319, 1308, 1114, 1070; HRMS (ESI) calcd for $C_{21}H_{12}BiF_9$: 644.0599, found 689.0592 ($M+HCO_2$).

Tris(4-fluorophenyl)bismuthine (14)

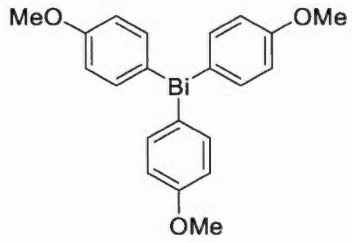


The general procedure was followed by 500 mg (1.6 mmol) of $BiCl_3$ was dissolved in 23 mL of THF. 4-fluorophenylmagnesium bromide 5.28 mmol was slowly added dropwise. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford 14 as a white solid (615 mg, 80%); m.p. 93-94°C. Spectral data: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.64 (dd, J = 8.4, 2.0 Hz, 2H), 7.08 (t, J = 9.2 Hz, 2H).

Tris(2-thienyl)bismuthine (15)

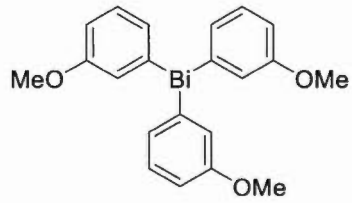
The general procedure was followed by 508mg (6.1 mmol) of $BiCl_3$ was dissolved in 30 mL of THF. 2-thienylmagnesium bromide 6.1 mmol was slowly added dropwise. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford 15 as a yellow solid (561 mg, 62%). Spectral data: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.69 (dd, J = 4.8, 0.7 Hz, 1H), 7.45 (dd, J = 3.3, 0.8 Hz, 1H), 7.19 (dd, J = 4.8, 1.4 Hz, 1H).

Tris(4-methoxyphenyl)bismuthine (16)



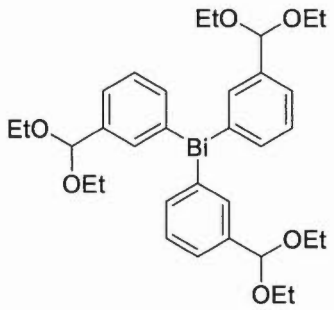
The general procedure was followed on a 4.4 mmol scale starting from bismuth chloride and 4-methoxyphenylmagnesium bromide. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford tris(4-methoxyphenyl)bismuthine (16) as a white solid (1.8 g,78%): m.p. 70-74°C. Spectral data: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.62 (d, J = 8.5 Hz, 2H), 6.92 (d, J = 8.5 Hz, 2H), 3.79 (s, 3H).

Tris(3-methoxyphenyl)bismuthine (17)



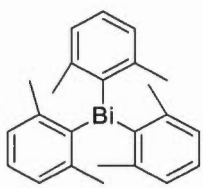
The general procedure was followed by 1.1 g (3.49 mmol) $BiCl_3$ was dissolved in 40 mL of THF. 3-methoxyphenylmagnesium bromide 11.52 mmol was slowly added dropwise. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford 17 as a yellow solid (1.0 g, 65%); m.p. 95-100°C. Spectral data: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37-7.31 (m, 3H), 6.85-6.82 (m, 1H), 3.72 (s, 3H).

Tris(3-(diethoxymethyl)phenyl)bismuthine (18)



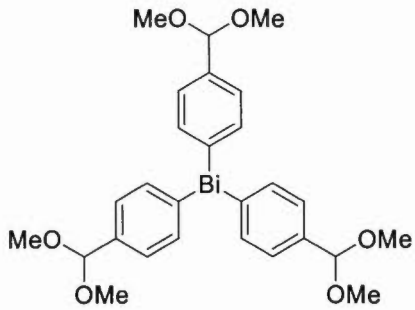
The general procedure was followed by 200 mg (1.4 mmol) of $BiCl_3$ was dissolved in 23 mL of THF. 3-(benzaldehyde diethylacetal) magnesium bromide 4.8 mmol was slowly added dropwise. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford 18 as a yellow oil (800 mg, 76%); R_f0.69 (20% EtOAc/hexanes); Spectral data: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.66 (d, J = 7.1 Hz, 1H), 7.44-7.33 (m, 2H), 5.44 (s, 1H), 3.62-3.43 (m, 4H), 1.18 (t, J = 7.1 Hz, 6H); 13C-NMR (75 MHz, CDCl3) δ 155.2, 140.5, 137.5, 135.7, 130.3, 126.1, 101.7, 61.0, 15.2; IR 5 (neat) 3647, 2983, 2874, 1699, 1433, 1108, 1045; HRMS (ESI) calcd for $C_{33}H_{45}BiO_6$: 746.3020, found (M+Na)+ 769.2912.

Tris(2,6-dimethylphenyl)bismuthine (19)



The general procedure was followed on a 2.5 mmol scale starting from bismuth chloride and 2,6-dimethylphenylmagnesium bromide. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford tris(2,6-dimethylphenyl)bismuthine (19) as a white solid (1.1 g, 84%): m.p. 128-130°C; Rf 0.80 (20% EtOAc/hexanes); Spectral data: ^{1}H-NMR (300 MHz, CDCl3) δ 7.14-7.10 (m, 3H), 2.34 (s, 6H).

Tris(4-(dimethoxymethyl)phenyl)bismuthine (20)



The general procedure was followed on a 3.2 mmol scale starting from bismuth chloride and 4-(dimethoxymethyl)phenylmagnesium bromide. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford tris(4-(dimethoxymethyl)phenyl)-bismuthine (20) as a yellow oil (2.1 g, 70%): R*f*0.32 (20% EtOAc/hexanes); Spectral data: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 7.8 Hz, 2H), 5.35 (s, 1H), 3.34 (s, 6H).

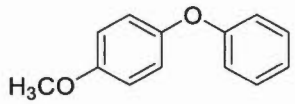
General Procedures for the *O*-Arylation of Phenols Using Organobismuthanes Were Prepared According to the Following Procedures:

Method A: In a sealed tube, the phenol (0.28 mmol) was dissolved in non-anhydrous solvent grade dichloromethane (3 mL). The organobismuthane (1.0 equiv) was added followed by copper (II) acetate (1.0 equiv) and triethylamine (3.0 equiv). The tube was sealed and heated at 50°C until completion as indicated by tlc analysis. The reaction mixture was cooled to r.t. and silica gel was added. The mixture was concentrated under reduced pressure and the crude product was purified by flash column chromatography using the indicated solvent system. The pure fractions were concentrated under reduced pressure to afford the desired pure product.

Method B: In a sealed tube, the phenol (0.28 mmol) was dissolved in non-anhydrous solvent grade dichloromethane (3 mL). The organobismuthane (1.0 equiv) was added

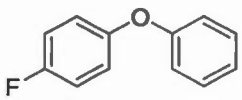
followed by copper (II) acetate (0.3 equiv) and triethylamine (3.0 equiv). The reaction tube was purged with 99.6% extra dry oxygen for 1 minute, sealed and heated at 50°C until completion as indicated by tlc analysis. The reaction mixture was cooled to r.t. and silica gel was added. The mixture was concentrated under reduced pressure and the crude product was purified by flash column chromatography using the indicated solvent system. The pure fractions were concentrated under reduced pressure to afford the desired pure product.

1-Methoxy-4-phenoxybenzene (30)



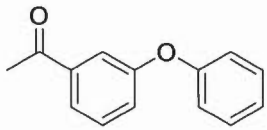
Method A was followed on a 0.24 mmol scale starting from 4-methoxyphenol. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford 30 as yellow oil (28 mg, 62%): R_f 0.50 (10% EtOAc/hexanes). Spectral data: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.23-7.17 (m, 2H), 6.98-6.78 (m, 7H), 3.72 (s, 3H).

1-Fluoro-4-phenoxybenzene (32)



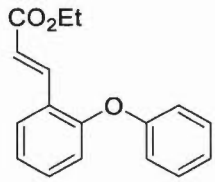
Method A was followed on a 0.27 mmol scale starting from 4-fluorophenol. The crude material was purified on silica gel (0.5% EtOAc/hexanes) followed by preparative thin layer chromatography to afford 32as a yellow oil in 90% purity (41 mg, 81%): R_f 0.57 (100% hexanes). Spectral data: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.38-7.31 (m, 2H), 7.13-6.98 (m, 7H).

1-(3-Phenoxyphenyl)ethanone (34)



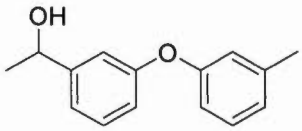
Method Bwas followed on a 0.36 mmol scale starting from 3'-hydroxyacetophenone. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford 34as yellow oil (67 mg, 86%): R_f 0.40 (10% EtOAc/hexanes). Spectral data:^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.69 (d, J = 7.8 Hz, 1H), 7.60-7.58 (m, 1H), 7.47-7.32 (m, 3H), 7.22 (dd, J = 8.1, 2.5, 1H), 7.15 (t, J = 7.4 Hz, 1H), 7.06-6.99 (m, 2H), 2.59 (s, 3H).

***(E)*-3-(2-Phenoxyphenyl)propenoic acid ethyl ester (36)**



Method A was followed on a 0.16 mmol scale starting from ethyl *trans*-2-hydroxycinnamate. The crude material was purified on silica gel (1% EtOAc/hexanes) to afford 36as a yellow oil (39 mg, 90%): R_f 0.40 (10% EtOAc/hexanes). Spectral data: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 16.2 Hz, 1H), 7.55 (dd, J = 7.8, 1.6 Hz, 1H), 7.29-7.18 (m, 3H), 7.07-7.01 (m, 2H), 6.92 (dd, J = 8.8, 1.1 Hz, 2H), 6.78 (dd, J = 8.3, 0.9 Hz, 1H), 6.47 (d, J = 16.2 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H). This compound was also prepared following method B on a 0.26 mmol scale starting from ethyl *trans*-2-hydroxycinnamate to afford 36 as yellow oil (64 mg, 92%).

α-Methyl-3-(3-methylphenoxy)benzene methanol (39)



Method B was followed on a 0.29 mmol scale starting from 3-hydroxy-α-methylbenzene methanol 37. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford 39as a yellow oil (63 mg, 94%): R_f 0.40 (30% EtOAc/hexanes); Spectral data: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.26-7.11 (m, 2H), 7.02 (d, J = 7.7 Hz, 1H), 6.97-6.95 (m, 1H), 6.88-6.78 (m, 2H), 6.76-6.72 (m, 2H), 4.79 (q, J = 6.5 Hz, 1H), 2.25 (s, 3H), 1.40 (d, J = 6.5 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 157.6, 157.1, 148.0, 140.0, 129.8, 129.5, 124.2, 120.0, 119.7, 117.7, 116.0, 115.8, 70.2, 25.2, 21.4; IR (neat) 3331, 2969, 1468, 1379, 1367, 1306, 1160, 1128, 951; HRMS (ESI) calcd for $C_{15}H_{16}O_2$: 228.1150, found $(M+H)^+$ 229.1240.

General procedures for the *O*-arylation of aminoalcohols

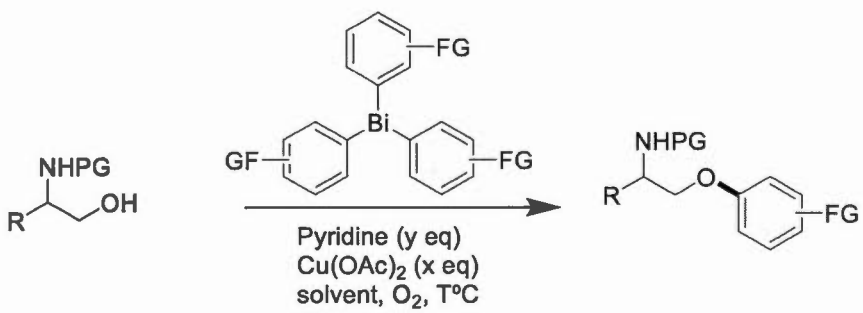


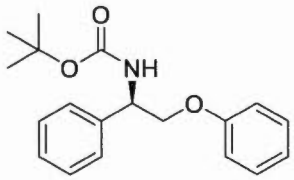
Table 1: Reaction Conditions: Method A and B

Method	Amino alcohol (n eq)	Ar_3Bi (A) (m eq)	$Cu(OAc)_2$ (x eq)	Pyridine (y eq)	Solvent	Temperature
A	1.0	1.0	0.3	1.2	Toluene	80 °C
B	1.0	1.0	1.0	3.O	DCM	50 °C

Method A: In a sealed tube, triarylbismuthine **A** (1.0 equiv) was added, followed by copper (II) acetate (0.3 equiv) and the aminoalcohol (1.0 equiv). The reagents were dissolved in anhydrous toluene (4 mL) and pyridine (1.2 equiv) was added to the mixture. The reaction tube was purged with dry oxygen for 30 seconds, sealed and heated at 80°C overnight. The reaction mixture was cooled to r.t., transferred and rinsed with EtOAc in a round bottom flask. Silica gel was added and the mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using the indicated eluent system to give the corresponding product.

Method B: Idem as method **A** except for copper (II) acetate (1.0 equiv instead of 0.3 equiv), pyridine (3.0 equiv instead of 1.2 equiv), in dichloromethane at 50°C.

(*R*)-*tert*-Butyl-(2-phenoxy-1-phenylethyl)carbamate (41)



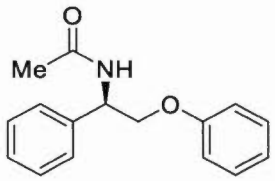
Method B was followed on a 0.21 mmol scale starting from *(R)-tert*-butyl (2-hydroxy-1-phenylethyl)carbamate40 and9. The crude product was purified on silica gel (10% EtOAc/hexanes) to afford 41 as a yellow solid (48 mg, 73%): m.p. 82°C. Spectral data: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34-7.26 (m, 4H), 7.23-7.18 (m, 3H), 6.89 (t, J = 7.3 Hz, 1H), 6.82 (d, J = 8.1 Hz, 2H), 5.26 (s(br), 1H), 4.99 (s(br), 1H), 4.19-4.08 (m, 2H), 1.36 (s, 9H).

(*R*)-*N*-(2-Phenoxy-1-phenylethyl)aniline (43a)

Method B was followed on a 0.36 mmol scale starting from *(R)*-2-phenyl-2-(phenylamino)ethanol42a and**9**. The crude product was purified on silica gel (5% EtOAc/hexanes) to afford 43a as a white solid (65 mg, 62%): m.p. 124°C; R_f 0.66 (20% EtOAc/hexanes); Spectral data: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.52-7.49 (m, 2H), 7.41-7.27 (m, 5H), 7.15-7.09 (m, 2H), 7.05-6.96 (m, 1H), 6.94-6.91 (m, 2H), 6.71 (t, J = 7.4 Hz, 1H), 6.60-6.57 (m, 2H), 4.74 (dd, J = 8.3, 3.8 Hz, 1H), 4.65 (s(br), 1H), 4.24 (dd, J = 9.6, 3.9 Hz, 1H), 4.08 (dd, J = 9.6, 8.5 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.4, 147.5, 140.2, 129.6, 129.2, 128.9, 127.8, 127.0, 121.4, 118.0, 114.8, 114.1, 72.0, 58.2; IR (neat) 3405, 3056, 3026, 2922, 2850, 1598, 1496, 1453,

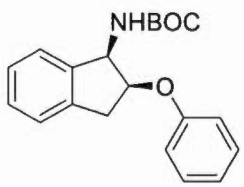
1234, 1173, 748, 690; HRMS (ESI) calcd for $C_{20}H_{19}NO$: 289.1467, found 290.1548 (M+H).

(*R*)-*N*-(2-Phenoxy-1-phenylethyl)acetamide (43b)



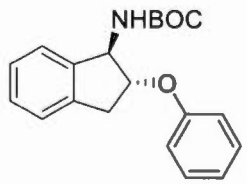
Method B was followed on a 0.28 mmol scale starting from *(R)-N*-(2-hydroxy-1-phenylethyl)acetamide42band 9. The crude product was purified on silica gel (15% EtOAc/hexanes) to afford 43b as a yellow oil (51 mg, 71%): R_f 0.10 (20% EtOAc/hexanes); Spectral data: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.48-7.41 (m, 3H), 7.39-7.31 (m, 4H), 7.03 (t, J = 7.4 Hz, 1H), 6.97-6.94 (m, 2H), 6.45 (d, J = 7.6 Hz, 1H), 5.49-5.43 (m, 1H), 4.35-4.26 (m, 2H), 2.10 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.7, 158.4, 139.3, 129.6, 128.7, 127.8, 127.1, 121.4, 114.7, 69.9, 52.5, 23.4; IR (neat) 3438, 3285, 3061, 3028, 2920, 2859, 1650, 1599, 1494, 1453, 1238, 751, 690; HRMS (ESI) calcd for $C_{16}H_{17}NO_2$: 255.1259, found 256.1310 (M+H). The connectivity was further confirmed by COSY-NMR analysis, demonstrating that the *O*-phenyl isomer has been formed.

***tert*-Butyl ((*1R,2S*)-2-phenoxy-2,3-dihydro-1*H*-inden-1-yl)carbamate (*cis*-45)**



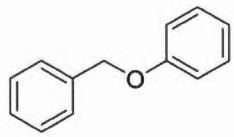
Method B was followed on a 0.20 mmol scale starting from *tert*-butyl ((*1R,2S*)-2-hydroxy-2,3-dihydro-*1H*-inden-1-yl)carbamate *cis*-44 and**9**. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford *cis*-45 as a yellow solid (44 mg, 68%): m.p. 106°C; R_f 0.57 (20% EtOAc/hexanes); Spectral data:^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.30-7.12 (m, 6H), 6.91-6.81 (m, 3H), 5.40-5.35 (m, 1H), 5.28-5.25 (m, 1H), 5.07 (s(br), 1H), 3.08 (d, J = 2.5 Hz, 2H), 1.40 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 157.6, 156.2, 141.7, 139.4, 129.6, 128.0, 127.2, 125.1, 124.1, 121.3, 115.8, 79.7, 78.8, 58.0, 36.9, 28.4; IR (neat) 3471, 3359, 3098, 3061, 2981, 2929, 1695, 1598, 1495, 1243, 1171, 1061; HRMS (ESI) calcd for $C_{20}H_{23}NO_3$: 325.1678, found 348.1578 (M+Na).

***tert*-Butyl ((*1R,2R*)-2-phenoxy-2,3-dihydro-1*H*-inden-1-yl)carbamate (*trans*-45)**



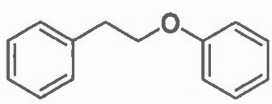
Method B was followed on a 0.20 mmol scale starting from *tert*-butyl ((*1R,2R*)-2-hydroxy-2,3-dihydro-*1H*-inden-1-yl)carbamate *trans*-44and 9. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford *trans*-45 as a white solid (45 mg, 75%): m.p. 115°C; R_f 0.46 (20% EtOAc/hexanes); Spectral data:^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.39-7.24 (m, 6H), 7.06-6.98 (m, 3H), 5.32 (s(br), 1H), 4.96-4.91 (m, 1H), 4.84 (s(br), 1H), 3.51 (dd, J = 16.4, 6.5 Hz, 1H), 3.04 (dd, J = 16.4, 4.8 Hz, 1H), 1.50 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.0, 155.4, 140.6, 139.9, 129.5, 128.6, 127.4, 125.1, 124.6, 121.1, 115.8, 83.8, 79.8, 61.4, 36.9, 28.4; IR (neat) 3338, 3089, 3050, 2974, 2875, 1689, 1519, 1493, 1235, 1166, 1055, 746; HRMS (ESI) calcd for $C_{20}H_{23}NO_3$: 325.1678, found 348.1562 (M+Na).

Benzyloxybenzene (47a)



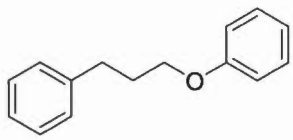
Method B was followed on a 0.46 mmol scale starting from phenylmethanol 46a and **9**. The crude material was purified on silica gel (heptane) to afford 47a as a yellow oil (29 mg, 34%): R_f 0.73 (20% EtOAc/hexanes); Spectral data: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.48-7.26 (m, 7H), 7.02-6.96 (m, 3H), 5.09 (s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.8, 137.1, 129.5, 128.6, 128.0, 127.5, 121.0, 114.9, 70.0; IR (neat) 3064, 3032, 2918, 1598, 1495, 1454, 1240, 1029, 752; HRMS (ESI) calcd for $C_{13}H_{12}O$: 184.0888, found 185.0967 (M+H).

Phenethoxybenzene (47b)



Method B was followed on a 0.41 mmol scale starting from 2-phenylethanol 46b and 9. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford 47b as a colorless oil (35 mg, 43%): R_f 0.75 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.39-7.27 (m, 7H), 7.01-6.93 (m, 3H), 4.22 (t, J = 7.1 Hz, 2H), 3.15 (t, J = 7.1 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.8, 138.3, 129.5, 129.0, 128.5, 126.5, 120.8, 114.6, 68.6, 35.8; IR (neat) 3063, 3028, 2927, 2870, 1597, 1586, 1497, 1472, 1243, 1037, 752; HRMS (ESI) calcd for $C_{14}H_{14}O$: 198.1045, found 199.1111 (M+H).

3-Phenoxypropylbenzene (47c)



Method B was followed on a 0.37 mmol scale starting from 3-phenylpropan-1-ol 46c and 9. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford47c as a yellow oil (34 mg, 43%): R_f 0.79 (20% EtOAc/hexanes); Spectral data:^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.38-7.23 (m, 7H), 7.03-6.95 (m, 3H), 4.03 (t, J = 6.3 Hz, 2H), 2.88 (t, J = 7.3 Hz, 2H), 2.22-2.13 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 159.1, 141.6, 129.5, 128.6, 128.5, 126.0, 120.6, 114.6, 66.8, 32.2, 30.9; IR (neat) 3062, 3027, 2927, 2869, 1600, 1586, 1497, 1469, 1245, 1039, 751, 691; HRMS (ESI) calcd for $C_{15}H_{16}O$: 212.1201, found 213.1277 (M+H).

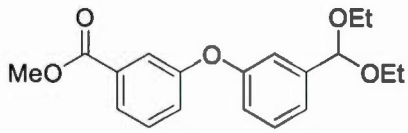
General Procedure for the *O*-Arylation of Phenols.

Compounds 49a-cwas prepared according to the following procedures:

Method A: In a sealed tube, the phenol (1.0 equiv) was dissolved in non-anhydrous solvent grade dichloromethane (3 mL). The organobismuthane (1.0 equiv) was added followed by copper (II) acetate (1.0 equiv) and Et_3N (3.0 equiv.). The tube was sealed and heated at 50°C during 3h. The reaction mixture was cooled to r.t. and silica gel was added. The mixture was concentrated under reduced pressure and the crude product was purified by flash column chromatography using the indicated solvent system. The pure fractions were concentrated under reduced pressure to afford the desired pure product.

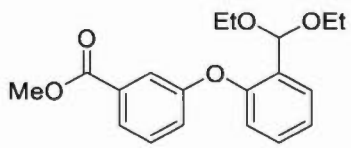
Method B: Idem as method **A** except for $Cu(OAc)_2$ (0.3 equiv) under O_2 during 16h.

Methyl 3-(3-(diethoxymethyl)phenoxy)benzoate (49a)



Method B was followed on a 0.16 mmol scale starting from methyl 3-hydroxybenzoate 48. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford 49a as a colorless oil (32 mg, 60%): R_f 0.62 (20% EtOAc/hexanes); Spectral data: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.77 (dt, J = 7.7, 1.3 Hz, 1H), 7.65 (dd, J = 2.6, 1.5 Hz, 1H), 7.42-7.31 (m, 2H), 7.27-7.24 (m, 2H), 7.20 (ddd, J = 8.2, 2.6, 1.1 Hz, 1H), 7.16 (t, J = 2.1 Hz, 1H), 6.97 (ddd, J = 7.95, 2.6, 1.2 Hz, 1H), 5.48 (s, 1H), 3.88 (s, 3H), 3.67-3.48 (m, 4H), 1.22 (t, J = 7.0 Hz, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.6, 157.5, 156.8, 141.6, 132.0, 129.9, 129.8, 124.4, 123.4, 122.2, 119.6, 119.0, 117.6, 101.1, 61.2, 52.4, 15.3; IR (neat) 3068, 2973, 2920, 2878, 1726, 1684, 1582, 1483, 1441, 1357, 1270, 1049, 901, 794, 753, 696; HRMS (ESI) calcd for $[C_{19}H_{22}O_5 + Na]^+$: 353.1359, found 353.1369.

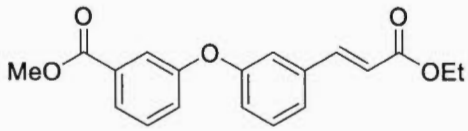
Methyl 3-(2-(diethoxymethyl)phenoxy)benzoate (49b)



Method B was followed on a 0.16 mmol scale starting from methyl 3-hydroxybenzoate 48. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford 409b as a colorless oil (39 mg, 74%): R_f 0.73 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.78-7.73 (m, 1H), 7.70 (dd, J = 7.6, 1.8 Hz, 1H), 7.64 (dd, J = 2.6, 1.5 Hz, 1H), 7.37 (t, J = 7.9 Hz, 1H), 7.28 (dt, J = 7.4, 1.8 Hz, 1H), 7.20 (td, J = 7.5, 1.3 Hz, 1H), 7.14 (ddd, J = 8.3, 2.6, 1.1 Hz, 1H), 6.88

(dd, J = 8.2, 1.5 Hz, 1H), 5.73 (s, 1H), 3.89 (s, 3H), 3.70-3.60 (m, 2H), 3.56-3.49 (m, 2H), 1.16 (t, J = 7.1 Hz, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.6, 158.2, 153.8, 131.9, 131.2, 129.9, 129.7, 128.0, 124.4, 124.0, 122.6, 119.7, 119.0, 97.6, 62.4, 52.3, 15.2; IR (neat) 3066, 2975, 2877, 1724, 1580, 1482, 1444, 1271, 1230, 1202, 1052, 994, 905, 754; HRMS (ESI) calcd for $[C_{19}H_{22}O_5 + Na]^+$: 353.1359, found 353.1363.

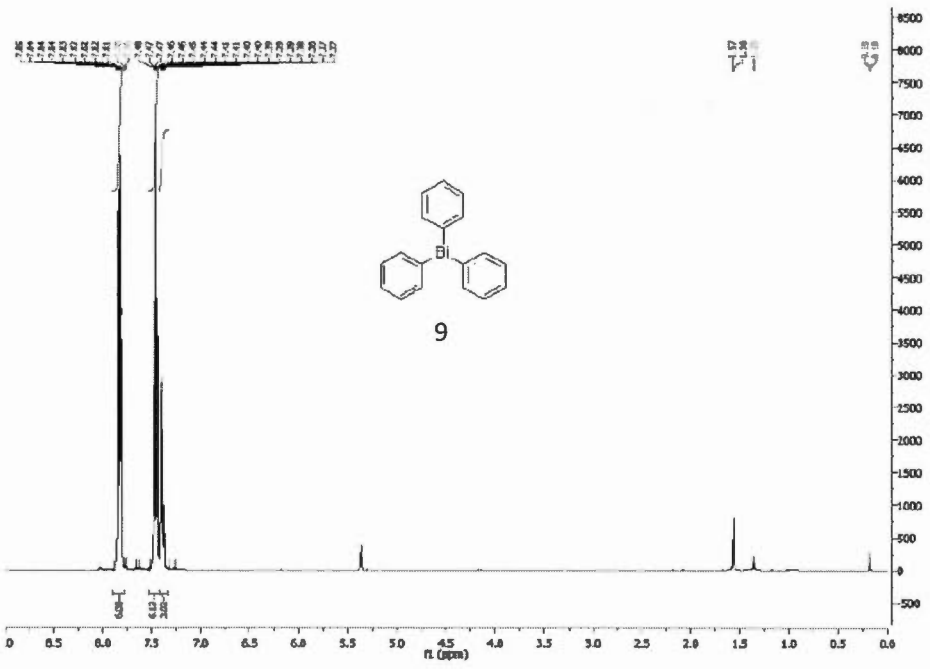
***(E)*-Methyl 3-(3-(3-ethoxy-3-oxoprop-1-en-1-yl)phenoxy)benzoate (49c)**



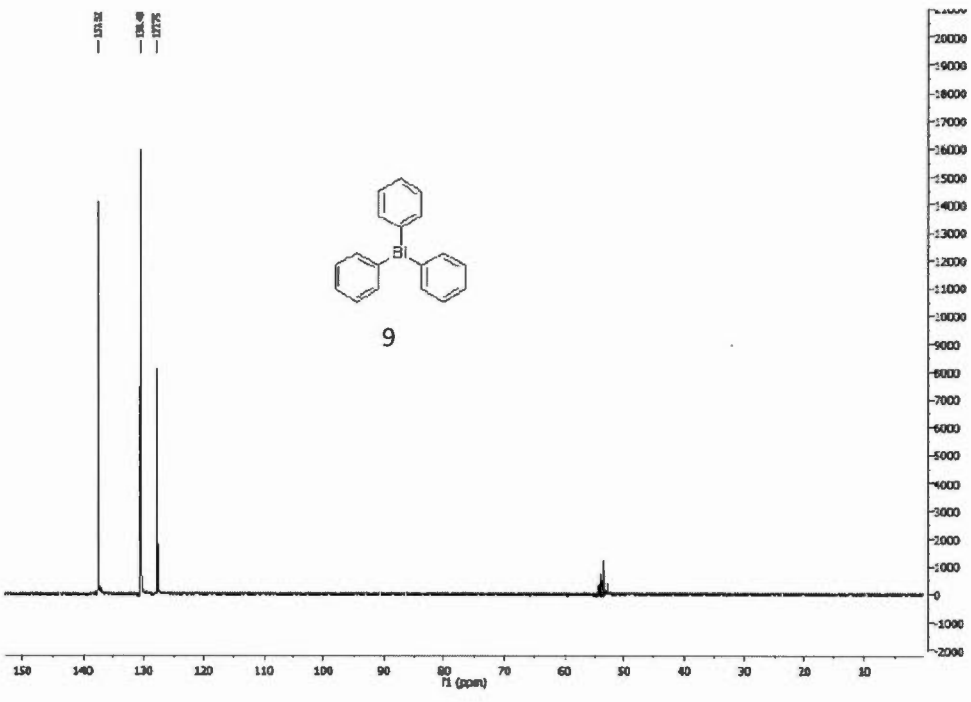
Method A was followed on a 0.25 mmol scale starting from methyl 3-hydroxybenzoate 48. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford 49c as a yellow oil (43 mg, 53%): R_f 0.61 (20% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.81 (td, J = 7.8, 1.3 Hz, 1H), 7.67-7.66 (m, 1H), 7.62 (d, J = 16.0 Hz, 1H), 7.46-7.40 (m, 1H), 7.39-7.34 (m, 1H), 7.30-7.27 (m, 1H), 7.22 (ddd, J = 8.2, 2.6, 1.1 Hz, 1H), 7.14 (t, J = 2.1 Hz, 1H), 7.02 (ddd, J = 8.0, 1.9, 1.2 Hz, 1H), 6.37 (d, J = 16.0 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 3.90 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.9, 166.5, 157.5, 157.0, 143.8, 136.6, 132.2, 130.5, 130.1, 124.9, 123.7, 123.6, 120.7, 120.0, 119.3, 118.0, 60.7, 52.4, 14.4; IR (neat) 3065, 2980, 2953, 2901, 1709, 1639, 1575, 1484, 1442, 1269, 1230, 1177, 1097, 1036, 983, 756; HRMS (ESI) calcd for $[C_{19}H_{18}O_5 + H]^+$: 327.1227, found 327.1224.

CHAPTER VI

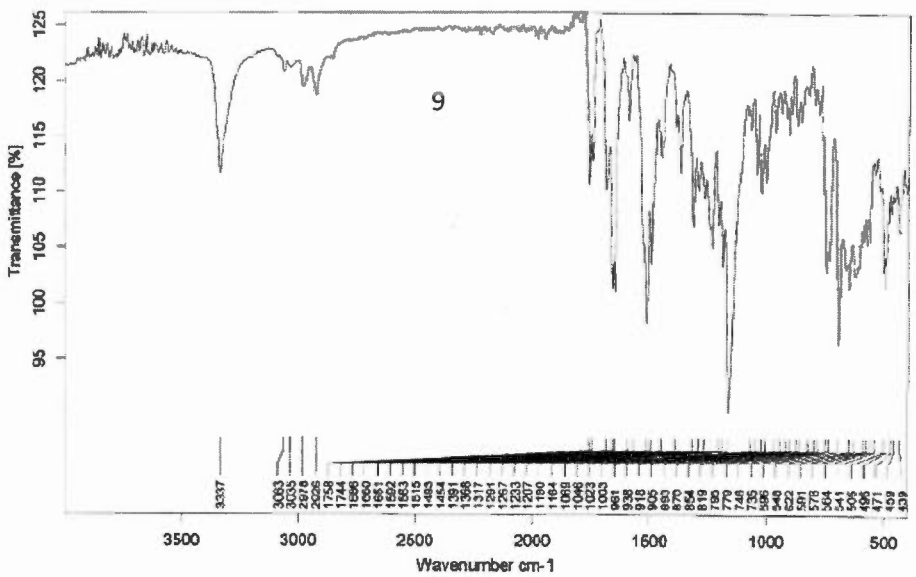
CHARACTERIZATION

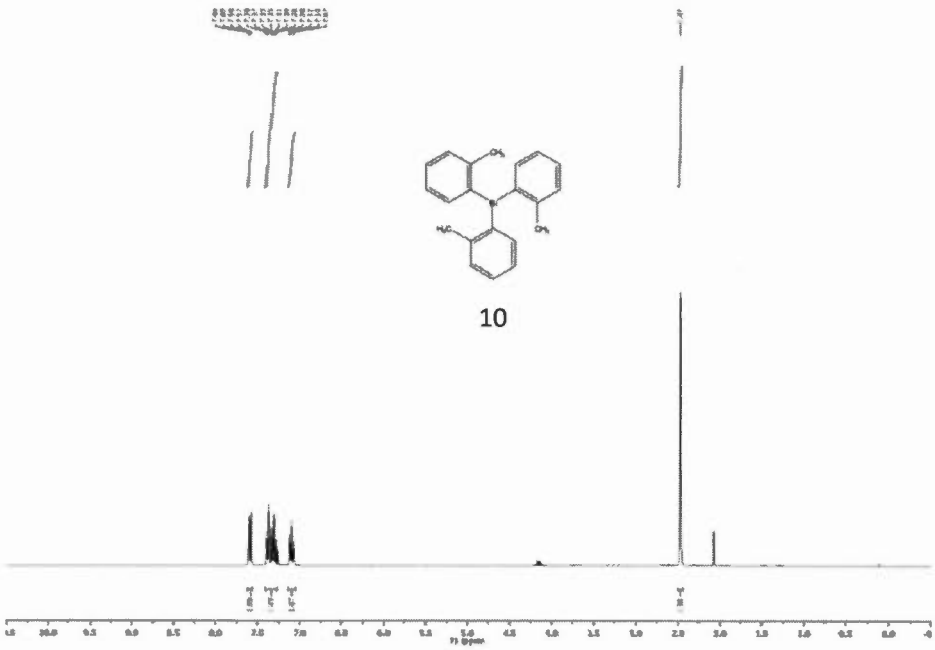


9

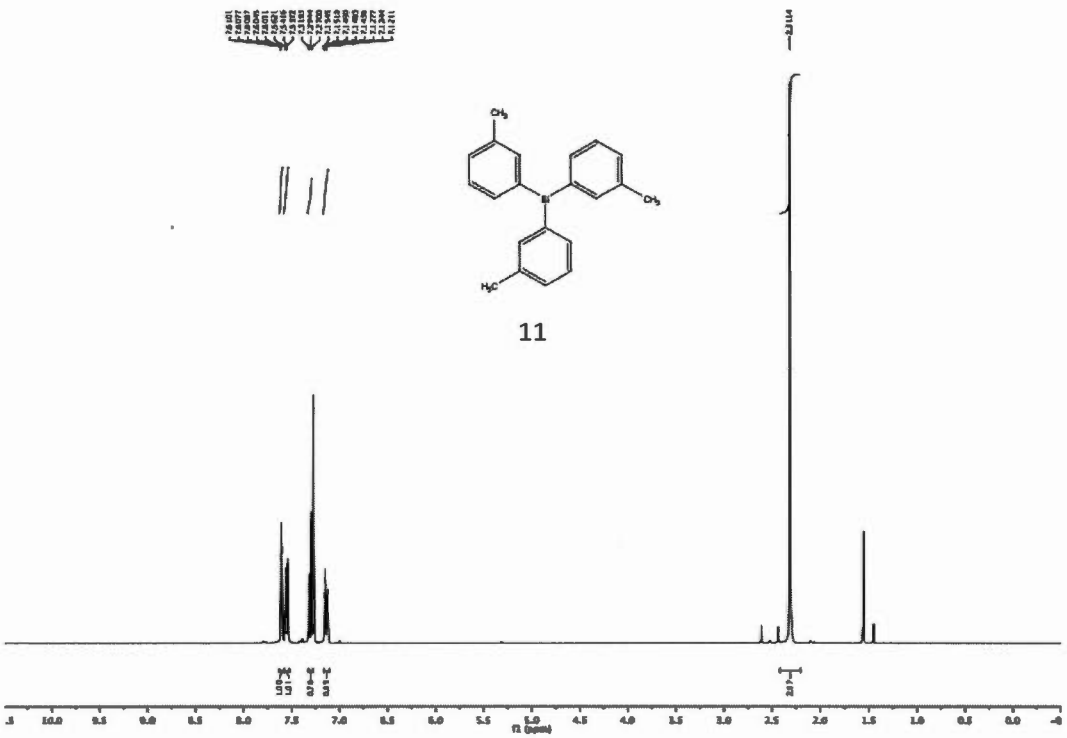


9


9
Transmittance [%]
125
120
115
110
105
100
95
3337
3063
3035
2918
2826
1758
1744
1686
1660
1661
1622
1583
1515
1489
1454
1391
1368
1317
1291
1267
1233
1207
1180
1164
1088
1046
1023
1003
981
938
916
903
890
870
854
819
799
779
748
735
696
640
622
591
578
564
541
505
497
477
457
439
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1



10



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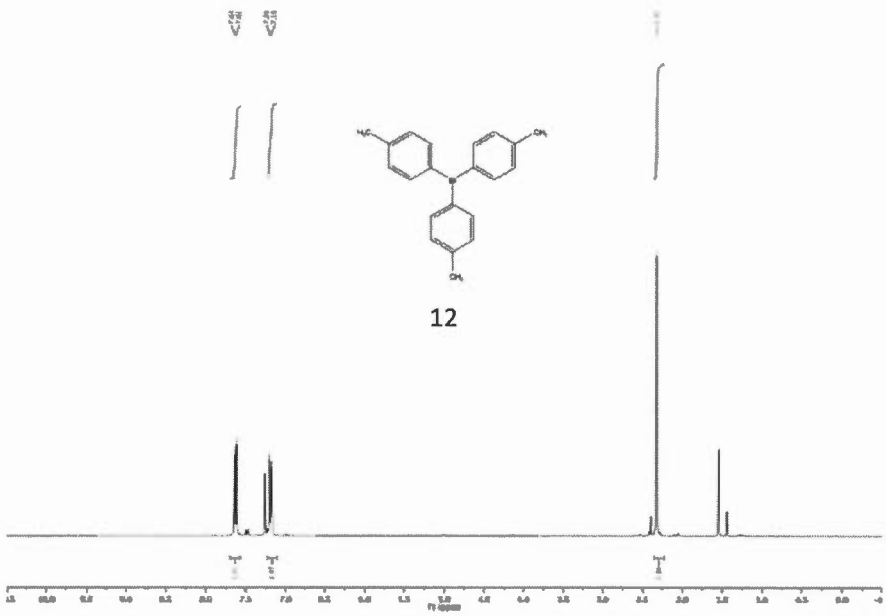

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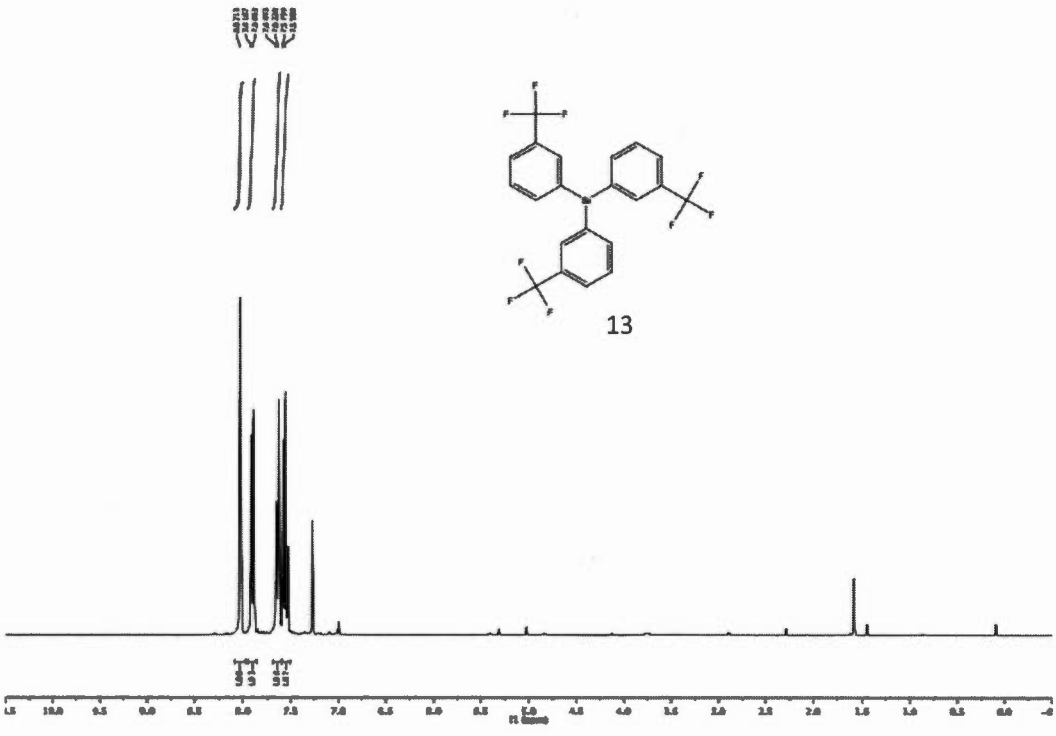

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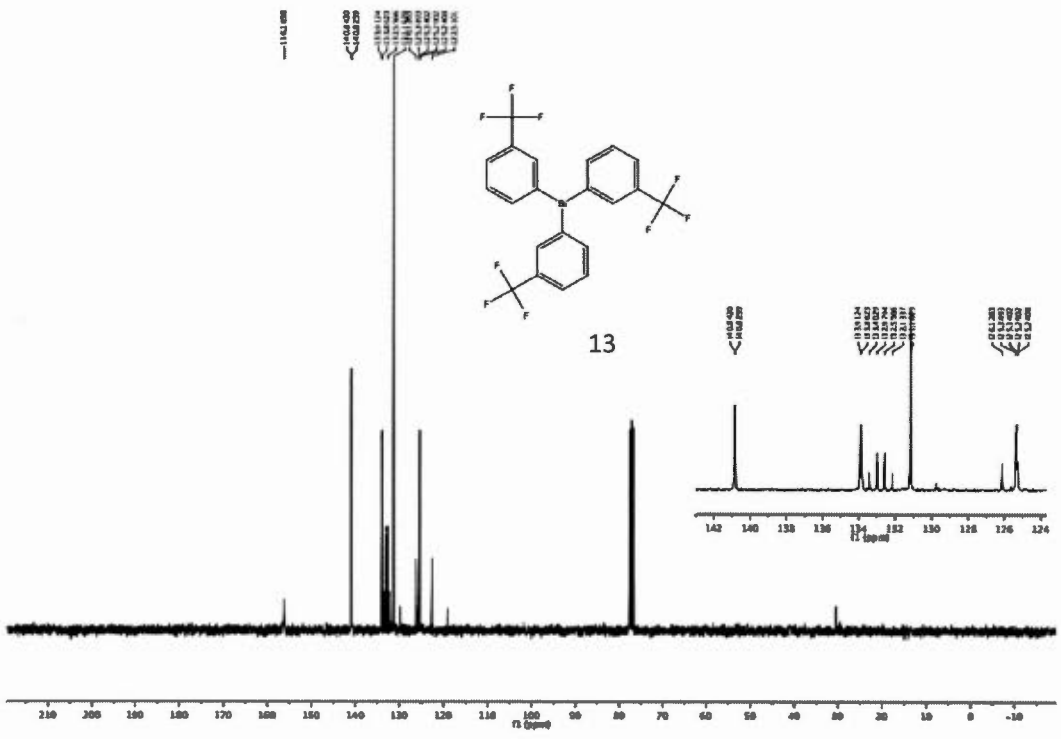

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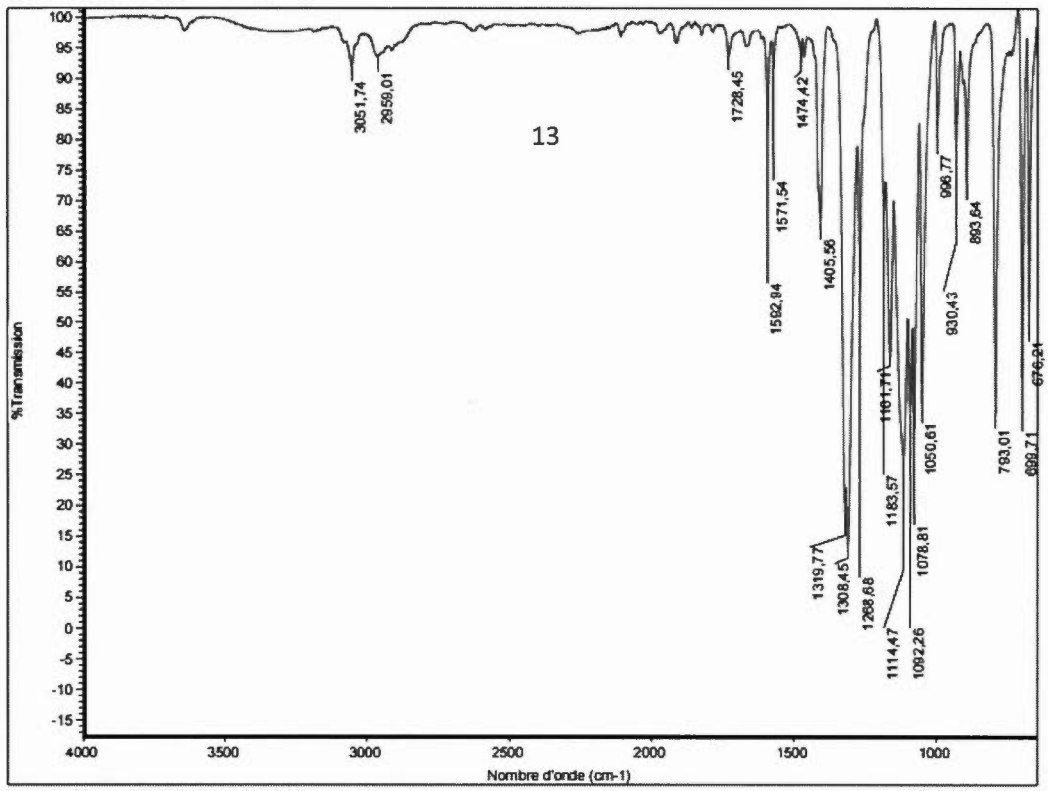
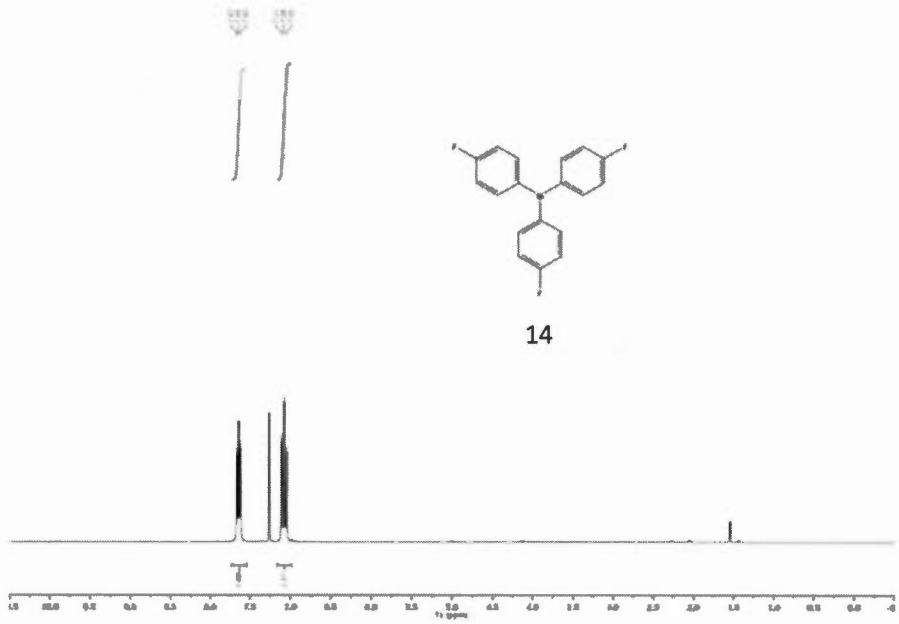

%Transmission
Nombre d'onde (cm-1)
4000
3500
3000
2500
2000
1500
1000
3051,74
2959,01
1728,45
1571,54
1474,42
1592,94
1405,56
1319,77
1308,45
1268,68
1183,57
1161,71
1114,47
1092,26
1078,81
1050,61
998,77
930,43
893,64
783,01
699,71
676,24

13



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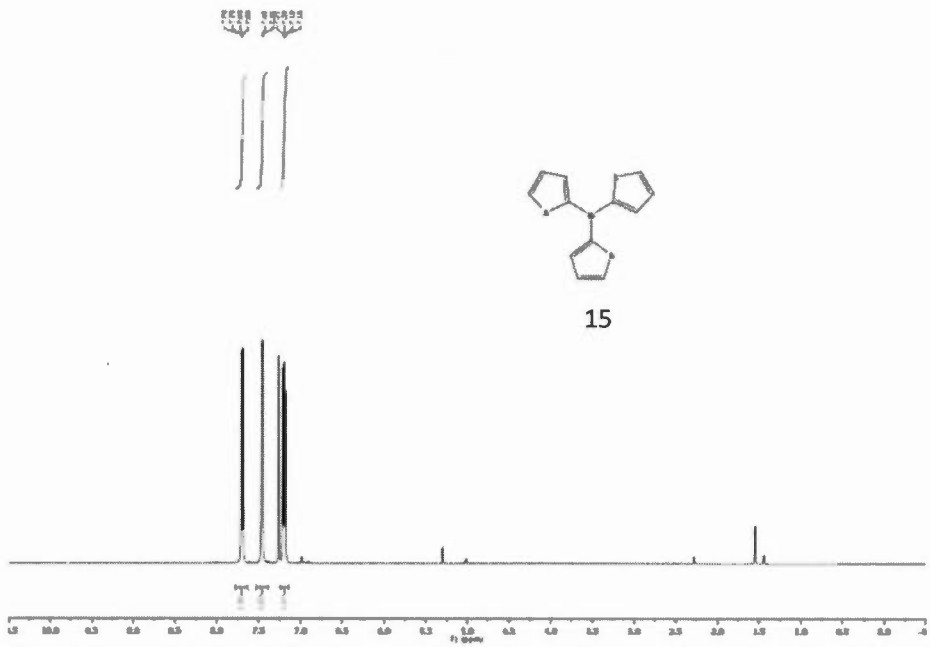
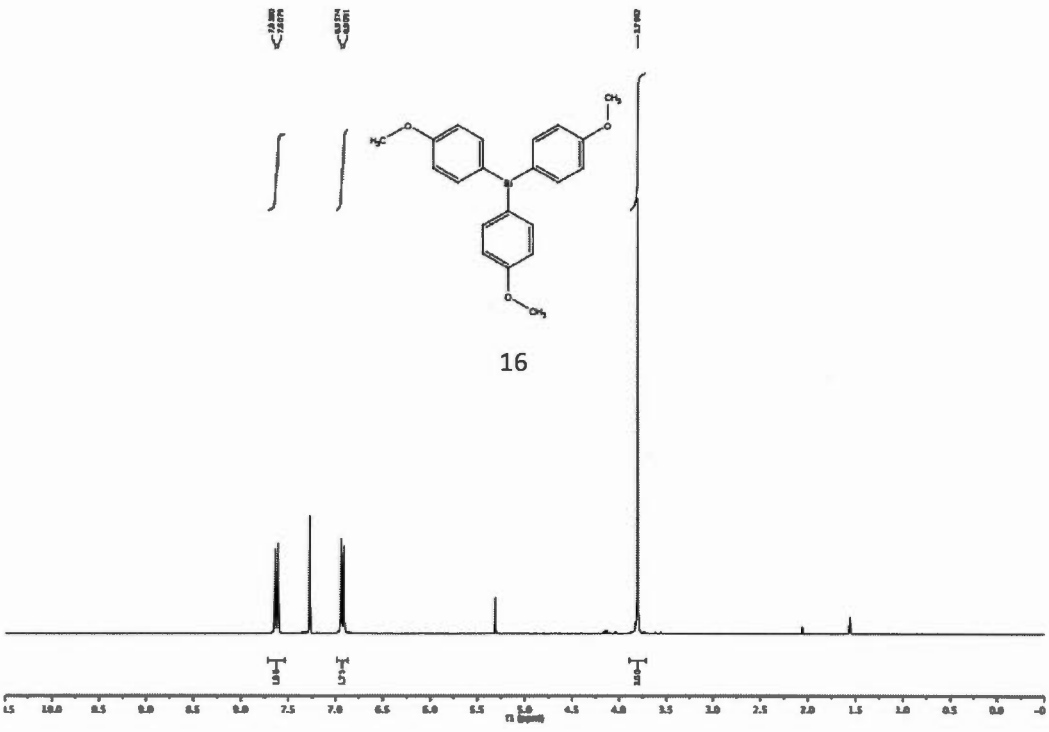
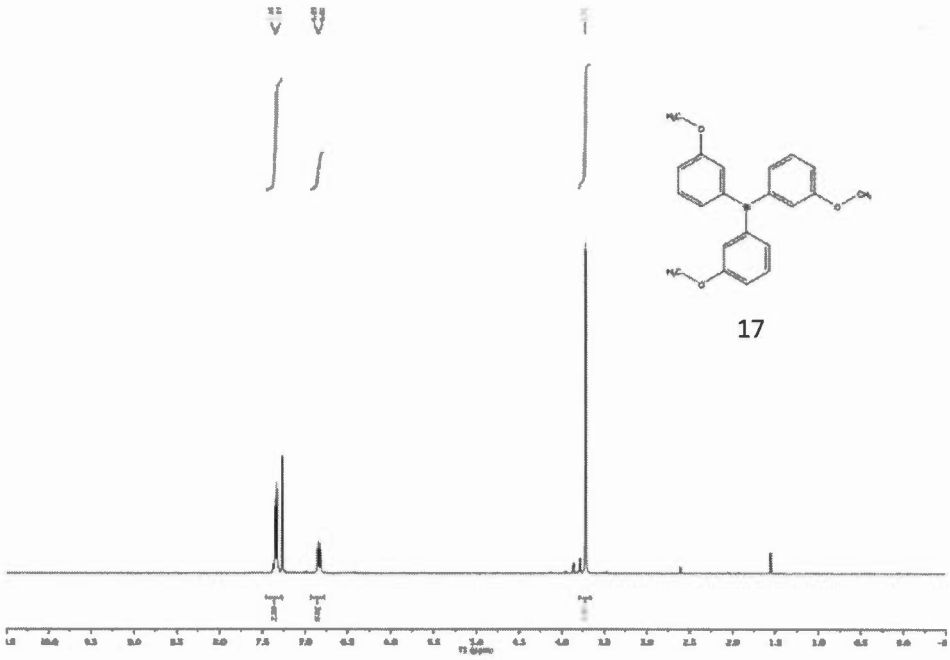


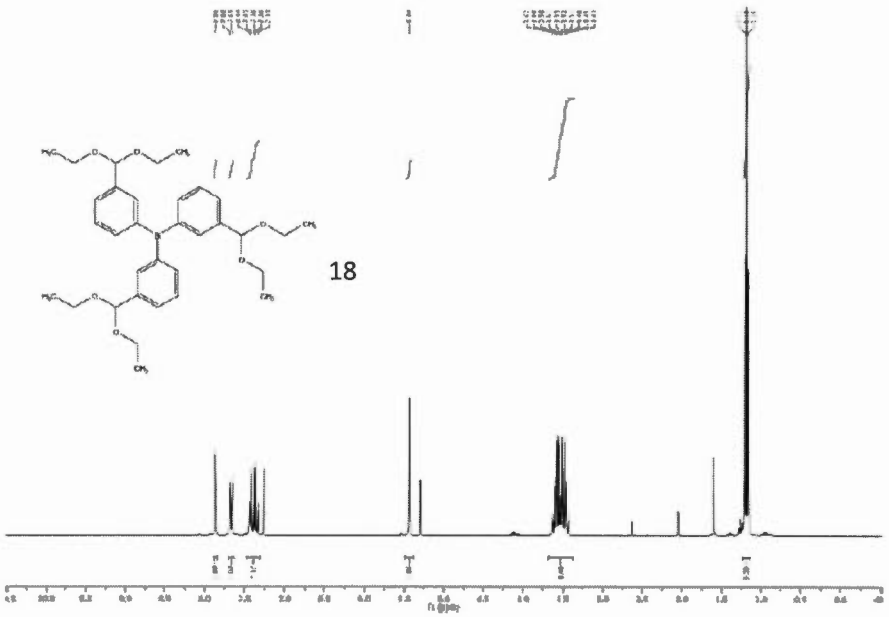
15



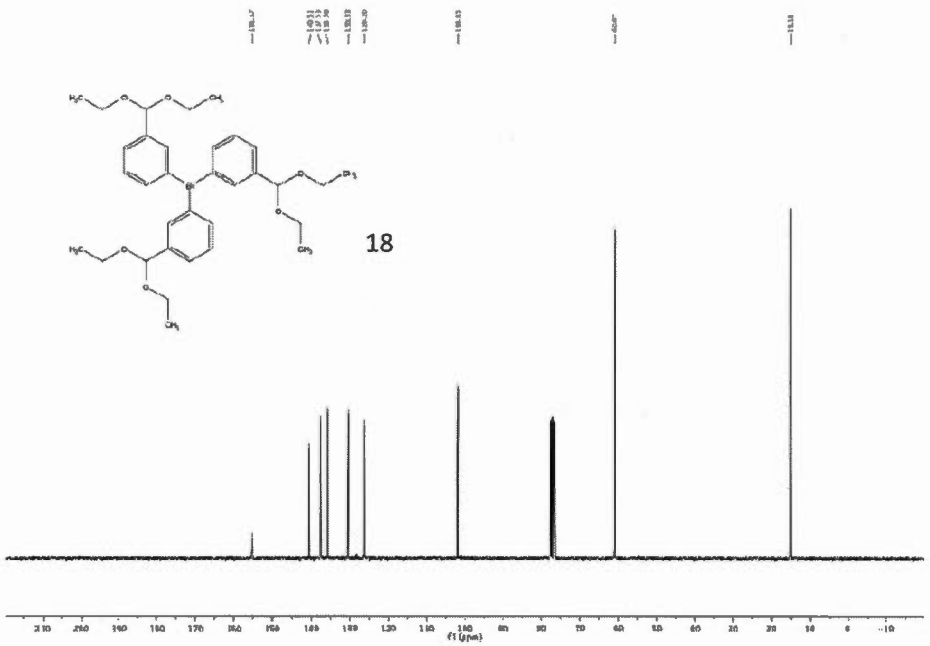
16



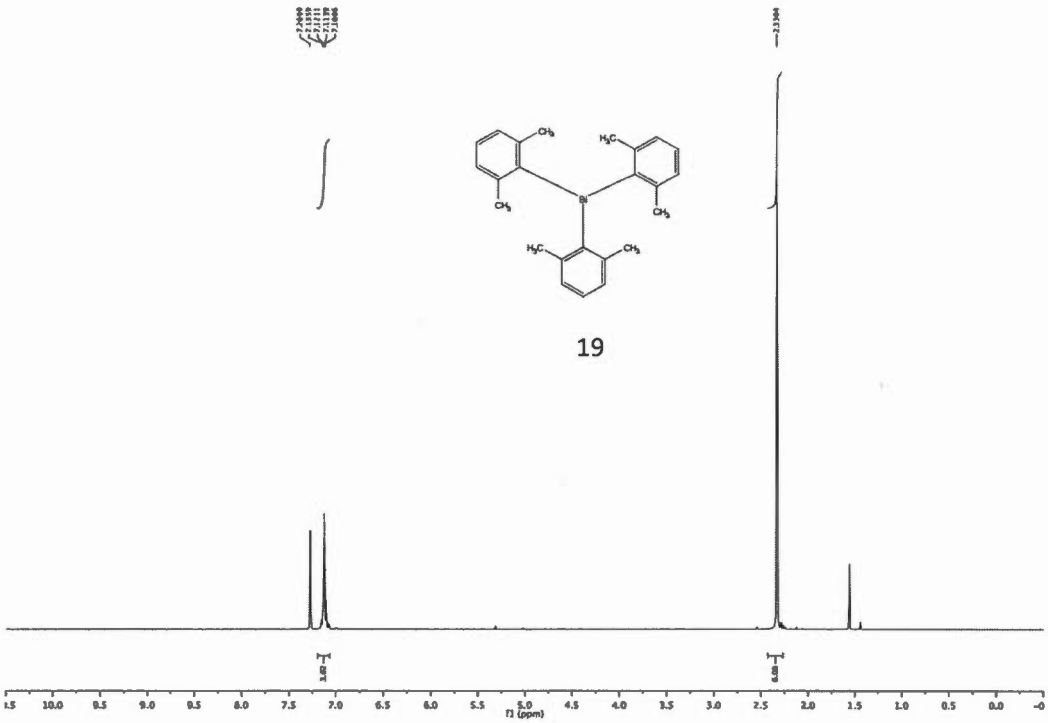
17



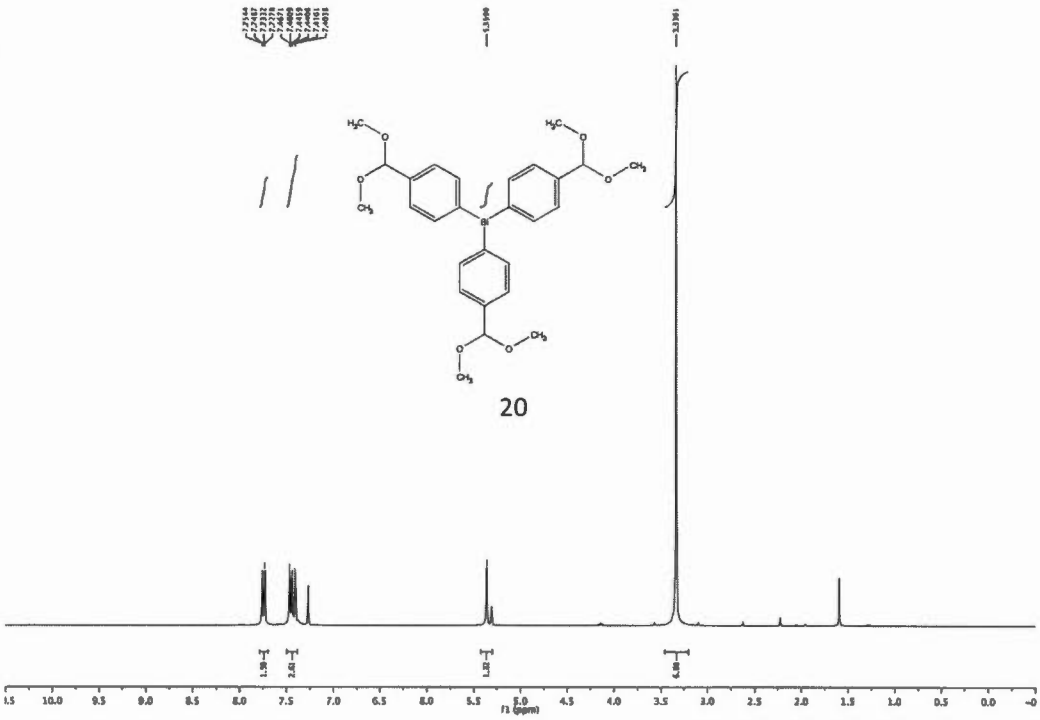
18



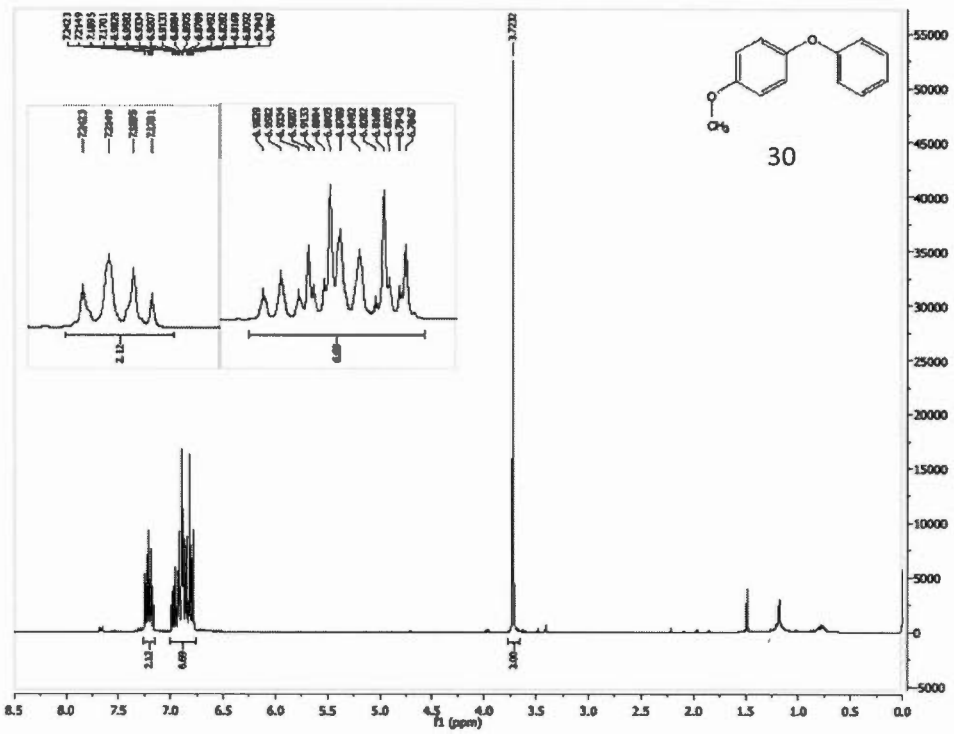
18

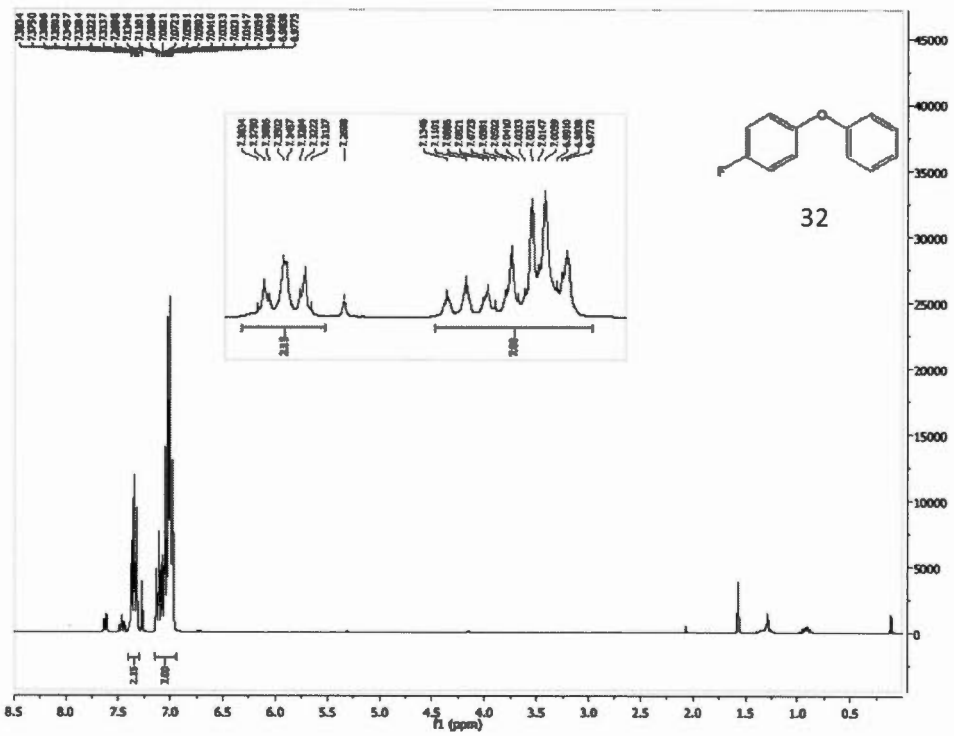


19

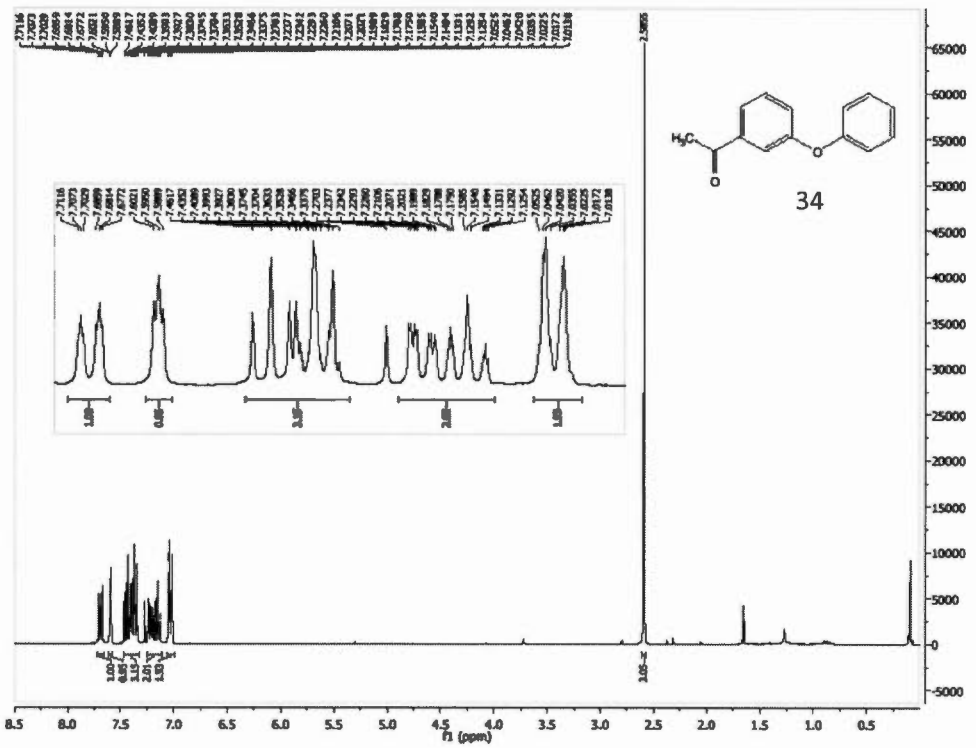


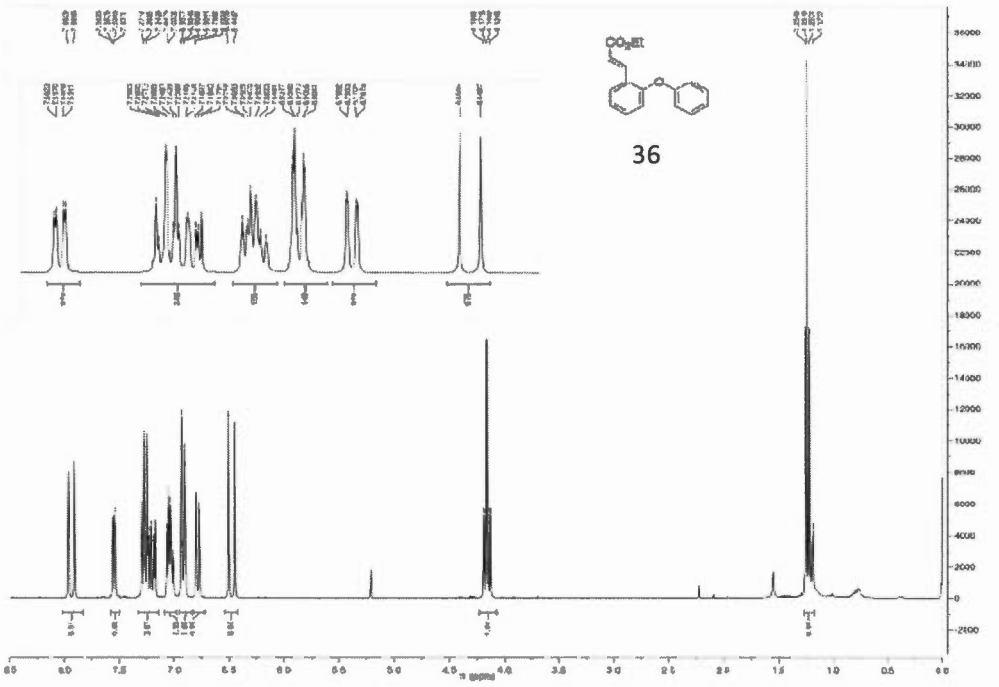
20


30
f1 (ppm)

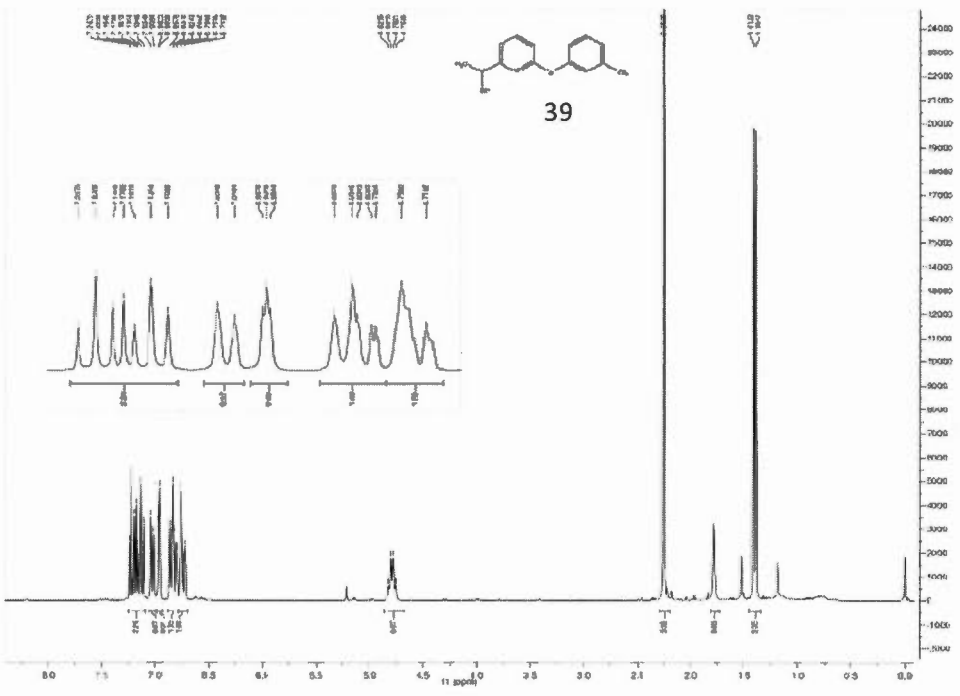

45000
40000
35000
30000
25000
20000
15000
10000
5000
0
2.15
2.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

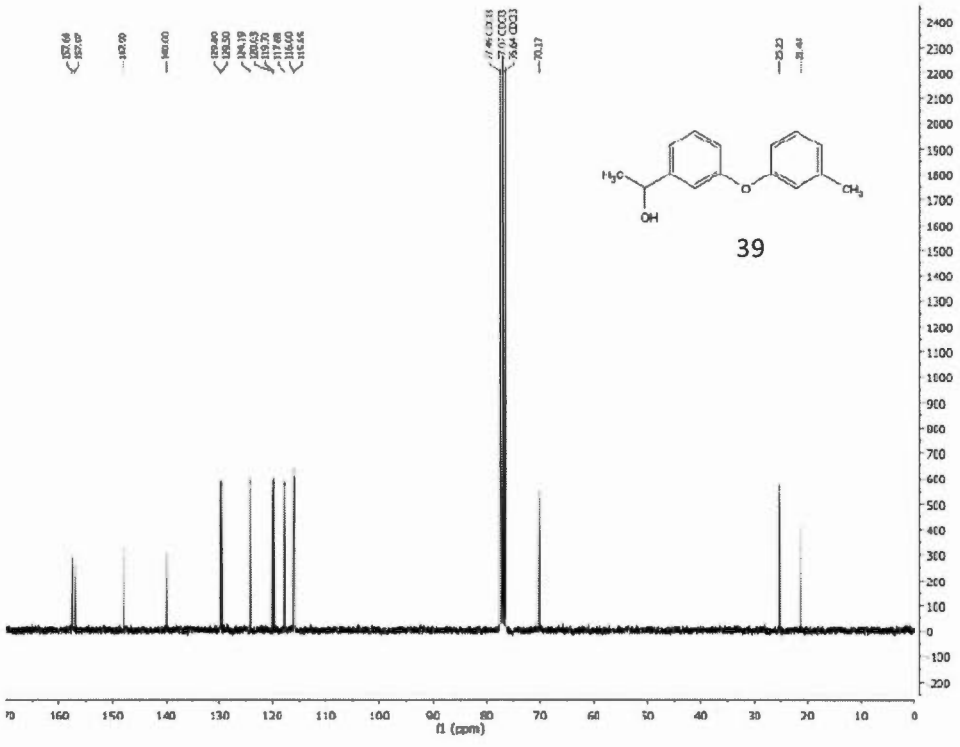
32


34
f1 (ppm)

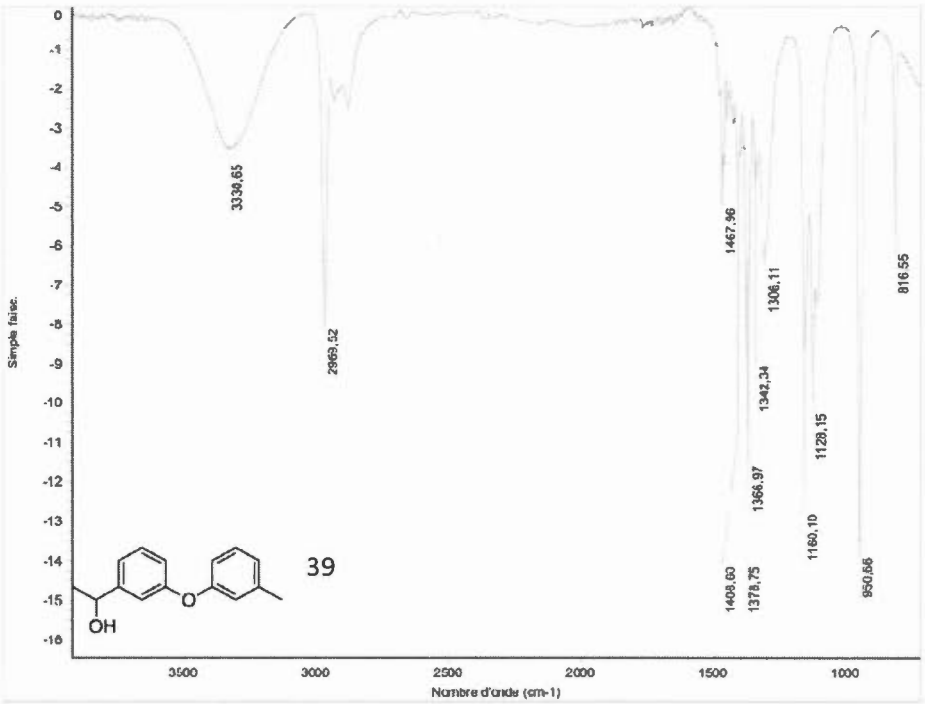


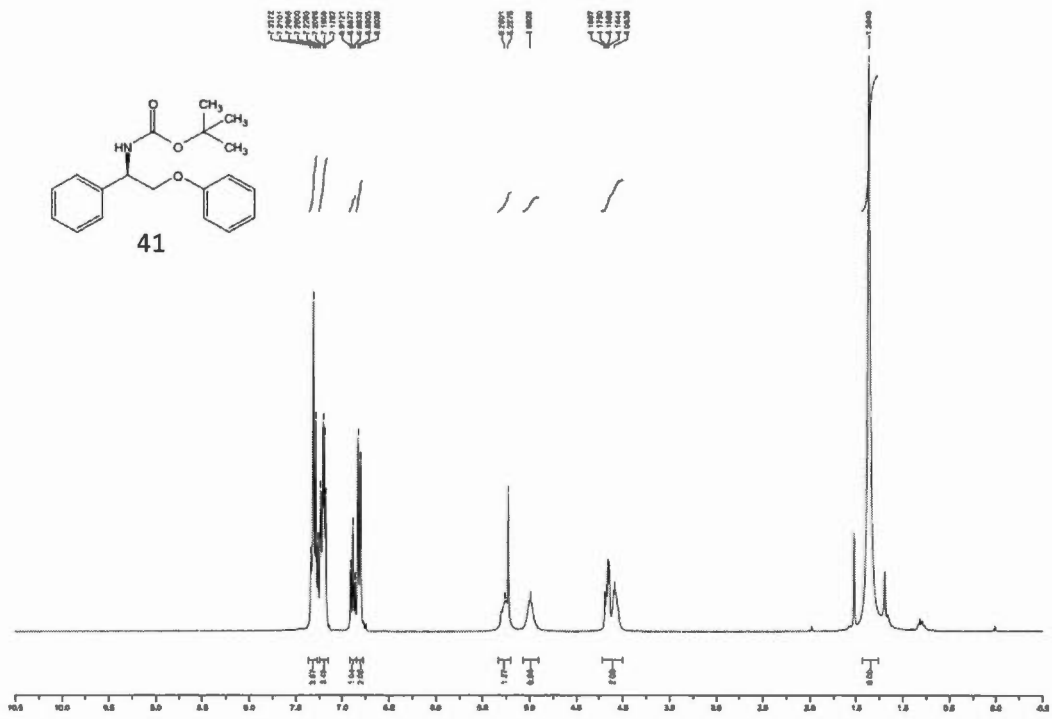
36


39

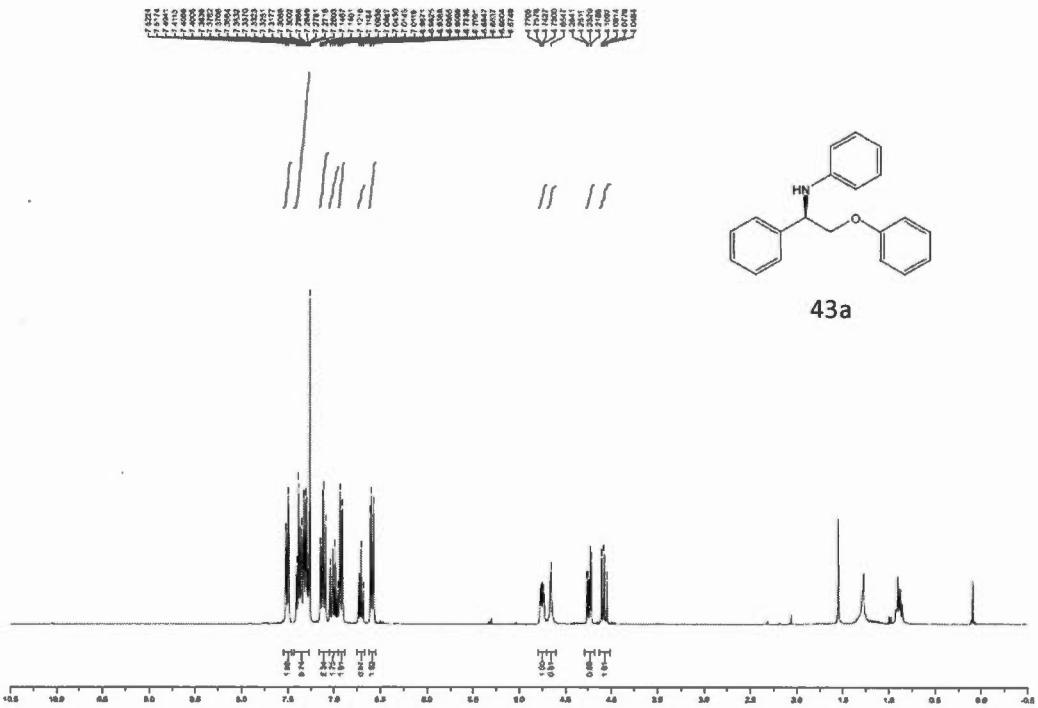


39

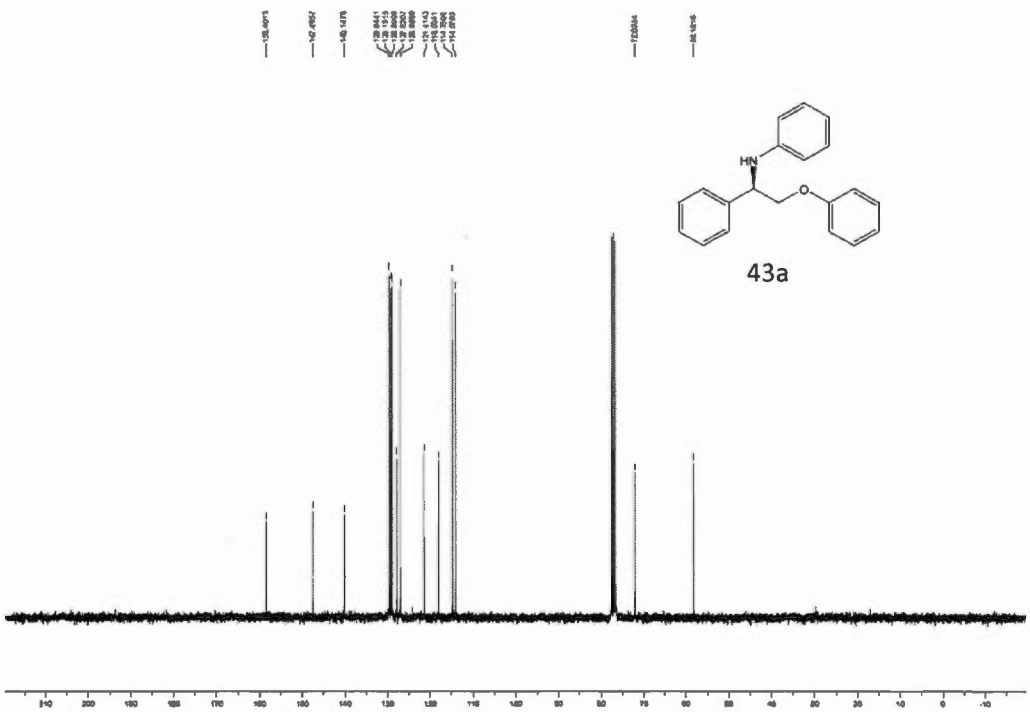

Simple faisc.
0
-1
-2
-3
-4
-5
-6
-7
-8
-9
-10
-11
-12
-13
-14
-15
-16
3334,65
2969,52
1467,96
1408,60
1378,75
1366,97
1342,34
1306,11
1160,10
1128,15
950,66
816,55
3500
3000
2500
2000
1500
1000
Nombre d'onde (cm-1)
39
OH
O



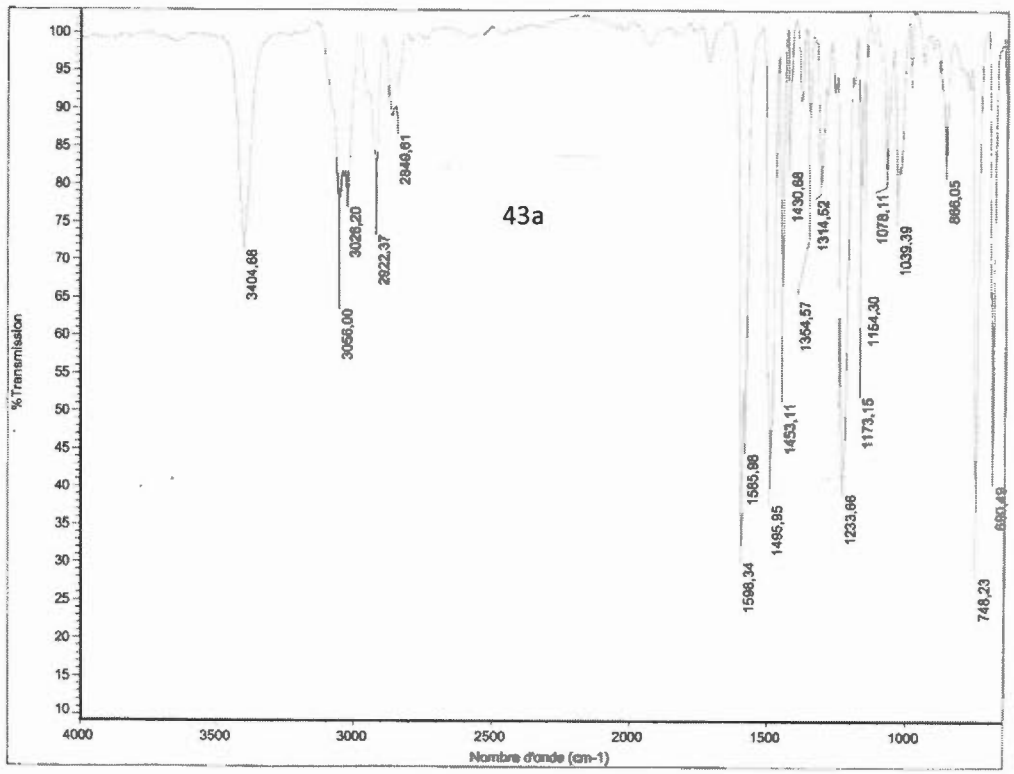
41

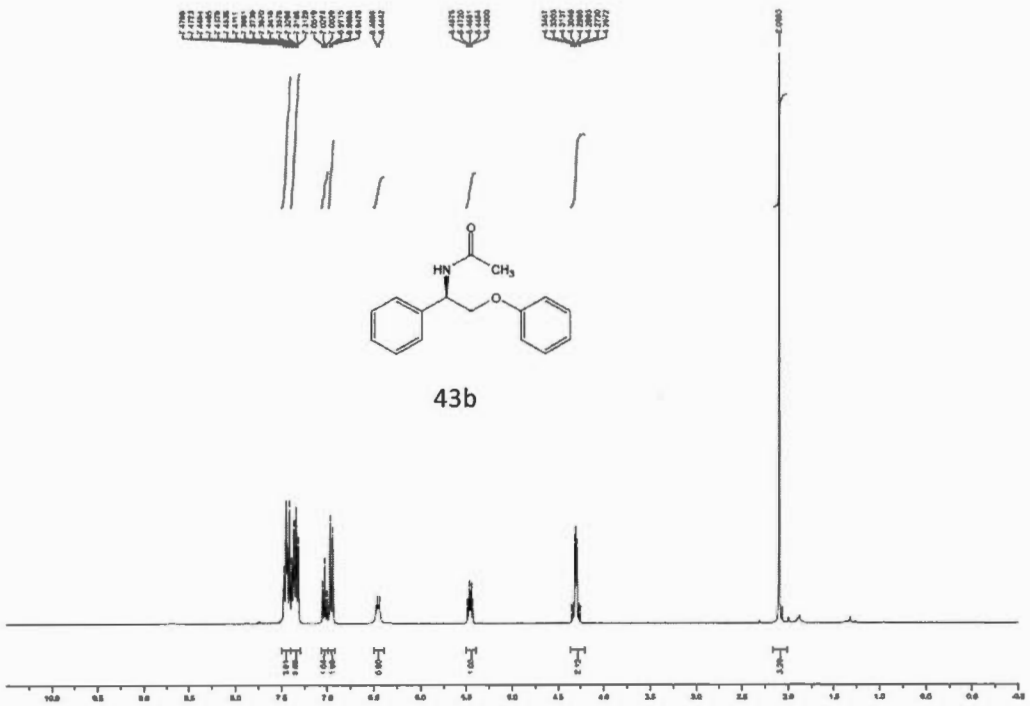


43a

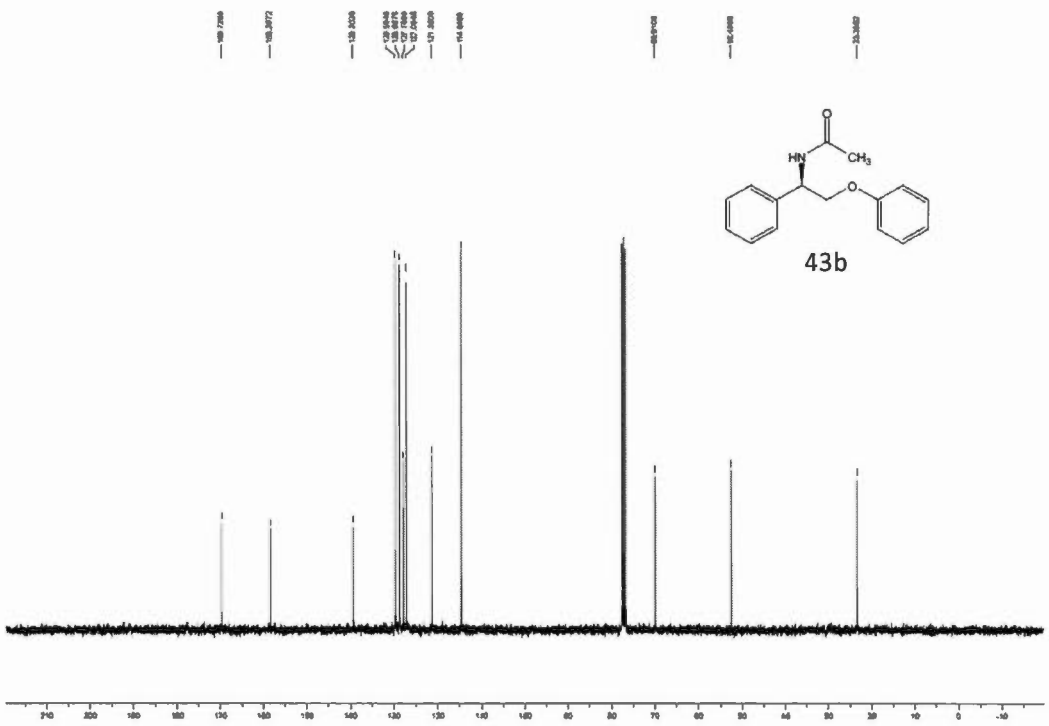


43a


43a
% Transmission
Nombre d'onde (cm-1)
3404,68
3056,00
3026,20
2922,37
2846,61
1598,34
1585,88
1495,95
1453,11
1430,68
1364,57
1314,52
1233,66
1173,15
1164,30
1078,11
1039,39
866,05
748,23
690,49

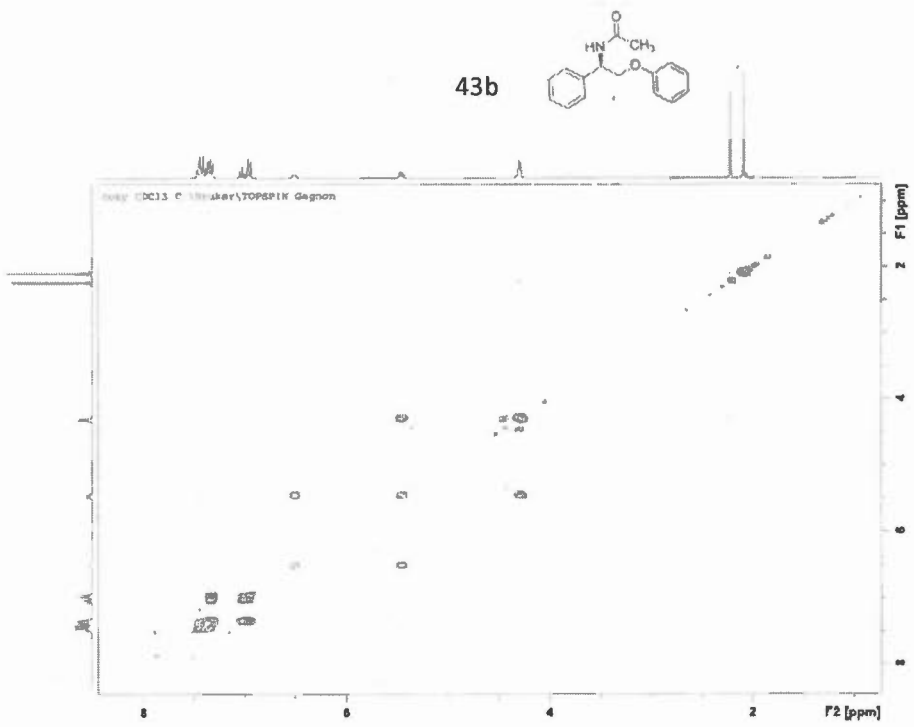


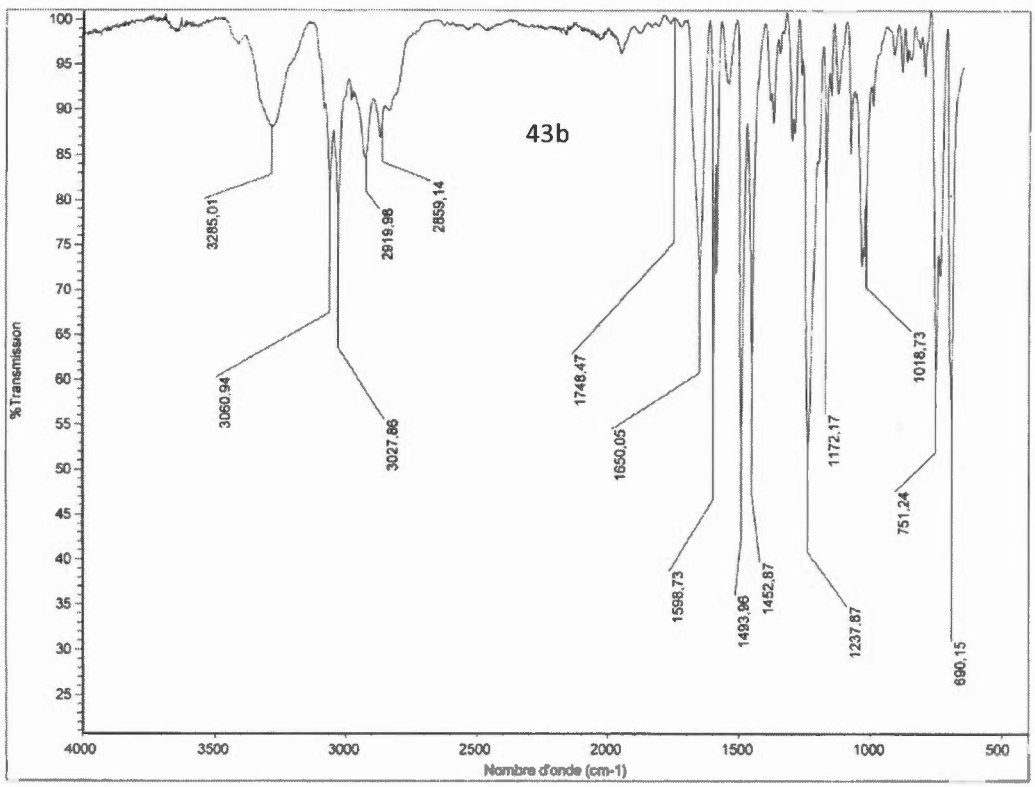
43b

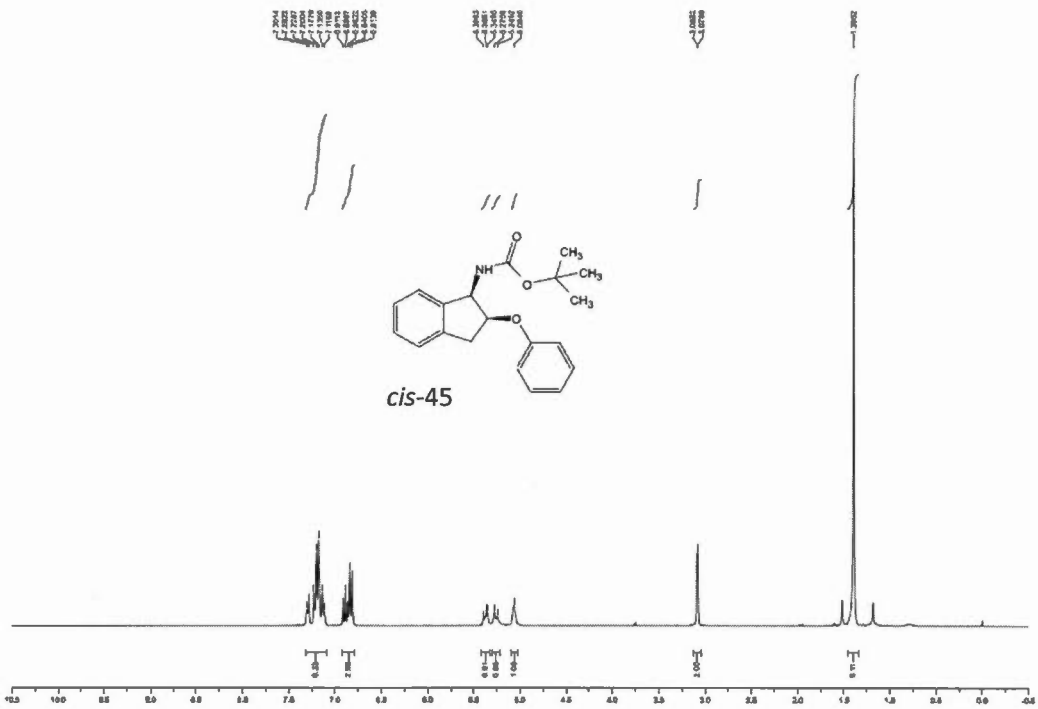


43b

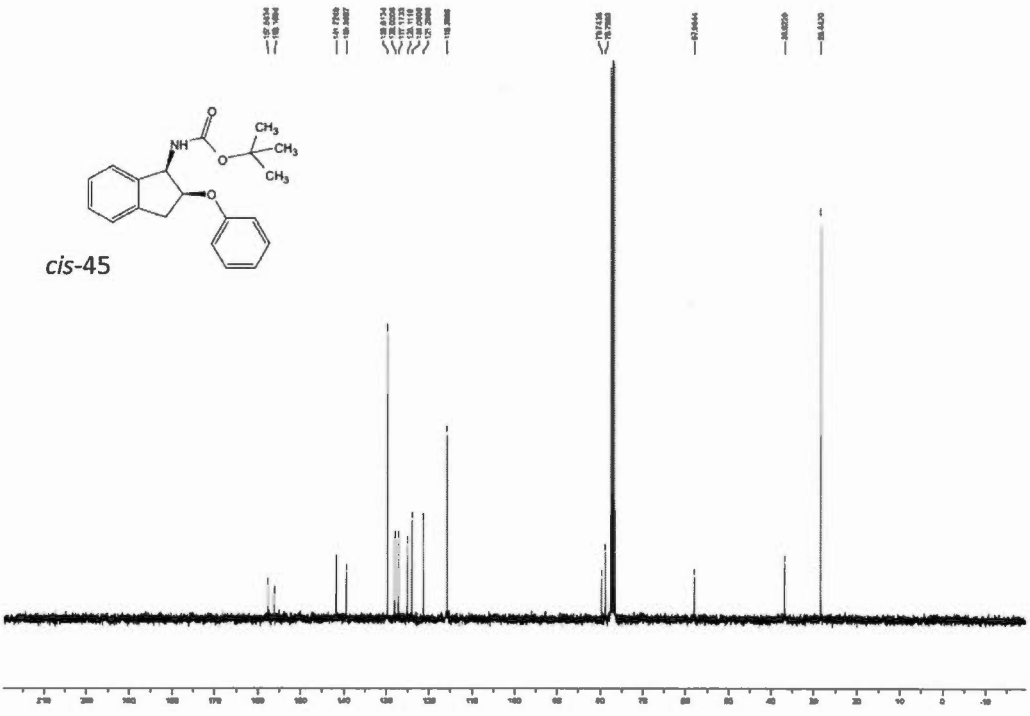
43b



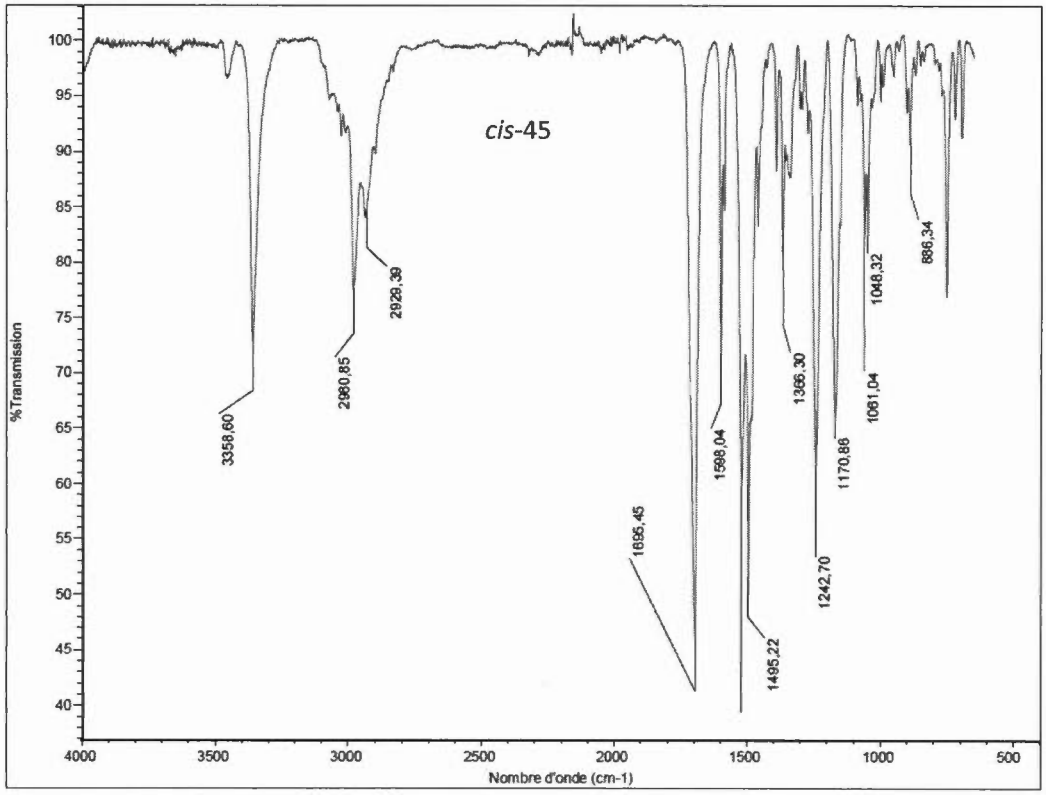

43b
%Transmission
Nombre d'onde (cm-1)
3285,01
3060,94
2919,88
2859,14
3027,86
1748,47
1650,05
1598,73
1493,96
1452,87
1237,87
1172,17
1018,73
751,24
690,15

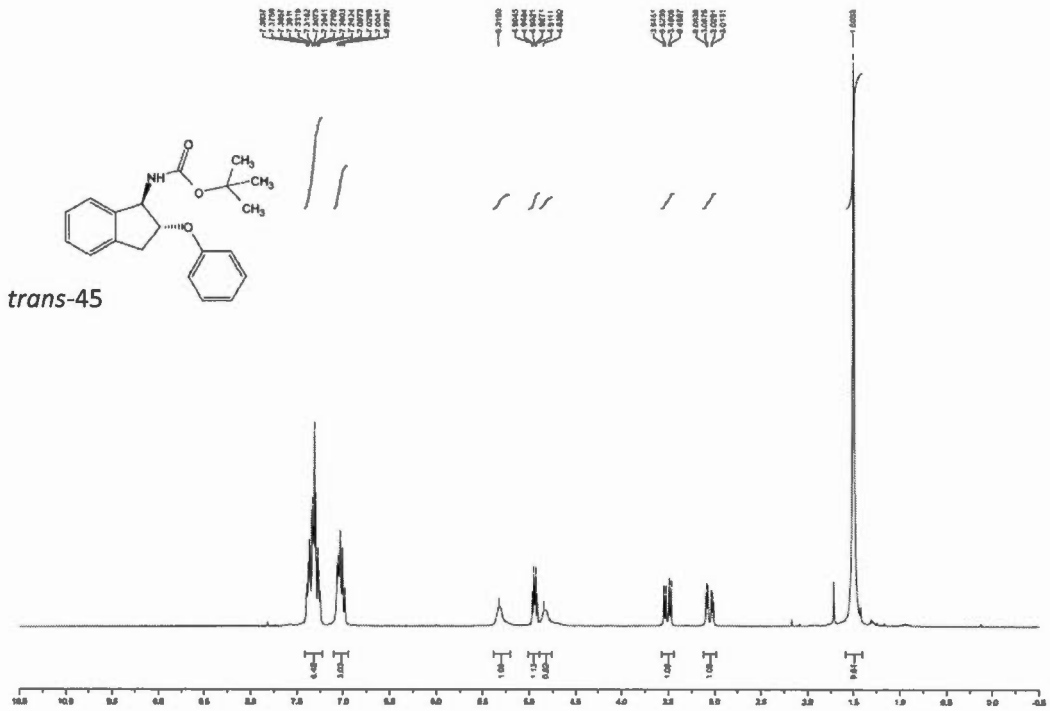


cis-45

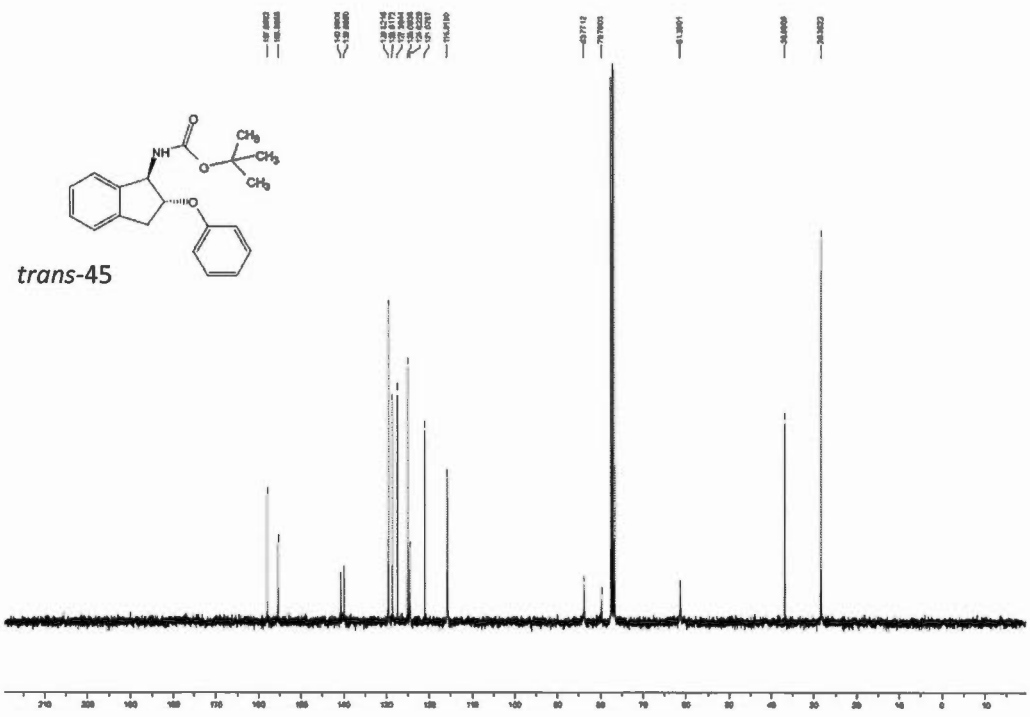


cis-45

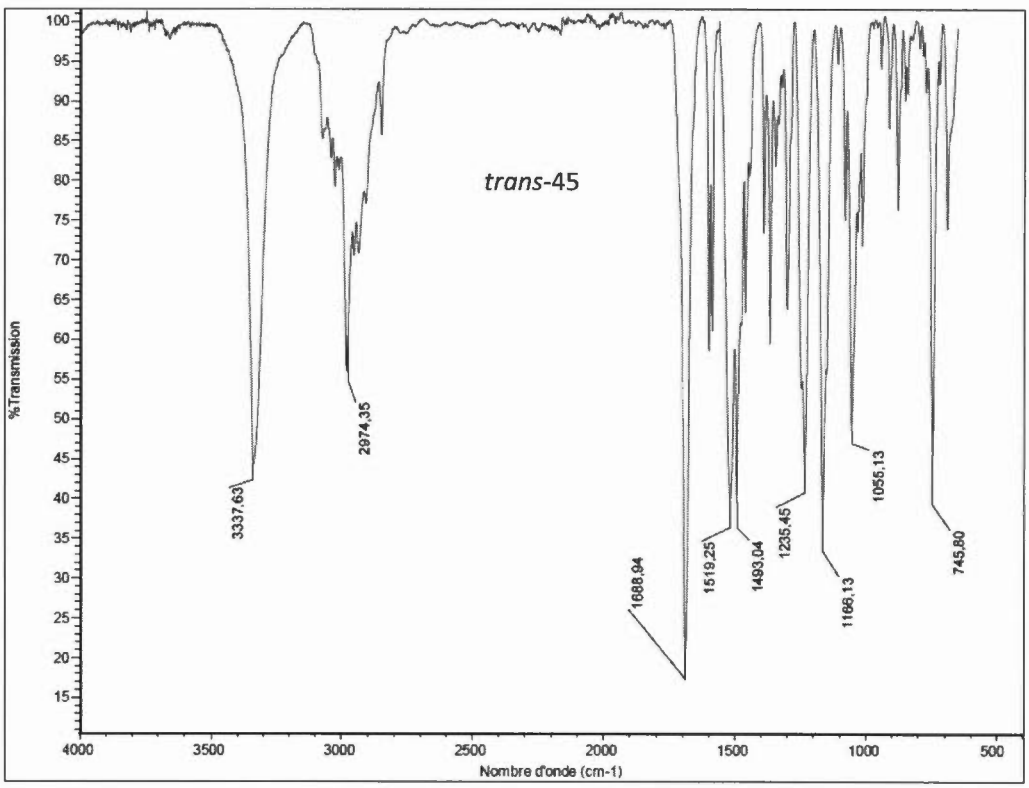

cis-45
%Transmission
Nombre d'onde (cm-1)
3358,60
2980,85
2929,39
1695,45
1598,04
1495,22
1366,30
1242,70
1170,86
1061,04
1048,32
886,34

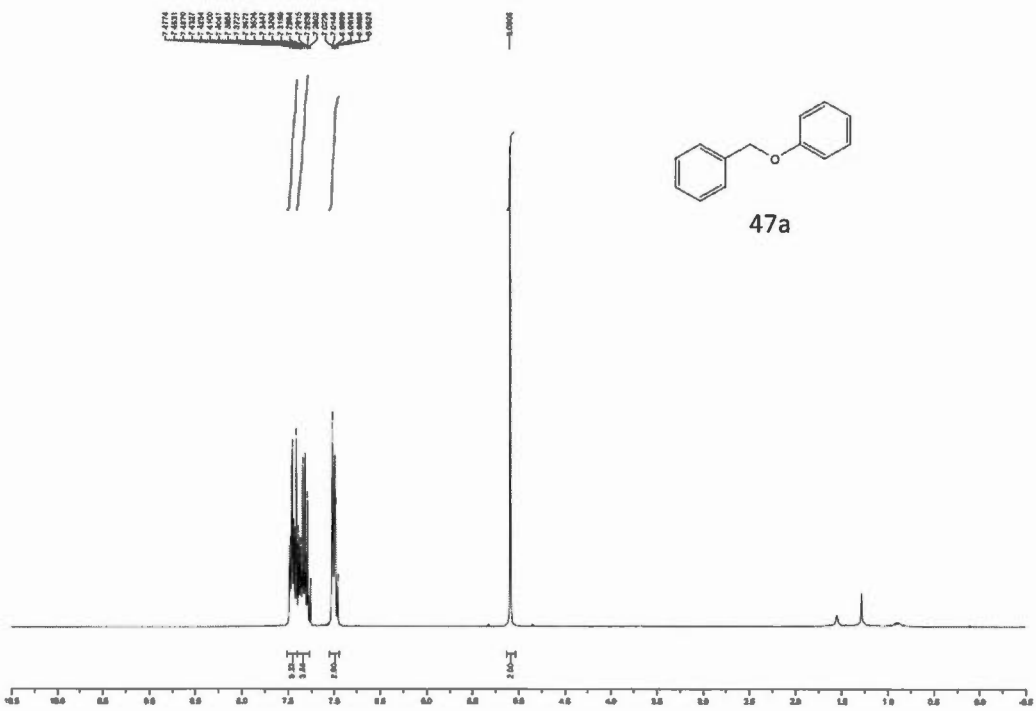


trans-45

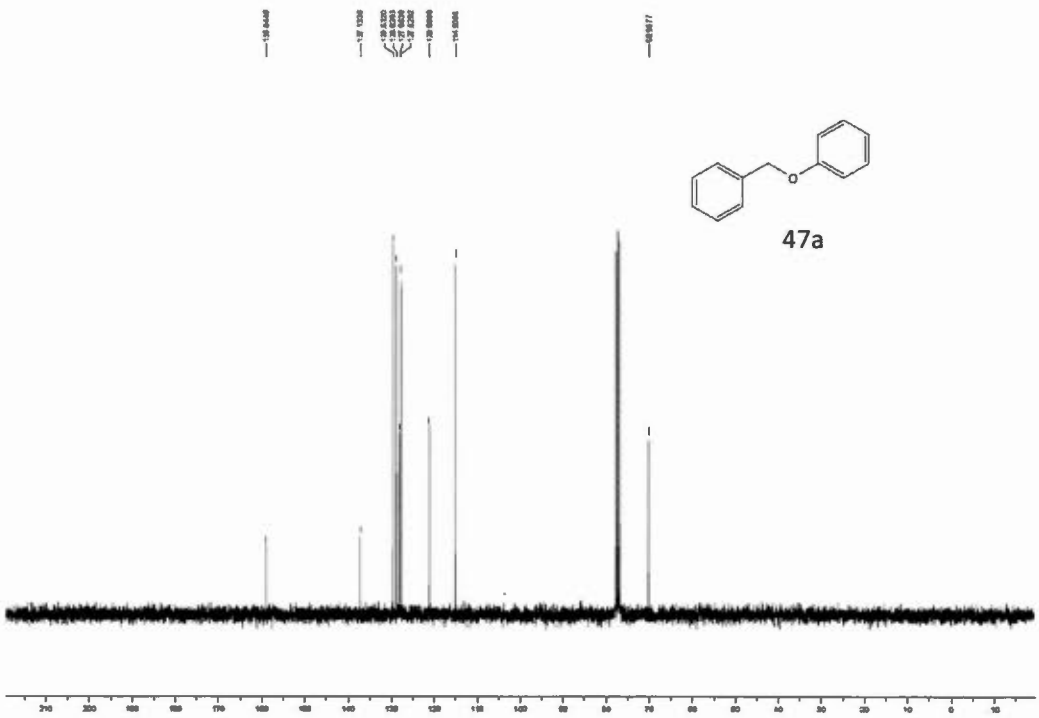


trans-45

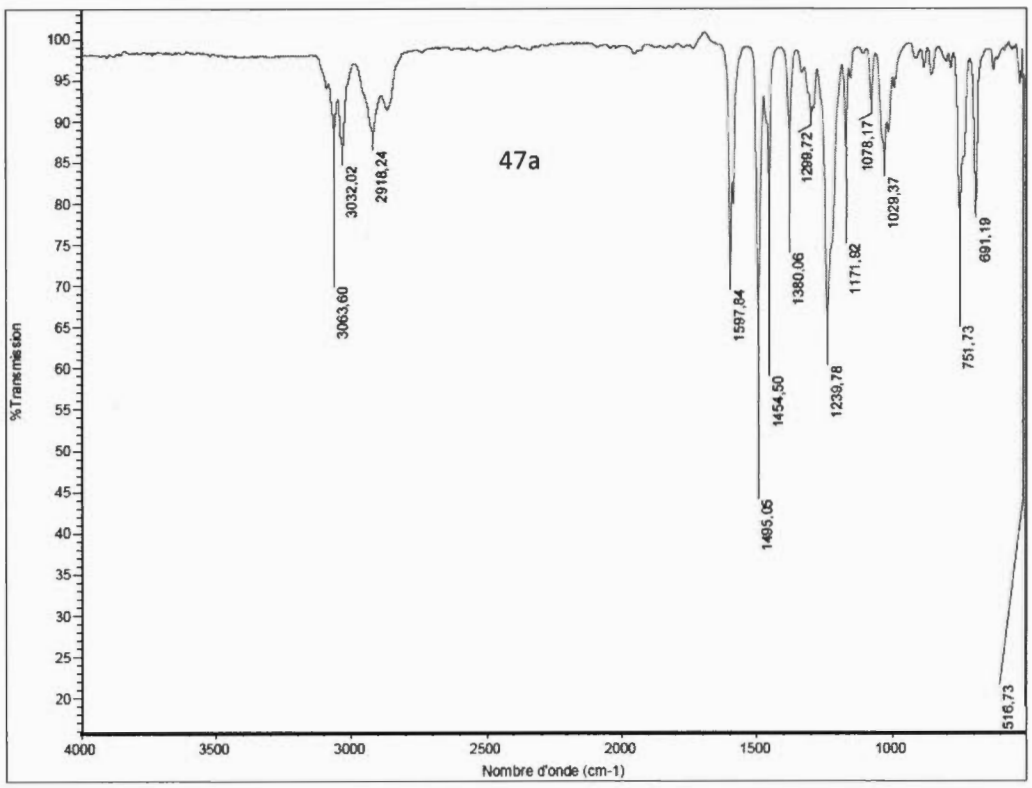

trans-45
%Transmission
Nombre d'onde (cm-1)
3337,63
2974,35
1688,94
1519,25
1493,04
1235,45
1166,13
1056,13
745,80

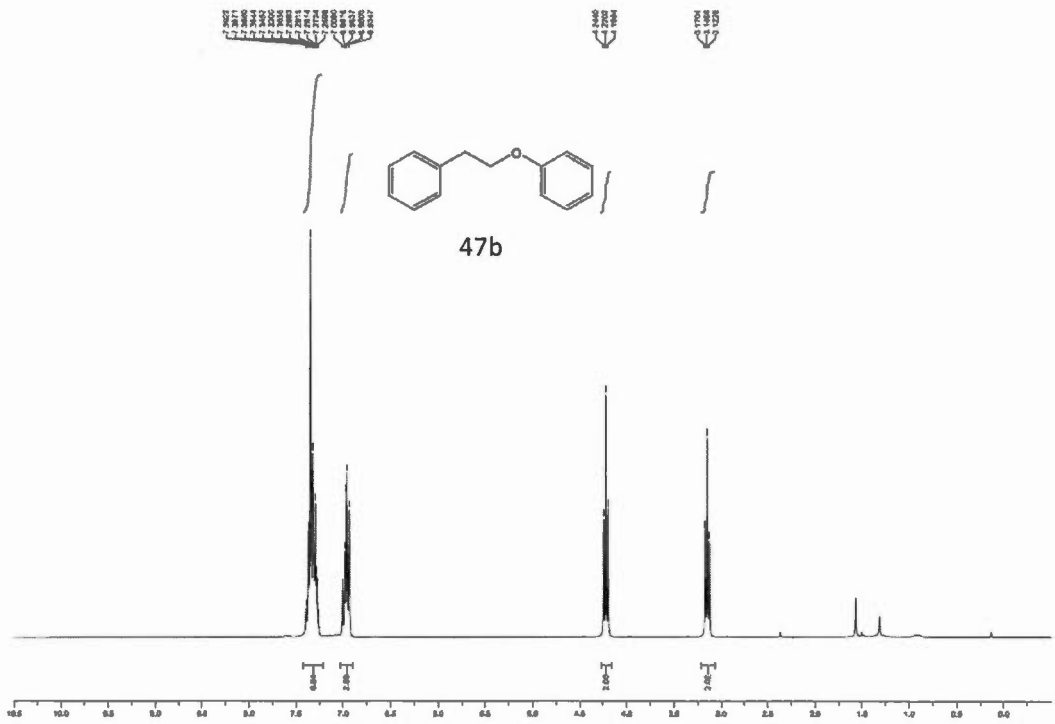


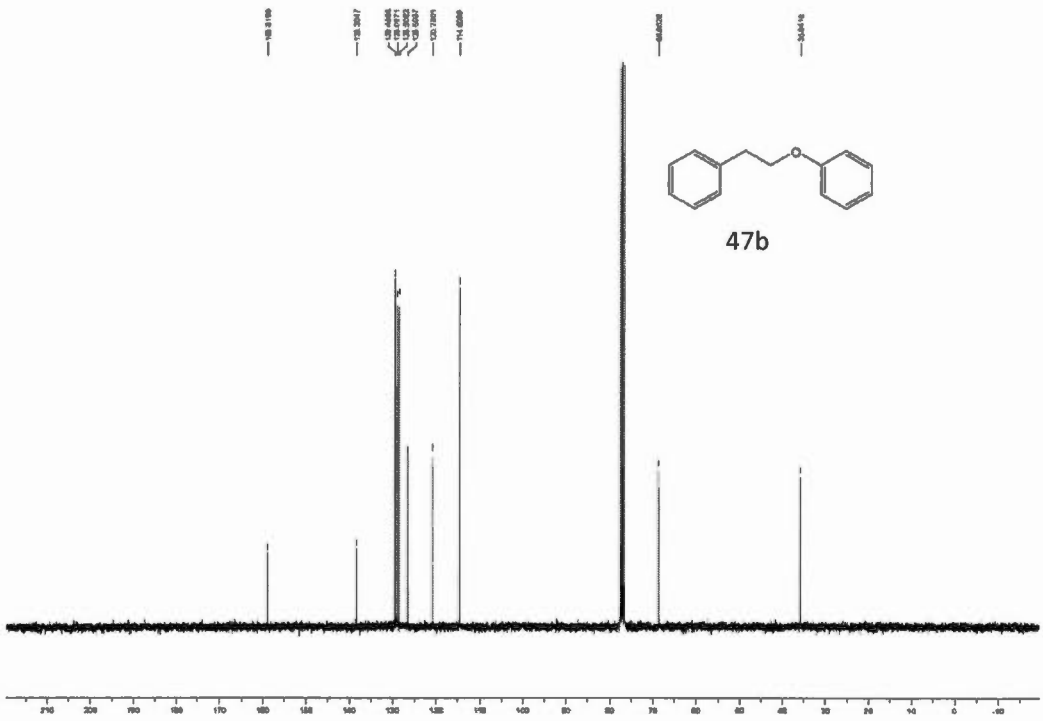
47a

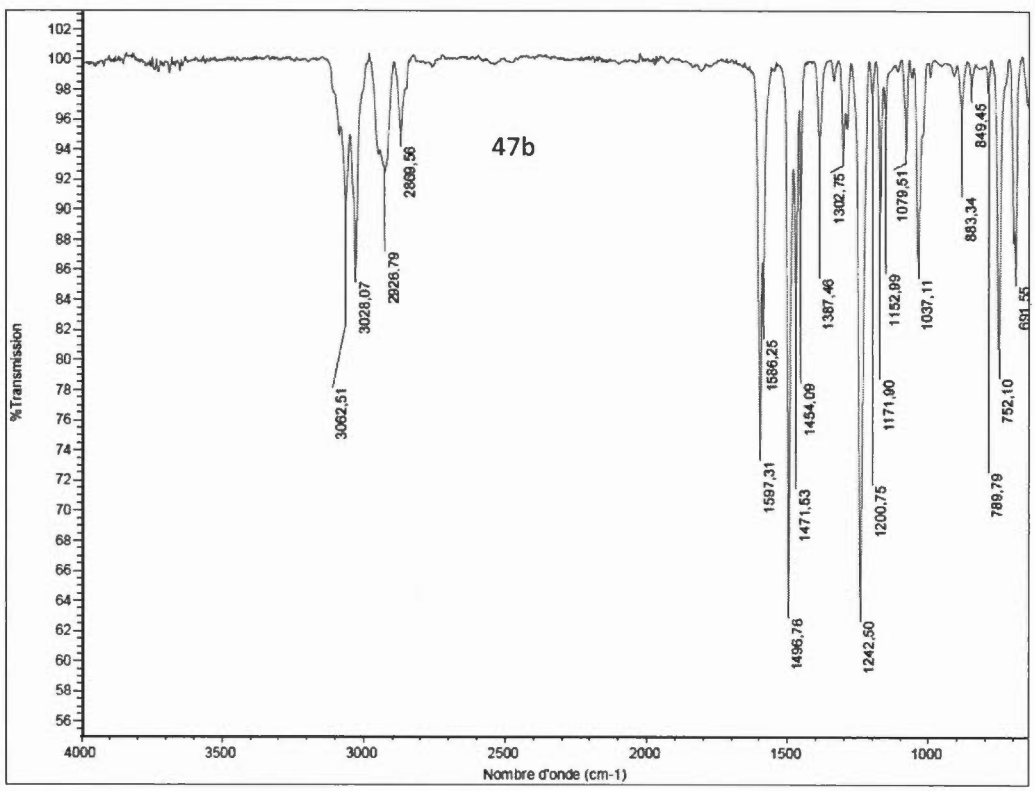


47a


47a
%Transmission
Nombre d'onde (cm-1)
3063,60
3032,02
2918,24
1597,84
1495,05
1454,50
1380,06
1299,72
1239,78
1171,82
1078,17
1029,37
751,73
691,19
516,73


47b


47b


47b
%Transmission
Nombre d'onde (cm-1)
4000
3500
3000
2500
2000
1500
1000
3062,51
3028,07
2926,79
2869,56
1597,31
1586,25
1496,76
1471,53
1454,09
1387,46
1302,75
1242,50
1200,75
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1152,99
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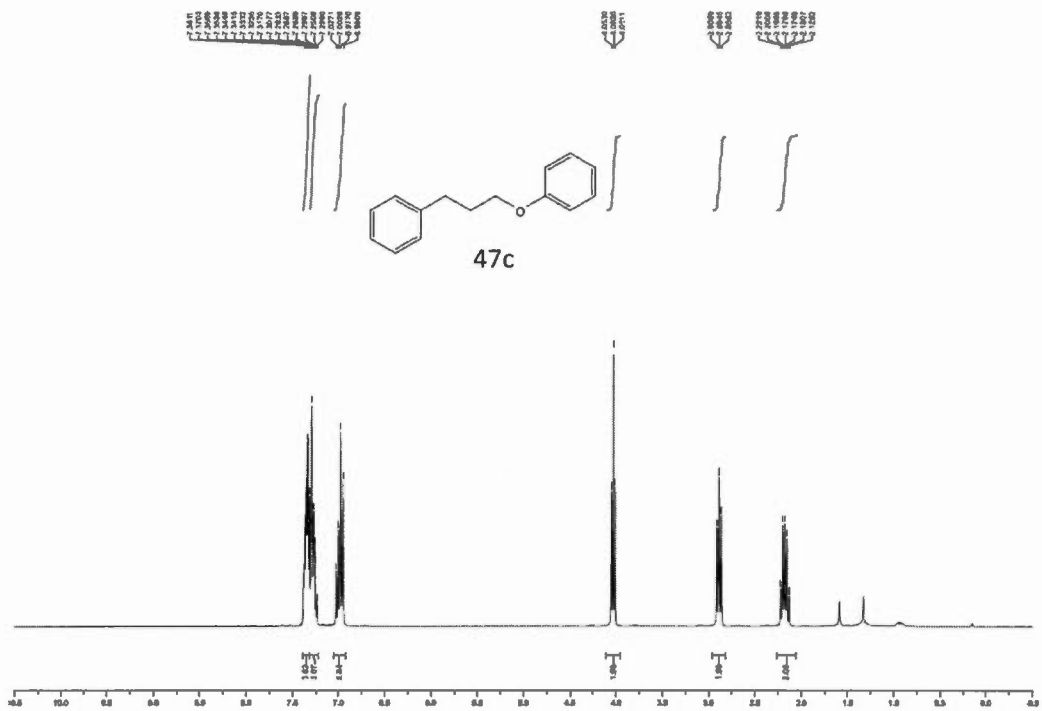
752,10
691,55



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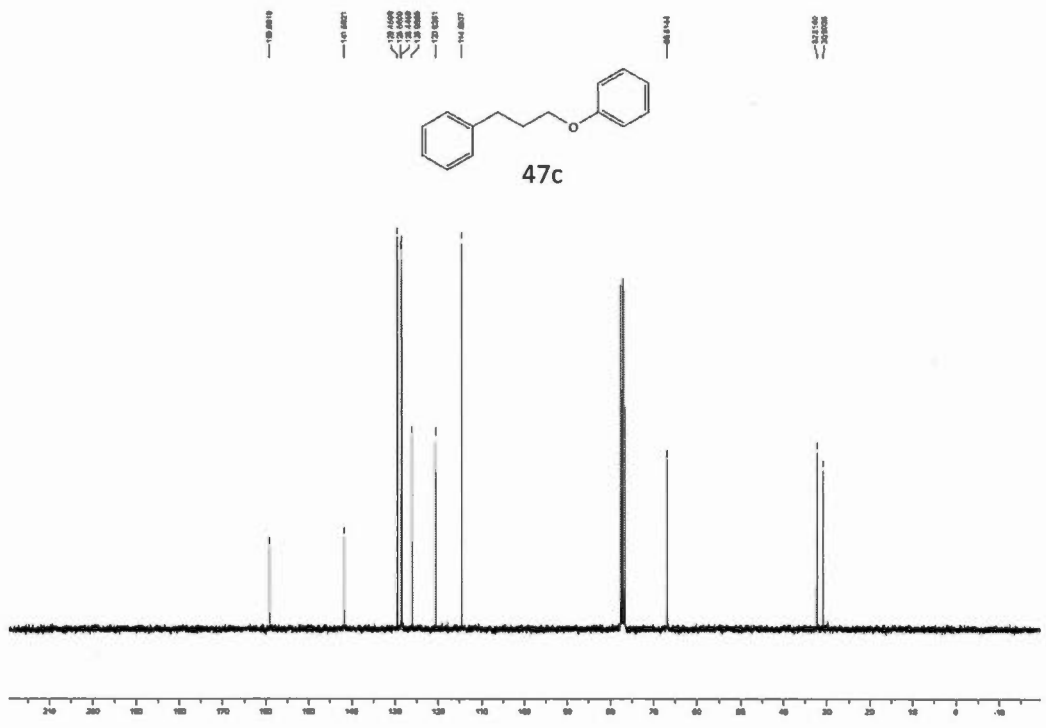

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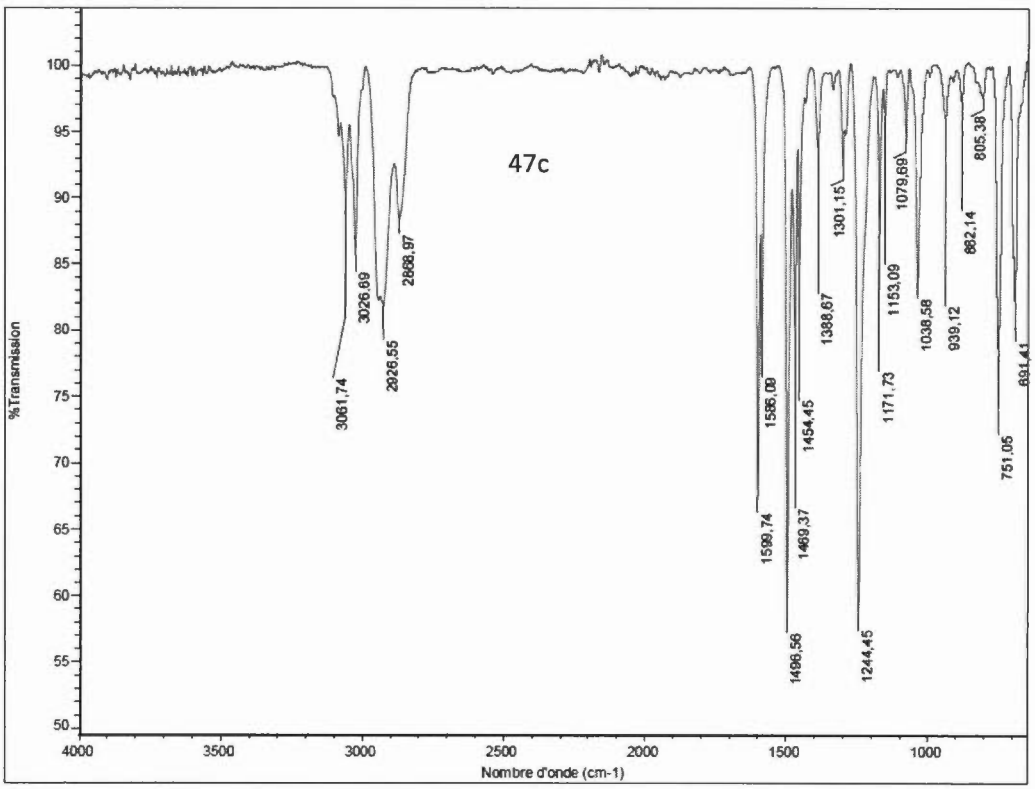
47c
%Transmission
Nombre d'onde (cm-1)
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3500
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2000
1500
1000
100
95
90
85
80
75
70
65
60
55
50
3061,74
3026,69
2926,55
2868,97
1599,74
1586,08
1496,56
1469,37
1454,45
1388,67
1301,15
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1171,73
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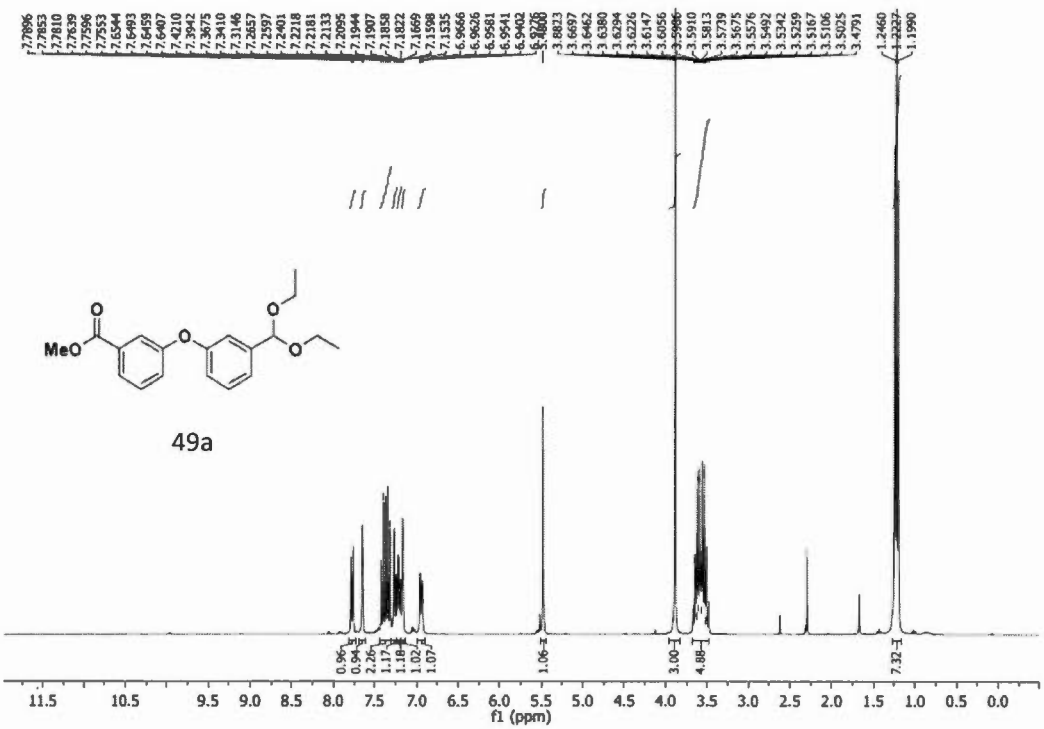
1079,68
1038,58
939,12
882,14
805,38
751,05
691,41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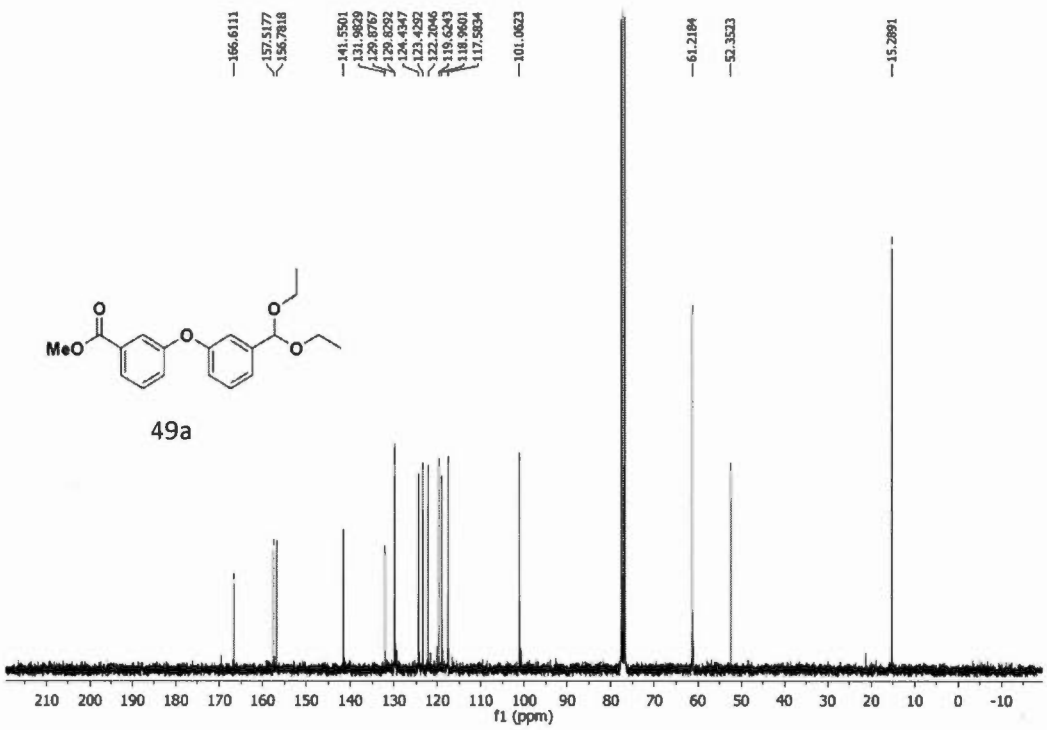
O
O
O
O
49a
f1 (ppm)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156.7818
141.5501
131.9829
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129.8292
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123.4292
122.2046
119.6243
118.9601
117.5834
101.0623
61.2184
52.3523
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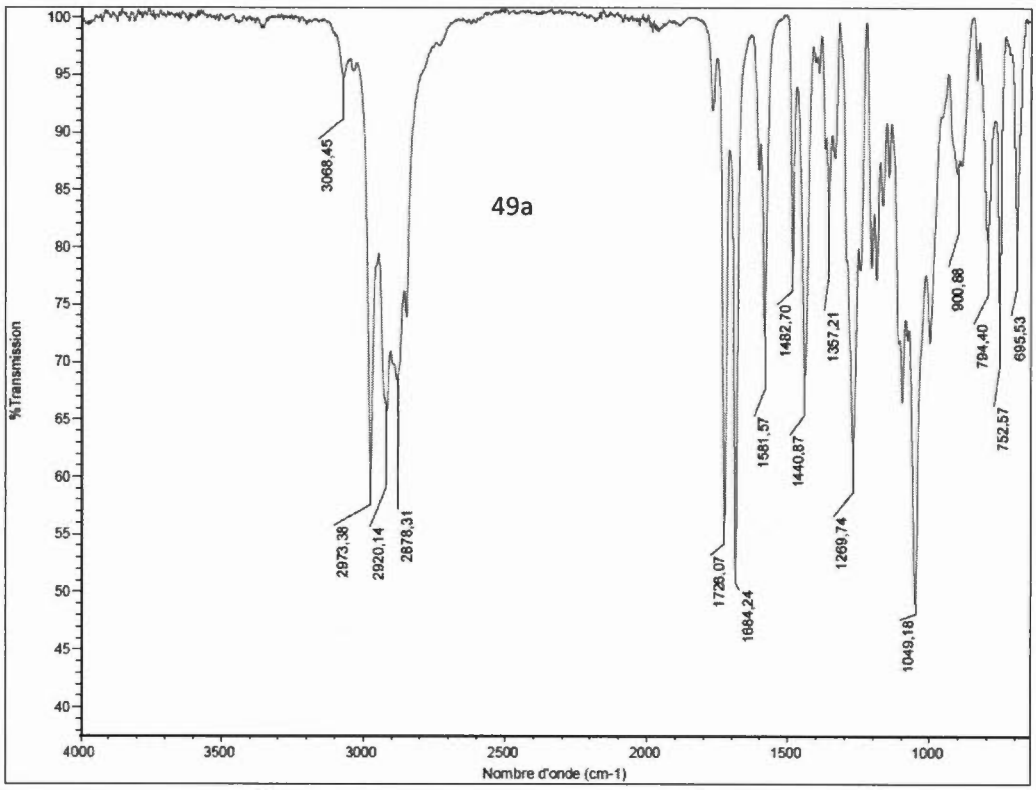
f1 (ppm)


49a
%Transmission
Nombre d'onde (cm-1)
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2973,38
2920,14
2878,31
1728,07
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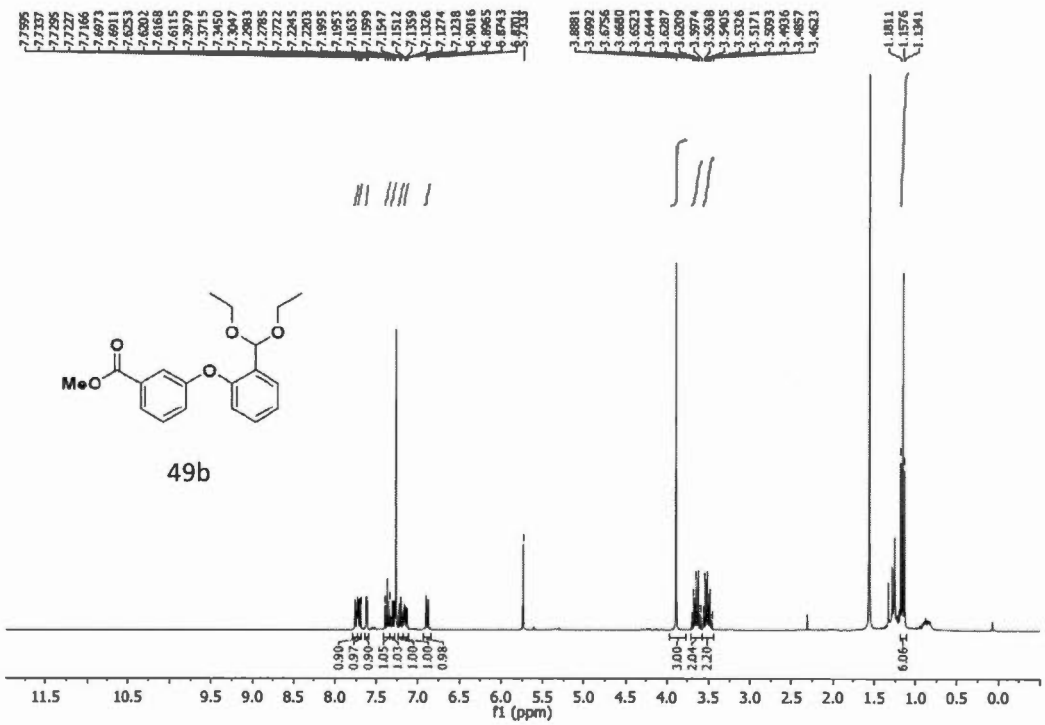
1581,57
1482,70
1440,87
1357,21
1269,74
1049,18
900,88
794,40
752,57
695,53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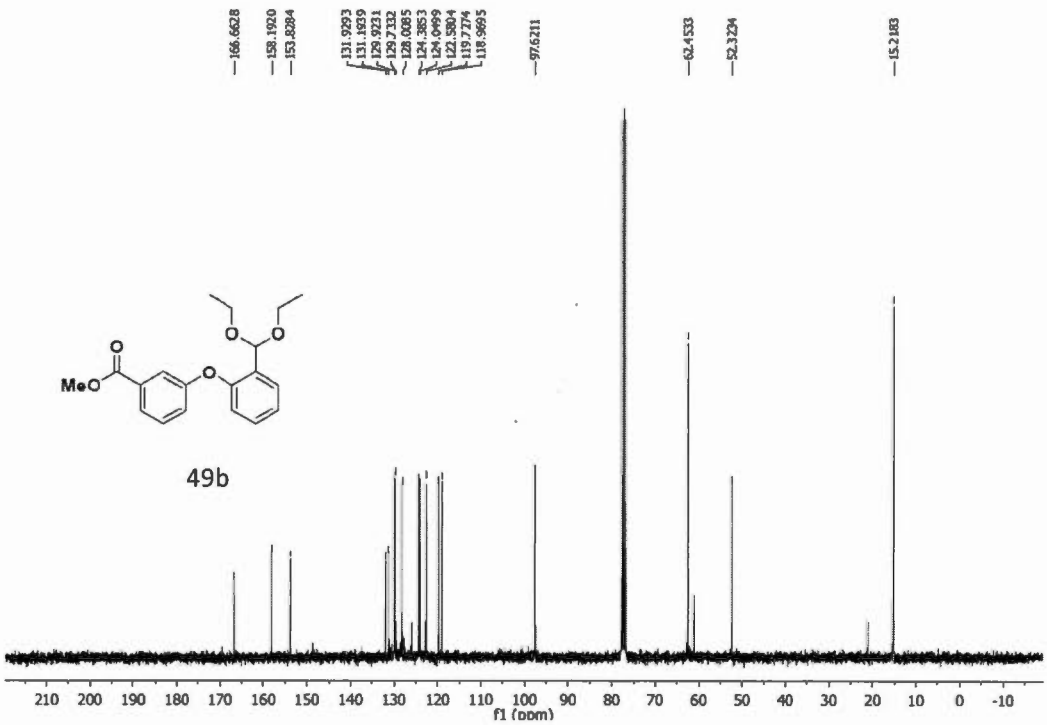
O
O
O
49b
f1 (ppm)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131.1939
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124.3853
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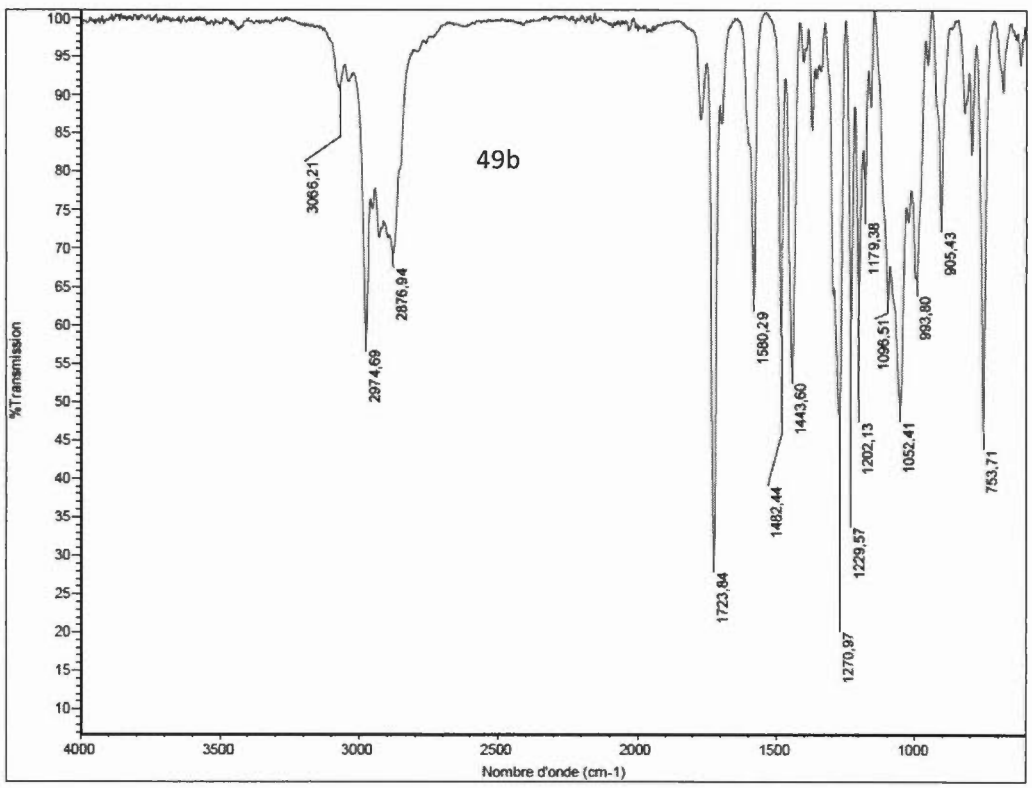
122.5804
119.7274
118.9695
97.6211
62.4533
52.3234
15.2183
MeO
O
O
O
49b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


49b
%Transmission
Nombre d'onde (cm-1)
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2974,69
2876,94
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1580,29
1482,44
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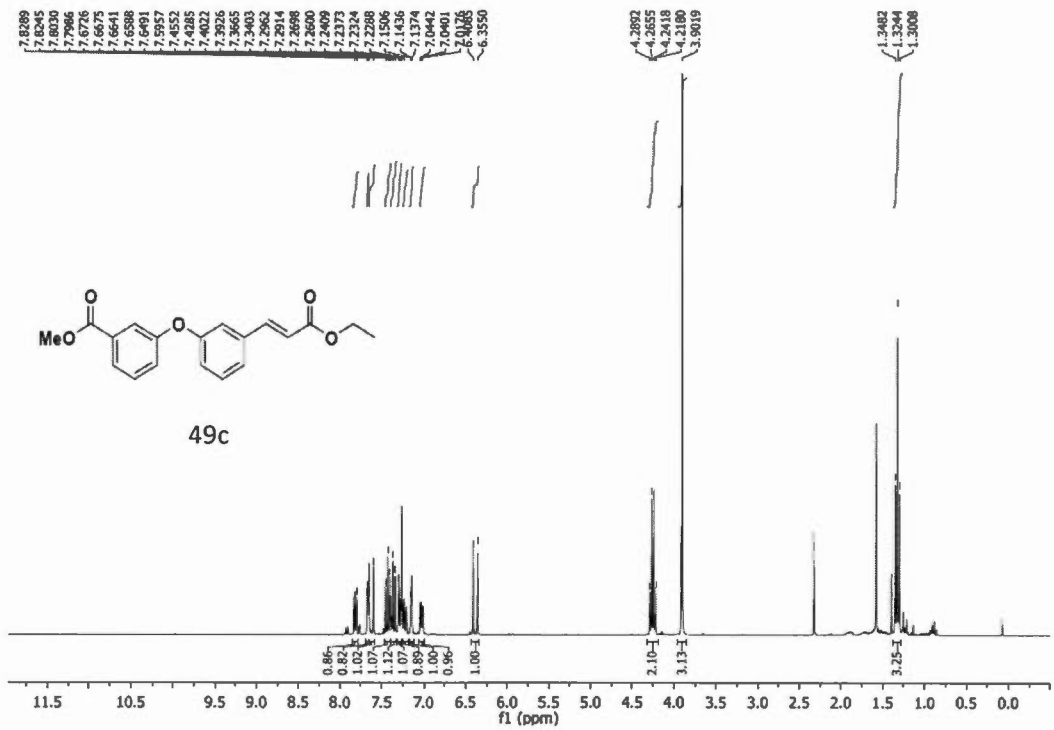
1052,41
993,80
905,43
753,71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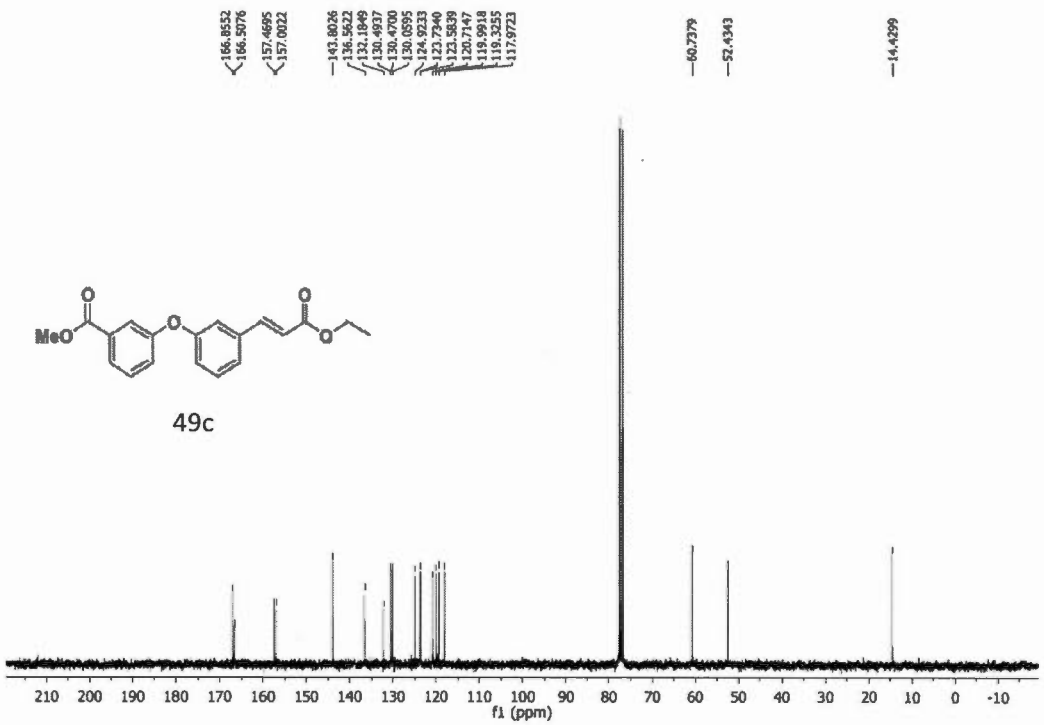
O
O
O
O
49c
f1 (ppm)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132.1849
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123.7340
123.5838
120.7147
119.9918
119.3255
117.9723
60.7379
52.4343
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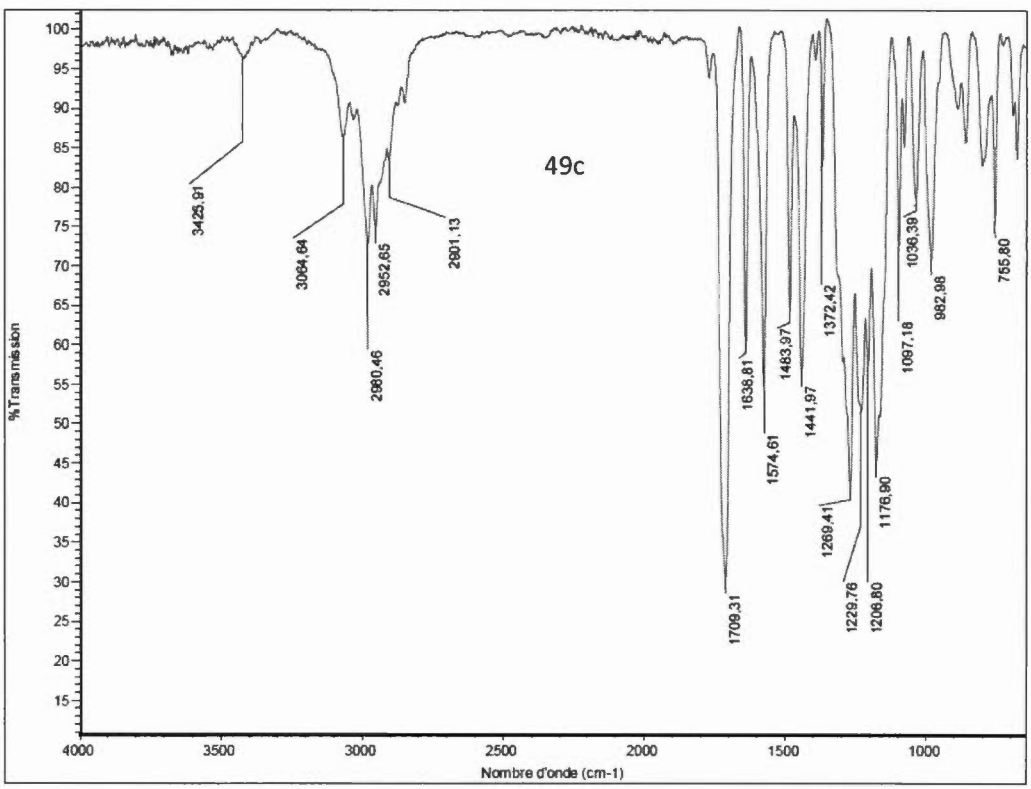
f1 (ppm)

49c


49c
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Nombre d'onde (cm-1)
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2901.13
1709.31
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1574.61
1483.97
1441.97
1372.42
1269.41
1229.76
1206.80
1176.90
1097.18
1036.39
982.98
755.80

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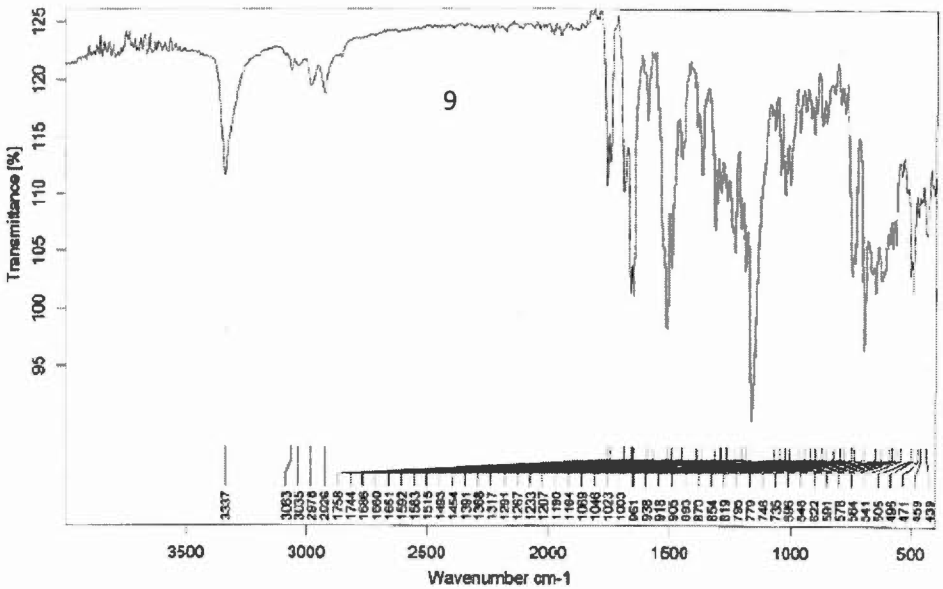
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Transmittance [%]
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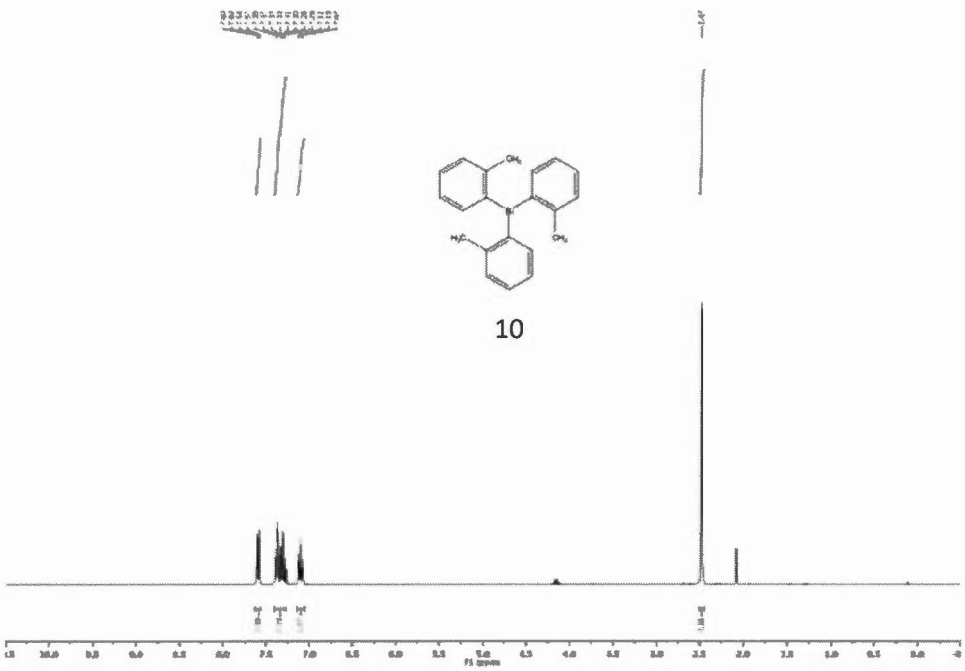
95
3337



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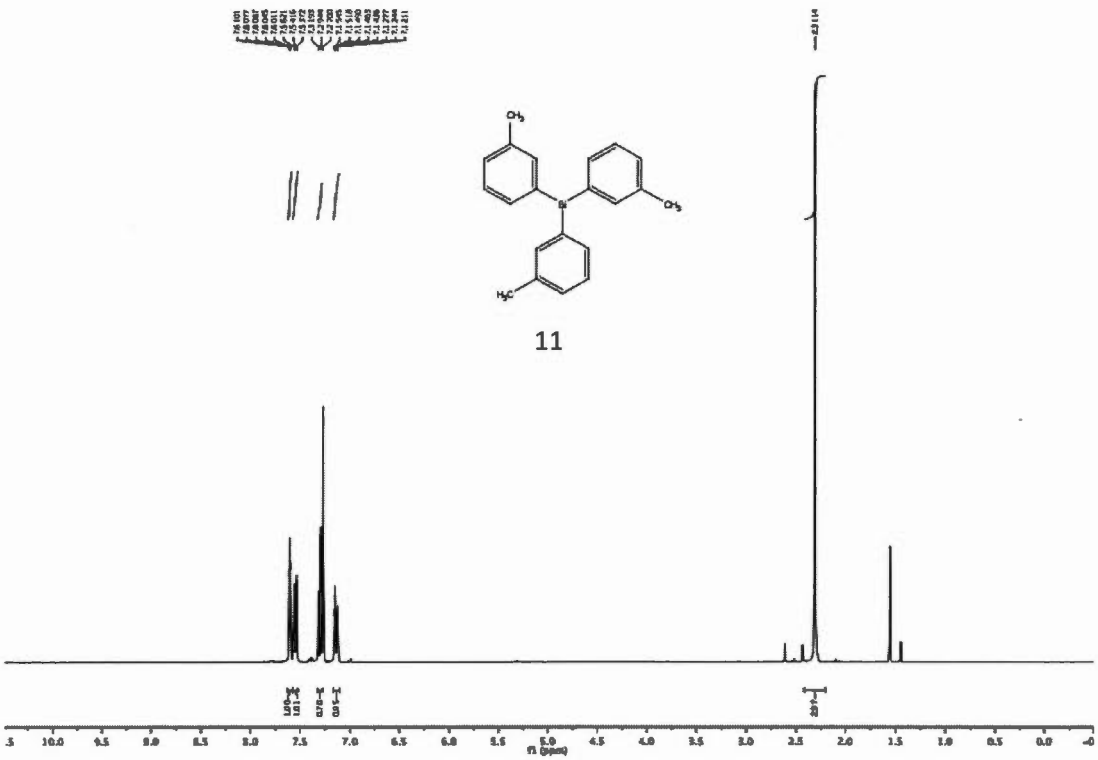

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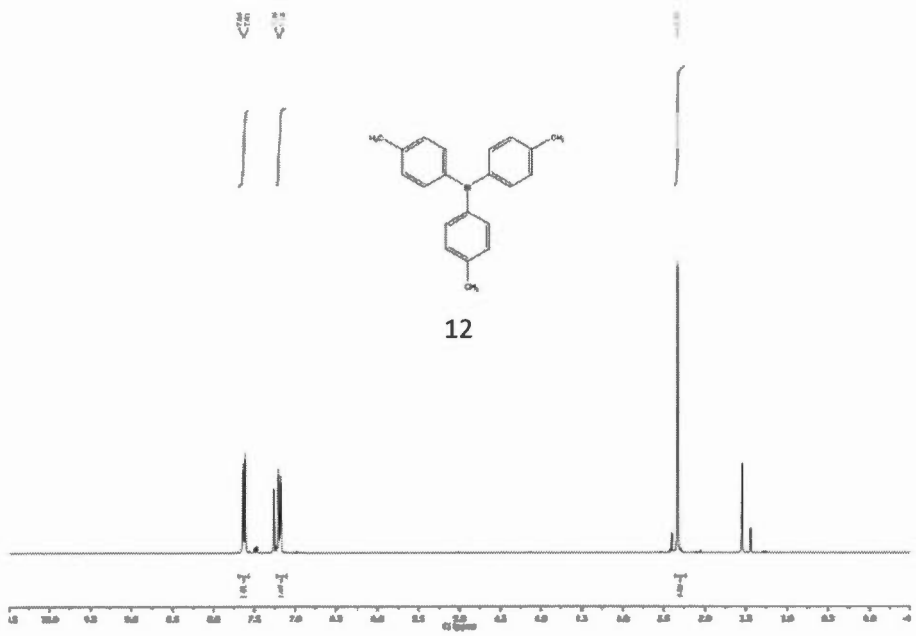

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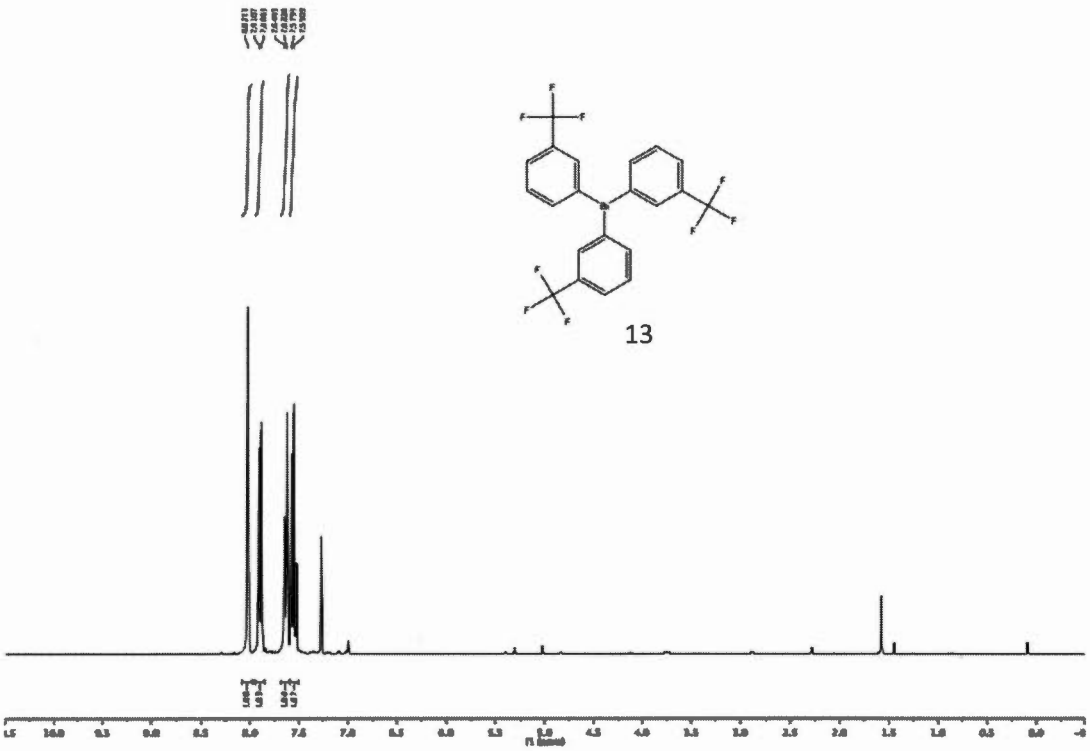

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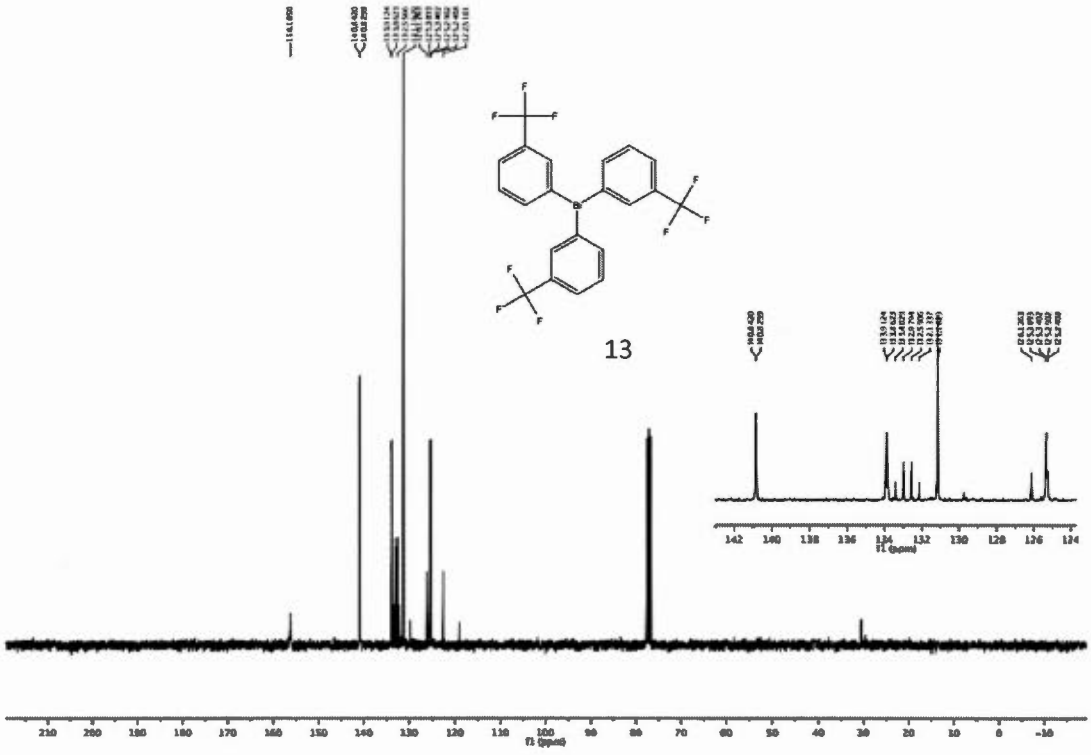

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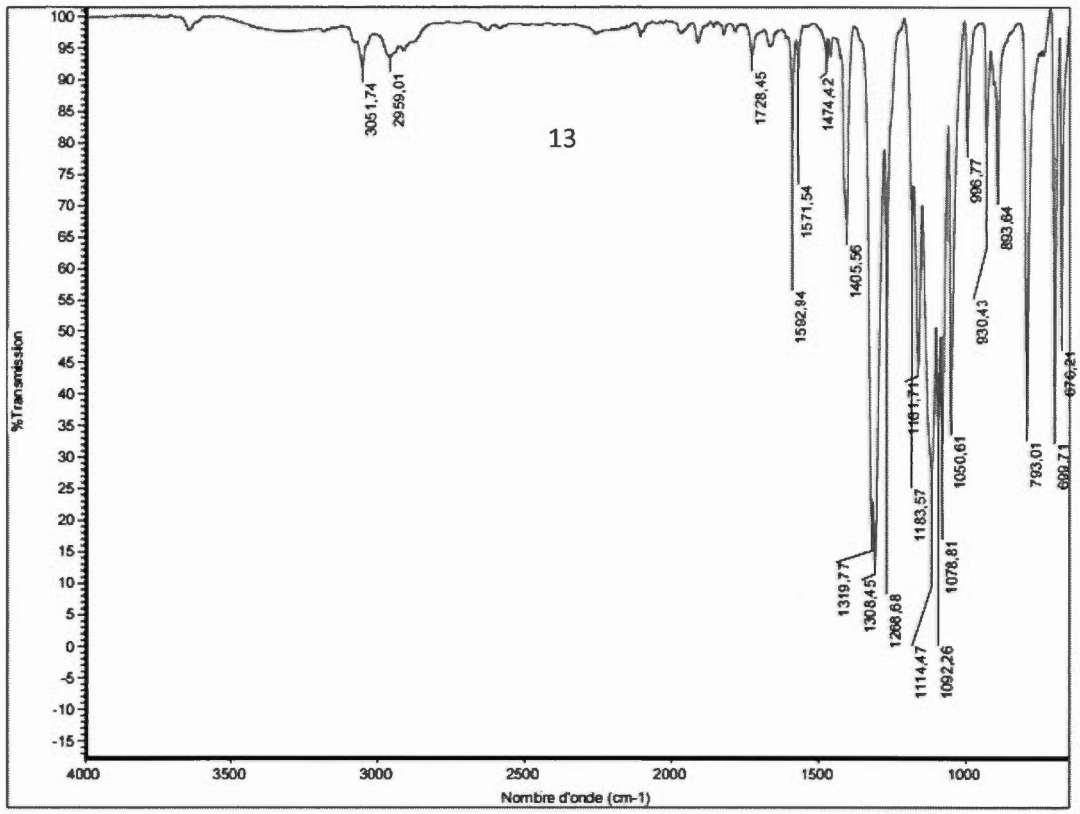
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%Transmission
Nombre d'onde (cm-1)
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1571,54
1474,42
1405,56
1319,77
1308,45
1266,68
1183,57
1161,71
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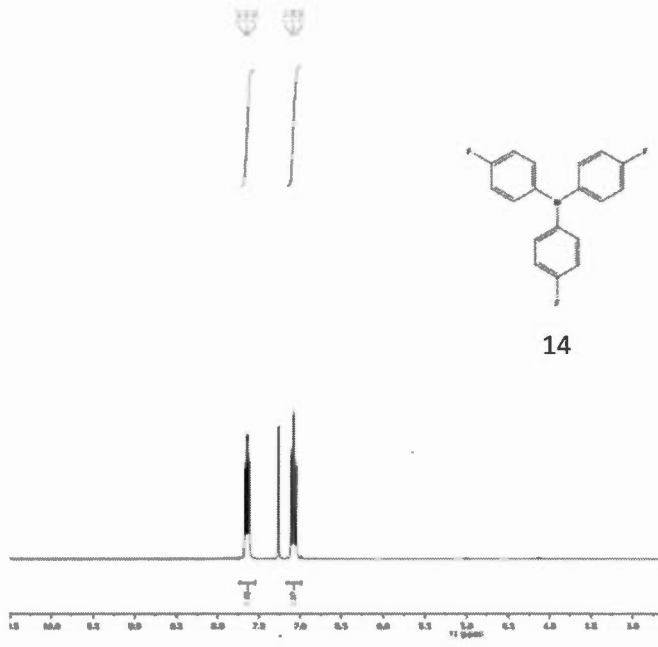
1092,26
1078,81
1050,61
996,77
930,43
883,64
793,01
699,71
676,24



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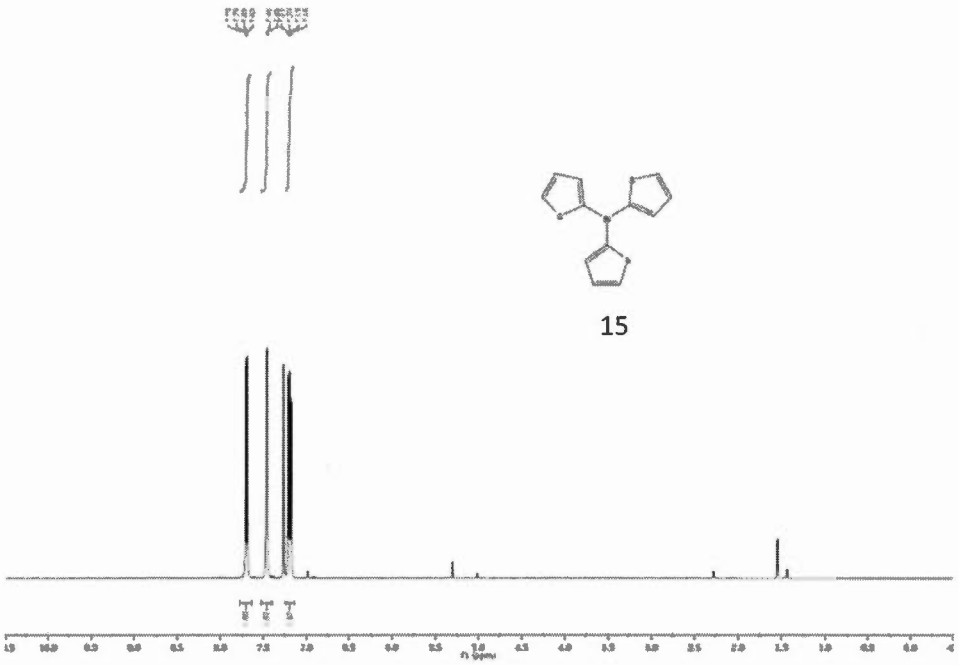

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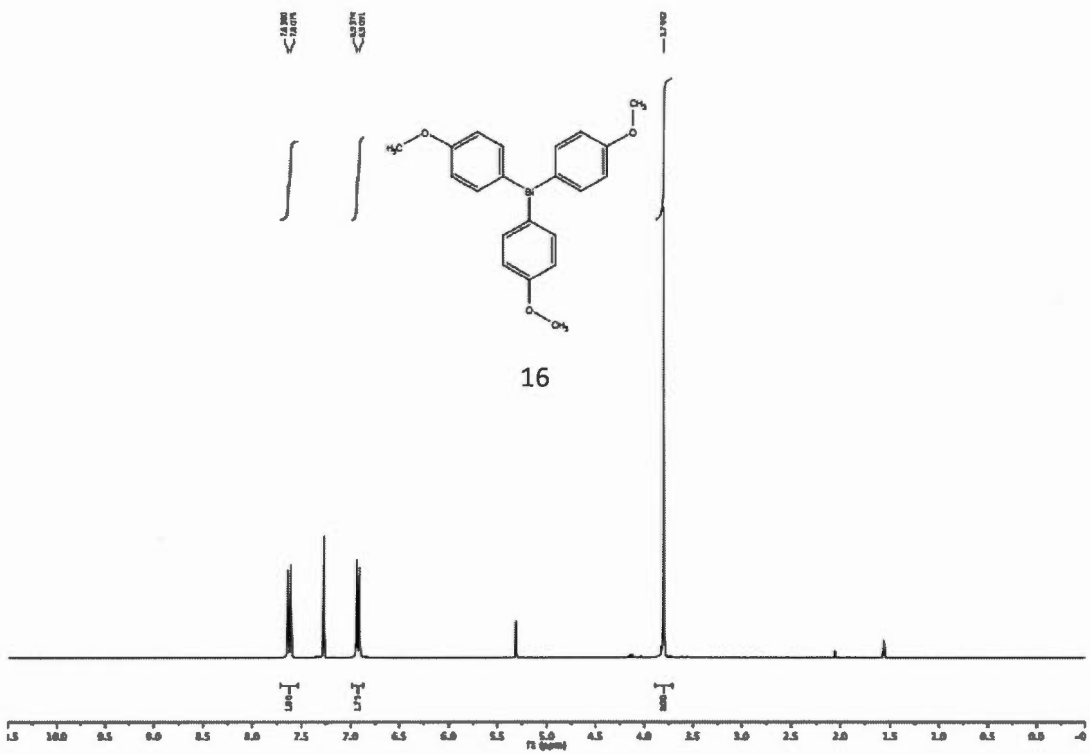

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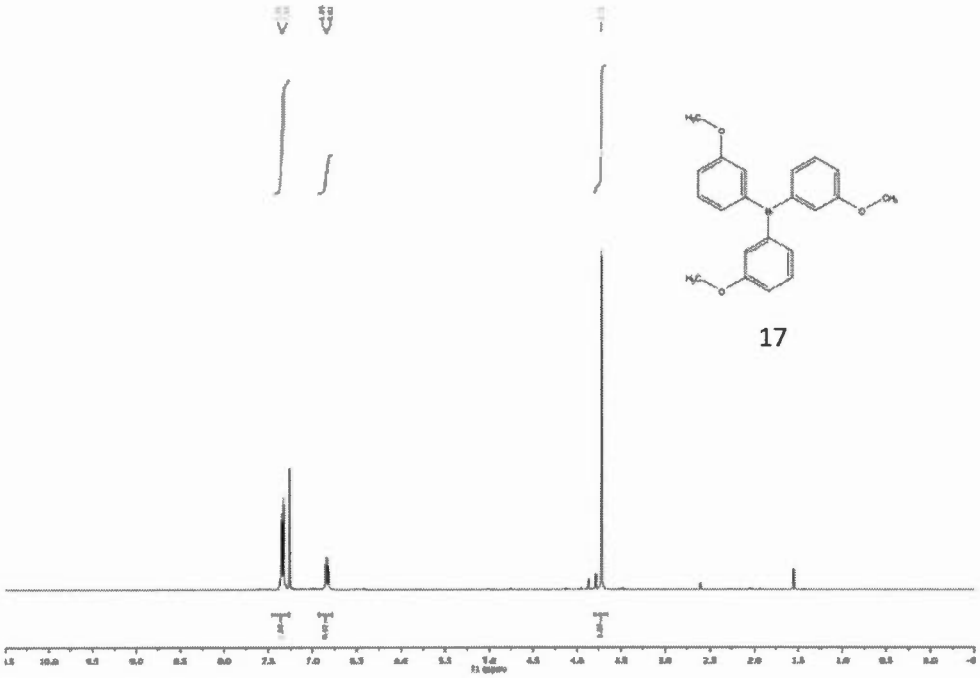

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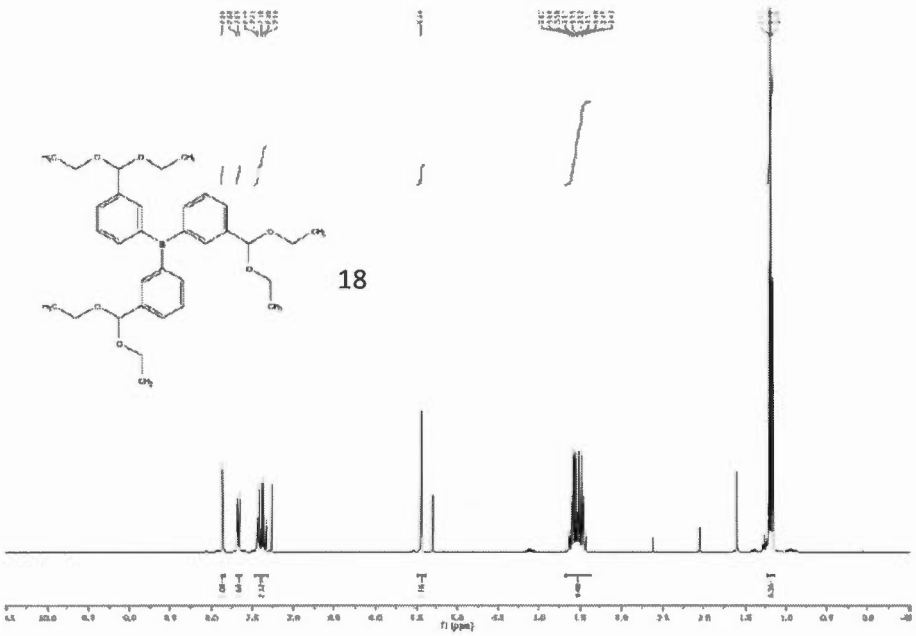

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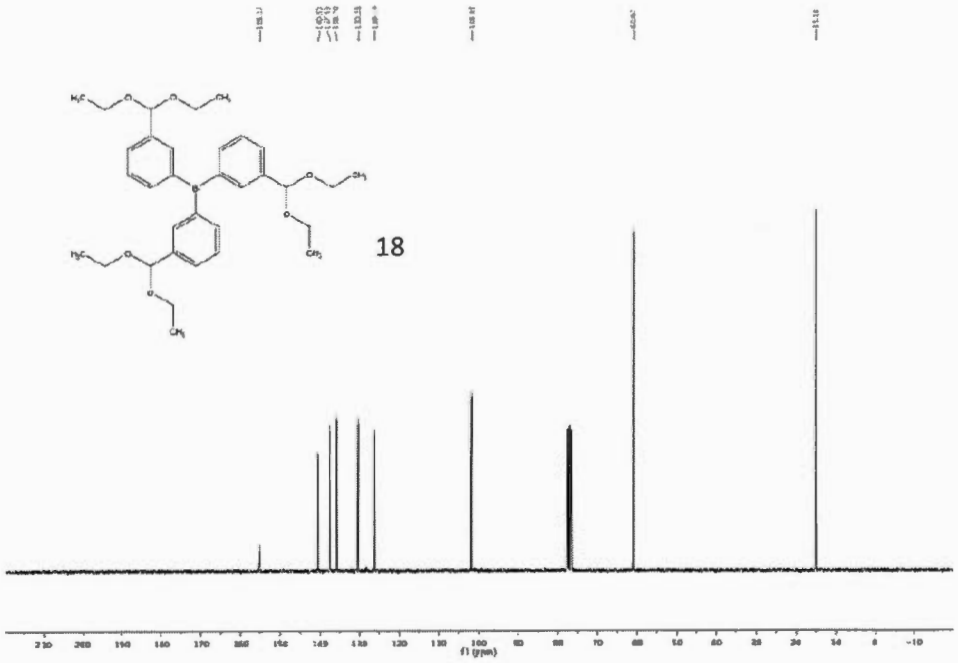

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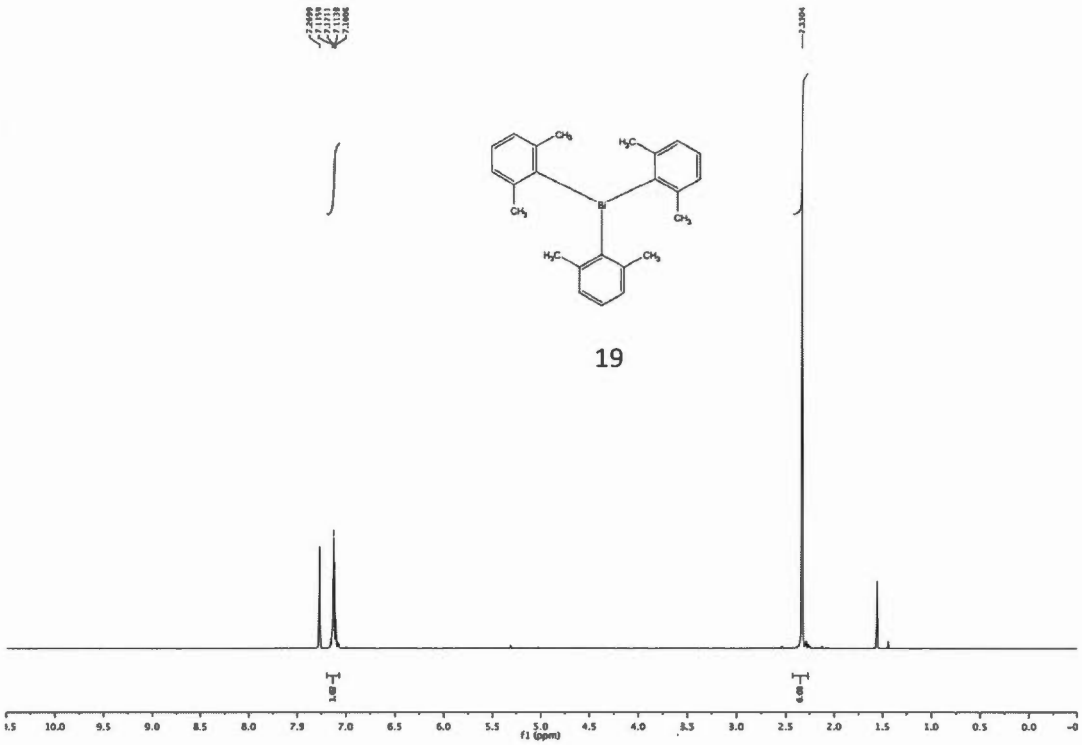
7.2699
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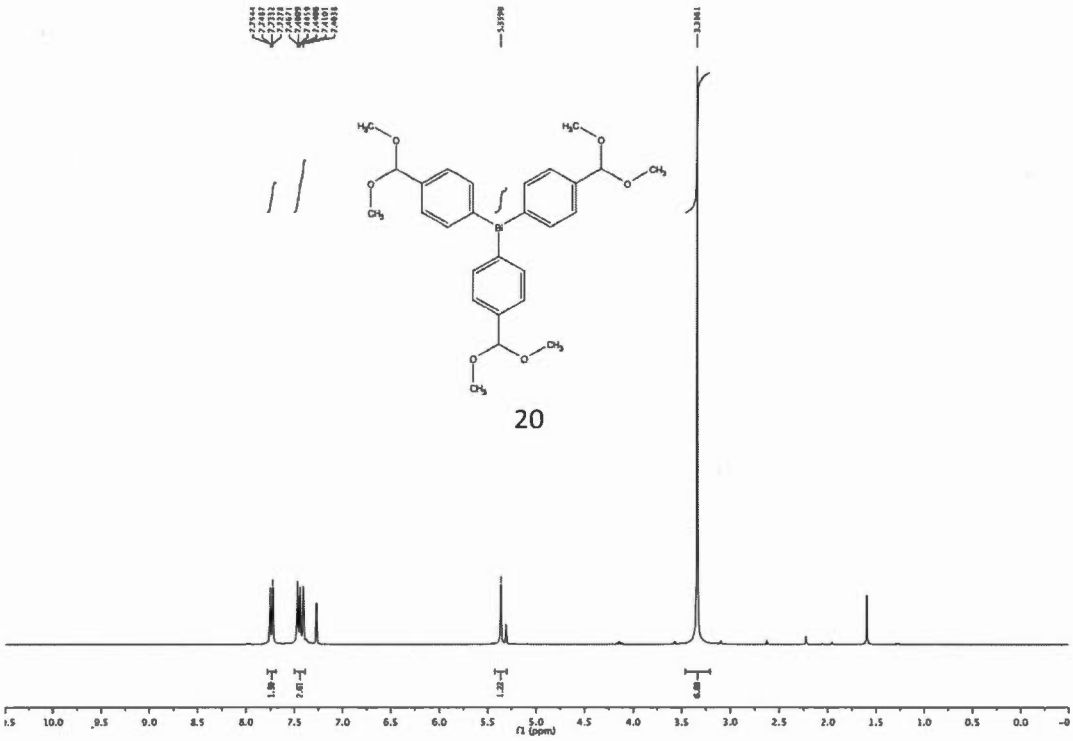
7.1153
7.1133
7.1006
2.2304
CH3
H3C
Bi
CH3
CH3
H3C
CH3
1.00
6.08
f1 (ppm)

19



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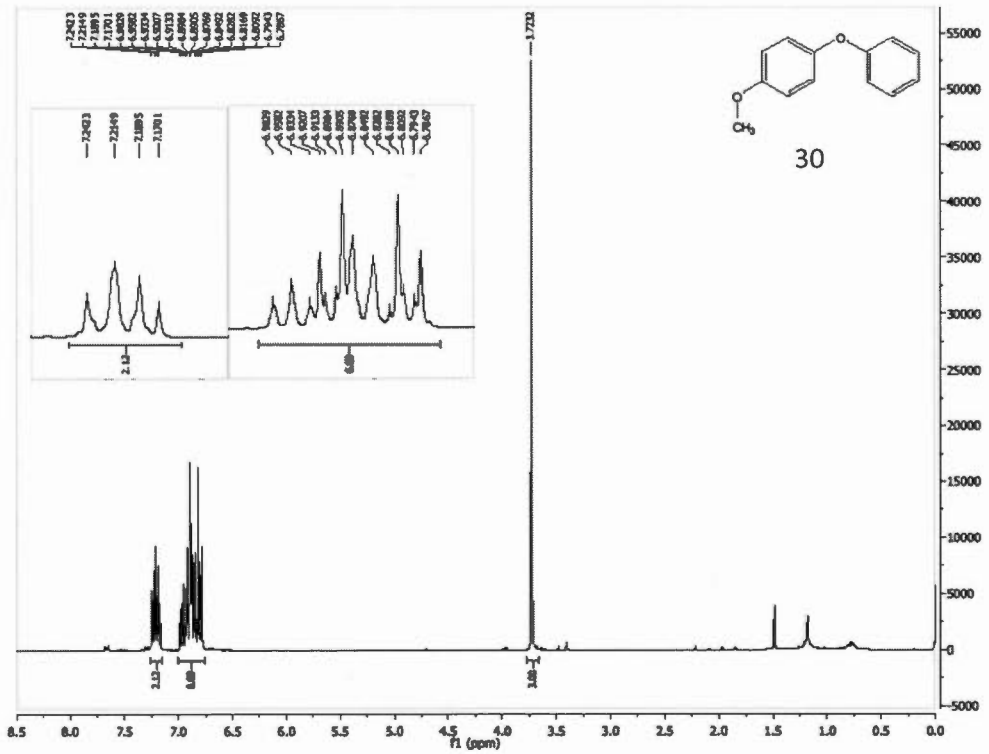
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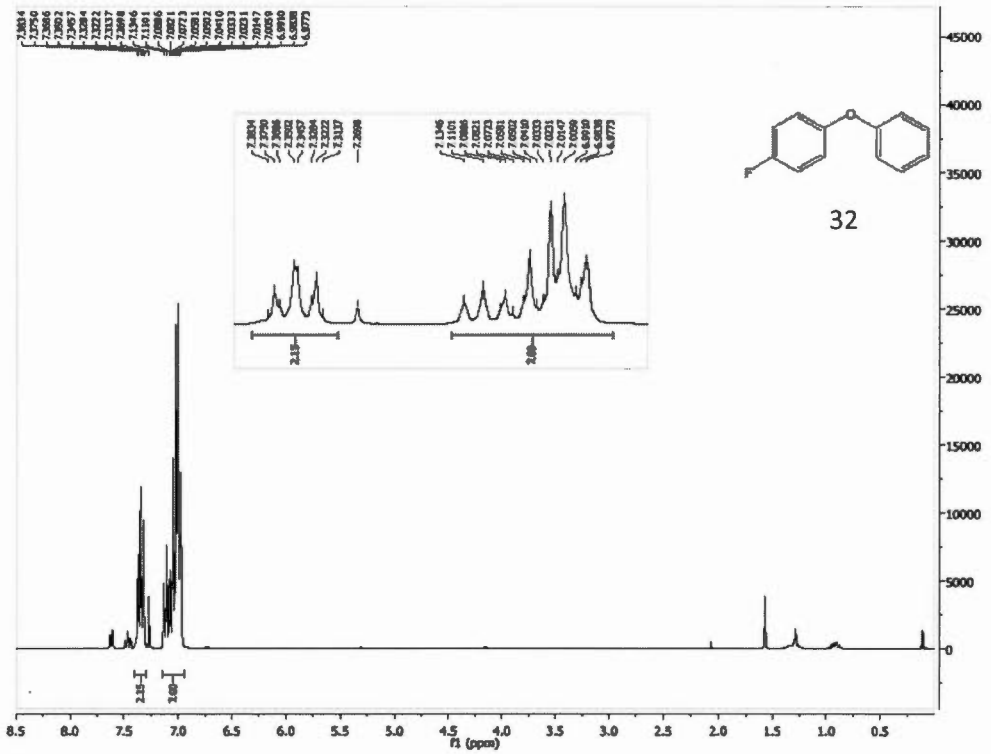
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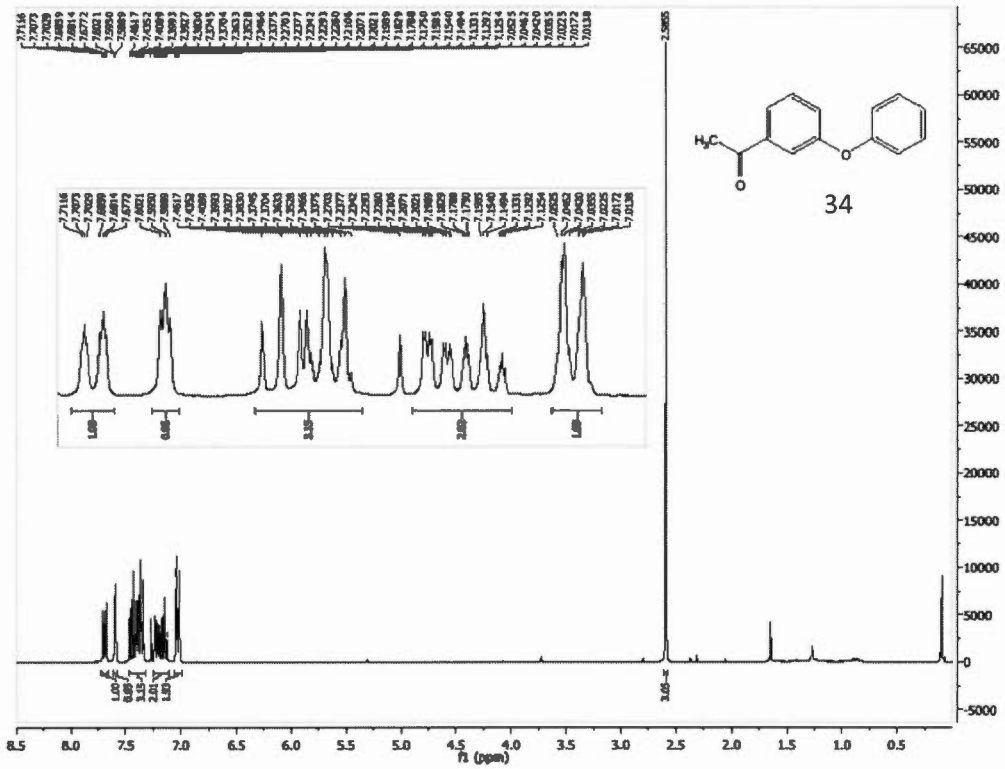
f1 (ppm)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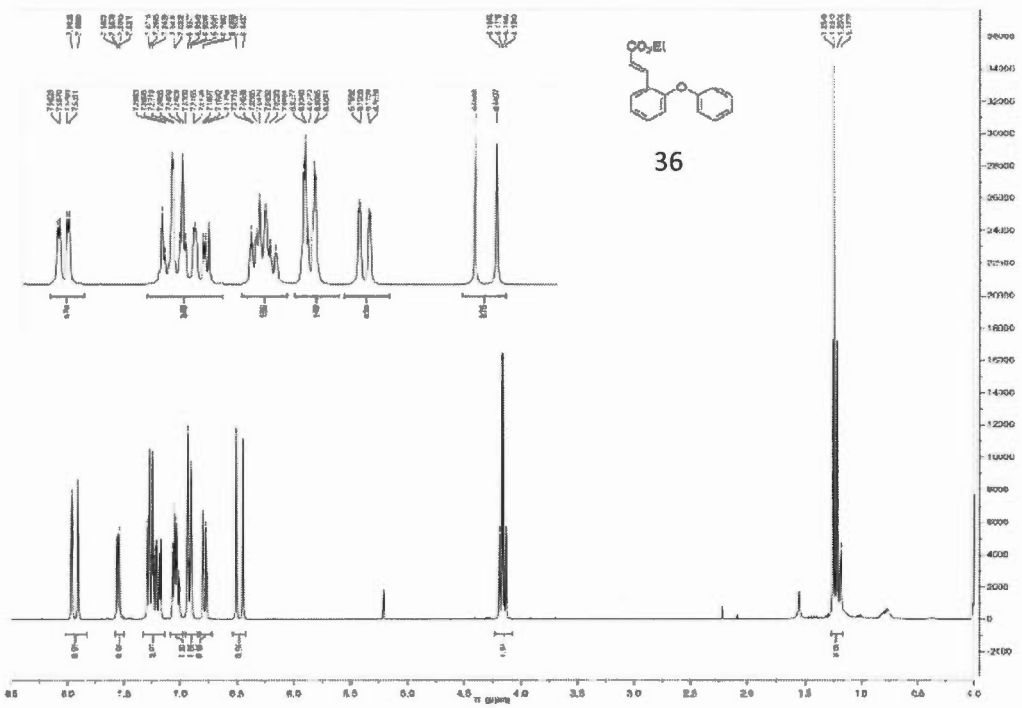
f1 (ppm)



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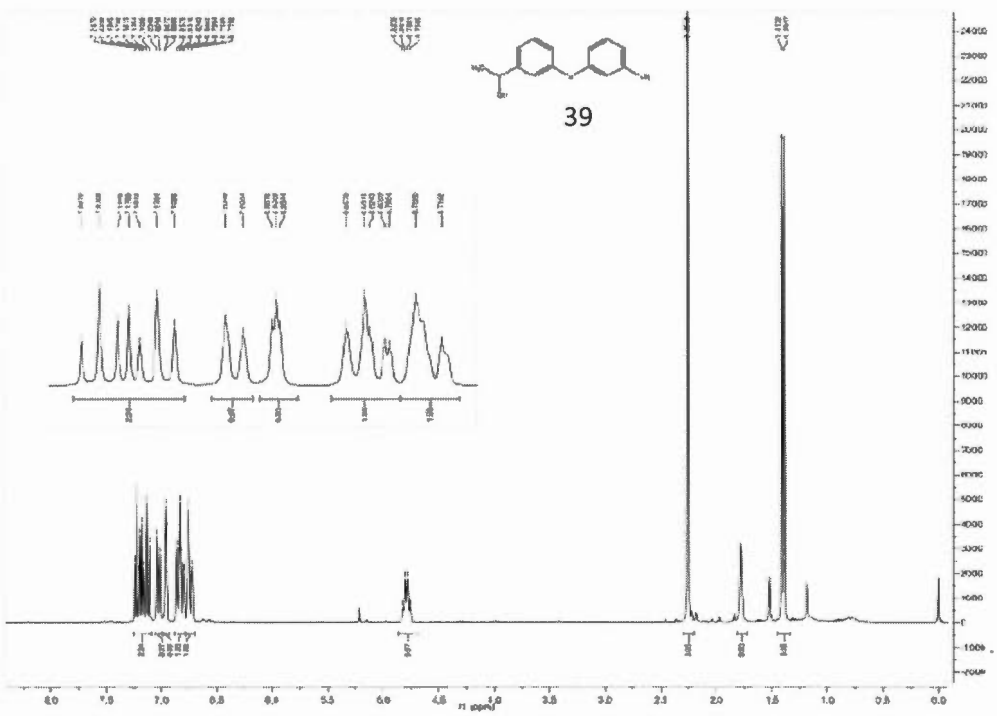

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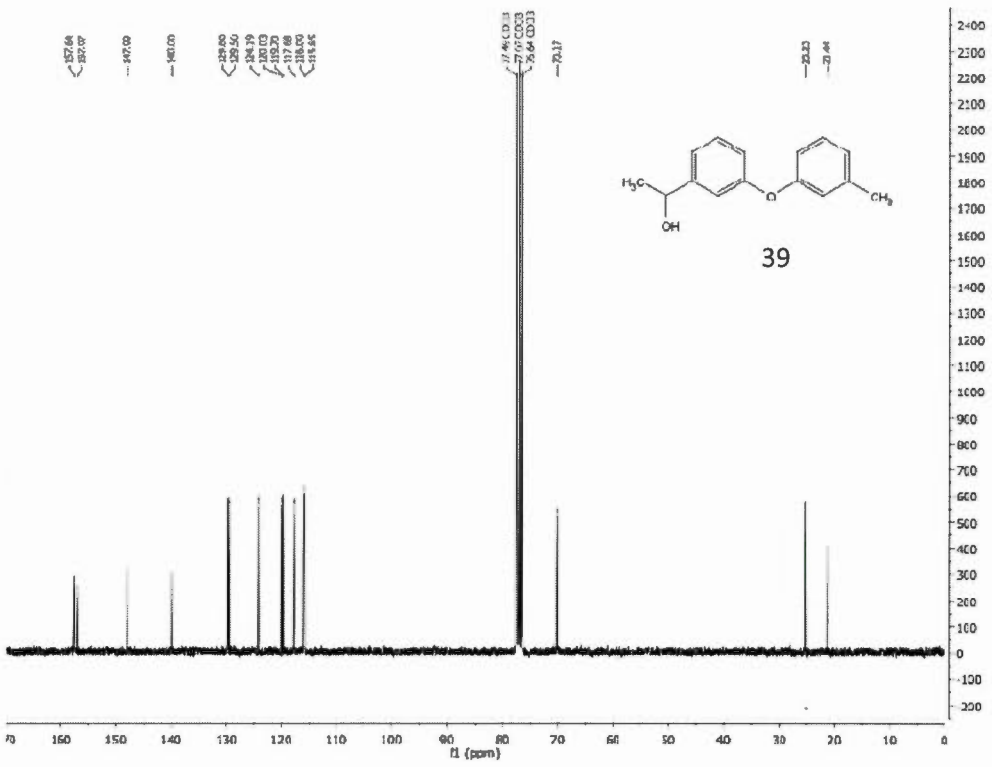
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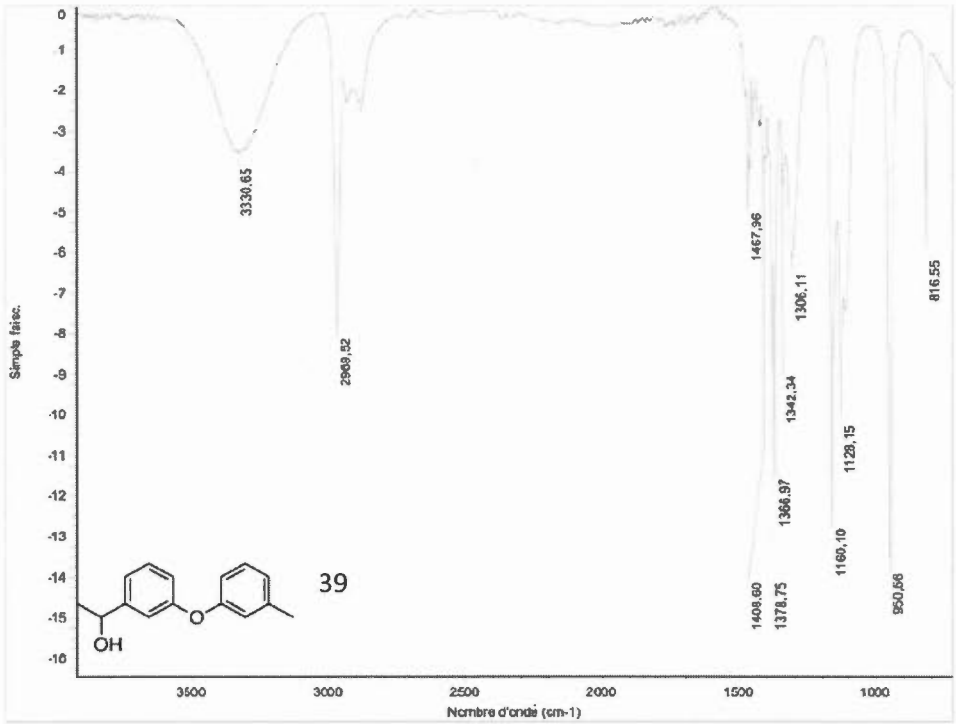
OH
O
CH3
39
f1 (ppm)


Simple faisc.
0
1
-2
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-5
-6
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-11
-12
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-15
-16
3330,65
2969,52
1467,96
1408,60
1378,75
1366,97
1342,34
1306,11
1160,10
1128,15
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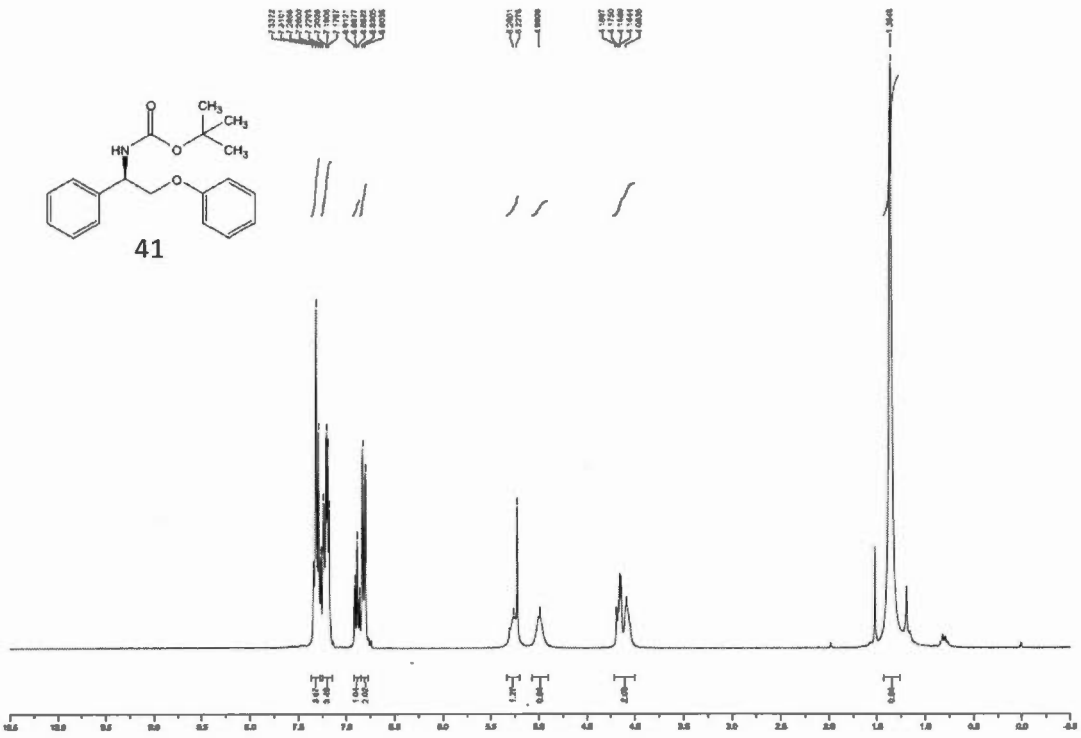
816,55
3500
3000
2500
2000
1500
1000
Nombre d'onde (cm-1)
OH
O
39



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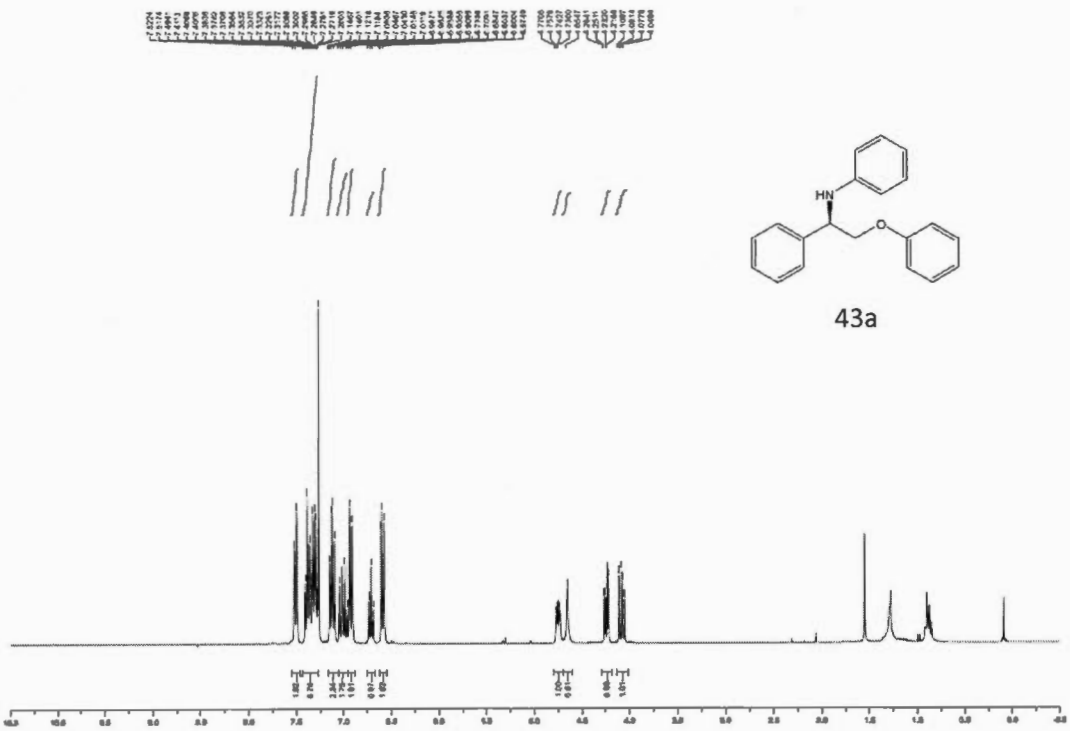

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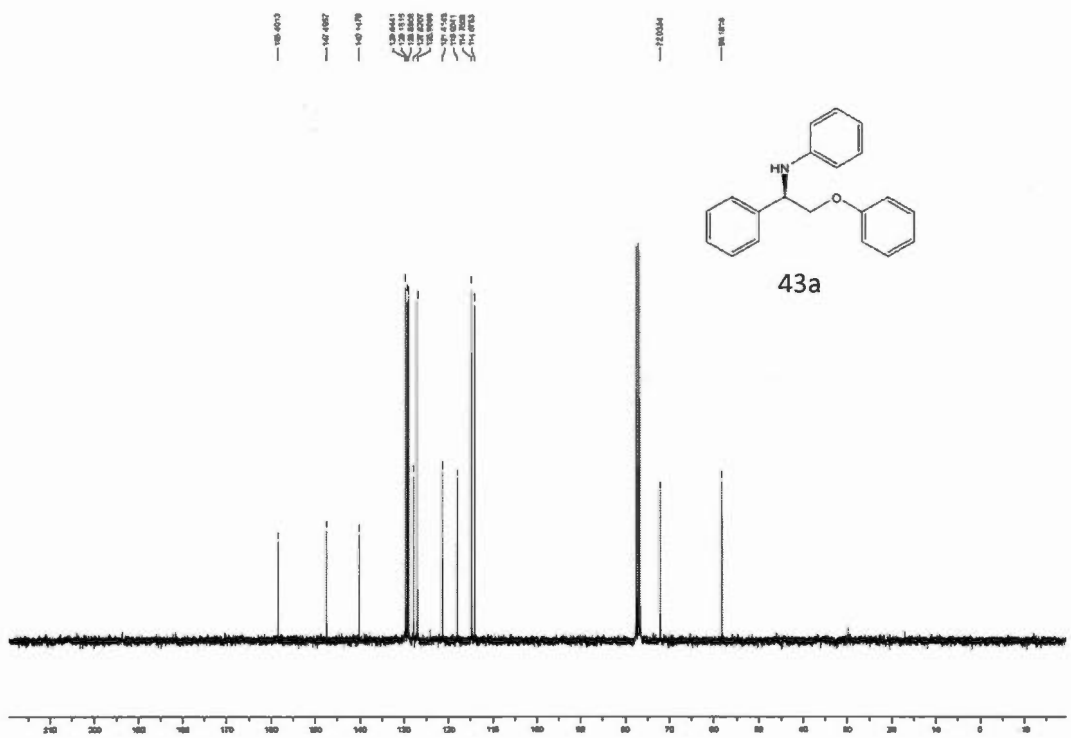

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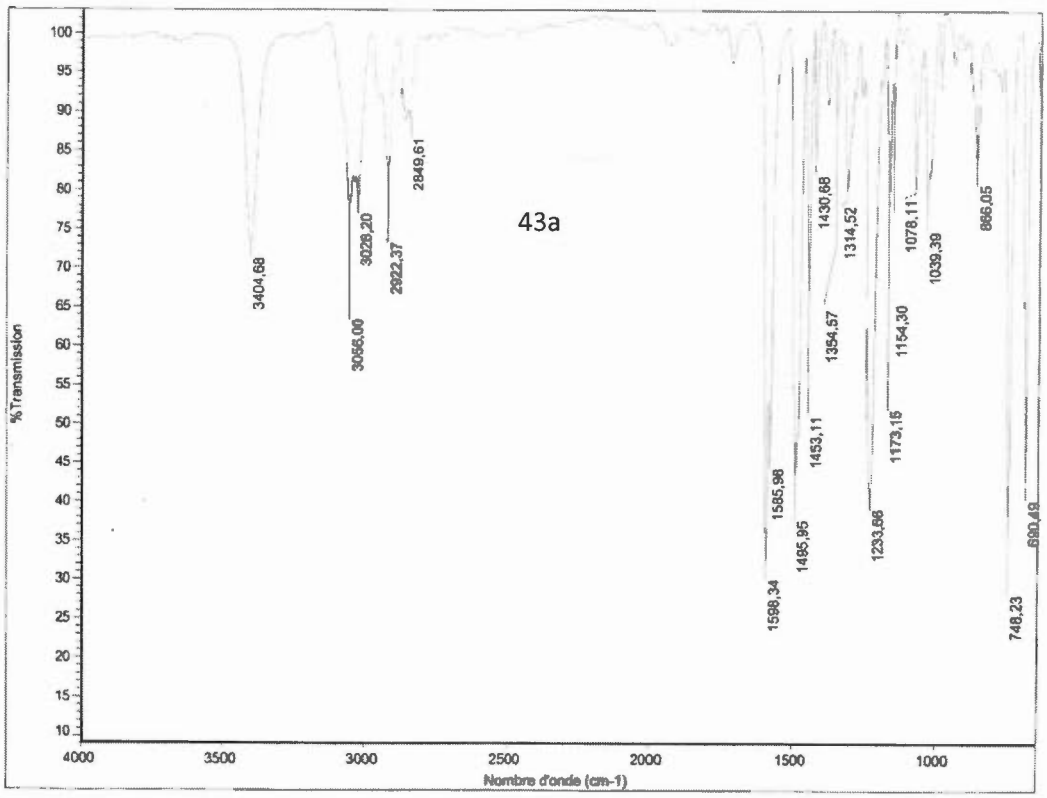
43a
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2849,61
1598,34
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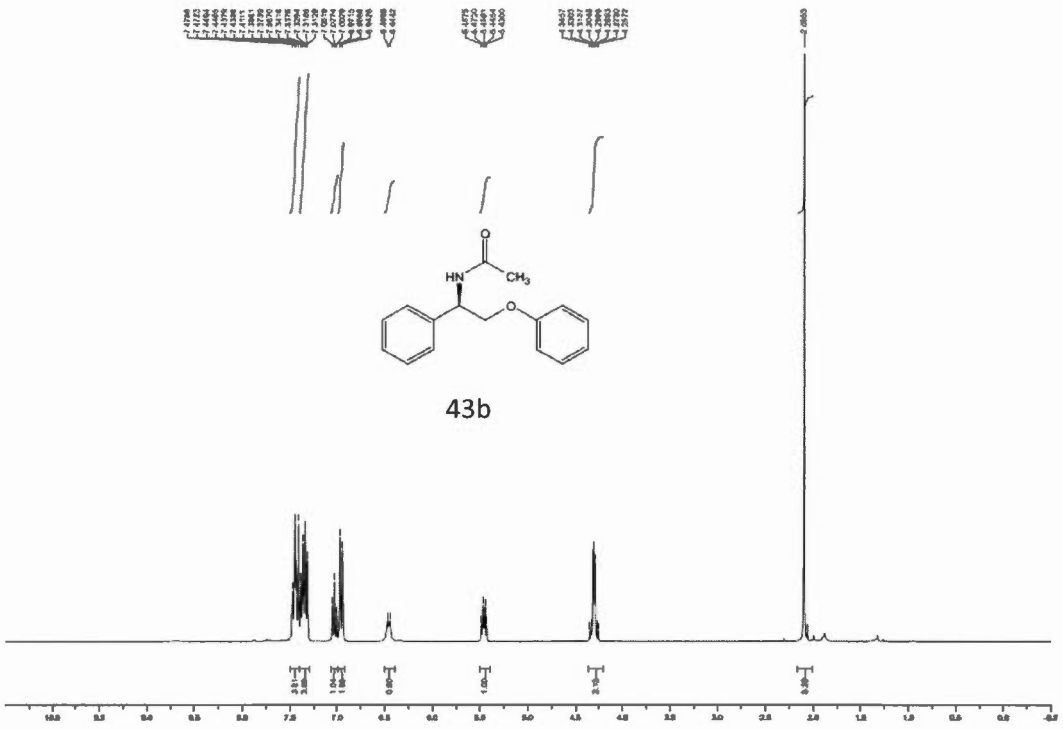
1039,39
866,05
748,23
690,48



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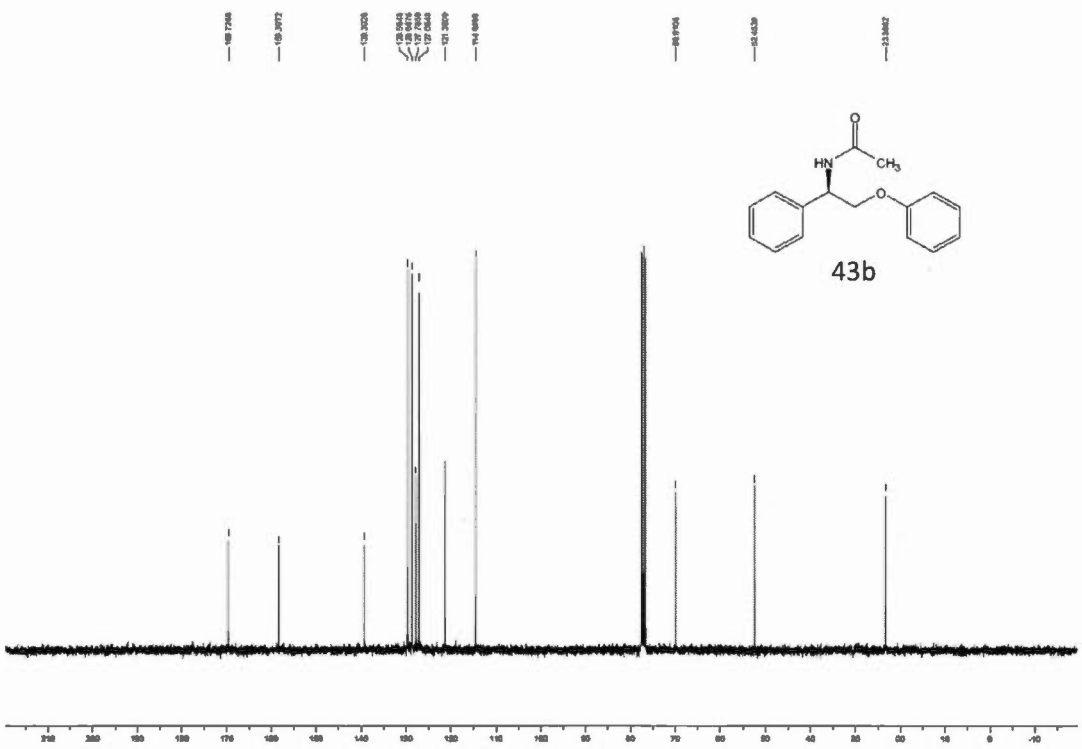
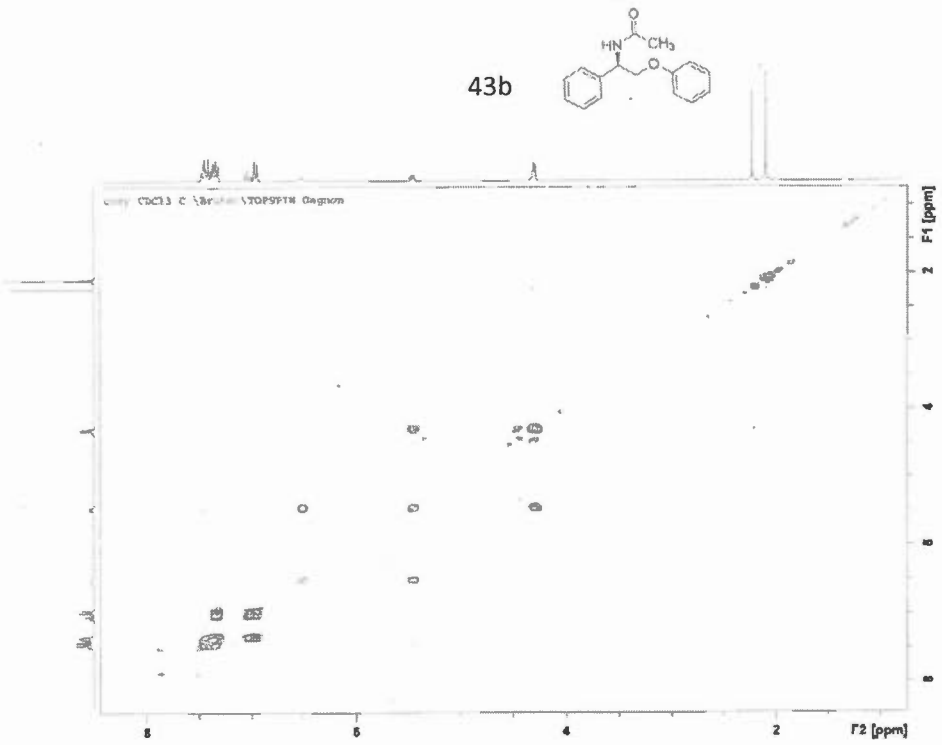
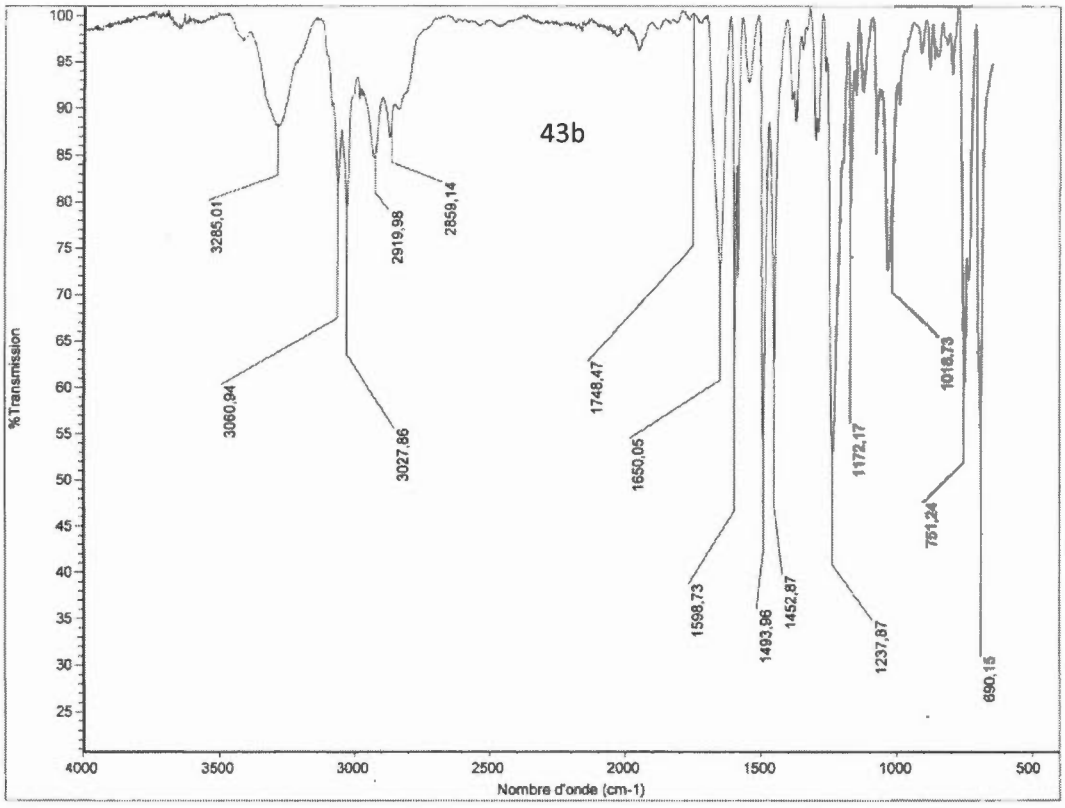


43b

43b




43b
%Transmission
Nombre d'onde (cm-1)
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2859,14
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1493,96
1452,87
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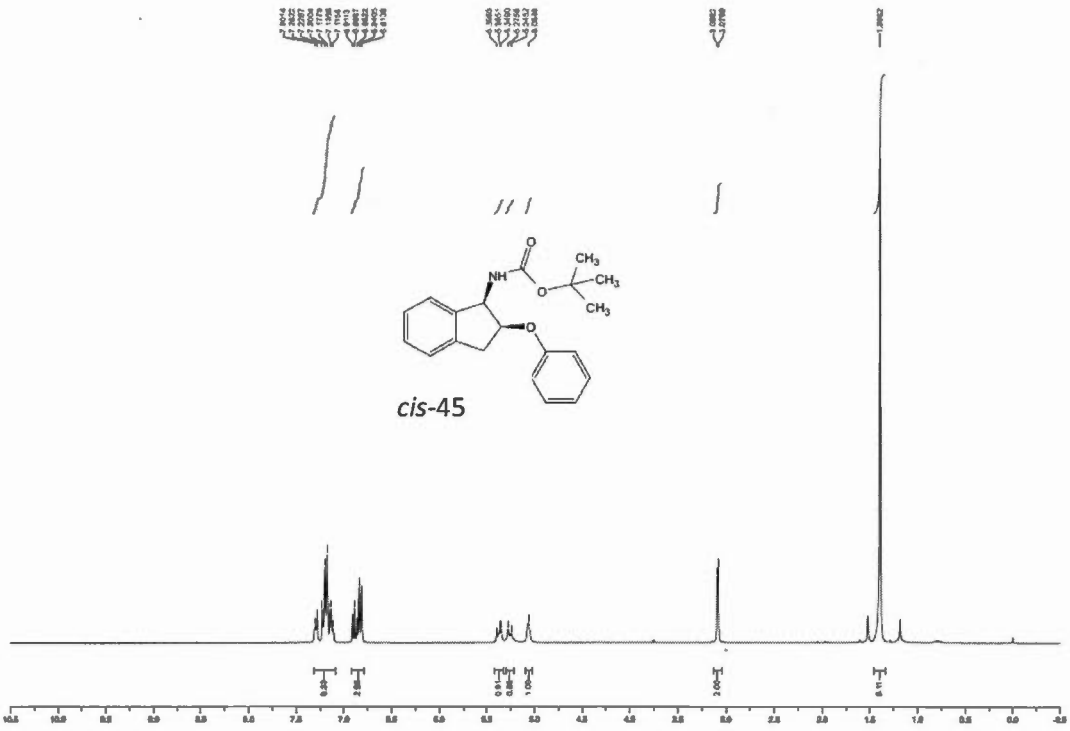
1172,17
1018,73
751,24
690,15



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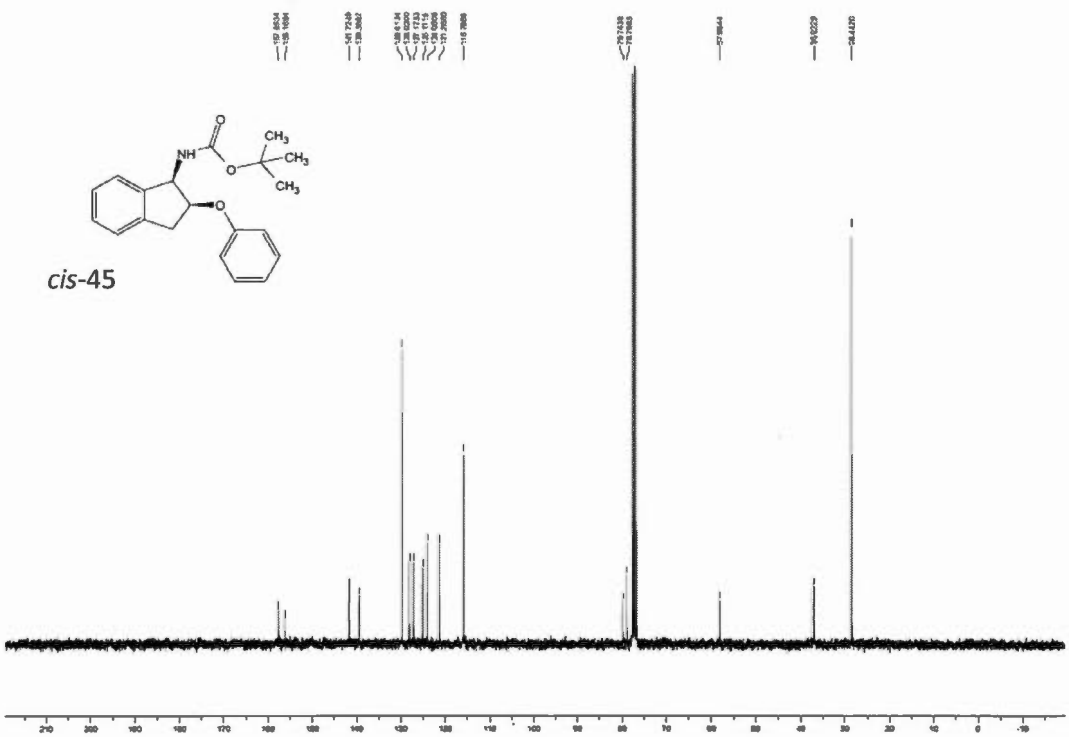

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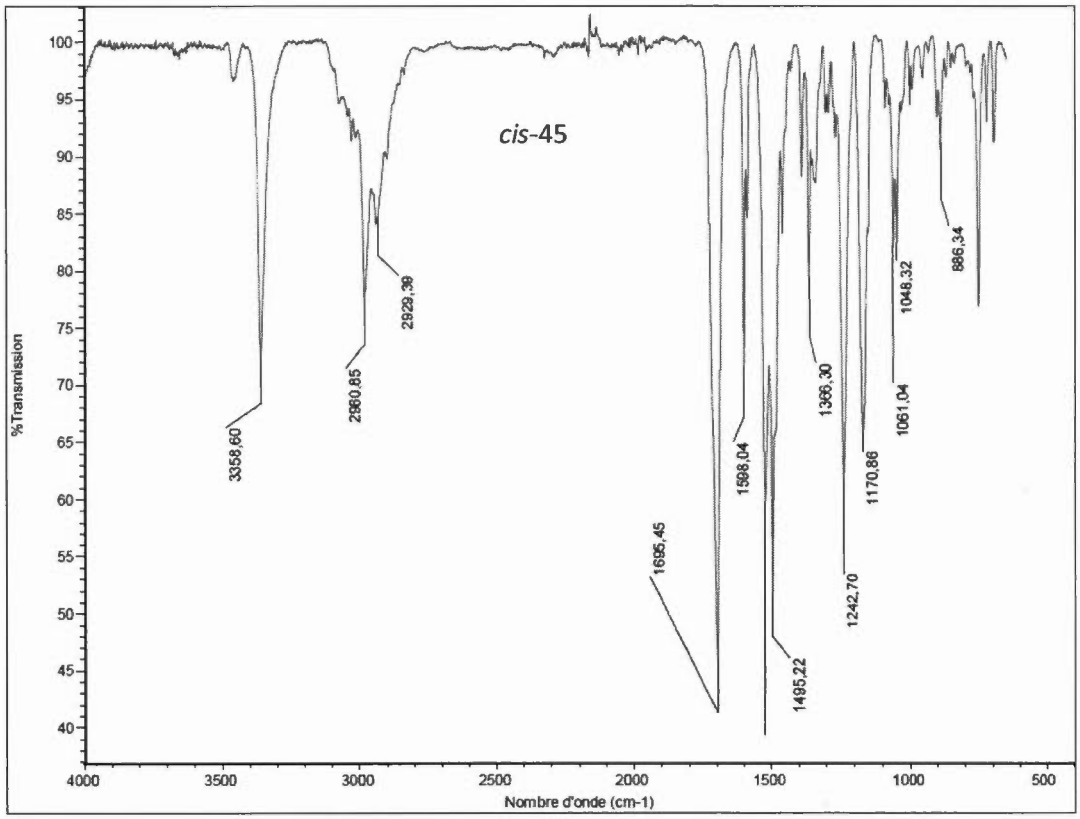
cis-45
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Nombre d'onde (cm-1)
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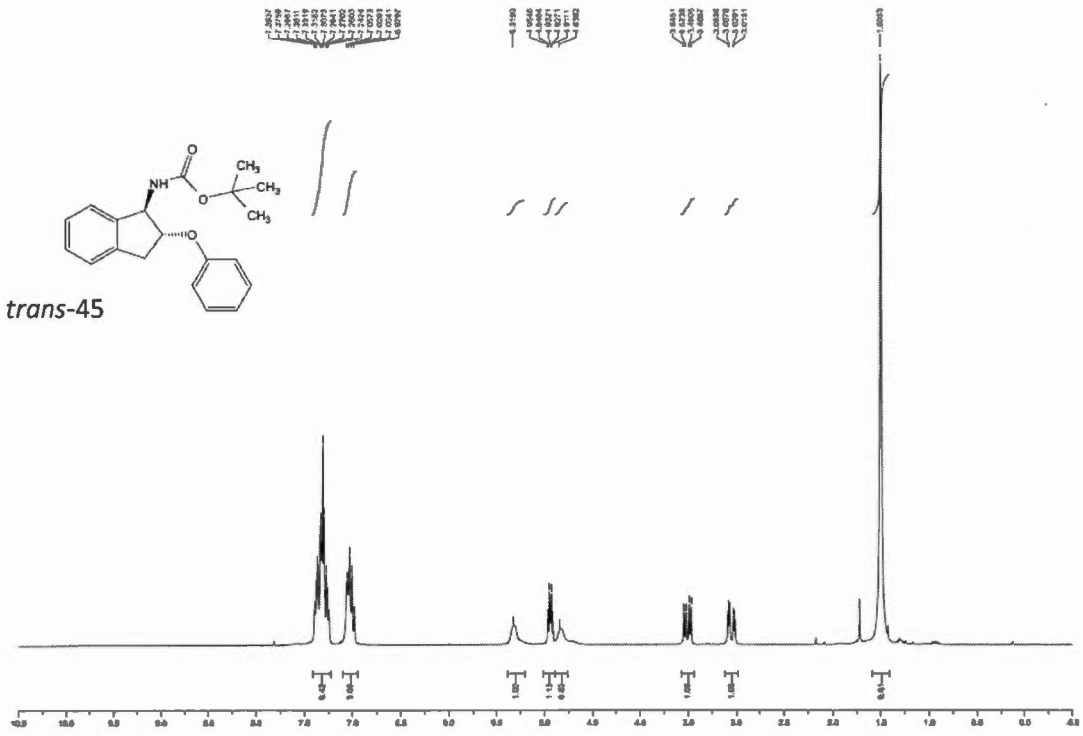
1170,86
1061,04
1048,32
886,34



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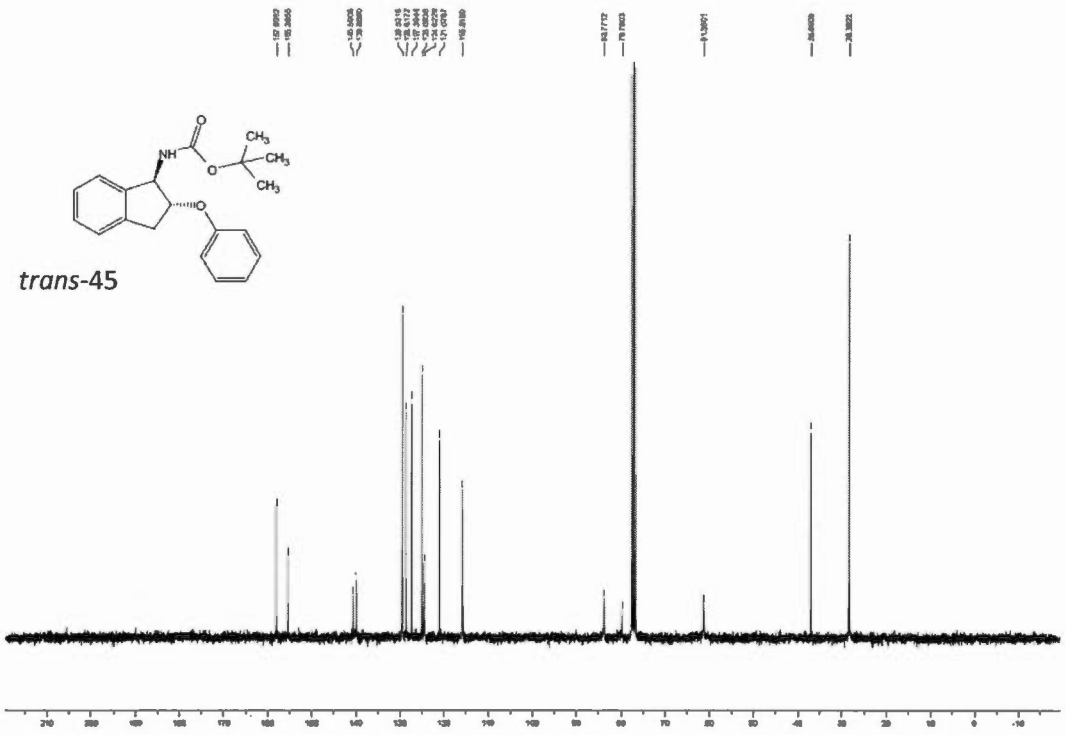

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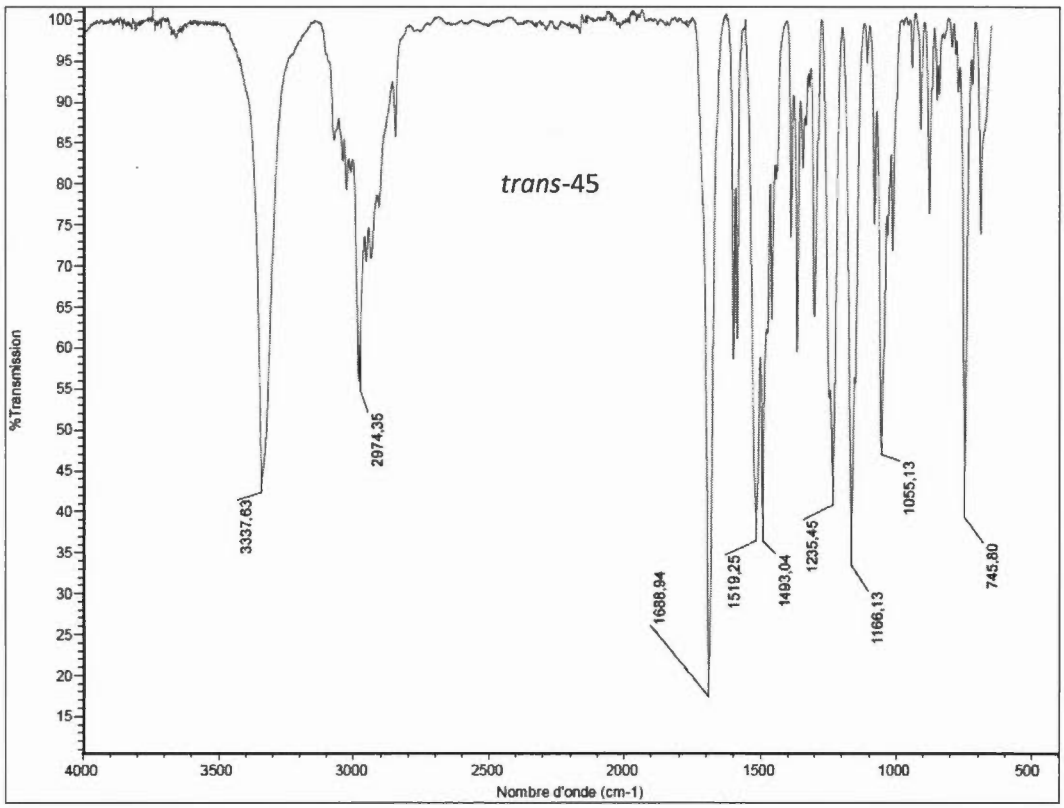
trans-45
%Transmission
Nombre d'onde (cm-1)
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1493,04
1235,45
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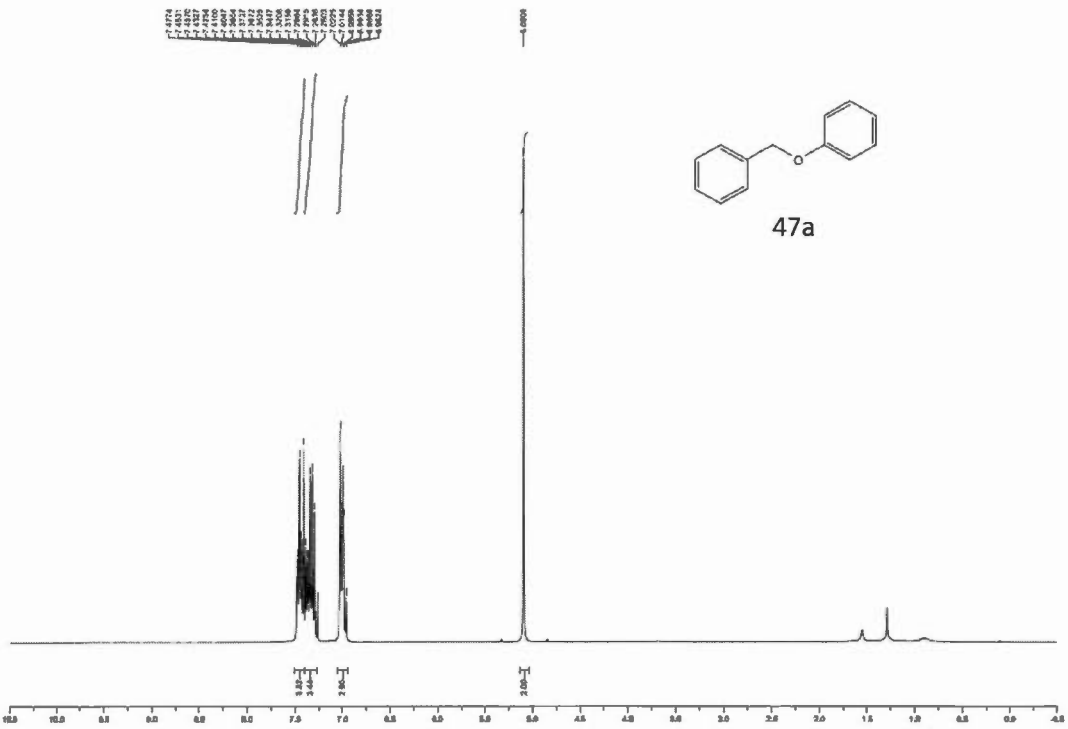
1055,13
745,80



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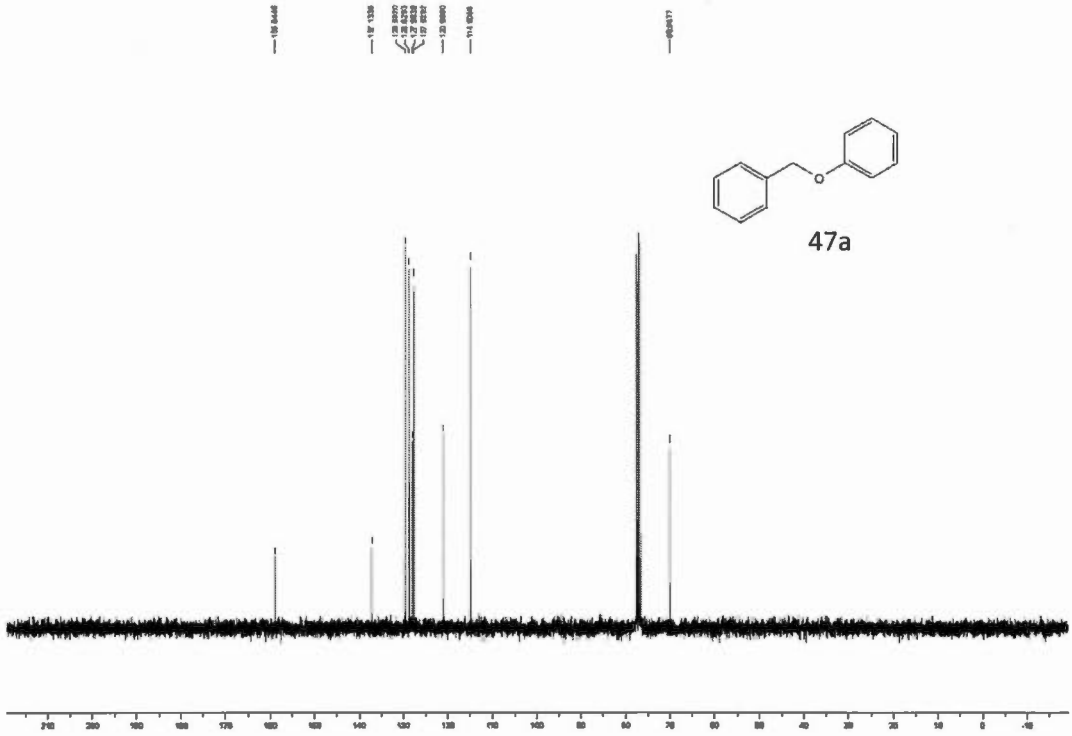
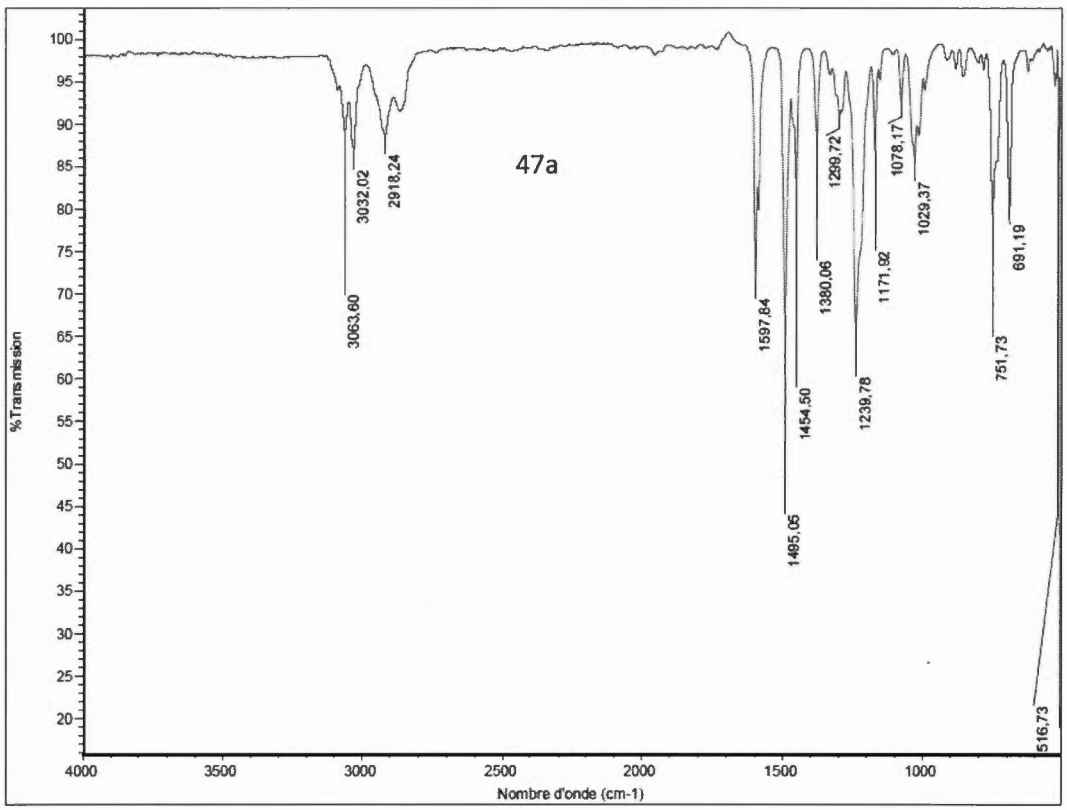


47a


47a
%Transmission
Nombre d'onde (cm-1)
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3500
3000
2500
2000
1500
1000
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
3063.60
3032.02
2918.24
1597.84
1485.05
1454.50
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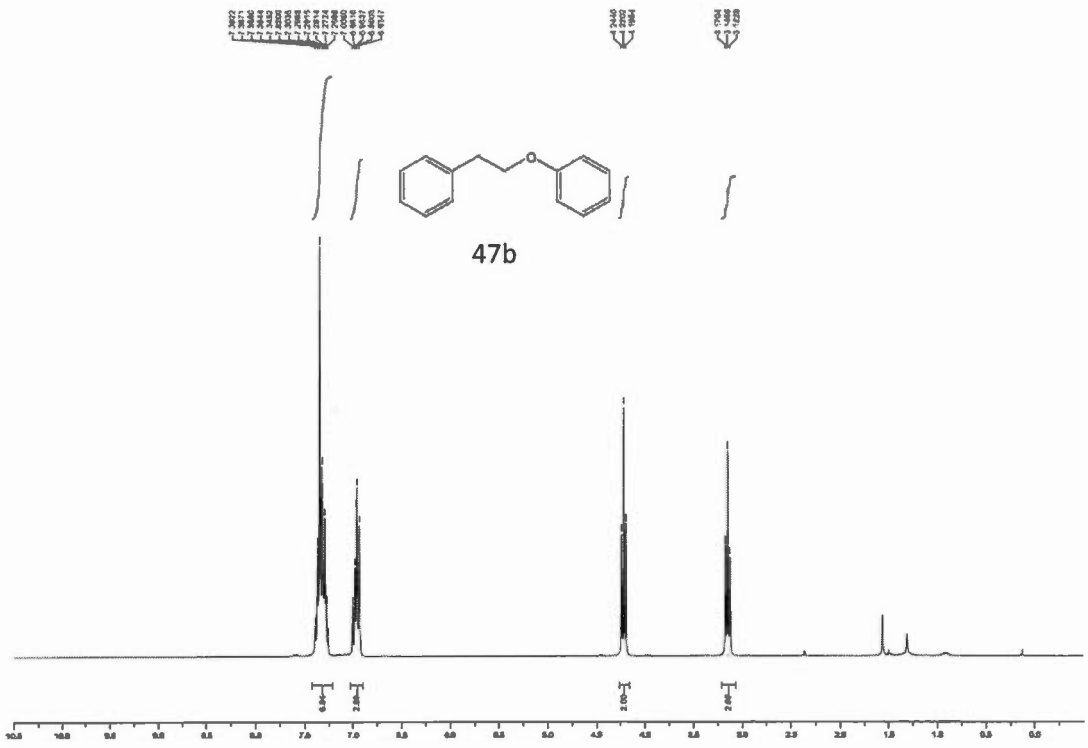
1239.78
1171.92
1078.17
1029.37
751.73
691.19
516.73



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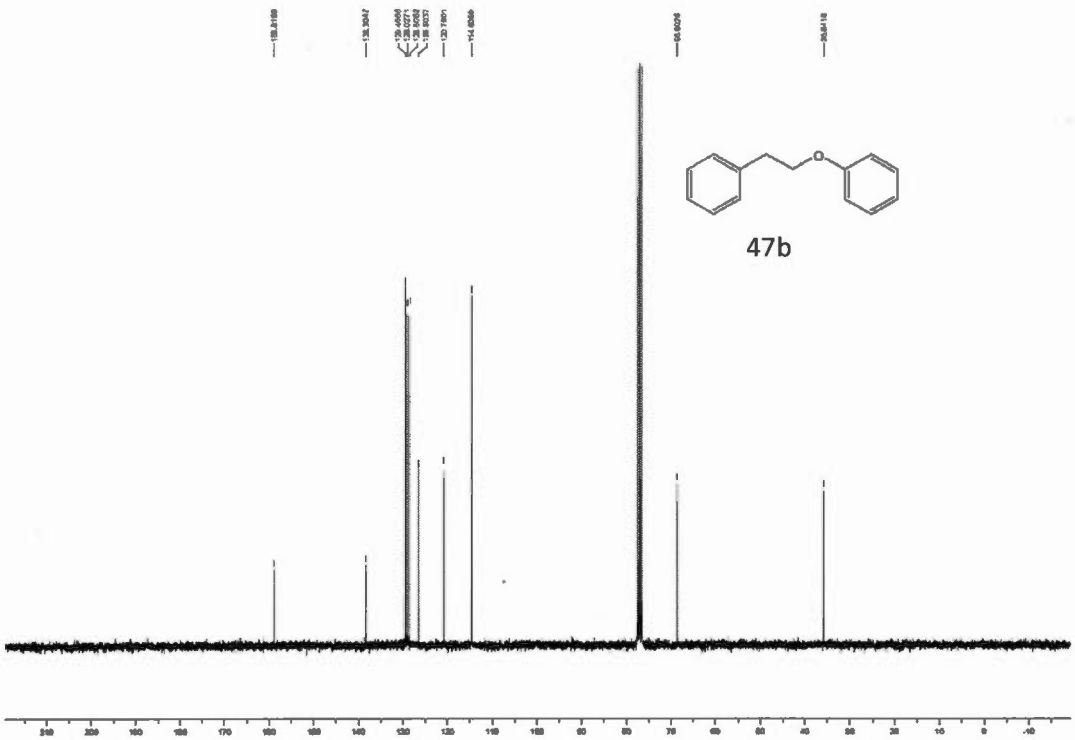
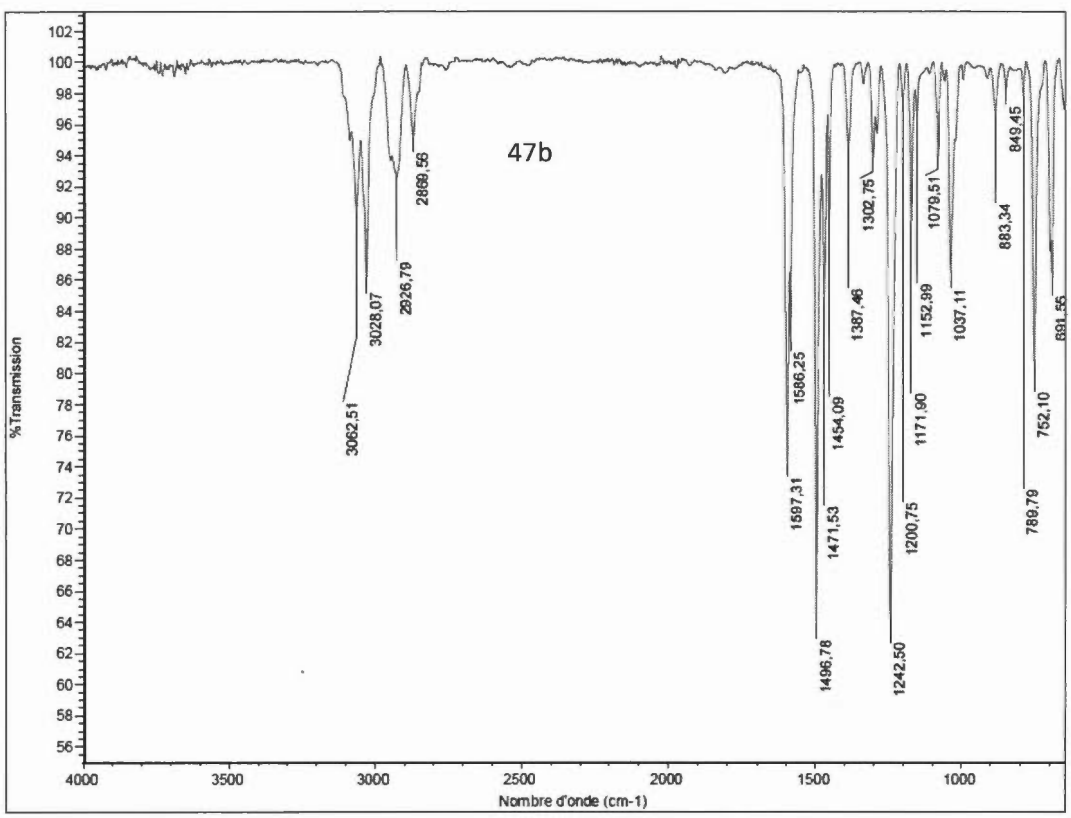


47b


47b
%Transmission
Nombre d'onde (cm-1)
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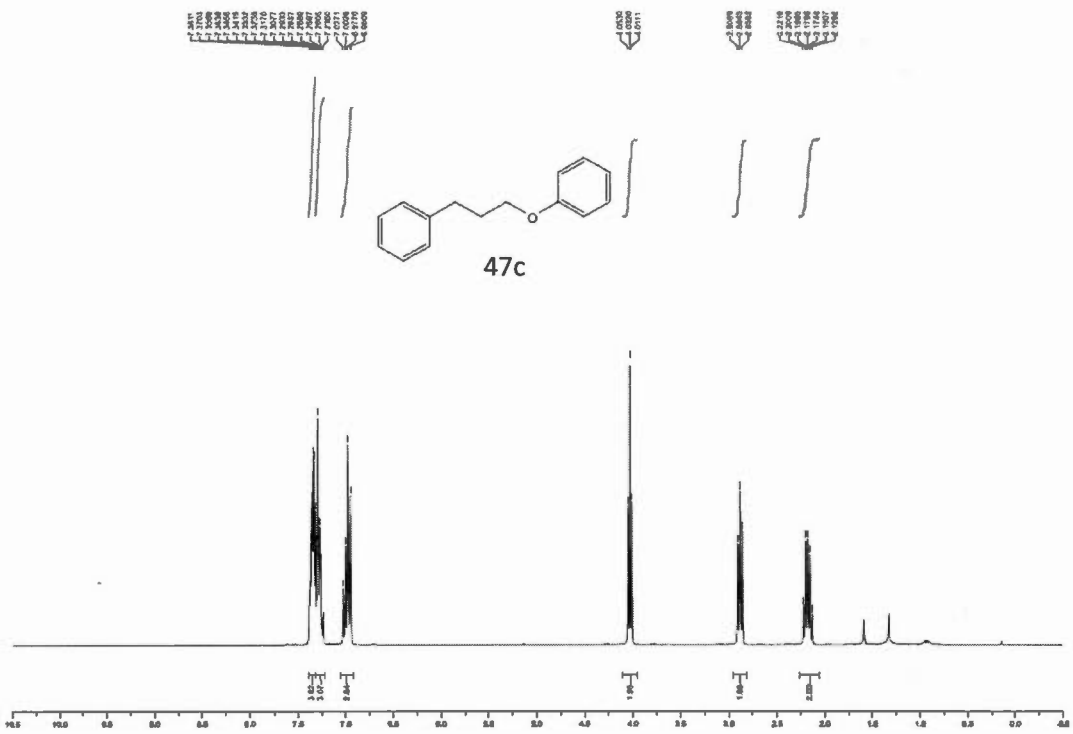
3500
3000
2500
2000
1500
1000
3062,51
3028,07
2926,79
2869,56
1597,31
1586,25
1496,78
1471,53
1454,09
1387,46
1302,75
1242,50
1200,75
1171,90
1152,99
1079,51
1037,11
883,34
849,45
789,79
752,10
691,55



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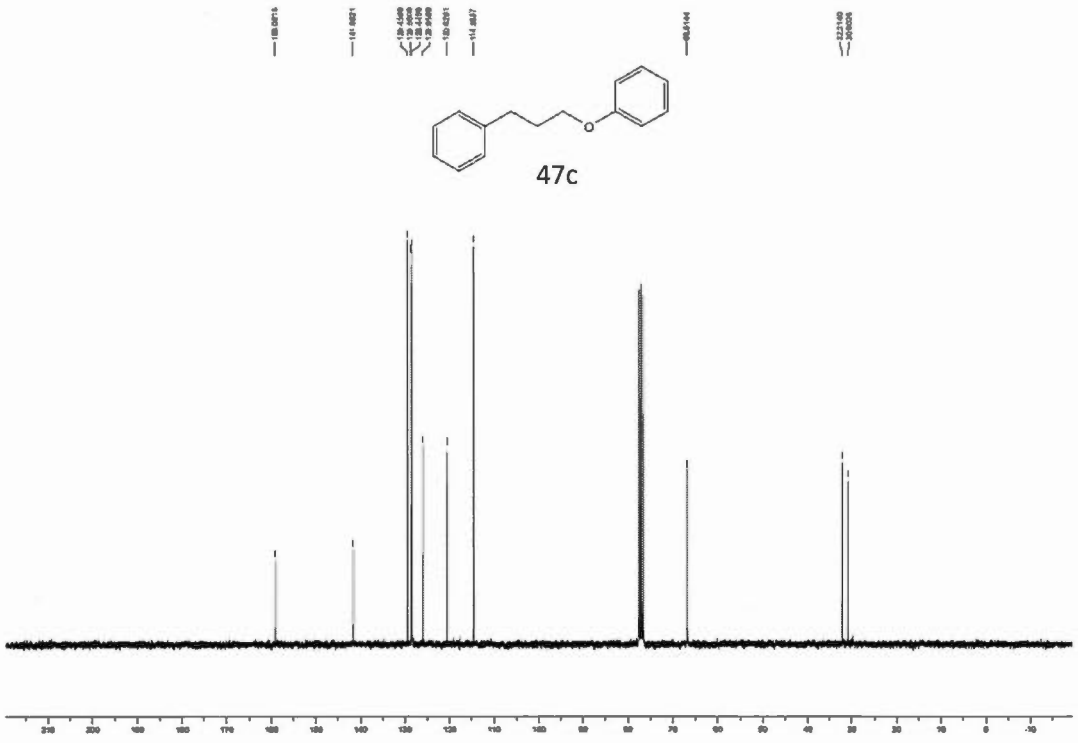
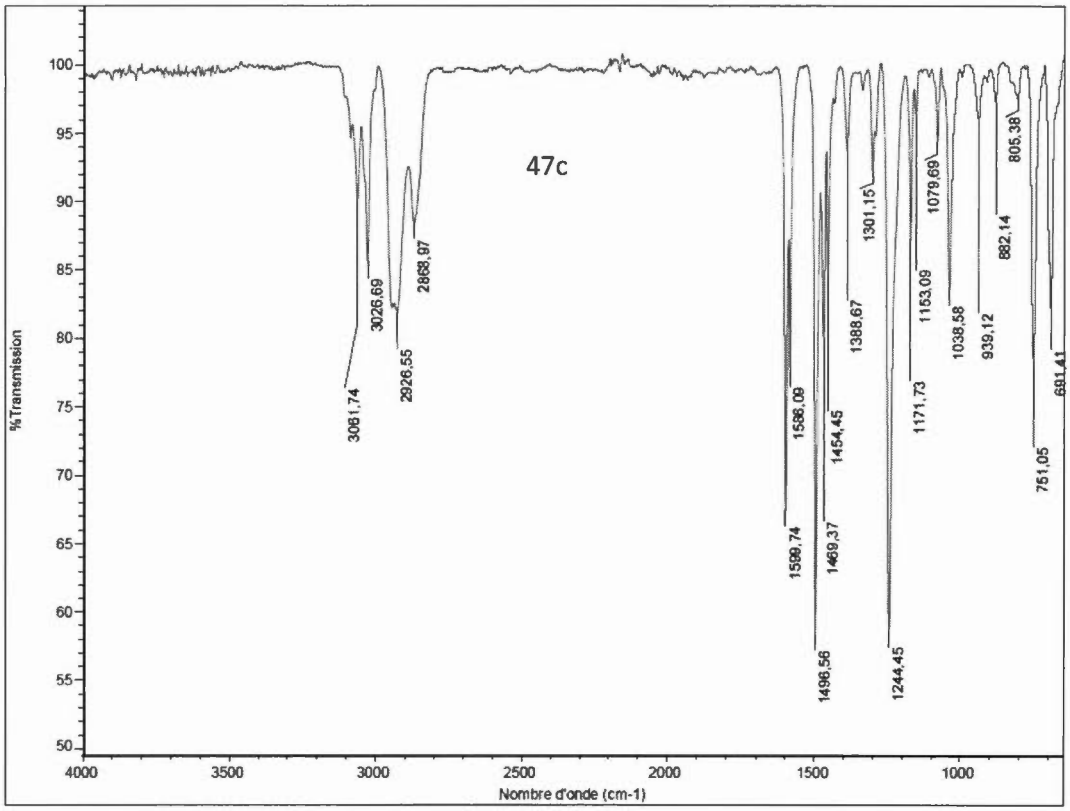
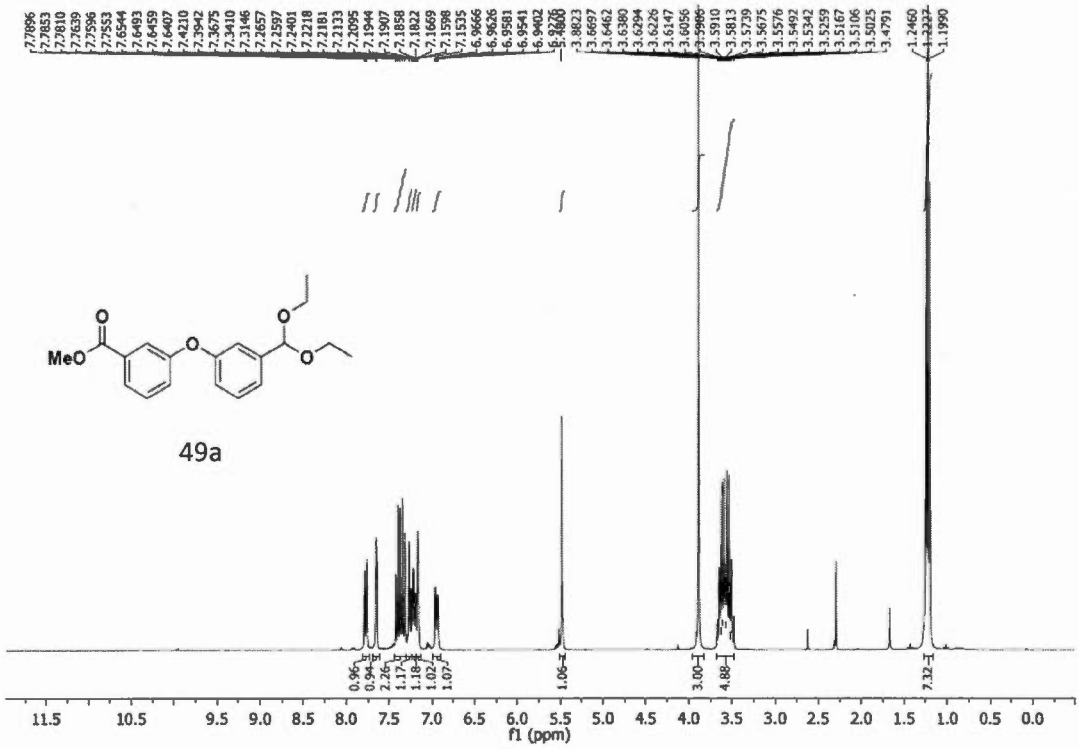
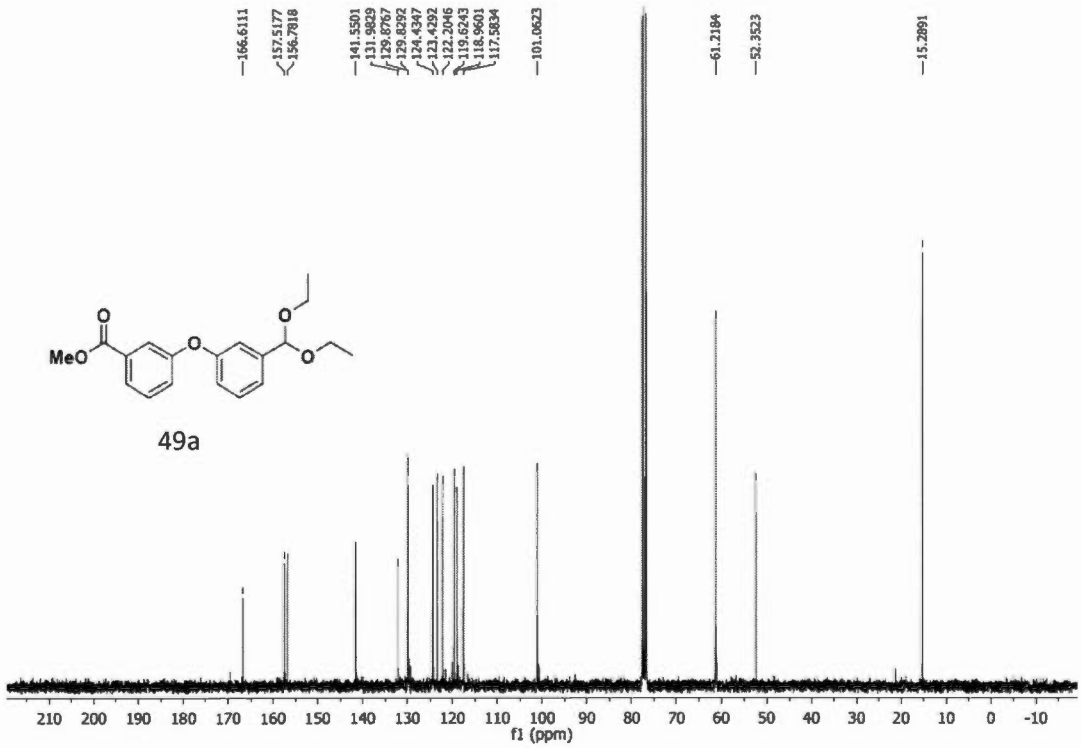


47c


47c
%Transmission
Nombre d'onde (cm-1)
100
95
90
85
80
75
70
65
60
55
50
4000
3500
3000
2500
2000
1500
1000
3061,74
3026,69
2926,55
2868,97
1598,74
1586,09
1496,56
1469,37
1454,45
1388,67
1301,15
1244,45
1171,73
1153,09
1079,69
1038,58
939,12
882,14
805,38
751,05
681,41


MeO
O
O
O
O
49a
f1 (ppm)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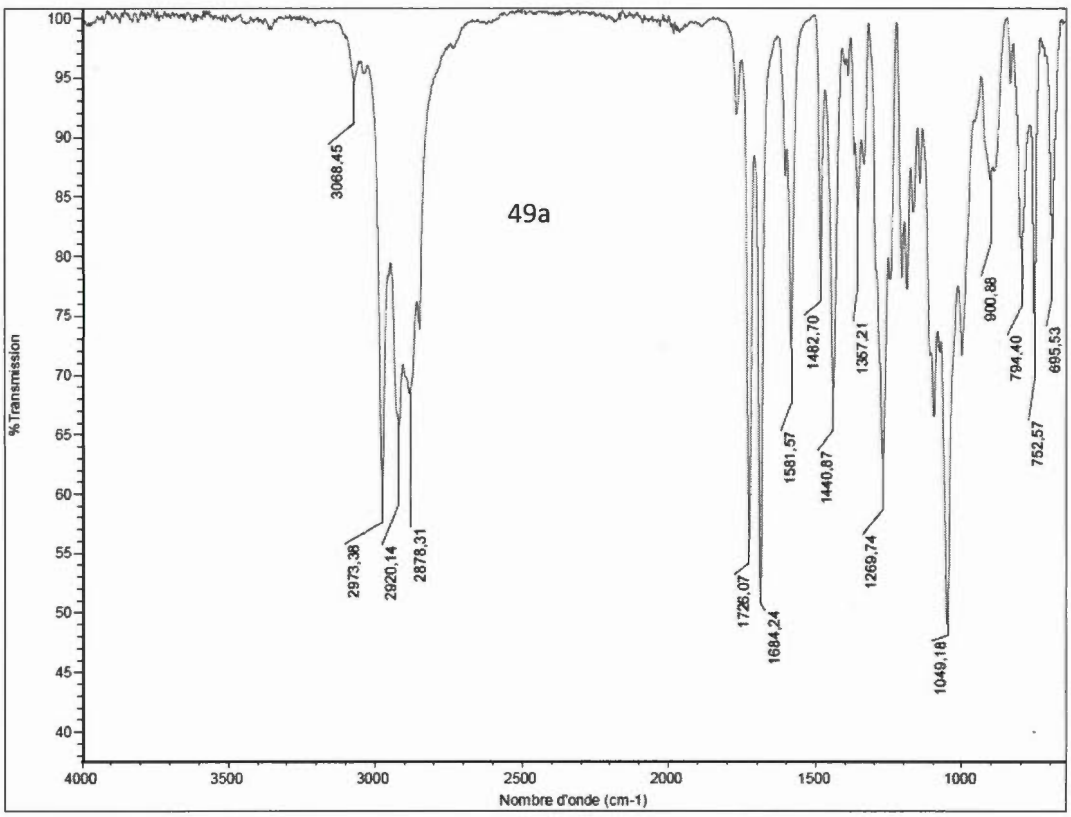
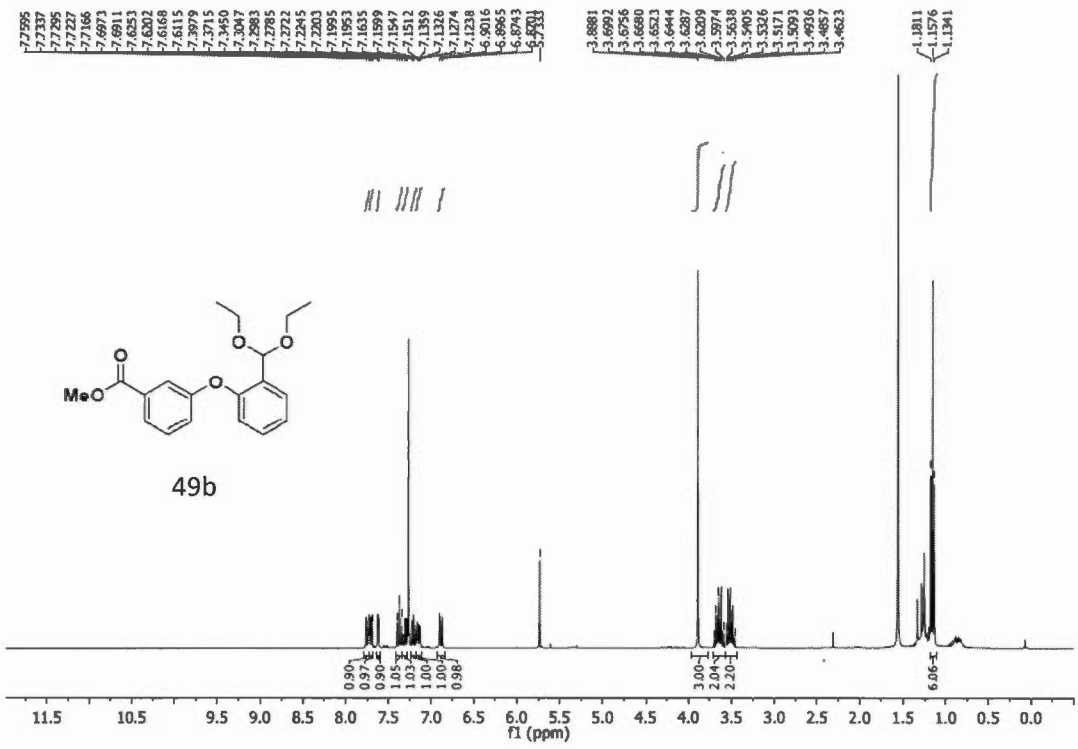
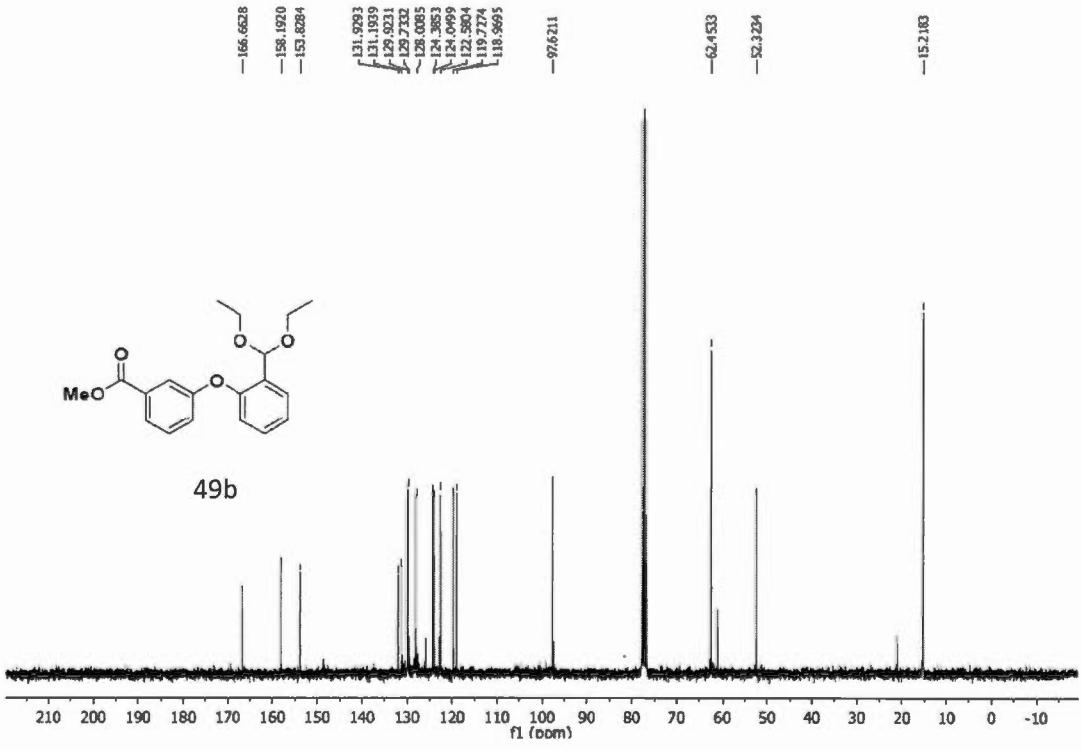
157.5177
156.7818
141.5501
131.9829
129.8767
129.8292
124.4347
123.4292
122.2046
119.6243
118.9601
117.5834
101.0623
61.2184
52.3523
15.2891
MeO
O
O
O
O
49a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


49a
% Transmission
Nombre d'onde (cm-1)
3068,45
2973,38
2920,14
2878,31
1726,07
1684,24
1581,57
1482,70
1440,87
1357,21
1269,74
1049,18
900,88
794,40
752,57
695,53


MeO
49b
f1 (ppm)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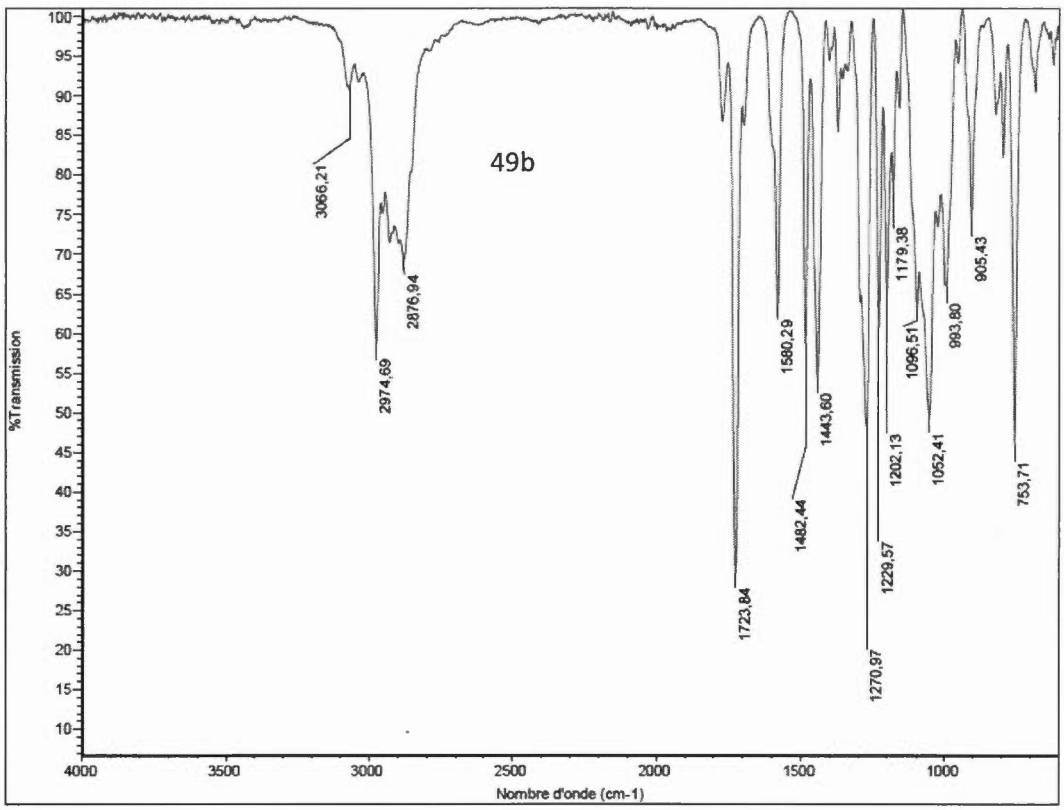
153.8284
131.9293
131.1939
129.9231
129.7332
128.0085
124.3853
124.0499
122.5804
119.7724
118.9695
97.6211
62.4533
52.3234
15.2183
MeO
O
O
O
O
49b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


49b
%Transmission
Nombre d'onde (cm-1)
3066,21
2974,69
2876,94
1723,84
1580,29
1482,44
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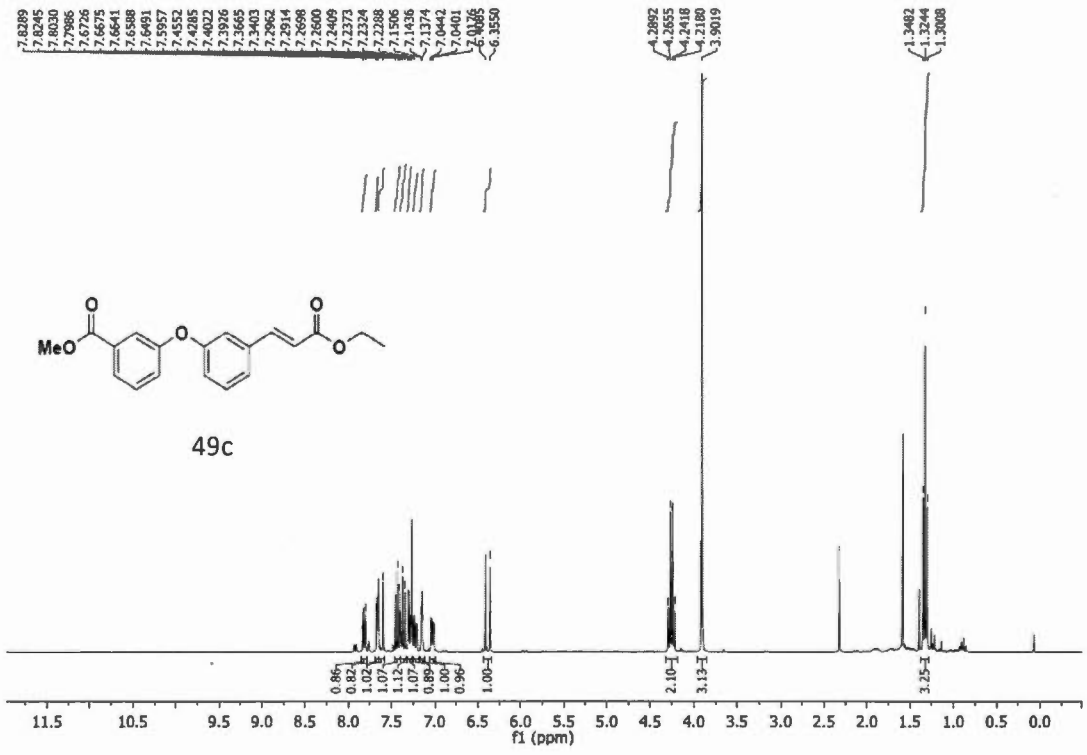
1229,57
1202,13
1179,38
1096,51
1052,41
993,80
905,43
753,71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7.8030
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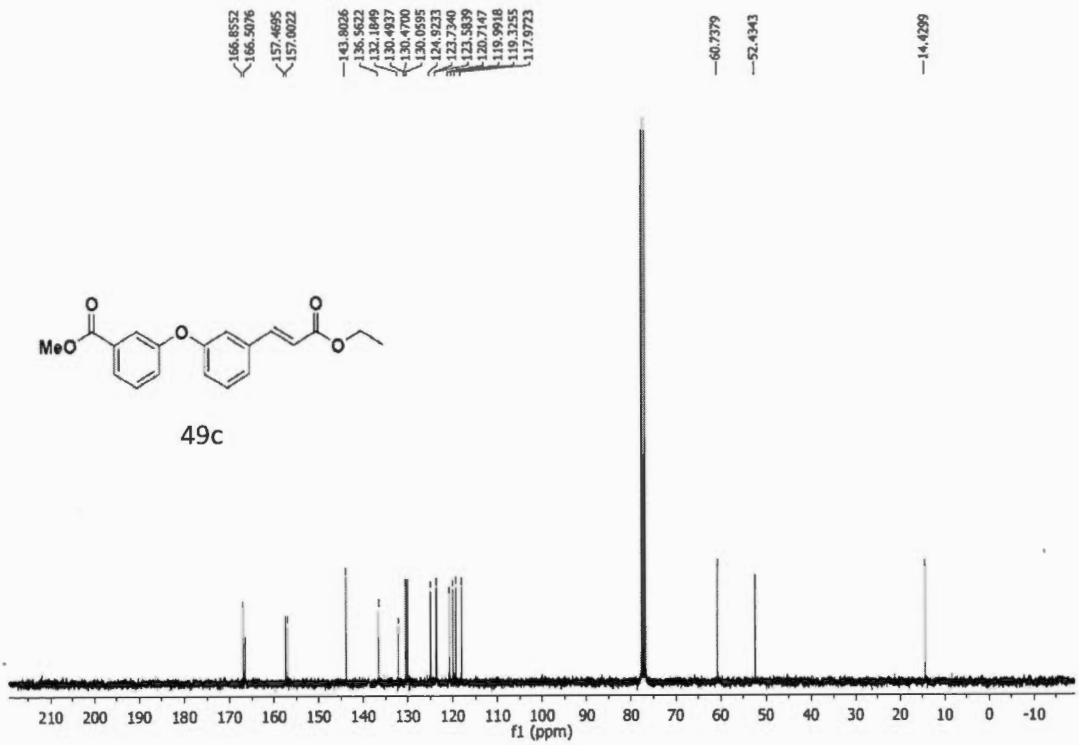
7.6726
7.6675
7.6641
7.6588
7.6491
7.5957
7.4552
7.4285
7.4022
7.3926
7.3665
7.3403
7.2962
7.2914
7.2698
7.2600
7.2409
7.2373
7.2324
7.2288
7.1506
7.1436
7.1374
7.0442
7.0401
6.3550
4.2892
4.2655
4.2418
4.2180
3.9019
1.3482
1.3244
1.3008
MeO
O
O
O
O
0.86
0.82
1.02
1.07
1.12
1.07
0.89
1.00
0.96
1.00
2.10
3.13
3.25
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

49c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157.0022
143.8026
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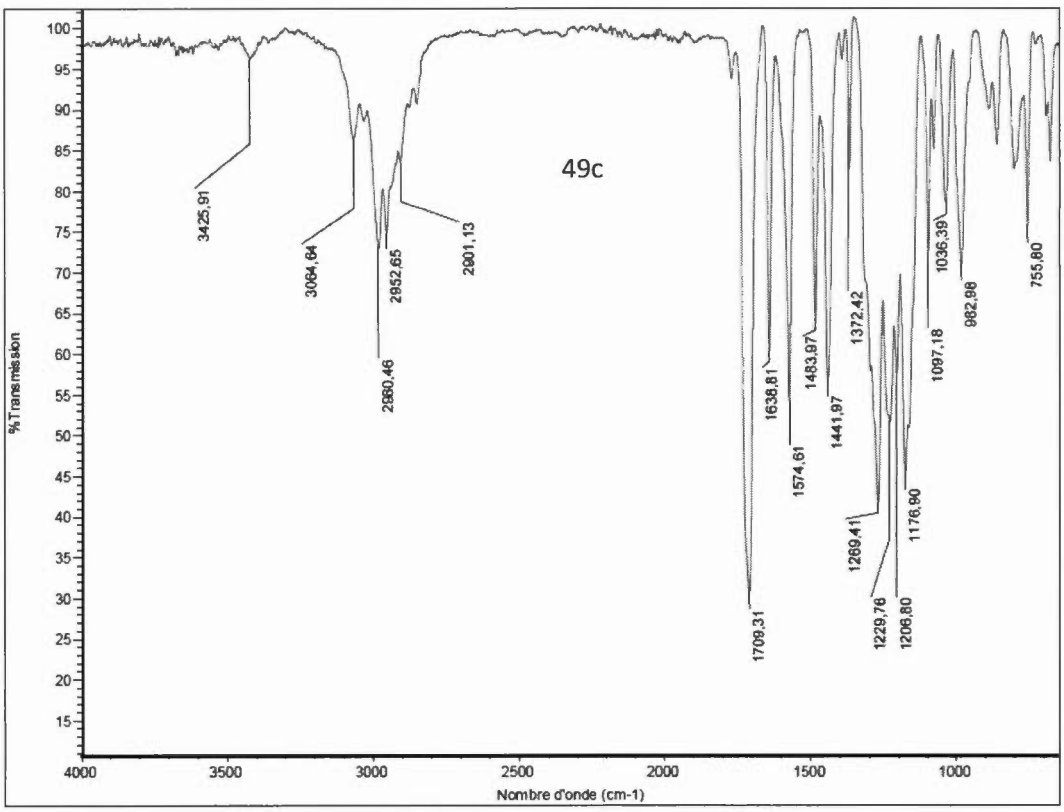
130.4700
130.0595
124.9233
123.7340
123.5839
120.7147
119.9918
119.3255
117.9723
60.7379
52.4343
14.4299
MeO
O
O
O
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

49c


49c
%Transmission
Nombre d'onde (cm-1)
3425,91
3064,64
2960,46
2932,65
2901,13
1709,31
1638,81
1574,61
1483,97
1441,97
1372,42
1269,41
1229,76
1206,80
1176,90
1097,18
1036,39
982,98
755,80

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Preparation of 3-*O*-aryl chloramphenicol derivatives via chemoselective copper-catalyzed O-arylation of (1*R*,2*R*)-(−)-*N*-BOC-2-amino-1-(4-nitrophenyl)-1,3-propanediol using triarylbismuthines

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ABSTRACT

A copper-catalyzed protocol for the chemoselective arylation of (1*R*,2*R*)-(−)-*N*-BOC-2-amino-1-(4-nitrophenyl)-1,3-propanediol using triarylbismuth reagents is reported. The reaction operates under simple and mild conditions, shows good functional group tolerance and allows the installation of *ortho*-, *meta*-, and *para*-substituted aryl groups in moderate to good yields. These arylated products are then transformed in two steps into their corresponding *N*-dichloroacetamide derivatives. This sequence provides an expedient access to 3-*O*-aryl chloramphenicol derivatives.

Introduction

Bismuth is the heaviest stable element of group 15 of the periodic table, also called the pnictogens. Despite its heavy atomic weight, elemental bismuth and its derived inorganic compounds show very low toxicity.[1] Organobismuthines (also called organobismuthanes) are a class of organometallic reagents that contain a C—Bi bond. These reagents are classified into two main groups: trivalent and pentavalent reagents where the bismuth center is at the +3 and +5 oxidation state respectively. Organobismuthines have gained popularity in the past years due to their ease of synthesis, air and moisture-stability, low toxicity, and high functional group tolerance.[2] In the 1980s, Barton and Finet reported a series of arylation reactions based on organobismuth compounds.[3] More recently, Rao greatly contributed to expanding the use of organobismuth compounds in palladium-catalyzed cross-coupling reactions.[4] Organobismuthines have also been used in total synthesis,[5] in methodology development,[6] in medicinal chemistry,[7] as ligands in metal-transition complexes,[8] and in polymerization reactions.[9]

Our group has reported over the past years a portfolio of copper and palladium-catalyzed reactions for the construction of C—C,[10] C—N[11], and C—O bonds[12] based on trialkyl and triarylbismuthines.[13] These methods operate under mild conditions, show very high functional group tolerance, and allow the installation of alkyl and aryl groups on medicinally relevant scaffolds.

We recently developed a copper-catalyzed method for the chemoselective O-arylation of 1,2-aminoalcohols **1** using highly functionalized triarylbismuthines **2** (Scheme 1A).[12a] As a continuation to these studies, we were interested in transposing this method to the arylation of 2-amino-1,3-diols. As an entry into this class of substrates, we focused our attention to the arylation of chloramphenicol derivatives (Scheme 1B).

Chloramphenicol is a natural antibiotic with wide spectrum antimicrobial activity.[14,15] It inhibits protein synthesis in bacteria by binding to the 50S ribosomal subunit.[16] Many studies on the derivatization of chloramphenicol have been disclosed, including the esterification[17] and acetalization[18] of the 1- and 3-hydroxyl groups, the alkylation and benzylation of the 3-hydroxyl group,[19] the formation of the 3-carboxylic acid derivatives,[20] the removal of the 1-hydroxyl,[21] and the replacement of the dichloroacetyl group by other amides and sulfonamides.[22] To our knowledge, there are no reports on the O-arylation of the 3-hydroxyl function of chloramphenicol. In the context of a broader program aimed at

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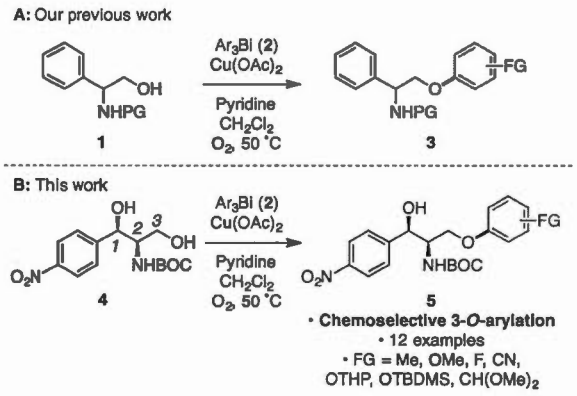


Scheme 1. (A) Copper-catalyzed O-arylation of 1,2-aminoalcohols **1** using triarylbismuthines **2** and (B) application to the chemoselective 3-O-arylation of the *N*-BOC derivative **4** of chloramphenicol.

developing new antibiotics, we were interested in exploring the impact of arylation of the 3-OH group of chloramphenicol.

We report herein a copper-catalyzed protocol to chemoselectively *O*-arylate the *N*-BOC derivative of chloramphenicol using triarylbismuthines. The *O*-aryl derivatives are then transformed in two easy steps into their corresponding *N*-dichloroacetamide derivatives. This sequence provides a rapid access to 3-*O*-aryl chloramphenicol derivatives.

Results and discussion

We began by preparing a set of triarylbismuthines bearing a variety of functional groups at the *ortho*, *meta*, and *para* position by adding organomagnesium reagents **B** (obtained from the corresponding aryl halides **A** using metallic magnesium or Knochel's procedure) over bismuth chloride (Fig. 1).[23] We described previously the synthesis and complete characterization of these triarylbismuthines,[13] except for **2k** which is unprecedented and which

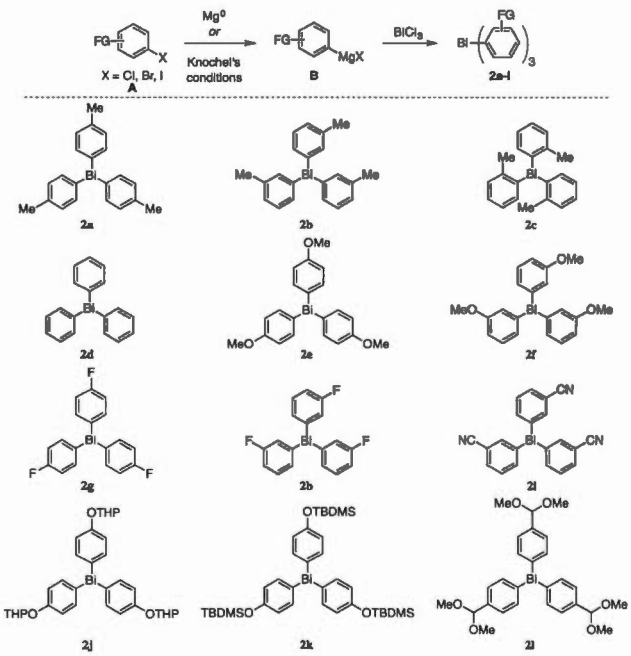
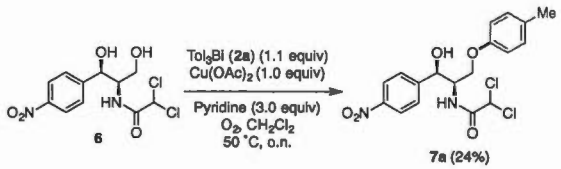


Figure 1. Organobismuthines **2a–l** used in this study.

we now report for the first time. This organobismuth reagent possesses a masked phenol group which is protected in the form of a silyl ether and which will be useful in our preliminary exploration of the SAR around the 3-*O*-aryl moiety. Triarylbismuthine **2k** was crystallized and analyzed by X-ray diffraction and shows a distorted pyramidal geometry in accordance with other triarylbismuthines.[23]

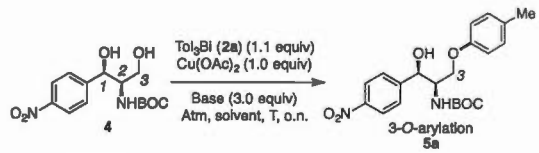
We then evaluated the feasibility of preparing 3-*O*-tolyl chloramphenicol **7a** by the direct tolylation of chloramphenicol **6** using conditions that we previously developed for the arylation of 1,2-aminoalcohols (Eq. 1).[12a] Thus, when **6** was treated with tritolylbismuthine **2a** in the presence of stoichiometric amount of copper acetate and excess pyridine at 50 °C overnight in dichloromethane under oxygen, only 24% of the corresponding 3-*O*-tolyl derivative **7a** was obtained. While this result was encouraging, we felt that a more efficient route was needed to access a variety of 3-*O*-aryl chloramphenicol derivatives. Other palladium or copper-catalyzed arylation reactions using aryliodides or arylboronic acids to directly arylate chloramphenicol **6** were also briefly tested with no success, motivating us to revise our strategy.



(1)

Suspecting that the dichloroacetyl group was responsible for the low yield in the arylation of chloramphenicol **6**, we next optimized the reaction on the *N*-BOC derivative **4**. Using 1.1 equiv of tritolylbismuth **2a**, 1.0 equiv of copper acetate, 3.0 equiv of pyridine in dichloromethane overnight at 50 °C under oxygen, product **5a** from O-arylation of the primary alcohol was obtained in 42% yield along with 10% of product from arylation of the secondary alcohol and 29% unreacted recovered starting material **4** (Table 1, entry 1). A drastic drop in the yield of the reaction was observed upon performing the reaction under air, showing that oxygen is essential (entry 2). Lower yields of **5a** were also observed upon performing the reaction in THF and acetonitrile at 50 °C (entries 3 and 4) or DMF and dioxane at 80 °C (entries 5 and 6). Product

Table 1
Optimization of the reaction conditions for the copper-catalyzed O-arylation of (1*R*,2*R*)-(−)-*N*-BOC-2-amino-1-(4-nitrophenyl)-1,3-propanediol **4** using tritolylbismuthine **2a**



Entry	Base	Solvent	Atm	*T* (°C)	5a[a] (%)
1[b]	Pyridine	CH_2Cl_2	O_2	50	42
2	Pyridine	CH_2Cl_2	Air	50	14
3	Pyridine	THF	O_2	50	17
4	Pyridine	CH_3CN	O_2	50	19
5	Pyridine	DMF	O_2	80	26
6	Pyridine	Dioxane	O_2	80	26
7	K_2CO_3	CH_2Cl_2	O_2	50	0
8	NMM[c]	CH_2Cl_2	O_2	50	40
9	Et_3N	CH_2Cl_2	O_2	50	26
10	DBU	CH_2Cl_2	O_2	50	14

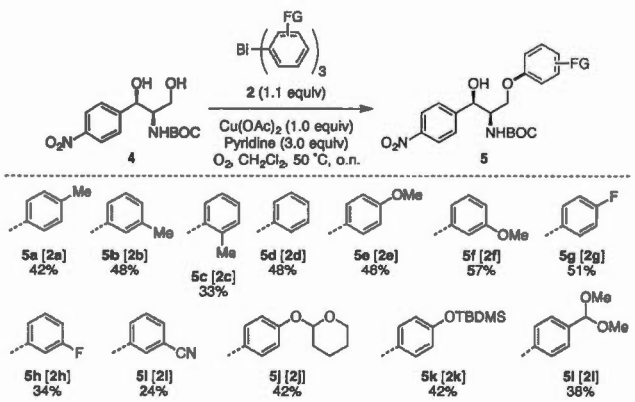
[a] Yields of isolated pure compound.
[b] The product of arylation of the secondary alcohol was isolated in 10% along with 29% of unreacted starting material **4**.
[c] NMM = *N*-methylmorpholine.

5a was not formed when pyridine was replaced by an inorganic base such as potassium carbonate (entry 7). Among other organic bases that were tested, *N*-methylmorpholine was found to give the highest yield of **5a** (entry 8) while triethylamine and DBU were found to give low yields of the desired product (entries 9 and 10). Arylation of **4** using tolylboronic acid and copper acetate was briefly attempted but failed to deliver the desired product **5a**. Therefore, the initial conditions, as we reported previously for the arylation of 1,2-aminoalcohols, were selected for the study of the triarylbismuthine scope.

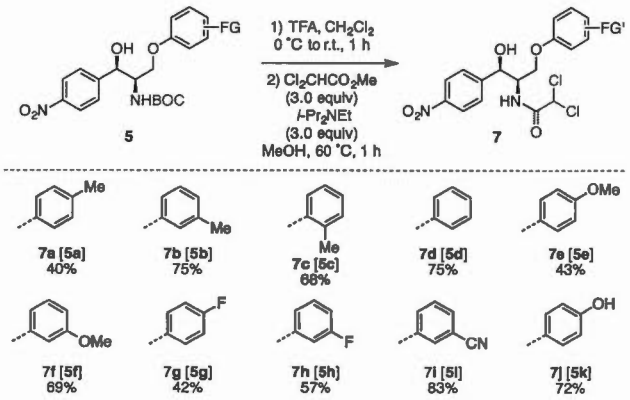
Having optimized the reaction conditions for the tolylation of the *N*-BOC derivative **4**, we then varied the nature of the triarylbismuthine **2** in order to establish the ability of the method to transfer aryl groups possessing various functional groups (Scheme 2). We first investigated the impact of the substitution pattern of the aryl group (i.e., *ortho*, *meta*, and *para*) on the arylation reaction. Unsurprisingly, the results show that tri(*p*-tolyl)bismuthine **2a** and tri(*m*-tolyl)bismuthine **2b** give similar yields of the arylation products **5a** and **5b**. The arylation using tri(*o*-tolyl)bismuthine **2c** afforded the corresponding product **5c** in slightly reduced yield, showing that the transfer of *ortho*-substituted aryl groups is challenging but yet possible. To calibrate the effect of substitution of the aryl group, both on the electronic and steric factors, we conducted the arylation reaction using the unsubstituted bismuth reagent **2d** and obtained the corresponding arylated product **5d** in 48% yield, showing that introduction of a methyl group at the *meta* and *para* position has no consequence on the efficiency of the reaction. The impact of the electronic nature of the aryl substituent was next investigated. Aryl groups possessing a *para*-methoxy (electron-donating) and a *meta*-methoxy (electron-withdrawing) substituent were transferred in 46% and 57% yields respectively (**5e**,**f**). Moreover, the transfer of aryl groups possessing a fluorine atom (**5g**,**h**) or functionalities such as a nitrile (**5i**), an *O*-protected phenol (**5j**,**k**) and an acetal (**5l**) was accomplished using this method.

We next converted the *N*-BOC-*O*-aryl derivatives **5** into the corresponding 3-*O*-aryl chloramphenicol derivatives **7** by first removing the BOC protecting group using trifluoroacetic acid and then installing the dichloroacetamide function by treatment with methyl dichloroacetate in the presence of diisopropylethyl amine (Scheme 3).

Using this simple two-step sequence, compounds **7a–j** were prepared in 40–83% yield. Treatment of compounds **5j** and **5l** under these conditions led to decomposition, possibly due to the presence of the acid-sensitive OTHP and acetal groups. In the case of derivative **5k**, the *tert*-butyldimethylsilyl group was removed



Scheme 2. Triarylbismuth scope in the 3-O-arylation of (1*R*,2*R*)-(−)-*N*-BOC-2-amino-1-(4-nitrophenyl)-1,3-propanediol **4**. Numbers in brackets indicate the organobismuth reagent that was used. Yields are for isolated pure compounds.[24]



Scheme 3. Preparation of 3-*O*-aryl chloramphenicol derivatives **7** from **5**. Number in brackets indicate the starting *N*-BOC derivative that was used in the reaction. Yields are for isolated pure compounds over two steps.[25,26]

during the treatment with trifluoroacetic acid, leading to the phenol derivative **7j** in 72% overall yield. The results show that the 3-O-arylation/BOC-deprotection/dichloro acetamidation sequence allows the preparation of 3-*O*-aryl chloramphenicol derivatives possessing substituents at all aromatic positions.

Conclusion

In summary, we have developed a chemoselective copper-catalyzed O-arylation reaction of (1*R*,2*R*)-(−)-*N*-BOC-2-amino-1-(4-nitrophenyl)-1,3-propanediol using triarylbismuthines. The method allows the transfer of *ortho*-, *meta*-, and *para*-substituted aryl groups, shows good functional group tolerance, and leads to arylation of the primary alcohol. The arylated products were expeditively transformed into the corresponding 3-*O*-arylchloramphenicol derivatives in two simple steps. The activity and metabolic stability of the prepared chloramphenicol derivatives against a panel of gram-negative and gram-positive bacteria will be investigated and results will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.08.021.

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21. (a) Ramaiah, P.; Rao, A. S. *Org. Prep. Proced. Int.* **1987**, *19*, 173–180; (b) Kalutharage, N.; Yi, C. S. *J. Am. Chem. Soc.* **2015**, *137*, 11105–11114.
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24. *General procedure for the O-arylation of (1R,2R)-(−)-N-BOC-2-amino-1-(4-nitrophenyl)-1,3-propanediol* (**4**): In a sealed tube, the *N*-BOC chloramphenicol derivative (**4**) (0.160 mmol) was dissolved in dichloromethane (2 mL). Triarylbismuthine reagent (**2**) (1.1 equiv) was added followed by copper (II) acetate (1.0 equiv) and pyridine (3.0 equiv). The tube was sparged with oxygen for 30 s, sealed, and heated at 50 °C for 16 h. The reaction mixture was cooled to rt, transferred in a flask, and the reaction tube was washed with dichloromethane. Silica gel was added and the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography using the indicated solvent system to afford the desired product (**5**).
25. *General procedure for the conversion of the N-BOC derivatives (5) into dichloroacetamide derivatives* (**7**): **Step 1**—Removal of the BOC protecting group: the *N*-BOC derivative **5** (0.06 mmol) was dissolved in dichloromethane (1 mL) and cooled to 0 °C. Trifluoroacetic acid (5.0 equiv) was added dropwise and the reaction mixture was warmed up to rt. The mixture was concentrated under reduced pressure and taken directly in the next step. **Step 2**—Installation of the dichloroacetamide: in a sealed tube, the TFA amine salt (0.06 mmol) was dissolved in MeOH (1 mL). Methyl dichloroacetate (3.0 equiv) was added followed by DIPEA (3.0 equiv). The resulting reaction mixture was stirred at 60 °C for 1 h. The mixture was cooled to rt and concentrated under reduced pressure to give the crude dichloroacetamide adduct. The crude product was purified by flash column chromatography on silica gel using the indicated eluent system to afford the desired product (**7**).
26. For another route to transform *N*-BOC chloramphenicol derivatives into chloramphenicol, see: Mateus, C. R.; Coelho, F. *J. Braz. Chem. Soc.* **2005**, *16*, 386–396.

Preparation of 3-*O*-Aryl Chloramphenicol Derivatives via Chemoselective Copper-Catalyzed *O*-Arylation of (1*R*,2*R*)-(−)-*N*-BOC-2-Amino-1-(4-Nitrophenyl)-1,3-Propanediol Using Triarylbismuthines

Supporting Information

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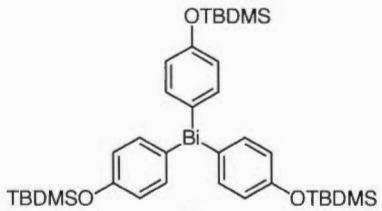
1. General information

Unless otherwise indicated, all reactions were run under argon in non-flame dried glassware. For reactions performed under oxygen, 99.6% extra dry oxygen was used. Unless otherwise stated, commercial reagents were used without further purification. Triarylbismuthines **2a**, **2c**, **2f**, **2g**, **2i** and **2j** were prepared according to Petiot, P.; Gagnon, A. *Eur. J. Org. Chem.* **2013**, 5282-5289. Triarylbismuthines **2b**, **2e**, **2h** and **2l** were prepared according to Petiot, P.; Dansereau, J.; Gagnon, A. *RSC Adv.* **2014**, *4*, 22255-22259. Triarylbismuthine **2d** was prepared according to Hébert, M.; Petiot, P.; Benoit, E.; Dansereau, J.; Ahmad, T.; Le Roch, A.; Ottenwaelder, X.; Gagnon, A. *J. Org. Chem.* **2016**, *81*, 5401-5416. The synthesis of triarylbismuthine **2k** is described below. Anhydrous solvents were obtained using an encapsulated solvent purification system and were further dried over 4 Å molecular sieves. The evolution of reactions was monitored by analytical thin-layer chromatography using silica gel 60 F254 precoated plates. Flash chromatography was performed employing 230-400 mesh silica using the indicated solvent system according to standard techniques. Melting points are uncorrected. Nuclear magnetic resonance spectra (^{1}H, ^{13}C) were recorded on a 300MHz or 600MHz spectrometer. Chemical shifts for ^{1}H-NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ 7.26 ppm; methanol, δ 3.31 ppm). Data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qt = quintuplet, dd = doublet of doublet, dt = doublet of triplet, m = multiplet), coupling constant *J* in Hz and integration. Chemical shifts for ^{13}C spectra are recorded in parts per million from tetramethylsilane using the central peak of deuterochloroform (δ 77.16 ppm) or the central peak of tetradeuteromethanol (δ 49.00 ppm) or the central peak of acetone (δ 205.86 and 30.92 ppm) as the internal standard. IR spectra were recorded on a FT-IR from thin films and are reported in reciprocal centimeters (cm^{-1}). HRMS were performed on a TOF LCMS analyzer using the electrospray (ESI) mode. The X-ray crystal structure of compound **2k** has been deposited at the Cambridge Crystallographic Data Centre and has been assigned the number CCDC 1487426.

2a. Synthesis of tris(4-((*tert*-butyldimethylsilyl)oxy)phenyl)bismuthine (2k)



2k

In a flask equipped with a magnetic stir bar and a condenser, bismuth chloride (500 mg, 1.6 mmol) was dissolved in anhydrous THF (23 mL) under argon and was cooled to –10°C (ice/acetone bath). (4-((*Tert*-butyldimethylsilyl)oxy)phenyl)magnesium bromide (5.23 mmol) was slowly added dropwise under argon. The reaction mixture was stirred at room temperature for one hour and heated at 65°C for 30 minutes. After cooling to r.t., the solution was diluted with sat. aq. $NaHCO_3$ (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (2 x 100 mL), sat. aq. NaCl (2 x 100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford tris(4-((*tert*-butyldimethylsilyl)oxy)phenyl)bismuthine **2k** as a white solid (418 mg, 31%): mp: 127-128°C; R_f0.28 (2% EtOAc/hexanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.56-7.51 (m, 2H), 6.86-6.82 (m, 2H), 0.98 (s, 9H), 0.19 (s, 6H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 155.5, 146.1, 138.8, 122.5, 25.8, 18.3, -4.2; IR (neat) 3048, 2954, 2925, 2889, 2852, 1573, 1487, 1254, 1168, 907, 837, 825, 776; HRMS (ESI) calcd for $C_{36}H_{57}BiO_3Si_3$: 830.3419, found 869.3075 $[M+K]^+$.

2b. X-Ray structure of tris(4-((*tert*-butyldimethylsilyl)oxy)phenyl)bismuthine (2k)

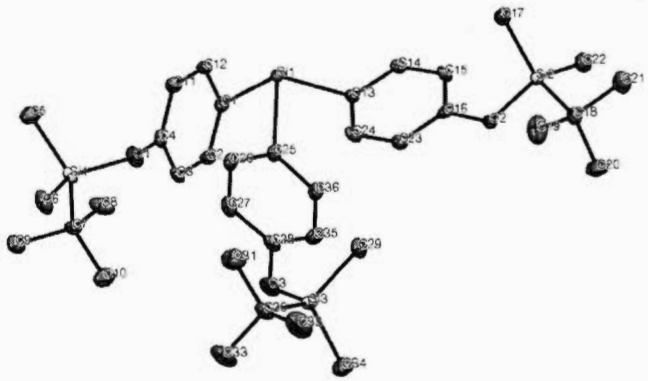
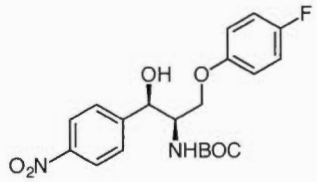


Figure S1. ORTEP view of **2k** at 50% ellipsoid probability. Hydrogen atoms are omitted for clarity. Selected bond lengths C1–Bi: 2.256 Å; C25–Bi: 2.238 Å; C13–Bi: 2.249 Å. Selected bond angles: C1–Bi–C13: 93.13 °; C13–Bi–C25: 95.35 °; C1–Bi–C25: 93.69 °.

Compounds **2k** was crystallized by the solvent diffusion technique according to the following procedure: 10 mg of **2k** was dissolved in a minimal amount of dichloromethane in an open vial. The vial was then placed in a bigger vial filled with hexanes with a loosely tightened cap. The vials were kept at room temperature until crystals were obtained. A colorless plate-like specimen of $C_{36}H_{57}BiO_3Si_3$, approximate dimensions 0.204 mm x 0.225 mm x 0.599 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 23710 reflections to a maximum θ angle of 27.68° (0.77 Å resolution), of which 9188 were independent (average redundancy 2.58, completeness = 99.5%, R_{int} = 4.72%, R_{sig} = 5.51%) and 8799 (95.77%) were greater than $2\sigma(F^2)$. The final cell constants of $\underline{a}$ = 13.2335(11) Å, $\underline{b}$ = 11.6830(1) Å, $\underline{c}$ = 13.5135(12) Å, β = 107.9740(10)°, volume = 1987.3(3) Å^3, are based upon the refinement of the XYZ-centroids of 9877 reflections above 20 σ(I). Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.607. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.4524 and 0.7456. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P 1 21 1, with Z = 4 for the formula unit, $C_{36}H_{57}BiO_3Si_3$. The final anisotropic

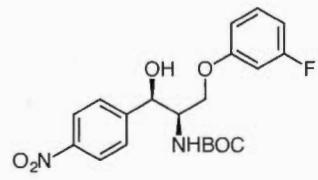
Tert-butyl ((1*R*,2*R*)-3-(4-fluorophenoxy)-1-hydroxy-1-(4-nitrophenyl)propan-2-yl)carbamate (5g)



5g

The general procedure was followed on a 0.160 mmole scale starting from (1*R*,2*R*)-(–)-*N*-BOC-2-amino-1-(4-nitrophenyl)-1,3-propanediol (**4**) and organobismuthine **2g**. The crude product was purified on silica gel (50% EtOAc/Hex) to afford **5g** as a white solid (33 mg, 51%): m.p. 130-135°C; R_f 0.50 (35% EtOAc/Hex); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.7 Hz, 2H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.02-6.96 (m, 2H), 6.86-6.81 (m, 2H), 5.21 (d, *J* = 3.0 Hz, 2H), 4.10-3.98 (m, 3H), 3.59 (s(br), 1H), 1.35 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 156.2, 154.0, 148.6, 147.5, 127.1, 123.6, 116.3, 116.0, 115.6, 115.5, 80.6, 73.1, 68.5, 55.2, 28.2; HRMS (ESI) calcd for $C_{20}H_{23}FN_2O_6$: 406.1540, found 429.1422 $[M+Na]^+$, 307.1090 $[M-BOC+H]^+$.

Tert-butyl((1*R*,2*R*)-3-(3-fluorophenoxy)-1-hydroxy-1-(4-nitrophenyl)propan-2-yl)carbamate (5h)

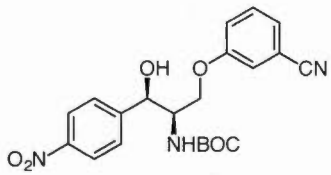


5h

The general procedure was followed on a 0.160 mmole scale starting from (1*R*,2*R*)-(–)-*N*-BOC-2-amino-1-(4-nitrophenyl)-1,3-propanediol (**4**) and organobismuthine **2h**. The crude product was purified on silica gel (50% EtOAc/Hex) to afford **5h** as a colorless oil (22 mg, 34%): R_f 0.59 (35% EtOAc/Hex); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.7 Hz, 2H), 7.56 (d, *J* = 8.6 Hz, 2H), 7.28-7.20 (m, 1H), 6.74-6.59 (m, 3H), 5.24-5.17 (m, 2H), 4.12-4.00 (m, 3H), 3.54 (s(br), 1H), 1.35 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 165.3, 162.0, 159.3, 159.2,

156.2, 148.5, 147.5, 130.6, 130.5, 127.1, 123.6, 110.1, 108.7, 108.4, 102.6, 102.3, 80.6, 72.7, 67.9, 55.5, 28.2; HRMS (ESI) calcd for $C_{20}H_{23}FN_2O_6$: 406.1540, found 407.1647 $[M+H]^+$.

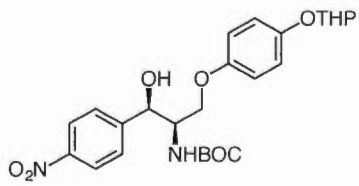
Tert-butyl((1*R*,2*R*)-3-(3-cyanophenoxy)-1-hydroxy-1-(4-nitrophenyl)propan-2-yl)carbamate (5i)



5i

The general procedure was followed on a 0.160 mmole scale starting from (1*R*,2*R*)-(–)-*N*-BOC-2-amino-1-(4-nitrophenyl)-1,3-propanediol (**4**) and organobismuthine **2i**. The crude product was purified on silica gel (50% EtOAc/Hex) to afford **5i** as a colorless oil (16 mg, 24%): R_f 0.51 (35% EtOAc/Hex); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.3 Hz, 2H), 7.59-7.54 (m, 2H), 7.42-7.13 (m, 4H), 5.22-4.94 (m, 2H), 4.19-4.05 (m, 3H), 3.55 (s(br), 1H), 1.34 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.2, 156.0, 148.5, 147.6, 130.6, 127.0, 125.3, 123.6, 119.5, 118.4, 117.7, 113.4, 80.6, 72.2, 67.6, 55.3, 28.2; HRMS (ESI) calcd for $C_{21}H_{23}N_3O_6$: 413.1587, found 436.1475 $[M+Na]^+$.

Tert-butyl((1*R*,2*R*)-1-hydroxy-1-(4-nitrophenyl)-3-(4-((tetrahydro-*2H*-pyran-2-yl)oxy)phenoxy)propan-2-yl)carbamate (5j)

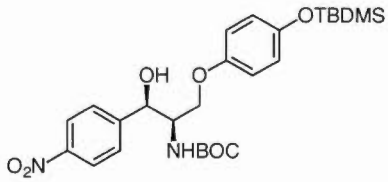


5j

The general procedure was followed on a 0.160 mmole scale starting from (1*R*,2*R*)-(–)-*N*-BOC-2-amino-1-(4-nitrophenyl)-1,3-propanediol (**4**) and organobismuthine **2j**. The crude product was purified on silica gel (50% EtOAc/Hex) to afford **5j** as a white solid (33 mg, 42%): m.p. 125-129°C; R_f 0.50 (35% EtOAc/Hex); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.7 Hz, 2H), 7.56 (d, *J* = 8.6 Hz, 2H), 7.01-6.98 (m, 2H), 6.82-6.79 (m, 2H), 5.31-5.19 (m, 3H),

4.10-3.91 (m, 4H), 3.68 (s(br), 1H), 3.63-3.55 (m, 1H), 1.86-1.82 (m, 2H), 1.70-1.59 (m, 4H), 1.35 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 156.1, 152.8, 151.9, 148.7, 147.5, 127.1, 123.5, 117.9, 115.4, 97.3, 80.4, 73.3, 68.7, 62.2, 55.5, 30.4, 28.2, 25.3, 18.9; HRMS (ESI) calcd for $C_{25}H_{32}N_2O_8$: 488.2159, 511.2035 $[M+Na]^+$.

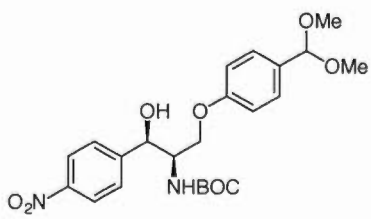
Tert-butyl((1*R*,2*R*)-3-(4-((*tert*-butyldimethysilyl)oxy)phenoxy)-1-hydroxy-1-(4-nitrophenyl)propan-2-yl)carbamate (5k)



5k

The general procedure was followed on a 0.160 mmole scale starting from (1*R*,2*R*)-(–)-*N*-BOC-2-amino-1-(4-nitrophenyl)-1,3-propanediol (**4**) and organobismuthine **2k**. The crude product was purified on silica gel (50% EtOAc/Hex) to afford **5k** as a yellow oil (35 mg, 42%): R_f 0.55 (35% EtOAc/Hex); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.19 (d, J = 8.7 Hz, 2H), 7.57 (d, J = 8.6 Hz, 2H), 6.76 (s, 4H), 5.27-5.21 (m, 2H), 4.09-4.00 (m, 3H), 3.62 (s(br), 1H), 1.35 (s, 9H), 0.97 (s, 9H), 0.17 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 156.1, 152.4, 150.3, 148.7, 147.5, 127.1, 123.5, 120.9, 115.4, 80.4, 73.5, 68.8, 55.5, 28.2, 25.7, 18.2, -4.5; HRMS (ESI) calcd for $C_{26}H_{38}N_2O_7Si$: 518.2448, found 541.2355 $[M+Na]^+$, 419.2014 $[M–BOC+H]^+$.

Tert-butyl((1*R*,2*R*)-3-(4-(dimethoxymethyl)phenoxy)-1-hydroxy-1-(4-nitrophenyl)propan-2-yl)carbamate (5l)



5l

The general procedure was followed on a 0.160 mmole scale starting from (1*R*,2*R*)-(–)-*N*-BOC-2-amino-1-(4-nitrophenyl)-1,3-propanediol (**4**) and organobismuthine **2l**. The crude product was purified on silica gel (50% EtOAc/Hex) to afford **5l** as a colorless oil (28 mg,

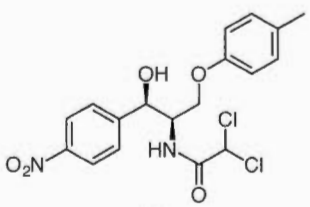
38%): R_f 0.51 (35% EtOAc/Hex); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.7 Hz, 2H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.38 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.35 (s, 1H), 5.27-5.18 (m, 2H), 4.14-4.03 (m, 3H), 3.56 (s(br), 1H), 3.31 (s, 6H), 1.35 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 157.9, 156.0, 148.5, 147.4, 131.5, 128.1, 127.0, 123.5, 114.0, 102.8, 80.5, 67.9, 55.7, 52.6, 28.1; HRMS (ESI) calcd for $C_{23}H_{30}N_2O_8$: 462.2002, found 507.1949 $[M+HCOO]^-$.

4. General procedure for the conversion of the *N*-BOC derivatives (5) into dichloroacetamide derivatives (7)

Step 1 – Removal of the BOC protecting group: The *N*-BOC derivative (**5**) (0.06 mmol) was dissolved in dichloromethane (1 mL) and cooled to 0°C. Trifluoroacetic acid (5.0 equiv) was added dropwise and the reaction mixture was warmed up to r.t. The mixture was concentrated under reduced pressure and taken directly in the next step.

Step 2 – Installation of the dichloroacetamide: In a sealed tube, the TFA amine salt (0.06 mmol) was dissolved in MeOH (1 mL). Methyl dichloroacetate (3.0 equiv) was added followed by DIPEA (3.0 equiv). The resulting reaction mixture was stirred at 60 °C for 1 hour. The mixture was cooled to r.t. and concentrated under reduced pressure to give the crude dichloroacetamide adduct. The crude product was purified by flash column chromatography on silica gel using the indicated eluent system to afford the desired product (**7**).

2,2-Dichloro-*N*-((1*R*,2*R*)-1-hydroxy-1-(4-nitrophenyl)-3-(*p*-tolyloxy)propan-2-yl)acetamide (7a)

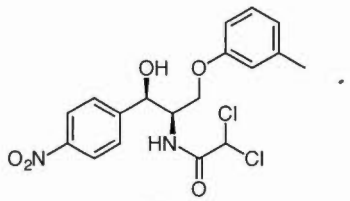


7a

The general procedure was followed on a 0.060 mmole scale starting from **5a**. The crude product was purified on silica gel (2% MeOH/DCM) to afford **7a** as a white solid (10 mg, 40%): m.p. 184°C; R_f 0.51 (10% MeOH/DCM); ^{1}H-NMR (300 MHz, MeOD-d4/CH_2Cl_2) δ 8.19 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 6.85 (d, *J* = 8.3 Hz, 2H),

6.24 (s, 1H), 5.23 (d, J =2.3 Hz, 1H), 4.58 (s(br), 1H), 4.50-4.40 (m, 1H), 4.25 (dd, J = 9.5, 6.6 Hz, 1H), 4.00 (dd, J = 9.5, 6.3 Hz, 1H), 2.27 (s, 3H); ^{13}C-NMR (75 MHz, MeOD-d4) δ 165.3, 156.4, 149.8, 147.3, 130.2, 129.5, 127.1, 122.8, 114.3, 70.1, 66.5, 65.9, 55.0, 19.1; HRMS (ESI) calcd for $C_{18}H_{18}Cl_2N_2O_5$: 412.0593, found 413.0647 $[M+H]^+$.

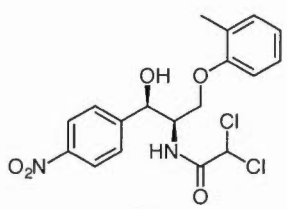
2,2-Dichloro-*N*-((1*R*,2*R*)-1-hydroxy-1-(4-nitrophenyl)-3-(*m*-tolyloxy)propan-2-yl)acetamide (7b)



7b

The general procedure was followed on a 0.071 mmole scale starting from **5b**. The crude product was purified on silica gel (1% MeOH/DCM) to afford **7b** as a white solid (22 mg, 75%): m.p. 150°C; R_f 0.52 (10% MeOH/DCM); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.26-8.22 (m, 2H), 7.60 (t, J = 8.5 Hz, 2H), 7.28-7.16 (m, 2H), 6.89-6.74 (m, 3H), 5.84 (s, 1H), 5.40 (d, J = 2.8 Hz, 1H), 4.51-4.44 (m, 1H), 4.27-4.17 (m, 2H), 3.23 (s(br), 1H), 2.37 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 164.5, 157.7, 147.7, 147.5, 140.0, 129.6, 126.9, 123.8, 122.9, 115.5, 111.5, 72.1, 67.5, 66.1, 54.6, 21.5; HRMS (ESI) calcd for $C_{18}H_{18}Cl_2N_2O_5$: 412.0593, found 413.0685 $[M+H]^+$.

2,2-Dichloro-*N*-((1*R*,2*R*)-1-hydroxy-1-(4-nitrophenyl)-3-(*o*-tolyloxy)propan-2-yl)acetamide (7c)

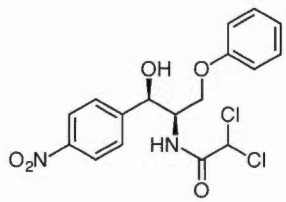


7c

The general procedure was followed on a 0.0716 mmole scale starting from **5c**. The crude product was purified on silica gel (1% MeOH/DCM) to afford **7c** as a white solid (20 mg, 68%): m.p. 119°C; R_f 0.51 (10% MeOH/DCM); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 8.7

Hz, 2H), 7.64 (d, *J* = 8.6 Hz, 2H), 7.30-7.22 (m, 3H), 6.99 (t, *J* = 7.0 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 5.87 (s, 1H), 5.45 (d, *J* = 2.7 Hz, 1H), 4.56-4.52 (m, 1H), 4.28 (d, *J* = 4.6 Hz, 2H), 3.27 (s(br), 1H), 2.31 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 164.8, 155.8, 147.8, 147.4, 131.2, 127.2, 126.8, 126.46, 126.43, 123.8, 121.9, 111.3, 72.5, 67.7, 66.1, 54.6, 16.4; HRMS (ESI) calcd for $C_{18}H_{18}Cl_2N_2O_5$: 412.0593, found 413.0654 $[M+H]^+$.

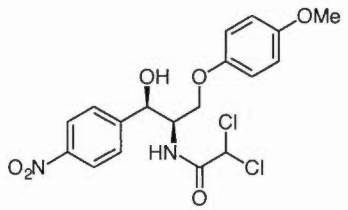
2,2-Dichloro-*N*-((1*R*,2*R*)-1-hydroxy-1-(4-nitrophenyl)-3-phenoxypropan-2-yl)acetamide (7d)



7d

The general procedure was followed on a 0.060 mmole scale starting from **5d**. The crude product was purified on silica gel (2% MeOH/DCM) to afford **7d** as a white solid (18 mg, 75%): m.p. 200°C; R_f 0.50 (10% MeOH/DCM); ^{1}H-NMR (300 MHz, $(CD_3)_2CO$) δ 8.19-8.15 (m, 2H), 7.73-7.71 (m 3H), 7.30-7.24 (m, 2H), 6.97-6.91 (m, 3H), 6.35 (s, 1H), 5.46-5.34 (m, 1H), 5.39-5.37 (m, 1H), 4.56-4.47 (m, 1H), 4.30 (dd, *J* = 9.6, 7.0 Hz, 1H), 4.08 (dd, *J* = 9.6, 5.9 Hz, 1H); ^{13}C-NMR (75 MHz, $(CD_3)_2CO$) δ 163.8, 158.6, 149.9, 147.3, 129.5, 127.4, 124.9, 123.0, 121.0, 114.7, 70.2, 66.5, 66.4, 54.9; HRMS (ESI) calcd for $C_{17}H_{16}Cl_2N_2O_5$: 398.0436, found 399.0521 $[M+H]^+$.

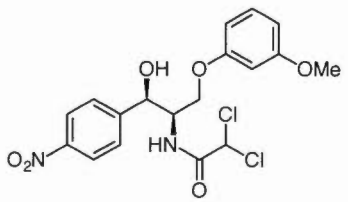
2,2-Dichloro-*N*-((1*R*,2*R*)-1-hydroxy-3-(4-methoxyphenoxy)-1-(4-nitrophenyl)propan-2-yl)acetamide (7e)



7e

The general procedure was followed on a 0.0704 mmole scale starting from **5e**. The crude product was purified on silica gel (1% MeOH/DCM) to afford **7e** as a white solid (13 mg, 43%): m.p. 150-152°C; R_f 0.50 (10% MeOH/DCM); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.23-8.18 (m, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 8.8 Hz, 1H), 6.90-6.83 (m, 4H), 5.82 (s, 1H), 5.37 (d, *J* = 2.8 Hz, 1H), 4.45-4.41 (m, 1H), 4.21-4.10 (m, 2H), 3.78 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 164.4, 154.8, 151.8, 147.7, 147.5, 126.8, 123.7, 115.8, 115.7, 114.9, 72.1, 68.5, 66.1, 55.7, 54.6; HRMS (ESI) calcd for $C_{18}H_{18}Cl_2N_2O_6$: 428.0542, found 429.0592 $[M+H]^+$.

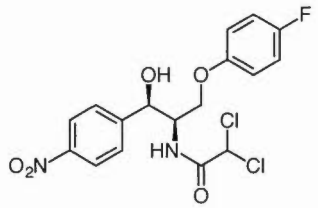
2,2-Dichloro-*N*-((1*R*,2*R*)-1-hydroxy-3-(3-methoxyphenoxy)-1-(4-nitrophenyl)propan-2-yl)acetamide (7f)



7f

The general procedure was followed on a 0.071 mmole scale starting from **5f**. The crude product was purified on silica gel (1% MeOH/DCM) to afford **7f** as a white solid (21 mg, 69%): m.p. 119°C; R_f 0.51 (10% MeOH/DCM); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.20-8.17 (m, 2H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.23-7.10 (m, 2H), 6.58-6.46 (m, 3H), 5.80 (s, 1H), 5.35 (d, *J* = 2.8 Hz, 1H), 4.46-4.41 (m, 1H), 4.19-4.14 (m, 2H), 3.78 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 164.5, 161.0, 158.9, 147.7, 147.5, 130.3, 126.8, 123.7, 107.4, 106.7, 101.3, 71.9, 67.3, 66.0, 55.4, 54.5; HRMS (ESI) calcd for $C_{18}H_{18}Cl_2N_2O_6$: 428.0542, found 429.0614 $[M+H]^+$.

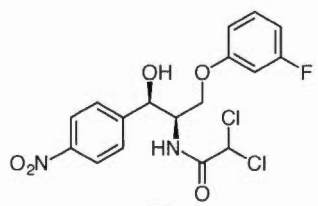
2,2-Dichloro-*N*-((1*R*,2*R*)-3-(4-fluorophenoxy)-1-hydroxy-1-(4-nitrophenyl)propan-2-yl)acetamide (7g)



7g

The general procedure was followed on a 0.057 mmole scale starting from **5g**. The crude product was purified on silica gel (2% MeOH/DCM) to afford **7g** as a white solid (10 mg, 42%): m.p. 196°C; R_f 0.50 (10% MeOH/DCM); ^{1}H-NMR (600 MHz, $(CD_3)_2CO$) δ 8.23-8.19 (m, 2H), 7.82 (d, *J* = 8.6 Hz, 1H), 7.75 (d, *J* = 8.7 Hz, 2H), 7.08-6.99 (m, 4H), 6.38 (s, 1H), 5.55 (s(br), 1H), 5.39 (d, *J* = 1.8 Hz, 1H), 4.54-4.52 (m, 1H), 4.31 (dd, *J* = 9.6, 6.9 Hz, 1H), 4.10 (dd, *J* = 9.5, 6.1 Hz, 1H), 3.31 (d, *J* = 4.3 Hz, 1H); ^{13}C-NMR (150 MHz, $(CD_3)_2CO$) δ 163.8, 158.2, 156.6, 154.9, 149.9, 147.3, 127.4, 123.0, 116.1, 116.0, 115.8, 115.6, 70.2, 67.3, 66.5, 54.9; HRMS (ESI) calcd for $C_{17}H_{15}Cl_2FN_2O_5$: 416.0342, found 417.0416 $[M+H]^+$.

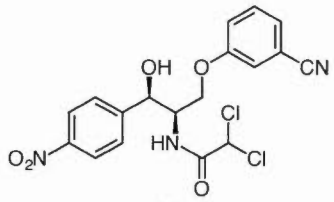
2,2-Dichloro-*N*-((1*R*,2*R*)-3-(3-fluorophenoxy)-1-hydroxy-1-(4-nitrophenyl)propan-2-yl)acetamide (7h)



7h

The general procedure was followed on a 0.055 mmole scale starting from **5h**. The crude product was purified on silica gel (2% MeOH/DCM) to afford **7h** as a white solid (13 mg, 57%): m.p. 177°C; R_f 0.53 (10% MeOH/DCM); ^{1}H-NMR (600 MHz, $(CD_3)_2CO$) δ 8.22-8.19 (m, 2H), 7.78-7.73 (m, 3H), 7.33-7.29 (m, 1H), 7.06-6.99 (m, 1H), 6.83-6.73 (m, 2H), 6.37 (s, 1H), 5.48-5.40 (m, 1H), 5.39 (s(br), 1H), 4.57-4.52 (m, 1H), 4.37-4.29 (m, 1H), 4.21-4.08 (m, 1H); ^{13}C-NMR (150 MHz, $(CD_3)_2CO$) δ 164.4, 163.8, 162.8, 160.1, 149.8, 147.3, 130.6, 127.5, 124.9, 123.1, 116.0, 110.8, 107.6, 70.1, 67.0, 65.5, 54.7; HRMS (ESI) calcd for $C_{17}H_{15}Cl_2FN_2O_5$: 416.0342, found 417.0413 $[M+H]^+$.

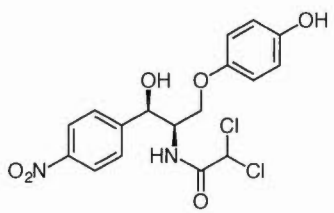
2,2-Dichloro-*N*-((1*R*,2*R*)-3-(3-cyanophenoxy)-1-hydroxy-1-(4-nitrophenyl)propan-2-yl)acetamide (7i)



7i

The general procedure was followed on a 0.0510 mmole scale starting from **5i**. The crude product was purified on silica gel (1% MeOH/DCM) to afford **7i** as a white solid (18 mg, 83%): m.p. 190-195°C; R_f 0.54 (10% MeOH/DCM); ^{1}H-NMR (300 MHz, $(CD_3)_2CO$) δ 8.25-8.19 (m, 2H), 7.84-7.74 (m, 3H), 7.53 (t, *J* = 7.9 Hz, 1H), 7.41-7.33 (m, 2H), 6.38 (s, 1H), 5.52-5.50 (m, 1H), 5.44-5.42 (m, 1H), 4.64-4.56 (m, 1H), 4.46 (dd, *J* = 9.5, 6.5 Hz, 1H), 4.25 (dd, *J* = 9.7, 6.3 Hz, 1H); ^{13}C-NMR (75 MHz, $(CD_3)_2CO$) δ 163.8, 158.8, 149.7, 147.4, 130.8, 127.4, 124.8, 123.1, 120.2, 118.2, 117.6, 113.2, 70.2, 67.1, 66.5, 54.7; HRMS (ESI) calcd for $C_{18}H_{15}Cl_2N_3O_5$: 423.0389, found 424.0454 $[M+H]^+$.

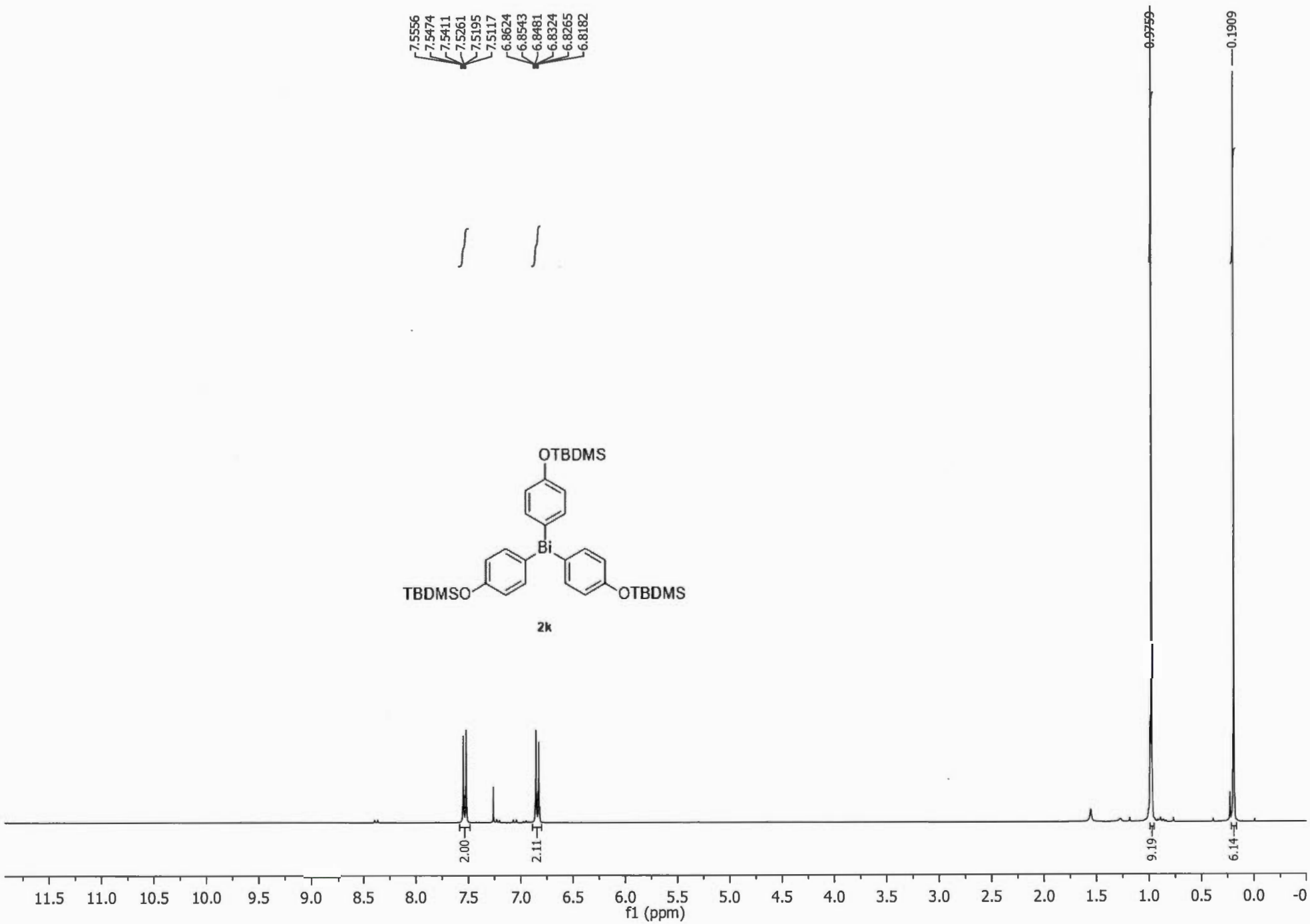
2,2-Dichloro-*N*-((1*R*,2*R*)-1-hydroxy-3-(4-hydroxyphenoxy)-1-(4-nitrophenyl)propan-2-yl)acetamide (7j)



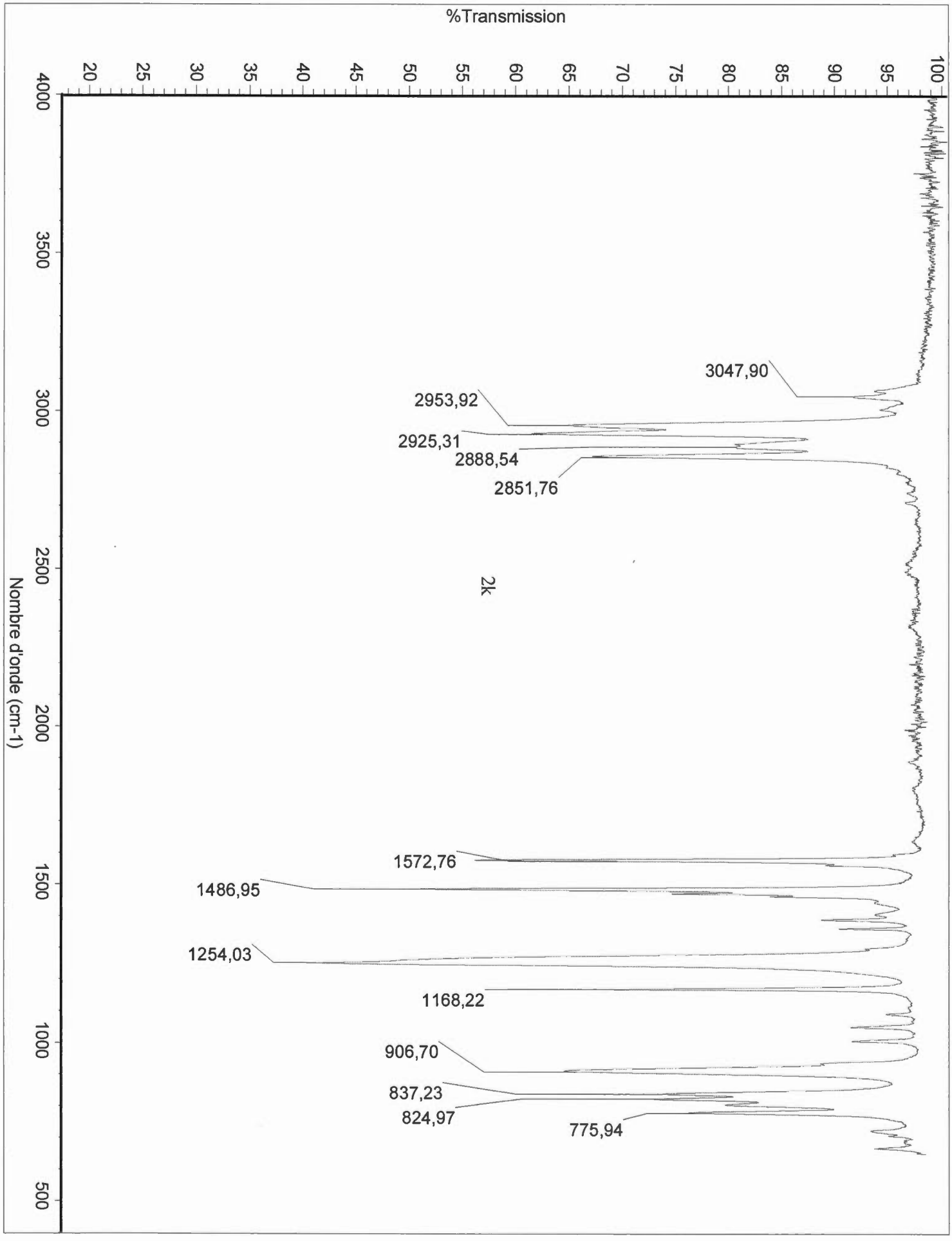
7j

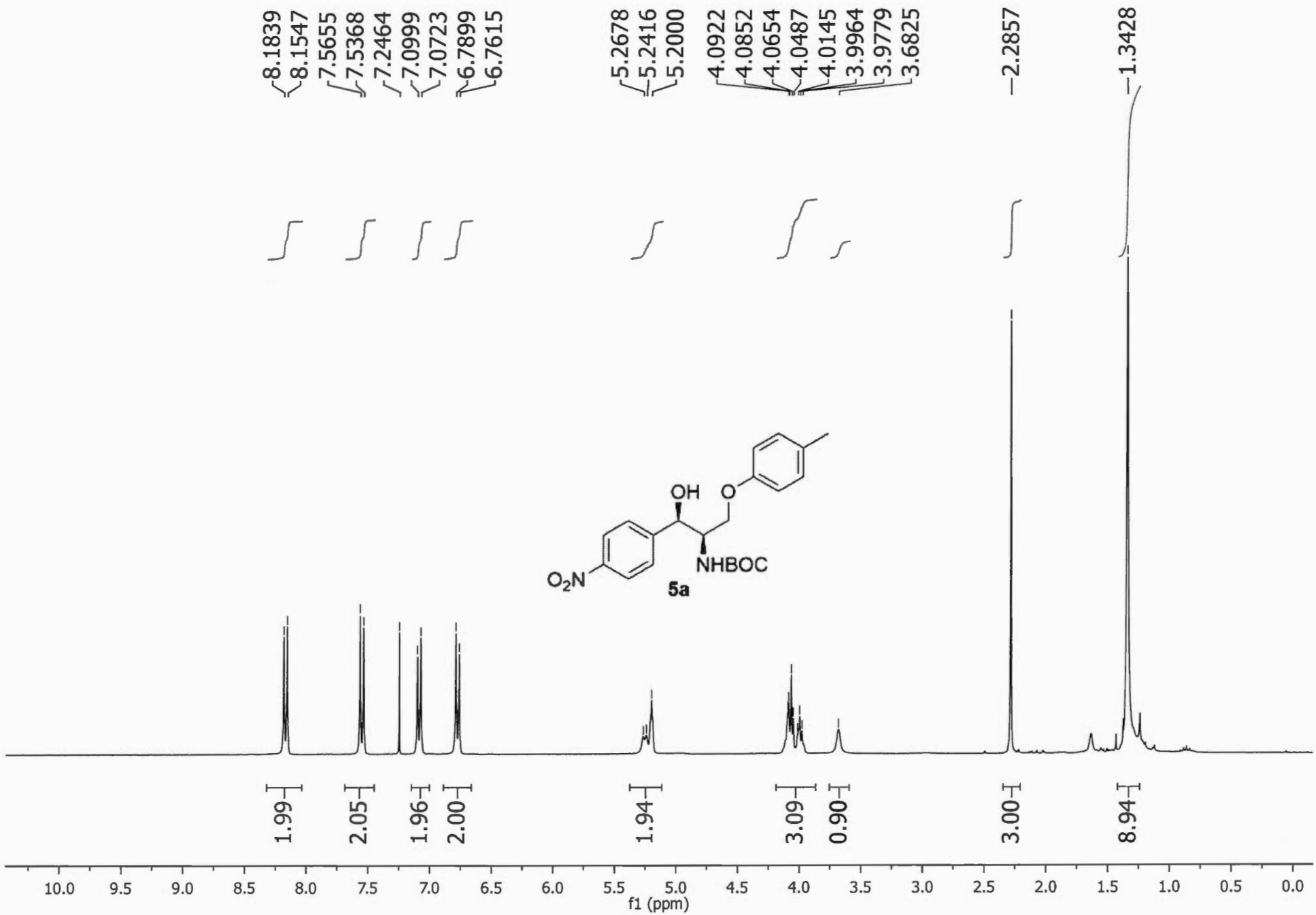
The general procedure was followed on a 0.067 mmole scale starting from **5k**. The crude product was purified on silica gel (1% MeOH/DCM) to afford **7j** as a white solid (20 mg, 72%): m.p. 163.5°C; R_f 0.53 (10% MeOH/DCM); ^{1}H-NMR (300 MHz, $(CD_3)_2CO$) δ 8.23-8.19 (m, 2H), 7.99 (s(br), 1H), 7.76-7.73 (m, 3H), 6.86-6.76 (m, 4H), 6.39 (s, 1H), 5.45 (s(br), 1H), 5.38 (s(br), 1H), 4.54-4.46 (m, 1H), 4.23 (dd, *J* = 9.6, 7.1 Hz, 1H), 4.03 (dd, *J* = 9.6, 5.9 Hz, 1H); ^{13}C-NMR (75 MHz, $(CD_3)_2CO$) δ 163.7, 151.84, 151.81, 150.0, 147.3, 127.4, 123.0, 115.9, 115.8, 70.2, 67.3, 66.5, 55.0; HRMS (ESI) calcd for $C_{17}H_{16}Cl_2N_2O_6$: 414.0385, found 415.0477 $[M+H]^+$.

5. ^{1}H-NMR and ^{13}C-NMR Spectra


7.5556
7.5474
7.5411
7.5261
7.5195
7.5117
6.8624
6.8543
6.8481
6.8324
6.8265
6.8182
0.0759
0.1909
OTBDMS
Bi
TBDMSO
OTBDMS
2k
2.00
2.11
9.19
6.14
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

TBDMSO
Bi
OTBDMS
OTBDMS
2k
155.4818
146.0639
138.8465
122.5313
25.8263
18.3437
-4.2183
f1 (ppm)


%Transmission
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
4000
3500
3000
2500
2000
1500
1000
500
Nombre d'onde (cm-1)
3047,90
2953,92
2925,31
2888,54
2851,76
2k
1572,76
1486,95
1254,03
1168,22
906,70
837,23
824,97
775,94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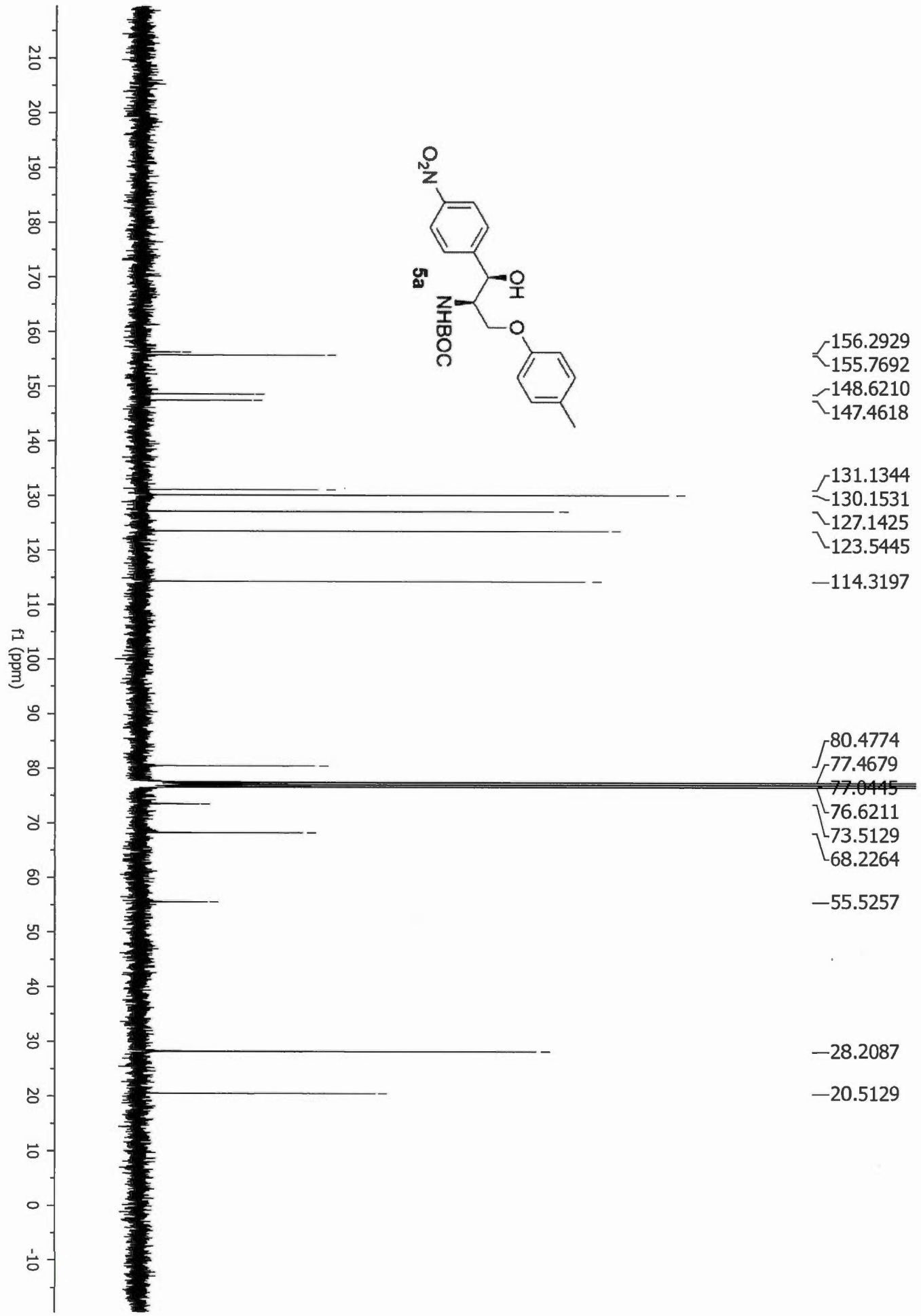
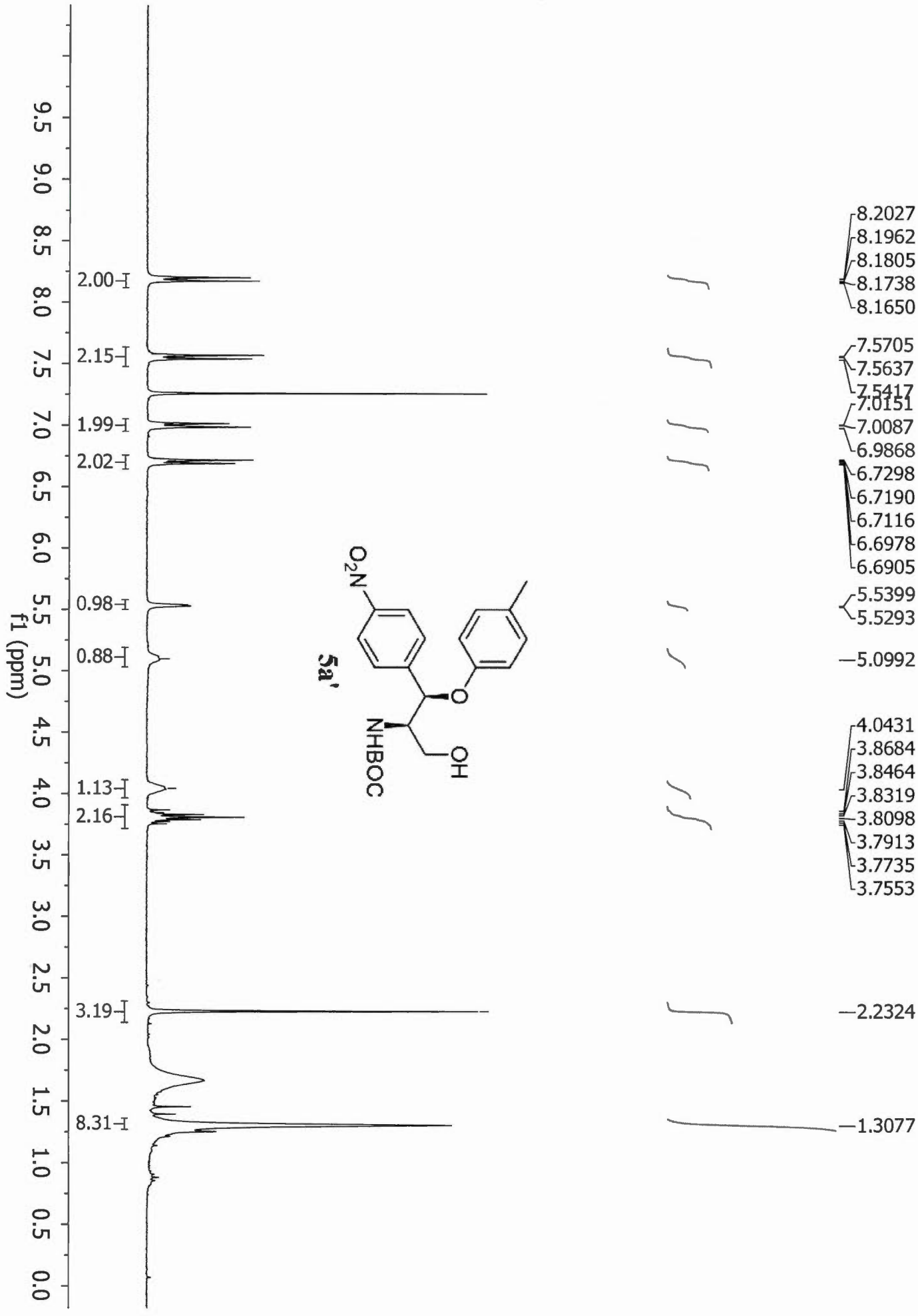
8.1547
7.5655
7.5368
7.2464
7.0999
7.0723
6.7899
6.7615
5.2678
5.2416
5.2000
4.0922
4.0852
4.0654
4.0487
4.0145
3.9964
3.9779
3.6825
2.2857
1.3428
OH
O
NHBOC
O2N
5a
1.99
2.05
1.96
2.00
1.94
3.09
0.90
3.00
8.94
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


O2N
OH
NHBOC
O
5a
156.2929
155.7692
148.6210
147.4618
131.1344
130.1531
127.1425
123.5445
114.3197
80.4774
77.4679
77.0445
76.6211
73.5129
68.2264
55.5257
28.2087
20.5129
f1 (ppm)


f1 (ppm)
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2.00
2.15
1.99
2.02
0.98
0.88
1.13
2.16
3.19
8.31
O2N
NHBOC
OH
O
5a'
8.2027
8.1962
8.1805
8.1738
8.1650
7.5705
7.5637
7.5417
7.0151
7.0087
6.9868
6.7298
6.7190
6.7116
6.6978
6.6905
5.5399
5.5293
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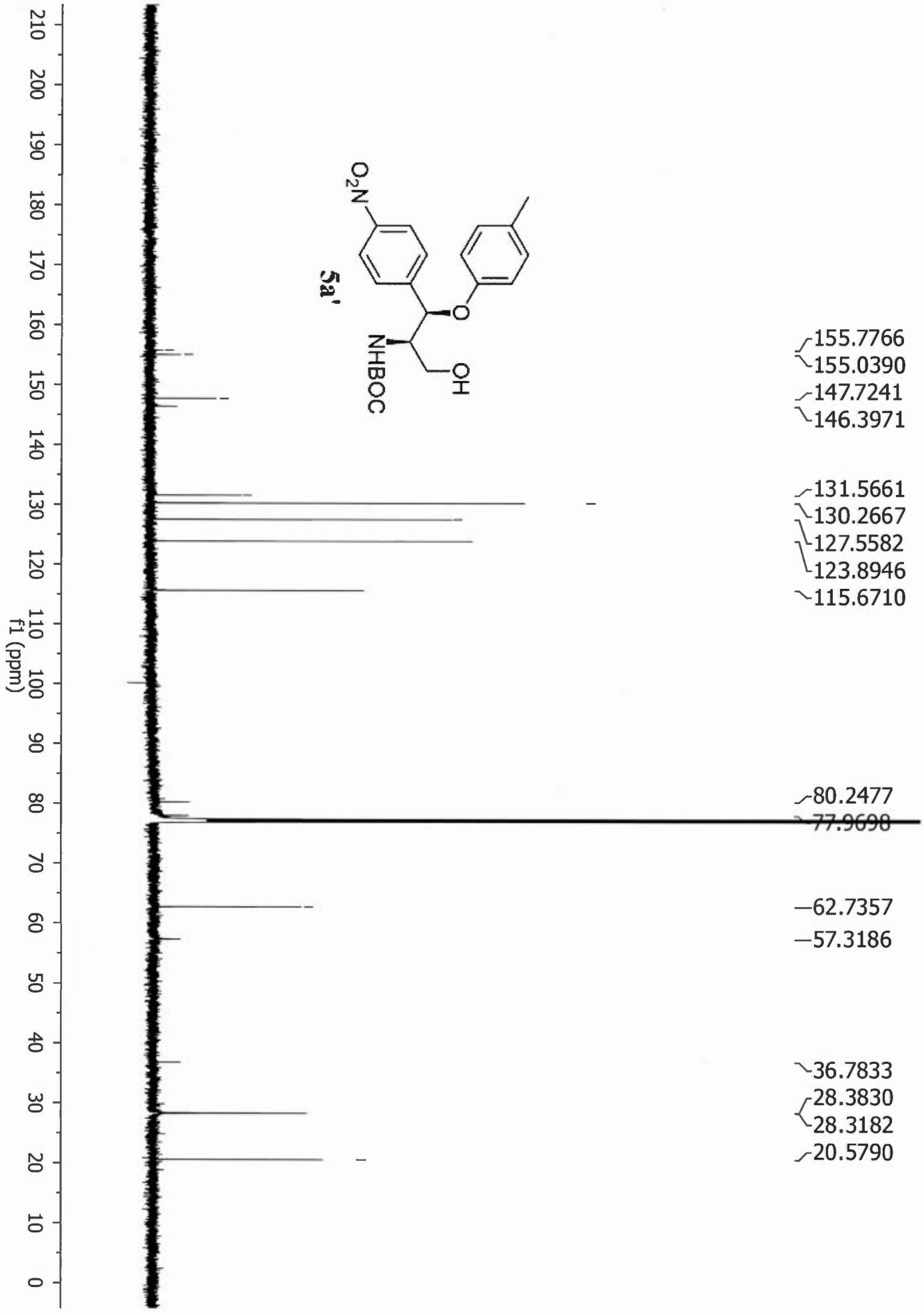
3.7913
3.7735
3.7553
2.2324
1.3077


5a'
O2N
NHBOC
OH
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155.0390
147.7241
146.3971
131.5661
130.2667
127.5582
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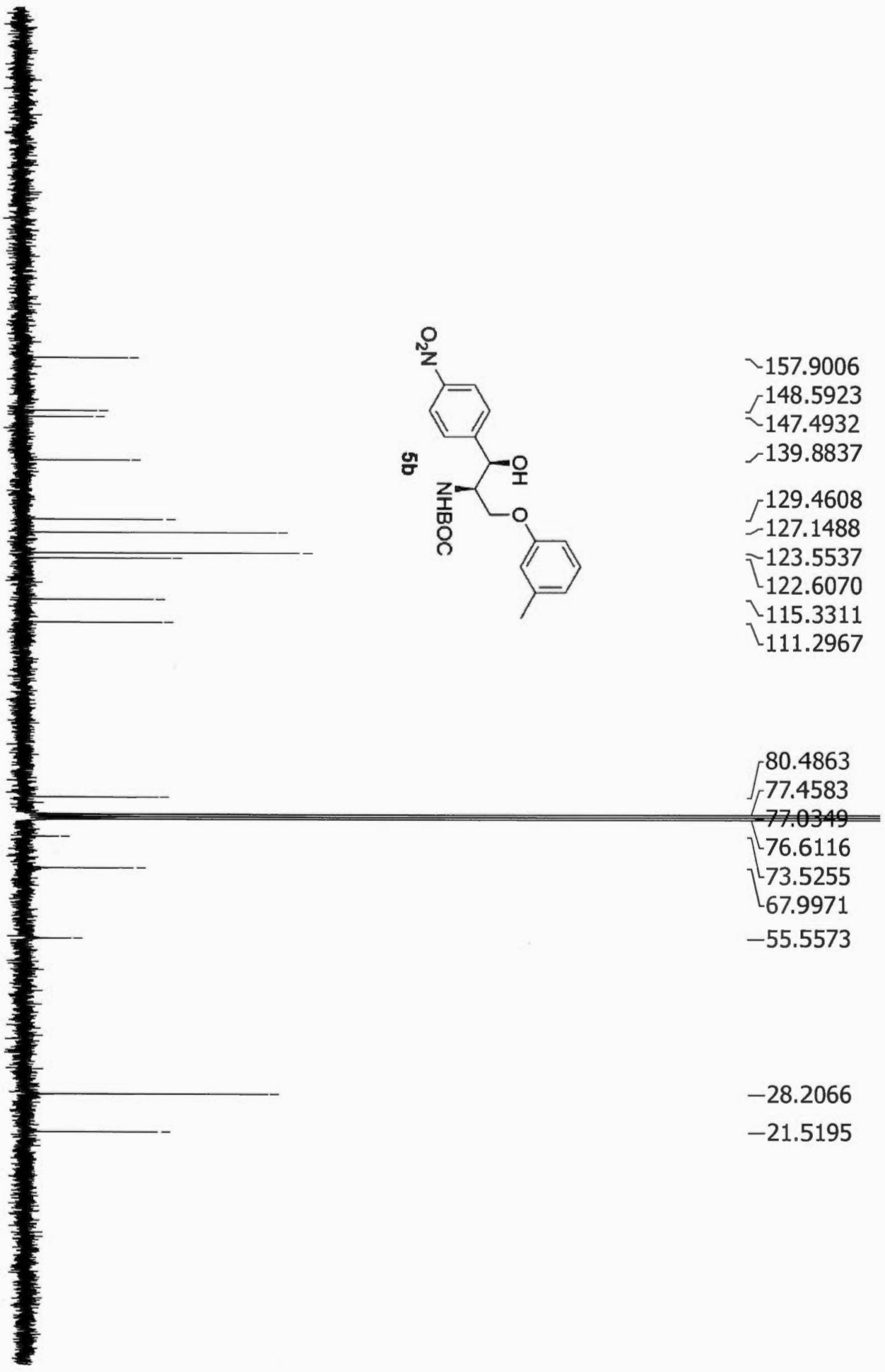
115.6710
80.2477
77.9690
62.7357
57.3186
36.7833
28.3830
28.3182
20.5790
f1 (ppm)

8.2111
8.1819
7.5913
7.5627
7.2595
7.2151
7.1892
7.1635
6.8431
6.8180
6.7168
6.6877
5.2333
5.2210
5.2089
4.1212
4.1008
4.0853
4.0306
3.6264
3.6167
2.3382
1.3623
2.00
2.06
1.84
1.02
1.93
1.99
3.18
1.03
3.10
8.80
O2N
OH
NHBOC
O
5b
f1 (ppm)


O2N
OH
NHBOC
O
5b
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147.4932
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129.4608
127.1488
123.5537
122.6070
115.3311
111.2967
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77.4583
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76.6116
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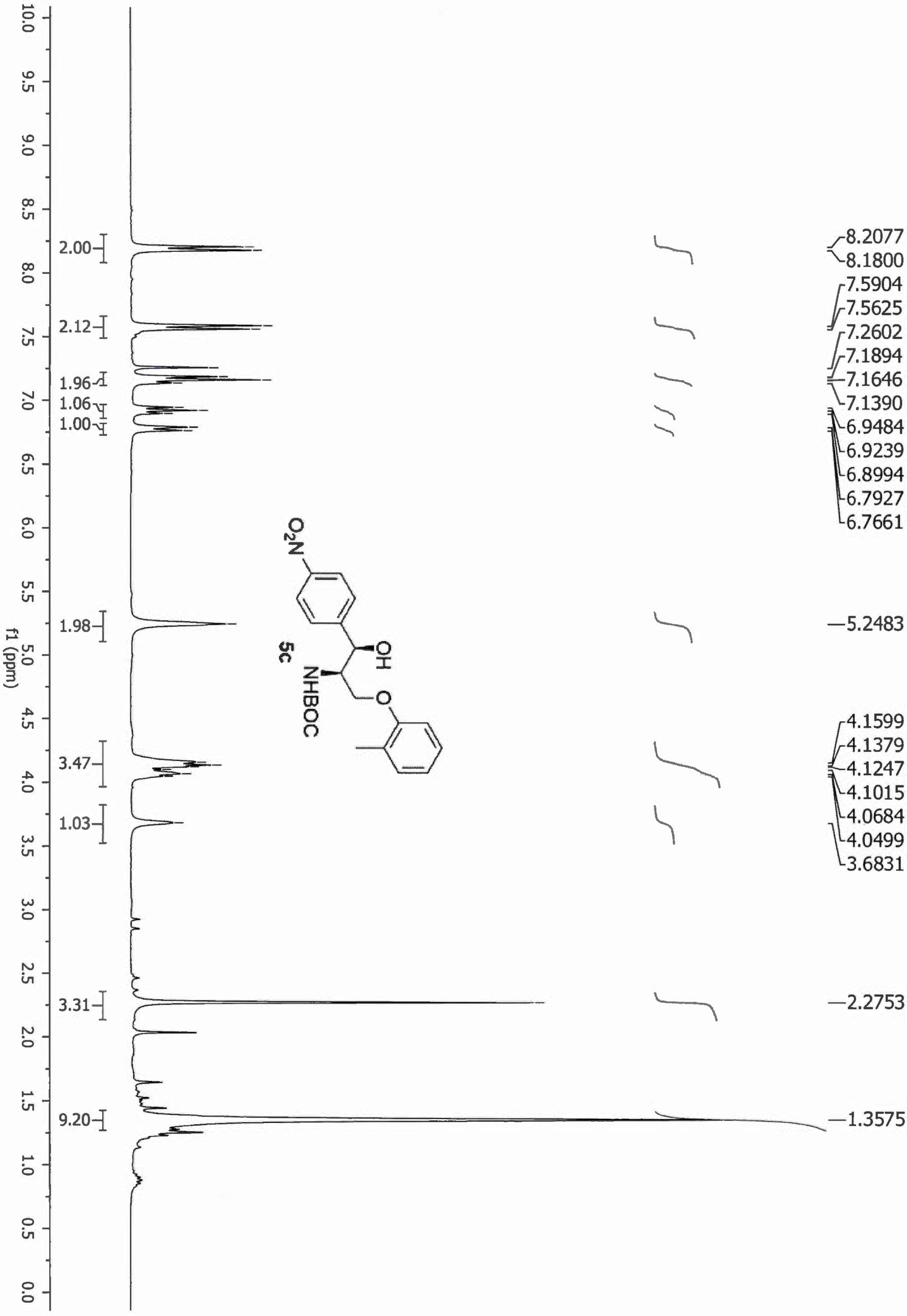
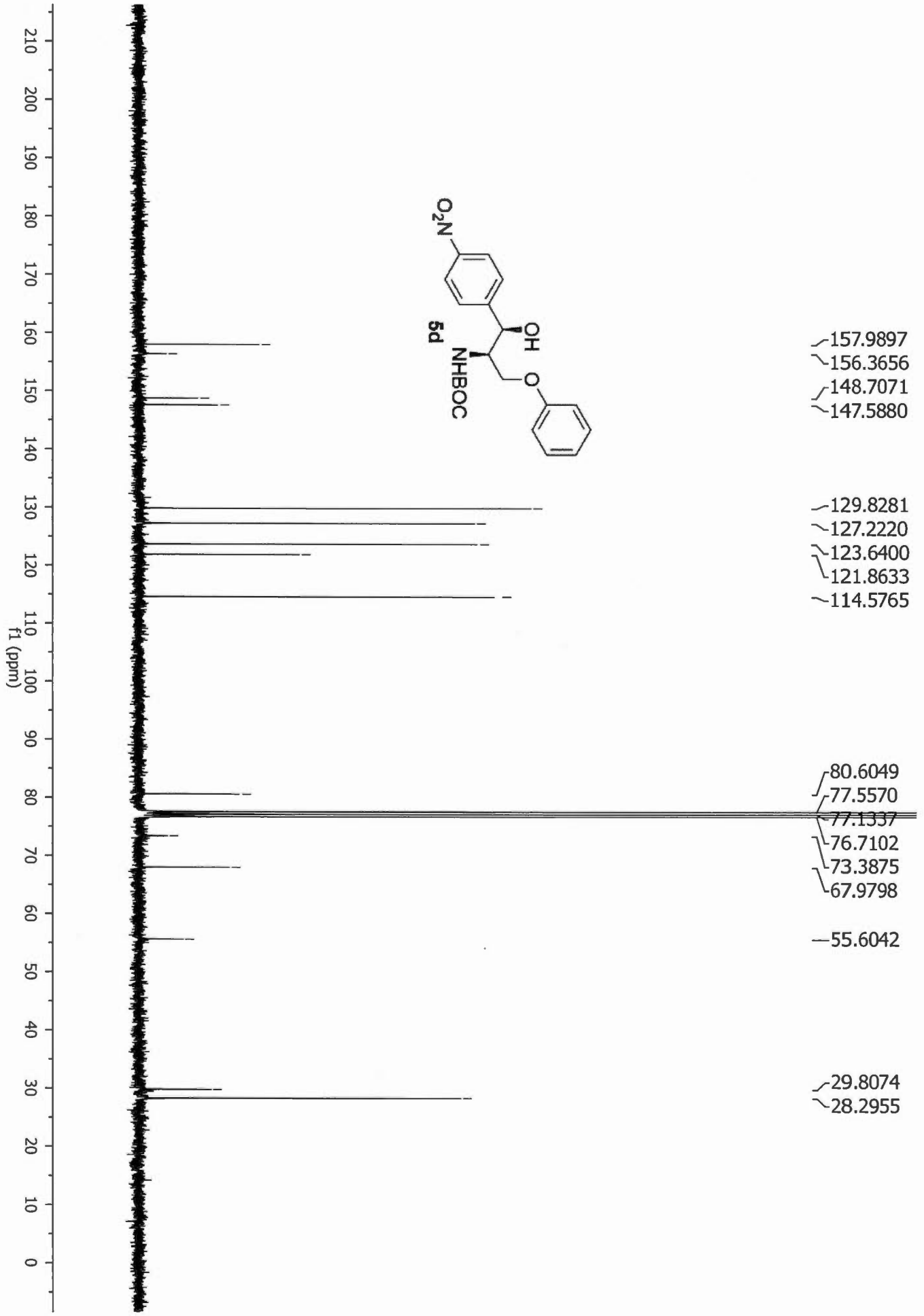
67.9971
55.5573
28.2066
21.5195



5c
NHBOC
OH
O
O2N
f1 (ppm)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2.00
2.12
1.96
1.06
1.00
1.98
3.47
1.03
3.31
9.20
8.2077
8.1800
7.5904
7.5625
7.2602
7.1894
7.1646
7.1390
6.9484
6.9239
6.8994
6.7927
6.7661
5.2483
4.1599
4.1379
4.1247
4.1015
4.0684
4.0499
3.6831
2.2753
1.3575

O2N
OH
NHBOC
O
5c
156.3493
156.1122
148.6613
147.6498
131.1338
127.2708
127.2116
126.5029
123.7049
121.6158
111.1675
80.6309
73.6662
68.4065
55.7301
28.3350
16.5083
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

8.1979
8.1690
7.5819
7.5531
7.3354
7.3078
7.2823
7.2600
7.0330
7.0085
6.9841
6.9108
6.8840
5.2276
5.2174
4.1347
4.1143
4.0982
4.0630
4.0432
4.0250
3.6709
1.3560
2.00
2.13
1.88
0.96
1.88
1.86
3.16
0.90
9.23
f1 (ppm)
O2N
OH
NHBOC
O
5d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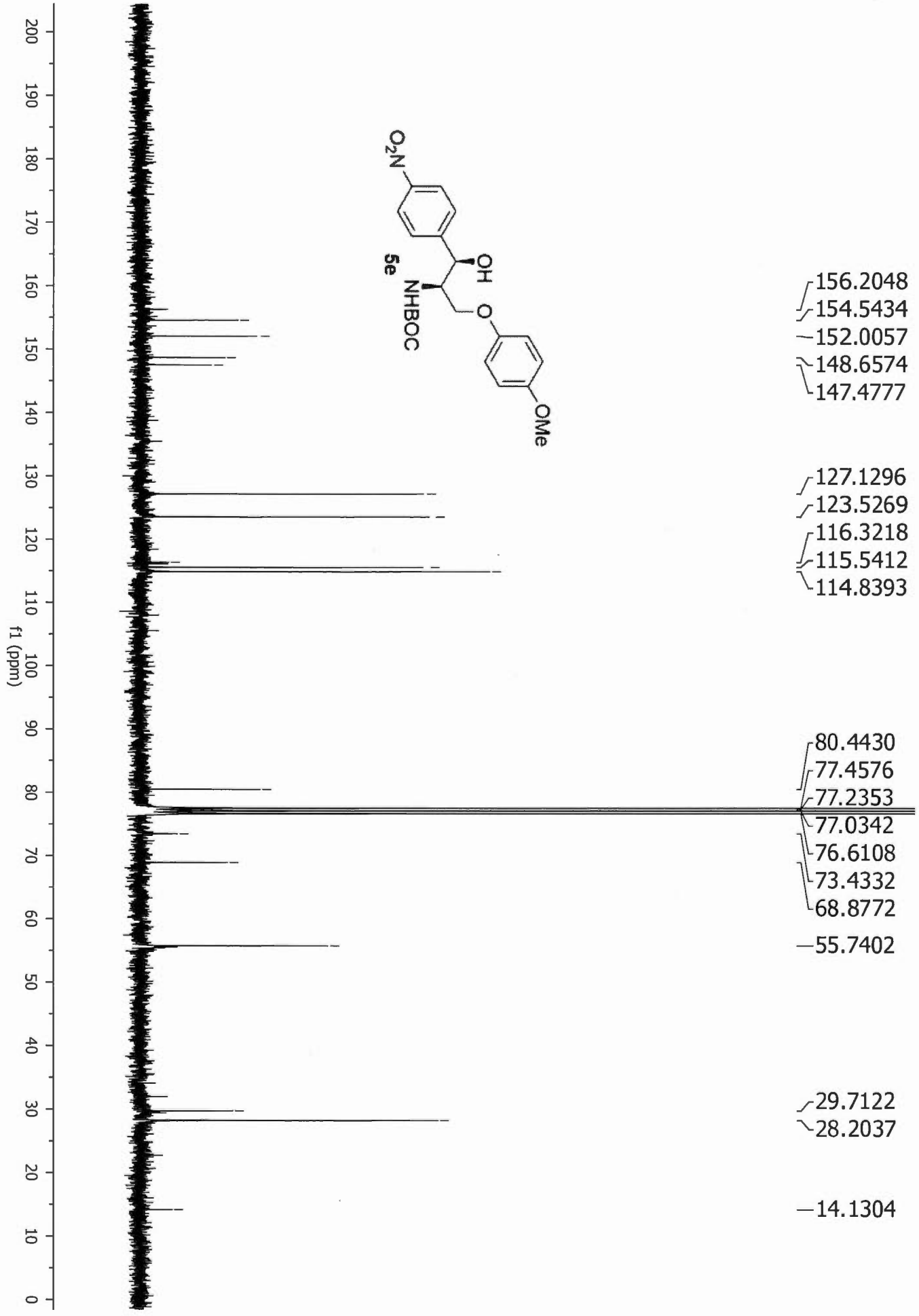
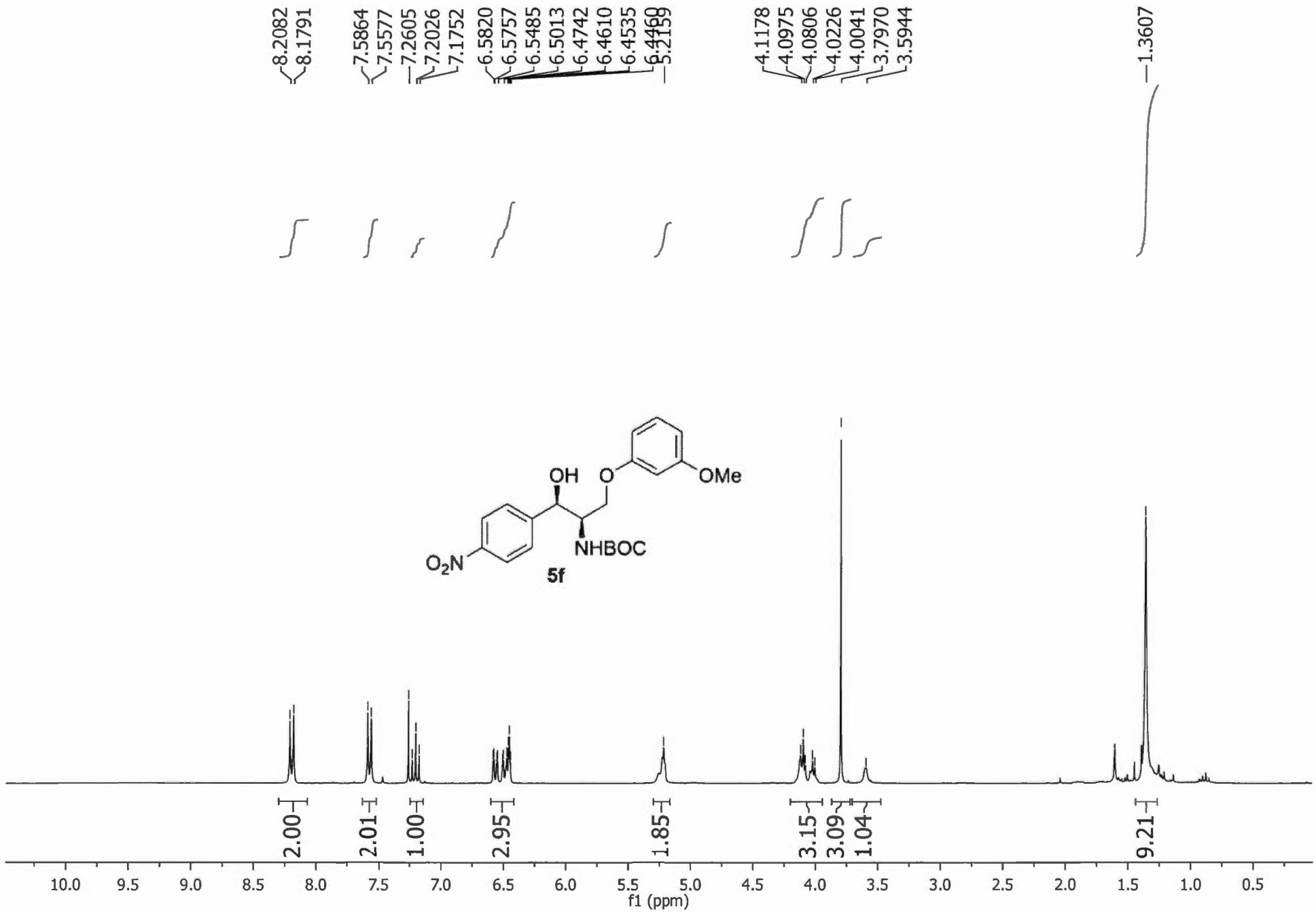
147.5880
129.8281
127.2220
123.6400
121.8633
114.5765
80.6049
77.5570
77.1337
76.7102
73.3875
67.9798
55.6042
29.8074
28.2955
f1 (ppm)
5d
NHBOC
OH
O
O2N

2.00
2.12
3.92
1.80
3.07
3.82
8.85
8.1920
8.1649
7.5747
7.5473
7.2603
6.8331
5.2064
4.0836
4.0598
4.0435
3.9955
3.9763
3.7716
1.3506
O2N
OH
NHBOC
O
OMe
5e
f1 (ppm)


5e
O_2N
OH
NHBOC
O
OMe
156.2048
154.5434
152.0057
148.6574
147.4777
127.1296
123.5269
116.3218
115.5412
114.8393
80.4430
77.4576
77.2353
77.0342
76.6108
73.4332
68.8772
55.7402
29.7122
28.2037
14.1304
f1 (ppm)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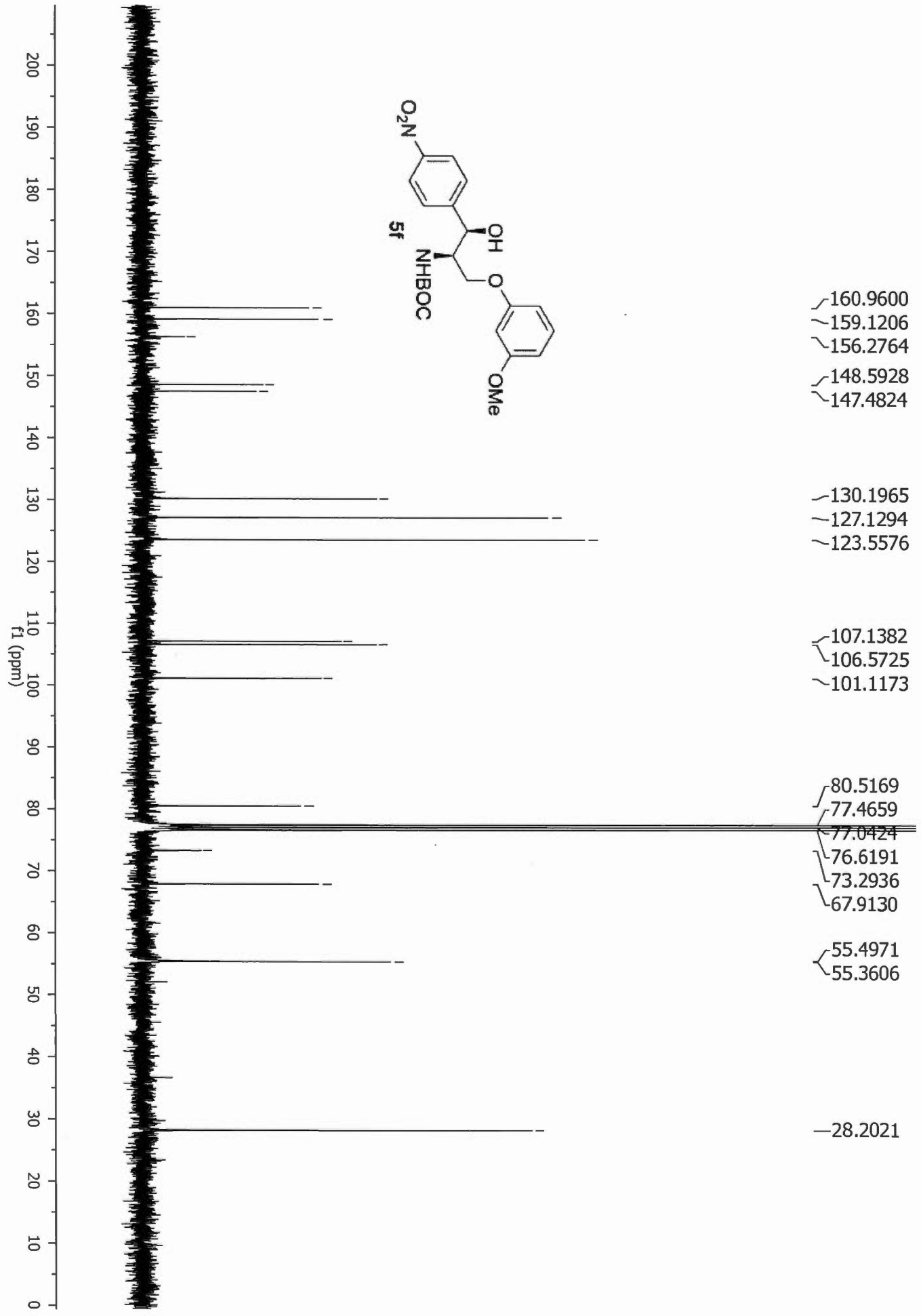
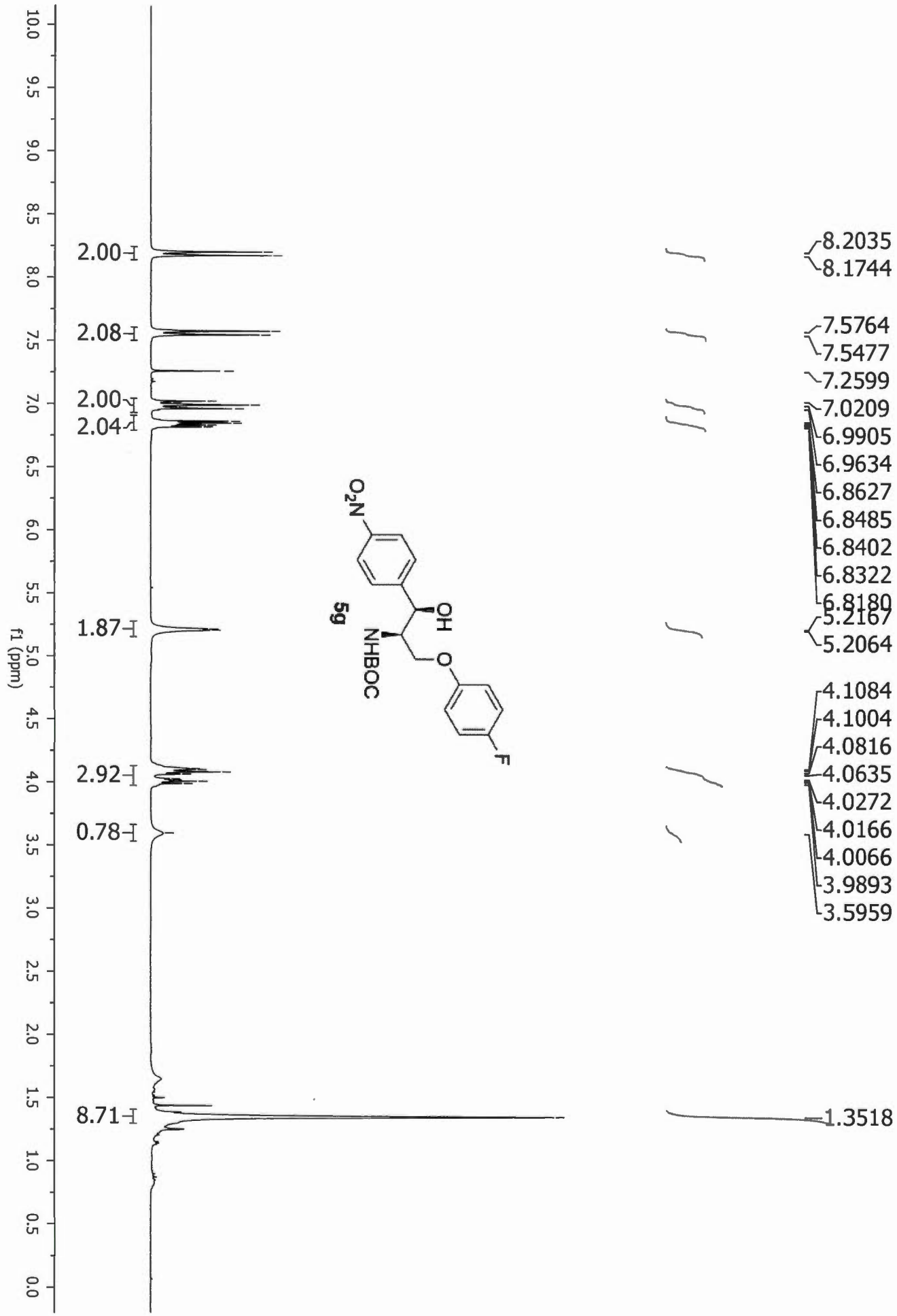
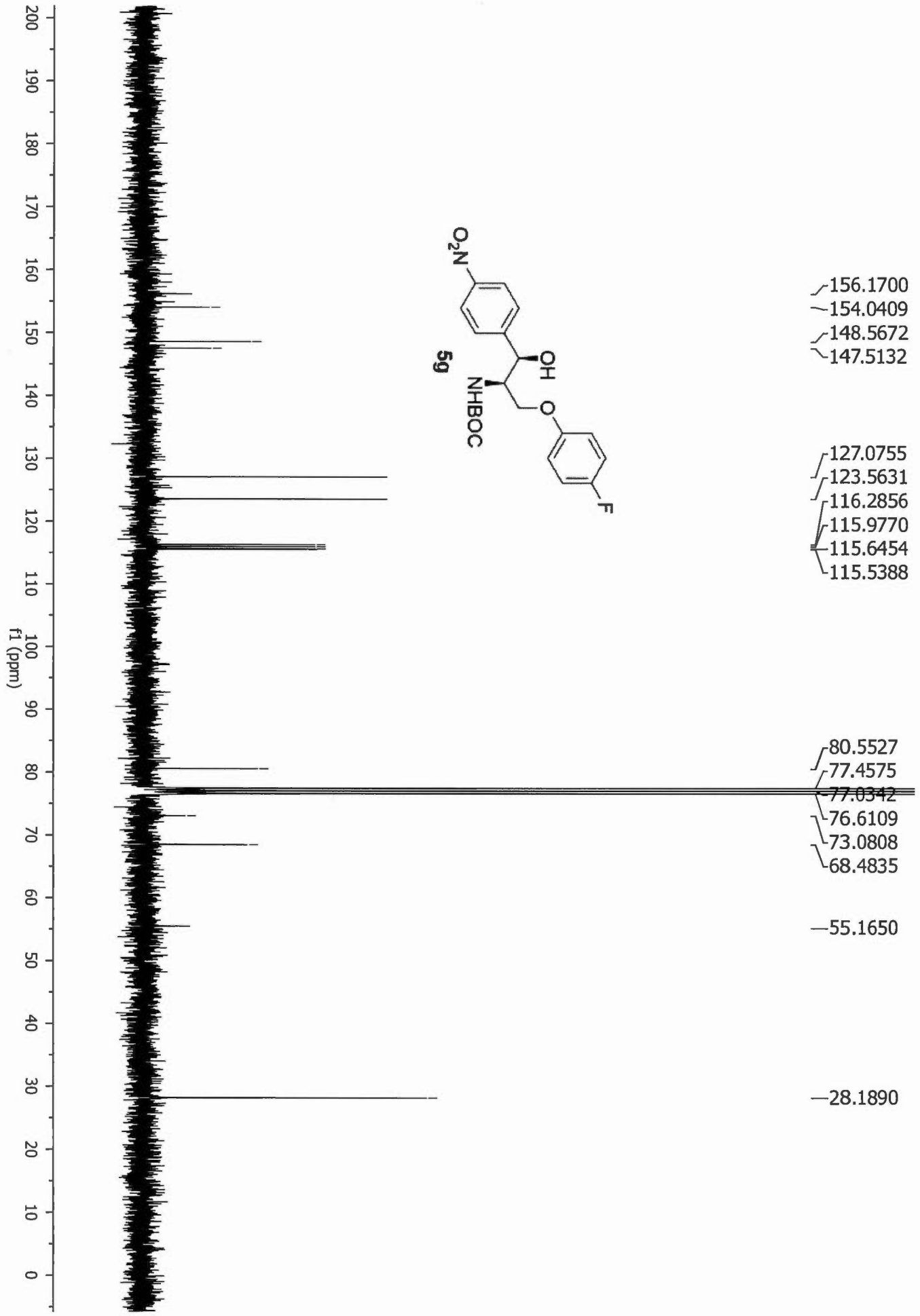
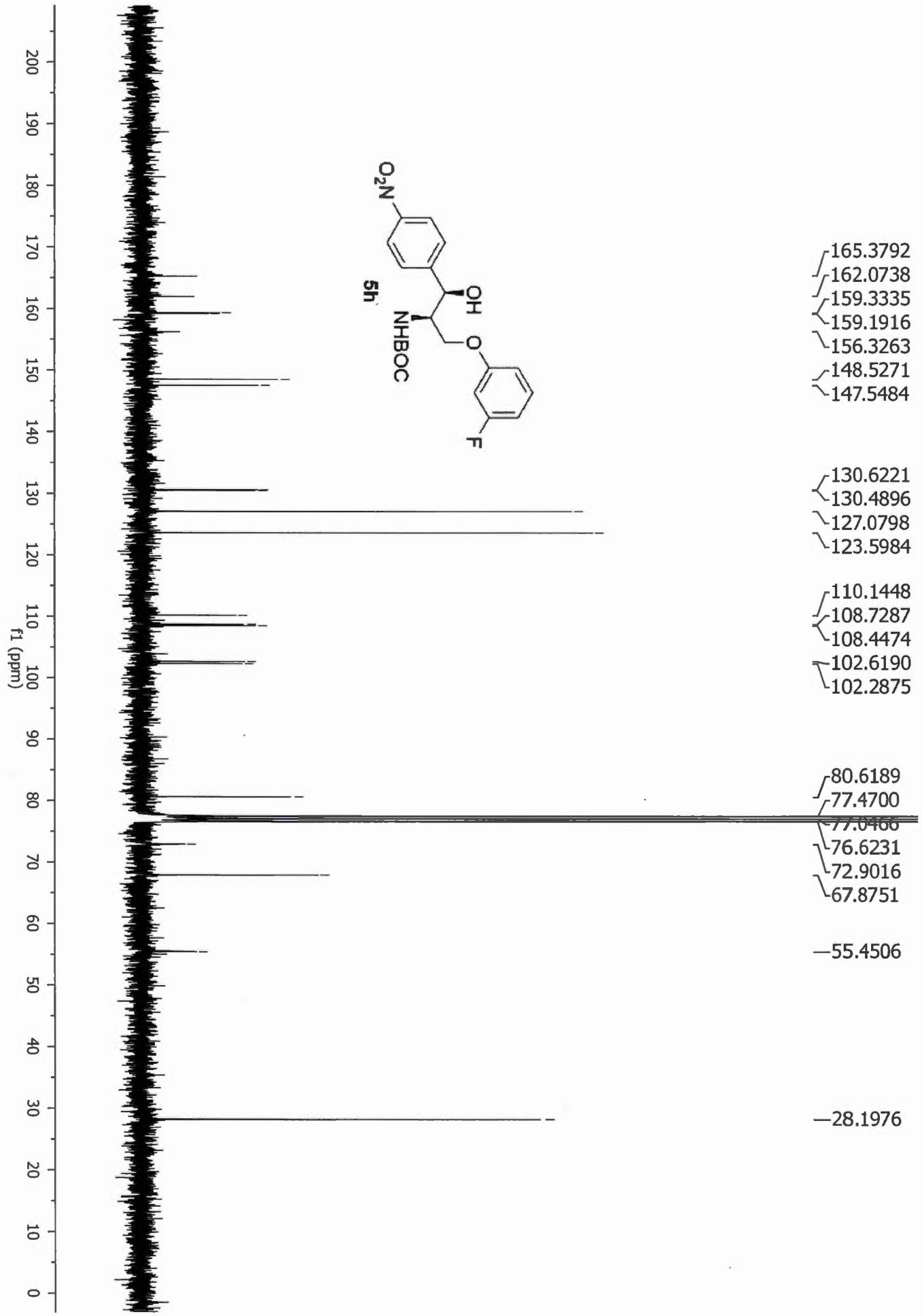
8.1791
7.5864
7.5577
7.2605
7.2026
7.1752
6.5820
6.5757
6.5485
6.5013
6.4742
6.4610
6.4535
6.4469
5.2159
4.1178
4.0975
4.0806
4.0226
4.0041
3.7970
3.5944
1.3607
OH
O
OMe
NHBOC
O2N
5f
2.00
2.01
1.00
2.95
1.85
3.15
3.09
1.04
9.21
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

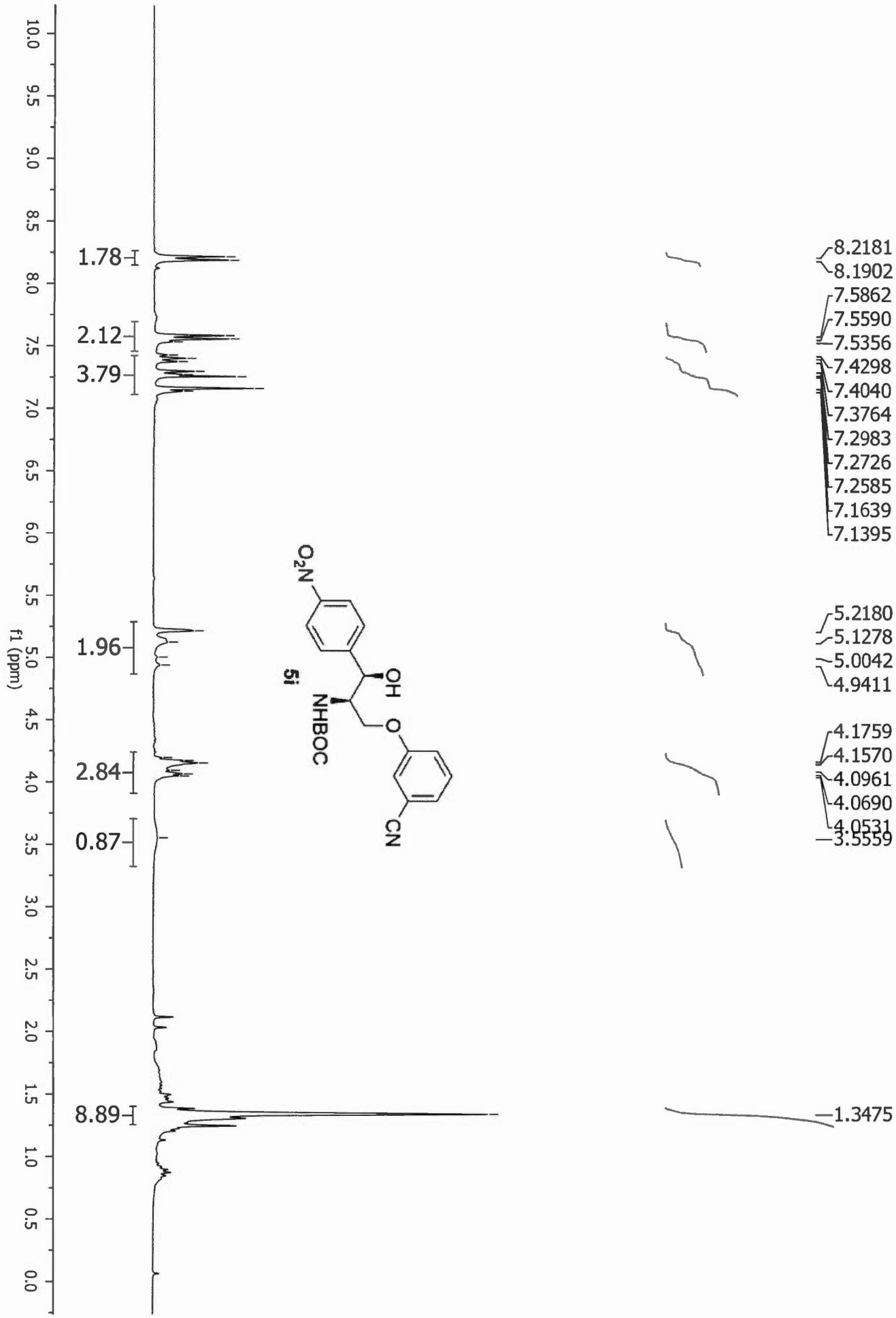

O2N
OH
NHBOC
O
OMe
5f
160.9600
159.1206
156.2764
148.5928
147.4824
130.1965
127.1294
123.5576
107.1382
106.5725
101.1173
80.5169
77.4659
77.0424
76.6191
73.2936
67.9130
55.4971
55.3606
28.2021
f1 (ppm)


f1 (ppm)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2.00
2.08
2.00
2.04
1.87
2.92
0.78
8.71
O2N
OH
NHBOC
O
F
5g
8.2035
8.1744
7.5764
7.5477
7.2599
7.0209
6.9905
6.9634
6.8627
6.8485
6.8402
6.8322
6.8180
5.2167
5.2064
4.1084
4.1004
4.0816
4.0635
4.0272
4.0166
4.0066
3.9893
3.5959
1.3518


156.1700
154.0409
148.5672
147.5132
127.0755
123.5631
116.2856
115.9770
115.6454
115.5388
80.5527
77.4575
77.0342
76.6109
73.0808
68.4835
55.1650
28.1890
f1 (ppm)
O2N
OH
NHBOC
O
F
5g

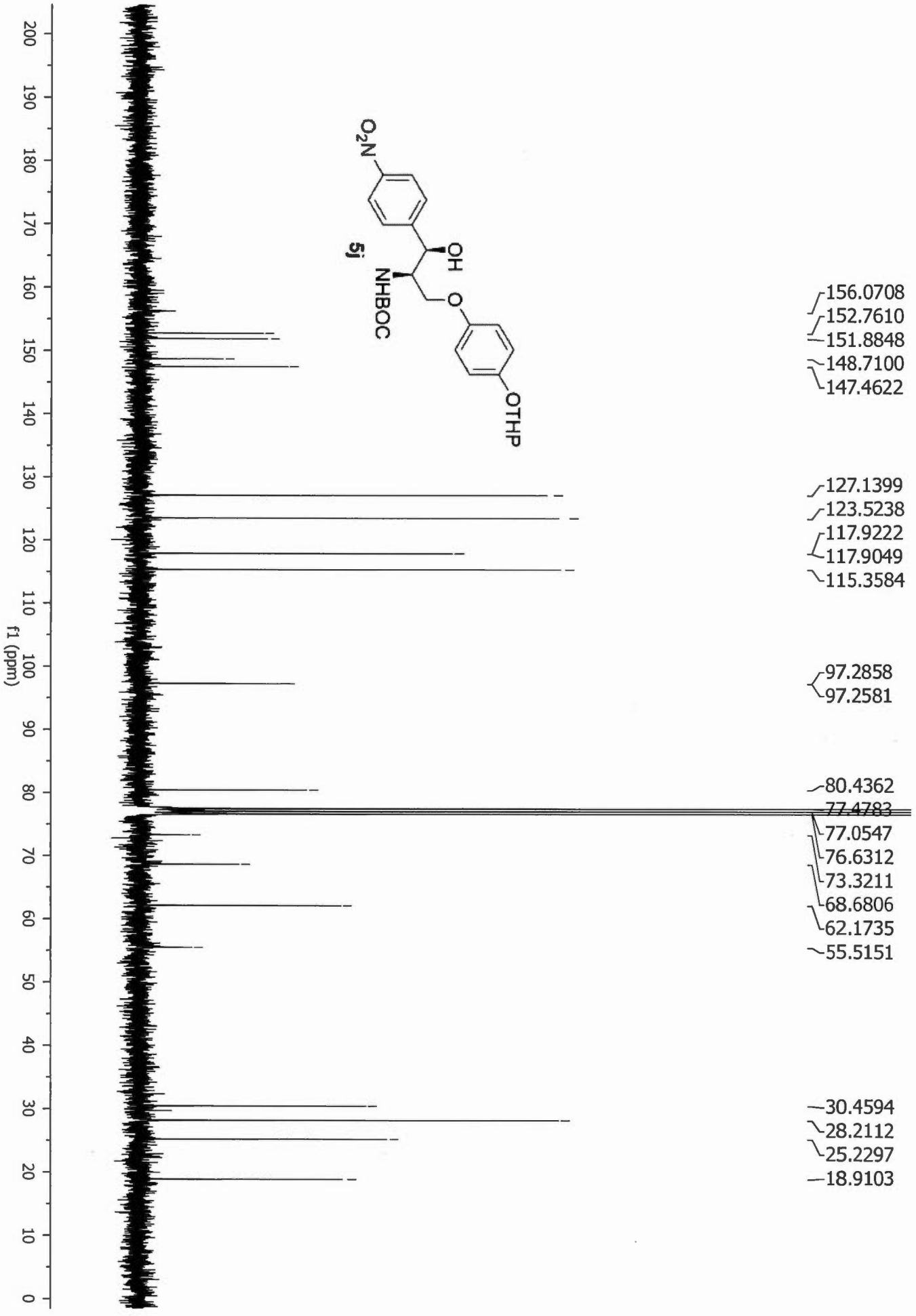
8.2059
8.1767
7.5772
7.5484
7.2602
7.2351
7.2305
6.7160
6.7084
6.7012
6.6921
6.6661
6.6472
6.6396
6.6043
5.2060
4.1245
4.1049
4.0863
4.0417
4.0196
4.0024
3.5428
1.3539
2.00
2.05
1.28
2.87
1.97
3.25
0.97
8.98
f1 (ppm)
O2N
OH
NHBOC
O
F
5h

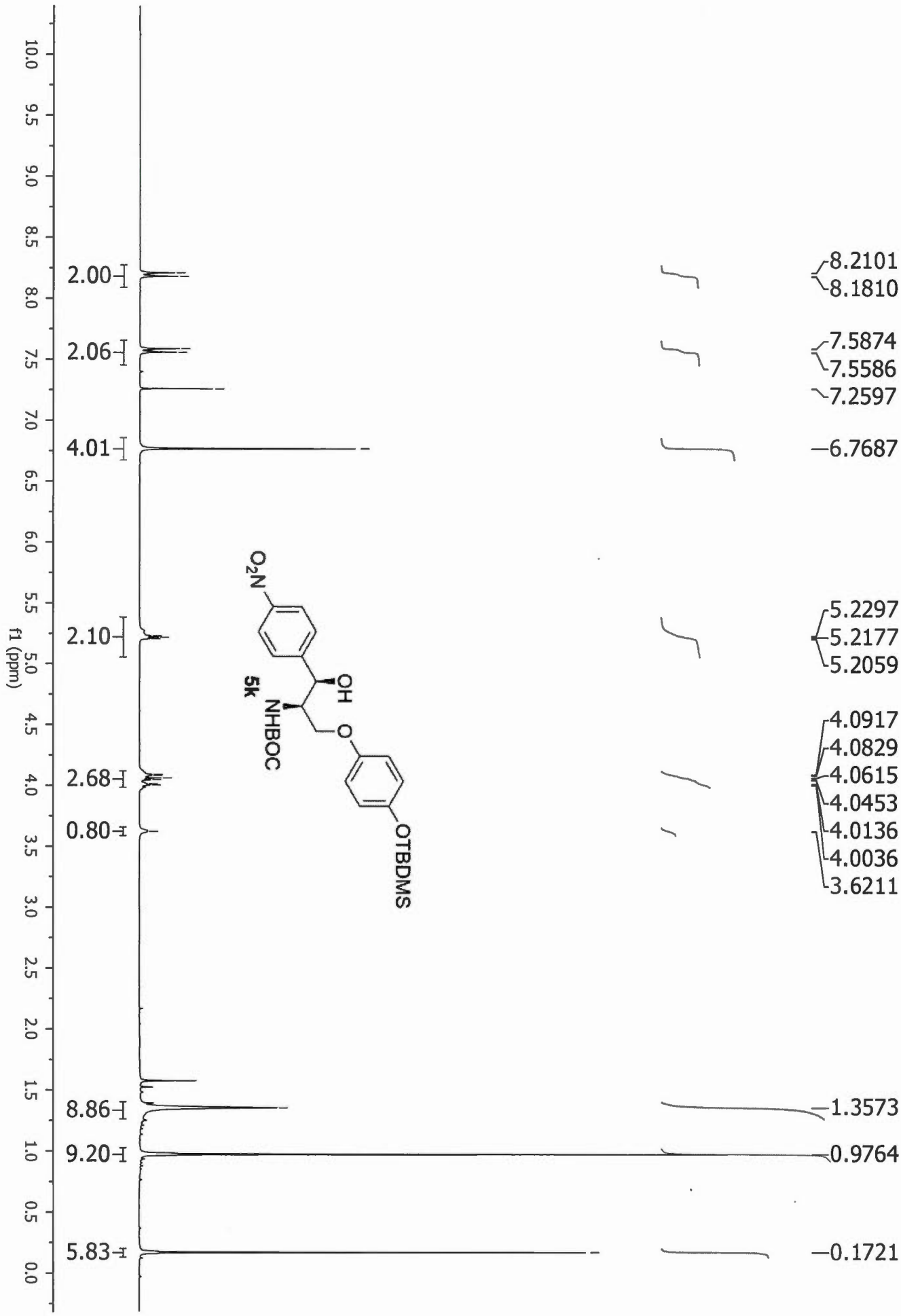

5h
O2N
OH
NHBOC
O
F
165.3792
162.0738
159.3335
159.1916
156.3263
148.5271
147.5484
130.6221
130.4896
127.0798
123.5984
110.1448
108.7287
108.4474
102.6190
102.2875
80.6189
77.4700
77.0466
76.6231
72.9016
67.8751
55.4506
28.1976
f1 (ppm)

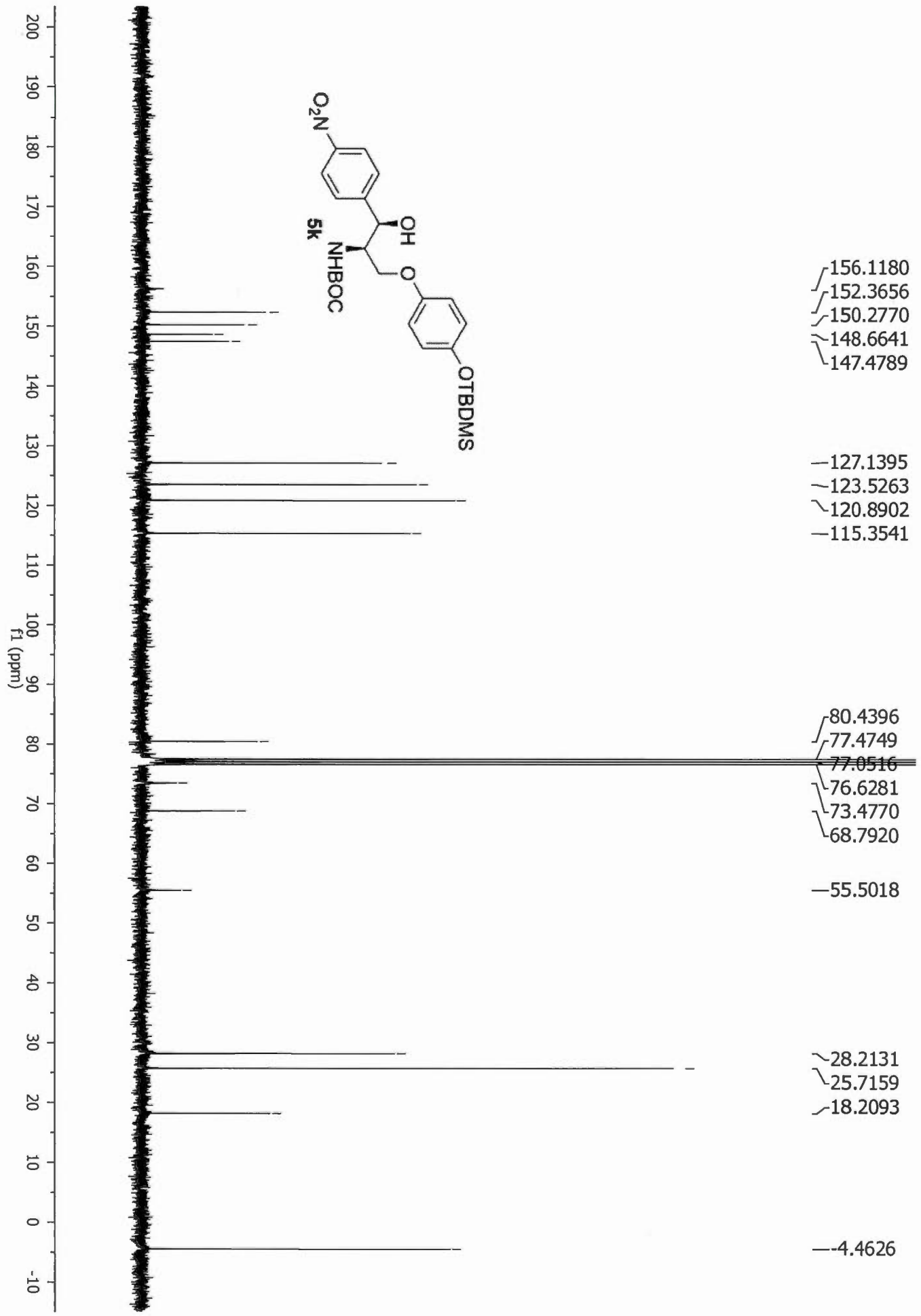

1.78
2.12
3.79
1.96
2.84
0.87
8.89
f1 (ppm)
8.2181
8.1902
7.5862
7.5590
7.5356
7.4298
7.4040
7.3764
7.2983
7.2726
7.2585
7.1639
7.1395
5.2180
5.1278
5.0042
4.9411
4.1759
4.1570
4.0961
4.0690
4.0531
3.5559
1.3475
O2N
OH
NHBOC
O
CN
5i

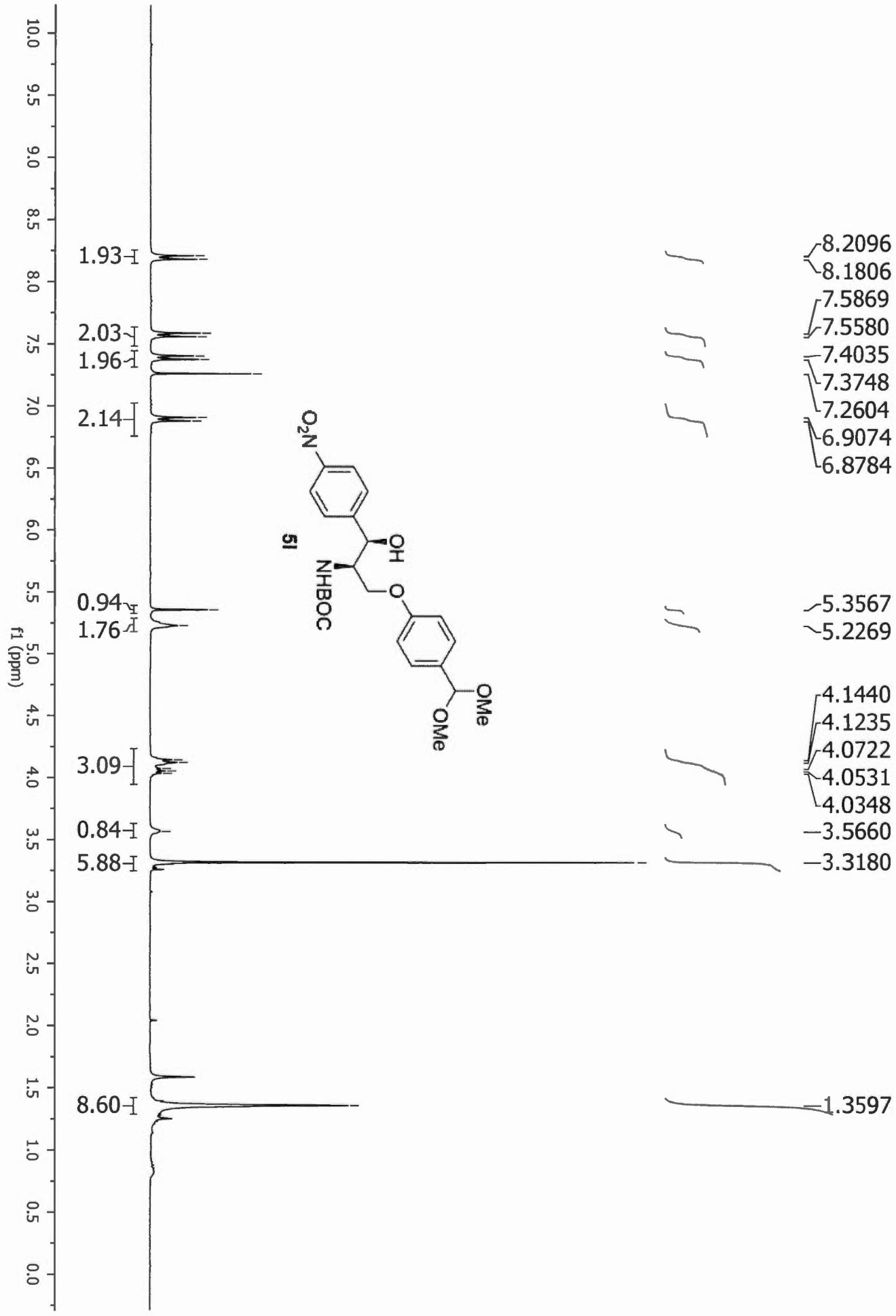
O2N
OH
NHBOC
O
CN
5i
158.1685
156.0390
148.5027
147.5585
130.6421
126.9937
125.3453
123.6026
119.5434
118.3824
117.7453
113.4487
80.6514
77.4552
77.0315
76.6081
72.2229
67.6263
55.3482
29.7092
28.1673
f1 (ppm)

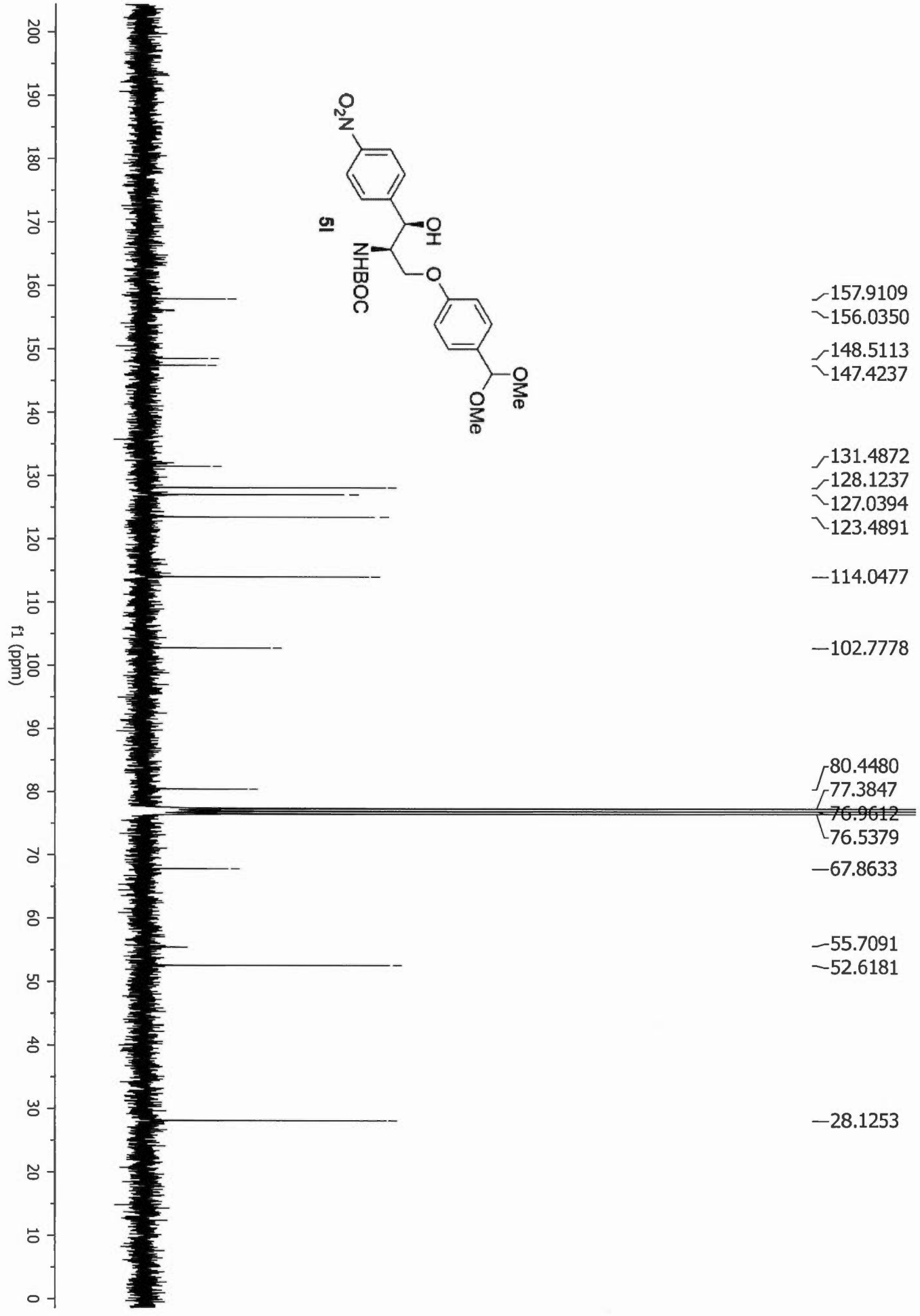
8.2001
8.1710
7.5783
7.5494
7.2596
7.0122
6.9895
6.9819
6.8282
6.8212
6.7980
5.3141
5.3033
5.2927
5.2177
5.2061
5.1947
4.1014
4.0894
4.0804
4.0598
4.0430
3.9996
3.9217
3.6110
1.8606
1.8506
1.8385
1.8335
1.8218
1.6890
1.6824
1.6669
1.6537
1.6318
1.6163
1.3531
2.00
2.10
2.04
1.98
2.96
4.31
2.02
2.21
3.76
9.44
O2N
OH
NHBOC
O
OTHP
5j
f1 (ppm)

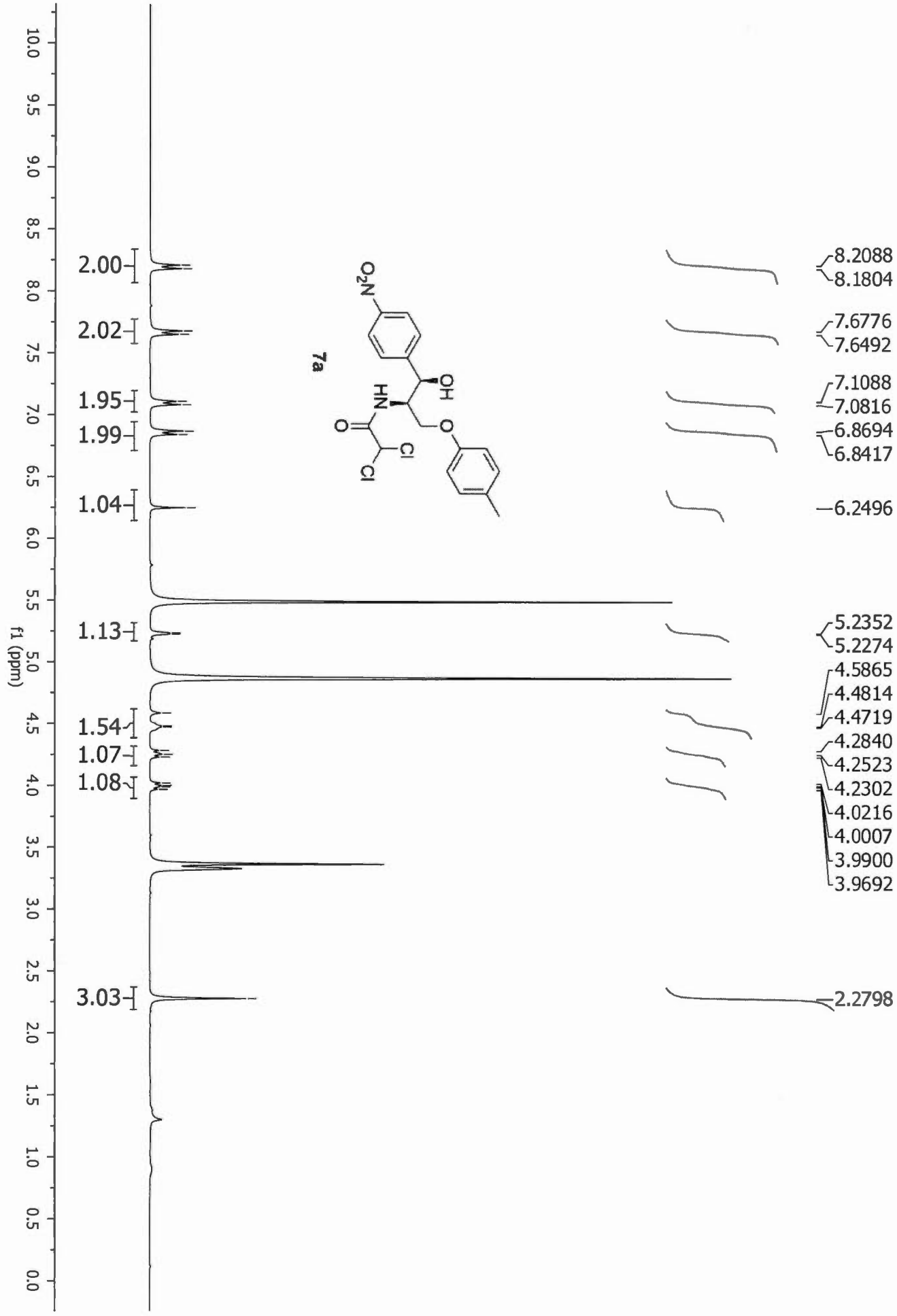

5j
O2N
OH
NHBOC
O
OTHP
156.0708
152.7610
151.8848
148.7100
147.4622
127.1399
123.5238
117.9222
117.9049
115.3584
97.2858
97.2581
80.4362
77.4783
77.0547
76.6312
73.3211
68.6806
62.1735
55.5151
30.4594
28.2112
25.2297
18.9103
f1 (ppm)

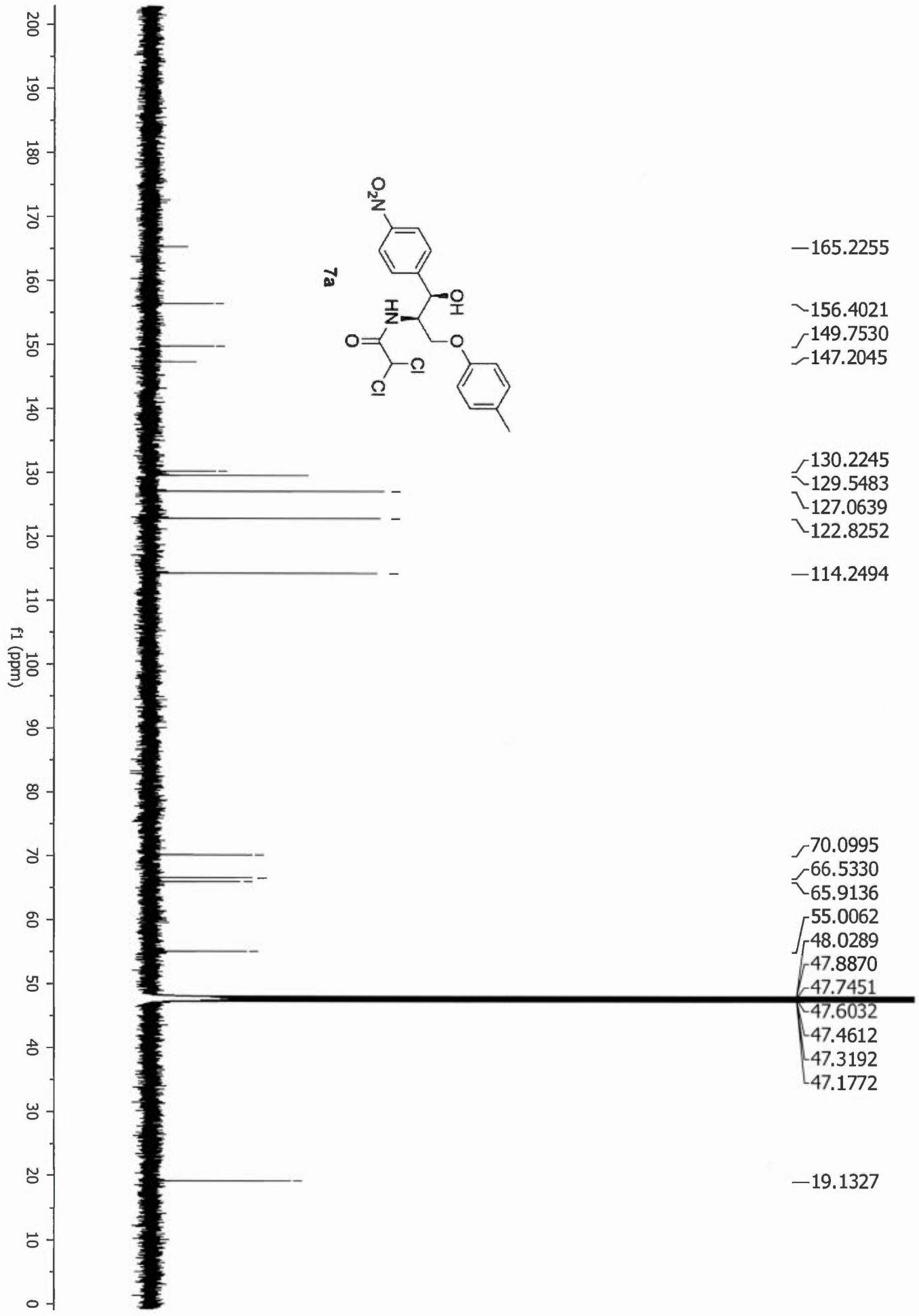

f1 (ppm)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2.00
2.06
4.01
2.10
2.68
0.80
8.86
9.20
5.83
8.2101
8.1810
7.5874
7.5586
7.2597
6.7687
5.2297
5.2177
5.2059
4.0917
4.0829
4.0615
4.0453
4.0136
4.0036
3.6211
1.3573
0.9764
0.1721
O2N
OH
NHBOC
O
OTBDMS
5k

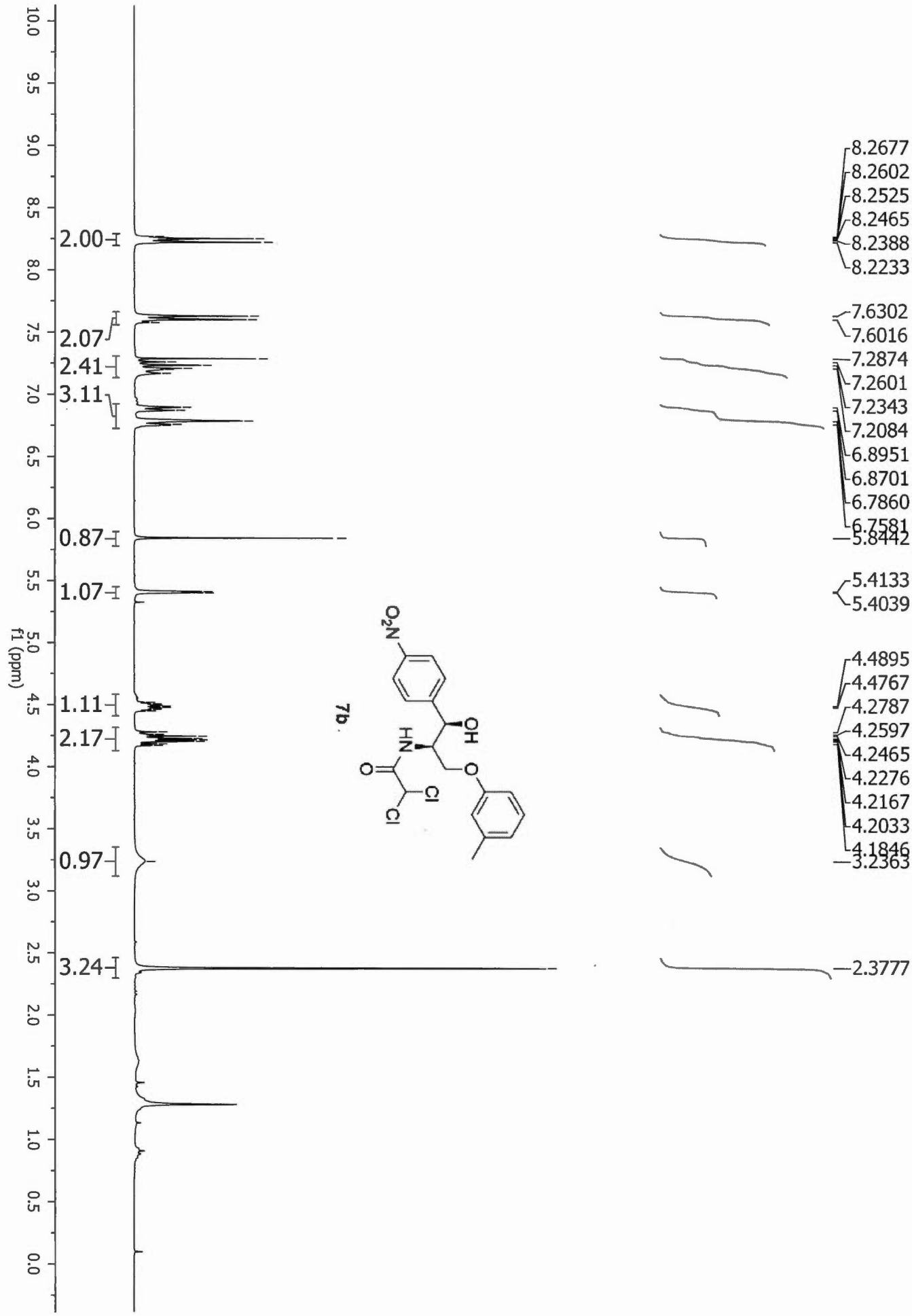

O2N
OH
5k
NHBOC
O
OTBDMS
156.1180
152.3656
150.2770
148.6641
147.4789
127.1395
123.5263
120.8902
115.3541
80.4396
77.4749
77.0516
76.6281
73.4770
68.7920
55.5018
28.2131
25.7159
18.2093
-4.4626
f1 (ppm)

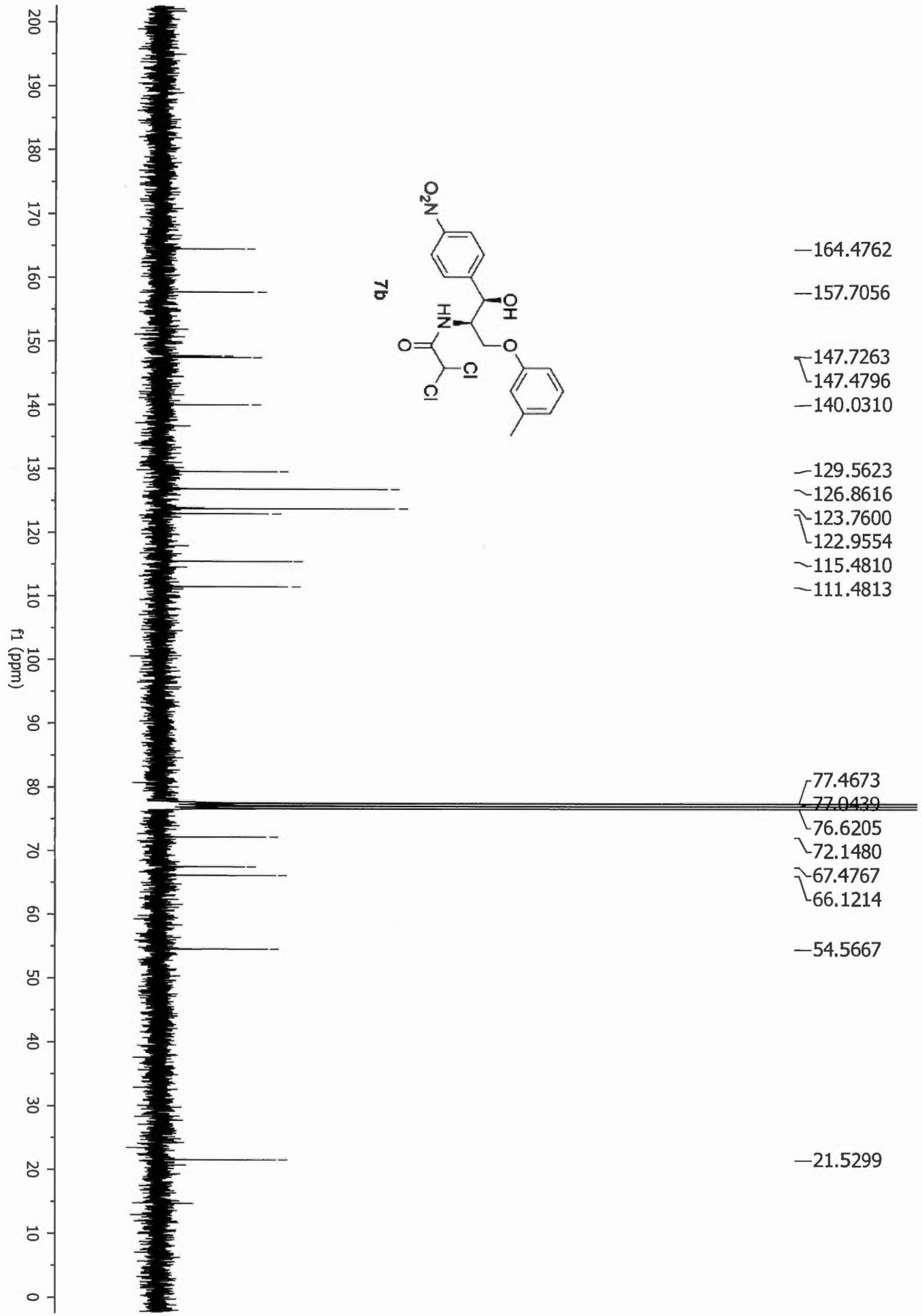

1.93
2.03
1.96
2.14
0.94
1.76
3.09
0.84
5.88
8.60
8.2096
8.1806
7.5869
7.5580
7.4035
7.3748
7.2604
6.9074
6.8784
5.3567
5.2269
4.1440
4.1235
4.0722
4.0531
4.0348
3.5660
3.3180
1.3597
O2N
OH
NHBOC
O
OMe
OMe
5l
f1 (ppm)

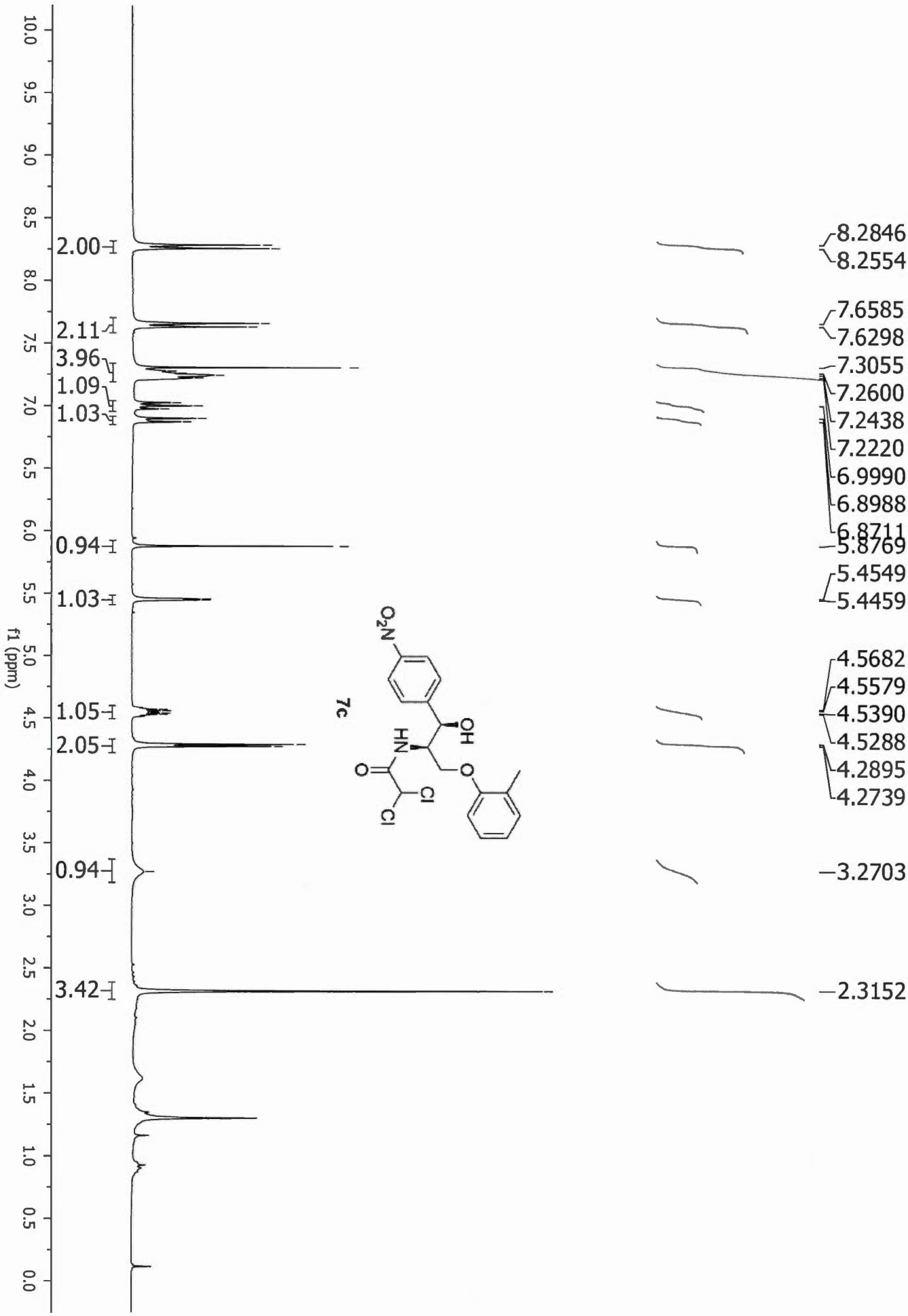

5l
O_2N
OH
NHBOC
O
OMe
OMe
157.9109
156.0350
148.5113
147.4237
131.4872
128.1237
127.0394
123.4891
114.0477
102.7778
80.4480
77.3847
76.9612
76.5379
67.8633
55.7091
52.6181
28.1253
f1 (ppm)

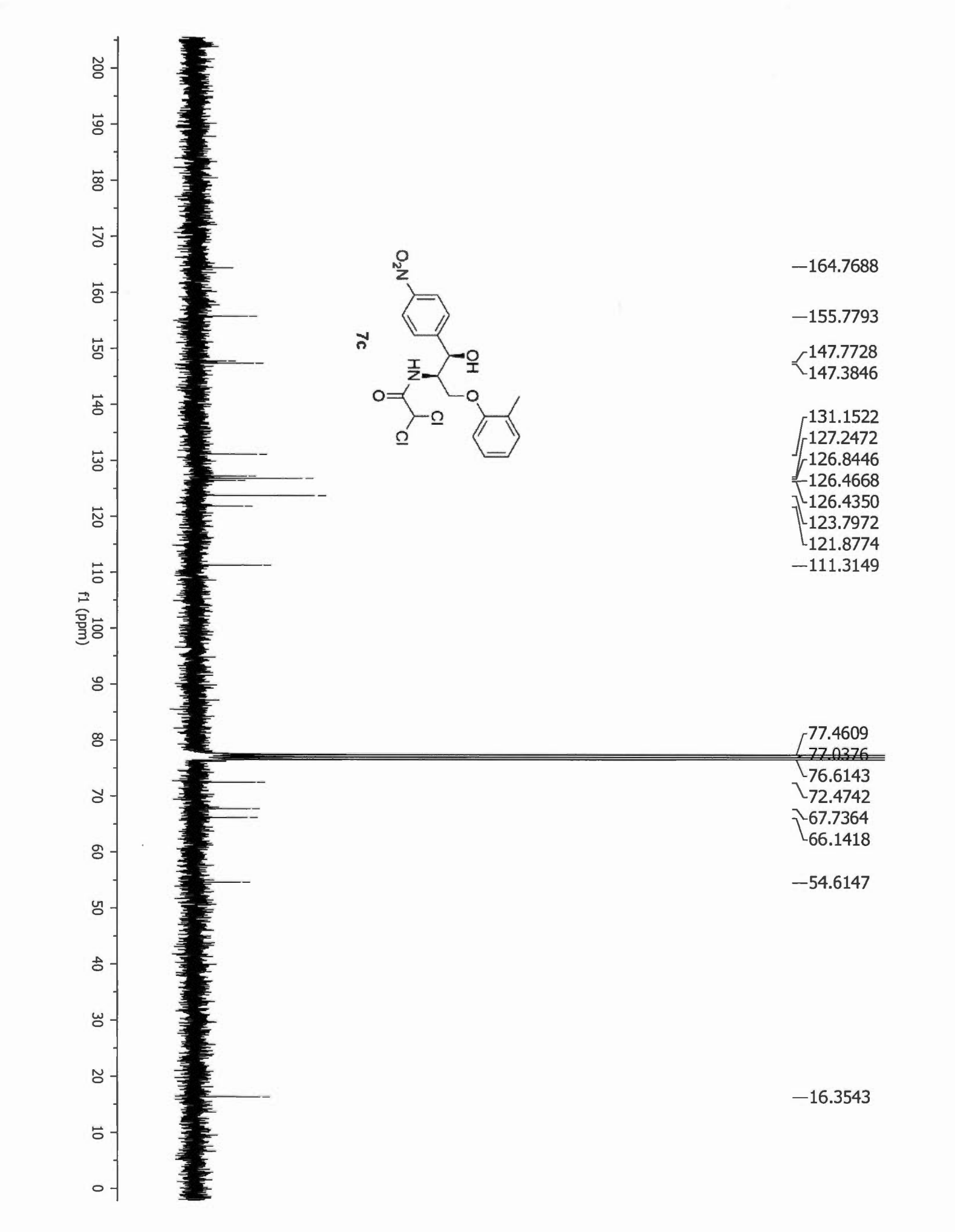

7a
2.00
2.02
1.95
1.99
1.04
1.13
1.54
1.07
1.08
3.03
8.2088
8.1804
7.6776
7.6492
7.1088
7.0816
6.8694
6.8417
6.2496
5.2352
5.2274
4.5865
4.4814
4.4719
4.2840
4.2523
4.2302
4.0216
4.0007
3.9900
3.9692
2.2798
f1 (ppm)

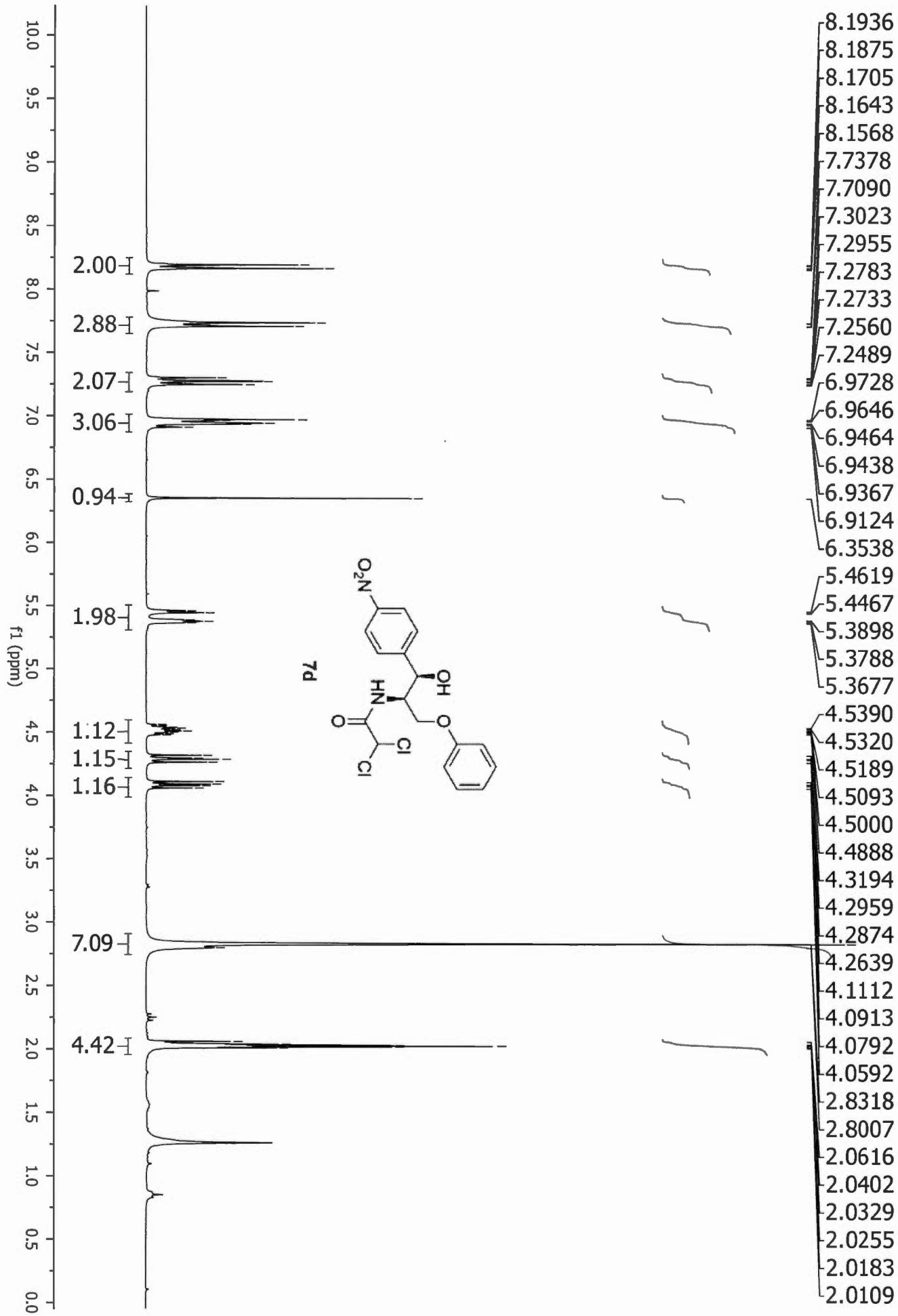

7a
O2N
OH
HN
O
Cl
Cl
O
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
165.2255
156.4021
149.7530
147.2045
130.2245
129.5483
127.0639
122.8252
114.2494
70.0995
66.5330
65.9136
55.0062
48.0289
47.8870
47.7451
47.6032
47.4612
47.3192
47.1772
19.1327

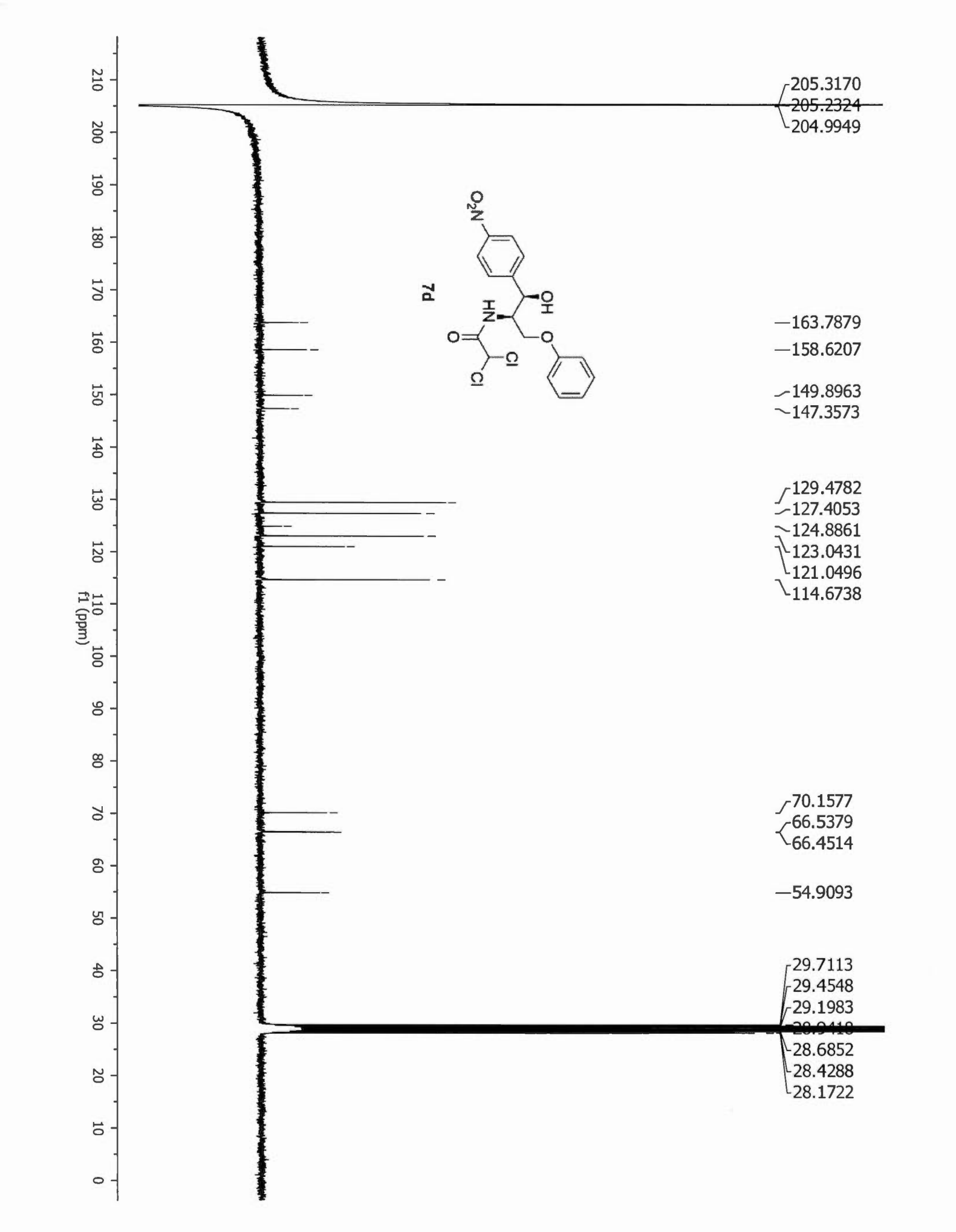

f1 (ppm)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2.00
2.07
2.41
3.11
0.87
1.07
1.11
2.17
0.97
3.24
7b
O2N
OH
HN
O
Cl
Cl
O
8.2677
8.2602
8.2525
8.2465
8.2388
8.2233
7.6302
7.6016
7.2874
7.2601
7.2343
7.2084
6.8951
6.8701
6.7860
6.7581
5.8442
5.4133
5.4039
4.4895
4.4767
4.2787
4.2597
4.2465
4.2276
4.2167
4.2033
4.1846
3.2363
2.3777


7b
O2N
OH
HN
O
Cl
Cl
O
164.4762
157.7056
147.7263
147.4796
140.0310
129.5623
126.8616
123.7600
122.9554
115.4810
111.4813
77.4673
77.0439
76.6205
72.1480
67.4767
66.1214
54.5667
21.5299
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


f1 (ppm)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2.00
2.11
3.96
1.09
1.03
0.94
1.03
1.05
2.05
0.94
3.42
7c
O2N
OH
HN
O
Cl
Cl
O
8.2846
8.2554
7.6585
7.6298
7.3055
7.2600
7.2438
7.2220
6.9990
6.8988
6.8711
5.8769
5.4549
5.4459
4.5682
4.5579
4.5390
4.5288
4.2895
4.2739
3.2703
2.3152


7c
O2N
OH
HN
O
Cl
Cl
O
164.7688
155.7793
147.7728
147.3846
131.1522
127.2472
126.8446
126.4668
126.4350
123.7972
121.8774
111.3149
77.4609
77.0376
76.6143
72.4742
67.7364
66.1418
54.6147
16.3543
f1 (ppm)


8.1936
8.1875
8.1705
8.1643
8.1568
7.7378
7.7090
7.3023
7.2955
7.2783
7.2733
7.2560
7.2489
6.9728
6.9646
6.9464
6.9438
6.9367
6.9124
6.3538
5.4619
5.4467
5.3898
5.3788
5.3677
4.5390
4.5320
4.5189
4.5093
4.5000
4.4888
4.3194
4.2959
4.2874
4.2639
4.1112
4.0913
4.0792
4.0592
2.8318
2.8007
2.0616
2.0402
2.0329
2.0255
2.0183
2.0109
2.00
2.88
2.07
3.06
0.94
1.98
1.12
1.15
1.16
7.09
4.42
7d
f1 (ppm)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147.3573
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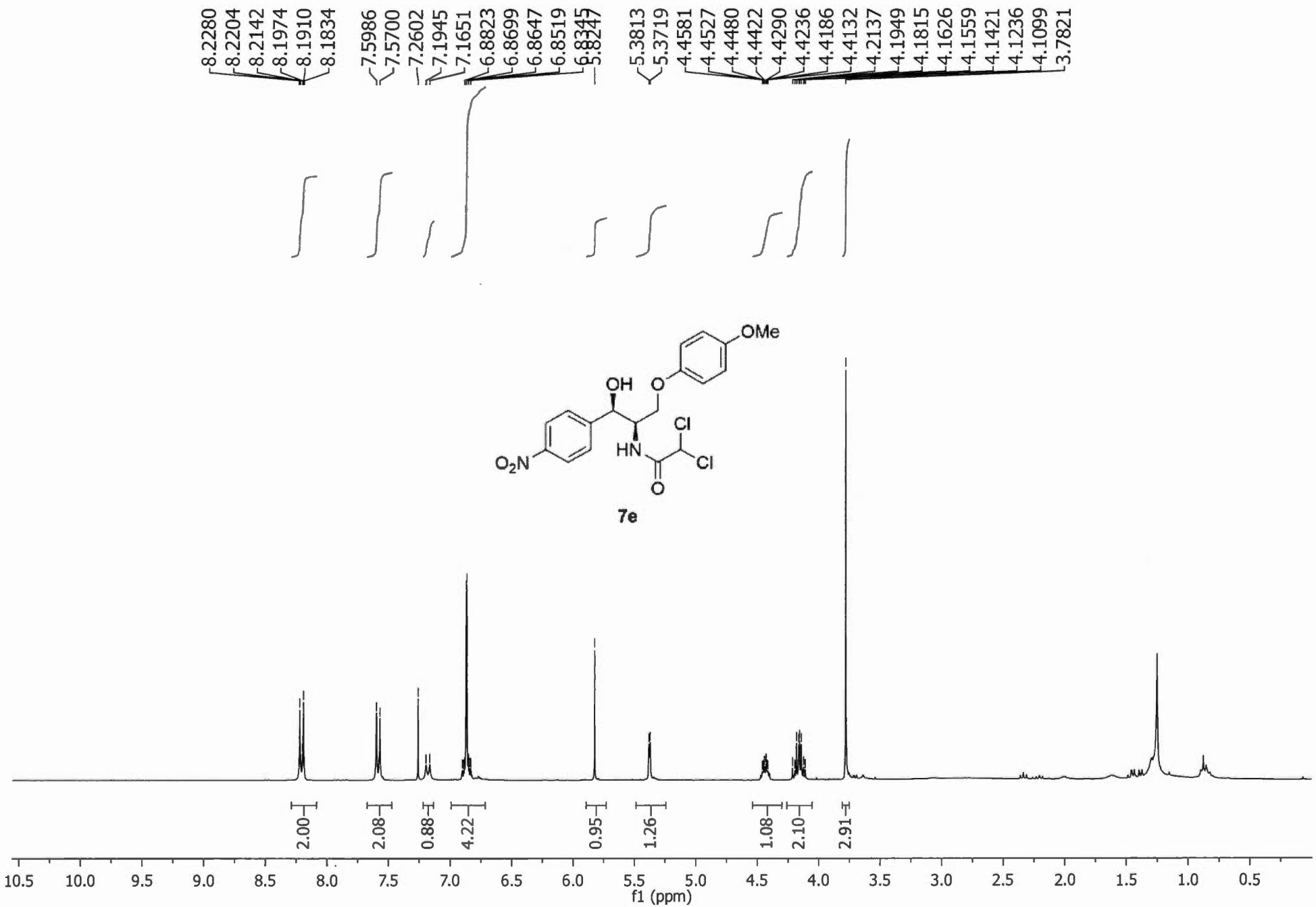
127.4053
124.8861
123.0431
121.0496
114.6738
70.1577
66.5379
66.4514
54.9093
29.7113
29.4548
29.1983
28.6852
28.4288
28.1722
7d
f1 (ppm)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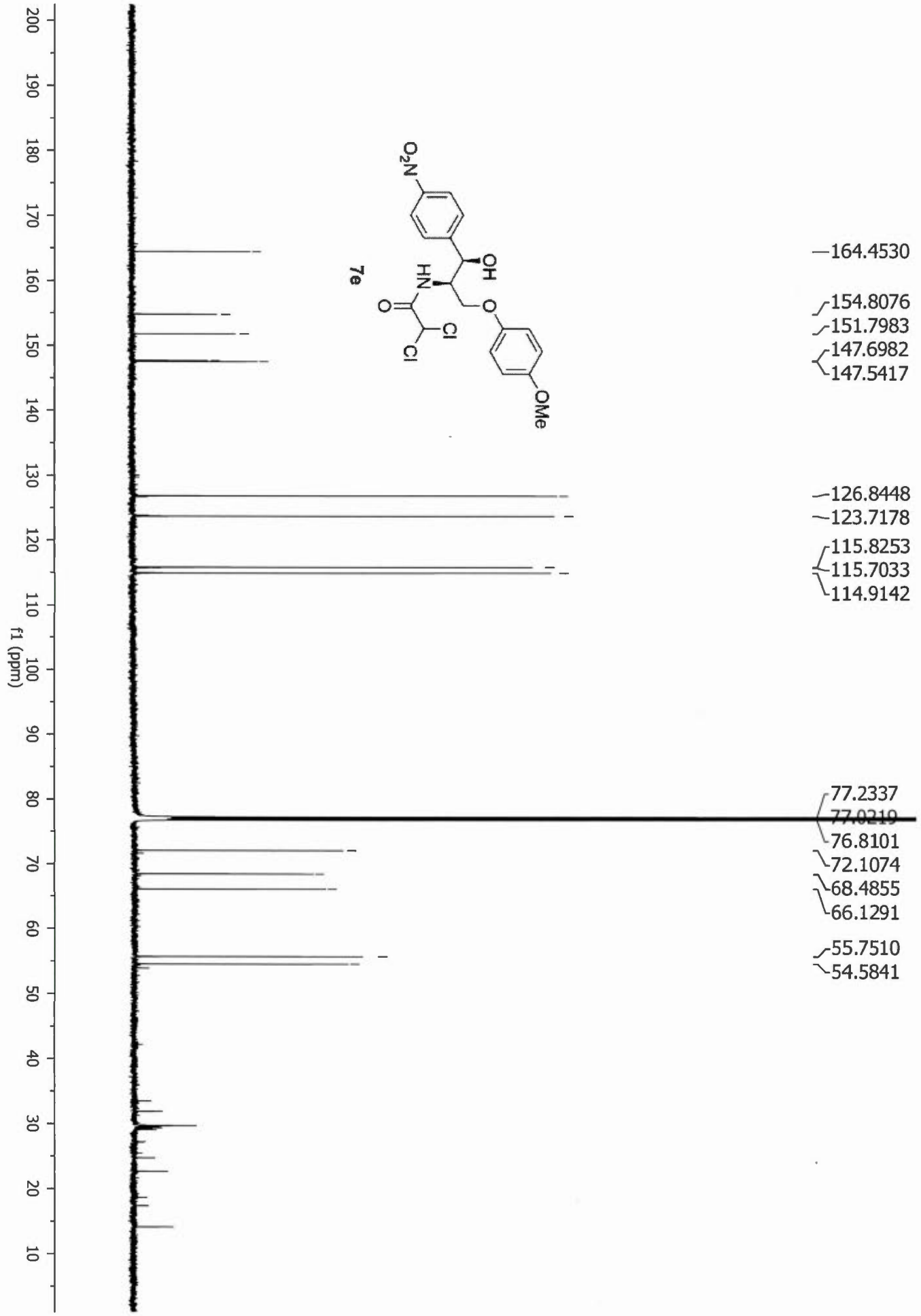
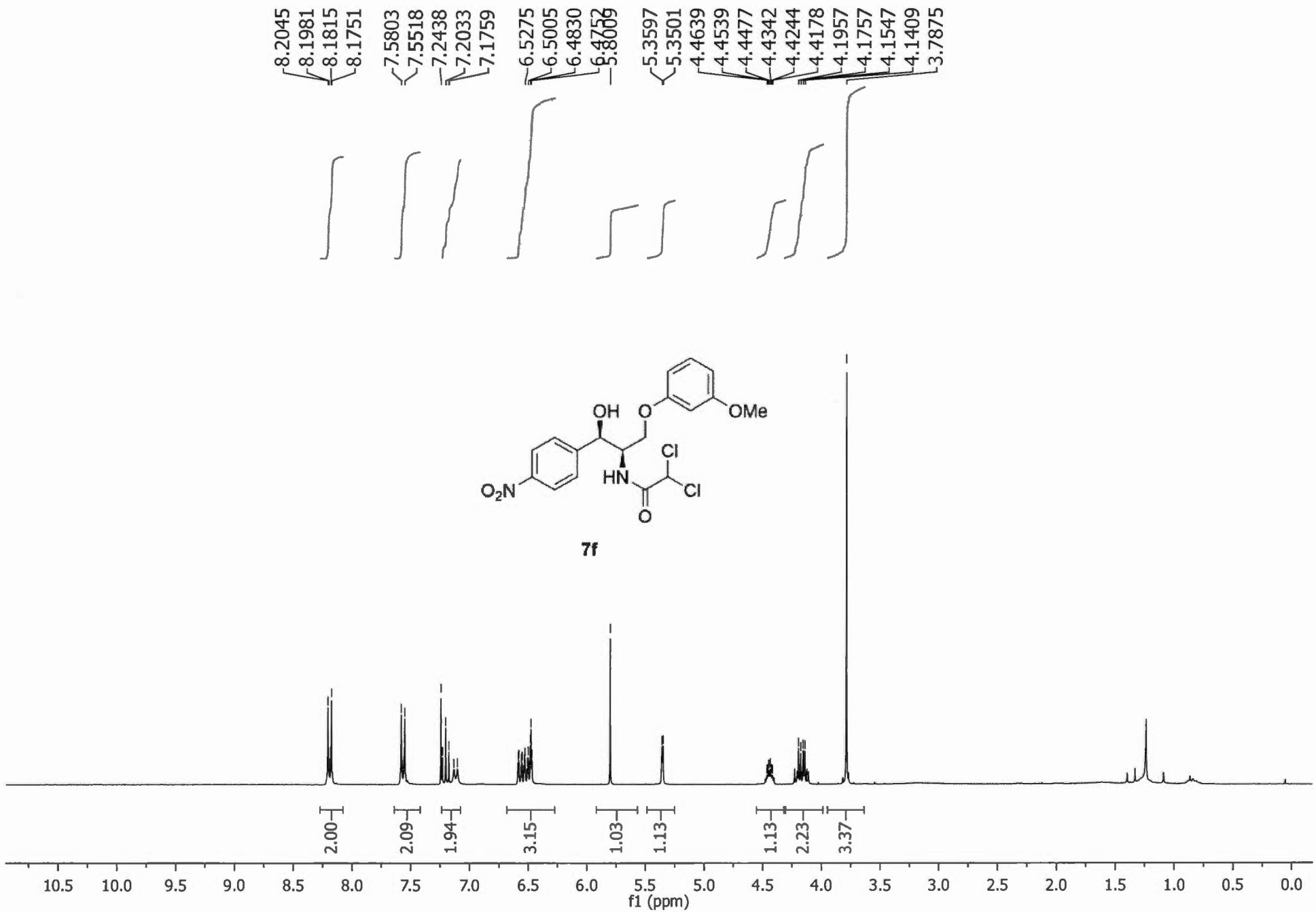
8.2204
8.2142
8.1974
8.1910
8.1834
7.5986
7.5700
7.2602
7.1945
7.1651
6.8823
6.8699
6.8647
6.8519
6.8345
5.8247
5.3813
5.3719
4.4581
4.4527
4.4480
4.4422
4.4290
4.4236
4.4186
4.4132
4.2137
4.1949
4.1815
4.1626
4.1559
4.1421
4.1236
4.1099
3.7821
OMe
OH
O
Cl
HN
Cl
O2N
O
7e
2.00
2.08
0.88
4.22
0.95
1.26
1.08
2.10
2.91
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


7e
O2N
OH
HN
O
Cl
Cl
O
OMe
164.4530
154.8076
151.7983
147.6982
147.5417
126.8448
123.7178
115.8253
115.7033
114.9142
77.2337
77.0219
76.8101
72.1074
68.4855
66.1291
55.7510
54.5841
f1 (ppm)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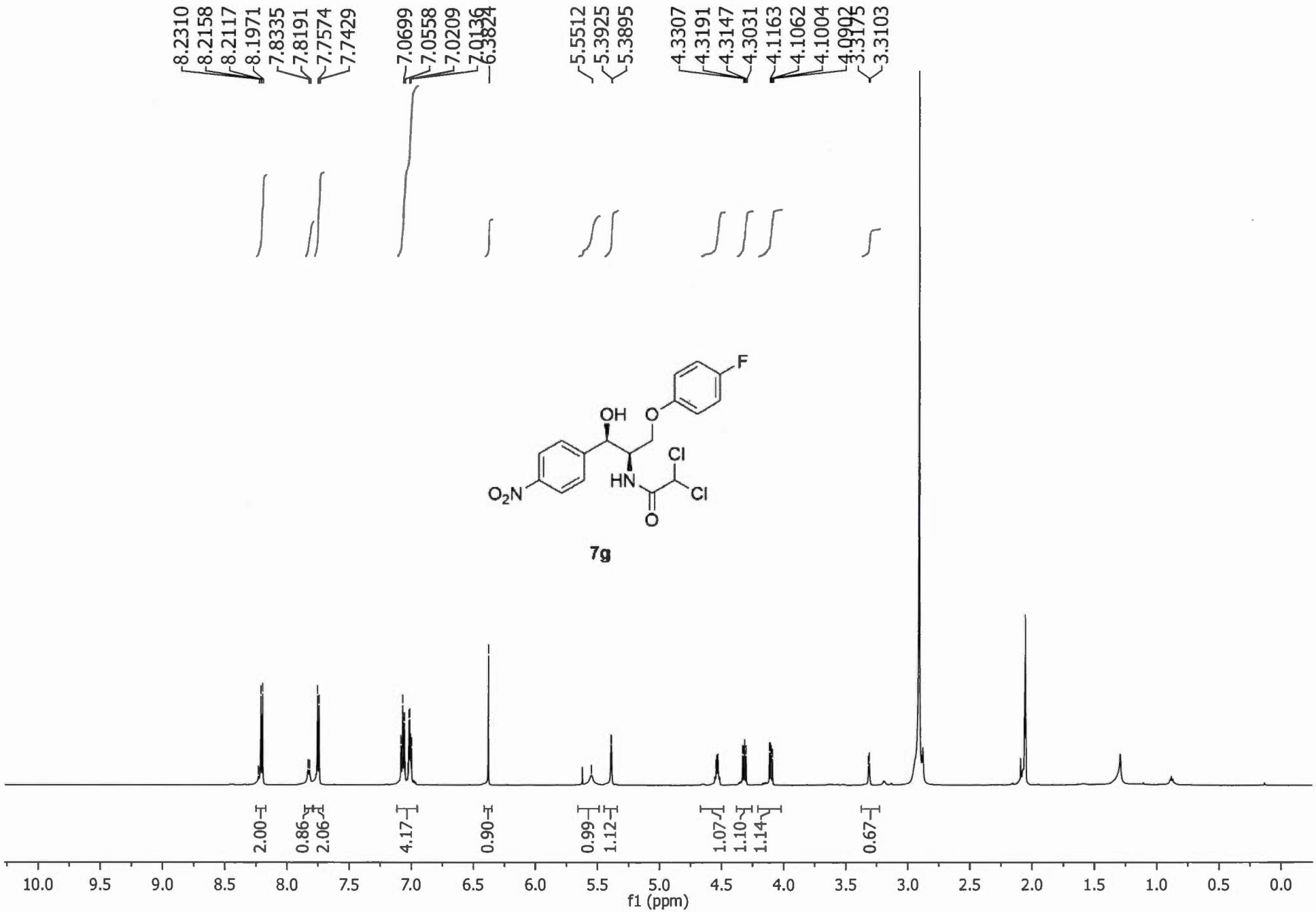
8.1981
8.1815
8.1751
7.5803
7.5518
7.2438
7.2033
7.1759
6.5275
6.5005
6.4830
6.4752
5.8009
5.3597
5.3501
4.4639
4.4539
4.4477
4.4342
4.4244
4.4178
4.1957
4.1757
4.1547
4.1409
3.7875
OH
O
OMe
Cl
HN
Cl
O2N
O
7f
2.00
2.09
1.94
3.15
1.03
1.13
1.13
2.23
3.37
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

7f
O2N
OH
HN
O
Cl
Cl
O
OMe
164.4759
161.0235
158.9064
147.7061
147.4877
130.2915
126.8377
123.7490
107.4495
106.7034
101.2887
77.4554
77.0321
76.6087
71.8689
67.2922
66.0990
55.4059
54.5230
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0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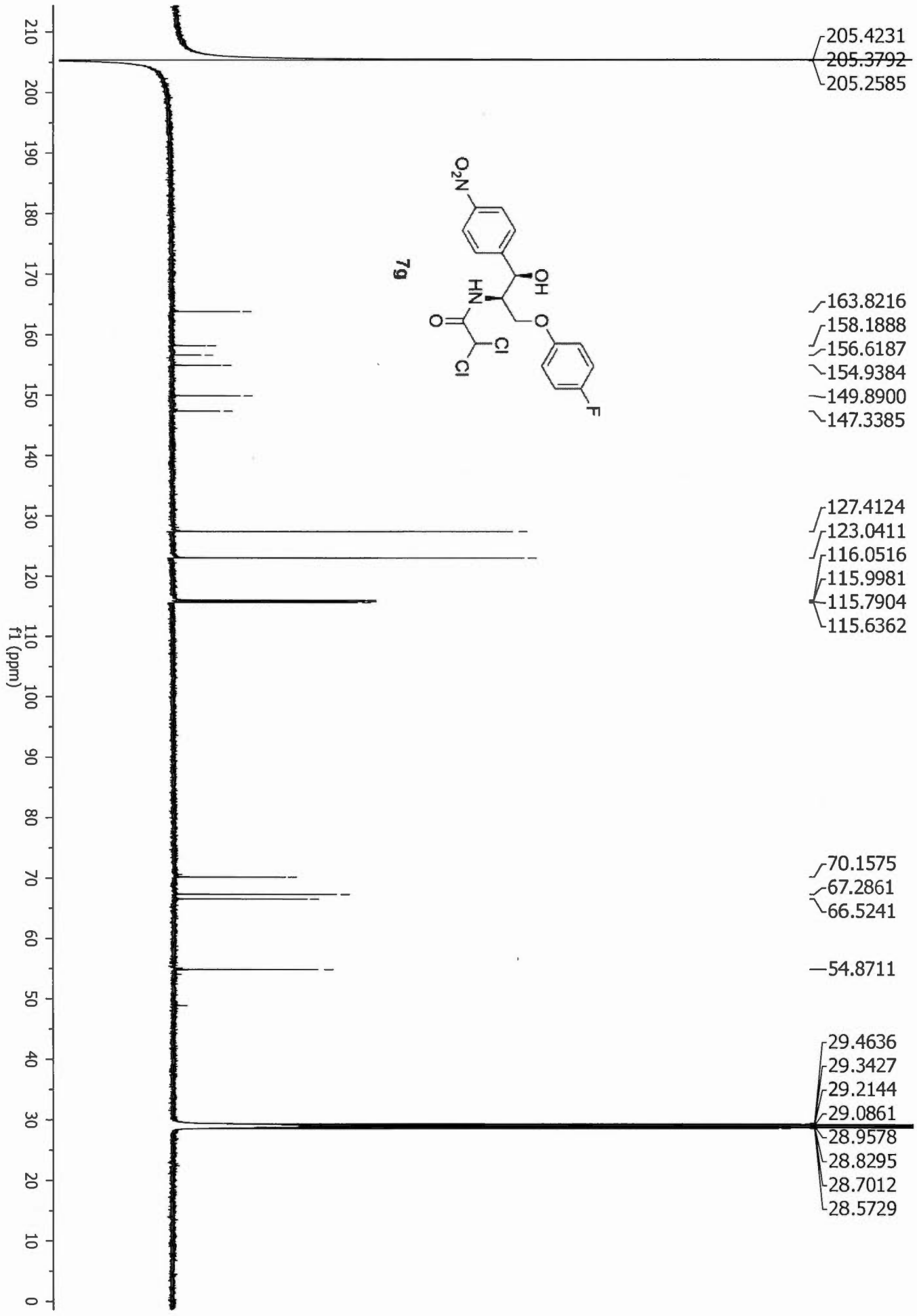
8.2117
8.1971
7.8335
7.8191
7.7574
7.7429
7.0699
7.0558
7.0209
7.0136
6.3824
5.5512
5.3925
5.3895
4.3307
4.3191
4.3147
4.3031
4.1163
4.1062
4.1004
4.0992
3.3175
3.3103
F
OH
O
Cl
HN
Cl
O2N
O
7g
2.00
0.86
2.06
4.17
0.90
0.99
1.12
1.07
1.10
1.14
0.67
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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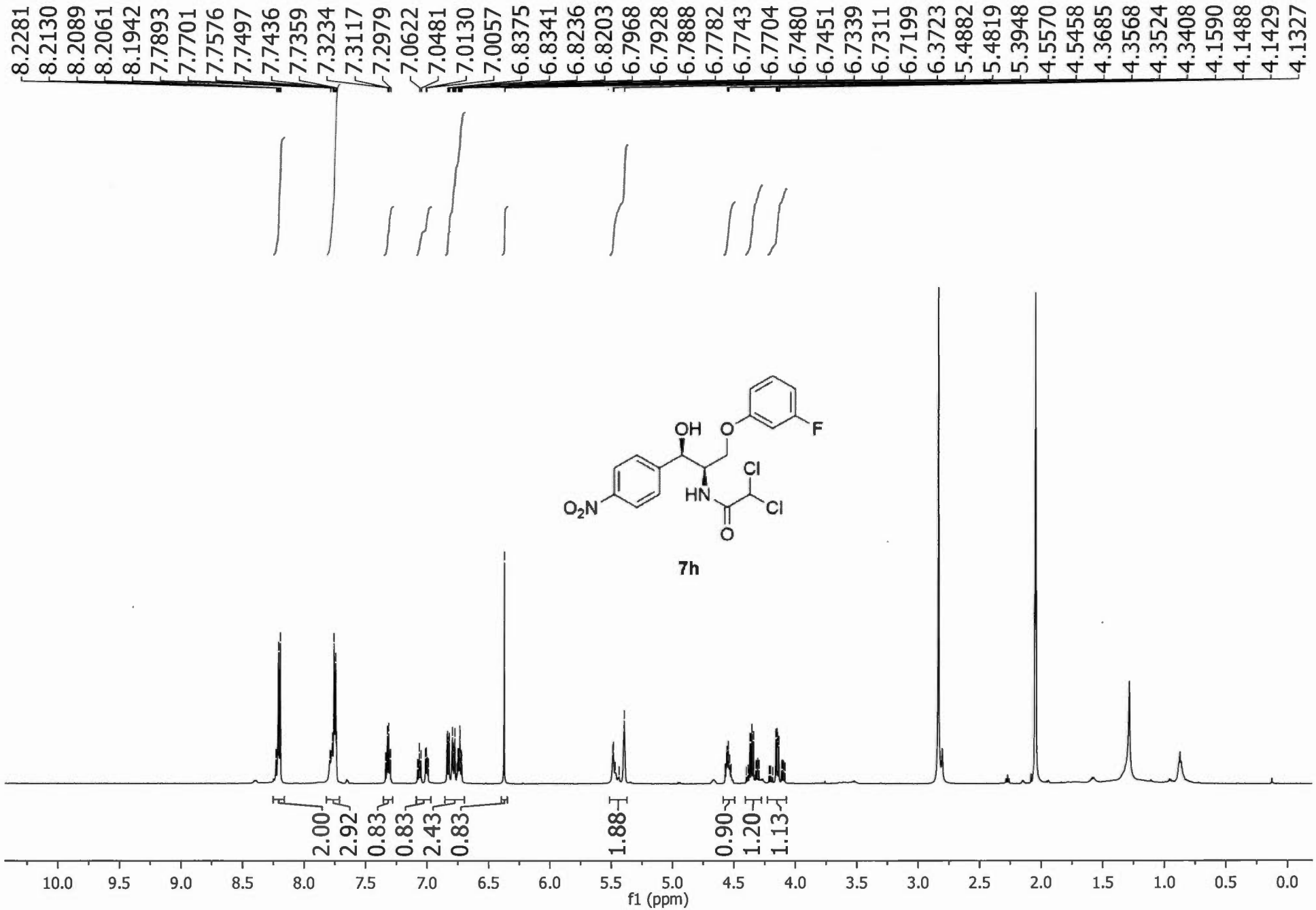
205.3792
205.2585
163.8216
158.1888
156.6187
154.9384
149.8900
147.3385
127.4124
123.0411
116.0516
115.9981
115.7904
115.6362
70.1575
67.2861
66.5241
54.8711
29.4636
29.3427
29.2144
29.0861
28.9578
28.8295
28.7012
28.5729
f1 (ppm)
7g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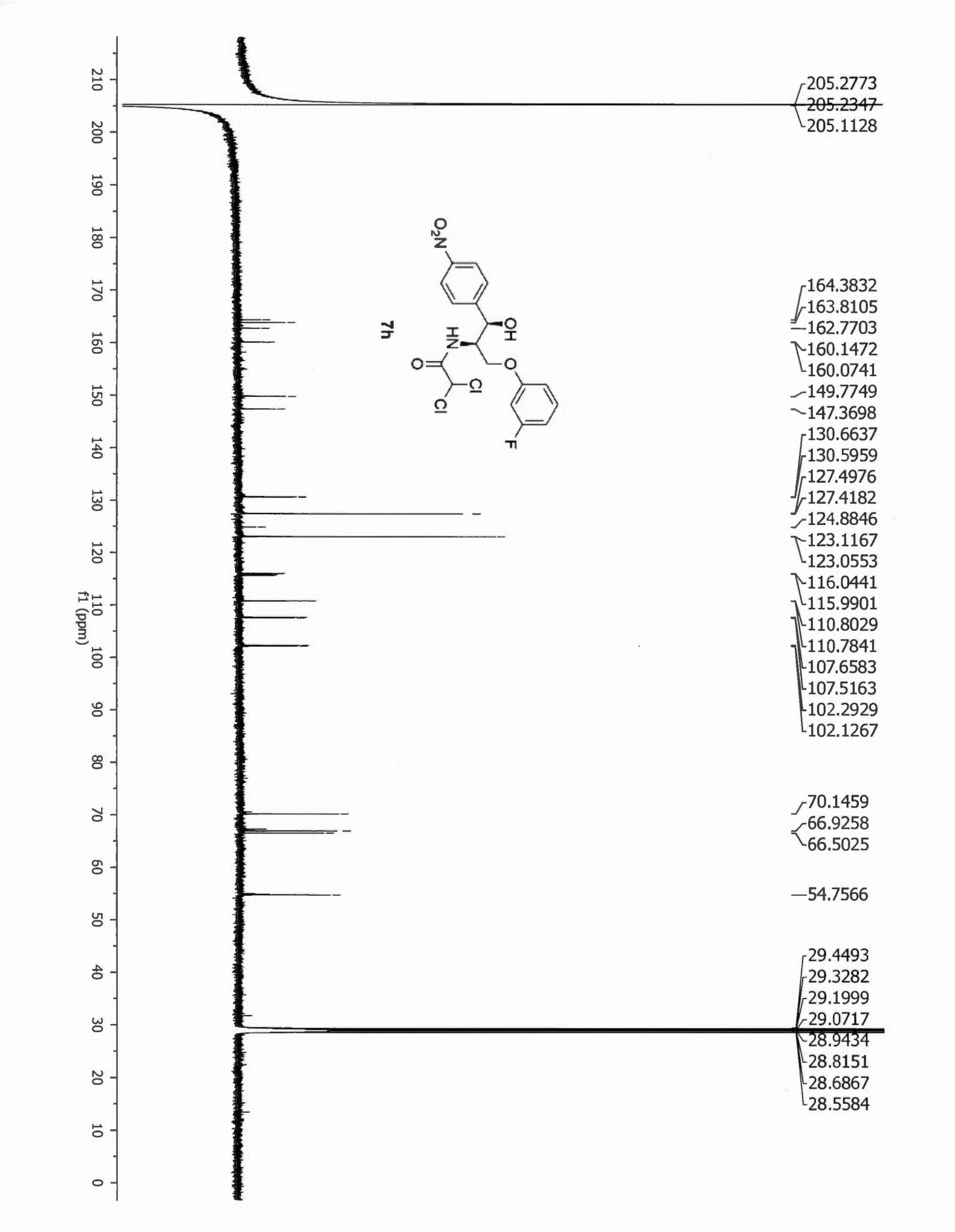
8.2061
8.1942
7.7893
7.7701
7.7576
7.7497
7.7436
7.7359
7.3234
7.3117
7.2979
7.0622
7.0481
7.0130
7.0057
6.8375
6.8341
6.8236
6.8203
6.7968
6.7928
6.7888
6.7782
6.7743
6.7704
6.7480
6.7451
6.7339
6.7311
6.7199
6.3723
5.4882
5.4819
5.3948
4.5570
4.5458
4.3685
4.3568
4.3524
4.3408
4.1590
4.1488
4.1429
4.1327
OH
O
F
Cl
HN
Cl
O2N
O
7h
2.00
2.92
0.83
0.83
2.43
0.83
1.88
0.90
1.20
1.13
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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147.3698
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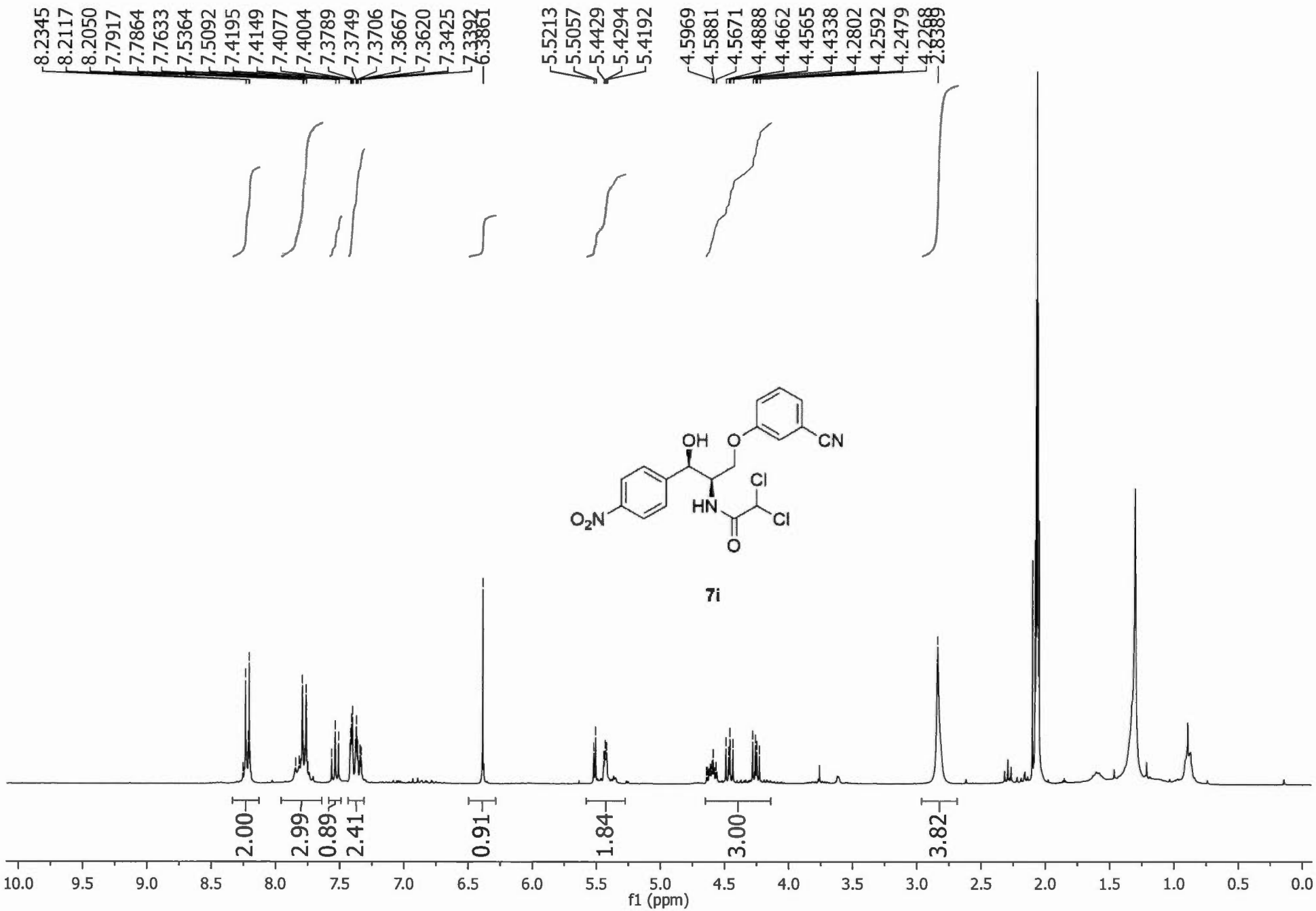
130.5959
127.4976
127.4182
124.8846
123.1167
123.0553
116.0441
115.9901
110.8029
110.7841
107.6583
107.5163
102.2929
102.1267
70.1459
66.9258
66.5025
54.7566
29.4493
29.3282
29.1999
29.0717
28.9434
28.8151
28.6867
28.5584
7h
f1 (ppm)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8.2050
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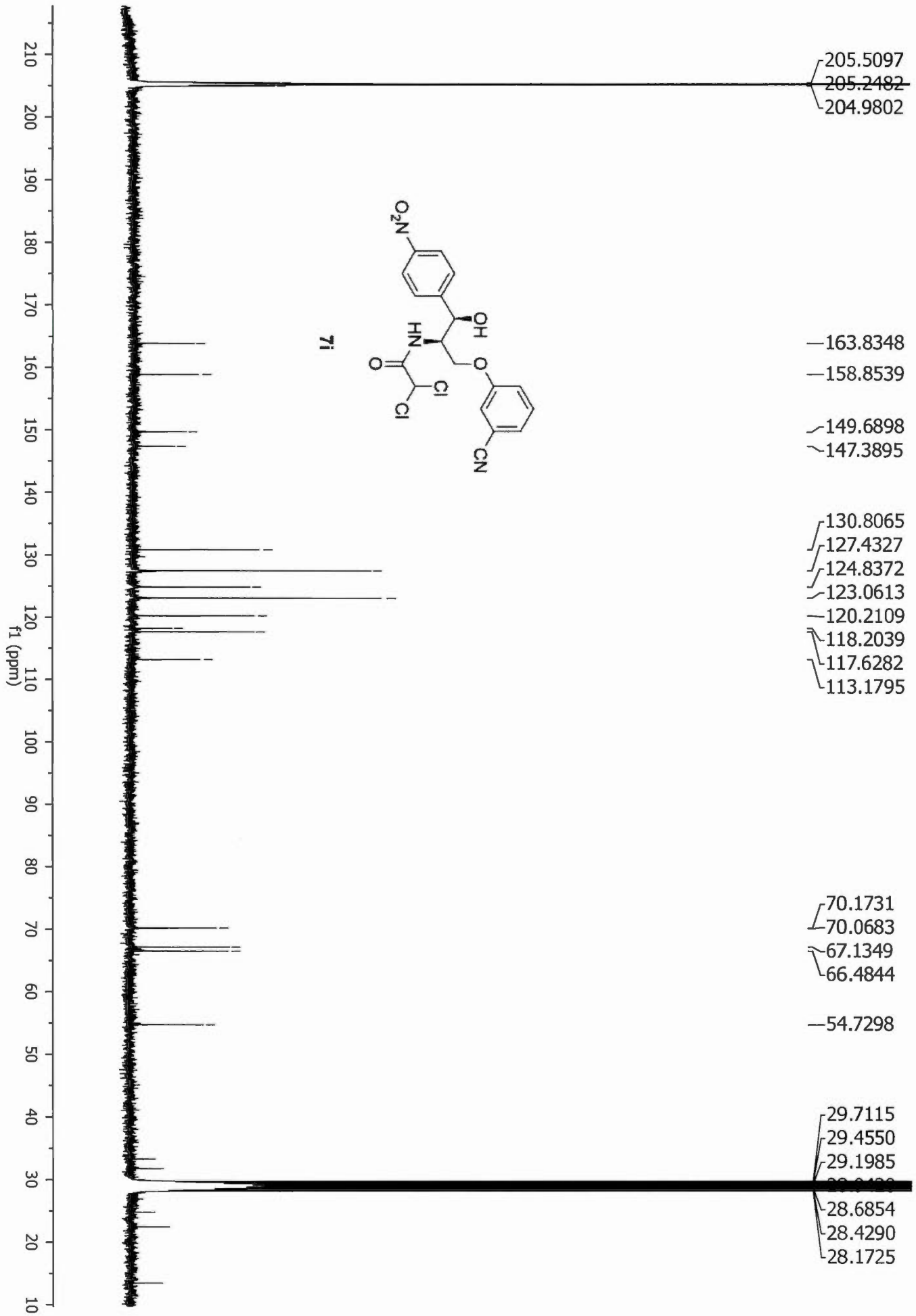
7.7864
7.7633
7.5364
7.5092
7.4195
7.4149
7.4077
7.4004
7.3789
7.3749
7.3706
7.3667
7.3620
7.3425
7.3392
6.3861
5.5213
5.5057
5.4429
5.4294
5.4192
4.5969
4.5881
4.5671
4.4888
4.4662
4.4565
4.4338
4.2802
4.2592
4.2479
4.2268
2.8389
OH
O
CN
Cl
HN
Cl
O2N
O
7i
2.00
2.99
0.89
2.41
0.91
1.84
3.00
3.82
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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147.3895
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127.4327
124.8372
123.0613
120.2109
118.2039
117.6282
113.1795
70.1731
70.0683
67.1349
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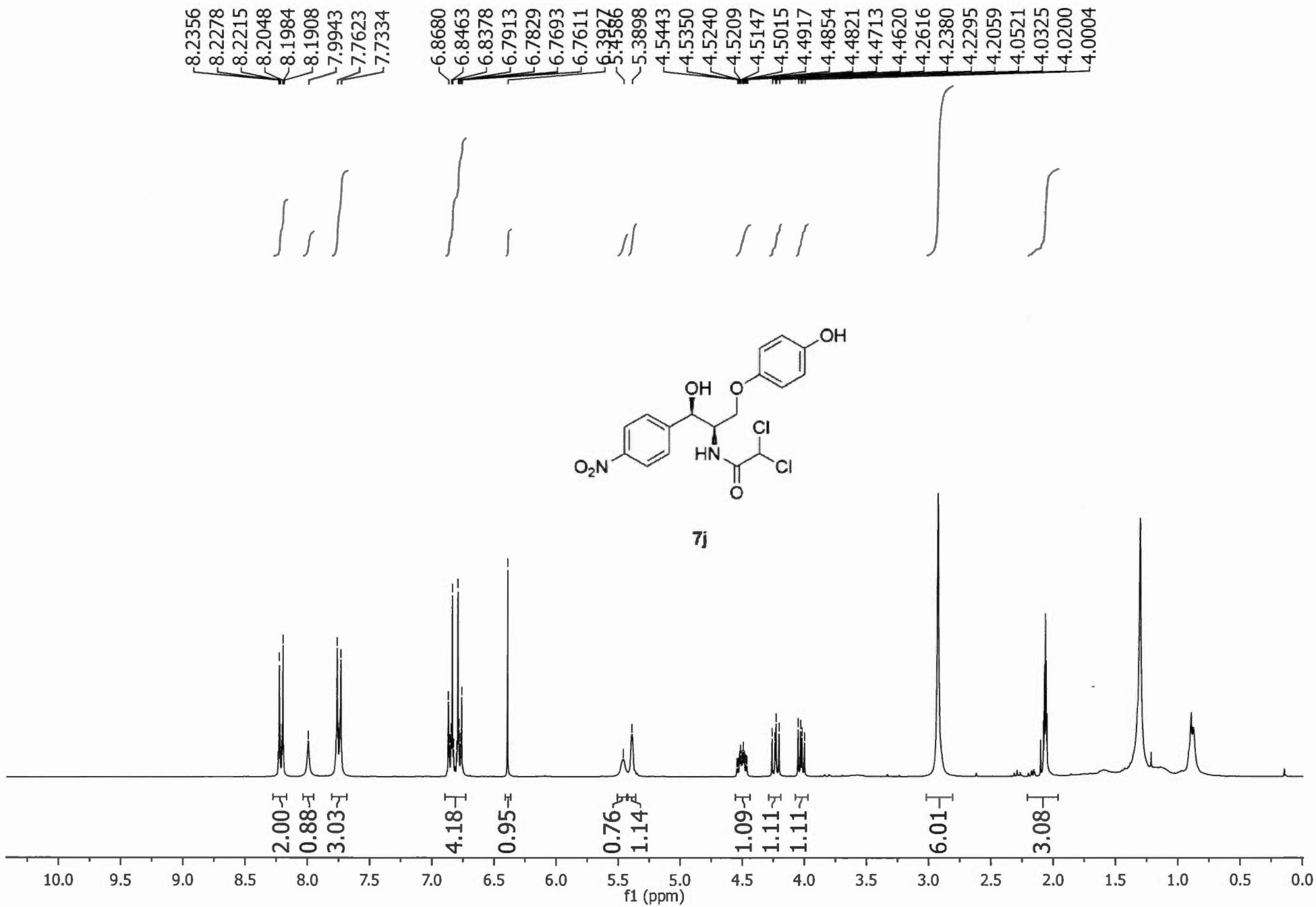
29.7115
29.4550
29.1985
28.6854
28.4290
28.1725
7i
f1 (ppm)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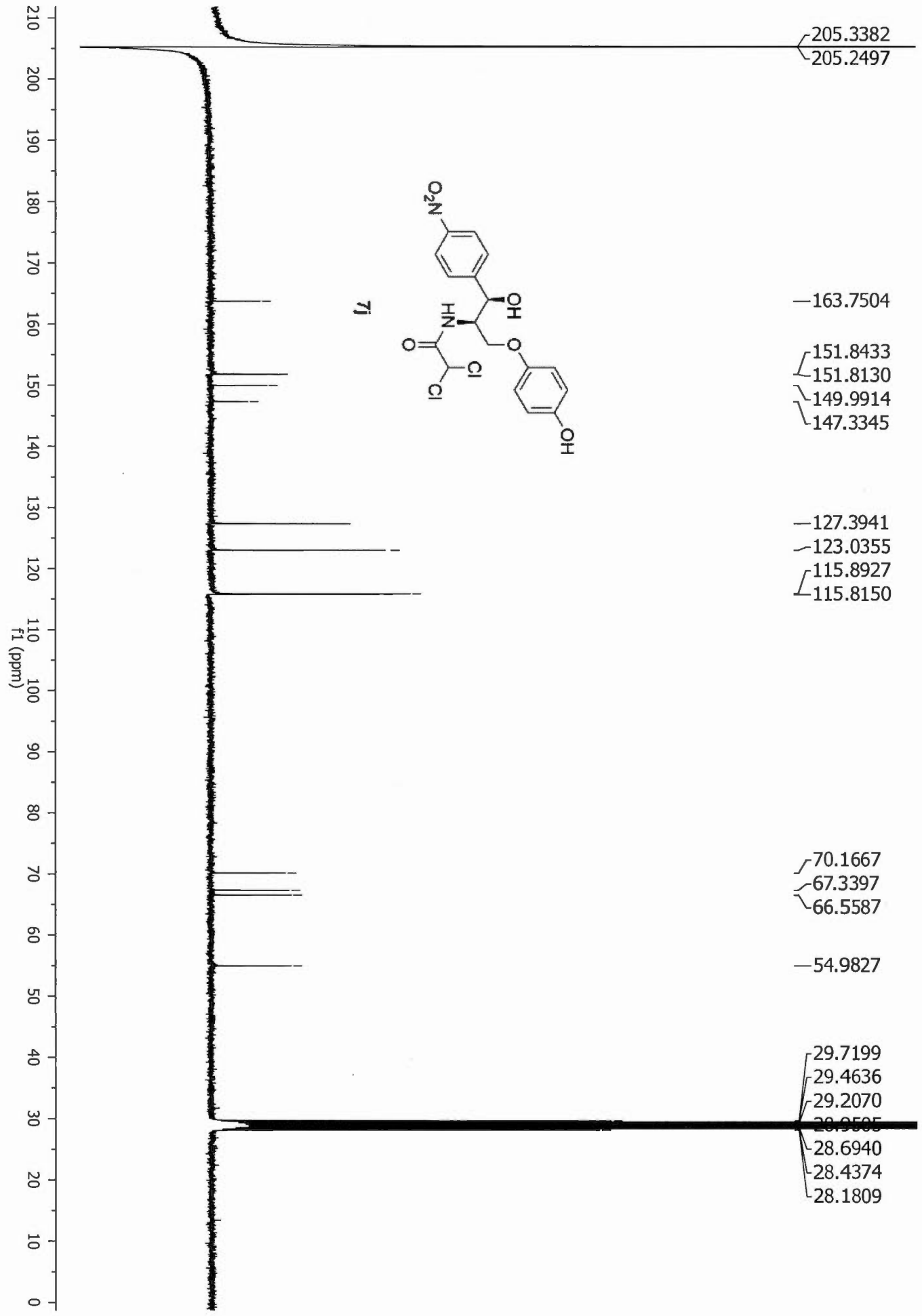
6.8463
6.8378
6.7913
6.7829
6.7693
6.7611
6.3927
5.4586
5.3898
4.5443
4.5350
4.5240
4.5209
4.5147
4.5015
4.4917
4.4854
4.4821
4.4713
4.4620
4.2616
4.2380
4.2295
4.2059
4.0521
4.0325
4.0200
4.0004
OH
O
OH
Cl
HN
Cl
O2N
O
7j
2.00
0.88
3.03
4.18
0.95
0.76
1.14
1.09
1.11
1.11
6.01
3.08
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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147.3345
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123.0355
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70.1667
67.3397
66.5587
54.9827
29.7199
29.4636
29.2070
28.6940
28.4374
28.1809
f1 (ppm)