

Synthesis of multicyclic ring systems including an alternate route to Meyers'
lactam derivatives

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Abstract

Synthesis of multicyclic ring systems including an alternate route to Meyers' lactam derivatives

The first half of this product was conducted at the University of East Anglia under the supervision of Dr S.P Bew and Professor Andrew Cammidge.

The potent antitumour antibiotics azinomycin A and B are of particular interest as targets for synthetic organic chemists due to their medicinal properties. The natural products comprise unique structures which includes the 1-azobicyclo[3.1.0]-hexane ring system and were originally isolated from *Streptomyces sahachiroi* and later from *Streptomyces griseofucus*. Their structures were defined in 1983 and since then there has been significant international competition in total synthesis of azinomycin A or B. Total asymmetric synthesis of azinomycin A was achieved in 2001 however further investigation is needed to provide alternative pathways for azinomycin B.

This investigation aims to synthesise compounds to then apply gold containing complexes towards the studies in formation of bicyclic aziridines; differing from current syntheses that require long reaction times and employing high temperatures. This project will aim to focus on the ability of catalytic quantities of Au(I) and or Au(III) to mediate the synthesis of 1-azabicyclo [3.1.1]-aziridines derived from optically active homopropargyl amines.

The second half of this product was conducted at the Université et INSA de Rouen, *Laboratoire COBRA (IRCOF)*, under the supervision of Dr Jean-François Brière and Sylvain Oudeyer within the heterocycles team directed by Dr Vincent Levacher.

The groups of Wallace and Levacher developed independently in 2003 a diastereoselective construction of chiral fused oxazolidinone lactams by utilising the use of Meyers' lactamisation methodology. This provided high atroposelection through a central C5 to axial chirality transfer.

The aim of this project will be directed towards the design of alternative strategies in the synthesis of keto-ester Meyers' lactam derivatives. Leading on to provide new atropos derivatives bearing different substituents to envisage them as novel ammonium salts for phase transfer catalysis.

Declaration

The research described in this thesis is, to the best of my knowledge, original except where due reference is made.

Daniel Wightman

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Abbreviations

Boc	<i>tert</i> -Butyloxycarbonyl
Bu	Butyl
d	Doublet
DCM	Dichloromethane
dd	Doublet of doublets
DMAP	4-(dimethylamino)pyridine
DNA	Deoxyribonucleic acid
<i>de</i>	Diastereoisomeric excess
EDA	Ethyl diazoacetate
<i>ee</i>	Enantiomeric excess
eq	Equivalent
Et	Ethyl
EtOH	Ethanol
ISC	Inter strand cross-link
m	Multiplet
Me	Methyl
MS	Mass Spectrometry
NMR	Nuclear Magnetic Resonance
NBS	<i>N</i> -Bromosuccinimide
OTf	Trifluoromethanesulfonate (triflate)
p.p.m	Parts per million
PTC	Phase transfer catalysis
PyTf	Pyridinium triflate
q	Quartet
rt	Room temperature
s	Singlet
t	Triplet
TLC	Thin Layer Chromatography
THF	Tetrahydrofuran
TMS	Trimethylsilyl-
TMSCHN ₂	Trimethylsilyldiazomethane

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1.0 Introduction

1.1 Azinomycin

Azinomycin A (**1**) and azinomycin B (**2**) were isolated from *Streptomyces sahachiroi* and *Streptomyces griseofucus*; the structures were elucidated in 1983 by Nagoaka *et al.* [1]

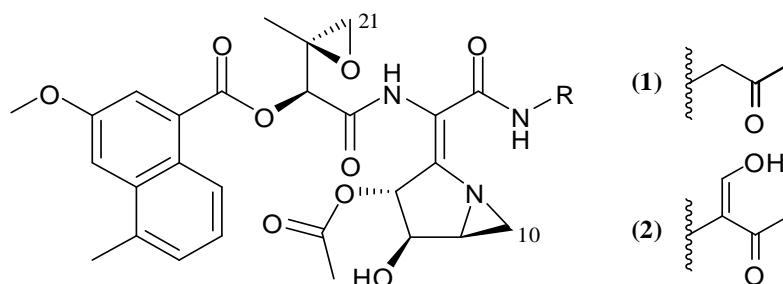


Figure 1: Structure of azinomycin A (**1**) and B (**2**)

The azinomycin natural products A and B have shown to possess potent *in vitro* cytotoxic activity; their mode of action appears to function *via* disrupting cellular DNA replication by interstrand cross-link (ISC) formation within the major groove of DNA. [2] The reactive epoxide and aziridine moieties are responsible for the cross-linking process. The cross linking by azinomycin B occurs by nucleophilic attack on C10 of the aziridine and C21 of the epoxide moiety by the lone pair of electrons from nitrogen at the N7 position that originate from two 5'-disposed guanine bases. This occurs in individual steps to form covalent bonds, exhibiting a binding sequence of 5'-GCC-3'/3'-CGG-5' (figure 2).

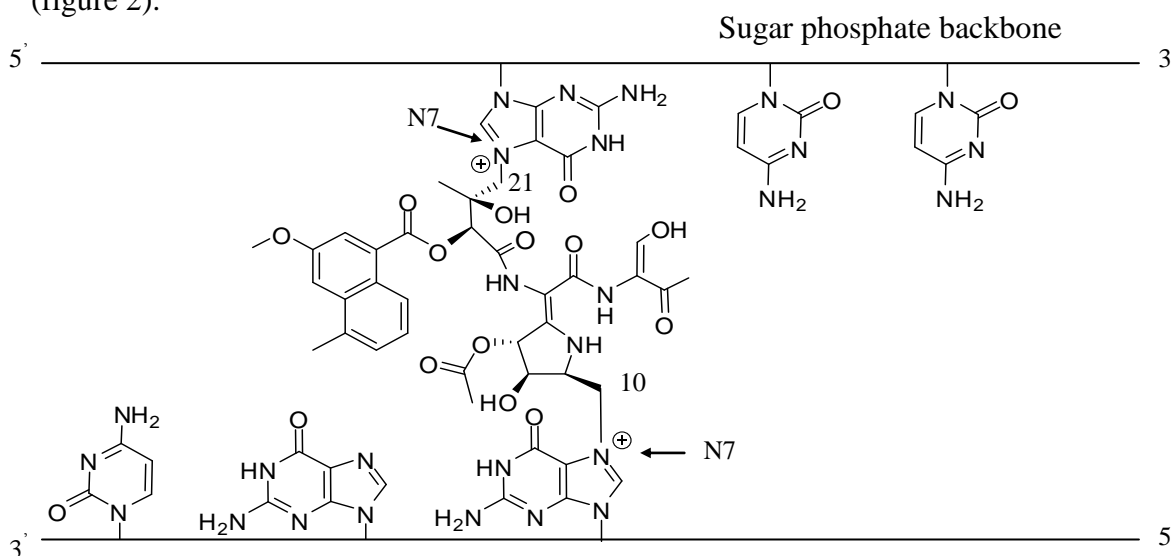
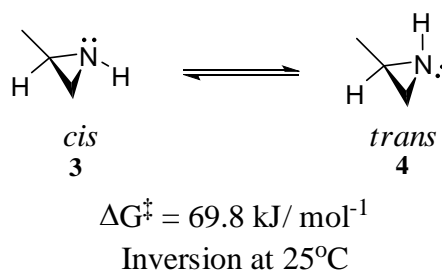


Figure 2: Binding of azinomycin B to DNA at sequence 5'-GCC-3'/3'-CGG-5'. [2]

Synthesis of functional ‘top half’ partial structures of azinomycin A and B have been reported [3] however a total synthesis of azinomycin B has not, although partial syntheses exist, the most difficult challenge is the introduction of the reactive azabicyclic system, particularly with respect to protecting group issues for the C12 hydroxyl group. [3-4]

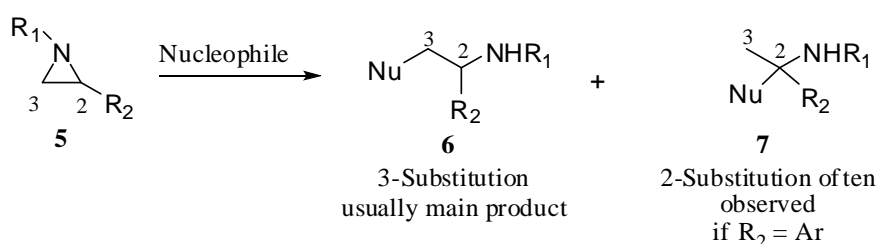
1.1.2 Physical Properties of the Aziridine Moiety

Aziridines are organic compounds comprising a nitrogen atom and two carbon atoms that are arranged to form a three membered heterocycle. The bond angles in aziridines are approximately 59.7° exhibiting a bonding model that can be described as bent. In comparison, the bond angles are less than the traditional hydrocarbon bond at 109.5° consequently resulting in the angle strain observed; this arrangement contributes to the high reactivity of aziridines. [5] The angle strain (approximately 111 kJ/ Mol^{-1} , comparable to ethylene oxide) increases the barrier to nitrogen inversion giving rise to isolation of *cis* and *trans* diastereomers. [6]



Scheme 1: Inversion of aziridine

It is not possible to assume bond angles of 60° in the aziridine bonding system with sp^3 hybridisation. Decreasing the bond angle about the amine nitrogen atom (C-N-C) results in an increase of p-character for the two bond hybrids participating in the C-N bonds. An increase in s-character is consequently observed with the hybrid involved in the nitrogen lone pair and the N-H bond making the bond lengths shorter. The increase in s-character causes the aziridine moiety to be less basic than acyclic aliphatic amines, displaying a pK_a of 7.98 for the conjugate acid. [7] Aziridines are susceptible to undergo ring-cleavage reactions due to the combination of the angle strain and the electronegativity of the heteroatom.



Scheme 2: Nucleophilic ring-opening of an aziridine. Ring-opening of an aziridine proceeds *via* nucleophilic attack directed at the least substituted position. [6]

1.2 Gold Complexes

1.2.1 Historical Perspective

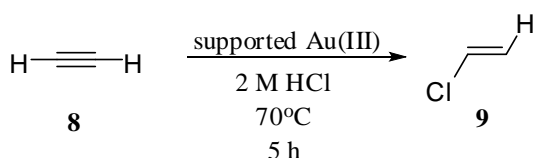
Over the last few years, gold containing complexes have increasingly become of interest for synthetic chemists.^[8] Once considered to be catalytically inactive, only a few reports of the use of gold as a catalyst existed, none however demonstrated the use of gold as a superior catalyst. Before 1960, only a few references were available on the catalytic activity of gold. The catalytic activity of gold was investigated using macroscopic gold as a wire, foil or powder, the results gave minimal indication that there was activity, surprisingly this work was not investigated further, but the potential was there to be investigated. Dulong and Thenard observed in 1983 that amongst other metals, gold catalysed the decomposition of ammonia.^[9]

In 1834, Michael Faraday observed that the reaction of hydrogen with oxygen was catalysed by gold at room temperature,^[9, 10, 11] this reaction was studied further in 1906 implementing a 'gold gauze and involved what must have been the first attempt to follow the kinetics of a catalysed reaction'.^[9, 12] It was later discovered in 1925 that the removal of dissolved oxygen and use of gold powder as a catalyst accounted for the positive effect observed.^[13, 14]

Bond *et al.* reported the use of supported gold catalysts for the hydrogenation of olefins in 1973.^[15] Haruta and Hutchings simultaneously but individually reported their research into the use of heterogeneous gold complexes as being the optimum catalyst. In the 1980's Haruta *et al.* investigated the low temperature aerobic oxidation of carbon monoxide to carbon dioxide with gold nanoclusters (approximately 2 – 4 nm in diameter) using oxide metals. This showed high reactivity even at -70°C ($\alpha\text{-Fe}_2\text{O}_3$ as support), demonstrating that the support of metal nanoclusters influences reaction temperature and that the size of gold clusters affects the activity, with smaller clusters expressing higher activity. Although the reaction mechanism was unclear, it was apparent that heterogeneous gold catalysts do have a unique catalytic activity towards oxidation reactions.^[16, 17, 18]

The temperature range at which activity for CO oxidation is observed was extended in 2006 by Lahr and Ceyer to as low as -203°C by using an Au/ Ni(III) surface, 'thus questioning the potential role of the oxide supports'.^[19, 20, 21, 22]

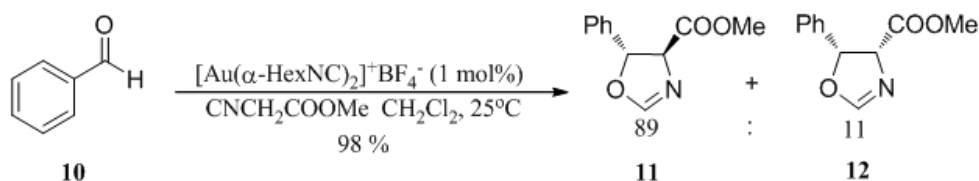
Hutchings discovered the efficiency of gold(III) by experiments that illustrated gold to be the most active and efficient catalyst for the hydrochlorination of ethyne (scheme 3).^[20]



Scheme 3: Gold catalyzed hydrochlorination of ethyne. ^[20]

The active gold(III) containing catalysts were prepared *via* impregnation of chloroauric acid solutions onto activated carbon. All metal chloride catalysts for this reaction deactivate with time on steam when used in a standard fixed bed reactor. However results from using gold catalyst systems showed a lower rate of deactivation than expected. ^[20]

These were some of the first reports that showed gold to be the optimal choice of catalyst in comparison to other metals. These results contradicted previous reports stating gold to be catalytically inactive. In 1986, Ito *et al.* demonstrated that gold was most favourable in a homogeneous catalytic asymmetric aldol reaction utilising a gold(I) catalyst and an enantiomerically pure ferrocene diphosphane ligand for the addition of a carbon nucleophile to a carbonyl group, obtaining yields ranging between 83 – 100 %. An example is illustrated in scheme 4. ^[23]



Scheme 4: Asymmetric aldol reaction of an isocyanoacetate with aldehydes using ferrocenylphosphine-gold(I) complex as catalyst to produce optically active 5-alkyl-2-oxazoline-4-carboxylates with high enantio- and diastereoselectivity. ^[23]

In 1991 further development in homogeneous catalysis was based on Hutchings heterogeneous hydrochlorination of acetylene; the addition of nucleophiles, i.e. to alkynes was investigated for alcohols, water, and amines by Fukuda and Utimoto. ^[24] Approximately seven years later in 1998, Teles *et al.* ^[25] showed that good turnovers and frequencies can be achieved using cationic gold(I) species for the addition of alcohols to alkynes. Earlier in 1996, Haruta *et al.* showed that high selectivity was achievable in the heterogeneous oxidation of propene to propene oxide with the application of gold on titania. ^[26] Two years later, Prati and Rossi showed that even the position of oxidation of different alcohols and carbohydrates with molecular oxygen was possible, contributing another breakthrough in gold catalysis. An example with the oxidation of propane-1,2-diol is shown (Figure 3). ^[27]

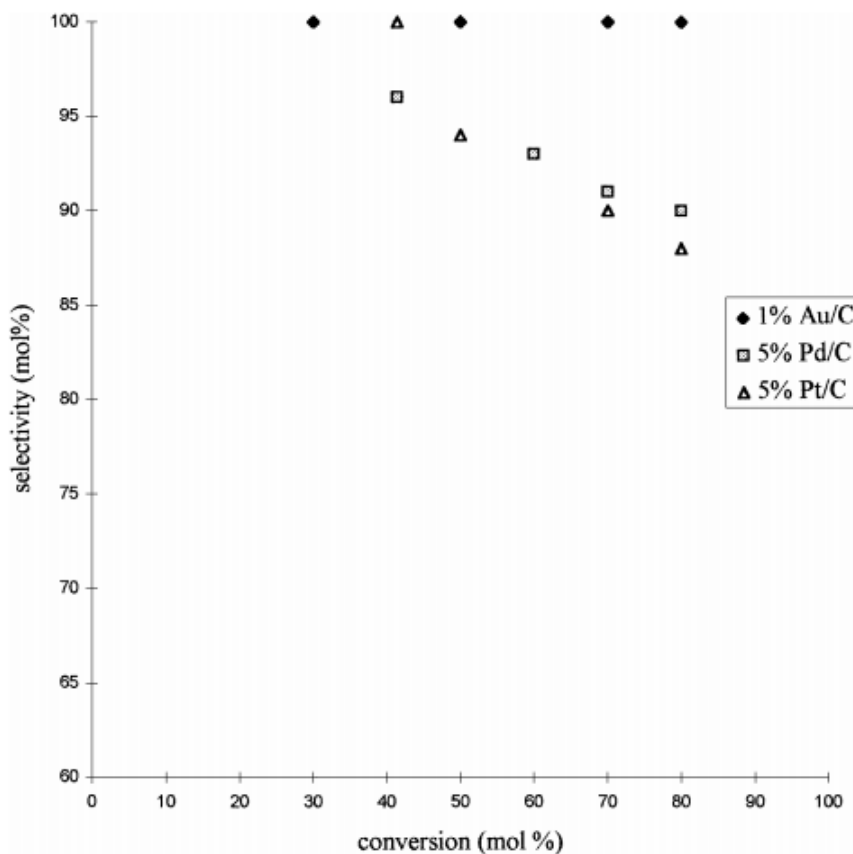


Figure 3. Oxidation of propane-1,2-diol using 1 % Au/C, 5 % Pd/C and 5 % Pt/C. Reaction conditions: NaOH/propane-1,2-diol = 1; diol/M = 1000; pO₂ = 300 kPa; t = 1 h, gold on carbon catalyst was prepared by deposition-precipitation method. ^[28]

In 2000, development into the nucleophilic addition from alkynes to olefins for both intramolecular additions of alcohols and the intermolecular addition of arenes by Hashmi *et al.* further work by Yang and He led to the evidence that the reactions of electron rich arenes proceed *via* an initial activation of an aryl-C - H bond. ^[28, 29] These are just a handful of reports that have emerged which have supplied the driving force necessary to lay down the tracks for further research. These systems have significant potential for a positive impact on the environment and economy because of their high selectivity and also the low temperature at which they function. ^[30]

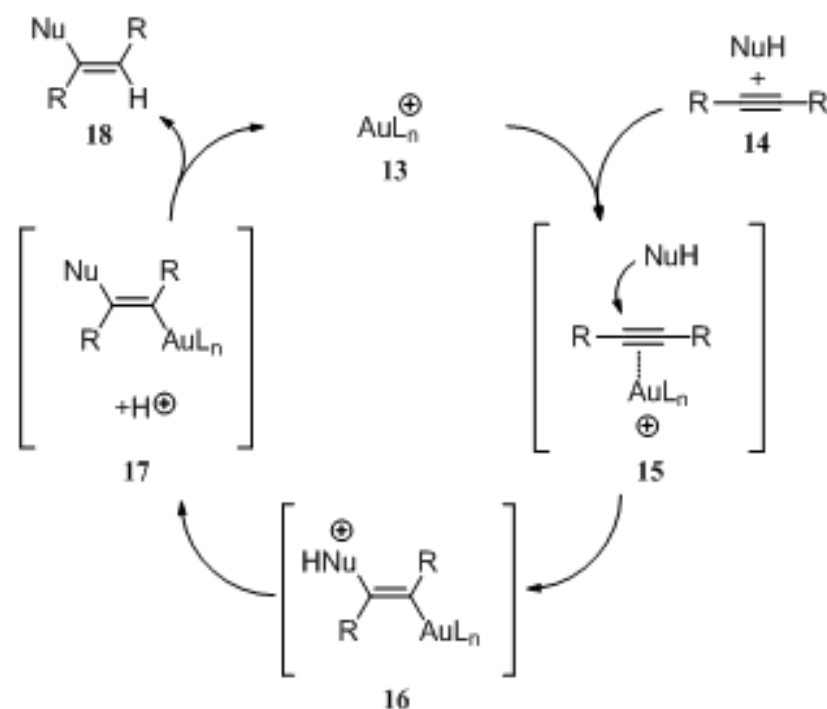
1.2.2 Nucleophilic Additions to π Systems

Activation of C - C triple bonds arises due to co-ordination to gold complexes making them susceptible to attack by nucleophiles. The same goes for carbonyl groups as they too can be activated for the addition of a nucleophile. In most cases without the catalyst, the reaction either does not occur or proceeds very slowly. The use of alkynes as substrate are commonly used, however alkenes have become frequently popular. [22, 30]

1.2.3 Fundamental Reactivity Pattern in Gold Catalysis

In the following reaction sequence (scheme 5), the activated gold catalyst **13** interacts with the π - system of the substrate **14** to generate the intermediate **15**, which subsequently undergoes nucleophile attack. The nucleophilic group in complex **16** contains a proton that undergoes deprotonation and then subsequent protodemetalation liberates the gold catalyst giving the reaction product **17** that subsequently affords **18**. It has been evident that this process occurs in an *anti* manner however '*syn* addition was reported using norbornenes'. [22,

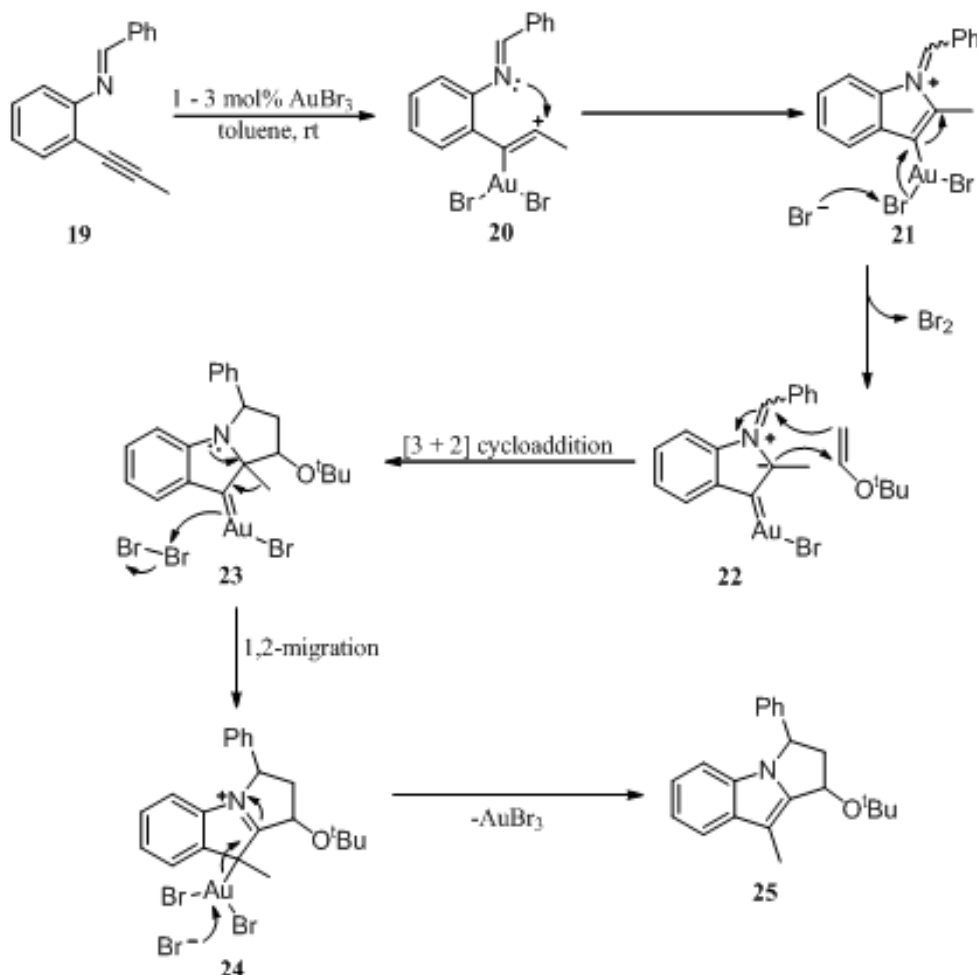
^{31]} The oxidation state of gold does not change in the catalytic cycle. [32]



Scheme 5: The most fundamental reactivity pattern in gold catalysis. [32]

1.2.4 Imine Cyclisation

The imine and alkyne functional groups play an important part in this project. The cyclisation reaction (scheme 6) was reported by Iwasawa *et al.* and serves as an interesting example of ring closure and thus illustrating the use of gold catalysis in cyclisation reactions.



Scheme 6: *In situ* generation of 1,3 dipoles.

Iwasawa *et al.* reports that only 1 - 3 mol% of the gold complex AuBr₃ was sufficient to promote the synthesis and '[3 + 2] cycloaddition of transition-metal-containing azomethine ylides derived from *N*-(*o*-alkynylphenyl) imines bearing an internal alkyne moiety'.^[22, 33]

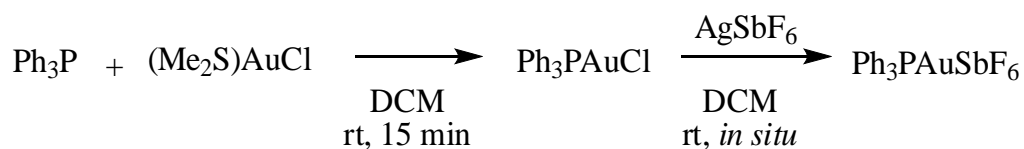
Gold(III) mediated 5-endo cyclisation of imine **19** and loss of bromine forms the azomethine ylide intermediate **22**. This leads to a 1,3-dipolar cycloaddition with an alkene to afford **23**, 1,2-migration of the methyl group delivers the product **25** and regeneration of the catalyst.^[33]

The ring closing mechanism of attack at the propargyl position from the imine is of particular interest, especially in the application of forming 1-aza-bicyclo [3.1.1]-aziridines. 'Alkynes are the most successful and most frequently used reaction partners for gold catalysts'.^[8a] The

mechanistic use of the alkyne functional group in application to this project will be discussed in more detail in the project aim.

1.2.5 Preparation of Catalysts

Gold catalysts can be utilised in cycloisomerisation reactions as demonstrated in scheme 6. ^[8a] Gold(I) catalysts exhibit carbophilic characteristics which is an important feature in this project. Phosphine gold(I) complexes such as Ph₃PAuCl will be used for the imine cyclisation due to their stability and high activity that can be induced by silver hexafluoroantimonate (AgSbF₆). This acts as a counter ion to the gold(I) complex, this subsequently generates the activated gold complex Ph₃PAuSbF₆ which will be formed *in situ* as shown in scheme 7. Toste *et al.* reports the use of 1 - 5 mol% catalytic amounts of Ph₃PAuSbF₆ in cyclisation reactions ^[34]; this will be discussed further in the project aim.



Scheme 7: Formation of Ph₃PAuCl and subsequent *in situ* activation by AgSbF₆. ^[34]

1.2.6 Properties and Application of Gold

Catalytic gold complexes are strong Lewis acids, giving the potential to stabilise cationic intermediates, the 14-electron [AuL]⁺ fragment is highly electrophilic. Gold(I) complexes present good chemoselectivity and functional group tolerance, ‘traits that are crucial for application in complex molecular environments’. ^[35] These features can be accounted for by its strong electronegativity (2.4) and relativistic effects. In Au, the relativistic contraction of the valence 6s or 6p orbitals and expansion of 5d orbitals due to shielding results in strengthened Au-L (Au-ligand) bonds.

The relativistic contraction of the 6s orbitals results in Au-L bonds being shorter than expected (figure 4). ^[8c] Contraction of the 6s orbital can stabilise electrons of the lowest unoccupied molecular orbital (LUMO) which explains Lewis acidity. Expansion of 5d orbitals can destabilise the highest unoccupied molecular orbital (HOMO), which might stabilise further intermediates. ^[36] Back bonding can result from the weak 5d to π* transitions which causes the Au(I)-π-alkene/alkyne complex to be more susceptible toward outer-sphere nucleophilic attack. ^[35, 8c, 37]

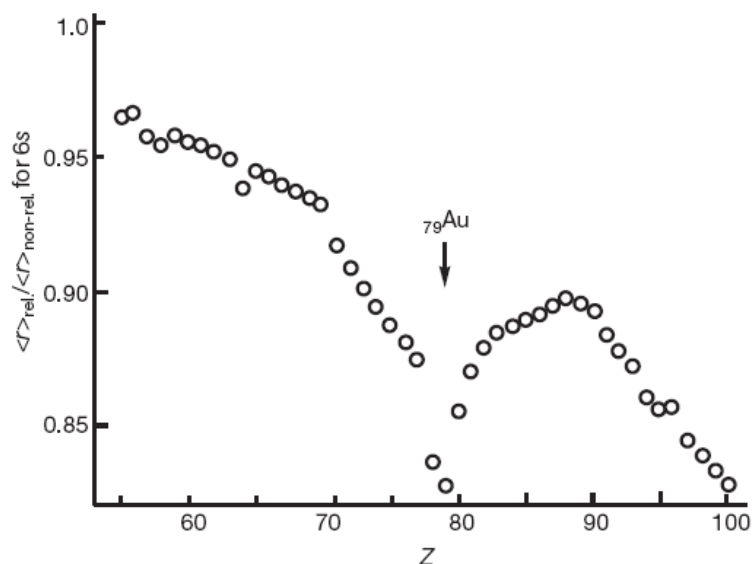


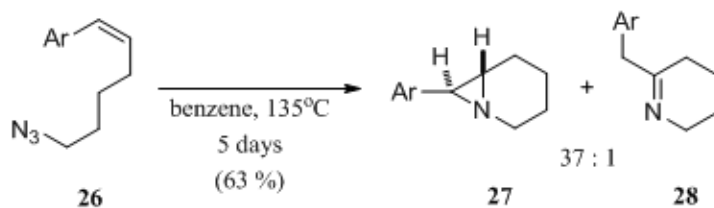
Figure 4: Calculated relativistic contraction of the 6s orbital. The relativistic and non-relativistic 6s orbital radii were determined computationally (Z = atomic number).^[36]

The phenomenon of ‘aurophilicity’ also accounts for the strength of Au-L bonds. Aurophilicity refers to the aggregation of gold complexes to form weak Au-Au interactions to produce a stabilising effect similar to that of hydrogen bonds. This is due to the increase in the Au^+ dipole polarisability that subsequently leads to an increase in dispersive type $d^{10} - d^{10}$ interactions. ‘Such aurophilic interactions can reach bond energies of up to 30 kJ mol^{-1} .^[38]

2.0 Results and Discussion

2.1 Aims of Research

In this project we aim to investigate the ability of catalytic quantities of Au(I) and or Au(III) to mediate the synthesis of 1-aza-bicyclo[3.1.1]-aziridines *via* imines derived from optically active homopropargyl amines. The requirement for an alternative synthesis of bicyclic aziridines is driven by their existence in the natural products azinomycin B and mitomycin A.^[6] Gold containing complexes have already proved efficient in application to total synthesis^[32] and show great potential for further expansion. Current routes of synthesis to bicyclic aziridines require high temperatures, long reaction times and utilise dangerous starting materials such as azides (scheme 8).^[39]



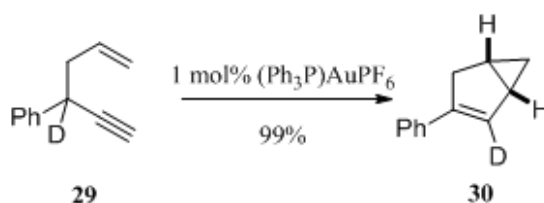
Scheme 8: Synthesis of a bicyclic aziridine by Kim *et al.*

The use of imines within gold mediated cyclisation reactions has returned limited reports and none that produces the aziridines of complexity that we propose.

2.2 Methodology

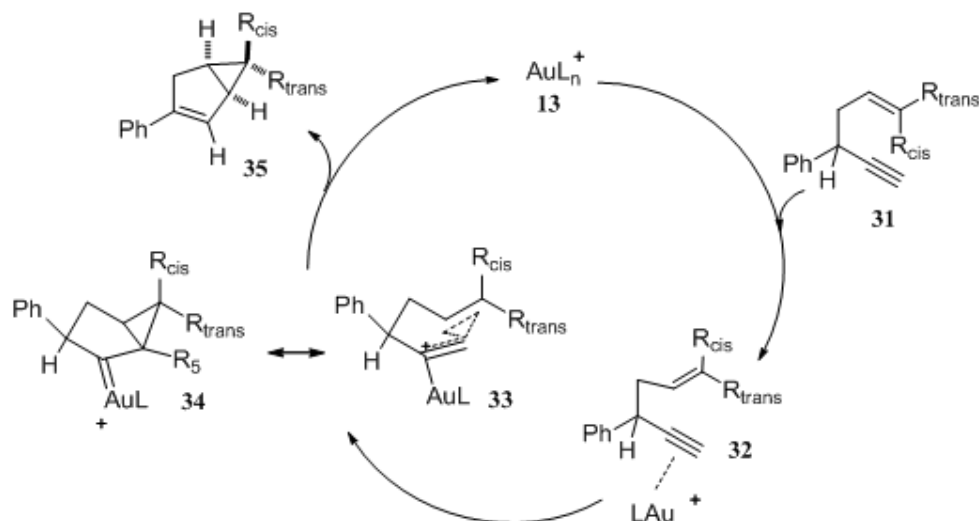
2.2.1 Mechanistic View

The formation and mechanism of bicyclo[3.1.0]hexane was reported by Toste *et al.* from labelling studies of a 1,5 enyne (**29**) with deuterium.^[34]



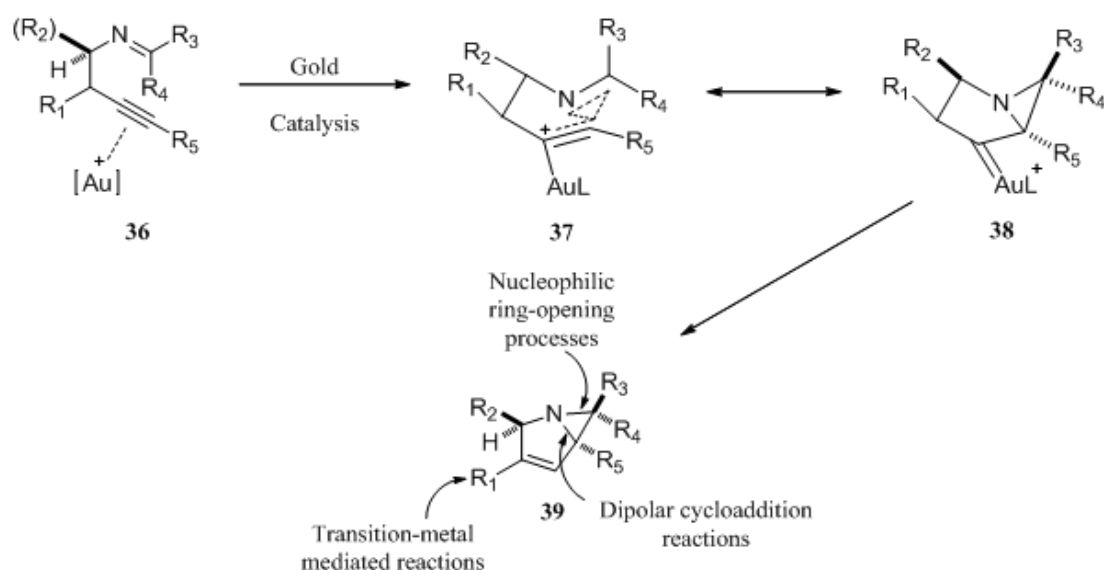
Scheme 9: Gold(I) catalysed conversion of a 1,5 enyne (**29**) to a bicyclo[3.1.0]hexene (**30**) in which the deuterium was selectively incorporated at the vinyl position.

Toste *et al.* studied the stereochemical course of the rearrangement and found that the gold(I)-catalysed reaction of substrates that contained 1,2-disubstituted olefins is stereospecific. From the data collected they proposed a mechanism that is outlined in scheme 10.^[34] Co-ordination of Au(I) to the alkyne (**31**) and subsequent nucleophilic addition of the pendant olefin produces cyclopropylcarbinyl cation **33** and **34**. A 1,2-hydrogen shift onto a cation or a gold(I) carbene provides the bicyclo[3.1.0]hexene product (**35**). By considering half-chair transition states, the stereoselectivity and stereospecificity of the reaction can be accounted for, in similarity to the acetylenic Cope re-arrangement.^[34]



Scheme 10: Proposed mechanism for Au(I)-catalysed cycloisomerisation ^[34]

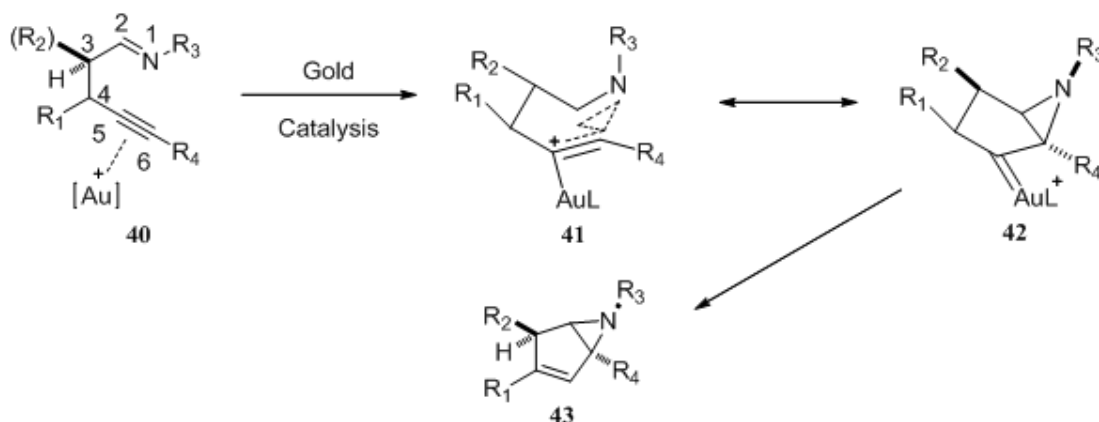
The mechanism outlined in scheme 10 is fundamental in the following proposed reaction sequence outlined in scheme 11.



Scheme 11: Proposed reaction sequence in the formation of 1-azobicyclo[3.1.1]-aziridines *via* gold catalysis of imines derived from optically active homopropargyl amines.

The reaction sequence (scheme 11) follows a similar pattern to scheme 10, the product (**39**) has the potential to undergo a variety of different reactions for further research. Potentially, different structural analogues of **42** can be synthesised *via* the same methodology to produce a range of heterocycles. Furthermore, transposing the nitrogen to generate compounds with

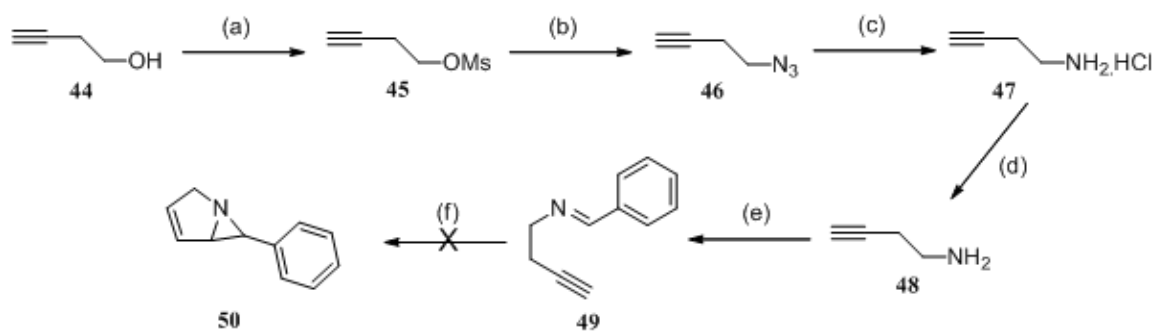
structural features such as **42** could then potentially generate **43** after alkyne activation and cyclisation by gold catalysis as illustrated in scheme 12.



Scheme 12: Proposed reaction sequence in the formation of bicyclic aziridines *via* gold catalysis of imines derived from optically active homopropargyl amines.

2.3 Previous work

The following reaction scheme conducted in the undergraduate research project provided a route to attempt cyclisation with gold catalysis.^[40]

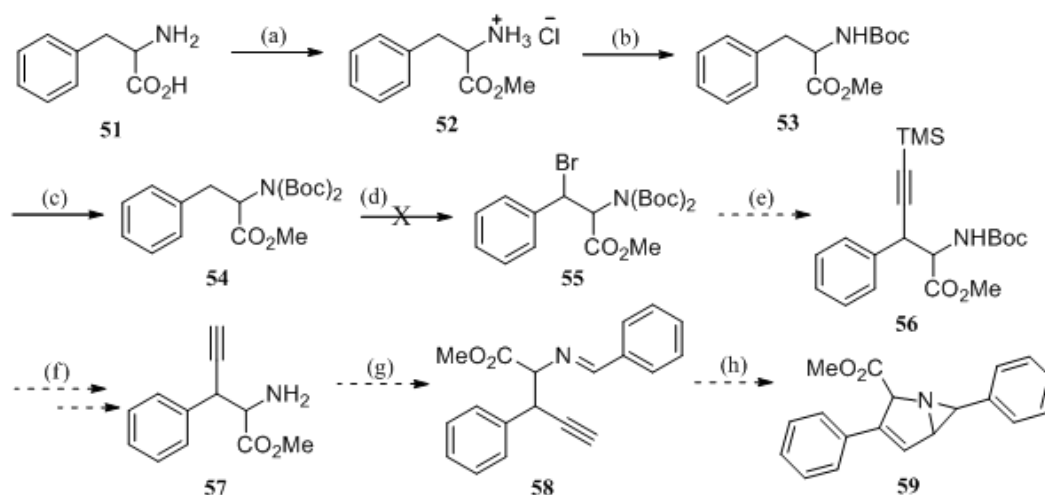


Scheme 13: Reaction conditions (a) MsCl, DCM, Et₃N, DMAP, 2 h at 0°C, 3 h at rt, 89 %; (b) NaN₃, DMF, 70°C, 3.5 h, 56 %; (c) Ph₃P, Et₂O, 2 h at 0°C, 20h at 25°C;^[41] (d) 10% NaOH, 25 % (2 steps); (e) Benzaldehyde, DCM, 48 %; (f) Au(I), DCM.^[34]

Unfortunately the product in scheme 13 (f) was not observed. A reason for this could be because in Toste's model (scheme 10, page 11), there is an aromatic ring that could help stabilise the transition state. A different approach is therefore needed to synthesise a precursor to attempt cyclisation *via* gold catalysis with the phenyl substituent.

2.4 Proposed reaction schemes

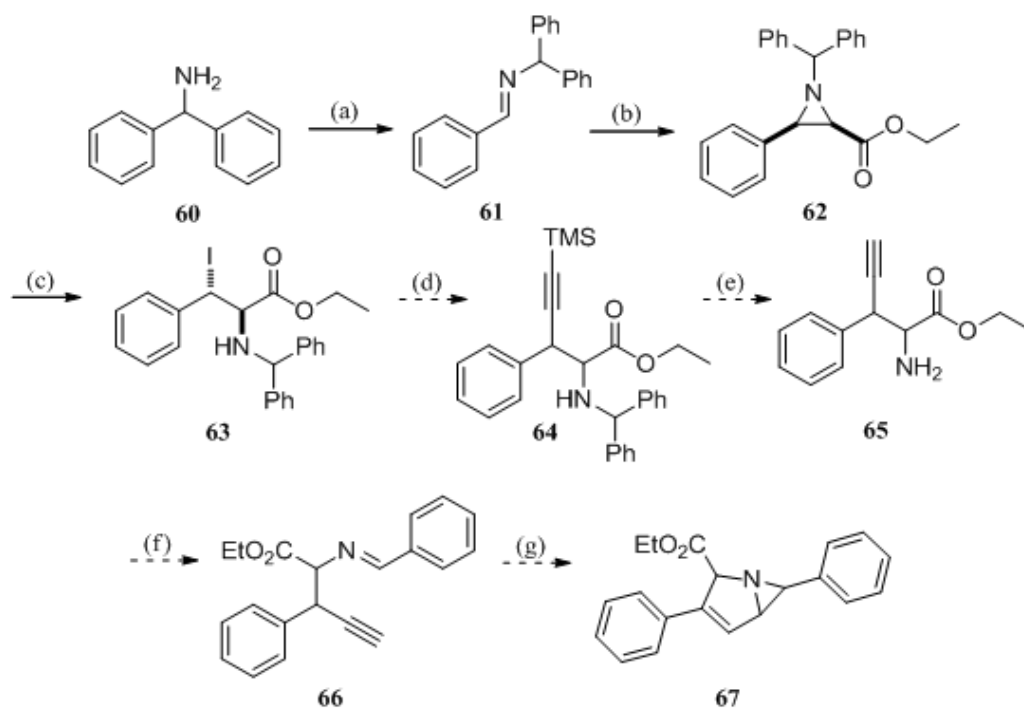
The following reaction schemes provide a potential approach to the synthesis of the desired propargyl amine whilst offering a series of interesting compounds. The Suzuki coupling will need to be attempted using TMS alkynylboronate. ^[42] Afterwards deprotection steps followed by imine formation should provide the desired propargyl imine to probe the gold catalysis methodology as performed on a similar compound by Toste *et al.* ^[34] (scheme 10, page 11).



Scheme 14: Reaction conditions (a) Acetyl chloride, Phenyl alanine, MeOH, 82 % (b) Boc₂O, NaHCO₃, H₂O, 1,4-dioxane, 65 % (c) Boc₂O, DMAP, Acetonitrile, 76 % (d) NBS, (trifluoromethyl) benzene, (e) TMS alkynylboronate, NiI₂, trans-2-aminocyclohexanol, NaHDMS, *i*-propanol, 60°C ^[43], (f) deprotection steps, (g) benzaldehyde, DCM, (h) Au(I), DCM. ^[34]

Methyl ester and Boc protection of the readily available amino acid Phenylalanine is well known chemistry and proceeded in good yield; however the free radical bromination step (scheme 14, d) following the procedure of Crich *et al.* ^[44] was unsuccessful. A reason for this could be due to not having the right equipment, for example, in the procedure, a 250W Krypton lamp was used, in this attempt; a 3W Xenon lamp was used. The difference in power of the lamp may not have produced the same photochemistry. In addition, the solvent of choice was CCl₄; this was substituted with (trifluoromethyl)benzene as suggested by a reviewer of the publication, ^[44] but unfortunately only starting material was observed by ¹H-NMR analysis. An alternative method is to form the iodo or bromo halogenated benzhydryl nitrogen protected phenylalanine ethyl ester derived from ring opening the benzhydryl

aziridine (scheme 15). Applying Fu's work *via* a Suzuki coupling mechanism should potentially be another viable pathway to obtain the desired propargyl imine.



Scheme 15: Reaction conditions (a) Benzaldehyde, Benzhydrylamine, DCM, 16 h (b) Ethyl diazoacetate, pyridinium triflate, DCM, 16 h (c) MgI_2 , diethyl ether (d) TMS alkyneboronate, NiI_2 , trans-2-aminocyclohexanol, NaHDMS, *i*-propanol, 60°C ^[43], (e) deprotection steps (f) Benzaldehyde, DCM (g) Au(I), DCM. ^[34]

These reaction schemes have been constructed to ensure the incorporation of the aromatic and alkyne group in the following relationship to the nitrogen atom as shown in figure 5.

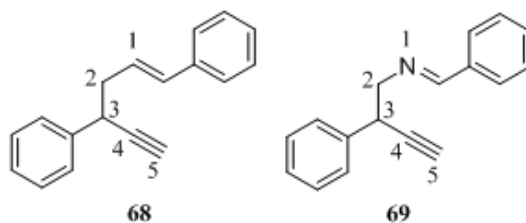
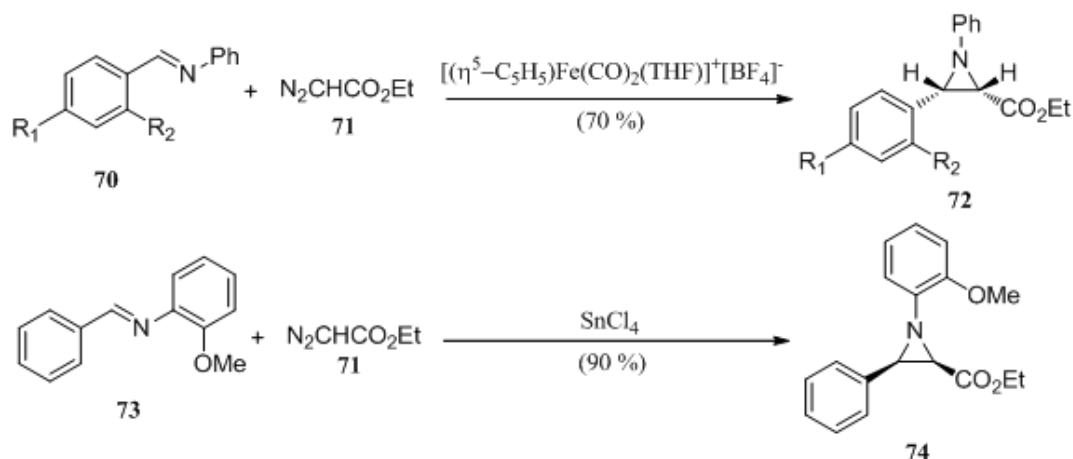


Figure 5: Toste's compound (**68**) and the desired compound (**69**).

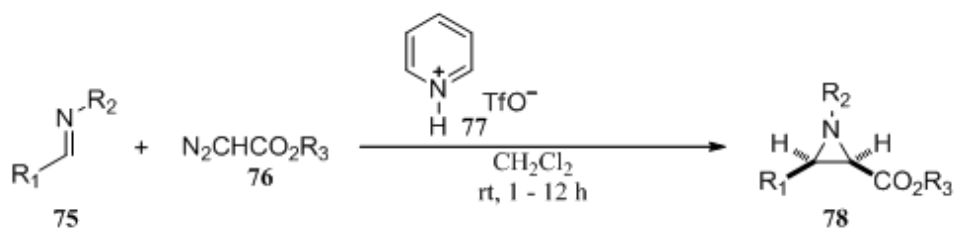
2.5 Preparation of aziridines by reaction of diazo compounds with imines

A major route used for the preparation of aziridines is the addition of carbenoids across an imine π -bond [C=C=N]. Ethyl acetate is commonly used to provide the carbon fragment. The reaction can be initiated by the application of various catalysts, such as the iron Lewis acid affording predominately the *cis*-aziridine. ^[45] The tin catalysed aziridination is another example (scheme 16). ^[46]



Scheme 16: Iron and tin catalysed activation of imines.

Previous research within our group identified pyridinium triflate as a good catalyst for the synthesis of *cis*-aziridines, proceeding to completion quickly and efficiently at ambient temperature and with only 1 – 10 mol% of the pyridinium triflate salt (scheme 17). ^[47]

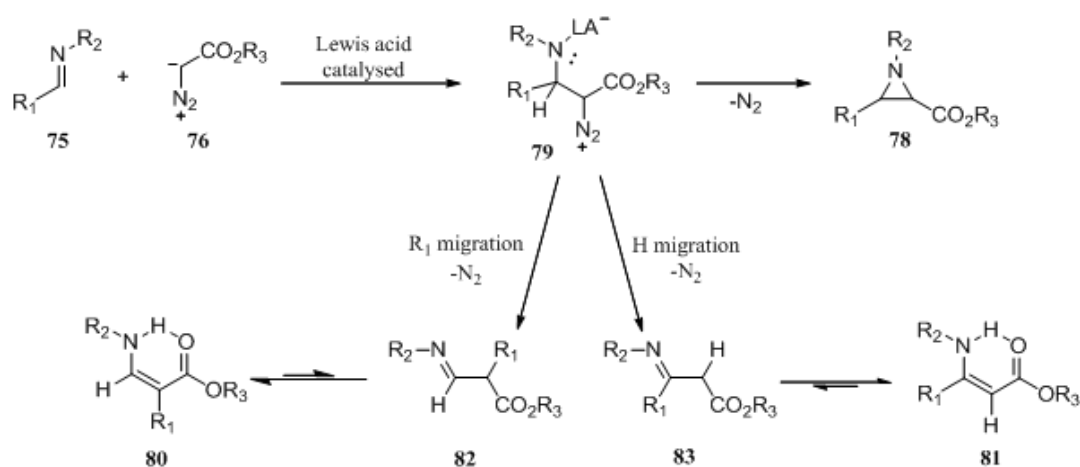


Scheme 17: Pyridinium triflate catalysed aza-Darzens reaction

Pyridinium triflate is synthesised from trifluoromethanesulfonic acid and pyridine following a published procedure. ^[48] The white compound produced should be stored in anhydrous conditions under an inert atmosphere to preserve the quality of the catalyst.

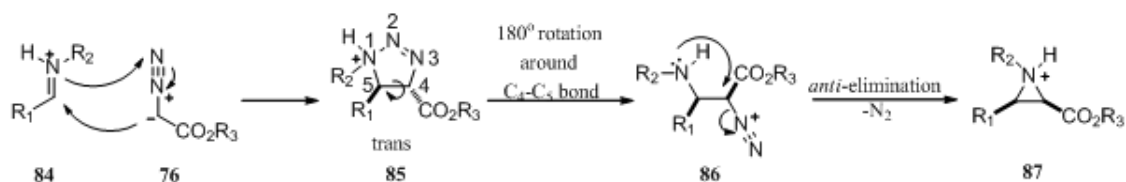
The accepted mechanism of the aza-Darzens reaction by Templeton *et al.* is described in (scheme 18, page 16). ^[49] Lewis acid activation of the imine allows the nucleophilic addition of diazoacetate reagents resulting in a zwitterions intermediate (79), subsequent ring closure

and loss of nitrogen forms the aziridine product (**78**). The equilibrium between (**78**) and enamides (**80**) and (**81**) was excluded by Templeton experimentally.



Scheme 18: Aza-Darzens mechanism proposed by Templeton *et al.* [49]

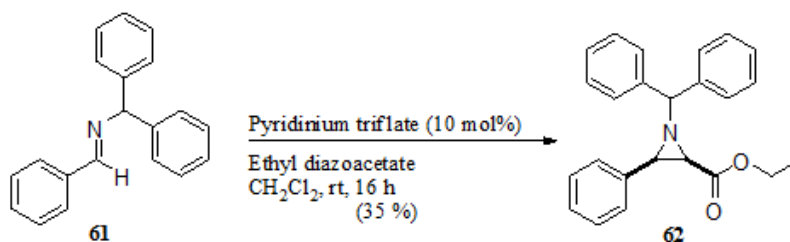
An alternative mechanistic pathway in the occurrence of a [3 + 2] dipolar cycloaddition between the double bond of *N*-substituted iminium ions and the triple-bond of the diazo moiety was suggested by a previous member of the group. [47]



Scheme 19: Proposed concerted [3+2] cycloaddition followed by *anti*-elimination to afford the *cis*-aziridine. [47]

2.6 Synthesis of *N*-protected benzhydryl aziridine

In relation to scheme 15(a) (page 14), the amine of choice in the imine formation was benzhydrylamine, this was selected to act as a protecting group for the nitrogen in the ring opening or coupling steps following aziridination. The imine formation proceeded in good yield (70 %). Subsequent aziridination of imine **61** (scheme 20) is described:



Scheme 20: Pyridinium triflate catalyzed aziridination of **61**.

The reaction was performed using anhydrous solvent and under an inert atmosphere. Unfortunately the synthesis of the benzhydryl aziridine (**62**, scheme 20) proceeded in low yield (35 %). ¹H-NMR analysis indicated a lot of starting material even after 24 hours, sometimes a second 10 mol% of pyridinium triflate was added in an attempt to catalyse the reaction. As expected nitrogen bubbles were observed indicating the start of the reaction but the formation appeared slow. The low yield could be due poor reactivity of the benzhydrylamine. Aziridine compounds can be easily identified by the doublets observed in the ¹H-NMR spectra. Typical $J_{2,3}$ values reported for *cis*- and *trans*-aziridines are 7 ± 0.5 Hz^[46] and 3 ± 0.5 Hz^[50] respectively. In this example (figure 6), the doublets corresponding to the *cis*-aziridine shown are at δ 3.21 and 2.66 ppm (d, $J = 6.9$ Hz, 1H) and 2.66 (d, $J = 6.8$ Hz, 1H)

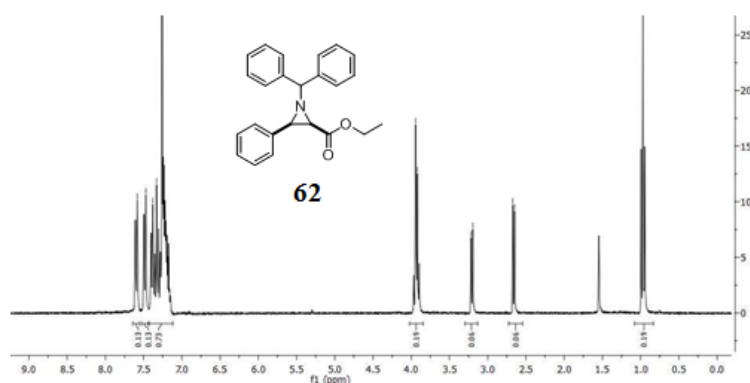
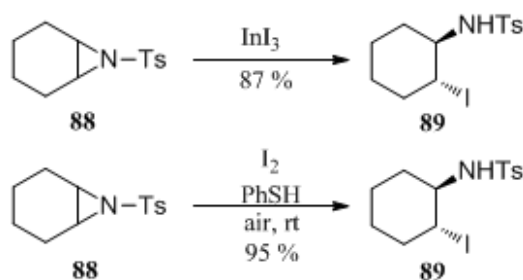


Figure 6: Compound **62**. ¹H-NMR (300 MHz, CDCl₃) δ 7.60 (d, $J = 7.3$ Hz, 2H), 7.48 (d, $J = 7.0$ Hz, 2H), 7.43 – 7.12 (m, 11H), 4.02 – 3.85 (m, 3H), 3.21 (d, $J = 6.9$ Hz, 1H), 2.66 (d, $J = 6.8$ Hz, 1H), 0.97 (t, $J = 7.1$ Hz, 3H).

2.7 MgBr₂ and MgI₂ mediated ring opening of aziridines

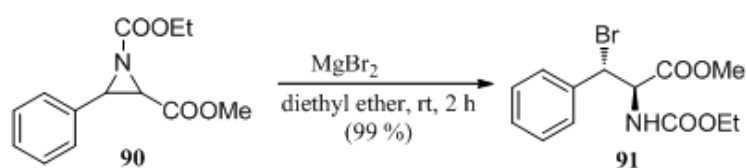
In order to test coupling reactions, introduction of a halogen atom was required. Aziridines undergo ring-opening reactions with a variety of nucleophiles. Halide-mediated ring opening has been reported by Yadav *et al.* with the use of InI₃^[51] and by Wu *et al.* with iodine promoted thiophenol;^[52] the latter being advantageous without the use of heavy metals.



Scheme 21: Halide mediated ring opening of an aziridine by Yadav and Wu *et al.*

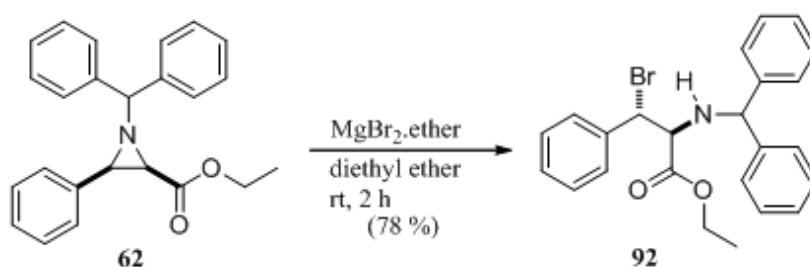
Aziridine **62** was tested with the conditions set by Wu *et al.* but there was difficulty in separation of what was suspected as the desired product and starting material.

Searching the literature returned some results with the use of magnesium bromide etherate in the ring opening of epoxides.^[53] More interestingly however was the use of magnesium iodide but more specifically magnesium bromide on aziridines by Righi *et al.* (scheme 22).^[54]



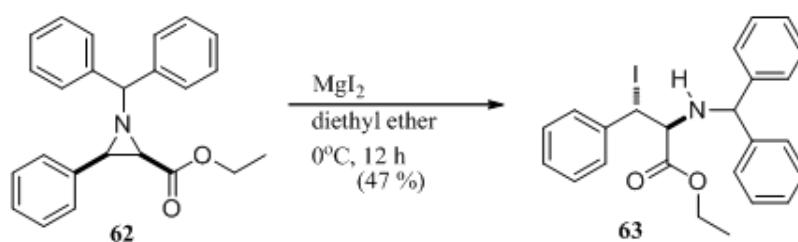
Scheme 22: MgBr_2 mediated ring-opening of an aziridine by Righi *et al.*^[54]

The conditions using magnesium bromide were applied on aziridine **62**.



Scheme 23: MgBr_2 mediated ring-opening of aziridine **62**.

The product (**92**) obtained by ring opening of aziridine (**62**) with magnesium bromide diethyl etherate proceeded in 78 % yield; the reaction was simple and clean. After the addition of $\text{MgBr}_2 \cdot \text{O}(\text{Et})_2$ a 'cloudy white' colour was observed. Afterwards the reaction was filtered and again through celite with diethyl ether. It was then tested whether MgI_2 could work as effectively (scheme 24).



Scheme 24: MgI_2 mediated ring-opening of aziridine **62**.

The MgI_2 is generated *in situ* from magnesium and iodine at 0°C before addition of the aziridine. The desired product **63** was obtained in 47 % yield; it should be recommended that the reaction is performed in the dark as the product is potentially light sensitive.

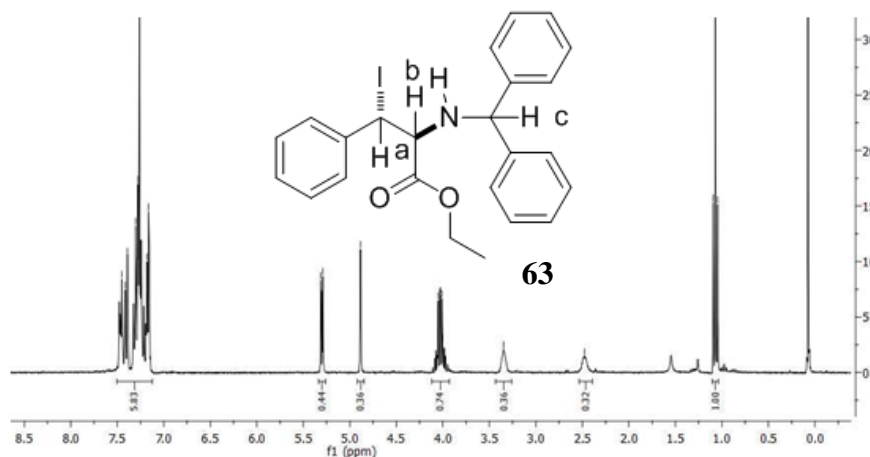
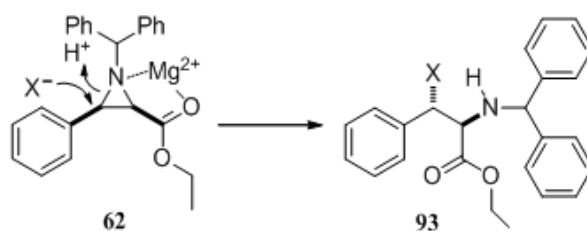


Figure 7: Compound **63** $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.51 – 7.12 (m, 15H), 5.30 (d, $J = 6.9$ Hz, 1H), 4.89 (s, 1H), 4.12 – 3.93 (m, 2H), 3.35 (s, 1H), 2.48 (s, 1H), 1.07 (t, $J = 7.1$ Hz, 3H)

The doublet at δ 5.30 ppm corresponds to (a); δ 3.35 is (b) and (c) relates to the singlet the benzhydryl group. Peaks at δ 4.12 – 3.93 (m, 2H) and 1.07 (t, $J = 7.1$ Hz, 3H) relate to the CH_2CH_3 group. The reaction was easier using MgBr_2 as it is commercially available and required less time, the iodo compounds are potentially light sensitive and for analytical purposes, samples had to be recorded early other the quality of the sample appeared to degrade over time.

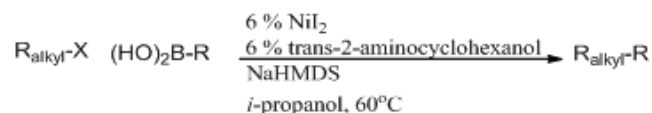
The role of the magnesium may co-ordinate to the nitrogen and oxygen atom (scheme 25).



Scheme 25: Possible mechanistic view; nucleophilic attack from the halide on the opposite side of the co-ordinated Mg^{2+} **62** affords the ring-opened product **93**.

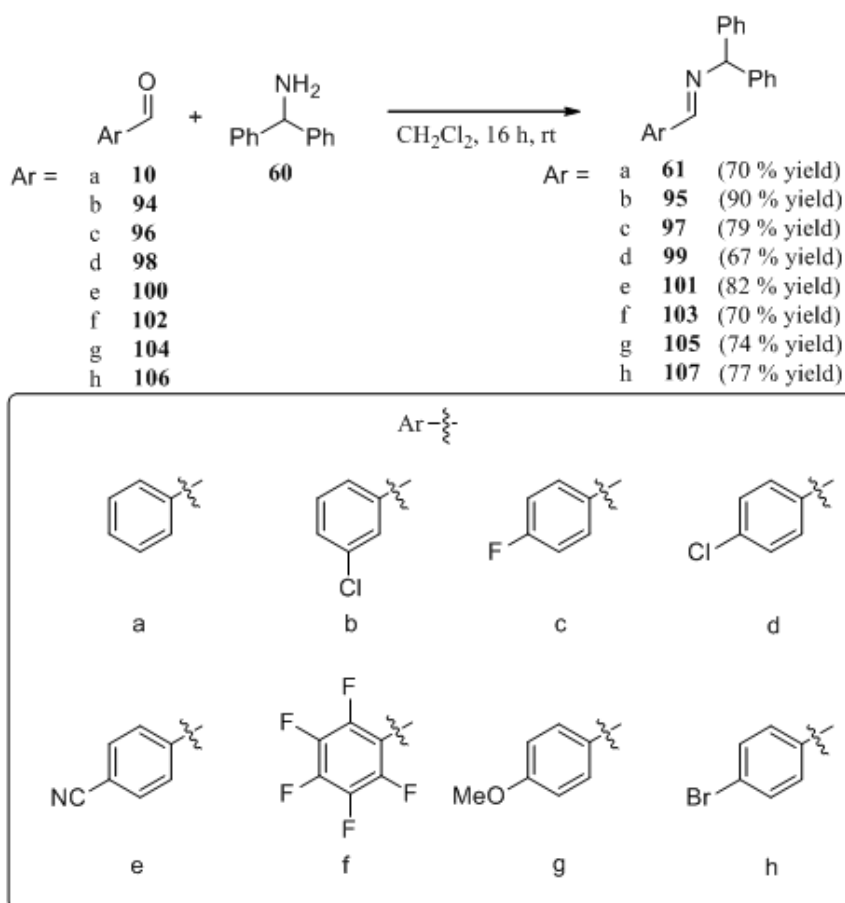
2.8 Suzuki cross coupling attempt

It was then envisaged that by considering the work of Fu *et al.* the following reaction could be applied to iodo **63** and bromo **92** compounds obtained (scheme 26).^[43]

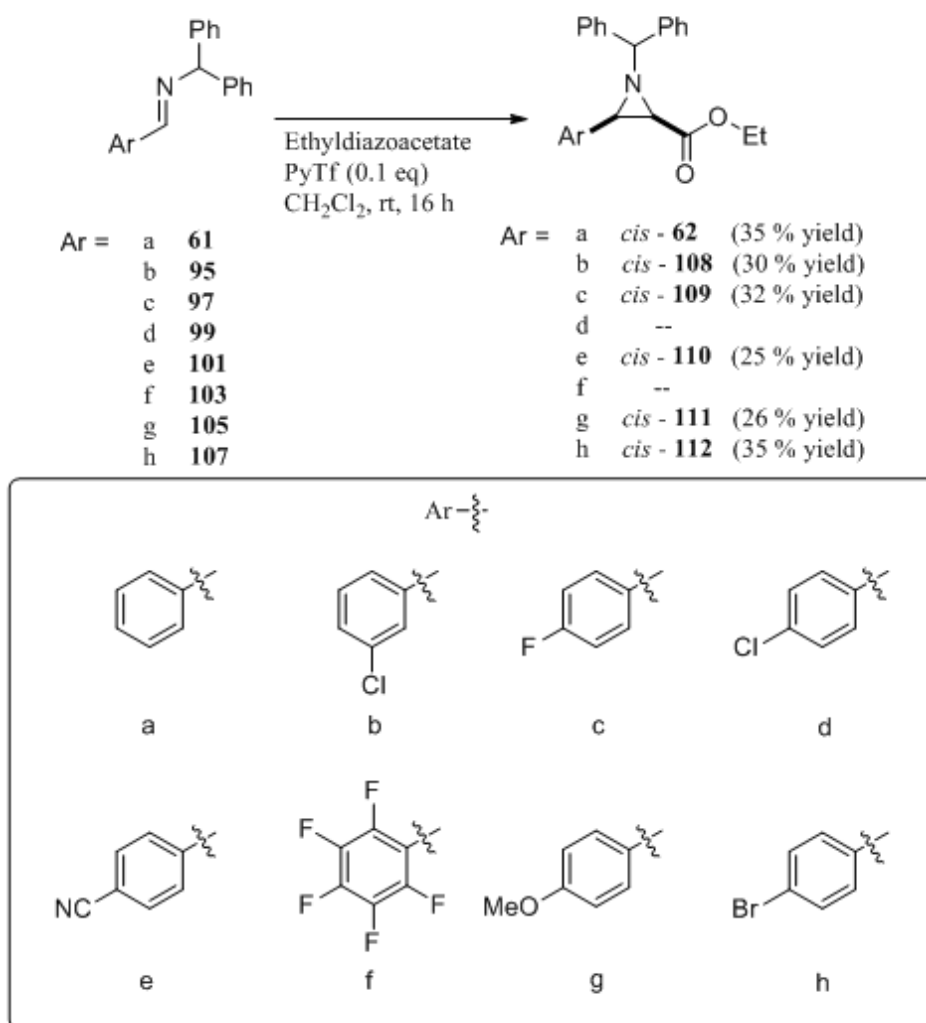


Scheme 26: Nickel-catalysed Suzuki reactions of inactivated alkyl halides

The cross-coupling reaction was attempted on both iodo **63** and bromo **92**, using NaHMDS or KHMDS with phenyl boronic acid. Unfortunately the product was not observed as confirmed by TLC and ¹H-NMR analysis. There was a large amount of starting material present along with aziridine **62**. The base present may have caused the iodo or bromo compound to revert to the aziridine form. The ring-opened compounds containing iodine and bromine were of interest and so attention was diverted to synthesising a range of compounds (schemes 27-29).

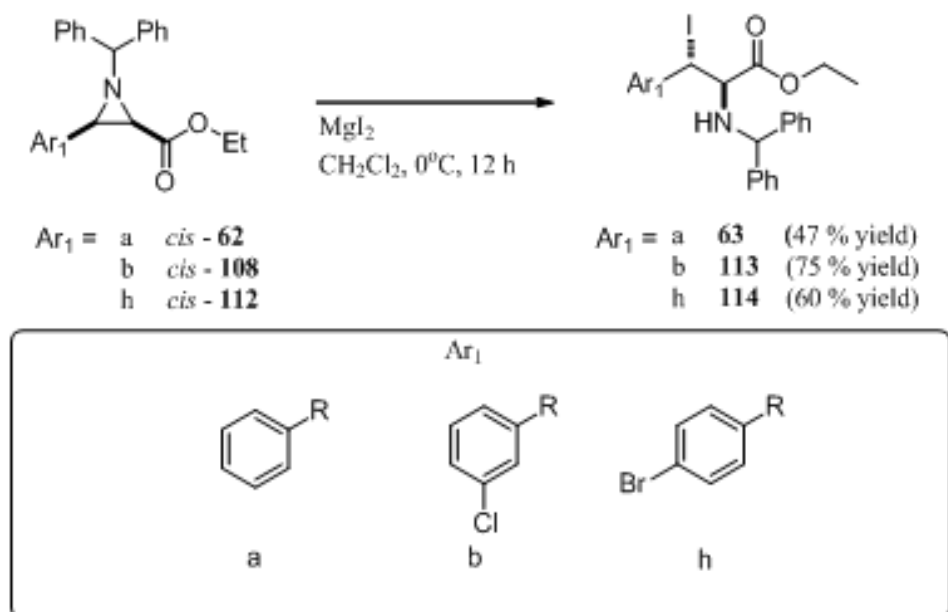


Scheme 27: Synthesis of imines from the corresponding aldehydes with benzhydramine. General reaction conditions: aldehyde (1 eq), amine (0.98 eq), DCM, rt, 16 h.



Scheme 28: Synthesis of aziridines from corresponding imines. General reaction conditions: Imine (1 eq), EDA (1.1 eq), PyTf (0.1 eq), DCM, rt, 16 h. Imines **99** and **103** were not carried forward onto aziridination.

Aziridination was attempted on the imines made from scheme 27. Unfortunately however, the aziridine products were obtained in low yield, a lot of imine starting material was observed from ¹H-NMR analysis. Purification *via* column chromatography proved difficult, the aziridine products that were successfully obtained are shown (scheme 28).



Scheme 29: Synthesis of iodo compounds from corresponding aziridines. General reaction conditions: Magnesium turnings (4 eq), I_2 (2 eq), DCM, 0°C , 12 h. Other compounds present in the previous schemes (27, 28 and 29) have been omitted from scheme 29 for simplicity, as they were not obtained.

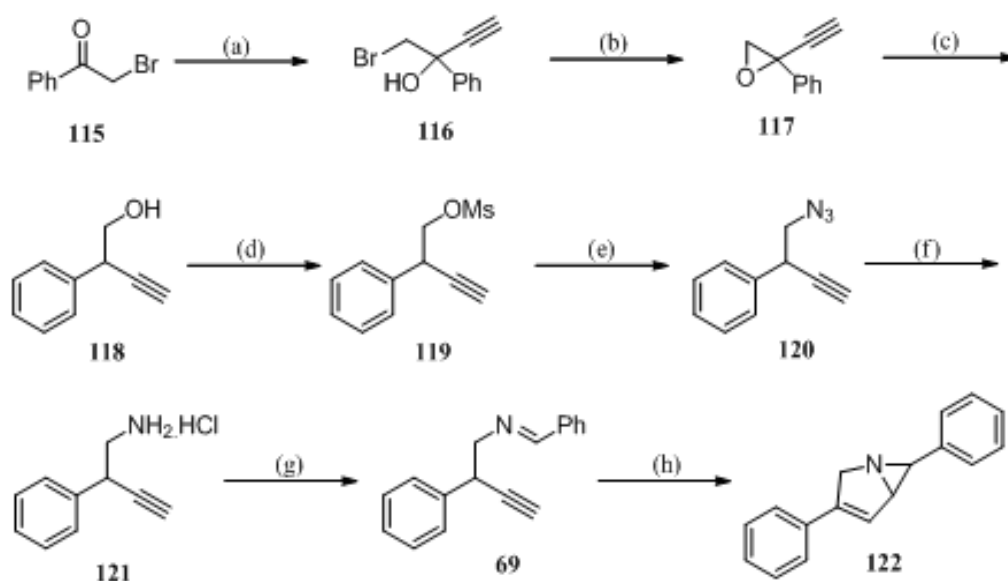
There was difficulty with the stability during the purification process of the iodo compounds, this often resulted in the deterioration of the compounds during chromatography. In all cases, they should be kept under dark conditions to help prevent this.

Ring opening of aziridine **62** (scheme 23, page 18) with MgBr_2 .etherate proceeded in good yield and less time was required, the compound is not light sensitive in comparison to the iodo compounds and is more stable; thus making this compound more convenient to make and store.

3.0 Conclusion

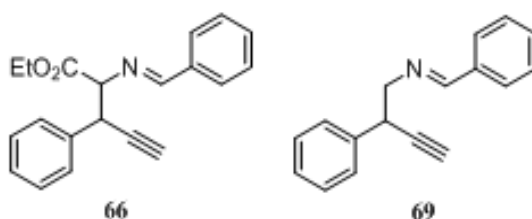
In conclusion, the free radical bromination attempt on double BOC protected phenyl alanine (scheme 14, d, page 13) may work as described in the literature,^[55] providing the correct equipment is applied. The bromo compound **92** is more stable, easier to make and should be made instead of the iodo compounds for simplicity. The aziridination reactions (scheme 28, page 21) proceeded in low yields, which is not ideal in this long synthesis route. Consequently, a different approach may be needed; a possible strategy is outlined in scheme 30, which builds on from the work performed in the undergraduate research project (scheme 13, page 12) from steps (d) to (h).

3.1 Future work



Scheme 30: Reaction conditions (a) ethynylmagnesium bromide (b) NaH, H₂O, THF, 0 to 23°C, 76% (2 steps)^[56] (c) MsCl, DCM, Et₃N, DMAP, 2 h at 0°C, 3 h at rt (d) NaN₃, DMF, 70°C, 3.5 h (e) Ph₃P, Et₂O, 2 h at 0°C, 20 h at 25°C,^[41] (f) 10% NaOH (g) Benzaldehyde, DCM (h) Au(I), DCM.^[34]

The reaction scheme 30 differs from the previous strategy (scheme 14, page 13) by incorporation of the alkyne moiety earlier on in the synthesis. Scheme 14 and scheme 30 however both envisage similar compounds (**66** and **69**) to test the gold catalysed cyclisation reaction (scheme 31).



Scheme 31: Key compounds to test the gold catalysed cyclisation reaction from different synthetic routes (scheme's 14 and 30).

These compounds share similarity to Toste's compound (**31**, page 11) and are viable compounds to test the gold catalysed cyclisation reaction.

4.0 Introduction to atropisomerism

4.1 Axial chirality

In 1848 the first resolution of tartaric acid was reported by Louis Pasteur, since then the synthesis of compounds containing one or more stereogenic centres has been of great interest and an important field in chemistry.^[57] Recognising chirality in compounds is a fundamental objective in design, discovery and development of new drugs in relation to the development of safe and stable substances that specifically target the cause of disease. Classical stereogenic-centre enantiomers have distinct biological and pharmaceutical properties; well known examples include the cases of thalidomide^[58] and perhexiline,^[59] whereby the different enantiomers led to unexpected effects in humans, thus emphasising the importance of addressing stereochemistry in drug development.^[60, 61] Although drugs such as ibuprofen are available to be sold as a racemic mixture with acceptable toxicological profiles.^[62] In contrast, less attention has been directed on axial chirality, but there has been recent recognition in the structural characteristics of biaryl compounds controlling pharmacological properties of bioactive compounds or for the design of efficient ligands in asymmetric catalysis.^[60-63]

Optical activity derived from axial chirality was first described by Christie and Kenner in 1922.^[64] Atropisomerism refers to a non-planar molecule exhibiting hindered rotation around its bonds at a given temperature, therefore allowing the isolation of two optically pure atropisomers. An arbitrary but functional definition can be applied to atropisomers to distinguish physically separable species; that when at a given temperature, a half-life of 1000 s (16.7 min) can be applied. Consequently, Oki found that the minimum free energy barrier ΔG^\ddagger required varies with temperature; eg. at 200K, $\Delta G^\ddagger = 61.6 \text{ kJ mol}^{-1}$ and at 300K, $\Delta G^\ddagger = 93.5 \text{ kJ mol}^{-1}$.^[65, 60]

The word ‘atropisomerism’ was introduced by Kuhn in 1933, the ‘a’ and ‘*tropos*’ translating from Greek to ‘not’ and ‘turn’ respectively.^[60] The presence of a stereogenic axis is prominent in these molecules and is usually influenced by bulky substituents at the *ortho* positions of an aryl ring. This results in restricted rotation around the biaryl bonds and can increase the atropisomerisation barrier in non-bridged biaryl compounds by their steric repulsion.^[60, 66]

4.2 Axial chirality in biomolecules

Axial chirality has been recently recognised as a decisive structural element to control pharmacological properties of bioactive compounds or for the design of efficient ligands in asymmetric catalysis. The presence of atropisomers has been found in a number of biologically active compounds, some examples include (+)-gossypol (**123**), (-)-steganone (**124**) and vancomycin (**125**).

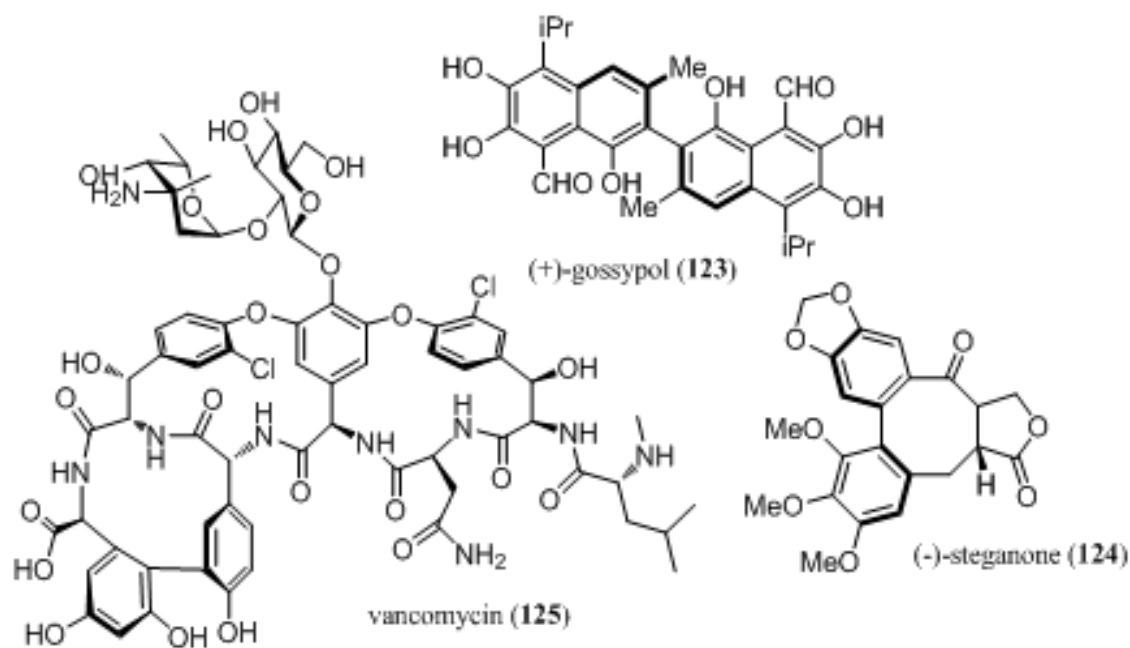


Figure 8: Structures of biological compounds containing single atropisomers in their structure.

Atropisomers are also useful in retaining chiral information in the design of effective chiral catalysts. The 2,2'-substituted 1,1'-binaphthyl system epitomised by the bisphosphine ligand BINAP (**126**) and the binaphthol BINOL (**127**) are classically known atropisomeric motifs in the field of enantioselective catalysis. First reported by Noyori *et al.* in 1980,^[67] the axial chirality in the backbone provides complete control of the position in space of the two phosphine groups.^[66]

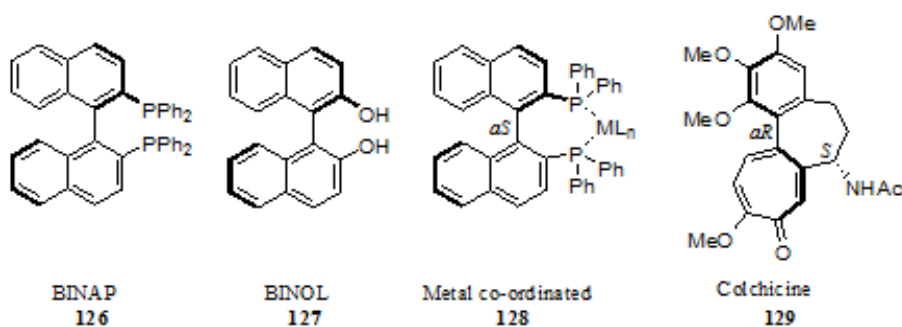
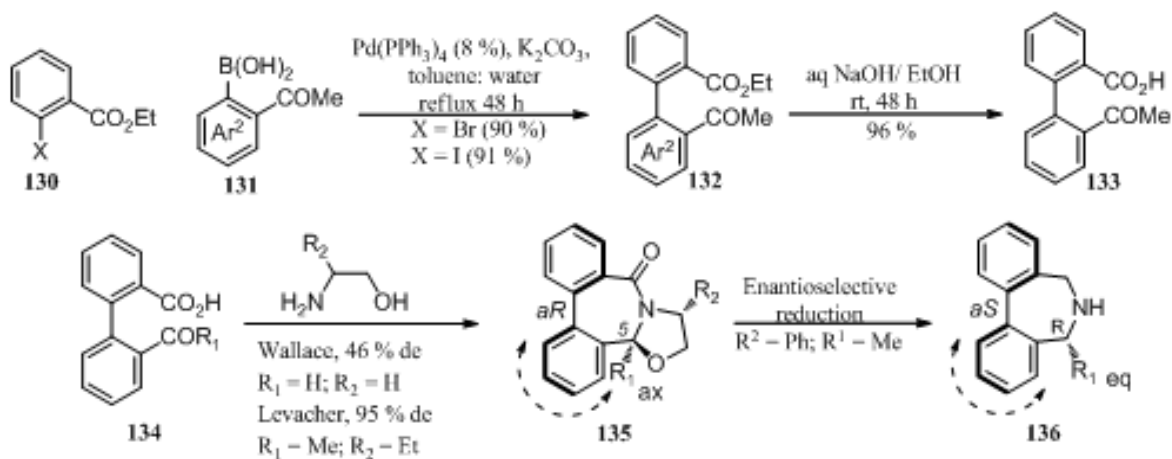


Figure 9: Structures of compounds containing axial chirality.

BINAP also has the ability to accommodate metal atoms to form complexes by chelating between the phosphine groups (**128**); this is accessible due to a degree of flexibility within the system. The co-ordinated metal BINAP complex such as Ru-BINAP is capable of catalysing asymmetric hydrogenation in high conversion and enantiomeric excess. ^[68] Colchicine **129** also exhibits this type of axis-centre relay, enabling the alkaloid to bind to tubulin and thus establishing itself as an effective cytotoxic agent. ^[69]

4.3 Current methodology

Among reported synthetic strategies, the catalytic atroposelective biaryls cross-coupling approach is still the most studied. Much less developed is the dynamic atroposelective convergence of pre-formed biaryls. The groups of Wallace ^[63a, 69-70] and Levacher ^[71] developed independently in 2003 a diastereoselective construction of chiral fused oxazolidinone lactams (scheme 32) from the corresponding aldo-acid ($R_1 = H$) or keto-ester ($R_1 = Me$) respectively. Employing the use of Meyer's lactamisation methodology provided high atroposelection through a central C5 to axial chirality transfer.



Scheme 32: Application of Meyer's lactamisation methodology.

Wallace's group published recently the synthesis of dibenzazepine **136** (scheme 32) *via* reduction events of Levacher's keto-ester derived **135** and prepared one ammonium salt for structure elucidation purposes; however no application in phase transfer catalysis (PTC) catalysis was reported.^[69] In view of developing novel PTC catalysts for the reaction in Levacher's field,^[72] the preparation of ammonium salts of type **144** (scheme 33, page 28) from **143** are envisaged and catalytic action to be investigated. This unpublished work is currently under investigation in Levacher's laboratory. Wallace's and Levacher's studies based on X-ray structures of **145** have shown the unique chirality transfer between C5 (*S*) and *a* namely R₁ provides *aR* axis and R₁ equatorial provides *aS* axis affording great opportunity for the design of new atropo-catalysts, the ones deriving from **143** or **144** being dynamic or *tropos* by nature. The last category has been rarely developed in organocatalysis.^[73]

Organocatalysts possessing an axial chirality have emerged as privileged ones like phosphoric acids,^[74] PTC catalysts,^[75] and iminium salts,^[76] most of which are derived from a binaphthyl backbone. Recently, Marouka,^[77] Lygo^[78] and Page,^[79] reported on new families of *tropos* organocatalysts whose axial absolute configuration was influenced by an extra stereogenic element outside the dibenzazepine ring (Figure 10).

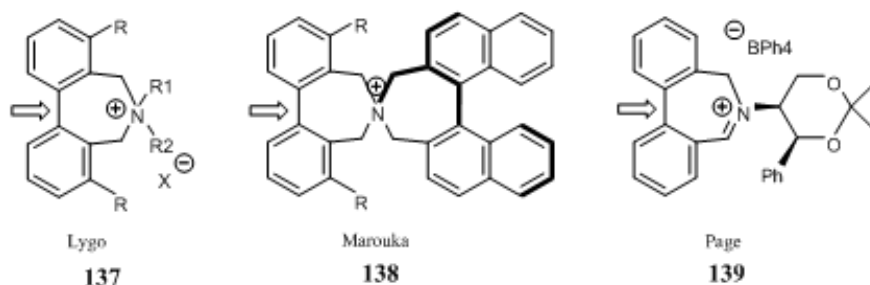


Figure 10: Known biaryl *tropos* catalysts, dynamic axial chirality influences by central R* or extra-axial C - C chirality.

Lygo and Marouka have not incorporated the extra-asymmetry element as chiral relay within the cyclic amino-tether of the dibenzazepine ring however Page *et al.* has recently reported a catalyst bearing an extra stereogenic centre both inside and outside of the lactam ring (Figure 11).^[80]

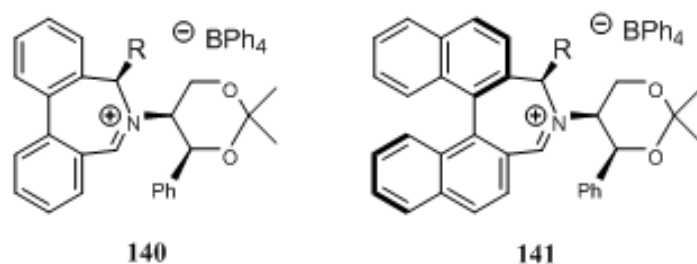
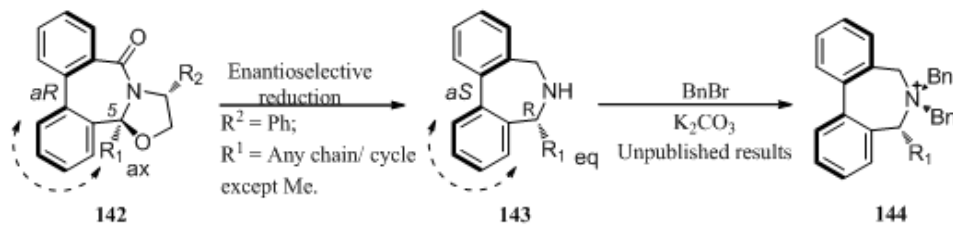


Figure 11: Recent catalysts developed by Page *et al.* These have proved to be successful for the asymmetric epoxidation of alkenes boasting high conversion and enantiomeric excess.

5.0 Results and Discussion

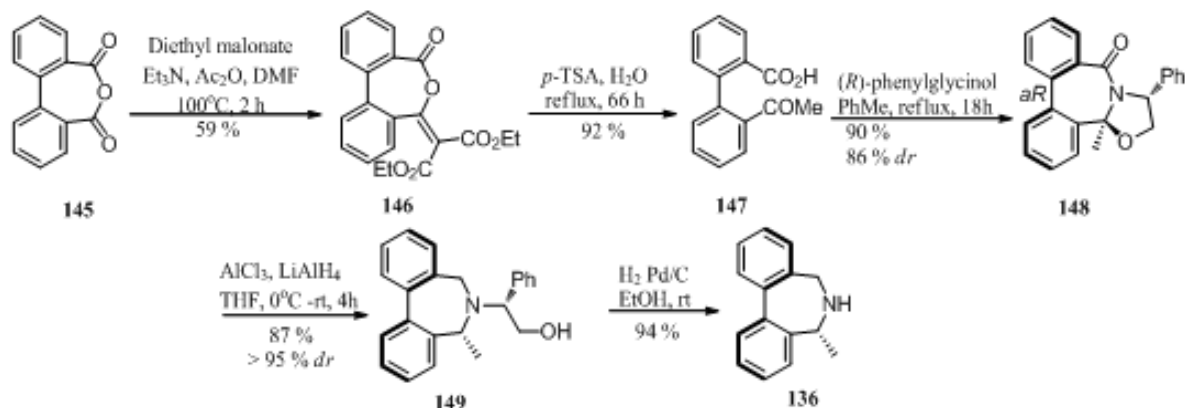
5.1 Aims of Research

The objective of the project is to provide new atropis derivatives bearing a different substituent at R_1 to envisage them as novel ammonium salts as phase transfer catalysts. The enantioselective construction of analogues axially chirality could also be envisaged (scheme 33).



Scheme 33: Variation of R_1 to envisage novel ammonium salts as phase transfer catalysts.

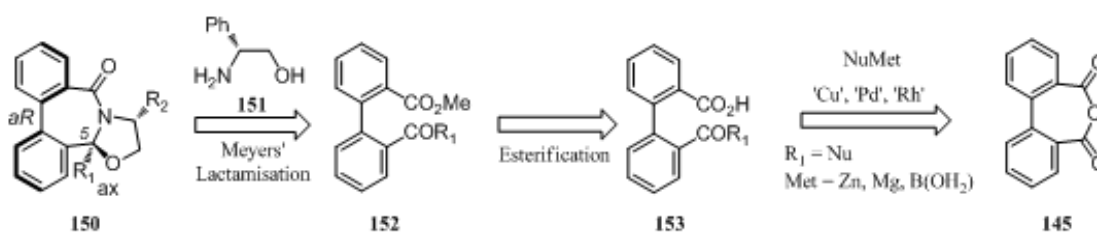
Current strategies from Levacher^[71] and Wallace^[63a, 69-70] (scheme 32, page 26) employing Suzuki cross coupling^[63a, 69-70] and ring opening of diphenic anhydride, scheme 34 (page 29) being an example,^[69] offering good yields and syntheses towards the synthesis of the dibenzazepine ring.



Scheme 34: Wallace synthesis of 5-methyl-6,7-dihydro-5H-dibenz[c,e]azepine

However these strategies do not enable variation of R_1 , whereas scheme 35 does; and so it is hypothesised that in the view of developing novel PTC catalysts for the reaction in Levacher's field, ^[72] the variation of R_1 may help improve the enantioselectivity in preparation of ammonium salts of type **144** from **143** (scheme 33, page 28).

Applying a retro-synthetic analysis delivers diphenic anhydride as a hypothesised suitable compound to test.



Scheme 35: Proposed strategy towards the design of keto-ester Meyer's lactams derivatives.

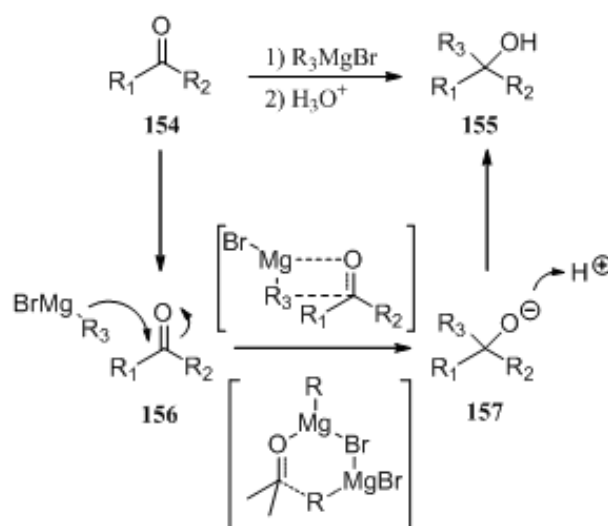
There are a range of publications that can be applied to test this methodology. ^[81]

5.2 Application of the Grignard reaction on diphenic anhydride

François Auguste Victor Grignard was awarded the Nobel prize in 1912 for his discovery of the organometallic reagents later named Grignard reagents. These reagents provided a method in generating carbon-carbon bonds employing magnesium to couple ketones and alkyl halides. The reactivity is drawn from polarisation; in carbonyl groups this occurs by electrons in the carbon-oxygen bond being pulled towards the more electronegative oxygen, providing a site for nucleophilic attack. This is opposite in Grignard reagents where the key bond is polarised in the opposite direction towards carbon – making carbon a nucleophilic centre. Grignard reagents are made by reacting magnesium turnings with alkyl halides in anhydrous ether solvents; however a limitation arises if the compound contains a functional

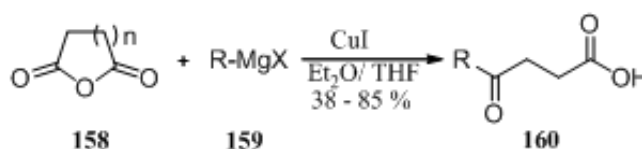
group capable of reacting with the Grignard reagent itself. ^[82] Grignard reagents are available from commercial sources and provides easy application without the requirement of generating the Grignard reagent thus saving time. The bottles should be stored under an inert atmosphere as Grignard reagents react very rapidly and exothermically with water to produce alkanes; consequently this can affect the quality of the reagent itself. The concentration can be tested by titration with diphenyl ditelluride, which acts as an indicator. ^[83]

The Grignard reaction involves an oxidative addition in the formation of the organometallic species; there is a change in oxidation state from Mg(0) to Mg(II). The reaction mechanism itself is not well understood but a possible representation is shown (scheme 36).



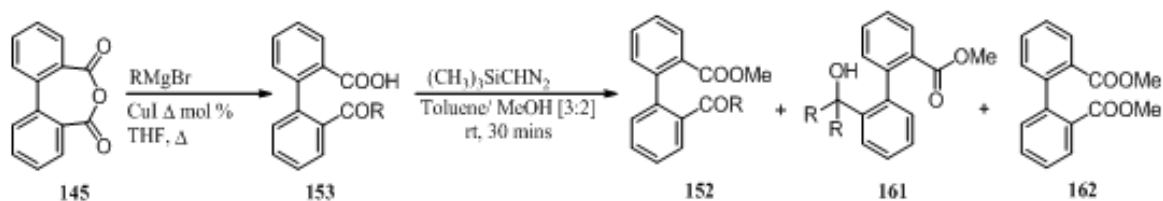
Scheme 36: Formation of a C – C bond in the Grignard reaction *via* possible transition states.

The first reaction that was attempted was based on work done by Lhommet *et al.* who used Grignard reagents in a condensation reaction with succinic or glutaric anhydrides in the presence of a catalytic amount of CuI in the preparation of 4- or 5-oxoacids (scheme 37). ^[81a]



Scheme 37: Ring opening of succinic or glutaric anhydrides in the presence of CuI.

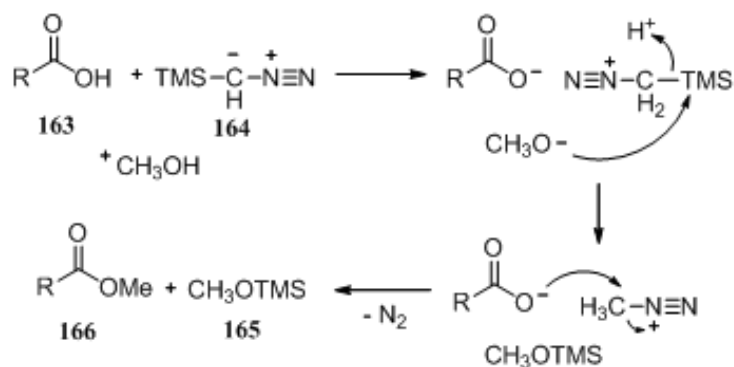
The reaction scheme above gave good yields and so the method was applied to diphenic anhydride (scheme 38, page 31).



Scheme 38: Addition of RMgBr to diphenic anhydride and products obtained.

The solvent of choice was anhydrous THF, however it should be noted that diphenic anhydride is insoluble in both THF and diethyl ether. The first attempts were performed with MeMgBr for 2 hours at -20°C ; upon drop-wise addition of the Grignard reagent, the insoluble anhydride had appeared to have dissolved. After the allocated time, $^1\text{H-NMR}$ analysis showed that there was little to no starting material left, however three methyl peaks at δ 2.181, 1.593 and 1.406 ppm were observed.

The crude mixture was inseparable by column chromatography; consequently an esterification reaction was then applied to the crude acid mixture by treating it with trimethylsilyldiazomethane for 30 minutes in toluene/ MeOH [3:2].^[84] MeOH must be present in the reaction to obtain the methyl esters in high yield.^[85]



Scheme 39: Esterification mechanism of the acid with TMSCHN₂ in toluene/ MeOH [3:2] as proposed in a review.^[84b]

One of the protons in the resulting methyl ester originates from the diazomethane, one from methanol, and the other the acidic proton dissociated from the carboxylic acid. The presence of MeOH also suppresses the formation of trimethylsilyl and trimethylsilylmethyl ester artifacts.

A series of reactions were then tested using MeMgBr with catalytic quantities of CuI in THF on diphenic anhydride (Table 1, page 33) in an attempt to find optimum conditions. MeMgBr was used as the product **152** with R = Me could be used in a known Meyers' lactamisation reaction differing only with the starting material bearing an 'OMe' leaving group, instead of a usual 'OEt'. It was soon discovered however that MeMgBr was not the best reagent to use as the formation of the double addition product **161** with R = Me was unavoidable. Increasing the amount of CuI from 0.1 eq to 1 eq helped lower the amount of the double addition by-product but also helped in the formation of a di-acid (**168**) that was subsequently transformed to (**162**) in the esterification process. In the absence of CuI the formation of the double addition by-product (**161**) was favoured. Varying the temperature did not help prevent the formation of the by-product (**161**) and only slowed the reaction down.

It was also found that the use of EtMgBr lowered the chance of double addition; however there was still not complete conversion; this resulted in the product containing the di-ester **162**. This product (**152** with R = Et) was obtained in higher yields (53 %) but was found to be 93 % pure containing an inseparable impurity (**162**).

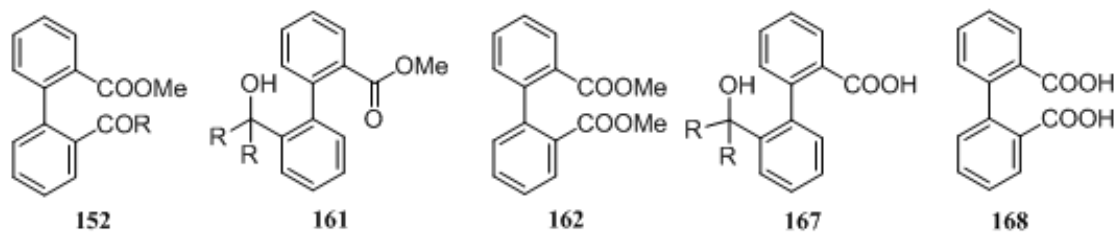


Table 1: Attempt to find optimum conditions for the Grignard addition on diphenic anhydride in the presence or absence of CuI.

DA (eq)/ mmol	Cat. (eq)	Grignard reagent (eq)	Reaction Temp (°C)	Time (h)	Yield* ¹ (%)	Conversion * ² %		
						169	155	168
1 / 1	CuI 0.1	MeMgBr 1.2	-20 rt	1h 1h	31 %	0	47	53
1/ 0.5* ³	CuI 0.1	MeMgBr 1.2	-20	1h	--	29	30	42
1/ 1	CuI 0.1	MeMgBr 1.2	-20	1h	35 %	0	49	51
1/ 0.5	CuI 0.1	MeMgBr 1	-20	2h	39 %	0	46	54
1/ 0.5	CuI 0.1	MeMgBr 1	-20 rt	1h 1h	31 %	0	47	53
1/ 0.5	CuI 0.1	MeMgBr 1	-78	4h	--	24	38	38
1/ 0.25	--	MeMgBr 1	-20	2h	--	12	33	55
1/ 0.25	CuI 1	MeMgBr 1	-20	2h	37 %	39	40	21
1/ 0.5	CuI 0.1	MeMgBr 1	rt	2h	--	0	45	55
1/ 0.5	CuI 0.2	MeMgBr 1	-20	2h	--	24	65	11
1/ 1	CuI 0.1	BnMgCl 1	-20 rt	4h 1h	--	Could not be calculated.		
1/ 0.5	CuI 0.1	EtMgBr 1.1	-20	2h	53% * ⁴	10.5	79	10.5

The reaction was performed in THF (0.2 M)

*¹ Yield accounts for **152** two steps from acid to ester without purification of the acid.

*² Ratio was calculated by comparing the integrals of ring opened anhydride/ acid/ by-product integral ratio.

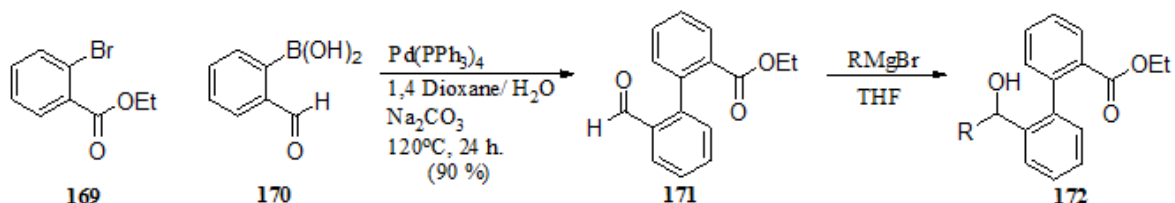
*³ Reaction quenched with NH₄Cl opposed to water and HCl, crude product was barely obtained, had to perform an acid wash to obtain more.

*⁴ 93 % pure containing an impurity that is inseparable by flash column chromatography

The major implication of these by-products is that they are difficult to separate from one another by column chromatography. When performing the reactions on a larger the scale, these by-products are even harder to remove. Consequently, an alternative strategy for the synthesis of Meyers' lactam derivatives is required.

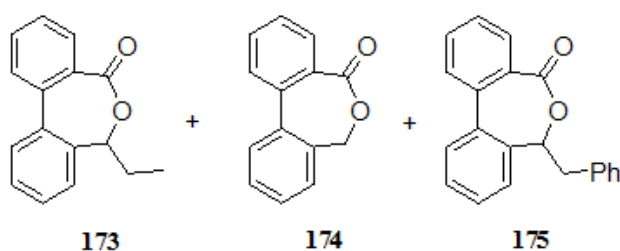
5.3 Suzuki-Miyaura cross coupling and further Grignard application

It was then envisaged that the Grignard addition on **171** would produce the desired compounds (**172**) to test the Meyers' lactamisation (scheme 40).

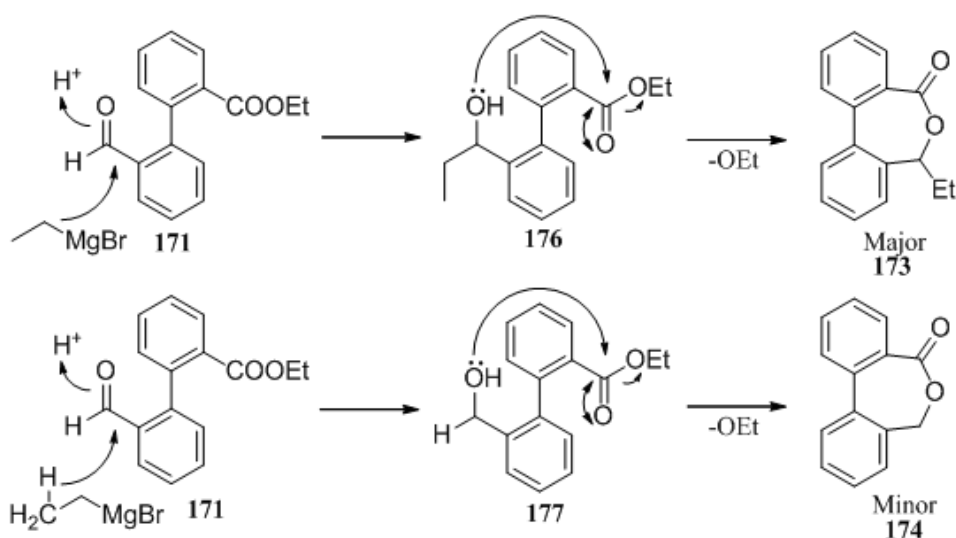


Scheme 40: Suzuki-Miyaura cross coupling and Grignard addition (EtMgBr and BnMgCl).

The Suzuki cross coupling reaction proceeded in 90 % yield, however unfortunately the desired compounds (**172**) following Grignard addition with EtMgBr or BnMgCl on **171** was not observed, as anticipated a lactonisation reaction occurred producing the following compounds:



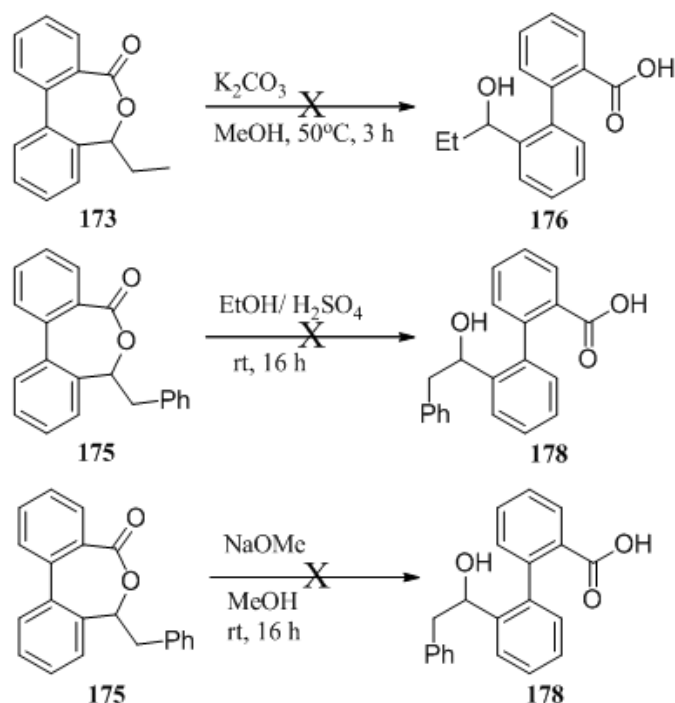
The lactonisation was likely to occur before the work up of the reaction. Compounds **173** and **174** were obtained when using EtMgBr and **175** from BnMgCl. The lactonisation reaction was likely to occur by the following mechanism:



Scheme 41: Formation of lactone products using EtMgBr.

The minor product was unexpected but was likely formed due to a hydride transfer to the aldehyde in a reduction step. Compound **174** was not observed in the reaction using BnMgCl .

Attempts to open the lactone rings were however unsuccessful (scheme 42).

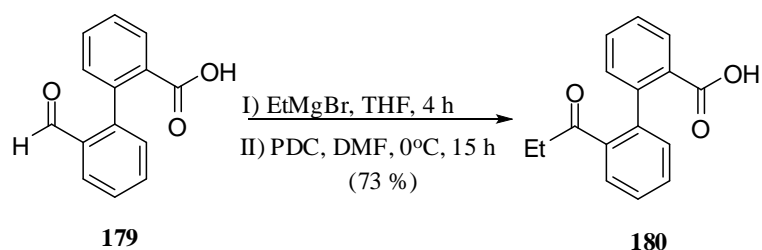


Scheme 42: The reactions were performed following procedures of similar reactions.^[86]

It is unsure whether the reaction occurred at all or if the lactonisation step occurred again to form the starting material. In all cases, the starting material was recovered following the work up.

5.4 Saponification, Grignard addition and oxidation

Searching the literature returned a publication by Crich *et al.*^[55] containing a useful reaction scheme:

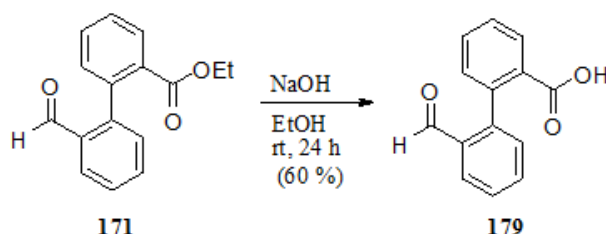


Scheme 43: Grignard addition and oxidation

Treatment of 2'-formylbiphenyl-2-carboxylic acid **179** with EtMgBr in THF afforded the hydroxyl acid which 'underwent lactonisation on standing, even at 0°C ; consequently it was immediately converted to the corresponding ketone **180** with pyridinium dichromate' in DMF

for 15 hours at 0°C. ^[55] Therefore, it is obvious that the carboxylic acid moiety following deprotonation to form the carboxylate could slow down the undesired lactonisation event allowing further chemistry to be achieved.

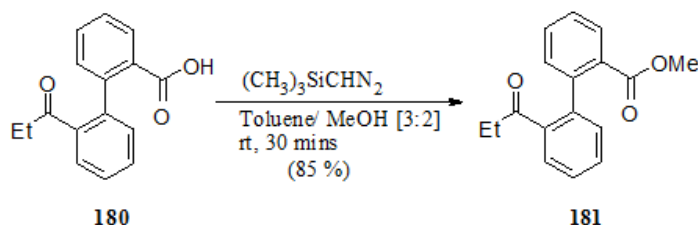
Saponification of **171** in 10 M NaOH afforded 2'-formylbiphenyl-2-carboxylic acid **179** in 60 % yield (scheme 44).



Scheme 44: Saponification of **171**

Grignard addition with EtMgBr and subsequent oxidation with PDC using the conditions provided by Crich *et al.* (scheme 43, page 35) afforded the desired product but in 50 % yield. The yield may be influenced by the time taken to start the oxidation step of the reaction due to lactonisation that is likely to occur. There was a one-hour period before the oxidation reaction was initiated.

Esterification of **180** using trimethylsilyldiazomethane (scheme 45) produced **181** in 85 % yield.

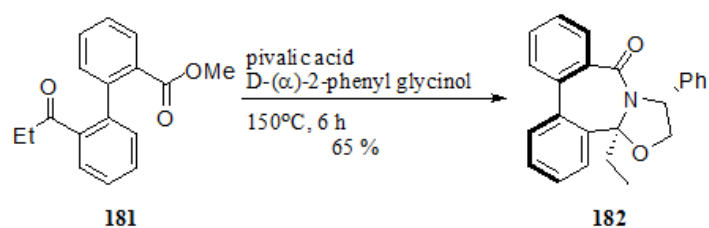


Scheme 45: Esterification using trimethylsilyldiazomethane

The esterification was described earlier (scheme 39, page 31), 1 – 1.5 eq is required or until a yellow colour persists, the reaction is indicated by the release of nitrogen bubbles. After completion the reaction should be quenched with acetic acid.

5.5 Meyers' lactamisation methodology

The application of Meyers' lactamisation methodology provided a diastereomerically enriched 7-membered lactam ring **182**; flanked by an ethyl instead of a methyl substituent showing, thereby that different groups can be tolerated at this position through this novel synthetic pathway.

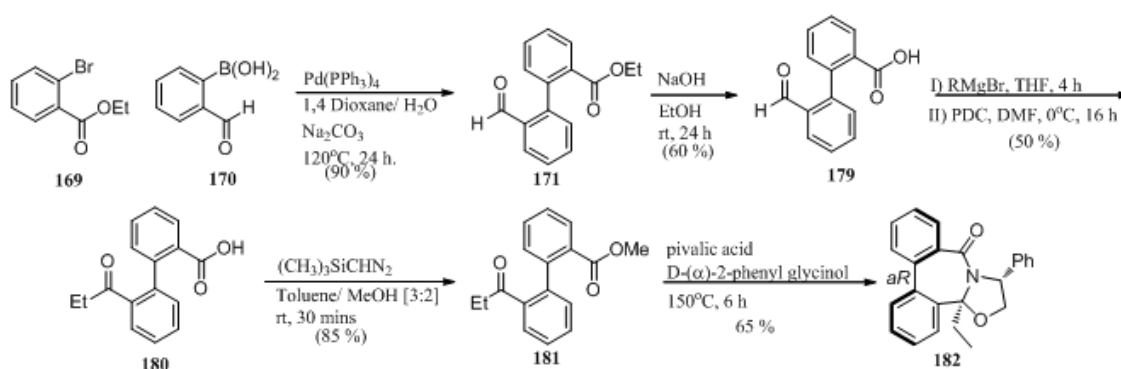


Scheme 46: Meyers' lactamisation of **181**.

The reaction proceeded in good yield but required a longer reaction time in comparison if $R_1 = \text{Me}$ (scheme 33, page 28). No solvent was required and the reaction was performed in a sealed microwave vial.

6.0 Conclusion

In conclusion, it was found that the CuI catalysed Grignard addition on diphenic anhydride was not suitable for large-scale reactions and produced unwanted by-products that were inseparable by flash column chromatography. The following reaction scheme was found to provide the desired Meyers' lactam product and gave good yields.

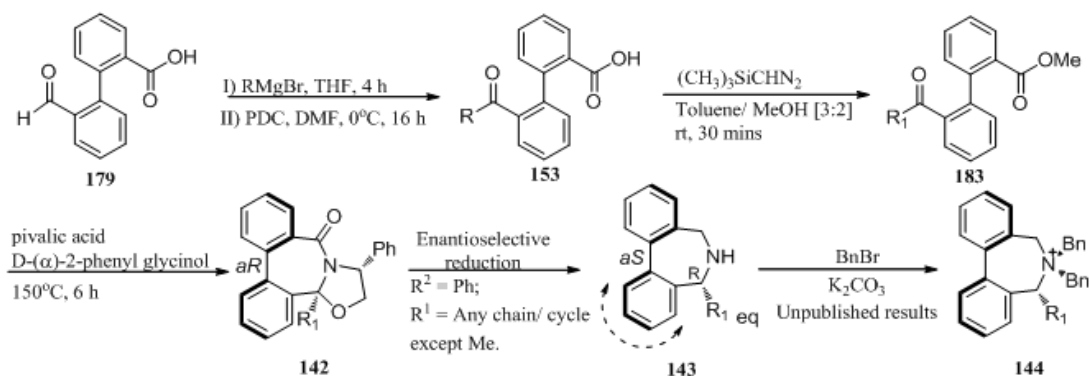


Scheme 47: Synthesis route for the design of Meyers' lactam derivatives and formation of Meyers' lactam products

The Suzuki-Miyaura reaction is a heterogeneous reaction that proceeds in good yield; subsequent saponification gives access to the acid **179** to that can then be probed with various Grignard reagents.

6.1 Future work

The designed route could possibly provide a library of Meyers' lactam compounds that could provide new atropis derivatives bearing a different substituent at R_1 to envisage them as novel ammonium salts as phase transfer catalysts.



Scheme 48: Possible route for the synthesis of new Meyers' lactam derivatives

The application of Grignard reagents featuring different substituents will need to be investigated on the acid **179**; trimethylsilyldiazomethane is useful for quick esterification but on large scale reactions a different esterification technique may prove better due to the cost, with a bulkier group, the Meyers lactamisation reaction may need more time due to steric hindrance.

The Meyers' lactamisation also proceeds directly on acids,^[69] and so this too could also be tested without the need for esterification. This route could potentially provide a route to a variety of Meyers lactam derivatives providing the efficiency of Grignard reagents on **179** to then envisage them as novel ammonium salts (**144**) as phase transfer catalysts following reduction steps of the Meyers lactam derivatives (**142**).

7.0 Experimental

7.1 General

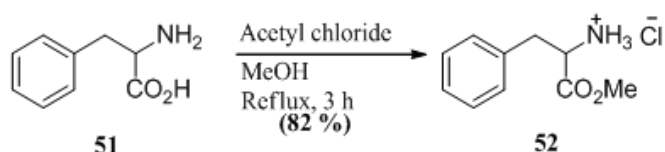
NMR solvents (CDCl_3 purchased from Apollo Scientific Limited) were dried over 4\AA molecular sieves prior to use. CDCl_3 was further filtered through basic alumina. All reactions described were carried out under a nitrogen or argon atmosphere in flame dried apparatus which were allowed to cool under vacuum. Anhydrous diethyl ether and dichloromethane were distilled over Na and under nitrogen/ argon. All other reagents were used directly from commercial sources unless otherwise stated. Pyridinium triflate^[48] and tetrakis (triphenylphosphine)palladium(0)^[87] were synthesised using published procedures by Marwitz and Coulson respectively. Column chromatography was carried out on silica gel (Fluka Silica Gel 60 70 – 230 mesh or 40-63 μm). Thin layer chromatography was performed on Merck plates (aluminium coated 0.2 mm silica gel 60 F₂₅₄), visualised under UV light (254 nm), and stained using *p*-anisaldehyde or potassium permanganate solution.

7.2 Identification

All products were characterized by $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, FT-IR and MALDI-TOF, ESI or HRMS. $^1\text{H-NMR}$ were recorded on a 300 MHz or 400 MHz spectrometer. $^{13}\text{C-NMR}$ spectra were acquired at 75.4 MHz operating with broad band 1H decoupling and unless otherwise stated deuterated chloroform was used as the solvent. Infra-red spectra were recorded using a Perkin Elmer 100 FT-IR spectrometer or IRTF spectrometer with solid dispersed on KBr pastille. Chemical shifts (δ) are reported in ppm and referenced to the residual solvent signal (CDCl_3 : δ 7.26 ppm for $^1\text{H-NMR}$ and δ 77.16 ppm for $^{13}\text{C-NMR}$ spectra). Peak multiplicities are designated as: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplets (dt), multiplet (m), broad (br). Coupling constants are reported in Hertz (Hz). Ion mass/charge (m/z) ratios are reported as values in atomic mass units. Melting points were recorded using open capillary tubes on melting point apparatus and are uncorrected.

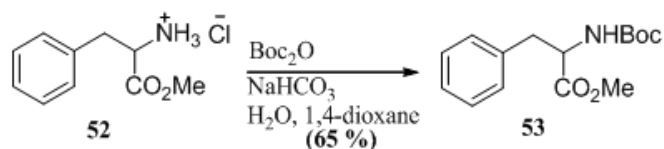
7.3 Procedure

Synthesis of 1-methoxy-1-oxo-3-phenylpropan-2-aminiumchloride



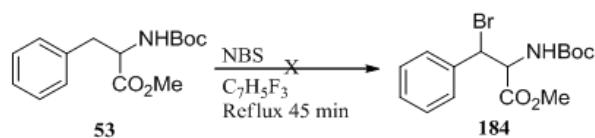
A 250 mL round bottomed flask was charged with phenylalanine (5 g, 30.3 mmol, 1 eq) dissolved in methanol (100 mL) and cool to 0°C. Acetyl chloride (4.30 mL, 60.6 mmol, 2 eq) was then added drop-wise over a period of 10 minutes and the reaction was allowed to stir under nitrogen for 3 hours. Afterwards, the solvent was removed and the impure product purified by recrystallisation with methanol/ diethyl ether [9:1] to afford white crystals (5.34 g, 82 % yield). M.p = 132 - 134°C. ¹H-NMR (400 MHz, CD₃OD) δ 7.35 – 7.23 (m, 5H), 4.30 (t, 1H), 3.77 (s, 3H), 3.29 – 3.13 (m, 2H). ¹³C-NMR (100 MHz, CD₃OD) δ 172.7, 136.2, 128.4, 127.7, 125.9, 63.8, 54.5, 37.4, 14.2. This compound was prepared using methods described by Fang *et al.* [88]

Synthesis of methyl-2-(tert-butoxycarbonylamino)-3-phenyl propanoate



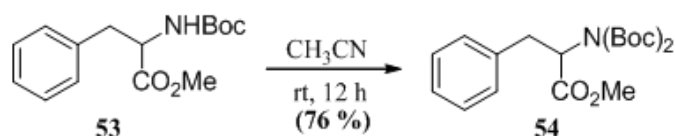
A 50 mL round bottomed flask charged with 1-methoxy-1-oxo-3-phenylpropan-2-aminium chloride, sodium bicarbonate (1.11 g, 13.16 mmol, 2.2 eq) in H₂O (5 mL). Boc anhydride (9 mmol, 1.5 eq) in 1,4-dioxane was then added drop-wise and the reaction was allowed to stir under nitrogen for 12 hours. Afterwards, the reaction mixture was extracted with ethyl acetate (2 x 10 mL), washed with 1N HCl (2 x 10 mL), brine (10 mL) and then dried of MgSO₄. Filtering and solvent removal under high vacuum afforded the product as a white crystalline solid (1.76 g, 68 % yield). M.p = 138 - 140°C ¹H NMR (400 MHz, CDCl₃) δ 7.34 – 7.06 (m, 5H), 4.97 (d, *J* = 9.3 Hz, 1H), 4.70 – 4.45 (m, 1H), 3.71 (s, 3H), 3.23 – 2.93 (m, 2H), 1.42 (s, 9H). ¹³C-NMR (100 MHz, CDCl₃) δ 171.5, 155.8, 136.7, 128.7, 127.5, 125.8, 79.6, 54.6, 52.1, 37.1, 28.6. This compound was prepared using methods described by Fang *et al.* [88]

Synthesis of methyl-3-bromo-2-(tert-butoxy-carbonylamino)-3-phenylpropanoate ^[44]



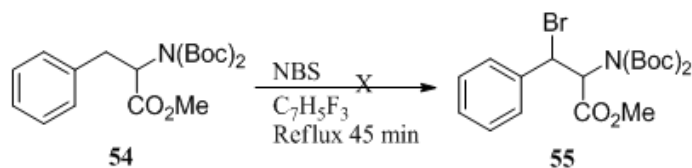
A 25 mL round bottom flask was charged with methyl-2-(tert-butoxycarbonylamino)-3-phenyl propanoate (100 mg, 0.358 mmol, 1 eq) in (trifluoromethyl)benzene (7.16 mL, 0.05 M). *N*-bromosuccinimide (63.7 mg, 0.358 mmol, 1 eq) was added and the reaction was subjected to the emission of a Xenon lamp (3W) whilst stirred under nitrogen. After 10 minutes the colour of the reaction turned from colourless to a cloudy orange. Analysis by ¹H-NMR showed only the presence of starting material, indicating the reaction was unsuccessful.

Synthesis of methyl-2-(bis(tert-butoxycarbonyl)amino)-3-phenylpropanoate



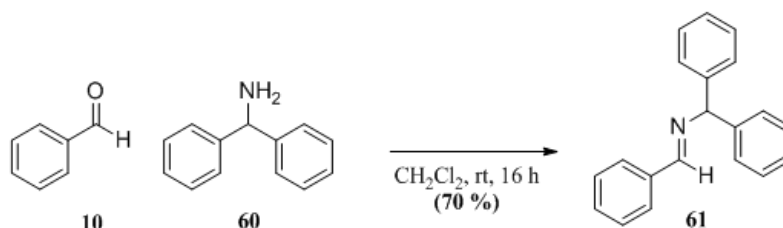
A 25 mL round bottomed flask was charged with methyl-2-(tert-butoxycarbonylamino)-3-phenyl propanoate (100 mg, 0.358 mmol, 1 eq) and 4-dimethylaminopyridine (44 mg, 0.358 mol, 1 eq) in acetonitrile (10 mL). The reaction mixture was treated with (Boc)₂O (234 mg, 1.07 mmol, 3 eq) and stirred at room temperature for 12 hours. A yellow colour was observed, the reaction mixture was concentrated with ethyl acetate and washed with saturated NH₄Cl solution, water and brine. The organic layer was dried over MgSO₄, filtered, and concentrated using a high vacuum. The impure product was then washed through a short plug of silica with diethyl ether. The desired product was observed as an orange oil, (0.103 g, 76 % yield). ¹H NMR (400 MHz, CDCl₃) δ 7.17 – 7.04 (m, 5H), 5.08 (dd, *J* = 10.5, 5.2 Hz, 1H), 3.68 (s, 3H), 3.36 (dd, *J* = 13.8, 4.7 Hz, 1H), 3.14 (dd, *J* = 13.7, 10.7 Hz, 1H), 1.31 (s, 18H). ¹³C-NMR (100 MHz, CDCl₃) δ 170.6, 152.4, 136.7, 128.5, 127.6, 125.8, 82.4, 58.6, 51.8, 36.1, 27.4. This compound had identical physicochemical values to what had been described before by Kokoto *et al.* ^[44, 89]

Synthesis of methyl-2-(bis(tert-butoxycarbonyl)amino)-3-bromo-3-phenylpropanoate ^[44]



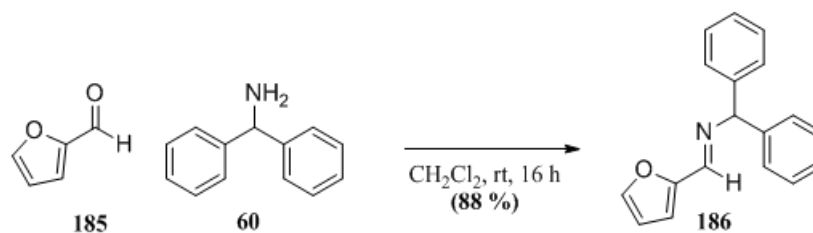
A 25 mL round bottom flask was charged with methyl-2-(tert-butoxycarbonylamino)-3-phenyl propanoate (103 mg, 0.271 mmol, 1 eq) in (trifluoromethyl)benzene (5.43 mL, 0.05 M). *N*-bromosuccinimide (63.7 mg, 0.358 mmol, 1 eq) was added and the reaction was subjected to the emission of a Xenon lamp (3W) whilst stirred under nitrogen. After 10 minutes the colour of the reaction turned from colourless to a cloudy orange. Analysis by ¹H-NMR showed only the presence of starting material, indicating the reaction was unsuccessful.

Synthesis of (*E*)-*N*-benzylidene-1,1-diphenylmethanamine



A 25 mL round bottom flask containing 4Å molecular sieves and magnetic stirrer bar were flame dried and cooled under a nitrogen atmosphere. Benzaldehyde (2.78 mmol, 1 eq) was added, dissolved in dry CH₂Cl₂ (5 mL) and allowed to stir for two minutes. To this mixture, benzhydramine (2.73 mmol, 0.98 eq) was added and the reaction was stirred vigorously at room temperature for 16 hours. The reaction mixture was filtered through a short plug of MgSO₄ and eluted with dry CH₂Cl₂ (2 x 10 mL), solvent removal *in vacuo* afforded the impure product as a solid. Purification of the impure product by recrystallation from petroleum ether (40 - 60°C) afforded the pure product as white crystals (0.52 g, 70 % yield). ¹H-NMR (400 MHz, CDCl₃) δ 8.42 (s, 1H), 8.01 – 7.72 (m, 2H), 7.55 – 7.00 (m, 13H), 5.62 (s, 1H). ¹³C-NMR (100 MHz, CDCl₃) δ 167.1, 160.9, 136.4, 130.9, 128.6, 128.6, 128.6, 127.8, 127.1, 78.0. IR (ATR) ν_{max} 3060, 3026, 2842, 1737, 1642, 1598, 1492, 1451, 1378, 1025, 753. MALDI-TOF-MS *m/z* 293.95 [M + Na]⁺. HRMS Calcd for C₂₀H₁₇N [M + H]⁺ 272.1434, found 272.1431.

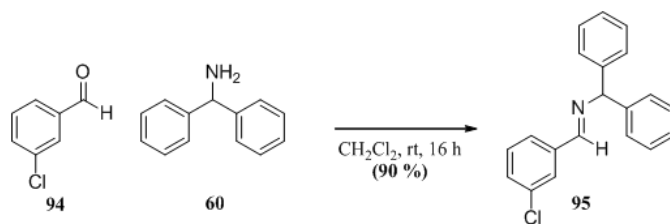
Synthesis of (*E*)-*N*-(furan-2-ylmethylene)-1,1-diphenylmethanamine



A 25 mL round bottom flask containing 4Å molecular sieves and magnetic stirrer bar were flame dried and cooled under a nitrogen atmosphere. 2-furaldehyde (2.78 mmol, 1 eq) was added, dissolved in dry CH₂Cl₂ (5 mL) and allowed to stir for two minutes. To this mixture, benzhydramine (2.73 mmol, 0.98 eq) was added and the reaction was stirred vigorously at room temperature for 16 hours. The reaction mixture was filtered through a short plug of MgSO₄ and eluted with dry CH₂Cl₂ (2 x 10 mL), solvent removal *in vacuo* afforded the impure product as a solid. Purification of the impure product by recrystallation from diethyl ether afforded the pure product as light yellow crystals (0.67 g, 88 % yield). ¹H-NMR (300 MHz, CDCl₃) δ 8.20 (s, 1H), 7.54 (d, *J* = 1.5 Hz, 1H), 7.42 – 7.16 (m, 10H), 6.81 (dd, *J* = 3.4, 0.6 Hz, 1H), 6.48 (dd, *J* = 3.4, 1.8 Hz, 1H), 5.58 (s, 1H). ¹³C-NMR (100 MHz, CDCl₃) δ 151.7, 149.8, 145.0, 143.4, 128.6, 127.9, 127.2, 114.8, 111.8, 78.1. IR (thin film cm⁻¹) 3104, 3084, 3060, 3026, 2850, 1951, 1762, 1645, 1597. 1492, 1452, 1392, 1361, 1269, 1200, 1018, 751, 699. HRMS Calcd for C₁₈H₁₅NO [M + H]⁺ 262.1226, found 262.1227.

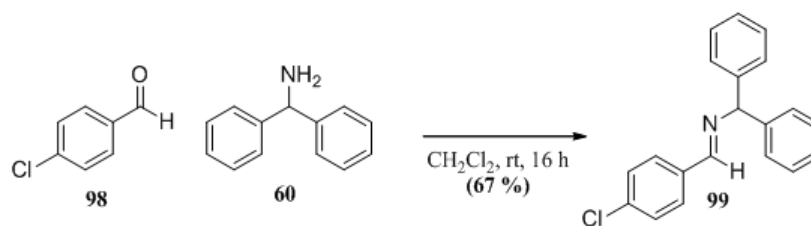
This compound had similar physicochemical values to what had been described before by Cainelli *et al.* [90]

Synthesis of (*E*)-*N*-(3-chlorobenzylidene)-1,1-diphenylmethanamine



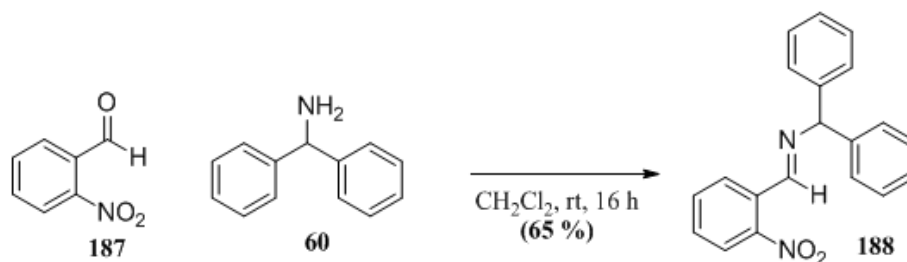
A 25 mL round bottom flask containing 4Å molecular sieves and magnetic stirrer bar were flame dried and cooled under a nitrogen atmosphere. 3-Chlorobenzaldehyde (2.78 mmol, 1 eq) was added, dissolved in dry CH₂Cl₂ (5 mL) and allowed to stir for two minutes. To this mixture, benzhydramine (2.73 mmol, 0.98 eq) was added and the reaction was stirred vigorously at room temperature for 16 hours. The reaction mixture was filtered through a short plug of MgSO₄ and eluted with dry CH₂Cl₂ (2 x 10 mL), solvent removal *in vacuo* afforded the impure product as a solid. Purification of the impure product by recrystallation from petroleum ether (40 - 60°C) afforded the pure product as colourless crystals (0.75 g, 90 % yield). ¹H-NMR (400 MHz, CDCl₃) δ 8.37 (s, 1H), 7.91 (s, 1H), 7.65 (dd, *J* = 8.9, 1.4 Hz, 1H), 7.50 – 7.13 (m, 12H), 5.61 (s, 1H). ¹³C-NMR (100 MHz, CDCl₃) δ 167.1, 159.4, 143.7, 138.1, 134.8, 130.9, 129.9, 128.6, 128.1, 127.7, 127.2, 127.0, 78.0. IR (ATR) ν_{max} 3026, 2844, 2335, 1737, 1642, 1597, 1570, 1492, 1452, 1376, 1212, 1026, 745. MALDI-TOF-MS *m/z* 327.83 [M]⁺. HRMS Calcd for C₂₀H₁₆N [M + H]⁺ 306.1004, found 306.1004.

Synthesis of (*E*)-*N*-(4-chlorobenzylidene)-1,1-diphenylmethanamine



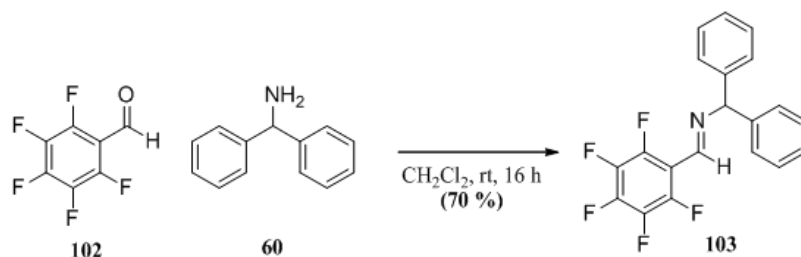
A 25 mL round bottom flask containing 4Å molecular sieves and magnetic stirrer bar were flame dried and cooled under a nitrogen atmosphere. 4-chlorobenzaldehyde (2.78 mmol, 1 eq) was added, dissolved in dry CH₂Cl₂ (10 mL) and allowed to stir for two minutes. To this mixture, benzhydramine (2.73 mmol, 0.98 eq) was added and the reaction was stirred vigorously at room temperature for 16 hours. The reaction mixture was filtered through a short plug of MgSO₄ and eluted with dry CH₂Cl₂ (2 x 10 mL), solvent removal *in vacuo* afforded the impure product as a solid. Purification of the impure product by trituration from petroleum ether (40 - 60°C) afforded the pure product as a white solid (0.56 g, 67 % yield). ¹H-NMR (400 MHz, CDCl₃) δ 8.38 (s, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.53 – 7.12 (m, 12H), 5.60 (s, 1H). ¹³C-NMR (100 MHz, CDCl₃) δ 159.6, 143.8, 136.8, 134.8, 129.8, 128.9, 128.6, 127.7, 127.2, 78.0. IR (ATR) ν_{max} 3025, 2843, 1641, 1595, 1490, 1451, 1086, 1013, 819. MALDI-TOF-MS *m/z* 327.79 [M + Na]⁺. Calcd for C₂₀H₁₆NCl [M + H]⁺ 306.1044, found 306.1047.

Synthesis of (*E*)-*N*-(2-nitrobenzylidene)-1,1-diphenylmethanamine



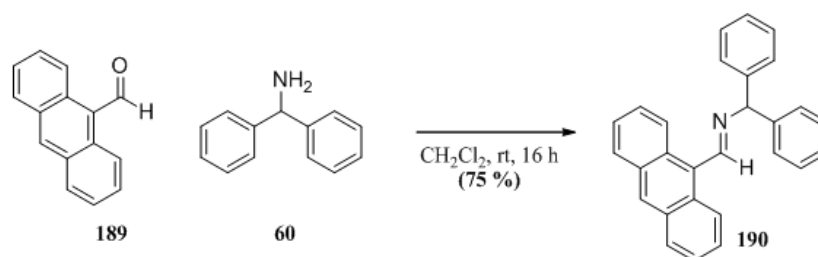
A 25 mL round bottom flask containing 4Å molecular sieves and magnetic stirrer bar were flame dried and cooled under a nitrogen atmosphere. 2-nitrobenzaldehyde (2.78 mmol, 1 eq) was added, dissolved in dry CH₂Cl₂ (5 mL) and allowed to stir for two minutes. To this mixture, benzhydramine (2.73 mmol, 0.98 eq) was added and the reaction was stirred vigorously at room temperature for 16 hours. The reaction mixture was filtered through a short plug of MgSO₄ and eluted with dry CH₂Cl₂ (2 x 10 mL), solvent removal *in vacuo* afforded the impure product as a solid. . Purification of the impure product by trituration from petroleum ether (40 - 60°C) afforded the pure product as an off white/ pale yellow solid, (0.56 g, 65 % yield). M.p = 92 - 94°C. ¹H-NMR (400 MHz, CDCl₃) δ 8.88 (s, 1H), 8.21 (dd, *J* = 7.8, 1.5 Hz, 1H), 8.05 – 7.95 (m, 1H), 7.70 – 7.60 (m, 1H), 7.59 – 7.48 (m, 1H), 7.46 – 7.20 (m, 10H), 5.72 (s, 1H). ¹³C-NMR (100 MHz, CDCl₃) δ 167.5, 157.0, 149.0, 143.1, 133.6, 131.2, 130.2, 128.7, 127.8, 127.4, 124.4, 78.2. IR (ATR) ν_{\max} 3027, 2855, 1636, 1598, 1572, 1522, 1492, 1344, 741, 698. MALDI-TOF-MS *m/z* 354.76 [M + K]⁺.

Synthesis of (*E*)-*N*-(perfluorobenzylidene)-1,1-diphenylmethanamine



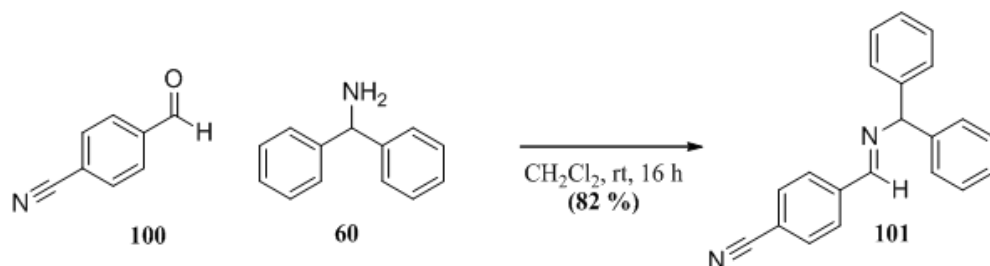
A 25 mL round bottom flask containing 4Å molecular sieves and magnetic stirrer bar were flame dried and cooled under a nitrogen atmosphere. Pentafluorobenzaldehyde (2.78 mmol, 1 eq) was added, dissolved in dry CH_2Cl_2 (5 mL) and allowed to stir for two minutes. To this mixture, benzhydramine (2.73 mmol, 0.98 eq) was added and the reaction was stirred vigorously at room temperature for 16 hours. The reaction mixture was filtered through a short plug of MgSO_4 and eluted with dry CH_2Cl_2 (2 x 10 mL), solvent removal *in vacuo* afforded the impure product as a solid. The compound was purified by recrystallation with petroleum ether (40 - 60°C) to afford white feather like crystals (0.69 g, 70 % yield). M. p = 75 – 77°C. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 8.55 (s, 1H), 7.53 – 7.15 (m, 10H), 5.60 (s, 1H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 167.2, 149.2, 143.1, 128.8, 127.6, 79.9. IR (film cm^{-1}): 3025, 2672, 2325, 1653, 1628, 1492, 1151, 1130, 1006, 956, 700. MALDI-TOF-MS m/z 361.31[M + Na] $^+$. HRMS Calcd for $\text{C}_{21}\text{H}_{12}\text{F}_5\text{N}$ [M + H] $^+$ 362.0963 found 362.0960.

Synthesis of (*E*)-*N*-(anthracen-9-ylmethylene)-1,1-diphenylmethanamine



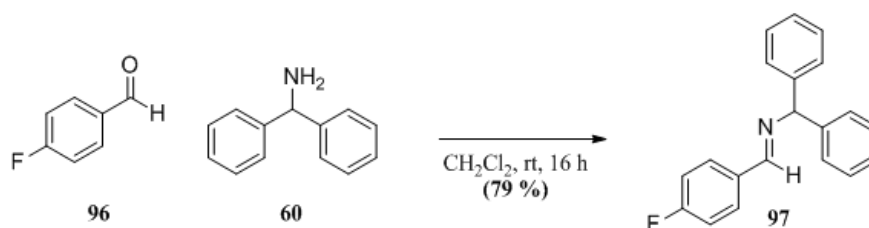
A 25 mL round bottom flask containing 4Å molecular sieves and magnetic stirrer bar were flame dried and cooled under a nitrogen atmosphere. 9-Anthraldehyde (2.78 mmol, 1 eq) was added, dissolved in dry CH₂Cl₂ (5 mL) and allowed to stir for two minutes. To this mixture, benzhydramine (2.73 mmol, 0.98 eq) was added and the reaction was stirred vigorously at room temperature for 16 hours. The reaction mixture was filtered through a short plug of MgSO₄ and eluted with dry CH₂Cl₂ (2 x 10 mL), solvent removal *in vacuo* afforded the impure product as a solid. The compound was purified by trituration with hot petroleum ether (40 - 60°C) to afford a yellow solid (0.75 g, 75 % yield). ¹H-NMR (400 MHz, CDCl₃) δ 9.65 (s, 1H), 8.50 (s, 3H), 8.02 (s, 2H), 7.72 – 7.25 (m, 14H), 5.96 (s, 1H). ¹³C-NMR (100 MHz, CDCl₃) δ 167.1, 160.7, 143.8, 131.4, 130.2, 129.7, 129.0, 128.9, 128.3, 128.1, 127.9, 127.3, 126.8, 125.3, 125.9, 80.3. IR (thin film, cm⁻¹) 3056, 3026, 2841, 1949, 1637, 1520, 1492, 1451, 1257, 1158, 1027, 889, 733. MALDI-TOF-MS *m/z* 394.76 [M + Na]⁺.

Synthesis of (*E*)-4-((benzhydrylimino)methyl)benzonitrile



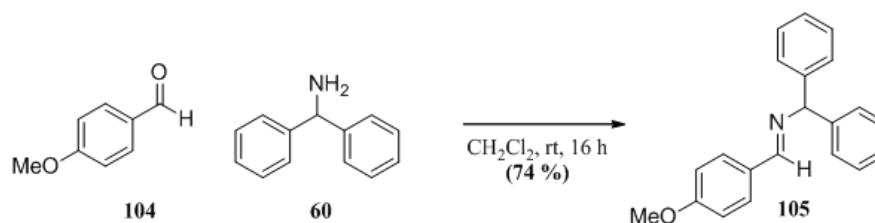
A 25 mL round bottom flask containing 4Å molecular sieves and magnetic stirrer bar were flame dried and cooled under a nitrogen atmosphere. 4-cyanobenzaldehyde (1.36 mmol, 1 eq) was added, dissolved in dry CH₂Cl₂ (5 mL) and allowed to stir for two minutes. To this mixture, benzhydrylamine (1.39 mmol, 0.98 eq) was added and the reaction was stirred vigorously at room temperature for 16 hours. The reaction mixture was filtered through a short plug of MgSO₄ and eluted with dry CH₂Cl₂ (2 x 10 mL), solvent removal *in vacuo* afforded the impure product as a solid. The compound was purified by trituration with hot petroleum ether (40 - 60°C) to afford a white solid, (0.334 g, 82 % yield). M.p = 103 - 105°C. ¹H-NMR (400 MHz, CDCl₃) δ 8.43 (s, 1H), 7.92 (d, *J* = 8.2 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.44 – 7.19 (m, 10H), 5.64 (s, 1H). ¹³C-NMR (100 MHz, CDCl₃) δ 167.1, 159.0, 143.4, 140.1, 132.5, 129.0, 128.7, 127.7, 127.4, 118.7, 114.1, 78.1. IR (film cm⁻¹): 2330, 1733, 1642, 1491, 1453, 1024, 826, 701, 474. MALDI-TOF-MS *m/z* 404.87 [M+Na]⁺. HRMS Calcd for C₂₁H₁₆N₂ [M + Na]⁺ 319.1206, found 319.1202.

Synthesis of (*E*)-*N*-(4-fluorobenzylidene)-1,1-diphenylmethanamine



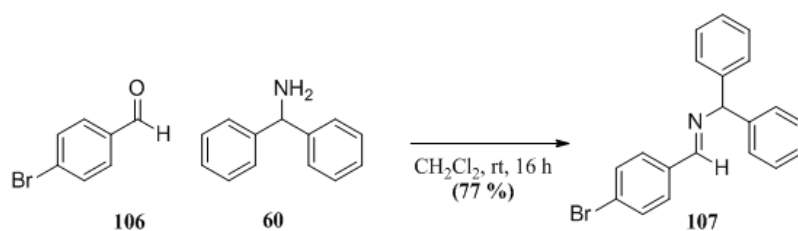
A 25 mL round bottom flask containing 4Å molecular sieves and magnetic stirrer bar were flame dried and cooled under a nitrogen atmosphere. 4-Fluorobenzaldehyde (2.78 mmol, 1 eq) was added, dissolved in dry CH₂Cl₂ (5 mL) and allowed to stir for two minutes. To this mixture, benzhydramine (2.73 mmol, 0.98 eq) was added and the reaction was stirred vigorously at room temperature for 16 hours. The reaction mixture was filtered through a short plug of MgSO₄ and eluted with dry CH₂Cl₂ (2 x 10 mL), solvent removal *in vacuo* afforded the impure product as a solid. The compound was purified by trituration with hot petroleum ether (40 - 60°C) to afford a white solid (0.62 g, 79 % yield). M.p = 50 - 52°C. ¹H-NMR (400 MHz, CDCl₃) δ 8.39 (s, 1H), 7.84 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.47 – 7.04 (m, 12H), 5.60 (s, 1H). ¹³C-NMR (100 MHz, CDCl₃) δ 167.1, 165.7, 163.2, 159.4, 143.9, 132.7, 130.5, 130.4, 128.6, 127.7, 127.2, 115.9, 115.6, 78.0. IR (ATR) ν_{max} 3062, 3026, 2841, 1641, 1227, 697. MALDI-TOF-MS *m/z* 311.87 [M + Na]⁺. HRMS Calcd for C₂₀H₁₆NF [M + H]⁺ 290.134, found 290.1342.

Synthesis of (*E*)-*N*-(4-methoxybenzylidene)-1,1-diphenylmethanamine



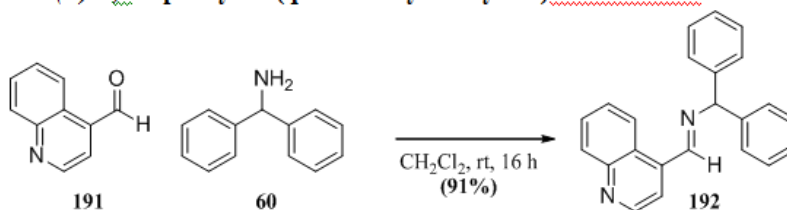
A 25 mL round bottom flask containing 4Å molecular sieves and magnetic stirrer bar were flame dried and cooled under a nitrogen atmosphere. 4-Methoxybenzaldehyde (2.78 mmol, 1 eq) was added, dissolved in dry CH₂Cl₂ (5 mL) and allowed to stir for two minutes. To this mixture, benzhydramine (2.73 mmol, 0.98 eq) was added and the reaction was stirred vigorously at room temperature for 16 hours. The reaction mixture was filtered through a short plug of MgSO₄ and eluted with dry CH₂Cl₂ (2 x 10 mL), solvent removal *in vacuo* afforded the impure product as a solid. The compound was purified by trituration with hot petroleum ether (40 - 60°C) to afford a white solid (0.61 g, 74 % yield). ¹H-NMR (400 MHz, CDCl₃) δ 8.37 (s, 1H), 7.80 (d, *J* = 8.8 Hz, 2H), 7.53 – 7.12 (m, 10H), 6.94 (d, *J* = 8.8 Hz, 2H), 5.58 (s, 1H), 3.83 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 161.8, 160.2, 144.2, 130.1, 129.4, 128.5, 127.8, 127.0, 114.0, 77.9, 55.5. IR (ATR) ν_{max} 2836, 1603, 1509, 1244, 1164, 1026, 698. MALDI-TOF-MS *m/z* 301.90 [M]⁺. HRMS Calcd for C₂₁H₁₉O [M]⁺ 302.1539, found 302.1544.

Synthesis of (*E*)-*N*-(4-bromobenzylidene)-1,1-diphenylmethanamine



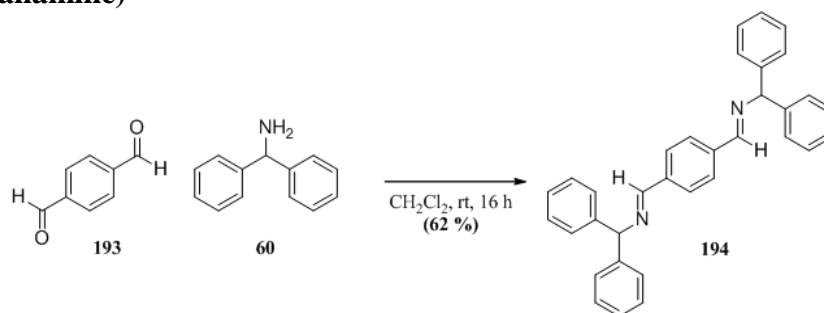
A 25 mL round bottom flask containing 4Å molecular sieves and magnetic stirrer bar were flame dried and cooled under a nitrogen atmosphere. 4-Methoxybenzaldehyde (2.78 mmol, 1 eq) was added, dissolved in dry CH₂Cl₂ (5 mL) and allowed to stir for two minutes. To this mixture, benzhydramine (2.73 mmol, 0.98 eq) was added and the reaction was stirred vigorously at room temperature for 16 hours. The reaction mixture was filtered through a short plug of MgSO₄ and eluted with dry CH₂Cl₂ (2 x 10 mL), solvent removal *in vacuo* afforded the impure product as a solid. The compound was purified by recrystallisation with petroleum ether (40 - 60°C) to afford light yellow crystals (0.75 g, 77 % yield). ¹H-NMR (400 MHz, CDCl₃) δ 8.37 (s, 1H), 7.72 (d, *J* = 6.7 Hz, 2H), 7.55 (d, *J* = 6.8 Hz, 2H), 7.41 (s, 4H), 7.34 (s, 4H), 7.26 (s, 2H), 5.61 (s, 1H). ¹³C-NMR (100 MHz, CDCl₃) δ 159.7, 143.8, 135.3, 131.9, 130.0, 128.6, 127.7, 127.2, 125.3, 78.0. IR (ATR) ν_{max} 3082, 3024, 2842, 2368, 1641, 1589, 1485, 1375, 1067, 1009, 697, 606, 499. MALDI-TOF-MS *m/z* 373.78 [M + Na]⁺. HRMS Calcd for C₂₀H₁₆NBr [M + H]⁺ 350.0539, found 350.0536 [M]⁺.

Synthesis of *(E)*-1,1-diphenyl-*N*-(quinolin-4-ylmethylene)methanamine



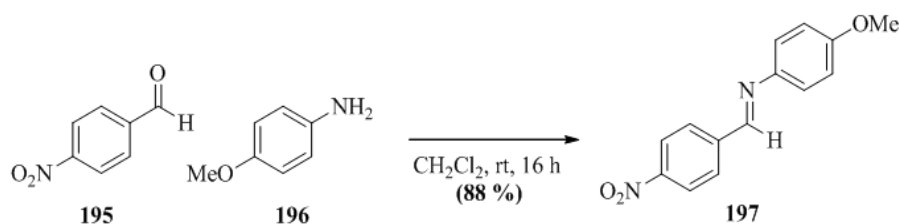
A 25 mL round bottom flask containing 4Å molecular sieves and magnetic stirrer bar were flame dried and cooled under a nitrogen atmosphere. 3-Quinolinecarboxaldehyde (2.78 mmol, 1 eq) was added, dissolved in dry CH₂Cl₂ (5 mL) and allowed to stir for two minutes. To this mixture, benzhydramine (2.73 mmol, 0.98 eq) was added and the reaction was stirred vigorously at room temperature for 16 hours. The reaction mixture was filtered through a short plug of MgSO₄ and eluted with dry CH₂Cl₂ (2 x 10 mL), solvent removal *in vacuo* afforded the impure product as a solid. The compound was purified by recrystallisation with petroleum ether (40 - 60°C) to afford a white solid (0.80 g, 91 % yield). M.p = 119 - 121°C. ¹H-NMR (300 MHz, CDCl₃) δ 9.45 (d, *J* = 2.1 Hz, 1H), 8.62 (s, 1H), 8.49 (d, *J* = 2.0 Hz, 1H), 8.14 (d, *J* = 9.0 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.82 – 7.70 (m, 1H), 7.64 – 7.53 (m, 1H), 7.51 – 7.13 (m, 10H), 5.69 (s, 1H). ¹³C-NMR (100 MHz, CDCl₃) δ 158.5, 150.1, 149.2, 143.6, 136.4, 130.7, 129.6, 129.0, 128.7, 128.6, 127.8, 127.6, 127.3, 127.3, 78.3. IR (ATR) ν_{max} 3060, 3025, 3025, 2847, 1640, 1597, 1569, 1491, 1452, 1361, 1025, 752. MALDI-TOF-MS *m/z* 322.94 [M]⁺. HRMS Calcd for C₂₃H₁₈N₂ [M + H]⁺ 323.1543, found 323.1540.

Synthesis of (*N,N'E,N,N'E*)-*N,N'*-(1,4-phenylenebis(methanylylidene))bis(1,1-diphenylmethanamine)



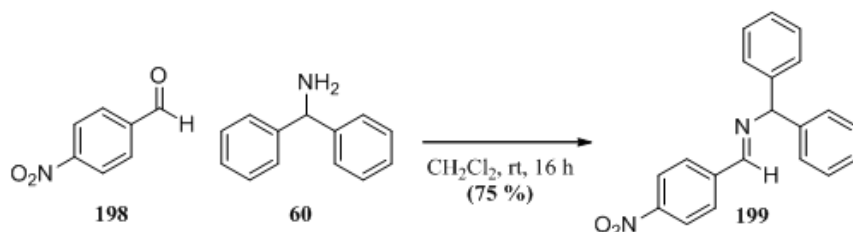
A 25 mL round bottom flask containing 4Å molecular sieves and magnetic stirrer bar were flame dried and cooled under a nitrogen atmosphere. Terephthalaldehyde (1.39 mmol, 1 eq) was added, dissolved in dry CH₂Cl₂ (5 mL) and allowed to stir for two minutes. To this mixture, benzhydramine (2.73 mmol, 1.96 eq) was added and the reaction was stirred vigorously at room temperature for 16 hours. The reaction mixture was filtered through a short plug of MgSO₄ and eluted with dry CH₂Cl₂ (2 x 10 mL), solvent removal *in vacuo* afforded the impure product as a solid. The compound was purified by trituration with hot petroleum ether (40 - 60°C) to afford a white solid (0.39 g, 62 % yield). M.p = 176 - 178°C. ¹H-NMR (400 MHz, CDCl₃) 8.46 (s, 2H), 7.91 (s, 4H), 7.47 – 7.21 (m, 20H), 5.64 (s, 2H). ¹³C-NMR (100 MHz, CDCl₃) δ 154.5, 154.3, 128.0, 127.6, 125.8, 113.7, 61.2, 56.4, 44.5, 36.1, 36.0, 32.4, 31.1, 28.3, 22.9, 14.3. IR (ATR) ν_{max} 3026, 2844, 1638, 1492, 1450, 1376, 1277, 1026, 859, 742. MALDI-TOF-MS *m/z* 486.85 [M + Na]⁺. HRMS Calcd for C₃₄H₂₈N₂ [M + H]⁺ 465.2325, found 465.2318

Synthesis of (*E*)-4-methoxy-N-(4-nitrobenzylidene)aniline



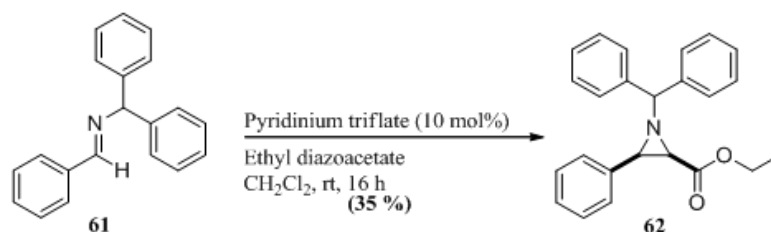
A 25 mL round bottom flask containing 4Å molecular sieves and magnetic stirrer bar were flame dried and cooled under a nitrogen atmosphere. 4-nitrobenzaldehyde (13.23 mmol, 1 eq) was added, dissolved in dry CH₂Cl₂ (5 mL) and allowed to stir for two minutes. To this mixture, 4-methoxyaniline (13.23 mmol, 1 eq) was added and the reaction was stirred vigorously at room temperature for 16 hours. The reaction mixture was filtered through a short plug of MgSO₄ and eluted with dry CH₂Cl₂ (2 x 10 mL), solvent removal *in vacuo* afforded the pure product as orange crystals (2.98 g, 88 % yield). ¹H-NMR (400 MHz, CDCl₃) δ 8.58 (s, 1H), 8.31 (d, *J* = 8.9 Hz, 2H), 8.05 (d, *J* = 8.9 Hz, 2H), 7.31 (d, *J* = 9.0 Hz, 2H), 6.96 (d, *J* = 9.0 Hz, 2H), 3.85 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 159.3, 154.9, 149.1, 143.7, 142.1, 129.2, 124.1, 122.8, 114.7, 55.7. IR (ATR) ν_{max} 2892, 2835, 1599, 1508, 1340, 1246, 1105, 1036, 848, 550. MALDI-TOF-MS *m/z* 256.78 [M]⁺.

Synthesis of (*E*)-*N*-(4-nitrobenzylidene)-1,1-diphenylmethanamine



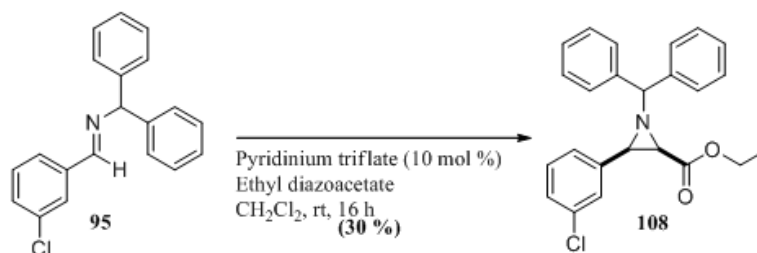
A 25 mL round bottom flask containing 4Å molecular sieves and magnetic stirrer bar were flame dried and cooled under a nitrogen atmosphere. 4-nitrobenzaldehyde (2.78 mmol, 1 eq) was added, dissolved in dry CH₂Cl₂ (5 mL) and allowed to stir for two minutes. To this mixture, benzhydramine (2.73 mmol, 0.98 eq) was added and the reaction was stirred vigorously at room temperature for 16 hours. The reaction mixture was filtered through a short plug of MgSO₄ and eluted with dry CH₂Cl₂ (2 x 10 mL), solvent removal *in vacuo* afforded the pure product as orange crystals (0.65 g, 75 % yield). ¹H-NMR (300 MHz, CDCl₃) δ 8.51 (s, 1H), 8.28 (d, *J* = 8.7 Hz, 2H), 8.01 (d, *J* = 9.0 Hz, 2H), 7.46 – 7.19 (m, 10H), 5.67 (s, 1H). ¹³C-NMR (100 MHz, CDCl₃) δ 158.68, 143.29, 141.80, 129.28, 128.75, 127.70, 127.45, 123.99, 78.27, 58.43. IR (ATR) ν_{\max} 1642, 1601, 1521, 1345, 1027, 911, 853, 640. MALDI-TOF-MS *m/z* 338.83 [M + K]⁺.

Synthesis of ethyl 1-benzhydryl-3-phenylaziridine-2-carboxylate



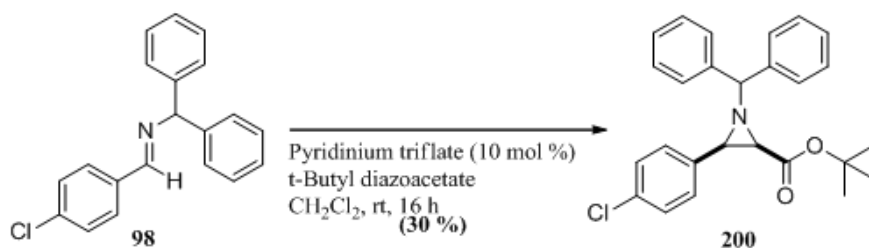
To a flame dried microwave vial charged (*E*)-*N*-benzylidene-1,1-diphenylmethanamine (1.47 mmol, 1 eq) and pyridinium triflate (0.15 mmol, 0.1 eq) dissolved in CH₂Cl₂ (4 mL) was added ethyl diazoacetate (1.62 mmol, 1.1 eq). The mixture was stirred vigorously for 16 hours under a nitrogen atmosphere. After the allocated time, the reaction mixture was filtered through a short plug of silica eluted with diethyl ether. Subsequent purification by flash column chromatography (elution with hexane / diethyl ether: 8:2) afforded the aziridine product as a white solid. (0.184 g, 35 % yield). M.p. = 113 – 115^oC. ¹H-NMR (300 MHz, CDCl₃) δ 7.60 (d, *J* = 7.3 Hz, 2H), 7.48 (d, *J* = 7.0 Hz, 2H), 7.43 – 7.12 (m, 11H), 4.02 – 3.85 (m, 3H), 3.21 (d, *J* = 6.9 Hz, 1H), 2.66 (d, *J* = 6.8 Hz, 1H), 0.97 (t, *J* = 7.1 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 168.0, 142.7, 142.6, 135.2, 128.7, 128.0, 127.7, 127.6, 127.5, 127.4, 77.9, 60.8, 48.2, 46.6, 14.2. IR (ATR) ν_{max} 3060, 3029, 2980, 2937, 1948, 1889, 1742, 1723, 1599, 1373, 1302, 1200, 1066, 863, 805, 624. HRMS Calcd for C₂₄H₂₃NO₂ [M + H]⁺ 358.1802, found 358.1797.

ethyl 1-benzhydryl-3-(3-chlorophenyl)aziridine-2-carboxylate



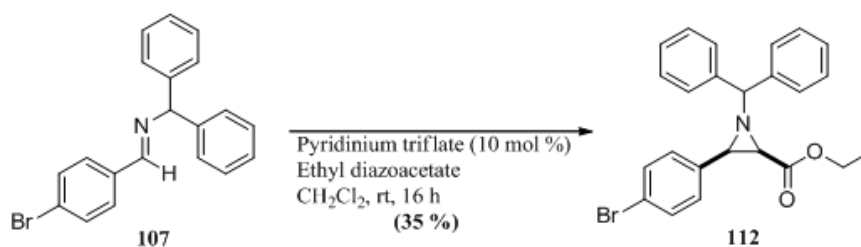
To a flame dried microwave vial charged (*E*)-*N*-(3-chlorobenzylidene)-1,1-diphenylmethanamine (0.327 mmol, 1 eq) and pyridinium triflate (0.033 mmol, 0.1 eq) dissolved in CH₂Cl₂ (1 mL) was added ethyl diazoacetate (0.360 mmol, 1.1 eq). The mixture was stirred vigorously for 16 hours under a nitrogen atmosphere. After the allocated time, the reaction mixture was filtered through a short plug of silica eluted with diethyl ether. Subsequent purification by flash column chromatography (elution with hexane / diethyl ether: 9:1) afforded the aziridine product as a white solid (0.038 g, 30 % yield). M.p = 63 – 65 °C. ¹H-NMR (300 MHz, CDCl₃) δ 7.60 (dd, *J* = 5.2, 3.5 Hz, 2H), 7.48 (dd, *J* = 5.3, 3.3 Hz, 2H), 7.42 (s, 1H), 7.38 – 7.15 (m, 9H), 4.03 – 3.92 (m, 3H), 3.17 (d, *J* = 6.8 Hz, 1H), 2.70 (d, *J* = 6.8 Hz, 1H), 1.03 (t, *J* = 7.1 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃) δ 167.8, 142.5, 142.4, 137.4, 133.9, 129.3, 128.8, 128.8, 128.2, 127.8, 127.8, 127.7, 127.5, 127.3, 126.3, 77.8, 60.9, 47.3, 46.6, 14.0. IR (ATR) ν_{max} 2363, 2328, 1722, 1599, 1200, 1006 cm⁻¹. MALDI-TOF-MS *m/z* 404.87 [M + Na]⁺. HRMS Calcd for C₂₄H₂₂NO₂ [M + H]⁺ 392.1412, found 392.1416.

Synthesis of tert-butyl 1-benzhydryl-3-(4-chlorophenyl)aziridine-2-carboxylate



To a flame dried microwave vial charged (*E*)-*N*-(4-chlorobenzylidene)-1,1-diphenylmethanamine (0.327 mmol, 1 eq) and pyridinium triflate (0.033 mmol, 0.1 eq) dissolved in CH₂Cl₂ (1 mL) was added t-butyl diazoacetate (0.360 mmol, 1.1 eq). The mixture was stirred vigorously for 16 hours under a nitrogen atmosphere. After the allocated time, the reaction mixture was filtered through a short plug of silica eluted with diethyl ether. Subsequent purification by flash column chromatography (elution with hexane / diethyl ether: 9:1) afforded the aziridine product as a white solid, (0.041 g, 30 % yield). M.p = 120 – 122 °C. ¹H-NMR (400 MHz, CDCl₃) δ 7.53 (d, *J* = 7.2 Hz, 2H), 7.37 (d, *J* = 7.1 Hz, 2H), 7.30 – 7.05 (m, 10H), 3.84 (s, 1H), 3.03 (d, *J* = 6.9 Hz, 1H), 2.50 (d, *J* = 6.9 Hz, 1H), 1.12 (s, 9H). ¹³C-NMR (100 MHz, CDCl₃) δ 169.9, 166.8, 161.9, 142.7, 142.6, 142.5, 135.2, 133.0, 129.4, 128.7, 128.7, 128.6, 127.9, 127.6, 127.4, 90.8, 81.4, 79.1, 62.3, 61.6, 47.5, 47.4, 46.8, 28.7, 27.9. IR (ATR) ν_{max} 2976, 2368, 2316, 1730, 1648, 1607, 1492, 1366, 1149, 1067, 843, 799, 744, 699. MALDI-TOF-MS *m/z* 419.84 [M]⁺. HRMS Calcd for C₂₆H₂₆ClNO₂ [M + H]⁺ 420.1725, found 420.1728.

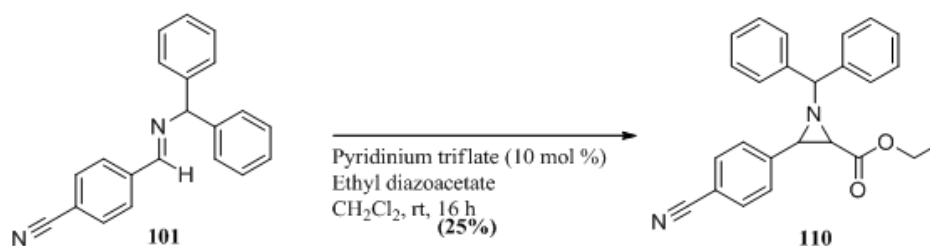
Synthesis of ethyl 1-benzhydryl-3-(4-bromophenyl)aziridine-2-carboxylate



To a flame dried microwave vial charged (*E*)-*N*-(4-bromobenzylidene)-1,1-diphenylmethanamine (0.214 mmol, 1 eq) and pyridinium triflate (0.021 mmol, 0.1 eq) dissolved in CH₂Cl₂ (1 mL) was added ethyl diazoacetate (0.236 mmol, 1.1 eq). The mixture was stirred vigorously for 16 hours under a nitrogen atmosphere. After the allocated time, the reaction mixture was filtered through a short plug of silica eluted with diethyl ether. Subsequent purification by flash column chromatography (elution with hexane / diethyl ether: 9:1) afforded the aziridine product as a white solid, (33 mg, 35 % yield). M.p. 118 – 122°C.

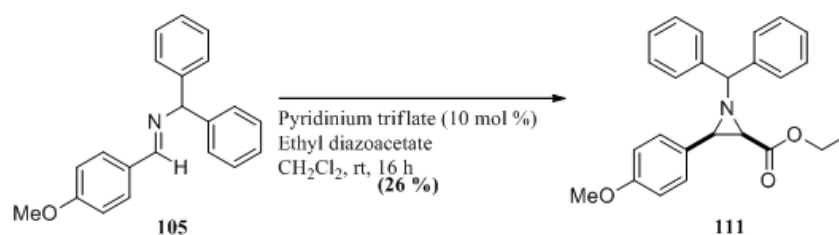
¹H-NMR (300 MHz, CDCl₃) δ 7.59 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.42 – 7.13 (m, 10H), 4.07 – 3.81 (m, 3H), 3.14 (d, *J* = 6.8 Hz, 1H), 2.69 (d, *J* = 6.8 Hz, 1H), 1.03 (t, *J* = 7.1 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 167.7, 167.2, 142.5, 142.4, 134.2, 131.1, 129.8, 128.8, 127.7, 127.6, 127.5, 127.3, 121.6, 77.8, 61.0, 47.6, 46.7, 14.2.

Synthesis of ethyl 1-benzhydryl-3-(4-cyanophenyl)aziridine-2-carboxylate



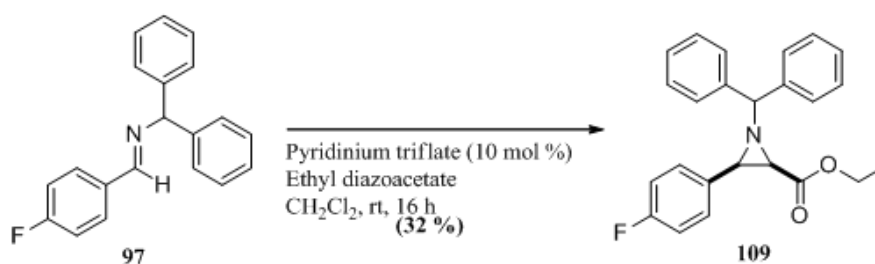
To a flame dried microwave vial charged (*E*)-4-((benzhydrylimino)methyl)benzonitrile (0.337 mmol, 1 eq) and pyridinium triflate (7.73 mmol, 0.1 eq) dissolved in CH₂Cl₂ (1 mL) was added ethyl diazoacetate (0.371 mmol, 1.1 eq). The mixture was stirred vigorously for 16 hours under a nitrogen atmosphere. After the allocated time, the reaction mixture was filtered through a short plug of silica with diethyl ether. Subsequent purification by flash column chromatography (elution with hexane / diethyl ether: 9:1) afforded the aziridine product as a white solid, (0.032 g, 25 % yield). M.p = 110 - 112 °C. ¹H-NMR (400 MHz, CDCl₃) δ 7.70 – 7.05 (m, 14H), 4.01 – 3.82 (m, 3H), 3.21 (d, *J* = 6.8 Hz, 1H), 2.75 (d, *J* = 6.8 Hz, 1H), 0.98 (t, *J* = 7.1 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 167.2, 142.29, 142.0, 141.0, 131.7, 128.7, 128.79, 127.7, 127.5, 127.5, 127.1, 119.0, 111.2, 61.0, 47.3, 46.9, 14.1. IR (ATR) ν_{max} 1741, 1610, 1202, 851, 703, 571 cm⁻¹. HRMS Calcd for C₂₅H₂₂N₂O₂ [M + H]⁺ 383.1754, found 383.1758.

Synthesis of ethyl 1-benzhydryl-3-(4-methoxyphenyl)aziridine-2-carboxylate



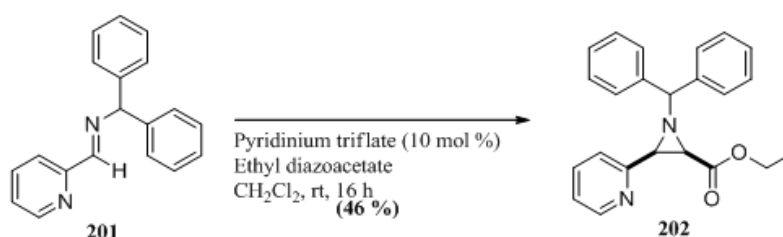
To a flame dried microwave vial charged (*E*)-N-(4-methoxybenzylidene)-1,1-diphenylmethanamine (0.332 mmol, 1 eq) and pyridinium triflate (0.033 mmol, 0.1 eq) dissolved in CH₂Cl₂ (1 mL) was added ethyl diazoacetate (0.365 mmol, 1.1 eq). The mixture was stirred vigorously for 16 hours under a nitrogen atmosphere. After the allocated time, the reaction mixture was filtered through a short plug of silica eluted with diethyl ether. Subsequent purification by flash column chromatography (elution with hexane / diethyl ether: 9:1) afforded the aziridine product as a white solid, (0.032 g, 25% yield). M.p = 113 - 115°C. ¹H-NMR (400 MHz, CDCl₃) δ 7.57 (d, *J* = 6.6 Hz, 2H), 7.46 (d, *J* = 7.3 Hz, 2H), 7.37 – 7.11 (m, 8H), 6.77 (d, *J* = 8.8 Hz, 2H), 4.02 – 3.85 (m, 3H), 3.73 (s, 3H), 3.14 (d, *J* = 6.8 Hz, 1H), 2.61 (d, *J* = 6.8 Hz, 1H), 1.00 (t, *J* = 7.1 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 168.0, 159.0, 142.7, 142.6, 129.0, 128.6, 127.6, 127.5, 127.3, 127.3, 127.2, 113.4, 77.8, 60.7, 55.3, 47.9, 46.5, 14.2. IR (ATR) ν_{max} 2988, 2342, 1741, 1612, 1514, 1452, 1375, 1301, 1249, 1179, 1097, 1068, 1035, 842, 810. MALDI-TOF-MS *m/z* 387.87 [M]⁺. HRMS Calcd for C₂₅H₂₅NO₃ [M + H]⁺ 388.1907, found 388.1902.

Synthesis of ethyl 1-benzhydryl-3-(4-fluorophenyl)aziridine-2-carboxylate



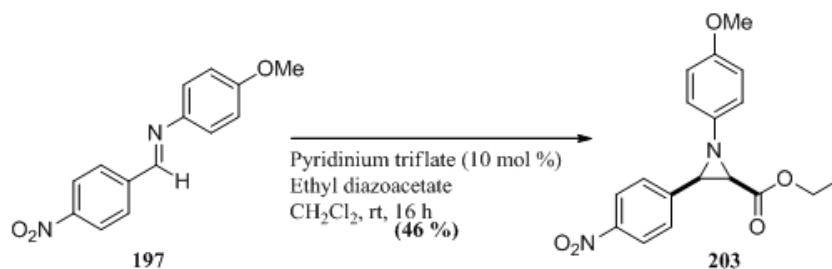
To a flame dried microwave vial charged (*E*)-*N*-(4-fluorobenzylidene)-1,1-diphenylmethanamine (0.346 mmol, 1 eq) and pyridinium triflate (0.035 mmol, 0.1 eq) dissolved in CH₂Cl₂ (1 mL) was added ethyl diazoacetate (0.380 mmol, 1.1 eq). The mixture was stirred vigorously for 16 hours under a nitrogen atmosphere. After the allocated time, the reaction mixture was filtered through a short plug of silica eluted with diethyl ether. Subsequent purification by flash column chromatography (elution with hexane / diethyl ether: 9:1) afforded the aziridine product as a white solid, (0.032 g, 25 % yield). ¹H-NMR (400 MHz, CDCl₃) δ 7.58 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 6.9 Hz, 2H), 7.42 – 7.14 (m, 8H), 6.99 – 6.88 (m, 2H), 4.01 – 3.86 (m, 3H), 3.17 (d, *J* = 6.8 Hz, 1H), 2.66 (d, *J* = 6.8 Hz, 1H), 1.01 (t, *J* = 7.1 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 167.8, 163.53, 161.1, 142.6, 142.4, 130.8, 129.6, 129.5, 128.6, 127.6, 127.4, 127.3, 114.9, 114.7, 77.8, 60.8, 47.4, 46.5, 14.2. IR (ATR) ν_{max} 3839, 2346, 1746, 1653, 1611, 1558, 1511, 1372, 1346, 1295, 1200, 1157, 1092, 1071, 1038, 949, 816, 801, 744. MALDI-TOF-MS *m/z* 414.90 [M + K]⁺. HRMS Calcd for C₂₄H₂₂FNO₂ [M + H]⁺ 376.1707, found 376.1711.

Synthesis of ethyl 1-benzhydryl-3-(pyridin-2-yl)aziridine-2-carboxylate



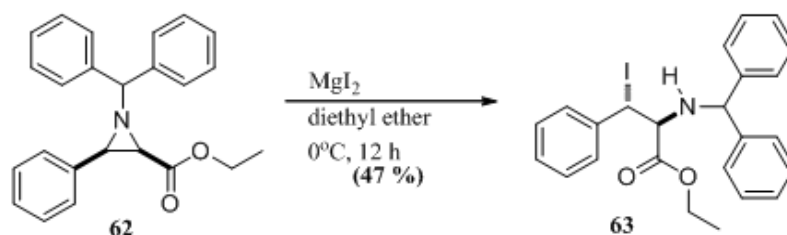
To a flame dried microwave vial charged (*E*)-*N*-(pyridine-2-ylmethylene) benzhydrylamine (0.261 mmol, 1 eq) and pyridinium triflate (0.026 mmol, 0.1 eq) dissolved in CH₂Cl₂ (4 mL) was added ethyl diazoacetate (0.287 mmol, 1.1 eq). The mixture was stirred vigorously for 16 hours under a nitrogen atmosphere. After the allocated time, the reaction mixture was filtered through a short plug of silica eluted with diethyl ether. Subsequent purification by flash column chromatography (elution with hexane / ethyl acetate: 5:1) afforded the aziridine product as a white solid, (43 mg, 46 % yield). M.p = 116 - 117°C. ¹H-NMR (300 MHz, CDCl₃) δ 8.44 (d, *J* = 4.7 Hz, 1H), 7.72 – 6.95 (m, 13H), 4.16 – 3.78 (m, 3H), 3.40 (d, *J* = 6.9 Hz, 1H), 2.78 (d, *J* = 6.9 Hz, 1H), 1.01 (t, *J* = 7.1 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃) δ 167.8, 155.4, 148.9, 142.6, 142.4, 136.2, 128.7, 127.7, 127.7, 127.5, 127.3, 122.9, 122.6, 77.6, 60.8, 49.3, 46.0, 13.9. IR (ATR) ν_{max} 3060, 3025, 2980, 1742, 1591, 1569, 1487, 1475, 1450, 1435, 1372, 1352, 1302, 1210, 1185, 1090, 1067, 1037, 998, 850, 746, 698. MALDI-TOF-MS *m/z* 359.11 [M + H]⁺.

Synthesis of ethyl 1-(4-methoxyphenyl)-3-(4-nitrophenyl)aziridine-2-carboxylate



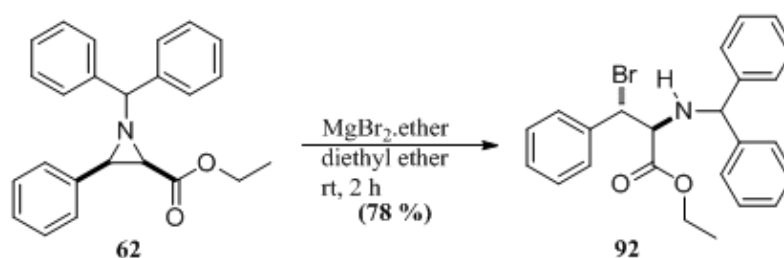
To a flame dried microwave vial charged (*E*)-4-methoxy-*N*-(4-nitrobenzylidene)aniline (0.261 mmol, 1 eq) and pyridinium triflate (0.026 mmol, 0.1 eq) dissolved in CH₂Cl₂ (4 mL) was added ethyl diazoacetate (0.287 mmol, 1.1 eq). The mixture was stirred vigorously for 16 hours under a nitrogen atmosphere. After the allocated time, the reaction mixture was filtered through a short plug of silica eluted with diethyl ether. Subsequent purification by flash column chromatography (elution with hexane / diethyl ether: 7:3) afforded the aziridine product as a yellow oil, (43 mg, 46 % yield. ¹H-NMR (300 MHz, CDCl₃) δ 8.22 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 2H), 4.15 – 3.92 (m, 2H), 3.78 (s, 3H), 3.58 (d, *J* = 6.8 Hz, 1H), 3.22 (d, *J* = 6.8 Hz, 1H), 1.05 (t, *J* = 7.1 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 167.2, 156.3, 147.7, 144.9, 142.3, 128.9, 123.4, 120.8, 114.7, 61.5, 55.7, 46.7, 46.2, 14.2. IR (ATR) ν_{\max} 1731, 1598, 1508, 1447, 1345, 1241, 1189, 1112, 1039, 907, 833, 757, 699, 534, 423, 414. MALDI-TOF-MS *m/z* 343.17 [M + H]⁺.

Synthesis of ethyl 2-(benzhydrylamino)-3-iodo-3-phenylpropanoate



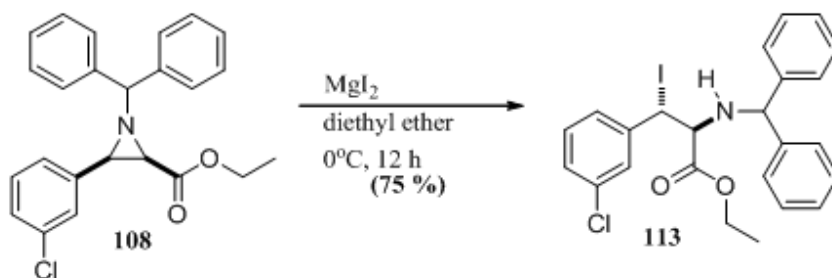
A flame dried microwave vial was charged with iodine (0.16 mmol, 2 eq) dissolved in diethyl ether (1 mL) affording a blood red solution and stirred under nitrogen for 5 minutes. Magnesium turnings (0.32 mmol, 4 eq) were then added and the mixture was stirred for approximately 1 hour under a nitrogen atmosphere at ambient temperature. When the solution of MgI_2 (0.16 mmol, 2 eq) became colourless and majority of the magnesium turnings had dissolved, ethyl 1-benzhydryl-3-phenylaziridine-2-carboxylate (0.079 mmol, 1 eq) dissolved in dichloromethane (0.5 mL) was added and the reaction was stirred for 12 hours in absence of light. A spatula of celite was added and the reaction mixture was stirred for 5 minutes before being filtered and washed with $\text{HCl}_{(\text{aq})}$ (2 x 5 mL, 0.01 M) and $\text{sat. NaHCO}_3_{(\text{aq})}$ (2 x 5 mL). Purification *via* flash column chromatography (elution with toluene) afforded the desired Iodo compound as a yellow solid. (17.5 mg, 47 % yield). M.p = 66 – 68°C. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.51 – 7.12 (m, 15H), , 5.30 (d, J = 6.9 Hz, 1H), 4.89 (s, 1H), 4.12 – 3.93 (m, 2H), 3.35 (s, 1H), 2.48 (s, 1H), 1.07 (t, J = 7.1 Hz, 3H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 144.3, 142.3, 140.5, 129.2, 128.8, 128.6, 128.5, 128.4, 128.0, 127.5, 127.4, 66.1, 65.6, 61.3, 35.4, 14.1, 1.03. IR (ATR) ν_{max} 2362, 1724, 1492, 1452, 1259, 1179, 1158, 1091, 1058, 1018, 910, 851, 746, 696, 667, 599, 471. MALDI-TOF-MS m/z 485.23 $[\text{M}]^+$. HRMS Calcd for $\text{C}_{24}\text{H}_{23}\text{INO}_2$ $[\text{M} + \text{H}]^+$ 486.0924, found 486.0922

Synthesis of ethyl 2-(benzhydrylamino)-3-bromo-3-phenylpropanoate



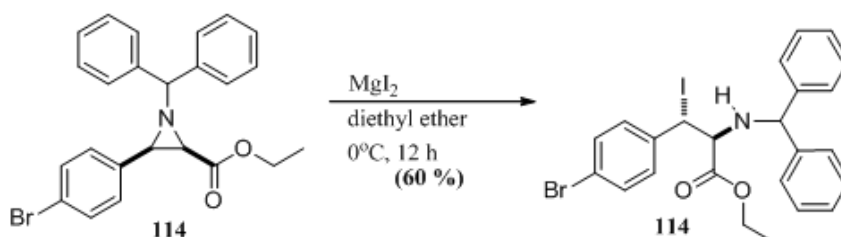
A 25 mL round bottom flask was charged with ethyl 1-benzhydryl-3-phenylaziridine-2-carboxylate (2.80 mmol, 1 eq) dissolved in dry diethyl ether (5 mL) and stirred vigorously for 5 minutes. Magnesium bromide diethyl etherate (4.20 mmol, 1.5 eq) was then added and the reaction was allowed to stir vigorously under a nitrogen atmosphere for 2 hours. The reaction mixture was then filtered through celite; solvent removal *in vacuo* afforded the desired product as a white solid. (0.096 g, 78 % yield). M.p = 75 - 77 °C. ¹H-NMR (400 MHz, CDCl₃) δ 7.49-7.36 (m, 2H), 7.35-7.08 (m, 8H), 7.07-6.90 (m, 5H), 5.26 (d, *J* = 4.7 Hz, 1H), 4.79 (s, 1H), 4.17-3.98 (m, 2H), 3.47 (d, *J* = 4.7 Hz, 1H), 1.12 (t, *J* = 7.1 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 171.8, 144.3, 142.3, 138.8, 129.1, 128.8, 128.7, 128.6, 128.3, 127.7, 127.5, 127.5, 127.2. IR (thin film, cm⁻¹) 2962, 2924, 2850, 1736, 1493, 1452, 1371, 1261, 1195, 1095, 1028, 913, 744, 697. MALDI-TOF MS *m/z* 437.7 [M+H]⁺. HRMS (NSI) Calcd for C₂₄H₂₃BrNO₂ [M + H]⁺ 438.1063, found 438.1070.

Synthesis of ethyl 2-(benzhydrylamino)-3-(3-chlorophenyl)-3-iodopropanoate



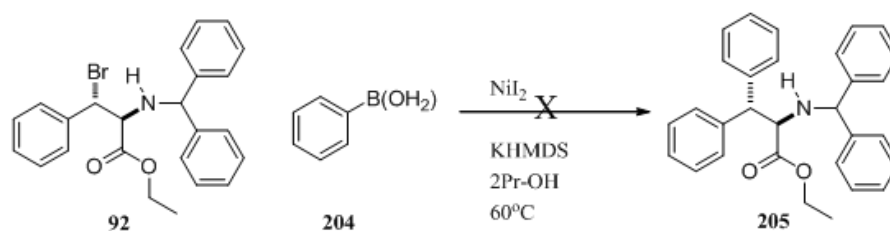
A flame dried microwave vial was charged with iodine (0.16 mmol, 2 eq) dissolved in diethyl ether (1 mL) affording a blood red solution and stirred under nitrogen for 5 minutes. Magnesium turnings (0.32 mmol, 4 eq) were then added and the mixture was stirred for approximately 1 hour under a nitrogen atmosphere at ambient temperature. When the solution of MgI_2 (0.16 mmol, 2 eq) became colourless and majority of the magnesium turnings had dissolved, ethyl 1-benzhydryl-3-(3-chlorophenyl)aziridine-2-carboxylate (0.079 mmol, 1 eq) dissolved in dichloromethane (0.5 mL) was added and the reaction was stirred for 12 hours in absence of light. A spatula of celite was added and the reaction mixture was stirred for 5 minutes before being filtered and washed with $HCl_{(aq)}$ (2 x 5 mL, 0.01 M) and sat. $NaHCO_{3(aq)}$ (2 x 5 mL). Purification *via* flash column chromatography (elution with toluene) afforded the desired Iodo compound as a yellow oil (32 mg, 78 % yield). 1H -NMR (300 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.48 – 7.10 (m, 13H), 5.26 (d, $J = 6.2$ Hz, 1H), 4.88 (s, 1H), 4.21 – 3.99 (m, 2H), 3.24 (s, 1H), 2.50 (s, 1H), 1.13 (t, $J = 7.1$ Hz, 3H). ^{13}C -NMR (100 MHz, $CDCl_3$) δ 171.2, 144.0, 142.4, 142.0, 134.0, 129.5, 129.5, 128.8, 128.6, 128.5, 127.9, 127.4, 127.3, 65.6, 65.5, 61.6, 58.4, 33.6, 14.3. IR (ATR) ν_{max} 1732, 1595, 1491, 1452, 1370, 1305, 1270, 1190, 1154, 1024, 798, 702. MALDI-TOF-MS m/z 557.68 $[M + K]^+$. HRMS Calcd for $C_{24}H_{23}ClINO_2$ $[M + H]^+$ 520.0535, found 520.0531.

Synthesis of ethyl 2-(benzhydrylamino)-3-(4-bromophenyl)-3-iodopropanoate



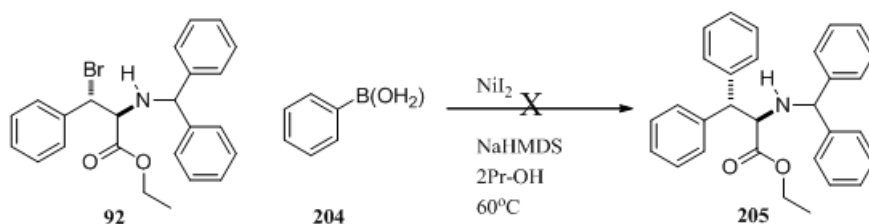
A flame dried microwave vial was charged with iodine (0.103 mmol, 2 eq) dissolved in diethyl ether (1 mL) affording a blood red solution and stirred under nitrogen for 5 minutes. Magnesium turnings (0.206 mmol, 3 eq) were then added and the mixture was stirred for approximately 1 hour under a nitrogen atmosphere at ambient temperature. When the solution of MgI_2 (0.103 mmol, 1.5 eq) became colourless and majority of the magnesium turnings had dissolved, ethyl 1-benzhydryl-3-(4-bromophenyl)aziridine-2-carboxylate (0.069 mmol, 1 eq) dissolved in dichloromethane (0.5 mL) was added and the reaction was stirred for 12 hours in absence of light. A spatula of celite was added and the reaction mixture was stirred for 5 minutes before being filtered through a short plug of alumina eluted with ethyl acetate. Purification *via* flash column chromatography (elution with toluene) afforded the desired Iodo compound as a yellow oil (22 mg, 60 % yield). $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.48 – 7.12 (m, 14H), 5.27 (d, $J = 6.4$ Hz, 1H), 4.88 (s, 1H), 4.16 – 4.02 (m, 2H), 3.25 (d, $J = 6.4$ Hz, 1H), 2.36 (s, 1H), 1.13 (t, $J = 7.1$ Hz, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 167.6, 167.2, 142.4, 142.3, 134.2, 131.03, 129.7, 128.7, 127.6, 127.5, 127.4, 127.3, 121.5, 77.7, 60.9, 47.5, 46.6, 14.2. IR (thin film, cm^{-1}) 3452, 3319, 3062, 2929, 2249, 1953, 1731, 1597, 1488, 1453, 1400, 1368, 1260, 1189, 1072, 1011, 910, 824, 745, 703. MALDI-TOF-MS m/z 587.25 $[\text{M} + \text{Na}]^+$. HRMS Calcd for $\text{C}_{24}\text{H}_{23}\text{BrINO}_2$ $[\text{M} + \text{H}]^+$ 564.0030, found 486.0027.

Attempted synthesis of (R)-ethyl 2-(benzhydrylamino)-3,3-diphenylpropanoate



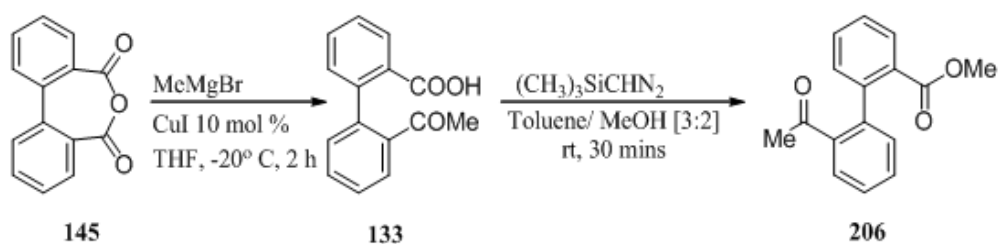
A flame dried 1 mL vial charged with phenyl boronic acid (0.118 mmol, 2 eq), nickel iodide (3.53 μmol , 0.06 eq), t-aminocyclohexanol hydrochloride (3.53 μmol , 0.06 eq), potassium bis(trimethylsilyl)amide (0.118 mmol, 2 eq) dissolved in 0.2 mL dry 2-PrOH was allowed to stir for 5 minutes. To this mixture was added ethyl 2-(benzhydrylamino)-3-bromo-3-phenylpropanoate (0.059 mmol, 1 eq), the reaction was then heated to 60°C and allowed to stir for 6 hours under a nitrogen atmosphere. The reaction was then filtered through a short plug of silica (elution with hexane/ether: 1:1). Solvent removal and analysis by $^1\text{H-NMR}$ showed that only starting material was observed.

Attempted synthesis of (R)-ethyl 2-(benzhydrylamino)-3,3-diphenylpropanoate

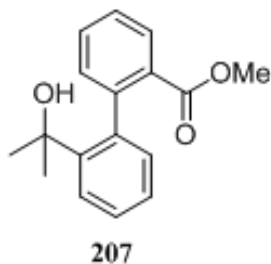


A flame dried 1 mL vial charged with phenyl boronic acid (0.118 mmol, 2 eq), nickel iodide (3.53 μmol , 0.06 eq), t-aminocyclohexanol hydrochloride (3.53 μmol , 0.06 eq), sodium bis(trimethylsilyl)amide (0.118 mmol, 2 eq) dissolved in 0.2 mL dry 2-PrOH was allowed to stir for 5 minutes. To this mixture was added ethyl 2-(benzhydrylamino)-3-bromo-3-phenylpropanoate (0.059 mmol, 1 eq), the reaction was then heated to 60°C and allowed to stir for 6 hours under a nitrogen atmosphere. The reaction was then filtered through a short plug of silica (elution with hexane/ether: 1:1). Solvent removal and analysis by $^1\text{H-NMR}$ showed that only starting material was observed.

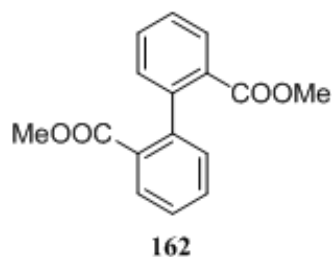
Synthesis of methyl 2'-acetylbiphenyl-2-carboxylate



A 10 mL round bottom flask was charged with CuI (0.095 g, 0.5 mmol, 0.1 eq) and dried under a vacuum using a heat gun. The flask was then purged with nitrogen gas and was added diphenic anhydride (0.112 g, 0.5 mmol, 1 eq). Anhydrous THF (2.5 mL) was added and the mixture stirred at -20°C for 10 minutes before dropwise addition of methyl magnesium bromide in diethyl ether (0.2 mL, 3 M, 0.6 mmol, 1.2 eq). After complete addition ca. 5 mins, the reaction was stirred vigorously under an argon atmosphere for two hours at -20°C . The reaction was then quenched with H_2O (1 mL) and HCl (1 mL, 2.4 M), filtered through celite and extracted with dichloromethane (10 mL). The organic layer was then washed with $\text{Na}_2\text{S}_2\text{O}_3$ (2 x 2.5 mL), NH_4Cl (2 x 5 mL) and dried over MgSO_4 ; solvent removal afforded the impure product as confirmed by NMR analysis. Without further purification, the impure product was dissolved in toluene/ MeOH [3:2] (5 mL), trimethylsilyldiazomethane (0.5 – 1 mmol, 1 – 1.5 eq) was added drop-wise and the reaction was stirred for 30 minutes under an argon atmosphere. The reaction was then quenched with acetic acid (1 mL), solvent evaporation and purification by flash chromatography (elution with petroleum ether / diethyl ether: 6:4) afforded the desired product as a colourless oil (44 mg, 35 % yield over two steps). $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.99 (dd, $J = 7.9, 1.3$ Hz, 1H), 7.73 (dd, $J = 7.2, 1.9$ Hz, 1H), 7.59 – 7.38 (m, 4H), 7.24 – 7.13 (m, 2H), 3.65 (s, 3H), 2.19 (s, 3H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 201.7, 176.4, 142.8, 140.9, 138.7, 131.7, 130.9, 130.8, 130.2, 130.2, 129.6, 128.2, 127.6, 127.4. IR ν_{max} (KBr): 3352, 3072, 3030, 2998, 2956, 2833, 2345, 1988, 1950, 1918, 1877, 1840, 1794, 1717 (ester), 1683 (ketone), 1596, 1569, 1480, 1435 (ketone CH_3), 1354, 1249 (ester), 1178. 114. 1124, 1094, 1077, 1051, 954, 826, 764, 750, 713, 664, 595, 546, 489 cm^{-1} .



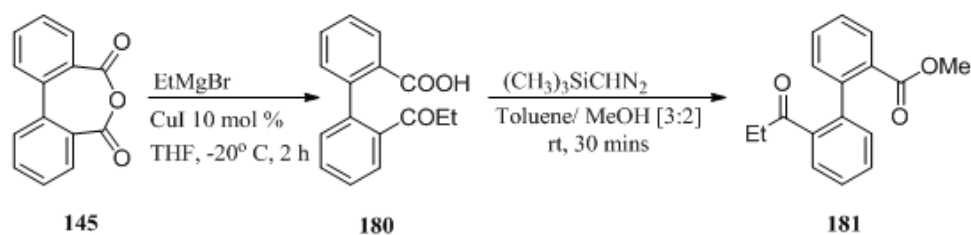
This reaction also produced methyl 2'-(2-hydroxypropan-2-yl)biphenyl-2-carboxylate that was isolated as a colourless oil (16 %). $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.86 (dd, $J = 7.7, 1.0$ Hz, 1H), 7.48 (ddd, $J = 7.4, 6.1, 1.2$ Hz, 2H), 7.42 – 7.14 (m, 4H), 6.89 (dd, $J = 7.6, 1.2$ Hz, 1H), 3.68 (s, 3H), 2.81 (s, 1H), 1.61 (s, 3H), 1.42 (s, 3H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 169.2, 146.2, 145.8, 138.9, 131.0, 130.9, 130.8, 129.6, 129.5, 127.5, 126.8, 126.1, 125.9, 73.9, 52.3, 32.7, 32.3. IR ν_{max} (KBr): 3444, 2974, 1705, 1597, 1433, 1362, 1289, 1252, 1126, 1085, 953, 755, 714 cm^{-1} . MS (ESI) $^+$: m/z 253.07 $[[\text{M-H}_2\text{O}] + \text{H}]^+$



The esterification part of the reaction also produced dimethyl biphenyl-2,2'-dicarboxylate as a colourless oil, but only if there was incomplete conversion of the starting material in the Grignard reaction step. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 8.01 (ddd, $J = 7.7, 1.5, 0.4$ Hz, 2H), 7.54 (td, $J = 7.5, 1.5$ Hz, 2H), 7.43 (td, $J = 7.6, 1.4$ Hz, 2H), 7.24 – 7.18 (m, 2H), 3.62 (s, 6H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 167.5, 143.4, 131.6, 130.3, 130.0, 129.5, 127.3, 51.9. IR ν_{max} (KBr): 2951, 1719, 1572, 1475, 1430, 1248, 1079, 1005, 961, 820, 760, 707 cm^{-1} . MS (ESI) $^+$: m/z 271 $[\text{M} + \text{H}]^+$

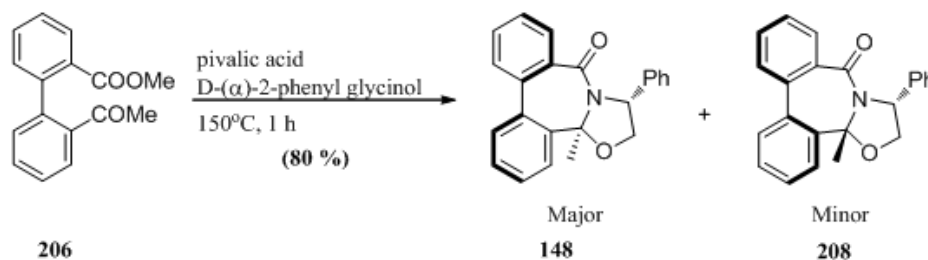
This compound had identical physicochemical values to what had been described before by Leung *et al.* ^[91]

Synthesis of methyl 2'-propionyl-[1,1'-biphenyl]-2-carboxylate



A 10 mL round bottom flask was charged with CuI (0.095 g, 0.5 mmol, 0.1 eq) and dried under a vacuum. The flask was then purged with nitrogen gas and charged with diphenic anhydride (0.112 g, 0.5 mmol, 1 eq). Anhydrous THF (2.5 mL) was added and the mixture stirred at -20°C for 10 minutes before drop-wise addition of ethyl magnesium bromide in THF (0.55 mL, 1 M, 0.55 mmol, 1.1 eq). After complete addition ca. 5 mins, the reaction was stirred vigorously under an argon atmosphere for two hours at -20°C . The reaction was then quenched with H_2O (1 mL) and HCl (1 mL, 2.4 M), filtered through celite and extracted with dichloromethane (10 mL). The organic layer was then washed with $\text{Na}_2\text{S}_2\text{O}_3$ (2 x 1 mL), NH_4Cl (2 x 1 mL) dried over MgSO_4 , filtered and solvent removed to afford the impure product as confirmed by NMR analysis. Without further purification, the impure product was dissolved in toluene/ MeOH [3:2] (5 mL), trimethylsilyldiazomethane (0.5 – 0.75 mmol, 1 – 1.5 eq) was added dropwise until a yellow colour persisted and the reaction was stirred for 30 minutes under an argon atmosphere. The reaction was then quenched with acetic acid (1 mL), evaporation of the solvent and purification by flash chromatography (elution with petroleum ether / diethyl ether: 8:2) afforded the desired product as a colourless oil (66.9 mg, 53 % yield over two steps) in 93 % purity containing an inseparable by-product. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.98 (dd, $J = 7.6, 1.2$ Hz, 1H), 7.70 – 7.63 (m, 1H), 7.57 – 7.38 (m, 4H), 7.18 (ddd, $J = 7.0, 4.8, 1.1$ Hz, 2H), 3.65 (s, 3H), 2.63 – 2.40 (m, 2H), 0.94 (t, $J = 7.3$ Hz, 3H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 205.2, 167.6, 142.7, 140.5, 139.0, 131.7, 130.9, 130.4, 130.3, 130.2, 129.7, 127.8, 127.6, 127.4, 52.0, 34.7, 8.4. IR ν_{max} (KBr): 2949, 1722, 1688, 1595, 1433, 1345, 1252, 1212, 1126, 1087, 1049, 1004, 946, 825, 752, 709 cm^{-1} . HRMS Calcd for $\text{C}_{17}\text{H}_{16}\text{O}_3$ [$\text{M} + \text{H}$] $^+$ 269.1178, found 269.1181.

Synthesis of (4bS,7R)-4b-methyl-7-phenyl-6,7-dihydrodibenzo[c,e]oxazolo[3,2-a]azepin-9(4bH)-one

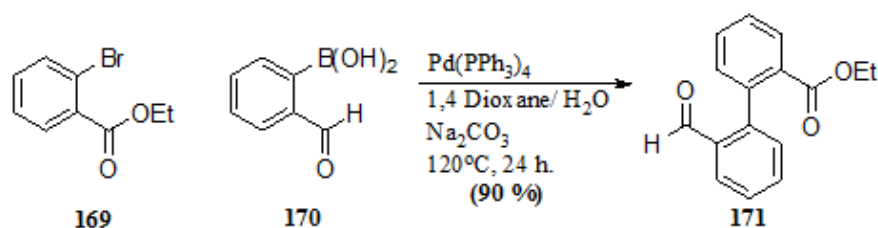


A 10 mL microwave vial, open to air was charged with methyl 2'-acetylbiphenyl-2-carboxylate (0.22 mmol, 1 eq), pivalic acid (0.264 mmol, 1.2 eq) and D-(α)-2-phenylglycinol (0.264 mmol, 1.2 eq). The resulting mixture was then heated to 150°C and stirred for 1 hour with vigorous stirring. Afterwards, the reaction was cooled to room temperature and extracted with dichloromethane (20 mL) and washed with HCl (1 M, 1 mL), saturated NaHCO₃ (10 mL) and dried over MgSO₄. Solvent removal and purification by flash chromatography (elution with EtOAc/ petroleum ether: 1:4) afforded a mixture of the two diastereomers and a fraction containing the pure minor diastereomer as colourless solids. (60 mg, 80 % yield). ¹H-NMR (300 MHz, CDCl₃) δ 7.89 (dd, J = 7.7, 1.1 Hz, 1H), 7.72 – 7.64 (m, 1H), 7.62 – 7.24 (m, 11H), 5.45 (d, J = 6.0 Hz, 1H), 4.41 (dd, J = 8.7, 6.3 Hz, 1H), 4.27 (dd, J = 8.7, 1.0 Hz, 1H), 1.54 (s, 3H). ¹³C-NMR (100 MHz) 165.0, 142.3, 141.3, 137.5, 136.3, 133.8, 131.7, 130.8, 129.3, 129.2, 129.0, 128.7, 128.5, 128.0, 127.3, 122.7, 94.3, 71.4, 62.1, 26.1. IR ν_{\max} (KBr): 2986, 2936, 2877, 1632, 1450, 1395, 1238, 1037, 742, 697 cm⁻¹.

The minor product was isolated in 2 % yield and had ¹H-NMR (300 MHz, CDCl₃) δ 7.97 (d, J = 7Hz, 1H); 7.72 (dd, J = 7 and 2Hz, 1H), 7.57 (dd, J = 7 and 2Hz, 1H), 7.52 (dd, J = 3 and 1Hz, 1H), 4.44 – 7.36 (m, 3H), 7.05 (m, 3H), 6.84 (m, 2H), 5.34 (dd, J = 5, and 6Hz, 1H), 4.50 (dd, J = 6 and 9Hz, 1H), 4.05 (dd, J = 5 and 9Hz, 1H), 1.41 (s, 3H). ¹³C-NMR (100 MHz) δ 163.9, 142.7, 139.7, 138.2, 135.2, 132.7, 131.6, 130.7, 129.8, 128.7, 128.4, 128.2, 128.0, 127.2, 126.4, 122.7, 93.5, 71.7, 62.9, 24.7.

These compounds had identical physicochemical values to what had been described before by Wallace *et al.* [69]

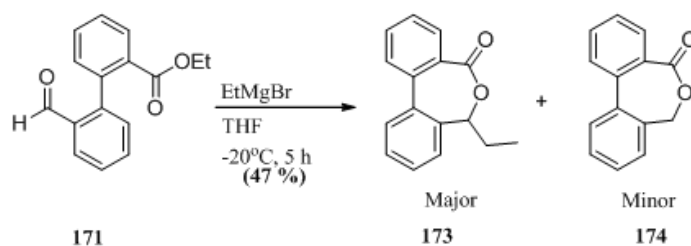
Synthesis of ethyl 2'-formylbiphenyl-2-carboxylate



A 25 mL Schlenk tube was charged with 2-formyl phenyl boronic acid (6 mmol, 1.2 eq) and Pd(PPh₃)₄ (0.044 mmol, 0.01 eq), dissolved in 1,4-dioxane (3 mL, 1.7 M) and stirred vigorously under an argon atmosphere before the addition of Na₂CO₃ (1.056, 10 mmol, 2 eq) and H₂O (2 mL, 5 M), to this heterogeneous mixture was added ethyl 2-bromobenzoate (5 mmol, 1 eq), the vial was sealed with a screw cap and stirred vigorously for 18 hours at 120°C. Afterwards the reaction was diluted with EtOAc (40 mL), H₂O (10 mL) and washed with brine (2 x 30 mL). The aqueous layer was then extracted with EtOAc (3 x 20 mL), the combined organic layer was then dried over MgSO₄ and concentrated *in vacuo* to afford the impure product that was subsequently purified by flash chromatography (elution with EtOAc/petroleum ether: 1:9) to afford the pure product as a free flowing colourless oil (1.146 g, 90 % yield). ¹H-NMR (300 MHz, CDCl₃) δ 9.80 (s, 1H), 8.09 – 7.97 (m, 2H), 7.64 – 7.46 (m, 4H), 7.34 – 7.20 (m, 2H), 4.04 (qd, *J* = 7.1, 1.6 Hz, 2H), 0.96 (t, *J* = 7.1 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ ¹³C-NMR (75 MHz, CDCl₃) δ 191.7, 166.9, 145.5, 139.1, 133.9, 133.2, 131.6, 131.5, 131.0, 130.4, 130.1, 128.2, 127.8, 127.2, 61.0, 13.6. IR ν_{max} (KBr): 1716, 1694, 1288, 1256, 758 cm⁻¹.

This compound had identical physicochemical values to what had been described before by Levacher *et al.* [92]

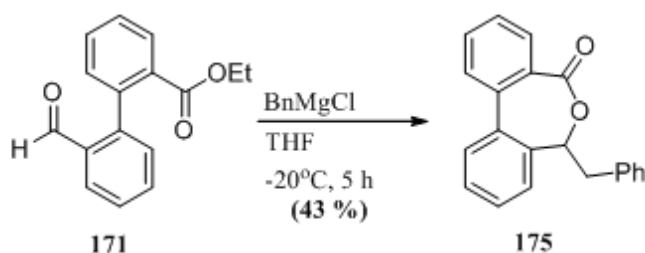
Synthesis of 7-ethyldibenzo[*c,e*]oxepin-5(7H)-one



A microwave vial charged with ethyl 2'-formylbiphenyl-2-carboxylate (0.197 mmol, 1 eq) was purged under an argon atmosphere and dissolved in THF (0.5 mL). The solution was then cooled to -20°C and stirred for 20 minutes before drop-wise addition of EtMgBr in THF (1 M, 0.197 mmol, 1 eq). The reaction was left to stir at -20°C for 2 hours under an argon atmosphere. The reaction was then quenched with the addition of H₂O (0.5 mL) and HCl (0.5 mL, 0.5 M), diluted with EtOAc (5 mL), washed with brine (3 x 2 mL), and the aqueous layer extracted with EtOAc (3 x 5 mL). The organic layer was combined and dried over MgSO₄ filtered and solvent removed to afford the impure product that was subsequently purified by flash column chromatography (elution with petroleum ether/ diethyl ether: 7:3) to afford the product as a colourless oil (22.17 mg, 47 % yield). ¹H-NMR (300 MHz, CDCl₃) δ 7.99 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.73 – 7.40 (m, 7H), 4.94 (dd, *J* = 8.8, 5.1 Hz, 1H), 2.47 – 2.09 (m, 2H), 1.15 (t, *J* = 7.3 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃) δ 170.3, 139.1, 137.5, 137.0, 132.6, 131.4, 131.1, 129.6, 129.2, 128.8, 128.7, 128.5, 124.4, 78.6, 24.0, 10.8. IR ν_{max} (KBr): 2791, 1705, 1598, 1449.2, 1334, 1277, 1125, 1098, 1046, 967, 760, 737, 655 cm⁻¹. MS (ESI)⁺: *m/z* 239.07 [M + H]⁺. HRMS Calcd for C₁₆H₁₄O₂ [M + H]⁺ 239.1072, found 239.1079.

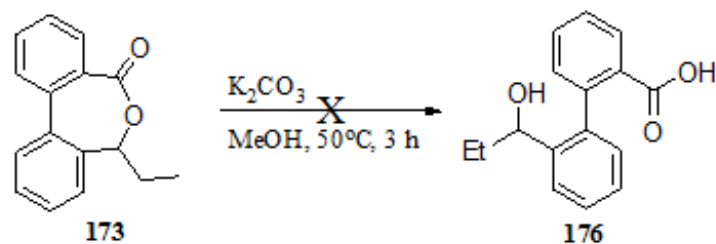
The minor product (dibenzo[*c,e*]oxepin-5(7H)-one) was isolated in 18 % yield and had ¹H-NMR (300 MHz, CDCl₃) δ 7.98 (dt, *J* = 15.2, 7.6 Hz, 1H), 7.74 – 7.33 (m, 7H), 5.03 (d, *J* = 15.9 Hz, 2H). ¹³C-NMR (75 MHz, CDCl₃) δ 170.4, 139.2, 137.4, 135.0, 132.7, 132.1, 130.8, 130.3, 128.9, 128.8, 128.8, 128.7, 128.6, 69.4. IR ν_{max} (KBr): 2925, 1708, 1600, 1458, 1371, 1268, 1108, 1088, 1047, 967, 767, 733, 701, 655, 616 cm⁻¹.

Synthesis of 7-benzylidibenzo[c,e]oxepin-5(7H)-one



A microwave vial charged with ethyl 2'-formylbiphenyl-2-carboxylate (0.787 mmol, 1 eq) was purged under an argon atmosphere and dissolved in THF (2 mL). The solution was then cooled to -20°C and stirred for 20 minutes before drop-wise addition of BnMgCl 20 % wt in THF (1.36 M, 0.787 mmol, 1 eq). After the addition a yellow/ green colour was observed. The reaction was left to stir at -20°C for 5 hours under an argon atmosphere. The reaction was then quenched with the addition of H_2O (2 mL) and HCl (2 mL, 0.5 M), diluted with EtOAc (10 mL), washed with brine (2 x 10 mL), and the aqueous layer extracted with EtOAc (3 x 5 mL). The organic layer was combined and dried over MgSO_4 , filtered and solvent removed to afford the impure product that was subsequently purified by flash column chromatography (elution with petroleum ether/ diethyl ether: 8:2) to afford the desired product as a white solid(100 mg, 43 % yield). $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.85 (dd, $J = 7.8, 1.1$ Hz, 1H), 7.68 – 7.40 (m, 7H), 7.31 – 7.16 (m, 5H), 5.26 (dd, $J = 9.4, 4.3$ Hz, 1H), 3.63 (dd, $J = 14.3, 9.4$ Hz, 1H), 3.44 (dd, $J = 14.3, 4.3$ Hz, 1H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 169.8, 138.9, 137.3, 137.2, 136.9, 132.6, 131.5, 130.8, 129.7, 129.4, 129.3, 128.7, 128.7, 128.5, 126.9, 124.5, 37.1. IR ν_{max} (KBr): 1708, 1600, 1497, 1273, 1241, 1118, 1009, 765, 736, 698 cm^{-1} . MS (ESI) $^+$: m/z 622.87 [$2\text{M} + \text{Na}$] $^+$.

Attempted synthesis of 2'-(1-hydroxypropyl)biphenyl-2-carboxylic acid

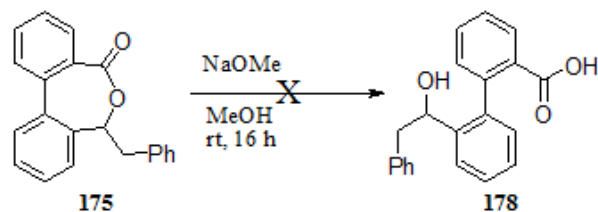


A round bottom flask was charged with 7-ethylbiphenyl-2-carboxylic acid (0.195 mmol, 1 eq), K_2CO_3 (0.293 mmol, 1.5 eq), dissolved in MeOH (1 mL) and heated to $50^\circ C$ for 3 hours. Solvent evaporation and analysis by NMR showed only starting material was present.

Attempted synthesis of 2'-(1-hydroxy-2-phenylethyl)biphenyl-2-carboxylic acid

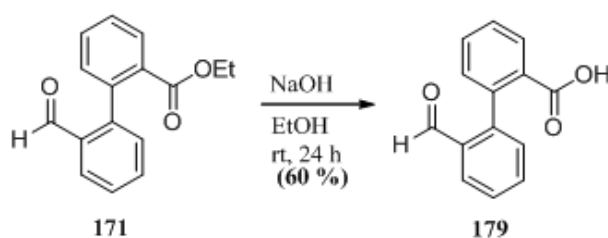


A microwave vial was charged with 7-benzylbiphenyl-2-carboxylic acid (0.101 mmol, 1 eq) and treated with acidified EtOH (0.5 mL) that was prepared by adding a drop of concentrated H_2SO_4 in 10 mL of EtOH. The reaction was stirred vigorously at ambient temperature for 16 hours. The solvent was evaporated, diluted with EtOAc (1 mL), washed with brine (1 mL), $NaHCO_3$ (1 mL) and brine again (1 mL). Dried over $MgSO_4$, filtered and solvent removed. Analysis by NMR indicated only starting material was present.



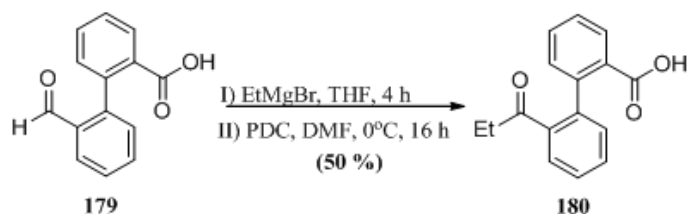
A microwave vial was charged with 7-benzylbiphenyl-2-carboxylic acid (0.066 mmol, 1 eq) was dissolved in MeOH (0.5 mL) and was added NaOMe (0.5 M in MeOH) (0.196 mmol, 3 eq), the reaction was stirred vigorously for 16 hours at ambient temperature. The reaction was diluted with EtOAc (3 mL) and washed with NH_4Cl (1 mL). Dried over $MgSO_4$, filtered and solvent evaporated. Analysis by NMR indicated only starting material was present.

Synthesis of 2'-acetylbiphenyl-2-carboxylic acid



A 100 mL round bottom flask charged with ethyl 2'-formylbiphenyl-2-carboxylate dissolved in ethanol (27 mL) and stirred for 20 minutes at 0°C before addition of 10 M aqueous NaOH (2.8 mL), the reaction was warmed to room temperature and stirred vigorously for 24 hours. Water (10 mL) was added and washed with DCM (20 mL). After treatment with 1 M HCl (pH = 3-4), the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated to afford the impure product that was subsequently purified by flash column chromatography (elution with diethyl ether/petroleum ether: 7:3) to afford the pure product as a white solid (0.624 mg, 60 % yield). M.p = 142 – 144°C. ¹H NMR (300 MHz, CDCl₃) δ 11.22 (broad, 1H), 9.77 (s, 1H), 8.10 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.98 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.66 – 7.44 (m, 4H), 7.25 (dd, *J* = 16.2, 7.0 Hz, 2H). ¹³C-NMR (75 MHz, CDCl₃) δ 191.9, 171.8, 144.9, 140.3, 133.8, 133.3, 132.5, 132.0, 131.3, 130.2, 129.3, 128.3, 128.0, 127.7. IR ν_{max} (KBr): 1719, 1681, 1225, 1197, 774 cm⁻¹.

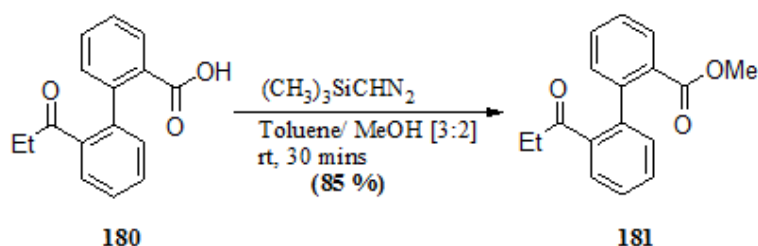
Synthesis of 2'-propionyl-[1, 1'-biphenyl]-2-carboxylic acid



A 25 mL round bottom flask charged with 2'-acetylbiphenyl-2-carboxylic acid (1.189 mmol, 1 eq) was purged under an argon atmosphere and dissolved in THF (1.56 mL), cooled to 0°C and stirred for 20 minutes before drop-wise addition of EtMgBr in THF (1 M, 2.62 mL, 2.62 mmol, 2.2 eq). The reaction was warmed to room temperature and stirred vigorously for 4 hours. Afterwards, the reaction was poured into ice cold HCl (10 mL, 1 M), extracted with diethyl ether (10 mL), washed with brine (3 x 5 mL). The organic layer was dried over MgSO₄, filtered and concentrated to afford 2'-(1-hydroxypropyl)-2-biphenylcarboxylic acid as a yellow oil. This hydroxyl acid underwent lactonisation on standing, even at 0°C; consequently, it was immediately converted to the corresponding ketone by stirring with pyridinium dichromate (1.56 g, 4.16 mmol, 3.5 eq) in DMF (3.2 mL) at 0°C for 16 hours. The reaction was then diluted with H₂O (35 mL), extracted with diethyl ether (4 x 20 mL), ethereal extracts combined and dried over MgSO₄, filtered and concentrated to ca. 10 mL before stirring with saturated aqueous Na₂SO₃ for 1 hour. The ether phase was then extracted with 5% NaOH (4 x 20 mL), cooled to 0°C followed by acidification to pH 2 with HCl (1 M), re-extraction with diethyl ether (4 x 20 mL), washed with brine (10 mL), dried over MgSO₄, filtered and concentrated to afford the keto acid. Purification by flash column chromatography (elution with diethyl ether/ petroleum ether: 8:2) afforded the desired product as a pale yellow oil that solidified on standing (151 mg, 50 % yield). ¹H-NMR (300 MHz, CDCl₃) δ 11.0 (broad, 1H), 8.04 – 7.87 (m, 1H), 7.74 – 7.61 (m, 1H), 7.56 – 7.39 (m, 4H), 7.21 – 7.09 (m, 2H), 2.65 (q, *J* = 7.2 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃) δ 205.9, 171.5, 142.5, 140.2, 138.2, 132.0, 130.7, 130.5, 130.4, 129.2, 127.5, 127.5, 34.5, 8.2. IR ν_{max} (KBr): 3489, 3080 – 2880, 1740, 1695, 1597, 1574 cm⁻¹.

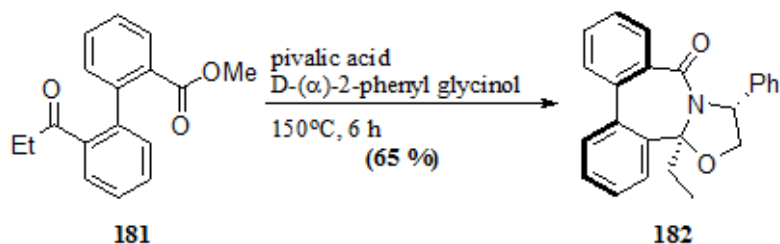
This compound had identical physicochemical values to what had been described before by Crich *et al.* [55]

Synthesis of methyl 2'-propionyl-[1,1'-biphenyl]-2-carboxylate



A round bottom flask was charged with 2'-propionyl-[1, 1'-biphenyl]-2-carboxylic acid (0.594 mmol, 1 eq) dissolved in toluene/ MeOH [3:2] (5 mL) and stirred for 10 minutes under an argon atmosphere before drop-wise addition of trimethylsilyldiazomethane (0.5 – 0.75 mmol, 1 – 1.5 eq) a yellow colour persisted, the reaction was stirred for 30 minutes under an argon atmosphere. The reaction was then quenched with acetic acid (1 mL), evaporation of the solvent removal and purification by flash chromatography (elution with petroleum ether / diethyl ether: 8:2) afforded the desired product as a colourless/ yellow oil (135 mg, 85 % yield). ¹H-NMR (300 MHz, CDCl₃) δ 7.98 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.70 – 7.63 (m, 1H), 7.57 – 7.38 (m, 4H), 7.18 (ddd, *J* = 7.0, 4.8, 1.1 Hz, 2H), 3.65 (s, 3H), 2.63 – 2.40 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃) δ 205.2, 167.6, 142.7, 140.5, 139.0, 131.7, 130.9, 130.4, 130.3, 130.2, 129.7, 127.8, 127.6, 127.4, 52.0, 34.7, 8.4. IR ν_{\max} (KBr): 2949, 1722, 1688, 1595, 1433, 1345, 1252, 1212, 1126, 1087, 1049, 1004, 946, 825, 752, 709 cm⁻¹. HRMS Calcd for C₁₇H₁₆O₃ [M + H]⁺ 269.1178, found 269.1181.

Synthesis of (4bS,7R)-4b-ethyl-7-phenyl-6,7-dihydrodibenzo[c,e]oxazolo[3,2-a]azepin-9(4bH)-one



A 10 mL microwave vial, open to air was charged with methyl 2'-propionylbiphenyl-2-carboxylate (1 eq), pivalic acid (1.2 eq) and D-(α)-2-phenyl glycinol (1.2 eq). The resulting mixture was then heated to 150°C and stirred for 6 hours with vigorous stirring. Afterwards, the reaction was cooled to room temperature and extracted with dichloromethane (20 mL) and washed with HCl (1 M, 1 mL), saturated NaHCO₃ (10 mL) and dried over MgSO₄. Solvent removal and purification by flash chromatography (elution with petroleum ether/diethyl ether: 6:4) afforded a white solid (38.6 mg, 65 % yield). ¹H-NMR (300 MHz, CDCl₃) δ 7.87 (dd, J = 7.7, 1.0 Hz, 1H), 7.72 – 7.26 (m, 12H), 5.48 (d, J = 5.7 Hz, 1H), 4.40 (dd, J = 8.7, 6.3 Hz, 1H), 4.31 (dd, J = 8.7, 1.3 Hz, 1H), 1.86 – 1.71 (m, 2H), 0.64 (t, J = 7.4 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃) δ 165.9, 140.8, 140.1, 137.1, 136.0, 133.6, 130.8, 130.3, 129.1, 128.8, 128.8, 128.6, 128.3, 128.1, 128.0, 127.6, 127.3, 124.1, 96.6, 70.8, 61.6, 30.6, 30.6, 9.1. IR ν_{\max} (KBr): 3018, 1620, 1569, 1493, 1444, 1393, 1285, 1170, 1119, 925, 869, 784, 696 cm⁻¹. HRMS Calcd for C₂₄H₂₁NO₂ MS (ESI)⁺: 356.1651, found 356.1649.

8.0 References

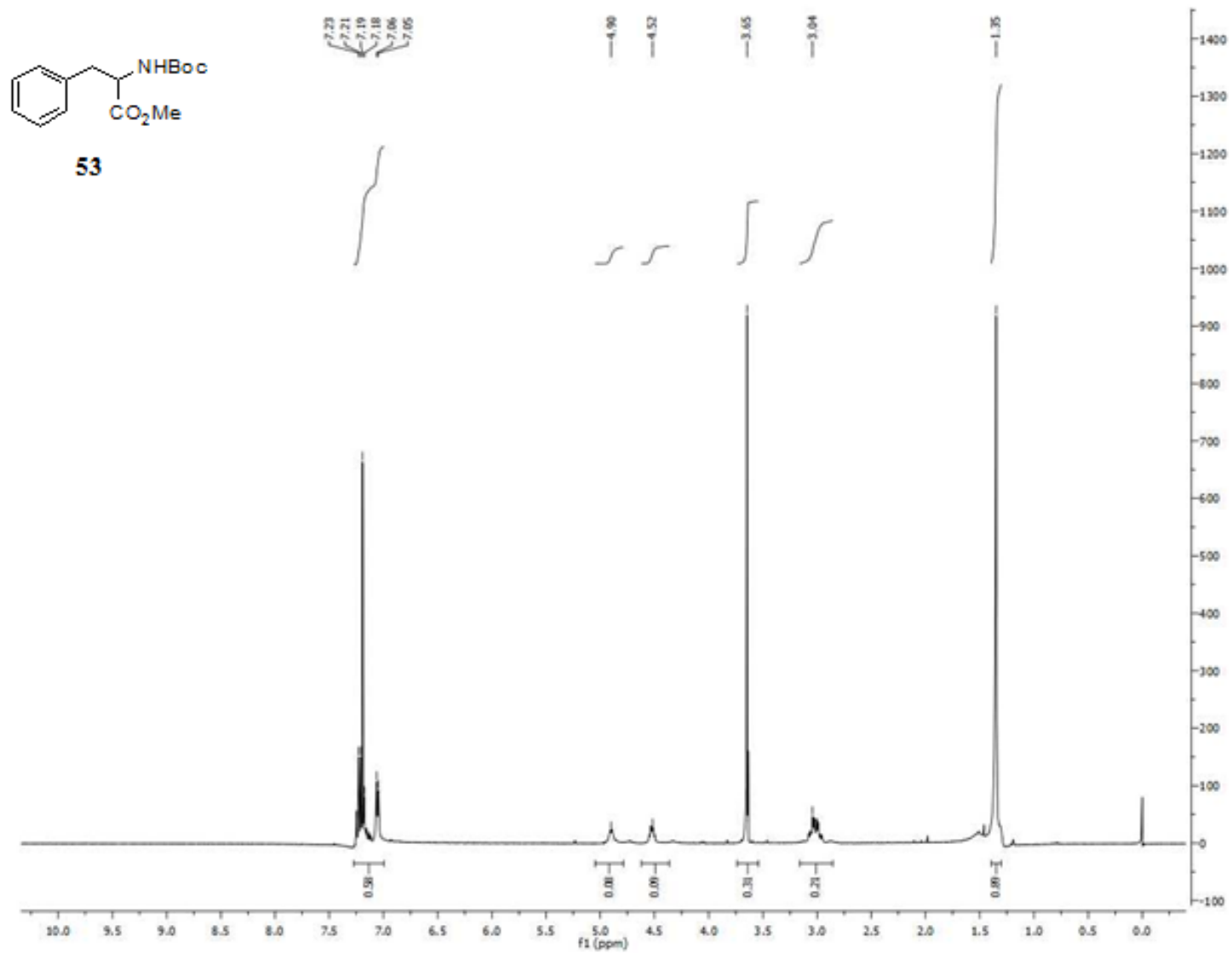
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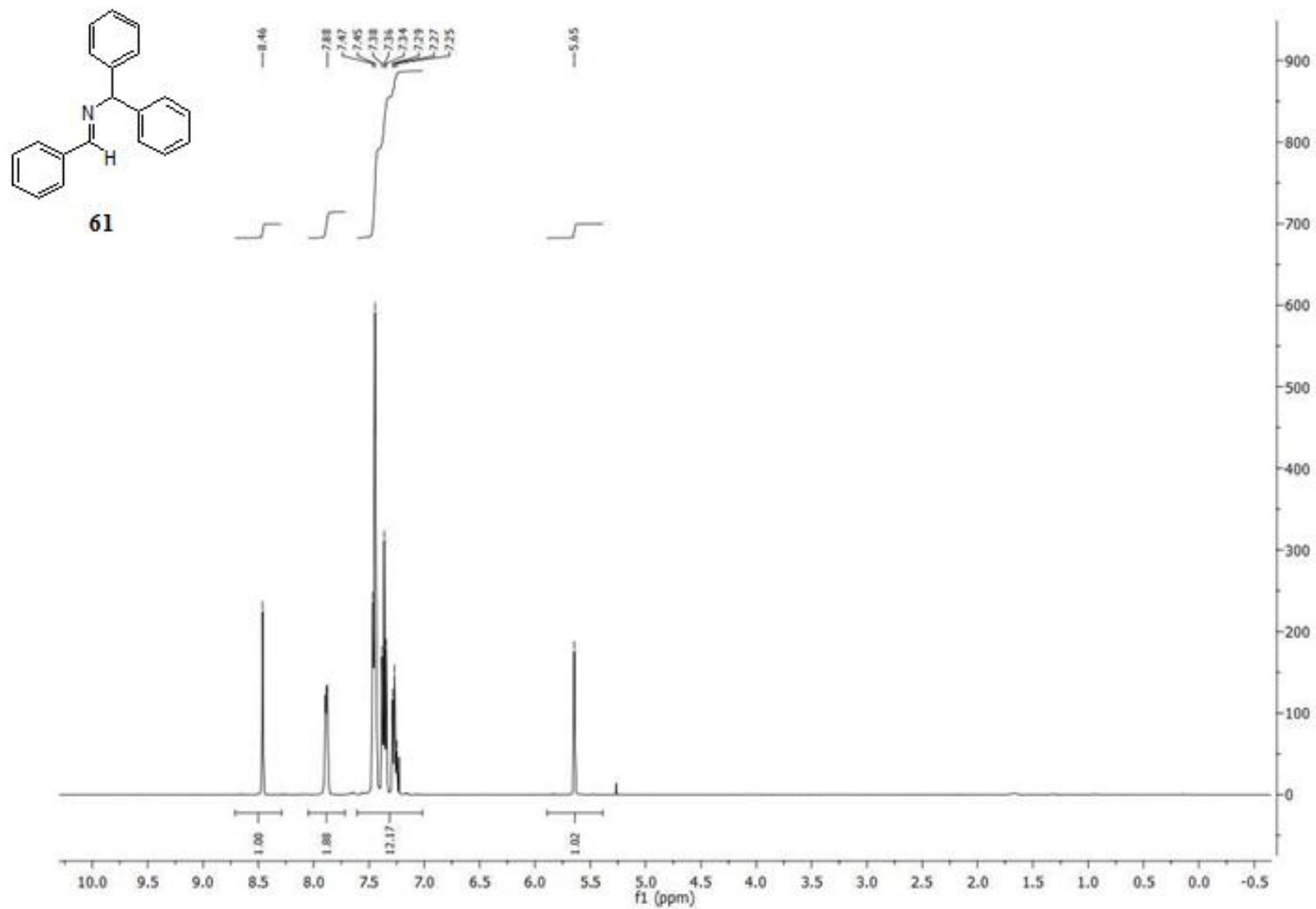
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APPENDIX

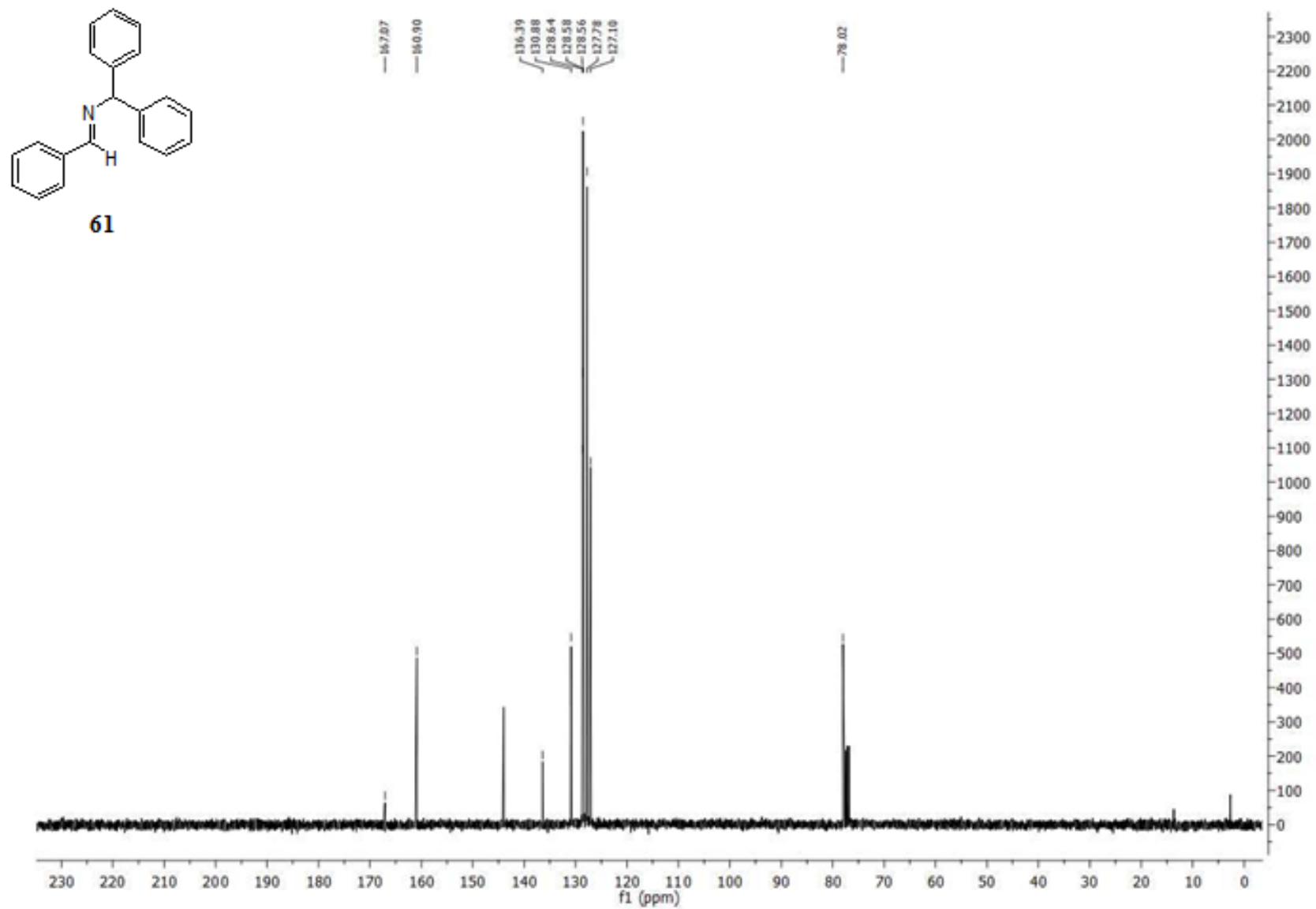
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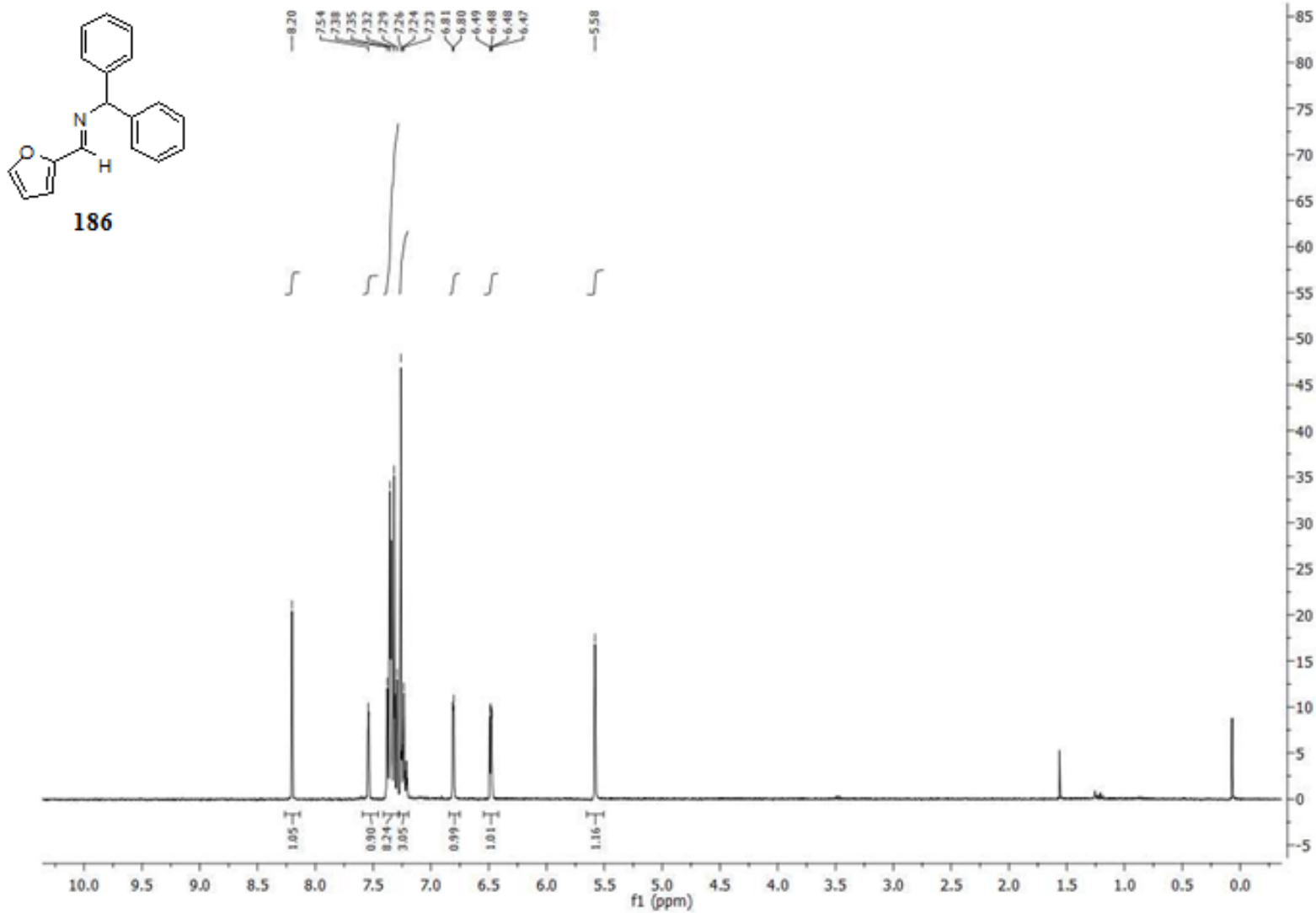
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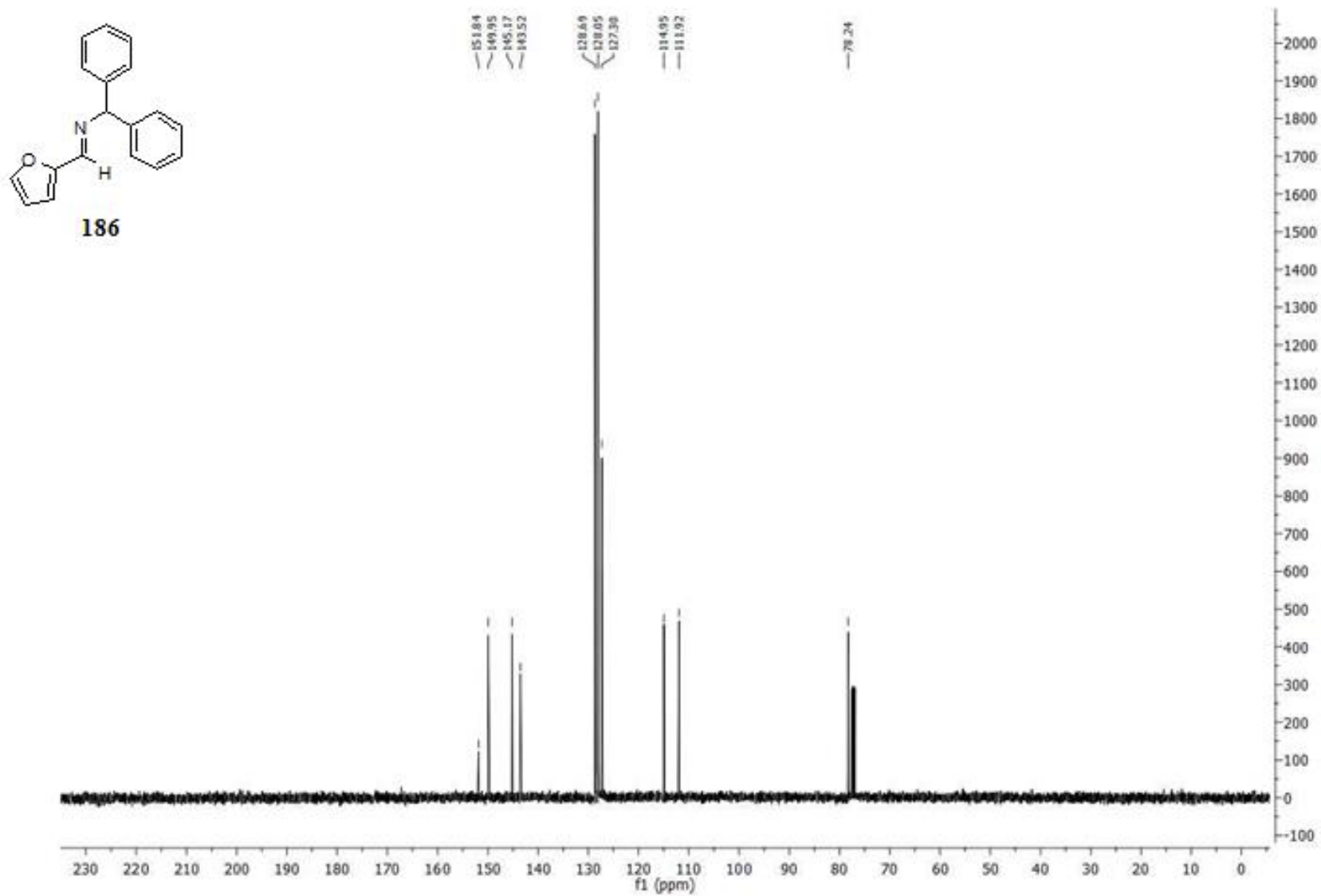
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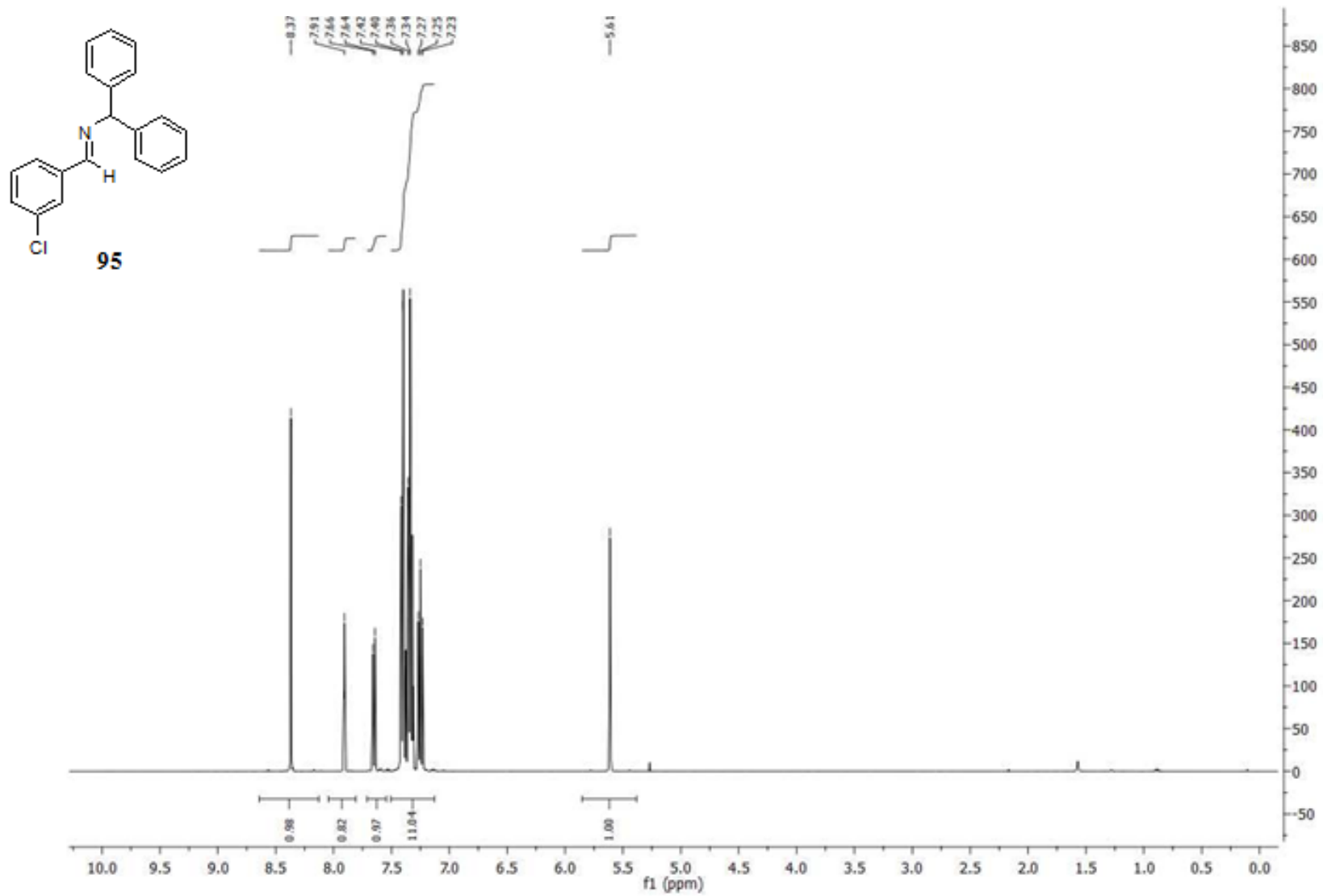
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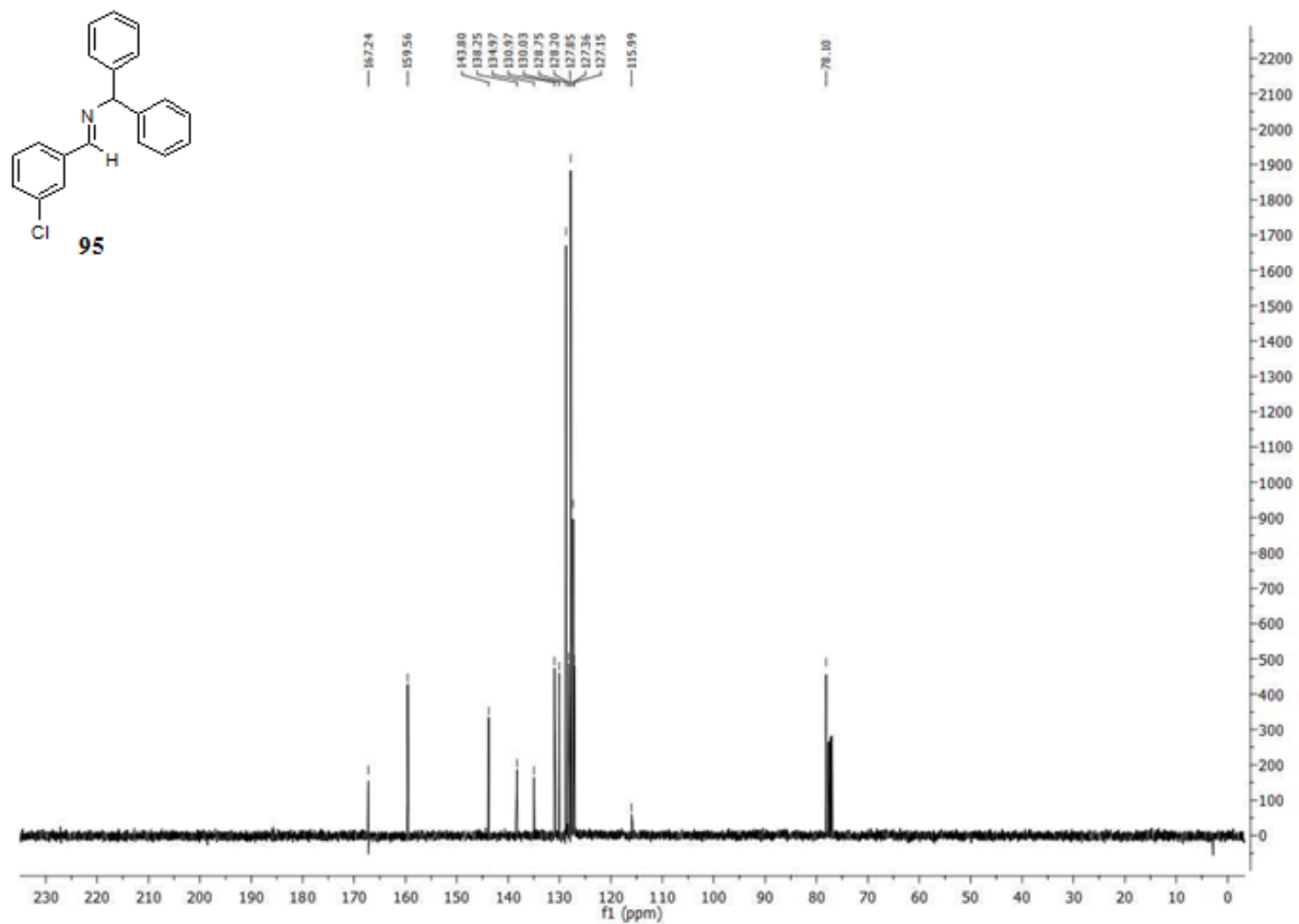
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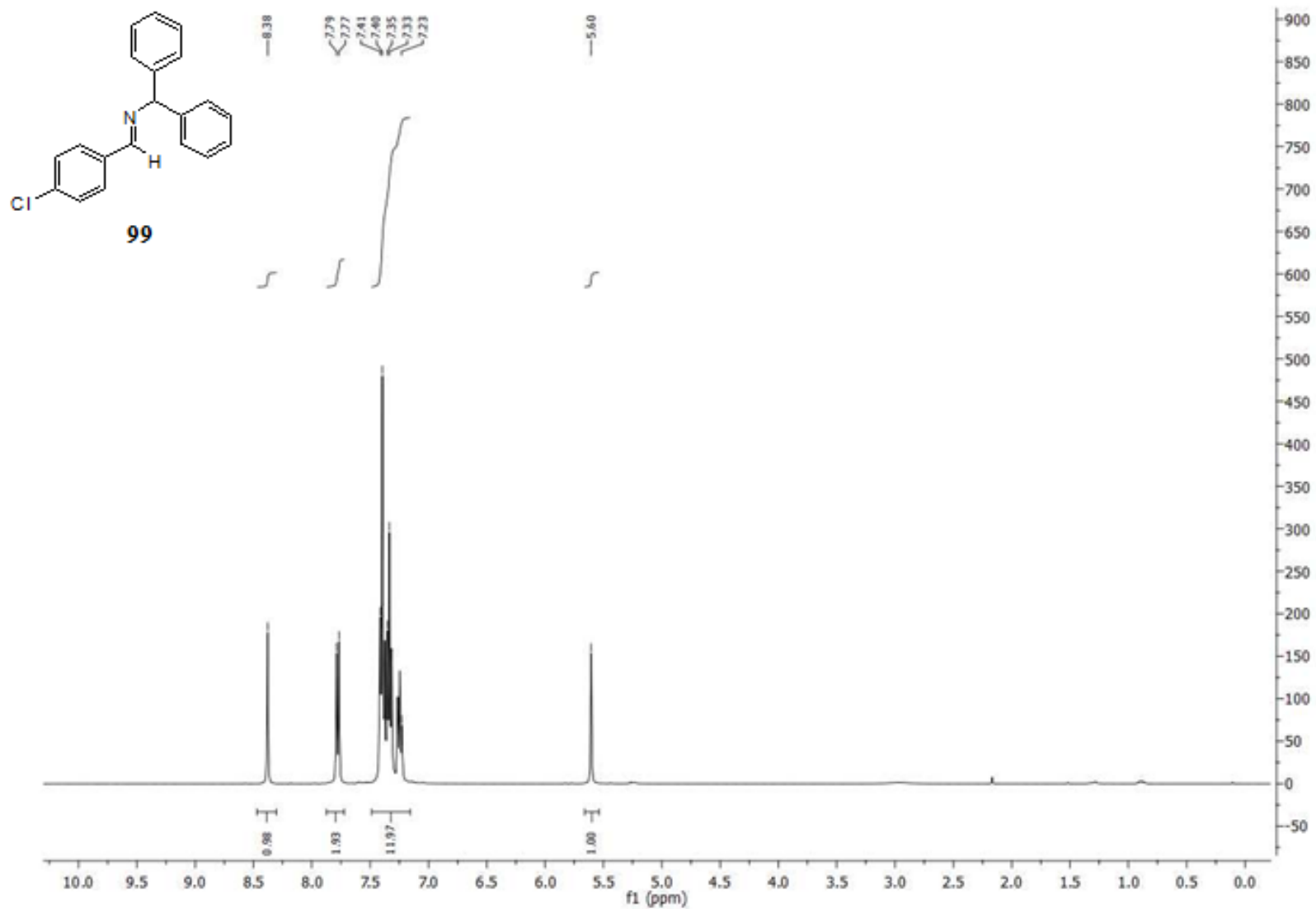
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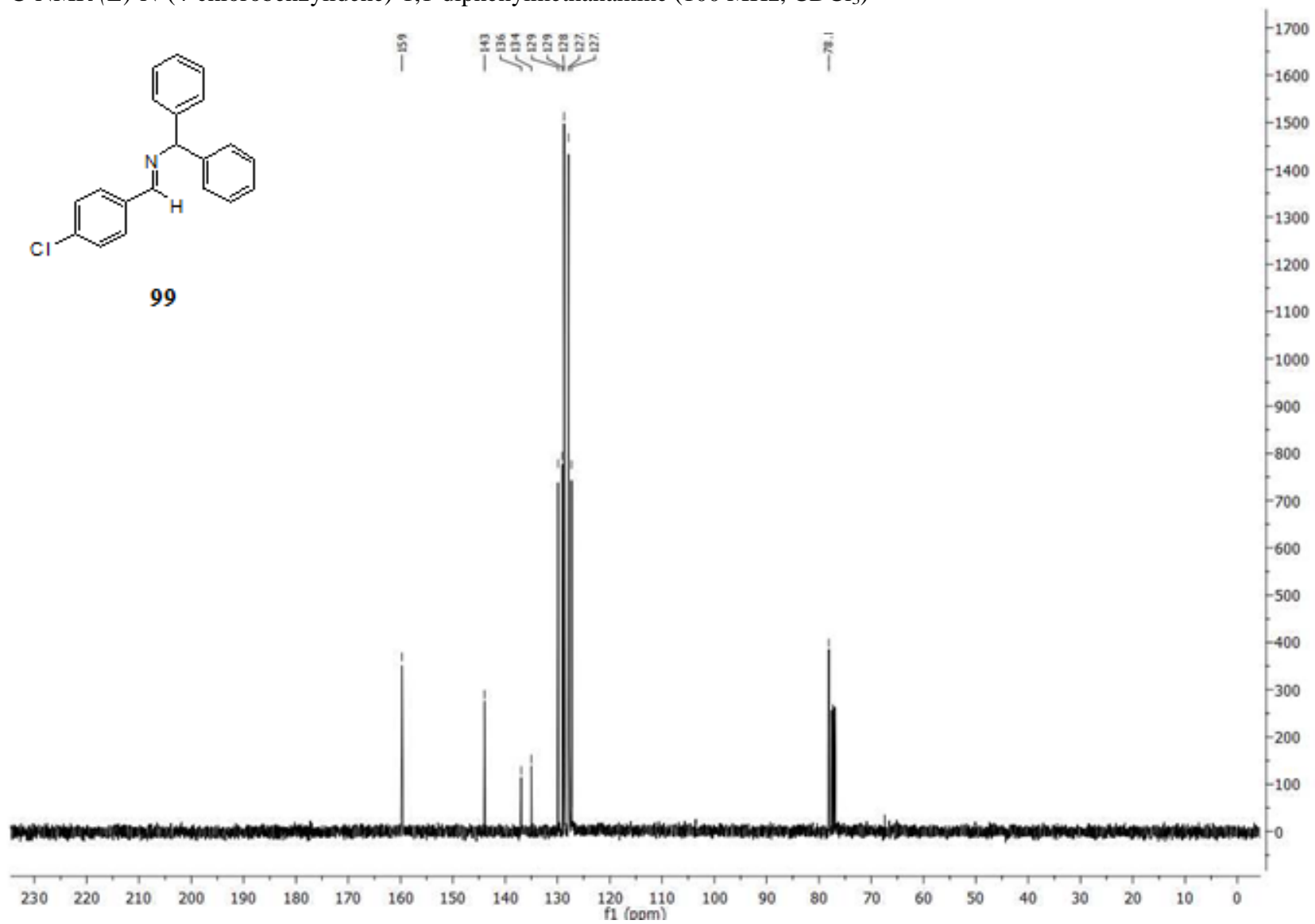
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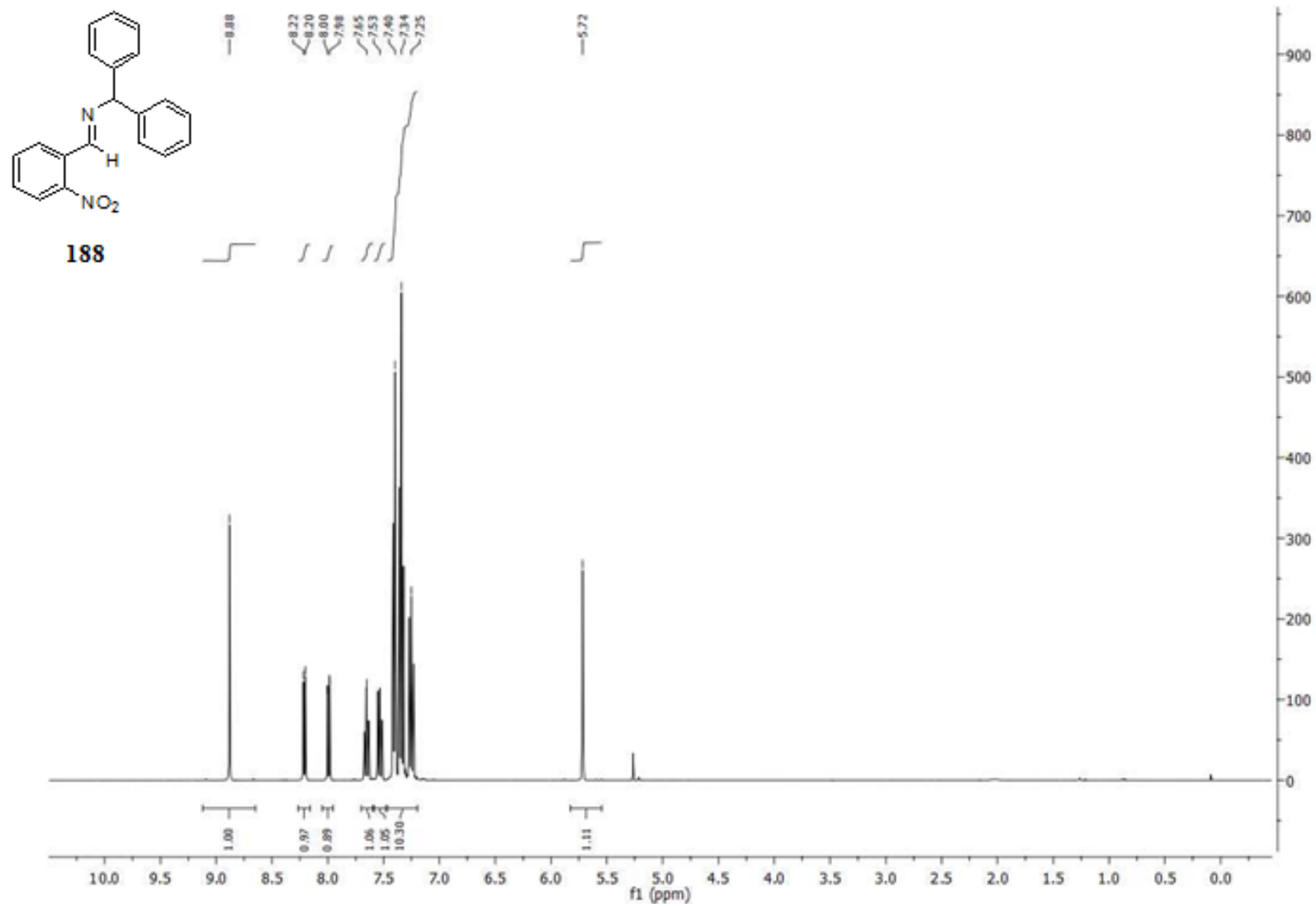
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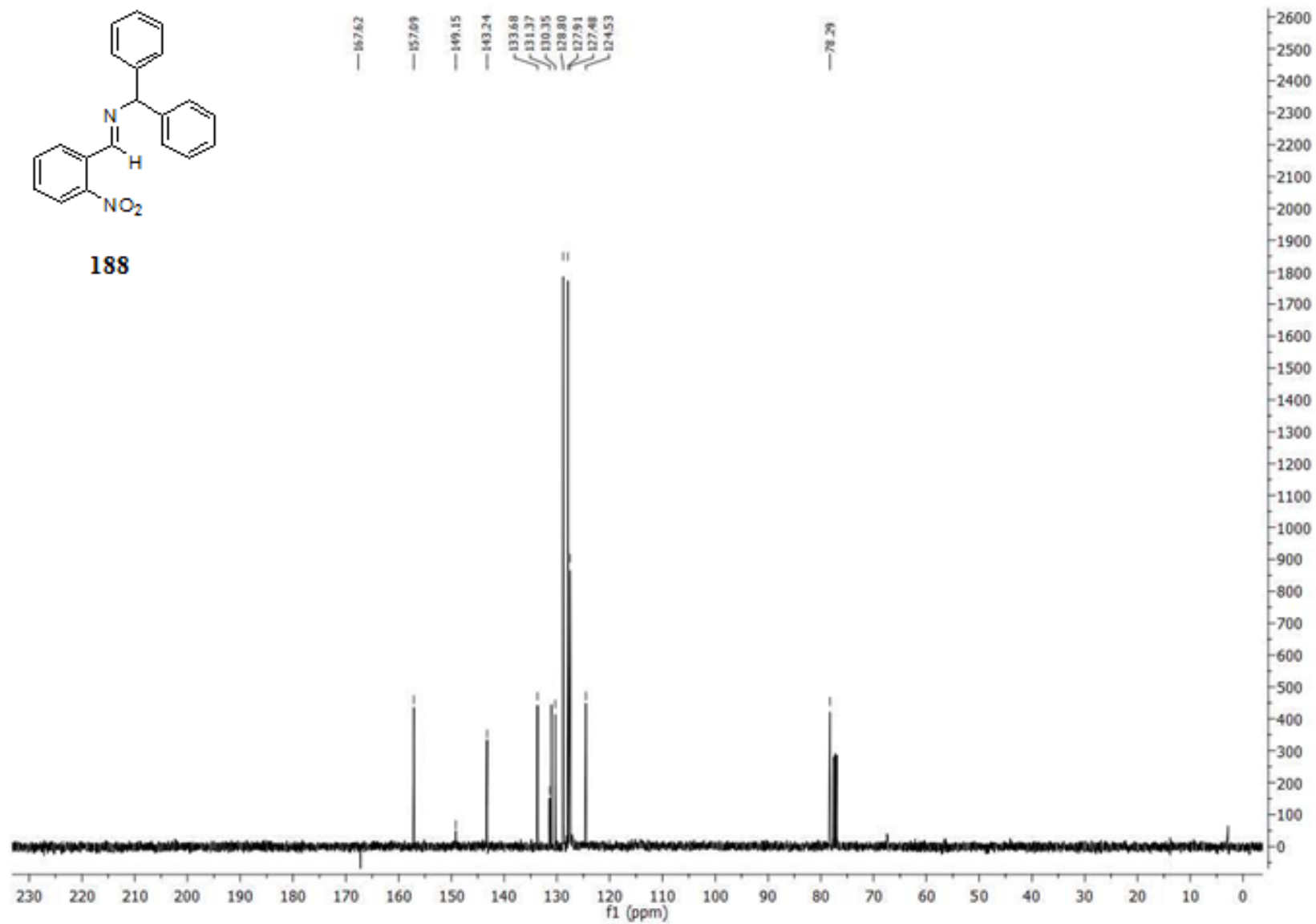
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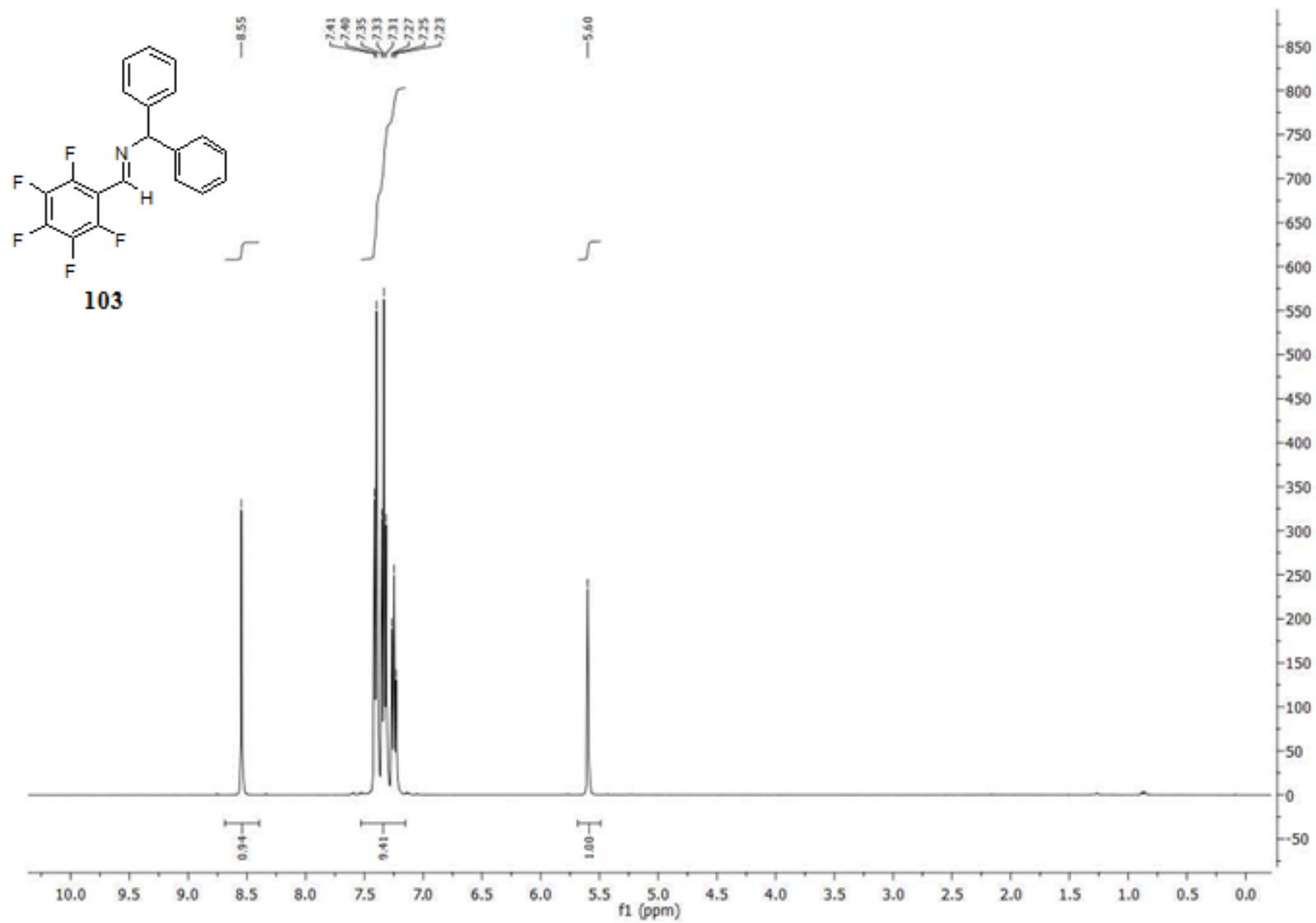
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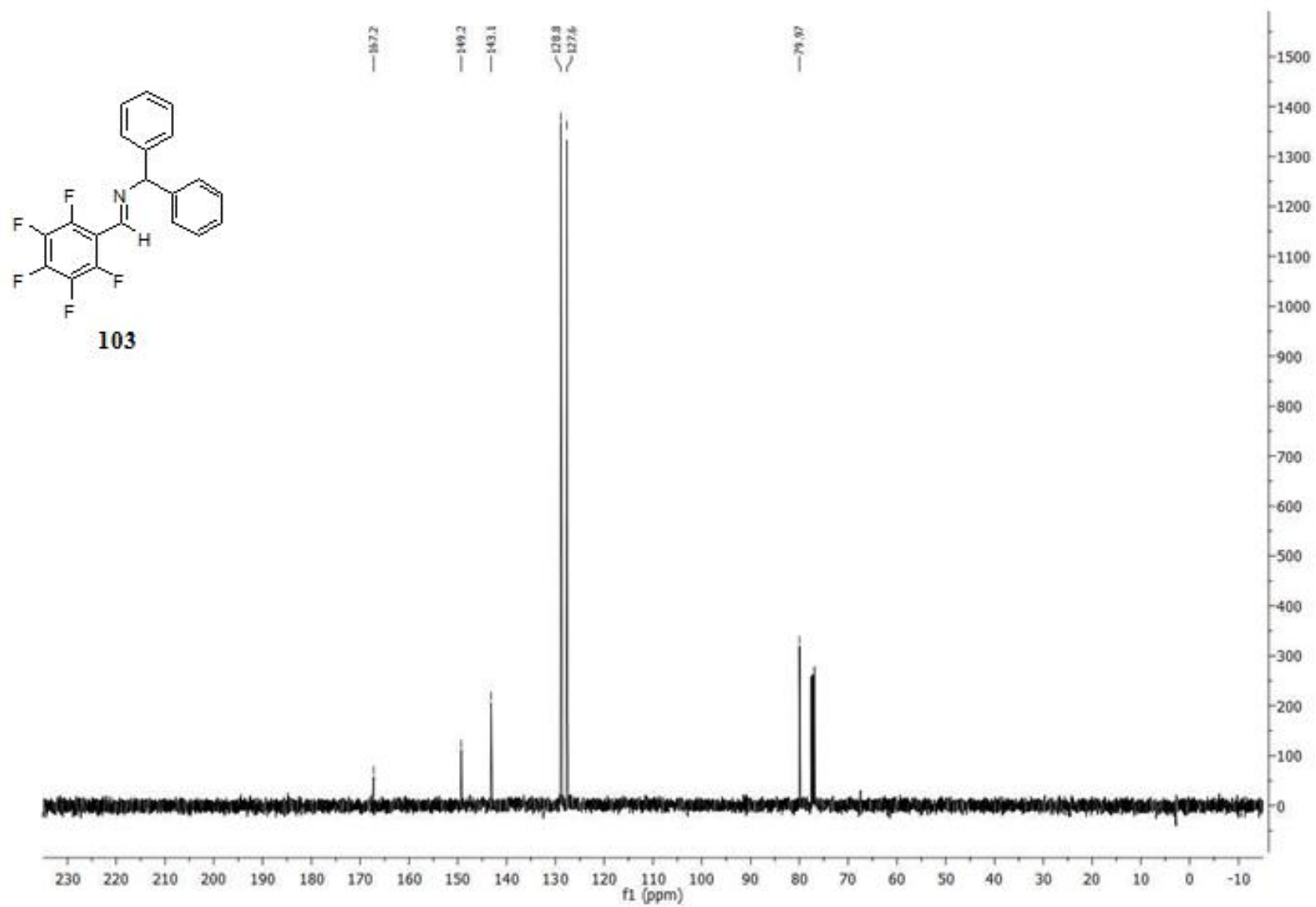
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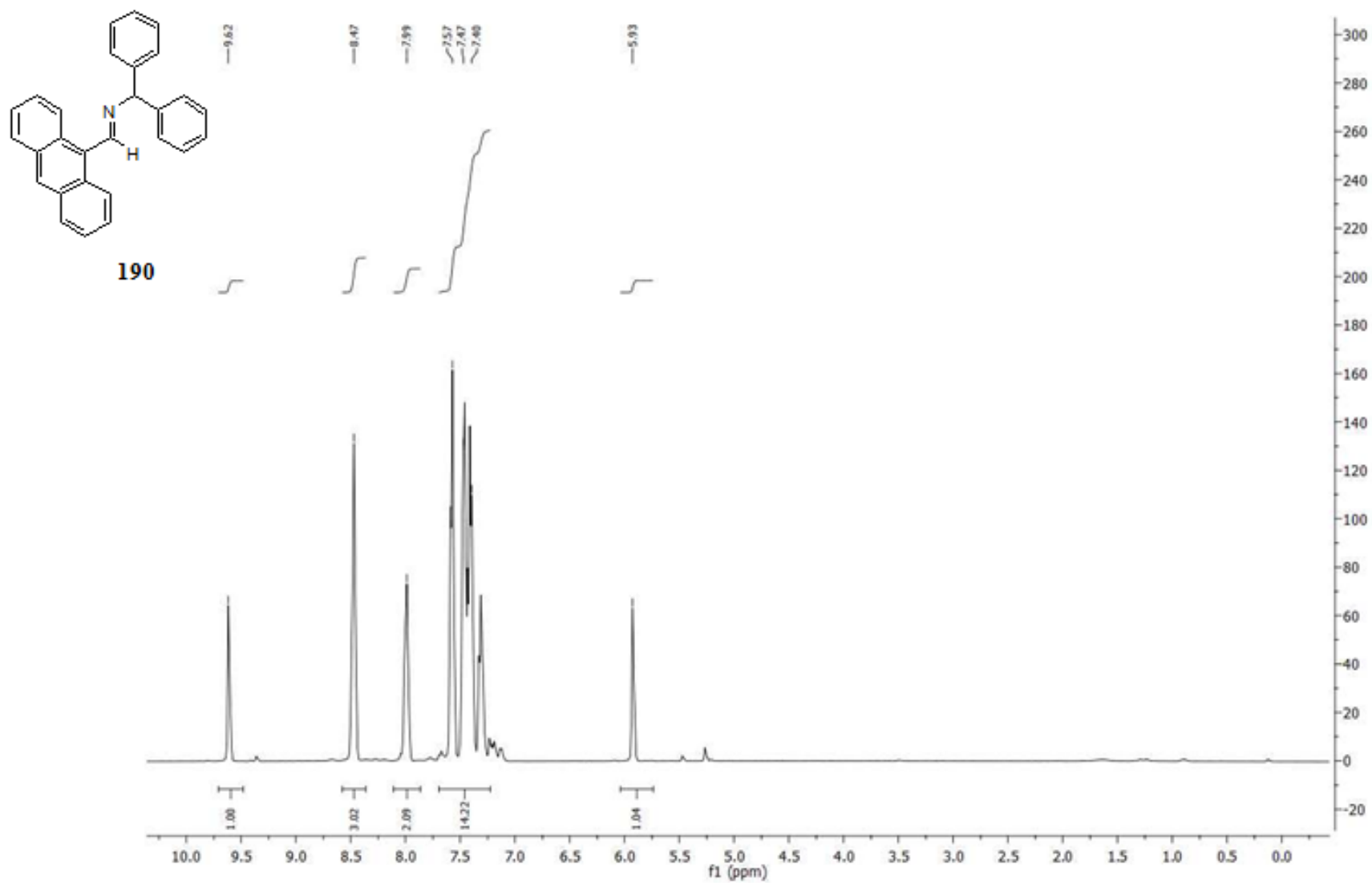
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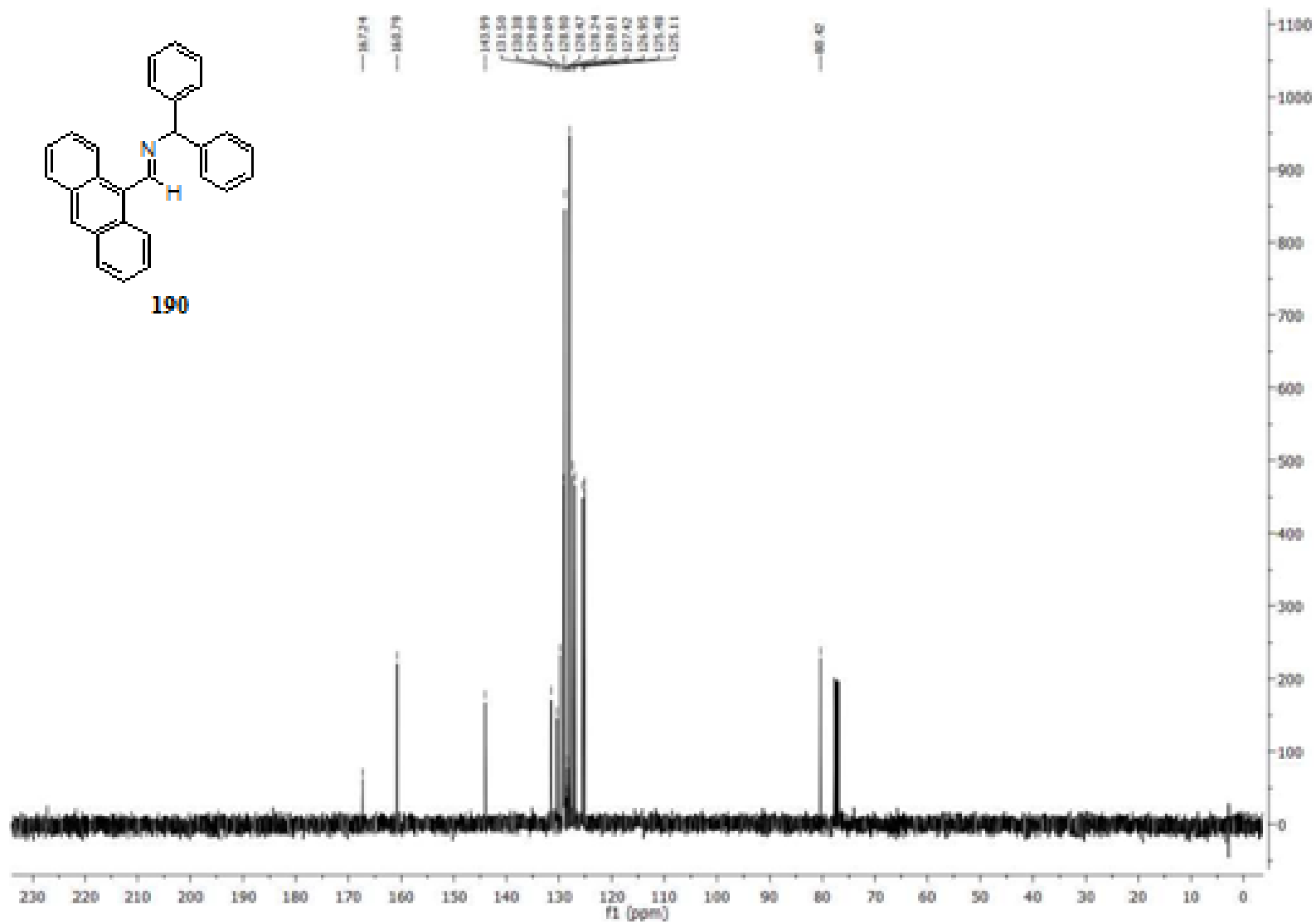
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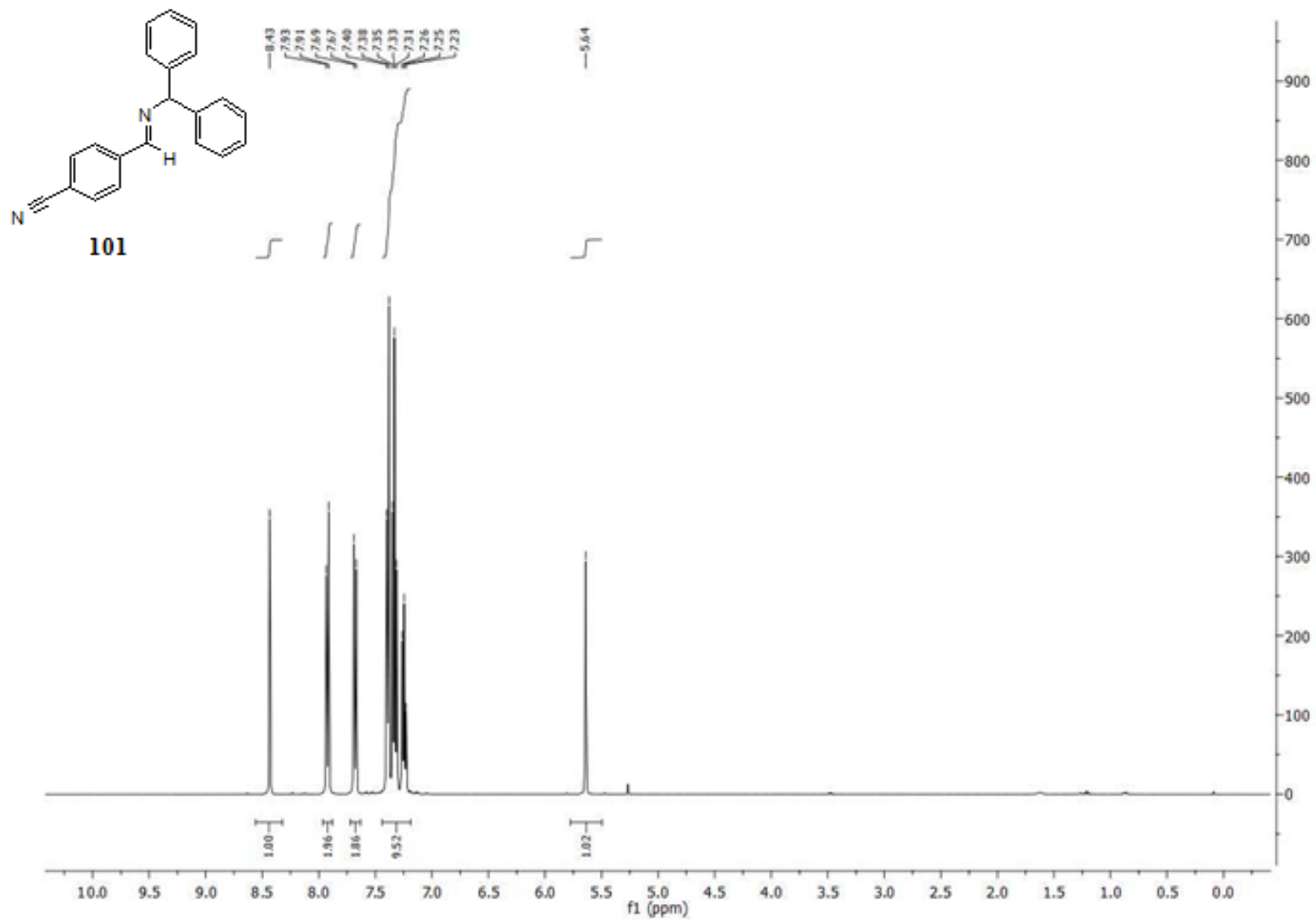
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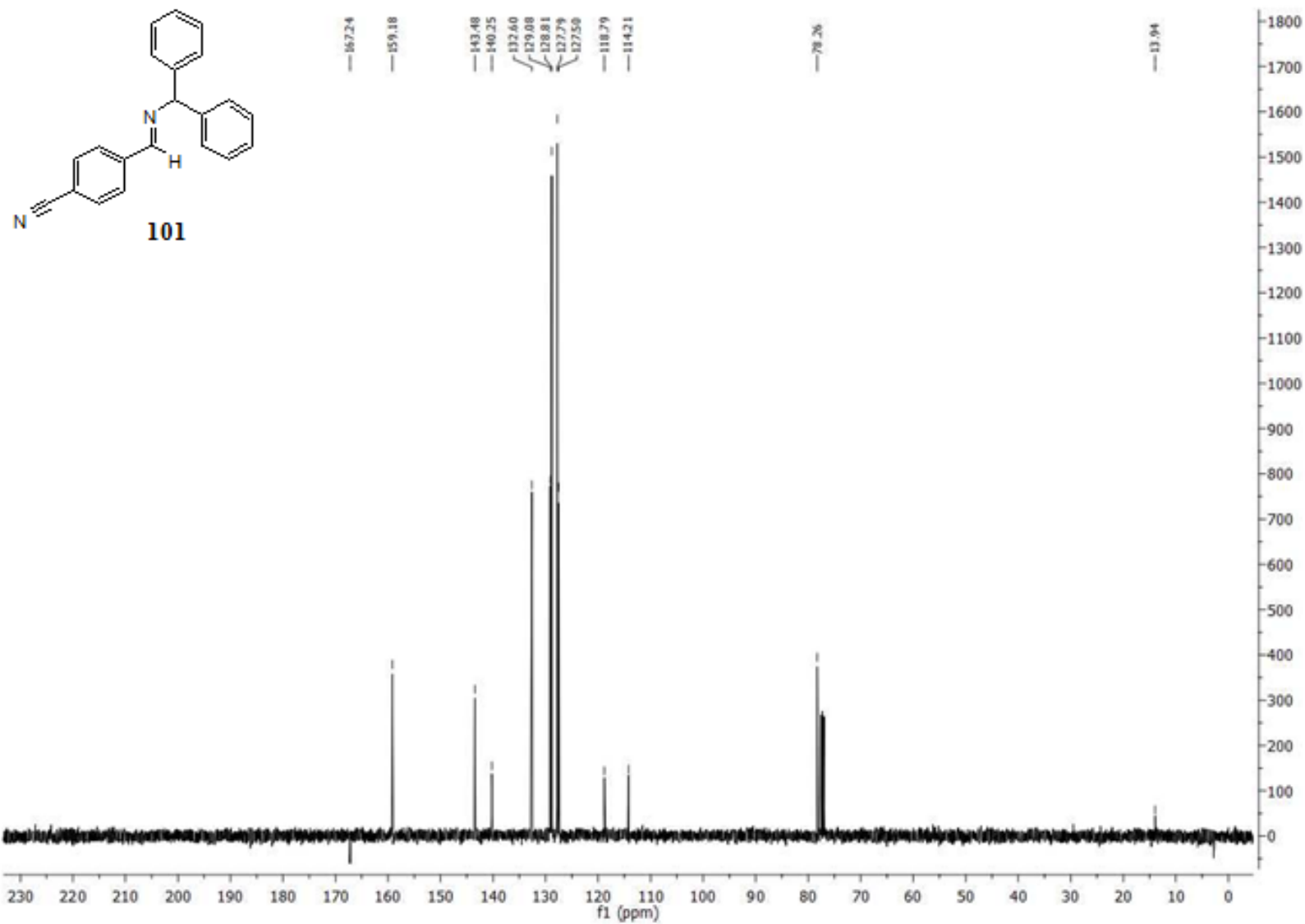
^{13}C -NMR (*E*)-*N*-(anthracen-9-ylmethylene)-1,1-diphenylmethanamine (100 MHz, CDCl_3)



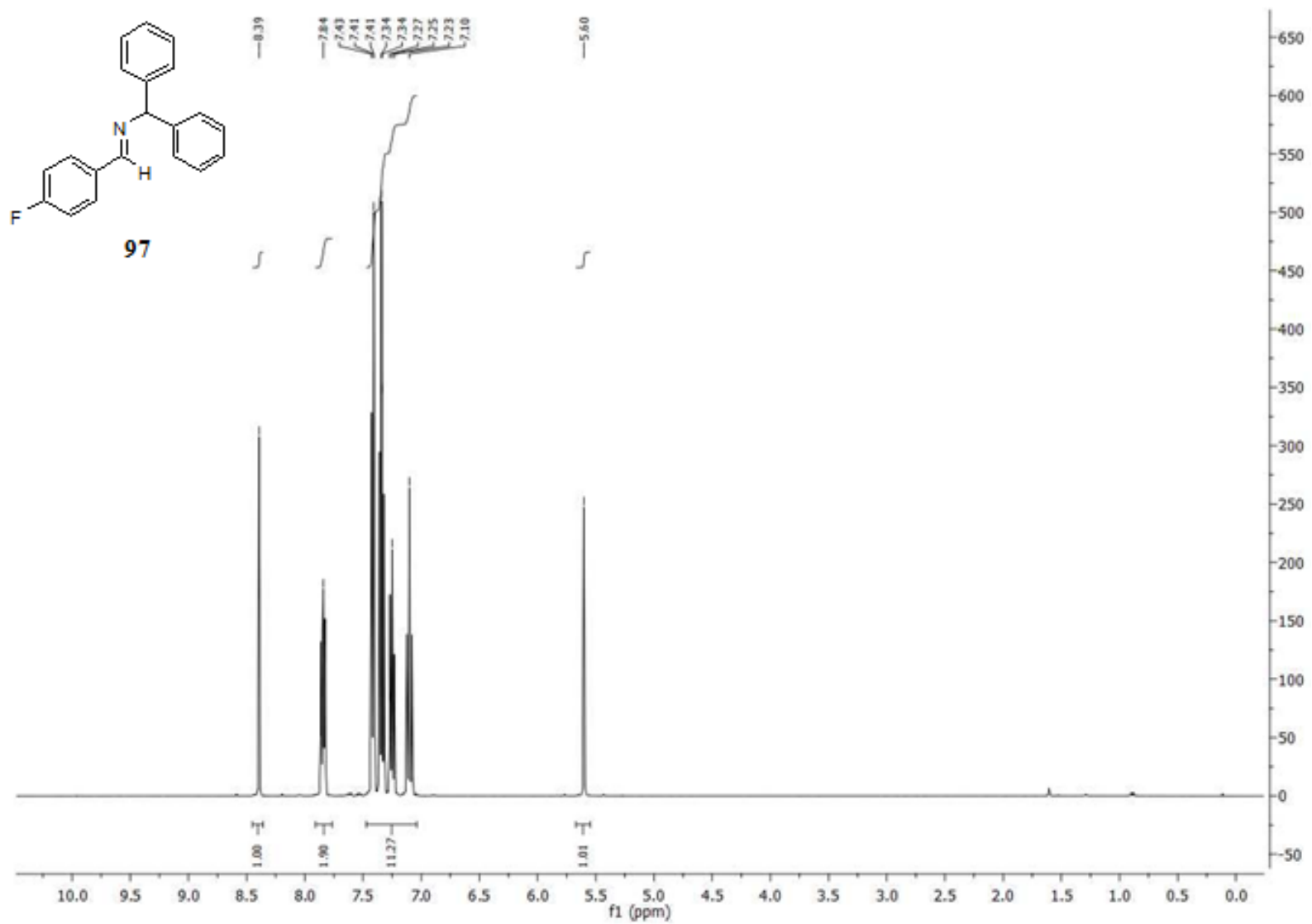
¹H-NMR (*E*)-4-((benzhydrylimino)methyl)benzonitrile (400 MHz, CDCl₃)



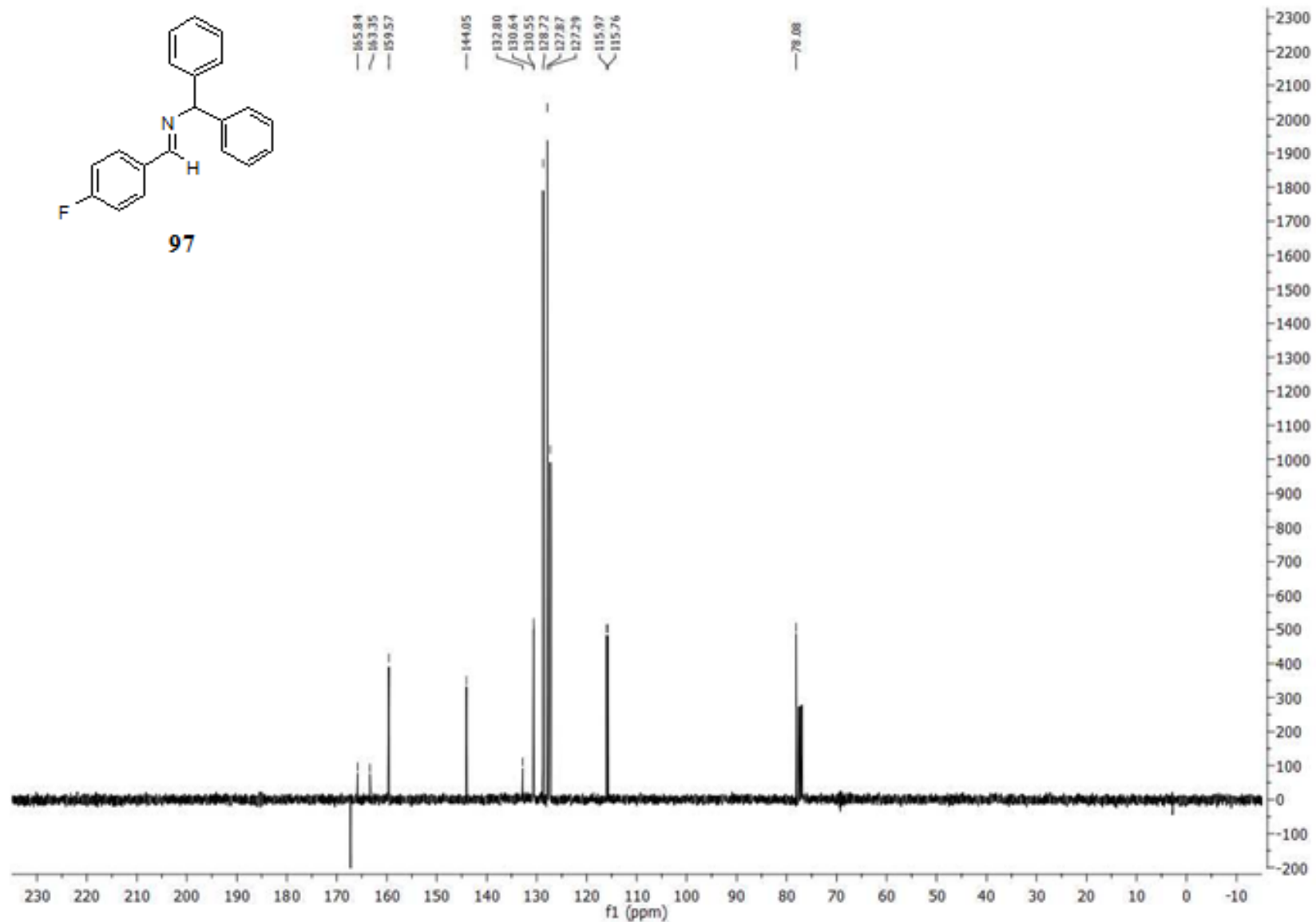
^{13}C -NMR (*E*)-4-((benzhydrylimino)methyl)benzonitrile (100 MHz, CDCl_3)



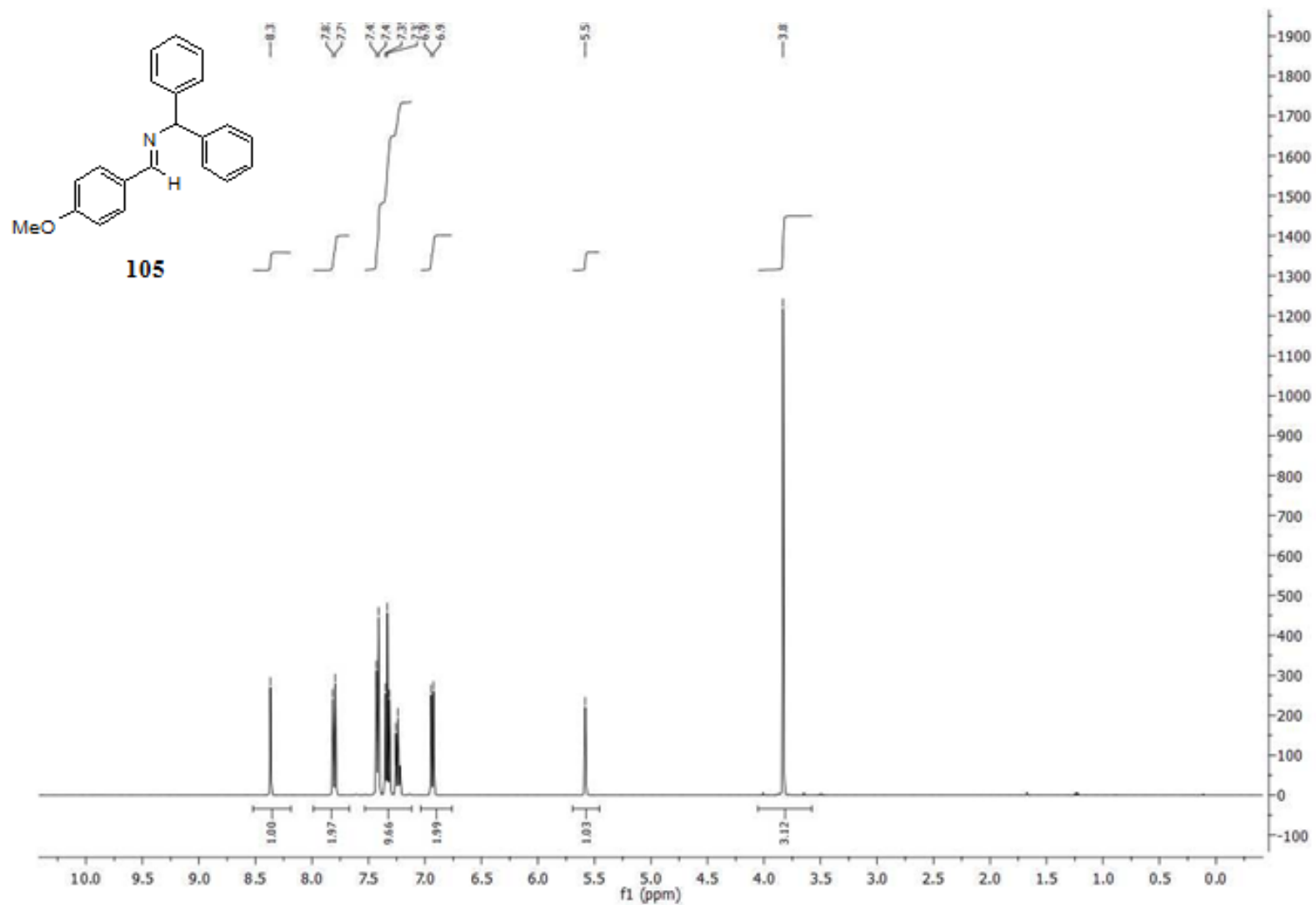
$^1\text{H-NMR}$ (*E*)-*N*-(4-fluorobenzylidene)-1,1-diphenylmethanamine (400 MHz, CDCl_3)



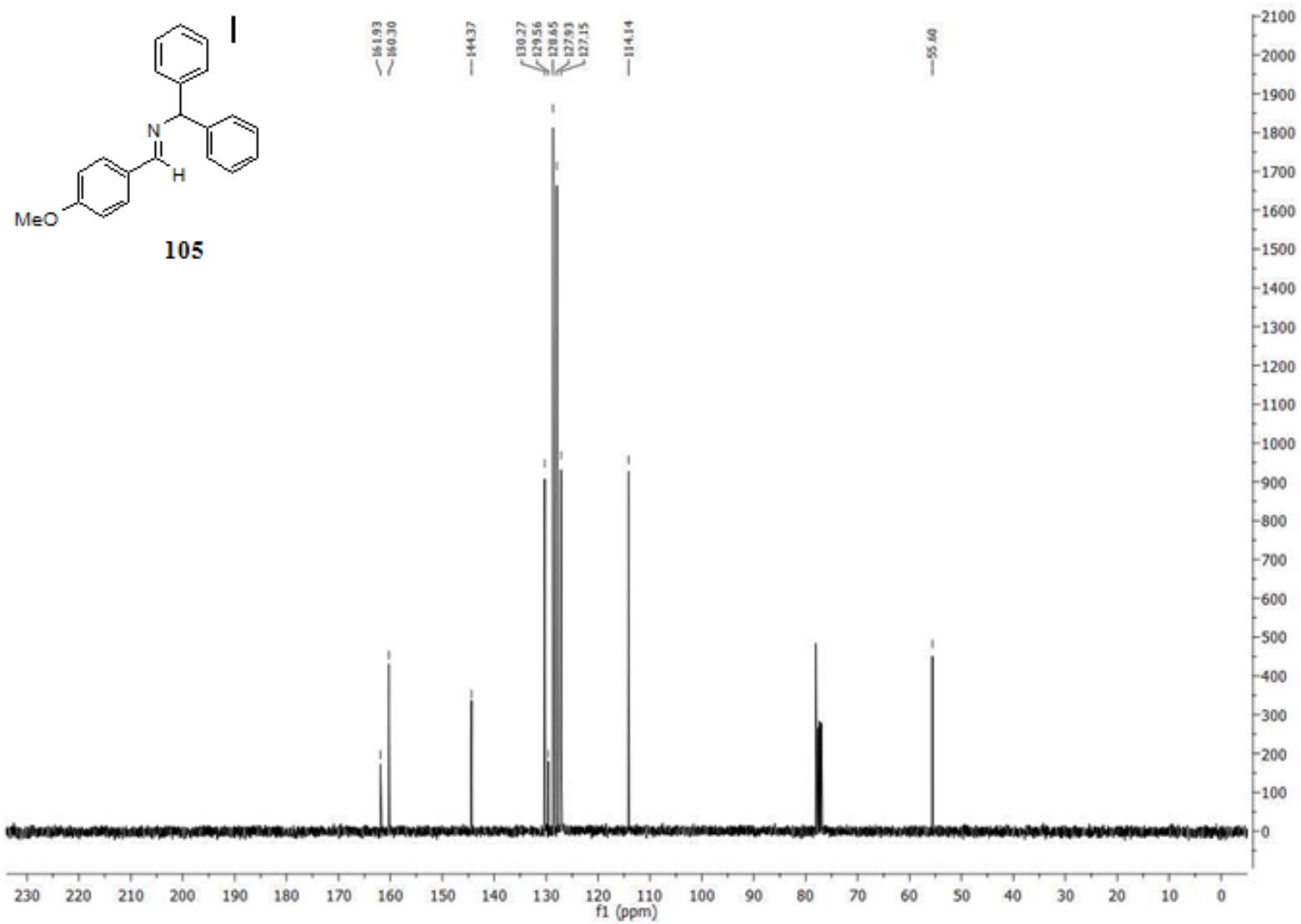
^{13}C -NMR (*E*)-N-(4-fluorobenzylidene)-1,1-diphenylmethanamine (100 MHz, CDCl_3)



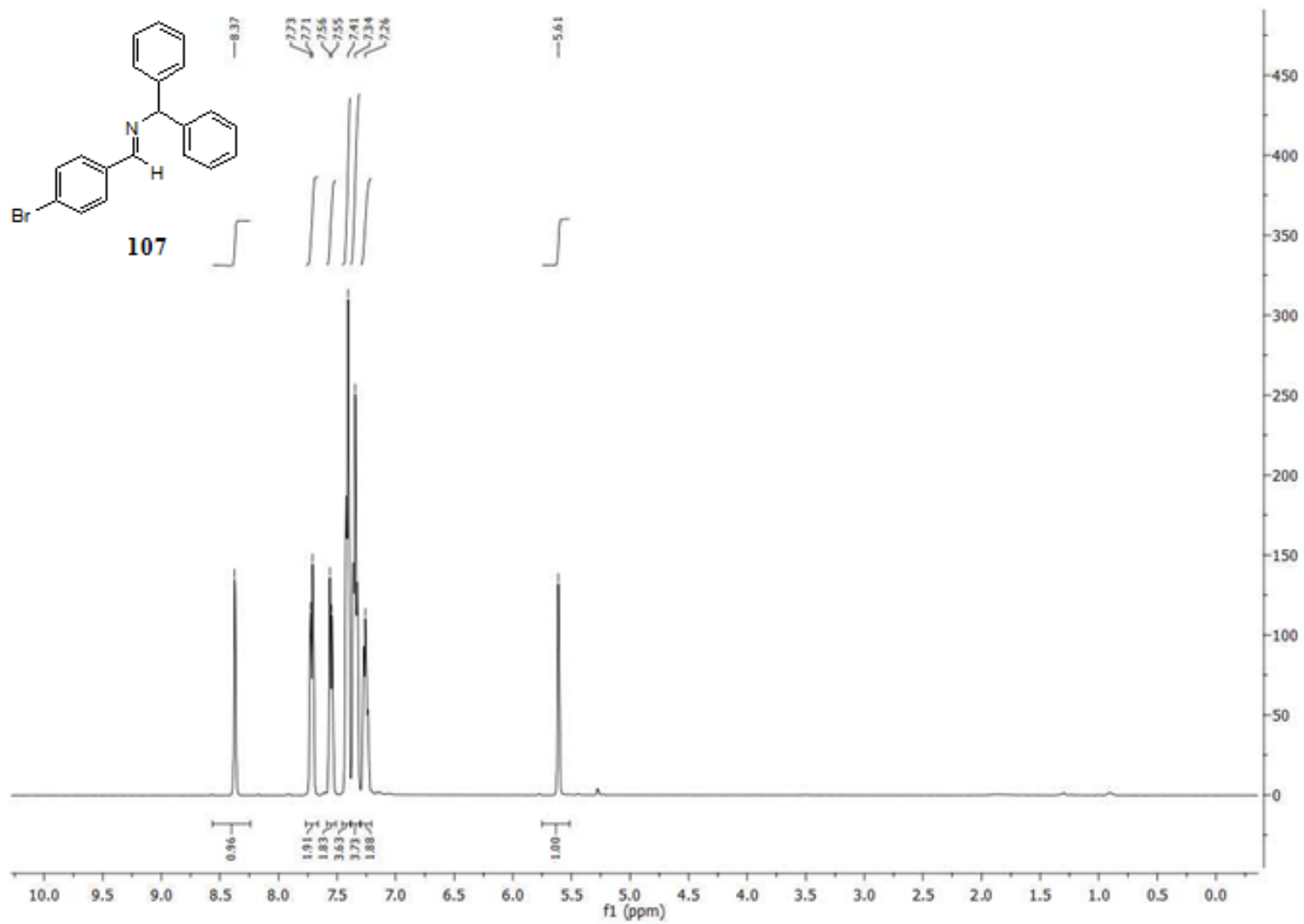
$^1\text{H-NMR}$ (*E*)-*N*-(4-methoxybenzylidene)-1,1-diphenylmethanamine (400 MHz, CDCl_3)



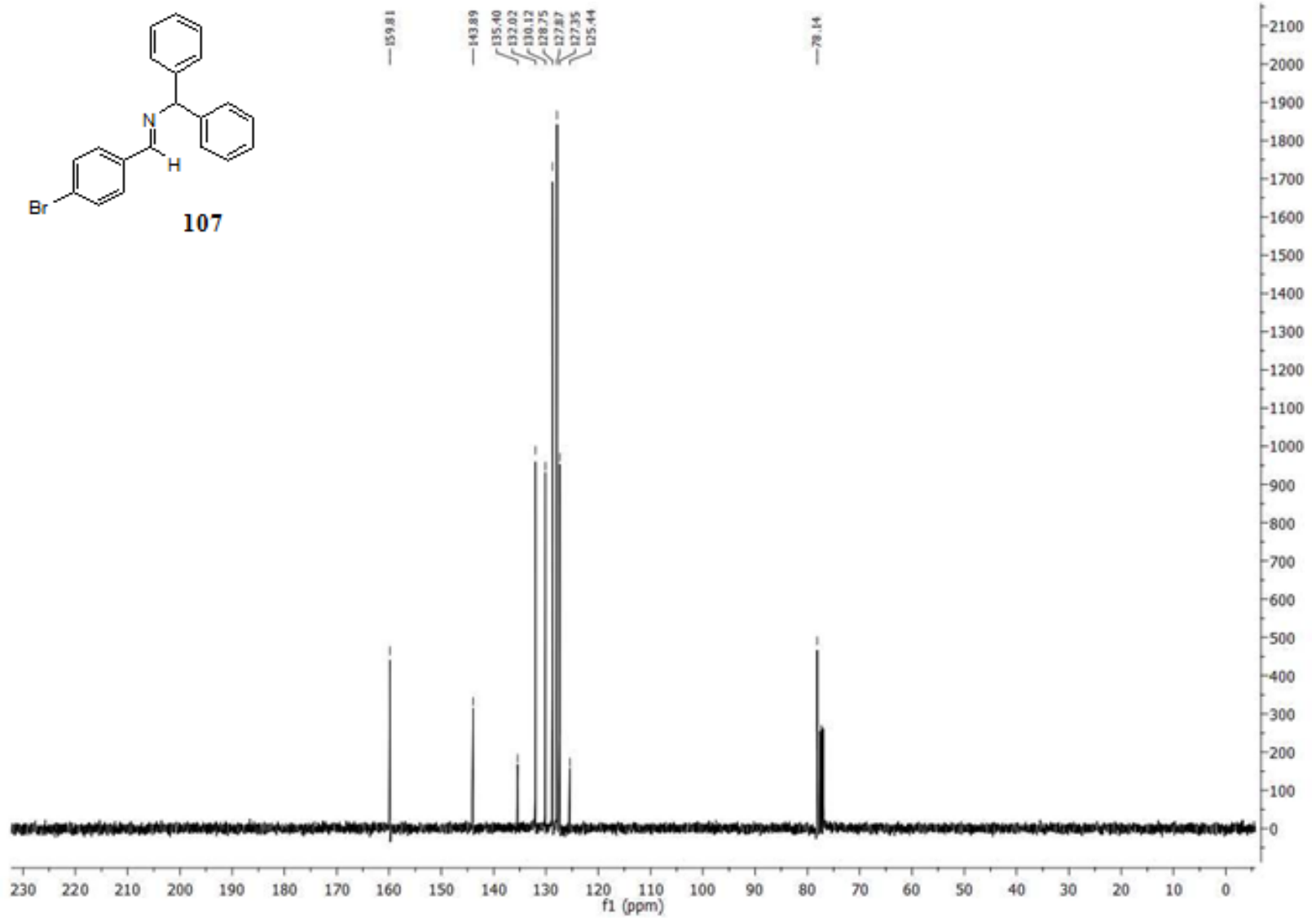
^{13}C -NMR (*E*)-*N*-(4-methoxybenzylidene)-1,1-diphenylmethanamine (100 MHz, CDCl_3)



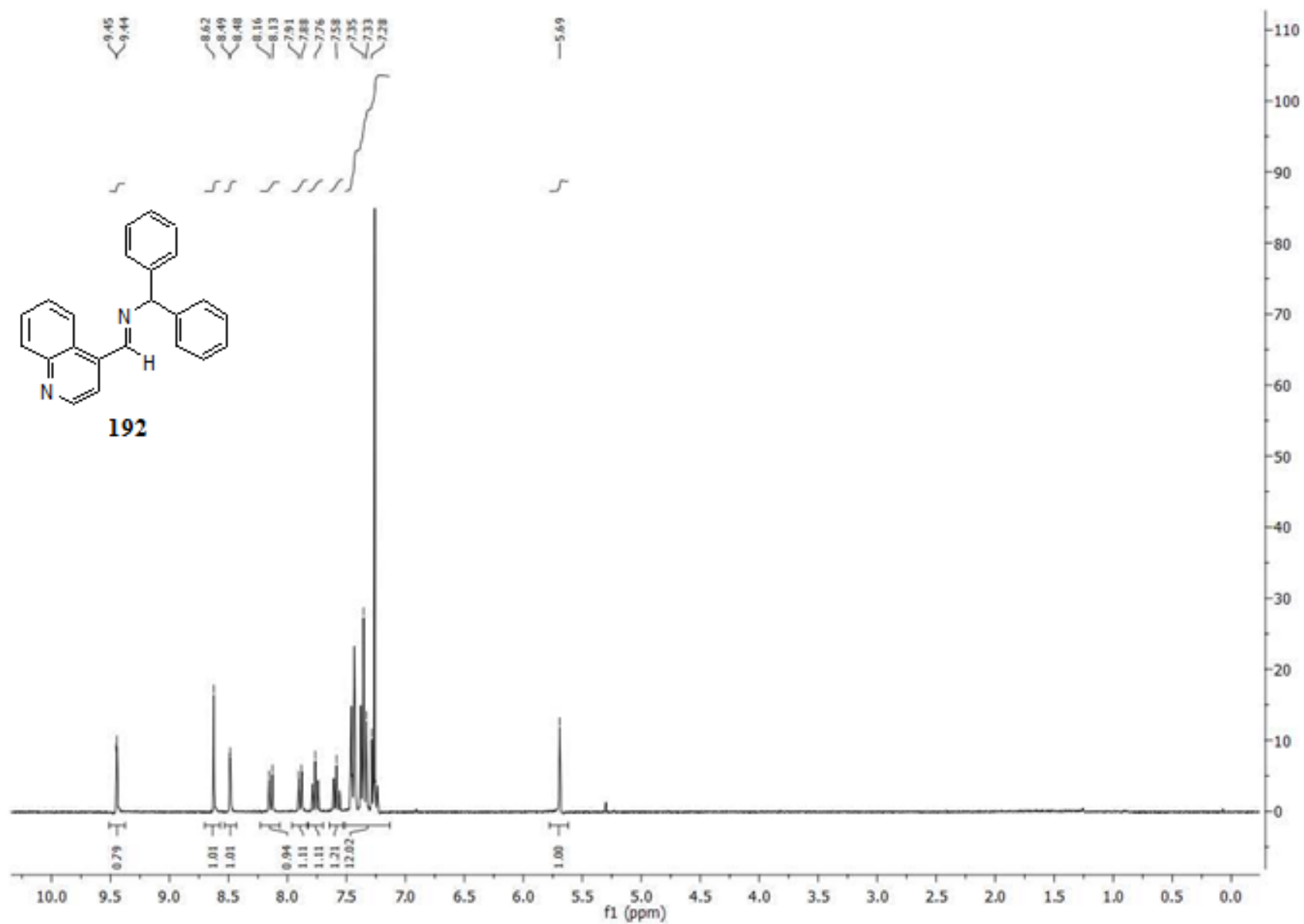
$^1\text{H-NMR}$ (*E*)-*N*-(4-bromobenzylidene)-1,1-diphenylmethanamine (400 MHz, CDCl_3)



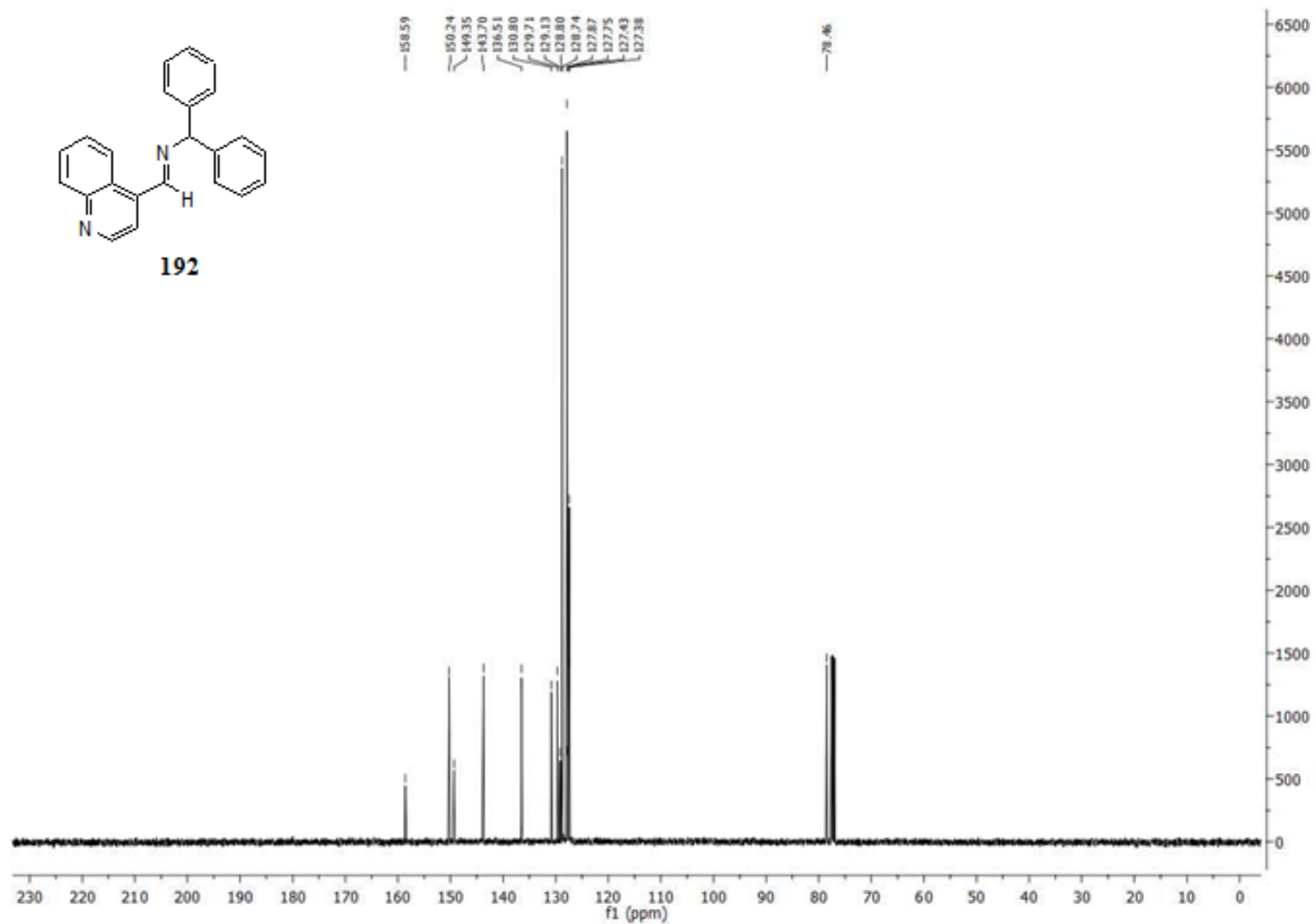
^{13}C -NMR (*E*)-*N*-(4-bromobenzylidene)-1,1-diphenylmethanamine (100 MHz, CDCl_3)



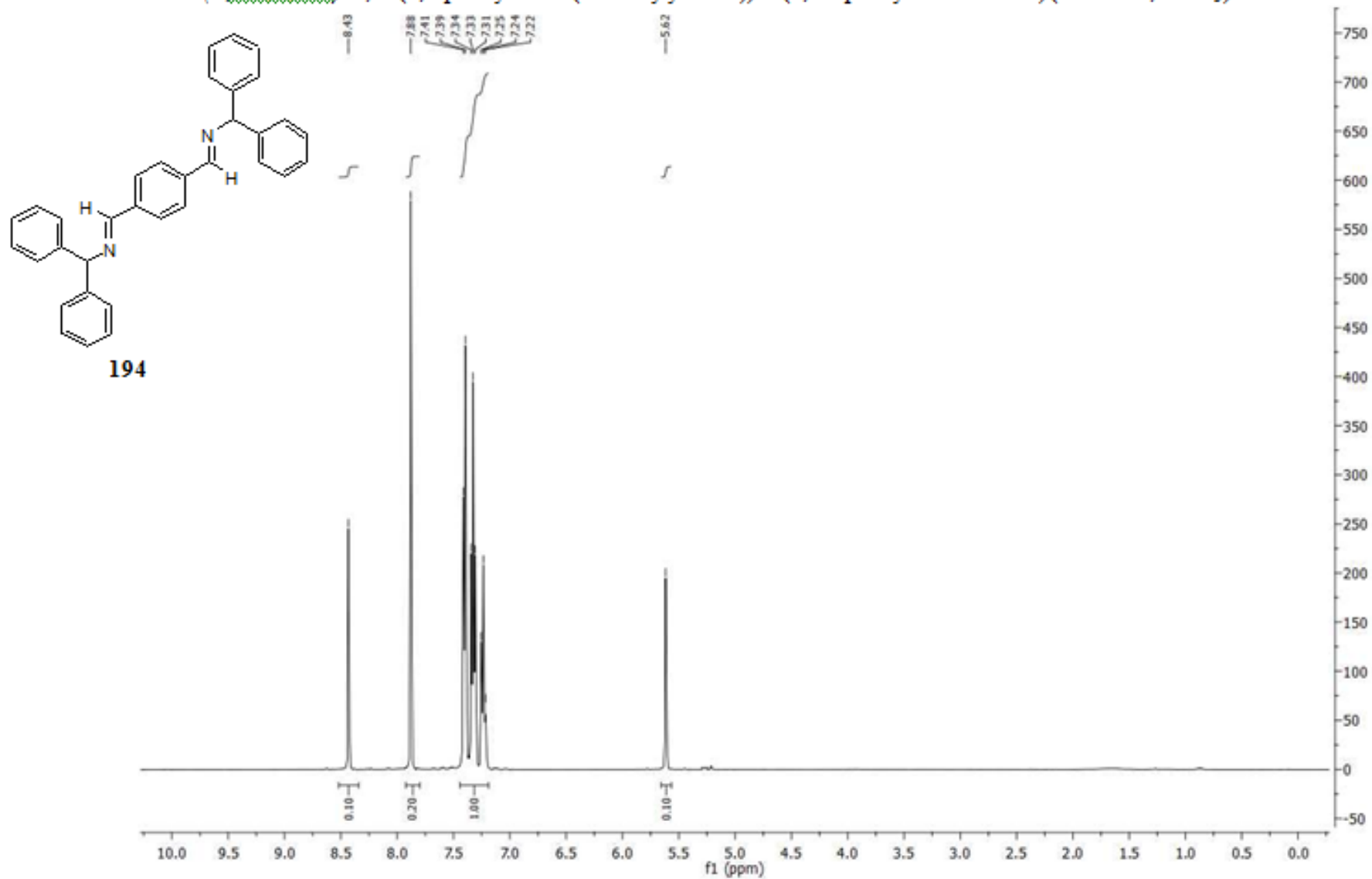
$^1\text{H-NMR}$ (*E*)-1,1-diphenyl-N-(quinolin-4-ylmethylene)ethanamine (300 MHz, CDCl_3)



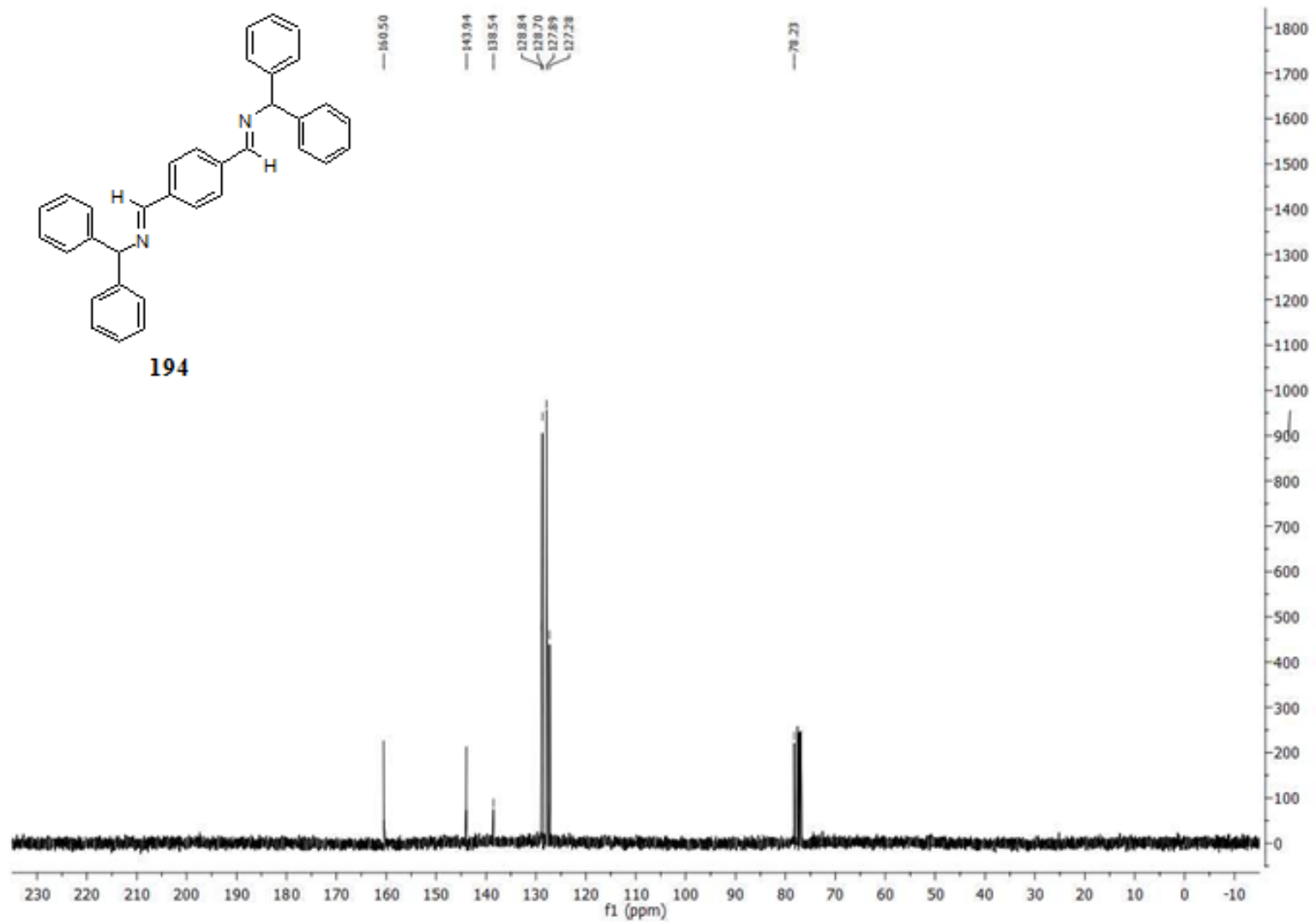
^{13}C -NMR (*E*)-1,1-diphenyl-*N*-(quinolin-4-ylmethylene)methanamine (100 MHz, CDCl_3)



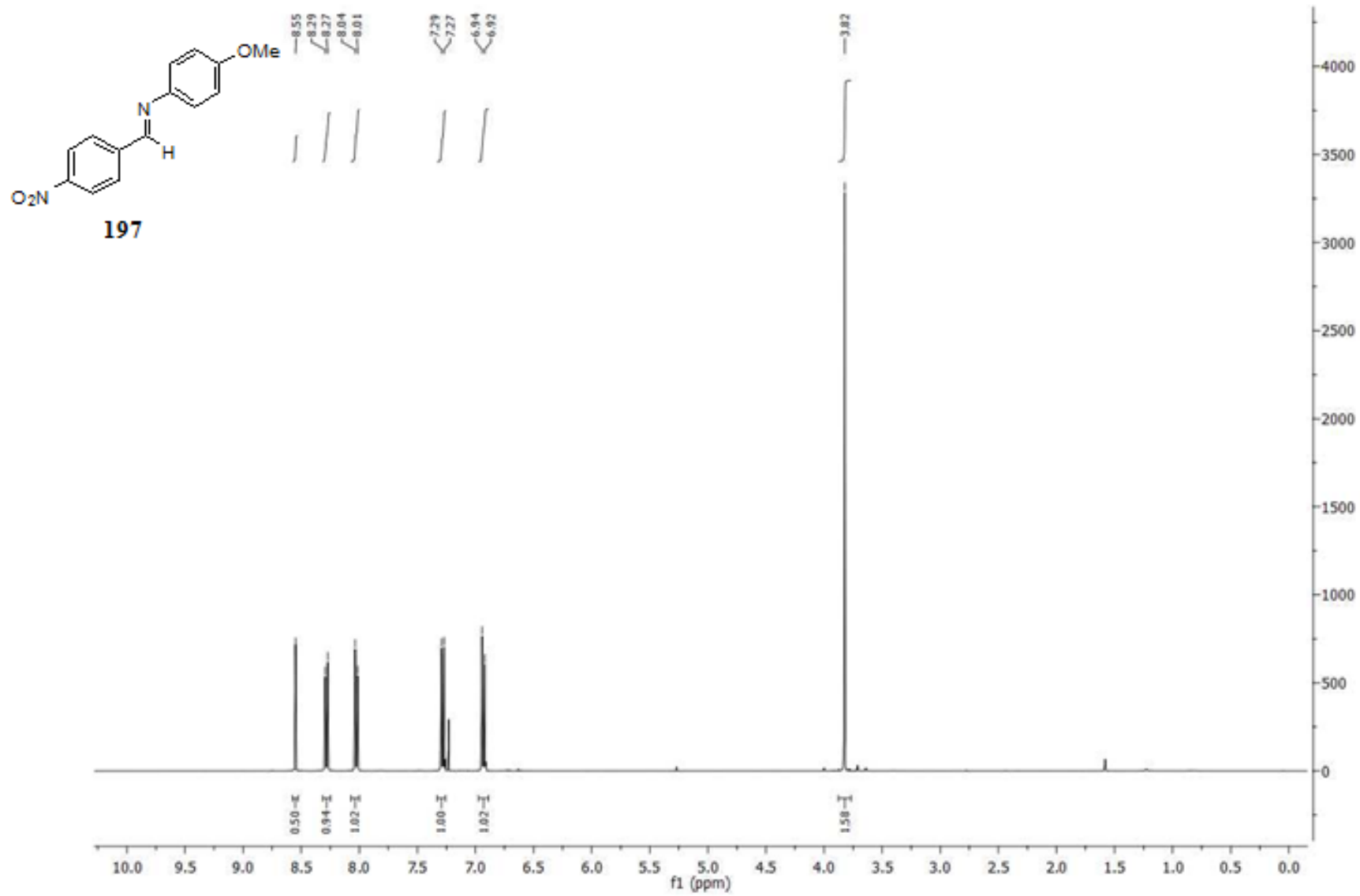
$^1\text{H-NMR}$ (*N,N'E,N,N'E*)-*N,N'*-(1,4-phenylenebis(methanylylidene))bis(1,1-diphenylmethanamine) (400 MHz, CDCl_3)



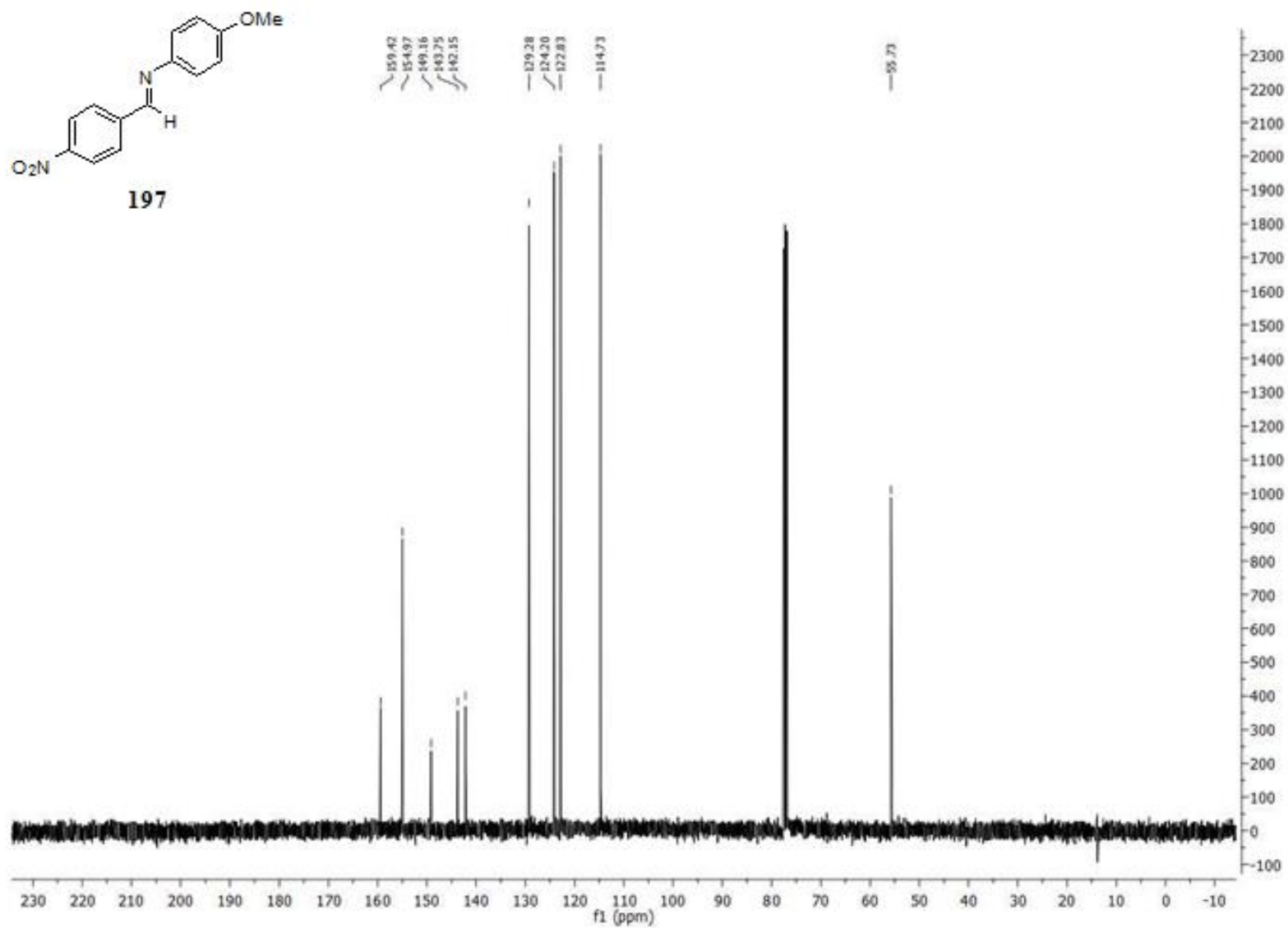
^{13}C -NMR (*N,N'E,N,N'E*)-*N,N'*-(1,4-phenylenebis(methanylylidene))bis(1,1-diphenylmethanamine) (100 MHz, CDCl_3)



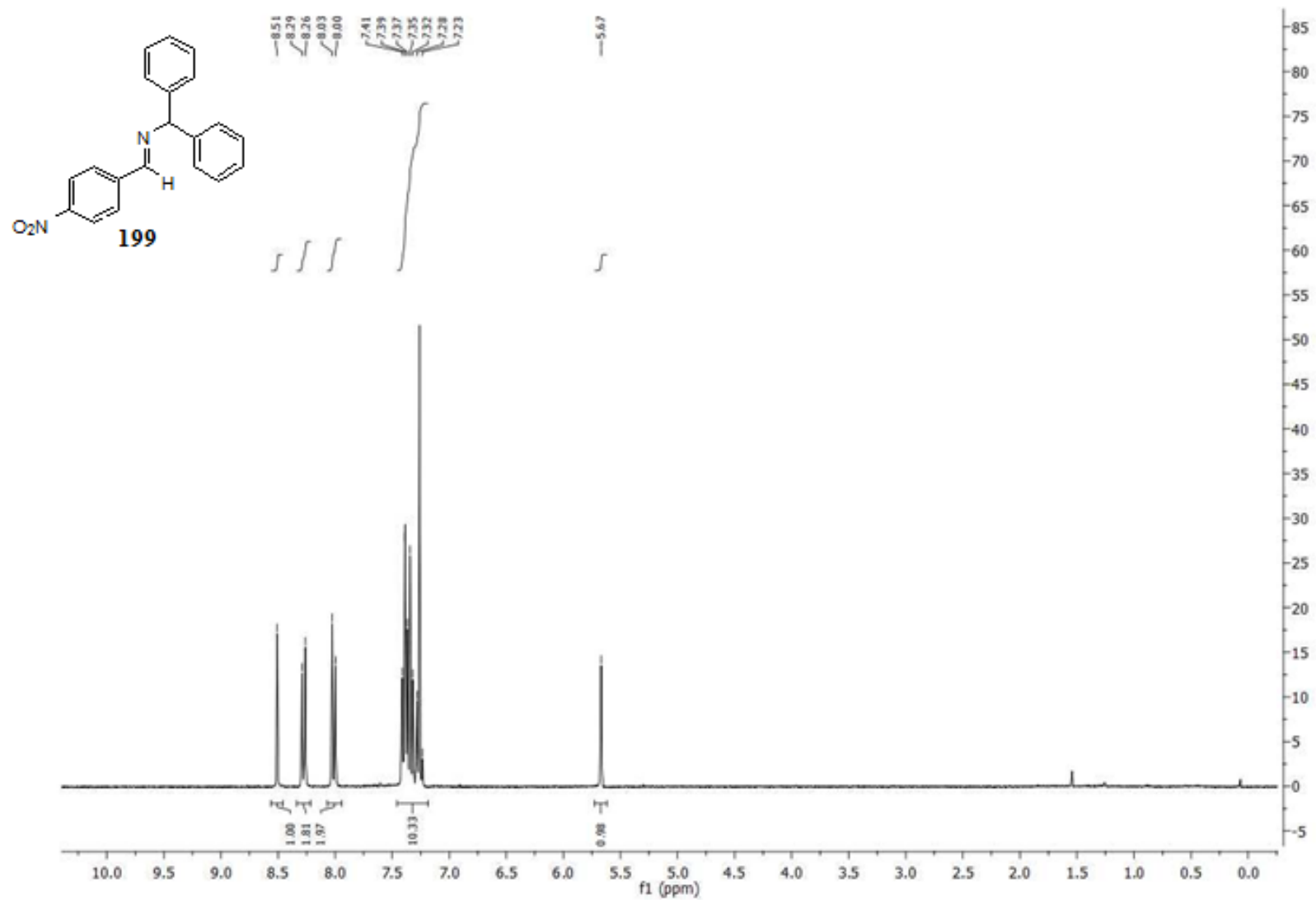
¹H-NMR (*E*)-4-methoxy-N-(4-nitrobenzylidene)aniline (400 MHz, CDCl₃)



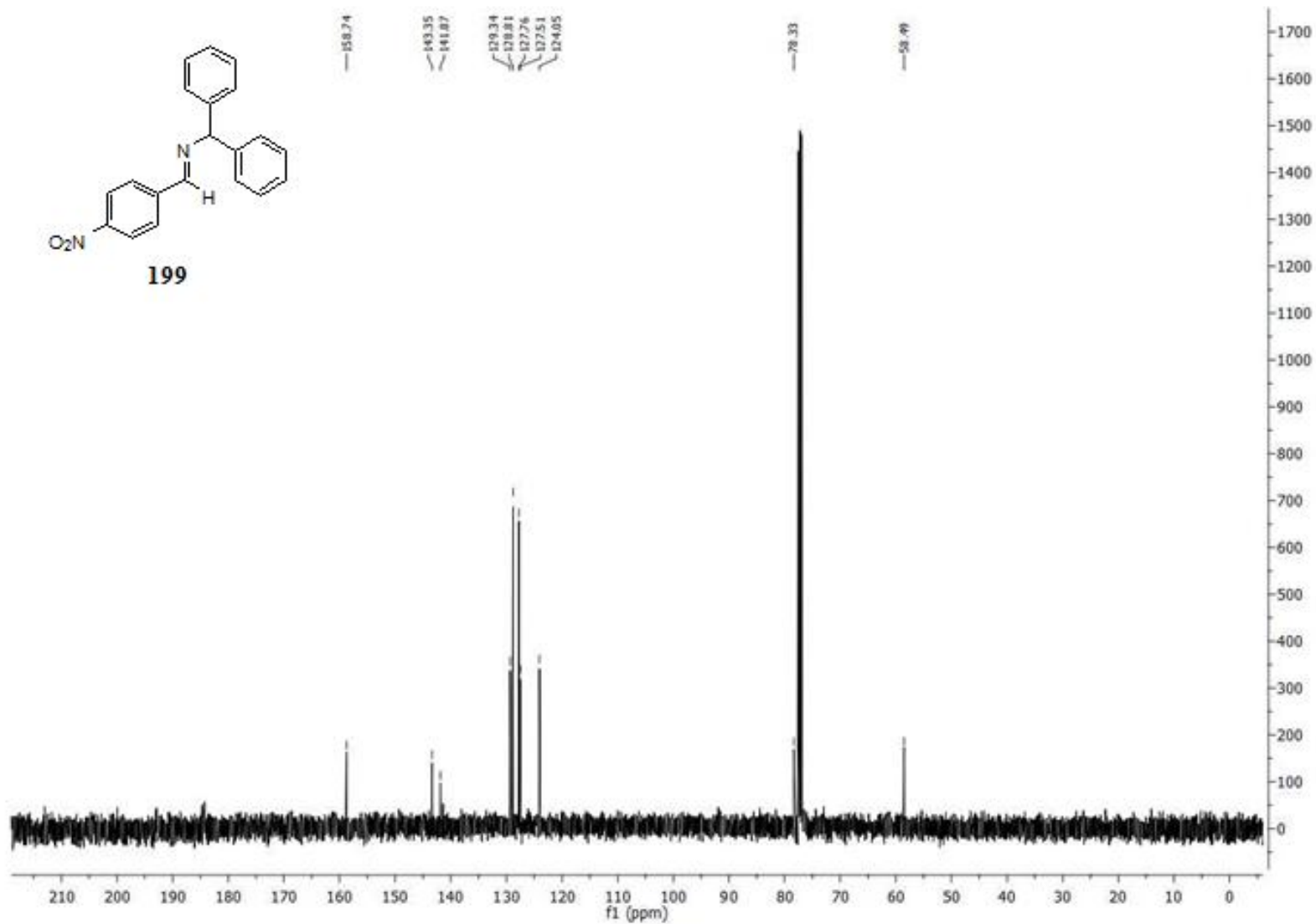
^{13}C -NMR (*E*)-4-methoxy-N-(4-nitrobenzylidene)aniline (100 MHz, CDCl_3)



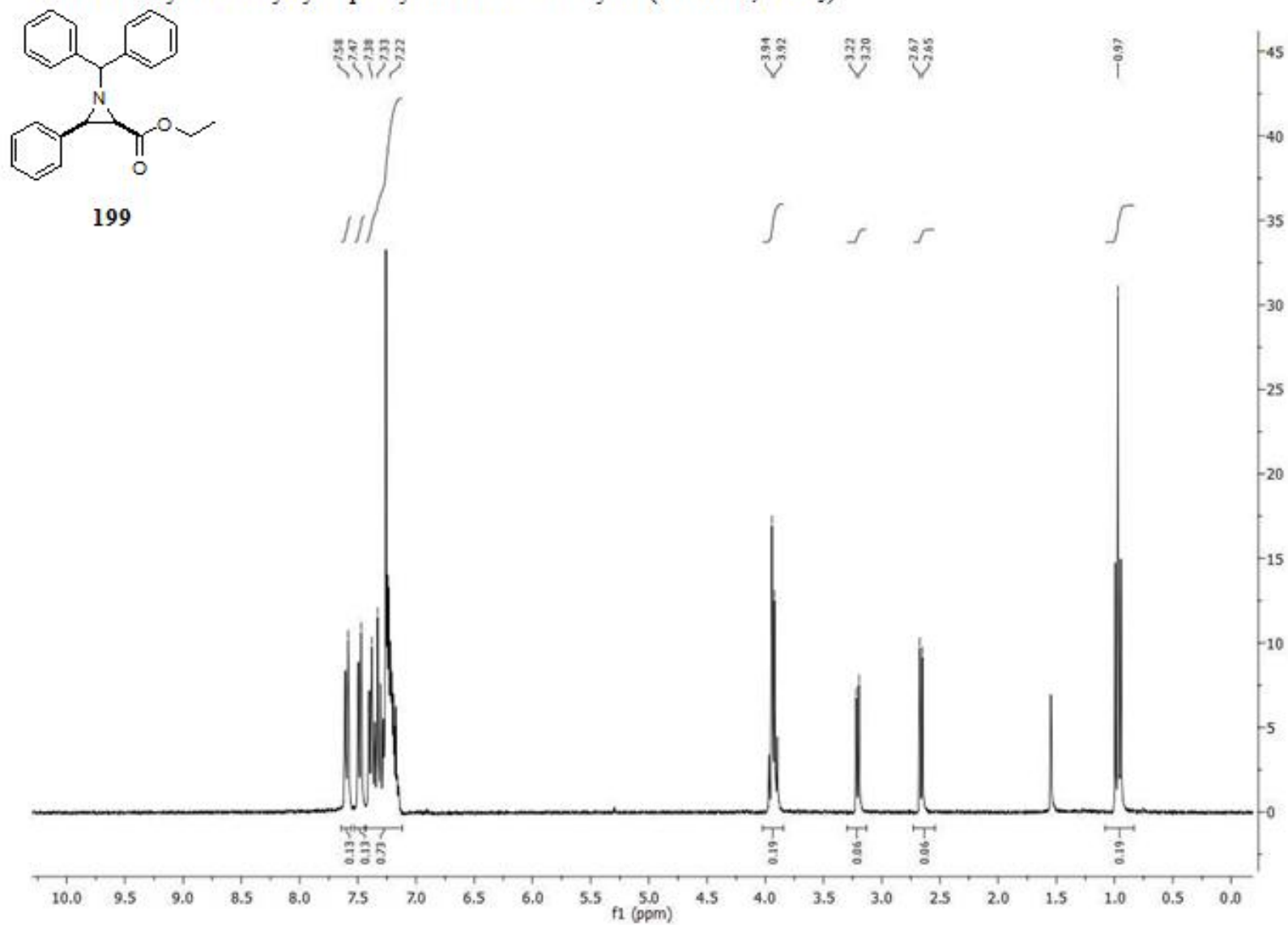
$^1\text{H-NMR}$ (*E*)-*N*-(4-nitrobenzylidene)-1,1-diphenylmethanamine (300 MHz, CDCl_3)



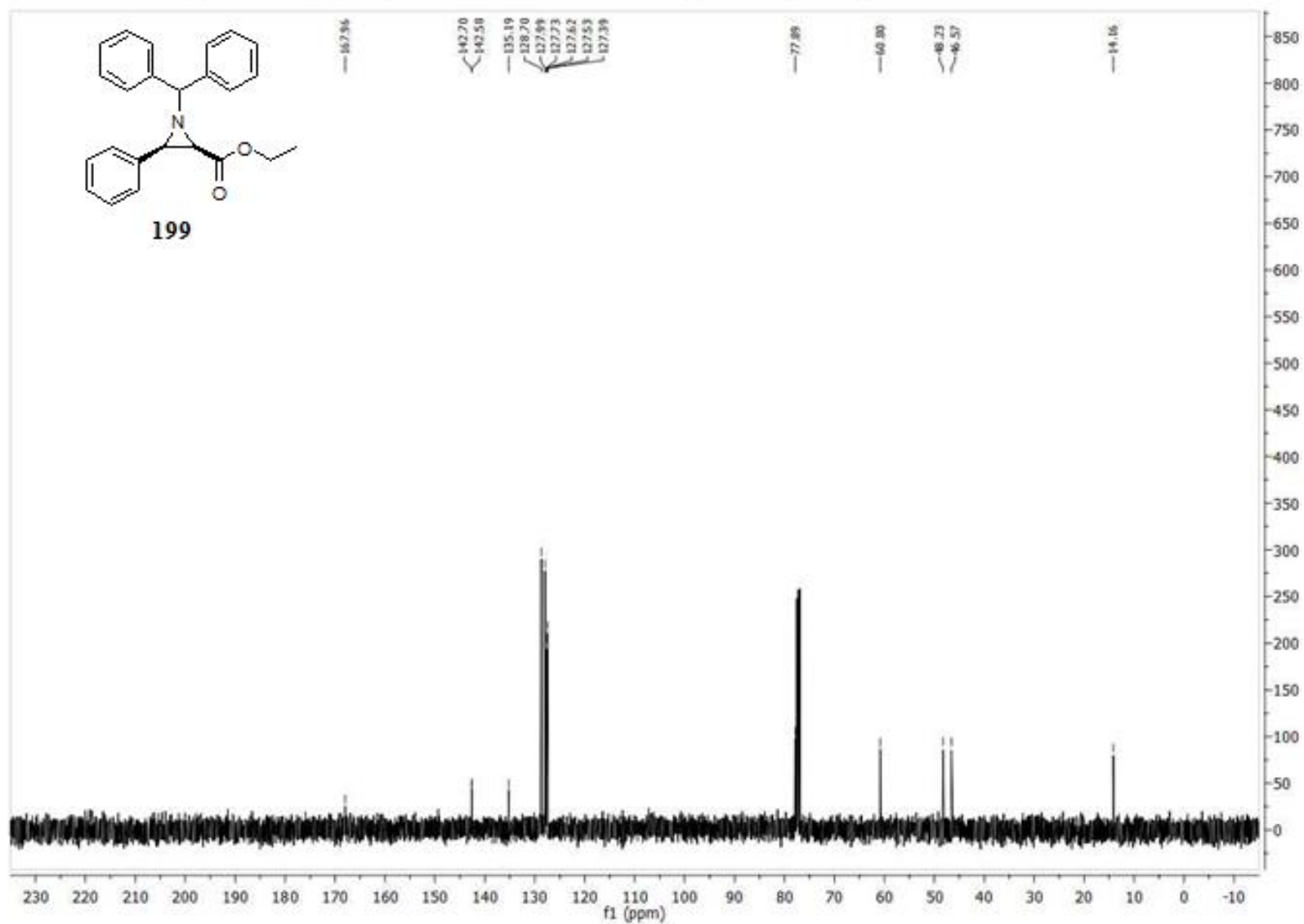
^{13}C -NMR (*E*)-*N*-(4-nitrobenzylidene)-1,1-diphenylmethanamine (100 MHz, CDCl_3)



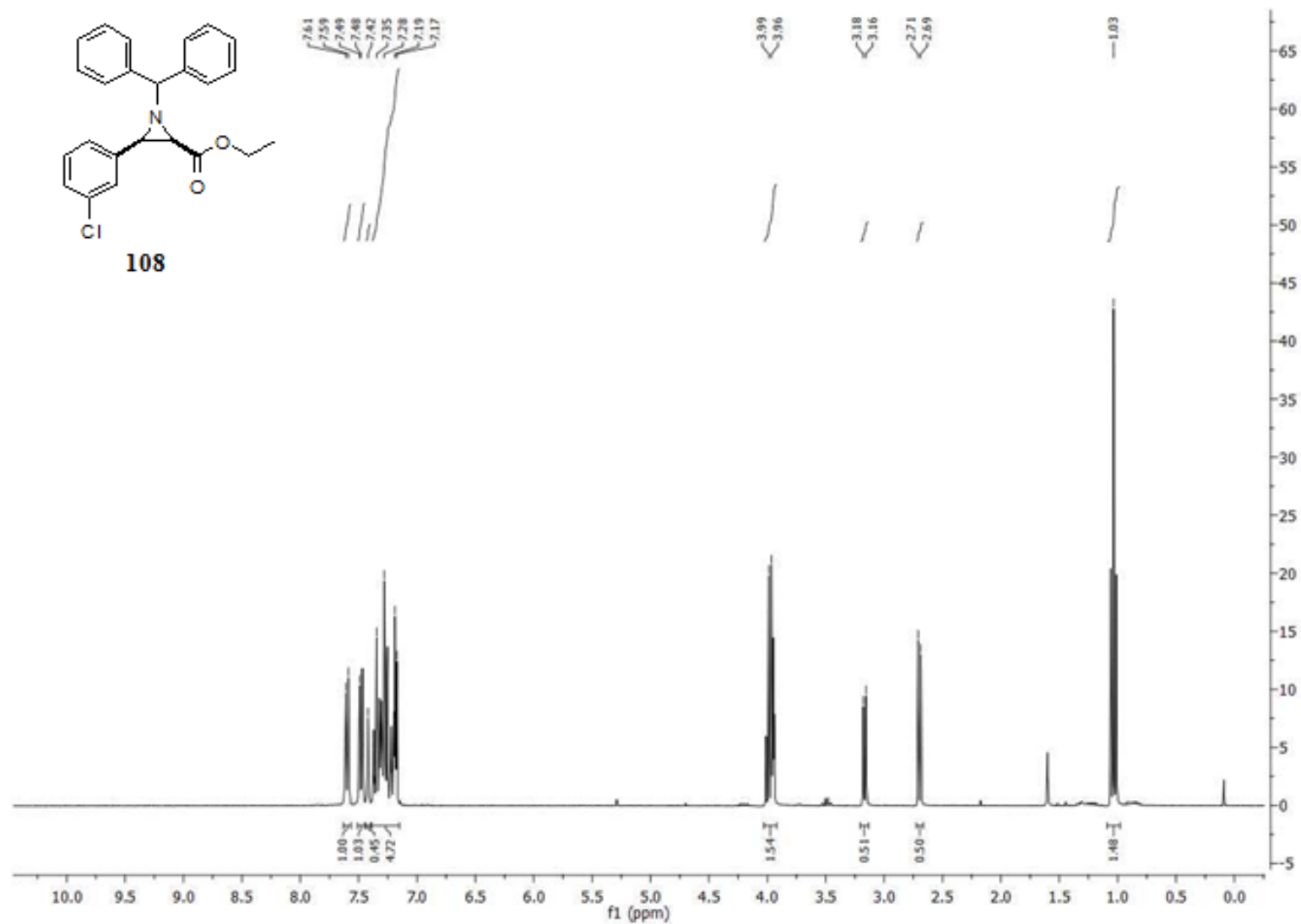
¹H-NMR ethyl 1-benzhydryl-3-phenylaziridine-2-carboxylate (400MHz, CDCl₃)



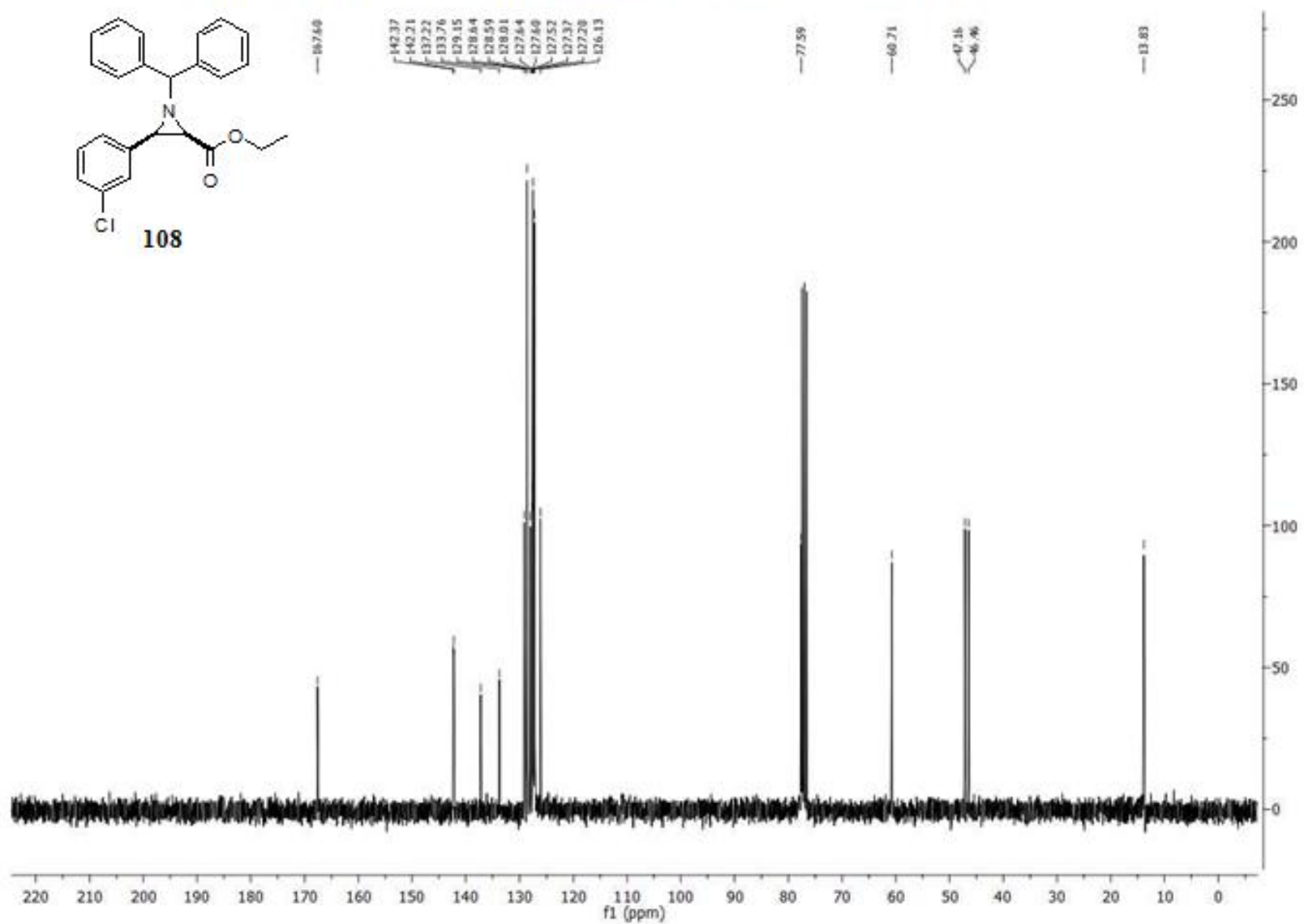
^{13}C -NMR ethyl 1-benzhydryl-3-phenylaziridine-2-carboxylate (100 MHz, CDCl_3)



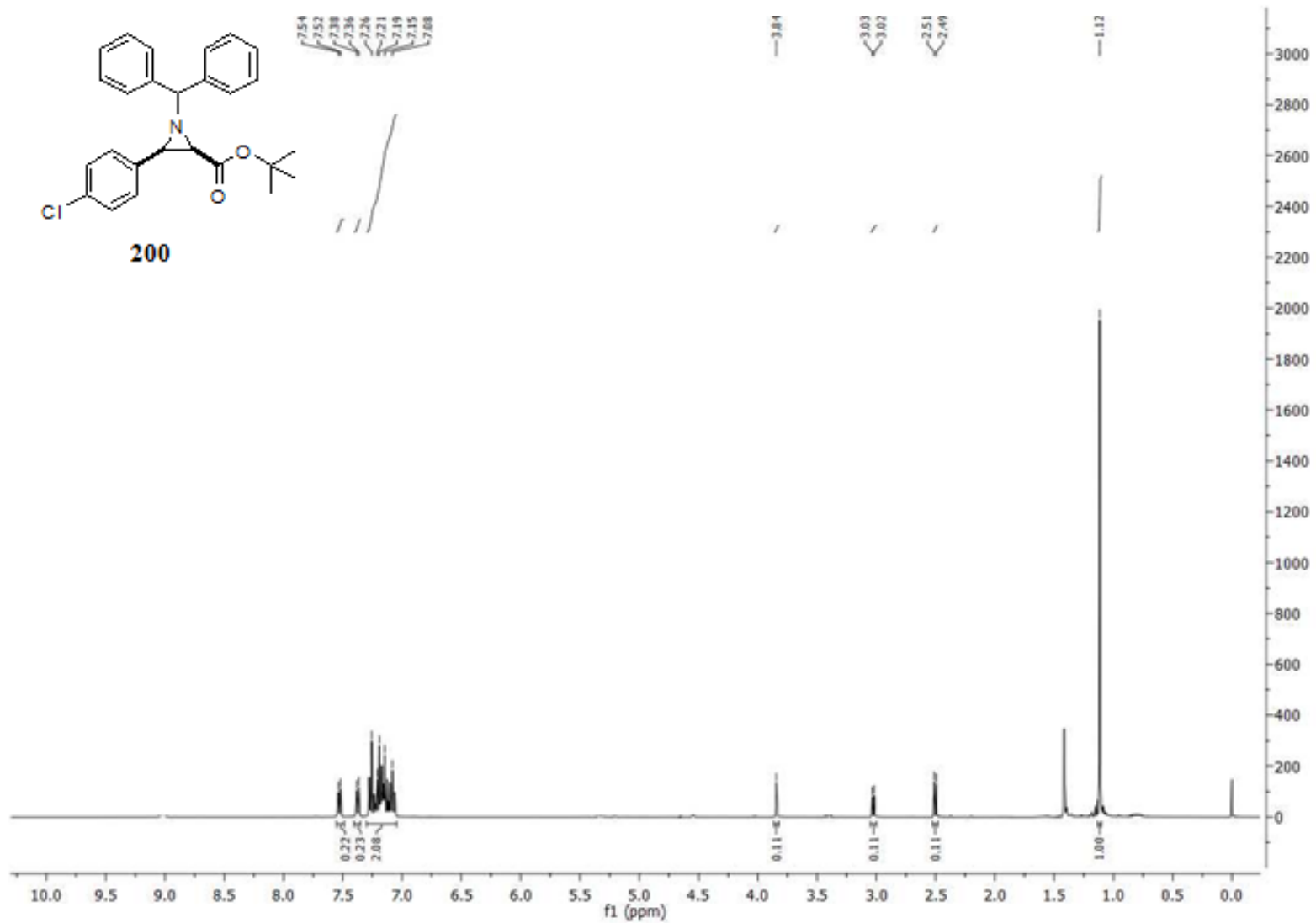
$^1\text{H-NMR}$ ethyl 1-benzhydryl-3-(3-chlorophenyl)aziridine-2-carboxylate (300 MHz, CDCl_3)



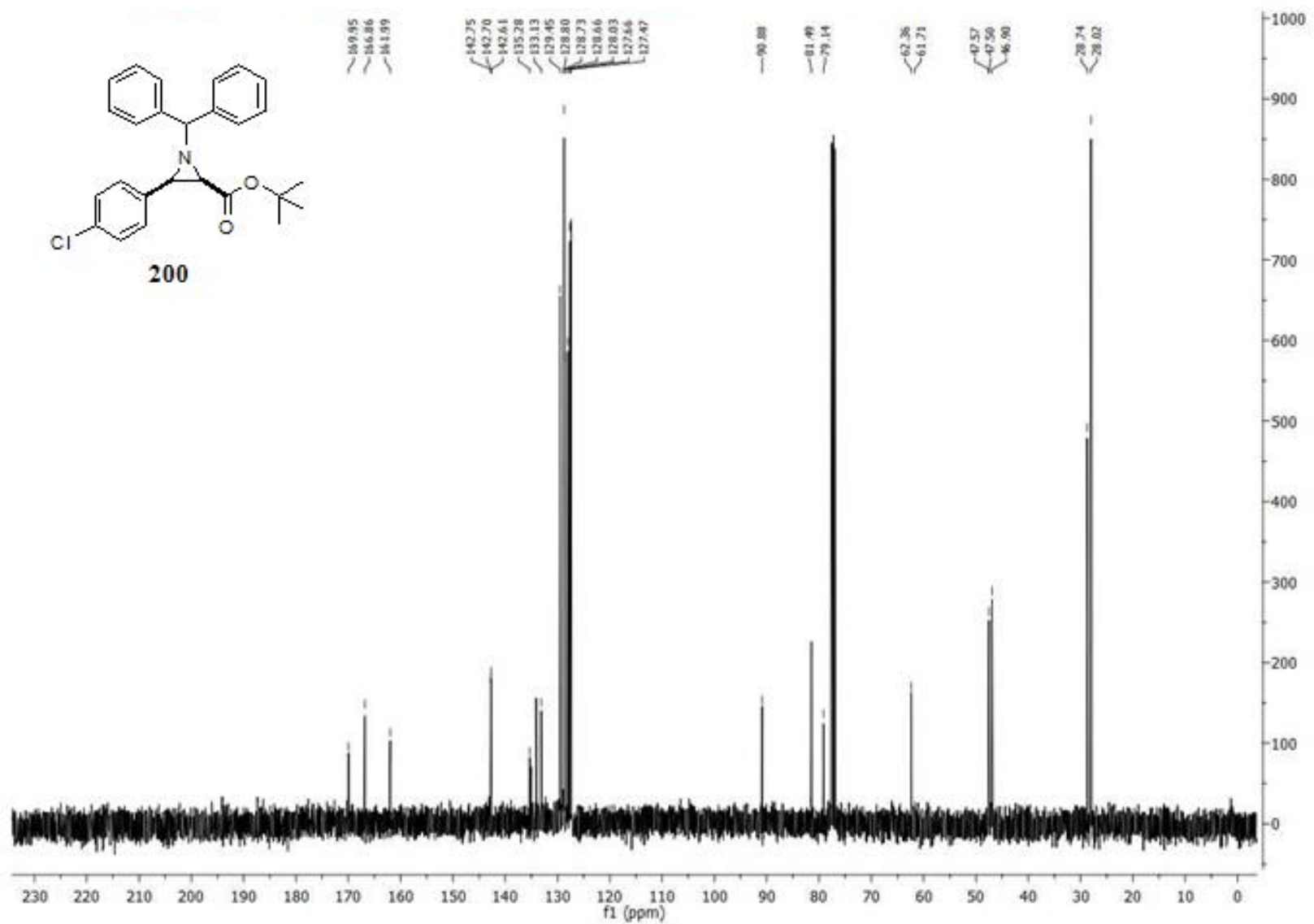
^{13}C -NMR ethyl 1-benzhydryl-3-(3-chlorophenyl)aziridine-2-carboxylate (75 MHz, CDCl_3)



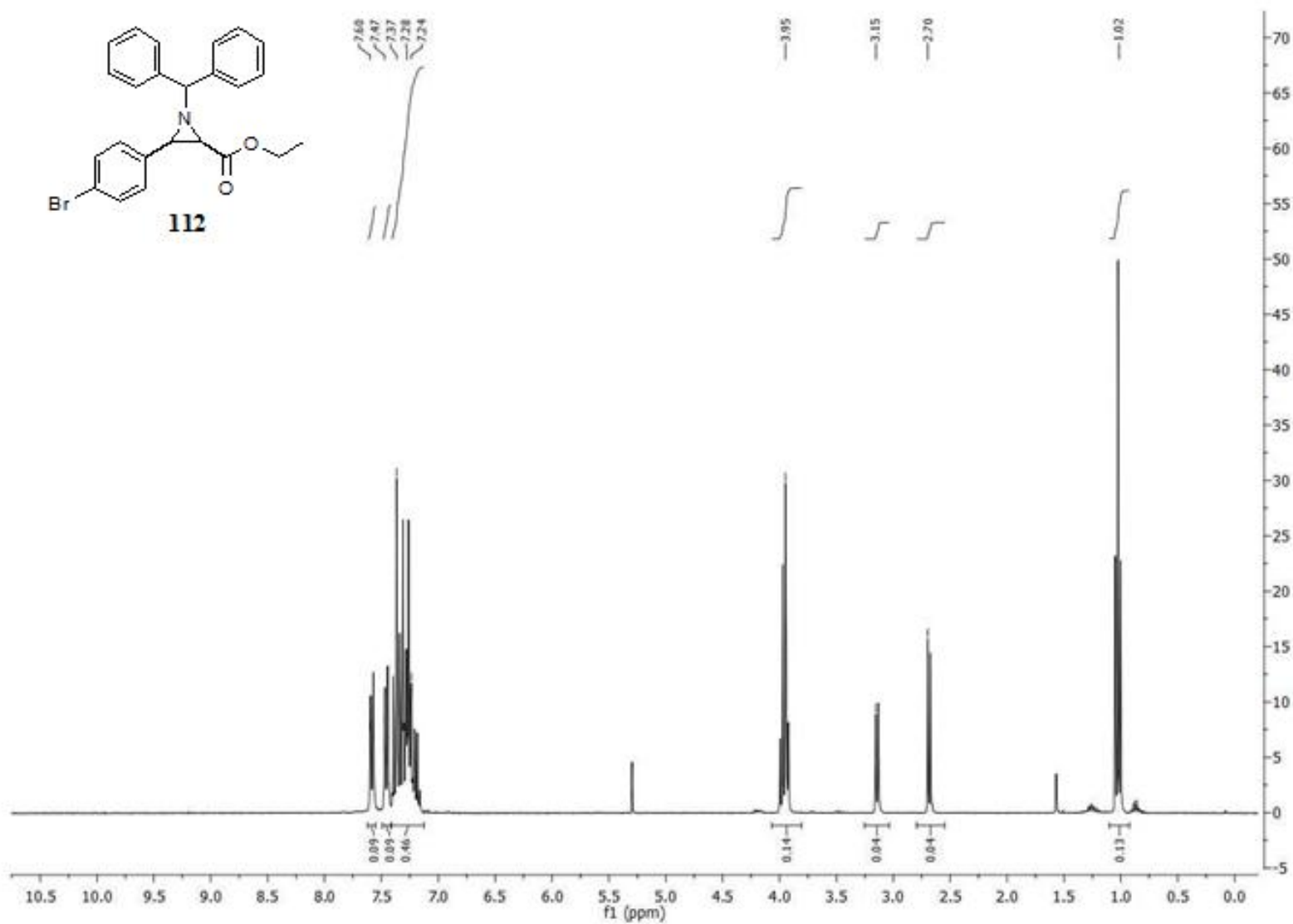
¹H-NMR tert-butyl 1-benzhydryl-3-(4-chlorophenyl)aziridine-2-carboxylate (400 MHz, CDCl₃)



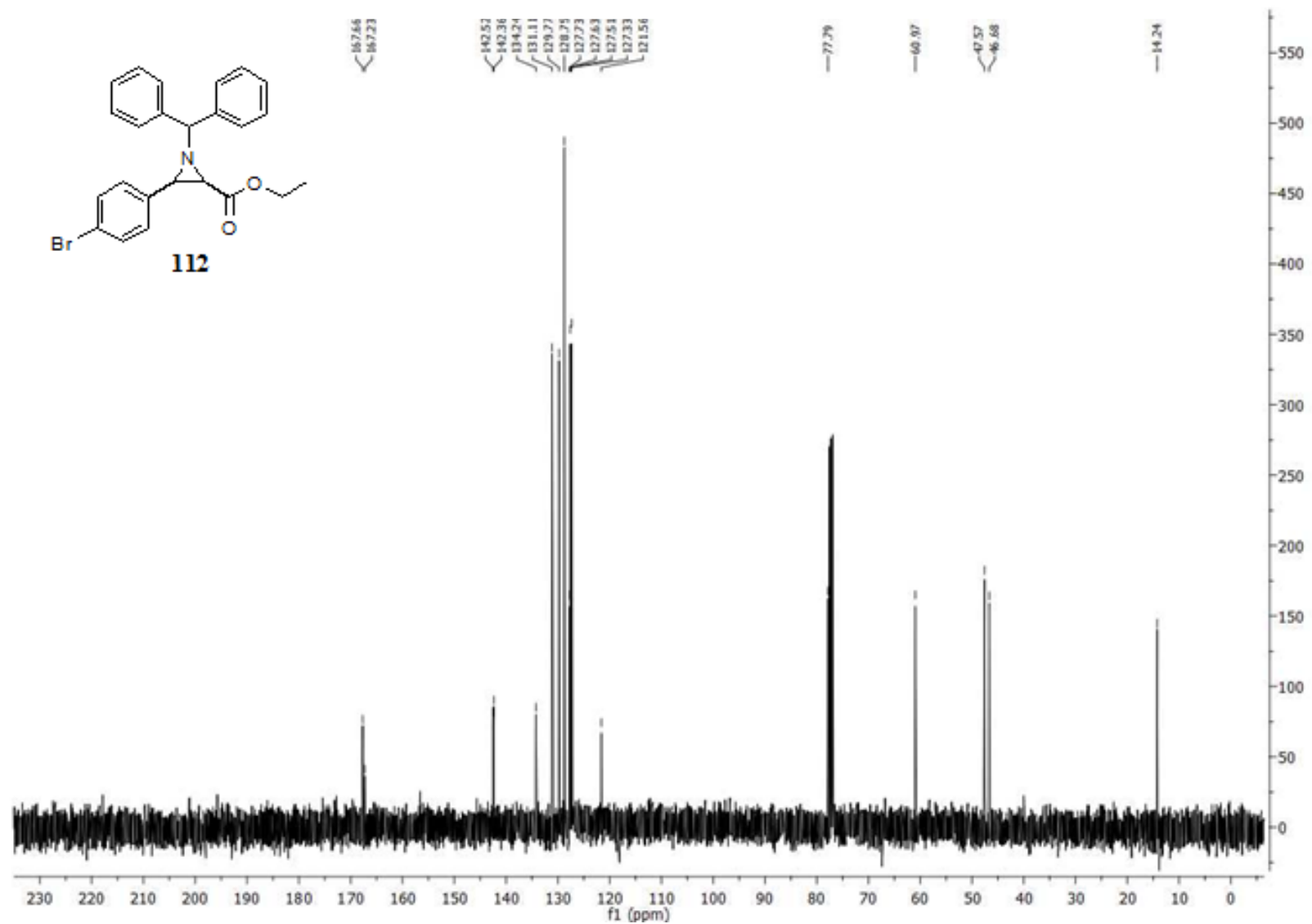
^{13}C -NMR ethyl 1-benzhydryl-3-(3-chlorophenyl)aziridine-2-carboxylate (75 MHz, CDCl_3)



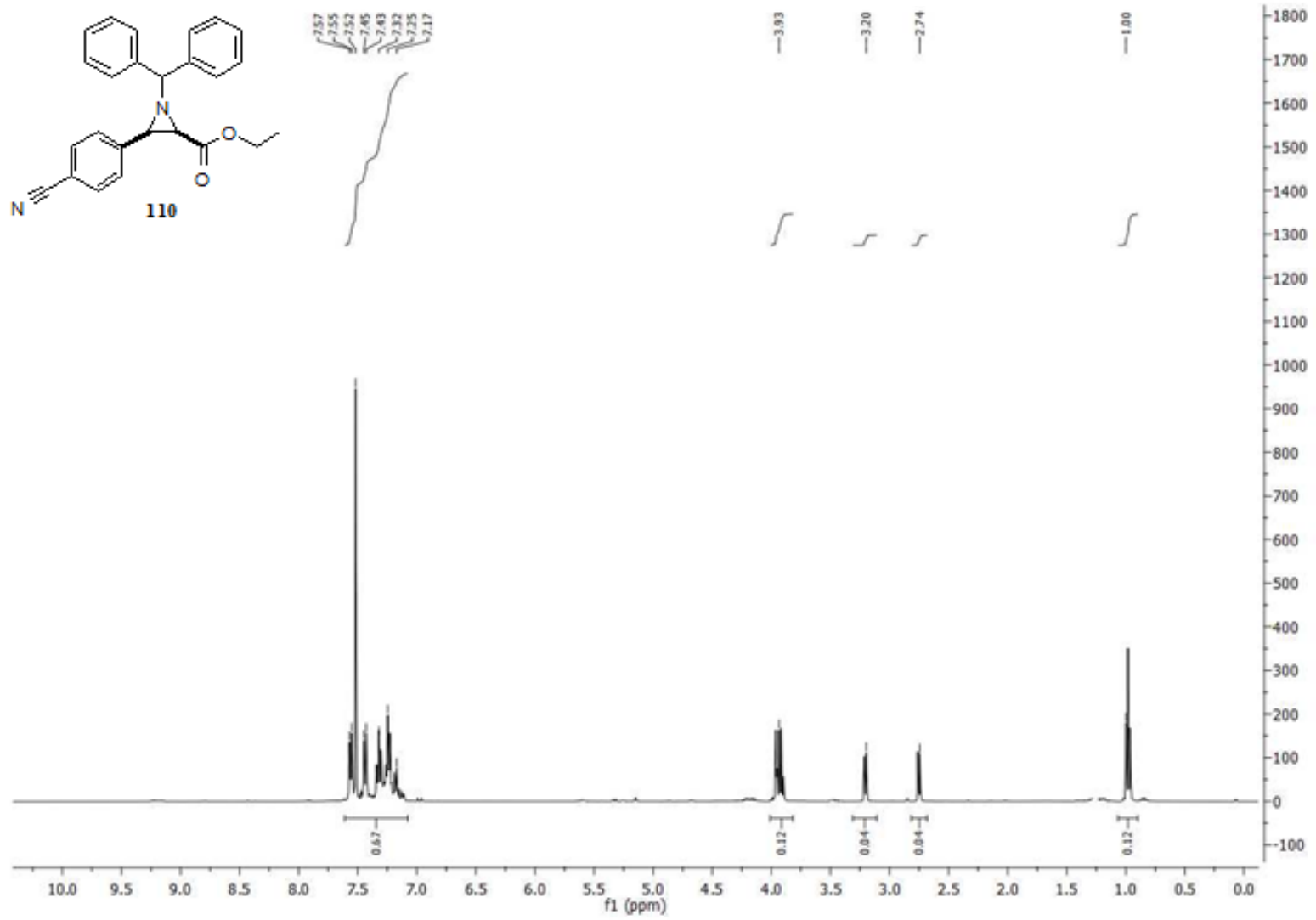
$^1\text{H-NMR}$ ethyl 1-benzhydryl-3-(4-bromophenyl)aziridine-2-carboxylate (300 MHz, CDCl_3)



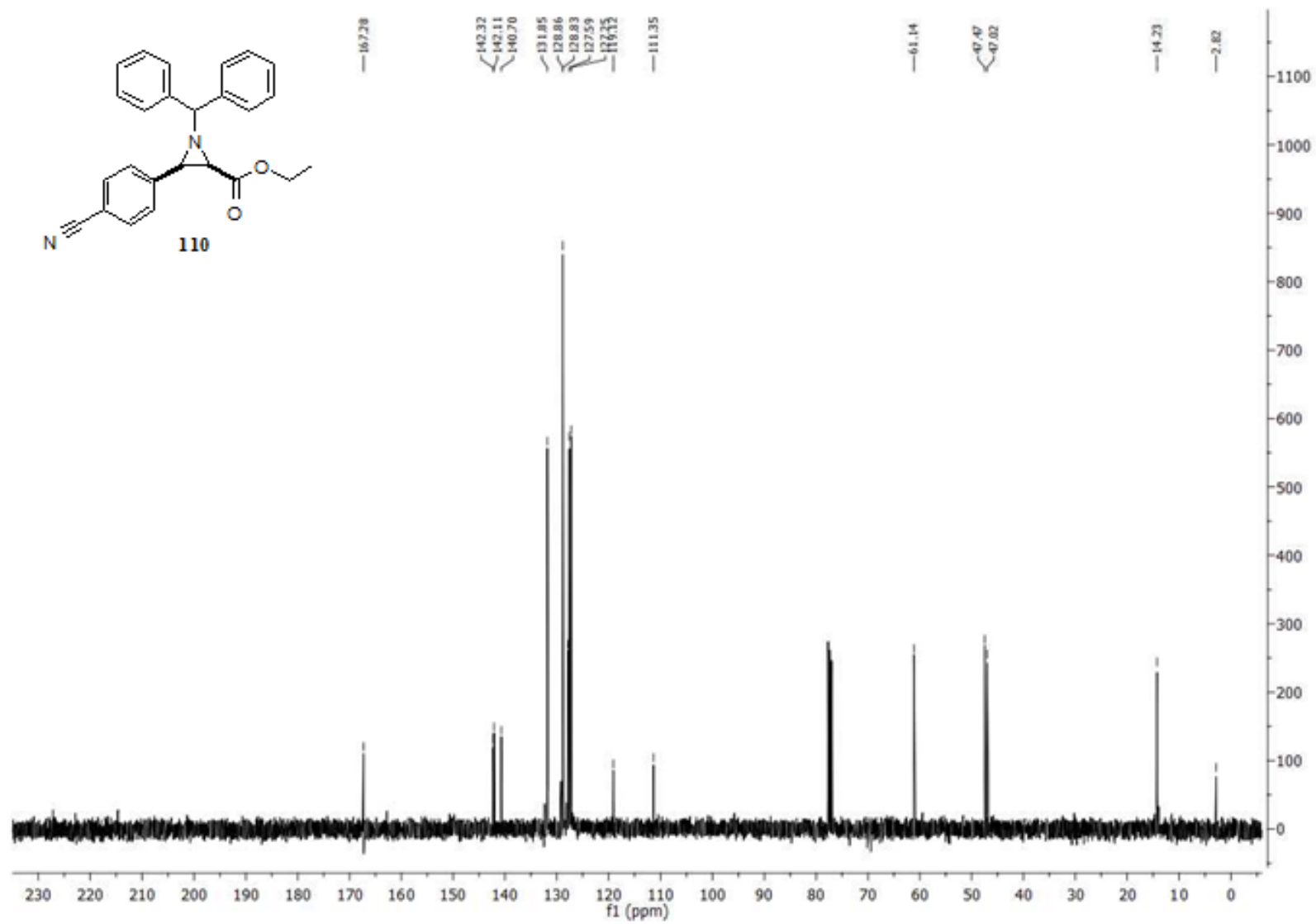
^{13}C -NMR ethyl 1-benzhydryl-3-(4-bromophenyl)aziridine-2-carboxylate (100 MHz, CDCl_3)



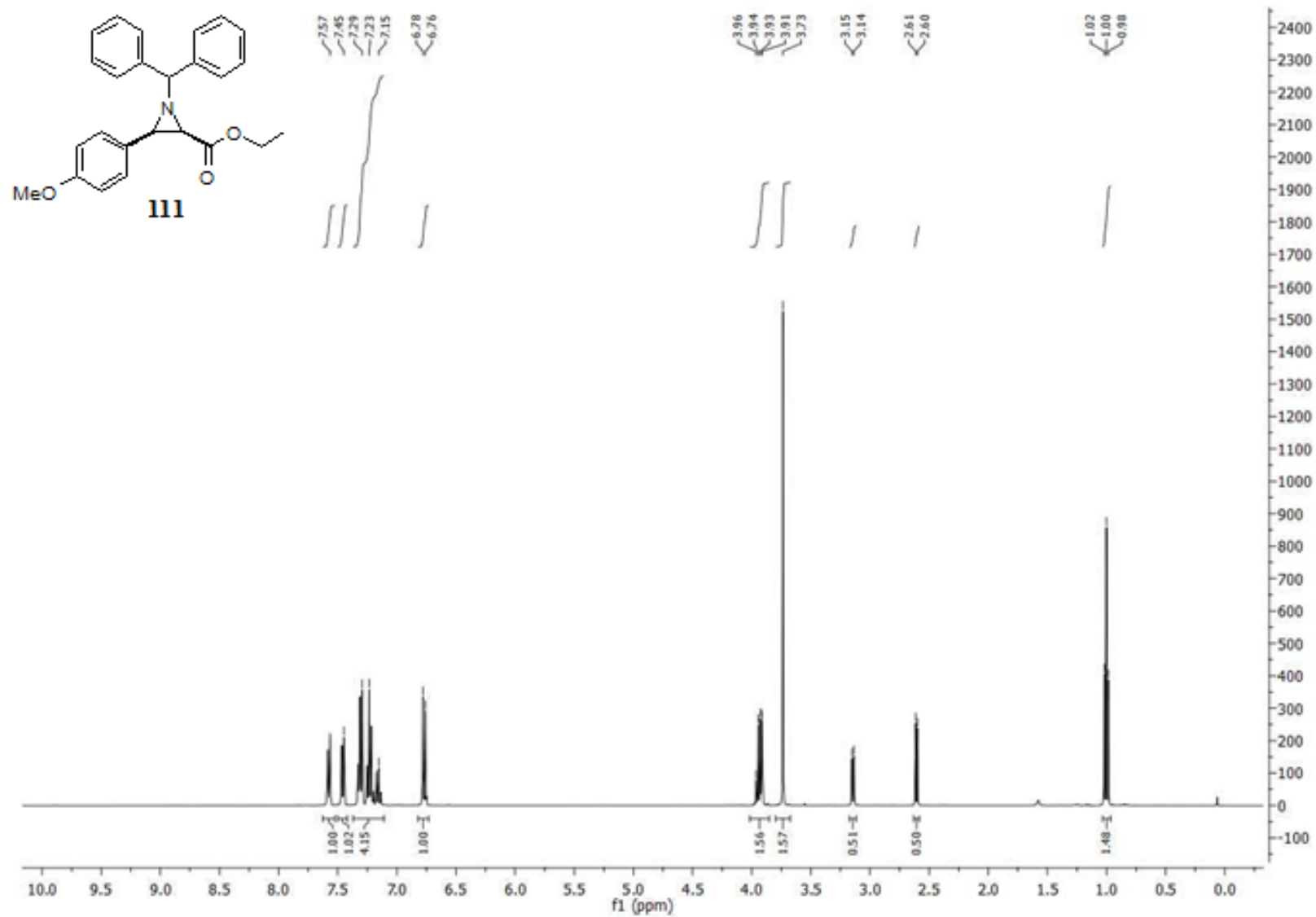
¹H-NMR ethyl 1-benzhydryl-3-(4-cyanophenyl)aziridine-2-carboxylate (400 MHz, CDCl₃)



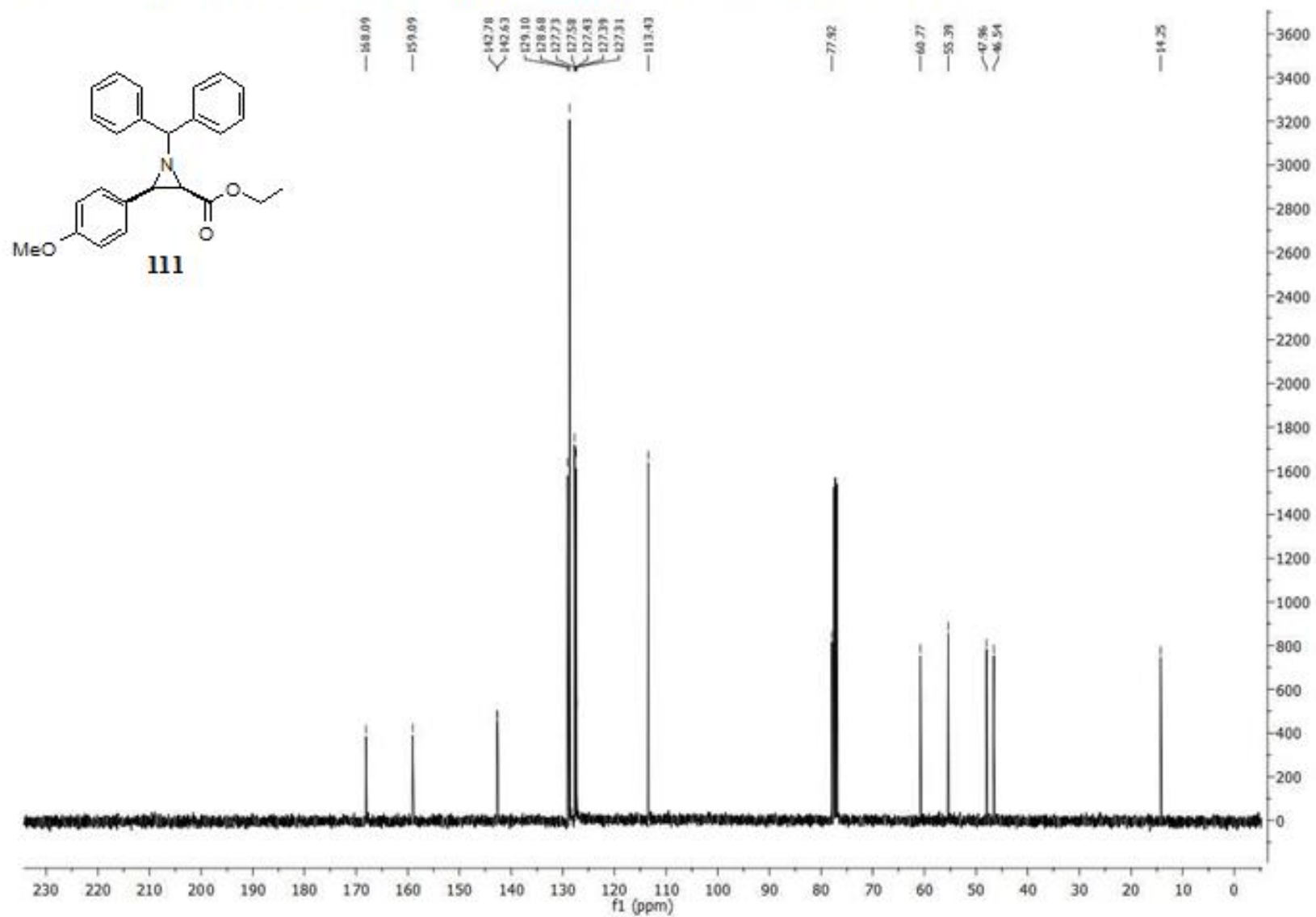
^{13}C -NMR ethyl 1-benzhydryl-3-(4-cyanophenyl)aziridine-2-carboxylate (100 MHz, CDCl_3)



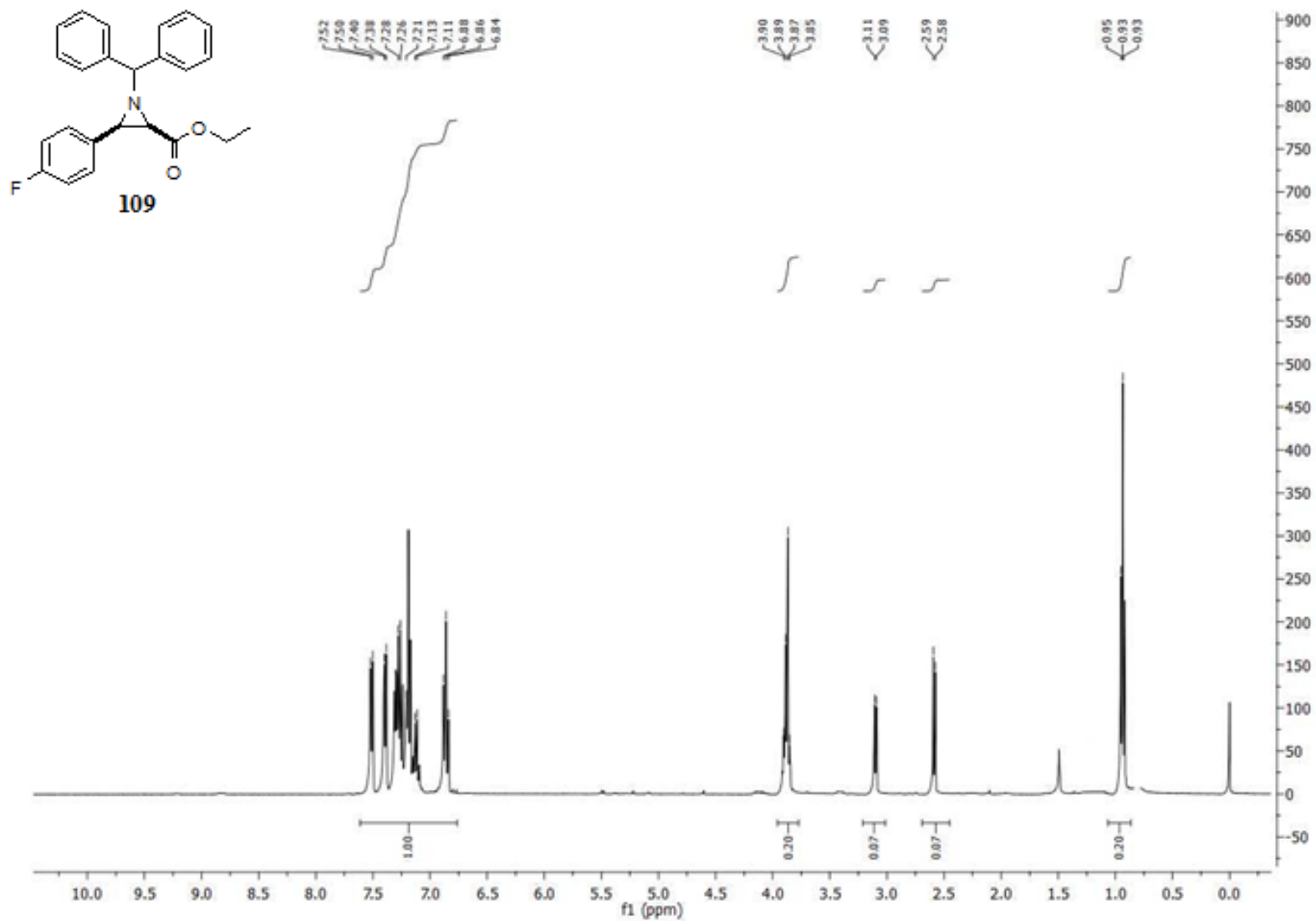
$^1\text{H-NMR}$ ethyl 1-benzhydryl-3-(4-methoxyphenyl)aziridine-2-carboxylate (400 MHz, CDCl_3)



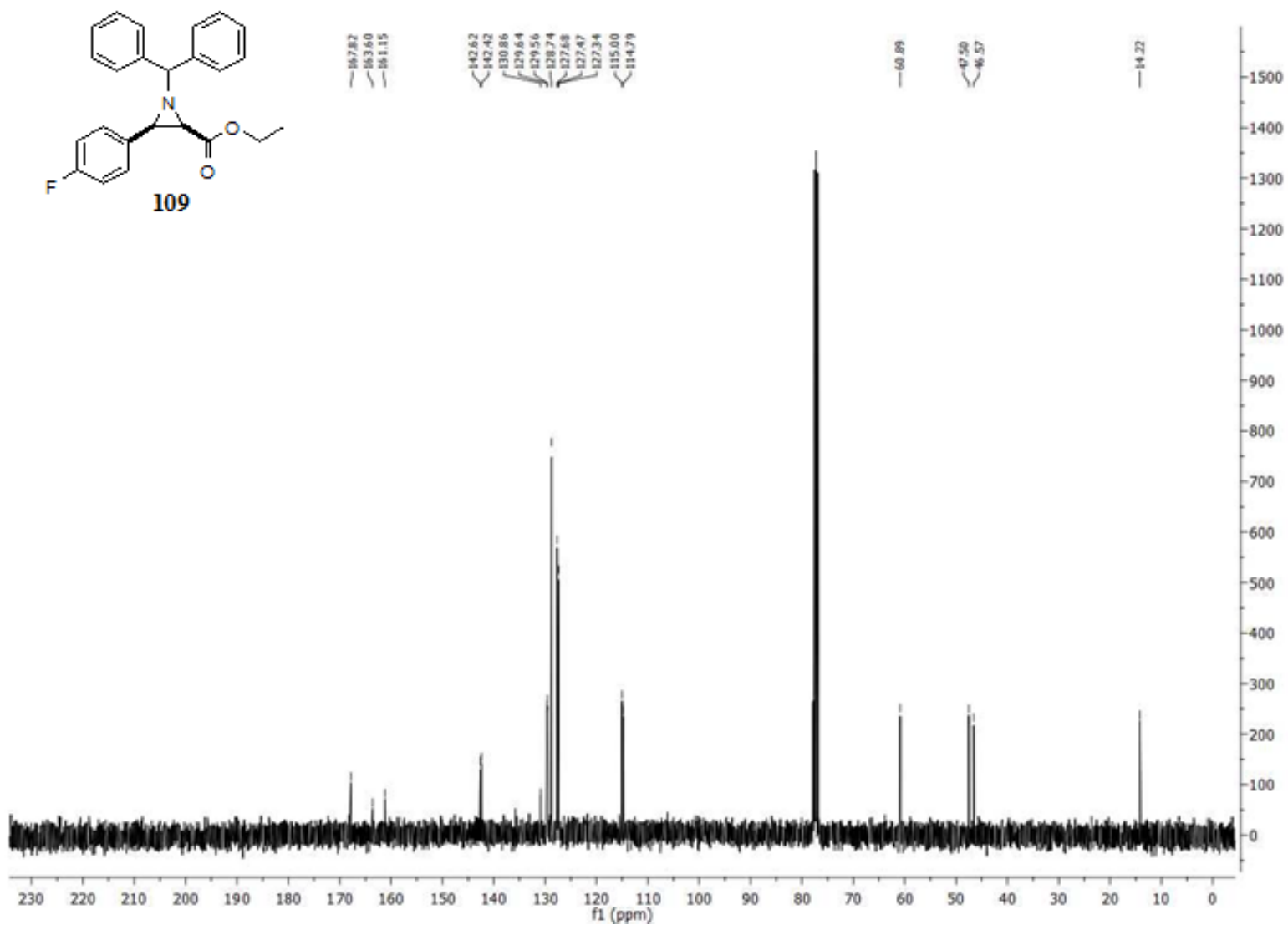
^{13}C -NMR ethyl 1-benzhydryl-3-(4-methoxyphenyl)aziridine-2-carboxylate (400 MHz, CDCl_3)



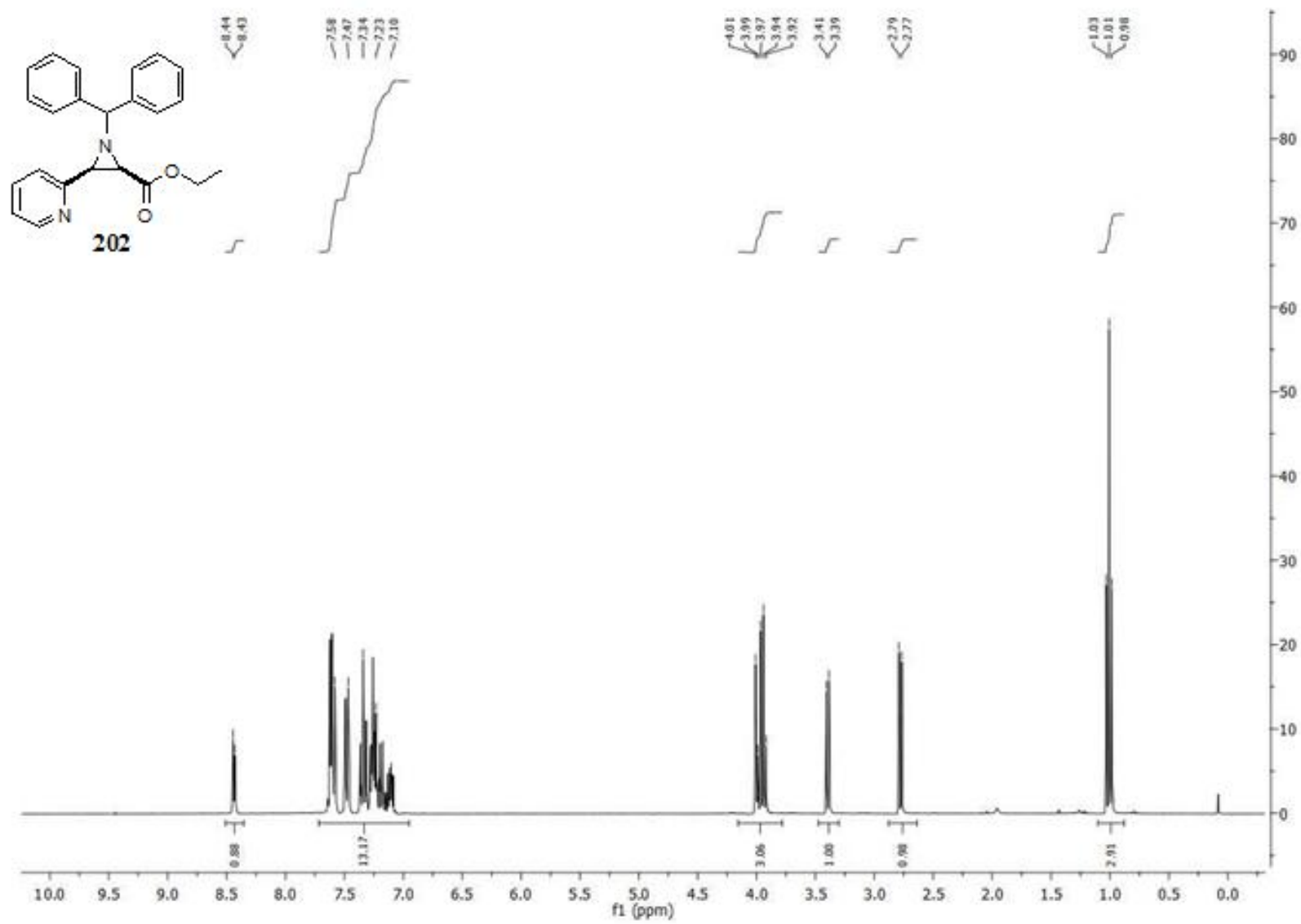
¹H-NMR ethyl 1-benzhydryl-3-(4-fluorophenyl)aziridine-2-carboxylate (400 MHz, CDCl₃)



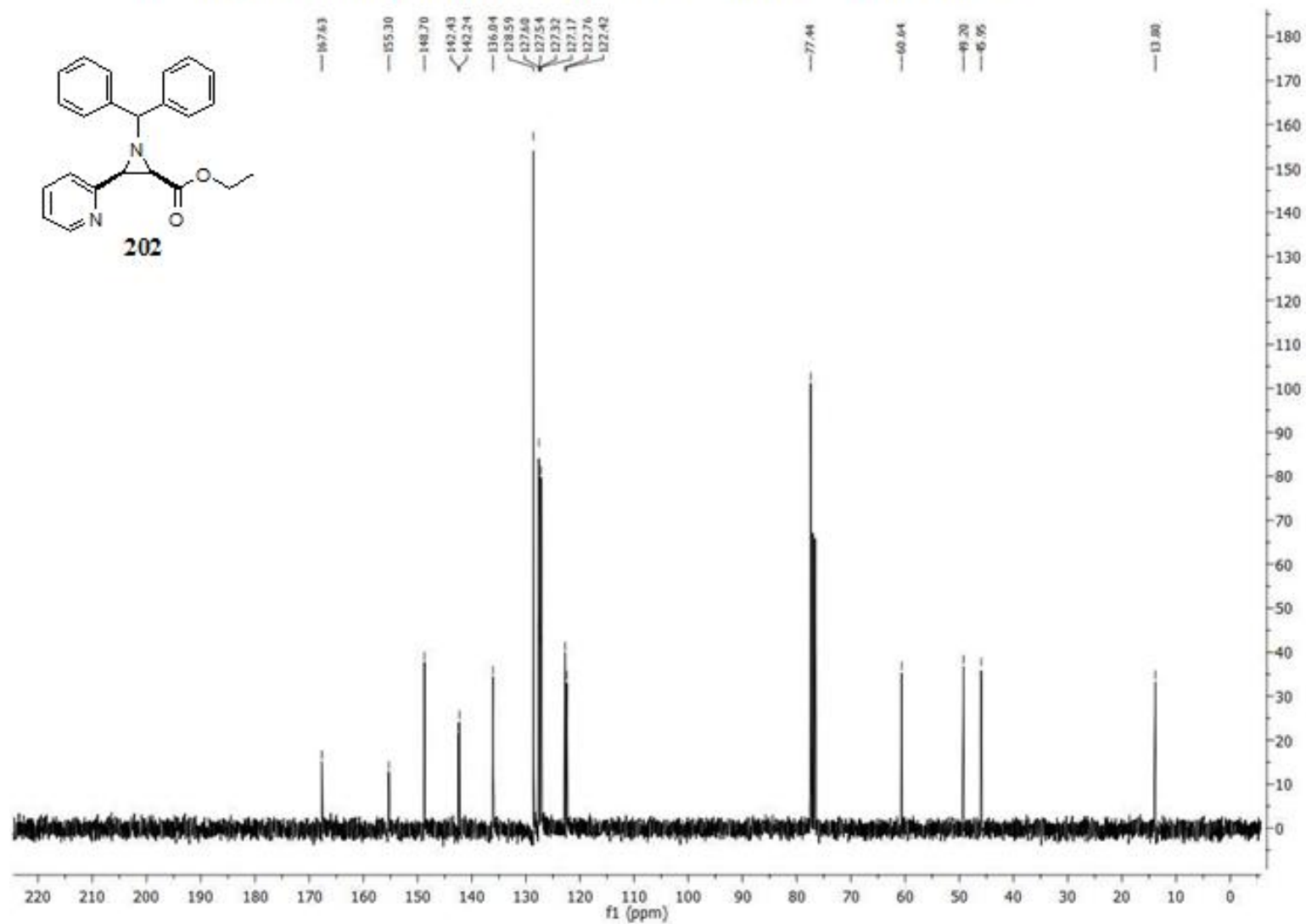
^{13}C -NMR ethyl 1-benzhydryl-3-(4-fluorophenyl)aziridine-2-carboxylate (100 MHz, CDCl_3)



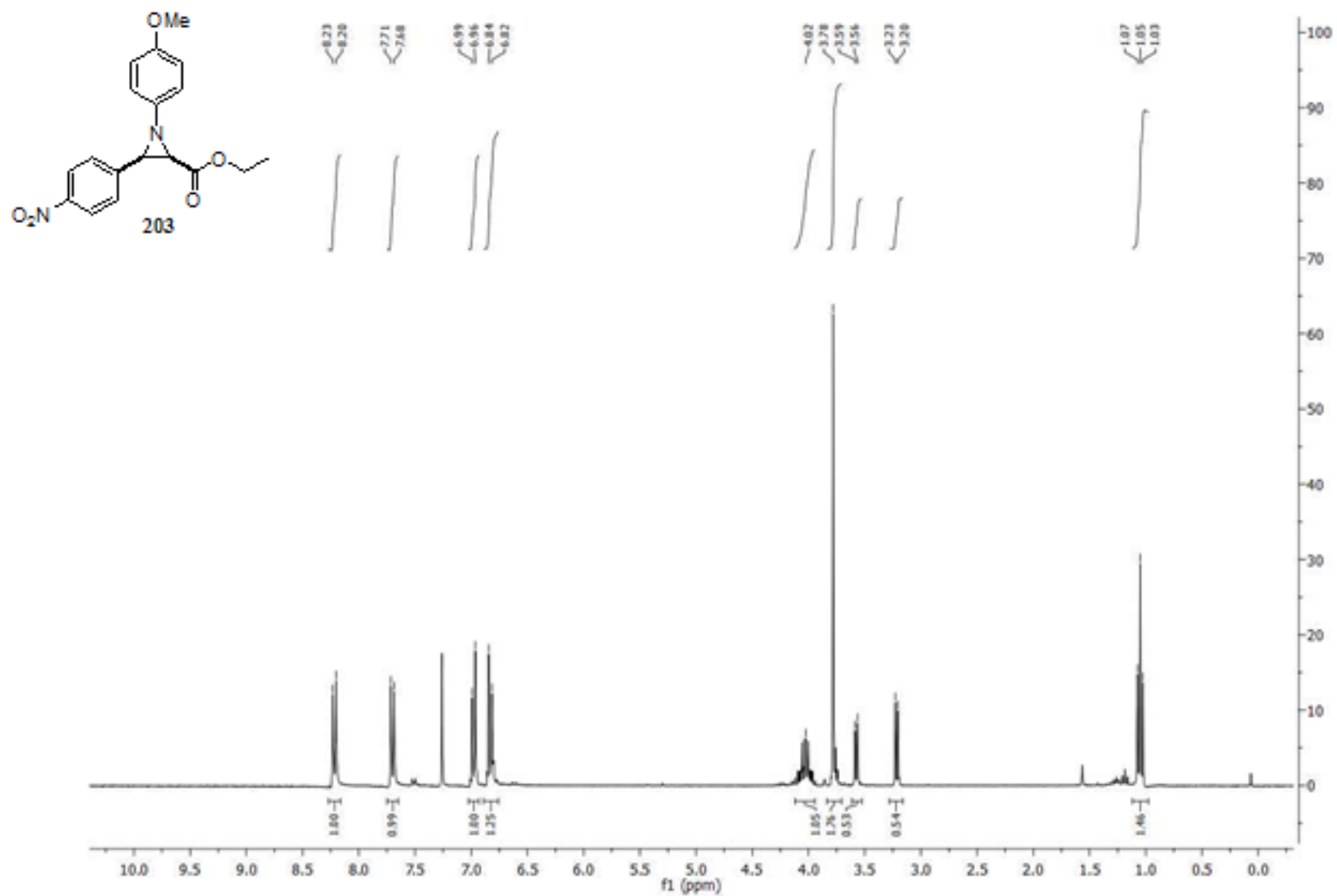
$^1\text{H-NMR}$ ethyl 1-benzhydryl-3-(pyridin-2-yl)aziridine-2-carboxylate (300 MHz, CDCl_3)



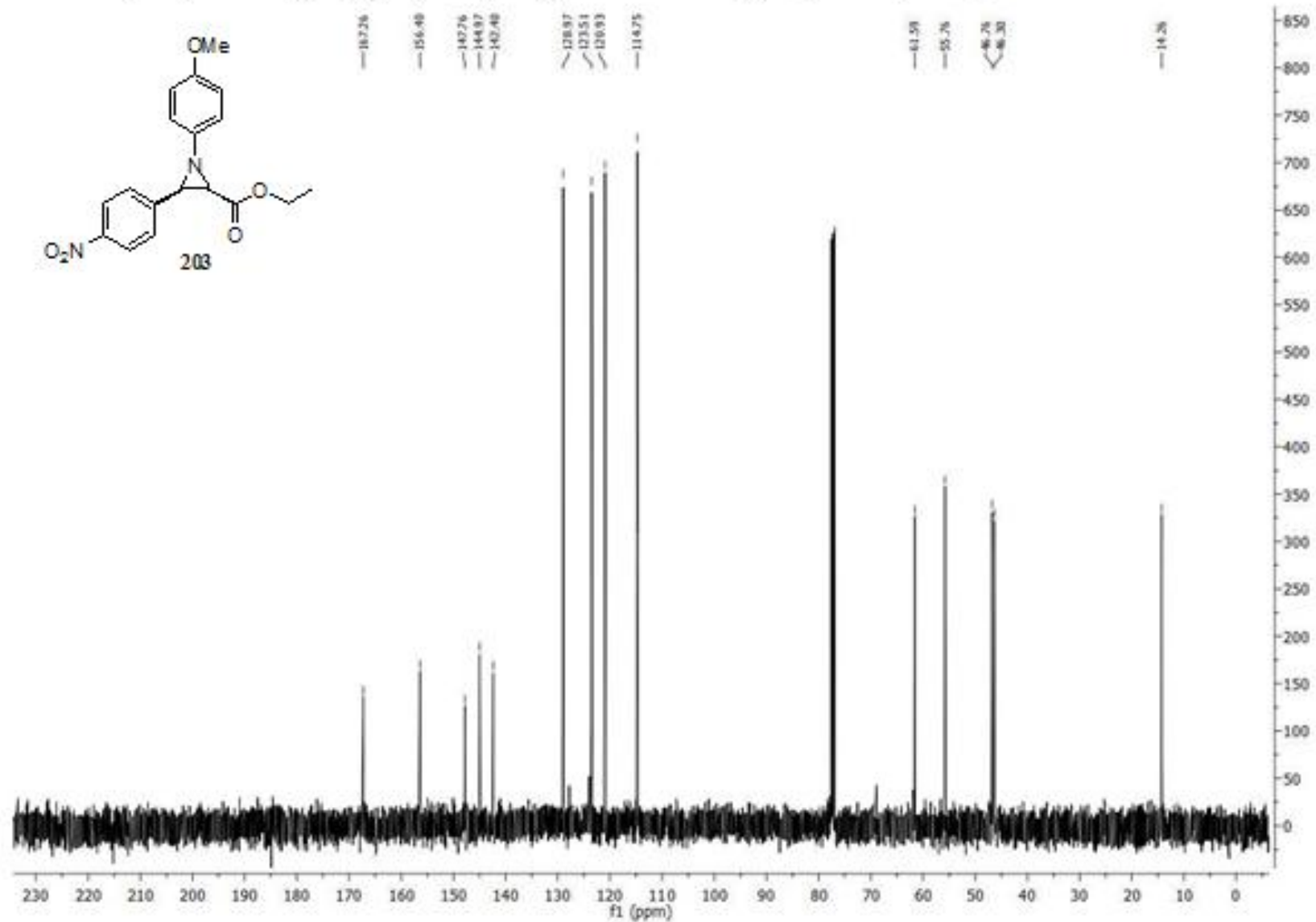
¹³C-NMR ethyl 1-benzhydryl-3-(pyridin-2-yl)aziridine-2-carboxylate (75 MHz, CDCl₃)



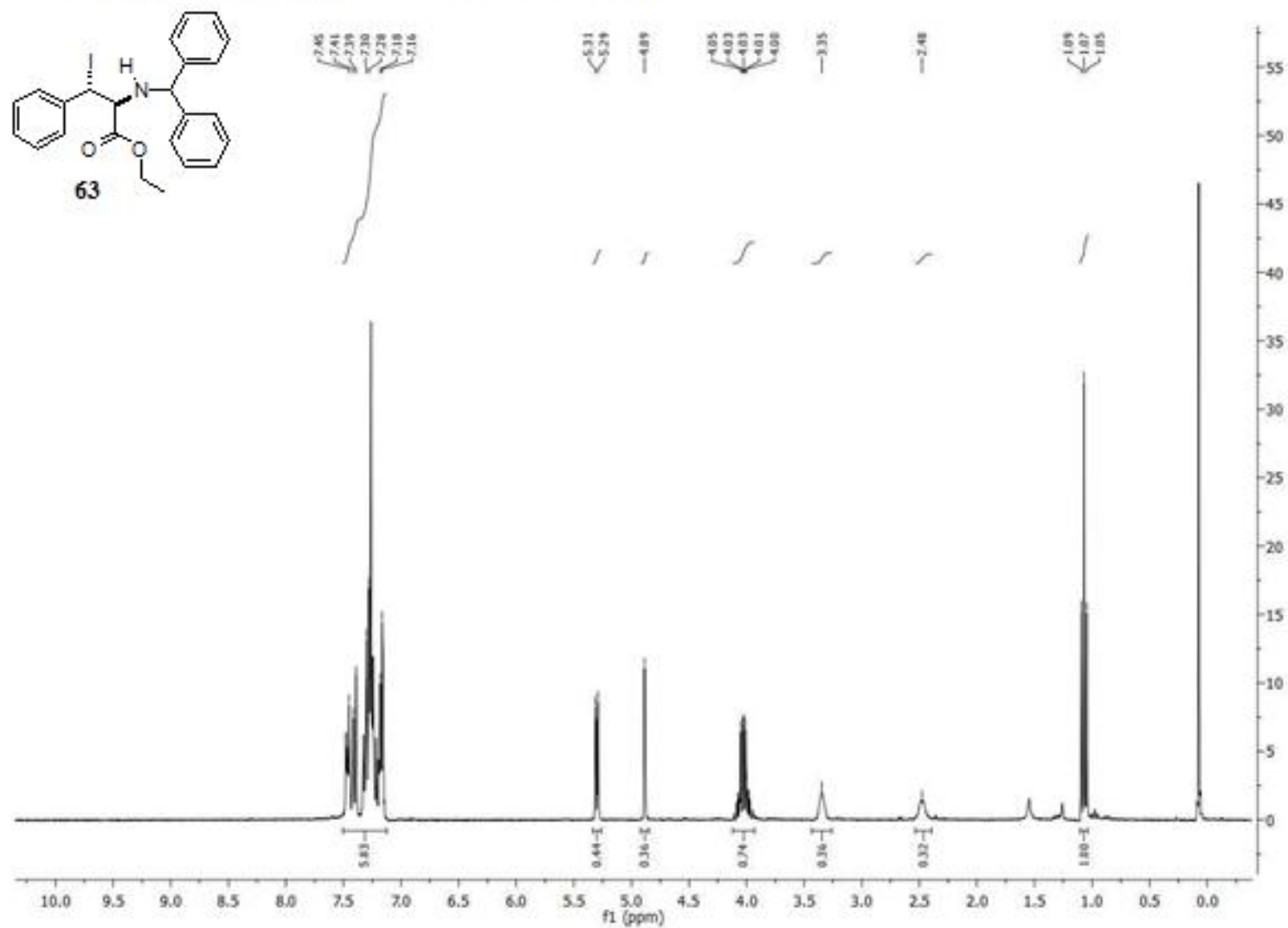
¹H-NMR ethyl 1-(4-methoxyphenyl)-3-(4-nitrophenyl)aziridine-2-carboxylate (300 MHz, CDCl₃)



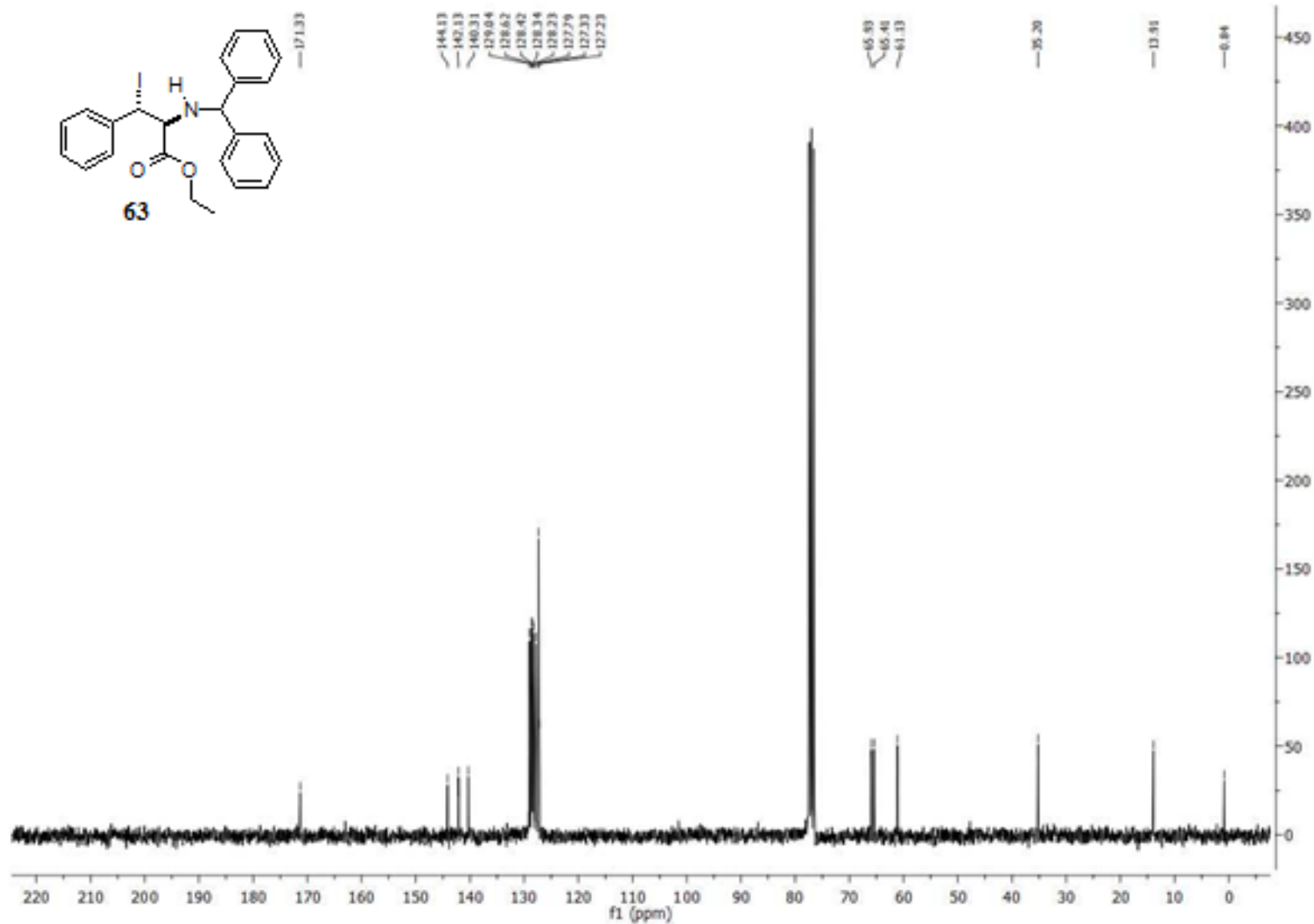
¹³C-NMR ethyl 1-(4-methoxyphenyl)-3-(4-nitrophenyl)aziridine-2-carboxylate (100 MHz, CDCl₃)



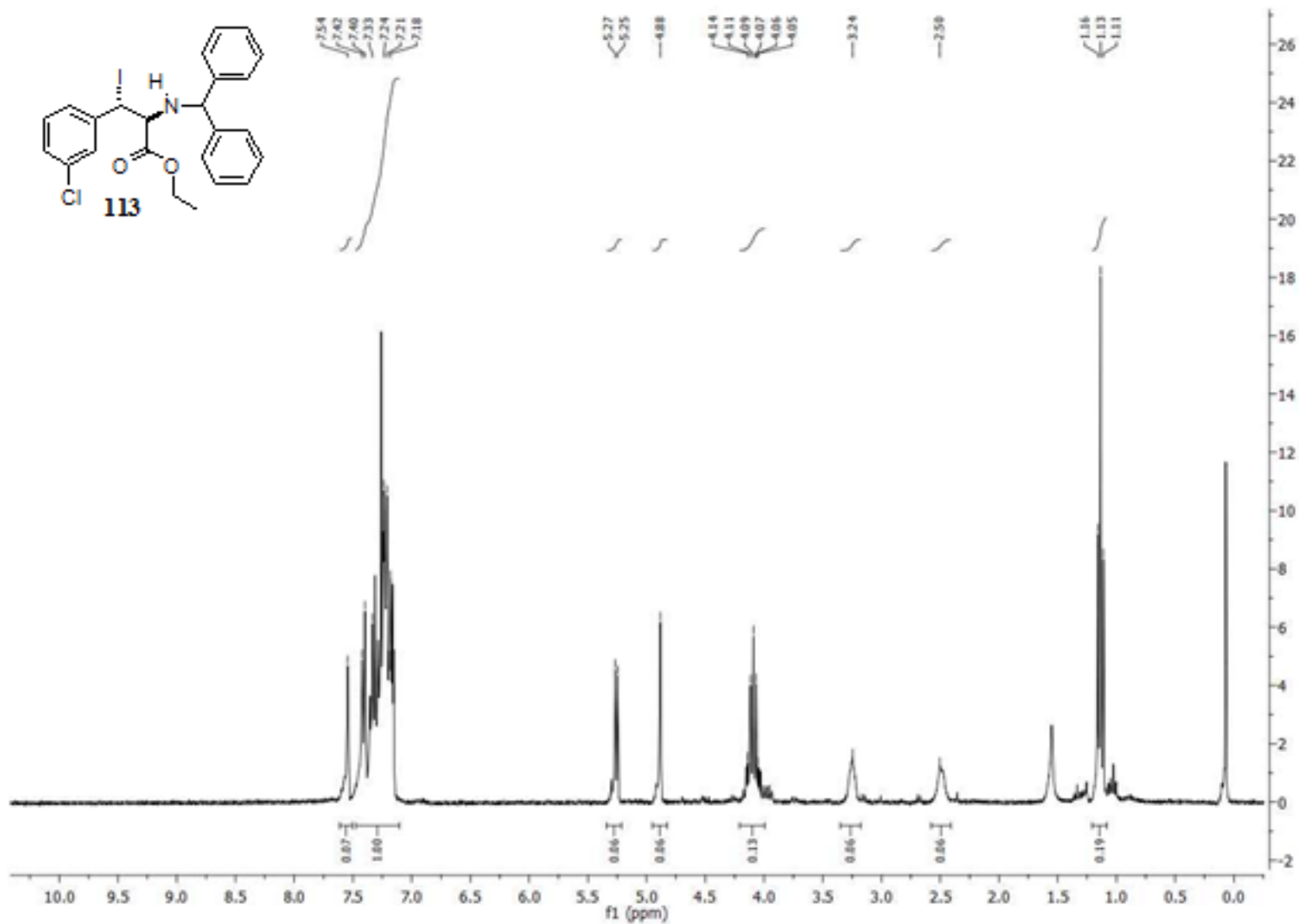
¹H-NMR ethyl 2-(benzhydrylamino)-3-iodo-3-phenylpropanoate (300 MHz, CDCl₃)



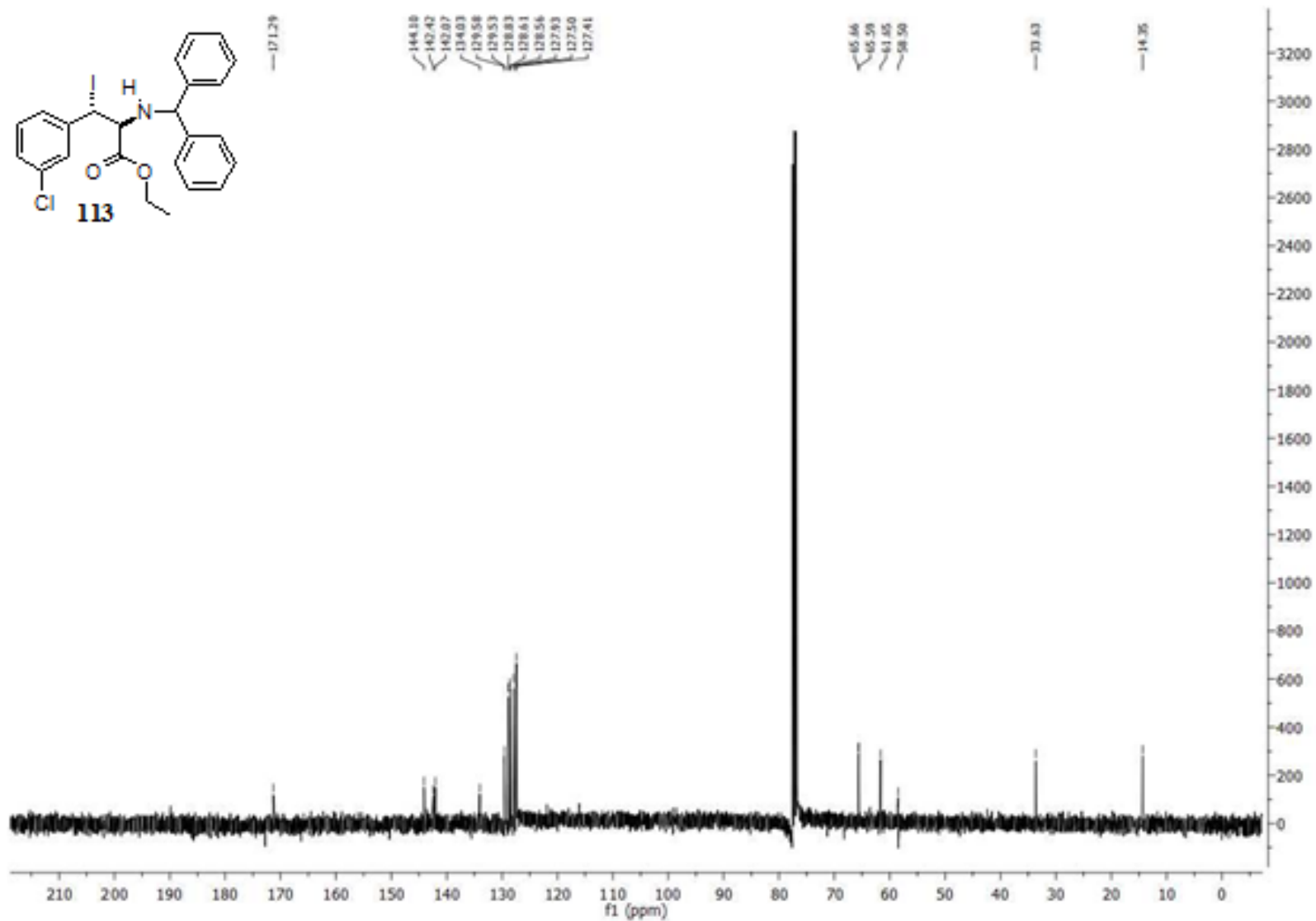
¹³C-NMR ethyl 2-(benzhydrylamino)-3-iodo-3-phenylpropanoate (75 MHz, CDCl₃)



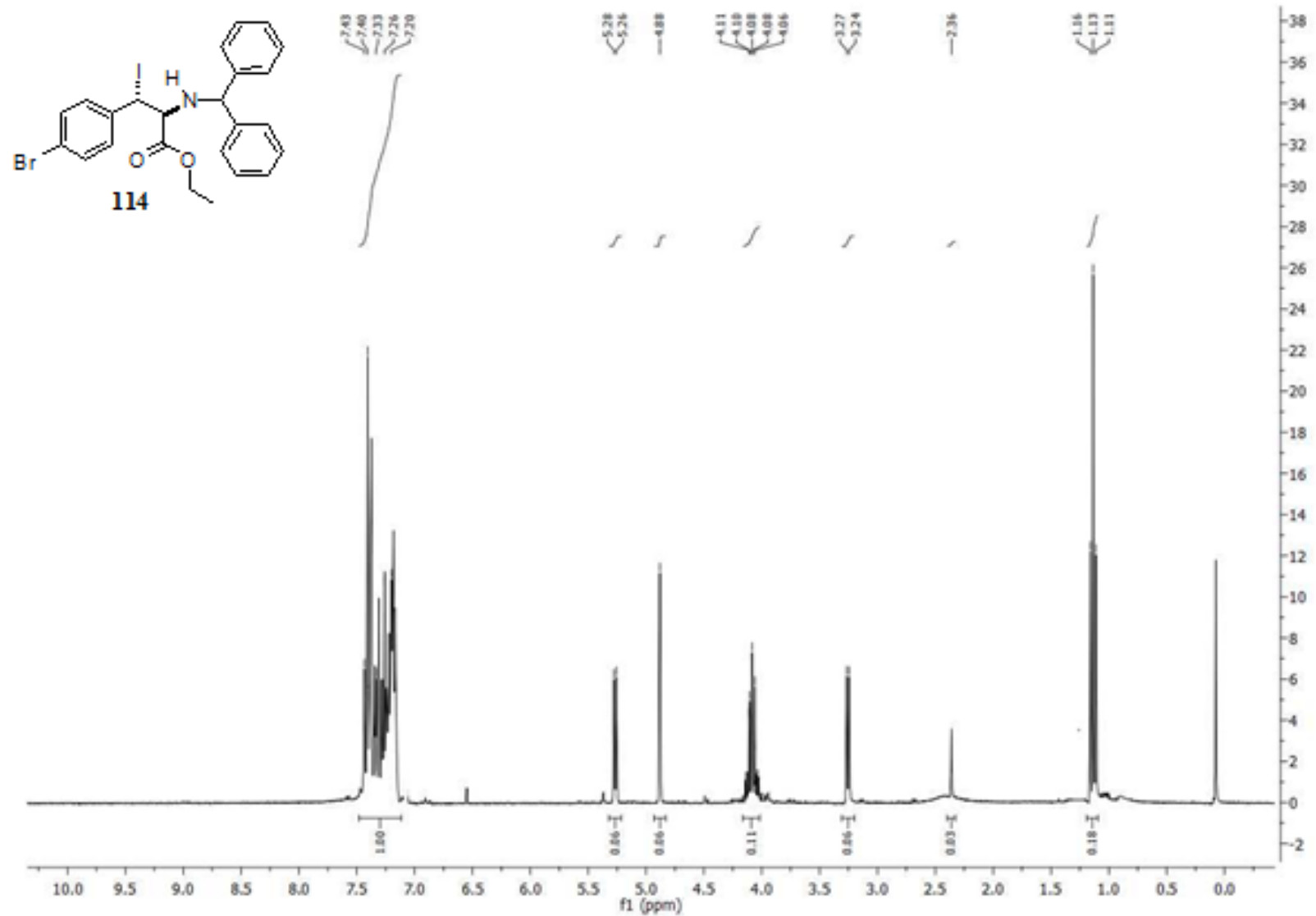
¹H-NMR ethyl 2-(benzhydrylamino)-3-(3-chlorophenyl)-3-iodopropanoate (300 MHz, CDCl₃)



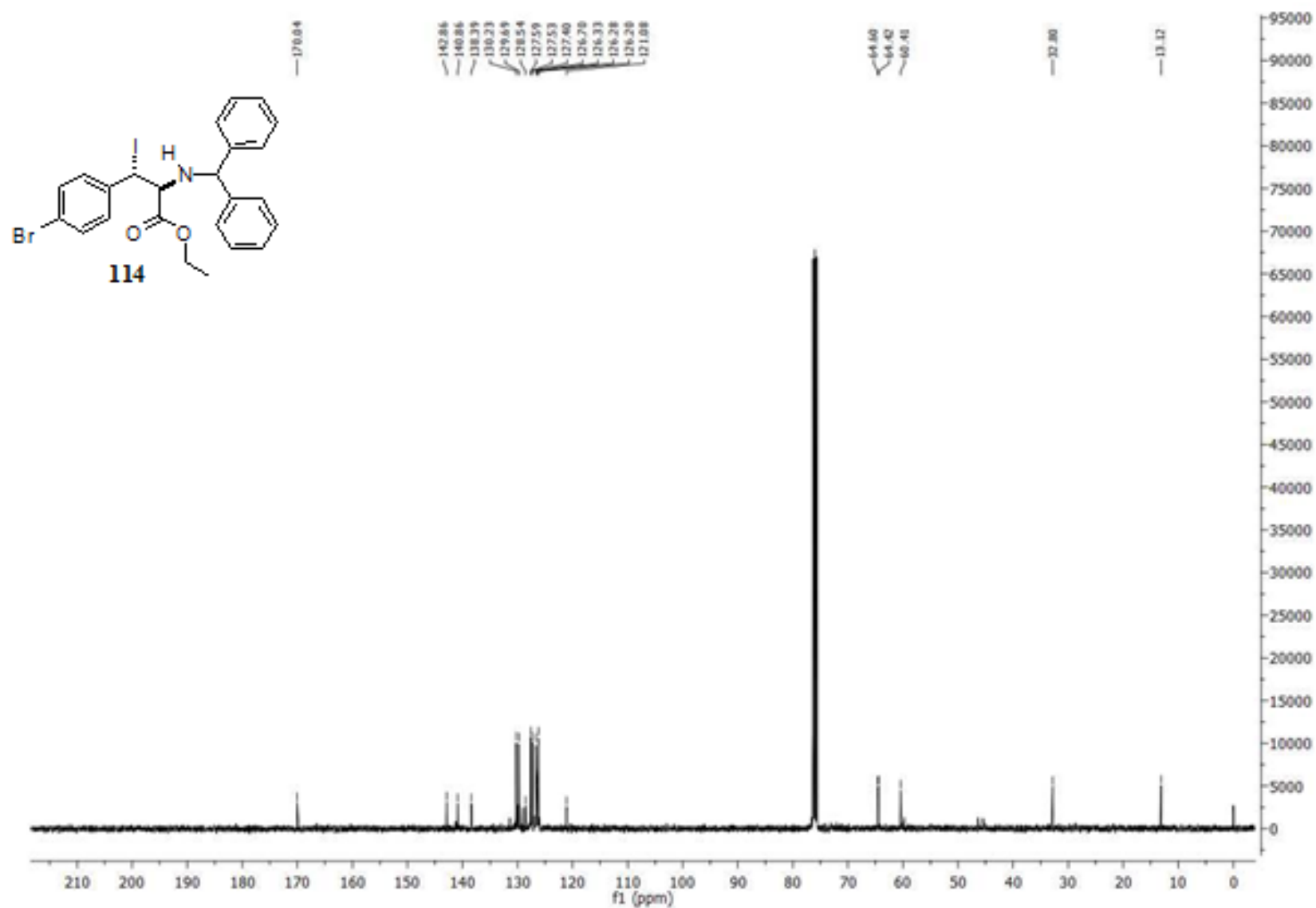
¹³C-NMR ethyl 2-(benzhydrylamino)-3-(3-chlorophenyl)-3-iodopropanoate (100 MHz, CDCl₃)



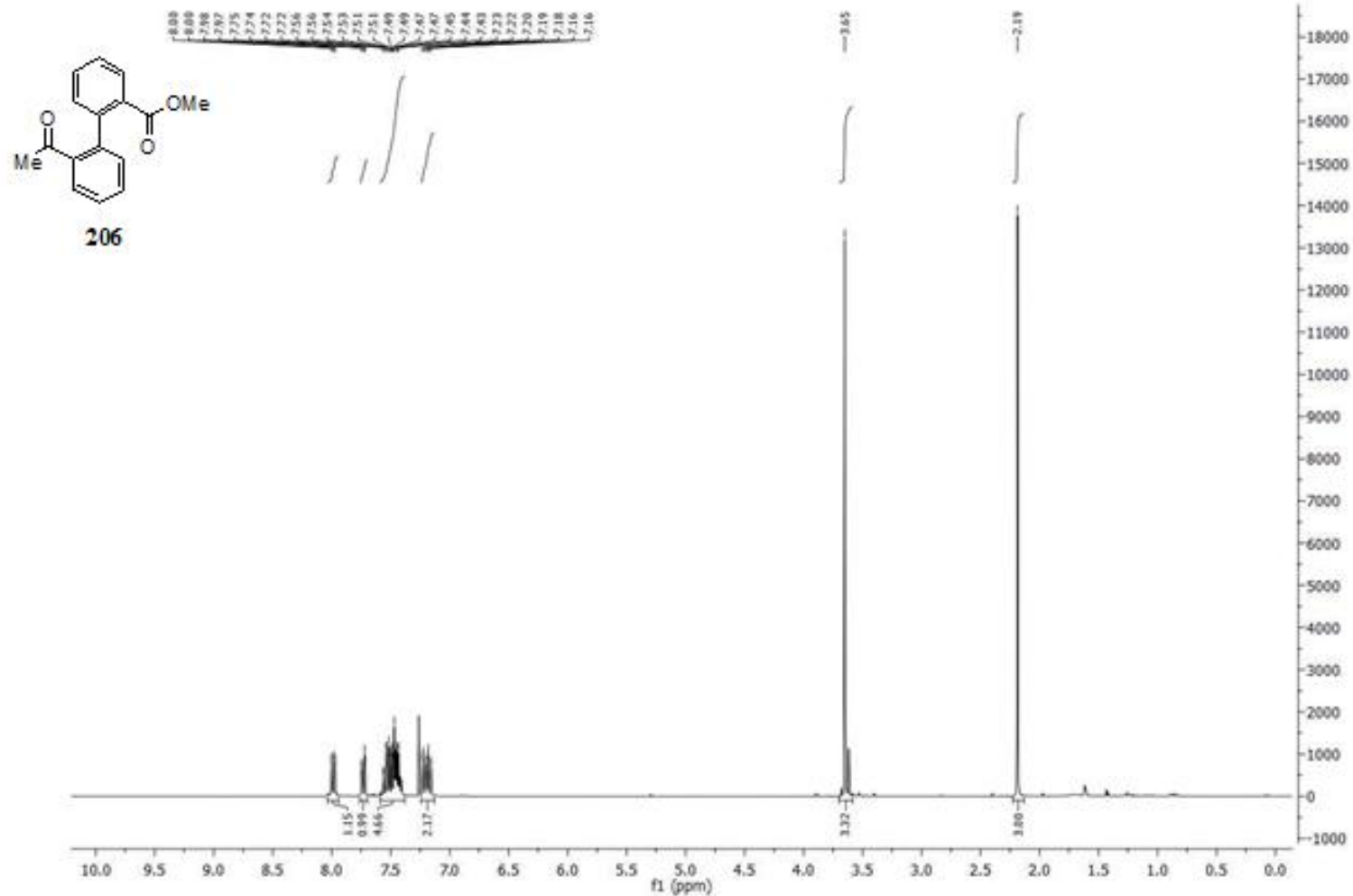
¹H-NMR ethyl 2-(benzhydrylamino)-3-(4-bromophenyl)-3-iodopropanoate (300 MHz, CDCl₃)



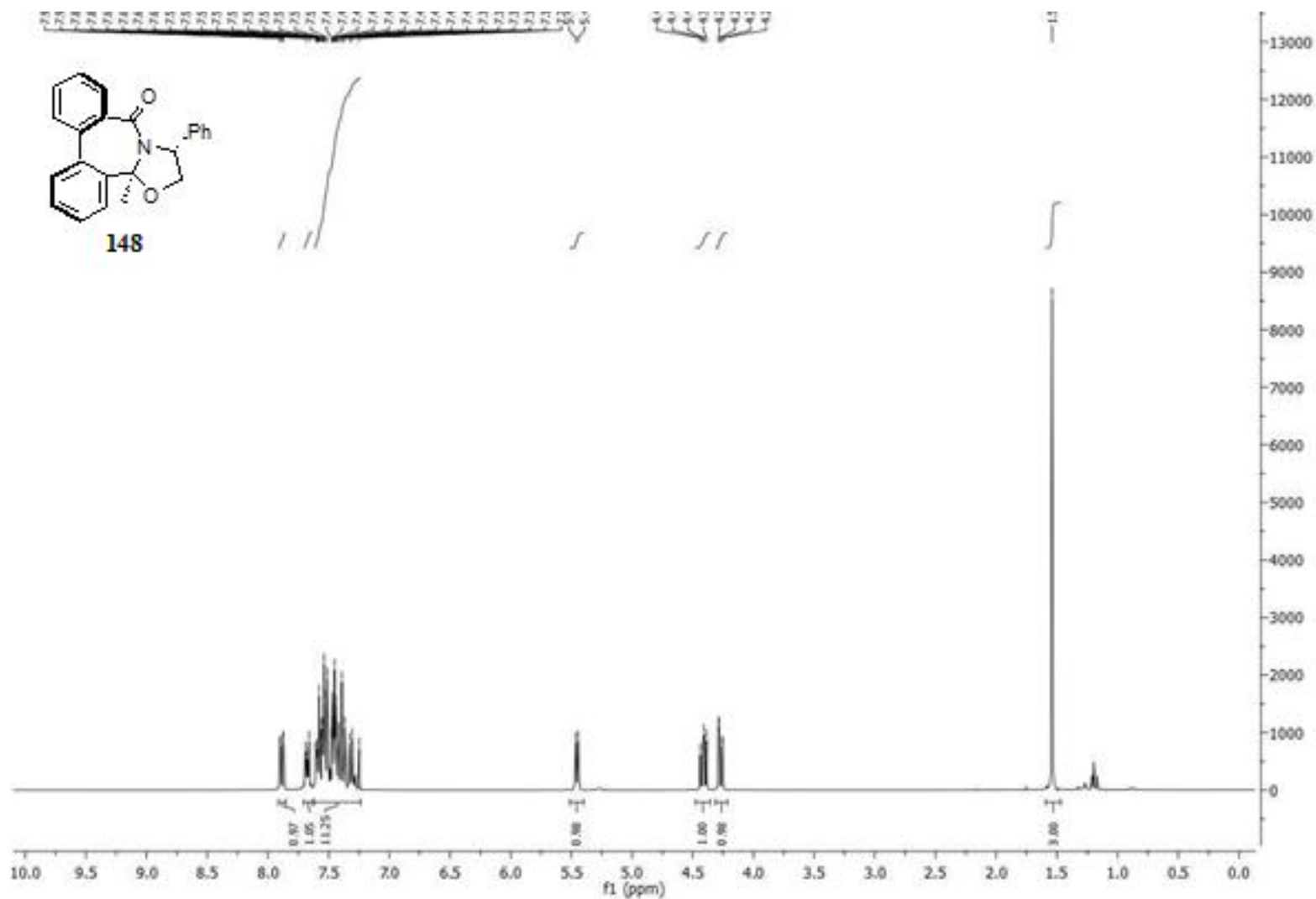
¹³C-NMR ethyl 2-(benzhydrylamino)-3-(4-bromophenyl)-3-iodopropanoate (100 MHz, CDCl₃)



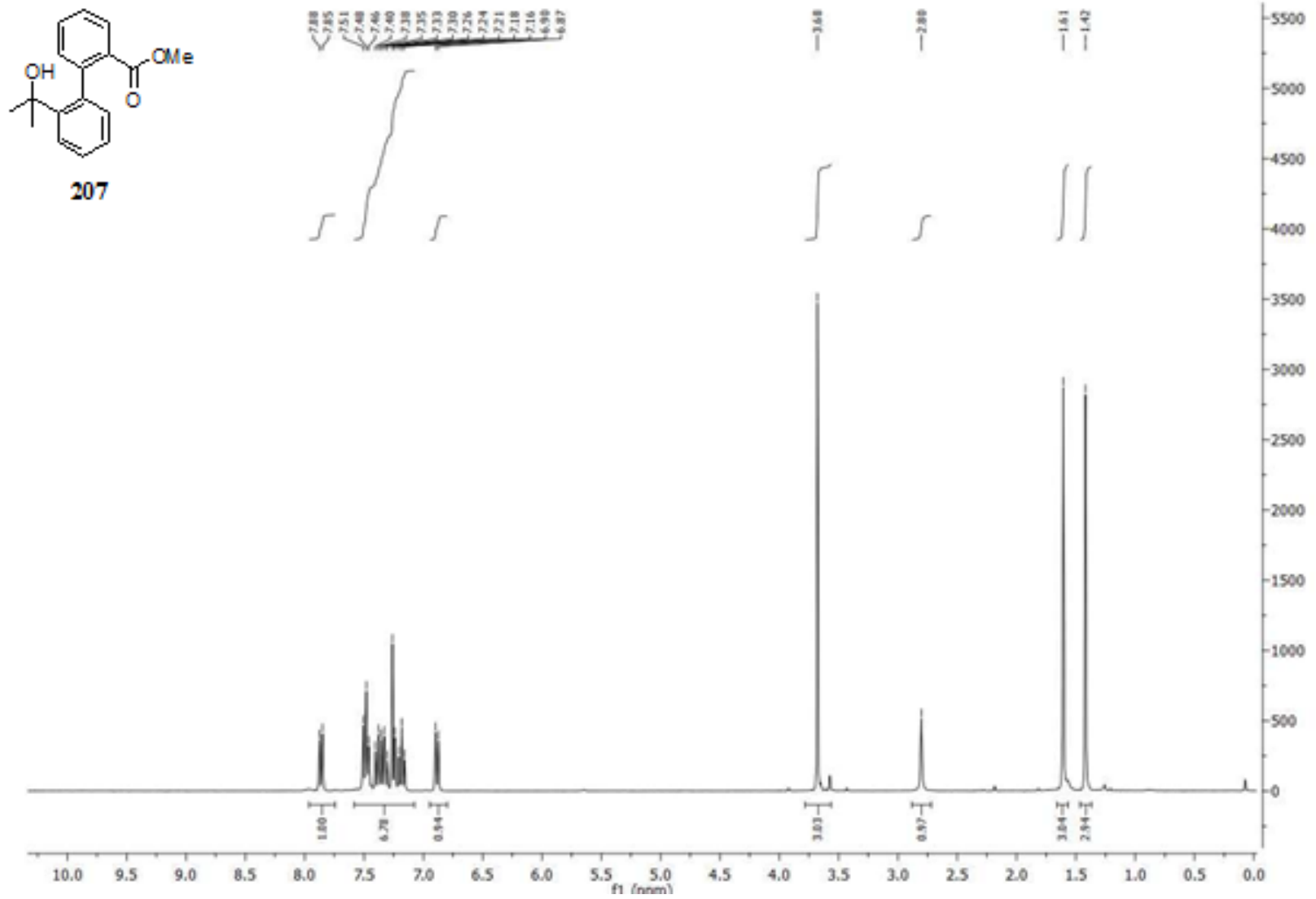
¹H-NMR methyl 2'-acetylphenyl-2-carboxylate (300 MHz, CDCl₃)



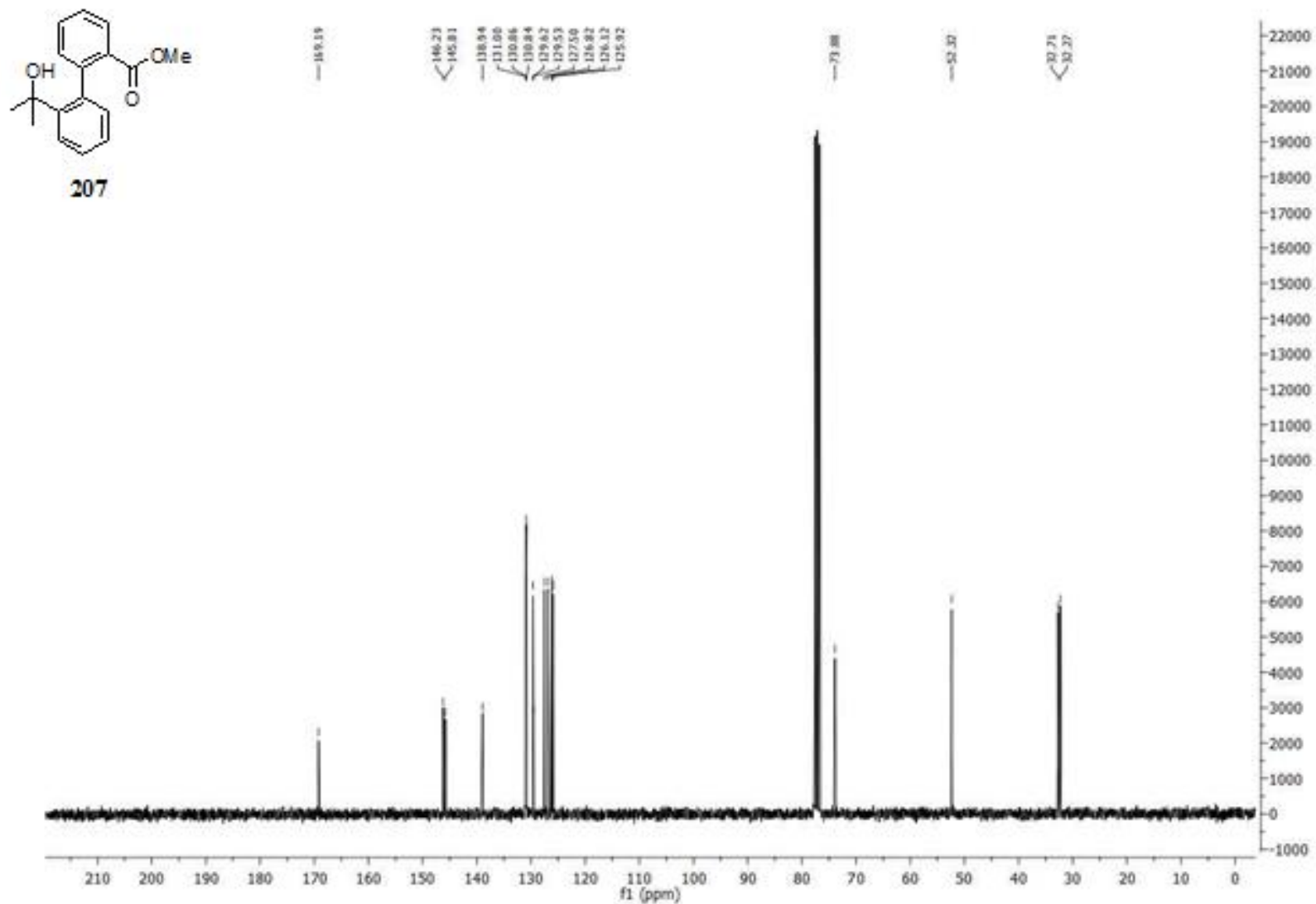
¹H-NMR (4Bs, 7R)-4b-methyl-7-phenyl-6,7-dihydrodibenzo[c, e] oxazolo[3,2-a]azepine-9(4bH)-one (300 MHz, CDCl₃)



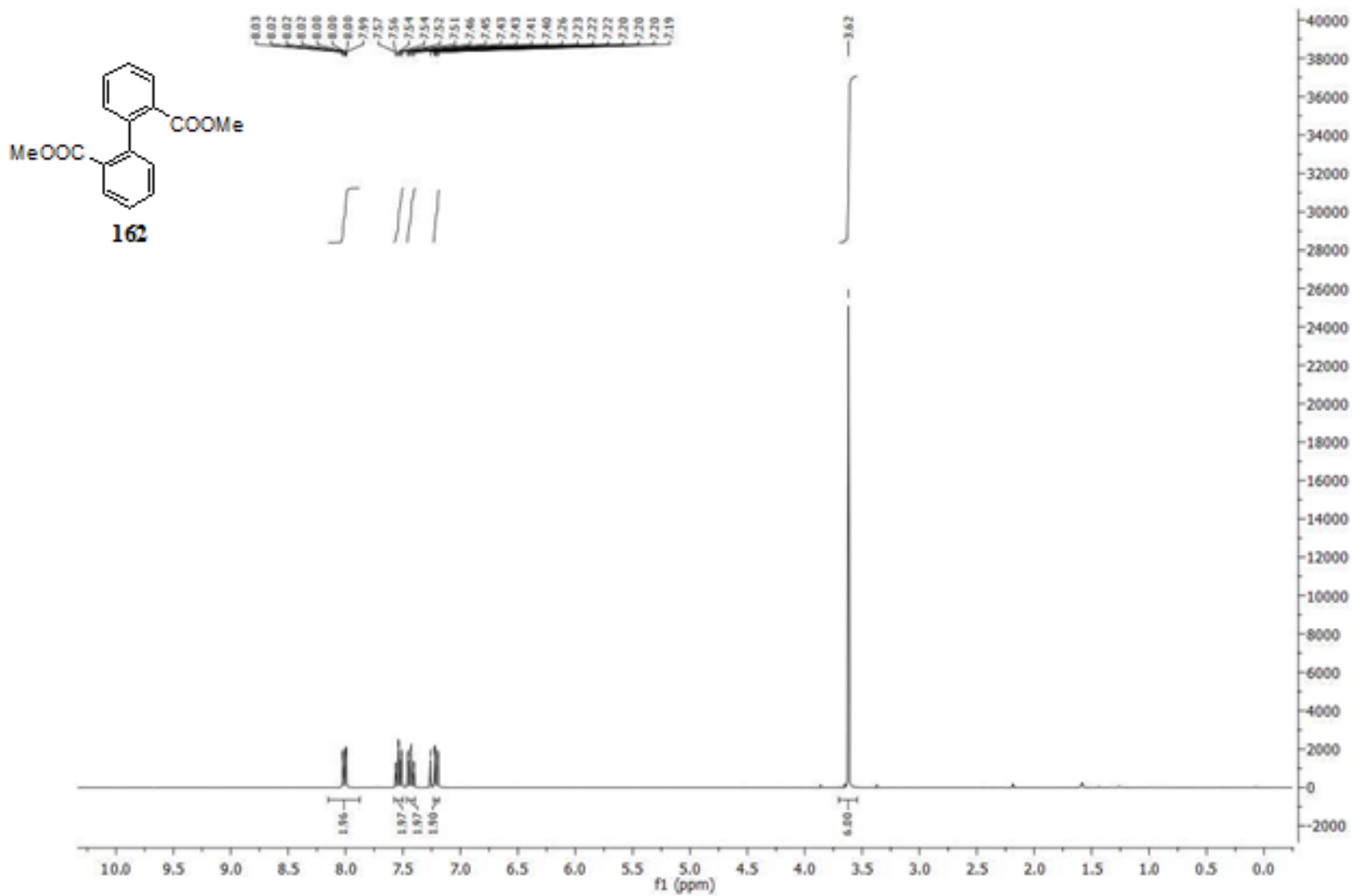
¹H-NMR methyl 2'-(2-hydroxypropan-2-yl)biphenyl-2-carboxylate (300 MHz, CDCl₃)



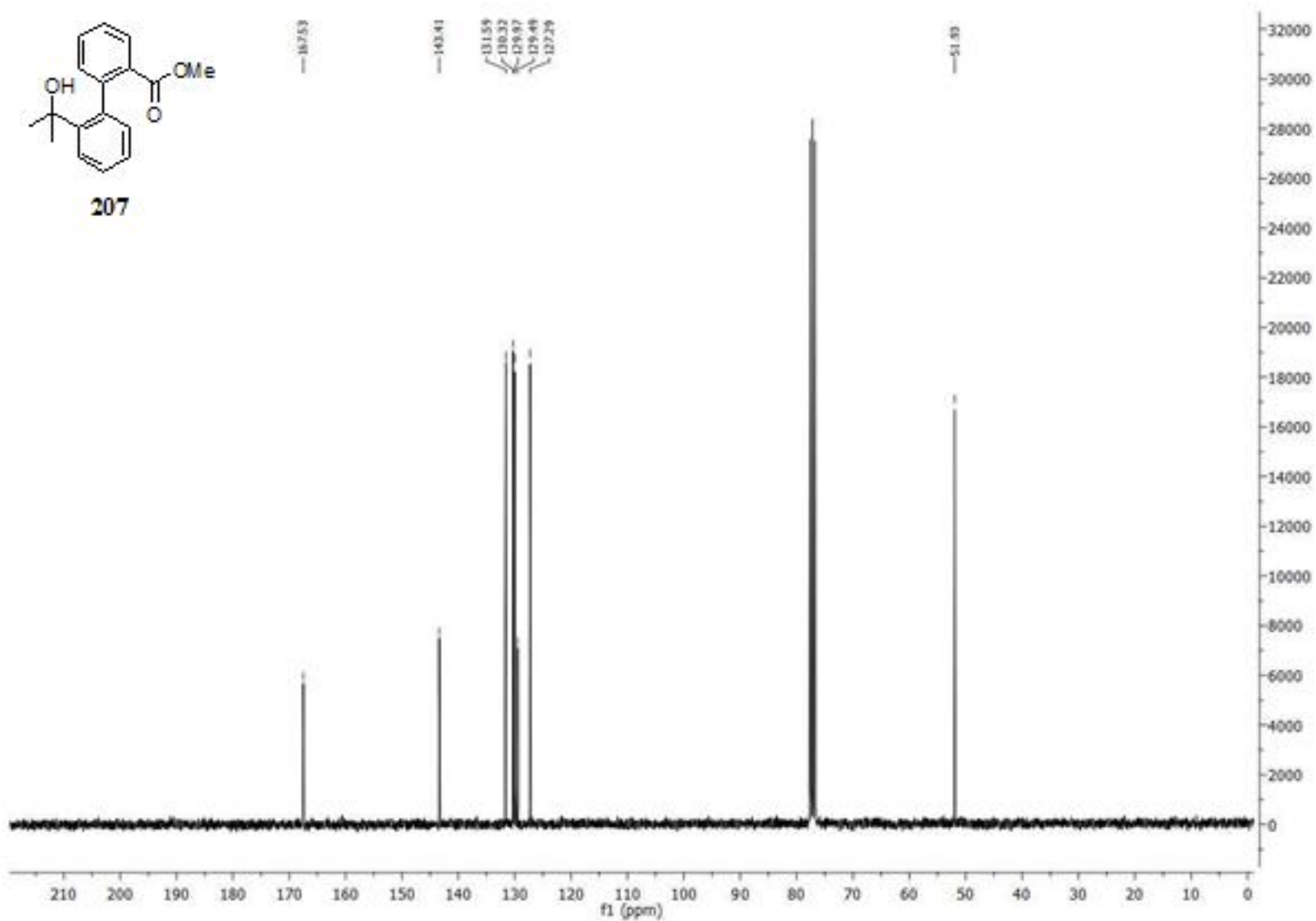
^{13}C -NMR methyl 2'-(2-hydroxypropan-2-yl)biphenyl-2-carboxylate (75 MHz, CDCl_3)



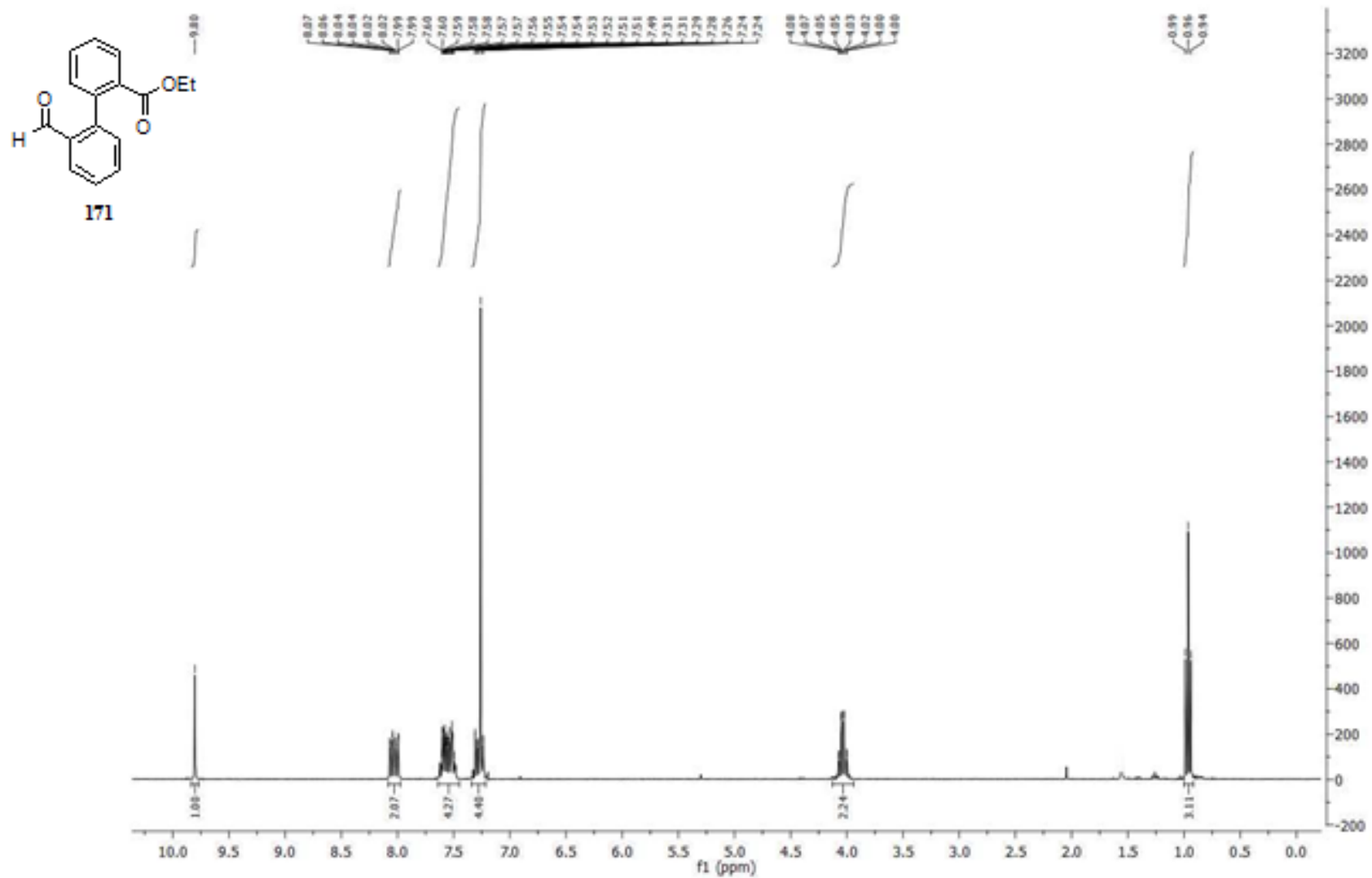
¹H-NMR dimethyl biphenyl-2,2'-dicarboxylate (300 MHz, CDCl₃)



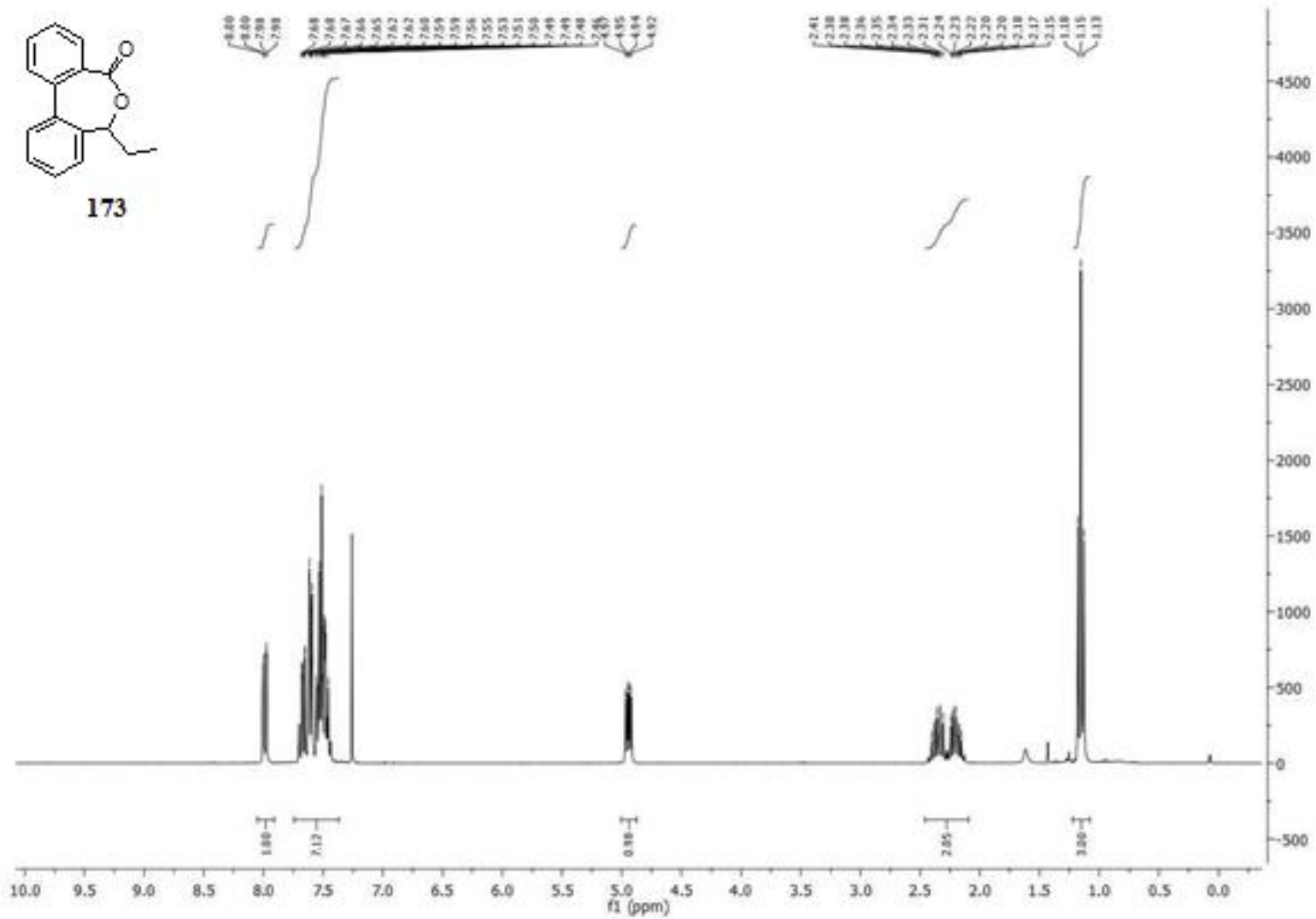
^{13}C -NMR dimethyl biphenyl-2,2'-dicarboxylate (100 MHz, CDCl_3)



¹H-NMR ethyl 2'-formylbiphenyl-2-carboxylate (300 MHz, CDCl₃)



$^1\text{H-NMR}$ 7-ethylidibenzo[*c,e*]oxepin-5(7*H*)-one (75 MHz, CDCl_3)



^{13}C -NMR 7-ethylidibenzo[*c,e*]oxepin-5(7*H*)-one (75 MHz, CDCl_3)

