# Synthetic Explorations into Carbon-Carbon and Carbon-Fluorine Bond Forming Reactions

by

**Khonde Nilesh Shrimant**
**10CC15A26012**

A thesis submitted to the
Academy of Scientific & Innovative Research
for the award of the degree of
DOCTOR OF PHILOSOPHY
in
SCIENCE

Under the supervision of

**Dr. Pradeep Kumar Tripathi**

Co- supervision of

**Dr. Murugan Muthukrishnan**

**CSIR-National Chemical Laboratory, Pune**

Academy of Scientific and Innovative Research
AcSIR Headquarters, CSIR-HRDC campus
Sector 19, Kamla Nehru Nagar,
Ghaziabad, U.P. – 201 002, India

**June-2022**

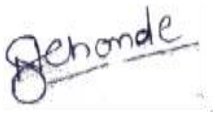
## Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled, *"Synthetic Explorations into Carbon-Carbon and Carbon-Fluorine Bond Forming Reactions"*, submitted by *Khonde Nilesh Shrimant* to the Academy of Scientific and Innovative Research (AcSIR), in partial fulfillment of the requirements for the award of the Degree of *Doctor of Philosophy in Science*, embodies original research work carried-out by the student under my/our supervision/guidance. I/We, further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material(s) obtained from other source(s) and used in this research work has/have been duly acknowledged in the thesis. Image(s), illustration(s), figure(s), table(s) *etc*., used in the thesis from other source(s), have also been duly cited and acknowledged.

| Research Student | Research Supervisor | Research Co-Supervisor |
|---|---|---|
| Mr. Khonde Nilesh S. | Dr. Pradeep Kumar Tripathi | Dr. M. Muthukrishnan |
| Date: 06/06/2022 | Date: 06/06/2022 | Date: 06/06/2022 |

## STATEMENTS OF ACADEMIC INTEGRITY

I, Khonde Nilesh Shrimant Ph.D. student of the Academy of Scientific and Innovative Research (AcSIR) with Registration No. 10CC15A26012 hereby undertake that, the thesis entitled "Synthetic Explorations into Carbon-Carbon and Carbon-Fluorine Bond Forming Reactions" has been prepared by me and that the document reports original work carried out by me and is free of any plagiarism in compliance with the UGC Regulations on *"Promotion of Academic Integrity and Prevention of Plagiarism in Higher Educational Institutions (2018)"* and the CSIR Guidelines for "*Ethics in Research and in Governance (2020)".*



**Signature of the Student**

Date: 06/06/2022
Place: CSIR-NCL, Pune

---

It is hereby certified that the work done by the student, under my supervision, is plagiarism-free in accordance with the UGC Regulations on *"Promotion of Academic Integrity and Prevention of Plagiarism in Higher Educational Institutions (2018)"* and the CSIR Guidelines for "*Ethics in Research and in Governance (2020)".*

**Signature of the Supervisor**

Dr. Pradeep Kumar Tripathi
Date: 06/06/2022
Place: CSIR-NCL, Pune

**Signature of the Co-Supervisor**

Dr. M. Muthukrishnan
Date: 06/06/2022
Place: CSIR-NCL, Pune

*This dissertation is*
*dedicated to*
***-My family and friend-***
*Whose constant love, trust, and*
*support*
*helped me to reach this*
*stage of my life*

# Contents:

Abbreviations
General remarks
Synopsis

## Chapter 1

**_para_-Quinone Methides (_p_-QMs): A building block for the Carbon-Carbon bond forming reactions**

1.1 Introduction
1.2 _p_-Quinone methides: A reactive intermediate in bio-synthesis
1.3 Application of _p_-QMs in the total synthesis of Narciclasine alkaloids
1.4 Reactivity of _p_-QMs towards diverse nucleophiles
1.5 Literature Reports
1.6 Conclusion
1.7 References

## Chapter-2 (section-A)

**$Tf_2NH$ catalyzed 1,6-conjugate addition of 2-hydroxy-_p_-quinone methides with _β_-functionalized ketones: Access to 2,3,4,9-tetrahydro-1_H_-xanthenones and 4_H_-chromene derivatives**

2A.1 Introduction
2A.2 Present Work
2A.3 Results and Discussion
2A.4 Conclusion
2A.5 Experimental Section
2A.6 NMR Data
2A.7 NMR Spectra
2A.8 XRD
2A.9 References

## Chapter-2 (Section-B)

**Metal-free, $Tf_2NH$-Catalyzed 1,6-Conjugate Addition of Imidazopyridine to *para*-Quinone Methides: Easy Access to C3-Functionalized Triarylmethane Imidazopyridine**

2B.1 Introduction
2B.2 Present Work
2B.3 Results and Discussion
2B.4 Conclusion
2B.5 Experimental Section
2B.6 NMR Data
2B.7 NMR Spectra
2B.8 XRD
2B.9 References

## Chapter-3

**Fluorine in organic synthesis: Carbon-Fluorine bond forming reactions**

3.1 Introduction
3.2 Synthesis of organofluorine compounds
3.3 Hydrogen bonding discovery in fluorine chemistry
3.4 Hydrogen bonding promoted $S_N2$ fluorination
3.5 Conclusion
3.6 References

## Chapter-4 (Section-A)

**Tri-*tert*-Butanolamine as an Organic Promoter in Nucleophilic Fluorination**

4A.1 Introduction

4A.2 Present Work
4A.3 Results and Discussion
4A.4 Conclusion
4A.5 Experimental Section
4A.6 NMR Data
4A.7 NMR Spectra of promoters **1**, **2** & **3**
4A.8 NMR Spectra of fluoro compounds
4A.9 References

## Chapter-4 (Section-B)

## Organocatalytic Route to the Enantioselective Synthesis of syn/anti-1,3-Fluoro Amines

4B.1 Introduction
4B.2 Literature Review
4B.3 Present Work
4B.4 Results and Discussion
4B.5 Synthetic Utility
4B.6 Attempted cleavage of N–N bond: Synthesis of 1,3-fluoro amines
4B.7 Conclusion
4B.8 Experimental Section
4B.9 NMR Data
4B.10 NMR Spectra
4B.11 Chiral HPLC Data
4B.12 References

## ACKNOWLEDGMENT

Ph.D. is like a long journey; an experience that takes you through the untraversed path, the green lush meadows and the island of Cyclopes to conquer the final goal fixed in mind. Once you achieve the target and turn back, you realize that all your efforts and the pain were worth going through. The small successes & the serendipitous discoveries, the frustrating failures & unexpected crystallizations, the imparted chemical wisdom & the laboratory camaraderie; they are all important parts of this beautiful voyage. But one can't succeed in this journey without the guidance and support of the research supervisor, co-supervisor, friends, and well-wishers. I am taking this opportunity to express my deepest gratitude to everyone who has helped and supported me throughout the course of my research journey.

First and foremost I would like to express my deep gratitude to my research supervisor, Dr. Pradeep Kumar Tripathi, INSA Sr. Scientist and co-supervisor, Dr. Murugan Muthukrishnan, Principal Scientist for allowing me to carry out this research work, whose expertise, understanding and patience added considerably to my doctoral degree experience. I wish to express my sincere thanks to the Doctoral Advisory Committee members, Dr. K. Krishnamoorthy, Dr. Santosh B. Mhaske and Dr. Utpal Das for thesis contribution in stimulating suggestions and encouragement to co-ordinate my work.

I am grateful to Prof. A. K. Nangia, Dr. Ashish Lele, Director CSIR-NCL, Dr. N. P. Argade (Head, Organic Chemistry Division), Dr. S. P. Chavan (Former Head, Organic Chemistry Division), for giving me this opportunity and providing all necessary infrastructure and facilities to carry out my research work. I specially thank Dr. Madhukar Shyam Said, for continuous valuable suggestions for manuscript writing and thesis correction. I also thank Dr. Ravindar Kontham, Dr. Sandip Shinde and Dr. J. M. Gajbhiye for valuable suggestions in my scientific career.

I would also like to acknowledge Dr. Sunita Barve, Mr. Gati Krushna Nayak and other staff members of the library for all kind of support and for giving access to the library.

I would also like to acknowledge all the support from office staffs of Organic Chemistry, Polymer and Physical and Material Division as well as Mrs. Catherine, Deepika, Rahul, Thangaraj, and Fernandes from OCD for their paperwork & other documentation related assistance.

I wish to express a great sense of gratitude to Dr. Angulwar, Mrs. Khobare, Mrs. Chanale, and all staff member of Dayanand Science College, Latur for their sincere effort and patience in guiding me during my post-graduate studies.

I would like to extend my sincere thanks to Dr. P. R. Rajamohanan and Dr. Udaya Kiran Marelli for their timely help in NMR analysis, Dr. Santhakumari for HRMS facility, Mrs. Sanas for HPLC facility, Mrs. Damase for IR facility, Mr. Sadafule for LC-MS and Dr. Borikar for GC-MS support.

Special thanks must go to my colleagues from NCL Dr. Sagar, Dr. Rohini, Ashok, Pramod, Dinesh, Nitai, Shubhangi, Ashwini, Priyanka, Hemant, Vinod, Umeshawari, Akash, Sangram, Dr. Mahesh, Balasaheb, Amit, Junaid, Meghana, Dr. Digambar, Mahendra, Dr. Popat, Satish, Kishor, Somanath, Datta, Madhukar, Abhijeet, Dr. Govinda, Dr. Nitin, Dr. Anupam, Dr. Namita, Jagjivan, Sazia, Dr. Dhananjay, Nagesh, Kailash, Dr. Abdul, Nirshad, Asish, Dr. Sayantan, Megha, and Balaji. I would also like to thank my friends, Nitin Gapat, Manoj Kshirsagar, Prashant Vetal, Tushar, Ganesh, Ramesh, Manoj, Shirish, Anant, Mujammil, Uday, Nitin, Prakash, Sopan, Rajendra, Jayant, Gajanan, Amol, Prithviraj, Sagar, Appasaheb, Rameshwar and Mayur.

I specially, thank my lab mates Dr. Brijesh, Dr. Jayant, Dr. Shruti, and Dr. Krishanu for helping in my Ph.D. I also would like to thank my summer trainees Vanshika Sharma, Supriya Sinha, and Satish Ajabe.

My family is always a source of inspiration and a great moral support for me in pursuing my education. I owe a lot to my beloved parents who encouraged and helped me at every stage of my personal and academic life and longed to see this achievement come true. Also I want to thank my sister, brother for their support in critical situations. Words fail for me to express my appreciation to my wife for her unconditional love and persistent confidence in me, has taken the load off my shoulder.

In conclusion, this research would not have been possible without the financial support of Council of Scientific and Industrial Research (CSIR), New Delhi and Academy of Scientific and Innovative Research (AcSIR).

I wish to thank the great scientific community whose achievements are a constant source of inspiration for me. Above all, I extend my gratitude to the Almighty God for giving me the wisdom, health, and strength to undertake this research work and enabling me to its completion.

Thank you all…!!!

Yours Sincerely

**Nilesh S. Khonde**

**Units**

| | |
|---|---|
| °C | Degree centigrade |
| mg | Milligram |
| h | Hour |
| Hz | Hertz |
| µg | Microgram |
| µL | Microlitre |
| mL | Millilitre |
| min | Minutes |
| MHz | Megahertz |
| mmol | Millimole |
| nm | Nanometre |
| ppm | Parts per million |

**Chemical Notations**

| | |
|---|---|
| Ac | Acetyl |
| AcOH | Acetic acid |
| $Ac_2O$ | Acetic anhydride |
| Ar | Aryl |
| MeCN | Acetonitrile |
| *n*-BuLi | *n*-Butyl lithium |
| DMAP | N,N'-Dimethylaminopyridine |
| $Et_2O$ | Diethyl Ether |
| *t*-BuOH | *tert*-Butyl alcohol |
| DCE | 1,2-Dichloroethane |
| MeOH | Methanol |
| $CDCl_3$ | Deuterated chloroform |
| $CD_3OD$ | Deuterated methanol |
| DDQ | 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone |
| Me | Methyl |
| Ph | Phenyl |
| DMF | N, N'-Dimethylformamide |
| EtOH | Ethanol |
| Et | Ethyl |

| | |
|---|---|
| EtOAc | Ethyl acetate |
| THF | Tetrahydrofuran |
| $LiBH_4$ | Lithium borohydride |
| $NaBH_4$ | Sodium borohydride |
| DBU | 1,8-Diazabicyclo 5.4.0 undec-7-ene |
| LiBr | Lithium bromide |
| DBAD | Dibenzyl azodicarboxylate |
| CsF | Cesium fluoride |
| $Et_3N$ | Triethylamine |
| *i*Pr | Isopropyl |
| *t-Bu* | *tert*-Butyl |
| KO*t*Bu | Potassium *tert*-butoxide |
| $K_2CO_3$ | Potassium carbonate |
| DMSO | Dimethyl sulfoxide |
| NFSI | N-Fluorobenzenesulfonimide |
| IMPY | Imidazo 2-*a*- pyridine |
| TBAF | Tetrabutylammonium Fluoride |
| *p*-QMs | *p*-Quinone methides |
| $Tf_2NH$ | Triflimide |

**Other Notations**

| | |
|---|---|
| calcd | Calculated |
| $\delta$ | Chemical shift |
| *J* | Coupling constant |
| equiv. | Equivalents |
| ESI | Electrospray ionization Mass spectrometry |
| HRMS | High Resolution Mass Spectrometry |
| IR | Infra-Red |
| m/z | Mass-to-charge ratio |
| mp | Melting Point |
| NMR | Nuclear Magnetic Resonance |
| rt | Room temperature |

## General remark

- $^{1}H$ and $^{13}C$ NMR analyses were done with Bruker 200 MHz, 400 MHz, and 500 MHz spectrometers. Chemical shift is expressed in ppm relative to TMS, using the residual solvent peak of deuterated solvents as a reference. Coupling constants calculated in Hertz. To represent the splitting pattern of NMR signal following abbreviations are used s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad. All deuterated solvents were used as received.
- Melting points were recorded on Buchi M-535, M-560 melting point apparatus by open capillary, are uncorrected and the temperature measured in degree centigrade.
- All reactions were monitored by Thin-layer chromatography (TLC) with 0.25mm pre-coated silica gel on aluminium sheets 20 x 20cm, Silica gel 60 $F_{254,}$ Merck grade, using various visualizing agents such as UV light, Iodine adsorbed on silica gel, ethanolic solution of phosphomolybdic acid (PMA), *p*-anisaldehyde or $KMnO_4$ followed by heating with a hot air gun for ~15 sec.
- All solvents and reagents were purified and dried according to documented procedures.
- All reactions were performed under an inert atmosphere using nitrogen or argon gas.
- The synthesized compounds were purified by column chromatography using silica gel (100–200 or 230–400 mesh size).
- Chemical name (IUPAC) and structures were drawn using ChemDraw Professional 15.1 software.
- The compounds, schemes, figures and table numbers given in each section of chapter refer to the particular section of chapter only.
- $^{19}F$ NMR was recorded on 376 MHz Bruker spectrometer with $^{1}H$–$^{19}F$ decoupled.
- All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such without further purification.

| | |
|---|---|
| **Synopsis of the Thesis to be submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Science** | |
| **Name of the Candidate** | **Mr. Khonde Nilesh Shrimant** |
| **Degree Enrollment No. & Date** | **Ph. D. in Science, 10CC15A26012, August 2015** |
| **Title of the Thesis** | **Synthetic Explorations into Carbon-Carbon and Carbon-Fluorine Bond Forming Reactions** |
| **Research Supervisor** | **Dr. Pradeep Kumar Tripathi** |
| **Research Co-Supervisor** | **Dr. Murugan Muthukrishnan** |

**Introduction**

The thesis mainly focus on exploration into carbon-carbon bond forming reactions through $Tf_2NH$ catalyzed 1,6-conjugate addition of 2-hydroxy-*p*-quinone methides with *β*-functionalized ketones, allows xanthenones and chromenes to be accessed in moderate to excellent yield with broad substrate scope and metal-free, $Tf_2NH$-catalyzed 1,6-conjugate addition of imidazopyridine to *para*-quinone methides, provides a diverse class of C3-functionalized triarylmethanes heterocyclic derivatives of imidazopyridine with a high yield within a short duration. We also investigated the carbon-fluorine bond forming reactions through tri-*tert*-BuOH amine organic promoter catalyzed nucleophilic fluorination of alkylsulfonates and alkyl halides with primary and secondary good leaving groups with cesium fluoride (CsF) in protic *tert*-BuOH solvent at 80 $^{o}$C and further developed Hayashi-Jørgensen organocatalyst promoted fluorination towards an organocatalytic route to the enantioselective synthesis of syn/anti-1,3-fluoro amines, affording excellent enantioselectivity and diastereoselectivity of 1,3-fluoro amines. The work demonstrated in this thesis has been divided into four chapters as described below.

**Statement of Problem**

To assist nucleophilic fluorination, various alkyl quaternary ammonium fluoride reagents have been developed for better solubility of fluoride ion in reaction. Despite good solubility of those reagents, some aspects of it concerning stability, moisture sensitivity, and by-product alkene formation issues need to be still addressed. The use of alkali metal fluorides has been limited due to their low solubility in organic media, thus reaction is usually performed under the presence of phase transfer catalyst (PTC), such as macrocyclic crown ethers, macrobicyclic cryptands, polydentate ligands, ionic liquids and oligoethylene glycols (PEG). However, some of the PTC's are quite expensive and their preparation requires lengthy procedure and it is also sometimes difficult to extract polar products from IL/PEG.

**Objectives**

To explore carbon-carbon bond formation through the reaction of hydroxy substituted *para*-quinone methides and *β*-functionalized cyclic ketones and also through the reaction of *para*-quinone methides and imidazopyridine using Brønsted acid $Tf_2NH$ catalyst which is known to activate the carbonyl group of *para*-quinone methides under metal-free and mild reaction conditions. We also wish to explore carbon-fluorine bond formation through reaction of alkylsulfonates and alkyl halides with cesium fluoride in presence of synthesized tri-*tert*-butanol amine organic promoter **1** in *tert*-BuOH at

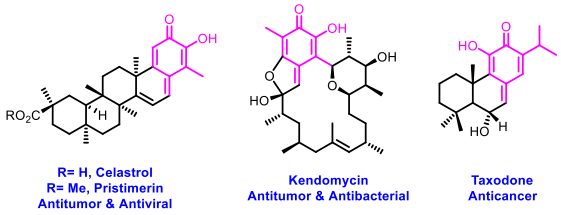
80 $^{o}$C and further explore the proline based Hayashi-Jørgensen catalyzed organocatalytic route to the enantioselective synthesis of syn/anti-1,3-fluoro amines for carbon-fluorine bond formation.

**Methodology**

***Working Chapter-1: para*-Quinone methides (*p*-QMs): A building block for the Carbon-Carbon bond forming reactions**

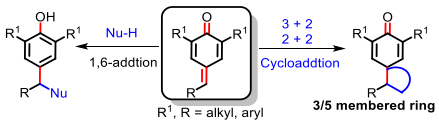
*p*-Quinone methides and their derivatives are common constituents of various biological systems. It could be formed by the degradation of tyrosine and ultimately to *p*-Cresol. *p*-Quinone methides play an important role as a reactive intermediate in the biosynthesis of lignin in plants. Various quinone methides core containing natural products show prominent biological activities. The quinone methide core ultimately responsible for the cytotoxins effects can be used as antitumor drugs, antibiotics, and DNA alkylators. *p*-Quinone methide core containing triterpenoid Celastrol and Pristimerin (the methyl ester of Celasterol) exhibits important pharmacological activity such as antioxidants (15 times more potent than α-tocopherol), anti-inflammatories, anticancer, insecticidal and antiviral activities. Other natural products like Kendomycin and Taxodone display anticancer and antibacterial activities.

**Figure: 1**




*p*-Quinone methide, the transient intermediate plays an important role as a Michael acceptor and gives conjugate addition with nucleophiles. Inspiring from nature, to explore the unprecedented reactivity, scientists have developed the stable isomer of *p*-QMs and studied the various type of reactions using a variety of nucleophiles and catalysts.

**Scheme: 1**



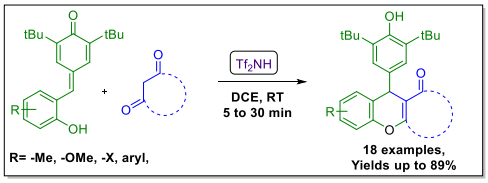

***Working Chapter-2***

***Section A:* $Tf_2NH$ catalyzed 1,6-conjugate addition of 2-hydroxy-*p*-quinone methides with *β*-Functionalized Ketones: Access to 2,3,4,9-Tetrahydro-1*H*-xanthenones and 4*H*-Chromene Derivatives**

In recent years, the *p*-quinone methides (*p*-QMs) have aroused great interest in the synthetic community due to their unique reactivity as powerful Michael acceptors with a variety of nucleophiles and ability to make complex architectures that are found in several pharmaceuticals and natural products. Structurally, *p*-QMs are regarded as neutral molecules with zwitterionic resonance entities. The *p*-QMs have the ability to undergo several reaction modes [4+2]-annulations, [3+2]-annualtion, and [2+1]-annulations. Due to the aromatization driving force of the cyclohexadiene moiety, *p*-QMs have been widely employed as 1,6-addition acceptors. *p*-QMs serve as an important intermediate in biosynthetic transformations, although this strategy would provide an efficient method for constructing cyclic scaffolds. In this section, a Brønsted acid catalyzed tandem 1,6-conjugate sequential cycloaddition reaction using 2-hydroxy-*p*-quinone methides and *β*-functionalized ketones is reported. The method allows xanthenones and chromenes to be accessed in

moderate to excellent yield with broad substrate scope, which could be further functionalized to give a versatile set of products.

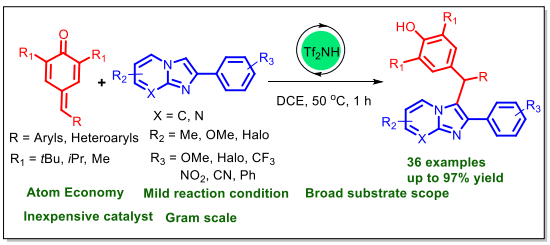
**Scheme: 2**




***Section B:*** **Metal-free, $Tf_2NH$-Catalyzed 1,6-Conjugate Addition of Imidazopyridine to *para*-Quinone Methides: Easy Access to C3-Functionalized Triarylmethane IMPY**

Nitrogen-containing triarylmethanes (TAMs) heterocyclic scaffold has attracted a great deal of interest amongst medicinal and synthetic chemist's world-wide due to its versatile application in medicinal chemistry. Such types of heterocyclic scaffolds are known to exhibit various biological activities including aromatase inhibitors, antifungal and anticancer etc. This has led to the development of number of drugs currently available in the market. *para*-Quinone methides (*p*-QMs) are one of the most powerful 1,6-Michael acceptors widely used to construct the diverse class of substituted aryl heterocyclic derivatives. Our group has developed the conjugate addition of allenol ester and butenolides to *para*-quinone methides to construct the biarylmethanes. In recent years, various heterocyclic nucleophiles are used for the construction of triarylmethane heterocyclic scaffolds using *para*-quinone methides *via* 1,6-conjugate addition using various Lewis acid/Brønsted acid catalysts. Heterocyclic nucleophiles including imidazole, indole, coumarin, oxindole, naphthols, are the few examples. More recently, Anand and co-workers developed bis(amino)cyclopropenium salt catalyzed 1,6-conjugate addition of indole to *p*-QMs. Imidazopyridine (IMPY) containing moiety shows various biological applications, having very broad application in pharmaceutical and agrochemical industries. These nitrogen-containing heterocyclic scaffolds exist in several natural products and drug molecules. To improve the pharmacokinetic properties of an imidazopyridine, various functional group transformations were developed on the C3 position. As a result number of C3-functionalized IMPY containing drug molecules are utilized in day-to-day life. In this section, an inexpensive and commercially available $Tf_2NH$-catalyzed 1,6-conjugate addition of imidazopyridine (IMPY) heterocycles to *para*-quinone methides (*p*-QMs) is reported. The present transformation provides a diverse class of C3-functionalized triarylmethanes heterocyclic derivatives of imidazopyridine. The given reaction protocol assumes significance with regard to atom economy, mild reaction condition. These metal-free transformations provided a very broad substrate scope of conjugate addition product with a high yield up to 97% within a short duration.

**Scheme: 3**



***Working Chapter-3:*** **Fluorine in organic synthesis: Carbon-Fluorine bond forming reactions**

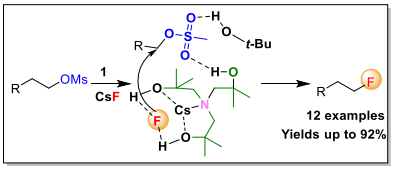
Replacement of hydrogen by fluorine in organic molecules significantly enhances the bioactivity due to the unique properties of fluorine. The element has several intriguing features such as lipophilicity, and high electronegativity. Its small size minimizes structural change resulting into the low steric perturbation and stability of the compounds. Thus the incorporation of fluorine into a bioactive molecules can assist in the development of both pharmacokinetic and pharmacodynamic properties. In radiopharmaceuticals longer half-life (110 min.) of radionuclide fluorine (F-18) has attracted more interest among the other radionuclides due to its vast application in development of imaging agents for positron emission tomography (PET). In addition, fluorinated compounds are used to investigate the biosynthetic pathway.

***Working Chapter-4***

***Section A:*** **Tri–*tert*-Butanolamine as an Organic Promoter in Nucleophilic Fluorination**

To assist nucleophilic fluorination, various alkyl quaternary ammonium fluoride reagents have been developed for better solubility of fluoride ion in reaction. Despite good solubility of those reagents, some aspects of it concerning stability, moisture sensitivity, and by-product alkene formation issues need to be still addressed. The alkali metal salts are abundant in nature, water soluble with reasonable stability. The water solubility of metal salts is very beneficial from a practical point of view, since it is easily washed after reaction during the work-up process. Thus alkali metal fluoride is considered as favorite fluoride source in industry for fluorination. Despite these advantages their use has been limited due to low solubility in organic media. Thus reaction is usually performed under the presence of phase transfer catalyst (PTC), such as macrocyclic crown ethers, macrobicyclic cryptands, polydentate ligands, ionic liquids and oligoethylene glycols (PEG) facilitating the solubility of alkali metal fluorides to generate active fluorine and thus accelerate the rate of reaction significantly. However, some of the PTC's are quite expensive and their preparation requires lengthy procedure and it is also sometimes difficult to extract polar products from IL/PEG. To overcome these problems the protic solvents such as *tert*-BuOH, *tert*-amyl acohol are found suitable media for nucleophilic fluorination using CsF. The [mim-$^{t}$OH][OMs] containing *tert*-OH and imidazolium IL, acts as an efficient catalyst in the nucleophilic substitution reactions. The [mim-$^{t}$OH][OMs] not only enhances the reactivity of metal fluoride but also provides the chemoselectivity of product compared to the other protocols. The bifunctional ionic liquid has the combined synergistic effect of IL and *tert*-OH group in the $S_N2$ fluorination. We hypothesized that such a process can also occur in the simple alkylamine containing *tert*-BuOH moiety, which has half identical structure moiety to that of the [2.2.2]cryptand. In this section, Tri-*tert*-butanol amine acts as promoter with alkali metal salts in the nucleophilic fluorination of alkylsulfonates. It significantly enhances the reactivity of alkali metal salts with minimum formation of side-products (alkene, ether, and alcohol) compared to other catalysts in fluorination reaction. The synergism of *tert*-alcohol and amine moiety plays a pivotal role in fluorination.

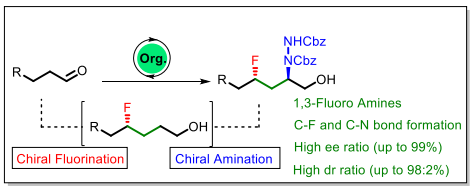
**Scheme: 4**



***Section B:*** **Organocatalytic Route to the Enantioselective Synthesis of syn/anti-1,3-Fluoro Amines**

In recent years, chemists have become more interested in using small organic molecules to catalyze organic reactions. As a result, organocatalysis has emerged both as a promising strategy and as an alternative to catalysis with expensive proteins or toxic metals. Proline is among the most successful secondary amine-based eco-friendly and proficient catalysts and is extensively explored for the asymmetric C-C bond and C-heteroatom bond formation. Proline and proline derived catalysts have been also widely employed for α-functionalization of carbonyl compounds such as α-aminoxylation, α-amination, α-halogenation, α-sulfenylation providing rapid, catalytic, and atom-economical access to enantiomerically pure products. The past few decades have witnessed a considerable surge of interest in the development of methods for the synthesis of biologically active fluorinated compounds. 1,3-Fluoro amines are one of the most bioactive fluorinated scaffolds present in several drug molecules. Especially the β-fluoro-α-amino acid derivative has been extensively used as a protein residue and also for PET imaging applications. In this section, a general organocatalytic method for the asymmetric synthesis of 1,3-fluoro amines has been developed. The strategy employs α-fluorination catalyzed by L-Proline derived Hayashi catalyst followed by Horner−Wadsworth−Emmons (HWE) olefination of aldehydes and subsequent proline-catalyzed α-amination as the key steps. The excellent enantioselectivity (up to 99%) and diastereoselectivity (up to 99:1%) of 1,3-fluoro amines were obtained.

**Scheme: 5**




**Summary/Conclusion**

In summary, we have achieved the synthesis of xanthenone and chromene derivatives through reaction of hydroxy substituted *para*-quinone methides and *β*-functionalized cyclic ketones and also developed the synthesis of unsymmetrical triaryl methane derivatives through reaction of *para*-quinone methides and imidazopyridine. Reaction works efficiently using $Tf_2NH$ as Brønsted acid catalyst and DCE as solvent. We also report the unique role of tri-*tert*-butanol amine organic promoter **1** as bifunctional promoter in nucleophilic fluorination using alkali metal fluorides. Our synthesized tri-*tert*-butanol amine organic promoter **1** has various advantages, such as easy access, and easy handling due to solid state which enhances nucleophilicity of alkali metal fluorides and minimizes the by-products formations such as alkene and ether in the reaction. We also developed an efficient organocatalytic approach to the enantioselective synthesis of syn/anti-1,3-fluoro amines. The resultant product γ-fluoro-α-amino alcohol derivatives serve as useful building blocks for the synthesis of biologically useful compounds particularly fluorinated amine acids.

**Future directions**

We believe that our synthesized xanthenone and chromene derivatives and triaryl methane heterocyclic derivatives would find enormous application in medicinal chemistry. So, the study related to bioactivity of these heterocycles would be undertaken further in our laboratory. In future, we plan to utilize our fluorination strategy to prepare the F-18-labeled radiotracers for positron emission tomography application as well.

# Chapter-1

# *para*-Quinone Methides (*p*-QMs): A building block for the Carbon-Carbon bond forming reactions

## 1.1 Introduction

*p*-Quinone methide frameworks are common constituents of various biological systems. It contains cyclohexadiene moiety with exocyclic methylene group and could be formed by the degradation of tyrosine and ultimately to *p*-Cresol. *p*-Quinone methides play an important role as a reactive intermediate in the bio-synthesis of lignin in plants.[1] The quinone methide core containing diverse natural products shows prominent biological activities, ultimately responsible for the cytotoxins effects which can be used as antitumor drugs, antibiotics, and DNA alkylators.[2]

*p*-Quinone methide core containing triterpenoid Celastrol and Pristimerin (the methyl ester of Celasterol) exhibits important pharmacological activity such as antioxidants (15 times more potent than α-tocopherol),[3] anti-inflammatories,[4] anticancer,[5,6] insecticidal[7] and antiviral[8] and contraceptive activities. Other natural products like Kendomycin are endothelin receptor antagonist and anti-osteoporosis agent while Taxodone exhibits an anticancer[9] and antibacterial[10] activities.

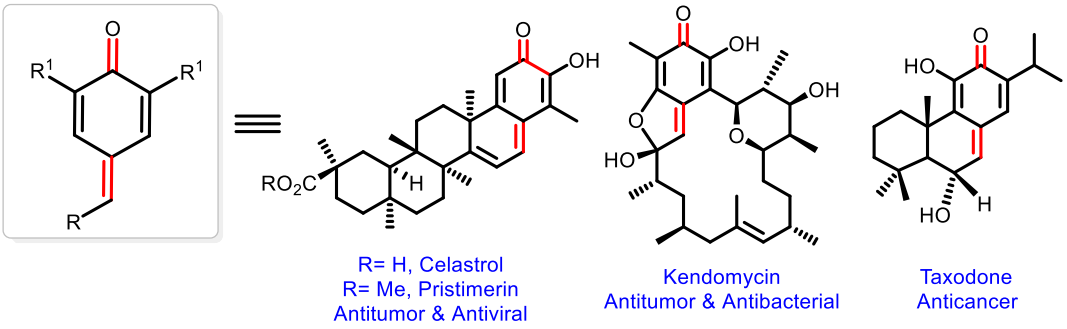


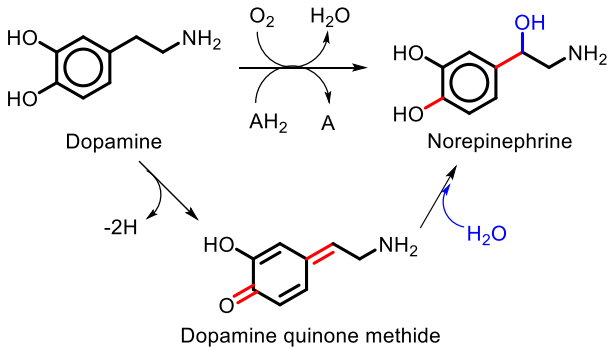

**Figure-1**: Natural products containing *p*-QM scaffold

The *p*-quinone methides structure being polar, becomes highly reactive intermediate in nature due to the presence of carbonyl group. Simple *p*-quinone methides are highly unstable and difficult to isolate at normal conditions due to their short-lived duration. It quickly reacts with nucleophiles and other reactants. Few structurally redesigned *p*-QMs have been assembled to stabilize it by putting bulky substituents near the carbonyl group; usually when it is the *tert*-butyl group, the respective *p*-QMs become highly stable and could be used further to study the chemical properties. The reactivity and thus the stability of quinone methides can be controlled by the existence of electron withdrawing or donating substituents on the ring respective to the carbonyl group.[11] Owing to driving force of aromatization, *p*-QMs are more reactive as compared to vinyl ketones. Hence, it distinguishes all their other transformations[12] and plays an important role as a reactive intermediate in the bio-synthesis.

## 1.2 *p*-Quinone methides: A reactive intermediate in bio-synthesis

### 1.2.1 Mechanism of dopamine hydroxylation reaction

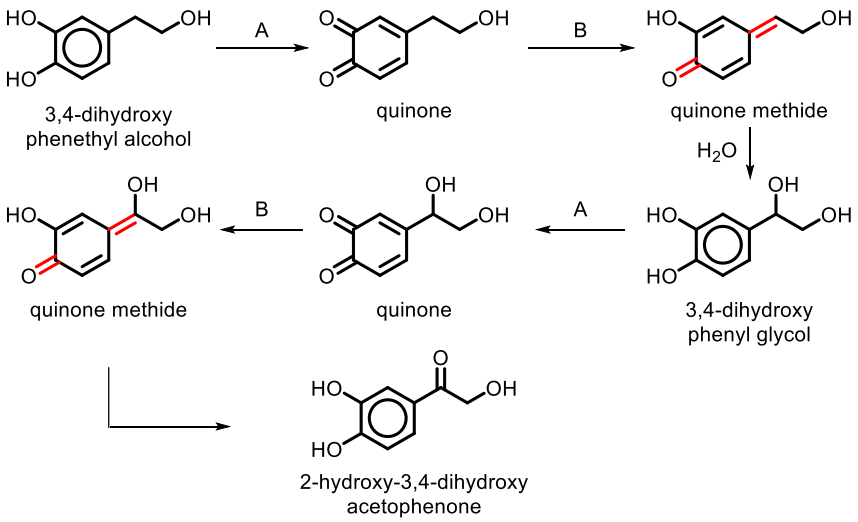
Initially the norepinephrine bio-synthetic pathway was reported through the oxidation of dopamine via formation of quinone methide intermediate followed by hydration.[13] The detailed mechanistic studies using labelled oxygen showed that dopamine-*β*-hydroxylase enzyme catalyzed hydroxylation followed by the addition of one atom of molecular oxygen into dopamine molecule.




**Scheme-1:** Dopamine hydroxylation mechanism

### 1.2.2 Enzyme catalyzed conversion of 3,4-dihydroxyphenethyl alcohol

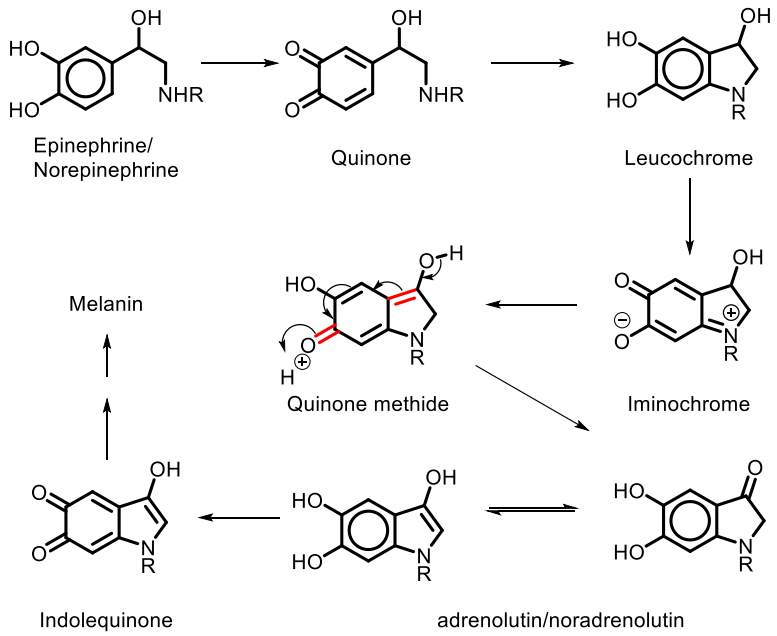
The enzyme Tyrosinase **(A)** converts 3,4-dihydroxyphenethyl alcohol to respective quinone by oxidation, which is further transformed to corresponding quinone methide via either enzymatic or nonenzymatic isomerization **(B)**. Quinone methide further reacts with water and forms addition product 3,4-dihydroxyphenyl glycol, which undergoes subsequent oxidation and second isomerization to give a transient quinone methide which is easily transformed to 2-hydroxy-3,4-dihydroxy acetophenone.[14]




**Scheme-2:** Transformations of 3,4-dihydroxyphenethyl alcohol

### 1.2.3 Transformation of epinephrine and norepinephrine to corresponding quinones

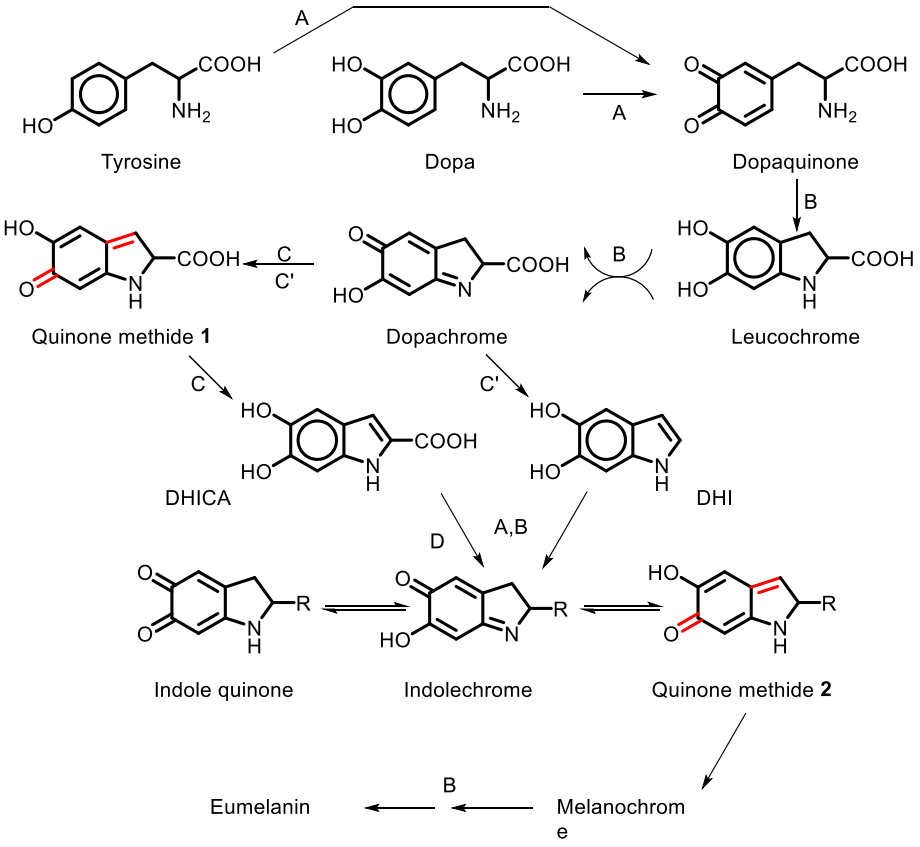
Epinephrine (R = Me) and norepinephrine (R = H) are readily oxidized to corresponding quinones. Further, these quinones undergo cyclization and oxidation to give iminochromes. Subsequently these get converted to quinone methide followed by isomerization to eventually produce adrenolutin/noradrenolutin. These serve as precursor in the synthesis of melanin pigment.[15]




**Scheme-3:** Transformations of epinephrine and norepinephrine

### 1.2.4 Revised bio-synthetic pathway (Raper–Mason) for Eumelanin

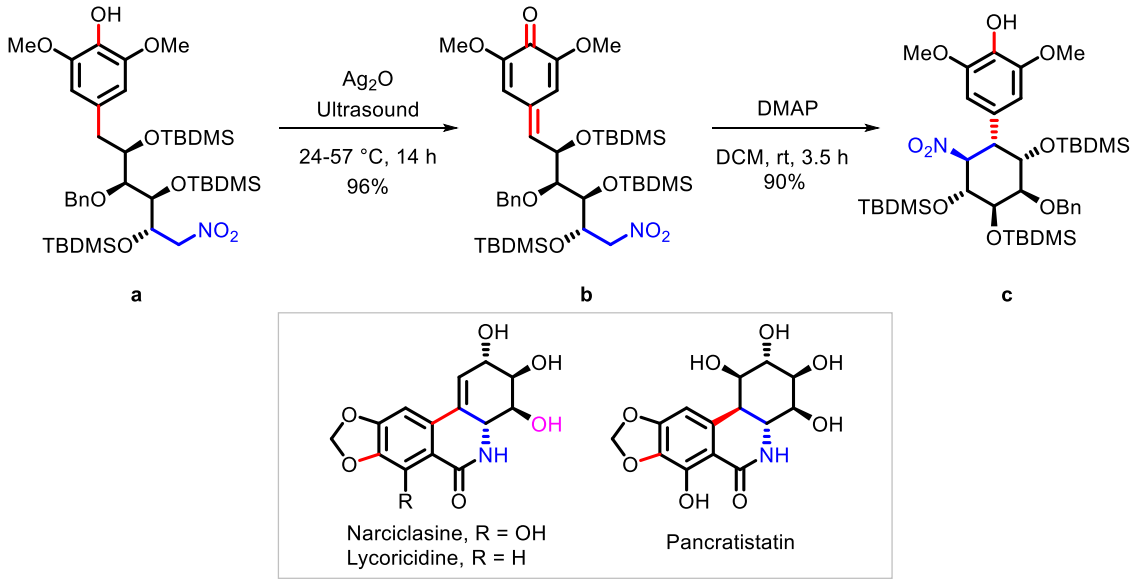
Tyrosinase enzyme **(A)** oxidizes both tyrosine and dopa to dopaquinone which on intramolecular cyclization gives leucochrome. Leucochrome undergoes nonenzymatic oxidation **(B)** to form dopachrome, which is followed by isomerization to give transient quinone methide **(1)**. That short lived quinone methide is further transformed to DHICA or DHI by enzymes mammalian DCT **(C)** or insect DCDT **(C')** respectively. The indoles DHICA or DHI is oxidized to reactive intermediate quinone methides by enzymes like tyrosinase, DHICA oxidase **(D)** or nonenzymatic reactions. Eventually, these reactive quinone methides of indole derivatives polymerize and form polymer of DHICA or DHI. (R = H for DHI derivative; and COOH for DHICA).[16]




**Scheme-4:** Eumelanin bio-synthesis

### 1.3 Application of *p*-QMs in the total synthesis of Narciclasine alkaloids

In 1997, Tetsuo Wada and co-worker demonstrated the application of *p*-QMs in the total synthesis of alkaloids narciclasine alkaloids from D-glucose, the key step of the proposed method was quinone methides initiated intra-cyclization reaction.[17]

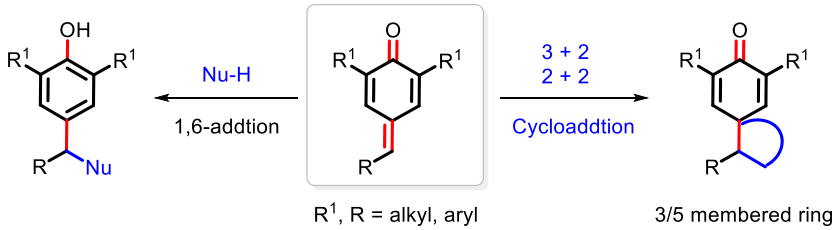



**Scheme-5:** Application of *p*-QMs in synthesis of Narciclasine alkaloids

They have prepared the phenol compound **(a)** using various organic transformation of D-glucose. The phenol **(a)** was oxidized with silver oxide to form the intermediate with *p*-quinone methide **(b)** core structure followed by the base mediated intra-molecular 1,6-conjugate addition to give the advanced intermediate **(c)** from which the proposed natural product could be synthesized by some more organic transformations.

### 1.4 Reactivity of *p*-QMs towards diverse nucleophiles

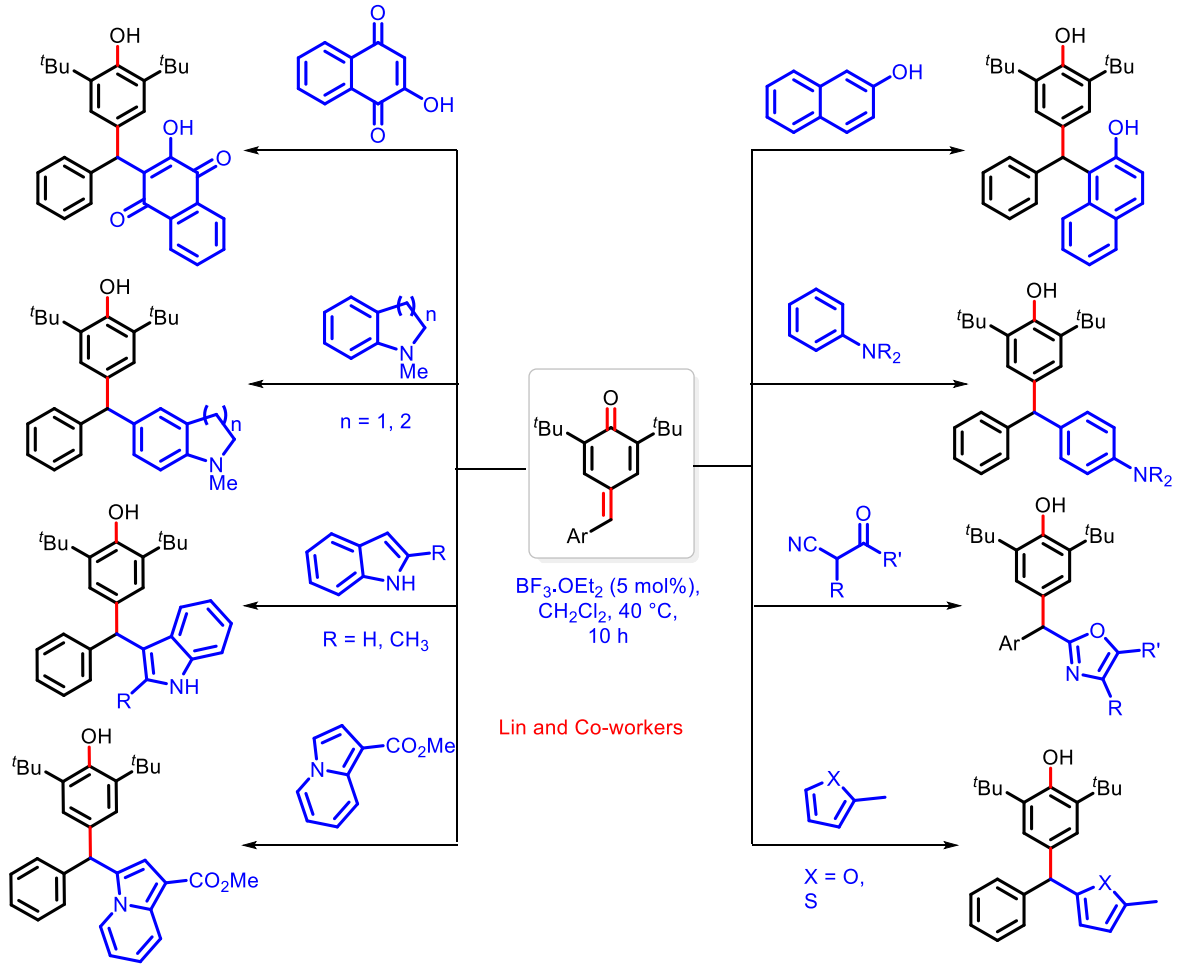
*p*-Quinone methide, the transient intermediate plays an important role as a Michael acceptor and gives conjugate addition with nucleophiles (Scheme-6). Inspired from nature, to explore the unprecedented reactivity, scientists have developed the stable isomer of *p*-QMs and studied several type of reactions using a variety of nucleophiles and catalysts.




**Scheme-6:** Reactivity of *p*-QMs

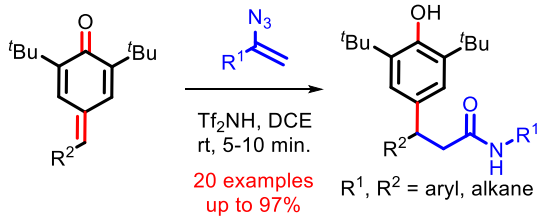
### 1.5 Literature Reports

Since last several years, *p*-QMs pull the attention to the organic chemists. Its unique reactivity[18] is extensively studied in the variety of organic transformations with an array of nucleophiles.[19] *p*-Quinone methide motif serves as powerful Michael acceptors, and the 1,6-conjugate addition reactions have been extensively explored by various group of chemists. In 2016, Lin and co-workers reported Lewis acid $BF_3$•$OEt_2$ catalyzed intermolecular 1,6-nucleophilic addition arylation of *p*-QMs with α-isocyanoacetamides (Scheme-7). The reported method facilitates synthesis of unsymmetrical triarylmethanes containing various heterocyclic moieties. Moreover, the method showed good functional group tolerance and gram scale, scalability.[20]



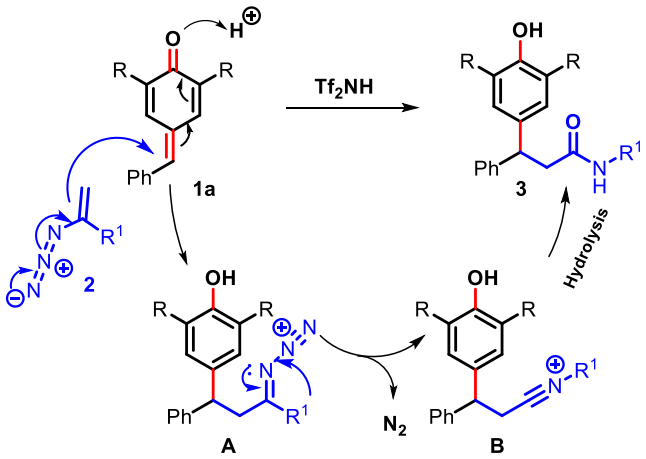

**Scheme-7:** $BF_3$•$OEt_2$ catalyzed intermolecular 1,6-nucleophilic addition

Our group has displayed Brønsted acid ($Tf_2NH$) catalyzed addition of vinyl azide with *p*-QMs for the synthesis of β-bis aryl amides. We have developed mild and efficient reaction condition as compared to $BF_3$•$OEt_2$ catalyzed reaction (Scheme-8).[21]



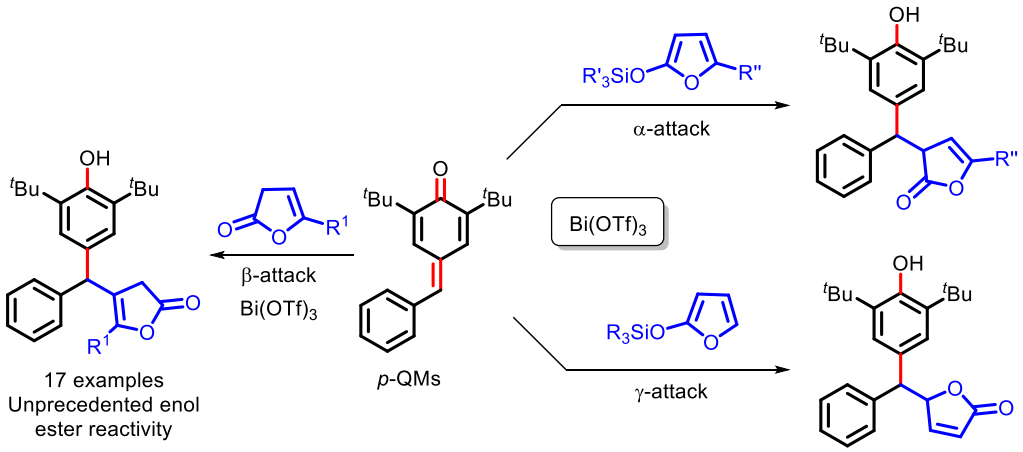

**Scheme-8:** $Tf_2NH$ catalyzed synthesis of β-bis aryl amides with *p*-QMs and vinyl azides

The plausible reaction mechanism (Scheme-9) shows that Brønsted acid activates *p*-QM which then reacts with vinyl azide **2**, leading to the formation of intermediate **(A)**. The intermediate **A** is highly susceptible to undergo Schmidt type rearrangement, and thus eventually furnishes the intermediate nitrilium ion **(B)**. Subsequent hydrolysis would produce the β-substituted aryl amides **3**.



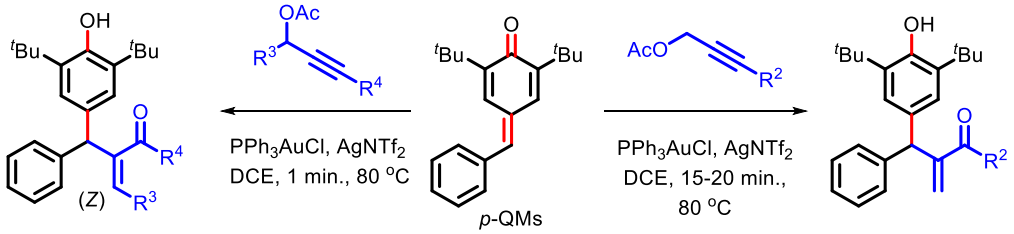

**Scheme-9:** Plausible mechanism

Simultaneously in 2018, our group further studied the selectivity of *p*-QMs toward nucleophilic addition of butenolides from α, β as well as γ-positions, and reported the synthesis of variety of diarylmethane substituted butenolide. The core structure is present in the important natural products of lignin and secolignan families. The Lewis acid catalyzed addition reaction (vinylogous Mukaiyama-Michael) was highly selective, silyloxyfuran exclusively attacks from α- or γ-position. (Scheme-10).[22]



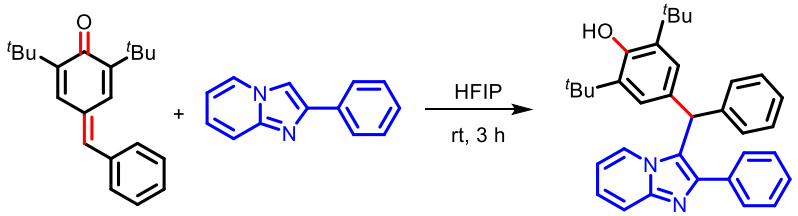

**Scheme-10:** Nucleophilic 1,6-conjugate addition of butenolides to *p*-Quinone methides

Also, we have reported conjugate addition of allenol ester with *p*-QMs. The nucleophile allenol ester was in-situ prepared from propargylic acetate via gold mediated [3,3]-sigma tropic rearrangement (Scheme-11). The established reaction has a broad substrate scope with a wide variety of *p*-QMs and allenol acetate, which produced selectively, sterically more stable Z-isomer of Morita-Baylis-Hillman product.[23]



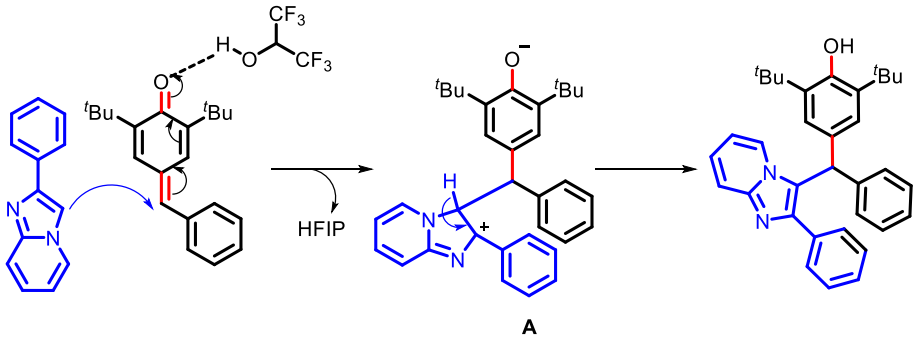

**Scheme-11:** Nucleophilic 1,6-conjugate addition of allenol ester to *p*-Quinone methides

Kilic and co-workers recently explored the reactivity of *p*-QMs for 1,6-conjugate addition reaction using imidazo[1,2-*a*]pyridines derivatives as nucleophile. They have reported this synthetic method without use of any metal catalyst and additive (Scheme-12).




**Scheme-12:** 1,6-conjugate addition of imidazopyridine to *para*-Quinone methides

The report shows the synthetic potential of *p*-QMs in the C3 alkylation the imidazo[1,2-*a*]pyridines. The functionalization of imidazopyridines has great importance in the pharmaceutical industry.[24]

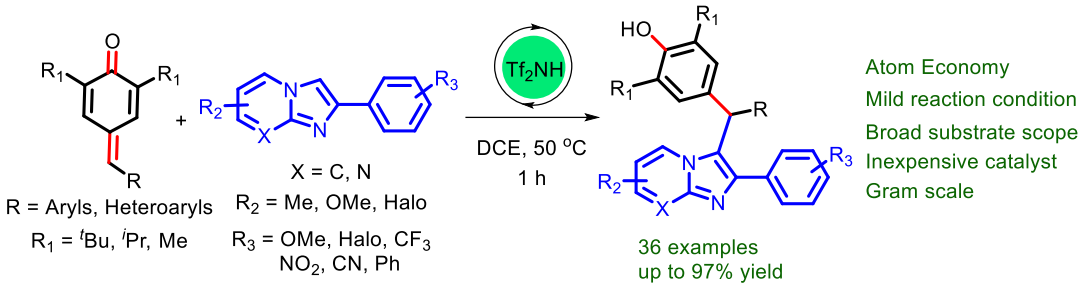



**Scheme-13:** Plausible mechanism

As illustrated in the proposed pathway (Scheme-13), imidazopyridine serves as a nucleophile and attacks on *p*-QMs in 1,6-addition fashion from the C3 position. This resulted into the reactive intermediate **A** as an addition product which on subsequent removal of proton eventually forms the 1,6-nucleophilic addition product.

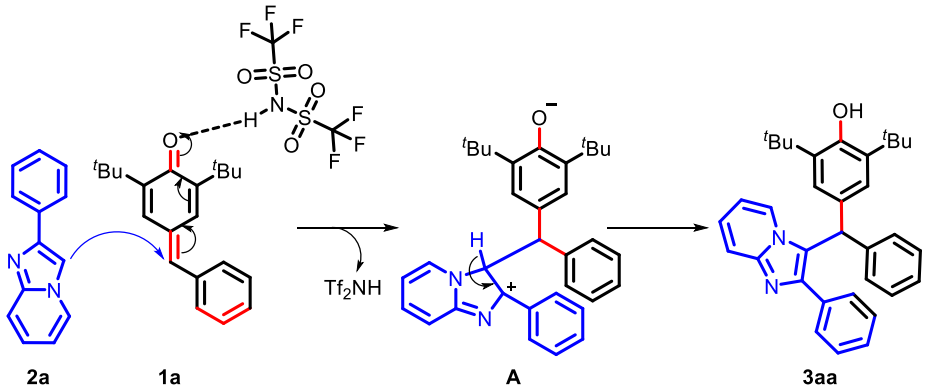
Simultaneously, our group also reported an efficient protocol for 1,6-conjugate addition of imidazopyridines to *para*-quinone methides in presence of Brønsted acid $Tf_2NH$ to provide triarylmethane heterocyclic derivatives of imidazopyridine (Scheme-14). Reaction works

efficiently to give maximum up to 97% yield of conjugate addition product. Our developed route has atom economy, mild reaction condition with broad substrate scope leading to the diverse range of triarylmethane heterocycles. We believe that these compounds would find enormous application in medicinal chemistry.[25]




**Scheme-14:** 1,6-conjugate addition of imidazopyridine to *para*-Quinone methides

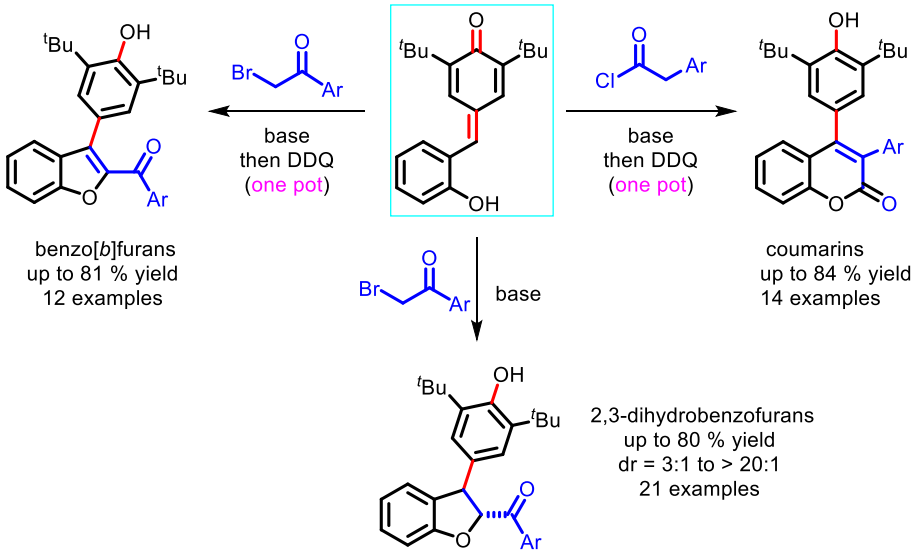
A plausible reaction mechanism for the 1,6-conjugate addition of *p*-QM **1a** with imidazopyridine **2a** is described (Scheme-15).




**Scheme-15.** A plausible mechanism for the formation of triarylmethane IMPY

The reaction mechanism for the formation of triarylmethane IMPY using triflimide (Scheme-15) is similar to the one as described in Scheme-13.

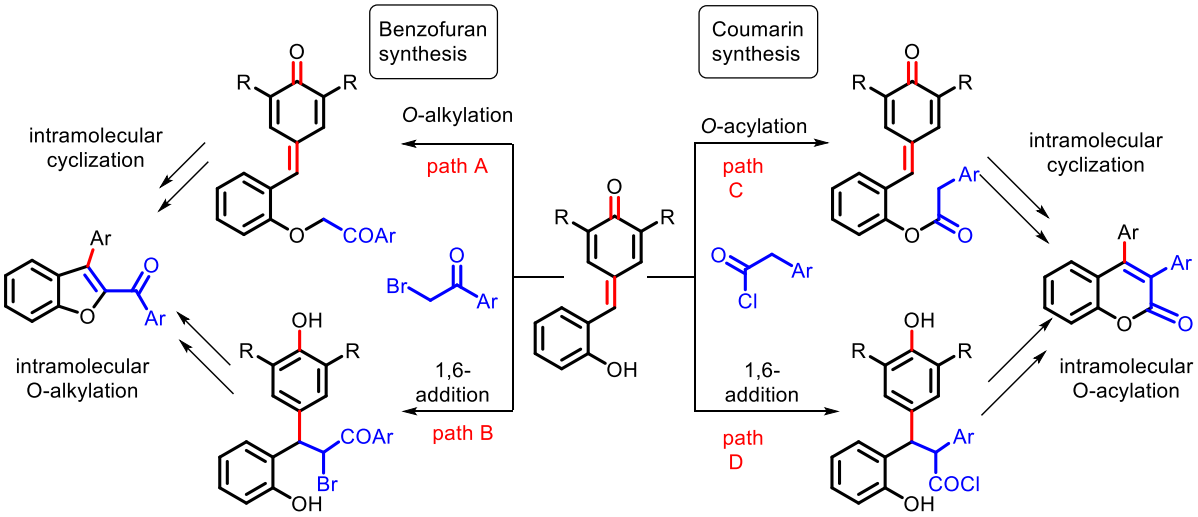
Anand and co-workers in 2019, have developed the methods for the synthesis of *trans*-2,3-dihydrobenzofurans (Scheme-16). The synthesis constitutes one-pot methodology with sequence of various reactions such as alkylation/acylation of *p*-QMs, followed by an intramolecular 1,6-conjugate addition and subsequent oxidation. The reaction showed good diastereoselectivity.




**Scheme-16:** Cesium Carbonate catalyzed One-pot Synthesis of Oxygen Based Heterocycles from 2-Hydroxyphenyl-substituted *p*-QMs

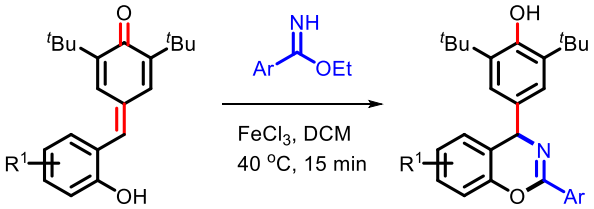
This methodology elaborates same strategy for the synthesis of O-heterocycles benzo[***b***]furans in one-pot synthesis via variety of in *situ* reactions with *p*-QMs. Via dehydrogenative oxidation of the benzofuran intermediates, 3,4-diaryl-substituted coumarin heterocycles was prepared. Thus the protocol developed gave an access to the wide range of oxygen based heterocycles, with core structure benzo[***b***]furans, coumarin derivatives (Scheme- 17).[26]

The authors have proposed two mechanistic pathways each for the benzofuran and coumarin heterocycles. The reaction proceeds via *O*-alkylation/*O*-acylation and 1,6-conjugate addition to the quinone methide skeleton. This could happen by 1$^{st}$ alkylation followed by 1,6-conjugate addition or vice versa (path **A** and **B** respectively) for the formation of benzofuran core structure. In a similar way the coumarin core structure is formed (the pathway **C** and **D** respectively).



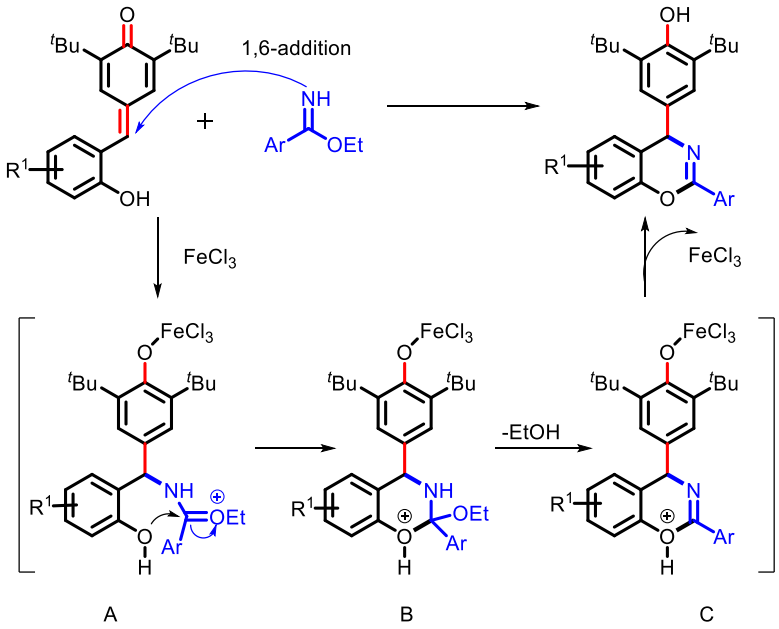

**Scheme-17:** Benzofuran and coumarin synthesis *via* 1,6-addition and intramolecular *O*-alkylation and *O*-acylation

In same year in 2019, Li-Ming Zhao and co-workers described iron chloride ($FeCl_3$) catalyzed 1,6-conjugate addition of imidates nucleophile with substituted *p*-QMs and eventually intramolecular ring closing to get 2,4-diaryl-1,3-benzoxazines (Scheme-18). The reaction condition was found to be mild and quick with wide functional group tolerance. [27]




**Scheme-18:** $FeCl_3$-catalyzed Annulation of ortho-Hydroxyphenyl-Substituted *P*-QMs with Imidates

The plausible mechanistic pathway is shown in Scheme-19. Lewis acid $FeCl_3$ activates *p*-QMs by coordinating at carbonyl site, followed by the attack of nucleophile i.e. imidates which forms the intermediate **A**. Subsequent intramolecular trans esterification (lactonization) leads to the cyclized intermediate **C** which undergoes a proton-transfer to obtain the heterocyclic product and $FeCl_3$ catalyst enters in next catalytic cycle.




**Scheme-19:** Plausible mechanism

## 1.6 Conclusion

In summary, this chapter highlights very briefly the current trends in methodology developments by using the reactivity of the *p*-QMs. *p*-QMs serves as a versatile Michael type acceptor and dienophile towards diverse nucleophiles. The reactivity of the *p*-QMs could be tuned with the wide range of nucleophiles for the 1,6-conjugate addition and cycloaddtion reactions to construct a variety of structural framework of synthetic interest.

## 1.7 References

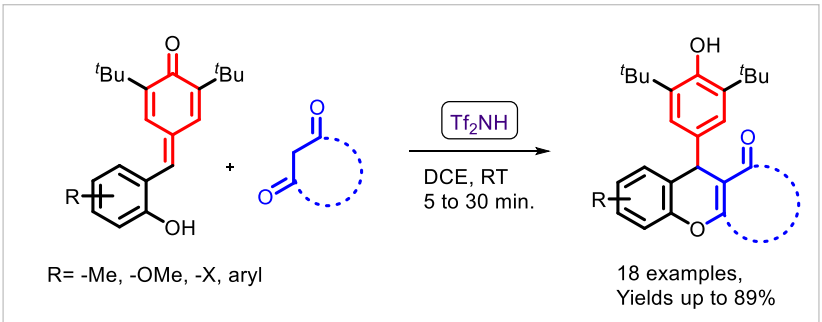

1. Stich, T. A.; Myers, W. K.; Britt, R. D. *Acc. Chem. Res.* **2014,** *47*, 2235−2243.
2. Wang, P.; Song, Y.; Zhang, L.; He, H.; Zhou, X. *Curr Med Chem.* **2005,** *12*, 2893−2913.
3. Allison, A. C.; Cacabelos, R.; Lombardi, V. R.; Alvarez, X. A.; Vigo, C. *Prog Neuropsychopharmacol Biol Psychiatry* **2001,** *25*, 1341−1357.
4. Kim, D. H.; Shin, E. K.; Kim, Y. H.; Lee, B. W.; Jun, J. G.; Park, J. H.; Kim. J. K. *Eur J Clin Invest.* **2009,** *39*, 819−827.
5. Lee, J. H.; Choi, K. J.; Seo, W. D.; Jang, S. Y.; Kim, M.; Lee, B. W.; Kim, J. Y.; Kang, S.; Park, K. H.; Lee, Y. S.; Bae, S. *Int J Mol Med.* **2011,** *27*, 441−446.
6. Tiedemann, R. E.; Schmidt, J.; Keats, J. J. *Blood* **2009,** *113*, 4027−4037.
7. Avilla, J.; Teixidò, A.; Velázquez, C.; Alvarenga, N.; Ferro, E.; Canela, R. *Journal of Agricultural and Food Chemistry* **2000,** *48*, 88−92.
8. Murayama, T.; Eizuru, Y.; Yamada, R.; Sadanari, H.; Matsubara, K.; Rukung, G.; Tolo, F. M.; Mungai, G. M.; Kofi-Tsekpo, M. *Antivir Chem Chemother* **2007,** *18*, 133−139.
9. Kupchan, S. M.; Karim, A.; Marcks, C. *J Am Chem Soc.* **1968,** *90*, 5923−5924.
10. Bajpai, Vivek K.; Kang, Sun Chul. *Journal of Bioscience.* **2010,** *35*, 533−538.
11. Thompson, D. C.; Thompson, J. A.; Sugumaran, M.; Moldeus, P. *Chem. Biol. Interact.* **1992,** *86*, 129−162.
12. Turner, A. B. *Q. Rev. Chem. Soc.* **1964,** *18*, 347−360.
13. Kaufman, S.; Bridgers, W. F.; Eisenberf, F.; Friedman, S. *Biochem. Biophys. Res. Commum.* **1962,** *9*, 497−502.
14. Semensi, V.; Sugumaran, M. *Sarcophaga bullata. Arch. Insect Biochem. Physiol.* **1989,** *10***,** 13−27.
15. Manini, P.; Panzella, L.; Napolitano, A.; d'Ischia, M. *Chem. Res. Toxicol*. **2007**, *20*, 1549−1555.
16. Cooksey, C. J.; Garratt, P. J.; Land, E. J.; Pavel, S.; Ramsden, C. A.; Riley, P. A.; Smit, N. P. M. *J. Biol. Chem*. **1997**, *272*, 26226−26235.
17. Wada, T.; Angle, S. R. *Tetrahedron Lett.* **1997**, *38*, 7955−7958.
18. a) Peter, M. G. *Angew. Chem., Int. Ed.* **1989,** *28*, 555−570. b) Angel, S. R.; Turnbull, K. D. *J. Am. Chem. Soc.* **1989,** *111*, 1136−1138. c) Angel, S. R.; Louie, M. S.; Mattson, H. L.; Yang, W. *Tetrahedron Lett.* **1989,** *30*, 1193−1196.

19. a) Takao, K. –i.; Sasaki, T.; Kozaki, T.; Yanagisawa, Y.; Tadano, K. –i.; Kawashima, A.; Shinonaga, H. *Org. Lett.* **2001,** *3*, 4291−4294. b) Groszek, G.; Błażej, S.; Brud, A.; Świerczyński, D.; Lemek, T. *Tetrahedron* **2006,** *62*, 2622−2630.
20. Gao, S.; Xu, X.; Yuan, Z.; Zhou, H.; Yao, H.; Lin, A. *Eur. J. Org. Chem.* **2016,** *2016*, 3006−3012.
21. Rathod, J.; Sharma, B. M.; Mali, P. S.; Kumar, P. *Synthesis* **2017**, *49*, 5224−5230.
22. Sharma, B. M.; Shinde, D. R.; Jain, R.; Begari, E.; Satbhaiya, S.; Gonnade, R. G.; Kumar, Pradeep. *Org. Lett.* **2018,** *20*, 2787−2791.
23. Sharma, B. M.; Rathod, J.; Gonnade, R. G.; Kumar, Pradeep. *J. Org. Chem*. **2018**, *83*, 9353−9363.
24. Lafzi, F.; Kilic, H. *Asian J. Org. Chem.* **2021,** *10*, 1814−1821.
25. Khonde, N. S.; Said, M. S.; Sabane, J. K.; Gajbhiye, J. M.; Kumar, Pradeep. *Tetrahedron* **2021,** *101*, 132510−132513.
26. Singh, G.; Kumar, S.; Chowdhury, A.; Anand, R. V. *J. Org. Chem.* **2019,** *84*, 15978−15989.
27. Zhang, J. R.; Jin, H. -S.; Wang, R. -B.; Zhao, L. M. *Adv. Synth. Catal.* **2019,** *361*, 4811−4816.

# Chapter-2 (Section-A)

## $Tf_2NH$ catalyzed 1,6-conjugate addition of 2-hydroxy-*p*-quinone methides with *β*-functionalized ketones: Access to 2,3,4,9-tetrahydro-1*H*-xanthenones and 4*H*-chromene derivatives

**Abstract**




A Brønsted acid catalyzed tandem 1,6-conjugate addition with sequential cycloaddition reaction using 2-hydroxy-*p*-quinone methides and *β*-functionalized ketones for the synthesis of xanthenone is reported. The developed strategy permits synthesis of xanthenone heterocycles with moderate to excellent yield with wide substrate scope, which could be further modified to access the variety of important products.

## 2A.1 Introduction

Oxygen-containing heterocyclic xanthenes and xanthenones[1] heterocyclic core have attracted much attention from natural product chemistry, medicinal chemistry and synthetic organic chemistry. Xanthene scaffold is widely found in many fluorescent dyes[2] and biologically active scaffolds.[3] Besides, fully unsaturated xanthenes and xanthenones, partially saturated 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones have fascinated a great deal of interest. Naturally occurring tetrahydroxanthenones such as blennolides A and B, isolated from the endophytic fungus Blennoria sp.[4] showed algicidal activities (Figure-1).

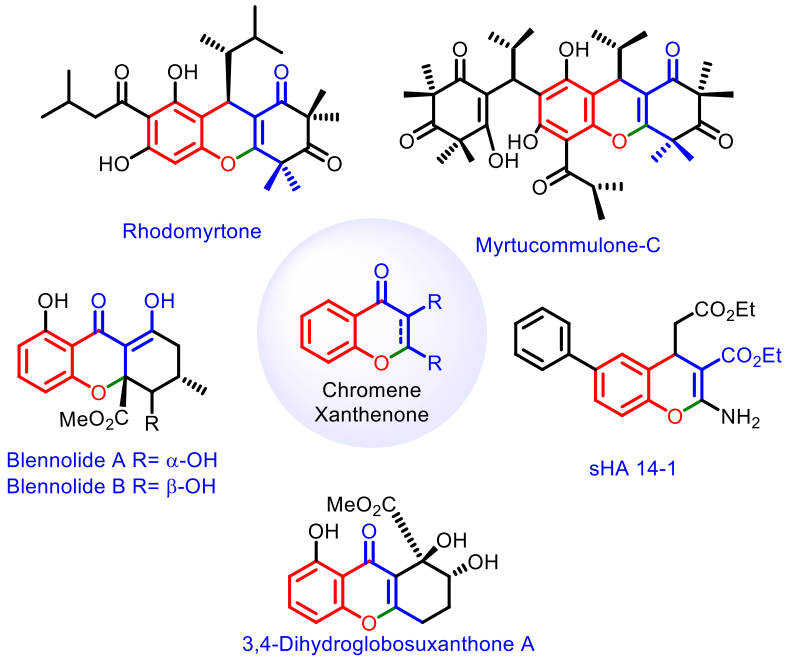



**Figure-1.** Biologically active tetrahydroxanthenone and 4*H*-chromene core containing natural products

Various synthetic approaches toward the synthesis of 2,3,4,4a-tetrahydro-1*H*- xanthene-1-one[5] unit have been explored. In contrast, only a few reports are known in literature for the direct construction of 2,3,4,9-tetrahydro-1*H*-xanthene-1-one moiety.

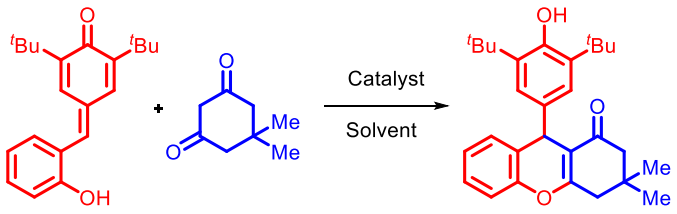
Chromene core frame work is present in many biologically active scaffolds such as enzyme inhibitors against a variety of targets.[6] 4*H*-Chromenes have cytotoxic anticancer,[7] neuroprotective,[8] antimicrobial,[9] antifungal[10] and antioxidant activity[11] and their derivatives are present in large amounts in the human diet due to their low mammalian toxicity.[12] For the

synthesis of chromenes, many classical methods have been developed based on 1,4-reduction of pyrylium ions[13] or the addition of phenol nucleophiles to benzopyrylium salts.[14]

Since last few years, *p*-quinone methides (*p*-QMs) have aroused great interest to the organic chemist due to their strong electrophilic and Michael acceptors reactivity with wide range of nucleophiles[15] and it has potential to construct complex organic framework found in several important pharmaceuticals and natural products.[16] Structurally, *p*-QMs are regarded as neutral molecules with zwitterionic resonance entities[17] and have the ability to undergo [4+2]-annulation,[18] [3+2]-annualtion,[19] and [2+1]-annulation reaction modes.[20] *p*-QMs have been widely employed as 1,6-addition acceptors,[21] since aromatization of quinone core ring is the main driving force for the reactivity. Therefore, *p*-QMs serve as an important intermediate in biosynthetic transformations; provide an efficient method for constructing cyclic scaffolds.

Very recently, Jiang and co-workers[22] in 2017, elegantly showed the silver/scandium- co-catalyzed bicyclization of *β*-alkynyl ketones and *p*-QMs. Recently, the reaction of *p*-QMs with vinyl azide and butenolides promoted by acid is reported by us.[23] Additionally, we also reported gold catalyzed reaction of allenol ester with *p*-QMs[24] to construct diarylmethine-substituted enones. Despite these elegant approaches, interest in conjugate addition using *p*-QM derivatives as building blocks still continues unabated.

### 2A.2 Present Work




**1a** **2a** **3a**

With the above literature background and as part of our on-going research program on reactivity of *p*-QMs for conjugate addition reaction, we proposed that acid catalyzed 1,6-conjugate addition and subsequent cycloaddition reactions of 2-hydroxy-*p*-QMs and *β*-functionalized cyclic ketones might provide a novel approach for the construction of various types of xanthenones. We hereby describe our recent findings on conjugate addition of *p*-QM derivatives to access the diverse range of xanthenes and related compounds.

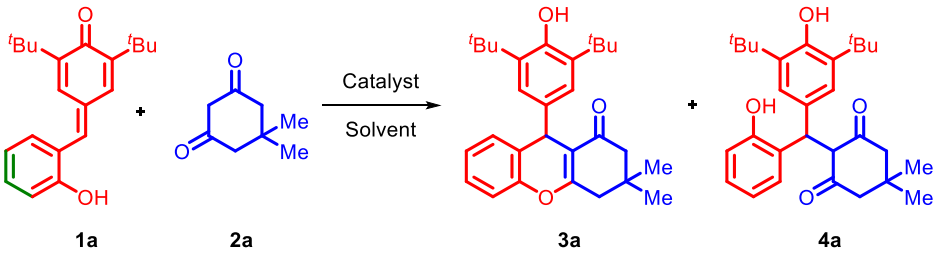
## 2A.3 Results and Discussion

### 2A.3.1 Optimization of reaction conditions

To exploit 1,6-conjugate addition reaction, we began our preliminary investigation with 2-hydroxy-*p*-QM **(1a)** and dimedone **(2a)** as a model substrate. The effect of several parameters like catalyst, solvent and temperature was explored on this reaction and the obtained results are summarized in Table-1. All the commercially available catalysts and reagents were used as received. In the beginning, to optimize the reaction conditions we carried out the reaction of *p*-QM **1a** and diketone **2a** in the presence of Lewis acid $BF_3.OEt_2$ as a catalyst in $CH_2Cl_2$ solvent at room temperature, the desired product **3a** was isolated in 48% yield **(Table-1, entry 1)**.

Uplifted by this primary outcome, and to optimize the best reaction condition, we have screened various known Lewis and Brønsted acids, such as $Bi(OTf)_3$, $BiCl_3$, $Sc(OTf)_3$, AgOTf, $Cu(OTf)_2$, $Tf_2NH$, PTSA **(Table-1, entries 3-9)** as catalyst. Among these catalysts $Tf_2NH$ was found to be the best with 72% yield **(Table-1, entry 8)**. Further, to check the effect of the solvent, we have tried reaction in different solvents like THF, $CH_3CN$ and DCE **(Table-1, entries 10-12)**. The combination of Brønsted acid $Tf_2NH$ with DCE was found to be superior **(Table-1, entry 12)**, to other solvents. In further endeavors to optimize the condition, when the reaction was carried out at 40 °C or higher temperature, the yield was reduced to 23% **(Table-1, entry 13)**.

**Table-1.** Optimization studies for the synthesis of 2,3,4,9-tetrahydro-1*H*-xanthene-1-one[a]




**1a** **2a** **3a** **4a**

| Entry | Catalyst | Solvent | Temp. | Time | %Yield[b] | |
|---|---|---|---|---|---|---|
| | | | | | 3a | 4a |
| 1 | $BF_3.OEt_2$ | DCM | RT | 5 min. | 48 | ND |
| 2 | [c]$BF_3.OEt_2$ | DCM | RT | 5 min. | 32 | ND |
| 3 | $Bi(OTf)_3$ | DCM | RT | 5 min. | ca. 37 | ND |

| | | | | | | |
|---|---|---|---|---|---|---|
| 4 | $BiCl_3$ | DCM | RT | 5 min. | ND | ND |
| 5 | $Sc(OTf)_3$ | DCM | RT | 10 min. | 25 | ND |
| 6 | AgOTf | DCM | RT | 15 min. | 35 | ND |
| 7 | $Cu(OTf)_2$ | DCM | RT | 4 h | ND | ND |
| 8 | $Tf_2NH$ | DCM | RT | 5 min. | 72 | ND |
| 9 | PTSA | DCM | RT | 10 min. | 51 | ND |
| 10 | $Tf_2NH$ | THF | RT | 15 min. | 43 | ND |
| 11 | $Tf_2NH$ | $CH_3CN$ | RT | 5 h | ND | ND |
| **12** | **$Tf_2NH$** | **DCE** | **RT** | **5 min.** | **89** | **ND** |
| 13 | $Tf_2NH$ | DCE | 40 °C | 5 min. | 23 | 52 |
| 14 | BH*a | DCE | 0 °C | 18 h | ND | 68 |
| 15 | BH*b | DCE | 20 °C | 12 h | ND | 80 |
| 16 | BH*c | DCE | 0 °C | 14 h | ND | 62 |
| 17 | BH*d | DCE | 0 °C | 13 h | ND | 71 |
| 18 | [d]BH*a/ $Tf_2NH$ | DCE | 0°C/RT | 12 h/5 min. | 85 | [e] |
| 19 | [d]BH*a/$Sc(OTf)_3$ | DCE | 0°C/RT | 12 h/15 min. | 82 | [e] |
| 20 | - | DCE | RT | 24 h | NR | |

[a]0.1 mmol **1a**, 0.69 equiv. **2a**, 10 mol% catalyst, 5 mol% unless otherwise stated and 1 mL of solvent. [b]Isolated yield. [c]0.1 mmol **1a**, 1.0 equiv. **2a**, BH* = Appropriate chiral phosphoric acid. [d]The reaction was first stirred with BINOL hydrogen phosphate for 12 h and followed by addition of acid. [e]Firstly, the compound **4a** was formed, in situ addition of $Tf_2NH$ or $Sc(OTf)_3$ after 12 h, **3a** was obtained within 5-10 min., NR = No reaction, ND = Not detected.

This might be due to the increase in temperature, the self-decomposition reaction of desired product **3a** is accelerated and thus eventually furnishing **4a** in 52% yield. As our desired product has pro-chiral centre and the reaction has no chiral environment so the product **3a** was obtained in racemic mixture. We also tried an asymmetric version of this reaction. The reaction was performed with various chiral phosphoric acids containing BINOL backbone at 0 °C. Unfortunately, we got undesired product **4a** only **(Table-1, entries 14-17)**. This could probably be due to the inefficiency of acid catalyst for activation of quinone methide to facilitate the cycloaddition reaction. Further we also tried the reaction with $Tf_2NH$ and $Sc(OTf)_3$ in combination of chiral phosphoric acid **(Table-1, entries 18-19)** producing the

desired product **(3a)** in 85% and 82% respectively, but unfortunately it was in racemic form as confirmed by HPLC. When the reaction was carried out at room temperature, it was complete within 5 minutes as confirmed by TLC.

By following literature ascendance, further reaction was screened for the effect of catalyst loading, and we found that 10 mol% of $Tf_2NH$ was best and suitable for this transformation **(Table-1, entry 12)**. When reaction was performed without acid catalyst, it was not successful and unreacted materials were recovered **(Table-1, entry 20)**, which clearly indicates that there is an important role of $Tf_2NH$ for triggering the reaction to complete the proposed transformation **(Table-1, entry 12)**.

### 2A.3.2 Substrate scope

After having optimized procedure in hand **(Table-1, entry 12)**, we moved forward to generalize the developed reaction. It was screened for diverse substrate scope and limitations of this transformation. We have scrutinized the reaction with an array of 2-hydroxy substituted *p*-QMs **(1a**-h**)** and *β*-functionalized ketones **(2a-d)** (Figure-2). 2-Hydroxy-substituted-*p*-QMs **(1a-h)**, containing both electron-withdrawing (F, Cl) and electron-donating substituents (Me, OMe) present on *p*-QMs were compatible under the developed reaction conditions affording moderate to excellent yields of the product **3**.

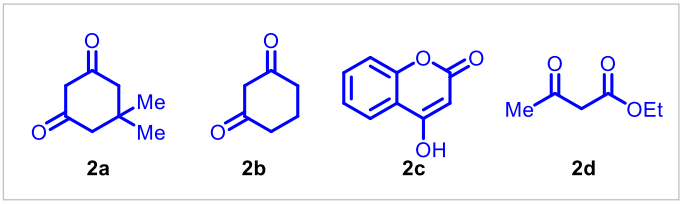


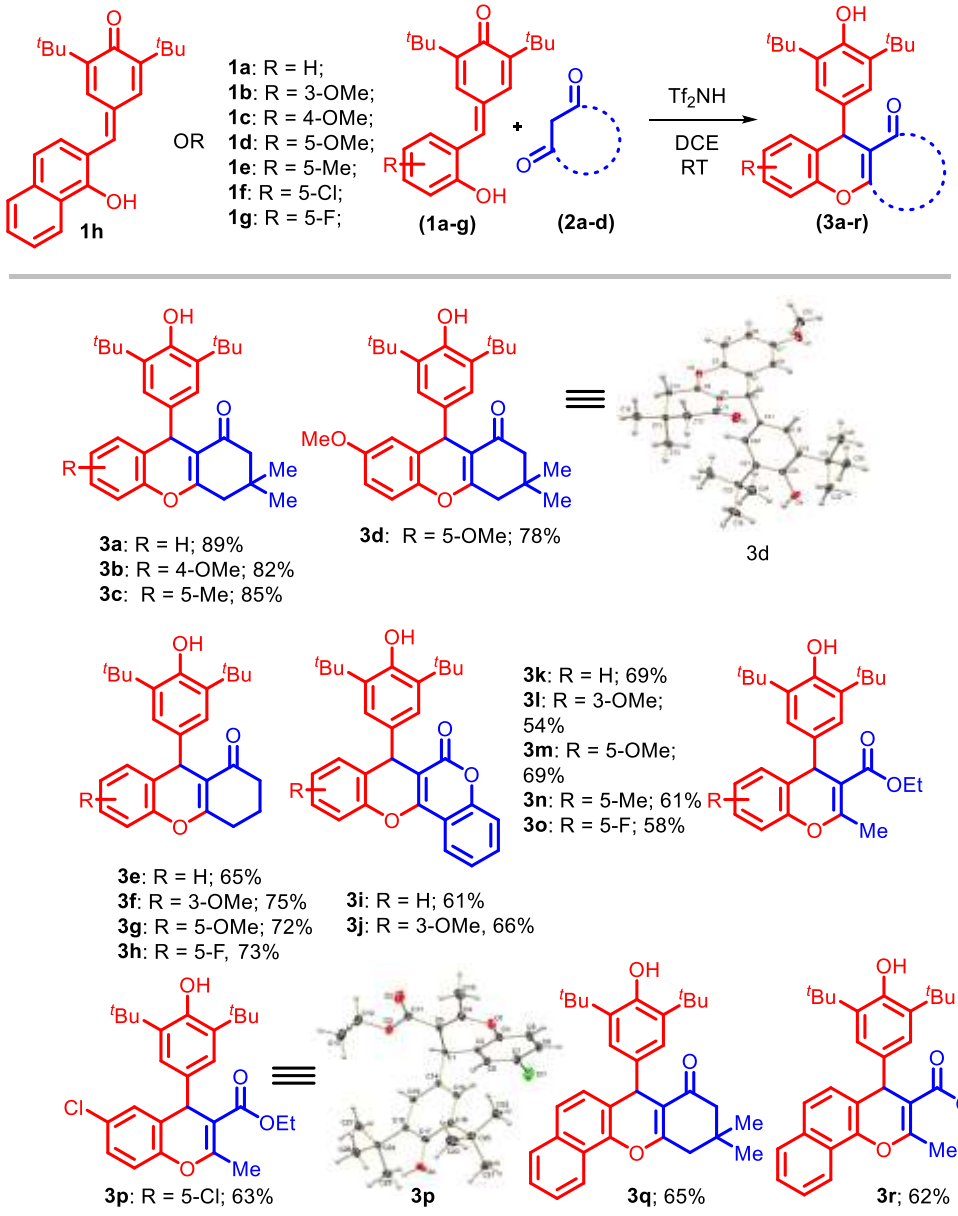

**Figure-2.** Scope for *β*-functionalized ketones

The scope of the developed protocol was studied by reacting *β*-functionalized ketone, dimedone **2a** with various 2-hydroxy-*p*-QMs **1a**, **1c-1e**, to give the xanthenone product **(3a-d)** in excellent yields **(78%-89%, Table-2)**. The proton NMR displayed the characteristic signals for all the functional group present on the core structure, such as singlet at δ 1.37 ppm with 18 H represents two *tert*-butyl groups of *p*-QMs. Two singlet signals at δ 5.00 and δ 4.89 ppm represents the benzylic CH group and –OH group respectively. In proton decoupled carbon NMR, the compound **3d** shows the twenty two different signals which are in accordance with proposed structure. Further, the elemental formula was confirmed by the

HRMS analysis. The structure of compound was determined by the single crystal XRD analysis of compound **3d**.

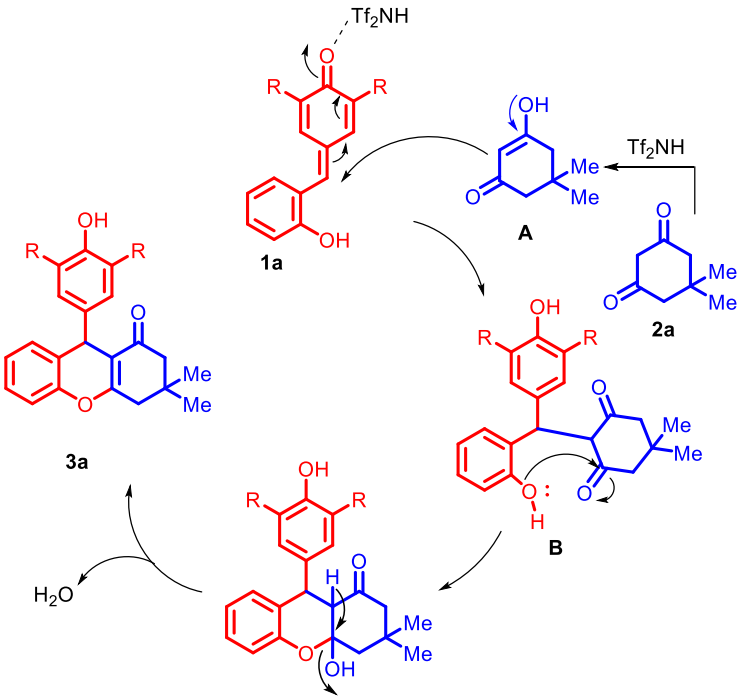
Similarly, cyclohexane-1,3-dione **2b** on reaction with *p*-QMs containing an electron donating substituents such as methoxy and electron withdrawing e.g. fluoro furnished the desired product **3e-h** in 65-75% yields. Interestingly, *β*-functionalized ketones, chromenone **2c** also underwent smooth cycloaddition reaction with *p*-QMs **1a-b** affording chromenone derivatives **(3i-j)** in reasonably good yield. This prompted us to investigate the scope of this reaction with acyclic *β*-functionalized ketone. Towards this aim, ethyl acetoacetate **2d** was used as substrate in sequential cycloaddition reaction with various 2-hydroxy-*p*-QMs. To our delight, the reaction worked smoothly giving rise the desired chromene derivatives **(3k-3p)** in 54-69% yields. The proton NMR displayed the characteristic signals for all the functional group present on the core structure, such as singlet at δ 1.39 ppm with 18 H represents two *tert*-butyl groups of *p*-QMs. Two singlet signals at δ 5.06 and δ 4.88 ppm represents the benzylic CH group and –OH group respectively. In proton decoupled carbon NMR, the compound **3p** shows the eighteen different signals which are in accordance with proposed structure. Further, the elemental formula was confirmed by the HRMS analysis. The structure of compound was determined by the single crystal XRD analysis of compound **3p**. Moreover, 2-hydroxy-*p*-quinone methides with the fused aromatic such as 2-naphthyl were also quite amenable under the optimized conditions. Thus, when naphthyl substituted 2-hydroxy-*p*-QM **1h** was reacted with *β*-functionalized ketones such as dimedone **2a** and ethyl acetoacetate **2d**, it gave the corresponding xanthenone **3q** and chromene-2-carboxylate **3r** in 65% and 62% yield respectively.

**Table-2.** Scope of 1,6-conjugate addition of 2-hydroxy-*p*-QMs, with various *β*-functionalized ketones




### 2A.3.3 The plausible reaction mechanism

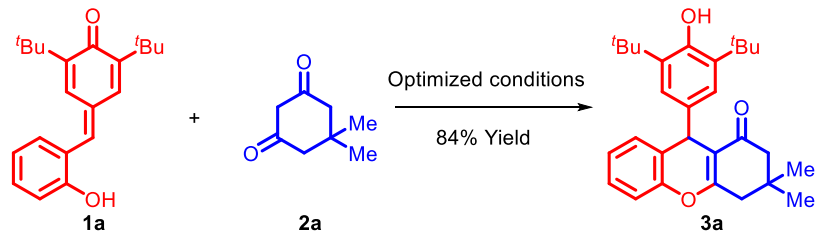
A plausible reaction mechanism for the 1,6-conjugate addition of 2-hydroxy-*p*-QM with *β*-functionalized ketone is illustrated in Scheme-1. 2-Hydroxy-*p*-QM is activated by Brønsted acid $Tf_2NH$; followed by attack of activated dimedone **[A]** resulted in the intermediate **[B].** Subsequently, the intramolecular oxa-nucleophilic addition affords the intermediate **[C]**, which loses a water molecule to eventually furnish the final product **3a**.




**Scheme-1.** A plausible mechanism for the formation of 2,3,4,9-tetrahydro-1*H*-xanthene-1-one

### 2A.3.4 Synthetic utility

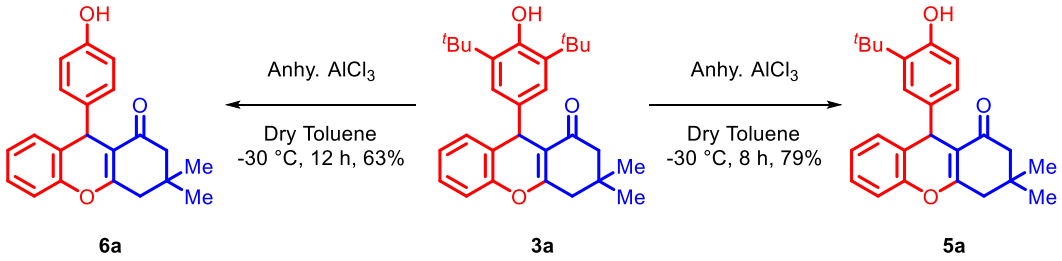
Finally, product modification was performed to exemplify the substrate scope and test the synthetic utility of our developed protocol, **3a** was prepared on a gram scale. As shown in Scheme-2, the desired product **3a** was obtained in 84% yield under optimized reaction condition.




**Scheme-2**. Gram scale synthesis of **3a**

Further, we demonstrated the product modification by performing removal of the *tert*-butyl group as shown in Scheme-3. Treatment of **3a** with anhydrous $AlCl_3$ on -30 °C in dry toluene afforded de-*tert*-butylated **5a** and **6a** in 79% and 63% yield respectively. The compound **6a**

represents core structural motif of many important pharmaceutically active and natural products.




**6a** **3a** **5a**

**Scheme-3.** De- *ter*t-butylation of 2,3,4,9-tetrahydro-1*H*-xanthene-1-one

## 2A.4 Conclusion

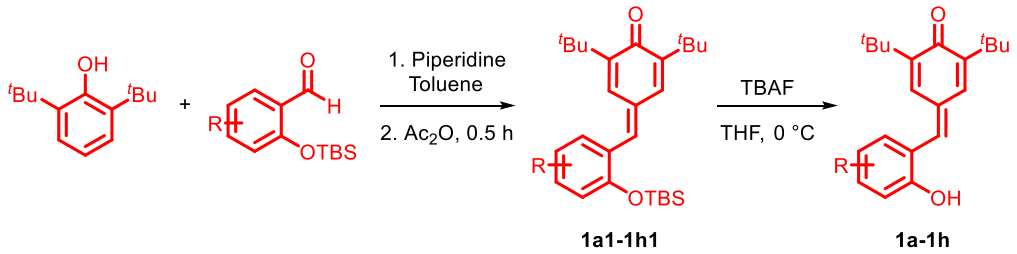
We have developed the protocol for a Brønsted acid ($Tf_2NH$) catalyzed 1,6-conjugate addition of *β*-functionalized ketone with various 2-hydroxy-*p*-QMs leading to the synthesis of xanthenone and chromene derivatives. The developed protocol requires mild reaction conditions and it tolerates with a variety of functional groups. The Brønsted acid is found to play a crucial role for activating both the reacting substrates. In addition, the developed method demonstrates the great feasibility for exploring *p*-QMs in domino reactions.

## 2A.5 Experimental Section

### 2A.5.1 General Information

Reactions were carried out under anhydrous conditions, using flame-dried glassware under a positive pressure of argon, unless otherwise stated. 1,2-Dichloroethane, $CH_2Cl_2$, $Et_3N$, and piperidine were distilled from $CaH_2$.$Et_2O$, toluene and THF were distilled from Na/benzophenone. Other reagents were obtained from commercial suppliers and used as received. The 2-hydroxy-*p*-quinone methides was prepared following the literature procedures. Air-sensitive reagents and solutions were transferred by syringe or cannula and were introduced into the apparatus through rubber septa. Reactions were monitored by thin-layer chromatography (TLC) with 0.25 mm pre-coated silica-gel plates (60 $F_{254}$). Plates were visualized with either UV light, iodine adsorbed on silica gel, or by immersion in an ethanolic solution of phosphomolybdic acid (PMA), *p*-anisaldehyde, or $KMnO_4$, followed by heating with a heat gun for ca. 15 s. Flash chromatography was carried out on silica gel (230–400 mesh). $^1H$ and $^{13}C$ NMR spectra were obtained with a 200, 400, or 500 MHz Bruker/JEOL spectrometer in $CDCl_3$. Coupling constants are given in Hertz. Chemical shifts are quoted in ppm relative to tetramethylsilane, using the residual solvent peak as a reference standard. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet and br. = broad. HRMS ($ESI^+$) spectra were recorded with an ORBITRAP mass analyzer. Infrared (IR) spectra were recorded with a FTIR spectrometer as thin films using NaCl plates, and wavenumbers are indicated in $cm^{-1}$. Chemical nomenclature was generated using ChemDraw Professional 15.1. **CCDC 1881335** (for **3d**) and **CCDC 1881316** (for **3p**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

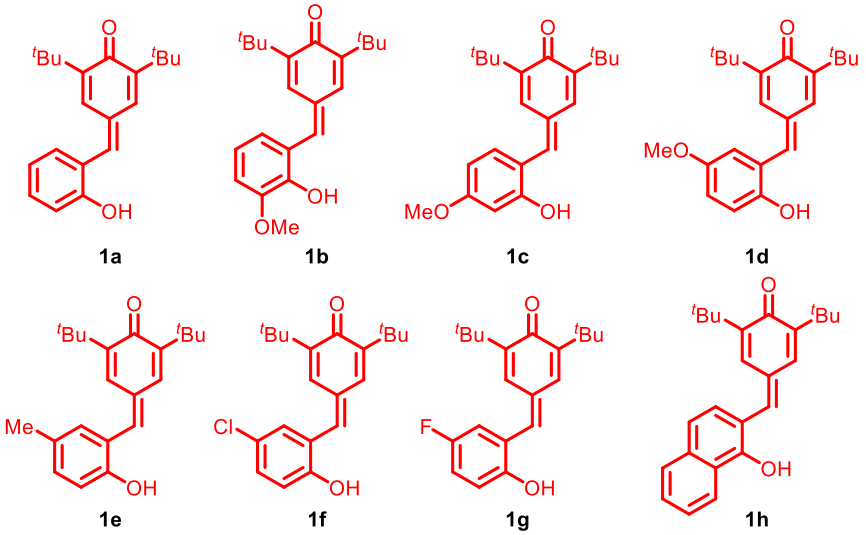
### 2A.5.2 General Procedure: Synthesis of 2-hydroxy-*p*-quinone methides[25]



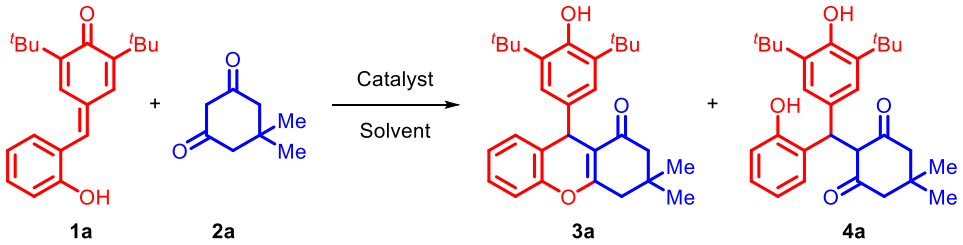

**1a1-1h1** **1a-1h**

A solution of phenols (1.1 equiv.) and aldehydes (1.0 equiv.) in toluene (5 mL/mmol substrate) was placed in a Dean-Stark apparatus which was heated to reflux. Piperidine (2.0 equiv.) was added dropwise slowly. Then, the temperature was raised to 140 °C and stirred for 12 h. After that, the reaction mixture was cooled to 120 °C and acetic anhydride (2.0 equiv.) was dropwise added. The stirring was continued for 0.5 h and the solution was poured on ice-water and extracted with $CH_2Cl_2$ (3 × 50 mL). The organic phases were combined, washed with brine and dried over anhydrous $Na_2SO_4$. Then the solvent was evaporated under reduced pressure and the corresponding products **1a1-1h1** were obtained after flash column chromatography (pentane/$Et_2O$ = 100/1 to 30/1).

To a solution of **1a1-1h1** (1.0 equiv.) in THF (10 mL/mmol substrate) at 0 °C was added tetrabutylammonium fluoride trihydrate (1.1 equiv.). The reaction mixture was stirred for 10 min. and a saturated $NH_4Cl$ solution was added dropwise to quench the reaction. The resulting solution was extracted with $Et_2O$ (3 × 20 mL). Then the combined organic phases were washed with brine and dried over anhydrous $Na_2SO_4$. The solvent was removed to give the crude product which was purified by flash column chromatography (pentane/$Et_2O$ = 10/1 to 4/1) to afford the desired compounds **1a-1h**.



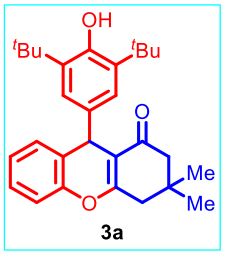

### 2A.5.3 General Procedure: Synthesis of 2,3,4,9-tetrahydro-1*H*-xanthene-1-one




2-Hydroxy-*p*-quinone methides **1(a-h)** (0.030-0.055 mmol, 15 mg, 1.0 equiv.), *β*-functionalized ketones containing active methylene compounds **2(a-d)** (0.8 equiv.) in 1 ml of DCE were taken into the oven dried 5 ml reaction vials with a magnetic bar. Then, 10 mol% triflimide ($Tf_2NH$) dissolved in 0.5 ml of DCE was added dropwise, and the reaction mixture stirred at room temperature for 5 min. The completion of the reaction was confirmed by the thin layer chromatography using pet. ether/ethyl acetate solvent system. The starting material 2-hydroxy-*p*-QM was completely consumed within 5 min. After the completion of the reaction, the reaction mass was concentrated under the high vacuum, and the crude product was purified by column chromatography on silica gel 100-200 mesh to obtain the product as solid.

**2A.6 NMR Data**

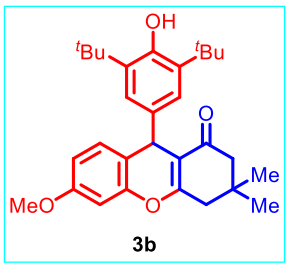
**9-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (3a):**




Compound **3a** was prepared according to General Procedure 2A.5.3. After column purification the product was obtained as white solid in 89% yield. **mp** = 134-136 ºC; $\boldsymbol{R_f}$ = 0.77 (pet. ether/ethyl acetate, 5:1); **IR ($CHCl_3$):** $\boldsymbol{\nu_{max}}$ = 3636, 2958, 1724, 1643, 1591, 1434, 1375, 1304, 1231, 1153, 1119, 1024, 889, 757 $cm^{-1}$; **$^1$H NMR** (400 MHz , $CDCl_3$) $\delta$ = 7.16 (br. s., 2 H), 7.06 (d, *J* = 7.3 Hz, 2 H), 7.00 (s, 2 H), 4.99 (s, 1 H), 4.94 (br. s., 1 H), 2.57 (br. s., 2 H), 2.27 (d, *J* = 5.5 Hz, 2 H), 1.37 (s, 18 H), 1.14 (br. s., 3 H), 1.09 (br. s., 3 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 196.9, 164.8, 152.2, 149.6, 136.8, 135.5, 129.9, 127.2, 126.3, 124.9, 124.0, 116.4, 114.0, 50.8, 41.6, 37.5, 34.2, 32.1, 30.3, 29.6, 27.1; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{29}H_{36}O_3$ $[M + Na]^+$ 455.2562, found 455.2557.

**……..**

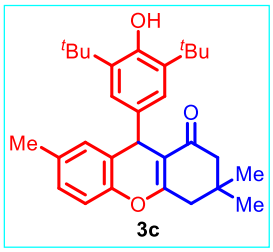
**9-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-6-methoxy-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (3b):**




Compound **3b** was prepared according to General Procedure 2A.5.3. After column purification the product was obtained as orange thick liquid in 82% yield. $\boldsymbol{R_f}$ = 0.60 (pet. ether/ethyl acetate, 5:1); **IR ($CHCl_3$):** $\boldsymbol{\nu_{max}}$ = 3633, 3352, 2959, 2926, 2873, 1648, 1602, 1504, 1462, 1436, 1373, 1283, 1218, 1159, 1115, 1033, 757 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.05 (d, *J* = 8.2 Hz, 1 H), 6.98 (s, 2 H), 6.67 - 6.57 (m, 2 H), 4.98 (s, 1 H), 4.87 (s, 1 H), 3.79 (s, 3 H), 2.55 (s, 2 H), 2.27 (d, *J* = 6.4 Hz, 2 H), 1.37 (s, 19 H), 1.14 (s, 3 H), 1.08 (s, 3 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 196.9, 164.5, 158.7, 152.1, 150.1, 137.1, 135.4, 130.4, 123.9, 118.5, 114.3, 111.5, 101.4, 55.4, 50.8, 41.6, 36.9, 34.2, 32.1, 30.3, 29.6, 27.1; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{30}H_{38}O_4$ $[M + Na]^+$ 485.2668, found 485.2663.

**……..**

**9-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3,3,7-trimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (3c):**

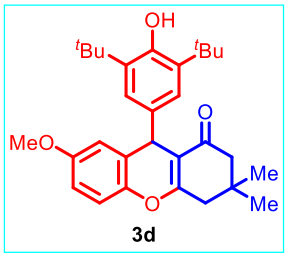


**3c**

Compound **3c** was prepared according to General Procedure 2A.5.3. After column purification the product was obtained as orange thick liquid in 85% yield. $R_f$ = 0.47 (pet. ether/ethyl acetate, 5:1); **IR ($CHCl_3$):** $\nu_{max}$ = 3631, 3382, 2959, 2873, 1702, 1648, 1594, 1489, 1460, 1433, 1375, 1307, 1209, 1154, 1121, 1070, 1032 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.00 (s, 2 H), 6.95 (s, 3 H), 5.00 (s, 1 H), 4.88 (s, 1 H), 2.56 - 2.53 (m, 2 H), 2.28 - 2.24 (m, 5 H), 1.37 (s, 19 H), 1.13 (s, 3 H), 1.07 (s, 3 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 196.8, 164.9, 152.1, 147.6, 136.9,135.4, 134.4, 130.0, 127.9, 125.9, 124.1, 116.1, 114.1, 77.3, 76.7, 50.8,41.6, 37.6, 34.2, 32.1, 30.3, 29.6, 27.0, 20.8; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{30}H_{38}O_3$ $[M + Na]^+$ 469.2719, found 469.2715.

**……..**

**9-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-7-methoxy-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (3d):**



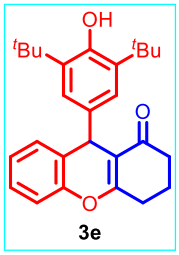
**3d**

Compound **3d** was prepared according to General Procedure 2A.5.3. After column purification the product was obtained as colourless solid in 78% yield. **mp** = 121-123 ºC; $R_f$ = 0.70 (pet. ether/ethyl acetate, 5:1); **IR ($CHCl_3$):** $\nu_{max}$ = 3636, 3451, 2958, 2875, 1640, 1594, 1492, 1462, 1433, 1377, 1323, 1286, 1219, 1150, 1118, 1031, 886, 818, 757 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.02 - 6.97 (m, 3 H), 6.73 - 6.65 (m, 2 H), 5.00 (s, 1 H), 4.89 (s, 1 H), 3.74 (s, 3 H), 2.61 - 2.49 (m, 2 H), 2.32 - 2.21 (m, 2 H), 1.37 (s, 19 H), 1.13 (s, 3 H), 1.08 (s, 3 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 196.9, 165.1, 156.5, 152.3, 143.8, 136.7, 135.6, 127.3, 124.0, 117.2, 114.1, 113.4, 113.1, 77.4, 77.1, 76.8, 55.6, 50.9, 41.7, 38.1, 34.3, 32.2, 30.4, 29.8, 27.1; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{30}H_{38}O_4$ $[M + Na]^+$ 485.2668, found 485.2662.

**……**

**9-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (3e):**

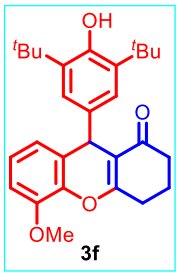
Compound **3e** was prepared according to General Procedure 2A.5.3. After column purification the product was obtained as colourless solid in 65% yield. **mp** = 198-200 ºC; $R_f$ =




0.40 (pet. ether/ethyl acetate, 5:1); **IR ($CHCl_3$):** $\nu_{max}$ = 3777, 3635, 3543, 2957, 1724, 1644, 1582, 1472, 1439, 1375, 1309, 1232, 1177, 1128, 1061, 994, 921, 861, 756, 652 $cm^{-1}$; **$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$ = 7.21 - 7.15 (m, 2 H), 7.10 - 7.04 (m, 2 H), 7.00 (s, 2 H), 5.02 (s, 1 H), 5.01 (s, 1 H), 2.72 (t, *J* = 5.0 Hz, 2 H), 2.46 (t, *J* = 5.0 Hz, 2 H), 2.12 - 2.01 (m, 2 H), 1.37 (s, 18 H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) $\delta$ = 197.0, 166.5, 152.2, 149.8, 136.6, 135.4, 129.8, 127.2, 126.3, 124.9, 124.2, 116.3, 115.3, 37.1, 37.1, 34.2, 30.3, 27.9, 20.4; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{27}H_{32}O_3$ $[M + Na]^+$ 427.2249, found 427.2244.

**……..**

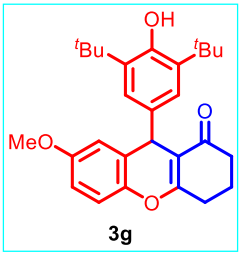
**9-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-5-methoxy-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (3f):**




Compound **3f** was prepared according to General Procedure 2A.5.3. After column purification the product was obtained as colourless solid in 75% yield. **mp** = 224-226 ºC; $R_f$ = 0.40 (pet. ether/ethyl acetate, 5:1); **IR ($CHCl_3$):** $\nu_{max}$ = 3782, 3635, 3451, 2956, 1732, 1643, 1611, 1584, 1479, 1434, 1377, 1324, 1274, 1224, 1183, 1126, 1091, 957, 893, 752 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.03 - 6.97 (m, 3 H), 6.78 (t, *J* = 8.2 Hz, 2 H), 5.05 - 4.98 (m, 2 H), 3.92 (s, 3 H), 2.83 (t, *J* = 4.9 Hz, 2 H), 2.52 - 2.36 (m, 2 H), 2.14 - 2.03 (m, 2 H), 1.37 (s, 18 H)**;** **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 197.1, 166.4, 152.2, 147.7, 139.3, 136.3, 135.4, 127.4, 124.6, 124.1, 121.4, 115.0, 109.6, 77.3, 76.7, 56.1, 37.2, 37.1, 34.3, 30.3, 27.9, 20.5; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{28}H_{34}O_4$ $[M + Na]^+$ 457.2355, found 457.2347.

**……..**

**9-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-7-methoxy-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (3g):**

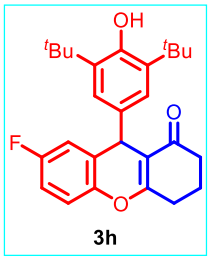



Compound **3g** was prepared according to General Procedure 2A.5.3. After column purification the product was obtained as colourless solid in 72% yield. **mp** = 197-199 ºC; $R_f$ = 0.29 (pet. ether/ethyl acetate, 5:1); **IR ($CHCl_3$):** $\nu_{max}$ = 3636, 3417, 2956, 2333, 1721, 1637, 1594, 1492, 1459, 1432, 1377, 1324, 1221, 1192, 1124, 1035, 997, 885, 815, 756 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.03 - 6.98 (m, 3 H), 6.69 (s, 2 H), 5.00 (s, 1 H), 4.97 (s, 1 H),

3.74 (s, 3 H), 2.70 (t, *J* = 4.9 Hz, 2 H), 2.49 - 2.35 (m, 2 H), 2.15 - 2.03 (m, 2 H), 1.38 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 197.0, 166.7, 156.5, 152.2, 144.0, 136.5, 135.4, 127.1, 124.1, 117.1, 114.5, 113.8, 113.2, 77.3, 76.7, 55.6, 37.6, 37.1, 34.3, 30.3, 27.9, 20.5; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{28}H_{34}O_4$ $[M + Na]^+$ 457.2355, found 457.2349.

**……..**

**9-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-7-fluoro-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (3h):**

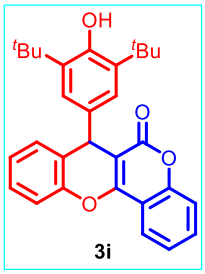


**3h**

Compound **3h** was prepared according to General Procedure 2A.5.3. After column purification the product was obtained as colourless solid in 73% yield. **mp** = 213-215 ºC; $R_f$ = 0.56 (pet. ether/ethyl acetate, 5:1); **IR ($CHCl_3$): $\nu_{max}$** = 3631, 3552, 2957, 2923, 2871, 1647, 1593, 1489, 1432, 1377, 1253, 1220, 1191, 1131, 1060, 999, 889, 863, 813, 760 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.07 - 6.97 (m, 3 H), 6.91 - 6.82 (m, 2 H), 5.04 (s, 1 H), 4.96 (s, 1 H), 2.71 (t, *J* = 4.9 Hz, 2 H), 2.50 - 2.34 (m, 2 H), 2.13 - 2.01 (m, 2 H), 1.38 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 196.9, 166.3, 152.4, 136.1, 135.6, 127.9, 124.1, 117.6, 117.5, 115.9, 115.7, 114.4, 114.2, 77.3, 76.7, 37.6, 37.0, 34.3, 30.3, 27.8, 20.4 ; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{27}H_{31}FO_3$ $[M + Na]^+$ 445.2155, found 445.2147.

**……..**

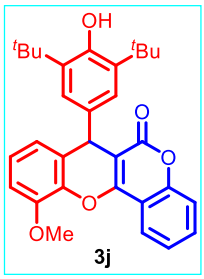
**7-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-6*H*,7*H*-chromeno[4,3-*b*]chromen-6-one (3i):**



**3i**

Compound **3i** was prepared according to General Procedure 2A.5.3. After column purification the product was obtained as pale yellow-solid in 61% yield. **mp** = 223-225 ºC; $R_f$ = 0.41 (pet. ether/ethyl acetate, 4:1); **IR ($CHCl_3$): $\nu_{max}$** = 3636, 2958, 2923, 2870, 1716, 1643, 1609, 1581, 1485, 1387, 1320, 1275, 1237, 1214, 1182, 1155, 1110, 1043, 757. $cm^{-1}$; **$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$ = 8.00 (br. s., 1 H), 7.50 (br. s., 1 H), 7.32 (br. s., 4 H), 7.21 (d, *J* = 7.6 Hz, 2 H), 7.13 (br. s., 1 H), 7.02 (br. s., 2 H), 5.17 (br. s., 1 H), 5.02 (br. s., 1 H), 1.30 (br. s., 18 H)**;** **$^{13}$C NMR** (125 MHz, $CDCl_3$) $\delta$ = 165.3, 161.8, 155.5, 152.6, 152.5, 149.6, 135.6, 135.2, 131.8, 130.1, 128.0, 125.7, 124.8, 124.1, 122.7, 116.7, 116.5, 114.8, 105.4, 38.8, 34.2, 30.2; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{30}H_{30}O_4$ $[M + Na]^+$ 477.2042, found 477.2036.

**7-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-11-methoxy-6*H*,7*H*-chromeno[4,3-*b*]chromen-6-one (3j):**

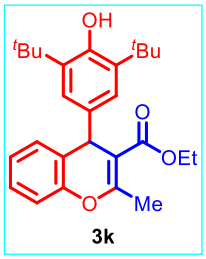


**3j**

Compound **3j** was prepared according to General Procedure 2A5.3. After column purification the product was obtained as colourless solid in 66% yield. **mp** = 131-134 ºC; $R_f$ = 0.57 (pet. ether/ethyl acetate, 4:1); **IR ($CHCl_3$):** $\nu_{max}$ = 3634, 3376, 2958, 2926, 2357, 1690, 1618, 1571, 1477, 1436, 1359, 1274, 1215, 1159, 1111, 1077, 1042, 947, 884, 758 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.76 (d, *J* = 7.6 Hz, 1 H), 7.53 - 7.49 (m, 1 H), 7.31 (d, *J* = 8.0 Hz, 1 H), 7.22 (s, 1 H), 7.07 (s, 2 H), 6.89 - 6.84 (m, 3 H), 6.05 (s, 1 H), 5.19 (s, 1 H), 3.90 (s, 3 H), 1.36 (s, 18 H)**;** **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 163.4, 160.5, 153.0, 152.6, 146.8, 143.3, 136.5, 131.6, 128.7, 126.8, 124.8, 123.7, 123.2, 122.2, 120.3, 116.4, 116.3, 110.0, 107.1, 106.9, 56.2, 42.3, 34.4, 30.2; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{31}H_{32}O_5$ $[M + Na]^+$ 507.2147, found 507.2142.

**……..**

**Ethyl 4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-methyl-4*H*-chromene-3-carboxylate (3k):**



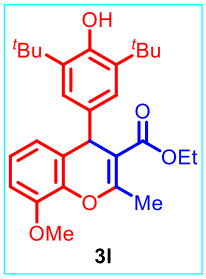
**3k**

Compound **3k** was prepared according to General Procedure 2A.5.3. After column purification the product was obtained as yellow solid in 69% yield. **mp** = 137-139 ºC; $R_f$ = 0.75 (pet. ether/ethyl acetate, 5:1); **IR ($CHCl_3$):** $\nu_{max}$ = 3637, 3454, 2959, 2924, 1707, 1640, 1585, 1484, 1434, 1373, 1331, 1287, 1218, 1157, 1108, 1064, 9866, 936, 895, 756 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.15 - 7.09 (m, 2 H), 7.02 (d, *J* = 8.3 Hz, 2 H), 6.97 (s, 2 H), 5.01 (s, 1 H), 4.94 (s, 1 H), 4.16 - 4.08 (m, 2 H), 2.48 (s, 3 H), 1.37 (s, 18 H), 1.20 (t, *J* = 7.1 Hz, 3 H)**;** **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 167.4, 160.0, 152.2, 149.8, 137.3, 135.5, 129.1, 127.2, 125.6, 124.4, 124.2, 116.0, 106.9, 60.0, 41.1, 34.2, 30.3, 19.4, 14.2; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{27}H_{34}O_4$ $[M + Na]^+$ 445.2355, found 445.2353.

**……..**

**Ethyl 4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-8-methoxy-2-methyl-4*H*-chromene-3-carboxylate (3l):**

Compound **3l** was prepared according to General Procedure 2A.5.3. After column purification the product was obtained as yellow solid in 54% yield. **mp** = 121-123 ºC; $R_f$ =

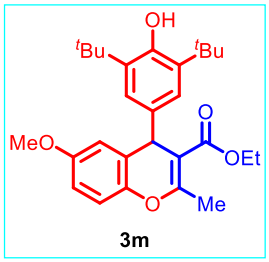


**3l**

0.55 (pet. ether/ethyl acetate, 5:1); **IR ($CHCl_3$):** $\nu_{max}$ = 3636, 2959, 1705, 1643, 1612, 1586, 1482, 1435, 1371, 1329, 1275, 1237, 1200, 1162, 1097, 1064, 1018, 990, 963, 756 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 6.99 (s, 2 H), 6.95 (t, *J* = 7.9 Hz, 1 H), 6.76 - 6.70 (m, 2 H), 5.01 (s, 1 H), 4.94 (s, 1 H), 4.11 (t, *J* = 7.3 Hz, 2 H), 3.91 (s, 3 H), 2.55 (s, 3 H), 1.38 (s, 18 H), 1.19 (t, *J* = 7.3 Hz, 3 H)**;** **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 167.3, 159.8, 152.2, 147.5, 139.4, 137.1, 135.4, 126.6, 124.2, 124.0, 120.7, 109.6, 106.8, 60.0, 56.1, 41.2, 34.2, 30.3, 19.4, 14.2; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{28}H_{36}O_5$ $[M + Na]^+$ 475.2460, found 475.2455.

……..

**Ethyl 4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-6-methoxy-2-methyl-4*H*-chromene-3-carboxylate (3m):**

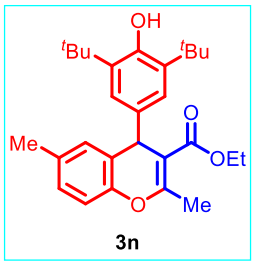


**3m**

Compound **3m** was prepared according to General Procedure 2A.5.3. After column purification the product was obtained as yellow solid in 69% yield. **mp** = 197-199 ºC; ***R*$_f$** = 0.67 (pet. ether/ethyl acetate, 5:1); **IR ($CHCl_3$):** $\nu_{max}$ = 3022, 2925, 2402, 1593, 1425, 1215, 1021, 759, 668 cm–1; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.00 - 6.94 (m, 3 H), 6.73 - 6.68 (m, 1 H), 6.61 (d, *J* = 3.1 Hz, 1 H), 5.02 (s, 1 H), 4.90 (s, 1 H), 4.16 - 4.07 (m, 2 H), 3.73 (s, 3 H), 2.47 (s, 3 H), 1.38 (s, 18 H), 1.20 (t, *J* = 7.0 Hz, 3 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 167.5, 160.4, 156.1, 152.2, 144.1, 137.2, 135.4, 126.5, 124.1, 116.8, 113.3, 113.0, 106.0, 59.9, 55.5, 41.5, 34.2, 30.3, 19.4, 14.2; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{28}H_{36}O_5$ $[M + Na]^+$ 475.2460, found 475.2453.

……..

**Ethyl 4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,6-dimethyl-4*H*-chromene-3-carboxylate (3n):**



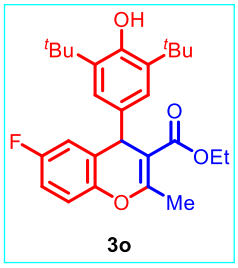
**3n**

Compound **3n** was prepared according to General Procedure 2A.5.3. After column purification the product was obtained as brown liquid in 61% yield. ***R*$_f$** = 0.60 (pet. ether/ethyl acetate, 5:1); **IR ($CHCl_3$):** $\nu_{max}$ = 3633, 3406, 2960, 2871, 1708, 1639, 1592, 1493, 1434, 1370, 1287,

1211, 1160, 1117, 1065, 987, 885, 816, 758 $cm^{-1}$; **$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$ = 6.98 (s, 2 H), 6.93 (d, *J* = 2.3 Hz, 2 H), 6.90 (s, 1 H), 5.02 (s, 1 H), 4.89 (s, 1 H), 4.12 (dd, *J* = 3.2, 7.1 Hz, 2 H), 2.47 (s, 3 H), 2.24 (s, 3 H), 1.38 (s, 18 H), 1.23 - 1.20 (m, 3 H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) $\delta$ = 167.4, 160.3, 152.1, 147.9, 137.4, 135.4, 133.8, 129.2, 127.9, 125.2, 124.2, 115.7, 106.8, 77.3, 76.7, 59.9, 41.1, 34.2, 30.3, 30.1, 29.4, 20.8, 19.4, 14.2; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{28}H_{36}O_4$ $[M + Na]^+$ 459.2511, found 459.250.

**……..**

**1-(4-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-6-fluoro-2-methyl-4*H*-chromen-3-yl)propan-1-one (3o):**

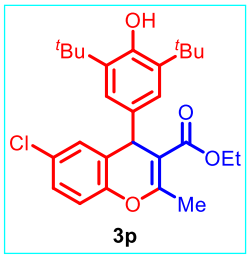


**3o**

Compound **3o** was prepared according to General Procedure 2A.5.3. After column purification the product was obtained as yellow liquid in 58% yield. $R_f$ = 0.55 (pet. ether/ethyl acetate, 5:1); **IR ($CHCl_3$): $\nu_{max}$** = 3637, 2960, 2874, 1708, 1646, 1597, 1490, 1434, 1372, 1324, 1268, 1209, 1148, 1103, 1066, 990, 871, 819, 759 $cm^{-1}$; **$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$ = 7.01 - 6.95 (m, 3 H), 6.84 (d, *J* = 3.1 Hz, 1 H), 6.80 - 6.77 (m, 1 H), 5.05 (s, 1 H), 4.90 (s, 1 H), 4.11 (dd, *J* = 7.2, 9.2 Hz, 2 H), 2.47 (s, 3 H), 1.38 (s, 18 H), 1.20 (t, *J* = 7.1 Hz, 3 H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) $\delta$ = 167.2, 159.9, 158.1, 152.4, 145.8, 136.8, 135.7, 127.2, 127.1, 124.1, 117.3, 117.2, 115.2, 115.0, 114.3, 114.1, 106.1, 60.0, 41.4, 34.2, 30.2, 19.3, 14.2; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{27}H_{33}FO_4$ $[M + Na]^+$ 463.2261, found 463.2259.

**……..**

**Ethyl 6-chloro-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-methyl-4*H*-chromene-3-carboxylate (3p):**



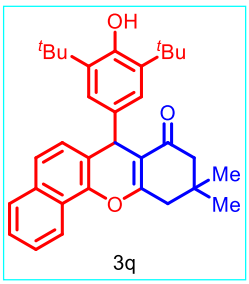
**3p**

Compound **3p** was prepared according to General Procedure 2A.5.3. After column purification the product was obtained as yellow solid in 63% yield. **mp** = 104-106 ºC; $R_f$ = 0.83 (pet. ether/ethyl acetate, 5:1); **IR ($CHCl_3$): $\nu_{max}$** = 3635, 3414, 2960, 1709, 1640, 1584, 1478, 1434, 1372, 1324, 1276, 1225, 1118, 1066, 987, 917, 882, 818, 761 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.12 - 7.06 (m, 2 H), 6.98 (s, 1 H), 6.95 (s, 2 H), 5.06 (s, 1 H), 4.88 (s, 1 H), 4.12 (dd, *J* = 4.0, 7.0 Hz, 2 H), 2.47 (s, 3 H), 1.39 (s, 18 H), 1.21 (t, *J* = 7.0 Hz, 3 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 167.0, 159.8, 152.4, 148.4, 136.7, 135.6, 129.0,

128.8, 127.3, 124.2, 117.4, 106.8, 77.3, 76.7, 60.1, 41.1, 34.2, 30.2, 19.3, 14.2; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{27}H_{33}ClO_4$ $[M + Na]^+$ 479.1965, found 479.1960.

……..

**7-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-10,10-dimethyl-7,9,10,11-tetrahydro-8*H*-benzo[*c*]xanthen-8-one (3q):**

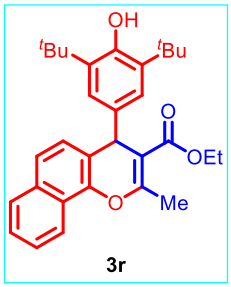


3q

Compound **3q** was prepared according to General Procedure 2A.5.3. After column purification the product was obtained as brown solid in 65% yield. **mp** = 145-147 ºC; $R_f$ = 0.64 (pet. ether/ethyl acetate, 5:1); **IR ($CHCl_3$):** $\nu_{max}$ = 3635, 3382, 3064, 2958, 2873, 1649, 1594, 1462, 1433, 1374, 1317, 1281, 1224, 1165, 1118, 1072, 1024, 965, 813, 755 $cm^{-1}$; **$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$ = 8.18 (d, *J* = 8.4 Hz, 1 H), 7.78 (s, 1 H), 7.73 (d, *J* = 9.2 Hz, 1 H), 7.40 (s, 1 H), 7.31 (d, *J* = 8.8 Hz, 1 H), 7.11 (s, 2 H), 5.61 (s, 1 H), 4.95 (s, 1 H), 2.59 (d, *J* = 5.3 Hz, 2 H), 2.30 (d, *J* = 8.0 Hz, 2 H), 1.32 (s, 18 H), 1.14 (s, 3 H), 1.03 (s, 3 H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) $\delta$ = 197.2, 164.4, 152.2, 147.9, 135.7, 135.3, 131.7, 128.5, 126.9, 125.0, 124.1, 119.1, 117.3, 115.2, 77.5, 77.3, 51.1, 41.6, 34.4, 34.2, 32.6, 30.5, 29.9, 27.1, 18.7; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{33}H_{38}O_3$ $[M + Na]^+$ 505.2719, found 505.2716.

……..

**Ethyl 1-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-methyl-1*H*-benzo[*f*]chromene-2-carboxylate (3r):**



**3r**

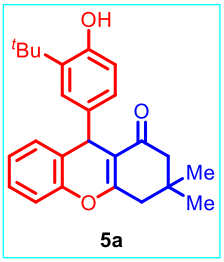
Compound **3r** was prepared according to General Procedure 2A.5.3. After column purification the product was obtained as yellow solid in 62% yield. **mp** = 128-130 ºC; $R_f$ = 0.68 (pet. ether/ethyl acetate, 5:1); **IR ($CHCl_3$):** $\nu_{max}$ = 3635, 2960, 2874, 1703, 1649, 1622, 1597, 1463, 1435, 1391, 1371, 1324, 1258, 1220, 1158, 1123, 1063, 983, 816, 758 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 8.02 (d, *J* = 7.9 Hz, 1 H), 7.75 (d, *J* = 7.9 Hz, 1 H), 7.68 (d, *J* = 8.5 Hz, 1 H), 7.43 (t, *J* = 7.6 Hz, 1 H), 7.38 - 7.31 (m, 1 H), 7.24 (d, *J* = 10.4 Hz, 1 H), 7.05 (s, 2 H), 5.55 (s, 1 H), 4.93 (s, 1 H), 4.20 (q, *J* = 7.3 Hz, 2 H), 2.48 (s, 3 H), 1.37 - 1.26 (m, 21 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 167.4, 159.9, 152.1, 148.0, 136.2, 135.2, 131.3, 131.1, 128.4, 128.2, 126.5, 124.6, 124.4, 123.3, 118.2, 117.1, 107.9,

77.3, 76.7, 60.2, 37.6, 34.1, 30.2, 19.4, 14.4; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{31}H_{36}O_4$ $[M + Na]^+$ 495.2511, found 495.2509.

**……..**

**General procedure for the synthesis of 5a and 6a:** In an oven-dried 50 mL round-bottomed flask, compound **3a** (50 mg, 0.11 mmol) was taken in dry toluene (10 mL) followed by the addition of anhydrous $AlCl_3$ (94.2 mg, 0.698 mmol) at once, under an argon atmosphere. The reaction mixture was stirred at -30 °C until the completion of reaction. Ice water was added to quench the $AlCl_3$. The mixture was extracted with EtOAc (3 × 15 mL), the combined organic layers were dried (anhydrous $Na_2SO_4$), and concentrated under reduced pressure followed by column chromatography purification to give **5a** and further **6a**.

**9-(3-(*tert*-Butyl)-4-hydroxyphenyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (5a):**

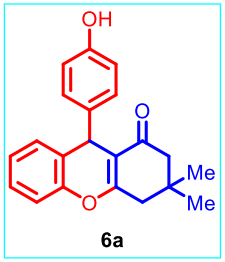


**5a**

White solid; 79% yield. **mp** = 121-123 °C; $\boldsymbol{R_f}$ = 0.70 (pet. ether/ethyl acetate, 5:1); **IR ($CHCl_3$):** $\boldsymbol{\nu_{max}}$ = 3347, 2955, 1635, 1592, 1472, 1423, 1378, 1303, 1230, 1189, 1087, 1025, 930, 877, 826, 757, 652. $cm^{-1}$; **$^1$H NMR** (200 MHz, $CDCl_3$) $\delta$ = 7.16 - 7.11 (m, 2 H), 7.10 - 7.03 (m, 3 H), 6.88 (dd, *J* = 2.2, 8.0 Hz, 1 H), 6.40 (d, *J* = 8.1 Hz, 1 H), 5.54 (s, 1 H), 4.95 (s, 1 H), 2.56 (s, 2 H), 2.27 (s, 2 H), 1.33 (s, 9 H), 1.13 (s, 3 H), 1.05 (s, 3 H); **$^{13}$C NMR** (50 MHz, $CDCl_3$) $\delta$ = 197.3, 164.8, 152.9, 149.4, 137.9, 135.9, 130.0, 127.3, 126.4, 125.9, 125.0, 116.4, 113.9, 50.8, 41.6, 37.2, 34.4, 32.2, 29.5, 27.1; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{25}H_{28}O_3$ $[M + Na]^+$ 399.1936, found 399.1931.

**……..**

**9-(4-Hydroxyphenyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (6a):**



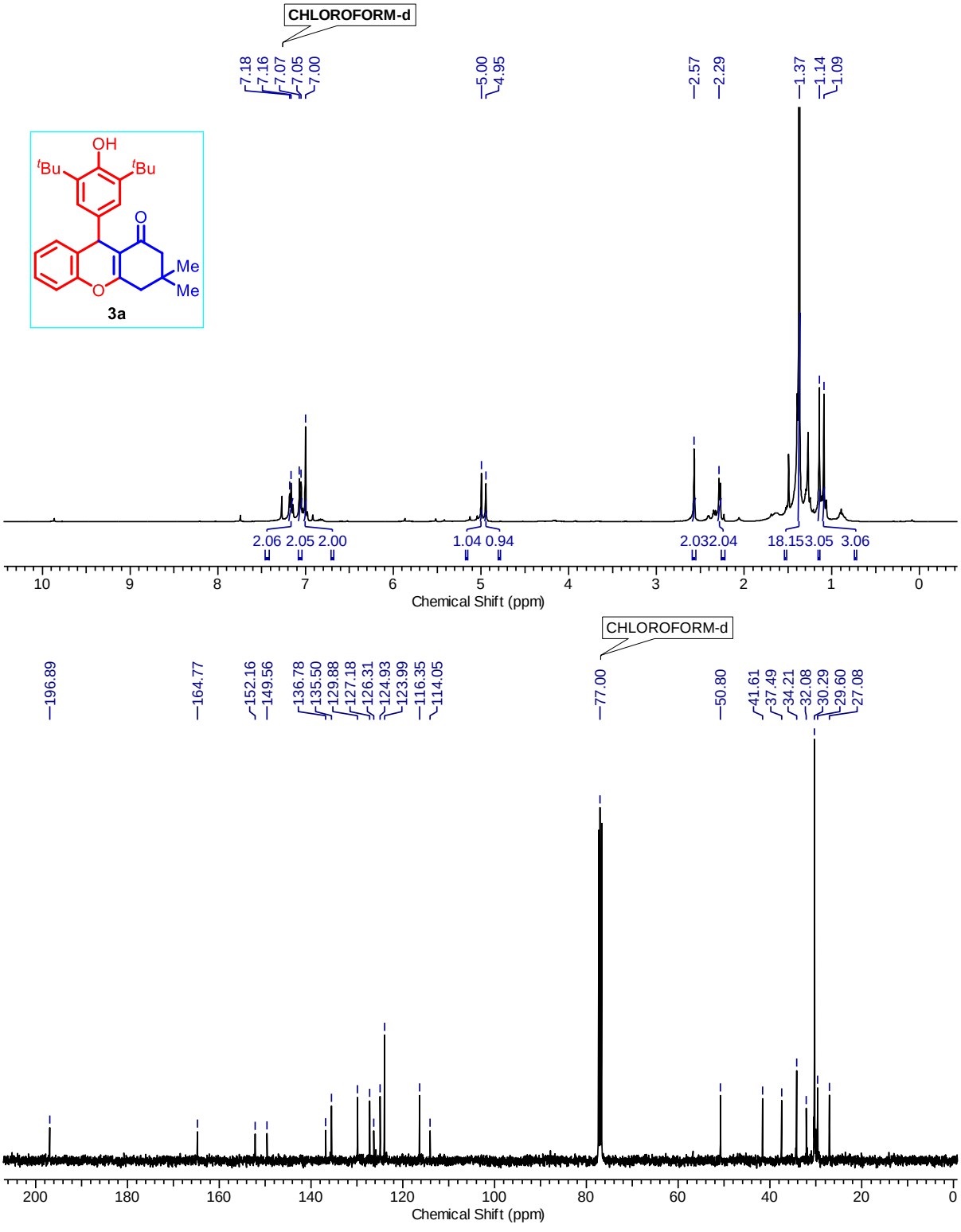
**6a**

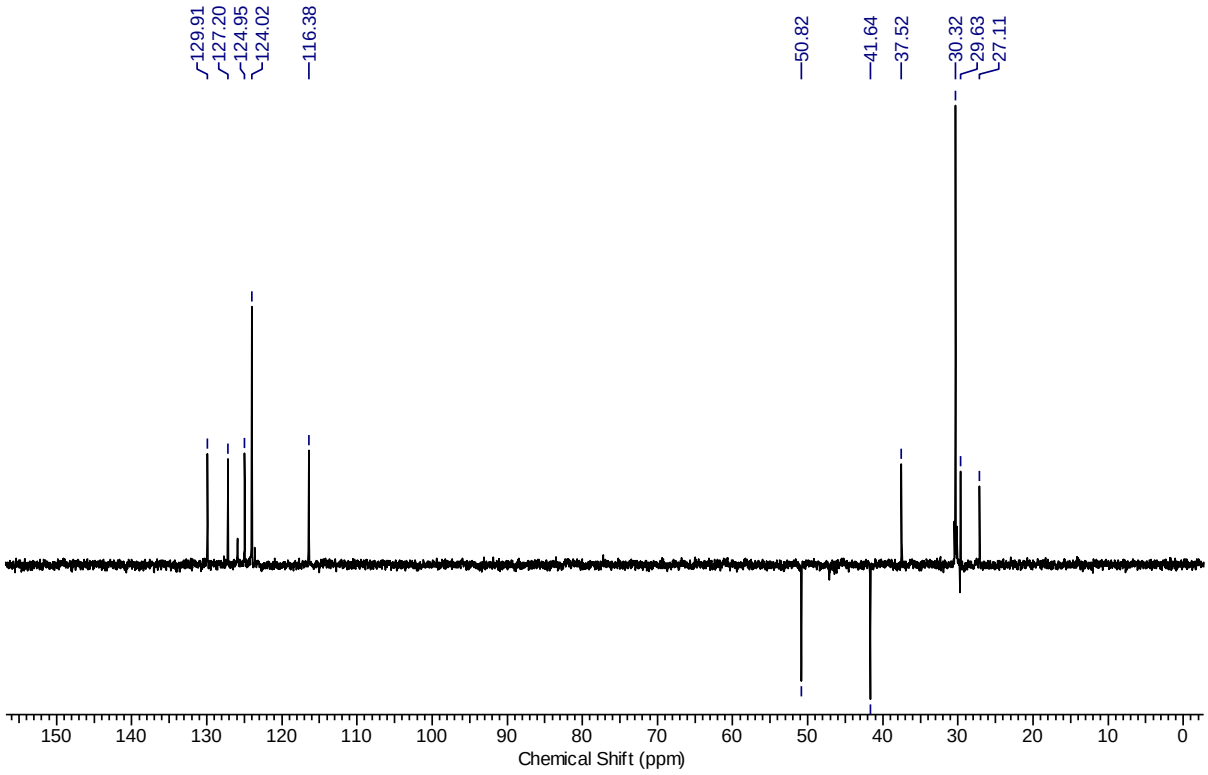
White solid; 63% yield. **mp** = 103-105 °C; $\boldsymbol{R_f}$ = 0.43 (pet. ether/ethyl acetate, 5:1); **IR ($CHCl_3$):** $\boldsymbol{\nu_{max}}$ = 3347, 2955, 1635, 1592, 1472, 1423, 1378, 1303, 1230, 1189, 1087, 1025, 930, 877, 826, 757, 652 $cm^{-1}$; **$^1$H NMR** (200 MHz, $CDCl_3$) $\delta$ = 7.16 - 7.12 (m, 1 H), 7.08 (d, *J* = 2.4 Hz, 3 H), 7.03 (s, 2 H), 6.61 (d, *J* = 8.5 Hz, 2 H), 6.01 (br. s., 1 H), 4.96 (s, 1 H), 2.56 (s, 2 H), 2.28 (s, 2 H), 1.12 (s, 3 H), 1.04 (s, 3 H); **$^{13}$C NMR** (50

MHz, $CDCl_3$) $\delta$ = 197.5, 164.8, 153.0, 149.4, 137.7, 135.9, 130.0, 127.3, 126.3, 126.0, 125.0, 116.4, 113.9, 50.8, 41.6, 37.2, 34.4, 32.2, 29.5, 29.4, 27.1; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{21}H_{20}O_3$ $[M + Na]^+$ 343.1310, found 343.1305.

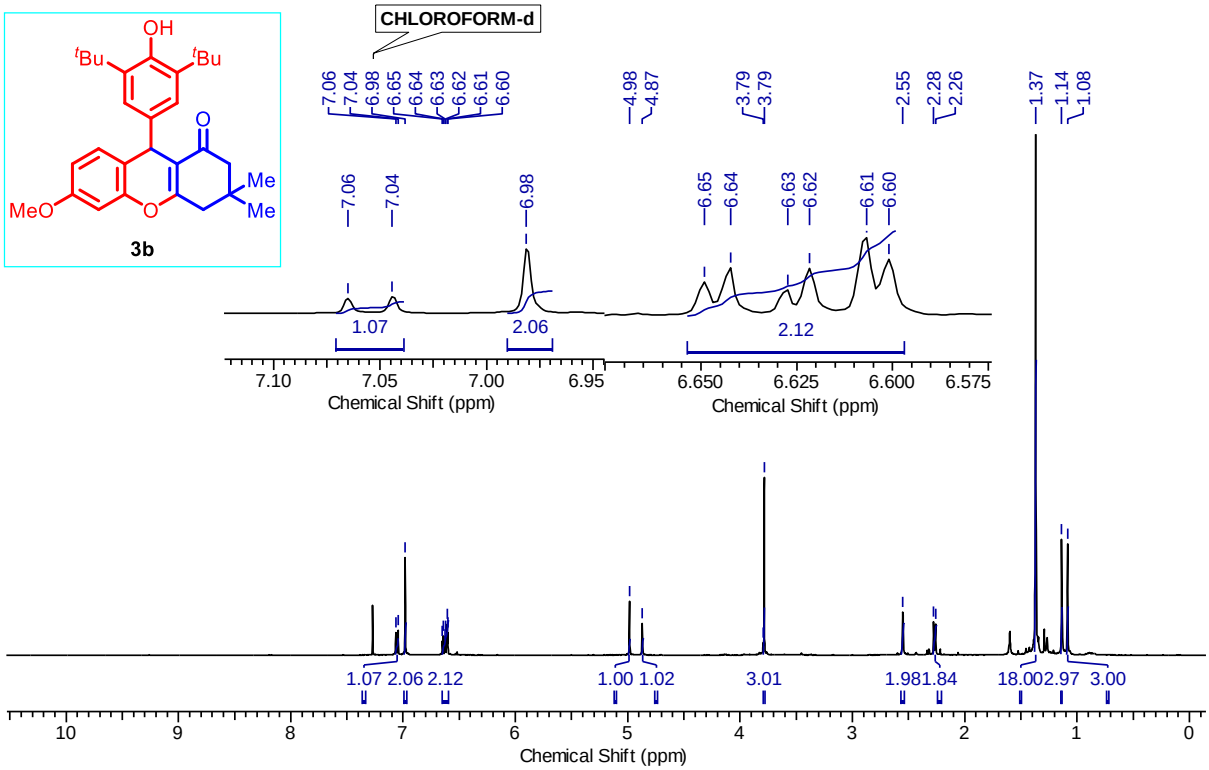
## 2A.7 NMR Spectra

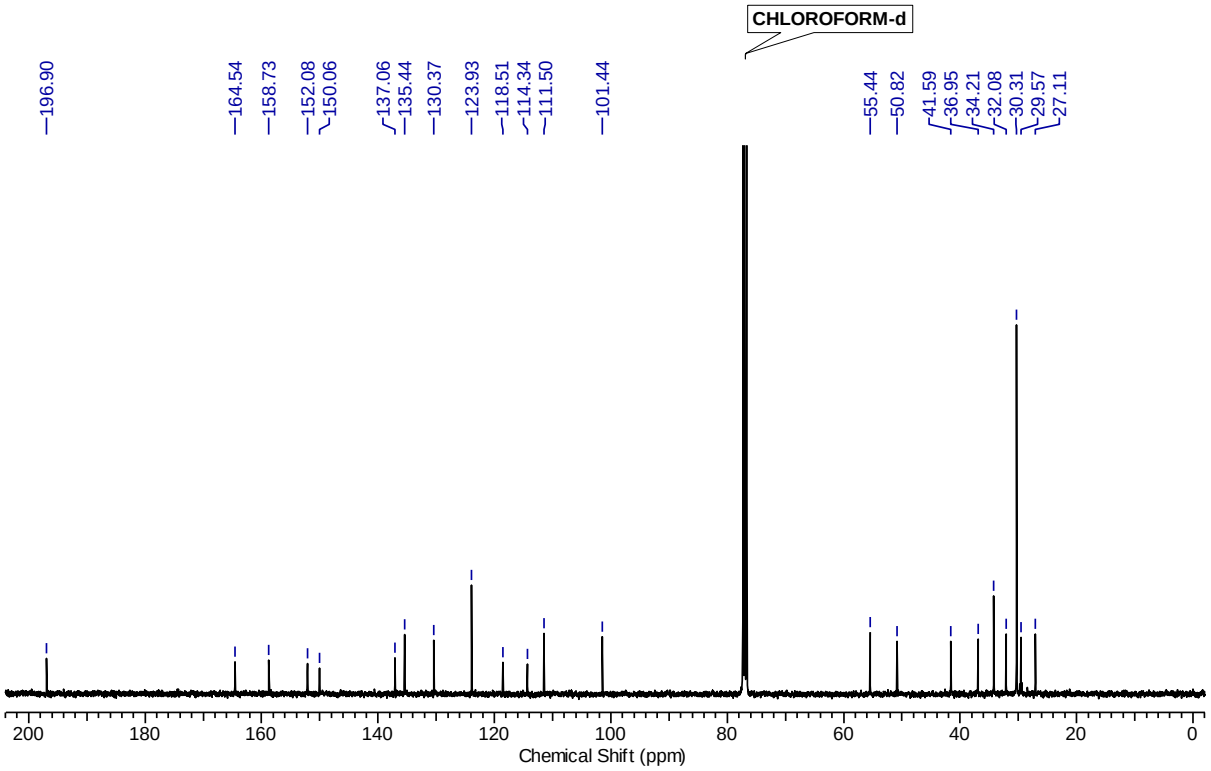
### 9-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (3a):

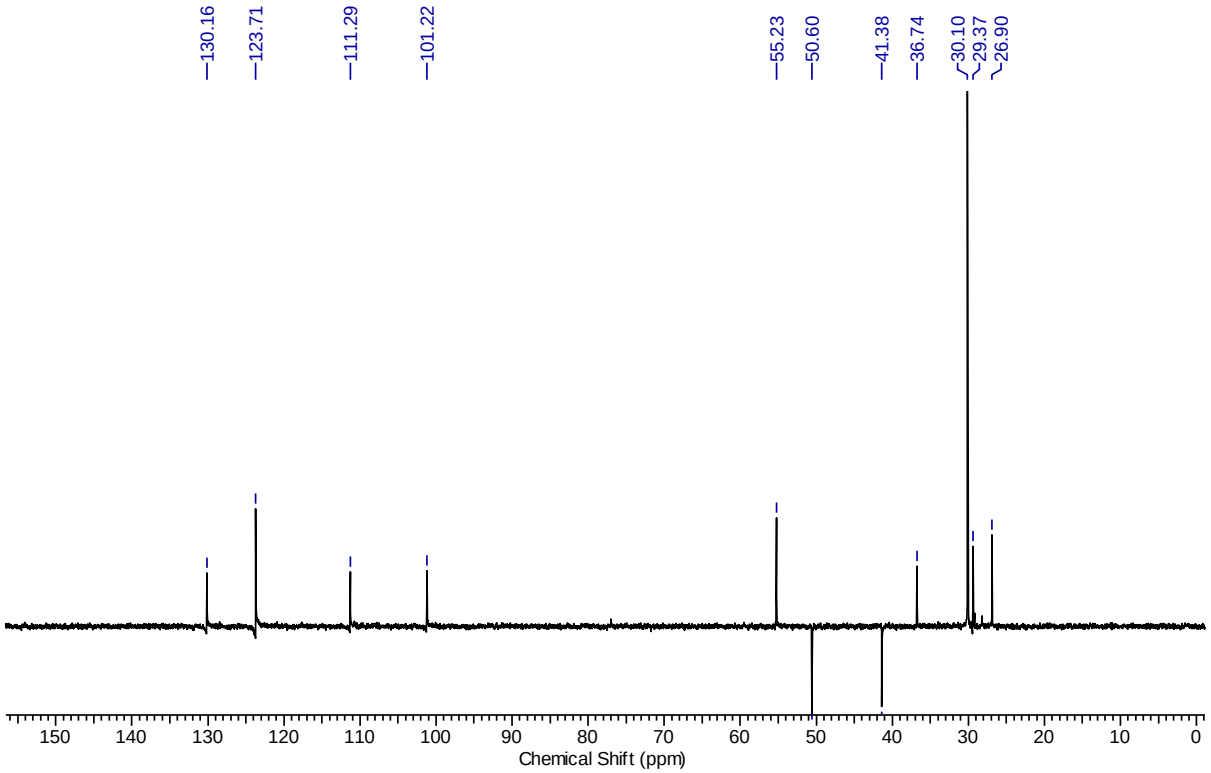




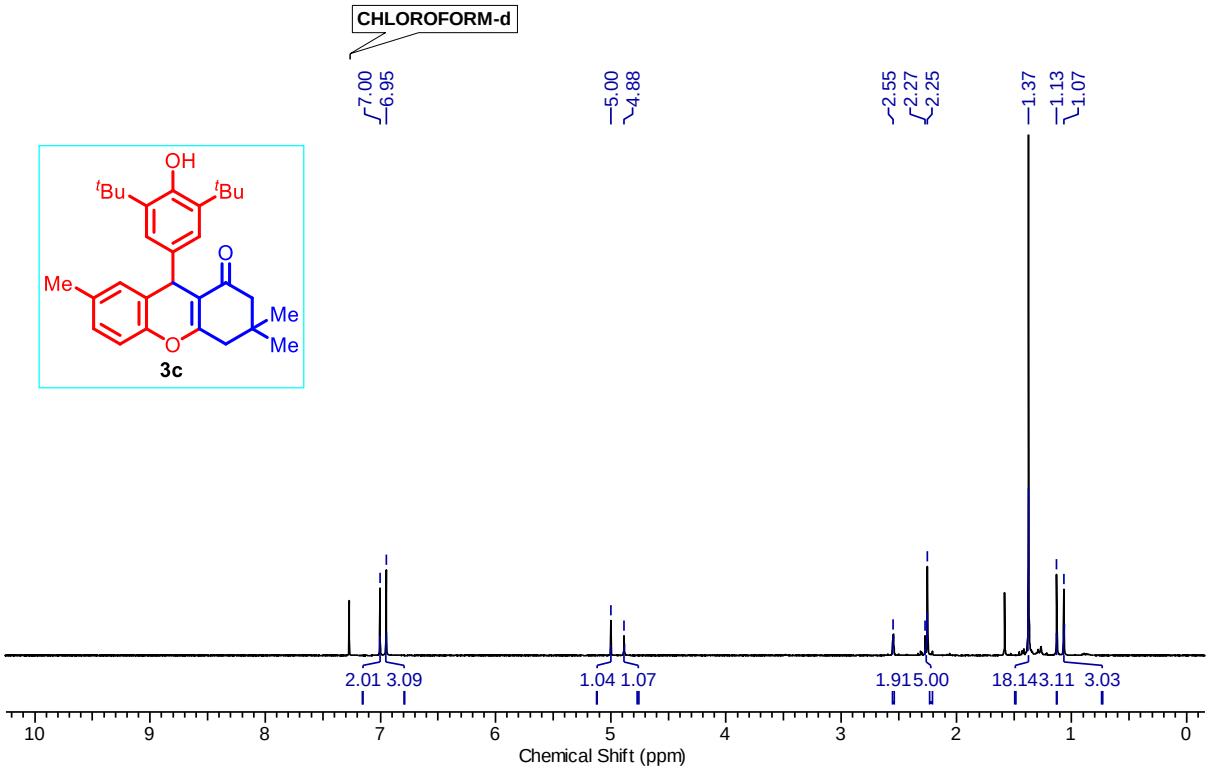

**9-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-6-methoxy-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (3b):**

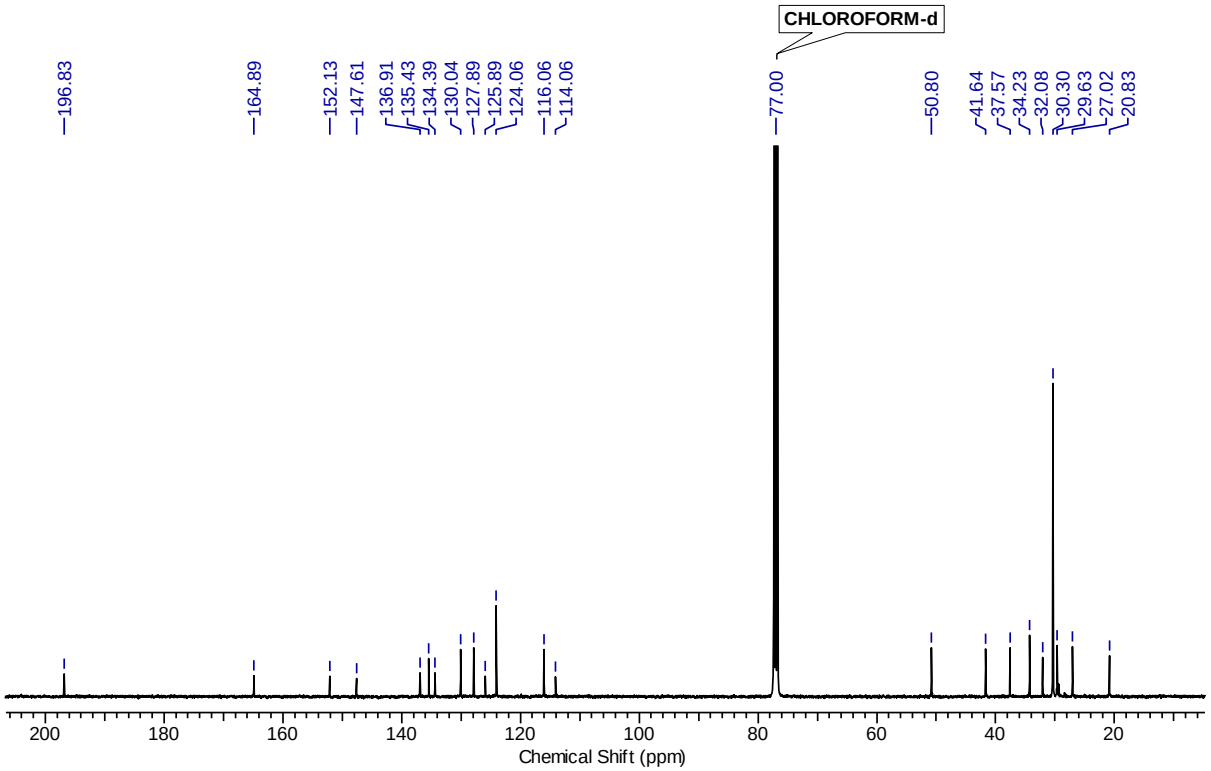



CHLOROFORM-d
196.90
164.54
158.73
152.08
150.06
137.06
135.44
130.37
123.93
118.51
114.34
111.50
101.44
55.44
50.82
41.59
36.95
34.21
32.08
30.31
29.57
27.11
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

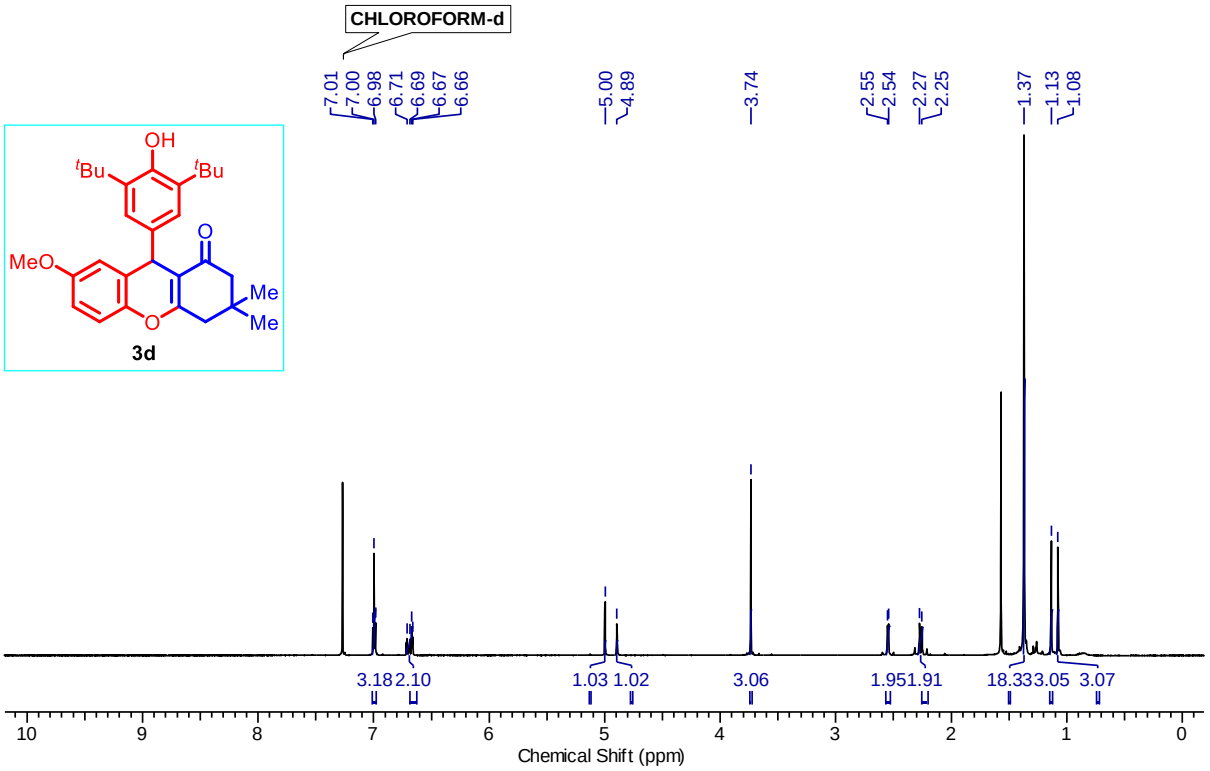

130.16
123.71
111.29
101.22
55.23
50.60
41.38
36.74
30.10
29.37
26.90
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

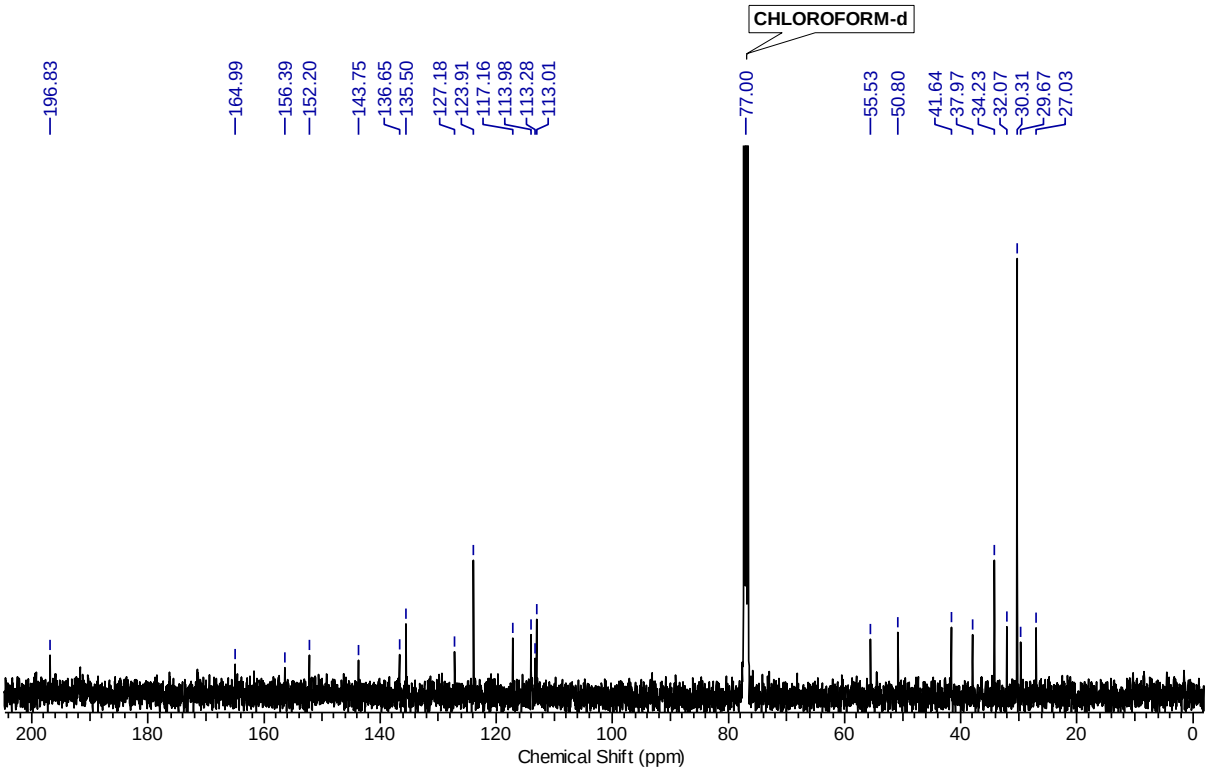
**9-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3,3,7-trimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (3c):**

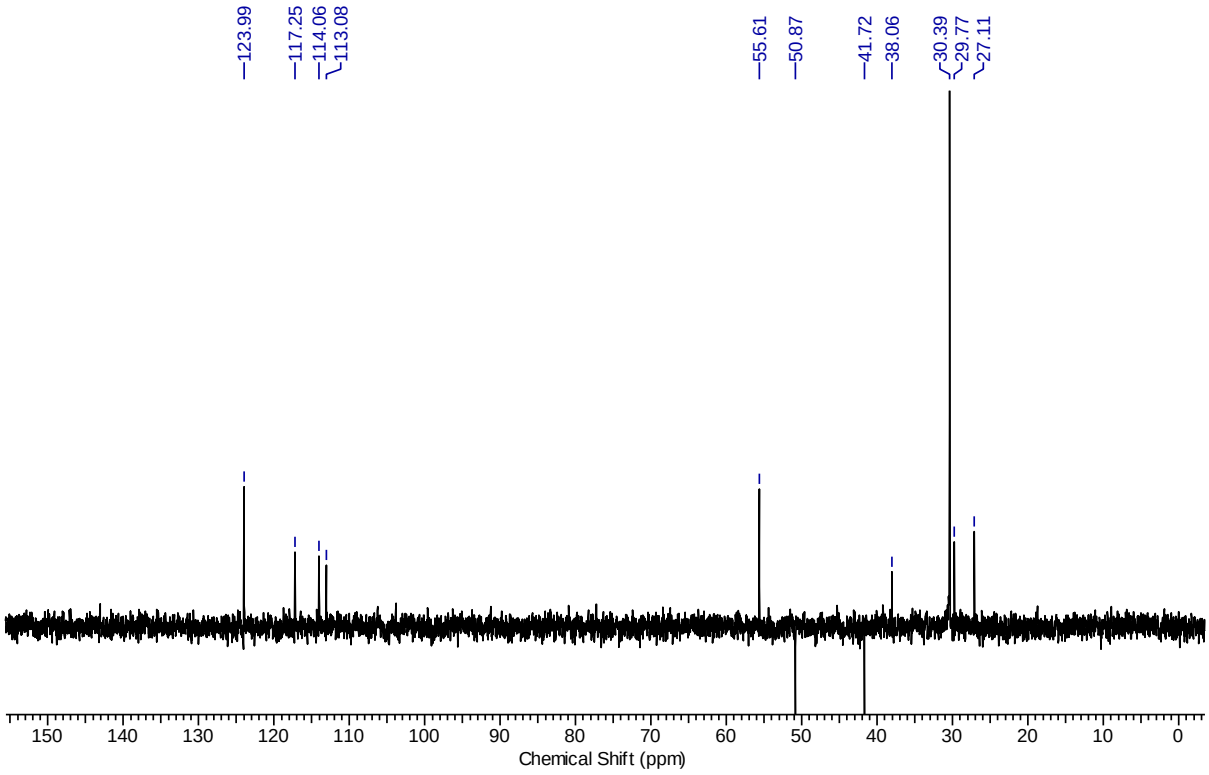


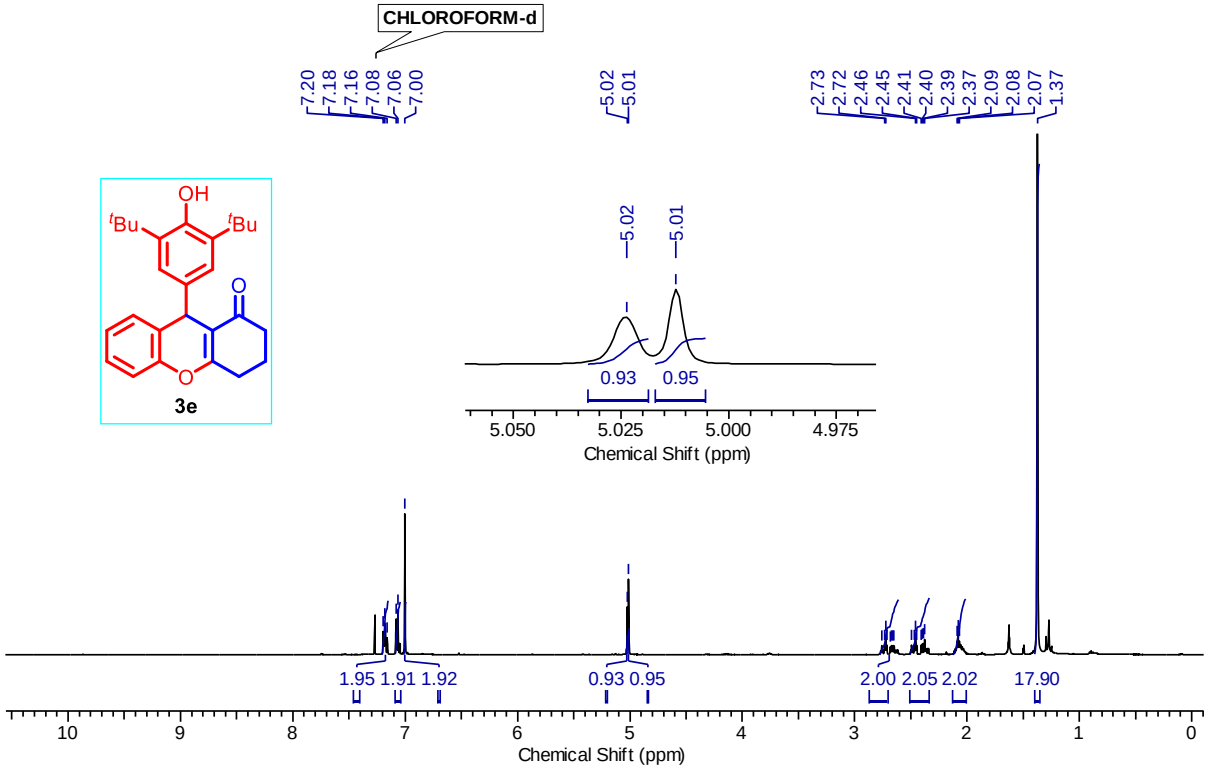
**9-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-7-methoxy-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (3d):**

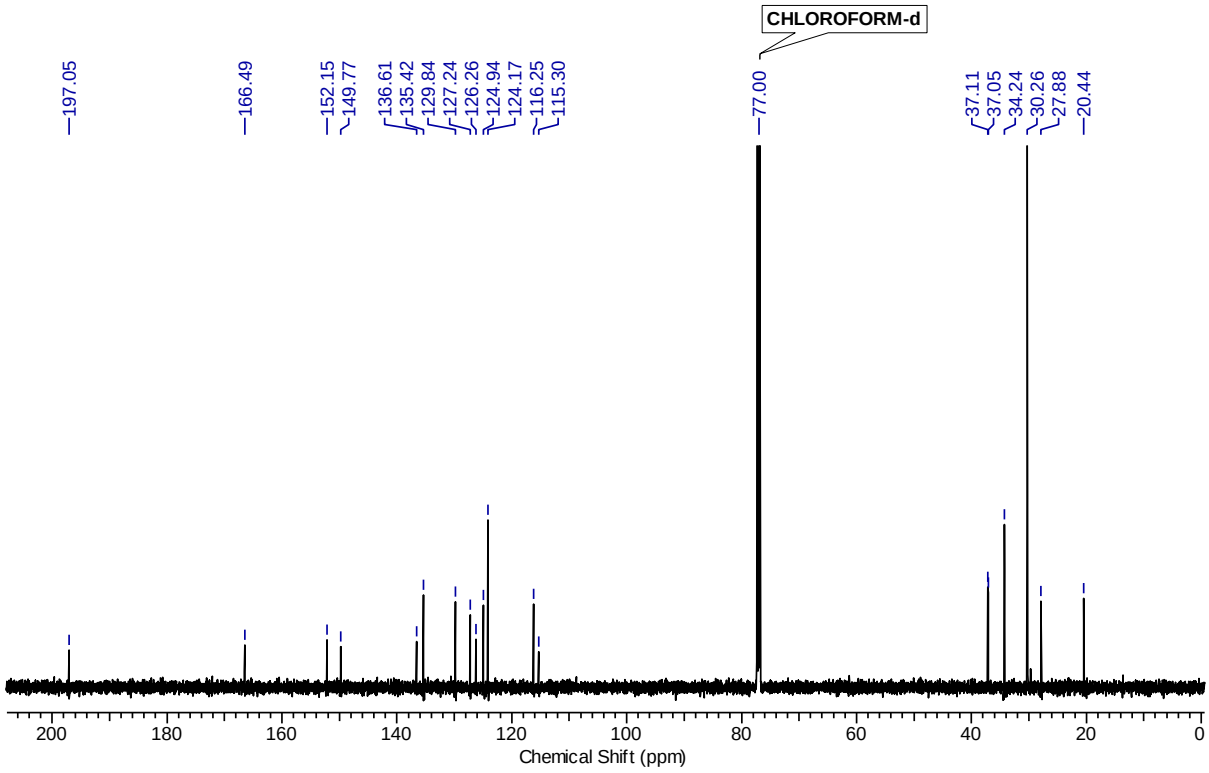


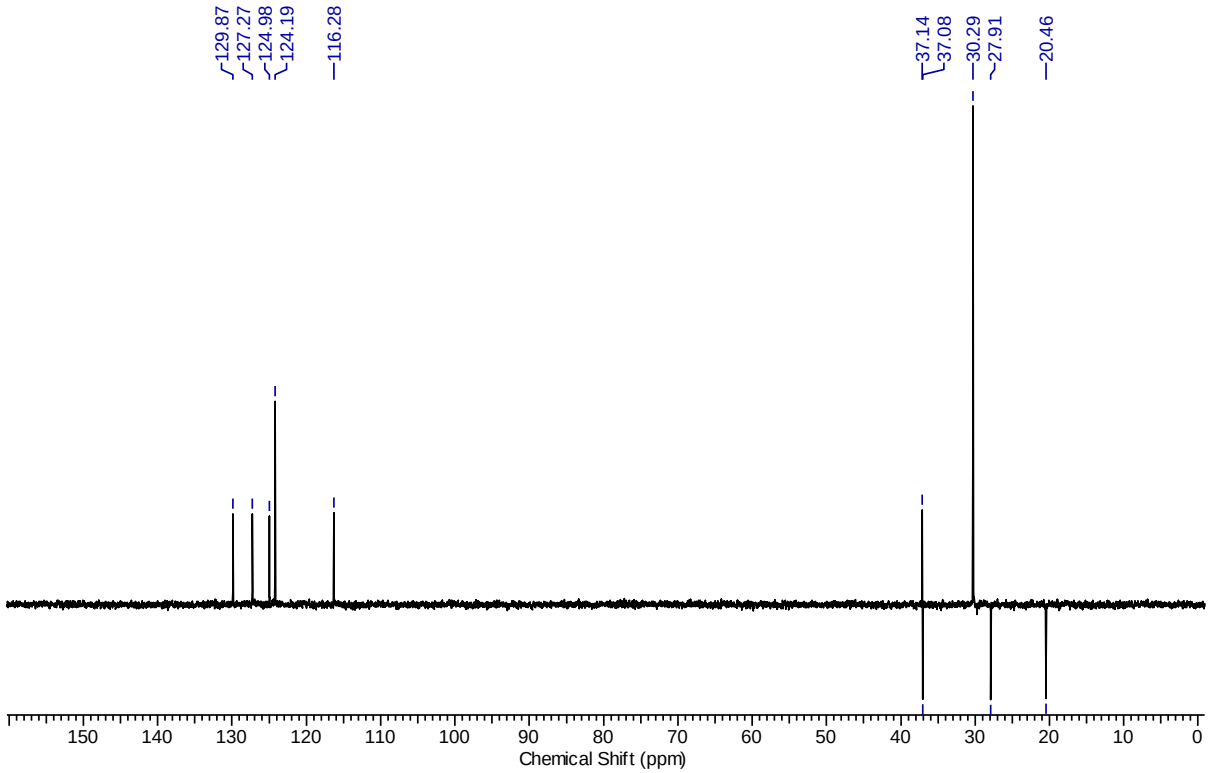





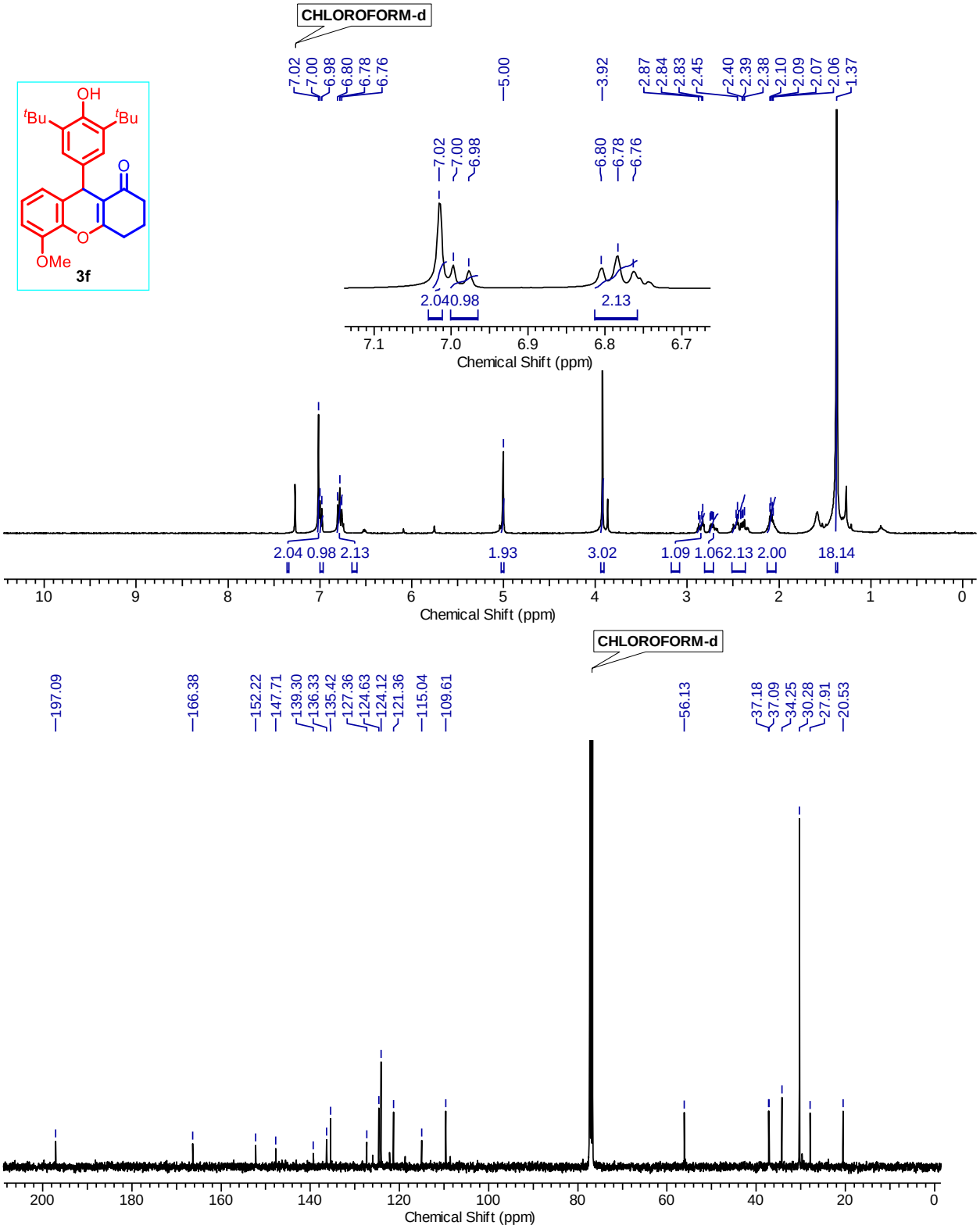

**9-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (3e):**

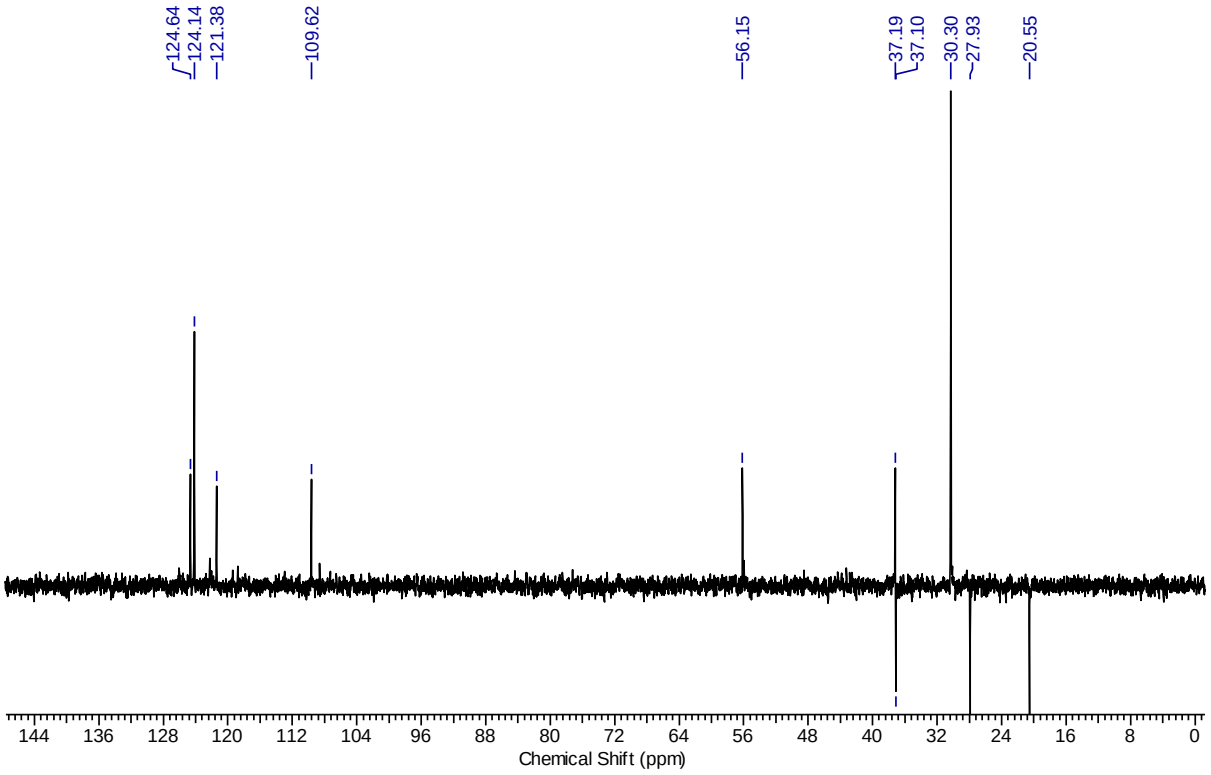



CHLOROFORM-d
197.05
166.49
152.15
149.77
136.61
135.42
129.84
127.24
126.26
124.94
124.17
116.25
115.30
77.00
37.11
37.05
34.24
30.26
27.88
20.44
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

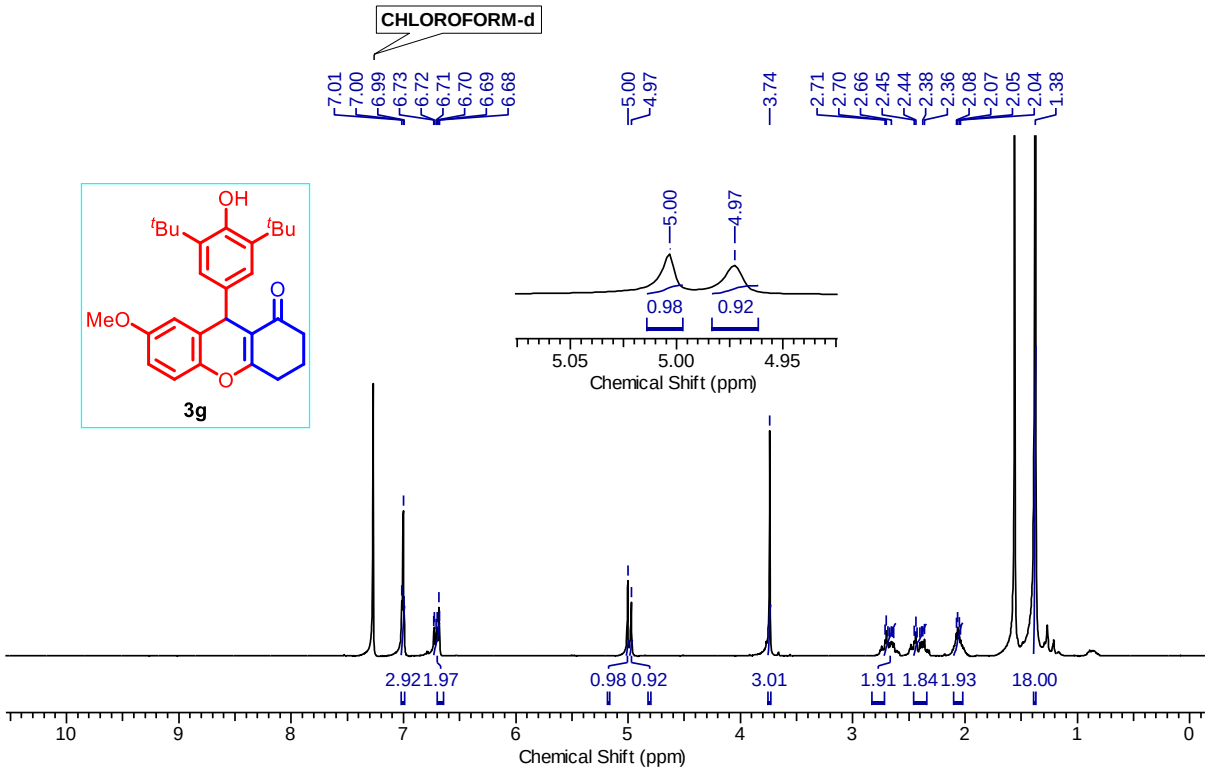

129.87
127.27
124.98
124.19
116.28
37.14
37.08
30.29
27.91
20.46
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

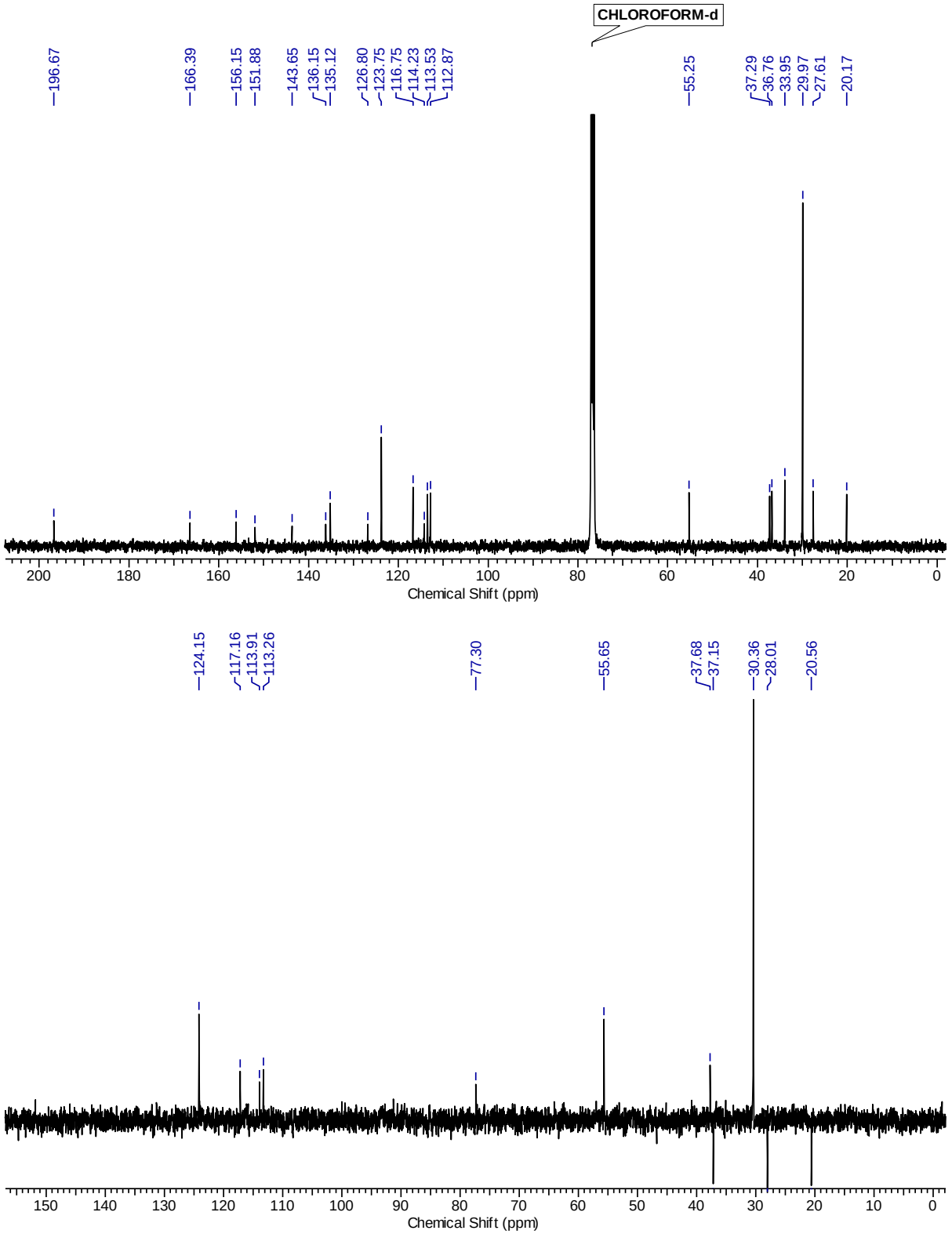
**9-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-5-methoxy-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (3f):**



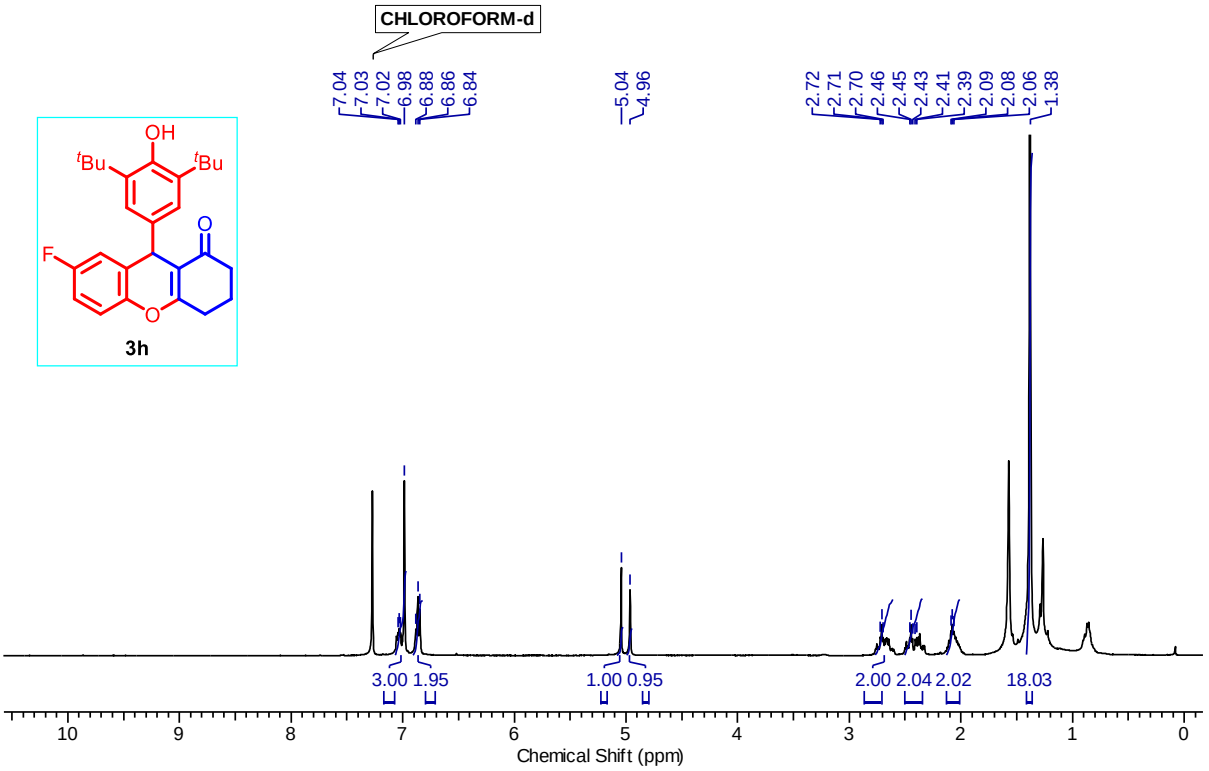


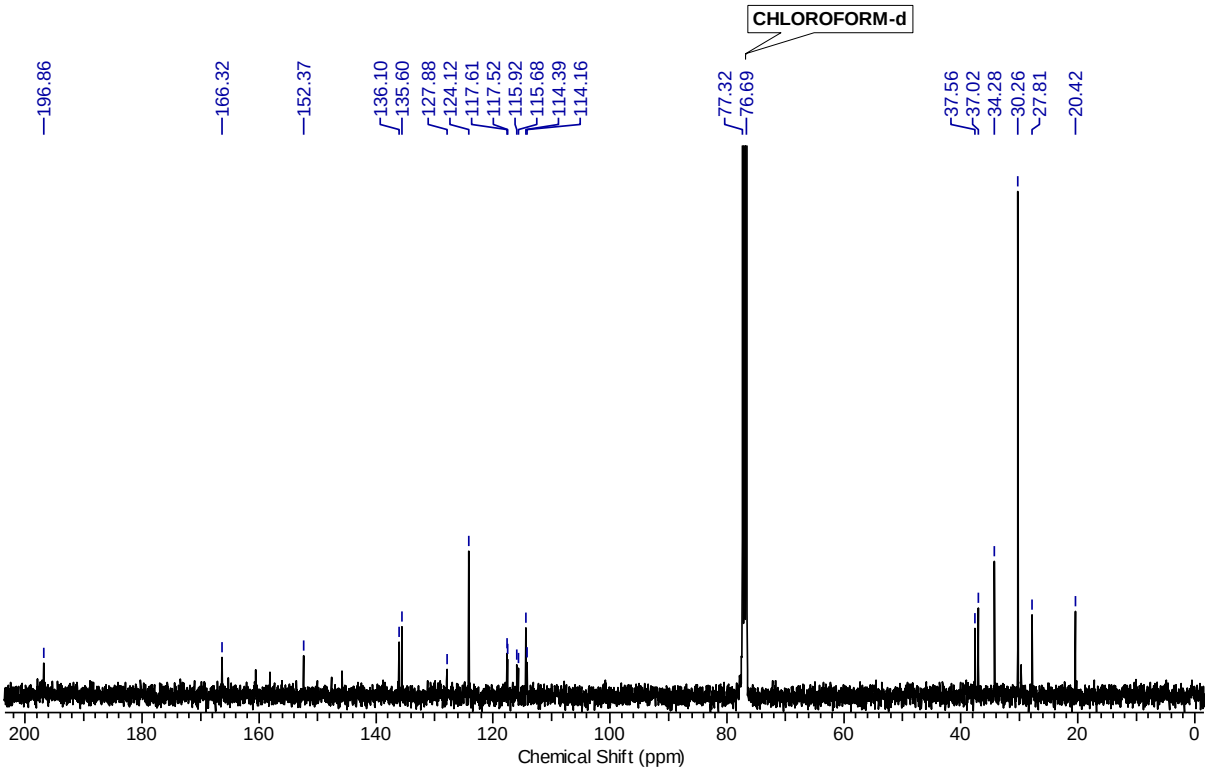

**9-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-7-methoxy-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (3g):**



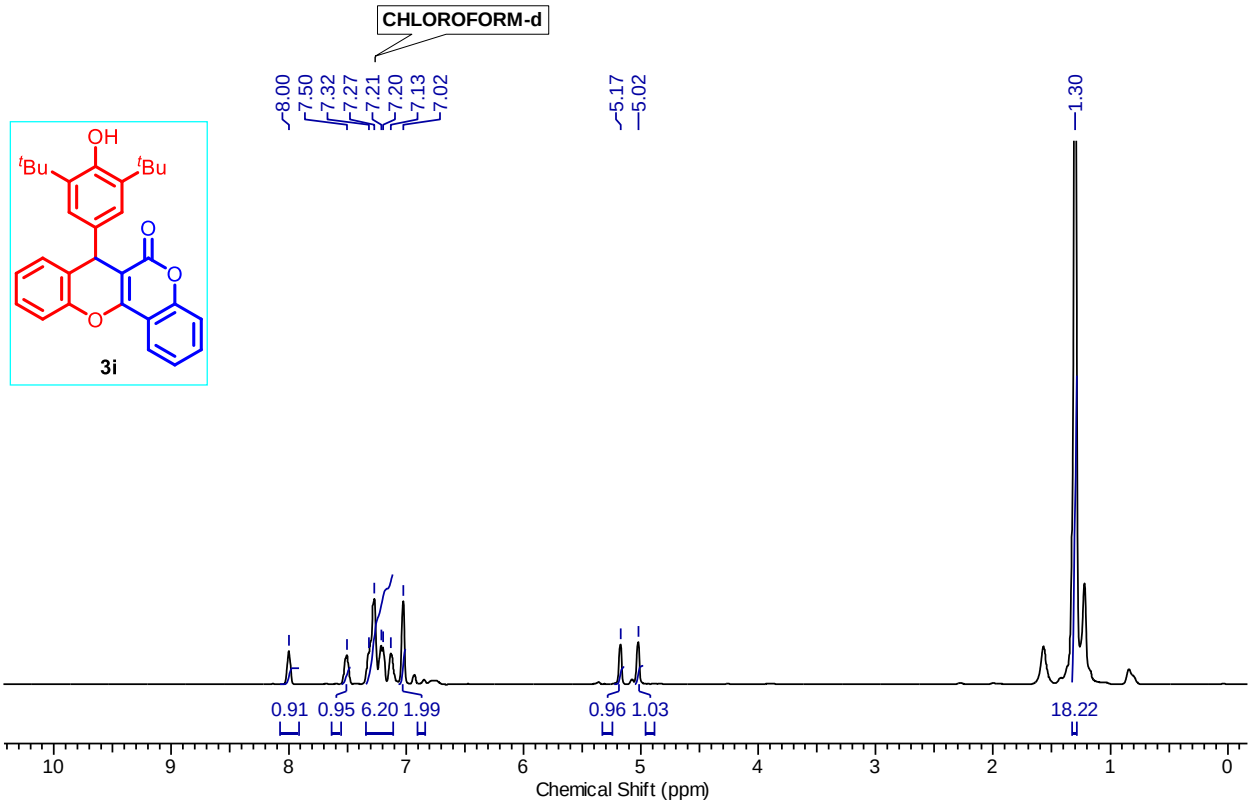

CHLOROFORM-d
196.67
166.39
156.15
151.88
143.65
136.15
135.12
126.80
123.75
116.75
114.23
113.53
112.87
55.25
37.29
36.76
33.95
29.97
27.61
20.17
Chemical Shift (ppm)
124.15
117.16
113.91
113.26
77.30
55.65
37.68
37.15
30.36
28.01
20.56
Chemical Shift (ppm)

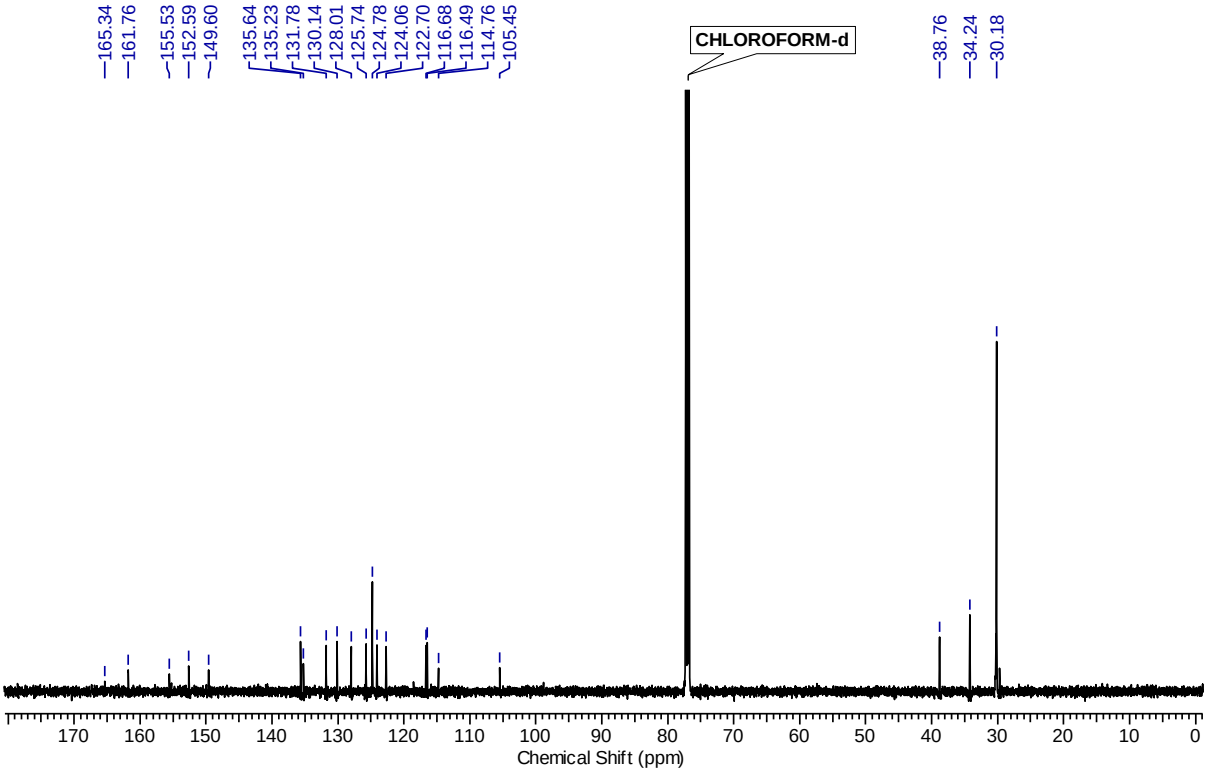
**9-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-7-fluoro-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (3h):**

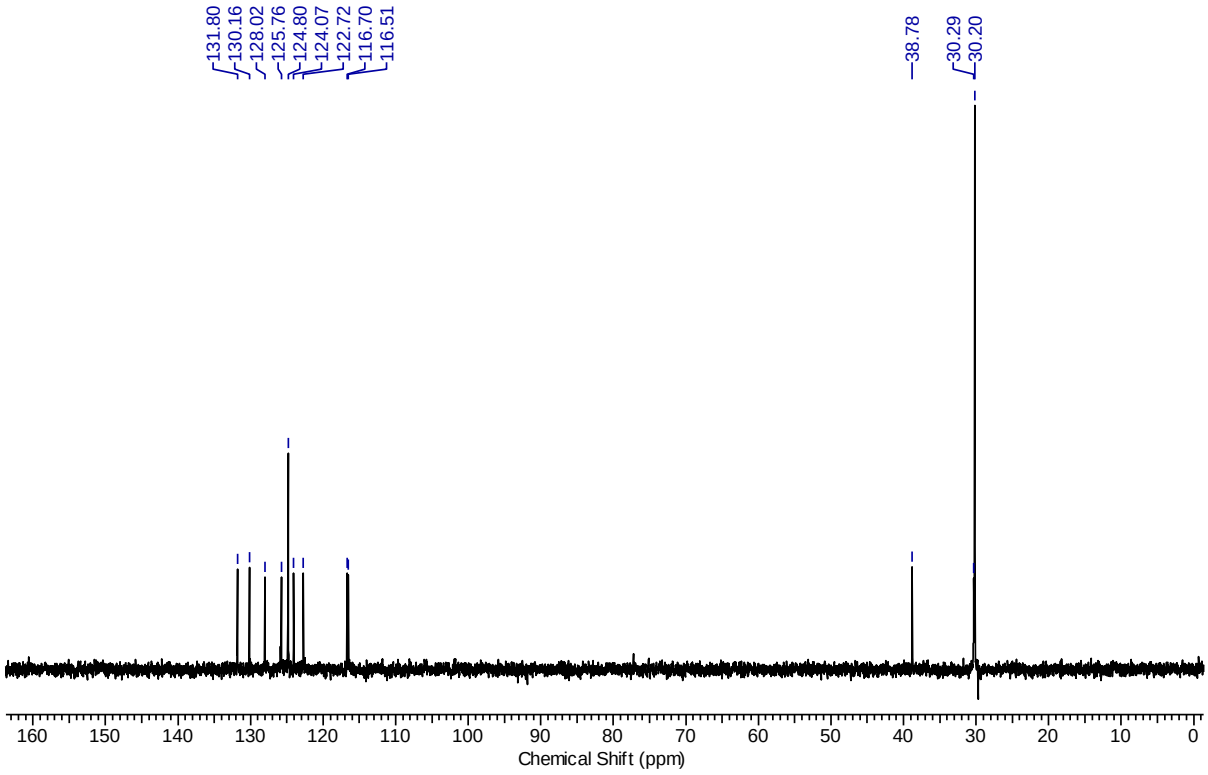


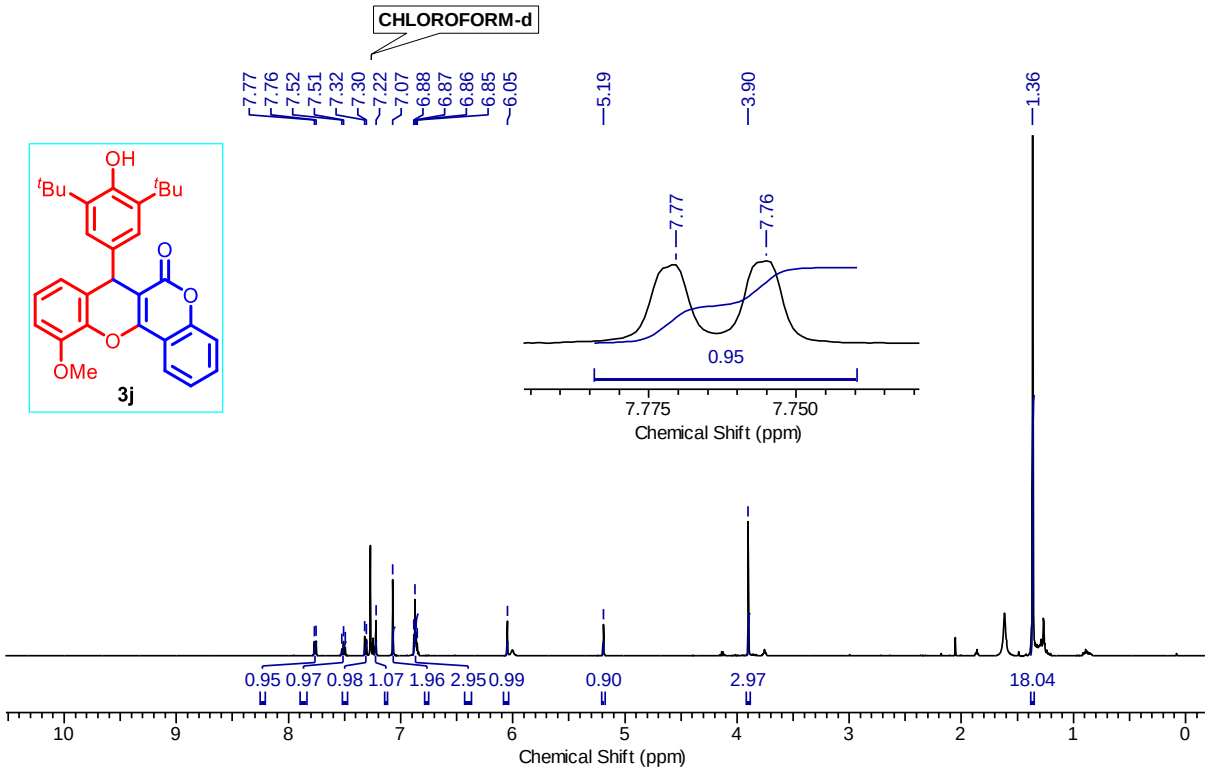
**7-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-6*H*,7*H*-chromeno[4,3-*b*]chromen-6-one (3i):**

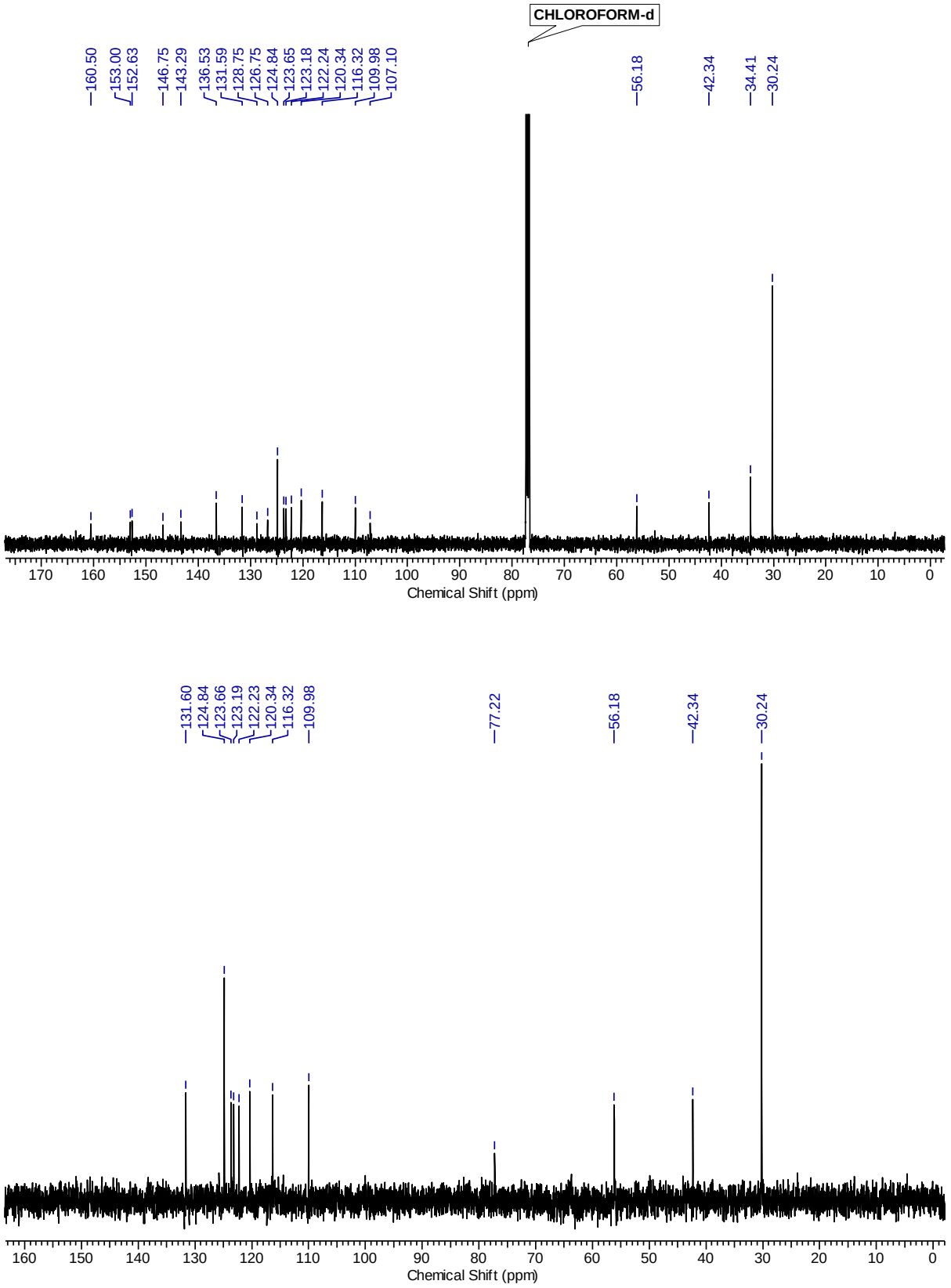


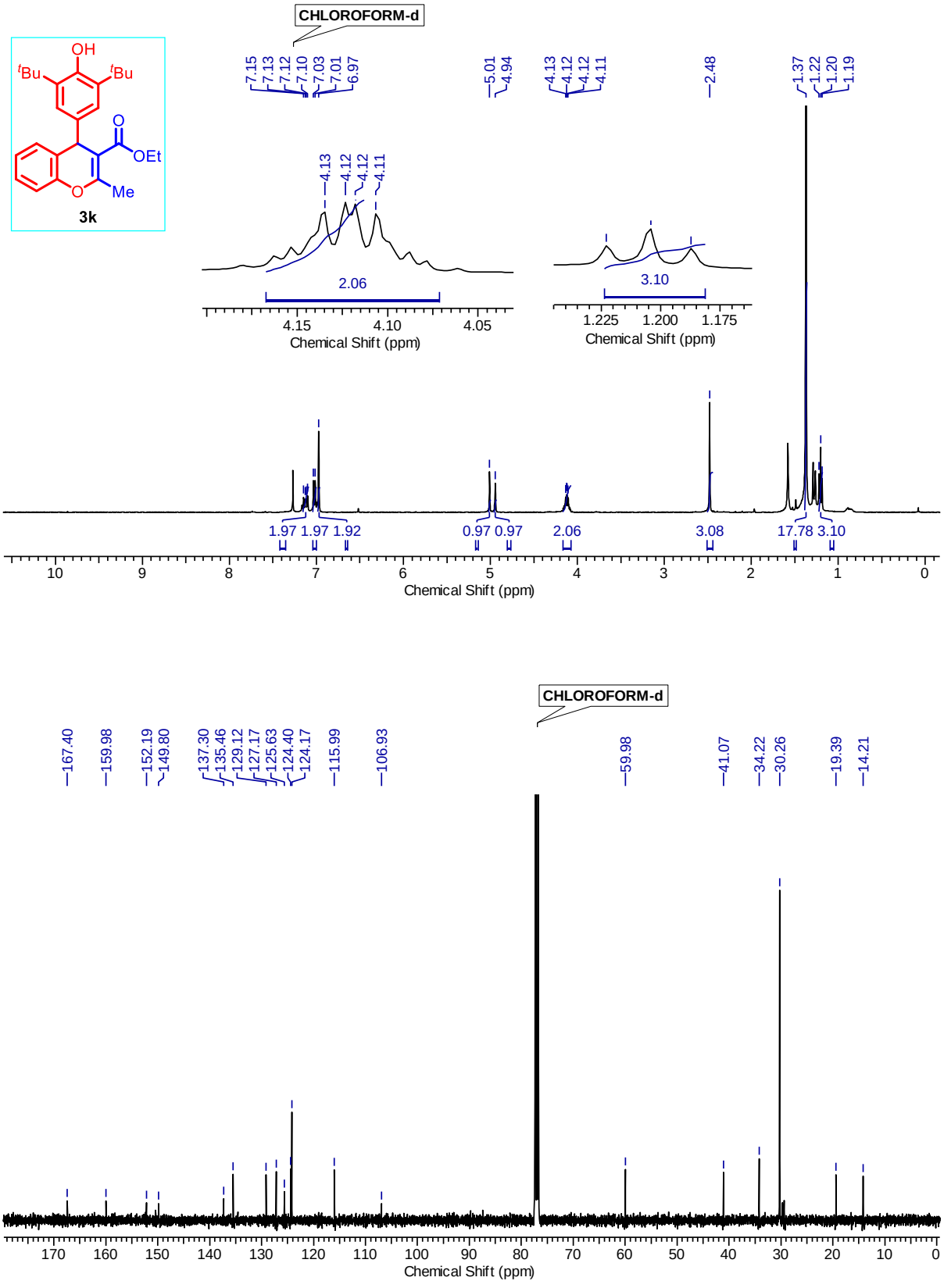


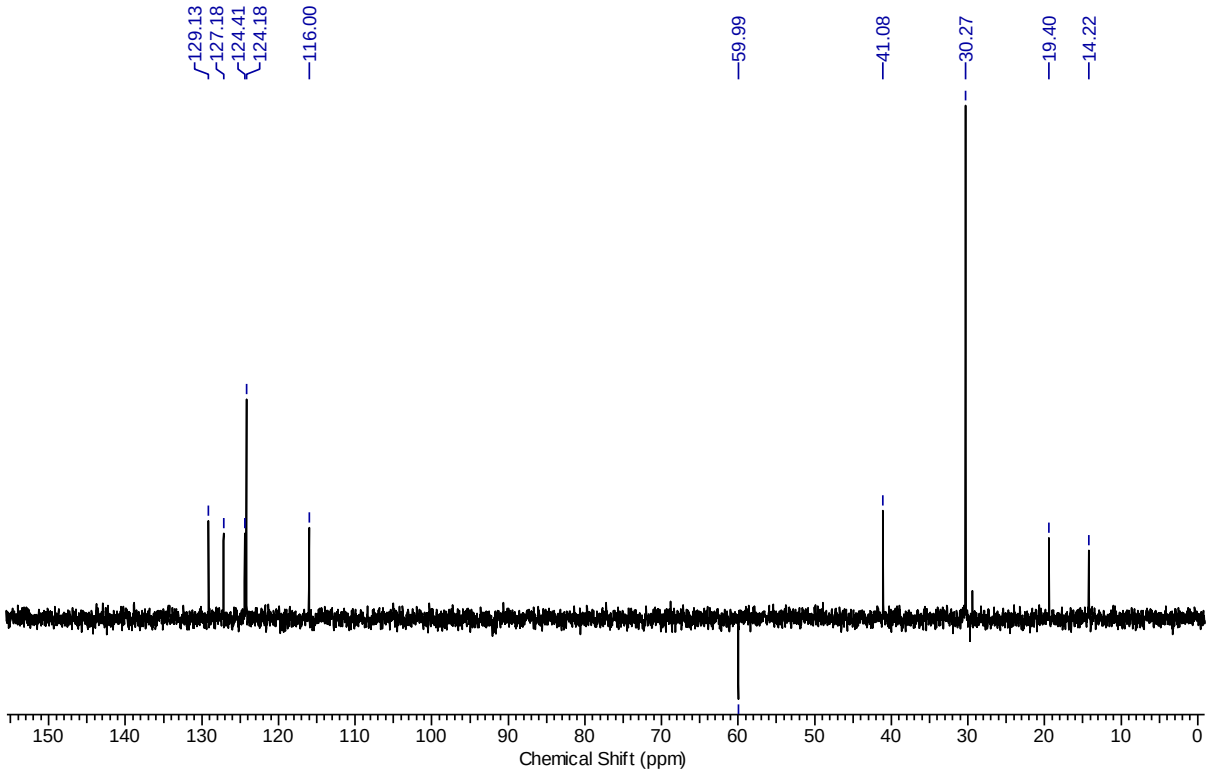

**7-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-11-methoxy-6*H*,7*H*-chromeno[4,3-*b*]chromen-6-one (3j):**



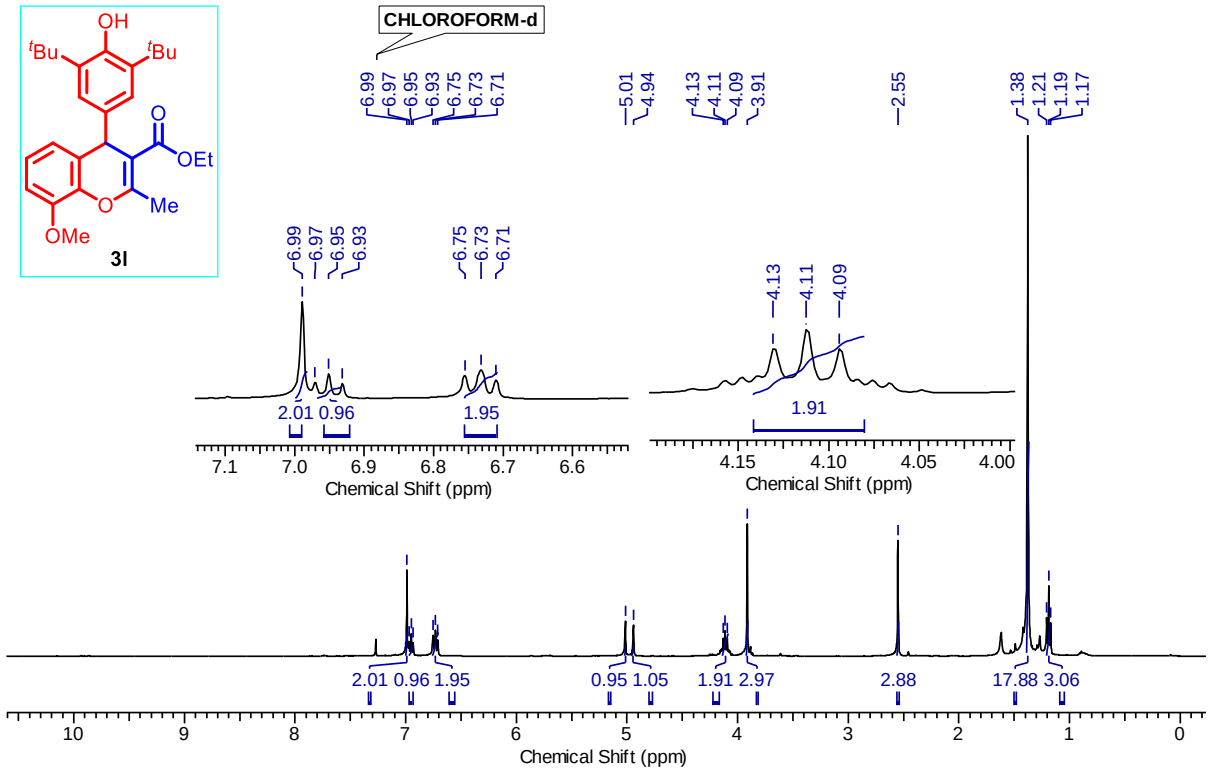

CHLOROFORM-d
160.50
153.00
152.63
146.75
143.29
136.53
131.59
128.75
126.75
124.84
123.65
123.18
122.24
120.34
116.32
109.98
107.10
56.18
42.34
34.41
30.24
Chemical Shift (ppm)
131.60
124.84
123.66
123.19
122.23
120.34
116.32
109.98
77.22
56.18
42.34
30.24
Chemical Shift (ppm)

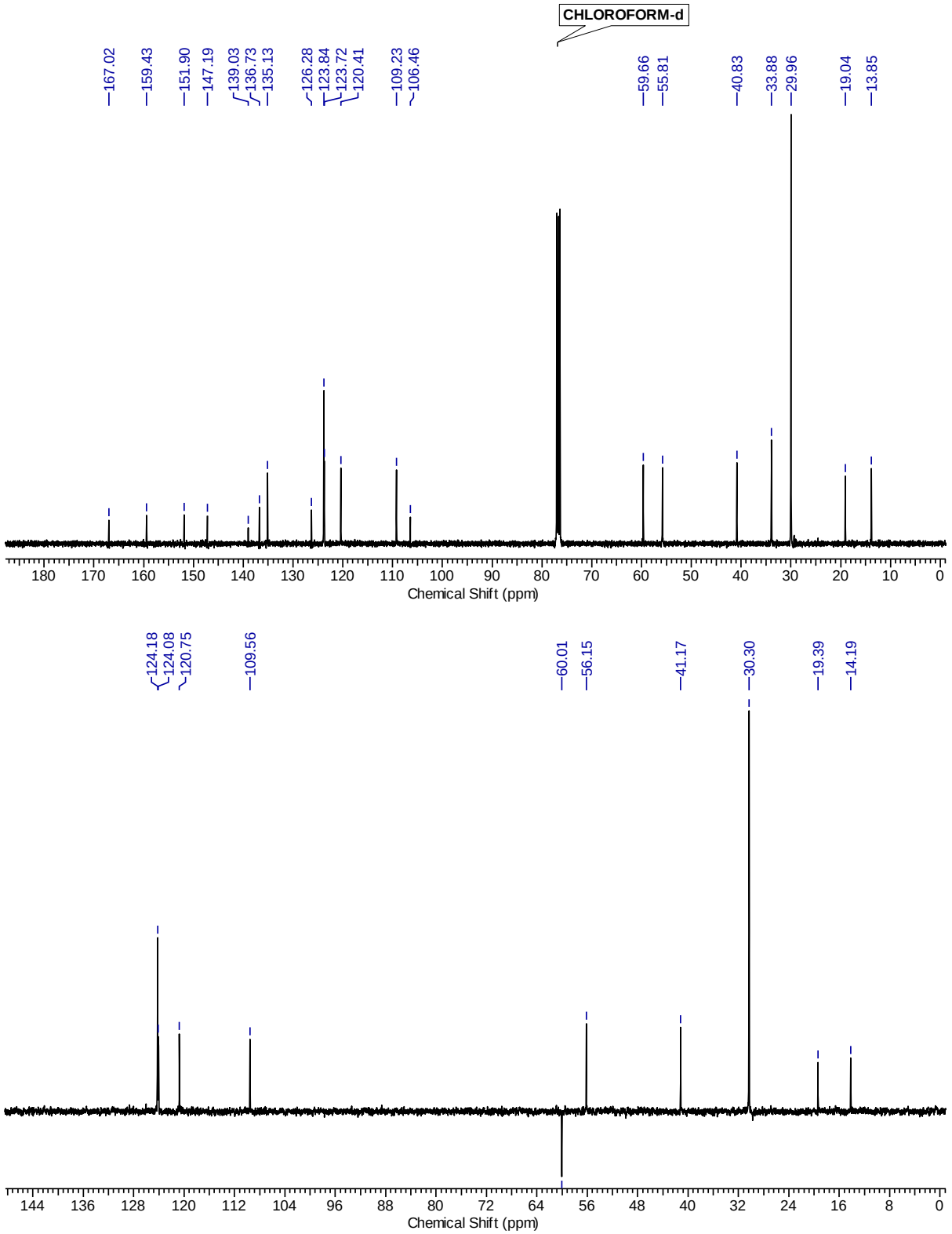
**Ethyl 4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-methyl-4*H*-chromene-3-carboxylate (3k):**



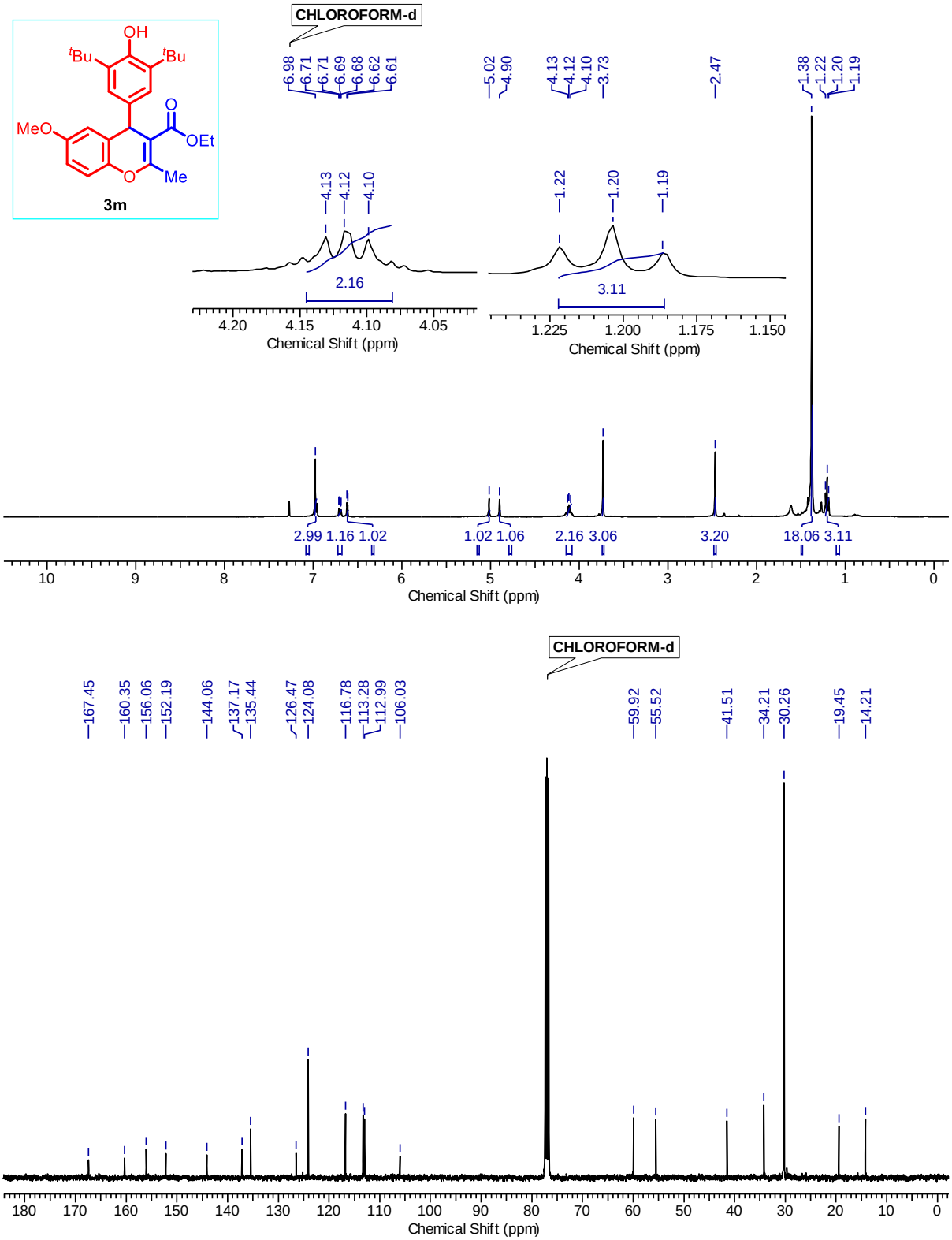



**Ethyl 4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-8-methoxy-2-methyl-4*H*-chromene-3-carboxylate (3l):**

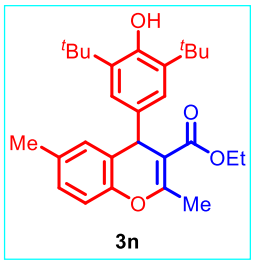



CHLOROFORM-d
167.02
159.43
151.90
147.19
139.03
136.73
135.13
126.28
123.84
123.72
120.41
109.23
106.46
59.66
55.81
40.83
33.88
29.96
19.04
13.85
Chemical Shift (ppm)
124.18
124.08
120.75
109.56
60.01
56.15
41.17
30.30
19.39
14.19
Chemical Shift (ppm)

**Ethyl 4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-6-methoxy-2-methyl-4*H*-chromene-3-carboxylate (3m):**

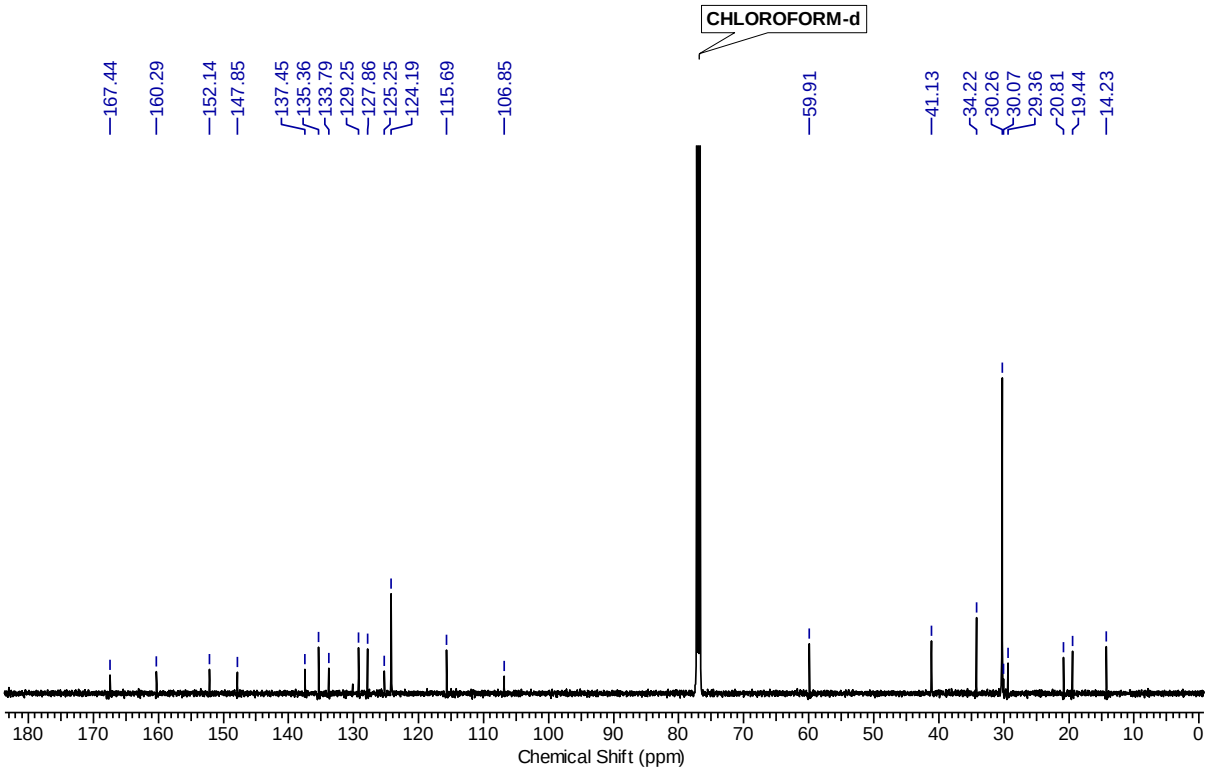


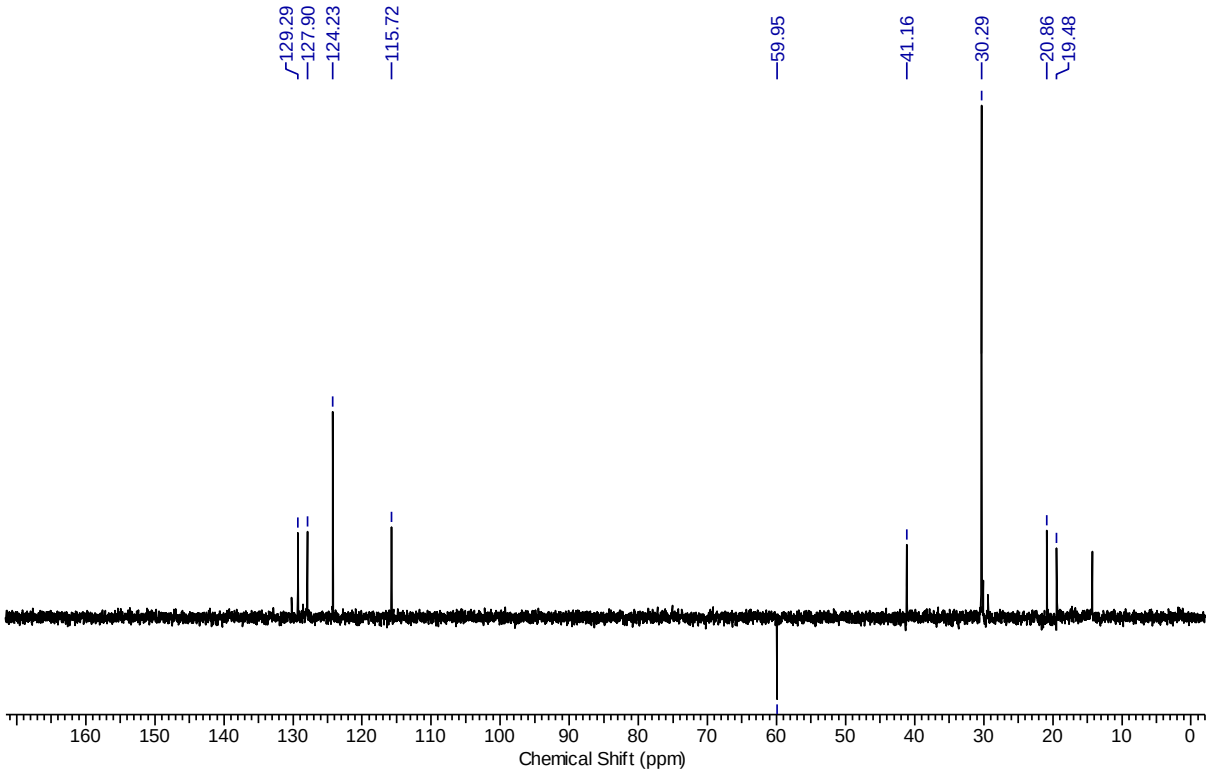
**Ethyl 4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,6-dimethyl-4*H*-chromene-3-carboxylate (3n):**



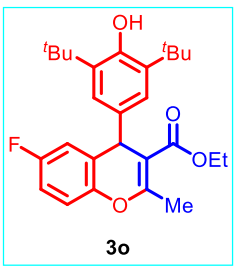


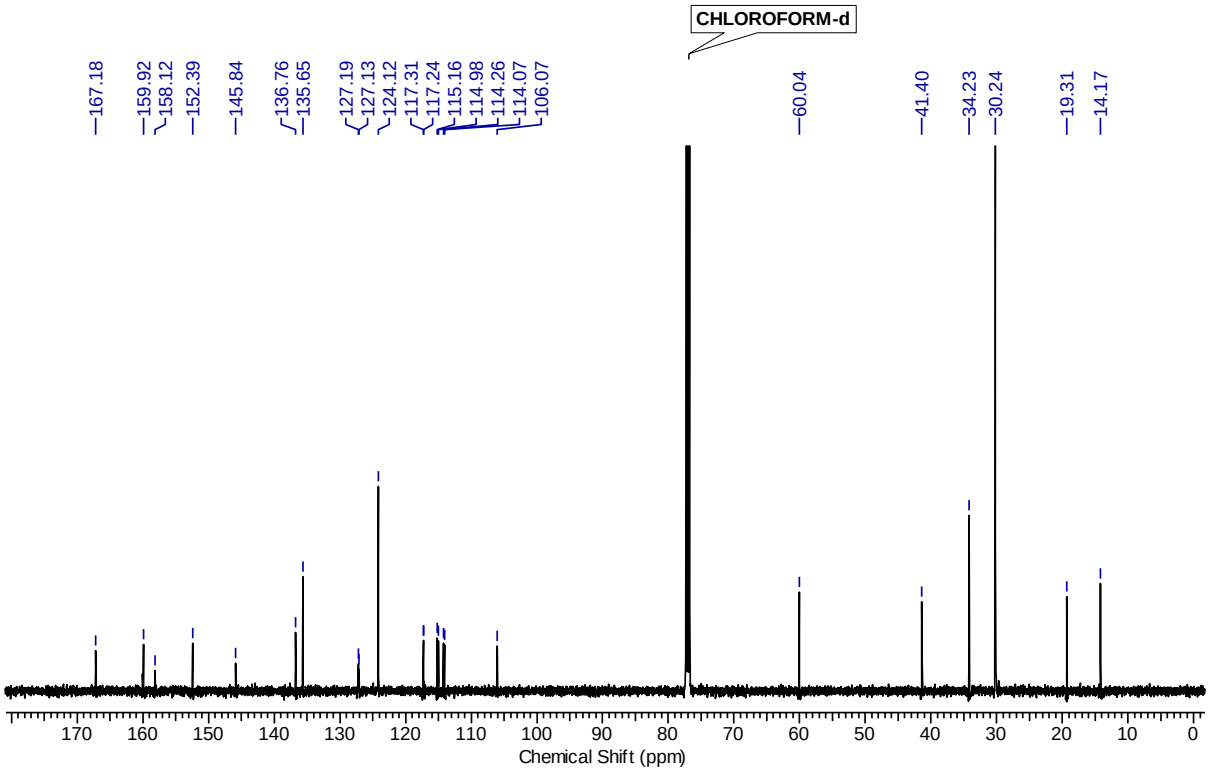




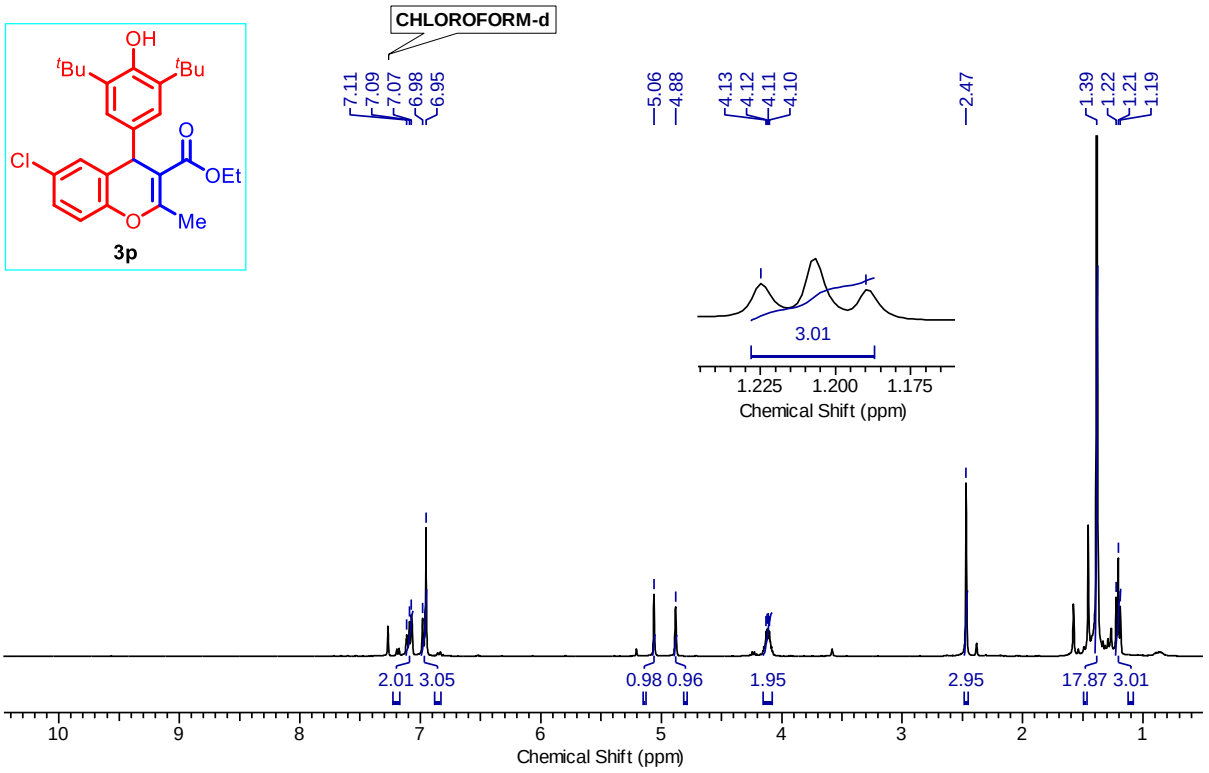


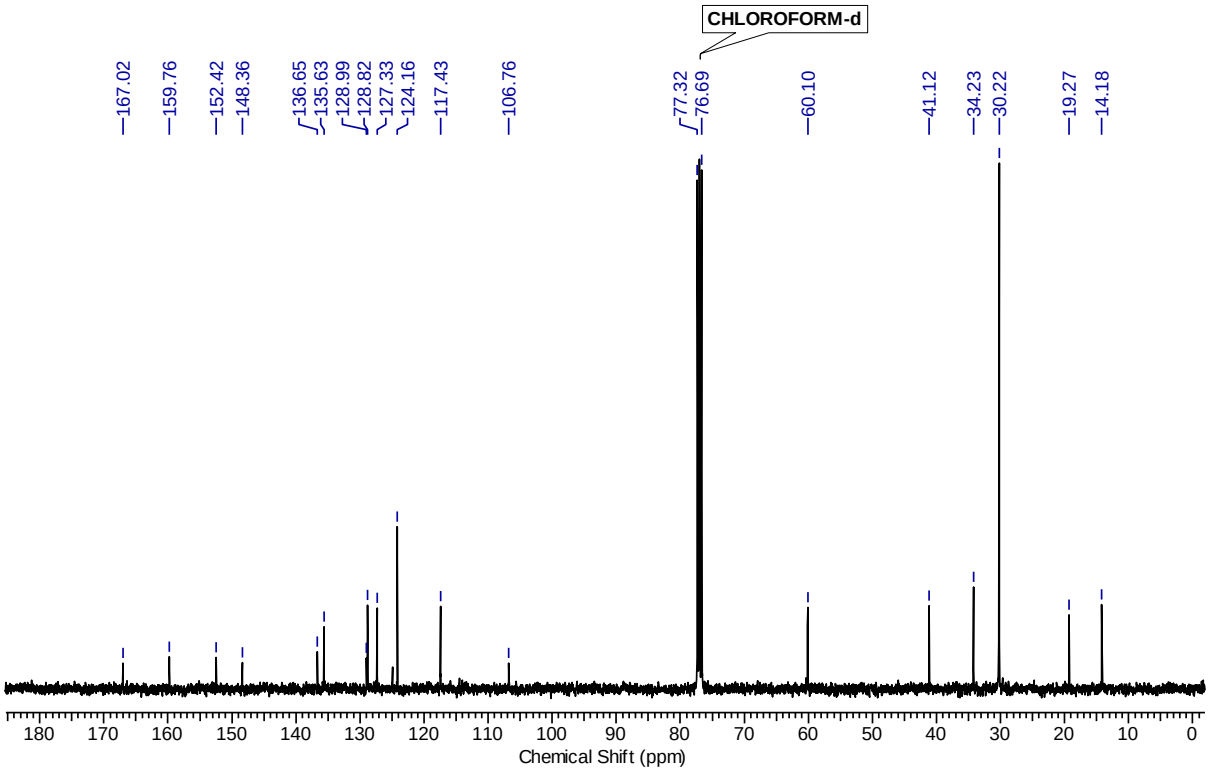

**1-(4-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-6-fluoro-2-methyl-4*H*-chromen-3-yl)propan-1-one (3o):**



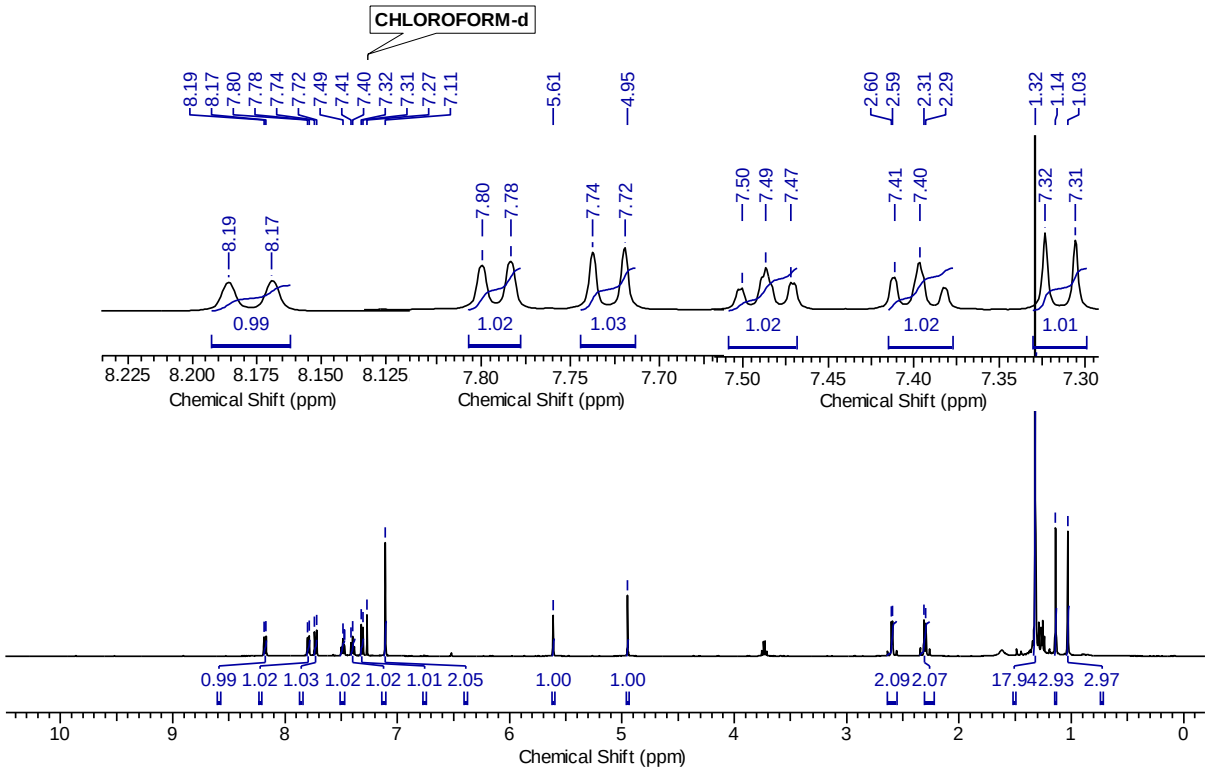


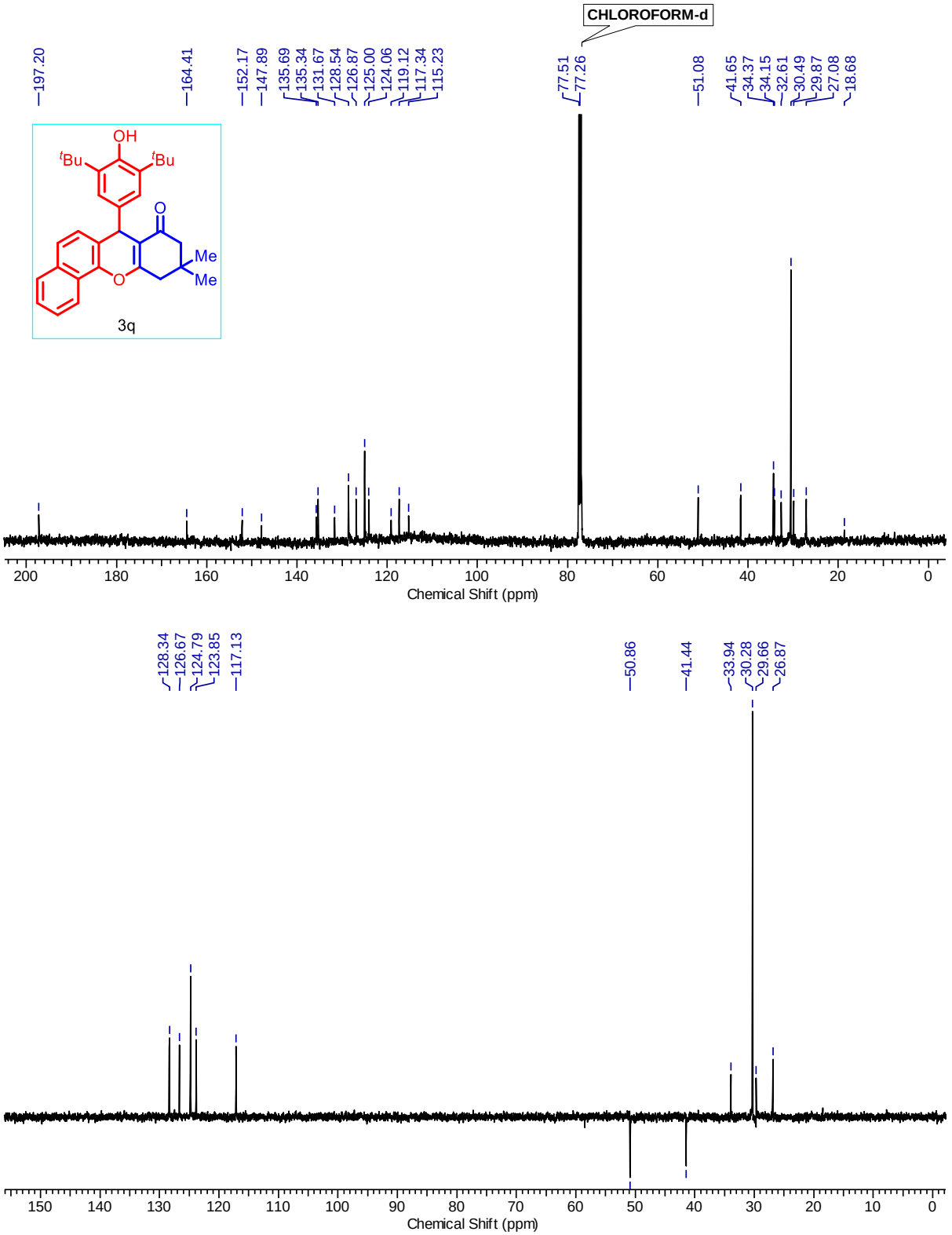

**Ethyl 6-chloro-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-methyl-4*H*-chromene-3-carboxylate (3p):**



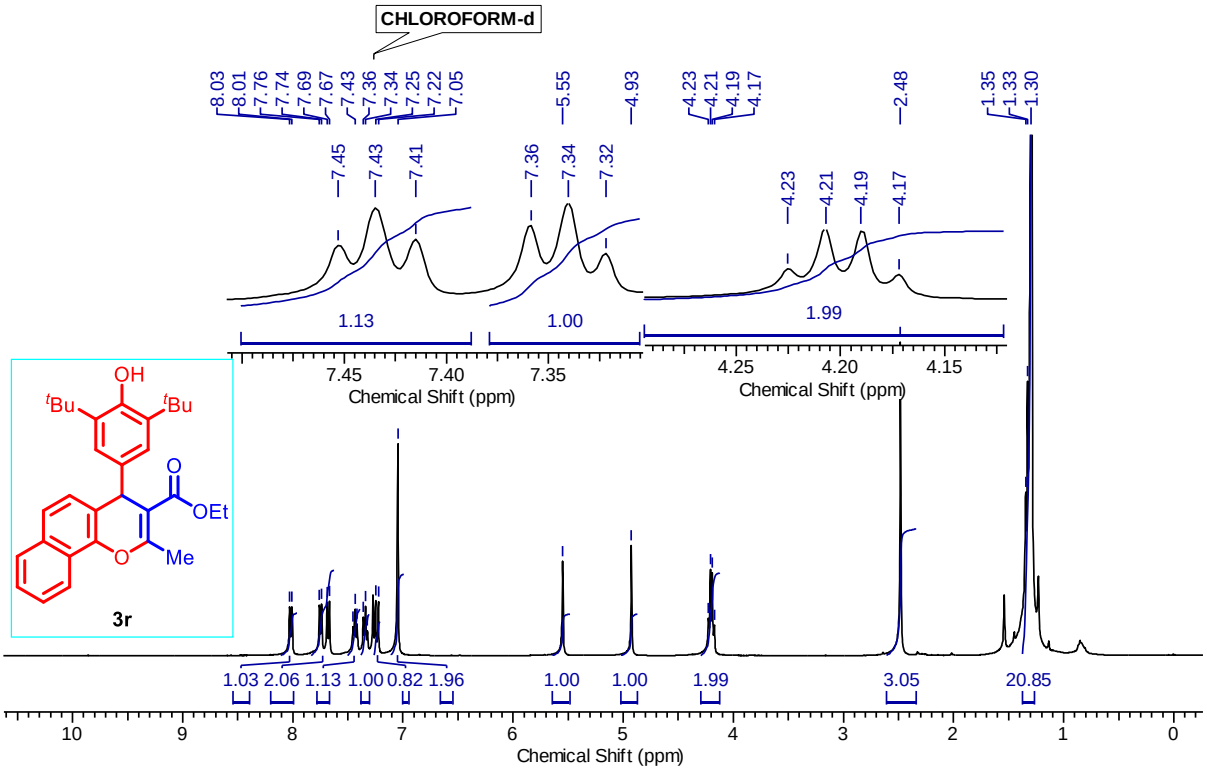


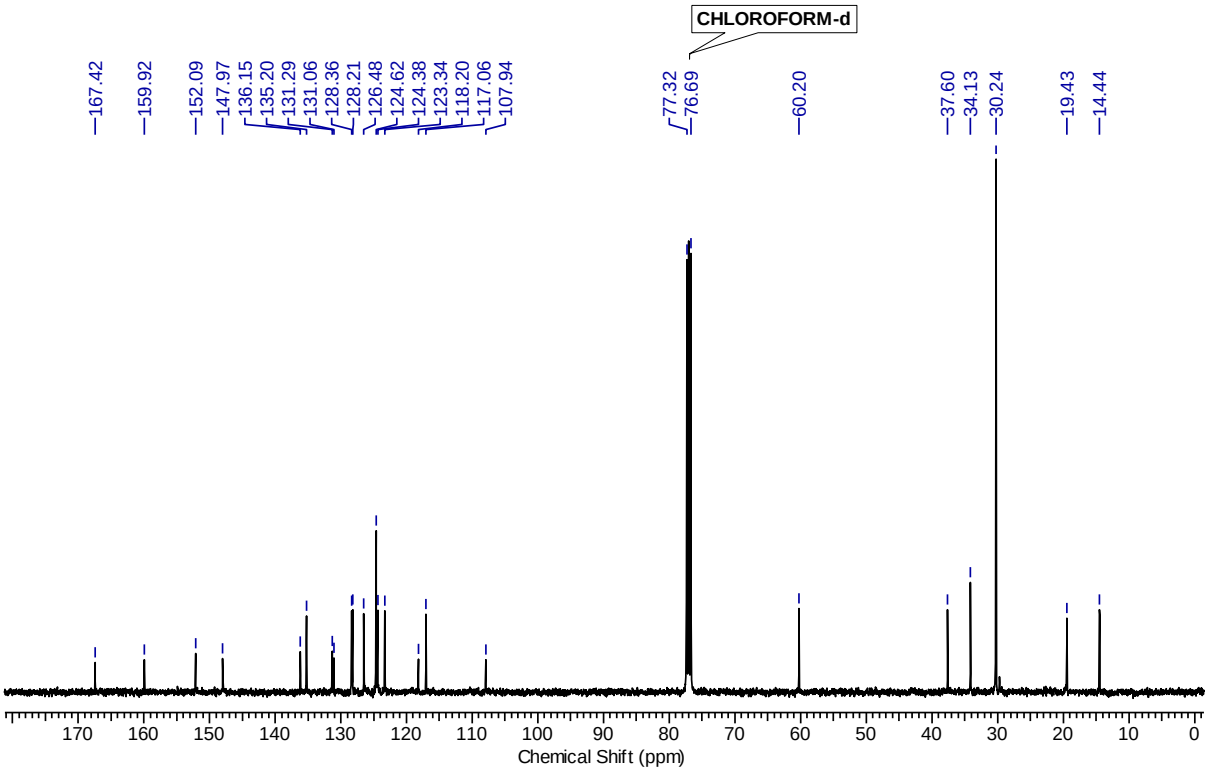

**7-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-10,10-dimethyl-7,9,10,11-tetrahydro-8*H*-benzo[*c*]xanthen-8-one (3q):**

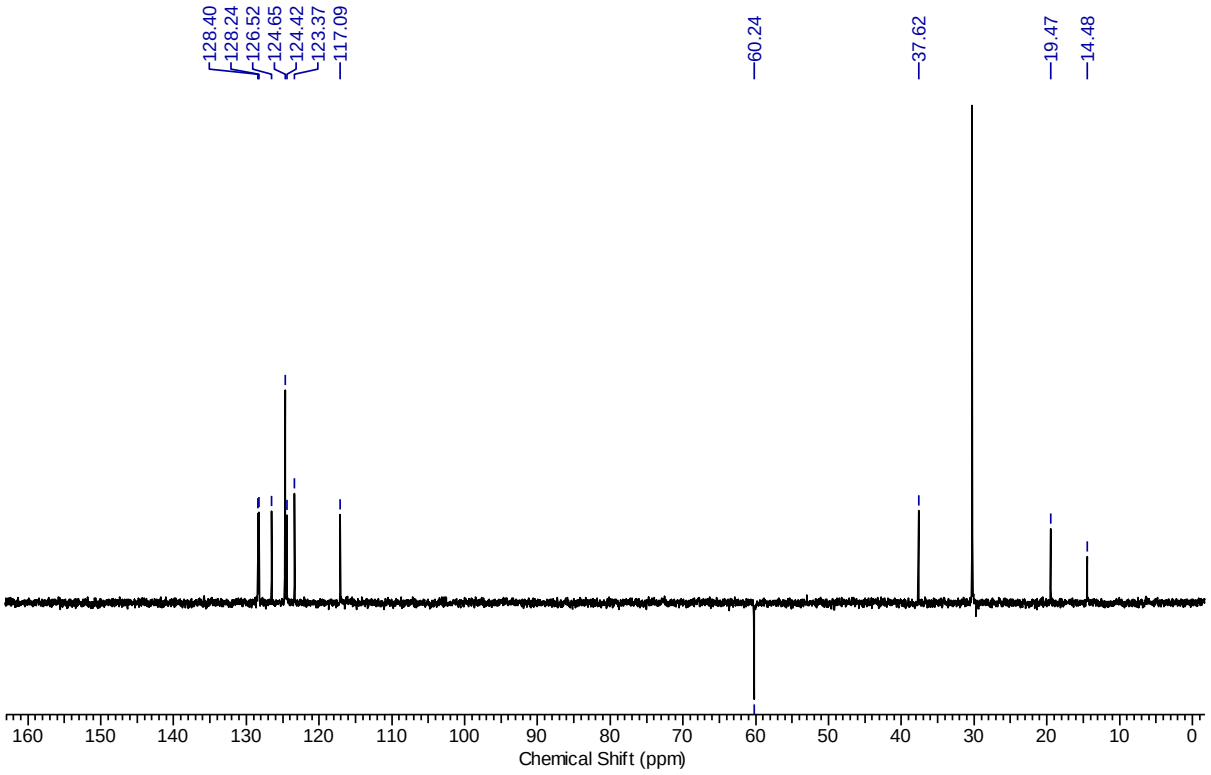



CHLOROFORM-d
197.20
164.41
152.17
147.89
135.69
135.34
131.67
128.54
126.87
125.00
124.06
119.12
117.34
115.23
77.51
77.26
51.08
41.65
34.37
34.15
32.61
30.49
29.87
27.08
18.68
OH
tBu
tBu
O
Me
Me
O
3q
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)
128.34
126.67
124.79
123.85
117.13
50.86
41.44
33.94
30.28
29.66
26.87
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

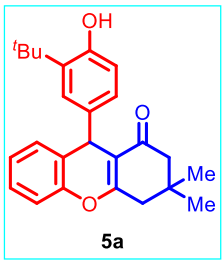
**Ethyl 1-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-methyl-1*H*-benzo[*f*]chromene-2-carboxylate (3r):**

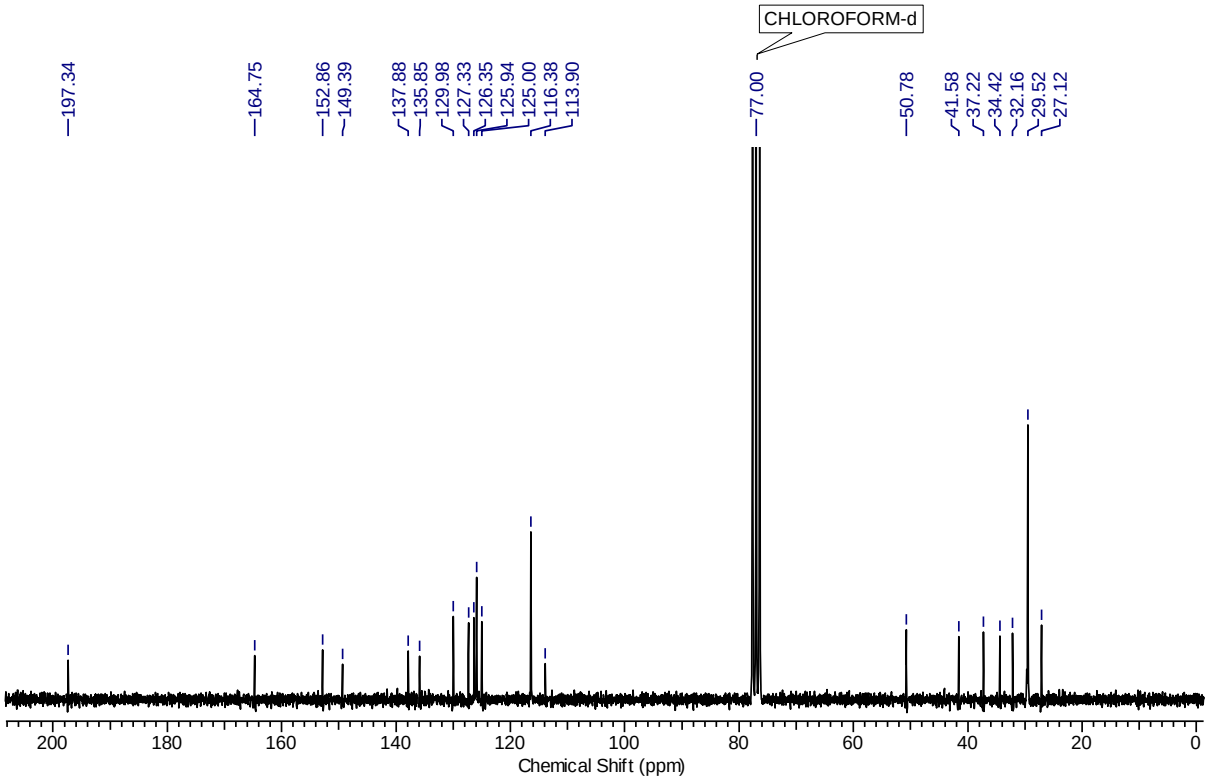


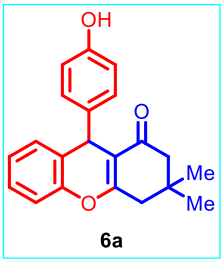


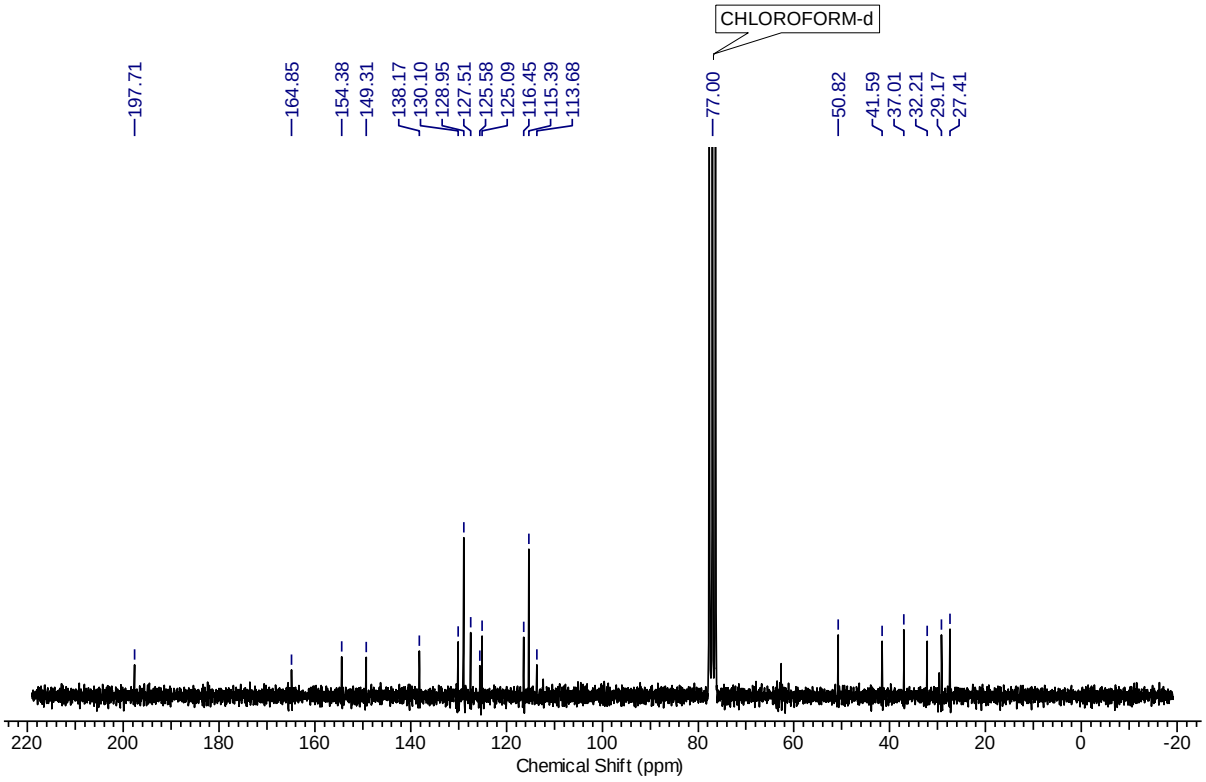

**9-(3-(*tert*-Butyl)-4-hydroxyphenyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (5a):**





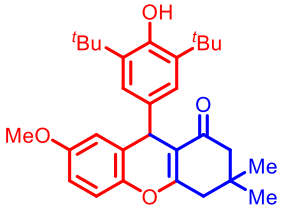
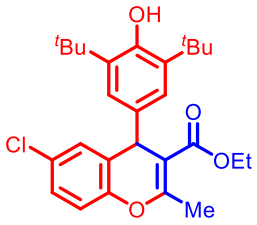
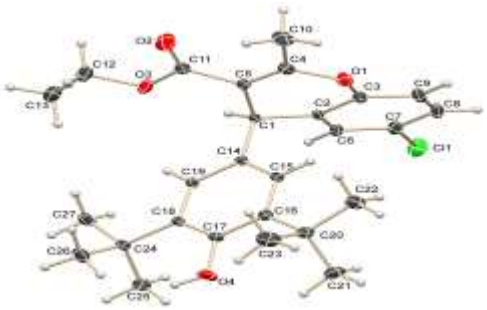

**9-(4-Hydroxyphenyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (6a):**




CHLOROFORM-d
197.71
164.85
154.38
149.31
138.17
130.10
128.95
127.51
125.58
125.09
116.45
115.39
113.68
77.00
50.82
41.59
37.01
32.21
29.17
27.41
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

## 2A.8 XRD

### 2A.8.1 X-Ray Crystallography

| Comp No. | Compound Structure | ORTEP Diagram |
|---|---|---|
| **(3d)** |  **CCDC 1881335** |  |
| **(3p)** |  **CCDC 1881316** |  |

### 2A.8.2 X-ray Crystallography

X-ray intensity data measurements of compounds 3d and 3p were carried out on a Bruker D8 VENTURE Kappa Duo PHOTON II CPAD diffractometer equipped with Incoatech multilayer mirrors optics. The intensity measurements were carried out at 100(2) K temperature with Mo micro-focus sealed tube diffraction source ($MoK_\alpha$ = 0.71073 Å). The X-ray generator was operated at 50 kV and 1.4 mA. A preliminary set of cell constants and an orientation matrix were calculated from three runs of 36 frames. Data were collected with $\omega$ scan width of 0.5° at different settings of $\varphi$ and $2\theta$ with a frame time of 10-20 secs (depending on the diffraction power of the crystals) keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX3 program (Bruker, 2016).[26] All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2016).[26] Using APEX3 (Bruker) program suite, the structure was solved with the ShelXS-97 (Sheldrick, 2008)[27] structure solution program,

using direct methods. The model was refined with version of ShelXL-2013 (Sheldrick, 2015)[28] using Least Squares minimization.All the hydrogen atoms were placed in a geometrically idealized position and constrained to ride on its parent atoms. An *ORTEP* III[29] view of compounds was drawn with 50% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary radii.

Crystal data of **3d**: $C_{30}H_{38}O_4$, M = 462.60, colorless block, 0.23 x 0.12 x 0.08 $mm^3$, monoclinic, space group $P2_1/c$, $a$ = 11.1402(5)Å, $b$ = 24.7200(10)Å, $c$ = 10.3172(5)Å, $\beta$ = 115.213(2)°, $V$ = 2570.5(2)$Å^3$, Z = 4, $T$ = 100(2) K, $2\theta_{max}$ = 65.16°, $D_{calc}$ (g $cm^{-3}$) = 1.195, $F(000)$ = 1000, $\mu$ ($mm^{-1}$) = 0.078, 49003 reflections collected, 9370 unique reflections ($R_{int}$ = 0.0362, $R_{sig}$ = 0.0291), 9370 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, $T_{min}$ = 0.982, $T_{max}$ = 0.994, 317 refined parameters, Good of Fit = $S$ = 1.065, $R1$ = 0.0477, $wR2$ = 0.1156 (all data $R$ = 0.0594, $wR2$ = 0.1218), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.475, $\Delta\rho_{min}$ = -0.243 ($eÅ^{-3}$).

Crystal data of **3p**: $C_{27}H_{33}ClO_4$, M = 456.98, colorless block, 0.20 x 0.12 x 0.06 $mm^3$, orthorhombic, space group $Pna2_1$, $a$ = 14.0165(6)Å, $b$ = 13.0040(5)Å, $c$ = 13.8194(6)Å, $V$ = 2518.87(18)$Å^3$, Z = 4, $T$ = 100(2) K, $2\theta_{max}$ = 72.636°, $D_{calc}$ (g $cm^{-3}$) = 1.205, $F(000)$ = 976, $\mu$ ($mm^{-1}$) = 0.181, 51445 reflections collected, 11870 unique reflections ($R_{int}$ = 0.0601, $R_{sig}$ = 0.0551), 8014 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, $T_{min}$ = 0.965, $T_{max}$ = 0.989, 299 refined parameters, Good of Fit = $S$ = 1.057, $R1$ = 0.0528, $wR2$ = 0.1209 (all data $R$ = 0.0643, $wR2$ = 0.1268), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.896, $\Delta\rho_{min}$ = -0.345 ($eÅ^{-3}$).

| Crystal Data | **3d** | **3p** |
|---|---|---|
| Formula | $C_{30}H_{38}O_4$ | $C_{27}H_{33}ClO_4$ |
| Mr | 462.60 | 456.98 |
| Temp. (K) | 100(2) K | 100(2) K |
| Wavelength | 0.71073 Å | 0.71073 Å |
| Crystal Syst., Sp. Gr | Monoclinic, $P\ 2_1/c$ | Orthorhombic, $P\ 2_1/na$ |
| Unit cell dimensions | a = 11.1402(5) Å; | a = 14.0165(6) Å; |

| | | |
|---|---|---|
| | b = 24.7200(10) Å; $\beta$ = 115.213(2)$^o$ c = 10.3172(5) Å | b = 13.0040(5) Å; c = 13.8194(6) Å |
| Volume (Å$^3$) | 2570.5(2) | 2518.87(18) |
| *Z* | 4 | 4 |
| $D_c$, *Mg/m$^3$* | 1.195 | 1.205 |
| $\mu$/*mm$^{-1}$* | 0.078 | 0.181 |
| *F(000)* | 1000 | 976 |
| Crystal size (mm$^3$) | 0.230 x 0.120 x 0.080 | 0.201 x 0.120 x 0.060 |
| $\theta_{min-max}$ | 2.332 to 32.596$^o$ | 2.596 to 36.318$^o$ |
| *h, k, l* (min, max) | (-16, 16), (-36, 37), (-15, 15) | (-23, 23), (-19, 21), (-23, 23) |
| *Number of reflections* | 49003 | 51445 |
| unique reflections | 9370 [R(int) = 0.0362] | 11870 [R(int) = 0.0601] |
| *Completeness at* $\theta_{max}$ | 99.7 % | 99.1 % |
| *Ab. Correct.* | Semi-empirical from equivalents | Semi-empirical from equivalents |
| $T_{min}$ | 0.994 | 0.989 |
| $T_{max}$ | 0.982 | 0.965 |
| Refinement method | Full-matrix least-squares on $F^2$ | Full-matrix least-squares on $F^2$ |
| *Number of parameters* | 317 | 299 |
| *Goodness-of-fit (S)* | 1.065 | 1.057 |
| Final R indices [I>2sigma(I)] | R1 = 0.0477, wR2 = 0.1156 | R1 = 0.0528, wR2 = 0.1209 |
| R indices (all data) | R1 = 0.0594, wR2 = 0.1218 | R1 = 0.0643, wR2 = 0.1268 |
| $\Delta\rho_{max}$, $\Delta\rho_{min}$(eÅ$^{-3}$) | +0.475, -0.243 e.Å$^{-3}$ | +0.896, -0.345 e.Å$^{-3}$ |
| CCDC No. | 1881335 | 1881316 |

## 2A.9 References

1. a) Masters, K. S.; Bräse, S. *Chem. Rev.* **2012,** *112*, 3717−3776. b) Chantarasriwong, O.; Batova, A.; Chavasiri, W. E.; Theodorakis, A. *Chem. Eur. J.* **2010,** *16*, 9944−9946. c) El-Seedi, H. R.; El-Barbary, M. A.; El-Ghorab, D. M. H.; Bohlin, L.; Borg-Karlson, A. K.; Göransson, U.; Verpoorte, R. *Curr. Med. Chem.* **2010,** *17*, 854−901. d) El-Seedi, H. R.; El-Ghorab, D. M. H.; El-Barbary, M. A.; Zayed, M. F.; Göransson, U.; Larsson, S.; Verpoorte, R. *Curr. Med. Chem.* **2009,** *16*, 2581−2626. e) Na, Y. J. *Pharm. Pharmacol.* **2009,** *61*, 707−712. f) Demirkiran, O. *Top. Heterocycl. Chem*. **2007,** *9*, 139−178. g) Sousa, M. E.; Pinto, M. M. M. *Curr. Med. Chem.* **2005,** *12*, 2447−2479. h) Brahmachari, G.; Mondal, S.; Gangopadhyay, A.; Gorai, D.; Mukhopadhyay, B.; Saha, S.; Brahmachari, A. K. *Chem. Biodivers.* **2004,** *1*, 1627−1651. i) Peres, V.; Nagem, T. J.; de Oliveira, F. F. *Phytochemistry* **2000,** *55*, 683−710.
2. a) Li, J.; Hu, M.; Yao, S. Q. *Org. Lett.* **2009,** *11*, 3008−3011. b) Wu, L.; Burgess, K. *J. Org. Chem.* **2008,** *73*, 8711−8718. C) Li, X.; Zhang, H.; Xie, Y.; Hu, Y.; Sun, H.; Zhu, Q. *Org. Biomol. Chem.* **2014,** *12*, 2033−2036.
3. a) Wrobel, J.; Sredy, J.; Moxham, C.; Dietrich, A.; Li, Z.; Sawicki, D. R.; Seestaller, L.; Wu, L.; Katz, A.; Sullivan, D.; Tio, C.; Zhang, Z. Y. *J. Med. Chem.* **1999,** *42*, 3199−3202. b) Cheng, C. C.; Dong, Q.; Liu, L.; Luo, Y. L.; Liu, L. F.; Chen, A.; Yu, C.; Savaraj, N.; Chou, T. *J. Med. Chem.* **1993,** *36*, 4108−4112.
4. Zhang, W.; Krohn, K.; Ullah-Zia.; Flörke, U.; Pescitelli, G.; Di Bari, L.; Antus, S.; Kurtán, T.; Rheinheimer, J.; Draeger, S.; Schulz, B. *Chem. Eur. J.* **2008,** *14*, 4913−4923.
5. a) Xia, A. B.; Xu, D. Q.; Luo, S. P.; Jiang, J. R.; Tang, J.; Wang, Y. F.; Xu, Z. Y.; *Chem. Eur. J.* **2010,** *16*, 801−804. b) Bugarin, A.; Connell, B. T. *J. Org. Chem.* **2009,** *74*, 4638−4641. c) Ravichandran, S.; Subramani, K.; Arunkumar, R. *Int. J. Chem Tech Res.* **2009,** *1*, 329−331. d) Nising, C. F.; Friedrich, A.; Bräse, S. *Synlett* **2007,** *19*, 2987−2990. (e) Rios, R.; Sundén, H.; Ibrahem, I.; Córdova, A. *Tetrahedron Lett.* **2007,** *48*, 2181−2184. f) Ohnemüller, U. K.; Nising, C. F.; Encinas, A.; Bräse, S. *Synthesis* **2007,** *14*, 2175−2185. g) Shi, Y. L.; Shi, M. *Synlett* **2005,** *17*, 2623−2626. h) Lesch, B.; Bräse, S. *Angew. Chem., Int. Ed.* **2004,** *43*, 115−118.

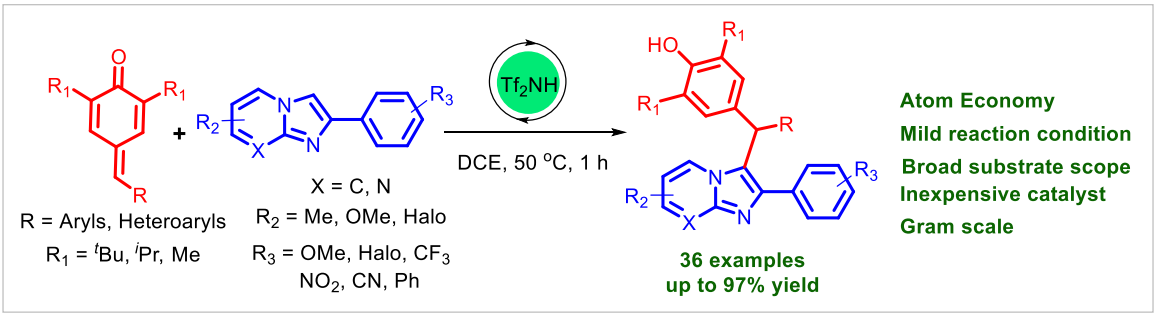
6. a) Makawana, J.; Mungra, D.; Patel, M.; Patel, R. *Bioorg. Med. Chem. Lett.* **2011,** *21*, 6166−6169. b) Li, S.; Li, F. Z.; Gong, J. X.; Yang, Z. *Org. Lett.* **2015,** *17*, 1240−1243.
7. Miao, H.; Yang, Z. *Org. Lett.* **2000,** *2*, 1765−1768.
8. Larget, R.; Lockhart, B.; Renard, P.; Largeon, M. *Bioorg. Med. Chem. Lett.* **2000,** *10*, 835−838.
9. Groweiss, A.; Cardellins, J. H.; Boyd, M. R. *J. Nat. Prod.* **2000,** *63*, 1537−1539.
10. Mori, K.; Audan, G.; Monti, H. *Synlett* **1998,** *03*, 259−260.
11. Pietta, P. J. *J. Nat. Prod.* **2000,** *63*, 1035−1042.
12. Beecher, G. R. *J. Nutr.* **2003,** *133*, 3248−3254.
13. a) Hsiao, C. C.; Liao, H. H.; Sugiono, E.; Atodiresei, I.; Rueping, M. *Chem. Eur. J.* **2013,** *19*, 9775−9779. b) Terada, M.; Yamanaka, T.; Toda, Y. *Chem. Eur. J.* **2013,** *19*, 13658−13662.
14. Yang, Z.; He, Y.; Toste, F. D. *J. Am. Chem. Soc.* **2016,** *138*, 9775−9778.
15. a) Angle, S. R.; Turnbull, K. D. *J. Am. Chem. Soc.* **1989,** *111*, 1136−1138. b) Angle, S. R.; Arnaiz, D. O. *J. Org. Chem.* **1990,** *55*, 3708−3710. c) Lou, Y.; Cao, P.; Jia, T.; Zhang, Y.; Wang, M.; Liao, J. *Angew. Chem. Int. Ed.* **2015,** *54*, 12134−12138. d) Gao, S.; Xu, X.; Yuan, Z.; Zhou, H.; Yao, H.; Lin, A. *Eur. J. Org. Chem.* **2016,** 3006−3012. e) Mahesh, S.; Kant, G.; Anand, R. V. *RSC Adv.* **2016,** *6*, 80718−80722. f) Huang, B.; Shen, Y.; Mao, Z.; Liu, Y.; Cui, S. *Org. Lett.* **2016,** *18*, 4888−4891. g) Xie, K. X.; Zhang, Z. P.; Li, X. *Org. Lett.* **2017,** *19*, 6708−6711.
16. a) Chauhan, P.; Kaya, U.; Enders, D. *Adv. Synth. Catal.* **2017,** *359*, 888−912. b) Caruana, L.; Fochi, M.; Bernardi, L. *Molecules* **2015,** *20*, 11733−11764. c) Parra, A.; Tortosa, M. *ChemCatChem* **2015,** *7*, 1524−1526.
17. Richter, D.; Hampel, N.; Singer, T.; Ofial, A. R.; Mayr, H. *Eur. J. Org. Chem.* **2009,** 3203−3211.
18. a) Zhao, K.; Zhi, Y.; Shu, T.; Valkonen, A.; Rissanen, K.; Enders, D. *Angew. Chem. Int. Ed.* **2016,** *55*, 12104−12108. b) Baik, W.; Lee, H. J.; Koo, S.; Kim, B. H. *Tetrahedron Lett.* **1998,** *39*, 8125−8128. c) Roper, J. M.; Everly, C. R. *J. Org. Chem.* **1988,** *53*, 2639−2642. d) McClure, J. D. *J. Org. Chem.* **1962,** *27*, 2365−2368. e) Xiong, Y. J.; Shi, S. Q.; Hao, W. J.; Tu, S. J.; Jiang, B. *Org. Chem. Front.* **2018,** *5*, 3483−3487.

19. a) Ma, C.; Huang, Y.; Zhao, Y. *ACS Catal.* **2016,** *6*, 6408−6412. b) Yuan, Z.; Wei, W.; Lin, A.; Yao, H. *Org. Lett.* **2016,** *18*, 3370−3373. c) Kim, S.; Kitano, Y.; Tada, M.; Chiba, K. *Tetrahedron Lett.* **2000,** *41*, 7079−7083.
20. a) Zhang, X. Z.; Du, J. Y.; Deng, Y. H.; Chu, W. D.; Yan, X.; Yu, K. Y.; Fan, C. A. *J. Org. Chem.* **2016,** *81*, 2598−2606. b) Huang, B.; Shen, Y.; Mao, Z.; Liu, Y.; Cui, S.; *Org. Lett.* **2016,** *18*, 4888−4891. c) Yuan, Z.; Fang, X.; Li, X.; Wu, J.; Yao, H.; Lin, A. *J. Org. Chem.* **2015,** *80*,11123−11130. d) Gai, K.; Fang, X.; Li, X.; Xu, J.; Wu, X.; Lin, A.; Yao, H. *Chem. Commun.* **2015,** *51*, 15831−15834.
21. a) Peter, M. G. *Angew. Chem. Int. Ed. Engl.* **1989,** *28*, 555−570. b) Itoh, T. *Prog. Polym. Sci.* **2001,** *26*, 1019−1059. c) Toteva, M. M.; Richard, J. P. *Adv. Phys. Org. Chem.* **2011,** *45*, 39−91. d) Parra, A.; Tortosa, M. *ChemCatChem.* **2015,** *7*, 1524−1526. e) Caruana, L.; Fochi, M.; Bernardi, L. *Molecules* **2015,** *20*, 11733−11764. f) Mei, G. J.; Xu, S. L.; Zheng, W. Q.; Bian, C. Y.; Shi, F. *J. Org. Chem.* **2018,** *83*, 1414−1421. g) Chen, K.; Hao, W. J.; Tu, S. J.; Jiang, B. *Green Chem.* **2019,** *21*, 675−683. h) Jiang, F.; Yuan, R.; Jin, L. W.; Mei, G. J.; Shi, F. *ACS Catal.* **2018,** *8*, 10234−10240. i) Liu, S.; Lan, X. C.; Chen, K.; Hao, W. J.; Li, G.; Tu, S. J.; Jiang, B. *Org. Lett*. **2017,** *19*, 3831−3834. j) Zhang, L.; Zhou, X.; Li, P.; Liu, Y.; Sun, Y.; Li, W. *RSC Adv.* **2017,** *7*, 39216−39220.
22. Chen, K.; Liu, S.; Wang, D.; Hao, W. J.; Zhou, P.; Ziang, S. J. B. *J. Org. Chem.* **2017,** *82*, 11524−11530.
23. a) Rathod, J.; Sharma, B. M.; Mali, P. S.; Kumar, P. *Synthesis* **2017,** *49*, 5224−5230. b) Sharma, B. M.; Shinde, D. R.; Jain, R.; Begari, E.; Satbhaiya, S.; Gonnade, R.; Kumar, P. *Org. Lett.* **2018,** *20*, 2787−2791.
24. Sharma, B. M.; Rathod, J.; Gonnade, R.; Kumar, P. *J. Org. Chem.* **2018,** *83*, 9353−9363.
25. Zhao, K.; Zhi, Y.; Shu, T.; Valkonen, A.; Rissanen, K.; Enders, D. *Angew. Chem. Int. Ed*. **2016**, *55*, 12104−12108.
26. Bruker (2016). *APEX3*, *SAINT* and *SADABS*. Bruker AXS Inc., Madison, Wisconsin, USA.
27. Sheldrick, G. M. *Acta Crystallogr*. **2008**, *A64*, 112−122.
28. Sheldrick, G. M. *Acta Crystallogr*. **2015,** *C71*, 3−8.
29. Farrugia, L. J. *J. Appl. Crystallogr.* **2012,** *45*, 849−854.

# Chapter-2 (Section-B)

# Metal-free, $Tf_2NH$-Catalyzed 1,6-Conjugate Addition of Imidazopyridine to *para*-Quinone Methides: Easy Access to C3-Functionalized Triarylmethane Imidazopyridine

## Abstract


An inexpensive and commercially available $Tf_2NH$-catalyzed 1, 6-conjugate addition of imidazopyridine (IMPY) heterocycles to *para*-quinone methides (*p*-QMs) is described. The present transformation provides a diverse class of C3-functionalized triarylmethanes heterocyclic derivatives of imidazopyridine. The given reaction protocol assumes significance with regard to atom economy, mild reaction condition. These metal-free transformations provided a very broad substrate scope of conjugate addition product with a high yield up to 97% within a short duration.

## 2B.1 Introduction

Nitrogen-containing triarylmethanes (TAMs) heterocyclic scaffold has versatile application in medicinal chemistry.[1] Therefore, it has attracted a great deal of interest amongst medicinal and synthetic chemists world-wide. These heterocyclic scaffolds are known to exhibit various biological activities including aromatase inhibitors, antifungal and anticancer etc.[2] This has led to the development of number of drugs currently available in the market.[3] Some representative examples of nitrogen-containing bioactive triarylmethane heterocycles are depicted in Figure-1A.[4]

*para*-Quinone methides (*p*-QMs) are extensively used to construct the diverse class of substituted aryl heterocyclic derivatives,[5] due to its powerful 1,6-Michael acceptors property. Our group has developed the construction of biarylmethane derivatives by conjugate addition of allenol ester and butenolides to *para*-quinone methides.[6] Various Lewis acid/Brønsted acid catalyzed[7] 1,6-conjugate addition of heterocyclic nucleophiles such as imidazole,[8] indole,[9] coumarin,[10] oxindole,[11] naphthols[12] to *para*-quinone methides are reported in literature for the construction of triarylmethane heterocyclic scaffolds. More recently, Anand and co-workers developed bis(amino)cyclopropenium salt catalyzed 1,6-conjugate addition of indole to *p*-QMs.[13]

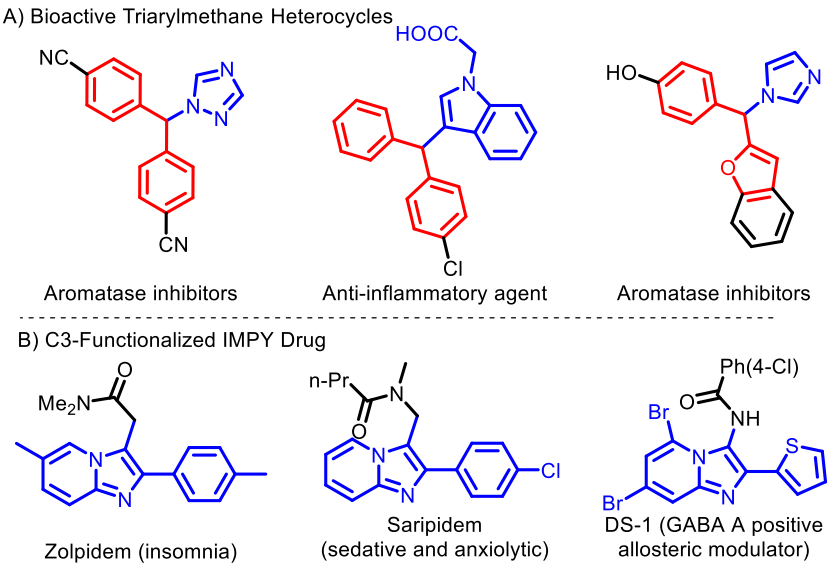


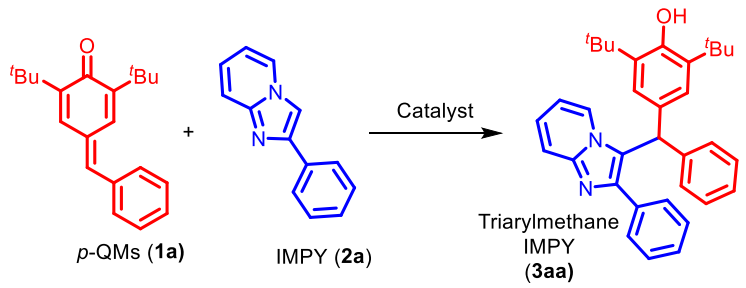

**Figure-1.** Nitrogen-containing bioactive triarylmethane heterocycles

Imidazopyridine (IMPY) containing moiety is known to exhibit broad range of application in both pharmaceutical and agrochemical industries.[14] These nitrogen-containing heterocyclic

scaffolds exist in several natural products and drug molecules.[15] Various functional group transformations were carried out on the C3 position[16] of an imidazopyridine to improve its pharmacokinetic properties. As a result, a number of C3-functionalized IMPY containing drug molecules were developed and being currently used in day-to-day life. Zolpidem,[17] Saripidem,[18] and DS-1[19] are some of the representative drug molecules shown in Figure-1B. Very recently Kilic *et al.*, developed C3-functionalization of imidazo[1,2-*a*]pyridines with *para*-quinone methides in presence of hexafluoro-2-propanol (HFIP).[20] However, the protocol developed is not very practical and associated with disadvantage since HFIP is a highly toxic, volatile and corrosive chemical[21] and a banned item in many countries.

### 2B.2 Present Work

In the backdrop of literature reports, it was worthwhile to explore the reactivity of *p*-QMs and nitrogen-containing heterocycles. As illustrated in Scheme-1, we envisioned that the 1,6-conjugate addition of imidazopyridine derivatives to *para*-quinone methides could lead to the diverse range of triarylmethane heterocycles under various reaction conditions catalyzed by various Lewis and Brønsted acids.




**Scheme-1:** Hypothesis for the 1,6-conjugate addition of IMPY to *p*-QMs

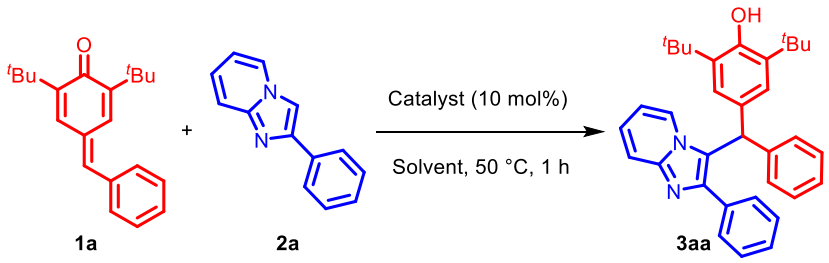
### 2B.3 Results and Discussion

#### 2B.3.1 Optimization of reaction conditions

To study the hypothesis of the 1,6-conjugate addition of IMPY to *p*-quinone methide, the optimization reaction was first carried out with commercially available $Tf_2NH$ as a Brønsted acid catalyst.[22]

Initially, the reaction was performed using dichloromethane as a solvent at 50 $^oC$ for 1 h in presence of 10 mol% of catalyst $Tf_2NH$, the desired product **3aa** was obtained with reasonable yield of 70% **(Table-1, entry 1)**.

**Table-1.** Optimization of one-pot synthesis of 2,6-di-*tert*-butyl-4-(phenyl(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)phenol from *para*-quinone methide and IMPY[a]



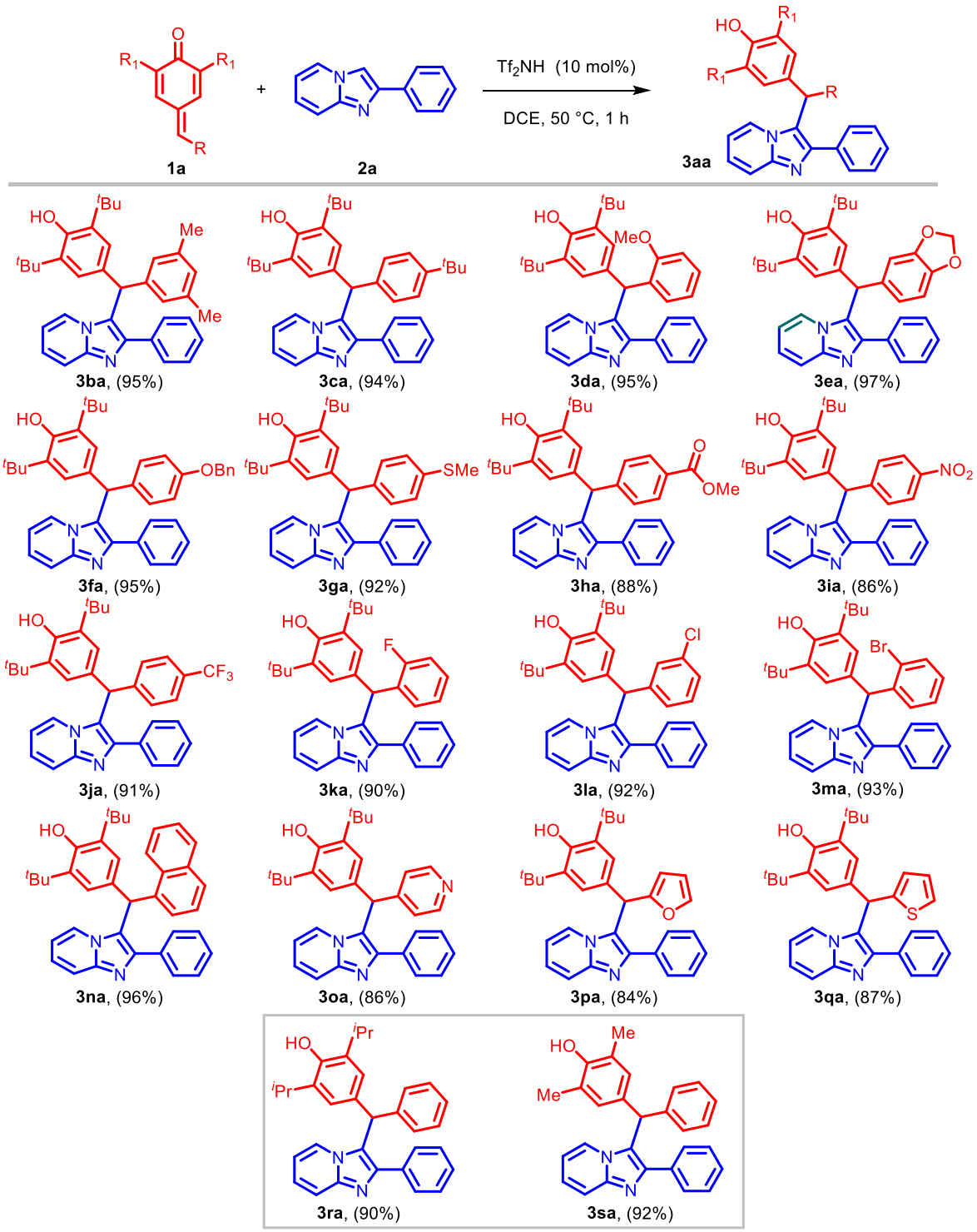

| Entry | Catalyst (10 mol%) | Solvent | Yield (%)[b] |
|---|---|---|---|
| 1 | $Tf_2NH$ | DCM | 70 |
| **2** | **$Tf_2NH$** | **DCE** | **93** |
| 3 | $Tf_2NH$ | Toluene | 61 |
| 4 | $Tf_2NH$ | THF | 52 |
| 5 | $CF_3COOH$ | DCE | NR |
| 6 | $CH_3COOH$ | DCE | NR |
| 7 | PTSA | DCE | 41 |
| 8 | $BF_3.OEt_2$ | DCE | 55 |
| 9 | $Fe(OTf)_3$ | DCE | 85 |
| 10 | $Ag(OTf)_2$ | DCE | 59 |
| 11 | $In(OTf)_3$ | DCE | NR |
| 12 | $Sc(OTf)_3$ | DCE | NR |
| 13 | $Bi(OTf)_3$ | DCE | 32 |
| 14 | $La(OTf)_3$ | DCE | NR |
| 15 | $Tf_2NH$ (5 mol%) | DCE | 80 |
| 16 | $Tf_2NH$ (1 mol%) | DCE | 67 |
| 17[c] | - | DCE | NR |
| 18[d] | $Tf_2NH$ | DCE | 94 |
| 19[e] | $Tf_2NH$ | DCE | 52 |

[a]Reaction conditions unless otherwise specified: **1a** (1.0 mmol), **2a** (1.0 mmol), and catalyst (10 mol%) in the anhydrous solvent at 50 °C. [b]Isolated yields of **3aa**. [c]Reaction without catalyst. [d]Reaction at 90 °C. [e]Reaction stirred for 24 h at room temperature.

Encouraged by this initial result, we next examined other solvents such as dichloroethane, toluene, and tetrahydrofuran at 50 $^{o}$C for 1 h in presence of 10 mol% $Tf_2NH$ **(Table-1, entries 2-4)**. We noticed that reaction works fruitfully in dichloroethane to rig out the conjugate addition product 2,6-di-*tert*-butyl-4-(phenyl(2-phenylimidazo[1,2-*a*]pyridin-3yl)methyl)phenol **3aa** in 93% yield **(Table-1, entry 2)**. The reaction conditions were further optimized by exploring several Brønsted acids such as $CF_3COOH$, $CH_3COOH$ and PTSA, but we did not observe any improvement in the yield **(Table-1, entries 5-7)** and got 41% yield of desired product **3aa** using PTSA as a Brønsted acid **(Table-1, entry 7)**. We next explored varieties of Lewis acid catalysts **(Table-1, entries 8-14)**. The reaction works with $BF_3.OEt_2$, $Fe(OTf)_3$ and $Ag(OTf)_2$ to give 55%, 85% and 59% yield of conjugate addition product **3aa (Table-1, entries 8-10)** respectively. Reaction works with $Bi(OTf)_3$ to give only poor yield of the product **(table-1, entry 13)**. We did not observe any reaction with $In(OTf)_3$, $Sc(OTf)_3$ and $La(OTf)_3$ Lewis acid catalysts **(Table-1, entries 11, 12 & 14)**. The use of 5 mol% of catalyst produced the appreciable yield of the product **(Table-1, entry 15)**. Further, reduction in catalyst (1 mol%) gave slightly less yield of desired product **(Table-1, entry 16)**. No conjugate addition product was obtained without catalyst **(Table-1, entry 17)**. When reaction was carried at 90 $^{o}$C, it gave 94% yield of desired product **3aa (Table-1, entry 18)**. On the other hand when reaction was performed at room temperature, it took longer time (24 h) to furnish 52% yield of conjugate addition product **3aa (Table-1, entry 19)**.

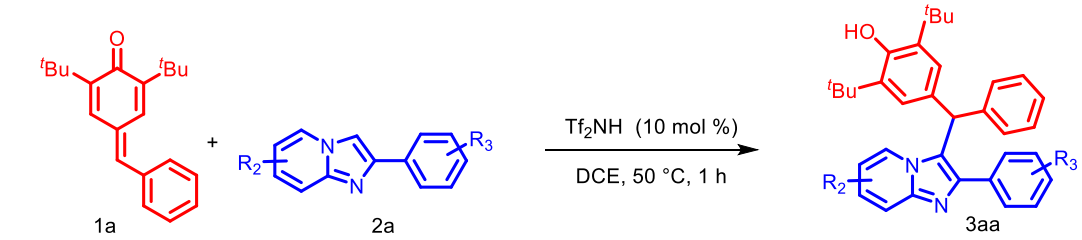
Having optimized the reaction conditions **(Table-1, entry 2)**, our next target was to investigate the generality and substrate scope of the reaction using various substituted *para*-quinone methides and results are summarized in Scheme-2. The methyl-substituted 3,5-dimethyl, 4-*tert*-butyl on *p*-QMs gave an excellent yield of the conjugated addition product **(entry 3ba-3ca, 94%-95% yield)**. The *p*-QMs such as 2-methoxy, 3,4-methylenedioxyphenyl, 4-OBn, and 4-thiotoluene bearing electron-donating substituents, reacted in efficient manner furnishing the desired product in excellent yield up to 97% **(entry 3da-3ga, 92%-97% yield)**. Similarly, 4-methoxycarbonyl, 4-nitro, and 4-trifluoromethyl containing electron-withdrawing groups on *p*-QMs gave only moderate to good yield of products **(entry 3ha-3ja, 86%-91% yield)**. Halogen substitution, 2-fluoro, 3-chloro, and 2-bromo on *p*-QMs also offered the corresponding products in high yield **(entry 3ka-3ma, 90%-93% yield)**. The *α*- naphthyl *para*-quinone methide also provided excellent yield **(entry 3na, 96% yield)**.

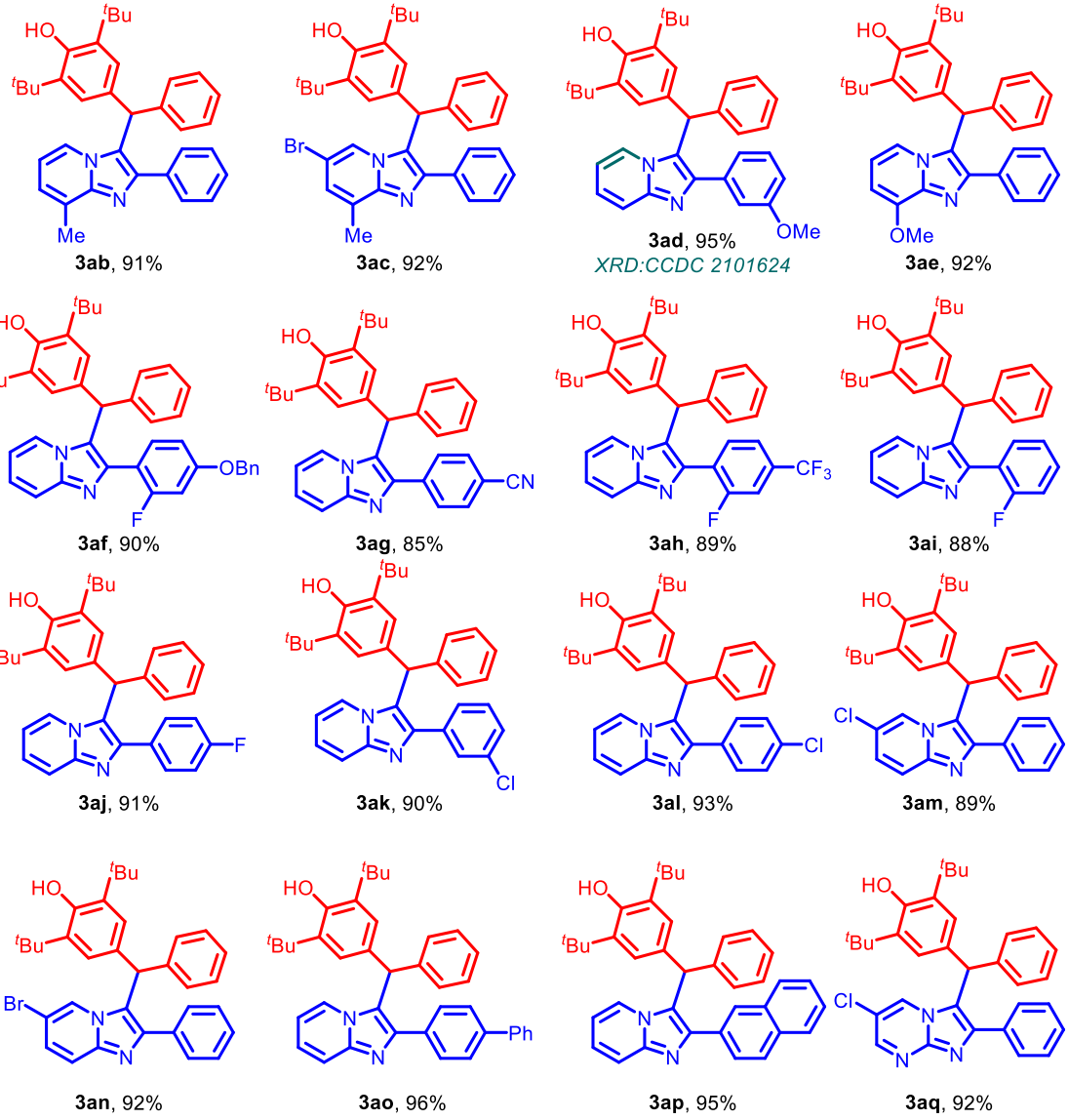
## 2B.3.2 Substrate scope of imidazo[1,2-*a*]pyridine on 1,6-conjugate addition of diverse *para*-quinone methides




[a]All reactions were performed with compound **1a** (1.0 mmol), **2a** (1.0 mmol), $Tf_2NH$ (10 mol%) in 5 mL of DCE at 50 °C on 0.5 mmol scales. [b]Isolated yield.

### 2B.3.3 Substrate scope of diverse imidazo [1,2-*a*]pyridines on 1,6-conjugate addition of *para*-quinone methide



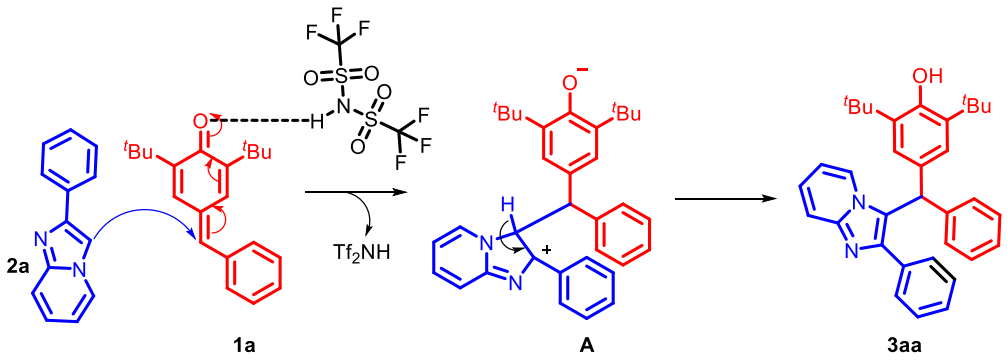




[a]All reactions were performed with compound **1a** (1.0 mmol), **2a** (1.0 mmol), $Tf_2NH$ (10 mol%) in 5 mL of DCE at 50 °C on 0.5 mmol scales. [b]Isolated yield.

*para*-Quinone methides, derived from pyridine, furan, and thiophene reacted smoothly to offer the conjugate addition product in good yields **(entry 3oa–3qa, 84%-87% yield)**. The isopropyl and methyl substitution of quinone ring gave a high yield of the corresponding products **(entry 3ra–3sa, 90%-92% yield)**. The substrate scope of the different substitutions on imidazopyridine (IMPY) derivatives was also explored and the results discussed in Scheme-3. Imidazopyridine bearing 8-methyl, 6-bromo-8-methyl-, 8-methoxy, 3'-methoxy and 2'-fluoro-4'-OBn electron-donating substituents react smoothly to furnish the excellent yield of conjugate addition products **(entry 3ab-3af, 90%-95% yield)**. The proton NMR displayed the characteristic signals for all the functional group present on the core structure, such as singlet at δ 1.31 ppm with 18 H represents two *tert*-butyl groups of *p*-QMs. Two singlet signals at δ 6.09 and δ 5.11 ppm represents the benzylic –CH group and –OH group respectively. In proton decoupled carbon NMR, the compound **3ad** shows the twenty two different signals which are in accordance with proposed structure. Further, the elemental formula was confirmed by the HRMS analysis. The structure was further confirmed by the single crystal x-ray analysis of **3ad (CCDC 2101624)**. The electron-withdrawing substitution 4'-cyano, and 2'-fluoro-4'-trifluoromethyl on imidazopyridine provided a good yield of the product **(entry 3ag-3ah, 85%-89% yield)**. Halogen derivatives F, Cl, Br of imidazopyridine reacted efficiently to produce good to excellent yield of addition product **(entry 3ai-3an, 88%-93% yield)**. The 4'-phenyl and *β*-naphthyl derivatives of imidazopyridine also furnished the conjugate addition product in excellent yield **(entry 3ao-3ap, 95%-96% yield)**. Similarly, imidazo[1,2-*a*]pyrimidine also gave a high yield of product **(entry 3aq, 92% yield)**.

### 2B.3.4 The plausible reaction mechanism

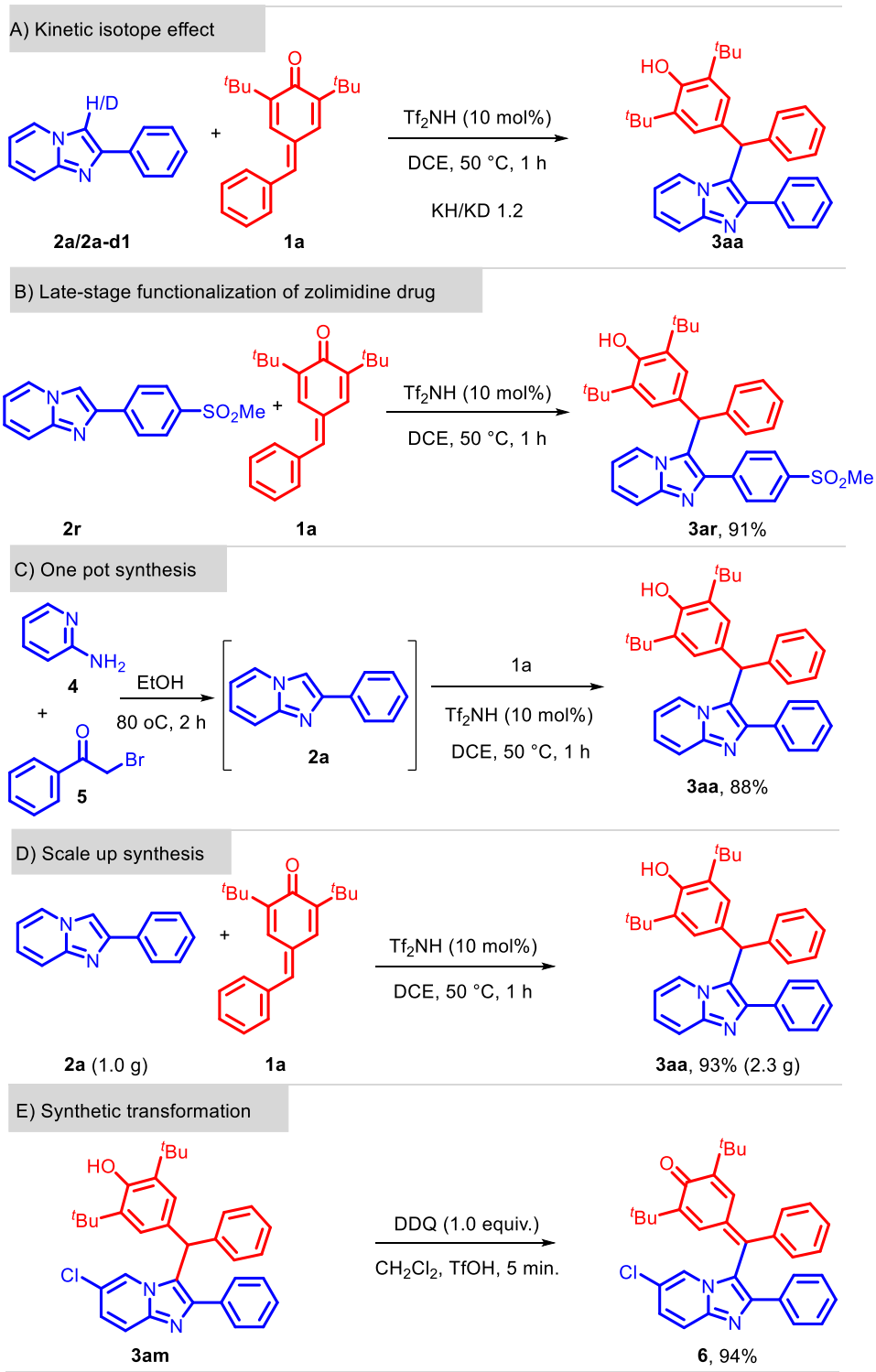
A plausible reaction mechanism for the 1,6-conjugate addition of *p*-QM **1a** with imidazopyridine **2a** is described in Scheme-2. The nucleophilic attack of imidazopyridine to *p*-QM occurred at the C3 position of imidazo[1,2-*a*]pyridine. An intermediate addition product **A** was formed, followed by a loss of proton and formation of 1,6-nucleophilic addition product **3aa**.




**Scheme-2.** A plausible mechanism for the formation of triarylmethane IMPY

### 2B.3.5 Reaction kinetics and synthetic application

Next we turned our attention to investigate the reaction kinetics and to demonstrate synthetic utility of our developed reaction protocol; results are illustrated in Scheme-3. The reaction kinetic isotope effect was performed on **1a** with **2a/2a-d1** as model substrates (Scheme-3A).We observe the ratio KH/KD 1.2, which shows the proton elimination was not a slow process (For details, see the experimental section). We further proceeded to explore the synthetic application of our proposed methodology. The late-stage functionalization of Zolimidine drug **(3ar)** was achieved using standard condition to furnish its triarylmethane derivative in 91% yield (Scheme-3B). The synthesis of IMPY derivative **2a** followed sequential addition of *p*-QMs **1a** in one-pot condition to offer desired product **3aa** in 88% yield (Scheme-3C). The scale up synthesis of the given reaction protocol is also demonstrated on 1.0 g scale of **2a** as starting material to give 93% yield (2.3 g) of **3aa** (Scheme-3D). Further, synthetic transformation of compound **(3am)** was achieved using DDQ to get oxidized compound **6** in 94% yield (scheme-3E).




**Scheme-3.** Reaction kinetics and synthetic application

## 2B.4 Conclusion

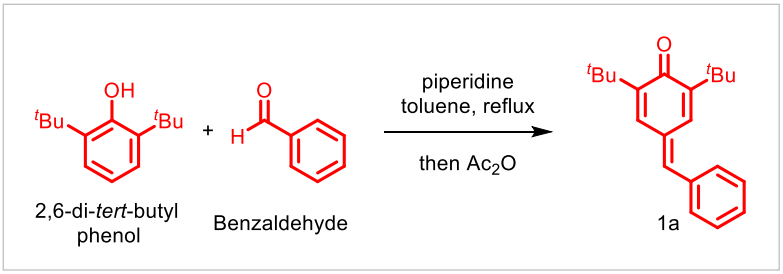
We have established an efficient protocol for 1,6-conjugate addition of imidazopyridines to *para*-quinone methides in presence of various Lewis or Brønsted acids to provide triarylmethane heterocyclic derivatives of imidazopyridine. Reaction works efficiently using $Tf_2NH$ to give maximum up to 97% yield of conjugate addition product. Our developed route has atom economy, mild reaction condition with broad substrate scope leading to the diverse range of triarylmethane heterocycles. We believe that these compounds would find enormous application in medicinal chemistry.

## 2B.5 Experimental Section

### 2B.5.1 General Information

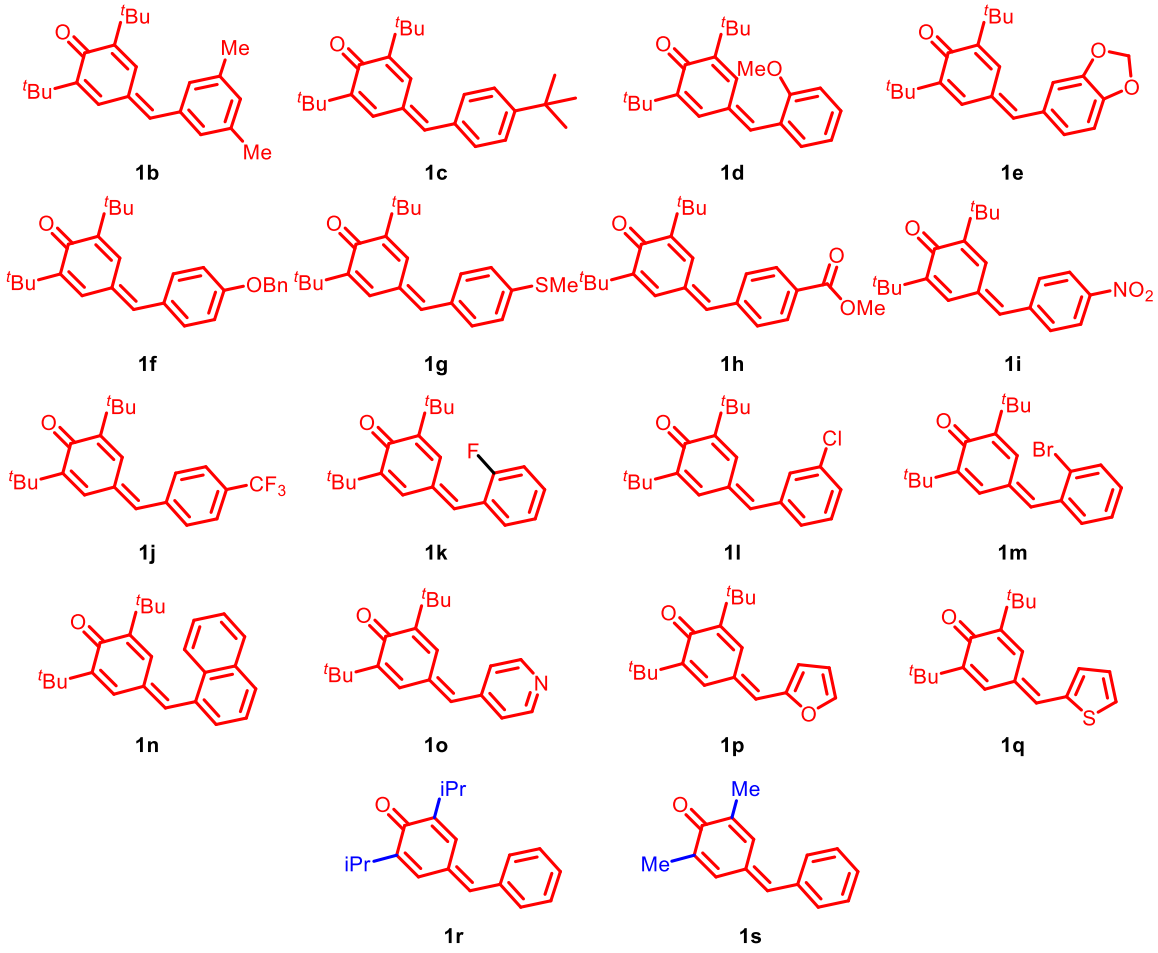
Reactions were carried out under anhydrous conditions, using flame-dried glassware under a positive pressure of argon, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm pre-coated silica-gel plates (60 $F_{254}$). Plates were visualized with either UV light, iodine adsorbed on silica gel, or by immersion in an ethanolic solution of phosphomolybdic acid (PMA), *p*-anisaldehyde, or KMnO4, followed by heating with a heat gun for ca. 15 s. Flash chromatography was carried out on silica gel (100–200 mesh). $^{1}H$ and $^{13}C$ NMR spectra were obtained with a 400 or 500 MHz spectrometer and $^{19}F$ NMR obtained with a 376 MHz spectrometer in $CDCl_3$ solution. Coupling constants (*J*) are given in Hertz (Hz), chemical shifts ($\delta$) are expressed in ppm relative to tetramethylsilane as a reference standard and the signals were reported as s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet and br. = broad. HRMS ($ESI^+$) spectra were recorded with an ORBITRAP mass analyzer. Infrared (IR) spectra were performed with a FTIR spectrometer as thin films using NaCl plates, and wavenumbers are indicated in $cm^{-1}$. Chemical nomenclature was generated using ChemDraw Professional 15.1. **CCDC 2101624** (for **3ad**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

### 2B.5.2 General Procedure: Synthesis of *para*-Quinone Methides 1a-1s[23, 24]

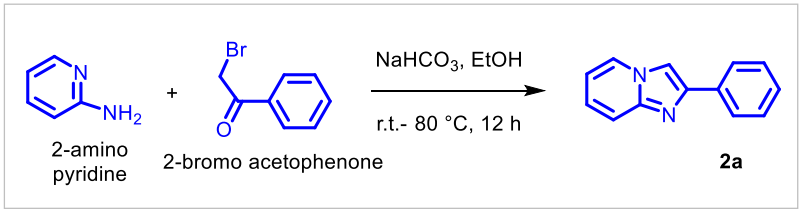



In an oven dried Dean-Stark apparatus, phenol (1.0 equiv.) and the corresponding aldehyde (1.0 equiv.) were taken in toluene (100 mL), the reaction mixture was heated to reflux followed by dropwise addition of piperidine (2.0 equiv.) within 1 h. The reaction mixture was continued to reflux for 6 h. After cooling just below the boiling point of the reaction mixture, acetic anhydride (2.0 equiv.) was added and stirring was continued for 30 min. Then the reaction mixture was poured on ice-water (500 mL) and extracted with $CH_2Cl_2$ (4 × 200 mL). The combined organic phase was dried over anhydrous $Na_2SO_4$, and the solvent was

evaporated under reduced pressure. The crude product was purified by column chromatography and further recrystallized from *n*-hexane, affording *para*-quinone methide in good yields.

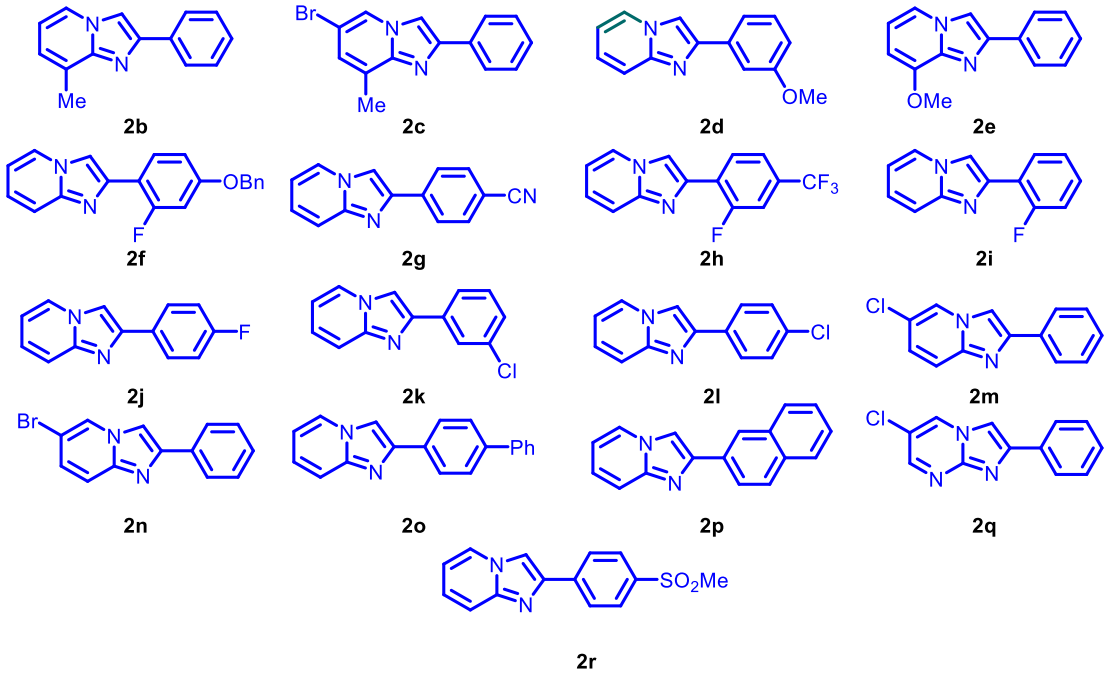



**2B.5.3 General Procedure: Synthesis of 2-phenylimidazo[1,2-*a*]pyridine 2a and its derivatives (2b-2r)**

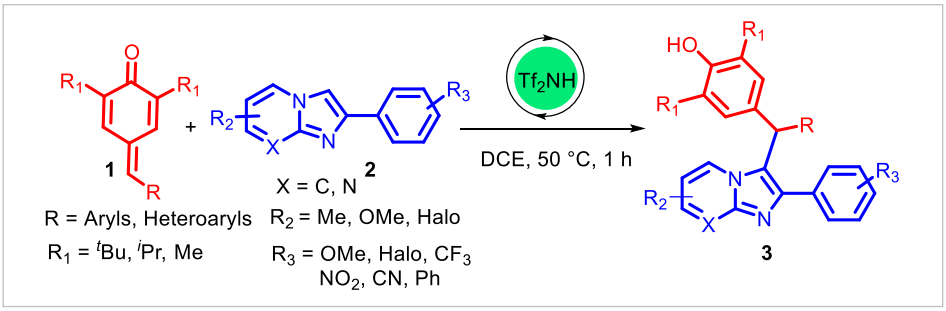



The mixture of 2-aminopyridine (1.05 equiv.), phenacyl bromide (1.0 equiv.), and sodium hydrogen carbonate (1.0 equiv.) in ethanol (4 mL) was stirred for 12 h at room temperature to 80 $^{o}$C temperature.[25] After completion, solution was evaporated in vacuo, and reaction mass was washed with diethyl ether to give the desired product **2a**. Use these products without

further purification. Other derivatives were also prepared from 2-aminopyridine and the corresponding 2-bromoacetophenones.



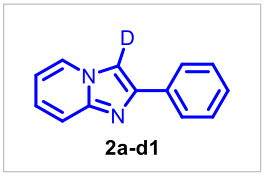

### 2B.5.4 General Procedure: Synthesis of C3-Functionalized Triarylmethane Heterocycles of Imidazopyridine 3



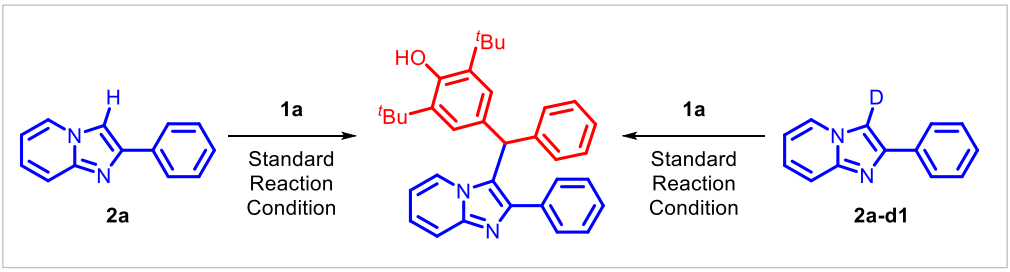

To a stirring solution of corresponding *para*-quinone methides (*p*-QMs) **1** (1.0 equiv.) and 2-phenylimidazo[1,2-*a*]pyridines **2** (1.0 equiv.) in dry $C_2H_4Cl_2$ (4 mL) at room temperature was added $Tf_2NH$ (10 mol%). The resulting solution was then stirred at 50 $^oC$ temperature for 1 h. The completion of the reaction was confirmed by the thin layer chromatography using pet. ether/ethyl acetate solvent system. After the completion of the reaction, the reaction mass was concentrated under the high vacuum, and the crude product was purified by column chromatography on silica gel 100 - 200 mesh to obtain corresponding conjugate addition product **3**.

### 2B.5.5 Reaction Kinetics Experiment

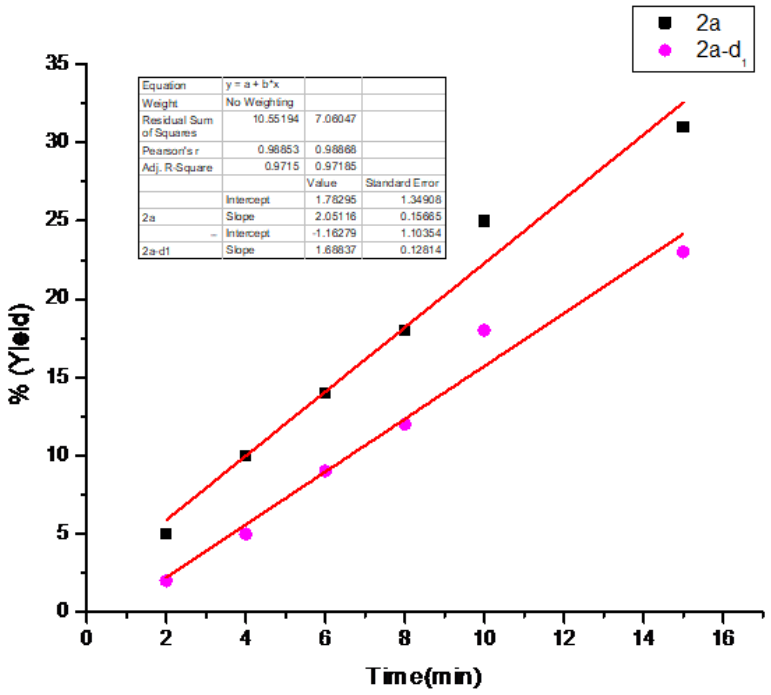
**2-phenylimidazo[1,2-*a*]pyridine-3-d (2a-$d_1$)**




In dry reaction vial, **2a** (1.0 equiv.) was dissolved in 10 mL toluene and $D_2O$ (3.0 equiv.) was added. Further reaction mixture was refluxed for 12 h. After completion, reaction mixture was filtered over $Na_2SO_4$. The solvent was concentrated under reduced pressure and the residue obtained was purified by column chromatography on 100 - 200 mesh silica gel using pet. ether/ethyl acetate to afford the product **2a-$d_1$** as a colourless solid in 99% yield and 92% deuterium. **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 8.11 (dd, *J* = 0.9, 6.8 Hz, 1 H), 7.99 - 7.93 (m, 2 H), 7.64 (d, *J* = 9.1 Hz, 1 H), 7.47 - 7.42 (m, 2 H), 7.37 - 7.31 (m, 1 H), 7.17 (ddd, *J* = 1.3, 6.8, 9.1 Hz, 1 H), 6.77 (dt, *J* = 0.9, 6.8 Hz, 1 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 145.6, 145.6, 133.7, 128.7, 127.9, 126.0, 125.5, 124.6, 117.5, 112.4.

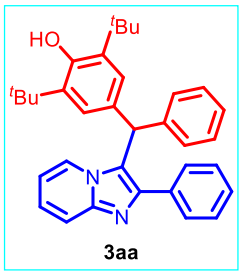



In two different experiments: in first set, *para*-quinone methide (*p*-QM) **1a** (1.0 equiv.) and 2-phenylimidazo[1,2-*a*]pyridine **2a** (1.0 equiv.) was added under standard reaction condition. In another set of reaction experiment *para*-quinone methide (*p*-QM) **1a** (1.0 equiv.) and 2-phenylimidazo[1,2-*a*]pyridine **2a-$d_1$** (1.0 equiv.) was added under standard reaction condition. Both reactions were stirred at 50 $^oC$ for 30 min. The final data was obtained by averaging the results of two independent experiments.


2a
2a-d1
% (Yield)
Time(min)
0
5
10
15
20
25
30
35
0
2
4
6
8
10
12
14
16
Equation y = a + b*x
Weight No Weighting
Residual Sum of Squares 10.55194 7.06047
Pearson's r 0.98853 0.98868
Adj. R-Square 0.9715 0.97185
Value Standard Error
Intercept 1.78295 1.34908
2a Slope 2.05116 0.15685
Intercept -1.16279 1.10354
2a-d1 Slope 1.66837 0.12814

## 2B.6 NMR Data

**2,6-Di-*tert*-butyl-4-(phenyl(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)phenol (3aa):**

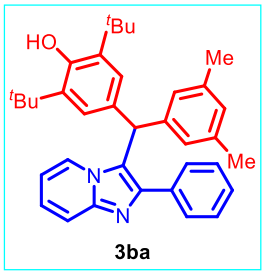


3aa

Synthesized according to General Procedure 2B.5.4. Orange solid in 93% yield. $\boldsymbol{R_f}$ = 0.4 (pet. ether/ethyl acetate = 7:3); **mp** = 156 $^{o}$C; **IR** ($CHCl_3$): $\nu_{max}$ = 3413, 2957, 1612, 1437, 1367, 1233, 911, 734; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.72 - 7.67 (m, 2 H), 7.60 (dd, $J$ = 1.4, 8.1 Hz, 2 H), 7.38 - 7.23 (m, 7 H), 7.12 (d, $J$ = 8.3 Hz, 2 H), 6.86 (s, 2 H), 6.60 - 6.55 (m, 1 H), 6.13 (s, 1 H), 5.11 (br. s., 1 H), 1.30 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 152.5, 144.7, 144.5, 140.3, 136.0, 134.5, 130.3, 129.8, 129.1, 128.8, 128.7, 128.6, 128.1, 127.6, 126.8, 125.4, 124.7, 124.2, 122.0, 117.5, 111.6, 46.6, 34.3, 30.2; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{34}H_{36}N_2O$ $[M + H]^+$ 489.2906, found 489.2908.

**……..**

**2,6-Di-*tert*-butyl-4-((3,5-dimethylphenyl)(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)phenol (3ba):**

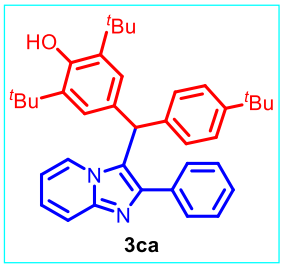


3ba

Synthesized according to General Procedure 2B.5.4. Orange solid in 95% yield. $\boldsymbol{R_f}$ = 0.5 (pet. ether/ethyl acetate = 7:3); **mp** = 168 $^{o}$C; **IR** ($CHCl_3$): $\nu_{max}$ = 3413, 2957, 1605, 1437, 1368, 1225, 755; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.74 - 7.65 (m, 2 H), 7.61 - 7.57 (m, 2 H), 7.37 - 7.29 (m, 3 H), 7.15 (ddd, $J$ = 1.1, 6.9, 8.9 Hz, 1 H), 6.87 (s, 1 H), 6.83 (s, 2 H), 6.74 (s, 2 H), 6.58 (dt, $J$ = 1.4, 6.9 Hz, 1 H), 6.05 (s, 1 H), 5.10 (s, 1 H), 2.23 (s, 6 H), 1.29 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 152.4, 144.8, 144.5, 140.0, 138.1, 135.7, 134.8, 130.0, 129.0, 128.4, 128.0, 127.4, 126.4, 125.5, 124.8, 123.9, 122.1, 117.4, 111.4, 46.4, 34.2, 30.2, 21.4; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{36}H_{40}N_2O$ $[M + H]^+$ 517.3219, found 517.3212.

**……..**

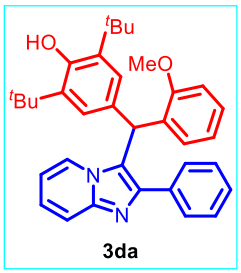
**2,6-Di-*tert*-butyl-4-((4-(*tert*-butyl)phenyl)(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)phenol (3ca):**




Synthesized according to General Procedure 2B.5.4. Yellow solid in 94% yield. $\boldsymbol{R_f}$ = 0.5 (pet. ether/ethyl acetate = 7:3); **mp** = 99 $^{o}$C; **IR** ($CHCl_3$): $\nu_{max}$ = 3393, 2959, 1521, 1436, 1351, 907, 733; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.71 - 7.65 (m, 2 H), 7.60 (d, *J* = 6.9 Hz, 2 H), 7.36 - 7.26 (m, 5 H), 7.18 - 7.10 (m, 1 H), 7.02 (d, *J* = 8.3 Hz, 2 H), 6.85 (s, 2 H), 6.57 (t, *J* = 6.8 Hz, 1 H), 6.09 (s, 1 H), 5.10 (s, 1 H), 1.29 (s, 27 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 152.4, 149.6, 144.8, 144.6, 137.2, 135.9, 134.8, 130.1, 129.1, 128.2, 128.1, 127.4, 125.5, 125.4, 124.9, 123.9, 122.2, 117.5, 111.4, 77.2, 76.7, 46.1, 34.4, 34.3, 31.3, 30.2; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{38}H_{44}N_2O$ $[M + H]^+$ 545.3532, found 545.3528.

**……..**

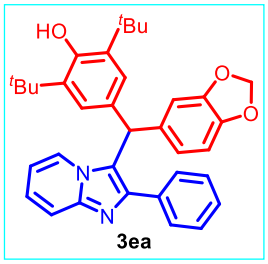
**2,6-Di-*tert*-butyl-4-((2-methoxyphenyl)(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)phenol (3da):**




Synthesized according to General Procedure 2B.5.4. Yellow solid in 95% yield. $\boldsymbol{R_f}$ = 0.6 (pet. ether/ethyl acetate = 7:3); **mp** = 128 $^{o}$C; **IR** ($CHCl_3$): $\nu_{max}$ = 3634, 2957, 1596, 1437, 1379,, 1235, 909, 733; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.73 (d, *J* = 7.0 Hz, 1 H), 7.66 (d, *J* = 9.0 Hz, 1 H), 7.55 - 7.51 (m, 2 H), 7.31 - 7.28 (m, 1 H), 7.27 - 7.20 (m, 2 H), 7.13 (ddd, *J* = 1.3, 6.8, 9.0 Hz, 1 H), 7.03 (dd, *J* = 1.4, 7.8 Hz, 1 H), 6.89 - 6.83 (m, 2 H), 6.79 - 6.73 (m, 2 H), 6.58 (dt, *J* = 1.3, 6.8 Hz, 1 H), 6.35 (s, 1 H), 5.06 (s, 1 H), 3.60 (s, 3 H), 1.27 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 157.1, 151.9, 144.2, 135.4, 134.8, 129.1, 129.0, 128.7, 128.5, 127.9, 127.4, 126.8, 124.8, 124.3, 123.3, 121.3, 120.1, 117.0, 111.0, 110.3, 76.7, 76.4, 55.0, 40.5, 33.9, 29.9; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{35}H_{38}N_2O_2$ $[M + H]^+$ 519.3012, found 519.3008.

**……..**

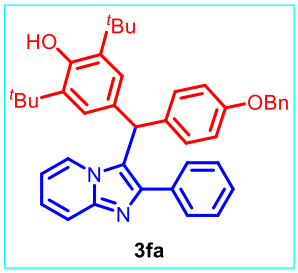
**4-(Benzo[*d*][1,3]dioxol-5-yl(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)-2,6-di-*tert*-butylphenol (3ea):**




Synthesized according to General Procedure 2B.5.4. Orange solid in 97% yield. $\boldsymbol{R_f}$ = 0.5 (pet. ether/ethyl acetate = 6:4); **mp** = 99 $^{o}$C; **IR** ($CHCl_3$): $\nu_{max}$ = 3414, 2957, 1519, 1437, 1351, 1240, 914, 733; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 8.31 (t, *J* = 1.8 Hz, 1 H), 8.11 (ddd, *J* = 0.9, 2.3, 8.2 Hz, 1 H), 7.94 - 7.89 (m, 1 H), 7.76 (d, *J* = 6.9 Hz, 1 H), 7.69 (d, *J* = 9.2 Hz, 1 H), 7.45 (t, *J* = 8.0 Hz, 1 H), 7.26 - 7.21 (m, 1 H), 6.86 (s, 2 H), 6.74 - 6.67 (m, 2 H), 6.57 - 6.52 (m, 2 H), 5.94 (s, 2 H), 5.91 (s, 1 H), 5.14 (s, 1 H), 1.29 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 152.8, 148.1, 147.7, 146.5, 144.9, 142.1, 136.7, 136.2, 135.0, 133.9, 129.5, 128.8, 125.3, 124.8, 124.6, 123.8, 122.9, 122.1, 121.8, 117.8, 112.3, 109.0, 108.4, 101.2, 46.7, 34.2, 30.1; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{35}H_{36}N_2O_3$ $[M]^+$ 532.2726, found.532.2722.

**……..**

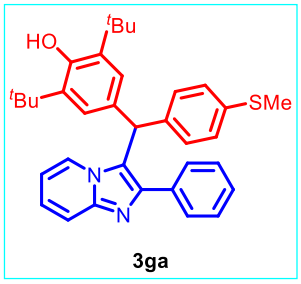
**4-((4-(Benzyloxy)phenyl)(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)-2,6-di-*tert*-butylphenol (3fa):**




Synthesized according to General Procedure 2B.5.4. Brown solid in 95% yield. $\boldsymbol{R_f}$ = 0.3 (pet. ether/ethyl acetate = 5:5); **mp** = 106 $^{o}$C; **IR** ($CHCl_3$): $\nu_{max}$ = 3630, 2957, 1515, 1439, 1354, 1234, 1020, 752; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.71 (d, *J* = 6.9 Hz, 2 H), 7.58 (d, *J* = 7.3 Hz, 2 H), 7.45 - 7.29 (m, 8 H), 7.20 - 7.12 (m, 1 H), 7.05 - 7.00 (m, *J* = 8.7 Hz, 2 H), 6.92 - 6.88 (m, *J* = 9.2 Hz, 2 H), 6.86 (s, 2 H), 6.59 (t, *J* = 6.6 Hz, 1 H), 6.06 (br. s., 1 H), 5.12 (s, 1 H), 5.05 (s, 2 H), 1.30 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 157.5, 152.5, 144.8, 136.9, 135.9, 130.1, 129.6, 129.1, 128.6, 128.1, 128.0, 127.5, 125.3, 124.8, 117.5, 114.9, 70.0, 45.8, 34.2, 30.2; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{41}H_{42}N_2O_2$ $[M + H]^+$ 595.3325, found 595.3322.

**……..**

**2,6-Di-*tert*-butyl-4-((4-(methylthio)phenyl)(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)phenol (3ga):**

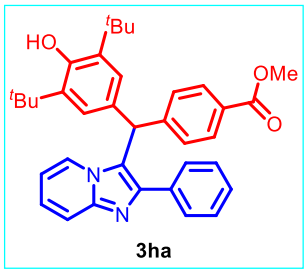


3ga

Synthesized according to General Procedure 2B.5.4**.** Yellow solid in 92% yield. $\boldsymbol{R_f}$ = 0.7 (pet. ether/ethyl acetate = 6:4); **mp** = 104 $^{o}$C; **IR** ($CHCl_3$): $\nu_{max}$ = 3412, 2957, 1490, 1435, 1367, 1227, 753; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.71 - 7.65 (m, 2 H), 7.59 (d, *J* = 6.9 Hz, 2 H), 7.39 - 7.29 (m, 3 H), 7.19 - 7.13 (m, 3 H), 7.03 (d, *J* = 8.2 Hz, 2 H), 6.86 (s, 2 H), 6.62 - 6.55 (m, 1 H), 6.08 (s, 1 H), 5.14 (s, 1 H), 2.46 (s, 3 H), 1.30 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 152.5, 144.9, 144.7, 137.2, 136.7, 136.0, 134.7, 129.6, 129.1, 128.1, 127.5, 126.6, 125.3, 124.7, 124.0, 121.7, 117.6, 111.6, 46.1, 34.3, 30.2, 15.7; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{35}H_{38}N_2OS$ $[M + H]^+$ 535.2783, found 535.2780.

**……..**

**Methyl 4-((3,5-di-*tert*-butyl-4-hydroxyphenyl)(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)benzoate (3ha):**

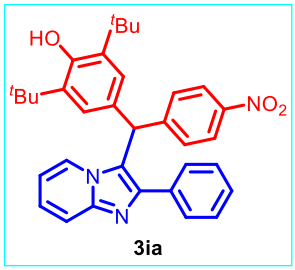


3ha

Synthesized according to General Procedure 2B.5.4. Orange solid in 88% yield. $\boldsymbol{R_f}$ = 0.4 (pet. ether/ethyl acetate = 7:3); **mp** = 108 $^{o}$C; **IR** ($CHCl_3$): $\nu_{max}$ = 3414, 2957, 1719, 1526, 1438, 1532, 1282, 909, 731; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 8.30 (s, 1 H), 8.09 (dd, *J* = 1.4, 8.2 Hz, 1 H), 7.97 - 7.93 (m, 2 H), 7.89 (d, *J* = 7.3 Hz, 1 H), 7.69 (d, *J* = 9.2 Hz, 1 H), 7.63 (d, *J* = 6.9 Hz, 1 H), 7.44 (t, *J* = 8.0 Hz, 1 H), 7.22 (ddd, *J* = 1.1, 6.8, 9.0 Hz, 1 H), 7.16 (d, *J* = 8.2 Hz, 2 H), 6.82 (s, 2 H), 6.66 (dt, *J* = 1.4, 6.9 Hz, 1 H), 6.04 (s, 1 H), 5.16 (s, 1 H), 3.89 (s, 3 H), 1.26 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 166.7, 153.0, 147.8, 145.4, 145.0, 142.4, 136.5, 136.4, 134.9, 130.1, 129.0, 128.9, 128.7, 125.3, 125.0, 124.3, 123.8, 122.2, 122.1, 117.9, 112.4, 52.2, 47.1, 34.3, 30.1; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{36}H_{38}N_2O_3$ $[M + H]^+$ 547.2961, found 547.2958.

**……..**

**2,6-Di-*tert*-butyl-4-((4-nitrophenyl)(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)phenol (3ia):**

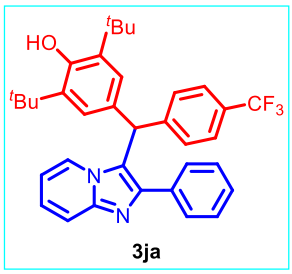


3ia

Synthesized according to General Procedure 2B.5.4. Brown solid in 86% yield. $\boldsymbol{R_f}$ = 0.3 (pet. ether/ethyl acetate = 5:5); **mp** = 182 $^{o}$C; **IR** ($CHCl_3$): $\nu_{max}$ = 3421, 2958, 1519, 1437, 1351, 909,734; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 8.16 - 8.04 (m, 2 H), 7.72 (d, $J$ = 8.8 Hz, 1 H), 7.61 (d, $J$ = 7.0 Hz, 1 H), 7.54 (d, $J$ = 6.3 Hz, 2 H), 7.35 (d, $J$ = 7.0 Hz, 3 H), 7.25 (s, 2 H), 7.20 (ddd, $J$ = 1.1, 6.8, 9.0 Hz, 1 H), 6.86 (s, 2 H), 6.63 (t, $J$ = 6.4 Hz, 1 H), 6.18 (s, 1 H), 5.22 (s, 1 H), 1.32 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 153.0, 148.4, 146.8, 145.1, 136.5, 129.5, 129.1, 128.3, 128.3, 127.9, 125.2, 124.5, 124.1, 123.8, 120.4, 117.9, 112.1, 46.7, 34.3, 30.2; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{34}H_{35}N_3O_3$ $[M + H]^+$ 534.2757, found 534.2755.

**……..**

**2,6-Di-*tert*-butyl-4-((2-phenylimidazo[1,2-*a*]pyridin-3-yl)(4-(trifluoromethyl)phenyl)methyl)phenol (3ja):**



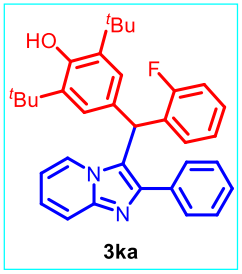
3ja

Synthesized according to General Procedure 2B.5.4. Yellow solid in 91% yield. $\boldsymbol{R_f}$ = 0.6 (pet. ether/ethyl acetate = 7:3); **mp** = 174 $^{o}$C; **IR** ($CHCl_3$): $\nu_{max}$ = 3412, 2957, 1623, 1435, 1324, 1123, 910, 737; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.72 (d, $J$ = 9.2 Hz, 1 H), 7.66 - 7.62 (m, 1 H), 7.58 - 7.52 (m, 4 H), 7.38 - 7.32 (m, 3 H), 7.22 (d, $J$ = 8.7 Hz, 2 H), 7.19 - 7.16 (m, 1 H), 6.86 (s, 2 H), 6.62 (dt, $J$ = 1.1, 6.8 Hz, 1 H), 6.15 (s, 1 H), 5.19 (s, 1 H), 1.31 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 152.8, 144.9, 144.7, 136.3, 134.4, 129.1, 129.0, 128.9, 128.2, 127.7, 125.6 (q, $J_{C\text{-}F}$ = 3.88 Hz), 125.3, 124.3, 121.0, 117.7, 111.9, 46.5, 34.3, 30.2; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -62.63; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{35}H_{35}F_3N_2O$ $[M + H]^+$ 557.2780, found 557.2773.

**……..**

**2,6-Di-*tert*-butyl-4-((2-fluorophenyl)(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)phenol (3ka):**

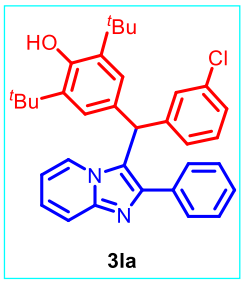
Synthesized according to General Procedure 2B.5.4. Orange solid in 90% yield. $\boldsymbol{R_f}$ = 0.6 (pet. ether/ethyl acetate = 6:4); **mp** = 114 $^{o}$C; **IR** ($CHCl_3$): $\nu_{max}$ = 3411, 2957, 1488, 1439, 1368, 1232, 910,737; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.71 - 7.66 (m, 2 H), 7.49 (dd, $J$ = 1.8, 7.8




Hz, 2 H), 7.31 - 7.23 (m, 4 H), 7.19 - 7.13 (m, 1 H), 7.09 - 6.99 (m, 3 H), 6.77 (s, 2 H), 6.66 - 6.54 (m, 1 H), 6.28 (s, 1 H), 5.10 (s, 1 H), 1.27 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 159.7 (d, $J_{C\text{-}F}$ = 247.29 Hz), 152.6, 145.1, 144.7, 136.0, 134.7, 130.0 (d, $J_{C\text{-}F}$ = 3.83 Hz), 129.0, 128.9, 128.3, 127.9, 127.8 (d, $J_{C\text{-}F}$ = 14.38 Hz), 127.4, 124.9, 124.2, 123.9, 120.4, 117.6, 115.7 (d, $J_{C\text{-}F}$ = 22.04 Hz), 111.7, 40.6, 34.2, 30.1; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -114.28; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{34}H_{35}FN_2O$ $[M]^+$ 506.2733, found 506.2720.

**……..**

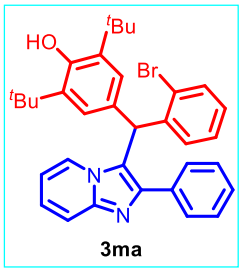
**2,6-Di-*tert*-butyl-4-((3-chlorophenyl)(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)phenol (3la):**




Synthesized according to General Procedure 2B.5.4. Yellow solid in 92% yield. ***R*$_f$** = 0.5 (pet. ether/ethyl acetate = 5:5); **mp** = 205 $^oC$; **IR** ($CHCl_3$): $\nu_{max}$ = 3392, 2958, 1486, 1437, 1367, 1233, ,909,734; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.70 - 7.63 (m, 2 H), 7.51 - 7.46 (m, 2 H), 7.33 - 7.22 (m, 5 H), 7.16 (ddd, *J* = 1.2, 6.7, 9.0 Hz, 1 H), 7.11 (d, *J* = 7.3 Hz, 2 H), 6.82 (s, 2 H), 6.59 (dt, *J* = 1.3, 6.8 Hz, 1 H), 6.05 (s, 1 H), 5.13 (s, 1 H), 1.29 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 152.6, 144.9, 143.6, 140.2, 136.0, 133.4, 133.4, 130.3, 129.7, 128.7, 128.6, 128.2, 126.9, 125.4, 124.6, 124.2, 122.1, 117.6, 111.7, 46.8, 34.2, 30.2; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{34}H_{35}ClN_2O$ $[M + H]^+$ 523.2516, found 523.2523.

**……..**

**4-((2-Bromophenyl)(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)-2,6-di-*tert*-butylphenol (3ma):**



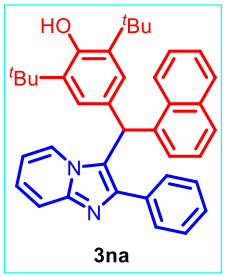

Synthesized according to General Procedure 2B.5.4. Yellow solid in 93% yield. ***R*$_f$** = 0.5 (pet. ether/ethyl acetate = 7:3); **mp** = 168 $^oC$; **IR** ($CHCl_3$): νmax = 3694, 3016, 1507, 1324, 1215, 1033, 759; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.70 - 7.66 (m, 1 H), 7.64 (d, *J* = 6.9 Hz, 1 H), 7.60 (dd, *J* = 1.4, 7.8 Hz, 1 H), 7.42 - 7.37 (m, 2 H), 7.26 - 7.20 (m, 3 H), 7.20 - 7.09 (m, 3 H), 7.02 (dd, *J* = 1.8, 7.8 Hz, 1 H), 6.71 (s, 2 H), 6.63 (dt, *J* = 1.1, 6.8 Hz, 1 H), 6.21 (s, 1 H), 5.10 (s, 1 H), 1.26 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 152.5,

145.3, 144.6, 140.0, 135.9, 134.8, 133.3, 130.5, 129.0, 128.6, 128.3, 127.7, 127.6, 127.2, 125.4, 125.2, 123.9, 120.7, 117.6, 111.8, 47.3, 34.2, 30.2; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{34}H_{35}BrN_2O$ $[M + H]^+$ 567.2011, found 567.2011.

**……..**

**2,6-Di-*tert*-butyl-4-(naphthalen-1-yl(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)phenol (3na):**

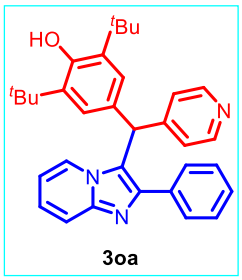
Synthesized according to General Procedure 2B.5.4. Brown solid in 96% yield. $\boldsymbol{R_f}$ = 0.4 (pet. ether/ethyl acetate = 6:4); **mp** = 82 °C; **IR** ($CHCl_3$): $\nu_{max}$ = 3390, 2957, 1437, 1368, 1232, 909, 735; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.88 (d, *J* = 8.2 Hz, 1 H), 7.80 (d, *J* = 7.8 Hz, 1 H), 7.74 (d, *J* = 8.7 Hz, 1 H), 7.69 (s, 1 H), 7.67 (dd, *J* = 1.1, 2.5 Hz, 1 H), 7.53 - 7.49 (m, 2 H), 7.45 (t, *J* = 7.6 Hz, 1 H), 7.40 - 7.31 (m, 2 H), 7.27 - 7.25 (m, 2 H), 7.18 (d, *J* = 7.3 Hz, 1 H), 7.15 - 7.10 (m, 1 H), 6.76 (s, 2 H), 6.67 (s, 1 H), 6.53 (t, *J* = 6.9 Hz, 1 H), 5.10 (s, 1 H), 1.22 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 152.4, 144.8, 144.7, 136.2, 135.8, 134.7, 133.9, 131.8, 129.7, 128.9, 128.7, 128.1, 128.0, 127.4, 126.5, 126.2, 125.6, 125.3, 124.4, 124.1, 123.9, 121.9, 117.5, 111.6, 44.1, 34.2, 30.1; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{38}H_{38}N_2O$ $[M + H]^+$ 539.3062, found 539.3066.



3na

**……..**

**2,6-Di-*tert*-butyl-4-((2-phenylimidazo[1,2-*a*]pyridin-3-yl)(pyridin-4-yl)methyl)phenol (3oa):**

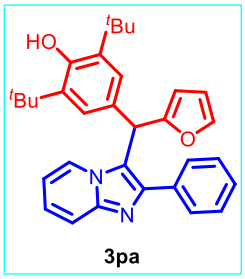


3oa

Synthesized according to General Procedure 2B.5.4. Orange solid in 86% yield. $\boldsymbol{R_f}$ = 0.3 (pet. ether/ethyl acetate = 5:5); **mp** = 195 °C; **IR** ($CHCl_3$): $\nu_{max}$ =3389, 2956, 1432, 1237, 913, 730; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 8.49 (d, *J* = 3.8 Hz, 1 H), 8.38 (br. s., 1 H), 7.77 (d, *J* = 9.1 Hz, 1 H), 7.67 (d, *J* = 7.0 Hz, 1 H), 7.53 (d, *J* = 6.1 Hz, 2 H), 7.41 - 7.30 (m, 4 H), 7.24 - 7.16 (m, 2 H), 6.86 (s, 2 H), 6.65 (t, *J* = 6.8 Hz, 1 H), 6.11 (s, 1 H), 5.19 (s, 1 H), 1.31 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 152.9, 149.8, 147.9, 144.9, 136.5, 129.2, 128.2, 127.9, 125.1, 124.7, 124.2, 123.5, 120.6, 117.8, 112.2, 44.5, 34.3, 30.1; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{33}H_{35}N_3O$ $[M + H]^+$ 490.2858, found 490.2857.

**……..**

**2,6-Di-*tert*-butyl-4-(furan-2-yl(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)phenol (3pa):**

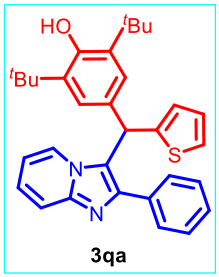


3pa

Synthesized according to General Procedure 2B.5.4. Orange solid in 84% yield. $\boldsymbol{R_f}$ = 0.6 (pet. ether/ethyl acetate = 7:3); **mp** = 120 $^{o}$C; **IR** ($CHCl_3$): $\nu_{max}$ = 3435, 2956, 1640, 1351, 919, 754; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.90 (td, *J* = 1.0, 7.1 Hz, 1 H), 7.71 - 7.66 (m, 3 H), 7.45 - 7.33 (m, 5 H), 7.21 - 7.16 (m, 1 H), 6.81 (s, 2 H), 6.64 (dt, *J* = 1.4, 6.9 Hz, 1 H), 6.36 (dd, *J* = 1.8, 3.2 Hz, 1 H), 6.15 (dd, *J* = 2.7, 3.7 Hz, 2 H), 5.15 (s, 1 H), 1.30 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 154.0, 152.7, 145.0, 144.7, 142.2, 136.0, 134.5, 129.1, 128.8, 128.3, 127.9, 127.7, 125.5, 124.3, 124.2, 119.4, 117.4, 111.4, 110.3, 108.4, 40.5, 34.2, 30.1; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{32}H_{34}N_2O_2$ $[M + H]^+$ 479.2699, found 479.2700.

**……..**

**2,6-Di-*tert*-butyl-4-((2-phenylimidazo[1,2-*a*]pyridin-3-yl)(thiophen-2-yl)methyl)phenol (3qa):**

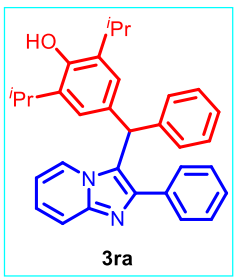


3qa

Synthesized according to General Procedure 2B.5.4. Orange solid in 87% yield. $\boldsymbol{R_f}$ = 0.6 (pet. ether/ethyl acetate = 7:3); **mp** = 108 $^{o}$C; **IR** ($CHCl_3$): $\nu_{max}$ = 3422, 2958, 1639, 1436, 1227, 754; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.79 (d, *J* = 6.9 Hz, 1 H), 7.71 - 7.64 (m, 3 H), 7.43 - 7.32 (m, 3 H), 7.23 - 7.19 (m, 1 H), 7.19 - 7.15 (m, 1 H), 6.97 (s, 2 H), 6.95 (dd, *J* = 3.7, 5.0 Hz, 1 H), 6.77 - 6.74 (m, 1 H), 6.63 (dt, *J* = 1.4, 6.9 Hz, 1 H), 6.31 (s, 1 H), 5.16 (s, 1 H), 1.32 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 152.8, 145.0, 144.8, 144.4, 136.0, 134.5, 129.7, 129.0, 128.3, 127.7, 126.8, 126.2, 125.1, 124.9, 124.7, 124.2, 121.4, 117.6, 111.5, 42.2, 34.3, 30.2; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{32}H_{34}N_2OS$ $[M + H]^+$ 495.2470, found 495.2471.

**……..**

**2,6-Diisopropyl-4-(phenyl(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)phenol (3ra):**



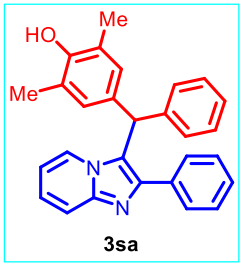
3ra

Synthesized according to General Procedure 2B.5.4. Orange solid in 90% yield. $\boldsymbol{R_f}$ = 0.7 (pet. ether/ethyl acetate = 6:4); **mp** = 144 $^{o}$C; **IR** ($CHCl_3$): $\nu_{max}$ = 3391, 2960, 1458, 1372, 1212, 753; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.67 - 7.59 (m, 4 H), 7.38 - 7.30 (m, 3 H), 7.28 - 7.18

(m, 3 H), 7.14 - 7.10 (m, 1 H), 7.07 (d, *J* = 6.9 Hz, 2 H), 6.73 (s, 2 H), 6.54 - 6.49 (m, 1 H), 6.15 (s, 1 H), 5.29 (br. s., 1 H), 3.09 (td, *J* = 6.9, 13.7 Hz, 2 H), 1.07 (dd, *J* = 3.7, 6.9 Hz, 12 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 148.9, 144.9, 144.7, 140.4, 134.6, 134.2, 131.1, 129.0, 128.6, 128.2, 127.6, 126.8, 124.8, 124.0, 123.9, 121.9, 117.5, 111.4, 46.4, 27.1, 22.7, 22.5; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{32}H_{32}N_2O$ $[M + H]^+$ 461.2593, found 461.2592.

**……..**

**2,6-Dimethyl-4-(phenyl(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)phenol (3sa):**

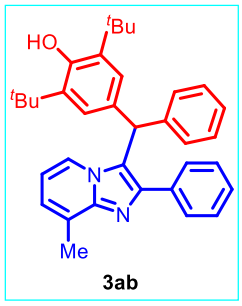


3sa

Synthesized according to General Procedure 2B.5.4. Orange solid in 92% yield. ***R*$_f$** = 0.3 (pet. ether/ethyl acetate = 5:5); **mp** = 134 $^oC$; **IR** ($CHCl_3$): $\nu_{max}$ = 3686, 3029, 2447, 1597, 1491, 1218, 910, 733; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.70 (d, *J* = 6.3 Hz, 2 H), 7.59 (d, *J* = 6.9 Hz, 2 H), 7.40 - 7.20 (m, 6 H), 7.17 - 7.05 (m, 3 H), 6.66 (s, 2 H), 6.54 (t, *J* = 6.8 Hz, 1 H), 6.11 (s, 1 H), 2.13 (s, 6 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 151.4, 144.9, 144.4, 140.2, 134.3, 130.6, 129.0, 128.7, 128.6, 128.2, 127.6, 126.8, 124.8, 124.2, 123.9, 121.7, 117.4, 111.8, 45.8, 16.3; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{28}H_{24}N_2O$ $[M + H]^+$ 405.1967, found 405.1948.

**……..**

**2,6-Di-*tert*-butyl-4-((8-methyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)phenol (3ab):**

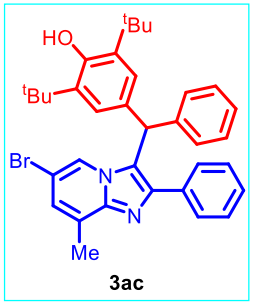


3ab

Synthesized according to General Procedure 2B.5.4. Orange solid in 91% yield. ***R*$_f$** = 0.4 (pet. ether/ethyl acetate = 7:3); **mp** = 109 $^oC$; **IR** ($CHCl_3$): $\nu_{max}$ = 3412, 2960, 1434, 1218, 707; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.61 - 7.56 (m, 3 H), 7.37 - 7.27 (m, 4 H), 7.26 - 7.19 (m, 2 H), 7.12 (d, *J* = 6.9 Hz, 2 H), 6.94 (d, *J* = 6.9 Hz, 1 H), 6.87 (s, 2 H), 6.49 (t, *J* = 7.1 Hz, 1 H), 6.09 (s, 1 H), 5.11 (s, 1 H), 2.69 (s, 3 H), 1.30 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 152.4, 145.2, 144.3, 140.6, 135.8, 135.1, 130.1, 129.3, 128.6, 128.5, 128.1, 127.3, 126.7, 125.5, 122.7, 122.6, 122.2, 111.4, 46.6, 34.2, 30.2, 17.3; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{35}H_{38}N_2O$ $[M + H]^+$ 503.3062, found 503.3064.

**……..**

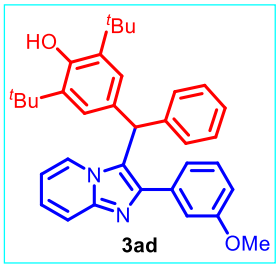
**4-((6-Bromo-8-methyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)-2,6-di-*tert*-butylphenol (3ac):**




Synthesized according to General Procedure 2B.5.4. Yellow solid in 92% yield. $\boldsymbol{R_f}$ = 0.3 (pet. ether/ethyl acetate = 7:3); **mp** = 152 $^{o}$C; **IR** ($CHCl_3$): $\nu_{max}$ = 3422, 2958, 1638, 3438, 1161, 911, 732; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.85 (s, 1 H), 7.60 (dd, *J* = 1.4, 8.0 Hz, 2 H), 7.51 (s, 1 H), 7.39 - 7.28 (m, 6 H), 7.12 (d, *J* = 7.1 Hz, 2 H), 6.85 (s, 2 H), 6.11 (s, 1 H), 5.15 (s, 1 H), 2.42 (d, *J* = 0.8 Hz, 3 H), 1.32 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 152.6, 145.0, 144.2, 140.0, 136.1, 134.5, 134.3, 129.7, 128.9, 128.8, 128.5, 128.2, 127.6, 127.0, 125.5, 124.8, 121.4, 116.5, 110.1, 46.6, 34.3, 30.2, 22.4; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{35}H_{37}BrN_2O$ $[M + H]^+$ 581.2168, found 581.2165.

**……..**

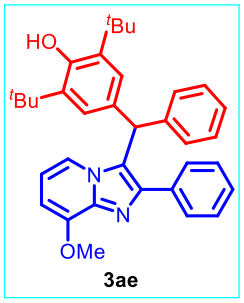
**2,6-Di-*tert*-butyl-4-((2-(3-methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)phenol (3ad):**




Synthesized according to General Procedure 2B.5.4. Yellow solid in 95% yield. $\boldsymbol{R_f}$ = 0.3 (pet. ether/ethyl acetate = 7:3); **mp** = 145 $^{o}$C; **IR** ($CHCl_3$): $\nu_{max}$ = 3635, 2959, 1597, 1486, 1317, 1227, 1076, 756; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.61 - 7.59 (m, 1 H), 7.59 - 7.57 (m, 2 H), 7.37 - 7.27 (m, 5 H), 7.26 - 7.20 (m, 2 H), 7.14 - 7.11 (m, 2 H), 6.94 (td, *J* = 1.1, 6.8 Hz, 1 H), 6.87 (s, 2 H), 6.49 (t, *J* = 6.9 Hz, 1 H), 6.09 (s, 1 H), 5.11 (s, 1 H), 2.69 (s, 3 H), 1.31 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 152.4, 145.2, 144.3, 140.6, 135.8, 135.1, 130.1, 129.3, 128.6, 128.6, 128.1, 127.3, 126.7, 125.5, 122.7, 122.6, 122.3, 111.4, 46.7, 34.2, 30.2, 17.3; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{35}H_{38}N_2O_2$ $[M + H]^+$ 519.3012, found 519.3010.

**……..**

**2,6-Di-*tert*-butyl-4-((8-methoxy-2-phenylimidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)phenol (3ae):**

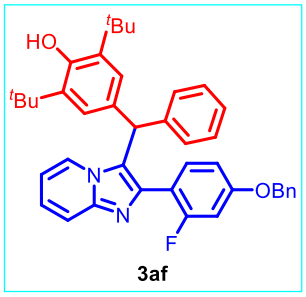


3ae

Synthesized according to General Procedure 2B.5.4. Yellow solid in 92% yield. $\boldsymbol{R_f}$ = 0.3 (pet. ether/ethyl acetate = 7:3); **mp** = 132 °C; **IR** ($CHCl_3$): $\nu_{max}$ = 3415, 2958, 1639, 1434, 1226, 1040, 758; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.73 - 7.62 (m, 2 H), 7.31 - 7.27 (m, 2 H), 7.27 - 7.19 (m, 3 H), 7.17 - 7.09 (m, 4 H), 6.87 (s, 3 H), 6.56 (t, $J$ = 6.9 Hz, 1 H), 6.16 (s, 1 H), 5.16 (s, 1 H), 3.75 (s, 3 H), 1.30 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 159.3, 152.5, 144.8, 144.4, 140.4, 136.0, 129.8, 129.1, 128.6, 128.5, 126.8, 125.3, 124.7, 124.1, 122.0, 121.5, 117.5, 114.1, 113.8, 111.6, 55.1, 46.5, 34.2, 30.1; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{35}H_{38}N_2O_2$ $[M + H]^+$ 519.3012, found 519.3006.

**……..**

**4-((2-(4-(Benzyloxy)-2-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)-2,6-di-*tert*-butylphenol (3af):**

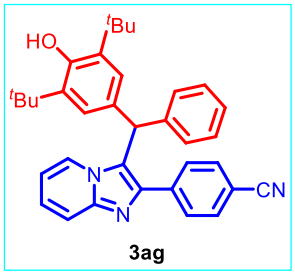


3af

Synthesized according to General Procedure 2B.5.4. Orange solid in 90% yield. $\boldsymbol{R_f}$ = 0.3 (pet. ether/ethyl acetate = 5:5); **mp** = 192 °C; **IR** ($CHCl_3$): $\nu_{max}$ = 3436, 2960, 1631, 1438, 1193, 908, 734; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.83 (d, $J$ = 6.9 Hz, 1 H), 7.78 (d, $J$ = 8.9 Hz, 1 H), 7.47 - 7.34 (m, 7 H), 7.33 - 7.23 (m, 4 H), 7.16 (d, $J$ = 7.1 Hz, 2 H), 7.10 - 7.01 (m, 1 H), 6.88 (t, $J$ = 6.8 Hz, 1 H), 6.76 (s, 2 H), 6.61 (d, $J$ = 8.4 Hz, 1 H), 6.53 (d, $J$ = 10.8 Hz, 1 H), 5.82 (br. s., 1 H), 5.05 (s, 1 H), 4.98 (br. s., 2 H), 1.27 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 161.7 (d, $J_{C\text{-}F}$ = 248.72 Hz), 160.5 (d, $J_{C\text{-}F}$ = 10.68 Hz), 152.6, 142.6 (d, $J_{C\text{-}F}$ = 7.63 Hz), 138.7, 136.1, 135.6, 132.3, 130.3, 128.9, 128.7, 128.2, 127.5, 127.3, 125.8, 124.9, 124.2, 121.3, 118.1, 115.8, 114.0, 110.5, 102.5 (d, $J_{C\text{-}F}$ = 26.70 Hz), 70.3, 47.1, 34.2, 30.1; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -113.1; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{41}H_{41}FN_2O_2$ $[M + H]^+$ 613.3230, found 613.3232.

**……..**

**4-(3-((3,5-Di-*tert*-butyl-4-hydroxyphenyl)(phenyl)methyl)imidazo[1,2-*a*]pyridin-2-yl)benzonitrile (3ag):**

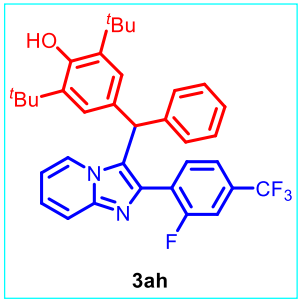


3ag

Synthesized according to General Procedure 2B.5.4. Yellow solid in 85% yield. $R_f$ = 0.4 (pet. ether/ethyl acetate = 5:5); **mp** = 208 °C; **IR** ($CHCl_3$): $\nu_{max}$ = 3406, 2959, 1607, 1438, 1236, 911, 736; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.72 - 7.67 (m, 2 H), 7.64 - 7.61 (m, *J* = 8.2 Hz, 2 H), 7.57 - 7.53 (m, *J* = 8.2 Hz, 2 H), 7.34 - 7.28 (m, 3 H), 7.24 - 7.19 (m, 1 H), 7.11 (d, *J* = 7.3 Hz, 2 H), 6.79 (s, 2 H), 6.65 (t, *J* = 7.3 Hz, 1 H), 6.03 (s, 1 H), 5.15 (s, 1 H), 1.28 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 152.7, 145.0, 142.6, 139.7, 139.5, 136.0, 131.6, 129.6, 129.3, 128.9, 128.6, 127.2, 125.4, 124.8, 124.6, 123.0, 119.0, 117.7, 112.2, 110.7, 46.9, 34.2, 30.1; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{35}H_{35}N_3O$ $[M + H]^+$ 514.2858, found 514.2843.

**……..**

**2,6-Di-*tert*-butyl-4-((2-(2-fluoro-4-(trifluoromethyl)phenyl)imidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)phenol (3ah):**

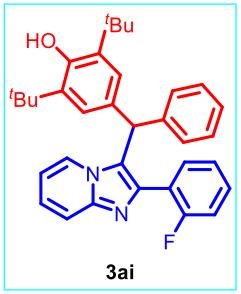


3ah

Synthesized according to General Procedure 2B.5.4. Yellow solid in 89% yield. $R_f$ = 0.5 (pet. ether/ethyl acetate = 5:5); **mp** = 167 °C; **IR** ($CHCl_3$): $\nu_{max}$ = 3522, 2960, 1480, 1453, 1239, 911, 747; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.74 - 7.65 (m, 2 H), 7.36 - 7.31 (m, 1 H), 7.31 - 7.28 (m, 1 H), 7.26 - 7.21 (m, 3 H), 7.17 (d, *J* = 6.9 Hz, 2 H), 7.10 (d, *J* = 9.3 Hz, 1 H), 6.75 (s, 2 H), 6.71 (t, *J* = 6.9 Hz, 1 H), 5.79 (s, 1 H), 5.00 (s, 1 H), 1.25 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 160.6(d, $J_{C\text{-}F}$ = 249.58 Hz), 152.4, 144.9, 139.3, 137.9, 135.3, 132.8(d, $J_{C\text{-}F}$ = 3.8 Hz), 129.4, 128.9, 128.7, 127.1, 125.9, 124.6, 124.3, 123.8, 120.1(q, $J_{C\text{-}F}$ = 3.81 Hz), 117.7, 112.3, 47.5, 34.1, 30.1; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -62.81, -109.09; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{35}H_{34}F_4N_2O$ $[M + H]^+$ 575.2686, found 575.2689.

**……..**

**2,6-Di-*tert*-butyl-4-((2-(2-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)phenol (3ai):**

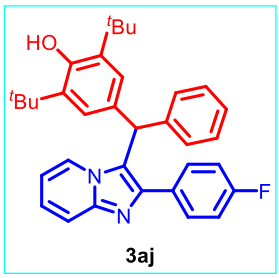


3ai

Synthesized according to General Procedure 2B.5.4. Orange solid in 88% yield. $\boldsymbol{R_f}$ = 0.5 (pet. ether/ethyl acetate = 7:3); **mp** = 139 $^oC$; **IR** ($CHCl_3$): $\nu_{max}$ = 3412, ,2957, 1496, 1437, 1229, 909, 736; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 8.55 (dd, $J$ = 1.8, 4.1 Hz, 1 H), 8.00 (dd, $J$ = 1.8, 6.9 Hz, 1 H), 7.40 (dt, $J$ = 1.6, 7.4 Hz, 1 H), 7.32 - 7.22 (m, 5 H), 7.15 (d, $J$ = 6.9 Hz, 2 H), 7.08 (t, $J$ = 7.1 Hz, 1 H), 6.96 (t, $J$ = 8.9 Hz, 1 H), 6.79 (s, 2 H), 6.72 (dd, $J$ = 4.1, 6.9 Hz, 1 H), 5.87 (s, 1 H), 5.07 (s, 1 H), 1.27 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 161.1 (d, $J_{C\text{-}F}$ = 248.24 Hz), 152.5, 149.5, 147.8, 140.8, 139.1, 135.6, 132.3 (d, $J_{C\text{-}F}$ = 2.87 Hz), 131.9, 129.9 (d, $J_{C\text{-}F}$ = 8.63 Hz), 129.0, 128.7, 128.6, 127.1, 125.5, 123.8, 122.3, 115.6 (d, $J_{C\text{-}F}$ = 22.04 Hz), 108.1, 46.9, 34.2, 30.1; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -114.16; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{34}H_{35}FN_2O$ $[M]^+$ 506.2733, found 506.2726.

**……..**

**2,6-Di-*tert*-butyl-4-((2-(4-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)phenol (3aj):**

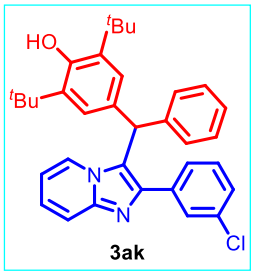


3aj

Synthesized according to General Procedure 2B.5.4. Orange solid in 91% yield. $\boldsymbol{R_f}$ = 0.4 (pet. ether/ethyl acetate = 7:3); **mp** = 152 $^oC$; **IR** ($CHCl_3$): $\nu_{max}$ = 3414, 2959, 1618, 1439, 1353, 1194, 910, 733; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.69 (d, $J$ = 6.9 Hz, 2 H), 7.55 - 7.46 (m, 2 H), 7.32 - 7.28 (m, 2 H), 7.27 - 7.25 (m, 1 H), 7.20 - 7.14 (m, 1 H), 7.11 (d, $J$ = 7.3 Hz, 2 H), 7.00 (t, $J$ = 8.2 Hz, 2 H), 6.82 (s, 2 H), 6.60 (t, $J$ = 7.1 Hz, 1 H), 6.04 (s, 1 H), 5.13 (br. s., 1 H), 1.29 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 163.6 (d, $J_{C\text{-}F}$ = 247.29 Hz), 152.6, 144.7, 143.7, 140.2, 135.9, 130.8 (d, $J_{C\text{-}F}$ = 7.67 Hz), 129.7, 128.7, 128.6, 126.9, 125.4, 124.6, 124.3, 121.8, 117.5, 115.1 (d, $J_{C\text{-}F}$ = 22.04 Hz), 111.7, 77.3, 34.2, 30.1; **$^{19}$F NMR** (376 MHz , $CDCl_3$) $\delta$ = -109.44; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{34}H_{35}FN_2O$ $[M + H]^+$ 507.2812, found 507.2805.

**……..**

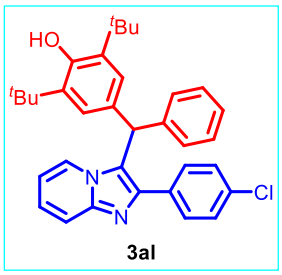
**2,6-Di-*tert*-butyl-4-((2-(3-chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)phenol (3ak):**




Synthesized according to General Procedure 2B.5.4. Yellow solid in 90% yield. $\boldsymbol{R_f}$ = 0.5 (pet. ether/ethyl acetate = 7:3); **mp** = 160 $^{o}$C; **IR** ($CHCl_3$): $\nu_{max}$ = 3695, 3011, 1589, 1437, 1220, 1095, 758; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.75 (s, 1 H), 7.68 (d, *J* = 8.8 Hz, 2 H), 7.50 (d, *J* = 7.8 Hz, 1 H), 7.44 - 7.40 (m, 1 H), 7.32 - 7.22 (m, 3 H), 7.21 - 7.14 (m, 2 H), 7.08 (d, *J* = 7.4 Hz, 2 H), 6.87 (s, 2 H), 6.60 (t, *J* = 7.4 Hz, 1 H), 6.05 (s, 1 H), 5.14 (s, 1 H), 1.31 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 152.7, 144.8, 143.1, 140.3, 136.9, 136.2, 131.9, 130.4, 129.8, 129.5, 128.8, 128.5, 127.6, 126.9, 125.3, 124.7, 124.3, 122.5, 122.2, 117.6, 111.8, 46.8, 34.3, 30.2; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{34}H_{35}ClN_2O$ $[M + H]^+$ 523.2516, found 523.2521.

**……..**

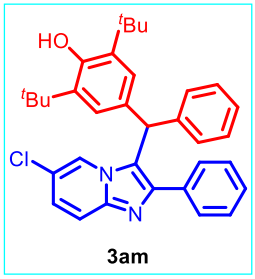
**2,6-Di-*tert*-butyl-4-((2-(4-chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)phenol (3al):**




Synthesized according to General Procedure 2B.5.4. Yellow solid in 93% yield. $\boldsymbol{R_f}$ = 0.5 (pet. ether/ethyl acetate = 7:3); **mp** = 141 $^{o}$C; **IR** ($CHCl_3$): $\nu_{max}$ = 3390, 2960, 1437, 1317, 1129, 909, 735; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.87 (s, 1 H), 7.76 (d, *J* = 7.8 Hz, 1 H), 7.69 (d, *J* = 9.2 Hz, 2 H), 7.54 (d, *J* = 7.8 Hz, 1 H), 7.42 (t, *J* = 7.8 Hz, 1 H), 7.32 - 7.22 (m, 3 H), 7.22 - 7.16 (m, 1 H), 7.08 (d, *J* = 7.3 Hz, 2 H), 6.86 (s, 2 H), 6.61 (dt, *J* = 1.4, 6.9 Hz, 1 H), 6.04 (s, 1 H), 5.15 (s, 1 H), 1.30 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 152.7, 144.9, 143.2, 140.3, 136.2, 135.6, 132.2, 130.2, 129.6, 128.8, 128.5, 128.4, 127.0, 125.7, 125.2, 124.7, 124.4, 124.1, 122.6, 117.7, 111.9, 46.8, 34.2, 30.1; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{34}H_{35}ClN_2O$ $[M + H]^+$ 523.2516, found 523.2521.

**……..**

**2,6-Di-*tert*-butyl-4-((6-chloro-2-phenylimidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)phenol (3am):**

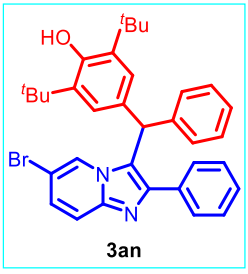


3am

Synthesized according to General Procedure 2B.5.4. Yellow solid in 89% yield. $\boldsymbol{R_f}$ = 0.5 (pet. ether/ethyl acetate = 7:3); **mp** = 154 $^oC$; **IR** ($CHCl_3$): $\nu_{max}$ = 3454, 2960, 143, 1227, 1105, 906, 759; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.70 (d, *J* = 1.8 Hz, 1 H), 7.60 (d, *J* = 9.6 Hz, 1 H), 7.57 (dd, *J* = 1.6, 8.0 Hz, 2 H), 7.37 - 7.27 (m, 6 H), 7.12 - 7.08 (m, 3 H), 6.81 (s, 2 H), 6.10 (s, 1 H), 5.13 (s, 1 H), 1.29 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 152.6, 145.7, 143.2, 139.7, 136.0, 134.2, 129.4, 129.0, 128.8, 128.5, 128.2, 127.8, 127.1, 125.4, 125.2, 122.6, 122.5, 119.6, 117.8, 46.5, 34.3, 30.1; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{34}H_{35}ClN_2O$ $[M + H]^+$ 522.2516, found 523.2513.

**……..**

**4-((6-Bromo-2-phenylimidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)-2,6-di-*tert*-butylphenol (3an):**

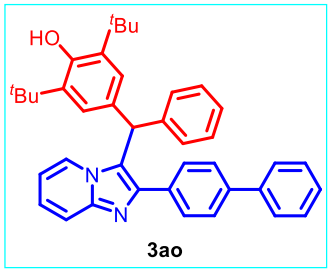


3an

Synthesized according to General Procedure 2B.5.4. Yellow solid in 92% yield. $\boldsymbol{R_f}$ = 0.5 (pet. ether/ethyl acetate = 7:3); **mp** = 175 $^oC$; **IR** ($CHCl_3$): $\nu_{max}$ = 3423, 2960, 1435, 1237, 1084, 908, 734; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.81 (d, *J* = 0.9 Hz, 1 H), 7.60 (dd, *J* = 1.4, 7.8 Hz, 2 H), 7.56 (d, *J* = 9.2 Hz, 1 H), 7.40 - 7.28 (m, 6 H), 7.20 (dd, *J* = 1.8, 9.6 Hz, 1 H), 7.12 (d, *J* = 7.3 Hz, 2 H), 6.84 (s, 2 H), 6.13 (s, 1 H), 5.17 (s, 1 H), 1.31 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 152.6, 145.4, 143.2, 139.8, 136.1, 134.2, 129.4, 128.9, 128.8, 128.5, 128.2, 127.8, 127.2, 127.1, 125.4, 124.8, 122.4, 118.1, 106.0, 46.5, 34.3, 30.1; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{34}H_{35}BrN_2O$ $[M + H]^+$ 567.2011, found 567.2022.

**……..**

**4-((2-([1,1'-Biphenyl]-4-yl)imidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)-2,6-di-*tert*-butylphenol (3ao):**



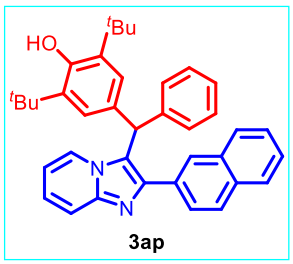
3ao

Synthesized according to General Procedure 2B.5.4. Brown solid in 96% yield. $\boldsymbol{R_f}$ = 0.5 (pet. ether/ethyl acetate =5:5); **mp** = 132 $^oC$; **IR** ($CHCl_3$): $\nu_{max}$ = 3412, 2956, 1438, 1368, 1236, 909, 735; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.71 - 7.66 (m, 4 H), 7.62 (d, *J*

= 7.1 Hz, 2 H), 7.58 (d, *J* = 8.4 Hz, 2 H), 7.45 (t, *J* = 7.6 Hz, 2 H), 7.37 - 7.33 (m, 1 H), 7.32 - 7.28 (m, 2 H), 7.25 (s, 1 H), 7.18 - 7.13 (m, 3 H), 6.88 (s, 2 H), 6.58 (dt, *J* = 1.0, 6.9 Hz, 1 H), 6.18 (s, 1 H), 5.12 (s, 1 H), 1.30 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 152.6, 144.9, 144.3, 140.9, 140.4, 140.1, 136.0, 133.8, 129.9, 129.4, 128.7, 128.6, 127.2, 127.0, 126.9, 126.8, 125.4, 124.7, 124.0, 122.0, 117.5, 111.5, 46.7, 34.3, 30.2; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{40}H_{40}N_2O$ $[M + H]^+$ 565.3219, found 565.3211.

**……..**

**2,6-Di-*tert*-butyl-4-((2-(naphthalen-2-yl)imidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)phenol (3ap):**

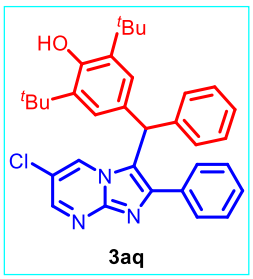


3ap

Synthesized according to General Procedure 2B.5.4. Brown solid in 95% yield. $R_f$ = 0.4 (pet. ether/ethyl acetate = 7:3); **mp** = 96 $^oC$; **IR** ($CHCl_3$): $\nu_{max}$ = 3390, 2957, 1609, 1437, 1360, 1234, 909, 737; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 8.05 (s, 1 H), 7.86 - 7.70 (m, 6 H), 7.50 - 7.43 (m, 3 H), 7.34 - 7.28 (m, 2 H), 7.22 - 7.17 (m, 1 H), 7.16 - 7.12 (m, 2 H), 6.91 (s, 2 H), 6.59 (dt, *J* = 1.1, 6.9 Hz, 1 H), 6.22 (s, 1 H), 5.12 (br. s., 1 H), 1.29 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 152.2, 144.6, 144.2, 140.2, 135.7, 132.9, 132.4, 131.8, 130.0, 129.7, 128.4, 128.4, 128.3, 127.9, 127.7, 127.4, 127.3, 126.7, 126.5, 125.6, 125.1, 124.4, 123.8, 122.0, 117.3, 111.3, 46.5, 33.9, 29.8; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{38}H_{38}N_2O$ $[M + H]^+$ 539.3062, found 539.3061.

**……..**

**2,6-Di-*tert*-butyl-4-((6-chloro-2-phenylimidazo[1,2-*a*]pyrazin-3-yl)(phenyl)methyl)phenol (3aq):**

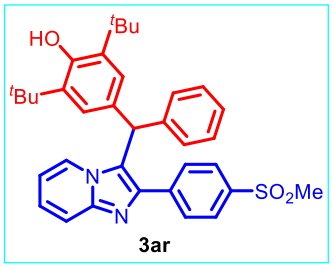


3aq

Synthesized according to General Procedure 2B.5.4. Yellow solid in 92% yield. $R_f$ = 0.3 (pet. ether/ethyl acetate = 3:7); **mp** = 208 $^oC$; **IR** ($CHCl_3$): $\nu_{max}$ = 3336, 2925, 1651, 1477, 1223, 934, 757; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 8.42 (d, *J* = 2.3 Hz, 1 H), 8.24 (s, 1 H), 7.89 (d, *J* = 2.7 Hz, 1 H), 7.70 - 7.67 (m, 2 H), 7.42 - 7.31 (m, 6 H), 7.09 (d, *J* = 6.9 Hz, 2 H), 6.80 (s, 2 H), 6.16 (s, 1 H), 5.20 (s, 1 H), 1.30 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 156.5, 152.9, 148.0, 147.4, 146.1, 139.3, 136.4, 133.5, 129.3, 129.1, 128.9, 128.4, 128.3, 127.4, 125.2, 121.1, 116.8, 46.5, 34.3, 30.1; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{33}H_{34}ClN_3O$ $[M + H]^+$ 524.2469, found 524.2467.

**……..**

**2,6-Di-*tert*-butyl-4-((2-(4-(methylsulfonyl)phenyl)imidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)phenol (3ar):**

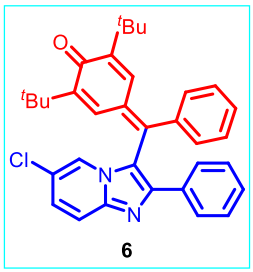


3ar

Synthesized according to General Procedure 2B.5.4. Yellow solid in 91% yield. $\boldsymbol{R_f}$ = 0.4 (pet. ether/ethyl acetate = 4:6); **mp** = 130 $^{o}$C; **IR** ($CHCl_3$): $\nu_{max}$ = 3425, 2957, 1311, 1192, 1148, 910, 734; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.84 (d, $J$ = 8.2 Hz, 3 H), 7.76 (d, $J$ = 6.9 Hz, 1 H), 7.67 (d, $J$ = 8.2 Hz, 2 H), 7.36 - 7.27 (m, 4 H), 7.11 (d, $J$ = 6.9 Hz, 2 H), 6.78 (s, 2 H), 6.75 (t, $J$ = 6.9 Hz, 1 H), 6.01 (s, 1 H), 5.14 (s, 1 H), 3.04 (s, 3 H), 1.27 (s, 18 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 152.8, 144.3, 139.3, 136.2, 129.9, 129.0, 128.6, 127.4, 127.0, 125.4, 124.8, 123.5, 117.1, 113.1, 46.8, 44.5, 34.2, 30.1; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{35}H_{38}N_2O_3S$ $[M + H]^+$ 567.2681, found 567.2680.

**……..**

**2,6-Di-*tert*-butyl-4-((6-chloro-2-phenylimidazo[1,2-*a*]pyridin-3-yl)(phenyl)methylene)cyclohexa-2,5-dien-1-one (6):**

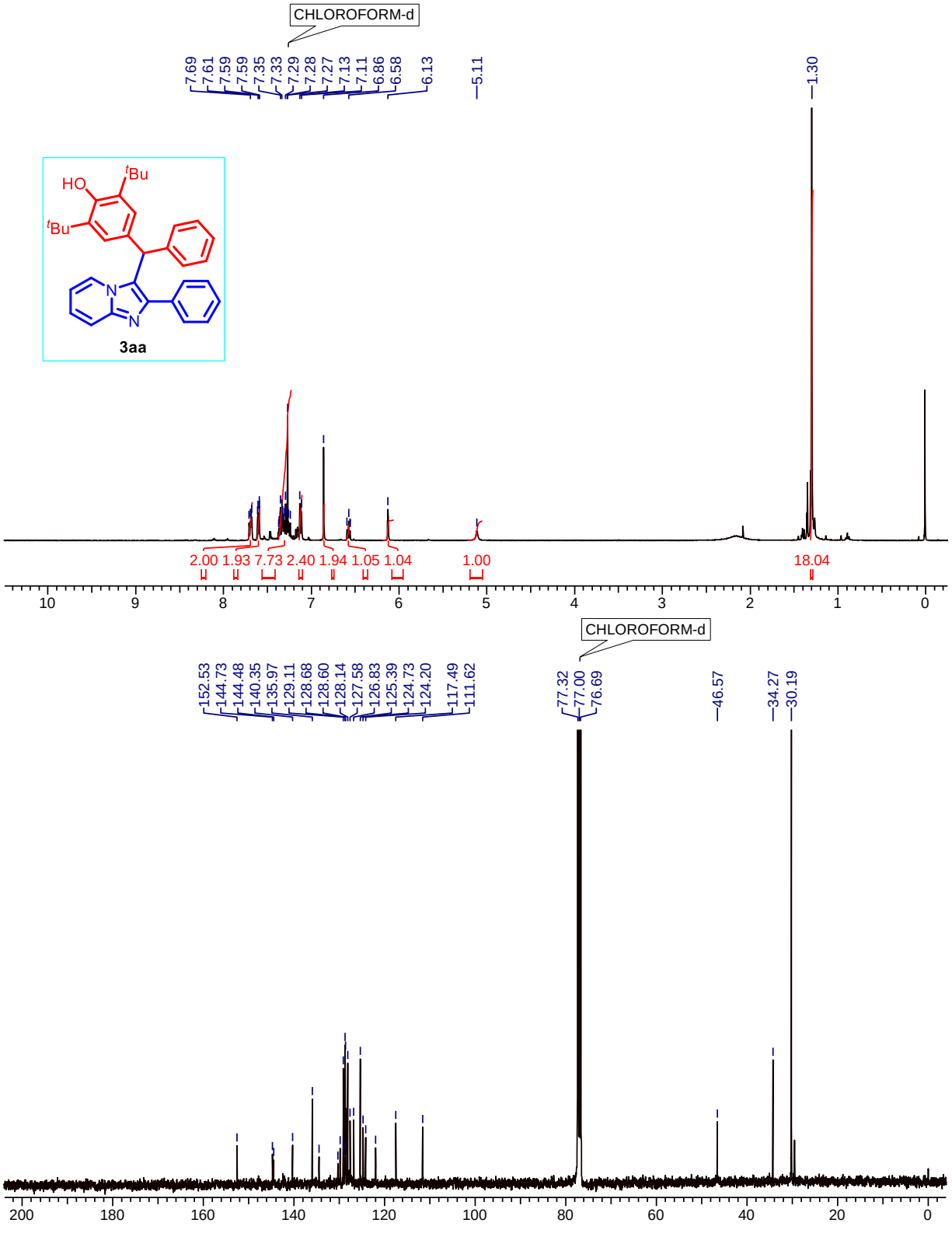


6

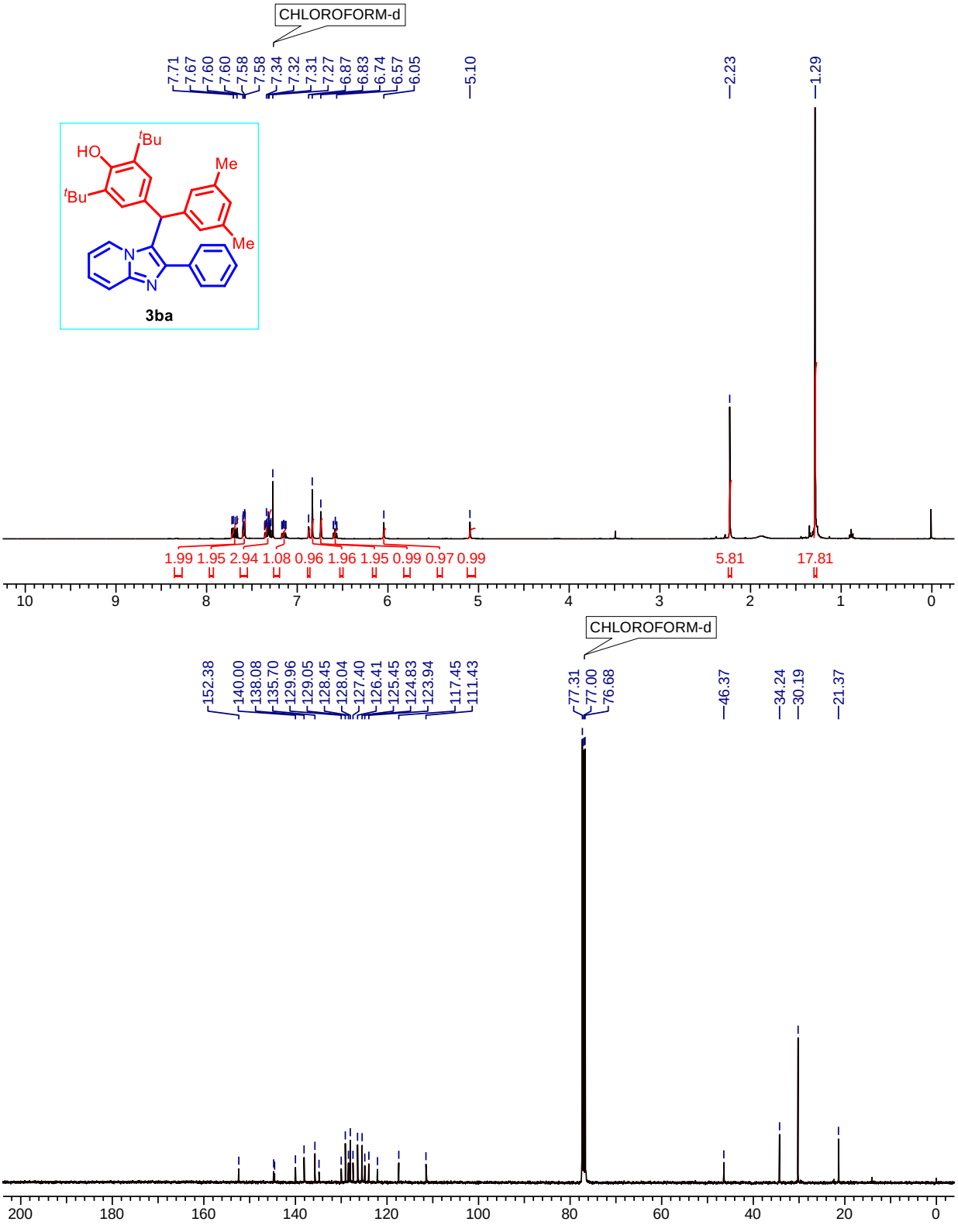
**3am** (1.0 equvi.) was dissolved in 5 mL $CH_2Cl_2$ and 1 mL TfOH and DDQ (1.0 equvi.) was added at 0 $^{o}$C. The resulting mixture was stirred for 5 min., quenched with 5 mL $H_2O$ and was extracted with $CH_2Cl_2$ (3×10 mL). The combined extracts were washed with saturated $NaHCO_3$ solution and dried over anhydrous $Na_2SO_4$. The solvent was concentrated under reduced pressure and the residue obtained was purified by column chromatography on 100-200 mesh silica gel using pet. ether/ethyl acetate to afford the product **6** as a yellow solid in 94% yield. $\boldsymbol{R_f}$ = 0.5 (pet. ether/ethyl acetate = 7:3); **mp** = 140 $^{o}$C; **IR** ($CHCl_3$): $\nu_{max}$ = 3066, 2555, 2252, 1607, 1494, 1349, 1172, 914, 732; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.71 - 7.64 (m, 3 H), 7.49 - 7.38 (m, 6 H), 7.35 (d, $J$ = 2.6 Hz, 1 H), 7.28-7.26 (m, 1 H), 7.24-7.22 (m, 2 H), 7.20 (d, $J$ = 2.0 Hz, 1 H), 6.83 (d, $J$ = 2.5 Hz, 1 H), 1.26 (s, 9 H), 0.96 (s, 9 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 185.9, 149.6, 148.9, 148.7, 145.1, 138.7, 136.6, 133.0, 132.2, 131.1, 130.9, 130.2, 130.0, 129.1, 128.4, 128.3, 127.4, 122.8, 121.0, 119.9, 118.0, 35.5, 35.1, 29.7, 29.5, 29.2; **HRMS** ($ESI^+$) *m/z* = calcd for $C_{34}H_{33}ClN_2O$ $[M + H]^+$ 521.2360, found 521.2334.

## 2B.7 NMR Spectra

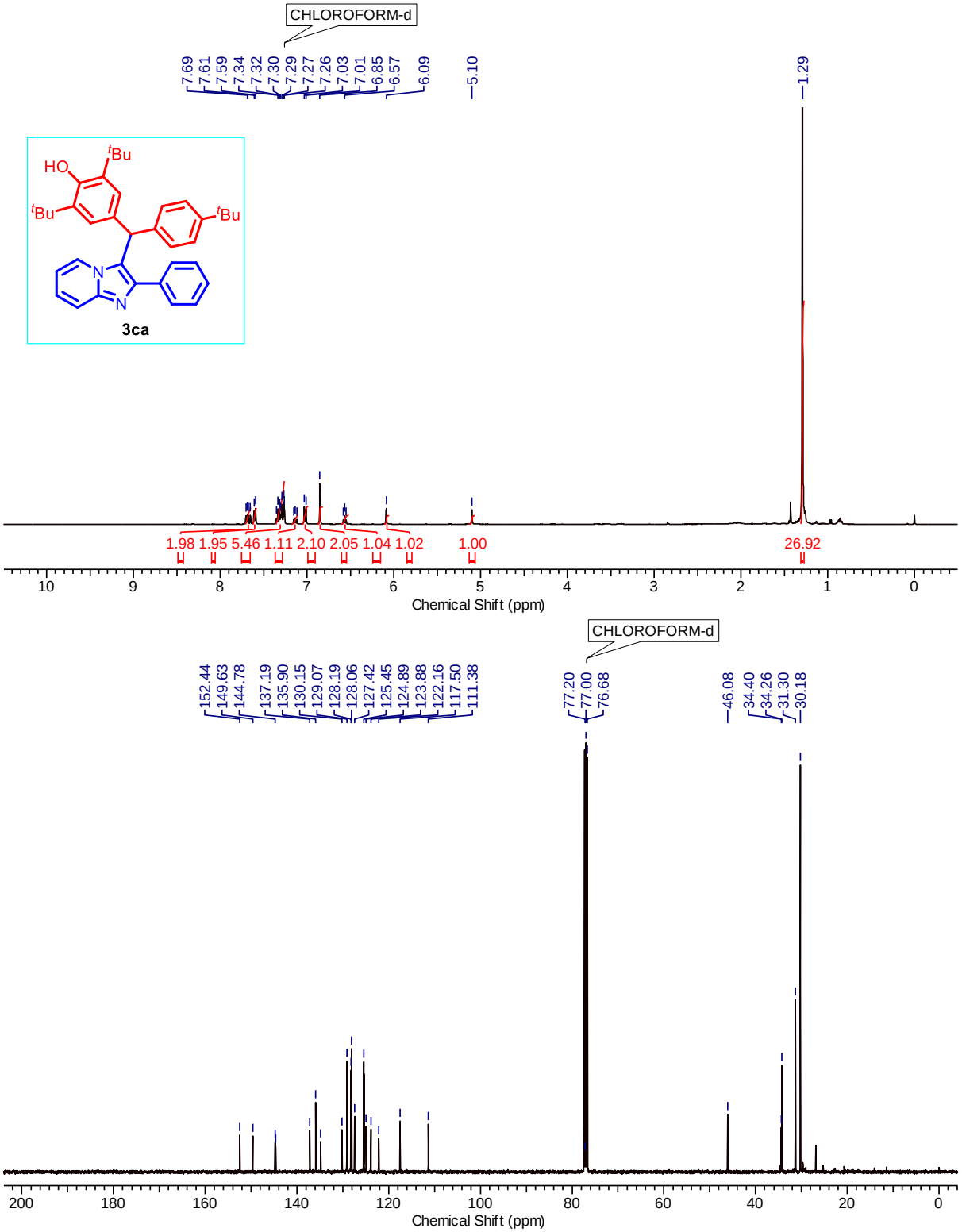
### 2,6-Di-*tert*-butyl-4-(phenyl(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)phenol (3aa):



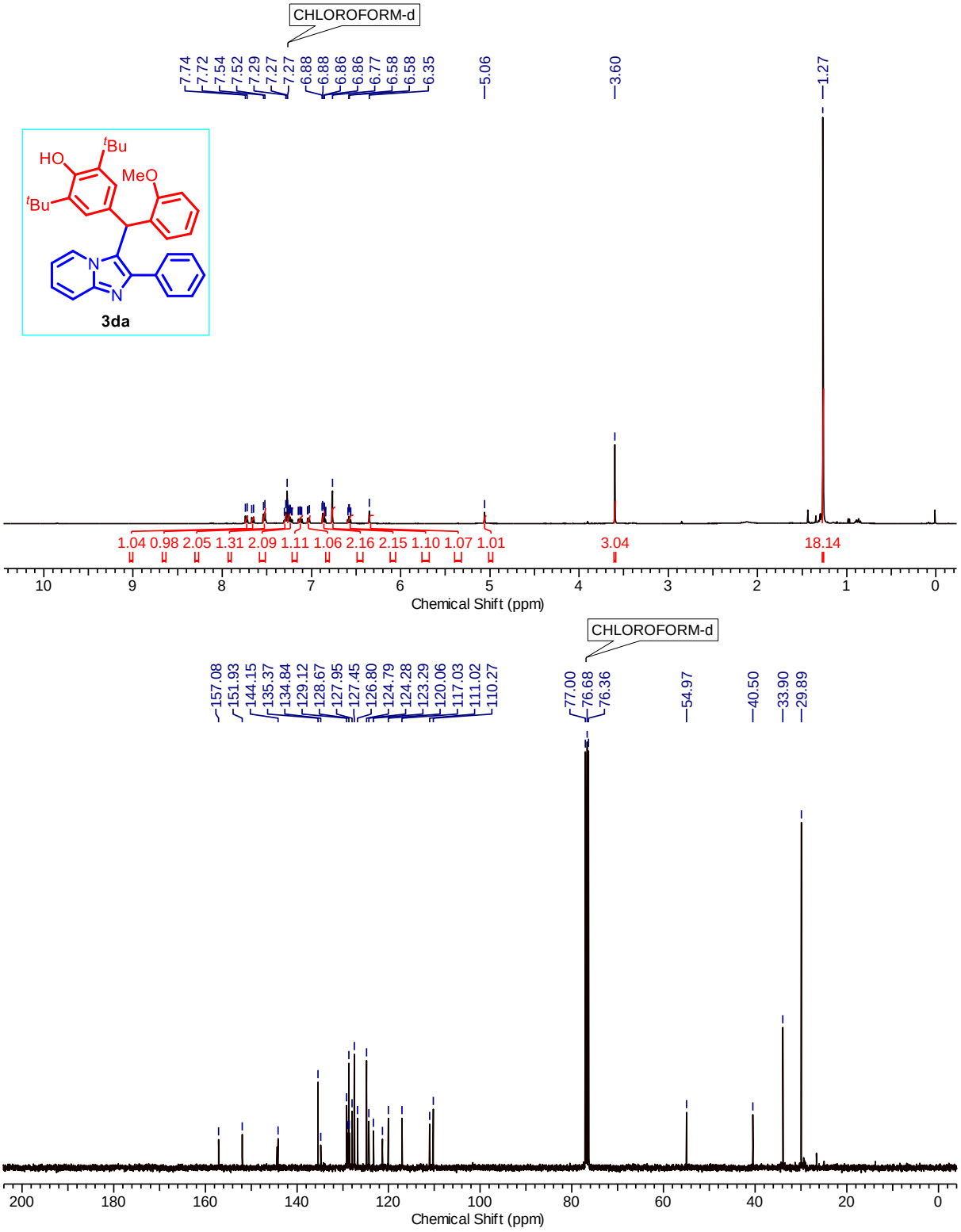
**2,6-Di-*tert*-butyl-4-((3,5-dimethylphenyl)(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)phenol (3ba):**



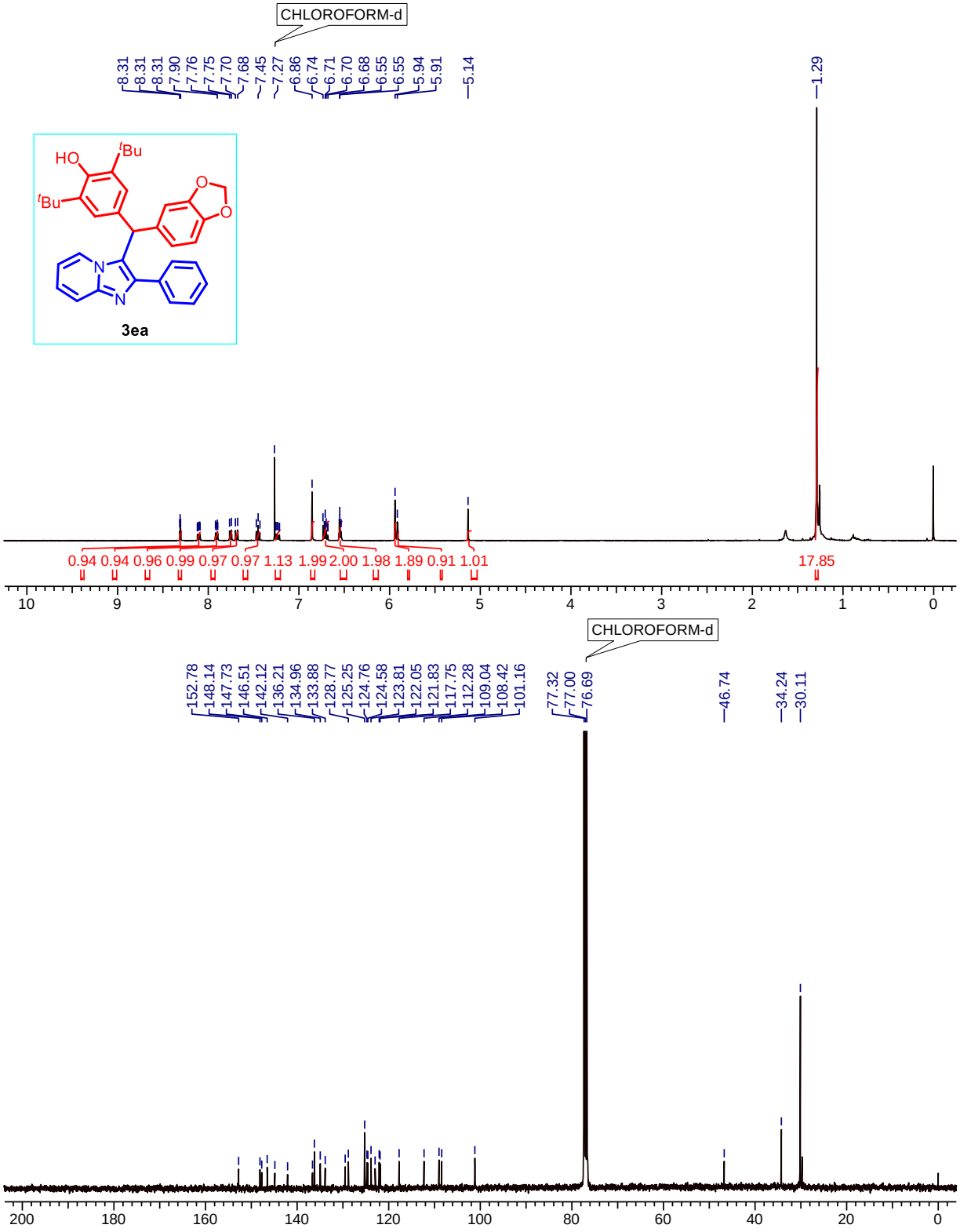
**2,6-Di-*tert*-butyl-4-((4-(*tert*-butyl)phenyl)(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)phenol (3ca):**



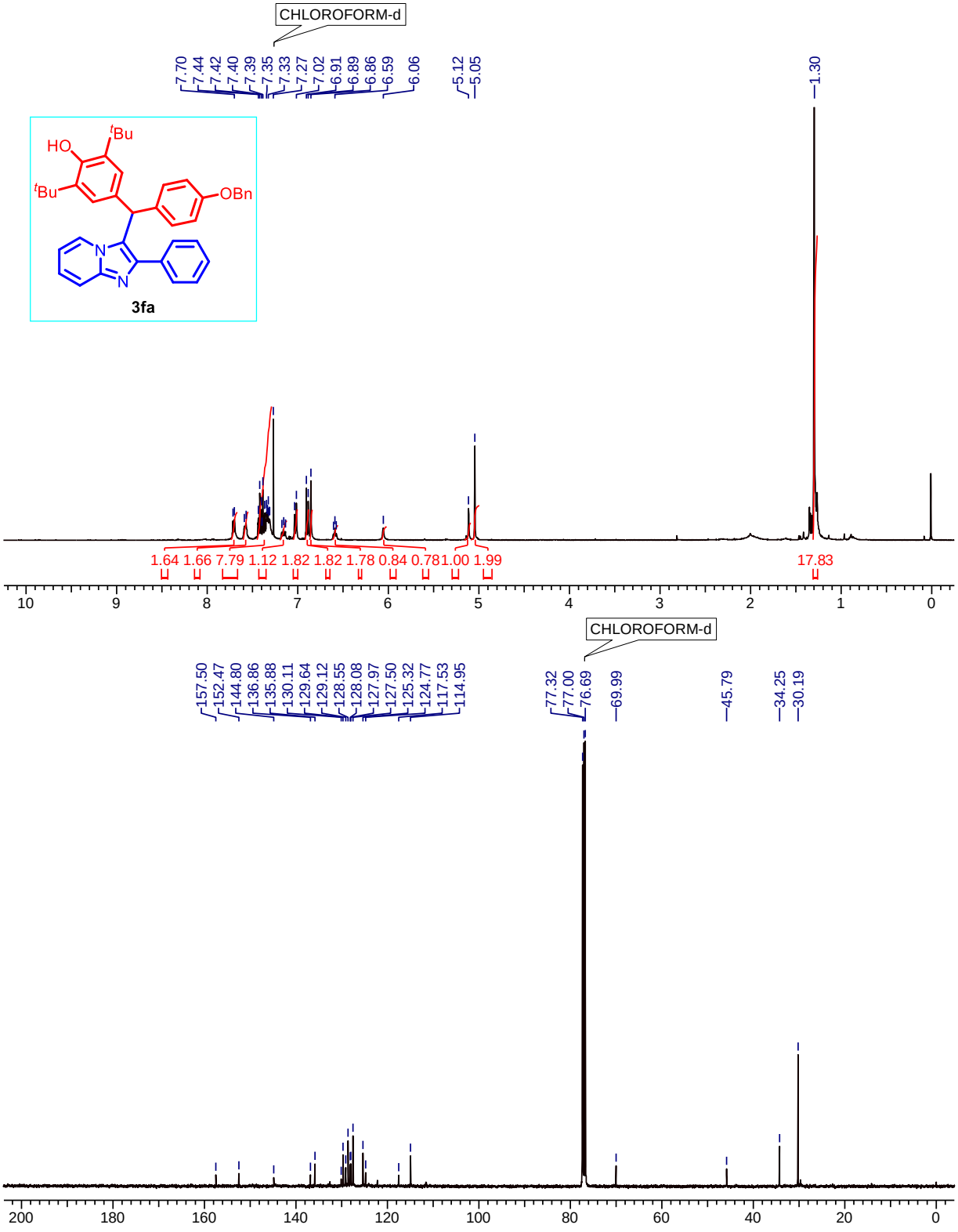
**2,6-Di-*tert*-butyl-4-((2-methoxyphenyl)(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)phenol (3da):**



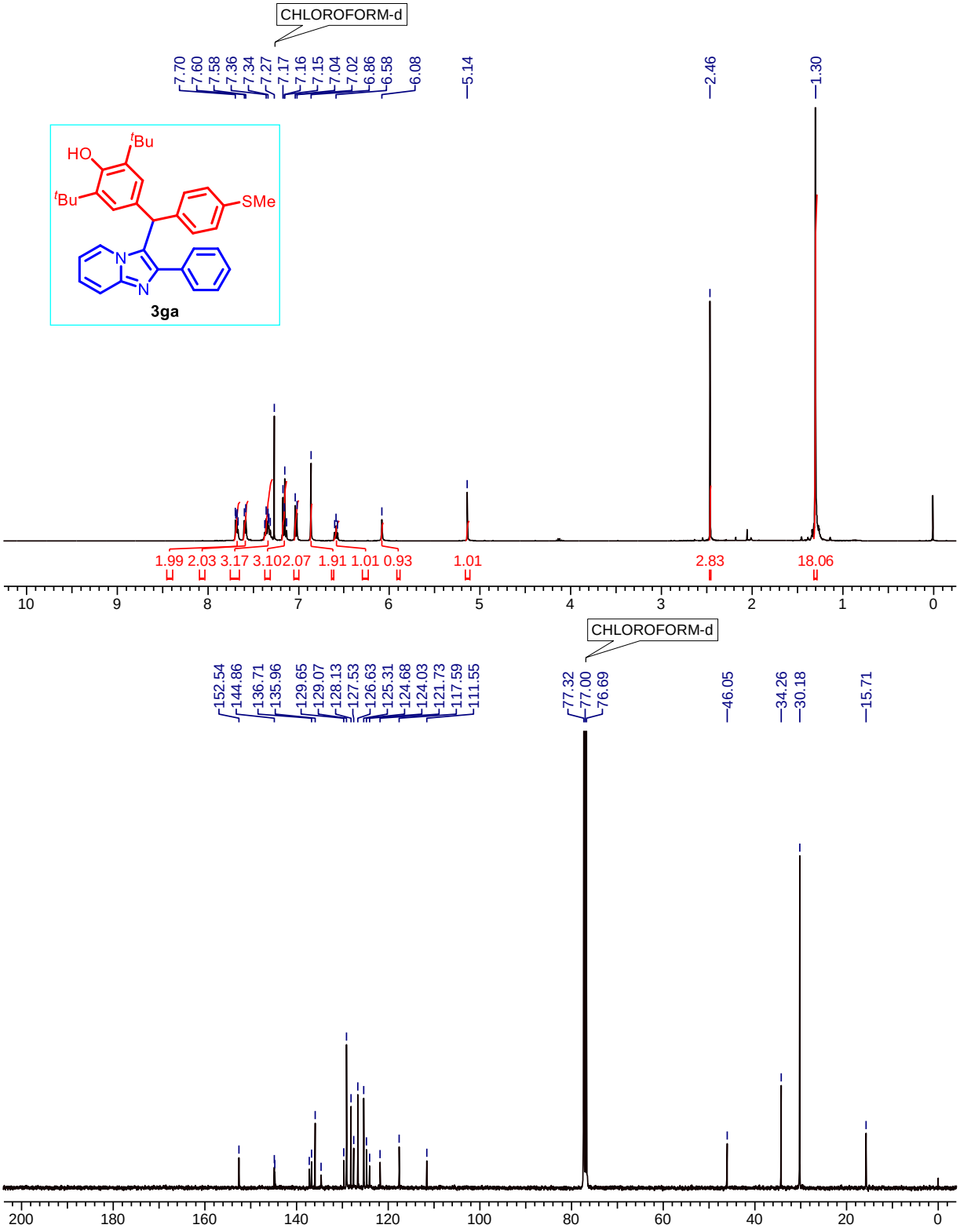
**4-(Benzo[*d*][1,3]dioxol-5-yl(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)-2,6-di-*tert*-butylphenol (3ea):**



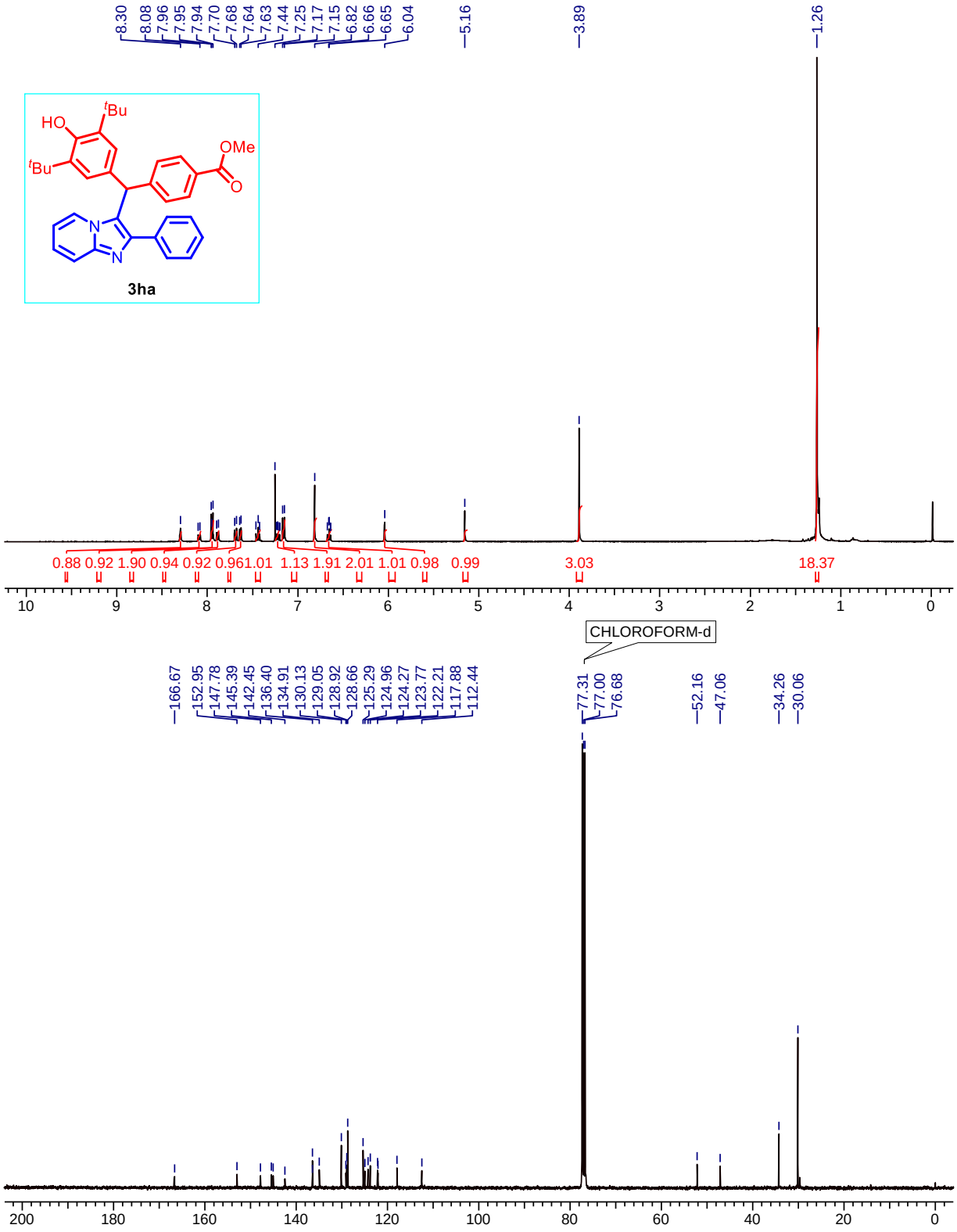
**4-((4-(Benzyloxy)phenyl)(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)-2,6-di-*tert*-butylphenol (3fa):**



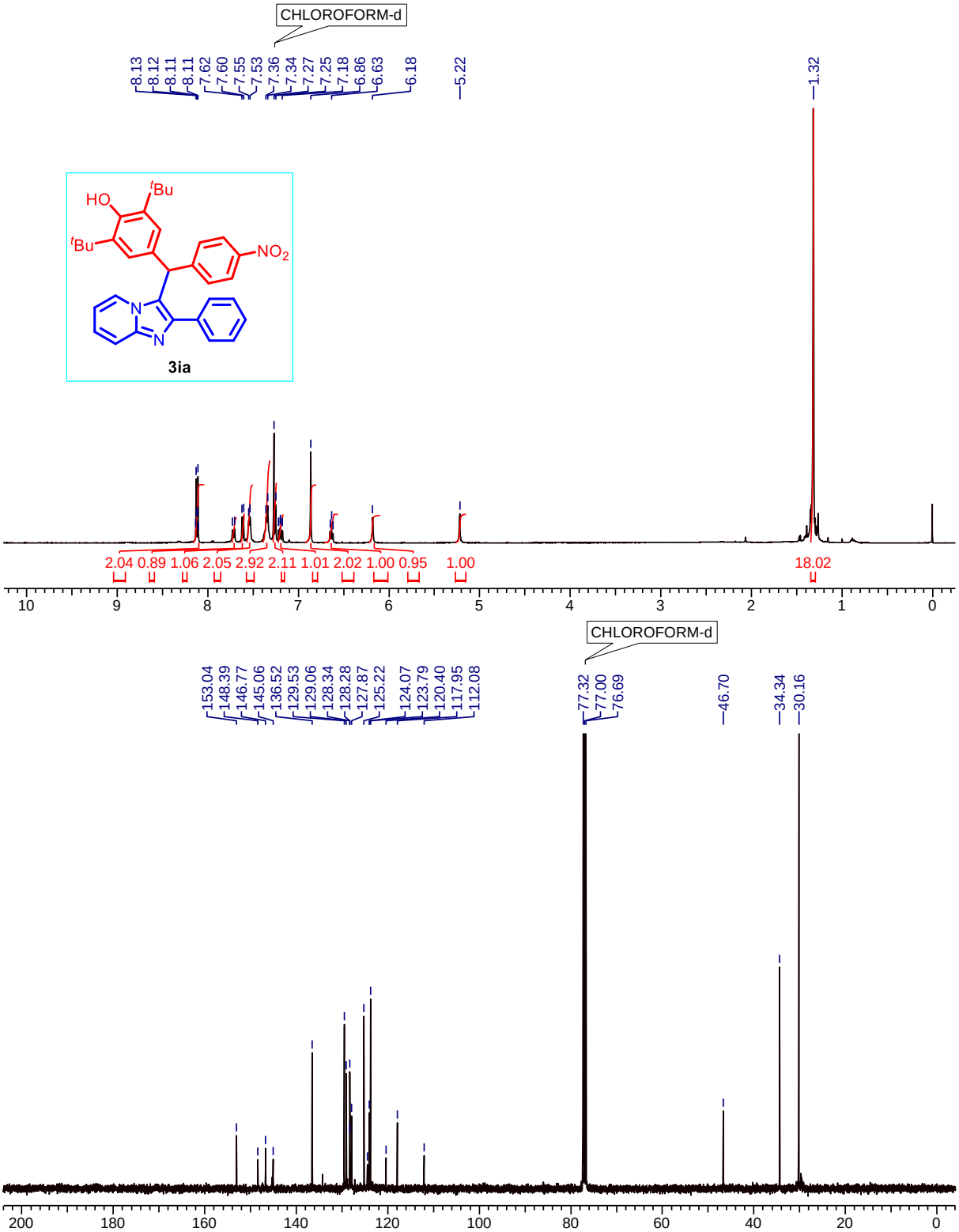
**2,6-Di-*tert*-butyl-4-((4-(methylthio)phenyl)(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)phenol (3ga):**



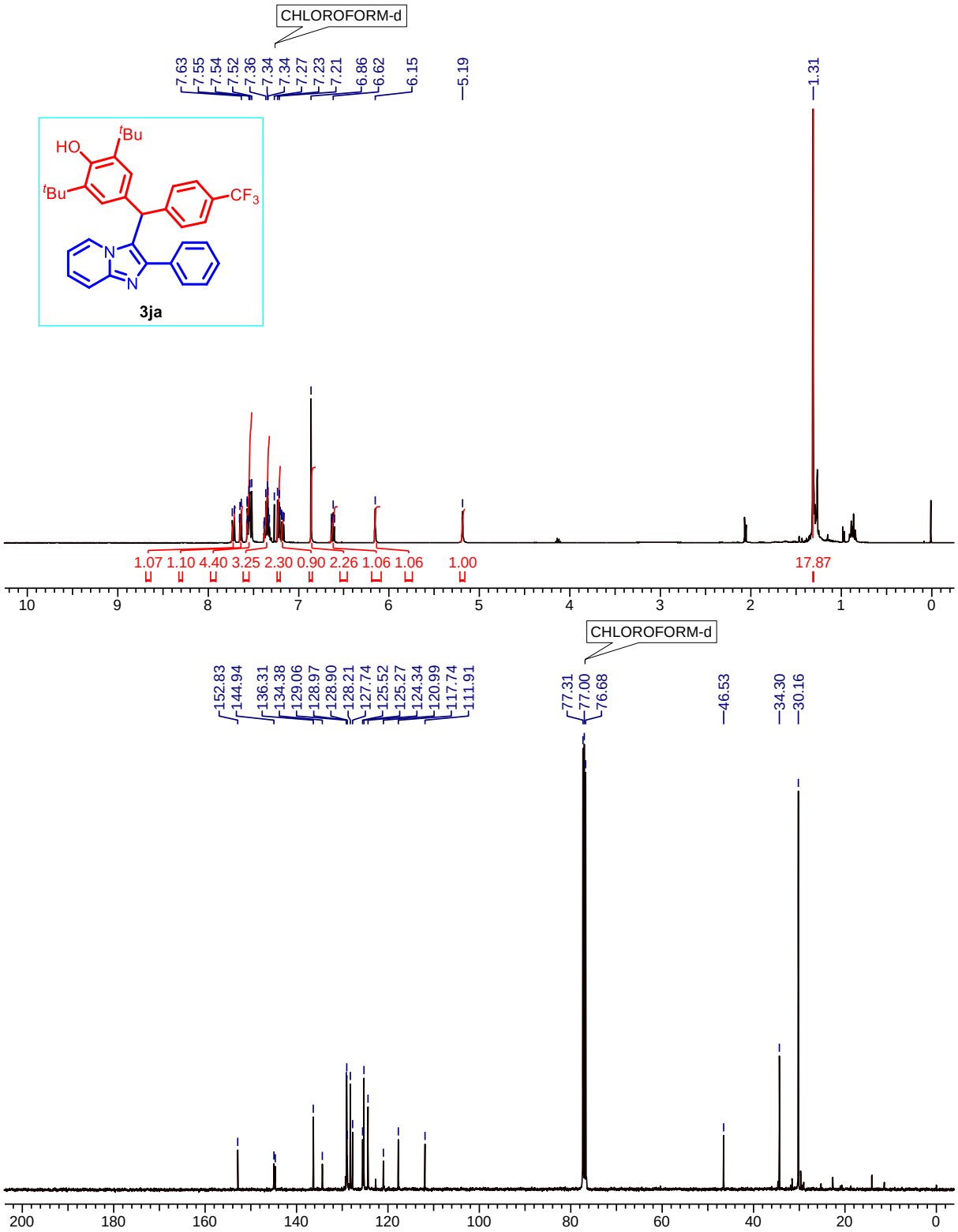
**Methyl 4-((3,5-di-*tert*-butyl-4-hydroxyphenyl)(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)benzoate (3ha):**

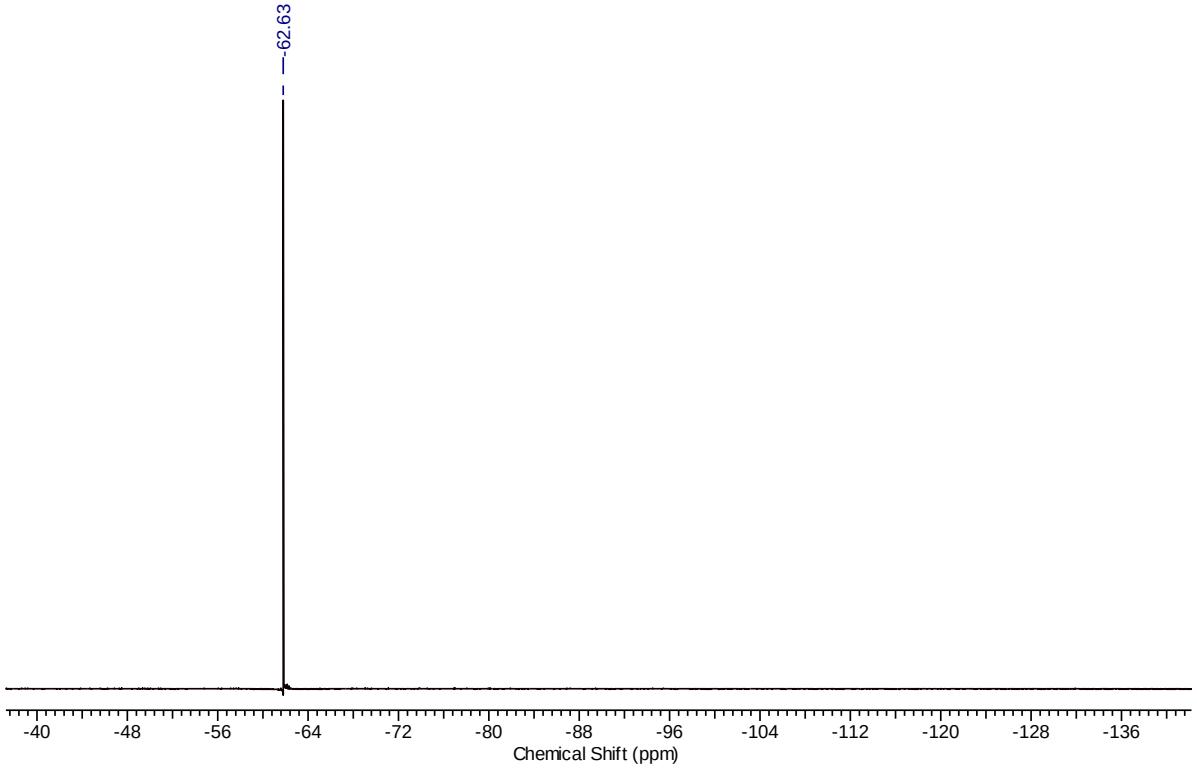


**2,6-Di-*tert*-butyl-4-((4-nitrophenyl)(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)phenol (3ia):**

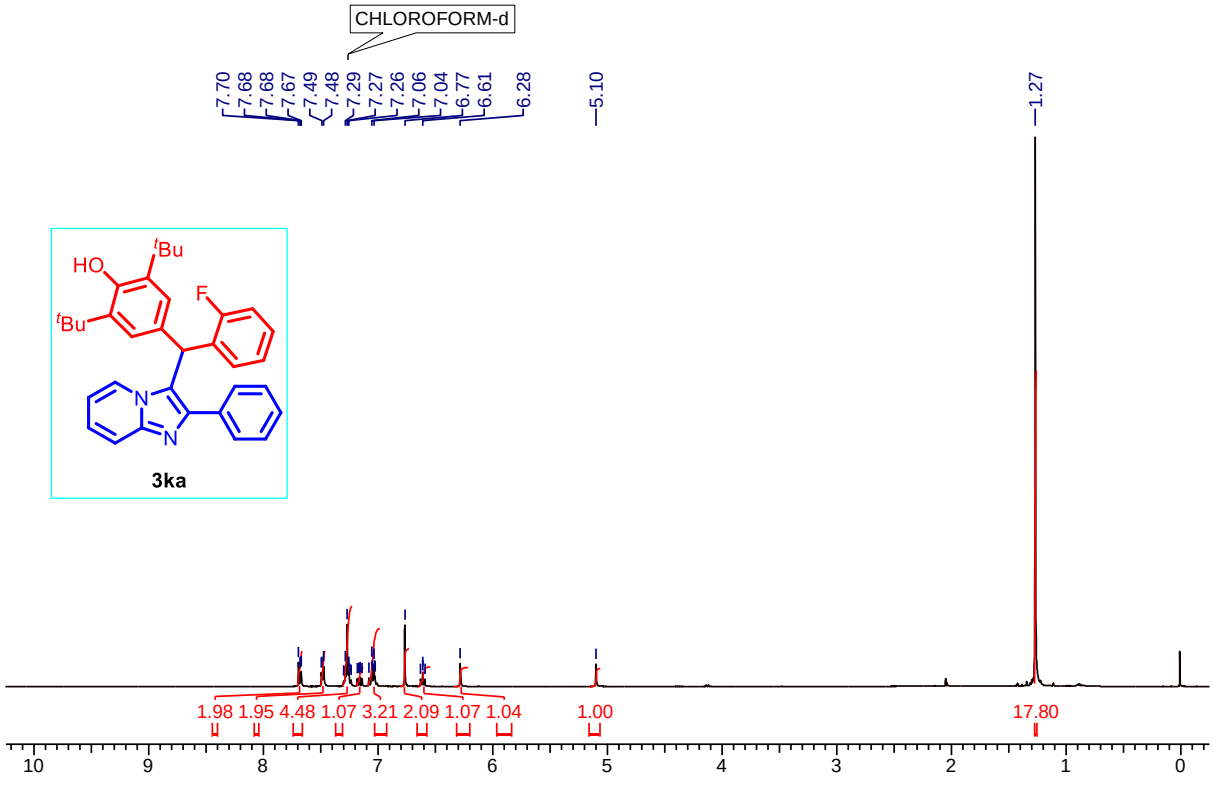


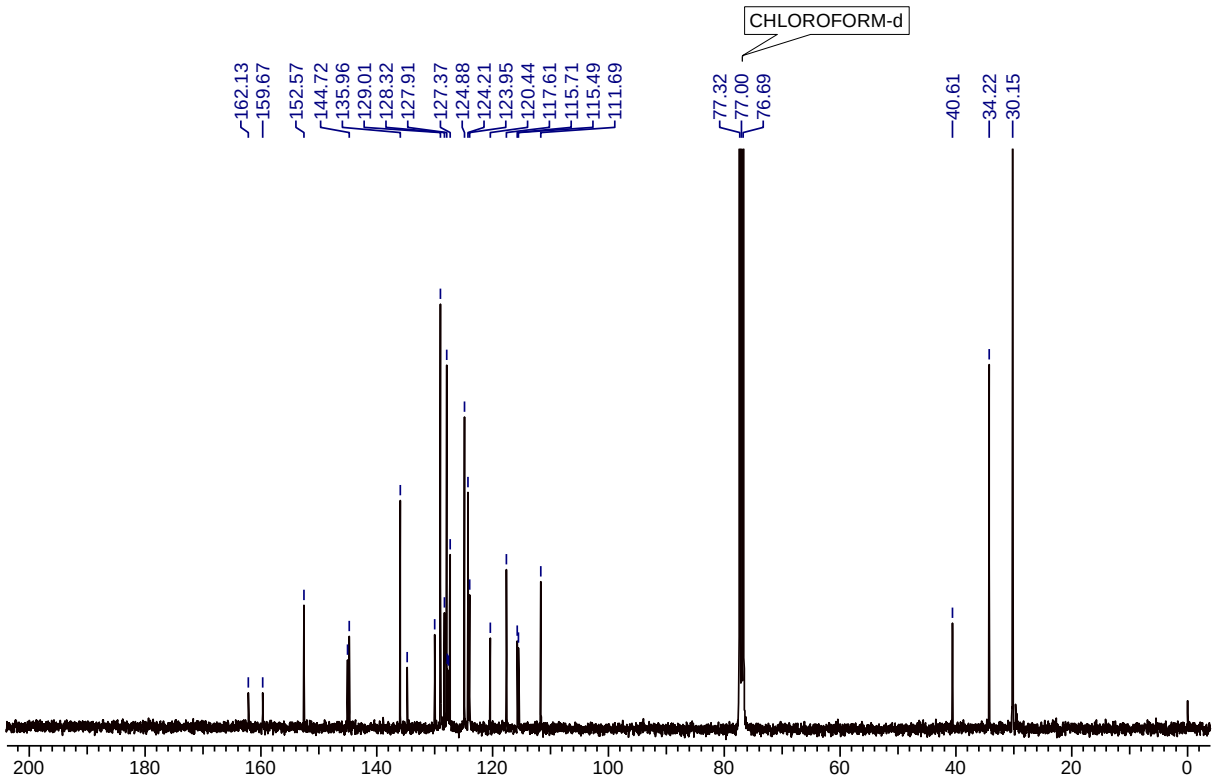
**2,6-Di-*tert*-butyl-4-((2-phenylimidazo[1,2-*a*]pyridin-3-yl)(4-(trifluoromethyl)phenyl)methyl)phenol (3ja):**

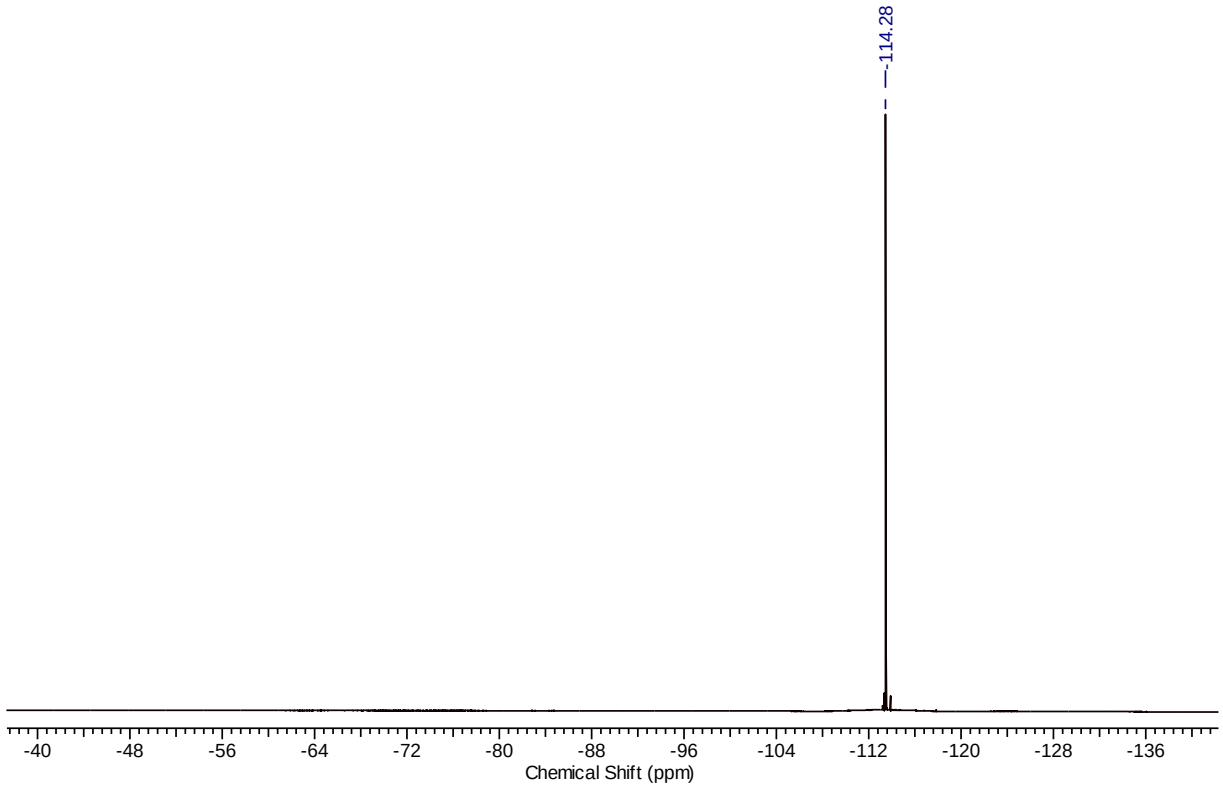




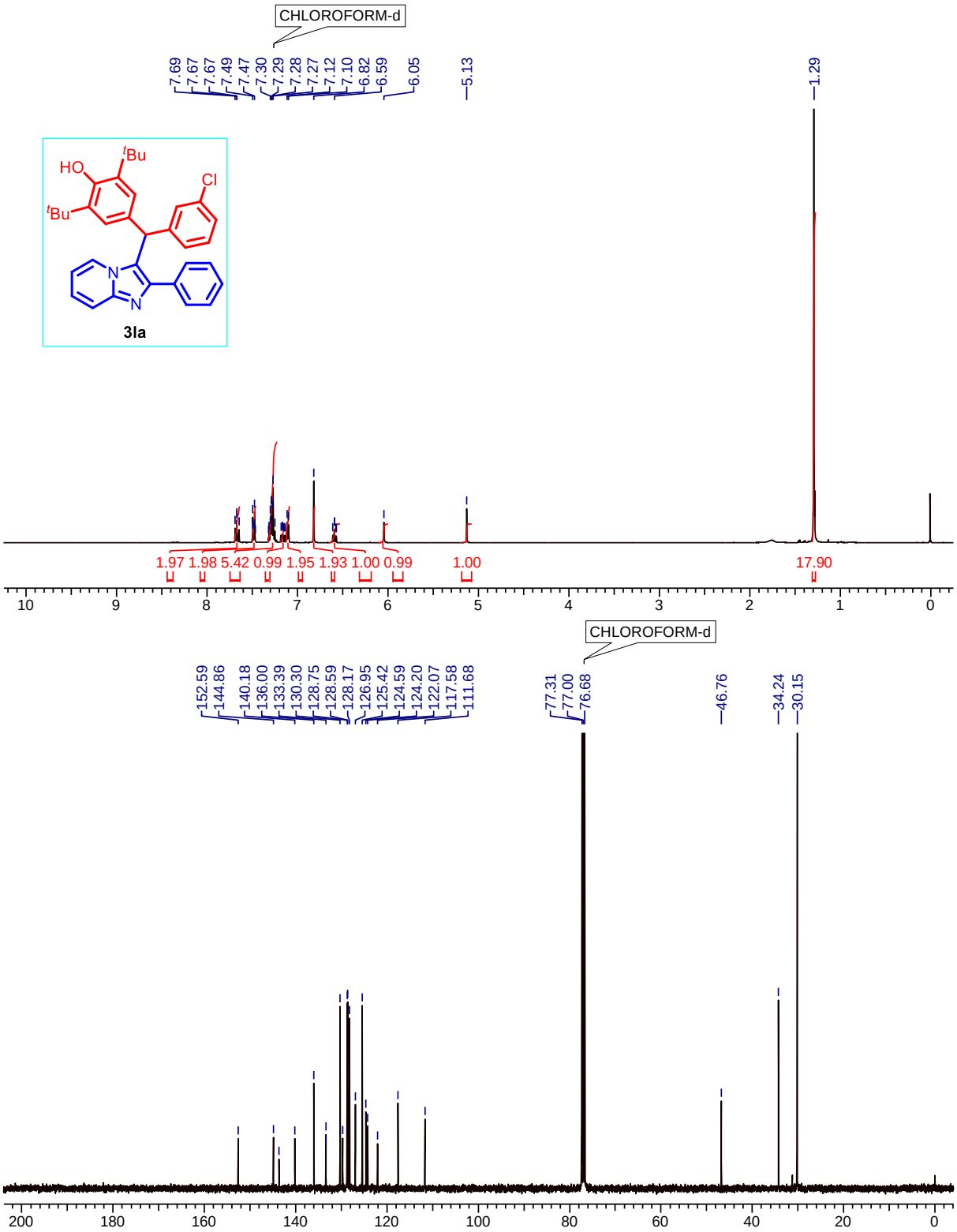

**2,6-Di-*tert*-butyl-4-((2-fluorophenyl)(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)phenol (3ka):**



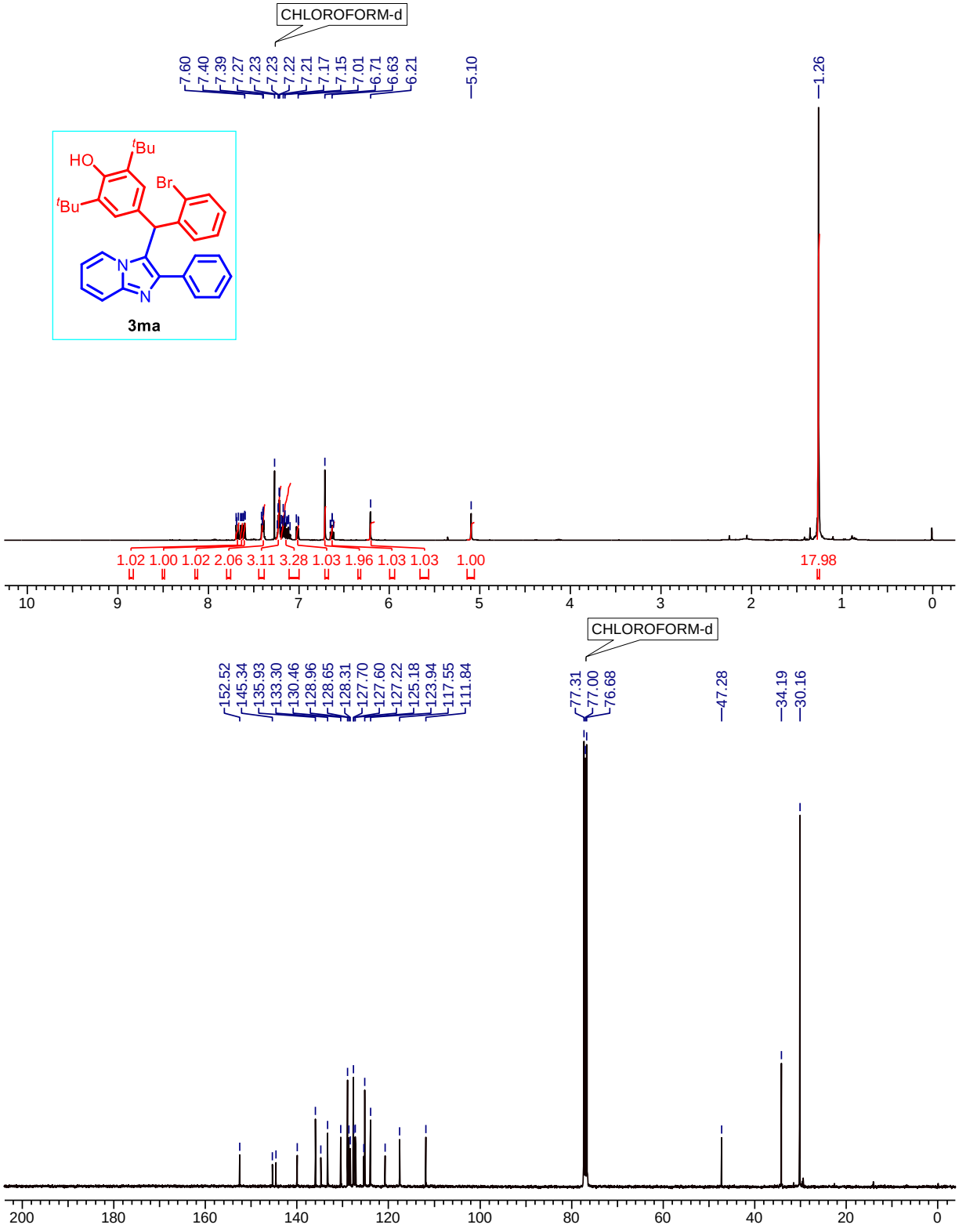

CHLOROFORM-d
162.13
159.67
152.57
144.72
135.96
129.01
128.32
127.91
127.37
124.88
124.21
123.95
120.44
117.61
115.71
115.49
111.69
77.32
77.00
76.69
40.61
34.22
30.15
200
180
160
140
120
100
80
60
40
20
0


-114.28
-40
-48
-56
-64
-72
-80
-88
-96
-104
-112
-120
-128
-136
Chemical Shift (ppm)

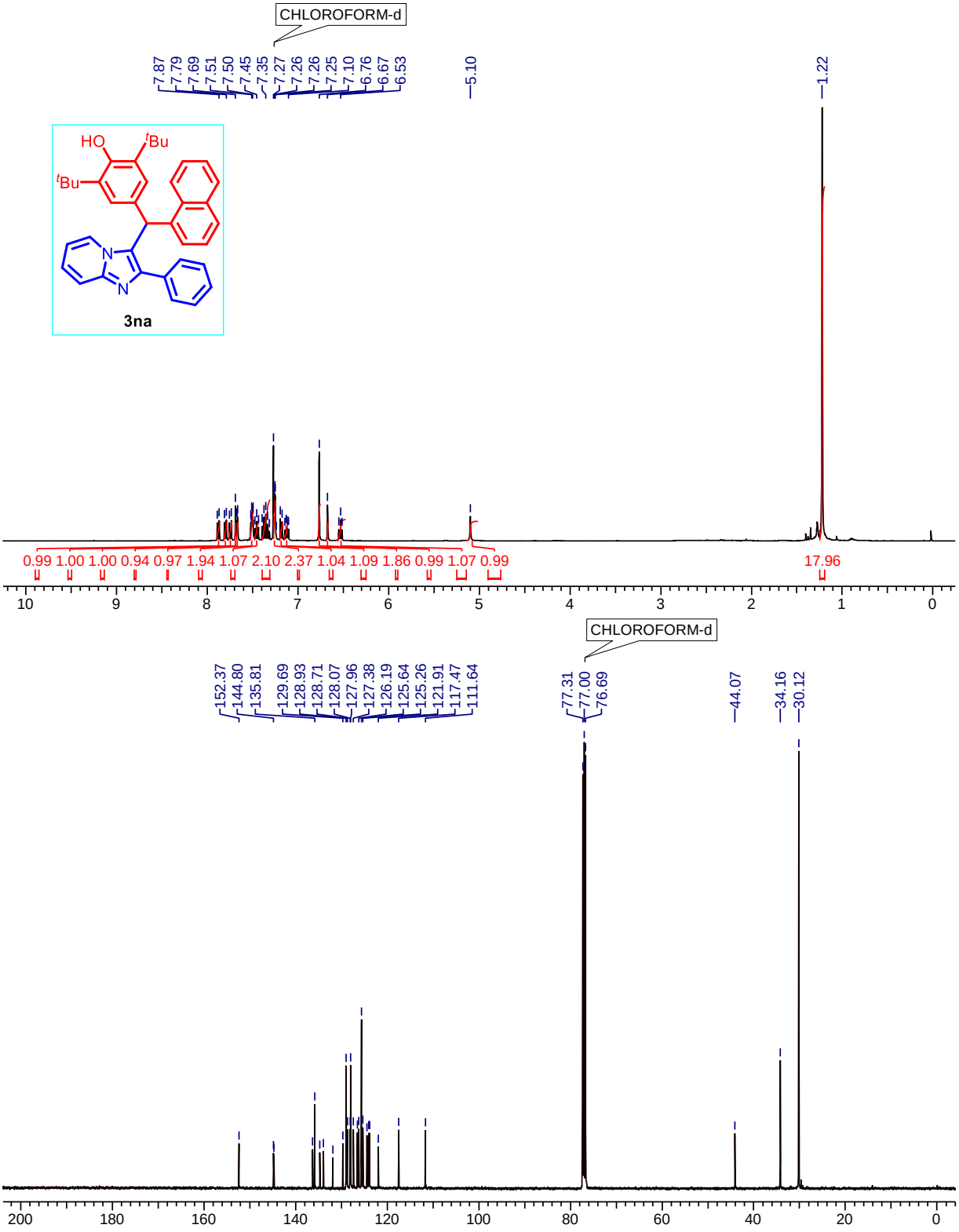
**2,6-Di-*tert*-butyl-4-((3-chlorophenyl)(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)phenol (3la):**



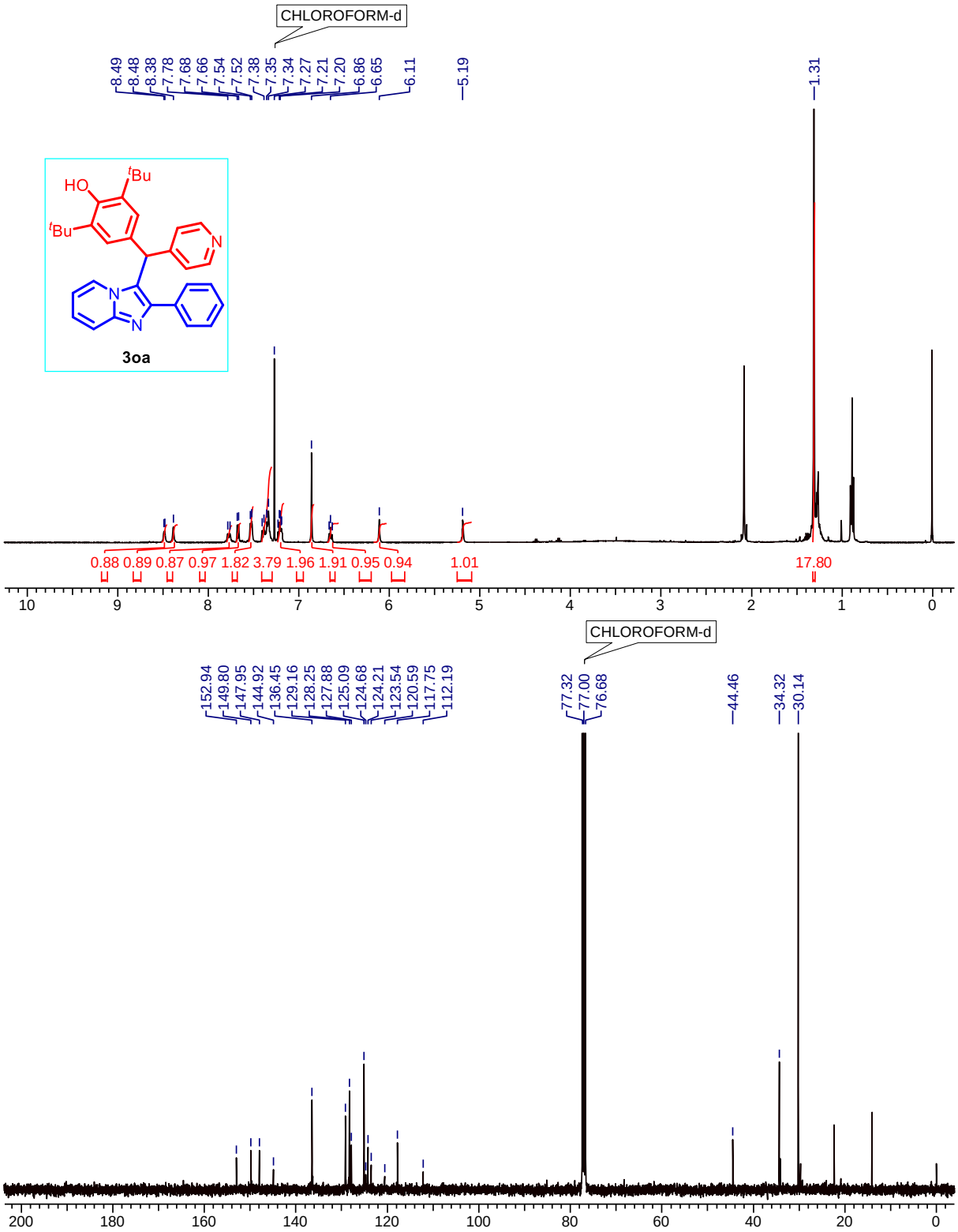
**4-((2-Bromophenyl)(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)-2,6-di-*tert*-butylphenol (3ma):**



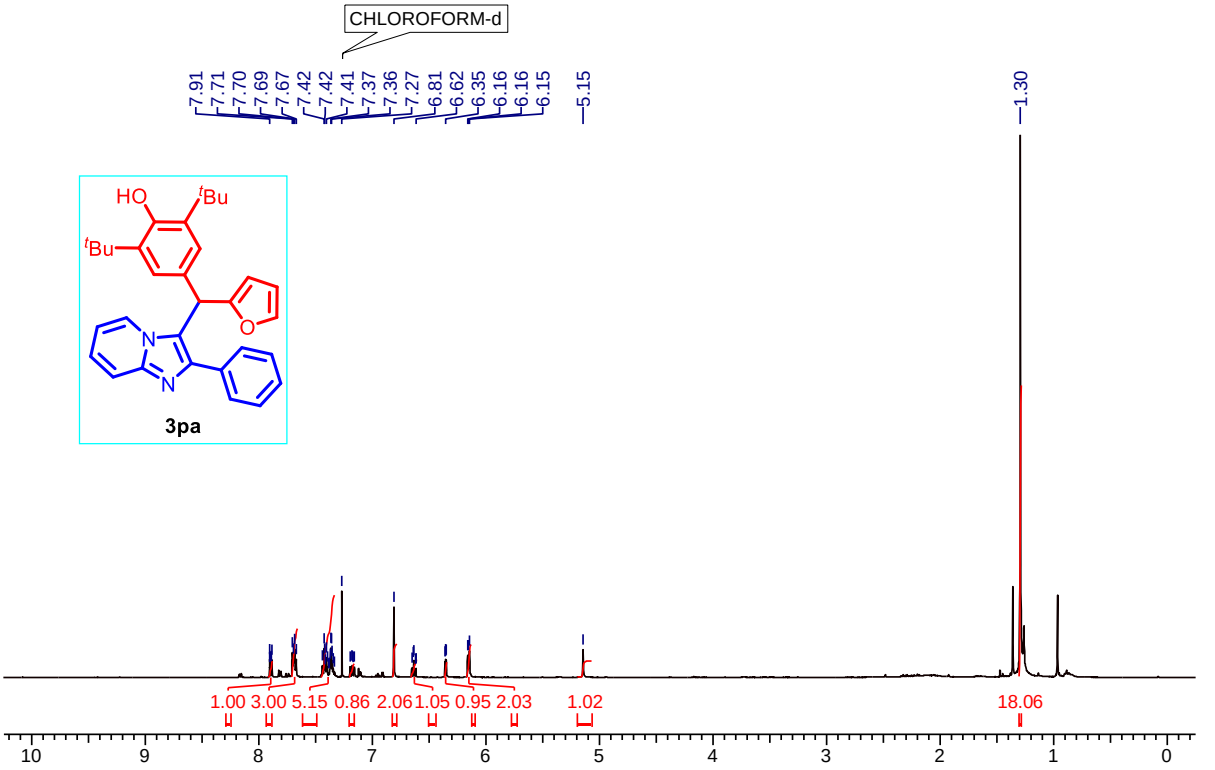
**2,6-Di-*tert*-butyl-4-(naphthalen-1-yl(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)phenol (3na):**

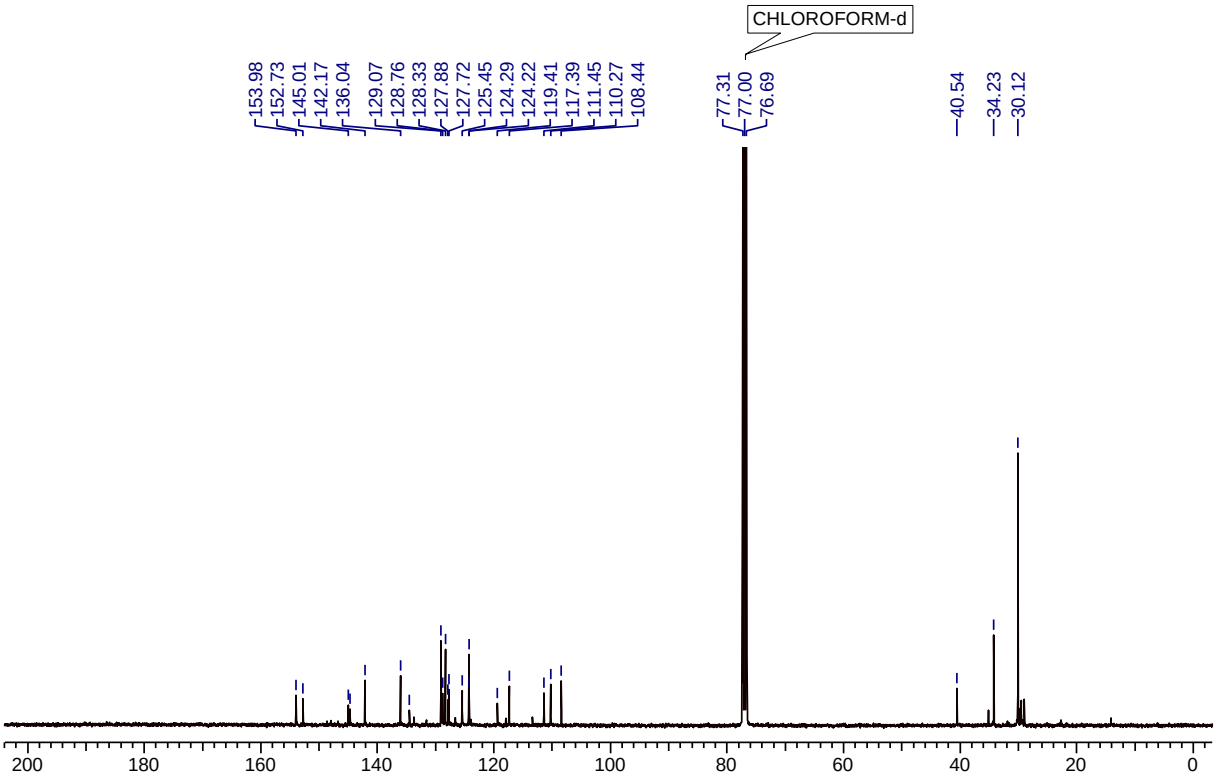


**2,6-Di-*tert*-butyl-4-((2-phenylimidazo[1,2-*a*]pyridin-3-yl)(pyridin-4-yl)methyl)phenol (3oa):**

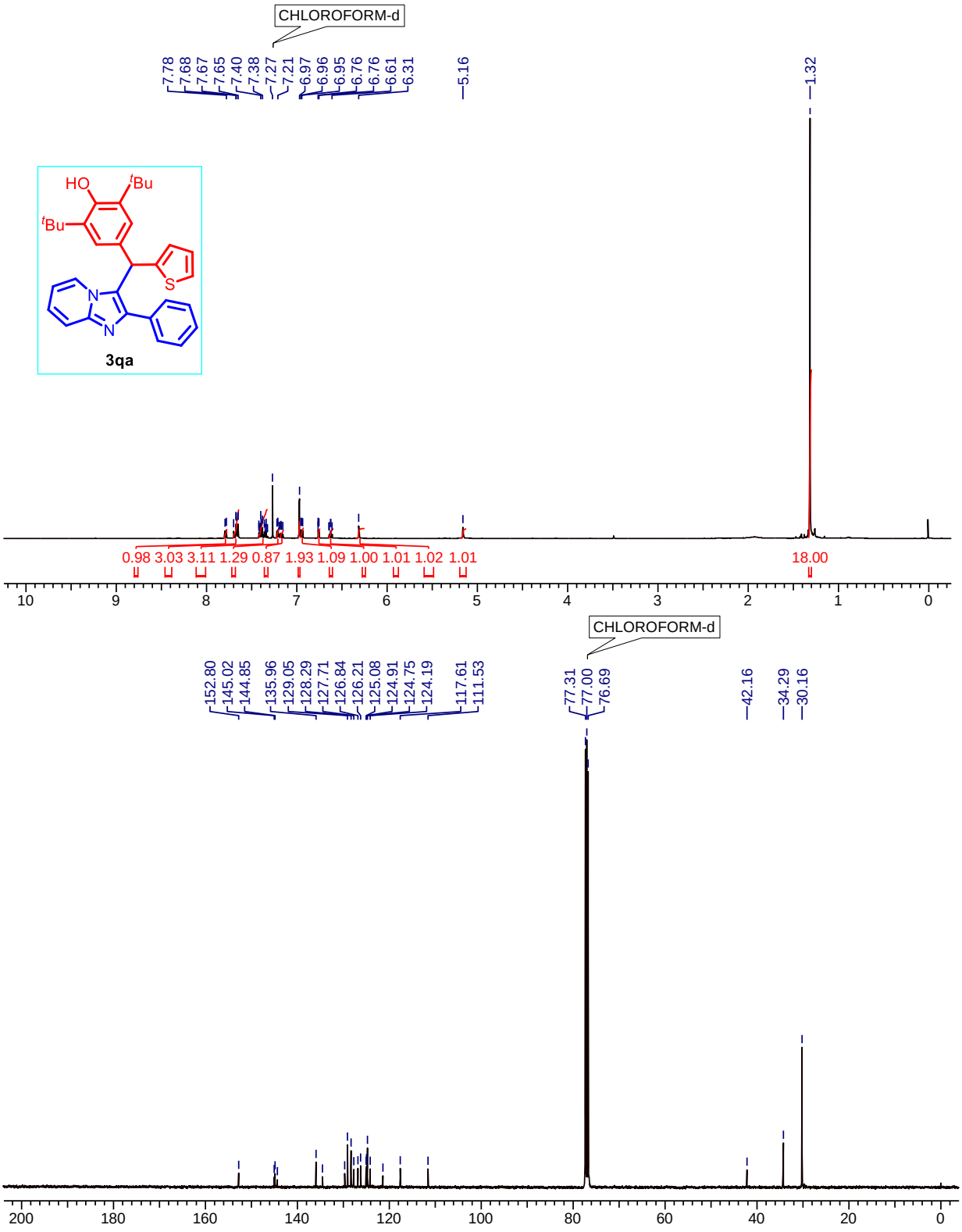


**2,6-Di-*tert*-butyl-4-(furan-2-yl(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)phenol (3pa):**

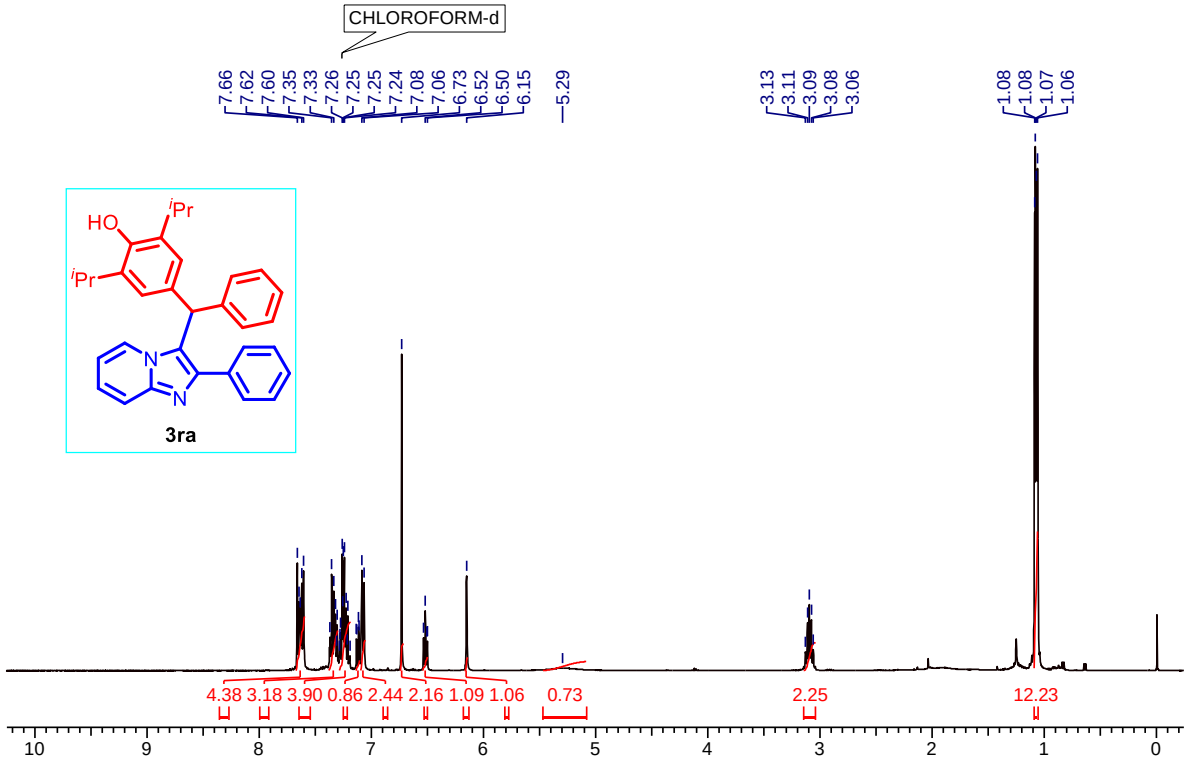


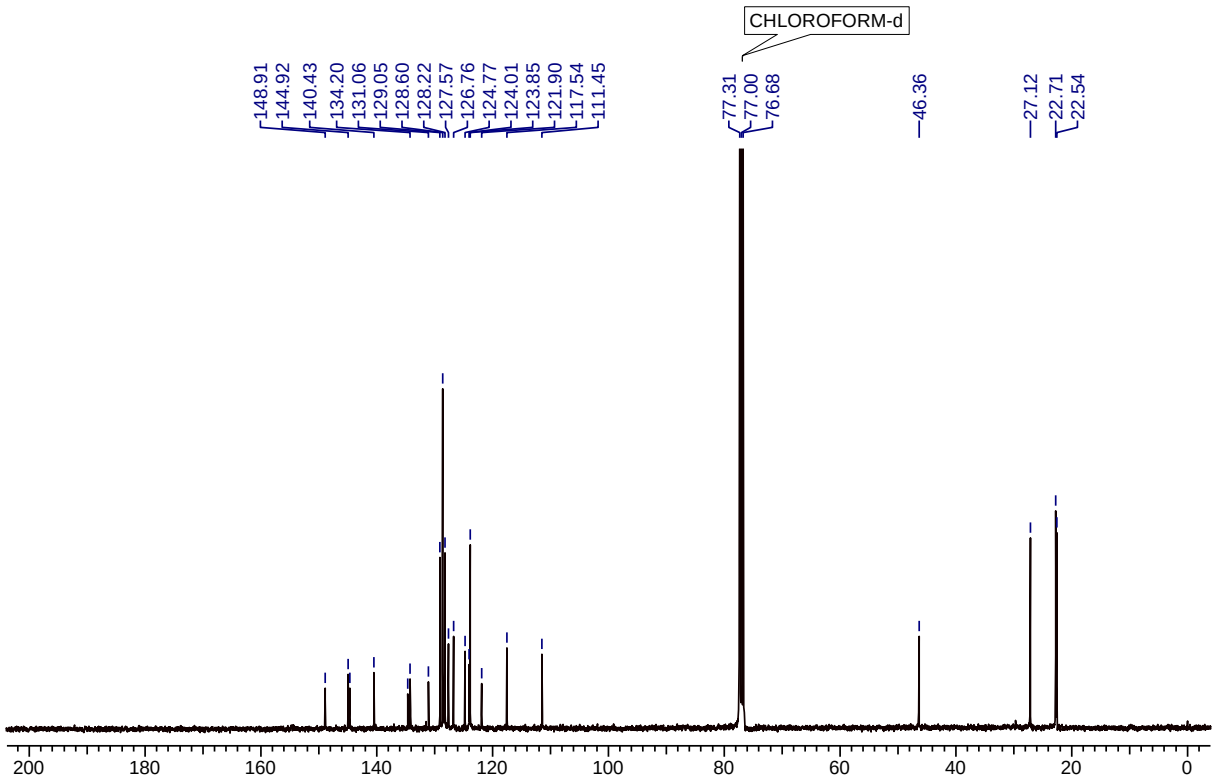



**2,6-Di-*tert*-butyl-4-((2-phenylimidazo[1,2-*a*]pyridin-3-yl)(thiophen-2-yl)methyl)phenol (3qa):**

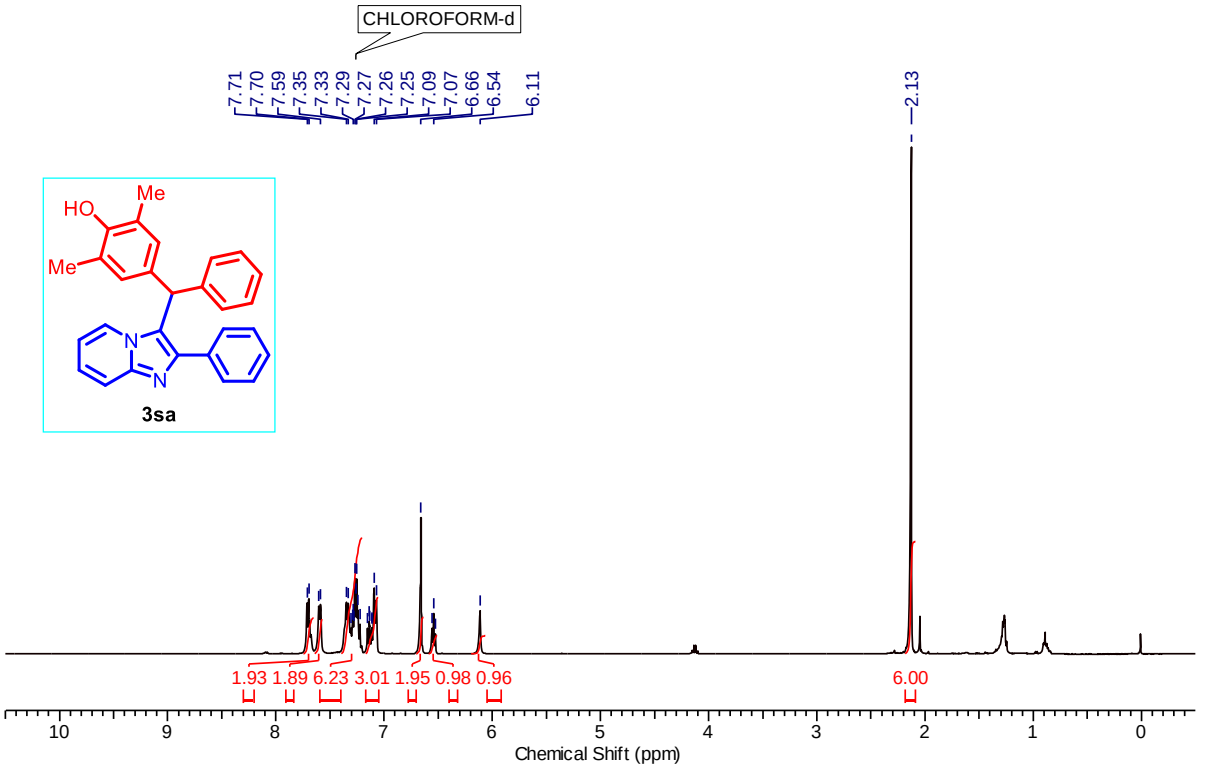


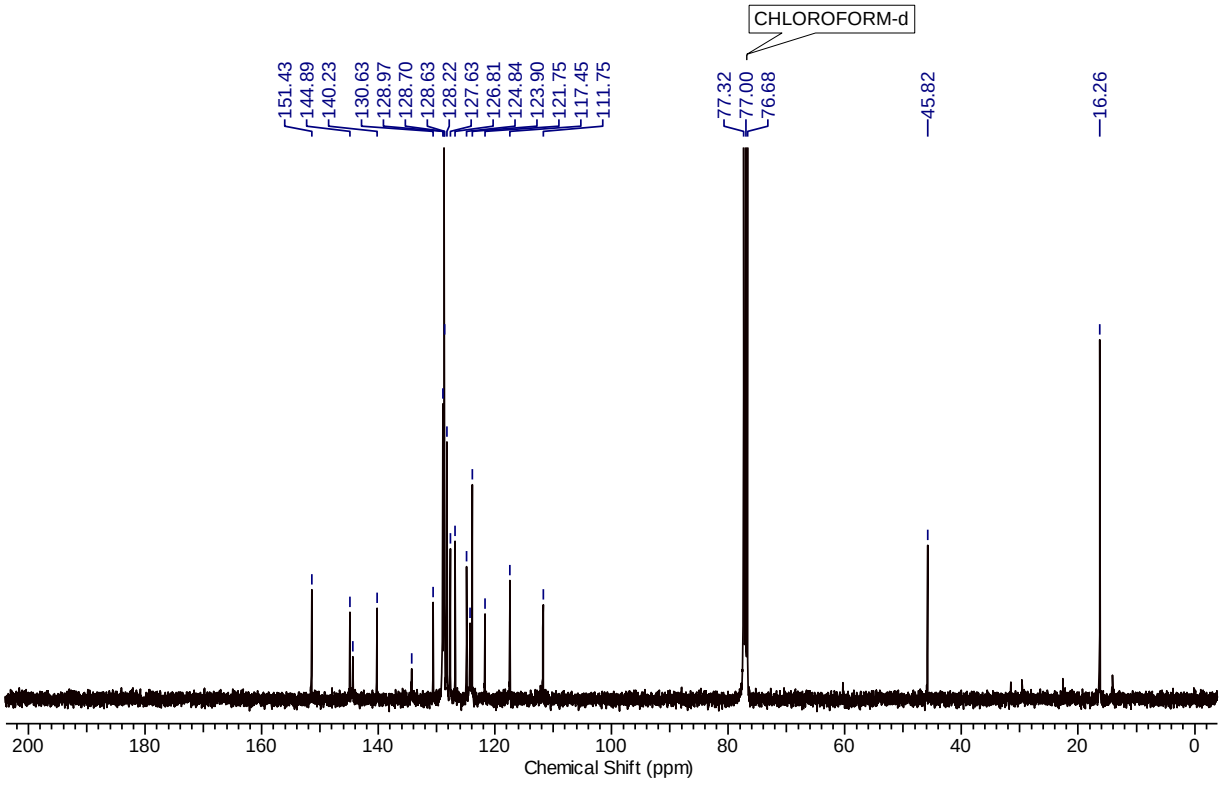
**2,6-Diisopropyl-4-(phenyl(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)phenol (3ra):**



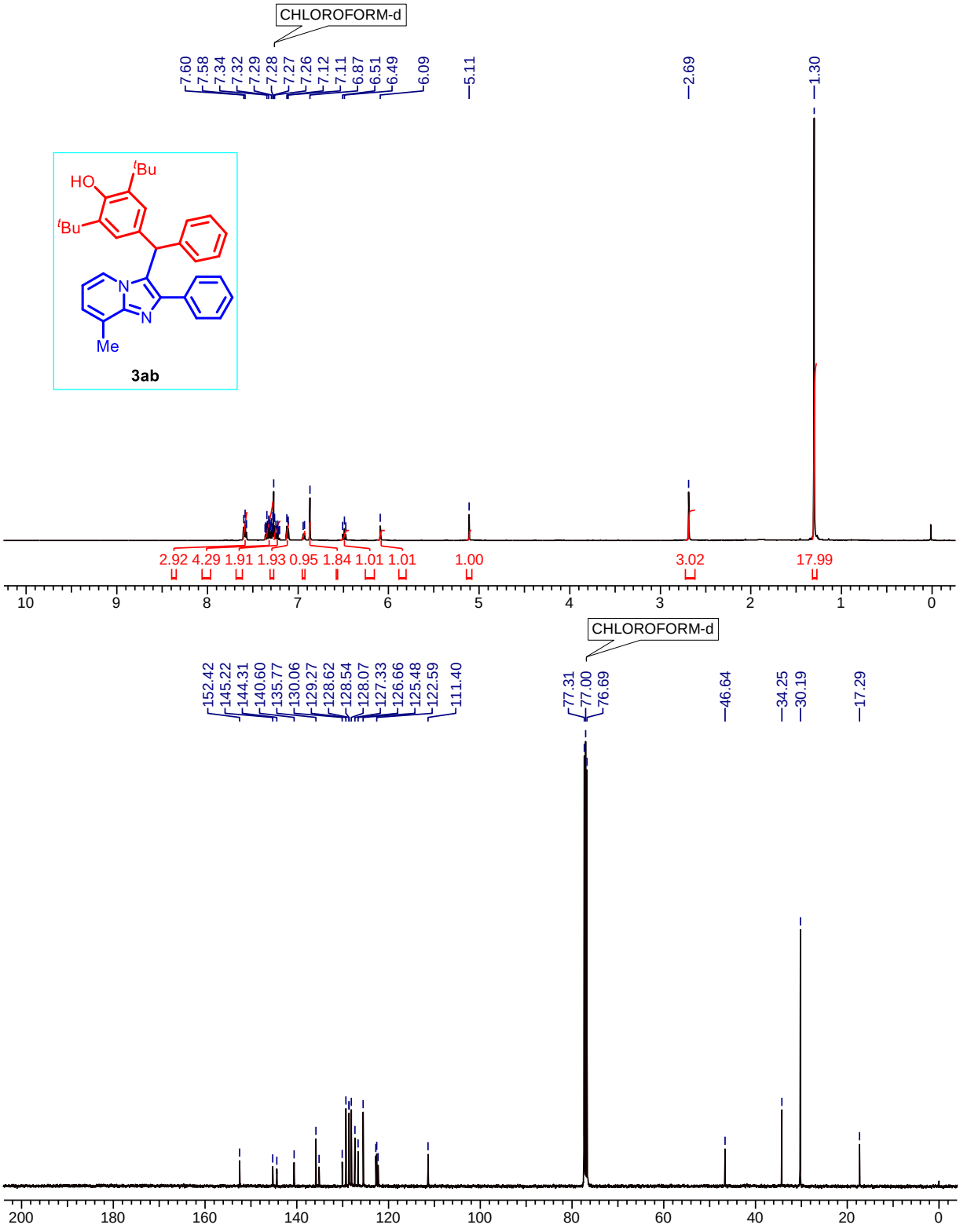



**2,6-Dimethyl-4-(phenyl(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)phenol (3sa):**

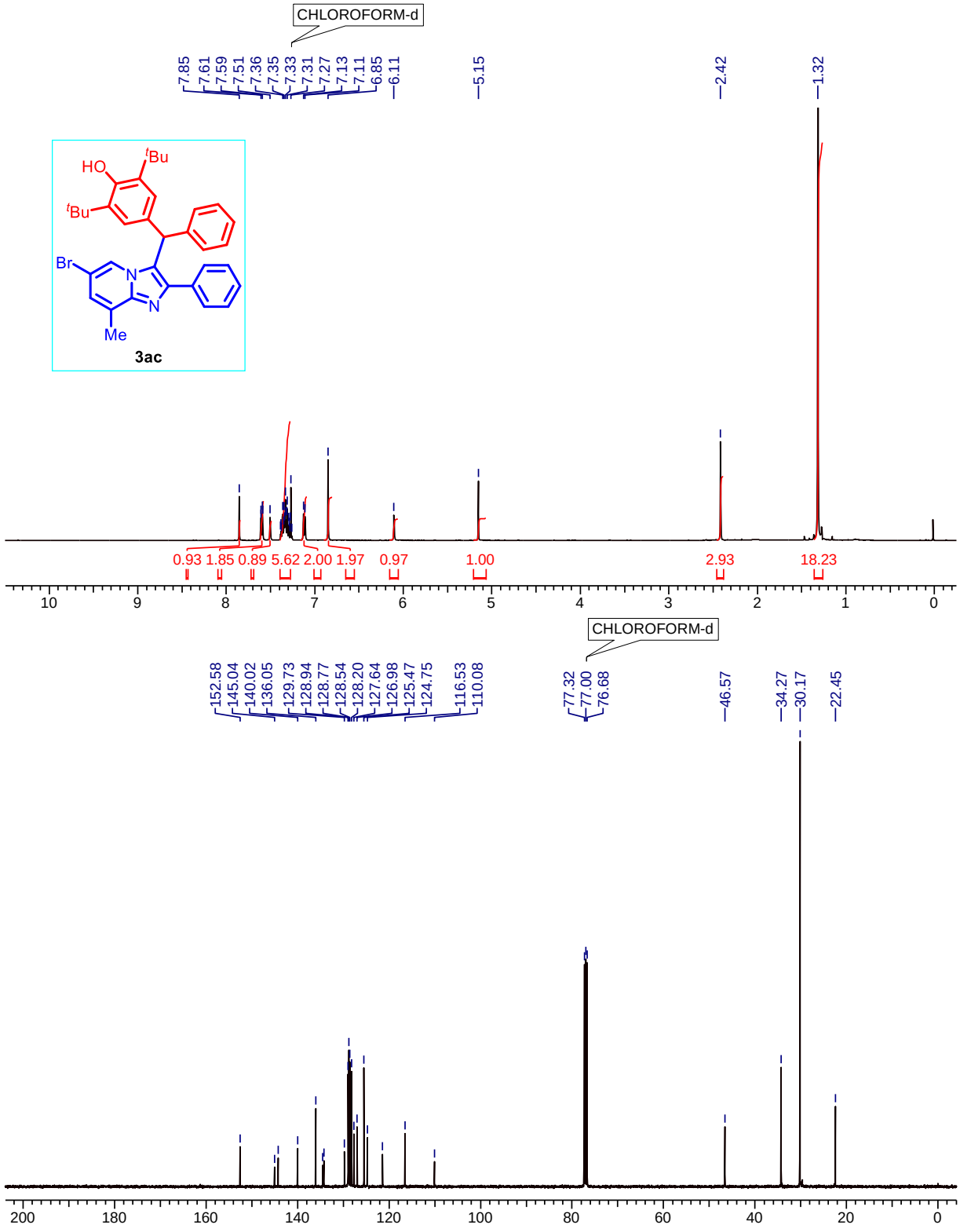


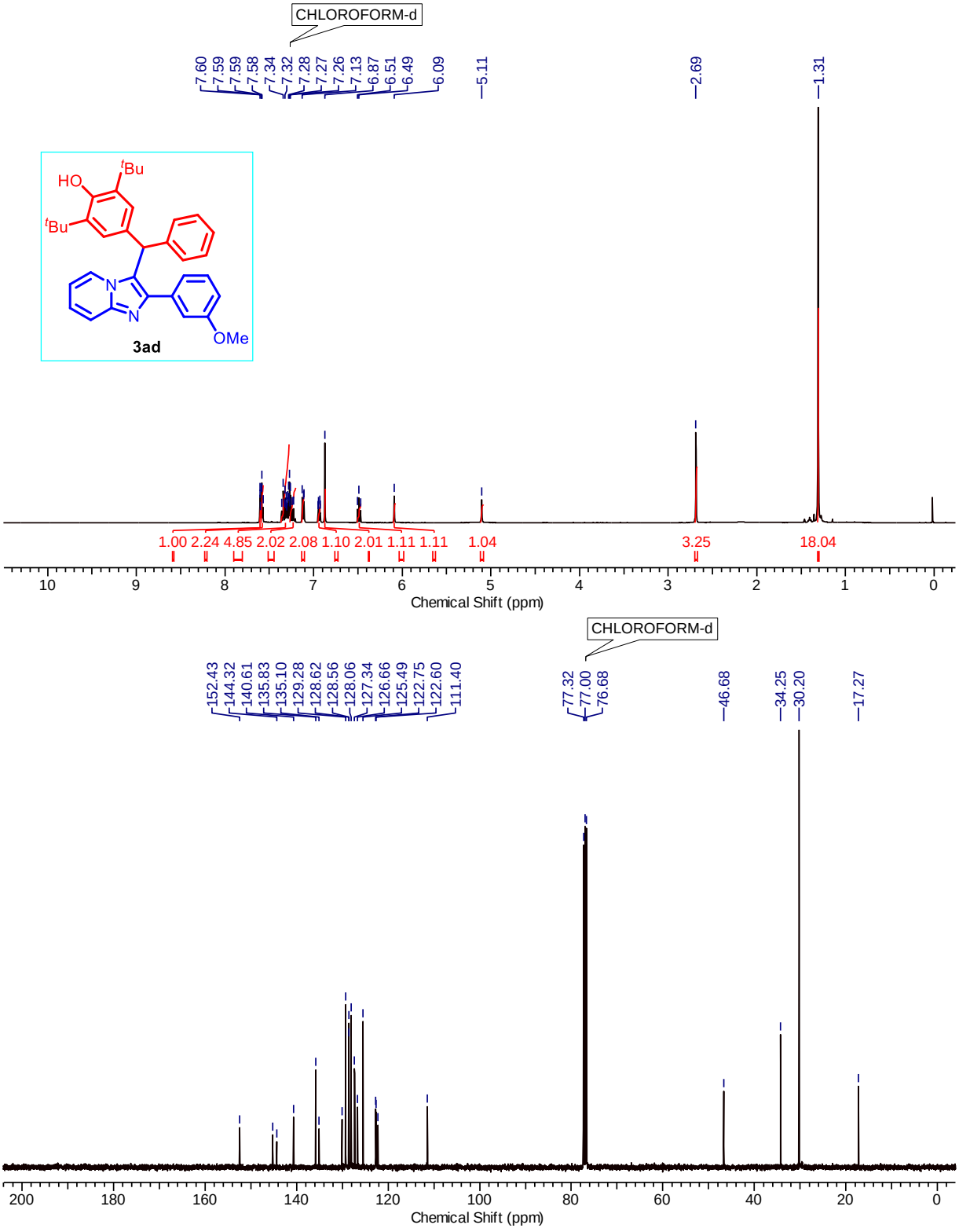
**2,6-Di-*tert*-butyl-4-((8-methyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)phenol (3ab):**



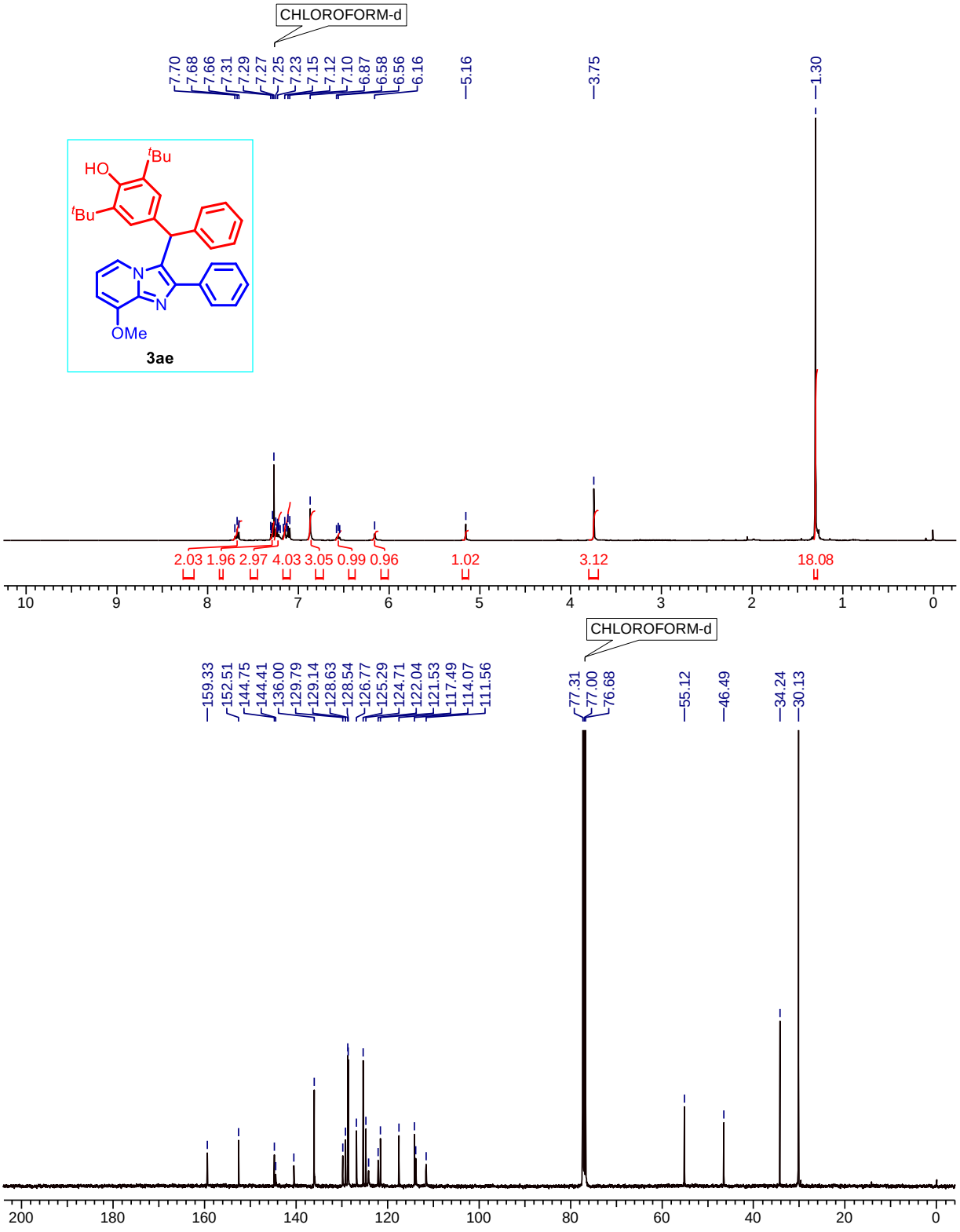
**4-((6-Bromo-8-methyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)-2,6-di-*tert*-butylphenol (3ac):**



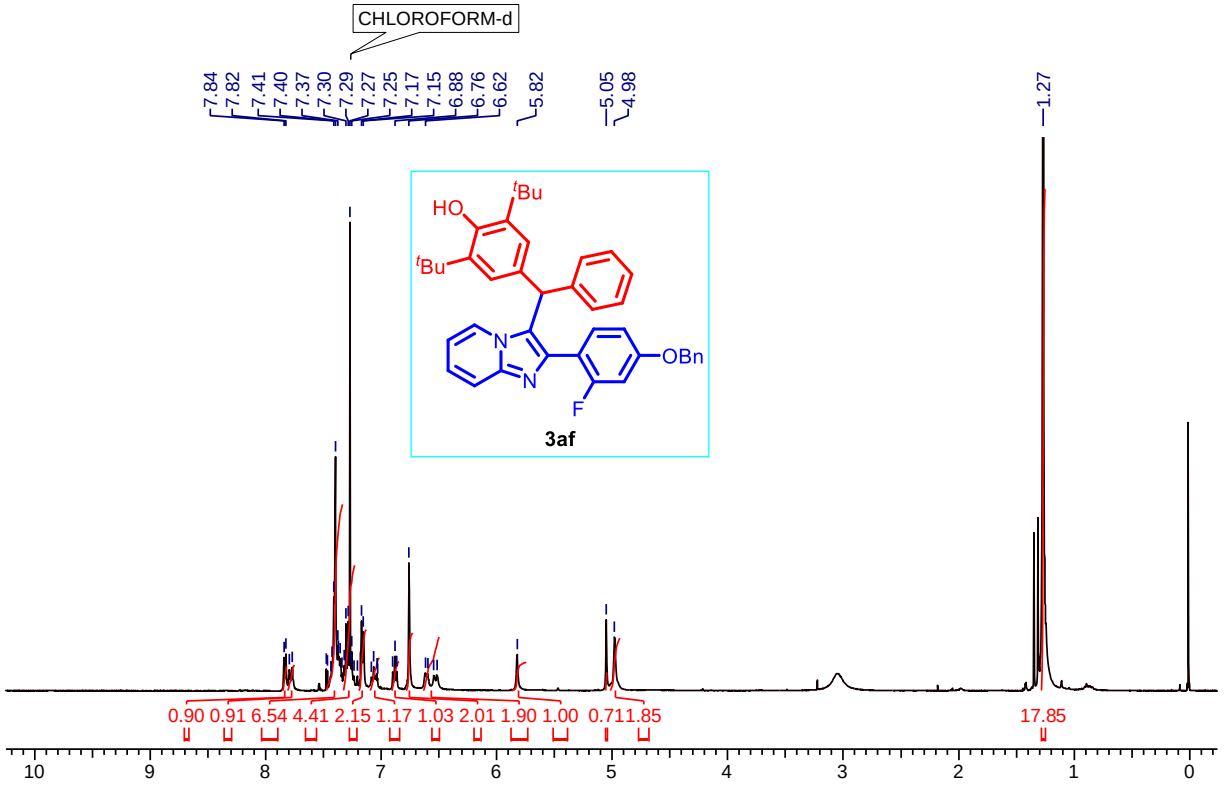
**2,6-Di-*tert*-butyl-4-((2-(3-methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)phenol (3ad):**

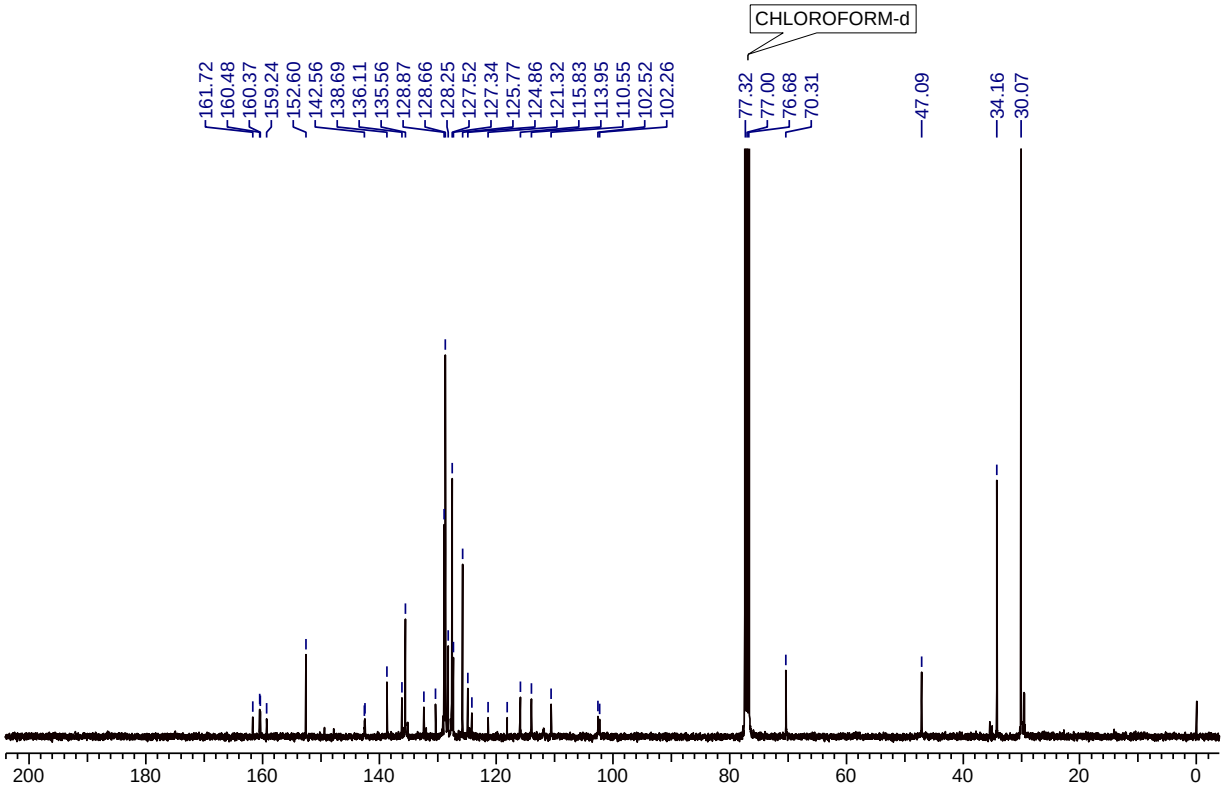


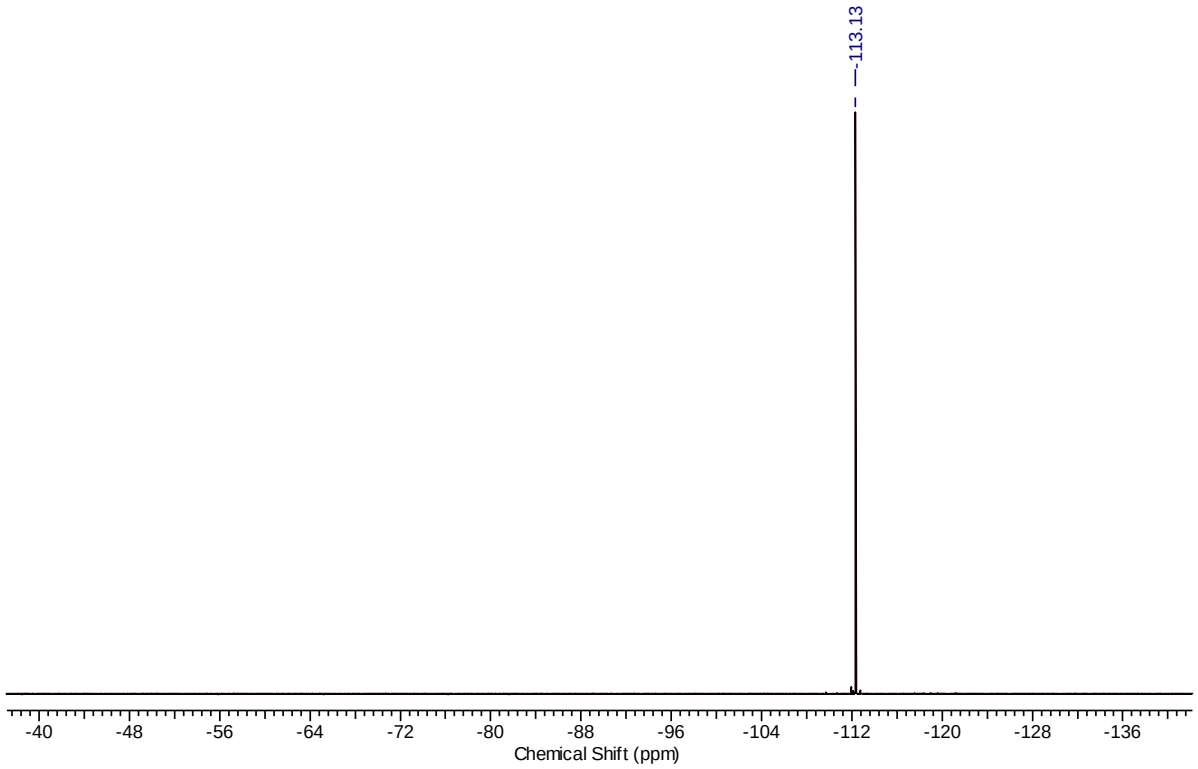
**2,6-Di-*tert*-butyl-4-((8-methoxy-2-phenylimidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)phenol (3ae):**



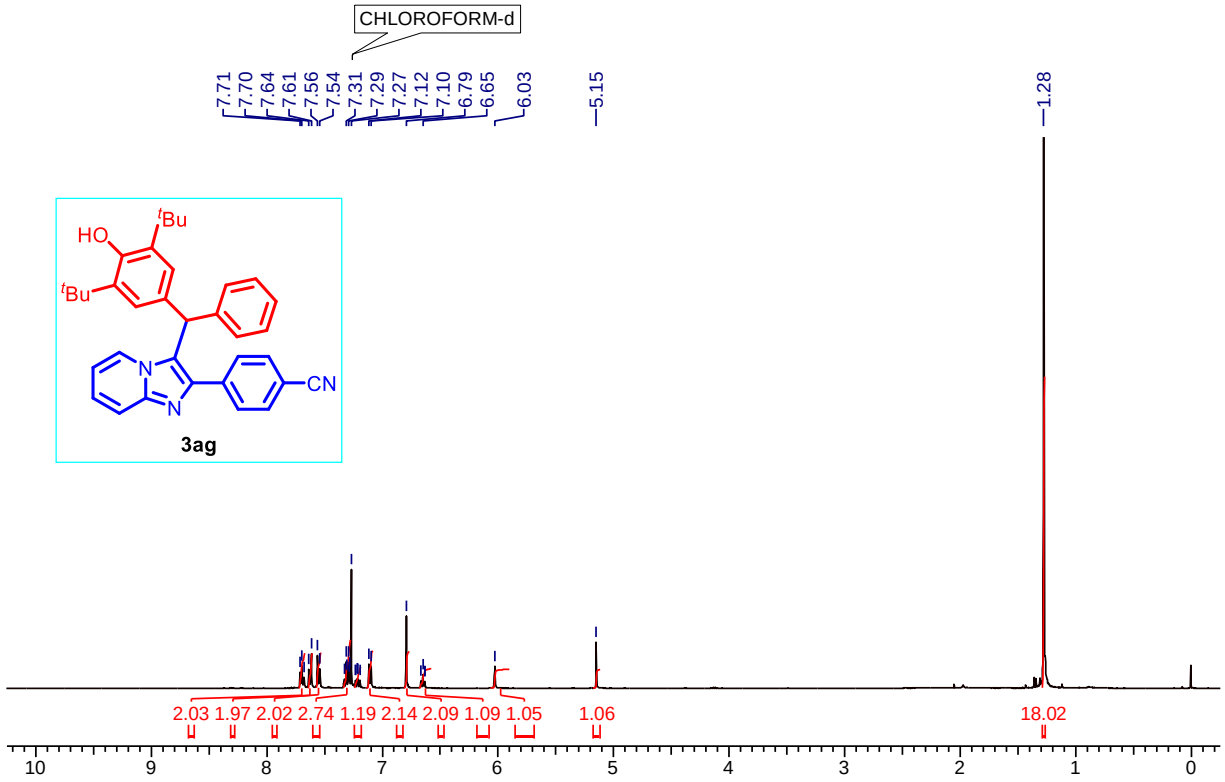
**4-((2-(4-(Benzyloxy)-2-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)-2,6-di-*tert*-butylphenol (3af):**

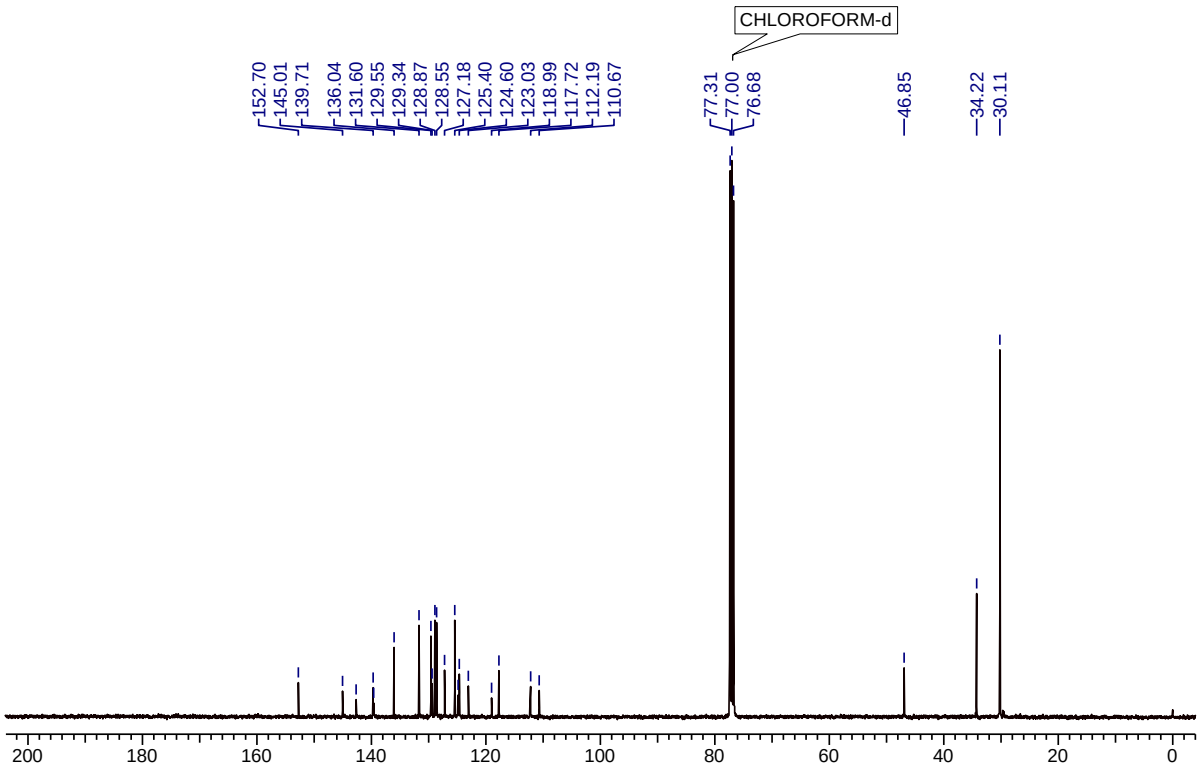


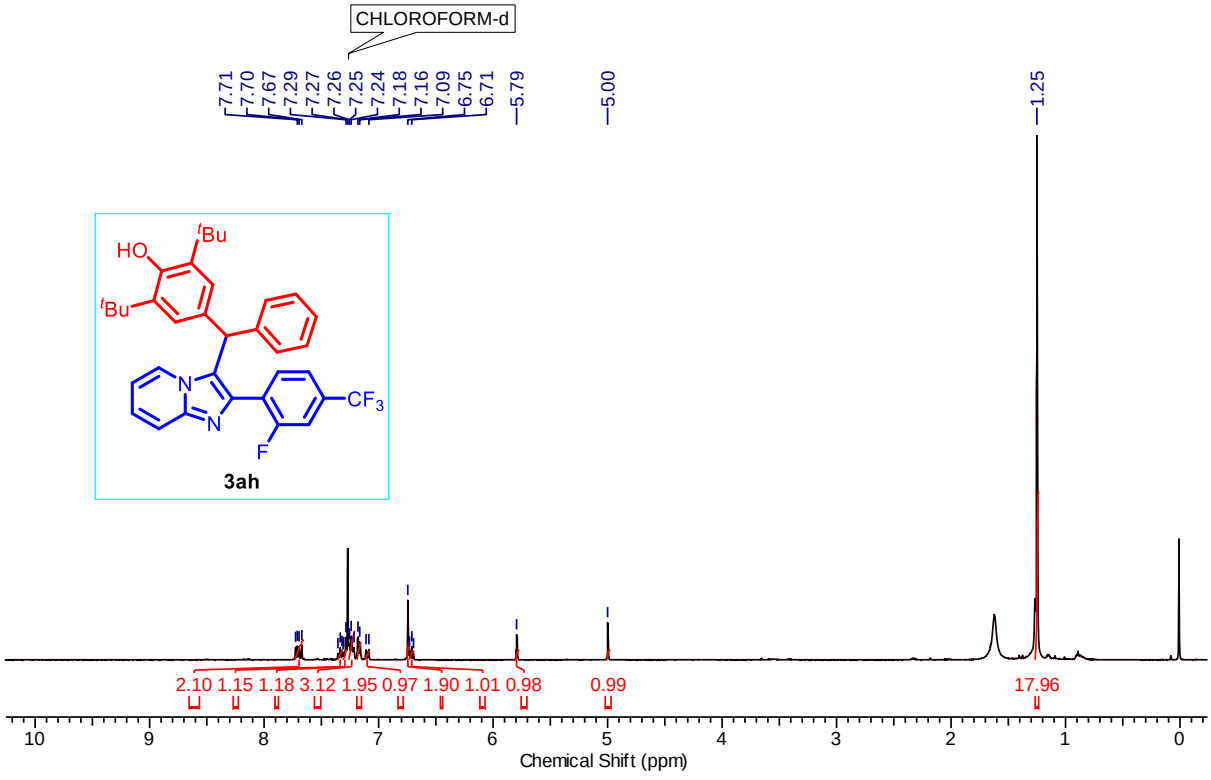


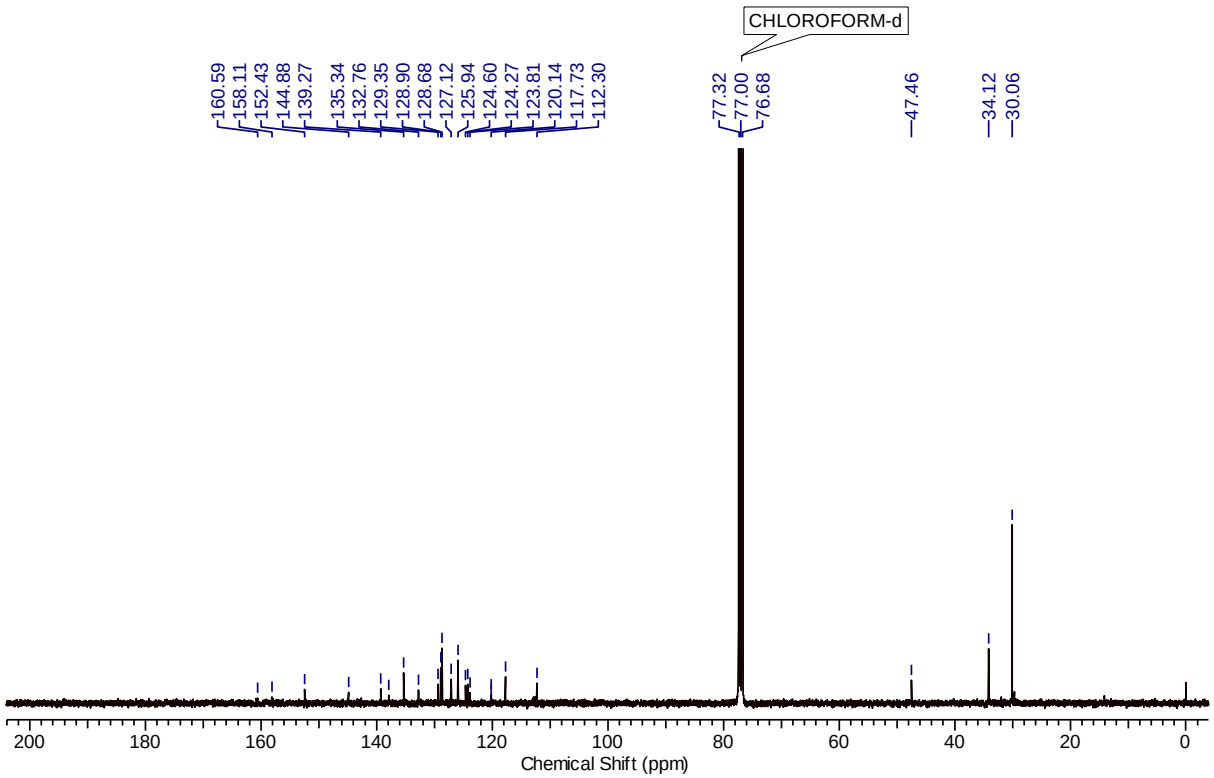

**4-(3-((3,5-Di-*tert*-butyl-4-hydroxyphenyl)(phenyl)methyl)imidazo[1,2-*a*]pyridin-2-yl)benzonitrile (3ag):**

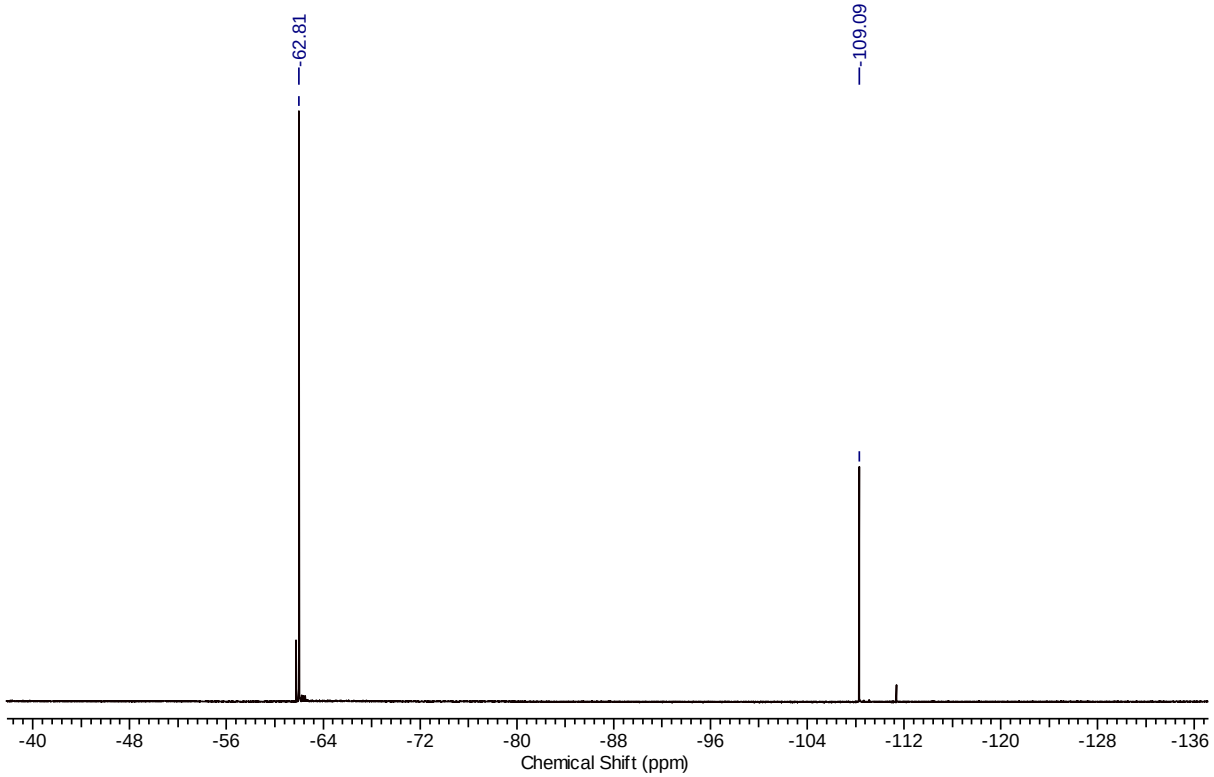




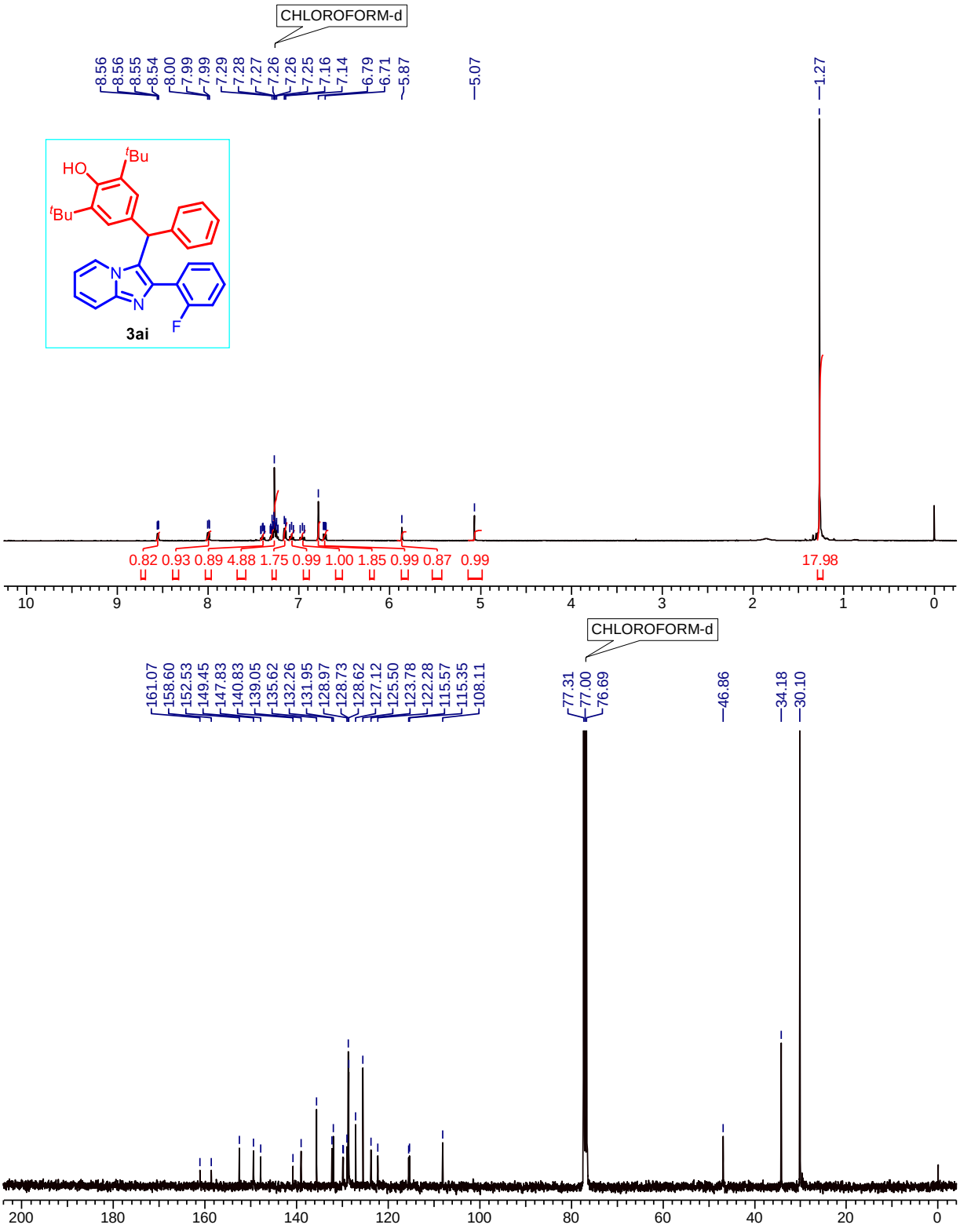

**2,6-Di-*tert*-butyl-4-((2-(2-fluoro-4-(trifluoromethyl)phenyl)imidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)phenol (3ah):**

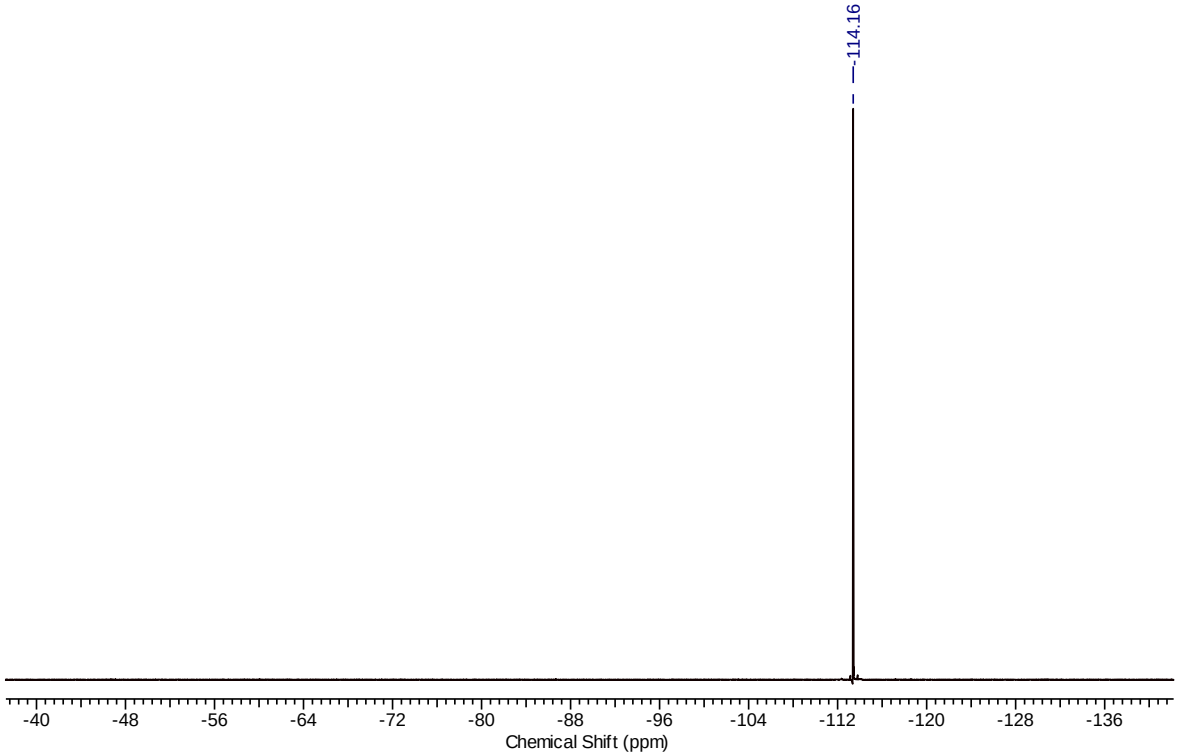



CHLOROFORM-d
160.59
158.11
152.43
144.88
139.27
135.34
132.76
129.35
128.90
128.68
127.12
125.94
124.60
124.27
123.81
120.14
117.73
112.30
77.32
77.00
76.68
47.46
34.12
30.06
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

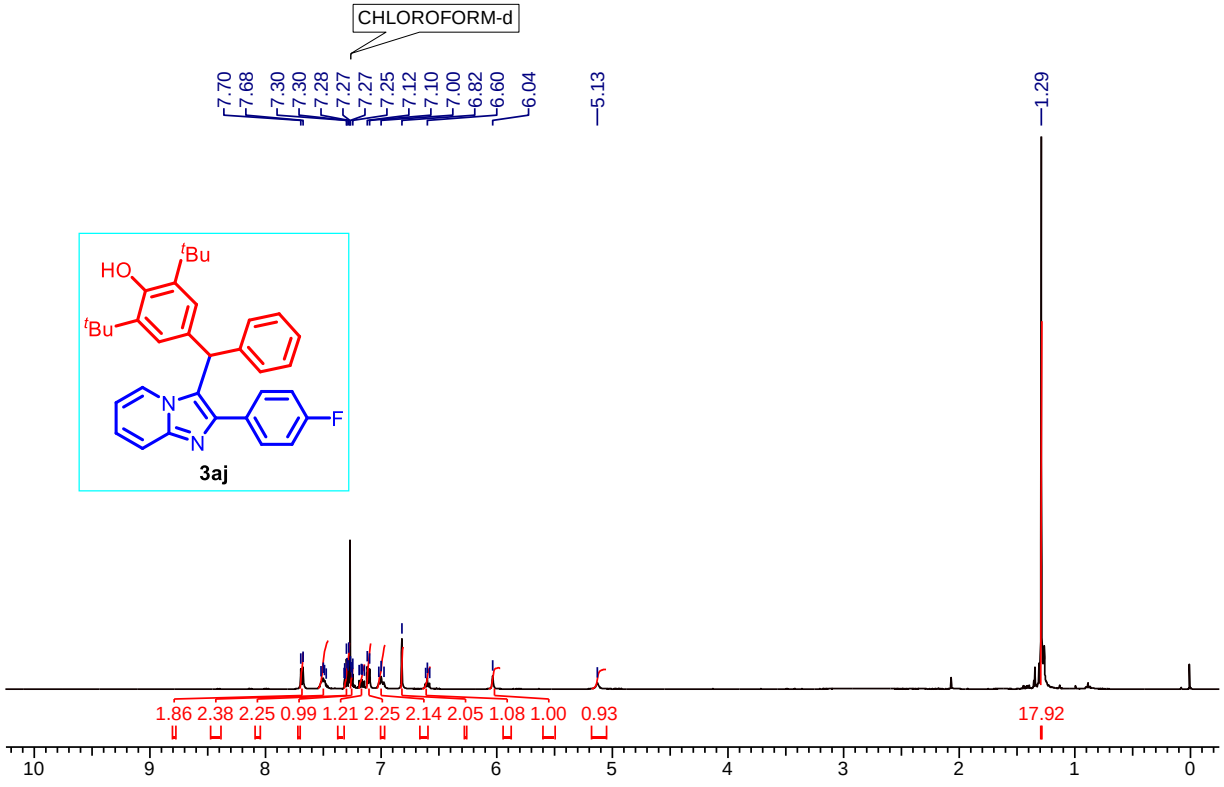

-62.81
-109.09
-40
-48
-56
-64
-72
-80
-88
-96
-104
-112
-120
-128
-136
Chemical Shift (ppm)

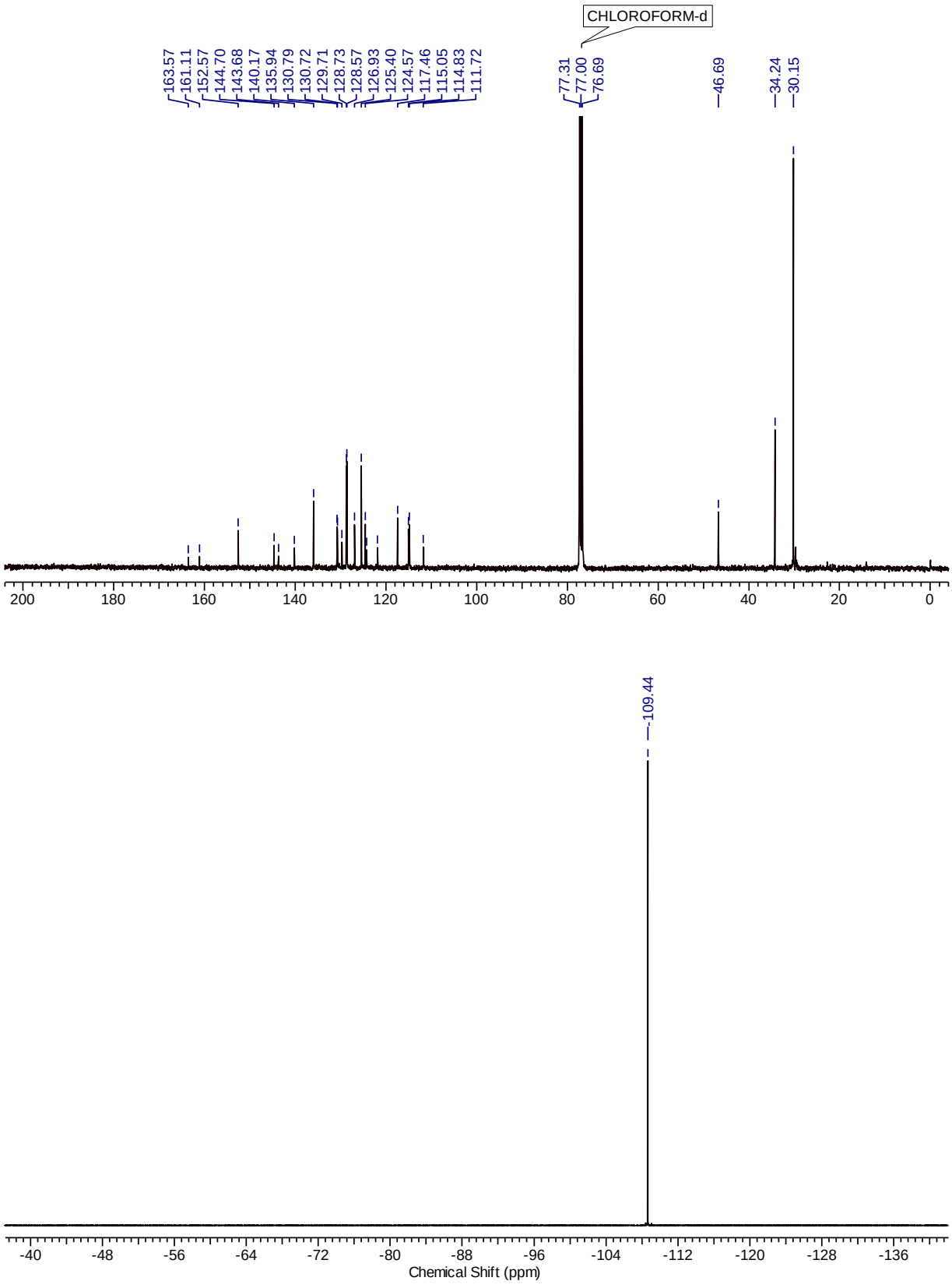
**2,6-Di-*tert*-butyl-4-((2-(2-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)phenol (3ai):**



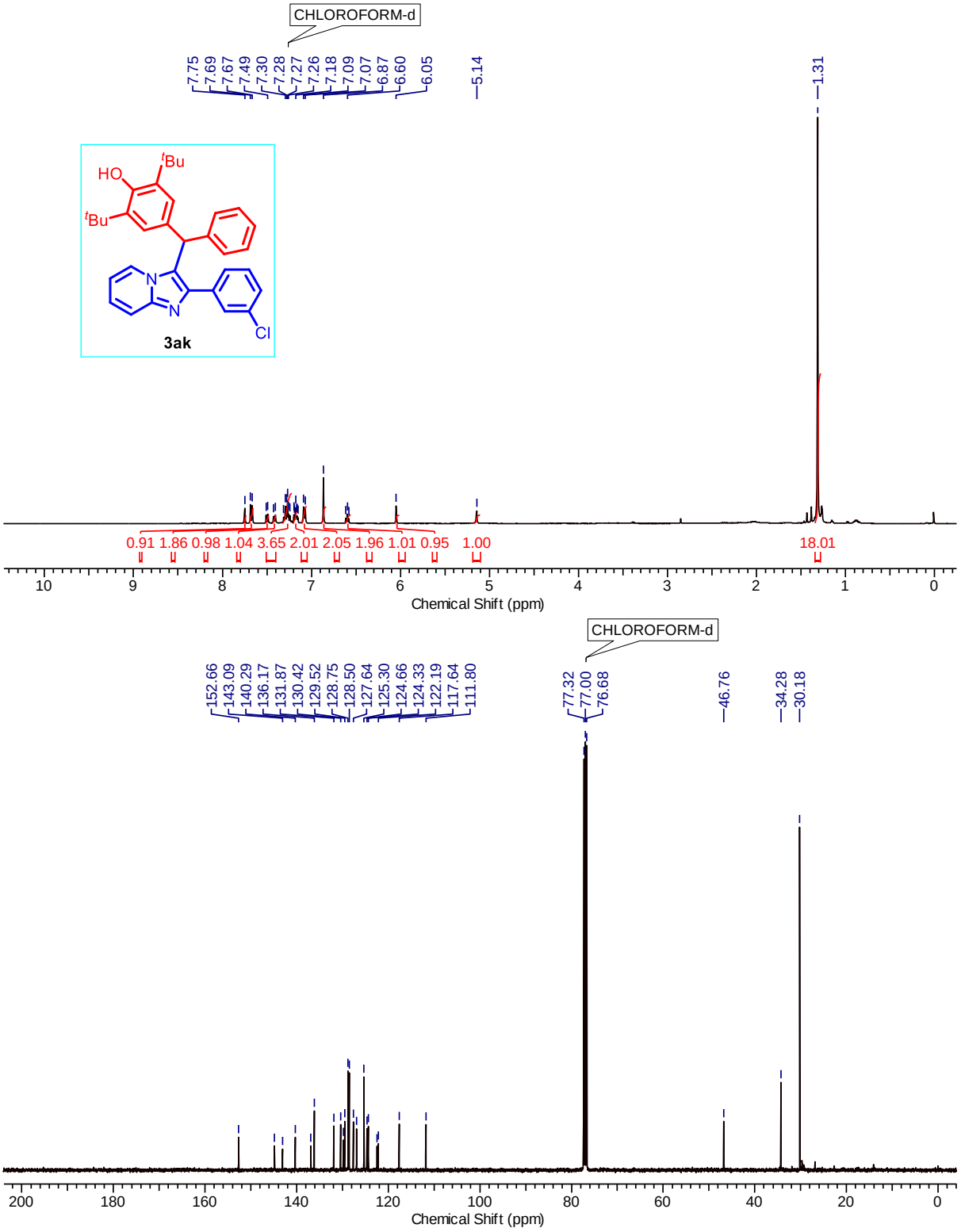



**2,6-Di-*tert*-butyl-4-((2-(4-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)phenol (3aj):**

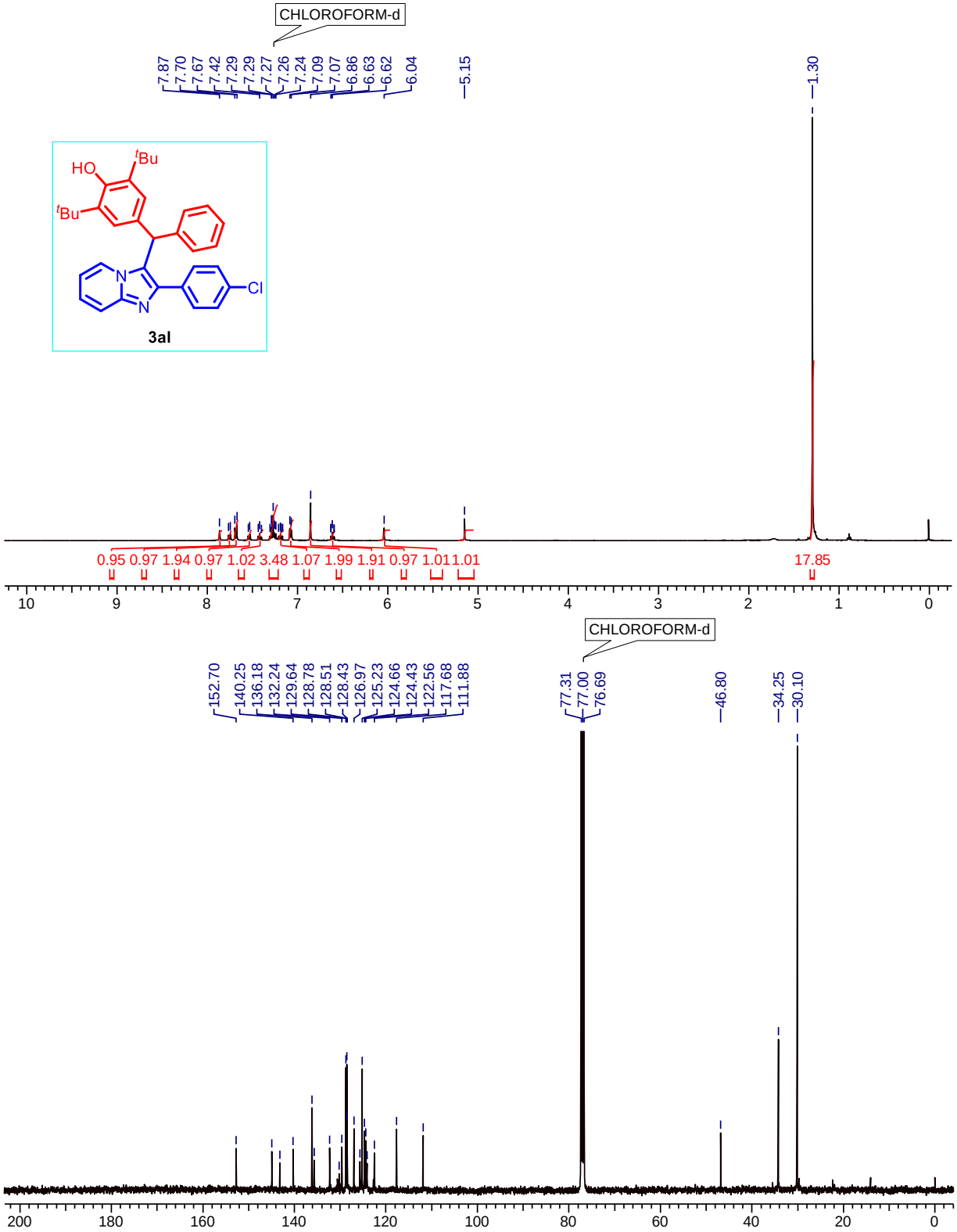



CHLOROFORM-d
163.57
161.11
152.57
144.70
143.68
140.17
135.94
130.79
130.72
129.71
128.73
128.57
126.93
125.40
124.57
117.46
115.05
114.83
111.72
77.31
77.00
76.69
46.69
34.24
30.15
200
180
160
140
120
100
80
60
40
20
0
-109.44
-40
-48
-56
-64
-72
-80
-88
-96
-104
-112
-120
-128
-136
Chemical Shift (ppm)

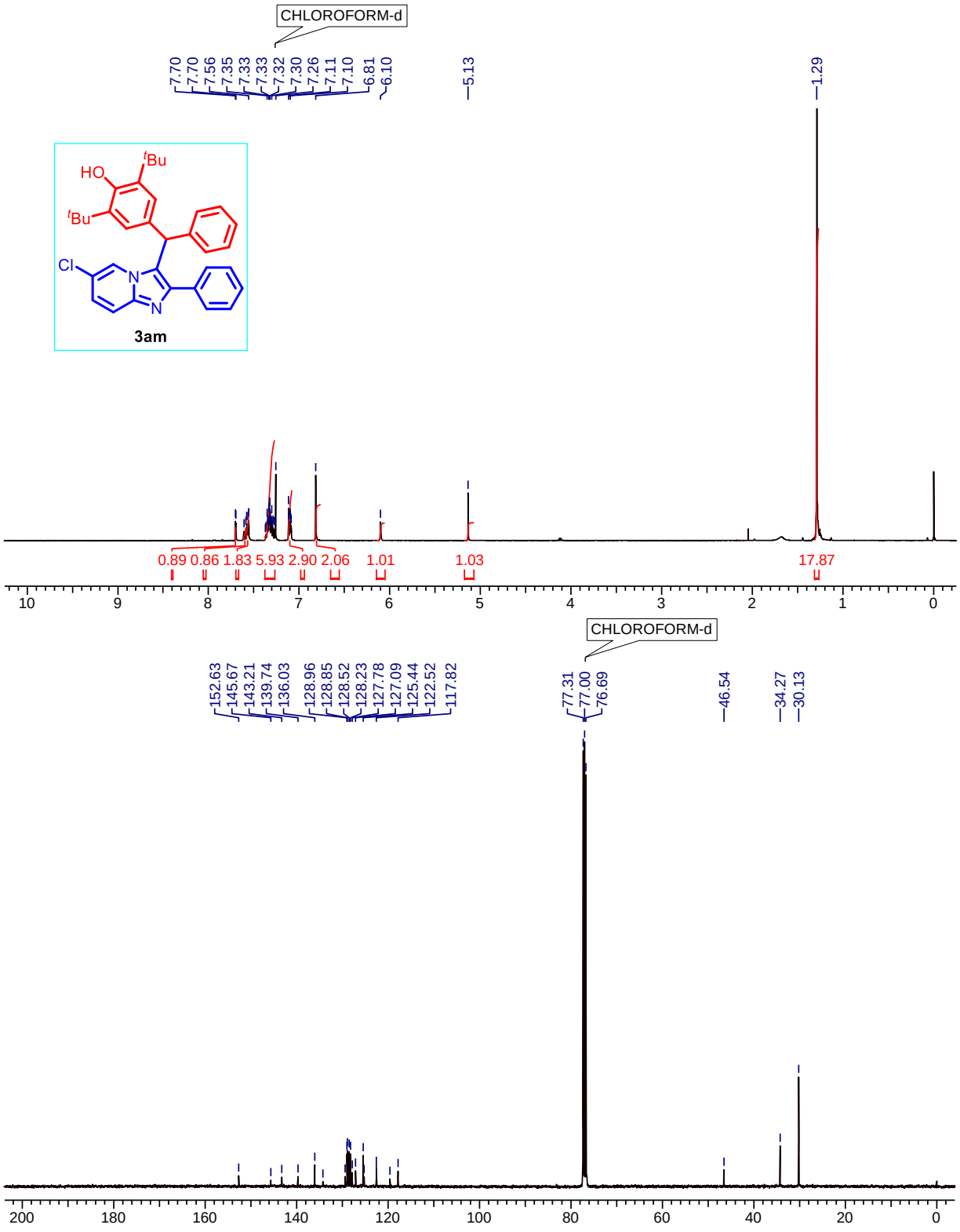
**2,6-Di-*tert*-butyl-4-((2-(3-chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)phenol (3ak):**



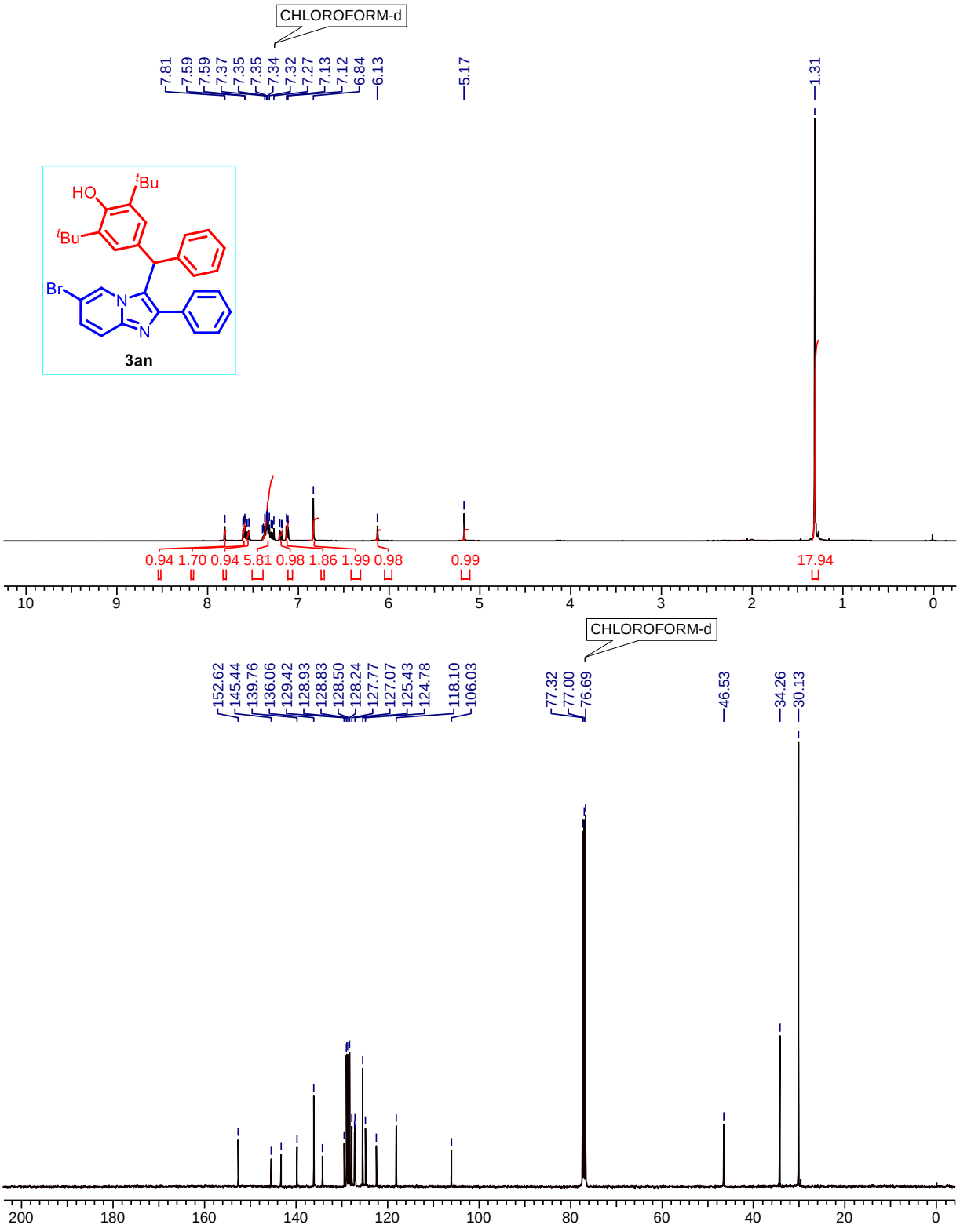
**2,6-Di-*tert*-butyl-4-((2-(4-chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)phenol (3al):**



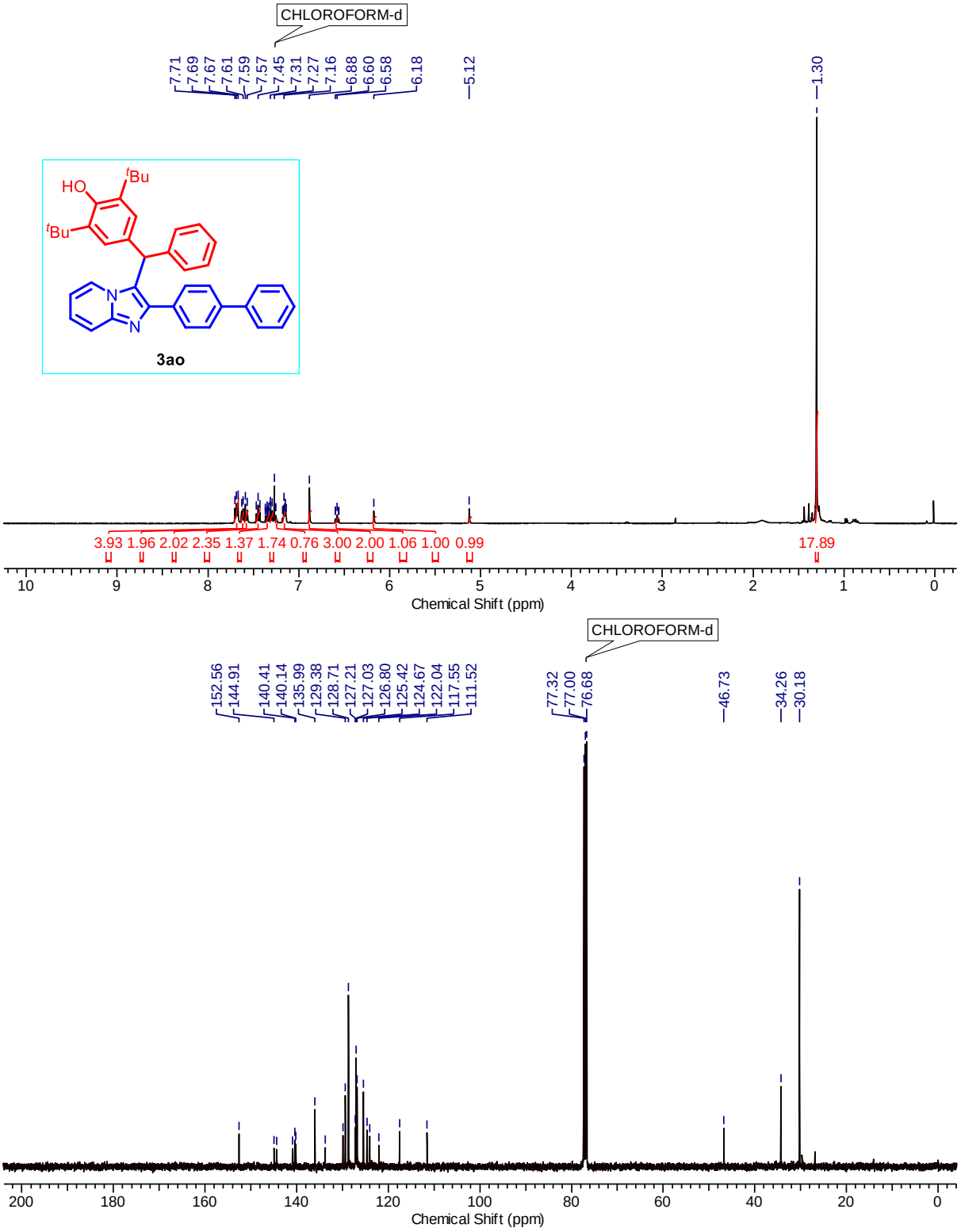
**2,6-Di-*tert*-butyl-4-((6-chloro-2-phenylimidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)phenol (3am):**



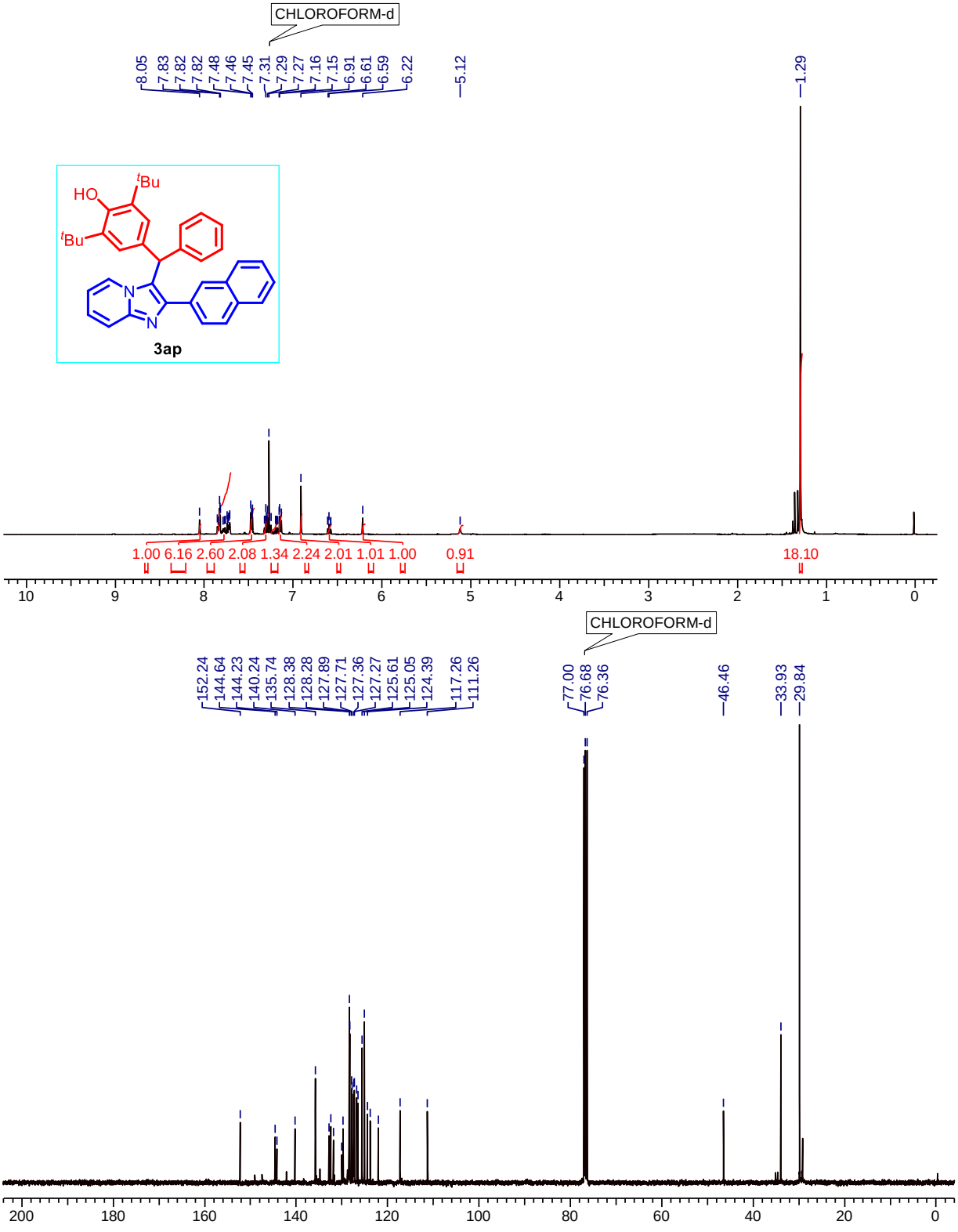
**4-((6-Bromo-2-phenylimidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)-2,6-di-*tert*-butylphenol (3an):**



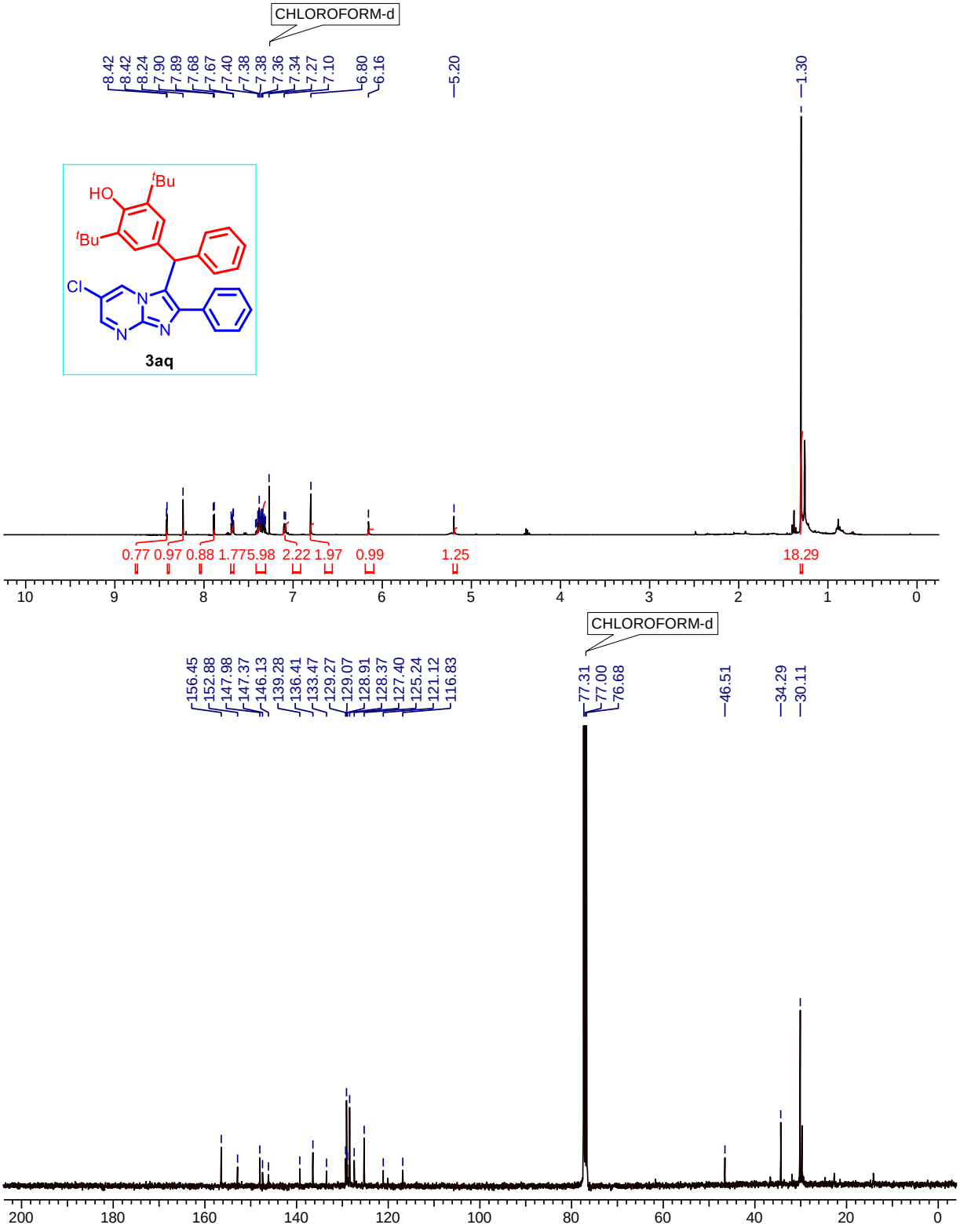
**4-((2-([1,1'-Biphenyl]-4-yl)imidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)-2,6-di-*tert*-butylphenol (3ao):**



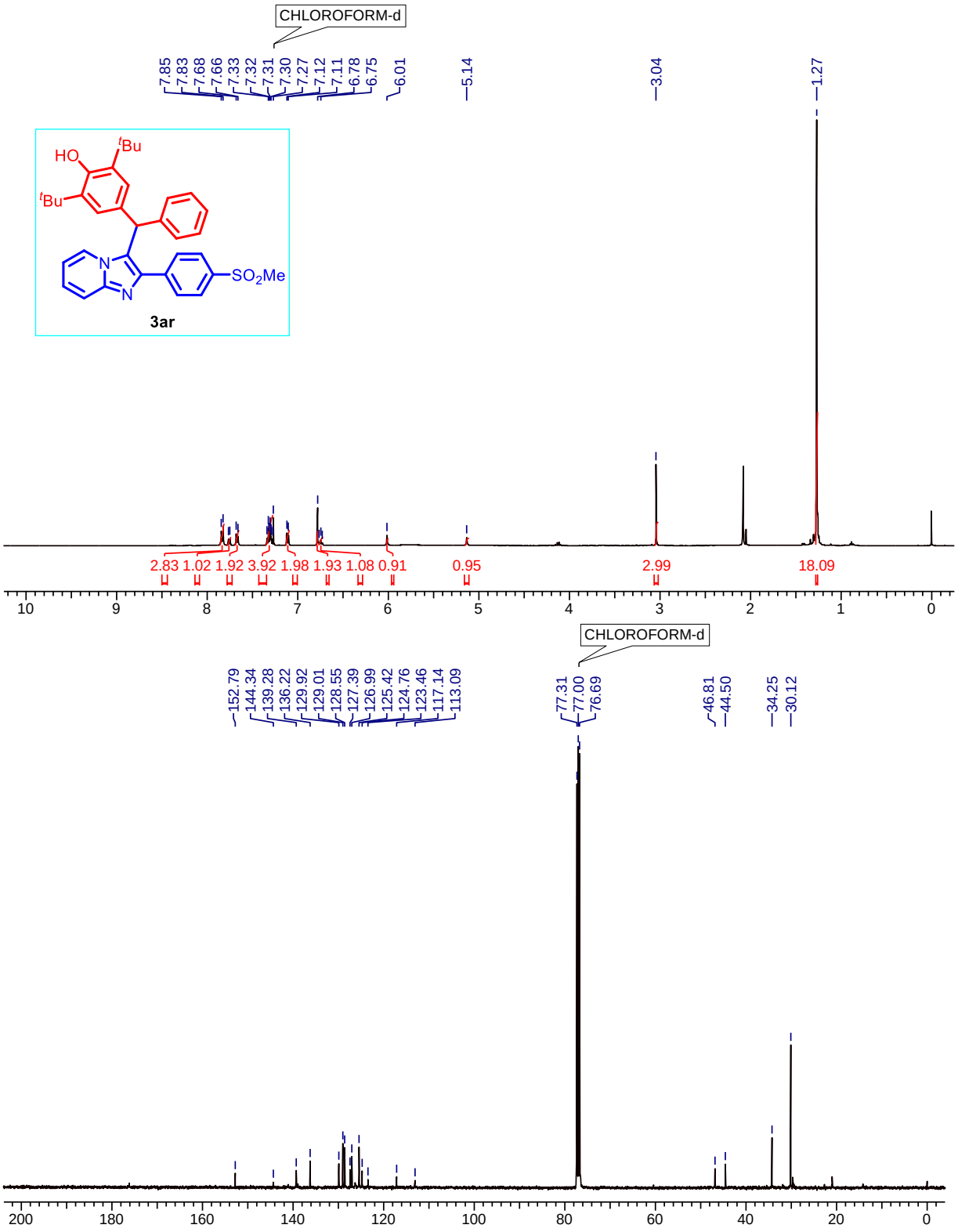
**2,6-Di-*tert*-butyl-4-((2-(naphthalen-2-yl)imidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)phenol (3ap):**



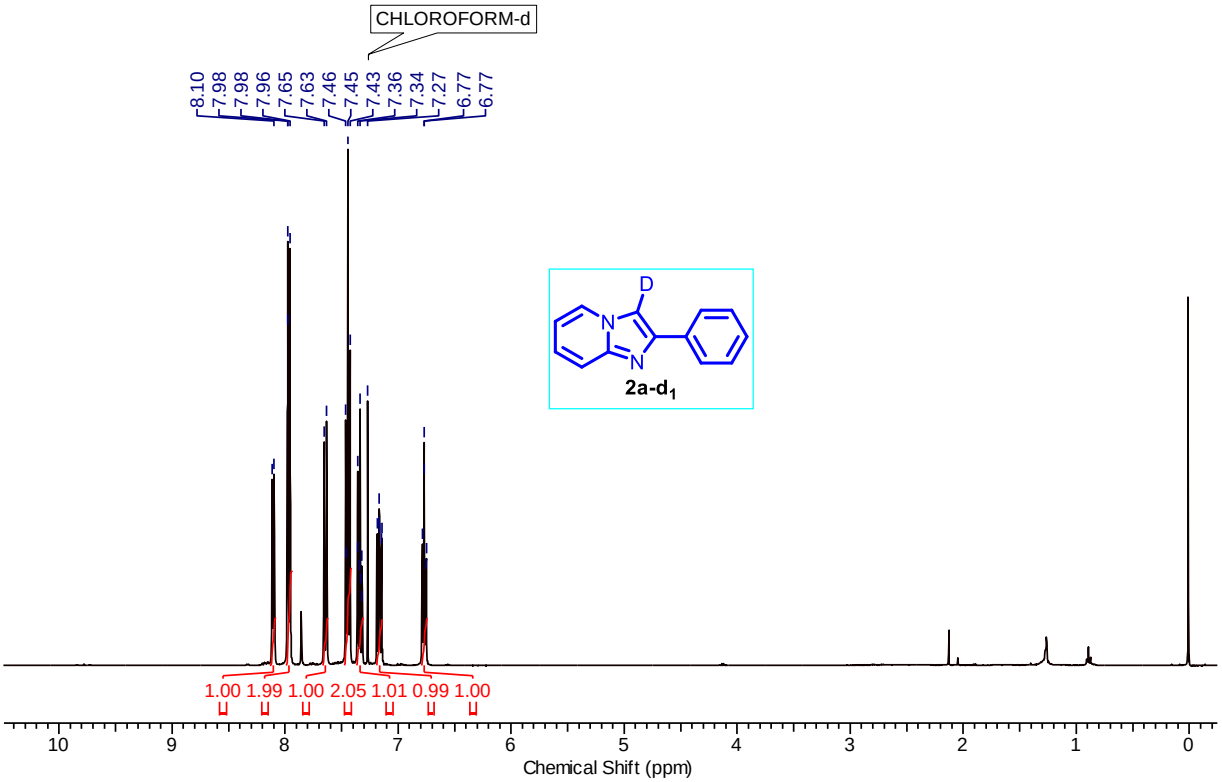
**2,6-Di-*tert*-butyl-4-((6-chloro-2-phenylimidazo[1,2-*a*]pyrazin-3-yl)(phenyl)methyl)phenol (3aq):**

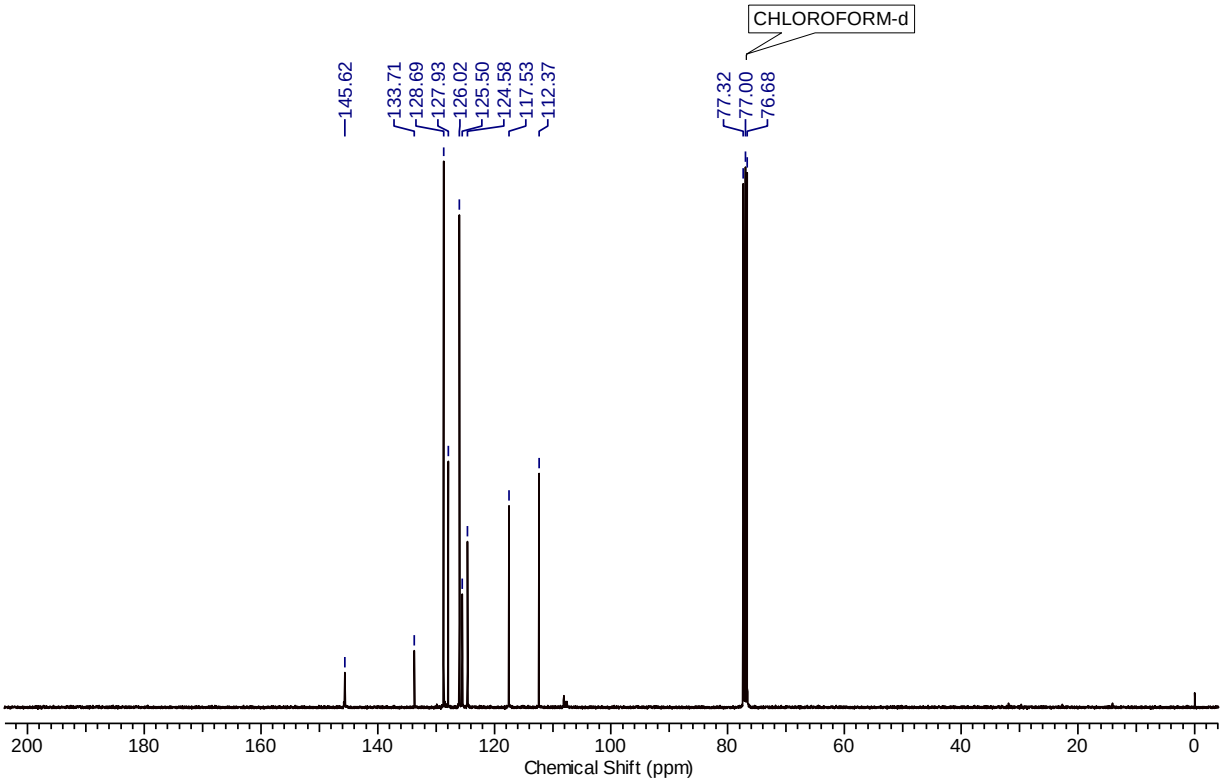


**2,6-Di-*tert*-butyl-4-((2-(4-(methylsulfonyl)phenyl)imidazo[1,2-*a*]pyridin-3-yl)(phenyl)methyl)phenol (3ar):**

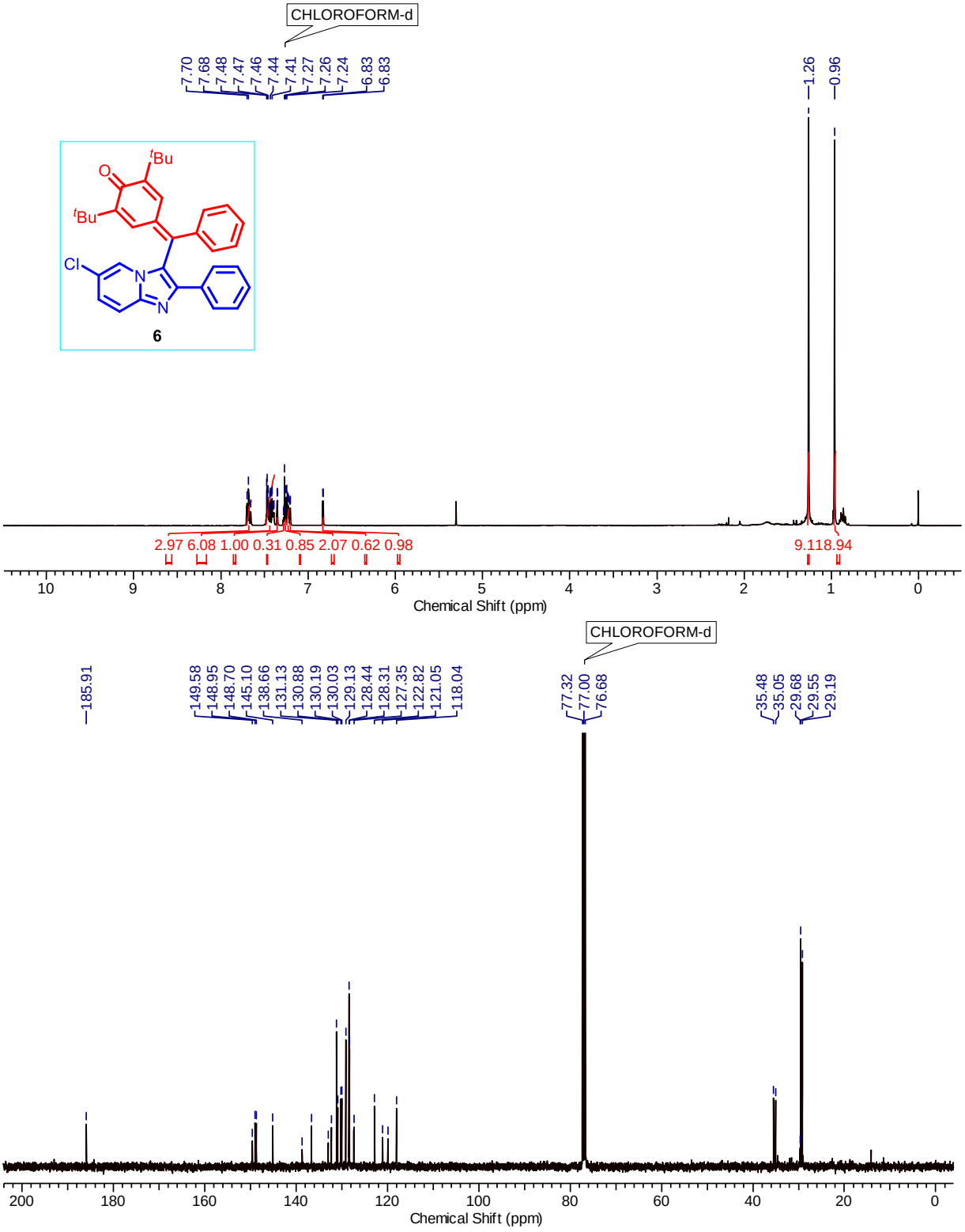


**2-Phenylimidazo[1,2-*a*]pyridine-3-d (2a-$d_1$):**



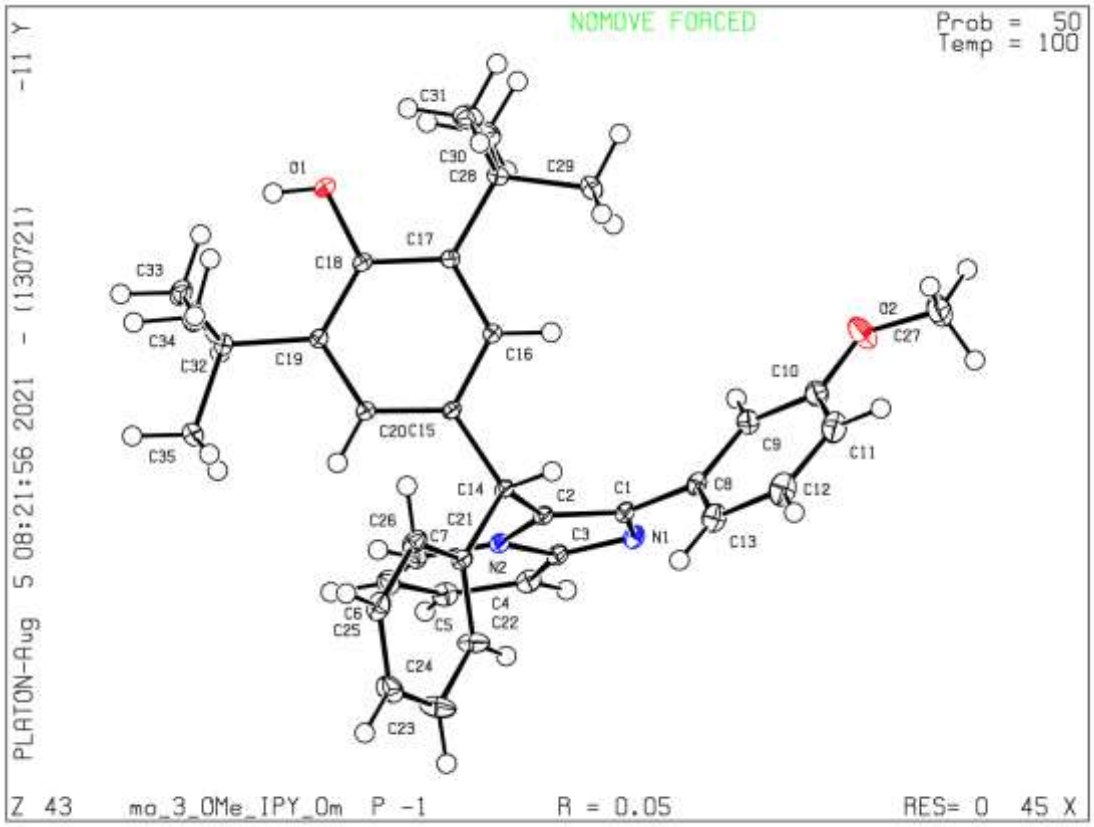
**2,6-Di-*tert*-butyl-4-((6-chloro-2-phenylimidazo[1,2-*a*]pyridin-3-yl)(phenyl)methylene)cyclohexa-2,5-dien-1-one (6):**



## 2B.8 XRD

An X-ray intensity data measurement of compound **3ad** was carried out on a Bruker D8 VENTURE Kappa Duo PHOTON II CPAD diffractometer equipped with Incoatech multilayer mirrors optics. The intensity measurements were carried out with Mo micro-focus/fine-focus sealed tube diffraction source ($MoK_\alpha$ = 0.71073Å) at 100 K temperature.

**X-ray crystallographic parameters of compound 3ad**




Bond precision: C-C = 0.0008 Å Wavelength = 0.71073

Cell: a = 10.6359 (14) b = 12.1651 (16) c = 13.3136 (18)

alpha = 117.113 (3) beta = 98.937 (3) gamma = 101.497 (3)

Temperature: 100 K

| | Calculated | Reported |
|---|---|---|
| Volume | 1441.5(3) | 1441.5(3) |
| Space group | P -1 | P -1 |
| Hall group | -P 1 | -P 1 |
| Moiety formula | $C_{35}$ $H_{38}$ $N_2$ $O_2$ | $C_{35}$ $H_{38}$ $N_2$ $O_2$ |
| Sum formula | $C_{35}$ $H_{38}$ $N_2$ $O_2$ | $C_{35}$ $H_{38}$ $N_2$ $O_2$ |
| Mr | 518.67 | 518.67 |
| Dx, g $cm^{-3}$ | 1.195 | 1.195 |
| Z | 2 | 2 |
| Mu ($mm^{-1}$) | 0.074 | 0.074 |
| F000 | 556.0 | 556.0 |
| F000’ | 556.21 | |
| h, k, l max | 20,23,25 | 20,22,25 |
| Nref | 20447 | 20272 |
| Tmin, Tmax | 0.990,0.993 | 0.990,0.993 |
| Tmin’ | 0.990 | |

Correction method = # Reported T Limits: Tmin = 0.990 Tmax = 0.993

AbsCorr = MULTI-SCAN

Data completeness = 0.991 Theta (max) = 42.251

R (reflections) = 0.0451 (17135) wR2 (reflections) = 0.1595(20272)

S = 1.140 Npar = 360

## 2B.9 References


1. a) Al-Qawasmeh, R. A.; Lee, Y.; Cao, M.-Y.; Gu, X.; Vassilakos, A.; Wright, J. A.; Young, A. *Bioorg. Med. Chem. Lett.* **2004,** *14*, 347–350. b) Parai, M. K.; Panda, G.; Chaturvedi, V.; Manju, Y. K.; Sinha, S. *Bioorg. Med. Chem. Lett.* **2008,** *18*, 289–292. c) Palchaudhuri, R.; Nesterenko, V.; Hergenrother, P. J. *J. Am. Chem. Soc.* **2008,** *130*, 10274–10281. d) Shiri, M.; Zolfigol, M. A.; Kruger, H. G.; Tanbakouchian, Z. *Chem. Rev.* **2010,** *110*, 2250–2293. e) He, Q. -L.; Sun, F. -L.; Zheng, X. -J.; You, S. -L. *Synlett* **2009,** 1111–1114. f) Duxbury, D. F. *Chem. Rev.* **1993,** *93*, 381–433. g) Li, X.; Xu, X.; Wei, W.; Lin, A.; Yao, H. *Org. Lett.* **2016,** *18*, 428–431.
2. a) Ghodsi, R.; Hemmateenejad, B. *Med. Chem. Res.* **2016,** *25*, 834–842. b) Antus, S. *Tetrahedron* **1982,** *38*, 133–137. c) Cho, S. D.; Yoon, K.; Chintharlapalli, S.; Abdelrahim, M.; Lei, P.; Hamilton, S.; Khan, S.; Ramaiah, S. K.; Safe, S. *Cancer Res.* **2007,** *67*, 674–683. d) Wood, P. M.; L. Woo, W. L.; Labrosse, J.-R.; Trusselle, M. N.; Abbate, S.; Longhi, G.; Castiglioni, E.; Lebon, F.; Purohit, A.; Reed, M. J.; Potter, B. V. L. *J. Med. Chem.* **2008,** *51*, 4226–4238.
3. a) Conn, M. M.; Jr. Rebek, J. *Chem. Rev.* **1997,** *97*, 1647–1668. b) Mondal, S.; Panda, G. *RSC Adv.* **2014,** *4*, 28317–28358.
4. Roy, D.; Panda, G. *Synthesis* **2019,** *51*, 4434–4442.
5. a) More, S. G.; Suryavanshi, G. M. *Org. Biomol. Chem.* **2019,** *17*, 3239–3248. b) Zhang, J.; Liu, J.; Dai, L.; Ge, Y.; Xu, L.; Xia, Y.; Xu, L.; Rong, L. *J. Heterocyclic Chem.* **2021,** *58*, 1179–1191.
6. a) Sharma, B. M.; Rathod, J.; Gonnade, R. G.; Kumar, P. *J. Org. Chem.* **2018,** *83*, 9353–9363. b) Sharma, B. M.; Shinde, D. R.; Jain, R.; Begari, E.; Satbhaiya, S.; Gonnade, R. G.; Kumar, P. *Org. Lett.* **2018,** *20*, 2787–2791.
7. a) Wenjun, L.; Xianhong, X.; Pengfei, Z.; Pengfei, L. *Chemistry - An Asian Journal* **2018,** *13*, 2350–2359. b) Lima, C. G. S.; Pauli, F. P.; de Souza, D. C. S.; Costa, A. S.; Forezi, L. S. M.; Ferreira, V. F.; da Silva, F. de C. *Eur. J. Org. Chem.* **2020,** 2650–2692. c) Wang, J. -Y.; Hao, W. -J.; Tu, S. -J.; Jiang, B. *Org. Chem. Front.* **2020,** *7*, 1743–1778. d) Liu, X.; Wu, X.; Zhang, L.; Lin, X.; Huang, D. *Synthesis* **2020,** *52*, 2311–2329.
8. Breugst, M.; Bautista, F. C.; Herbert Mayr, H. *Chem. Eur. J.* **2012,** *18*, 127–137.

9. a) Wang, J.-R.; Jiang, X. -L.; Hang, Q. -Q.; Zhang, S.; Mei, G. -J.; Shi, F. *J. Org. Chem.* **2019,** *84*, 7829−7839. b) Goswami, P.; Anand, R. V. *ChemistrySelect* **2016,** *1*, 2556−2559.
10. Kumaran, S.; Prabhakaran, M.; Mariyammal, N.; Parthasarathy, K. *Org. Biomol. Chem.* **2020,** *18*, 7837−7841.
11. Gao, S.; Xu, X.; Yuan, Z.; Zhou, H.; Yao, H.; Lin, A. *Eur. J. Org. Chem.* **2016,** 3006−3012.
12. Zhou, T.; Li, S.; Huang, B.; Li, C.; Zhao, Y.; Chen, J.; Chen, A.; Xiao, Y.; Liu, L.; Zhang, J. *Org. Biomol. Chem.* **2017,** *15*, 4941−4945.
13. Ranga, P. K.; Ahmad, F.; Nager, P.; Rana, P. S.; Anand, R. V. *J. Org. Chem.* **2021,** *86*, 4994−5010.
14. a) Devi, N.; Singh, D.; Rawal, K. R.; Bariwal, J.; Singh, V. *Current Topics in Medicinal Chemistry* **2016,** *16*, 2963−2994. b) Kishbaugh, T. L. S. *Current Topics in Medicinal Chemistry* **2016,** *16*, 3274−3302. c) Wu, H. Y.; de O. Silva, J.; Becker, S.; Becker, J. O. *Journal of Pest Science* **2021,** *94*, 573−583. d) Fisher, M. H.; Lusi, A. *J. Med. Chem.* **1972,** *15*, 982−985.
15. a) Krause, M.; Foks, H.; Gobis, K. *Molecule* **2017,** *23*, 399−423. b) Goel, R.; Luxami, V.; Paul, K. *Current Topics in Medicinal Chemistry* **2016,** *16*, 3590−3616.
16. a) Tashrifi, Z.; Mohammadi-Khanaposhtani, M.; Larijani, B.; Mahdavi, M. *Eur. J. Org. Chem.* **2020,** 269−284. b) Ma, C. -H.; Chen, M.; Feng, Z. -W.; Zhang, Y.; Wang, J.; Jiang, Y. -Q.; Yu, B. *New J. Chem.* **2021,** *45*, 9302−9314. c) Said, M. S.; Mishra, A.; Pandole, S.; Nayak, R. A.; Kumar, P.; Gajbhiye, J. M. *Asian J. Org. Chem.* **2019,** *8*, 2143−2148.
17. Sanger, D. J.; Depoortere, H. *CNS Drug Reviews* **1998,** *4*, 323−340.
18. Sanger, D. J. *Behavioural Pharmacology* **1995,** *6*, 116−126.
19. Wafford, K. A.; van Niel, M. B.; Ma, Q. P.; Horridge, E.; Herd, M. B.; Peden, D. R. *Neuropharmacology* **2009,** *56*, 182−189.
20. Lafzi, F.; Kilic, H. *Asian J. Org. Chem.* **2021,** *10*, 1814−1821.
21. Bhattacharya, T.; Ghosh, A.; Maiti, D. *Chem. Sci.* **2021,** *12*, 3857−3870.
22. a) Satbhaiya, S.; Khonde, N. S.; Rathod, J.; Gonnade, R.; Kumar, P. *Eur. J. Org. Chem.* **2019,** 3127−3133. b) Rathod, J.; Sharma, B. M.; Mali, P. S.; Kumar, Pradeep *Synthesis* **2017,** *49*, 5224−5230.

23. Sharma, B. M.; Shinde, D. R.; Jain, R.; Begari, E.; Satbhaiya, S.; Gonnade, R. G.; Kumar, P. *Org. Lett.* **2018,** *20*, 2787−2791.
24. Chu, W. D.; Zhang, L. F.; Bao, X.; X. Zhao, H.; Zeng, C.; Du, J. Y.; Zhang, G. B.; Wang, F. X.; Ma, X. Y.; Fan, C. A. *Angew. Chem. Int. Ed.* **2013,** *52*, 9229−9233.
25. Li, Q.; Zhou, M.; Han, L.; Cao, Q.; Wang, X.; Zhao, L.; Zhou, J.; Zhang, H. *Chem Biol Drug Des* **2015,** *86*, 849−856.

# Chapter-3

# Fluorine in organic synthesis: Carbon-Fluorine bond forming reactions

### 3.1 Introduction

The small size and high electro-negativity values help the fluorine atom to bind at many active sites of enzymes and bio-molecules through hydrogen bonding.[1] Due to these ability incorporation of a fluorine atom in an organic molecule significantly alters pKa, stability, bio-selectivity, lipophilicity, permeability, metabolic pathways and pharmacokinetic properties.[2] Consequently, fluoro-organic chemistry has been exploited extensively in drug discovery,[3] agrochemical,[4] and material sciences.[5] At present, about 30% of the marketed drugs contain at least one fluorine atom and the number of fluorinated drugs is increasing exponentially.[6] The favourable half-life time of the $^{18}F$ isotope (109.8 min) led to applications in positron emission tomography (PET) using radiotracers labelled with $^{18}F$.[7]

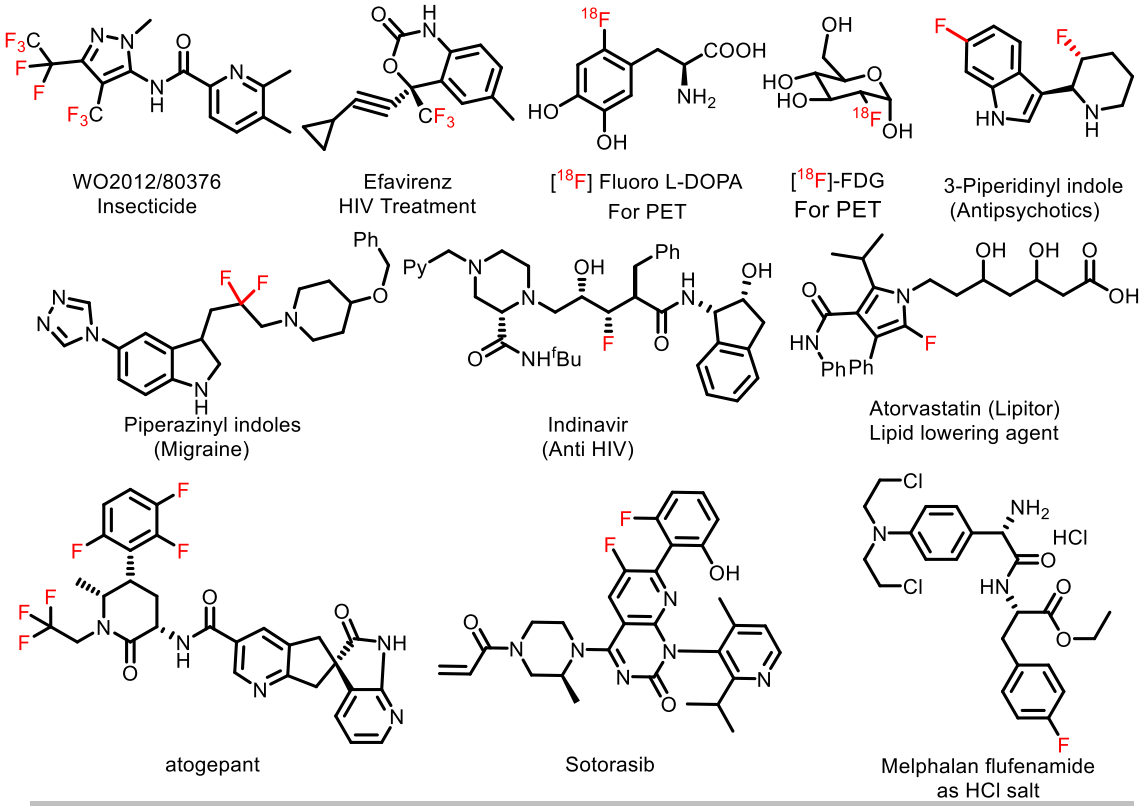



**Figure-1.** Fluorinated drugs available in the market

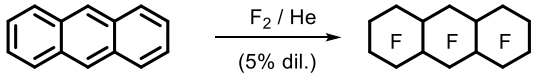
Besides, the high sensitivity of $^{19}F$ in NMR (nuclear magnetic resonance) and MRI (magnetic resonance imaging) experiments make this nucleus ideal for bio-analytical and bio-imaging studies.[8]

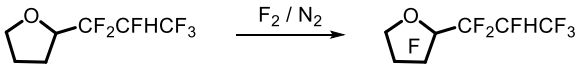
### 3.2 Synthesis of organofluorine compounds

Organofluorine compounds can be synthesized by following few general methods.

### 3.2.1 Direct fluorination using fluorine gas

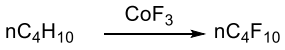
Fluorine is a pale yellow gas. It is known to liquify at -188 $^{o}$C to give a yellowish orange liquid, and solidify at -220 $^{o}$C to produce a yellow solid. Fluorine is one of the most reactive, substance and powerful oxidizing agent. Its name is derived from the Latin verb "fluere" (to flow).

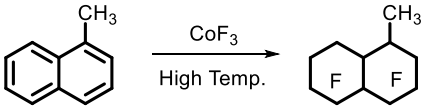



### 3.2.2 Fluorination using transition metal fluorides

Transition metal fluorides have been demonstrated for the fluorination of various organic compounds.




### 3.2.3 Fluorination using HF

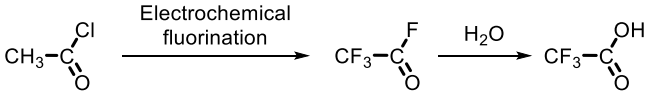
HF is known for the fluorination through two different mechanistic pathways i.e., oxidative fluorination and halogen exchange reaction.

**a) Oxidative fluorinations**

Oxidative fluorination could be achieved either by electrochemical method or by use of the additional oxidizing agents.

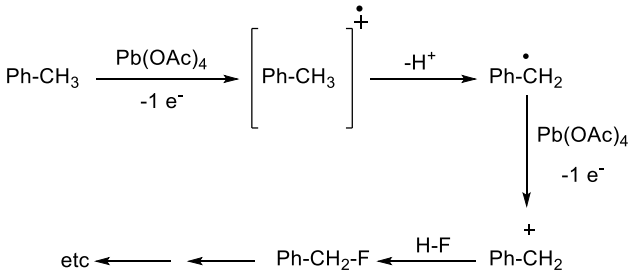
**i) Electrochemical fluorination**

Electrolysis of hydrogen fluoride solution at 5-6V, oxidized the fluoride to fluorine gas and that could be used for the fluorination reaction.



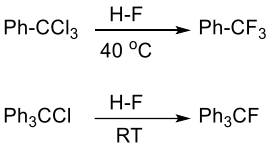

**ii) Other oxidative fluorination with HF**

Specific C-H bond could be functionalized to C-F bond by using supporting oxidizing agent with HF.




**b) Halogen exchange using hydrogen fluoride (HALEX)**

Halex is not an oxidative, it is just a formal nucleophilic substitution.

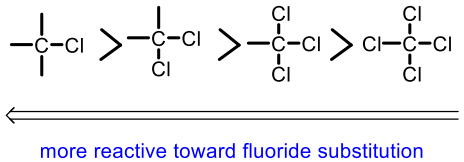



### 3.2.4 Fluorination using alkali metal fluorides

In aqueous medium the $F^-$ ion does not show a good nucleophilic character, but in aprotic solvent fluoride ion acts as powerful nucleophile so all metal fluoride reagent displayed reactivity in aprotic solvents.

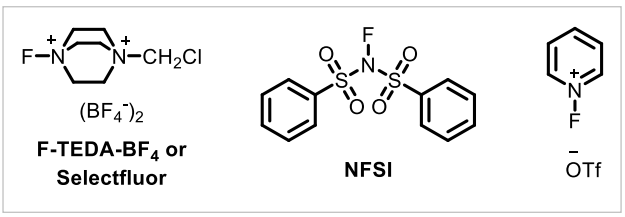
$$CsF \rangle KF \rangle\rangle NaF \rangle LiF$$

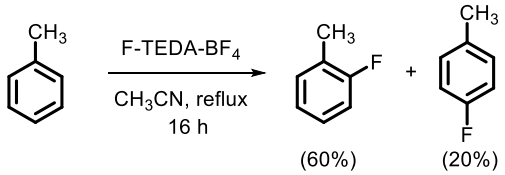
Potassium fluoride is more popular among the researcher due to its availability, stability and low cost.

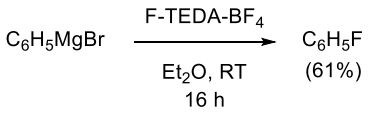



### 3.2.5 Electrophilic fluorination[9]

To incorporate fluorine atom in organic compound, the most of reports are for the application of the fluoride ion as fluorinating reagent. There are very few literature reports where fluorine is used as $F^+$ (electrophilic fluorine), there is wide scope for the exploration of electrophilic fluorination of organic compounds.

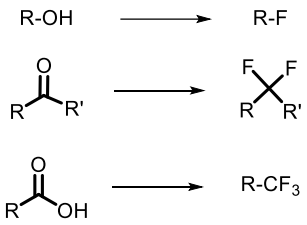





### 3.2.6 Sulfur tetrafluoride and other safer equivalents for fluorination

Recently, due to excellent fluorodeoxygenation reactivity of sulfur tetrafluoride, it became a popular fluorinating reagent.

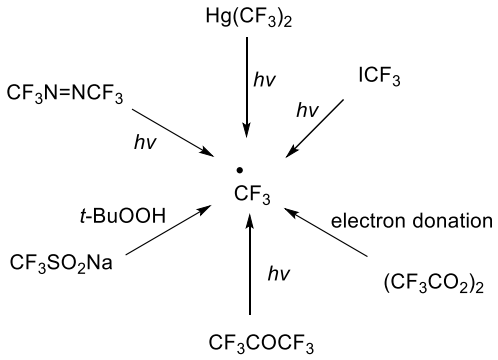



The safer "friendlier" fluorodeoxygenation, DAST $[(CH_3CH_2)_2N\text{-}SF_3]$ reagents is commercially available. DAST can replace hydroxyl group with fluoride and also it can convert carbonyl group to *gem*-difluoride functionality.


### 3.2.7 Fluorination using trifluoromethylating agents[10]

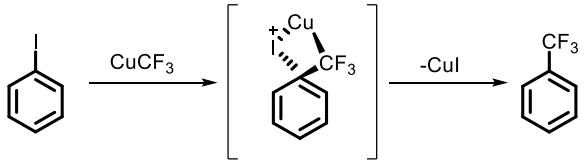
#### i) Trifluoromethylation via radical intermediate

Trifluoromethyl group can easily be incorporated in organic framework by using its active radical intermediates. There are several methods reported for the in *situ* generation of trifluoromethyl radical.



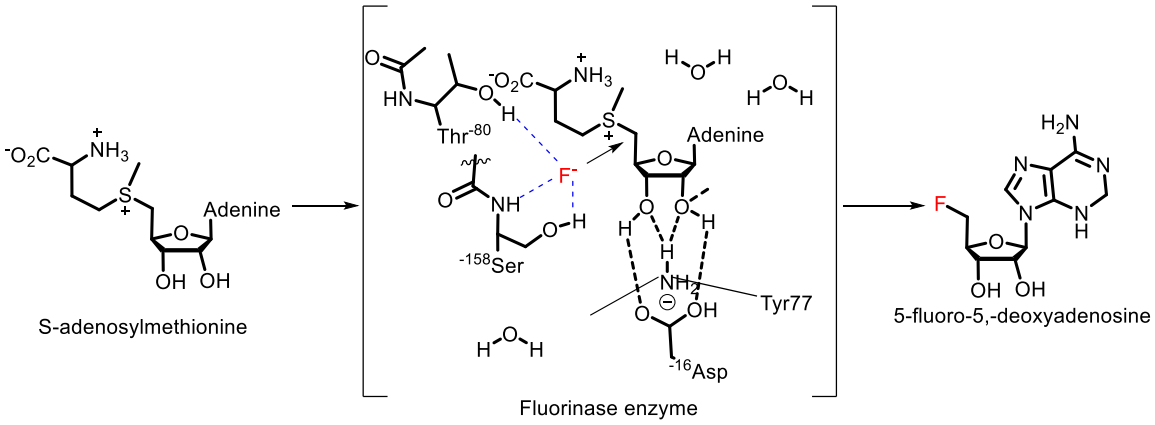
**ii) Trifluoromethylation via Nucleophilic reaction**

Due to very high importance of trifluoromethyl group in the pharmaceutically important molecules there is massive interest for the development of the best and efficient methodology for the incorporation of trifluoromethyl group in organic aromatic compounds. The much-explored area for that is conversion of aryl iodide to Ar-$CF_3$.




### 3.3 Hydrogen bonding discovery in fluorine chemistry

D. O'Hagan and co-workers reported nature's creativity of hydrogen-bonded fluoride complex mediation for the nucleophilic fluorination of *S*-adenosyl-L-methionine catalyzed by the fluorinase enzyme (Scheme-1). The crystal structure proves that fluorination reaction proceeds *via* nucleophilic displacement of the thionine leaving group using fluorine atom which is co-ordinated through hydrogen bonding.[11]



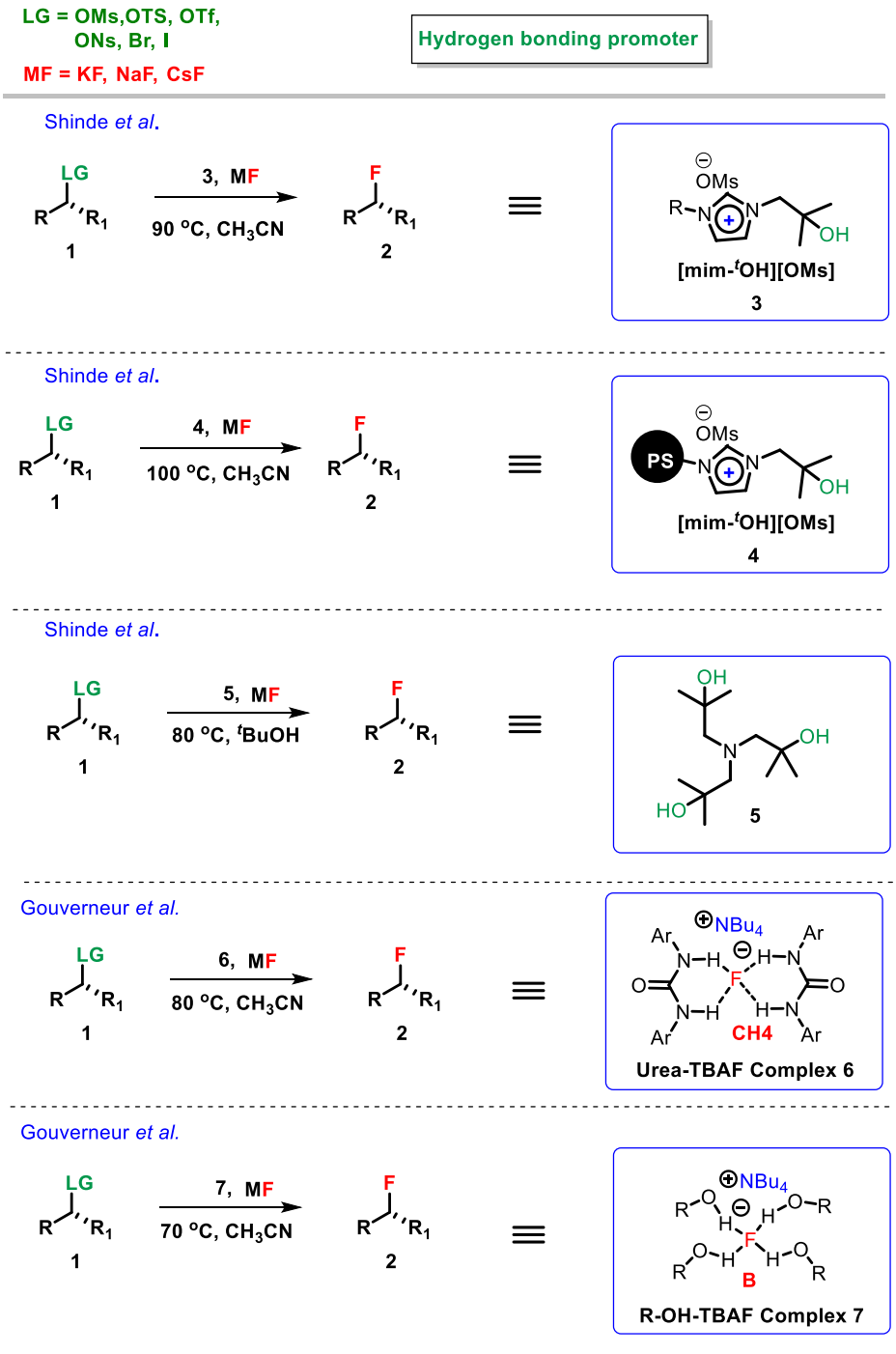

**Scheme-1.** Nature's nucleophilic fluorination

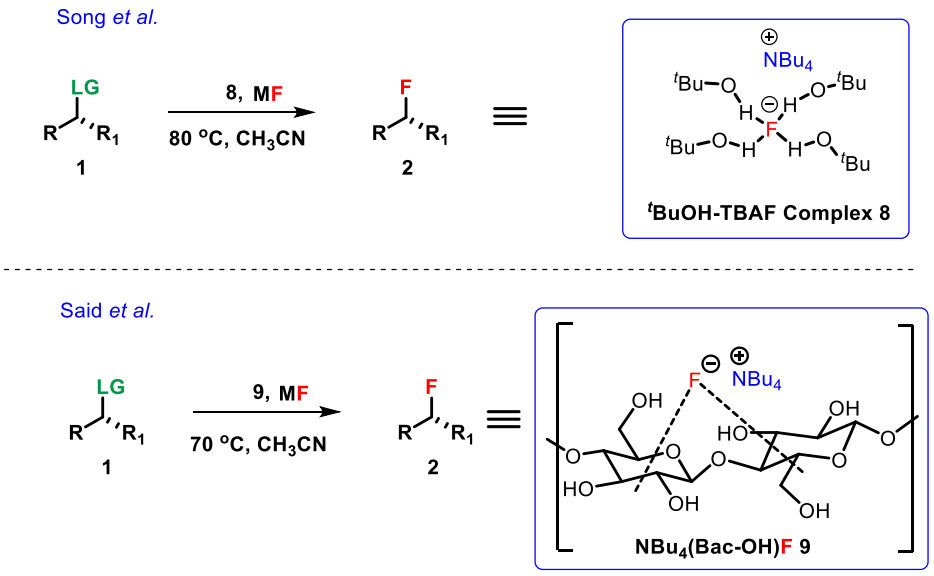
These hydrogen bonding interactions reduce the basicity of fluoride, consequently enhancing ''Effective fluoride nucleophilicity.'' This extensive study shows that hydrogen bonding is a key factor in the nucleophilic fluorination reaction. Hydrogen bonding enhances the nucleophilicity, reduces the basicity and controls the reactivity of the fluorine atoms.[12]

### 3.4 Hydrogen bonding promoted $S_N2$ fluorination

After the discovery of hydrogen bonding in $S_N2$ fluorination, several hydrogen bonding assisted $S_N2$ fluorination are reported in the literature and few representative examples are depicted in Scheme-2. Lee and co-workers have developed a new n-oligo ethylene glycol

(oligoEGs) as multirole promoters for nucleophilic fluorination or other nucleophilic substitution reaction using alkali metal salts.[13]






**Scheme-2.** Hydrogen bonding promoted $S_N2$ fluorination

Recently, Shinde *et al.* developed polymer supported ionic liquid, a heterogeneous promoter for the $S_N2$ fluorination.[14] In continuation, we have also reported functionalized ionic liquid and tri–*tert*-butanolamine promoters for nucleophilic fluorination.[15] The Gouverneur group also synthesized a urea and alcohol complex with TBAF to study their reactivity toward the aliphatic fluorination.[16,17] Song and co-workers have reported ($^t$BuOH)$_4$/TBAF, a stable and less hydroscopic complex for the $S_N2$ fluorination.[18]

Very recently, Said and co-workers synthesized a cellulose supported TBAF, as stable and heterogeneous complex which they used it for aliphatic fluorination in batch and continuous flow reactions.[19]

### 3.5 Conclusion

Fluorine is an important element present in various medicinal and agrochemical substances. All fluorinating salt including metal fluoride and quaternary ammonium halides are basic in nature and known to give the alkene (E2 elimination) as the major product. Nature strongly recommended that the involvement of hydrogen bonding is an essential factor for the $S_N2$ fluorination. Hydrogen bonding increases nucleophilicity and reduced the basicity of the fluorine atom. The fluoride salts used with hydrogen bonding sources give $S_N2$ fluorination products in high percentage while the use of fluoride salts without hydrogen bonding furnishes elimination E2 product in high percentage.

### 3.6 References


1. O'Hagan, D.; Deng, H. *Chem. Rev.* **2015**, *115*, 634–649. b) Park, B. K.; Kitteringham, N. R.; O'Neill, P. M. *Annual review* **2001**, *41*, 443–470. c) Berkowitz, D. B.; Karukurichi, K. R.; Salud-Bea, R. D.; Nelson, L.; McCune, C. D. *J. Fluor Chem.* **2008,** *129*, 731–742.
2. a) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359–4365. b) Shah, P.; Westwell, A. D. *J. Enzyme Inhib. Med. Chem.* **2007**, *22*, 527–540. c) O'Hagan, D. *Chem. Soc. Rev*. **2008**, *37*, 308–319. d) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315–8359.
3. a) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422–518. b) Fujiwara, T.; O'Hagan, D. *J. Fluor. Chem*. **2014**, *167*, 16–29.
4. a) Theodoridis, G. *Advances in Fluorine Science,* **2006**, *2,*121–175; b) Berger, R.; Resnati, G.; Metrangolo, P.; Weberd, E. J. *Chem. Soc. Rev.* **2011**, *40*, 3496–3508.
5. a) Chronopoulos, D. D.; Bakandritsos, A.; Pykal, M.; Zboˇriland, R.; Otyepka, M. *Appl. Mater. Today* **2017,** *9,* 60–70. b) Son, J. H.; Wang, W.; Xu, T.; Liang, Y.; Wu, Y.; Li, G.; Yu, L. *J. Am. Chem. Soc*. **2011,** *133*, 1885–1894. c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320–330.
6. a) Wang, J.; Sánchez-Roselló, M.; Aceña, J.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Soc. Rev*. **2014**, *114*, 2432–2506. b) Schwarzenberg, J.; Radu, C. G.; Benz, M.; Fueger, B.; Tran, A. Q.; Phelps, O. M.; Witte, E. N.; Satyamurthy, N.; Czernin, J.; Schiepers, C. *Eur. J. Nucl. Med. Mol. Imaging* **2011**, *38*, 711–721.
7. a) Mitterhauser, M.; Wadsak, W. *Pharmaceuticals* **2014,** *7*, 765–778. b) Preshlock, S.; Tredwell, M.; Gouverneur, V. *Chem. Rev*. **2016**, *116*, 719–766.
8. a) Miller, P. W.; Long, N. J.; Vilar, R.; Gee, A. D. *Angew. Chem. Int. Ed.* **2008**, *47*, 8998–9033. b) Scott, P. J. H. *Angew. Chem. Int. Ed.* **2009**, *48*, 6001–6004. c) Alauddin, M. M. *Am. J. Nucl. Med. Mol. Imaging* **2012**, *2*, 55–76.
9. Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999,** *55*, 12431–12477.
10. Bhowmick, A. C. *J. Sci. Res.* **2021,** *13*, 317–333.
11. a) O'Hagan, D.; Schaffrath, C.; Cobb, S. L.; Hamilton, J. T. G.; Murphy, C. D. *Natur*e **2002**, *416,* 279–280. b) O'Hagan, D.; Deng, H. *Chem. Rev.* **2015,** *115*, 634–649. c) Dong, C.; Huang, F.; Deng, H.; Schaffrath, C.; Spencer, J. B.; O'Hagan, D.; Naismith, J. H. *Nature* **2004**, *427*, 561–566.
12. a) Lee, J.; Oliveira, M. T.; Jang, H. B.; Lee, S.; Chi, D. Y.; Kim, D. W.; Song, C. E. *Chem.*

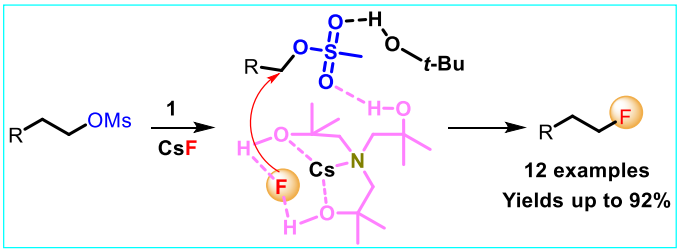
*Soc. Rev*. **2016**, *45*, 4638–4650. b) Ibba, Francesco.; Pupo, Gabriele.; Thompson, Amber L.; Brown, John M.; Claridge, Timothy D. W.; Gouverneur, Véronique. *J. Am. Chem. Soc.* **2020,** *142*, 46, 19731–19744.

13. Shinde, S. S.; Lee, B. S.; Chi, D. Y. *Org. Lett.* **2008**, *10*, 733–735.
14. Shinde, S. S.; Patil, S. N**.** *Org. Biomol. Chem.* **2014,** *12*, 9264–9271.
15. Shinde, S. S.; Khonde, N. S.; Kumar, P. *ChemistrySelect* **2017,** *2*, 118–122.
16. Pfeifer, L.; Engle, K M.; Pidgeon, G. W.; Sparkes, H. A.; Thompson, A. L.; Brown, J. M.; Gouverneur, V. *J. Am. Chem. Soc.* **2016**, *138*, 13314–13325.
17. Engle, K. M.; Pfeifer, L.; Pidgeon, G. W.; Giuffredi, G. T.; Thompson, A. L.; Paton, R. S.; Brown, J. M.; Gouverneur, V. *Chem. Sci*. **2015**, *6*, 5293–5302.
18. Lee, J. W.; Yan, H.; Jang, H. B.; Kim, H. K.; Park, S. W.; Lee, S.; Chi, D. Y.; Song, C.E. *Angew. Chem. Int. Ed.* **2009,** *48*, 7683–7686.
19. Said, M. S.; Khonde, N. S.; Thorat, M. N.; Atapalkar, R. S.; Kulkarni, A. A.; Gajbhiye, J. M.; Dastager, S. G. *Asian J. Org. Chem.* **2020,** *9*, 1022–1026.

# Chapter-4 (Section-A)

# Tri–*tert*-Butanolamine as an Organic Promoter in Nucleophilic Fluorination

## Abstract




Tri-*tert*-butanol amine acts as promoter with alkali metal salts in the nucleophilic fluorination of alkylsulfonates. It significantly enhances the reactivity of alkali metal salts with minimum formation of side-products (alkene, ether, and alcohol) compared to other catalysts in fluorination reaction. The synergism of *tert*-alcohol and amine moiety plays a pivotal role in fluorination.

## 4A.1 Introduction

In organic molecules, replacement of hydrogen by fluorine significantly enhances its bioactivity.[1] The fluorine atom has high electronegativity (3.98 on Pauling scale), small size (van der Waals radius 1.47 $A^{o}$), and lipophilicity like some fascinating features. Its small size minimizes structural change resulting into the low steric perturbation and stability of the compounds.[2] Due to these properties, incorporation of a fluorine atom into bioactive molecules can influence significantly pKa, bio-selectivity, permeability, pharmacokinetic and pharmacodynamic properties.[3]

The favorable half-life time of the $^{18}F$ isotope (109.8 min.) led to its application in development of imaging agents for positron emission tomography (PET) using radiotracers labelled with $^{18}F$.[4] In addition fluorinated compounds are used to investigate the biosynthetic pathway.[5]

In organic synthesis, displacement of alkylsulfonate/halide anion of specific aliphatic organo-molecules by fluorine atom is one of the most challenging task to organic chemists.[6] Various alkyl quaternary ammonium fluoride reagents have been developed for facilitating nucleophilic fluorination due to better solubility of fluoride ion in reaction.[7] Despite good solubility of alkyl quaternary ammonium fluoride reagents, some aspects of it concerning stability, moisture sensitivity, and by-product alkene formation issues need to be still addressed.

The alkali metal salts are abundant in nature, easily available and water soluble with reasonable stability. As metal salts are soluble in water, it is very beneficial from a practical

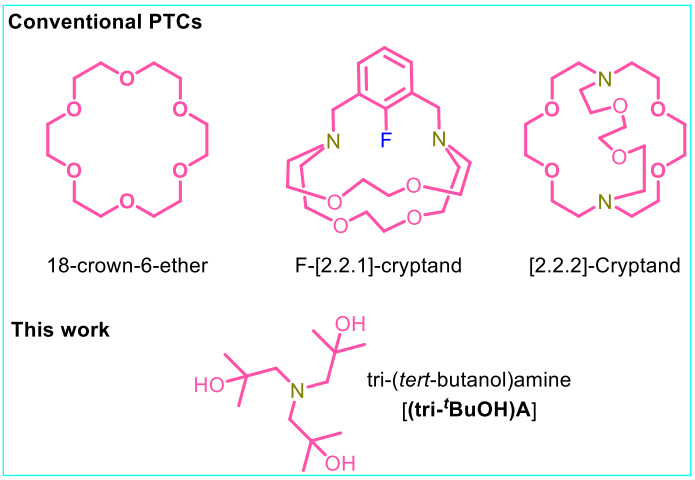


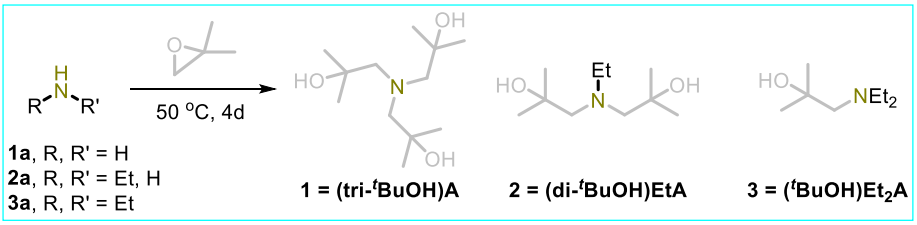

**Figure-1.** Structures of Representative PTCs and Tri-*tert*-butanolamine

point of view as it is easily washed after reaction during the work-up process. Thus, in industry for fluorination reaction, alkali metal fluoride is considered as favorite source of

fluorine. Besides these advantages, the use of alkali metal salt for nucleophilic fluorination reaction is not straight forward, because of their low solubility in organic media. To perform fluorination in organic media with alkali metal fluoride salts, various phase transfer catalyst (PTC)[8] has been used such as macrocyclic crown ethers,[8a] macrobicyclic cryptands,[8b] (Figure-1) polydentate ligands,[8c] ionic liquids[9] and oligoethylene glycols (PEG).[10] These phase transfer catalysts facilitate the solubility of alkali metal fluorides to generate active fluorine and accelerate the rate of reaction significantly. However, some of the PTCs are quite expensive and their synthesis requires lengthy procedure[11] and it is also sometimes difficult to extract polar products from IL/PEG. To overcome these problems the protic solvents such as *tert*-BuOH, *tert*-amyl alcohol are found suitable media for nucleophilic fluorination using CsF.[12] Our earlier finding of the specifically designed hybridized molecule [mim-$^t$OH][OMs] containing *tert*-OH and imidazolium IL, acts as an efficient catalyst[13] by not only enhancing the reactivty of metal fluoride but also providing the chemoselectivity of product compared to other protocols[14] in the nucleophilic substitution reactions. The bifunctional ionic liquid has the combined cooperative effect of IL and *tert*-OH group in the $S_N2$ fluorination.[15] We postulated that such a process can also occur in the simple alkylamine containing *tert*-BuOH moiety, which has half identical structure moiety to that of the [2.2.2]cryptand (Figure-1).

### 4A.2 Present Work

Keeping literature background in mind and to validate our hypothesis herein, we wish to describe the unraveled role of *tert*-butanolamine (Figure-1) as promoter/ligand for nucleophilic fluorination with various substrates of sulfonate esters and halo-leaving groups. *tert*-Butanol functionalized amines **1–3** were synthesized by modifying the procedure reported by Mun *et al.* (Scheme-1).[16]




**Scheme-1.** Synthesis of *tert*-butanol amines

A solvent-free reaction of isobutylene oxide and substituted ethylamine or ammonia at 50 $^o$C for 4 days yielded quantitatively with respect to Tri-*tert*-butanolamine [(tri-$^t$BuOH)A] **1**, 1-[Ethyl (2-hydroxy-2-methylpropyl) amino]-2-methyl propan-2-ol [(di-$^t$BuOH)EtA] **2**, and 1-

(Diethylamino)-2-methyl-2-propanol [(mono-$^{t}$BuOH)Et$_2$A] **3**. Compounds **1–2** are obtained as while solid, compound **3** is liquid at room temperature.

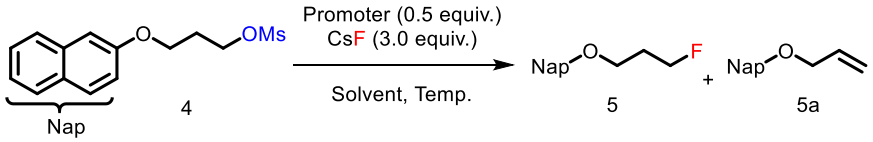
### 4A.3 Results and Discussion

#### 4A.3.1 Optimization of reaction conditions

Table-1 demonstrates the reactivity of PTC (18-crown-6) including synthesized *tert*-BuOH amine promoters **1, 2,** and **3** in fluorination of 2-(3- methanesulfonyloxypropyl) naphthalene **(4)** as a model compound with alkali metal fluorides TBAF, CsF, NaF, KF, and RbF in protic (*t*-BuOH, *t*-amyl alcohol) and aprotic media ($CH_3CN$) at 60 $^{o}$C, 80 $^{o}$C and 100 $^{o}$C respectively. Reaction of 2-(3- methanesulfonyloxypropyl) naphthalene **(4)** with TBAF in absence of promoter in $CH_3CN$ at 60 $^{o}$C for 1 h produced 40% desired fluoroalkane **5** along with 55% side-product alkene **5a (Table-1, entry 1)**. The traditional 18-crown-6-ether in $CH_3CN$ at 60 $^{o}$C for 6 h with CsF gave the desired 2-(3-fluoropropyloxy) naphthalene in 46% yield along with alkene as by-product **(Table-1, entry 2)**. Same reaction was performed with CsF in $CH_3CN$ at 60 $^{o}$C for 3 h in the presence of synthesized promoters **1, 2** and **3** having various *tert*-BuOH moieties, affording desired fluoroalkane **5** along with small amount of side-product alkene **5a**. However, the (tri-$^{t}$BuOH)A **(1)** catalyzed reaction, afforded **5** in higher 84% yield, much better compared to promoters **3** in 59% and **2** in 72% yield **(Table-1, entries 3-5)**. These results suggest that (tri-$^{t}$BuOH)A, may have chelating ability with metal fluoride, enabling fluoride as better nucleophile in the reaction. The reaction conditions were further optimized by carrying reaction using promoter **1** at 80 $^{o}$C instead of 60 $^{o}$C in $CH_3CN$ for 1 h, the amount of by-product increased significantly with 12% yield **(Table-1, entry 6)**. In order to optimize the reaction conditions, we switched from aprotic media and moved towards protic media. Interestingly, fluorination in the presence of promoter **1** in protic solvents, such as *tert*-BuOH or *tert*-amyl alcohol gave the desired fluoroalkane **5** in excellent 93% and 90% yield respectively within 2 h **(Table-1, entry 7-8)**. But the same reaction in the absence of promoter **1** took longer time, 6 h **(Table-1, entry 9)**.[12] On the other hand, slow reaction was observed with the use of 0.1 equiv. of promoter **1** affording only 68% yield of the product **(Table-1, entry 10)**. Similarly, the use of excess amount of promoter **1**, gave 76% yield of desired fluorinated product along with significant amount of by-product alkene 14% yield and trace amount of corresponding alkoxyethers **(Table-1, entry 11)**. Comparison of the reactivity with other alkali metal fluorides such as NaF, KF and RbF were also examined **(Table-1, entries 12-14)**. Reaction didn't proceed with NaF at all. While reaction

with KF and RbF produced the fluoro-product **5** in moderate to appreciable yield (34-78% yield).

**Table-1.** Nucleophilic Fluorination with Metal Fluorides using *t*-BuOH-Amine as a Promoter[a]




| Entry | Promoter (0.5 equiv.) | Solvent (3 mL) | Temp.( °C) | Time (h) | Products Yield (%)[b] | |
|---|---|---|---|---|---|---|
| | | | | | **5** | **5a** |
| 1 | TBAF/- | $CH_3CN$ | 60 | 1 | 40 | 55 |
| 2 | 18-crown-6 | $CH_3CN$ | 60 | 6 | 46 | 8 |
| 3 | CsF/**3** | $CH_3CN$ | 60 | 3 | 59 | 19 |
| 4 | CsF/**2** | $CH_3CN$ | 60 | 3 | 72 | 11 |
| 5 | CsF/**1** | $CH_3CN$ | 60 | 3 | 84 | 9[c] |
| 6 | CsF/**1** | $CH_3CN$ | 80 | 1 | 80 | 12[c] |
| **7** | **CsF/1** | ***t*-BuOH** | **80** | **2** | **93** | **Trace[c]** |
| 8 | CsF/**1** | *t*-amyl alcohol | 80 | 2 | 90 | ND[d] |
| 9[e] | CsF- | *t*-BuOH | 80 | 6 | 92 | ND |
| 10 | CsF/**1** (0.1 equiv.) | *t*-BuOH | 80 | 6 | 68 | ND |
| 11[f] | CsF/**1** (2.0 equiv.) | *t*-BuOH | 80 | 30 min. | 76 | 14 |
| 12 | NaF/**1** | *t*-BuOH | 100 | 12 | ND | ND |
| 13 | KF/**1** | *t*-BuOH | 80 | 6 | 34 | ND |
| 14 | RbF/**1** | *t*-BuOH | 80 | 3 | 78 | ND |

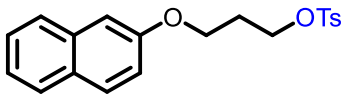
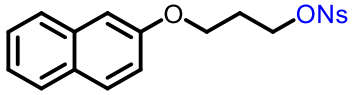
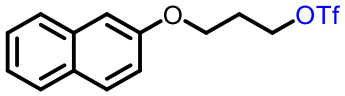
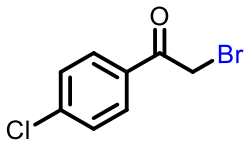
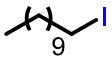
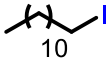
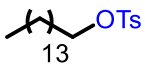
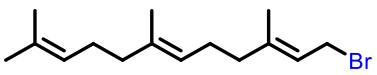
[a]All reactions were carried out on a 1.0 mmol scale of Mesylate-**(4)**, using 3.0 mmol of metal fluoride, 0.5 equiv. of (tri-$^t$BuOH)A in solvent at 80 $^o$C. [b]Isolated yield. [c]Determined by $^1$H NMR. [d]ND = Not detected. [e]see Ref.[12]. [f]Trace 2-(3-(*t*-butoxy)propoxy) naphthalene by-product observed.

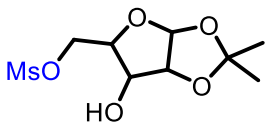
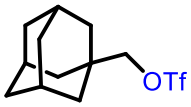
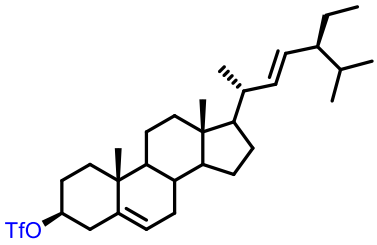
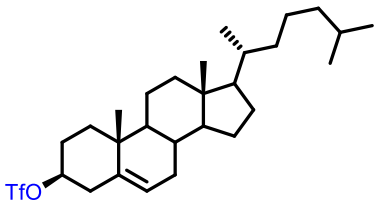
### 4A.3.2 Substrate scope

Having optimized the reaction conditions for fluorination **(Table-1, entry 7)**, we further explored this reaction to examine the generality with different substrates containing primary and secondary leaving groups such as triflate, tosylate, nosylate and halogen substituents as shown in **Table-2**. The reaction of OTf containing substrate in the presence of promoter **1** was much faster giving the desired fluoro-product **5** in 81% yield along with 6% yield of the alkene as side-product **(Table-2, entry 3)**. The proton NMR displayed the characteristic signals for 2 H attached to fluorine as multiplet at $\delta$ 4.79 - 4.64 ppm. In proton decoupled carbon NMR, the compound shows the signals for carbon attached to fluorine at $\delta$ 81.4 ($J_{C\text{-}F}$ = 164.03 Hz), and in proton decoupled fluorine NMR, the compound shows characteristic signal for fluorine at $\delta$ -221.95 which are in accordance with proposed structure. Further, the elemental formula was confirmed by the HRMS analysis. Interestingly, the reaction with OTs & ONs substrates gave fluoro-product **5** in 90% & 92% yields respectively **(Table-2, entry 1-2)**. Displacement of halogen from 4-chloro-bromoacetophenone to 4-chloro-fluoro acetophenone was found to be chemoselective furnishing good yield of corresponding fluorinated product **(Table-2, entry 4)**. Reaction of linear aliphatic substrates such as 1-iodoundecane in the presence of (tri-$^t$BuOH)A **(1)** gave 80% yield of the desired fluoro-product along with 16% corresponding alkene by-product **(Table-2, entry 5)**. In contrast to this result, the same reaction with 1-iodododecane in the presence of [2.2.2]cryptand furnished the by-product as major (69% yield) and fluoro-product as minor (31% yield) and reaction was also found to be very sluggish **(Table-2, entry 6)**.[19] These results suggest that the elimination of by-product is favored over nucleophilic fluorination in cryptand catalyzed reaction due to the generation of "naked" fluorine in much higher concentration in the reaction. When pentadecane substrate with tosylate as leaving group was used, it afforded 92% yield of fluoro-product **(Table-2, entry 7)**. These findings may be attributed to the coordinating properties of sulfonate ester moiety with (tri-$^t$BuOH)A **(1)** which enhances interactions with nucleophilic fluorine and leaving groups. The allylic bromo compound, a derivative of farnesol, and precursor for pyrophosphate synthesis in sesquiterpenoid biosynthesis, produced 1-fluoro-fernesol in 65% yield **(Table-2, entry 8)**. Over all, the salient features of this protocol are that it works additionally even with halogen substrates.

Further, the sugar molecule and admantane with primary OMs and OTf as leaving groups resulted in 87% and 80% yield of the corresponding fluoro-product respectively **(Table-2, entry 9-10)**. We have also performed the fluorination reactions on secondary leaving group of natural steroid substrates, such as stigmasterol and cholesterol containing OTf as a leaving group; these were successfully converted into 2-fluoro-stigmasterol and 2-fluoro-cholesterol in reasonable good yields (70%-82% yield) respectively **(Table-2, entry 11-12)**.

**Table-2.** (tri-$^{t}$BuOH)A **(1)** mediated Fluorination of Various Substrates[a]

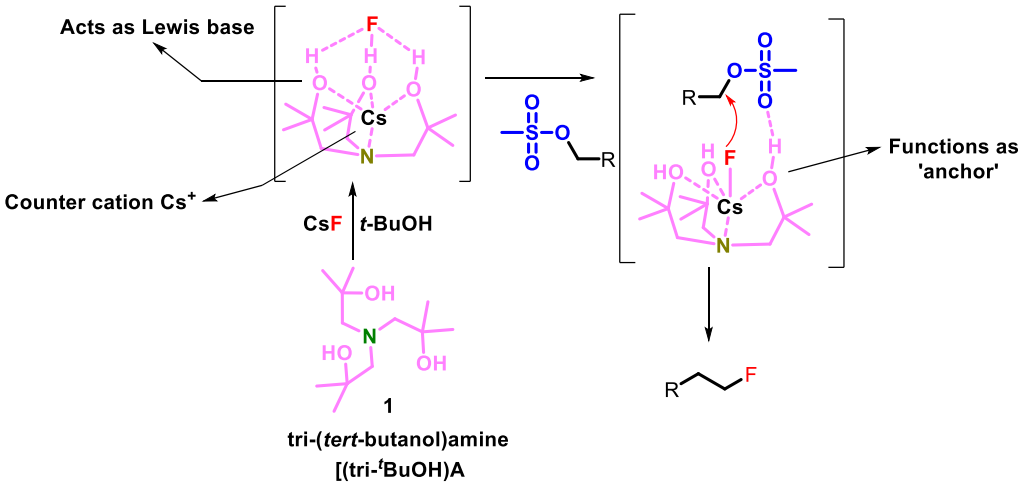
| Entry | Substrates | Temp.( $^{o}$C) | Time (h) | Yield (%)[b] | |
|---|---|---|---|---|---|
| | | | | F-product | alkene |
| 1 |  | 80 | 3 | 90 | ND[e] |
| 2 |  | 80 | 2.5 | 92 | ND |
| 3 |  | 80 | 50 min. | 81 | 6[c] |
| 4 |  | 80 | 2.5 | 84 | ND |
| 5 |  | 80 | 6 | 80 | 16 |
| 6[d] |  | 80 | 24 | 31 | 69 |
| 7 |  | 80 | 3 | 92 | ND |
| 8 |  | 80 | 4 | 65 | ND |

| | | | | | |
|---|---|---|---|---|---|
| 9 |  | 80 | 5 | 87 | ND |
| 10 |  | 80 | 7 | 80 | ND |
| 11 |  | 80 | 12 | 70 | 11[c] |
| 12 |  | 100 | 12 | 82 | 8 |

[a]Unless otherwise noted, All reactions carried out on 1.0 mmol scale of SM under condition of Table-1, entry 7. [b]Isolated yield. [c]Determined by $^1$H NMR. [d]From Ref. No. [19]. [e]ND = Not detected.

### 4A.3.3 The plausible reaction mechanism

Based on overall results, the -OH groups in the *t*-butanol moieties of promoter seem to act as Lewis base acting on the counter cation $Cs^+$, as in the case of fluorination promoted by *t*-butanol.[12] The role of nitrogen atom may also be similar, as depicted in Scheme-2.




**Scheme-2.** Proposed mechanism for fluorination

It would be especially interesting to examine whether the metal fluoride reacts as a contact ion pair (M…F) [10, 12, 17, 18] or as a "naked" nucleophile[20] (that is, dissociated MF; $M^+ + F^-$). Thus, we believe that the three terminal *tert*-OH of promoter **1** function as 'anchors' to collect the nucleophile and the substrate in an ideal configuration for the nucleophilic fluorination. However, the mechanism of the described reaction is not clear at this point, and this would need further study.

### 4A.4 Conclusion

In summary, we report the unique role of tri-*tert*-butanol amine, (tri-$^t$BuOH)A **(1)** as bifunctional promoter in nucleophilic fluorination using alkali metal salts, which significantly enhances the nucleophilicity of fluoride and minimizes the by-products formations such as alkene and ether in the reaction. (tri-$^t$BuOH)A **(1)** has various advantages, such as easy access, and easy handling due to solid state. Although the mechanism of this promoter metal complex formation remains to be elucidated, we have illustrated the application of tri-*tert*-butanolamine as promoter/ligand for alkali metal salts in specific reaction. We also believe that this fluorination strategy can be executed to prepare F-18-labelled radiotracers for positron emission tomography.

## 4A.5 Experimental Section

### 4A.5.1 General Information

All chemicals were obtained from commercial suppliers and were used without further purification unless otherwise stated. Flash chromatography was carried out using Merck silica gel 60 (230 - 400 mesh). Analytical thin layer chromatography (TLC) was performed with Merck Silica gel 60 $F_{254}$. Visualization on TLC was monitored by UV light or anisaldehyde indicator. $^{1}H$ and $^{13}C$ NMR spectra were obtained with a 400 or 500 MHz spectrometer and $^{19}F$ NMR obtained with a 376 MHz spectrometer in $CDCl_3$ solution. All chemical shifts ($\delta$) are reported in parts per million downfield from tetramethylsilane as internal standard. Spin multiplets are reported as s (singlet), d (doublet), t (triplet), q (quartet), br. (broad) and m (multiplet). Coupling constants (*J*) are reported in hertz (Hz).

### 4A.5.2 General Procedure: Synthesis of *tert*-butanolamine promoters 1, 2 & 3

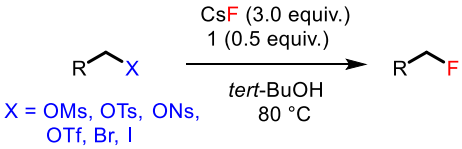
**Tri-*tert*-butanolamine [(tri-$^{t}$BuOH)A, 1]:** Isobutylene oxide (3.3 mmol) and ammonia (1.0 mmol, 7 N in MeOH) were added to a screw cap vial containing stirring bar. The vial was tightly sealed by Teflon tape. The mixture was maintained at room temperature for overnight and was then heated at 50 $^{o}$C for 4 days. The removal of volatile compounds at reduced pressure gave the desired product **1** as colorless solid in 97% yield. **mp** = 68 $^{o}$C. **$^{1}$H NMR** (500 MHz, $CDCl_3$) $\delta$ = 3.40 (br.s, 3 H), 2.74 (s, 6 H), 1.23 (s, 18 H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) $\delta$ = 70.7, 69.9, 28.4.

**1-[Ethyl (2-hydroxy-2-methyl propyl) amino]-2-methyl propan-2-ol [(di-$^{t}$BuOH)EtA, 2]:** Isobutylene oxide (2.2 mmol) and ethylamine (1.0 mmol) were added to a screw cap vial containing stirring bar. The vial was tightly sealed by Teflon tape. The mixture was maintained at room temperature for overnight and was then heated at 50 °C for 4 days. The removal of volatile compounds at reduced pressure gave the desired product **2** as colorless solid in 97% yield. **mp** = 41 $^{o}$C. **$^{1}$H NMR** (500 MHz, $CDCl_3$) $\delta$ = 3.43 (br.s, 2 H), 2.71 - 2.60 (m, 2 H), 2.60 - 2.52 (s, 4 H), 1.19 (s, 12 H), 1.03 (t, *J* = 7.1 Hz, 3 H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) $\delta$ = 71.1, 67.8, 53.3, 27.9, 12.6.

**1-(Diethyl amino)-2-methyl-2-propanol [(mono-$^{t}$BuOH)Et$_2$A, 3]:** Isobutylene oxide (1.1 mmol) and diethyl amine (1.0 mmol) were added to a screw cap vial containing stirring bar. The vial was tightly sealed by Teflon tape. The mixture was maintained at room temperature for overnight and was then heated at 50 $^{o}$C for 4 days. The removal of volatile compounds at reduced pressure gave the desired product **3** as yellow colour oil in 95%

yield. **$^{1}$H NMR** (500 MHz, $CDCl_3$) $\delta$ = 3.86 (br.s, 1 H), 2.68 - 2.58 (m, 4 H), 2.37 (s, 2 H), 1.14 (s, 6 H), 1.07 - 0.96 (t, 6 H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) $\delta$ = 68.7, 64.7, 49.2, 28.2, 12.1.

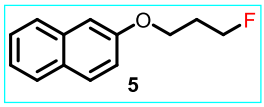
### 4A.5.3 General Procedure: $S_N2$ Fluorination




In a flame dried reaction vials or round bottom flask sulfonate, tosylate, nosylate, triflate and halide precursors (1.0 mmol) was taken in 3 mL *tert*-butanol followed by addition of tri-*tert*-butanolamine **1** (0.5 mmol) and CsF (3.0 mmol). The reaction was flushed using $N_2$ and heated at 80 $^{o}$C and reaction progress was monitored by TLC. The reaction mixture was filtered using small pad of $Na_2SO_4$ and solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography using (EtOAc/hexane) to afford fluorinated products.

**4A.6 NMR Data**

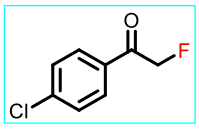
**2-(3-Fluoro-*n*-propoxy) naphthalene (5):** Synthesized according to General Procedure




4A.5.3 in 93% yield. 2-(3-Mesyl-*n*-propoxy) naphthalene was used as a substrate, to afford 2-(3-fluoro-*n*-propoxy) naphthalene as a colourless liquid. **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.83 - 7.71 (m, 3 H), 7.46 (t, $J$ = 7.3 Hz, 1 H), 7.39 - 7.33 (m, 1 H), 7.21 - 7.13 (m, 2 H), 4.79 - 4.64 (m, 2 H), 4.24 (t, $J$ = 6.1 Hz, 2 H), 2.34 - 2.18 (m, 2 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 156.7, 134.5, 129.4, 129.0, 127.6, 126.7, 126.4, 123.7, 118.8, 106.7, 81.4 ($J_{C\text{-}F}$ = 164.03 Hz), 63.5 ($J_{C\text{-}F}$ = 5.73 Hz), 30.5 ($J_{C\text{-}F}$ = 20.03 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -221.95. **HRMS** ($ESI^+$) *m/z* = calcd for $C_{13}H_{13}FO$ $[M]^+$ 204.2444, found 204.2446.

**……..**

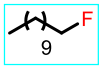
**1-(4-chlorophenyl)-2-fluoroethan-1-one:** Synthesized according to General Procedure




4A.5.3 in 84% yield. 2-bromo-1-(4-chlorophenyl)ethan-1-one (entry 4) was used as a substrate, to give 2-fluoro-1-phenylethan-1-one as a yellow colour liquid. **$^{1}$H NMR** (500 MHz, $CDCl_3$) $\delta$ = 7.87 (d, $J$ = 8.2 Hz, 2 H), 7.49 (d, $J$ = 8.7 Hz, 2 H), 5.55 - 5.43 (m, 2 H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) $\delta$ = 192.6 ($J_{C\text{-}F}$ = 15.33 Hz), 140.7, 132.1, 129.4, 129.4, 129.3, 84.5 ($J_{C\text{-}F}$ = 184.03 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -229.67. **HRMS** ($ESI^+$) *m/z* = calcd for $C_8H_6ClFO$ $[M]^+$ 172.5834, found 172.5830.

**……..**

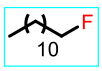
**1-Fluoroundecane:** Synthesized according to General Procedure 4A.5.3 in 80% yield. 1-




bromoundecane (entry 5) was used as a substrate, to give 1-fluoroundecane as a colourless liquid. **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 4.52 - 4.37 (m, 2 H), 1.77 - 1.63 (m, 2 H), 1.44 - 1.37 (m, 2 H), 1.28 (br. s., 14 H), 0.89 (t, $J$ = 6.7 Hz, 3 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 84.9 ($J_{C\text{-}F}$ = 164.03 Hz), 31.9, 30.5 ($J_{C\text{-}F}$ = 20.03 Hz), 29.6, 29.6, 29.6, 29.5, 29.3, 29.3, 25.2, 25.1, 22.7, 14.1; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -218.01. **HRMS** ($ESI^+$) *m/z* = calcd for $C_{11}H_{23}F$ $[M]^+$ 174.1784, found 174.1780.

**……..**

**1-Fluorododecane:** Synthesized according to General Procedure 4A.5.3 in 31% yield. 1-

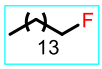



bromododecane (entry 6) was used as a substrate, to give 1-fluorododecane as a colourless liquid. **$^{1}$H NMR** (500 MHz, $CDCl_3$) $\delta$ = 4.50 - 4.38 (m, 2 H), 1.78 - 1.61 (m, 2 H), 1.39 (dd, $J$ = 14.3, 6.4 Hz, 3 H), 1.28 (br.s., 15 H), 0.89 (t, $J$ = 6.7 Hz, 3 H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) $\delta$ = 84.9 ($J_{C\text{-}F}$ = 164.44 Hz), 31.9, 30.5 ($J_{C\text{-}F}$ = 20.73 Hz), 29.6,

29.6, 29.6, 29.5, 29.3, 29.3, 25.2, 25.1, 22.7, 14.1; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -218.01. **HRMS** ($ESI^+$) *m/z* = calcd for $C_{12}H_{25}F$ $[M]^+$ 188.1940, found 188.1936.

**……..**

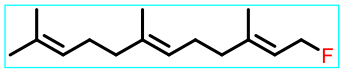
**1-Fluoropentadecane:** Synthesized according to General Procedure 4A.5.3 in 92% yield. 1-




Bromopentadecane (entry 7) was used as a substrate, to give 1-fluoropentadecane as a colourless liquid. **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 4.52 - 4.37 (m, 2 H), 1.77 - 1.63 (m, 2 H), 1.44 - 1.36 (m, 2 H), 1.35 - 1.24 (m, 22 H), 0.92 - 0.86 (m, 3 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 85.1 ($J_{C\text{-}F}$ = 164.03 Hz), 31.9, 30.5 ($J_{C\text{-}F}$ = 19.07 Hz), 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 25.2 ($J_{C\text{-}F}$ = 6.9 Hz), 22.7, 14.1; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -217.98. **HRMS** ($ESI^+$) *m/z* = calcd for $C_{15}H_{31}F$ $[M]^+$ 230.2410, found 230.2428.

**……..**

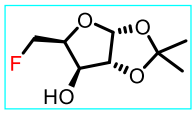
**(2*E*, 6*E*)-1-Fluoro-farnesane:** Synthesized according to General Procedure 4A.5.3 in 65%




yield. (2*E*, 6*E*)-1-bromo-farnesane (entry 8) was used as a substrate, to give (2*E*, 6*E*)-1-fluoro-farnesane as a colourless liquid. **$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$ = 5.50 (d, *J* = 7.3 Hz, 1 H), 5.11 (m, 2 H), 4.97- 4.85 (m, 2 H), 2.13 - 1.99 (m, 8 H), 1.73 (d, *J* = 4.9 Hz, 3 H), 1.69 (s, 3 H), 1.61 (s, 6 H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) $\delta$ = 144.2, 135.6, 131.4, 124.3, 123.5, 119.0 ($J_{C\text{-}F}$ = 17.73 Hz), 80.2 ($J_{C\text{-}F}$ = 156.44 Hz), 39.7, 39.5, 26.7, 26.1, 25.7, 17.7, 16.5, 16.0; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -207.62. **HRMS** ($ESI^+$) *m/z* = calcd for $C_{15}H_{25}F$ $[M]^+$ 225.1940, found 225.1938.

**……..**

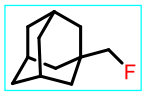
**5-(Fluoromethyl)-2, 2-dimethyltetrahydrofuro [2, 3-d][1, 3] dioxol-6-ol:** Synthesized




according to General Procedure 4A.5.3 in 87% yield. 5-(Mesylmethyl)-2, 2-dimethyltetrahydrofuro [2, 3-*d*][1, 3] dioxo-6-ol (entry 9) was used as a substrate, to give 5-(fluoromethyl)-2, 2-dimethyltetrahydrofuro [2, 3-*d*][1, 3] dioxol-6-ol, as a yellow colour liquid. **$^1$H NMR** (500 MHz, $CDCl_3$) δ = 6.30 (d, *J* = 3.4 Hz, 1 H), 5.23 (d, *J* = 3.7 Hz, 1 H), 5.17 - 5.10 (m, 1 H), 4.79 - 4.73 (m, 2 H), 4.31 - 4.25 (m, 1 H), 1.40 (s, 3 H), 1.43 (s, 3 H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) 113.9, 108.2, 87.5, 84.6, 78.3 ($J_{C\text{-}F}$ = 23.61 Hz), 77.22, 27.9, 27.2; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -222.18. **HRMS** ($ESI^+$) *m/z* = calcd for $C_8H_{13}FO_4$ $[M]^+$ 192.0798, found 192.0795.

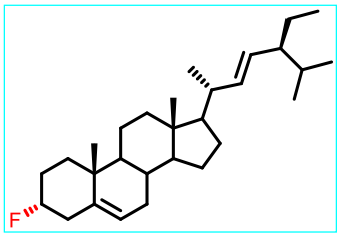
**……..**

**(3*r*, 5*r*, 7*r*)-1-(Fluoromethyl)adamantane:** Synthesized according to General Procedure 4A.5.3 in 80% yield. ((3*r*,5*r*,7*r*)-adamantan-1-yl)methyl trifluoromethanesulfonate (entry 10) was used as a substrate, to give (3*r*, 5*r*, 7*r*)-1-(fluoromethyl)adamantane as a colourless liquid. **$^{1}$H NMR** (500 MHz, $CDCl_3$) $\delta$ = 4.00 - 3.91 (m, 2 H), 2.01 (br. s., 3 H), 1.75 (d, $J$ = 12.2 Hz, 2 H), 1.67 (d, $J$ = 12.2 Hz, 2 H), 1.60 - 1.52 (m, 8 H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) $\delta$ = 93.6 ($J_{C\text{-}F}$ = 170.71 Hz), 38.2, ($J_{C\text{-}F}$ = 3.14 Hz), 37.0, 27.9; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -230.84 (t , $J$ = 47.92 Hz). **HRMS** ($ESI^+$) *m/z* = calcd for $C_{11}H_{17}F$ $[M]^+$ 168.1314, found 168.1320.



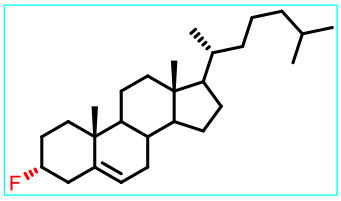
**……..**

**Stigmasteryl fluoride:** Synthesized according to General Procedure 4A.5.3 in 70% yield. Stigmasteryl triflate (entry 11) was used as a substrate, to give stigmasteryl fluoride as a yellowish solid. **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 5.34 (d, $J$ = 5.0 Hz, 1 H), 5.16 (dd, $J$ = 8.8, 15.3 Hz, 1 H), 5.02 (dd, $J$ = 8.6, 15.1 Hz, 1 H), 3.33 - 3.25 (m, 1 H), 2.33 - 2.20 (m, 2 H), 2.06 - 1.96 (m, 3 H), 1.89 - 1.80 (m, 2 H), 1.75 - 1.68 (m, 1 H), 1.56 - 1.49 (m, 6 H), 1.48 - 1.40 (m, 3 H), 1.27 (d, $J$ = 7.2 Hz, 2 H), 1.19 - 1.14 (m, 3 H), 1.06 - 1.00 (m, 9 H), 0.85 (d, $J$ = 6.1 Hz, 3 H), 0.81 (d, $J$ = 7.6 Hz, 6 H), 0.70 (s, 3 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ = 141.3, 138.3, 129.2, 121.3, 76.3, 56.9 ($J_{C\text{-}F}$ = 84.8 Hz), 51.2, 50.3, 42.2, 40.5, 40.0, 39.7, 37.4, 36.9, 31.9 ($J_{C\text{-}F}$ = 6.68 Hz), 29.4, 28.9, 25.4, 24.4, 21.2, 21.1, 19.4, 19.0, 12.2, 12.0; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -79.99. **HRMS** ($ESI^+$) *m/z* = calcd for $C_{29}H_{47}F$ $[M]^+$ 414.6934, found 414.6935.



**……..**

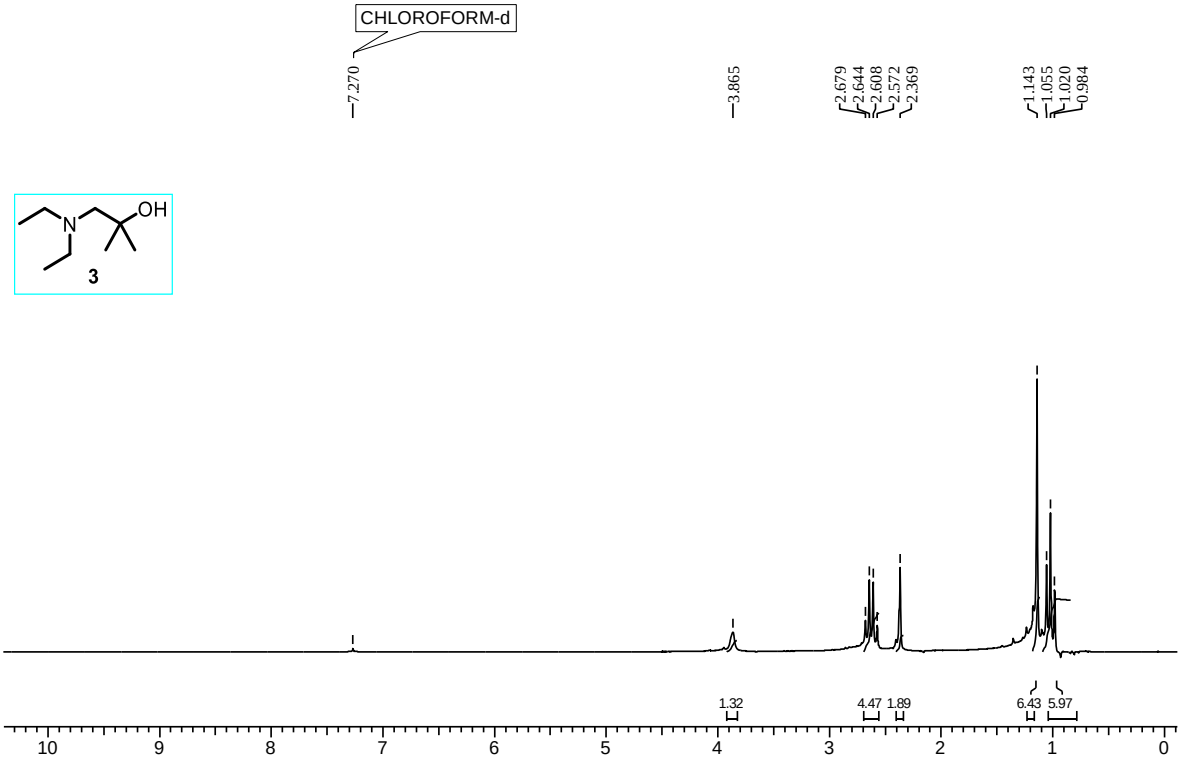
**Cholesteryl fluoride:** Synthesized according to General Procedure 4A.5.3 in 82% yield. Cholesteryl triflate (entry 12) was used as a substrate, to give cholesteryl fluoride as a yellowish solid. **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 5.37 - 5.29 (m, 1 H), 3.34 - 3.23 (m, 1 H), 2.34 - 2.17 (m, 2 H), 2.03 - 1.95 (m, 2 H), 1.88 - 1.81 (m, 3 H), 1.56 - 1.44 (m, 6 H), 1.39 - 1.24 (m, 6 H), 1.20 - 1.04 (m, 8 H), 1.01 (s, 4 H), 0.92 (d, $J$ = 6.5 Hz, 3 H), 0.89 - 0.86 (m, 6 H), 0.68 (s, 3 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 141.3, 121.3, 76.3, 56.8 ($J_{C\text{-}F}$ = 80.11 Hz), 50.3, 42.3, 40.1, 39.8, 39.5, 37.4, 36.9, 36.2, 35.8, 32.0 ($J_{C\text{-}F}$ = 7.63 Hz), 31.6, 29.4, 28.2, 28.0, 24.3, 23.8, 22.8, 22.6, 21.1, 19.4, 18.7, 14.1, 11.9; **$^{19}$F NMR** (376

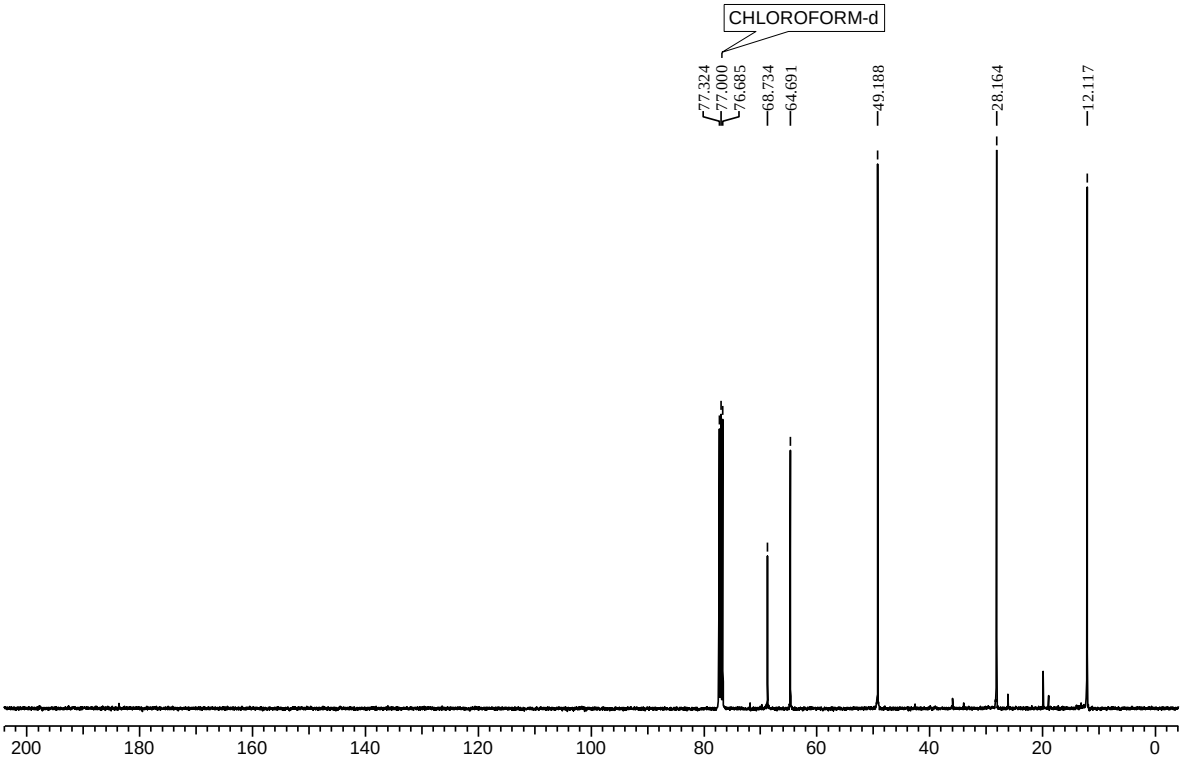


MHz, $CDCl_3$) $\delta$ = -79.47. **HRMS** ($ESI^+$) *m/z* = calcd for $C_{27}H_{45}F$ $[M]^+$ 388.6554, found 388.6551.

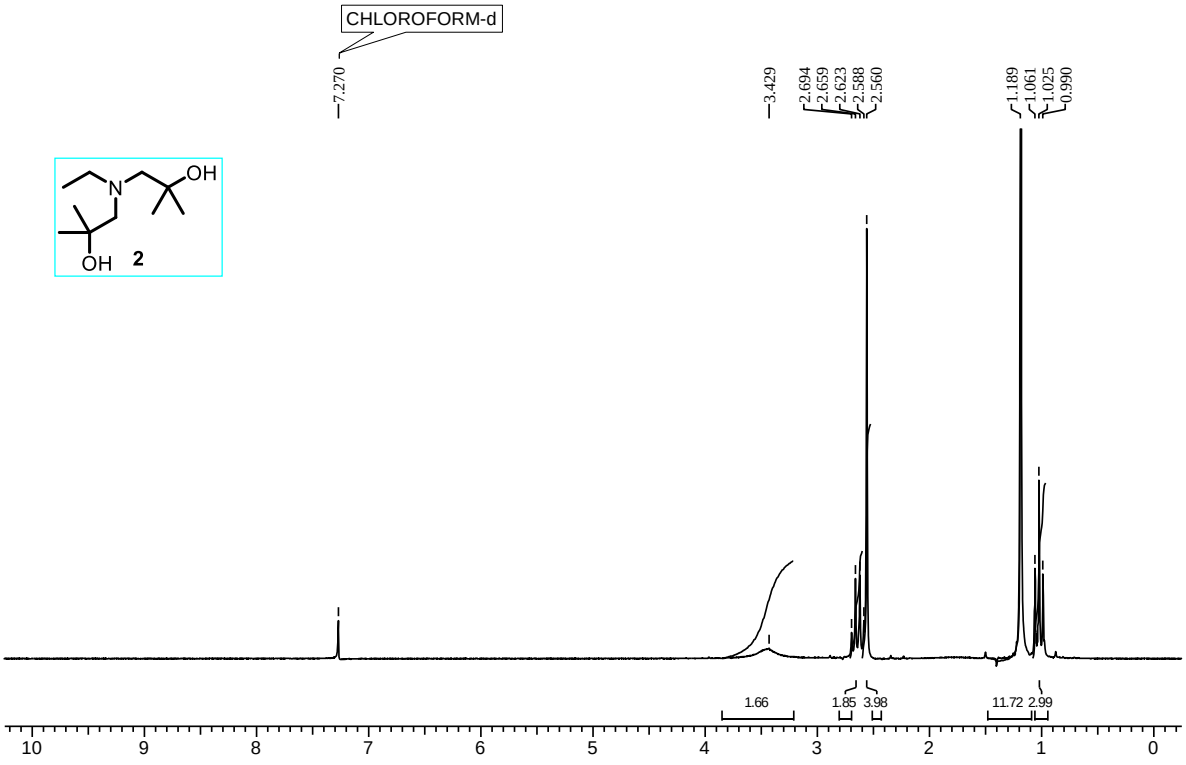
## 4A.7 NMR Spectra of promoters 1, 2 & 3

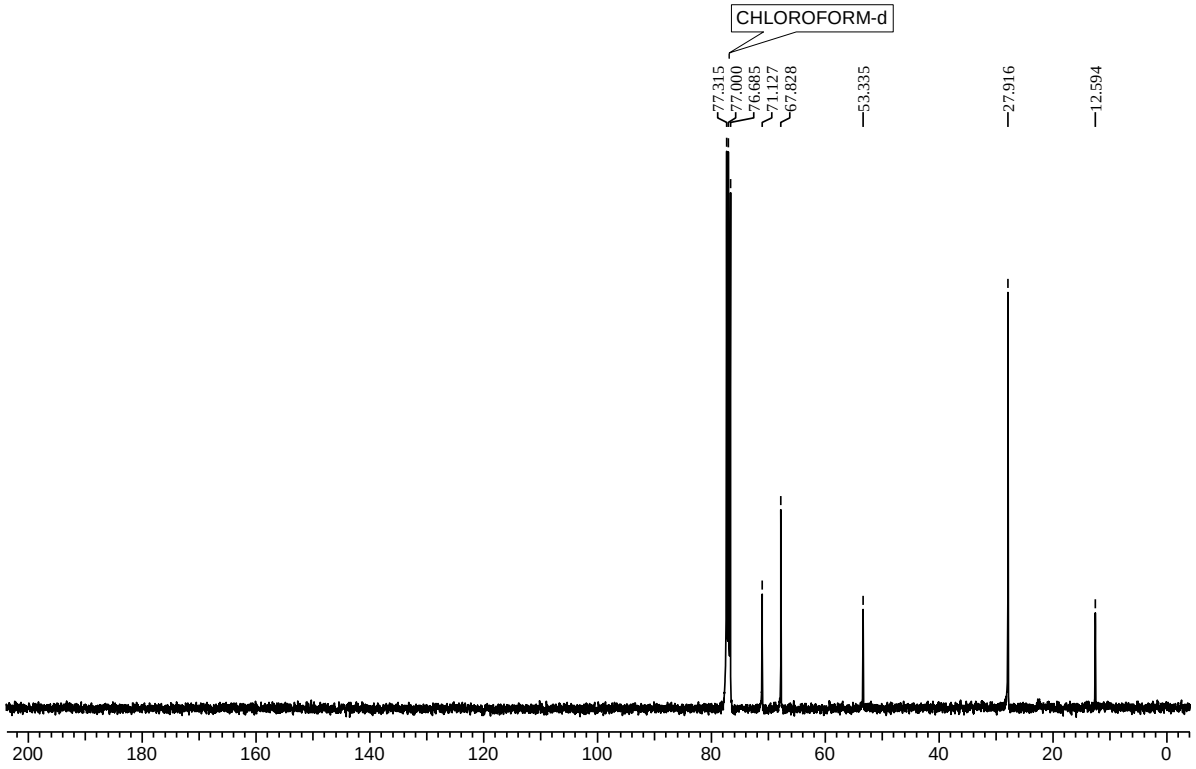
### 1-(Diethyl amino)-2-methyl-2-propanol (3)



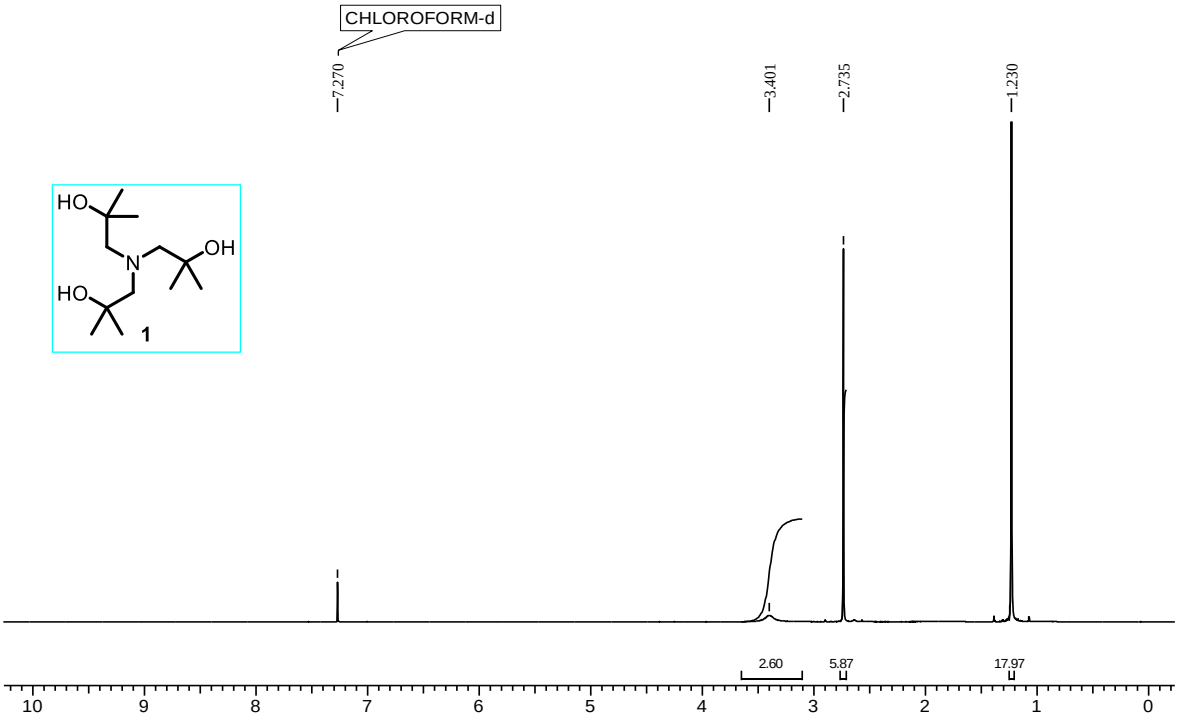



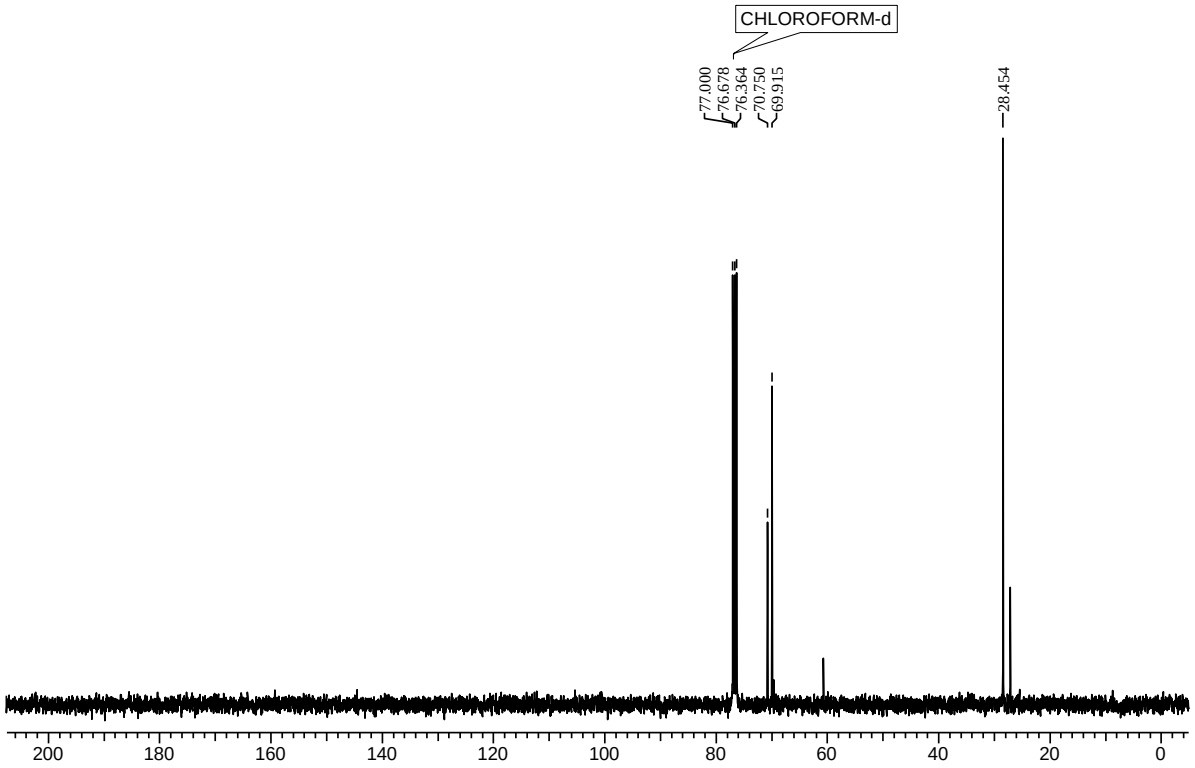
**1-[Ethyl (2-hydroxy-2-methyl propyl) amino]-2-methyl propan-2-ol (2)**



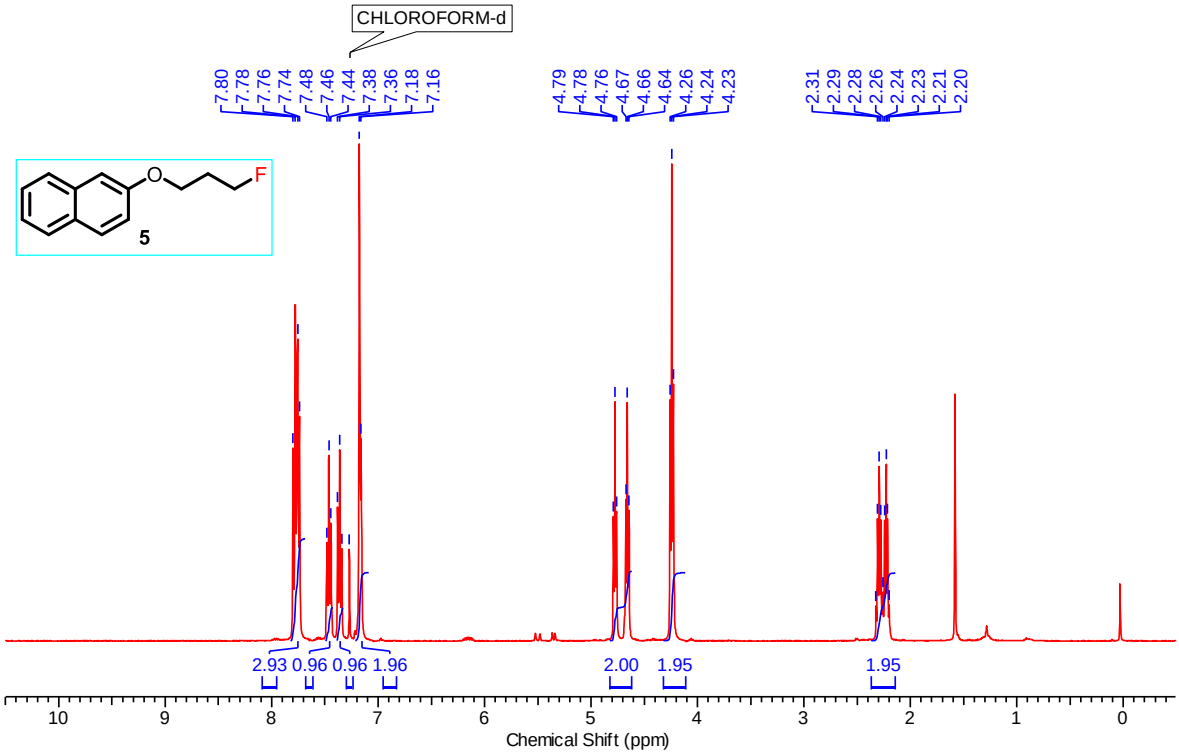
**Tri-*tert*- butanol amine (1)**

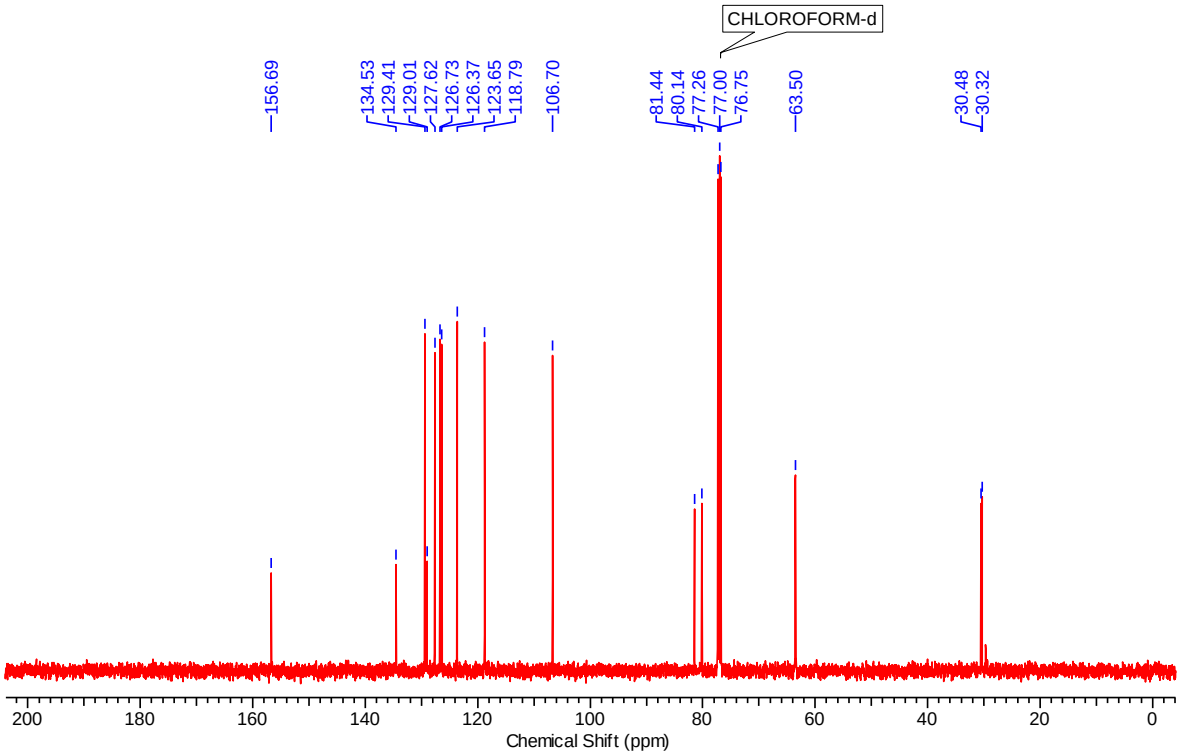


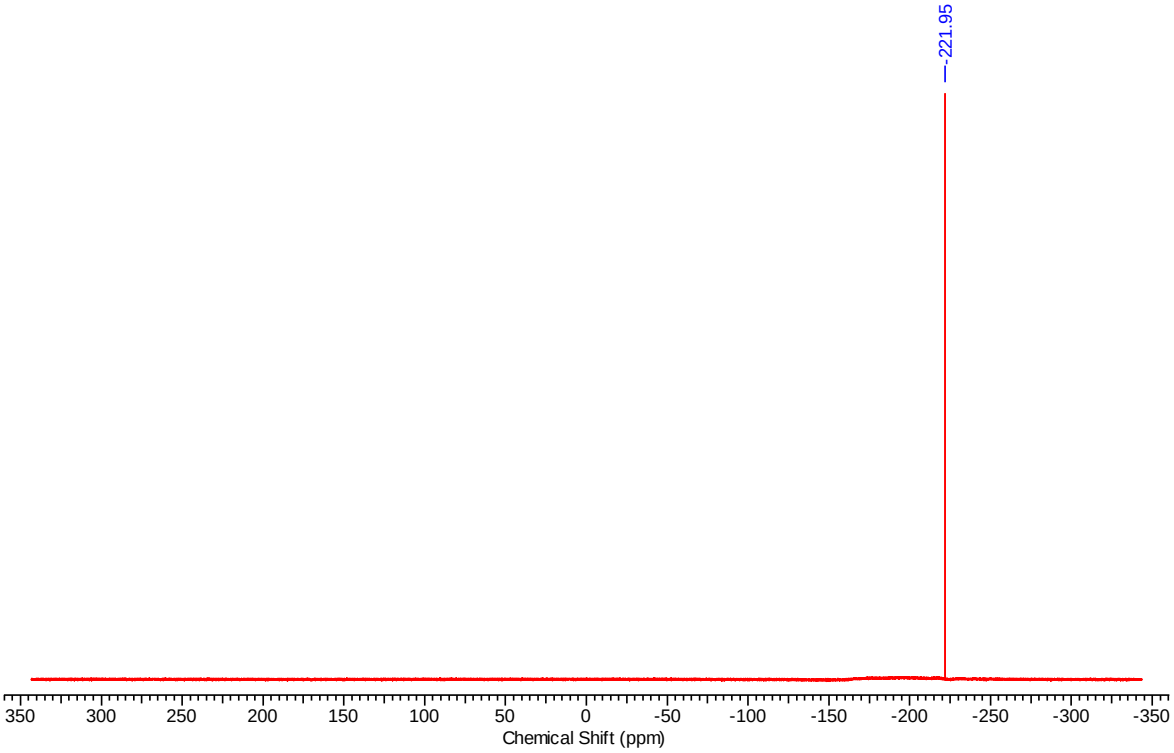



## 4A.8 NMR Spectra of Fluoro compounds

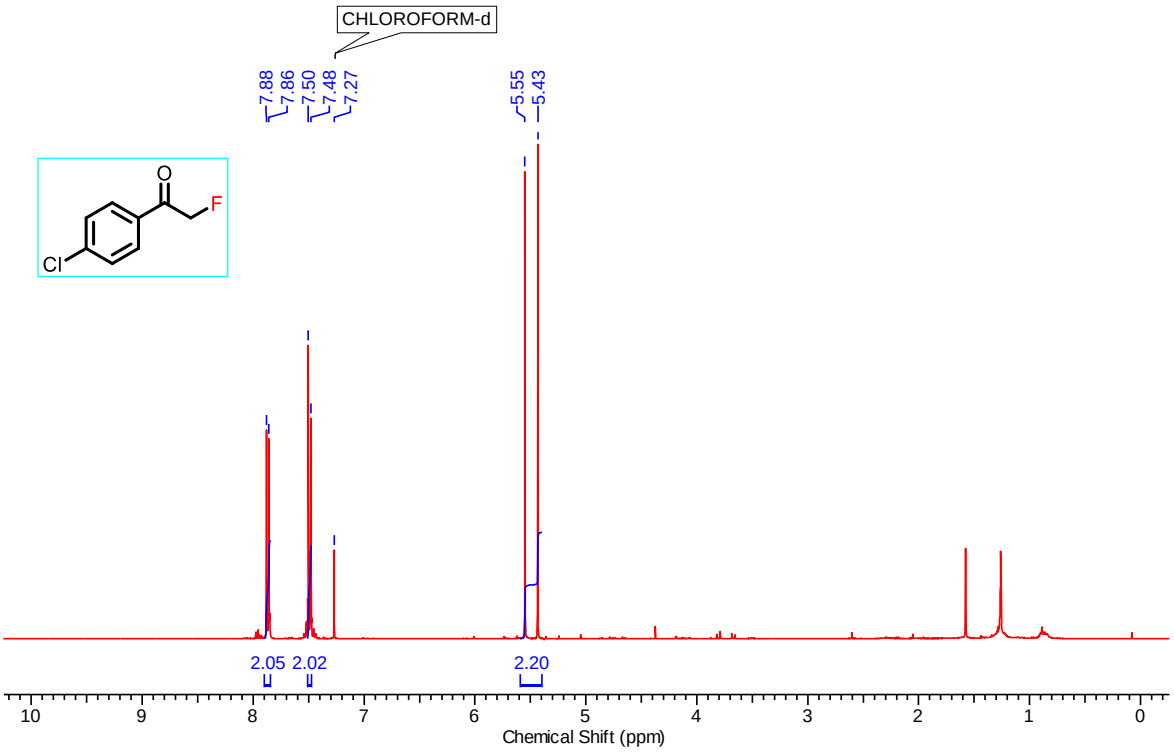
### 2-(2-Fluoro-*n*-propoxy) naphthalene (5)

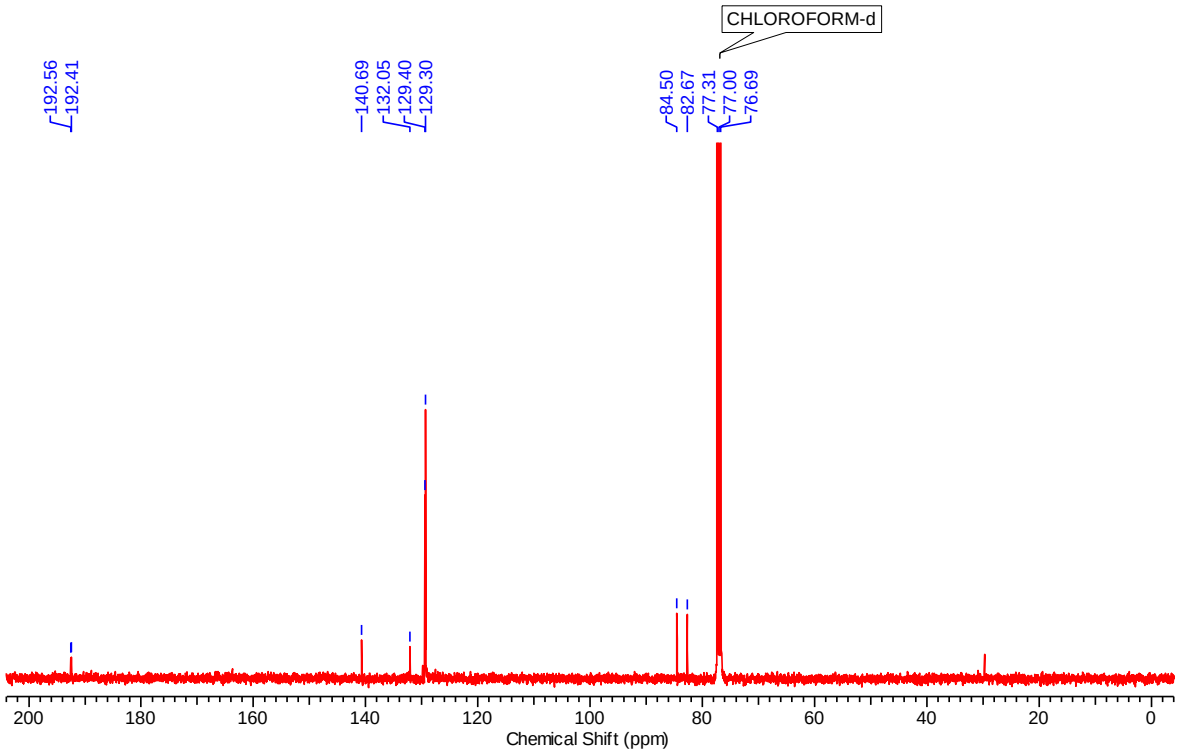


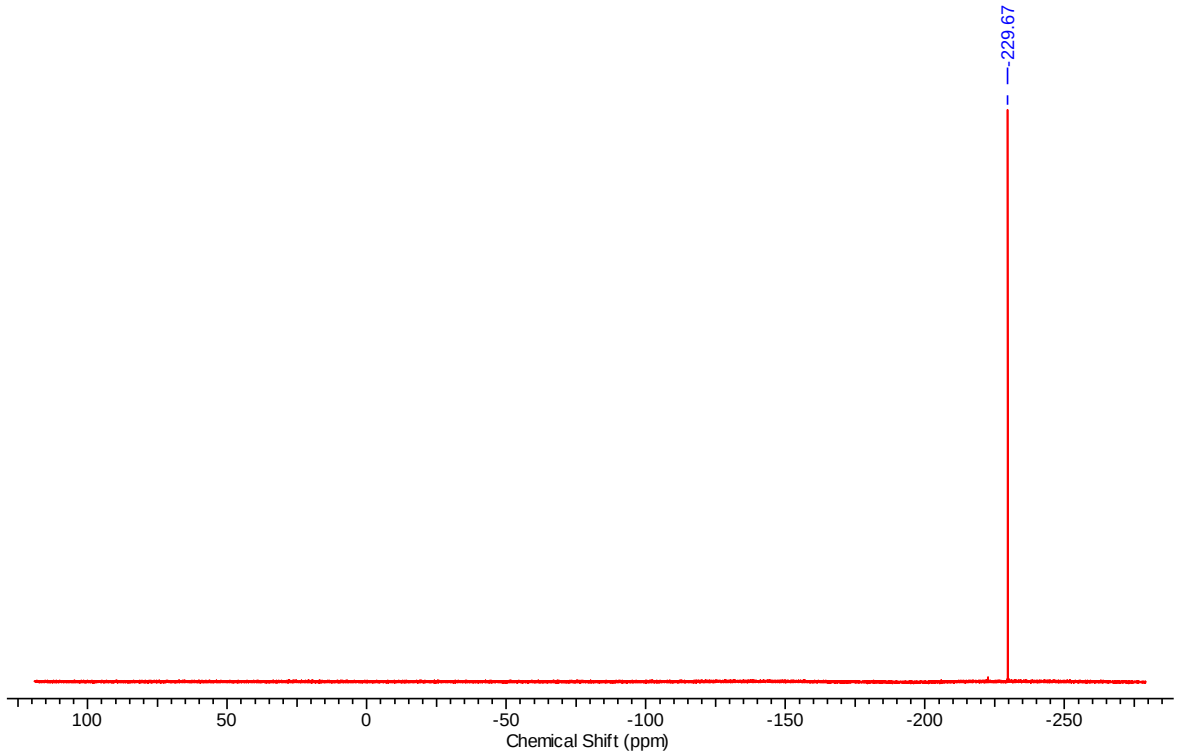





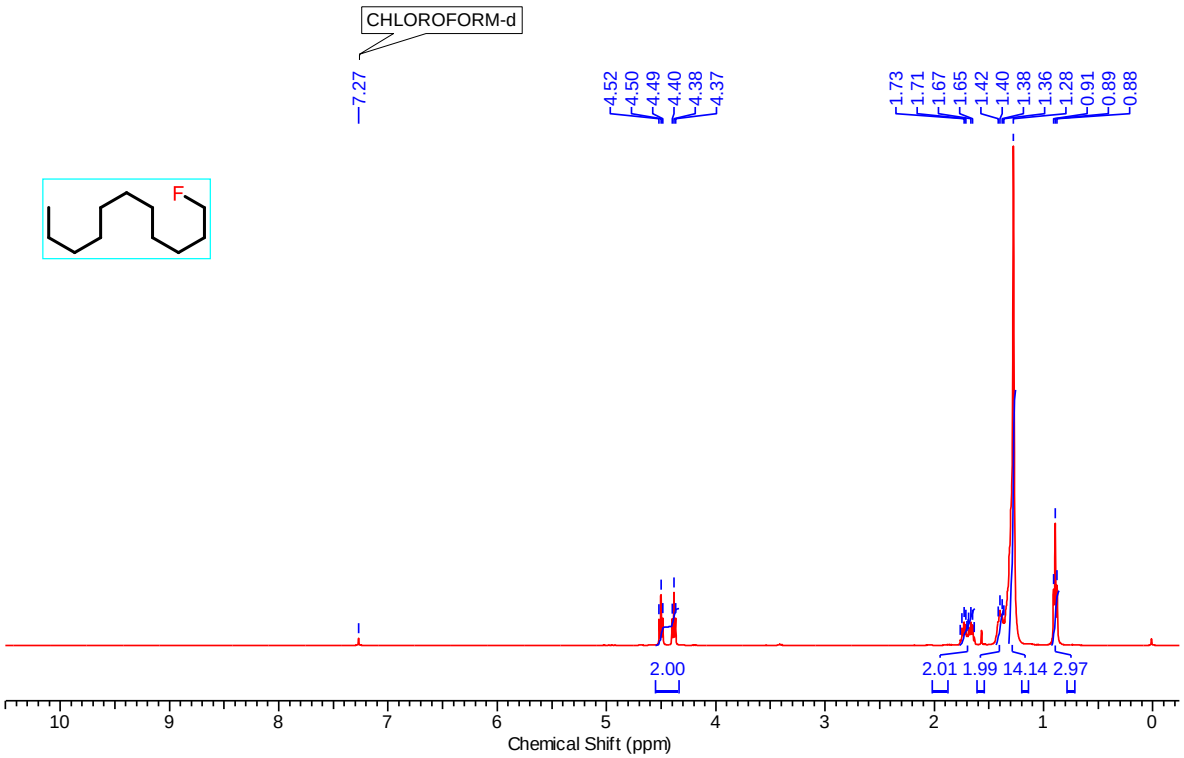

**1-(4-chlorophenyl)-2-fluoroethan-1-one**

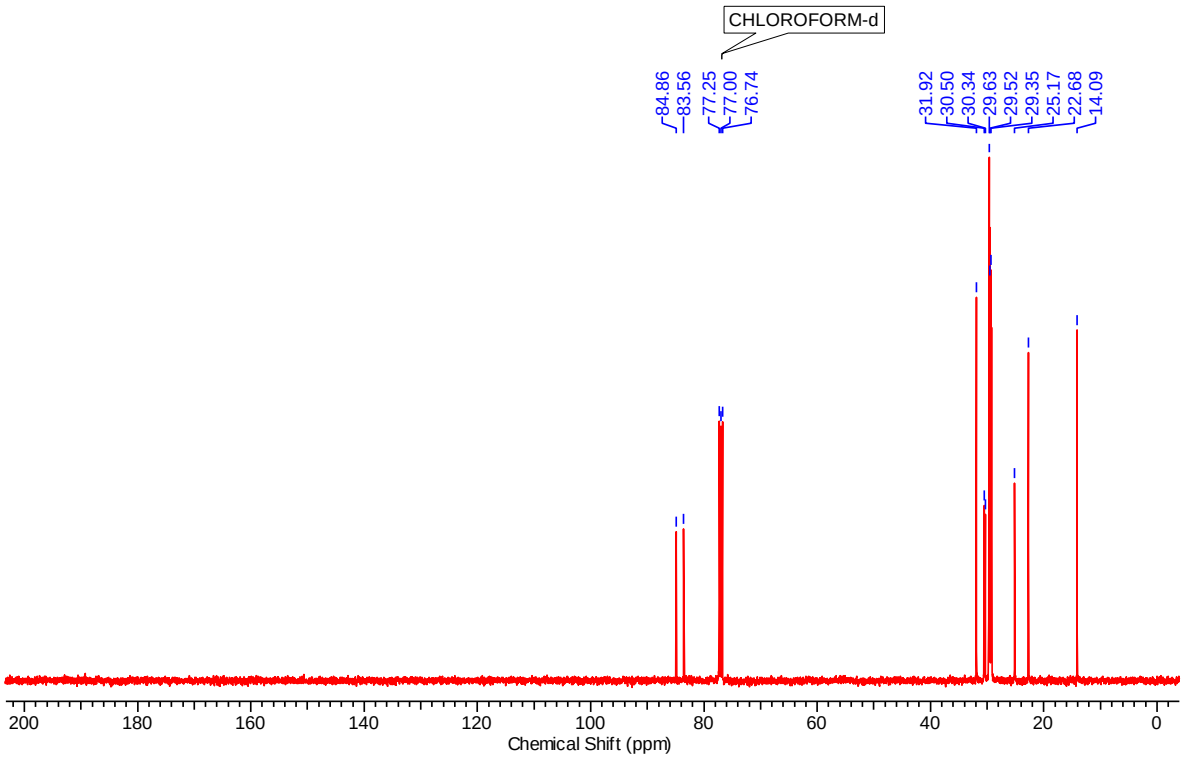


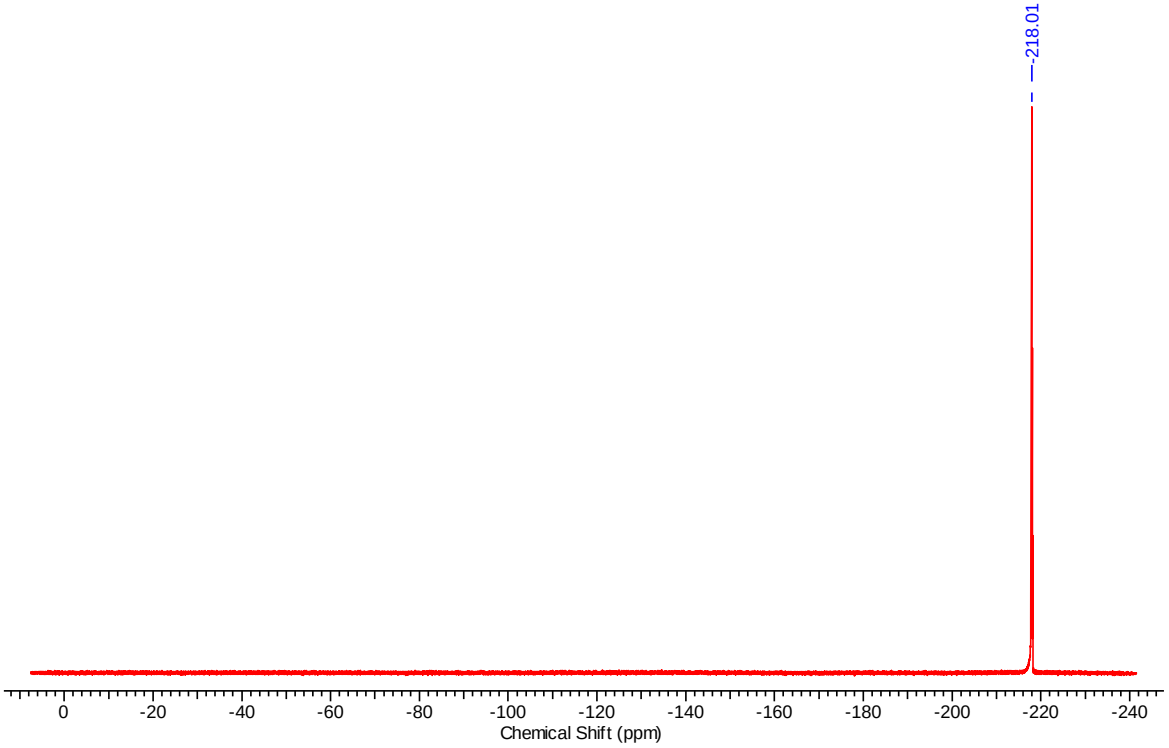

CHLOROFORM-d
192.56
192.41
140.69
132.05
129.40
129.30
84.50
82.67
77.31
77.00
76.69
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


-229.67
100
50
0
-50
-100
-150
-200
-250
Chemical Shift (ppm)

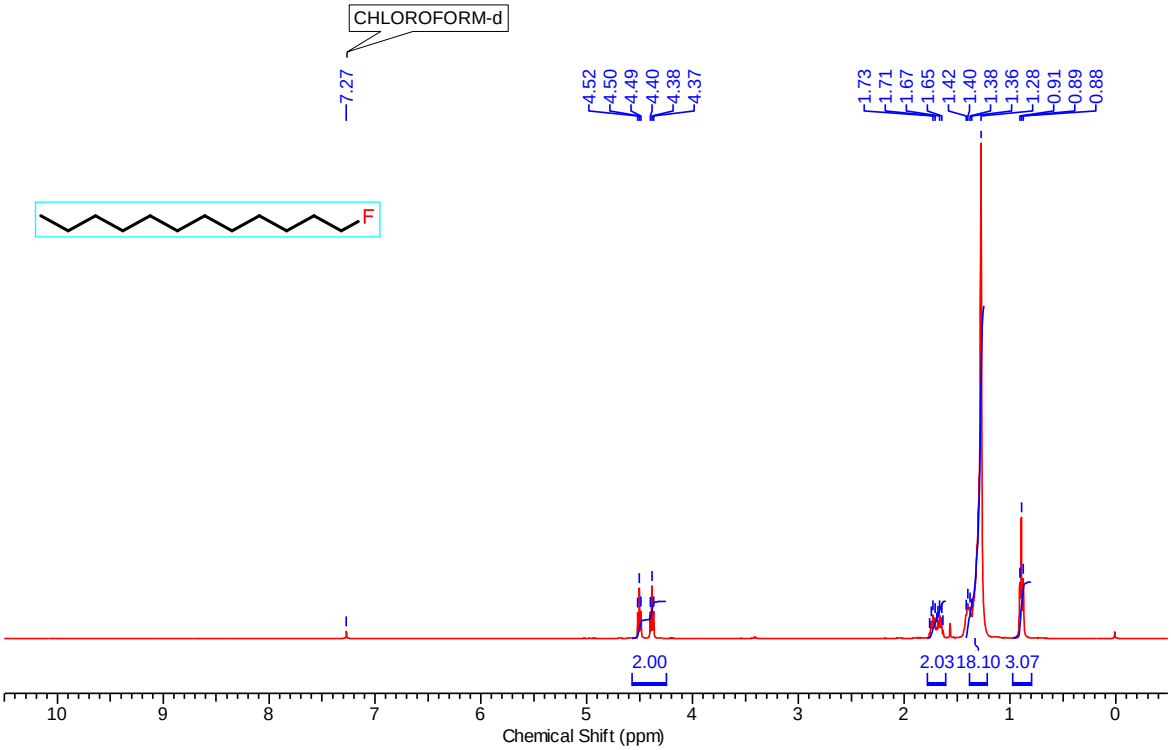
**1-fluoroundecane**

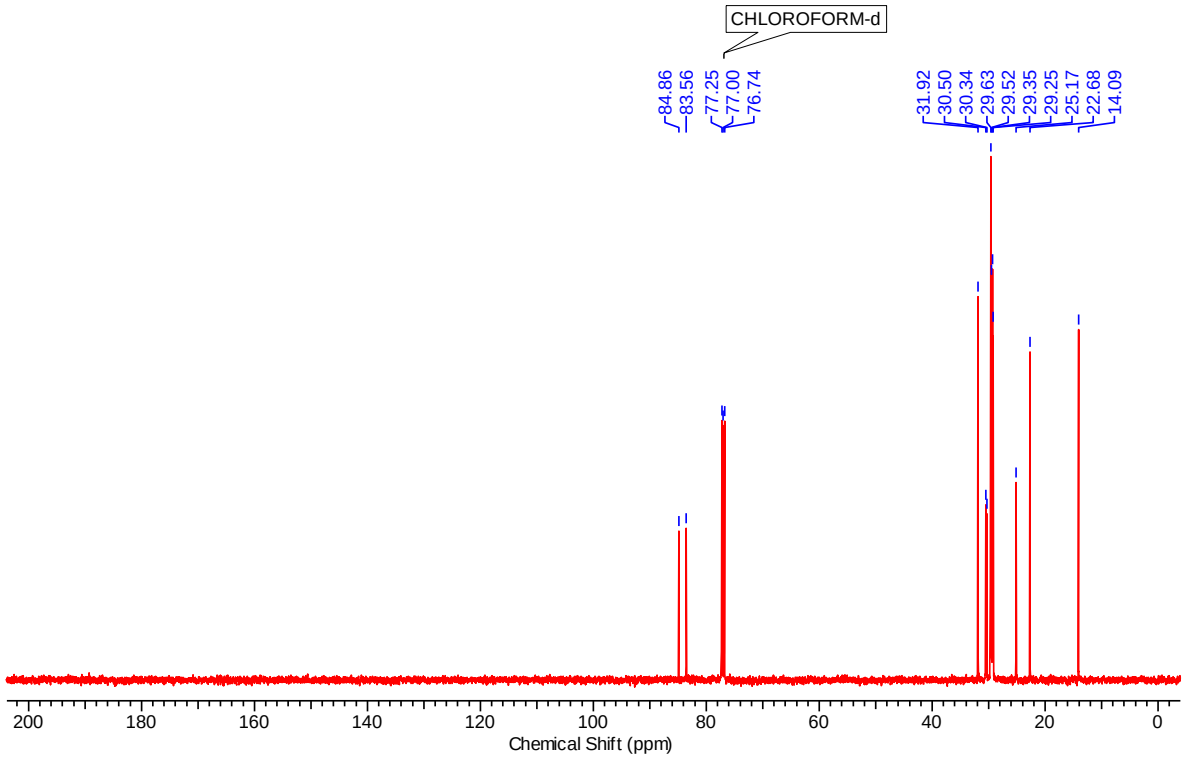


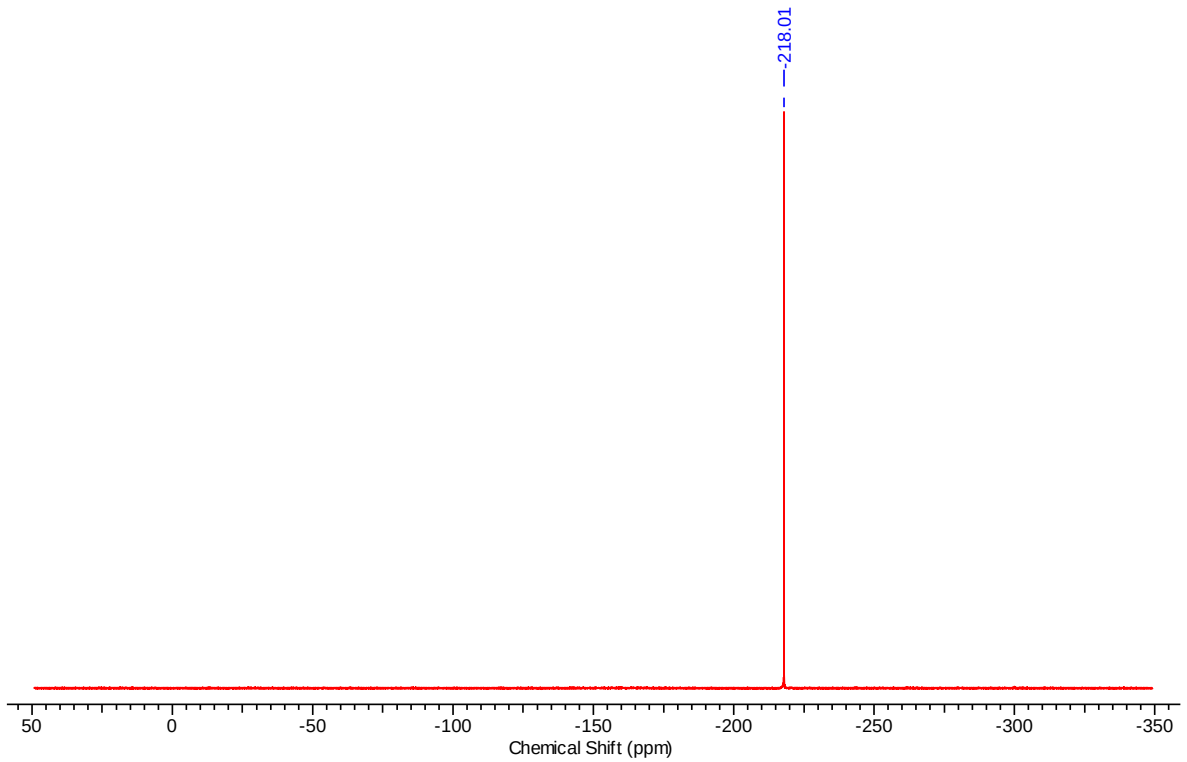





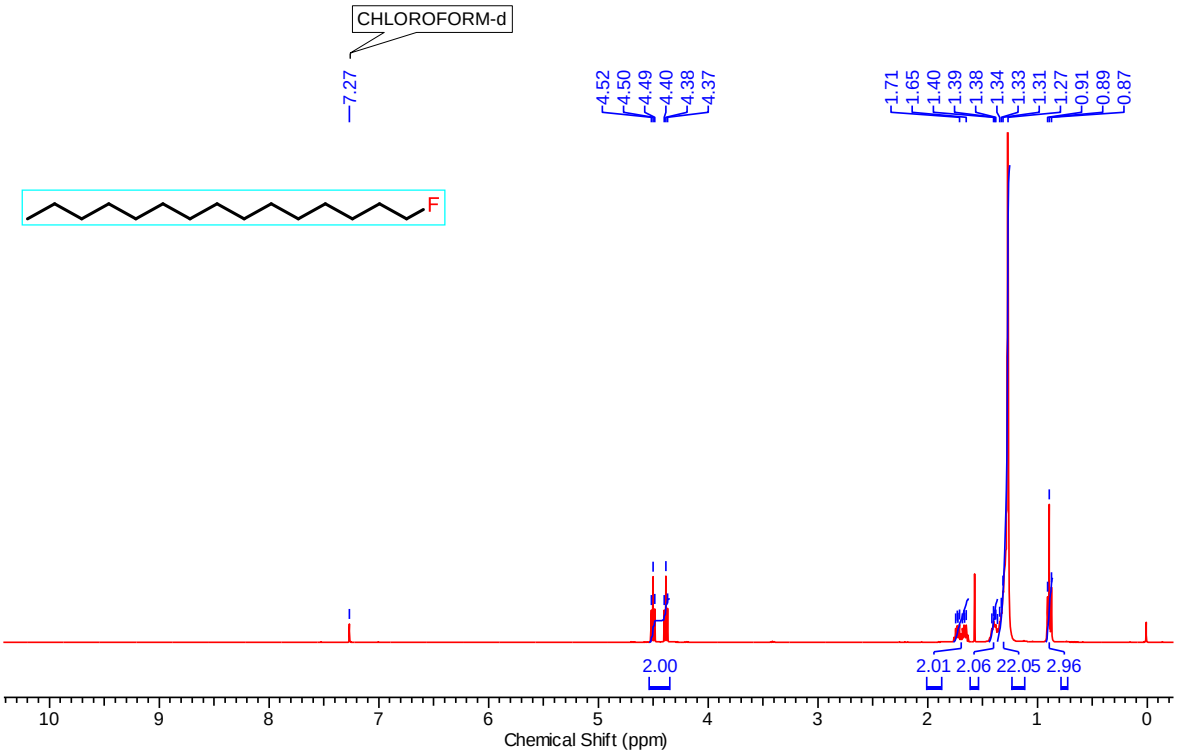

**1-fluorododecane**

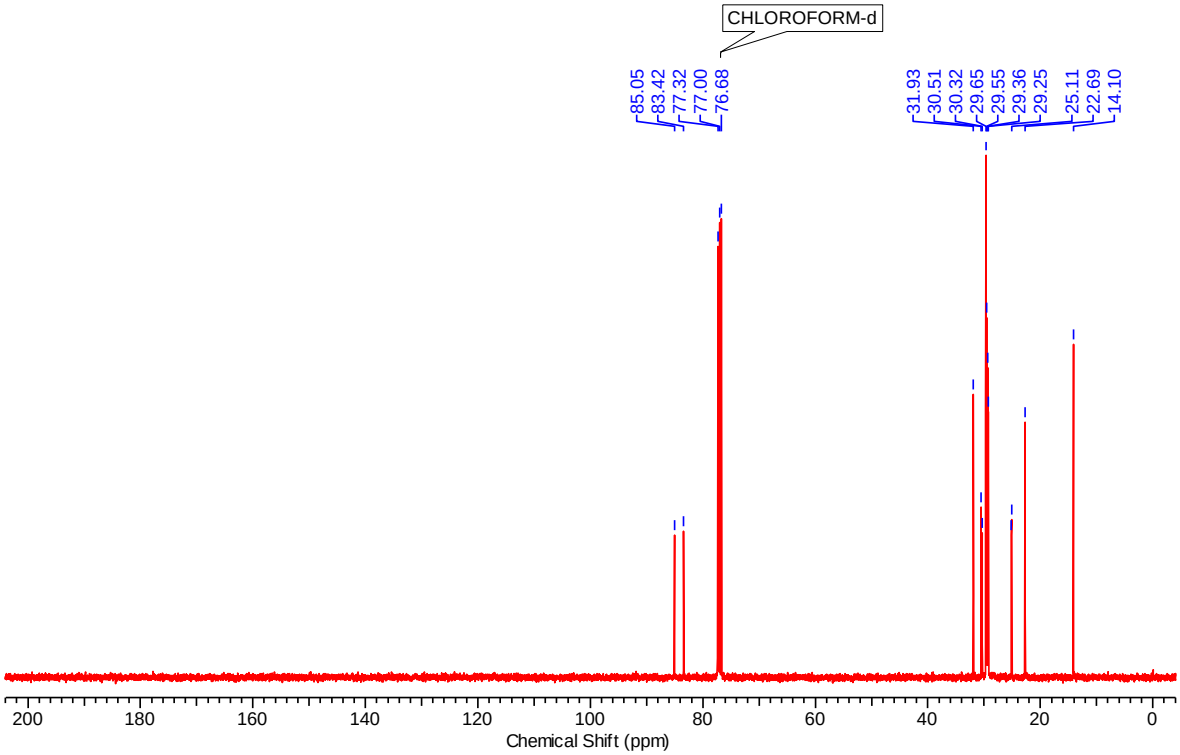


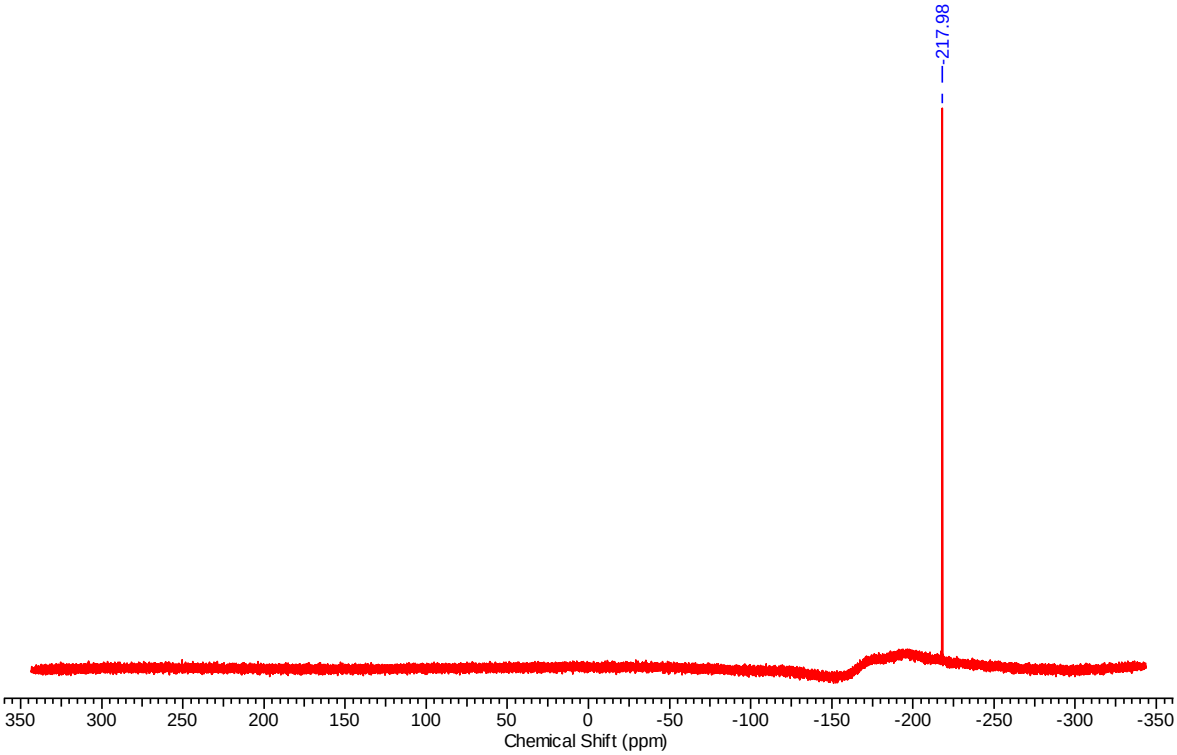

CHLOROFORM-d
84.86
83.56
77.25
77.00
76.74
31.92
30.50
30.34
29.63
29.52
29.35
29.25
25.17
22.68
14.09
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


-218.01
50
0
-50
-100
-150
-200
-250
-300
-350
Chemical Shift (ppm)

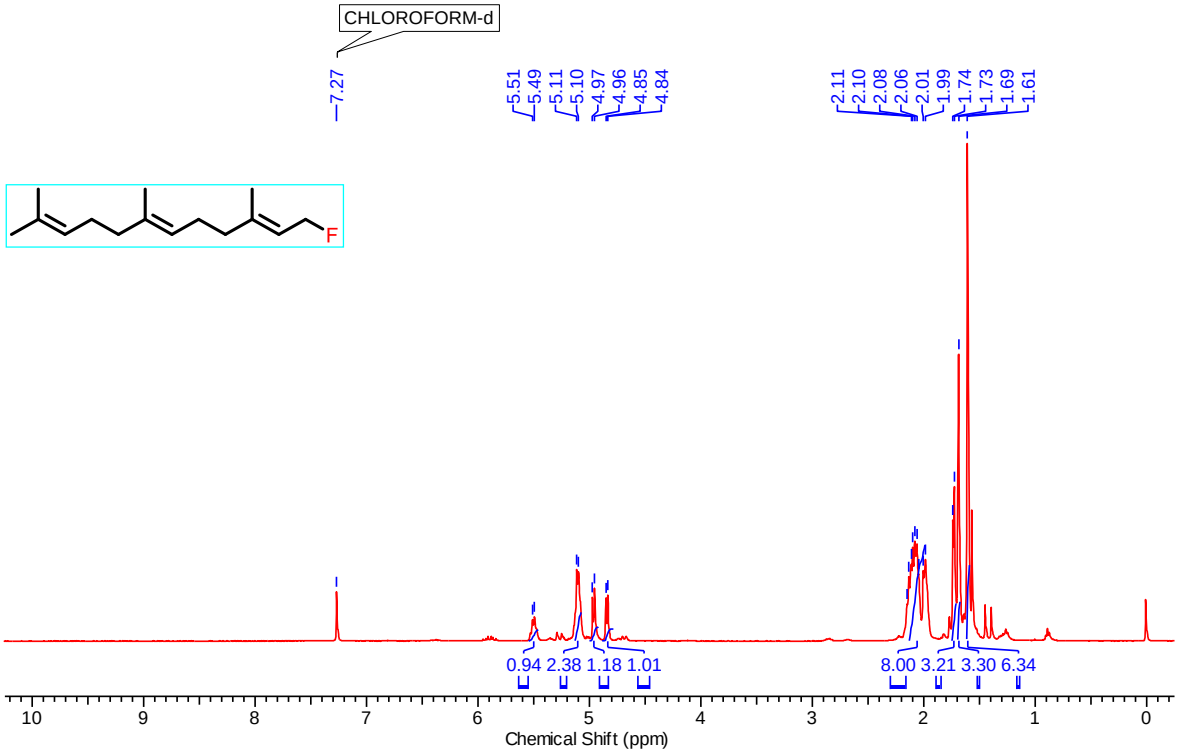
**1-fluoropentadecane**

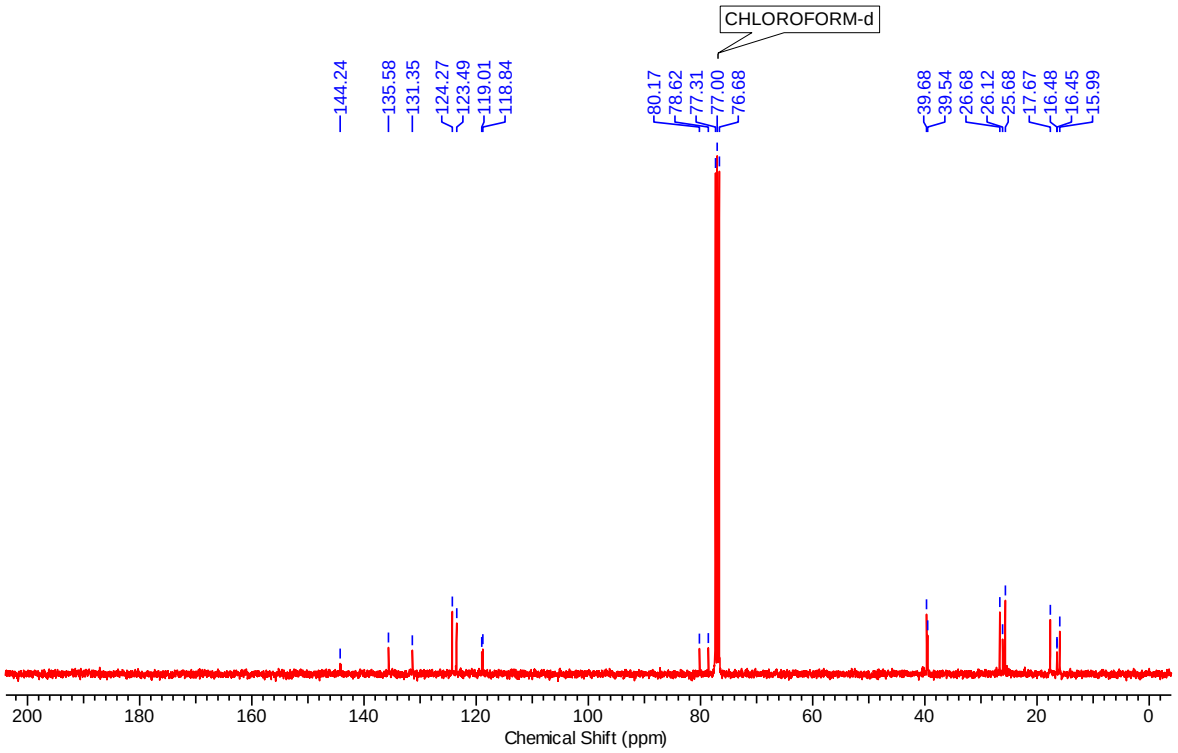


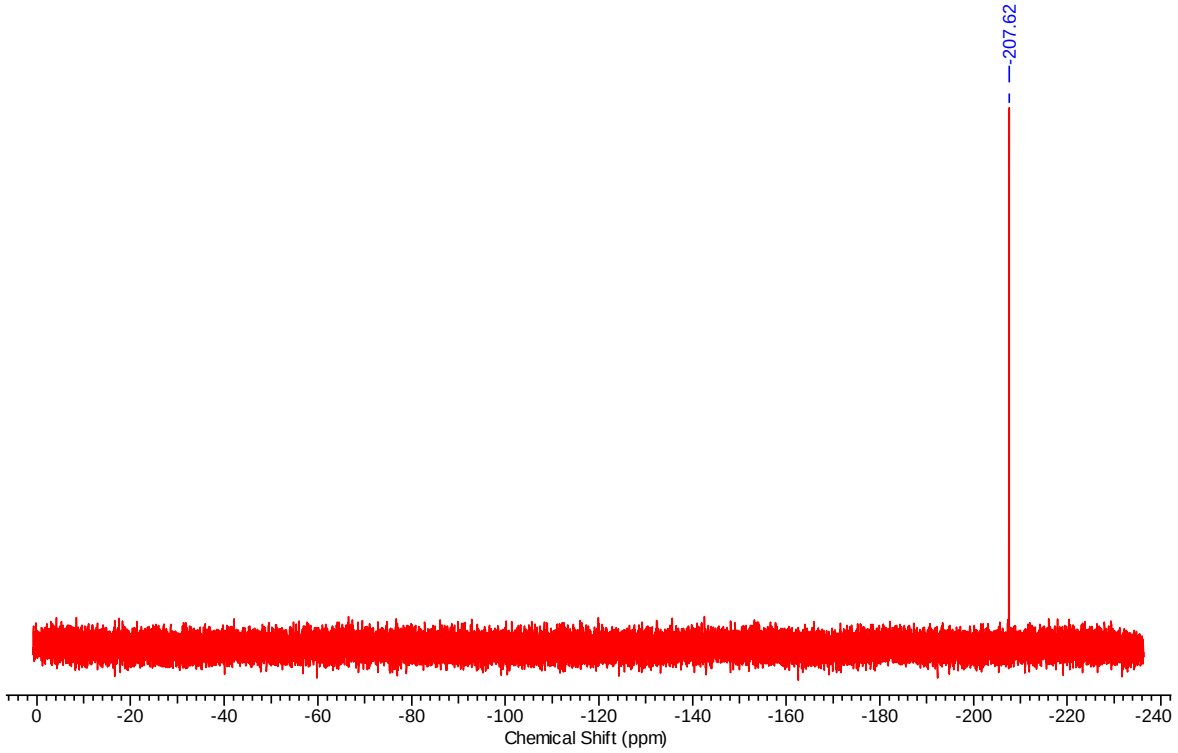





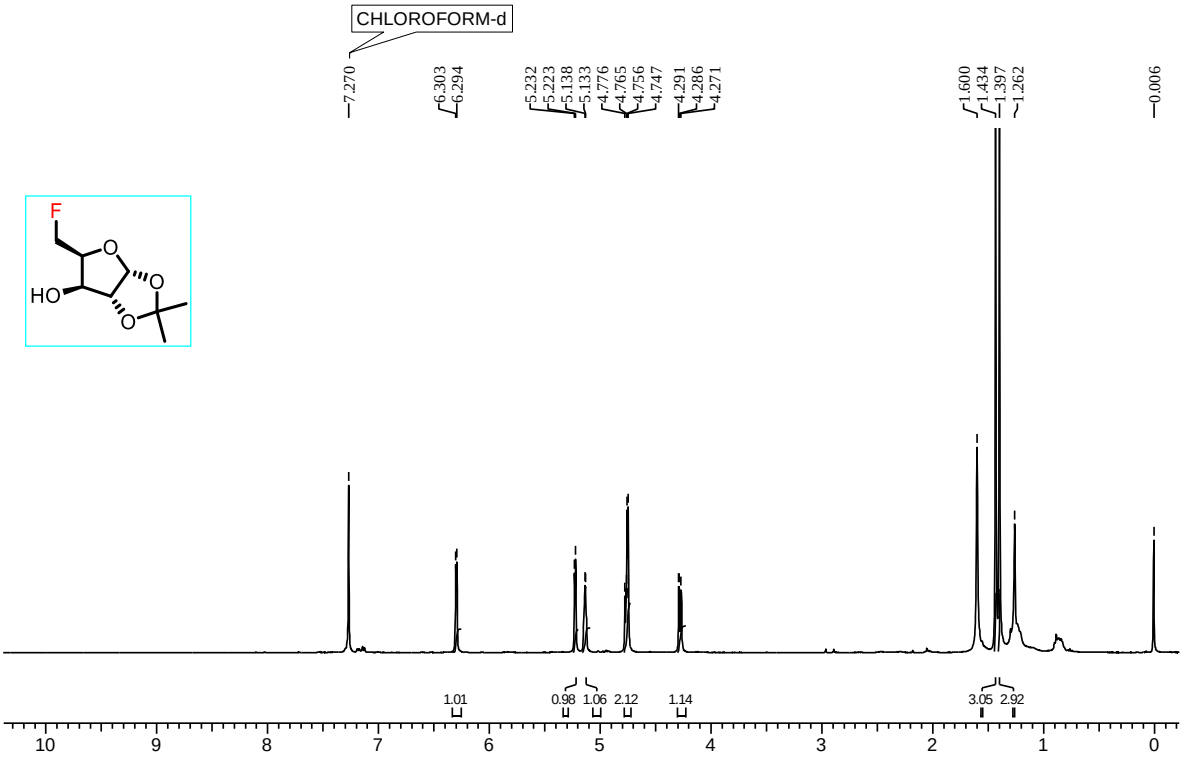

**(2*E*, 6*E*)-1-fluoro-farnesane**

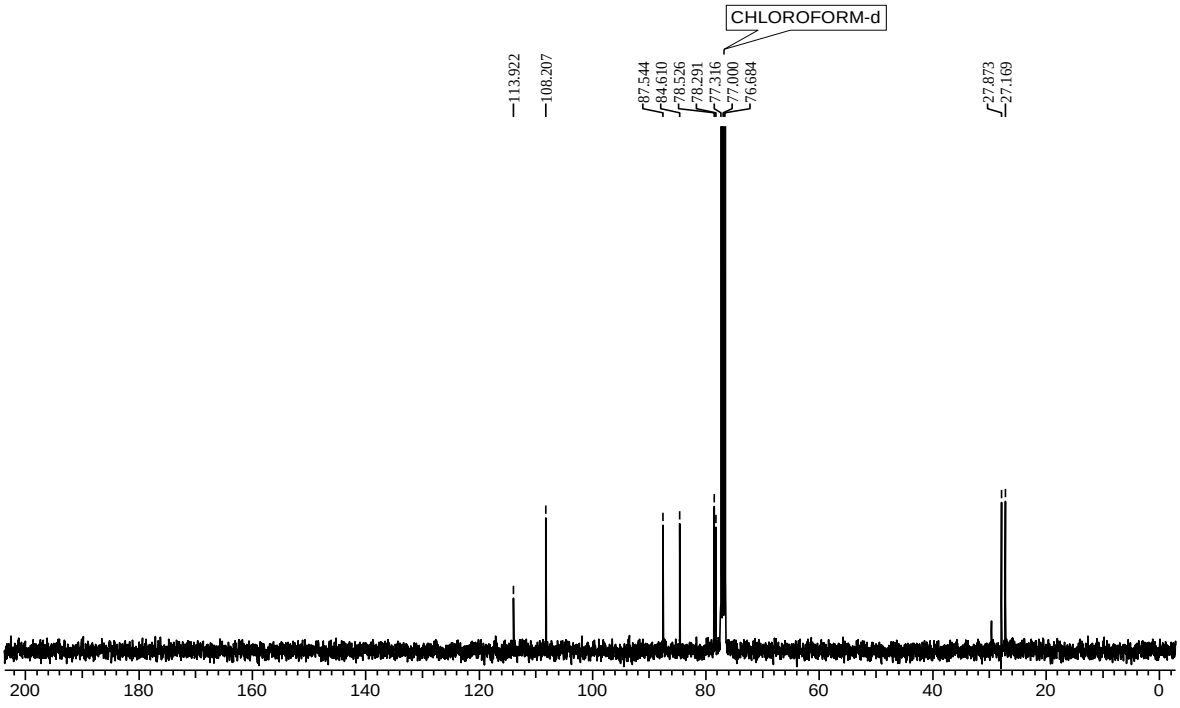


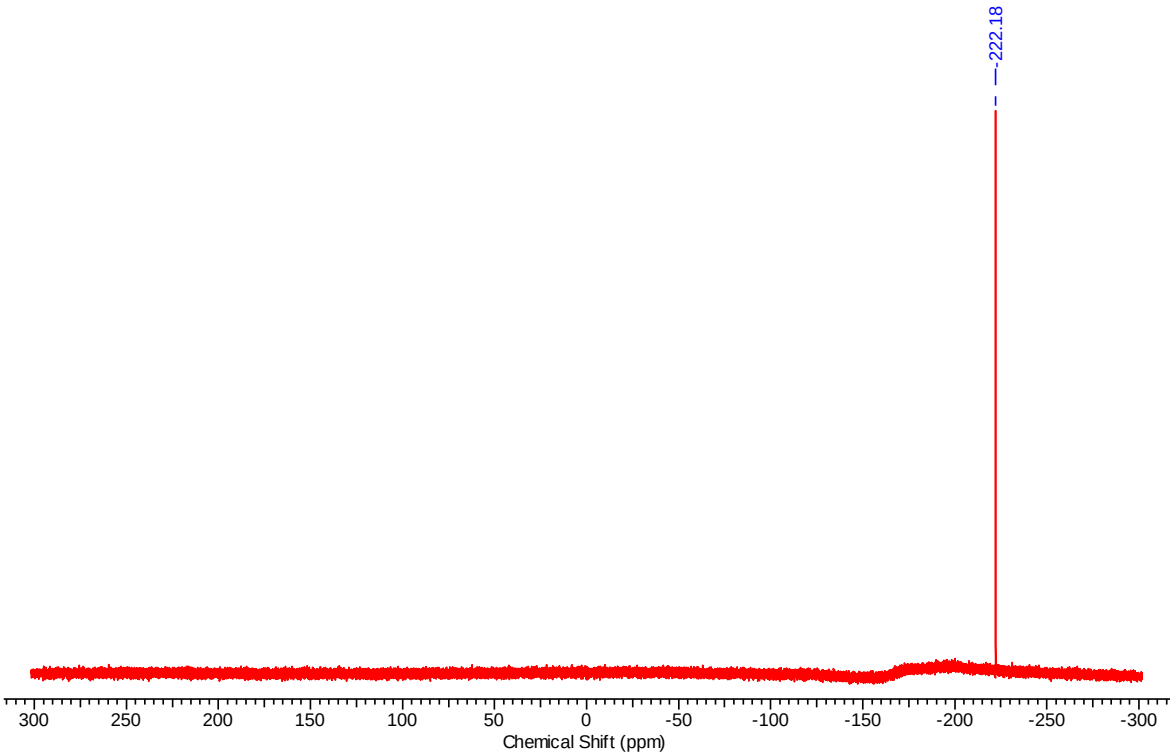

CHLOROFORM-d
144.24
135.58
131.35
124.27
123.49
119.01
118.84
80.17
78.62
77.31
77.00
76.68
39.68
39.54
26.68
26.12
25.68
17.67
16.48
16.45
15.99
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


-207.62
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
Chemical Shift (ppm)

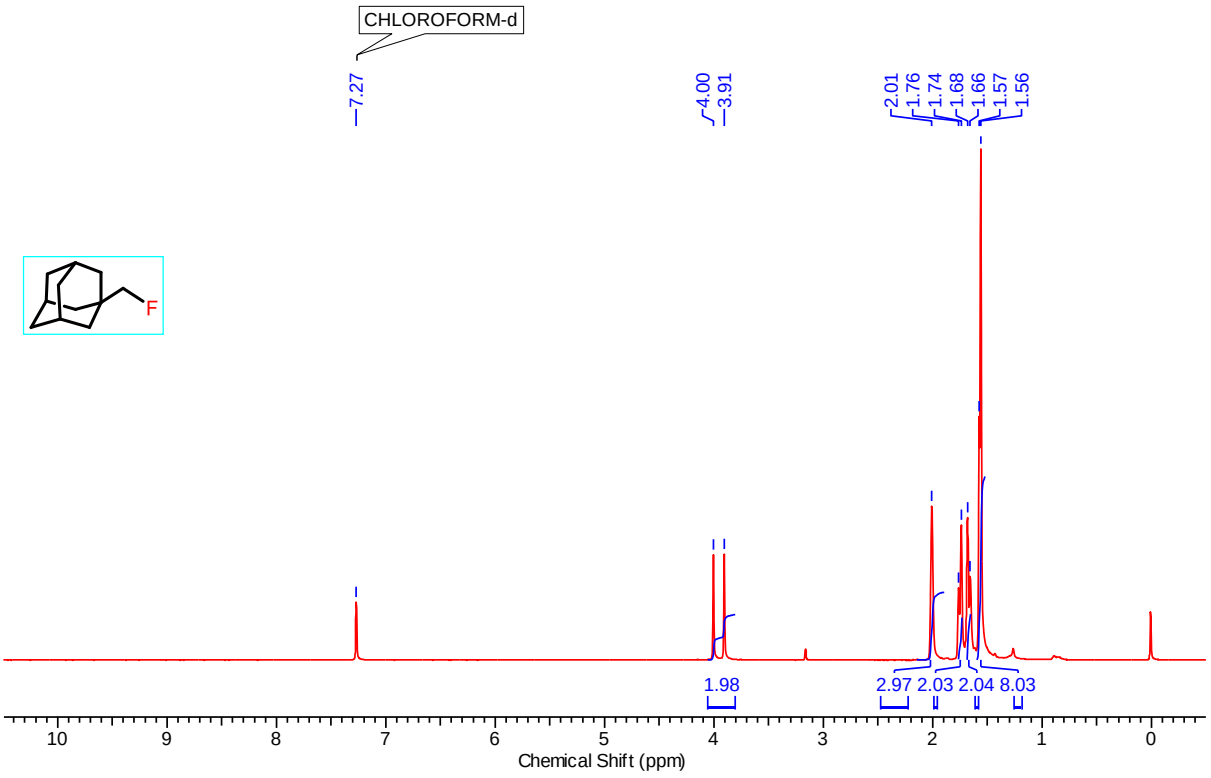
**5-(fluoromethyl)-2, 2-dimethyltetrahydrofuro [2, 3-*d*] [1, 3] dioxol-6-ol**

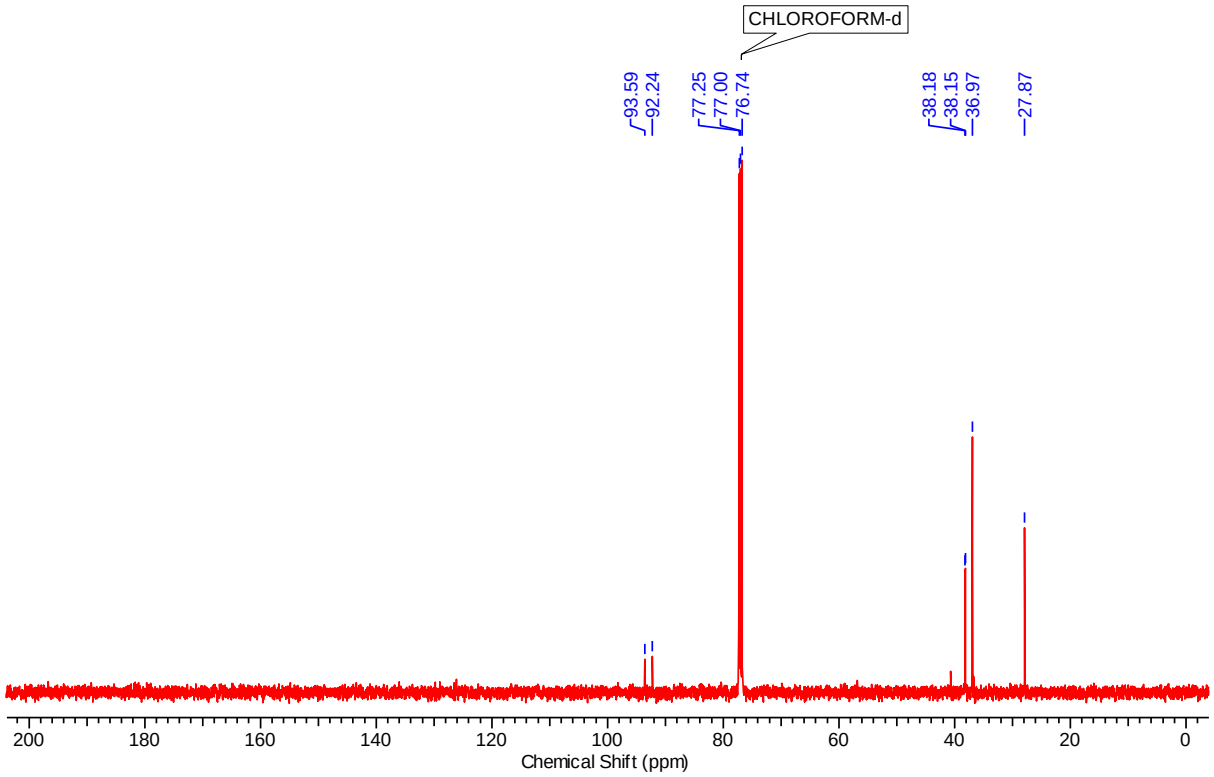


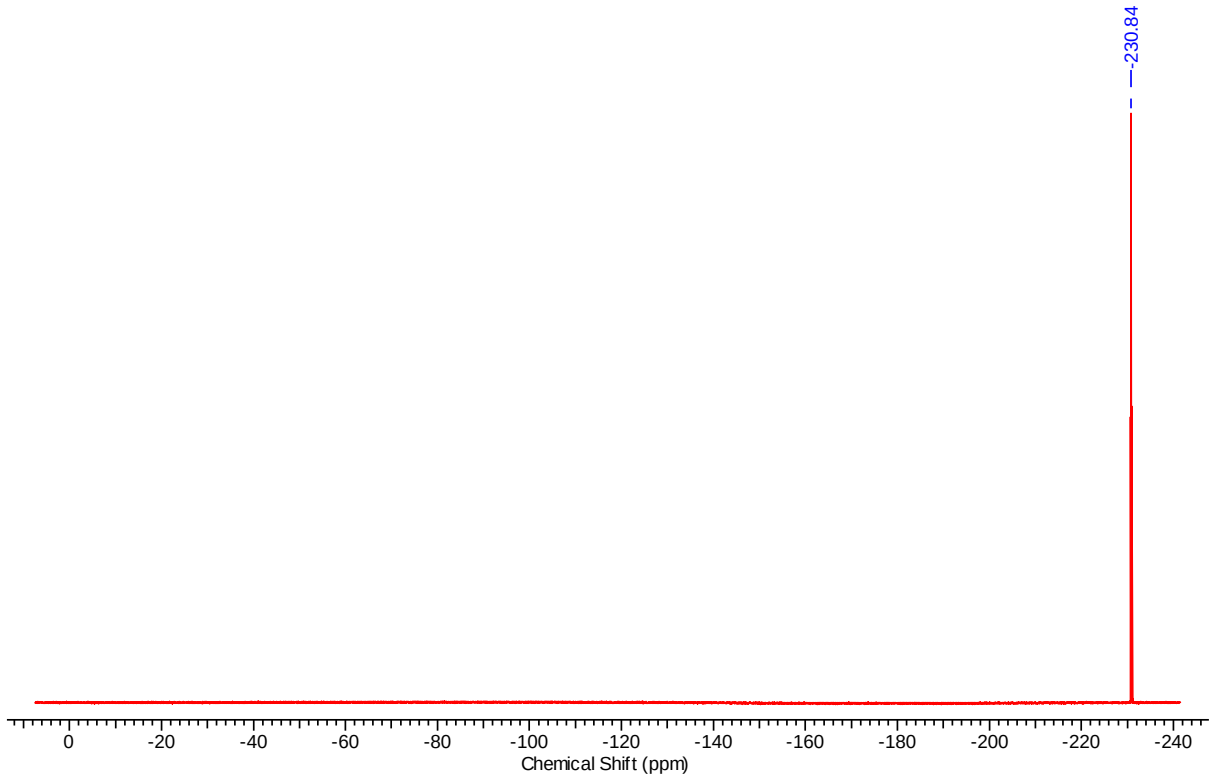





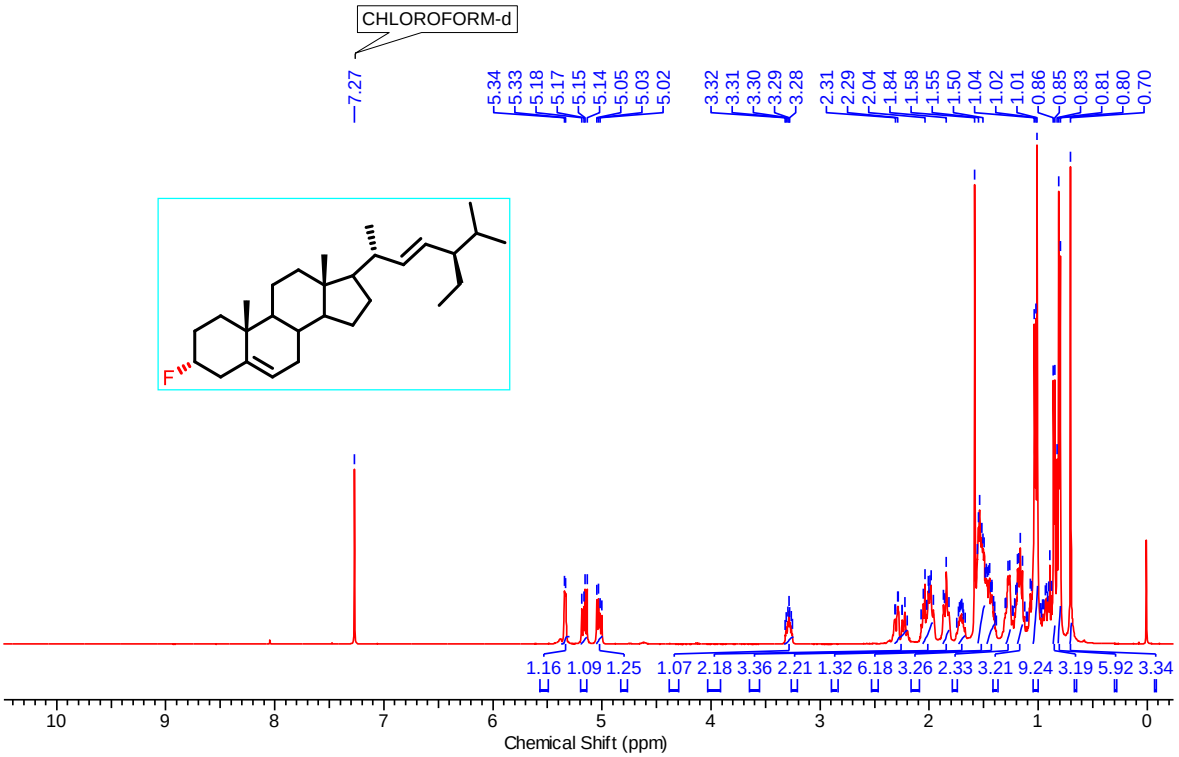

**(3*r*, 5*r*, 7*r*)-1-(fluoromethyl) adamantane**

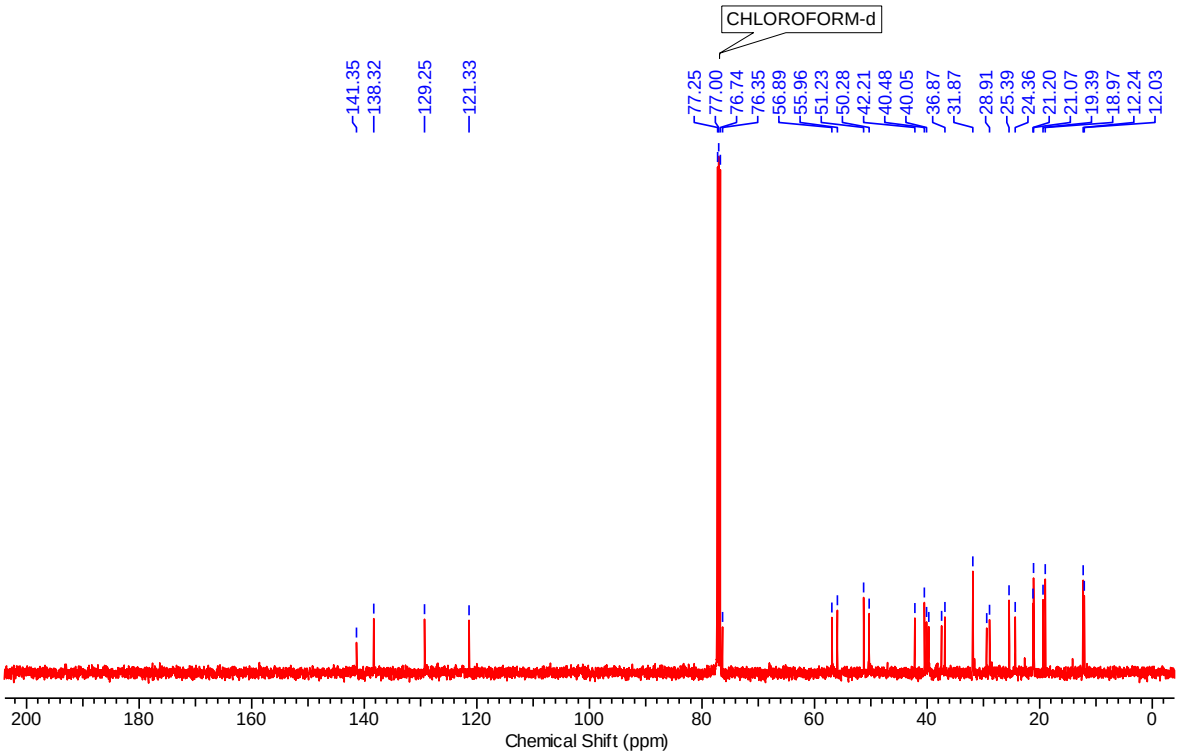


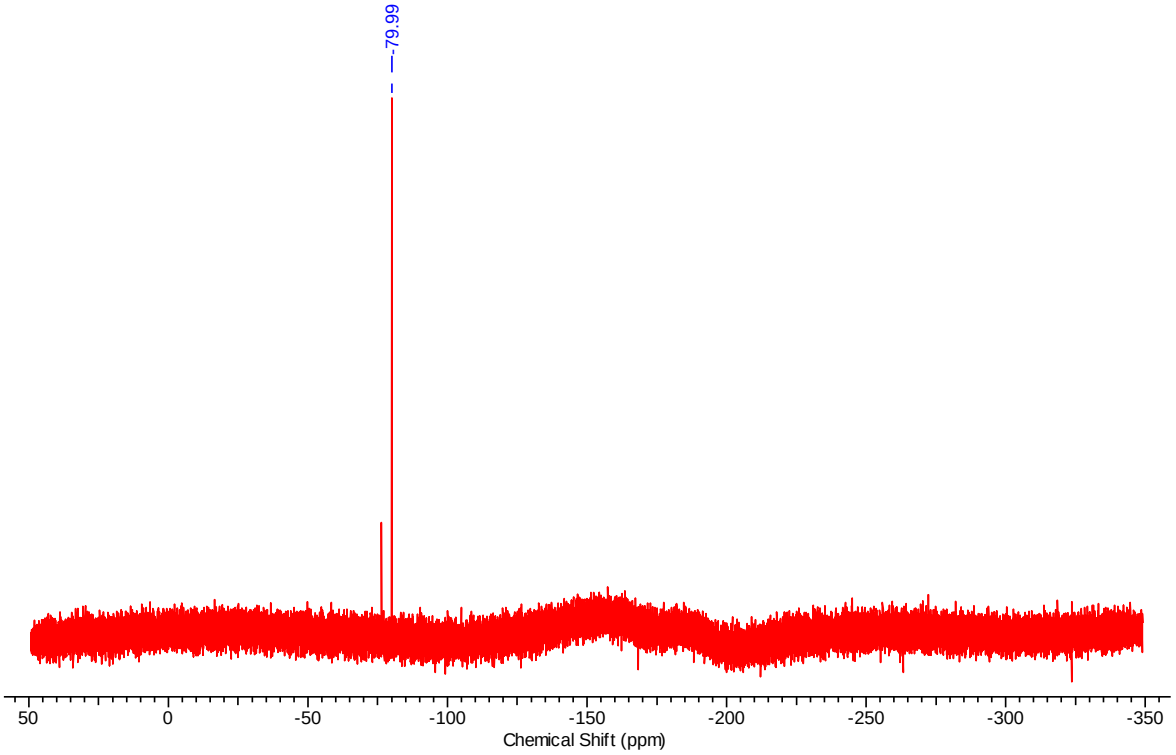

CHLOROFORM-d
93.59
92.24
77.25
77.00
76.74
38.18
38.15
36.97
27.87
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


-230.84
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
Chemical Shift (ppm)

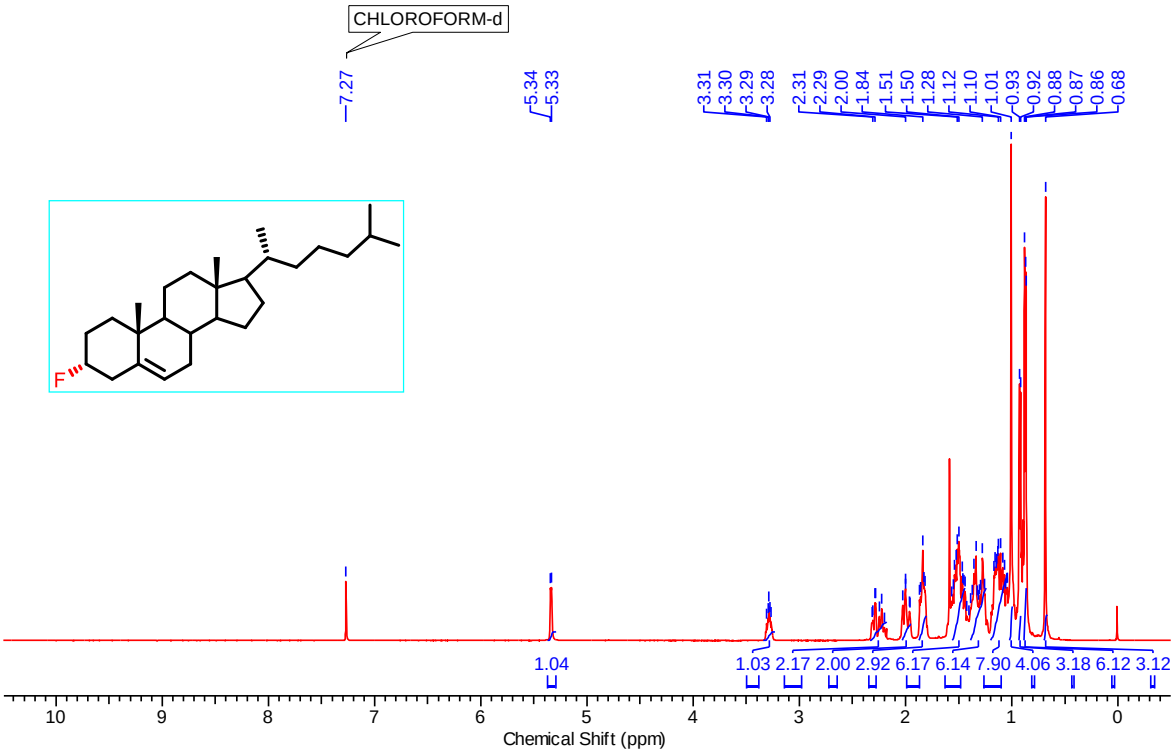
**Stigmasteryl fluoride**

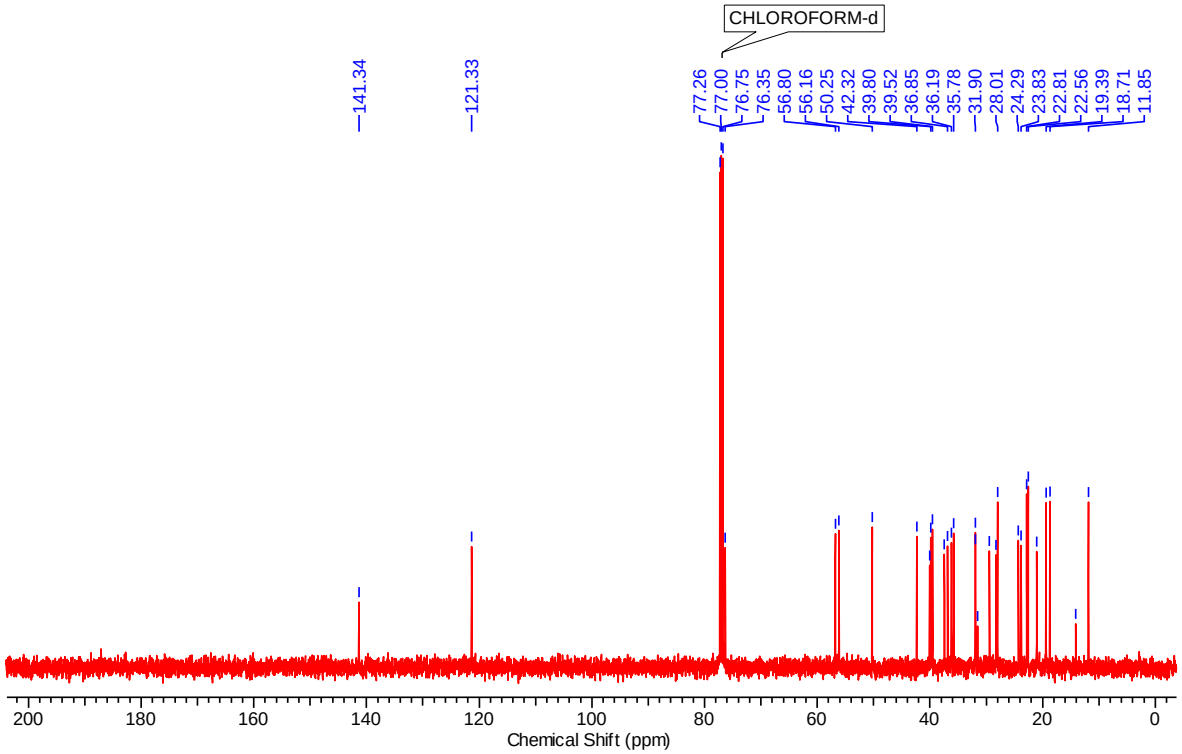


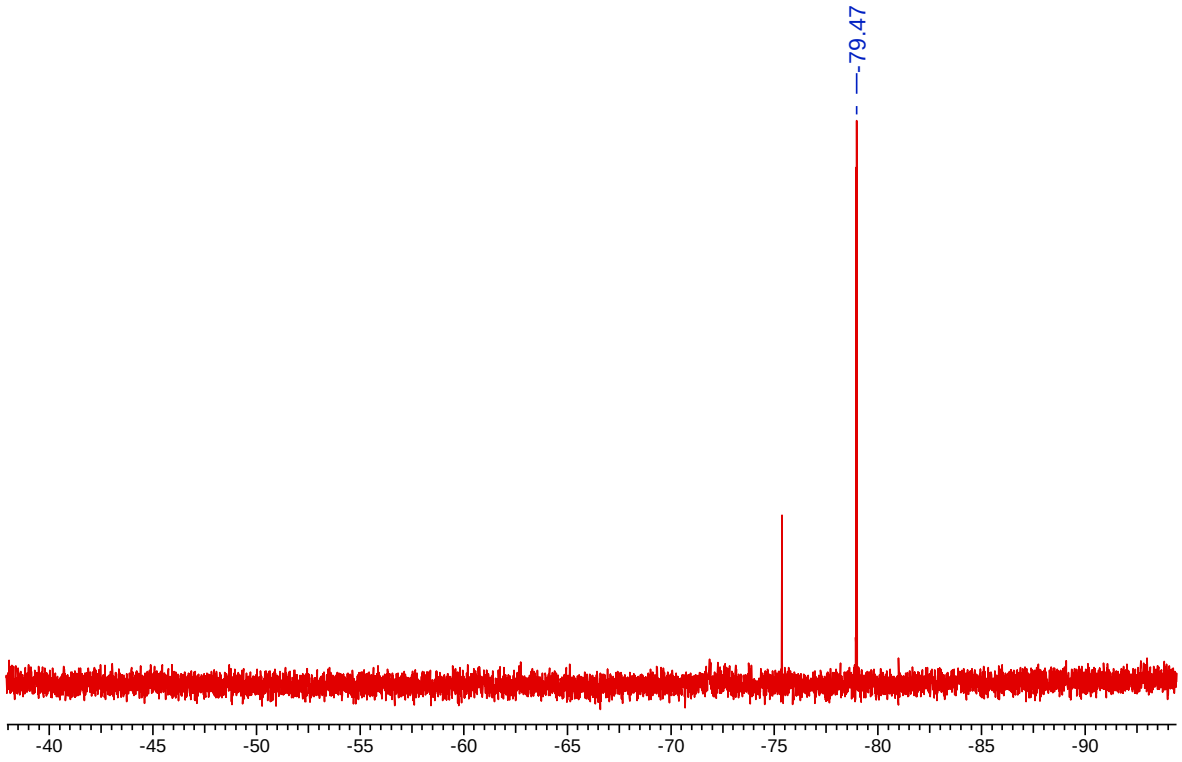






**Cholesteryl fluoride**




CHLOROFORM-d
141.34
121.33
77.26
77.00
76.75
76.35
56.80
56.16
50.25
42.32
39.80
39.52
36.85
36.19
35.78
31.90
28.01
24.29
23.83
22.81
22.56
19.39
18.71
11.85
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


-79.47
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90

## 4A.9 References


1. a) Kumar, R. N.; Dev, G. J.; Ravikumar, N.; Swaroop, D. K.; Debanjan, B.; Bharath, G.; Narsaiah, B.; Jain, S. N.; Rao, A. G. *Bioorg. Med. Chem. Lett.* **2016,** *26*, 2927–2930. b) Sonar, S. S.; Sadaphal, S. A.; Pokalwar, R. U.; Shingate, B. B.; Shingare, M. S. *J. Hetero. Chem.* **2010,** *47*, 441–445.
2. Reviews on Application of Fluorine in Industries: a) Wang, J.; Sanchez- Rosello, M.; Acena, J. L.; Pozo, C. D.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014,** *114*, 2432–2506. b) Fujiwara, T.; O'Hagan, D. *J. Fluorine Chem.* **2014,** *167*, 16–29. c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soci. Rev.* **2008,** *37*, 320–330. d) O'Hagan, D. *Chem. Soc. Rev.* **2008,** *37*, 308–319.
3. Reviews on Bioactive Fluorine: a) Wang, J.; Sanchez-Rosello, M.; Acena, J. L.; Pozo, C. D.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014,** *114*, 2432–2506. b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008,** *37*, 320–330.
4. a) Alauddin, M. M. *Am. J. Nucl. Med. Mol. Imaging.* **2012,** *2*, 55–76. b) Miller, P. W.; Long, N. J.; Vilar, R.; Gee, A. D. *Angew. Chem. Int. Ed.* **2008,** *47*, 8998–9033. c) Kil, H. S.; Cho, H. Y.; Lee, S. J.; Oh, S. J.; Chi, D. Y. *J. Label. Compd. Radiopharm.* **2013,** *56*, 619–626. d) Park, C.; Lee, B. S.; Chi, D. Y. *Org. Lett.* **2013,** *17*, 4346–4349.
5. a) Faraldos, J. A.; Zhao, Y.; O'Maille, P. E.; Noel, J. P.; Coates, R. M. *ChemBioChem.* **2007,** *8*, 1826–18833. b) Cascon, O.; Touchet, S.; Miller, D. J.; Conzalez, V; Faraldos, J. A.; Allemann, R. K. *Chem. Commun.* **2012,** *48*, 9702–9704.
6. Recent review on Nucleophilic Fluorination: a) Lee, J—W.; Oliveira, M. T.; Jang, H. B.; Lee, S.; Chi, D. Y.; Kim, D. W.; Song, C. E. *Chem. Soc. Rev.* **2016,** *45*, 4638–4650. b) Walker, M. C.; Chang, M. C. *Chem. Soc. Rev.* **2014,** *43*, 6527–6536.
7. a) Sung, H.; DiMagno, S. G. *J. Am. Chem. Soc.* **2005,** *127*, 2050–2051. b) Kim, K.-Y.; Kim, B. C.; Lee, H. B.; Shin, H. *J. Org. Chem.* **2008,** *73*, 8106–8108. c) Kim, D. W.; Jeong, H.-J.; Kim, S. T.; Sohn, M.-H. *Angew. Chem.* **2008,** *120*, 8532–8534.
8. a) Pilcher, A. S.; Ammon, H. L.; DeShong, P. *J. Am. Chem. Soc.* **1995,** *117*, 5166–5167. b) Gobbi, A.; Landini, D.; Maia, A.; Secci, D. *J. Org. Chem.* **1995,** *60*, 5954–5957. c) Kim, J.; Ichimura, A. S.; Huang, R. H.; Redko, M.; Philips, R. C.; Jackson, J. E.; Dye, J. L. *J. Am. Chem. Soc.* **1999,** *121*, 10666–10667. b) Landini, D.; Maia, A.;

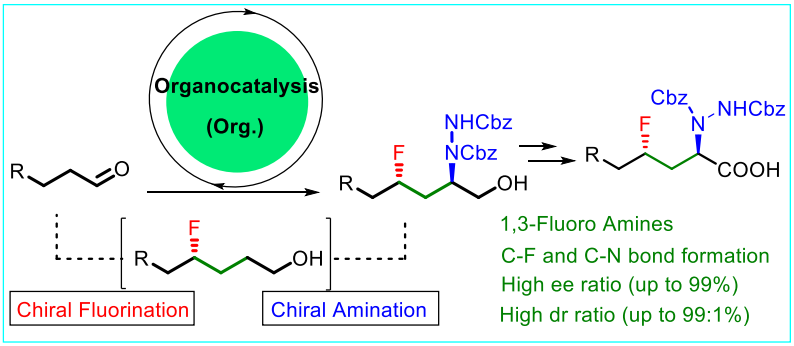
Montanari, F.; Tundo, P. *J. Am. Chem. Soc.* **1979,** *101*, 2526–2530. e) Plenio, H. *ChemBioChem.* **2004,** *5*, 650–655.

9. a) Kim, D. W.; Song, C. E.; Chi, D. Y. *J. Am. Chem. Soc.* **2002,** *124*, 10278–10279. b) Kim, D. W.; Song, C. E.; Chi, D. Y. *J. Org. Chem.* **2003,** *68*, 4281–4285. c) Shinde, S. S.; Chi, H. M.; Lee, B. S.; Chi, D. Y. *Tetrahedron Lett.* **2009,** *50*, 6654–6657.
10. Lee, J. W.; Yan, H.; Jang, H. B.; Kim, H. K.; Park, S. -W.; Lee, S.; Chi, D. Y.; Song, C. E. *Angew. Chem. Int. Ed.* **2009,** *48*, 7683–7686.
11. Krakowiak, K. E.; Bradshaw, J. S.; An, H.; Izatt, R. M. *Pure & Appl.Chem.* **1993,** *65*, 511–514.
12. Kim, D. W.; Ahn, D. -S.; Oh, Y. -H.; Lee, S.; Kil, H. S.; Oh, S. J.; Lee, S. J.; Kim, J. S.; Ryu, J. S.; Moon, D. H.; Chi, D. Y. *J. Am. Chem. Soc.* **2006,** *128*, 16394–16397.
13. Krakowiak, K.; Bradshaw, E. J. S.; An, H.; Izatt, R. M. *Pure & Appl.Chem.* **1993,** *65*, 511–514.
14. a) Shinde, S. S.; Lee, B. S.; Chi, D. Y. *Org. Lett.* **2008,** *10*, 733–735. b) Shinde, S. S.; Patil, S. N. *Org. Biomol. Chem.* **2014,** *12*, 9264–9271. c) Shinde, S. S.; Patil, S. N.; Ghatge, A.; Kumar, P. *New J. Chem.* **2015,** *39*, 4368–4374. d) Shinde, S. S.; Lee, B. S.; Chi, D. Y. *Tetrahedron Lett.* **2008,** *49*, 4245–4248. e) Said, M. S.; Khandare, L.; Shinde, S. S. *Tetrahedron Lett.* **2017,** *58*, 59–62.
15. Oh, Y. -H.; Jang, H. B.; Song, S.; Im, M. J.; Kim, S. -Y.; Park, S. -W.; Chi, D. Y.; Song, C. E.; Lee, S. *Org. Biomol. Chem.* **2011,** *9*, 418–422.
16. Mun, S. -D.; Lee, J.; Kim, S. H.; Hong, Y.; Ko, Y. -H.; Shin, Y. K.; Lim, J. H.; Hong, C. S.; Do, Y.; Kim, Y. *J Organomet. Chem.* **2007,** *692*, 3519–3525.
17. Oh, Y. -H.; Ahn, D. -S.; Chung, S. -Y.; Jeong, J. -H.; Park, S. -W.; Lee, S.; Oh, S. J.; Kim, D. W.; Kil, H. S.; Chi, D. Y. *J. Phys. Chem. A* **2007,** *111*, 10152–10161.
18. Kim, J.-Y.; Kim, D. W.; Song, C. E.; Chi, D. Y.; Lee, S. *J. Phys. Org. Chem.* **2013,** *26*, 9–14.
19. Schwesinger, R.; Link, R.; Wenzl, P.; Kossek, S. *Chem. Eur. J.* **2006,** *12*, 438–445.
20. Jadhav, V. H.; Choi, W.; Lee, S. -S.; Lee, S.; Kim, D. W. *Chem. Eur. J.* **2016,** *22*, 4515–4520.

# Chapter-4 (Section-B)

# Organocatalytic Route to the Enantioselective Synthesis of syn/anti-1,3-Fluoro Amines

## Abstract


A general organocatalytic method for the asymmetric synthesis of 1,3-fluoro amines has been developed. The strategy employs α-fluorination catalyzed by L-Proline derived Hayashi catalyst followed by Horner−Wadsworth−Emmons (HWE) olefination of aldehydes and subsequent proline-catalyzed α-amination as the key steps. The excellent enantioselectivity (up to 99%) and diastereoselectivity (up to 99:1%) of 1,3-fluoro amines were obtained.

## 4B.1 Introduction

Fluorine is one of the most commonly available and lavish elements found in various pharmaceuticals[1] and agrochemical substances.[2] The importance of fluorine in medicinal chemistry is well documented.[3] Indeed, an increasing number of drugs containing fluorine suggest that its presence in the molecule has special and added advantages to their activity. Currently, more than 30% of drugs available in the market are fluorinated compounds. Incorporation of the fluorine atom mainly by replacement of a C–H bond or C–O bond alters the molecular properties such as solubility, metabolic stability and bio-availability to a great extent.[4] Additionally, the $^{18}F$ radioisotopes of fluorine find enormous application in nuclear medicine and radiopharmaceutical chemistry.[5] The past few decades have witnessed a considerable surge of interest in the development of methods for the synthesis of biologically active fluorinated compounds.[6] 1,3-Fluoro amines are one of the most bioactive fluorinated scaffolds present in several drug molecules. Especially, the β-fluoro, α-amino acid derivative has been extensively used as a protein residue and also for PET imaging applications. Some representative examples are depicted in Figure-1.[7]

In the backdrop of green chemistry, the organocatalysis has emerged as promising strategy to do an organic transformation. Consequently, researchers are highly prompted for the development of methodology which can the replace the toxic metal and the expensive protein reagents with small organic molecule for the organic transformations.

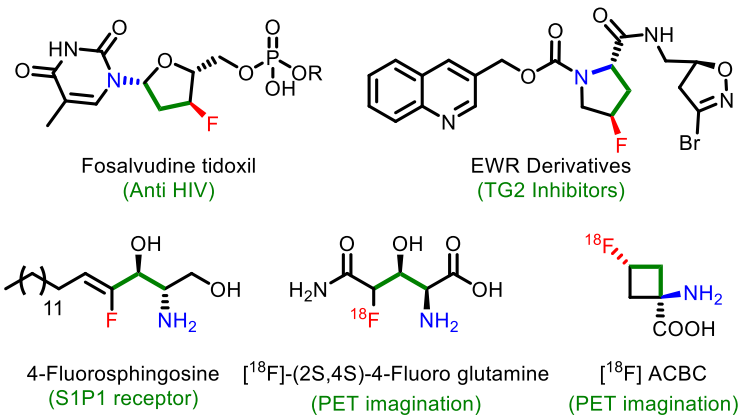



**Figure-1.** Some representative examples of bioactive fluorinated amino alcohols, acids and drug molecules

Proline is among the most successful secondary amine-based environment friendly and highly efficient catalysts for an organic transformation. This has been widely explored for

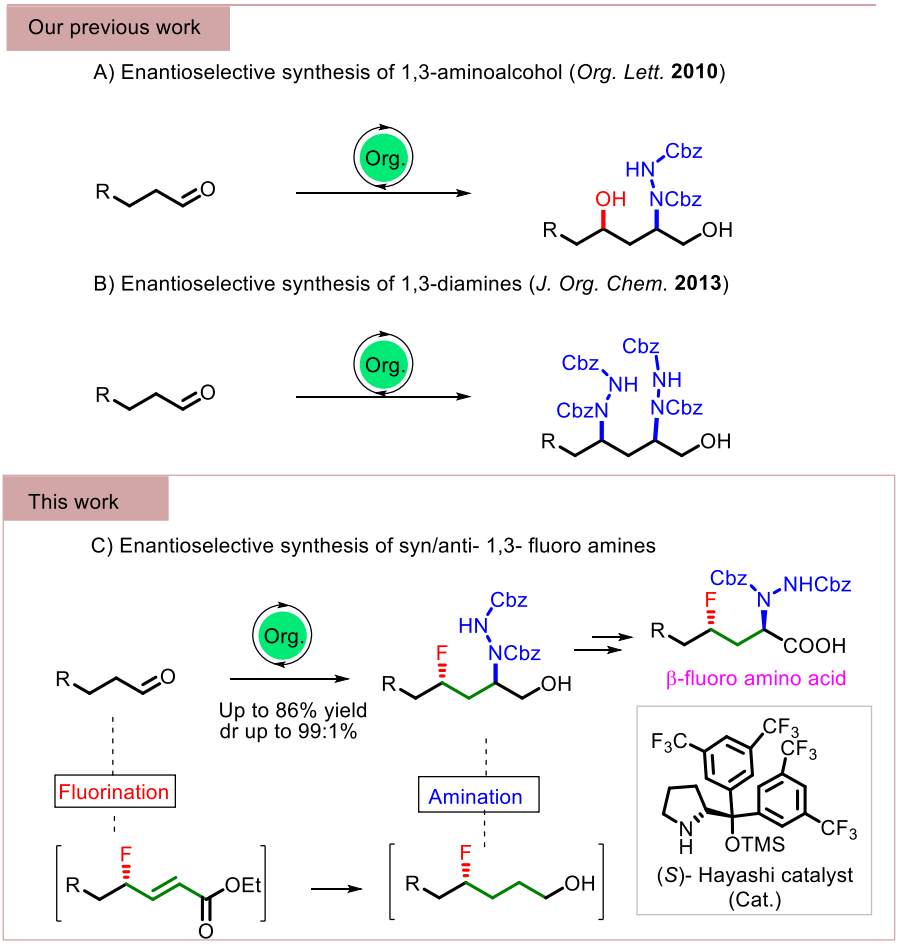
asymmetric induction during construction of C–C and C–heteroatom bond.[8] Proline and proline derived catalysts have been also widely employed for α-functionalization of carbonyl compounds such as α-aminoxylation, α-amination, α-halogenation, α-sulfenylation. This enables an easy access of synthetic process which is rapid, catalytic, and atom-economical for enantiomerically pure products.[9-10]

### 4B.2 Literature Review

Recently, our group has developed an iterative approach to the enantiopure synthesis of syn/anti-1,3-amino alcohols[11]/diamines[12] based on proline-catalyzed sequential α-aminoxylation/amination of aldehydes shown in Scheme-1A. The synthetic application and usefulness of these newly developed organocatalytic and other related reported methodologies were further demonstrated in the synthesis of various bioactive compounds containing polyols and amino alcohols.[13] Recently, as a part of our research interest in the fluorine chemistry, we have also reported nucleophilic $S_N2$ fluorination to construct the new C–F bond.[14]

### 4B.3 Present Work

With the above literature background, and as a part of our research interest in fluorine chemistry and the development of new organocatalytic methodologies, herein, we envisioned that the sequential α-fluorination, catalyzed by proline-based Hayashi-Jørgensen catalyst followed by HWE olefination and subsequent proline-catalyzed amination could easily give us stereo-controlled synthetic access to 1,3-fluoro amines shown in Scheme-1B. It is noteworthy that, γ-fluoro, α, β-unsaturated ester can serve as a promising building block for the construction of various biologically important compounds. We proposed the synthetic strategy for 1,3-fluoro amines as illustrated in Scheme-1.



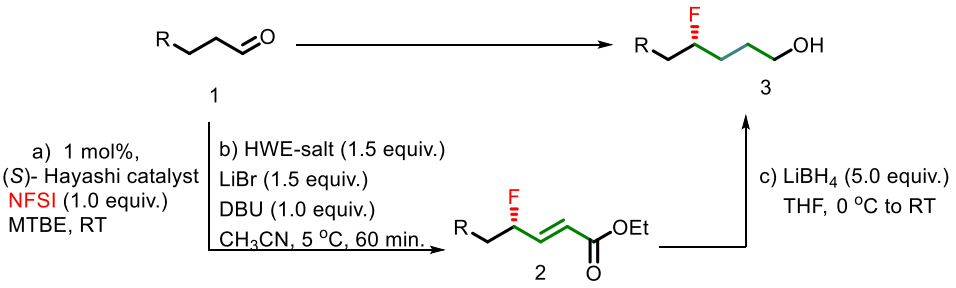

**Scheme-1.** Our previous work and the present work on the synthesis of 1,3- fluoro amines

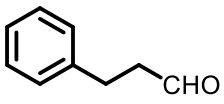
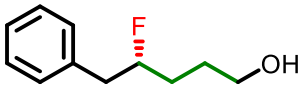
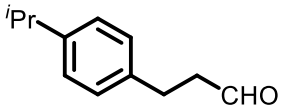
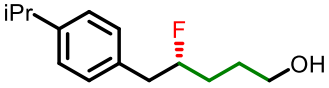
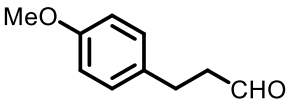
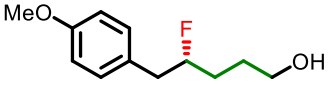
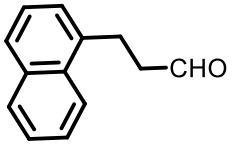
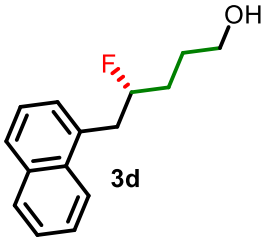
## 4B.4 Results and Discussion

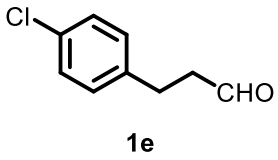
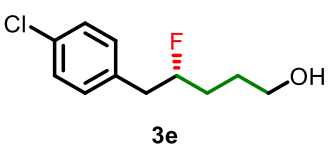
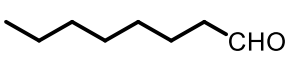
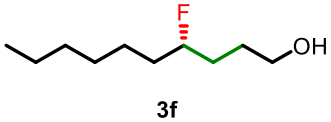
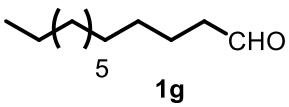
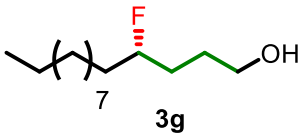
We started our initial investigation employing a variety of aldehydes **1a-g** which on α-fluorination using NFSI as fluorine source and 1 mol% (*S*)-Hayashi catalyst gave α-fluoro aldehydes (Scheme-2). Since, the α-fluoro carbonyl compounds are highly prone to racemization, the reaction in *situ* is subjected for the HWE olefination using triethyl phosphonoacetate which successfully produces the desired corresponding products **2a-g** (γ-fluoro, α,β-unsaturated esters) in good to excellent yield. The proton NMR of γ-fluoro, α,β-unsaturated ester **2a** displayed the characteristic signals at $\delta$ 7.04 - 6.92 (m, 1 H), 6.11 (td, $J$ = 1.6, 15.8 Hz, 1 H) for trans olefinic protons, and also multiplet at δ 5.42 - 5.21 ppm for 1 H, attached to fluorine. In proton decoupled carbon NMR, the compound shows the signals at $\delta$ 165.8 for ester group, 144.1 ($J_{C\text{-}F}$ = 18.8 Hz), 121.7 ($J_{C\text{-}F}$ = 10.9 Hz) for olefinic carbon, 92.4 ($J_{C\text{-}F}$ = 176.5 Hz) for fluorinated carbon, and in proton decoupled fluorine NMR, the compound shows characteristic signal at $\delta$ -181.88, which are in accordance with proposed

structure. The compound also shows +7.47 optical rotation and 1721 $cm^{-1}$ frequency in IR region, the presence of carbonyl ester. Further, the elemental formula was confirmed by the HRMS analysis. These intermediates γ-fluoro, α,β-unsaturated

**Scheme-2.** Synthesis of fluoro alcohols




| Sr. No. | Aldehyde (1) | Fluoro alcohol (3) | Yield%[a] | ee%[b] |
|---|---|---|---|---|
| **1** |  **1a** |  **3a** | 92 | 99 |
| **2** |  **1b** |  **3b** | 91 | 99 |
| **3** |  **1c** |  **3c** | 92 | 95 |
| **4** |  **1d** |  **3d** | 95 | 91 |

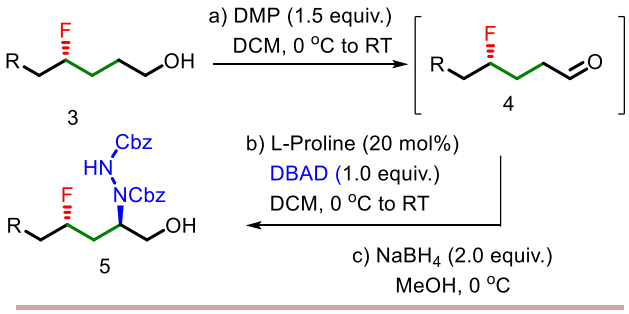
| | | | | |
|---|---|---|---|---|
| **5** |  **1e** |  **3e** | 95 | 98 |
| **6** |  **1f** |  **3f** | 90 | 94 |
| **7** |  **1g** |  **3g** | 91 | 93 |

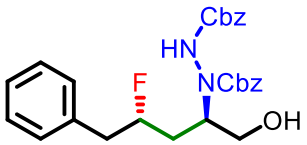
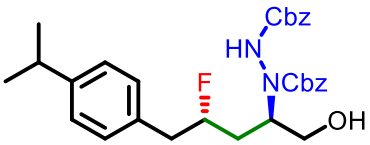
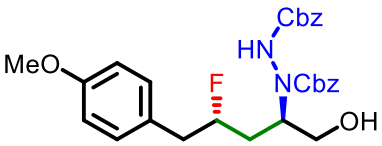
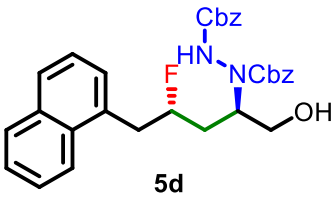
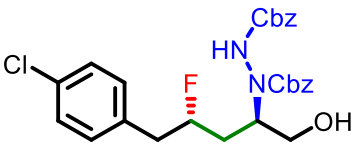
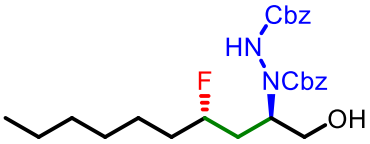
[a]Isolated yield. [b]ee% was calculated using chiral HPLC.

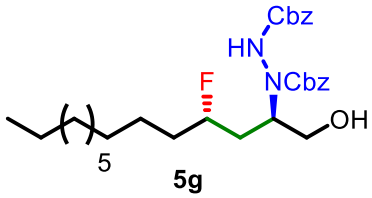
esters **2a-g** serve as a precursor to introduce amine functionality at 3-position by further synthetic manipulation. The observed configuration of the stereogenic center in α-fluoro aldehyde generated using (*S*)-Hayashi catalyst and electrophilic NFSI is based on the detailed study reported under similar reaction conditions by Jørgensen *et al.*[15] It may be pertinent to mention here that fluoro olefins are well documented as isosteres of peptides/peptidomimetics[16] and are very important, particularly in protein design.[17] The reaction was found to be quite general as it works with a variety of aldehydes such as phenyl, substituted phenyl, naphthyl, and aliphatic, etc.(yield up to 74% - 87 %). Further, these fluoro unsaturated esters were reduced using $LiBH_4$ to give γ-fluoro alcohols **3a-g** (yield up to 90% - 95%) and excellent enantioselectivities (ee up to 91% - 99%) as shown in Scheme-2. The proton NMR for γ-fluoro alcohol **3a** displayed the characteristic signals multiplet at $\delta$ 4.84 - 4.62 ppm for 1 H, attached to fluorine and multiplet at 3.75 - 3.56 for 2 H, attached to –OH functionality. In proton decoupled carbon NMR, the compound shows the absence of signal at $\delta$ 165.8 for ester group, and disappearance of signals for olefinic carbons at 144.1 ($J_{C\text{-}F}$ = 18.8 Hz), 121.7 ($J_{C\text{-}F}$ = 10.9 Hz) and appearance of new signal at 95.3 ($J_{C\text{-}F}$ = 170.9 Hz) for fluorinated carbon, 62.4 for –OH attached carbon, and in proton decoupled fluorine NMR, the compound shows characteristic signal at $\delta$ -178.71, which are in accordance with proposed structure. The compound also shows -2.42 optical rotation and 3366 $cm^{-1}$ stretching

frequency for alcoholic –OH. Further, the elemental formula was confirmed by the HRMS analysis. With these fluoro alcohols **3a-g** in hand, we next turned our attention introducing the amine functionality at 3-position with respect to the fluoro group. As depicted in Scheme-3, the DMP oxidation of fluoro alcohol **3** furnished the corresponding aldehyde **4** which was subsequently subjected to L-Proline catalyzed α-amination reaction using dibenzyl azodicarboxylate (DBAD) as a nitrogen source to afford the α-amino aldehyde, which on in situ reduction with sodium borohydride led to the anti- 1,3-fluoro amines **5** in good yield and high diastereomeric ratio as determined from chiral HPLC analysis. The proton NMR for anti-1,3-fluoro amine **5a** displayed the characteristic signals multiplet at $\delta$ 4.32 - 4.11 ppm for 1 H, attached to nitrogen and multiplet at 3.53 - 3.43 for 2 H, attached to –OH functionality. In proton decoupled carbon NMR, the compound shows the signals at $\delta$ 91.9 ($J_{C\text{-}F}$ = 171.6 Hz) for fluorinated carbon, 62.1 for –OH attached carbon, 57.2 for nitrogen attached carbon, and in proton decoupled fluorine NMR, the compound shows characteristic signal at $\delta$ -178.64, which are in accordance with proposed structure. The compound also shows -5.88 optical rotation and 98:2% dr. Further, the elemental formula was confirmed by the HRMS analysis. The stereochemistry of the newly incorporated amino group at the 3-position can be tuned by using the D / L-Proline which enables the access of either of the stereoisomers. This strategy is well explored in our group in earlier report on the enantio and diastereoselective synthesis of syn/anti-1,3-amino alcohols.[11] We further explored the applicability of this reaction with variety of functionalized aldehydes (Scheme-3). The developed reaction sequence unveiled, broad substrate scope with high functional group tolerance such as alkyl, aryl, substituted aryl groups and also with excellent diastereoselectivities

**Scheme-3.** Synthesis of anti-1,3-fluoro amine

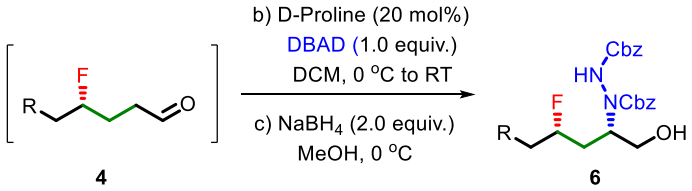


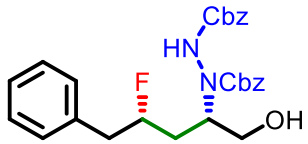
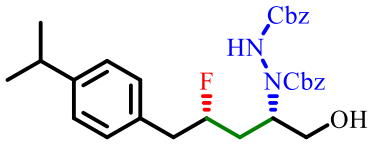
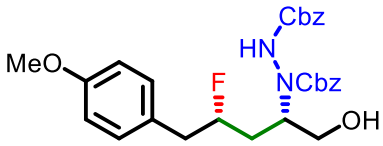
| Entry | 3 | anti-1,3-fluoro amine (5) | Overall yield%[a] | dr%[b] |
|---|---|---|---|---|
| 1 | 3a |  **5a** | 81 | 98:2 |
| 2 | 3b |  **5b** | 79 | 98:2 |
| 3 | 3c |  **5c** | 65 | 98:2 |
| 4 | 3d |  **5d** | 85 | 99:1 |
| 5 | 3e |  **5e** | 81 | 92:8 |
| 6 | 3f |  **5f** | 69 | 98:2 |

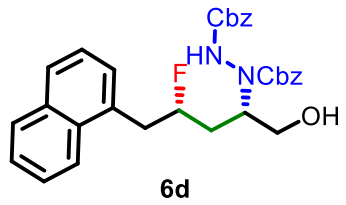
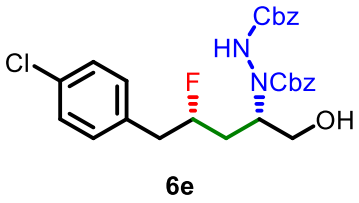
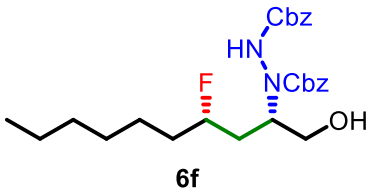
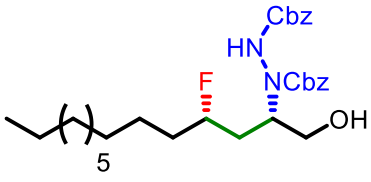
| | | | | |
|---|---|---|---|---|
| **7** | **3g** |  **5g** | 70 | 99:1 |

[a]Isolated yield. [b]dr ratio was calculated using chiral HPLC.

**Scheme-4.** Synthesis of syn-1,3-fluoro amine




| Entry | 3 | syn-1,3-fluoro amine (6) | Overall yield%[a] | dr%[b] |
|---|---|---|---|---|
| **1** | **3a** |  **6a** | 85 | 63:37 |
| **2** | **3b** |  **6b** | 77 | 63:37 |
| **3** | **3c** |  **6c** | 67 | 58:42 |

| | | | | |
|---|---|---|---|---|
| **4** | **3d** |  **6d** | 84 | 56:44 |
| **5** | **3e** |  **6e** | 86 | 69:31 |
| **6** | **3f** |  **6f** | 75 | 66:34 |
| **7** | **3g** |  **6g** | 72 | 43:57 |

[a]Isolated yield. [b]dr ratio was calculated using chiral HPLC.

(92:8% - 99:1%) (HPLC analysis, see the experimental section) and good yields (65% - 85%) were obtained for the products (Scheme-3).

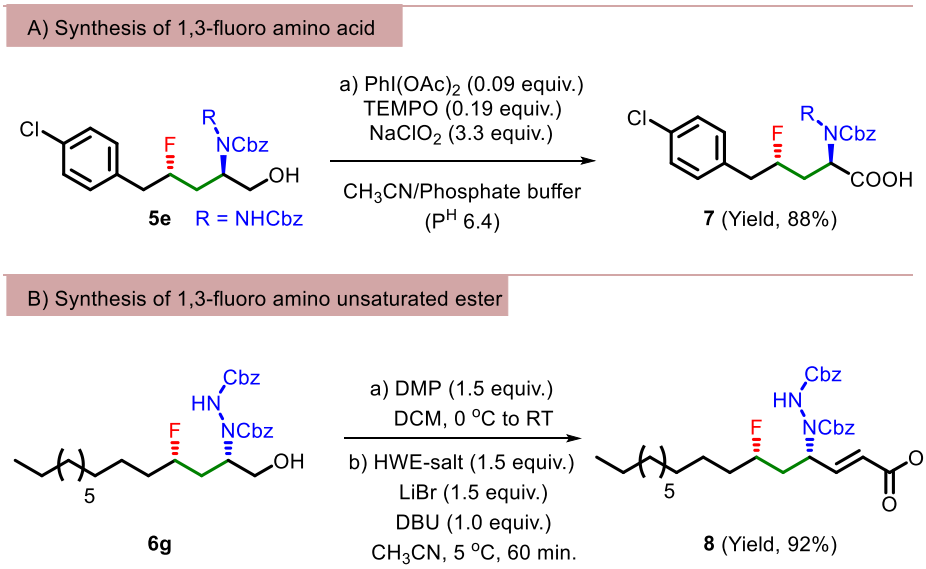
Interestingly, when the amination was performed on substrate **3a-3g** using the same sequence of reactions and D-Proline as a catalyst, we obtained syn-1,3-fluoro amines **6a-g** in 67% - 86% yield and 43:57% - 69:31% diastereomeric ratio (Scheme-4) (HPLC analysis, see the experimental section). The compound syn-1,3-fluoro amine **6a** shows -2.2 optical rotation and 63:37% dr. Further, the elemental formula was confirmed by the HRMS analysis.

By careful analysis of the diastereomeric ratio in the case of both syn-**6a-g** and anti-**5a-g** product, it appears that there is some influence of the existing stereo centres in the molecule, which also play an important role for the asymmetric induction in newly generated stereo centre and thus favours the formation of anti-diastereomer. The stereo selectivity in the syn-

isomer **6a-g** was little lower as compared to the corresponding anti-isomer **5a-g**. This might be due to considerable steric bulk present on the attacking nitrogen precursor from the syn-side.

We anticipate the multi-functional product **5** & **6** could serve as a useful building block in the synthesis of compounds of biological importance.

### 4B.5 Synthetic Utility




**Scheme-5.** Synthesis of 1,3-fluoro amino acid and synthesis of 1,3-fluoro amino unsaturated ester

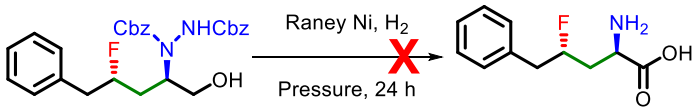
Further, we turned our attention to demonstrate the synthetic utility of this protocol as depicted in Scheme-5. The alcohol **5e** was oxidized to get the 1,3-fluoro amino acid **7** in 88% yield (Scheme-5A). In yet another synthetic manipulation, the DMP oxidation of alcohol **6g** followed by the HWE olefination furnished the desired 1,3-fluoro amino unsaturated ester **8** in 92% yield (Scheme-5B).

### 4B.6 Attempted cleavage of N–N bond: Synthesis of 1,3-fluoro amines

The cleavage of N–N bond was tried under different conditions. As shown in Scheme-6, the well-established Raney Nickel was employed to cleave the N–N bond under hydrogenation conditions according to the literature procedures.[11,12] The above cleavage was carried out with freshly prepared Raney Ni under $H_2$ using 60 psi, 80 psi, 100 psi. However, we could not succeed with the reaction. The use of high pressure 150 psi resulted only into the

decomposed product. The failure of reaction could presumably be attributed to the presence of strong intra-molecular hydrogen bonding with fluorine. Nevertheless, the use of other alternative reagents such as lithium aluminium hydride in THF, $H_2$/Pd on C, Zn in presence of HCl or acetic acid, $H_2$/$Pd(OH)_2$/C, $SmI_2$ for the N–N bond cleavage based on literature precedences is still in progress in our lab. The results will be reported in due course of time.

**Scheme-6.** Attempted cleavage of N–N bond under various conditions




**5a** **9**

| Sr. No. | Reaction Conditions | Observations |
|---|---|---|
| **1** | Raney Ni (excess), $H_2$, 60 psi, 24 h | No Reaction |
| **2** | Raney Ni (excess), $H_2$, 80 psi, 24 h | No Reaction |
| **3** | Raney Ni (excess), $H_2$, 100 psi, 24 h | No Reaction |
| **4** | Raney Ni (excess), $H_2$, 150 psi, 24 h | Decomposed (Highly polar spot observed) |

### 4B.7 Conclusion

We have developed an efficient organocatalytic approach to the enantioselective synthesis of 1,3-fluoro amines from commercially available starting material using sequential α-fluorination and α-amination reactions of an aldehyde in high enantio- and diastereoselectivity. The synthetic strategy allows the implementation of the desirable stereocenters of both fluoro and amino at 1,3-positions. The resultant product γ-fluoro, α-amino alcohol derivatives serve as useful building blocks for the synthesis of biologically useful compounds particularly fluorinated amino acids.

## 4B. 8 Experimental Section

### 4B.8.1 General Information

All chemicals were purchased from commercial suppliers and used without further purification. NMR spectra were recorded at 400 MHz ($^{1}$H), 100 MHz ($^{13}$C), and 376 MHz ($^{19}$F) in $CDCl_3$ solution. The chemical shifts are expressed in parts per million ($\delta$) and are referenced to tetramethylsilane (TMS) as the internal standard and the signals were reported as s (singlet), d (doublet), t (triplet), br. (broad) and m (multiplet) and coupling constants *J* were given in Hz. HRMS analysis were performed on a Q-TOF mass analyzer using the ESI ionization method. TLC was performed with Merck Silica gel 60 $F_{254}$. Silica gel (60–120 mesh) was used for column chromatography. Chiral HPLC performed on Agilent Technologies 1260 Infinity & Prominence-i LC-2030C 3D Plus Liquid Chromatography.

### 4B.8.2 General Procedure-1

**Organocatalytic α-fluorination followed by HWE olefination of aldehyde**

To a stirred solution of aldehyde (1.5 equiv.), catalyst (*S*)-2-[bis-(3, 5-bistrifluoromethyl-phenyl)-trimethylsilanyloxy- methyl]-pyrrolidine (1.0 mol%) was added at room temperature in MTBE (10.0 mL) under argon condition. After 30 min., N-fluorodibenzenesulfonimide (NFSI) (1.0 equiv.) was added to the reaction in one portion. The reaction mixture was then stirred for 12 h at room temperature. Then the reaction mixture was filtered off and washed with pentane (3.0 times) and concentrated under reduced pressure to give the crude product of α-fluoro aldehyde.[18]

The crude α-fluoro aldehyde (1.0 equiv.) was dissolved in 20 mL of dry acetonitrile. Then lithium bromide (1.5 equiv.), triethyl phosphonoacetate (1.5 equiv.), and DBU (1.0 equiv.) were added under argon condition at 0 $^{o}$C. The reaction mixture was stirred at 5 $^{o}$C temperature for 60 min. and the progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched using aqueous ammonium chloride solution and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The crude product was then purified by flash column chromatography to afford the pure olefinic fluoro ester.[19]

### 4B.8.3 General Procedure-2

**Reduction of olefinic fluoro ester to saturated fluoro alcohol**

To a stirred solution of corresponding olefinic fluoro ester (1.0 equiv.) was added $LiBH_4$ (5.0 equiv.) at 0 $^oC$ in dry THF (15 mL) under argon condition. The reaction mixture was stirred at room temperature and the progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched using aqueous ammonium chloride solution and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The crude product was then purified by flash column chromatography to afford the pure saturated fluoro alcohol.[19]

### 4B.8.4 General Procedure-3

**Synthesis of γ-fluoro amino alcohol**

To a stirred solution of corresponding saturated fluoro alcohol (1.0 equiv.) was added Dess Martin periodinane (1.5 equiv.) at 0 $^oC$ in dry DCM (10 mL) under argon condition. Then the reaction mixture was stirred at room temperature for 1 h and reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with aqueous $NaHCO_3/Na_2S_2O_3$ (1:1) solution until the reaction mixture becomes clear. Then the reaction mixture was extracted with DCM (3 × 20 mL) and combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$. The solvent was concentrated under reduced pressure to afford the crude corresponding saturated γ-fluoro aldehyde, which was directly used in the next step without purification.[19]

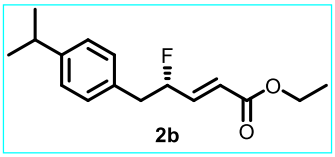
In dry DCM (10 mL), L/D-Proline (20 mol%) was stirred at room temperature for 30 min. under argon condition. Then corresponding γ-fluoro aldehyde (1.0 equiv.) was added at 0 $^oC$ and stirred for 10 min. The further reaction mixture was stirred at room temperature for 60 min. Then DBAD (1.0 equiv.) was added to the reaction mixture at room temperature and stirred until the yellow colour disappeared.[20] Reaction progress was monitored by TLC. After completion of the reaction, additionally, 5 mL of methanol was added to the reaction mixture. Then $NaBH_4$ (2.0 equiv.) was added in one portion at 0 $^oC$ and further stirred for 30 min. The reaction mixture was quenched using aqueous ammonium chloride solution and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried

over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The crude product was then purified by flash column chromatography to afford the pure γ-fluoro amino alcohol.[19]

**4B.9 NMR Data**

**Ethyl (*S*,*E*)-4-fluoro-5-phenylpent-2-enoate (2a)**

Synthesized according to General Procedure-1. 3-Phenyl propanal **(1a)** was used as a substrate, to give ethyl (*S*,*E*)-4-fluoro-phenylpent-2-enoate **(2a)** as a colourless liquid; 87% yield. **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.41 - 7.24 (m, 5 H), 7.04 - 6.92 (m, 1 H), 6.11 (td, *J* = 1.6, 15.8 Hz, 1 H), 5.42 - 5.21 (m, 1 H), 4.26 (q, *J* = 7.2 Hz, 2 H), 3.17 - 2.99 (m, 2 H), 1.35 (t, *J* = 7.1 Hz, 3 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 165.8, 144.1 ($J_{C\text{-}F}$ = 18.8 Hz), 135.6 ($J_{C\text{-}F}$ = 4.3 Hz), 129.4, 128.6, 127.0, 121.7 ($J_{C\text{-}F}$ = 10.9 Hz), 92.4 ($J_{C\text{-}F}$ = 176.5 Hz), 60.6, 41.4 ($J_{C\text{-}F}$ = 22.2 Hz), 14.2; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -181.88; **$[\alpha]_D^{25}$** = +7.47 (c = 0.8, $CHCl_3$); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$2984, 1721, 1272, 1174, 1039, 704; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{13}H_{15}FO_2$ $[M + H]^+$ 223.1134, found 223.1123.




……..

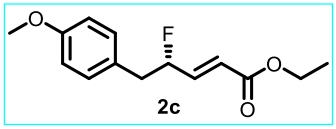



**Ethyl (*S*,*E*)-4-fluoro-5-(4-isopropylphenyl)pent-2-enoate (2b)**

Synthesized according to General Procedure-1. 3-(4-isopropylphenyl)propanal **(1b)** was used as a substrate, to give ethyl (*S*,*E*)-4-fluoro-5-(4-isopropylphenyl)pent-2-enoate **(2b)** as a colourless liquid; 80% yield. **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.22 - 7.14 (m, 4 H), 7.01 - 6.89 (m, 1 H), 6.09 (td, *J* = 1.5, 15.9 Hz, 1 H), 5.33 - 5.21 (m, 1 H), 4.23 (q, *J* = 7.1 Hz, 2 H), 3.11 - 2.86 (m, 3 H), 1.31 (t, *J* = 7.1 Hz, 3 H), 1.26 (d, *J* = 6.9 Hz, 6 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 165.9, 147.6, 144.4 ($J_{C\text{-}F}$ = 18.3 Hz), 132.9 ($J_{C\text{-}F}$ = 4.5 Hz), 129.3, 126.6, 121.6 ($J_{C\text{-}F}$ = 10.6 Hz), 92.5 ($J_{C\text{-}F}$ = 177.0 Hz), 60.6, 41.0 ($J_{C\text{-}F}$ = 21.3 Hz), 33.7, 23.9, 14.2; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -181.74; **$[\alpha]_D^{25}$** = +70.14 (c = 2, $CHCl_3$); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$2964, 1722, 1272, 1173, 1041, 820; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{16}H_{21}FO_2$ $[M + H]^+$ 265.1604, found 265.1599.

……..

**Ethyl (*S*,*E*)-4-fluoro-5-(4-methoxyphenyl)pent-2-enoate (2c)**

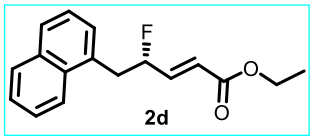



Synthesized according to General Procedure-1. 3-(4-Methoxyphenyl)propanal **(1c)** was used as a substrate, to give

ethyl (*S*,*E*)-4-fluoro-5-(4-methoxyphenyl)pent-2-enoate **(2c)** as a colourless liquid; 75% yield. **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.14 (d, *J* = 8.5 Hz, 2 H), 6.97 - 6.90 (m, 1 H), 6.89 - 6.84 (m, 2 H), 6.05 (td, *J* = 1.6, 15.8 Hz, 1 H), 5.35 - 5.23 (m, 1 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 3.81 (s, 3 H), 3.11 - 2.85 (m, 2 H), 1.30 (t, *J* = 7.1 Hz, 3 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 165.9, 158.6, 144.3 ($J_{C\text{-}F}$ = 19.0 Hz), 130.4, 127.6 ($J_{C\text{-}F}$ = 4.5 Hz), 121.7 ($J_{C\text{-}F}$ = 10.6 Hz), 114.0, 92.6 ($J_{C\text{-}F}$ = 176.2 Hz), 60.6, 55.2, 40.5 ($J_{C\text{-}F}$ = 22.1 Hz), 14.2; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -181.94; **$[\alpha]_D^{25}$** = +64.47 (c = 1, $CHCl_3$); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$2928, 1721, 1513, 1254, 1174, 1037, 819; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{14}H_{17}FO_3$ $[M + H]^+$ 253.1240, found. 253.1252.

**……..**

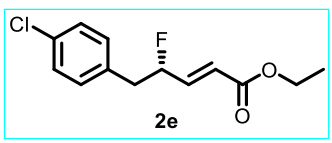
**Ethyl (*S*,*E*)-4-fluoro-5-(naphthalen-2-yl)pent-2-enoate (2d)**




Synthesized according to General Procedure-1. 3-(Naphthalen-2-yl)propanal **(1d)** was used as a substrate, to give ethyl (*S*,*E*)-4-fluoro-5-(naphthalen-2-yl)pent-2-enoate **(2d)** as a colourless liquid; 85% yield. **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 8.01 (d, *J* = 8.4 Hz, 1 H), 7.90 (dd, *J* = 1.1, 8.3 Hz, 1 H), 7.82 (d, *J* = 8.1 Hz, 1 H), 7.59 - 7.50 (m, 2 H), 7.48 - 7.39 (m, 2 H), 7.07 - 6.96 (m, 1 H), 6.12 (td, *J* = 1.6, 15.8 Hz, 1 H), 5.59 - 5.32 (m, 1 H), 4.23 (q, *J* = 7.1 Hz, 2 H), 3.61 - 3.41 (m, 2 H), 1.31 (t, *J* = 7.1 Hz, 3 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 165.8, 144.3 ($J_{C\text{-}F}$ = 18.3 Hz), 133.9, 131.9, 131.6 ($J_{C\text{-}F}$ = 5.3 Hz), 128.9, 128.0, 127.9, 126.3, 125.7, 125.4, 123.2, 121.6 ($J_{C\text{-}F}$ = 10.6 Hz), 91.8 ($J_{C\text{-}F}$ = 177.7 Hz), 60.6, 38.4 ($J_{C\text{-}F}$ = 22.8 Hz), 14.1; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -180.00; **$[\alpha]_D^{25}$** = +297.68 (c = 4, $CHCl_3$); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$2981, 1720, 1273, 1173, 1036, 787; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{17}H_{17}FO_2$ $[M + H]^+$ 273.1291, found 273.1285.

**……..**

**Ethyl (*S*,*E*)-5-(4-chlorophenyl)-4-fluoropent-2-enoate (2e)**

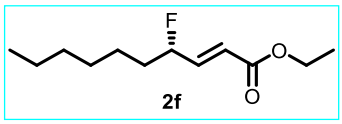



Synthesized according to General Procedure-1. 3-(4-chlorophenyl)propanal **(1e)** was used as a substrate, to give ethyl (*S*,*E*)-5-(4-chlorophenyl)-4-fluoropent-2-enoate **(2e)** as a colourless liquid; 82% yield. **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.32 - 7.23 (m, 2 H), 7.15 (d, *J* = 8.3 Hz, 2 H), 6.97 - 6.77 (m, 1 H), 6.04 (td, *J* = 1.5, 15.8 Hz, 1 H), 5.36 - 5.24 (m, 1 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 3.07 - 2.88 (m, 2 H), 1.29 (t, *J* = 7.1 Hz, 3 H); **$^{13}$C NMR** (100 MHz,

$CDCl_3$) $\delta$ = 165.7, 143.7 ($J_{C\text{-}F}$ = 18.3 Hz), 134.0 ($J_{C\text{-}F}$ = 3.8 Hz), 132.9, 130.7, 128.7, 122.0 ($J_{C\text{-}F}$ = 11.4 Hz), 92.0($J_{C\text{-}F}$ = 177.7 Hz), 60.7, 40.6 ($J_{C\text{-}F}$ = 22.1 Hz), 14.1; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -182.42; **$[\alpha]_D^{25}$** = -0.51 (c = 3.3, $CHCl_3$); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$2983, 1716, 1663, 1488, 1303, 1272, 1176, 1090, 1033, 845, 710; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{13}H_{14}ClFO_2$ $[M + H]^+$ 257.0739, found 257.0732.

**……..**

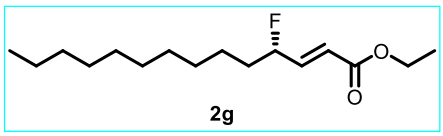
**Ethyl (*S,E*)-4-fluorodec-2-enoate (2f)**




Synthesized according to General Procedure-1. Octanal **(1f)** was used as a substrate, to give ethyl (*S,E*)-4-fluorodec-2-enoate **(2f)** as a colourless liquid; 74% yield. **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 6.99 - 6.75 (m, 1 H), 6.05 (td, *J* = 1.6, 15.8 Hz, 1 H), 5.27 - 4.94 (m, 1 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 1.82 - 1.59 (m, 2 H), 1.48 - 1.38 (m, 2 H), 1.37 - 1.23 (m, 9 H), 0.95 - 0.82 (m, 3 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 166.0, 145.2 ($J_{C\text{-}F}$ = 19.0 Hz), 121.0 ($J_{C\text{-}F}$ = 11.4 Hz), 92.2 ($J_{C\text{-}F}$ = 173.9 Hz), 60.6, 34.8 ($J_{C\text{-}F}$ = 21.3 Hz), 31.6, 28.9, 24.5, 24.4, 22.5, 14.2, 14.0; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -184.07; **$[\alpha]_D^{25}$** = +95.06 (c = 4, $CHCl_3$); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$2931, 1724, 1460, 1270, 1175, 1041, 979, 864; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{12}H_{21}FO_2$ $[M + H]^+$ 217.1604, found. 217.1598.

**……..**

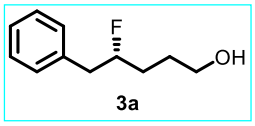
**Ethyl (*S,E*)-4-fluorotetradec-2-enoate (2g)**




Synthesized according to General Procedure-1. Dodecanal **(1g)** was used as a substrate, to give ethyl (*S,E*)-4-fluorotetradec-2-enoate **(2g)** as a colourless liquid; 79% yield. **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.01 - 6.77 (m, 1 H), 6.06 (td, *J* = 1.6, 15.8 Hz, 1 H), 5.17 - 5.08 (m, 1 H), 4.22 (q, *J* = 7.1 Hz, 2 H), 1.78 - 1.64 (m, 2 H), 1.49 - 1.40 (m, 2 H), 1.32 - 1.26 (m, 17 H), 0.91 - 0.86 (m, 3 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 166.1, 145.3 ($J_{C\text{-}F}$ = 19.0 Hz), 121.1 ($J_{C\text{-}F}$ = 11.4 Hz), 92.2 ($J_{C\text{-}F}$ = 173.1 Hz), 60.6, 34.8 ($J_{C\text{-}F}$ = 21.3 Hz), 31.9, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 29.3, 24.5, 24.5, 22.7, 14.2, 14.1; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -184.06; **$[\alpha]_D^{25}$** = +34.73 (c = 2, $CHCl_3$); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$2925, 1723, 1460, 1271, 1175, 1041, 979, 785; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{16}H_{29}FO_2$ $[M + H]^+$ 273.2230, found 273.2222.

**……..**

**(*R*)-4-fluoro-5-phenylpentan-1-ol (3a)**

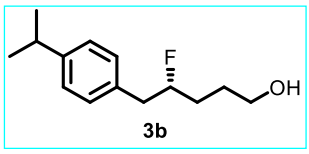


3a

Synthesized according to General Procedure 2. Ethyl (*S*,*E*)-4-fluoro-phenylpent-2-enoate **(2a)** was used as a substrate, to give (*R*)-4-fluoro-5-phenylpentan-1-ol **(3a)** as a colourless liquid; 92% yield. **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.36 - 7.21 (m, 5 H), 4.84 - 4.62 (m, 1 H), 3.75 - 3.56 (m, 2 H), 3.09 - 2.79 (m, 2 H), 1.79 - 1.67 (m, 4 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 137.2 ($J_{C\text{-}F}$ = 5.3 Hz), 129.3, 128.4, 126.5, 95.3 ($J_{C\text{-}F}$ = 170.9 Hz), 62.4, 41.7 ($J_{C\text{-}F}$ = 21.3 Hz), 31.1 ($J_{C\text{-}F}$ = 20.6 Hz), 28.3 ($J_{C\text{-}F}$ = 3.0 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -178.71. The ee was determined by Prominence-*i*LC-2030C 3D Plus UV detector HPLC on a Daicel Chiralcel OD-H column (250 × 4.6 mm) with *i*PrOH/hexane (10:90) as the eluent, flow rate 1.0 mL/min. ($\lambda$ = 254 nm). $R_t$ (min): 7.545 (major enantiomer), 8.387 (minor enantiomer). **$[\alpha]_D^{25}$** = -2.42 (c = 0.5, $CHCl_3$, 99% ee); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$3366, 2930, 1597, 1445, 1048, 743, 698; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{11}H_{15}FO$ $[M + H]^+$ 183.1185, found 183.1179.

**……..**

**(*R*)-4-fluoro-5-(4-isopropylphenyl)pentan-1-ol (3b)**

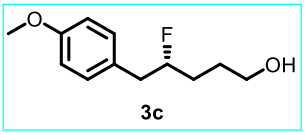


3b

Synthesized according to General Procedure 2. Ethyl (*S*,*E*)-4-fluoro-5-(4-isopropylphenyl)pent-2-enoate **(2b)** was used as a substrate, to give (*R*)-4-fluoro-5-(4-isopropylphenyl)pentan-1-ol **(3b)** as a colourless liquid; 91% yield. **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.20 - 7.14 (m, 4 H), 4.72 - 4.58 (m, 1 H), 3.80 - 3.59 (t, 2 H), 3.04 - 2.77 (m, 3 H), 1.83 - 1.65 (m, 4 H), 1.25 (d, *J* = 6.9 Hz, 6 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 147.1, 134.4 ($J_{C\text{-}F}$ = 4.5 Hz), 129.4, 129.3, 126.5, 95.5 ($J_{C\text{-}F}$ = 170.1 Hz), 62.6, 41.4 ($J_{C\text{-}F}$ = 22.1 Hz), 33.7, 31.1 ($J_{C\text{-}F}$ = 20.6 Hz), 28.4 ($J_{C\text{-}F}$ = 3.8 Hz), 24.0; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -178.61. The ee was determined by Prominence-*i*LC-2030C 3D Plus UV detector HPLC on a Daicel Chiralcel OD-H column(250 × 4.6 mm) with *i*PrOH/ hexane (10:90) as the eluent, flow rate 1.0 mL/min. ($\lambda$ = 254 nm). $R_t$ (min): 5.332 (major enantiomer), 6.467 (minor enantiomer). **$[\alpha]_D^{25}$** = -4.36 (c = 0.3, $CHCl_3$, 99% ee); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$3368, 2953, 1513, 1455, 1053, 815; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{14}H_{21}FO$ $[M + H]^+$ 225.1655, found. 225.1650.

**……..**

**(*R*)-4-fluoro-5-(4-methoxyphenyl)pentan-1-ol (3c)**

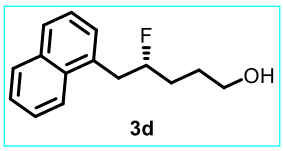


3c

Synthesized according to General Procedure 2. Ethyl (*S*,*E*)-4-fluoro-5-(4-methoxyphenyl)pent-2-enoate **(2c)** was used as a substrate, to give (*R*)-4-fluoro-5-(4-methoxyphenyl)pentan-1-ol **(3c)** as a colourless liquid; 92% yield. **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.20 - 7.07 (m, *J* = 8.4 Hz, 2 H), 6.91 - 6.80 (m, 2 H), 4.80 - 4.56 (m, 1 H), 3.80 (s, 3 H), 3.72 - 3.64 (m, 2 H), 3.00 - 2.76 (m, 2 H), 1.82 - 1.64 (m, 4 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 158.3, 130.3, 129.2 ($J_{C\text{-}F}$ = 4.5 Hz), 113.9, 95.5 ($J_{C\text{-}F}$ = 170.9 Hz), 77.3, 62.5, 55.2, 40.9 ($J_{C\text{-}F}$ = 31.3 Hz), 31.0 ($J_{C\text{-}F}$ = 20.6 Hz), 28.4 ($J_{C\text{-}F}$ = 3.8 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -178.82. The ee was determined by Agilent Technologies 1260 VWD UV detector HPLC on a Daicel Chiralcel OD-H column (250 × 4.6 mm) with *i*PrOH/ hexane (10:90) as the eluent, flow rate 1.0 mL/min. (λ = 254 nm). $R_t$ (min): 10.260 (major enantiomer), 9.570 (minor enantiomer). **$[\alpha]_D^{25}$** = -5.1 (c = 0.5, $CHCl_3$, 95% ee); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$3367, 2924, 1611, 1512, 1454, 1245, 1035, 815; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{12}H_{17}FO_2$ $[M + H]^+$ 213.1291, found 213.1285.

**……..**

**(*R*)-4-fluoro-5-(naphthalen-2-yl)pentan-1-ol (3d)**

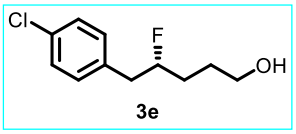


3d

Synthesized according to General Procedure 2. Ethyl (*S*,*E*)-4-fluoro-5-(naphthalen-2-yl)pent-2-enoate **(2d)** was used as a substrate, to give (*R*)-4-fluoro-5-(naphthalen-2-yl)pentan-1-ol **(3d)** as a colourless liquid; 95% yield. **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 8.03 (d, *J* = 8.3 Hz, 1 H), 7.88 (dd, *J* = 1.2, 8.2 Hz, 1 H), 7.78 (d, *J* = 8.0 Hz, 1 H), 7.57 - 7.48 (m, 2 H), 7.46 - 7.38 (m, 2 H), 5.02 - 4.85 (m, 1 H), 3.69 (t, *J* = 5.7 Hz, 2 H), 3.55 - 3.27 (m, 2 H), 1.87 - 1.66 (m, 4 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 133.9, 133.3 ($J_{C\text{-}F}$ = 5.3 Hz), 132.1, 128.9, 127.7, 127.5, 126.1, 125.6, 125.5, 123.6, 94.8 ($J_{C\text{-}F}$ = 171.6 Hz), 62.5, 38.9 ($J_{C\text{-}F}$ = 22.8 Hz), 31.6 ($J_{C\text{-}F}$ = 20.8 Hz), 28.5 ($J_{C\text{-}F}$ = 3.8 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -176.76. The ee was determined by Prominence-*i*LC-2030C 3D Plus UV detector HPLC on a Daicel Chiralcel OD-H column (250 × 4.6 mm) with *i*PrOH/ hexane (10:90) as the eluent, flow rate 1.0 mL/min. (λ = 254 nm). $R_t$ (min): 12.735 (major enantiomer), 15.002 (minor enantiomer). **$[\alpha]_D^{25}$** = -16.36 (c = 0.3, $CHCl_3$, 91% ee); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$3366, 2925, 1730, 1594, 1450, 1389, 1057, 785; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{15}H_{17}FO$ $[M + Na]^+$ 255.1161, found. 255.1155.

……..

**(*R*)-5-(4-chlorophenyl)-4-fluoropentan-1-ol (3e)**

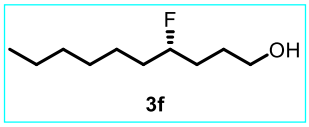


3e

Synthesized according to General Procedure 2. Ethyl (*S*,*E*)-5-(4-chlorophenyl)-4-fluoropent-2-enoate **(2e)** was used as a substrate, to give (*R*)-5-(4-chlorophenyl)-4-fluoropentan-1-ol **(3e)** as a colourless liquid; 95% yield. **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.31 - 7.23 (m, 2 H), 7.14 (d, *J* = 8.3 Hz, 2 H), 4.82 - 4.52 (m, 1 H), 3.74 - 3.51 (m, 2 H), 3.02 - 2.73 (m, 2 H), 1.83 - 1.55 (m, 4 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 135.6 ($J_{C\text{-}F}$ = 4.5 Hz), 132.3, 130.6, 128.4, 94.9 ($J_{C\text{-}F}$ = 171.6 Hz), 62.2, 40.9 ($J_{C\text{-}F}$ = 21.3 Hz), 31.0 ($J_{C\text{-}F}$ = 20.6 Hz), 28.2 ($J_{C\text{-}F}$ = 3.8 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -179.35. The ee was determined by Agilent Technologies 1260 VWD UV detector HPLC on a Daicel Chiralcel OD-H column (250 × 4.6 mm) with *i*PrOH/ hexane (10:90) as the eluent, flow rate 1.0 mL/min. ($\lambda$ = 254 nm). $R_t$ (min): 7.940 (major enantiomer), 8.720 (minor enantiomer). **$[\alpha]_D^{25}$** = -2.66 (c = 4.4, $CHCl_3$, 98% ee); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$3411, 2942, 1640, 1490, 1294, 1054, 805; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{11}H_{14}ClFO$ $[M + H]^+$ 217.0790, found. 217.0784.

……..

**(*S*)-4-fluorodecan-1-ol (3f)**

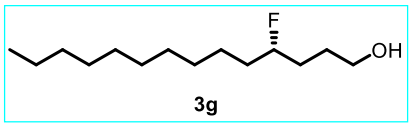


3f

Synthesized according to General Procedure 2. Ethyl (*S*,*E*)-4-fluorodec-2-enoate **(2f)** was used as a substrate, to give (*S*)-4-fluorodecan-1-ol **(3f)** as a colourless liquid; 90% yield. **$^{1}$H NMR** (400MHz, $CDCl_3$) $\delta$ = 4.69 - 4.35 (m, 1 H), 3.77 - 3.58 (m, 2 H), 1.74 - 1.60 (m, 6 H), 1.34 - 1.27 (m, 8 H), 0.91 - 0.88 (m, 3 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 95.3 ($J_{C\text{-}F}$ = 167.0 Hz), 62.7, 35.3 ($J_{C\text{-}F}$ = 21.3 Hz), 31.7, 31.6, 31.4, 29.1, 28.4 ($J_{C\text{-}F}$ = 3.8 Hz), 25.1 ($J_{C\text{-}F}$ = 4.5 Hz), 22.6, 14.0; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -180.13. The ee was determined by Agilent Technologies 1260 VWD UV detector HPLC on a Daicel Chiralcel OD-H column (250 × 4.6 mm) with *i*PrOH/ hexane (10:90) as the eluent, flow rate 1.0 mL/min. ($\lambda$ = 254 nm). $R_t$ (min): 3.167 (major enantiomer), 3.593 (minor enantiomer). **$[\alpha]_D^{25}$** = +7.86 (c = 0.5, $CHCl_3$, 94% ee); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$3354, 2928, 1457, 1381, 1053, 723; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{10}H_{21}FO$ $[M + H]^+$ 177.1655, found 177.1649.

……..

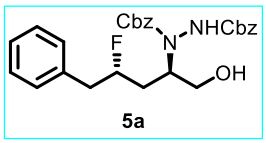
**(*S*)-4-fluorotetradecan-1-ol (3g)**




Synthesized according to General Procedure 2. Ethyl (*S*,*E*)-4-fluorotetradec-2-enoate **(2g)** was used as a substrate, to give (*S*)-4-fluorotetradecan-1-ol **(3g)** as a colourless liquid; 91% yield. **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 4.64 - 4.37 (m, 1 H), 3.76 - 3.60 (m, 2 H), 1.79 - 1.60 (m, 6 H), 1.60 - 1.42 (m, 3 H), 1.27 (s, 13 H), 0.92 - 0.86 (m, 3 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 95.3 ($J_{C\text{-}F}$ = 167.0 Hz), 62.6, 35.3 ($J_{C\text{-}F}$ = 21.3 Hz), 31.9, 31.6, 31.4, 29.6, 29.6, 29.5, 29.5, 29.4, 29.3, 28.4 ($J_{C\text{-}F}$ = 3.8 Hz), 25.1 ($J_{C\text{-}F}$ = 4.5 Hz), 22.7, 14.1; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -180.11. The ee was determined by Prominence-*i*LC-2030C 3D Plus UV detector HPLC on a Daicel Chiralcel OD-H column (250 × 4.6 mm) with *i*PrOH/ hexane (10:90) as the eluent, flow rate 1.0 mL/min. (λ = 254 nm). $R_t$ (min): 5.216 (major enantiomer), 5.972 (minor enantiomer). **$[\alpha]_D^{25}$** = +3.66 (c = 0.5, $CHCl_3$, 93% ee); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$3366, 2919, 1461, 1215, 1058, 993, 758; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{14}H_{29}FO$ $[M + H]^+$ 233.2281, found 233.2284.

**……..**

**Dibenzyl 1-((2*R*,4*S*)-4-fluoro-1-hydroxy-5-phenylpentan-2-yl)hydrazine-1,2-dicarboxylate (5a)**

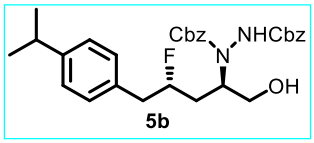



Synthesized according to General Procedure 3. (*R*)-4-fluoro-5-phenylpentan-1-ol **(3a)** was used as a substrate and L-Proline as an organocatalyst, to give dibenzyl 1-((2*R*,4*S*)-4-fluoro-1-hydroxy-5-phenylpentan-2-yl)hydrazine-1,2-dicarboxylate **(5a)** as a waxy solid; 81% yield. **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.35 - 7.11 (m, 15 H), 6.61 - 6.46 (m, 1 H), 5.32 - 5.09 (m, 4 H), 4.80 - 4.49 (m, 2 H), 4.32 - 4.11 (m, 1 H), 3.53 - 3.43 (m, 2 H), 3.05 - 2.75 (m, 2 H), 1.85 - 1.42 (m, 2 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 156.8, 155.9, 136.6, 136.4, 136.1, 135.7 ($J_{C\text{-}F}$ = 15.2 Hz), 135.0, 129.3, 128.6, 128.5, 128.5, 128.2, 127.8, 127.7, 126.8, 126.7, 91.9 ($J_{C\text{-}F}$ = 171.6 Hz), 68.6, 68.4, 68.2, 62.1, 61.7, 57.2, 55.8, 41.1 ($J_{C\text{-}F}$ = 22.1 Hz), 32.2 ($J_{C\text{-}F}$ = 24.4 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -178.64. Diastereomeric ratio was determined by HPLC analysis; 98:2 dr. UV detector: Agilent Technologies 1260 VWD. Column: OD-H (250 × 4.6 mm). Flow rate: 1.0 mL/min. (λ = 254 nm). *i*PrOH/petroleum ether (20:80); $t_R$ for (*anti*)-isomer = 12.800 min. and $t_R$ for (*syn*)-isomer = 10.887 min. **$[\alpha]_D^{28}$** = -5.88 (c = 1.2,

$CHCl_3$); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$3272, 2929, 1684, 1531, 1423, 1279, 1059, 747; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{27}H_{29}FN_2O_5$ $[M + H]^+$ 481.2139, found. 481.2133.

**……..**

**Dibenzyl 1-((2*R*,4*S*)-4-fluoro-1-hydroxy-5-(4-isopropylphenyl)pentan-2-yl)hydrazine-1,2-dicarboxylate (5b)**

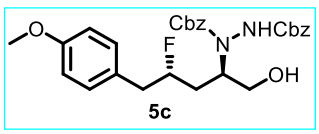


**5b**

Synthesized according to General Procedure 3. (*R*)-4-fluoro-5-(4-isopropylphenyl)pentan-1-ol **(3b)** was used as a substrate and L-Proline as an organocatalyst, to give dibenzyl 1-((2*R*,4*S*)-4-fluoro-1-hydroxy-5-(4-isopropylphenyl)pentan-2-yl)hydrazine-1,2-dicarboxylate **(5b)** as a waxy solid; 79% yield. **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.42 - 7.26 (m, 10 H), 7.14 (t, *J* = 7.3 Hz, 2 H), 7.09 - 7.01 (m, 2 H), 5.32 - 5.06 (m, 4 H), 4.79 - 4.55 (m, 2 H), 4.30 - 4.07 (m, 1 H), 3.57 - 3.43 (m, 2 H), 3.05 - 2.70 (m, 3 H), 1.76 - 1.47 (m, 2 H), 1.23 - 1.21 (d, *J* = 6.9 Hz, 6 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 156.7, 155.9, 147.5, 135.8 ($J_{C\text{-}F}$ = 17.7 Hz), 135.0, 133.8, 133.6, 129.2, 128.6, 128.5, 128.3, 128.0, 127.8, 126.7, 92.0 ($J_{C\text{-}F}$ = 171.6 Hz), 68.7, 68.6, 68.3, 62.2, 57.4, 55.9, 40.7 ($J_{C\text{-}F}$ = 21.9 Hz), 33.7, 32.1 ($J_{C\text{-}F}$ = 29.5 Hz), 23.9; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -177.17. Diastereomeric ratio was determined by HPLC analysis; 98:2 dr. UV detector: Agilent Technologies 1260 VWD. Column: OD-H (250 × 4.6 mm). Flow rate: 1.0 mL/min. (λ = 254 nm). *i*PrOH/petroleum ether (20:80); $t_R$ for (*anti*)-isomer = 9.950 min. and $t_R$ for (*syn*)-isomer = 13.387 min. **$[\alpha]_D^{28}$** = -8.43 (c = 0.8, $CHCl_3$); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$3271, 2958, 1682, 1528, 1422, 1257, 1057, 757; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{30}H_{35}FN_2O_5$ $[M + H]^+$ 523.2603, found 523.2599.

**……..**

**Dibenzyl 1-((2*R*,4*S*)-4-fluoro-1-hydroxy-5-(4-methoxyphenyl)pentan-2-yl)hydrazine-1,2-dicarboxylate (5c)**



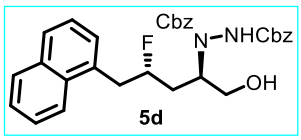
**5c**

Synthesized according to General Procedure 3. (*R*)-4-fluoro-5-(4-methoxyphenyl)pentan-1-ol **(3c)** was used as a substrate and L-Proline as an organocatalyst, to give dibenzyl 1-((2*R*,4*S*)-4-fluoro-1-hydroxy-5-(4-methoxyphenyl)pentan-2-yl)hydrazine-1,2-dicarboxylate **(5c)** as a waxy solid; 65% yield. **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.25 - 7.19 (m, 10 H), 7.01 - 6.96 (m, 2 H), 6.76 (d, *J* = 7.9 Hz, 2 H), 5.23 - 4.93 (m, 4 H), 4.70 - 4.36 (m, 3 H), 3.70 (d, *J* = 13.9 Hz, 3 H), 3.36 (br. s., 2 H), 2.92 - 2.63 (m, 2 H), 1.60 - 1.30 (m, 2 H); **$^{13}$C NMR** (100 MHz,

$CDCl_3$) $\delta$ = 158.5, 156.8, 135.7 ($J_{C\text{-}F}$ = 17.1 Hz), 135.5, 135.0, 130.4, 130.2, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.8, 127.5, 114.0, 114.0, 92.0 ($J_{C\text{-}F}$ = 171.6 Hz), 68.7, 68.5, 68.4, 68.3, 67.9, 62.2, 61.8, 55.2, 40.2 ($J_{C\text{-}F}$ = 20.9 Hz), 32.0 ($J_{C\text{-}F}$ = 16.2 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -178.25. Diastereomeric ratio was determined by HPLC analysis; 98:2 dr. UV detector: Agilent Technologies 1260 VWD. Column: OD-H (250 × 4.6 mm). Flow rate: 0.5 mL/min. (λ = 254 nm). *i*PrOH/petroleum ether (10:90); $t_R$ for (*anti*)-isomer = 36.603min. and $t_R$ for (*syn*)-isomer =42.620 min. **$[\alpha]_D^{28}$** = -8.35 (c = 0.7, $CHCl_3$); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$3288, 2925, 1718, 1510, 1412, 1255, 1033, 755; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{28}H_{31}FN_2O_6$ $[M + H]^+$ 511.2244, found 511.2238.

**……..**

**Dibenzyl 1-((2*R*,4*S*)-4-fluoro-1-hydroxy-5-(naphthalen-2-yl)pentan-2-yl)hydrazine-1,2-dicarboxylate (5d)**

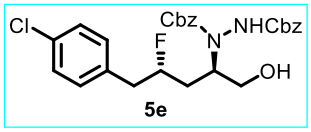


5d

Synthesized according to General Procedure 3. (*R*)-4-fluoro-5-(naphthalen-2-yl)pentan-1-ol **(3d)** was used as a substrate and L-Proline as an organocatalyst, to give dibenzyl 1-((2*R*,4*S*)-4-fluoro-1-hydroxy-5-(naphthalen-2-yl)pentan-2-yl)hydrazine-1,2-dicarboxylate **(5d)** as a waxy solid; 85% yield. **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 8.00-7.94 (d, *J* = 32.04 Hz, 1 H), 7.87 - 7.85 (m, 1 H), 7.78 - 7.77 (d, *J* = 8.0 Hz, 1 H), 7.52 - 7.49 (m, 2 H), 7.43 - 7.32 (m, 11 H), 6.80 - 6.67 (m, 1 H), 5.23 - 5.14 (m, 4 H), 4.92 - 4.58 (m, 1 H), 4.40 - 4.24 (m, 1 H), 3.52 - 3.23 (m, 4 H), 1.85 - 1.52 (m, 2 H); **$^{13}$C NMR** (100MHz, $CDCl_3$) $\delta$ = 156.8, 155.9, 135.7 ($J_{C\text{-}F}$ = 20.9 Hz), 135.0, 133.8, 132.6, 131.9, 128.8, 128.5, 128.4, 128.2, 127.7, 127.6, 126.2, 125.6, 125.4, 123.4, 91.2 ($J_{C\text{-}F}$ = 172.6 Hz), 68.6, 68.2, 62.1, 57.1, 55.6, 38.0 ($J_{C\text{-}F}$ = 20.9 Hz), 32.7 ($J_{C\text{-}F}$ = 20.8 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -177.32. Diastereomeric ratio was determined by HPLC analysis; 99:1dr. UV detector: Agilent Technologies 1260 VWD. Column: OD-H (250 × 4.6 mm). Flow rate: 1.0 mL/min. (λ = 254 nm). *i*PrOH/petroleum ether (10:90); $t_R$ for (*anti*)-isomer = 17.420 min. and $t_R$ for (*syn*)-isomer = 20.990 min. **$[\alpha]_D^{28}$** = -6.96 (c = 2.1, $CHCl_3$); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$3279, 2952, 1731, 1524, 1419, 1221, 1060, 747; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{31}H_{31}FN_2O_5$ $[M + H]^+$ 531.2295, found 531.2289.

**……..**

**Dibenzyl 1-((2*R*,4*S*)-5-(4-chlorophenyl)-4-fluoro-1-hydroxypentan-2-yl)hydrazine-1,2-dicarboxylate (5e)**

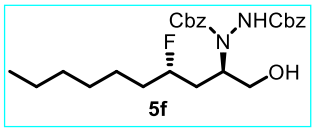


**5e**

Synthesized according to General Procedure 3. (*R*)-5-(4-chlorophenyl)-4-fluoropentan-1-ol **(3e)** was used as a substrate and L-Proline as an organocatalyst, to give dibenzyl 1-((2*R*,4*S*)-5-(4-chlorophenyl)-4-fluoro-1-hydroxypentan-2-yl)hydrazine-1,2-dicarboxylate **(5e)** as a waxy solid; 81% yield. **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.37 - 7.27 (m, 12 H), 7.15 - 7.08 (m, 2 H), 5.25 - 5.10 (m, 4 H), 4.79 - 4.67 (m, 2 H), 4.46 - 4.22 (m, 1 H), 3.52 - 3.47 (m, 2 H), 2.94 - 2.76 (m, 2 H), 1.76 - 1.46 (m, 2 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 157.0, 155.9, 135.6 ($J_{C\text{-}F}$ = 19.8 Hz), 135.0, 132.5, 130.6, 128.6, 128.4, 128.2, 127.7, 91.3 ($J_{C\text{-}F}$ = 172.6 Hz), 68.6, 68.2, 62.0, 57.0, 55.5, 40.5 ($J_{C\text{-}F}$ = 20.9 Hz), 32.6 ($J_{C\text{-}F}$ = 16.2 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -180.01. Diastereomeric ratio was determined by HPLC analysis; 92:8dr. UV detector: Agilent Technologies 1260 VWD. Column: OD-H (250 × 4.6 mm). Flow rate: 1.0 mL/min. (λ = 254 nm). *i*PrOH/petroleum ether (10:90); $t_R$ for (*anti*)-isomer = 12.943 min. and $t_R$ for (*syn*)-isomer = 9.840 min. **$[\alpha]_D^{28}$** = -1.86 (c = 1.3, $CHCl_3$); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$3435, 2951, 1712, 1496, 1412, 1264, 1058, 748; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{27}H_{28}ClFN_2O_5$ $[M + H]^+$515.1744, found 515.1740.

**……..**

**Dibenzyl 1-((2*R*,4*S*)-4-fluoro-1-hydroxydecan-2-yl)hydrazine-1,2-dicarboxylate (5f)**



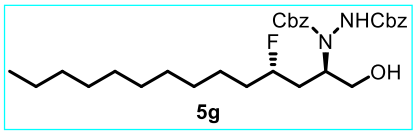
**5f**

Synthesized according to General Procedure 3. (*S*)-4-fluorodecan-1-ol **(3f)** was used as a substrate and L-Proline as an organocatalyst, to give dibenzyl 1-((2*R*,4*S*)-4-fluoro-1-hydroxydecan-2-yl)hydrazine-1,2-dicarboxylate **(5f)** as a waxy solid; 69% yield. **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.41 - 7.28 (m, 10 H), 6.51 (br. s., 1 H), 5.30 - 5.11 (m, 4 H), 4.71 - 4.08 (m, 3 H), 3.60 - 3.34 (m, 2 H), 1.76 - 1.48 (m, 4 H), 1.33 - 1.23 (m, 8 H), 0.89 (t, *J* = 6.8 Hz, 3 H); **$^{13}$C NMR** (100MHz, $CDCl_3$) $\delta$ = 156.8, 156.4, 135.8, 135.7, 135.1, 128.7, 128.6, 128.5, 128.5, 128.3, 128.1, 127.5, 93.2 ($J_{C\text{-}F}$ = 163.27 Hz), 68.6, 68.4, 68.2, 61.9, 59.1, 58.0, 35.9 ($J_{C\text{-}F}$ = 20.6 Hz), 32.9 ($J_{C\text{-}F}$ = 19.0 Hz), 31.6, 29.7, 28.9, 24.7, 24.6, 22.5, 14.0; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -181.54. Diastereomeric ratio was determined by HPLC analysis; 98:2 dr. UV detector: Agilent Technologies 1260 VWD. Column: OD-H (250 × 4.6 mm). Flow rate: 1.0 mL/min. (λ = 254 nm). *i*PrOH/petroleum ether (10:90); $t_R$ for (*anti*)-isomer = 34.073

min. and $t_R$ for (*syn*)-isomer = 31.033 min. **[α]$_D^{28}$** = -6.47 (c =0.5, $CHCl_3$); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$3421, 2929, 1718, 1641, 1454, 1261, 1057, 746; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{26}H_{35}FN_2O_5$ $[M + H]^+$ 475.2608, found 475.2602.

**……..**

**Dibenzyl 1-((2*R*,4*S*)-4-fluoro-1-hydroxytetradecan-2-yl)hydrazine-1,2-dicarboxylate (5g)**

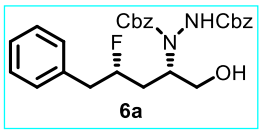


5g

Synthesized according to General Procedure 3. (*S*)-4-fluorotetradecan-1-ol **(3g)** was used as a substrate and L-Proline as an organocatalyst, to give dibenzyl 1-((2*R*,4*S*)-4-fluoro-1-hydroxytetradecan-2-yl)hydrazine-1,2-dicarboxylate **(5g)** as a waxy solid; 70% yield. **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.41 - 7.28 (m, 10 H), 6.57 (br. s., 1 H), 5.28 - 5.11 (m, 4 H), 4.62 - 4.35 (m, 2 H), 3.62 - 3.40 (m, 2 H), 1.78 - 1.44 (m, 4 H), 1.34 - 1.22 (m, 16 H), 0.89 (t, *J* = 6.8 Hz, 3 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 156.9, 155.8, 135.8, 135.7, 135.0, 128.6, 128.5, 128.3, 127.9, 127.7, 91.9 ($J_{C\text{-}F}$ = 169.3 Hz), 68.6, 68.2, 57.1, 55.5, 34.8 ($J_{C\text{-}F}$ = 20.6 Hz), 32.9 ($J_{C\text{-}F}$ = 16.7 Hz), 31.9, 29.7, 29.6, 29.6, 29.5, 29.5, 29.3, 29.3, 25.1, 22.7, 14.1; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -180.94. Diastereomeric ratio was determined by HPLC analysis; 99:1 dr. UV detector: Agilent Technologies 1260 VWD. Column: OD-H (250 × 4.6 mm). Flow rate: 1.0 mL/min. (λ = 254 nm). *i*PrOH/petroleum ether (10:90); $t_R$ for (*anti*)-isomer = 23.763 min. and $t_R$ for (*syn*)-isomer = 21.520 min. **[α]$_D^{28}$** = -5.34 (c = 1, $CHCl_3$); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$3267, 2923, 1734, 1680, 1426, 1338, 1220, 1054, 734; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{30}H_{43}FN_2O_5$ $[M + H]^+$ 531.3234, found 531.3228.

**……..**

**Dibenzyl 1-((2*S*,4*S*)-4-fluoro-1-hydroxy-5-phenylpentan-2-yl)hydrazine-1,2-dicarboxylate (6a)**



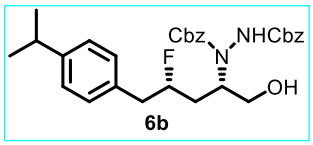
6a

Synthesized according to General Procedure 3. (*R*)-4-fluoro-5-phenylpentan-1-ol **(3a)** was used as a substrate and D-Proline as an organocatalyst, to give dibenzyl 1-((2*S*,4*S*)-4-fluoro-1-hydroxy-5-phenylpentan-2-yl)hydrazine-1,2-dicarboxylate **(6a)** as a waxy solid; 85% yield. **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.42 - 7.23 (m, 13 H), 7.22 - 7.09 (m, 2 H), 6.51 (br. s., 1 H), 5.34 - 5.09 (m, 4 H), 4.95 - 4.49 (m, 2 H), 4.29 - 4.11 (m, 1 H), 3.55 - 3.41 (m, 2 H), 3.02 - 2.72 (m, 2 H), 1.72 - 1.52 (m, 2 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 159.1, 158.4, 156.7, 156.3, 136.1, 135.7 ($J_{C\text{-}F}$ = 14.8 Hz) , 135.0, 129.4, 129.3, 128.6, 128.6, 128.3, 128.1, 127.5, 126.9,

94.8 ($J_{C\text{-}F}$ = 161.9 Hz), 94.4, 92.7, 68.7, 68.5, 68.4, 68.2, 62.2, 61.8, 57.8, 57.2, 42.1 ($J_{C\text{-}F}$ = 22.4 Hz), 41.9, 41.8, 32.2 ($J_{C\text{-}F}$ = 19.7 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -179.44. Diastereomeric ratio was determined by HPLC analysis; 63:37 dr. UV detector: Agilent Technologies 1260 VWD. Column: OD-H (250 × 4.6 mm). Flow rate: 1.0 mL/min. (λ = 254 nm). *i*PrOH/petroleum ether (20:80); $t_R$ for (*anti*)-isomer = 12.860 min and $t_R$ for (*syn*)-isomer = 10.737 min. **$[\alpha]_D^{28}$** = -2.2 (c = 1.0, $CHCl_3$); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$3272, 2929, 1684, 1531, 1423, 1279, 1059, 747; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{27}H_{29}FN_2O_5$ $[M + H]^+$ 481.2133, found 481.2129.

**……..**

**Dibenzyl 1-((2*S*,4*S*)-4-fluoro-1-hydroxy-5-(4-isopropylphenyl)pentan-2-yl)hydrazine-1,2-dicarboxylate (6b)**

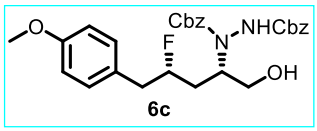


**6b**

Synthesized according to General Procedure 3. (*R*)-4-fluoro-5-(4-isopropylphenyl)pentan-1-ol **(3b)** was used as a substrate and D-Proline as an organocatalyst, to give dibenzyl 1-((2*S*,4*S*)-4-fluoro-1-hydroxy-5-(4-isopropylphenyl)pentan-2-yl)hydrazine-1,2-dicarboxylate **(6b)** as a waxy solid; 77% yield. **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.39 - 7.28 (m, 10 H), 7.19 - 7.11 (m, 2 H), 7.10 - 7.03 (m, 2 H), 5.27 - 5.03 (m, 4 H), 4.80 - 4.65 (m, 2 H), 4.19 - 4.14 (m, 1 H), 3.50 - 3.43 (m, 2 H), 3.01 - 2.79 (m, 3 H), 1.77 - 1.47 (m, 2 H), 1.28 - 1.20 (m, 6 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 159.0, 158.4, 156.8, 155.9, 147.4, 135.7 ($J_{C\text{-}F}$ = 13.7 Hz), 135.0, 133.7, 129.2, 128.6, 128.5, 128.3, 127.9, 127.8, 126.6, 93.0, 92.1 ($J_{C\text{-}F}$ = 171.6 Hz), 91.4, 68.6, 68.5, 68.2, 62.1, 57.3, 55.9, 40.7 ($J_{C\text{-}F}$ = 22.1 Hz), 33.6, 32.2 ($J_{C\text{-}F}$ = 25.2 Hz), 23.9; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -177.21. Diastereomeric ratio was determined by HPLC analysis; 63:37 dr. UV detector: Agilent Technologies 1260 VWD. Column: OD-H (250 × 4.6 mm). Flow rate: 1.0 mL/min. (λ = 254 nm). *i*PrOH/petroleum ether (20:80); $t_R$ for (*anti*)-isomer = 12.077 min. and $t_R$ for (*syn*)-isomer = 10.093 min. **$[\alpha]_D^{28}$** = -5.44 (c = 0.6, $CHCl_3$); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$3424, 2958, 1641, 1412, 1262, 1219, 1057, 770; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{30}H_{35}FN_2O_5$ $[M + H]^+$ 523.2603, found 523.2601.

**……..**

**Dibenzyl 1-((2*S*,4*S*)-4-fluoro-1-hydroxy-5-(4-methoxyphenyl)pentan-2-yl)hydrazine-1,2-dicarboxylate (6c)**

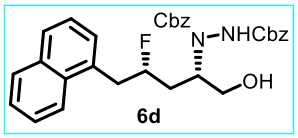


**6c**

Synthesized according to General Procedure 3. (*R*)-4-fluoro-5-(4-methoxyphenyl)pentan-1-ol **(3c)** was used as a substrate and D-Proline as an organocatalyst, to give dibenzyl 1-((2*S*,4*S*)-4-fluoro-1-hydroxy-5-(4-methoxyphenyl)pentan-2-yl)hydrazine-1,2-dicarboxylate **(6c)** as a waxy solid; 67% yield. **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.35 - 7.19 (m, 10 H), 7.08 - 6.96 (m, 2 H), 6.84 - 6.75 (m, 2 H), 5.21 - 4.96 (m, 4 H), 4.67 - 4.48 (m, 3 H), 3.77 - 3.63 (m, 3 H), 3.38 (br. s., 2 H), 2.94 - 2.64 (m, 2 H), 1.74 - 1.33 (m, 2 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 159.2, 158.5, 156.8, 155.9, 135.8 ($J_{C\text{-}F}$ = 17.1 Hz), 135.0, 130.3, 128.7, 128.6, 128.3, 128.0, 127.8, 114.1, 94.4, 93.0, 92.0 ($J_{C\text{-}F}$ = 171.6 Hz), 76.8, 68.7, 68.6, 68.3, 62.2, 61.9, 55.2, 40.2 ($J_{C\text{-}F}$ = 20.9 Hz), 32.1 ($J_{C\text{-}F}$ = 23.8 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -179.50. Diastereomeric ratio was determined by HPLC analysis; 58:42 dr. UV detector: Agilent Technologies 1260 VWD. Column: OD-H (250 × 4.6 mm). Flow rate: 0.5 mL/min. ($\lambda$ = 254 nm). *i*PrOH/petroleum ether (10:90); $t_R$ for (*anti*)-isomer = 42.467 min. and $t_R$ for (*syn*)-isomer = 36.703 min. **$[\alpha]_D^{28}$** = -2.03 (c = 4.6, $CHCl_3$); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$3444, 3025, 2949, 1716, 1615, 1510, 1411, 1254, 1034, 757; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{28}H_{31}FN_2O_6[M + H]^+$ 511.2239, found 511.2236.

**……..**

**Dibenzyl 1-((2*S*,4*S*)-4-fluoro-1-hydroxy-5-(naphthalen-2-yl)pentan-2-yl)hydrazine-1,2-dicarboxylate (6d)**



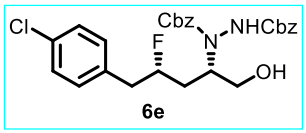
**6d**

Synthesized according to General Procedure 3. (*R*)-4-fluoro-5-(naphthalen-2-yl)pentan-1-ol **(3d)** was used as a substrate and D-Proline as an organocatalyst, to give dibenzyl 1-((2*S*,4*S*)-4-fluoro-1-hydroxy-5-(naphthalen-2-yl)pentan-2-yl)hydrazine-1,2-dicarboxylate **(6d)** as a waxy solid; 84% yield. **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 8.01 - 7.85 (m, 1 H), 7.81 (d, *J* = 5.0 Hz, 1 H), 7.77 - 7.68 (m, 1 H), 7.47 (d, *J* = 4.0 Hz, 2 H), 7.38 - 7.19 (m, 11 H), 6.60 - 6.28 (m, 1 H), 5.21 - 5.00 (m, 4 H), 4.89 - 4.66 (m, 2 H), 4.29 - 4.10 (m, 1H), 3.63 - 3.12 (m, 4 H), 1.86 - 1.48 (m, 2 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 158.9, 158.5, 156.8, 155.9, 135.7 ($J_{C\text{-}F}$ = 16.0 Hz), 135.0, 133.8, 132.6, 131.9, 128.8, 128.6, 128.4, 128.2, 127.6, 126.2, 125.6, 125.4, 123.4, 92.3, 91.4 ($J_{C\text{-}F}$ = 173.1 Hz), 90.6, 68.6, 68.3, 68.2, 62.1, 57.1, 55.6, 38.0 ($J_{C\text{-}F}$ = 22.8 Hz), 32.7 ($J_{C\text{-}F}$ = 20.6 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -177.32. Diastereomeric ratio

was determined by HPLC analysis; 56:44 dr. UV detector: Agilent Technologies 1260 VWD. Column: OD-H (250 × 4.6 mm). Flow rate: 1.0 mL/min. (λ = 254 nm). *i*PrOH/petroleum ether (10:90); $t_R$ for (*anti*)-isomer = 22.940 min. and $t_R$ for (*syn*)-isomer = 18.157 min. **$[\alpha]_D^{28}$** = -4.90 (c = 1.1, $CHCl_3$); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$3434, 2958, 1687, 1683, 1414, 1260, 1220, 1058, 765; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{31}H_{31}FN_2O_5$ $[M + H]^+$ 531.2290, found 531.2285.

**……..**

**Dibenzyl 1-((2*S*,4*S*)-5-(4-chlorophenyl)-4-fluoro-1-hydroxypentan-2-yl)hydrazine-1,2-dicarboxylate (6e)**

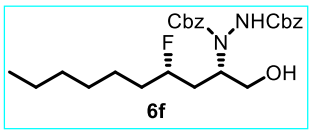


**6e**

Synthesized according to General Procedure 3. (*R*)-5-(4-chlorophenyl)-4-fluoropentan-1-ol **(3e)** was used as a substrate and D-Proline as an organocatalyst, to give dibenzyl 1-((2*S*,4*S*)-5-(4-chlorophenyl)-4-fluoro-1-hydroxypentan-2-yl)hydrazine-1,2-dicarboxylate **(6e)** as a waxy solid; 86% yield. **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.42 - 7.23 (m, 12 H), 7.17 - 7.01 (m, 2 H), 6.89 (br. s., 1 H), 5.21 - 5.14 (m, 4 H), 4.86 - 4.59 (m, 2 H), 4.50 - 4.34 (m, 1 H), 3.45 (br. s., 2 H), 2.88 - 2.83 (m, 2 H), 1.83 - 1.47 (m, 2 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 159.1, 158.5, 156.7, 156.2, 135.6 ($J_{C\text{-}F}$ = 18.1 Hz), 134.9, 134.6, 132.5, 132.3, 130.6, 128.5, 128.3, 128.1, 127.5, 127.3, 93.5, 92.1, 91.1 ($J_{C\text{-}F}$ = 172.6 Hz), 68.5, 68.3, 68.1, 61.9, 61.5, 57.5, 56.9, 40.9 ($J_{C\text{-}F}$ = 20.9 Hz), 32.6 ($J_{C\text{-}F}$ = 16.8 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -180.22. Diastereomeric ratio was determined by HPLC analysis; 69:31 dr. UV detector: Agilent Technologies 1260 VWD. Column: OD-H (250 × 4.6 mm). Flow rate: 1.0 mL/min. (λ = 254 nm). *i*PrOH/petroleum ether (10:90); $t_R$ for (*anti*)-isomer = 13.350 min. and $t_R$ for (*syn*)-isomer = 10.040 min. **$[\alpha]_D^{28}$** = -2.10 (c = 2.4, $CHCl_3$); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$3436, 2950, 1714, 1494, 1411, 1262, 1057, 748; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{27}H_{28}ClFN_2O_5$ $[M + H]^+$ 515.1744, found 515.1739.

**……..**

**Dibenzyl 1-((2*S*,4*S*)-4-fluoro-1-hydroxydecan-2-yl)hydrazine-1,2-dicarboxylate (6f)**



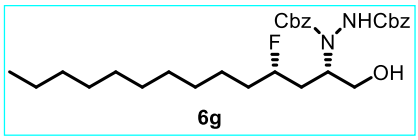
**6f**

Synthesized according to General Procedure 3. (*S*)-4-fluorodecan-1-ol **(3f)** was used as a substrate and D-Proline as an organocatalyst, to give dibenzyl 1-((2*S*,4*S*)-4-fluoro-1-hydroxydecan-2-yl)hydrazine-1,2-dicarboxylate **(6f)** as a waxy solid; 75% yield. **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.41 - 7.28 (m, 10 H), 6.59 (br. s., 1 H), 5.35 - 5.12 (m, 4 H), 4.70 -

4.50 (m, 2 H), 4.20 - 4.08 (m, 1 H), 3.59 - 3.35 (m, 2 H), 1.73 - 1.45 (m, 4 H), 1.32 - 1.24 (m, 8 H), 0.91 - 0.88 (m, 3 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 159.1, 158.4, 156.8, 156.4, 135.8, 135.7, 135.1, 128.6, 128.6, 128.4, 128.2, 128.0, 127.5, 94.6 ($J_{C\text{-}F}$ = 164.9 Hz), 94.1, 92.7, 68.5, 68.5, 68.4, 68.3, 68.2, 61.9, 59.1, 58.0, 35.8 ($J_{C\text{-}F$ = 18.2 Hz), 35.5, 32.7 ($J_{C\text{-}F$ = 18.1 Hz), 31.6, 29.7, 28.9, 24.7, 22.5, 14.0; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -181.54. Diastereomeric ratio was determined by HPLC analysis; 66:34 dr. UV detector: Agilent Technologies 1260 VWD. Column: OD-H (250 × 4.6 mm). Flow rate: 1.0 mL/min. (λ = 254 nm). *i*PrOH/petroleum ether (10:90); $t_R$ for (*anti*)-isomer = 34.757 min. and $t_R$ for (*syn*)-isomer = 30.810 min. **$[\alpha]_D^{28}$** = +5.56 (c = 1.7, $CHCl_3$); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$3391, 2928, 1718, 1501, 1454, 1333, 1220, 1053, 769; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{26}H_{35}FN_2O_5$ $[M + H]^+$ 475.2603, found 475.2599.

**……..**

**Dibenzyl 1-((2*S*,4*S*)-4-fluoro-1-hydroxytetradecan-2-yl)hydrazine-1,2-dicarboxylate (6g)**

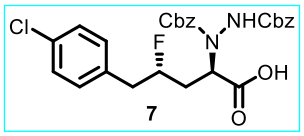


6g

Synthesized according to General Procedure 3. (*S*)-4-fluorotetradecan-1-ol **(3g)** was used as a substrate and D-Proline as an organocatalyst, to give dibenzyl 1-((2*S*,4*S*)-4-fluoro-1-hydroxytetradecan-2-yl)hydrazine-1,2-dicarboxylate **(6g)** as a waxy solid; 72% yield. **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.41 - 7.28 (m, 10 H), 6.71 - 6.52 (m, 1 H), 5.31 – 5.10 (m, 4 H), 4.62 - 4.50 (m, 2 H), 4.40 - 4.22 (m, 1 H), 3.62 - 3.38 (m, 2 H), 1.70 - 1.46 (m, 4 H), 1.27 (s, 16 H), 0.91 - 0.88 (m, 3 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 159.1, 158.5, 156.9, 155.8, 135.8, 135.7, 135.0, 128.6, 128.5, 128.3, 127.9, 127.7, 92.6, 91.7 ($J_{C\text{-}F$ = 167.8 Hz), 91.3, 68.6, 68.2, 62.3, 57.1, 55.6, 34.8 ($J_{C\text{-}F$ = 20.0 Hz), 33.1 ($J_{C\text{-}F$ = 16.2 Hz), 31.9, 29.7, 29.6, 29.5, 29.5, 29.4, 29.3, 25.1, 22.7, 14.1; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -180.97. Diastereomeric ratio was determined by HPLC analysis; 43:57 dr. UV detector: Agilent Technologies 1260 VWD. Column: OD-H (250 × 4.6 mm). Flow rate: 1.0 mL/min. (λ = 254 nm). *i*PrOH/petroleum ether (10:90); $t_R$ for (*anti*)-isomer = 20.880 min. and $t_R$ for (*syn*)-isomer = 24.443 min. **$[\alpha]_D^{28}$** = -1.10 (c = 0.5, $CHCl_3$); IR ($CHCl_3$, $cm^{-1}$): $\nu_{max}$3435, 2923, 1644, 1427, 1339, 1220, 1052, 770; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{30}H_{43}FN_2O_5$ $[M + H]^+$ 531.3229, found 531.3224.

**……..**

**(2*R*,4*S*)-2-(1,2-bis((benzyloxy)carbonyl)hydrazineyl)-5-(4-chlorophenyl)-4-fluoropentanoic acid (7)**

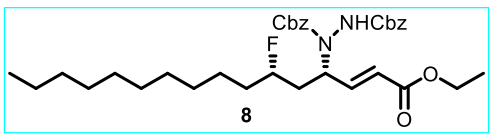


7

To a stirred solution of dibenzyl 1-((2*R*,4*S*)-5-(4-chlorophenyl)-4-fluoro-1-hydroxypentan-2-yl)hydrazine-1,2-dicarboxylate **(5e)** (1.0 equiv.) in $CH_3CN$ (8 mL)/ phosphate buffer ($_pH$ 6.4) (0.4 mL) were added $PhI(OAc)_2$ (0.09 equiv.) and TEMPO (0.19 equiv.) at room temperature, then the mixture was cooled to 0 $^oC$. To the stirring mixture was added $NaClO_2$ (3.3 equiv.) at the same temperature and the resulting solution was warmed to room temperature. After stirring at the same temperature for 10 h, the mixture was quenched with saturated $NH_4Cl$, and extracted with EtOAc five times. The organic layer was washed with 1 M aqueous HCl, brine and dried over $Na_2SO_4$. The solvent was removed under reduced pressure to afford (2*R*,4*S*)-2-(1,2-bis((benzyloxy)carbonyl)hydrazineyl)-5-(4-chlorophenyl)-4-fluoropentanoic acid **(7)** as a waxy solid in 88% yield. **$^1$H NMR** (400 MHz, $MeOD_4$) $\delta$ = 7.25 (br. s., 10 H), 7.13 (br. s., 4 H), 5.08 (br. s., 4 H), 4.92 - 4.73 (m, 2 H), 2.83 - 2.16 (m, 2 H), 2.16 - 1.99 (m, 2 H); **$^{13}$C NMR** (100 MHz, $MeOD_4$) $\delta$ = 174.7, 159.1, 158.9, 158.4, 157.8, 137.8 ($J_{C\text{-}F}$ = 17.17 Hz), 133.4, 132.2, 129.7, 129.5, 129.4, 129.3, 129.1, 128.7, 93.8, 92.8 ($J_{C\text{-}F}$ = 169.75 Hz), 69.4, 68.5, 60.4, 59.1, 41.9 ($J_{C\text{-}F}$ = 20.98 Hz), 41.4, 41.2, 35.9, 35.5, 35.2 ($J_{C\text{-}F}$ = 21.93 Hz); **$^{19}$F NMR** (376 MHz, $MeOD_4$) $\delta$ = -184.45. **$[\alpha]_D^{28}$** = +41.34 (c = 2, $CH_3OH$); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$3423, 2095, 1642, 1495, 1300, 1220, 1054, 753; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{27}H_{26}ClFN_2O_6$ $[M + H]^+$ 529.1542, found 529.1538.

**……..**

**Dibenzyl 1-((4*S*,6*S*,*E*)-1-ethoxy-6-fluoro-1-oxohexadec-2-en-4-yl)hydrazine-1,2-dicarboxylate (8)**



8

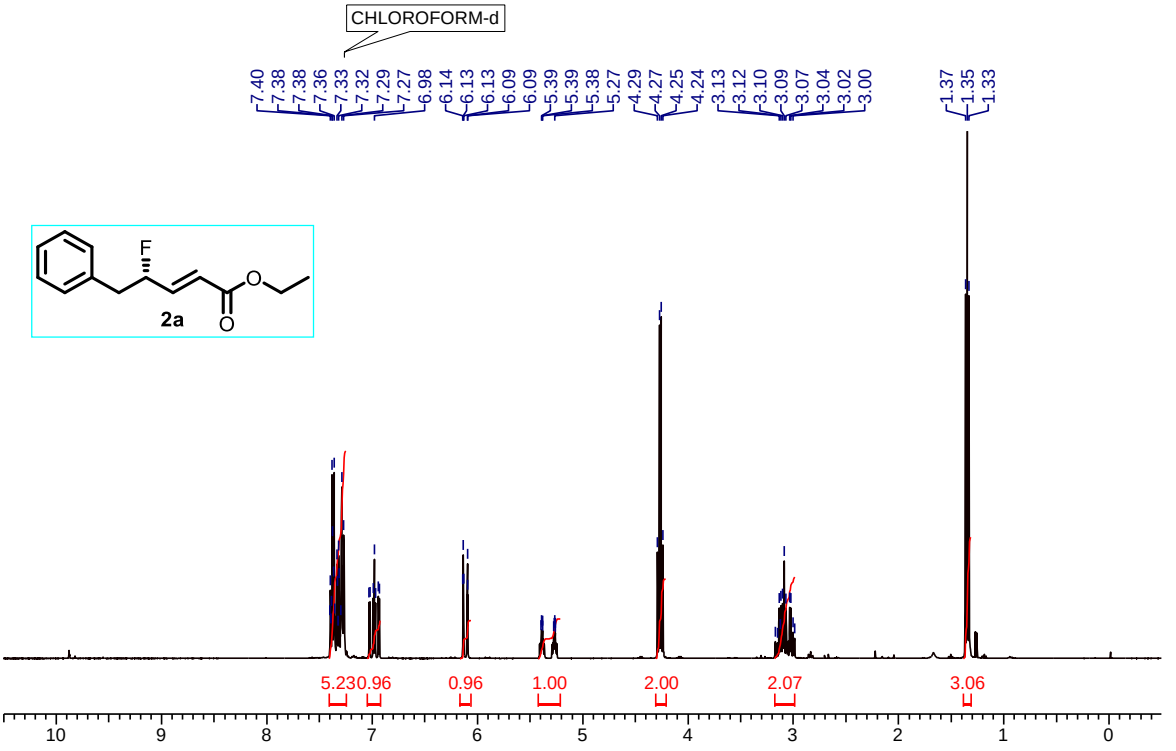
To a stirred solution of corresponding dibenzyl 1-((2*S*,4*S*)-4-fluoro-1-hydroxytetradecan-2-yl)hydrazine-1,2-dicarboxylate **(6g)** (1.0 equiv.) was added Dess Martin periodinane (1.5 equiv.) at 0 $^oC$ in dry DCM (10 mL) under argon condition. Then the reaction mixture was stirred at room temperature for 1 h and reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with aqueous $NaHCO_3/Na_2S_2O_3$ (1:1) solution until the reaction mixture becomes clear. Then the reaction mixture was extracted with DCM (3 × 20 mL) and combined organic

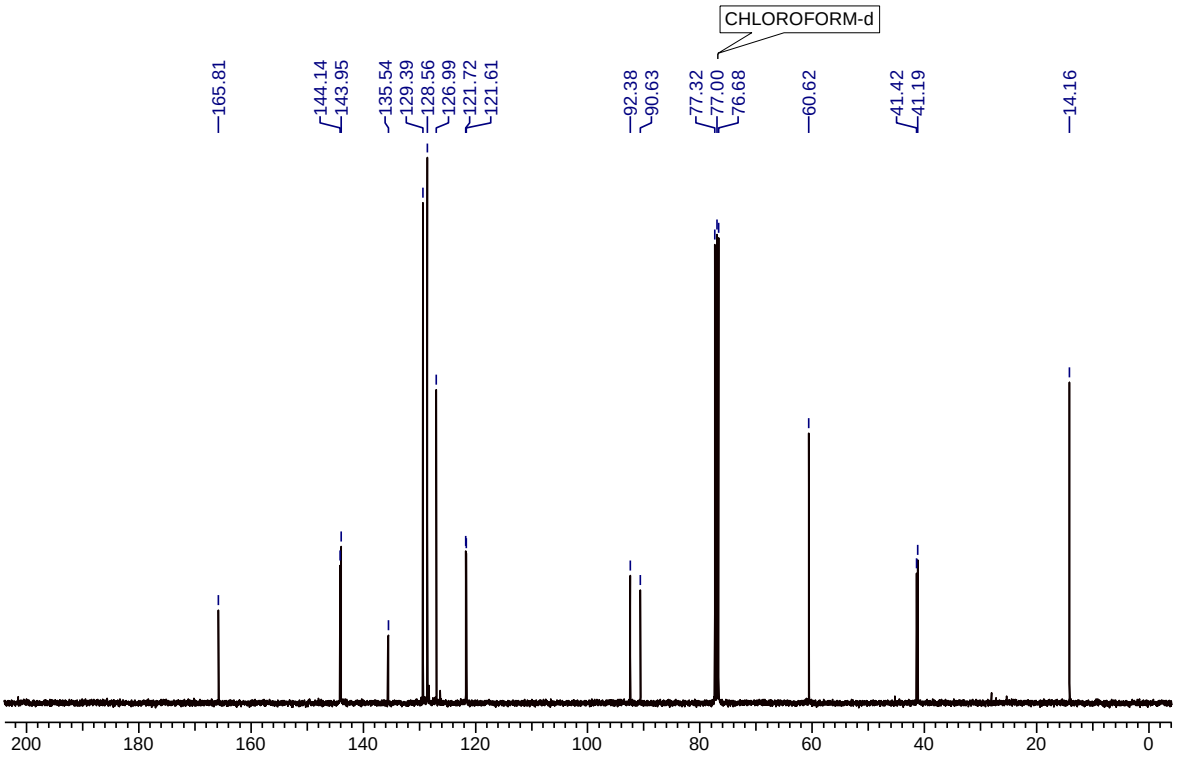
layers were washed with brine, dried over anhydrous $Na_2SO_4$. The solvent was concentrated under reduced pressure to afford the crude corresponding aldehyde, which was directly used in the next step without purification.

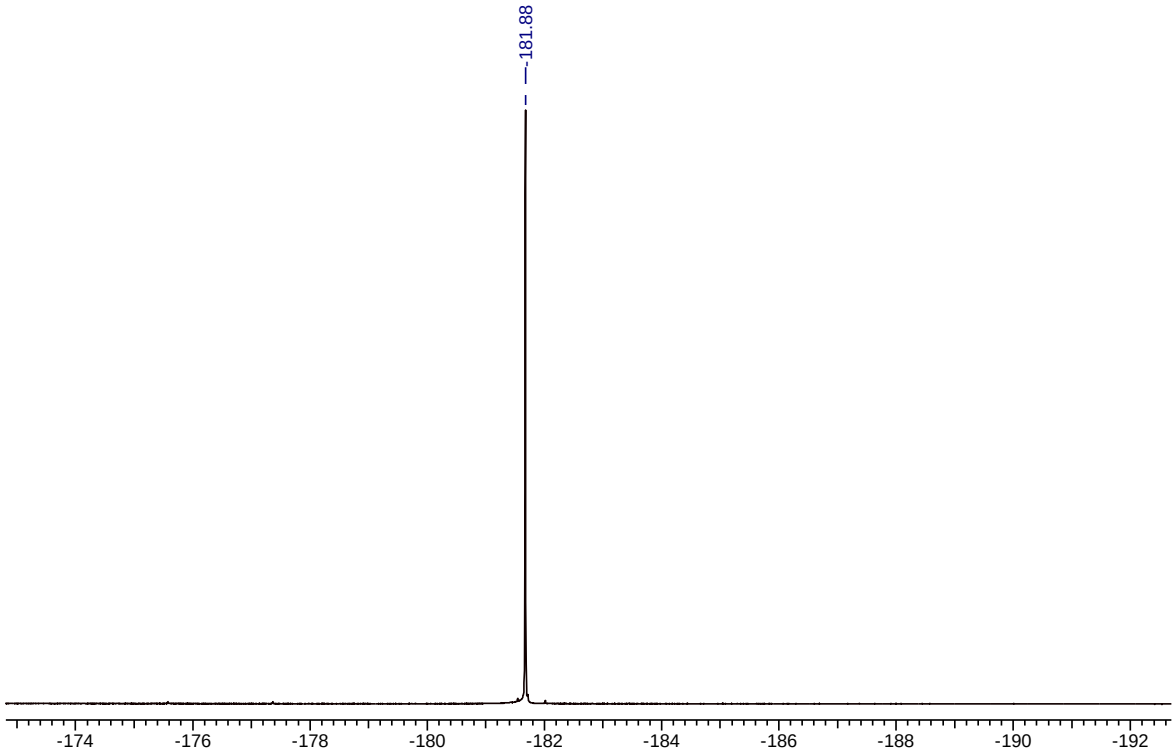
The crude aldehyde (1.0 equiv.) was dissolved in 20 mL of dry acetonitrile. Then lithium bromide (1.5 equiv.), triethyl phosphonoacetate (1.5 equiv.), and DBU (1.0equiv.) were added under argon condition at 0 $^oC$. The reaction mixture was stirred at 5 $^oC$ temperature for 60 min. and the progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched using aqueous ammonium chloride solution and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The crude product was then purified by flash column chromatography to afford the pure dibenzyl 1-((4*S*,6*S*,*E*)-1-ethoxy-6-fluoro-1-oxohexadec-2-en-4-yl)hydrazine-1,2-dicarboxylate **(8)** as a waxy solid in 92% yield. **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ = 7.40 - 7.11 (m, 10 H), 7.00 (br. s., 1 H), 6.87 (d, *J* = 10.0 Hz, 1 H), 5.89 (br. s., 1 H), 5.10 (br. s., 4 H), 4.89 - 4.42 (m, 1 H), 4.11 (q, *J* = 7.1 Hz, 2 H), 1.87 - 1.36 (m, 5 H), 1.32 - 1.17 (m, 18 H), 0.86 (t, *J* = 6.8 Hz, 3 H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ = 166.0, 156.8, 156.5, 155.8, 155.4, 144.8, 144.0, 143.6, 135.5, 135.4, 128.5, 128.4, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.4, 126.8, 123.6, 123.0, 122.7, 91.6 ($J_{C\text{-}F}$ = 171.64 Hz), 68.3, 67.7, 65.0, 60.5, 55.9, 55.2, 36.5, 35.4, 35.1 ($J_{C\text{-}F}$ = 20.60 Hz), 31.8, 29.5, 29.5, 29.4, 29.4, 29.4, 29.3, 29.2, 29.2, 29.1, 24.8, 22.6, 14.0, 14.0; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta$ = -182.13. **$[\alpha]_D^{28}$** = -1.34 (c = 1.7, $CHCl_3$); **IR** ($CHCl_3$, $cm^{-1}$): $\nu_{max}$3421, 2926, 1715, 1456, 1277, 1218, 1041, 761; **HRMS** ($ESI^+$) (*m/z*) calcd for $C_{34}H_{47}FN_2O_6$ $[M + H]^+$ 599.3491, found 599.3490.

## 4B.10 NMR Spectra

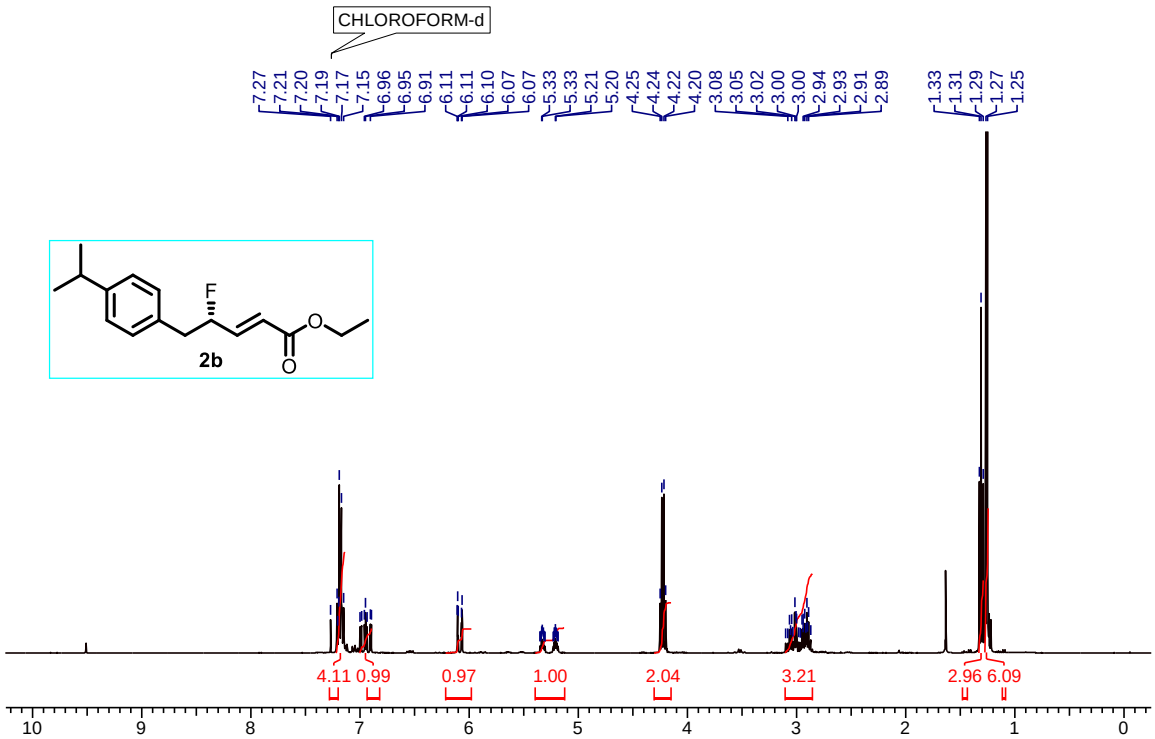
### Ethyl (*S*,*E*)-4-fluoro-5-phenylpent-2-enoate (2a)

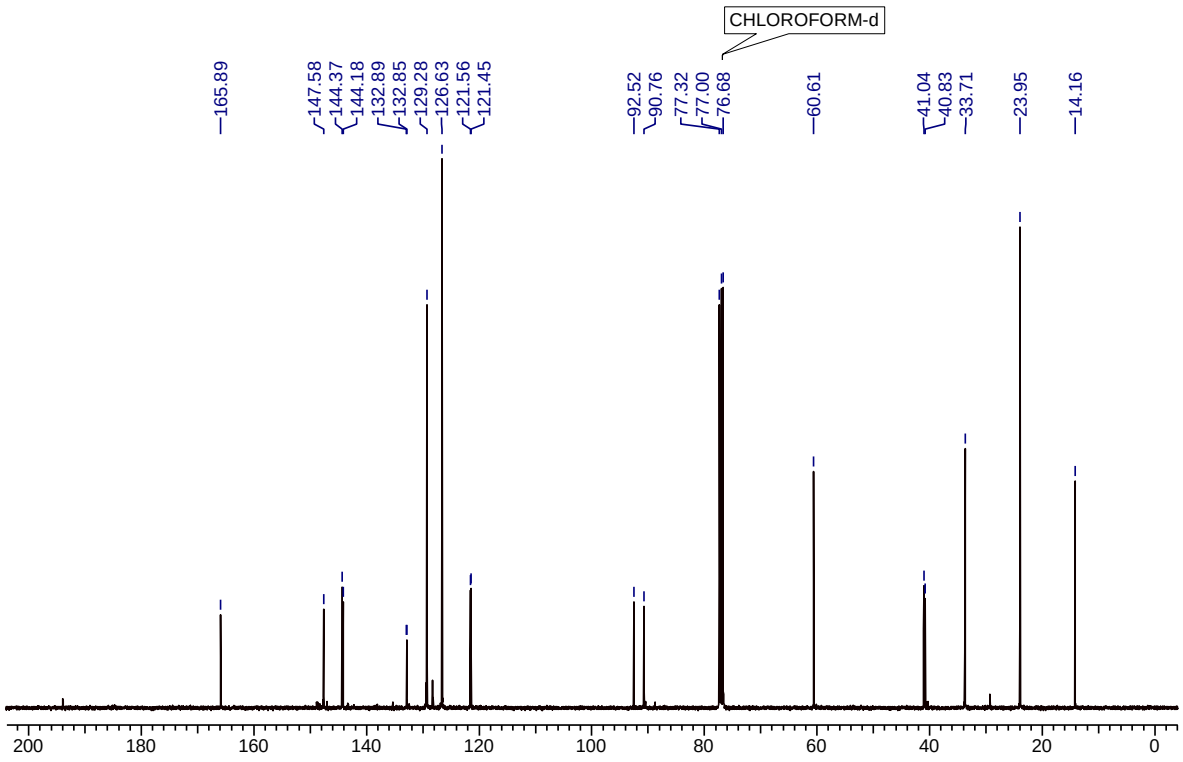


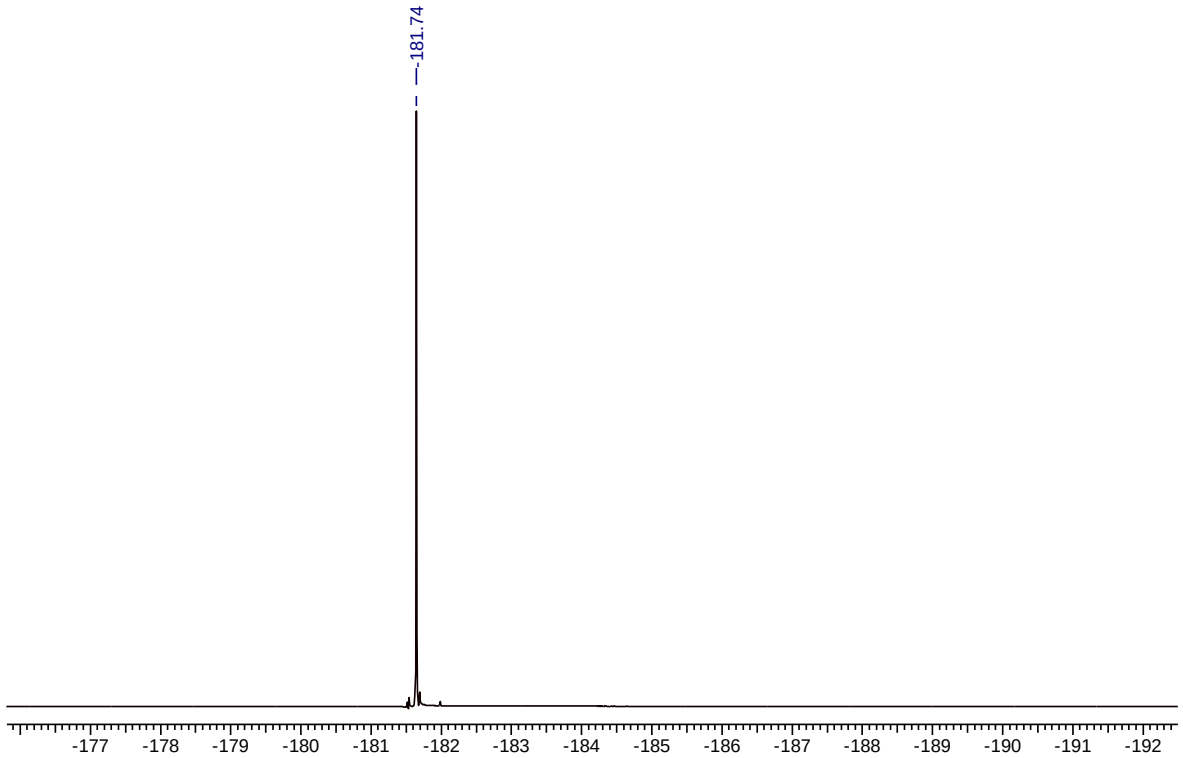





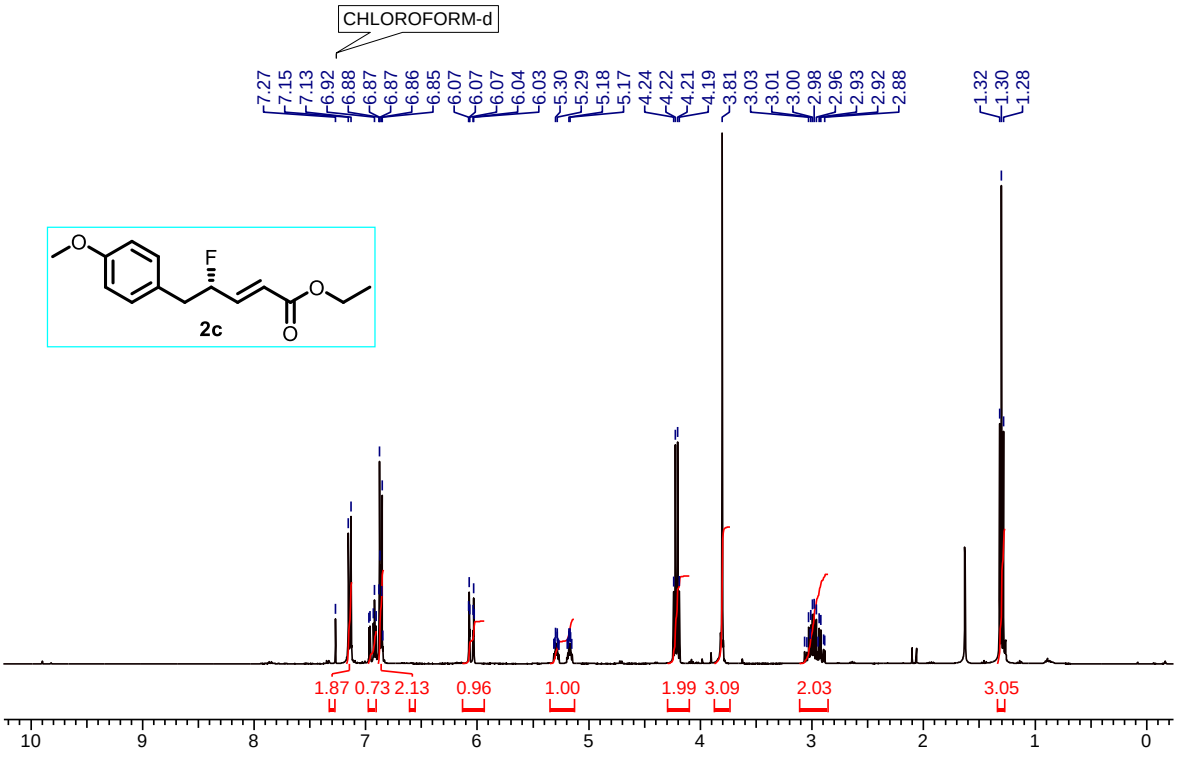

**Ethyl (*S*,*E*)-4-fluoro-5-(4-isopropylphenyl)pent-2-enoate (2b)**

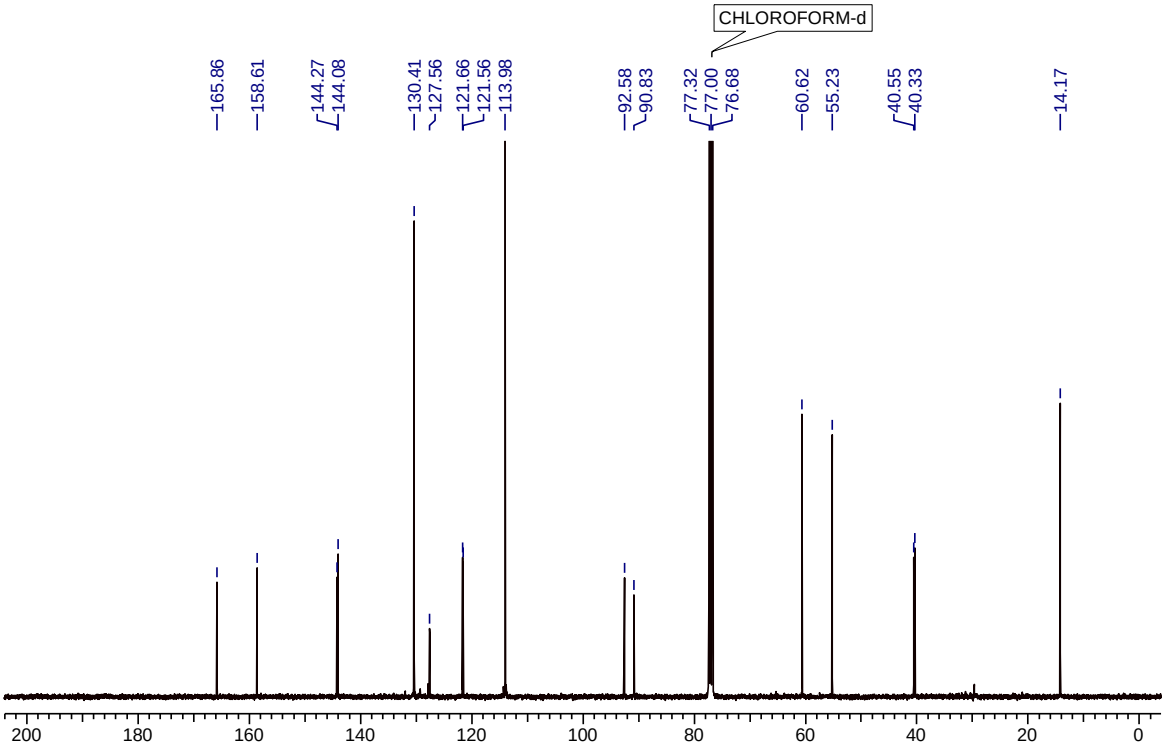


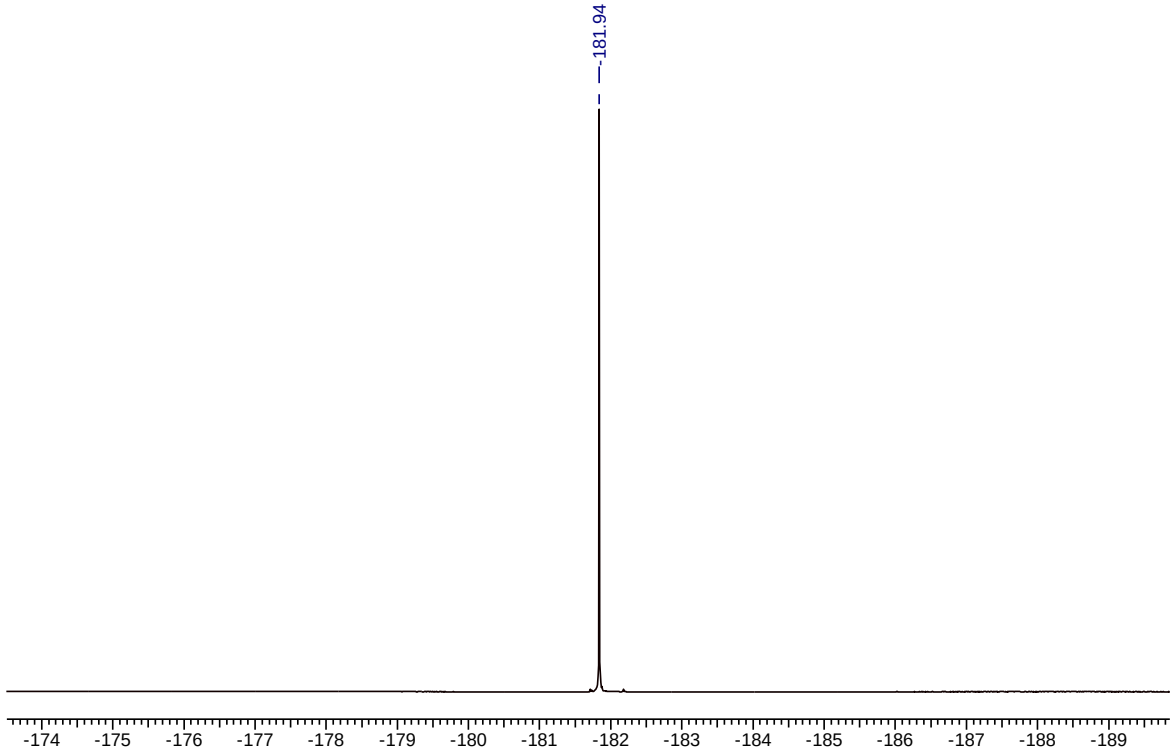

CHLOROFORM-d
165.89
147.58
144.37
144.18
132.89
132.85
129.28
126.63
121.56
121.45
92.52
90.76
77.32
77.00
76.68
60.61
41.04
40.83
33.71
23.95
14.16
200
180
160
140
120
100
80
60
40
20
0


-181.74
-177
-178
-179
-180
-181
-182
-183
-184
-185
-186
-187
-188
-189
-190
-191
-192

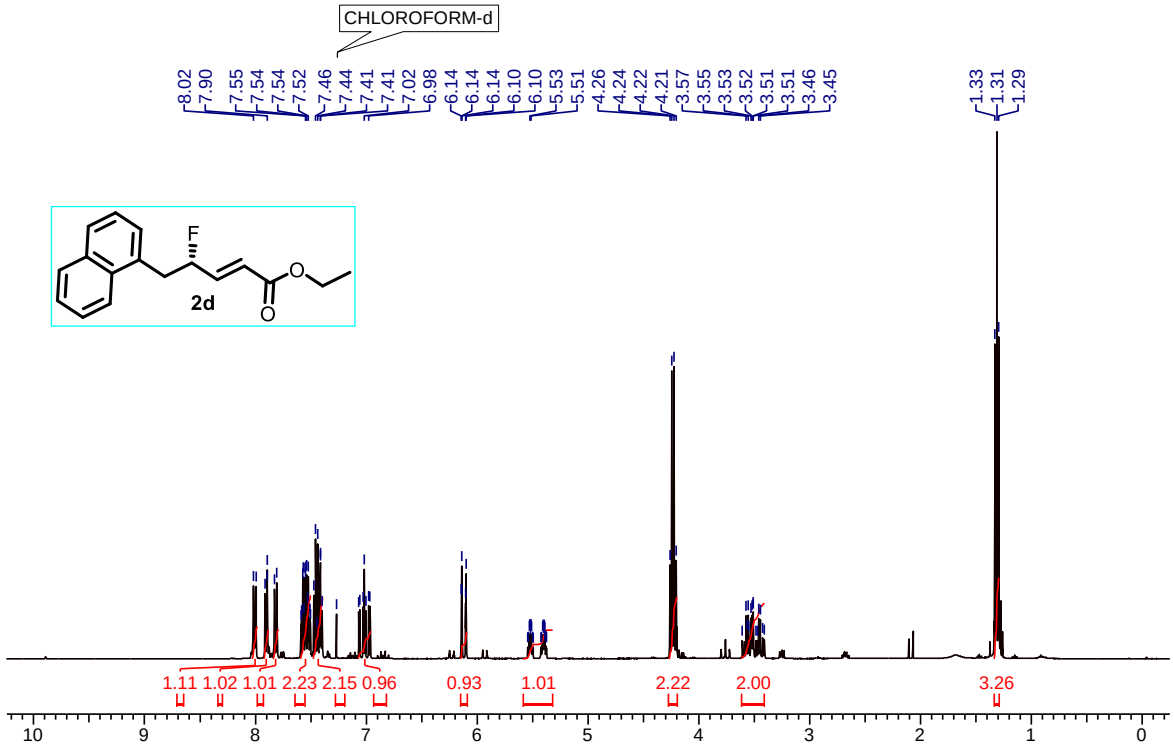
**Ethyl (*S*,*E*)-4-fluoro-5-(4-methoxyphenyl)pent-2-enoate (2c)**

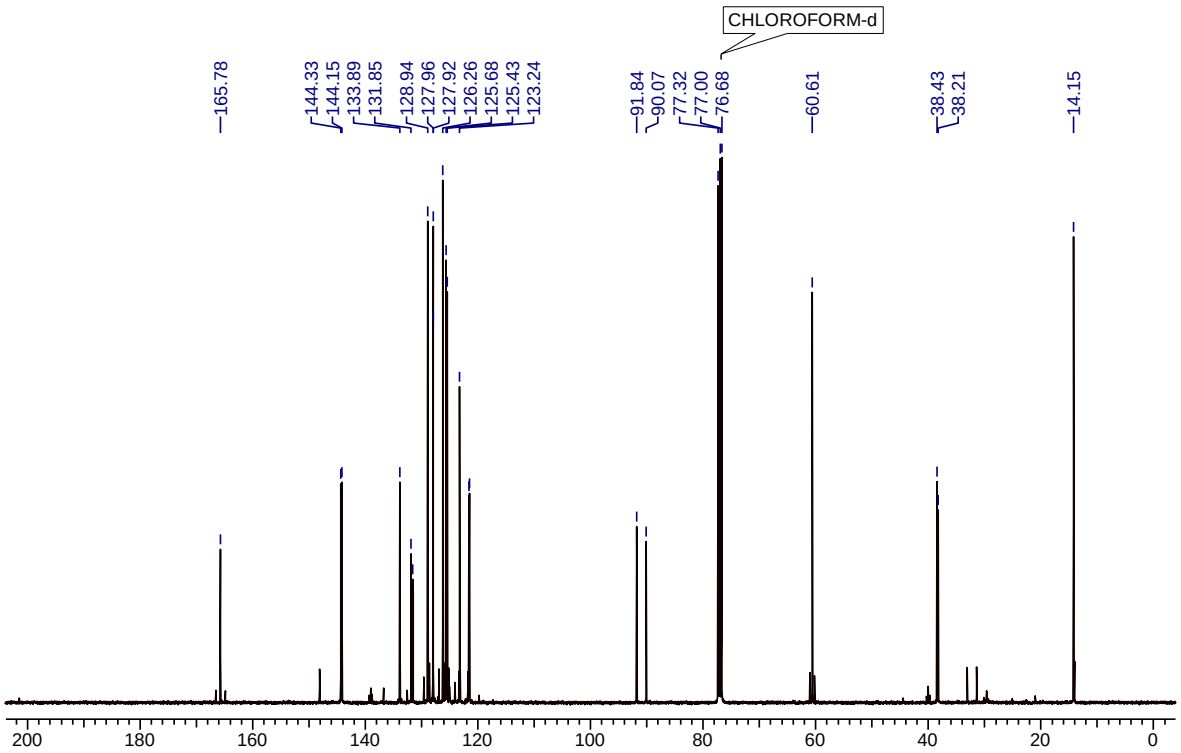


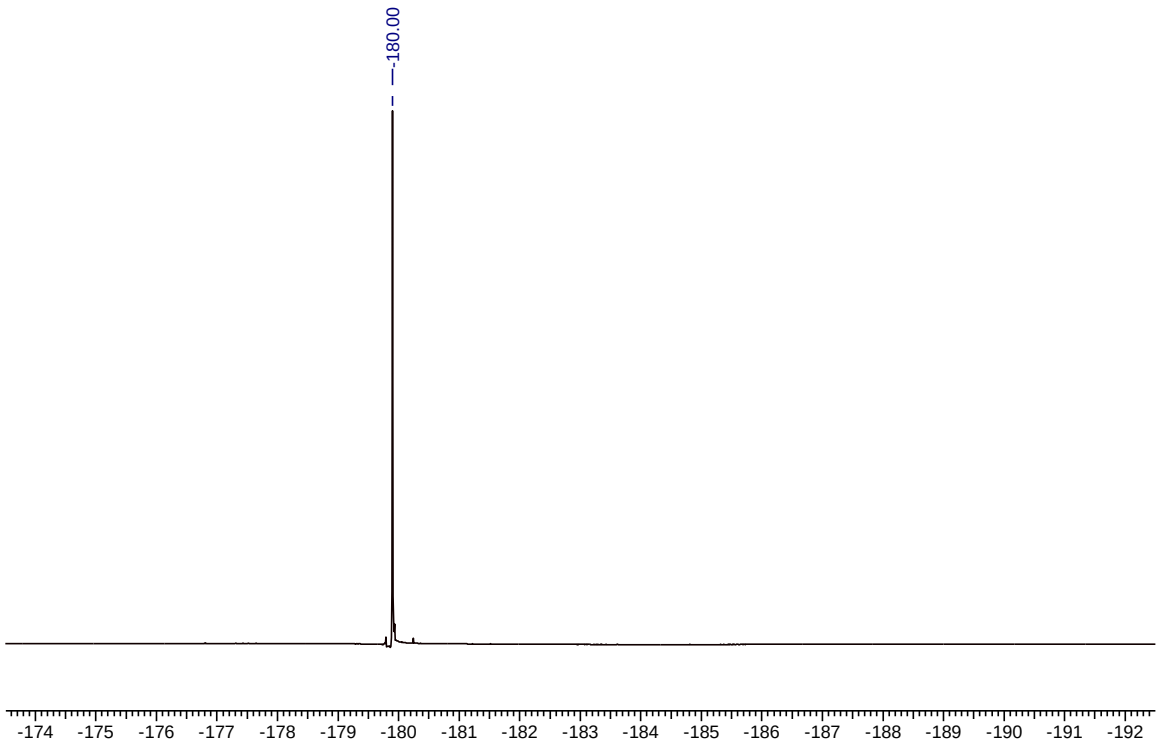





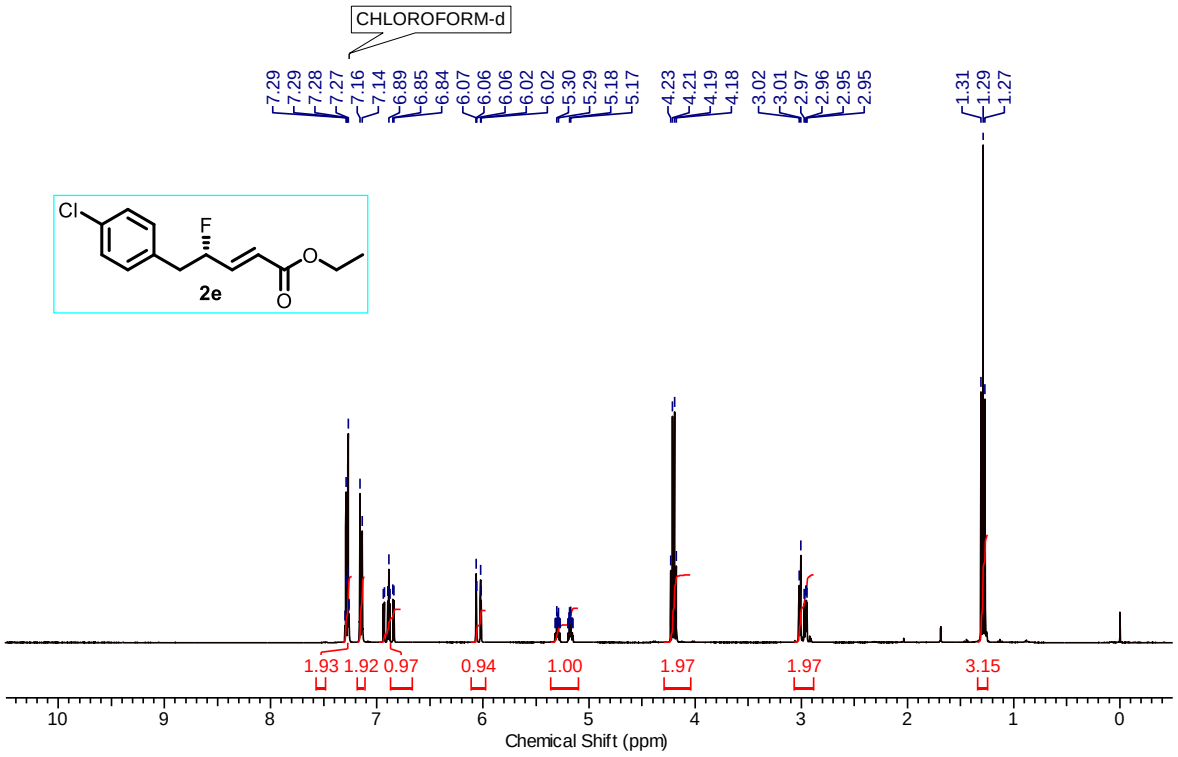

**Ethyl (*S*,*E*)-4-fluoro-5-(naphthalen-2-yl)pent-2-enoate (2d)**

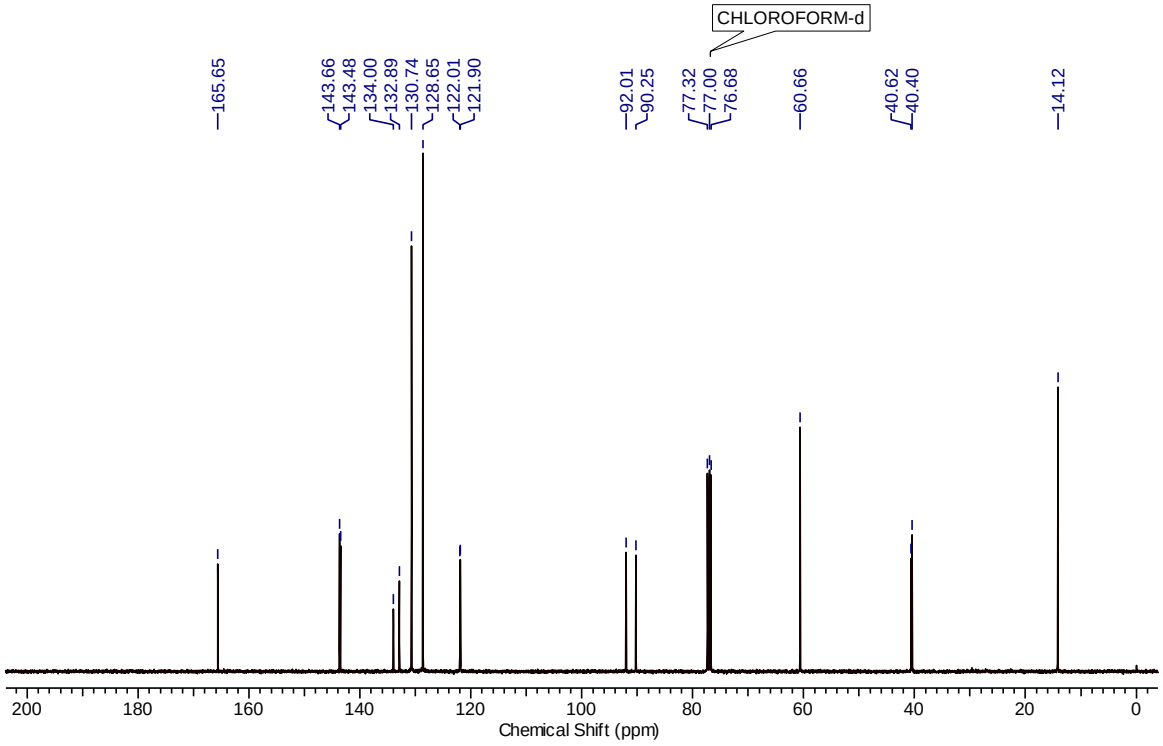


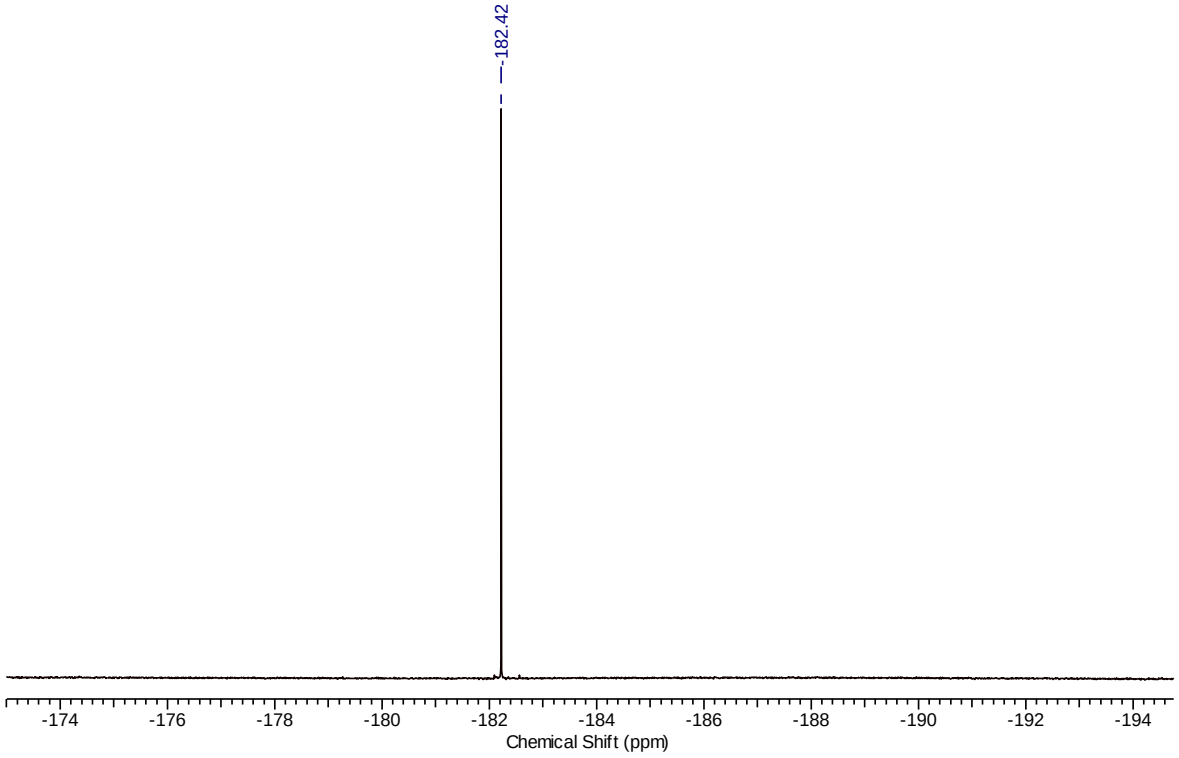

CHLOROFORM-d
165.78
144.33
144.15
133.89
131.85
128.94
127.96
127.92
126.26
125.68
125.43
123.24
91.84
90.07
77.32
77.00
76.68
60.61
38.43
38.21
14.15
200
180
160
140
120
100
80
60
40
20
0


-180.00
-174
-175
-176
-177
-178
-179
-180
-181
-182
-183
-184
-185
-186
-187
-188
-189
-190
-191
-192

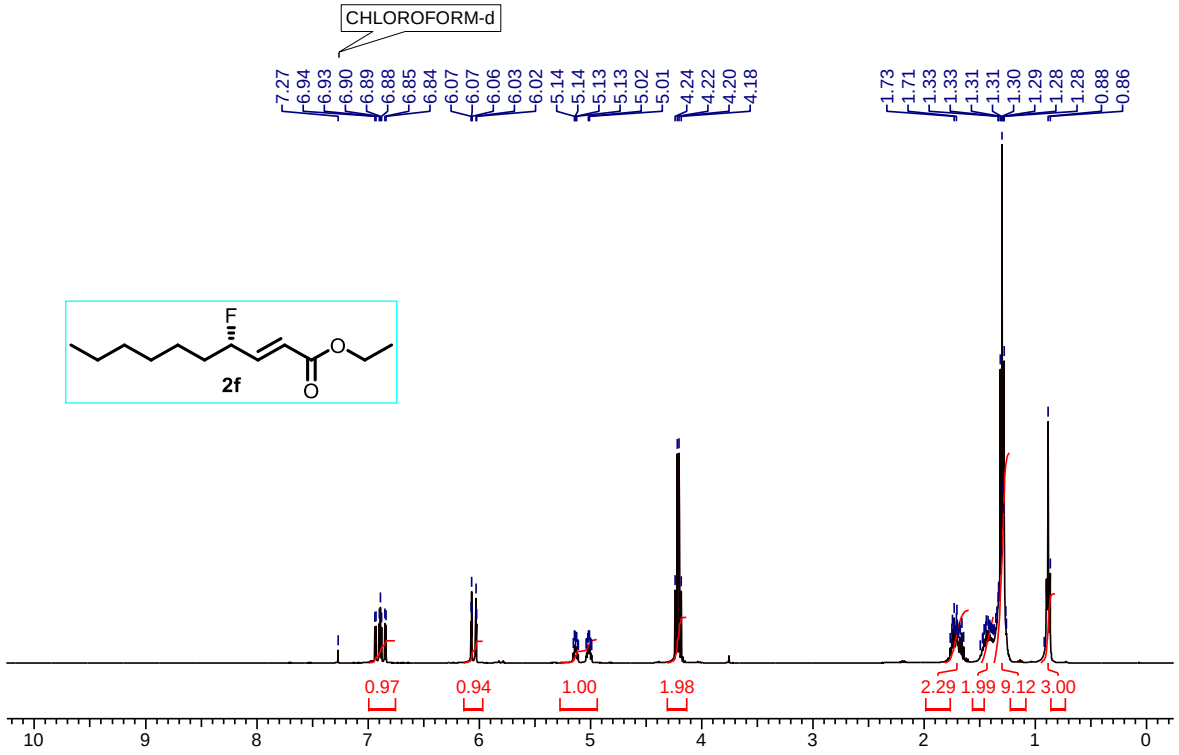
**Ethyl (*S,E*)-5-(4-chlorophenyl)-4-fluoropent-2-enoate (2e)**

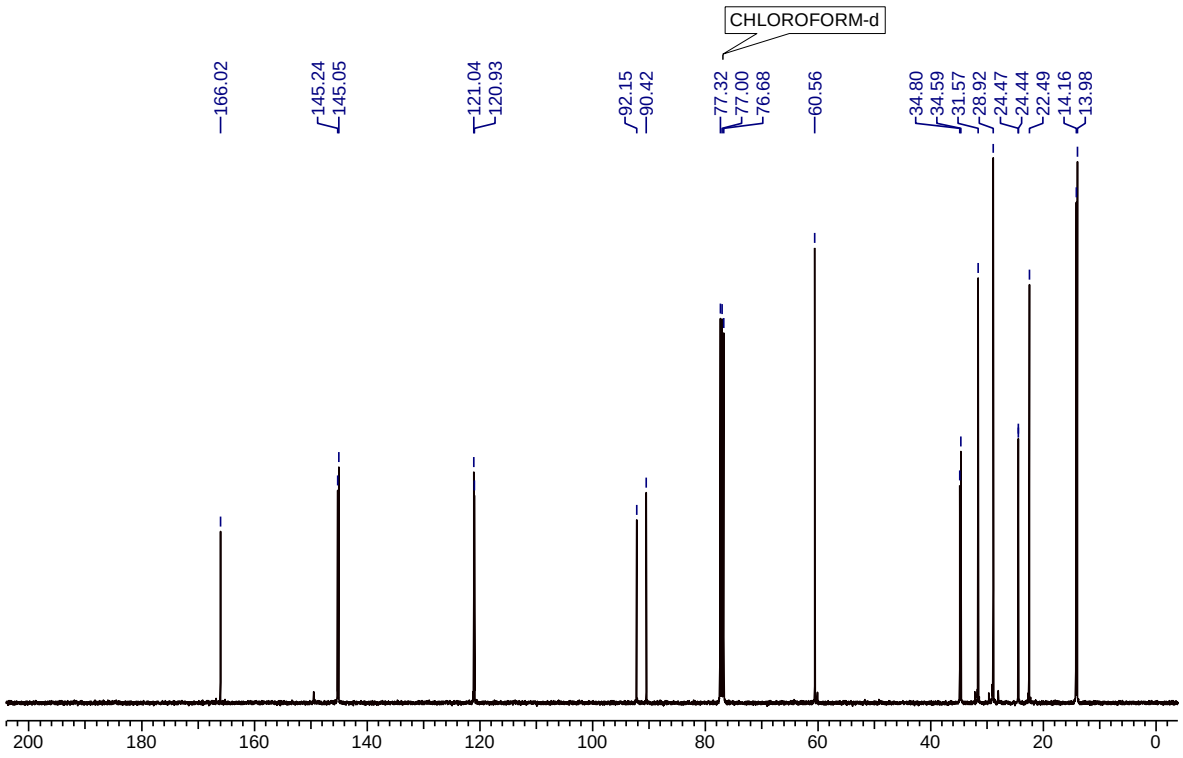


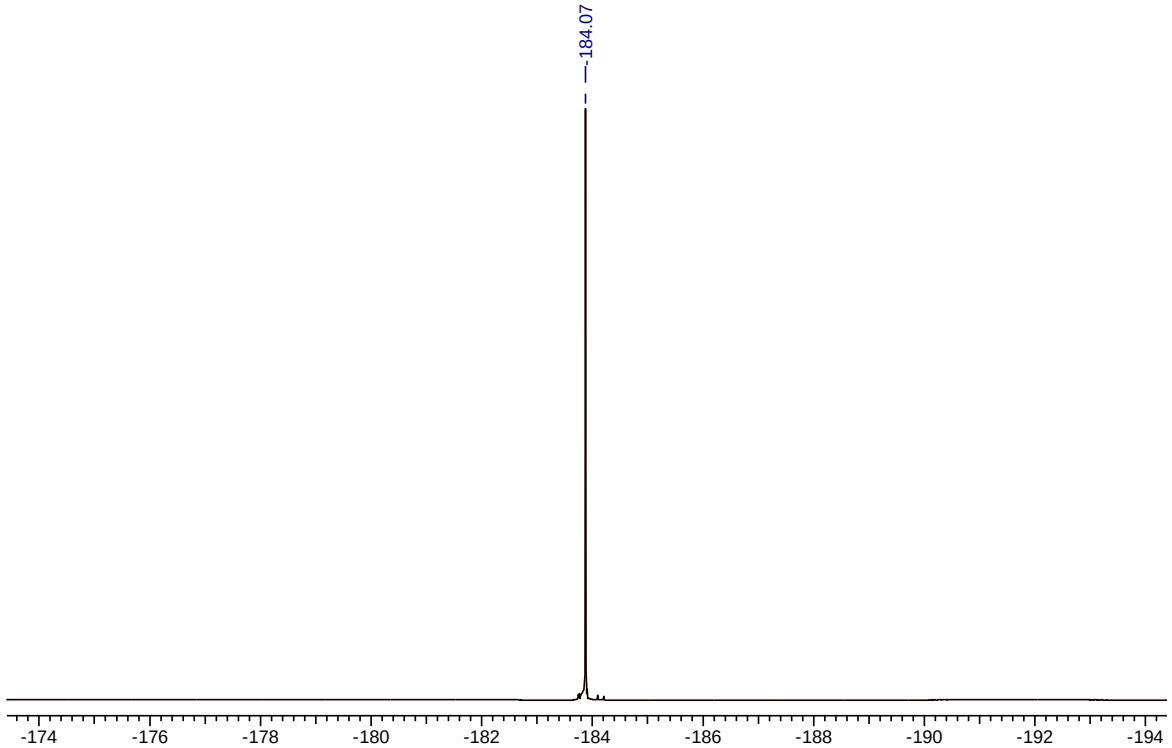





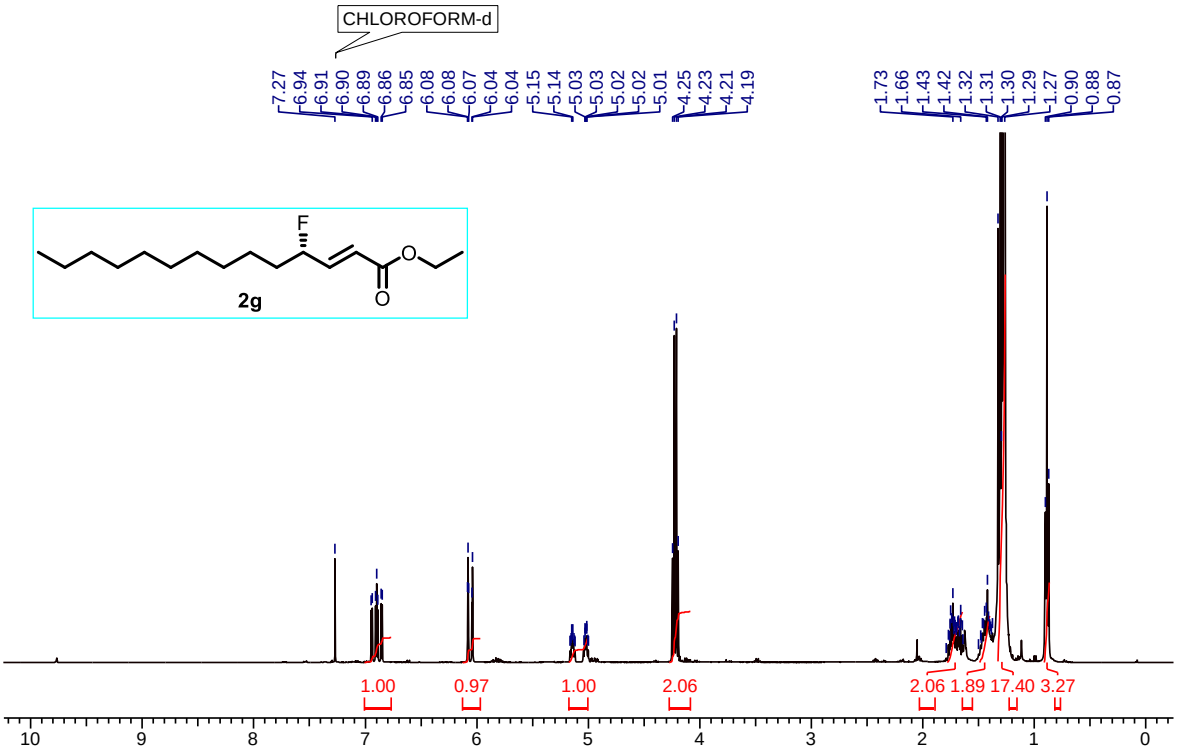

**Ethyl (*S*,*E*)-4-fluorodec-2-enoate (2f)**

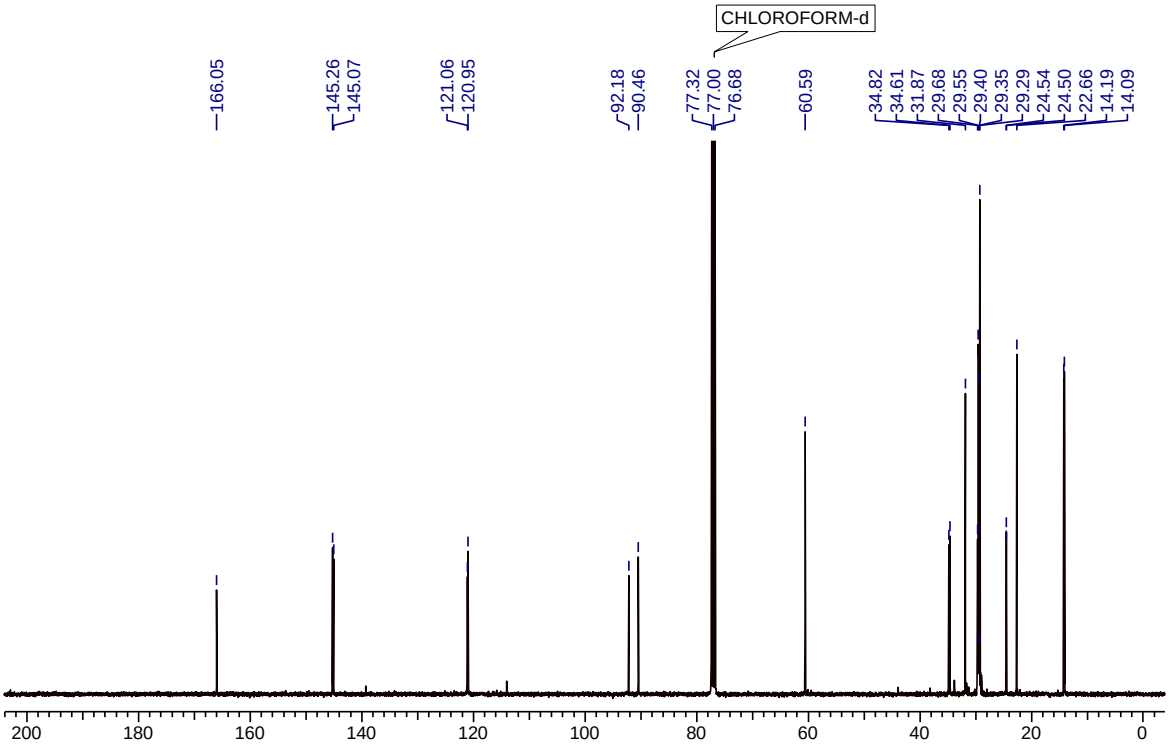


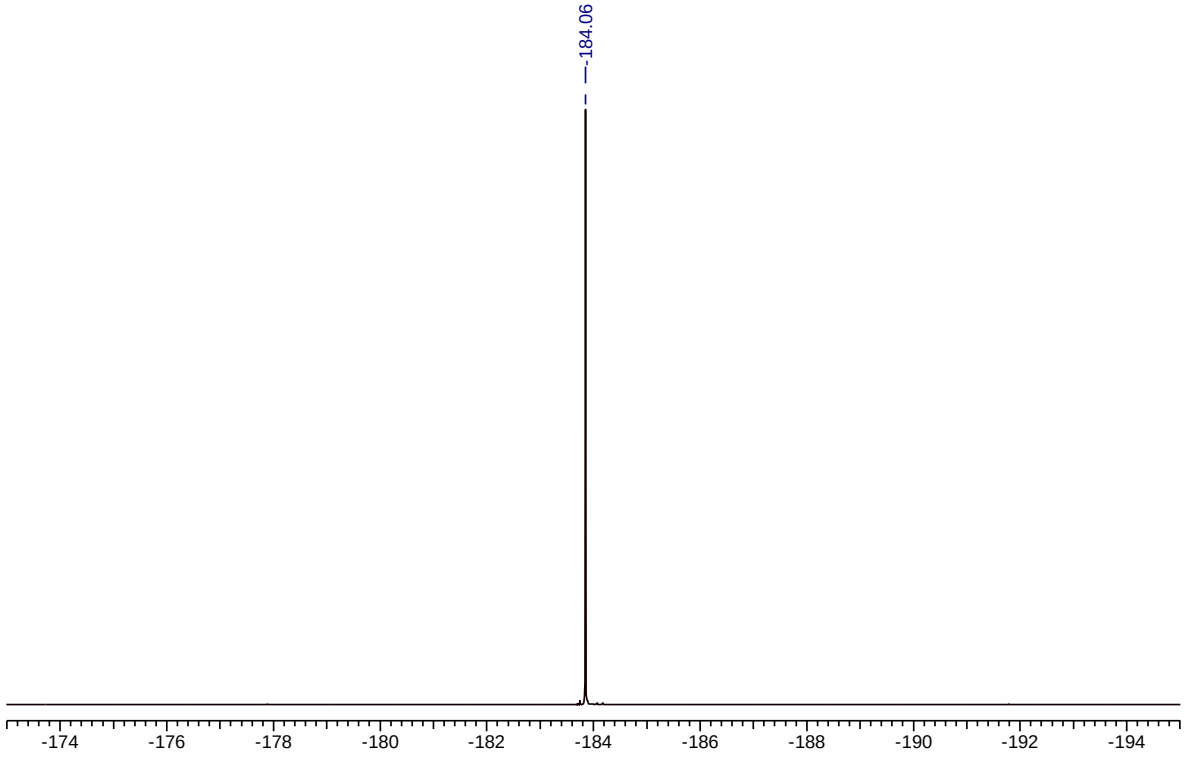

CHLOROFORM-d
166.02
145.24
145.05
121.04
120.93
92.15
90.42
77.32
77.00
76.68
60.56
34.80
34.59
31.57
28.92
24.47
24.44
22.49
14.16
13.98
200
180
160
140
120
100
80
60
40
20
0


-184.07
-174
-176
-178
-180
-182
-184
-186
-188
-190
-192
-194

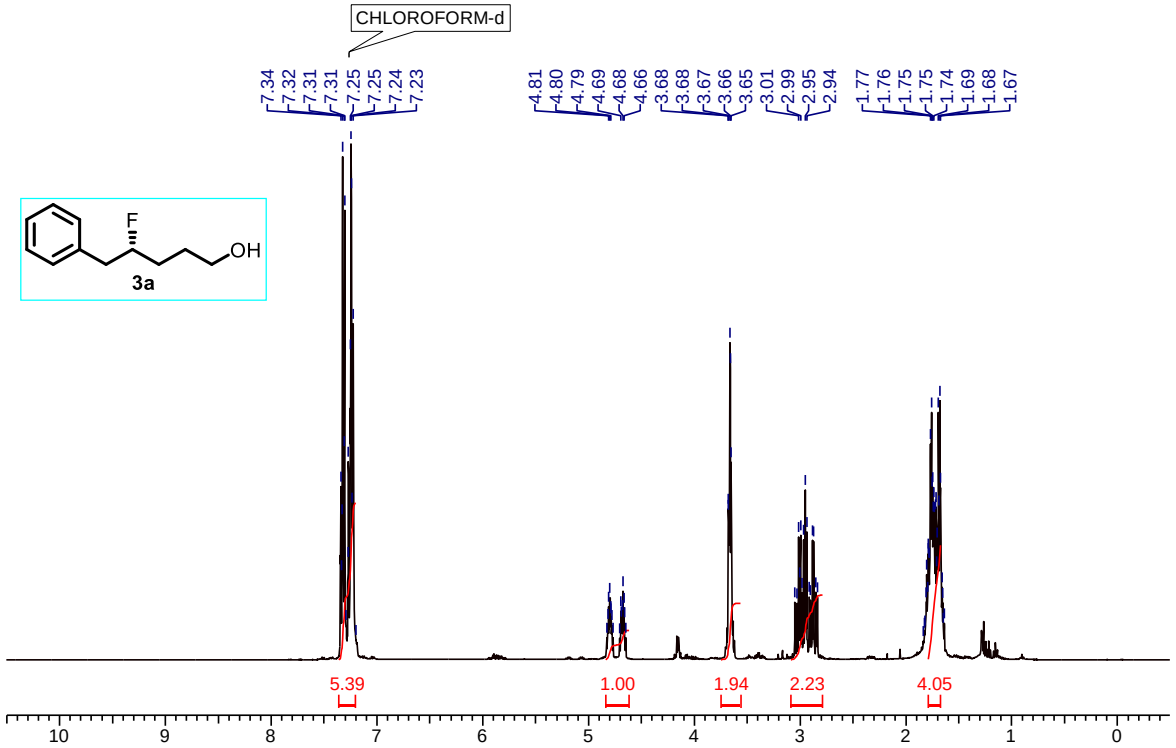
**Ethyl (*S*,*E*)-4-fluorotetradec-2-enoate (2g)**

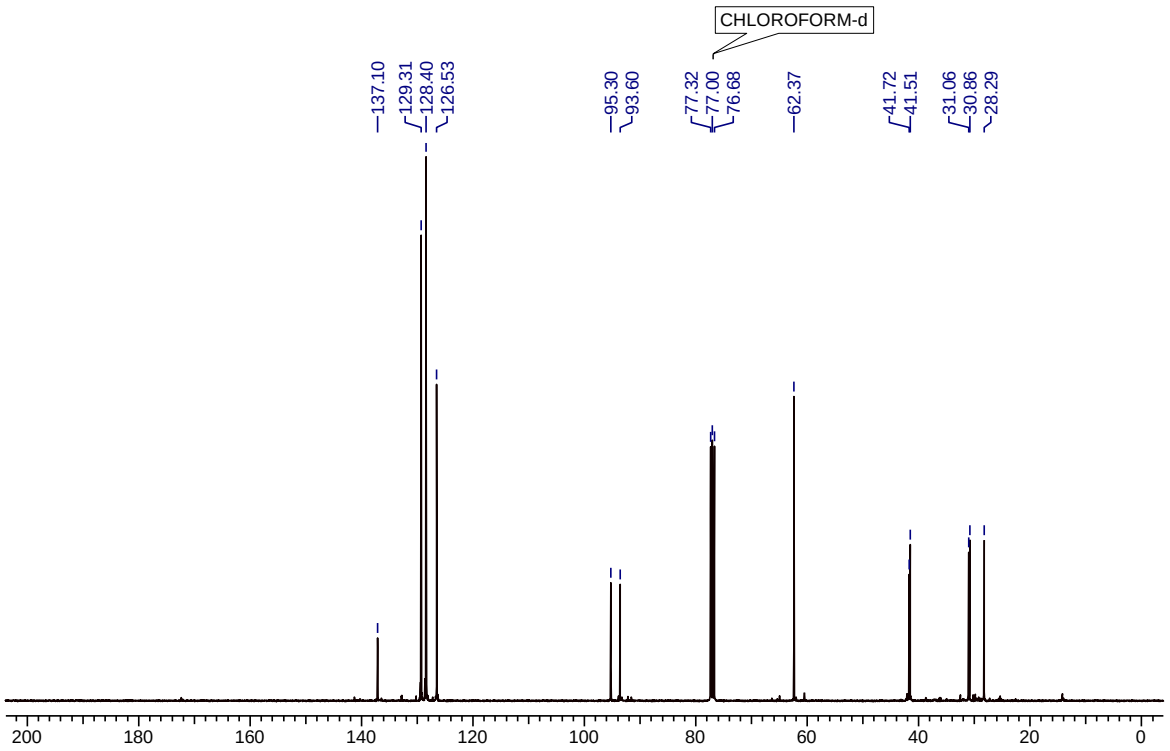


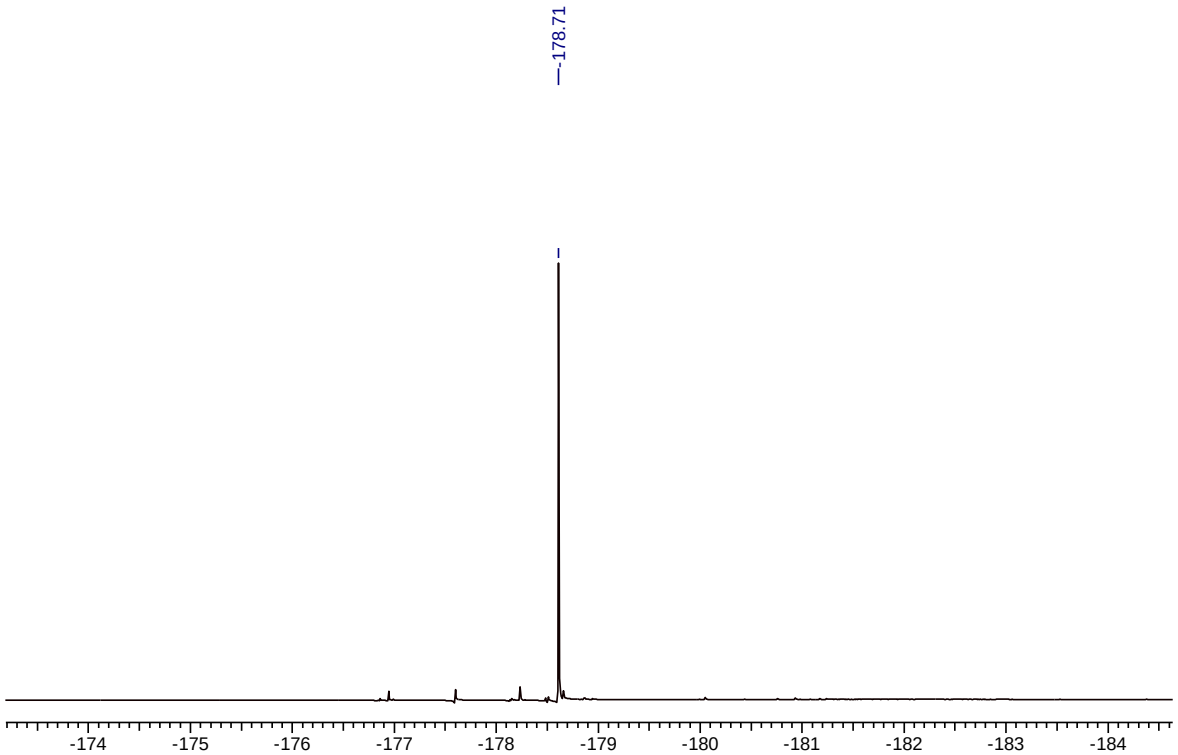





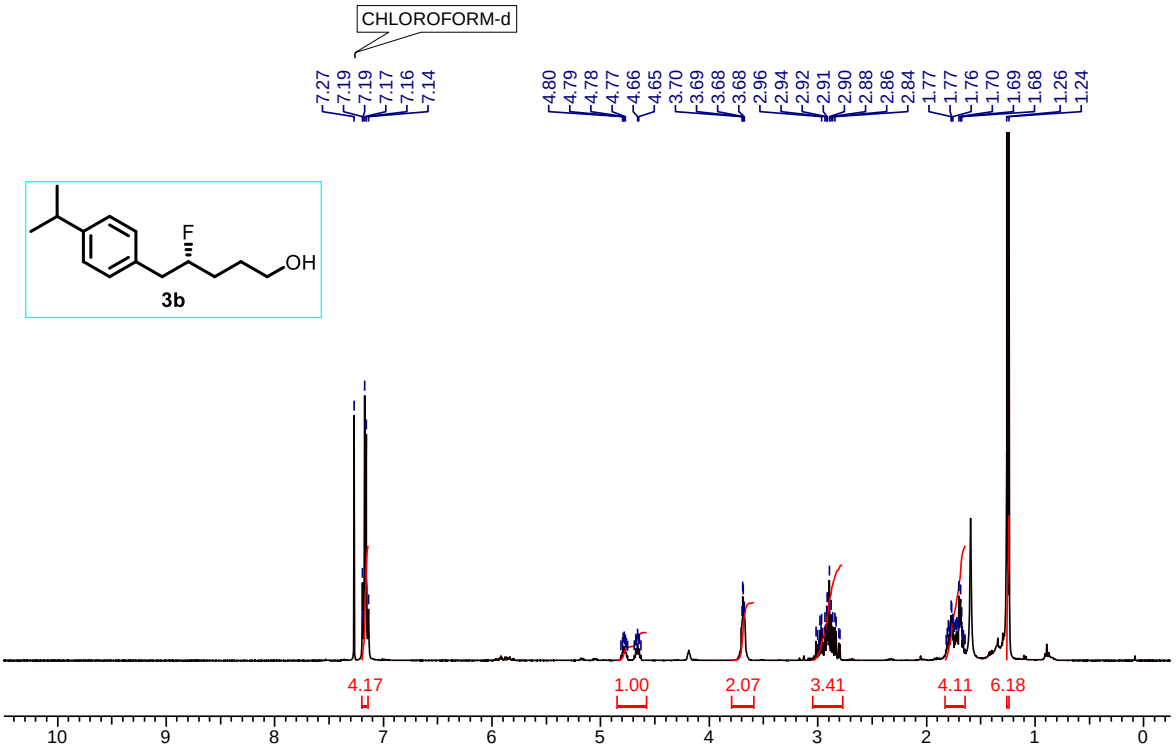

**(*R*)-4-fluoro-5-phenylpentan-1-ol (3a)**

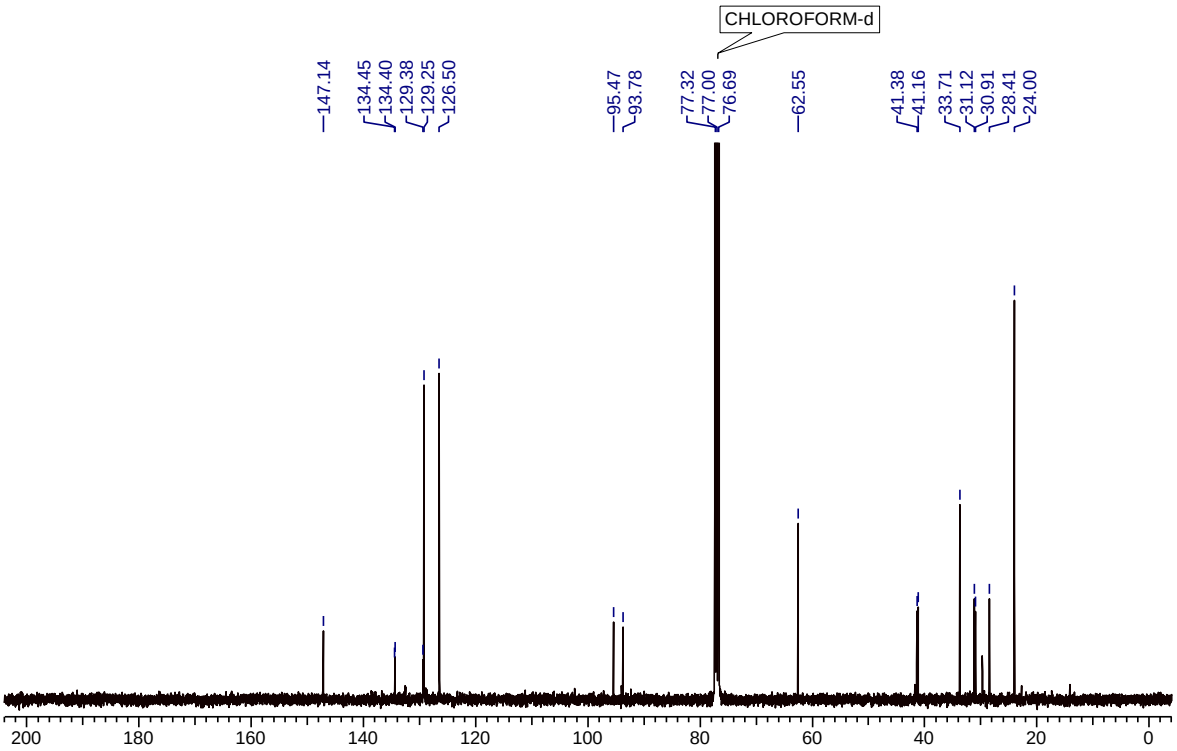


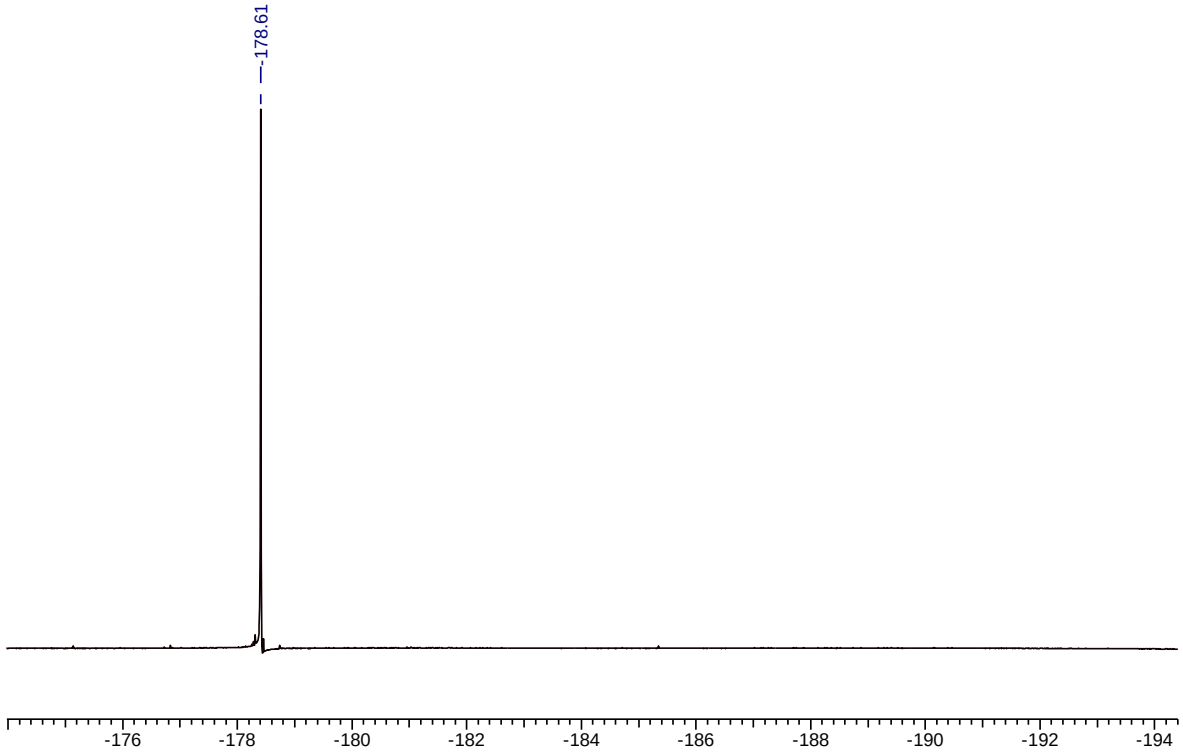

CHLOROFORM-d
137.10
129.31
128.40
126.53
95.30
93.60
77.32
77.00
76.68
62.37
41.72
41.51
31.06
30.86
28.29
200
180
160
140
120
100
80
60
40
20
0


-178.71
-174
-175
-176
-177
-178
-179
-180
-181
-182
-183
-184

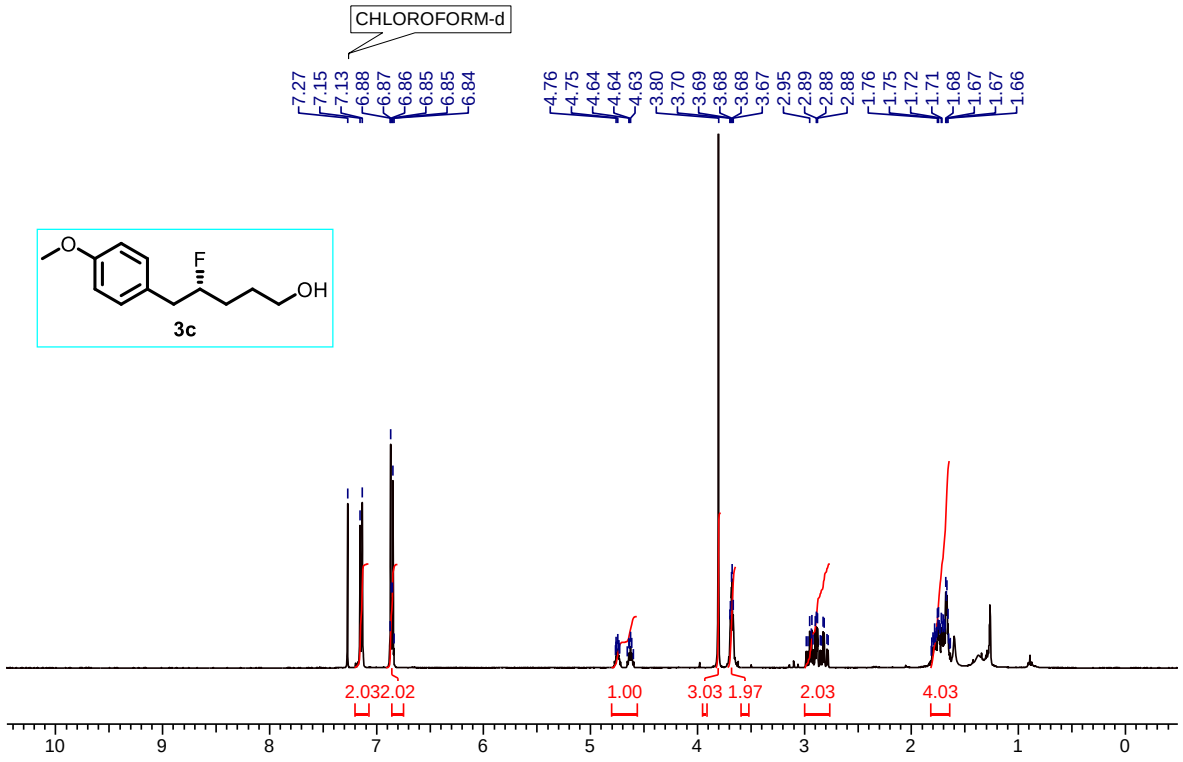
**(*R*)-4-fluoro-5-(4-isopropylphenyl)pentan-1-ol (3b)**

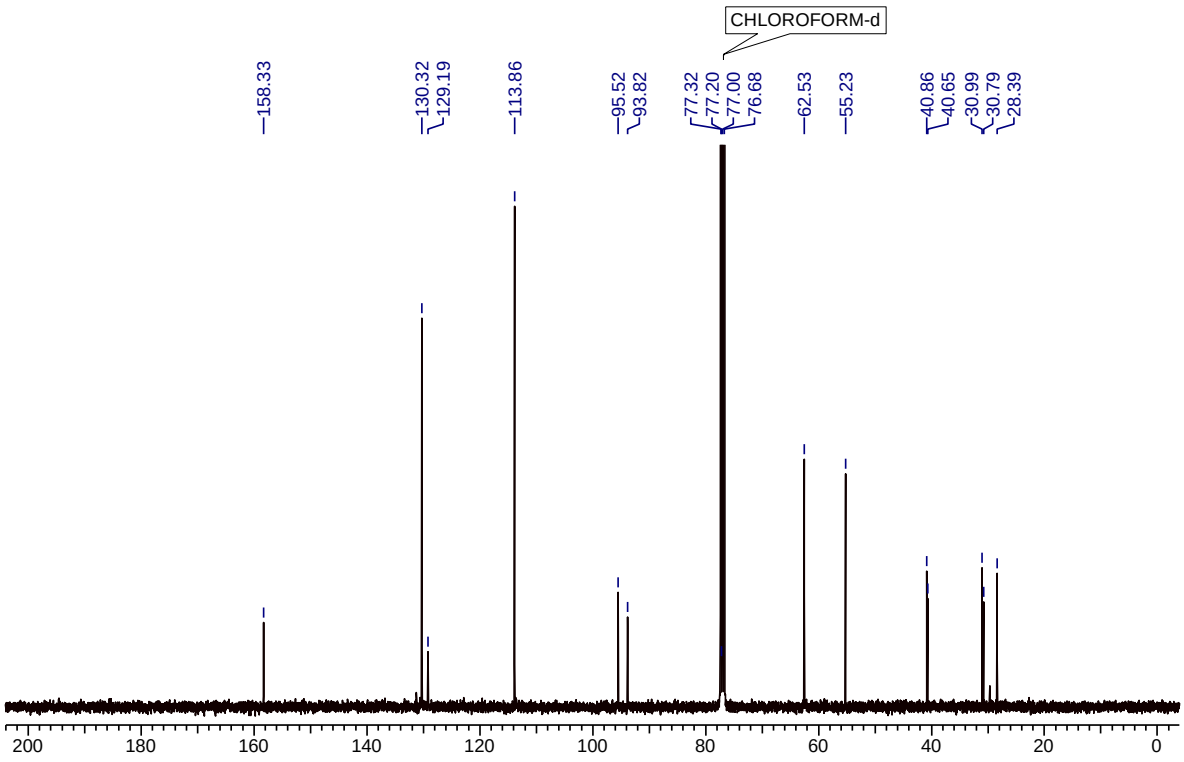


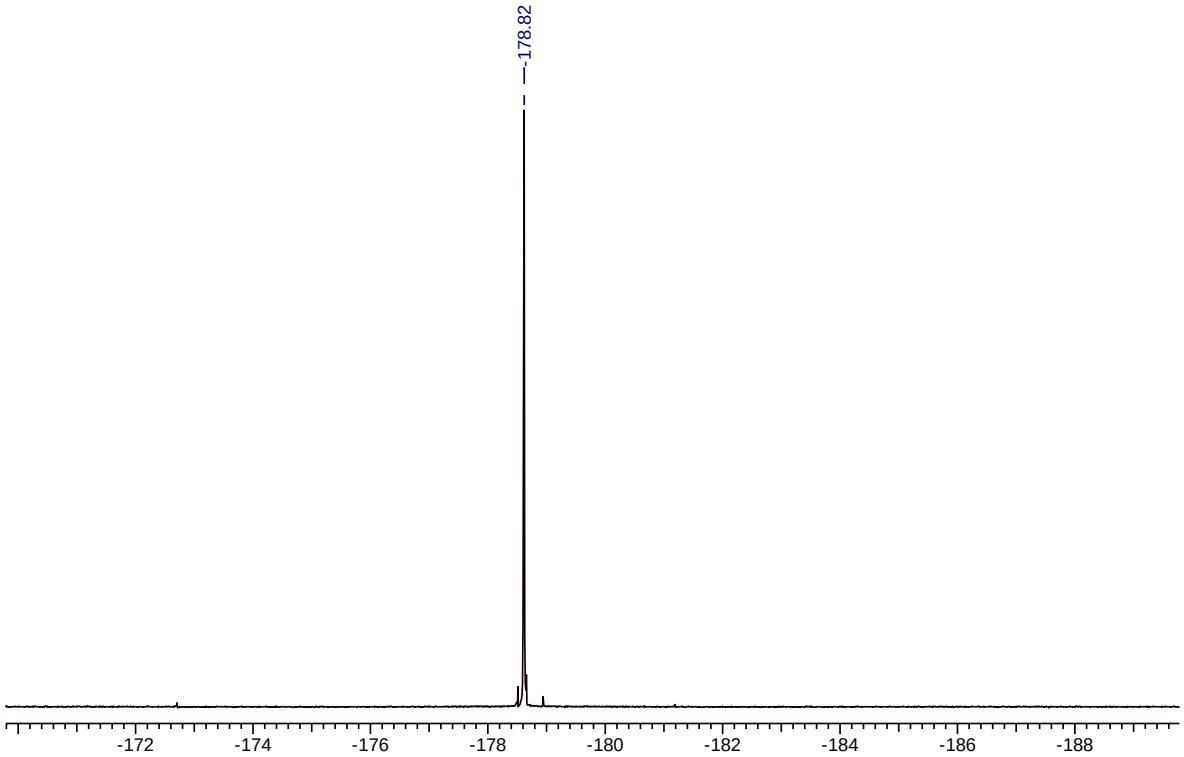





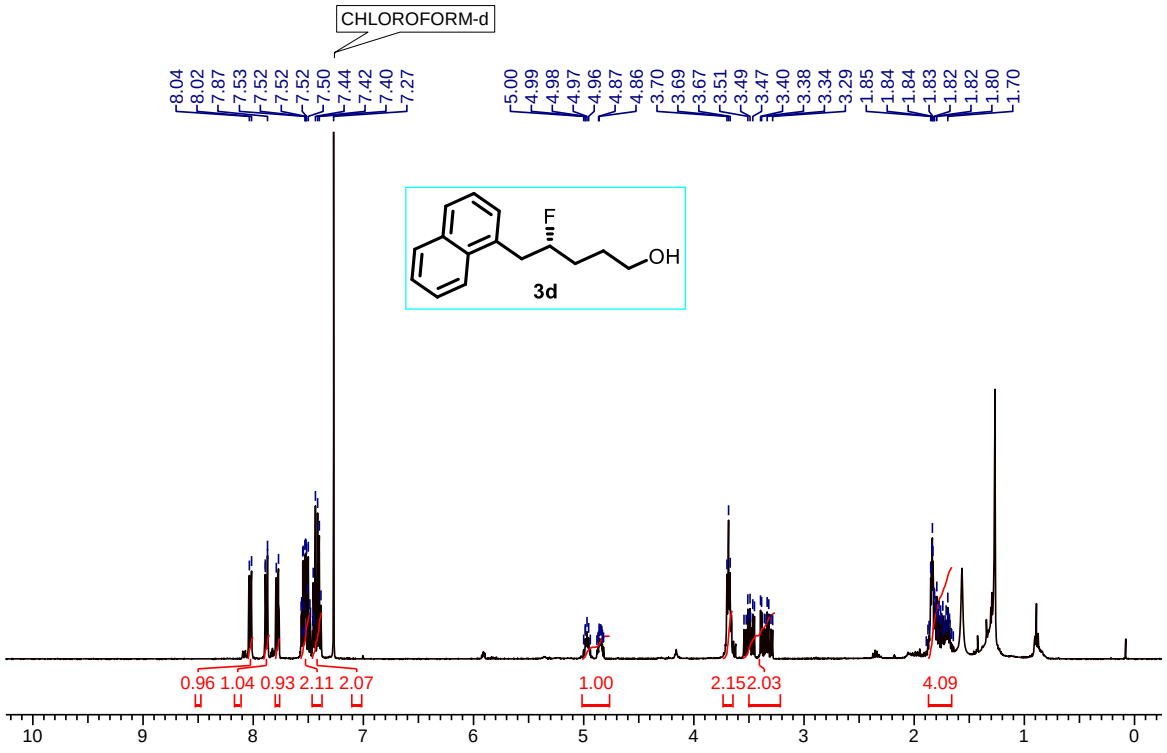

**(*R*)-4-fluoro-5-(4-methoxyphenyl)pentan-1-ol (3c)**

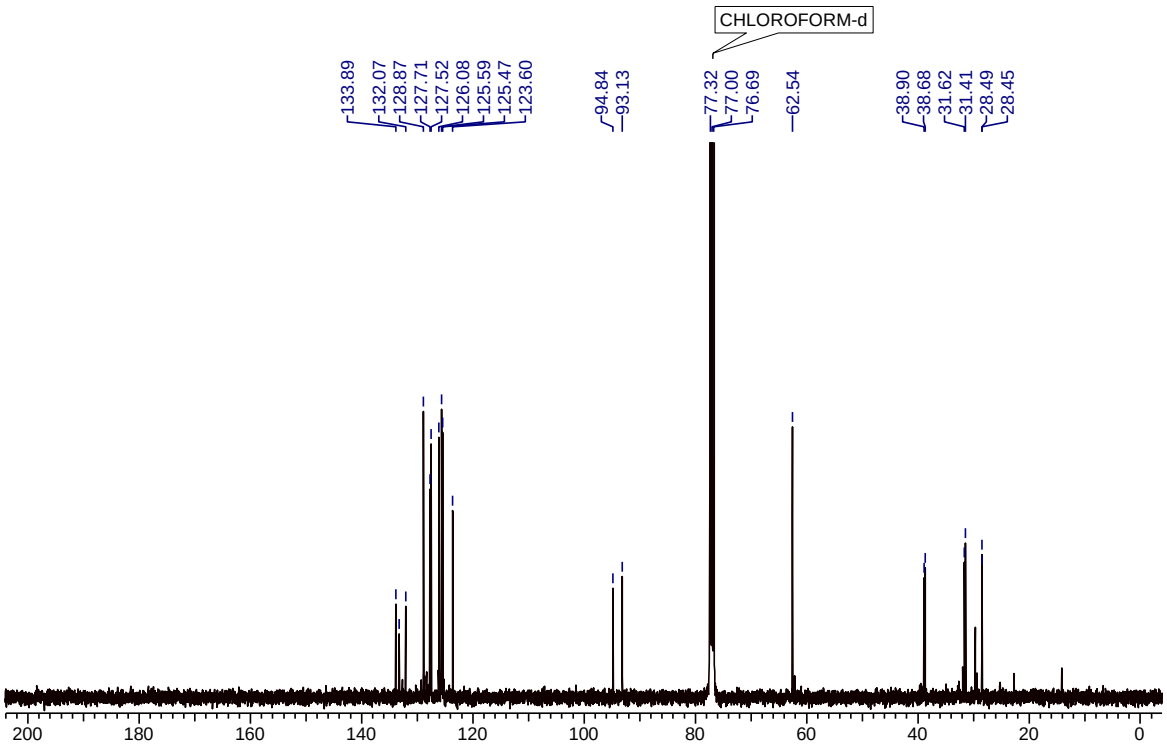


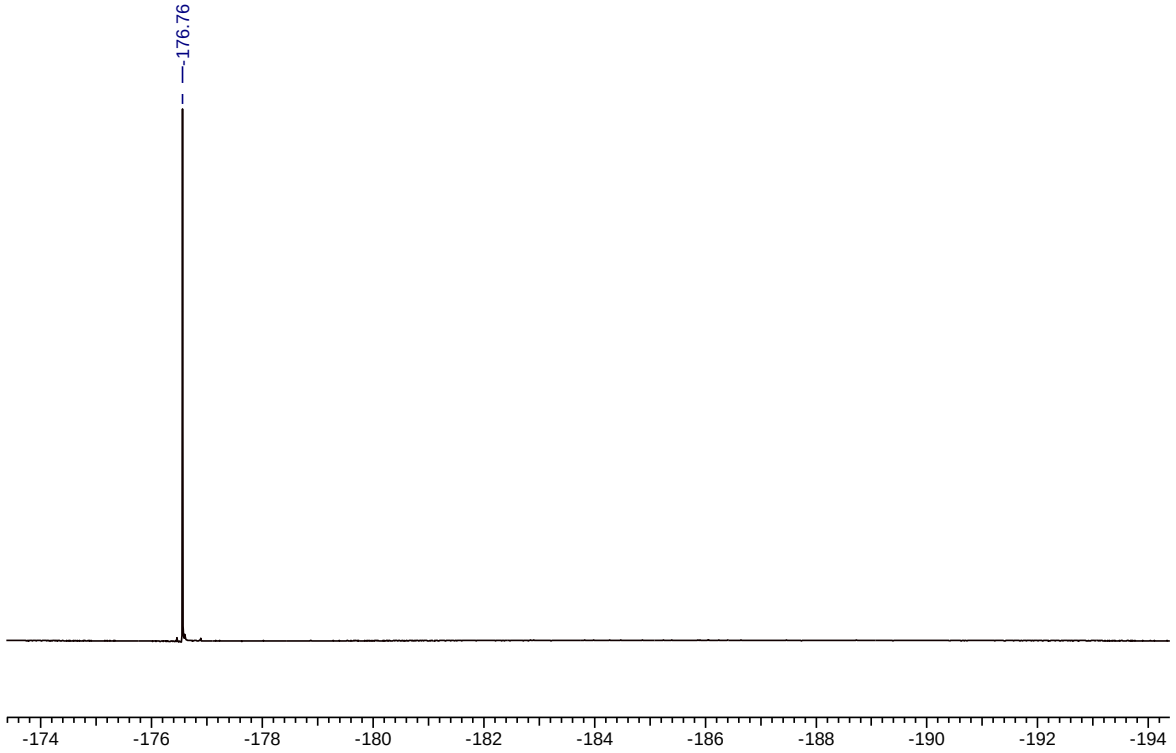

CHLOROFORM-d
158.33
130.32
129.19
113.86
95.52
93.82
77.32
77.20
77.00
76.68
62.53
55.23
40.86
40.65
30.99
30.79
28.39
200
180
160
140
120
100
80
60
40
20
0


178.82
-172
-174
-176
-178
-180
-182
-184
-186
-188

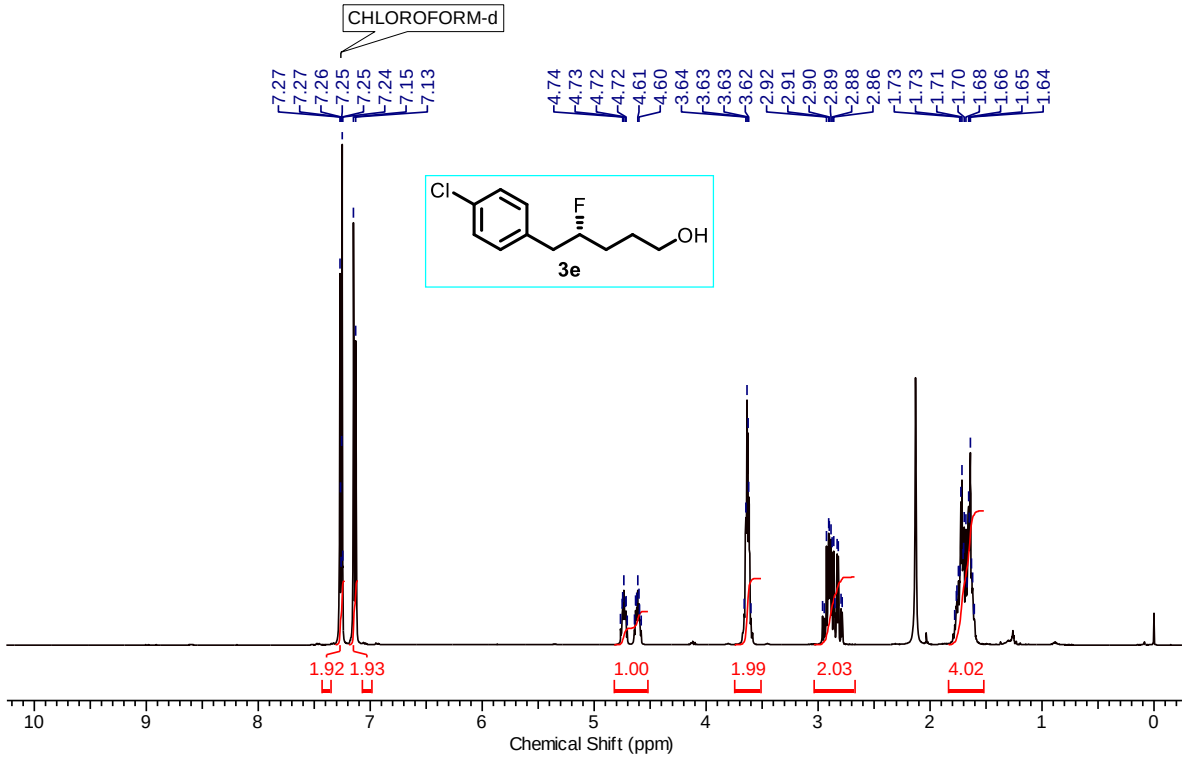
**(*R*)-4-fluoro-5-(naphthalen-2-yl)pentan-1-ol (3d)**

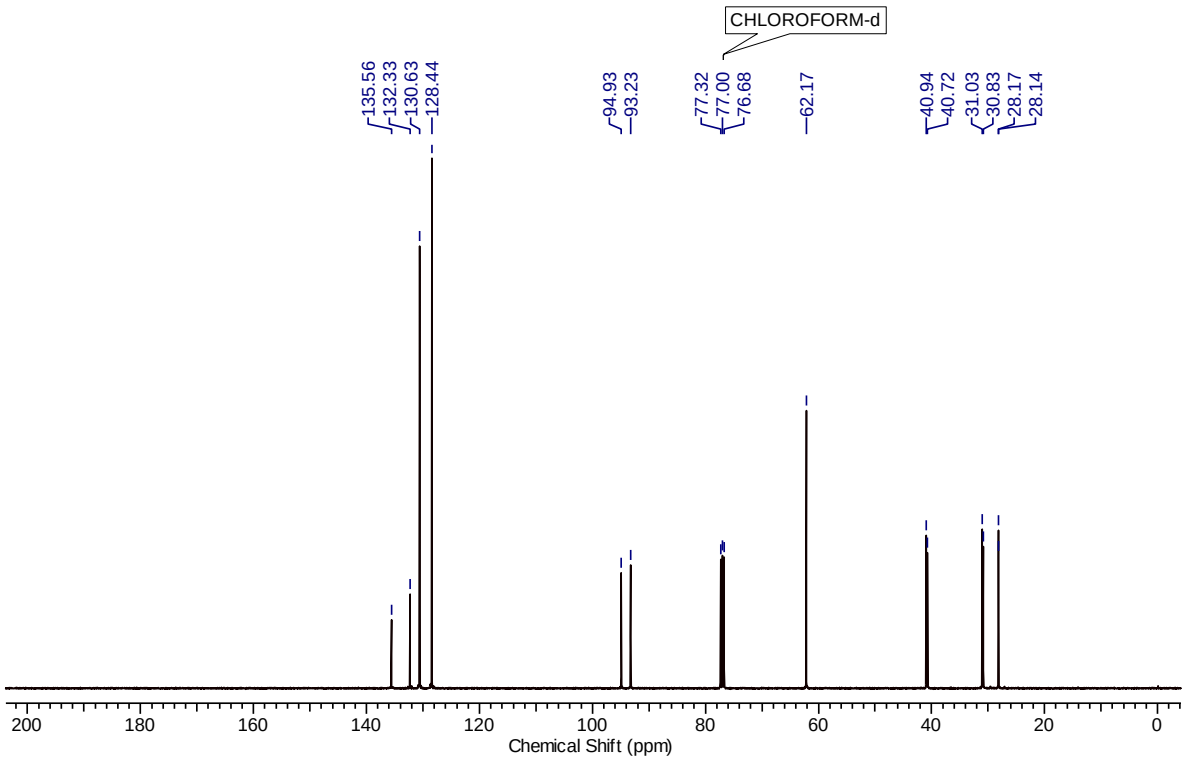


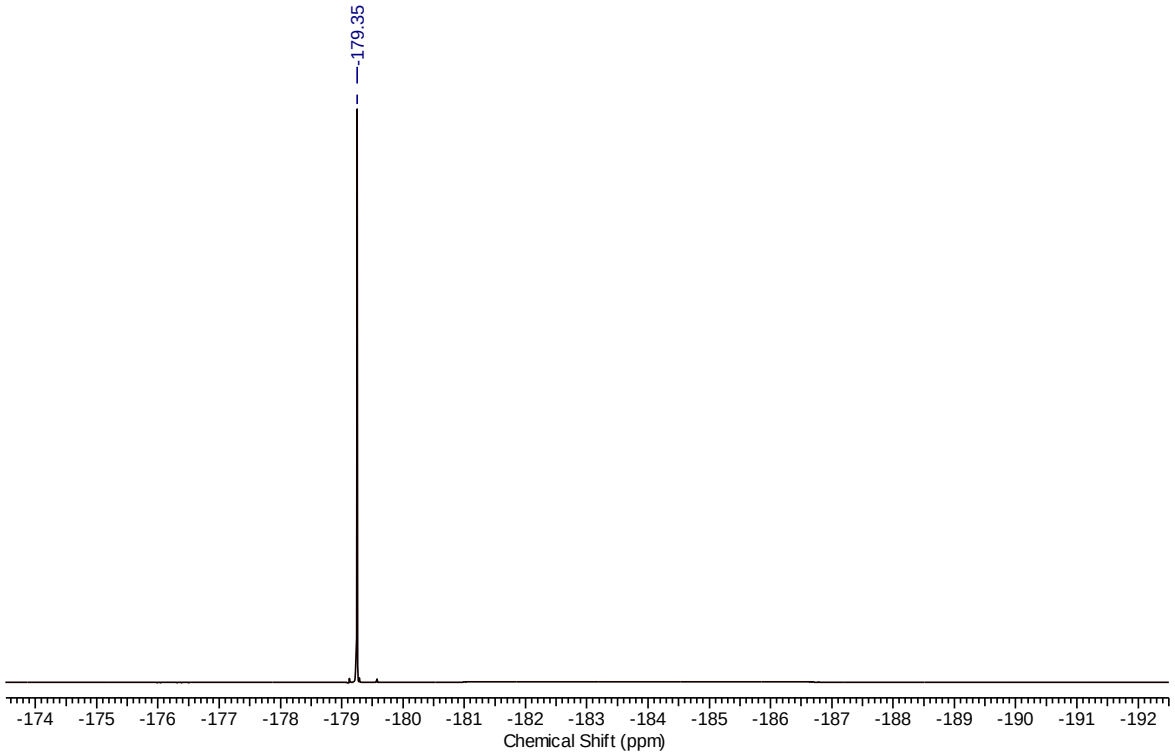





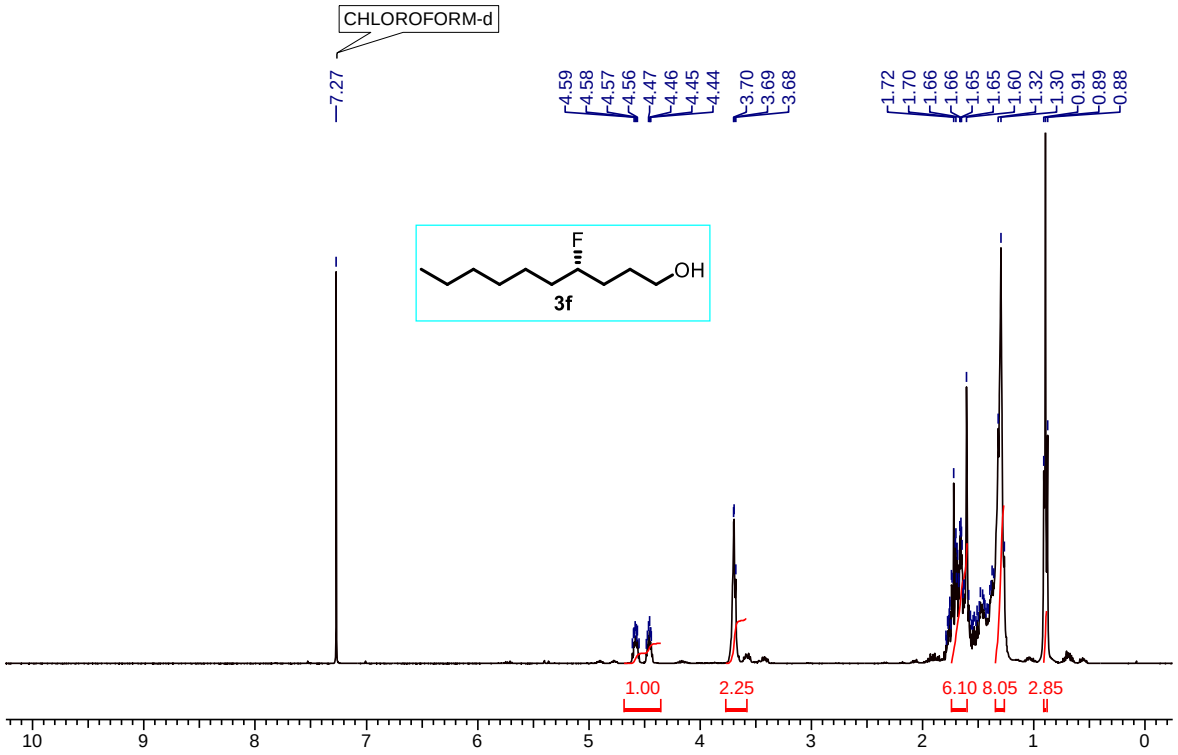

**(*R*)-5-(4-chlorophenyl)-4-fluoropentan-1-ol (3e)**

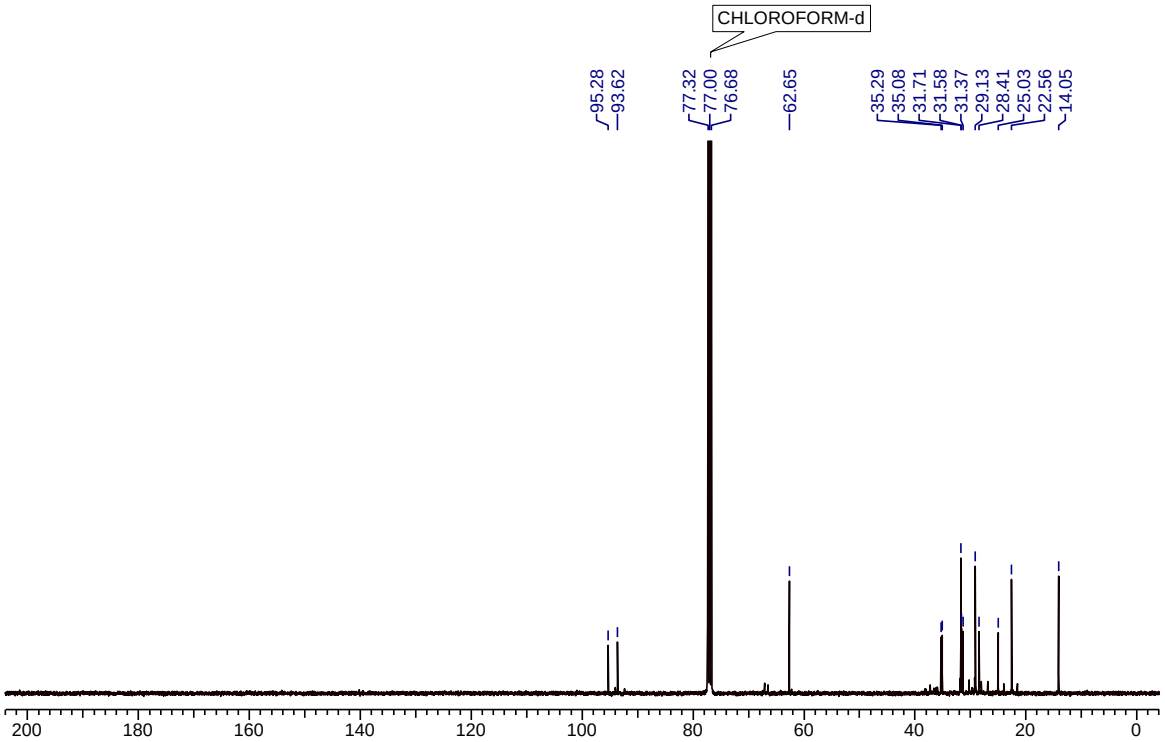


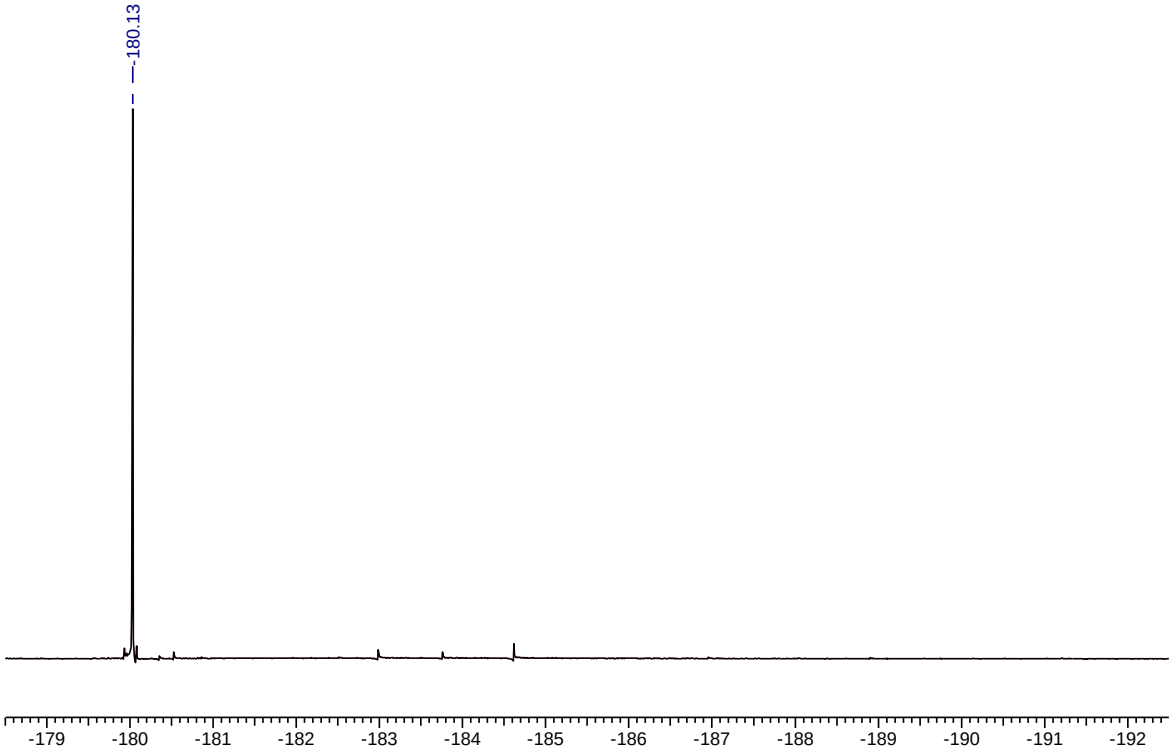

CHLOROFORM-d
135.56
132.33
130.63
128.44
94.93
93.23
77.32
77.00
76.68
62.17
40.94
40.72
31.03
30.83
28.17
28.14
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


-179.35
-174
-175
-176
-177
-178
-179
-180
-181
-182
-183
-184
-185
-186
-187
-188
-189
-190
-191
-192
Chemical Shift (ppm)

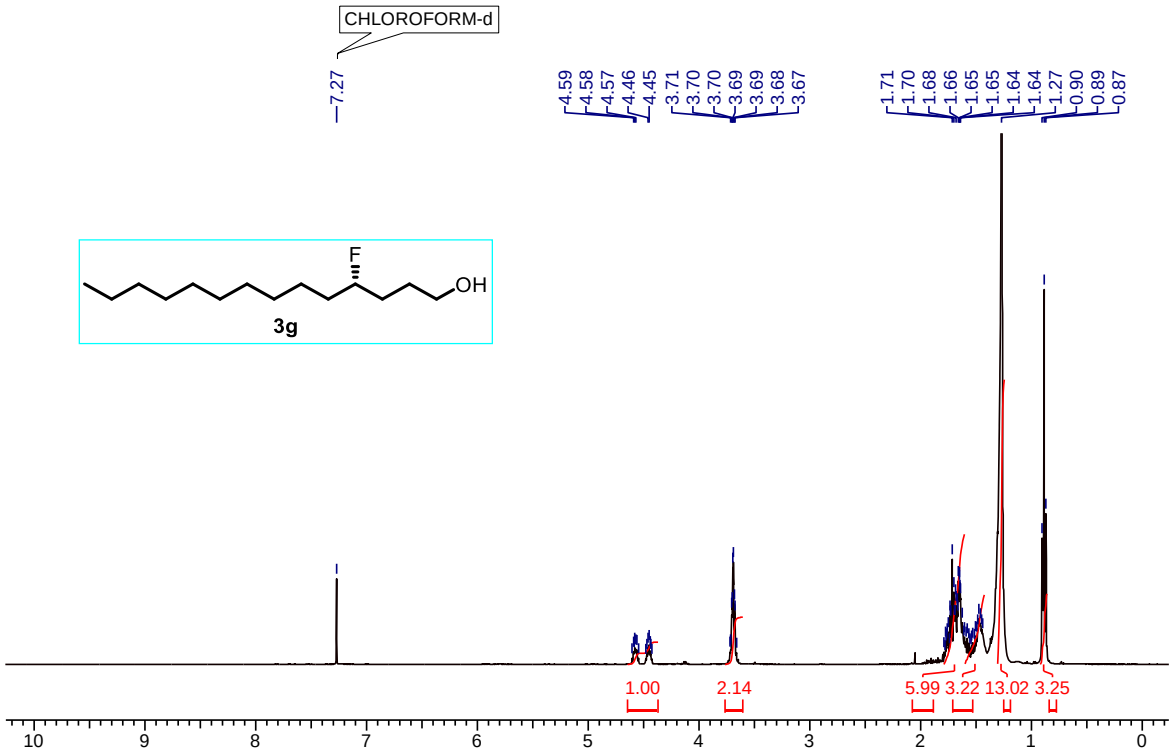
**(*S*)-4-fluorodecan-1-ol (3f)**

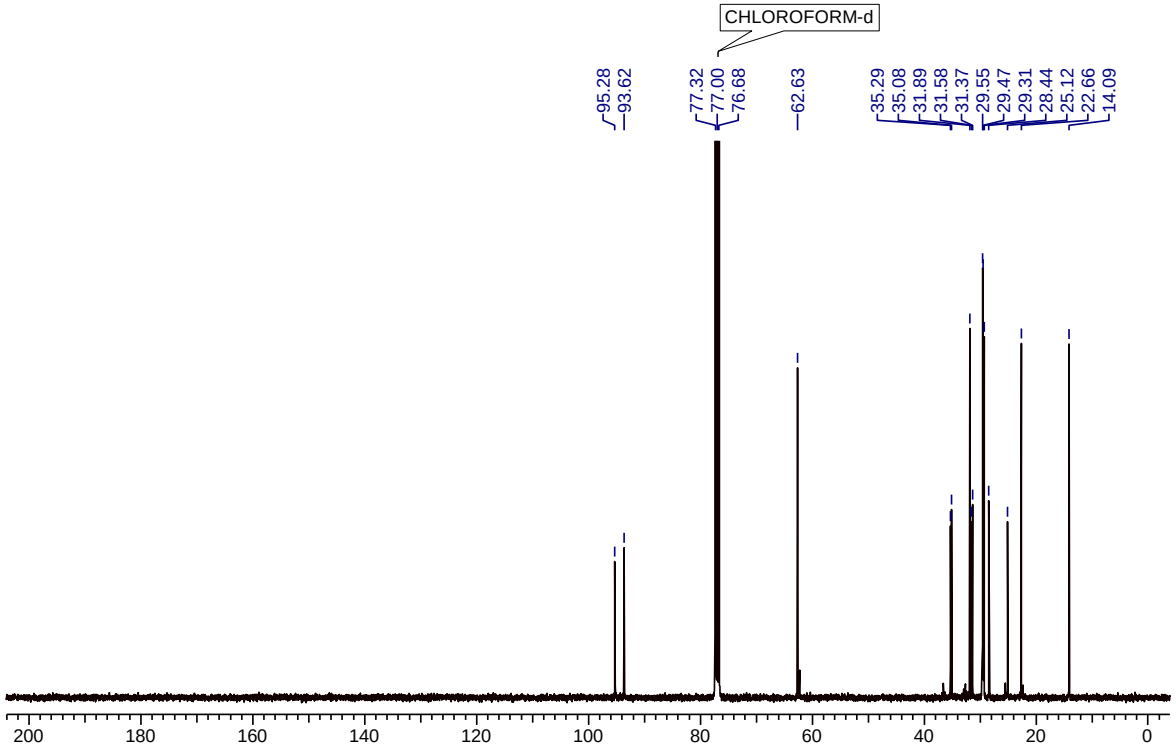


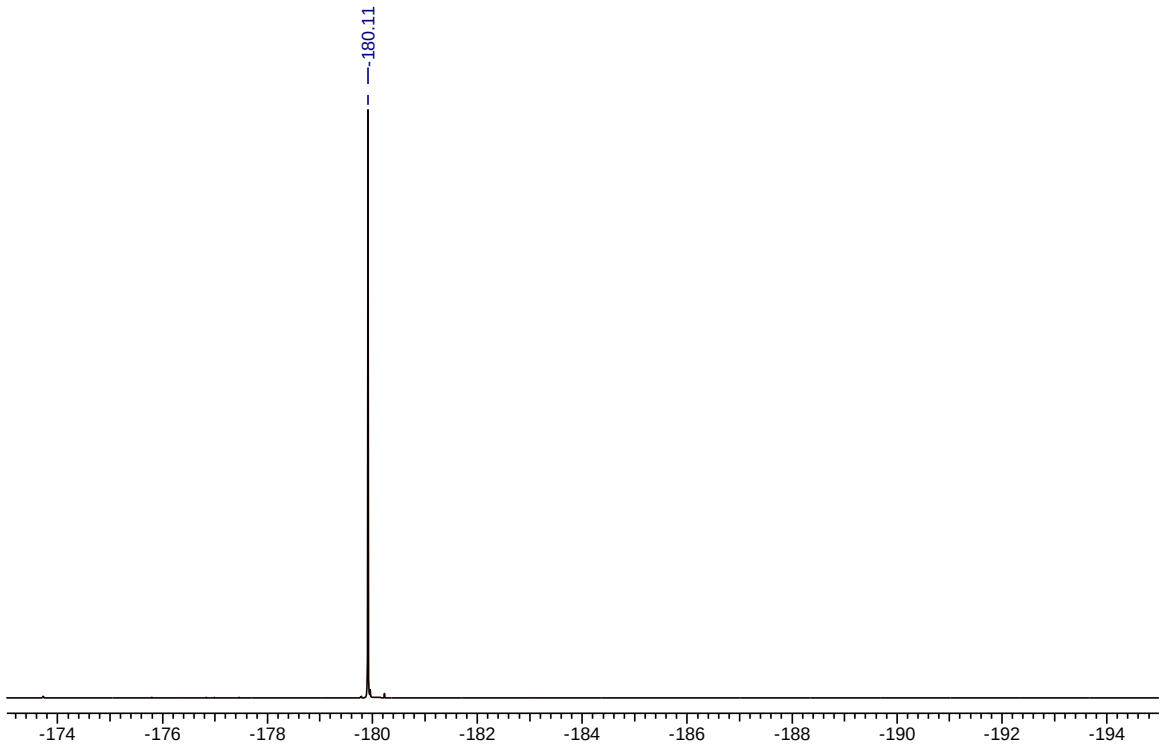





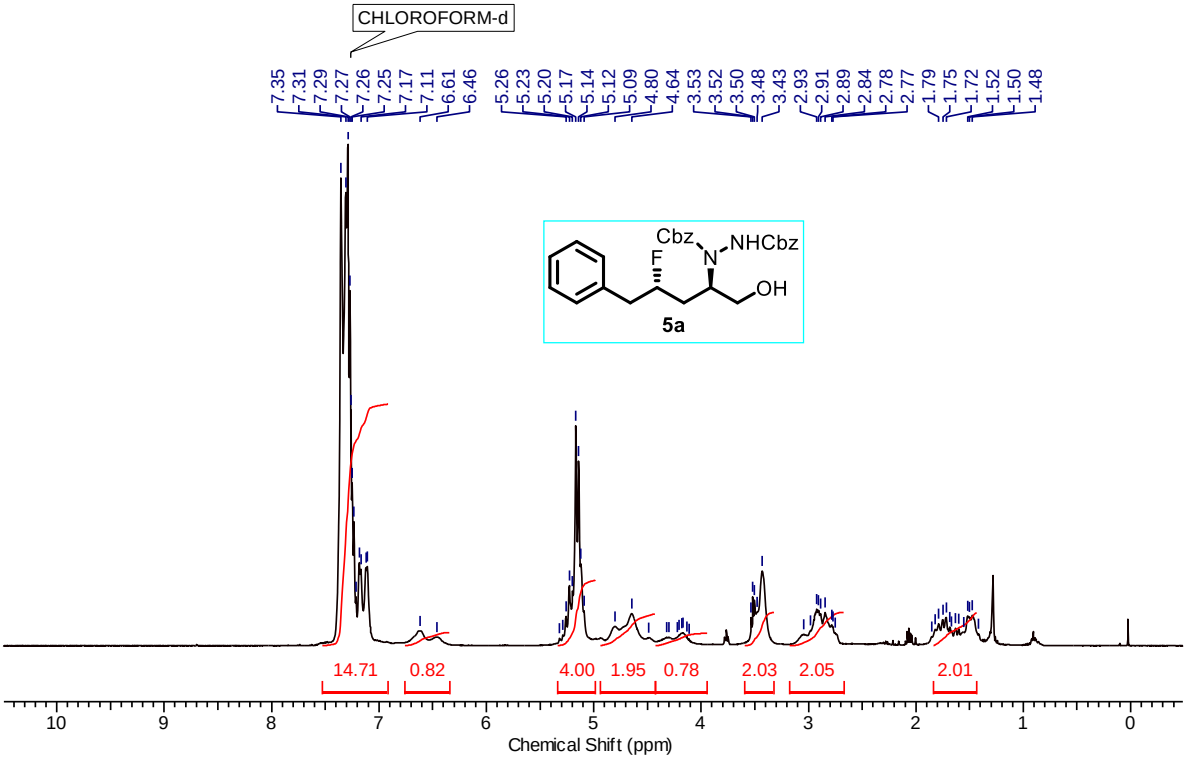

**(*S*)-4-fluorotetradecan-1-ol (3g)**

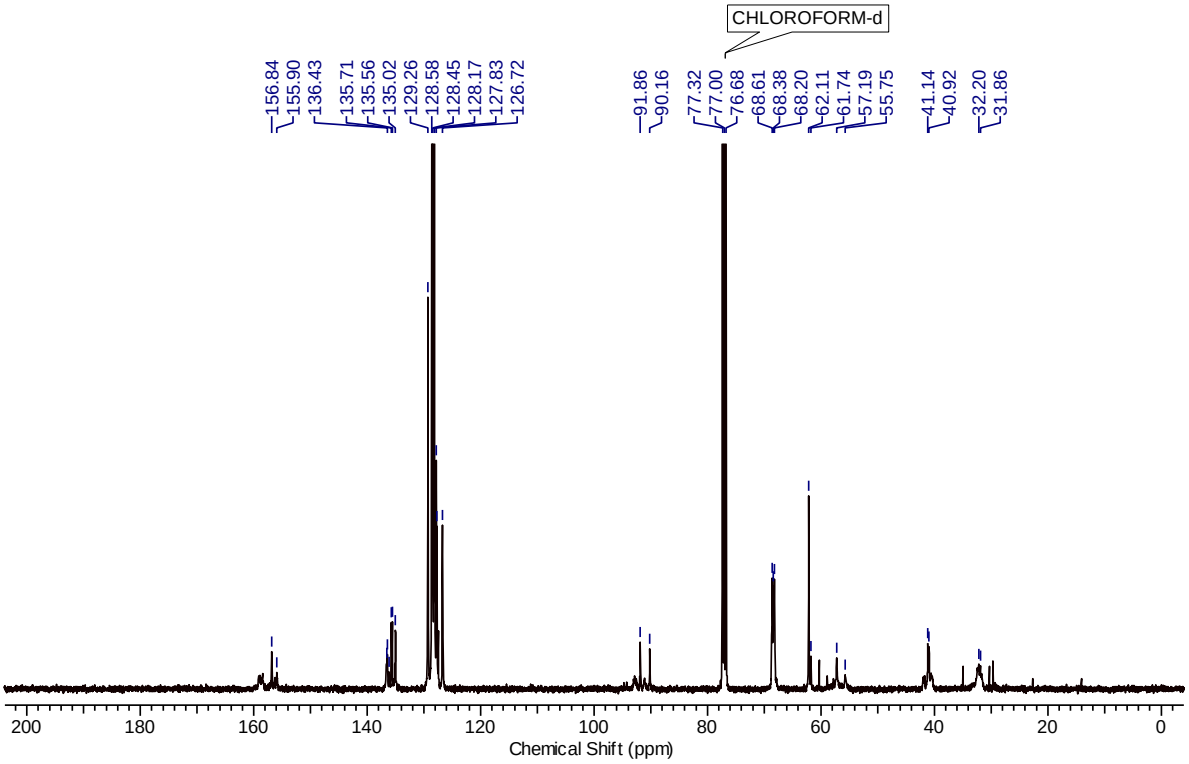


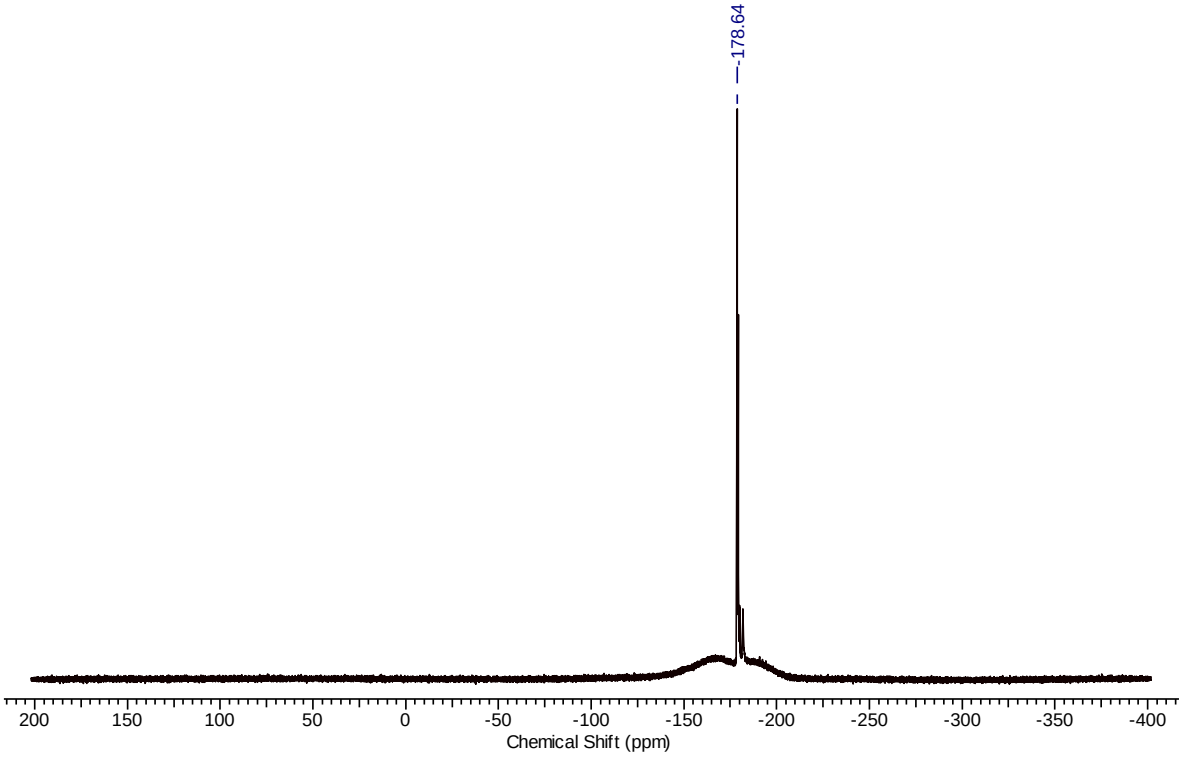

CHLOROFORM-d
95.28
93.62
77.32
77.00
76.68
62.63
35.29
35.08
31.89
31.58
31.37
29.55
29.47
29.31
28.44
25.12
22.66
14.09
200
180
160
140
120
100
80
60
40
20
0


-180.11
-174
-176
-178
-180
-182
-184
-186
-188
-190
-192
-194

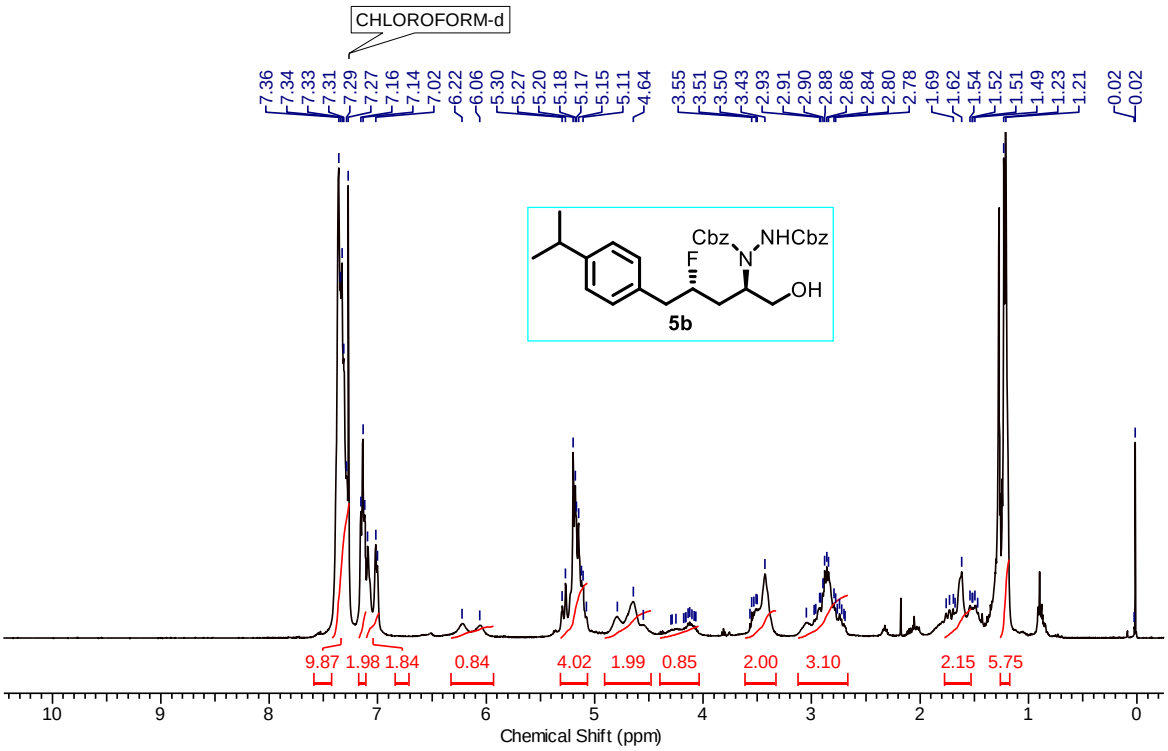
**Dibenzyl 1-((2*R*,4*S*)-4-fluoro-1-hydroxy-5-phenylpentan-2-yl)hydrazine-1,2-dicarboxylate (5a)**

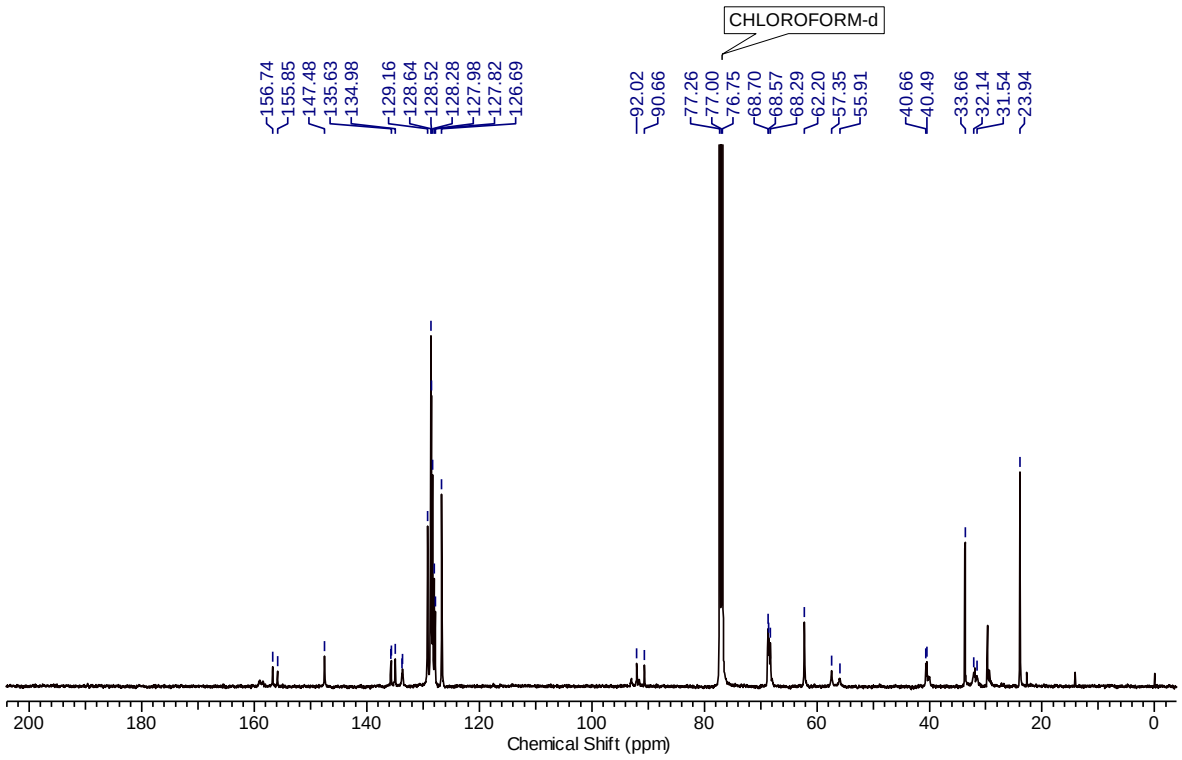


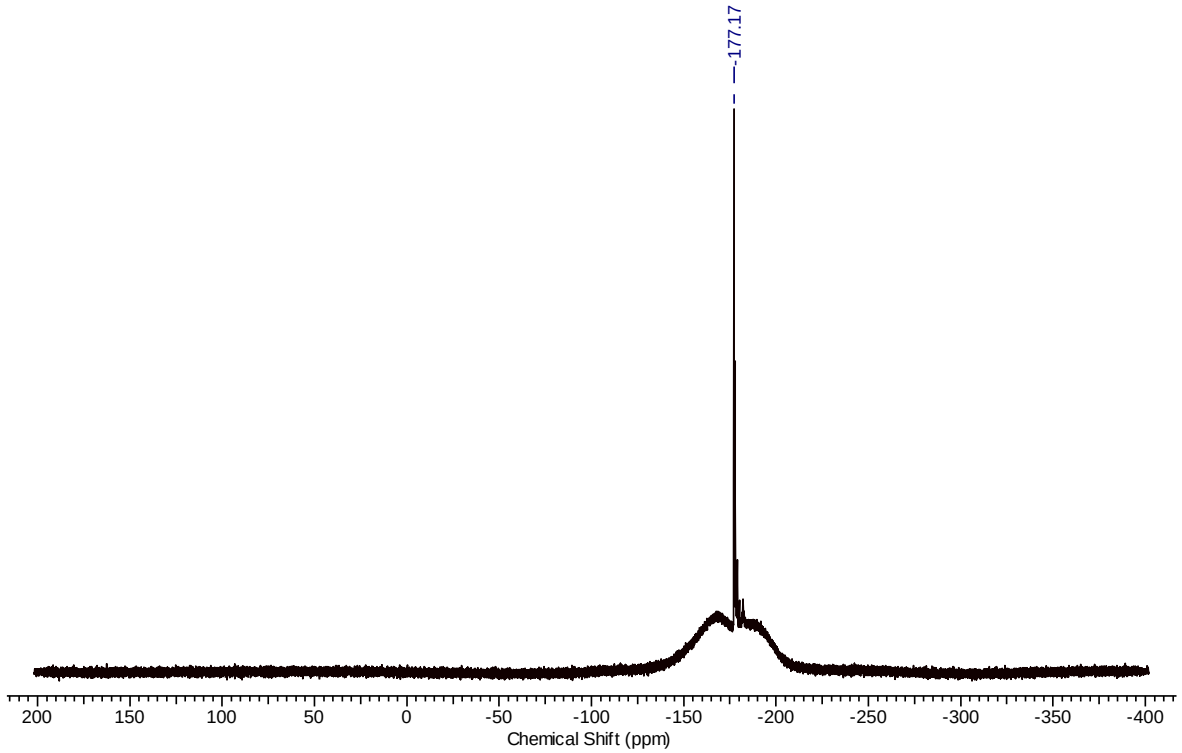





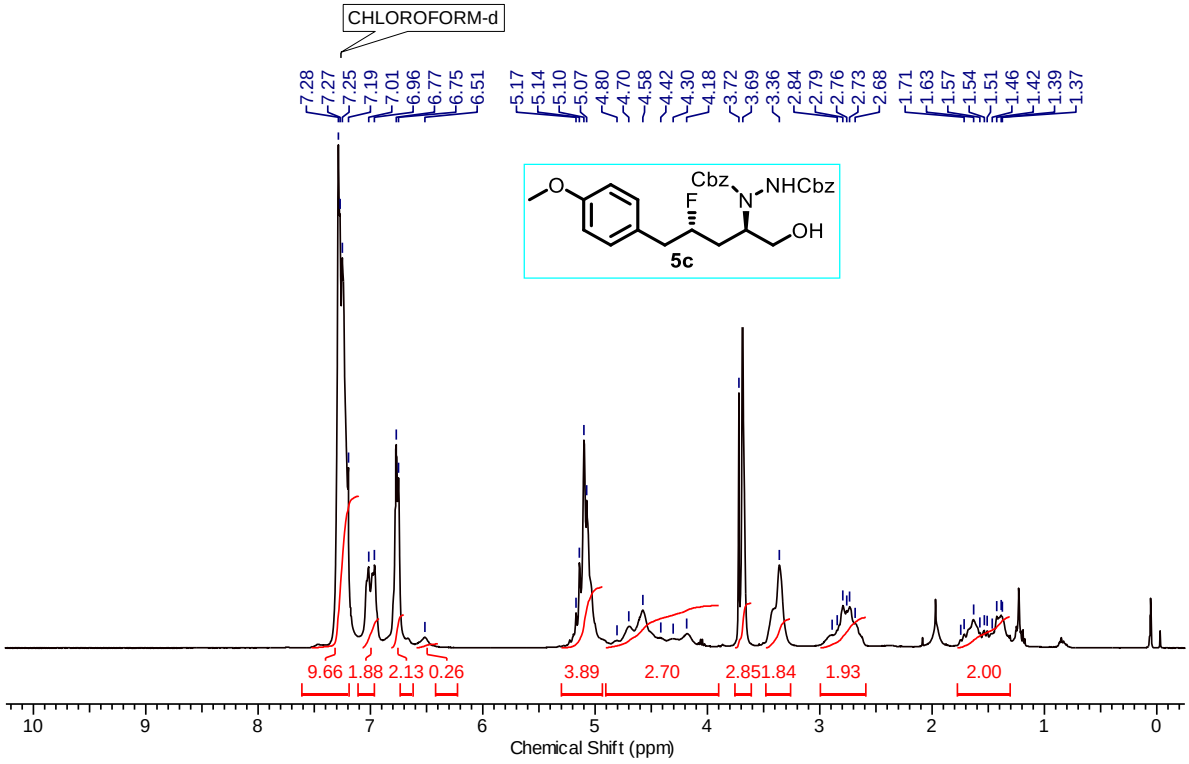

**Dibenzyl 1-((2*R*,4*S*)-4-fluoro-1-hydroxy-5-(4-isopropylphenyl)pentan-2-yl)hydrazine-1,2-dicarboxylate (5b)**

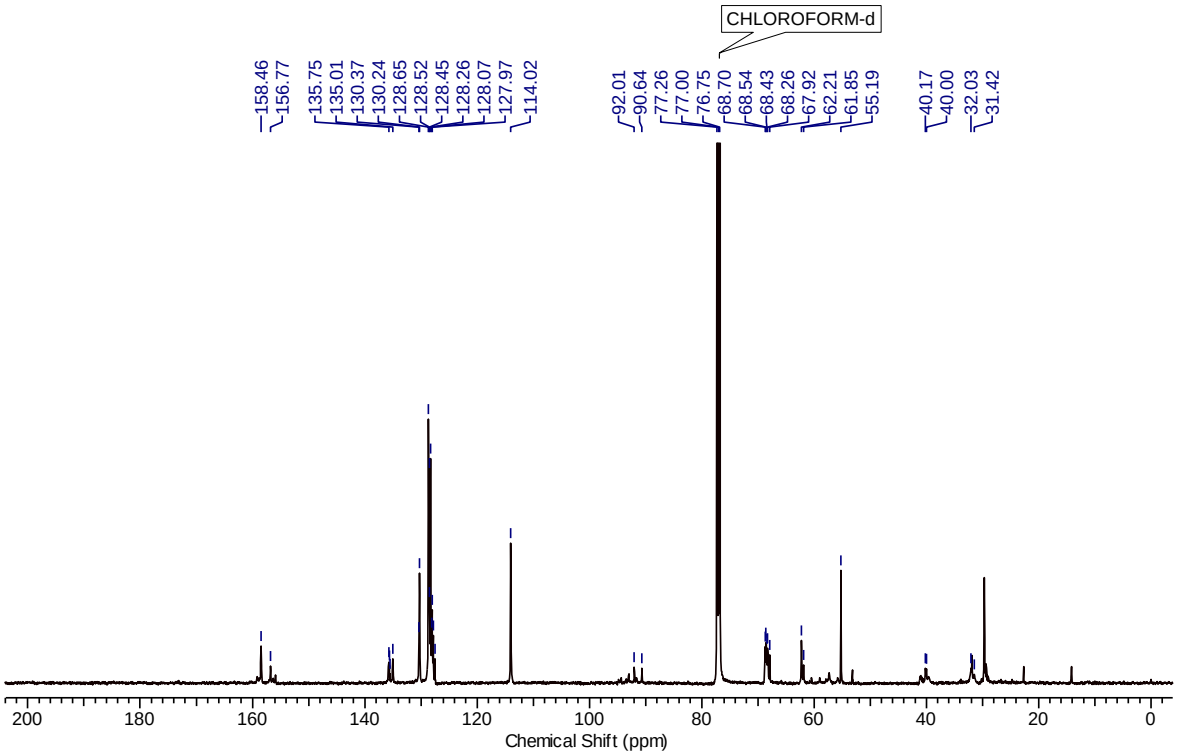


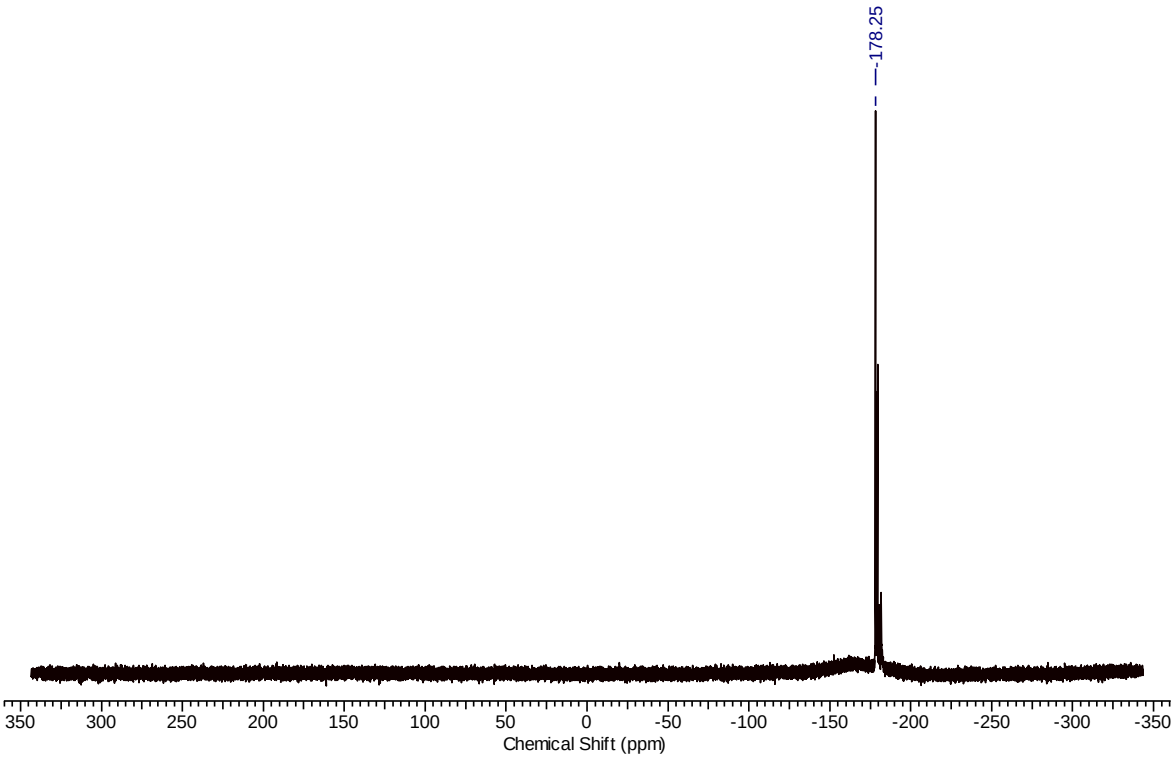

CHLOROFORM-d
156.74
155.85
147.48
135.63
134.98
129.16
128.64
128.52
128.28
127.98
127.82
126.69
92.02
90.66
77.26
77.00
76.75
68.70
68.57
68.29
62.20
57.35
55.91
40.66
40.49
33.66
32.14
31.54
23.94
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


-177.17
200
150
100
50
0
-50
-100
-150
-200
-250
-300
-350
-400
Chemical Shift (ppm)

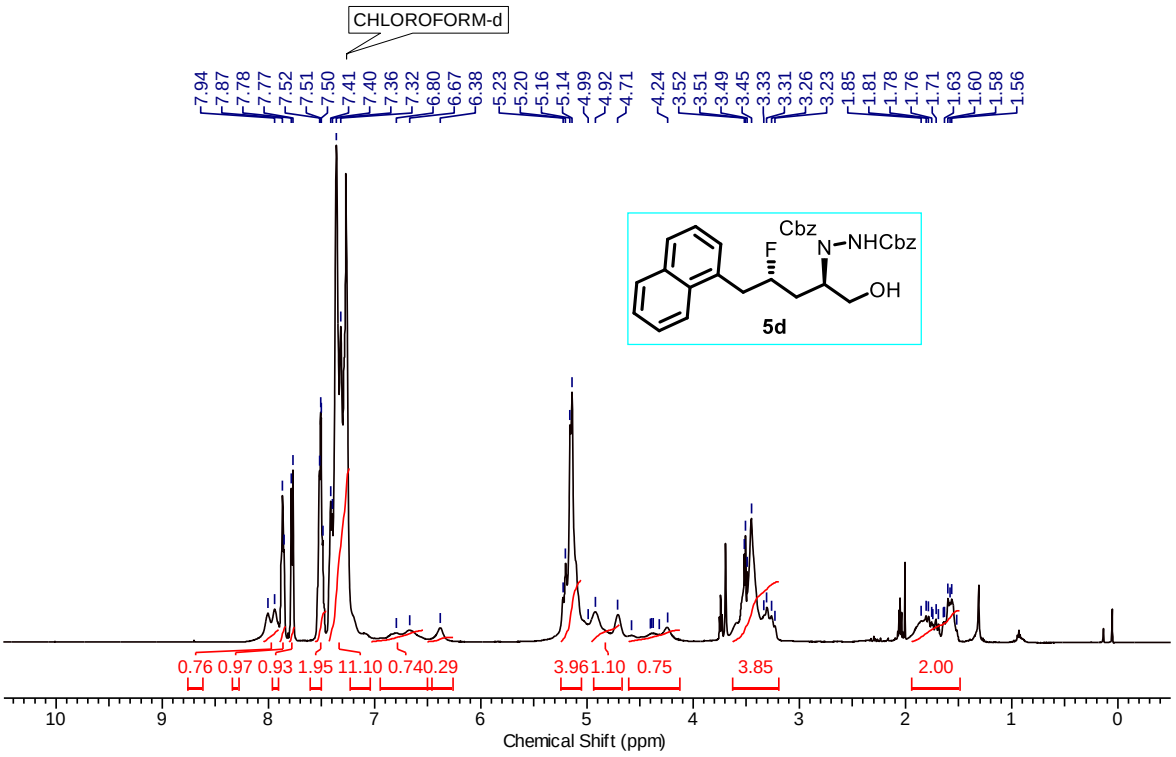
**Dibenzyl 1-((2*R*,4*S*)-4-fluoro-1-hydroxy-5-(4-methoxyphenyl)pentan-2-yl)hydrazine-1,2-dicarboxylate (5c)**

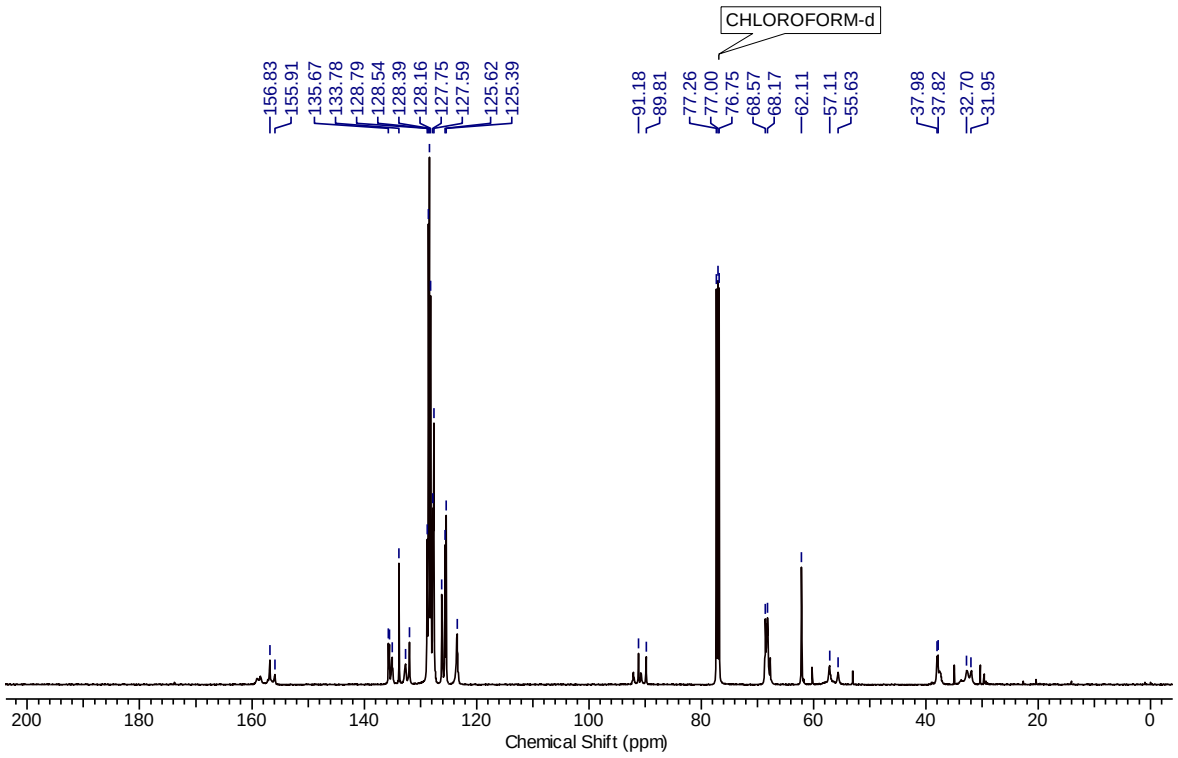


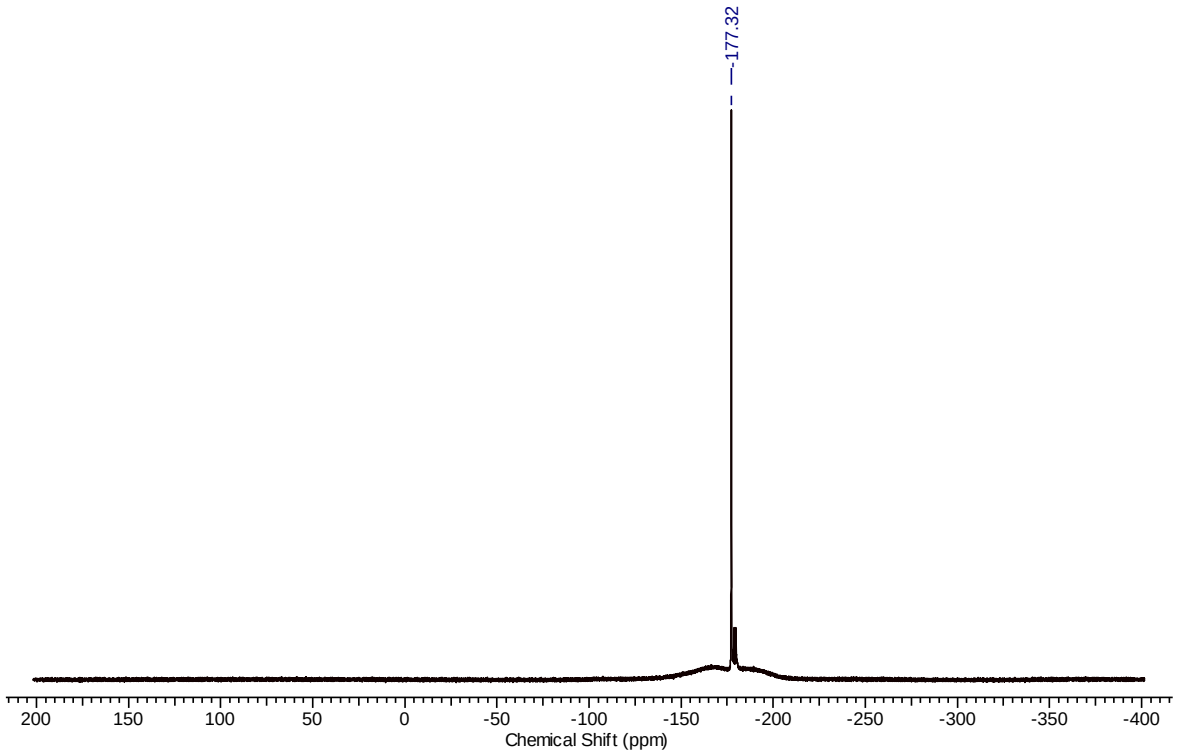





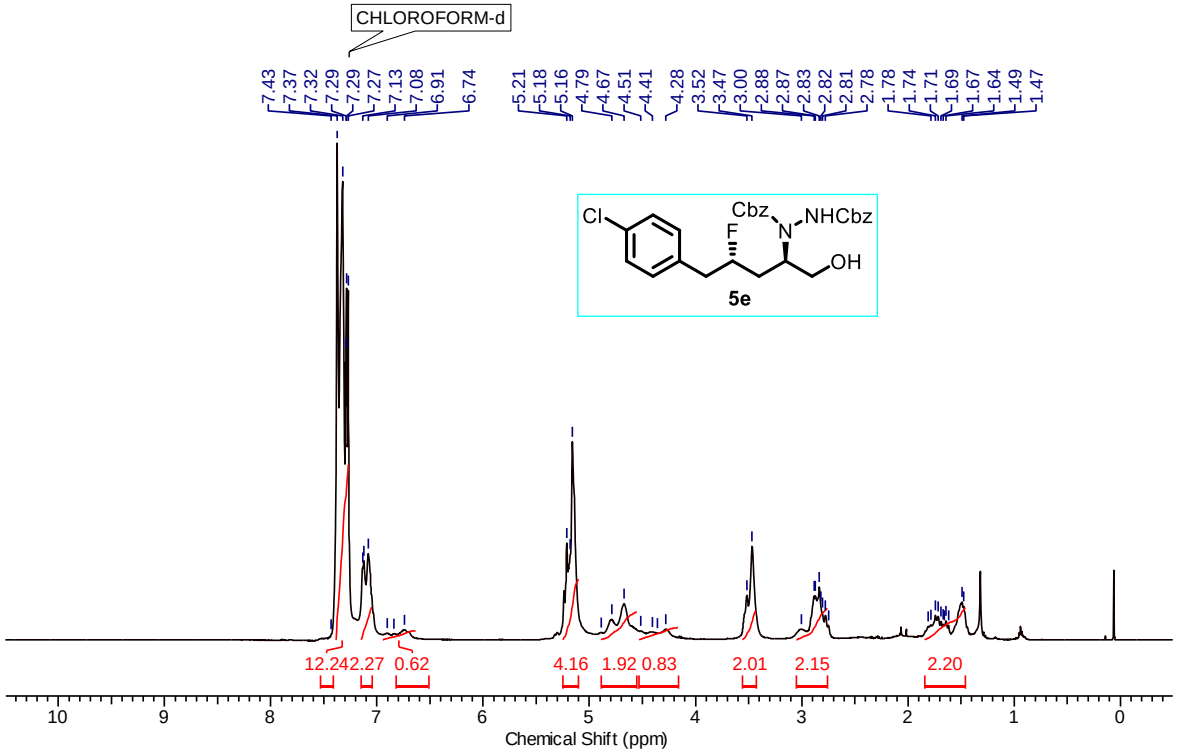

**Dibenzyl 1-((2*R*,4*S*)-4-fluoro-1-hydroxy-5-(naphthalen-2-yl)pentan-2-yl)hydrazine-1,2-dicarboxylate (5d)**

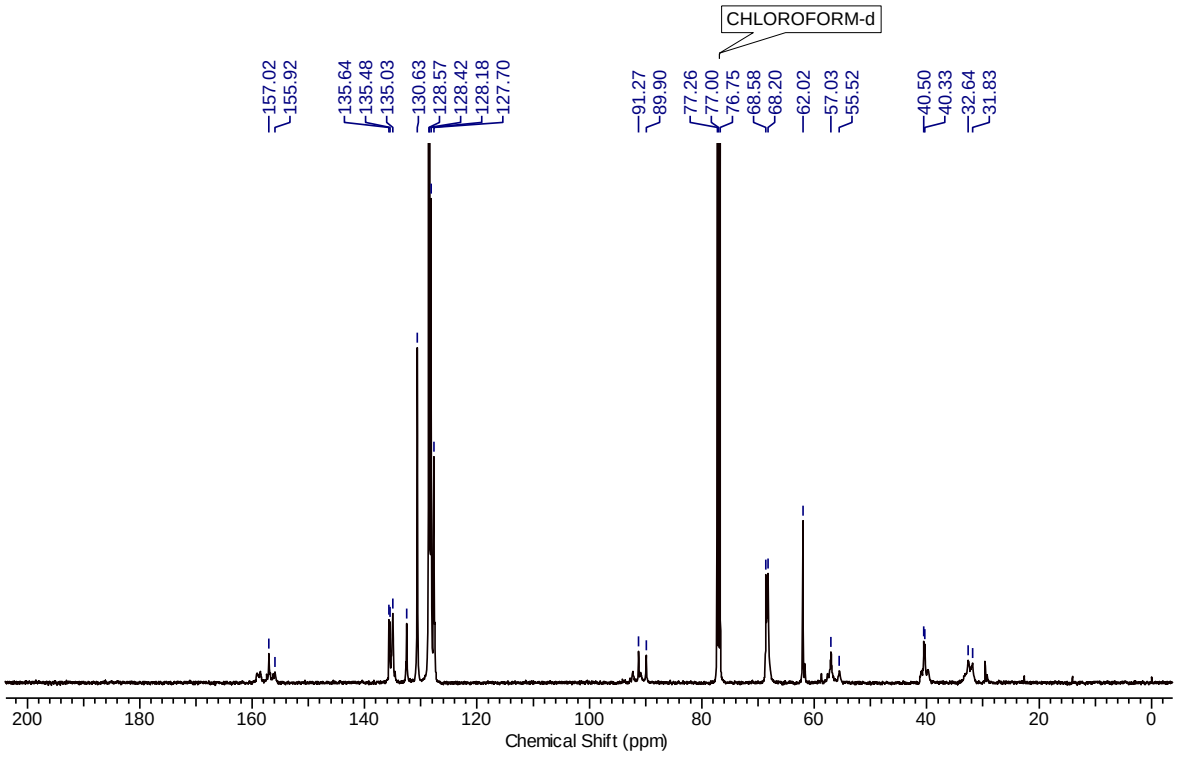


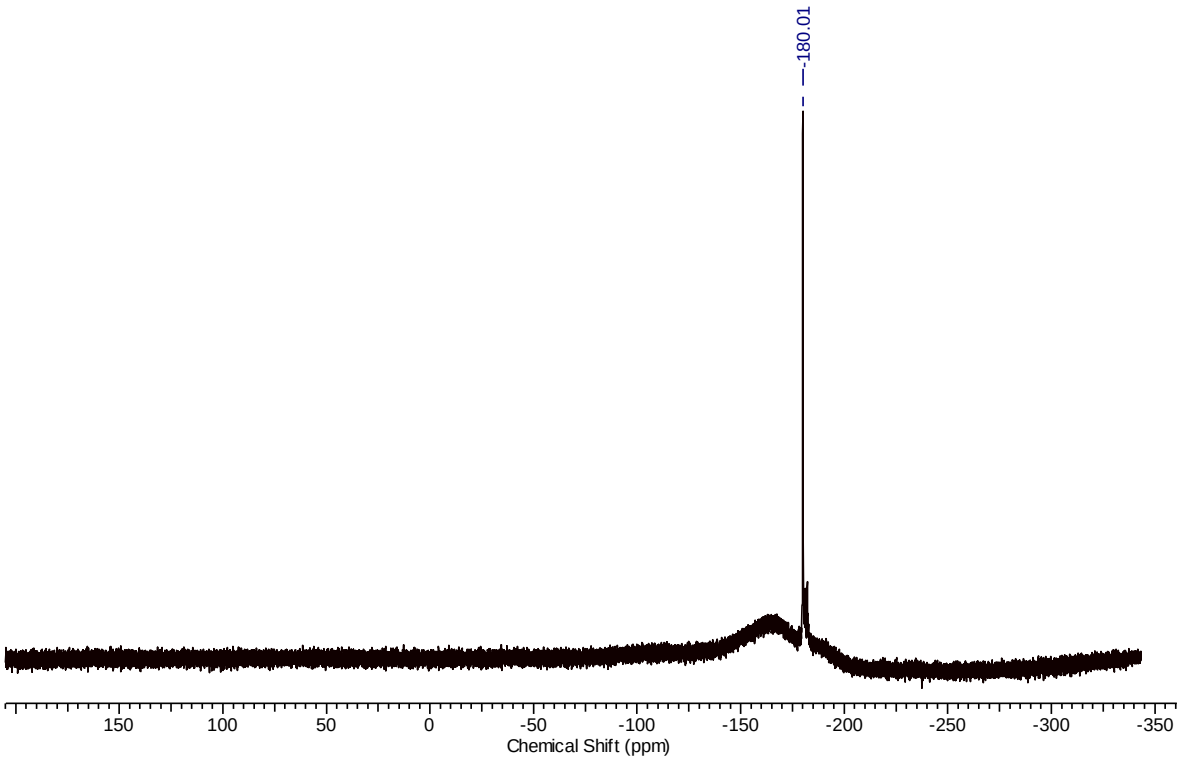

CHLOROFORM-d
156.83
155.91
135.67
133.78
128.79
128.54
128.39
128.16
127.75
127.59
125.62
125.39
91.18
89.81
77.26
77.00
76.75
68.57
68.17
62.11
57.11
55.63
37.98
37.82
32.70
31.95
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


-177.32
200
150
100
50
0
-50
-100
-150
-200
-250
-300
-350
-400
Chemical Shift (ppm)

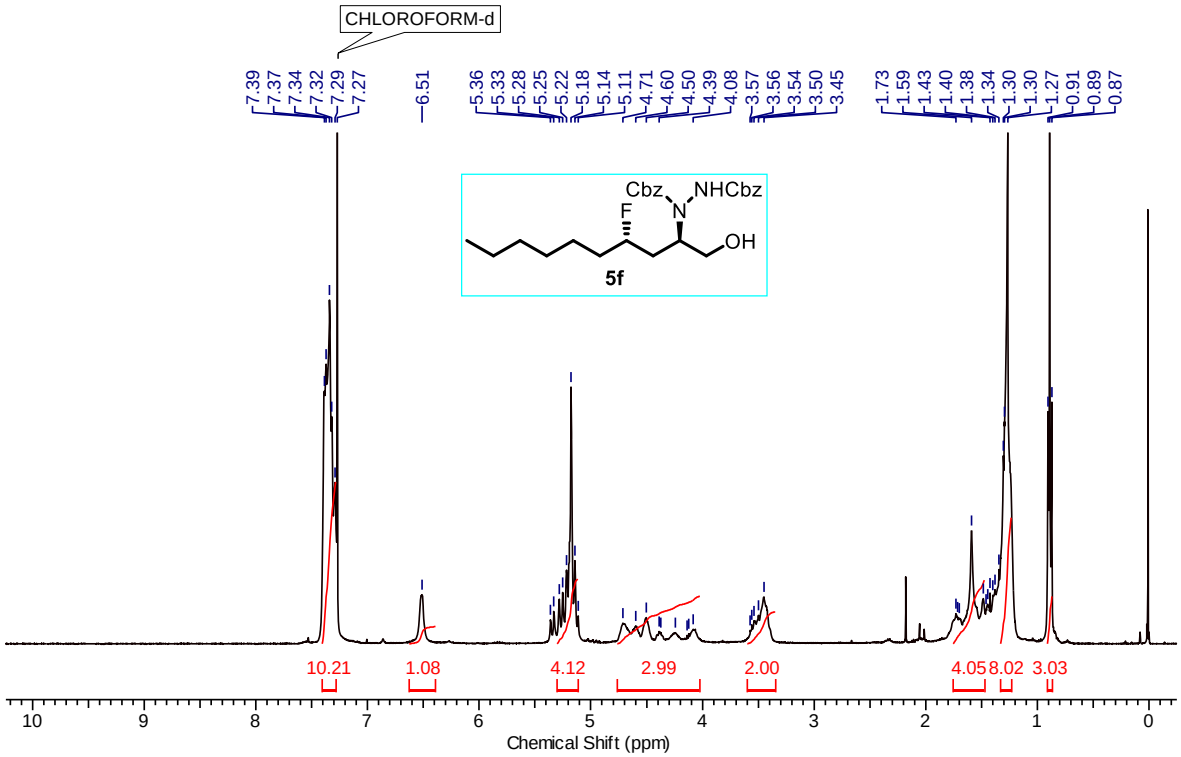
**Dibenzyl 1-((2*R*,4*S*)-5-(4-chlorophenyl)-4-fluoro-1-hydroxypentan-2-yl)hydrazine-1,2-dicarboxylate (5e)**

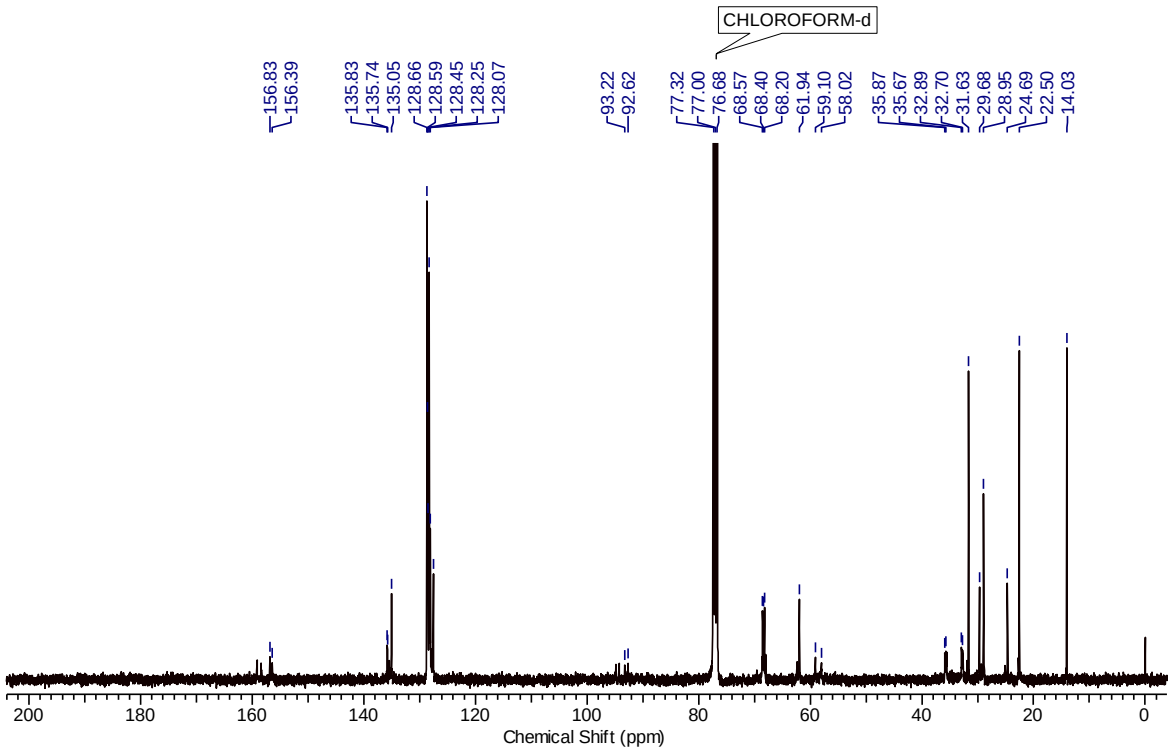


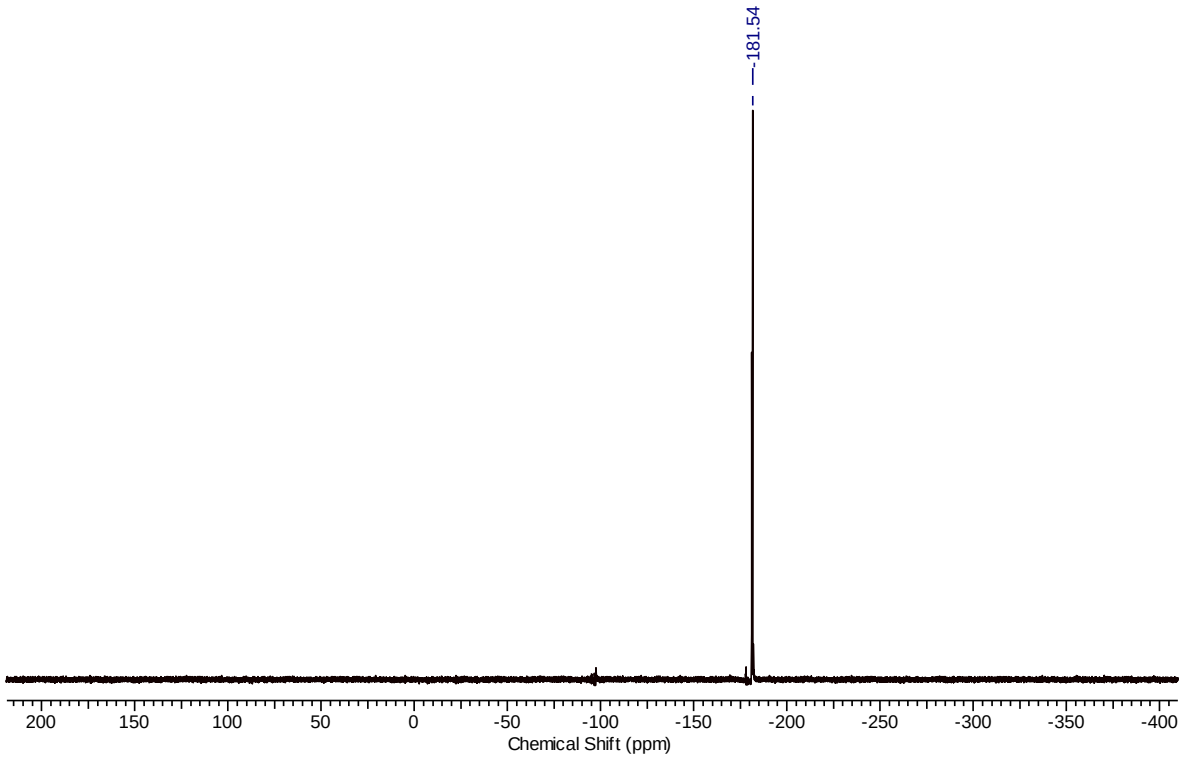





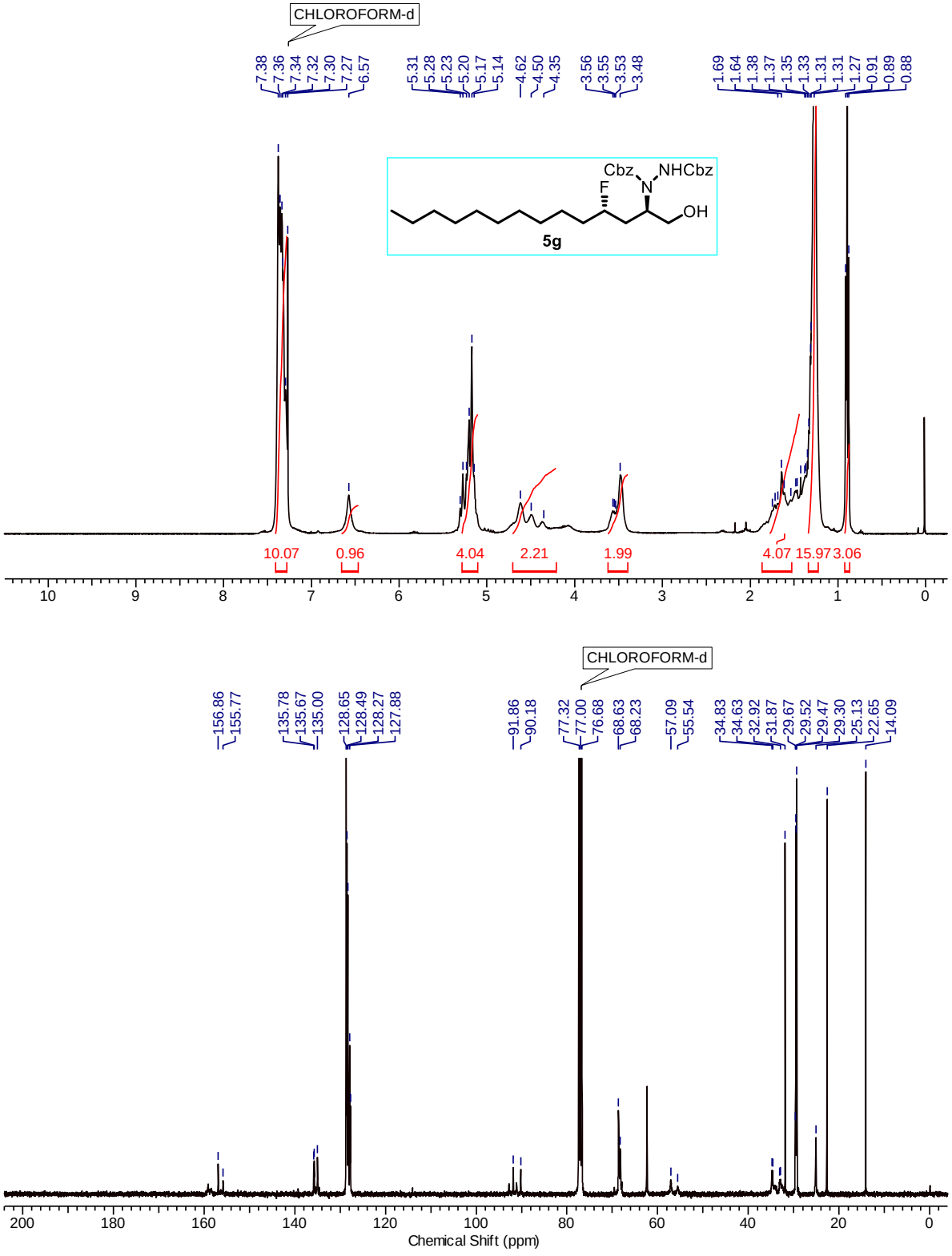

**Dibenzyl 1-((2*R*,4*S*)-4-fluoro-1-hydroxydecan-2-yl)hydrazine-1,2-dicarboxylate (5f)**

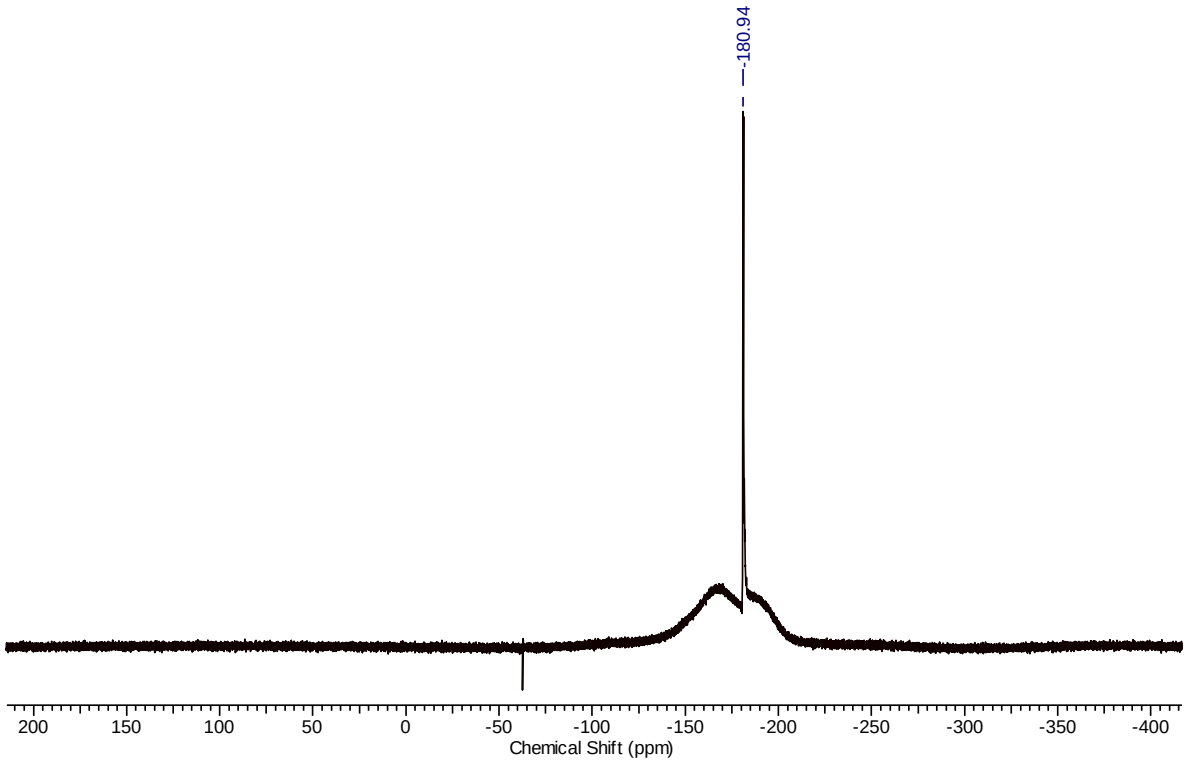



CHLOROFORM-d
156.83
156.39
135.83
135.74
135.05
128.66
128.59
128.45
128.25
128.07
93.22
92.62
77.32
77.00
76.68
68.57
68.40
68.20
61.94
59.10
58.02
35.87
35.67
32.89
32.70
31.63
29.68
28.95
24.69
22.50
14.03
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

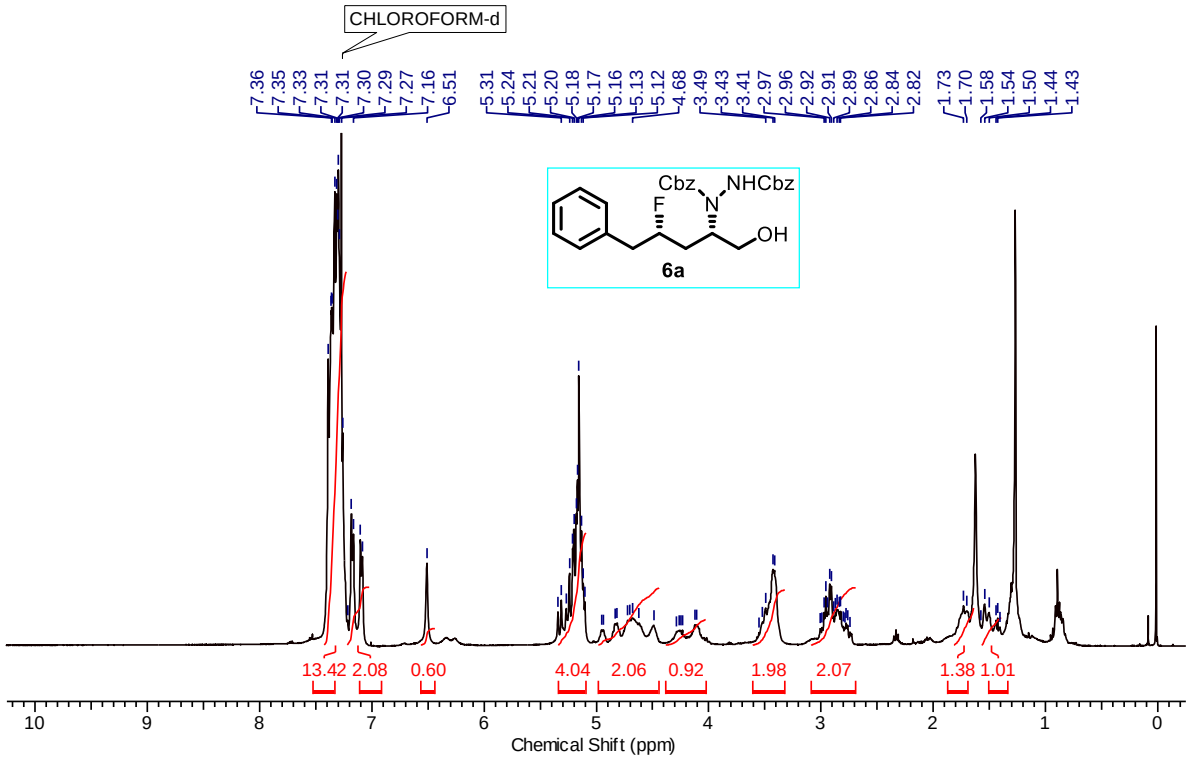

181.54
200
150
100
50
0
-50
-100
-150
-200
-250
-300
-350
-400
Chemical Shift (ppm)

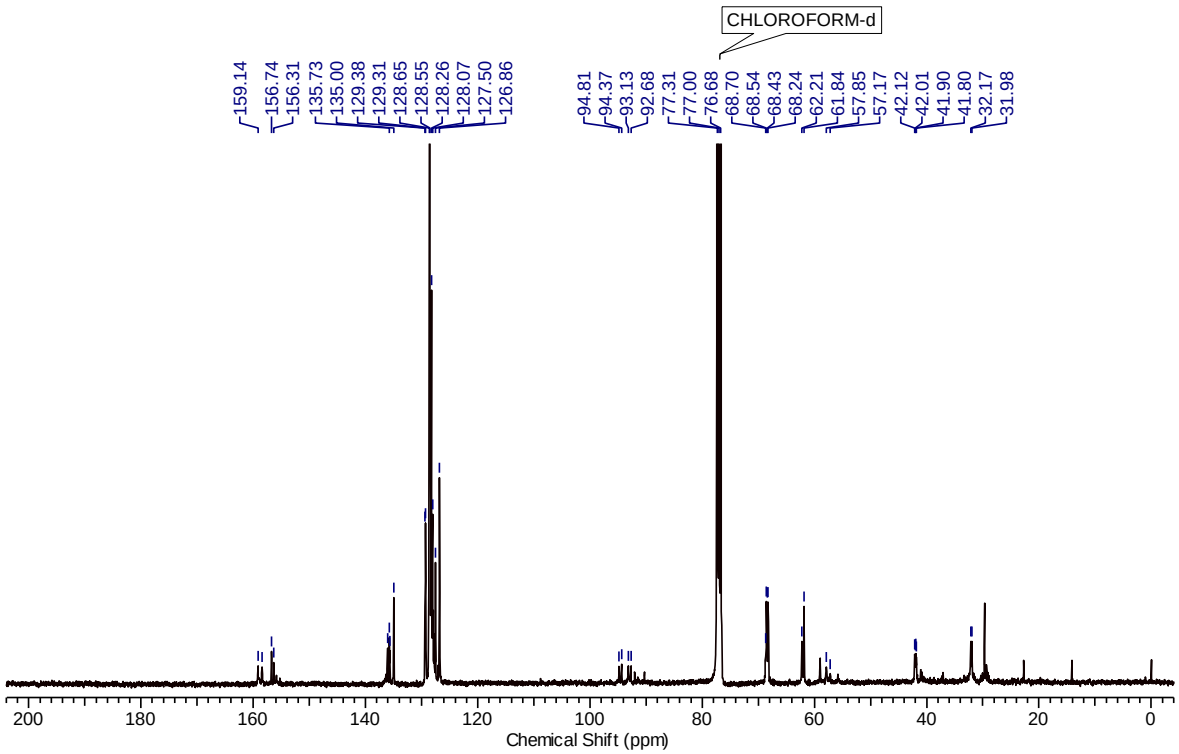
**Dibenzyl 1-((2*R*,4*S*)-4-fluoro-1-hydroxytetradecan-2-yl)hydrazine-1,2-dicarboxylate (5g)**

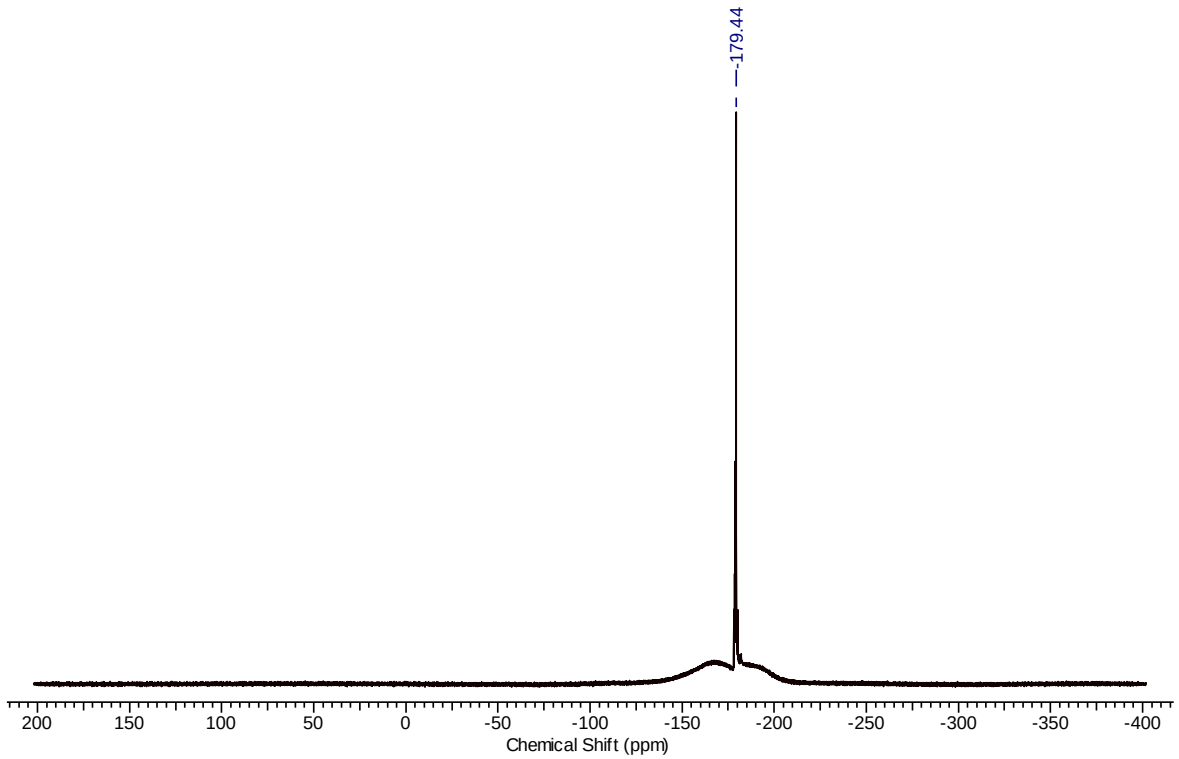




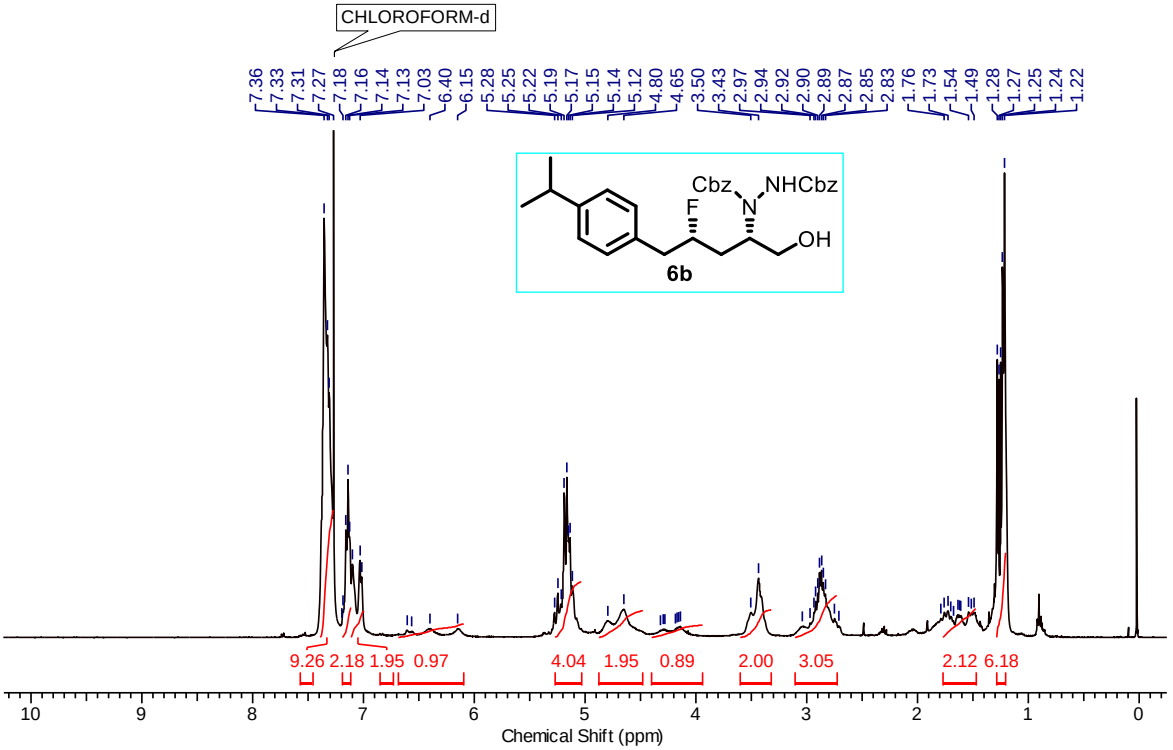

**Dibenzyl 1-((2*S*,4*S*)-4-fluoro-1-hydroxy-5-phenylpentan-2-yl)hydrazine-1,2-dicarboxylate (6a)**

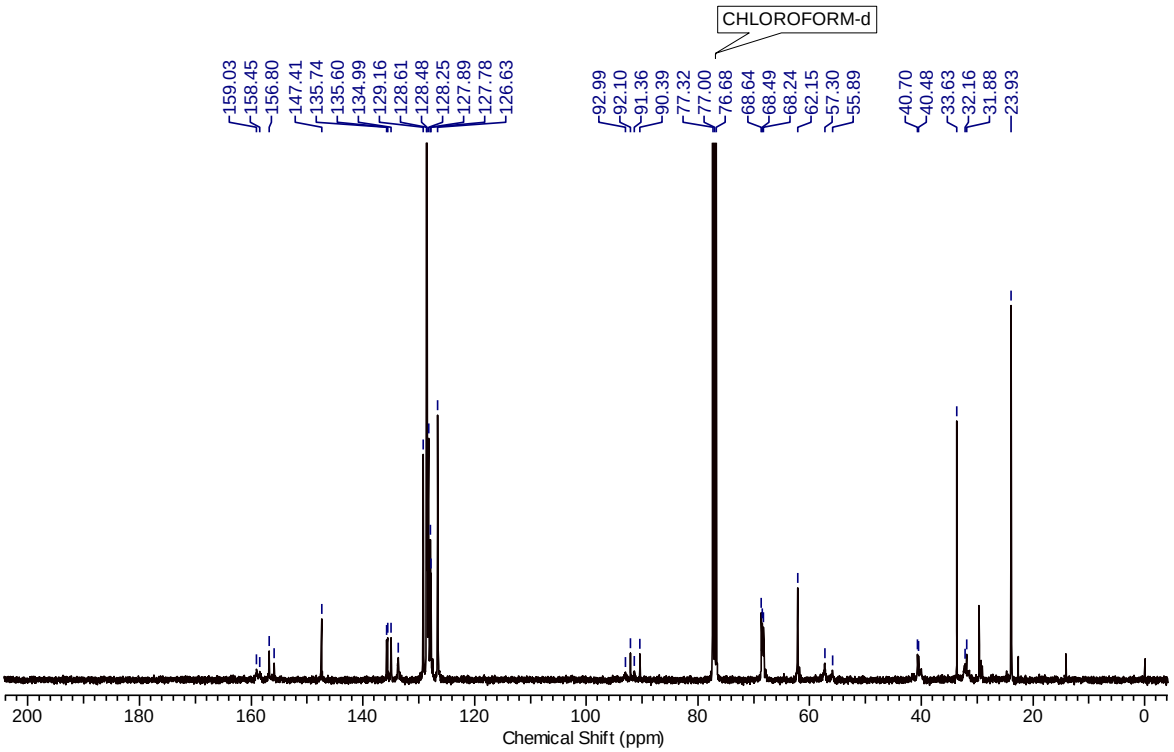


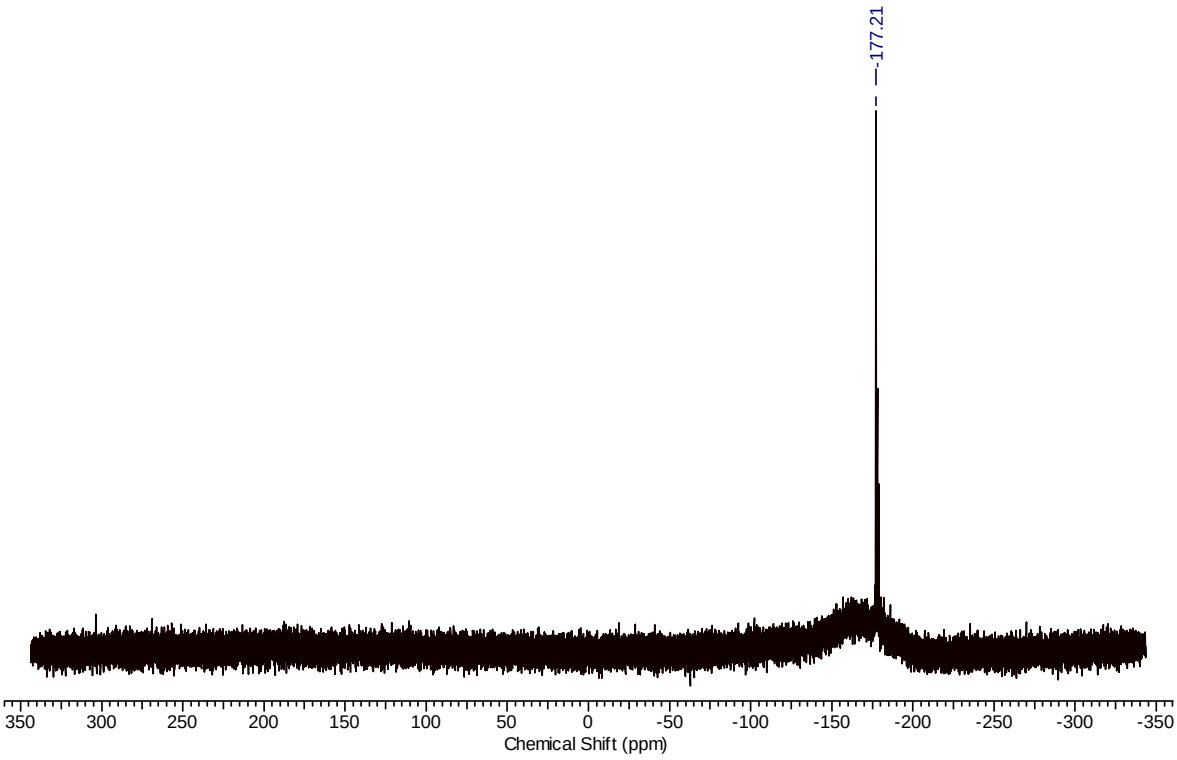

CHLOROFORM-d
159.14
156.74
156.31
135.73
135.00
129.38
129.31
128.65
128.55
128.26
128.07
127.50
126.86
94.81
94.37
93.13
92.68
77.31
77.00
76.68
68.70
68.54
68.43
68.24
62.21
61.84
57.85
57.17
42.12
42.01
41.90
41.80
32.17
31.98
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


179.44
200
150
100
50
0
-50
-100
-150
-200
-250
-300
-350
-400
Chemical Shift (ppm)

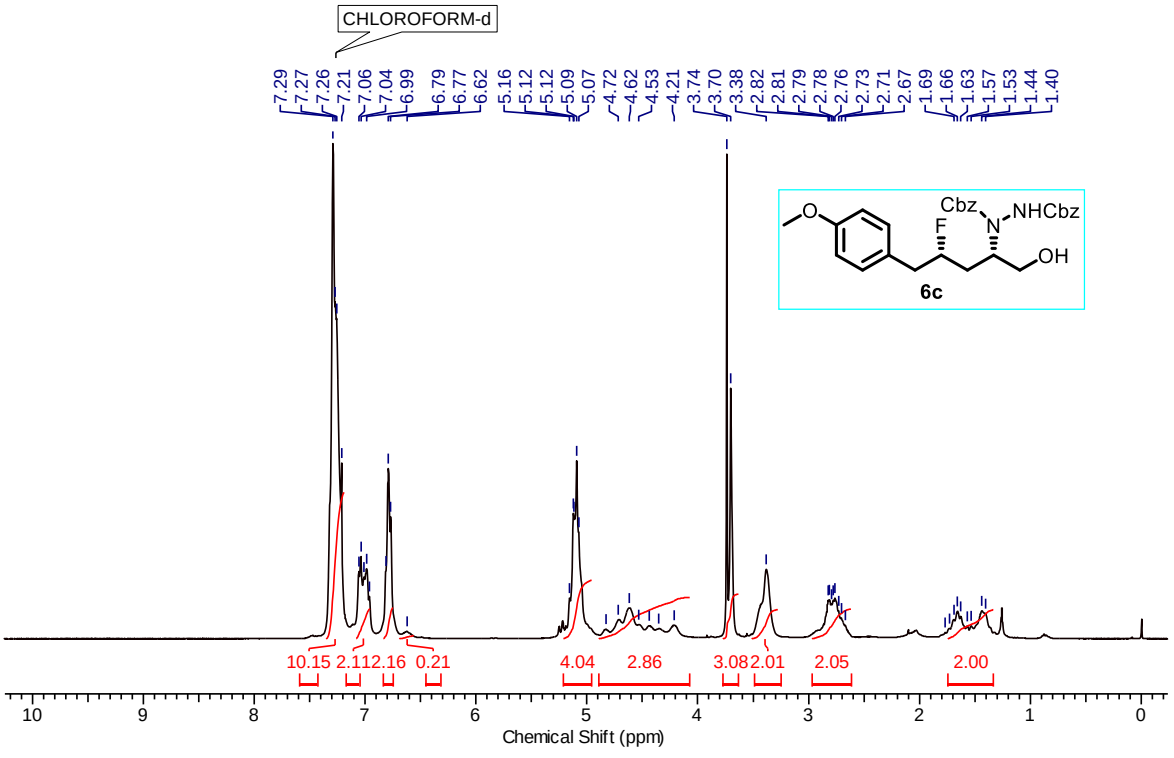
**Dibenzyl 1-((2*S*,4*S*)-4-fluoro-1-hydroxy-5-(4-isopropylphenyl)pentan-2-yl)hydrazine-1,2-dicarboxylate (6b)**

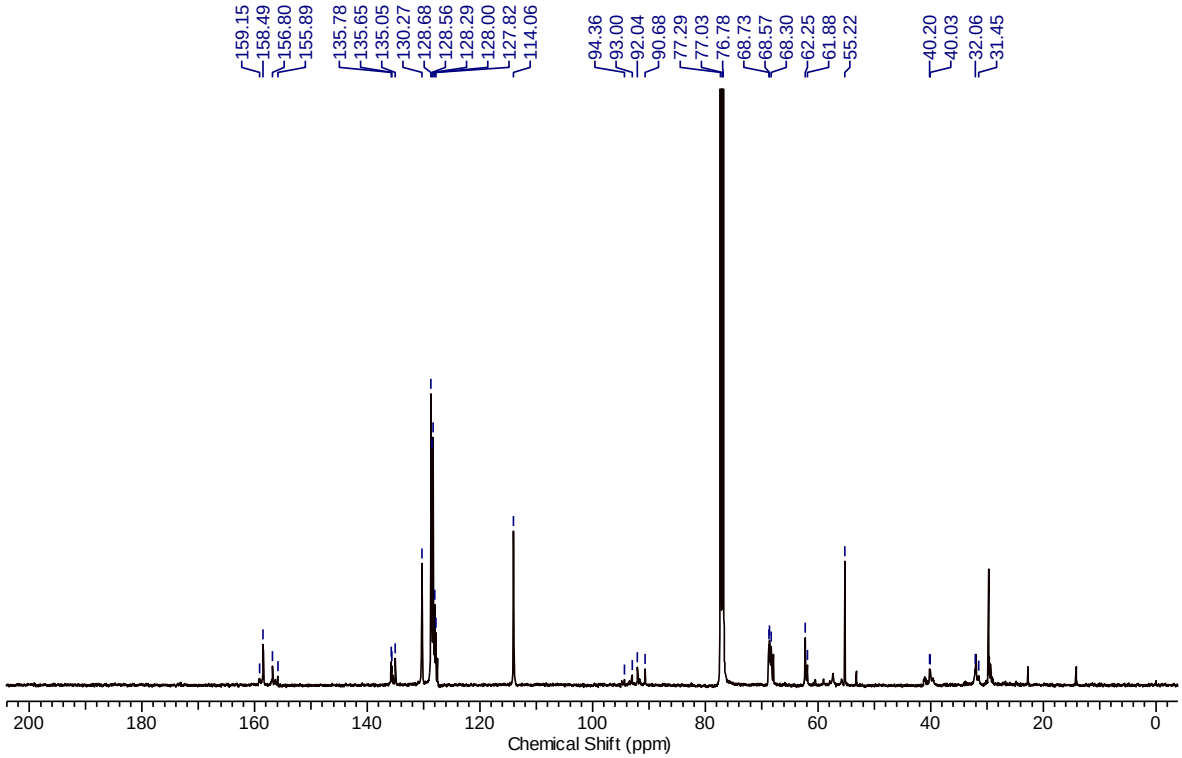


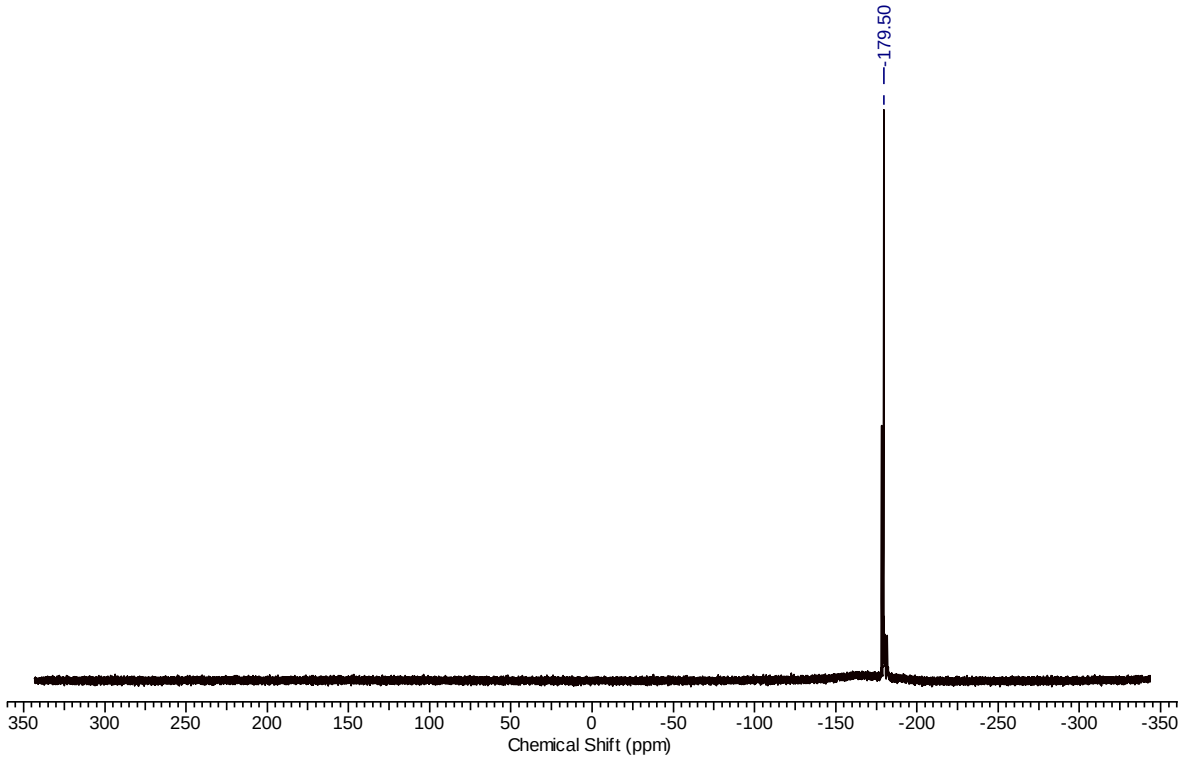





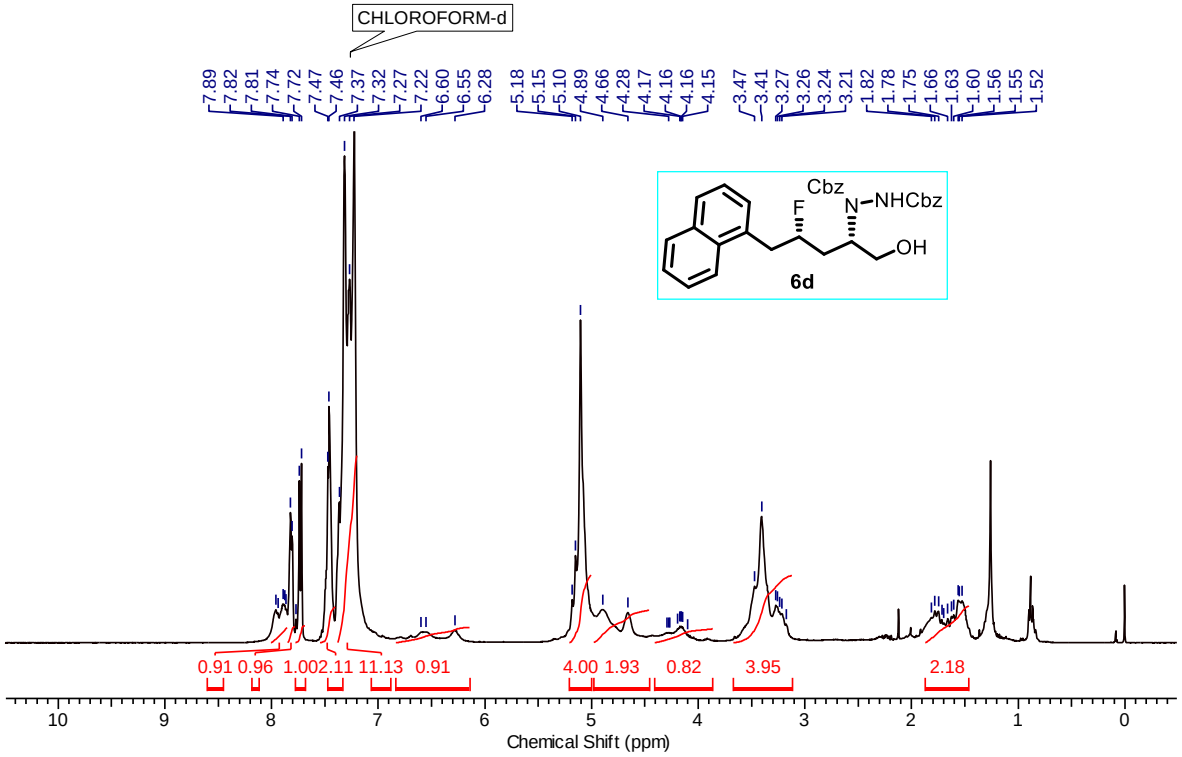

**Dibenzyl 1-((2*S*,4*S*)-4-fluoro-1-hydroxy-5-(4-methoxyphenyl)pentan-2-yl)hydrazine-1,2-dicarboxylate (6c)**

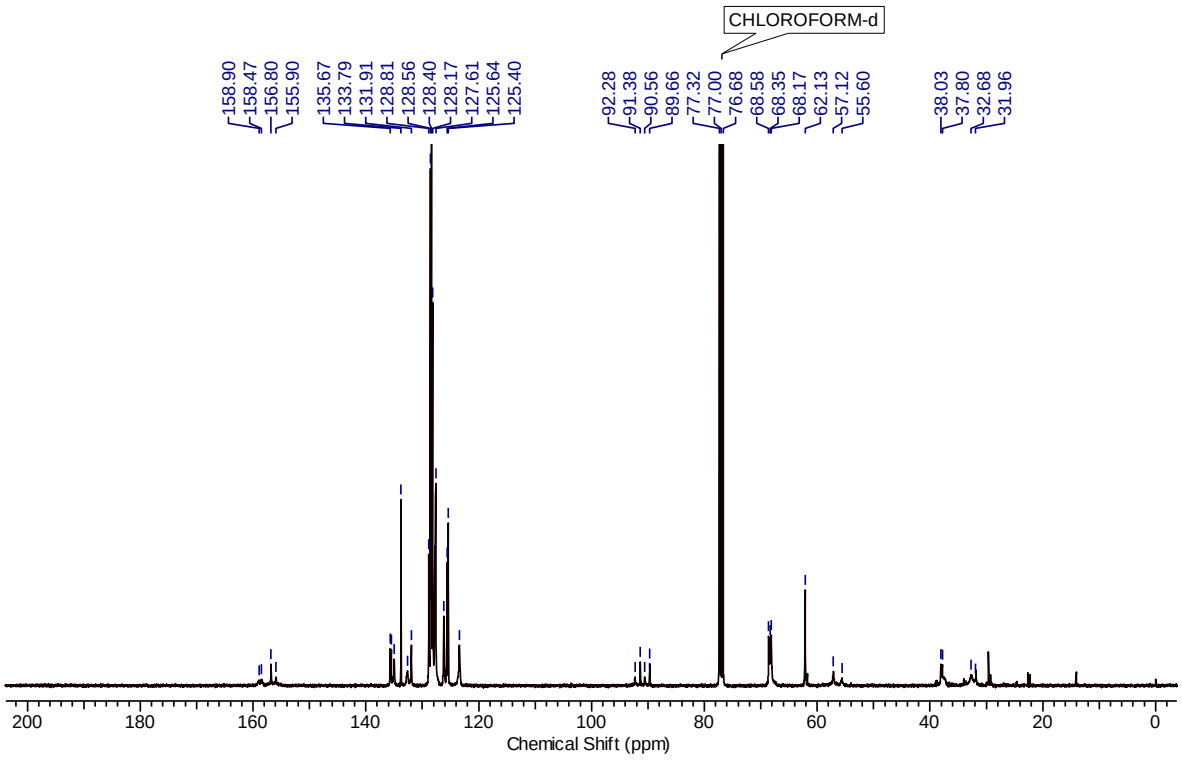


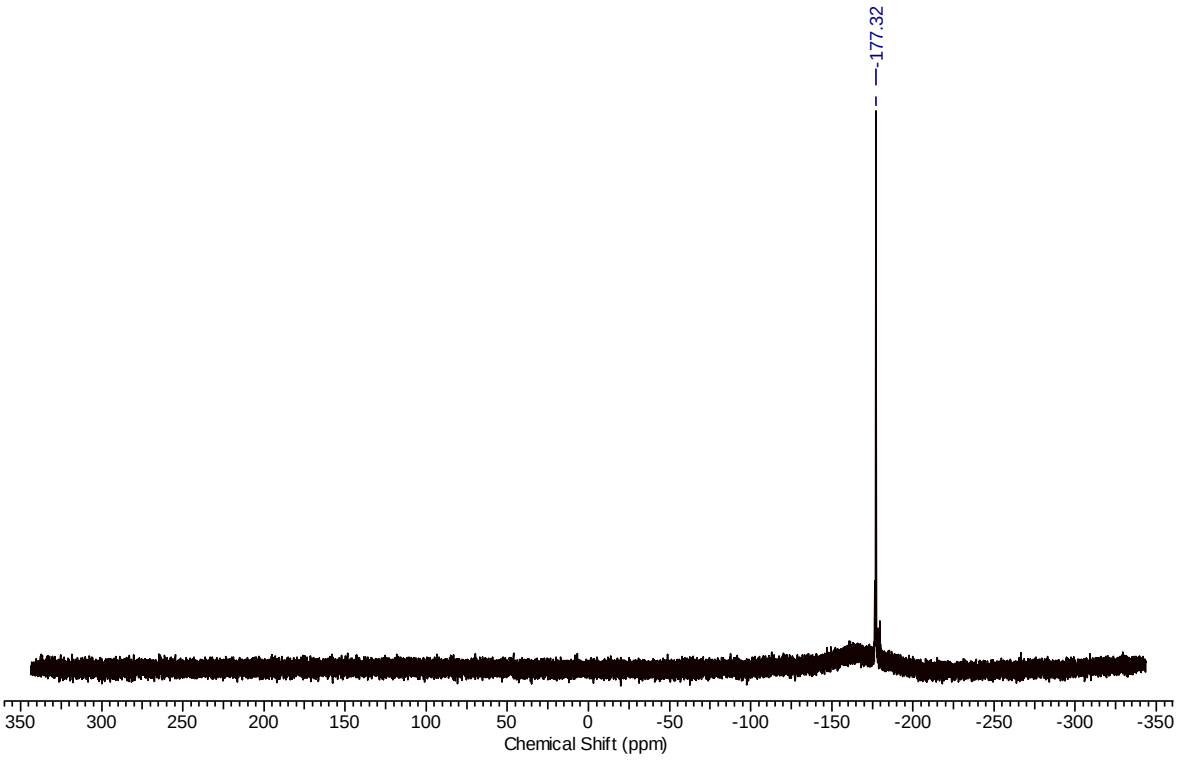

159.15
158.49
156.80
155.89
135.78
135.65
135.05
130.27
128.68
128.56
128.29
128.00
127.82
114.06
94.36
93.00
92.04
90.68
77.29
77.03
76.78
68.73
68.57
68.30
62.25
61.88
55.22
40.20
40.03
32.06
31.45
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


179.50
350
300
250
200
150
100
50
0
-50
-100
-150
-200
-250
-300
-350
Chemical Shift (ppm)

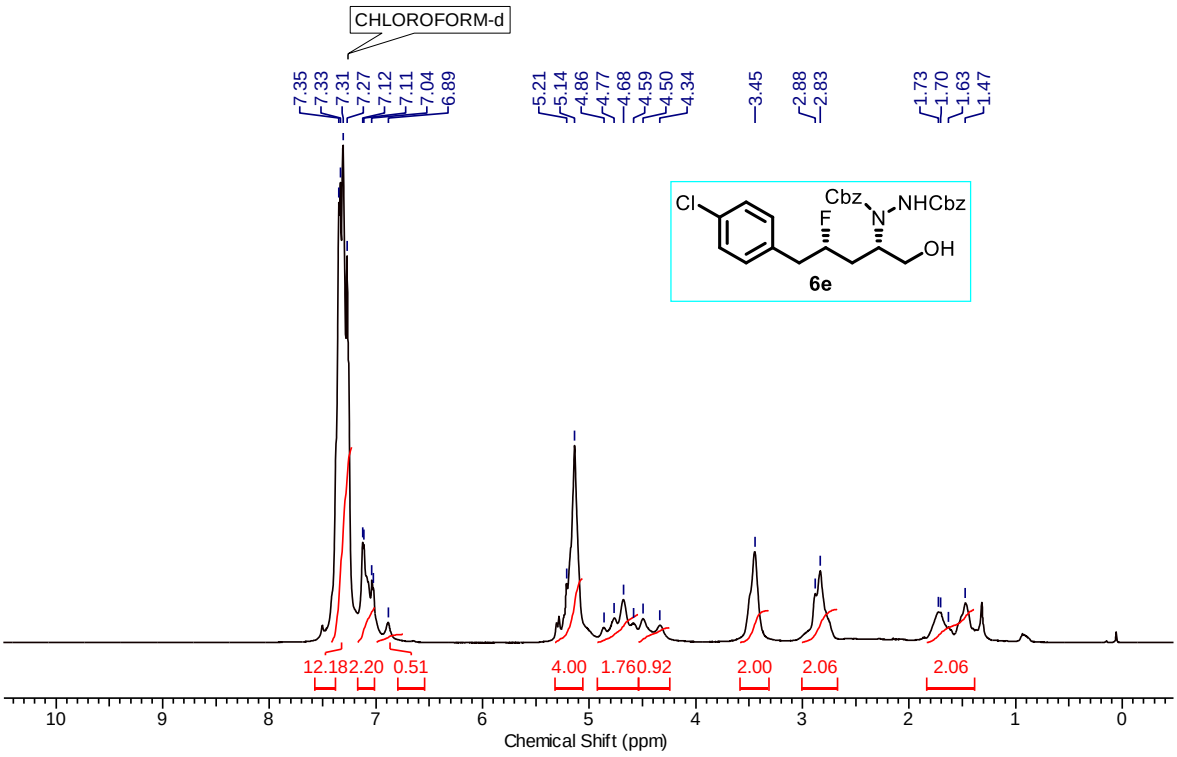
**Dibenzyl 1-((2*S*,4*S*)-4-fluoro-1-hydroxy-5-(naphthalen-2-yl)pentan-2-yl)hydrazine-1,2-dicarboxylate (6d)**

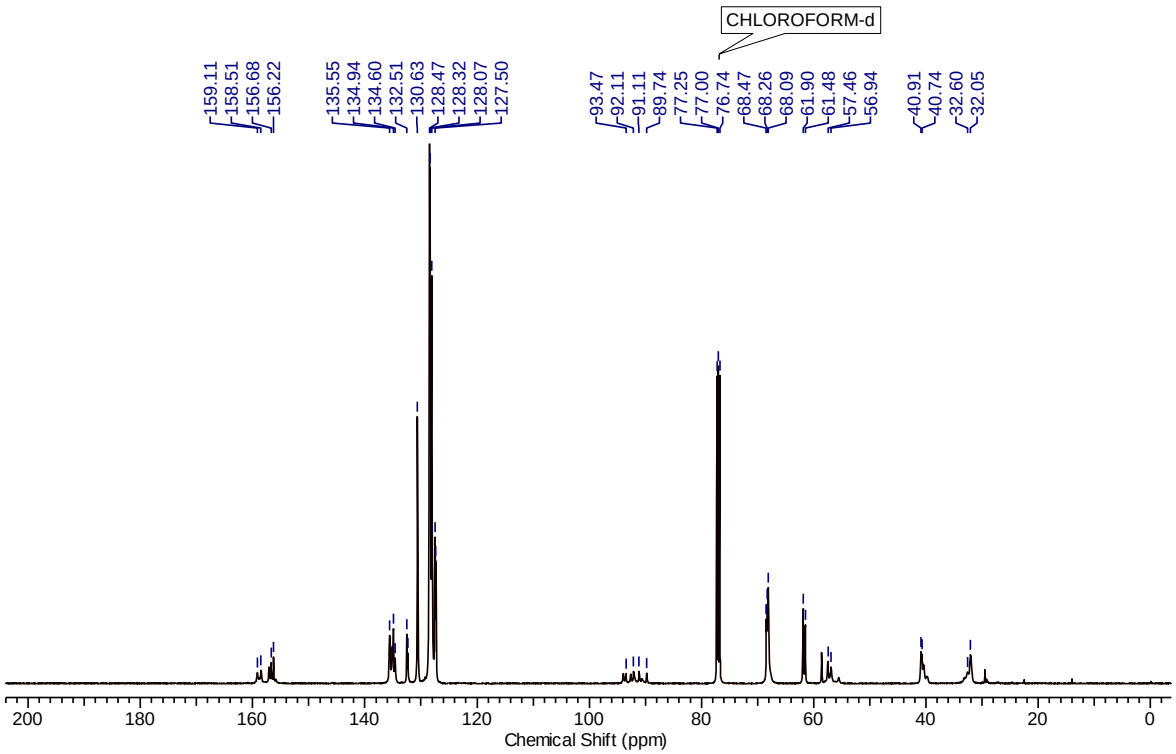


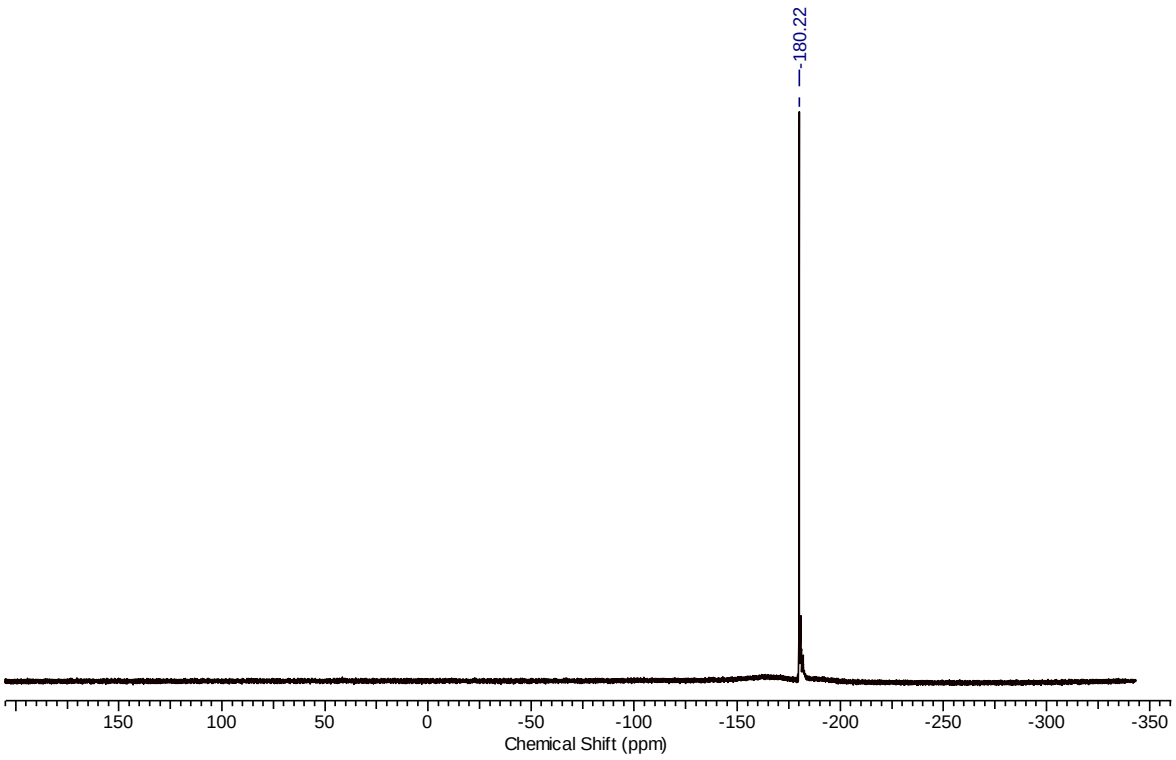





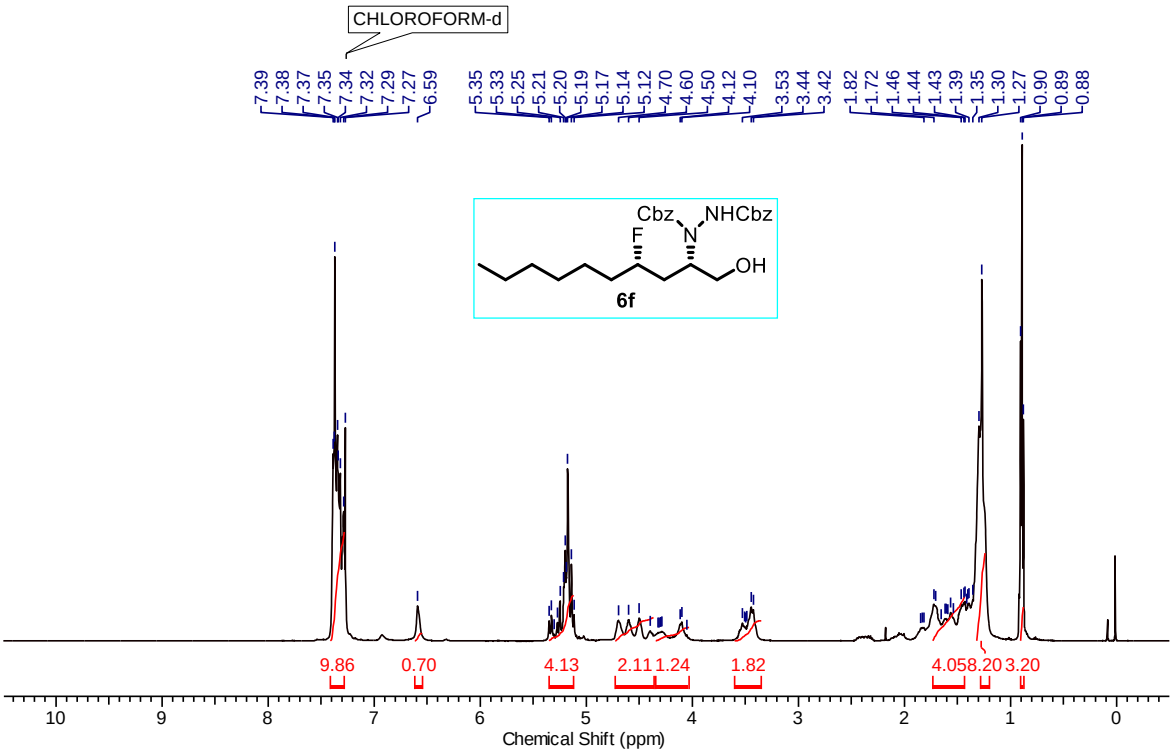

**Dibenzyl 1-((2*S*,4*S*)-5-(4-chlorophenyl)-4-fluoro-1-hydroxypentan-2-yl)hydrazine-1,2-dicarboxylate (6e)**

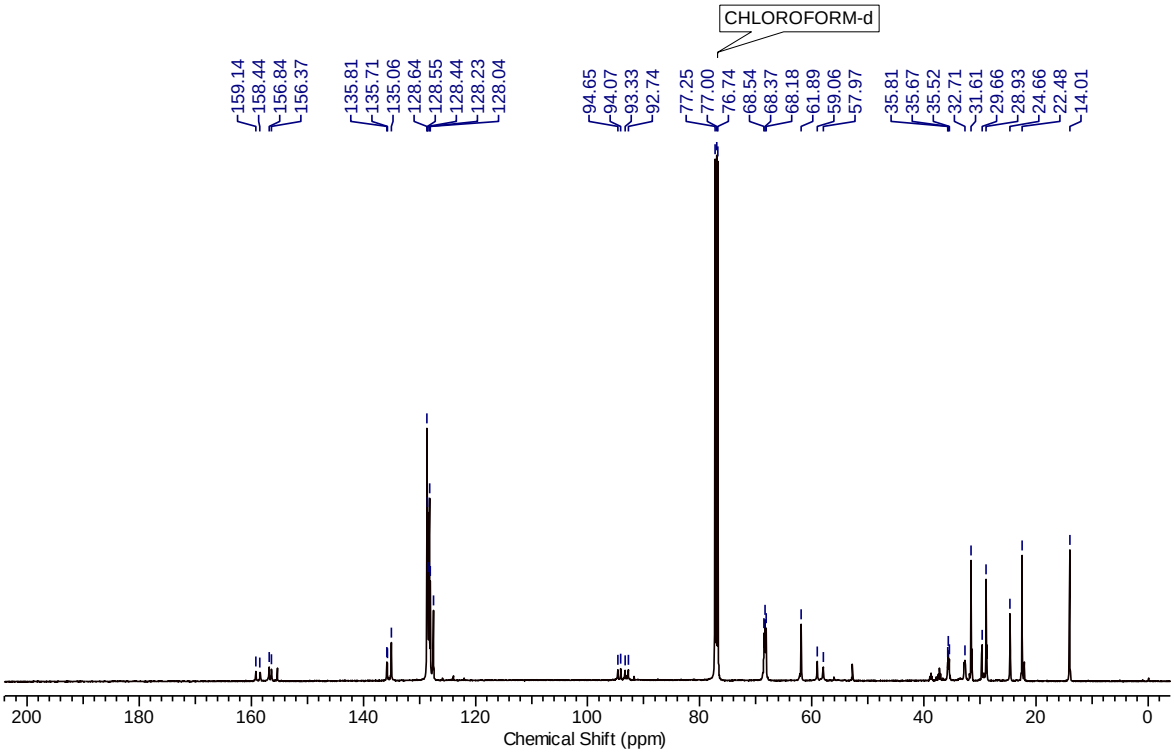


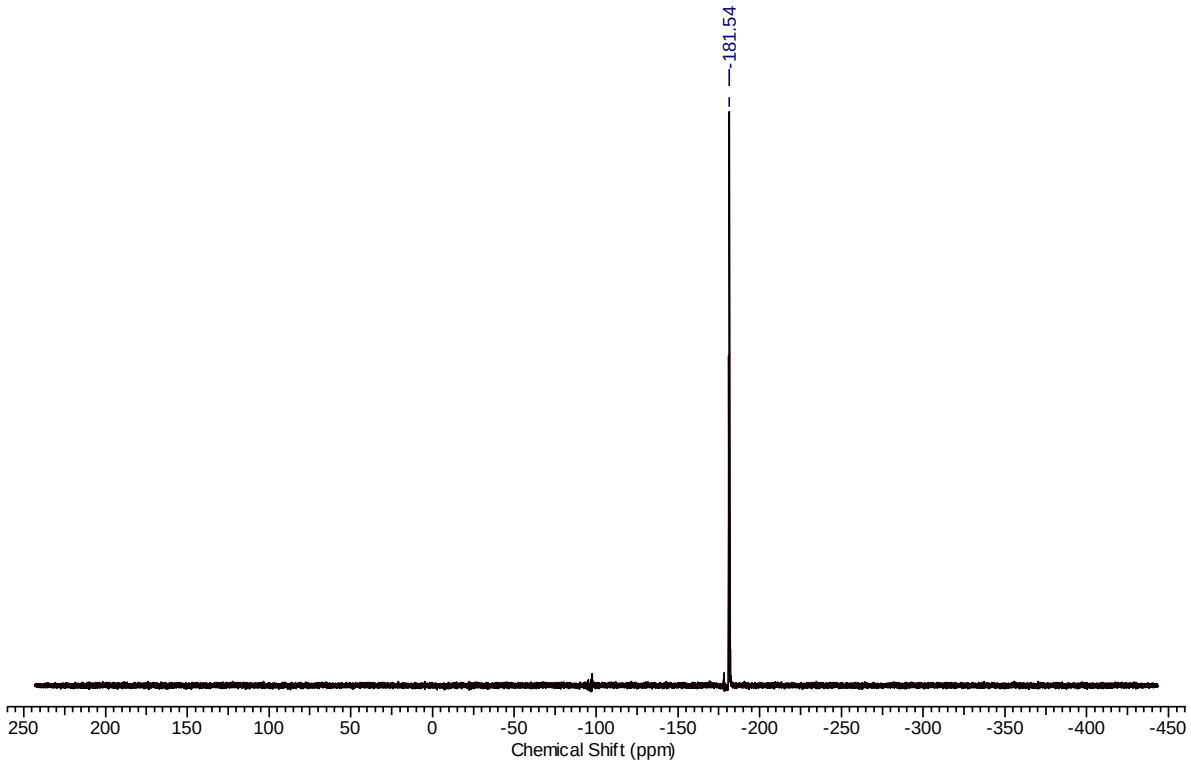

CHLOROFORM-d
159.11
158.51
156.68
156.22
135.55
134.94
134.60
132.51
130.63
128.47
128.32
128.07
127.50
93.47
92.11
91.11
89.74
77.25
77.00
76.74
68.47
68.26
68.09
61.90
61.48
57.46
56.94
40.91
40.74
32.60
32.05
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


180.22
150
100
50
0
-50
-100
-150
-200
-250
-300
-350
Chemical Shift (ppm)

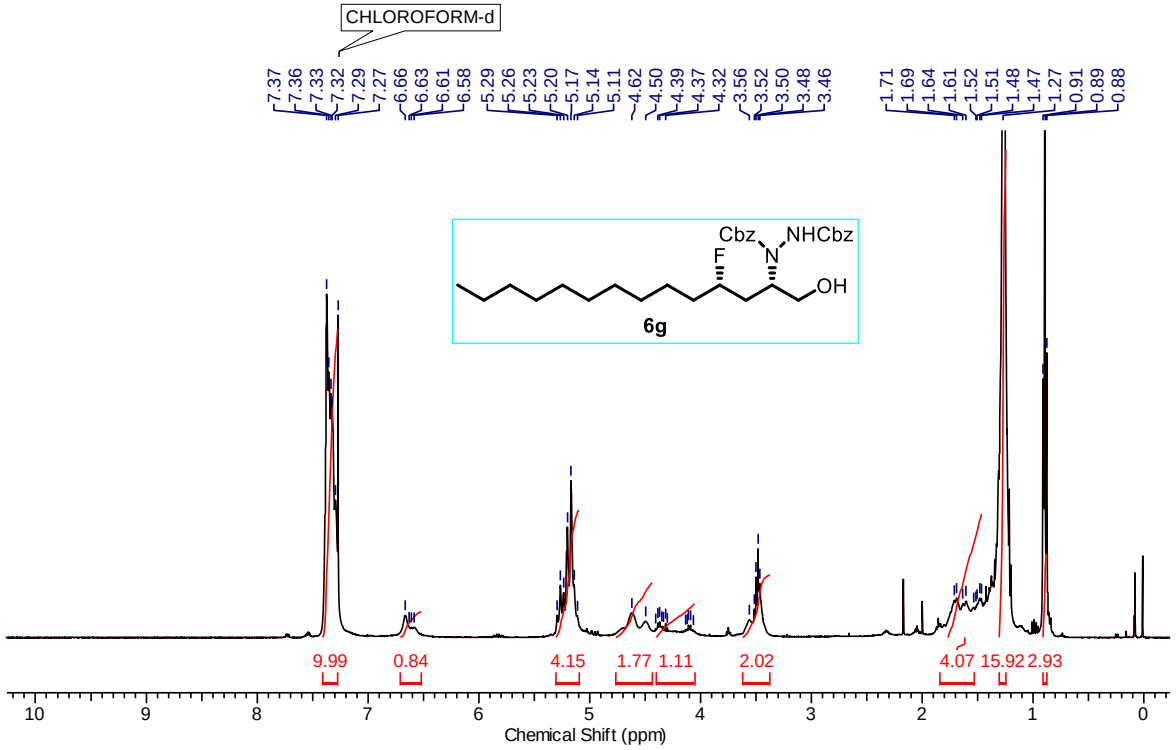
**Dibenzyl 1-((2*S*,4*S*)-4-fluoro-1-hydroxydecan-2-yl)hydrazine-1,2-dicarboxylate (6f)**

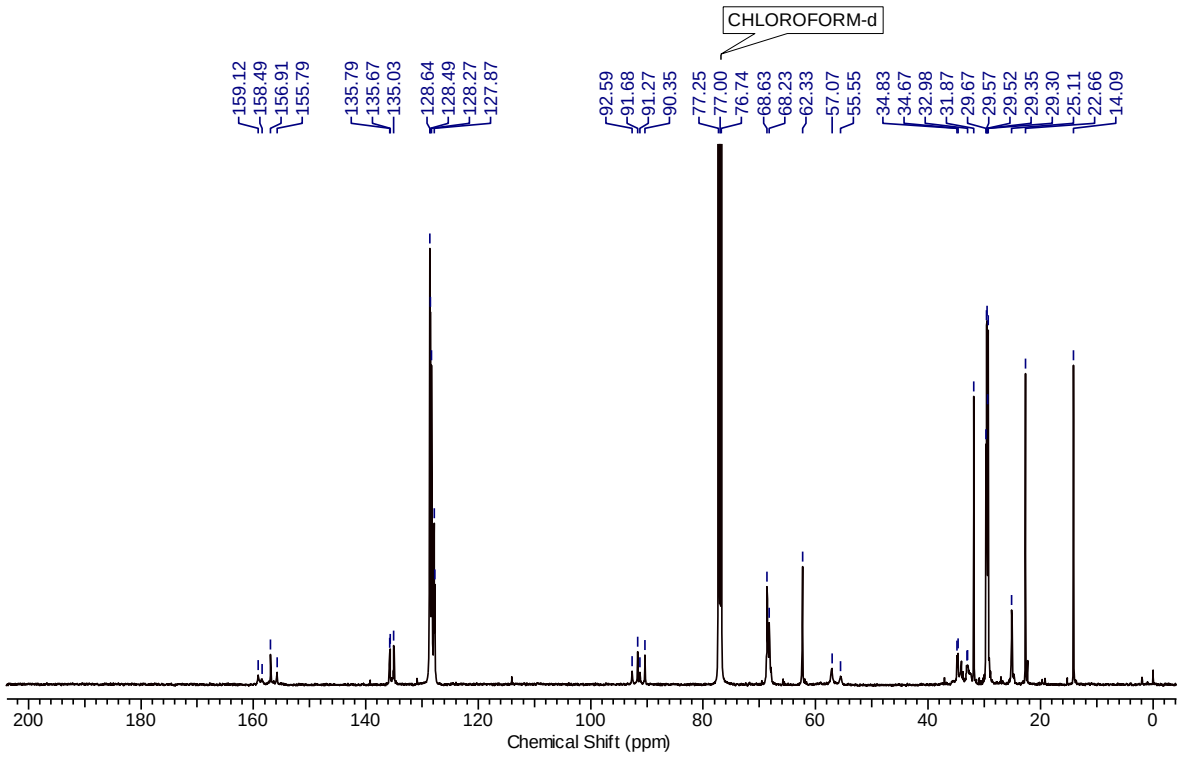


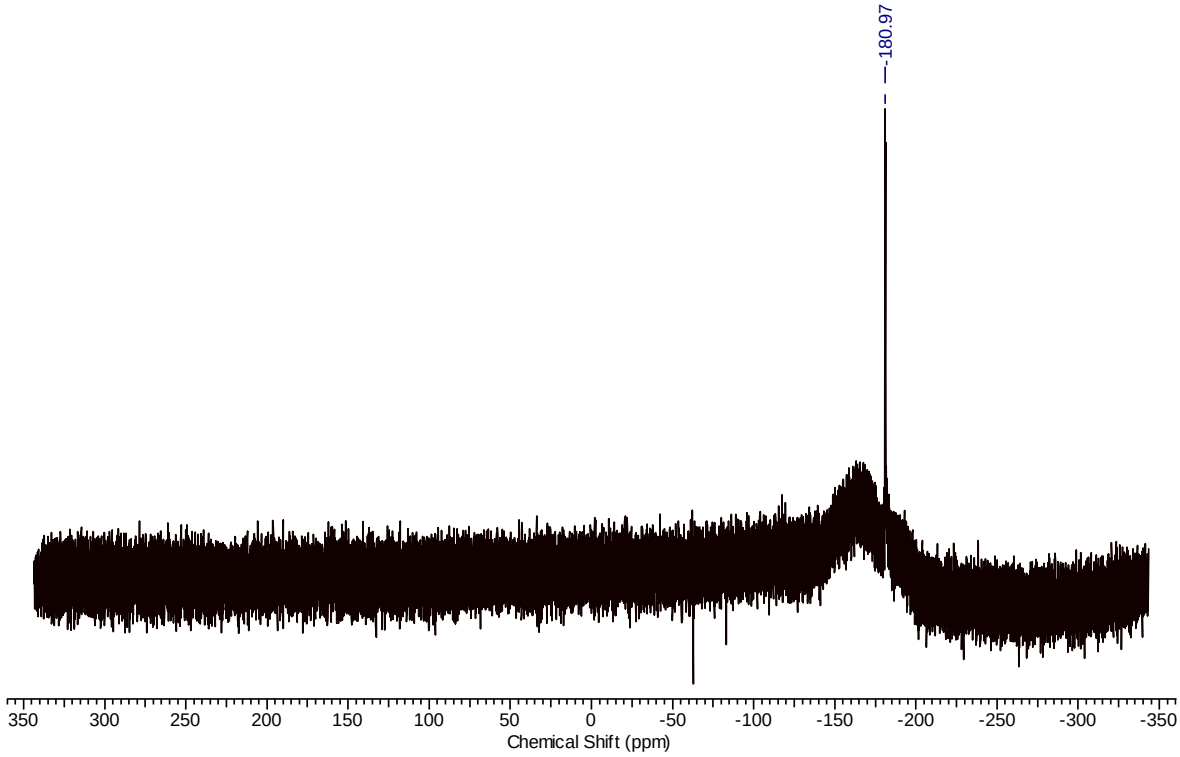





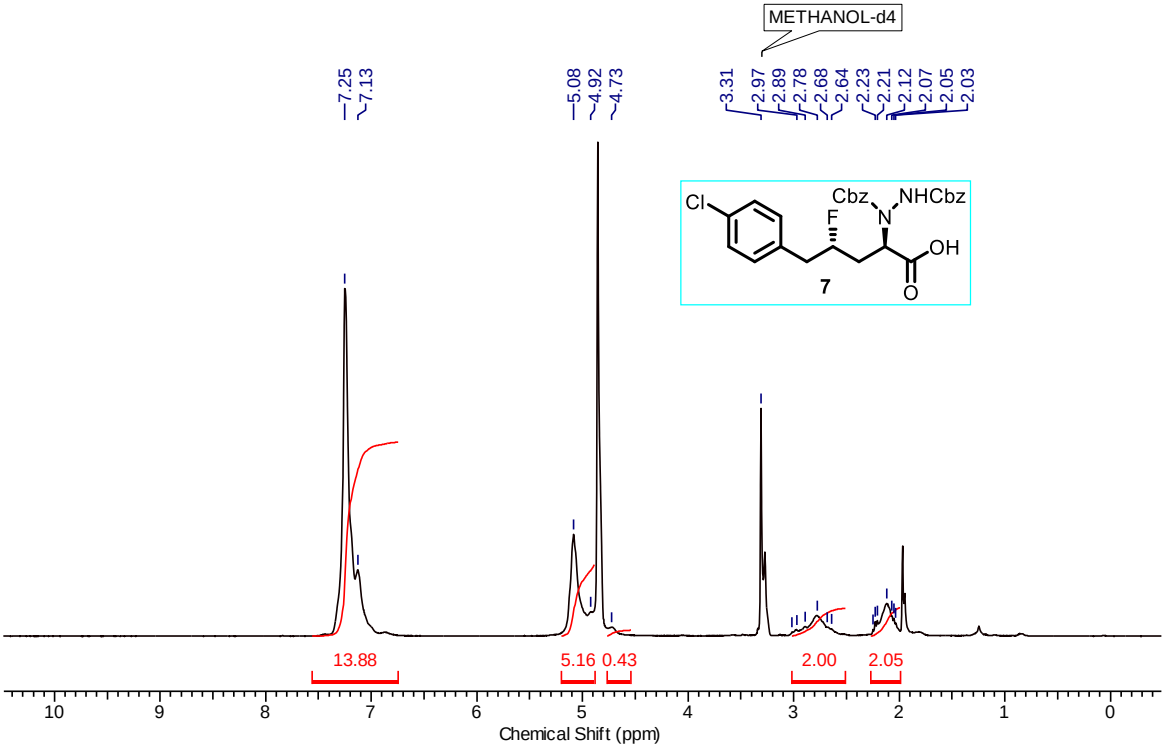

**Dibenzyl 1-((2*S*,4*S*)-4-fluoro-1-hydroxytetradecan-2-yl)hydrazine-1,2-dicarboxylate (6g)**

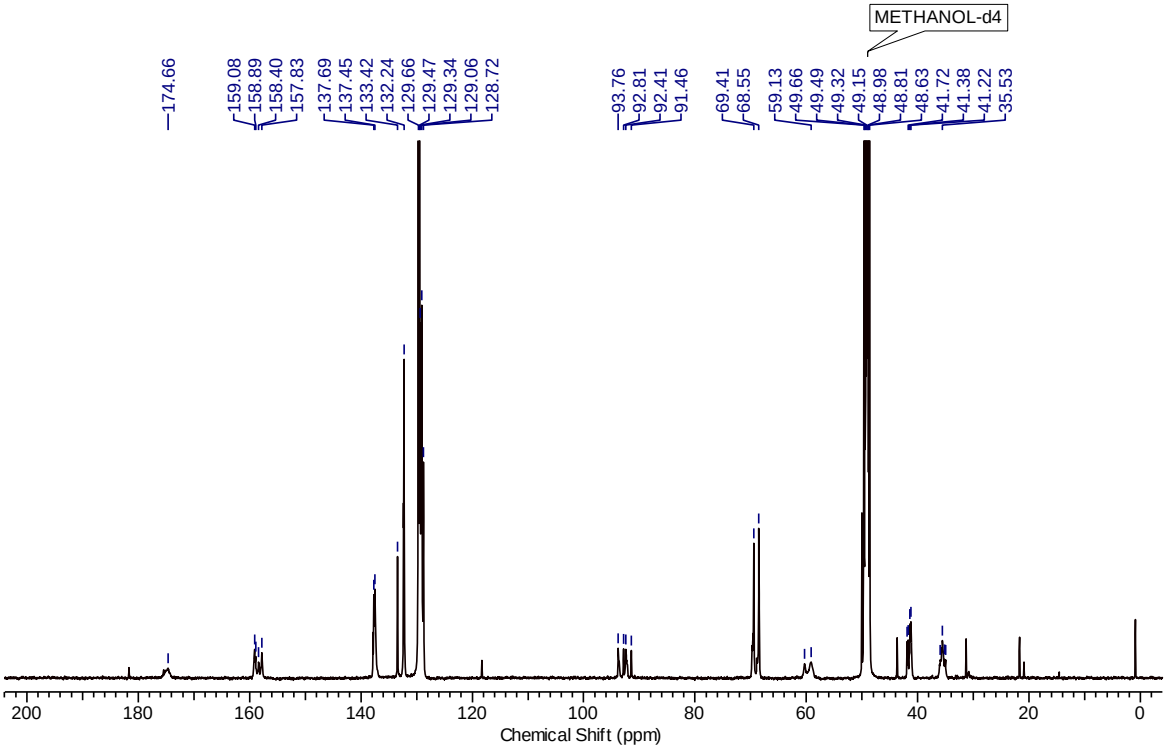


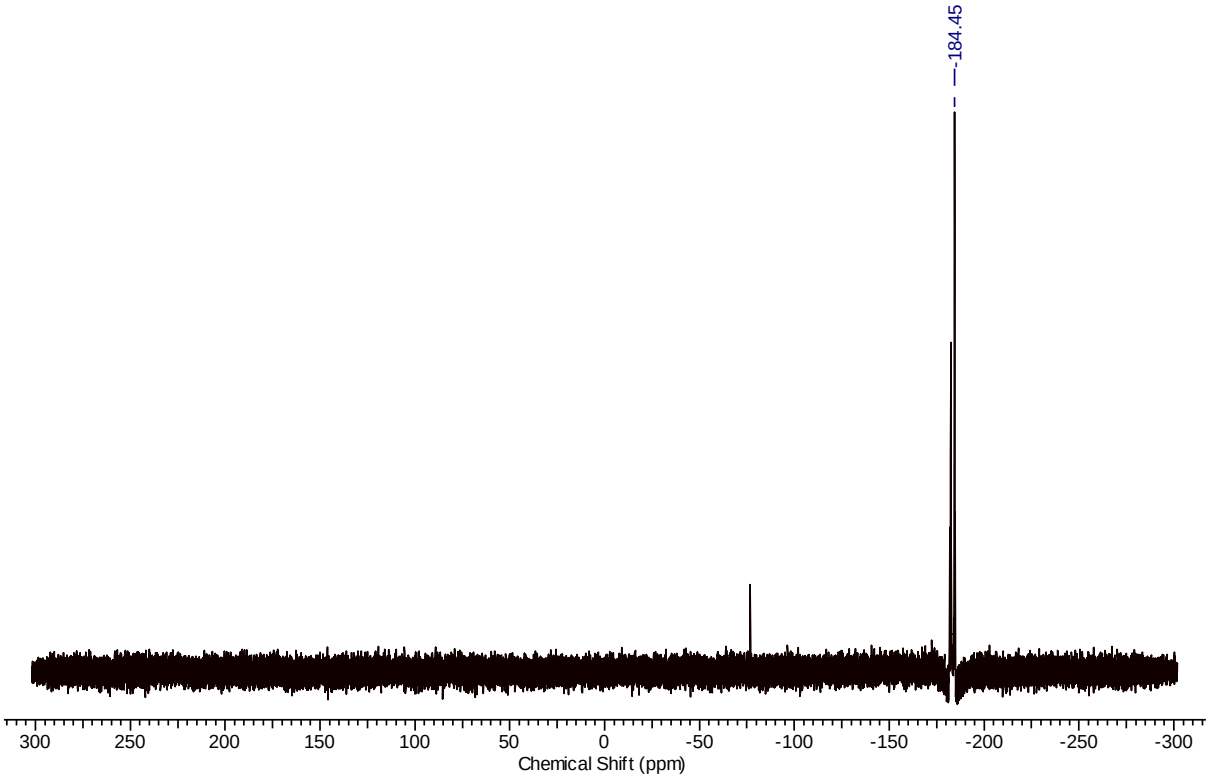

CHLOROFORM-d
159.12
158.49
156.91
155.79
135.79
135.67
135.03
128.64
128.49
128.27
127.87
92.59
91.68
91.27
90.35
77.25
77.00
76.74
68.63
68.23
62.33
57.07
55.55
34.83
34.67
32.98
31.87
29.67
29.57
29.52
29.35
29.30
25.11
22.66
14.09
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


-180.97
350
300
250
200
150
100
50
0
-50
-100
-150
-200
-250
-300
-350
Chemical Shift (ppm)

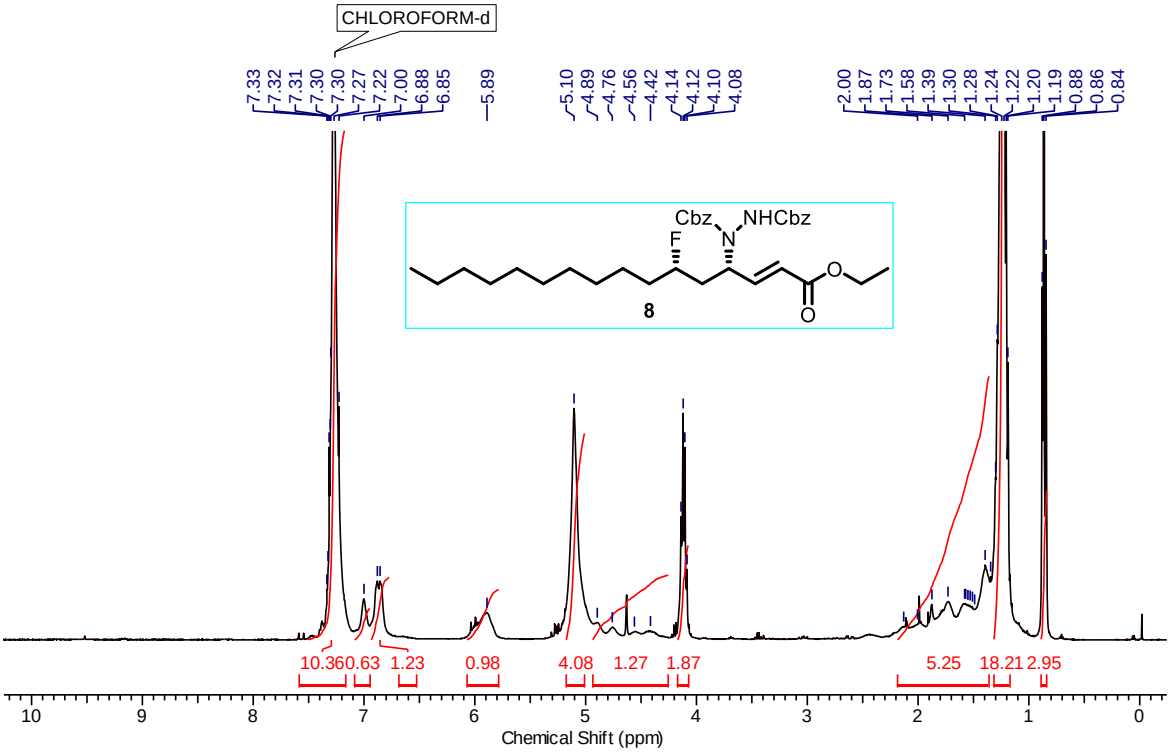
**(2*R*,4*S*)-2-(1,2-bis((benzyloxy)carbonyl)hydrazineyl)-5-(4-chlorophenyl)-4-fluoropentanoic acid (7)**

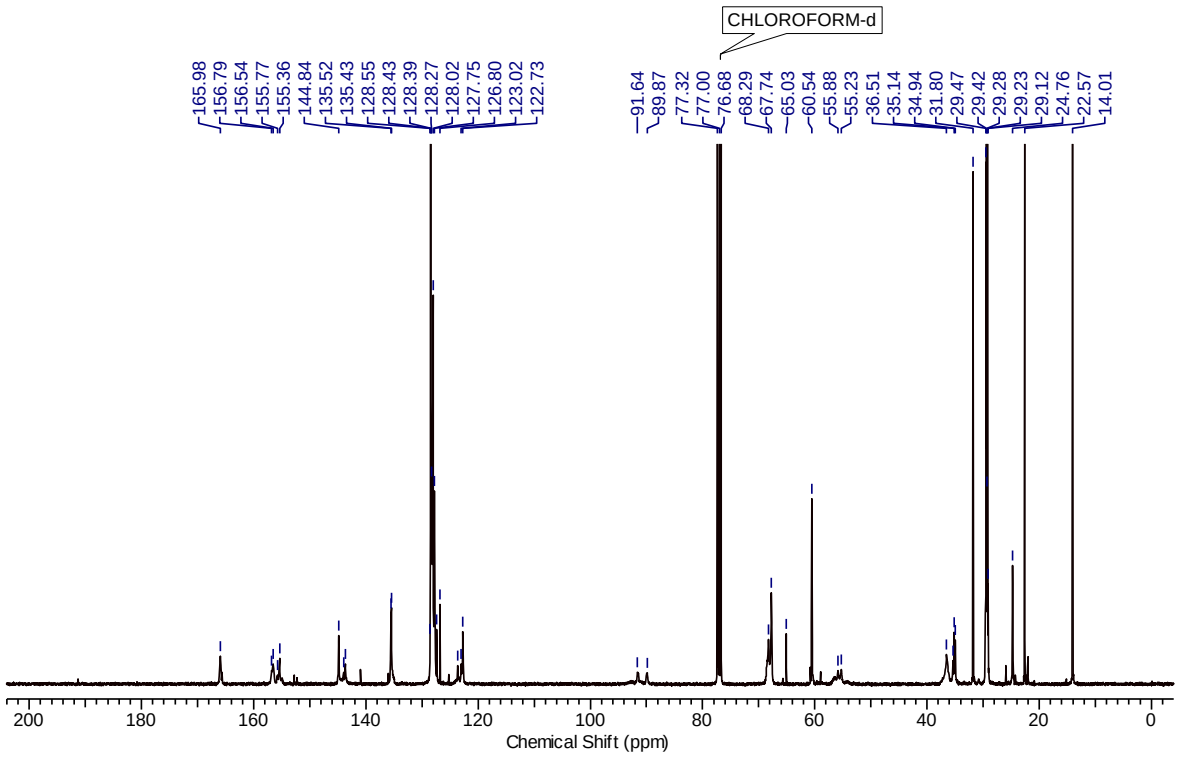


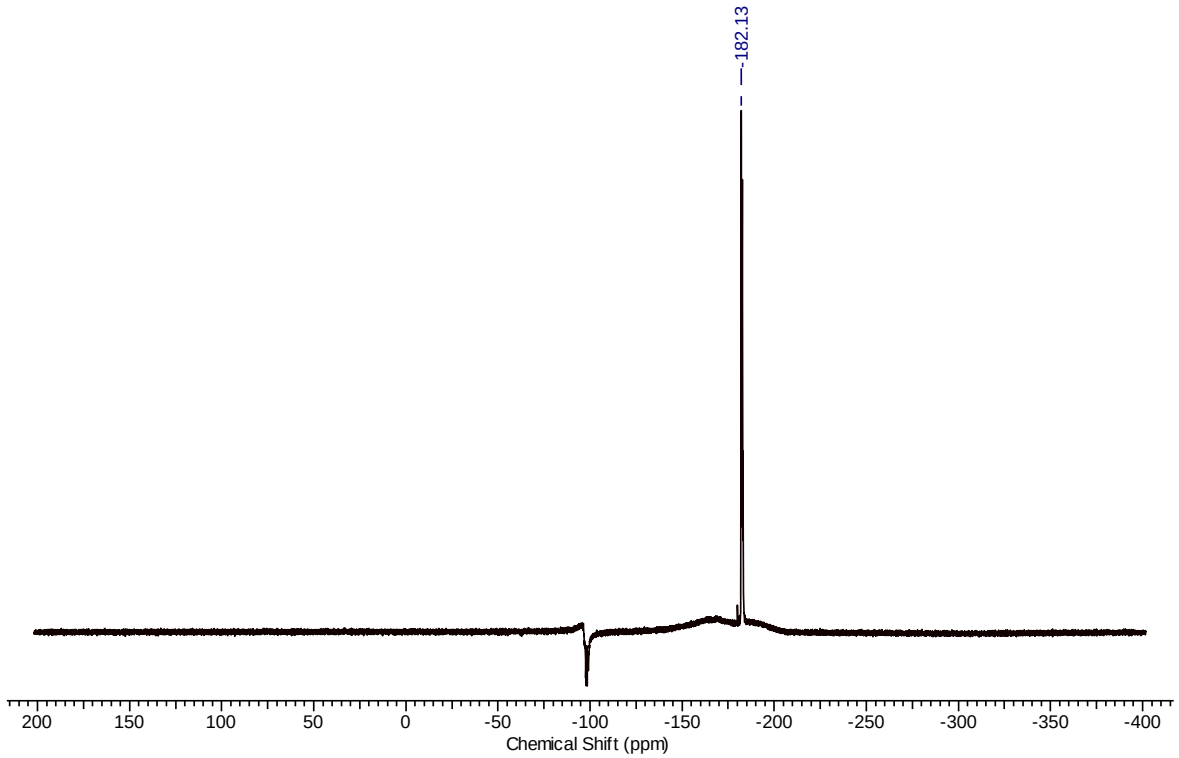






**Dibenzyl 1-((4*S*,6*S*,*E*)-1-ethoxy-6-fluoro-1-oxohexadec-2-en-4-yl)hydrazine-1,2-dicarboxylate (8)**

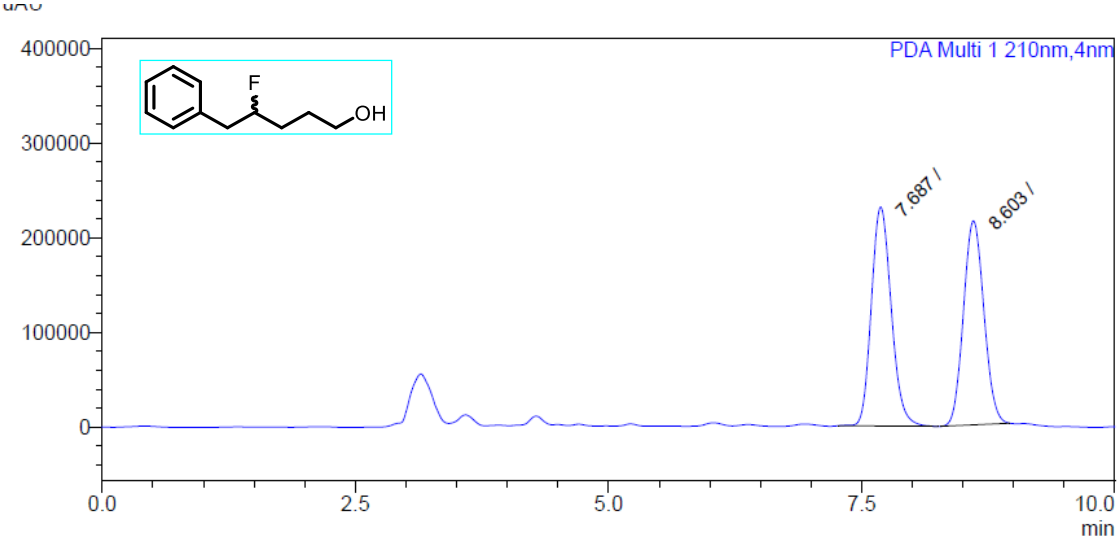



CHLOROFORM-d
165.98
156.79
156.54
155.77
155.36
144.84
135.52
135.43
128.55
128.43
128.39
128.27
128.02
127.75
126.80
123.02
122.73
91.64
89.87
77.32
77.00
76.68
68.29
67.74
65.03
60.54
55.88
55.23
36.51
35.14
34.94
31.80
29.47
29.42
29.28
29.23
29.12
24.76
22.57
14.01
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


-182.13
200
150
100
50
0
-50
-100
-150
-200
-250
-300
-350
-400
Chemical Shift (ppm)

## 4B.11 Chiral HPLC Data

### 4-fluoro-5-phenylpentan-1-ol (Recemic)

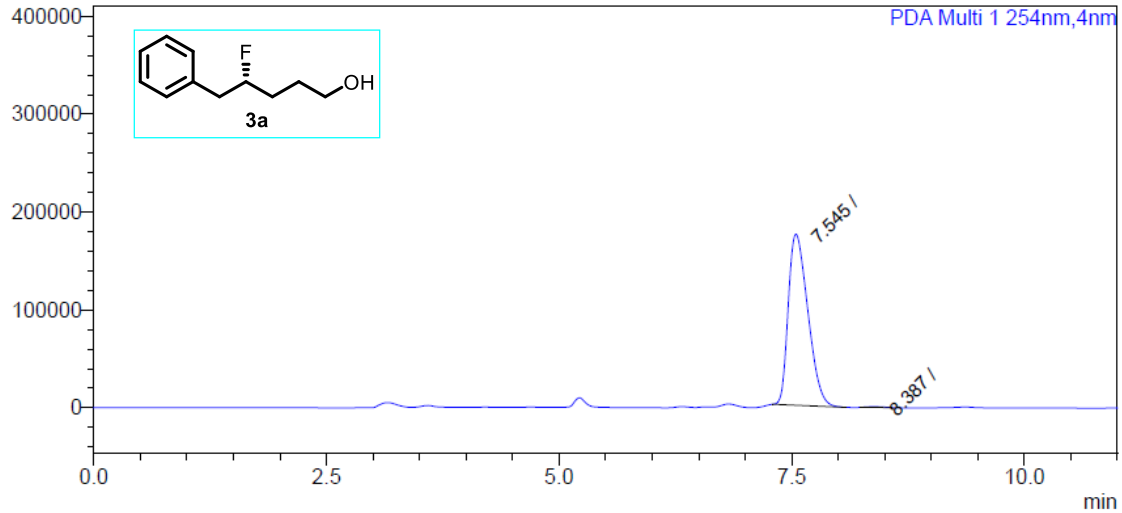



**<Peak Table>**

PDA Ch1 210nm

| Peak# | Name | Ret. Time | Area | Area% | Height | Height% |
|---|---|---|---|---|---|---|
| 1 | | 7.687 | 3165203 | 51.082 | 231130 | 51.785 |
| 2 | | 8.603 | 3031084 | 48.918 | 215192 | 48.215 |
| Total | | | 6196287 | 100.000 | 446322 | 100.000 |

### (*R*)-4-fluoro-5-phenylpentan-1-ol (3a)

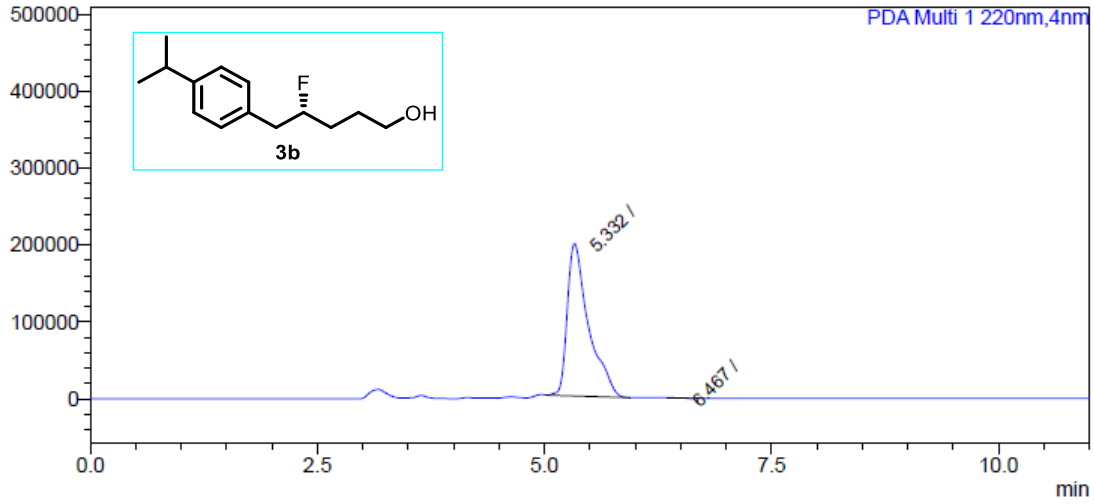



**<Peak Table>**

PDA Ch1 254nm

| Peak# | Name | Ret. Time | Area | Area% | Height | Height% |
|---|---|---|---|---|---|---|
| 1 | | 7.545 | 2565131 | 99.660 | 174896 | 99.565 |
| 2 | | 8.387 | 8764 | 0.340 | 763 | 0.435 |
| Total | | | 2573894 | 100.000 | 175660 | 100.000 |

**(*R*)-4-fluoro-5-(4-isopropylphenyl)pentan-1-ol (3b)**

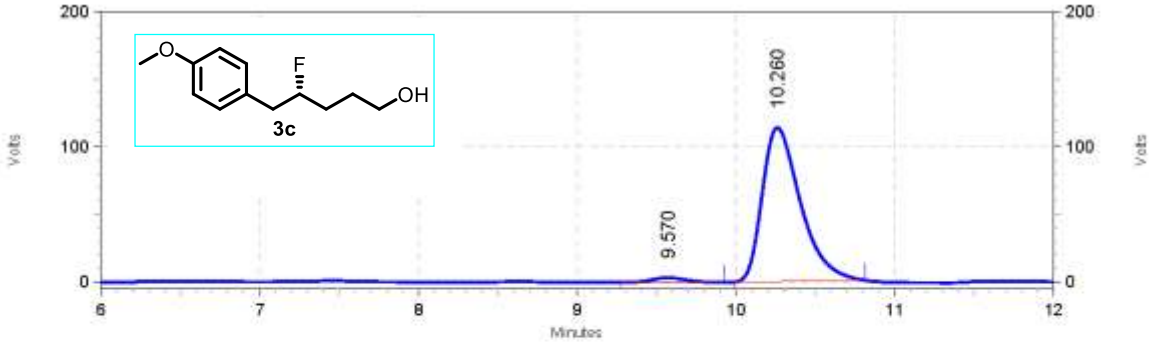



**<Peak Table>**

PDA Ch1 220nm

| Peak# | Name | Ret. Time | Area | Area% | Height | Height% |
|---|---|---|---|---|---|---|
| 1 | | 5.332 | 3247500 | 99.899 | 198293 | 99.841 |
| 2 | | 6.467 | 3294 | 0.101 | 315 | 0.159 |
| Total | | | 3250794 | 100.000 | 198608 | 100.000 |

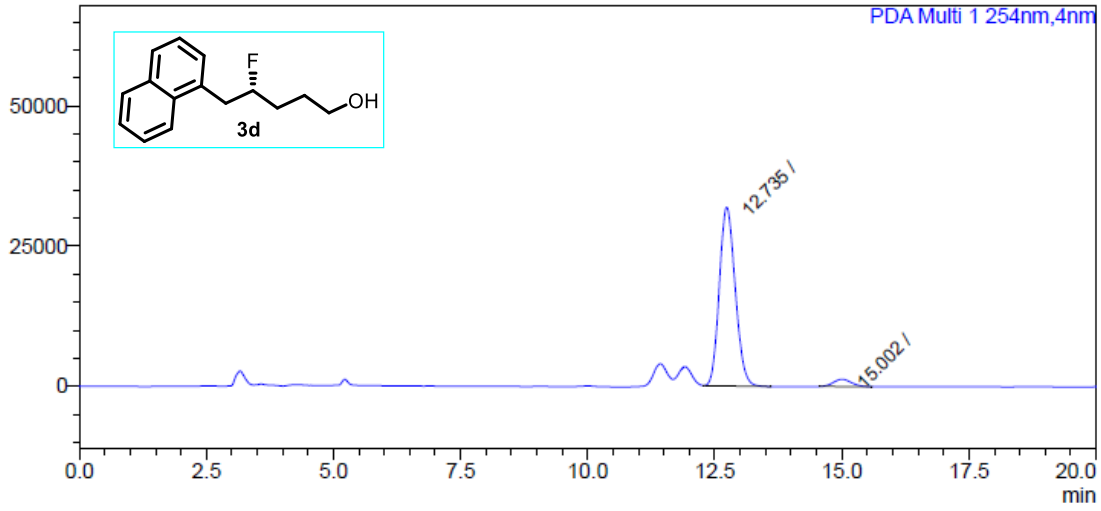
**(*R*)-4-fluoro-5-(4-methoxyphenyl)pentan-1-ol (3c)**




**VWD: Signal A,**
**254 nm Results**

| Retention Time | Area | Area % | Height | Height % |
|---|---|---|---|---|
| 9.570 | 840148 | 2.56 | 57846 | 2.94 |
| 10.260 | 31975053 | 97.44 | 1909713 | 97.06 |
| Totals | 32815201 | 100.00 | 1967559 | 100.00 |

**(*R*)-4-fluoro-5-(naphthalen-2-yl)pentan-1-ol (3d)**

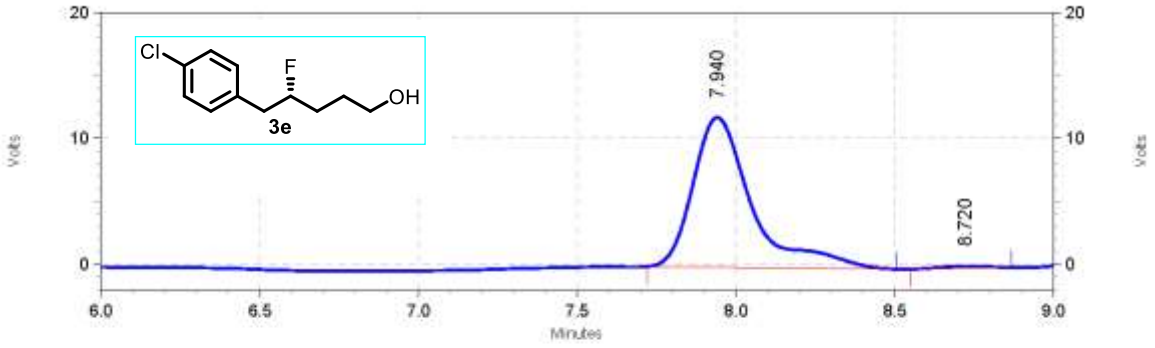



**<Peak Table>**

PDA Ch1 254nm

| Peak# | Name | Ret. Time | Area | Area% | Height | Height% |
|---|---|---|---|---|---|---|
| 1 | | 12.735 | 695589 | 95.616 | 31866 | 96.098 |
| 2 | | 15.002 | 31890 | 4.384 | 1294 | 3.902 |
| Total | | | 727479 | 100.000 | 33160 | 100.000 |

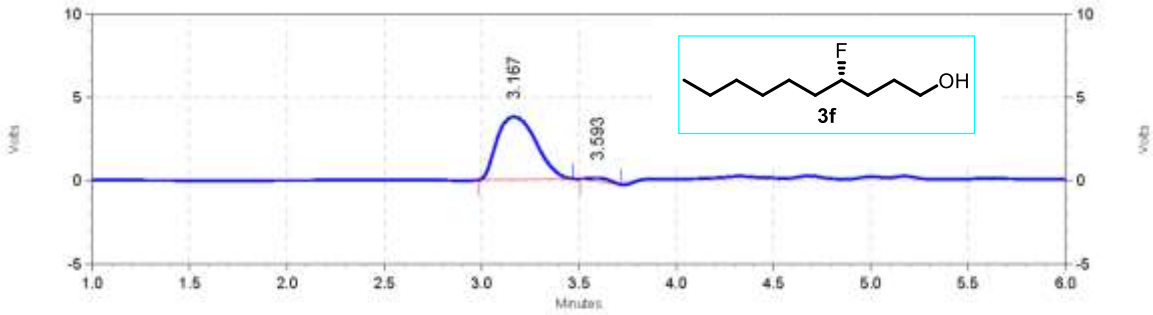
**(*R*)-5-(4-chlorophenyl)-4-fluoropentan-1-ol (3e)**




**VWD: Signal A, 253 nm Results**

| Retention Time | Area | Area % | Height | Height % |
|---|---|---|---|---|
| 7.940 | 2563766 | 98.98 | 199651 | 98.70 |
| 8.720 | 26413 | 1.02 | 2621 | 1.30 |
| Totals | 2590179 | 100.00 | 202272 | 100.00 |

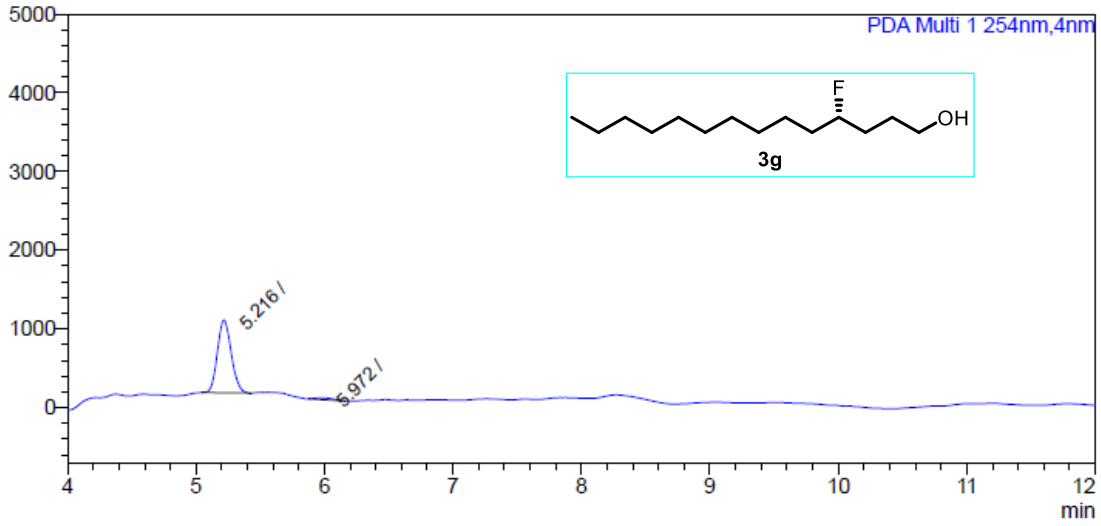
**(*S*)-4-fluorodecan-1-ol (3f)**




**VWD: Signal A,**
**254 nm Results**

| Retention Time | Area | Area % | Height | Height % |
|---|---|---|---|---|
| 3.167 | 880512 | 97.08 | 63145 | 94.86 |
| 3.593 | 26498 | 2.92 | 3425 | 5.14 |
| Totals | 907010 | 100.00 | 66570 | 100.00 |

**(*S*)-4-fluorotetradecan-1-ol (3g)**

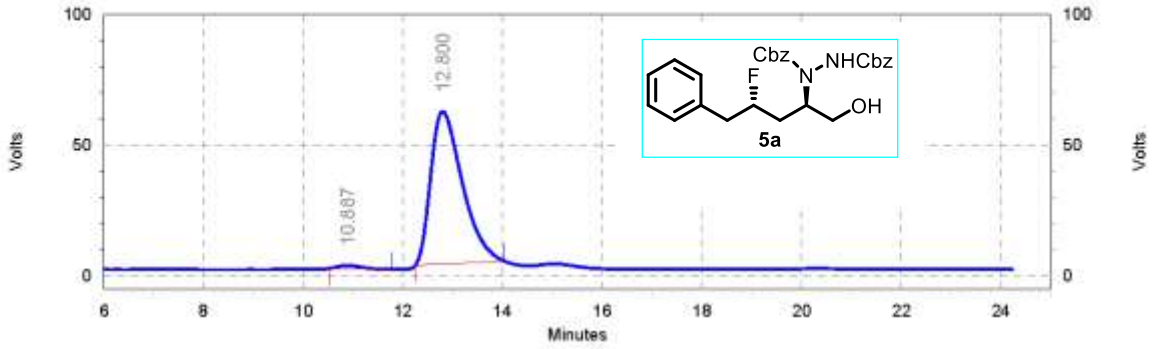



**<Peak Table>**

PDA Ch1 254nm

| Peak# | Name | Ret. Time | Area | Area% | Height | Height% |
|---|---|---|---|---|---|---|
| 1 | | 5.216 | 6918 | 96.708 | 925 | 97.490 |
| 2 | | 5.972 | 235 | 3.292 | 24 | 2.510 |
| Total | | | 7154 | 100.000 | 949 | 100.000 |

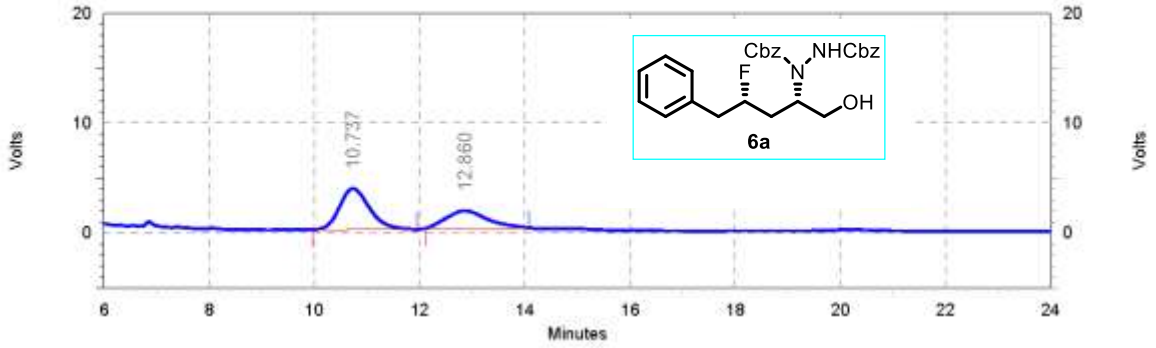
**Dibenzyl 1-((2*R*,4*S*)-4-fluoro-1-hydroxy-5-phenylpentan-2-yl)hydrazine-1,2-dicarboxylate (5a)**




**VWD: Signal A, 253 nm Results**

| Retention Time | Area | Area % | Height | Height % |
|---|---|---|---|---|
| 10.887 | 670320 | 1.53 | 21607 | 2.16 |
| 12.800 | 43000149 | 98.47 | 977884 | 97.84 |
| Totals | 43670469 | 100.00 | 999491 | 100.00 |

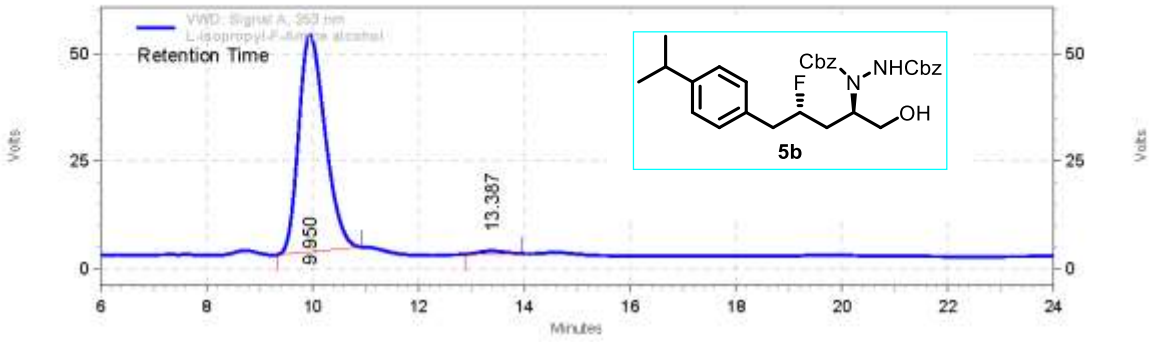
**Dibenzyl 1-((2*S*,4*S*)-4-fluoro-1-hydroxy-5-phenylpentan-2-yl)hydrazine-1,2-dicarboxylate (6a)**




**VWD: Signal A, 253 nm Results**

| Retention Time | Area | Area % | Height | Height % |
|---|---|---|---|---|
| 10.737 | 2467954 | 63.17 | 62558 | 70.07 |
| 12.860 | 1438647 | 36.83 | 26720 | 29.93 |
| Totals | 3906601 | 100.00 | 89278 | 100.00 |

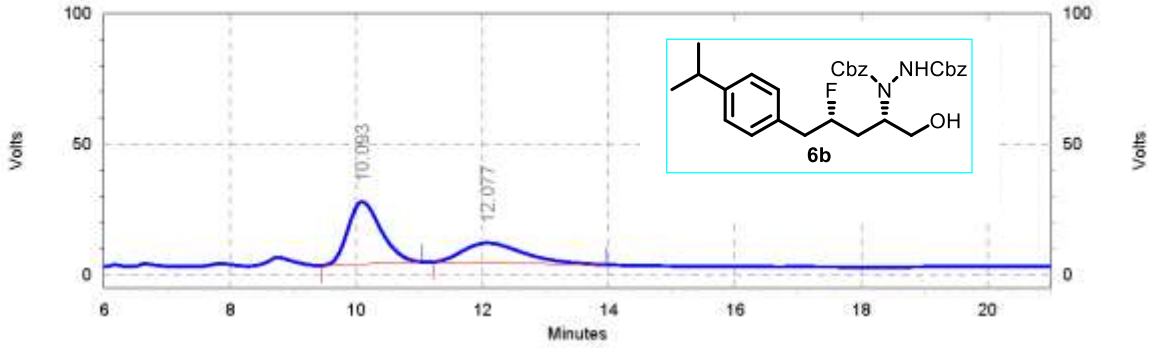
**Dibenzyl 1-((2*R*,4*S*)-4-fluoro-1-hydroxy-5-(4-isopropylphenyl)pentan-2-yl)hydrazine-1,2-dicarboxylate (5b)**




**VWD: Signal A, 253 nm Results**

| Retention Time | Area | Area % | Height | Height % |
|---|---|---|---|---|
| 9.950 | 29330155 | 98.62 | 847250 | 98.59 |
| 13.387 | 409166 | 1.38 | 12132 | 1.41 |
| Totals | 29739321 | 100.00 | 859382 | 100.00 |

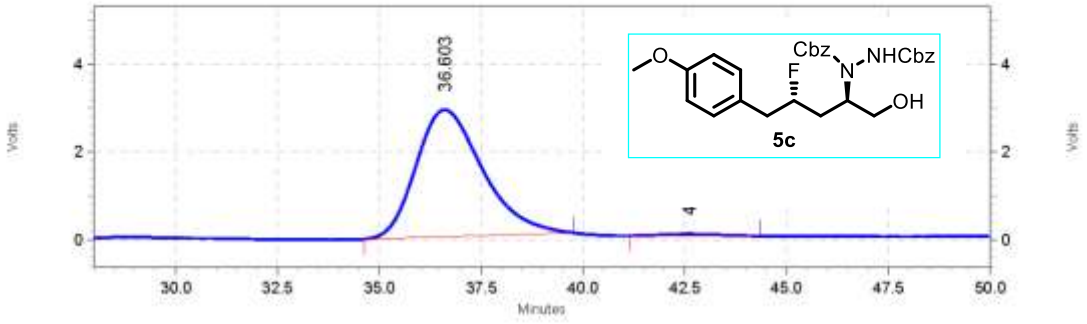
**Dibenzyl 1-((2*S*,4*S*)-4-fluoro-1-hydroxy-5-(4-isopropylphenyl)pentan-2-yl)hydrazine-1,2-dicarboxylate (6b)**




**VWD: Signal A, 253 nm Results**

| Retention Time | Area | Area % | Height | Height % |
|---|---|---|---|---|
| 10.093 | 14503673 | 63.18 | 398794 | 75.87 |
| 12.077 | 8453947 | 36.82 | 126844 | 24.13 |
| Totals | 22957620 | 100.00 | 525638 | 100.00 |

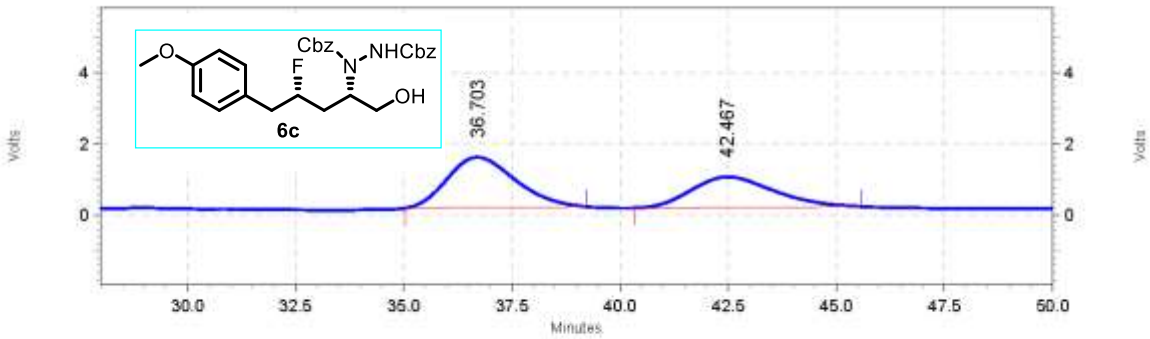
**Dibenzyl 1-((2*R*,4*S*)-4-fluoro-1-hydroxy-5-(4-methoxyphenyl)pentan-2-yl)hydrazine-1,2-dicarboxylate (5c)**




**VWD: Signal A,**
**253 nm Results**

| Retention Time | Area | Area % | Height | Height % |
|---|---|---|---|---|
| 36.603 | 5510226 | 98.67 | 48520 | 98.49 |
| 42.620 | 74227 | 1.33 | 744 | 1.51 |
| Totals | 5584453 | 100.00 | 49264 | 100.00 |

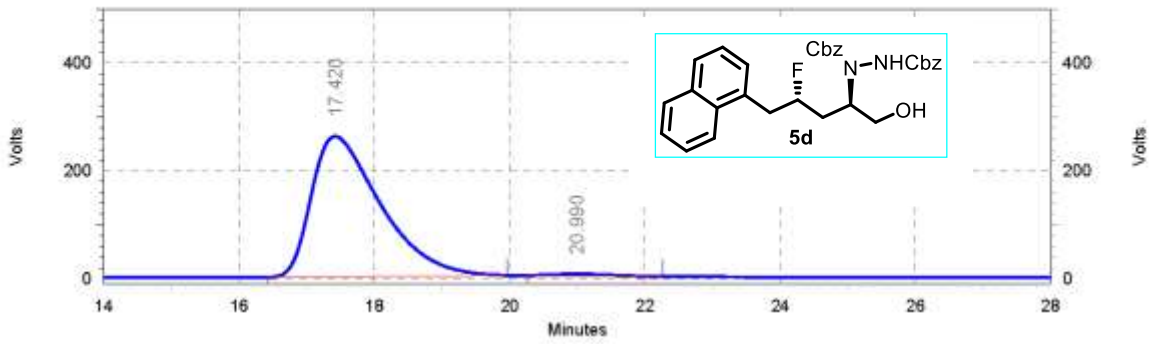
**Dibenzyl 1-((2*S*,4*S*)-4-fluoro-1-hydroxy-5-(4-methoxyphenyl)pentan-2-yl)hydrazine-1,2-dicarboxylate (6c)**




**VWD: Signal A,**
**253 nm Results**

| Retention Time | Area | Area % | Height | Height % |
|---|---|---|---|---|
| 36.703 | 2577801 | 57.56 | 23627 | 62.25 |
| 42.467 | 1900736 | 42.44 | 14329 | 37.75 |
| Totals | 4478537 | 100.00 | 37956 | 100.00 |

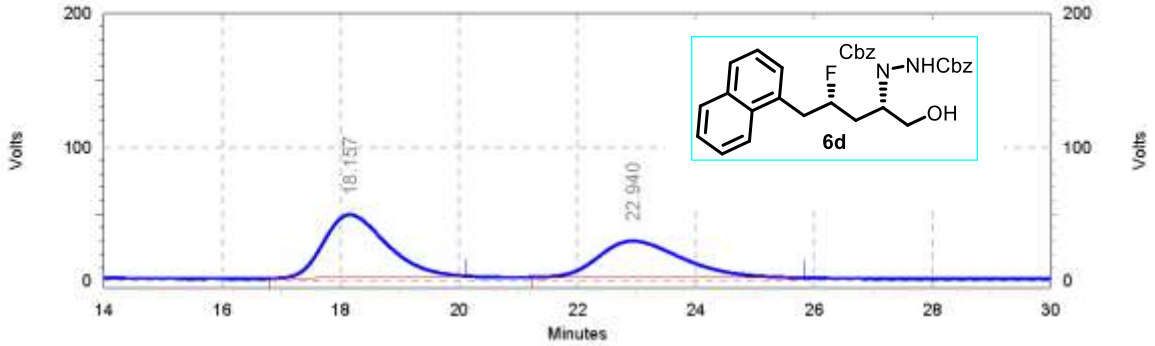
**Dibenzyl 1-((2*R*,4*S*)-4-fluoro-1-hydroxy-5-(naphthalen-2-yl)pentan-2-yl)hydrazine-1,2-dicarboxylate (5d)**




**VWD: Signal A, 253 nm Results**

| Retention Time | Area | Area % | Height | Height % |
|---|---|---|---|---|
| 17.420 | 309678961 | 98.86 | 4376016 | 98.65 |
| 20.990 | 3562784 | 1.14 | 59960 | 1.35 |
| Totals | 313241745 | 100.00 | 4435976 | 100.00 |

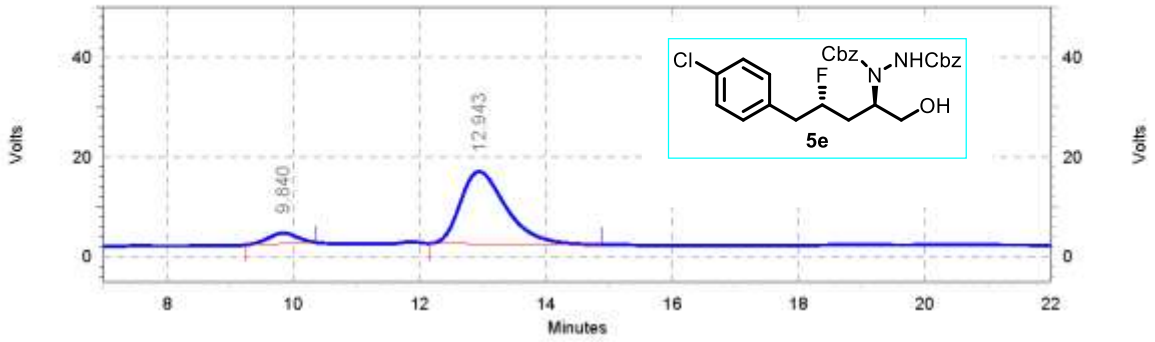
**Dibenzyl 1-((2*S*,4*S*)-4-fluoro-1-hydroxy-5-(naphthalen-2-yl)pentan-2-yl)hydrazine-1,2-dicarboxylate (6d)**




**VWD: Signal A, 253 nm Results**

| Retention Time | Area | Area % | Height | Height % |
|---|---|---|---|---|
| 18.157 | 57688717 | 56.26 | 785459 | 63.25 |
| 22.940 | 44847949 | 43.74 | 456416 | 36.75 |
| Totals | 102536666 | 100.00 | 1241875 | 100.00 |

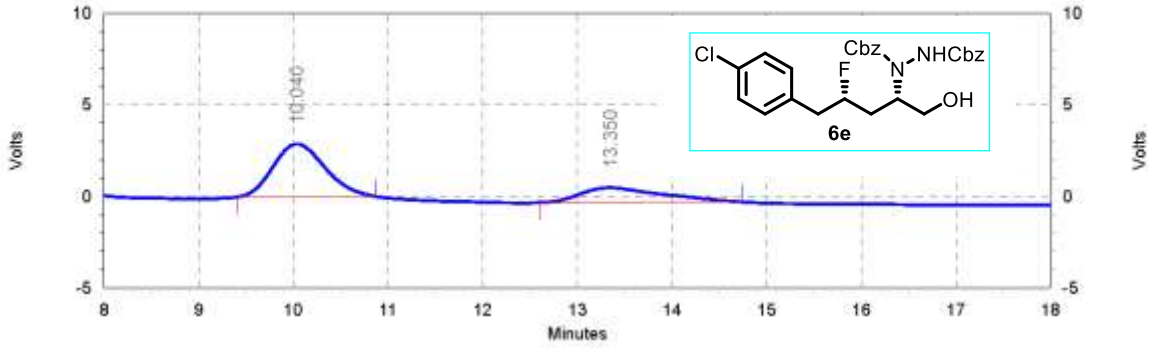
**Dibenzyl 1-((2*R*,4*S*)-5-(4-chlorophenyl)-4-fluoro-1-hydroxypentan-2-yl)hydrazine-1,2-dicarboxylate (5e)**




**VWD: Signal A, 253 nm Results**

| Retention Time | Area | Area % | Height | Height % |
|---|---|---|---|---|
| 9.840 | 1136359 | 8.53 | 35638 | 12.79 |
| 12.943 | 12180056 | 91.47 | 242964 | 87.21 |
| Totals | 13316415 | 100.00 | 278602 | 100.00 |

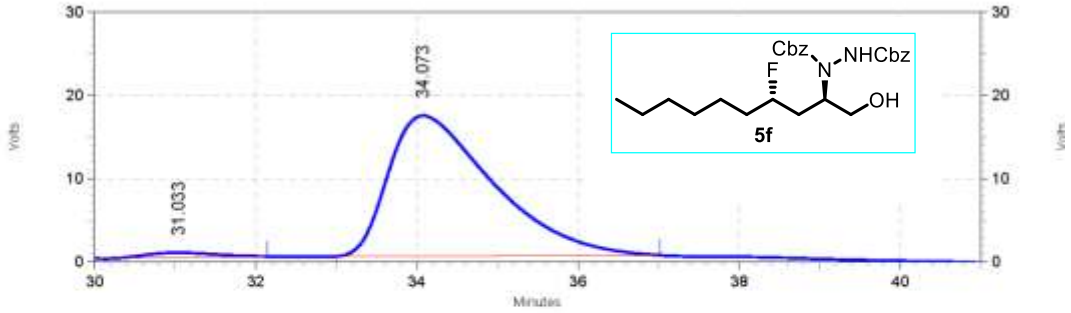
**Dibenzyl 1-((2*S*,4*S*)-5-(4-chlorophenyl)-4-fluoro-1-hydroxypentan-2-yl)hydrazine-1,2-dicarboxylate (6e)**




**VWD: Signal A, 253 nm Results**

| Retention Time | Area | Area % | Height | Height % |
|---|---|---|---|---|
| 10.040 | 1843414 | 69.37 | 48411 | 78.23 |
| 13.350 | 813887 | 30.63 | 13468 | 21.77 |
| Totals | 2657301 | 100.00 | 61879 | 100.00 |

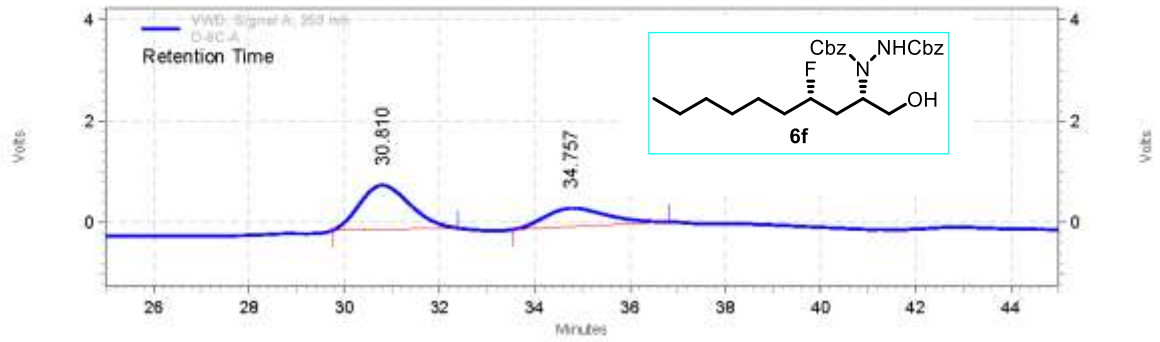
**Dibenzyl 1-((2*R*,4*S*)-4-fluoro-1-hydroxydecan-2-yl)hydrazine-1,2-dicarboxylate (5f)**




**VWD: Signal A, 253 nm Results**

| Retention Time | Area | Area % | Height | Height % |
|---|---|---|---|---|
| 31.033 | 561866 | 2.16 | 9684 | 3.32 |
| 34.073 | 25408526 | 97.84 | 282060 | 96.68 |
| Totals | 25970392 | 100.00 | 291744 | 100.00 |

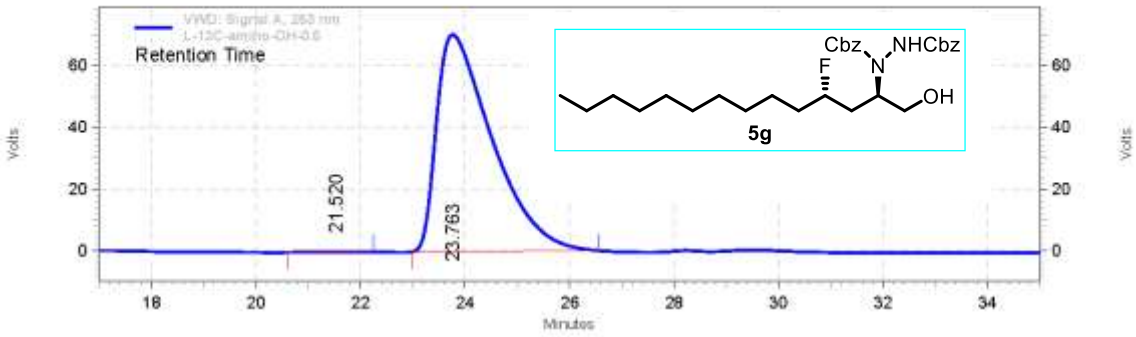
**Dibenzyl 1-((2*S*,4*S*)-4-fluoro-1-hydroxydecan-2-yl)hydrazine-1,2-dicarboxylate (6f)**




**VWD: Signal A, 253 nm Results**

| Retention Time | Area | Area % | Height | Height % |
|---|---|---|---|---|
| 30.810 | 1067836 | 66.02 | 14623 | 70.59 |
| 34.757 | 549539 | 33.98 | 6093 | 29.41 |
| Totals | 1617375 | 100.00 | 20716 | 100.00 |

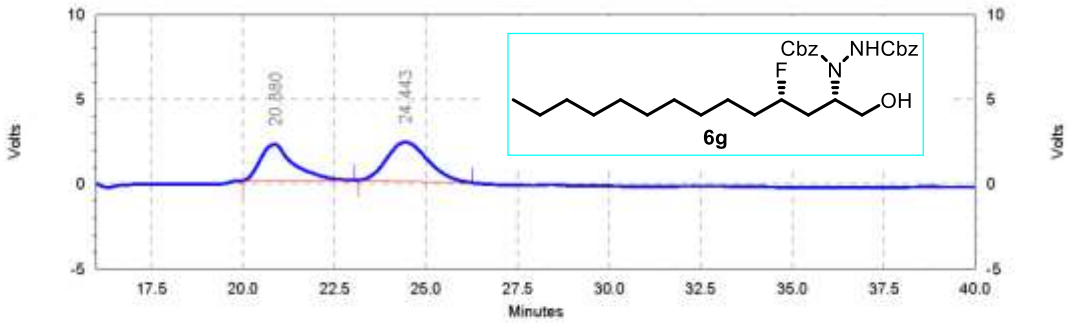
**Dibenzyl 1-((2*R*,4*S*)-4-fluoro-1-hydroxytetradecan-2-yl)hydrazine-1,2-dicarboxylate (5g)**




**VWD: Signal A, 253 nm Results**

| Retention Time | Area | Area % | Height | Height % |
|---|---|---|---|---|
| 21.520 | 168339 | 0.19 | 2987 | 0.25 |
| 23.763 | 86964941 | 99.81 | 1179897 | 99.75 |
| Totals | 87133280 | 100.00 | 1182884 | 100.00 |

**Dibenzyl 1-((2*S*,4*S*)-4-fluoro-1-hydroxytetradecan-2-yl)hydrazine-1,2-dicarboxylate (6g)**




**VWD: Signal A, 253 nm Results**

| Retention Time | Area | Area % | Height | Height % |
|---|---|---|---|---|
| 20.880 | 2262805 | 42.66 | 35699 | 47.95 |
| 24.443 | 3041796 | 57.34 | 38759 | 52.05 |
| Totals | 5304601 | 100.00 | 74458 | 100.00 |

## 4B.12 References


1. a) O'Hagan, D.; Deng, H. *Chem. Rev.* **2015,** *115*, 634−649. b) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015,** *58*, 8315−8359.
2. a) Theodoridis, G. *Advances in Fluorine Science* **2006,** *2*, 121−175. b) Fujiwara, T.; O'Hagan, D. *J. Fluor. Chem.* **2014,** *167*, 16−29.
3. a) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016,** *116*, 422−518. b) Isanbor, C.; O'Hagan, D. *J. Fluor. Chem.* **2006,** *127*, 303−319. c) Kirk, K. L. *J. Fluor. Chem.* **2006,** *127*, 1013−1029. d) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015,** *58*, 8315−8359.
4. a) Niel, M.; Collins, I.; Beer, M. S.; Broughton, H. B.; Cheng, S. S.; Goodacre, C.; Heald, A.; Locker, K. L.; MacLeod, A. M.; Morrison, D.; Moyes, C. R.; O'Connor, D.; Pike, A.; Rowley, M.; Russell, M. G. N.; Sohal, B.; Stanton, J. A.; Thomas, S.; Verrier, H.; Watt, A. P.; Cas-tro, J. L. *J. Med. Chem.* **1999,** *42*, 2087−2104. b) Shah, P.; Westwell, A. D. *J. Enzyme Inhib. Med. Chem.* **2007,** *22*, 527–540. c) Smart, B. C. *J. Fluor. Chem.* **2001,** *109*, 3−11. d) O'Hagan, D.; Rzepa, H. S. *Chem. Commun.* **1997,** 645−652. e) Schlosser, M.; Michel, D. *Tetrahedron* **1996,** *52*, 99−108.
5. a) Adama, M. J.; Wilbur, D. *Chem. Soc. Rev.* **2005,** *34*, 153−163. b) Butsch, V.; Börgel, F.; Galla, F.; Schwegmann, K.; Her-mann, S.; Schäfers, M.; Riemann, B.; Wünsch, B.; Wagner, S. *J. Med. Chem.* **2018,** *61*, 4115−4134.
6. a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008,** *37*, 320−330. b) Wang, J.; Sánchez-Roselló, M.; Aceña, J.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Soc. Rev.* **2014,** *114*, 2432−250. c) Filler, R.; Kobayashi, Y.; Yagripolskii (Eds.), L. M. Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications. Elsevier, Amsterdam, **1993**.
7. a) Moschner, J.; Stulberg, V.; Fernandes, R.; Huhmann, S.; Leppkes, J.; Koksch, B. *Chem. Rev.* **2019,** *119*, 10718−10801. b) Shendage, D. M.; Fröhlich, R.; Bergander, K.; Haufe, G. *Eur. J. Org. Chem.* **2005,** 719−727. c) Qui, X. -L.; Meng, W. -D.; Qing, F. -L. *Tetrahedron* **2004,** *60*, 6711−6745.
8. a) Notz, W.; Tanaka, F.; Barbas, C.F. *Acc. Chem. Res.* **2004,** *37*, 580−591. b) Gaunt, M. J.; Johansson, C.C.; McNally, A.; T. Ngoc, Vo. *Today* **2007,** *12*, 8−27; c) Dalko,

P. I. Enantioselective Organocatalysis: Reactions and Experimental Procedures; Wiley-VCH: Weinheim, **2007**. d) MacMillian, D. W. C. *Nature* **2008,** *455*, 304−308. e) Casas, J.; Engqvist, M.; Ibrahem, I.; Kaynak, B.; Cordova, A. *Angew. Chem. Int. Ed.* **2005,** *44*, 1343−1345. f) List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000,** *122*, 2395−2396. g) Hechavarria Fonseca, M. T.; List, B. *Angew. Chem. Int. Ed.* **2004,** *43*, 3958−3960. h) Kumar, P.; Satbhaiya, S. Proline and Proline derived organocatalysts in the synthesis of heterocycles in "Advances in green and sustainable chemistry." Elsevier vol. 2, **2021,** 2015−2051.

9. For α-functionalization reviews, see: a) Franzen, J.; Mari-go, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005,** 127, 18296−18304. b) Guillena, G.; Ramon, D. J. *Tetrahedron: Asymmetry* **2006,** *17*, 1465−1492. c) For a comprehensive review on α-aminoxylation, see: Merino, P.; Tejero, T. *Angew. Chem. Int. Ed.* **2004,** *43*, 2995−2997.
10. a) List, B. *J. Am. Chem. Soc.* **2002,** *124*, 5656−5657. b) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bogevig, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002,** *124*, 6254−6255. d) Vogt, H.; Vanderheiden, S.; Brase, S. *Chem. Commun.* **2003,** 2448−2449.
11. Jha, V.; Kondekar, N. B.; Kumar, P. *Org. Lett.* **2010,** *12*, 2762−2765.
12. Kumar, P.; Jha, V.; Gonnade, R. *J. Org. Chem.* **2013,** *78*, 11756−11764.
13. a) Dwivedi, N.; Kumar, P. *Acc. Chem. Res.* **2013,** *46*, 289−299. b) Kumar, P.; Sharma, B. M. *Synlett* **2018,** *29*, 1944−1956.
14. a) Shinde, S. S.; Khonde, N. S.; Kumar, P. *ChemistrySelect* **2017,** *2*, 118−122. b) Said, M. S.; Mishra, A.; Pandole, S.; Nayak, R. A.; Kumar, P.; Gajbhiye, J. M. *Asian J. Org. Chem.* **2019,** *8*, 2143−2148.
15. Marigo, M.; Fielenbach, D.; Braunton. A.; Kjaersgaard, A.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005,** *44*, 3703−3706.
16. a) Abraham, R. J.; Ellison, S. L. R.; Schonholzer, P.; Thomas, W. A. *Tetrahedron* **1986,** *42*, 2101−2110. b) Allmendinger, T.; Felder, E.; Hungerbühler, E. *Tetrahedron Lett.* **1990,** *31*, 7301−7304. c) Boros, L. G.; De Corte, B.; Gimi, R. H.; Welch, J. T.; Wu, Y.; Handschumacher, R. E. *Tetrahedron Lett.* **1994,** *35*, 6033−6036. d) Welch, J. T.; Lin, J.; Boros, L. G.; De Corte, B.; Bogmann, K.; Gimi, R. In Frontiers of Fluorine Chemistry (Eds.: I. Ojima, J. R. McCarthy, J. T. Welch), Fluoro-olefin Isosteres as

Peptidomimetics ACS Symposium Series 639, American Chemical Society, Washington, DC, **1996,** pp. 129−142.

17. Yoder, N. S.; Kumar, K. *Chem. Soc. Rev.* **2002,** *31*, 335−341.
18. Marigo, M.; Fielenbach, D.; Braunton, A.; Kjaersgaard, A.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 3703−3706.
19. Kumar, P.; Jha, V.; Gonnade, R. *J. Org. Chem.* **2013**, *78*, 11756−11764.
20. Baumann, T.; Vogt, H.; Brase, S. *Eur. J. Org. Chem.* **2007**, 266−282.

# ABSTRACT

**Name of the Student:** Khonde Nilesh Shrimant **Registration No.:**10CC15A26012
**Faculty of Study:** Organic Chemistry Division **Year of Submission:** 2022
**AcSIR academic centre/CSIR Lab:** CSIR-NCL
**Name of the Supervisor(s):** Dr. Pradeep Kumar Tripathi
**Name of the Co-Supervisor(s):** Dr. M. Muthukrishnan
**Title of the thesis:** Synthetic Explorations into Carbon-Carbon and Carbon-Fluorine Bond Forming Reactions

*p*-Quinone methide frameworks are common constituents of various biological systems. It contains cyclohexadiene moiety with exocyclic methylene group and could be formed by the degradation of tyrosine and ultimately to *p*-Cresol. The quinone methide core containing diverse natural products shows prominent biological activities. The *p*-quinone methides structure is being polar, and becomes highly reactive intermediate in nature due to the presence of carbonyl group. Simple *p*-quinone methides are highly unstable and difficult to isolate at normal conditions due to their short-lived duration. It quickly reacts with nucleophiles and other reactants. Few structurally redesigned *p*-QMs have been assembled to stabilize it by putting bulky substituents near the carbonyl group; usually when it is the *tert*-butyl group, the respective *p*-QMs become highly stable and could be used further to study the chemical properties. *p*-Quinone methide, the transient intermediate plays an important role as a Michael acceptor and gives conjugate addition with nucleophiles.

The small size and high electro-negativity values help the fluorine atom to bind at many active sites of enzymes and bio-molecules through hydrogen bonding. Due to these ability incorporation of a fluorine atom in an organic molecule significantly alters pKa, stability, bio-selectivity, lipophilicity, permeability, metabolic pathways and pharmacokinetic properties. Consequently, fluoro-organic chemistry has been exploited extensively in drug discovery, agrochemical, and material sciences. At present, about 30% of the marketed drugs contain at least one fluorine atom and the number of fluorinated drugs is increasing exponentially. The favourable half-life time of the $^{18}F$ isotope (109.8 min) led to applications in positron emission tomography (PET) using radiotracers labelled with $^{18}F$.

The thesis mainly focus as on exploration into carbon-carbon bond forming reactions through $Tf_2NH$ catalyzed 1,6-conjugate addition of 2-hydroxy-*p*-quinone methides with *β*-functionalized ketones, allows xanthenones and chromenes to be accessed in moderate to excellent yield with broad substrate scope and metal-free, $Tf_2NH$-catalyzed 1,6-conjugate addition of imidazopyridine to *para*-quinone methides, provides a diverse class of C3-functionalized triarylmethanes heterocyclic derivatives of imidazopyridine with a high yield within a short duration.

We also investigated the carbon-fluorine bond forming reactions through tri-*tert*-BuOH amine organic promoter catalyzed nucleophilic fluorination of alkylsulfonates and alkyl halides with primary and secondary good leaving groups with cesium fluoride (CsF) in protic *tert*-BuOH solvent at 80 $^oC$ and further developed Hayashi-Jørgensen organocatalyst promoted fluorination towards an organocatalytic route to the enantioselective synthesis of syn/anti-1,3-fluoro amines, affording excellent enantioselectivity and diastereoselectivity of 1,3-fluoro amines.

## List of publication(s) in SCI Journal(s) (published & accepted) emanating from the thesis work

1. **N. S. Khonde**, M. S. Said, J. K. Sabane, J. M. Gajbhiye, Pradeep Kumar, "Metal-free, $Tf_2NH$-catalyzed 1,6-conjugate addition of imidazopyridine to para-quinone methides: Easy access to C3-functionalized triarylmethane imidazopyridine" Tetrahedron **2021**, 101, 132510.
2. S. Satbhaiya, **N. S. Khonde**, J. Rathod, R. Gonnade, Pradeep Kumar, "$Tf_2NH$ catalyzed 1,6-conjugate addition of 2-hydroxy-p-quinone methides with β-Functionalized Ketones: Access to 2,3,4,9-Tetrahydro-1H-xanthenones and 4H-Chromene Derivatives" Eur. J. Org. Chem. **2019**, 2019, 3127-3133.
3. S. S. Shinde, **N. S. Khonde**, Pradeep Kumar, "Tri–tert-Butanolamine as an Organic Promoter in Nucleophilic Fluorination" ChemistrySelect **2017**, 2, 118-122.
4. **N. S. Khonde**, M. S. Said, R. Udavant, Pradeep Kumar, "Organocatalytic Route to the Enantioselective Synthesis of syn/anti-1,3-Fluoro Amines" Manuscript under preparation

## List of publication(s) in SCI Journal(s) (published & accepted) other than thesis

1. M. S. Said, **N. S. Khonde**, M. N. Thorat, R. S. Atapalkar, A. A. Kulkarni, J. M. Gajbhiye, S. G. Dastager, "A New TBAF Complex, Highly Stable, Facile and Selective Source for Nucleophilic Fluorination: Application in Batch and Flow Chemistry*" Asian J. Org. Chem*. **2020**, *9*, 1022-1026.
2. M. S. Said, G. R. Navale, A. Yadav, **N. S. Khonde**, S. S. Shinde, A. Jha, "Effect of *tert*-alcohol functional imidazolium salts on oligomerization and fibrillization of amyloid β (1–42) peptide" *Biophys. Chem*, **2020**, *267*, 106480.

## List of Poster Presented with Details

1. National Science Day Poster presentation at CSIR-National Chemical Laboratory, Pune (February 25-27, **2017**):

**Title:** Tri–*tert*-Butanolamine as an Organic Promoter in Nucleophilic Fluorination

**Abstract:** Tri-*tert*-butanol amine acts as promoter with alkali metal salts in the nucleophilic fluorination of alkylsulfonates. It significantly enhances the reactivity of alkali metal salts with minimum formation of side-products (alkene, ether, and alcohol) compared to other catalysts in fluorination reaction. The synergism of *tert*-alcohol and amine moiety plays a pivotal role in fluorination.

ChemPubSoc Europe

DOI: 10.1002/ejoc.201900370

EurJOC European Journal of Organic Chemistry

Full Paper

Synthetic Methodology

# $Tf_2NH$ catalyzed 1,6-conjugate addition of 2-hydroxy-*p*-quinone methides with $\beta$-Functionalized Ketones: Access to 2,3,4,9-Tetrahydro-1*H*-xanthenones and 4*H*-Chromene Derivatives

Shruti Satbhaiya,[a] Nilesh S. Khonde,[a,b] Jayant Rathod,[a,b] Rajesh Gonnade,[b,c] and Pradeep Kumar*[a,b]

**Abstract:** A Brönsted acid catalyzed tandem 1,6-conjugate sequential cycloaddition reaction using 2-hydroxy-*p*-quinone methides and $\beta$-functionalized ketones is reported. The method allows xanthenones and chromenes to be accessed in moderate to excellent yield with broad substrate scope, which could be further functionalized to give a versatile set of products.

## Introduction

In a valuable class of oxygen-containing heterocyclic molecules, xanthenes and xanthenones[1] have attracted much attention from natural product chemistry, medicinal chemistry and synthetic organic chemistry. Xanthene scaffold is widely found in many fluorescent dyes[2] and biologically active scaffolds.[3] In addition to fully unsaturated xanthenes and xanthenones, partially saturated compounds such as 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones have fascinated a great deal of interest. Naturally occurring tetrahydroxanthenones exhibit antibacterial, antifungal properties. For instance, blennolides A and B, isolated from the endophytic fungus *Blennoria* sp.[4] showed algicidal activities (Figure 1).

Consequently, several synthetic approaches toward the synthesis of 2,3,4,4a-tetrahydro-1*H*- xanthene-1-one[5] unit have been explored. In contrast, only a few methods are available for the direct synthesis of 2,3,4,9-tetrahydro-1*H*-xanthene-1-one.

Chromene moiety forms the core structure of biologically active molecules such as enzyme inhibitors against a variety of targets.[6] 4*H*-Chromenes have attracted much attention from medicinal chemistry due to their cytotoxic anticancer,[7] neuroprotective,[8] antimicrobial,[9] antifungal[10]and antioxidant activity.[11] Chromene derivatives are present in large amounts in the human diet due to their low mammalian toxicity.[12] For the synthesis of chromenes, many classical methods have been developed based on 1,4-reduction of pyrylium ions[13] or the addition of phenol nucleophiles to benzopyrylium salts.[14]

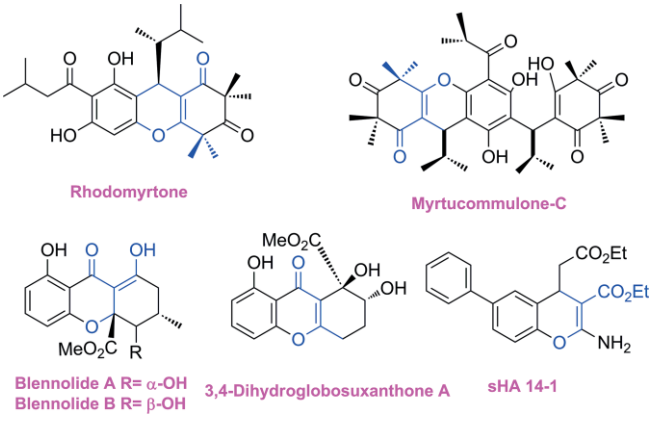



Figure 1. Selected biologically active natural products with tetrahydroxanthenone and 4*H*-chromene core.

In recent years, the *p*-quinone methides (*p*-QMs) have aroused great interest in the synthetic community due to their unique reactivity as powerful Michael acceptors with a variety of nucleophiles [15] and ability to make complex architectures that are found in several pharmaceuticals and natural products.[16] Structurally, *p*-QMs are regarded as neutral molecules with zwitterionic resonance entities.[17] The *p*-QMs have the ability to undergo several reaction modes [4+2]-annulations,[18] [3+2]-annualtion,[19] and [2+1]-annulations.[20] Due to the aromatization driving force of the cyclohexadiene moiety, *p*-QMs have been widely employed as 1,6-addition acceptors.[21] *p*-QMs serve as an important intermediate in biosynthetic transformations, although this strategy would provide an efficient method for constructing cyclic scaffolds.

Until very recently in 2017, Jiang and co-workers[22] elegantly showed the silver/scandium-co-catalyzed bicyclization of $\beta$-alkynyl ketones and *p*-QMs. Recently, our own group has developed acid-catalyzed 1,6-conjugate addition reaction of *p*-QMs with vinyl azide and butenolides.[23] In addition, we also reported the synthesis of diarylmethine-substituted enones

[a] *Division of Organic chemistry, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune-411008, India*
*E-mail: pk.tripathi@ncl.res.in*
*http://academic.ncl.res.in/pk.tripathi*
[b] *Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India*
[c] *Physical and Material Chemistry Division, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune-411008, India*

*Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201900370.*

through gold catalyzed reaction of allenol ester with *p*-QMs.[24] Despite these elegant approaches, interest in conjugate addition using *p*-QM derivatives as building blocks still continues unabated.

As a part of our ongoing research program on the reactivity of *p*-QMs for conjugate addition reaction, we envisioned that acid catalyzed 1,6-conjugate addition and subsequent cycloaddition reactions of 2-hydroxy-*p*-QMs and $\beta$-functionalized cyclic ketones would not only fulfil the task of developing cyclization reactions of *p*-QMs but also provide easy access to xanthenones and chromenes molecules. We hereby wish to report our recent findings on the conjugate addition of *p*-QM derivatives to access the diverse range of xanthenone and chromene related compounds.

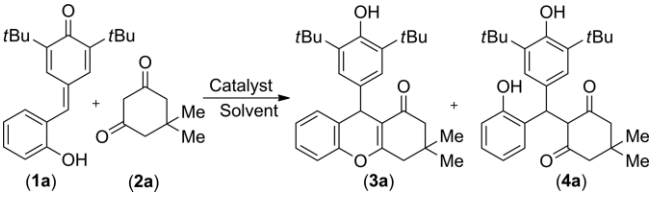
## Results and Discussion

To exploit 1,6-conjugate addition reaction, we started our preliminary investigation with the reaction of 2-hydroxy-*p*-QM **(1a)** and dimedone **(2a)** as a model substrate. Table 1 summarizes the effect of several parameters on this reaction. All the commercially available catalysts and reagents were used as received. An initial experiment was conducted with **1a** and **2a** in the presence of $BF_3{\cdot}OEt_2$ as a catalyst in $CH_2Cl_2$ solvent at room temperature. Gratifyingly, the desired product **3a** was isolated in 48 % yield (Table 1, entry 1).

Encouraged by this initial result, we next screened various Lewis and Brönsted acid catalysts, such as $Bi(OTf)_3$, $BiCl_3$, $Sc(OTf)_3$, AgOTf, $Cu(OTf)_2$, $Tf_2NH$, PTSA (Table 1, entries 3–9) to define the best catalyst for this reaction. Among the above catalysts examined, $Tf_2NH$ was found to be the most effective one to give the desired product in 72 % yield (Table 1, entry 8). The reaction conditions were further optimized by varying solvents such as THF, $CH_3CN$ and DCE (Table 1, entries 10–12), and the results revealed that DCE was superior (Table 1, entry 12), to other solvents. In order to optimize the reaction conditions, the reaction was performed at a higher temperature like 40 °C, but the yield dropped to 23 % (Table 1, entry 13). The reason for low yield may be attributed to the increase in reaction temperature. This could result into the acceleration of self-decomposition of desired cyclized product **3a** and we thus obtained **4a** in 52 % yield. As the reaction led to the formation of product **3a** in a nearly racemic form, we considered attempting an asymmetric version of the same reaction. To this end we tested chiral phosphoric acids containing bulky groups on the BINOL backbone at 0 °C, but unfortunately, we observed only **4a** as a product (Table 1, entries 14–17). This could probably be attributed to the inefficiency of catalyst to cycloaddition reaction. For sequential cycloaddition reaction we added $Tf_2NH$ and $Sc(OTf)_3$ (Table 1, entries 18–19) with various chiral phosphoric acid, we obtained the desired product **(3a)** in 85 % and 82 % respectively in racemic form only. When the reaction was carried out at room temperature, it was complete within 5 minutes as confirmed by TLC.

As per the literature precedence, we further examined the effect of catalyst loading and it was found that 10 mol-% of $Tf_2NH$ was suitable for this transformation affording the desired

Table 1. Optimization studies for the synthesis of 2,3,4,9-tetrahydro-*1H*-xanthene-1-one.[a]




| Entry | Catalyst | Solvent | Temp. | Time | % Yield [b] | |
|---|---|---|---|---|---|---|
| | | | | | **3a** | **4a** |
| 1 | $BF_3{\cdot}OEt_2$ | DCM | r.t. | 5 min | 48 | ND |
| 2 | [c]$BF_3{\cdot}OEt_2$ | DCM | r.t. | 5 min | 32 | ND |
| 3 | $Bi(OTf)_3$ | DCM | r.t. | 5 min | ca. 37 | ND |
| 4 | $BiCl_3$ | DCM | r.t. | 5 min | ND | ND |
| 5 | $Sc(OTf)_3$ | DCM | r.t. | 10 min | 25 | ND |
| 6 | AgOTf | DCM | r.t. | 15 min | 35 | ND |
| 7 | $Cu(OTf)_2$ | DCM | r.t. | 4 h | ND | ND |
| 8 | $Tf_2NH$ | DCM | r.t. | 5 min | 72 | ND |
| 9 | PTSA | DCM | r.t. | 10 min | 51 | ND |
| 10 | $Tf_2NH$ | THF | r.t. | 15 min | 43 | ND |
| 11 | $Tf_2NH$ | $CH_3CN$ | r.t. | 5 h | ND | ND |
| **12** | **$Tf_2NH$** | **DCE** | **r.t.** | **5 min** | **89** | **ND** |
| 13 | $Tf_2NH$ | DCE | 40 °C | 5 min | 23 | 52 |
| 14 | BH*a | DCE | 0 °C | 18 h | ND | 68 |
| 15 | BH*b | DCE | 20 °C | 12 h | ND | 80 |
| 16 | BH*c | DCE | 0 °C | 14 h | ND | 62 |
| 17 | BH*d | DCE | 0 °C | 13 h | ND | 71 |
| 18 | [d]BH*a/$Tf_2NH$ | DCE | 0 °C/r.t. | 12 h/5 min | 85 | [e] |
| 19 | [d]BH*a/$Sc(OTf)_3$ | DCE | 0 °C/r.t. | 12 h/15 min | 82 | [e] |
| 20 | – | DCE | r.t. | 24 h | NR | |

[a] 0.1 mmol**1a**, 0.69 equiv. **2a**, 10 mol-% catalyst, 5 mol-% unless otherwise stated and 1 mL of solvent. [b] Isolated yield. [c] 0.1 mmol **1a**, 1 equiv. **2a**, BH*= Appropriate chiral phosphoric acid (for the structure of BH*, see the SI). [d] The reaction was first stirred with BINOL hydrogen phosphate for 12 h and followed by addition of acid. [e] Firstly, the compound **4a** was formed, in situ addition of $Tf_2NH$ or $Sc(OTf)_3$ after 12 h, **3a** was obtained within 5–10 min, NR= no reaction, ND = Not detected.

product in excellent yield (Table 1, entry 12). No product formation was observed in the absence of any acidic catalyst (Table 1. entry 20), which clearly indicates that $Tf_2NH$ is actually acting as a catalyst for this transformation. (Table 1, entry 12).

Having optimized the reaction conditions, the scope and limitations of this transformation were examined using a wide range of 2-hydroxy substituted *p*-QMs **(1a-h)** and $\beta$-functionalized ketones **(2a-d)** (Figure 2). 2-Hydroxy-substituted-*p*-QMs **(1a–h),** containing various substitutions, were screened. Both electron-withdrawing (F, Cl) and electron-donating substituents (Me, OMe) present on *p*-QMs were compatible under the developed reaction conditions affording moderate to excellent yields of the product **3**.

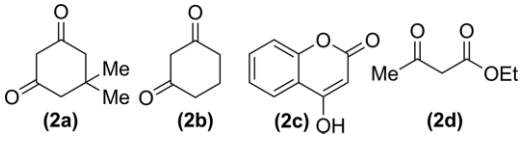
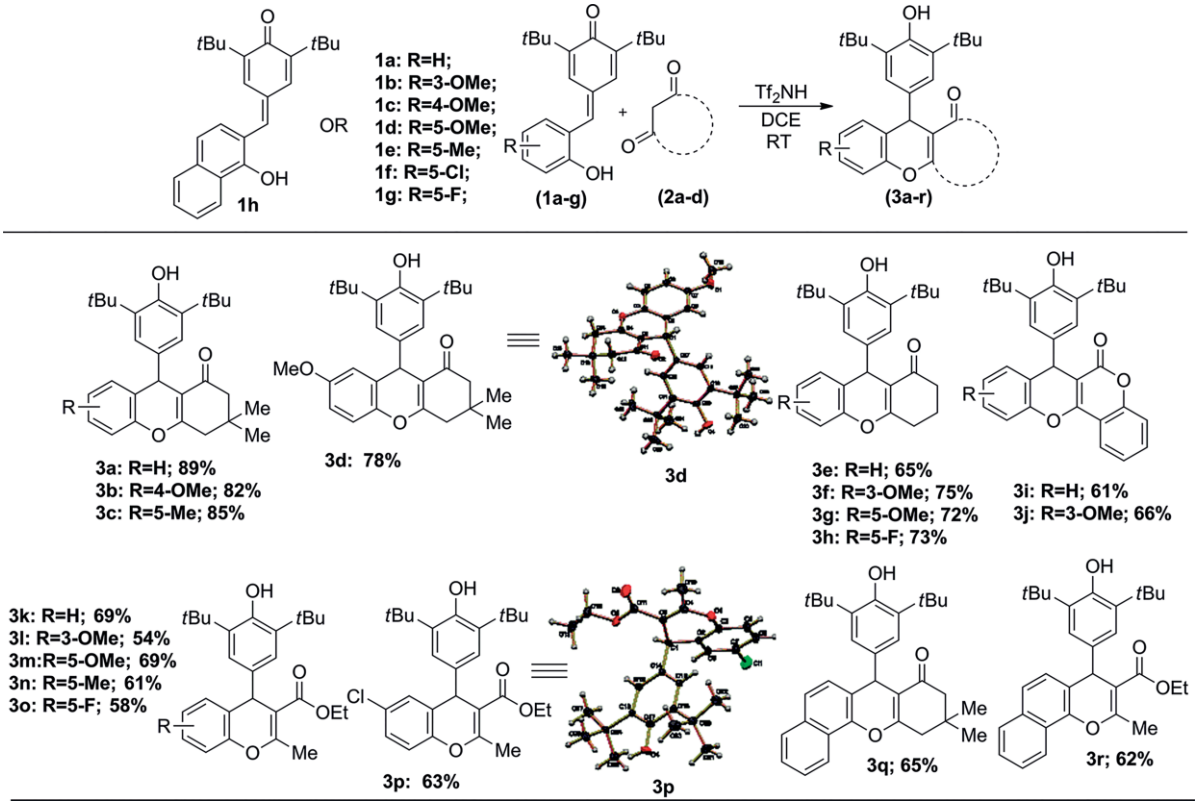



Figure 2. Scope for $\beta$-functionalized ketones.

As shown in Table 2, $\beta$-functionalized ketone,dimedone **2a** reacted smoothly with various 2-hydroxy-*p*-QMs **1a, 1c**–**1e,** to give the xanthenone product **(3a-d)** in excellent yields. Simi-

Table 2. Scope of 1,6-conjugate addition of 2-hydroxy-*p*-QMs, with various $\beta$-functionalized ketones.

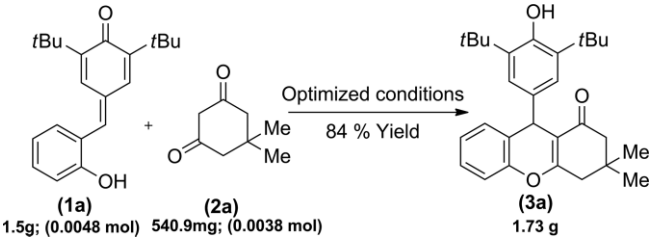



larly, cyclohexane-1,3-dione **2b** on reaction with *p*-QMs containing an electron donating substituents such as methoxy and electron withdrawing e.g. fluoro furnished the desired product **3e–h** in 65–75 % yields. Interestingly, $\beta$-functionalized ketones, chromenone **2c** also underwent smooth cycloaddition reaction with *p*-QMs **1a–b** affording chromenone derivatives **(3i–j)** in reasonably good yield. This prompted us to investigate the scope of this reaction with acyclic $\beta$-functionalized ketone. Towards this aim, ethyl acetoacetate **2d** was used as substrate in sequential cycloaddition reaction with various 2-hydroxy-*p*-QMs. To our delight, the reaction worked smoothly giving rise the desired chromene derivatives **(3k–3p)** in 54–69 % yields. The structures of products **3d** and **3p** were further confirmed by single-crystal X-ray analysis (Table 2, See the supporting information).

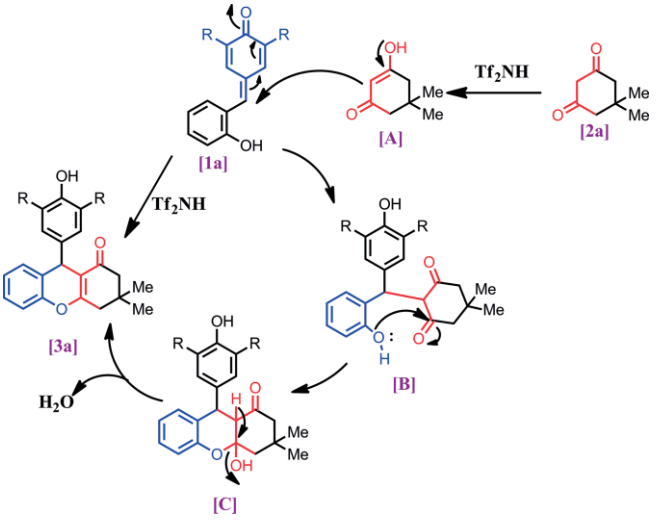
Moreover, 2-hydroxy-*p*-quinone methides with the fused aromatic such as 2-naphthyl were also quite amenable under the optimized conditions. Thus, when naphthyl-substituted 2-hydroxy-*p*-QM **1h** was treated with $\beta$-functionalized ketones such as dimedone **2a** and ethyl acetoacetate **2d**, it gave the corresponding xanthenone **3q** and chromene-2-carboxylate **3r** in 65 % and 62 % yield respectively.

Further to extend the substrate scope and test the synthetic utility of our method, **3a** was prepared on a gram scale. As shown in Scheme 1, the desired product **3a** was obtained in 84 % yield under optimized reaction condition.

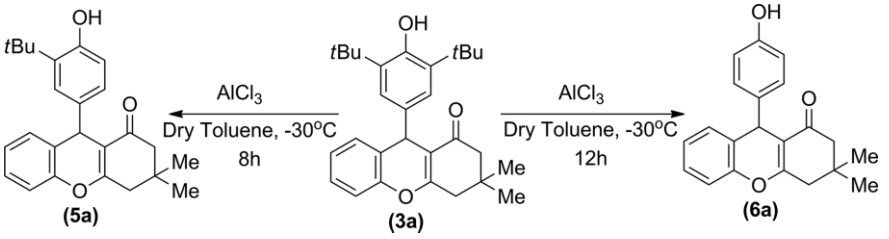
A plausible reaction mechanism for the 1,6-conjugate addition of 2-hydroxy-*p*-QM with $\beta$-functionalized ketone is depicted in Scheme 2. 2-Hydroxy-*p*-QM is activated by Brönsted




Scheme 1. Gram scale synthesis of **3a**.




Scheme 2. A plausible mechanism for the formation of 2,3,4,9-tetrahydro-1*H*-xanthene-1-one.




Scheme 3. De-*tert*-butylation of 2,3,4,9-tetrahydro-1*H*-xanthene-1-one.

acid $Tf_2NH$; followed by attack of activated dimedone [A] resulted in the intermediate [B]. Subsequently, the intramolecular oxa-nucleophilic addition affords the intermediate [C], which loses a water molecule to eventually furnish the final product **3a.**

As shown in Scheme 3, some useful transformations of this process were also presented. Treatment of **3a** with anhydrous $AlCl_3$ on –30 °C in dry toluene afforded de-*tert*-butylated **5a** and **6a** in 79 % and 63 % yield respectively. The compound **6a** represents a privileged pharmaceutically active and naturally occurring structural motif.

## Conclusions

In conclusion, we have successfully developed a $Tf_2NH$ catalyzed 1,6-conjugate addition of $\beta$-functionalized ketone with various 2-hydroxy-*p*-QMs leading to the synthesis of xanthenone and chromene derivatives. This transformation occurs at mild conditions and is tolerant to a variety of functional groups. The Brönsted acid is found to play a crucial role for activating both the reacting substrates. In addition, this protocol demonstrates the great practicability of utilizing *p*-QMs in domino reactions.

## Experimental Section

Reactions were carried out under anhydrous conditions, using flame-dried glassware under a positive pressure of argon, unless otherwise stated. 1,2-Dichloroethane, $CH_2Cl_2$, $Et_3N$, and piperidine were distilled from $CaH_2$. $Et_2O$, toluene and THF were distilled from Na/benzophenone. Other reagents were obtained from commercial suppliers and used as received. 2-Hydroxy-*p*-quinone methides was prepared following the literature procedures (for procedure see SI). Air-sensitive reagents and solutions were transferred by syringe or cannula and were introduced into the apparatus through rubber septa. Reactions were monitored by thin-layer chromatography (TLC) with 0.25 mm pre-coated silica-gel plates (60 F254). Plates were visualized with either UV light, iodine adsorbed on silica gel, or by immersion in an ethanolic solution of phosphomolybdic acid (PMA), *p*-anisaldehyde, or $KMnO_4$, followed by heating with a heat gun for ca. 15 s. Flash chromatography was carried out on silica gel (230–400 mesh). $^1H$ and $^{13}C$ NMR spectra were obtained with a 200, 400, or 500 MHz Bruker/JEOL spectrometer in $CDCl_3$. Coupling constants are given in Hertz. Chemical shifts are quoted in ppm relative to tetramethylsilane, using the residual solvent peak as a reference standard. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, *t* = triplet, q = quartet, quint = quintet, m = multiplet and br. = broad. HRMS ($ESI^+$) spectra were recorded with an ORBITRAP mass analyzer. Infrared (IR) spectra were recorded with a FTIR spectrometer as thin films using NaCl plates, and wavenumbers are indicated in $cm^{-1}$. Chemical nomenclature was generated using ChemBioDraw Ultra 15.0. CCDC 1881335 (for **3d**), and 1881316 (for **3p**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

**General Procedure for the synthesis of 2,3,4,9-tetrahydro-1*H*-xanthene-1-one:**2-Hydroxy-*p*-quinone methide**1(a–h)** (0.030–0.055 mmol, 15 mg, 1 equiv.), $\beta$-functionalized ketones**2(a-d)** (0.8 equiv.) in 1 mL of DCE were taken into the oven dried 5 mL reaction vials with a magnetic bar. Then, 10 mol-% trifilamide ($Tf_2NH$) dissolved in 0.5 mL of DCE was added dropwise, and the reaction mixture stirred at room temperature for 5 min. The completion of the reaction was confirmed by the thin layer chromatography using pet ether/ethyl acetate solvent system. After the completion of the reaction, the reaction mass was concentrated under the high vacuum, and the crude product was purified by column chromatography on silica gel 100–200 mesh to obtain the product.

**9-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (3a):** Compound **3a** was prepared using 2-hydroxy-*p*-QM **1a** and $\beta$-functionalized ketone (dimedone) **2a** following general procedure. After column purification the product was obtained as white solid in 89 % yield. mp = 134–136 °C; $R_f$ = 0.77 (pet ether/ethyl acetate, 5:1); IR ($CHCl_3$):$\tilde{\nu}_{max}$ = 3636, 2958, 1724, 1643, 1591, 1434, 1375, 1304, 1231, 1153, 1119, 1024, 889, 757 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ = 7.16 (br. s, 2 H), 7.06 (d, *J* = 7.3 Hz, 2 H), 7.00 (s, 2 H), 4.99 (s, 1 H), 4.94 (br. s, 1 H), 2.57 (br. s, 2 H), 2.27 (d, *J* = 5.5 Hz, 2 H), 1.37 (s, 18 H), 1.14 (br. s, 3 H), 1.09 (br. s, 3 H);$^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 196.9, 164.8, 152.2, 149.6, 136.8, 135.5, 129.9, 127.2, 126.3, 124.9, 124.0, 116.4, 114.0, 50.8, 41.6, 37.5, 34.2, 32.1, 30.3, 29.6, 27.1; HRMS ($ESI^+$) *m/z* = calcd. for $C_{29}H_{36}O_3$ $[M + Na]^+$ 455.2562, found 455.2557.

**9-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-6-methoxy-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (3b):** Compound **3b** was prepared using 4-OMe substituted 2-hydroxy-*p*-QM **1c** and $\beta$-functionalized ketone (dimedone) **2a** following general procedure. After column purification the product was obtained as orange thick liquid in 82 % yield. $R_f$ = 0.60 (pet. ether/ethyl acetate, 5:1); IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3633, 3352, 2959, 2926, 2873, 1648, 1602, 1504, 1462, 1436, 1373, 1283, 1218, 1159, 1115, 1033, 757 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.05 (d, *J* = 8.2 Hz, 1 H), 6.98 (s, 2 H), 6.67–6.57 (m, 2 H), 4.98 (s, 1 H), 4.87 (s, 1 H), 3.79 (s, 3 H), 2.55 (s, 2 H), 2.27 (d, *J* = 6.4 Hz, 2 H), 1.37 (s, 19 H), 1.14 (s, 3 H), 1.08 (s, 3 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ = 196.9, 164.5, 158.7, 152.1, 150.1, 137.1, 135.4, 130.4, 123.9, 118.5, 114.3, 111.5, 101.4, 55.4, 50.8, 41.6, 36.9, 34.2, 32.1, 30.3, 29.6, 27.1; HRMS ($ESI^+$) *m/z* = calcd. for $C_{30}H_{38}O_4$ $[M + Na]^+$ 485.2668, found 485.2663.

**9-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3,3,7-trimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (3c):** Compound **3d** was prepared using 5-Me substituted 2-hydroxy-*p*-QM **1e** and $\beta$-functionalized ketone (dimedone) **2a** following general procedure. After column

purification the product was obtained as orange thick liquid in 85 % yield. $R_f$ = 0.47 (pet. ether/ethyl acetate, 5:1); IR ($CHCl_3$):$\tilde{\nu}_{max}$ = 3631, 3382, 2959, 2873, 1702, 1648, 1594, 1489, 1460, 1433, 1375, 1307, 1209, 1154, 1121, 1070, 1032 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ = 7.00 (s, 2 H), 6.95 (s, 3 H), 5.00 (s, 1 H), 4.88 (s, 1 H), 2.56–2.53 (m, 2 H), 2.28–2.24 (m, 5 H), 1.37 (s, 19 H), 1.13 (s, 3 H), 1.07 (s, 3 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ = 196.8, 164.9, 152.1, 147.6, 136.9, 135.4, 134.4, 130.0, 127.9, 125.9, 124.1, 116.1, 114.1, 77.3, 76.7, 50.8, 41.6, 37.6, 34.2, 32.1, 30.3, 29.6, 27.0, 20.8; HRMS (ESI$^+$) *m/z* = calcd. for $C_{30}H_{38}O_3$ [M + Na]$^+$ 469.2719, found 469.2715.

**9-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-7-methoxy 3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (3d):** Compound **3c** was prepared using 5-OMe substituted 2-hydroxy-*p*-QM **1d** and $\beta$-functionalized ketone (dimedone) **2a** following general procedure. After column purification the product was obtained as colourless solid in 78 % yield. mp= 121–123 °C; $R_f$ = 0.70 (pet. ether/ethyl acetate, 5:1); IR ($CHCl_3$):$\tilde{\nu}_{max}$ = 3636, 3451, 2958, 2875, 1640, 1594, 1492, 1462, 1433, 1377, 1323, 1286, 1219, 1150, 1118, 1031, 886, 818, 757 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ = 7.02–6.97 (m, 3 H), 6.73–6.65 (m, 2 H), 5.00 (s, 1 H), 4.89 (s, 1 H), 3.74 (s, 3 H), 2.61–2.49 (m, 2 H), 2.32–2.21 (m, 2 H), 1.37 (s, 19 H), 1.13 (s, 3 H), 1.08 (s, 3 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ = 196.9, 165.1, 156.5, 152.3, 143.8, 136.7, 135.6, 127.3, 124.0, 117.2, 114.1, 113.4, 113.1, 77.4, 77.1, 76.8, 55.6, 50.9, 41.7, 38.1, 34.3, 32.2, 30.4, 29.8, 27.1; HRMS (ESI$^+$) *m/z* = calcd. for $C_{30}H_{38}O_4$ [M + Na]$^+$ 485.2668, found 485.2662.

**9-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (3e**): Compound **3e** was prepared using 2-hydroxy-*p*-QM **1a** and $\beta$-functionalized ketone (cyclohexane-1,3-dione) **2b** following general procedure. After column purification the product was obtained as colourless solid in 65 % yield. mp= 198–200 °C; $R_f$ = 0.40 (pet ether/ethyl acetate, 5:1); IR ($CHCl_3$):$\tilde{\nu}_{max}$ = 3777, 3635, 3543, 2957, 1724, 1644, 1582, 1472, 1439, 1375, 1309, 1232, 1177, 1128, 1061, 994, 921, 861, 756, 652 $^{cm-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 7.21–7.15 (m, 2 H), 7.10–7.04 (m, 2 H), 7.00 (s, 2 H), 5.02 (s, 1 H), 5.01 (s, 1 H), 2.72 (t, *J* = 5.0 Hz, 2 H), 2.46 (t, *J* = 5.0 Hz, 2 H), 2.12–2.01 (m, 2 H), 1.37 (s, 18 H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ = 197.0, 166.5, 152.2, 149.8, 136.6, 135.4, 129.8, 127.2, 126.3, 124.9, 124.2, 116.3, 115.3, 37.1, 37.1, 34.2, 30.3, 27.9, 20.4; HRMS (ESI$^+$) *m/z* = calcd. for $C_{27}H_{32}O_3$ [M + Na]$^+$ 427.2249, found 427.2244.

**9-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-5-methoxy-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (3f):** Compound **3f** was prepared using 3-OMe substituted 2-hydroxy-*p*-QM **1b** and $\beta$-functionalized ketone (cyclohexane-1,3-dione) **2b** following general procedure. After column purification the product was obtained as colourless solid in 75 % yield. m.p. 224–226 °C; $R_f$ = 0.40 (pet. ether/ethyl acetate, 5:1); IR ($CHCl_3$):$\tilde{\nu}_{max}$ = 3782, 3635, 3451, 2956, 1732, 1643, 1611, 1584, 1479, 1434, 1377, 1324, 1274, 1224, 1183, 1126, 1091, 957, 893, 752 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ = 7.03–6.97 (m, 3 H), 6.78 (t, *J* = 8.2 Hz, 2 H), 5.05–4.98 (m, 2 H), 3.92 (s, 3 H), 2.83 (t, *J* = 4.9 Hz, 2 H), 2.52–2.36 (m, 2 H), 2.14–2.03 (m, 2 H), 1.37 (s, 18 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ= 197.1, 166.4, 152.2, 147.7, 139.3, 136.3, 135.4, 127.4, 124.6, 124.1, 121.4, 115.0, 109.6, 77.3, 76.7, 56.1, 37.2, 37.1, 34.3, 30.3, 27.9, 20.5; HRMS (ESI$^+$) *m/z* = calcd. for $C_{28}H_{34}O_4$ [M + Na]$^+$ 457.2355, found 457.2347.

**9-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-7-methoxy-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (3g):** Compound **3g** was prepared using 5-OMe substituted 2-hydroxy-*p*-QM **1d** and $\beta$-functionalized ketone (cyclohexane-1,3-dione) **2b** following general procedure. After column purification the product was obtained as colourless solid in 72 % yield. m.p. 197–199 °C; $R_f$ = 0.29 (pet. ether/ethyl acetate, 5:1); IR ($CHCl_3$):$\tilde{\nu}_{max}$ = 3636, 3417, 2956, 2333, 1721, 1637, 1594, 1492, 1459, 1432, 1377, 1324, 1221, 1192, 1124, 1035, 997, 885, 815, 756 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ = 7.03–6.98 (m, 3 H), 6.69 (s, 2 H), 5.00 (s, 1 H), 4.97 (s, 1 H), 3.74 (s, 3 H), 2.70 (t, *J* = 4.9 Hz, 2 H), 2.49–2.35 (m, 2 H), 2.15–2.03 (m, 2 H), 1.38 (s, 18 H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 197.0, 166.7, 156.5, 152.2, 144.0, 136.5, 135.4, 127.1, 124.1, 117.1, 114.5, 113.8, 113.2, 77.3, 76.7, 55.6, 37.6, 37.1, 34.3, 30.3, 27.9, 20.5; HRMS (ESI$^+$) *m/z* = calcd. for $C_{28}H_{34}O_4$ [M + Na]$^+$ 457.2355, found 457.2349.

**9-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-7-fluoro-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (3h):** Compound **3h** was prepared using 5-flouro substituted 2-hydroxy-*p*-QM **1g** and $\beta$-functionalized ketone (cyclohexane-1,3-dione) **2b** following general procedure. After column purification the product was obtained as colourless solid in 73 % yield. m.p. 213–215 °C; $R_f$ = 0.56 (pet. ether/ethyl acetate, 5:1); IR ($CHCl_3$):$\tilde{\nu}_{max}$ = 3631, 3552, 2957, 2923, 2871, 1647, 1593, 1489, 1432, 1377, 1253, 1220, 1191, 1131, 1060, 999, 889, 863, 813, 760 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ= 7.07–6.97 (m, 3 H), 6.91–6.82 (m, 2 H), 5.04 (s, 1 H), 4.96 (s, 1 H), 2.71 (t, *J* = 4.9 Hz, 2 H), 2.50–2.34 (m, 2 H), 2.13–2.01 (m, 2 H), 1.38 (s, 18 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ= 196.9, 166.3, 152.4, 136.1, 135.6, 127.9, 124.1, 117.6, 117.5, 115.9, 115.7, 114.4, 114.2, 77.3, 76.7, 37.6, 37.0, 34.3, 30.3, 27.8, 20.4; HRMS (ESI$^+$) *m/z* = calcd. for $C_{27}H_{31}FO_3$ [M + Na]$^+$ 445.2155, found 445.2147.

**7-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-6*H*,7*H*-chromeno[4,3-b]-chromen-6-one (3i):** Compound **3i** was prepared using 2-hydroxy-*p*-QM **1a** and $\beta$-functionalized ketone (chromenone) **2c** following general procedure. After column purification the product was obtained as pale-yellow solid in 61 % yield. m.p. 223–225 °C; $R_f$ = 0.41 (pet. ether/ethyl acetate, 4:1); **IR ($CHCl_3$):$\tilde{\nu}_{max}$ =** 3636, 2958, 2923, 2870, 1716, 1643, 1609, 1581, 1485, 1387, 1320, 1275, 1237, 1214, 1182, 1155, 1110, 1043, 757. $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ= 8.00 (br. s, 1 H), 7.50 (br. s, 1 H), 7.32 (br. s, 4 H), 7.21 (d, *J* = 7.6 Hz, 2 H), 7.13 (br. s, 1 H), 7.02 (br. s, 2 H), 5.17 (br. s, 1 H), 5.02 (br. s, 1 H), 1.30 (br. s, 18 H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ= 165.3, 161.8, 155.5, 152.6, 152.5, 149.6, 135.6, 135.2, 131.8, 130.1, 128.0, 125.7, 124.8, 124.1, 122.7, 116.7, 116.5, 114.8, 105.4, 38.8, 34.2, 30.2; HRMS (ESI$^+$) *m/z* = calcd. for $C_{30}H_{30}O_4$ [M + Na]$^+$ 477.2042, found 477.2036.

**7-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-11-methoxy-6*H*,7*H*-chromeno[4,3-b]chromen-6-one (3j):** Compound **3j** was prepared using 3-methoxy substituted 2-hydroxy-*p*-QM **1b** and $\beta$-functionalized ketone (chromenone) **2c** following general procedure. After column purification the product was obtained as colourless solid in 66 % yield. mp= 131–134 °C; $R_f$ = 0.57 (pet. ether/ethyl acetate, 4:1); IR ($CHCl_3$):$\tilde{\nu}_{max}$ = 3634, 3376, 2958, 2926, 2357, 1690, 1618, 1571, 1477, 1436, 1359, 1274, 1215, 1159, 1111, 1077, 1042, 947, 884, 758 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ= 7.76 (d, *J* = 7.6 Hz, 1 H), 7.53–7.49 (m, 1 H), 7.31 (d, *J* = 8.0 Hz, 1 H), 7.22 (s, 1 H), 7.07 (s, 2 H), 6.89–6.84 (m, 3 H), 6.05 (s, 1 H), 5.19 (s, 1 H), 3.90 (s, 3 H), 1.36 (s, 18 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ= 163.4, 160.5, 153.0, 152.6, 146.8, 143.3, 136.5, 131.6, 128.7, 126.8, 124.8, 123.7, 123.2, 122.2, 120.3, 116.4, 116.3, 110.0, 107.1, 106.9, 56.2, 42.3, 34.4, 30.2; HRMS (ESI$^+$) *m/z* = calcd. for $C_{31}H_{32}O_5$ [M + Na]$^+$ 507.2147, found 507.2142.

**Ethyl 4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-methyl-4*H*-chromene-3-carboxylate (3k):** Compound **3k** was prepared using 2-hydroxy-*p*-QM **1a** and $\beta$-functionalized ketone (ethyl acetoacetate) **2d** following general procedure. After column purification the product was obtained as yellow solid in 69 % yield. mp= 137–139 °C; $R_f$= 0.75 (pet. ether/ethyl acetate, 5:1); IR ($CHCl_3$):$\tilde{\nu}_{max}$ = 3637, 3454, 2959, 2924, 1707, 1640, 1585, 1484, 1434, 1373, 1331, 1287, 1218, 1157, 1108, 1064, 9866, 936, 895, 756 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ = 7.15–7.09 (m, 2 H), 7.02 (d, *J* = 8.3 Hz, 2 H), 6.97 (s, 2 H), 5.01 (s, 1 H), 4.94 (s, 1 H), 4.16–4.08 (m, 2 H), 2.48 (s, 3 H), 1.37 (s, 18 H), 1.20 (t, *J* = 7.1 Hz, 3 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ = 167.4,

160.0, 152.2, 149.8, 137.3, 135.5, 129.1, 127.2, 125.6, 124.4, 124.2, 116.0, 106.9, 60.0, 41.1, 34.2, 30.3, 19.4, 14.2; HRMS (ESI$^+$) $m/z$ = calcd. for $C_{27}H_{34}O_4$ [M + Na]$^+$ 445.2355, found 445.2353.

**Ethyl 4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-8-methoxy-2-methyl-4*H*-chromene-3-carboxylate (3l):** Compound **3l** was prepared using 3-methoxy substituted 2-hydroxy-*p*-QM **1b** and $\beta$-functionalized ketone (ethyl acetoacetate) **2d** following general procedure. After column purification the product was obtained as yellow solid in 54 % yield. m.p. 121–123 °C; $R_f$ = 0.55 (pet. ether/ethyl acetate, 5:1); IR ($CHCl_3$):$\tilde{\nu}_{max}$ = 3636, 2959, 1705, 1643, 1612, 1586, 1482, 1435, 1371, 1329, 1275, 1237, 1200, 1162, 1097, 1064, 1018, 990, 963, 756 cm$^{-1}$;$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 6.99 (s, 2 H), 6.95 (t, $J$ = 7.9 Hz, 1 H), 6.76–6.70 (m, 2 H), 5.01 (s, 1 H), 4.94 (s, 1 H), 4.11 (t, $J$ = 7.3 Hz, 2 H), 3.91 (s, 3 H), 2.55 (s, 3 H), 1.38 (s, 18 H), 1.19 (t, $J$ = 7.3 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 167.3, 159.8, 152.2, 147.5, 139.4, 137.1, 135.4, 126.6, 124.2, 124.0, 120.7, 109.6, 106.8, 60.0, 56.1, 41.2, 34.2, 30.3, 19.4, 14.2; HRMS (ESI$^+$) $m/z$ = calcd. for $C_{28}H_{36}O_5$ [M + Na]$^+$ 475.2460, found 475.2455.

**Ethyl 4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-6-methoxy-2-methyl-4*H*-chromene-3-carboxylate (3m):** Compound **3m** was prepared using 5- methoxy substituted 2-hydroxy-*p*-QM **1d** and $\beta$-functionalized ketone (ethyl acetoacetate) **2d** following general procedure. After column purification the product was obtained as yellow solid in 69 % yield. m.p. 197–199 °C; $R_f$ = 0.67 (pet. ether/ethyl acetate, 5:1); IR ($CHCl_3$):$\tilde{\nu}_{max}$ = 3022, 2925, 2402, 1593, 1425, 1215, 1021, 759, 668 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.00–6.94 (m, 3 H), 6.73–6.68 (m, 1 H), 6.61 (d, $J$ = 3.1 Hz, 1 H), 5.02 (s, 1 H), 4.90 (s, 1 H), 4.16–4.07 (m, 2 H), 3.73 (s, 3 H), 2.47 (s, 3 H), 1.38 (s, 18 H), 1.20 (t, $J$ = 7.0 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 167.5, 160.4, 156.1, 152.2, 144.1, 137.2, 135.4, 126.5, 124.1, 116.8, 113.3, 113.0, 106.0, 59.9, 55.5, 41.5, 34.2, 30.3, 19.4, 14.2; HRMS (ESI$^+$) $m/z$ = calcd. for $C_{28}H_{36}O_5$ [M + Na]$^+$ 475.2460, found 475.2453.

**Ethyl 4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,6-dimethyl-4*H*-chromene-3-carboxylate (3n):** Compound **3n** was prepared using 5- methyl-substituted 2-hydroxy-*p*-QM **1e** and $\beta$-functionalized ketone (ethyl acetoacetate) **2d** following general procedure. After column purification the product was obtained as brown liquid in 61 % yield. $R_f$= 0.60 (pet. ether/ethyl acetate, 5:1); IR ($CHCl_3$):$\tilde{\nu}_{max}$ = 3633, 3406, 2960, 2871, 1708, 1639, 1592, 1493, 1434, 1370, 1287, 1211, 1160, 1117, 1065, 987, 885, 816, 758 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ = 6.98 (s, 2 H), 6.93 (d, $J$ = 2.3 Hz, 2 H), 6.90 (s, 1 H), 5.02 (s, 1 H), 4.89 (s, 1 H), 4.12 (dd, $J$ = 3.2, 7.1 Hz, 2 H), 2.47 (s, 3 H), 2.24 (s, 3 H), 1.38 (s, 18 H), 1.23–1.20 (m, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ = 167.4, 160.3, 152.1, 147.9, 137.4, 135.4, 133.8, 129.2, 127.9, 125.2, 124.2, 115.7, 106.8, 77.3, 76.7, 59.9, 41.1, 34.2, 30.3, 30.1, 29.4, 20.8, 19.4, 14.2; HRMS (ESI$^+$) $m/z$ = calcd. for $C_{28}H_{36}O_4$ [M + Na]$^+$ 459.2511, found 459.2508.

**1-(4-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-6-fluoro-2-methyl-4*H*-chromen-3-yl)propan-1-one (3o):** Compound **3o** was prepared using 5- fluoro substituted 2-hydroxy-*p*-QM **1g** and $\beta$-functionalized ketone (ethyl acetoacetate) **2d** following general procedure. After column purification the product was obtained as yellow liquid in 58 % yield. $R_f$= 0.55 (pet. ether/ethyl acetate, 5:1); IR ($CHCl_3$):$\tilde{\nu}_{max}$ = 3637, 2960, 2874, 1708, 1646, 1597, 1490, 1434, 1372, 1324, 1268, 1209, 1148, 1103, 1066, 990, 871, 819, 759 cm$^{-1}$;$^1$H NMR (500 MHz, $CDCl_3$) $\delta$ = 7.01–6.95 (m, 3 H), 6.84 (d, $J$ = 3.1 Hz, 1 H), 6.80–6.77 (m, 1 H), 5.05 (s, 1 H), 4.90 (s, 1 H), 4.11 (dd, $J$ = 7.2, 9.2 Hz, 2 H), 2.47 (s, 3 H), 1.38 (s, 18 H), 1.20 (t, $J$ = 7.1 Hz, 3 H); $^{13}$C NMR (125 MHz, CDCl$^3$) $\delta$ = 167.2, 159.9, 158.1, 152.4, 145.8, 136.8, 135.7, 127.2, 127.1, 124.1, 117.3, 117.2, 115.2, 115.0, 114.3, 114.1, 106.1, 60.0, 41.4, 34.2, 30.2, 19.3, 14.2; HRMS (ESI$^+$) $m/z$ = calcd. for $C_{27}H_{33}FO_4$ [M + Na]$^+$ 463.2261, found 463.2259.

**Ethyl 6-chloro-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-methyl-4*H*-chromene-3-carboxylate (3p):** Compound **3p** was prepared using 5-chloro substituted 2-hydroxy-*p*-QM **1f** and $\beta$-functionalized ketone (ethyl acetoacetate) **2d** following general procedure. After column purification the product was obtained as yellow solid in 63 % yield. **mp**= 104–106 °C; $R_f$ = 0.83 (pet. ether/ethyl acetate, 5:1); IR ($CHCl_3$):$\tilde{\nu}_{max}$ = 3635, 3414, 2960, 1709, 1640, 1584, 1478, 1434, 1372, 1324, 1276, 1225, 1118, 1066, 987, 917, 882, 818, 761 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.12–7.06 (m, 2 H), 6.98 (s, 1 H), 6.95 (s, 2 H), 5.06 (s, 1 H), 4.88 (s, 1 H), 4.12 (dd, $J$ = 4.0, 7.0 Hz, 2 H), 2.47 (s, 3 H), 1.39 (s, 18 H), 1.21 (t, $J$ = 7.0 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 167.0, 159.8, 152.4, 148.4, 136.7, 135.6, 129.0, 128.8, 127.3, 124.2, 117.4, 106.8, 77.3, 76.7, 60.1, 41.1, 34.2, 30.2, 19.3, 14.2; HRMS (ESI$^+$) $m/z$ = calcd. for $C_{27}H_{33}ClO_4$ [M + Na]$^+$ 479.1965, found 479.1960.

**12-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-9,9-dimethyl-8,9,10,12-tetrahydro-11*H*-benzo[a]xanthen-11-one (3q):** Compound **3q** was prepared using naphthyl-substituted 2-hydroxy-*p*-QM **1h** and $\beta$-functionalized ketone (dimedone) **2a** following general procedure. After column purification the product was obtained as brown solid in 65 % yield. m.p. 145–147 °C; $R_f$ = 0.64 (pet. ether/ethyl acetate, 5:1); IR ($CHCl_3$):$\tilde{\nu}_{max}$ = 3635, 3382, 3064, 2958, 2873, 1649, 1594, 1462, 1433, 1374, 1317, 1281, 1224, 1165, 1118, 1072, 1024, 965, 813, 755 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ = 8.18 (d, $J$ = 8.4 Hz, 1 H), 7.78 (s, 1 H), 7.73 (d, $J$ = 9.2 Hz, 1 H), 7.40 (s, 1 H), 7.31 (d, $J$ = 8.8 Hz, 1 H), 7.11 (s, 2 H), 5.61 (s, 1 H), 4.95 (s, 1 H), 2.59 (d, $J$ = 5.3 Hz, 2 H), 2.30 (d, $J$ = 8.0 Hz, 2 H), 1.32 (s, 18 H), 1.14 (s, 3 H), 1.03 (s, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ = 197.2, 164.4, 152.2, 147.9, 135.7, 135.3, 131.7, 128.5, 126.9, 125.0, 124.1, 119.1, 117.3, 115.2, 77.5, 77.3, 51.1, 41.6, 34.4, 34.2, 32.6, 30.5, 29.9, 27.1, 18.7; HRMS (ESI$^+$) $m/z$ = calcd. for $C_{33}H_{38}O_3$ [M + Na]$^+$ 505.2719, found 505.2716.

**Ethyl 1-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-methyl-1*H*-benzo[f]chromene-2-carboxylate (3r):** Compound **3r** was prepared using naphthyl-substituted 2-hydroxy-*p*-QM **1h** and $\beta$-functionalized ketone (ethyl acetoacetate) **2d** following general procedure. After column purification the product was obtained as yellow solid in 62 % yield. m.p. 128–130 °C; $R_f$ = 0.68 (pet. ether/ethyl acetate, 5:1); IR ($CHCl_3$):$\tilde{\nu}_{max}$ = 3635, 2960, 2874, 1703, 1649, 1622, 1597, 1463, 1435, 1391, 1371, 1324, 1258, 1220, 1158, 1123, 1063, 983, 816, 758 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 8.02 (d, $J$ = 7.9 Hz, 1 H), 7.75 (d, $J$ = 7.9 Hz, 1 H), 7.68 (d, $J$ = 8.5 Hz, 1 H), 7.43 (t, $J$ = 7.6 Hz, 1 H), 7.38–7.31 (m, 1 H), 7.24 (d, $J$ = 10.4 Hz, 1 H), 7.05 (s, 2 H), 5.55 (s, 1 H), 4.93 (s, 1 H), 4.20 (q, $J$ = 7.3 Hz, 2 H), 2.48 (s, 3 H), 1.37–1.26 (m, 21 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 167.4, 159.9, 152.1, 148.0, 136.2, 135.2, 131.3, 131.1, 128.4, 128.2, 126.5, 124.6, 124.4, 123.3, 118.2, 117.1, 107.9, 77.3, 76.7, 60.2, 37.6, 34.1, 30.2, 19.4, 14.4; HRMS (ESI$^+$) $m/z$ = calcd. for $C_{31}H_{36}O_4$ [M + Na]$^+$ 495.2511, found 495.2509.

**General procedure for the synthesis of 5a and 6a:** In an oven-dried 50 mL round-bottomed flask, compound **3a** (50 mg, 0.11 mmol) was taken in anhyd toluene (10 mL) followed by the addition of anhyd $AlCl_3$ (94.2 mg, 0.698 mmol) at once, under an argon atmosphere. The reaction mixture was stirred at –30 °C until the completion of reaction. Ice water was added to quench the $AlCl_3$. The mixture was extracted with EtOAc (3 × 15 mL), the combined organic layers were dried (anhyd $Na_2SO_4$) and concentrated under reduced pressure followed by column chromatography purification to give **5a** and further **6a**.

**9-(3-(*tert*-Butyl)-4-hydroxyphenyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (5a):** White solid; 79 % yield. mp = 121–123 °C. $R_f$ = 0.70 (pet. ether/ethyl acetate, 5:1); IR ($CHCl_3$):$\tilde{\nu}_{max}$ =

3347, 2955, 1635, 1592, 1472, 1423, 1378, 1303, 1230, 1189, 1087, 1025, 930, 877, 826, 757, 652. $cm^{-1;1}$H NMR (200 MHz, $CDCl_3$) $\delta$ = 7.16–7.11 (m, 2 H), 7.10–7.03 (m, 3 H), 6.88 (dd, $J$ = 2.2, 8.0 Hz, 1 H), 6.40 (d, $J$ = 8.1 Hz, 1 H), 5.54 (s, 1 H), 4.95 (s, 1 H), 2.56 (s, 2 H), 2.27 (s, 2 H), 1.33 (s, 9 H), 1.13 (s, 3 H), 1.05 (s, 3 H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ = 197.3, 164.8, 152.9, 149.4, 137.9, 135.9, 130.0, 127.3, 126.4, 125.9, 125.0, 116.4, 113.9, 50.8, 41.6, 37.2, 34.4, 32.2, 29.5, 27.1; HRMS (ESI$^+$) $m/z$ = calcd. for $C_{25}H_{28}O_3$ [M + Na]$^+$ 399.1936, found 399.1931.

**9-(4-Hydroxyphenyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (6a):** White solid; 63 % yield. mp = 103–105 °C; $R_f$ = 0.43 (pet. ether/ethyl acetate, 5:1); IR ($CHCl_3$):$\tilde{\nu}_{max}$ = 3347, 2955, 1635, 1592, 1472, 1423, 1378, 1303, 1230, 1189, 1087, 1025, 930, 877, 826, 757, 652 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ = 7.16–7.12 (m, 1 H), 7.08 (d, $J$ = 2.4 Hz, 3 H), 7.03 (s, 2 H), 6.61 (d, $J$ = 8.5 Hz, 2 H), 6.01 (br. s, 1 H), 4.96 (s, 1 H), 2.56 (s, 2 H), 2.28 (s, 2 H), 1.12 (s, 3 H), 1.04 (s, 3 H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ = 197.5, 164.8, 153.0, 149.4, 137.7, 135.9, 130.0, 127.3, 126.3, 126.0, 125.0, 116.4, 113.9, 50.8, 41.6, 37.2, 34.4, 32.2, 29.5, 29.4, 27.1; HRMS (ESI$^+$) $m/z$ = calcd. for $C_{21}H_{20}O_3$ [M + Na]$^+$ 343.1310, found 343.1305.

## Acknowledgments

S. S. gratefully acknowledges the DST-SERB for the award of a national postdoctoral fellowship (PDF/2017/000663). N. S. K & J. R. are thankful to CSIR for the award of fellowship. P. K. thanks INSA New Delhi for the financial support in the form of INSA Senior Scientist program.

**Keywords:** Xanthenones · 1,6-Conjugated addition · Chromenes · β-Functionalized ketone · Brönsted acid

[1] a) K. S. Masters, S. Bräse, *Chem. Rev.* **2012**, *112*, 3717–3776; b) O. Chantarasriwong, A. Batova, W. Chavasiri, E. A. Theodorakis, *Chem. Eur. J.* **2010**, *16*, 9944–9946; c) H. R. El-Seedi, M. A. El-Barbary, D. M. H. El-Ghorab, L. Bohlin, A. K. Borg-Karlson, U. Göransson, R. Verpoorte, *Curr. Med. Chem.* **2010**, *17*, 854–901; d) H. R. El-Seedi, D. M. H. El-Ghorab, M. A. El-Barbary, M. F. Zayed, U. Göransson, S. Larsson, R. Verpoorte, *Curr. Med. Chem.* **2009**, *16*, 2581–2626; e) Y. J. Na, *Pharm. Pharmacol.* **2009**, *61*, 707–712; f) O. Demirkiran, *Top. Heterocycl. Chem.* **2007**, *9*, 139–178; g) M. E. Sousa, M. M. M. Pinto, *Curr. Med. Chem.* **2005**, *12*, 2447–2479; h) G. Brahmachari, S. Mondal, A. Gangopadhyay, D. Gorai, B. Mukhopadhyay, S. Saha, A. K. Brahmachari, *Chem. Biodiversity* **2004**, *1*, 1627–1651; i) V. Peres, T. J. Nagem, F. F. de Oliveira, *Phytochemistry* **2000**, *55*, 683–710.

[2] a) J. Li, M. Hu, S. Q. Yao, *Org. Lett.* **2009**, *11*, 3008–3011; b) L. Wu, K. Burgess, *J. Org. Chem.* **2008**, *73*, 8711–8718; c) X. Li, H. Zhang, Y. Xie, Y. Hu, H. Sun, Q. Zhu, *Org. Biomol. Chem.* **2014**, *12*, 2033–2036.

[3] a) J. Wrobel, J. Sredy, C. Moxham, A. Dietrich, Z. Li, D. R. Sawicki, L. Seestaller, L. Wu, A. Katz, D. Sullivan, C. Tio, Z. Y. Zhang, *J. Med. Chem.* **1999**, *42*, 3199–3202; b) C. C. Cheng, Q. Dong, L. Liu, Y. L. Luo, L. F. Liu, A. Chen, C. Yu, N. Savaraj, T. Chou, *J. Med. Chem.* **1993**, *36*, 4108–4112.

[4] W. Zhang, K. Krohn, Zia-Ullah, U. Flörke, G. Pescitelli, L. Di Bari, S. Antus, T. Kurtán, J. Rheinheimer, S. Draeger, B. Schulz, *Chem. Eur. J.* **2008**, *14*, 4913–4923.

[5] a) A. B. Xia, D. Q. Xu, S. P. Luo, J. R. Jiang, J. Tang, Y. F. Wang, Z. Y. Xu, *Chem. Eur. J.* **2010**, *16*, 801–804; b) A. Bugarin, B. T. Connell, *J. Org. Chem.* **2009**, *74*, 4638–4641; c) S. Ravichandran, K. Subramani, R. Arunkumar, *Int. J. Chem. Tech. Res.* **2009**, *1*, 329–331; d) C. F. Nising, A. Friedrich, S. Bräse, *Synlett* **2007**, *19*, 2987–2990; e) R. Rios, H. Sundén, I. Ibrahem, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 2181–2184; f) U. K. Ohnemüller, C. F. Nising, A. Encinas, S. Bräse, *Synthesis* **2007**, *14*, 2175–2185; g) Y. L. Shi, M. Shi, *Synlett* **2005**, *17*, 2623–2626; h) B. Lesch, S. Bräse, *Angew. Chem. Int. Ed.* **2004**, *43*, 115–118; *Angew. Chem.* **2004**, *116*, 118.

[6] a) J. Makawana, D. Mungra, M. Patel, R. Patel, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6166–6169; b) S. Li, F. Z. Li, J. X. Gong, Z. Yang, *Org. Lett.* **2015**, *17*, 1240–1243.

[7] H. Miao, Z. Yang, *Org. Lett.* **2000**, *2*, 1765–1768.

[8] R. Larget, B. Lockhart, P. Renard, M. Largeon, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 835–838.

[9] A. Groweiss, J. H. Cardellins, M. R. Boyd, *J. Nat. Prod.* **2000**, *63*, 1537–1539.

[10] K. Mori, G. Audan, H. Monti, *Synlett* **1998**, *03*, 259–260.

[11] P. J. Pietta, *J. Nat. Prod.* **2000**, *63*, 1035–1042.

[12] G. R. Beecher, *J. Nutr.* **2003**, *133*, 3248–3254.

[13] a) C. C. Hsiao, H. H. Liao, E. Sugiono, I. Atodiresei, M. Rueping, *Chem. Eur. J.* **2013**, *19*, 9775–9779; b) M. Terada, T. Yamanaka, Y. Toda, *Chem. Eur. J.* **2013**, *19*, 13658–13662.

[14] Z. Yang, Y. He, F. D. Toste, *J. Am. Chem. Soc.* **2016**, *138*, 9775–9778.

[15] a) S. R. Angle, K. D. Turnbull, *J. Am. Chem. Soc.* **1989**, *111*, 1136–1138; b) S. R. Angle, D. O. Arnaiz, *J. Org. Chem.* **1990**, *55*, 3708–3710; c) Y. Lou, P. Cao, T. Jia, Y. Zhang, M. Wang, J. Liao, *Angew. Chem. Int. Ed.* **2015**, *54*, 12134–12138; *Angew. Chem.* **2015**, *127*, 12302; d) S. Gao, X. Xu, Z. Yuan, H. Zhou, H. Yao, A. Lin, *Eur. J. Org. Chem.* **2016**, 3006–3012; e) S. Mahesh, G. Kant, R. V. Anand, *RSC Adv.* **2016**, *6*, 80718–80722; f) B. Huang, Y. Shen, Z. Mao, Y. Liu, S. Cui, *Org. Lett.* **2016**, *18*, 4888–4891; g) K. X. Xie, Z. P. Zhang, X. Li, *Org. Lett.* **2017**, *19*, 6708–6711.

[16] a) P. Chauhan, U. Kaya, D. Enders, *Adv. Synth. Catal.* **2017**, *359*, 888–912; b) L. Caruana, M. Fochi, L. Bernardi, *Molecules* **2015**, *20*, 11733–11764; c) A. Parra, M. Tortosa, *ChemCatChem* **2015**, *7*, 1524–1526.

[17] D. Richter, N. Hampel, T. Singer, A. R. Ofial, H. Mayr, *Eur. J. Org. Chem.* **2009**, 3203–3211.

[18] a) K. Zhao, Y. Zhi, T. Shu, A. Valkonen, K. Rissanen, D. Enders, *Angew. Chem. Int. Ed.* **2016**, *55*, 12104–12108; *Angew. Chem.* **2016**, *128*, 12283; b) W. Baik, H. J. Lee, S. Koo, B. H. Kim, *Tetrahedron Lett.* **1998**, *39*, 8125–8128; c) J. M. Roper, C. R. Everly, *J. Org. Chem.* **1988**, *53*, 2639–2642; d) J. D. McClure, *J. Org. Chem.* **1962**, *27*, 2365–2368; e) Y. J. Xiong, S. Q. Shi, W. J. Hao, S. J. Tu, B. Jiang, *Org. Chem. Front.* **2018**, *5*, 3483–3487.

[19] a) C. Ma, Y. Huang, Y. Zhao, *ACS Catal.* **2016**, *6*, 6408–6412; b) Z. Yuan, W. Wei, A. Lin, H. Yao, *Org. Lett.* **2016**, *18*, 3370–3373; c) S. Kim, Y. Kitano, M. Tada, K. Chiba, *Tetrahedron Lett.* **2000**, *41*, 7079–7083.

[20] a) X. Z. Zhang, J. Y. Du, Y. H. Deng, W. D. Chu, X. Yan, K. Y. Yu, C. A. Fan, *J. Org. Chem.* **2016**, *81*, 2598–2606; b) Z. Yuan, X. Fang, X. Li, J. Wu, H. Yao, A. Lin, *J. Org. Chem.* **2015**, *80*, 11123–11130; c) K. Gai, X. Fang, X. Li, J. Xu, X. Wu, A. Lin, H. Yao, *Chem. Commun.* **2015**, *51*, 15831–15834.

[21] a) M. G. Peter, *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 555–570; *Angew. Chem.* **1989**, *101*, 572; b) T. Itoh, *Prog. Polym. Sci.* **2001**, *26*, 1019–1059; c) M. M. Toteva, J. P. Richard, *Adv. Phys. Org. Chem.* **2011**, *45*, 39–91; d) G. J. Mei, S. L. Xu, W. Q. Zheng, C. Y. Bian, F. Shi, *J. Org. Chem.* **2018**, *83*, 1414–1421; e) K. Chen, W. J. Hao, S. J. Tu, B. Jiang, *Green Chem.* **2019**, *21*, 675–683; f) F. Jiang, R. Yuan, L. W. Jin, G. J. Mei, F. Shi, *ACS Catal.* **2018**, *8*, 10234–10240; g) S. Liu, X. C. Lan, K. Chen, W. J. Hao, G. Li, S. J. Tu, B. Jiang, *Org. Lett.* **2017**, *19*, 3831–3834; h) L. Zhang, X. Zhou, P. Li, Y. Liu, Y. Sun, W. Li, *RSC Adv.* **2017**, *7*, 39216–39220.

[22] K. Chen, S. Liu, D. Wang, W. J. Hao, P. Zhou, S. J. B. Ziang, *J. Org. Chem.* **2017**, *82*, 11524–11530.

[23] a) J. Rathod, B. M. Sharma, P. S. Mali, P. Kumar, *Synthesis* **2017**, *49*, 5224–5230; b) B. M. Sharma, D. R. Shinde, R. Jain, E. Begari, S. Satbhaiya, R. Gonnade, P. Kumar, *Org. Lett.* **2018**, *20*, 2787–2791.

[24] B. M. Sharma, J. Rathod, R. Gonnade, P. Kumar, *J. Org. Chem.* **2018**, *83*, 9353–9363.

Received: March 8, 2019

Tetrahedron 101 (2021) 132510

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Metal-free, $Tf_2NH$-catalyzed 1, 6-conjugate addition of imidazopyridine to *para*-quinone methides: Easy access to C3-functionalized triarylmethane imidazopyridine

Nilesh S. Khonde [a, b, 1], Madhukar S. Said [a, b, 1], Jagjivan K. Sabane [a, b], Jayant M. Gajbhiye [a, b, **], Pradeep Kumar [a, b, *]

[a] Division of Organic Chemistry, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune, 411008, India
[b] Academy of Scientific and Innovative Research (AcSIR), Ghaziabad, 201002, India

ARTICLE INFO

*Article history:*
Received 26 August 2021
Received in revised form
4 October 2021
Accepted 18 October 2021
Available online 21 October 2021

*Keywords:*
Imidazopyridine
*para*-Quinone methide
Brønsted acid
1,6-Conjugate addition
C3-functionalization

ABSTRACT

An inexpensive and commercially available $Tf_2NH$-catalyzed 1,6-conjugate addition of imidazopyridine (IMPY) heterocycles to *para*-quinone methides (*p*-QMs) is reported. The present transformation provides a diverse class of C3-functionalized triarylmethanes heterocyclic derivatives of imidazopyridine. These metal-free transformations provided a very broad substrate scope of conjugate addition product with a high yield up to 97% within a short duration.



## 1. Introduction

Nitrogen-containing triarylmethanes (TAMs) heterocyclic scaffold has attracted a great deal of interest amongst medicinal and synthetic chemists world-wide due to its versatile application in medicinal chemistry [1]. Such type of heterocyclic scaffolds are known to exhibit various biological activities including aromatase inhibitors, antifungal and anticancer etc. [2]. This has led to the development of number of drugs currently available in the market [3]. Few representative examples of these nitrogen-containing bioactive triarylmethane heterocycles are depicted in Fig.-1A [4].

*para*-Quinone methides (*p*-QMs) are one of the most powerful 1,6-Michael acceptors widely used to construct the diverse class of substituted aryl heterocyclic derivatives [5]. Our group has developed the conjugate addition of allenol ester and butenolides to *para*-quinone methides to construct the biarylmethanes [6]. In recent years, various heterocyclic nucleophiles are used for the construction of triarylmethane heterocyclic scaffolds using *para*-quinone methides *via* 1,6-conjugate addition using various Lewis acid/Brønsted acid catalysts [7]. Heterocyclic nucleophiles including imidazole [8], indole [9], coumarin [10], oxindole [11], naphthols [12] are the few examples. More recently, Anand and co-workers developed bis(amino)cyclopropenium salt catalyzed 1,6-conjugate addition of indole to *p*-QMs [13].

Imidazopyridine (IMPY) containing moiety is known to exhibit broad range of application in both pharmaceutical and agrochemical industries [14]. These nitrogen-containing heterocyclic scaffolds exist in several natural products and drug molecules [15]. To improve the pharmacokinetic properties of an imidazopyridine, various functional group transformations were carried out on the C3 position [16]. As a result, a number of C3-functionalized IMPY containing drug molecules were developed and being currently used in day-to-day life. Zolpidem [17], Saripidem [18], and DS-1 [19] are some of the representative drug molecules shown in Fig-1B. Very recently Kilic et al. reported C3-functionalization of imidazo [1,2-*a*]pyridines with *para*-quinone methides in presence of hexafluoro-2-propanol (HFIP) [20].

* Corresponding author. Division of Organic Chemistry, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune, 411008, India.
** Corresponding author. Division of Organic Chemistry, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune, 411008, India
*E-mail address:* pk.tripathi@ncl.res.in (P. Kumar).
[1] These Authors contributed equally.

https://doi.org/10.1016/j.tet.2021.132510
0040-4020/

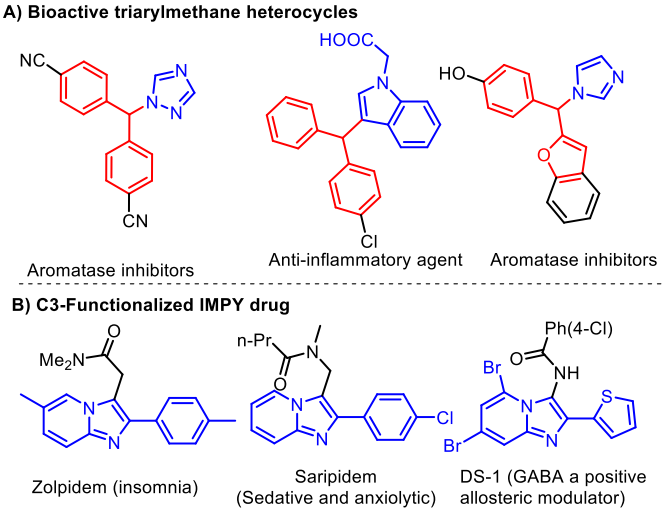


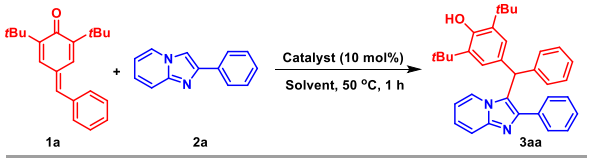

**Figure-1.** Nitrogen-containing bioactive triarylmethane heterocycles.

As a part of our ongoing research program on the synthetic utility of *p*-QMs, we now wish to report the synthesis of diverse range of triarylmethane heterocycles *via* 1, 6-conjugate addition of imidazopyridine derivatives to *para*-quinone methides under various Lewis and Brønsted acid catalysis employing various reaction conditions. The optimization reaction was first carried out with commercially available $Tf_2NH$ as a Brønsted acid catalyst which is known to activate the carbonyl group of *p*-QMs [21].

As shown in Table 1, initially the reaction was performed using different solvents such as dichloromethane, dichloroethane, toluene, tetrahydrofuran at 50 °C for 1 h in presence of 10 mol% of catalyst **(entries 1–4)**. We observed that reaction works efficiently in dichloroethane to furnish the conjugate addition product 2,6-di-*tert*-butyl-4-(phenyl(2-phenylimidazo [1,2-*a*]pyridin-3yl)methyl) phenol **3aa** in 93% yield **(entry 2)**. Further, we screened several Brønsted acids, but we did not observe any improvement in the yield of the desired product **3aa (entries 5–7)**. We next explored varieties of Lewis acid catalysts **(entries 8–12)**. The reaction works with $BF_3 \cdot OEt_2$, $Fe(OTf)_3$ and $Ag(OTf)_2$ to give 55%, 85% and 59% yield of conjugate addition product **3aa (entries 8–10)** respectively. The use of 5 mol% of catalyst produced the appreciable yield of the product **(entry 13)**. Further, reduction in catalyst (1 mol%) gave slightly less yield of desired product **(entry 14)**. No conjugate addition product was obtained without catalyst **(entry 15)**.

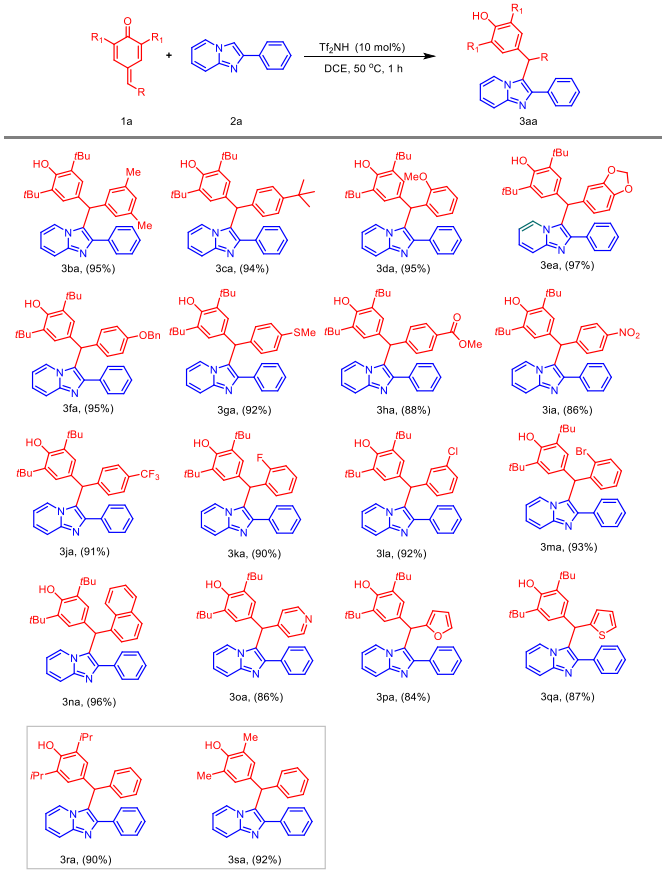
Having optimized the reaction conditions, our next plan was to explore the substrate scope of the reaction using various substituted *para*-quinone methides and results are shown in Scheme 1. The methyl-substituted 3,5-dimethyl, 4-*tert*-butyl on *p*-QMs gave an excellent yield of the conjugated addition product **(entry 3ba-3ca, 94%-95% yield)**. The *p*-QMs bearing electron-donating groups such as 2-methoxy, 3,4-methylenedioxyphenyl, 4-OBn, and 4-thiotoluene, reacted in efficient manner furnishing the desired product in excellent yield up to 97% **(entry 3da-3ga, 92%-97% yield)**. Similarly, electron-withdrawing groups such as 4-methoxycarbonyl, 4-nitro, and 4-trifluoromethyl on *p*-QMs gave only moderate to good yield of products **(entry 3ha-3ja, 86%-91% yield)**. Halogen substitution, 2-fluoro, 3-chloro, and 2-bromo on *p*-QMs also offered the corresponding products in high yield **(entry 3ka-3ma, 90%-93% yield)**. The α-naphthyl containing *para*-quinone methide also provided excellent yield **(entry 3na, 96%**

**Table 1**
Optimization of one-pot synthesis of 2,6-di-*tert*-butyl-4-(phenyl(2-phenylimidazo [1,2-*a*]pyridin-3-yl)methyl)phenol from *para*-quinone methide and IMPY.[a].




| Entry | Catalyst (10 mol%) | Solvent | Yield (%)[b] |
|---|---|---|---|
| **1** | $Tf_2NH$ | DCM | 70 |
| 2 | **$Tf_2NH$** | **DCE** | **93** |
| **3** | $Tf_2NH$ | Toluene | 61 |
| **4** | $Tf_2NH$ | THF | 52 |
| **5** | $CF_3COOH$ | DCE | NR |
| **6** | $CH_3COOH$ | DCE | NR |
| **7** | PTSA | DCE | 41 |
| **8** | $BF_3 \cdot OEt_2$ | DCE | 55 |
| **9** | $Fe(OTf)_3$ | DCE | 85 |
| **10** | $Ag(OTf)_2$ | DCE | 59 |
| **11** | $In(OTf)_3$ | DCE | NR |
| **12** | $Sc(OTf)_3$ | DCE | NR |
| **13** | $Tf_2NH$ (5 mol %) | DCE | 80 |
| **14** | $Tf_2NH$ (1 mol %) | DCE | 67 |
| 15[c] | – | DCE | NR |

[a] Reaction conditions unless otherwise specified: **1a** (1.0 equiv.), **2a** (1.0 equiv.), and catalyst (10 mol%) in anhydrous solvent at 50 °C on 0.5 mmol scales.
[b] Isolated yields of **3aa**.
[c] No catalyst.

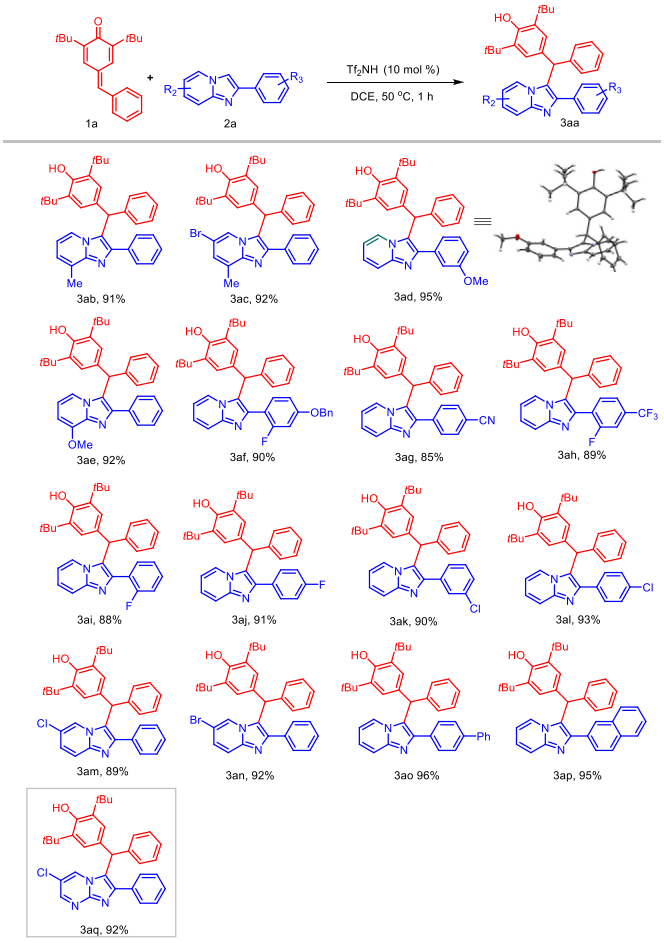



**Scheme 1.** The substrate scope of imidazo [1,2-*a*]pyridine on 1,6-conjugate addition of diverse *para*-quinone methides
[a]All reactions were performed with compound **1a** (1.0 equiv.), **2a** (1.0 equiv.), $Tf_2NH$ (10 mol%) in 5 mL of DCE at 50 °C on 0.5 mmol scales. [b]Isolated yield.

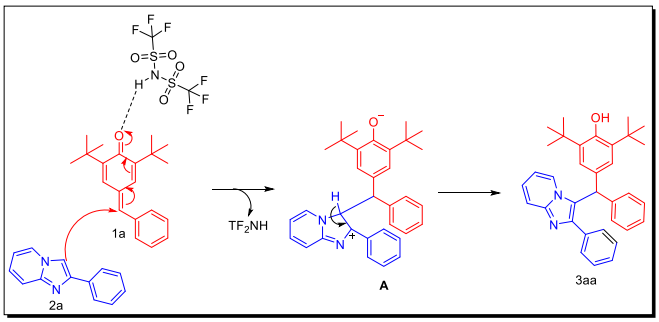
**yield**). *para*-Quinone methides, derived from heterocycles such as pyridine, furan, and thiophene reacted smoothly to offer the conjugate addition product in good yields **(entry 3oa–3qa, 84%-87% yield)**. The isopropyl and methyl substitution of quinone ring gave a high yield of the corresponding products **(entry 3ra–3sa, 90%-92% yield)**.

The substrate scope of the different substitutions on imidazopyridine (IMPY) derivatives was also explored and the results summarized in Scheme 2. The electron-donating substituents such as 8-methyl, 6-bromo-8-methyl-, 8-methoxy, 3′-methoxy and 2′-fluoro-4′-OBn on imidazopyridine react smoothly to furnish the excellent yield of conjugate addition products **(entry 3 ab-3af, 90%-95% yield)**. The structure was further confirmed by the single crystal x-ray analysis of **3ad (CCDC 2101624)**. The electron-withdrawing substitution 4′-cyno, and 2′-fluoro-4′-trifluoromethyl on imidazopyridine provided a good yield of the product **(entry 3 ag-3ah, 85%-89% yield)**. Halogen derivatives F, Cl, Br of imidazopyridine reacted efficiently to produce good to excellent yield of addition product **(entry 3ai-3an, 88%-93% yield)**. The 4′-phenyl and $\beta$-naphthyl derivatives of imidazopyridine also furnished the conjugate addition product in excellent yield **(entry 3ao-3ap, 95%-96% yield)**. Similarly, imidazo [1,2-*a*]pyrimidine also gave a high yield of product **(entry 3aq, 92% yield)**.

A plausible reaction mechanism for the 1,6-conjugate addition of *p*-QM **1a** with imidazopyridine **2a** is depicted in Scheme 3. The

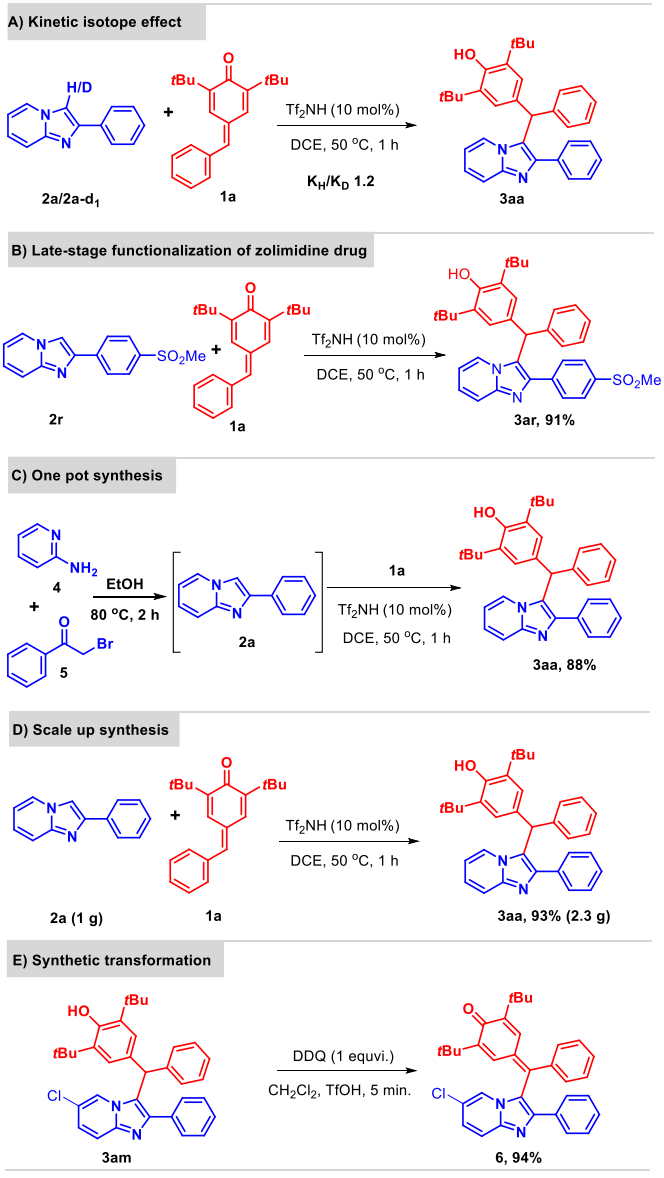



**Scheme 2.** The substrate scope of diverse imidazo [1,2-*a*]pyridines on 1,6-conjugate addition of *para*-quinone methide.
[a]All reactions were performed with compound **1a** (1.0 equiv.), **2a** (1.0 equiv.), $Tf_2NH$ (10 mol%) in 5 mL of DCE at 50 °C on 0.5 mmol scales. [b]Isolated yield.




**Scheme 3.** Plausible reaction mechanism.

nucleophilic attack of imidazopyridine to *p*-QM occurred at the C3 position of imidazo [1,2-*a*]pyridine. An intermediate addition product **A** was formed, followed by a loss of proton and formation of 1, 6-nucleophilic addition product **3aa**.




**Scheme 4.** Reaction kinetics and synthetic applications.

Next we turned our attention to investigate the reaction kinetics and synthetic utility of our reaction protocol; results are summarized in Scheme 4. The reaction kinetic isotope effect was demonstrated on **1a** with **2a/2a-$d_1$** as model substrates (Scheme 4A). We observe the ratio KH/KD 1.2 which shows the proton elimination was not a slow process (for more details see ESI$^{+}$). We further proceeded to explore the synthetic application of our reaction protocol. The late-stage functionalization of zolimidine drug **(3ar)** was achieved using standard condition to furnish its triarylmethane derivative in 91% yield (Scheme 4B). The synthesis of IMPY derivative **2a** followed by sequential addition of *p*-QMs **1a** in one-pot condition to offer desired product **3aa** in 88% yield (Scheme 4C). The scale up synthesis of the given reaction protocol is also demonstrated on 1 g scale of **2a** as starting material to give 93% yield (2.3 g) of **3aa** (Scheme 4D). Further, synthetic transformation of compound **(3am)** was achieved using DDQ to get oxidized compound **6** in 94% yield (Scheme 4E).

In conclusion, we have developed an efficient protocol for 1,6-conjugate addition of imidazopyridines to *para*-quinone methides in presence of various Lewis or Brønsted acids to provide triarylmethane heterocyclic derivatives of imidazopyridine. Reaction works efficiently using $Tf_2NH$ to give maximum up to 97% yield of conjugate addition product. Our developed route has atom economy, with broad substrate scope leading to the diverse range of triarylmethane heterocycles. We believe that these compounds would find enormous application in medicinal chemistry. Currently, the study related to bioactivity of these heterocycles is under progress in our laboratory.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgments

N. S. K., M. S. S. and J. K. S. thank CSIR, New Delhi (India) for a Senior Research Fellowship. Financial support from INSA, New Delhi (India) in form of INSA Senior Scientist program is gratefully acknowledged.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132510.

## References

[1] (a) R.A. Al-Qawasmeh, Y. Lee, M.-Y. Cao, X. Gu, A. Vassilakos, J.A. Wright, A. Young, Bioorg. Med. Chem. Lett 14 (2004) 347–350;
(b) M.K. Parai, G. Panda, V. Chaturvedi, Y.K. Manju, S. Sinha, Bioorg. Med. Chem. Lett 18 (2008) 289–292;
(c) R. Palchaudhuri, V. Nesterenko, P.J. Hergenrother, J. Am. Chem. Soc. 130 (2008) 10274–10281;
(d) M. Shiri, M.A. Zolfigol, H.G. Kruger, Z. Tanbakouchian, Chem. Rev. 110 (2010) 2250–2293;
(e) Q.-L. He, F.-L. Sun, X.-J. Zheng, S.-L. You, Synlett (2009) 1111–1114;
(f) D.F. Duxbury, Chem. Rev. 93 (1993) 381–433;
(g) X. Li, X. Xu, W. Wei, A. Lin, H. Yao, Org. Lett. 18 (2016) 428–431.
[2] (a) R. Ghodsi, B. Hemmateenejad, Med. Chem. Res. 25 (2016) 834–842;
(b) S. Antus, Tetrahedron 38 (1982) 133–137;
(c) S.D. Cho, K. Yoon, S. Chintharlapalli, M. Abdelrahim, P. Lei, S. Hamilton, S. Khan, S.K. Ramaiah, S. Safe, Cancer Res. 67 (2007) 674–683;
(d) P.M. Wood, L.W.L. Woo, J.-R. Labrosse, M.N. Trusselle, S. Abbate, G. Longhi, E. Castiglioni, F. Lebon, A. Purohit, M.J. Reed, B.V.L. Potter, J. Med. Chem. 51 (2008) 4226–4238.
[3] (a) M.M. Conn, J. Rebek Jr., Chem. Rev. 97 (1997) 1647–1668;
(b) S. Mondal, G. Panda, RSC Adv. 4 (2014) 28317–28358.
[4] D. Roy, G. Panda, Synthesis 51 (2019) 4434–4442.
[5] (a) S.G. More, G.M. Suryavanshi, Org. Biomol. Chem. 17 (2019) 3239–3248;
(b) J. Zhang, J. Liu, L. Dai, Y. Ge, L. Xu, Y. Xia, L. Xu, L. Rong, J. Heterocycl. Chem. 58 (2021) 1179–1191.
[6] (a) B.M. Sharma, J. Rathod, R.G. Gonnade, P. Kumar, J. Org. Chem. 83 (2018) 9353–9363;
(b) B.M. Sharma, D.R. Shinde, R. Jain, E. Begari, S. Satbhaiya, R.G. Gonnade, P. Kumar, Org. Lett. 20 (2018) 2787–2791.
[7] (a) L. Wenjun, X. Xianhong, Z. Pengfei, L. Pengfei, Chem. Asian J. 13 (2018) 2350–2359;
(b) C.G.S. Lima, F.P. Pauli, D.C.S. de Souza, A.S. Costa, L.S.M. Forezi, V.F. Ferreira, F. de C. da Silva, Eur. J. Org Chem. (2020) 2650–2692;
(c) J.-Y. Wang, W.-J. Hao, S.-J. Tu, B. Jiang, Org. Chem. Front. 7 (2020) 1743–1778;
(d) X. Liu, X. Wu, L. Zhang, X. Lin, D. Huang, Synthesis 52 (2020) 2311–2329.
[8] M. Breugst, F.C. Bautista, H. Herbert Mayr, Chem. Eur J. 18 (2012) 127–137.
[9] (a) J.-R. Wang, X.-L. Jiang, Q.-Q. Hang, S. Zhang, G.-J. Mei, F. Shi, J. Org. Chem. 84 (2019) 7829–7839;
(b) P. Goswami, R.V. Anand, Chemistry 1 (2016) 2556–2559.
[10] S. Kumaran, M. Prabhakaran, N. Mariyammal, K. Parthasarathy, Org. Biomol. Chem. 18 (2020) 7837–7841.
[11] S. Gao, X. Xu, Z. Yuan, H. Zhou, H. Yao, A. Lin, Eur. J. Org Chem. (2016) 3006–3012.
[12] T. Zhou, S. Li, B. Huang, C. Li, Y. Zhao, J. Chen, A. Chen, Y. Xiao, L. Liu, J. Zhang, Org. Biomol. Chem. 15 (2017) 4941–4945.
[13] P.K. Ranga, F. Ahmad, P. Nager, P.S. Rana, R.V. Anand, J. Org. Chem. 86 (2021) 4994–5010.
[14] (a) N. Devi, D. Singh, K.R. Rawal, J. Bariwal, V. Singh, Curr. Top. Med. Chem. 16 (2016) 2963–2994;
(b) T.L.S. Kishbaugh, Curr. Top. Med. Chem. 16 (2016) 3274–3302;
(c) H.Y. Wu, J. de O. Silva, S. Becker, J.O. Becker, J. Pest. Sci. 94 (2021) 573–583;
(d) M.H. Fisher, A. Lusi, J. Med. Chem. 15 (1972) 982–985.
[15] (a) M. Krause, H. foks, K. Gobis, Molecules 23 (2017) 399–423;
(b) R. Goel, V. Luxami, K. Paul, Curr. Top. Med. Chem. 16 (2016) 3590–3616.
[16] (a) Z. Tashrifi, M. Mohammadi-Khanaposhtani, B. Larijani, M. Mahdavi, Eur. J. Org Chem. (2020) 269–284;
(b) C.-H. Ma, M. Chen, Z.-W. Feng, Y. Zhang, J. Wang, Y.-Q. Jiang, B. Yu, New J. Chem. 45 (2021) 9302–9314;
(c) M.S. Said, A. Mishra, S. Pandole, R.A. Nayak, P. Kumar, J. M Gajbhiye, Asian J. Org. Chem. 8 (2019) 2143–2148.
[17] D.J. Sanger, H. Depoortere, CNS Drug Rev. 4 (1998) 323–340.
[18] D.J. Sanger, Behav. Pharmacol. 6 (1995) 116–126.
[19] K.A. Wafford, M.B. van Niel, Q.P. Ma, E. Horridge, M.B. Herd, D.R. Peden, Neuropharmacology 56 (2009) 182–189.
[20] F. Lafzi, H. Kilic, Asian J. Org. Chem. 10 (2021) 1814–1821.
[21] (a) S. Satbhaiya, N.S. Khonde, J. Rathod, R. Gonnade, P. Kumar, Eur. J. Org Chem. (2019) 3127–3133;
(b) J. Rathod, B.M. Sharma, P.S. Mali, P. Kumar, Synthesis 49 (2017) 5224–5230.

ChemPubSoc Europe

DOI: 10.1002/slct.201601735

Chemistry SELECT Full Papers

Organic & Supramolecular Chemistry

# Tri–*tert*-Butanolamine as an Organic Promoter in Nucleophilic Fluorination

Sandip S. Shinde,* Nilesh S. Khonde, and Pradeep Kumar[a]

Tri-*tert*-butanol amine acts as promoter with alkali metal salts in the nucleophilic fluorination of alkylsulfonates. It significantly enhances the reactivity of alkali metal salts with minimum formation of side-products (alkene, ether, and alcohol) compared to other catalysts in fluorination reaction. The synergism of *tert*-alcohol and amine moiety plays a pivotal role in fluorination.

## Introduction

Replacement of hydrogen by fluorine in organic molecules significantly enhances the bioactivity due to the unique properties of fluorine.[1] The element has several intriguing features such as lipophilicity, and high electronegativity. Its small size minimizes structural change resulting into the low steric perturbation and stability of the compounds.[2] Thus the incorporation of fluorine into a bioactive molecules can assist in the development of both pharmacokinetic and pharmacodynamic properties.[3]

In radiopharmaceuticals longer half-life (110 min.) of radionuclide fluorine (F-18) has attracted more interest among the other radionuclides due to its vast application in development of imaging agents for positron emission tomography (PET).[4] In addition, fluorinated compounds are used to investigate the biosynthetic pathway.[5]

In this context, nucleophilic substitution is one of the powerful method in organic synthesis to incorporate fluorine by displacement of alkylsulfonate/halide anion of specific aliphatic organo-molecules.[6] To assist nucleophilic fluorination, various alkyl quaternary ammonium fluoride reagents have been developed for better solubility of fluoride ion in reaction.[7] Despite good solubility of those reagents, some aspects of it concerning stability, moisture sensitivity, and by-product alkene formation issues need to be still addressed.

The alkali metal salts are abundant in nature, water soluble with reasonable stability. The water solubility of metal salts is very beneficial from a practical point of view, since it is easily washed after reaction during the work-up process. Thus alkali metal fluoride is considered as favorite fluoride source in industry for fluorination. Despite these advantages their use has been limited due to low solubility in organic media. Thus reaction is usually performed under the presence of phase transfer catalyst (PTC),[8] such as macrocyclic crown ethers,[8a] macrobicyclic cryptands[8b](Figure 1) polydentate ligands[8c], ionic liquids[9] and oligoethylene glycols (PEG)[10] facilitate the solubility of alkali metal fluorides to generate active fluorine and accelerate the rate of reaction significantly. However, some of the PTC are quite expensive and their preparation requires lengthy procedure[11] and it is also sometimes difficult to extract polar products from IL/PEG. To overcome these problems the protic solvents such as *tert*-BuOH, *tert*-amyl acohol are found suitable media for nucleophilic fluorination using CsF.[12] Our previous finding of the specifically designed hybridized molecule[mim-$^t$OH][OMs] containing *tert*-OH and imidazolium IL, acts as an efficient catalyst in the nucleophilic substitution reactions.[13] The [mim-tOH][OMs] not only enhances the reactivty of metal fluoride but also provides the chemoselectivity of product compared to the other protocols.[14] The bifunctional ionic liquid has the combined synergistic effect of IL and *tert*-OH group in the $S_N2$ fluorination.[15] We hypothesized that such a process can also occur in the simple alkylamine

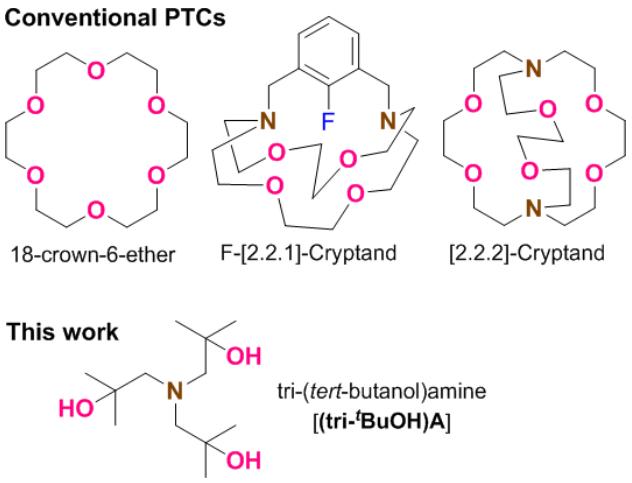



**Figure 1.** Structures of Representative PTCs and Tri-*tert*-butanolamine.

[a] *Dr. S. S. Shinde, N. S. Khonde, Dr. P. Kumar*
Division of Organic Chemistry
National Chemical Laboratory (CSIR-NCL)
Dr. Homi Bhabha Road, Pashan, Pune 411008, India
E-mail: ss.shinde@ncl.res.in

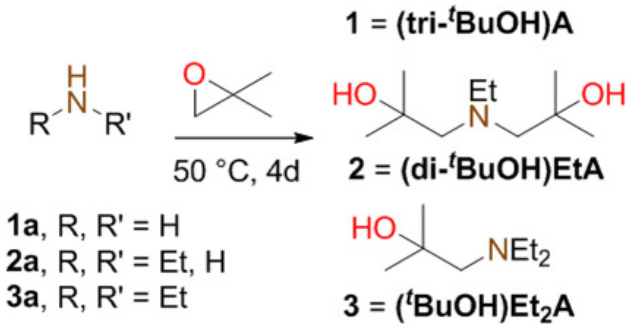
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/slct.201601735

containing *tert*-BuOH moiety, which has half identical structure moiety to that of the [2.2.2]cryptand (Fig 1).

## Results and Discussion

Herein, we report the unprecedented role of *tert*-butanolamine (Figure 1) as promoter /ligand for nucleophilic fluorination with various substrates of sulfonate esters and halo-leaving groups.

*tert*-Butanol functionalized amines **1–3** were prepared by modifying the procedure reported by Mun et al. (Scheme 1).[16]

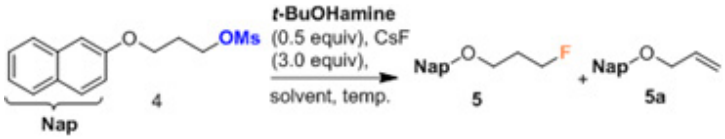



**Scheme 1.** Synthesis of *tert*-butanol amines.

Compounds **1–2** are obtained as solid while compound **3** is liquid at room temperature.

Table 1 illustrates the reactivity of various PTCs including synthesized *tert*-BuOH amines **1**, **2**, and **3** in fluorination of 2-(3-methanesulfonyloxypropyl) naphthalene (**4**) as a model compound with alkali metal fluorides CsF, KF, and RbF in protic (*t*-BuOH) and aprotic media ($CH_3CN$) at 80 °C. The conventional 18-crown-6-ether gave the desired 2-(3-fluoropropyloxy)-naphthalene in 46% yield along with alkene as by-product (entry 2). Same reaction was performed in the presence of promoters **1**, **2** and **3** having various *tert*-BuOH moieties, affording desired fluoroalkane **5** along with small amount of side-product alkene **5a.** However, the (tri-$^t$BuOH)A (**1**) catalyzed reaction, afforded **5** in higher 84% yield, much better compared to promoters **3** and **2** (entries 3–5). These results indicate that (tri-$^t$BuOH)A, may have chelating ability with metal fluoride, enabling fluoride as better nucleophile in the reaction. With reaction using promoter **1** at 80 °C instead of 60 °C, the amount of by-product increased significantly (entry 6). Interestingly, fluorination in the presence of **1** in protic solvents, such as *tert*-BuOH or *tert*-amyl alcohol gave the desired fluoroalkane **5** in excellent 93% and 90% yield respectively within 2 h (entry 7–8). But the same reaction in the absence of promoter **1** took

**Table 1.** Nucleophilic Fluorination with Metal Fluorides using *t*-BuOH-Amine as a Promoter.[a]



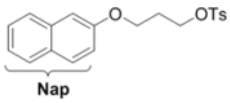
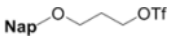
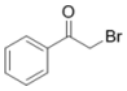
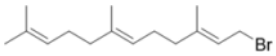
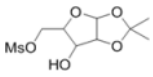
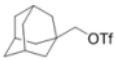
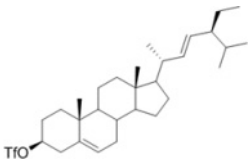
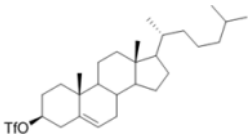

| Entry | MF/Promoter (0.5 equiv) | Solvent (3 mL) | Temp. (°C) | Time (h) | Products yield (%)[b] **5** | **5a** |
|---|---|---|---|---|---|---|
| 1 | TBAF/ - | $CH_3CN$ | 60 | 1 | 40 | 55 |
| 2 | CsF/18-crown-6 | $CH_3CN$ | 60 | 6 | 46 | 8 |
| 3 | CsF/**3** | $CH_3CN$ | 60 | 3 | 59 | 19 |
| 4 | CsF/**2** | $CH_3CN$ | 60 | 3 | 72 | 11 |
| 5 | CsF/**1** | $CH_3CN$ | 60 | 3 | 84 | 9[c] |
| 6 | CsF/**1** | $CH_3CN$ | 80 | 1 | 80 | 12[c] |
| 7 | CsF/**1** | *t*-BuOH | 80 | 2 | 93 | trace[c] |
| 8 | CsF/**1** | *t*-amyl alcohol | 80 | 2 | 90 | ND[d] |
| 9[e] | CsF/- | *t*-BuOH | 80 | 6 | 92 | ND |
| 10 | CsF/**1** (0.1) | *t*-BuOH | 80 | 6 | 68 | ND |
| 11[f] | CsF/**1** (2.0) | *t*-BuOH | 80 | 30 min | 76 | 14 |
| 12 | NaF /**1** | *t*-BuOH | 100 | 12 | ND | ND |
| 13 | KF/**1** | *t*-BuOH | 80 | 6 | 34 | ND |
| 14 | RbF/**1** | *t*-BuOH | 80 | 3 | 78 | ND |

[a] All reactions were carried out on a 1.0 mmol scale of Mesylate-(**4**), using 3.0 mmol of metal fluoride, 0.5 equiv. of (tri-$^t$BuOH)A in solvent at 80 °C. [b] Isolated yield. [c] Determined by $^1$HNMR. [d] ND = not detected. [e] see Ref.[12]. [f] Trace 2-(3-(*t*-butoxy)propoxy) naphthalene by-product observed.

A solvent-free reaction of isobutylene oxide and substituted ethylamine or ammonia at 50 °C for 4 days yielded quantitatively the corresponding Tri-*tert*-butanolamine [(tri-$^t$BuOH)A, **1**], 1-[Ethyl (2-hydroxy-2-methylpropyl) amino]-2-methyl propan-2-ol [(di-$^t$BuOH)EtA, **2**], and 1-(Diethylamino)-2-methyl-2-propanol [(mono-$^t$BuOH)EtA, **3**].

longer time, 6 h (entry 9).[12] On the other hand, slow reaction was observed with the use of 0.1 equiv. of **1** affording only 68% yield of the product (entry 10). Similarly the use of excess amount of **1**, gave 76% yield of desired fluorinated product along with significant amount of by-product alkene and trace amount of corresponding alkoxyethers (entry 11). Comparison of the reactivity with other alkali metal fluorides such as NaF,

**Table 2.** (tri-$^t$BuOH)A mediated Fluorination of Various Substrates.[a]

| Entry | Substrates | Temp. (°C) | Time (h) | Yield (%)[b] F-product | alkene |
|---|---|---|---|---|---|
| 1 |  | 80 | 3 | 90 | ND[e] |
| 2 |  | 80 | 2.5 | 92 | ND |
| 3 |  | 80 | 50 min | 81 | 6[c] |
| 4 |  | 80 | 30 min | 38 | ND |
| 5 |  | 80 | 6 | 80 | 16 |
| 6[d] |  | 80 | 24 | 31 | 69 |
| 7 |  | 80 | 3 | 92 | ND |
| 8 |  | 60 | 4 | 65 | ND |
| 9 |  | 80 | 5 | 87 | ND |
| 10 |  | 80 | 7 | 80 | ND |
| 11 |  | 80 | 12 | 70 | 11[c] |
| 12 |  | 100 | 12 | 82 | 8 |

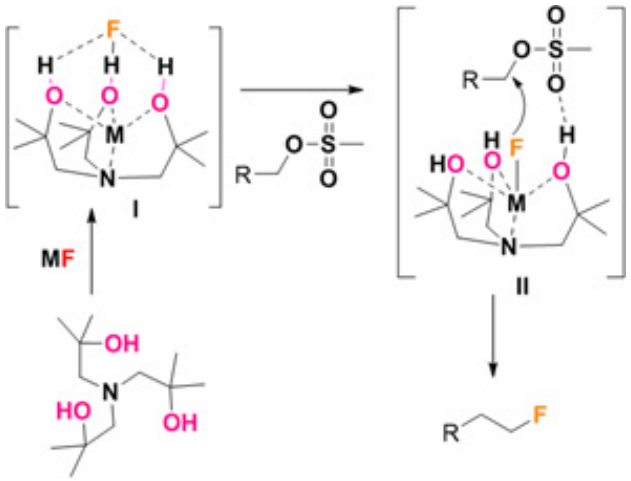
[a] Unless otherwise noted, All reactions carried out on 1.0 mmol scale of SM under condition of entry 6 Table 1.[b] Isolated yield [c] Determined by 1H NMR. [d] From Ref. No [20]. [e] ND = not detected

KF, and RbF was also examined (entries 12–14). While reaction with NaF didn't proceed at all, KF and RbF gave the fluoro-product **5** in moderate to appreciable yield.

Having optimized the reaction conditions for fluorination, we further investigated this reaction with different substrates containing primary and secondary leaving groups such as triflate, tosylate, nosylate and halogen as shown in Table 2. The reaction of OTf containing substrate in the presence of promoter **1** was much faster giving the desired fluoro compound **5** in 81% yield along with 6% yield of the alkene as side product ( entry 3). However, the reaction with OTs & ONs substrates gave **5** as the only product in 90 & 92% yields respectively (entry 1&2). Displacement of halogen from bromoacetophenone to fluoro acetophenone gave poor yield of corresponding fluorinated product (entry 4). Reaction of linear aliphatic substrates containing iodo as leaving group in the presence of (tri-$^t$BuOH)A, gave 80% yield of the desired fluoroproduct along with 16% corresponding alkene by-product (entry 5). In contrast to this result, the same reaction with 1-iodoundecane in the presence of [2.2.2]cryptand furnished the by-product as major and fluoro product as minor (31% yield, entry 6).[19] These results suggest that the elimination of by-product is favored over nucleophilic fluorination in cryptand catalyzed reaction due to the generation of "naked" fluorine in much higher concentration in the reaction. Same substrate with tosylate as leaving group afforded 92% yield of fluoroproduct (entry 7). These findings may be attributed to the coordinating properties of sulfonate ester moiety with (tri-$^t$BuOH)A which enhances interactions with nucleophilic fluorine and leaving groups. The allylic bromo compound, a derivative of farnesol, and precursor for pyrophosphate synthesis in sesquiterpenoid biosynthesis, afforded 1-fluoro-farnesol in 65% yield (entry 8). Over all, the salient features of this protocol are that it works additionally even with halogen substrates. Further the sugar molecule and admantane with primary OMs and OTf as leaving groups, resulted in 87% and 80% yield of the corresponding fluoro-product respectively (entries 9 and 10).

We have also performed the fluorination reactions on secondary leaving group of natural steroid substrates, such as stigmasterol and cholesterol; these were successfully converted into 2-fluoro- stigmasterol and 2-fluoro-cholesterol in reasonable good yields (entries 11 and 12).

Based on overall results, The -OH groups in the *t*-butanol moieties of promoter seem to act as Lewis base acting on the counter cation Cs+, as in the case of fluorination promoted by *t*-butanol.[12] The role of nitrogen atom may also be similar, as depicted in Scheme 2. It would be especially interesting to




**Scheme 2.** Proposed mechanism for Fluorination.

examine whether the metal fluoride reacts as a contact ion pair (M…F)[10,12,17,18] or as a "naked" nucleophile[20] (that is, dissociated MF; $M^+ + F^-$). Thus we believe that the three terminal *tert*-OH of promoter **1** function as 'anchors' to collect the nucleophile and the substrate in an ideal configuration for the nucleophilic fluorination. However, the mechanism of the described reaction is not clear at this point, and this would need further study.

## Conclusions

In conclusion, we report the unique role of tri-*tert*-butanol amine, (tri-$^t$BuOH)A as bifunctional promoter in nucleophilic fluorination using alkali metal salts, which significantly enhances the nucleophilicity of fluoride and minimizes the by-products formations such as alkene and ether in the reaction. (tri-$^t$BuOH)A has various advantages, such as easy access, and easy handling due to solid state. Although the mechanism of this promoter metal complex formation remains to be elucidated, we have illustrated the application of tri-*tert*-butanolamine as promoter/ligand for alkali metal salts in specific reaction. We also believe that this fluorination strategy can be executed to prepare F-18-labeled radiotracers for positron emission tomography.

## *Acknowledgements*

S. S. Shinde would like to thank Department of Science and Technology (DST), India for financial support in form of the Fast Track Young scientist and Ramanujan fellowship. N. Khonde is thankful to UGC, India for JRF fellowship. We are grateful to Director CSIR-NCL for his constant support and encouragement.

## *Conflict of interest*

The authors declare no conflict of interest.

**Keywords:** *tert*-Butanolamine · Fluorination · Nucleophilic Substitution · Organocatalyst

[1] a) R. N. Kumar, G. J. Dev, N. Ravikumar, D. K. Swaroop, B. Debanjan, G. Bharath, B. Narsaiah, S. N. Jain, A. G. Rao, *Bioorg. Med. Chem. Lett.* **2016**, *26*, 2927–2930; b) S. S. Sonar, S. A. Sadaphal, R. U. Pokalwar, B. B. Shingate, M. S. Shingare, *J. Hetero. Chem.* **2010**, *47*, 441–445.

[2] Reviews on Application of Fluorine in Industries: a) J. Wang, M. Sanchez-Rosello, J. L. Acena, C. D. Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506; b) T. Fujiwara, D. O'Hagan, *J. Fluorine Chem.* **2014**, *167*, 16–29; c) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soci. Rev.* **2008**, *37*, 320–330; d) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308–319.

[3] Reviews on Bioactive Fluorine: a) J. Wang, M. Sanchez-Rosello, J. L. Acena, C. D. Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506; b) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330.

[4] a) M. M. Alauddin, *Am. J. Nucl. Med. Mol. Imaging.* **2012**, *2*, 55–76; b) P. W. Miller, N. J. Long, R. Vilar, A. D. Gee, *Angew. Chem. Int. Ed.* **2008**, *47*, 8998–9033; c) H. S. Kil, H. Y. Cho, S. J. Lee, S. J. Oh, D. Y. Chi, *J. Label. Compd. Radiopharm.* **2013**, *56*, 619–626; d) C. Park, B. S. Lee, D. Y. Chi, *Org. Lett.* **2013**, *17*, 4346–4349.

[5] a) J. A. Faraldos, Y. Zhao, P. E. O'Maille, J. P. Noel, R. M. Coates, *ChemBioChem.* **2007**, *8*, 1826–18833; b) O. Cascon, S. Touchet, D. J. Miller, V. Conzalez, J. A. Faraldos, R. K. Allemann, *Chem. Commun.* **2012**, *48*, 9702–9704.

[6] Recent review on Nucleophilic Fluorination: a) J–W. Lee, M. T. Oliveira, H. B. Jang, S. Lee, D. Y. Chi, D. W. Kim, C. E. Song, *Chem. Soc. Rev.* **2016**, *45*, 4638–4650; b) M. C. Walker, M. C. Chang, *Chem. Soc. Rev.* **2014**, *43*, 6527–6536

[7] a) H. Sung, S. G. DiMagno, *J. Am. Chem. Soc.* **2005**, *127*, 2050–2051; b) K.-Y. Kim, B. C. Kim, H. B. Lee, H. Shin, *J. Org. Chem.* **2008**, *73*, 8106–8108; c) D. W. Kim, H.-J. Jeong, S. T. Kim, M.-H. Sohn, *Angew. Chem.* **2008**, *120*, 8532–8534.

[8] a) A. S. Pilcher, H. L. Ammon, P. DeShong, *J. Am. Chem. Soc.* **1995**, *117*, 5166 −5167; b) A. Gobbi, D. Landini, A. Maia, D. Secci, *J. Org. Chem.* **1995**, *60*, 5954–5957; c) J. Kim, A. S. Ichimura, R. H. Huang, M. Redko, R. C. Philips, J. E. Jackson, J. L. Dye, *J. Am. Chem. Soc.* **1999**, *121*, 10666–10667; b) D. Landini, A. Maia, F. Montanari, P. Tundo, *J. Am. Chem. Soc.* **1979**, *101*, 2526–2530; e) H. Plenio, *ChemBioChem.* **2004**, *5*, 650–655.

[9] a) D. W. Kim, C. E. Song, D. Y. Chi, *J. Am. Chem. Soc.* **2002**, *124*, 10278–10279; b) D. W. Kim, C. E. Song, D. Y. Chi, *J. Org. Chem.* **2003**, *68*, 4281–4285; c) S. S. Shinde, H. M. Chi, B. S. Lee, D. Y. Chi, *Tetrahedron Lett.* **2009**, *50*, 6654–6657.

[10] J. W. Lee, H. Yan, H. B. Jang, H. K. Kim, S.-W. Park, S. Lee, D. Y. Chi, C. E. Song, *Angew. Chem. Int. Ed.* **2009**, *48*, 7683 −7686.

[11] K. E. Krakowiak, J. S. Bradshaw, H. An, R. M. Izatt, *Pure & Appl.Chem.* **1993**, *65*, 511–514, reference cited theirin.

[12] D. W. Kim, D.-S. Ahn, Y.-H. Oh, S. Lee, H. S. Kil, S. J. Oh, S. J. Lee, J. S. Kim, J. S. Ryu, D. H. Moon, D. Y. Chi, *J. Am. Chem. Soc.* **2006**, *128*, 16394–16397.

[13] K. E. Krakowiak, J. S. Bradshaw, H. An, R. M. Izatt, *Pure & Appl.Chem.* **1993**, *65*, 511–514, reference cited therein.

[14] a) S. S. Shinde, B. S. Lee, D. Y. Chi, *Org. Lett.* **2008**, *10*, 733–735; b) S. S. Shinde, S. N. Patil, *Org. Biomol. Chem.* **2014**, *12*, 9264–9271; c) S. S. Shinde, S. N. Patil, A. Ghatge, P. Kumar, *New J. Chem.* **2015**, *39*, 4368–4374; d) S. S. Shinde, B. S. Lee, D. Y. Chi, *Tetrahedron Lett.* **2008**, *49*, 4245–4248; e) M. S. Said, L. Khandare, S. S. Shinde, *Tetrahedron Lett.* doi.org/10.1016/j.tetlet.2016.11.099.

[15] J.-L. G. Ruano, A. Parra, I. Alonso, S. Fustero, C. D. Pozo, Y. Arroyo, A. Sanz-Tejedor, *Chem. Eur. J.* **2011**, *17*, 6142–6147.

[16] Y.-H. Oh, H. B. Jang, S. Song, M. J. Im, S.-Y. Kim, S.-W. Park, D. Y. Chi, C. E. Song, S. Lee, *Org. Biomol. Chem.* **2011**, *9*, 418–422.
[17] S.-D. Mun, J. Lee, S. H. Kim, Y. Hong, Y.-H. Ko, Y. K. Shin, J. H. Lim, C. S. Hong, Y. Do, Y. Kim, *J. Organomet. Chem.* **2007**, *692*, 3519–3525.
[18] Y.-H. Oh, D.-S. Ahn, S.-Y. Chung, J.-H. Jeong, S.-W. Park, S. Lee, S. J. Oh, D. W. Kim, H. S. Kil, D. Y. Chi, *J. Phys. Chem. A* **2007**, *111*, 10152–10161.
[19] J.-Y. Kim, D. W. Kim, C. E. Song, D. Y. Chi, S. Lee, *J. Phys. Org. Chem.* **2013**, *26*, 9–14.
[20] R. Schwesinger, R. Link, P. Wenzl, S. Kossek, *Chem. Eur. J.* **2006**, *12*, 438–445.
[21] V. H. Jadhv, W. Choi, S.-S. Lee, S. Lee, D. W. Kim, *Chem. Eur. J.* **2016**, *22*, 4555.

Submitted: November 11, 2016
Accepted: December 14, 2016

# Author's Profile


## Nilesh S. Khonde

Division of Organic Chemistry
National Chemical Laboratory,
Dr. Homi Bhabha Road, Pune, (India), 411 008.
**Mobile No.** +91 8600239193/ 8149731472
**Email ID:** khondenilesh4@gmail.com


**Nilesh S. Khonde** was born in 1989, in Udgir (Maharashtra), India. He completed his graduation from Maharashtra Udaygiri Mahavidyalaya, Udgir, in 2009, post-graduation in organic chemistry from Dayanand Science College, Latur, in 2011 and also completed B.Ed. from Matoshri Kesharbai Kale College of Education, Latur, in 2012 under Swami Ramanand Teerth Marathwada University, Nanded. He has been awarded the UGC fellowship for perusing his Ph.D. degree in organic chemistry division of CSIR-National Chemical Laboratory under the guidance of Dr. Pradeep Kumar Tripathi. His research interest focuses around the development of highly selective Carbon-Carbon and Carbon-Fluorine bond forming reactions.

**Supervised/Trained**

Trained 3 post-graduate students during Ph.D. tenure.

## Erratum