Exploiting Ligand Effects in Development of New Methods and Total Synthesis with Pd-catalyzed C(sp^3)–H activation

Inauguraldissertation

zur

Erlangung der Würde eines Doktors der Philosophie

vorgelegt

Philosophisch-Naturwissenschaftlichen Fakultät

der Universität Basel

von

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2023

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät auf Antrag von:

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Basel, 19.09.2023

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Acknowledgements

This thesis has been an exercise of resilience and a show of creativity, which would not have been possible without the full involvement of me, as an author, but also of significant amount of people who enabled, supported and mentored (voluntarily or not) me throughout this journey. Therefore, I would like to express my sincere gratitude to those who were with me over these years.

The first and foremost gratitude to express is to Prof. Dr. Olivier Baudoin. Without the acceptance to join his group in April 2019, none of this would have been possible. The stay in Basel truly formed me as an individual and a professional, for which I am deeply grateful.

Similarly, I am thankful to Prof. Dr. Thomas R. Ward for co-supervising my PhD stay and Prof. Dr. Karl Gademann for agreeing to co-examinate this work. In addition, Prof. Dr. Daniel Häussinger must be acknowledged for chairing my PhD defence.

My gratitude also extends to the post-doctoral students Dr. Matthew Wheatley for the proofreading of this thesis and Dr. Stefania Vergura for collaborative work on the total synthesis of Indidene natural products.

I acknowledge the entire Baudoin group for providing a warm and thoughtful environment for my personal and professional development. In particular, I would like to remark Rafael Lombardi, Maria Tsitopoulou, Andrea Geraci and Silas Battisti as those who supported me in this journey the most. You have truly shaped my soul, my heart and me. Your support and friendship truly transformed me into a better human being. Another acknowledgement goes to my labmates, especially aforementioned Silas and Matthew, as well as to Diana Cavalli for excellent banter and atmosphere in the lab. Please also accept my apologies for all the stinky chemistry I had to perform. I hope that the PhD journeys that almost all of you are undergoing now would be as smooth as possible. Many thanks to also the former members of the Baudoin group, namely Dr. Yann Baumgartner and Dr. Pierre Thesmar, for helpful guidance.

Окремо я хотів би виділити моїх українських колег Олександра Вихівського, Сніжану Зайцеву та Валерію Гуцкалову, що підтримували мене впродовж усієї аспірантури та під час повномасштабного вторгнення. У такий складний час мати підтримку однодумців особливо важливо, за що я дуже вдячний. Це також відноситься і до всіх інших українців (не тільки з Базеля, але і з Цюриха та інших міст Європи), що мали на мене такий підтримуючий вплив.

Авжеж, велика подяка і шана Збройним силам України за те, що в мене все ще є дім і місце, до якого я можу повернутись.

Я дякую Дарії Загородній, що постійно і грунтовно підтримувала мене на психологічному і життєвому рівнях. Без цієї підтримки кінець аспірантури був би непосильний.

Особливу подяку я хотів би висловити Віталію Смалю, що дуже сильно допоміг з пошуком цього місця і котрому я завдячую цей професійний початок.

Звісно, велика подяка моїй мамі та татові, що дали мені велику свободу у здобутті свого майбутнього фаху та підтримували на шляху до наукового ступеня. На жаль, завершення цієї аспірантури не зостала моя бабуся, якій я теж дуже вдячний.

My journey to a PhD title not only contained professional growth, but also tremendous personal one. Along the way, I have met amazing people from all walks of life and all corners of the world. There are lots who I want to acknowledge, however, for the sake of brevity, I would like to broadly mention:

- All tenants of Signalstrasse 35a, who I had a pleasure of interacting. This accounts for around 50 people, who were all instrumental in the formation of my worldviews, supported me over this long path and made me feel welcome.
- The members of the Department of Chemistry, both fellow students and staff. From indispensable advice, a sense of community to help in navigating the hellscapes of work-related bureaucracy. From these, I would like to mention the Werkstatt team (for keeping the infrastructure in order), Marina Mambelli-Johnson and Nathalie Plattner-Longhi (for helping on interactions with the University and the State).
- The members of the PCC of the Department of Chemistry with whom I had an excellent time organizing events and improving the Department of Chemistry.

This section is a comprehensive list of the people who genuinely influenced my life and to whom I am grateful. If you haven’t found yourself on it, that doesn’t mean that I am not grateful – please contact me within a few business days of you not noticing yourself here and it will be fixed.

No sharks are hidden in this thesis. Or are they?

Abstract

Owing to the everlasting pursuit for the economical and sustainable development of molecular complexity, methods that enable the selective functionalization of C(sp^3)–H bonds are highly desirable. In this context, transition metal catalyzed C(sp^3)–H activation has emerged as a promising tool for enabling and simplifying synthetic routes towards valuable natural products, building blocks and other molecules of interest.

Motivated by previous developments in the field of Pd^0-catalyzed C(sp^3)–H activations, we sought to implement lessons learned on C–H arylation in an intermolecular fashion. We have managed to successfully identify conditions for a selectivity switch in arylation of heteroaromatic ketones with a competent coordinating ability from a classic α-selectivity to β-selectivity via the simple introduction of a pyridone ligand. These compounds are important blocks for the pharmaceutical industry and therefore, the development of a method for their expedient functionalization would simplify potential SAR studies. During our investigation, the origins this selectivity switch were probed, and it was found that they operate under different mechanistic manifolds, with α-arylation operating under a classical Pd^{II}–Pd^{IV} mechanism while β-arylation proceeded via a more exotic Pd-mediated desaturation-1,4-addition mechanism.

At the same time, the problem of enantioselective intramolecular methylene C(sp^3)–H activation – a previously unsolved challenge – was found to be possible by mediation of IBiox-type NHC ligands. Following on an initial reporting of this method, we sought to expand potential applications towards total synthesis of Indidene natural products. This was achieved via Pd^0-mediated methylene C(sp^3)–H activation as a key step, with a further divergent functionalization. Installation of a ketone side chain from a common diol precursor lead towards synthesis of Indidene A, while installation of the biphenyl system led towards Indidene C. The latter natural product was also synthesized in an enantioselective fashion with a high degree of enantioselectivity. Current efforts center around elucidation of the proposed structure.

Keywords: C–H activation, palladium, total synthesis, heteroaromatic ketones, arylation, ligand control, natural product, enantioselective synthesis.

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Works published or prepared during these PhD studies

Methylene C(sp^3)–H Arylation Enables Stereoselective Synthesis and Structure Revision of Indidene Natural Products, Anton Kudashev, Stefania Vergura, Marco Zuccarello, Thomas Bürgi, Olivier Baudoin, *Angewandte Chemie International Edition* **2023**, e202316103.

Site-Selective Pd-Catalyzed C(sp^3)−H Arylation of Heteroaromatic Ketones, Anton Kudashev, Olivier Baudoin, *Chemistry – A European Journal* **2021**, *27*, 17688-17694.

Chiral Catalysts for Pd^0-Catalyzed Enantioselective C–H Activation, Oleksandr Vyhivskyi, Anton Kudashev, Takeru Miyakoshi, Olivier Baudoin, *Chemistry – A European Journal* **2021**, *27*, 1231-1257.

Abbreviations (alphabetical):

Ac: acetyl

Ad: adamantyl

Ar: aryl

BCB: benzocyclobutene

BINAP: 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl

Bn: benzyl

Cbz: carbonyloxybenzoyl

CDI: 1,1’-carbonyldiimidazole

CMD: concerted metalation-deprotonation

CPME: cyclopentyl methyl ether

DBE: dibutyl ether

DCE: 1,2-dichloroethane

DCM: dichloromethane

DFT: density functional theory

DG: directing group

DHIQ: dihydroisoquinoline

Diox: 1,4-dioxane

DIPEA: N,N-diisopropylethylamine

DMA: N,N-dimethylacetamide

DME: 1,2-dimethoxyethane

DMF: N,N-dimethylformamide

DMSO: dimethylsulfoxide

DPPA: diphenylphosphoryl azide

DPPF: 1,1'-Bis(diphenylphosphino)ferrocene

DTBF: 1,1'-Bis(di-*tert*-butylphosphino)ferrocene

ECD: electronic circular dichroism

EOM: ethyloxymethyl

Et: ethyl

FGI: functional group interconversion

GVL: γ-valerolactone

HBTU: 3-[Bis(dimethylamino)methyliumyl]-3H-benzotriazol-1-oxide hexafluorophosphate

HFIP: 1,1,1,3,3,3-hexafluoroisopropanol

Ile: *iso*-leucine

i-Pr: *iso*-propyl

LLS: longest linear sequence

Me: methyl

MOM: methoxymethyl

MTBE: methyl *tert*-butyl ether

n-Bu: *n*-butyl

NHC: N-heterocyclic carbene

n-Pr: *n*-propyl

PEG: poly(ethyleneglycol)

Ph: phenyl

Pht: phtaloyl

Piv: pivaloyl

PyBOP: (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate

rpm: rotations per minute

t-Am: *tert*-amyl

TBDPS: tert-butyldiphenylsilyl

TBS: tert-butyldimethylsilyl

t-Bu: *tert*-butyl

TCE: tetrachloroethylene

TEA: triethylamine

TEP: Tolman electronic parameter

Tf: trifluorosulfonyl

TFE: 2,2,2-trifluoroethanol

TFT: α,α,α-trifluorotoluene

TM: transition metal

Val: valine

VCD: vibrational circular dichroism

XRD: X-ray diffraction

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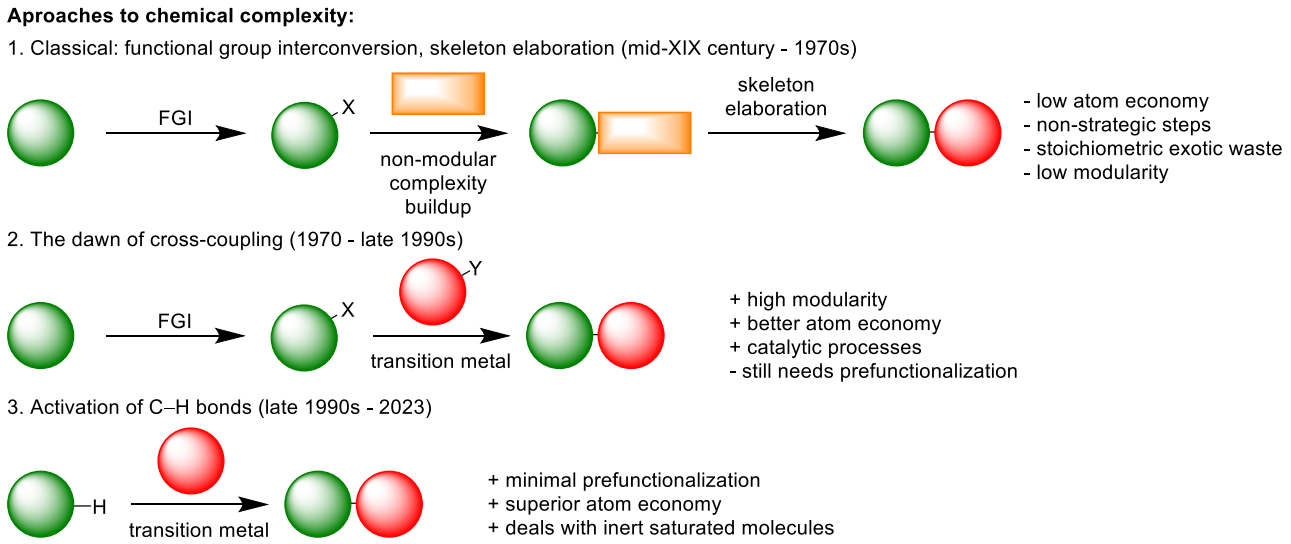
Part I: General Introduction

1.1 The dawn of organic chemistry, drivers of change and use of transition metals

Historical overview

The modern discipline of organic chemistry has, throughout the years, dealt with an ever-increasing degree of complexity. The beginning of it could be traced to the first half of the 19th century, when a string of syntheses of organic molecules, such as 1828 synthesis of urea by Wöhler[1] and 1845 synthesis of acetic acid by Kolbe[2], challenged and toppled the predominant idea of vitalism. In recent decades, efficient approaches towards assembly of molecules of ever-increasing complexity were developed, which was accompanied by the development of complex stoichiometric transformations (Scheme 1a) involving a plethora of reagents of different origins and types. With this approach, marvelous feats of synthesis were achieved, where the typical synthetic problems such as regio-, chemo and enantioselectivity, were solved with limited resources. However, starting from the second half of the 20th century, a growing focus on environmental concerns has led to the desire for more "green" processes.



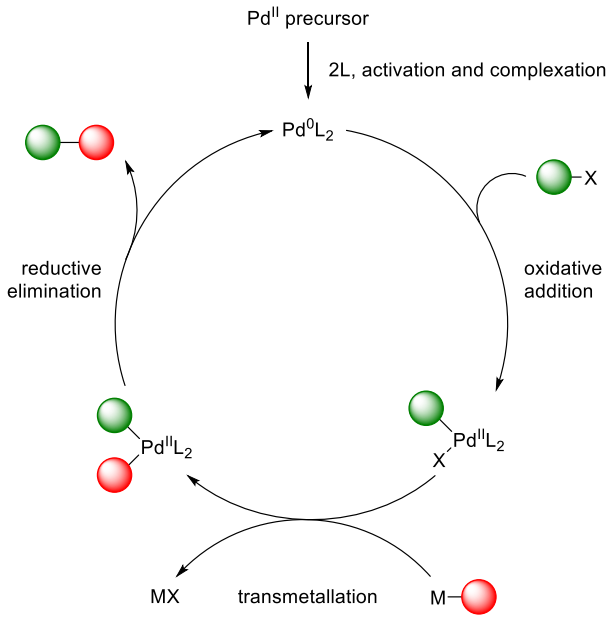
Scheme 1. Historical approaches towards build-up of molecular complexity.

Metal catalysis

In this regard, the mass drive on the development of catalytic metal-based methods is an evolutionary step, with Pd-based catalytic reactions being extensively explored to form the basis of a modern organic chemist toolkit. Compared to classical stoichiometric transformations, catalytic TM transformations allow for a very quick buildup of complexity *via* few well-understood functionalities rather than exchange between multitude of those

(Scheme 1b). Of particular note are cross-coupling reacitons, whose importance was realized in 2010 with the award of the Nobel prize in chemistry. [3] This chemistry, at the time of writing, enjoys high popularity and ever-increasing interest. This approach simplified synthetic logic for a large quantity of processes. While cross-couplings are a step forward towards a hypothetical ideal reaction, they usually they require two specifically pre-functionalized substrates, which adds steps to the overall synthesis and decreases atom and step-economy. One way to achieve greater ideality is by removing the prefunctionalization steps (Scheme 1c). In this case, functionalization directly from a C–H bond would be advantageous. However, there are challenges associated with such approach: high bond energy (~100 kcal/mol as in the case of C(sp^3)–H bonds) barrier is a reactivity challenge and the ubiquity of such bonds is a regioselectivity challenge.

The mechanism of popular Pd-catalyzed cross-couplings has been extensively studied. While the mechanism of such transformations exhibits the same hallmarks, the variability usually comes in the form of prefunctionalized substrates involved in the transformations (Scheme 2).



Scheme 2. Generalized mechanism for Pd-catalyzed cross-couplings

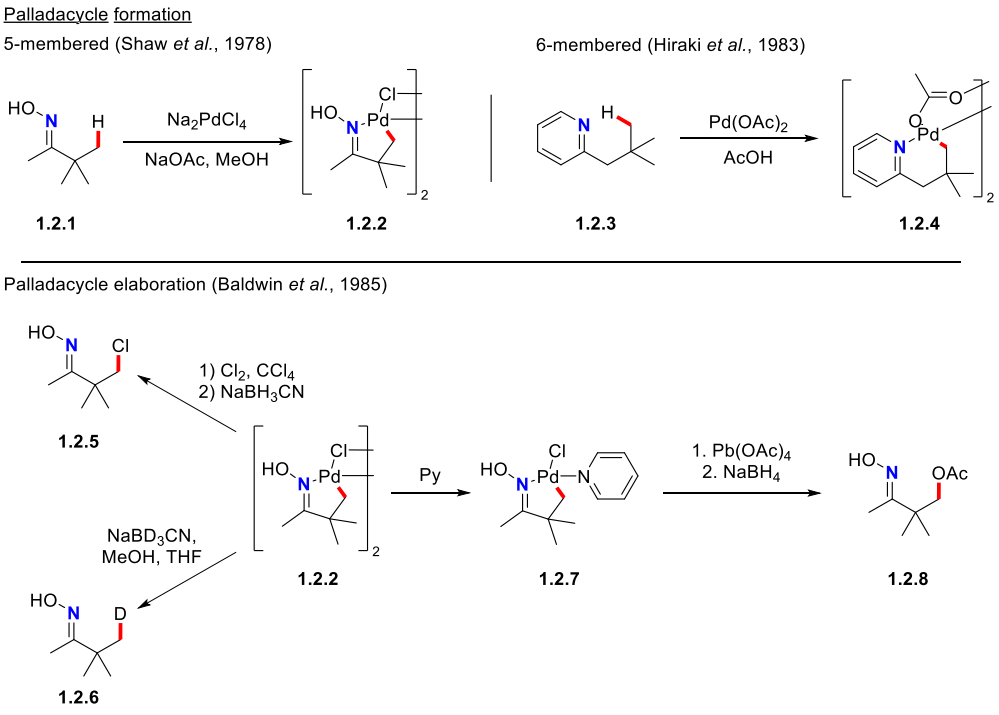
A Pd^0 species, either introduced in this oxidation state or reduced *in situ* from common Pd^{II} salts is generated in a certain ligand environment. It undergoes an oxidative addition event with an organo(pseudo)halide species (first coupling partner) to generate an organopalladium species with the Pd center in +2 oxidative state. This is followed by a transmetalation event with an organoheteroatomic (second coupling partner) compound to generate a complex bearing both reaction partners. Finally, a reductive elimination releases the coupled product and regenerates of the Pd center to its starting oxidative state of zero.

1.2 C(sp^3)–H activation: what, where, when?

Under certain conditions, transition metals can functionalize C(sp^3)–H bonds.[4][5][6][7][8][9] Although the first precedent of C–H activation was set by Otto Dimroth as far back as 1902[10] with the formation of arylmercury acetates, the first catalytic C(sp^3)–H activation method was disclosed by Shilov in 1969, where a deuterium scrambling was observed between methane and deuterium oxide via platinum catalysis.[11] While highly impractical by modern standards (for example, by use of stoichiometric Pt^{IV} oxidant), it highlighted the potential of the C–H activation field. Activation of C(sp^3)–H bonds was found to be not exclusive to platinum and plethora of other metals were investigated extensively.

Palladium in activation of C(sp^3)–H bonds

Among metals investigated for C–H activation, palladium is arguably the most studied. While there are precedents for undirected C–H activation (mostly applied to C(sp^2)–H bonds), in order to activate a specific C(sp^3)–H bond the use of directing groups becomes highly advantageous. Some of the first examples of C(sp^3)–H bond activation for this metal were reported in the preparation of cyclometalated Pd-complexes.[12]

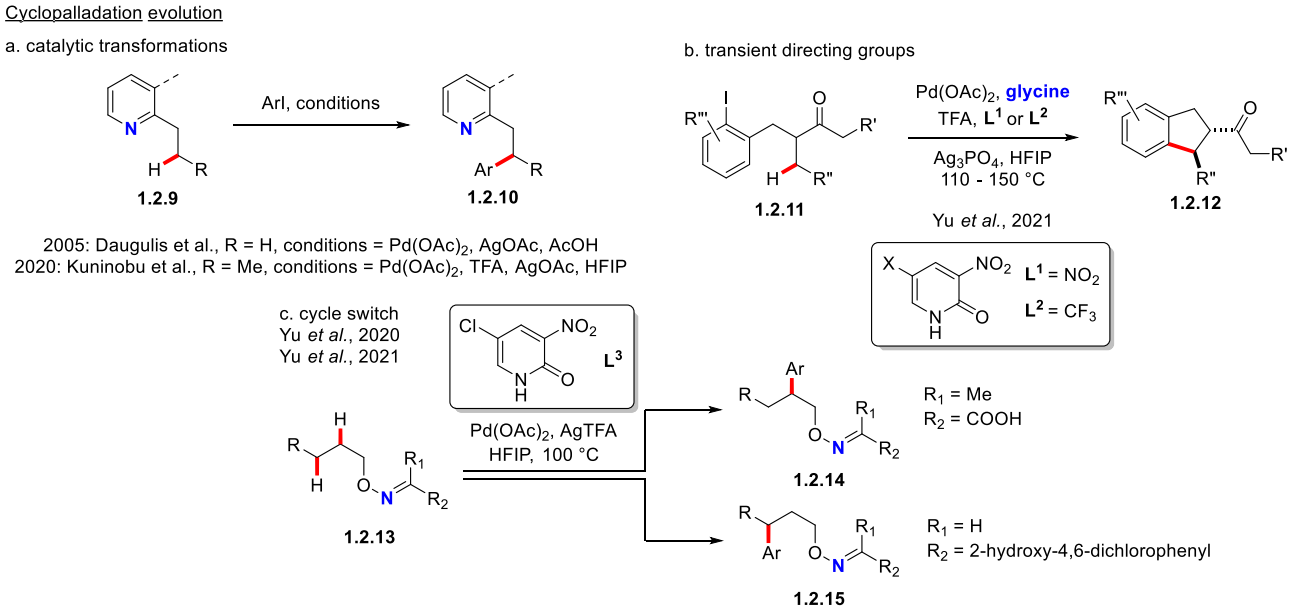


Scheme 3. Early examples of stoichiometric cyclopalladation and their subsequent transformations.

In 1978, the Shaw group reported a stoichiometric cyclopalladation of oximes using NaOAc as a base (Scheme 3, top).[13] In particular, pinacolone oxime **1.2.1** underwent smooth cyclopalladation to yield dimer **1.2.2**. This reactivity of palladium is not exclusive to oximes

and can form cycles of different size depending on the ligand sphere and the substrate, as was demonstrated by Hiraki group (Scheme 3).[14][15] Cyclopalladation, as reported by Shaw and Hiraki, was a curious transformation but ultimately of low utility. The added value to the transformation would come from transforming the Pd–C bond into functionalized products possessing new C–C or C–heteroatom connections. This was achieved by Baldwin group in 1985 (Scheme 3, bottom).[16] By taking the dimer **1.2.2** disclosed by Shaw group and subjecting it to various conditions, it was possible to obtain the products with a substituted Pd–C bond. This bond was transformed into a C–Cl bond with chlorine (**1.2.5**) and a C–D bond by the action of sodium cyanoborodeuteride (**1.2.6**). Oxidation though was not facile, however an additional monomerization with pyridine to **1.2.7** followed by treatment with a $Pb(OAc)_4$ led to the desired acetylated product **1.2.8**.

Non-removable directing groups (usually tailored to be common motifs in medicinal chemistry) have been extensively investigated[17][18] in catalytic Pd-catalyzed C(sp^3)–H activation processes (**1.2.9** → **1.2.10**) and constitute an organic continuation of initial discoveries made by Hiraki group (Scheme 4a).

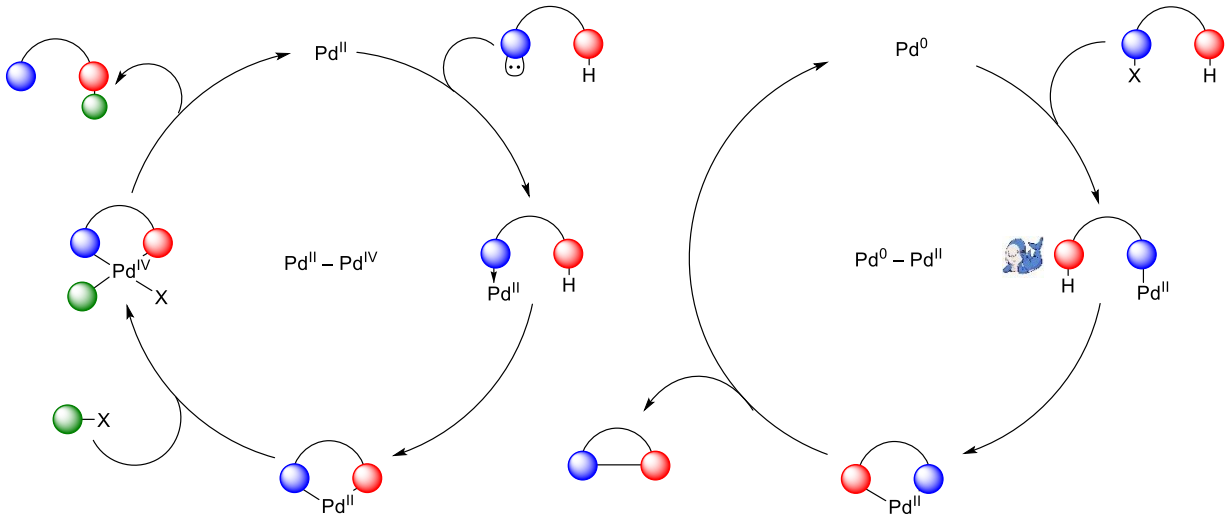


Scheme 4. Catalytic evolution of the cyclopalladation reactions.

Simultaneously, processes using fixed, removable and transient directing groups have been developed to enable a broad range of C–X bond introductions. The Yu group has thoroughly investigated Pd^{II}-catalyzed C(sp^3)–H activation over the course of the last two decades.[19] Amino acid-based transient directing groups allowed for any carbonyl compound that can form an imine *in situ* to become a site for direction in intramolecular[20] and intermolecular[21][22][23][24][25][26] fashion without prior DG installation (**1.2.11** → **1.2.12**,

Scheme 4b). Similarly, by tailoring the nature of this directing group, it is possible to manipulate the regioselectivity of C(sp^3)–H activation by geometrically favoring the palladacycle of a certain size (**1.2.13** → **1.2.14** and **1.2.15**, Scheme 4c).[27]

While there are multiple possible mechanistic pathways, for Pd-catalyzed C(sp^3)–H activation the two most investigated ones are Pd^{II}-Pd^{IV} and Pd^0-Pd^{II} (Scheme 5). Other manifolds for Pd-catalyzed C(sp^3)–H activation (such as one that involve Pd^{II}-Pd^0 mechanism) are outside the scope of this thesis and are comprehensively covered elsewhere, in particularly of works of groups of Yu and Gaunt.[28][29][30]



Scheme 5. Pd^{II}-catalysis vs. Pd^0-catalysis – manifold comparison.

These manifolds differ in their interaction with the directing groups: while Pd^{II} species tend to be coordinatively involved with these elements, Pd^0 species usually undergo oxidative addition. Pd^{II}-Pd^{IV} manifold involves coordination of the Pd to the substrate, a C–H activation event with the formation of a desired palladacycle, followed by oxidative addition to form a Pd^{IV} species, which undergoes rapid reductive elimination to form desired product. In contrast, the Pd^0-Pd^{II} manifold undergoes an oxidative addition of a Pd^0 species to form Pd^{II} species, which then activates a C–H bond to yield a palladacycle. Subsequent reductive elimination yields the desired product to regenerate a Pd^0 catalyst. The activation of a C(sp^3)–H bond usually happens via concerted metalation-deprotonation (CMD) mechanism, in which an active base (usually an efficient bidentate ligand, such as carbonate or carboxylate which can perform ligand slip easily) bound to the Pd center, with the help of agostic interactions of the Pd center and the prerequisite C–H bond, abstracts the hydrogen and, in effect, generates a C–Pd bond. This type of mechanism, first proposed in 1955 for the acetolysis of dialkylmercury derivatives,[31] has been extensively investigated for plethora of transition metal manifolds,[32][33] including those involving Pd.[34]

1.3 Ligands of Pd-catalyzed C(sp^3)–H activation: classes and general use

Properties of common Pd ligands

The reactivity of a particular catalytic system heavily depends on the stereoelectronic environment of the metal center. Modification of this environment in homogeneous catalysis is achieved by addition of ligands, which bind to the metal center. By modulating their steric and electronic parameters, lability and binding modes, it is possible to tune the reactivity for a system of interest with high levels of control. Quantification of ligand properties, therefore, could lead to accurate reactivity predictions.

One of the most studied ligand types, phosphines, have several gauges of their parameters. The first inquiries into quantification of electronic properties were described by Strohmeier and Müller in 1967, who plotted an electronic series of phosphine adducts to certain metal carbonyl complexes in regards to the CO stretching frequency displayed.[35] This approach, in turn, was used by Tolman to produce a quantitative trend by measuring the A_1 IR band of a CO stretching frequency of $Ni(CO)_3L$ complexes, where L was a phosphine. This electronic parameter ν, also known as Tolman electronic parameter, could be estimated for unknown phosphines, as long as coefficient χ is known for that particular substituent (equation 1).

$$For\ PX_1X_2X_3: \qquad \nu = 2056.1 + \sum_{j=1}^{3} \chi_i \tag{1}$$

Since the advent of TEP, various additional systems were explored for quantification of electronic properties of phosphines based on ν_{CO} of other metal carbonyl complexes[36], via ^{31}P spectroscopic analysis of the phosphoselenides[37], and computationally with DFT[38].

Steric properties of the phosphines could also be determined and quantified, as reported by Tolman.[39][40] In it, the cone angle θ for the phosphines was defined as an “apex angle of a cylindrical cone, centered 2.28 Å away from the center of the phosphorus atom, which just touches the van der Waals radii of the outermost atoms of the model”. A graphical representation of this concept is displayed on Figure 1 (left). This term is mostly limited to symmetrical (that is, with three same substituents) and with relatively low amount of internal degrees of freedom.

Modern cross-coupling and C–H activation catalysis has moved on from simple symmetrical phosphines to more sophisticated ligand architectures, for which cone angle θ is not wholly descriptive. Using the same principle, Nolan in 1999 proposed a two-parameter model based on crystallography data of Cp*Ru(L)Cl complexes.[41] This model was then replaced

by a more general parameter disclosed by Cavallo[42] and Nolan[43], which measured percentage of volume occupied by a ligand within a sphere of r = 3.5 Å, distanced 2 Å away from the metal center, or, as is it often referred, percentage of buried volume (%V_{bur}, Figure 1, right). This parameter was initially calculated experimentally via XRD, however, proprietary software utilizing DFT calculations has simplified this calculation.[44] Buried volume measurement has found significant utility for the quantification of NHC properties and other ligands for which cone angle could not represent their properties accurately.

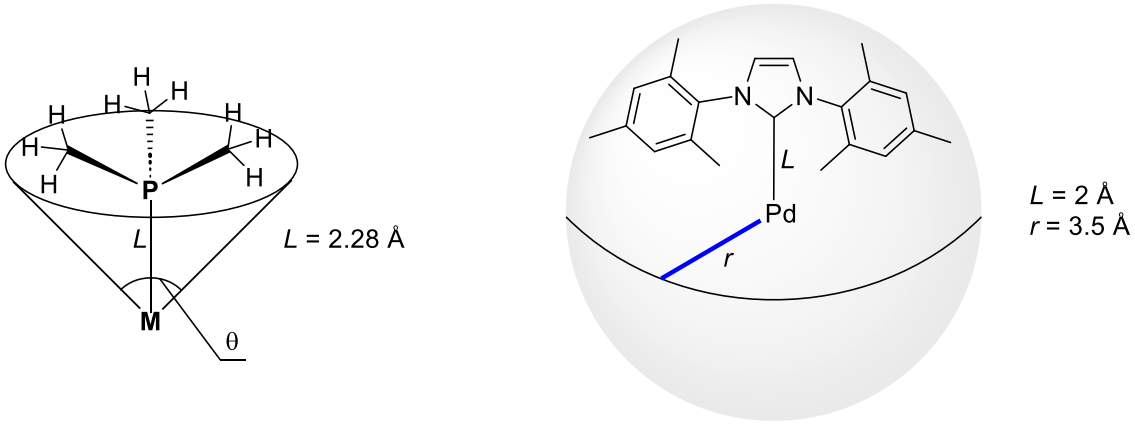


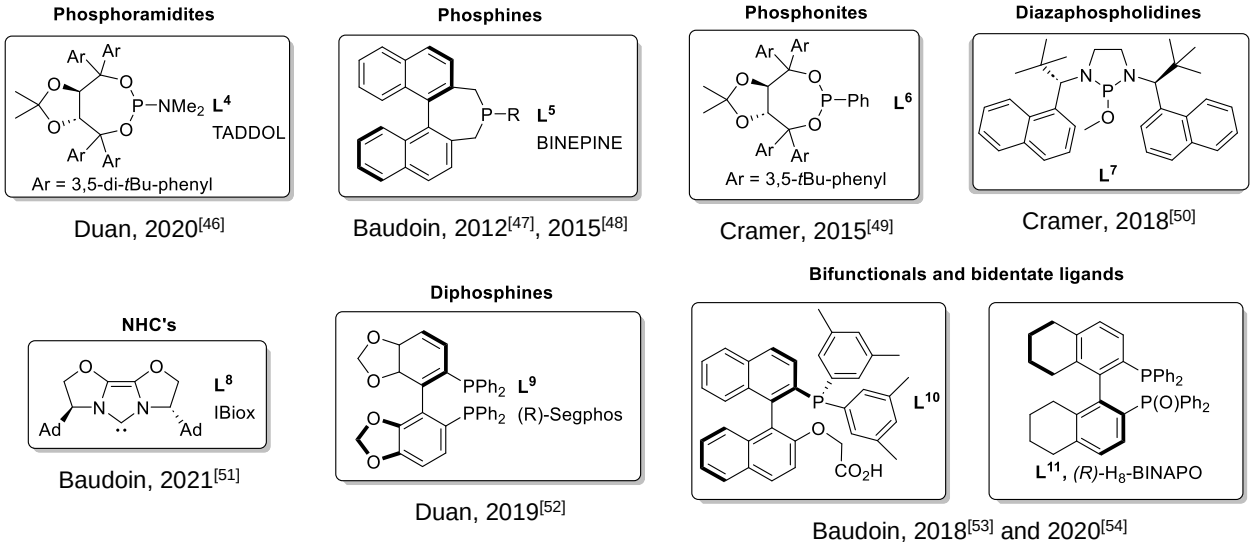
Figure 1. Cone angle θ as described by Tolman (left) and %V_{bur} – steric parametrization of NHC's (right, as shown for Pd–IMes complex).

Ligands of Pd-catalyzed C–H activation

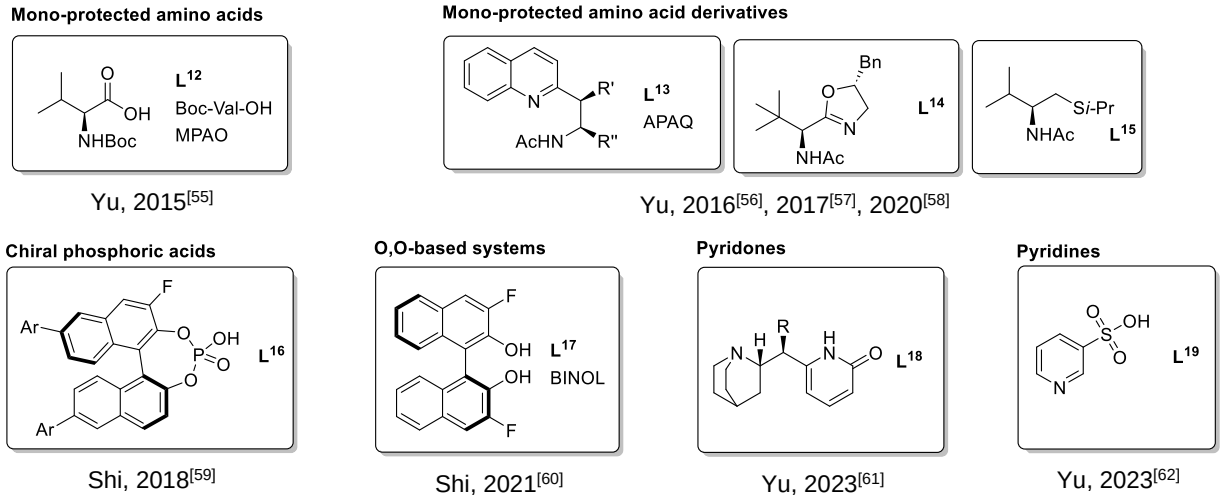
Pd^0-catalyzed C–H activation, bearing roots from related Pd-catalyzed cross-couplings, have inherited a set of well-defined chracterized ligands. Our group comprehensively covered their role in enantioselective Pd^0-catalyzed C–H activation.[45] A short breakdown of the ligand classes for Pd^0-catalysis is offered on Scheme 6. The most popular types are monodentate (**L**^{4}-**L**^{7}), bidentate (**L**^{9}) and hemilablie (**L**^{10}, **L**^{11}) P-based systems, as well as NHCs (**L**^{8}).

Pd^{II}-catalysis commonly employs different ligands (Scheme 7) compared to Pd^0-catalysis. The rate-determining step is usually the C–H activation process for Pd^0 catalysis whereas for Pd^{II}-catalysis, oxidative addition is often rate determining. This is rationalized by the formation of a highly oxidized Pd^{IV} species, from which reductive elimination is facilitated by electron-withdrawing ligands. It is reflected in the ligand choice for a potential Pd^{II}-process. Pd^{II} ligands tend to be N-based rather than P-based to prevent reduction of the active species. They often possess the ability to bind in a κ^2 fashion and able to perform ligand slip to a κ^1 mode to facilitate proton abstraction. These ligands are also predominantly polydentate, which allows for efficient manipulation of the metal complex geometry.

Therefore, monoprotected amino acids (**L[12]**) and their derivatives (**L[13]**-**L[15]**), CPA's (**L[16]**), O,O-based systems (**L[17]**), pyridones (**L[18]**) and pyridine-based systems (**L[19]**) constitute a popular choice of ligands for Pd^{II}-based research.



Scheme 6. Ligands of Pd^{0}-catalyzed C–H activation and some representative examples



Scheme 7. Ligands of Pd^{II}-catalyzed C–H activation.

Ligand choice greatly shapes possible C(sp^3)–H activation processes. The reactivity of a particular system is not only influenced by electronic and steric factors. It can also be influenced by the mechanism of the transformation itself, for example, by facilitating proton abstraction via concerted metalation-deprotonation (CMD). This field has been grown throughout the past decade, through which varied technical solutions to the issues of C(sp^3)–H activation were found, as well as other, related processes have been discovered and explored.

1.4 Similar processes that may happen under C–H activation conditions

As was remarked in the previous sections, cross-coupling chemistry was extensively investigated in relation to the possible reaction partners. Commonly used coupling partners have formed the backbone for Pd-catalyzed C(sp^3)–H activation research. However, a plethora of other, non-C–H activation processes also use these starting materials, with some evolving similar to Pd-catalyzed C(sp^3)–H activation conditions and catalyst architectures.

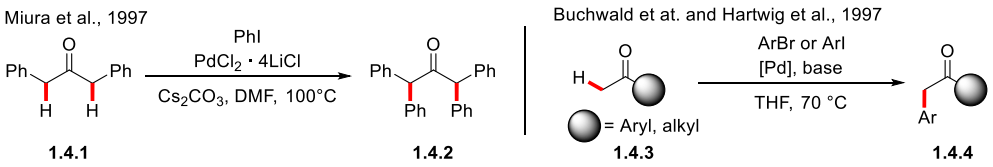
Pd-catalyzed enolate arylation

A very common feature of Pd-catalyzed C(sp^3)–H activation is the presence of an active base which participates in proton abstraction during the C–H activation step. This is achieved through synergistic agostic interactions of Pd center with the set C–H bond, which is then formally deprotonated by the active base coordinated to the Pd center. In certain systems with acidic C–H bonds, deprotonation happens before entering the coordination sphere of Pd. In that case, formal CMD mediated C–H activation step is replaced by a formal transmetallation step or a non-CMD mediated C–H activation step.

Examples of such systems are the C(sp^3)–H bonds in α-position to a carbonyl group (and their corresponding enolates). Pd-catalyzed enolate arylation stands out as one of those transformations.[63][64][65][66] Following the first disclosure by Fauvarque and Jutland in 1979, few potential challenges were encountered:

- The pK_a of carbonyl compounds vary greatly in organic solvents, with values typically laying in the range of 12 to 35.[67]
- Usually alkali metal enolates are stable at cryogenic conditions while the cross-coupling chemistry is undertaken at room or elevated temperatures, therefore making condensation a plausible (and undesired) alternative to cross-coupling.
- C-bound enolates often times possess β-hydrogens, which allows β-hydrogen elimination to be a competitive process to reductive elimination.

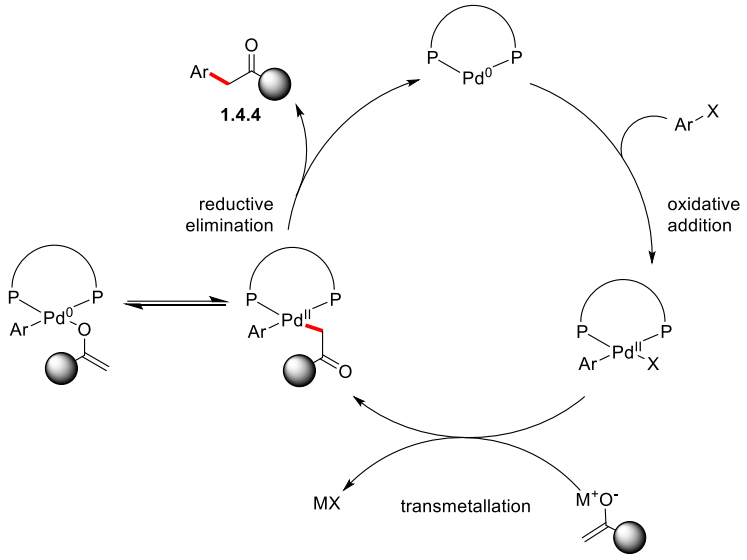
Sporadic research that addressed these problems appeared, but the real breakthrough came in 1997, when simultaneously Miura[68] (**1.4.1** → **1.4.2**), Buchwald[69] and Hartwig[70] groups (**1.4.3** → **1.4.4**) disclosed their direct enolate arylation protocols (Scheme 8).



Buchwald: BINAP / Tol-BINAP, $Pd_2(dba)_3$, NaO*t*-Bu
Hartwig: DPPF / DTPF, $Pd(dba)_2$, KHMDS / NaO*t*-Bu

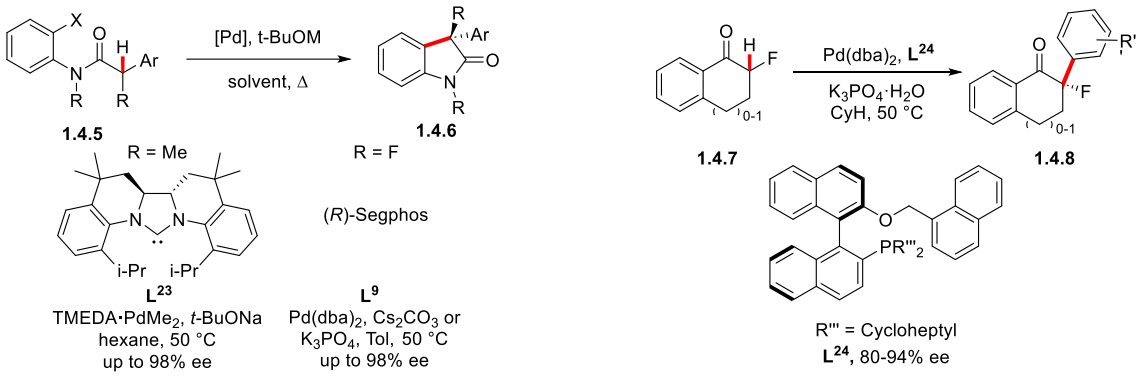
Scheme 8. First examples of practical enolate arylation protocols.

In the cases of the Buchwald and Hartwig protocols, a key feature is the use of bidentate phosphine ligands, DPPF (**L**^{20}) / DTBF (**L**^{21}) or BINAP (**L**^{22}). This particular combination was successful in catalyzing the transformation in good yield, without adverse side reactions, and β-hydrogen elimination. The mechanism of this transformation was rigorously investigated to propose generalized process scheme (Scheme 9).



Scheme 9. Generalized mechanism of Pd-catalyzed enolate arylation.

In a typical enolate arylation, an aryl halide undergoes oxidative addition to the Pd^0-center, which subsequently undergoes ligand substitution with the *in situ* generated enolate. This Pd-enolate exists in two forms – as an O- and as a C-enolate, the latter undergoes reductive elimination that results in α-arylated carbonyl compound **1.4.4**. This manifold, while able to produce the desired α-arylated product, is unable to do so in an enantioselective fashion due to subsequent deprotonation of the generated enantioenriched product and equilibration into racemic mixture. Therefore, in order to mitigate base-mediated racemization, carbonyl-containing compounds with secondary C(sp^3)–H bonds in α-positions are used (Scheme 10).



Murakami, 2011[71] and Hartwig, 2017[72]

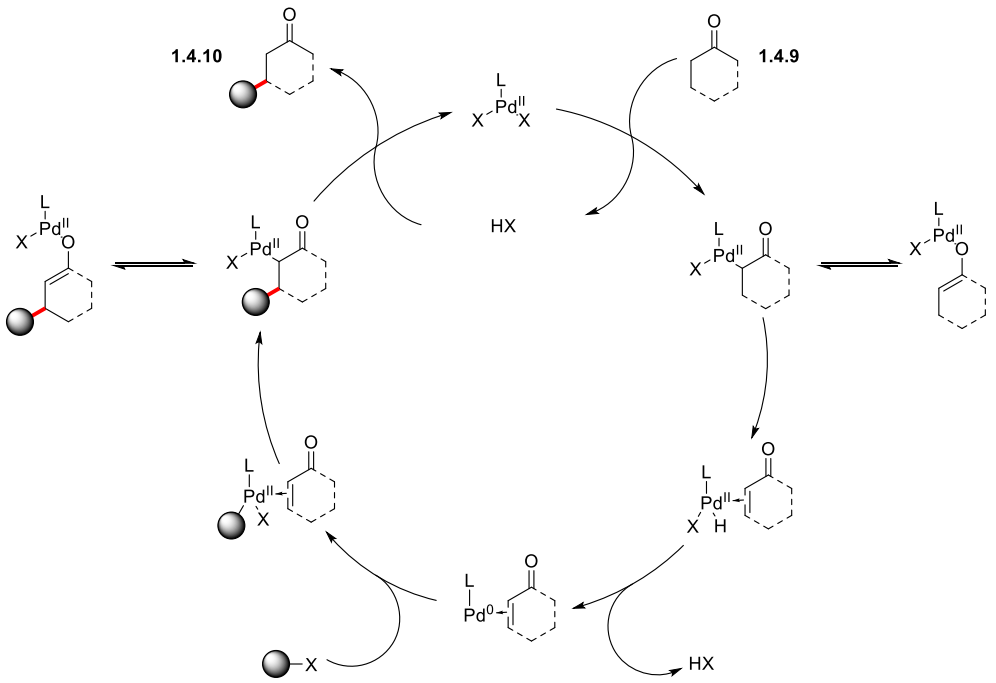
Hartwig, 2016[73]

Scheme 10. Prominent examples of enantioselectve α-arylation of carbonyl compounds.

Pd-catalyzed desaturation – addition

β-arylation of carbonyl compounds is a related process to α-arylation. In this regard, major strides have been made in the field of C(sp^3)–H activation, with examples of directed arylation of amides or with transient directing groups via CMD processes. Our group also have contributed to it with migrative Pd-catalyzed couplings[74]. However, an alternative mode of reactivity that involves desaturation and subsequent addition of arylpalladium species onto the generated double bond is also viable.

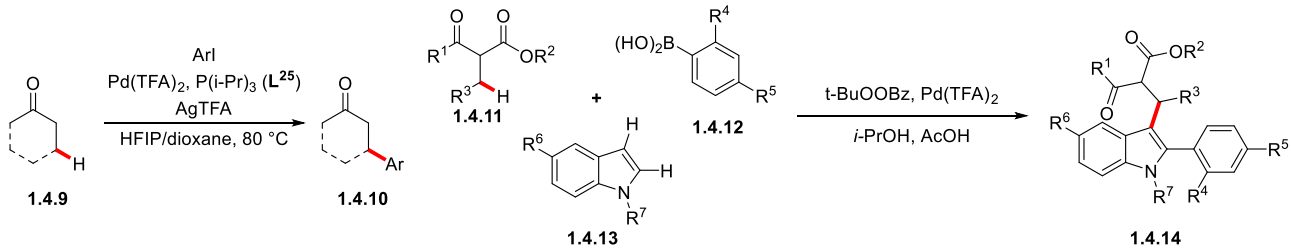
The roots of this manifold stem from three fundamental mechanistic steps. The first event, desaturation, constitutes a formal oxidation process and is part of fundamental textbook chemistry, such as the Saegusa-Ito oxidation.[75] However, the Saegusa-Ito oxidation requires the pre-installation of a silyl enol ether and uses stoichiometric organic oxidant. Further upgrades made by the Stahl group[76] removed this requirement for the silyl enol ether and made use of molecular oxygen as a sole oxidant to reoxidize the formed Pd^0 species. While the methods of Saegusa-Ito and Stahl make use of oxidants, one could also employ oxidative addition in order to generate a nucleophilic carbon-palladium species. This step is well known and well researched, as is conjugate addition event.[77] These steps utilize relatively similar Pd species and they may unite under a single mechanistic manifold (Scheme 11).



Scheme 11. Mechanism of a Pd-catalyzed desaturation – addition.

The implementation of such reactivity happened simultaneously with utilization of Ir-catalyzed photochemical approach disclosed by MacMillan group[78], as well as with Pd, as shown by groups of Dong[79][80][81] and Pihko[82], which follow closely the mechanism disclosed in Scheme 11.

The coordination sphere of Pd requires fitting electronic parameters. The first generation of conditions made use of electron-rich phosphines, such as P(*i*-Pr)$_3$ **L^{25}**, to facilitate the transformation. However, this imposed some limitations: the reaction was sensitive towards external oxidants and moisture, required the use of silver salts as halogen abstractors and was somewhat limited in scope. The introduction of electron-deficient sulfur-based ligands alleviated this while expanding the scope of the transformation.



Dong, 2013[79] Pihko, 2013[82]

Scheme 12. Application of Pd-catalyzed desaturation – addition of aryls.

The broad ability of palladium to exhibit different reactivity is highly dependent on the nature of the coordination sphere. In this regard, a plethora of ligand families were developed and

successfully employed, as was shown, to facilitate C(sp^3)–H activation and other related reactions.

1.5 Chiral NHC use for Pd^0-catalyzed C-H activation

Characteristic of NHC's as ligands for Pd

In Pd^0-catalyzed C–H activation and other metal-catalyzed C–H activations[83], N-heterocyclic carbene (NHC's) derived ligands are very potent. When comparing to phosphine- and other phosphorus-derived ligands, there are several key differences between these ligand families, namely:

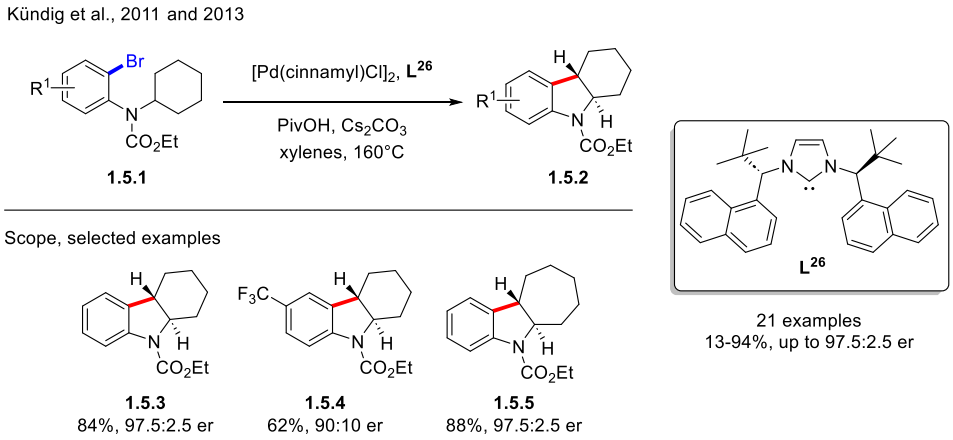
a) Tolman electronic parameters for NHC's, calculated from CO stretching frequencies in the complexes of the $M(CO)_x(NHC)$ type, exhibit strong electron-donating properties, generally exceeding those displayed by phosphine ligands.
b) The strength of bonding between the NHC and metal center usually exceeds that of phosphorus-derived ligands due to strong σ-donation and extensive π-back-bonding. This, in turn, means that the NHC stays bound to the metal center throughout the entirety of the catalytic cycle.
c) In contrast to phosphines, which are sterically characterized by bite and cone angles, the main steric parameter that is applied to NHC's is buried volume (V_{bur}, %) – a volume that is occupied by the NHC within a sphere with radius of 2Å centered around the metal center.

It stands to reason when considering the distinct properties of phosphine and NHC ligands that there could be potential different uses between these classes of ligands. As previously stated, strong bonding between NHC and a metal center (in this case, Pd) results in a complex that is exceptionally stable to decomposition and dissociation. Strong electron donating and back donating properties facilitate propagation of certain catalytic steps, while the bulky nature of NHC's compress the reaction space and eases the transfer of chiral information from the catalyst to the substrate. These distinct features have seen NHC ligands applied in transformations hitherto unreported with phosphine derived ligands, such as the C–H activation of methylene $C(sp^3)$–H bonds.

Examples of Pd-NHC catalysis for $C(sp^3)$–H activation

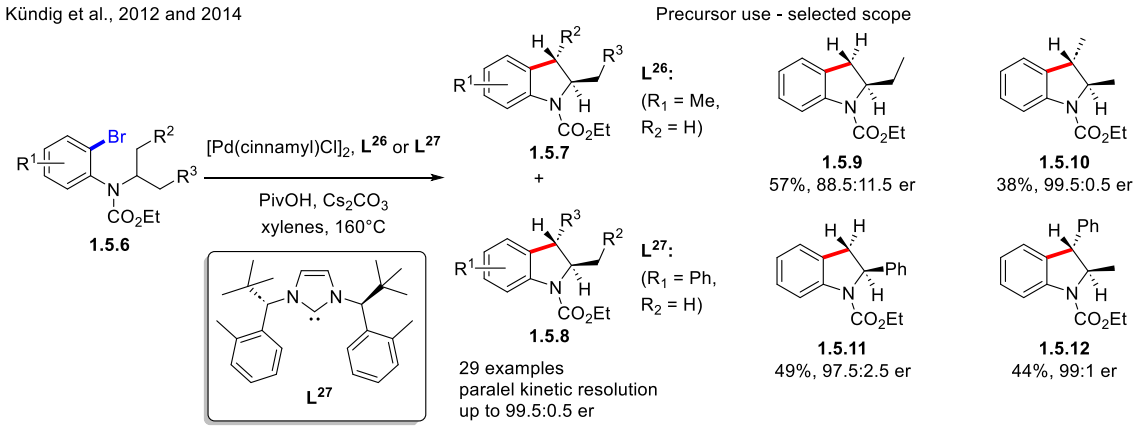
In 2011, the Kündig group reported the first use of NHC's in the Pd^0-catalyzed enantioselective $C(sp^3)$–H activation for the synthesis of enantioenriched indolines **1.5.2** (Scheme 13).[84] The C_2-symmetric ligand architecture of **L[26]**, initially employed by the groups of Enders[85] and Hermann[86] enabled the activation of a challenging methylene $C(sp^3)$–H bond in a highly stereoselective fashion by the use of bulky nitrogen substituents to ensure good quadrant differentiation. This reaction engendered fused indoline products

1.5.3, **1.5.4**, **1.5.5** in good yields and enantioselectivity. Further investigation of reactivity done by the group in 2013 extended the reaction scope.[87] DFT calculations were also performed therein to probe the exact mechanism of the transformation. They initially proposed pivalate-assisted CMD process was found to be valid, confirming observed stereoselectivities.



Scheme 13. Methylene C(sp^3)–H activation in synthesis of fused indolines

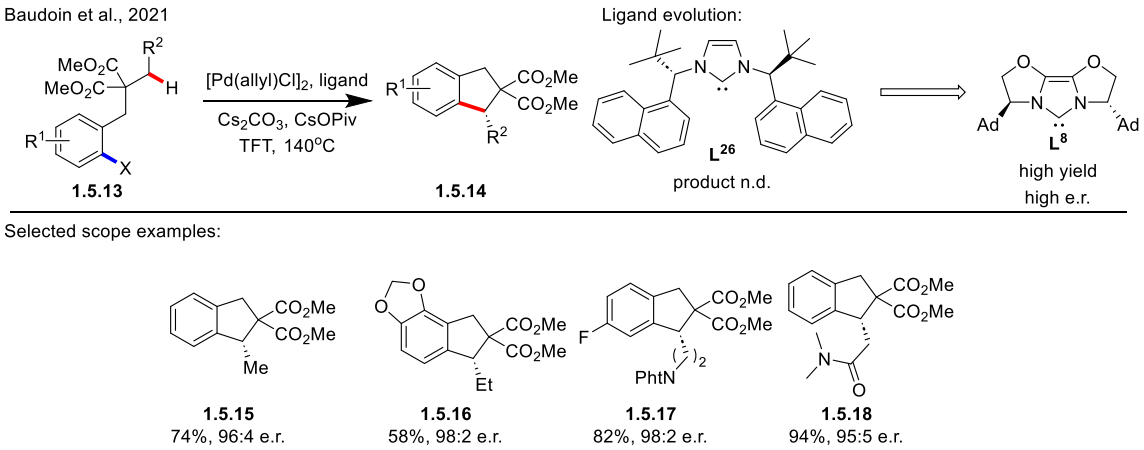
With minimal alteration of the reaction conditions and ligand architecture, such catalytic system was found to be capable of parallel kinetic resolution (PKR) when compounds with asymmetric substituents R^2 and R^3 were employed (Scheme 14).[88][89] This transformation was remarkably efficient in the resolving of enantiomers by transforming them into a 1:1 mixture of indoline regioisomers **1.5.7** and **1.5.8** with high degree of enantioselectivity. The substrate scope contained a broad range of alkyl substituents (**1.5.9** –**1.5.12**).



Scheme 14. PKR in C(sp^3)–H arylation enabled by Pd-NHC system.

Fused polycyclic systems are less challenging in the context of methylene C(sp^3)–H arylation due to a more rigid structure. In 2021, the Baudoin group has disclosed a protocol that enables the intramolecular C(sp^3)–H arylation on a flexible alkyl chain, which was

previously a challenge due to a higher degree of freedom of the alkyl group, meaning that the reaction intermediates were not as rigidly defined (Scheme 15).[51] In order to enable the formation of the indane product **1.5.14**, several changes to the system were examined. A change from the Enders/Hermann type **L^{26}** to more electron donating and bulkier IBiox-type NHC disclosed by Glorius group allowed for a higher constrainment of the reaction space required to contract the reaction site.[90][91][92] Simultaneous exploitation of angle compression by the two methyl esters further compressed the reaction space to boost overall efficiency of the transformation. A broad, diverse scope (**1.5.15** – **1.5.17**) was tolerated by even *in situ* base-mediated racemization sensitive α-carbonylated amide substrates (**1.5.18**). High conversion and enantioselectivity of the transformation was achieved by the use of IBiox.Ad **L^{8}**. This was attributed to high %V_{Bur} and quadrant differentiation respectively, which exerted effective reaction site control.



Scheme 15. Methylene C(sp^3)–H arylation on a flexible alkyl chain.

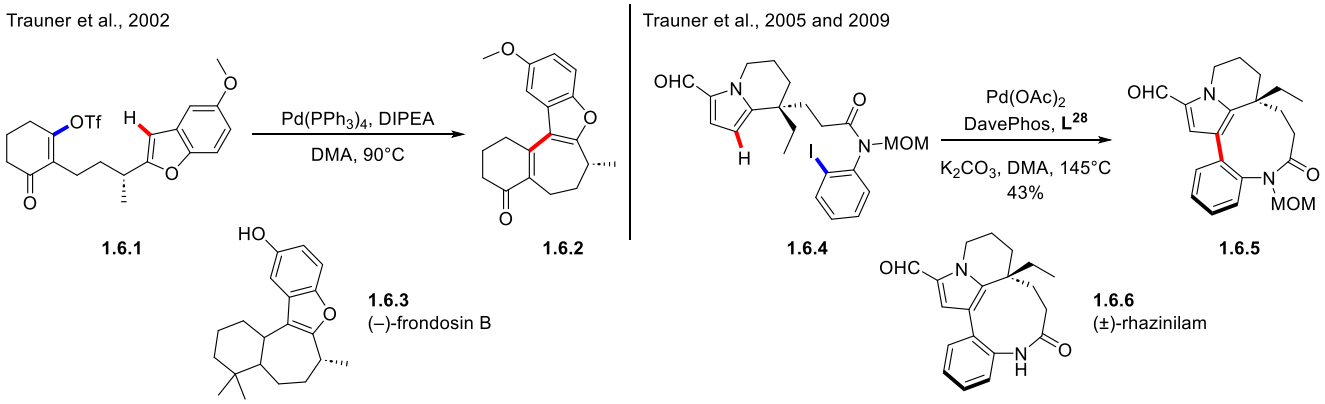
Disclosure of this reactivity enabled the exploration of total synthesis of Indidene[93] and Renifolin[94] natural products (vide infra).

NHC's enable very challenging C–H activations in an efficient and enantioselective fashion. Transformations, which were previously impossible under a Pd^0–manifold (such as activation of unbiased methylene C(sp^3)–H bonds) were shown to be possible, viable, and, thus, found their niche in total synthesis.

1.6 Applications of Pd^0–catalyzed C(sp^3)–H activation: total synthesis

Formerly, the discipline of total synthesis did not consider C(sp^3)–H activation as a viable synthetic strategy due to limitations of early C(sp^3)–H activation methodology. These transformations often required harsh conditions and tailored substrates to proceed. However, as the limitations of C–H activation processes were addressed, they gained popularity in the total synthesis community. These developments were focused on transition metal catalysis with platinum group metals. Among them, Pd-catalyzed C-H activation has a rich history of use in the context of total synthesis.[95][96]

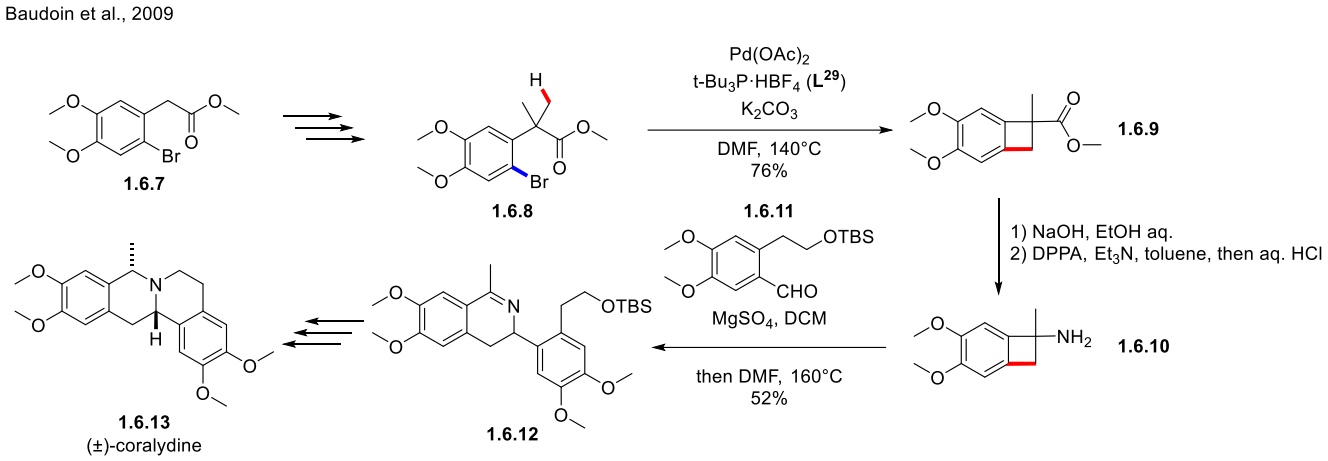
The earliest examples of Pd^0-catalysed C-H activation in total synthesis are the activation of C(sp^2)–H bonds. Representative syntheses involving this particular type of activation are syntheses of (–)-frondosin B **1.6.3** in 2002[97] and (±)-rhazinal **1.6.6** of 2005[98] and 2009[99] completed by the Trauner group (Scheme 16).



Scheme 16. Examples of Pd^0-catalyzed C(sp^2)-H activation in total synthesis.

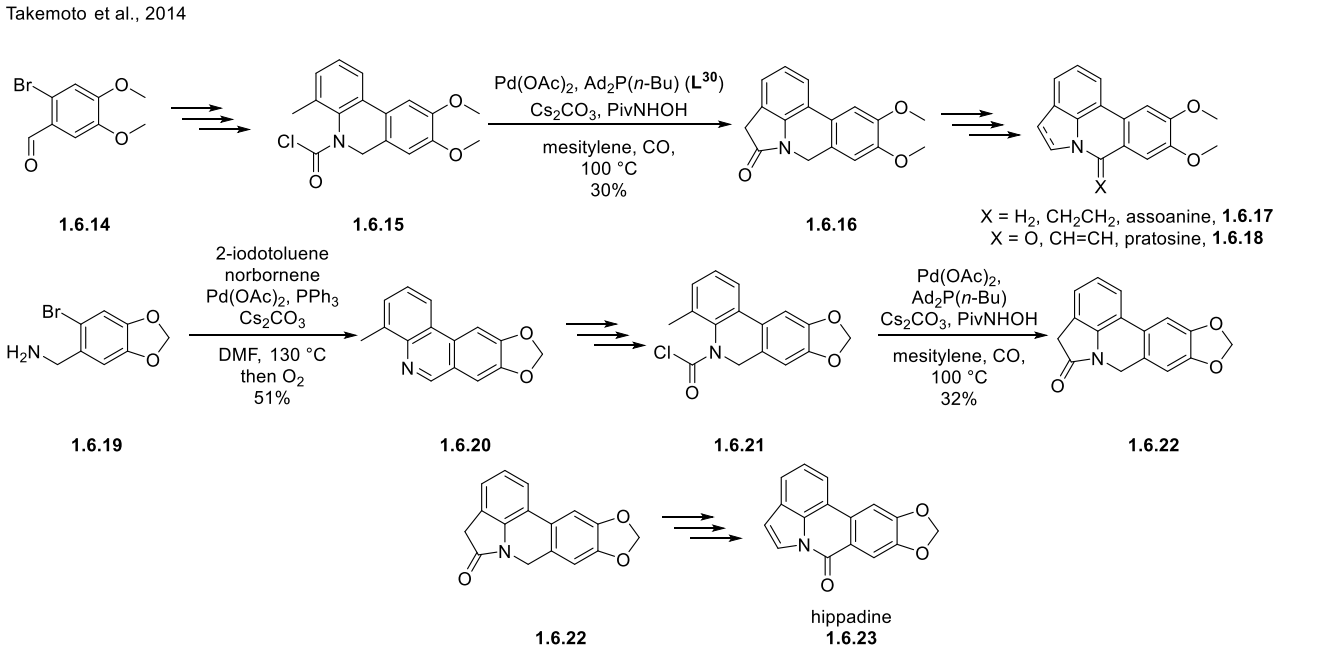
Both sequences involved the coupling of an aryl iodide with a heterocycle under Pd/aryl phosphine catalysis (**1.6.1** → **1.6.2**, PPh_3; **1.6.4** → **1.6.5**, **L[28]**), which remained a system of choice for C(sp^2)–H activation bearing total synthesis.

One of the earliest reports on the use of Pd^0-catalyzed C(sp^3)–H activations was given by the Baudoin group in their synthesis of (±)-coralydine (Scheme 17).[99] Utilizing previously disclosed work on formation of BCB's[100], an intermediate benzocyclobutene **1.6.9** was synthesized via C(sp^3)–H activation. After elaboration of the side chain ester to **1.6.10** and imine condensation with **1.6.11**, a subsequent 6π-electrocyclization furnished DHIQ **1.6.12**, which could be further elaborated to furnish (±)-coralydine **1.6.13**. Here, electron-rich tri(*tert*-butyl)phosphine **L[29]** facilitated the challenging formation of the benzocyclobutane via C(sp^3)–H arylation, by easing oxidative addition and with high steric bulk, which enabled reductive elimination of the formed palladacycle.



Scheme 17. Synthesis of (±)-coralydine.

In 2014, Takemoto group has employed a C(sp^3)–H activation protocol to furnish Amaryllidaceae alkaloids (Scheme 18).[101] By utilizing previously disclosed method, they were able to successfully construct an oxindole core by employing a tricyclic carbamoyl chloride **1.6.15** to yield tetracyclic **1.6.16**.[102] **1.6.16** then could be transformed into two natural compounds, assoanine **1.6.17** and pratosine **1.6.18**.



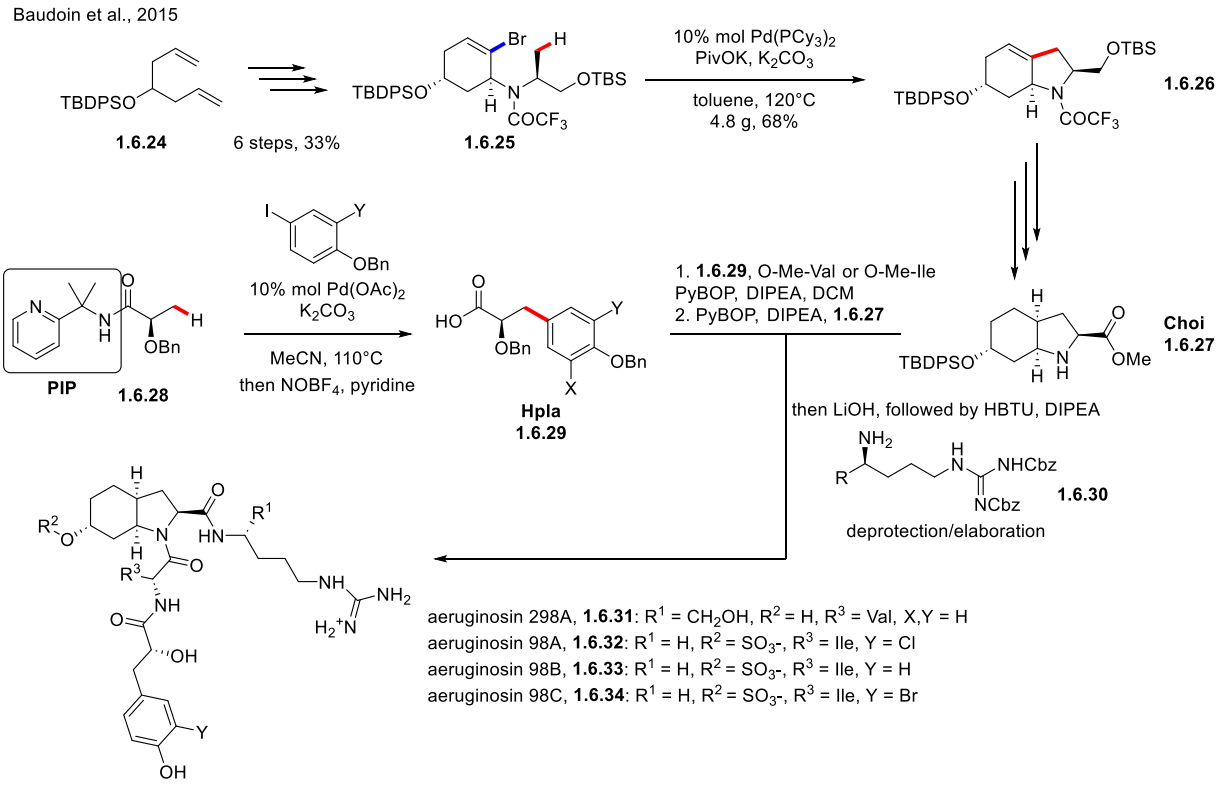
Scheme 18. Synthesis of Amaryllidaceae alkaloids *via* transformation of carbamoyl chlorides.

On the other hand, hippadine **1.6.23** was obtained via Cattelani reaction of benzylamine **1.6.19** with 2-iodotoluene, which was then transformed to the desired natural product. Here,

a use of Ad_2PBu ligand (**L**[30]) was a ligand of choice, effecting the course of the reaction similar to that seen in the synthesis of (±)-coralydine.

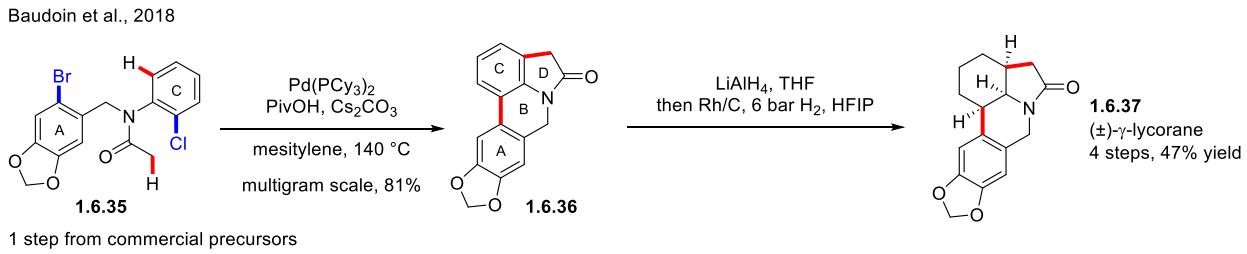
A further development in the arena of total synthesis with the activation of methyl C(sp^3)–H bonds was demonstrated by Baudoin and co-workers in 2015 with the synthesis of the Aeruginosin family of natural products (Scheme 19).[103][104]

A further improvement of the catalytic system used enabled the activation of methyl groups with β-hydrogens, which are prone to β-hydride elimination.[47][105] The introduction of $Pd(PCy_3)_2$ as a catalyst eliminated the catalyst preformation step and facilitated efficient transformation. Such approach was used to construct octahydroindole (Choi) fragment **1.6.27** of the molecule, by subjecting alaninol **1.6.25** to Pd^0-catalyzed C(sp^3)–H activation. The other fragment (Hpla, **1.6.29**) was assembled via Pd^{II}-catalyzed directed C(sp^3)–H arylation of **1.6.28**. This provided the synthesis with a point of divergence, whereby installation of different aryl moieties would ultimately lead to different natural product (**1.6.31** – **1.6.34**).



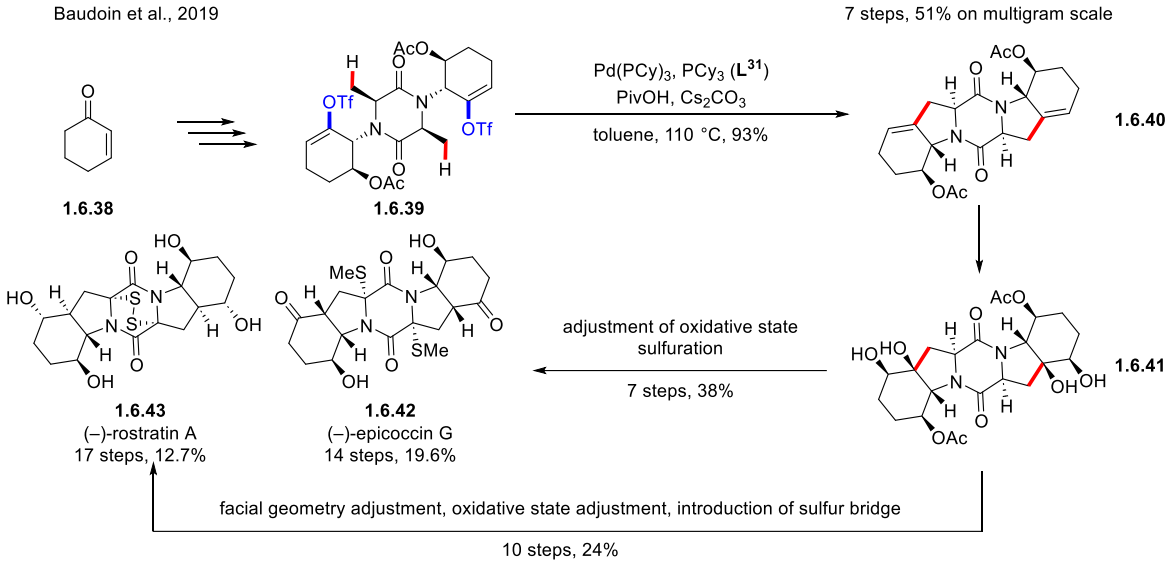
Scheme 19. Aeruginosin family of natural products – synthesis highlights.

This methodology was further explored by Baudoin group, with a synthesis of (±)-γ-lycorane in 2018[36] (Scheme 20) and the divergent synthesis of (–)-epicoccin G and (–)-rostratin A in 2019[106][107] (Scheme 21).



Scheme 20. Exploitation of multiple C–H activations – γ-lycorane.

The synthesis of γ-lycorane (and other Amaryllidaceae alkaloid congeners) was only possible with a judicious choice of aryl halide starting fragments. A potentially problematic mixture of products could be obtained, so in order to alleviate this issue, the starting material contained an aryl bromide and chloride unit, which enabled oxidative addition to take place in the desired order (**1.6.35**). This ensured high isolated yield of 81% in scale and selectivity for the desired B-C-D ring system **1.6.36**. Further manipulations with the oxidative state of the molecules provided (±)-γ-lycorane **1.6.37**, as well as other congeners.

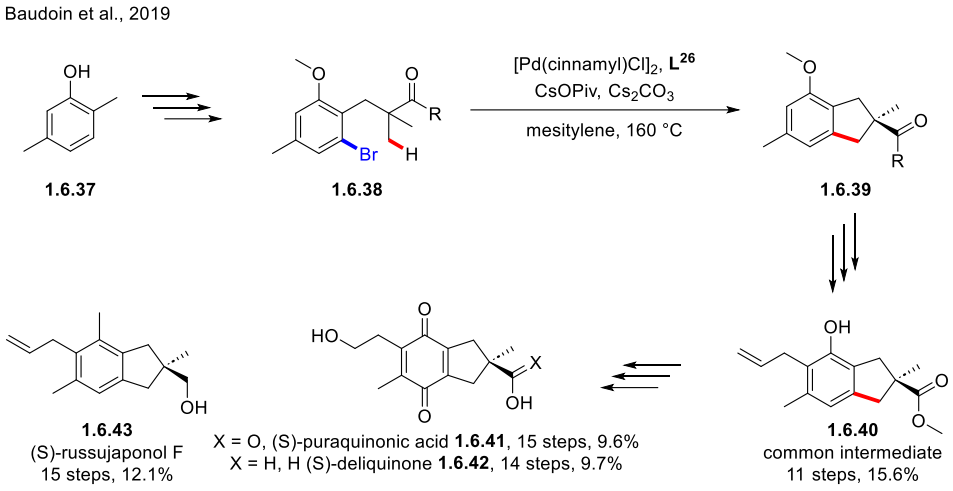


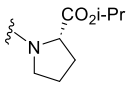
Scheme 21. Exploitation of multiple C–H activations – (–)-epicoccin G and (–)-rostratin A.

The synthesis of these two pentacyclic dithioketopiperazines (DTP) could be considered a further implementation of the approach. DTP's are a popular and challenging research targets due to the pentacyclic systems presented. With this in mind, precursor ditriflate **1.6.39** was obtained *via* elaboration of cyclohexanone **1.6.38** and further dimerization. After a brief optimization, this system was found to be highly competent in the generation of pentacyclic intermediate **1.6.40** in gram scale, which was further used as a divergence point. Subsequent hydroxylation, adjustment of the oxidation level, and sulfuration of the intermediate **1.6.41** led to (–)-epiccocin G **1.6.42** with an improvement to the yield and step

count with what the group of Nicolaou reported.[108] To obtain the other desired target, a sequence of elimination-hydrogenation led to establishment of the desired *trans*-configuration and opened a path towards (–)-rostratin A **1.6.42**, which was successfully executed.

The catalytic systems shown before all suffer from a natural limitation. Namely, inability to set stereocenters which results in reliance on preset stereocenters that usually come from the chiral pool. While not necessarily debilitating, this represented a challenge when an all-carbon stereocenter needs to be constructed. This issue was addressed in 2019 by the synthesis of (nor)illudalane sesquiterpenes (S)-puraquinonic acid **1.6.41**, (S)-deliquinone **1.6.42** and (S)-russujaponol F **1.6.43** disclosed by the Baudoin group (Scheme 22).[109][110]



#	R	NHC	Outcome[1]
1	OMe		92%, 66:34 e.r.
2		**L**^{26}	82%, 87:13 e.r.

[1] Isolated yield on 0.2 mmol scale.

Scheme 22. Construction of a full-carbon stereocenter – (nor)illudalane sesquiterpenes.

By the use of the Enders/Hermann type NHC (**L**^{26}), it was possible to desymmetrize two methyl groups with great yield and moderate enantioselectivity. To improve the enantioselectivity, a combination of chiral substrate **1.6.38** (table entry 2) and NHC **L**^{26} was used, which represent a matching, synergistic case. Further FGI and a Claisen rearrangement led to a common intermediate **1.6.40**, which served as a divergence point in the synthesis of all the desired natural products by manipulation of the oxidation state of the aromatic core and hydroxylation of the side-chain.

Overall, Pd^0-catalysis is a versatile tool for total synthesis. These methods have been predominantly focused on oxidative addition guided intramolecular C–H activation. The number of types of C–H bonds that could be activated has been drastically expanded to include activated and non-activated C(sp^2)–H bonds and methyl C(sp^3)–H bonds. This was usually performed via Pd/phosphine catalysis. However, such systems were inadequate in terms of activation of unbiased methylene C(sp^3)–H bonds, which, for a long time, was an unobtainable goal. New developments in Pd/NHC catalysis have opened this possibility, which we have exploited throughout our development of total synthesis of Indidene natural products.

1.7 Aim of this thesis

As was shown in the previous sections, the alteration of ligands in the context of metal-catalyzed C(sp^3)–H activation enables a great diversity of transformations. Given the expertise of our research group in utilization of various classes of ligands in the context of Pd-catalyzed C–H activation, we were perfectly positioned to explore such effects.

Therefore, the aim of this work was to explore various ligand-mediated Pd-catalyzed C–H activations with the aim of developing new reactivity and exploitation of said developments in total synthesis of natural products.

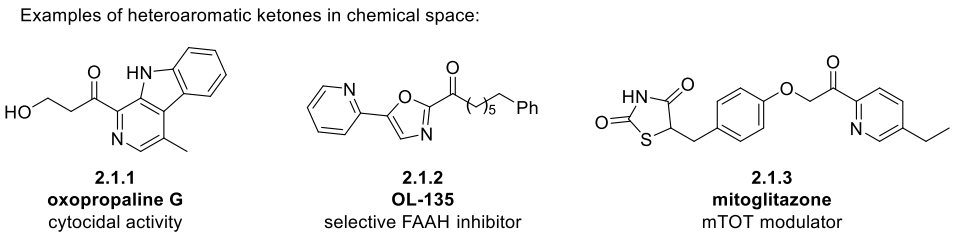
In the first part of this thesis, our developments towards an intramolecular, site-selective C(sp^3)–H activation of heteroaromatic ketones are disclosed. Such ketones are found in pharmaceutically relevant targets and natural products. This transformation could be potentially relevant in a setting beyond academic labs owing to the potential for post-functionalization of this class of compounds, as well can serve as a jumping point for other types of functionalization.

In the second part, the total synthesis of bioactive natural products from the Indidene family is examined, with the key retrosynthetic disconnection being a challening Pd^0-catalyzed methylene C(sp^3)–H activation. These natural products possess a promising anticancer and anti-inflammatory activity and, together with the prior developments in synthesis of indane-containing natural products, represent a good target for the aforementioned method. With it, we also sought to clarify the structure of the natural products from the family.

Part II: Pd-Catalyzed C(sp^3)−H Arylation of Heteroaromatic Ketones

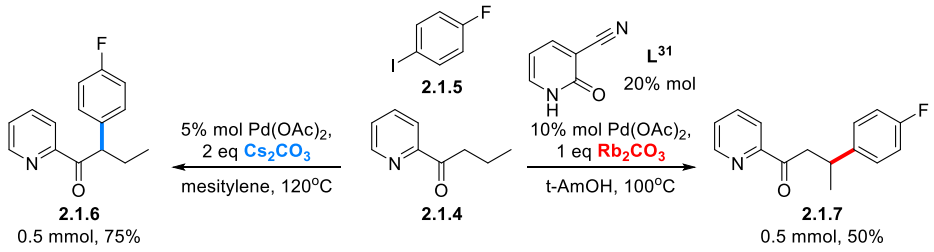
2.1 Research summary

Heteroaromatic ketones hold a significant position in the realm of medicinal chemistry, serving as a recurring element in both synthetic and naturally occurring molecules with notable biological effects (Scheme 23).[111][112] Consequently, this category of compounds receives considerable attention in the field of drug discovery, where the creation of extensive and diverse modified libraries is crucial. Although techniques for modification of the side-chain of these ketones exist, the application they find is limited, necessitating expensive *de novo* synthesis. Therefore, a unified manifold may represent an item of interest.



Scheme 23. Heteroaromatic ketones in chemical space.

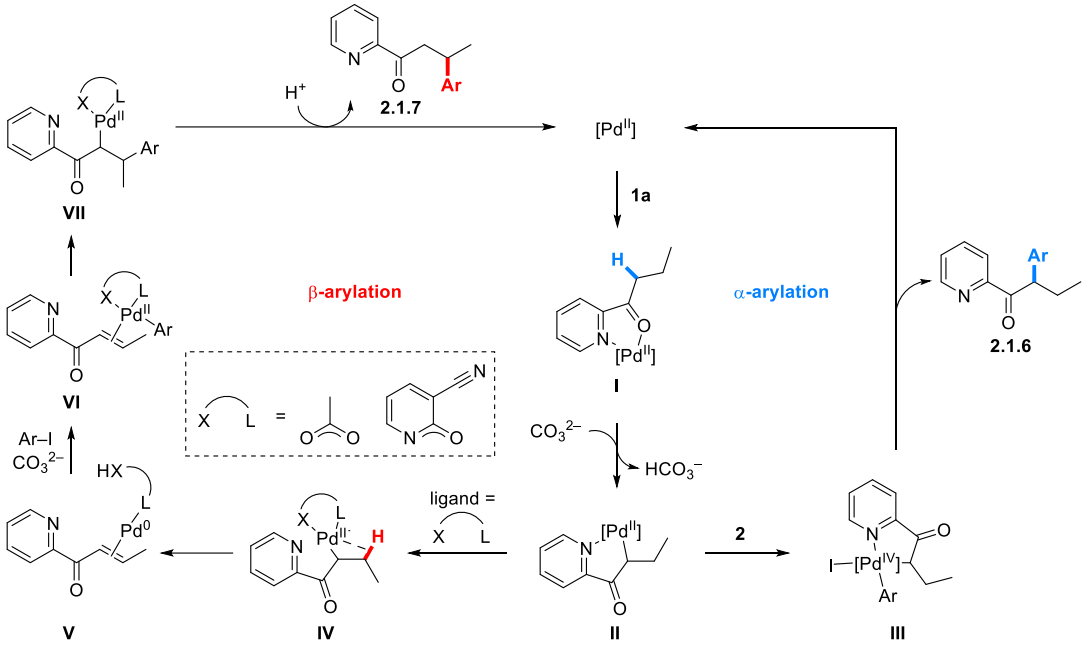
During our investigation of the intermolecular Pd-catalyzed directed C(sp^3)–H arylations, we found suitable conditions for the α- and β-arylation of 2-butanoylpyridine **2.1.4** (Scheme 24). This set of transformations was enabled mainly by using electron-deficient 2-pyridone **L^{31}**, which efficiently ligated to the Pd center. Additional modification of the base and solvent allowed for efficient generation of a single regioisomer (**2.1.6** or **2.1.7**).



Scheme 24. Divergent C(sp^3)–H arylation of 2-butanoylpyridine.

Throughout the investigation, the protocol for α-arylation was shown to be broadly applicable, with 31 substrates bearing a diverse assortment of substituents on the aryl, heteroketone and chain part of the molecule being synthesized. While at the same time, β-arylation was narrower in scope, with 5 entries disclosed mostly focusing on variations of the aryl substituent.

To probe the mechanism of this selectivity switch, we performed a set of mechanistic experiments. These experiments indicated that the α-arylation proceeds *via* Pd^{II}-Pd^{IV} C–H arylation manifold rather than enolate arylation, while β-arylation, although initially assumed to be a similar process, proceeds via desaturative functionalization. This allowed us to propose a unified mechanistic hypothesis (Scheme 25).



Scheme 25. Generalized mechanistic manifold for α- and β-arylation of heteroaromatic ketones.

In the following part of the manuscript, we disclose our full investigation of C–H α- and β-arylation of heteroaromatic ketones in the form of a full paper.[113]

2.2 Publication about this work

A. Kudashev, O. Baudoin, *Chemistry – A European Journal* **2021**, *27*, 17688-17694.

Chemistry–A European Journal
Full Paper
doi.org/10.1002/chem.202103467
Chemistry Europe
European Chemical Societies Publishing

Site-Selective Pd-Catalyzed C(sp^3)–H Arylation of Heteroaromatic Ketones

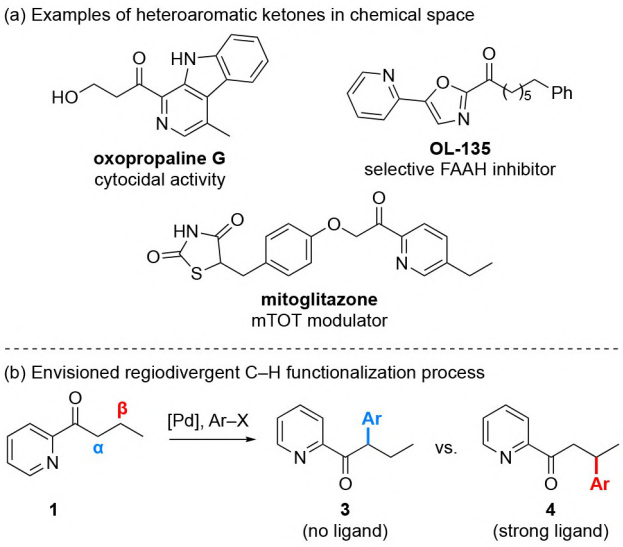
Anton Kudashev[a] and Olivier Baudoin*[a]

Abstract: A ligand-controlled site-selective C(sp^3)–H arylation of heteroaromatic ketones has been developed using Pd catalysis. The reaction occurred selectively at the α- or β-position of the ketone side-chain. The switch from α- to β-arylation was realized by addition of a pyridone ligand. The α-arylation process showed broad scope and high site- and chemoselectivity, whereas the β-arylation was more limited. Mechanistic investigations suggested that α-arylation occurs through C–H activation/oxidative addition/reductive elimination whereas β-arylation involves desaturation and aryl insertion.

Introduction

Heteroaromatic ketones represent a diverse chemical space present in numerous bioactive molecules, natural products, and other functional molecules (Scheme 1a).[1–3] Therefore, this class of compounds is the subject of regular studies in medicinal chemistry as a gateway to new drug candidates, usually through costly and time-consuming de novo synthesis.

In this context, the development of an operationally simple regiodivergent post-functionalization strategy is desirable to facilitate further discoveries. Toward this goal, we envisioned that a heterocycle-directed, site-selective Pd-catalyzed C–H activation process could, with minimal tuning, be developed to access diversely functionalized heteroaromatic ketones. While non-directed C(sp^2)–H activation strategies were successfully employed to functionalize heterocycles,[4] the site-selective functionalization of aliphatic chains remains a major challenge.[5] To date, this has been achieved either by employing particular reagents that change the selectivity-determining step,[6] or by designing new directing groups in combination with suitable ligands.[7] However, switching the selectivity by simply altering the reaction conditions has not yet been realized, to the best of our knowledge. Arylation at the α-position of heteroaromatic ketones was reported via Pd^0-catalyzed coupling of the corresponding enolate with an aryl iodide.[8] In addition, Pd^{II}-catalyzed nitrogen-directed C–H arylation was established as an efficient tool to arylate non-keto heteroarenes via 5-membered palladacycle intermediates.[9] On the other hand, the selective C(sp^3)–H arylation of the β-position of (hetero)aromatic ketones is limited to a Rh/Cu-catalyzed method involving in situ desaturation.[10,11] Pd-catalyzed β-arylation reactions involving such a desaturation/conjugate addition mechanism have been reported, but are limited to dialkylketones.[12,13] Importantly, no unified manifold for a facile selectivity switch exists, which prompted us to investigate such a possibility (Scheme 1b). We hypothesized that the α- versus β-selectivity in the arylation of heteroaromatic ketones such as **1** could be controlled by changing the reaction conditions to affect the coordination of the metal to the pyridine nitrogen. In particular, in the absence of a strong ligand, α-arylation should occur to produce ketone **3** through pyridine-directed C–H activation. Conversely, the presence of a strong exogeneous ligand could open up the desaturation/



Scheme 1. Regiodivergent arylation of heteroaromatic ketones: relevance and current work.

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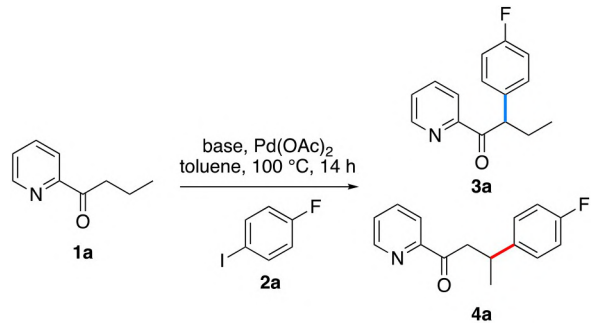
Supporting information for this article is available on the WWW under https://doi.org/10.1002/chem.202103467

conjugate addition pathway leading to β-arylated ketone **4**. Given our earlier contributions to the fields of C(sp^3)–H activation[14] and migratory arylation,[15] we sought to explore the possibility of such a selectivity control.

Results and Discussion

We commenced our studies by investigating the effect of the base in the arylation of 2-butyrylpyridine **1a** with aryl iodide **2a** (Table 1). The strongest bases examined (K_3PO_4, Cs_2CO_3 and KOH) all furnished the α-arylated product **3a** as the major product together with a minor amount of product **4a** (entries 1–3). In contrast, the use of an acetate base selectively gave rise to the β-functionalized product, albeit in lower yields

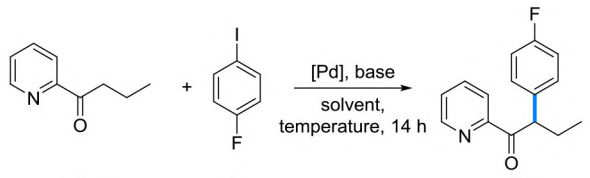
Table 1. Initial exploration of the site-selectivity.[a]



entry	base	% yield **3a** [b]	% yield **4a**[b]
1	K_3PO_4	15	5
2	Cs_2CO_3	45	1
3	KOH	37	6
4	KOAc	0	12
5	AgOAc	0	16

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), base (0.1 mmol), toluene (1 mL). [b] NMR yield using 1,1,2-trichloroethylene as an external standard.

Table 2. Optimization of α-selective arylation.[a]



entry	Base (equiv)	Solvent, *c*	*T*, °C	% yield **3a**[b]
1	Cs_2CO_3 (1)	TFT, 0.1 M	100	68
2	Cs_2CO_3 (2)	TFT, 0.1 M	100	78
3	Cs_2CO_3 (2)	mesitylene, 0.1 M	100	95
4[c]	Cs_2CO_3 (2)	mesitylene, 0.1 M	100	72
5[c]	Cs_2CO_3 (2)	mesitylene, 0.2 M	100	80 (77)
6[c][d]	Cs_2CO_3 (2)	mesitylene, 0.2 M	100	74
7[c][d][e]	Cs_2CO_3 (2)	mesitylene, 0.4 M	120	88 (75)

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), base (according to the table), solvent. [b] NMR yield using 1,1,2-trichloroethylene as an external standard, isolated yield in parenthesis. [c] Performed on 0.5 mmol scale. [d] Using 1.25 equiv of **2a**. [e] Using 5 mol% $Pd(OAc)_2$. TFT = α,α,α-trifluorotoluene.

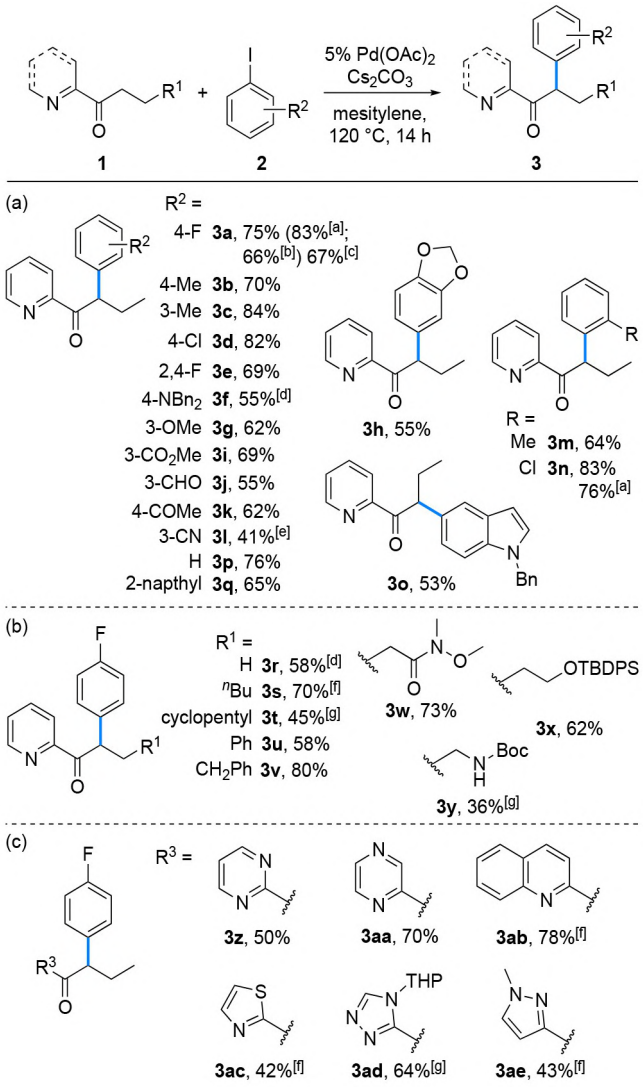
(entries 4–5). This preliminary study already demonstrated the feasibility of a conditions-based selectivity switch, and prompted us to further optimize each reaction separately.

It was possible to reach an optimum for the α-arylation reaction by tuning the stoichiometry and solvent (Table 2; see the Supporting Information for more details). The best performance was achieved in non-polar, aprotic solvents (entries 1–3), and in particular mesitylene (entry 3). Increasing the amount of Cs_2CO_3 to 2 equiv proved to be beneficial (entries 1–2). The reaction could be performed on a 5x scale at increasing concentrations (entries 4, 5 and 7), while simultaneously reducing the amount of required aryl iodide (entry 6) and palladium acetate (entry 7).

Under these conditions, the target α-arylated product **3a** was isolated in good yield on small (0.5 mmol, 77%) and preparative (2.5 mmol, 83%; 12.5 mmol, 66%) scale alike (Scheme 2a). In order to study the tolerance of these mildly basic conditions towards diverse substitution patterns, a range of aryl halides and heteroaromatic ketones were reacted. Starting off with the variation of substituents on the aryl iodide partner, both electron-deficient and electron-rich groups provided a good overall performance. Among these are alkyl groups (**3b**, **3c**), single or multiple halides (**3a**, **3d** and **3e**), a protected amine (**3f**) and protected phenols (**3g** and **3h**), products of which were obtained in good yields. Carbonyl substituents, such as unprotected ketone **3k** and aldehyde **3j**, as well as an ester **3i** were also formed in moderate yield. Interestingly, *ortho*-substituted aryl iodides were also reactive, and afforded target compounds **3m** and **3n** in good yields. Switching from an aryl iodide to a bromide was also possible with only a slightly lower efficiency (67% instead of 75%). Aryl chlorides proved to be unreactive, hence providing a handle for further functionalization (**3d**, **3n**). Finally, when aryl nitriles or heteroaryl iodides were used (**3l**, **3o**), a more moderate yield of product was obtained. This might be explained by inhibitive coordination of the aryl component to palladium and unproductive decay of the catalytically active species. Of note, further C–H arylation of **3o** at the indole ring was not observed. Finally, non-substituted and polycyclic aryl iodides, as represented by products **3p** and **3q**, were well tolerated.

Next, we investigated the reactivity of pyridyl ketones possessing different aliphatic chains (Scheme 2b). A shorter (**3r**) or a longer (**3s**) linear chain, as well as various terminal substituents (**3t**–**3v**) provided satisfying results (45–80% yields). Interestingly, the β-arylated product was not observed for substrates with R^1 = H and Ph, containing a more activated (i.e. primary or benzylic) β-position. Introducing functional groups gave varied, but satisfactory levels of performance: while Weinreb amide-bearing ketone **3w** and protected alcohol **3x** were obtained in good yields (62–73%), the Boc-protected amine **3y** was obtained in more modest yield (38%), presumably due to the same inhibitive coordination as mentioned before.

Obviously, the outcome of directed C–H activation reactions is heavily dependent on the nature of the directing group. To study the effect of the latter, we examined the reactivity of ketones with different heteroaromatic cores (Scheme 2c). We

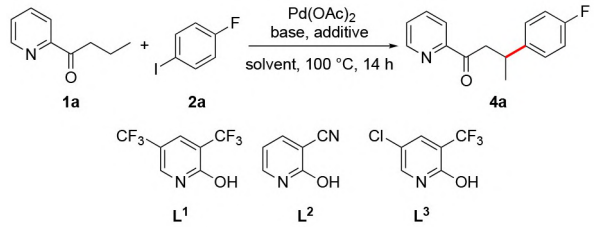


Scheme 2. Scope of the α-selective arylation of heteroaromatic ketones. Reaction conditions: **1** (0.5 mmol), **2** (0.625 mmol, 1.25 equiv), $Pd(OAc)_2$ (5 mol%), Cs_2CO_3 (1 mmol, 2 equiv). [a] Using 2.5 mmol of ketone **1**. [b] Using 12.5 mmol of ketone **1**. [c] Using the aryl bromide instead of the iodide. [d] Using 0.5 mmol (1 equiv) of **2**. [e] Using 10 mol% $Pd(OAc)_2$. [f] Using 1 mmol (2 equiv) of **2**. [g] Using 0.75 mmol (1.5 equiv) of **2**.

were pleased to find that the developed protocol could be expanded beyond pyridine-based substrates. Indeed, substrates bearing pyrimidine, pyrazine or quinoline moieties, which are all able to coordinate to Pd, gave the corresponding products **3z**–**3ab** in moderate to good yields. Moreover, five-membered heterocycles, as shown with thiazole (**3ac**), 1,2,4-triazole (**3ad**) and pyrazole (**3ae**) derivatives, were found to be competent substrates and furnished the desired α-arylated ketones in moderate yields.

Next, we decided to investigate the β-selective arylation in greater detail, which proved to be a formidable task. Our attempts to optimize the reaction conditions are summarized in Table 3. While we were able to single out conditions to achieve a high α/β selectivity, simple base and solvent variations did

Table 3. Optimization of the β-arylation of ketone **1a**.[a]

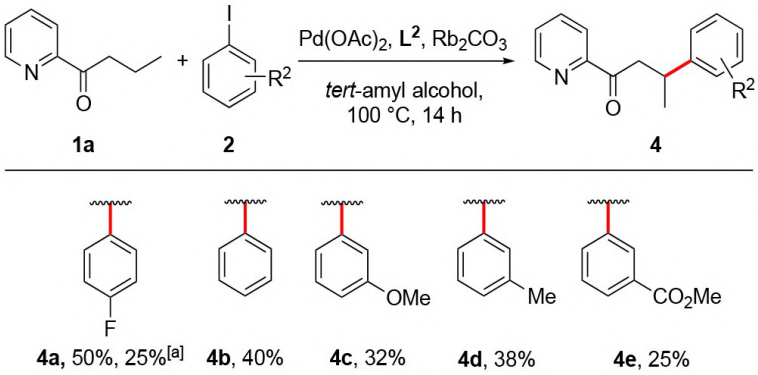


entry	base, additive (equiv)	solvent, c	ligand (mol%)	% yield **4a**[b]
1	AgOAc (1)	tol, 0.1 M	–	16
2	AgTFA (3) TFA (3)	*m*-xyl, 0.1 M	–	27
3	KOAc (1)	*t*-AmOH, 0.1 M	*N*-Ac-Gly (20)	21
4	K_2CO_3 (1.5)	*t*-AmOH, 0.1 M	L^1 (20)	39
5[c]	Rb_2CO_3 (1.5)	*t*-AmOH, 0.2 M	L^3 (20)	40
6[d]	Rb_2CO_3 (1)	*t*-AmOH, 0.2 M	L^2 (20)	50

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), base (0.1 mmol), toluene (1 mL). [b] NMR yield using 1,1,2-trichloroethylene as an external standard. [c] Using 0.2 mmol of ketone **1a**. [d] Using 0.5 mmol of ketone **1a**. tol = toluene, *m*-xyl = *m*-xylene, *t*-AmOH = *tert*-amyl alcohol.

not increase the yield of the β-arylated ketone **4a** beyond 20% (entry 1). Inclusion of additives such as TFA, in combination with AgTFA, only marginally increased the yield (entry 2). Then, we turned our attention to the addition of stronger ligands, which were introduced by Yu and co-workers to accelerate various C–H activation reactions and, in some cases, modulate the site-selectivity.[16] Whereas mono-*N*-protected amino acids (MPAAs) such as *N*-Ac-Gly did not improve the yield (entry 3), the recently introduced pyridone ligands[17] were more successful, with electron-deficient pyridones L^1–L^3 providing the best results (entries 4–6). After further optimization, it was possible to obtain the target β-arylated ketone **4a** in 50% yield on a 0.5 mmol scale using Rb_2CO_3 as the base and *tert*-amyl alcohol as the solvent (entry 6). Despite the moderate yield, a total selectivity for the β-position was observed. This is remarkable considering that a similar stoichiometric base (i.e., carbonate) is employed for α-selective reaction, and demonstrates a strong ligand control over the site-selectivity. In addition, no diarylated product was observed under these conditions. Further modifications such as ligand combinations did not furnish any tangible increase in isolated yield, despite extensive investigations.

With these conditions in hand, other aryl iodides were tested (Scheme 3). Unfortunately, despite the high selectivity observed for the corresponding β-arylated products, the yields were all lower than the one obtained with **2a**. Similar to the α-arylation, an aryl bromide was reactive albeit with a lower yield. Regrettably, it was not possible to transpose this reactivity towards other heteroaromatic ketones in synthetically useful yields. Therefore, the current results serve as a proof of concept that ligand-controlled selectivity switch is possible without modifying the substrates, but synthetic utility remains to be improved.

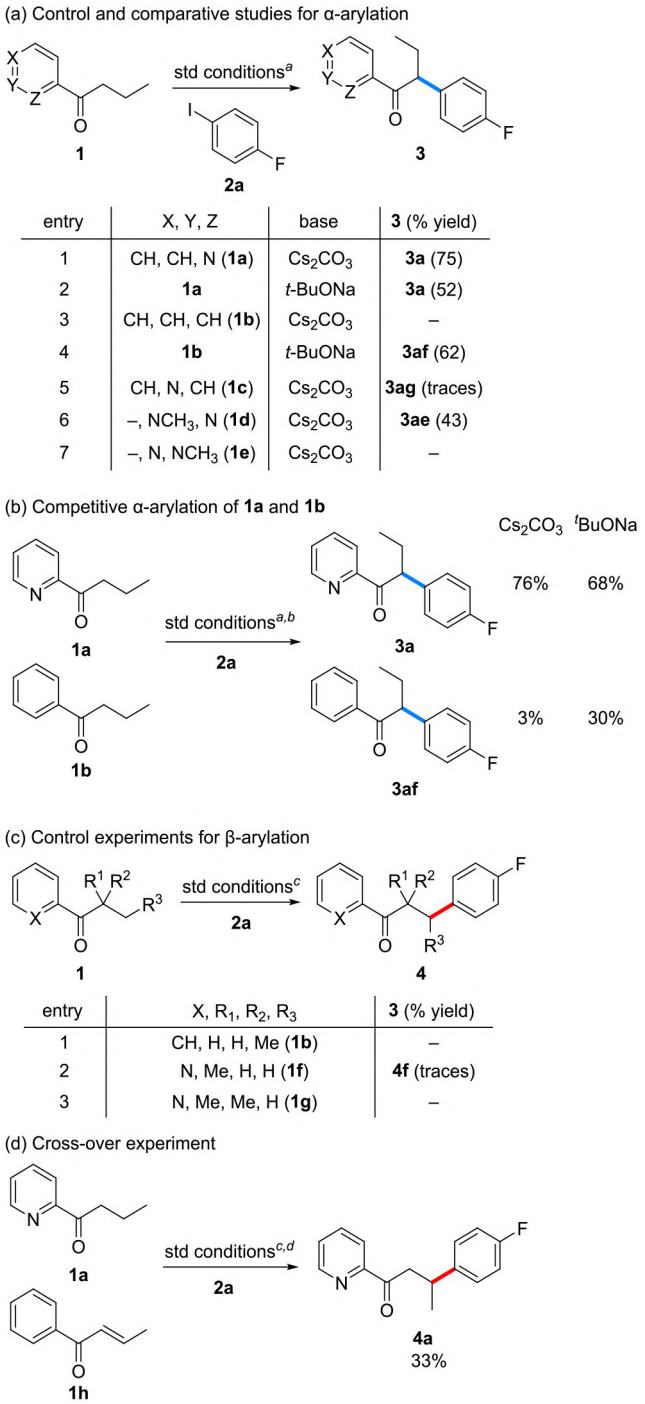


Scheme 3. Scope of the β-selective arylation of heteroaromatic ketones. Reaction conditions: **1a** (0.5 mmol), **2** (1 mmol), $Pd(OAc)_2$ (10 mol%), L^2 (20 mol%), Rb_2CO_3 (0.5 mmol). [a] Using the bromide instead of the iodide.

To get insights into the α-arylation process, we performed a series of comparative studies (Scheme 4). First off, to probe the competition between C–H activation and enolate arylation pathways, we compared the action of *t*-BuONa against Cs_2CO_3 (Scheme 4a). Sodium *tert*-butoxide is a strong base, which should facilitate rapid deprotonation at the α-position in a heteroaromatic ketone to form its corresponding enolate, thus shifting the process from C–H activation to enolate arylation.[8] Indeed, when model ketone **1a** was tested, both bases gave rise to product **3a**, albeit with a higher yield for Cs_2CO_3 (entries 1–2). In contrast, when butyrophenone **1b** lacking coordination ability was utilized, only *t*-BuONa provided the arylated product **3af** (entries 3–4). Moreover, the 3-pyridinyl ketone **1c** lacking directing ability only provided traces of product (entry 5). Likewise, whereas the 3-substituted pyrazole derivative **1d** provided α-arylated ketone **3ae** in moderate yield (entry 6, see also Scheme 2), the analogous 5-pyrazolyl ketone **1e** failed to react under the optimized conditions (entry 7). In parallel, we compared the performance of Cs_2CO_3 and *t*-BuONa on base-sensitive substrates containing a methyl ketone (product **3k**, see Scheme 2) or Weinreb amide (product **3w**). Whereas Cs_2CO_3 provided **3k** and **3w** in good yields, these products were not obtained in the presence of *t*-BuONa, with only decomposition being observed. Finally, a competitive reaction between ketones **1a** and **1b** under standard α-arylation conditions revealed a near-exclusive formation of **3a** when Cs_2CO_3 was employed, while a mixture of **3a** and **3af** was observed under *t*BuONa mediation (Scheme 4b). Taken together, these results indicate that the reaction employing Cs_2CO_3 requires coordination of Pd to the substrate nitrogen atom without preformation of the ketone enolate, whereas the latter is probably formed with *t*-BuONa. Moreover, the use of the less basic carbonate enables an increased chemoselectivity compared with *t*-BuONa. Similarly, the nature of β-arylation was investigated via comparative studies (Scheme 4c). As expected, butyrophenone **1b** did not yield any β-arylated product under optimized conditions (entry 1), thereby pointing again at the crucial coordination to the pyridine nitrogen atom. Increasing the number of methyl groups at the α-position dramatically decreased (entry 2) and even suppressed (entry 3) β-arylation, which excludes a direct C–H activation mechanism at the β-position and indicates that a desaturation mechanism is operative. A cross-over experiment with saturated pyridyl ketone **1a** and unsaturated phenyl ketone **1h** led to the exclusive formation of product **4a** (Scheme 4d), which indicates the intramolecular nature of this reaction.

Based on these elements and literature precedents on directed C–H activation,[9] as well as desaturation-mediated functionalization,[12,13] a unified mechanistic proposal is depicted in Scheme 5. Coordination of the pyridine to Pd^{II} (complex **I**) favors deprotonation with carbonate to give 5-membered palladacycle **II**. This deprotonation could occur through concerted metalation-deprotonation.[18] In the absence of a strong LX-type ligand, oxidative addition of the aryl iodide occurs to give Pd^{IV} intermediate **III**, which upon reductive elimination delivers the α-arylated product **3** with concomitant recycling of Pd^{II}. The presence of an LX-type ligand, and in particular pyridone,[19] induces the decoordination from pyridine (**II**→**IV**) and enables β-H elimination[20] to furnish **V**. In the latter, Pd^0 remains coordinated to the alkene, as indicated by the lack of cross-over in Scheme 4d. Oxidative addition of the aryl iodide and base-mediated abstraction of HI leads to **VI**, which undergoes migratory insertion to provide **VII** and, upon protonation, delivers β-arylated product **4** and recycled Pd^{II}. Obviously, we are aware that this mechanism is likely oversimplified and other pathways such as those involving Pd^0 catalysis[8] cannot be excluded at this point.

Finally, further functionalization of the obtained α-arylated products is possible (Scheme 6). In particular, compound **3n**, which possesses an *ortho*-chlorine atom was smoothly cyclized under standard Pd^0-catalyzed C–H arylation conditions[21] to obtain benzo[f]quinolinol **5a** in 85% yield, hence establishing a sequential C–H arylation route to this class of compounds.



entry	X, Y, Z	base	3 (% yield)
1	CH, CH, N (**1a**)	Cs_2CO_3	**3a** (75)
2	**1a**	*t*-BuONa	**3a** (52)
3	CH, CH, CH (**1b**)	Cs_2CO_3	–
4	**1b**	*t*-BuONa	**3af** (62)
5	CH, N, CH (**1c**)	Cs_2CO_3	**3ag** (traces)
6	–, NCH_3, N (**1d**)	Cs_2CO_3	**3ae** (43)
7	–, N, NCH_3 (**1e**)	Cs_2CO_3	–

entry	X, R_1, R_2, R_3	3 (% yield)
1	CH, H, H, Me (**1b**)	–
2	N, Me, H, H (**1f**)	**4f** (traces)
3	N, Me, Me, H (**1g**)	–

Scheme 4. Control and comparative studies. [a] Reaction conditions: **1** (0.5 mmol), **2a** (0.625 mmol, 1.25 equiv), $Pd(OAc)_2$ (5 mol%), Cs_2CO_3 or *t*-BuONa (1 mmol), mesitylene, 120 °C, 14 h. [b] Additional 0.5 mmol (1 equiv) of **1b** was used. [c] Reaction conditions: **1a** (0.5 mmol), **2** (1 mmol), $Pd(OAc)_2$ (10 mol%), L^2 (20 mol%), Rb_2CO_3 (0.5 mmol), *tert*-amyl alcohol, 100 °C, 14 h. [d] Additional 0.5 mmol (1 equiv) of **1h** was used. Yields in reactions (b)-(d) refer to NMR yields using 1,1,2-trichloroethylene as an external standard.

Conclusion

A switchable site-selective arylation of heteroaromatic ketones by employing Pd-catalyzed directed C–H activation was developed. The α-arylation reaction employed mildly basic conditions and proved efficient and chemoselective on a broad range of aryl iodide and ketone substrates, including various heteroarenes. Employing a pyridone ligand allowed to switch the selectivity towards β-arylation, without having to rely on substrate modification, albeit with a much lower efficiency and generality. This work demonstrates the feasibility of conditions-controlled site-selectivity in metal-catalyzed C(sp^3)–H functionalization.

Experimental Section

General procedure for α-arylation: To an oven-dried threaded culture tube (10 mL) equipped with a PTFE-coated magnetic stirrer cesium carbonate (2 equiv) was charged. The tube was then introduced into the glovebox, where palladium acetate (5% mol) was charged. The tube was closed with a septum and removed from the glovebox, then ketone **1**, aryl halide **2** (1.25 equiv) and mesitylene (0.4 M) were added by syringe. The septum was then replaced in a flow of argon with a screwcap and the reaction mixture was stirred in a heating block at 120 °C for 14 h. The reaction mixture was then cooled to r. t., diluted with CH_2Cl_2 (2 mL) and filtered over a pad of Celite. Solids were then washed with CH_2Cl_2 (2×2 mL) and the combined filtrate was evaporated at reduced pressure, dry-loaded onto Celite and subjected to column chromatography to yield the corresponding α-arylated product **3**.

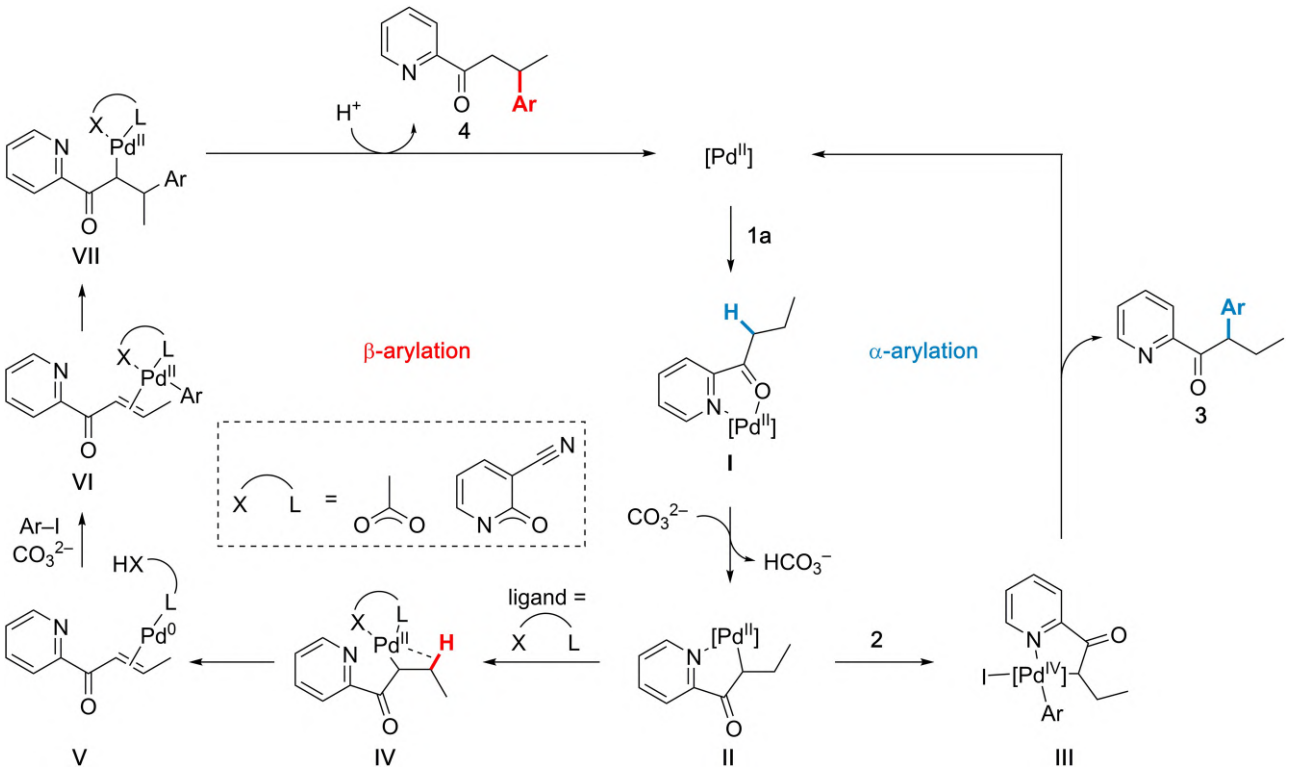
General procedure for β-arylation: To an oven-dried threaded culture tube (10 mL) equipped with a PTFE-coated magnetic stirrer rubidium carbonate (1 equiv) and L^2 (20 mol%) were charged. The tube was then introduced into the glovebox, where palladium acetate (10% mol) was charged. The tube was closed with a septum and removed from the glovebox, then ketone **1**, aryl halide **2** (2 equiv) and *tert*-amyl alcohol (0.2 M) were added by syringe. The septum was then replaced in a flow of argon with a screwcap and the reaction mixture was stirred in a heating block at 100 °C for 14 h. The reaction mixture was then cooled to r. t., diluted with CH_2Cl_2 (2 mL) and filtered over a pad of Celite. Solids were then washed with CH_2Cl_2 (2x2 mL) and the combined filtrate was evaporated at reduced pressure, dry-loaded onto Celite and subjected to column chromatography to yield the corresponding β-arylated product **4**.

Acknowledgements

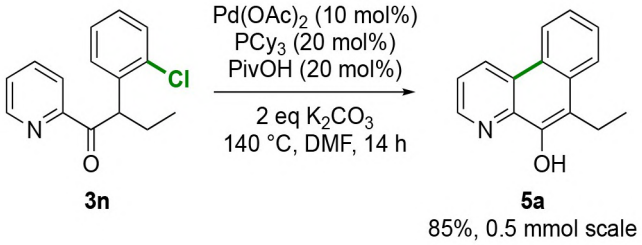
This work was financially supported by the Swiss National Science Foundation (grant # 200021_184608) and the University of Basel. We thank Dr. D. Häussinger for NMR experiments, and Dr. M. Pfeffer for MS analyses. Open access funding provided by Universitat Basel.

Conflict of Interest

The authors declare no conflict of interest.



Scheme 5. Mechanistic proposal.



Scheme 6. Post-functionalization reaction.

Keywords: arylation · C–H activation · palladium · site-selectivity

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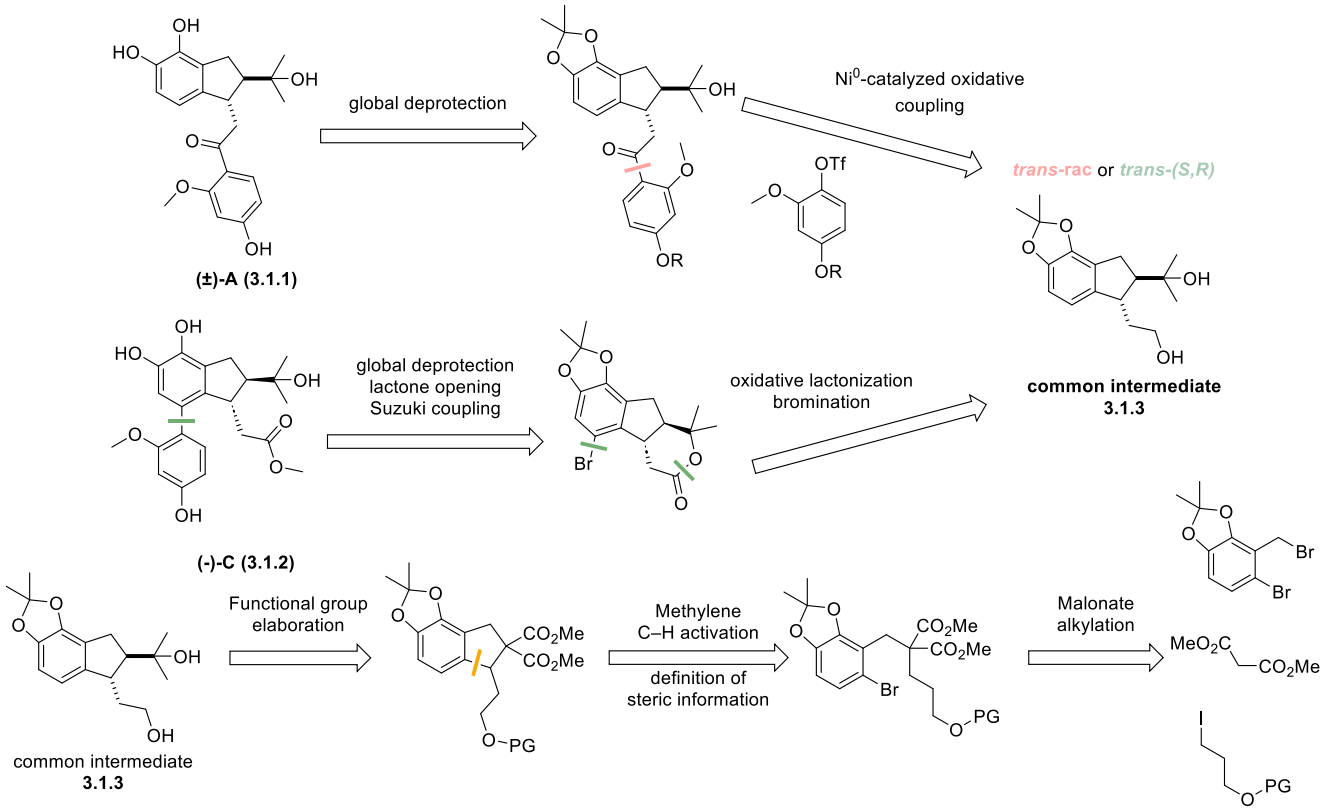
Manuscript received: September 23, 2021
Version of record online: November 11, 2021

Part III: Methylene C(sp^3)–H activation enables stereoselective synthesis and structure correction of Indidene natural products

** Work realized in collaboration with Dr. Stefania Vergura during her postdoctoral stay in our group and Dr. Marco Zuccarello during his PhD studies, as well as Prof. Dr. Thomas Bürgi, who performed VCD calculations.*

3.1 Research summary

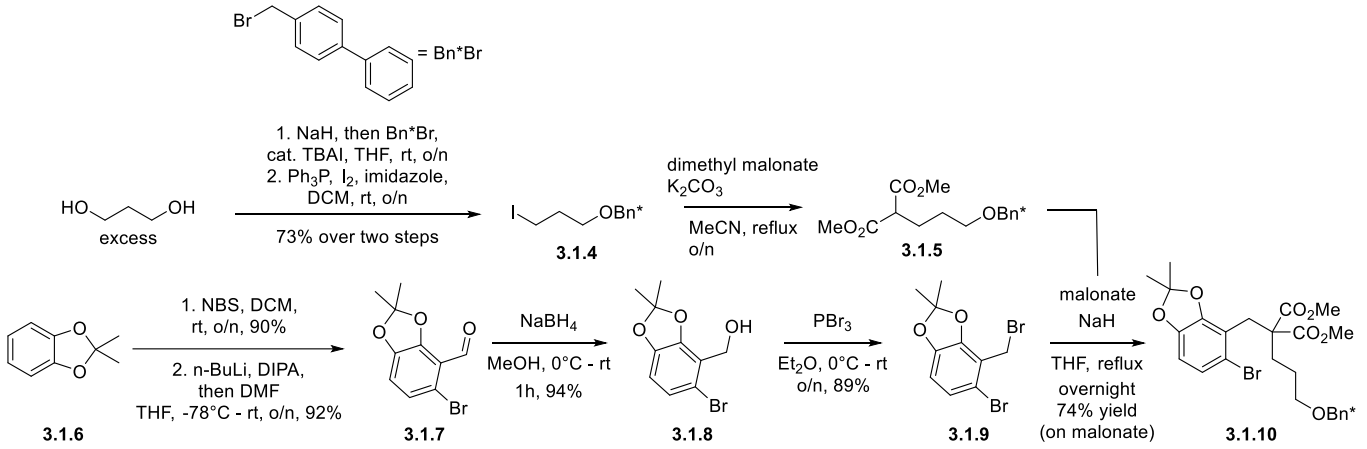
While we were investigating α-/β-selective arylation in heteroaromatic ketones, our group successfully tackled the problem of enantioselective methylene C(sp^3)–H activation. In particular, this discovery has given us access to enantiomerically enriched 2,3-dihydro-1H-indene scaffolds, which are abundantly represented in biologically active molecules.[114] Our attention fell onto Indidene[93] and Renifolin[94] families of natural products, which possess mild anti-cancer and anti-inflammatory properties excellent for further SAR studies and a general polyhydroxylated scaffold,[115] which are challenging to construct. This was also coupled with a certain degree of ambiguity in the structural assignment: while the assignment of configuration of Indidene A via XRD left little doubt, structures of Indidene B and C were assigned using a combination of calculated ECD and NOESY spectra. Curiously, near identical ^{1}H and ^{13}C data for both molecules and a unusual *cis*-configuration of Indidene B, not found within both families of natural products, introduced a degree of doubt into the initial assignment. We were prompted to explore the synthesis of two Indidene family members, (±)-Indidene A (**3.1.1**) and (–)-Indidene C (**3.1.2**). Our retrosynthetic plan towards these natural products is shown on Scheme 26.



Scheme 26. Retrosynthetic plan for (±)-Indidene A and (-)-Indidene C.

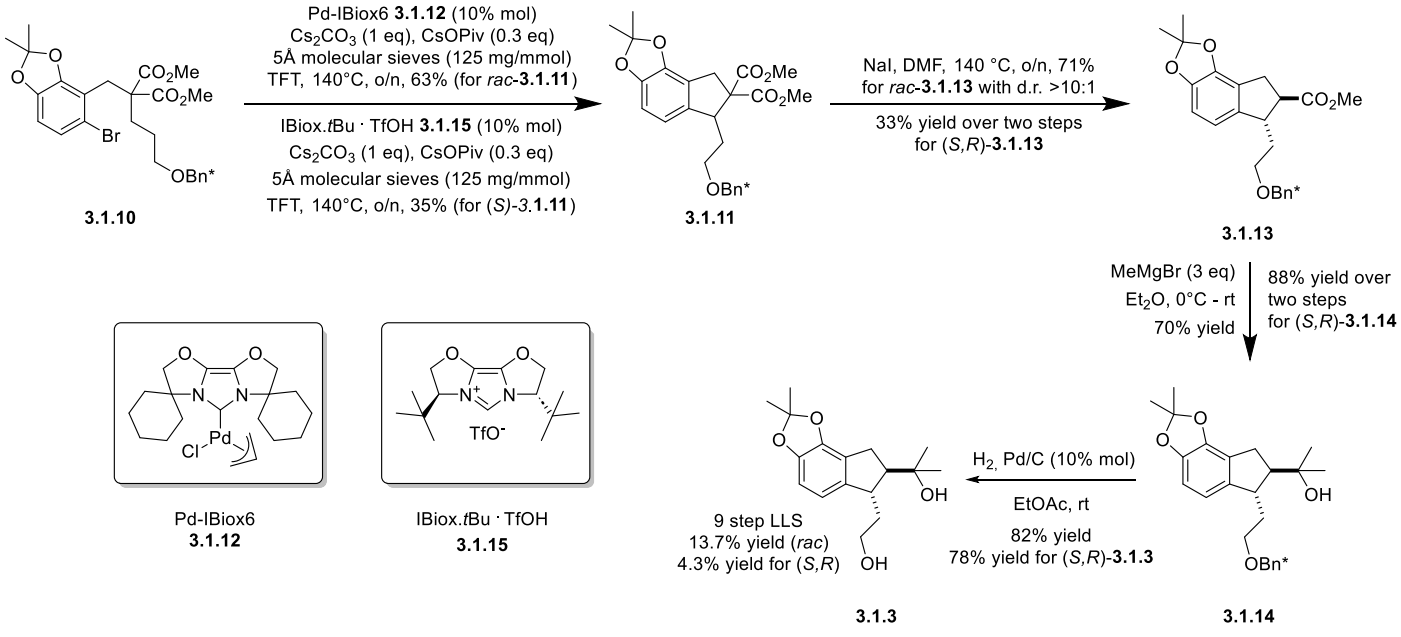
In it, we envisioned that it is possible to access both natural products from a common intermediate – diol **3.1.3**, which, in turn, can be obtained from the product of C–H activation. Precursor to the C–H activation could be further disassembled with malonate alkylation towards simple starting materials.

We first proceeded with the synthesis of the common intermediate (Scheme 27).



Scheme 27. Synthesis of the common intermediate – synthesis of C–H precursor.

The C-H activation precursor was obtained from a convergent synthesis of two fragments – a sidechain **3.1.5** and a bromide core **3.1.9**. They were sequentially coupled to dimethyl malonate to yield the C-H activation precursor **3.1.10**.

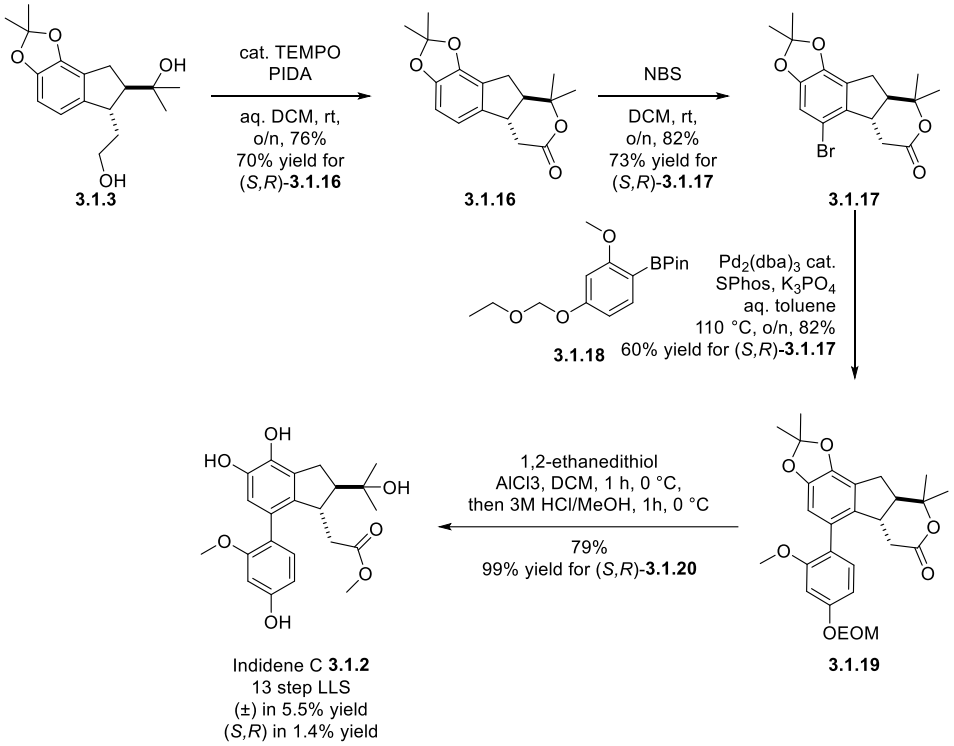


Scheme 28. Synthesis of the common intermediate – C–H activation and further elaboration.

We discovered that standard C-H activation conditions, disclosed in the parent article, were not fully suited for our substrate (Scheme 28). By modification of the substrate to include, as well as introduction of a pre-defined complex **3.1.12**, we were able to stabilize the performance of the C-

H activation and avoid costly prep-HPLC separation of the side products to yield C-H activation product in 63% yield. Further manipulations on the malonate group and deprotection yielded the common intermediate, diol **3.1.3** in 9 steps (LLC) and 13.7% yield overall.

From here, the synthesis diverges. Careful adjustment of the oxidation state of the diol **3.1.3** and introduction of the bromide on the catechol core gave rise to bromide **3.1.17**, which was then subjected to Pd-catalyzed Suzuki cross-coupling to yield biphenyl **3.1.19**, which then could be subsequently globally deprotected to yield (±)-Indidene C **3.1.2** (Scheme 29). Upon careful inspection of the spectroscopical data of the obtained product, a discrepancy was observed in the NOESY data, with the obtained material closely resembling other isolated natural product, Indidene B. SC-XRD of the obtained racemic sample has confirmed the expected *trans*-configuration, thus showing that **3.1.2** is *rac*-Indidene C.

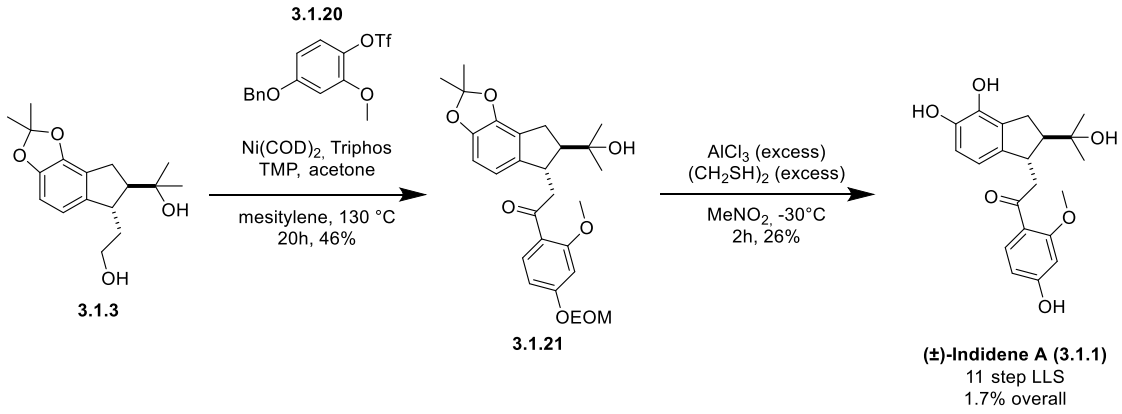


Scheme 29. Route to Indidene C.

An enantioselective synthesis of (*S,R*)-Indidene C was facilitated by the use of preformed Pd-(*S,S*)-IBiox.tBu **3.1.15** to yield (*S*)-**3.1.11** in high enantioselectivity (99:1 e.r.), albeit in a dimished yield of 35%. Further elaboration afforded (*S,R*)-configured diol **3.1.3** in 4.1% yield and no loss of enantiopurity, followed by abovementioned construction of (*S,R*)-Indidene C **3.1.2** in 1.4% yield. Assignment of configuration was initially performed based on previous work and was further confirmed by VCD studies of (*S,R*)-**3.1.16**. Upon examination of the optical rotation of the (*S,R*)-**3.1.2**, a sign discrepancy between the value described for (-)-Indidene C and a value obtained was found. Further ECD measurements gave a very close resemblance of the obtained spectra with the recorded spectra of the initially assigned (+)-Indidene B. We thus propose a reassignment

of the structures of Indidene B and C, suggesting that both of them are enantiomers of the same general structure 3.1.2, with Indidene B represented by the (*S,R*)-**3.1.2** and Indidene C being its enantiomer, (*R,S*)-**3.1.2**.

Diol **3.1.3** was subjected to Ni^0-catalyzed dehydrogenative cross-coupling with a triflate **3.1.20**, as per modified protocol first disclosed by Newman in 2019[116] to yield ketone **3.1.21** in 46% yield. Final deprotection has turned out to be challenging, with current best conditions yielding 22% of (±)-Indidene A **3.1.1** (Scheme 30).



Scheme 30. Route to (±)-Indidene A.

Overall, we have achieved the enantioselective synthesis of (+)-Indidene C and a racemic synthesis of (±)-Indidene A in an expedient, convergent fashion. This was enabled by the use of methylene C(sp^3)–H activation as a key step, allowing for selective construction of the indane core. The synthesis of (±)-Indidene A was facilitated by the use of Ni-catalyzed dehydrogenative coupling and was achieved in 11 steps in 1.7% yield. Indidene C was obtained in racemic and enantioselective modes in 13 steps in 5.5% and 1.4% yield, respectively. Both relative and absolute configuration of Indidene C were inequivocally assigned and reassigned compared to the original isolation report.

3.2 Material about this work

Methylene C(sp^3)–H Arylation Enables the Stereoselective Synthesis and Structure Revision of Indidene Natural Products, Anton Kudashev, Stefania Vergura, Marco Zuccarello, Thomas Bürgi, Olivier Baudoin, *Angew. Chem. Int. Ed.* **2023**, e202316103.

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Licensed Content Title	Methylene C(sp3)−H Arylation Enables the Stereoselective Synthesis and Structure Revision of Indidene Natural Products
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Title of new work	Exploiting Ligand Effects in Development of New Methods and Total Synthesis with Pd-catalyzed C(sp3)–H activation
Institution name	University of Basel
Expected presentation date	Dec 2023
Requestor Location	Dr. Anton Kudashev Signalstr. 35a Basel, 4058 Switzerland Attn: Dr. Anton Kudashev
Publisher Tax ID	EU826007151
Total	0.00 CHF

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How to cite: Angew. Chem. Int. Ed. 2023, e202316103
doi.org/10.1002/anie.202316103

C–H Activation

Methylene C(sp^3)–H Arylation Enables the Stereoselective Synthesis and Structure Revision of Indidene Natural Products

*Anton Kudashev[+], Stefania Vergura[+], Marco Zuccarello, Thomas Bürgi, and Olivier Baudoin**

Dedicated to Thomas Ward on the occasion of his 60th birthday

Abstract: The divergent synthesis of two indane polyketides of the indidene family, namely (±)-indidene A (11 steps, 1.7 %) and (+)-indidene C (13 steps, 1.3 %), is reported. The synthesis of the *trans*-configured common indane intermediate was enabled by palladium(0)-catalyzed methylene C(sp^3)–H arylation, which was performed in both racemic and enantioselective (e.r. 99:1) modes. Further elaboration of this common intermediate by nickel-catalyzed dehydrogenative coupling allowed the rapid installation of the aroyl moiety of (±)-indidene A. In parallel, the biphenyl system of (±)- and (+)-indidene C was constructed by Suzuki–Miyaura coupling. These investigations led us to revise the structures of indidenes B and C.

Indane-based scaffolds are prevalent in several classes of secondary metabolites, including polyketides, terpenes and alkaloids.[1] They are also abundantly found in a great variety of biologically active molecules.[2] In particular, indidenes[3] and renifolins[4] are prenylated polyketides which were isolated from the South Eastern Asian plants *Streblus indicus* and *Desmodium renifolium*, respectively, and were found to exhibit mild in vitro cytotoxicity towards cancer cell lines (Figure 1). In addition, anti-inflammatory properties were recently reported for involucrasin C, an indane polyketide structurally similar to indidene A.[5] Given their significant bioactivity, these natural products are good candidates for medicinal chemistry studies. In spite of this potential interest, no total synthesis of these molecules has been reported, to the best of our knowledge.

Strategies towards the construction of indane cores vary substantially with plethora of noncatalytic and catalytic methods being well represented.[6] On the other hand, transition-metal-catalyzed C–H functionalization methodologies have been increasingly employed in total synthesis of complex natural products, often resulting in more straightforward synthetic sequences.[7] In particular, the indane fragment of several natural products was constructed through C–H functionalization methods based on Pd,[8] Rh,[9] and Ir[10] catalysts. Our group has contributed to this field by developing palladium(0)-catalyzed C(sp^3)–H activation-based reactions for the synthesis of cyclic systems relevant to natural product synthesis.[11,12,8a,b] Based on this experience, we decided to explore the total synthesis of (±)-indidene A and (−)-indidene C.

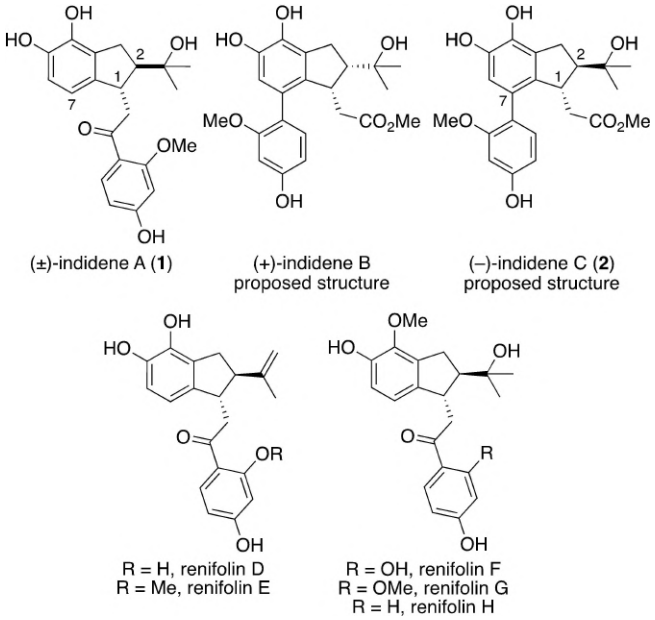

Figure 1. Selected members of the indidene and renifolin polyketides.

Structurally, these two sets of polyketides mainly differ from the attachment of the same oxygenated benzene ring at the C_1 or C_7 position of the *trans*-configured indane ring, respectively. These molecules also possess heavily hydroxylated aromatic rings, which are prone to oxidation[13] and are synthetically challenging to access in unprotected form. While indidene A was isolated in racemic form with the *trans* relative configuration, indidenes B and C were reported as enantiopure *cis* and *trans* diastereoisomers with the absolute configuration indicated in Figure 1.[3] In the case of indidene A, the structural assignment was performed

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by X-ray diffraction (XRD) analysis and leaves very little room for doubt. In contrast, the assignment of the relative and absolute configuration of indidenes B and C was performed by ROESY experiments and comparative electronic circular dichroism (ECD) analysis, and appeared more ambiguous upon closer examination. In particular, we were intrigued that indidene B is the only indidene/renifolin congener being reported with a *cis* configuration. Moreover, the ^{1}H and ^{13}C NMR spectra of indidenes B and C are nearly identical despite their opposite relative configuration. This ambiguity represented an opportunity to clarify the structure of these molecules by chemical synthesis. Therefore, we embarked onto the synthesis of indidenes A and C, and opted to employ C(sp^3)–H arylation as a strategy to construct the indane core.

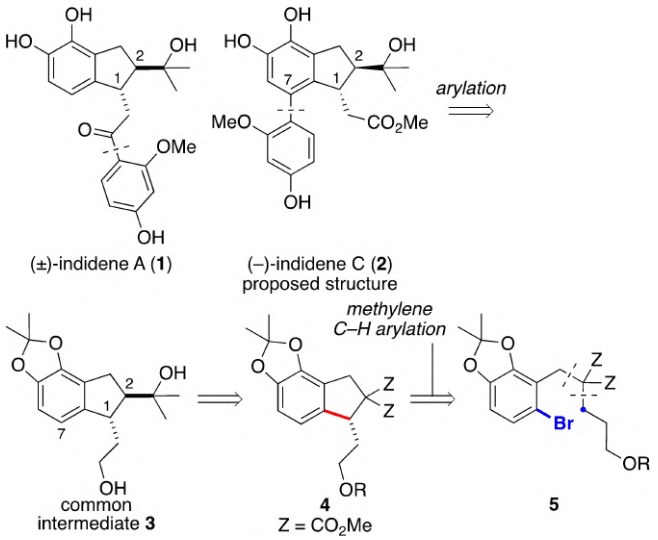
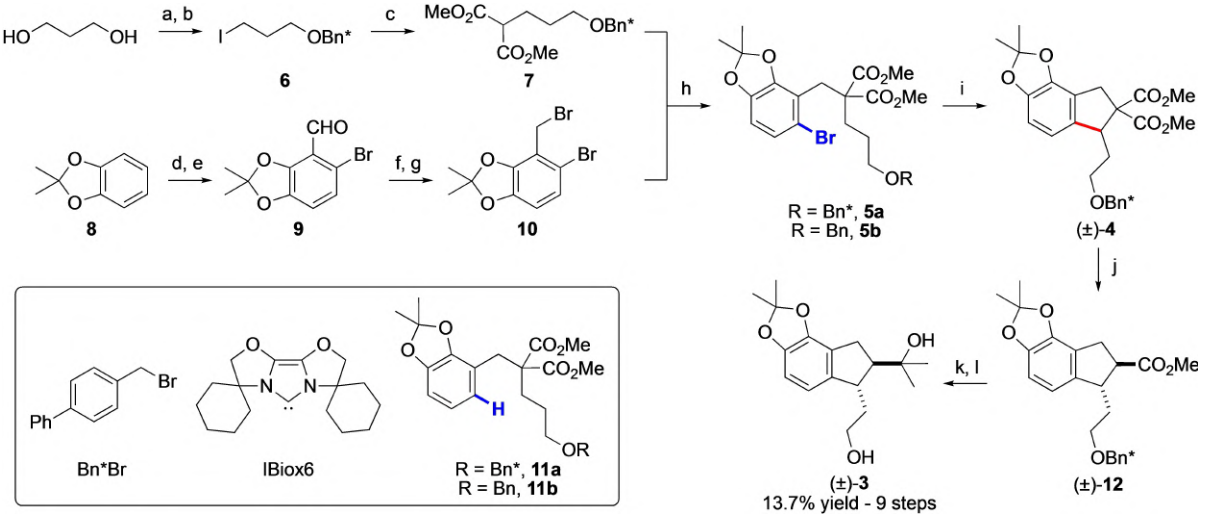


Figure 2. Retrosynthesis of indidene natural products.

Our retrosynthetic analysis is depicted in Figure 2. We hypothesized that indidenes A and C could stem from a common *trans* indanediol intermediate **3**, where installation of the dioxygenated aromatic ring on the C_1 methylenecarbonyl group would lead to indidene A (**1**), whereas arylation at the C_7 position would furnish indidene C (**2**). The common intermediate **3** could subsequently, through functional-group interconversion, be traced back to indane intermediate **4** possessing a single stereogenic center, which could arise from aryl bromide **5** by racemic (for indidene A) or enantioselective (for indidene C) methylene C(sp^3)–H arylation. This transformation is challenging, as secondary C–H bonds are generally unreactive in the absence of a neighboring activating group.[14] In this regard, our group recently reported a palladium(0)-catalyzed enantioselective methylene C(sp^3)–H arylation method,[15] in which a bulky IBiox-type N-heterocyclic carbene (NHC) ligand[16] allowed to solve this reactivity issue and provided high enantioselectivities. This bond disconnection furnishes a linear precursor **5**, which should be easily obtained by sequential alkylation of dimethyl malonate. This strategy would allow for a facile manipulation of structural elements, while keeping nonstrategic steps to the minimum required.[17]

We started our investigations by testing the feasibility of our plan towards the construction of common intermediate **3** (Scheme 1), and subsequently of target products **1** and **2**, in racemic mode. To this purpose, we first explored the synthesis of C–H arylation precursor **5a**. This was achieved by parallel synthesis of two alkyl halides, which were then sequentially employed in the alkylation of dimethyl malonate. The first halide was constructed by monobenzylation of 1,3-propanediol, followed by iodination[18] to yield iodide

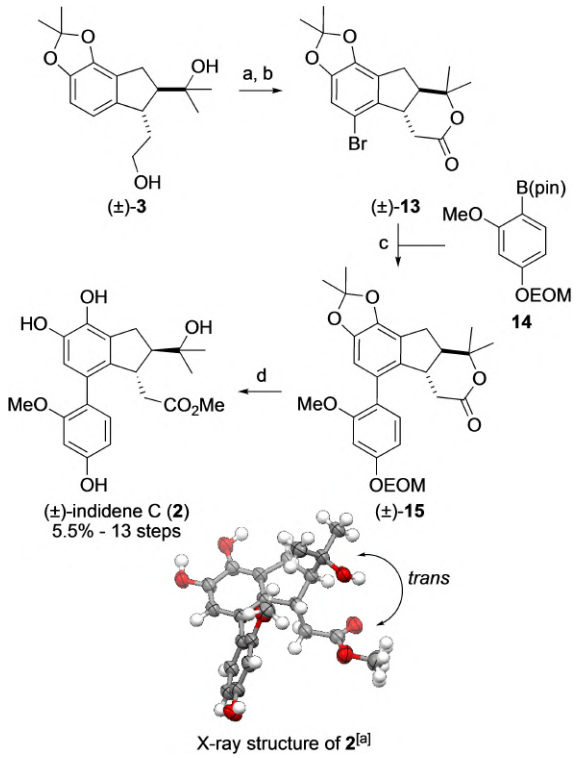


Scheme 1. Synthesis of common intermediate (±)-**3**. Reaction conditions: a) NaH, $(n\text{-Bu})_4NI$ (10 mol%), Bn*Br, THF, 25 °C; b) Ph_3P, I_2, imidazole, CH_2Cl_2, 25 °C, 73% over two steps; c) dimethyl malonate, K_2CO_3, MeCN, 78%; d) NBS, DMF, 25 °C, 90%; e) *i*-Pr_2NLi, then DMF, THF, −78→25 °C, 92%; f) $NaBH_4$, MeOH, 0→25 °C, 94%; g) PBr_3, Et_2O, 0→25 °C, 93%; h) **7**, NaH, then **10**, THF, 70 °C, 74%; i) [Pd(IBiox6)(π-allyl)Cl] (10 mol%), CsOPiv, Cs_2CO_3, 5 Å molecular sieves, trifluorotoluene, 140 °C, 63%; j) NaI, DMF, 140 °C, 48% of *trans*-**12** (d.r. >20:1) + 25% of *trans/cis*-**12** (d.r. 3:4), 71% combined yield of *trans* diastereoisomer after equilibration (NaOMe, MeOH); k) MeMgBr, THF, 0→25 °C, 70%, l) Pd/C, H_2, EtOAc, 25 °C, 82%. DMF = *N*,*N*-dimethylformamide, NBS = *N*-bromosuccinimide.

6 (73% yield over two steps), which was then attached to dimethyl malonate (78% yield). The 4-phenylbenzyl protecting group (Bn*) was chosen for practical reasons (see below). The second component **10** was synthesized from commercially available protected catechol **8** by electrophilic bromination (90% yield), followed by regioselective formylation to furnish bromoaldehyde **9** (92% yield). Subsequent reduction and bromination yielded dibromide **10** in 87% yield over two steps, which was then attached to the malonate **7** to provide the C–H arylation precursor **5a** (74% yield). Initially, we submitted aryl bromide **5b** possessing a more standard benzyl protecting group to the C(sp^3)–H arylation protocol using a catalyst formed in situ from [Pd(π-allyl)Cl]$_2$ and the NHC precursor IBiox6•HOTf[19] (see the Supporting Information for details). This provided appreciable yields of C–H arylation product, however the reproducibility was found to be inconsistent from batch to batch. Moreover, competitive protodehalogenation occurred to significant extents (compound **11b**), as already observed with substrates bearing electron-donating substituents on the benzene ring.[15] This led to major purification issues, as the most reliable separation method involved preparatory HPLC, which was suboptimal for production of the material on scale. To tackle these issues, we switched to the use of the well-defined complex [Pd(IBiox6)(π-allyl)Cl], which ensured reproducibility on scale. Our initial attempts to suppress formation of the protodehalogenated product **11b** by further modifying the reaction conditions were unfruitful, and therefore we shifted our efforts towards improving the separation. Gratifyingly, employing 4-phenylbenzyl (Bn*) instead of Bn as protecting group (substrate **5a**) allowed a facile purification by recrystallization, and delivered C–H arylation product **4** in 63% yield.

After exploration of the key step, we continued our investigations towards the synthesis of common diol **3**. The Krapcho decarboxylation of compound **4** was facile and biased towards the formation of the thermodynamically favored *trans* monoester **12**, however with a modest diastereomeric ratio (d.r. 3:1). Gratifyingly, a single recrystallization of the crude mixture furnished *trans*-**12** in 48% yield with an excellent diastereoisomeric purity (d.r. >20:1). Of note, the diastereoisomeric mixture recovered from the mother liquors (d.r. 3:4) could be further equilibrated under basic conditions (NaOMe/MeOH) to furnish *trans*-**12** in 92% yield and with a d.r. of 10:1 (71% combined yield of *trans*-**12**). DFT calculations confirmed the higher stability of the *trans* over the *cis* diastereoisomer by 1.6 kcal/mol (see the Supporting Information for details). Next, a double Grignard addition to the monoester **12** (70% yield) followed by hydrogenolysis of the Bn* group (82% yield) delivered the common diol intermediate (±)-**3** in 13.7% overall yield over 9 steps (longest linear sequence, LLS, from **8**).

Next, we went on with the synthesis of (±)-indidene C (Scheme 2). First, diol **3** was oxidized under mild conditions (TEMPO, PIDA) to yield the corresponding lactone (76%), the aromatic ring of which could be brominated site-selectively[20] to furnish aryl bromide **13** in 86% yield. Then, the biphenyl system of indidene C was constructed by

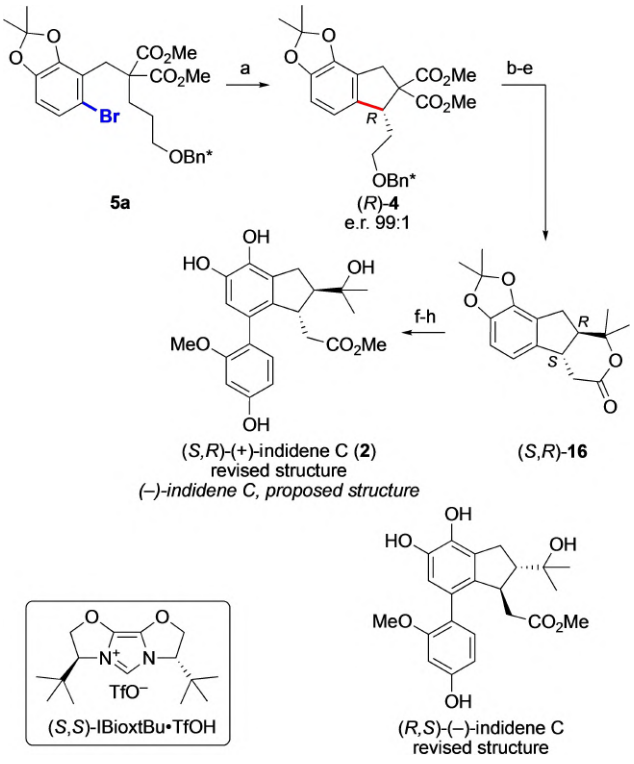


Scheme 2. Synthesis of (±)-indidene C. Reaction conditions: a) PIDA, TEMPO (30 mol%), aq. CH_2Cl_2, 25 °C, 76%; b) NBS, CH_2Cl_2, 25 °C, 86%; c) $Pd_2(dba)_3$ (5 mol%), SPhos (20 mol%), K_3PO_4, aq. toluene, 110 °C, 78%; d) $AlCl_3$, 1,2-ethanedithiol, CH_2Cl_2, 1 °C, then 3 M HCl, MeOH, 1 °C, 79%. [a] Thermal ellipsoids shown at 50% probability. PIDA = (diacetoxyiodo)benzene; TEMPO = 2,2,6,6-tetramethylpiperidine 1-oxyl; SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl.

Suzuki–Miyaura coupling with boronate **14**, which was accessed in 2 steps from a commercial precursor. Using Buchwald's SPhos ligand,[21] the two *ortho*-substituted reactants **13**–**14** successfully underwent cross-coupling to give the desired biphenyl product **15** in 78% yield. On paper, it should be possible to deprotect both acetonide and EOM protecting groups on **15** with concomitant opening of the lactone under acidic conditions. With this in mind, we conducted an extensive screen of acidic conditions that could enable such a transformation (see the Supporting Information for details). Our main problem was the relatively high stability of the acetonide, which was carried throughout the entire synthesis. Therefore, we designed a sequence in which global deprotection with excess 1,2-ethanedithiol and $AlCl_3$ was followed by in situ quenching with methanolic HCl. This precisely optimized protocol furnished (±)-**2** in 79% yield. Overall, (±)-indidene C was obtained in 5.5% yield over 13 steps (LLS). As expected, the spectral data of the synthetic material gave a close match to those reported for both *nat*-**2** and the *cis*-configured indidene B (see Figure 1 for structures). To settle this configurational matter, we resorted to single-crystal XRD of (±)-**2**,[22] which unequivocally confirmed its *trans* configuration.

While XRD gave no room for doubt regarding the relative configuration of indidene C, we conducted its enantioselective synthesis in order to elucidate its absolute configuration (Scheme 3). The C–H arylation reaction was performed by using the combination of $[Pd(\pi\text{-allyl})Cl]_2$ and chiral NHC precursor (*S*,*S*)-IBioxtBu•TfOH,[23] hence resulting in the formation of (*R*)-**4** with excellent enantioselectivity (e.r. 99:1), but diminished efficiency (35 % yield of isolated product, 62 % NMR yield) compared to the racemic mode. Indeed, the formation of the protodehalogenated side product **11a** (see Scheme 1) was significantly more pronounced with the chiral catalyst than with IBiox6. Other chiral IBiox ligands such as IBioxAd, which provided superior results in our previous study,[15] did not furnish a notable improvement, and therefore the more accessible IBioxtBu ligand was retained. The absolute configuration of the C–H arylation product **4** was first ascribed as (*R*) in analogy to the previous study.[15] Further steps towards the final target were performed using similar conditions to the racemic synthesis. The absolute configuration of lactone intermediate **16** was further confirmed to be (*S*,*R*) by vibrational circular dichroism (VCD) analysis,[24] which showed a very good match between experimental and calculated spectra (Figure 3). This method is particularly powerful when crystals suitable for absolute configuration determination by XRD analysis cannot be obtained, such as in the present case. Finally, (*S*,*R*)-indidene C (e.r. >99:1) was obtained in 1.3 % overall yield over 13 steps. Surprisingly, the specific optical rotation measured from the synthetic sample (+18.6°) did not correlate with the reported value for indidene C (−32°), but rather with the reported value for indidene B (+42°). In addition, the ECD spectrum of the synthetic material matched the reported ECD spectrum for (+)-indidene B (see the Supporting Information for details). Unfortunately, we were unable to compare our synthetic sample with authentic samples of indidenes B and C. Interestingly, the latter were isolated upon purification by HPLC on a chiral stationary phase. Therefore, we hypothesize that the isolated indidenes B and C are actually enantiomers of the same *trans* diastereoisomer, rather than diastereoisomers, and that indidene C occurs as a racemate, similar to indidene A. As we have prepared (+)-(*S,R)*-indidene C, we propose that (−)-indidene C actually possesses the (*R,S)* configuration (Scheme 3, bottom right).

Finally, we explored the synthesis of indidene A, which was isolated as a racemate,[3] from the common intermediate **3** (Scheme 4). First, we considered classical approaches for the installation of the aroyl group on the C_1 side chain through sequential oxidation/1,2-addition, either through the aldehyde or the Weinreb amide intermediate. However, this strategy entails multiple oxidation and protection/deprotection steps at the primary and tertiary alcohols of the C_1 and C_2 substituents. To avoid this, the nickel-catalyzed dehydrogenative coupling disclosed by Newman and co-workers[25] would furnish an attractive solution. Indeed, this direct protocol would only affect the primary alcohol at C_1 and should be compatible with the unprotected tertiary alcohol at C_2. With this in mind, triflate **17**, which was synthesized from commercially available materials in 4 steps, was subjected to the Ni^0-catalyzed dehydrogenative coupling with diol **3**. To our pleasure, this transformation, after significant optimization (see the Supporting Information for details), delivered the expected ketone **18** in 47 % isolated yield. Despite its moderate efficiency, this method avoids nonstrategic oxidation and protection/deprotection



Scheme 3. Enantioselective synthesis of (+)-(*S*,*R*)-indidene C and structural revisions. Reaction conditions: a) $[Pd(\pi\text{-allyl})Cl]_2$ (5 mol %), (*S*,*S*)-IBioxtBu•TfOH (10 mol %), CsOPiv, Cs_2CO_3, trifluorotoluene, 140 °C, 35 % (62 % NMR yield); b) NaI, DMF, 140 °C, 33 %; c) MeMgBr, THF, 0 °C, 88 %; d) Pd/C, H_2, EtOAc, 25 °C, 78 %; e) PIDA, TEMPO (30 mol %), aq. CH_2Cl_2, 25 °C, 70 %; f) NBS, CH_2Cl_2, 25 °C, 73 %; g) $Pd_2(dba)_3$ (5 mol %), SPhos (20 mol %), K_3PO_4, aq. toluene, 110 °C, 60 %; h) $AlCl_3$, 1,2-ethanedithiol, CH_2Cl_2, 1 °C, then 3 M HCl, MeOH, 1 °C, 99 %.

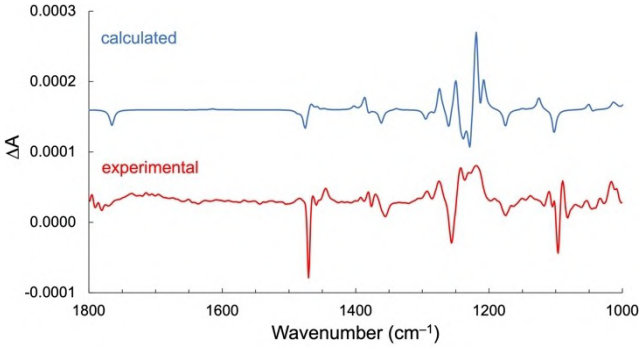
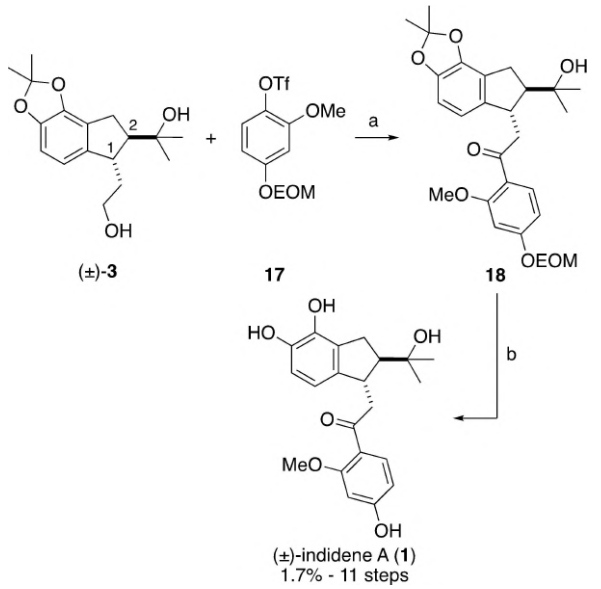


Figure 3. Experimental (red) and calculated (blue) vibrational circular dichroism (VCD) spectra of lactone (*S*,*R*)-**16**.



Scheme 4. Synthesis of indidene A. Reaction conditions: a) $Ni(COD)_2$ (10 mol%), Triphos (12 mol%), acetone, TMP, mesitylene, 130 °C, 47%; b) $AlCl_3$, 1,2-ethanedithiol, $MeNO_2$, −20 °C, 26%. Triphos = 1,1,1-tris(diphenylphosphinomethyl)ethane; TMP = 2,2,6,6-tetramethylpiperidine.

steps and directly affords ketone **18**. The latter required again global deprotection to generate the desired natural product. To our dismay, the conditions that successfully furnished indidene C were found unsuitable for the deprotection of **18**, presumably due to the presence of the ketone group. Fortunately, a modification of these conditions ($AlCl_3$, 1,2-ethanedithiol, $MeNO_2$, −20 °C) enabled the formation of (±)-indidene A (**1**), albeit in 26% yield (1.7% overall yield over 11 steps). The spectroscopic data of the synthetic material fully matched those reported for the isolated product. As the *trans* configuration of indidene A was unequivocally assigned by XRD,[3] this serves as an additional proof of the *trans* configuration of diol **3** and by extension of the reassigned indidenes B and C.

In conclusion, we achieved the divergent synthesis of (±)-indidene A, (±)-indidene C and (+)-(*S,R*)-indidene C (aka indidene B) in 11 and 13 steps, respectively. This was enabled by a rapid assembly of the indane core through methylene C(sp^3)–H arylation, and subsequent elaboration to generate a common *trans* indane intermediate (**3**). (±)-Indidene A was synthesized from the latter using a step-economical nickel-catalyzed dehydrogenative coupling to install the aroyl group at C_1. In parallel, indidene C was obtained from the same intermediate using a Suzuki–Miyaura coupling to assemble the biaryl system. This work allowed the structure confirmation of (±)-indidene A and the structure revision of indidenes B and C. It could also serve as a strong basis for further SAR studies and to access structurally related indane polyketides.

Acknowledgements

The Swiss National Science Foundation (grant #200021_184608) and University of Basel financially supported this work. We thank Dr. D. Häussinger, University of Basel, for NMR experiments, Dr. M. Pfeffer, University of Basel, for MS analyses, Dr. Sylvie Mittelheisser, University of Basel, for elemental analysis, Dr. Michael Devereux, University of Basel, for preliminary calculations, and Dr. Farzaneh Fadaei Tirani, EPFL, for X-ray analysis. Open access funding was provided by University of Basel.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Cross-Coupling · C–H Activation · Natural Products · Total Synthesis

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Manuscript received: October 24, 2023
Accepted manuscript online: November 23, 2023
Version of record online: ■■, ■■

Communications

C–H Activation

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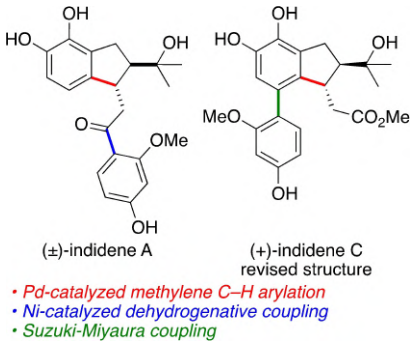
Methylene C(sp^3)–H Arylation Enables the Stereoselective Synthesis and Structure Revision of Indidene Natural Products

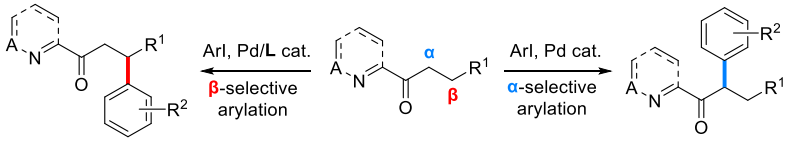


The indane polyketides indidenes A and C were synthesized from a common intermediate through nickel-catalyzed dehydrogenative coupling and Suzuki–Miyaura coupling, respectively. The common diol intermediate was obtained by palladium-catalyzed methylene C–H arylation, which was performed in both racemic and enantioselective modes. This study led to the revision of the absolute configuration of indidene C.

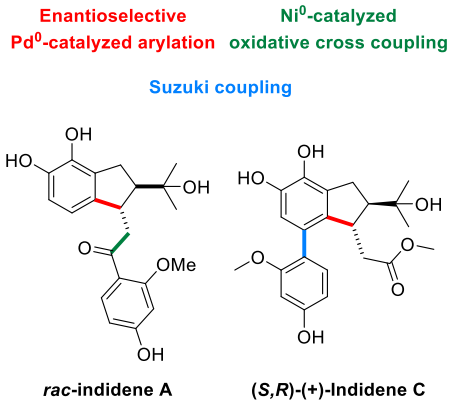
General conclusion

As was examined throughout the course of the general introduction, the changing focus of modern society towards sustainability and resource economy has manifested in a scenario where catalytic methods are highly desirable due to their inherent sustainability. Pd-catalyzed C(sp^3)–H activation, in this regard, represents an atom-economic evolution of the cross-coupling reactions and has developed, from the first observation by Shilov in 1969[4], until now from an impractical scientific curiosity to a viable synthetic methodology.

In Section 2, we explored site-selective Pd-catalyzed arylations of heteroaromatic ketones. The use of pyridone ligands allows an efficient selectivity switch of the process from classical α-arylation to β-arylation. A mechanistic switch from the Pd^{II}-mediated C–H activation to Pd-mediated desaturation – conjugate addition results in this differing selectivity. We established the scope of both transformations and have shown potential for post-functionalization[77].



In the second part of the thesis, we have turned our attention to total synthesis of Indidene natural products. We have undertaken a synthesis of the two natural products, (±)-Indidene A and (*S,R*)-Indidene C. The synthesis of both these molecules was enabled by enantioselective methylene C(sp^3)–H activation. The relative and absolute configuration and structure of (*S,R*)-(+)-Indidene C were elucidated in the process of our investigation, while the acquisition of Indidene A was enabled by the use of Ni-catalyzed dehydrogenative cross-coupling. The disclosure of the route towards synthesis of these molecules may encourage further investigations into their biological activity.



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Experimental section

Part I: Pd-Catalyzed C(sp^3)−H Arylation of Heteroaromatic Ketones

Numbering based on A. Kudashev, O. Baudoin, *Chem. Eur. J.* **2021**, *27*, 17688-17694.

General methods

Techniques:

All reactions involving air-sensitive material were carried out in pre-dried glassware under an argon atmosphere by using Schlenk techniques employing double-line argon-vacuum lines and working in an argon-filled glove box. Analytical thin layer chromatography (TLC) was performed using pre-coated Merck silica gel 60 F254 plates (0.25 mm). Visualization of the developed chromatogram was performed by UV absorbance (254 nm or 365 nm) or TLC stains (vanillin, $KMnO_4$ or anise). Chromatography was performed on Biotage® Isolera™ instrument using prepackaged Claricep™ (Agela Technologies) or Sfär™ Silica Duo 60 µm (Biotage) normal phase cartridges of varying size with indicated solvent systems in order of increasing polarity.

Chemicals:

Anhydrous solvents were purchased from Sigma-Aldrich, Acros Organics or Fluorochem. Solvents that were involved in C–H activation processes were additionally degassed by bubbling argon through (*tert*-amyl alcohol, DMF) or three cycles of freeze-pump-thaw (mesitylene) and were stored under the atmosphere of argon in Schlenk flasks. Solvents used for substrate synthesis were purchased from Avantor and used as received.

Palladium salts were purchased from Sigma-Aldrich and stored in an argon-filled glovebox at ambient temperature. Other chemicals were purchased from Sigma-Aldrich, Acros Organics, Alfa Aesar, Apollo Scientific, Fluorochem or Enamine and used as received unless specified otherwise.

Instrumentation:

GCMS analyses were performed with a Shimadzu QP2010SB GCMS apparatus on a Rtx®-5ms-Low-Bleed column lined with a mass (EI) detection system. HPLC analyses was performed using a Shimadzu Prominence system with SIL-20A auto sampler, CTO-20AC column oven, LC-20AD pump system, DGU-20A3 degasser and SPD-M20A Diode Array or UV/VIS detector.

Melting points were obtained on a Büchi melting point M-565, and are uncorrected.

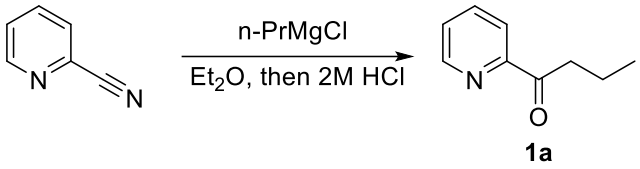
IR spectra were recorded on an ATR Varian Scimitar 800 and are reported in reciprocal centimeters (cm^{-1}).

Nuclear magnetic resonance spectra were recorded on a Bruker Advance 250 (250 MHz), Advance 500 (500 MHz) and Advance 600 (600 MHz) in deuterated chloroform (residual peaks ^{1}H δ 7.26 ppm, ^{13}C δ 77.16 ppm) unless otherwise noted. ^{19}F NMR spectra were referenced to internal trifluorotoluene. (δ -63.72 ppm). Both ^{13}C and ^{19}F NMR spectra are $^{1}H(\{^{1}H\})$ decoupled unless otherwise stated. Data are reported in parts per million (ppm) as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, ddd = doublet of doublet of doublet and brs = broad singlet), coupling constant in Hz and integration.

High resolution mass spectra were recorded by Dr. M. Pfeffer (Department of Chemistry, University of Basel) on a Bruker maXis 4G QTOF ESI mass spectrometer.

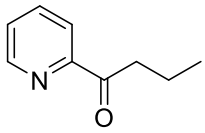
Synthesis of starting materials

- **Representative procedure A – preparation of 1-(pyridin-2-yl)butan-1-one 1a**



1a

A vigorously stirred solution of picolinonitrile (20.8 g/19.3 mL, 0.2 mol) in diethyl ether (250 mL) was cooled to -20°C (30% aq. MeOH/dry ice) and solution of n-propylmagnesium chloride (1.1 eq, 0.22 mol, 110 mL of 2 mol/L solution in diethyl ether) was added dropwise. Upon completion, cooling bath was removed and a thick yellow slurry was stirred overnight. Reaction mixture was then cooled to 0°C (ice/water) and quenched by portionwise addition of 200 mL of 2M HCl (*caution: vigorous and exothermic*) and left stirring for 30 minutes. Reaction mixture is then basified (pH > 9) by addition of 2M NaOH. Ethyl acetate (200 mL) was then added and aqueous layer was separated. Aqueous layer was washed once with ethyl acetate and combined organic layer was washed with sat. $NaHCO_3$ solution and water. Organics were then dried over Na_2SO_4 and evaporated at reduced pressure. Resulting crude was then applied onto SNAP KP-Sil 340g cartridge and purified by column chromatography (10-20% EtOAc in cyclohexane) to yield 1-(pyridin-2-yl)butan-1-one (26.2 g) as a yellow liquid.



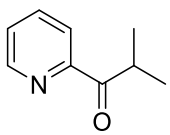
1-(pyridin-2-yl)butan-1-one (1a)

Prepared as stated above. The compound is described[1].

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.65 (dd, *J* = 4.8, 0.8 Hz, 1H), 8.01 (ddd, *J* = 7.8, 1.1, 1.1 Hz, 1H), 7.80 (ddd, *J* = 7.7, 7.7, 1.8 Hz, 1H), 7.44 (dd, *J* = 4.8, 1.2 Hz, 1H), 3.20 – 3.14 (t, *J* = 7.5 Hz, 3H), 1.74 (h, *J* = 7.4 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.18, 153.71, 149.01, 137.00, 127.09, 121.88, 39.79, 17.57, 14.02.

According to the procedure above, these compounds were synthesized:



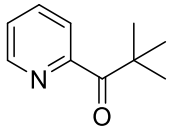
2-methyl-1-(pyridin-2-yl)propan-1-one (1f)

Prepared from picolinonitrile (0.52 g) and isopropylmagnesium bromide (2.75 mL of 2M THF solution) to yield 0.4 g (54%) of titular compound as an orange oil. The compound is described[1].

[1] Wu Q.,Han S., Ren X., Lu H., Li J., Zou D., Wu D., Wu Y., *Org. Lett.* **2018**, *20*, 20, 6345–6348

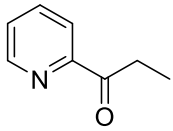
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.03 (ddd, *J* = 7.8, 1.1, 1.1 Hz, 1H), 7.82 (ddd, *J* = 7.6, 7.6, 1.7 Hz, 1H), 7.44 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 4.10 (hept, *J* = 6.8 Hz, 1H), 1.20 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 205.85, 153.07, 148.99, 137.02, 126.97, 122.58, 34.34, 18.78.



2,2-dimethyl-1-pyridin-2-yl-propan-1-one (1g)

This compound was prepared according to a described[2] procedure from 2.1 g of 2-picolinonitrile to yield 0.7 g of title compound (21%). Analytical data matched that described.

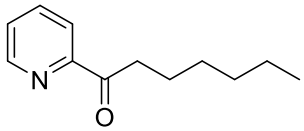


1-(pyridin-2-yl)propan-1-one (1i)

Prepared from picolinonitrile (2.6 g) and ethylmagnesium bromide (9.2 mL of 3M diethyl ether solution) to yield 1.91 g (57%) of titular compound as yellow oil. The compound is described[1].

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.04 (ddd, *J* = 7.9, 1.1, 1.1 Hz, 1H), 7.83 (ddd, *J* = 7.7, 7.7, 1.8 Hz, 1H), 7.46 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 3.24 (q, *J* = 7.3 Hz, 2H), 1.22 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.67, 153.55, 149.01, 136.94, 127.08, 121.80, 31.19, 8.04.



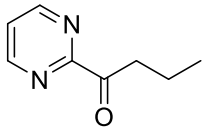
1-(pyridin-2-yl)heptan-1-one (1j)

Prepared from picolinonitrile (2.08 g) and n-propylmagnesium chloride (13.8 mL of 2M THF solution) to yield 1.7 g (45%) of titular compound as an orange oil. The compound is described[3].

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.02 (ddd, *J* = 7.9, 1.1, 1.1 Hz, 1H), 7.81 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.44 (ddd, *J* = 7.6, 4.8, 1.3 Hz, 1H), 3.20 (t, *J* = 7.5 Hz, 1H), 1.76 – 1.66 (m, 2H), 1.45 – 1.26 (m, 6H), 0.92 – 0.82 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.34, 153.72, 149.01, 136.96, 127.06, 121.88, 37.84, 31.80, 29.15, 24.07, 22.67, 14.17.

[2] Prathapan S., Robinson K. E., Agosta W. C., *J. Am. Chem. Soc.* **1992**, *114*, 5, 1838–1843
[3] Sharma S., Kumar M., Vishwakarma R. A., Verma M.K., Singh P. P., *J. Org. Chem.* 2018, 83, 20, 12420–12431



1-(pyrimidin-2-yl)butan-1-one (1k)

Prepared from 2-cyanopyrimidine (2.62 g) and n-propylmagnesium chloride (11 mL of 2M THF solution) to yield 2.71 g (71%) of titular compound as an orange oil.

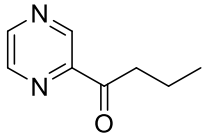
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (d, *J* = 4.8 Hz, 1H), 7.41 (t, *J* = 4.9 Hz, 1H), 3.17 (t, *J* = 7.1 Hz, 1H), 1.73 (h, *J* = 7.4 Hz, 1H), 0.95 (t, *J* = 7.4 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.87, 160.23, 157.63, 122.93, 40.94, 17.46, 13.73.

HRMS (ESI): Calcd for $C_8H_{10}N_2O$, $[M+Na]^+$: 173.0685, found: 173.0688.

IR (neat): v (cm^{-1}) 2965, 2874, 1713, 1561, 1374, 1012, 815, 744.

Rf: 0.46 (EtOAc)



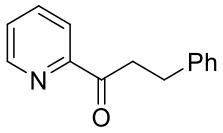
1-(pyrazin-2-yl)butan-1-one (1l)

Prepared from 2-cyanopyrazine (2.1 g) and n-propylmagnesium chloride (11 mL of 2M THF solution) to yield 0.25 g (8%) of titular compound as a red oil. The compound is described[4].

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23 (d, *J* = 1.5 Hz, 1H), 8.75 (d, *J* = 2.5 Hz, 1H), 8.64 (dd, *J* = 2.5, 1.5 Hz, 1H), 3.17 (t, *J* = 7.3 Hz, 2H), 1.78 (h, *J* = 7.4 Hz, 2H), 1.02 (t, *J* = 7.4 Hz, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.55, 147.80, 143.80, 143.62, 39.91, 17.35, 13.95.

Rf: 0.33 (20% EtOAc in cyclohexane)



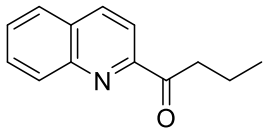
3-phenyl-1-(pyridin-2-yl)propan-1-one (1m)

Prepared from picolinonitrile (2.08 g) and phenethylmagnesium chloride (22 mL of 1M THF solution) to yield 2.8 g (66%) of titular compound as yellow oil. The compound is described[5].

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.05 (ddd, *J* = 7.8, 1.1, 1.1 Hz, 1H), 7.82 (ddd, *J* = 7.7, 1.8 Hz, 1H), 7.45 (ddd, *J* = 7.6, 4.8, 1.3 Hz, 1H), 7.34 – 7.25 (m, 4H), 7.23 – 7.15 (m, 1H), 3.61 – 3.55 (m, 2H), 3.12 – 3.05 (m, 2H).

[4] Wang X.-Z., Zeng C.-C., *Tetrahedron* **2019**, 75, 1425-1430
[5] Boblak K. N., Klumpp D. A., *J. Org. Chem.* 2014, 79, 12, 5852–5857

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.09, 153.44, 149.06, 141.54, 136.97, 128.60, 128.50, 127.21, 126.07, 121.90, 39.51, 29.98.

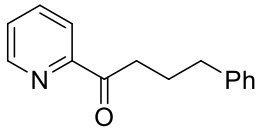


1-(quinolin-2-yl)butan-1-one (1n)

Prepared from 2-quinolinecarbonitrile (1 g) and n-propylmagnesium chloride (3.9 mL of 2M THF solution, 1.2 eq) to yield 1.18 g (91%) of titular compound as beige solid. The compound is described[6].

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 – 8.23 (m, 1H), 8.21 – 8.17 (m, 1H), 8.15 – 8.09 (m, 1H), 7.89 – 7.83 (m, 1H), 7.78 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.64 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 3.38 (d, *J* = 7.6 Hz, 2H), 1.83 (h, *J* = 7.4 Hz, 2H), 1.06 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.76, 153.35, 147.34, 136.97, 130.69, 130.04, 129.71, 128.55, 127.78, 118.30, 39.52, 17.77, 14.12.



4-phenyl-1-(pyridin-2-yl)butan-1-one (1o)

Prepared from picolinonitrile (1 g) and (3-phenylpropyl)magnesium bromide solution in diethyl ether to yield 1.92 g (85%) of titular compound as yellow oil. (3-phenylpropyl)magnesium bromide solution was prepared by dropwise addition 1-bromo-3-phenylpropane (3.04 mL) to a suspension of magnesium (0.49 g) and iodine (25 mg) in diethyl ether (20 mL) and stirred for 3 hours. The compound is described[7].

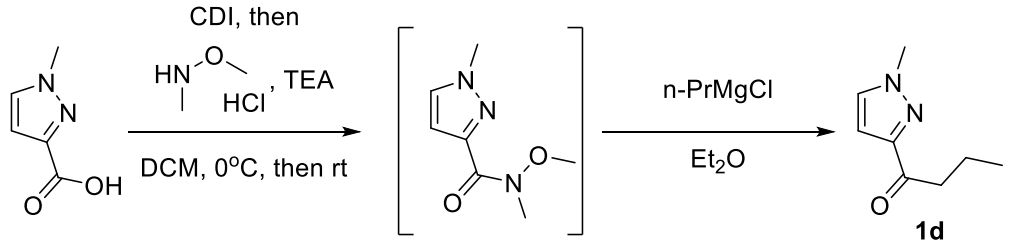
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.05 (ddd, *J* = 7.8, 1.1, 1.1 Hz, 1H), 7.84 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.47 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.27 – 7.23 (m, 2H), 7.23 – 7.17 (m, 1H), 3.27 (t, *J* = 7.5 Hz, 1H), 2.76 (dd, *J* = 8.6, 6.8 Hz, 2H), 2.17 – 2.07 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.82, 153.49, 148.92, 141.98, 136.87, 128.53, 128.34, 127.03, 125.85, 121.75, 37.16, 35.38, 25.62.

[6] Siddaraju Y., Lamani M., Prahbu K. R., *J. Org. Chem.* 2014, 79, 9, 3856–3865
[7] W. Sun, L. Wang, C. Xia, C. Liu, *Angew. Chem. Int. Ed.* **2018**, *57*, 5501.

❖ **Preparation of other ketone compounds**

1-(1-methyl-1H-pyrazol-3-yl)butan-1-one (1d)



To a 50 mL round bottom flask equipped with PTFE-coated magnetic stirbar 1-methyl-1H-pyrazole-3-carboxylic acid (1 g, 7.9 mmol) was charged. 20 mL of DCM are then added; resulting mixture was then cooled to 0 °C (ice/water). 1,1'-Carbonyldiimidazole (1.67 g, 10.3 mmol, 1.3 eq) was then added portionwise. Resulting mixture was stirred at that temperature for 1.5 hours. N,O-dimethylhydroxylamine hydrochloride (1.06 g, 10.3 mmol, 1.3 eq) was added afterwards in a single portion, followed by slow addition of triethylamine (3.3 mL, 23.8 mmol, 3 eq). Cooling was then removed and reaction mixture was then left to stir at room temperature overnight. After aging, reaction mixture was diluted with water. Organic layer was extracted and washed once with sat. $NaHCO_3$ solution and water, dried over Na_2SO_4 and evaporated at reduced pressure. 1.15 g (77%, rated as 90% pure) of N-methoxy-N,1-dimethyl-1H-pyrazole-3-carboxamide is recovered as a beige, transparent liquid, which is then used in the next step without purification.

To a 100 mL round bottom flask equipped with PTFE-coated magnetic stirbar product of previous transformation (1.15 g, 90%, 6.12 mmol) was charged, followed by dissolution in 30 mL of diethyl ether. Resulting mixture was cooled to -20°C (30% aq. MeOH/dry ice) and n-propylmagnesium chloride (7.65 mL of 2 M solution in diethyl ether) was added dropwise. Reaction mixture was then left to stir overnight at rt. After aging, mixture was then quenched with sat. NH_4Cl solution, followed by water. Solution was extracted three times with EtOAc, combined organics were then dried over Na_2SO_4 and evaporated at reduced pressure. Resulting crude was then dryloaded onto diatomaceous earth and loaded onto a Claricep™ 20 g cartridge. Column chromatography (0-25% EtOAc in cyclohexane) yielded 0.77 g (83%) of titular compound as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 2.4 Hz, 1H), 6.75 (d, *J* = 2.3 Hz, 1H), 3.95 (s, 3H), 2.94 (t, *J* = 7.5 Hz, 2H), 1.79 – 1.68 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H).

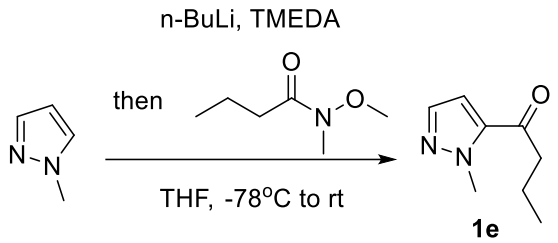
^{13}C NMR (126 MHz, $CDCl_3$) δ 196.36, 151.46, 131.71, 106.99, 40.83, 39.63, 17.82, 14.00.

HRMS (ESI): Calcd for $C_8H_{12}N_2O$, $[M+Na]^+$: 175.0842, found: 175.0844.

IR (neat): v (cm^{-1}) 2962, 1678, 1469, 1360, 1209, 1059, 954, 892, 771.

Rf: 0.22 (20% EtOAc in cyclohexane)

1-(1-methyl-1H-pyrazol-5-yl)butan-1-one (1e)



To an oven-dried two-neck flask equipped with a PTFE-coated magnetic stirbar, under the atmosphere of argon N-methylpyrazole (0.83 mL, 10 mmol) was charged, followed by dry THF (15 mL) and TMEDA (1.72 mL, 1.15 eq). Reaction mixture was then cooled to -78°C (dry ice/acetone) and n-butyllithium (4.4 mL of 2.5 M solution in hexane, 1.1 eq) was added dropwise. Upon completion of addition, reaction was stirred for 1h at that temperature. After aging, a solution of N-methoxy-N-methylbutyramide (1.44 g, 1.1 eq) in 30 mL of THF was added dropwise. Reaction was then left in the cooling bath to slowly warm up to rt overnight. Mixture was then quenched by addition of sat. NH_4Cl solution, followed by water. Solution was extracted three times with EtOAc, combined organics were then dried over Na_2SO_4 and evaporated at reduced pressure. Resulting crude was then dryloaded onto diatomaceous earth and loaded onto a Claricep™ 20 g cartridge. Column chromatography (0-25% EtOAc in cyclohexane) yielded 0.34 g (22%) of titular compound as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 2.1 Hz, 1H), 6.81 (d, *J* = 2.1 Hz, 1H), 4.15 (s, 3H), 2.84 – 2.77 (m, 2H), 1.73 (h, *J* = 7.4 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).

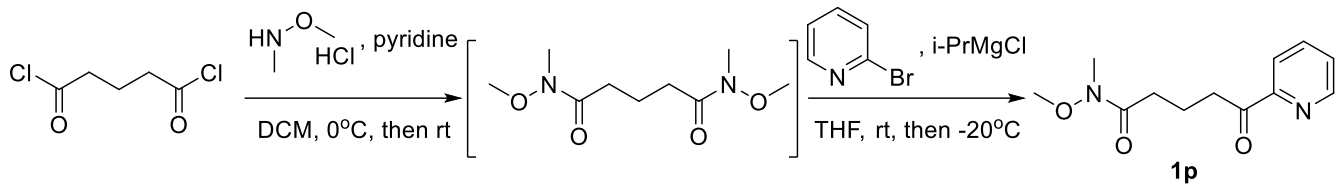
^{13}C NMR (126 MHz, $CDCl_3$) δ 191.93, 138.65, 137.62, 111.32, 42.53, 40.35, 17.83, 13.88.

HRMS (ESI): Calcd for $C_8H_{12}N_2O$, $[M+H]^+$: 153.1022, found: 153.1020.

IR (neat): v (cm^{-1}) 2962, 1678, 1453, 1318, 1218, 966, 785.

Rf: 0.42 (20% EtOAc in cyclohexane)

N-methoxy-N-methyl-5-oxo-5-(pyridin-2-yl)pentanamide (1p)



To a 250 mL round bottom flask, glutaryl chloride (3.2 mL, 25 mmol) was charged, followed by addition of DCM (63 mL) and N,O-dimethylhydroxylamine hydrochloride (5.12 g, 52.5 mmol, 2.1 eq). Resulting mixture was cooled to 0 °C (ice/water) and pyridine (8.5 mL, 105 mmol, 4.2 eq) was added dropwise. After completion, reaction is stirred for 3.5 hours at room temperature, after which 0.5 M hydrochloric acid solution was added. Organic layer was separated and extracted additionally once with 0.5 M HCl and twice with sat. $NaHCO_3$ solution. Remaining organic layer was dried over Na_2SO_4 and evaporated at reduced pressure to yield 5 g of N,N-dimethoxy-N,N-dimethylglutaramide as a brown liquid, which was used in the next step without purification.

To an oven-dried 100 mL two-neck flask equipped with PTFE-coated magnetic stirbar, under the atmosphere of argon 2-bromopyridine (2.14 mL, 22 mmol, 2.4 eq) was added, followed by dry THF (50 mL). To this mixture isopropylmagnesium bromide (8.21 mL of 2.9 M solution in 2-MeTHF, 23.8 mmol, 2.6 eq) was added slowly. After completion of addition, reaction was left stirring overnight. During this time precipitation occurred. After aging, reaction mixture was cooled to -20°C (30% aq. MeOH/dry ice) and a solution of N,N-dimethoxy-N,N-dimethylglutaramide (2 g, 9.6 mmol) in 10 mL of THF was added dropwise. Cooling was removed and reaction mixture was then left stirring for 4 hours at room temperature. After completion of these steps, reaction was quenched by addition of sat. NH_4Cl solution, followed by water. Solution was extracted three times with EtOAc, combined organics were then dried over Na_2SO_4 and evaporated at reduced pressure. Resulting crude was then dryloaded onto diatomaceous earth and purified by column chromatography (0-50% EtOAc in cyclohexane) to yield 0.63 g (29%) of titular compound as a brown liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.03 (ddd, *J* = 7.9, 1.1, 1.1 Hz, 1H), 7.82 (ddd, *J* = 7.8, 7.8, 1.8 Hz, 1H), 7.45 (ddd, *J* = 7.5, 4.7, 1.3 Hz, 1H), 3.67 (s, 3H), 3.31 (t, *J* = 7.2 Hz, 2H), 3.17 (s, 3H), 2.56 (t, *J* = 7.5 Hz, 2H), 2.08 (p, *J* = 7.3 Hz, 2H).

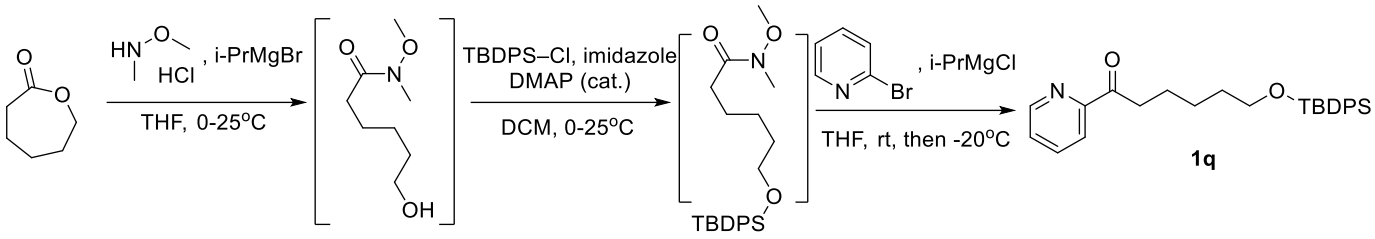
^{13}C NMR (126 MHz, $CDCl_3$) δ 201.50, 174.24, 153.48, 149.01, 136.94, 127.14, 121.78, 61.29, 37.23, 32.27, 31.25, 18.92.

HRMS (ESI): Calcd for $C_{12}H_{16}N_2O_3$, $[M+Na]^+$: 259.1053, found: 259.1056.

IR (neat): ν (cm^{-1}) 2931, 1698, 1651, 1384, 978, 769.

Rf: 0.1 (20% EtOAc in cyclohexane)

6-((tert-butyldiphenylsilyl)oxy)-1-(pyridin-2-yl)hexan-1-one (1q)



Preparation of ketone **1r** was performed with known procedures.[8,9]

Isopropylmagnesium chloride (3 eq, 52.5 mmol, 18 mL of 2.9 M solution in 2-MeTHF) was added dropwise to a mixture of 2-oxepanone (2 g, 17.5 mmol) and N,O-dimethylhydroxylamine hydrochloride (2.56 g, 26.3 mmol, 1.5 eq) in THF (60 mL) at 0 °C. The resulting mixture was then warmed to r.t. After 1 h, it was cooled to 0 °C, and of sat. NH_4Cl solution was added, followed by water. The phases were separated, and the aqueous layer was extracted with DCM twice. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide 6-hydroxy-N-methoxy-N-methylhexanamide, which was used without purification in the next reaction.

Into a 100 mL round-bottom flask equipped with PTFE-coated magnetic stirbar product of previous transformation (2 g, 11.4 mmol) was charged and subsequently dissolved in DCM (25 mL). Reaction was then cooled to 0 °C (ice/water); imidazole (1.1 g, 14.8 mmol, 1.3 eq) and DMAP (139 mg, 1.14 mmol, 0.1 eq) were added, followed by dropwise addition of TBDPS–Cl (3 mL, 11.6 mmol, 1.02 eq).
Cooling bath was then removed and reaction was stirred for 1 hour, by which time TLC control (20% EtOAc in cyclohexane) indicated full consumption of the material. Reaction mixture was quenched by addition of water. Layers were separated and organics were additionally washed twice with water and once with brine. Organics were then dried over Na_2SO_4 and evaporated at reduced pressure. Resulting crude was then dryloaded onto diatomaceous earth and purified by column chromatography (0-25% EtOAc in cyclohexane) to yield 2.7 g of TBDPS-protected alcohol, which was used in the next step.

To an oven-dried 100 mL two-neck flask equipped with PTFE-coated magnetic stirbar, under the atmosphere of argon 2-bromopyridine (0.57 mL, 5.8 mmol, 1.2 eq) was added, followed by dry THF (25 mL). To this mixture isopropylmagnesium bromide (2.1 mL of 2.9 M solution in 2-MeTHF, 6.1 mmol, 1.25 eq) was added slowly. After completion of addition, reaction was left stirring overnight. During this time precipitation occurred. After aging, reaction mixture was cooled to -20°C (30% aq. MeOH/dry ice) and a solution of previously obtained silyl ether (2 g, 4.8 mmol) in 5 mL of THF was added dropwise. Cooling was removed and reaction mixture was then left stirring overnight at room temperature. After completion of these steps, reaction was quenched by addition of sat. NH_4Cl solution, followed by water. Solution was extracted three times with EtOAc, combined organics were then dried over Na_2SO_4 and evaporated at reduced pressure. Resulting

[8] Bissember A. C., Levina A., Fu. G. C., *J. Am. Chem. Soc.* **2012**, *134*, 34, 14232–14237
[9] Zhang C.-H., Gao Q., Li M., Wang J.-F., Yu C.-M., Mao B., *Org. Lett.* **2021**, *23*, 10, 3949–3954

crude was then dryloaded onto diatomaceous earth and purified by column chromatography (0-30% EtOAc in cyclohexane) to yield 0.37 g (18%) of titular compound as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.05 (ddd, *J* = 7.8, 1.1, 1.1 Hz, 1H), 7.85 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.72 – 7.63 (m, 4H), 7.48 (ddd, *J* = 7.5, 4.8, 1.3 Hz, 1H), 7.45 – 7.28 (m, 7H), 3.67 (t, *J* = 6.4 Hz, 2H), 3.22 (d, *J* = 7.5 Hz, 2H), 1.78 – 1.67 (m, 2H), 1.67 – 1.58 (m, 2H), 1.53 – 1.43 (m, 2H), 1.04 (s, 9H).

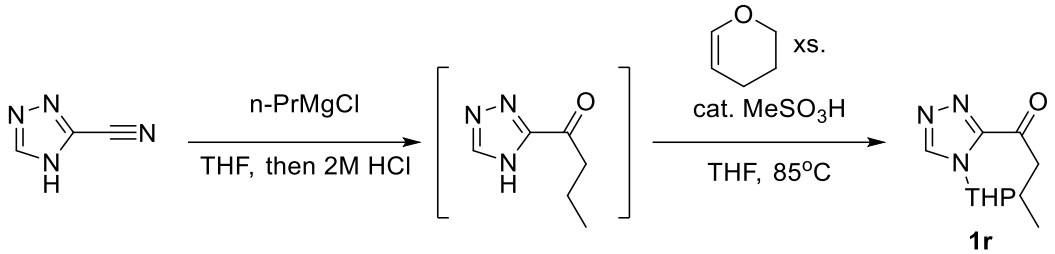
^{13}C NMR (126 MHz, $CDCl_3$) δ 202.02, 153.50, 148.89, 137.23, 135.72, 134.27, 129.62, 127.72, 127.17, 122.01, 63.93, 37.93, 32.59, 27.02, 25.73, 23.93, 19.36.

HRMS (ESI): Calcd for $C_{27}H_{33}NO_2Si$, $[M+Na]^+$: 454.2173, found: 454.2176.

IR (neat): v (cm^{-1}) 3052, 2933, 2859, 1698, 1463, 1110, 705.

Rf: 0.6 (20% EtOAc in cyclohexane)

1-(4-(tetrahydro-2H-pyran-2-yl)-4H-1,2,4-triazol-3-yl)butan-1-one (1r)



1r

Compound was prepared according to a modified Representative procedure A. 4H-1,2,4-triazole-3-carbonitrile (0.941 g, 10 mmol) and solution of n-propylmagnesium chloride (2.5 eq, 25 mmol, 12.5 mL of 2 mol/L solution in diethyl ether) in THF (25 mL) were used. During acidification, 18.8 mL (3.75 eq, 37.5 mmol of HCl) of 2M HCl was used. These amendments yield 0.7 g (50%) of titular compound as white crystalline solid.

1-(4H-1,2,4-triazol-3-yl)butan-1-one (0.2 g, 1.44 mmol) was charged into a threaded culture tube with PTFE-coated magnetic stirbar and dissolved in THF (2 mL). 3,4-Dihydro-2H-pyran (0.66 mL, 5 eq) and methanesulfonic acid (5 µL, 5% mol) were added sequentially. The culture tube was sealed with a cap and then subjected to stirring in an heating block at 85°C overnight. After aging, reaction mixture was cooled to room temperature, diluted with EtOAc and extracted with sat. $NaHCO_3$ solution and brine. Organics were then dried over Na_2SO_4 and evaporated at reduced pressure. Resulting crude was then dryloaded onto diatomaceous earth and purified by column chromatography (0-100% EtOAc in cyclohexane) to yield 0.2 g (62%) of titular compound as a transparent honey-like oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 5.52 (dd, *J* = 9.0, 2.8 Hz, 1H), 4.11 – 4.04 (m, 1H), 3.77 – 3.67 (m, 1H), 3.05 (t, *J* = 7.4 Hz, 2H), 2.24 – 2.14 (m, 1H), 2.11 – 1.97 (m, 2H), 1.86 – 1.61 (m, 6H), 0.99 (t, *J* = 7.4 Hz, 3H).

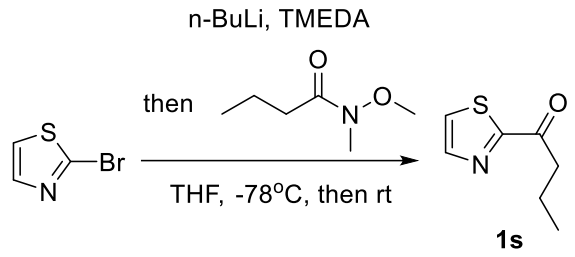
^{13}C NMR (126 MHz, $CDCl_3$) δ 193.98, 160.16, 143.27, 86.90, 67.87, 41.66, 30.83, 24.80, 21.67, 17.49, 13.91.

HRMS (ESI): Calcd for $C_{11}H_{17}N_3O_2$, $[M+Na]^+$: 246.1213, found: 246.1217.

IR (neat): v (cm^{-1}) 2939, 2872, 1702, 1445, 1198, 1088, 1043, 998, 914.

Rf: 0.32 (50% EtOAc in cyclohexane)

1-(thiazol-2-yl)butan-1-one (1s)



To an oven-dried, 50 mL two-neck flask equipped with a PTFE-coated magnetic stirbar, under the atmosphere of argon 2-bromothiazole (0.9 mL) was added, followed by dry THF (15 mL) and TMEDA (1.65 mL, 1.1 eq). Reaction mixture was then cooled to -78°C (dry ice/acetone) and n-butyllithium (4 mL of 2.5 M solution in hexane, 1 eq) was added dropwise. Resulting mixture was then stirred for 30 min at this temperature. After aging, a solution of N-methoxy-N-methylbutyramide (1.31 g, 1 eq) in 5 mL of THF was added dropwise. The vessel was then allowed to naturally warm up inside the bath to room temperature overnight. Reaction was then quenched by addition of sat. NH_4Cl solution, followed by water. Solution was extracted three times with EtOAc, combined organics were then dried over Na_2SO_4 and evaporated at reduced pressure. Resulting crude was then diluted with DCM and loaded onto a Claricep™ 20 g cartridge. Column chromatography (0-25% EtOAc in cyclohexane) yielded 1 g (64%) of titular compound as a brown oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 3.0 Hz, 1H), 7.66 (d, *J* = 3.0 Hz, 1H), 3.14 (t, *J* = 7.5 Hz, 1H), 1.81 (h, *J* = 7.4 Hz, 2H), 1.02 (t, *J* = 7.4 Hz, 3H).

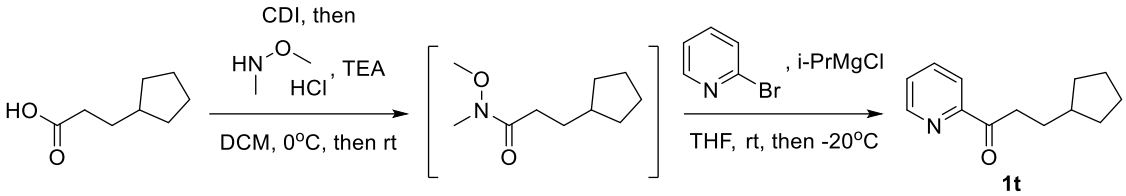
^{13}C NMR (126 MHz, $CDCl_3$) δ 194.19, 167.55, 144.78, 126.17, 40.55, 17.72, 13.92.

HRMS (ESI): Calcd for C_7H_9NOS, $[M+H]^+$: 156.0478, found: 156.0476.

IR (neat): v (cm^{-1}) 2964, 2875, 1683, 1391, 1226, 965, 747, 618.

Rf: 0.6 (20% EtOAc in cyclohexane)

3-cyclopentyl-1-(pyridin-2-yl)propan-1-one (1t)



To a 250 mL round bottom flask equipped with PTFE-coated magnetic stirbar 3-cyclopentylpropionic acid (4.28 mL, 30 mmol) was charged. 60 mL of DCM are then added; resulting mixture was then cooled to 0 °C (ice/water). 1,1'-Carbonyldiimidazole (5.35 g, 33 mmol, 1.1 eq) was then added portionwise. Resulting mixture was stirred at that temperature for 1.5 hours. N,O-dimethylhydroxylamine hydrochloride (3.21 g, 33 mmol, 1.1 eq) was added afterwards in a single portion, followed by slow addition of triethylamine (12.5 mL, 90 mmol, 3 eq). Cooling was then removed and reaction mixture was then left to stir at room temperature overnight. After aging, reaction mixture was diluted with water. Organic layer was extracted and washed once with sat. $NaHCO_3$ solution and water, dried over Na_2SO_4 and evaporated at reduced pressure. 5 g (90%) of 3-cyclopentyl-N-methoxy-N-methylpropanamide is recovered as a beige, transparent liquid, which is then used in the next step without purification.

To an oven-dried 25 mL two-neck flask equipped with PTFE-coated magnetic stirbar, under the atmosphere of argon 2-bromopyridine (0.975 mL, 10 mmol, 1 eq) was added, followed by dry THF (3 mL). To this mixture isopropylmagnesium bromide (3.9 mL of 2.9 M solution in 2-MeTHF, 11 mmol, 1.1 eq) was added slowly. After completion of addition, reaction was left stirring overnight. During this time precipitation occurred. After aging, reaction mixture was cooled to -20°C (30% aq. MeOH/dry ice) and a solution of 3-cyclopentyl-N-methoxy-N-methylpropanamide (1.9 g, 10.3 mmol, 1.03 eq) in 5 mL of THF was added dropwise. Cooling was removed and reaction mixture was then left stirring overnight at room temperature. After completion of these steps, reaction was quenched by addition of sat. NH_4Cl solution, followed by water. Solution was extracted three times with EtOAc, combined organics were then dried over Na_2SO_4 and evaporated at reduced pressure. Resulting crude was then dryloaded onto diatomaceous earth and purified by column chromatography (X-Y% EtOAc in cyclohexane) to yield 1.05 g (52%) of titular compound as an orange liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.03 (ddd, *J* = 7.9, 1.1, 1.1 Hz, 1H), 7.82 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.45 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 3.26 – 3.20 (m, 2H), 1.92 – 1.77 (m, 3H), 1.77 – 1.71 (m, 2H), 1.67 – 1.56 (m, 2H), 1.55 – 1.45 (m, 2H), 1.22 – 1.09 (m, 2H).

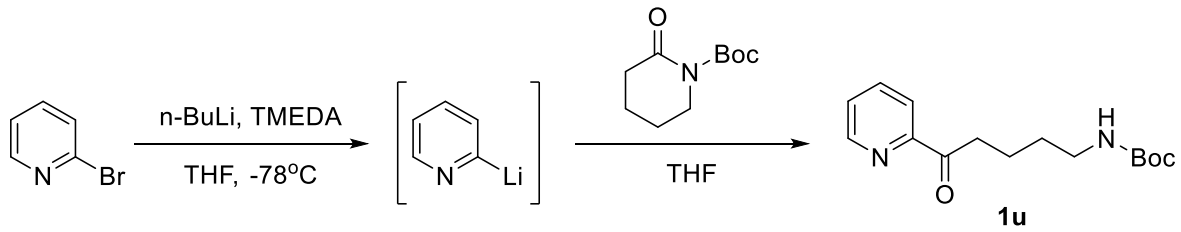
^{13}C NMR (126 MHz, $CDCl_3$) δ 202.50, 153.73, 149.05, 136.99, 127.09, 121.93, 40.00, 37.16, 32.77, 30.34, 25.34.

HRMS (ESI): Calcd for $C_{13}H_{17}NO$, $[M+H]^+$: 204.1383, found: 204.1384.

IR (neat): v (cm^{-1}) 2949, 2866, 1697, 1584, 1216, 995, 890, 752, 631.

Rf: 0.32 (50% EtOAc in cyclohexane)

tert-butyl (6-oxo-6-(pyridin-2-yl)hexyl)carbamate (1u)



1u

To an oven-dried 100 mL two-neck flask equipped with a PTFE-coated stirbar under the atmosphere of argon 2-bromopyridine (0.73 mL, 7.5 mmol, 1.5 eq), N,N,N',N'-tetramethylethylenediamine (1.12 mL, 7.5 mmol, 1.5 eq) and THF (20 mL) were charged. Resulting mixture is then cooled to -78 °C (acetone/dry ice) and n-butyllithium (3 mL of 2.5 M solution in hexanes, 7.5 mmol, 1.5 eq) was added dropwise into the solution. Reaction mixture was then stirred at this temperature for 2 hours. Upon aging, a solution of tert-butyl 2-oxopiperidine-1-carboxylate (1 g, 5 mmol, 1 eq) in THF (10 mL) was added dropwise and reaction mixture is stirred at -78 °C for 2 hours. Reaction is then allowed to reach room temperature, after which water is added. Resulting biphasic mixture is extracted with EtOAc three times, organic extracts are dried over Na_2SO_4 and evaporated at reduced pressure. Resulting crude was then dryloaded onto diatomaceous earth and purified by column chromatography (0-40% EtOAc in cyclohexane) to yield 0.8 g (58%) of titular compound as a yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 – 8.63 (m, 1H), 8.03 – 7.97 (m, 1H), 7.81 (ddd, *J* = 7.8, 1.8 Hz, 1H), 7.45 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 4.73 – 4.71 (brs, 1H), 3.21 (t, *J* = 7.3 Hz, 2H), 3.18 – 3.12 (m, 2H), 1.75 (p, *J* = 7.6 Hz, 2H), 1.57 (p, *J* = 7.1 Hz, 2H), 1.41 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.84, 156.13, 153.41, 149.03, 137.03, 127.22, 121.88, 79.14, 40.36, 37.28, 29.61, 28.53, 21.21.

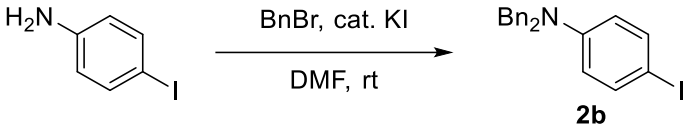
HRMS (ESI): Calcd for $C_{15}H_{22}N_2O_3$, $[M+Na]^+$: 301.1523, found: 301.1529.

IR (neat): v (cm^{-1}) 3373, 2961, 1696, 1521, 1336, 1273, 1171.

Rf: 0.19 (20% EtOAc in cyclohexane).

❖ **Preparation of aryl components**

N,N-dibenzyl-4-iodoaniline (2b)



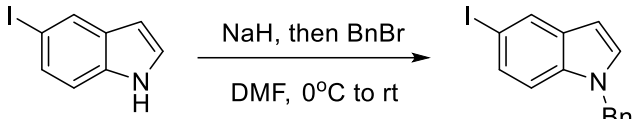
2b

This compound was synthesized according to a described procedure[10] from 2.2 g of 4-iodoaniline to yield 2.67 g (67%) of titular compound as white needles. Analytical data of obtained sample matched those described.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 2H), 7.36 – 7.31 (m, 4H), 7.29 – 7.24 (m, 2H), 7.24 – 7.20 (m, 4H), 6.55 – 6.48 (m, 2H), 4.63 (s, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.71, 137.90, 128.89, 127.24, 126.68, 115.01, 54.47.

1-benzyl-5-iodo-1H-indole (2c)



2c

This compound was synthesized according to a described procedure[11] from 0.6 g of 5-iodoindole to yield 0.65 g (78%) of titular compound as pale yellow flakes. Analytical data of obtained sample matched those described.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 1.7, 0.6 Hz, 1H), 7.32 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.26 – 7.15 (m, 4H), 7.06 – 6.94 (m, 5H), 6.40 (dd, *J* = 3.1, 0.9 Hz, 1H), 5.21 (s, 2H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.16, 135.54, 131.43, 130.13, 129.93, 129.23, 128.98, 128.55, 127.93, 126.82, 111.87, 101.18, 83.24, 50.38.

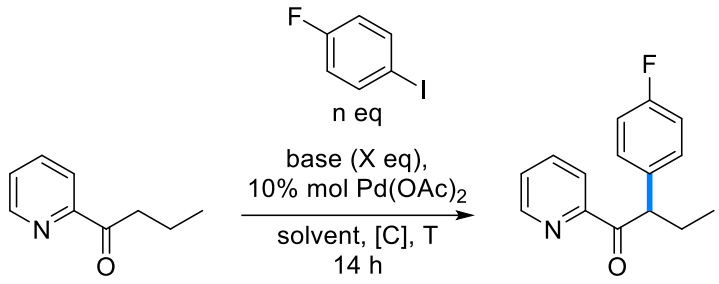
[10] Goldup S. M., Leigh D.A., Lusby P. J., McBurney R. T., Slawin A. M. Z., *Angew. Chem. Int. Ed.* **2008**, *47*, 3381 – 3384

[11] Arendt K. A., Doyle A. G., *Angew. Chem. Int. Ed.* **2015**, *54*, 9876 –9880

Products of α-functionalization

❖ Optimization studies for α-functionalization

Table 3.1. Base and solvent optimization for α-functionalization[a]

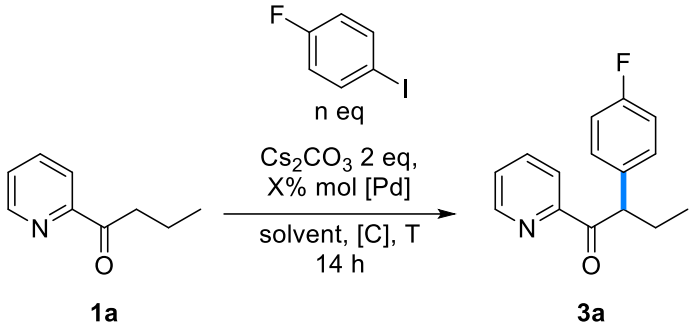


1a **3a**

Entry	Base (X)	n	T, °C	Solvent, [C]	Yield, α	Yield, β	Comment
1	Cs_2CO_3 (1)	2	100	Toluene, 0.1 M	45	1	Initial base screening
2	Rb_2CO_3 (1)				22	6	
3	NaOtBu (1)				46	3	
4	KOH (1)				37	6	
5	NaOH (1)				33	6	
6	CsOH (1)				40	3	
7	Cs_2CO_3 (1)	2	100	HFIP, 0.1 M	1	5	Initial solvent screening
8				DCE, 0.1 M	12	6	
9				H_2O, 0.1 M	22	3	
10				PEG400, 0.1 M	2	4	
11				t-AmylOH, 0.1 M	23	12	
12				t-BuOH,0.1 M	21	9	
13				AcOH, 0.1 M	0	3	
14				Dioxane, 0.1 M	13	0	
15				DMSO, 0.1 M	0	0	
16				TFT, 0.1 M	68	0	
17				TFE, 0.1 M	12	10	
18	Cs_2CO_3 (1)	2	100	TFT, 0.1 M	68	0	Base quantity determination
19	Cs_2CO_3 (1.5)				68	0	
20	Cs_2CO_3 (2)				78	0	
21	Cs_2CO_3 (2.5)				55	0	
22	Cs_2CO_3 (1)	2	100	m-xylene, 0.1 M	72	0	Secondary solvent screening
23				mesitylene, 0.1 M	95	0	
24				TCE, 0.1 M	6	0	
25				GVL, 0.1 M	0	0	
26				DME, 0.1 M	69	0	
27				2-MeTHF, 0.1 M	76	0	
28				MTBE, 0.1 M	84	0	

[a]Performed on 0.1 mmol scale, using 0.2 mmol (1 eq) of **1a** and appropriate quantity of **2a** with appropriate base, additives and solvent. Yield was determined by ^{1}H NMR with 1,1,2-trichloroethylene as an external standard.

Table 3.2. Scale optimization for α-functionalization[a]



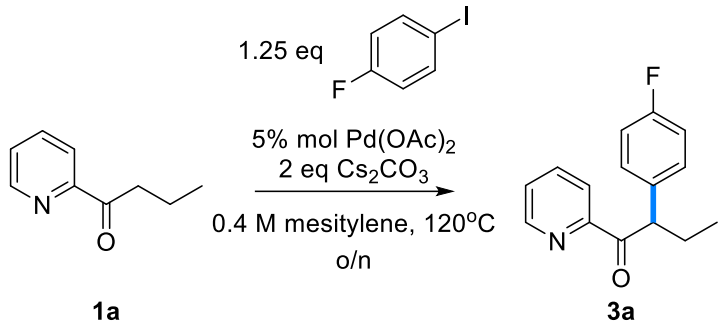
1a **3a**

Varied scale, mmol

Entry	n	X	T, °C	Solvent, [C]	[Pd]	Scale, mmol	Yield, α	Comment
29	2	10	100	Mesitylene, 0.1M	$Pd(OAc)_2$	0.1	95 (63)	Scale up to 0.25 mmol
30	2	10	100			0.25	66 (53)	
31	2	10	90			0.25	19	Temperature screen
32	2	10	110			0.25	65 (38)	
33	2	10	100			0.5	72	250 rpm stirring
34	2	10	100	Mesitylene, 0.2M		0.5	80 (77)	1000 rpm stirring
35	1.25	5	100			0.5	74	Eq of aryl iodides
36	1.5	5	120			0.5	90 (71)	
37	1.25	5	120		PdI_2	0.5	56	Other Pd salts
38	1.25	5	120		$Pd(OPiv)_2$	0.5	85	
39	1.25	5	120	Mesitylene, 0.4M	$Pd(OAc)_2$	0.5	88 (75)	Finalized conditions

[a]Performed on 0.1 mmol scale, using 0.2 mmol (1 eq) of **1a** and appropriate quantity of **2a** with appropriate base, additives and solvent. Yield was determined by ^1H NMR with 1,1,2-trichloroethylene as an external standard.

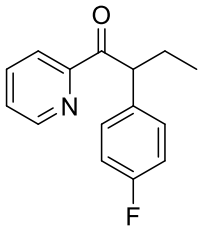
❖ **Representative procedure B - preparation of 2-(4-fluorophenyl)-1-(pyridin-2-yl)butan-1-one 3a**



1a **3a**

To an oven-dried threaded culture tube (10 mL) equipped with PTFE-coated magnetic stirbar cesium carbonate (326 mg, 1 mmol, 2 eq) was charged. Tube was then introduced to the glovebox, where palladium acetate (reagent grade, 98%; 5.6 mg, 0.025 mmol) was charged. Tube was then closed with a septum and removed from the glovebox, where 1-(pyridin-2-yl)butan-1-one (74 µL, 0.5 mmol), 1-fluoro-4-iodobenzene (73 µL, 0.625 mmol, 1.25 eq) and mesitylene (1.25 mL) are added via syringe. Septum was then replaced in a flow of argon with a screwcap and reaction mixture was then stirred in a heating block at 120°C for 14 hours. Reaction mixture was then cooled to room temperature, diluted with DCM (2 mL) and filtered over a pad of Celite. Solids were then washed with DCM (2x2 mL) and combined filtrate evaporated at reduced pressure (60°C, 5 mbar). Residue is then dryloaded onto Celite and subjected to column chromatography (Claricep 20g cartridge, 0-20% EtOAc in cyclohexane) to yield 91 mg (75%) of 2-(4-fluorophenyl)-1-(pyridin-2-yl)butan-1-one as a yellow liquid that solidified upon standing.

Similarly, this transformation was performed at 2.5 mmol and 12.5 mmol scale to yield 500 mg (83%) and 2 g (66%) of titular compound.



2-(4-fluorophenyl)-1-(pyridin-2-yl)butan-1-one (3a)

Prepared as stated above. Compound was also prepared from 1-(pyridin-2-yl)butan-1-one (74 µL) and 1-fluoro-4-bromobenzene (69 µL, 1.25 eq) to yield titular compound in 69% yield. Compound consistency and analytical data match in both cases.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.00 (ddd, *J* = 7.8, 1.1, 1.1 Hz, 1H), 7.77 (ddd, *J* = 7.8, 7.7, 1.7 Hz, 1H), 7.40 (ddd, *J* = 7.5, 4.8, 1.3 Hz, 1H), 7.37 – 7.32 (m, 2H), 6.98 – 6.90 (m, 2H), 5.28 (t, *J* = 7.6 Hz, 1H), 2.23 – 2.11 (m, 1H), 1.94 – 1.81 (m, 1H), 0.90 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.61, 161.89 (d, *J* = 244.8 Hz), 153.15, 148.95, 136.99, 135.04 (d, *J* = 3.2 Hz), 130.56 (d, *J* = 7.9 Hz), 127.12, 122.81, 115.36 (d, *J* = 21.2 Hz), 51.62, 26.28, 12.28.

^{19}F NMR (471 MHz, $CDCl_3$) δ -117.29 (s).

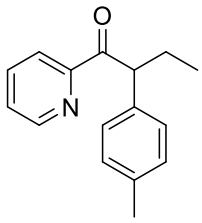
HRMS (ESI): Calcd for $C_{15}H_{14}FNO$, $[M+H]^+$: 244.1132, found: 244.1135.

Mp: 65°C

IR (neat): v (cm-^{1}) 3054, 2965, 2919, 1693, 1506, 1219, 994, 821, 773.

Rf: 0.5 (20% EtOAc in cyclohexane)

According to this procedure, following compounds were synthesized:



1-(pyridin-2-yl)-2-(p-tolyl)butan-1-one (3b)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 µL) and 4-iodotoluene (136 mg, 1.25 eq) to yield 81 mg (68%) of titular compound as a dark blue solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.97 (ddd, *J* = 7.9, 1.1, 1,1 Hz, 1H), 7.73 (ddd, *J* = 7.7, 7,7, 1.7 Hz, 1H), 7.36 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.30 – 7.19 (m, 2H), 7.08 – 7.00 (m, 2H), 5.25 (t, *J* = 7.6 Hz, 1H), 2.25 (s, 3H), 2.22 – 2.10 (m, 1H), 1.95 – 1.83 (m, 1H), 0.89 (t, *J* = 7.4 Hz, 3H).

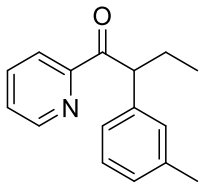
^{13}C NMR (126 MHz, $CDCl_3$) δ 201.86, 153.46, 148.93, 136.90, 136.41, 136.32, 129.30, 128.96, 126.94, 122.81, 52.14, 26.23, 21.17, 12.39.

HRMS (ESI): Calcd for $C_{16}H_{17}NO$, $[M+H]^+$: 240.1383, found: 240.1385.

Mp: 55°C

IR (neat): v (cm-^{1}) 2963, 2923, 2873, 1688, 1580, 1435, 1214, 994, 802.

Rf: 0.64 (20% EtOAc in cyclohexane)



1-(pyridin-2-yl)-2-(m-tolyl)butan-1-one (3c)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 µL) and 3-iodotoluene (136 mg) to yield 100 mg (84%) of titular compound as a dark green oil.

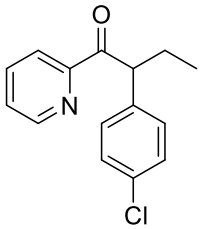
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.00 (ddd, *J* = 7.8, 1.1, 1.1 Hz, 1H), 7.75 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.39 (ddd, *J* = 7.5, 4.7, 1.2 Hz, 1H), 7.22 – 7.17 (m, 2H), 7.17 – 7.09 (m, 1H), 7.00 – 6.96 (m, 1H), 5.26 (t, *J* = 7.6 Hz, 1H), 2.29 (s, 3H), 2.22 – 2.14 (m, 1H), 1.96 – 1.84 (m, 1H), 0.91 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.86, 153.45, 148.95, 139.29, 138.12, 136.90, 129.61, 128.40, 127.63, 126.97, 126.27, 122.81, 52.44, 26.35, 21.55, 12.44.

HRMS (ESI): Calcd for $C_{16}H_{17}NO$, $[M+H]^+$: 240.1383, found: 240.1386.

IR (neat): v (cm-^{1}) 3054, 2964, 1693, 1605, 1461, 1345, 1211, 1090, 995, 781, 689, 617

Rf: 0.57 (20% EtOAc in cyclohexane)



2-(4-chlorophenyl)-1-(pyridin-2-yl)butan-1-one (3d)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 µL) and 4-iodochlorobenzene (77 µL) to yield 107 mg (82%) of titular compound as a green solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.00 (ddd, *J* = 7.9, 1.1, 1.1 Hz, 1H), 7.77 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.41 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.36 – 7.30 (m, 2H), 7.25 – 7.19 (m, 2H), 5.27 (t, *J* = 7.6 Hz, 1H), 2.23 – 2.11 (m, 1H), 1.94 – 1.81 (m, 1H), 0.90 (t, *J* = 7.4 Hz, 3H).

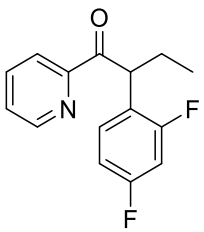
^{13}C NMR (126 MHz, $CDCl_3$) δ 201.36, 153.07, 148.98, 137.91, 137.02, 132.70, 130.46, 128.71, 127.19, 122.83, 51.87, 26.18, 12.29.

HRMS (ESI): Calcd for $C_{16}H_{17}NO$, $[M+H]^+$: 260.0837, found: 260.0840.

Mp: 49°C

IR (neat): v (cm-^{1}) 3055, 2960, 2923, 1694, 1490, 1329, 1275, 1215, 1091, 991, 810, 751.

Rf: 0.56 (20% EtOAc in cyclohexane)



2-(2,4-difluorophenyl)-1-(pyridin-2-yl)butan-1-one (3e)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 µL) and 2,4-difluoroiodobenzene (75 µL) to yield 90 mg (69%) of titular compound as a yellow crystalline solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.01 (ddd, *J* = 7.9, 1.1, 1.1 Hz, 1H), 7.78 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.41 (ddd, *J* = 7.6, 4.8, 1.3 Hz, 1H), 7.32 – 7.23 (m, 1H), 6.82 – 6.72 (m, 2H), 5.49 (dd, *J* = 8.4, 6.6 Hz, 1H), 2.20 – 2.11 (m, 1H), 1.90 – 1.76 (m, 1H), 0.96 – 0.90 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.03, δ 162.45 (dd, *J* = 108.1, 11.6 Hz), 160.48 (dd, *J* = 110.1, 11.6 Hz), 152.97, 149.15, 136.94, 130.37 (dd, *J* = 9.6, 5.7 Hz), 127.17, 122.67, 122.65 (dd, *J* = 15.6, 3.8 Hz), 111.43 (d, *J* = 3.8 Hz), 103.88 (dd, *J* = 26.9, 25.2 Hz), 44.79 (d, *J* = 1.4 Hz), 25.67, 12.10.

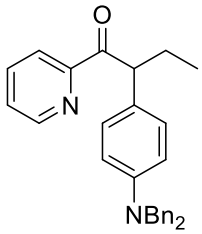
^{19}F NMR (471 MHz, $CDCl_3$) δ -113.48 (d, *J* = 7.2 Hz), -113.87 (d, *J* = 7.3 Hz).

HRMS (ESI): Calcd for $C_{16}H_{17}NO$, $[M+H]^+$: 262.1038, found: 262.1041.

Mp: 90°C

IR (neat): v (cm^{-1}) 2962, 2934, 2875, 1696, 1602, 1502, 1429, 1278, 1141, 964, 851, 783.

Rf: 0.54 (20% EtOAc in cyclohexane)



2-(4-(dibenzylamino)phenyl)-1-(pyridin-2-yl)butan-1-one (3f)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 µL) and N,N-dibenzyl-4-iodoaniline (200 mg, 1 eq) to yield 116 mg (55%) of titular compound as a yellow oil.

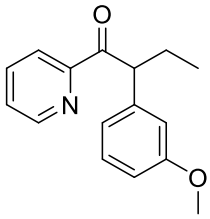
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 7.87 (ddd, *J* = 7.9, 1.1, 1.1 Hz, 1H), 7.59 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.22 (ddd, *J* = 7.6, 4.8, 1.3 Hz, 1H), 7.19 – 7.14 (m, 4H), 7.15 – 7.04 (m, 8H), 6.58 – 6.50 (m, 2H), 5.10 (t, *J* = 7.6 Hz, 1H), 4.46 (s, 4H), 2.12 – 2.00 (m, 1H), 1.82 – 1.70 (m, 1H), 0.80 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.97, 153.63, 148.84, 148.22, 138.78, 136.78, 129.79, 128.67, 127.11, 126.93, 126.79, 126.77, 122.77, 112.58, 54.26, 51.09, 26.17, 12.47.

HRMS (ESI): Calcd for $C_{29}H_{28}N_2O$, $[M+H]^+$: 421.2274, found: 421.2271.

IR (neat): v (cm^{-1}) 3083, 2963, 1690, 1516, 1452, 1357, 1231, 995, 729.

Rf: 0.58 (20% EtOAc in cyclohexane)



2-(3-methoxyphenyl)-1-(pyridin-2-yl)butan-1-one (3g)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 µL) and 3-iodoanisole (75 µL) to yield 79 mg (62%) of titular compound as a yellow oil.

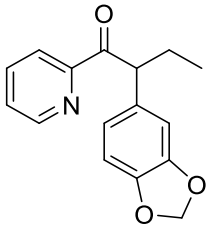
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.99 (ddd, *J* = 7.9, 1.1, 1.1 Hz, 1H), 7.74 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.38 (ddd, *J* = 7.5, 4.8, 1.3 Hz, 1H), 7.16 (t, *J* = 7.9 Hz, 1H), 7.01 – 6.92 (m, 2H), 6.71 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 5.27 (t, *J* = 7.5 Hz, 1H), 3.76 (s, 3H), 2.25 – 2.12 (m, 1H), 1.97 – 1.85 (m, 1H), 0.92 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.57, 159.71, 153.35, 148.91, 140.91, 136.90, 129.42, 126.99, 122.78, 121.50, 114.70, 112.27, 55.25, 52.49, 26.18, 12.37.

HRMS (ESI): Calcd for $C_{16}H_{17}NO_2$, $[M+H]^+$: 256.1332, found: 256.1335.

IR (neat): v (cm^{-1}) 3055, 2964, 1694, 1598, 1486, 1461, 1260, 1150, 1048, 995, 877, 781.

Rf: 0.5 (20% EtOAc in cyclohexane)



2-(benzo[d][1,3]dioxol-5-yl)-1-(pyridin-2-yl)butan-1-one (3h)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 µL) and 1-iodo-3,4-methylenedioxybenzene (155 mg) to yield 74 mg (55%) of titular compound as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (ddd, *J* = 4.7, 1.8, 0.9 Hz, 1H), 7.99 (ddd, *J* = 7.8, 1.1, 1.1 Hz, 1H), 7.74 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.37 (ddd, *J* = 7.5, 4.7, 1.2 Hz, 1H), 6.91 (d, *J* = 1.7 Hz, 1H), 6.83 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 5.90 – 5.83 (m, 2H), 5.20 (t, *J* = 7.6 Hz, 1H), 2.18 – 2.07 (m, 1H), 1.92 – 1.74 (m, 1H), 0.90 (t, *J* = 7.4 Hz, 3H).

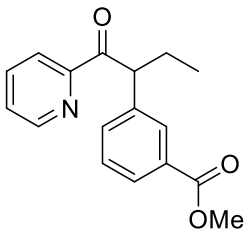
^{13}C NMR (126 MHz, $CDCl_3$) δ 201.56, 153.27, 148.90, 147.72, 146.43, 136.89, 133.01, 127.04, 122.75, 122.34, 109.34, 108.27, 100.94, 51.88, 26.15, 12.25.

HRMS (ESI): Calcd for $C_{16}H_{15}NO_3$, $[M+H]^+$: 270.1125, found: 270.1126.

Mp: 69°C

IR (neat): v (cm^{-1}) 2964, 2907, 1681, 1482, 1247, 1038, 933, 849, 800, 694.

Rf: 0.55 (20% EtOAc in cyclohexane)



methyl 3-(1-oxo-1-(pyridin-2-yl)butan-2-yl)benzoate (3i)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 µL) and methyl 3-iodobenzoate (164 mg, 1.5 eq) to yield 92 mg (65%) of titular compound as a colourless oil.

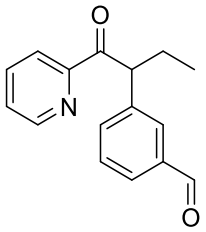
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.09 – 8.05 (m, 1H), 8.01 (ddd, *J* = 7.9, 1.1, 1.1 Hz, 1H), 7.85 (ddd, *J* = 7.7, 1.7, 1.2 Hz, 1H), 7.77 (ddd, *J* = 7.7, 7.7, 1.8 Hz, 1H), 7.64 – 7.58 (m, 1H), 7.41 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 1H), 5.35 (t, *J* = 7.5 Hz, 1H), 3.89 (s, 3H), 2.26 – 2.15 (m, 1H), 1.98 – 1.86 (m, 1H), 0.91 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.36, 167.22, 153.05, 149.03, 139.90, 137.00, 133.72, 130.50, 130.31, 128.62, 128.20, 127.19, 122.82, 52.32, 52.21, 26.32, 12.35.

HRMS (ESI): Calcd for $C_{17}H_{17}NO_3$, $[M+H]^+$: 284.1281, found: 284.1282.

IR (neat): v (cm-^{1}) 2963, 1721, 1583, 1435, 1280, 1196, 1107, 995, 752.

Rf: 0.4 (20% EtOAc in cyclohexane)



3-(1-oxo-1-(pyridin-2-yl)butan-2-yl)benzaldehyde (3j)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 µL) and 3-iodobenzaldehyde (116 mg) to yield 57 mg (45%) of titular compound as a yellow oil.

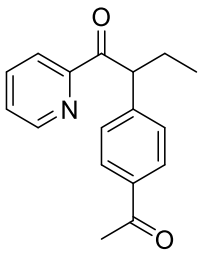
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.96 (s, 1H), 8.66 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.00 (ddd, *J* = 7.8, 1.1, 1.1 Hz, 1H), 7.94 – 7.89 (m, 1H), 7.76 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.72 – 7.64 (m, 2H), 7.46 – 7.37 (m, 2H), 5.40 5.40 (t, *J* = 7.6 Hz, 1H), 2.28 – 2.17 (m, 1H), 1.98 – 1.86 (m, 1H), 0.90 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.15, 192.44, 152.84, 149.02, 140.68, 137.02, 136.75, 135.23, 130.70, 129.21, 128.05, 127.27, 122.78, 52.10, 26.30, 12.29.

HRMS (ESI): Calcd for $C_{16}H_{17}NO_2$, $[M+H]^+$: 254.1176, found: 254.1180.

IR (neat): v (cm-^{1}) 2966, 2735, 1697, 1583, 1459, 1234, 995, 789.

Rf: 0.33 (20% EtOAc in cyclohexane)



2-(4-acetylphenyl)-1-(pyridin-2-yl)butan-1-one (3k)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 µL) and 4-iodoacetophenone (154 mg) to yield 66 mg (49%) of titular compound as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.01 (ddd, *J* = 7.9, 1.1, 1.1 Hz, 1H), 7.89 – 7.83 (m, 2H), 7.78 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.52 – 7.46 (m, 2H), 7.41 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 5.36 (t, *J* = 7.6 Hz, 1H), 2.54 (s, 3H), 2.28 – 2.15 (m, 1H), 1.98 – 1.85 (m, 1H), 0.91 (t, *J* = 7.4 Hz, 3H).

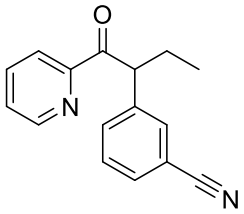
^{13}C NMR (126 MHz, $CDCl_3$) δ 201.02, 197.95, 153.00, 149.02, 145.10, 137.04, 135.86, 129.33, 128.67, 127.27, 122.84, 52.68, 26.70, 26.20, 12.32.

HRMS (ESI): Calcd for $C_{17}H_{17}NO_2$, $[M+H]^+$: 268.1332, found: 268.1335.

Mp: 51°C

IR (neat): v (cm-^{1}) 3052, 2968, 2879, 1668, 1601, 1414, 1360, 1270, 1010, 956, 810, 748.

Rf: 0.25 (20% EtOAc in cyclohexane)



3-(1-oxo-1-(pyridin-2-yl)butan-2-yl)benzonitrile (3l)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 µL) and 3-iodobenzonitrile (172 mg) to yield 51 mg (41%) of titular compound as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.02 (ddd, *J* = 7.8, 1.1, 1.1 Hz, 1H), 7.79 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.75 – 7.70 (m, 1H), 7.64 (dt, *J* = 7.9, 1.5 Hz, 1H), 7.49 – 7.44 (m, 1H), 7.45 – 7.42 (m, 2H), 7.36 (t, *J* = 7.8 Hz, 1H), 5.35 (t, *J* = 7.6 Hz, 1H), 2.25 – 2.14 (m, 1H), 1.94 – 1.82 (m, 1H), 0.89 (t, *J* = 7.4 Hz, 3H).

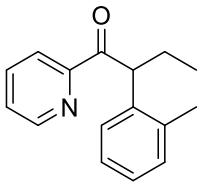
^{13}C NMR (126 MHz, $CDCl_3$) δ 200.70, 152.61, 149.07, 141.01, 137.12, 133.50, 132.93, 130.57, 129.30, 127.44, 122.84, 119.00, 112.57, 51.89, 26.22, 12.23.

HRMS (ESI): Calcd for $C_{16}H_{14}N_2O$, $[M+H]^+$: 251.1179, found: 251.1178.

Mp: 48°C

IR (neat): v (cm^{-1}) 3057, 2959, 2229, 1689, 1581, 1480, 1306, 1207, 1145, 995, 932, 810, 786, 693.

Rf: 0.26 (20% EtOAc in cyclohexane)



1-(pyridin-2-yl)-2-(o-tolyl)butan-1-one (3m)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 µL) and 2-iodotoluene (80 µL) to yield 77 mg (64%) of titular compound as a dark green solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (ddd, *J* = 4.8, 1.7, 1.0 Hz, 1H), 7.99 (ddd, *J* = 7.9, 1.1, 1.1 Hz, 1H), 7.74 (td, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.36 (ddd, *J* = 7.5, 4.7, 1.2 Hz, 1H), 7.22 – 7.16 (m, 1H), 7.15 – 7.10 (m, 1H), 7.13 – 7.01 (m, 2H), 5.43 (t, *J* = 7.4 Hz, 1H), 2.60 (s, 3H), 2.23 – 2.11 (m, 1H), 1.89 – 1.76 (m, 1H), 0.93 (t, *J* = 7.4 Hz, 3H).

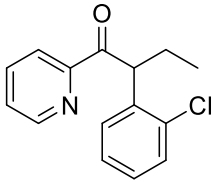
^{13}C NMR (126 MHz, $CDCl_3$) δ 202.34, 153.58, 148.92, 138.16, 137.34, 136.85, 130.57, 127.23, 126.94, 126.65, 126.16, 122.53, 48.55, 26.59, 20.28, 12.35.

HRMS (ESI): Calcd for $C_{16}H_{17}NO$, $[M+H]^+$: 240.1383, found: 240.1388.

Mp: 56°C

IR (neat): v (cm^{-1}) 3050, 2969, 2935, 1686, 1581, 1435, 1310, 1215, 995, 758, 685.

Rf: 0.52 (20% EtOAc in cyclohexane)



2-(2-chlorophenyl)-1-(pyridin-2-yl)butan-1-one (3n)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 µL) and 2-iodochlorobenzene (76 µL) to yield 108 mg (83%) of titular compound as a dark green liquid.

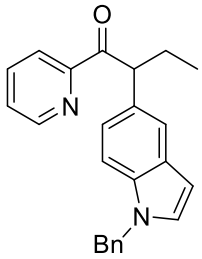
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.00 (ddd, *J* = 7.8, 1.1, 1.1 Hz, 1H), 7.76 (ddd, *J* = 7.7, 7.7, 1.8 Hz, 1H), 7.41 – 7.33 (m, 2H), 7.30 – 7.24 (m, 1H), 7.16 (td, *J* = 7.5, 1.5 Hz, 1H), 7.11 (td, *J* = 7.7, 1.8 Hz, 1H), 5.71 (t, *J* = 7.3 Hz, 1H), 2.24 – 2.11 (m, 1H), 1.92 – 1.80 (m, 1H), 0.97 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.58, 153.24, 149.19, 137.64, 136.84, 134.90, 129.82, 129.11, 127.93, 127.02, 126.93, 122.56, 49.29, 26.06, 12.25.

HRMS (ESI): Calcd for $C_{15}H_{14}ClNO$, $[M+H]^+$: 260.0837, found: 260.0841.

IR (neat): v (cm^{-1}) 3057, 2966, 1696, 1582, 1459, 1242, 1037, 745.

Rf: 0.58 (20% EtOAc in cyclohexane)



2-(1-benzyl-1H-indol-5-yl)-1-(pyridin-2-yl)butan-1-one (3o)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 µL) and N-benzyl-5-iodoindole (208 mg) to yield 94 mg (53%) of titular compound as a light brown solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 – 8.46 (m, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.58 – 7.52 (m, 1H), 7.46 (td, *J* = 7.7, 1.2 Hz, 1H), 7.15 – 7.06 (m, 5H), 7.04 (d, *J* = 8.5 Hz, 1H), 6.98 – 6.91 (m, 2H), 6.89 (d, *J* = 3.2 Hz, 1H), 6.34 (d, *J* = 3.1 Hz, 1H), 5.27 (t, *J* = 7.5 Hz, 1H), 5.04 (s, 2H), 2.20 – 2.08 (m, 1H), 1.92 – 1.80 (m, 1H), 0.82 (t, *J* = 7.4 Hz, 3H).

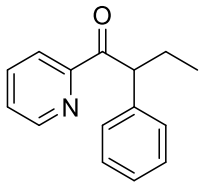
^{13}C NMR (126 MHz, $CDCl_3$) δ 202.09, 153.59, 148.77, 137.48, 136.68, 135.52, 130.26, 128.93, 128.74, 128.43, 127.62, 126.94, 126.66, 122.99, 122.71, 121.30, 109.67, 101.61, 52.30, 50.09, 26.98, 26.54, 12.47.

HRMS (ESI): Calcd for $C_{24}H_{22}N_2O$, $[M+H]^+$: 260.0837, found: 260.0841

Mp: 91°C

IR (neat): v (cm^{-1}) 2968, 1686, 1580, 1481, 1318, 1181, 1010, 722.

Rf: 0.46 (20% EtOAc in cyclohexane)



2-phenyl-1-(pyridin-2-yl)butan-1-one (3p)

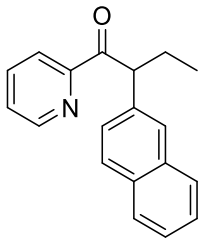
Prepared from 1-(pyridin-2-yl)butan-1-one (74 µL) and iodobenzene (69 µL) to yield 86 mg (76%) of titular compound as a greenish blue liquid. Analytical data matched with that described in literature.[12]

[12] Li B. X., Le D. N., Mack K. A., McClory A., Lim N.-K., Cravillion T., Savage S., Han C., Collum D. B., Zhang H., Gosselin F., *J. Am. Chem. Soc.* **2017**, *139*, 31, 10777–10783

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.00 (ddd, *J* = 7.8, 1.1, 1.1 Hz, 1H), 7.76 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.42 – 7.37 (m, 3H), 7.28 – 7.21 (m, 2H), 7.19 – 7.14 (m, 1H), 5.29 (t, *J* = 7.6 Hz, 1H), 2.26 – 2.14 (m, 1H), 1.98 – 1.85 (m, 1H), 0.91 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.78, 153.40, 148.95, 139.41, 136.92, 129.11, 128.56, 127.00, 126.83, 122.81, 52.54, 26.28, 12.39.

Rf: 0.59 (20% EtOAc in cyclohexane)



2-(naphthalen-2-yl)-1-(pyridin-2-yl)butan-1-one (3q)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 µL) and 2-iodonaphtalene (159 mg) to yield 89 mg (65%) of titular compound as a green liquid.

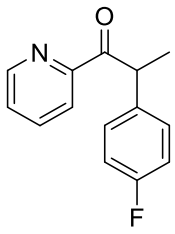
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.02 (ddd, *J* = 7.8, 1.1, 1.1 Hz, 1H), 7.86 – 7.82 (m, 1H), 7.81 – 7.75 (m, 3H), 7.72 (ddd, *J* = 7.7, 7.7, 1.8 Hz, 1H), 7.59 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.47 – 7.38 (m, 2H), 7.35 (ddd, *J* = 7.5, 4.8, 1.3 Hz, 1H), 5.48 (t, *J* = 7.6 Hz, 1H), 2.37 – 2.25 (m, 1H), 2.11 – 1.99 (m, 1H), 0.97 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.57, 153.30, 148.91, 136.91, 133.62, 132.53, 128.16, 127.87, 127.84, 127.65, 127.33, 126.99, 125.97, 125.68, 122.80, 52.72, 26.24, 12.41.

HRMS (ESI): Calcd for $C_{19}H_{17}NO$, $[M+Na]^+$: 298.1202, found: 298.1205.

IR (neat): v (cm^{-1}) 3055, 2964, 1693, 1582, 1342, 1214, 995, 815, 745.

Rf: 0.5 (20% EtOAc in cyclohexane)



2-(4-fluorophenyl)-1-(pyridin-2-yl)propan-1-one (3r)

Prepared from 1-(pyridin-2-yl)propan-1-one (68 mg) and 1-fluoro-4-iodobenzene (58 µL, 1 eq) to yield 67 mg (59%) of titular compound as an yellow oil that solidified upon standing.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.00 (ddd, *J* = 7.9, 1.1, 1.1 Hz, 1H), 7.76 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.39 (ddd, *J* = 7.5, 4.8, 1.3 Hz, 1H), 7.39 – 7.31 (m, 2H), 7.00 – 6.90 (m, 2H), 5.48 (q, *J* = 7.1 Hz, 1H), 1.53 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.78, 161.80 (d, *J* = 244.8 Hz), 152.83, 148.92, 136.98, 136.66 (d, *J* = 3.2 Hz), 130.09 (d, *J* = 8.0 Hz), 127.11, 122.89, 115.38 (d, *J* = 21.2 Hz), 44.17, 18.34.

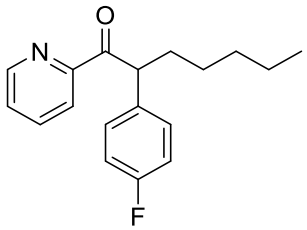
^{19}F NMR (471 MHz, $CDCl_3$) δ -117.33 (s).

HRMS (ESI): Calcd for $C_{14}H_{12}FNO$, $[M+H]^+$: 230.0976, found: 230.0979.

Mp: 34°C

IR (neat): v (cm^{-1}) 3062, 2979, 1694, 1505, 1327, 1223, 1160, 958, 841, 751.

Rf: 0.54 (20% EtOAc in cyclohexane)



2-(4-fluorophenyl)-1-(pyridin-2-yl)heptan-1-one (3s)

Prepared from 1-(pyridin-2-yl)heptan-1-one (96 mg) and 1-fluoro-4-iodobenzene (116 µL, 2 eq) to yield 100 mg (70%) of titular compound as a dark brown liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (ddd, *J* = 4.8, 2.6, 0.8 Hz, 1H), 8.00 (ddd, *J* = 7.9, 1.1, 1.1 Hz, 1H), 7.75 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.44 – 7.32 (m, 3H), 6.99 – 6.89 (m, 2H), 5.39 (t, *J* = 7.6 Hz, 1H), 2.20 – 2.09 (m, 1H), 1.90 – 1.79 (m, 1H), 1.38 – 1.18 (m, 6H), 0.89 – 0.79 (m, 3H).

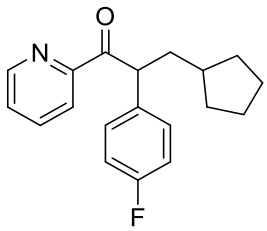
^{13}C NMR (126 MHz, $CDCl_3$) δ 201.61, 161.84 (d, *J* = 244.8 Hz), 153.10, 148.94, 136.95, 135.28 (d, *J* = 3.2 Hz), 130.51 (d, *J* = 7.9 Hz), 127.08, 122.80, 115.34 (d, *J* = 21.2 Hz), 49.84, 33.13, 31.88, 27.39, 22.57, 14.11.

^{19}F NMR (471 MHz, $CDCl_3$) δ -117.30 (s).

HRMS (ESI): Calcd for $C_{18}H_{20}FNO$, $[M+H]^+$: 286.1602, found: 286.1605.

IR (neat): v (cm^{-1}) 2929, 2859, 1697, 1508, 1225, 770.

Rf: 0.66 (20% EtOAc in cyclohexane)



3-cyclopentyl-2-(4-fluorophenyl)-1-(pyridin-2-yl)propan-1-one (3t)

Prepared from 3-cyclopentyl-1-(pyridin-2-yl)propan-1-one (102 mg) and 1-fluoro-4-iodobenzene (87 µL, 1.5 eq) to yield 66 mg (44%) of titular compound as a brown liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.00 (ddd, *J* = 7.8, 1.1, 1.1 Hz, 1H), 7.76 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.43 – 7.34 (m, 3H), 7.00 – 6.90 (m, 2H), 5.48 (t, *J* = 7.6 Hz, 1H), 2.14 (dt, *J* = 13.4, 7.5 Hz, 1H), 1.96 – 1.86 (m, 1H), 1.84 – 1.74 (m, 1H), 1.73 – 1.52 (m, 4H), 1.51 – 1.37 (m, 2H), 1.25 – 1.07 (m, 2H).

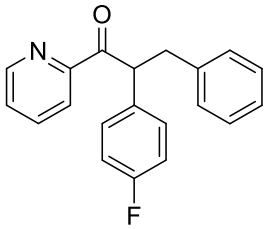
^{13}C NMR (126 MHz, $CDCl_3$) δ 201.66, 161.84 (d, *J* = 244.9 Hz), 153.05, 148.98, 136.93, 135.38 (d, *J* = 3.2 Hz), 130.56 (d, *J* = 7.9 Hz), 127.08, 122.81, 115.33 (d, *J* = 21.2 Hz), 48.94, 39.45, 38.22, 33.13, 32.61, 25.23, 25.21.

^{19}F NMR (471 MHz, $CDCl_3$) δ -117.33.

HRMS (ESI): Calcd for $C_{19}H_{20}FNO$, $[M+H]^+$: 298.1602, found: 298.1604.

IR (neat): v (cm^{-1}) 2948, 2865, 1696, 1508, 1224, 995, 635.

Rf: 0.6 (20% EtOAc in cyclohexane)



2-(4-fluorophenyl)-3-phenyl-1-(pyridin-2-yl)propan-1-one (3u)

Prepared from 3-phenyl-1-(pyridin-2-yl)propan-1-one (106 mg) and 1-fluoro-4-iodobenzene (87 µL, 1.5 eq) to yield 88 mg (58%) of titular compound as a dark solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (d, *J* = 4.8 Hz, 1H), 7.96 (d, *J* = 7.9 Hz, 1H), 7.69 (t, *J* = 7.7 Hz, 1H), 7.36 – 7.29 (m, 3H), 7.22 – 7.05 (m, 5H), 6.90 (t, *J* = 8.6 Hz, 2H), 5.72 (t, *J* = 7.6 Hz, 1H), 3.52 (dd, *J* = 13.9, 7.7 Hz, 1H), 3.11 (dd, *J* = 13.8, 7.6 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.59, 161.90 (d, *J* = 245.4 Hz), 152.74, 148.93, 139.71, 136.88, 134.52 (d, *J* = 3.2 Hz), 130.64 (d, *J* = 8.0 Hz), 129.21, 128.28, 127.12, 126.17, 122.81, 51.72, 39.14.

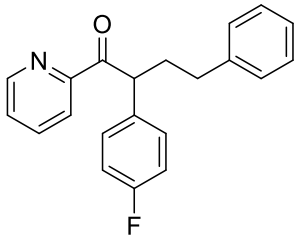
^{19}F NMR (471 MHz, $CDCl_3$) δ -116.87.

HRMS (ESI): Calcd for $C_{20}H_{16}FNO$, $[M+H]^+$: 306.1289, found: 306.1289.

Mp: 90°C

IR (neat): v (cm^{-1}) 3053, 2918, 1689, 1503, 1353, 1222, 1158, 953, 809, 696.

Rf: 0.5 (20% EtOAc in cyclohexane)



2-(4-fluorophenyl)-4-phenyl-1-(pyridin-2-yl)butan-1-one (3v)

Prepared from 4-phenyl-1-(pyridin-2-yl)butan-1-one (113 mg) and 1-fluoro-4-iodobenzene (87 µL, 1.5 eq) to yield 120 mg (75%) of titular compound as an orange oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.99 (ddd, *J* = 7.9, 1.1, 1.1 Hz, 1H), 7.77 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.41 (ddd, *J* = 7.5, 4.8, 1.3 Hz, 1H), 7.39 – 7.35 (m, 2H), 7.29 – 7.20 (m, 2H), 7.22 – 7.13 (m, 3H), 7.04 – 6.91 (m, 2H), 5.42 (t, *J* = 7.4 Hz, 1H), 2.65 – 2.44 (m, 3H), 2.22 – 2.11 (m, 1H).

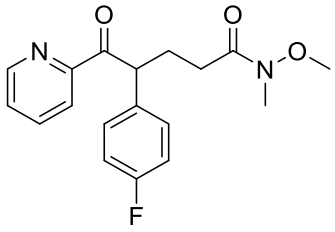
^{13}C NMR (126 MHz, $CDCl_3$) δ 201.17, 161.96 (d, *J* = 245.1 Hz), 152.98, 148.97, 141.92, 137.00, 136.48, 134.85 (d, *J* = 3.1 Hz), 130.67, 128.52 (d, *J* = 14.8 Hz), 127.18, 126.01, 122.88, 115.50 (d, *J* = 21.2 Hz), 49.62, 34.80, 33.95.

^{19}F NMR (471 MHz, $CDCl_3$) δ -117.02.

HRMS (ESI): Calcd for $C_{21}H_{18}FNO$, $[M+H]^+$: 320.1445, found: 320.1445.

IR (neat): v (cm^{-1}) 3058, 2928, 1695, 1506, 1339, 1224, 995, 824, 749, 700.

Rf: 0.5 (20% EtOAc in cyclohexane)



4-(4-fluorophenyl)-N-methoxy-N-methyl-5-oxo-5-(pyridin-2-yl)pentanamide (3w)

Prepared from N-methoxy-N-methyl-5-oxo-5-(pyridin-2-yl)pentanamide (118 mg) and 1-fluoro-4-iodobenzene (87 µL, 1.5 eq) to yield 120 mg (73%) of titular compound as an dark brown liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 7.99 (ddd, *J* = 7.8, 1.1, 1.1 Hz, 1H), 7.76 (ddd, *J* = 7.7, 1.7 Hz, 1H), 7.44 – 7.33 (m, 3H), 6.99 – 6.85 (m, 2H), 5.47 – 5.40 (m, 1H), 3.55 (s, 3H), 3.14 (s, 3H), 2.50 – 2.33 (m, 3H), 2.27 – 2.16 (m, 1H).

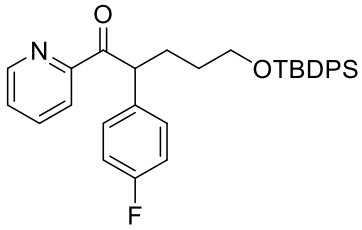
^{13}C NMR (126 MHz, $CDCl_3$) δ 200.87, 174.07, 161.98 (d, *J* = 245.3 Hz), 152.91, 149.00, 136.96, 134.56 (d, *J* = 3.2 Hz), 130.71 (d, *J* = 8.0 Hz), 127.15, 122.85, 115.50 (d, *J* = 21.3 Hz), 61.25, 49.39, 32.33, 29.86, 27.72.

^{19}F NMR (471 MHz, $CDCl_3$) δ -116.89 (s).

HRMS (ESI): Calcd for $C_{18}H_{19}FN_2O_3$, $[M+Na]^+$: 353.1272, found: 353.1272.

IR (neat): v (cm^{-1}) 2938, 1705, 1659, 1507, 1224, 995.

Rf: 0.11 (50% EtOAc in cyclohexane)



5-((tert-butyldiphenylsilyl)oxy)-2-(4-fluorophenyl)-1-(pyridin-2-yl)pentan-1-one (3x)

Prepared from 6-((tert-butyldiphenylsilyl)oxy)-1-(pyridin-2-yl)hexan-1-one (216 mg) and 1-fluoro-4-iodobenzene (87 µL, 1.5 eq) to yield 162 mg (62%) of titular compound as an yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (ddd, *J* = 4.7, 1.8, 0.9 Hz, 1H), 8.00 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.79 (td, *J* = 7.7, 1.7 Hz, 1H), 7.62 (dt, *J* = 7.9, 1.3 Hz, 4H), 7.48 – 7.30 (m, 10H), 6.97 – 6.88 (m, 2H), 5.38 (t, *J* = 7.8 Hz, 1H), 3.61 (t, *J* = 6.4 Hz, 2H), 2.17 – 2.06 (m, 1H), 1.91 – 1.80 (m, 1H), 1.67 – 1.50 (m, 2H), 1.38 – 1.28 (m, 2H), 1.00 (s, 9H).

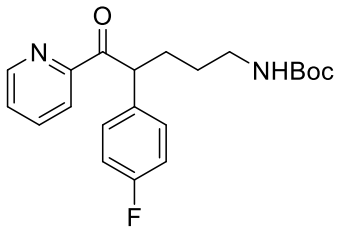
^{13}C NMR (126 MHz, $CDCl_3$) δ 201.34, 165.08, 161.91 (d, *J* = 244.8 Hz), 152.89, 148.79, 137.25, 135.70, 135.01 (d, *J* = 3.3 Hz), 130.57 (d, *J* = 7.9 Hz), 129.62, 127.70, 127.19, 122.95, 115.41 (d, *J* = 21.2 Hz), 63.79, 49.89, 32.88, 26.97, 23.96, 19.33.

^{19}F NMR (376 MHz, $CDCl_3$) δ -117.32.

HRMS (ESI): Calcd for $C_{33}H_{36}FNO_2Si$, $[M+H]^+$: 526.2572, found: 526.2582.

IR (neat): v (cm^{-1}) 2932, 2859, 1696, 1507, 1428, 1225, 1109, 822, 705.

Rf: 0.66 (20% EtOAc in cyclohexane)



tert-butyl (3-(4-fluorophenyl)-4-oxo-4-(pyridin-2-yl)butyl)carbamate (3y)

Prepared from tert-butyl (5-oxo-5-(pyridin-2-yl)pentyl)carbamate (139 mg) and 1-fluoro-4-iodobenzene (87 µL, 1.5 eq) to yield 67 mg (36%) of titular compound as an orange oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.98 (ddd, *J* = 7.8, 1.1, 1.1 Hz, 1H), 7.76 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.40 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.41 – 7.30 (m, 2H), 6.97 – 6.89 (m, 2H), 5.36 (t, *J* = 7.6 Hz, 1H), 4.71 (bs, 1H), 3.27 – 3.01 (m, 1H), 2.17 – 2.11 (m, 1H), 1.92 – 1.81 (m, 1H), 1.47 – 1.36 (m, 11H).

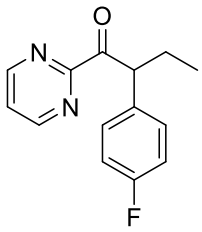
^{13}C NMR (126 MHz, $CDCl_3$) δ 201.12, 161.94 (d, *J* = 245.3 Hz), 156.04, 152.81, 148.99, 137.05, 134.64 (d, *J* = 3.2 Hz), 130.54 (d, *J* = 8.0 Hz), 127.23, 122.85, 115.47 (d, *J* = 21.3 Hz), 79.14, 49.40, 40.28, 30.20, 28.53, 27.93, 27.02.

^{19}F NMR (471 MHz, $CDCl_3$) δ -116.93.

HRMS (ESI): Calcd for $C_{21}H_{25}FN_2O_3$, $[M+Na]^+$: 395.1741, found: 395.1741.

IR (neat): v (cm^{-1}) 3364, 2975, 2932, 1692, 1506, 1224, 1162, 995, 817, 732.

Rf: 0.24 (20% EtOAc in cyclohexane)



2-(4-fluorophenyl)-1-(pyrimidin-2-yl)butan-1-one (3z)

Prepared from 1-(pyrimidin-2-yl)butan-1-one (75 mg) and 1-fluoro-4-iodobenzene (73 µL) to yield 61 mg (50%) of titular compound as an orange solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (d, *J* = 4.9 Hz, 2H), 7.37 (t, *J* = 4.8 Hz, 1H), 7.34 – 7.28 (m, 1H), 6.98 – 6.89 (m, 1H), 5.08 (d, *J* = 7.5 Hz, 1H), 2.27 – 2.15 (m, 1H), 1.94 – 1.82 (m, 1H), 0.91 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.02, 162.03 (d, *J* = 245.4 Hz), 160.23, 157.68, 134.15 (d, *J* = 3.1 Hz), 130.71 (d, *J* = 8.0 Hz), 122.84, 115.58 (d, *J* = 21.3 Hz), 53.68, 26.15, 12.20.

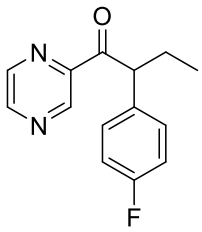
^{19}F NMR (471 MHz, $CDCl_3$) δ -116.77 (s).

HRMS (ESI): Calcd for $C_{14}H_{13}FN_2O$, $[M+H]^+$: 245.1085 , found: 245.1085.

Mp: 72°C

IR (neat): v (cm^{-1}) 3046, 2972, 2922, 2877, 1713, 1560, 1505, 1406, 1217, 1009, 835, 775,

Rf: 0.14 (20% EtOAc in cyclohexane)



2-(4-fluorophenyl)-1-(pyrazin-2-yl)butan-1-one (3aa)

Prepared from 1-(pyrazin-2-yl)butan-1-one (75 mg) and 1-fluoro-4-iodobenzene (73 µL) to yield 86 mg (70%) of titular compound as a light orange solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.19 (d, *J* = 1.5 Hz, 1H), 8.69 (d, *J* = 2.4 Hz, 1H), 8.61 (dd, *J* = 2.5, 1.5 Hz, 1H), 7.36 – 7.28 (m, 2H), 7.00 – 6.91 (m, 2H), 5.10 (t, *J* = 7.6 Hz, 1H), 2.23 – 2.11 (m, 1H), 1.94 – 1.82 (m, 1H), 0.90 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.81, 162.07 (d, *J* = 245.7 Hz), 147.74, 147.39, 144.65, 143.51, 134.23 (d, *J* = 3.1 Hz*)*, 130.56 (d, *J* = 8.1 Hz), 115.64 (d, *J* = 21.3 Hz), 52.30, 26.05, 12.23.

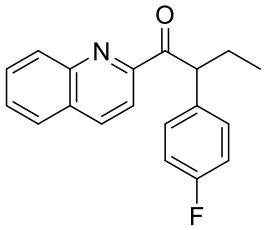
^{19}F NMR (471 MHz, $CDCl_3$) δ -116.63 (s).

HRMS (ESI): Calcd for $C_{14}H_{13}FN_2O$, $[M+H]^+$: 245.1085 , found: 245.1082.

Mp: 96°C

IR (neat): v (cm^{-1}) 2972, 1690, 1503, 1225, 1007, 818.

Rf: 0.32 (20% EtOAc in cyclohexane)



2-(4-fluorophenyl)-1-(quinolin-2-yl)butan-1-one (3ab)

Prepared from 1-(quinolin-2-yl)butan-1-one (75 mg) and 1-fluoro-4-iodobenzene (116 µL, 2 eq) to yield 115 mg (79%) of titular compound as a brown solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 – 8.22 (m, 1H), 8.22 – 8.20 (m, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.86 – 7.81 (m, 1H), 7.78 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.63 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.48 – 7.39 (m, 2H), 6.99 – 6.88 (m, 2H), 5.55 (t, *J* = 7.6 Hz, 1H), 2.30 – 2.18 (m, 1H), 2.01 – 1.89 (m, 1H), 0.95 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.69, 161.84 (d, *J* = 244.8 Hz), 152.52, 147.15, 136.99, 135.29 (d, *J* = 3.1 Hz), 130.61 (d, *J* = 7.9 Hz), 130.03, 129.62, 128.68, 127.70, 118.90, 115.35 (d, *J* = 21.2 Hz), 51.52, 26.14, 12.32.

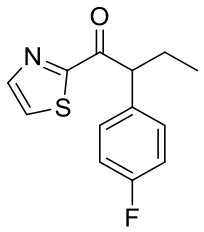
^{19}F NMR (471 MHz, $CDCl_3$) δ -117.38 (s).

HRMS (ESI): Calcd for $C_{19}H_{16}FNO$, $[M+H]^+$: 294.1289 , found: 294.1289.

Mp: 73°C

IR (neat): v (cm^{-1}) 2963, 1691, 1599, 1504, 1331, 1220, 993, 809.

Rf: 0.69 (20% EtOAc in cyclohexane)



2-(4-fluorophenyl)-1-(thiazol-2-yl)butan-1-one (3ac)

Prepared from 1-(thiazol-2-yl)butan-1-one (78 mg) and 1-fluoro-4-iodobenzene (116 µL, 2 eq) to yield 52 mg (42%) of titular compound as an brown oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 3.0 Hz, 1H), 7.63 (d, *J* = 3.0 Hz, 1H), 7.43 – 7.34 (m, 2H), 7.02 – 6.93 (m, 2H), 4.94 (t, *J* = 7.6 Hz, 1H), 2.26 – 2.14 (m, 1H), 1.96 – 1.84 (m, 1H), 0.91 (t, *J* = 7.4 Hz, 3H).

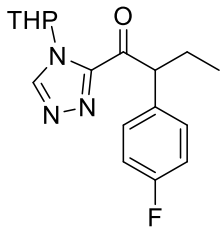
^{13}C NMR (126 MHz, $CDCl_3$) δ 193.68, 167.08, 163.11, 161.16, 144.86, 134.17 (d, *J* = 3.2 Hz), 130.45 (d, *J* = 7.9 Hz), 126.76, 115.58 (d, *J* = 21.3 Hz), 53.83, 26.36, 12.21.

^{19}F NMR (471 MHz, $CDCl_3$) δ -116.62 (s).

HRMS (ESI): Calcd for $C_{13}H_{12}FNOS$, $[M+H]^+$: 250.0696 , found: 250.0695.

IR (neat): v (cm-^{1}) 2965, 1676, 1507, 1383, 1220, 1088, 959, 815, 757.

Rf: 0.54 (20% EtOAc in cyclohexane)



2-(4-fluorophenyl)-1-(4-(tetrahydro-2H-pyran-2-yl)-4H-1,2,4-triazol-3-yl)butan-1-one (3ad)

Prepared from 1-(4-(tetrahydro-2H-pyran-2-yl)-4H-1,2,4-triazol-3-yl)butan-1-one (112 mg) and 1-fluoro-4-iodobenzene (87 µL, 1.5 eq) to yield 102 mg (76%) of titular compound as an light yellow oil. The compound was recovered as an inseparable 1/1 mixture of diastereomers.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 3.5 Hz, 1H), 7.37 – 7.27 (m, 1H), 6.98 – 6.87 (m, 2H), 5.47 (ddd, *J* = 8.9, 7.2, 2.9 Hz, 1H), 4.73 (td, *J* = 7.6, 3.7 Hz, 1H), 4.06 – 3.93 (m, 1H), 3.74 – 3.62 (m, 1H), 2.15 (dddd, *J* = 18.1, 16.5, 10.5, 3.1 Hz, 2H), 2.07 – 1.91 (m, 2H), 1.90 – 1.77 (m, 1H), 1.74 – 1.58 (m, 3H), 0.86 (td, *J* = 7.3, 1.1 Hz, 3H).

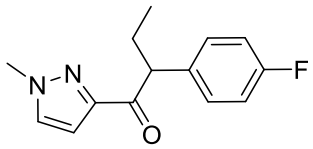
^{13}C NMR (126 MHz, $CDCl_3$) δ 193.24, 161.98 (d, *J* = 245.2 Hz), 159.67 (d, *J* = 6.5 Hz), 143.37 (d, *J* = 29.2 Hz), 134.33 (dd, *J* = 3.2, 1.9 Hz), 130.41 (d, *J* = 7.9 Hz), 115.39 (dd, *J* = 21.3, 1.3 Hz), 86.72 (d, *J* = 2.4 Hz), 67.61 (d, *J* = 33.8 Hz), 54.99 (d, *J* = 5.7 Hz), 30.56 (d, *J* = 16.5 Hz), 25.98 (d, *J* = 2.5 Hz), 24.69, 21.43 (d, *J* = 24.1 Hz), 12.10 (d, *J* = 2.7 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) δ -116.93 (d, *J* = 5.5 Hz).

HRMS (ESI): Calcd for $C_{17}H_{20}FN_3O_2$, $[M+Na]^+$: 340.1432, found: 340.1429.

IR (neat): v (cm^{-1}) 2964, 2872, 1710, 1508, 1223, 1043, 913, 822, 648.

Rf: 0.22 (50% EtOAc in cyclohexane)



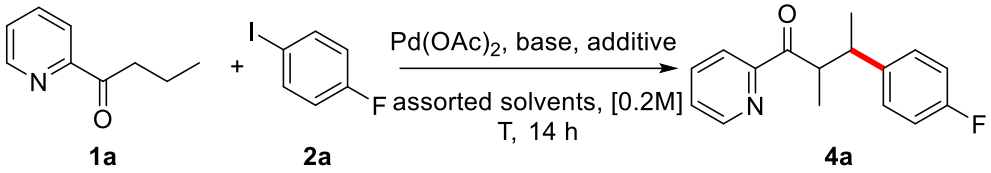
2-(4-fluorophenyl)-1-(1-methyl-1H-pyrazol-3-yl)butan-1-one (3ae)

Prepared from 1-(1-methyl-1H-pyrazol-3-yl)butan-1-one (76 mg) and 1-fluoro-4-iodobenzene (116 µL, 2 eq) to yield 53 mg (43%) of titular compound as an orange oil.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 2H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.00 – 6.90 (m, 2H), 6.73 (d, *J* = 2.3 Hz, 1H), 4.74 (t, *J* = 7.6 Hz, 1H), 3.93 (s, 3H), δ 2.22 – 2.10 (m, 1H), 1.89 – 1.77 (m, 1H)., 0.88 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 195.92, 161.87 (d, *J* = 244.6 Hz), 150.88, 135.53 (d, *J* = 3.1 Hz), 131.89, 130.23 (d, *J* = 7.9 Hz), 115.24 (d, *J* = 21.2 Hz), 107.65, 53.98, 39.64, 26.42, 12.25.
^{19}F NMR (471 MHz, $CDCl_3$) δ -117.53 (s)
HRMS (ESI): Calcd for $C_{14}H_{15}FN_2O$, $[M+Na]^+$: 269.1061, found: 269.1064.
IR (neat): v (cm^{-1}) 2964, 1680, 1508, 1466, 1361, 1212, 1061, 819, 792.
Rf: 0.24 (20% EtOAc in cyclohexane)

Products of β-functionalization

❖ Optimization studies for β-functionalization

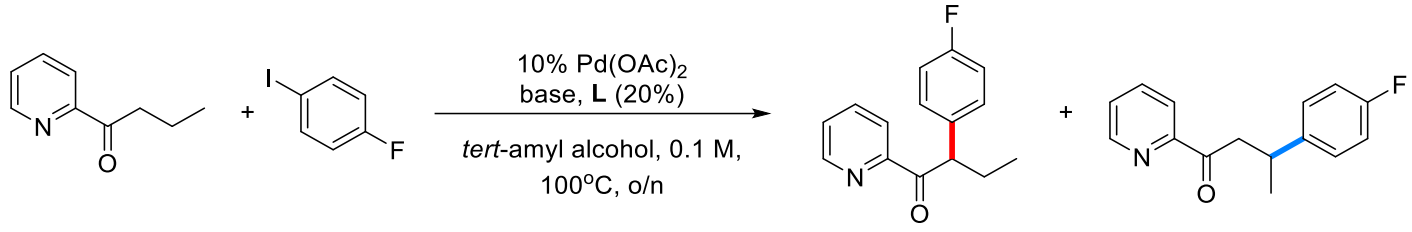
Table 4.1. Screening for β-functionalization with silver[a]



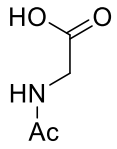
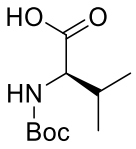
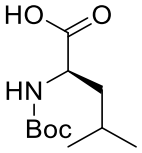
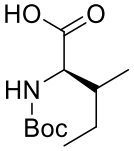
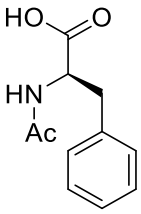
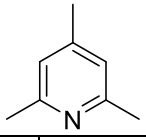
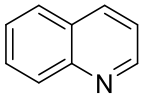
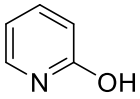
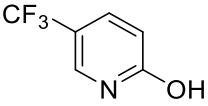
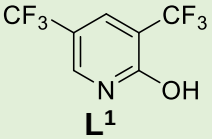
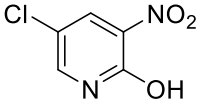
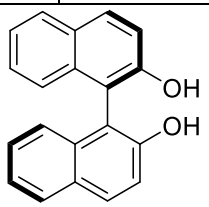
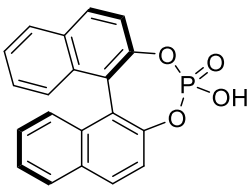
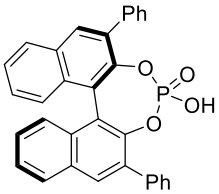
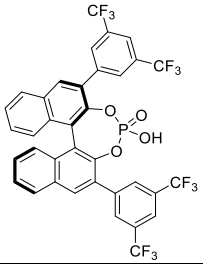
Base (eq)	Additive (eq)	Solvent, C	T, °C	[Pd]	Yield **4a**, %
AgOAc (1)	None	Toluene	100	$Pd(OAc)_2$	6
AgOAc (1)	TFA (1.5)				18
Ag_2CO_3 (1)	None				0
Ag_2CO_3 (1)					4
AgOAc (2)					5
AgOAc (3)					5
AgTFA (1.5)	TFA (1.5)	HFIP			7
AgTFA (1.5)	TFA (1.5)	Diox			15
AgTFA (1.5)	TFA (1.5)	DCE			11
AgTFA (1.5)	TFA (1.5)	m-xylene			19
AgTFA (1.5)	TFA (1.5)	mesitylene			17
AgTFA (1.5)	TFA (1.5)	TFT			17
AgTFA (1.5)	TFA (1.5)	toluene		$Pd(TFA)_2$	15
AgTFA (3)	TFA (3)	m-xylene		$Pd(OAc)_2$	23
Ag_3PO_4 (1)	TFA (3)				19
AgOTf (3)	TFA (3)	Toluene, 0.1M			6
AgTFA (3)	TFA (3)				26
AgTFA (3)	TFA (3), LiOTf (3)	Toluene			12
AgTFA (3)	TFA (3), LiCl (3)				19
AgTFA (3)	TFA (3)	Toluene, 0.4M			16
AgTFA (3)	TFA (3), NaCl (3)	Toluene			18
AgTFA (3)	TFA (3), KCl (3)				6
AgTFA (3)	TFA (3)	Toluene	140		16
AgOAc (3)	none				6
AgTFA (3)	TFA (3)	m-xylene, 0.1M	100		27
AgTFA (3)	TFA (1.5)	Toluene	90		15

[a]Performed on 0.2 mmol scale, using 0.2 mmol (1 eq) of **1a** and 0.4 mmol (2 eq) of **2a** with appropriate base, additives and solvent. Yield was determined by ^{1}H NMR with 1,1,2-trichloroethylene as an external standard.

Table 4.2. Ligand screening for β-functionalization

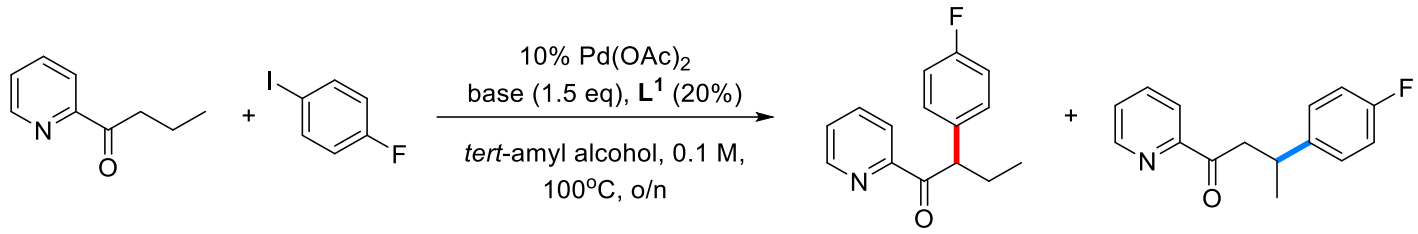


1a **2a** **3a** **4a**

									
0/21[b]	8/11[c]	0/21[b]	8/10[c]	0/19[b]	10/12[c]	0/15[b]	10/13[c]	0/24[b]	9/15[c]
				(BnO)$_2$PO$_2$H		PivOH			
0/23[b]	8/8[c]	0/22[b]	11/8[c]	-		8/15[c]		0/21[b]	5/13[c]
				 **L[1]**					
0/27[b]	0/19[c]	0/31[b]	0/21[c]	0/40[b]	0/39[c]	0/16[b]	6/20[c]	0/13[b]	9/15[c]
						IPr		IMes	
-	3/11[c]	-	2/10[c]	-	10/11[c]	-	3/12[c]	-	3/4[c]
IAd				–					
-		8/4[c]		0/21[b]		10/8[c]			

[a] Performed on 0.1 mmol scale, using 0.1 mmol (1 eq) of **1a** and 0.2 mmol (2 eq) of **2a** with appropriate base, additives and solvent. Yield was determined by ^{1}H NMR with 1,1,2-trichloroethylene as an external standard. Yield listed as % yield of **3a**/**4a**. [b] 1 eq of KOAc used as base. [c] 1.5 eq of K_2CO_3 used as a base.

Table 4.3. Oxidant-free base screening

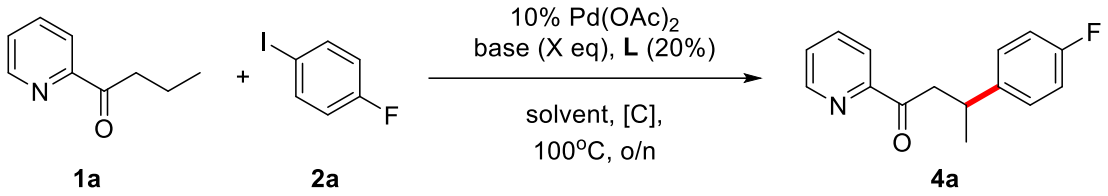


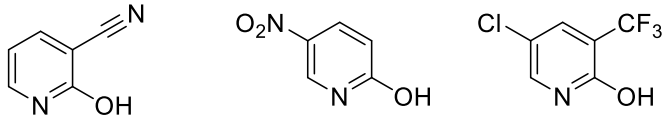
1a **2a** **3a** **4a**

Entry #	Base	Yield **3a**/**4a**, %
1	NaOAc	0/10
2	Na_2CO_3	0/17
3	KOAc	0/40
4	K_2CO_3	0/39
5	CsOAc	0/30
6	Cs_2CO_3	10/42
7	AgOAc	0/9
8	Ag_2CO_3	0/5
9	Na_2HPO_4 x $2H_2O$	0/6
10	$KHCO_3$	0/15
11	K_2HPO_4	0/6

[a] Performed on 0.1 mmol scale, using 0.1 mmol (1 eq) of **1a** and 0.2 mmol (2 eq) of **2a** with appropriate base, additives and solvent. Yield was determined by ^{1}H NMR with 1,1,2-trichloroethylene as an external standard.

Table 4.4. Additional ligand/base screening[a]



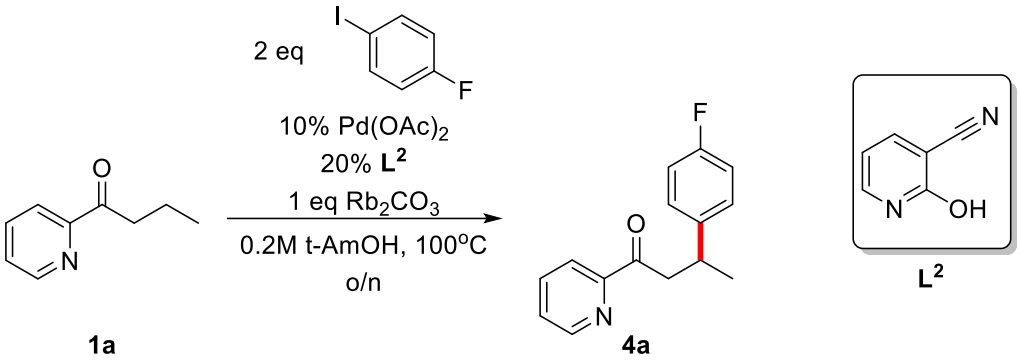


L² L³ L⁴

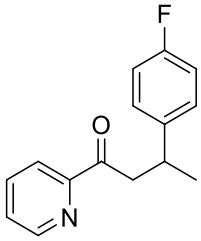
Entry #	L	Base	X, eq	Solvent	C, M	Yield **4a**, %
1	**L¹**	K_2CO_3	1.5	*t*-AmOH	0.2	49
2	**L³**					33
3						39
4	**L⁴**			MeOH		15
5				EtOH		27
6				TFE		28
7				MTBE		40
8				CPME		31
9				DBE		17
10				DME		18
11				THF		34
12				2-MeTHF		35
13				toluene		29
14				TFT		19
15				DCE		31
16				mesitylene		13
17				m-xylene		25
18				o-xylene		26
19				dioxane		18
20		Rb_2CO_3		t-AmOH		40
21		RbOAc				39
22		CsOPiv				38
23		KOPiv				42
24		Cs_2CO_3				25
25		KOAc				37
26	**L²**	Rb_2CO_3				28
27			2			20
28			1.25			32
29			1			46
30[b]						50 (50)

[a] Performed on 0.2 mmol scale, using 0.2 mmol (1 eq) of **1a** and 0.4 mmol (2 eq) of **2a** with appropriate base, additives and solvent. Yield was determined by ^{1}H NMR with 1,1,2-trichloroethylene as an external standard. Isolated yield stated in parethesis. [b] Reaction performed on 0.5 mmol scale.

❖ **Representative procedure C: preparation of 3-(4-fluorophenyl)-1-(pyridin-2-yl)butan-1-one 4a**



To an oven-dried threaded culture tube (10 mL) equipped with PTFE-coated magnetic stirbar rubidium carbonate (116 mg, 0.5 mmol, 1 eq) and 3-cyanopyridin-2-one (12 mg, 0.1 mmol, 20% mol) were charged. Tube was then introduced to the glovebox, where palladium acetate (11.2 mg, 0.05 mmol) was charged. Tube was then closed with a septum and removed from the glovebox, where 1-(pyridin-2-yl)butan-1-one (74 µL, 0.5 mmol), 1-fluoro-4-iodobenzene (116 µL, 1 mmol, 2 eq) and tert-amyl alcohol (2.5 mL) are added via syringe. Septum was then replaced in a flow of argon with a screwcap and reaction mixture was then stirred in a heating block at 100°C for 14 hours. Reaction mixture was then cooled to room temperature, diluted with DCM (2 mL) and filtered over a pad of Celite. Solids were then washed with DCM (2x2 mL) and combined filtrate evaporated at reduced pressure (60°C, 5 mbar). Residue is then dryloaded onto Celite and subjected to column chromatography (Claricep 20g cartridge, 0-15% EtOAc in cyclohexane) to yield 60 mg (50%) of 3-(4-fluorophenyl)-1-(pyridin-2-yl)butan-1-one as a yellow liquid.



<u>3-(4-fluorophenyl)-1-(pyridin-2-yl)butan-1-one (4a)</u>

Prepared as stated above. Compound was also prepared from 1-(pyridin-2-yl)butan-1-one (74 µL) and 1-fluoro-4-bromobenzene (110 µL, 2 eq) to yield titular compound in 25% yield. Compound consistency and analytical data match in both cases.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.91 (ddd, *J* = 7.8, 1.1, 1.1 Hz, 1H), 7.73 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.38 (ddd, *J* = 7.6, 4.8, 1.3 Hz, 1H), 7.21 – 7.13 (m, 2H), 6.93 – 6.82 (m, 2H), 3.54 – 3.33 (m, 3H), 1.25 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.62, 161.41 (d, *J* = 243.5 Hz), 153.57, 149.00, 142.48 (d, *J* = 3.2 Hz), 137.03, 128.49 (d, *J* = 7.7 Hz), 127.24, 121.97, 115.20 (d, *J* = 21.1 Hz), 45.98, 34.84, 22.58.

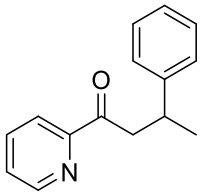
^{19}F NMR (471 MHz, $CDCl_3$) δ -118.43 (s).

HRMS (ESI): Calcd for $C_{15}H_{14}FNO$, $[M+Na]^+$: 266.0952, found: 266.0953.

IR (neat): v (cm^{-1}) 2964, 1696, 1510, 1360, 1221, 995, 834, 771.

Rf: 0.5 (20% EtOAc in cyclohexane)

According to this procedure, following compounds were synthesized:



3-phenyl-1-(pyridin-2-yl)butan-1-one (4b)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 µL) and iodobenzene (111 µL, 2 eq) to yield 46 mg (41%) of titular compound as a dark yellow liquid.

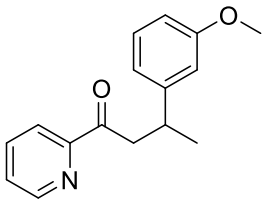
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 7.91 (ddd, *J* = 7.8, 1.1, 1.1 Hz, 1H), 7.71 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.35 (ddd, *J* = 7.5, 4.7, 1.3 Hz, 1H), 7.24 – 7.16 (m, 4H), 7.11 – 7.06 (m, 1H), 3.56 – 3.37 (m, 3H), 1.26 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.77, 153.67, 148.98, 146.88, 136.84, 128.51, 127.15, 127.11, 126.21, 121.94, 45.89, 35.46, 22.40.

HRMS (ESI): Calcd for $C_{15}H_{15}NO$, $[M+H]^+$: 226.1226, found: 226.1225.

IR (neat): v (cm^{-1}) 2961, 1694, 1582, 1493, 1394, 1352, 1297, 1221, 1146, 995, 907, 762.

Rf: 0.46 (20% EtOAc in cyclohexane)



3-(3-methoxyphenyl)-1-(pyridin-2-yl)butan-1-one (4c)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 µL) and 3-iodoanisole (119 µL, 2 eq) to yield 42 mg (33%) of titular compound as a yellow oil.

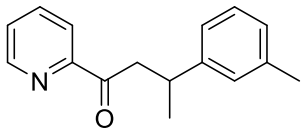
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 7.99 (ddd, *J* = 7.8, 1.1, 1.1 Hz, 1H), 7.80 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.44 (ddd, *J* = 7.5, 4.7, 1.2 Hz, 1H), 7.20 (t, *J* = 7.9 Hz, 1H), 6.92 – 6.87 (m, 1H), 6.87 – 6.82 (m, 1H), 6.71 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 3.78 (s, 3H), 3.65 – 3.42 (m, 3H), 1.33 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.74, 159.75, 153.66, 148.98, 148.62, 136.98, 129.47, 127.16, 121.96, 119.52, 113.01, 111.41, 55.25, 45.80, 35.53, 22.35.

HRMS (ESI): Calcd for $C_{16}H_{17}NO_2$, $[M+Na]^+$: 278.1151, found: 278.1151.

IR (neat): v (cm^{-1}) 2961, 1697, 1600, 1260, 1045, 995, 773, 701.

Rf: 0.41 (20% EtOAc in cyclohexane)



1-(pyridin-2-yl)-3-(m-tolyl)butan-1-one (4d)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 µL) and 3-iodotoluene (128 µL, 2 eq) to yield 46 mg (38%) of titular compound as a dark yellow liquid.

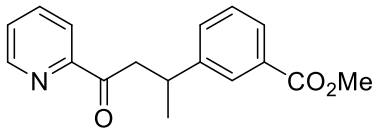
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (ddd, *J* = 4.7, 1.8, 0.9 Hz, 1H), 8.00 (ddd, *J* = 7.8, 1.1, 1.1 Hz, 1H), 7.81 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.45 (ddd, *J* = 7.5, 4.8, 1.3 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.13 – 7.06 (m, 2H), 7.03 – 6.95 (m, 1H), 3.62 – 3.43 (m, 3H), 2.32 (s, 3H), 1.32 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.76, 153.62, 148.90, 146.86, 138.03, 137.12, 128.43, 127.94, 127.19, 127.01, 124.11, 122.05, 45.93, 35.42, 22.46, 21.62.

HRMS (ESI): Calcd for $C_{16}H_{17}NO$, $[M+H]^+$: 240.1383, found: 240.1383.

IR (neat): v (cm^{-1}) 2963, 1697, 1583, 1358, 1308, 1218, 995, 772, 706.

Rf: 0.5 (20% EtOAc in cyclohexane)



methyl 3-(4-oxo-4-(pyridin-2-yl)butan-2-yl)benzoate (4e)

Prepared from 1-(pyridin-2-yl)butan-1-one (74 µL) and methyl 3-iodobenzoate (262 mg, 2 eq) to yield 37 mg (26%) of titular compound as an yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.99 – 7.94 (m, 2H), 7.84 (ddd, *J* = 7.7, 1.7, 1.2 Hz, 1H), 7.79 (ddd, *J* = 7.6, 7.6, 1.7 Hz, 1H), 7.52 – 7.46 (m, 1H), 7.43 (ddd, *J* = 7.6, 4.8, 1.3 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 1H), 3.89 (s, 3H), 3.65 – 3.45 (m, 3H), 1.35 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.42, 167.33, 153.49, 148.99, 147.22, 136.99, 131.99, 130.36, 128.55, 128.20, 127.56, 127.23, 121.92, 52.13, 45.69, 35.34, 22.31.

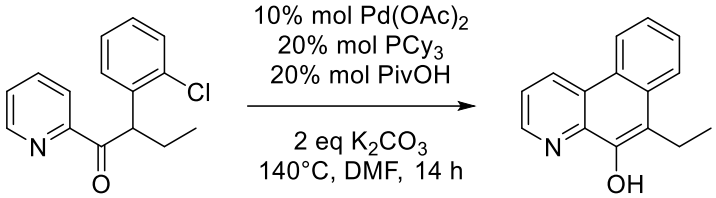
HRMS (ESI): Calcd for $C_{17}H_{17}NO_3$, $[M+Na]^+$: 306.1101, found: 306.1100.

IR (neat): v (cm^{-1}) 2957, 1720, 1584, 1435, 1286, 1204, 995, 755.

Rf: 0.32 (20% EtOAc in cyclohexane)

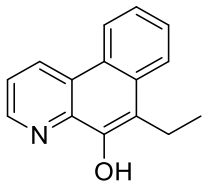
Products of post-functionalization

- Synthesis of 6-ethylbenzo[f]quinolin-5-ol 5a



3n **5a**

To an oven-dried microwave vial (30 mL) equipped with PTFE-coated magnetic stirbar 2-(2-chlorophenyl)-1-(pyridin-2-yl)butan-1-one (130 mg, 0.5 mmol, synthesized *via* Representative procedure B) and potassium carbonate (138 mg, 1 mmol, 2 eq) were charged. Tube was then introduced to the glovebox, where palladium acetate (reagent grade, 98%; 11.2 mg, 0.05 mmol), tricyclohexylphosphine (28 mg, 0.1 mmol), and pivalic acid (10.2 mg, 0.1 mmol) were charged. Reaction was then sealed with a septum and reintroduced into a separate glovebox, where DMF (5 mL) was added. Septum was then replaced with a crimp cap and removed from the glovebox. Reaction mixture was then stirred in a heating block at 140 °C for 14 hours, after which it was cooled to room temperature, diluted with DCM (2 mL) and filtered over a pad of Celite. Solids were then washed with DCM (2x2 mL) and combined filtrate evaporated at reduced pressure (60°C, 5 mbar). Residue was then dryloaded onto Celite and subjected to column chromatography (Claricep 20g cartridge, 0-20% EtOAc in cyclohexane) to yield 90 mg (85%) of 6-ethylbenzo[f]quinolin-5-ol as a deep red oil.



<u>6-ethylbenzo[f]quinolin-5-ol (5a)</u>

Prepared as stated above.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H), 7.89 (ddd, *J* = 8.0, 1.1, 1.1 Hz, 1H), 7.76 (ddd, *J* = 8.0, 7.5, 1.8 Hz, 1H), 7.64 (ddd, *J* = 7.7, 1.3, 0.7 Hz, 1H), 7.52 (ddd, *J* = 8.2, 0.9, 0.9 Hz, 1H), 7.33 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.30 – 7.23 (m, 1H), 7.19 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 3.29 (q, *J* = 7.5 Hz, 2H), 1.35 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.23, 151.34, 149.74, 148.69, 136.46, 130.40, 125.24, 122.61, 122.28, 122.02, 120.97, 120.28, 111.44, 17.61, 14.34.

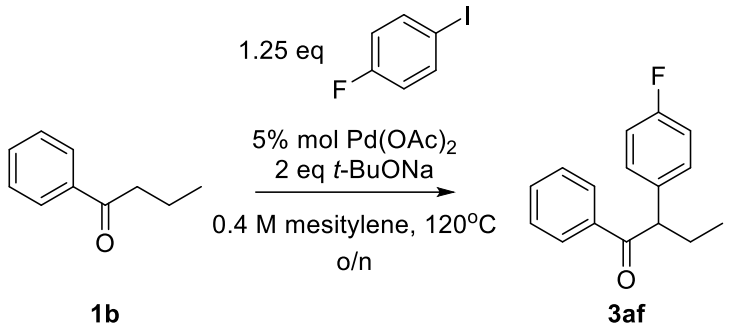
HRMS (ESI): Calcd for $C_{15}H_{13}NO$, $[M+H]^+$: 224.1070, found: 224.1074

IR (neat): v (cm^{-1}) 3059, 2928, 1604, 1455, 1347, 1249, 1128, 743.

Rf: 0.75 (20% EtOAc in cyclohexane)

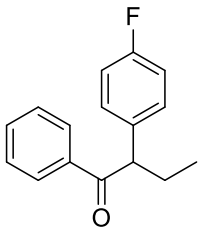
Products of control experiments

- **Synthesis of 2-(4-fluorophenyl)-1-phenylbutan-1-one 3af**



1b **3af**

To an oven-dried threaded culture tube (10 mL) equipped with PTFE-coated magnetic stirbar sodium *tert*-butoxide (96 mg, 1 mmol, 2 eq) was charged. Tube was then introduced to the glovebox, where palladium acetate (reagent grade, 98%; 5.6 mg, 0.025 mmol) was charged. Tube was then closed with a septum and removed from the glovebox, where 1-phenylbutan-1-one (75 µL, 0.5 mmol), 1-fluoro-4-iodobenzene (73 µL, 0.625 mmol, 1.25 eq) and mesitylene (1.25 mL) are added via syringe. Septum was then replaced in a flow of argon with a screwcap and reaction mixture was then stirred in a heating block at 120°C for 14 hours. Reaction mixture was then cooled to room temperature, diluted with DCM (2 mL) and filtered over a pad of Celite. Solids were then washed with DCM (2x2 mL) and combined filtrate evaporated at reduced pressure (60°C, 5 mbar). Residue is then dryloaded onto Celite and subjected to column chromatography (Claricep 20g cartridge, 0-20% EtOAc in cyclohexane) to yield 91 mg (75%) of 2-(4-fluorophenyl)-1-phenylbutan-1-one as an orange oil.



2-(4-fluorophenyl)-1-phenylbutan-1-one (3af)

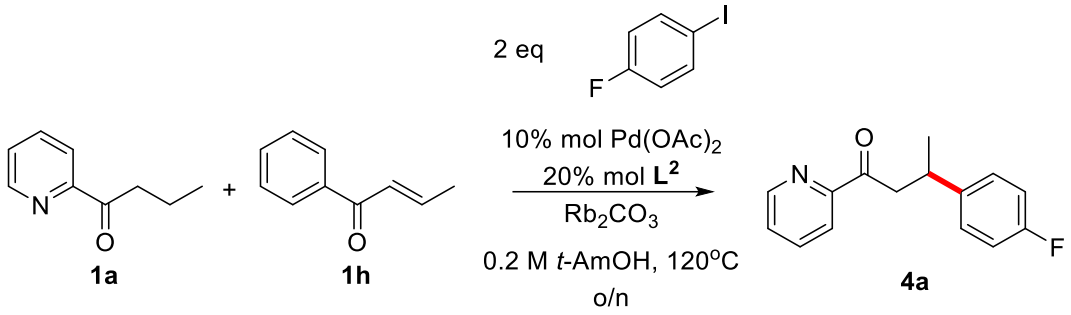
Prepared as stated above. This compound is described.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 – 7.92 (m, 2H), 7.53 – 7.46 (m, 1H), 7.44 – 7.35 (m, 2H), 7.31 – 7.25 (m, 2H), 7.04 – 6.92 (m, 2H), 4.44 (t, *J* = 7.3 Hz, 1H), 2.24 – 2.12 (m, 1H), 1.90 – 1.77 (m, 1H), 0.90 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.20, 162.01 (d, *J* = 245.5 Hz), 137.02, 135.42 (d, *J* = 3.2 Hz), 133.06, 129.90 (d, *J* = 7.9 Hz), 128.73, 128.70, 115.84 (d, *J* = 21.3 Hz), 54.62, 27.34, 12.35.

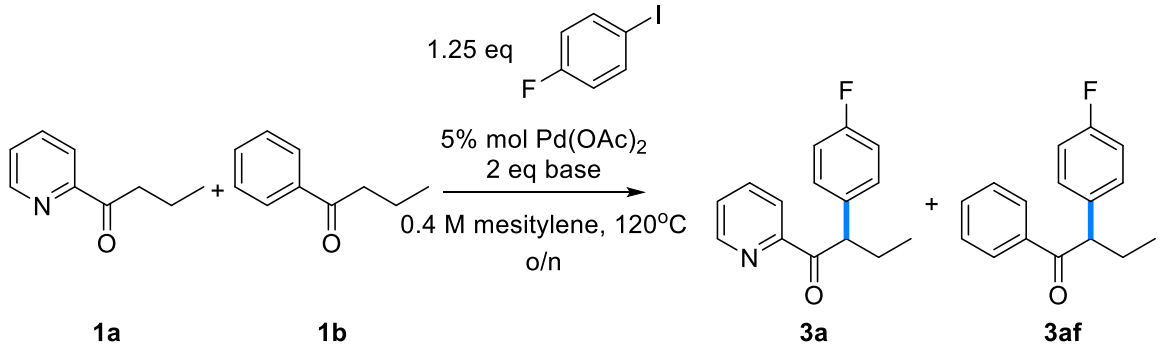
^{19}F NMR (471 MHz, $CDCl_3$) δ -116.79 (s).

❖ **Competitive experiment between ketones 1a and 1h**



To an oven-dried threaded culture tube (10 mL) equipped with PTFE-coated magnetic stirbar rubidium carbonate (116 mg, 0.5 mmol, 1 eq) and 3-cyanopyridin-2-one (12 mg, 0.1 mmol, 20% mol) were charged. Tube was then introduced to the glovebox, where palladium acetate (11.2 mg, 0.05 mmol) was charged. Tube was then closed with a septum and removed from the glovebox, where 1-(pyridin-2-yl)butan-1-one (74 µL, 0.5 mmol), 1-phenylbut-2-en-1-one (73 mg, 0.5 mmol), 1-fluoro-4-iodobenzene (116 µL, 1 mmol, 2 eq) and tert-amyl alcohol (2.5 mL) are added via syringe. Septum was then replaced in a flow of argon with a screwcap and reaction mixture was then stirred in a heating block at 100°C for 14 hours. Reaction mixture was then cooled to room temperature, diluted with DCM (2 mL) and filtered over a pad of Celite. Solids were then washed with DCM (2x2 mL) and combined filtrate evaporated at reduced pressure (60°C, 5 mbar). Residue was then diluted with $CDCl_3$ and 1,1,2-trichloroethylene is added, after which the mixture is analyzed via ^1H NMR.

❖ **Competitive experiment between ketones 1a and 1b**



To an oven-dried threaded culture tube (10 mL) equipped with PTFE-coated magnetic stirbar cesium carbonate (when used, 326 mg, 1 mmol, 2 eq) was charged. Tube was then introduced to the glovebox, where palladium acetate (reagent grade, 98%; 5.6 mg, 0.025 mmol) and sodium *tert*-butoxide (when used, 96 mg, 1 mmol, 2 eq) was charged. Tube was then closed with a septum and removed from the glovebox, where 1-(pyridin-2-yl)butan-1-one (74 µL, 0.5 mmol), butyrophenone (75 µL, 0.5 mmol, 1 eq) 1-fluoro-4-iodobenzene (73 µL, 0.625 mmol, 1.25 eq) and mesitylene (1.25 mL) are added via syringe. Septum was then replaced in a flow of argon with a screwcap and reaction mixture was then stirred in a heating block at 120°C for 14 hours. Reaction mixture was then cooled to room temperature, diluted with DCM (2 mL) and filtered over a pad of Celite. Solids were then washed with DCM (2x2 mL) and combined filtrate evaporated at reduced pressure (60°C, 5 mbar). Residue was then diluted with $CDCl_3$ and 1,1,2-trichloroethylene is added, after which the mixture is analyzed via ^1H NMR to determine the ratio of products **3a** and **3af**.

Part II: Methylene C(sp^3)−H Arylation Enables the Stereoselective Synthesis and Structure Revision of Indidene Natural Products

Numbering based on the article presented in section 3.

Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

Methylene C(sp^3)–H Arylation Enables the Stereoselective Synthesis and Structure Revision of Indidene Natural Products

*A. Kudashev, S. Vergura, M. Zuccarello, T. Bürgi, O. Baudoin**

Table of contents:

1. General methods

Techniques:

All reactions involving air-sensitive material were carried out in pre-dried glassware under an argon atmosphere by using Schlenk techniques employing double-line argon-vacuum lines and working in an argon-filled glove box. Analytical thin layer chromatography (TLC) was performed using pre-coated Merck silica gel 60 F254 plates (0.25 mm). Visualization of the developed chromatogram was performed by UV absorbance (254 nm or 365 nm) or TLC stains (vanillin, $KMnO_4$ or anise). Chromatography was performed on Biotage® Isolera™ instrument using prepackaged Claricep™ (Agela Technologies) or Sfär™ Silica Duo 60 µm (Biotage) normal phase cartridges of varying size with indicated solvent systems in order of increasing polarity.

All reaction glassware, as well as stirbars, were left in the oven set at 110°C overnight prior to use.

Chemicals:

Anhydrous solvents were purchased from Sigma-Aldrich or Acros Organics. 1,1,1-trifluorotoluene (TFT), mesitylene (Mes) and N,N-dimethylformamide (DMF) were additionally degassed by bubbling argon through for 1h and were stored inside a Ar-filled glovebox. Solvents used for substrate synthesis were purchased from Avantor or Sigma-Aldrich and used as received unless otherwise stated.

Palladium salts were purchased from Sigma-Aldrich and stored in an argon-filled glovebox at ambient temperature. Other chemicals were purchased from Sigma-Aldrich, Acros Organics, Alfa Aesar, Apollo Scientific, Fluorochem or Enamine and used as received unless specified otherwise. IBiox-type ligand precursors used in this work (IBiox6, IBiox.*t*Bu), as well as their defined complexes were synthesized by the procedure disclosed in a previous work.[1]

Instrumentation:

GCMS analyses were performed with a Shimadzu QP2010SB GCMS apparatus on a Rtx®-5ms-Low-Bleed column lined with a mass (EI) detection system. HPLC analyses was performed using a Shimadzu Prominence system with SIL-20A auto sampler, CTO-20AC column oven, LC-20AD pump system, DGU-20A3 degasser and SPD-M20A Diode Array or UV/VIS detector.

Melting points were obtained on a Büchi melting point M-565, and are uncorrected.

IR spectra were recorded on an ATR Varian Scimitar 800 and are reported in reciprocal centimeters (cm^{-1}).

Nuclear magnetic resonance spectra were recorded on a Bruker Advance 250 (250 MHz), Advance 500 (500 MHz) and Advance 600 (600 MHz) in deuterated chloroform (residual

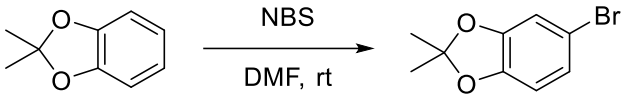
peaks ^{1}H δ 7.26 ppm, ^{13}C δ 77.16 ppm) unless otherwise noted. ^{13}C spectra are $^{1}H(\{^{1}H\})$ decoupled unless otherwise stated. ^{19}F spectra $^{1}H(\{^{1}H\})$ decoupled. are Data are reported in parts per million (ppm) as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, ddd = doublet of doublet of doublet and brs = broad singlet), coupling constant in Hz and integration.

High resolution mass spectra were recorded by Dr. M. Pfeffer (Department of Chemistry, University of Basel) on a Bruker maXis 4G QTOF ESI mass spectrometer. Elemental analysis was performed by Dr. Sylvie Mittelheisser (Department of Chemistry, University of Basel) on a Elementar Vario MICRO Cube instrument.

2. Synthesis of a common C–H activation precursor

2.1 Assembly of the bromide core – dibromide **10**

5-bromo-2,2-dimethylbenzo[d][1,3]dioxole (bromocathehol 19)



8 **19**

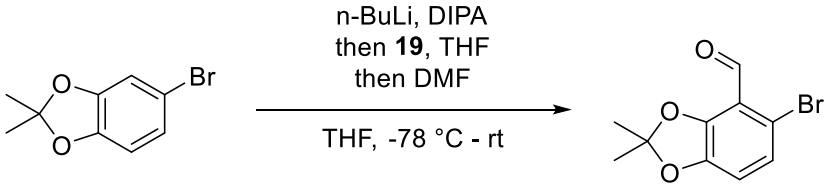
In a 500 mL round-bottom flask equipped with an egg-shaped PTFE–coated stirring bar, cathehol **8** (17 g, 113 mmol, 1 eq) was deposited, followed by dissolution in dry DMF (127 mL). NBS (19.8 g, 111 mmol, 0.98 eq) was added portionwise (1/4 of overall amount every 2 mins) to the reaction mixture under stirring. The resulting reaction mixture was stirred overnight at ambient temperature. Upon aging, reaction mixture was diluted with water (250 mL) and MTBE (125 mL). After vigorous stirring, layers were separated in a separatory funnel and aqueous layer was washed twice more with MTBE (2x125 mL). Combined organic layer was washed three times with brine (250 mL), dried over Na_2SO_4, filtered and evaporated at reduced pressure to yield 23.28 g (90%) of the titular compound **19** as a yellow oil. This compound is described.[2]

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.86 (d, *J* = 2.0 Hz, 1H), 6.60 (d, *J* = 8.2 Hz, 1H), 1.67 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.5, 147.0, 123.8, 119.1, 112.5, 112.2, 109.5, 25.9.

IR (neat), ν (cm^{-1}): 2992, 1480, 1379, 1233, 978, 837, 632.

5-bromo-2,2-dimethylbenzo[d][1,3]dioxole-4-carbaldehyde (benzaldehyde 9)



19 **9**

In a 1 L three-neck round-bottom flask equipped with an egg-shaped PTFE–coated stirring bar under the atmosphere of Ar N,N-diisopropylamine (DIPA, 16.2 mL, 115 mmol, 1.25 eq), was added and dissolved in THF (58 mL, 0.5M) under stirring. Resulting solution was cooled to -78 °C (acetone/dry ice) and n-BuLi (2.5M in hexanes, 46.1 mL, 115 mmol, 1.25 eq) was added dropwise. Reaction mixture was aged for 15 min, after which a solution of bromocathehol **19** (21.13 g, 92.2 mmol, 1 eq) in THF (92 mL, 1M) was added dropwise. The resulting mixture was then aged for 1 h at this temperature with precipitation of white solid. A solution of DMF (8.9 mL, 115 mmol, 1.25 eq) in THF (115 mL, 1M) was then added dropwise. Resulting mixture was left to warm to ambient temperature with stirring overnight.

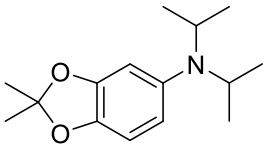
Upon aging, the reaction mixture was quenched by addition of sat. aq. NH_4Cl (50 mL), followed by dilution with water (300 mL) and EtOAc (300 mL). Resulting mixture was vigorously stirred, after which layers were separated in a separatory funnel. Aqueous layer was subsequently washed twice more with EtOAc (2x200 mL) and combined organic layer was washed twice with brine (2x250 mL). Resulting organic layer was dried over Na_2SO_4, filtered and evaporated at reduced pressure to yield 20.62 g (89%) of the titular compound **9** as a yellow oil. This compound is described.[3]

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.28 (s, 1H), 7.05 (d, *J* = 8.2 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 1.75 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 190.6, 149.7, 148.6, 125.6, 121.8, 117.3, 115.0, 113.5, 26.2.

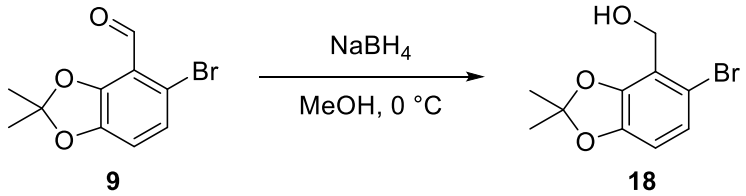
Notes:

- A common side product that was observed during this reaction is a product of addition of DIPA **S1**. With the reported procedure, the formation of this side product is minimal (<5% of the mass), however if the formation of this side product is significant, it is possible to remove it via column chromatography on the next step.



S1

(5-bromo-2,2-dimethylbenzo[d][1,3]dioxol-4-yl)methanol (alcohol 20)



9 **18**

In a 500 mL round-bottom flask equipped with an egg-shaped PTFE–coated stirring bar benzaldehyde **9** (12.4 g, 48.2 mmol, 1 eq) was dissolved in MeOH (127 mL) under stirring. Resulting solution was cooled to 0 °C (ice bath) and $NaBH_4$ (1.82 g, 48.2 mmol, 1 eq) was added portionwise. Reaction mixture was then stirred at this temperature for 1 h. Progress was monitored by TLC (1/4 EtOAc/cyclohexane).

After completion, reaction mixture was transferred to a separatory funnel and diluted with water (300 mL) and EtOAc (300 mL). Layers were vigorously mixed and separated. Aqueous layer was then washed twice more with EtOAc (2x100 mL) and the combined organic layer was washed once with brine (200 mL). Resulting organic phase was dried over Na_2SO_4, filtered and evaporated at reduced pressure to yield 11.7 g (94%) of the title compound **18** as a dark yellow oil.

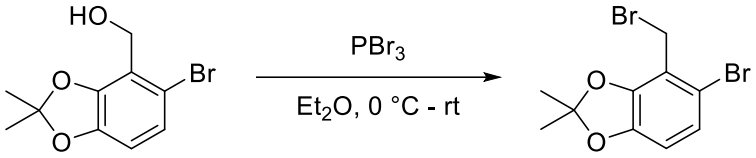
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (d, *J* = 8.2 Hz, 1H), 6.56 (d, *J* = 8.2 Hz, 1H), 4.72 (s, 2H), 1.69 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.1, 147.0, 124.7, 121.4, 119.6, 114.5, 109.1, 59.7, 26.1.

HRMS (ESI): Calcd for $C_{10}H_{11}BrO_3Ag$, $[M+Ag]^+$: 366.8920, found 366.8908.

IR (neat), ν (cm^{-1}): 3398, 2991, 1461, 1254, 1037, 1005, 976.

5-bromo-4-(bromomethyl)-2,2-dimethylbenzo[d][1,3]dioxole (dibromide 10)



20 **10**

In a 250 mL round-bottom flask equipped with an egg-shaped PTFE–coated stirring bar, alcohol **20** (17.3 g, 66.8 mmol, 1 eq) was dissolved in Et_2O (228 mL) at 0 °C (ice bath) under stirring. Phosphorus tribromide (2.07 mL, 22 mmol, 0.33 eq) was then added dropwise. The cooling was then removed and the resulting mixture was stirred overnight at ambient temperature. Progress was monitored by TLC (1/4 EtOAc in cyclohexane).

Upon completion, reaction mixture is quenched by dilution with water (200 mL). After vigorous stirring, the layers were separated in a separatory funnel. Aqueous layer is washed once with Et_2O (100 mL), after which combined organic layer was washed once with water (100 mL) and brine (100 mL). Resulting organic phase was dried over Na_2SO_4, filtered and evaporated at reduced pressure to yield 20 g (93%) of the title compound **10** as a pale yellow oil which solidifies upon standing.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (d, *J* = 8.2 Hz, 1H), 6.56 (d, *J* = 8.3 Hz, 1H), 4.55 (s, 2H), 1.71 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.4, 147.1, 124.9, 120.2, 119.0, 114.9, 109.6, 26.9, 26.0.

HRMS (ESI): Calcd for $C_{10}H_{10}Br_2O_2Ag$, $[M+Ag]^+$: 428.8078, found 428.8139.

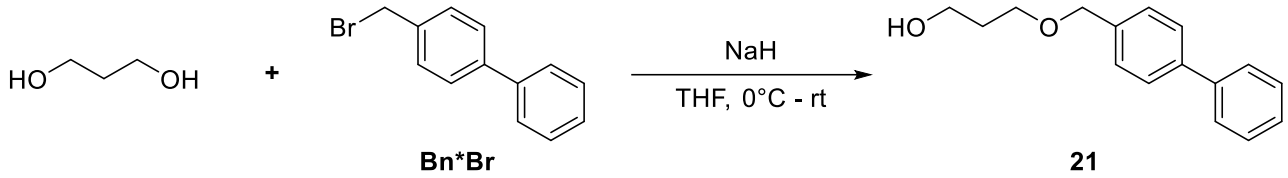
IR (neat), v (cm^{-1}): 2986, 1461, 1377, 1249, 1207, 1023, 975, 905.

Rf: 0.73 (20% EtOAc in cyclohexane).

mp: 55 °C.

2.2 Assembly of the malonate fragment – malonate **7**

3-([1,1'-biphenyl]-4-ylmethoxy)propan-1-ol (monoalcohol 21)



Bn*Br **21**

In a 500 mL round-bottom flask equipped with an egg-shaped PTFE–coated stirring bar, NaH (60% dispersion in oil, 944 mg, 23.6 mmol, 1.1 eq) was suspended in THF (70 mL) under 0°C (ice bath) cooling. To it a solution of 1,3-propanediol (3.1 mL, 42.9 mmol, 2 eq) in THF (5 mL) was added dropwise over a period of 5 min. Resulting mixture was then kept stirring for 30 min, after which a solution of 4-bromomethylbiphenyl (5.3 g, 21.5 mmol, 1 eq, **Bn*Br**) in THF (10 mL) was added. Resulting brown solution was left stirring overnight at room temperature. A formation of precipitate was observed.

Resulting mixture was quenched by addition of water (150 mL), which was followed up by addition of EtOAc (150 mL). Resulting mixture was vigorously stirred for 30 min, after which it was transferred to a separatory funnel, where the layers were separated. Aqueous layer was further washed twice more with EtOAc, after which united organic extracts were washed once with brine. Resulting organic phase was dried over Na_2SO_4, filtered and evaporated at reduced pressure. Resulting crude was then diluted in DCM, deposited on a Biotage® Sfär cartridge, and subjected to column chromatography (cyclohexane/EtOAc, 0-100%) to yield 3.93 g (76%) of titular compound **21** as a brown oil that crystallized upon standing.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 – 7.56 (m, 4H), 7.48 – 7.38 (m, 4H), 7.39 – 7.32 (m, 1H), 4.57 (s, 2H), 3.85 – 3.78 (m, 2H), 3.71 (t, *J* = 5.8 Hz, 2H), 2.29 (brs, 1H), 1.90 (p, *J* = 5.8 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.0, 140.9, 137.3, 128.9, 128.3, 127.4, 127.4, 127.2, 73.2, 69.7, 62.1, 32.3.

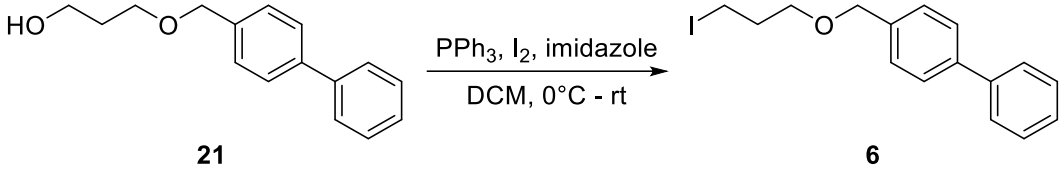
HRMS (ESI): Calcd for $C_{16}H_{18}O_2$, $[M+Na]^+$: 265.1199, found: 265.1204.

IR (neat), ν (cm^{-1}): 3317, 2862, 1485, 1364, 1079, 1005, 753.

mp: 40°C

Rf: 0.11 (20% EtOAc in cyclohexane)

4-((3-iodopropoxy)methyl)-1,1'-biphenyl (iodide 6)



21 **6**

In a 250 mL round-bottom flask equipped with an egg-shaped PTFE–coated stirring bar, alcohol **21** (3.9 g, 16.1 mmol) was dissolved in DCM (65 mL) and then cooled to 0°C (ice bath). To this solution, imidazole (1.37 g, 20.1 mmol, 1.25 eq) and triphenylphosphine (4.43 g, 16.9 mmol, 1.05 eq) were added, followed by a slow addition of iodine (4.49 g, 17.7 mmol, 1.1 eq). The color of solution has changed from light yellow to dark brown. The ice bath was removed and reaction mixture was left stirring overnight at room temperature.

After confirmation of conversion via TLC, reaction mixture was quenched by addition of saturated aqueous Na_2SO_3 solution (100 mL), followed by additional dilution with DCM (35 mL). Resulting mixture was vigorously stirred, after which transferred to a separatory funnel. Layers were separated; aqueous layer was washed once with DCM. Combined organic layers were washed with brine and the resulting organic phase was dried over Na_2SO_4, filtered and evaporated at reduced pressure. Resulting crude was then diluted in DCM, deposited on a Biotage® Sfär cartridge, and subjected to column chromatography (cyclohexane/EtOAc, 0-10%) to yield 5.1 g (90%) of titular compound **6** as a transparent oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.58 (m, 4H), 7.49 – 7.41 (m, 4H), 7.40 – 7.33 (m, 1H), 4.58 (s, 2H), 3.60 (t, *J* = 5.8 Hz, 2H), 3.34 (t, *J* = 6.8 Hz, 2H), 2.13 (p, *J* = 6.3 Hz, 2H).

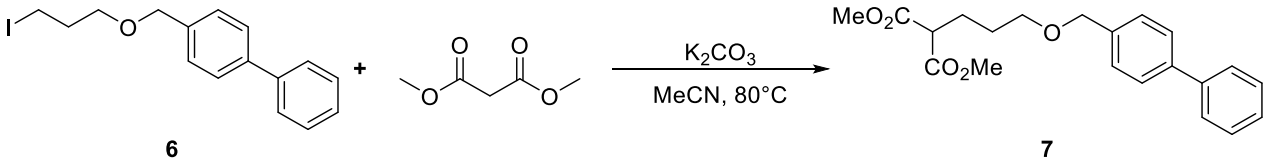
^{13}C NMR (126 MHz, $CDCl_3$) δ 141.0, 140.8, 137.4, 128.9, 128.3, 127.4, 127.3, 127.2, 73, 69.8, 33.6, 3.6.

HRMS (ESI): Calcd for $C_{16}H_{17}IO$, $[M+Na]^+$: 375.0216, found: 375.0217.

IR (neat), v (cm^{-1}): 3028, 2858, 1487, 1361, 1181, 1099, 760.

Rf: 0.7 (20% EtOAc in cyclohexane)

dimethyl 2-(3-([1,1'-biphenyl]-4-ylmethoxy)propyl)malonate (malonate 7)



6 **7**

In a 250 mL round-bottom flask equipped with an egg-shaped PTFE–coated stirring bar, iodide **6** (1.7 g, 4.8 mmol, 1.05 eq) was dissolved in MeCN (50 mL). To it, dimethyl malonate (0.53 mL, 4.6 mmol, 1 eq) and potassium carbonate (1.27 g, 9.2 mmol, 2 eq) were added. Resulting vessel was then equipped with a Vigreux condenser and mixture was then heated (oil bath) to reflux overnight.

This mixture was then cooled to room temperature and filtered through a Nutsche filter. Solids were washed three times with MeCN and resulting filtrate was then evaporated at reduced pressure. Residue was then taken up with water and EtOAc, stirred vigorously and transferred to a separatory funnel. Layers were separated; aqueous layer was washed twice more with EtOAc. Combined organic layer was washed with brine once, was dried over Na_2SO_4, filtered and evaporated at reduced pressure. Resulting crude was then diluted in cyclohexane, deposited on a Biotage® Sfär cartridge, and subjected to column chromatography (cyclohexane/EtOAc, 0-20%) to yield 1.28 g (78%) of titular compound **7** as a transparent oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 – 7.55 (m, 4H), 7.48 – 7.39 (m, 4H), 7.39 – 7.32 (m, 1H), 4.54 (s, 2H), 3.74 (s, 6H), 3.53 (t, J = 6.3 Hz, 2H), 3.44 (t, J = 7.5 Hz, 1H), 2.05 (q, J = 7.8 Hz, 2H), 1.73 – 1.64 (m, 2H).

^{13}C NMR (126 MHz, CDCl3) δ 169.9, 141.0, 140.6, 137.6, 128.9, 128.2, 127.3, 127.2, 127.2, 72.7, 69.7, 52.6, 51.5, 27.5, 25.9.

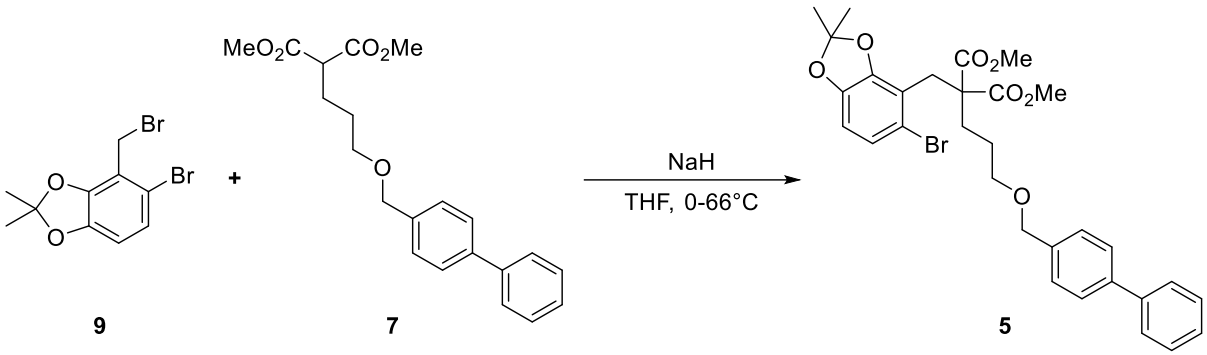
HRMS (ESI): Calcd for $C_{21}H_{24}O_5$, $[M+Na]^+$: 379.1516, found: 379.1518.

IR (neat), ν (cm^{-1}): 2952, 2862, 1735, 1436, 1225, 1156, 1099, 1009.

Rf: 0.3 (20% EtOAc in cyclohexane)

2.3 Assembly the common C–H activation precursor **5**

Dimethyl 2-(3-([1,1'-biphenyl]-4-ylmethoxy)propyl)-2-((5-bromo-2,2-dimethylbenzo[d][1,3]-dioxol-4-yl)methyl)malonate (precursor 5)



In a 250 mL round-bottom flask equipped with an egg-shaped PTFE–coated stirring bar, NaH (60% dispersion in mineral oil, 172 mg, 4.3 mmol, 1.2 eq) was suspended in THF (15 mL) under cooling at 0°C (ice bath). To it, malonate **7** (1.28 g, 3.6 mmol, 1 eq) solution in THF (15 mL) was added dropwise. Resulting mixture was stirred at this temperature, after which dibromide **10** (1.27 g, 3.95 mmol, 1.1 eq) solution in THF (10 mL) was added. The reaction vessel was equipped with a Vigreux condenser and mixture was then heated (oil bath) to reflux overnight.

After aging, the resulting mixture was cooled to ambient temperature and diluted with water, followed by EtOAc. The resulting mixture was vigorously stirred, after which it is transferred to separatory funnel. Layers are separated and aqueous layer was washed twice more with EtOAc. Combined organic layer was washed with brine once, was dried over Na_2SO_4, filtered and evaporated at reduced pressure. Resulting crude was then diluted in DCM and dryloaded onto Celite, deposited on a Biotage® Sfär cartridge, and subjected to column chromatography (cyclohexane/EtOAc, 0-25%) to yield 1.25 g (58%) of titular compound **5** as a transparent viscous oil which solidifies upon standing.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 – 7.53 (m, 4H), 7.48 – 7.40 (m, 2H), 7.40 – 7.31 (m, 3H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.50 (d, *J* = 8.3 Hz, 1H), 4.50 (s, 2H), 3.73 (s, 6H), 3.50 (s, 2H), 3.45 (t, *J* = 6.7 Hz, 2H), 1.95 – 1.88 (m, 2H), 1.71 – 1.64 (m, 2H), 1.60 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 147.8, 146.5, 141.1, 140.6, 137.7, 128.9, 128.2, 127.4, 127.3, 127.2, 125.2, 118.8, 118.1, 116.9, 108.6, 72.6, 70.5, 57.7, 52.5, 33.5, 29.6, 25.9, 25.3.

HRMS (ESI): Calcd for $C_{31}H_{33}BrO_7$, $[M+Na]^+$: 619.1302, found: 619.1310.

IR (neat), ν (cm^{-1}): 2951, 1731, 1457, 1215, 1101, 1038, 975.

mp: 83°C

Rf: 0.72 (50% EtOAc in cyclohexane)

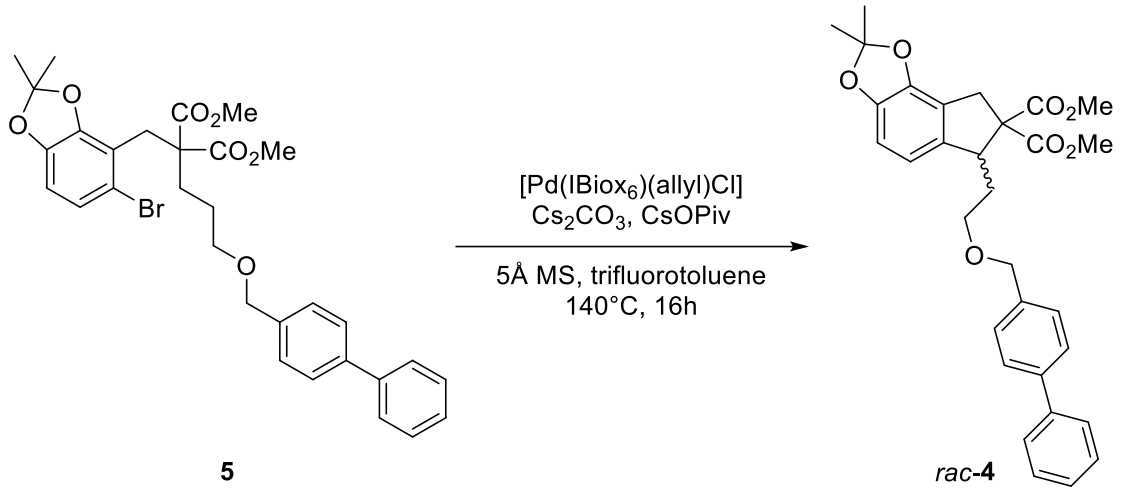
Notes:

- Occasionally, crystallization of the substrate does not occur, usually due to high viscosity of the material or leftover cyclohexane residues in trace amounts. This does not impede the following reaction, however it is of high convenience to obtain crystalline material, as high viscosity of the material prevents facile dispensation.

3. C–H activation: procedure and disscussion

3.1 C–H activation protocol

dimethyl 6-(2-([1,1'-biphenyl]-4-ylmethoxy)ethyl)-2,2-dimethyl-6,8-dihydro-7H-indeno[4,5-d][1,3]dioxole-7,7-dicarboxylate (C–H product *rac*-4)



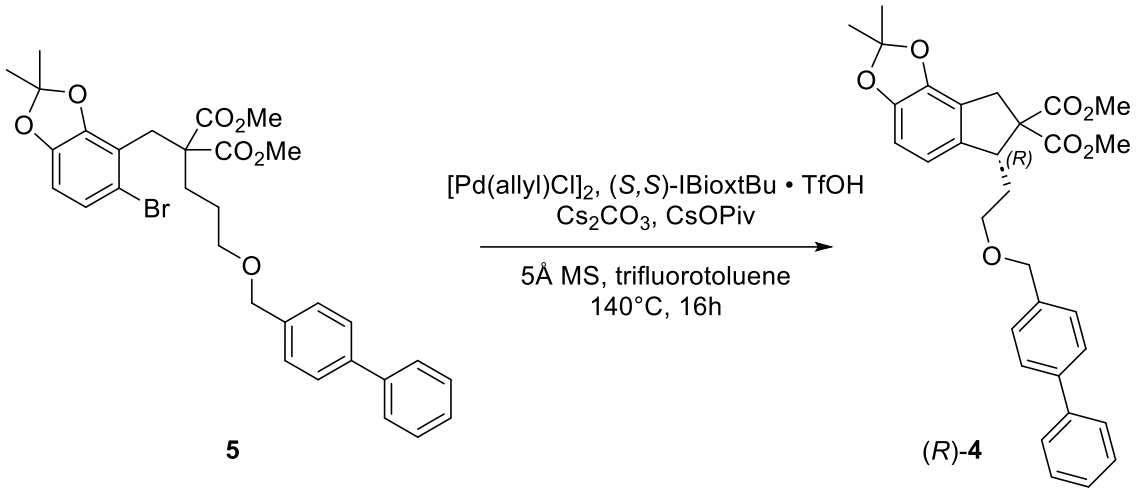
In a 20 mL single-use oven-dried crimp vial equipped with a PTFE-coated magnetic stirbar (1.5 cm), C–H precursor **5** (299 mg, 0.5 mmol, 1 eq) was deposited, followed by [Pd(IBiox$_6$)(allyl)Cl] (23.6 mg, 0.05 mmol, 0.1 eq). The unplugged vial was then introduced into an Ar–filled glovebox, where Cs2CO3 (163 mg, 0.5 mmol, 1 eq), CsOPiv (35.1 mg, 0.15 mmol, 30% mol) and 5Å molecular sieves (62.5 mg) were added. Trifluorotoluene (5 mL) was then added and the reaction vessel was sealed by a crimp cap equipped with a septum. Assembled reaction vessel was then removed from glovebox, sonicated for aprox. 5 mins (to ensure maximal homogeneity) and then introduced to a heating block pre-heated to 140°C. Reaction vessel was then stirred for 16 hours at 1000 rpm at this temperature.

Upon aging, reaction mixture was then cooled and filtered through a pad of Celite. Vessel and the filter cake were then washed three times with dichloromethane. Collected filtrate is then carefully concentrated to yield a residue which was then checked via NMR with an internal standard (nitromethane). Upon verification, all residue was deposited onto silica and purified by column chromatography (0-20% EtOAc in cyclohexane) to yield a mixture of C–H activation product and a product of dehalogenation.

The obtained mixture was then recrystallized as follows: a round-bottom flask containing the mix was supplied with an egg-shaped PTFE-coated magnetic stirbar and taken up in n-hexane (10 mL per gram of mix). While stirring, n-hexane was boiled to the point of effervescence and kept at this state by the means of a heatgun. This sequence was then followed by a dropwise addition of EtOAc into the boiling mixture until homogeneity was observed. The stirbar was then removed by a magnetic removal tool and the mixture was left to cool to ambient temperature undisturbed. After aprox. 20 min of standing, crystals should start forming. After overnight aging, the mixture was placed into the fridge (4°C) overnight. This allows full formation of crystals. The supernatant liquid was then removed

by decantation and a small (~3 mL) portion of n-hexanes was introduced, stirred gently and decanted to wash away supernatant mother liquor. After such manipulations, resulting crystals are dried on the rotovap (45°C, 0.1 mbar). The crystals are then analyzed for dehalogenation product content. These operations give 167 mg (63% yield, 98% assay) of the C–H product *rac*-**4** as a white powder.

dimethyl 6-(2-([1,1'-biphenyl]-4-ylmethoxy)ethyl)-2,2-dimethyl-6,8-dihydro-7H-indeno[4,5-d][1,3]dioxole-7,7-dicarboxylate (C–H product *(R)*-4)



In a 10 mL single-use oven-dried crimp vial equipped with a PTFE-coated magnetic stirbar (1.5 cm), C–H precursor **5** (120 mg, 0.2 mmol, 1 eq) was deposited, followed by $[Pd(allyl)Cl]_2$ (3.7 mg, 0.01 mmol, 0.05 eq) and (*S,S*)-IBiox.tBu•TfOH[4] (8.3 mg, 0.02 mmol, 0.1 eq). The unplugged vial was then introduced into an Ar–filled glovebox, where Cs_2CO_3 (65.2 mg, 0.2 mmol, 1 eq), CsOPiv (14 mg, 0.06 mmol, 30% mol) and 5Å molecular sieves (25 mg) were added. Trifluorotoluene (2 mL) was then added and the reaction vessel was sealed by a crimp cap equipped with a septum. Assembled reaction vessel was then removed from glovebox, sonicated for aprox. 5 mins (to ensure maximal homogeneity) and then introduced to a heating block pre-heated to 140°C. Reaction vessel was then stirred for 16 hours at 1000 rpm at this temperature.

Upon aging, reaction mixture was then cooled and filtered through a pad of Celite. Vessel and the filter cake were then washed three times with dichloromethane. Collected filtrate is then carefully concentrated to yield a residue which was then checked via NMR with an internal standard (nitromethane). Upon verification, all residue was deposited onto silica and purified by column chromatography (0-20% EtOAc in cyclohexane) to yield a mixture of C–H activation product and a product of dehalogenation. Recrystallization via racemic procedure yielded 36 mg (35%) of C–H product (*R*)-**4** with 99:1 enantiomeric ratio.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 – 7.55 (m, 4H), 7.48 – 7.40 (m, 4H), 7.38 – 7.31 (m, 1H), 6.54 (d, *J* = 7.8 Hz, 1H), 6.51 (d, *J* = 7.9 Hz, 1H), 4.55 (q, *J* = 11.8 Hz, 2H), 4.01 (dd, *J* = 10.4, 4.7 Hz, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.69 (d, *J* = 16.8 Hz, 1H), 3.60 – 3.50 (m, 2H),

3.30 (d, *J* = 16.7 Hz, 1H), 1.87 – 1.77 (m, 1H), 1.66 (s, 3H), 1.65 (s, 3H), 1.63 – 1.57 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 170.3, 146.9, 143.1, 141.1, 140.8, 138.1, 137.6, 128.9, 128.4, 127.4, 127.3, 127.3, 119.1, 118.1, 116.7, 106.9, 72.8, 67.8, 66.2, 53.1, 52.8, 46.4, 34.9, 31.0, 26.1.

HRMS (ESI): Calcd for $C_{31}H_{32}O_7$, $[M+Na]^+$: 539.2040, found: 539.2039.

IR (neat), v (cm^{-1}): 2930, 1737, 1601, 1471, 1208.

mp: 132°C

Rf: 0.6 (20% EtOAc in cyclohexane)

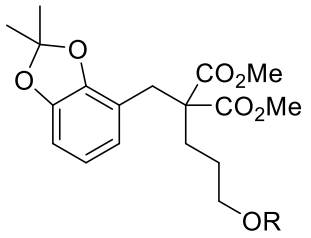
$[\alpha]_D^{25}$ = -103.1° (c = 1, $CHCl_3$)

Chiral HPLC data: Chiralpak OD-H column 4.6 x 250 mm, 90/10 heptane/isopropanol, 1 mL/min, 254 nm, t_R(minor, *S*) = 12.6 min, t_R(major, *R*) = 16.7 min, , 99:1 e.r.

3.2 Discussion on development of the procedure

A suite of recurring issues that are worth mentioning complemented the implementation of this procedure. Our initial investigation into this particular methylene C(sp^3)–H activation started with a benzyl-bearing starting material **5b**. Already with this material we have observed good formation of the C–H activation product **4b**, two specific issues were observed, which complicated further scale implementation of the synthesis.

Usually, throughout the course of this reaction, numerous impurities are generated. Most of them could be separated in a facile way either through column chromatography or via subsequent recrystallization. However, two impurities in particular represented a challenge for purification: protodehalogenated product **11** and starting material **4**. While starting material **4** is usually not present in the product mix and, thus, was not very problematic, protodehalogenation was an omnipresent process. Throughout the course of our investigation, no reaction furnished material without any protodehalogenation.



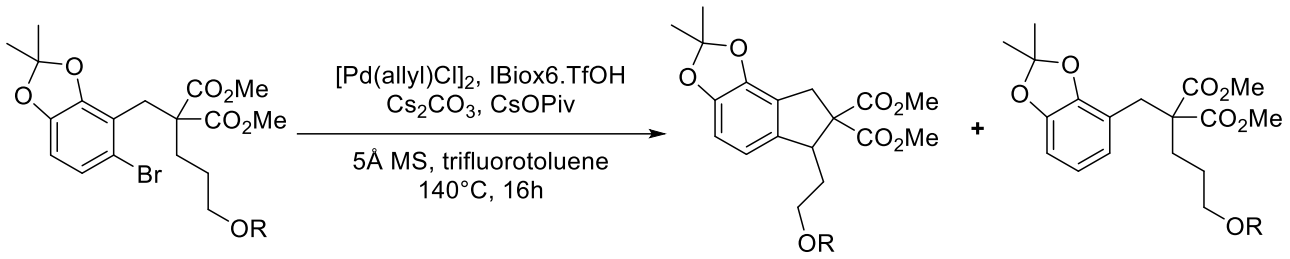
protodehalogenation product **11**

In our initial investigation of the methylene C(sp^3)–H activation, where an extensive investigation was performed, this problem also persisted, however a solution in preparatory HPLC was found. While a viable solution for a methodology scope, it was wholly unsuited for scaling, as the run times and solvent consumption per run was not sustainable for production on gram scale with our setup. Thus, a better solution was required.

Therefore, since prevention of formation of **11** was not possible (*vide infra*), we have focused on facilitation of removal of the side-products via crystallization. Our original approach, which focused on the use of benzyl as a protecting group, offered a material in a form of easily melting crystals. We decided to screen benzyl-type protecting groups (and other protecting group on the chain), which may have offered better crystallization.

The *p*-biphenyl derivative **4a** provided good recrystallization outcome and yield, thus it was chosen for further development. This choice offered additional unexpected benefits in performance. In particular, while scale-up beyond 0.5 mmol scale were unfruitful, performance at this scale was stabilized at around 50-60% yield with low quantity of fully unsuccessful reactions. Similarly, crystalline nature of the starting material **4** helps with stirring, as starting material does not stick to the stirbar. This also proved beneficial during enantioselective C–H activation, as performance with stereodefined ligands, such as (*S,S*)-IBioxtBu, is usually less efficient.

Table 3.2.1. Protecting group optimization.

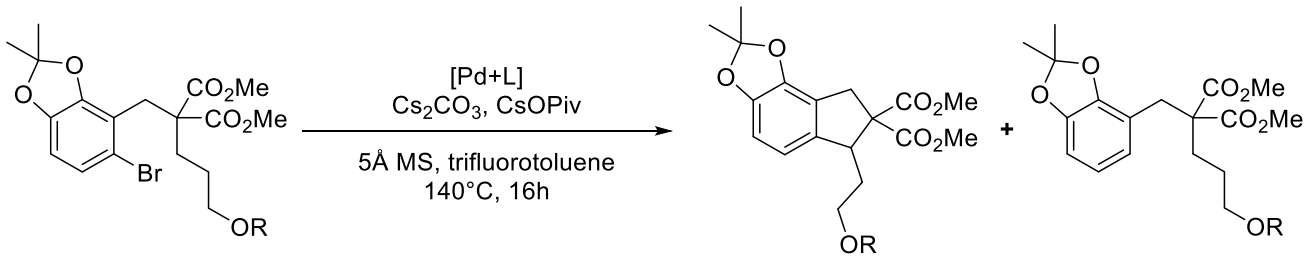


5 **4** **11**

#	R	C–H arylation outcome[1]		Crystallization outcome[2]
		4, %	**11**, %	
1	Bn	40-60 (see table 3.2.2)	20-30	Easily melting crystals
2	TIPS	No reaction		–
3	TBDPS			
4	(*p*-trifluoromethyl)benzyl	58	7	No appreciable crystallization
5	(*p*-nitro)benzyl	41	10	
6	3,5-difluorobenzyl	50	8	Crystals contained **11**.
7	*p*-biphenyl (Bn*)	52	9	46% overall yield after recrystallization, no **11**.

[1] Yield and ratio product-dehalo determined after initial column purification via ^{1}H NMR yield w/ CH_3NO_2 as internal standard at 0.2 mmol scale. Crystallinity assayed by direct observation, outcome after dissolution in minimal possible amount of boiling n-hexanes/EtOAc and then prolonged (overnight) cooling in the freezer (-20°C).

Table 3.2.2. Further optimization.

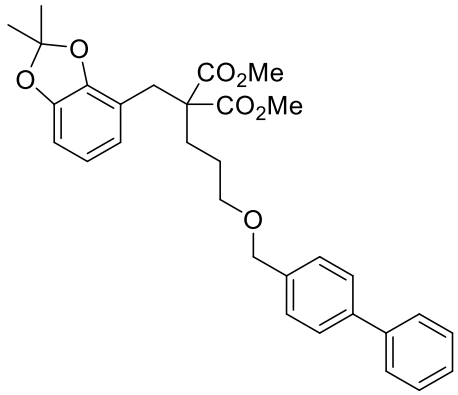


5 **4** **11**

#	R	[Pd+L], other conditions	C–H arylation outcome, %			Comment
			5, %	**4**, %	**11**, %	
1	Bn	[Pd(allyl)Cl]$_2$ (5% mol) + IBiox6•TfOH (10% mol)	50	30	20	Repeated three times, results overall same.
2		Same as #1, new batches of reagents and solvent	15	60	25	
3		Same as #1, +5% v/v DMF	10	70	20	Conditions non-reproducible.
4		As #3, repeated	30	0	30	
5	Bn*	[(IBiox6)Pd(allyl)Cl] (10% mol)	0	60	20	Rest is non-identifiable. Average yield over 30+ batches.

[1] Outcome stated as ^{1}H NMR yield of 0.5 mmol scale reaction w/ CH_3NO_2 as internal standard.

dimethyl 2-(3-([1,1'-biphenyl]-4-ylmethoxy)propyl)-2-((2,2-dimethylbenzo[d][1,3]dioxol-4-yl)methyl)malonate (protodehalogenated 11a)



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 – 7.54 (m, 4H), 7.48 – 7.42 (m, 2H), 7.41 – 7.33 (m, 3H), 6.66 (t, *J* = 7.7 Hz, 1H), 6.61 (dd, *J* = 7.7, 1.3 Hz, 1H), 6.47 (dd, *J* = 7.8, 1.3 Hz, 1H), 4.52 (s, 2H), 3.74 (s, 6H), 3.48 (t, *J* = 6.7 Hz, 2H), 3.26 (s, 2H), 1.93 – 1.84 (m, 2H), 1.71 – 1.64 (m, 2H), 1.61 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 147.0, 146.7, 141.1, 140.6, 137.6, 128.9, 128.2, 127.4, 127.24, 127.20, 123.1, 121.0, 117.3, 117.2, 107.4, 72.7, 70.5, 58.5, 52.5, 32.1, 28.7, 26.0, 24.9.

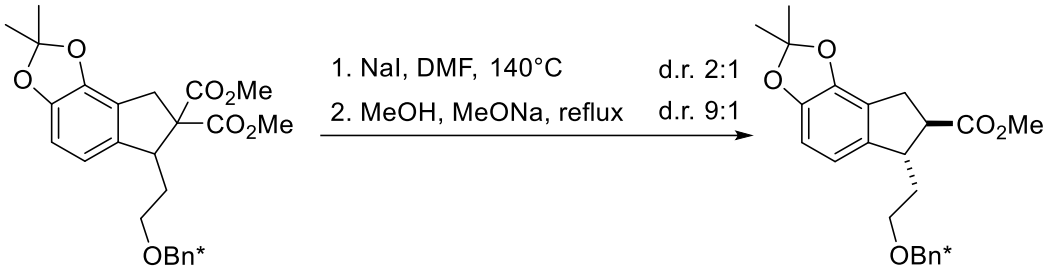
HRMS (ESI): Calcd for $C_{31}H_{34}O_7$, $[M+Na]^+$: 541.2197, found: 541.2208.

IR (neat), v (cm^{-1}): 2951, 2860, 1733, 1462, 1255, 1201, 1113.

Rf: 0.6 (20% EtOAc in cyclohexane)

4. Synthesis of common intermediate

methyl *trans*-6-(2-([1,1'-biphenyl]-4-ylmethoxy)ethyl)-2,2-dimethyl-7,8-dihydro-6H-indeno[4,5-d][1,3]dioxole-7-carboxylate (monoester 12)



4 **12**

To an oven-dried 10 mL microwave vial (Biotage) equipped with a PTFE-covered magnetic stirbar C–H activation product **4** (205 mg, 0.397 mmol, 1 eq) compound was deposited via evaporation of a DCM solution. To it, sodium iodide (119 mg, 0.794 mmol, 2 eq) was added and the vial was introduced into the glovebox, where DMF was added (2 mL). The vial was then sealed with a crimp cap with a septum, taken out of the glovebox, sonicated for aprox. 5 mins (to ensure maximal homogeneity) and then introduced to a heating block pre-heated to 140°C. Reaction vessel was then stirred for 16 hours at 1000 rpm at this temperature. Progress of the reaction was monitored after aging via TLC (1/4 EtOAc/cyclohexane). After confirmation, reaction mixture was cooled to room temperature and diluted with water. Reaction mixture was then transferred to the extraction funnel, followed by washing of reaction vessel with MTBE. This mix was then shaken together and organics were separated. Aqueous layer was then washed twice more with MTBE, and combined organic layer was washed fivefold with brine. Organic layer was dried over Na_2SO_4, filtered and evaporated at reduced pressure. This residue was dissolved in DCM and dry-loaded onto silica and then subjected to column chromatography (0-10% EtOAc in cyclohexane) to afford decarboxylated product **12** with d.r. 2:1. This product is subjected to the same recrystallization protocol that was applied to C–H product **4** to yield 88 mg (48%) of titular compound as a beige solid and 46 mg (25%) of monoester **12** with d.r. 3:4.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 – 7.53 (m, 4H), 7.48 – 7.38 (m, 4H), 7.37 – 7.32 (m, 1H), 6.58 (s, 2H), 4.53 (s, 2H), 3.67 (s, 3H), 3.64 (td, *J* = 6.5, 1.0 Hz, 2H), 3.62 – 3.58 (m, 1H), 3.22 – 3.04 (m, 3H), 2.23 – 2.14 (m, 1H), 1.89 (d, *J* = 129.3 Hz, 1H), 1.70 – 1.63 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8, 146.6, 143.0, 141.1, 140.6, 139.8, 137.7, 128.9, 128.2, 127.4, 127.3, 127.2, 121.5, 118.0, 115.5, 107.0, 72.9, 68.7, 52, 50.8, 45.7, 35.1, 31.8, 26.12, 26.08.

HRMS (ESI): Calcd for $C_{29}H_{30}O_5$, $[M+Na]^+$: 481.1985, found: 481.1991.

IR (neat), ν (cm^{-1}): 1981, 1735, 1471, 1253, 1100.

mp: 96°C

Rf: 0.76 (50% EtOAc in cyclohexane)

This reaction was also performed with (*R*)-**4** on 277 mg scale to yield 80 mg (33%) of (*S,R*)-**12** over two steps. The separation was achieved by preparatory HPLC.

$[\alpha]_D^{25}$ = -31.8° (c = 1, $CHCl_3$)

Chiral HPLC data: Chiralpak OD-H column 4.6 x 250 mm, 95/5 heptane/isopropanol, 1 mL/min, 254 nm, t_R(minor, *R,S*) = 12.3 min, t_R(major, *S,R*) = 13.6 min, 99:1 d.r.

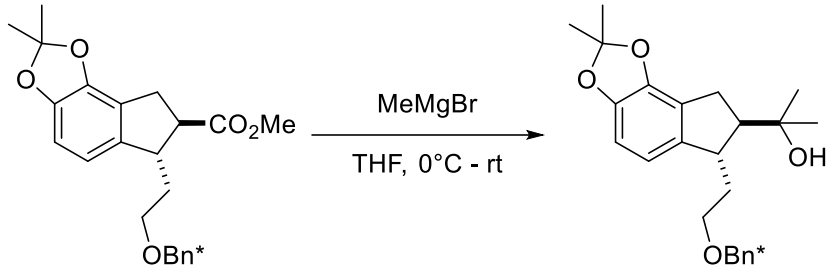
Notes:

- It is possible to improve the diastereomeric ratio in favor of *trans*-isomer of **12** by performing the equilibration of the mixture by a protocol that follows:

To an oven-dried 10 mL microwave vial (Biotage) equipped with a PTFE-covered magnetic stirbar C–H a residue of **12** recovered after recrystallization (46 mg, 0.1 mmol, 1 eq) was deposited, followed by dissolution in MeOH (1 mL). A 25% solution of MeONa in MeOH (34.3 µL, 0.15 mmol, 1.5 eq) was then added. The vessel was then sealed with a crimp cap and placed in an aluminum heating block heated to 70 °C and kept there with stirring for 16 h. Upon aging, reaction mixture was cooled to rt and acidified with aq. 1M HCl to slightly acidic (5-6) pH, diluted with water and EtOAc. After vigorous stirring, layers were separated in a separatory funnel. Aqueous layer was then washed twice with EtOAc and united organic layer was then washed once with brine. Organic layer was then dried over Na_2SO_4, filtered and filtrate evaporated at reduced pressure to yield monoester **12** (42 mg, 92%) with d.r. 10:1.

Following this protocol, we were able to convert mixtures with wide ranges (from 3:4 to 2:1) of d.r. to mixtures with high content of *trans*-isomer, typically 10:1 d.r..

2-((6S,7R)-6-(2-([1,1'-biphenyl]-4-ylmethoxy)ethyl)-2,2-dimethyl-7,8-dihydro-6H-indeno[4,5-d][1,3]dioxol-7-yl)propan-2-ol (monoprotected diol 22)



12 **22**

To an oven-dried 50 mL round-bottom flask equipped with a PTFE-coated magnetic stirbar, solution of monoester **12** (518 mg, 1.13 mmol, 1 eq) in DCM was evaporated. The flask was then capped with a septum and atmosphere inside was exchanged for argon with Schlenk techniques. To this flask, THF (12 mL, 0.1M) was introduced and material is then dissolved. Reaction mixture was cooled to 0°C (ice bath) and to it a solution of methylmagnesium bromide (3M solution in diethyl ether, 1.13 mL, 3.39 mmol, 3 eq) is added slowly. The cooling bath is then removed and the reaction mixture is stirred overnight. Completion of the reaction is then judged by TLC (1/4 EtOAc/cyclohexane). Upon completion, reaction was quenched by addition of saturated aqueous NH_4Cl (5 mL) and was further diluted with water (20 mL) and EtOAc (25 mL). This mixture was then stirred vigorously and transferred to a separatory funnel, where layers were separated. Aqueous layer was then washed twice more with EtOAc (25 mL) and united organic layer was washed with brine. Organic layer was then dried over Na_2SO_4, filtered and filtrate evaporated at reduced pressure to yield monoprotected diol **22** (385 mg, 74%) as a yellow viscous oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 – 7.55 (m, 4H), 7.49 – 7.40 (m, 4H), 7.39 – 7.32 (m, 1H), 6.57 (s, 2H), 4.59 (d, *J* = 11.8 Hz, 1H), 4.55 (d, *J* = 11.9 Hz, 1H), 3.68 (t, *J* = 6.1 Hz, 2H), 3.30 (dt, *J* = 7.6, 4.8 Hz, 1H), 3.01 (dd, *J* = 16.9, 9.2 Hz, 1H), 2.72 (dd, *J* = 16.9, 4.6 Hz, 1H), 2.42 (dt, *J* = 9.1, 4.5 Hz, 1H), 2.33 (brs, 1H), 2.07 – 1.99 (m, 1H), 1.99 – 1.91 (m, 1H), 1.68 (s, 3H), 1.67 (s, 3H), 1.18 (s, 3H), 1.12 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.1, 142.7, 141.9, 141.0, 140.8, 137.3, 128.9, 128.4, 127.4, 127.3, 127.2, 123.1, 117.6, 115.6, 106.8, 73.2, 73.0, 69.0, 55.8, 43.6, 36.9, 30.1, 28.5, 26.1 26.0, 25.5.

HRMS (ESI): Calcd for $C_{30}H_{34}O_4$, $[M+Na]^+$: 481.2349, found: 481.2344.

IR (neat), v (cm^{-1}): 3428, 2970, 2932, 2860, 1469, 1374, 1247, 1100, 1010.

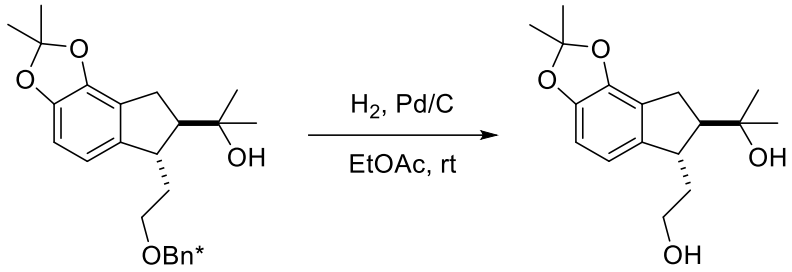
Rf: 0.65 (50% EtOAc in cyclohexane)

This reaction was also performed with (*S,R*)-**11** on 80 mg scale to yield 70 mg (88%) of (*S,R*)-**22**.

$[\alpha]_D^{25}$ = -5.4° (c = 1, $CHCl_3$)

Chiral HPLC data: Chiralpak OD-H column 4.6 x 250 mm, 90/10 heptane/isopropanol, 1 mL/min, 254 nm, t_R(minor, R,S) = 9.6 min, t_R(major, S,R) = 18.3 min, , 99:1 e.r.

2-((6S,7R)-6-(2-hydroxyethyl)-2,2-dimethyl-7,8-dihydro-6H-indeno[4,5-d][1,3]dioxol-7-yl)propan-2-ol (diol 3)



22 **3**

To a 50 mL round-bottom flask containing monoprotected diol **22** (250 mg, 0.174 mmol, 1 eq), 10% palladium on activated charcoal (58 mg, 0.0174 mmol, 0.1 eq) and a PTFE-coated magnetic stirbar was charged. Reaction mixture is then capped with a septum and evacuated with argon. Ethyl acetate (5 mL, 0.1M) was added and stirred for 5 minutes. Hydrogen gas (dispensed into a double-walled balloon) was then bubbled through the reaction mixture until no more hydrogen remained in the balloon. Empty balloon was replaced with a filled one and reaction mixture was then left to stir for 16 hours at ambient temperature. Reaction progress was checked via TLC (1/1 EtOAc/cyclohexane). Upon completion, reaction mixture was then bubbled with argon for 30 minutes, opened up and filtered through a pad of Celite. Filter cake was then washed multiple times with EtOAc and filtrate was then evaporated at reduced pressure. Residue was then taken up in DCM and deposited onto a Biotage® Sfär cartridge and subjected to column chromatography (0-100% EtOAc/cyclohexane) to yield diol **3** (112 mg, 70%) as a viscous transparent gum.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.59 (d, *J* = 7.9 Hz, 1H), 6.57 (d, *J* = 7.8 Hz, 1H), 3.87 – 3.70 (m, 2H), 3.35 (dt, *J* = 9.4, 3.9 Hz, 1H), 3.34 (brs, 1H), 3.04 (dd, *J* = 17.1, 9.7 Hz, 1H), 2.64 (brs, 1H), 2.62 (dd, *J* = 17.1, 3.9 Hz, 1H), 2.45 (dt, *J* = 9.7, 3.8 Hz, 1H), 2.02 – 1.92 (m, 1H), 1.76 – 1.67 (m, 1H), 1.66 (s, 6H), 1.27 (s, 3H), 1.05 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.1, 142.7, 142.3, 122.8, 117.7, 115.5, 107.0, 74.0, 61.0, 54.0, 43.0, 40.0, 30.5, 29.5, 26.1, 26, 24.3.

HRMS (ESI): Calcd for $C_{17}H_{24}O_4$, $[M+Na]^+$: 315.1567, found: 315.1566.

IR (neat), ν (cm^{-1}): 3337, 2933, 1469, 1376, 1247, 1012.

Rf: 0.15 (50% EtOAc in cyclohexane)

This reaction was also performed with (*S,R*)-**22** on 70 mg scale to yield 35 mg (78%) of (*S,R*)-**3**.

$[\alpha]_D^{25}$ = +30° (c = 1, $CHCl_3$)

Chiral HPLC data: Chiralpak OD-H column 4.6 x 250 mm, 80/20 heptane/isopropanol, 1 mL/min, 207 nm, t_R(minor, S) = 4.1 min, t_R(major, R) = 4.6 min, 98:2 e.r.

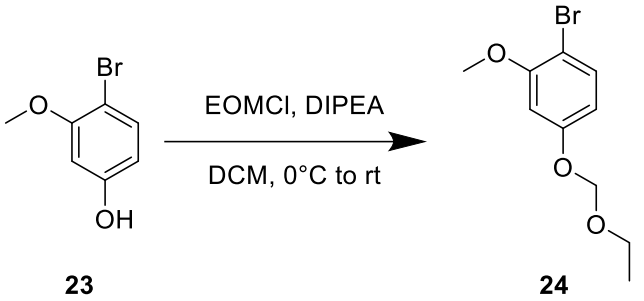
Notes:

- Diol **3** is a liquid with high viscosity. It was found that during evaporation this compound tends to form light foam, which spread the compound over the drying apparatus. It is recommended to dry this compound via gradual application of vacuum.
- The starting material is not soluble in MeOH, a more common hydrogenation solvent.

5. Towards (+)–indidene C

5.1 Synthesis of boronate **13**

1-bromo-4-(ethoxymethoxy)-2-methoxybenzene (methoxybromide 24)



23 **24**

In a 100 mL round-bottom flask equipped with a PTFE-covered magnetic stirrer phenol **23** (2.5 g, 12.3 mmol, 1 eq) was charged and dissolved in DCM (25 mL). Stirring was engaged and reaction mixture is cooled to 0°C (ice bath), after which DIPEA (3.44 mL, 19.7 mmol, 1.6 eq) is added, followed by slow addition of EOMCl (1.5 mL, 16 mmol, 1.3 eq). Reaction mixture was then stirred overnight at ambient temperature. The course of reaction was monitored by TLC (20% EtOAc in cyclohexane). Upon completion, pending reaction mixture was diluted with water and vigorously stirred. Formed mixture was then transferred to a separatory funnel and the layers were separated. Aqueous layer was washed twice more with DCM (2x25 mL). Combined organic layer was additionally washed with brine, dried over Na_2SO_4, filtered and evaporated at reduced pressure. Residue was then deposited onto a Biotage® Sfär cartridge and subjected to column chromatography (0-20% EtOAc/cyclohexane) to yield methoxybromide **24** (2.4 g, 75%) as a faintly yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.7 Hz, 1H), 6.63 (d, *J* = 2.7 Hz, 1H), 6.57 (dd, *J* = 8.7, 2.7 Hz, 1H), 5.20 (s, 2H), 3.87 (s, 3H), 3.72 (q, *J* = 7.1 Hz, 2H), 1.22 (t, *J* = 7.1 Hz, 3H).

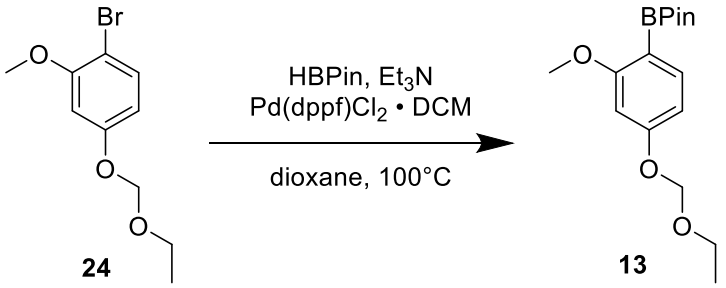
^{13}C NMR (126 MHz, $CDCl_3$) δ 158.1, 156.7, 133.3, 109.1, 103.6, 101.7, 93.5, 64.5, 56.3, 15.2.

HRMS (ESI): calcd. for $C_{10}H_{13}BrO_3Ag$ $[M+Ag]^+$: 368.9079, found 368.9076.

IR (neat), v (cm^{-1}): 2977, 1604, 1350, 1255, 1145, 1005.

Rf: 0.5 (20% EtOAc in cyclohexane).

2-(4-(ethoxymethoxy)-2-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (boronate 13)



To a 30 mL oven-dried microwave vial (Biotage) methoxybromide **24** (1.25 g, 4.8 mmol, 1 eq) was deposited and vial was introduced into the glovebox, where Pd(dppf)Cl2 • DCM (196 mg, 0.24 mmol, 0.05 eq) was added. Vial was then capped with a crimp cap with a septum and taken out from the glovebox. After cooling to 0°C (ice bath) and engagement of stirring, dioxane (9.6 mL, 0.05 M) and triethylamine (3.33 mL, 24 mmol, 5 eq) were added. This was followed by HBPin (2.1 mL, 14.4 mmol, 3 eq), that was added dropwise (caution: heavy effervescence is possible). Reaction was then prestirred at ambient temperature for 5 minutes, after which the mixture was subjected to heating at 100°C overnight. The reaction mixture turns dark pink within few minutes of heating.

Upon aging, reaction mixture was cooled to room temperature and then subsequently cooled to 0°C (ice bath). Methanol is added dropwise (careful, vigorous effervescence) until no gas evolution is witnessed. Resulting mixture was transferred into a round-bottom flask and was evaporated at reduced pressure. Remaining residue was dry-loaded onto silica and subjected to column chromatography (0-10% EtOAc in cyclohexane) to yield boronate **13** (670 mg, 45%) as a viscous oil which solidified into light brown crystals upon standing.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.2 Hz, 1H), 6.63 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.53 (d, *J* = 2.1 Hz, 1H), 5.24 (s, 2H), 3.81 (s, 3H), 3.72 (q, *J* = 7.1 Hz, 2H), 1.33 (s, 12H), 1.21 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 161.5 138.3, 107.2, 99.7, 93.0, 83.3, 64.5, 56.0, 24.9, 15.2.

HRMS (ESI): Calcd for $C_{16}H_{25}BO_5$, $[M+Na]^+$: 331.1687, found: 331.1692.

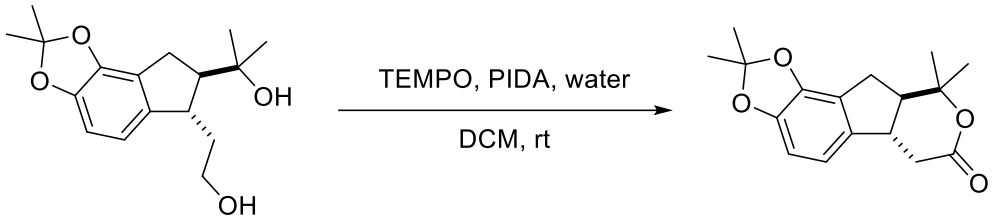
IR (neat): 2977, 1600, 1419, 1349, 1162, 1010.

Rf: 0.28 (20% EtOAc in cyclohexane)

Mp: 58°C

5.2 Synthesis of bromolactone **13**

(5bS,9aR)-2,2,9,9-tetramethyl-5b,9,9a,10-tetrahydro-[1,3]dioxolo[4',5':4,5]indeno[2,1-c]pyran-7(6H)-one (lactone 16)



3 **16**

In a 25 mL round-bottom flask equipped with a PTFE-coated magnetic stirbar diol **3** (110 mg, 0.375 mmol, 1 eq) was deposited and dissolved in DCM (6 mL) and water (0.75 mL). Stirring was engaged, and TEMPO (18 mg, 0.112 mmol, 0.3 eq) was added, followed by (diacetoxyiodo)benzene (302 mg, 0.938 mmol, 2.5 eq). Following mixture was then stirred vigorously at ambient temperature overnight. Completion of reaction was monitored via TLC (1/1 EtOAc/cyclohexane). Upon completion, reaction mixture was diluted with water (10 mL) and DCM (4 mL). After mixing, the layers were separated and the organic layer was dried over Na_2SO_4, filtered and evaporated at reduced pressure. Leftover residue was then redissolved in DCM, dry-loaded onto silica and subjected to column chromatography (0-100% ethyl acetate in cyclohexane) to yield lactone **16** (82 mg, 76%) as a pale yellow solid.

^{1}H NMR (500 MHz, CDCl3) δ 6.60 (dd, J = 7.7, 0.8 Hz, 1H), 6.54 (dd, J = 7.7, 1.3 Hz, 1H), 3.30 – 3.17 (m, 2H), 2.97 (dd, J = 14.7, 7.0 Hz, 1H), 2.55 (ddt, J = 14.7, 11.8, 1.0 Hz, 1H), 2.51 – 2.43 (m, 1H), 2.21 (td, J = 12.0, 7.0 Hz, 1H), 1.68 (s, 3H), 1.67 (s, 3H), 1.52 (s, 3H), 1.47 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 147.2, 143.5, 138.1, 121.7, 118.2, 114.4, 106.8, 85.1, 55.1, 39.8, 36.7, 29.9, 28.9, 26.1, 26.1, 23.5.

HRMS (ESI): Calcd for $C_{17}H_{20}O_4$, $[M+Na]^+$: 311.1254, found 311.1251.

IR (neat), v (cm^{-1}): 2992, 1707, 1463, 1244, 1099, 960.

Rf: 0.23 (20% EtOAc in cyclohexane).

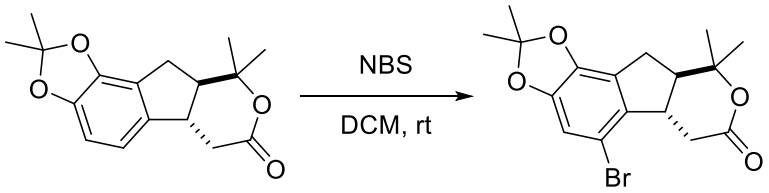
Mp: 165 °C

This reaction was also performed with (*S,R*)-**3** on 29 mg scale to yield 20 mg (70%) of (*S,R*)-**27**.

$[\alpha]_D$ = 1.6° (c = 1, $CHCl_3$)

Chiral HPLC data: Chiralpak OD-H column 4.6 x 250 mm, 90/10 heptane/isopropanol, 1 mL/min, 205 nm, t_R(minor, R,S) = 11.7 min, t_R(major, S,R) = 13.7 min, 97:3 e.r.

(5bS,9aR)-5-bromo-2,2,9,9-tetramethyl-5b,9,9a,10-tetrahydro-[1,3]dioxolo[4',5':4,5]indeno[2,1-c]pyran-7(6H)-one (bromolactone 13)



16 **13**

To a 10 mL oven-dried threaded culture tube equipped with a PFTE-coated magnetic stirbar lactone **16** (82 mg, 0.284 mmol, 1 eq) was deposited and dissolved in DCM (2.8 mL, 0.1M). NBS (56 mg, 0.313 mmol, 1.1 eq) was added in one portion and the reaction vessel was capped. Stirring was continued overnight at ambient temperature. Upon aging, reaction mixture was quenched with saturated aqueous sodium thiosulfate (3 mL) and futher diluted with water (2 mL) and DCM (2 mL). Resulting mixture was mixed, after which layers were separated. Aqueous layer was additionally washed twice with DCM. Combined organics were then washed with brine three times, dried over Na_2SO_4 and evaporated at reduced pressure to yield bromolactone **13** (90 mg, 86%) as a yellow powder which was used further without additional purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (s, 1H), 3.80 (dd, *J* = 17.9, 5.1 Hz, 1H), 3.34 (td, *J* = 12.3, 5.3 Hz, 1H), 2.98 (dd, *J* = 14.8, 7.2 Hz, 1H), 2.61 (dd, *J* = 17.9, 12.5 Hz, 1H), 2.55 – 2.48 (m, 1H), 2.28 (td, *J* = 12.1, 7.2 Hz, 1H), 1.67 (s, 6H), 1.51 (s, 3H), 1.45 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 148.2, 143.3, 135.7, 123.7, 119.7, 111.2, 108.5, 83.9, 54.6, 41.7, 38.1, 29.8, 29.1, 26.1, 26, 23.3.

HRMS (ESI): Calcd for $C_{17}H_{19}BrO_4$, $[M+Na]^+$: 389.0359, found: 389.0356.

IR (neat), v (cm^{-1}): 2979, 1722, 1471, 1244, 1106.

Rf: 0.2 (20% EtOAc in cyclohexane)

Mp: 190 °C

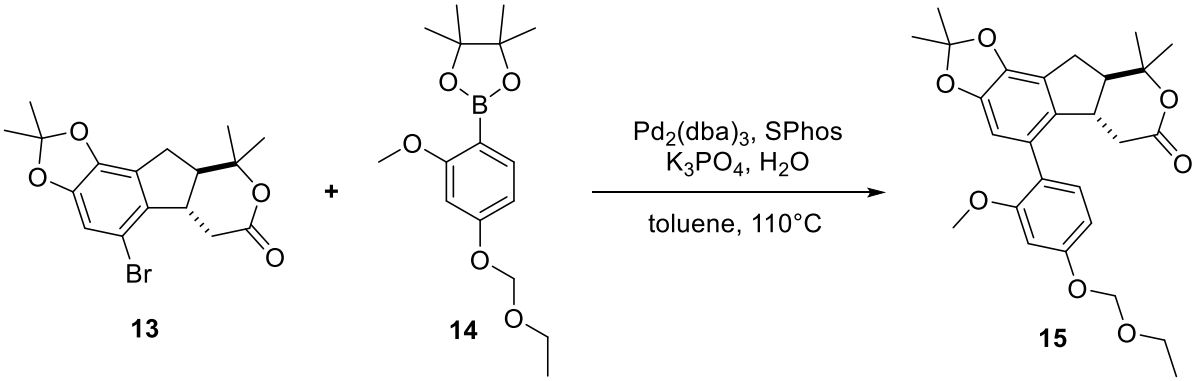
This reaction was also performed with (*S,R*)-**16** on 15 mg scale to yield 14 mg (73%) of (*S,R*)-**13**.

$[\alpha]_D$ = 64.2° (c = 1, $CHCl_3$)

Chiral HPLC data: Chiralpak IA column 4.6 x 250 mm, 90/10 heptane/isopropanol, 1 mL/min, 204 nm, t_R(minor, R,S) = 8.3 min, t_R(major, S,R) = 9.4 min, 99:1 e.r.

5.3 Suzuki-Miyaura coupling – biphenyl **15**

(5bS,9aR)-5-(4-(ethoxymethoxy)-2-methoxyphenyl)-2,2,9,9-tetramethyl-5b,9,9a,10-tetrahydro-[1,3]dioxolo[4',5':4,5]indeno[2,1-c]pyran-7(6H)-one (biphenyl 15)



To an oven-dried microwave (Biotage) 10 mL vial equipped with a PTFE-coated magnetic stirbar bromolactone **13** (36.8 mg, 0.1 mmol, 1 eq) was deposited, followed by potassium phosphate (63.8 mg, 0.3 mmol, 3 eq) and boronate **14** (37.1 mg, 0.12 mmol, 1.2 eq). The vessel was introduced into a glovebox, where $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol, 5% mol) and SPhos (8.2 mg, 0.02 mmol, 20% mol) were added, followed by toluene (1.2 mL). Reaction was then capped with a crimp cap and taken out from the glovebox, after which degassed water (0.12 mL) was added. Resulting mixture was then stirred vigorously at 110°C overnight in an aluminium heating block. Upon aging, reaction mixture was cooled to room temperature and diluted with water (5 mL) and EtOAc (4 mL). The layers were mixed via stirring and separated in a separatory funnel. Aqueous layer was additionally washed twice more with EtOAc and combined organic layer was washed once with brine, dried over Na_2SO_4 and evaporated at reduced pressure. Residue was then taken up in DCM and dry-loaded onto silica, which then was subjected to column chromatography (0-50% EtOAc in cyclohexane) to yield biphenyl **15** (38 mg, 81%) as a beige solid. The compound is present as two rotamers in 6:4 ratio.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (d, *J* = 8.3 Hz, 0.6H, major), 6.93 (dt, *J* = 8.2, 1.0 Hz, 0.4H, minor), 6.70 – 6.63 (m, 1.4H), 6.61 (d, *J* = 2.3 Hz, 0.6H, major), 6.52 (s, 1H, minor), 6.47 (s, 1H, major), 5.29 – 5.22 (m, 2H), 3.82 – 3.74 (m, 2H), 3.78 (s, 2H, major), 3.75 (s, 1H, minor), 3.36 (ddt, *J* = 19.0, 12.9, 6.1 Hz, 2H), 2.97 (ddd, *J* = 14.6, 7.1, 2.7 Hz, 2H), 2.57 (ddd, *J* = 14.6, 12.0, 9.4 Hz, 2H), 2.37 (ddd, *J* = 28.1, 18.0, 5.1 Hz, 2H), 2.20 (dtd, *J* = 24.3, 12.1, 7.1 Hz, 1H), 2.11 (dd, *J* = 18.0, 12.5 Hz, 0.4H, minor), 1.98 (dd, *J* = 18.0, 12.5 Hz, 0.6H, major), 1.71 (s, 2H, minor), 1.69 (s, 4H, major), 1.48 (s, 3H), 1.46 (s, 2H. major), 1.44 (s, 1, minor), 1.27 (td, *J* = 7.1, 2.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3 (major), 171.3 (minor), 158.7 (major), 158.6 (minor), 157.7 (minor), 157.5 (major), 146.9 (major), 146.7 (minor), 142.6 (major), 142.6 (minor), 136.5 (major), 135.7 (minor), 131.6 (major), 131.1 (minor), 127.2 (minor), 127.2 (major), 122.6 (major), 122.2 (minor), 121.8 (minor), 121.4 (major), 118.4 (major), 118.4 (minor), 109.5 (minor), 109.1 (major), 107.5 (major), 107.1 (minor), 100.6 (minor), 100.0 (major),

93.5 (major), 93.4 (minor), 84.4 (major), 84.3 (minor), 64.6, 55.7 (major), 55.6 (minor), 55.0 (minor), 54.9 (major), 40.8 (major), 40.0 (minor), 37.0 (major), 36.9 (minor), 29.8, 28.7, 26.2 (minor), 26.2 (major), 26.2, 23.3 (major), 23.3 (minor), 15.3.

HRMS (ESI): Calcd for $C_{27}H_{32}O_7$, $[M+Na]^+$: 491.2040, found: 491.2048.

IR (neat), v (cm^{-1}): 2977, 1721, 1476, 1254, 1101, 1017.

Rf: 0.1 (20% EtOAc in cyclohexane)

Mp: 185 °C

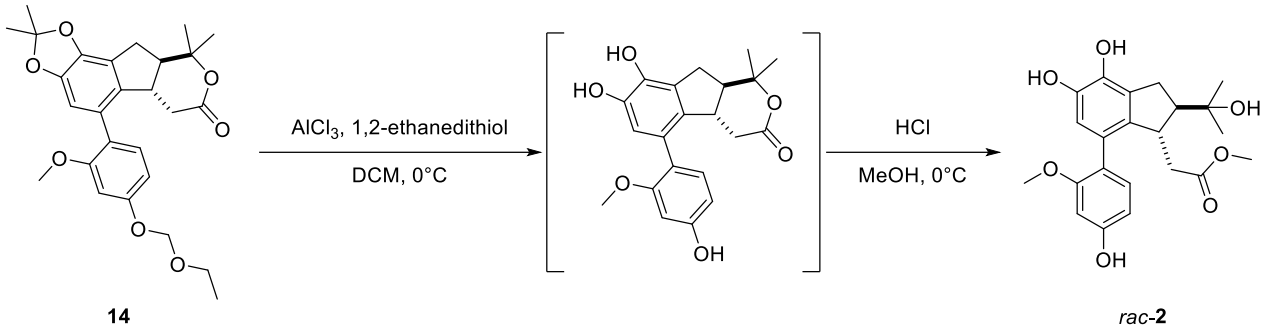
This reaction was also performed with (S,R)-**12** on a 10 mg scale to yield 7.7 mg (60%) of (S,R)-**14**.

$[\alpha]_D$ = 27.9° (c = 0.77, $CHCl_3$)

Chiral HPLC data: Chiralpak OD-H column 4.6 x 250 mm, 80/20 heptane/isopropanol, 1 mL/min, 224 nm, t_R(minor, R,S) = 10.1 min, t_R(major, S,R) = 14.4 min, , 99:1 e.r.

5.4 Deprotection protocol

Indidene C (2)



To an oven-dried microwave (Biotage) 30 mL vial equipped with a PTFE-coated magnetic stirbar biphenyl **15** (46.8 mg, 0.1 mmol, 1 eq) is deposited, followed by 1,2-ethanedithiol (84 µL, 1 mmol, 10 eq). This residue was dissolved in dry DCM (10 mL) and cooled to 1 °C (ice bath, temperature monitored with a thermocouple). To this mixture under stirring aluminium chloride (53 mg, 0.4 mmol, 4 eq) is added in one portion. Reaction mixture is then capped and stirred at the same temperature for 1 h. After aging, 3M solution of HCl in MeOH (10 mL) is added in one portion under cooling and the temperature was maintained at 1-3 °C (ice bath, temperature monitored with a thermocouple). After 1 h, reaction mixture was quenched at this temperature with sat. aq. $NaHCO_3$ until pH = ~9. Reaction mixture is then transferred to a separatory funnel, where EtOAc (30 mL) and water (30 mL) are added. After vigorous mixing and layer separation, aqueous layer was washed twice more with EtOAc (30 mL). Combined organic layer was collected, dried over Na_2SO_4 and evaporated at reduced pressure. Residue was then taken up in EtOAc and dry-loaded onto silica, which then was subjected to column chromatography (10-100% EtOAc in cyclohexane) to yield indidene C *rac*-**2** (32 mg, 79%) as a beige solid.

^{1}H NMR (500 MHz, MeOD) δ 6.89 (d, *J* = 8.1 Hz, 1H), 6.48 (d, *J* = 2.3 Hz, 1H), 6.43 (s, 3H), 6.40 (dd, *J* = 8.1, 2.3 Hz, 1H), 3.72 (s, 3H), 3.50 (s, 3H), 3.47 (ddd, *J* = 10.2, 3.5, 1.7 Hz, 1H), 3.00 – 2.94 (m, 2H), 2.21 (ddd, *J* = 6.2, 4.8, 1.7 Hz, 1H), 2.15 (dd, *J* = 15.1, 3.6 Hz, 1H), 2.04 (dd, *J* = 15.1, 10.2 Hz, 1H), 1.13 (s, 3H), 1.05 (s, 3H).

^{13}C NMR (126 MHz, MeOD) δ 173.8, 157.7, 157.3, 143.5, 139.5, 136.5, 131.2, 129.2, 126.5, 121.1, 116.0, 106.7, 98.7, 72.7, 54.6, 54.2, 50.4, 43.3, 39.3, 29.4, 25.6, 24.7.

HRMS (ESI): Calcd for $C_{27}H_{32}O_7$, $[M+Na]^+$: 491.2040, found: 491.2048.

IR (neat), ν (cm^{-1}): 3978, 1705, 1608, 1498, 1447, 1293, 1200, 1113, 1038.

Rf: 0.51 (EtOAc)

Mp: 219 °C (decomposition)

This reaction was also performed with (*S,R*)-**14** on a 7.7 mg scale to yield 7 mg (99%) of (*S,R*)-**2.**

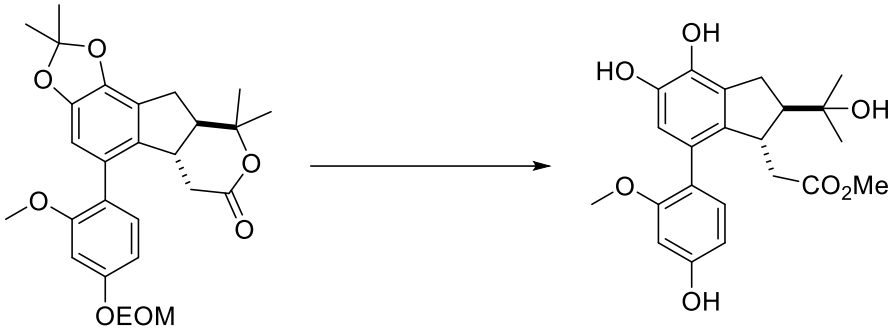
$[\alpha]_D$ = 18.6° (c = 0.4, MeOH)

Chiral HPLC data: Chiralpak AD-H column 4.6 x 250 mm, 80/20 heptane/isopropanol, 1 mL/min, 204 nm, t_R(minor, R,S) = 11.1 min, t_R(major, S,R) = 14.4 min, 99:1 e.r.

6.5 Discussion on a deprotection step of indidene C

As was mentioned in the main text, the deprotection of biphenyl **15** turned out to be a non-trivial task. This global deprotection needed three events to occur simultaneously: the deprotection of the acetonide, of mixed acetal and the opening of the lactone to furnish methyl ester. All of these events are possible under the conditions of an acidic hydrolysis, thus we focused on acidic conditions for the deprotection. This was, unfortunately, accompanied by degradation of the indane core, which turned out to be unstable under acidic conditions. Therefore, a careful balance must be stricken. We probed deprotection by subjecting small quantities (1-5 mg) of the biphenyl (±)-**15** to the conditions listed and then analysing the crude after usual work-up (sat. $NaHCO_3$/EtOAc extraction) for the presence of listed protecting groups (Table 5.5.1).

Table 5.5.1. Initial deprotection attempts.

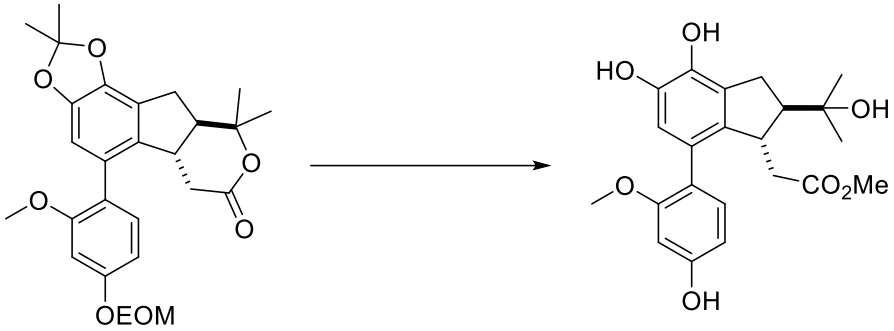


#	Conditions	Moiety **removed**/**not removed**/**partially removed**				Comment
		acetonide	EOM	lactone	Core deg.	
1[a]	0.021M soln. in 1.5M HCl/MeOH/CPME, 100°C, o/n					Core degradation, but everything is removed. Septum burst.
2	0.021M soln. in 1.5M HCl/MeOH, reflux, o/n					
3	0.021M soln. in 3M HCl/MeOH, rt, o/n					
4	0.1M soln. in MeOH, 2 eq MeONa, 1h reflux					Just degradation.
5[b]	0.01M soln. in 1M HCl/MeOH, 0°C, 2h					Both EOM and lactone are easily dealt.
6	0.01M soln. in 3M HCl/MeOH, 0°C, 1h					
7	0.01M soln. in 3M HCl/MeOH, 0°C, 14h					
8	0.01M soln. in 3M HBr/AcOH/MeOH, 0°C, 14h					Positive ID on ^{1}H, ^{13}C.
9[c]	0.01M soln. in 3M HBr/AcOH/MeOH, 0°C, 14h					

[a] 5 mg scale. [b] 1 mg scale. [c] 2.5 mg scale.

We initially identified our first hit with conditions #9, however it turned out to be non-scalable – esterless material was furnished on scale-up instead (Table 5.5.2).

Table 5.5.2. Initial hit validation.

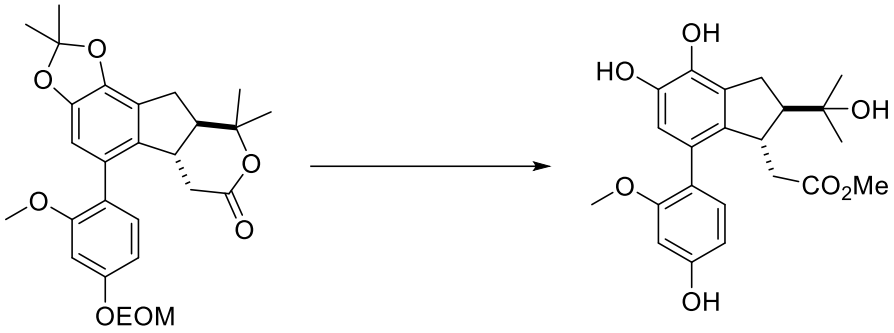


#	Conditions	Moiety **removed**/**not removed**/**partially removed**				Comment
		acetonide	EOM	lactone	Core deg.	
1[a]	0.1 eq $NaBAr^F$, 0.01 M aq. THF, rt and reflux					
2	0.1 eq $NaBAr^F$, 0.01 M aq. MeOH, rt and reflux					No reaction.
3	0.01M soln. in 3M HCl/MeOH, 50°C, 15 mins					Some nat. prod. observed, mostly deg.
4	0.01M soln. in 3M HCl/MeOH, 50°C, 5 mins					Only partial removal of acetonide, deg.
5[b]	0.01M soln. in 3M HBr/AcOH/MeOH, 0°C, 14h					32% isolated yield of esterless material.

[a] 1 mg scale. [b] 10 mg scale.

While opening of the lactone and removal of the EOM turned out to be facile, removal of acetonide was associated with difficulties due to its low reactivity towards acid hydrolysis. Therefore, we turned our attention to trans-ketalization protocols that made use of Lewis acids and dithiols. This was immediately successful with the conditions similar to that of the deprotection of Indidene A and resulted in an overall deprotection that constituted the final method (Table 5.5.3).

Table 5.5.3. Finalization of the conditions.



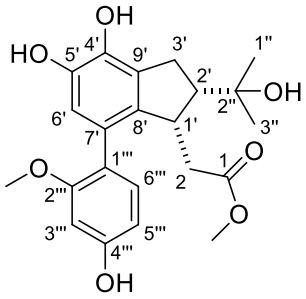
#	Conditions	Moiety **removed**/**not removed**/**partially removed**				Comment
		acetonide	EOM	lactone	Core deg.	
1[b]	4 eq $AlCl_3$, 10 eq 1,2-ethanedithiol, 0.01M DCM, 0 °C, work-up then HCl/MeOH					
2[a]	As above, HCl/MeOH before work-up.					
3	4 eq $SnCl_2$, 10 eq 1,2-ethanedithiol, 0.01M DCM, 0 °C					
4	1 eq $AlCl_3$, 10 eq 1,2-ethanedithiol, 0.01M DCM, 0 °C					No reaction.
5[d]	4 eq $AlCl_3$, 10 eq 1,2-ethanedithiol, 0.01M DCM, 0 °C, work-up then HCl/MeOH, extraction with DCM					Low recovery – only 7% yield
6[d]	As above, extraction with EtOAc, $AlCl_3$ new.					50% yield.
7	4 eq $AlCl_3$, 10 eq 1,2-ethanedithiol, 0.01M DCM, 0 °C, then HCl/MeOH, then work-up extraction with EtOAc					80% yield.
8	As above, 20 mg scale					~80% yield.
9	0.1 mmol scale					Final conditions. 79% yield.

[a] 1 mg scale. [b] 2.5 mg scale. [c] 5 mg scale. [d] 10 mg scale.

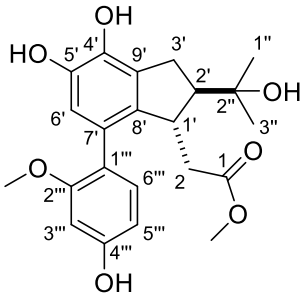
5.6 Comparison of the synthetic sample with the natural one

^{1}H and ^{13}C NMR comparison:

Table 5.6.1. Comparison table for NMR data of synthetic sample and reported material for indidenes B and C.



Indidene B



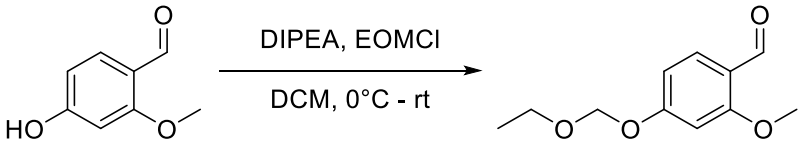
Indidene C

Atom position	Synthetic sample		Indidene B[5]		Indidene C[5]	
	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)
1	175.2		175		175	
2	40.69	2.15 (dd, 15.1, 3.5) 2.04 (dd, 15.1, 10.2)	40.63	2.16, dd (15.1, 3.4) 2.06, dd (15.1, 10.3)	40.6	2.14, dd (15.0, 3.5) 2.02, dd (15.0, 10.2)
1’	44.70	3.47 (ddd, 10.2, 3.5, 1.7)	44.61	3.47, ddd (10.3, 3.4, 1.6)	44.57	3.47, ddd (10.2, 3.5, 1.5)
2’	56.0	2.21 (dt, 4.8, 1.7)	56.0	2.22, dt (5.3, 1.6)	56.0	2.22, dt (5.3, 1.5)
3’	30.8	2.96 (d, 5.3)	30.8	2.98, d (5.3)	30.8	2.96, d (5.3)
4’	140.9		140.9		140.9	
5’	144.9		144.9		144.9	
6’	117.4	6.43, s	117.3	6.45, s	117.3	6.43, s
7’	127.9		127.9		127.9	
8’	137.9		137.8		137.8	
9’	130.6		130.6		130.6	
1’’	27.0	1.13, s	27.0	1.13, s	27.0	1.13, s
2’’	74.1		74.1		74.1	
3’’	26.1	1.05, s	26.1	1.04, s	26.1	1.04, s
1’’’	122.5		122.4		122.4	
2’’’	158.8		158.7		158.7	
3’’’	100.1	6.48 (d, 2.3)	100.1	6.50, d (1.7)	100.1	6.48, d (1.7)
4’’’	159.1		159.0		159.0	
5’’’	108.1	6.40 (dd, 8.2, 2.3)	108	6.42, dd (8.1, 1.7)	108	6.41, dd (8.1, 1.7)
6’’’	132.6	6.89 (d, 8.1)	132.6	6.90, d (8.1)	132.6	6.89, d (8.1)
CH_3-O-2’’’	55.6	3.72, s	55.6	3.73, s	55.6	3.72, s
CH_3-O-1	51.9	3.50, s	51.9	3.51, s	51.9	3.51, s

6. Divergence towards (±)–indidene A

6.1 Synthesis of a triflate **17**

4-(ethoxymethoxy)-2-methoxybenzaldehyde (aldehyde 26)



25 **26**

To a 100 mL round-bottom flask equipped with a PTFE-coated magnetic stirbar aldehyde **25** (2 g, 13.1 mmol, 1 eq) was charged, followed by DCM (27 mL). Reaction mixture was then cooled to 0°C (ice bath) and DIPEA (1.83 mL, 10.5 mmol, 1.6 eq) was added, followed by a slow addition of EOMCl (1.6 mL, 17.1 mmol, 1.3 eq). Resulting mixture was then stirred at ambient temperature for 16 hours. Completion was monitored via TLC (1/4 EtOAc/cyclohexane). Upon completion, reaction mixture was diluted with water and DCM, which was followed by vigorous stirring, followed by a transfer to a separatory funnel. After separation of the formed layers, aqueous layer was washed once with DCM and combined organic layer was washed with brine. Organic layer was then dried over Na_2SO_4, filtered and evaporated at reduced pressure to afford aldehyde **26** (2.66 g, 96%) as a light brown liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.30 (d, *J* = 0.8 Hz, 1H), 7.79 (d, *J* = 8.7 Hz, 1H), 6.68 (ddd, *J* = 8.6, 2.2, 0.8 Hz, 1H), 6.60 (d, *J* = 2.2 Hz, 1H), 5.28 (s, 2H), 3.90 (s, 3H), 3.73 (q, *J* = 7.1 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H).

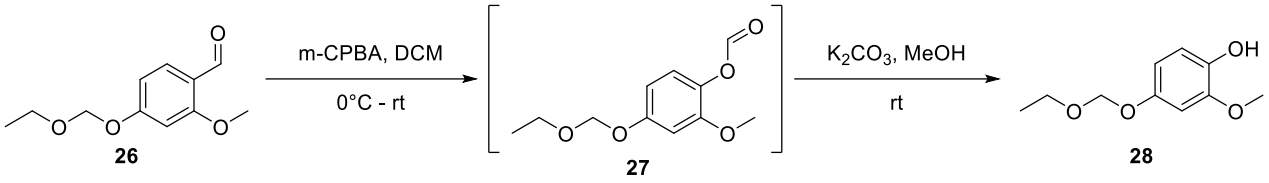
^{13}C NMR (126 MHz, $CDCl_3$) δ 188.6, 164.1, 163.7, 130.7, 119.7, 108.3, 99.6, 93.0, 64.9, 55.8, 15.2.

HRMS (ESI): calcd for $C_{11}H_{14}O_4Na$, $[M+Na]^+$: 233.0784, found 233.0784.

IR (neat), ν (cm^{-1}): 2977, 1678, 1602, 1465, 1261, 1104, 995.

Rf: 0.3 (20% EtOAc in cyclohexane).

4-(ethoxymethoxy)-2-methoxyphenol (monophenol 28)



To a 250 mL round-bottom flask equipped with a PTFE-coated magnetic stirbar aldehyde **26** (2.66 g, 12.7 mmol, 1 eq) was charged, followed by DCM (60 mL). Stirring was engaged and reaction mixture was cooled to 0°C (ice bath), after which m-CPBA (77% purity, 4.25 g, 19 mmol, 1.5 eq) was added portionwise. Reaction mixture is then left stirring vigorously for 5 hours at ambient temperature. Precipitation is observed after ca. 30 minutes. Reaction progress is monitored via TLC (1/4 EtOAc/cyclohexane). Upon completion, reaction mixture is quenched by slow addition of saturated aqueous sodium thiosulfate, followed by saturated sodium bicarbonate. Obtained mixture was stirred vigorously, after which it was transferred to a separatory funnel. Organic layer was collected and aqueous layer was washed twice with DCM. Combined organic layers were then washed with aqueous saturated sodium bicarbonate, twice with brine, dried over Na_2SO_4, filtered and evaporated at reduced pressure to afford product of Bayer-Villiger rearrangement formate **27** as a yellow oil.

The vessel containing this oil is then charged with a PTFE-coated magnetic stirbar and methanol (64 mL), followed by potassium carbonate (3.5 g, 25.3 mmol, 2 eq). Reaction mixture was then stirred vigorously for 16 hours at ambient temperature. A color change is observed from yellow to dark-brown within one hour. Reaction progress is monitored via TLC (1/4 EtOAc/cyclohexane). After completion, reaction mixture was acidified with 1M HCl until slightly acidic (pH 5-6) to dissolve all suspended solids and ethyl acetate was charged. Reaction mixture was then stirred vigorously and transferred to a separatory funnel, where layers were separated. Aqueous layer was then washed twice with EtOAc; combined organic layers are washed once with brine, dried over Na_2SO_4, filtered and evaporated at reduced pressure. Remaining residue was then dry-loaded onto Celite and subjected to column chromatography (0-20% EtOAc in cyclohexane) to yield monophenol **28** (1.76 g, 70% over two steps) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (d, *J* = 8.7 Hz, 1H), 6.63 (d, *J* = 2.7 Hz, 1H), 6.57 (dd, *J* = 8.7, 2.7 Hz, 1H), 5.27 (s, 1H), 5.15 (s, 2H), 3.87 (s, 3H), 3.74 (q, *J* = 7.1 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H).

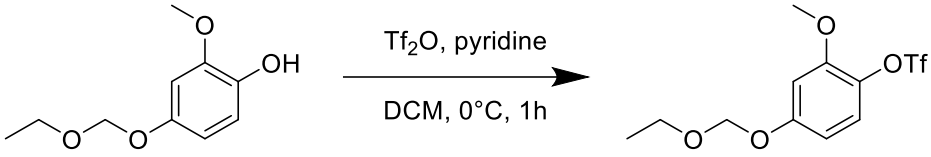
^{13}C NMR (126 MHz, $CDCl_3$) δ 151.3, 147.0, 140.8, 114.4, 108.4, 101.5, 94.3, 64.2, 56.1, 15.3.

HRMS (ESI): calcd. for $C_{10}H_{13}O_4$ $[M]^-$: 197.0819, found 197.0820.

IR (neat), v (cm^{-1}): 3423, 2976, 1738, 1612, 1512, 1230, 1152, 1011.

Rf: 0.28 (20% EtOAc in cyclohexane)

4-(ethoxymethoxy)-2-methoxyphenyl trifluoromethanesulfonate (triflate 17)



28 **17**

To a 50 mL round-bottom flask equipped with a PTFE-coated magnetic stirbar monophenol **28** (300 mg, 1.5 mmol, 1 eq) was charged and diluted with DCM (17.5 mL). Stirring was engaged and reaction mixture was cooled to 0°C (ice bath), after which pyridine (0.24 mL, 3 mmol, 2 eq) was added, followed by slow addition of triflic anhydride (0.31 mL, 1.8 mmol, 1.2 eq). Upon addition, reaction mixture was stirred at this temperature for 1h. Completion was monitored via TLC (1/4 EtOAc/cyclohexane). Upon completion, reaction mixture was diluted with water and stirred vigorously. Resulting mixture was transferred to a separatory funnel, where layers were separated. Organic layer was additionally washed with saturated aqueous $NaHCO_3$ and brine. Resulting organic layer dried over Na_2SO_4, filtered and evaporated at reduced pressure to yield triflate **17** (465 mg, 93%) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.9 Hz, 1H), 6.71 (d, *J* = 2.7 Hz, 1H), 6.63 (dd, *J* = 9.0, 2.8 Hz, 1H), 5.21 (s, 2H), 3.88 (s, 3H), 3.73 (q, *J* = 7.1 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.1, 152.3, 133.5, 122.9, 118.9 (q, *J* = 320.5 Hz), 107.4, 102.2, 93.5, 64.7, 56.3, 15.2.

^{19}F NMR (471 MHz, $CDCl_3$) δ -73.9.

Elemental analysis, %: C: 40, H: 3.97 calc., C: 40.02, H: 3.88 found.

IR (neat), v (cm^{-1}): 2980, 2903, 1611, 1505, 1421, 1204.

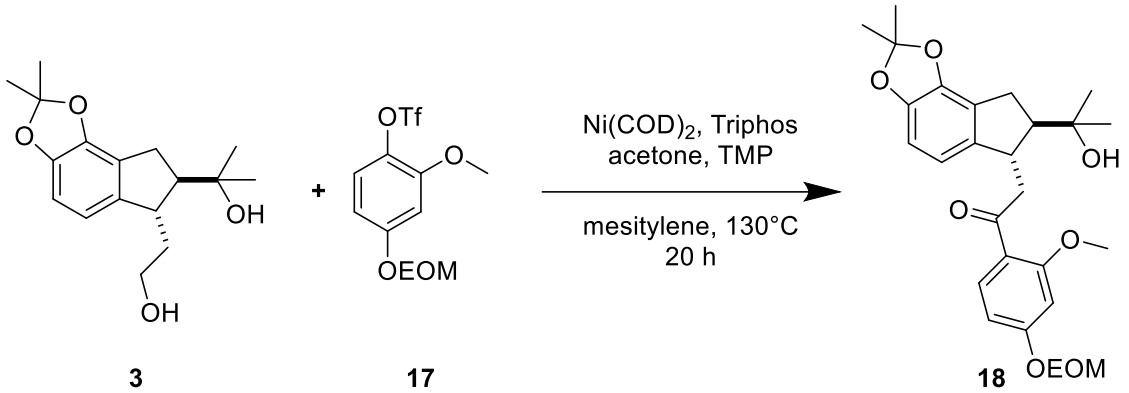
Rf: 0.46 (20% EtOAc in cyclohexane)

Notes:

- Attempt of column chromatorgraphy on this compound has resulted in a decomposition of the purified triflate **17** upon evaporation. The quality of triflate after work-up is generally good, therefore column chromatography or any other additional purification may be unneeded.

6.2 Ni^0-catalyzed dehydrogenative coupling

1-(4-(ethoxymethoxy)-2-methoxyphenyl)-2-((6S,7R)-7-(2-hydroxypropan-2-yl)-2,2-dimethyl-7,8-dihydro-6H-indeno[4,5-d][1,3]dioxol-6-yl)ethan-1-one (ketone 18)



3 **17** **18**

To an oven-dried 10 mL microwave (Biotage) vial diol **3** (29.2 mg, 0.1 mmol, 1 eq) is deposited via stock solution of DCM and evaporated. Triflate **17** (49.5 mg, 0.15 mmol, 1.5 eq) was then deposited. Vial was then introduced into the glovebox, where $Ni(COD)_2$ (2.8 mg, 0.01 mmol, 0.1 eq) and Triphos (7.5 mg, 0.012 mmol, 0.12 eq) were added, followed by addition of mesitylene (0.5 mL, 0.2M). Reaction mixture was capped with a septum crimp cap, reintroduced into the normal atmosphere and acetone (37 µL, 0.5 mmol, 5 eq) and 2,2,6,6-tetramethylpiperidine (34 µL, 0.2 mmol, 2 eq) were added. Reaction mixture was then homogenized by brief (<5 min) sonication and then subjected to stirring in an aluminium heating block heated to 130°C for 20 hours. Upon aging, reaction mixture was cooled to room temperature and was filtered through a silica gel plug. The plug is then washed multiple times with EtOAc to ensure recovery of the product. Recovered filtrate was then evaporated and residue then dry-loaded onto silica and deposited onto a Biotage® Sfär cartridge and subjected to column chromatography (0-100% EtOAc/cyclohexane) to yield ketone **18** (22 mg, 47%) as a yellow viscous oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.7 Hz, 1H), 6.68 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.61 – 6.51 (m, 3H), 5.26 (s, 2H), 3.84 (s, 3H), 3.83 – 3.79 (m, 1H), 3.73 (q, *J* = 7.1 Hz, 2H), 3.64 (brs, 1H), 3.32 (dd, *J* = 18.6, 4.6 Hz, 1H), 3.26 (dd, *J* = 18.6, 8.9 Hz, 1H), 3.04 (dd, *J* = 17.0, 9.2 Hz, 1H), 2.69 (dd, *J* = 17.0, 3.6 Hz, 1H), 2.33 (dt, *J* = 9.2, 3.4 Hz, 1H), 1.68 (s, 3H), 1.66 (s, 3H), 1.25 – 1.20 (m, 6H), 1.00 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.7, 162.6, 161.1, 146.2, 142.7, 141.9, 133.0, 123.2, 121.6, 117.7, 115.6, 108.0, 107.0, 100.0, 93.1, 73.0, 64.8, 56.8, 55.7, 51.9, 41.6, 30.3, 29.4, 26.1, 24.5, 15.2.

HRMS (ESI): Calcd for $C_{27}H_{34}O_7$, $[M+Na]^+$: 493.2197, found: 493.2200.

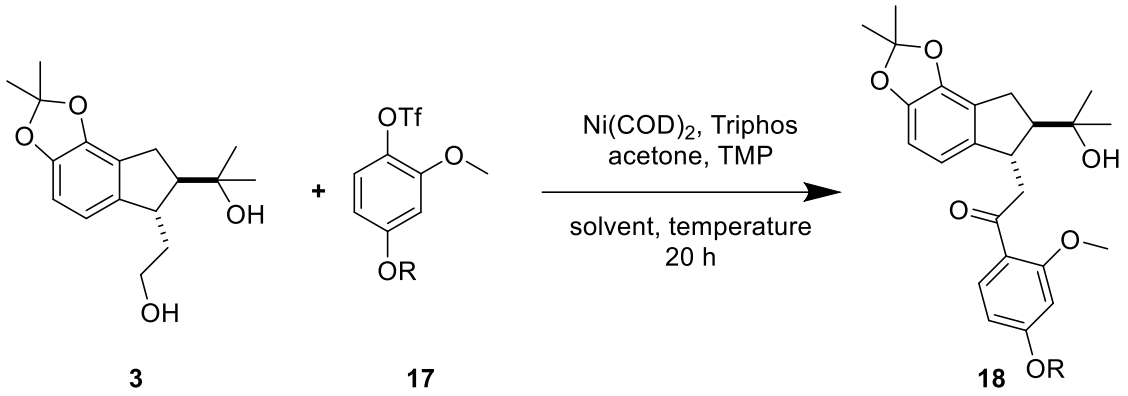
IR (neat), ν (cm^{-1}): 3001, 1634, 1444, 1376, 1039.

Rf: 0.17 (20% EtOAc in cyclohexane)

6.3 Discussion on Ni^0-catalyzed dehydrogenative coupling

Under original reaction conditions[6], there was a single example of a compound containing tertiary alcohol was described in intermediate yield. Given that and general unattractiveness of any other potential route variant involving 1,2-addition due to significant increase in step count, we attempted to engage diol **3** directly in the coupling. We were pleased to observe the formation of the desired product, albeit reaction turned out to be sensitive towards purity of reagents.

Table 5.3.1. Optimization of Ni-catalyzed dehydrogenative coupling.



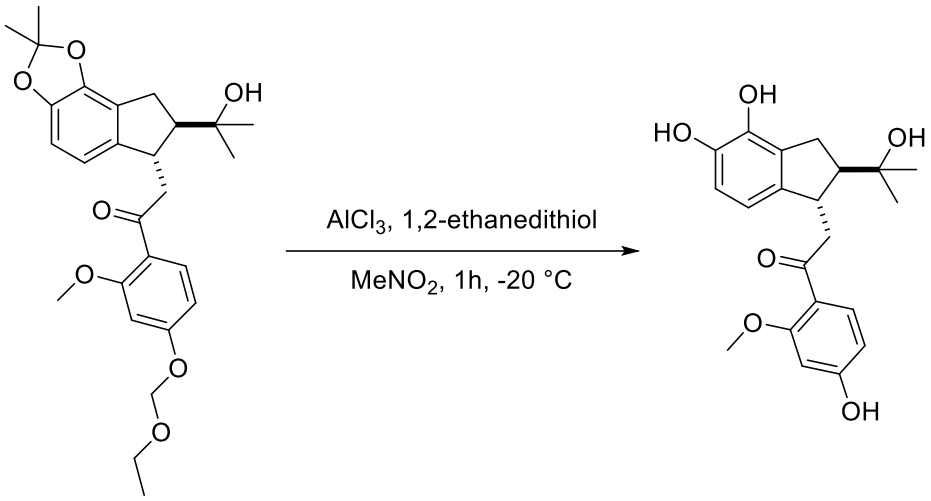
3 **17** **18**

#	R	Conditions/change*	Isolated yield **18**, %
1	Bn	**17** (1.5 eq), acetone (5 eq), TMP (2 eq), $Ni(COD)_2$ (10% mol), Triphos (12% mol), toluene, 130°C, 20 h	5
2		As above, mesitylene as solvent, TMP distilled (CaH_2) and degassed. Acetone distilled and degassed prior to use.	52
3		As above, 140°C	53
4		As entry 2, 3 eq **17**	41
5		As entry 2, 10 eq acetone	33
6		As entry 2, 0.2 mmol scale	50
7	EOM	Same as entry 2	47
8	EOM	Same as entry 2, 0.2 mmol scale	25

*All reactions performed at 0.1 mmol scale with [0.2M] concentration unless stated otherwise.

6.4 Deprotection towards (±)-indidene A

(±)-indidene A (*rac*-1)



18 *rac*-**1**

To an oven-dried microwave (Biotage) 10 mL vial equipped with a PTFE-coated magnetic stirbar ketone **18** (5 mg, 0.0106 mmol, 1 eq) is deposited, followed by 1,2-ethanedithiol (10 µL, 0.106 mmol, 10 eq). This residue was dissolved in dry $MeNO_2$ (0.2 mL) and cooled to -20 °C (30% aq. MeOH/dry ice). To this mixture under stirring aluminium chloride (12.8 mg, 0.0956 mmol, 9 eq) is added in one portion. Reaction mixture is then capped and stirred at the same temperature for 1 h. Upon aging, reaction was quenched with aq. sat. $NaHCO_3$ and diluted with EtOAc. After vigorous stirring and layer separation, aqueous layer was extracted twice more with EtOAc. United organic layer was dried over Na_2SO_4, filtered and evaporated at reduced pressure. Residue was then dryloaded onto silica and subjected to column chromatography (0-100% EtOAc in cyclohexane) to afford 1 mg (26%) of the title compound *rac*-**1** as a yellow gum.

^{1}H NMR (600 MHz, CD_3OD) δ 7.68 (d, *J* = 8.5 Hz, 1H), 6.55 (d, *J* = 8.0 Hz, 1H), 6.47 (d, *J* = 2.1 Hz, 1H), 6.46 – 6.40 (m, 2H), 3.85 (s, 3H), 3.63 (td, *J* = 6.8, 3.2 Hz, 1H), 3.27 – 3.14 (m, 2H), 2.98 (dd, *J* = 17.0, 9.0 Hz, 1H), 2.82 (dd, *J* = 17.0, 3.7 Hz, 1H), 2.25 (dt, *J* = 8.9, 3.6 Hz, 1H), 1.06 (s, 3H), 1.03 (s, 3H).

^{13}C NMR (151 MHz, CD_3OD) δ 202.5, 165.1, 163.0, 144.7, 141.9, 140.5 133.9, 130.6, 120.8, 115.8, 115.2, 109.0, 100.0, 74.0, 62.9, 57.0, 56.0, 52.8, 44.2, 31.2, 27.5, 26.4, 14.5.

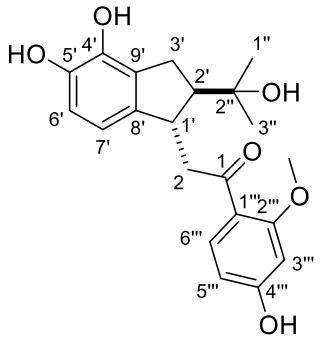
HRMS (ESI): Calcd for $C_{21}H_{24}O_6Na$, $[M+Na]^+$: 395.1465, found 395.1461.

IR (neat), ν (cm^{-1}): 3277, 2970, 1638, 1600, 1469, 1261, 1205, 1029.

Rf: 0.52 (100% EtOAc).

6.5 Comparison of the synthetic sample and a natural one

^{1}H and ^{13}C NMR comparison:



Indidene A

Atom position	Synthetic sample		Indidene A[5]	
	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)
1	202.4		202.5	
2	52.8	3.27-3.14 (m)	52.8	3.26 (m)
1’	44.2	3.63, td (6.8, 3.2)	44.2	3.64, td (6.8, 3.4)
2’	57.0	2.25, dt, (8.9, 3.6)	57.0	2.26, dt (8.9, 3.7)
3’	31.2	2.98, dd (17.0, 9.0) 2.82, dd (17.0, 3.7)	31.2	2.98, dd (17.0, 8.9) 2.82, dd (17.0, 3.7)
4’	141.9		141.9	
5’	144.7		144.7	
6’	115.1	6.55, d (8.0)	115.2	6.55, d (8.5)
7’	115.8	6.46 – 6.40 (m)	115.8	6.44, d (8.5)
8’	140.5		140.6	
9’	130.6		130.7	
1’’	27.5	1.06, s	27.5	1.06, s
2’’	74.0	1.03, s	74.0	1.04, s
3’’	26.42		26.45	
1’’’	120.7		120.9	
2’’’	163.1		163.0	
3’’’	99.9	6.47, d (2.1)	99.9	6.47, d (2.1)
4’’’	165.2		165.0	
5’’’	109.0	6.46 – 6.40 (m)	109.0	6.42, dd (8.5, 2.1)
6’’’	134.0	7.68, d (8.5)	133.9	7.67, d (8.5)
CH_3-O-2’’’	56.0	3.85, s	56.0	3.84, s

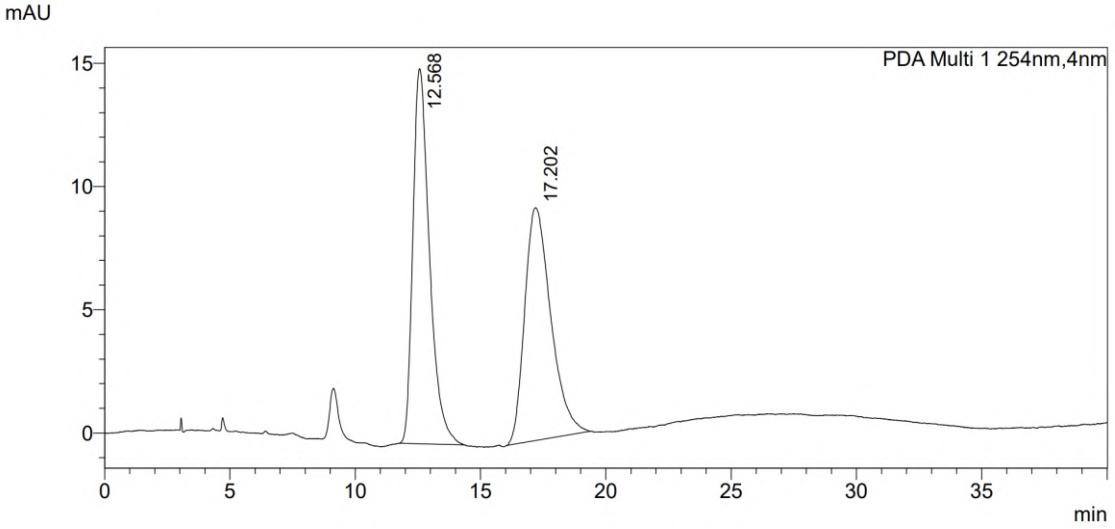
Table 6.5.1. Comparison of NMR data for Indidene A.

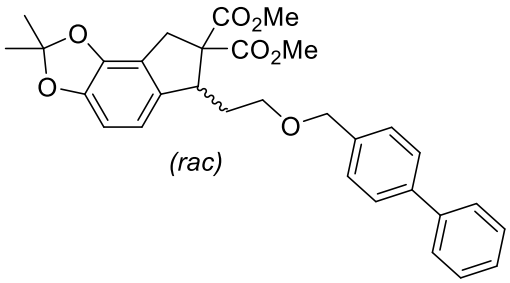
8. Chiral HPLC data

8.1 C–H activation product and common precursor

dimethyl 6-(2-([1,1'-biphenyl]-4-ylmethoxy)ethyl)-2,2-dimethyl-6,8-dihydro-7H-indeno[4,5-d][1,3]dioxole-7,7-dicarboxylate (C–H product 4)

<Chromatogram>



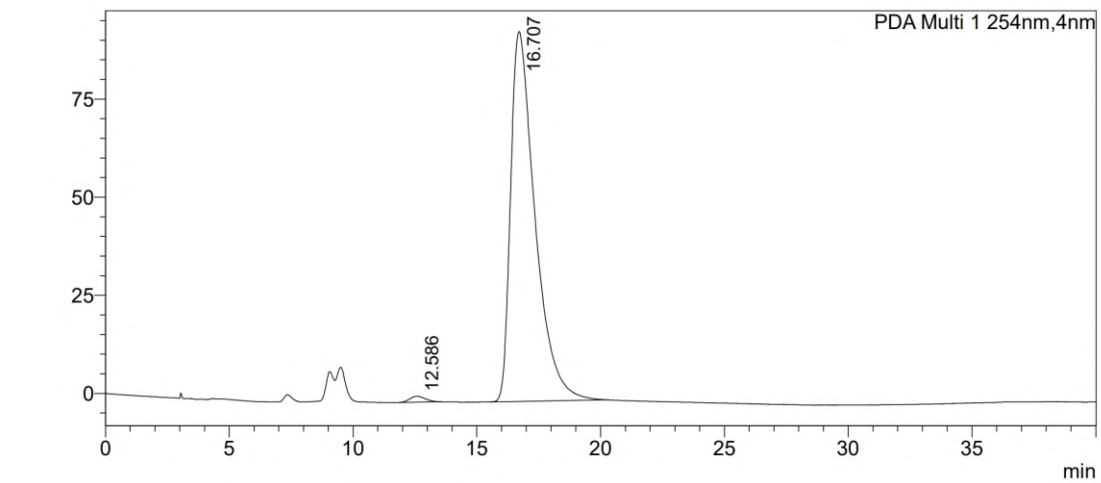


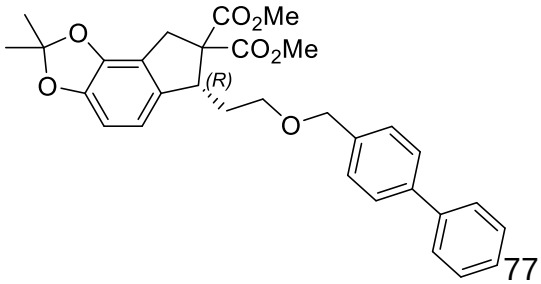
<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Area%
1	12.568	700870	50.583
2	17.202	684701	49.417
Total		1385571	100.000

<Chromatogram>



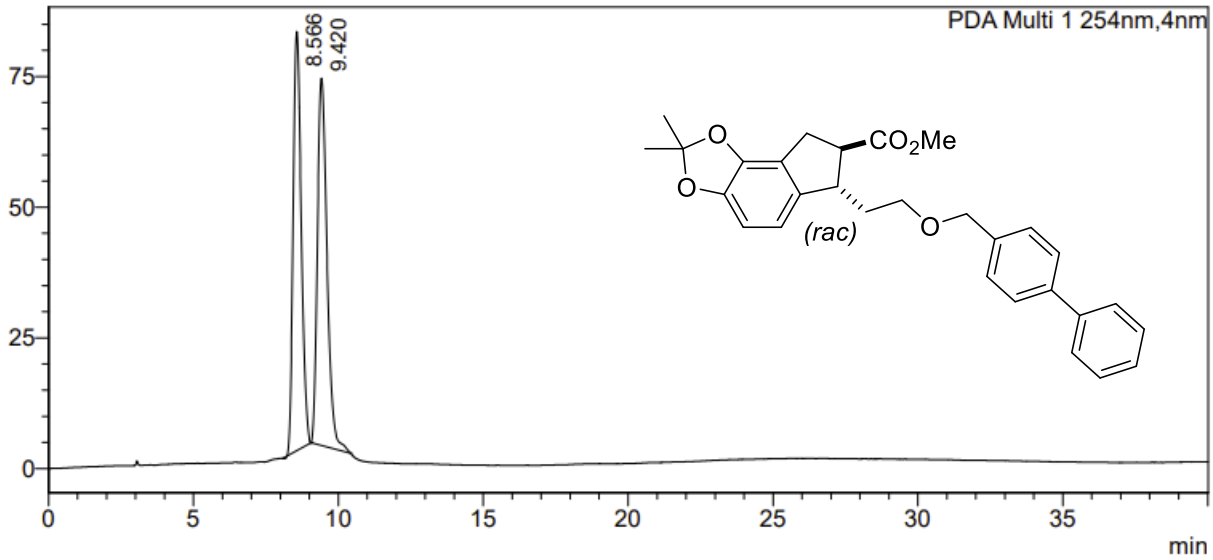


<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Area%
1	12.586	67083	1.027
2	16.707	6463202	98.973
Total		6530285	100.000

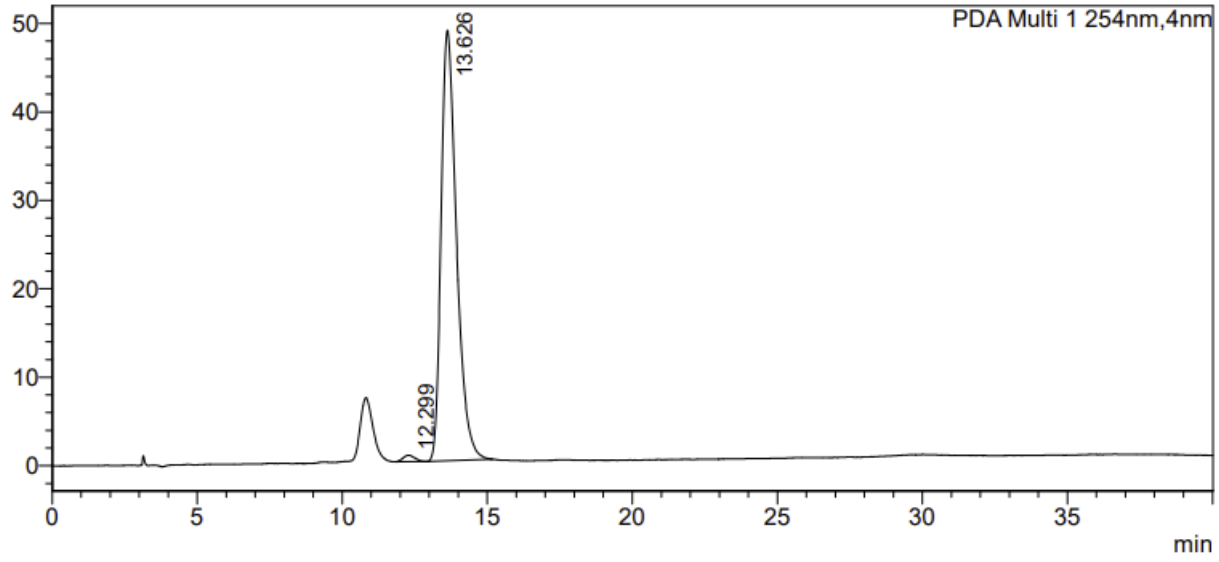
methyl *trans*-6-(2-([1,1'-biphenyl]-4-ylmethoxy)ethyl)-2,2-dimethyl-7,8-dihydro-6H-indeno[4,5-d][1,3]dioxole-7-carboxylate (monoester 12)



<Peak Table>

PDA Ch1 254nm

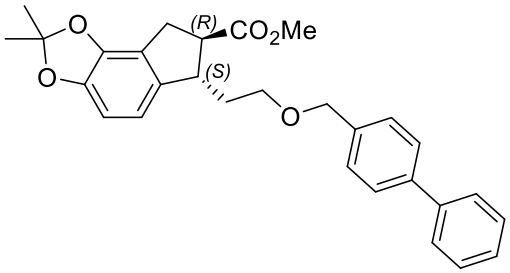
Peak#	Ret. Time	Area	Area%
1	8.566	1549125	48.914
2	9.420	1617892	51.086
Total		3167017	100.000



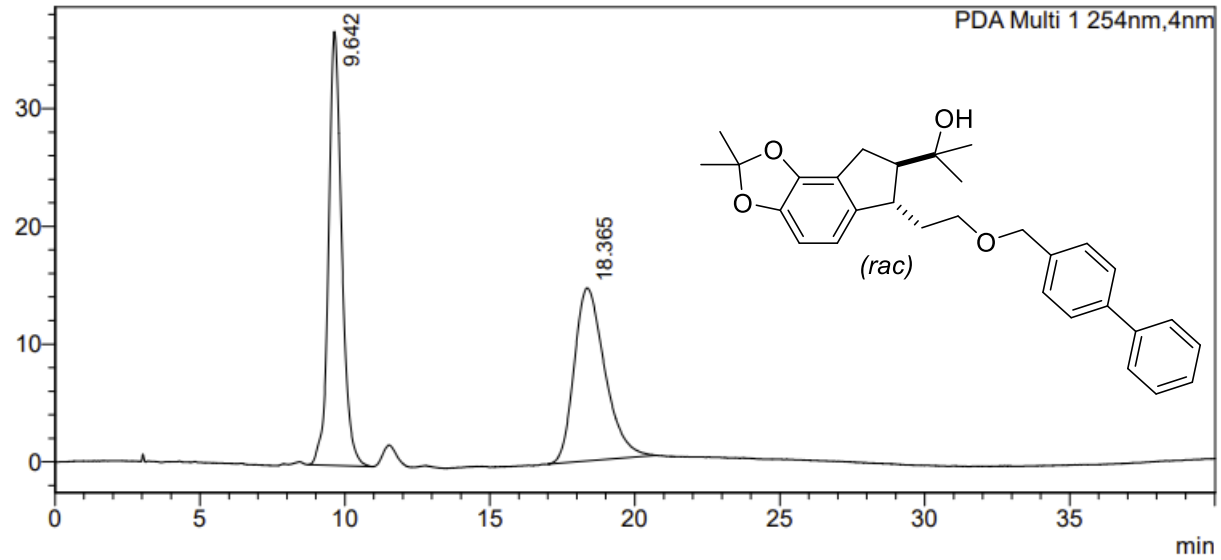
<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Area%
1	12.299	20133	1.110
2	13.626	1793010	98.890
Total		1813143	100.000



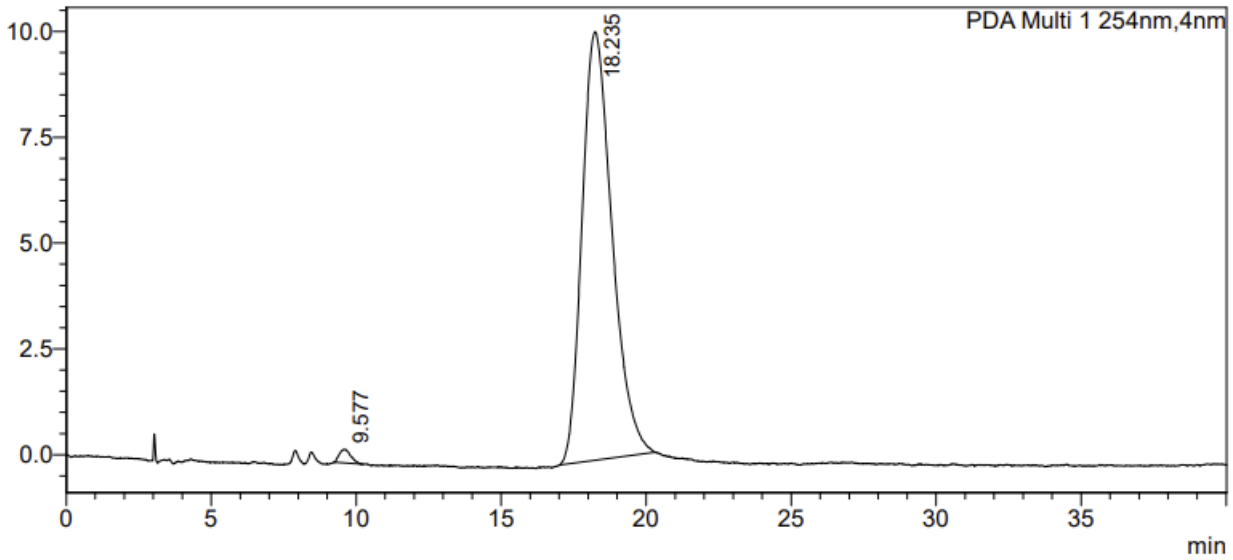
2-((6S,7R)-6-(2-([1,1'-biphenyl]-4-ylmethoxy)ethyl)-2,2-dimethyl-7,8-dihydro-6H-indeno[4,5-d][1,3]dioxol-7-yl)propan-2-ol (monoprotected diol 22)



<Peak Table>

PDA Ch1 254nm

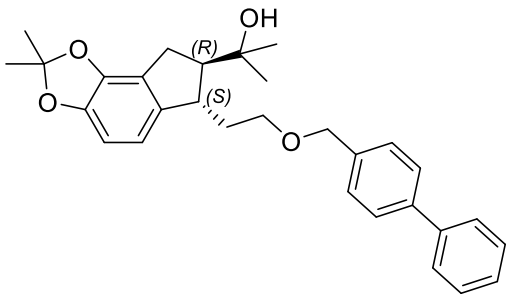
Peak#	Ret. Time	Area	Area%
1	9.642	1167757	51.998
2	18.365	1078028	48.002
Total		2245785	100.000



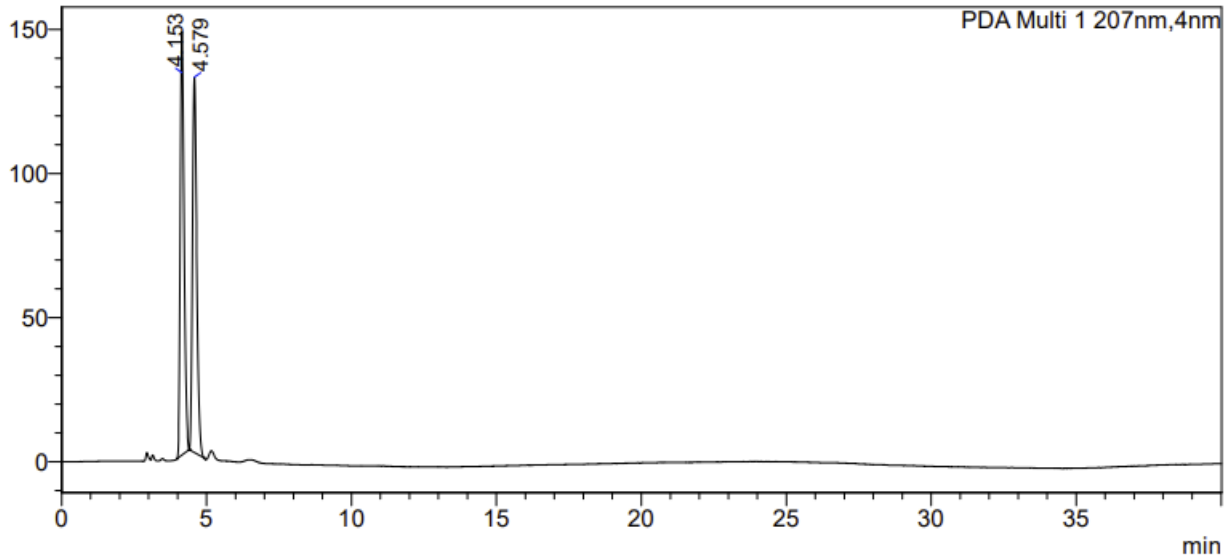
<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Area%
1	9.577	8636	1.173
2	18.235	727892	98.827
Total		736528	100.000



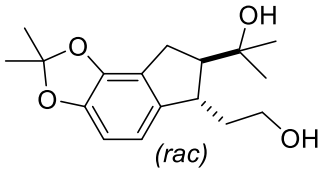
2-((6S,7R)-6-(2-hydroxyethyl)-2,2-dimethyl-7,8-dihydro-6H-indeno[4,5-d][1,3]dioxol-7-yl)propan-2-ol (diol 3)



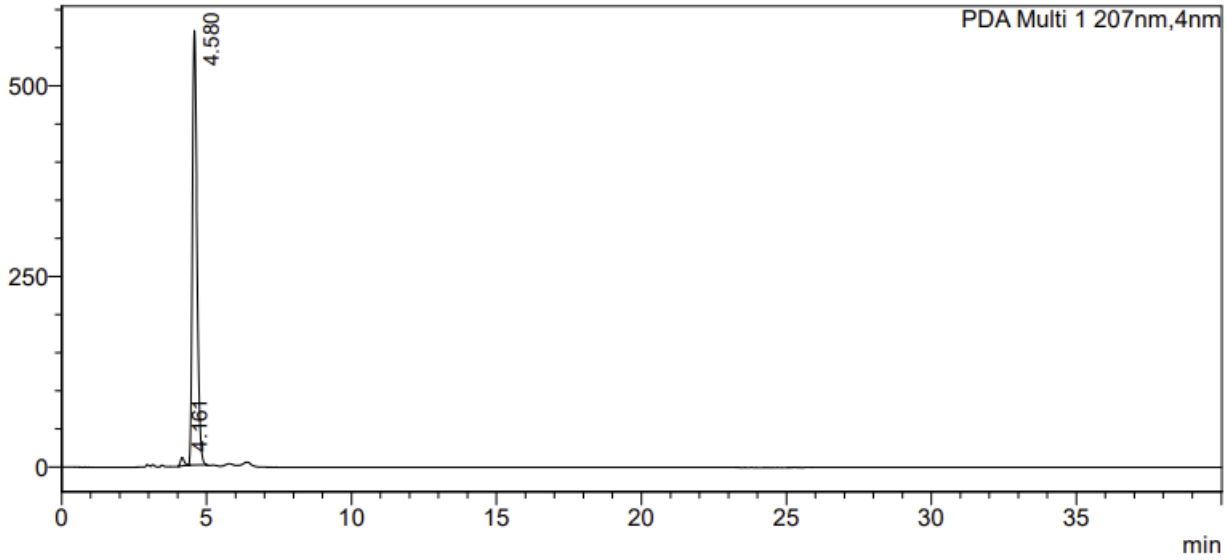
<Peak Table>

PDA Ch1 207nm

Peak#	Ret. Time	Area	Area%
1	4.153	1312243	49.695
2	4.579	1328348	50.305
Total		2640591	100.000



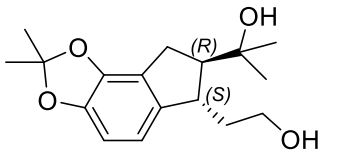
mAU



<Peak Table>

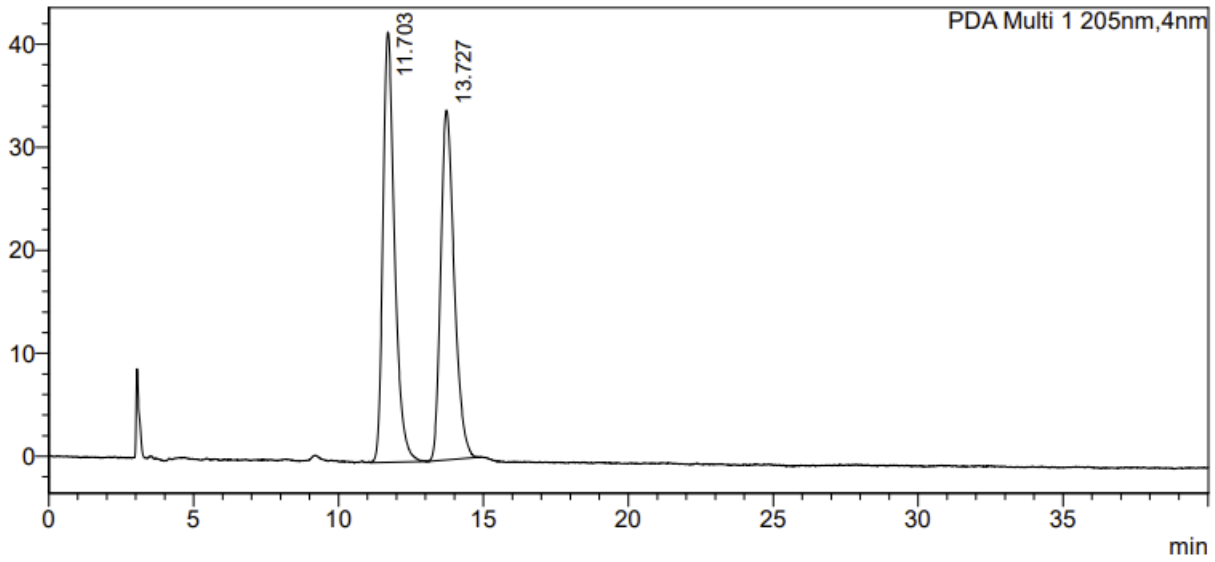
PDA Ch1 207nm

Peak#	Ret. Time	Area	Area%
1	4.161	93116	1.459
2	4.580	6288363	98.541
Total		6381479	100.000



8.2 Divergence towards Indidene C

(5bS,9aR)-2,2,9,9-tetramethyl-5b,9,9a,10-tetrahydro-[1,3]dioxolo[4',5':4,5]indeno[2,1-c]pyran-7(6H)-one (lactone 16)



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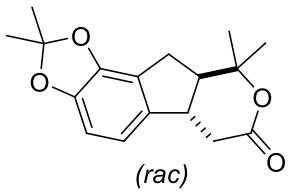
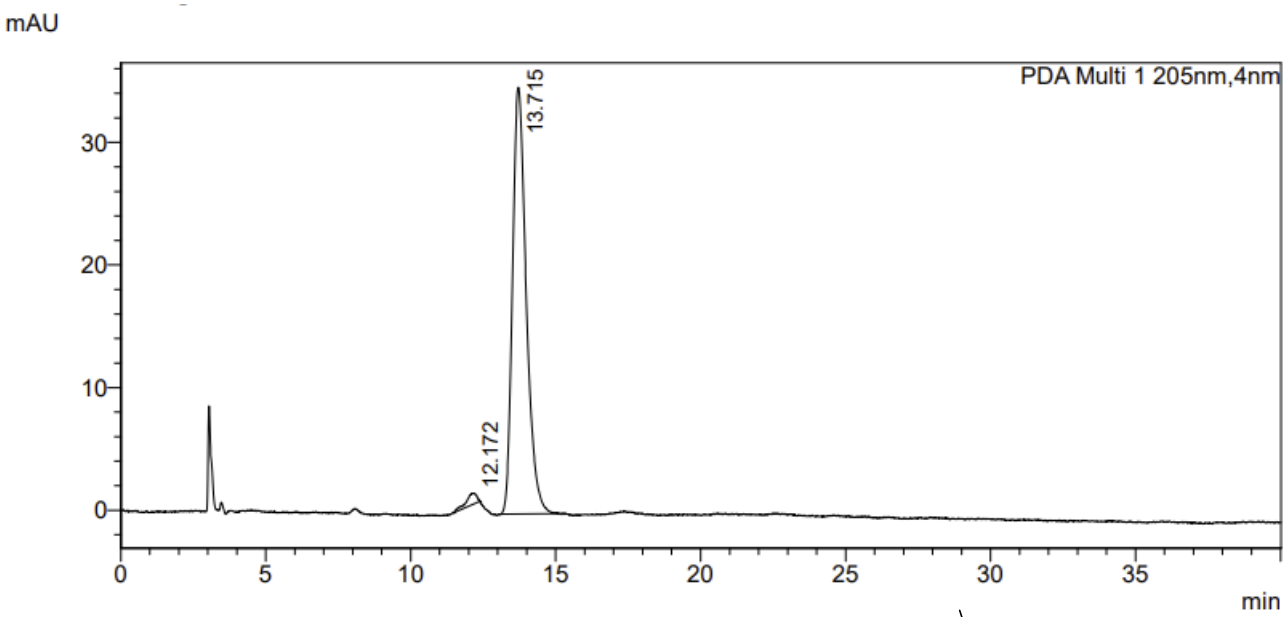
PDA Ch1 205nm

Peak#	Ret. Time	Area	Area%
1	11.703	1168230	51.394
2	13.727	1104864	48.606
Total		2273094	100.000

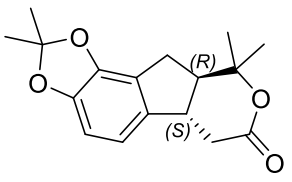




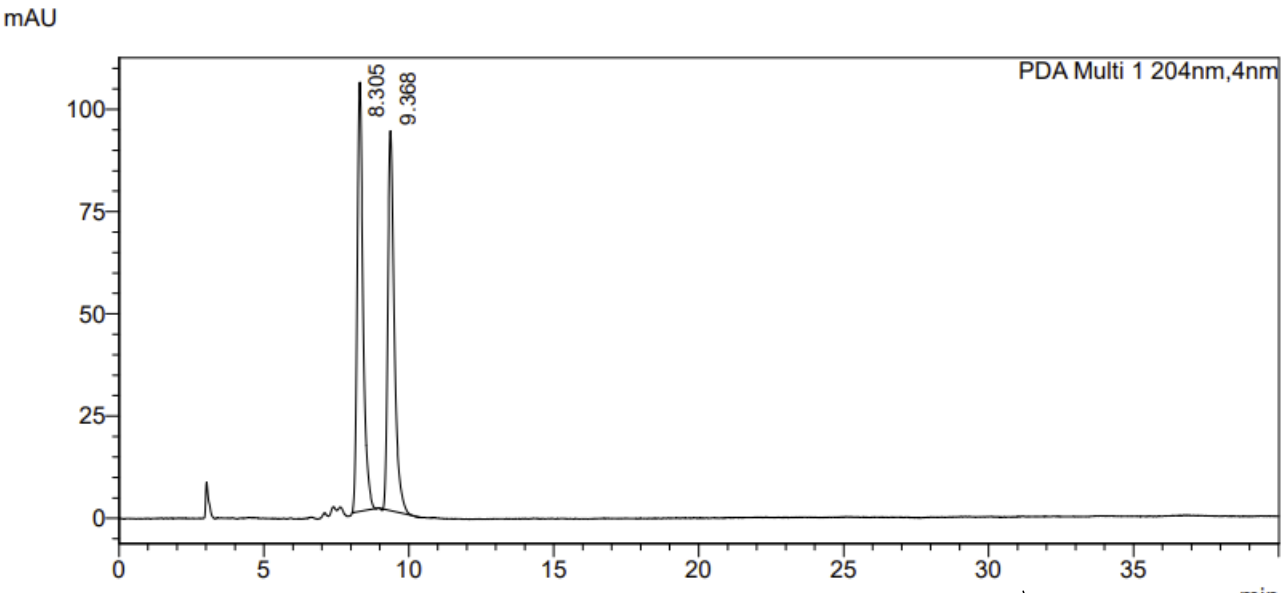
<Peak Table>

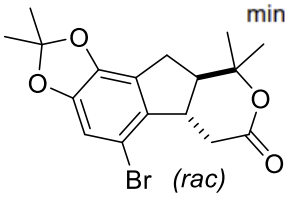
PDA Ch1 205nm

Peak#	Ret. Time	Area	Area%
1	12.172	24179	2.069
2	13.715	1144673	97.931
Total		1168852	100.000



(5bS,9aR)-5-bromo-2,2,9,9-tetramethyl-5b,9,9a,10-tetrahydro-[1,3]dioxolo[4',5':4,5]indeno[2,1-c]pyran-7(6H)-one (bromolactone 13)

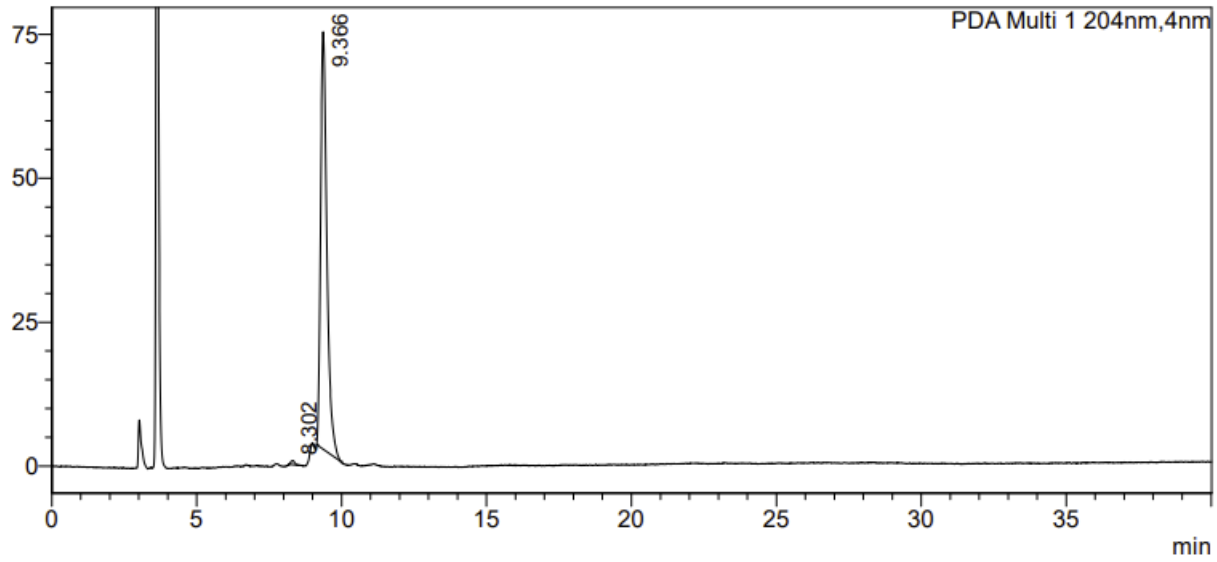




<Peak Table>

PDA Ch1 204nm

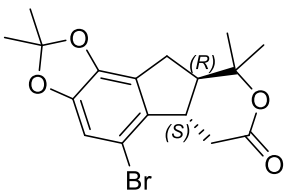
Peak#	Ret. Time	Area	Area%
1	8.305	1474592	50.480
2	9.368	1446571	49.520
Total		2921163	100.000



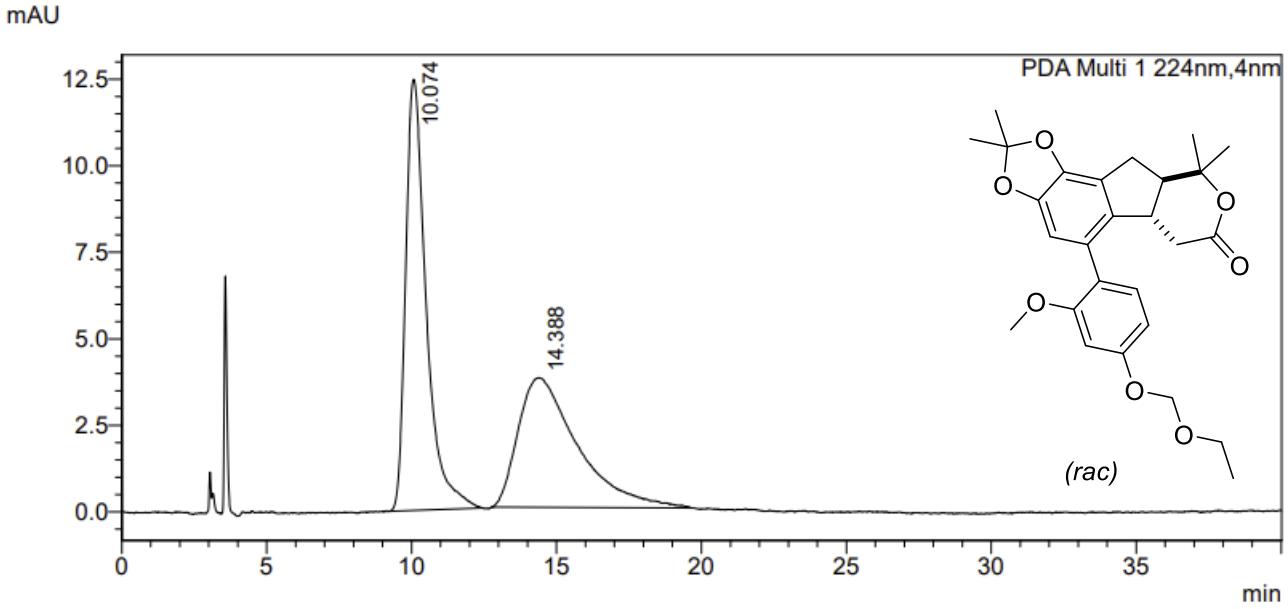
<Peak Table>

PDA Ch1 204nm

Peak#	Ret. Time	Area	Area%
1	8.302	6108	0.553
2	9.366	1097631	99.447
Total		1103739	100.000



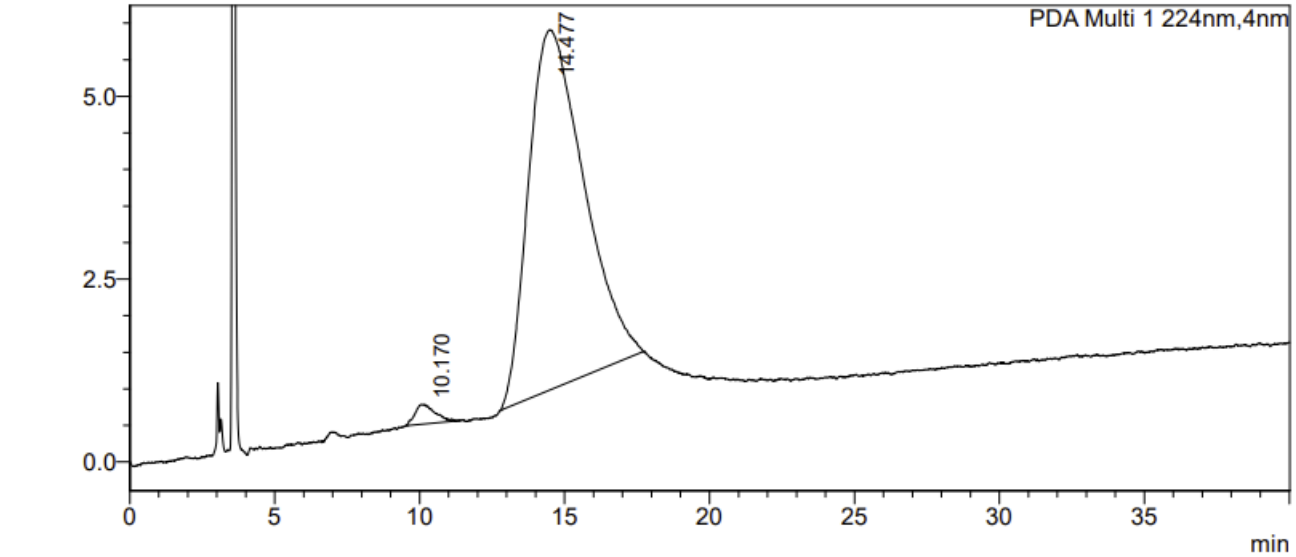
(5bS,9aR)-5-(4-(ethoxymethoxy)-2-methoxyphenyl)-2,2,9,9-tetramethyl-5b,9,9a,10-tetrahydro-[1,3]dioxolo[4',5':4,5]indeno[2,1-c]pyran-7(6H)-one (biphenyl 15)



<Peak Table>

PDA Ch1 224nm

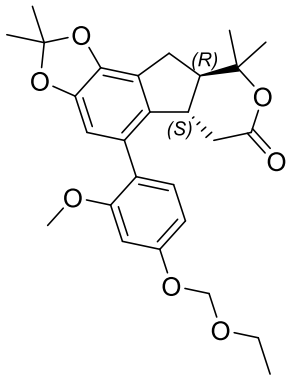
Peak#	Ret. Time	Area	Area%
1	10.074	612381	53.419
2	14.388	533986	46.581
Total		1146367	100.000



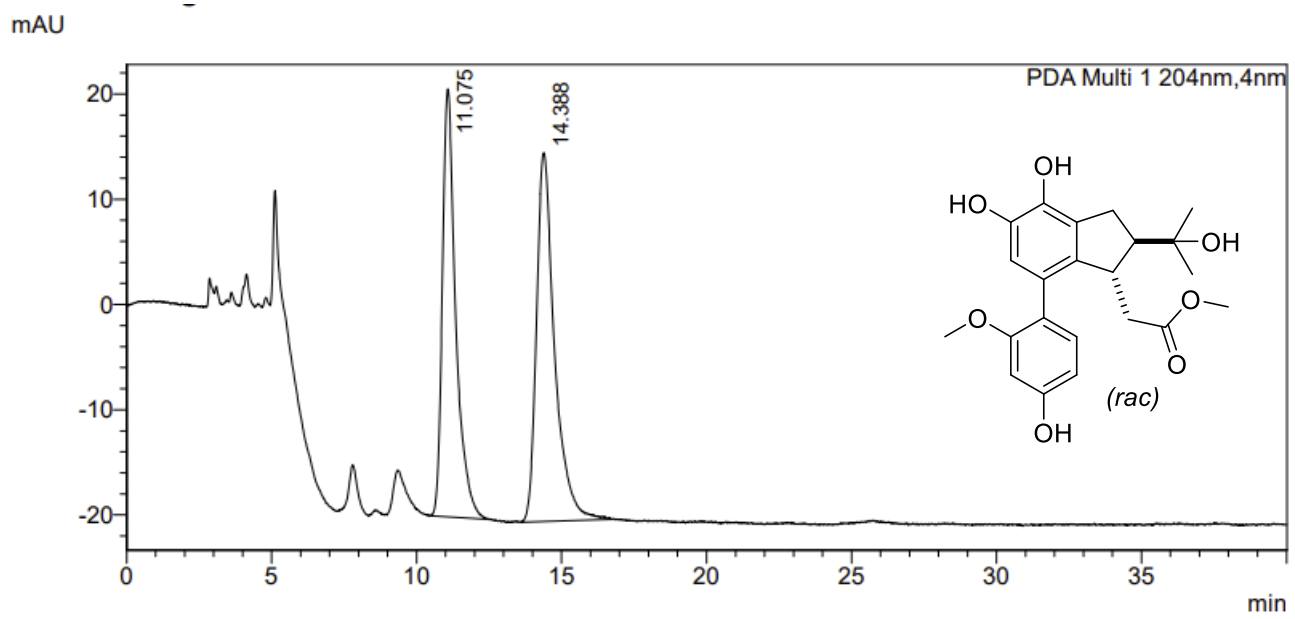
<Peak Table>

PDA Ch1 224nm

Peak#	Ret. Time	Area	Area%
1	10.170	12923	1.939
2	14.477	653573	98.061
Total		666496	100.000



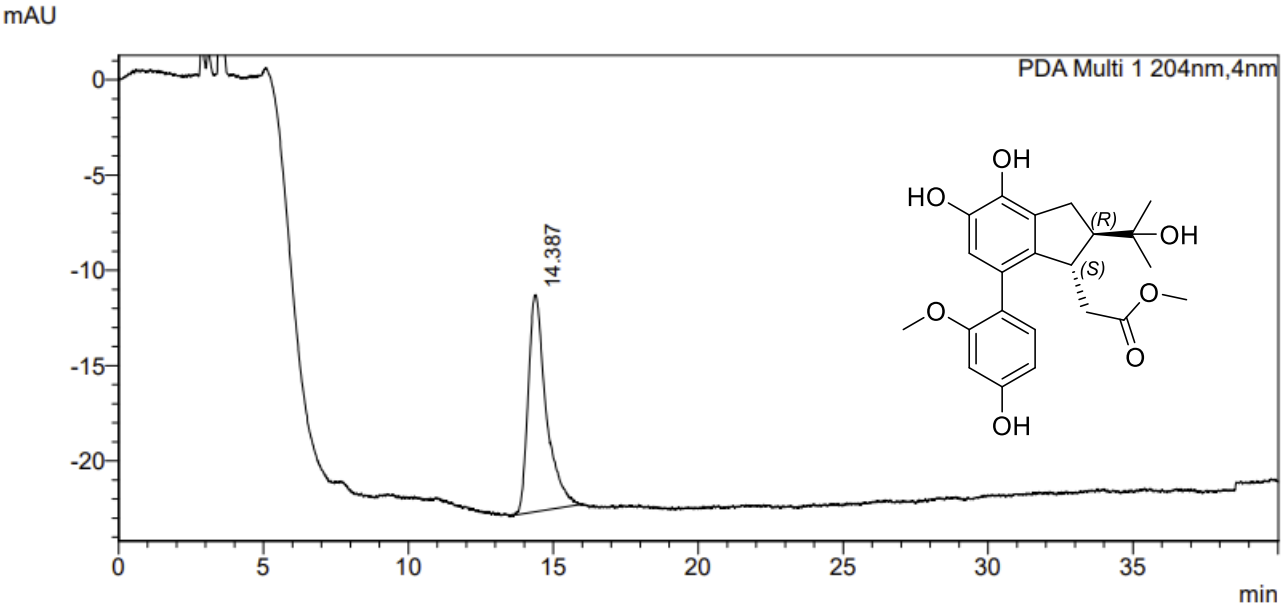
Indidene C (2)



<Peak Table>

PDA Ch1 204nm

Peak#	Ret. Time	Area	Area%
1	11.075	1298646	46.179
2	14.388	1513534	53.821
Total		2812180	100.000



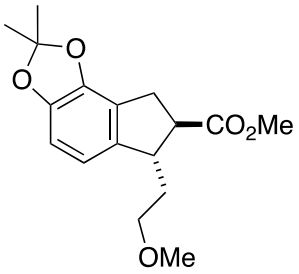
<Peak Table>

PDA Ch1 204nm

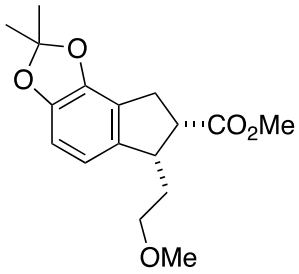
Peak#	Ret. Time	Area	Area%
1	14.387	490464	100.000
Total		490464	100.000

9. Computational details for DFT calculations

Calculations for the stability of isomers of **12** were performed using the Spartan '20 software (Wavefunction, Inc.) for the following model molecules:

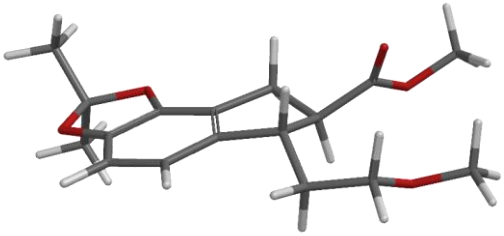


trans

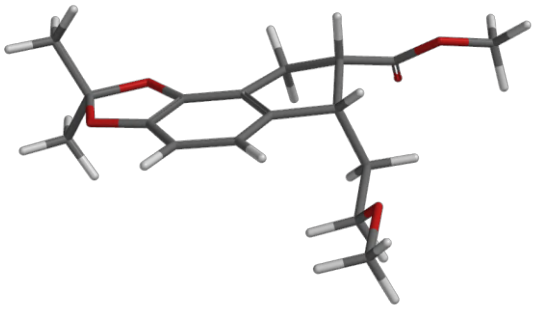


cis

For each diastereoisomer, a set of 10 lowest energy conformers was first obtained using the conformer distribution method and MMFF molecular mechanics. Then, the geometry of all conformers was reoptimized by DFT using the ω-B97X-D functional/6-311+G** basis set in vacuum at 298 K. The Boltzmann averaged free energies were calculated to be -650815.48 kcal/mol for the *trans* diastereoisomer and -650813.83 kcal/mol for the *cis* diastereoisomer, hence Δ*G* = 1.6 kcal/mol in favor of the former. The lowest energy conformers of the *trans* and *cis* diastereoisomers are shown below.



trans, G = -650815.48 kcal/mol



cis, G = -650813.83 kcal/mol

□*G* = -1.6 kcal/mol

10. Computational details for VCD computations

IR and vibrational circular dichroism (VCD) spectra were recorded on a Bruker PMA 50 accessory coupled to a Tensor 27 Fourier transform infrared spectrometer. A photoelastic modulator (Hinds PEM 90) set at l/4 retardation was used to modulate the handedness of the circular polarized light. Demodulation was performed by a lock-in amplifier (SR830 DSP). An optical low-pass filter (< 1800 cm^{-1}) in front of the photoelastic modulator was used to enhance the signal/noise ratio. Spectra were recorded with a transmission cell equipped with CaF_2 windows and a 0.2 mm spacer. Solutions were prepared in $CDCl_3$ at concentrations of about 2 mg in 250 µL. The pure solvent was used as the reference both for the IR and VCD measurements. Both sample and reference were measured at a resolution of 4 cm^{-1} by averaging about 9'000 scans in total for sample and reference, respectively. The reference VCD spectrum was subtracted from the sample spectrum. Spectra are presented without further data processing.

The geometry optimizations, vibrational frequencies, IR absorption and VCD intensities for lactone (*S,R*)-**16** were calculated with Density Functional Theory (DFT) using the B3LYP functional and a 6-311++G(d,p) basis set. Frequencies were scaled by a factor of 0.985. IR absorption and VCD spectra were constructed from calculated dipole and rotational strengths assuming Lorentzian band shape with a half-width at half maximum of 4 cm^{-1}. All calculations were performed using Gaussian16.

Only one conformer was found using CREST (Conformer-Rotamer Ensemble Sampling Tool).

Figure 10.1. Schematic representation of geometry-optimized (*S,R*)-**16**.

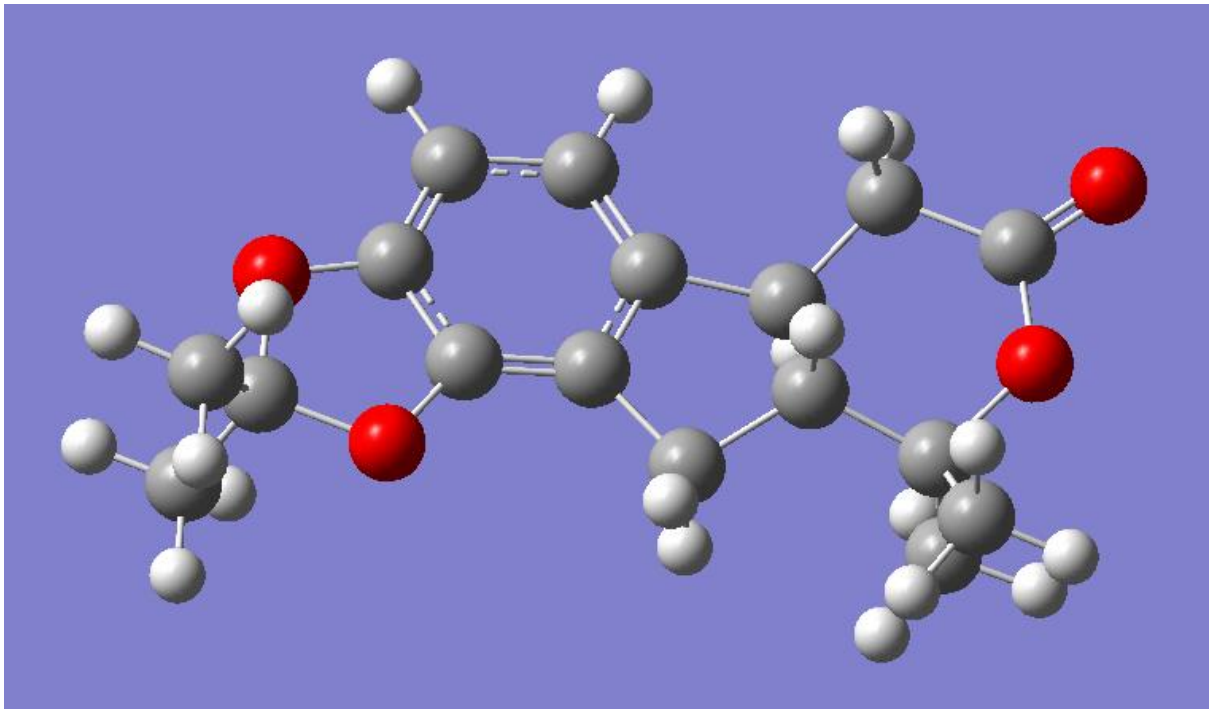


Figure 10.2. Simulated IR spectra of geometry-optimized (*S,R*)-**16** (black) and measured IR spectra for (*S,R*)-**16** (red).

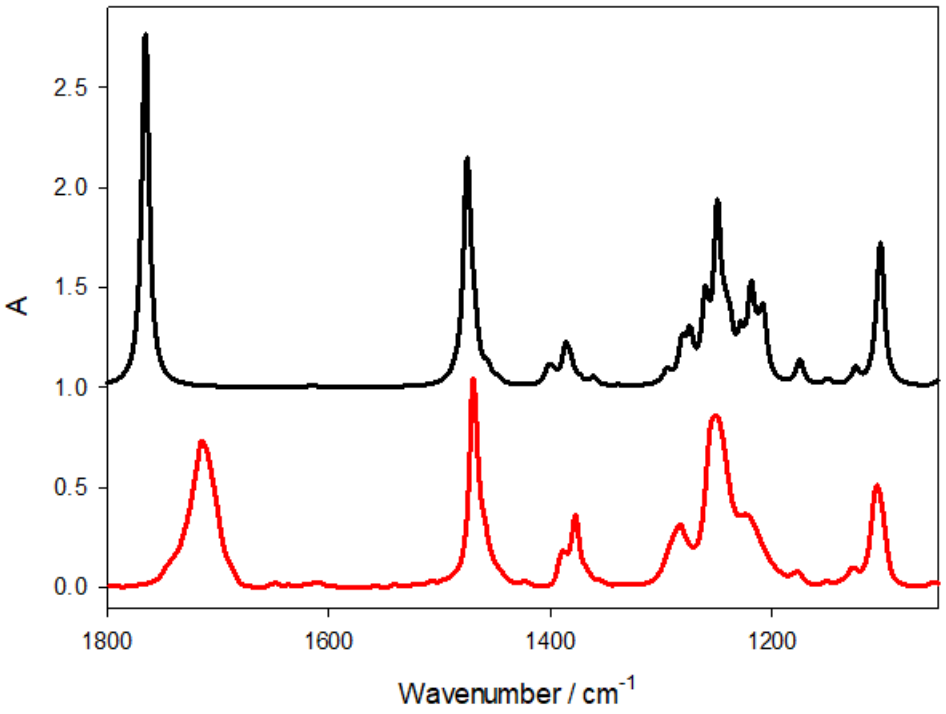
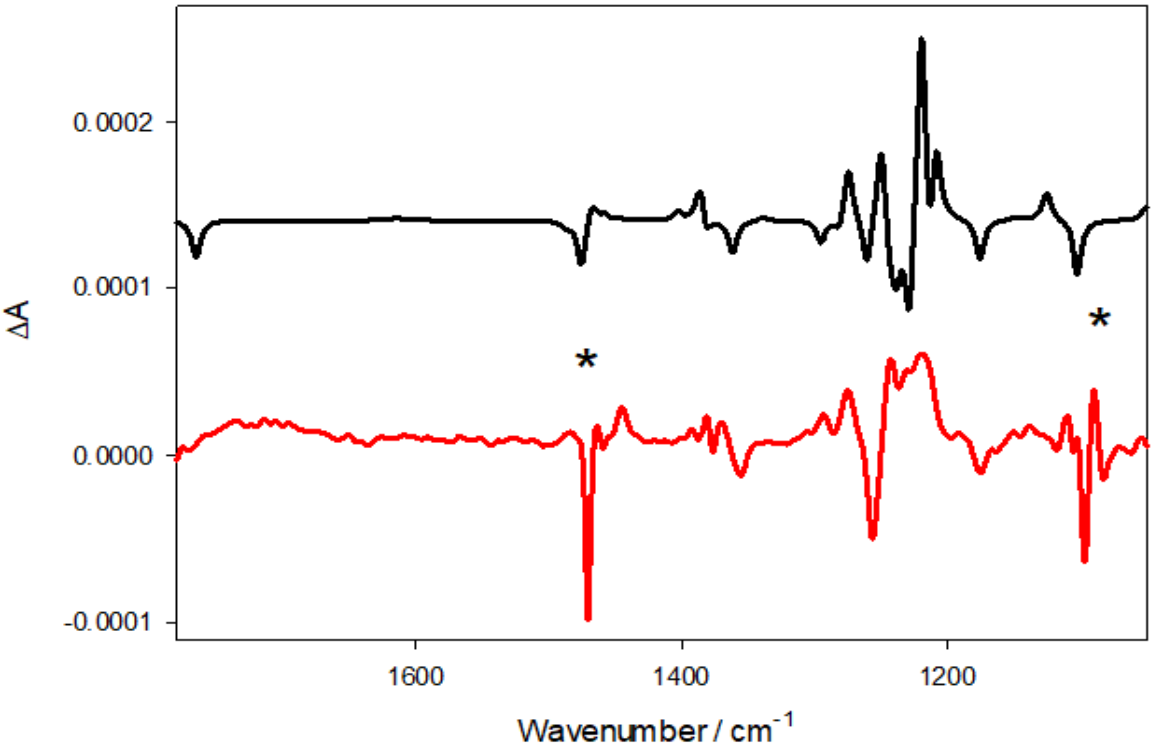


Figure 10.3. Simulated VCD spectra of geometry-optimized (*S,R*)-**16** (black) and measured IR spectra for (*S,R*)-**16** (red).



11. X-Ray diffraction data

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) ak10_twin1_hklf5

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: ak10_twin1_hklf5

```
Bond precision:   C-C = 0.0035 A          Wavelength=1.54184

Cell:             a=12.5728(4)     b=15.5338(5)       c=10.3358(3)
                  alpha=90         beta=95.030(3)     gamma=90
Temperature:      140 K

                  Calculated                Reported
Volume            2010.84(11)               2010.85(12)
Space group       P 21/c                    P 1 21/c 1
Hall group        -P 2ybc                   -P 2ybc
Moiety formula    C22 H26 O7                C22 H26 O7
Sum formula       C22 H26 O7                C22 H26 O7
Mr                402.43                    402.43
Dx,g cm-3         1.329                     1.329
Z                 4                         4
Mu (mm-1)         0.820                     0.820
F000              856.0                     856.0
F000'             858.88
h,k,lmax          15,19,12                  15,19,12
Nref              4150                      4251
Tmin,Tmax         0.863,0.937               0.686,1.000
Tmin'             0.788

Correction method= # Reported T Limits: Tmin=0.686 Tmax=1.000
AbsCorr = GAUSSIAN

Data completeness= 1.024          Theta(max)= 75.182

R(reflections)= 0.0647( 3456)                wR2(reflections)=
                                             0.1945( 4251)
S = 1.072                 Npar= 285
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level C

```
PLAT906_ALERT_3_C Large K Value in the Analysis of Variance ......      2.058 Check
PLAT911_ALERT_3_C Missing FCF Refl Between Thmin & STh/L=    0.600         64 Report
PLAT918_ALERT_3_C Reflection(s) with I(obs) much Smaller I(calc) .          6 Check
PLAT920_ALERT_1_C Theta(Max)  in CIF and FCF Differ by ...........       0.39 Degree
PLAT939_ALERT_3_C Large Value of Not (SHELXL) Weight Optimized S .      10.18 Check
```

Alert level G

```
PLAT002_ALERT_2_G Number of Distance or Angle Restraints on AtSite          8 Note
PLAT072_ALERT_2_G SHELXL First  Parameter in WGHT  Unusually Large       0.11 Report
PLAT176_ALERT_4_G The CIF-Embedded .res File Contains SADI Records          1 Report
PLAT432_ALERT_2_G Short Inter X...Y Contact  O4       ..C11      .       2.90 Ang.
                                          1-x,1/2+y,1/2-z  =      2_655 Check
PLAT860_ALERT_3_G Number of Least-Squares Restraints .............          6 Note
PLAT870_ALERT_4_G ALERTS Related to Twinning Effects Suppressed ..          ! Info
PLAT912_ALERT_4_G Missing # of FCF Reflections Above STh/L=  0.600        173 Note
PLAT931_ALERT_5_G CIFcalcFCF  Twin Law ( 1 0 0)         Est.d BASF       0.22 Check
PLAT941_ALERT_3_G Average HKL Measurement Multiplicity ...........        1.1 Low
```

```
   0 ALERT level A = Most likely a serious problem - resolve or explain
   0 ALERT level B = A potentially serious problem, consider carefully
   5 ALERT level C = Check. Ensure it is not caused by an omission or oversight
   9 ALERT level G = General information/check it is not something unexpected

   1 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
   3 ALERT type 2 Indicator that the structure model may be wrong or deficient
   6 ALERT type 3 Indicator that the structure quality may be low
   3 ALERT type 4 Improvement, methodology, query or suggestion
   1 ALERT type 5 Informative message, check
```

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

Publication of your CIF in IUCr journals

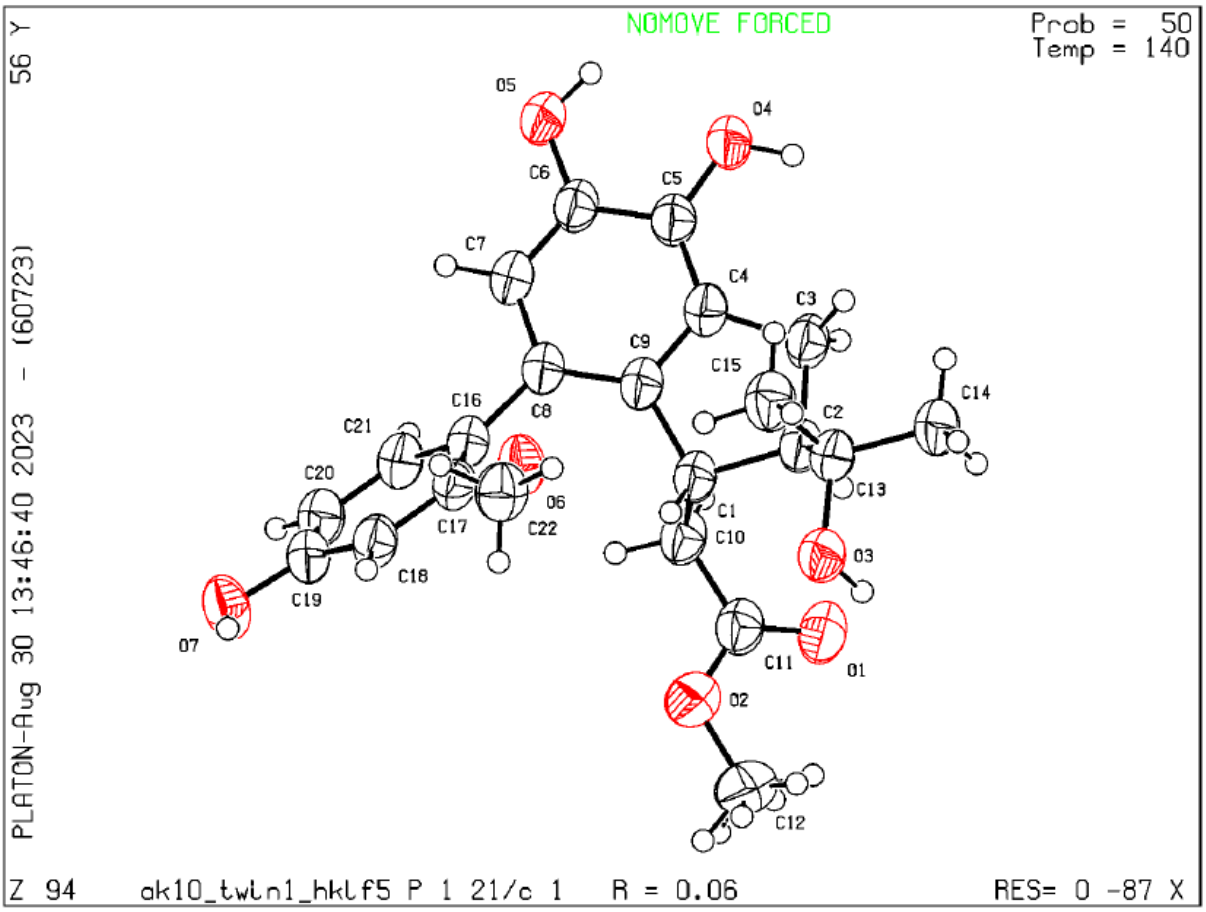
A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica*, *Journal of Applied Crystallography*, *Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E* or *IUCrData*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

PLATON version of 06/07/2023; check.def file version of 30/06/2023

Datablock ak10_twin1_hklf5 - ellipsoid plot

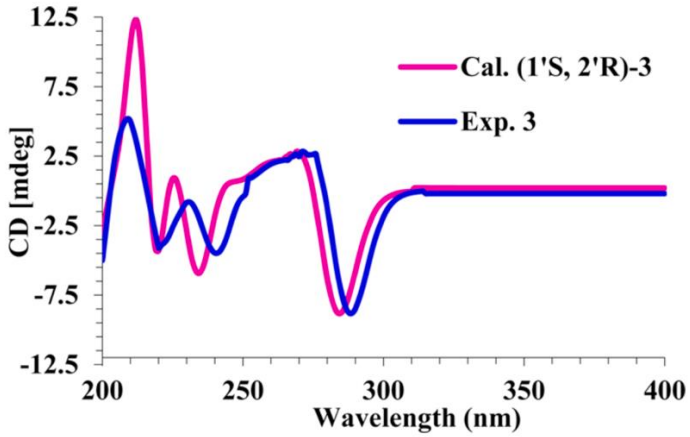


12. Details for ECD spectroscopy

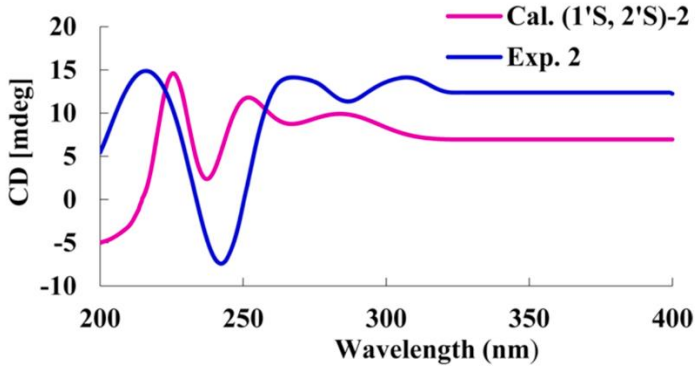
CD measurements were performed on a JASCOJ-1500CD spectrophotometer. The spectra were measured in a 1 cm quartz glass cuvette with three accumulations. The raw data was plotted smoothed without further baseline correction. The measurements were performed in acetonitrile at 20°C. Original isolation study did not state the precise parameters for the ECD measurements, thus our measurements were performed in acetonitrile at 20°C and concentration for the measurement of ECD data for synthetic (+)-indidene C was set at $1.75x10^{-4}$ M.

Figure 12.1. Comparison of ECD spectra for synthetic (+)-indidene C and nominal (–)-indidene C and (+)-indidene B.

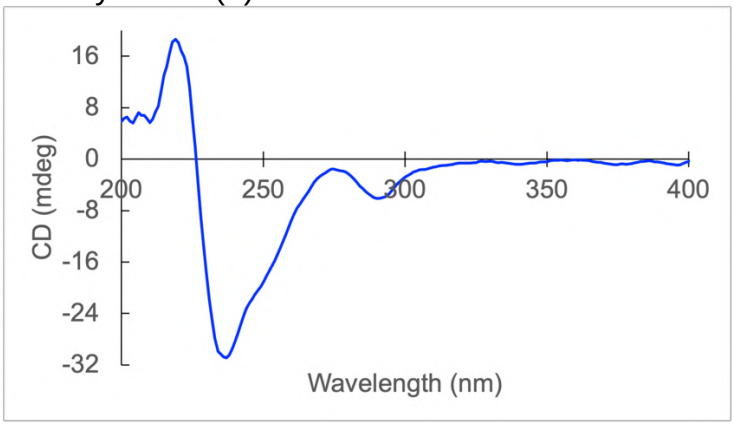
a) Reported experimental and calculated ECD for nominal (–)-indidene C



b) Reported experimental and calculated ECD for nominal (+)-indidene B



c) Experimental ECD for synthetic (+)-indidene C



References

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[3] R. J. Mattson, C. P. Sloan, C. C. Lockhart, J. D. Catt, Q. Gao, S. Huang, *J. Org. Chem.* **1999**, *64*, 8004–8007.

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[5] R. He, X. Huang, Y. Zhang, L. Wu, H. Nie, D. Zhou, B. Liu, S. Deng, R. Yang, S. Huang, Z. Nong, J. Li, Y. Huang, *J. Nat. Prod.* **2016**, *79*, 2472–2478.

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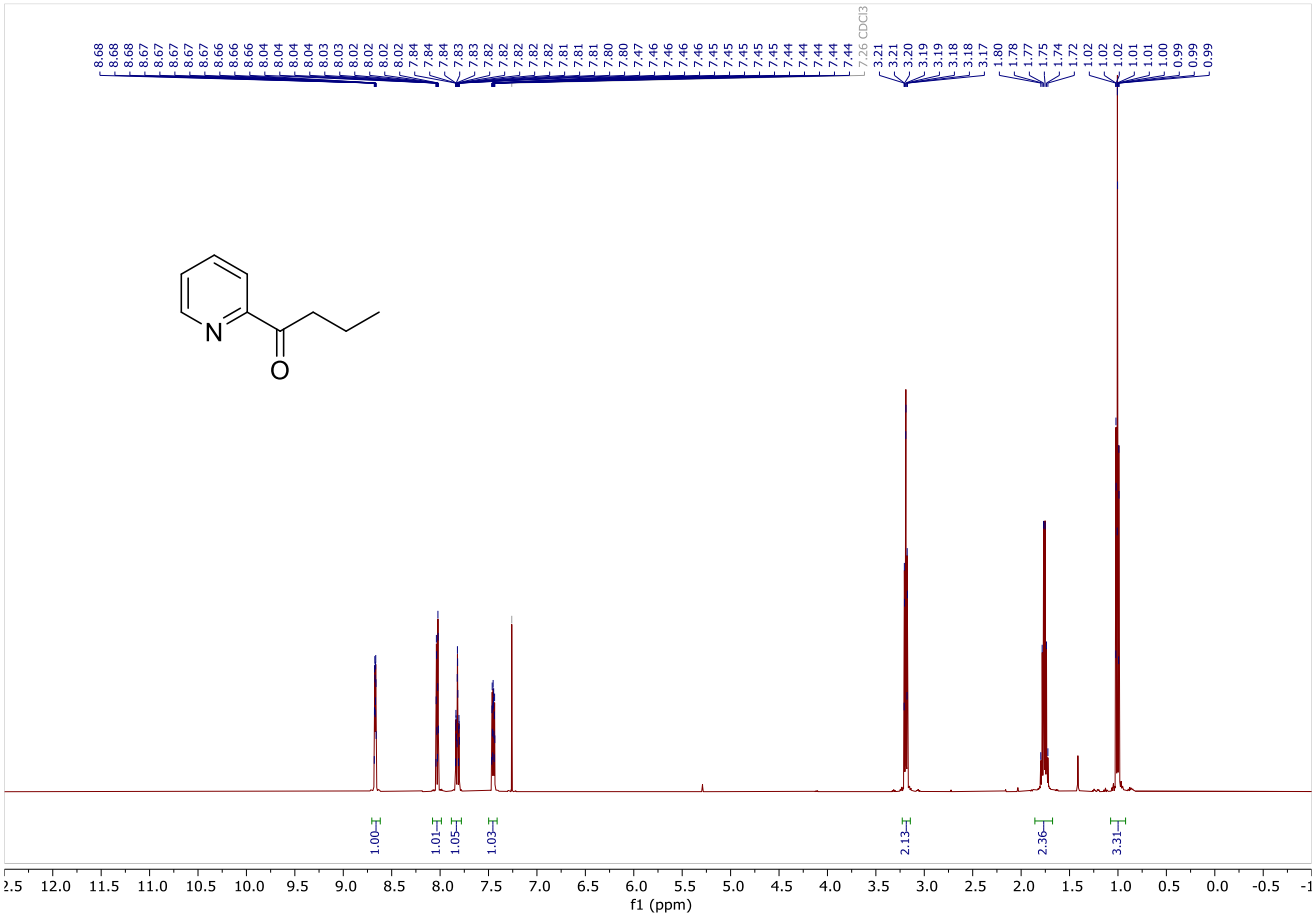
NMR data

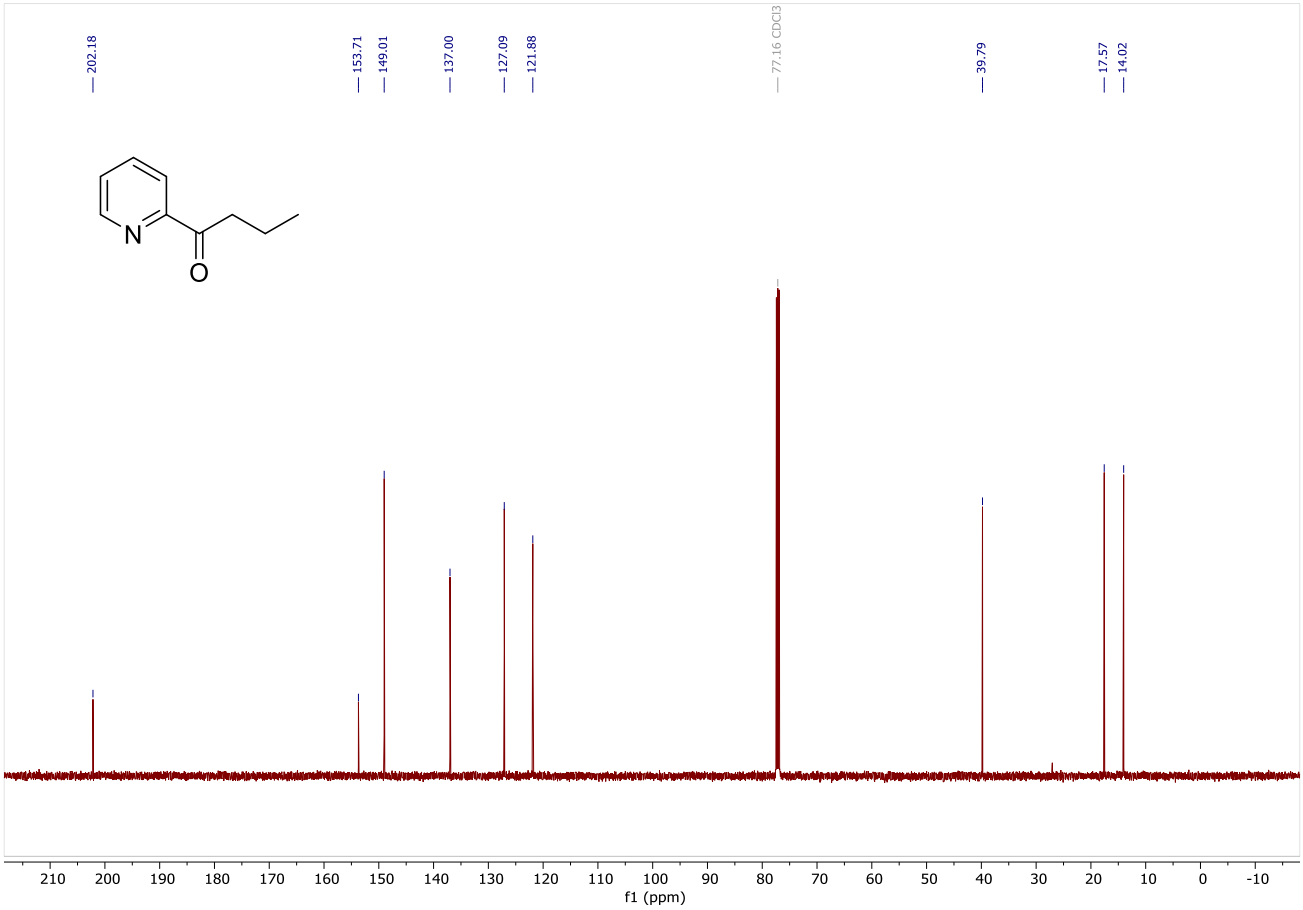
Part I: Pd-Catalyzed C(sp^3)−H Arylation of Heteroaromatic Ketones

Numbering based on A. Kudashev, O. Baudoin, *Chem. Eur. J.* **2021**, *27*, 17688-17694.

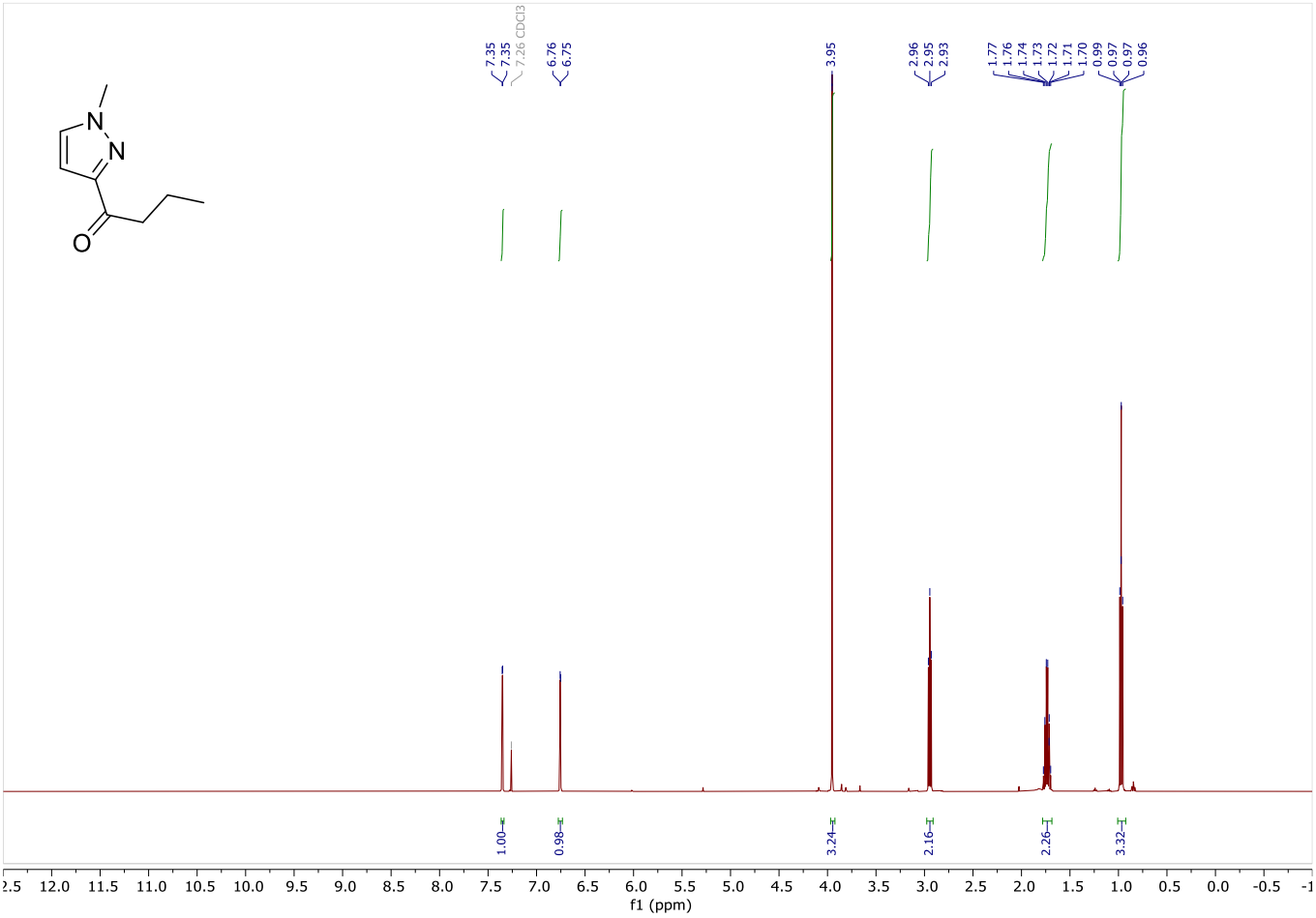
NMR spectra – starting materials

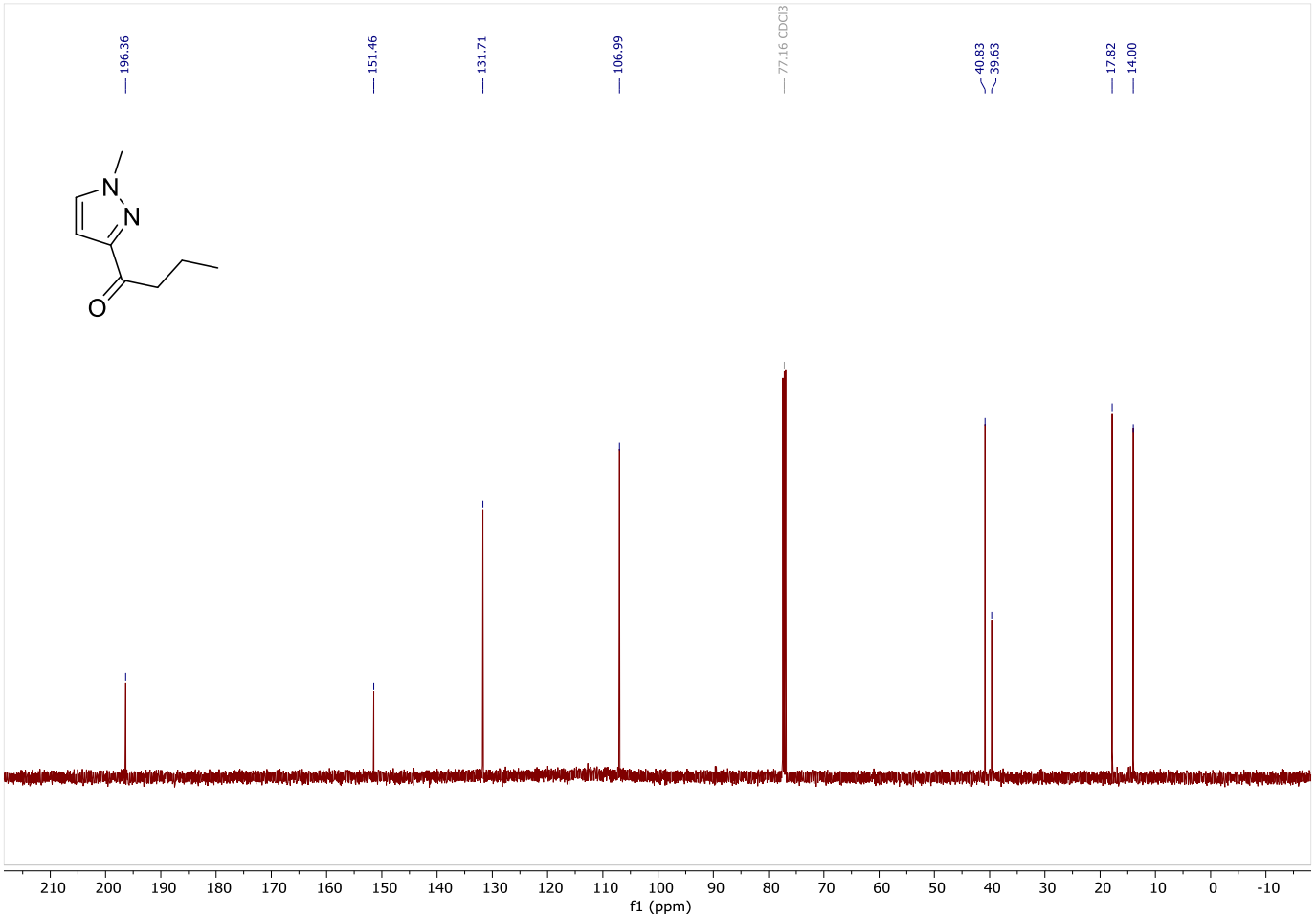
1-(pyridin-2-yl)butan-1-one (1a)



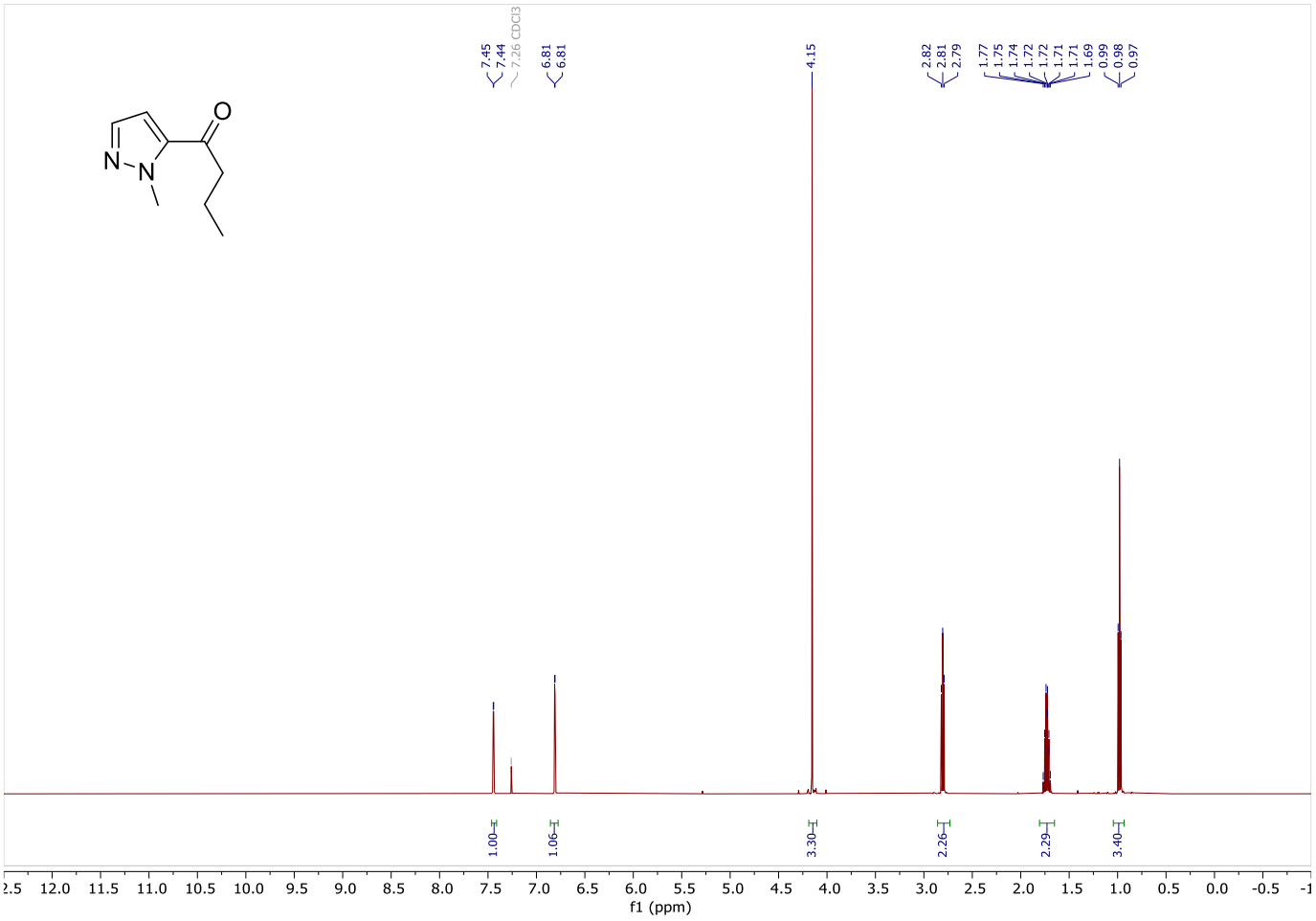


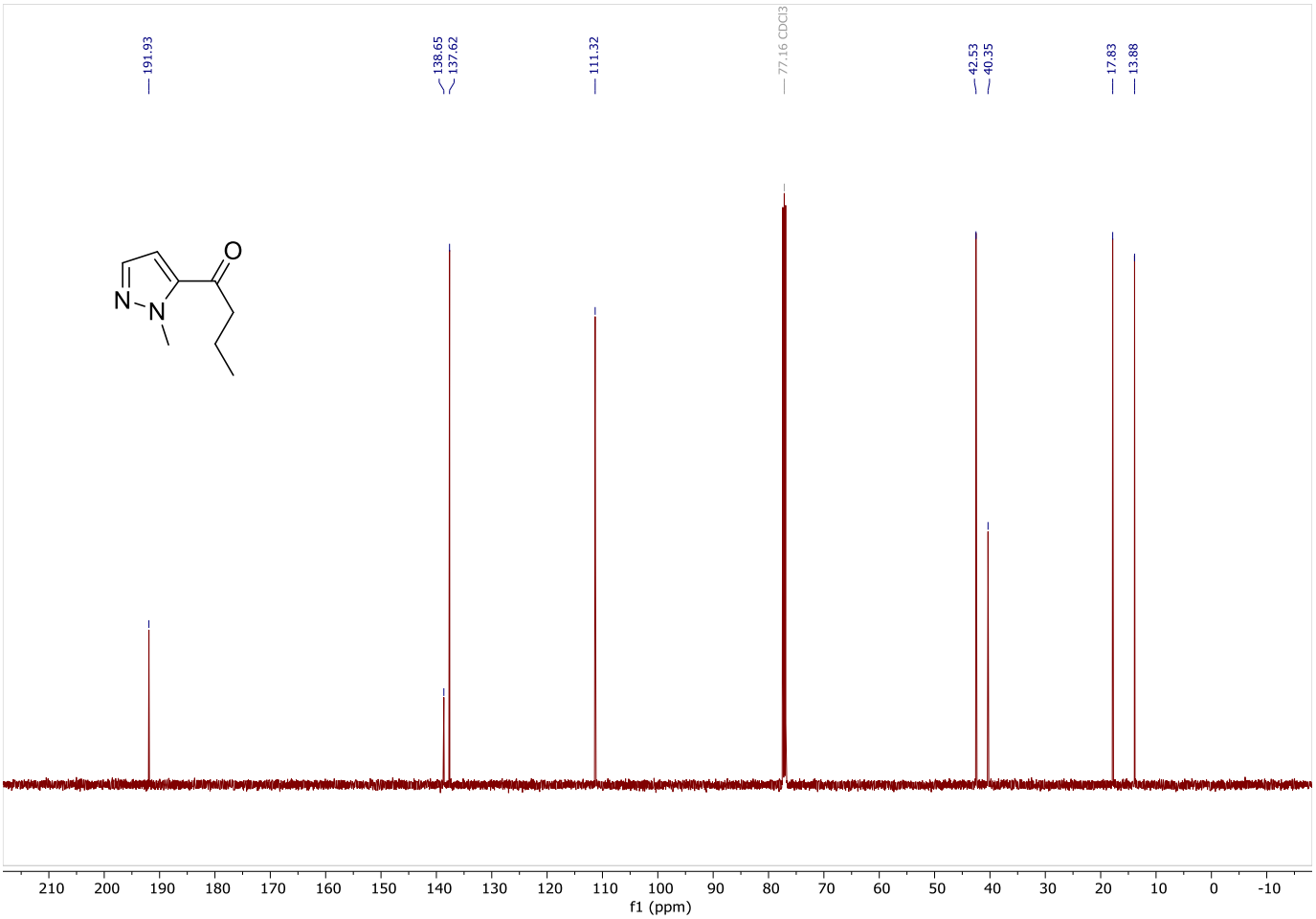
1-(1-methyl-1H-pyrazol-3-yl)butan-1-one (1d)



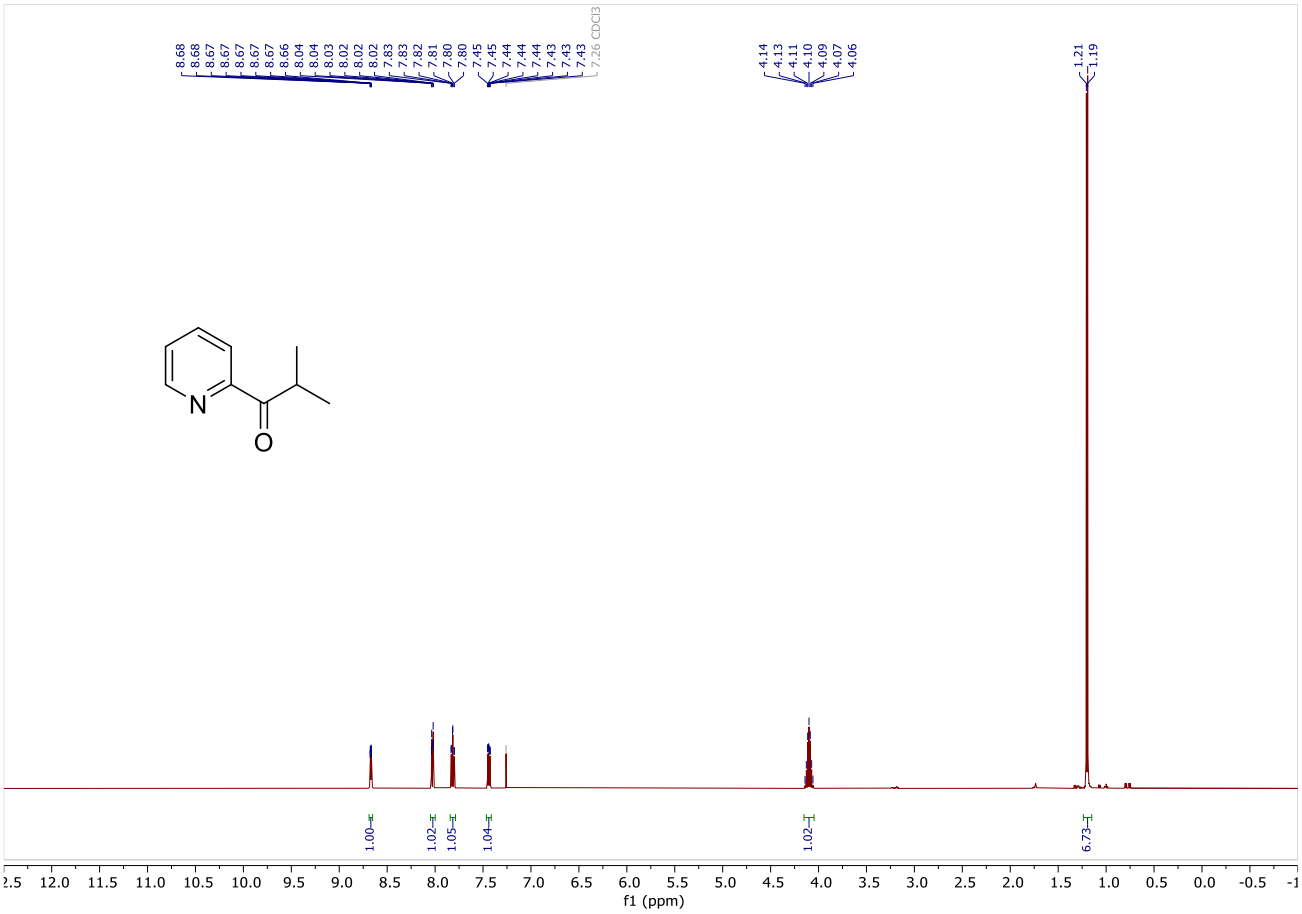


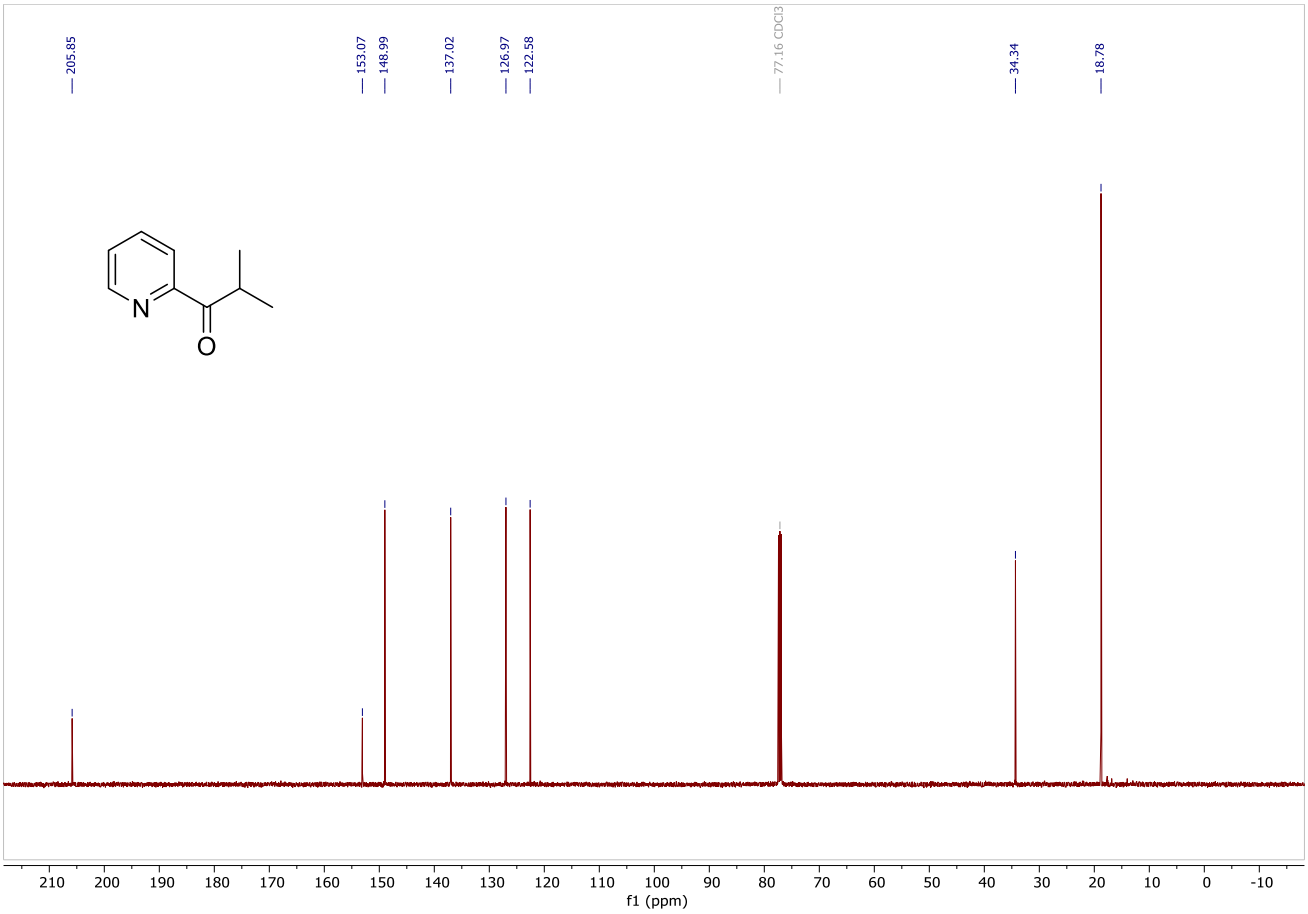
1-(1-methyl-1H-pyrazol-5-yl)butan-1-one (1e)



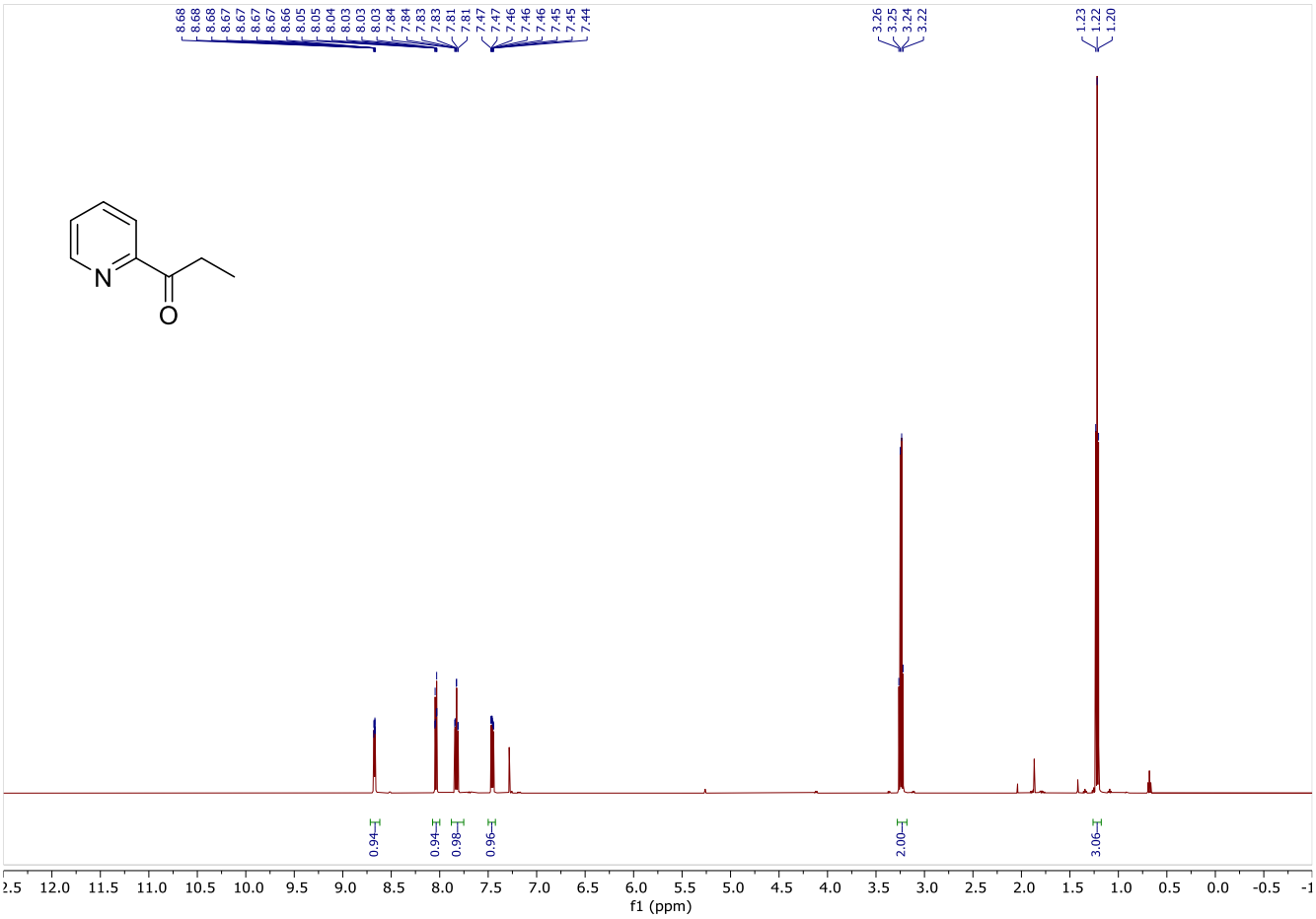


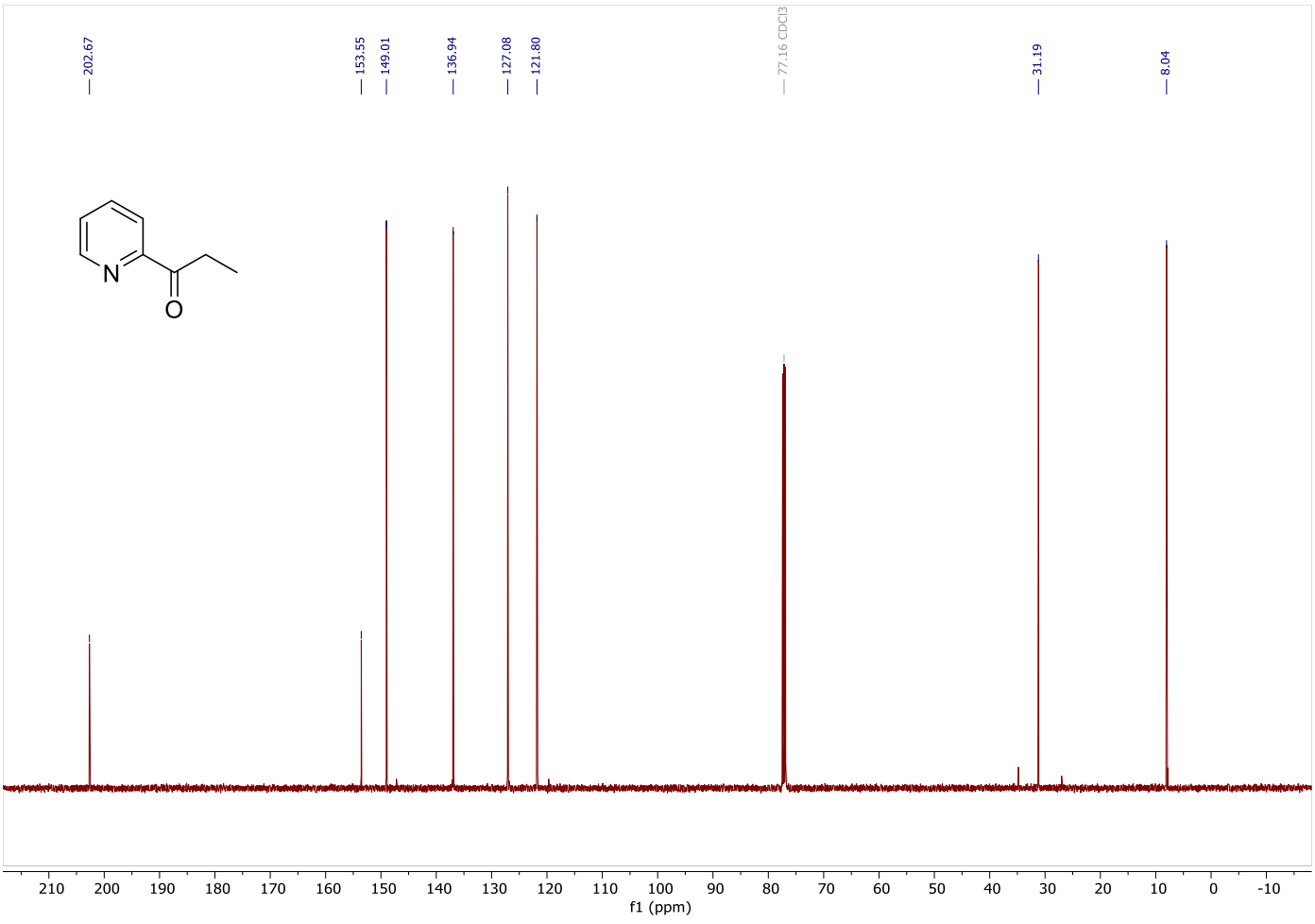
2-methyl-1-(pyridin-2-yl)propan-1-one (1f)



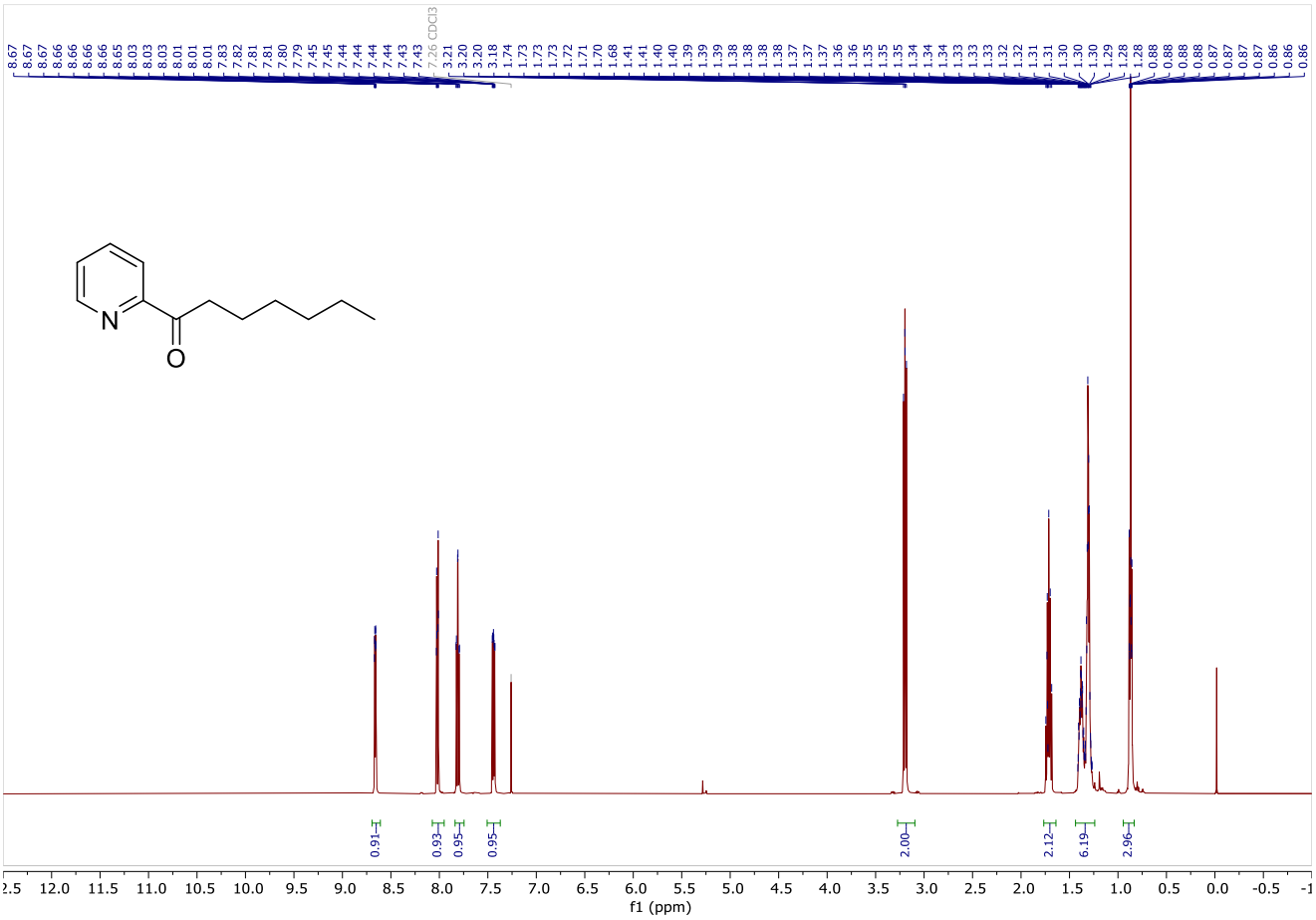


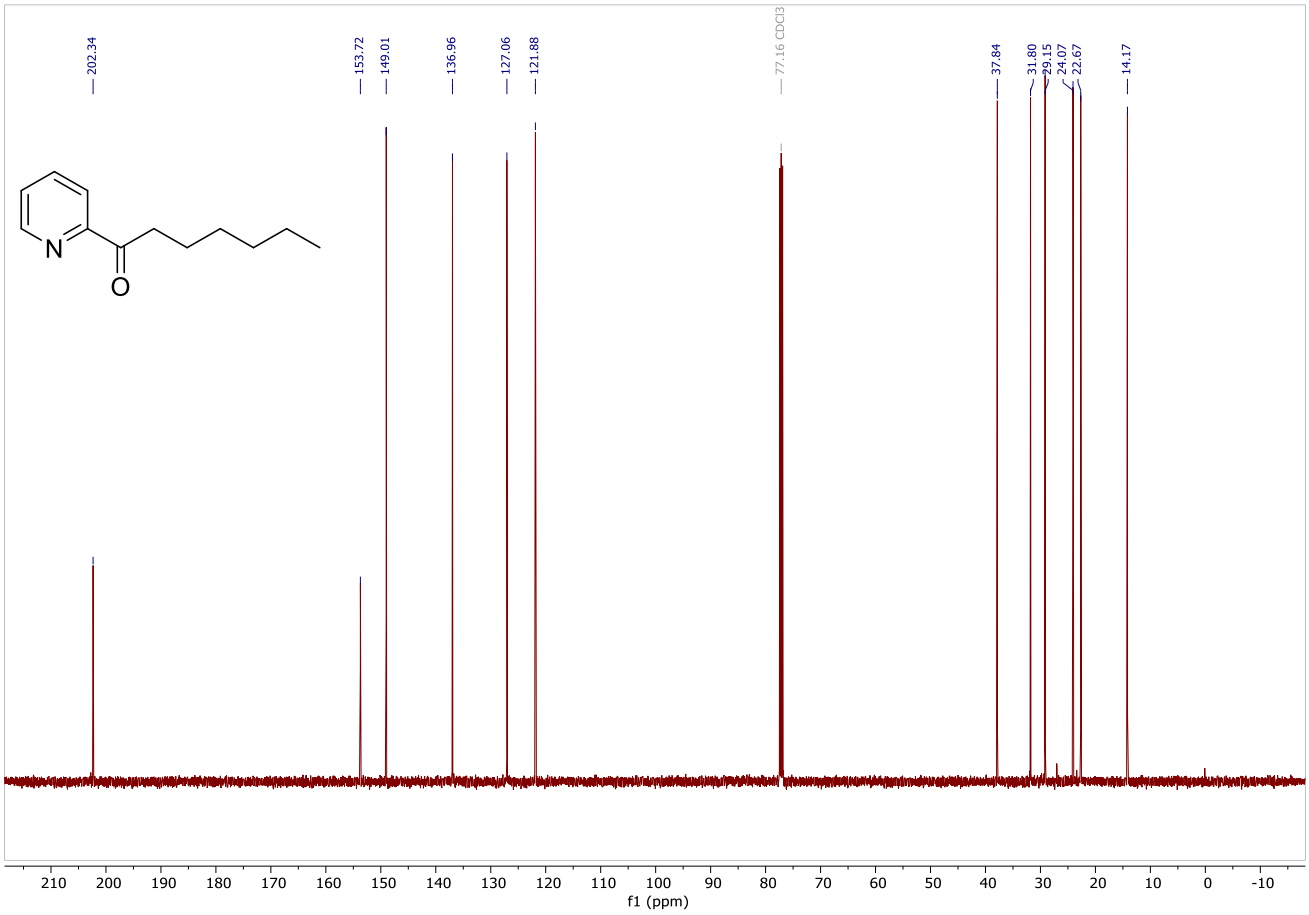
1-(pyridin-2-yl)propan-1-one (1i)



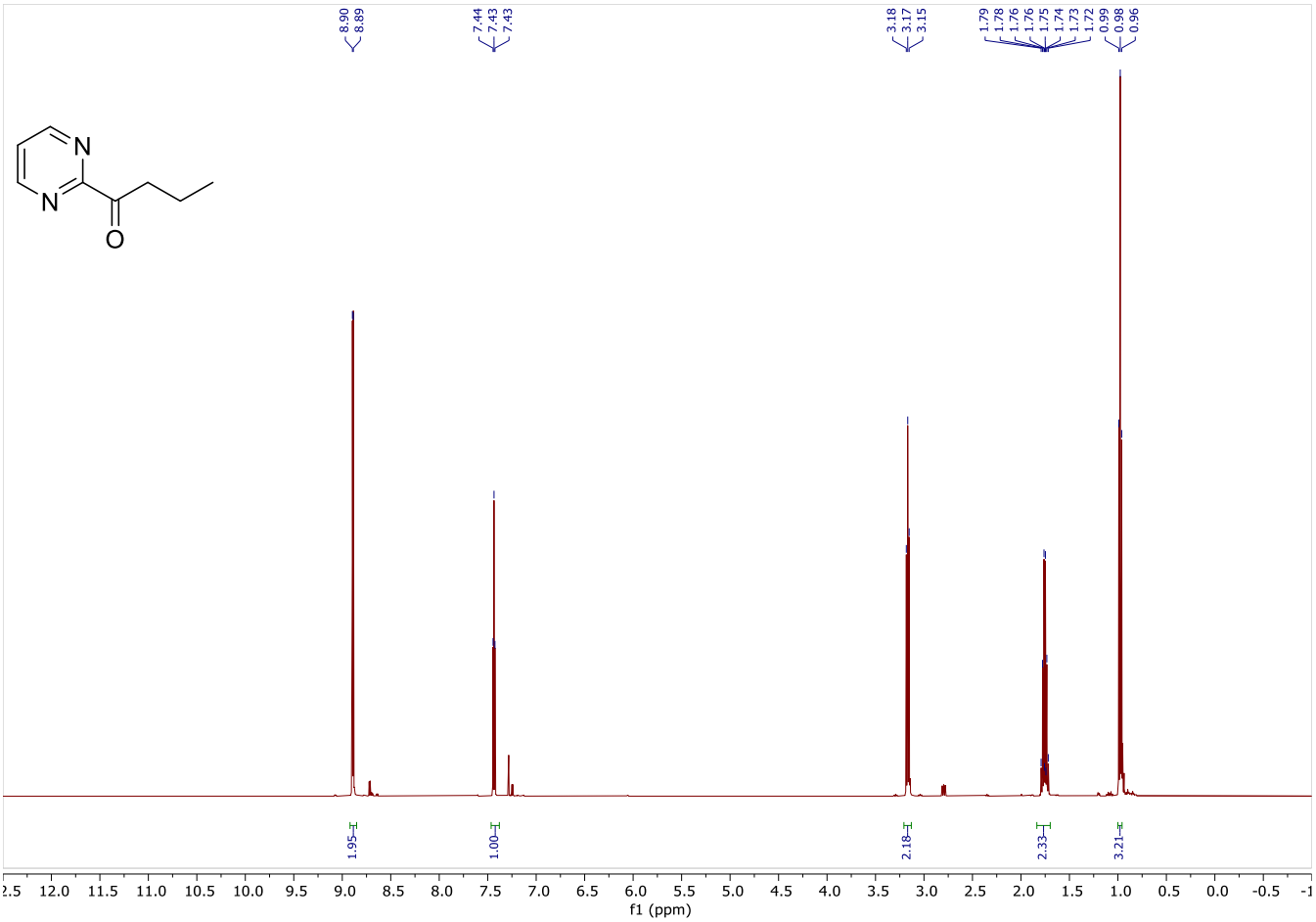


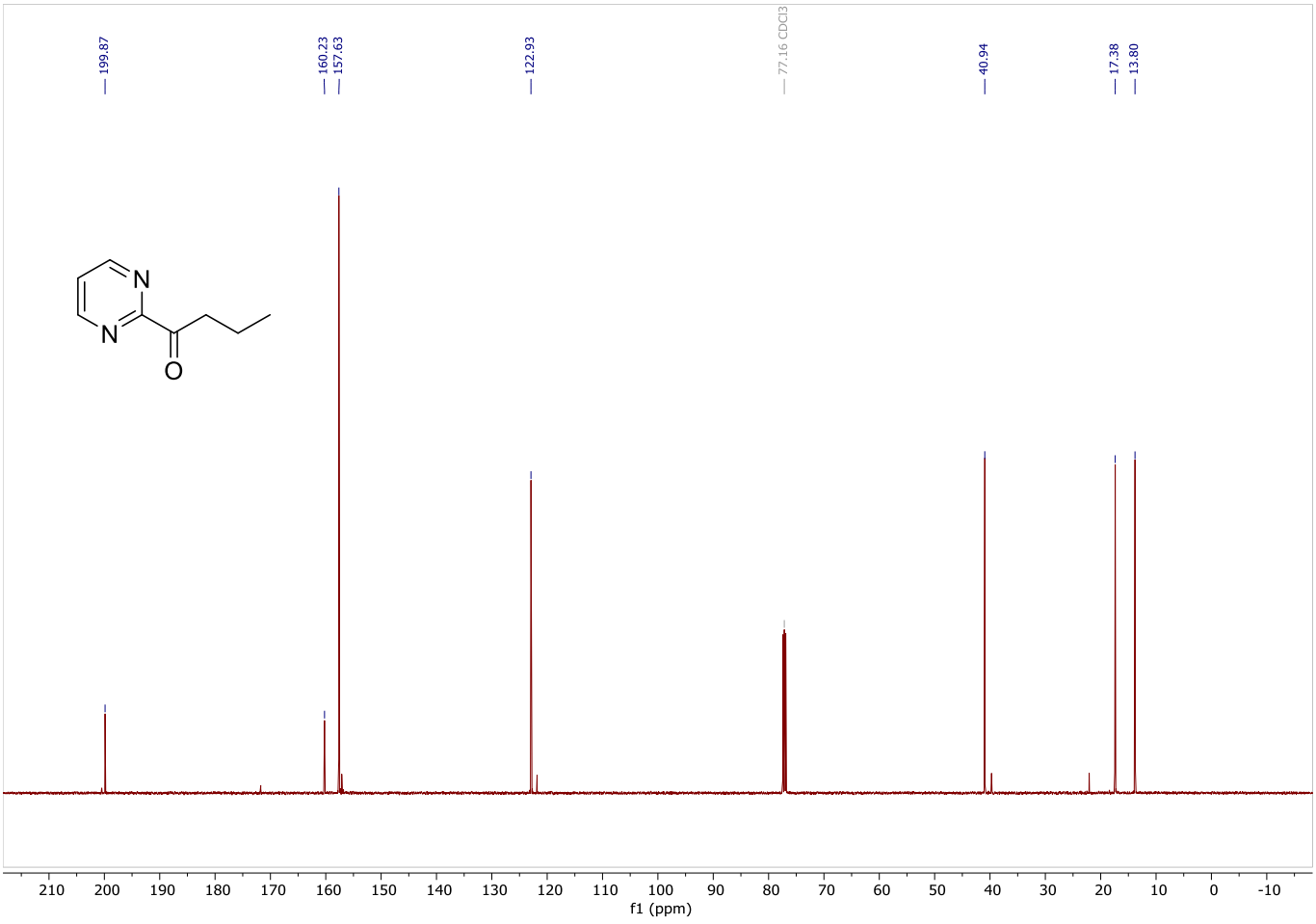
1-(pyridin-2-yl)heptan-1-one (1j)



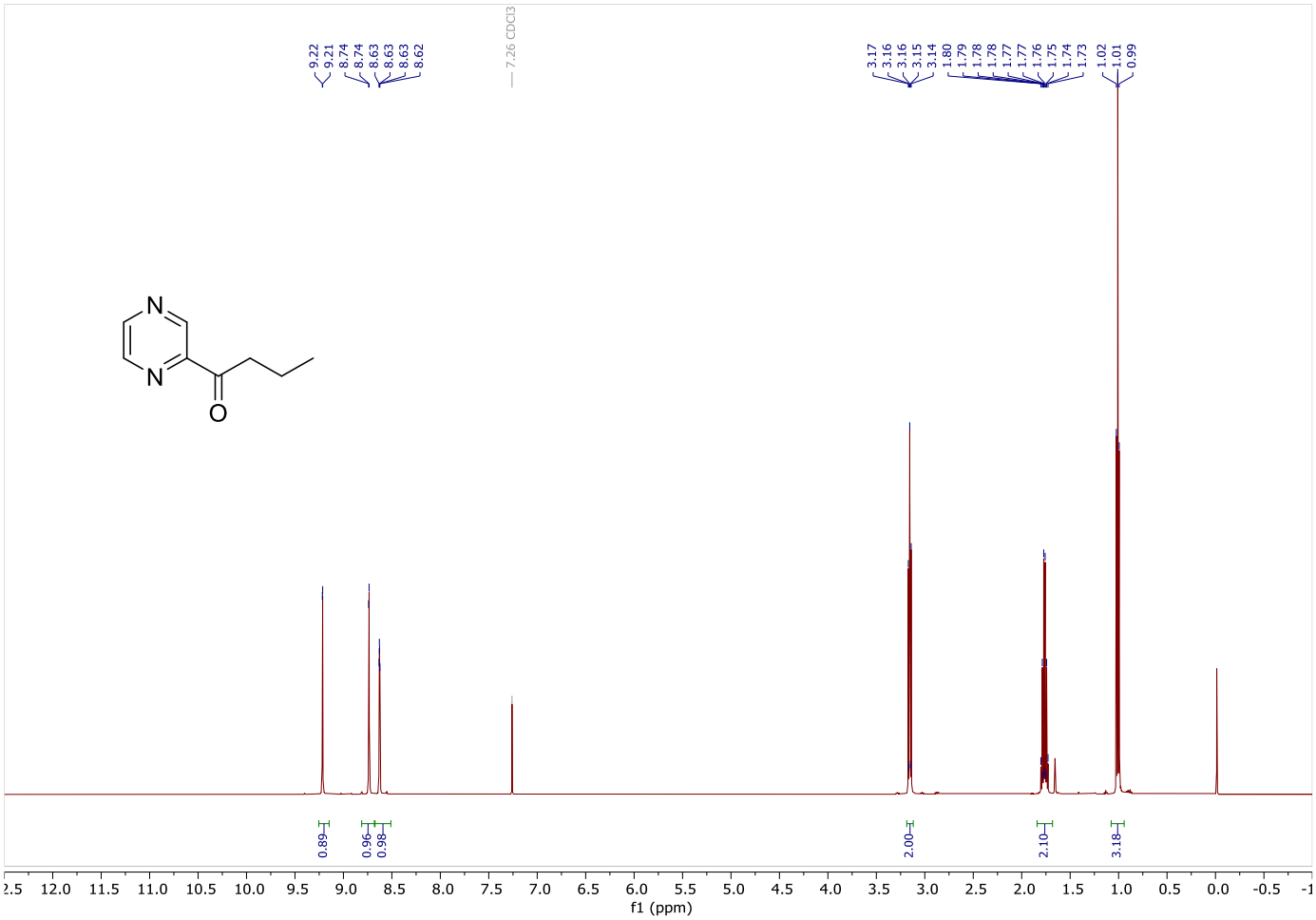


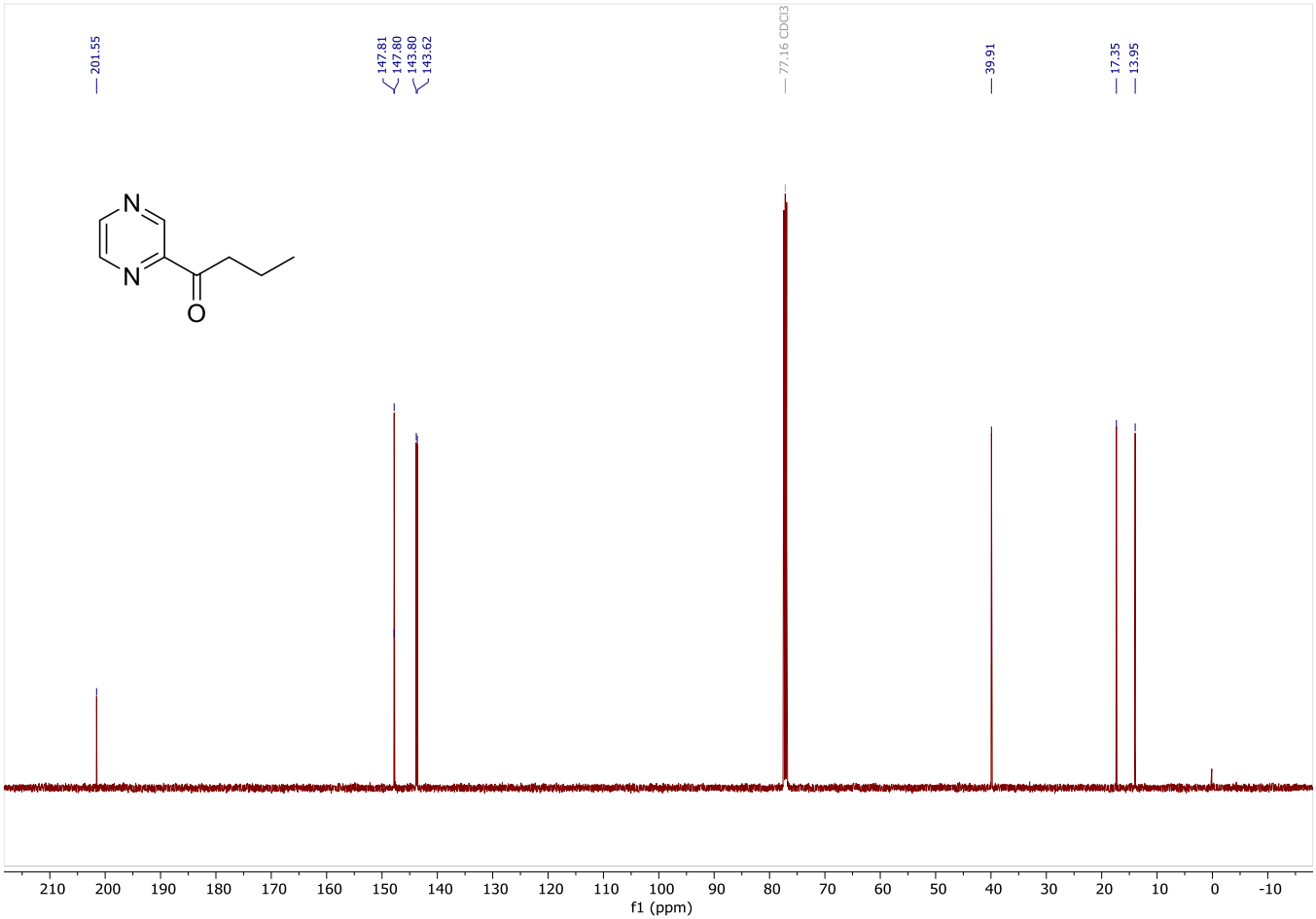
1-(pyrimidin-2-yl)butan-1-one (1k)



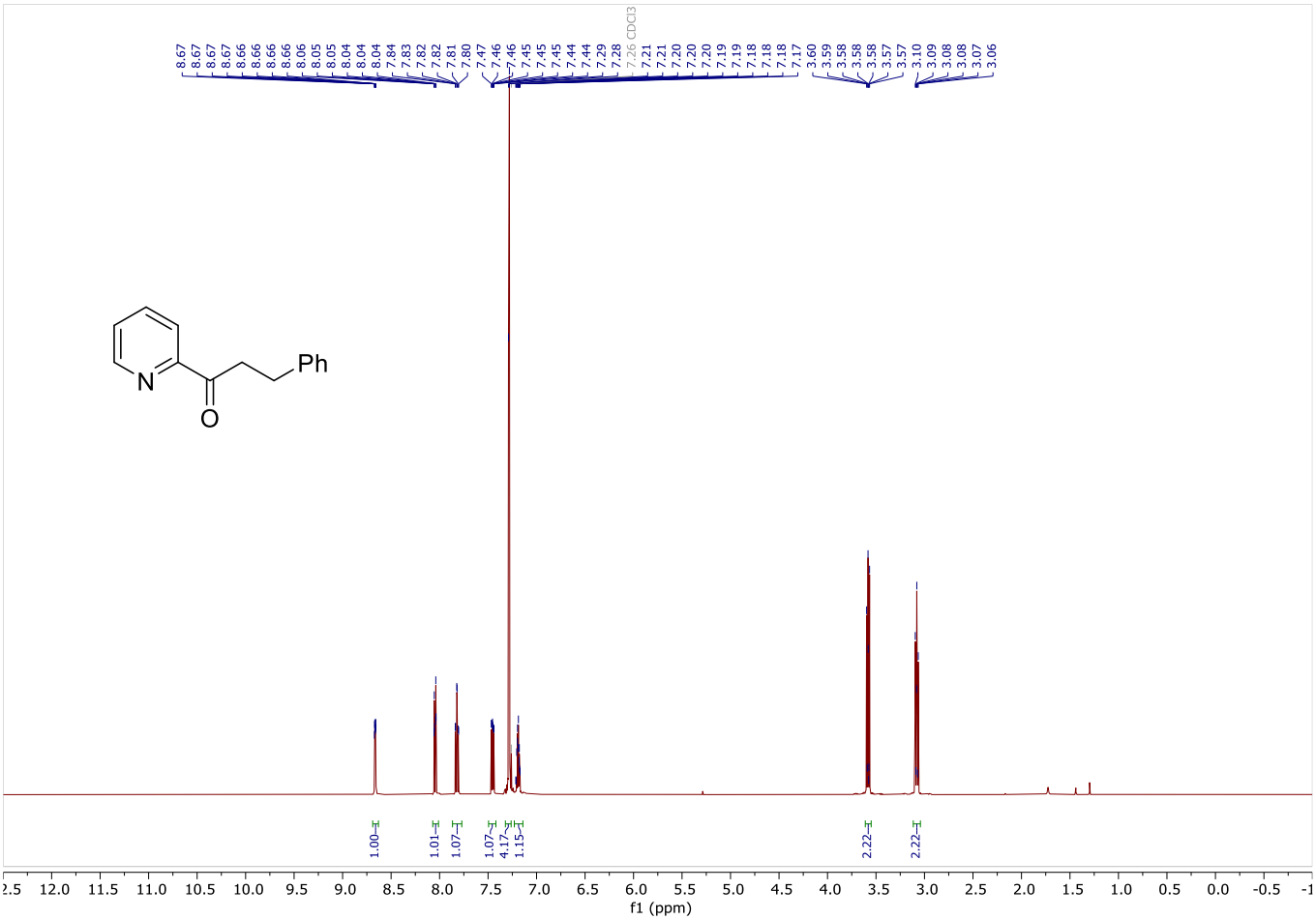


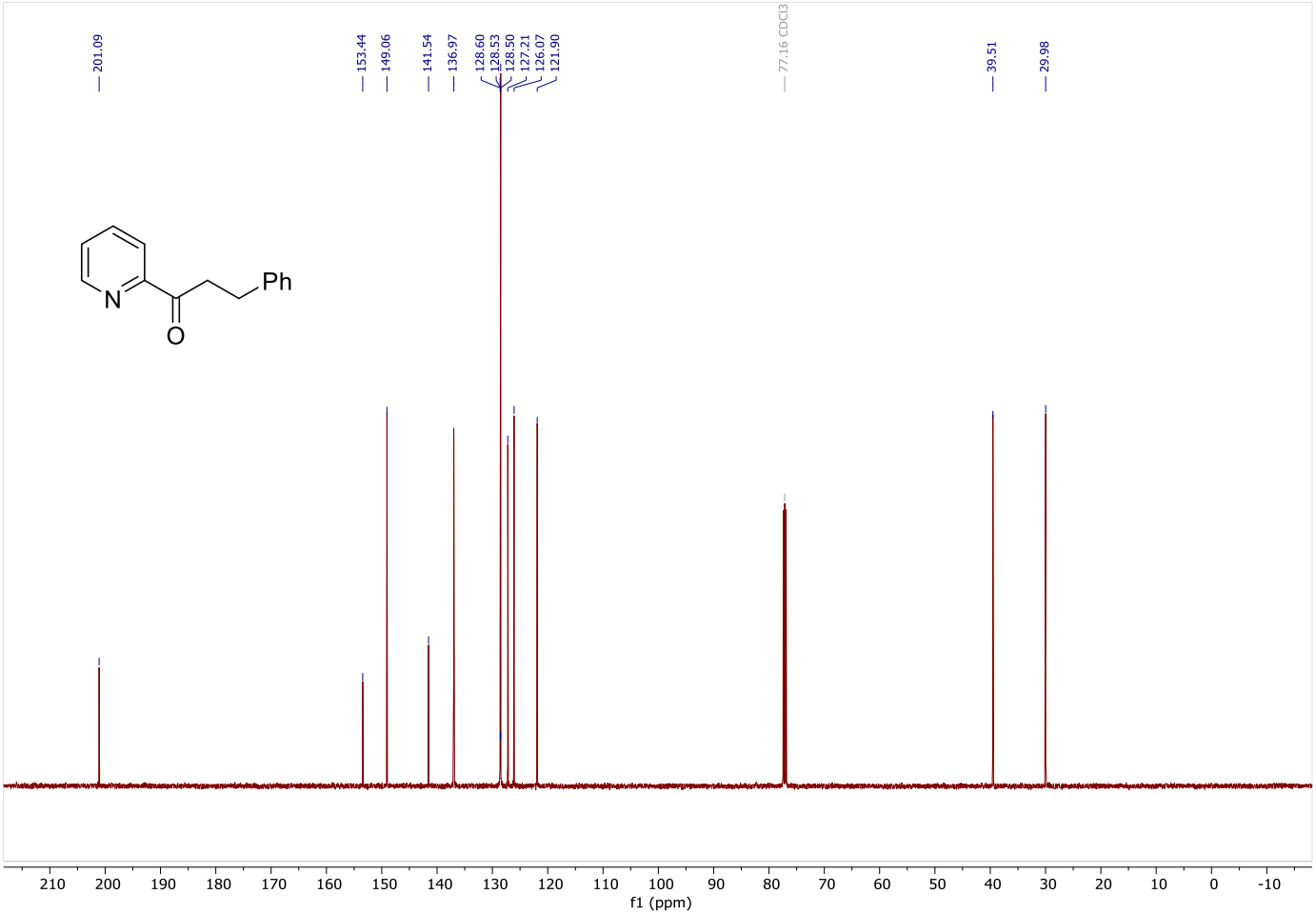
1-(pyrazin-2-yl)butan-1-one (1l)



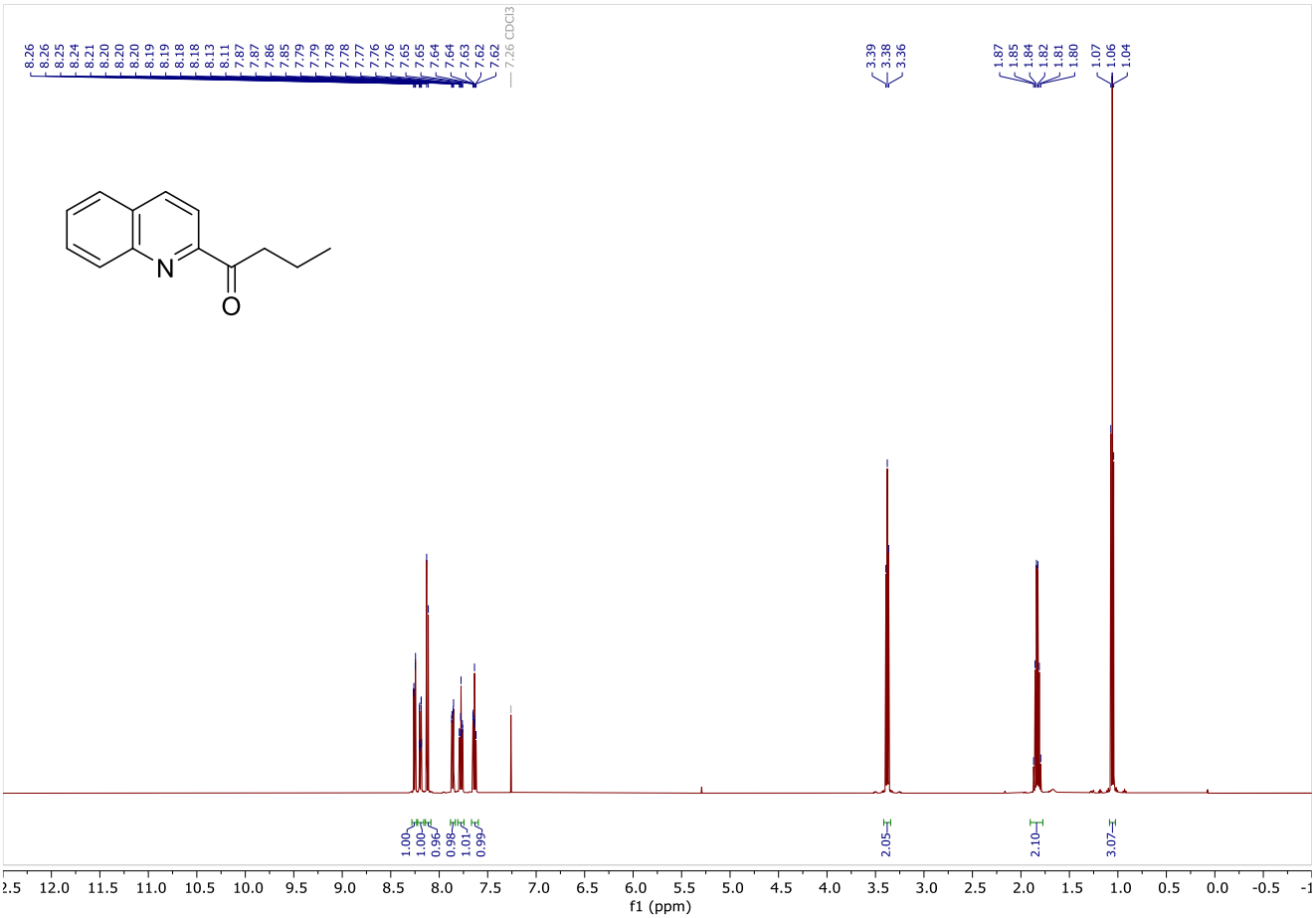


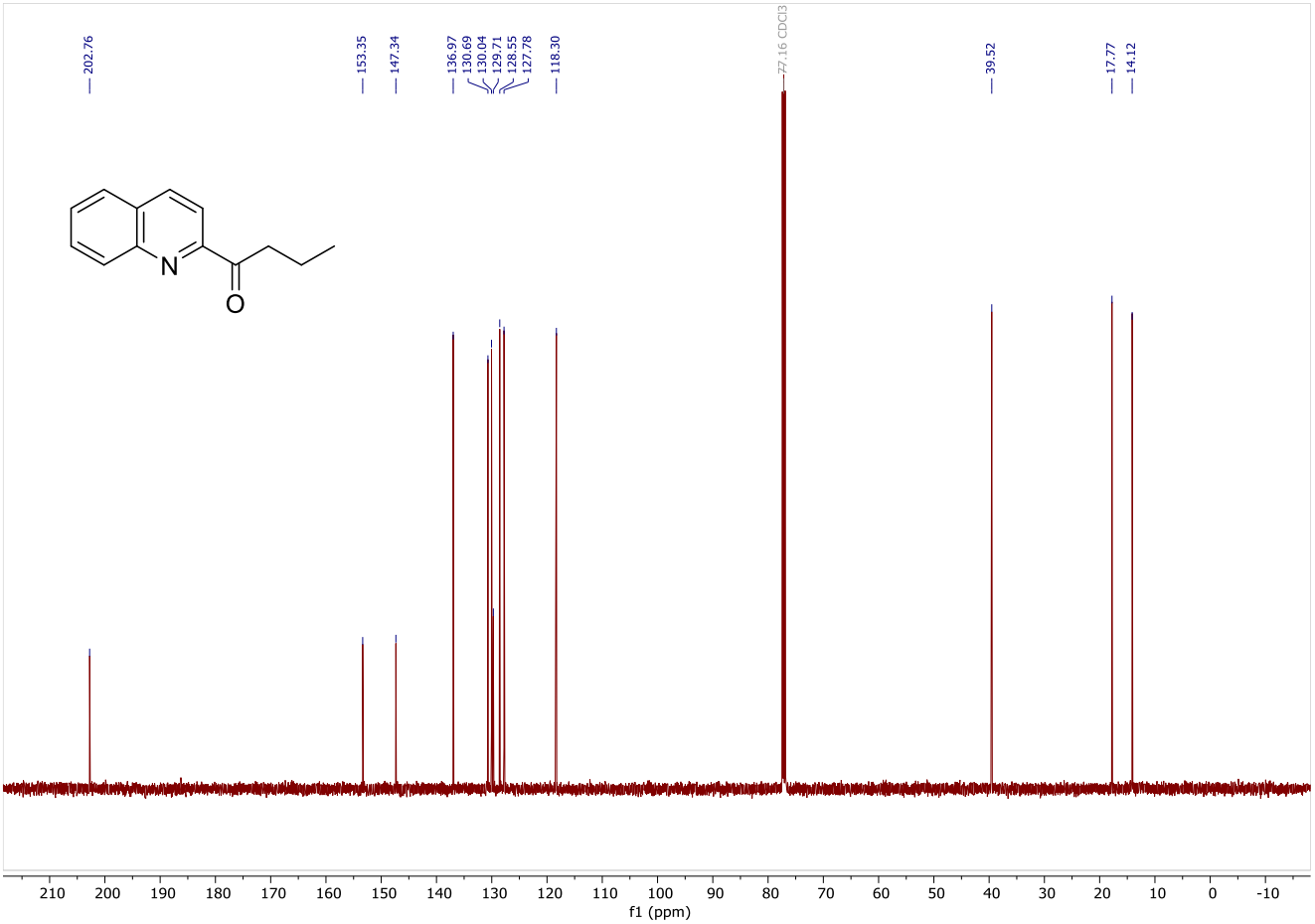
3-phenyl-1-(pyridin-2-yl)propan-1-one (1m)



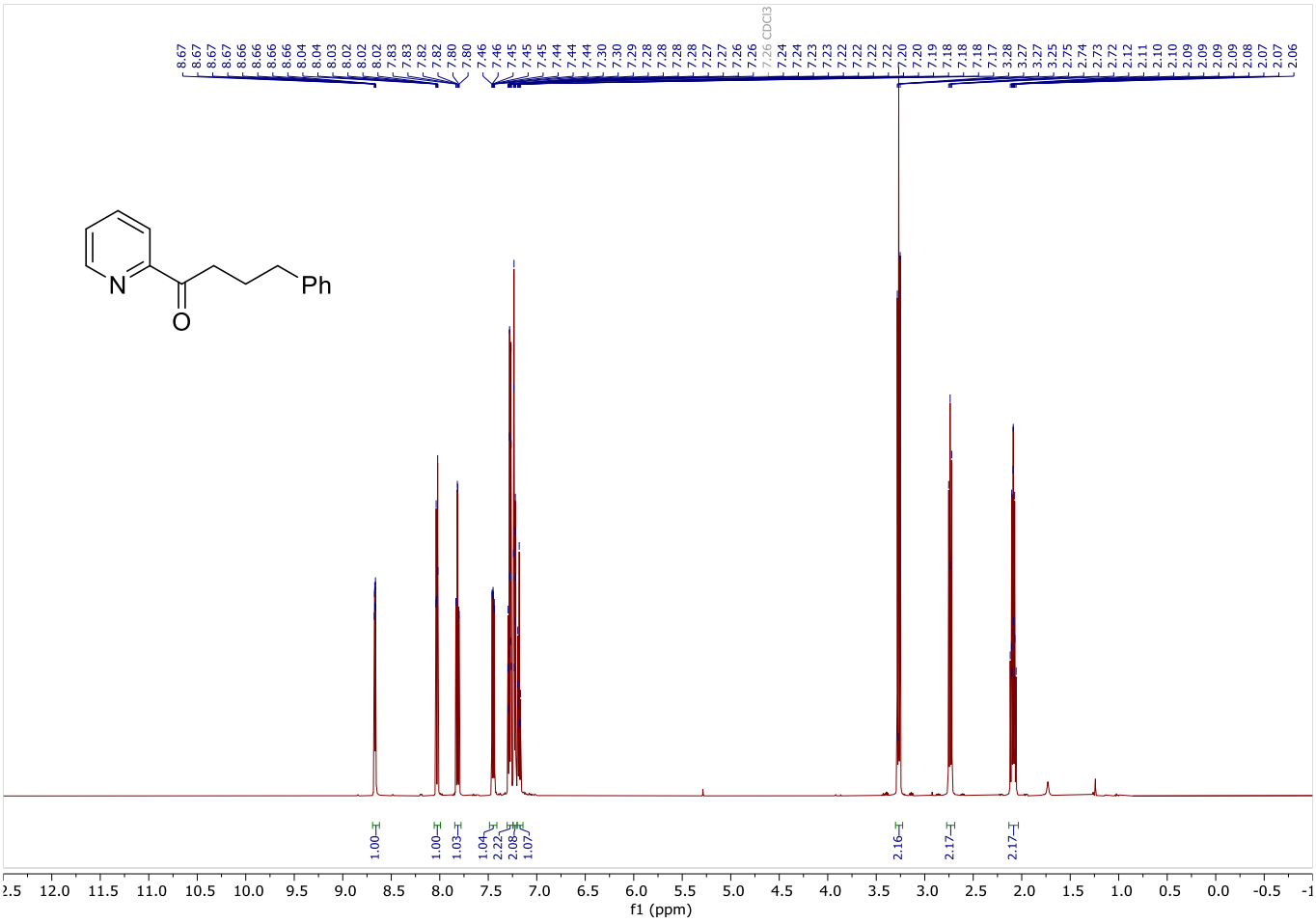


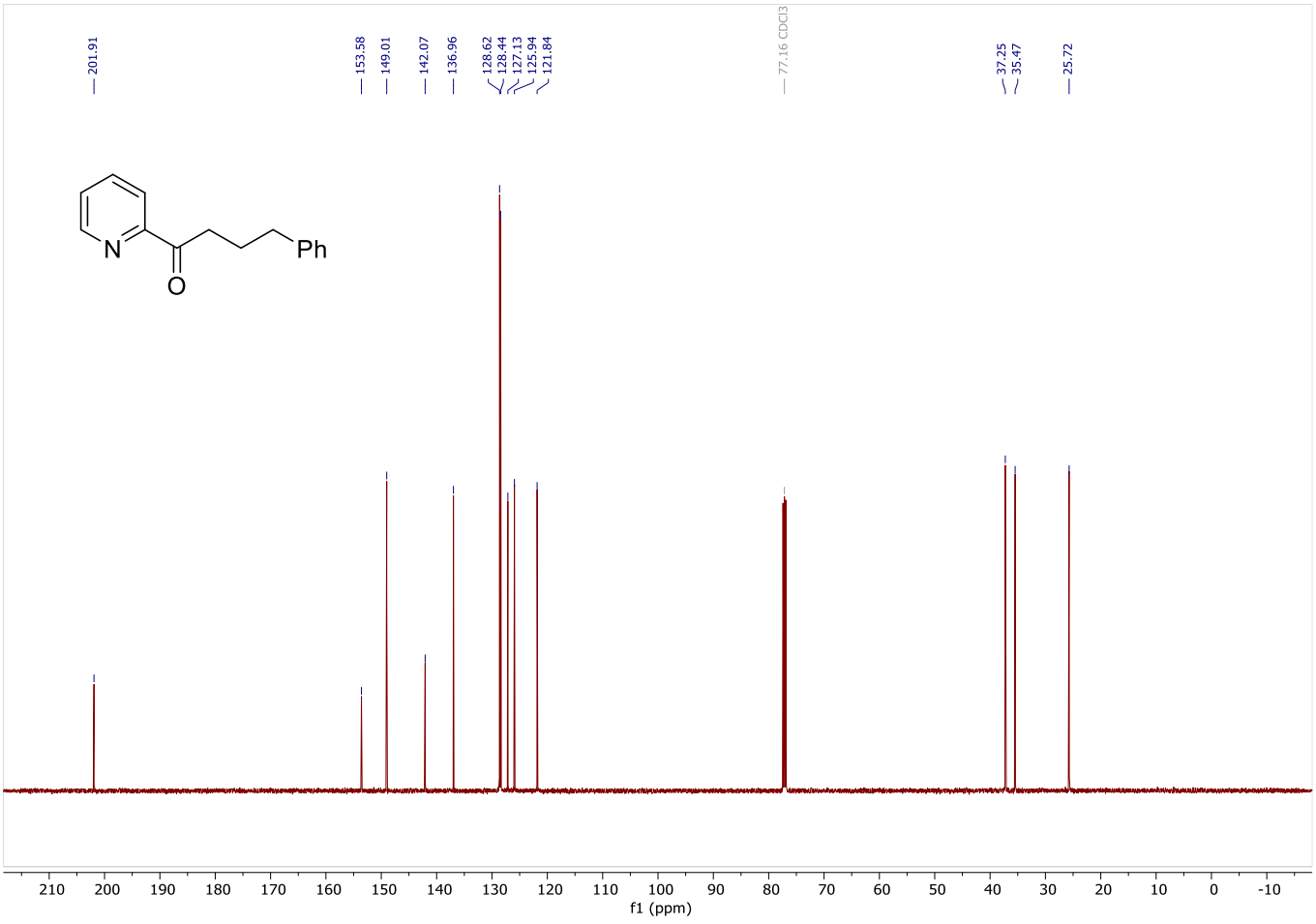
1-(quinolin-2-yl)butan-1-one (1n)



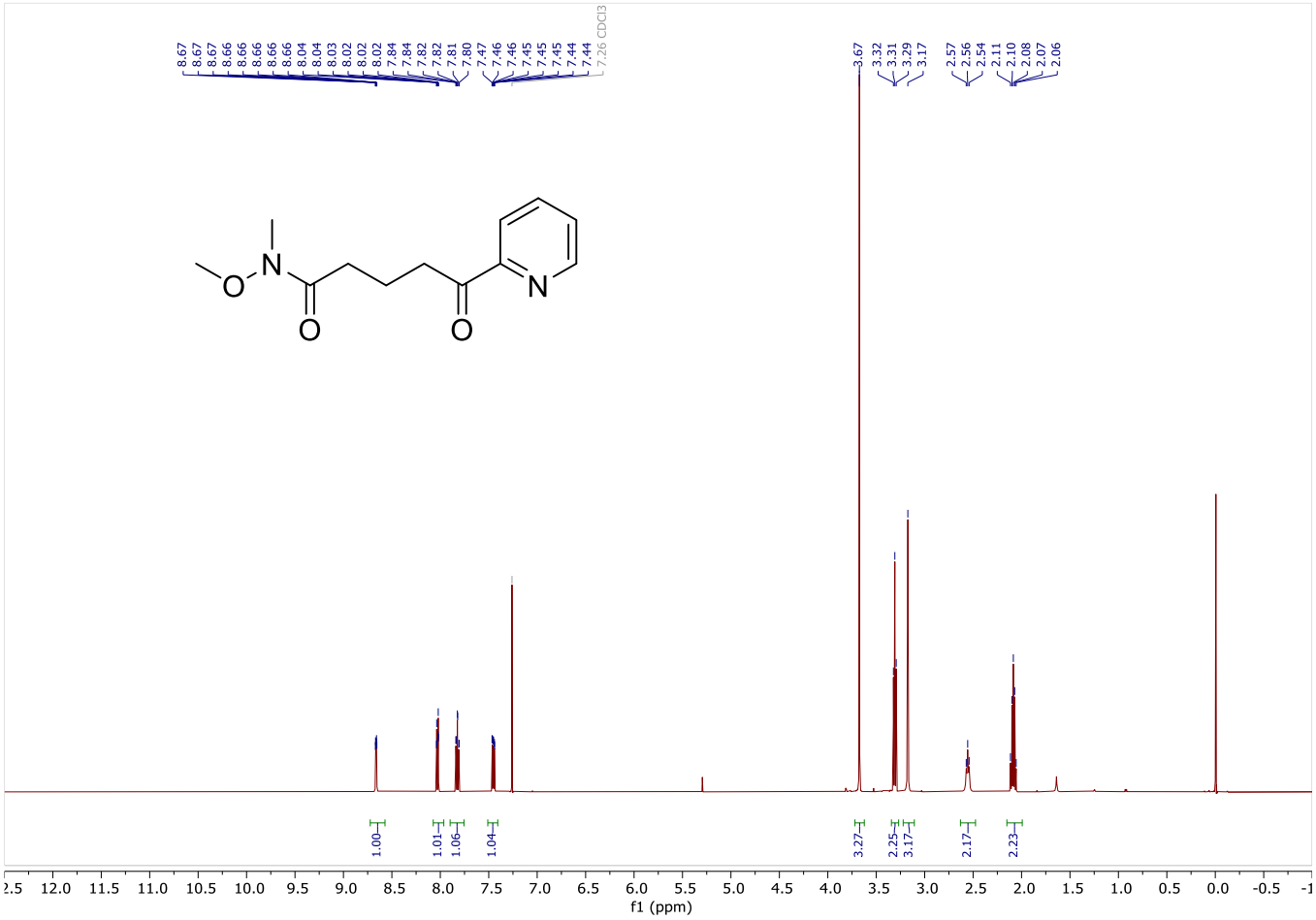


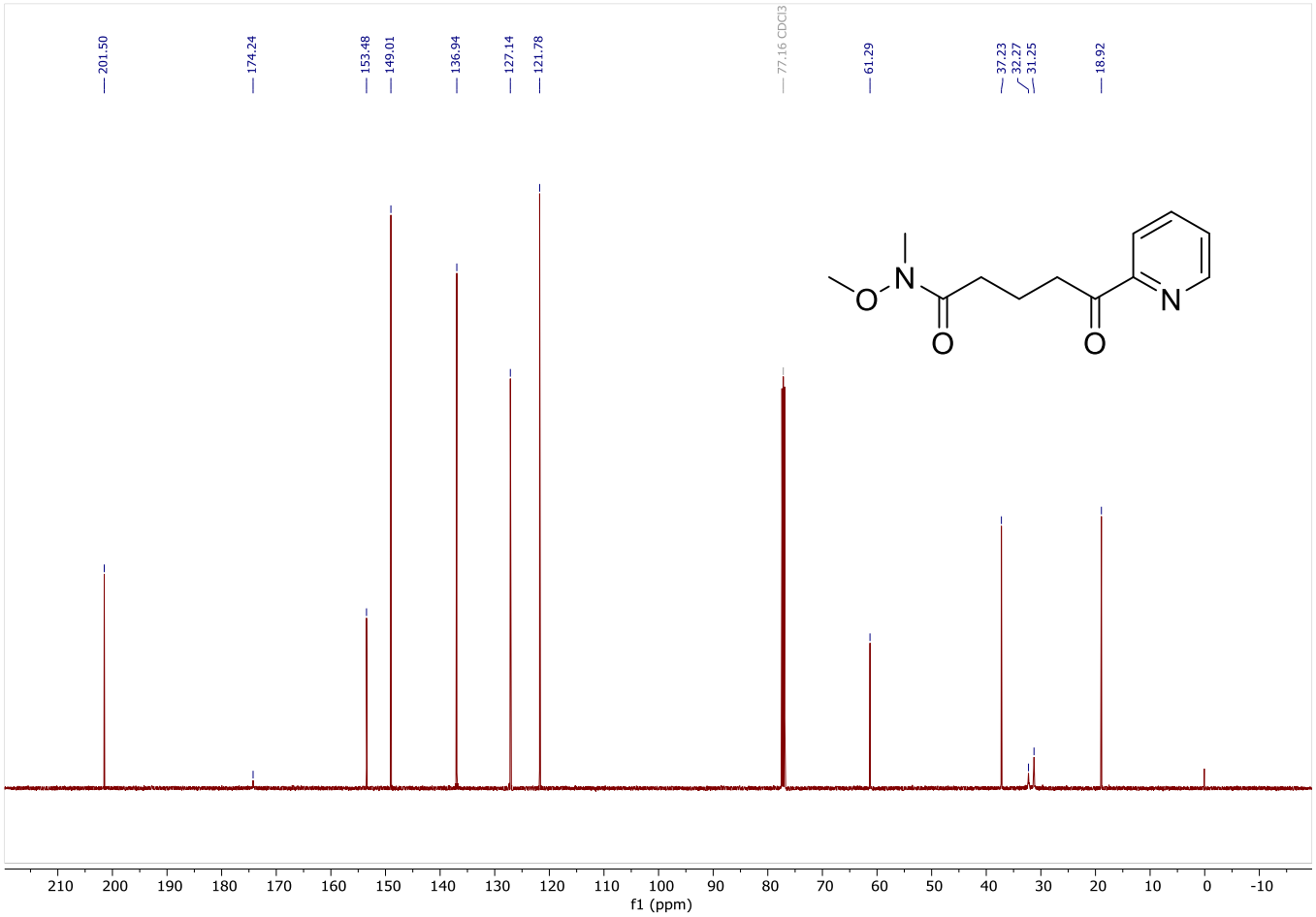
4-phenyl-1-(pyridin-2-yl)butan-1-one (1o)



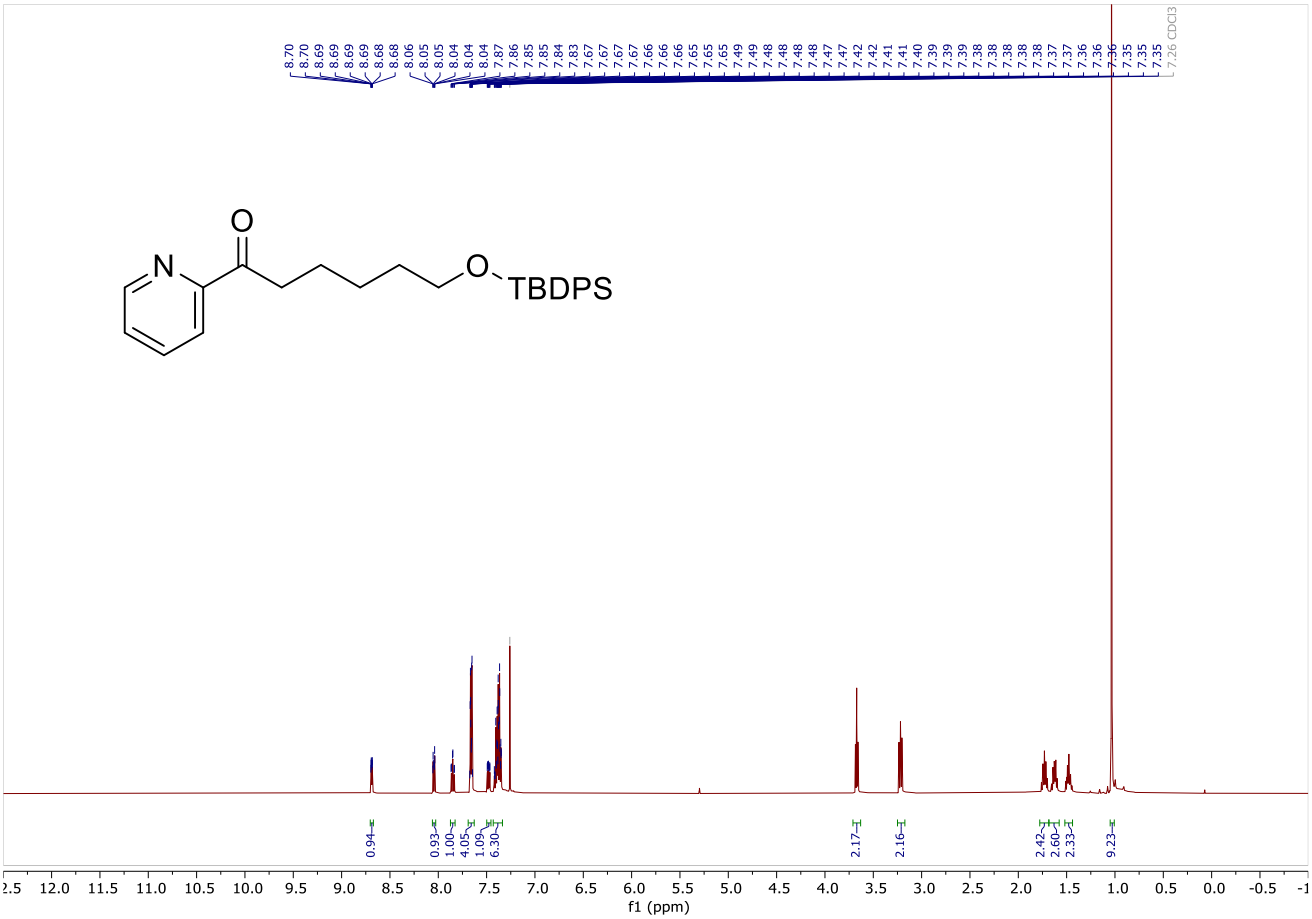


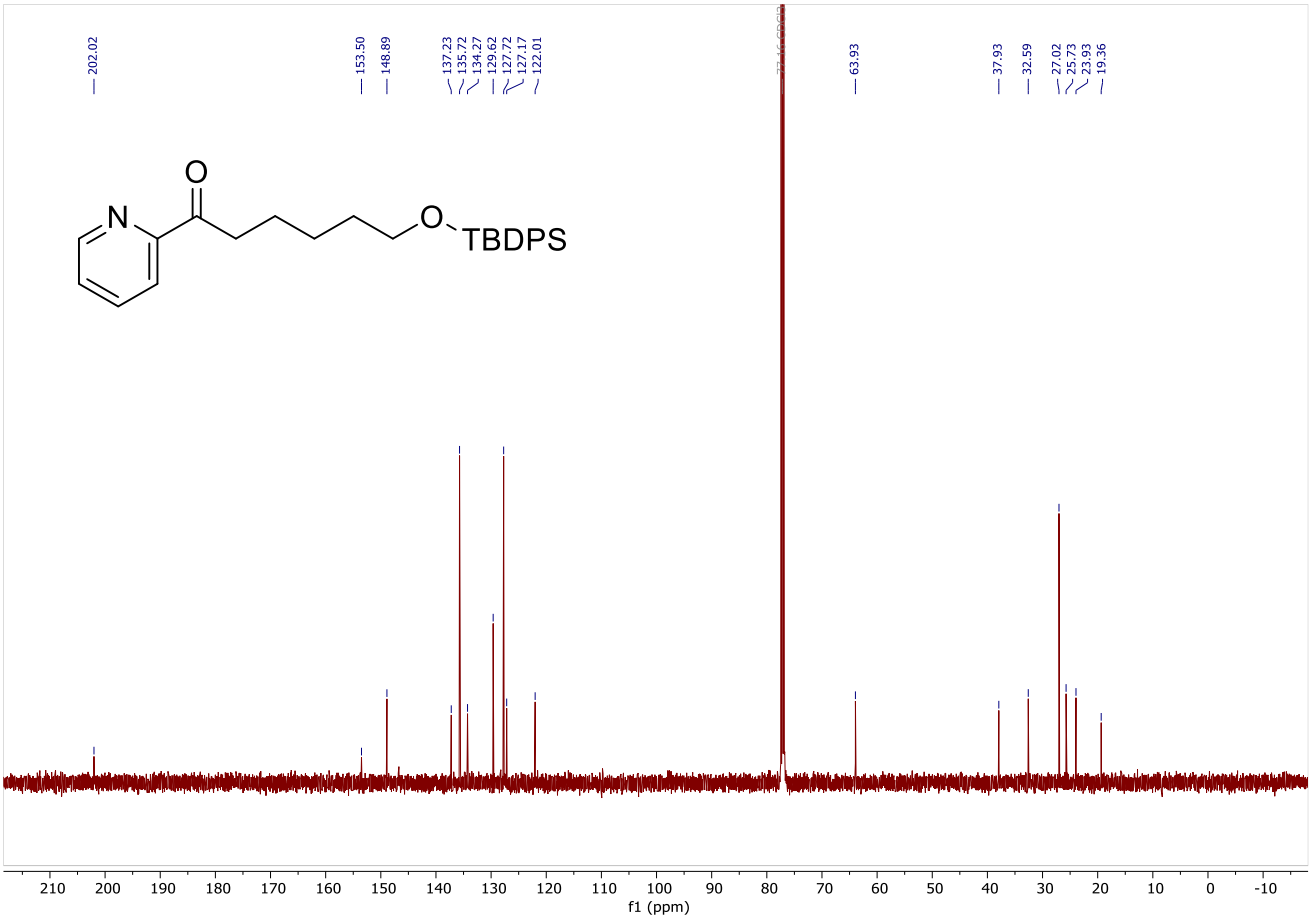
N-methoxy-N-methyl-5-oxo-5-(pyridin-2-yl)pentanamide (1p)



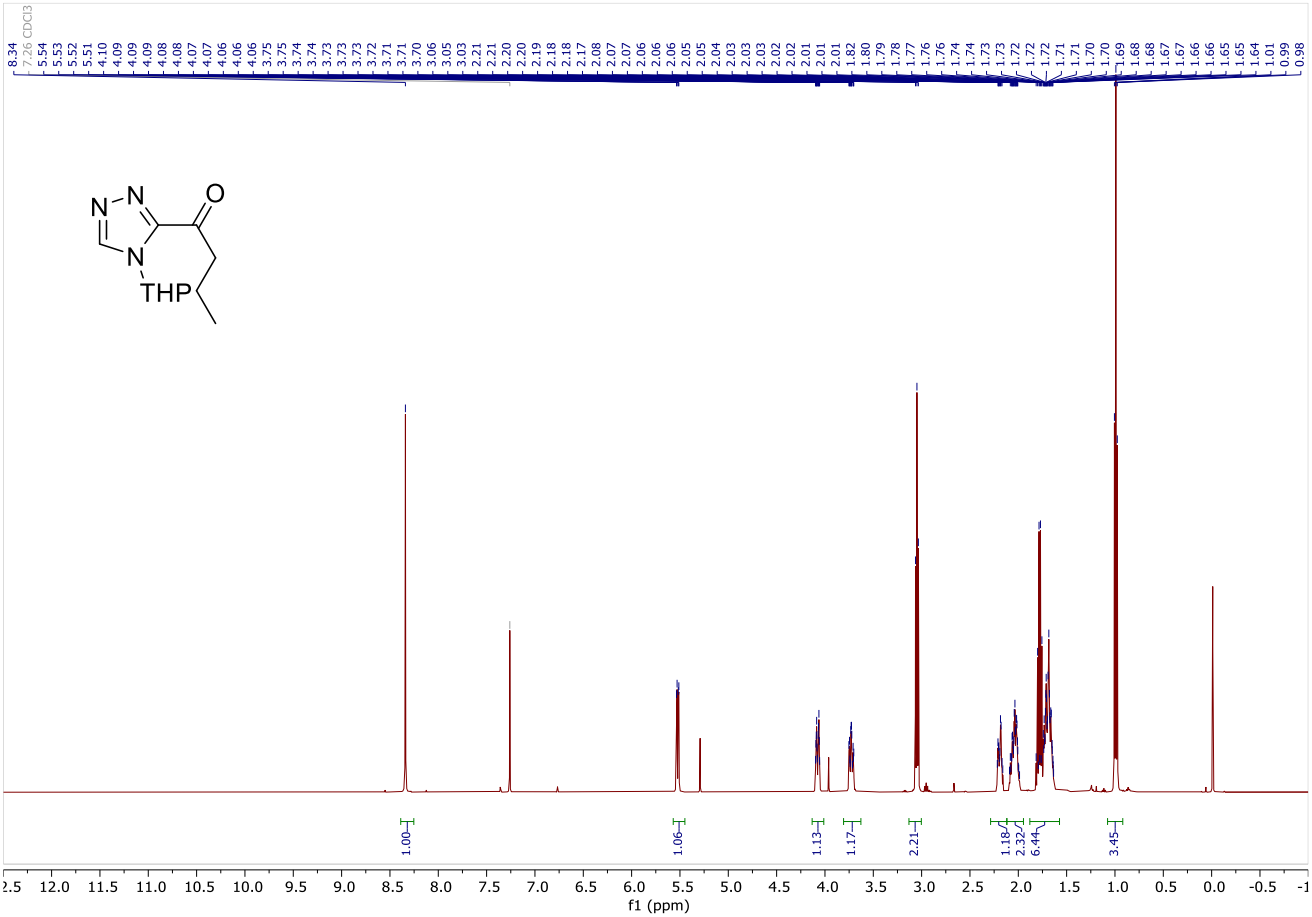


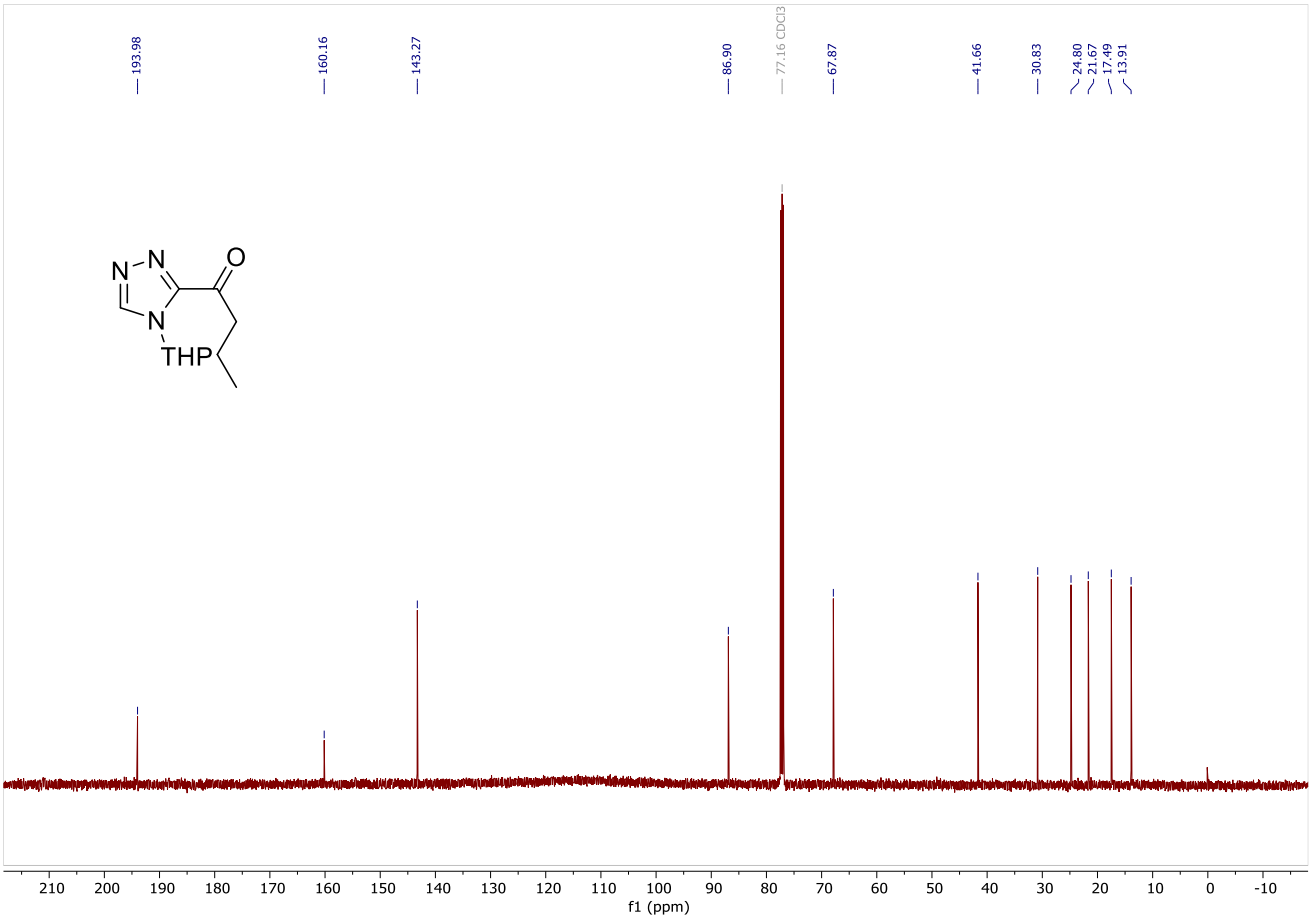
6-((tert-butyldiphenylsilyl)oxy)-1-(pyridin-2-yl)hexan-1-one (1g)



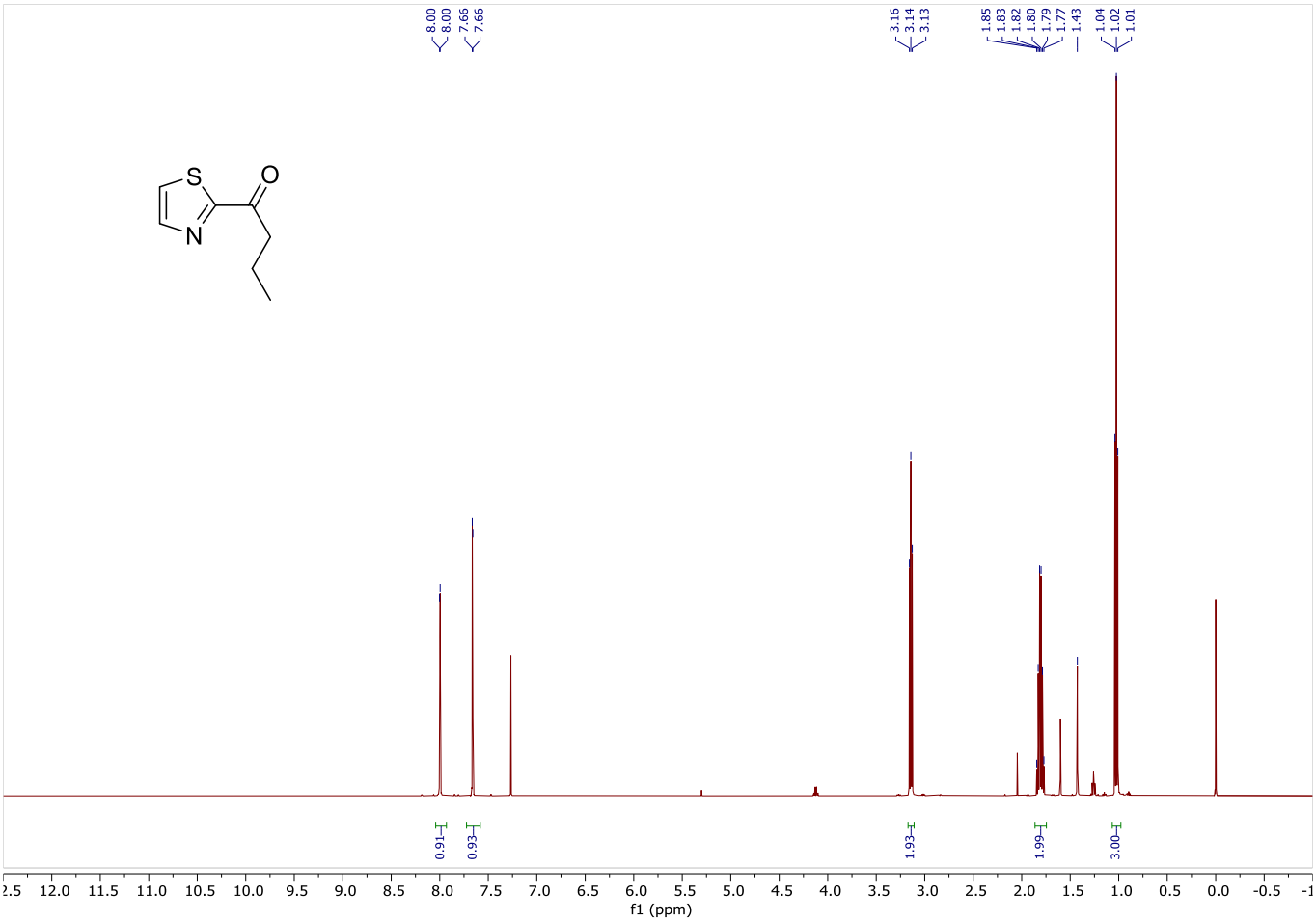


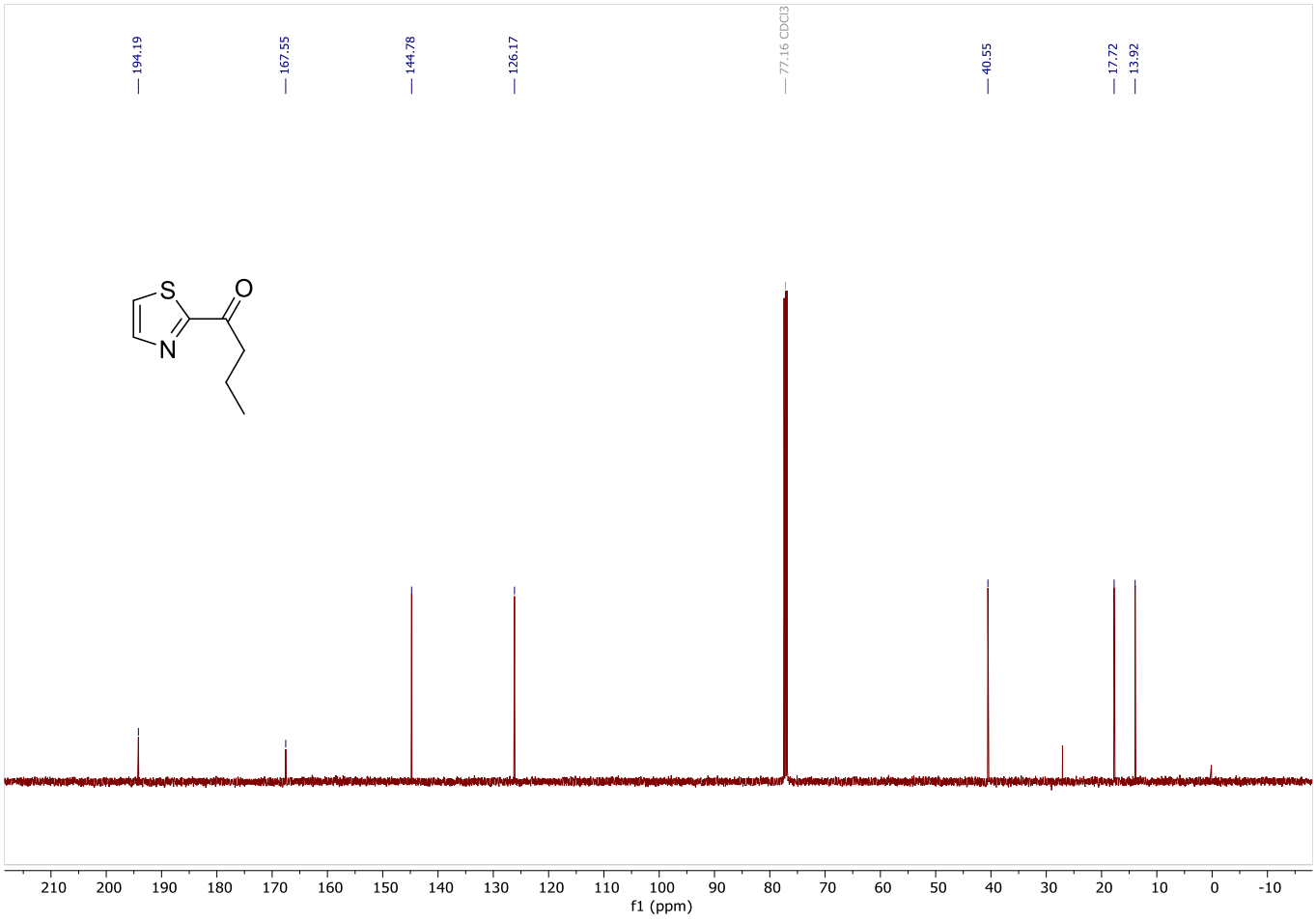
1-(4-(tetrahydro-2H-pyran-2-yl)-4H-1,2,4-triazol-3-yl)butan-1-one (1r)



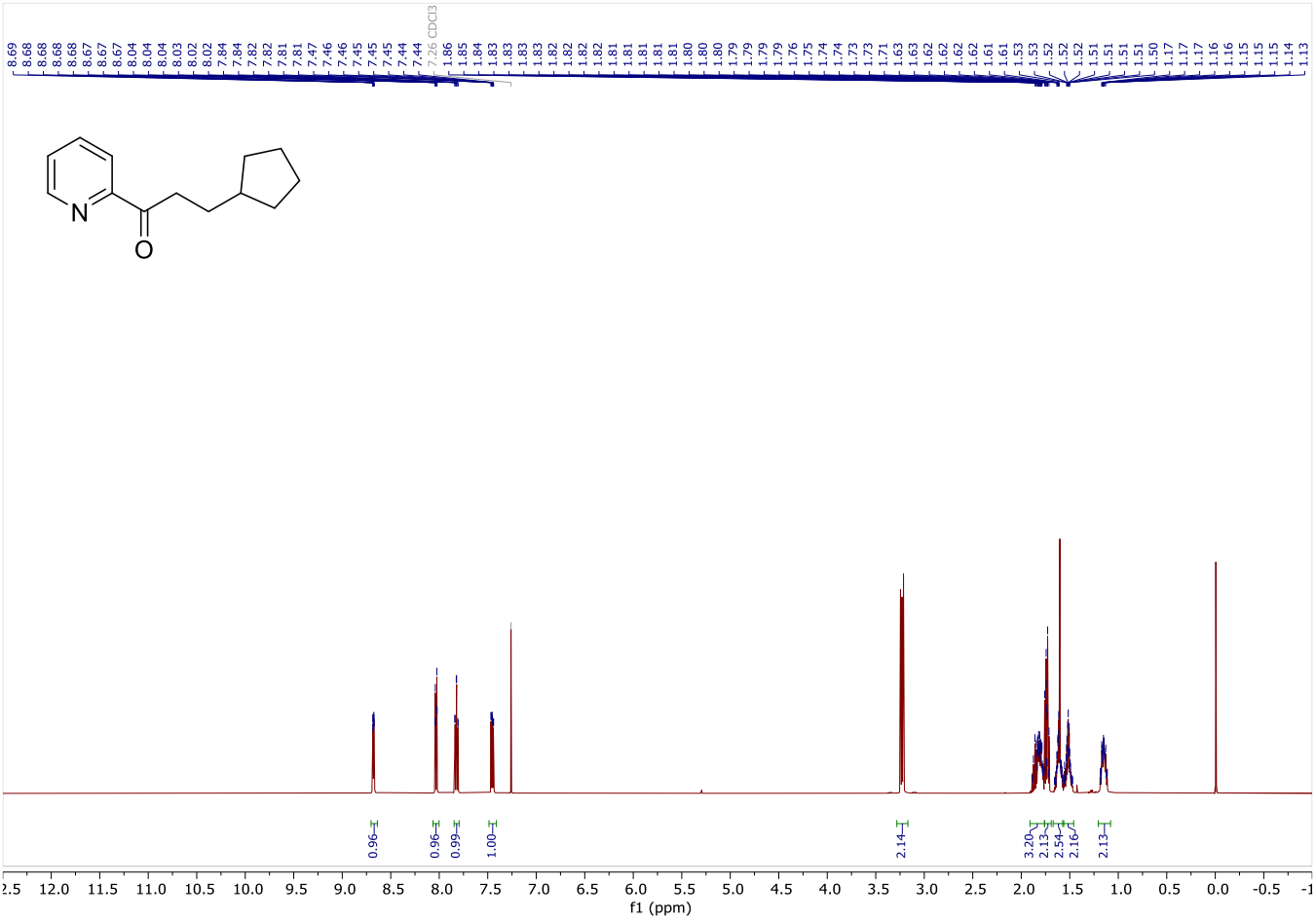


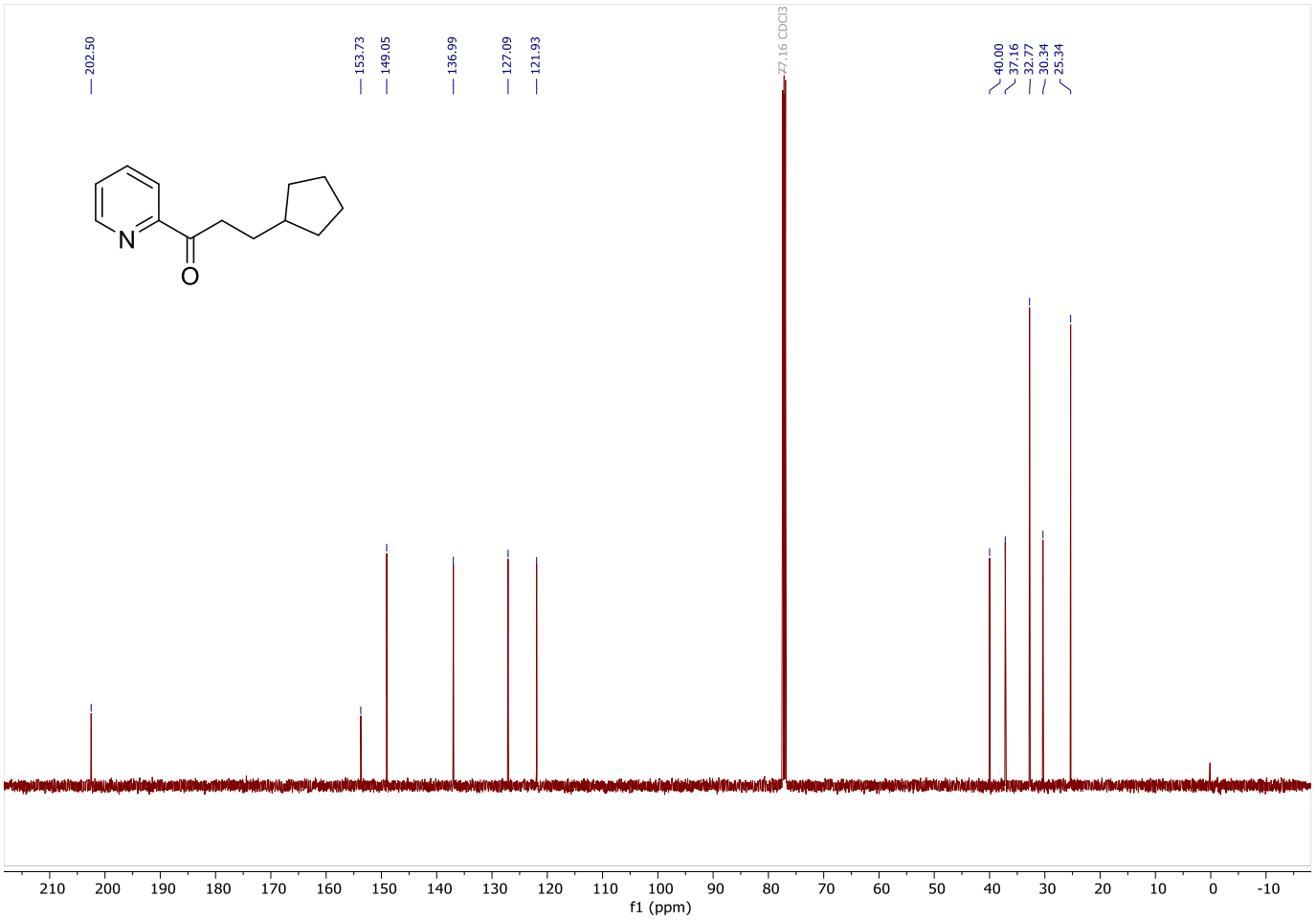
1-(thiazol-2-yl)butan-1-one (1s)



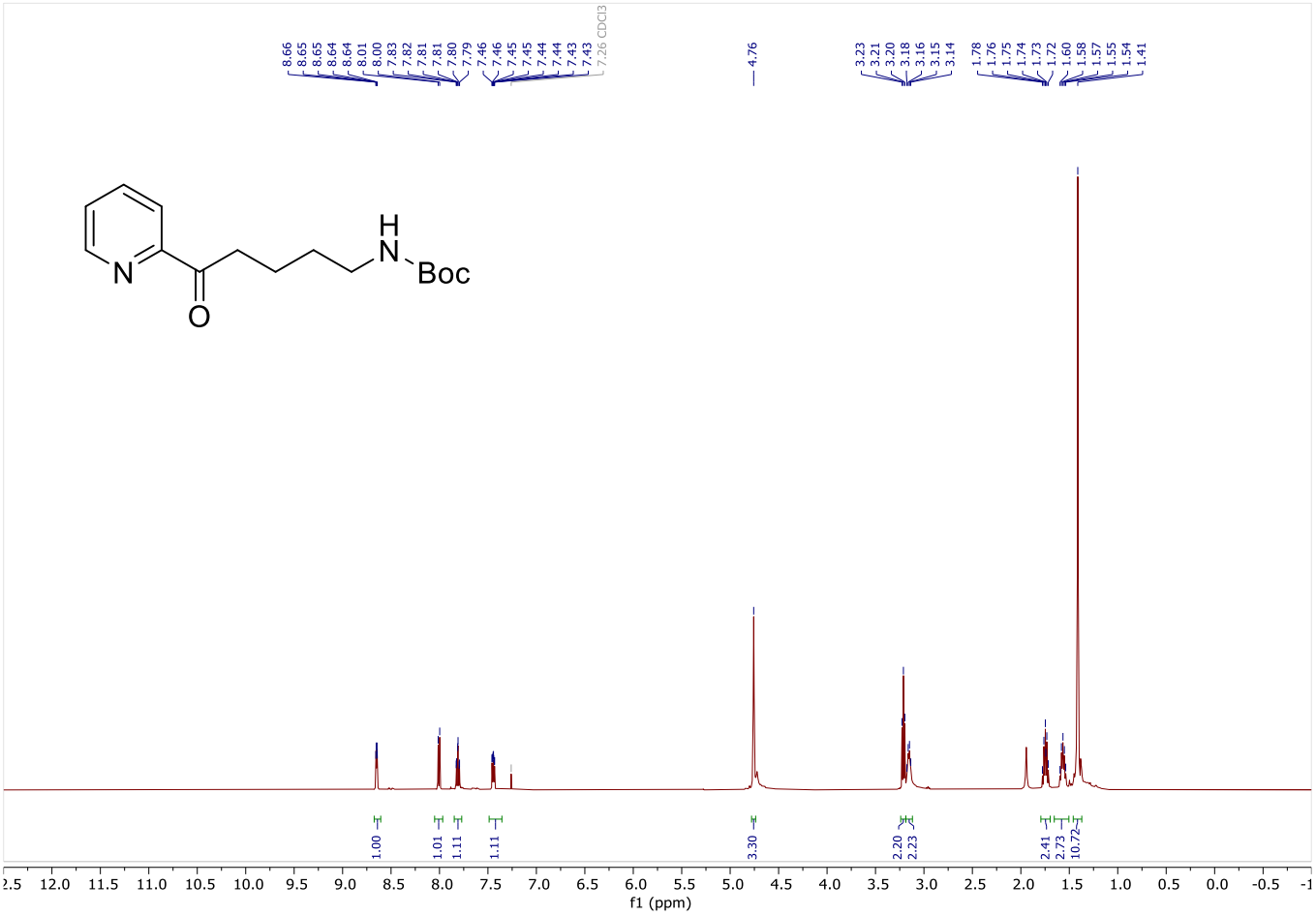


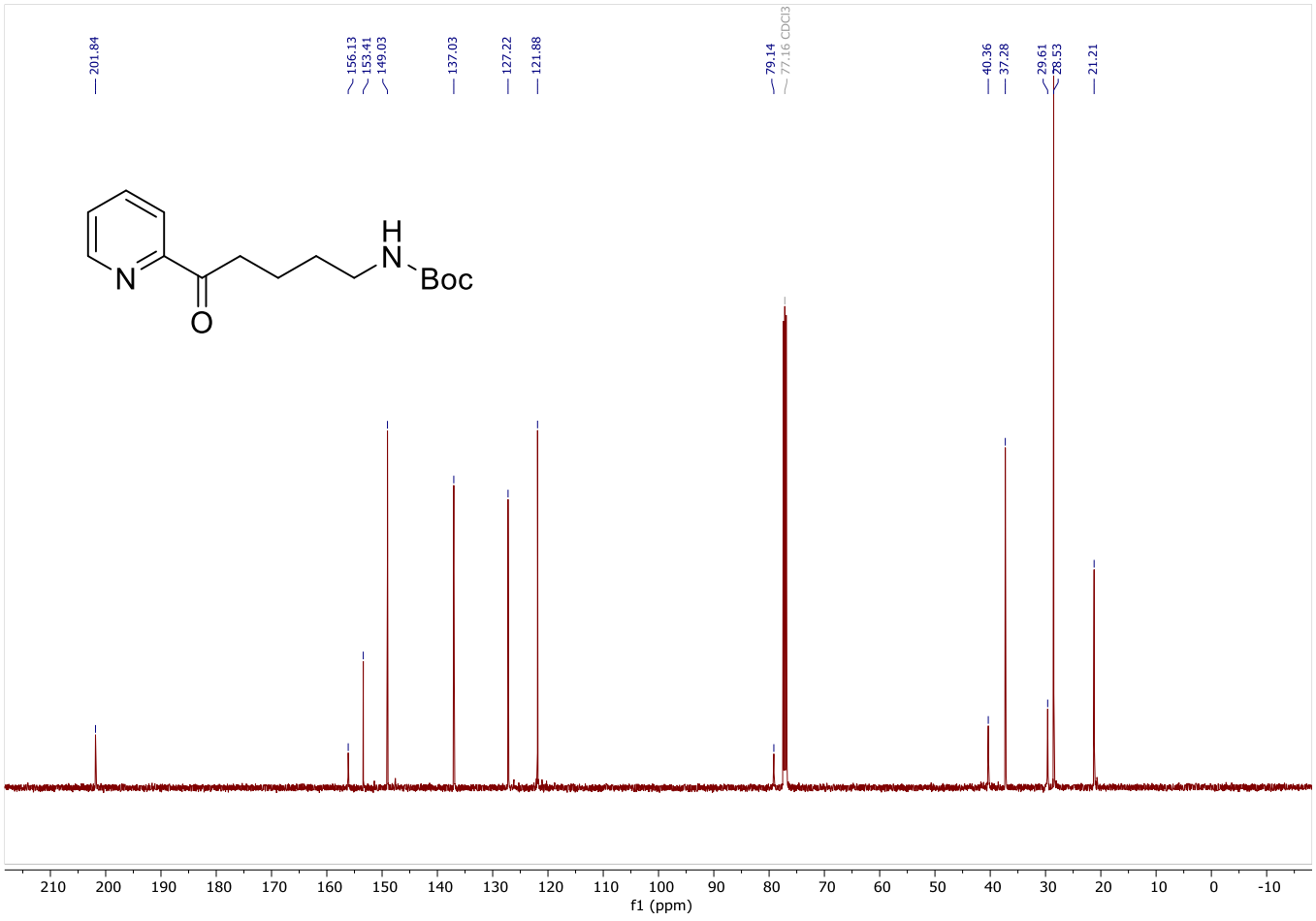
3-cyclopentyl-1-(pyridin-2-yl)propan-1-one (1t)



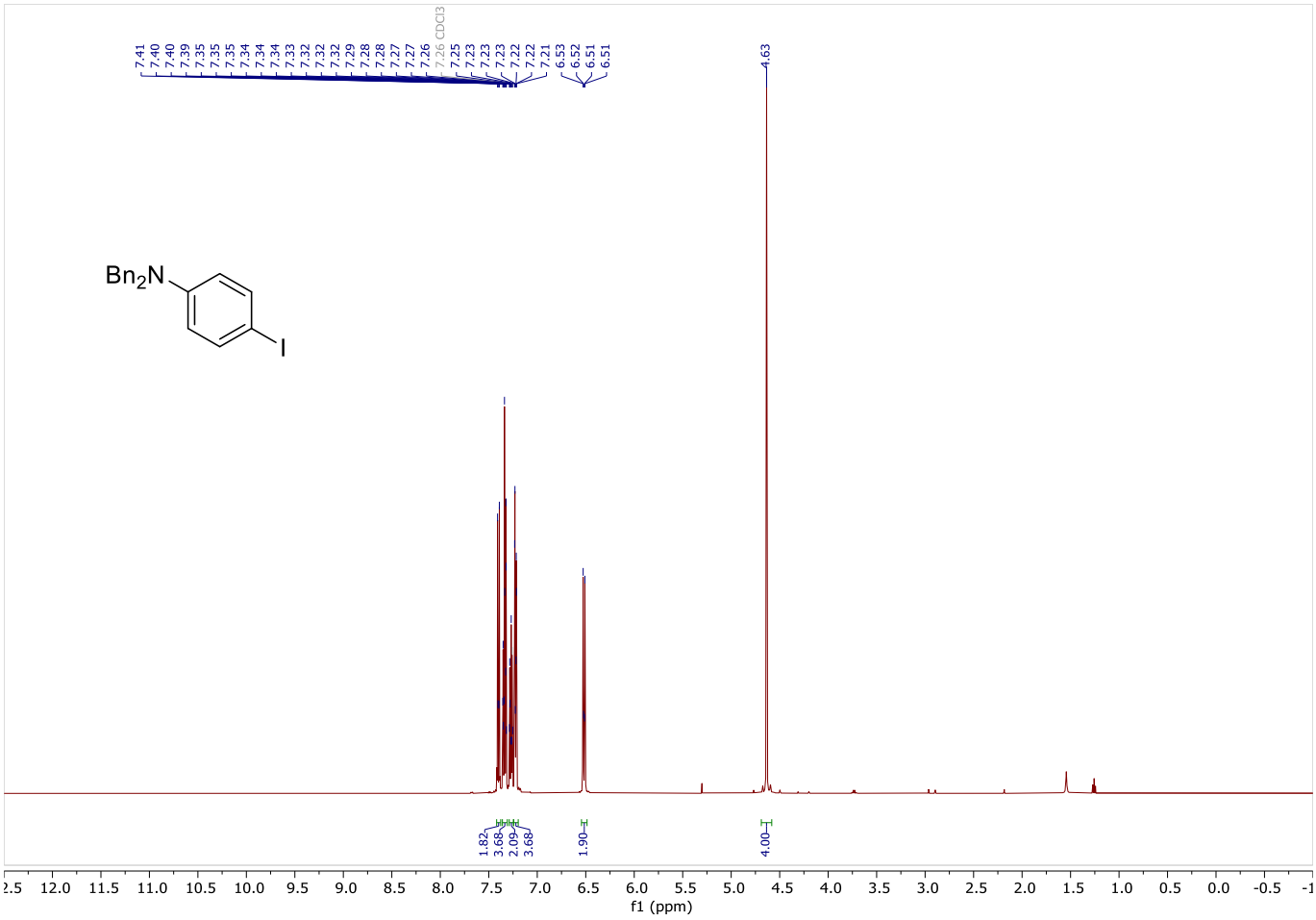


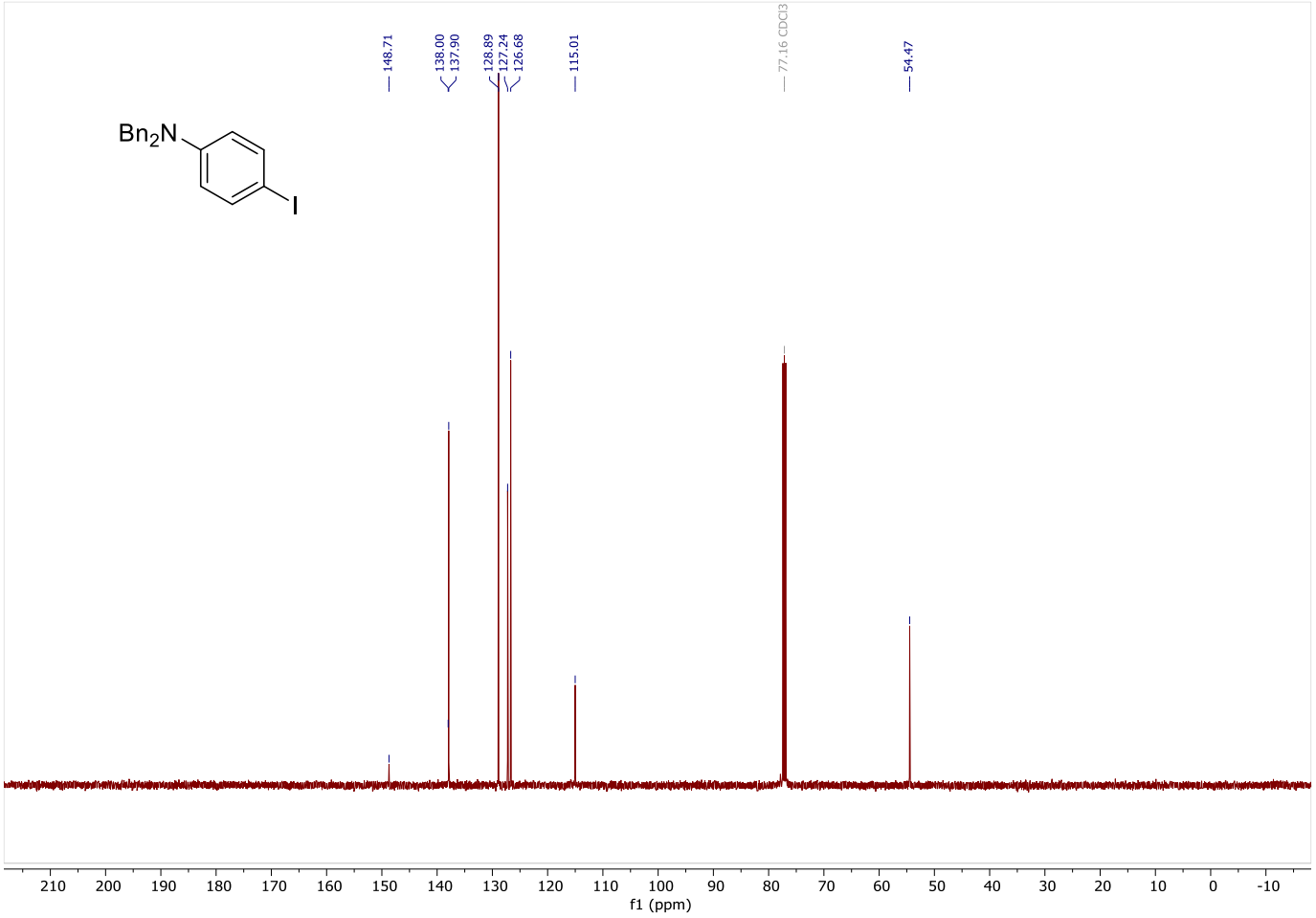
tert-butyl (6-oxo-6-(pyridin-2-yl)hexyl)carbamate (1u)



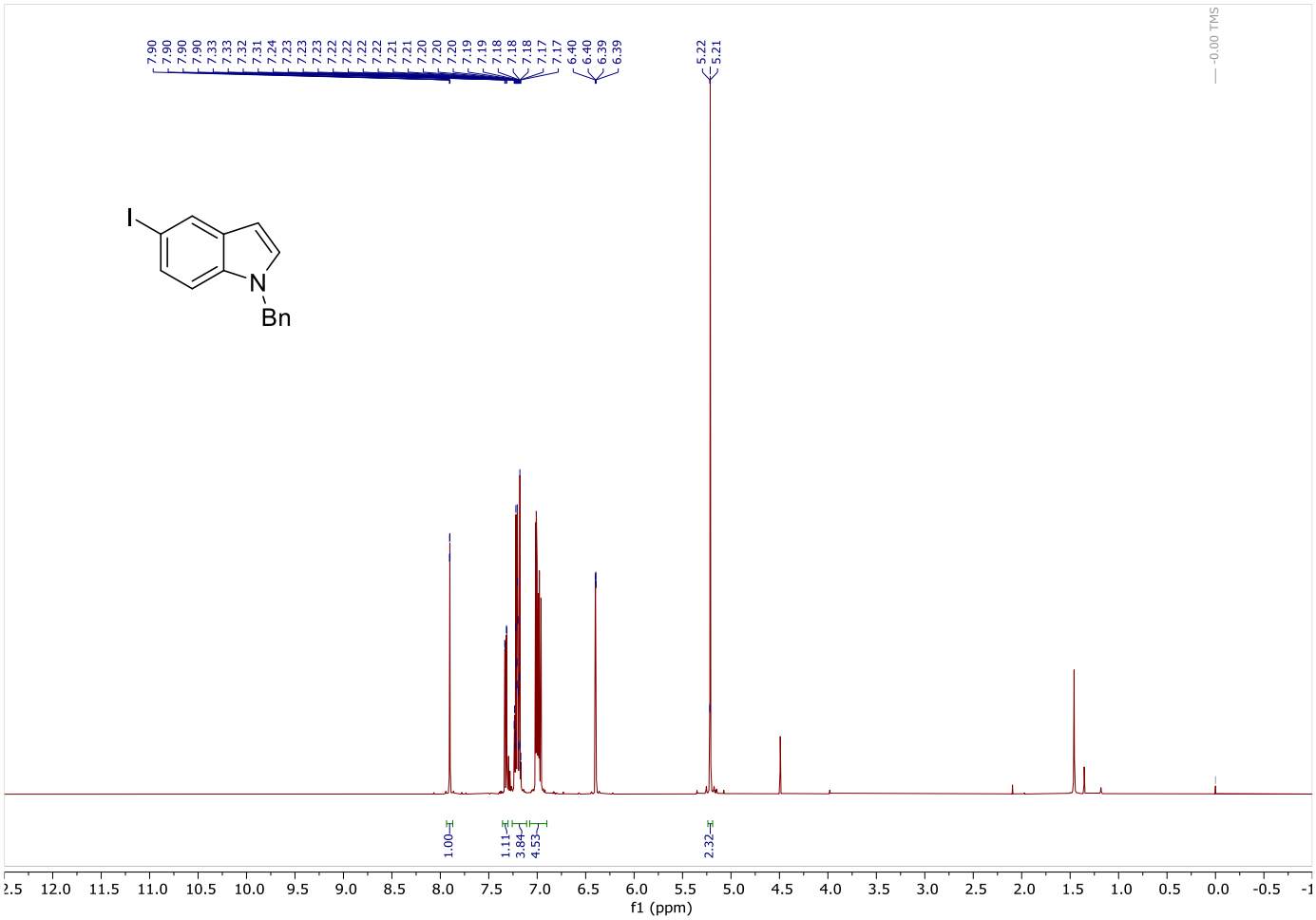


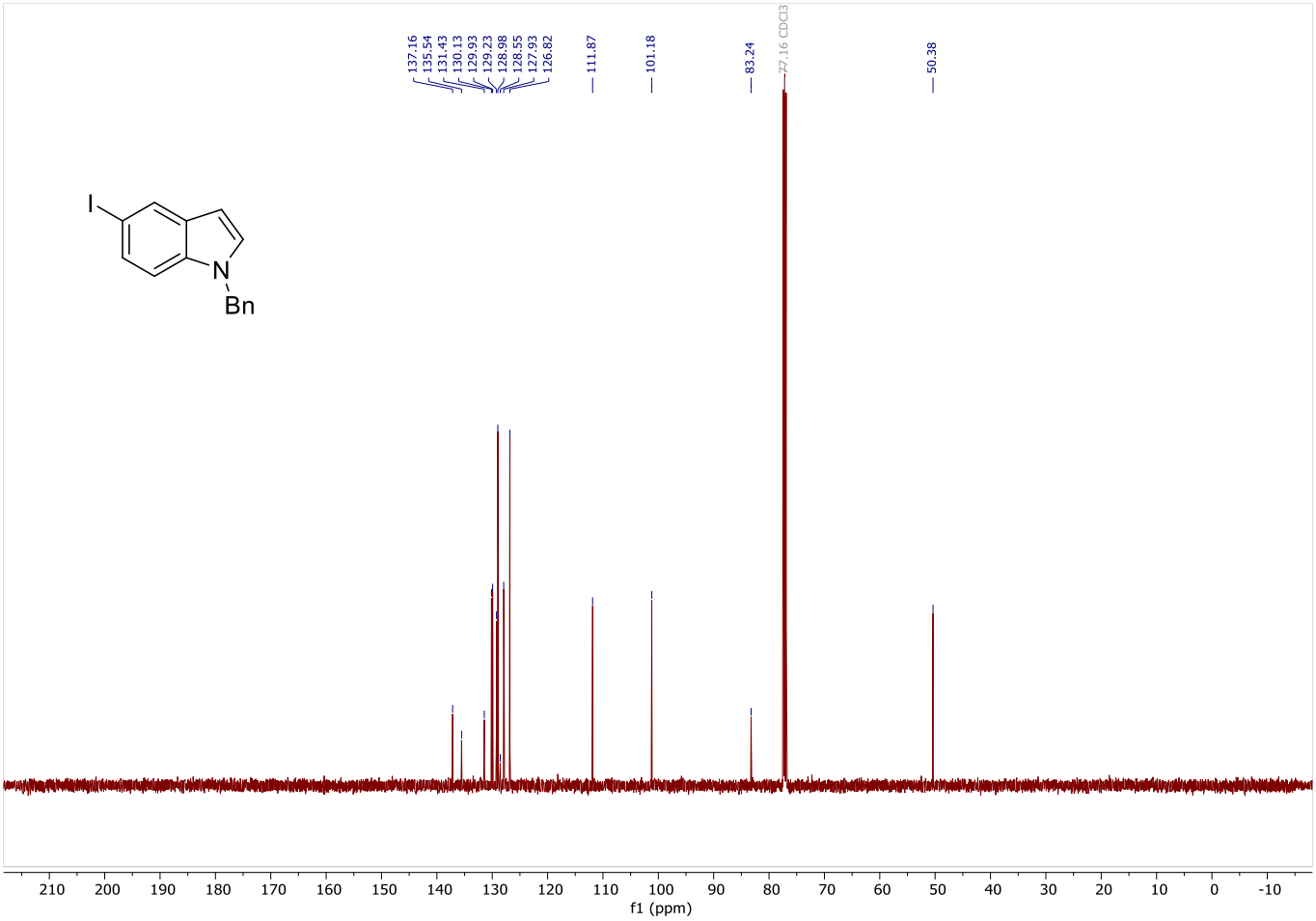
N,N-dibenzyl-4-iodoaniline (2b)





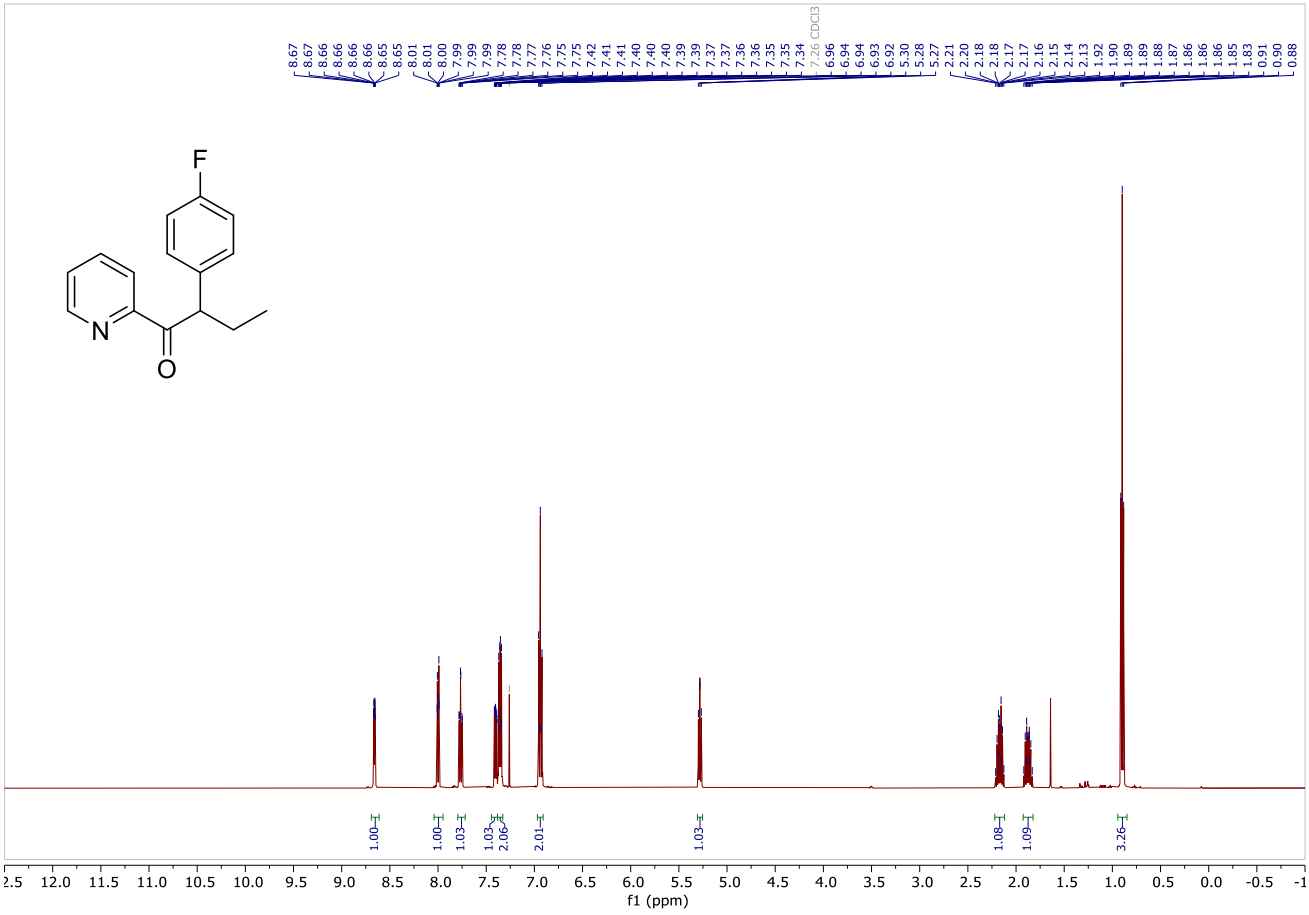
1-benzyl-5-iodo-1H-indole (2c)

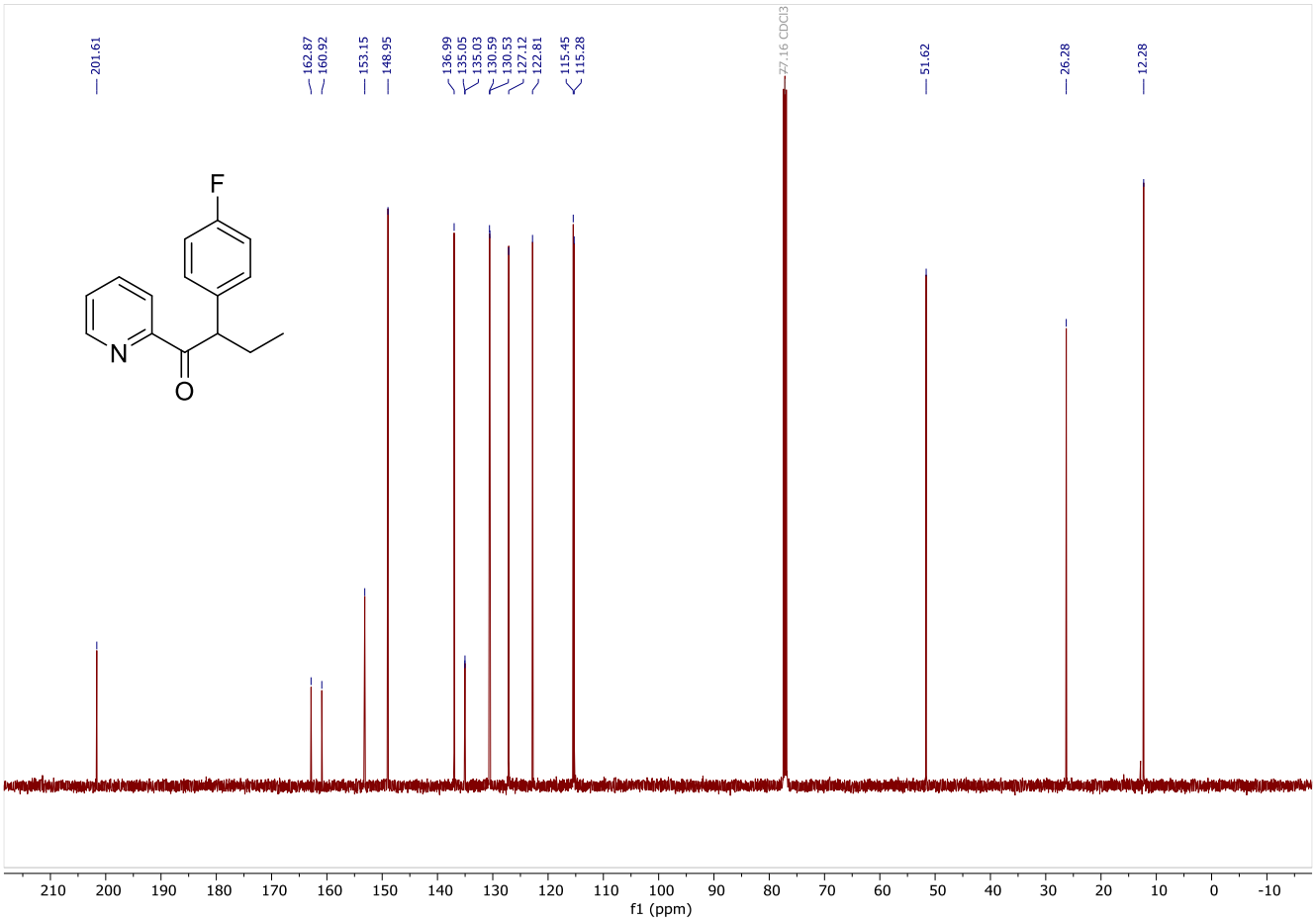




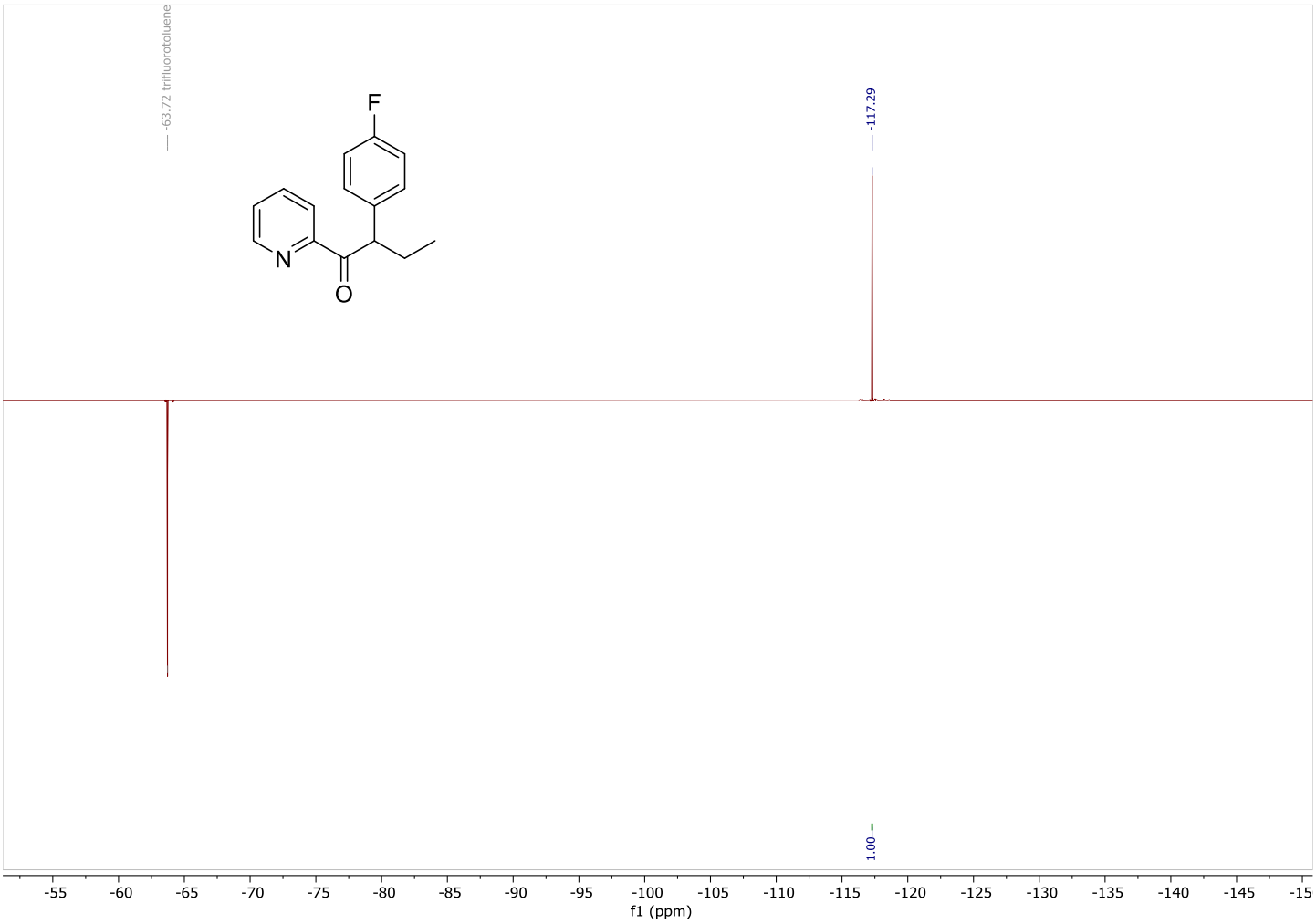
NMR spectra – products of α-functionalization

2-(4-fluorophenyl)-1-(pyridin-2-yl)butan-1-one (3a)

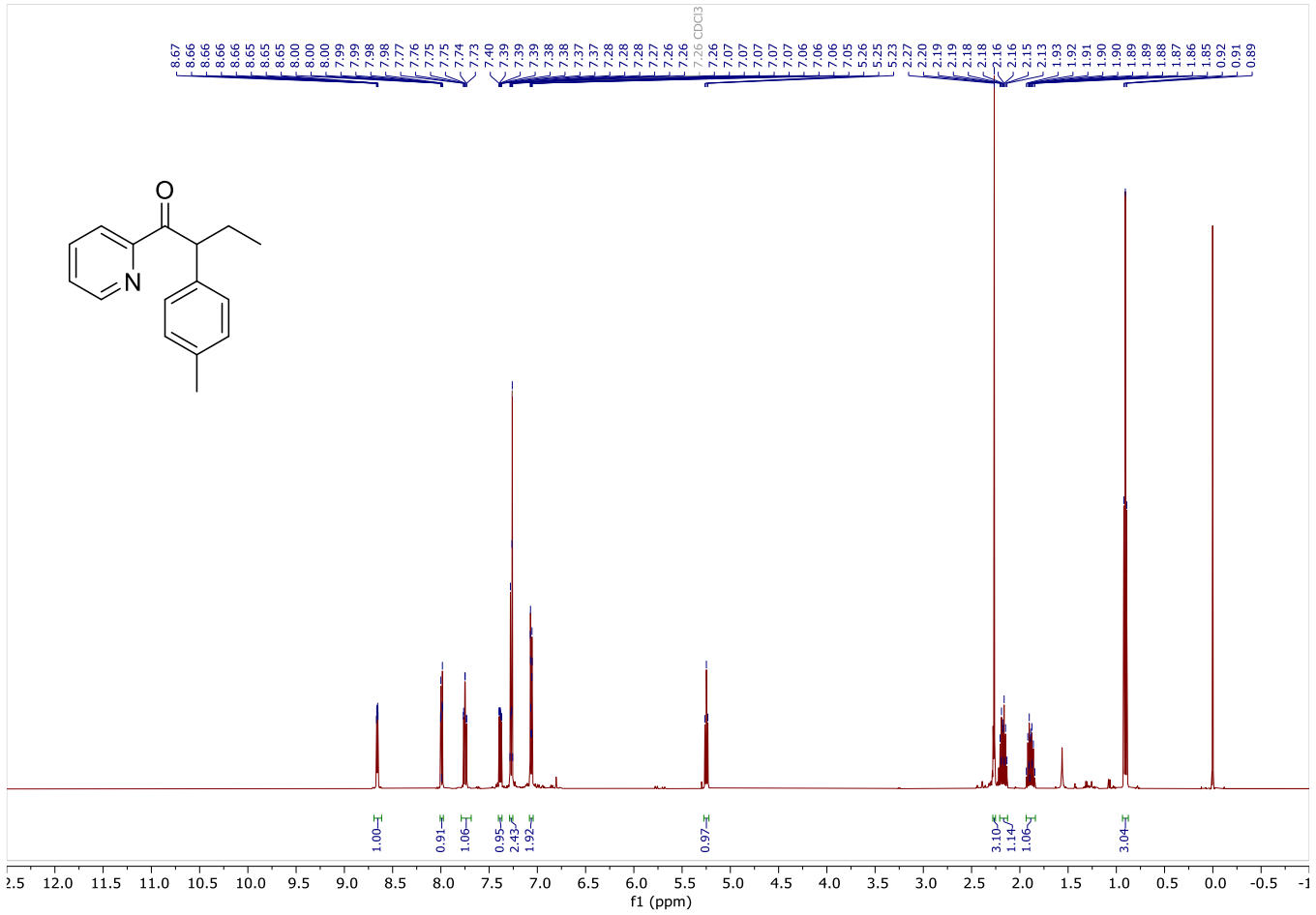


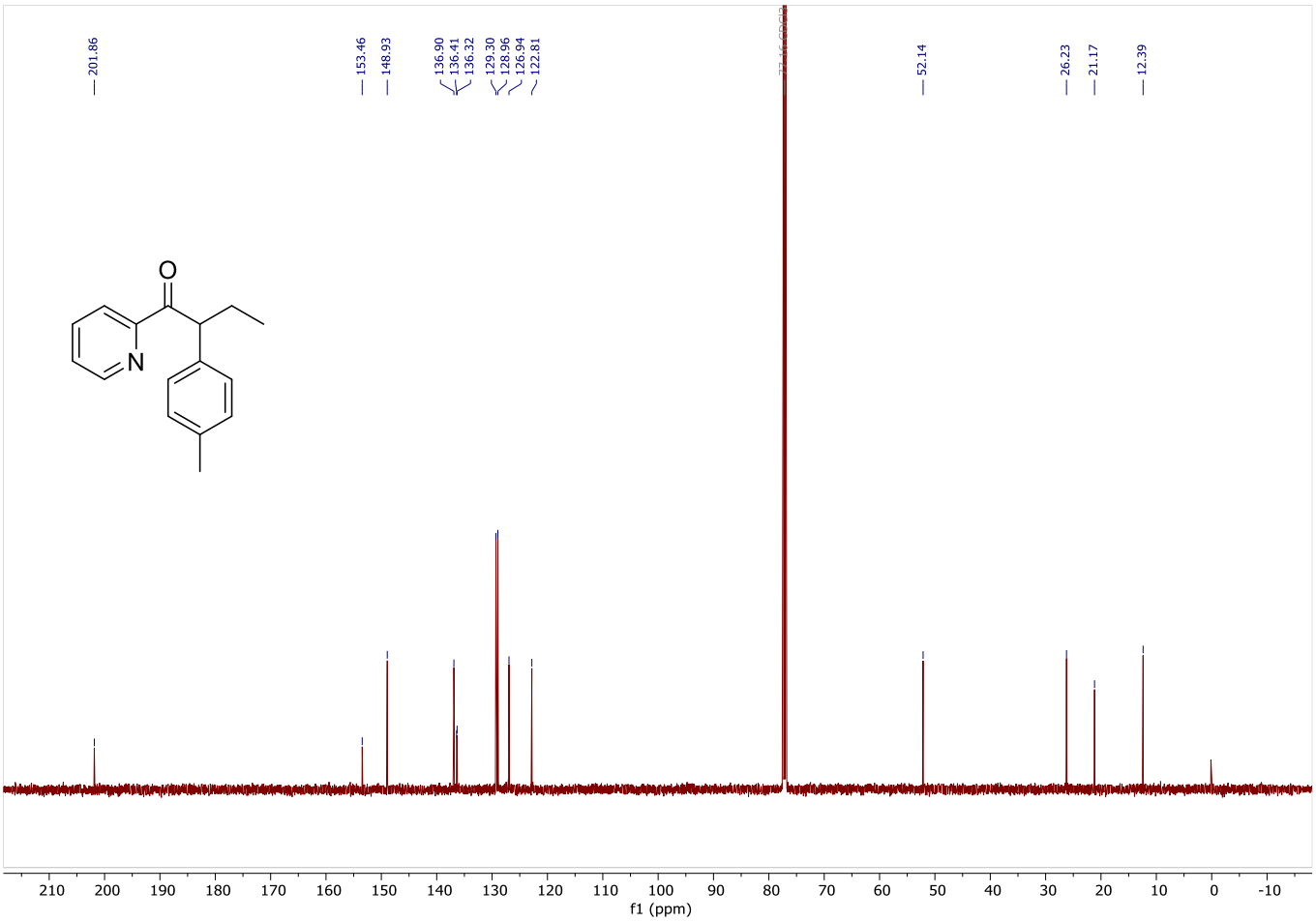


2-(4-fluorophenyl)-1-(pyridin-2-yl)butan-1-one (3a)

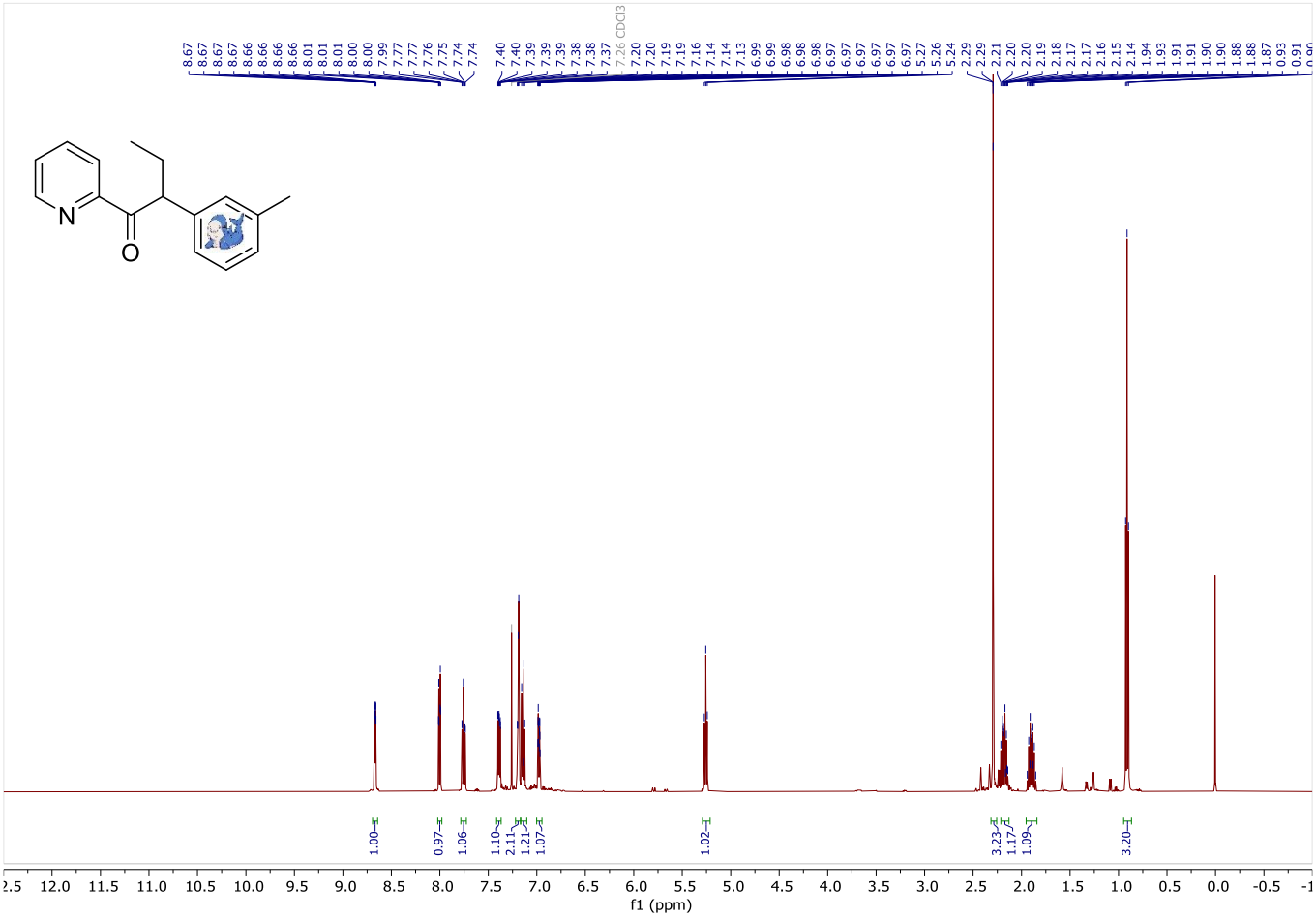


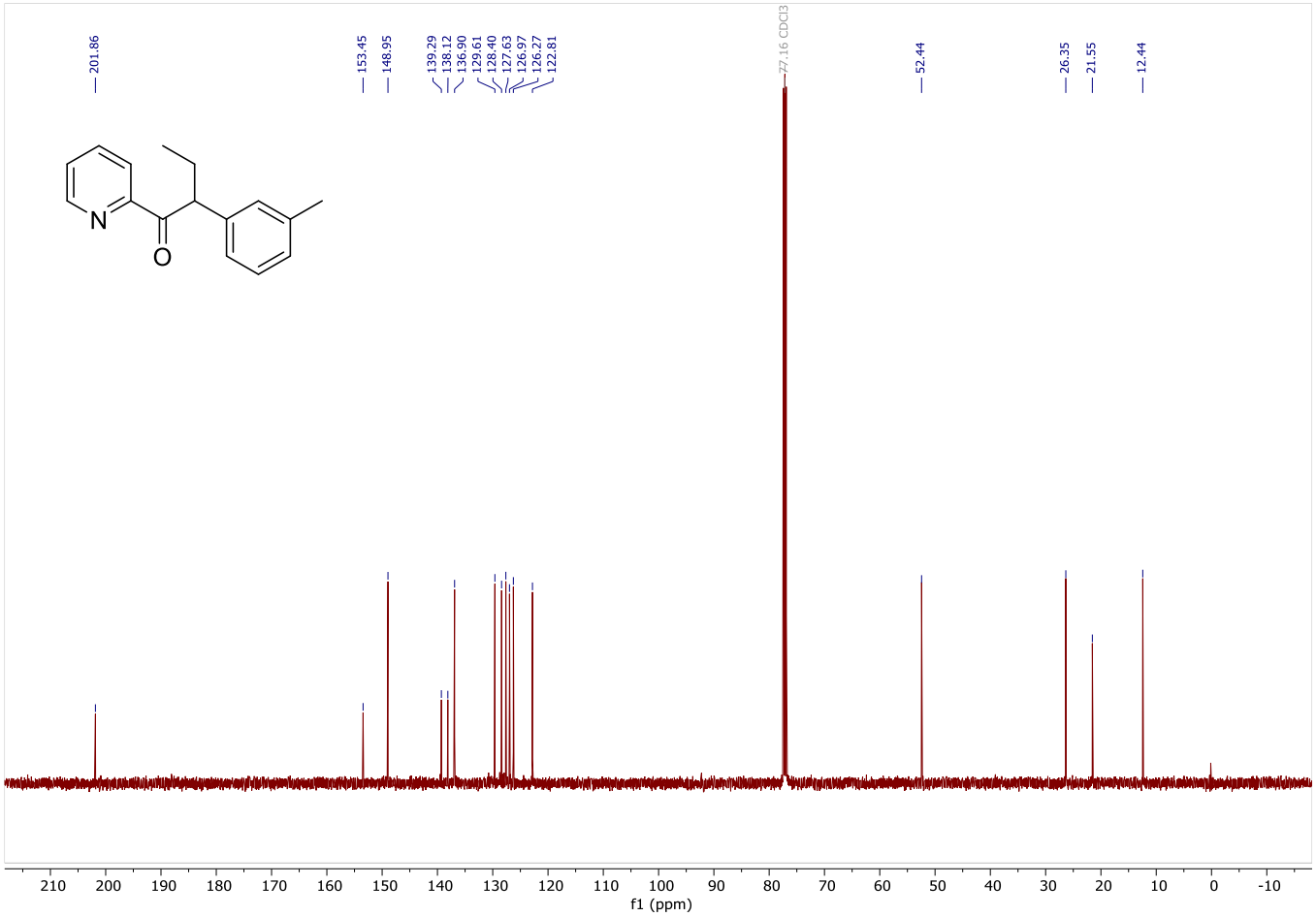
1-(pyridin-2-yl)-2-(p-tolyl)butan-1-one (3b)



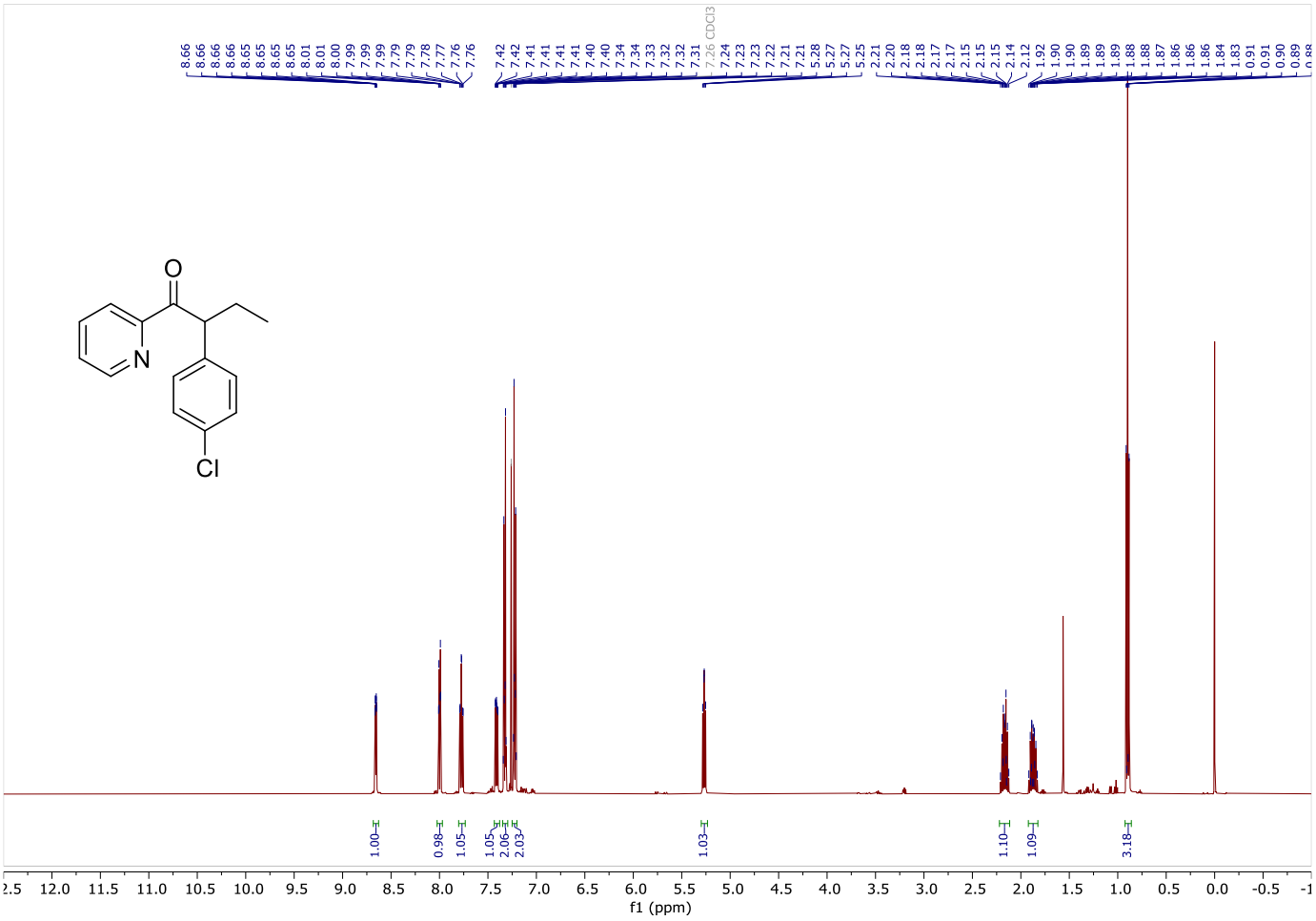


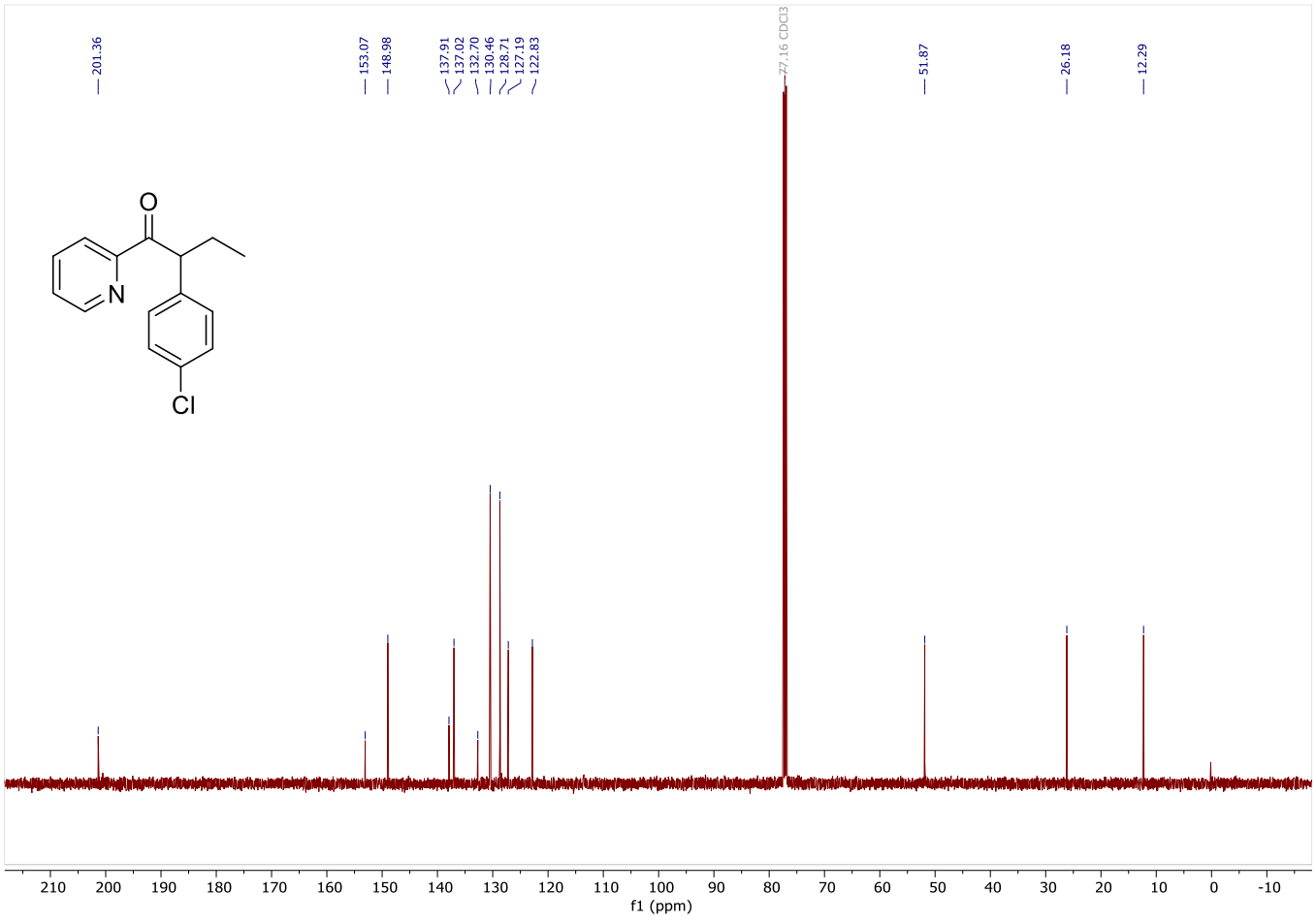
1-(pyridin-2-yl)-2-(m-tolyl)butan-1-one (3c)



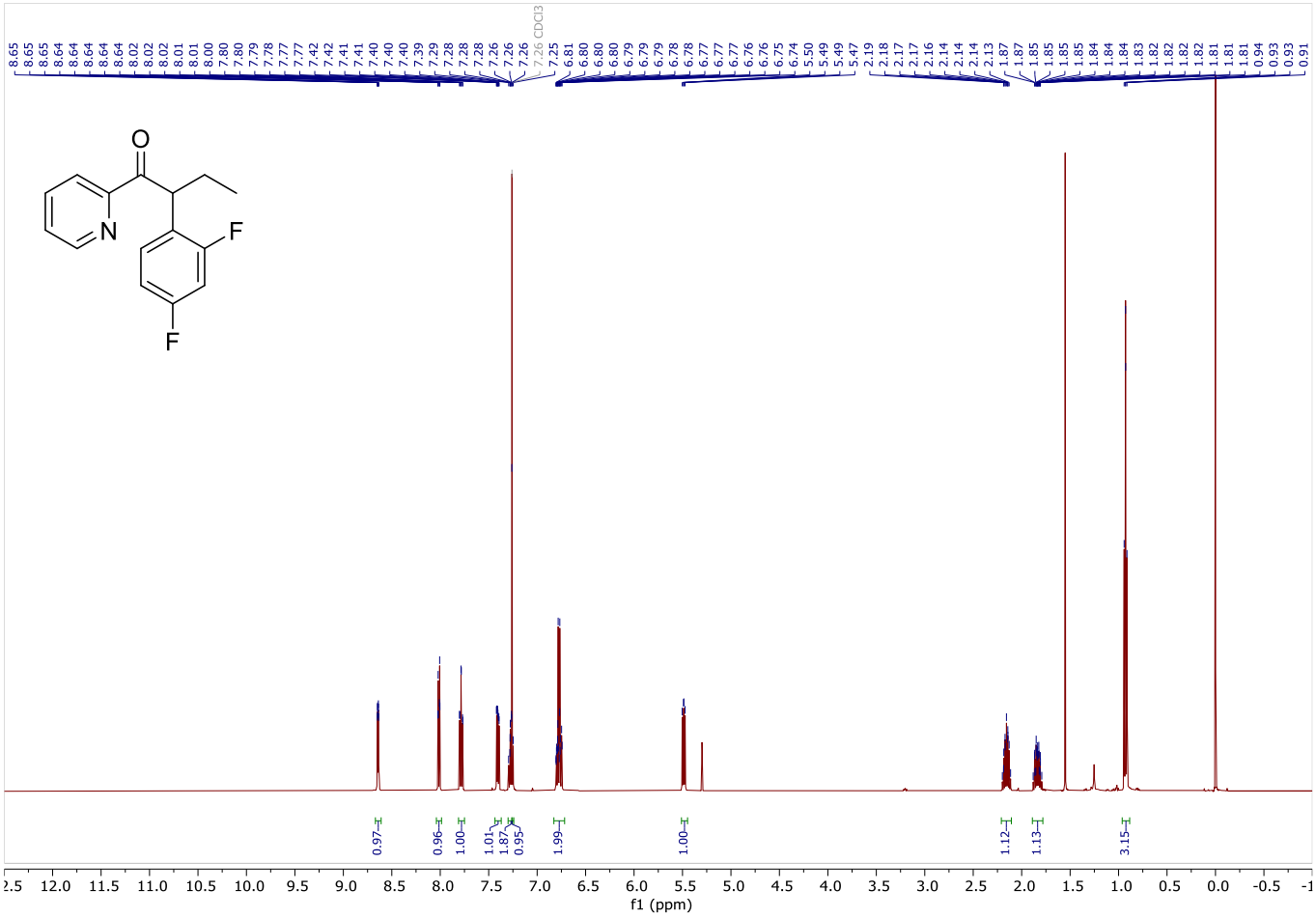


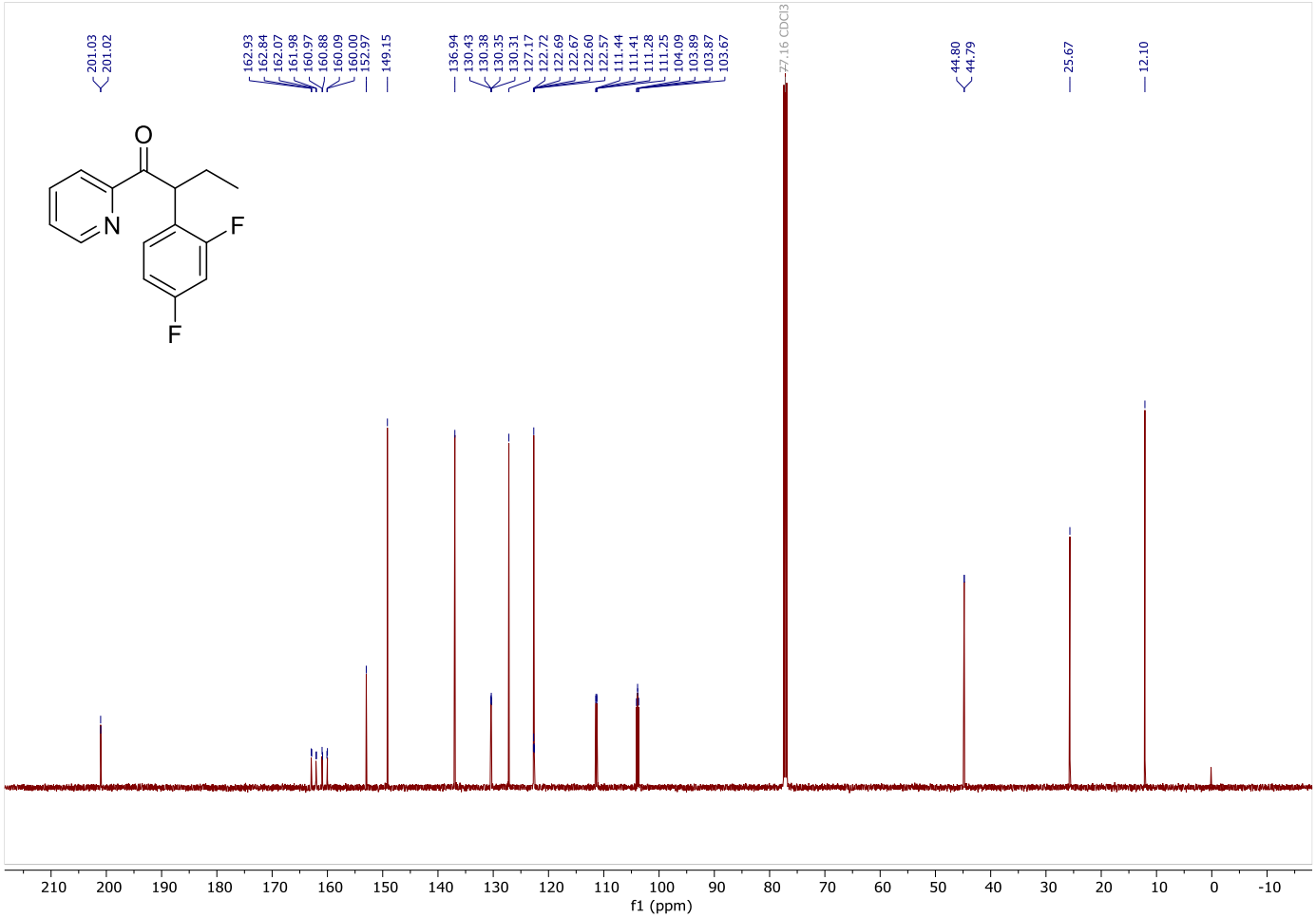
2-(4-chlorophenyl)-1-(pyridin-2-yl)butan-1-one (3d)



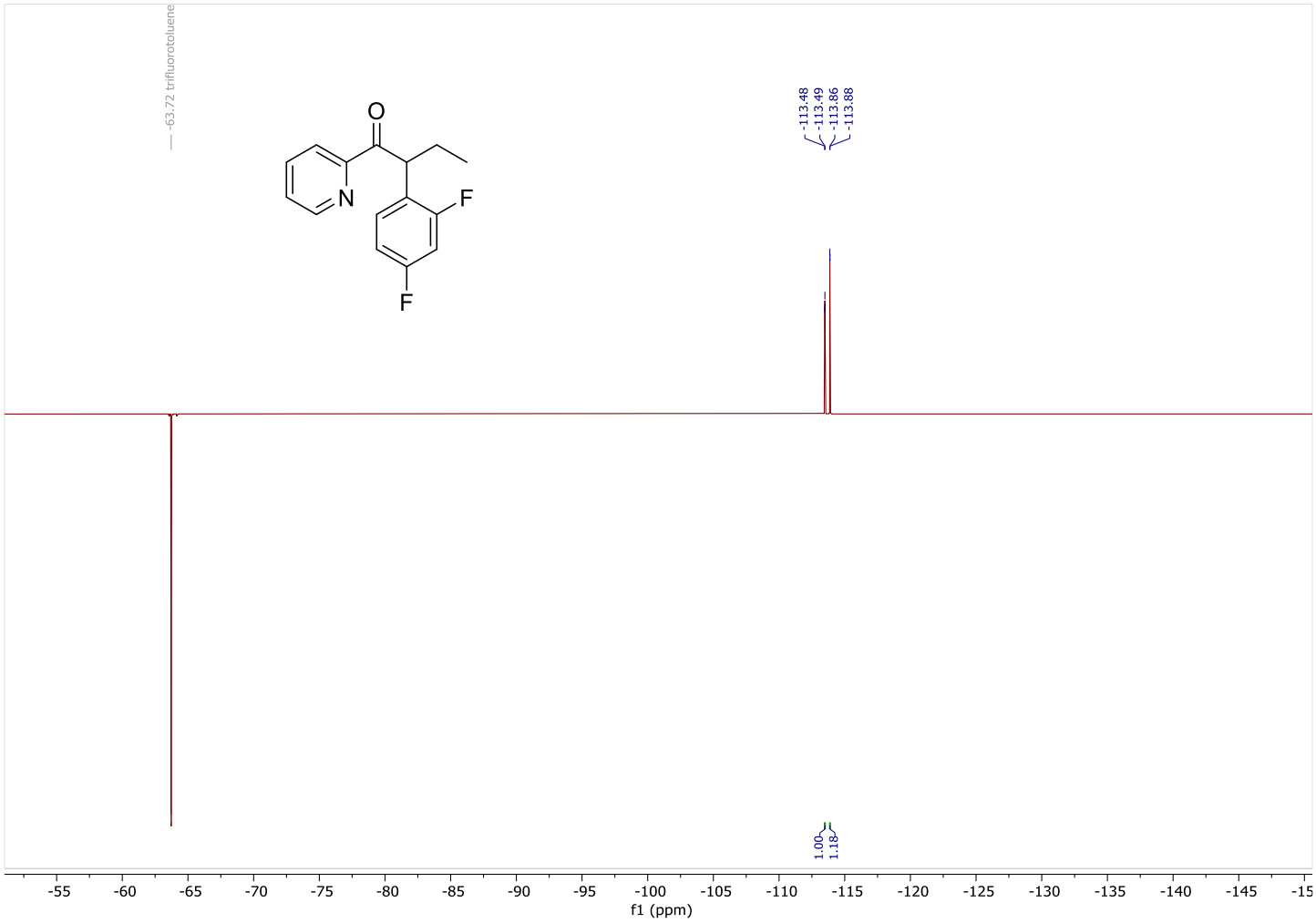


2-(2,4-difluorophenyl)-1-(pyridin-2-yl)butan-1-one (3e)

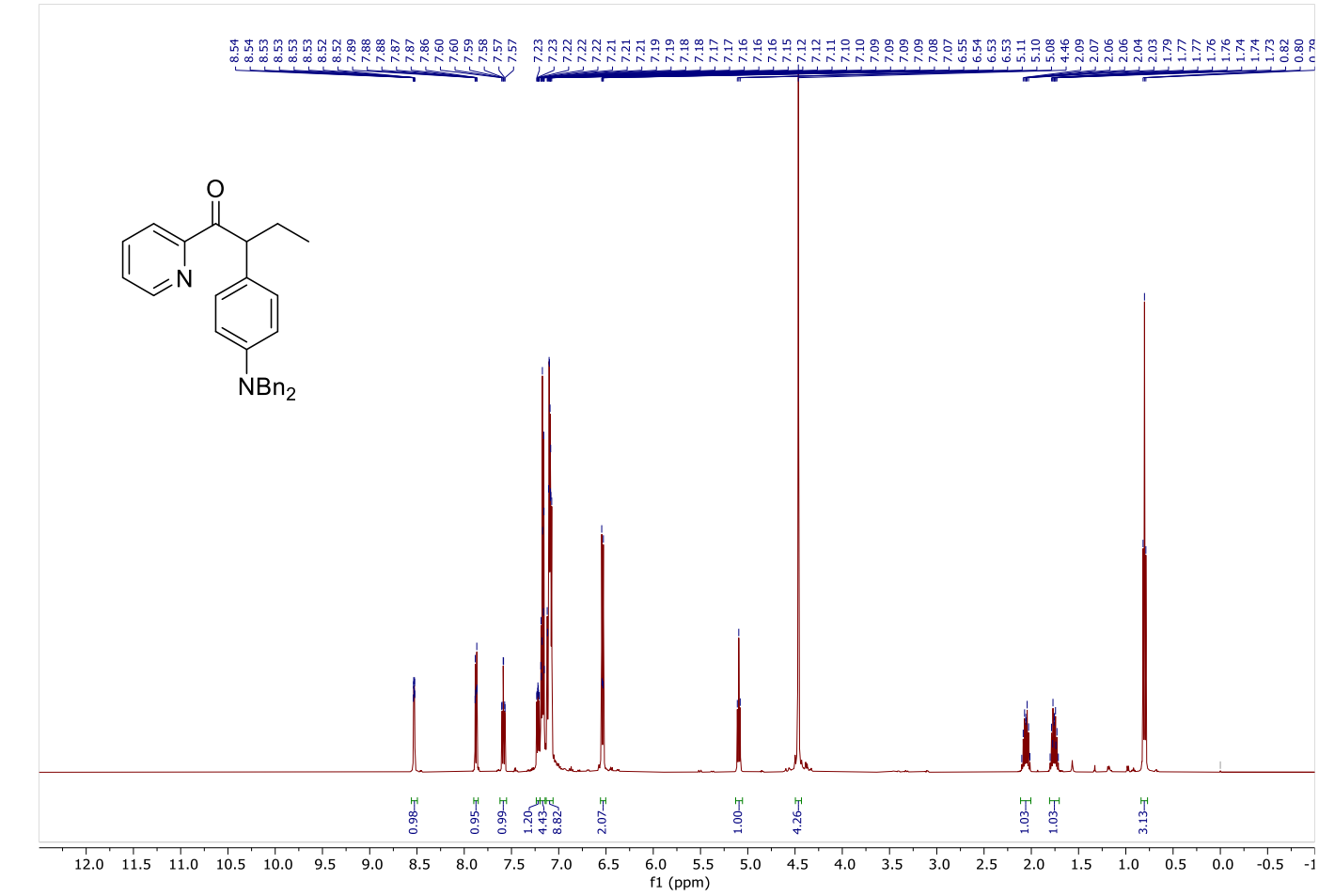


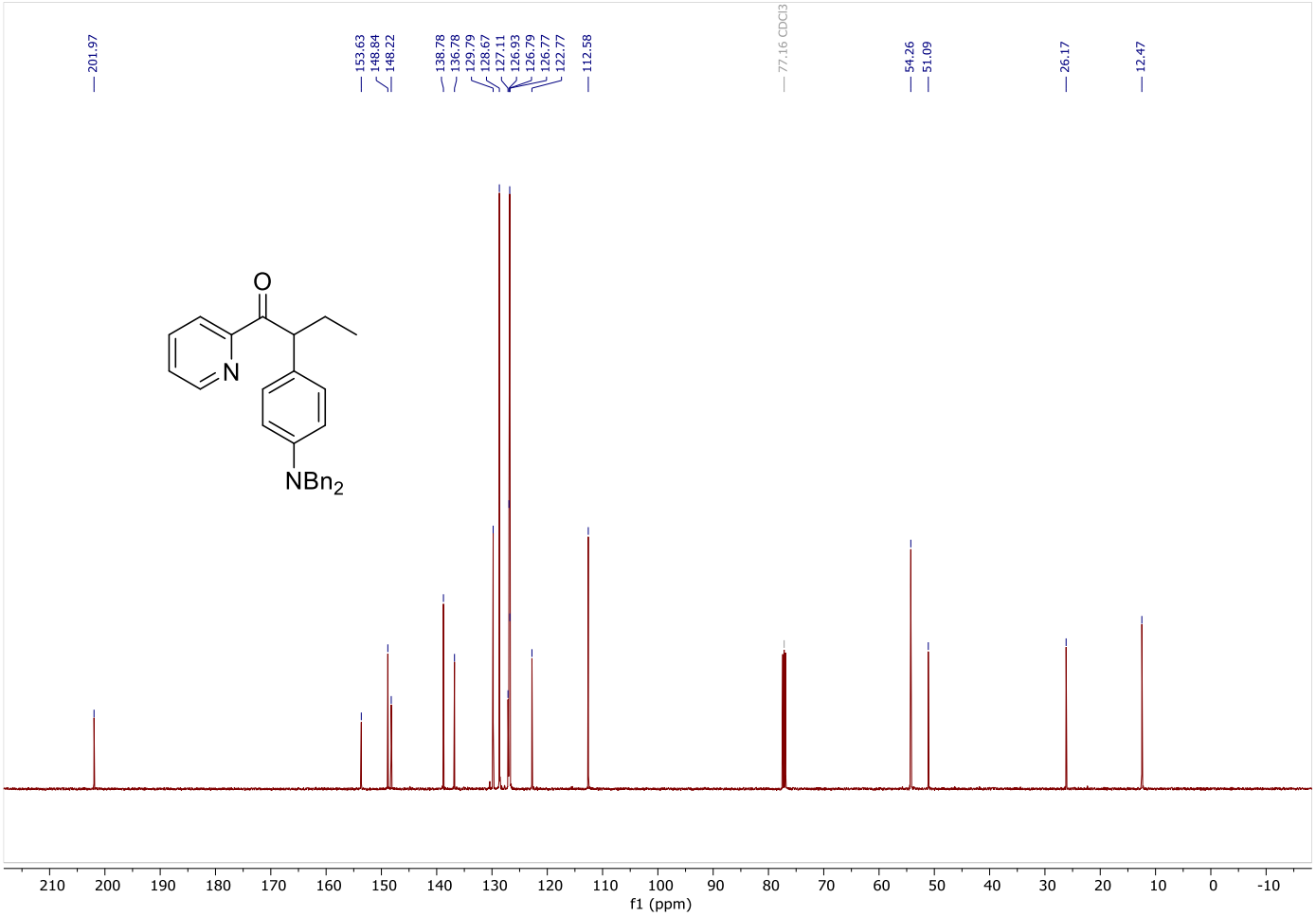


2-(2,4-difluorophenyl)-1-(pyridin-2-yl)butan-1-one (3e)

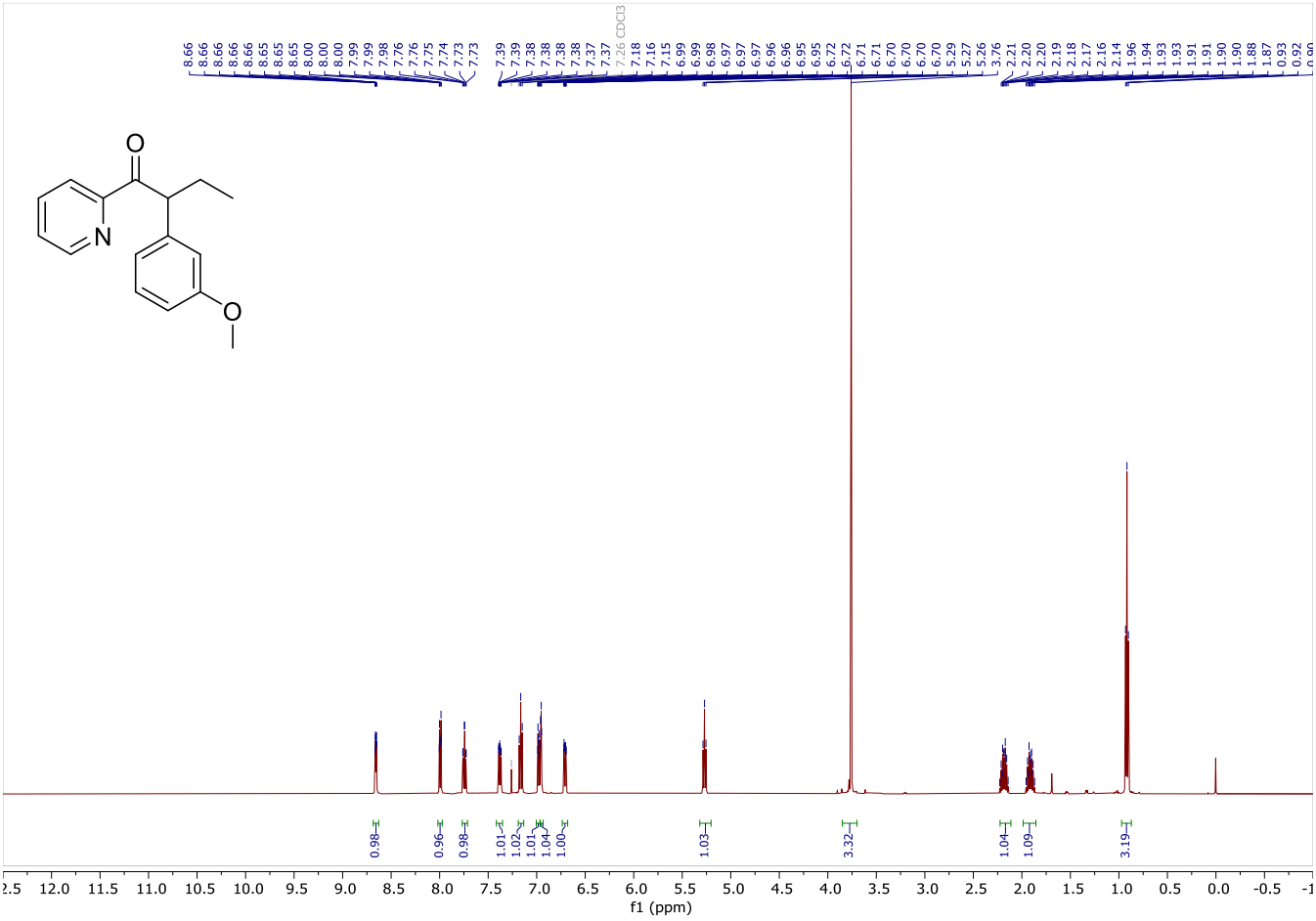


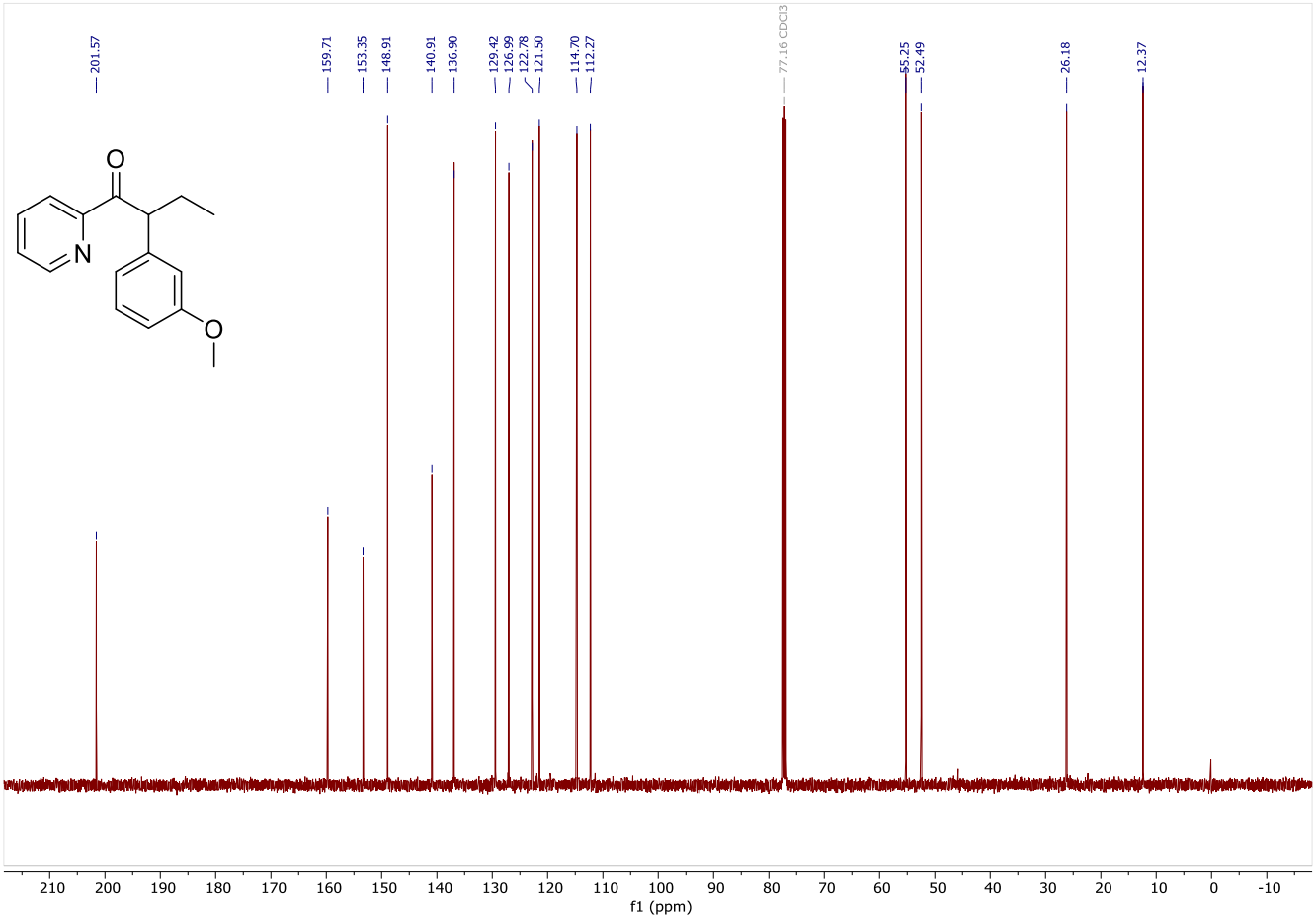
2-(4-(dibenzylamino)phenyl)-1-(pyridin-2-yl)butan-1-one (3f)



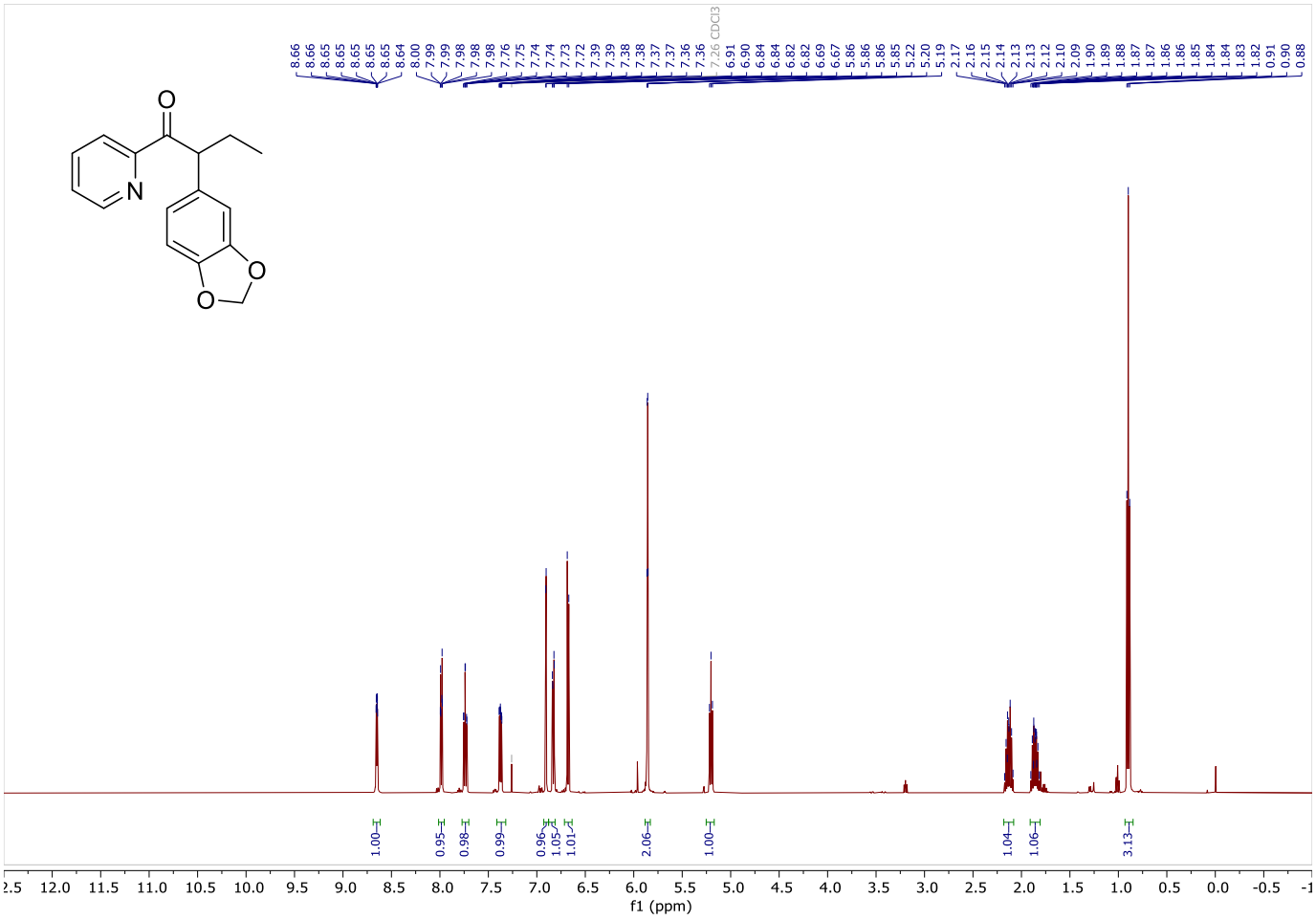


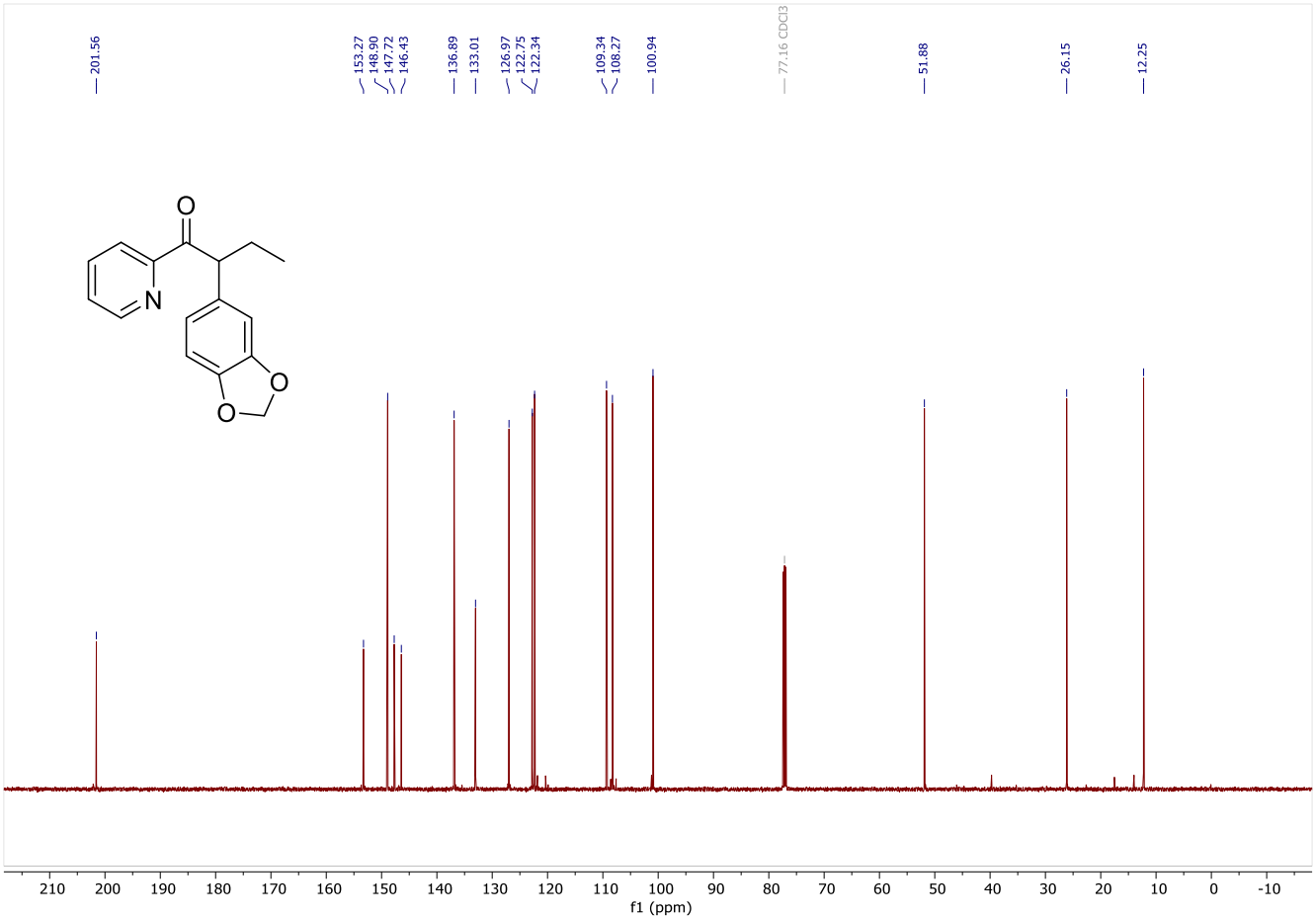
2-(3-methoxyphenyl)-1-(pyridin-2-yl)butan-1-one (3g)



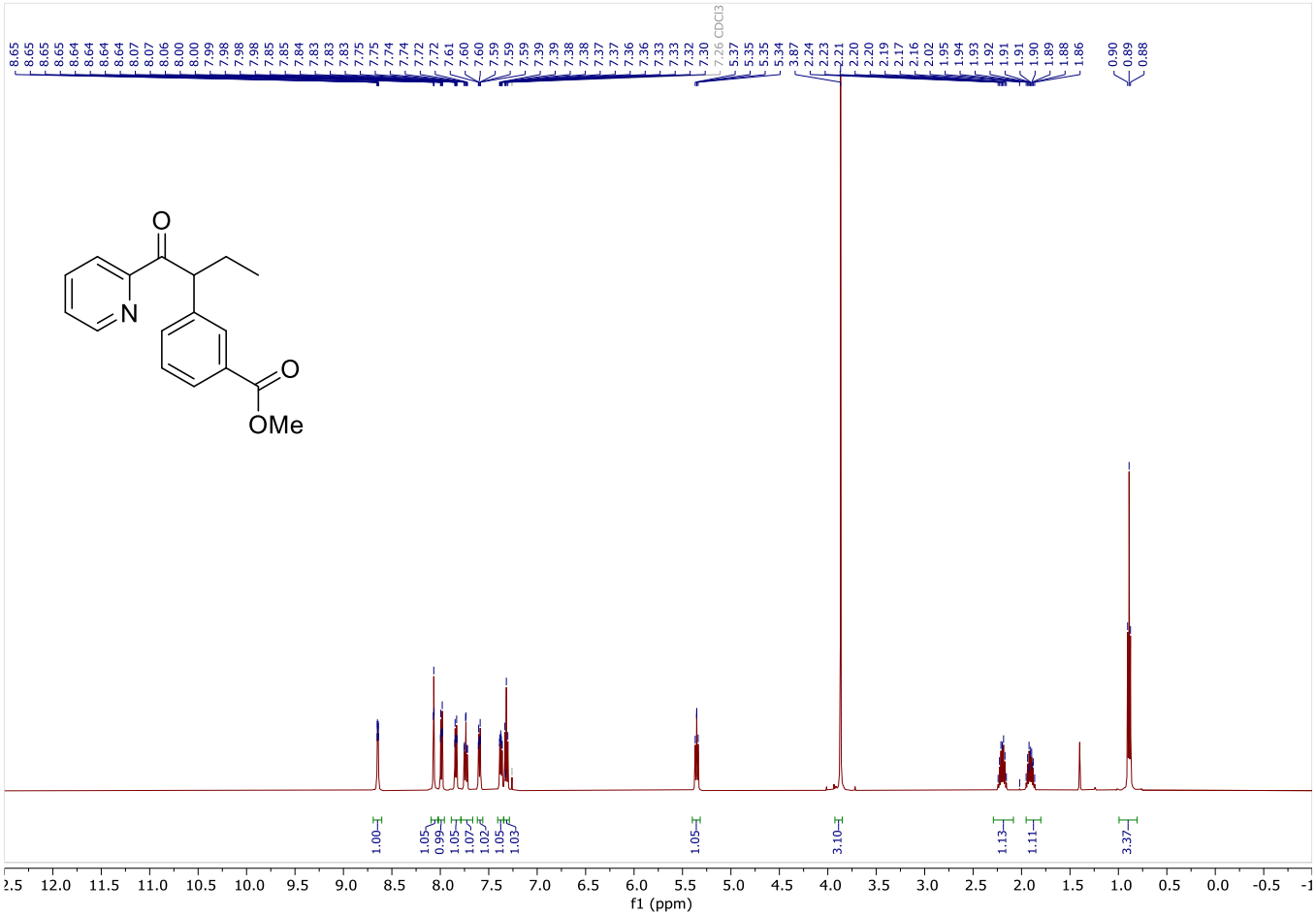


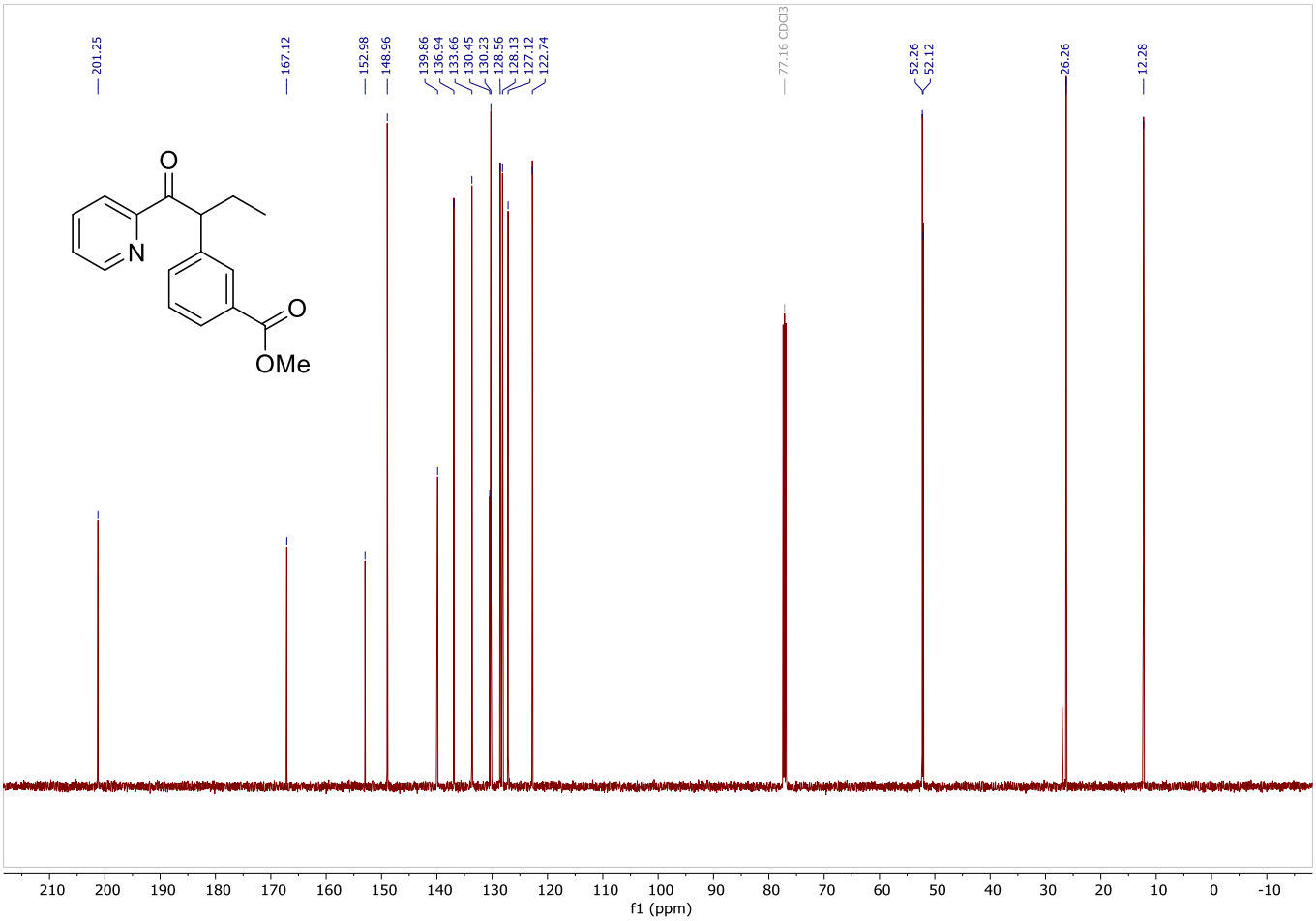
2-(benzo[d][1,3]dioxol-5-yl)-1-(pyridin-2-yl)butan-1-one (3h)



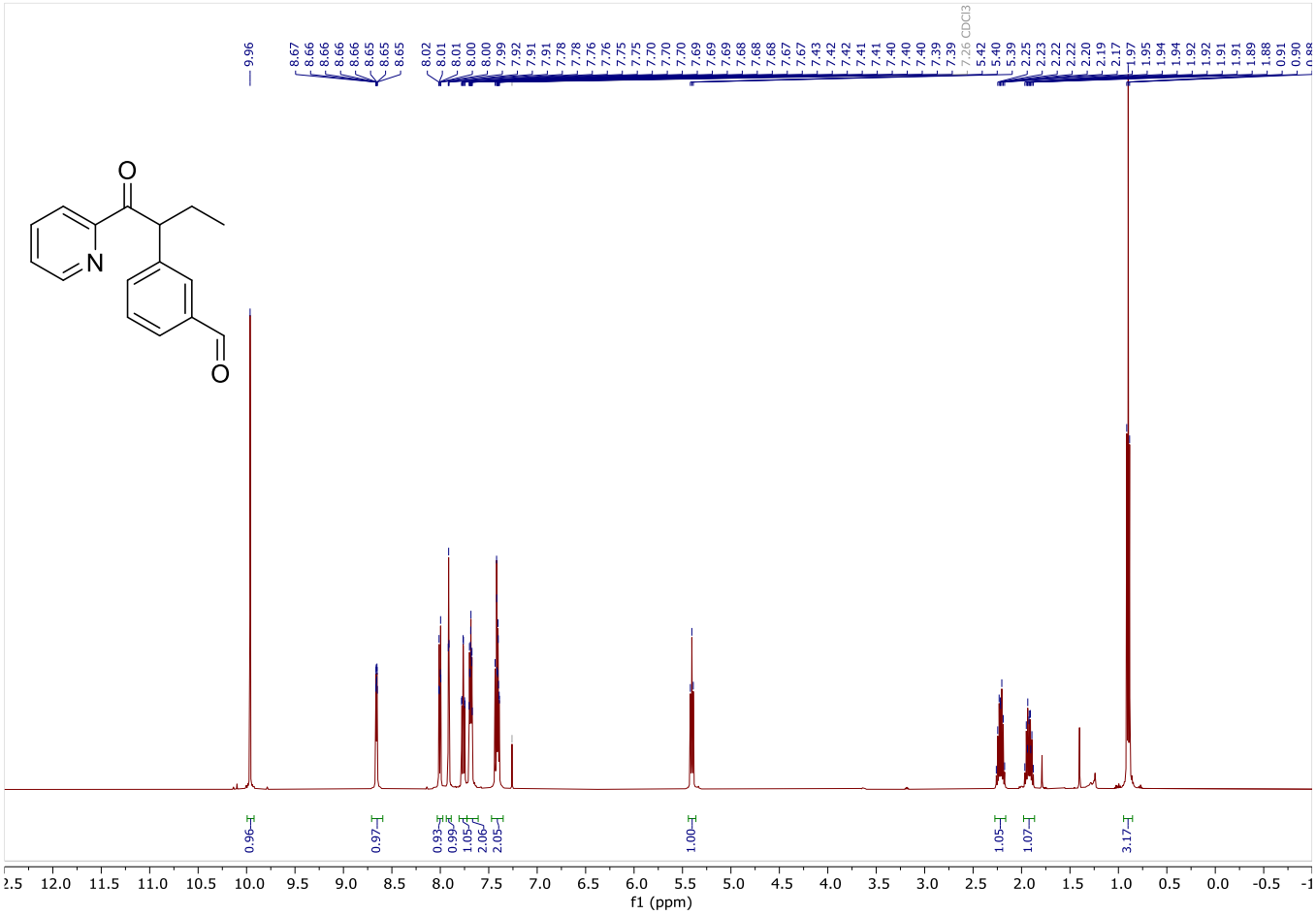


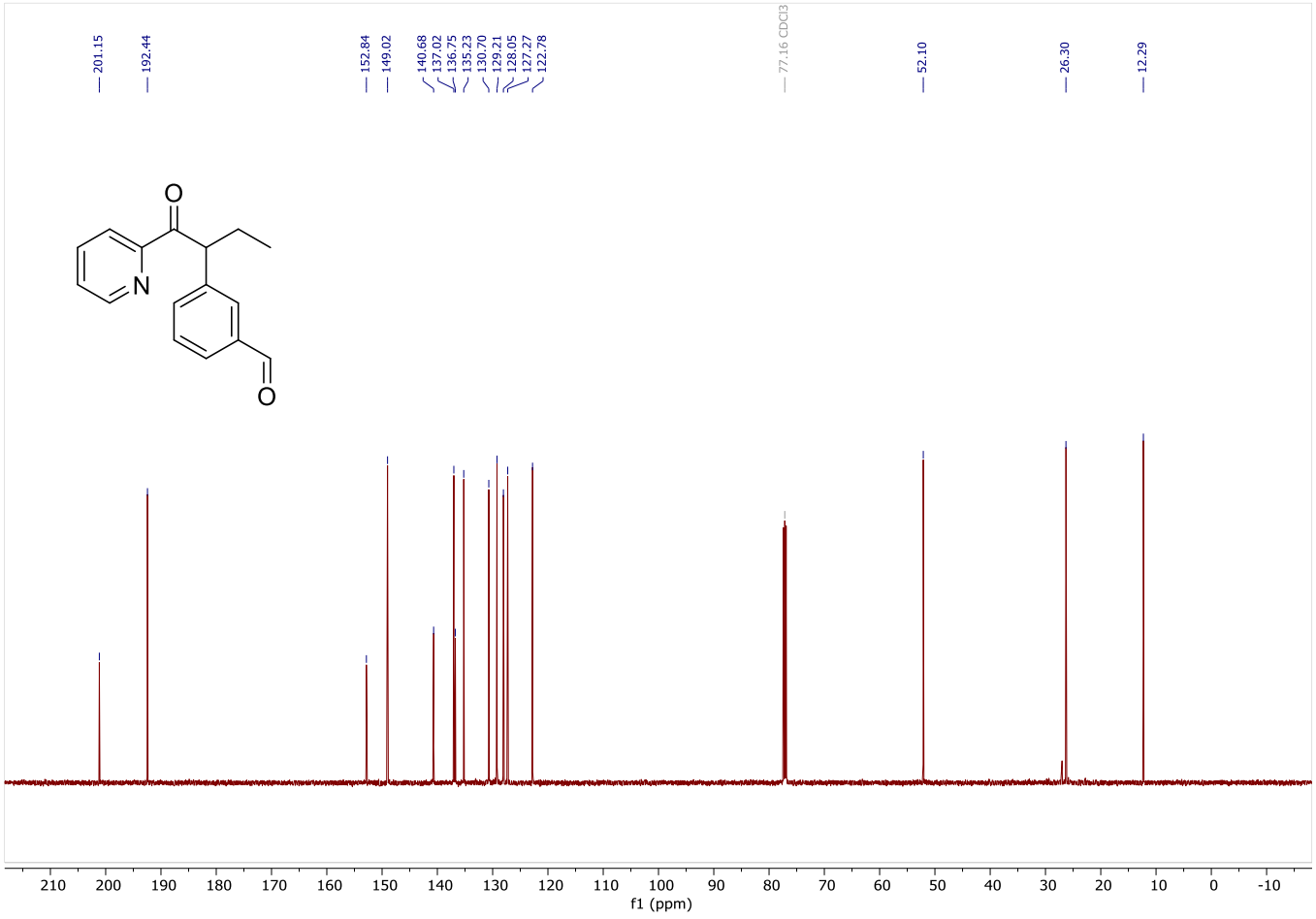
methyl 3-(1-oxo-1-(pyridin-2-yl)butan-2-yl)benzoate (3i)



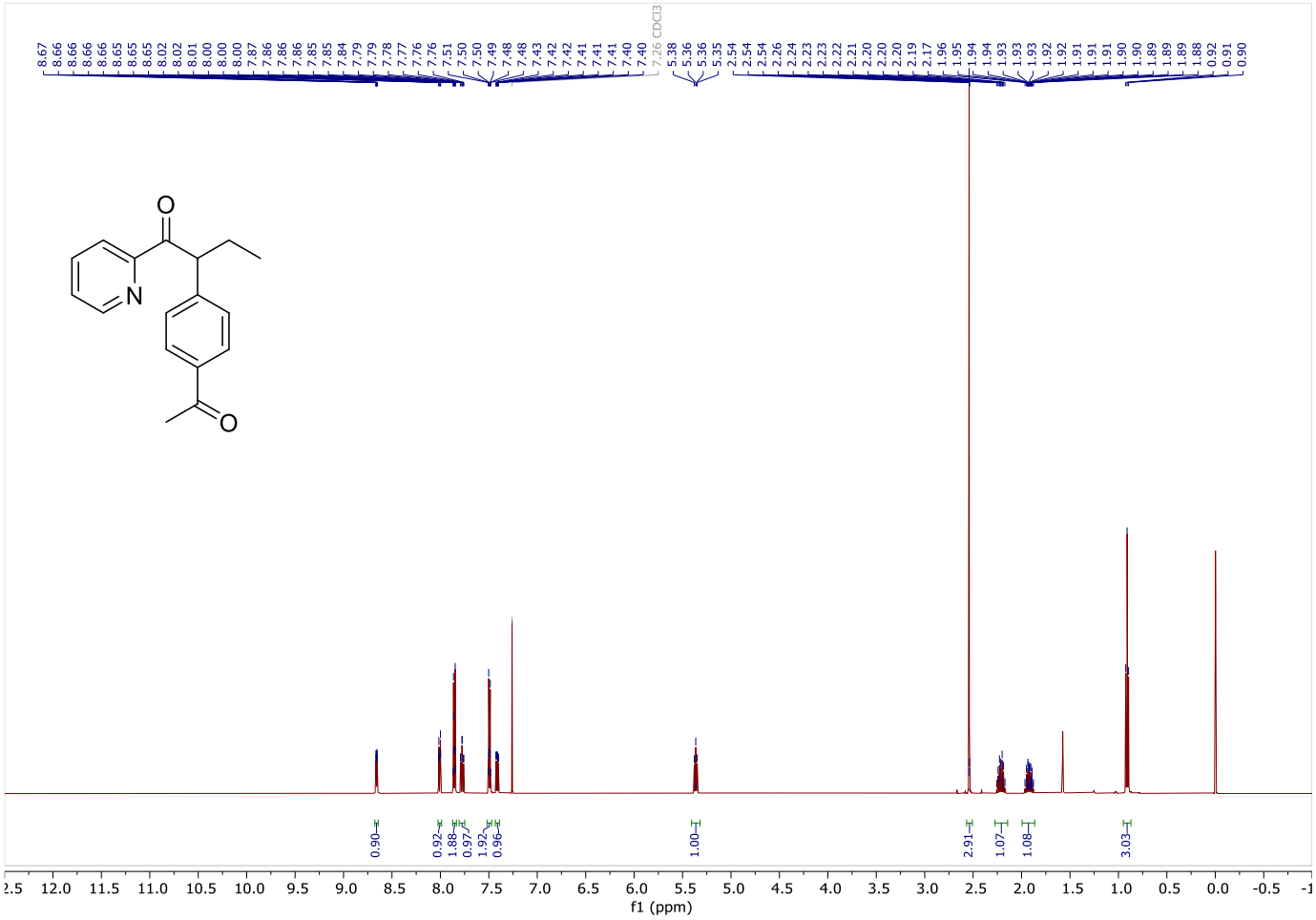


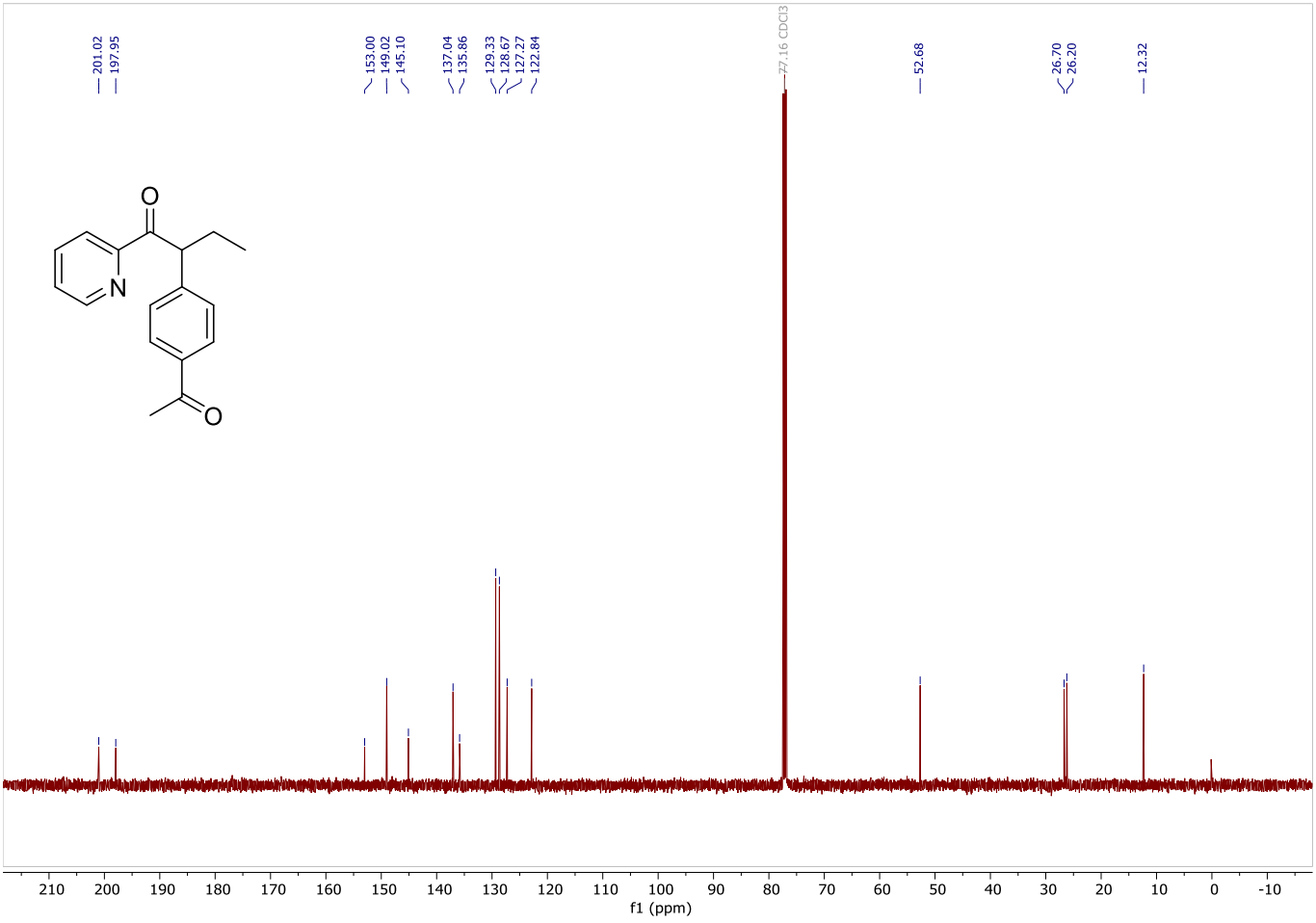
3-(1-oxo-1-(pyridin-2-yl)butan-2-yl)benzaldehyde (3j)



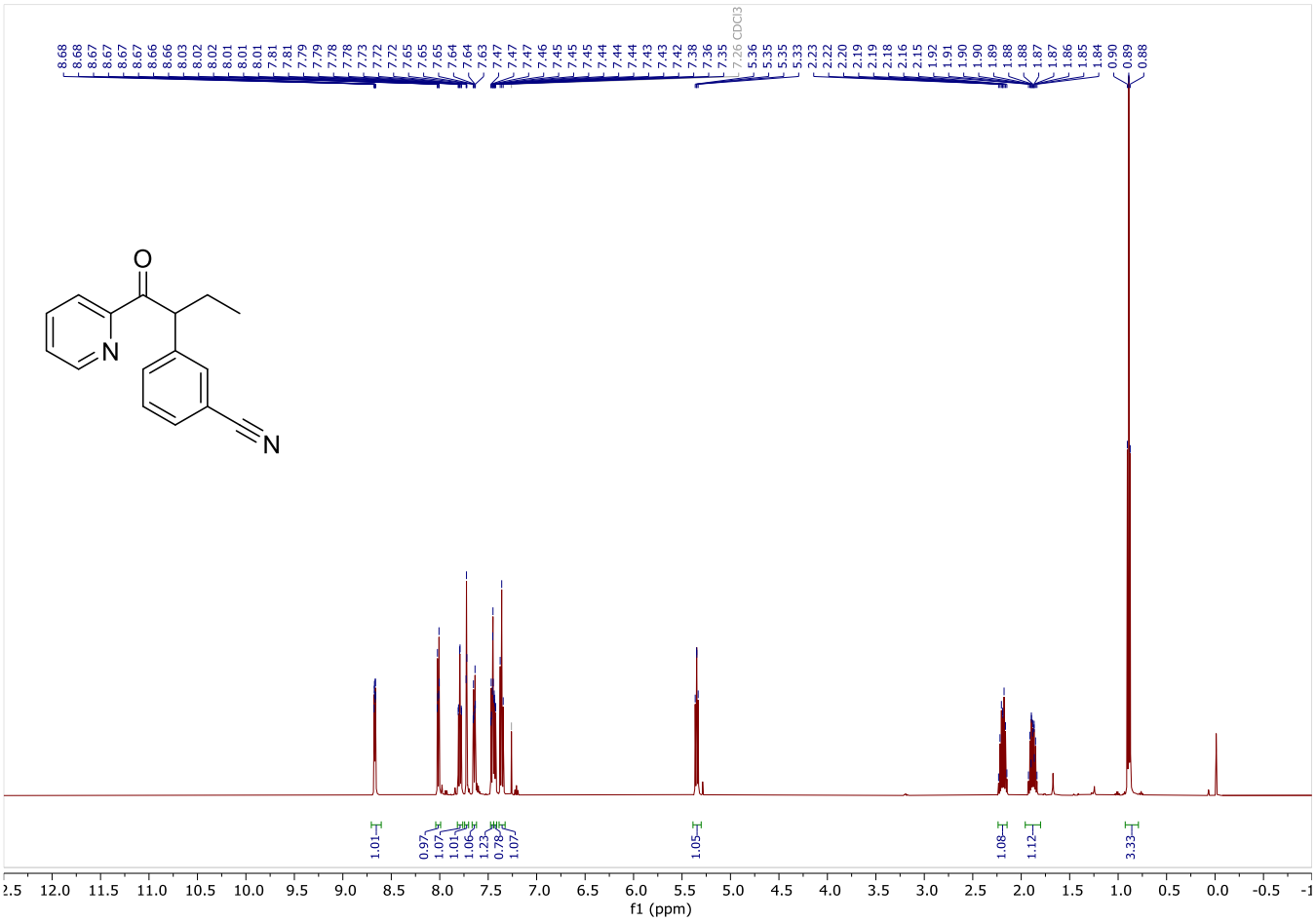


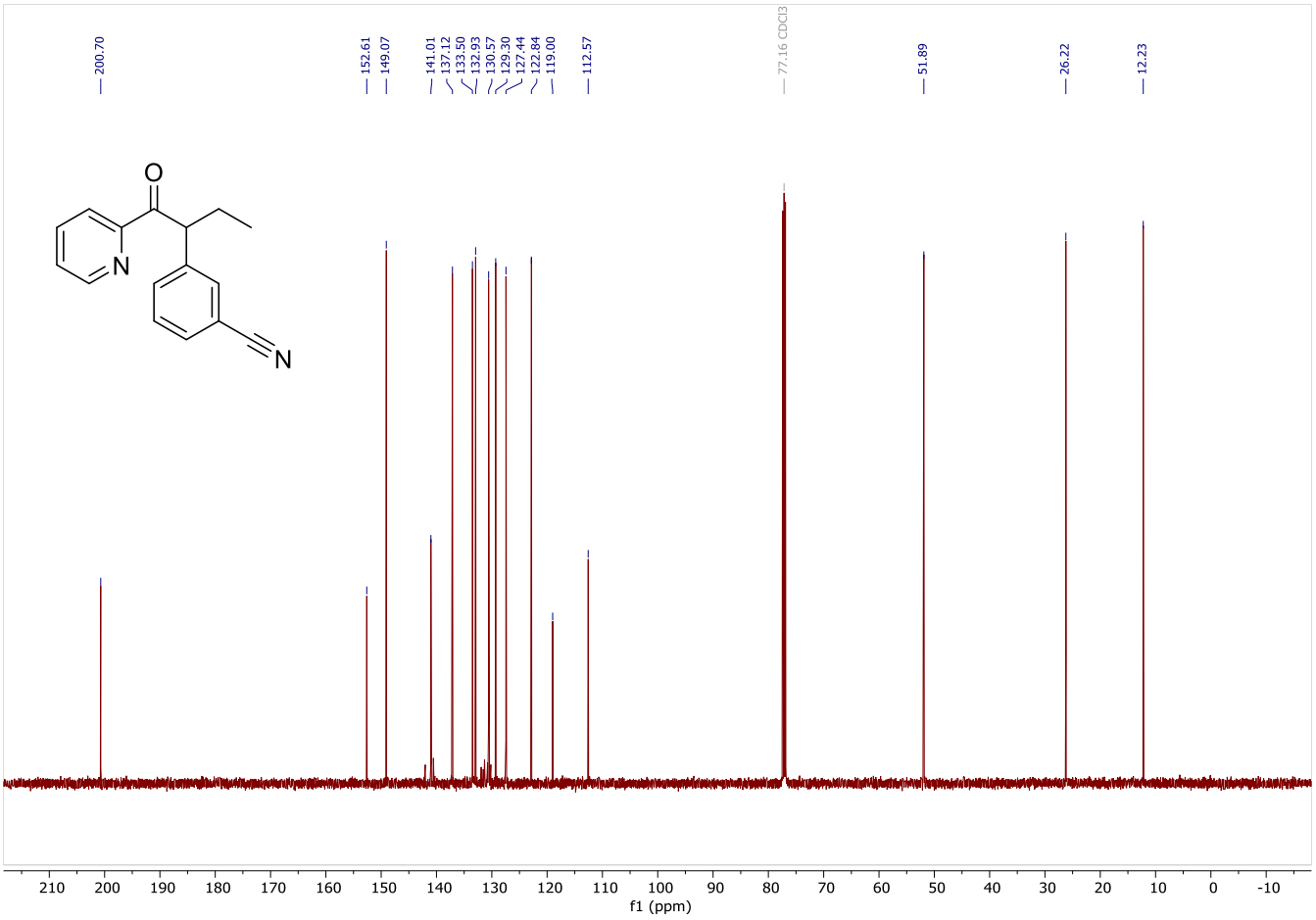
2-(4-acetylphenyl)-1-(pyridin-2-yl)butan-1-one (3k)



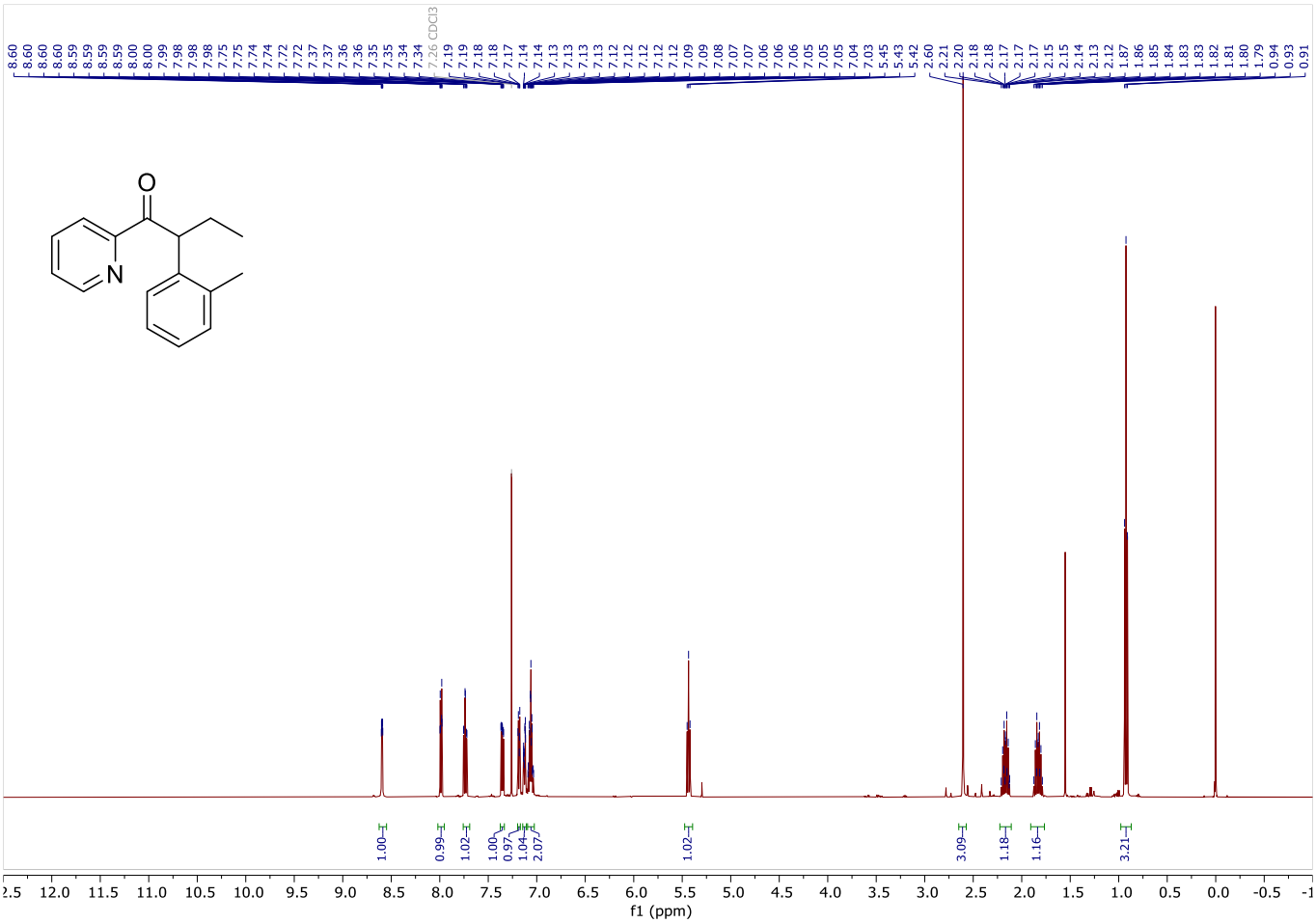


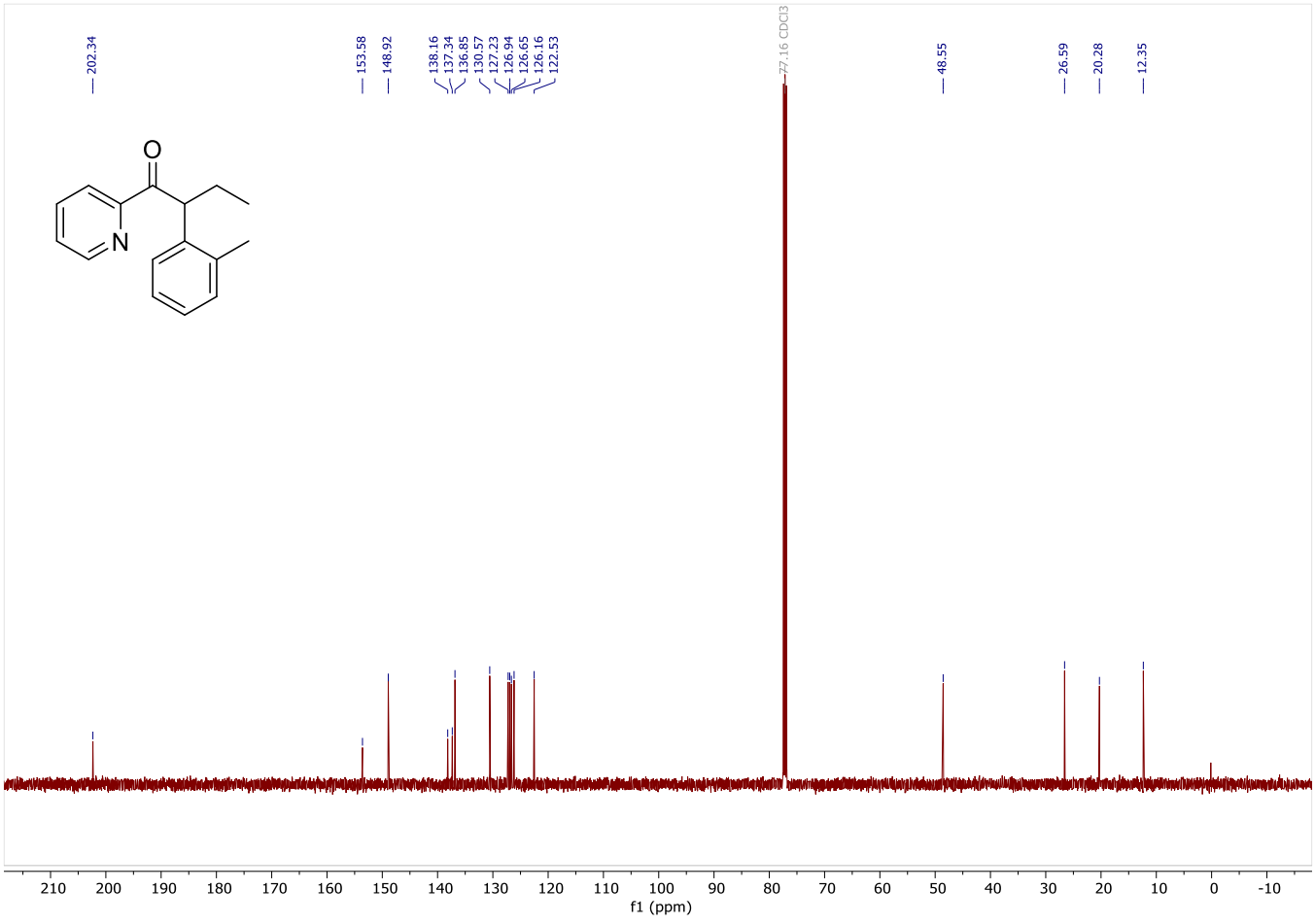
3-(1-oxo-1-(pyridin-2-yl)butan-2-yl)benzonitrile (3l)



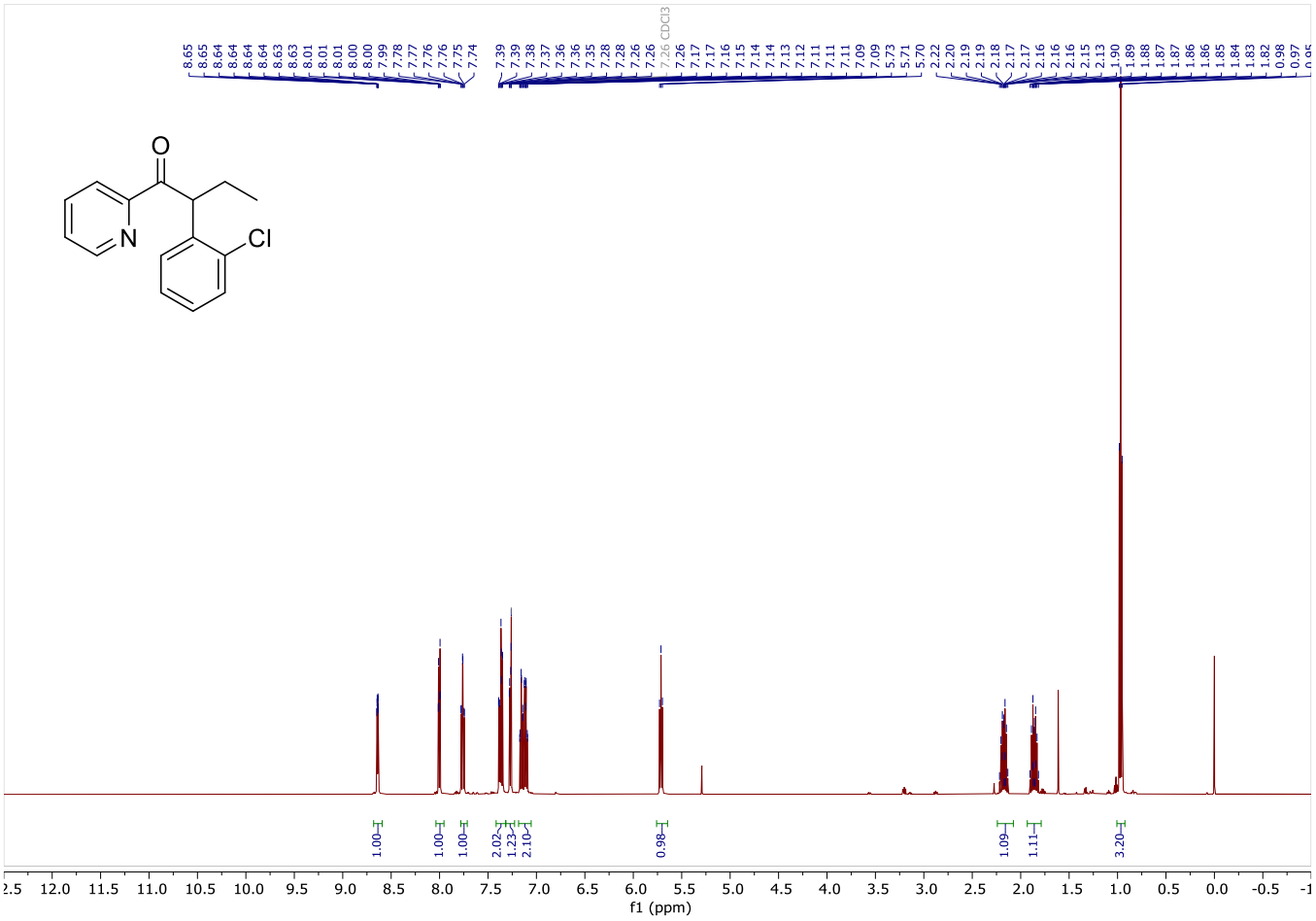


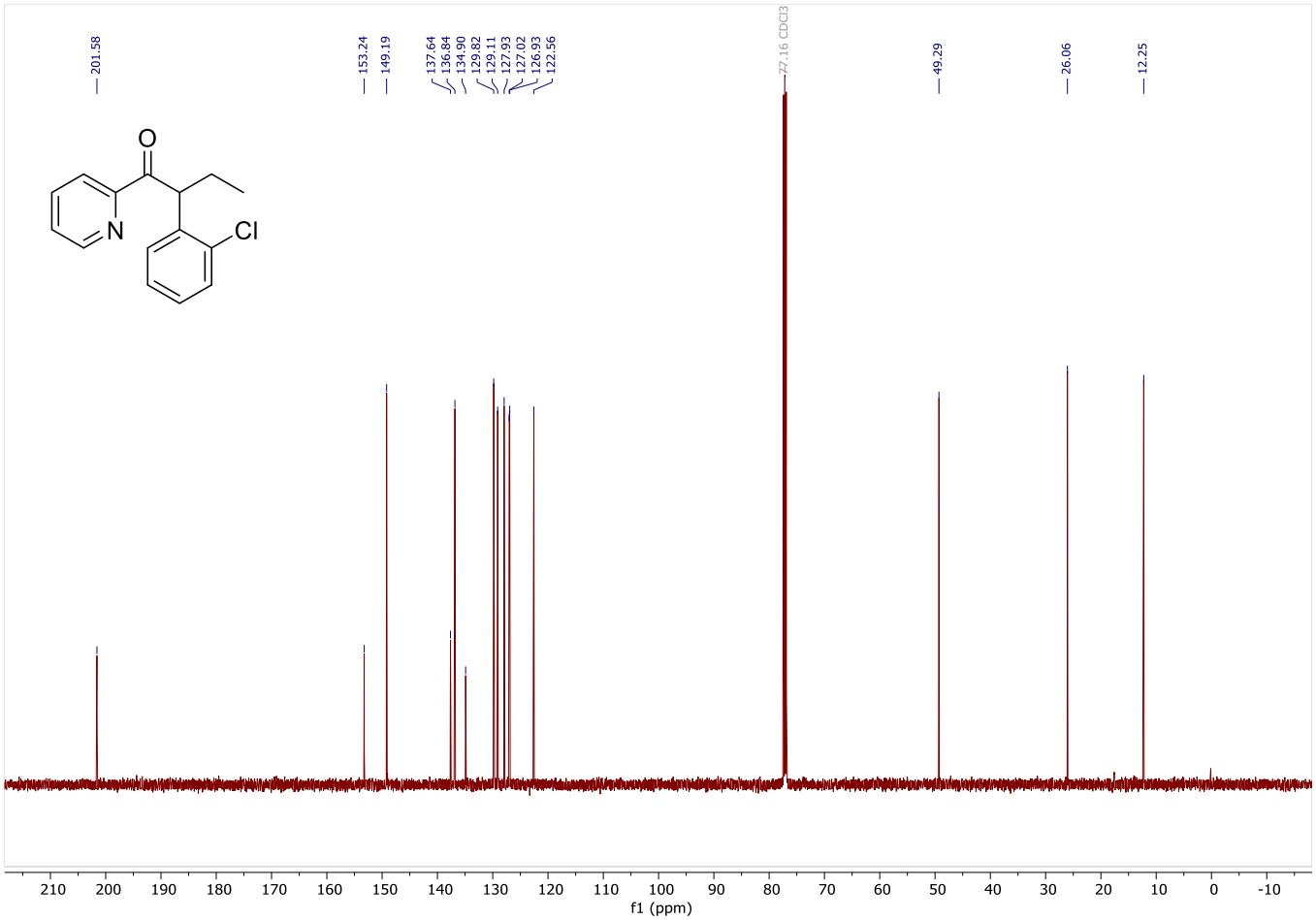
1-(pyridin-2-yl)-2-(o-tolyl)butan-1-one (3m)



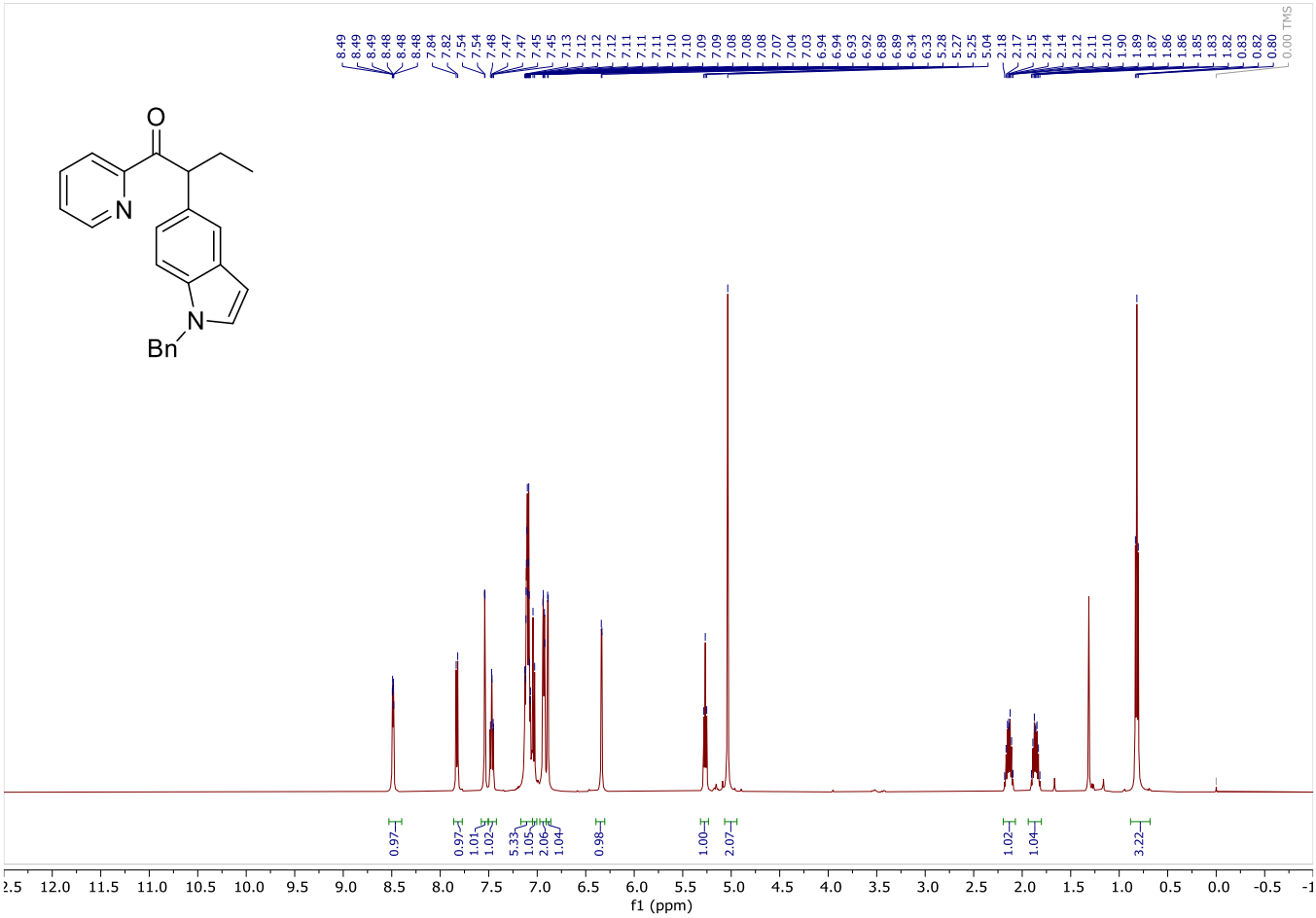


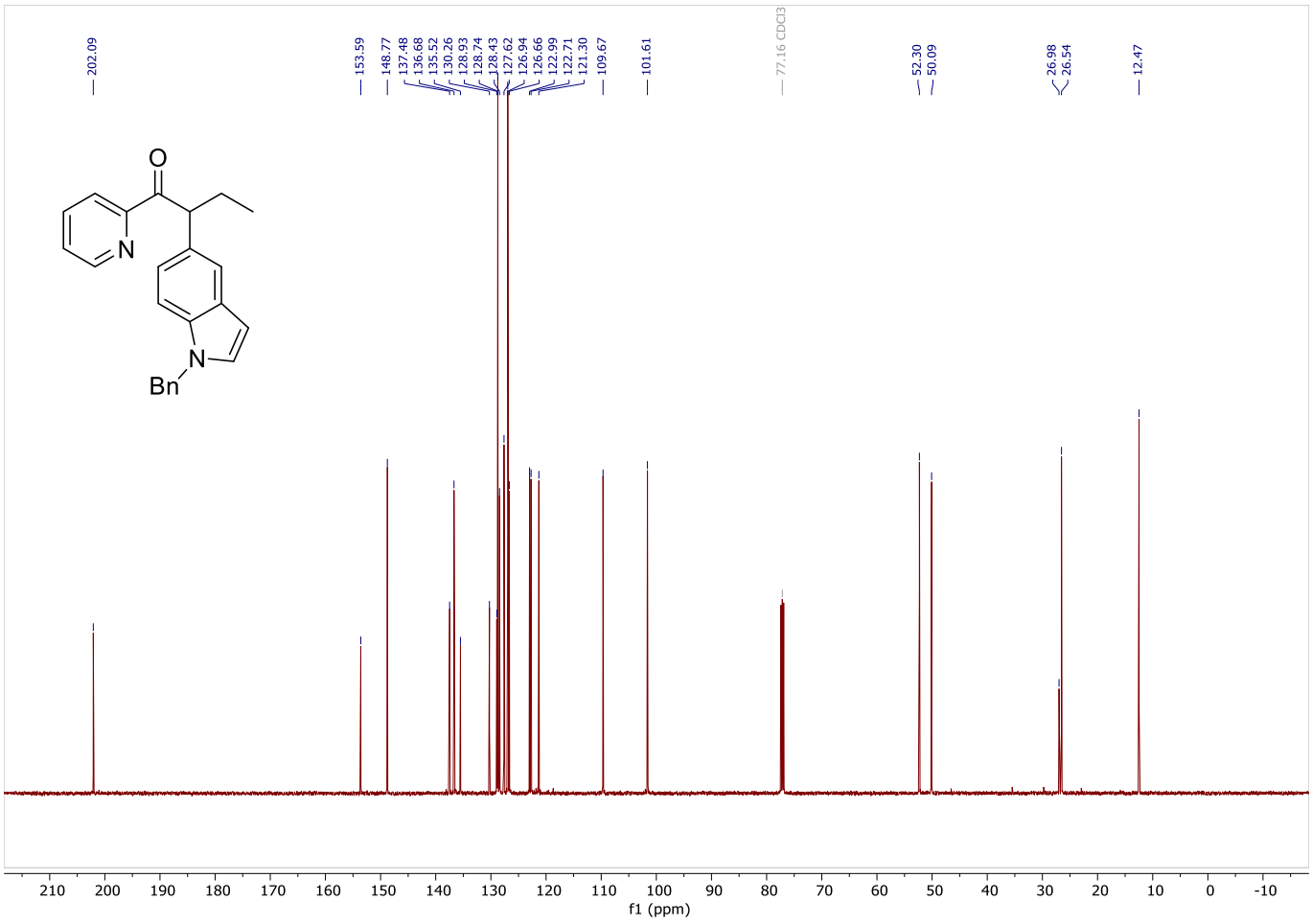
2-(2-chlorophenyl)-1-(pyridin-2-yl)butan-1-one (3n)



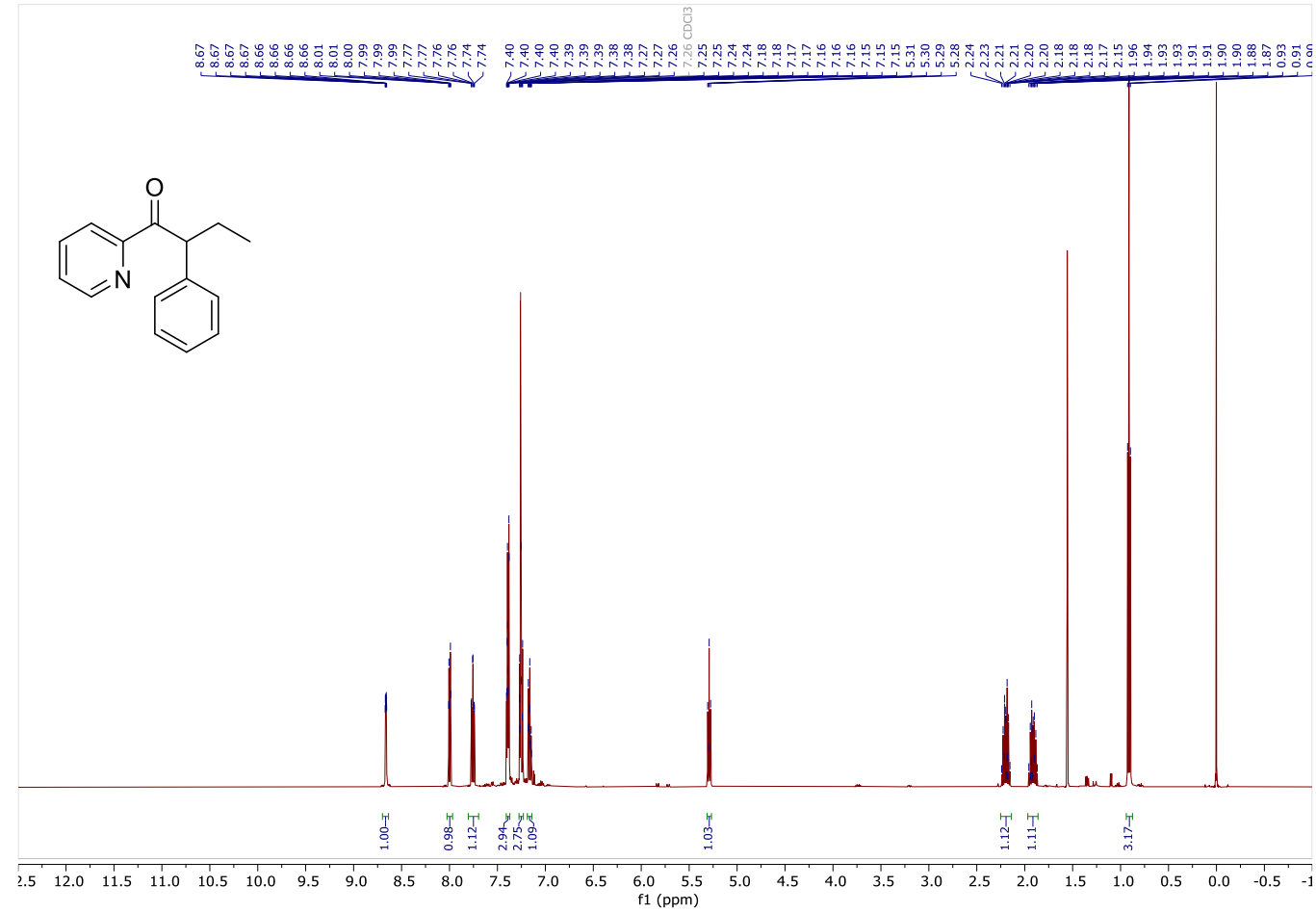


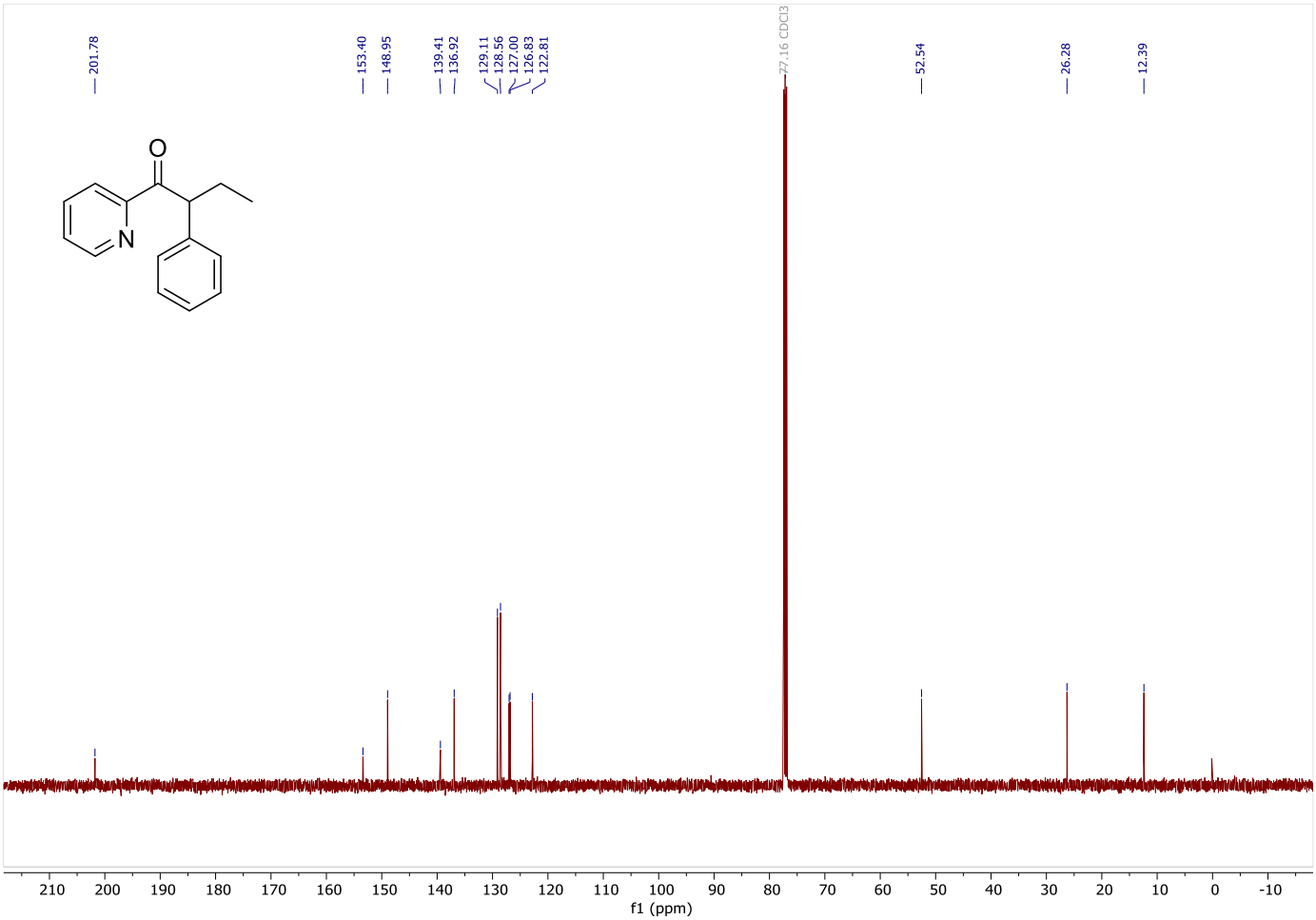
2-(1-benzyl-1H-indol-5-yl)-1-(pyridin-2-yl)butan-1-one (3o)



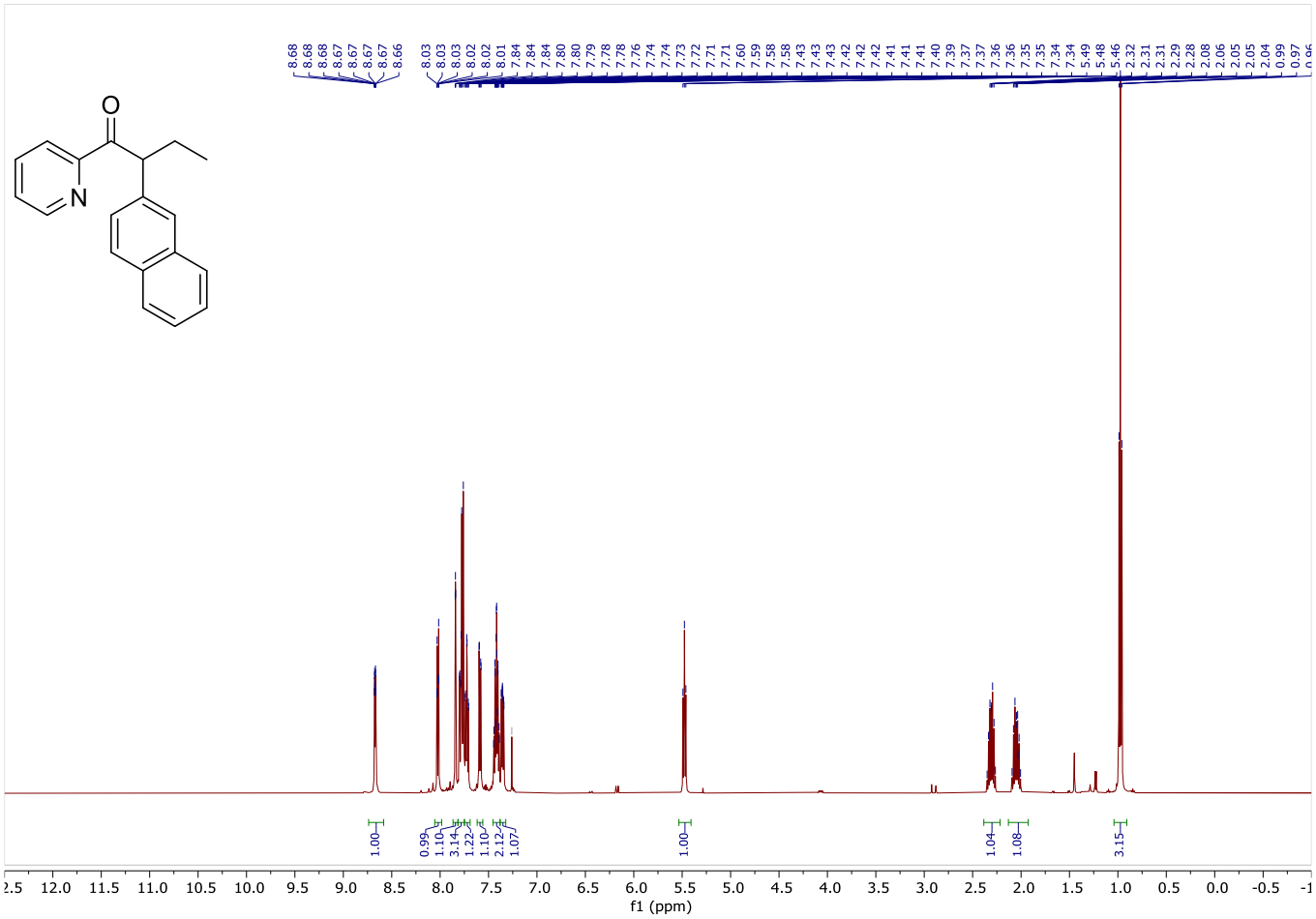


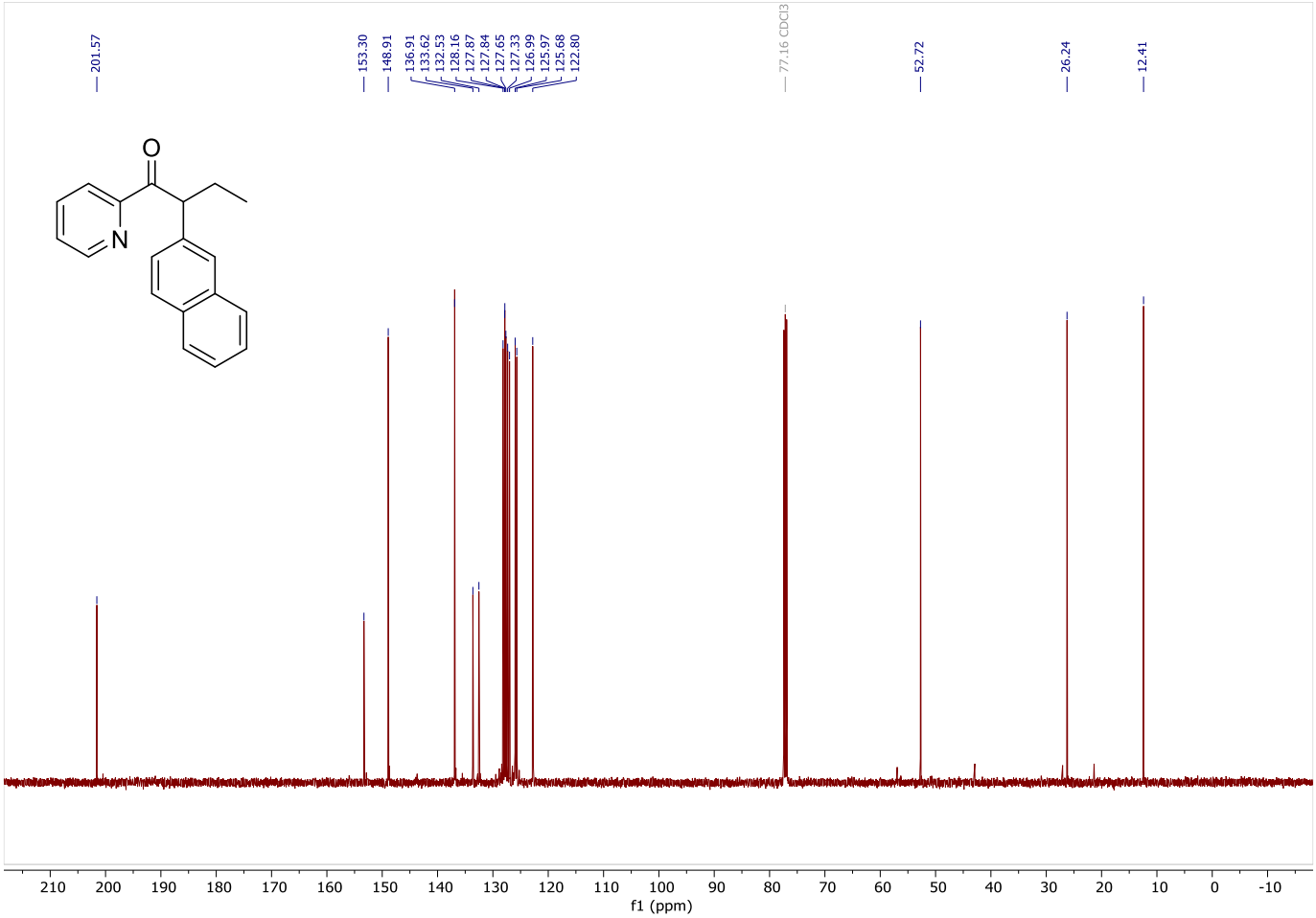
2-phenyl-1-(pyridin-2-yl)butan-1-one (3p)



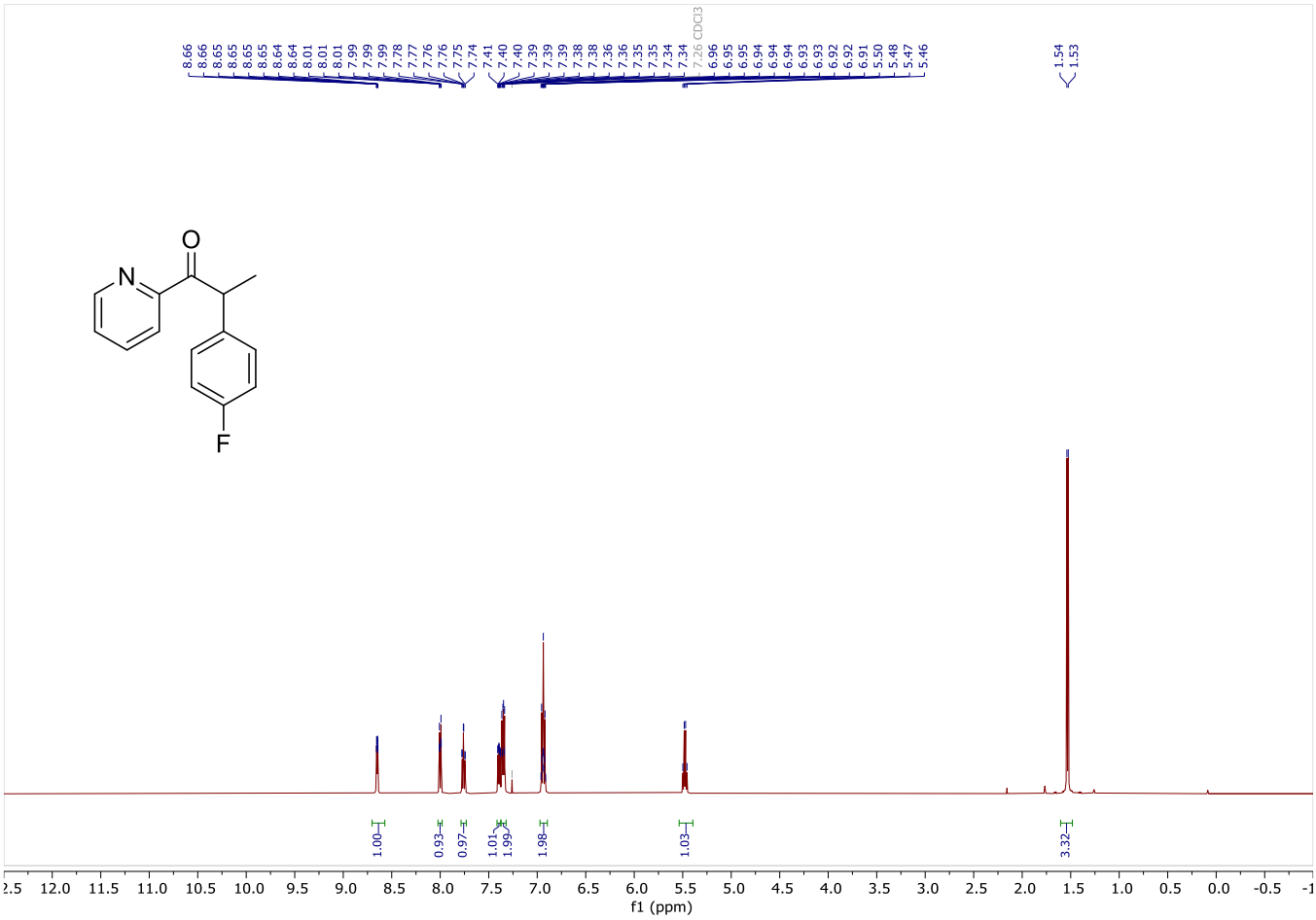


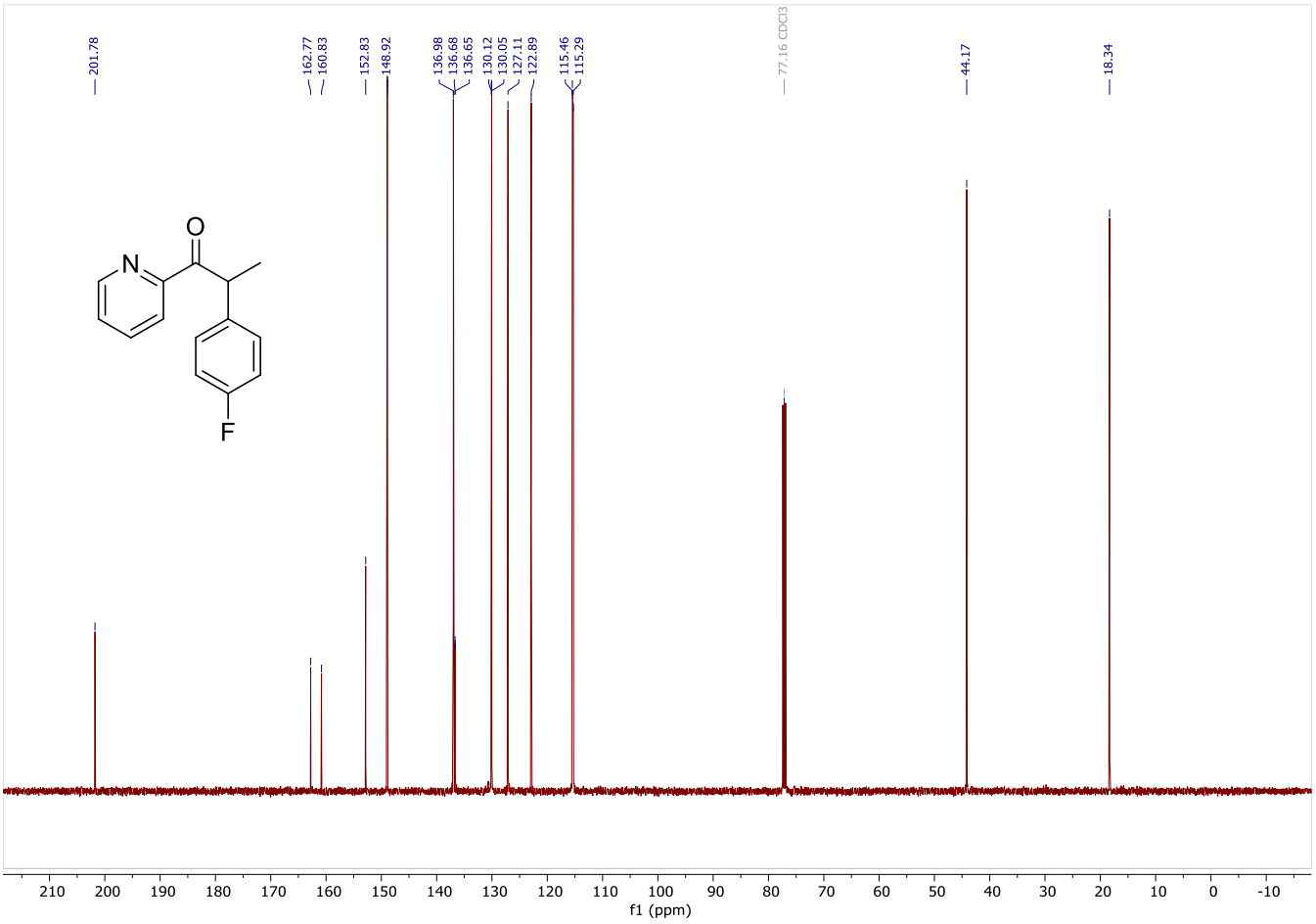
2-(naphthalen-2-yl)-1-(pyridin-2-yl)butan-1-one (3q)



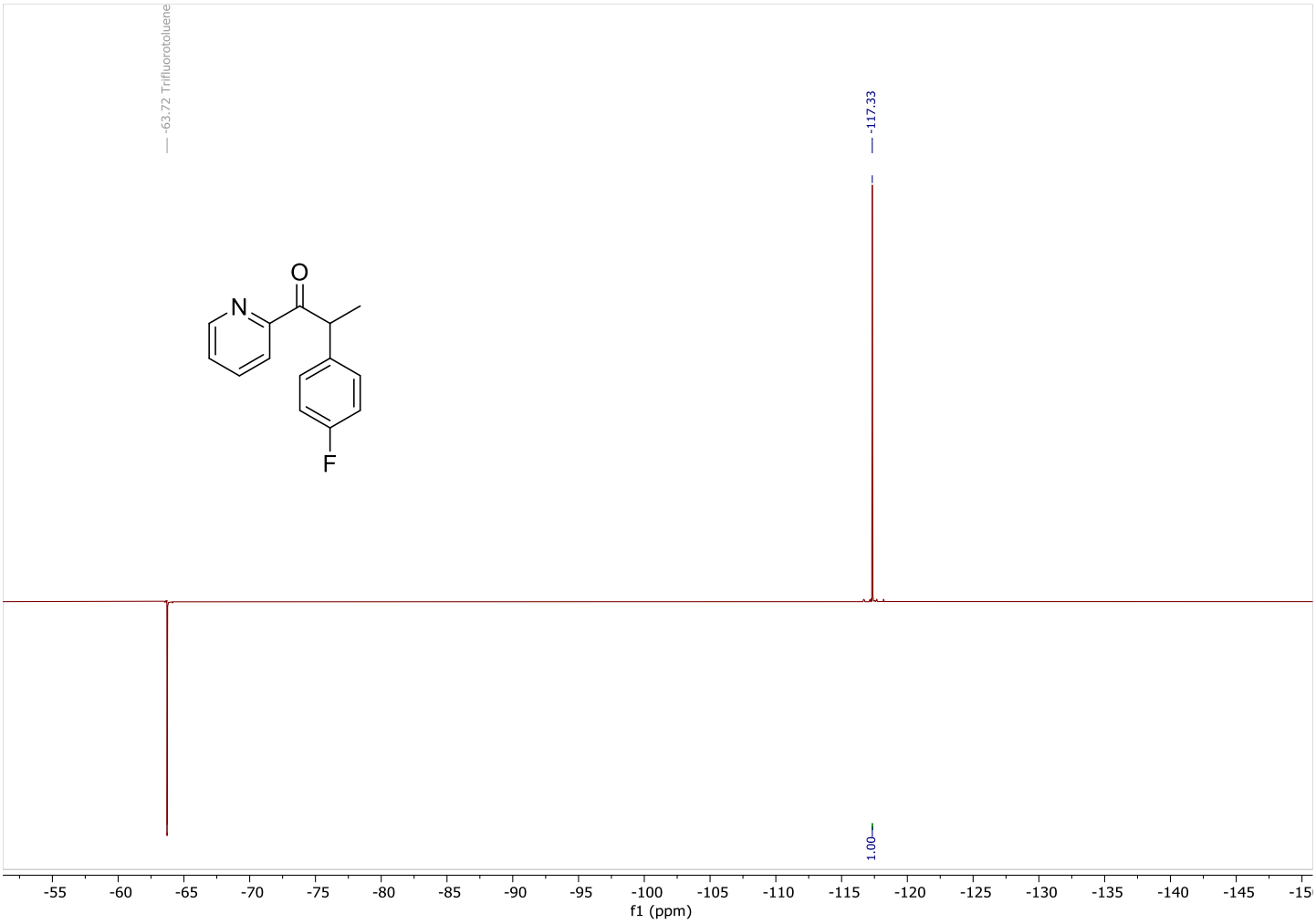


2-(4-fluorophenyl)-1-(pyridin-2-yl)propan-1-one (3r)

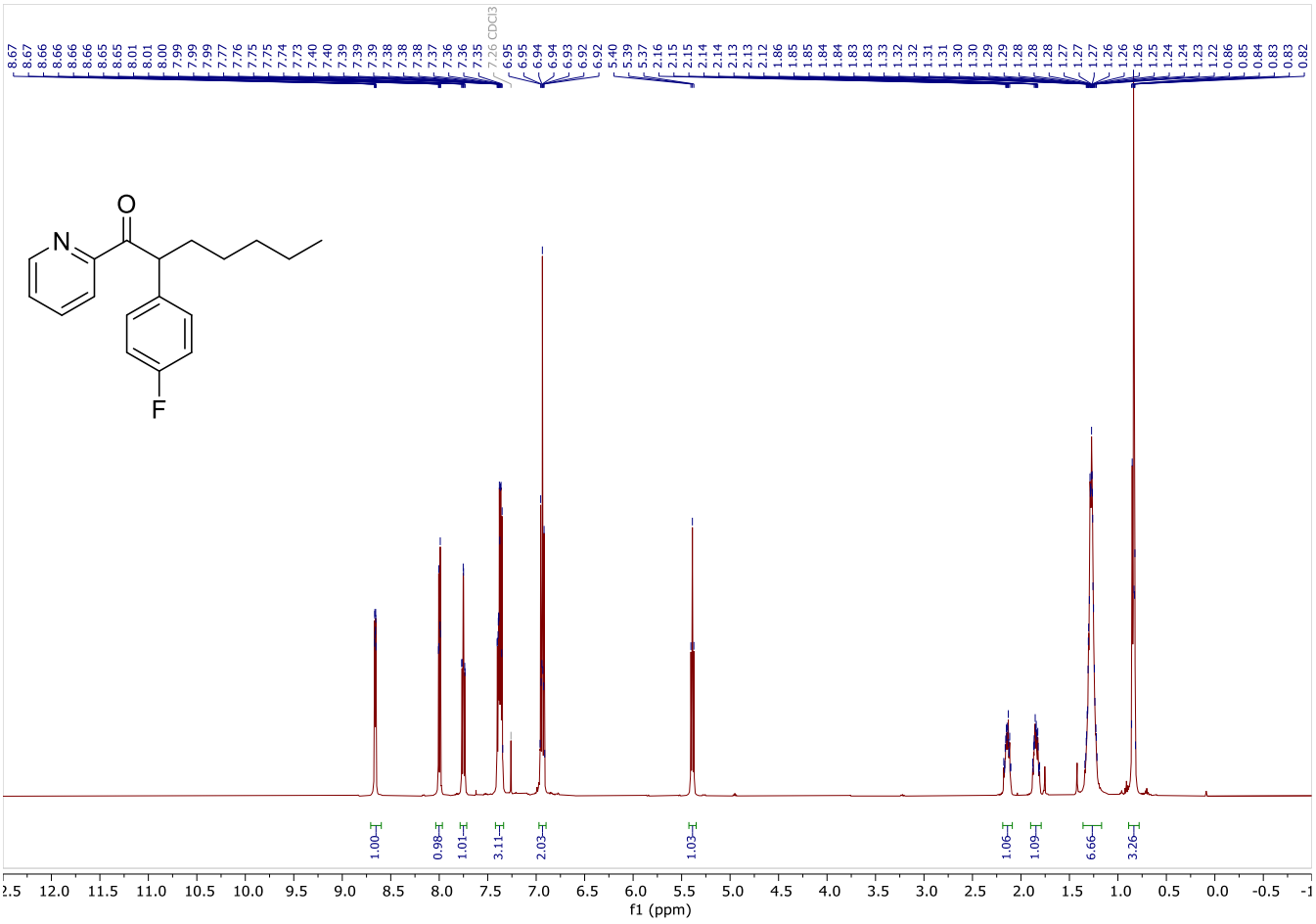


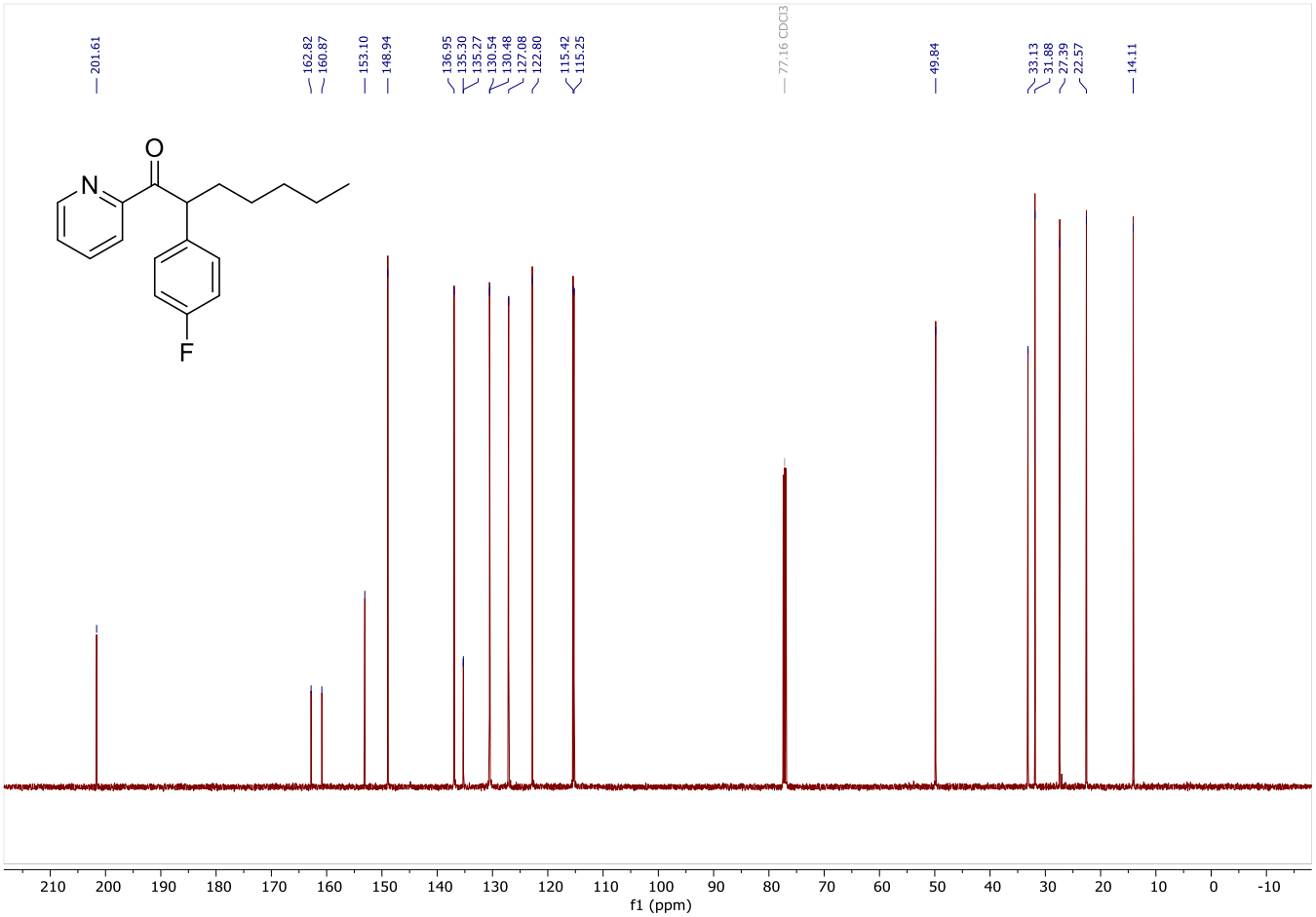


2-(4-fluorophenyl)-1-(pyridin-2-yl)propan-1-one (3r)

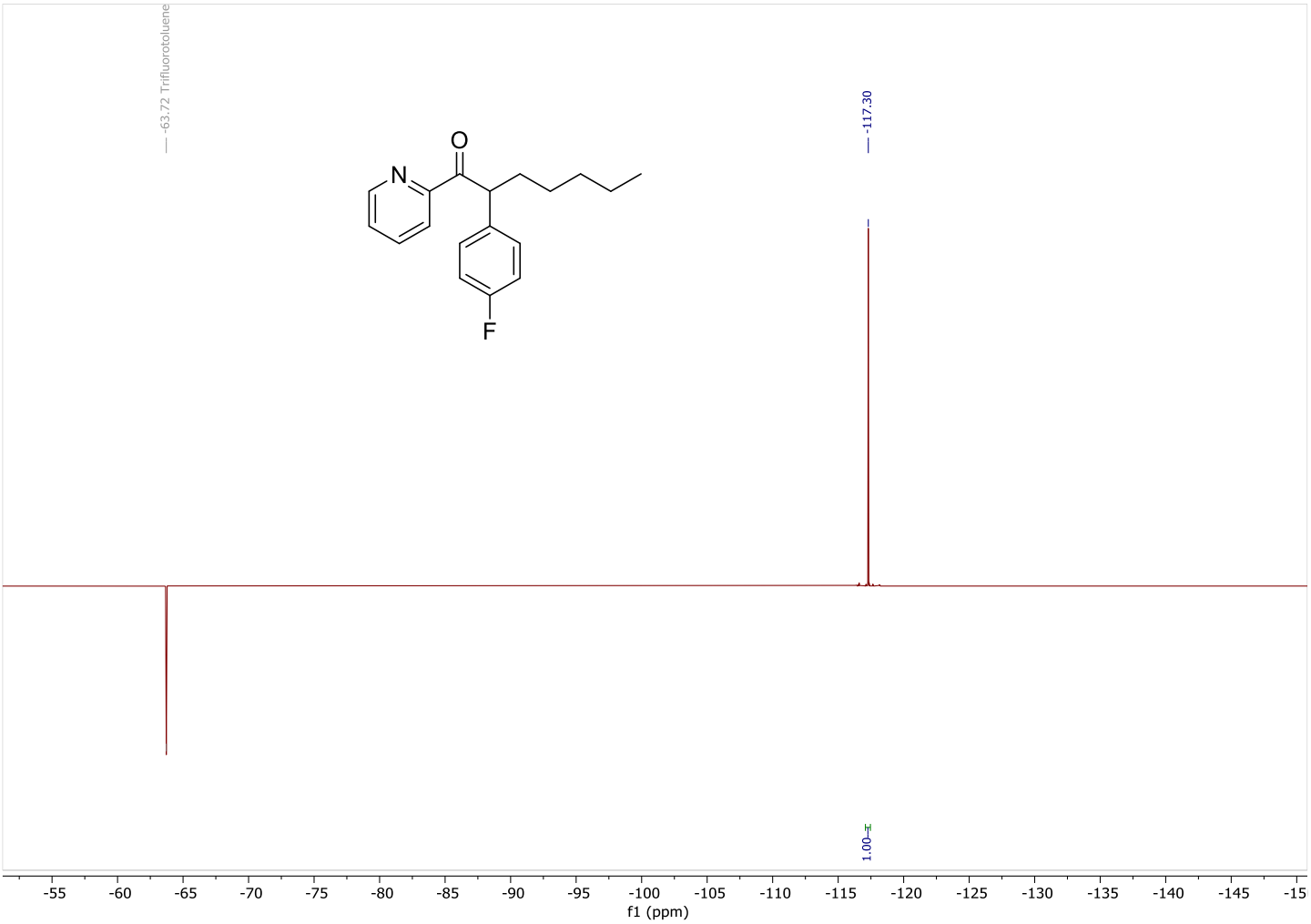


2-(4-fluorophenyl)-1-(pyridin-2-yl)heptan-1-one (3s)

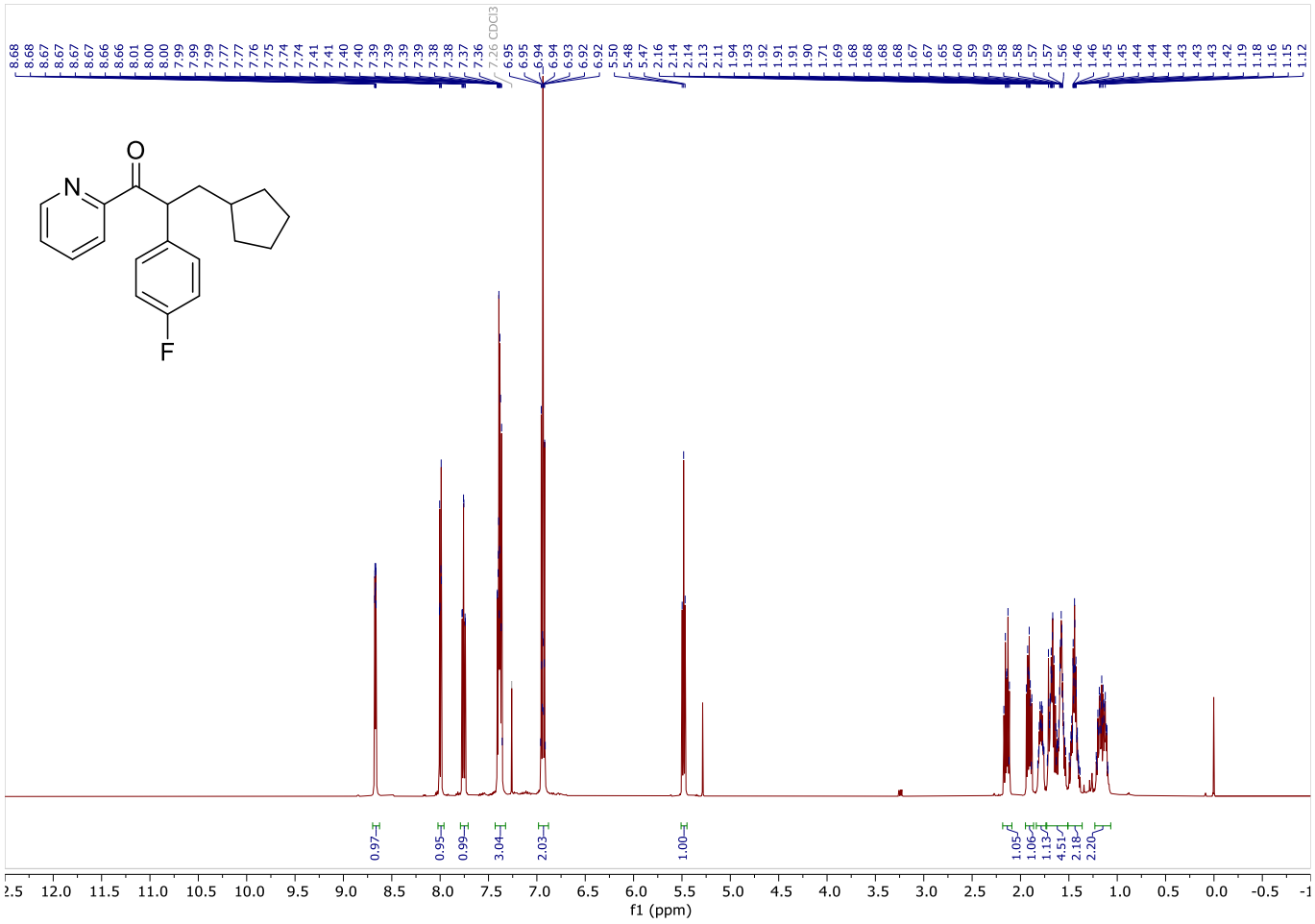


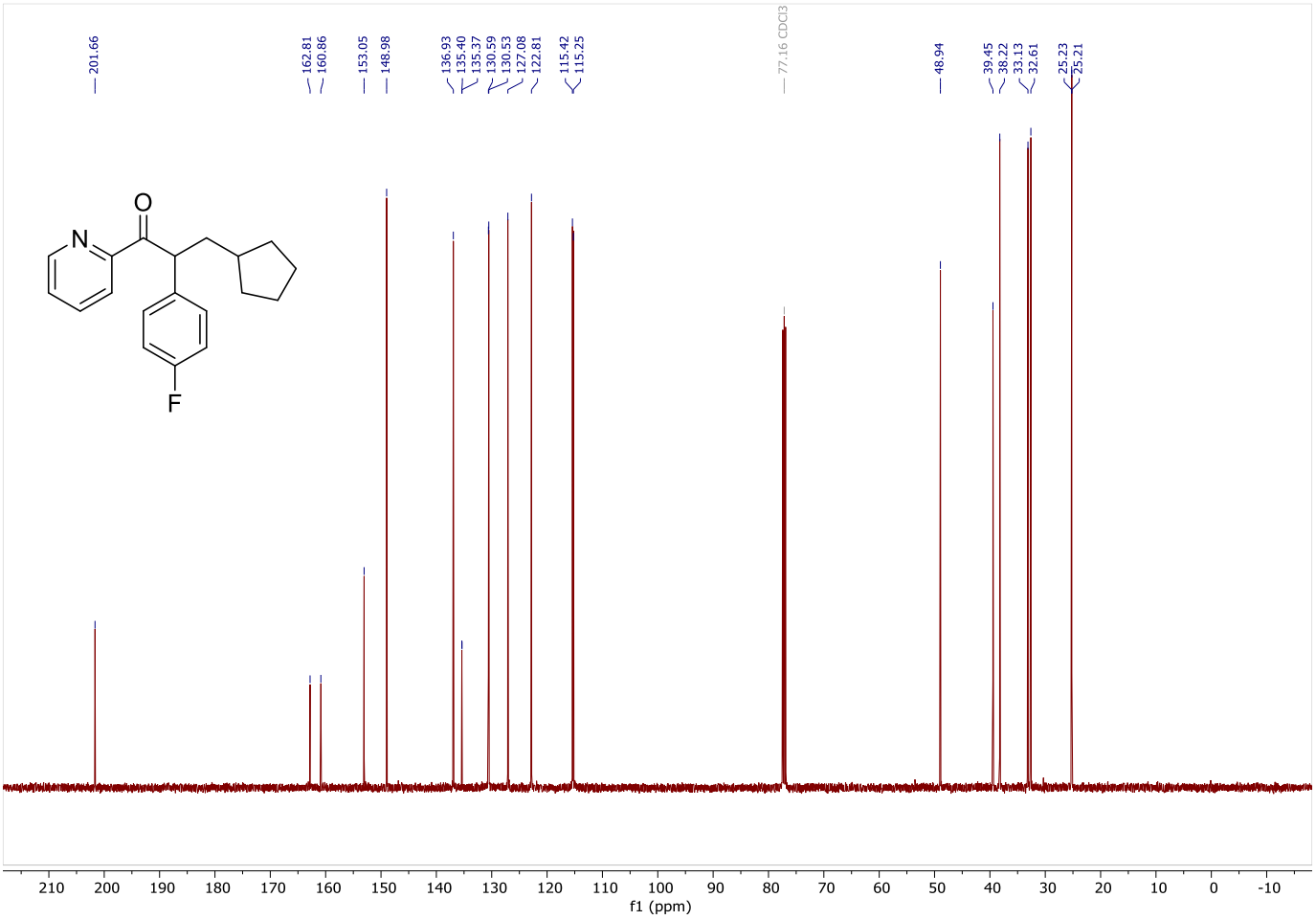


2-(4-fluorophenyl)-1-(pyridin-2-yl)heptan-1-one (3s)

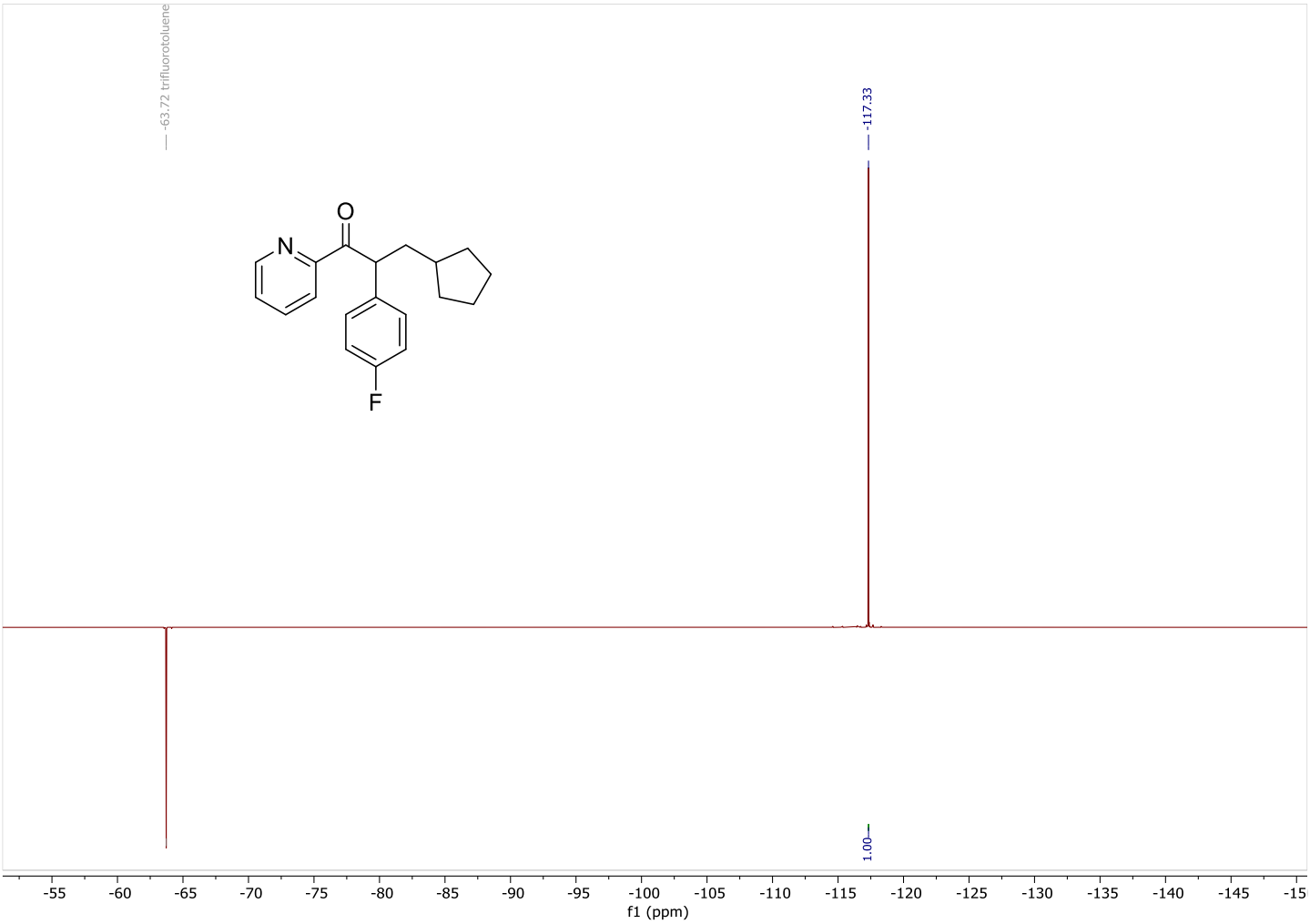


3-cyclopentyl-2-(4-fluorophenyl)-1-(pyridin-2-yl)propan-1-one (3t)

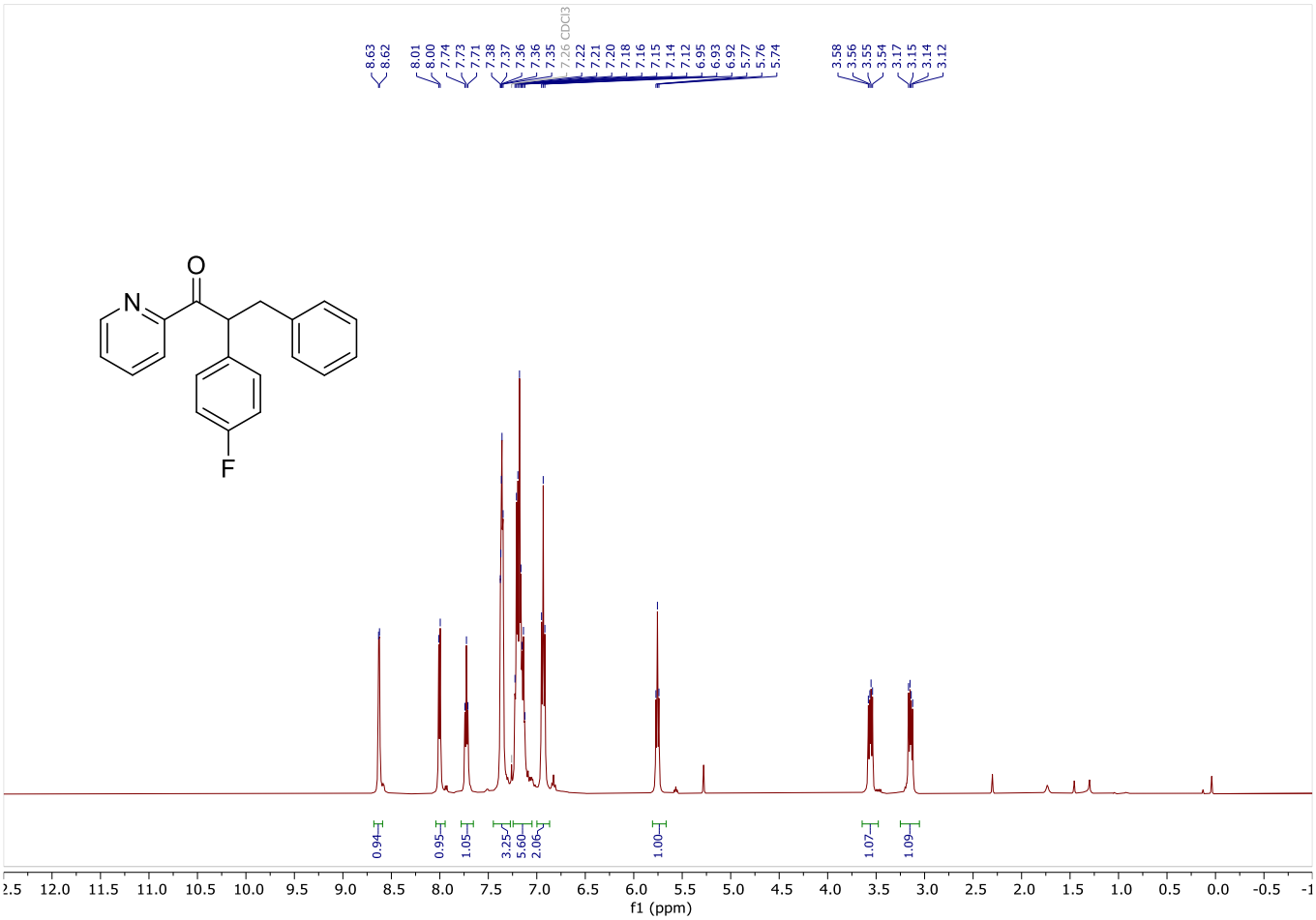


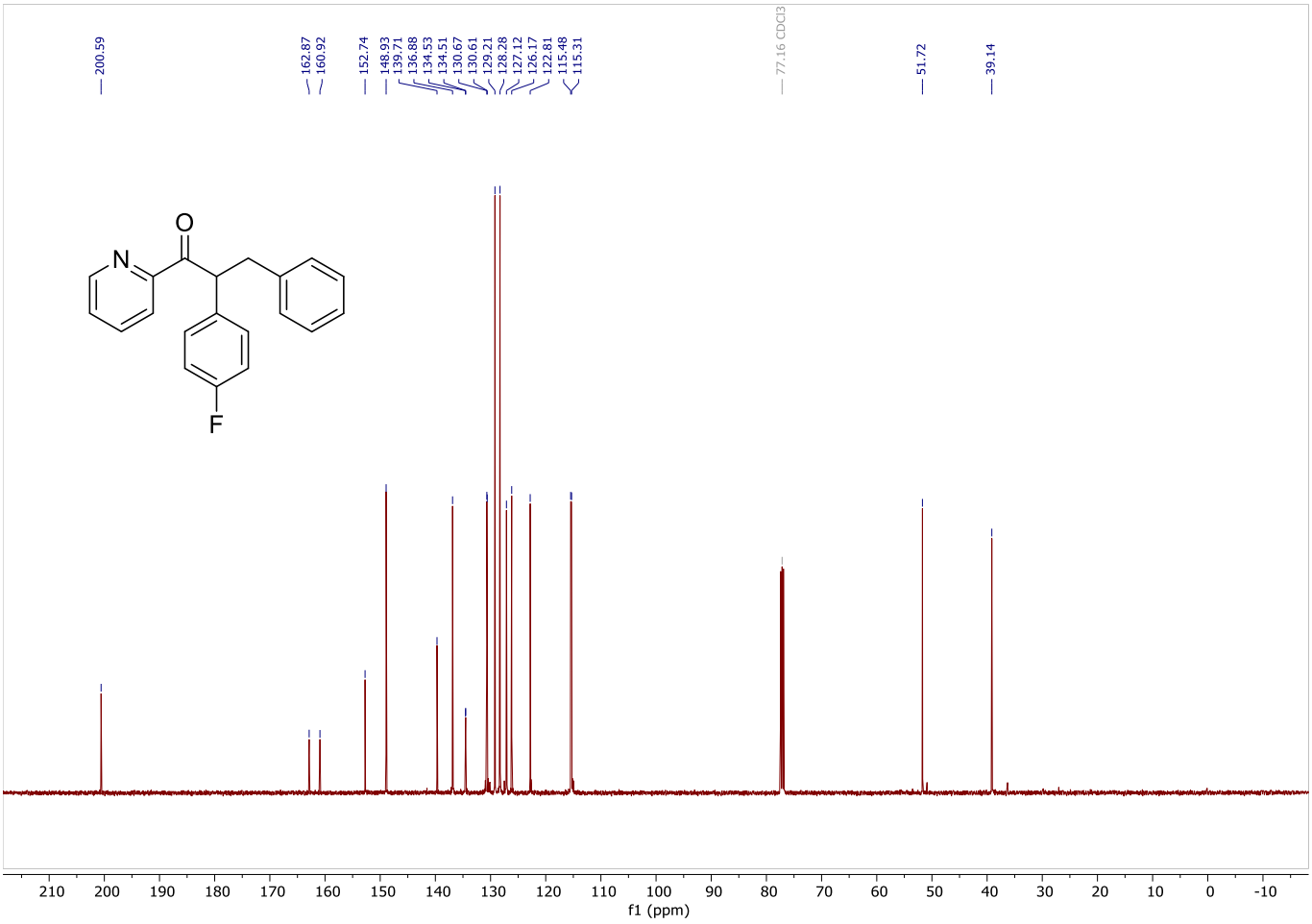


3-cyclopentyl-2-(4-fluorophenyl)-1-(pyridin-2-yl)propan-1-one (3t)

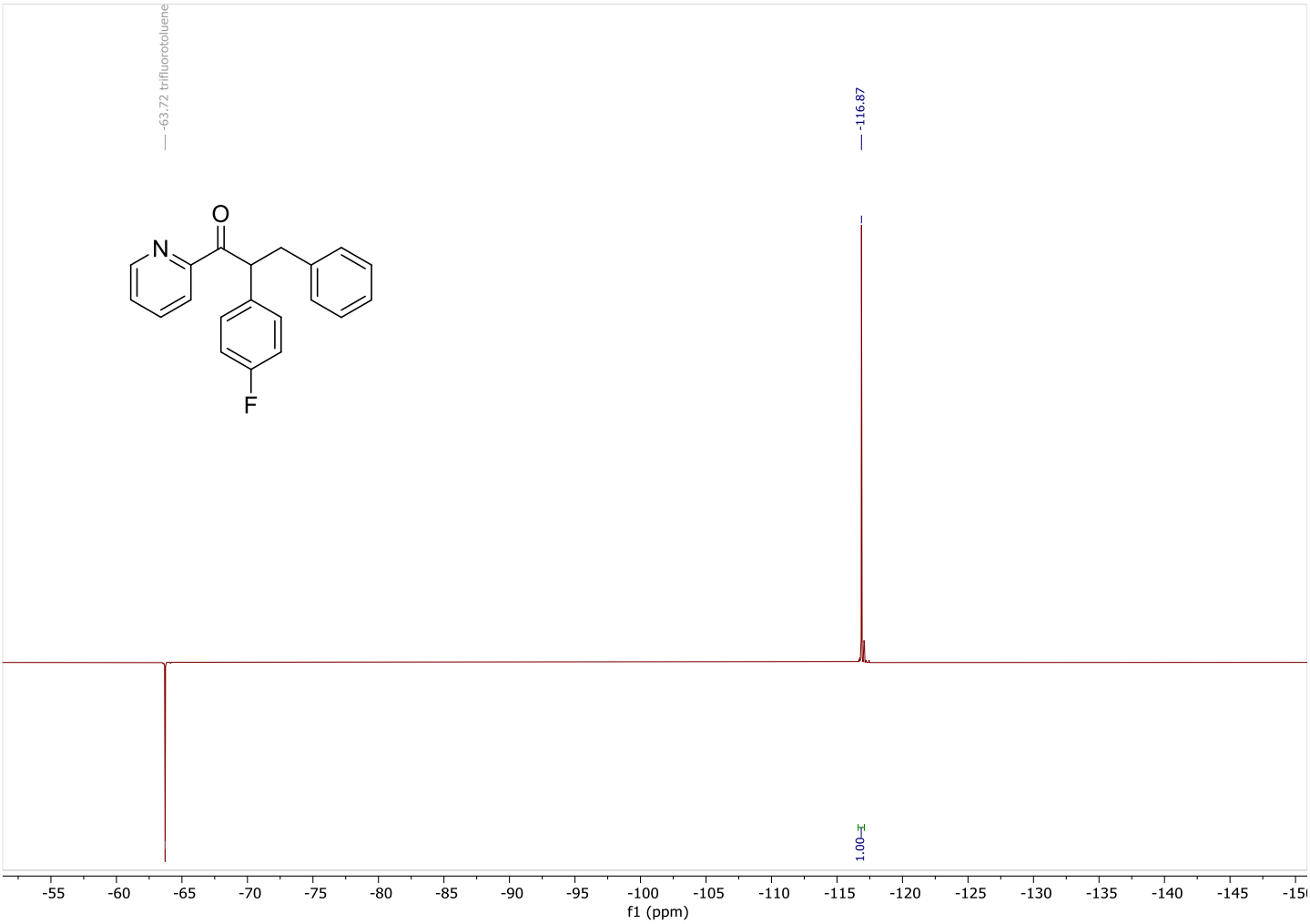


2-(4-fluorophenyl)-3-phenyl-1-(pyridin-2-yl)propan-1-one (3u)

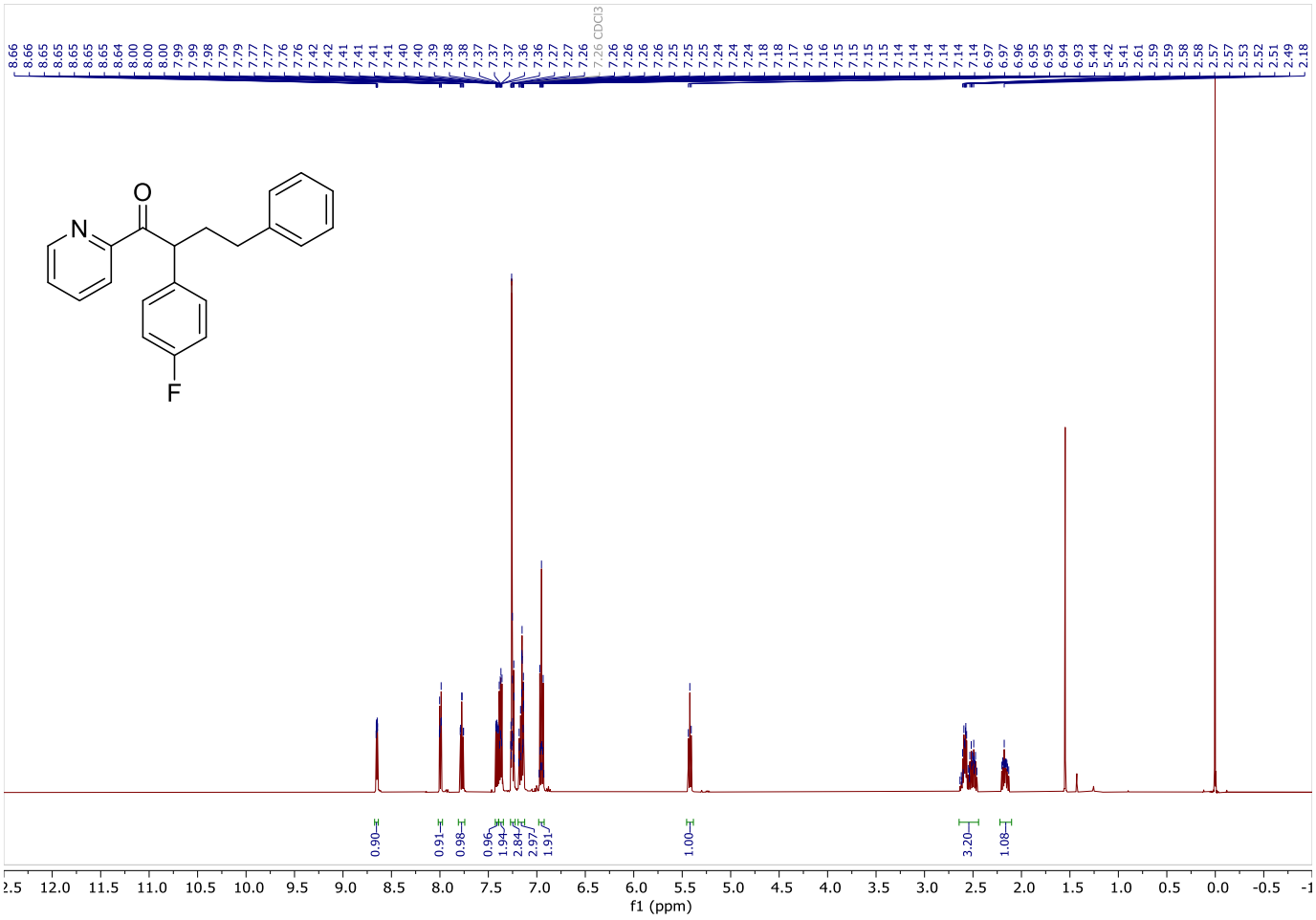


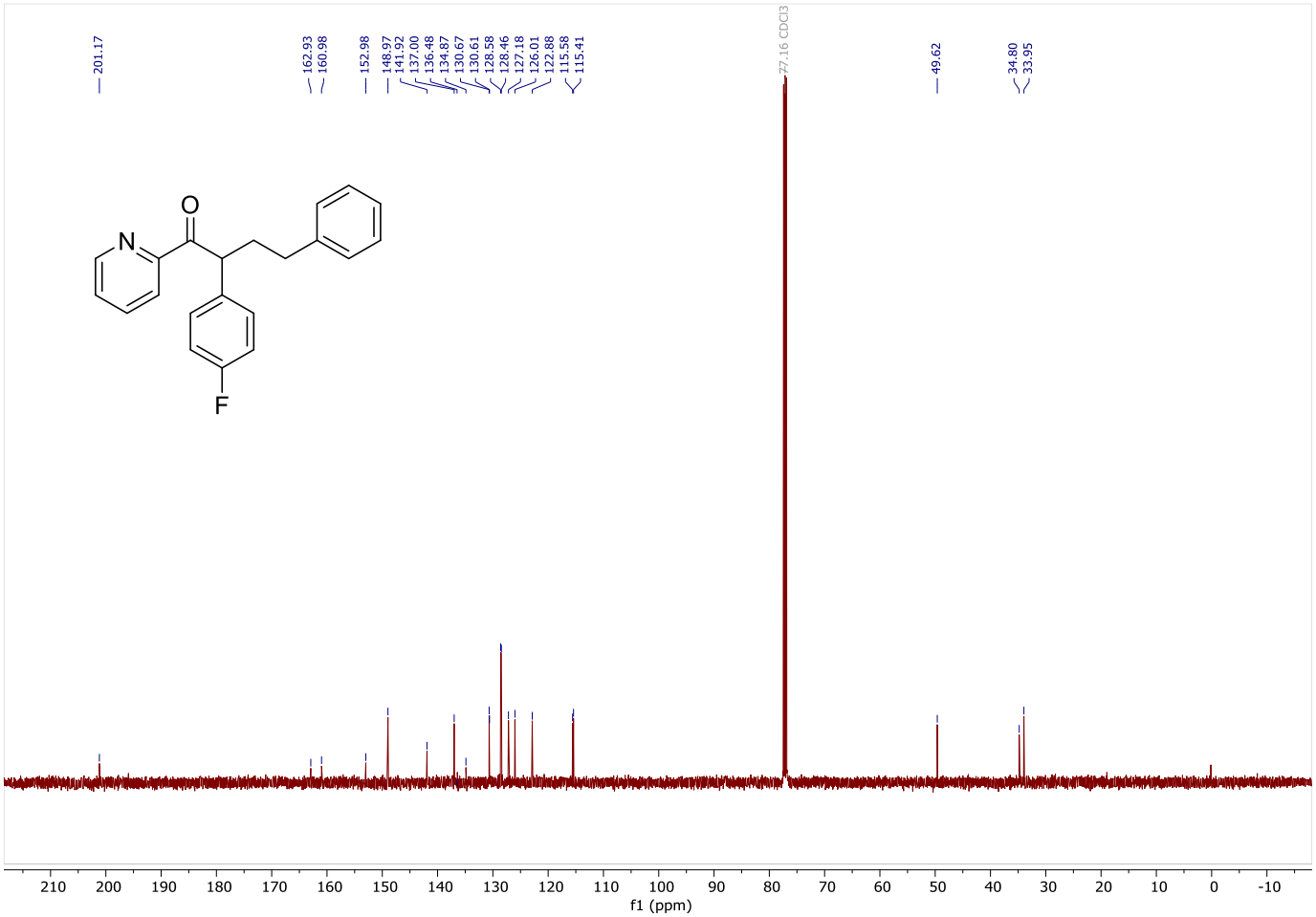


2-(4-fluorophenyl)-3-phenyl-1-(pyridin-2-yl)propan-1-one (3u)

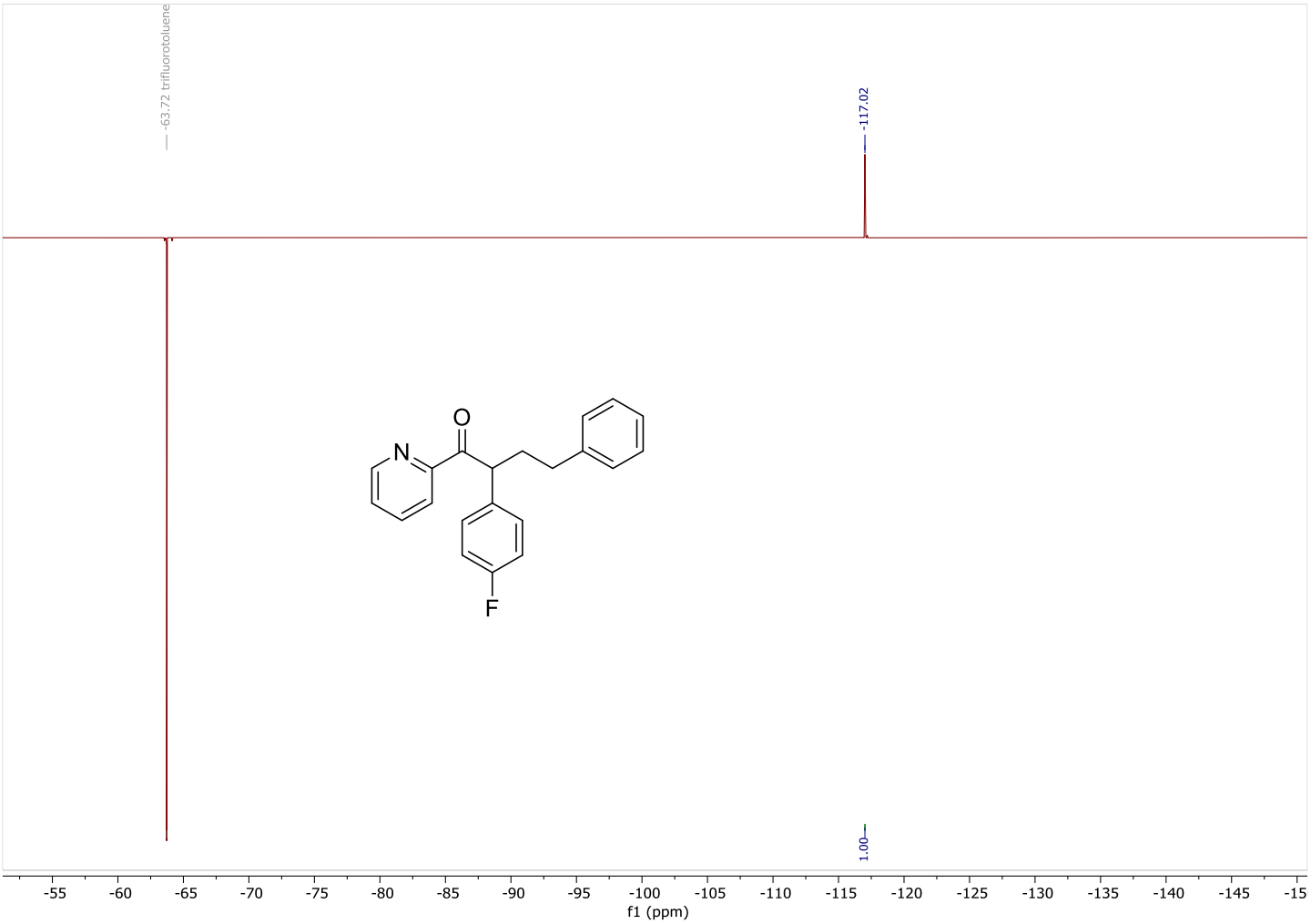


2-(4-fluorophenyl)-4-phenyl-1-(pyridin-2-yl)butan-1-one (3v)

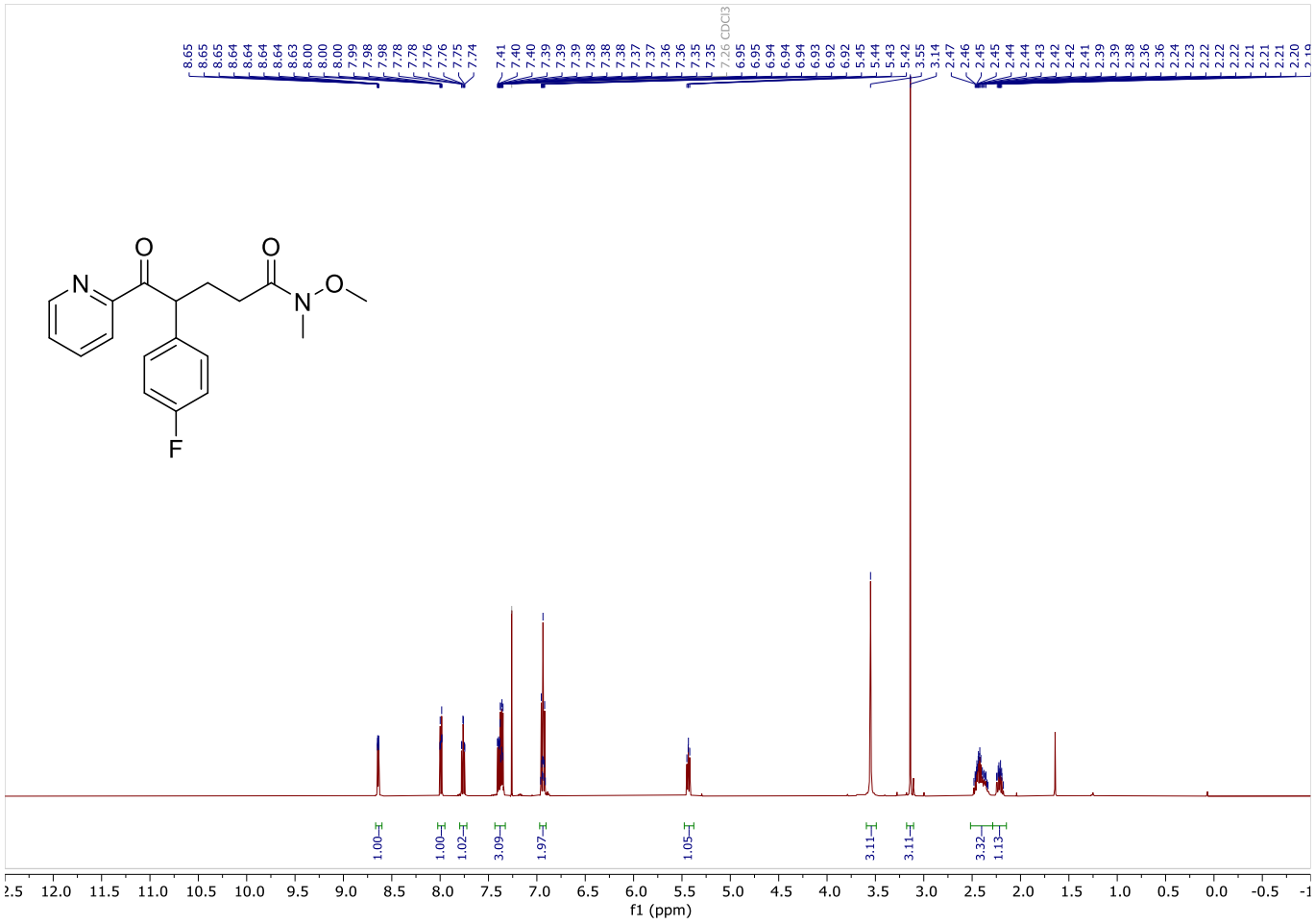


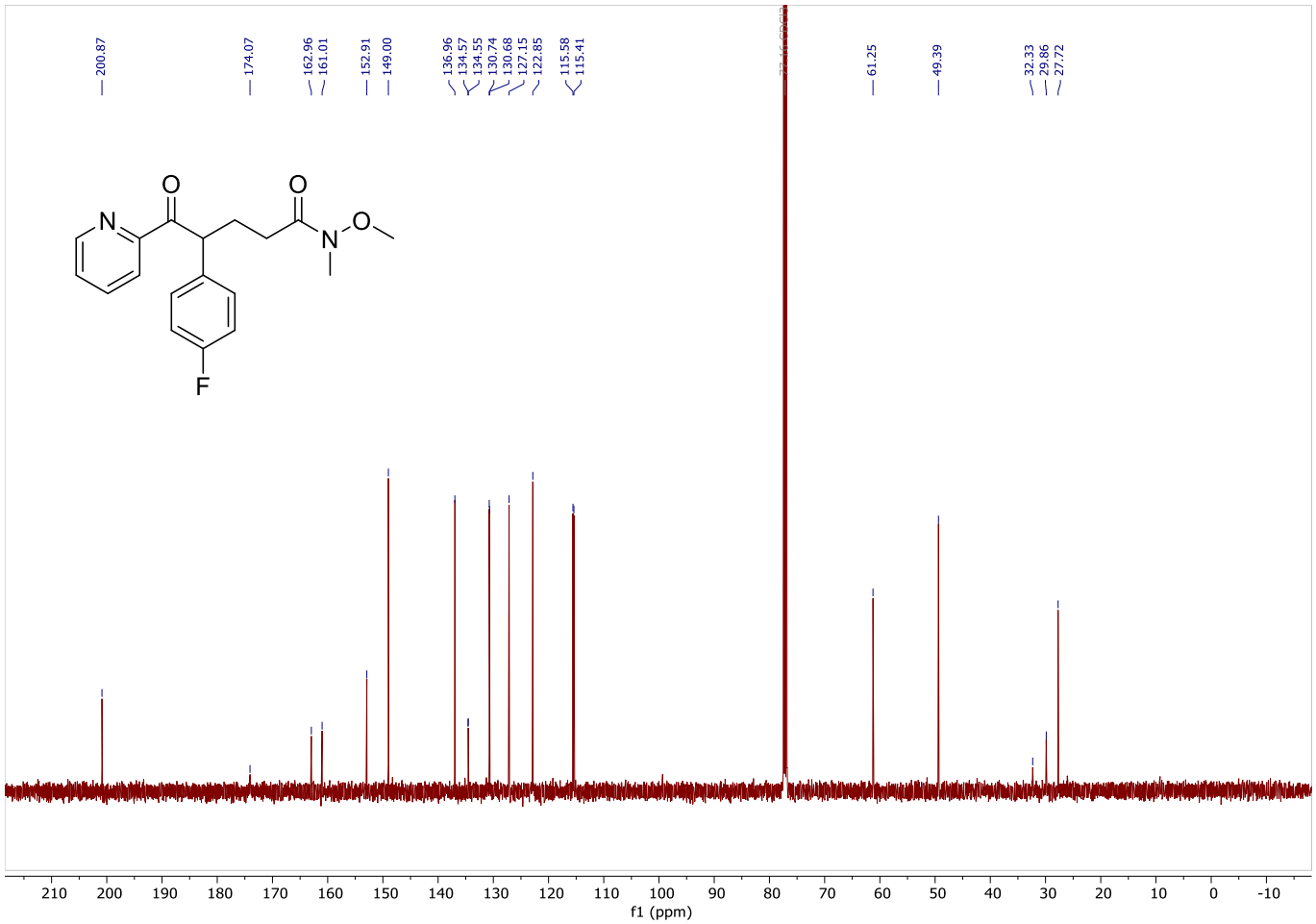


2-(4-fluorophenyl)-4-phenyl-1-(pyridin-2-yl)butan-1-one (3v)

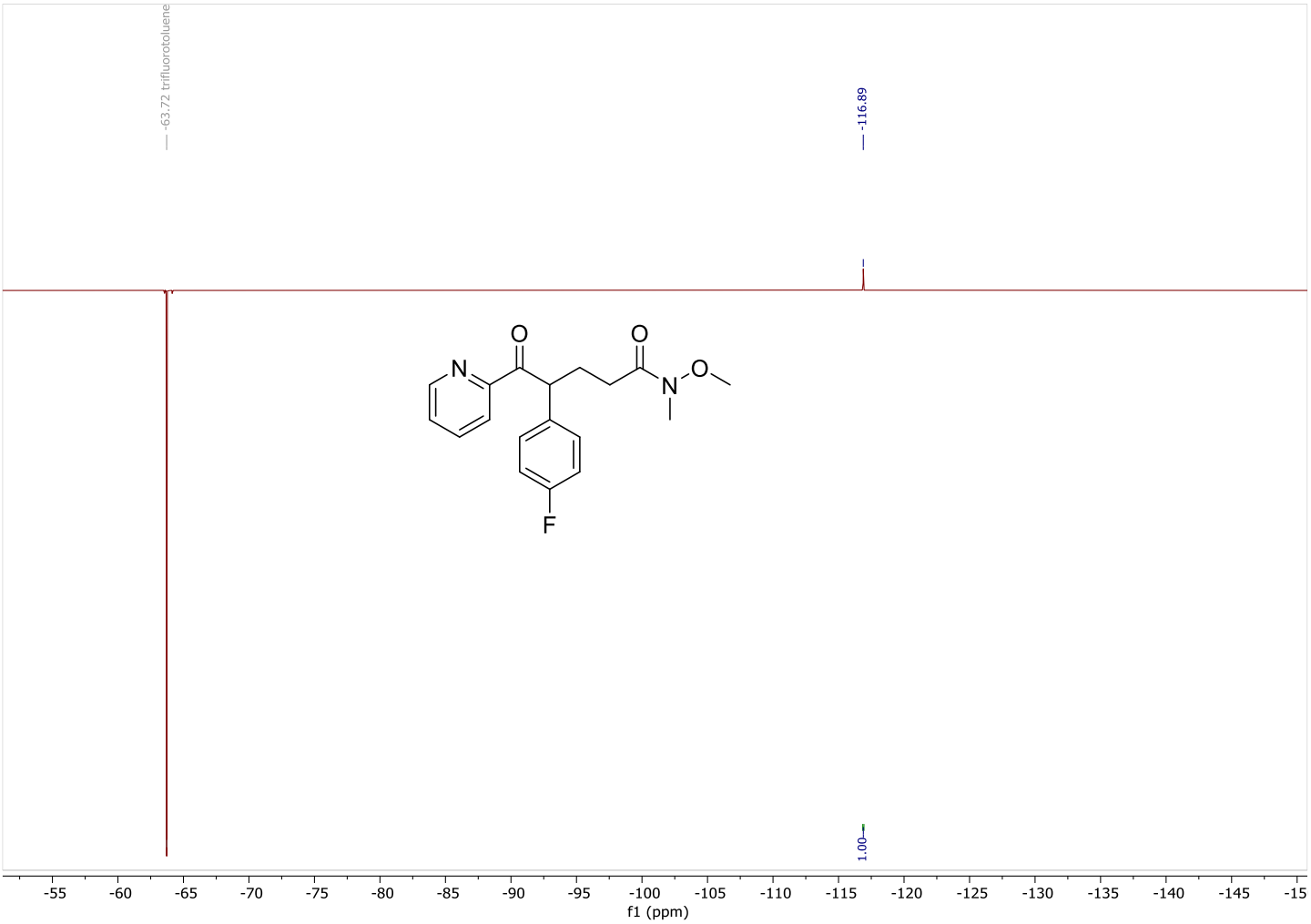


4-(4-fluorophenyl)-N-methoxy-N-methyl-5-oxo-5-(pyridin-2-yl)pentanamide (3w)

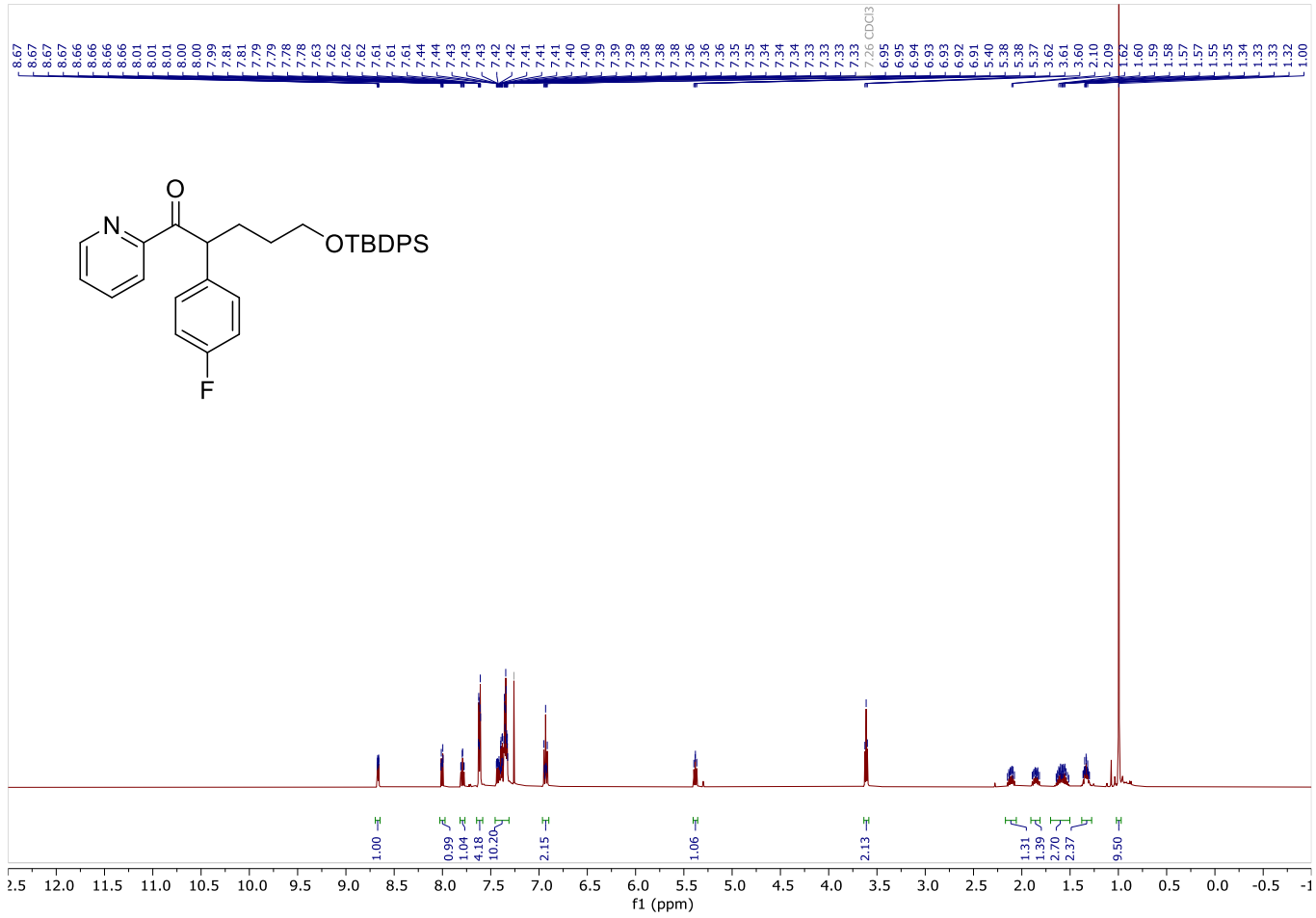


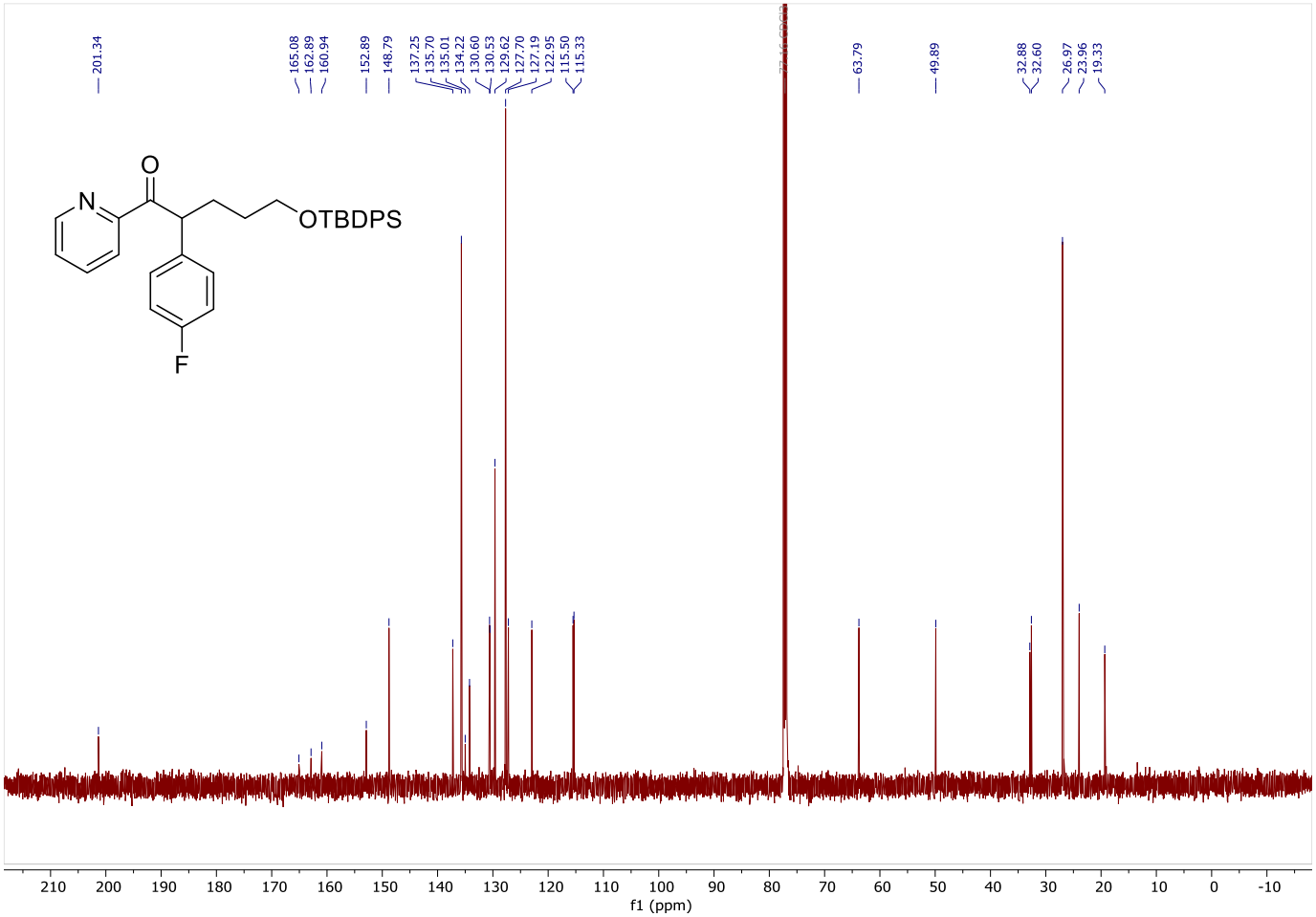


4-(4-fluorophenyl)-N-methoxy-N-methyl-5-oxo-5-(pyridin-2-yl)pentanamide (3w)

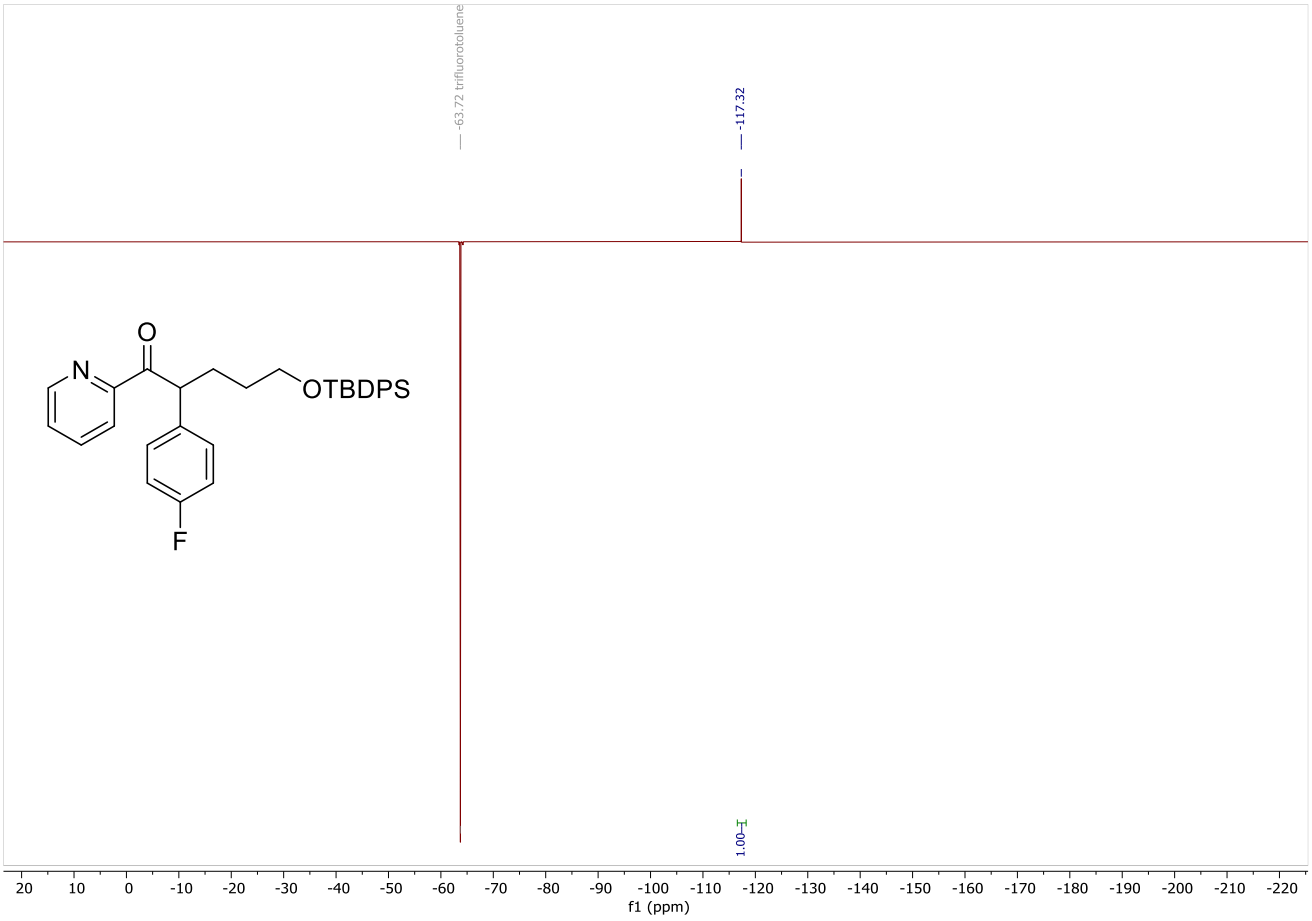


5-((tert-butyldiphenylsilyl)oxy)-2-(4-fluorophenyl)-1-(pyridin-2-yl)pentan-1-one (3x)

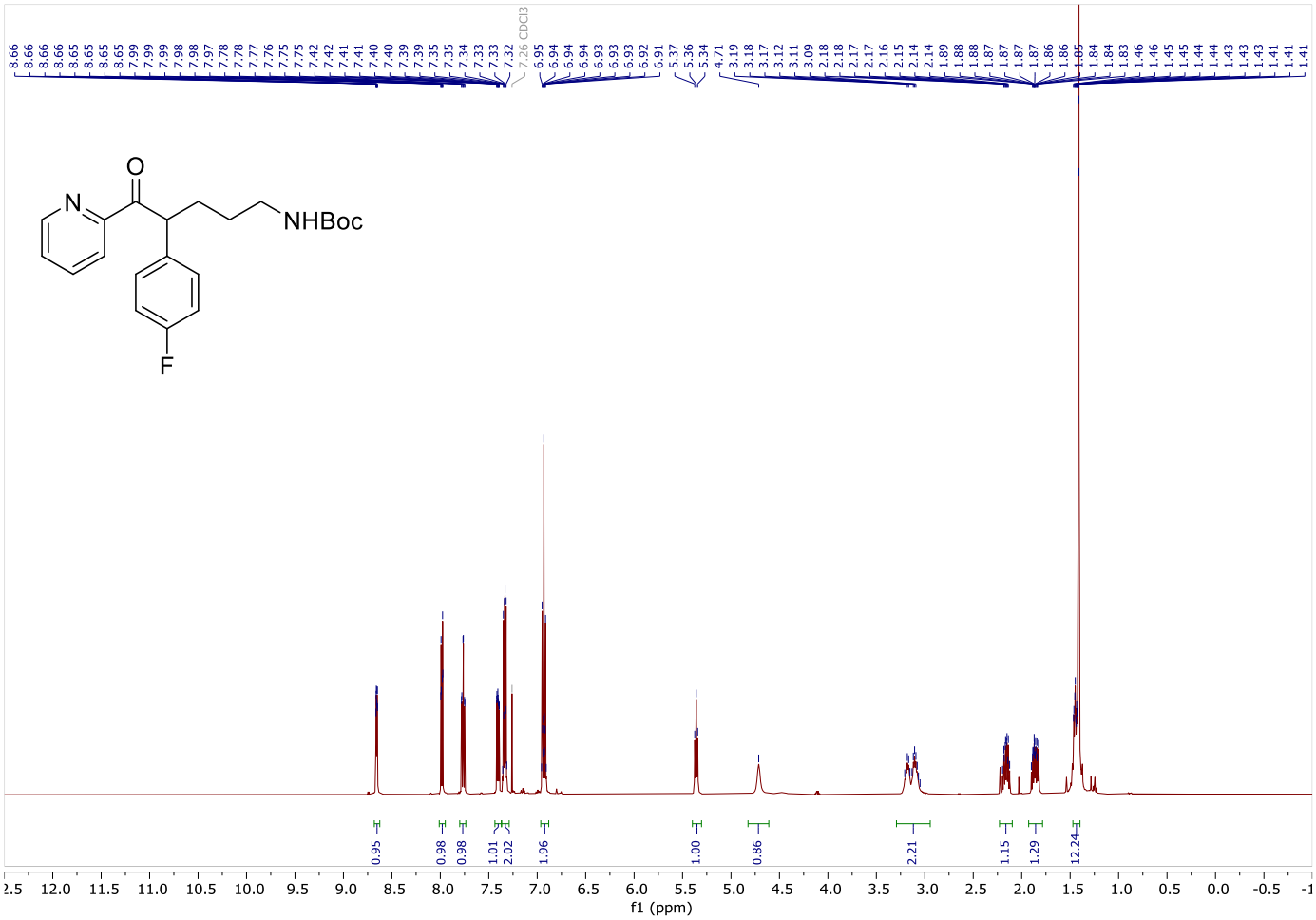


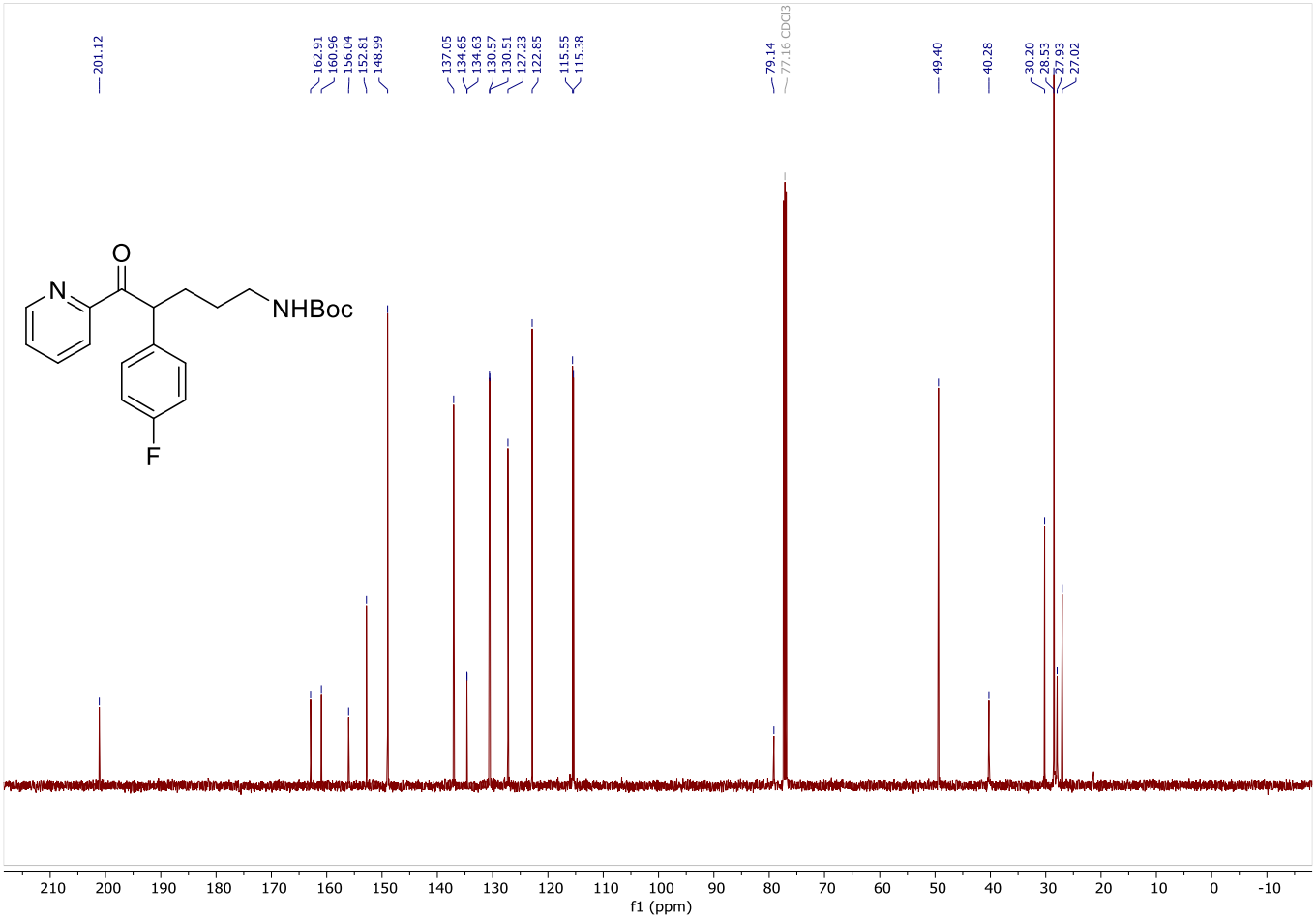


5-((tert-butyldiphenylsilyl)oxy)-2-(4-fluorophenyl)-1-(pyridin-2-yl)pentan-1-one (3x)

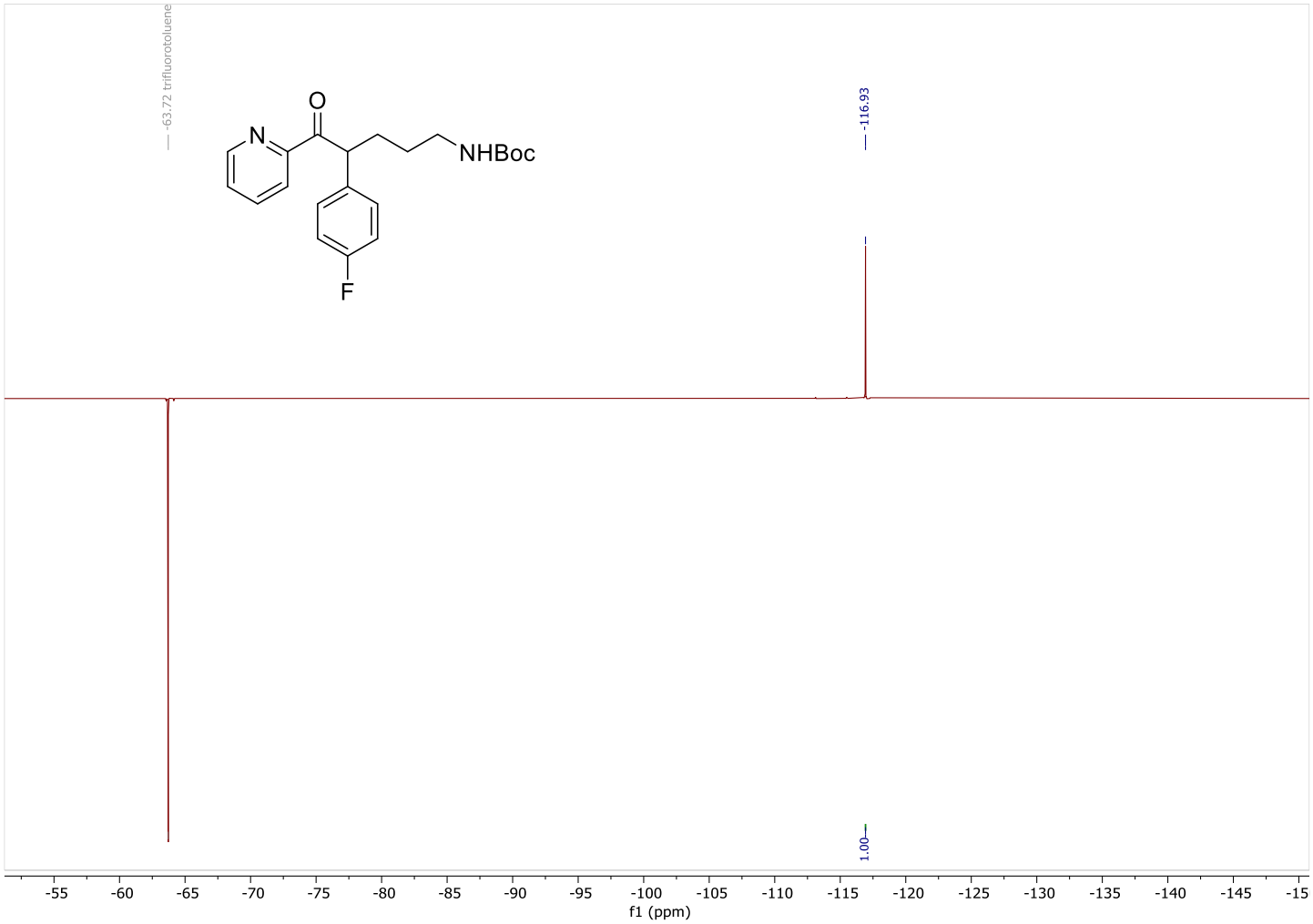


tert-butyl (3-(4-fluorophenyl)-4-oxo-4-(pyridin-2-yl)butyl)carbamate (3y)

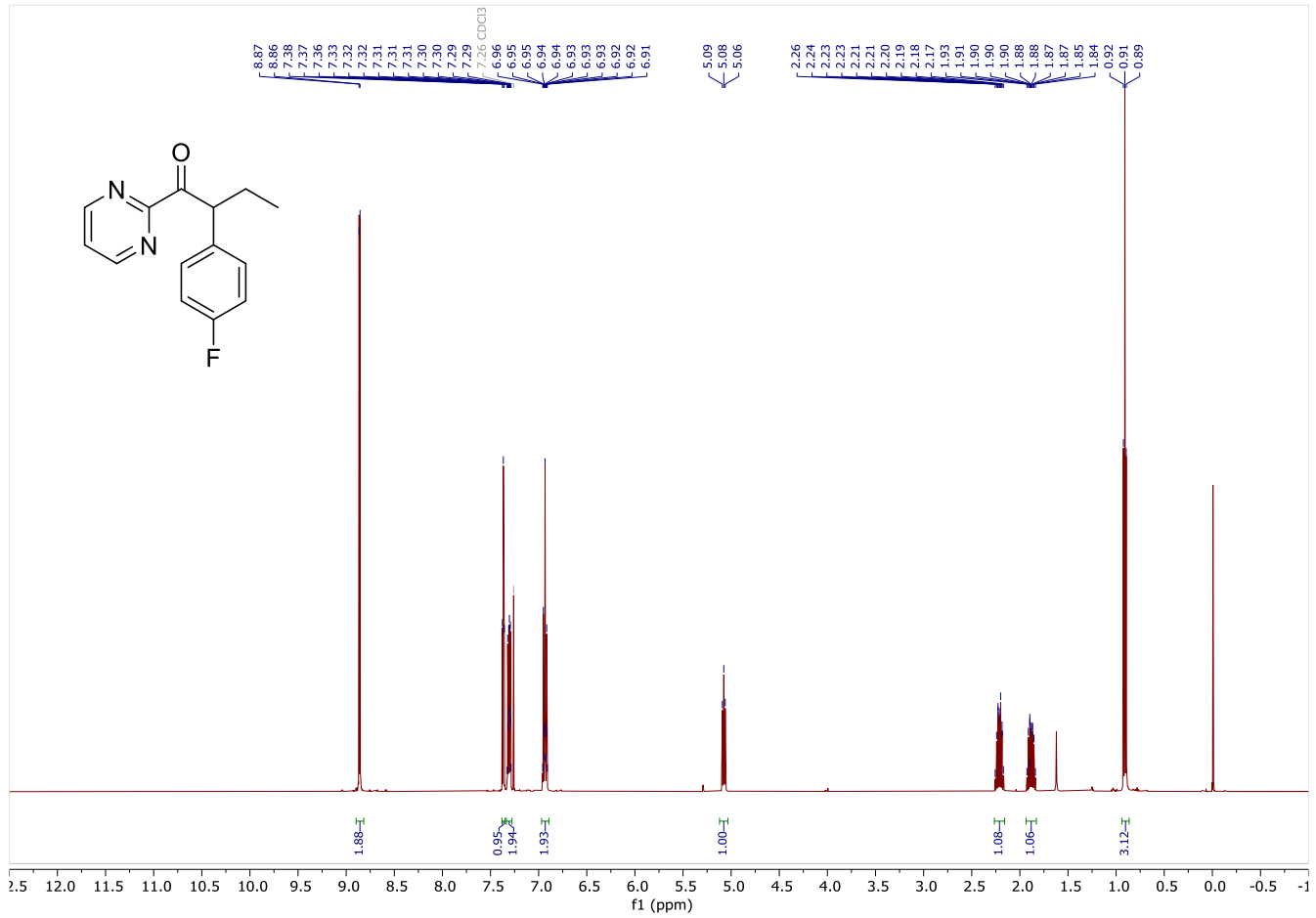


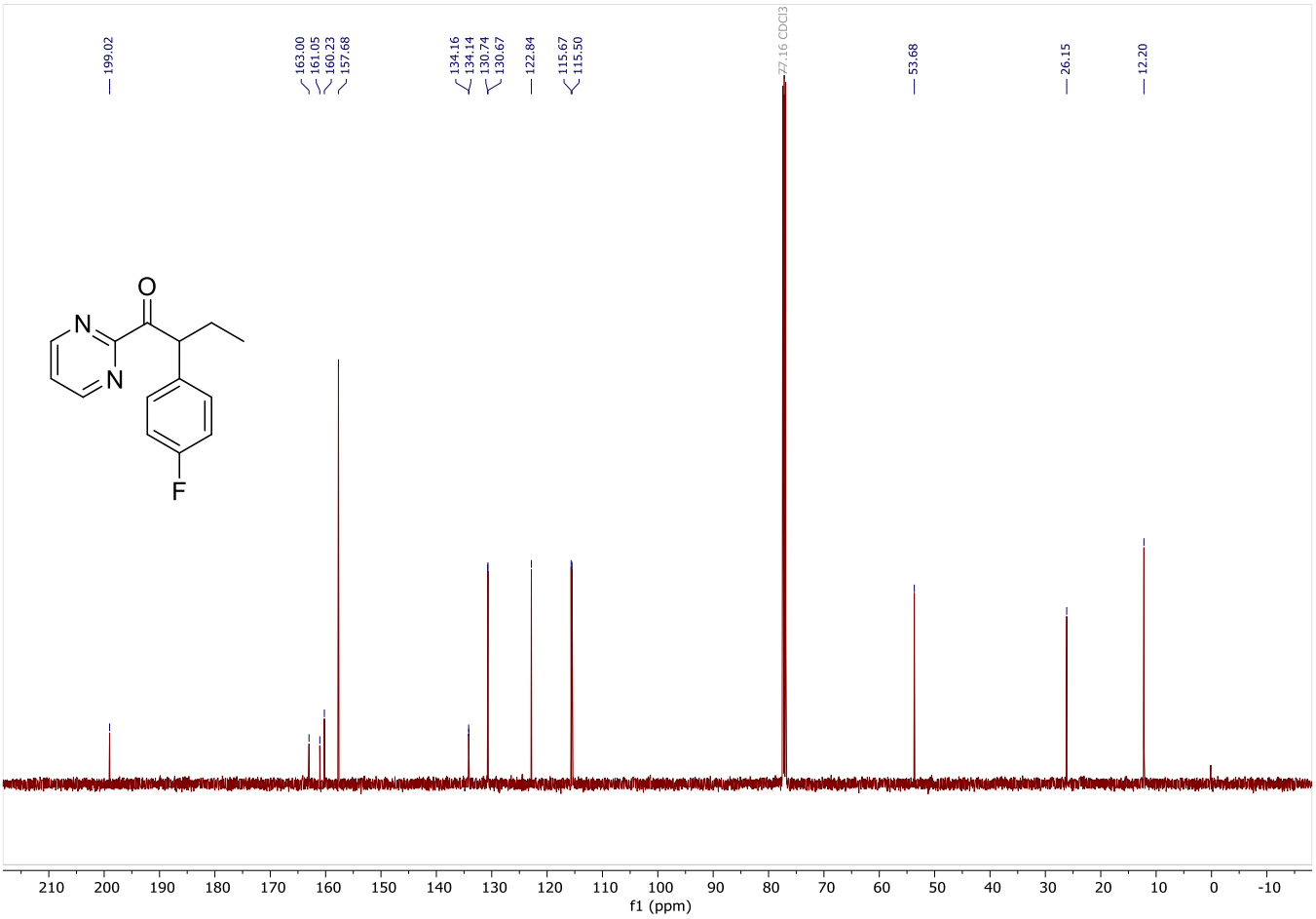


tert-butyl (3-(4-fluorophenyl)-4-oxo-4-(pyridin-2-yl)butyl)carbamate (3y)

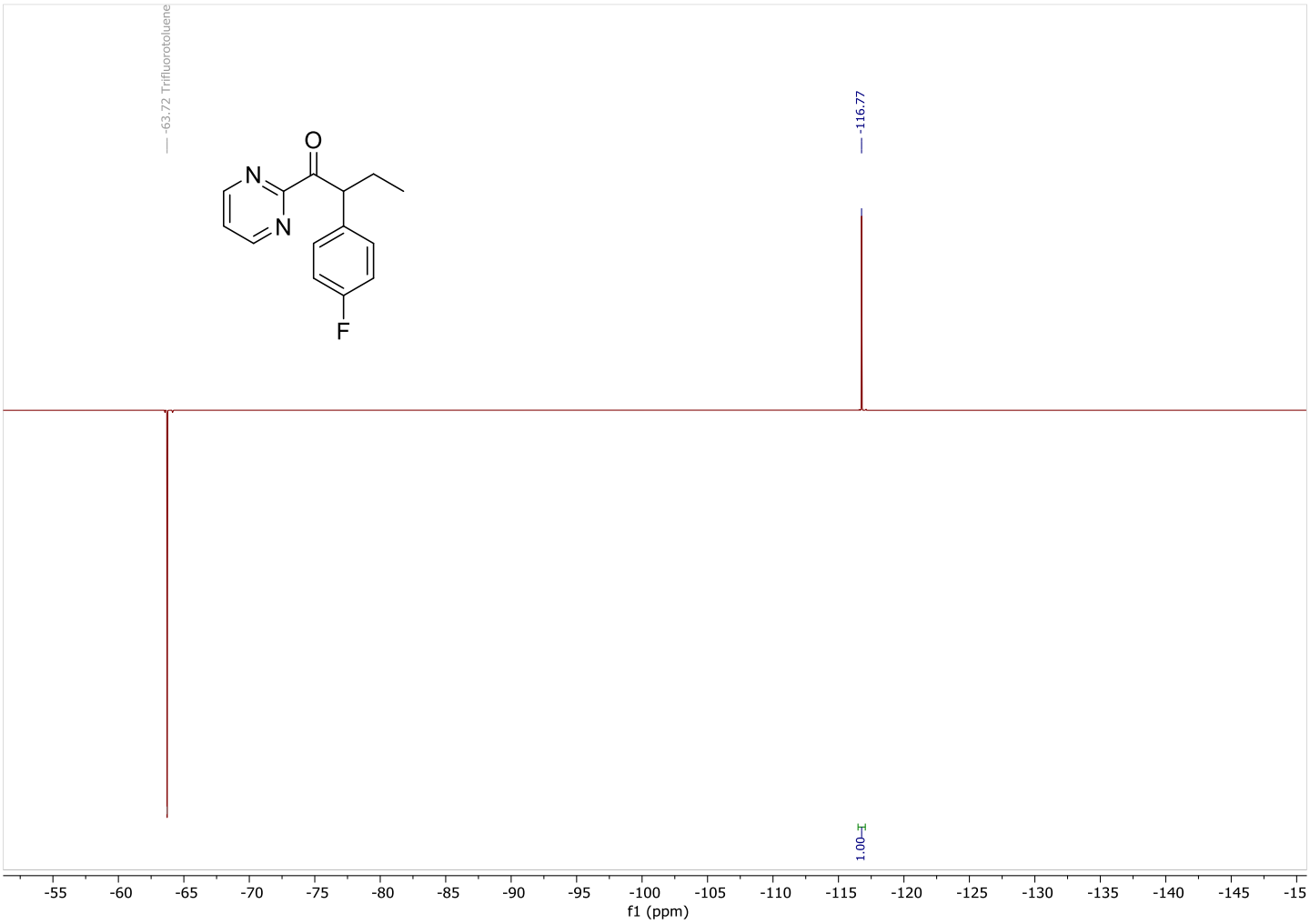


2-(4-fluorophenyl)-1-(pyrimidin-2-yl)butan-1-one (3z)

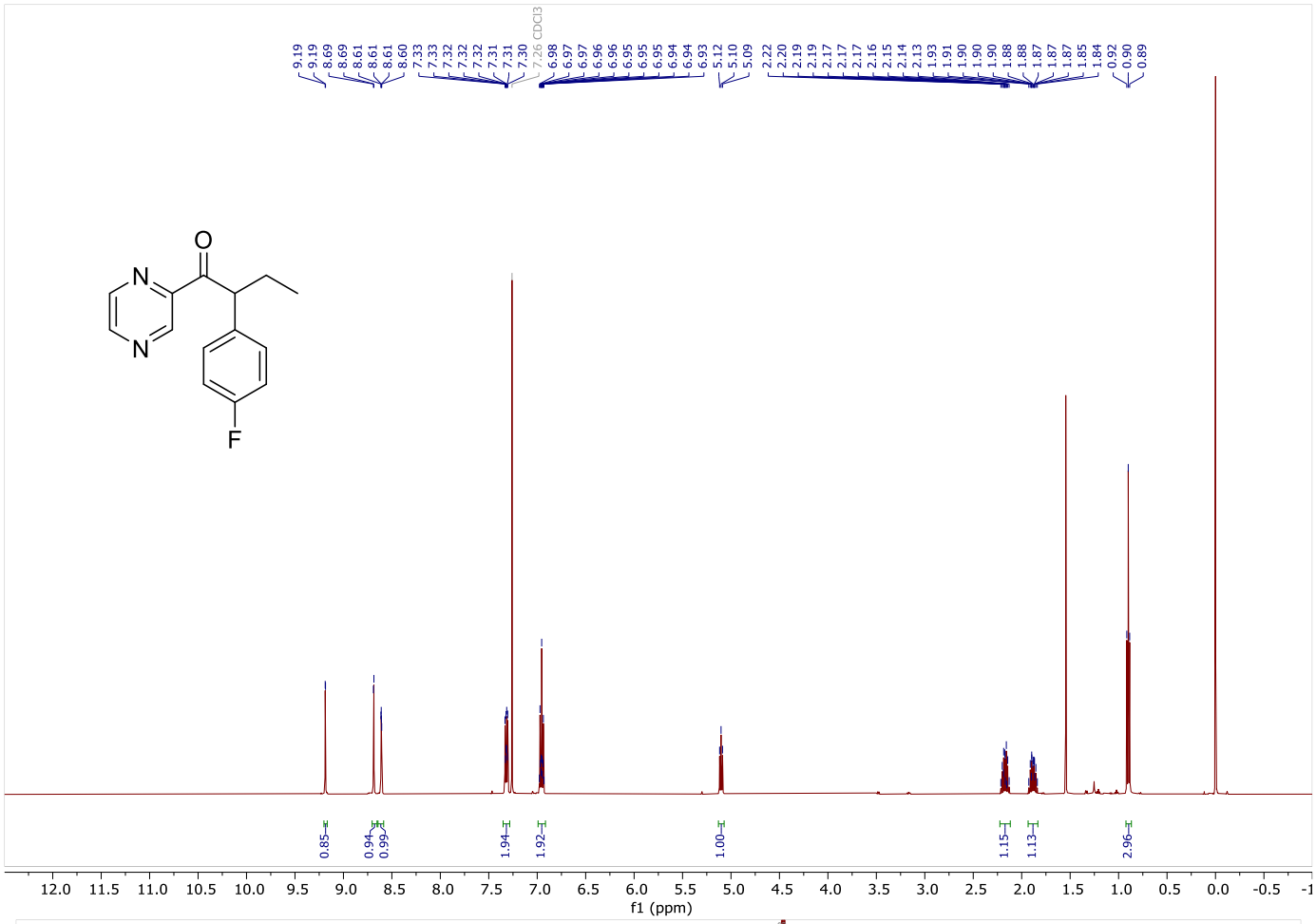


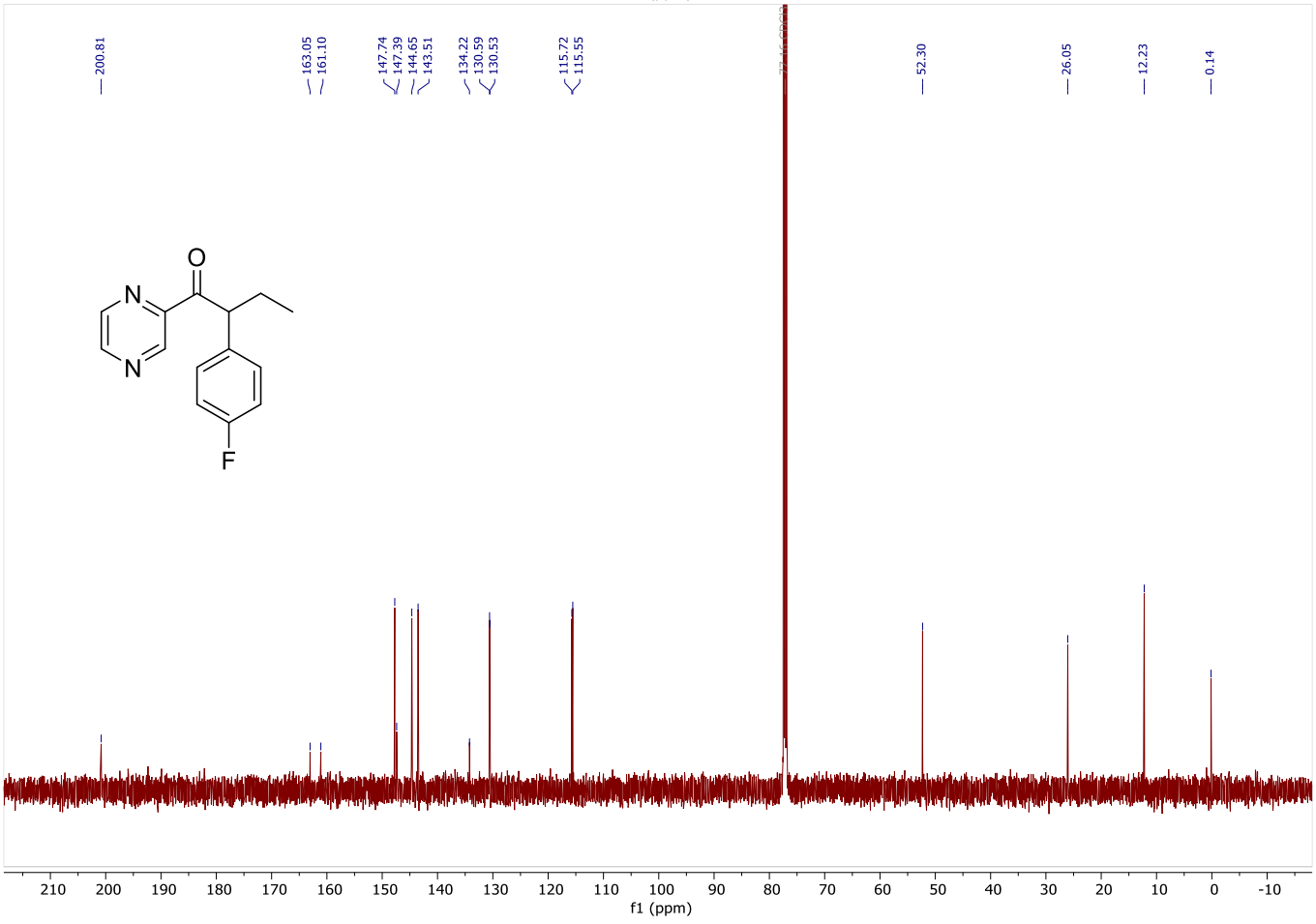


2-(4-fluorophenyl)-1-(pyrimidin-2-yl)butan-1-one (3z)

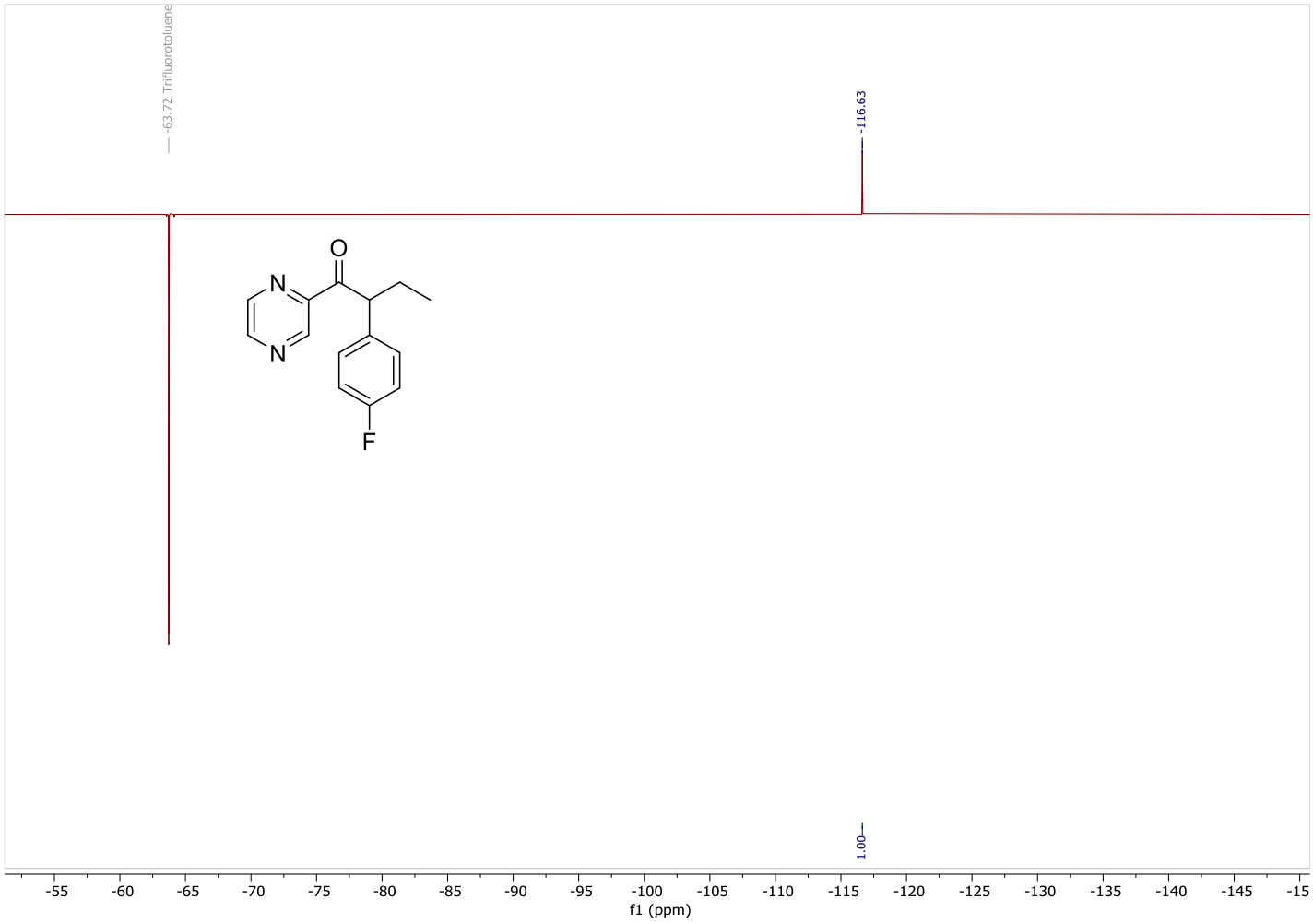

-63.72 Trifluorotoluene
-116.77
O
N
N
F
1.00
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-15
f1 (ppm)

2-(4-fluorophenyl)-1-(pyrazin-2-yl)butan-1-one (3aa)

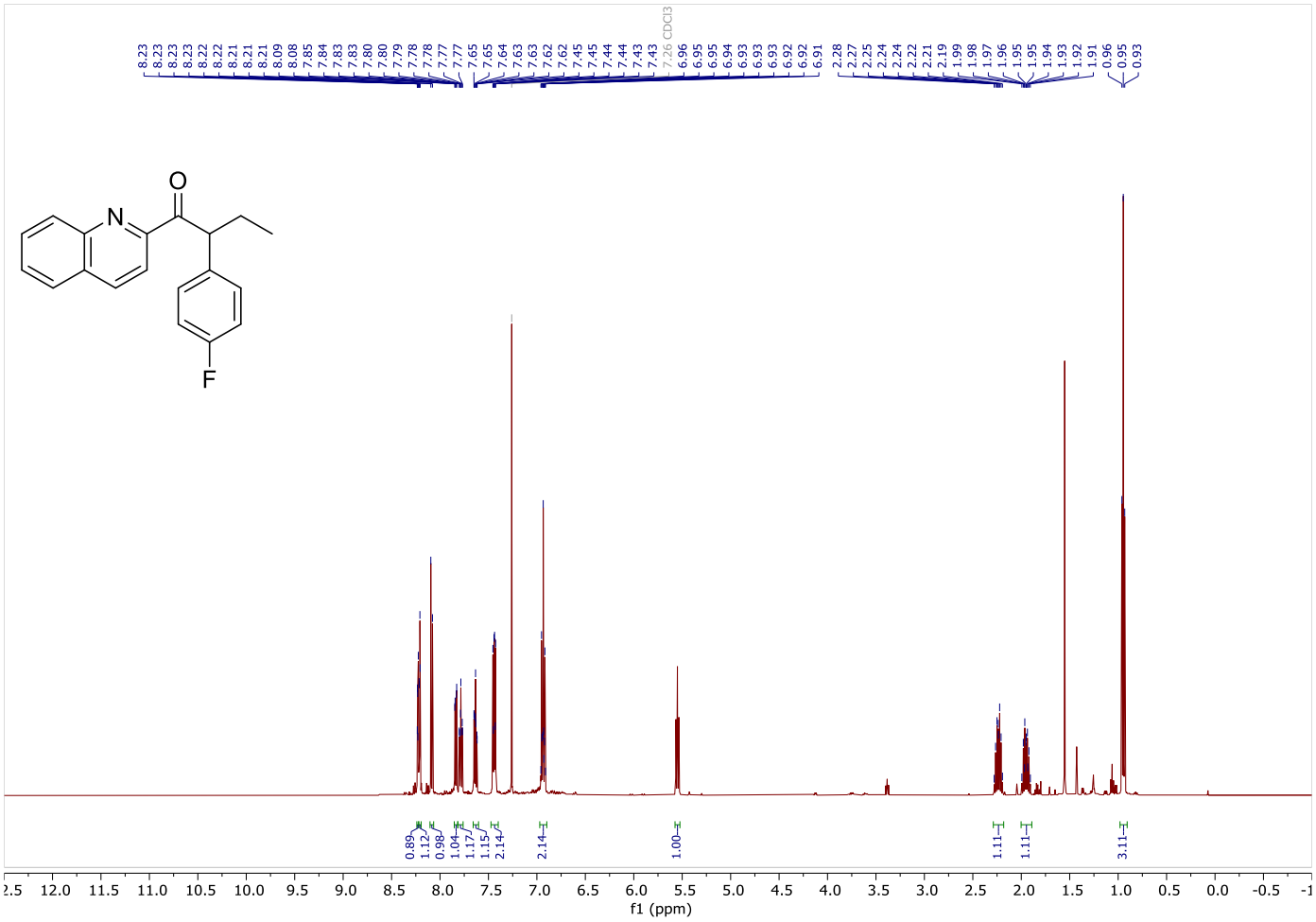


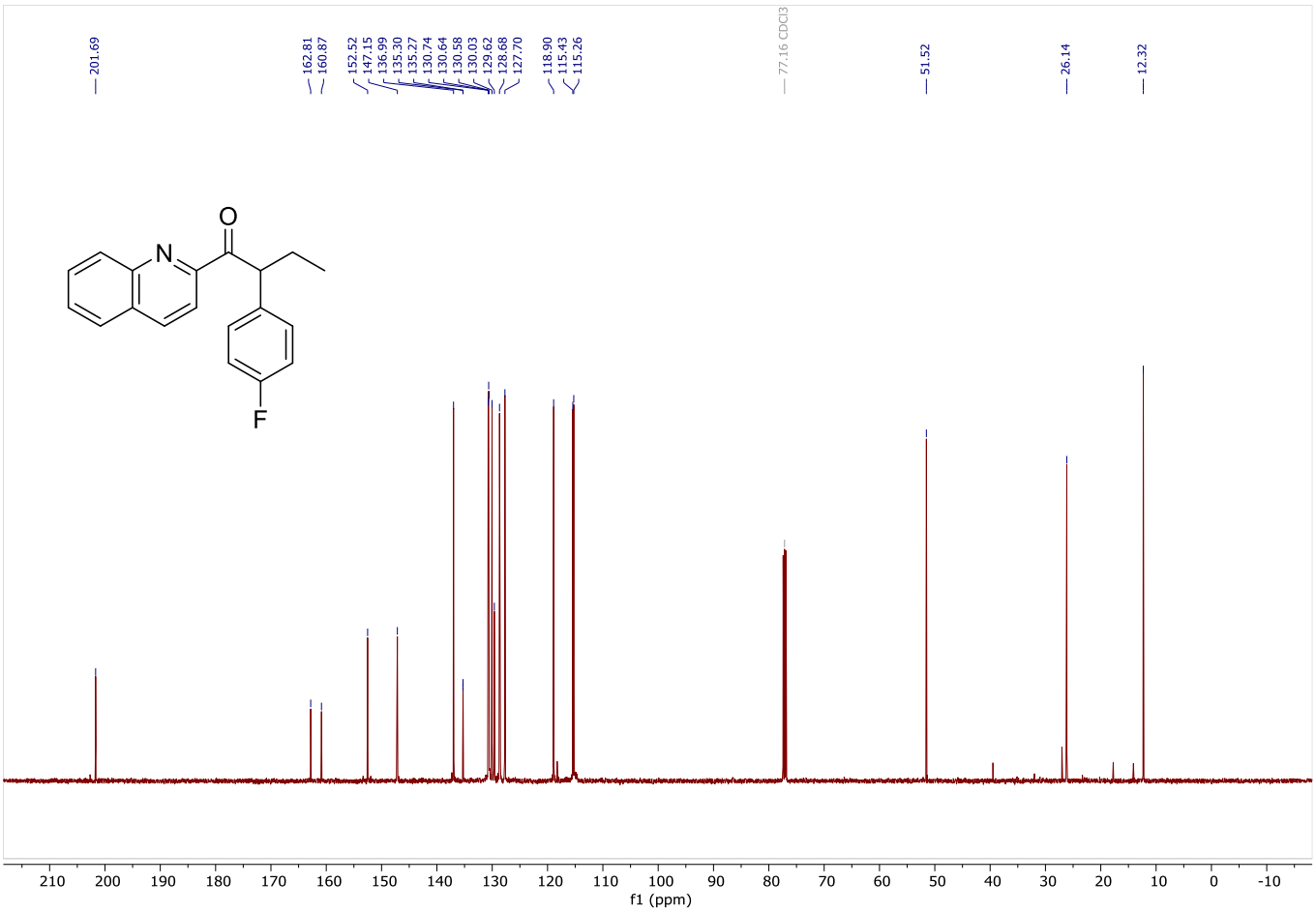


2-(4-fluorophenyl)-1-(pyrazin-2-yl)butan-1-one (3aa)

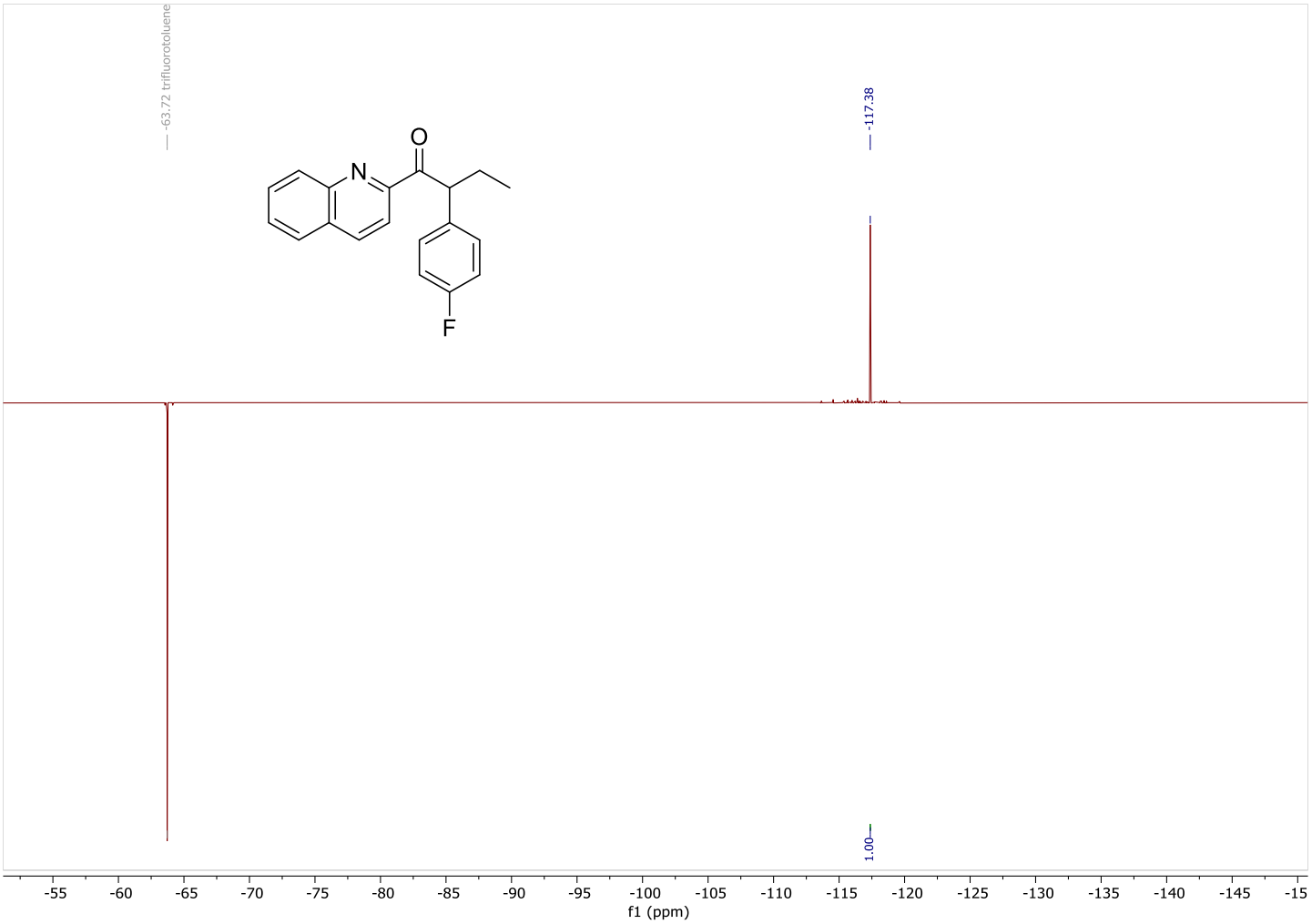


2-(4-fluorophenyl)-1-(quinolin-2-yl)butan-1-one (3ab)

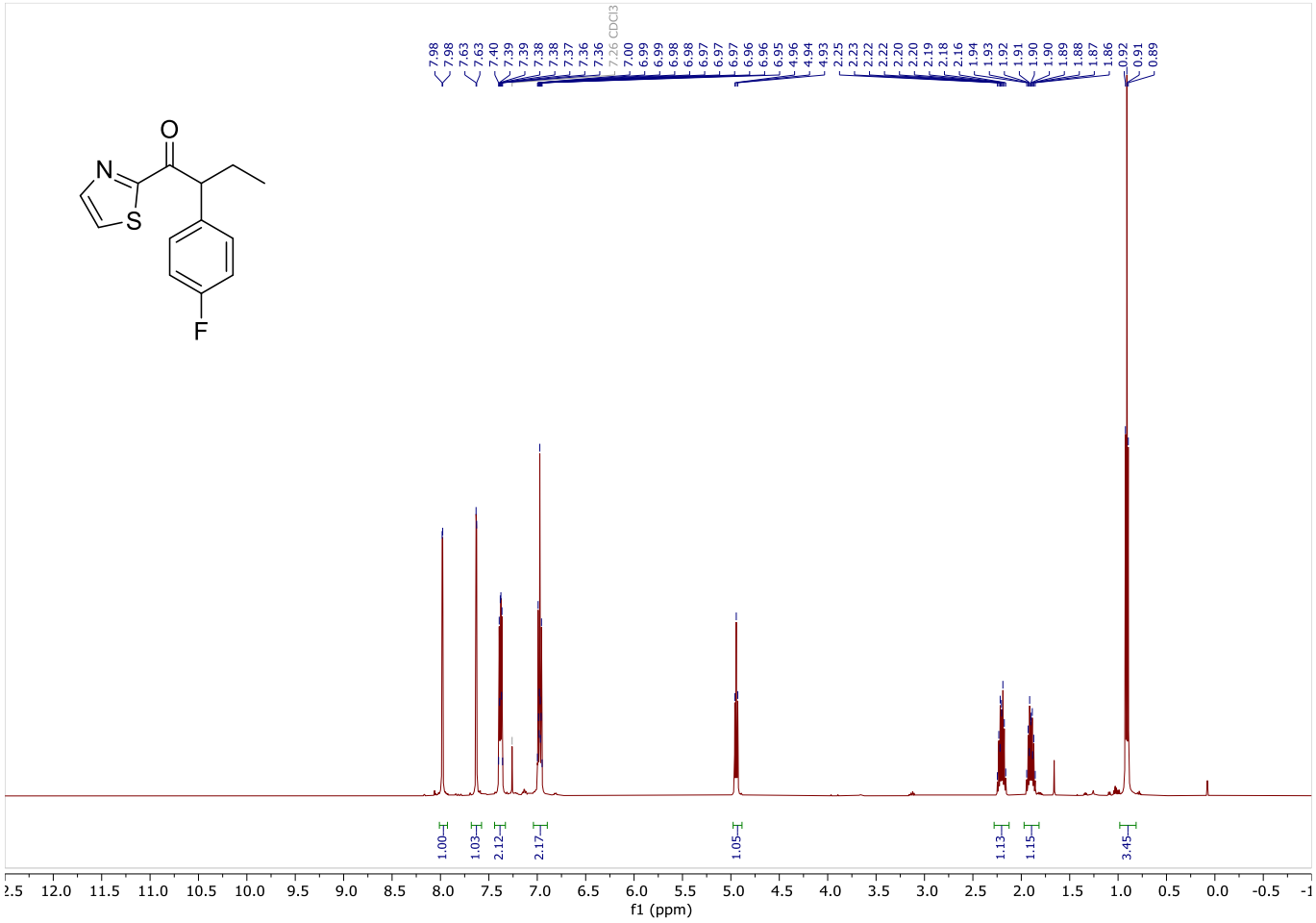


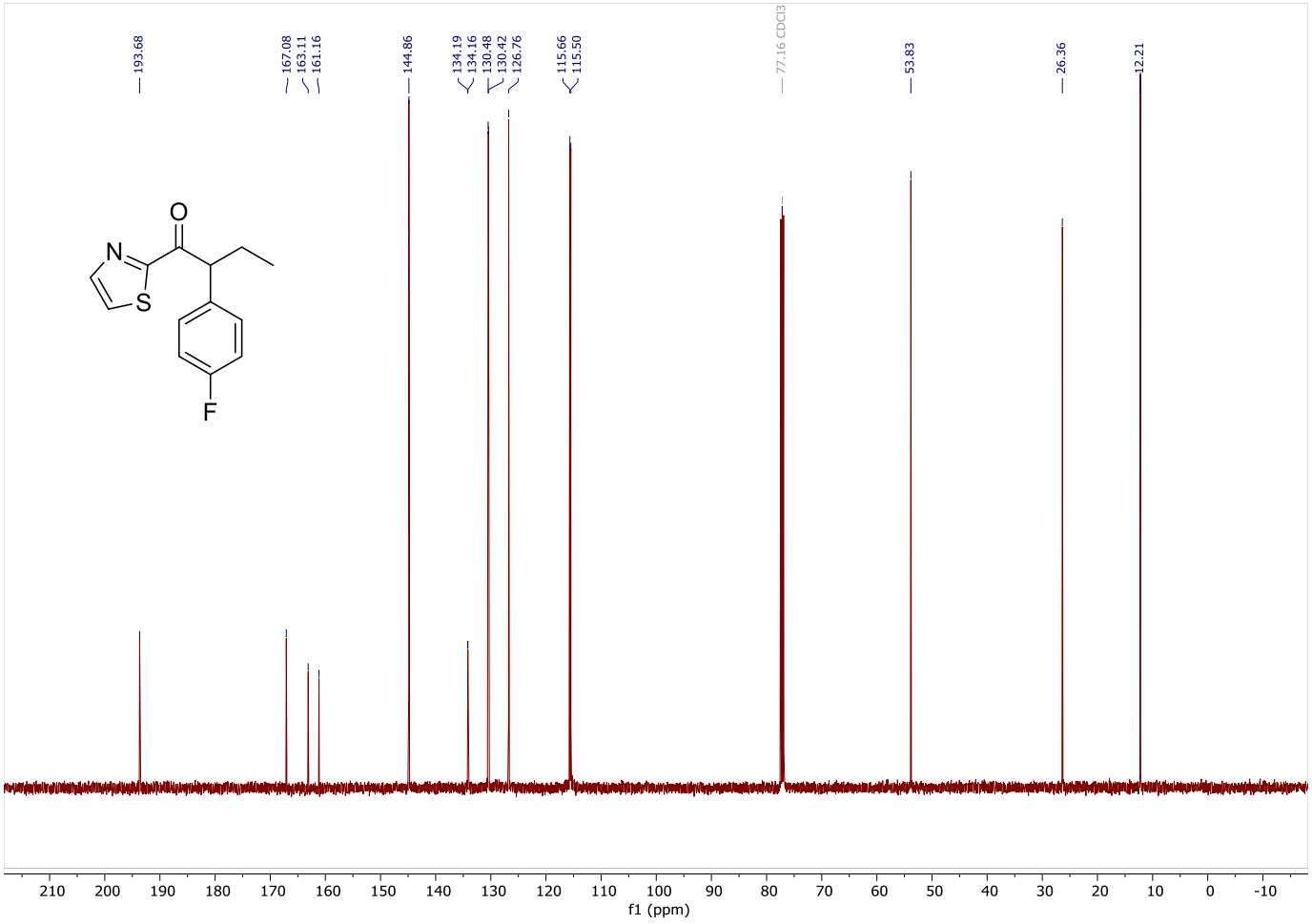


2-(4-fluorophenyl)-1-(quinolin-2-yl)butan-1-one (3ab)

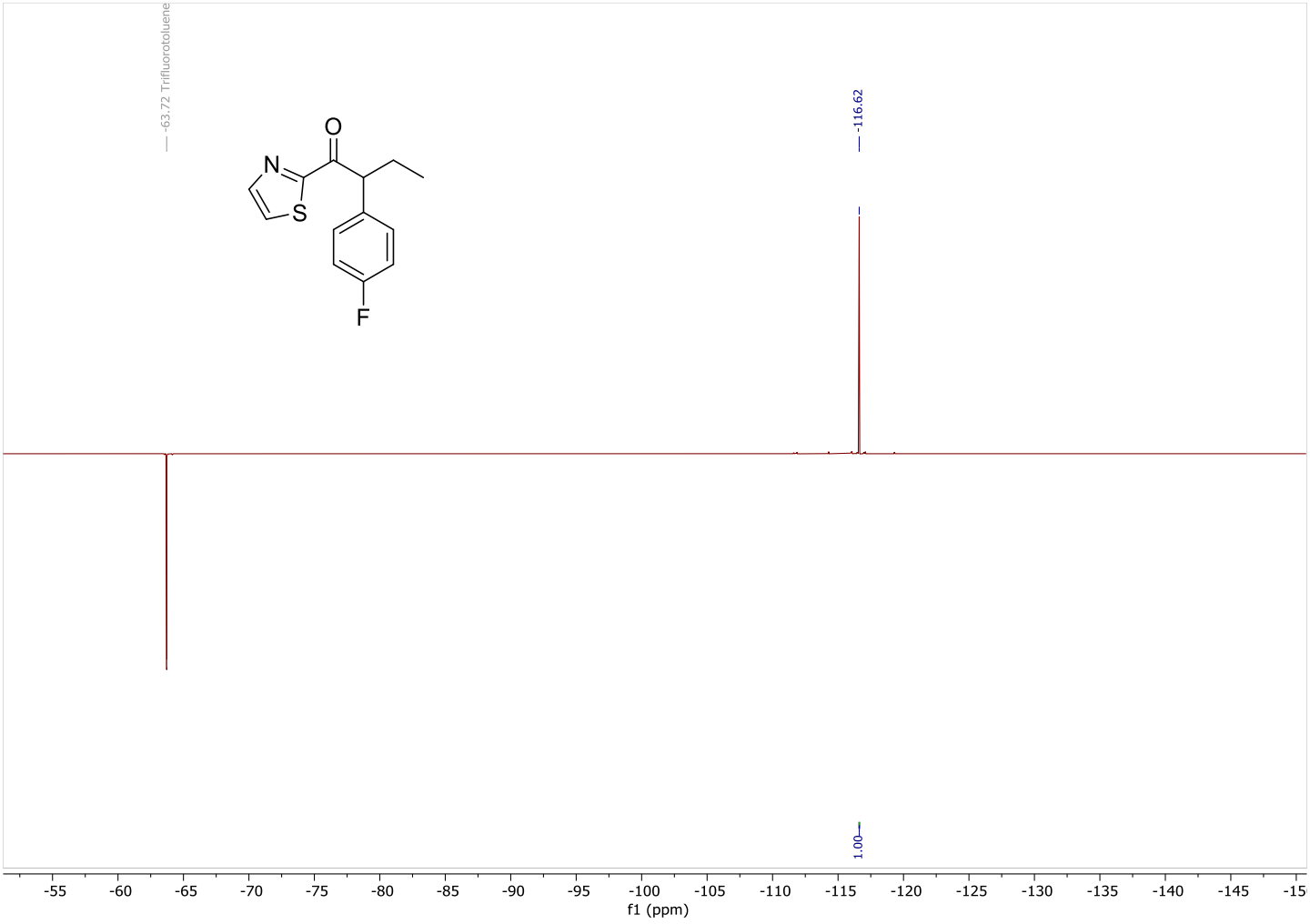


2-(4-fluorophenyl)-1-(thiazol-2-yl)butan-1-one (3ac)

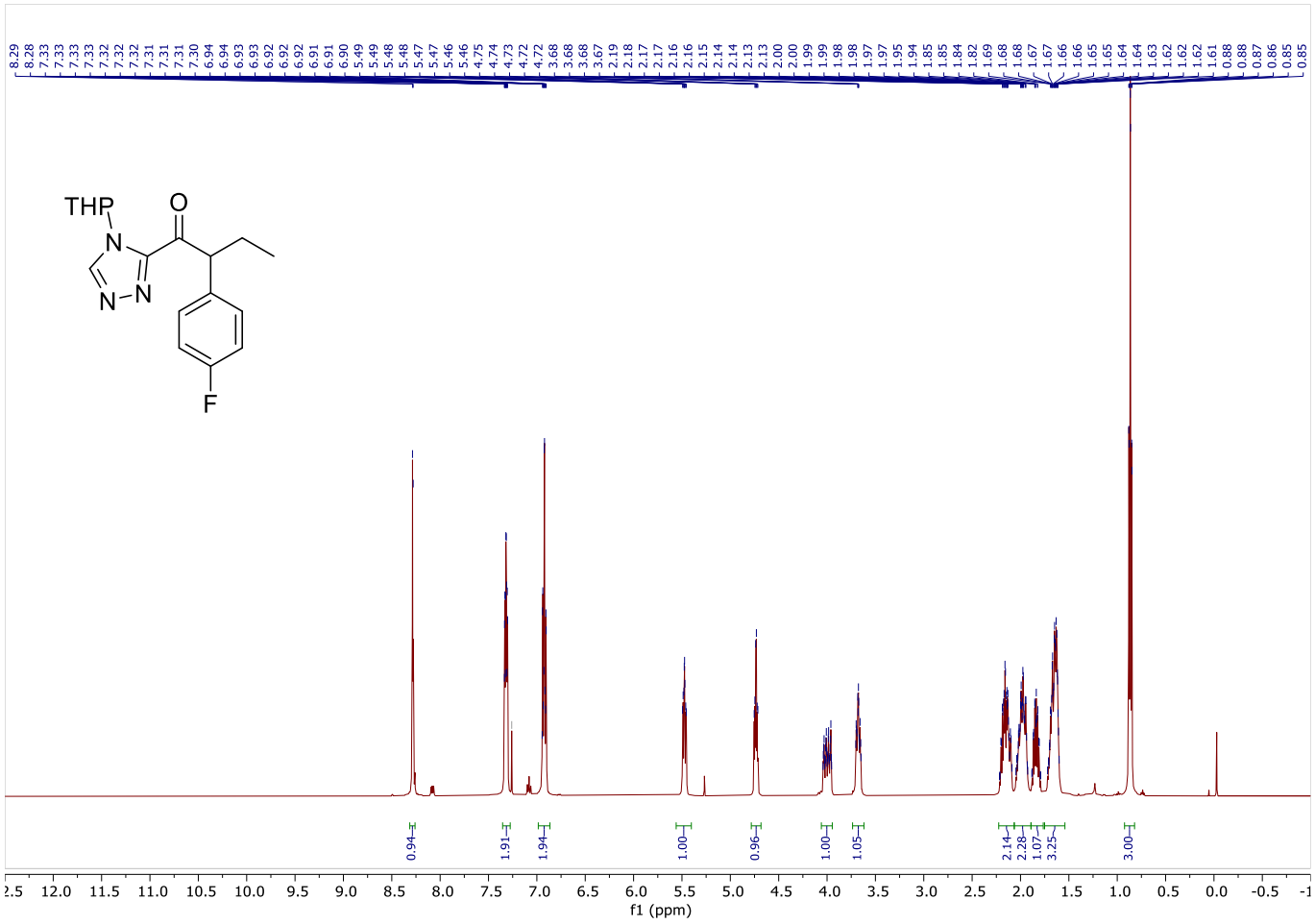


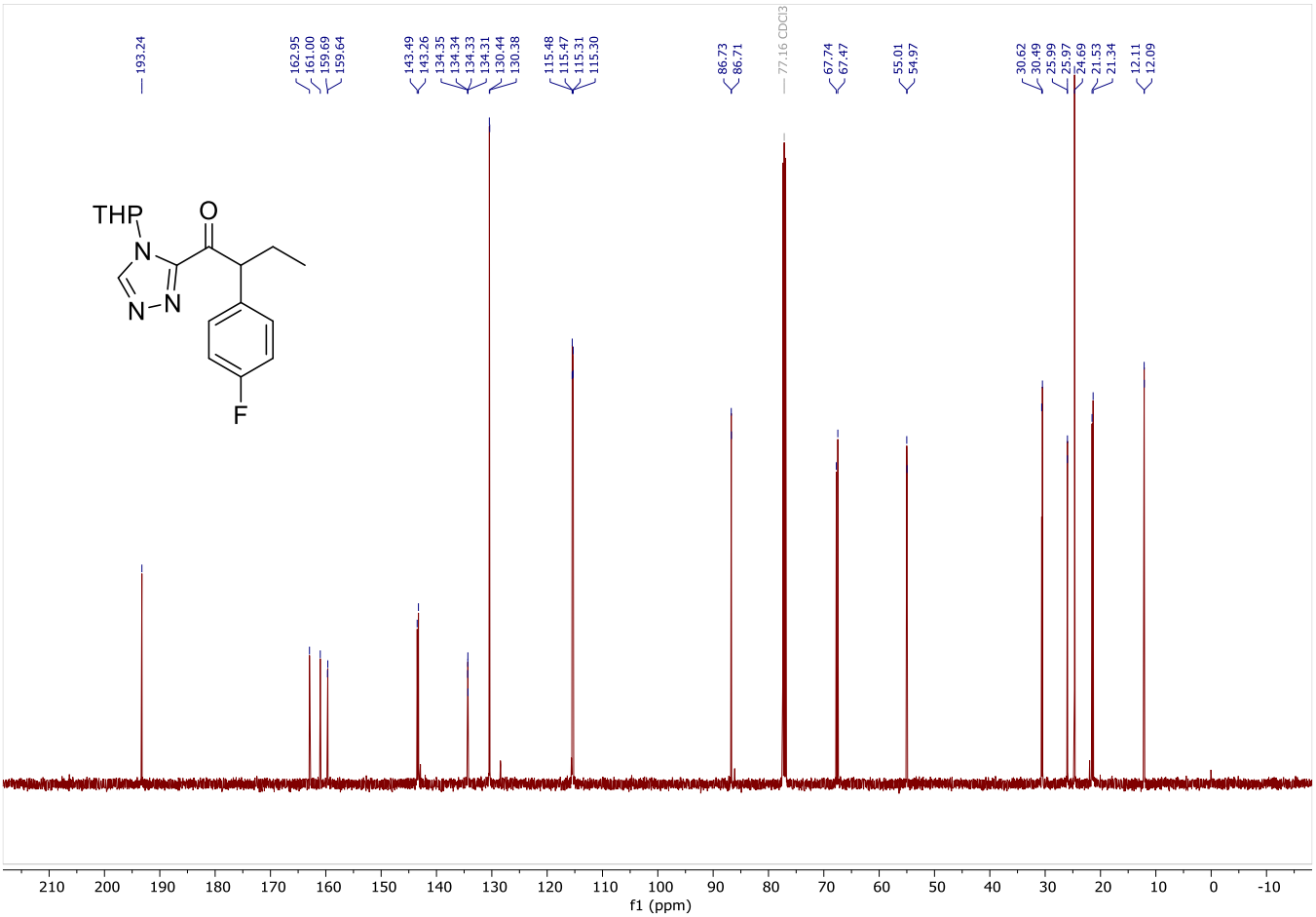


2-(4-fluorophenyl)-1-(thiazol-2-yl)butan-1-one (3ac)

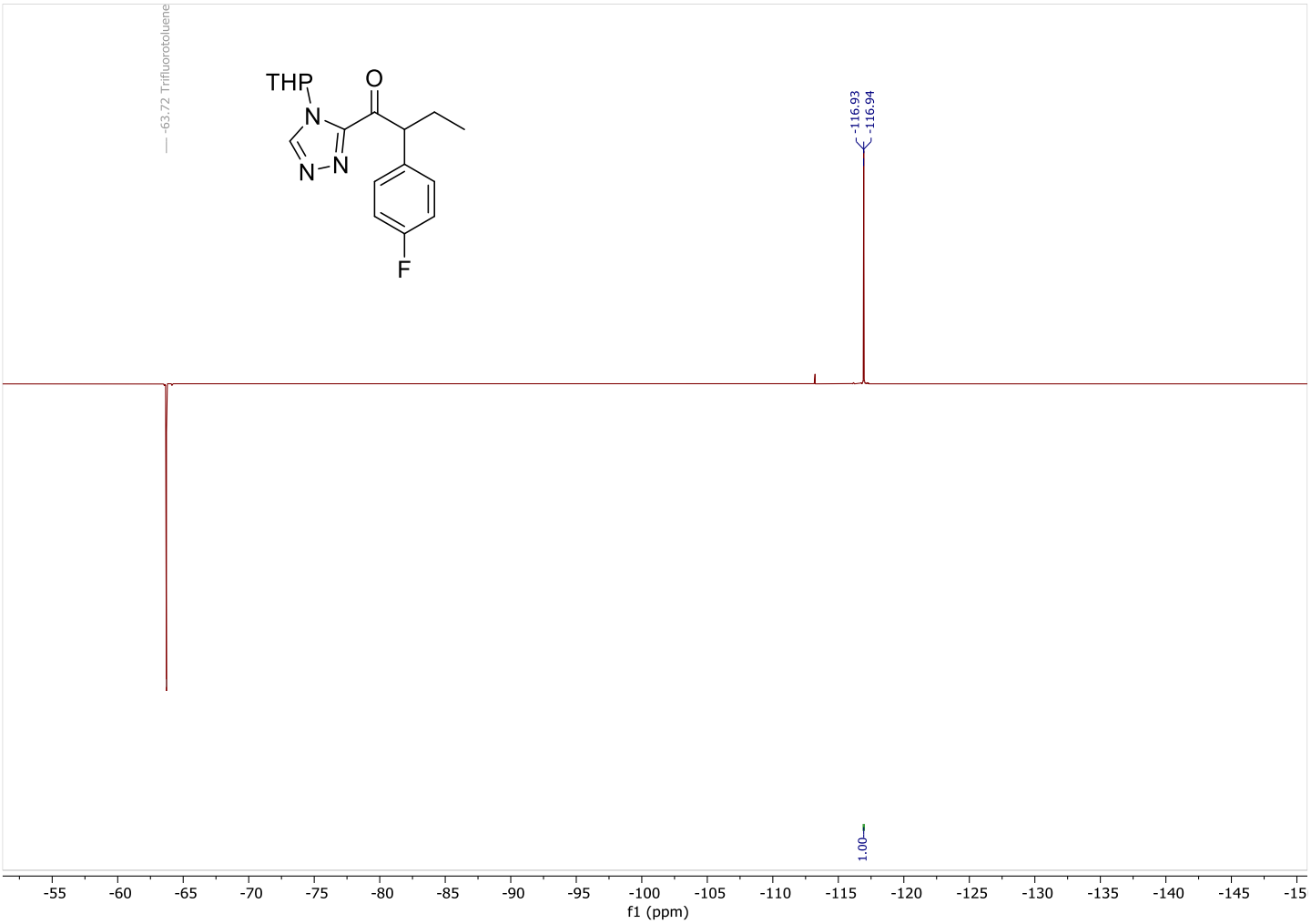


2-(4-fluorophenyl)-1-(4-(tetrahydro-2H-pyran-2-yl)-4H-1,2,4-triazol-3-yl)butan-1-one (3ad)

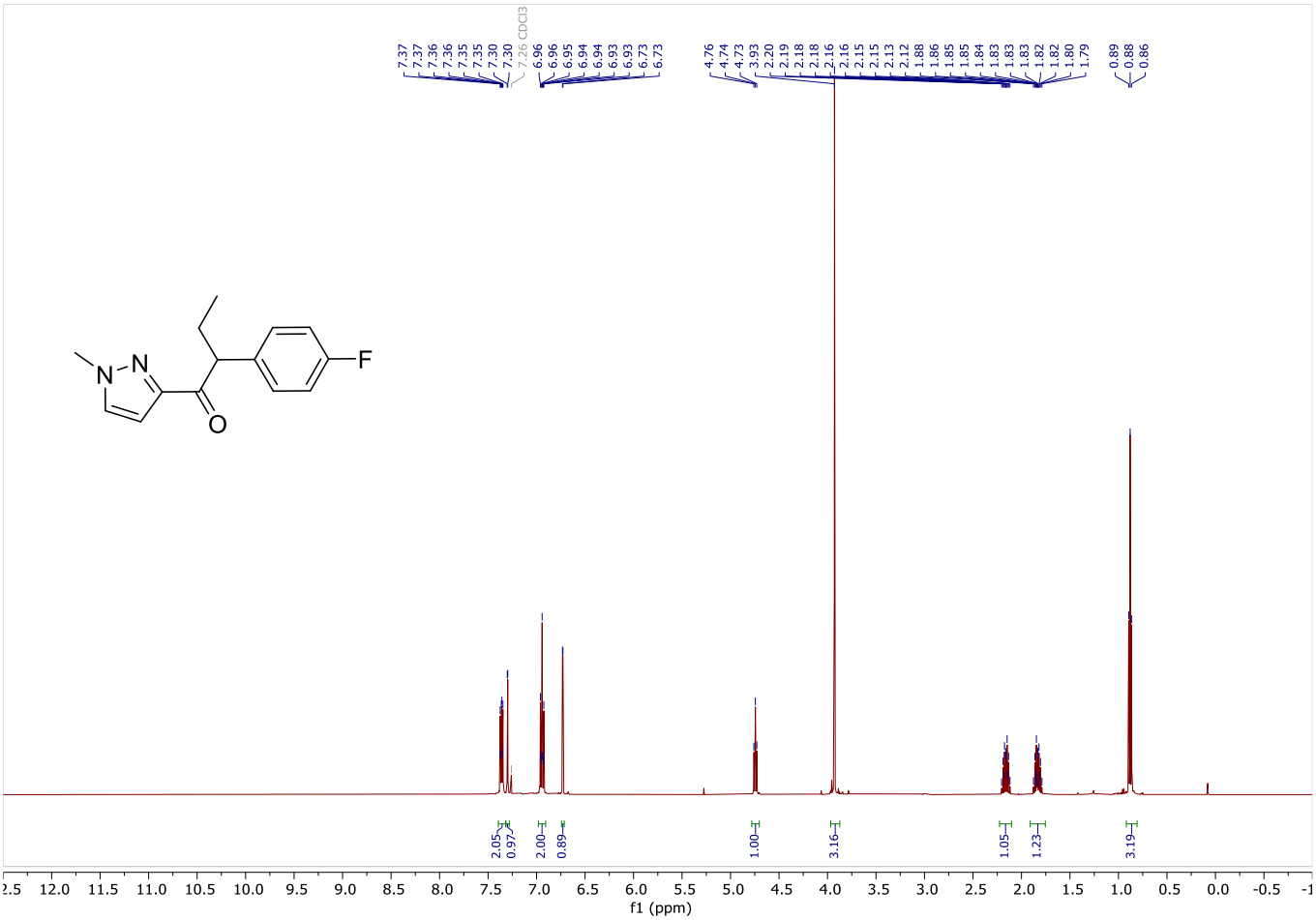


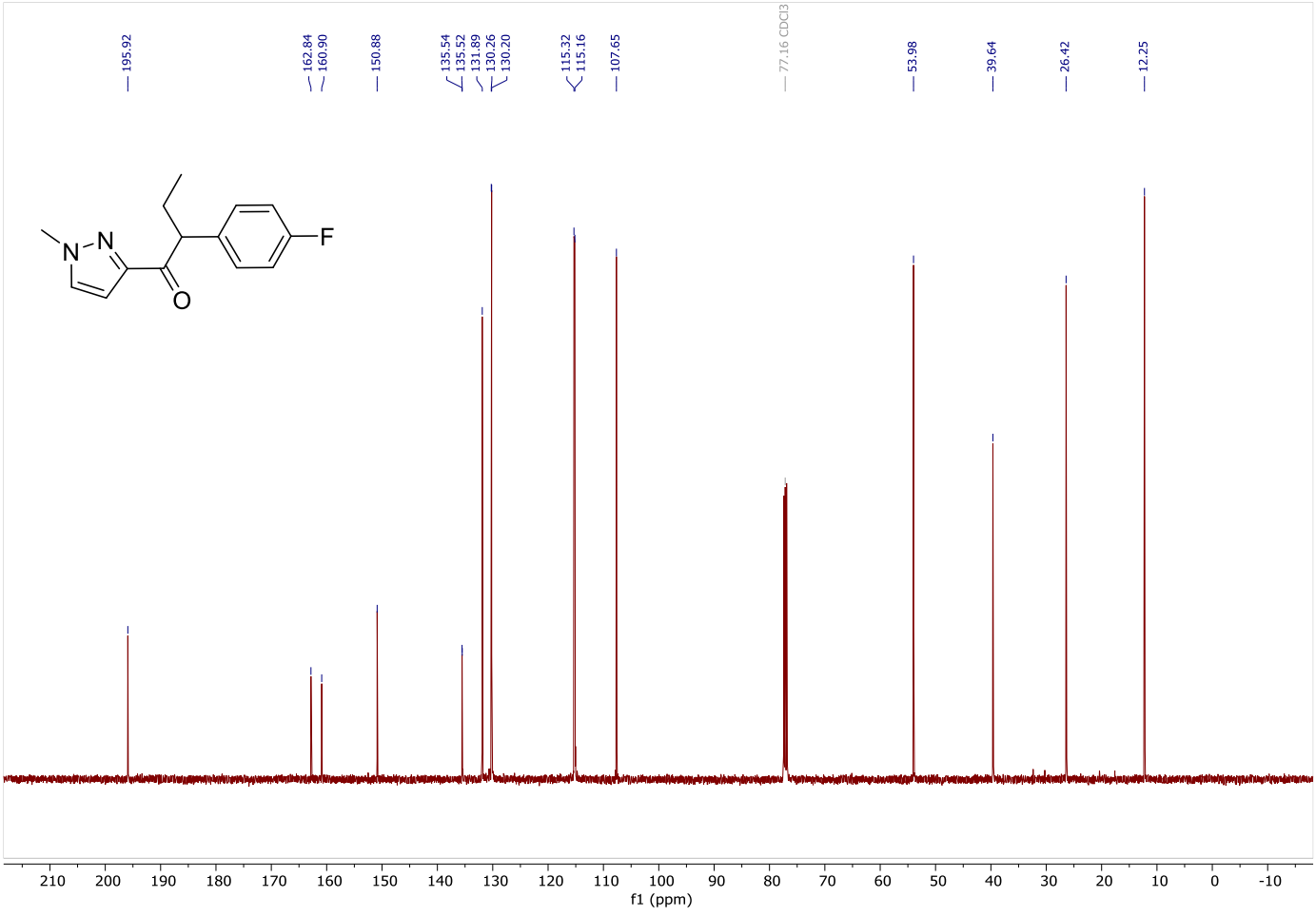


2-(4-fluorophenyl)-1-(4-(tetrahydro-2H-pyran-2-yl)-4H-1,2,4-triazol-3-yl)butan-1-one (3ad)

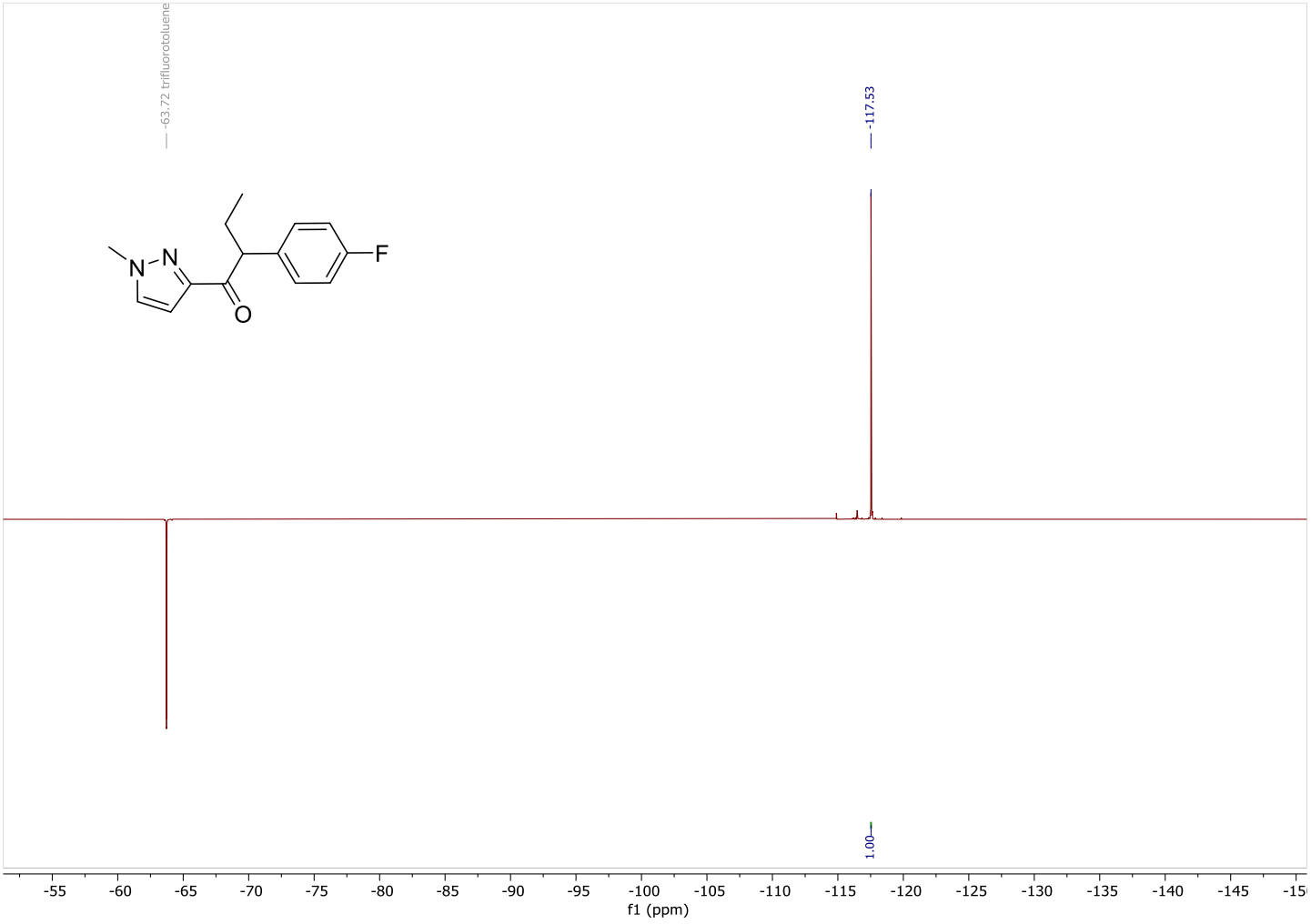


2-(4-fluorophenyl)-1-(1-methyl-1H-pyrazol-3-yl)butan-1-one (3ae)



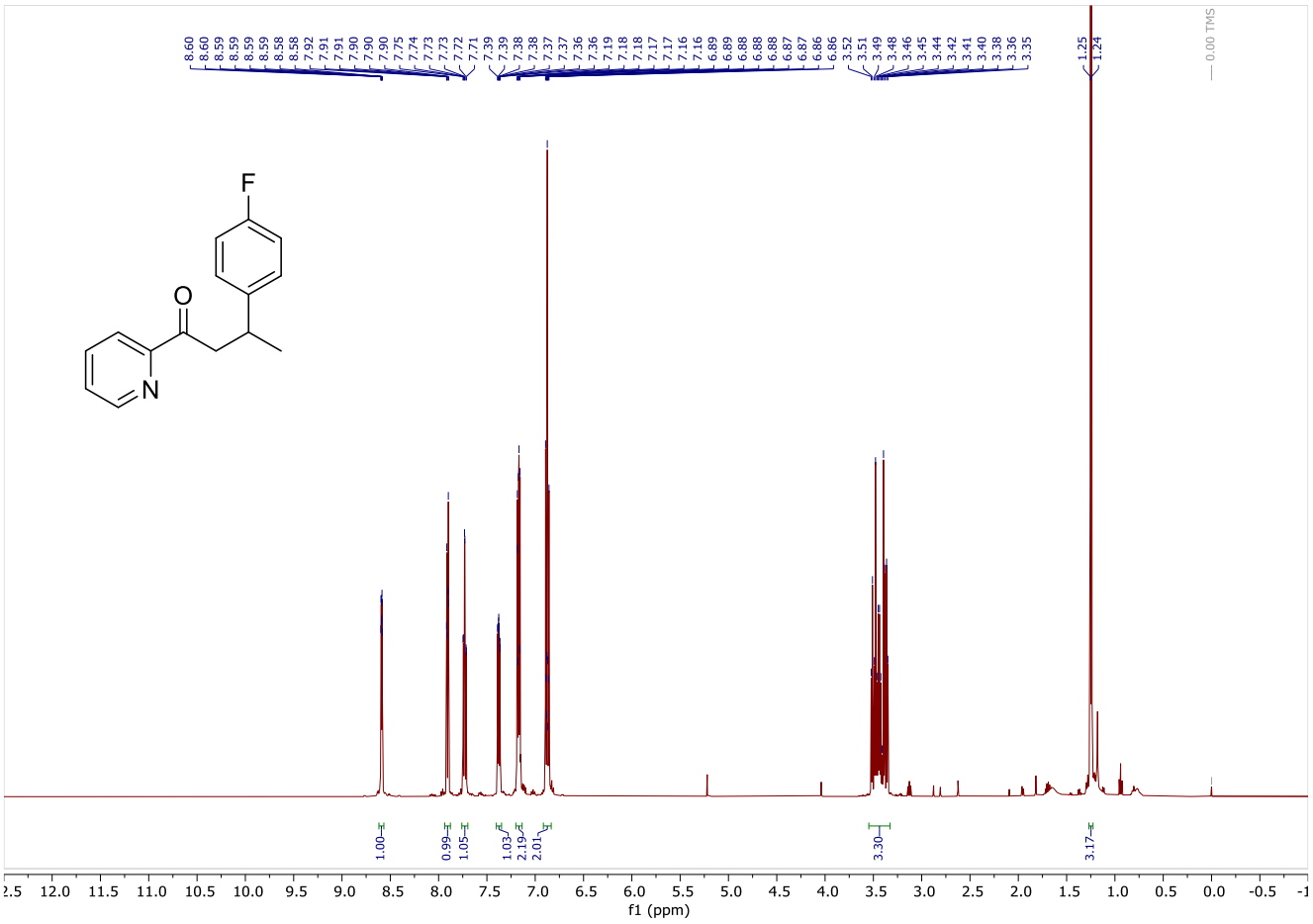


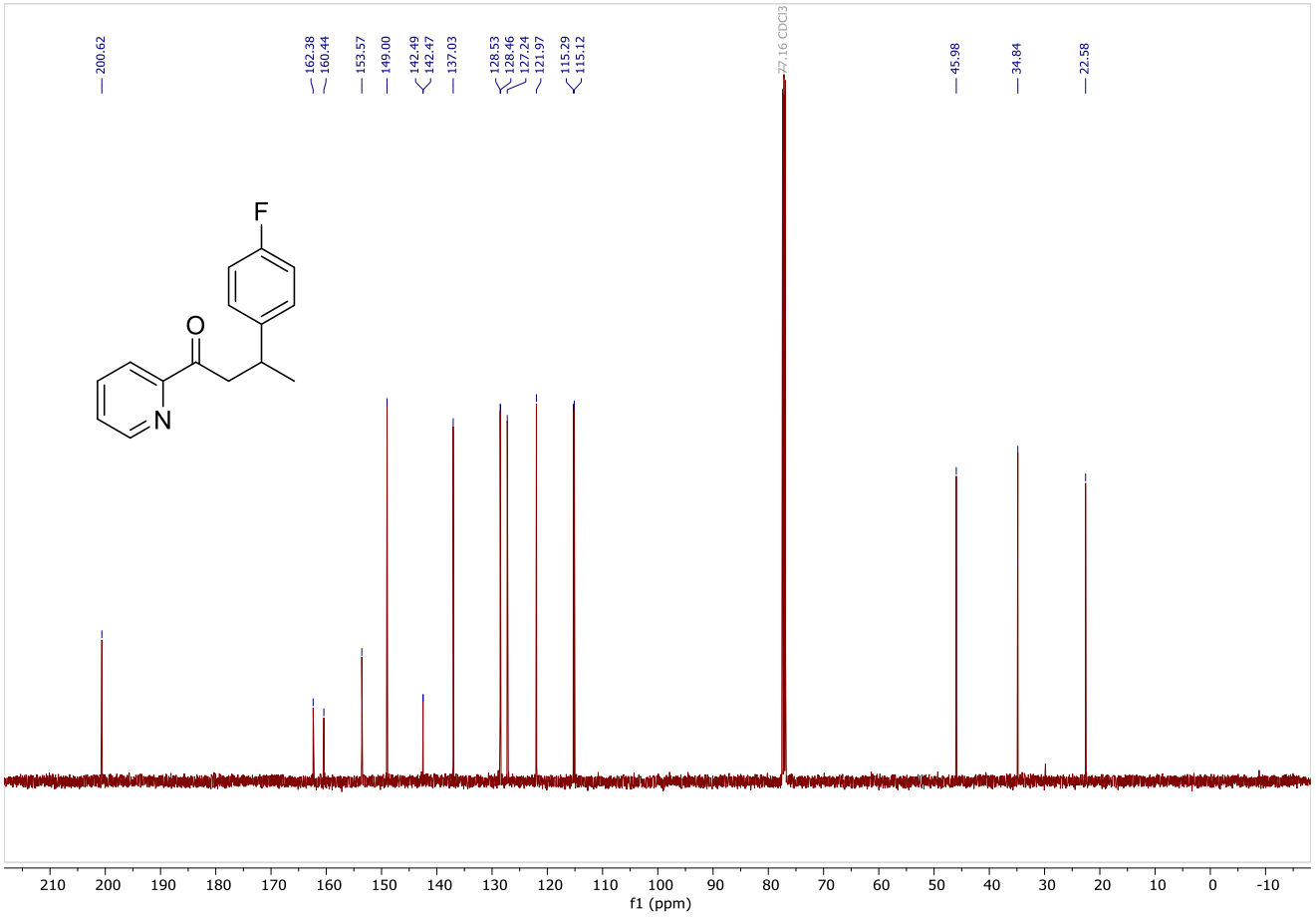
2-(4-fluorophenyl)-1-(1-methyl-1H-pyrazol-3-yl)butan-1-one (3ae)



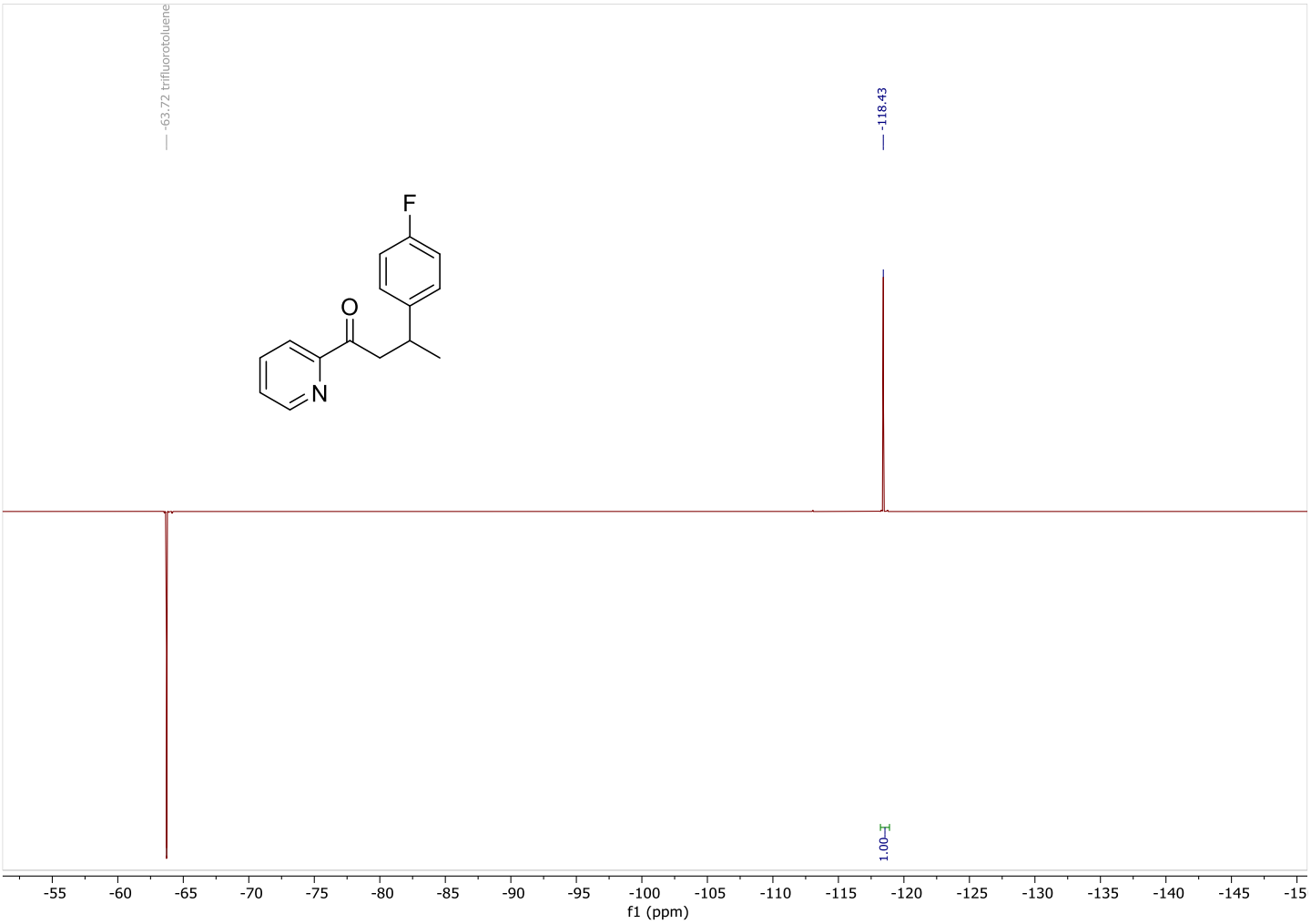
NMR spectra – products of β-functionalization

3-(4-fluorophenyl)-1-(pyridin-2-yl)butan-1-one (4a)

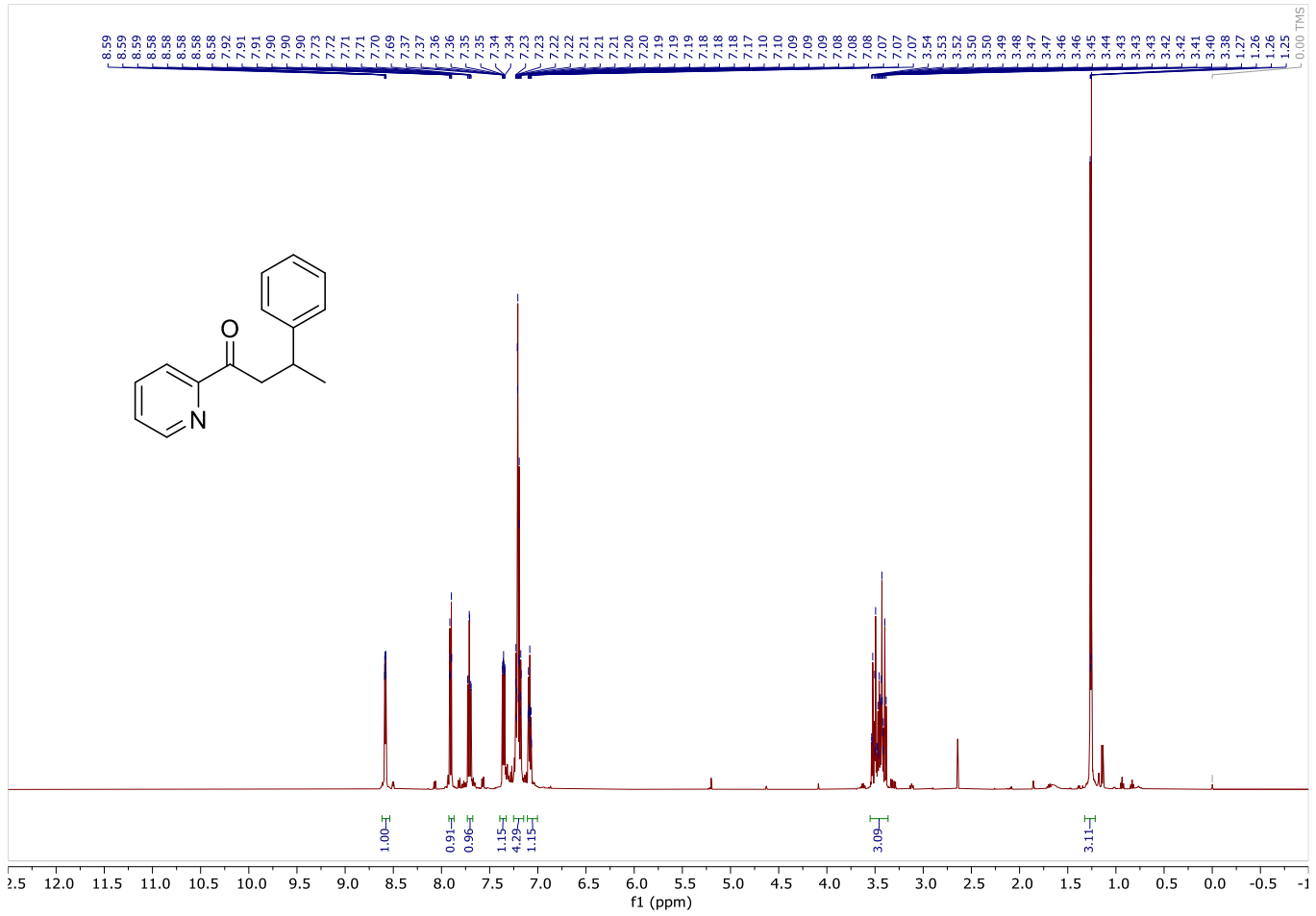


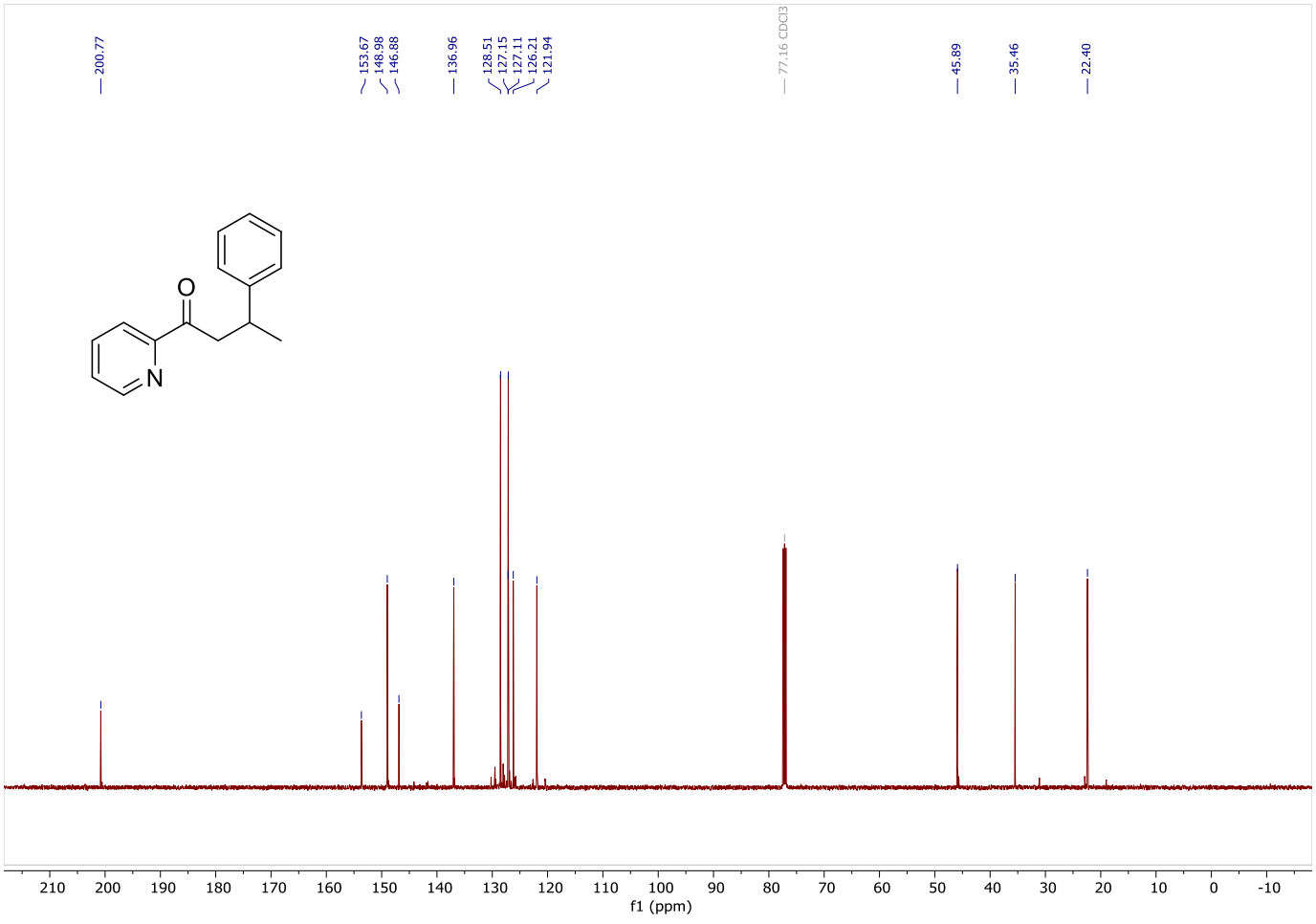


3-(4-fluorophenyl)-1-(pyridin-2-yl)butan-1-one (4a)

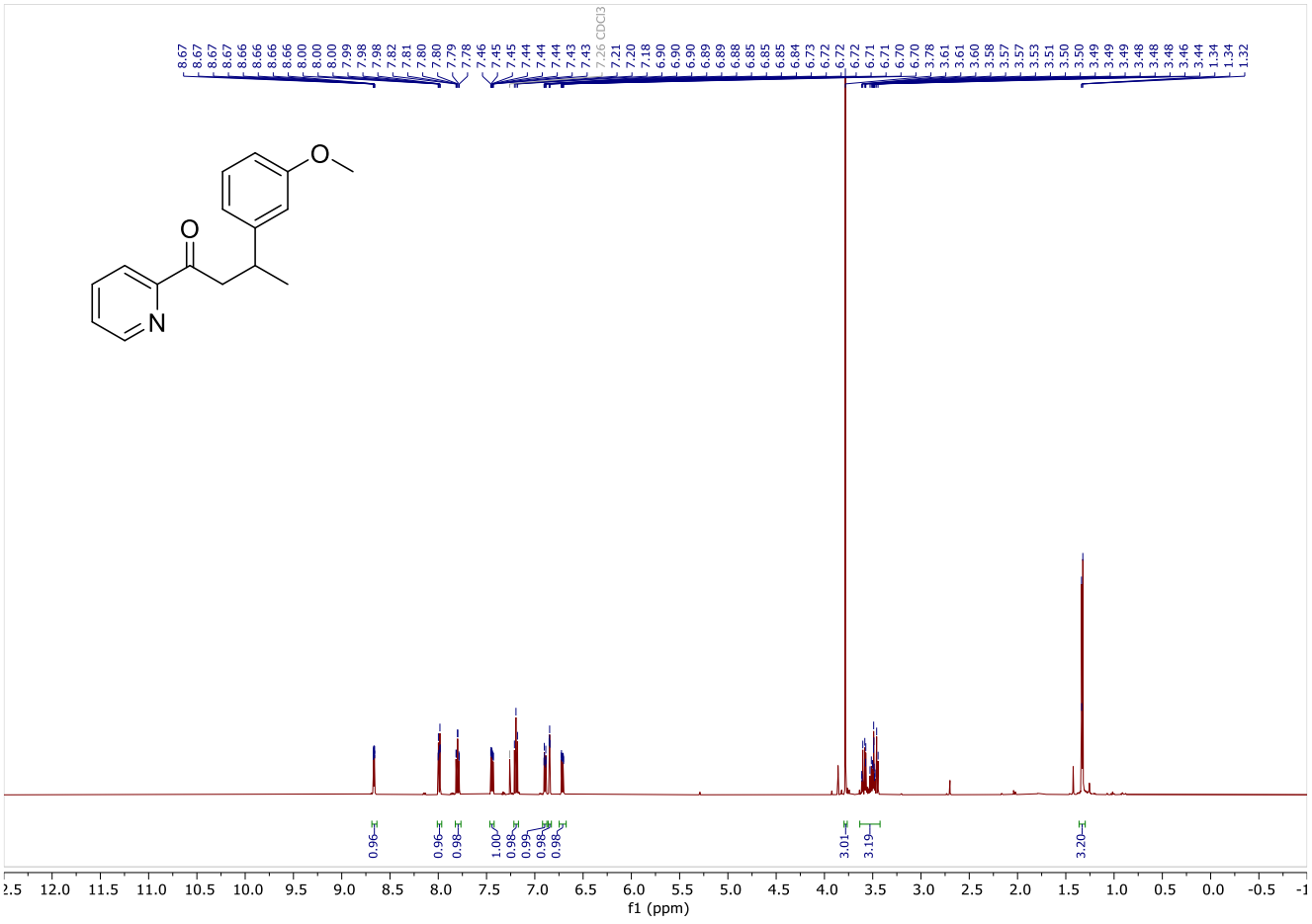


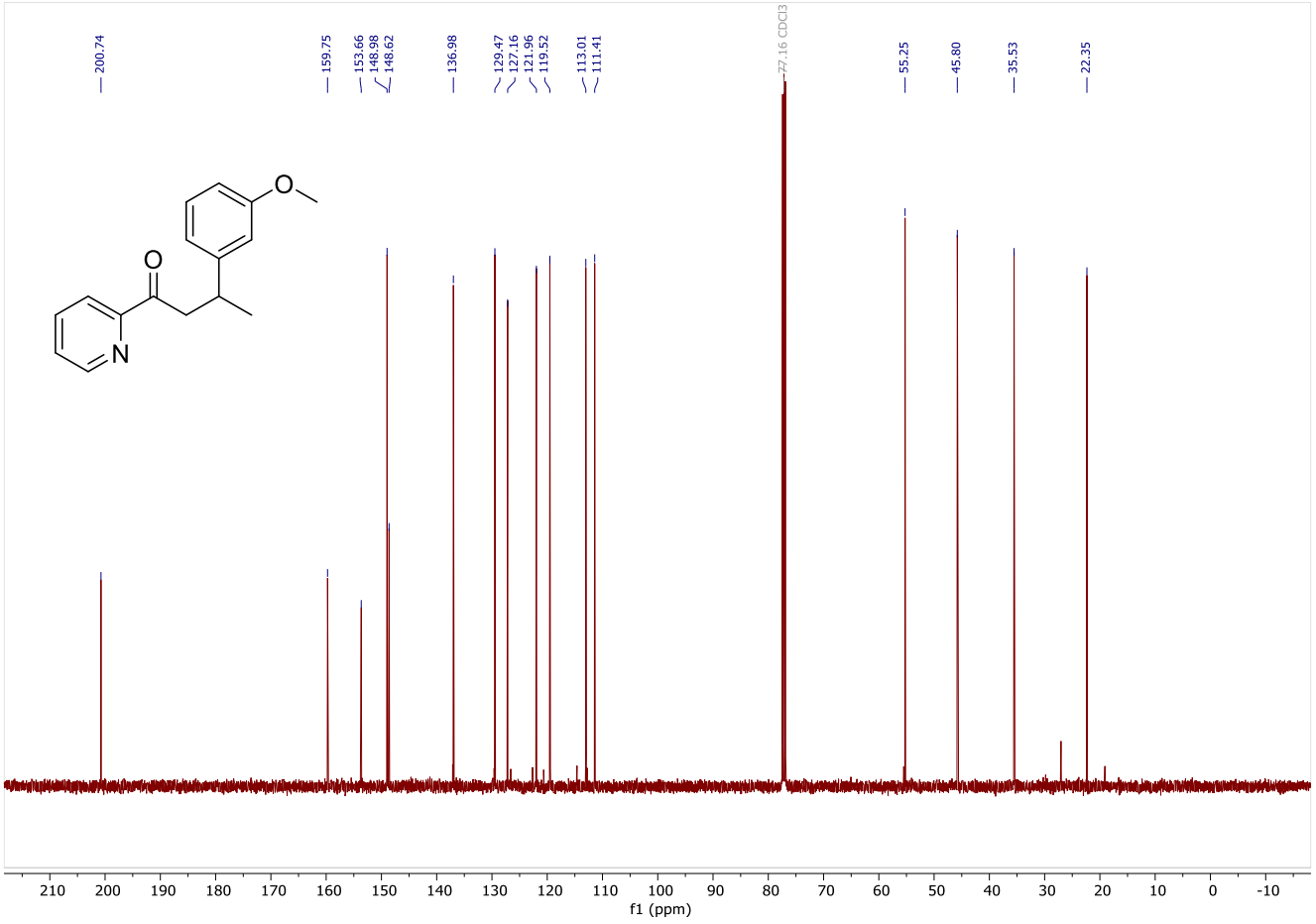
3-phenyl-1-(pyridin-2-yl)butan-1-one (4b)



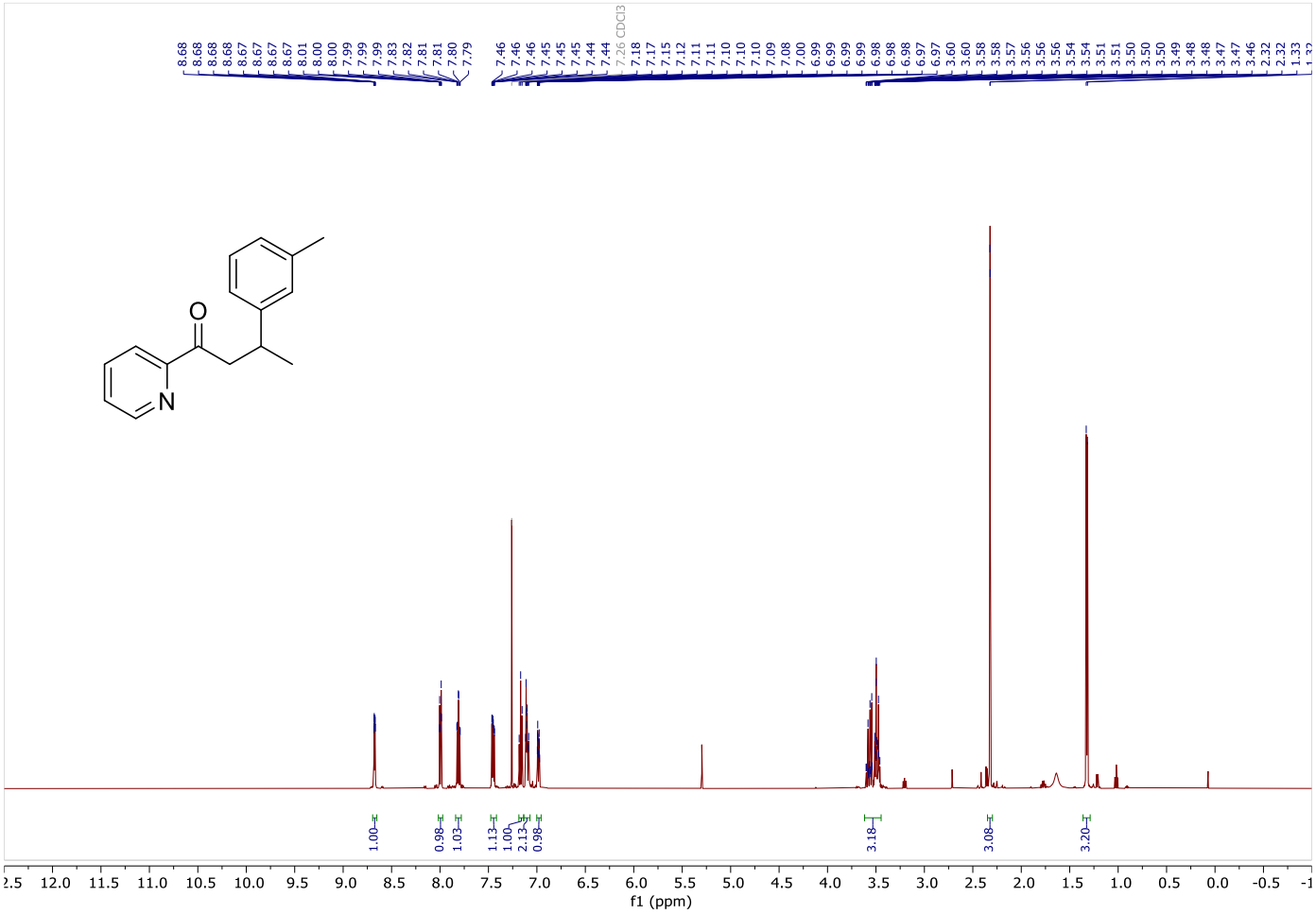


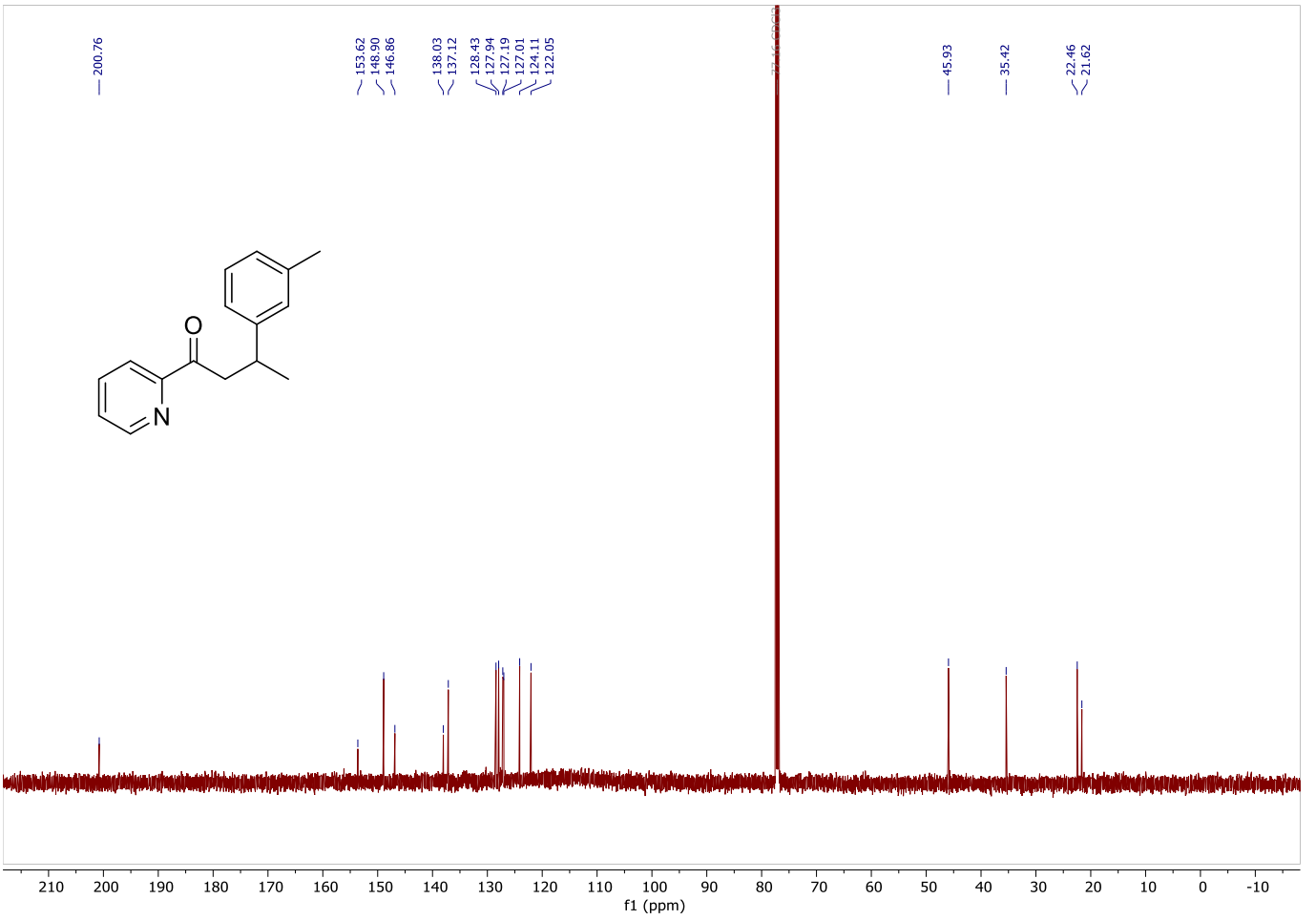
3-(3-methoxyphenyl)-1-(pyridin-2-yl)butan-1-one (4c)



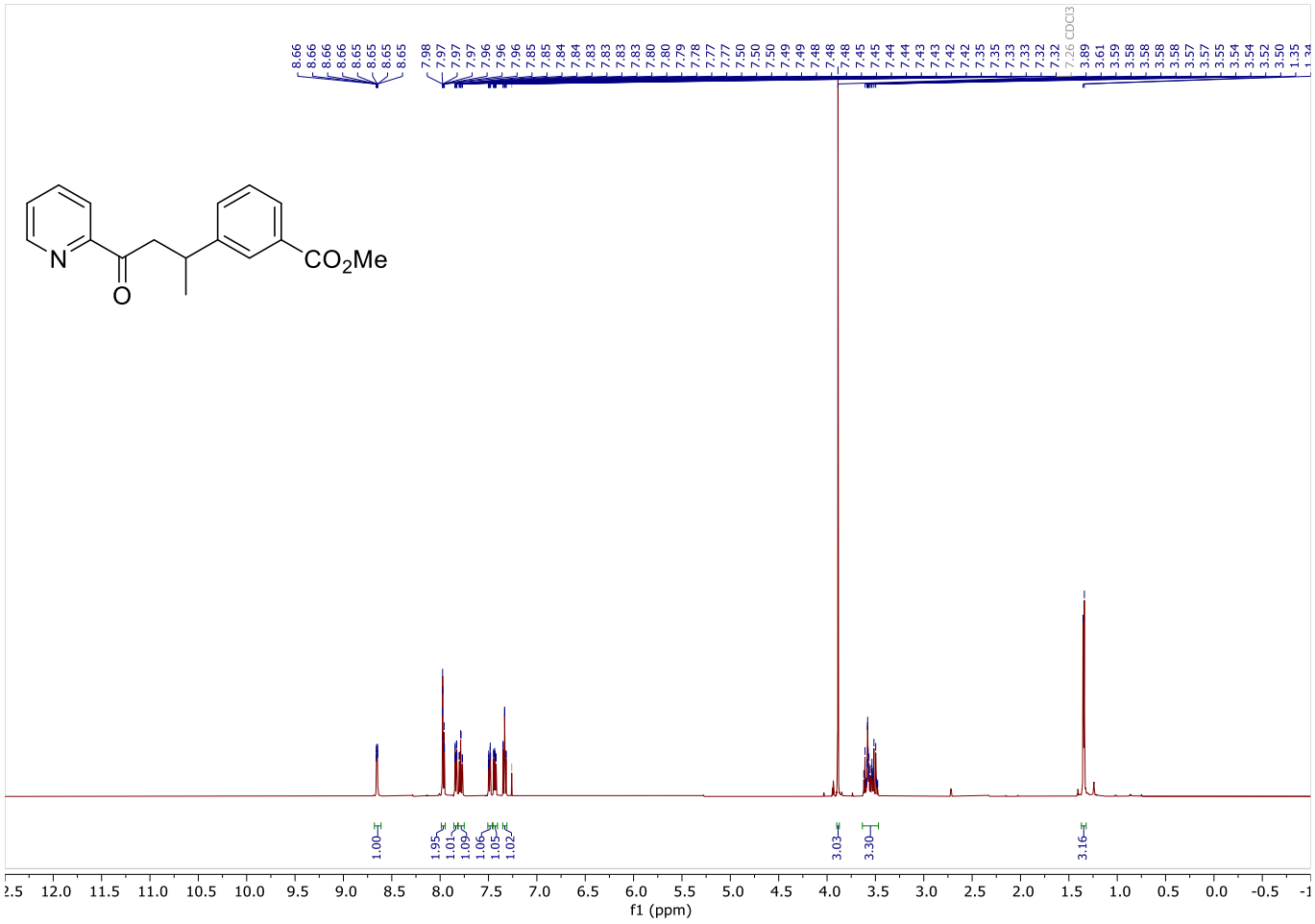


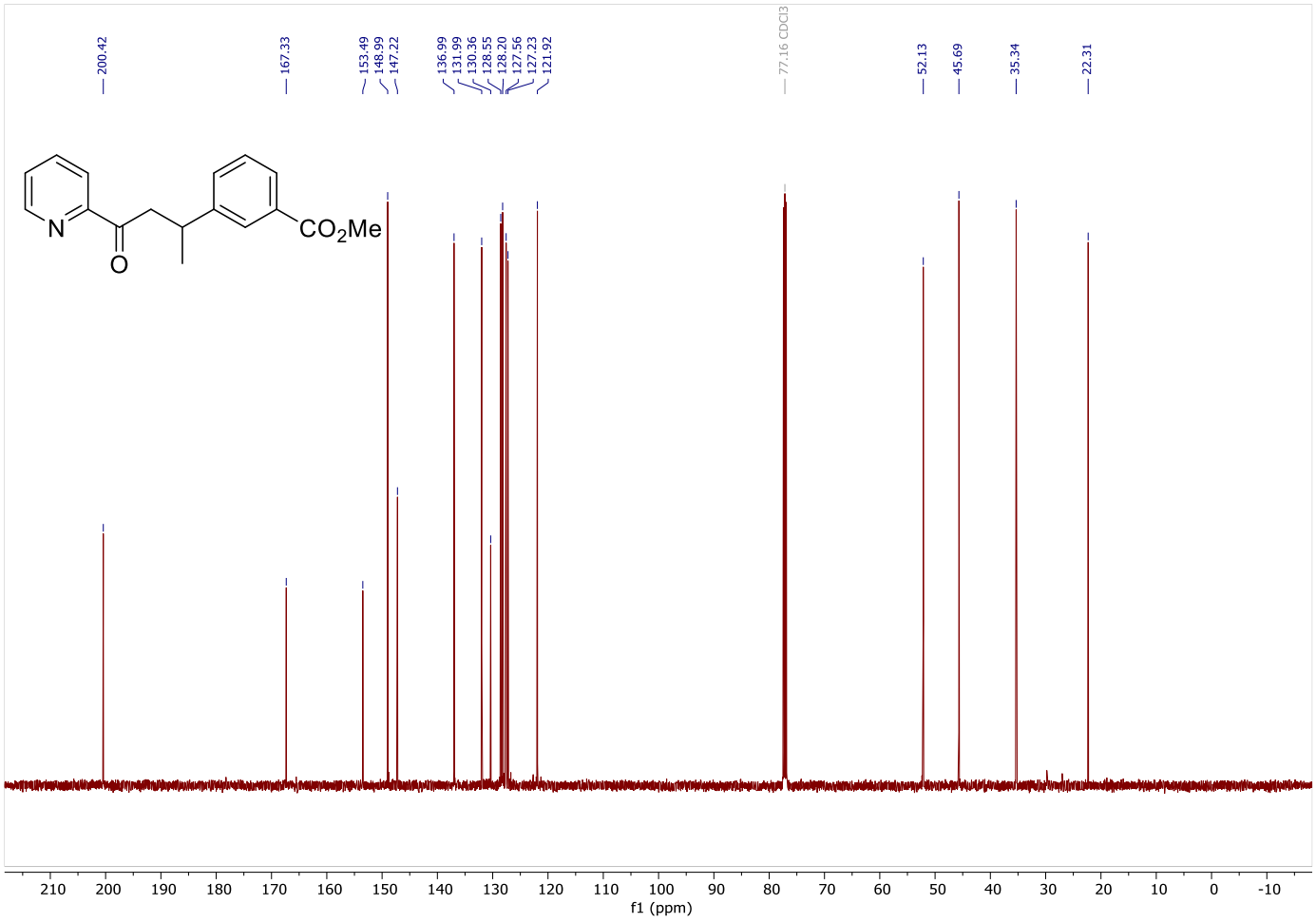
1-(pyridin-2-yl)-3-(m-tolyl)butan-1-one (4d)





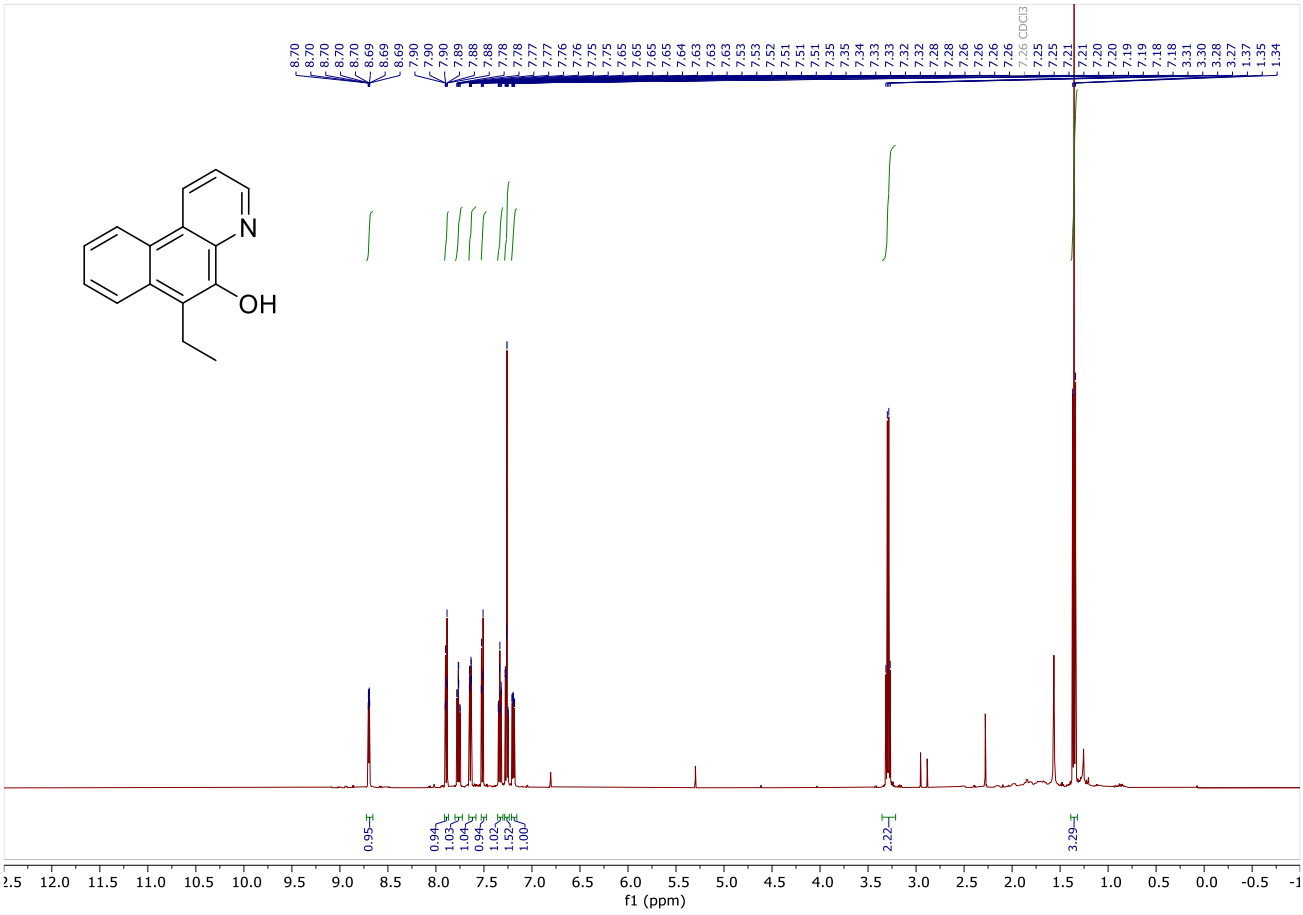
methyl 3-(4-oxo-4-(pyridin-2-yl)butan-2-yl)benzoate (4e)

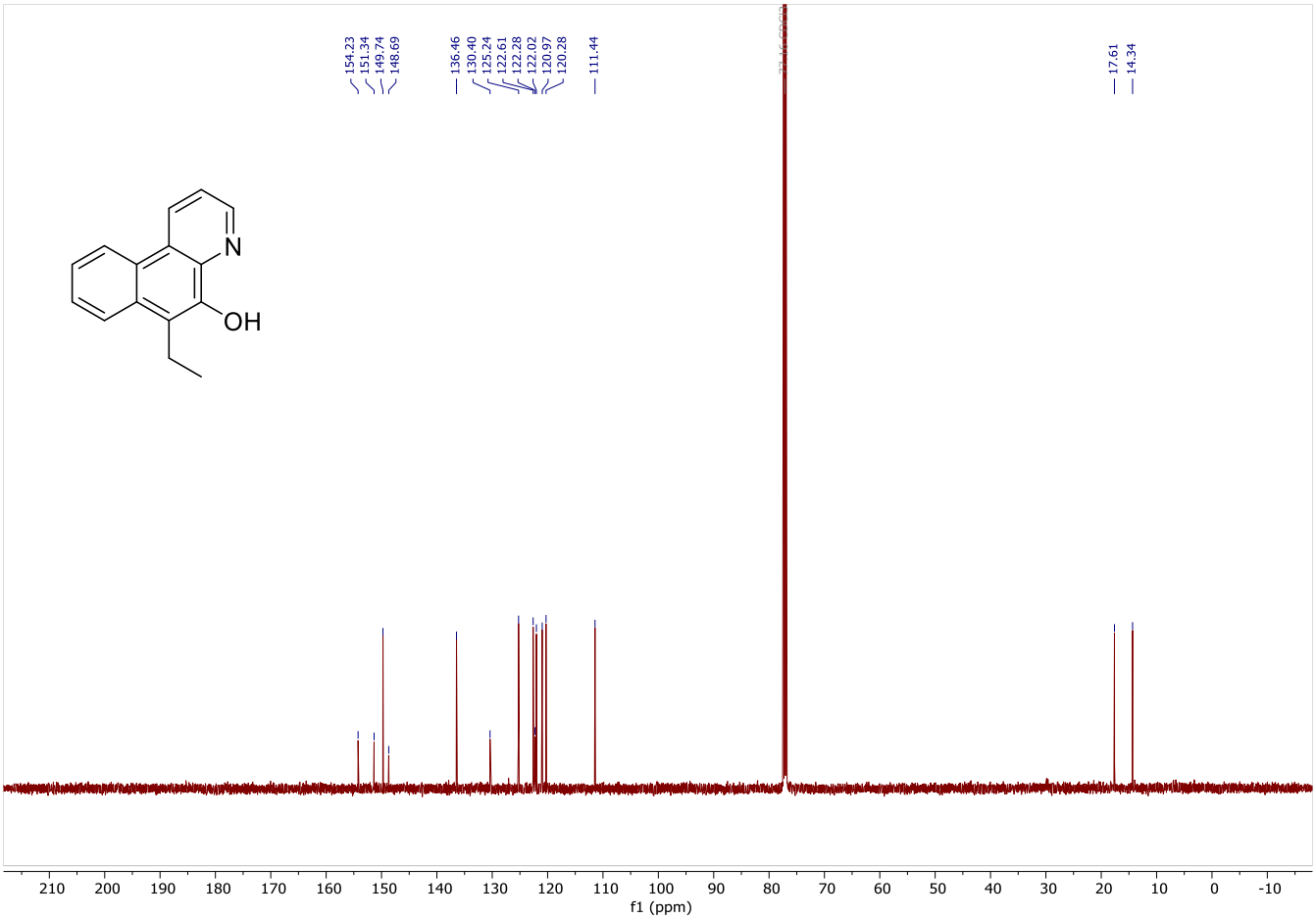




NMR spectra – post-functionalization products

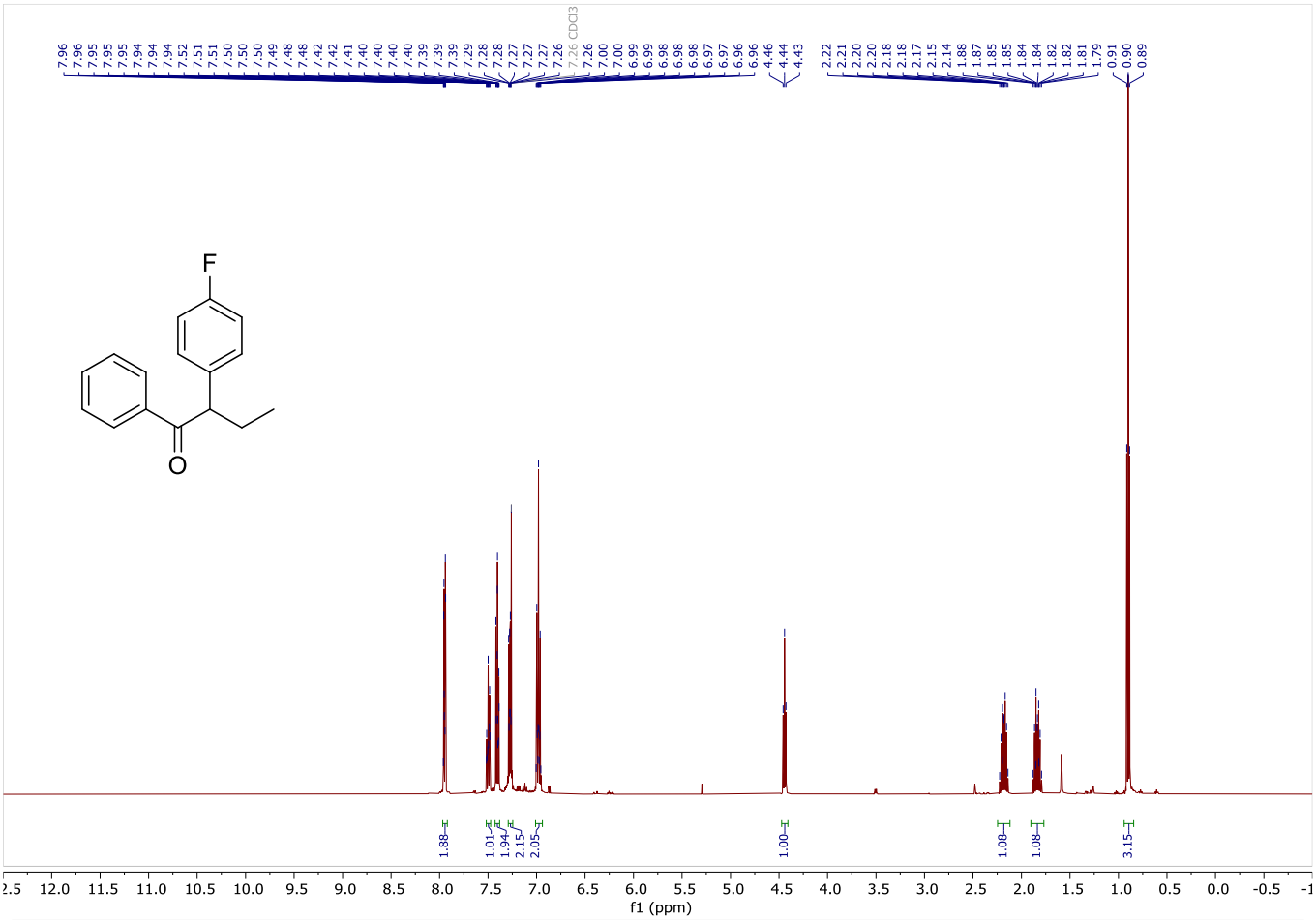
6-ethylbenzo[f]quinolin-5-ol (5a)

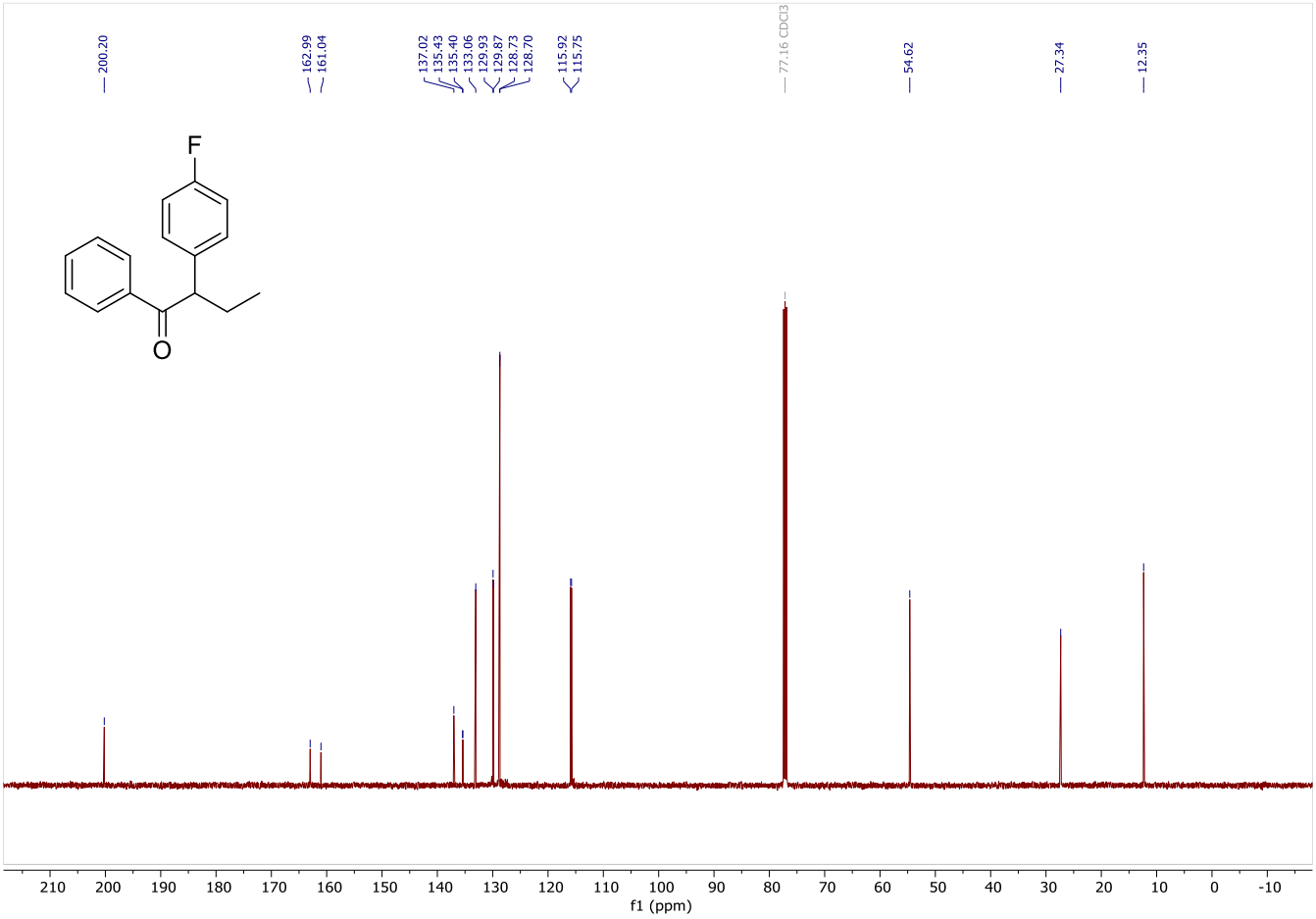




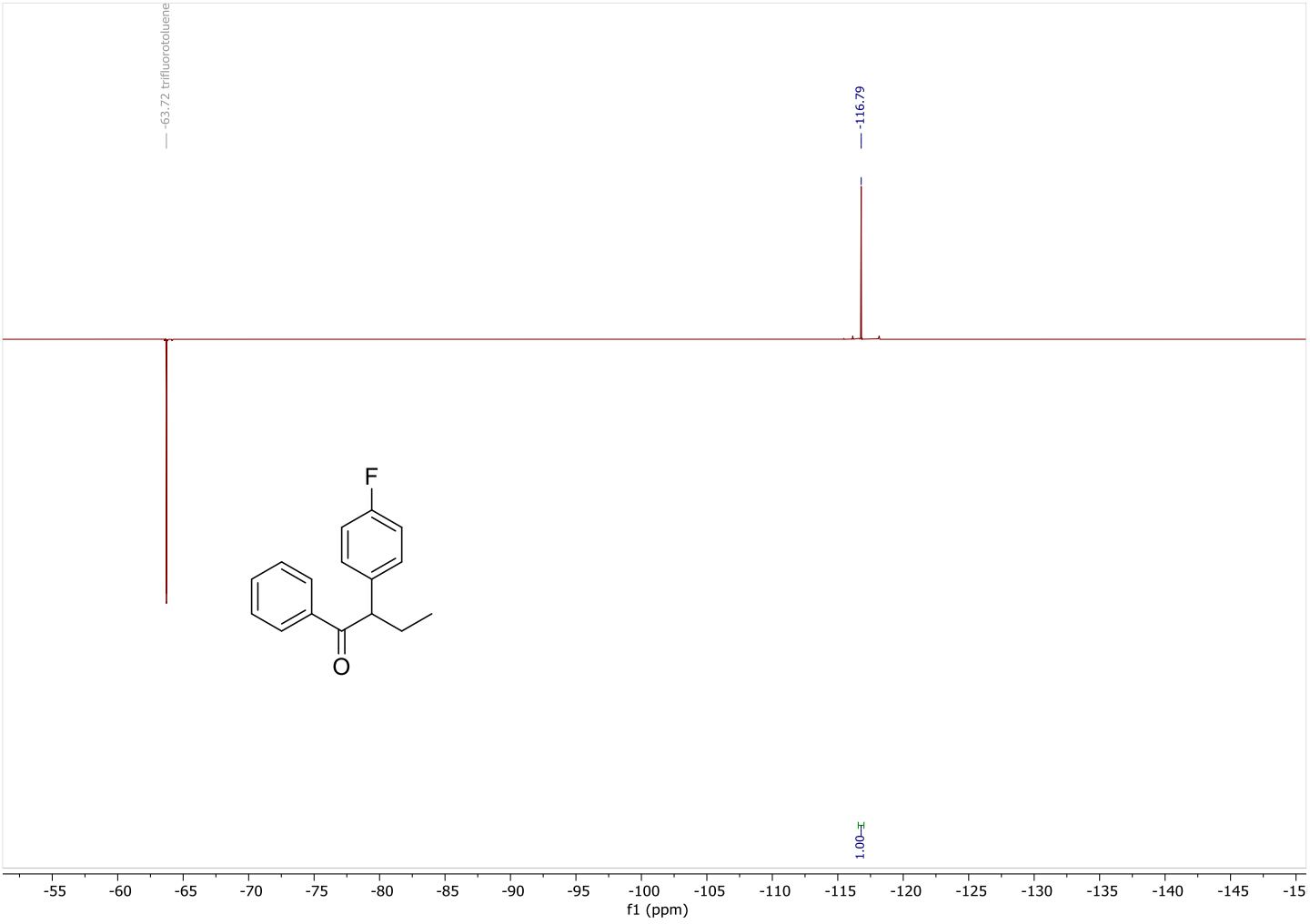
NMR spectra – products of control experiments

2-(4-fluorophenyl)-1-phenylbutan-1-one (3af)





2-(4-fluorophenyl)-1-phenylbutan-1-one (3af)



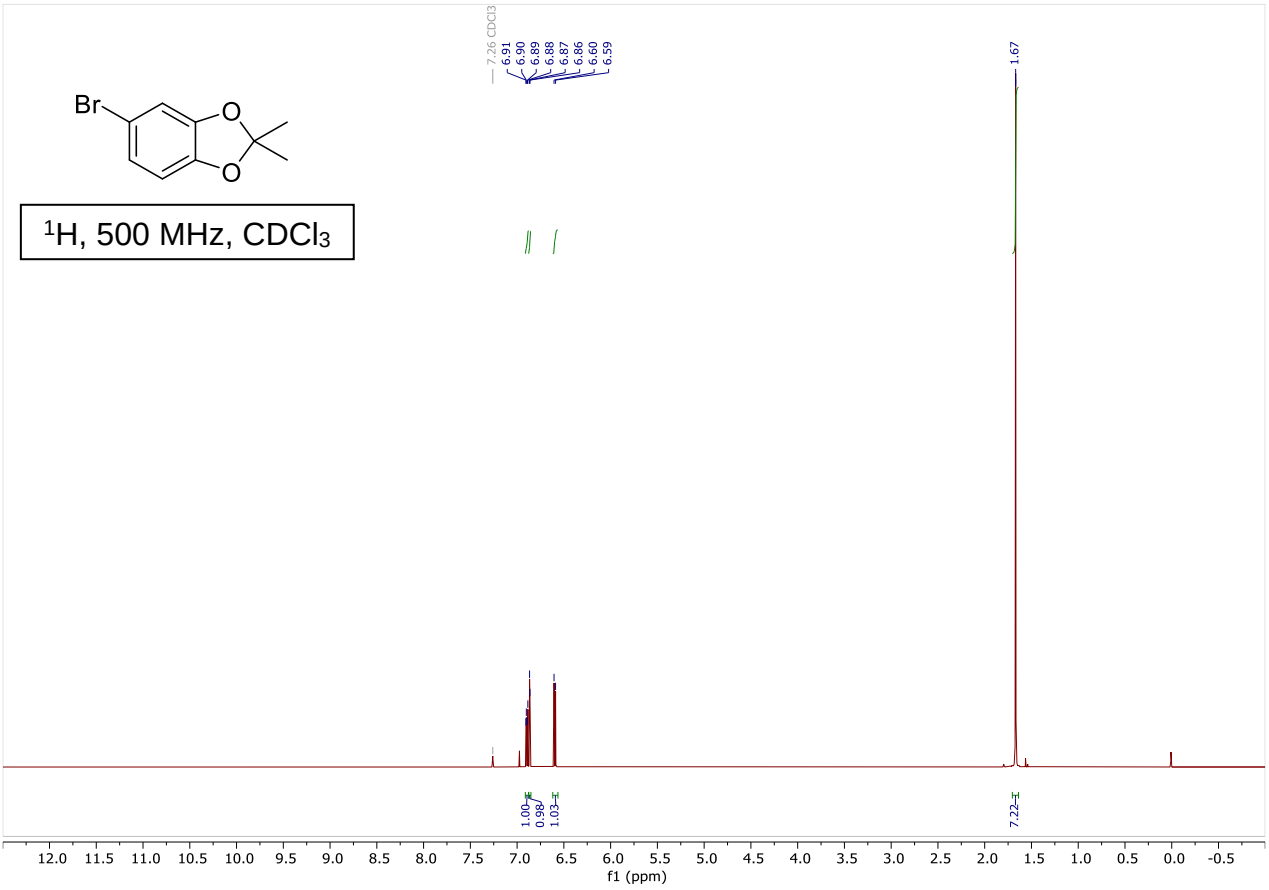
Part II: Methylene C(sp^3)−H Arylation Enables the Stereoselective Synthesis and Structure Revision of Indidene Natural Products

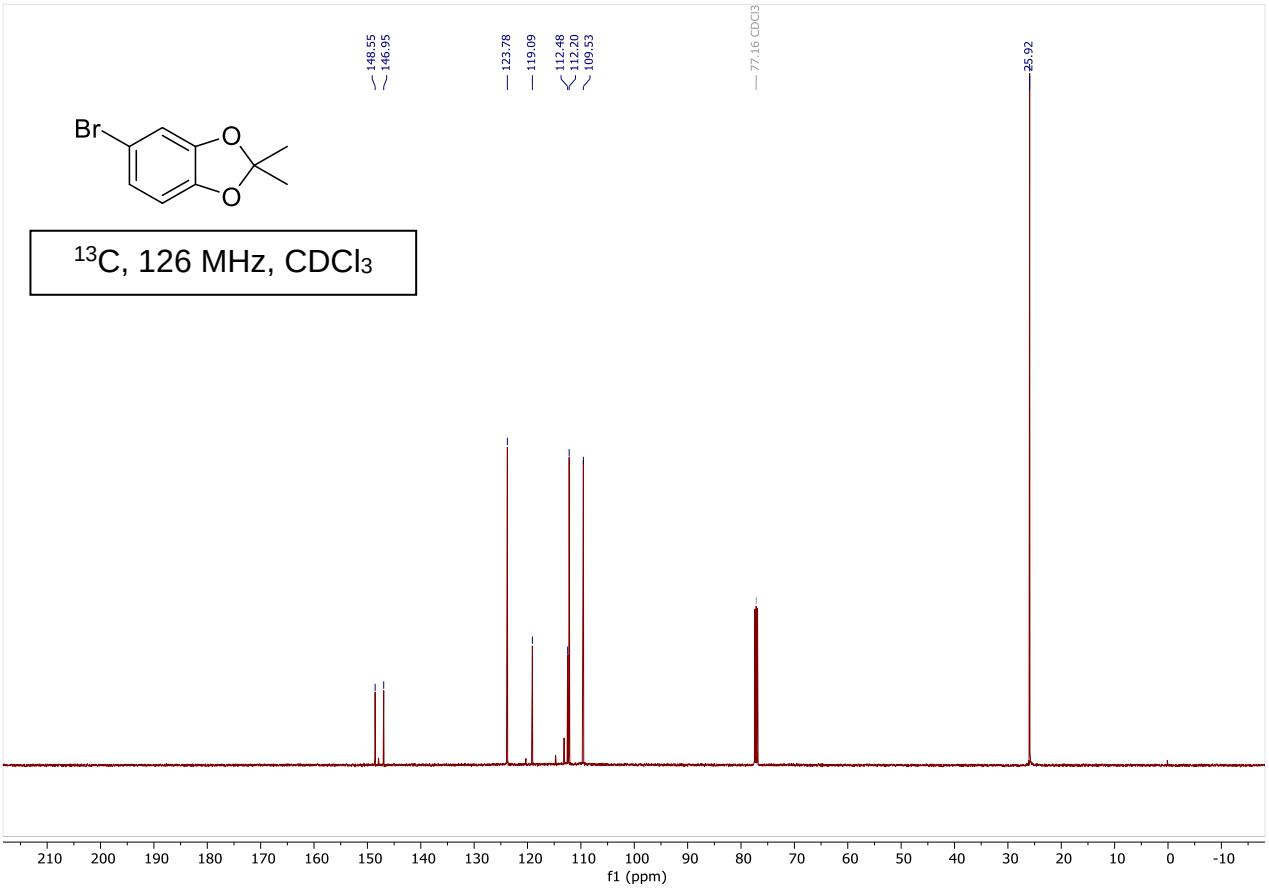
Numbering based on article presented in section 3.

7. NMR spectra

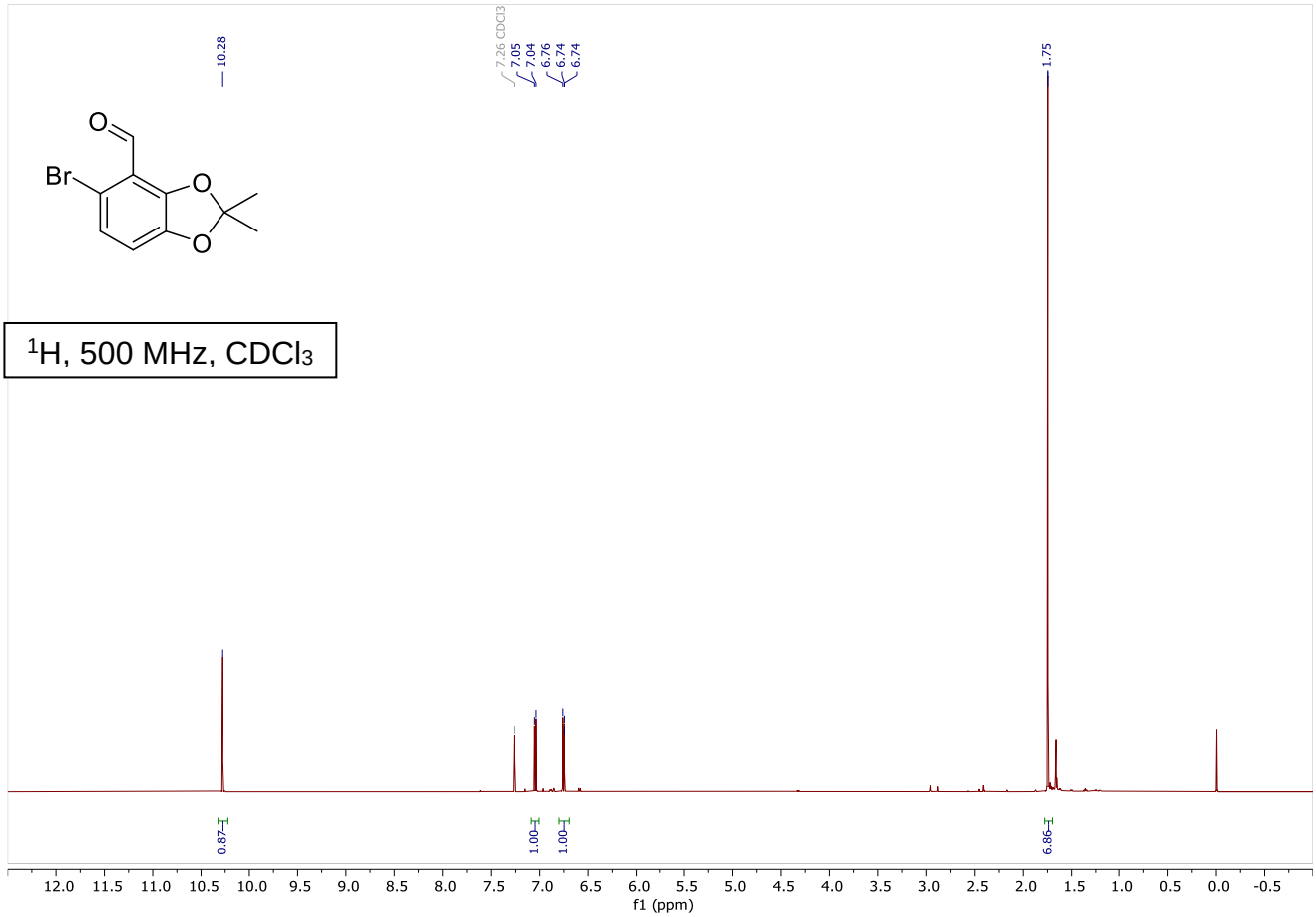
7.1 C–H activation precursor

5-bromo-2,2-dimethylbenzo[d][1,3]dioxole (bromocathehol 19)

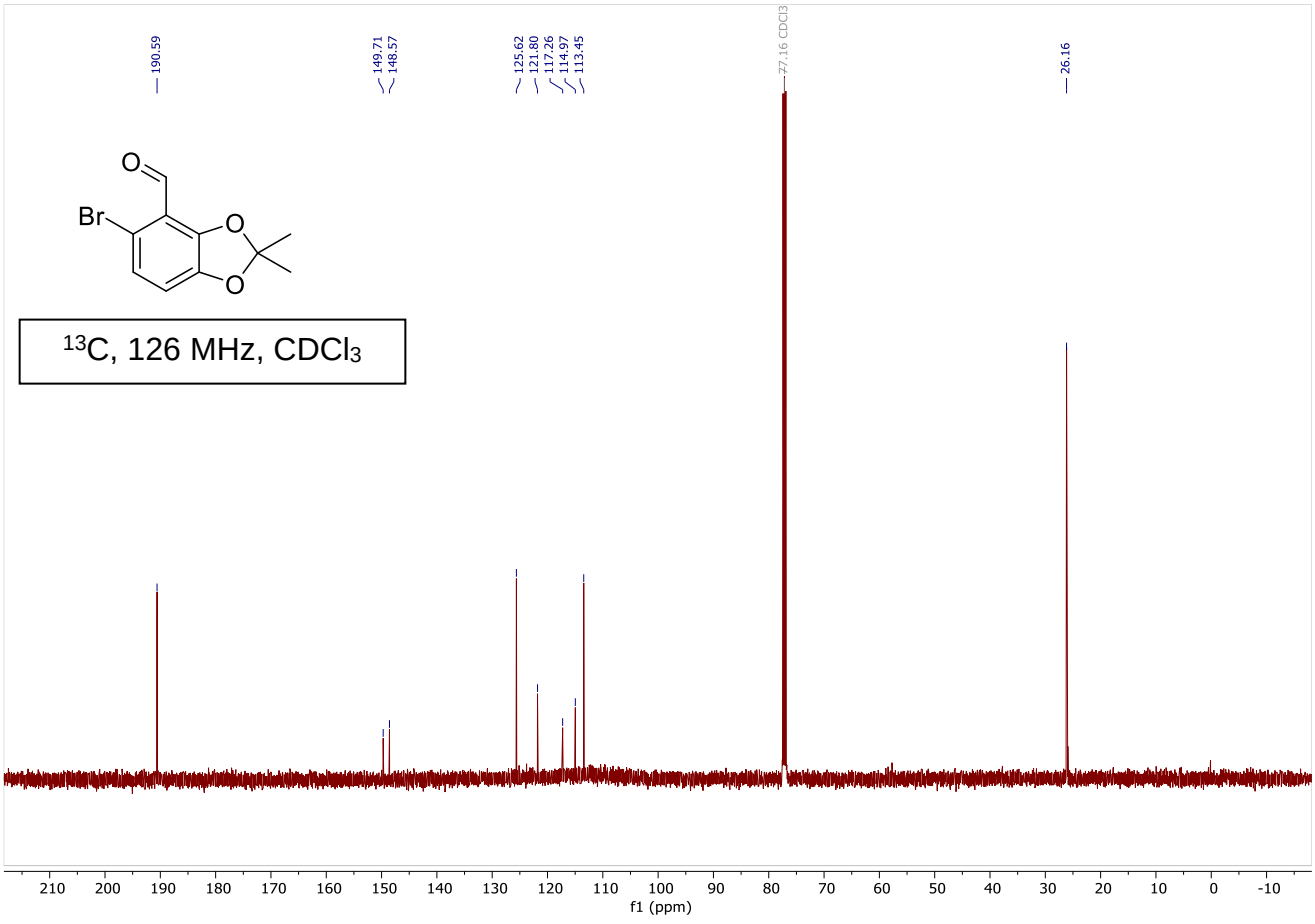




5-bromo-2,2-dimethylbenzo[d][1,3]dioxole-4-carbaldehyde (bromoaldehyde 9)

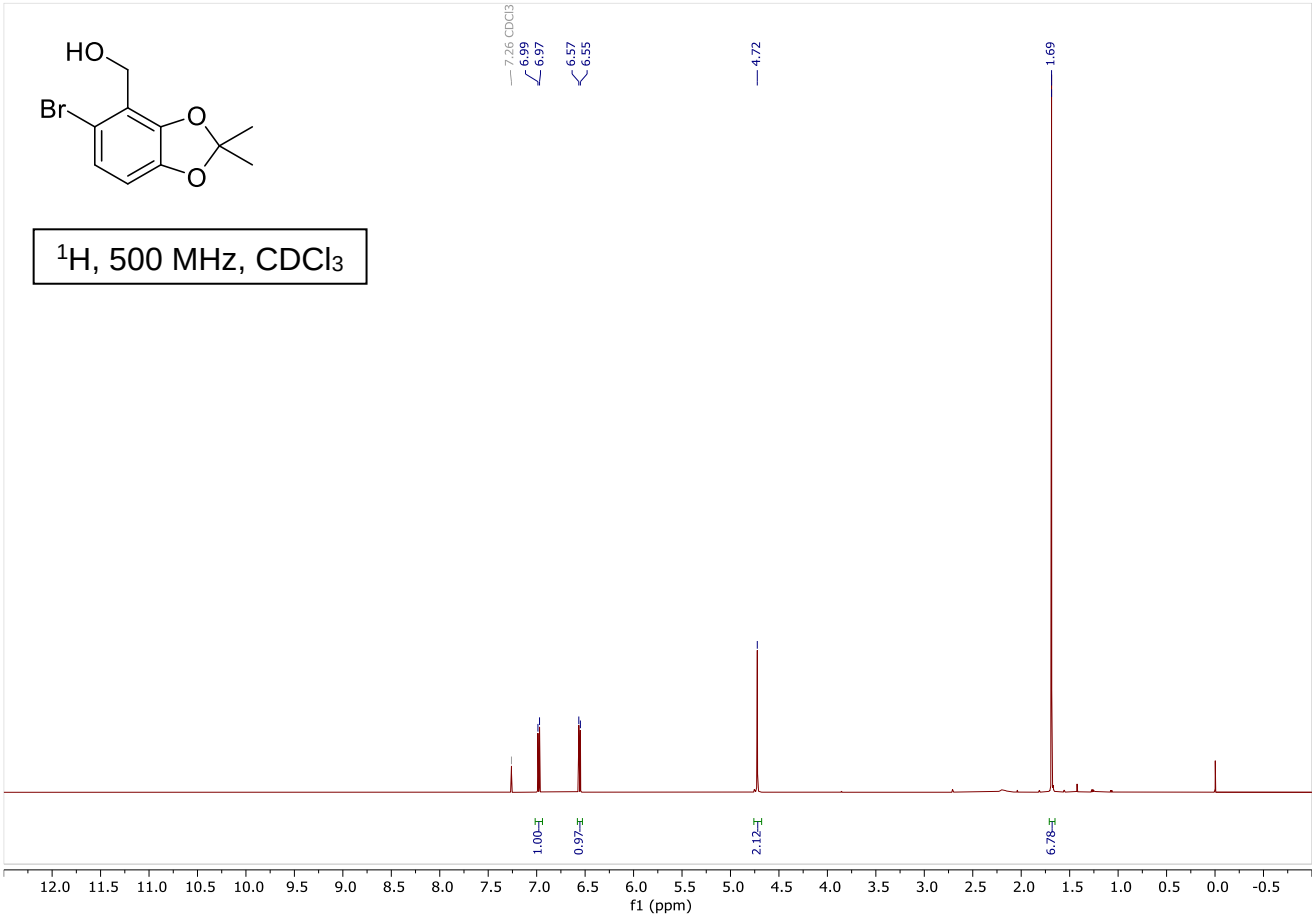


^{1}H, 500 MHz, $CDCl_3$

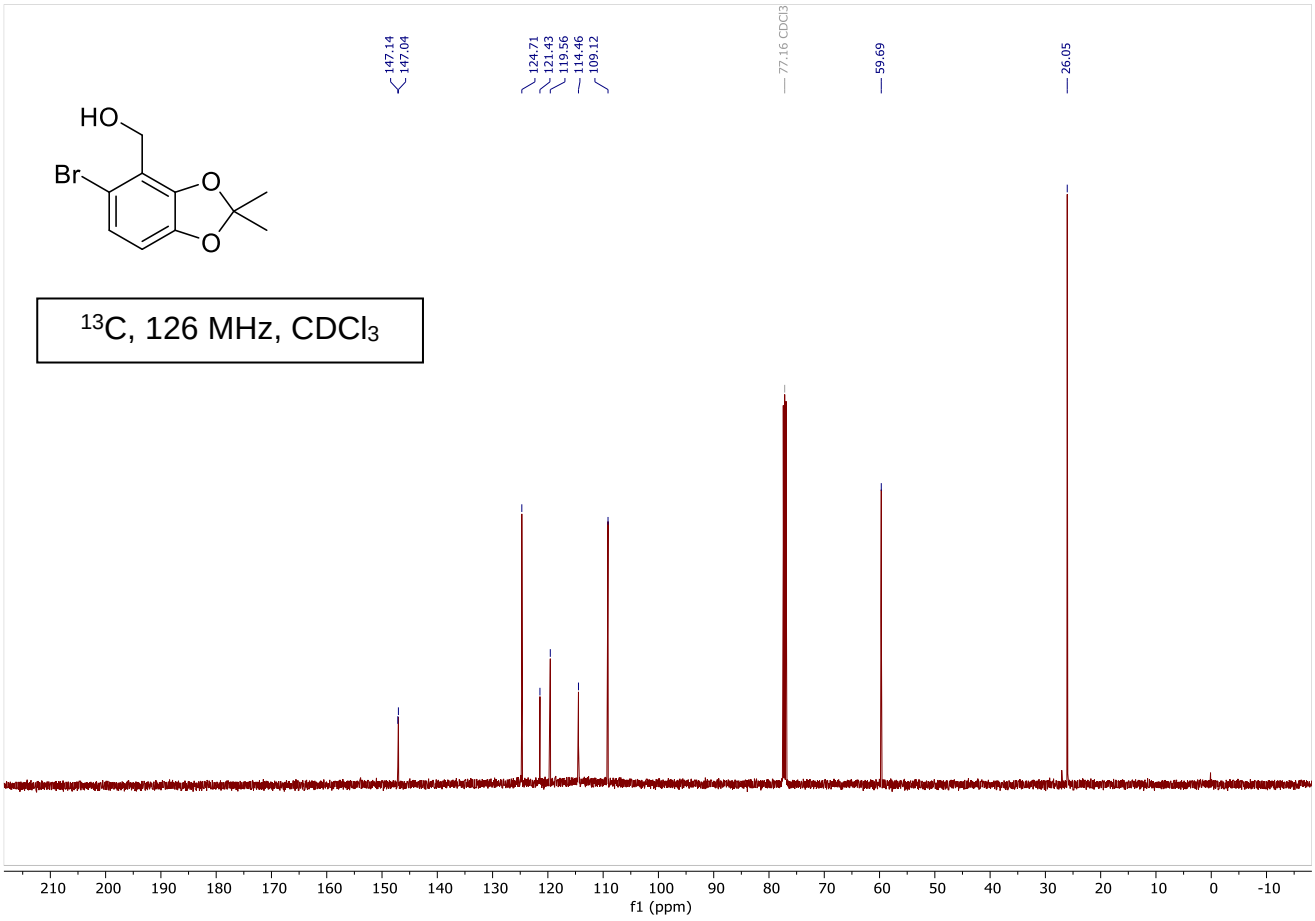


^{13}C, 126 MHz, $CDCl_3$

(5-bromo-2,2-dimethylbenzo[d][1,3]dioxol-4-yl)methanol (alcohol 20)

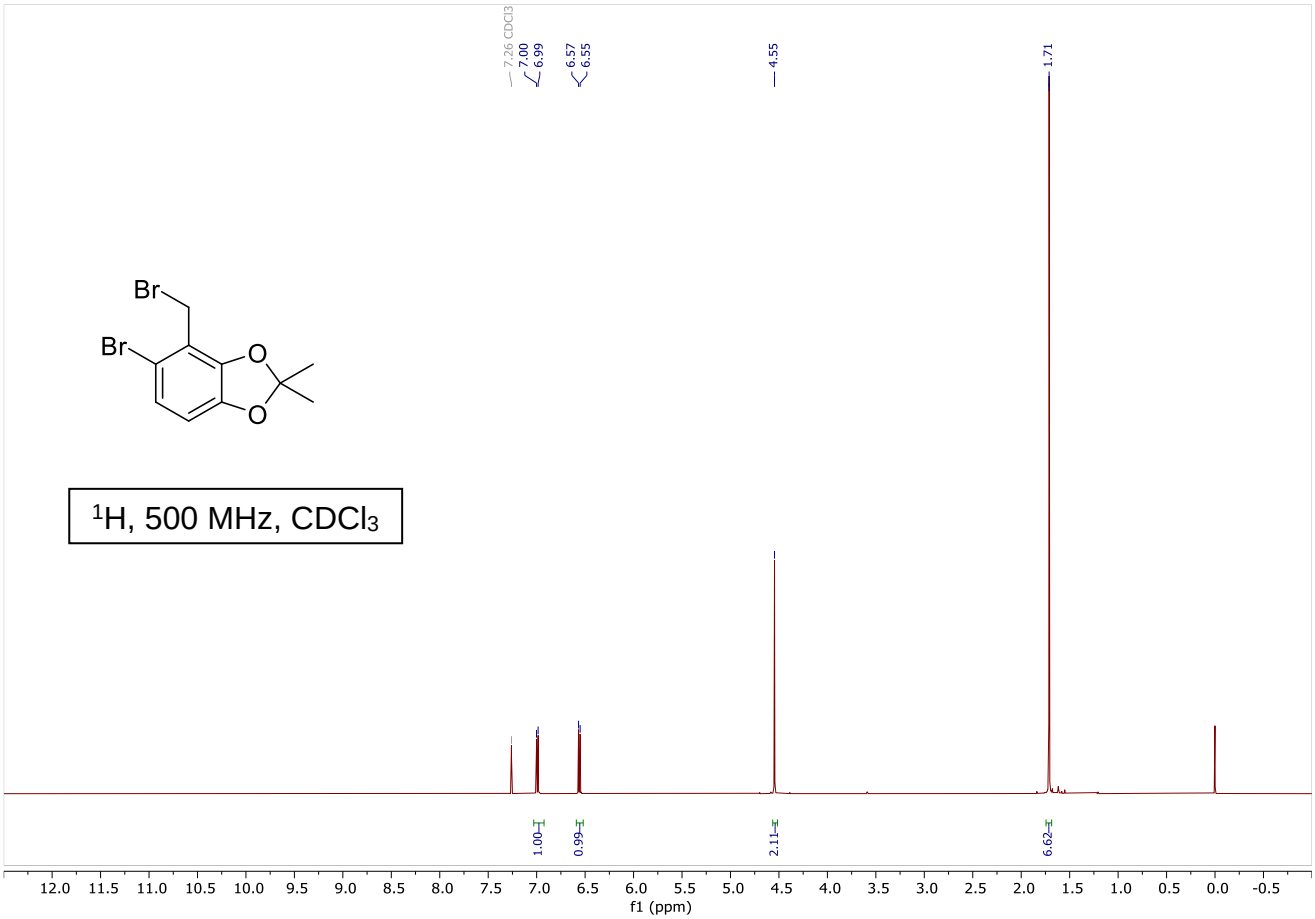


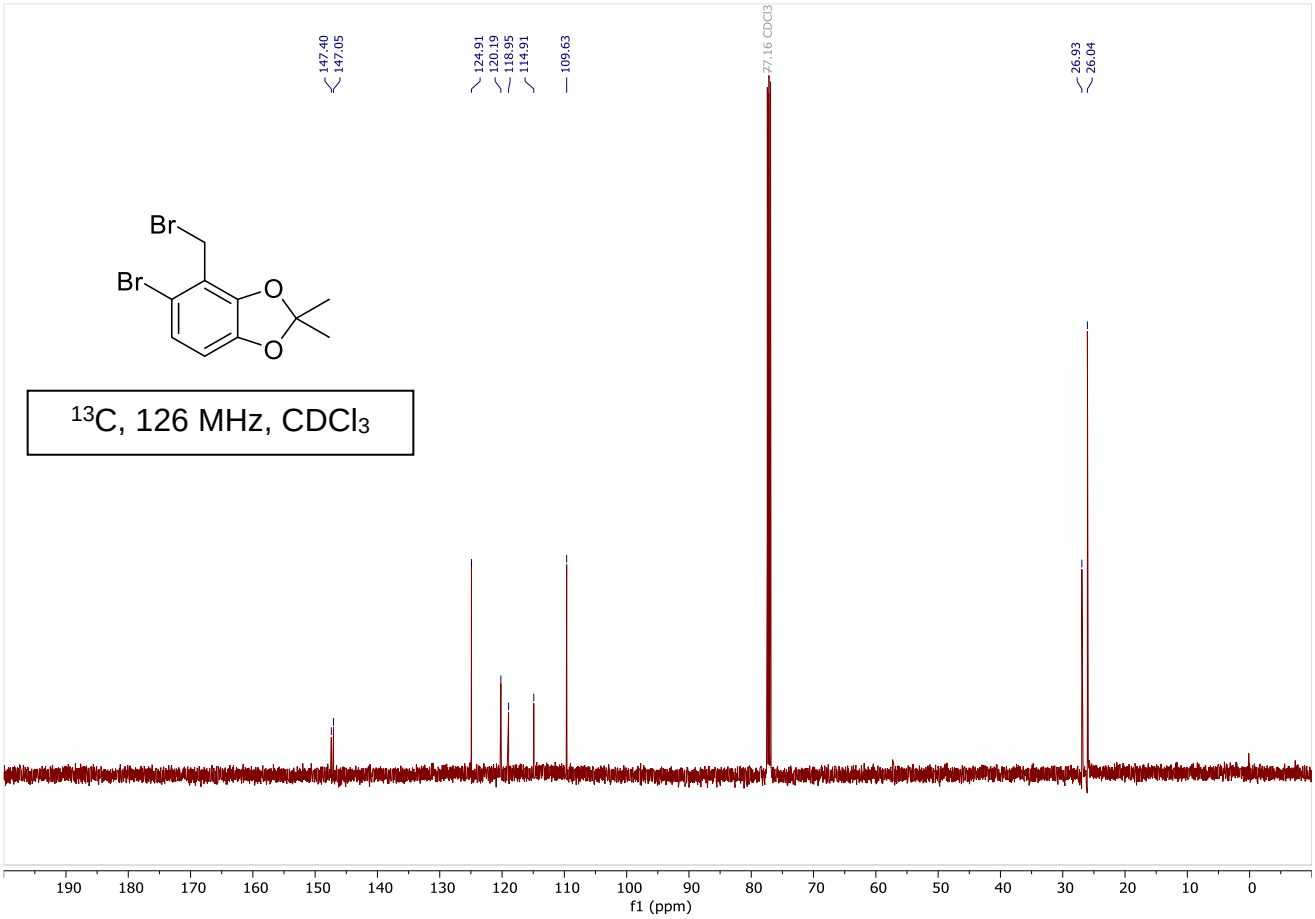
^{1}H, 500 MHz, $CDCl_3$



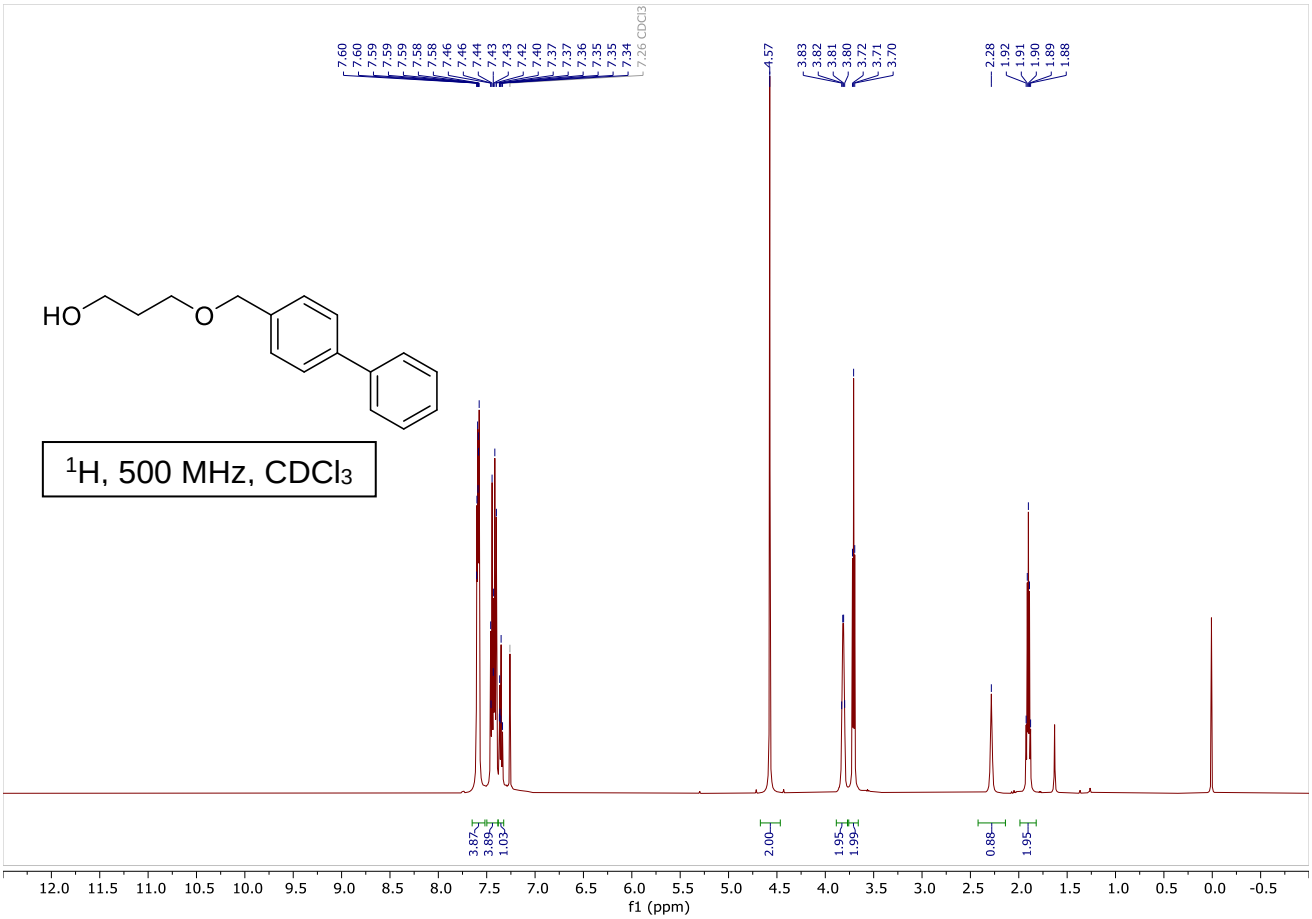
^{13}C, 126 MHz, $CDCl_3$

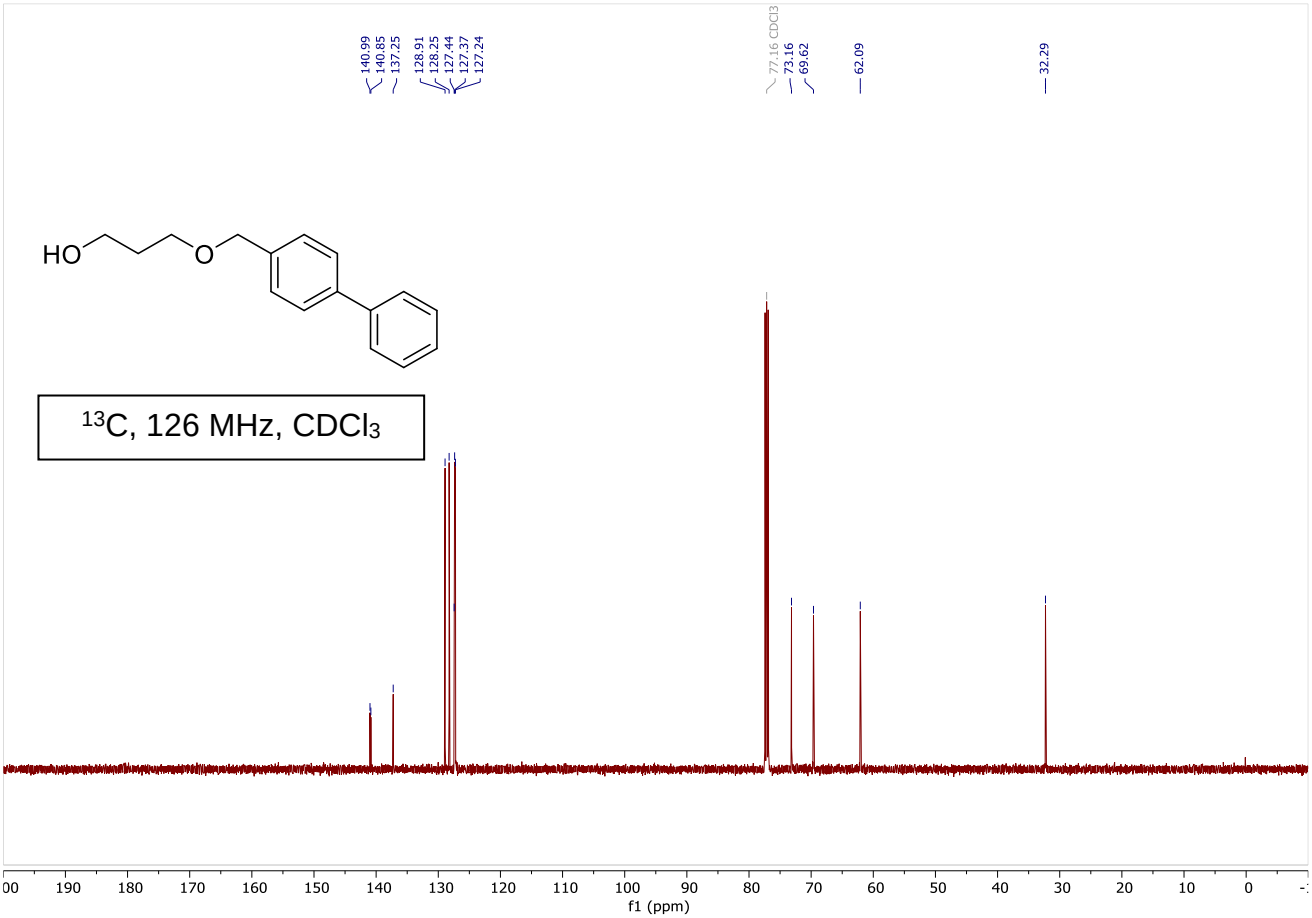
5-bromo-4-(bromomethyl)-2,2-dimethylbenzo[d][1,3]dioxole (dibromide 10)



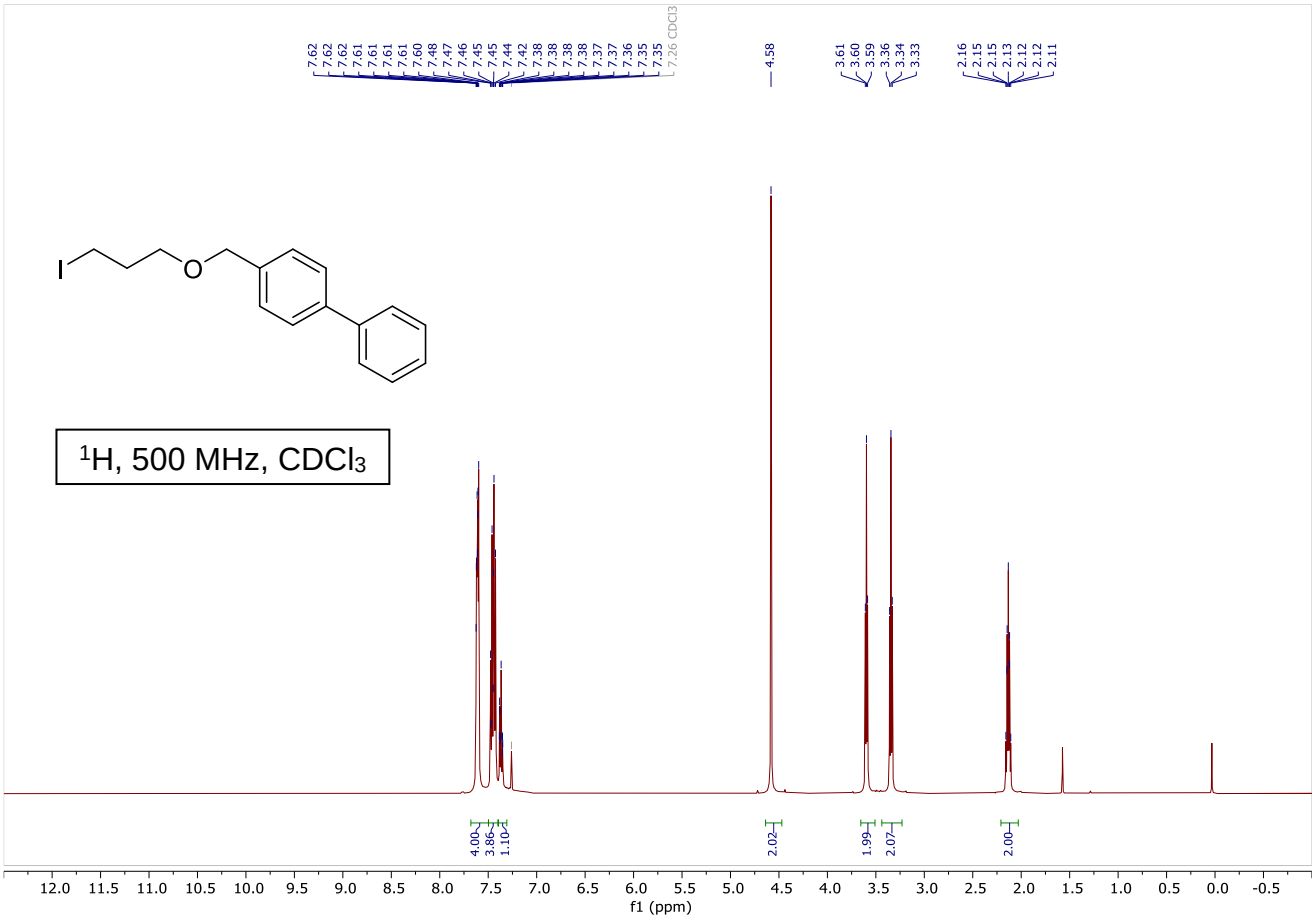


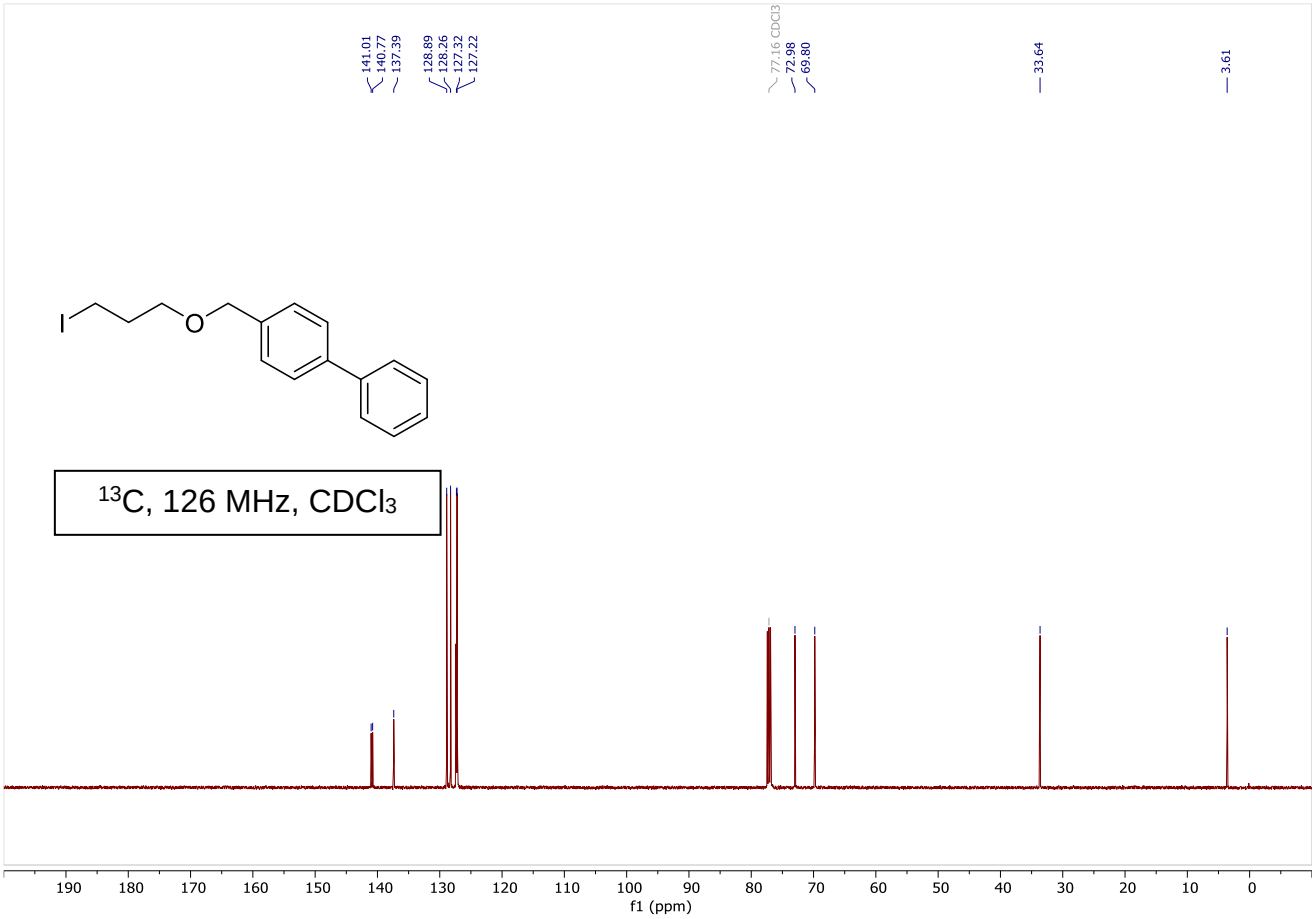
3-([1,1'-biphenyl]-4-ylmethoxy)propan-1-ol (monoalcohol 21)



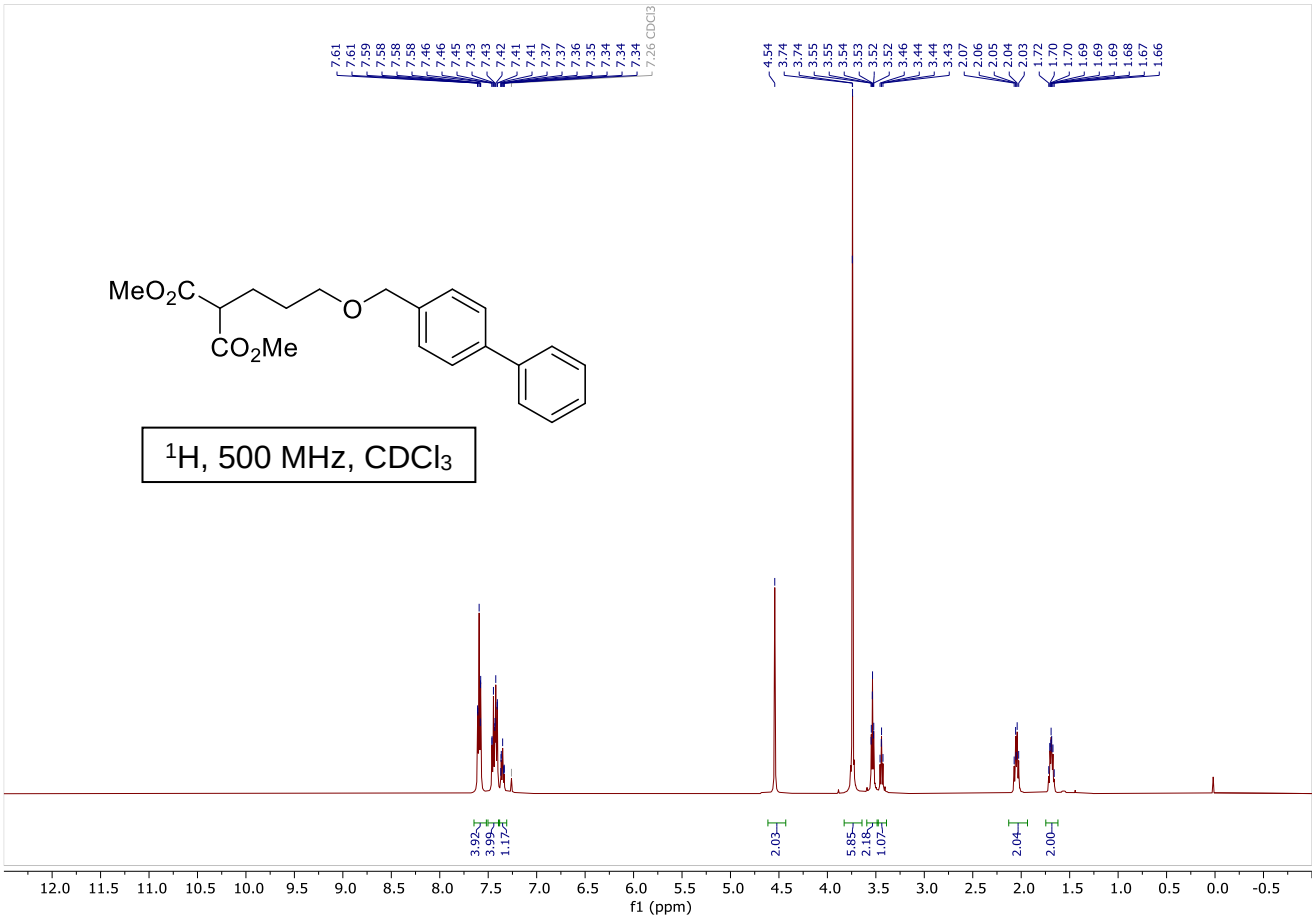


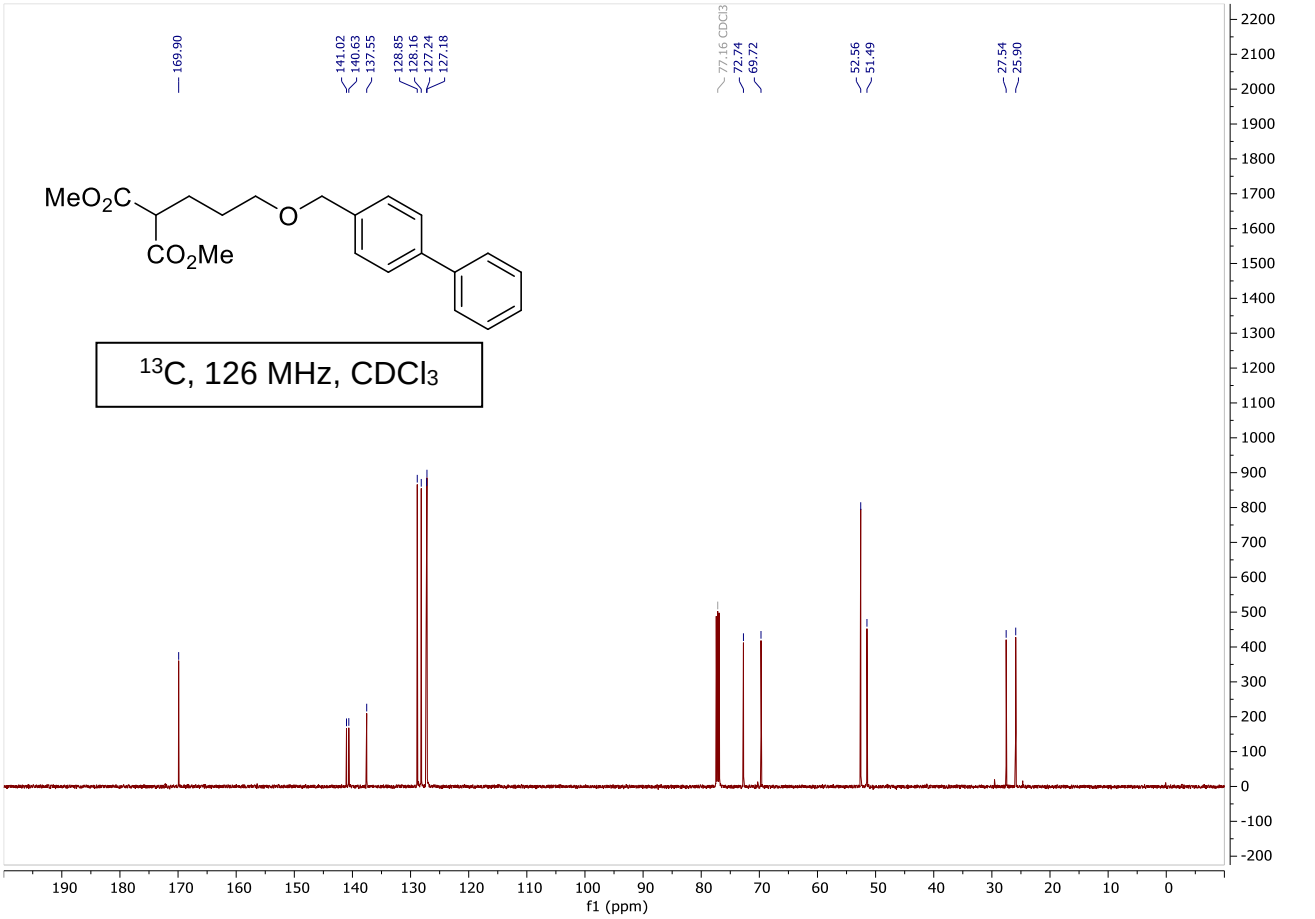
4-((3-iodopropoxy)methyl)-1,1'-biphenyl (iodide 6)



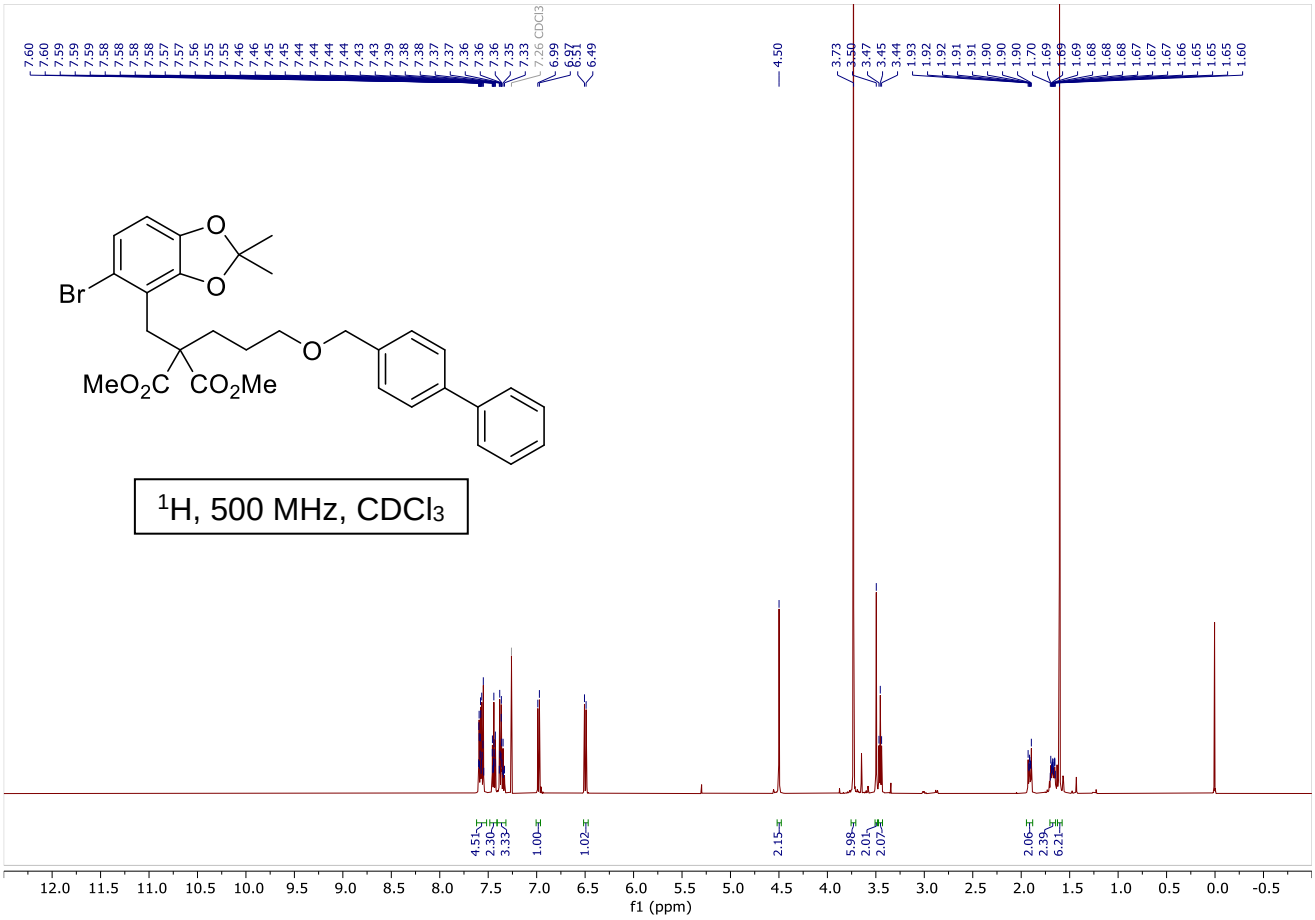


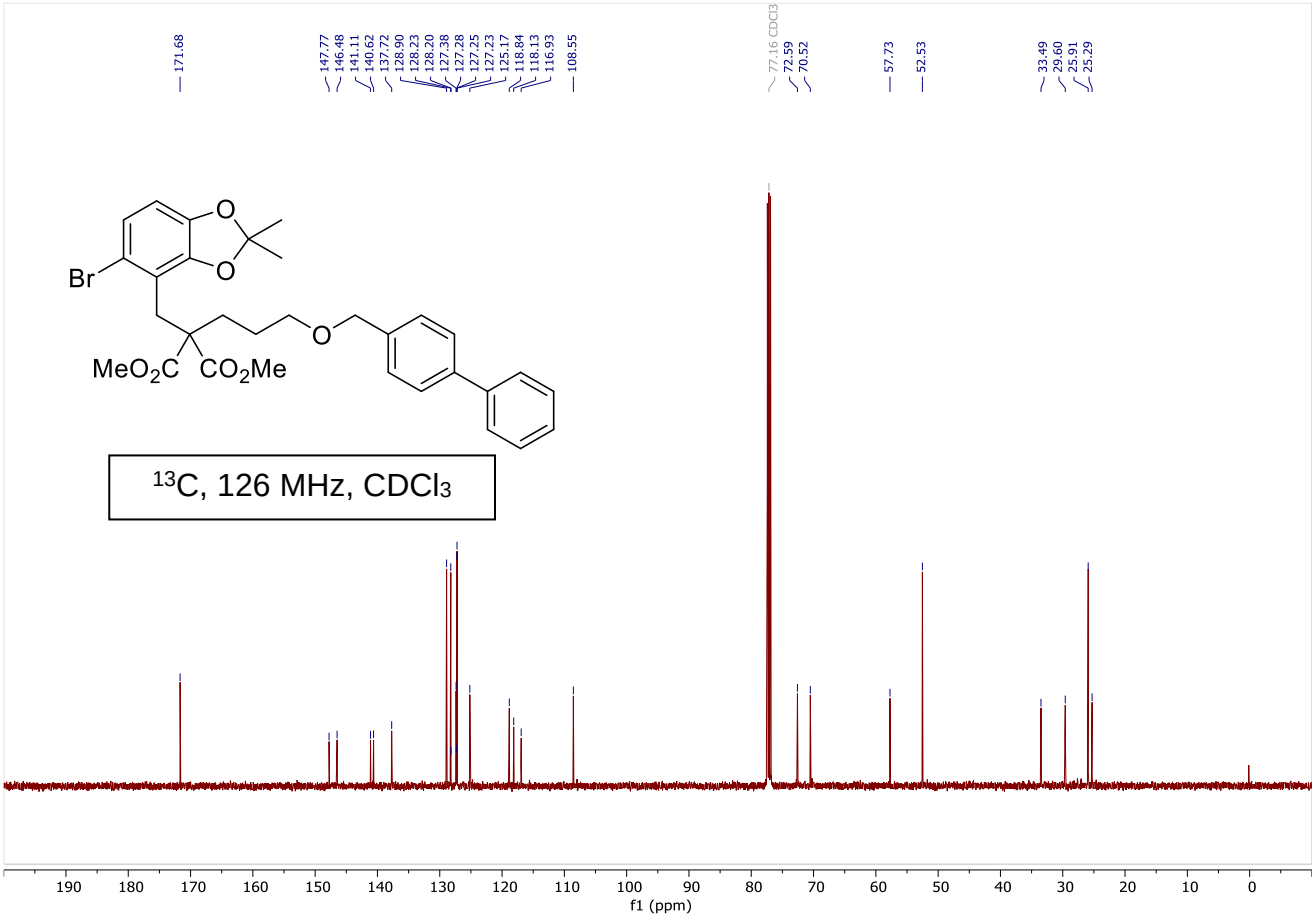
dimethyl 2-(3-([1,1'-biphenyl]-4-ylmethoxy)propyl)malonate (malonate 7)



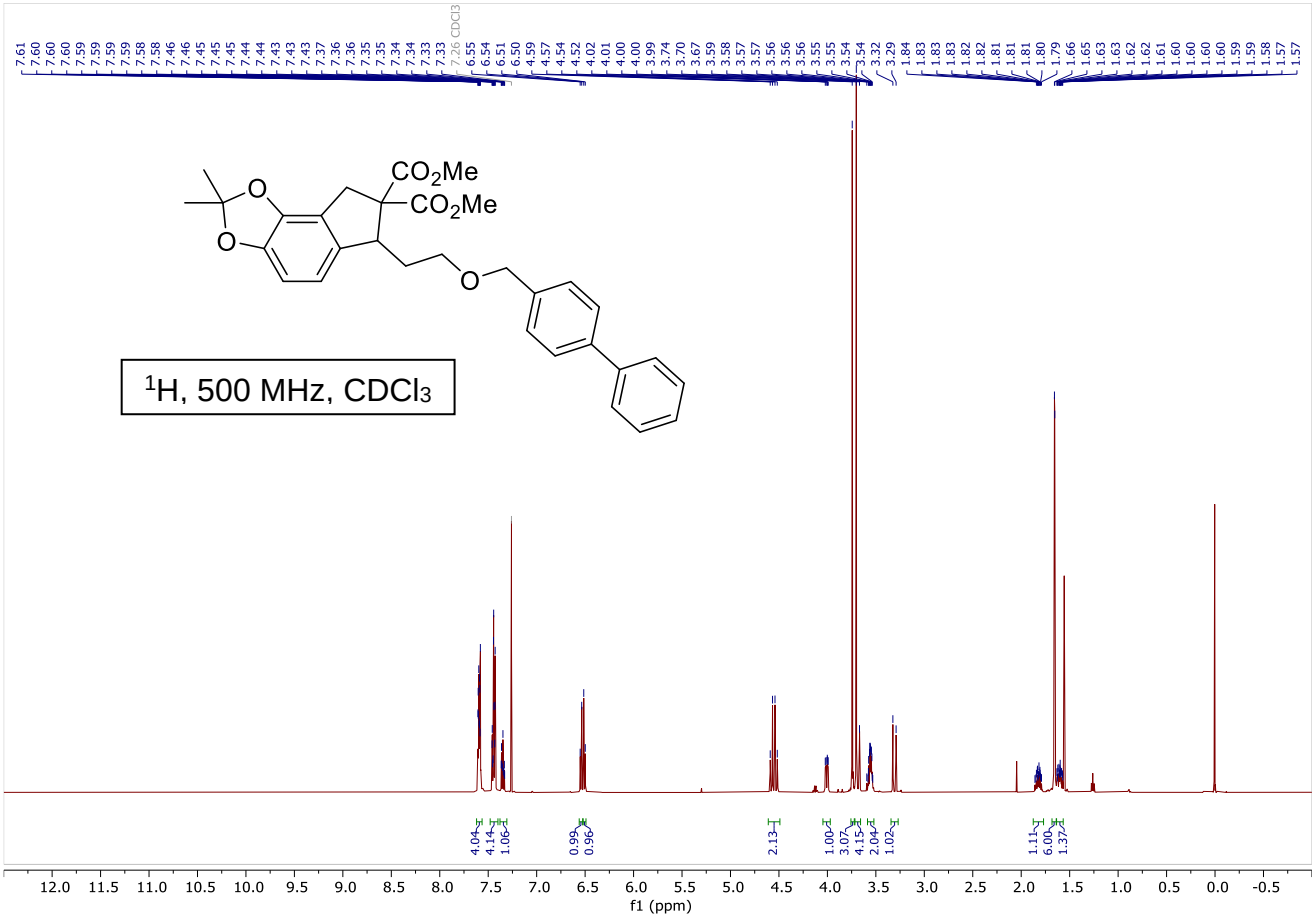


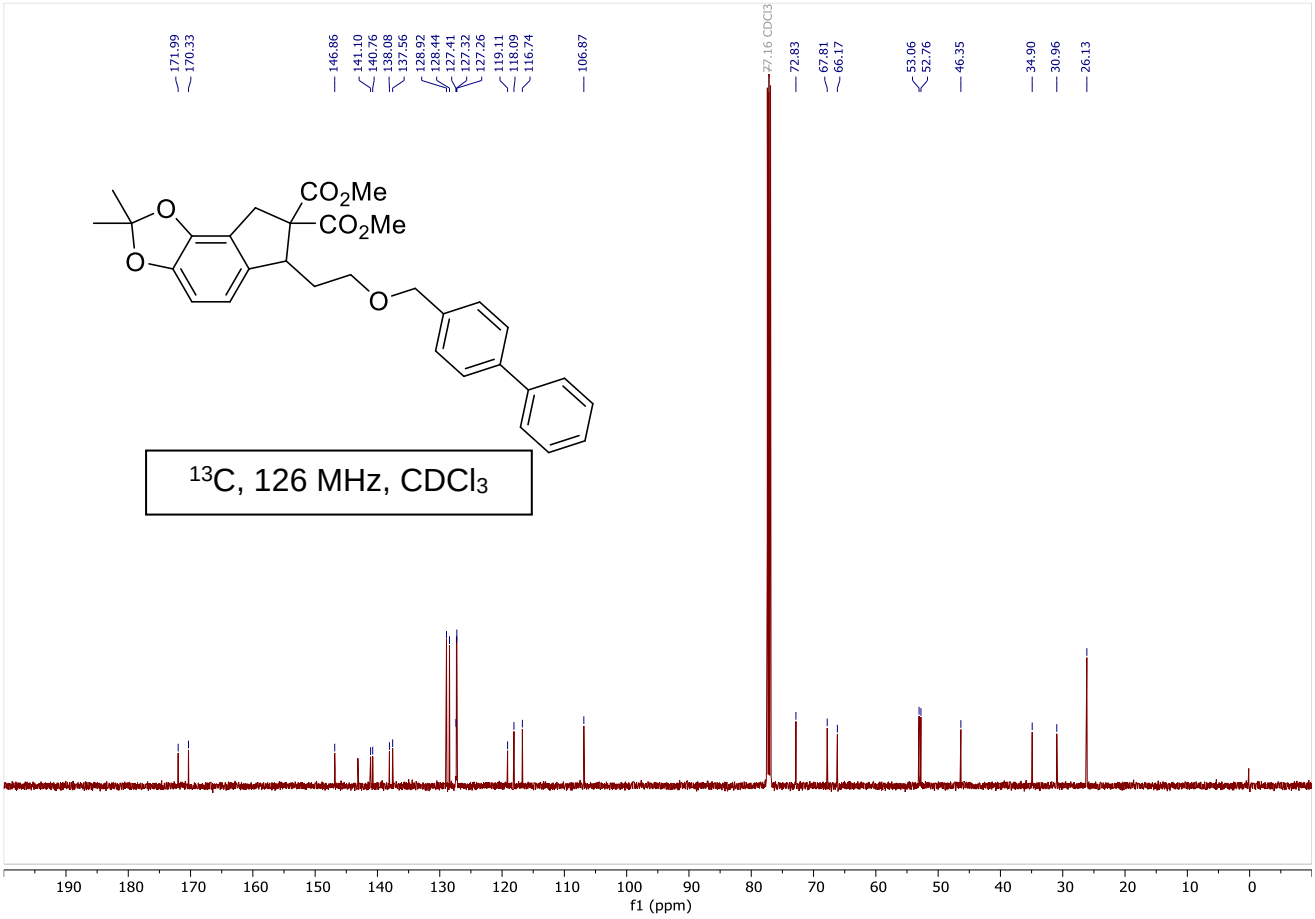
dimethyl 2-(3-([1,1'-biphenyl]-4-ylmethoxy)propyl)-2-((5-bromo-2,2-dimethylbenzo[d][1,3]-dioxol-4-yl)methyl)malonate (precursor 5)





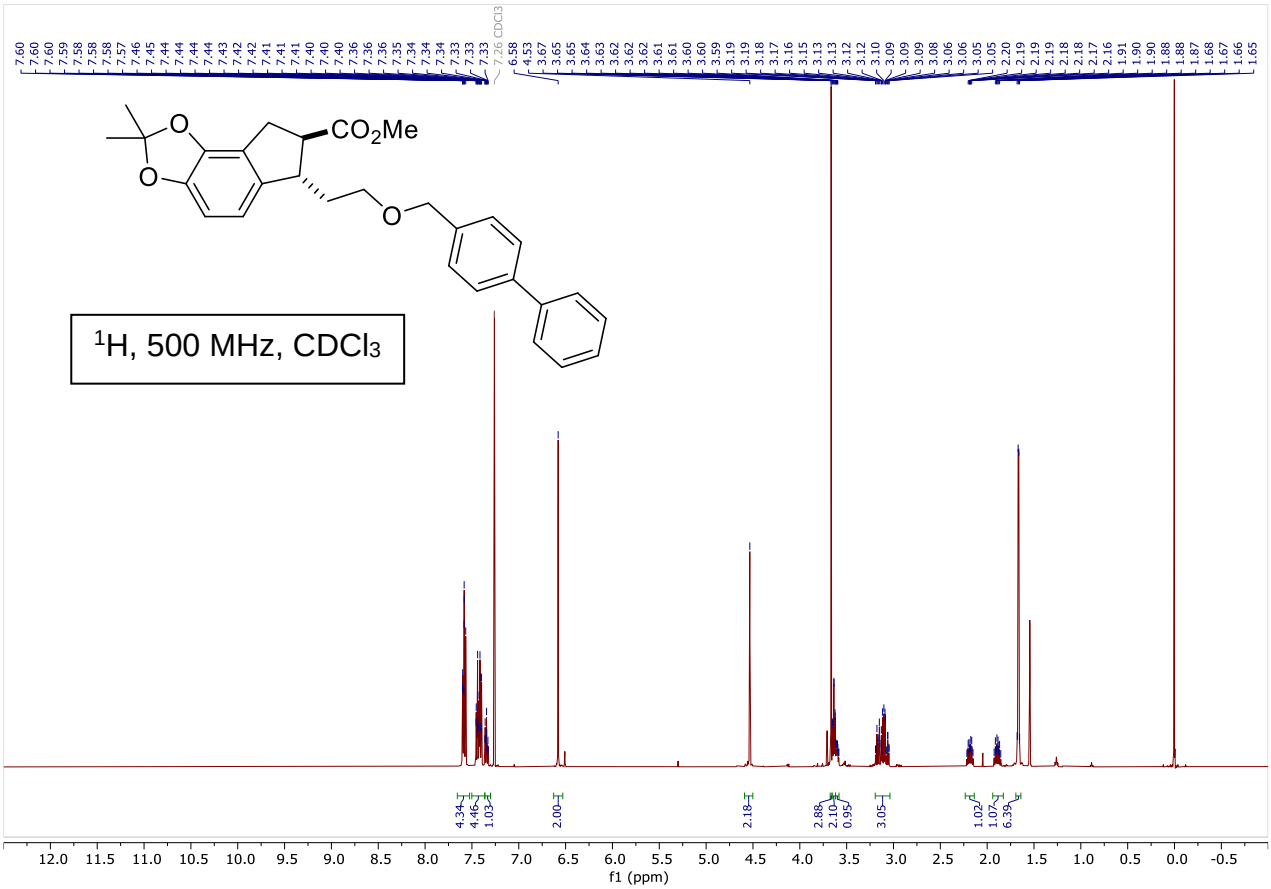
dimethyl 6-(2-([1,1'-biphenyl]-4-ylmethoxy)ethyl)-2,2-dimethyl-6,8-dihydro-7H-indeno[4,5-d][1,3]dioxole-7,7-dicarboxylate (C–H product 4)

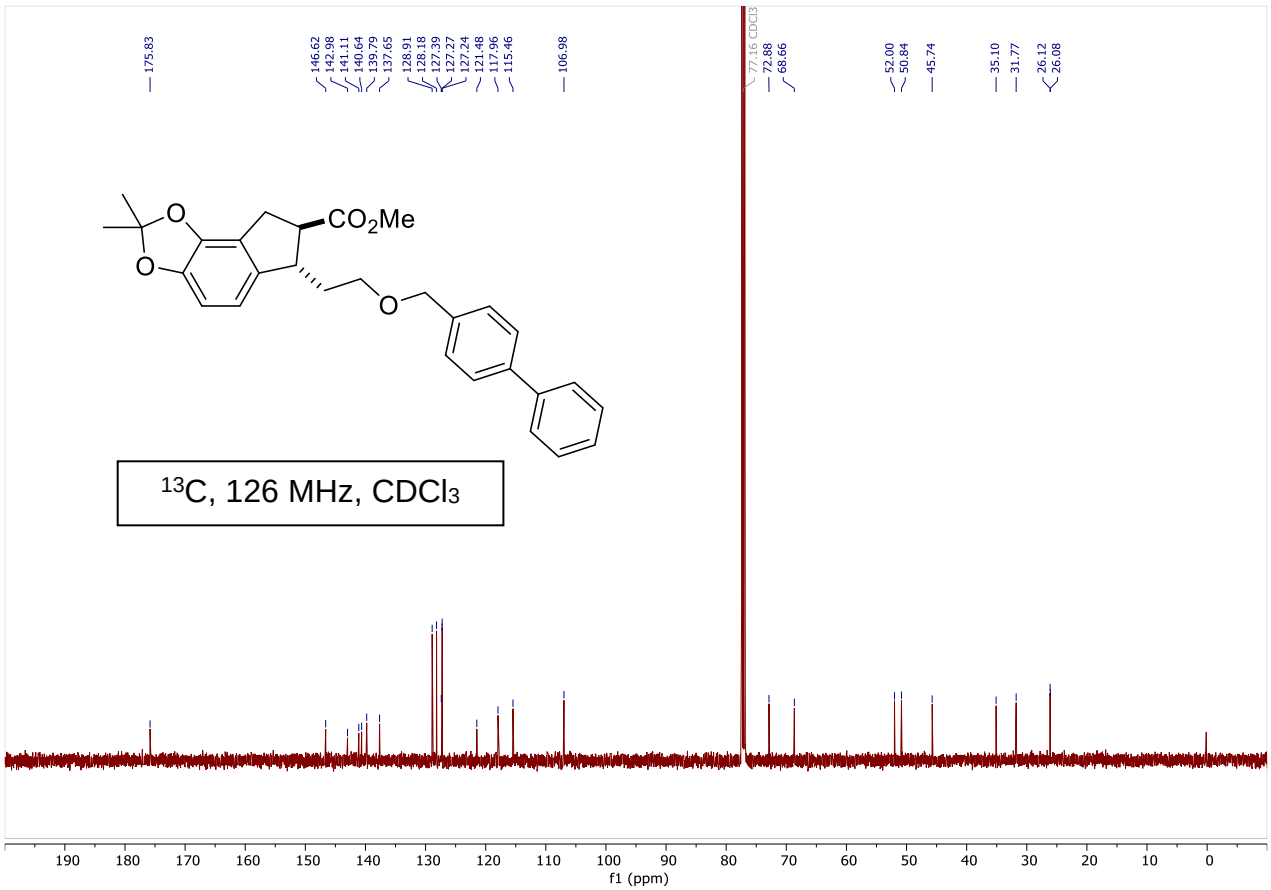




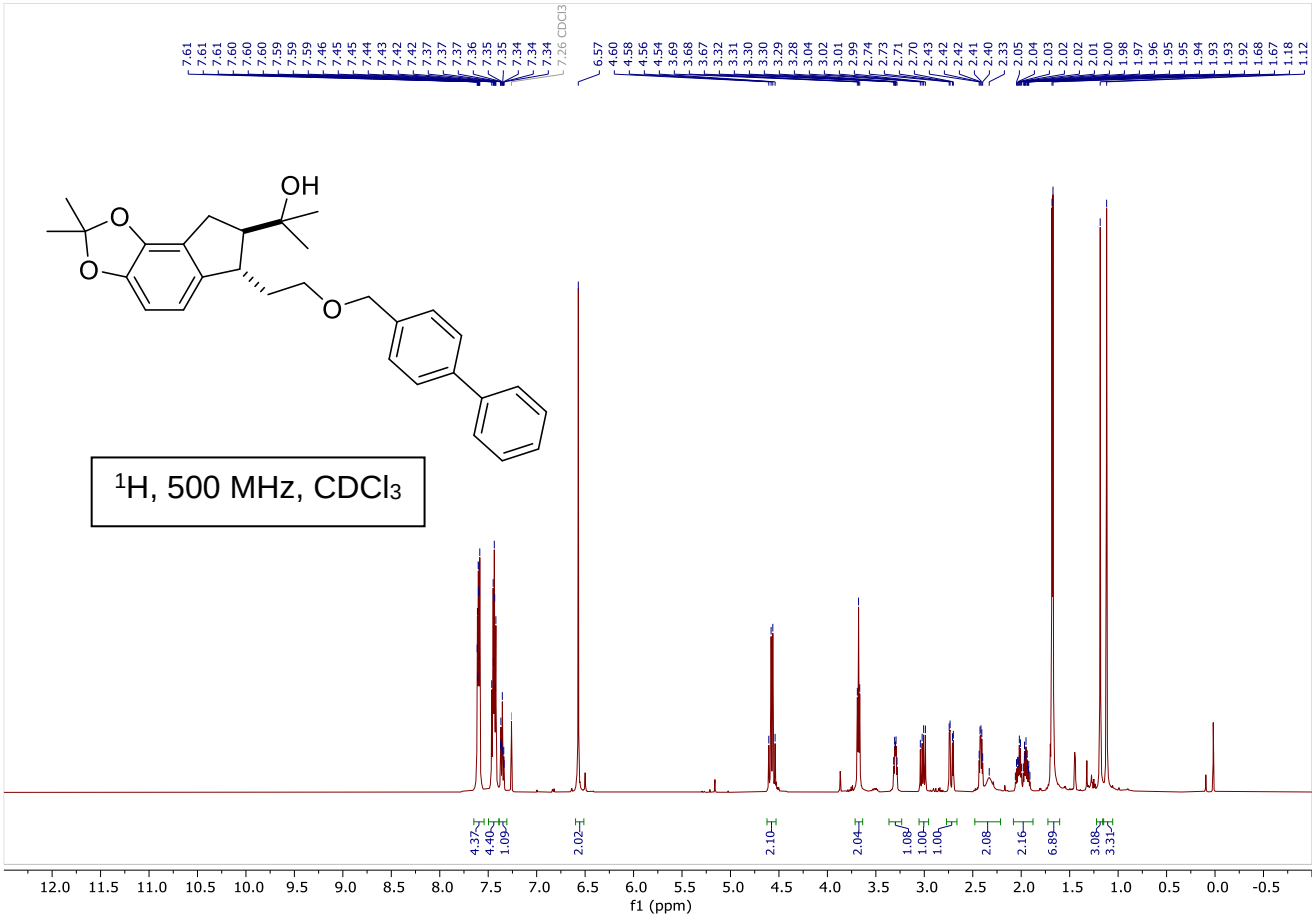
7.2 Common precursor

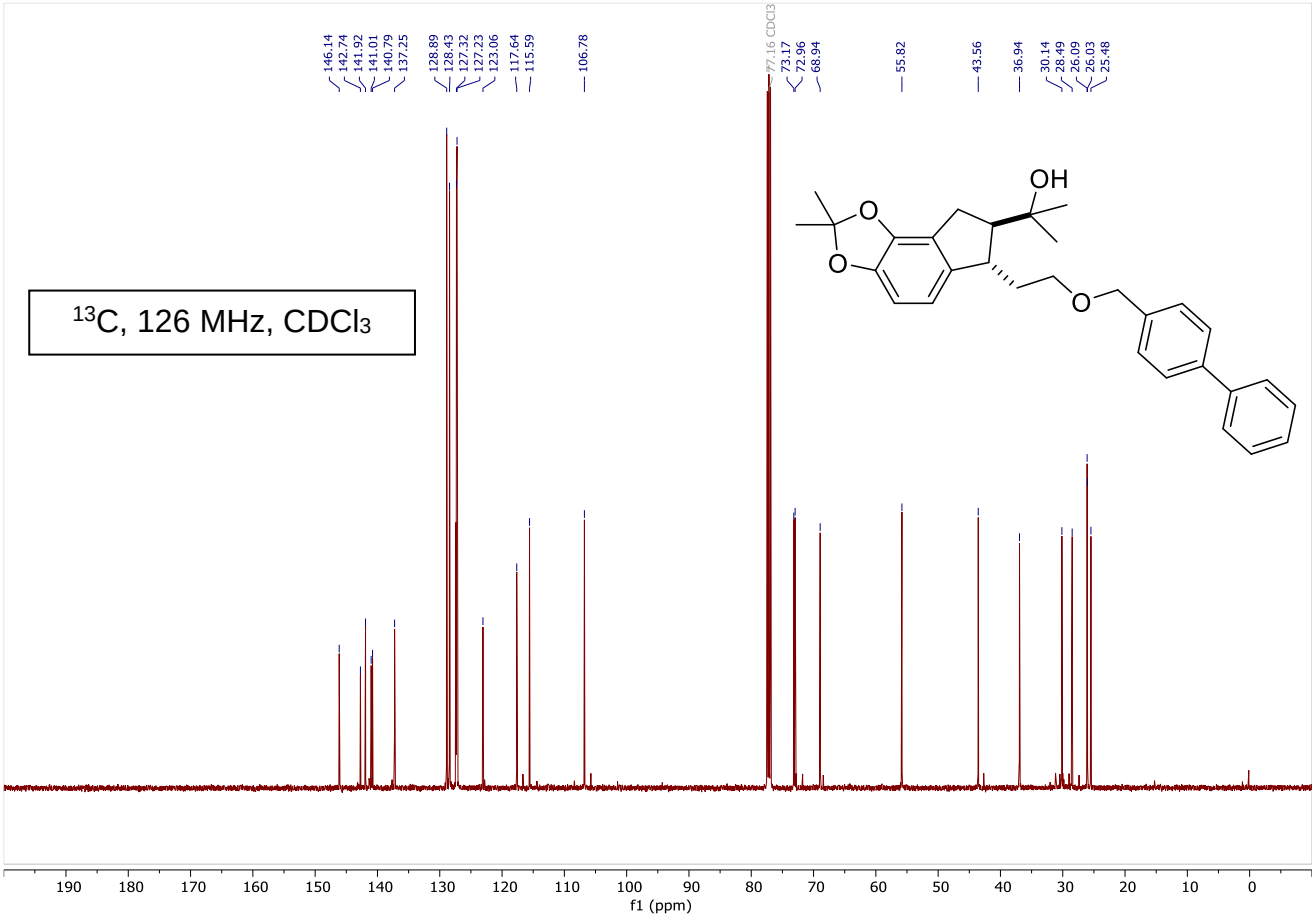
methyl *trans*-6-(2-([1,1'-biphenyl]-4-ylmethoxy)ethyl)-2,2-dimethyl-7,8-dihydro-6H-indeno[4,5-d][1,3]dioxole-7-carboxylate (monoester 12)



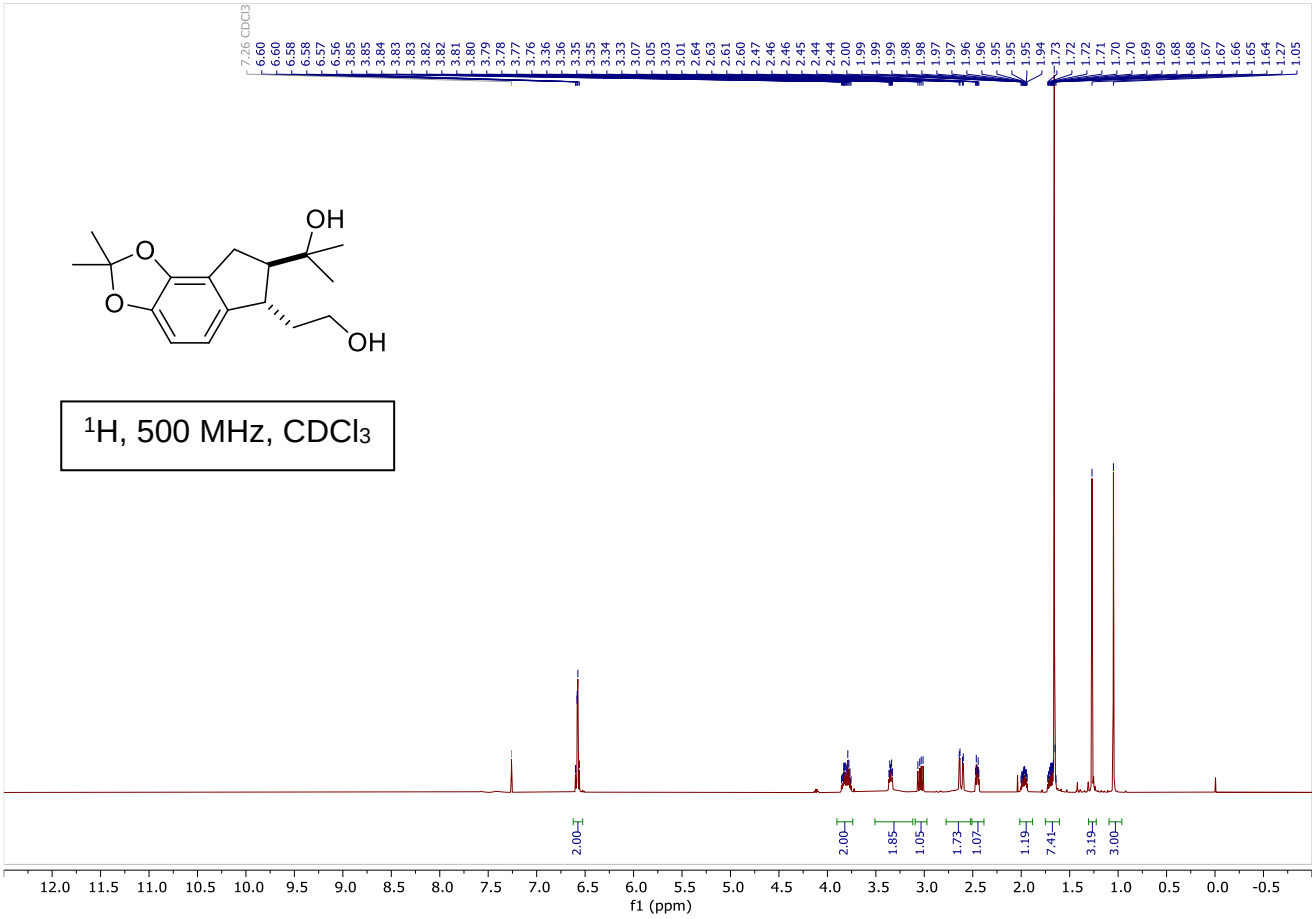


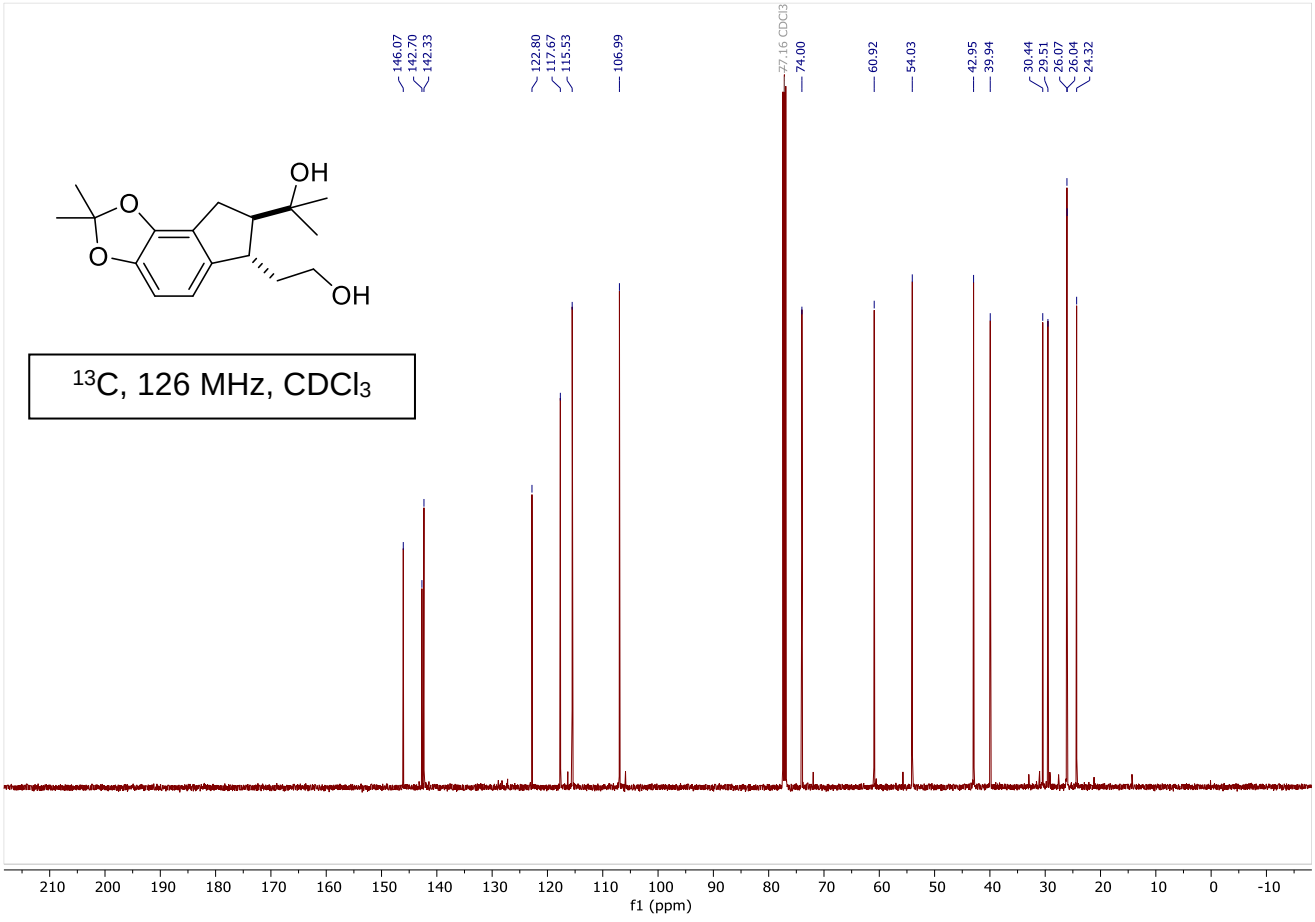
2-((6S,7R)-6-(2-([1,1'-biphenyl]-4-ylmethoxy)ethyl)-2,2-dimethyl-7,8-dihydro-6H-indeno[4,5-d][1,3]dioxol-7-yl)propan-2-ol (monoprotected diol 22)





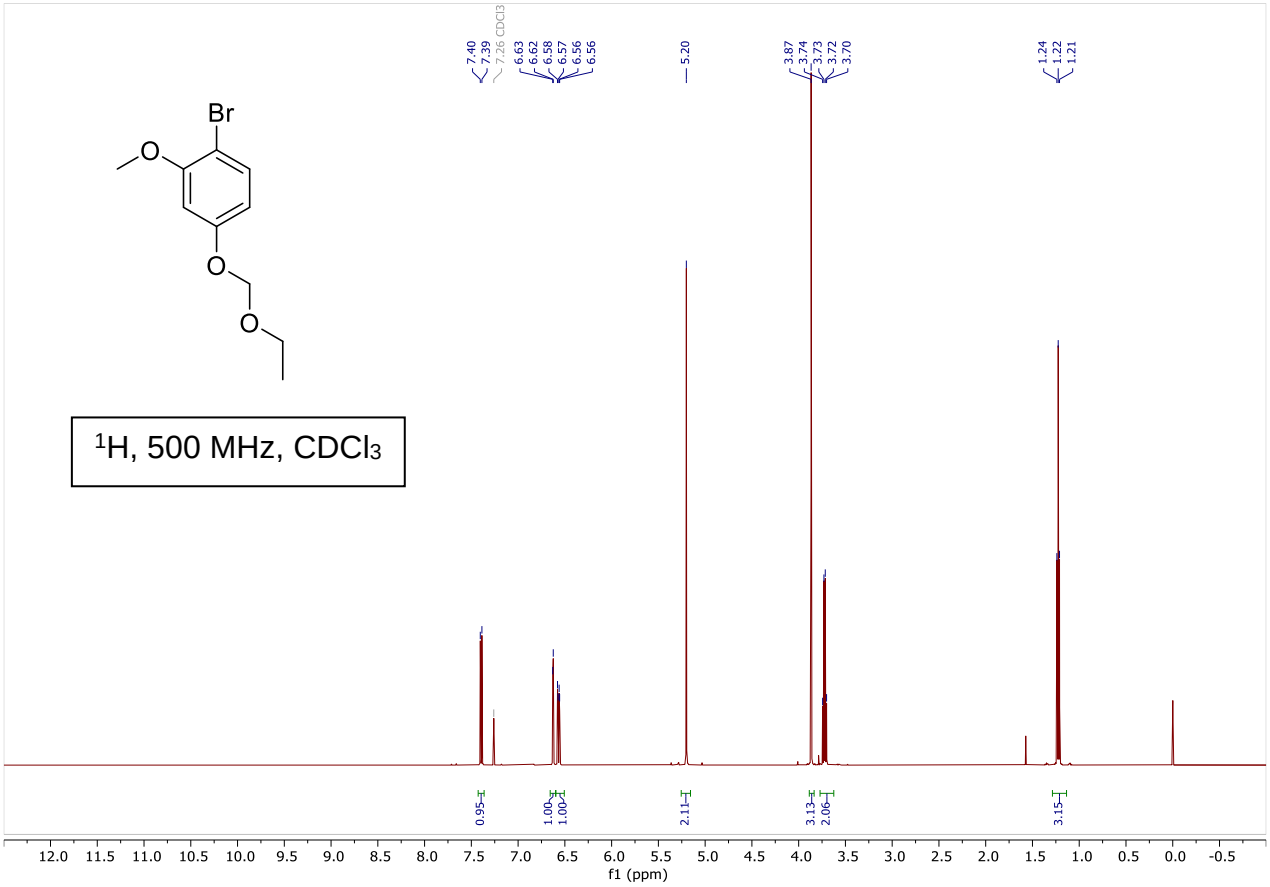
2-((6S,7R)-6-(2-hydroxyethyl)-2,2-dimethyl-7,8-dihydro-6H-indeno[4,5-d][1,3]dioxol-7-yl)propan-2-ol (diol 3)



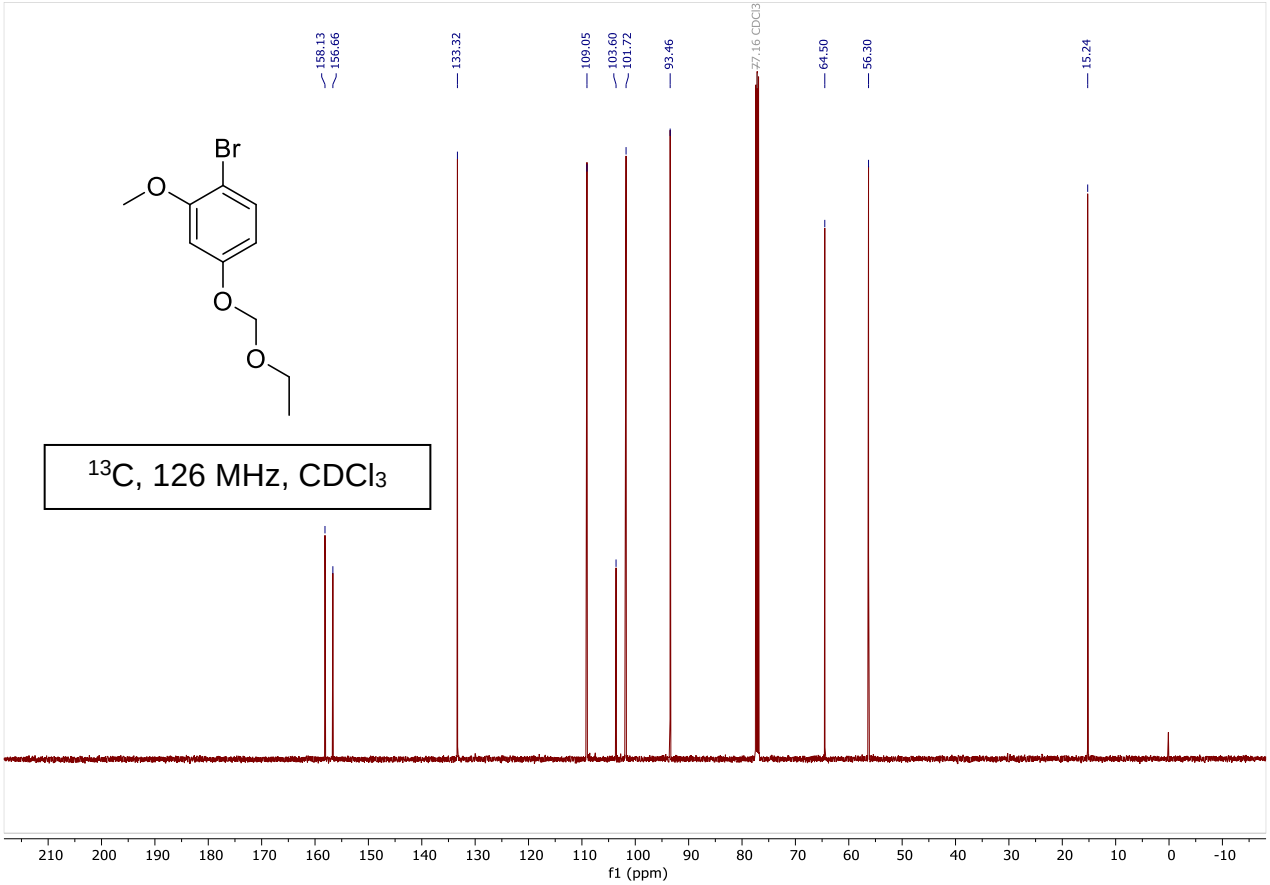


7.3 Divergence towards Indidene C

1-bromo-4-(ethoxymethoxy)-2-methoxybenzene (methoxybromide 24)

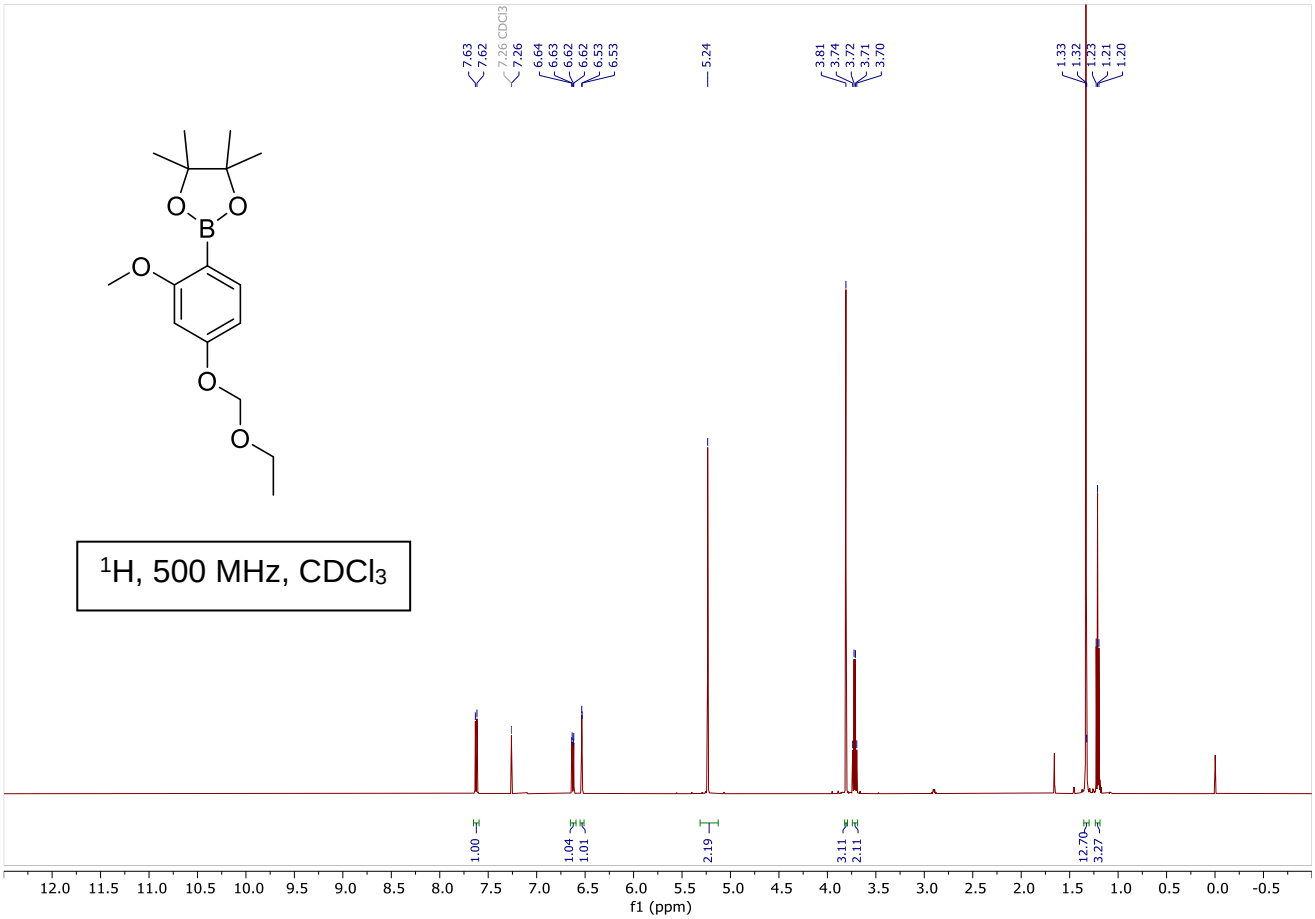


^{1}H, 500 MHz, $CDCl_3$

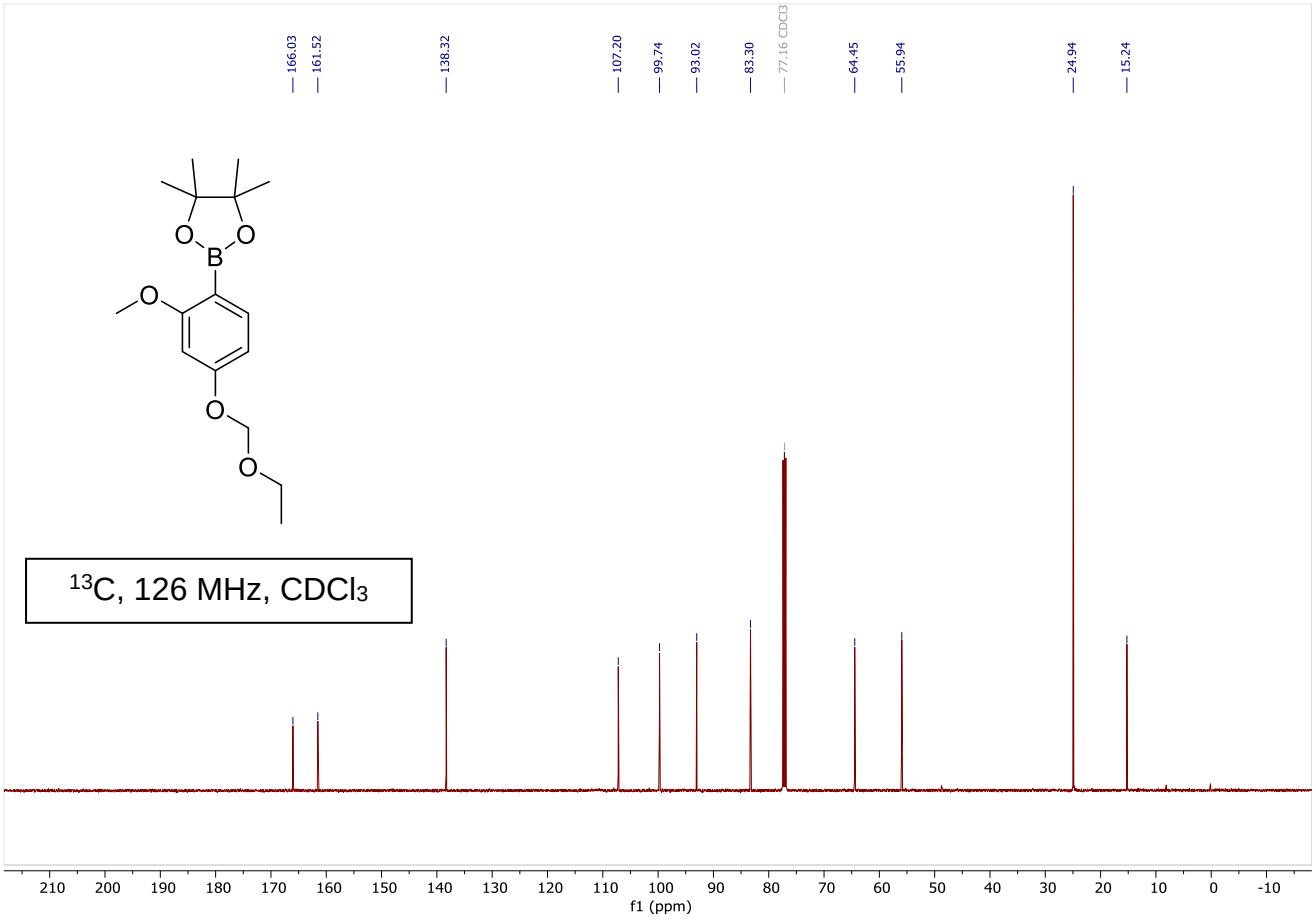


^{13}C, 126 MHz, $CDCl_3$

2-(4-(ethoxymethoxy)-2-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (boronate 14)

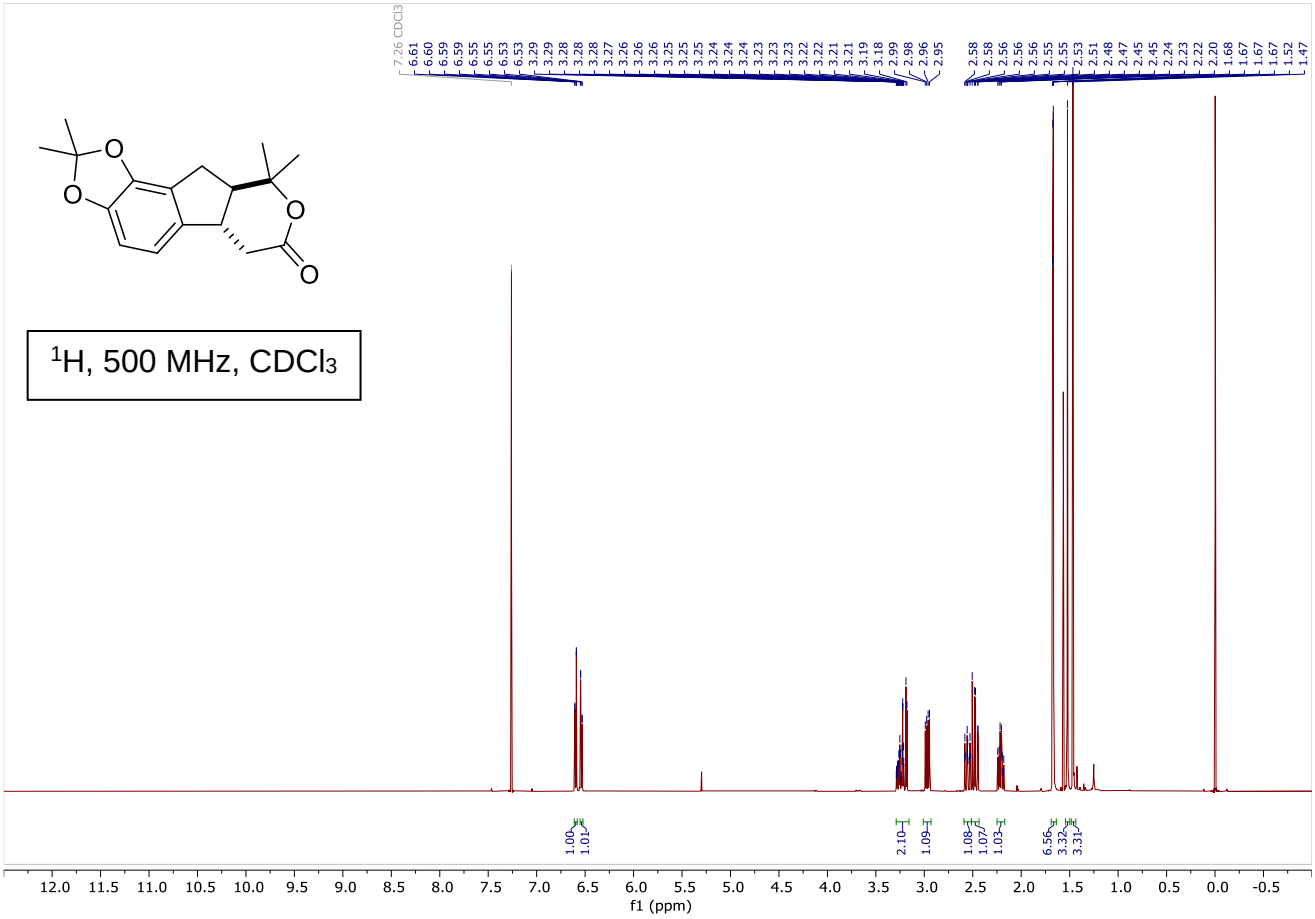


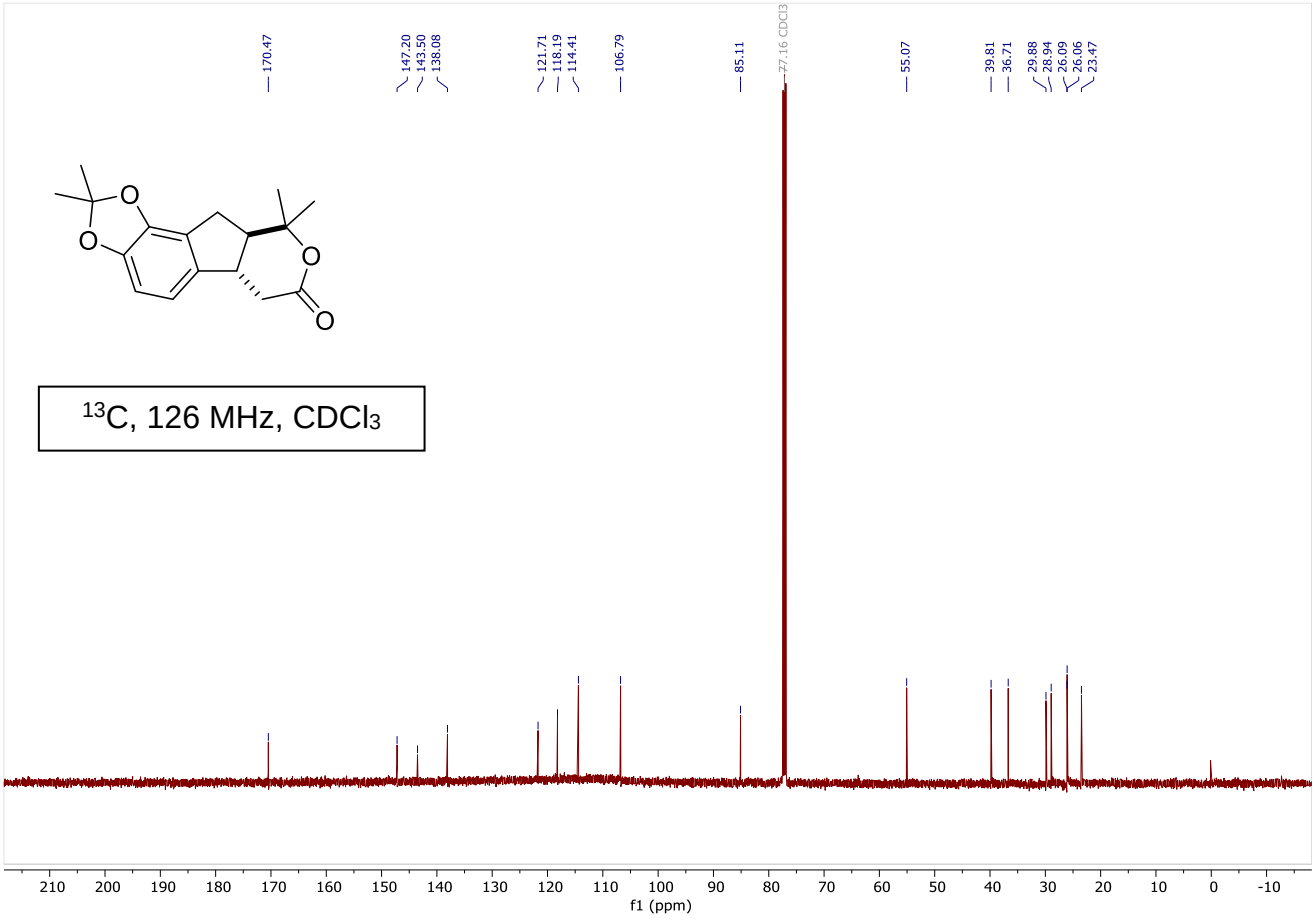
^{1}H, 500 MHz, $CDCl_3$



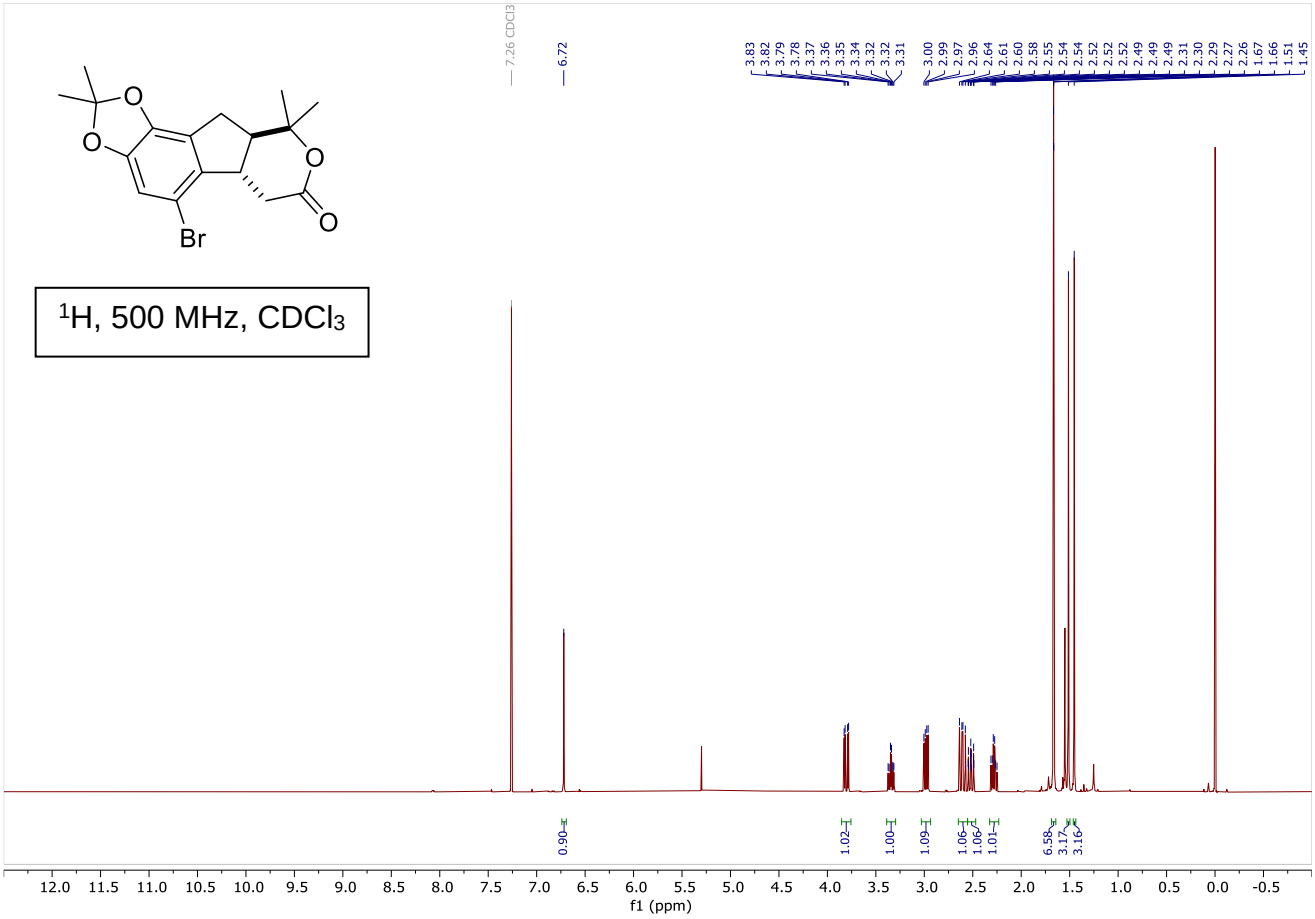
^{13}C, 126 MHz, $CDCl_3$

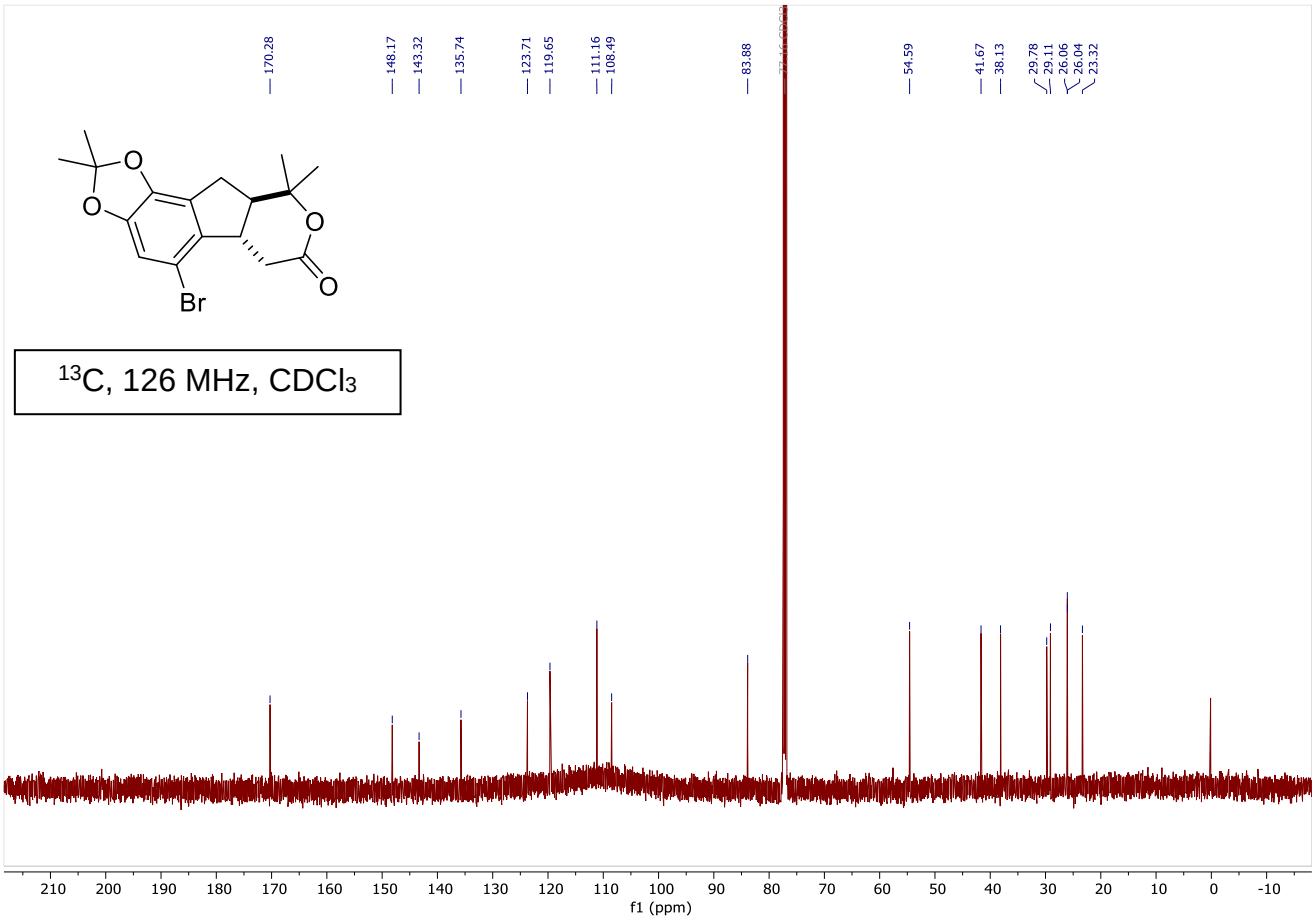
(5bS,9aR)-2,2,9,9-tetramethyl-5b,9,9a,10-tetrahydro-[1,3]dioxolo[4',5':4,5]indeno[2,1-c]pyran-7(6H)-one (lactone 16)



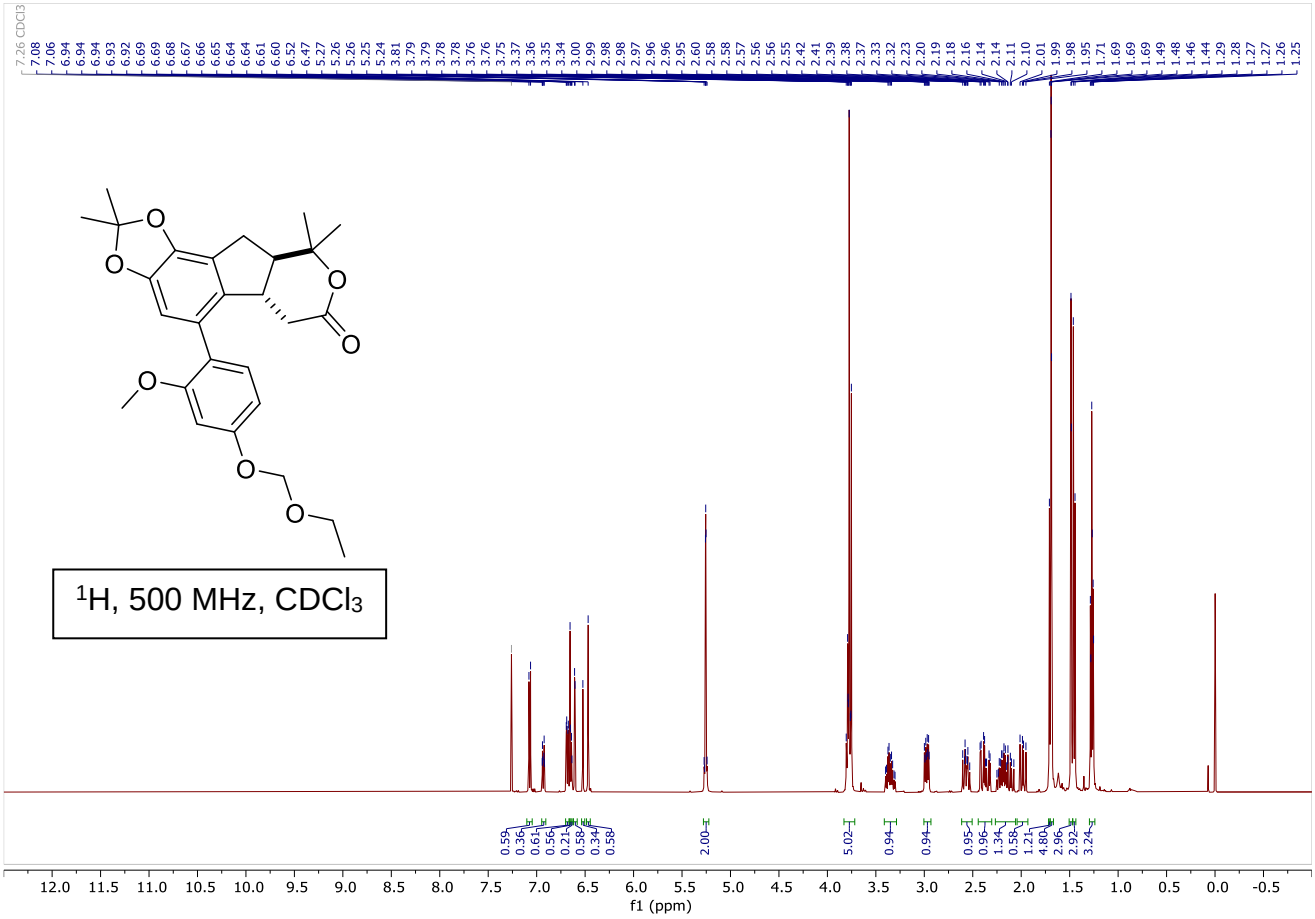


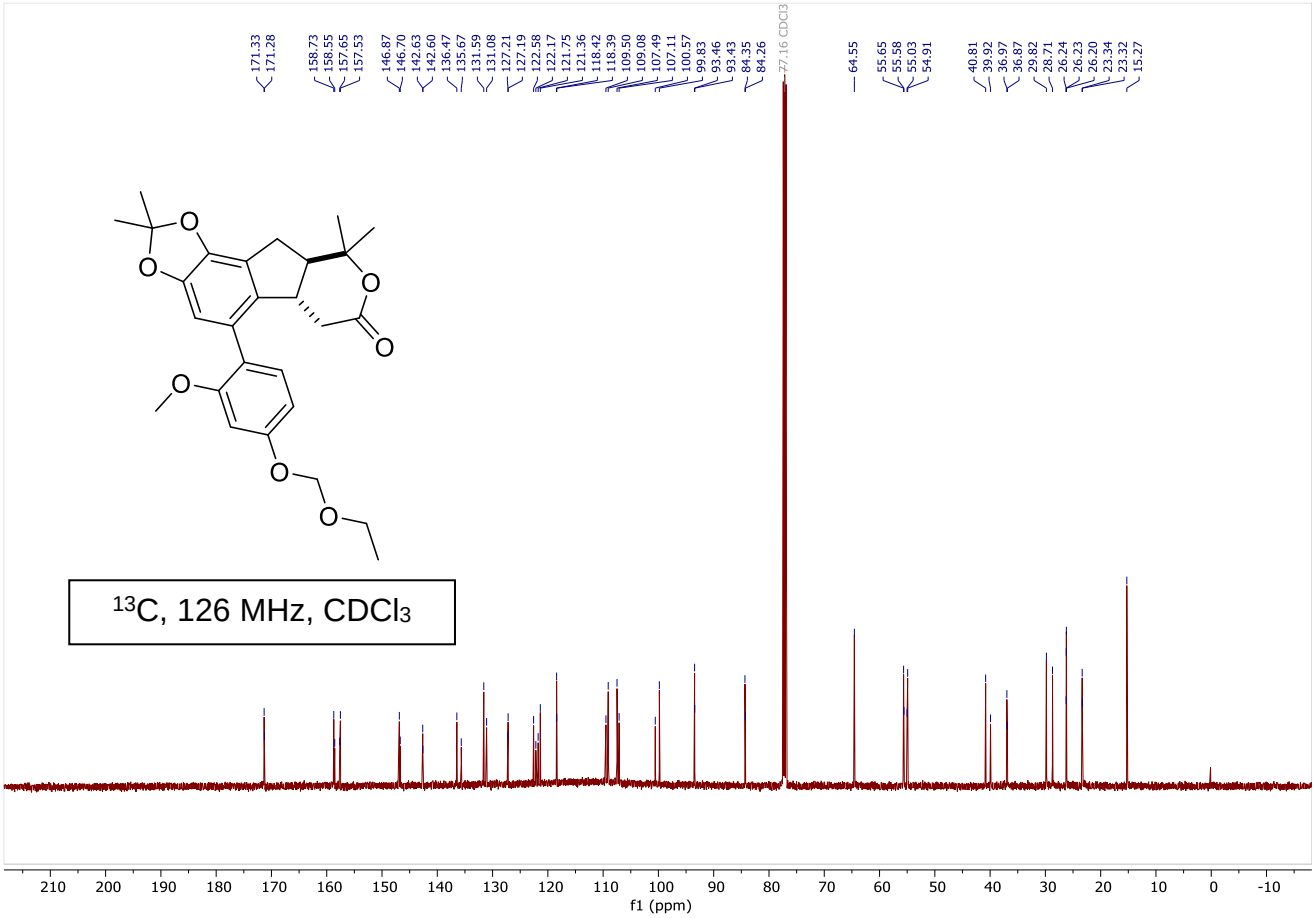
(5bS,9aR)-5-bromo-2,2,9,9-tetramethyl-5b,9,9a,10-tetrahydro-[1,3]dioxolo[4',5':4,5]indeno[2,1-c]pyran-7(6H)-one (bromolactone 13)

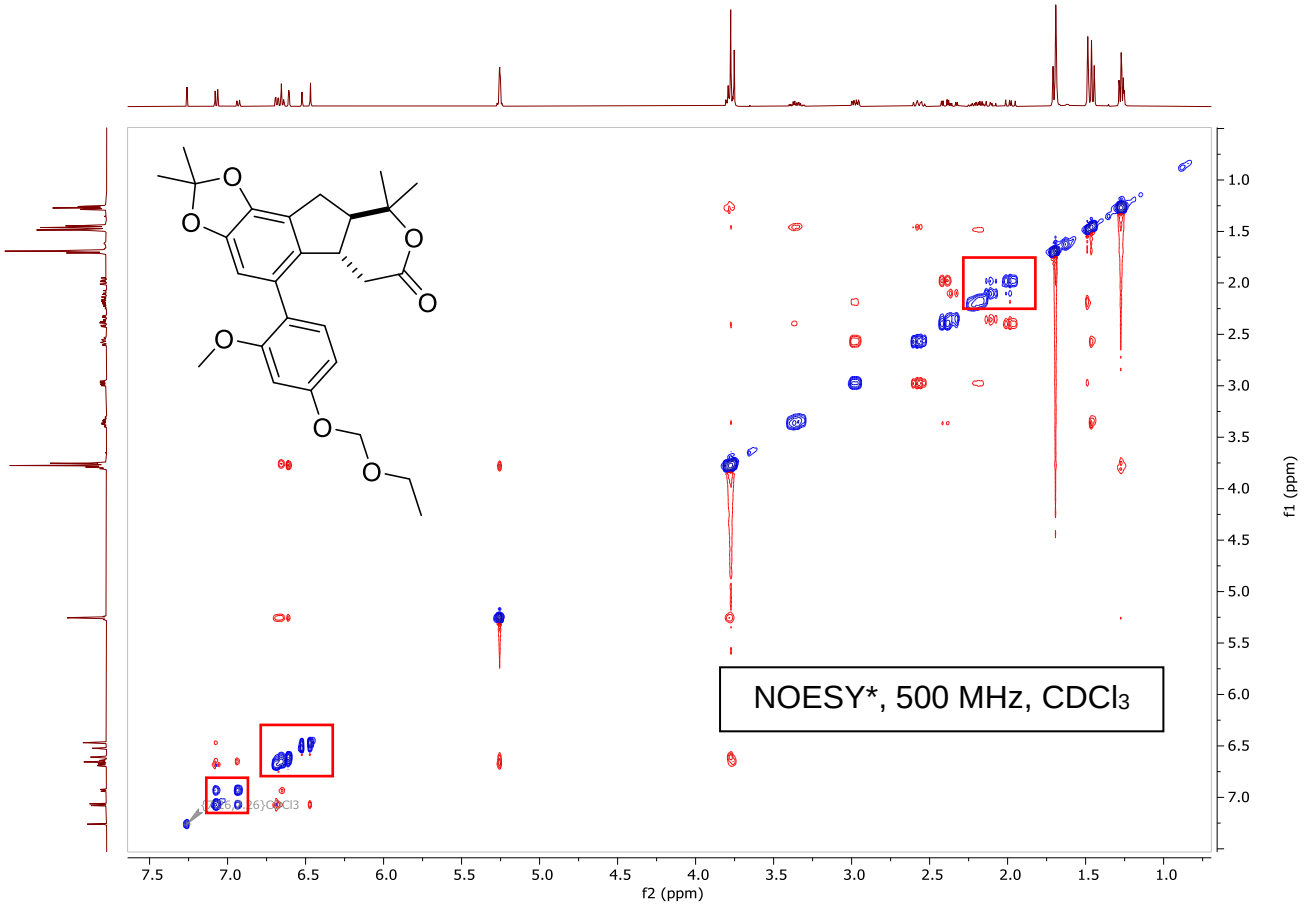




(5bS,9aR)-5-(4-(ethoxymethoxy)-2-methoxyphenyl)-2,2,9,9-tetramethyl-5b,9,9a,10-tetrahydro-[1,3]dioxolo[4',5':4,5]indeno[2,1-c]pyran-7(6H)-one (biphenyl 15)

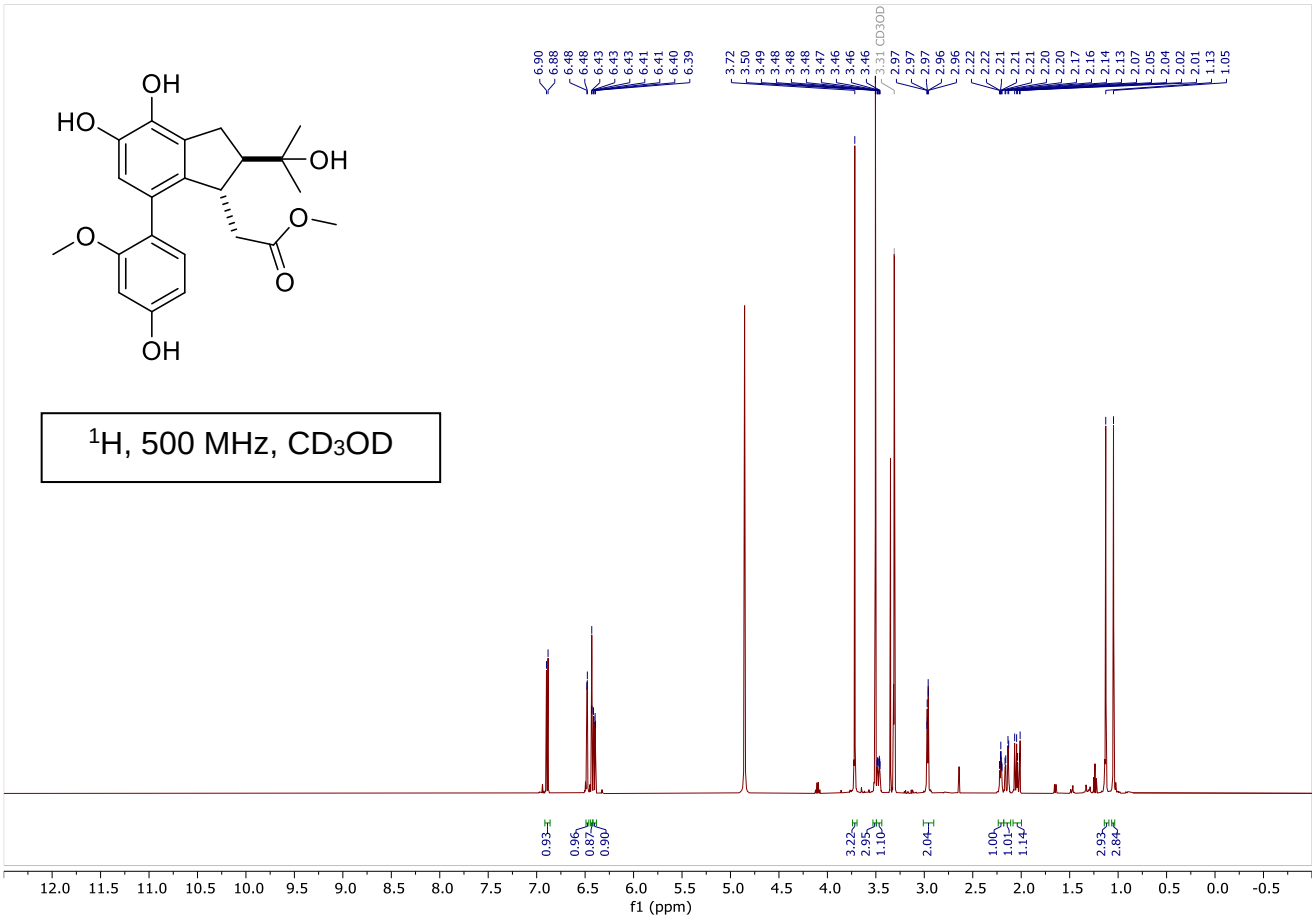


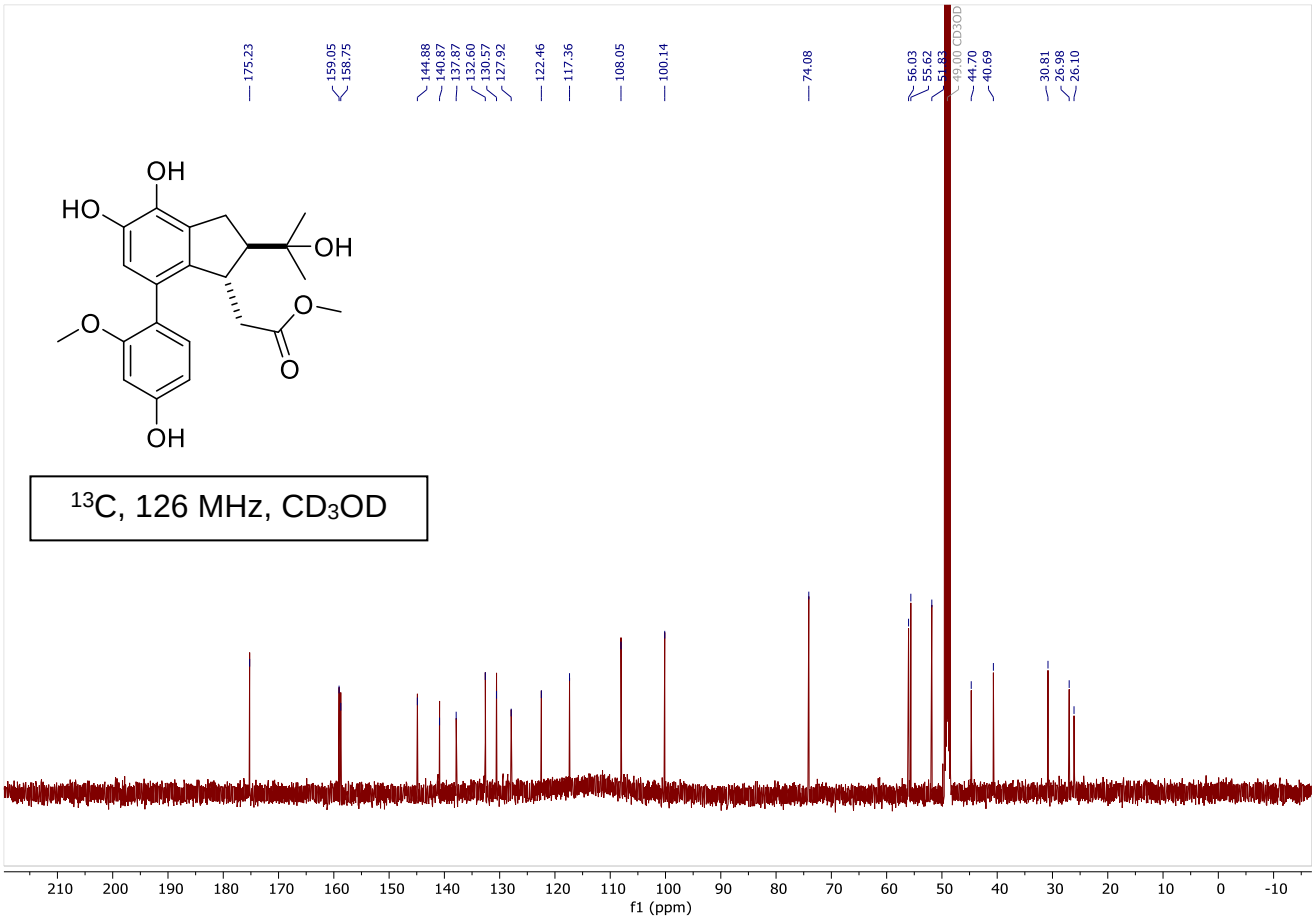


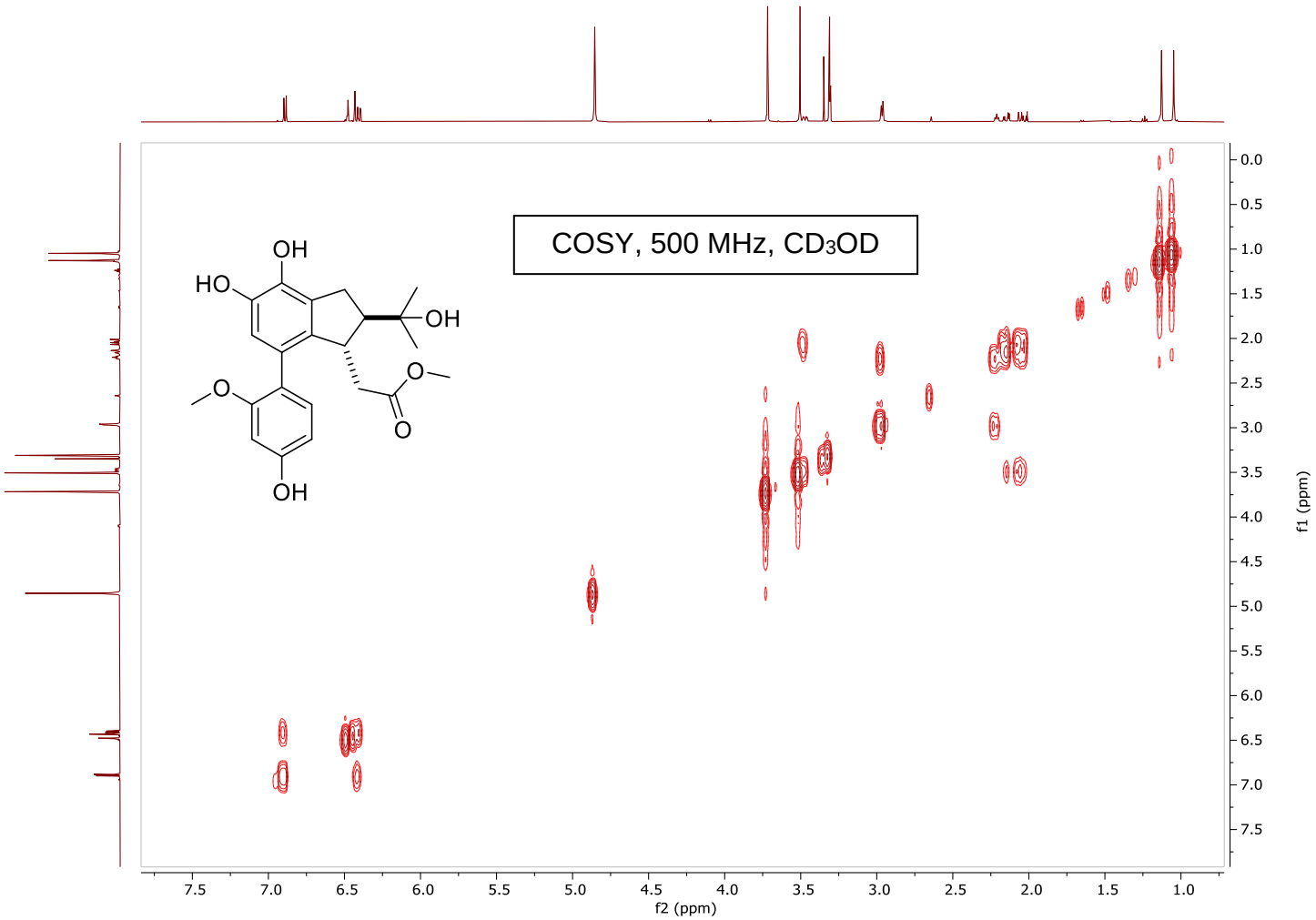


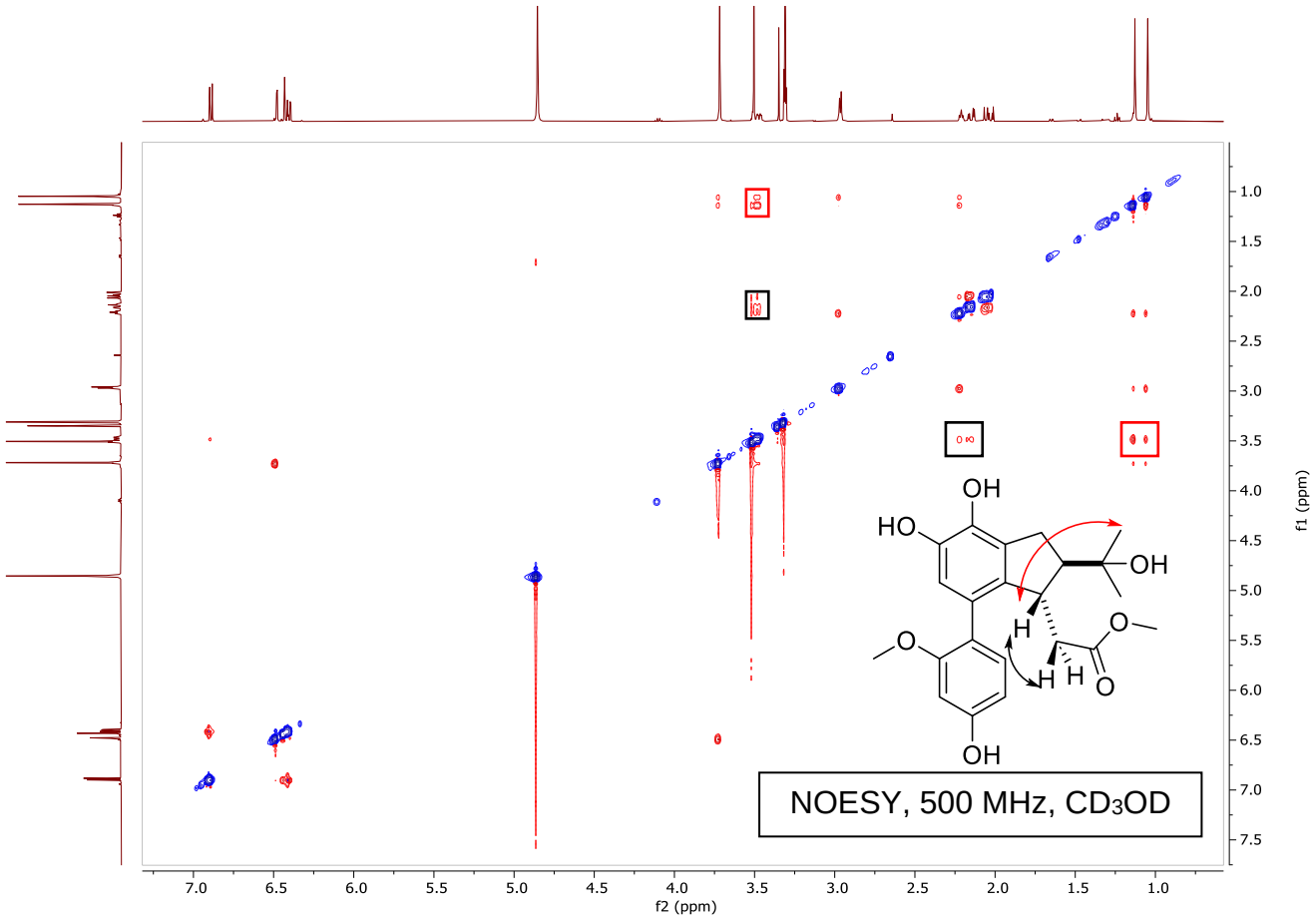
*Highlighted with red boxes are EXSY correlations between major and minor rotamers of biphenyl **15**.

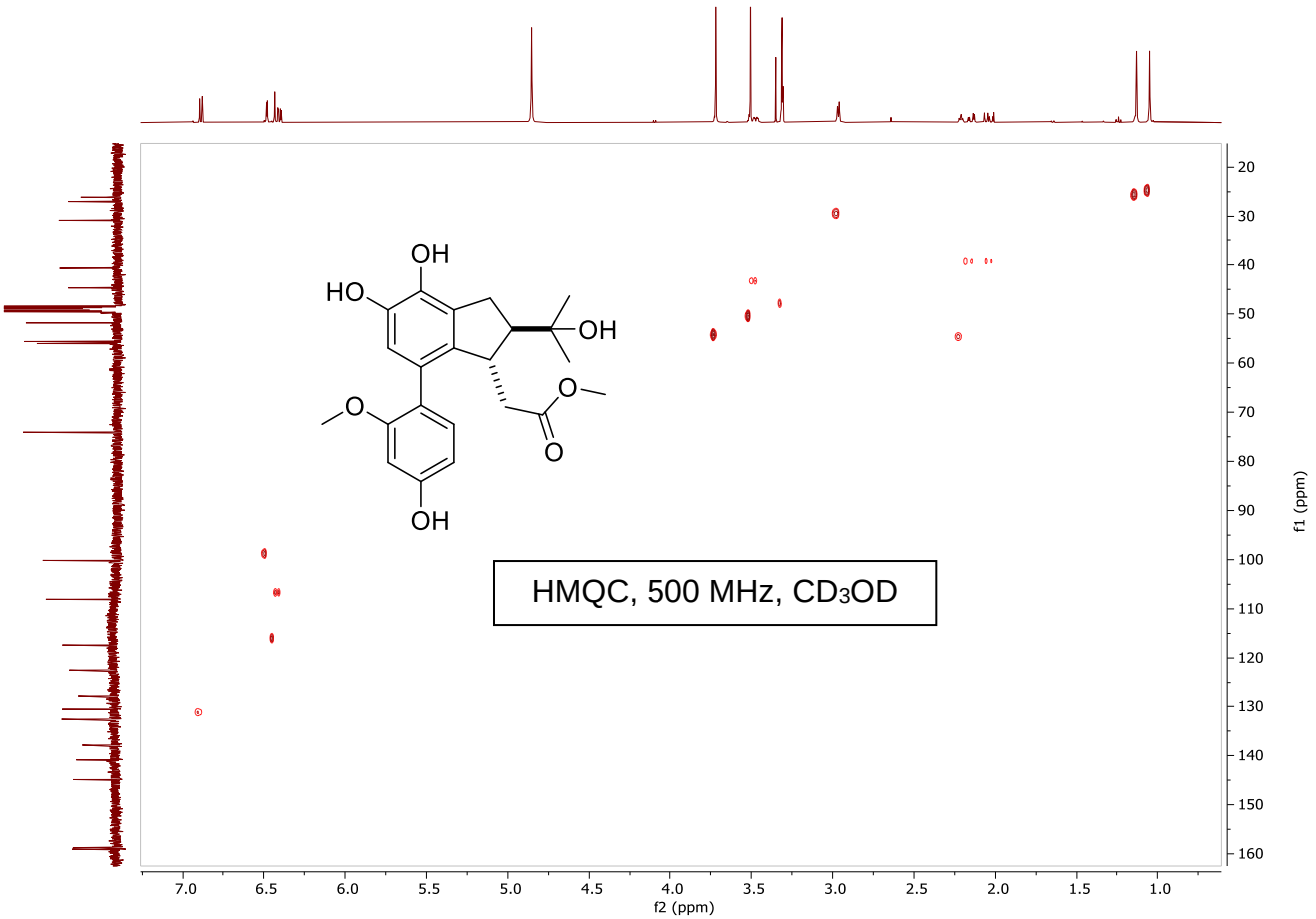
(±)–Indidene C (*rac*-2)

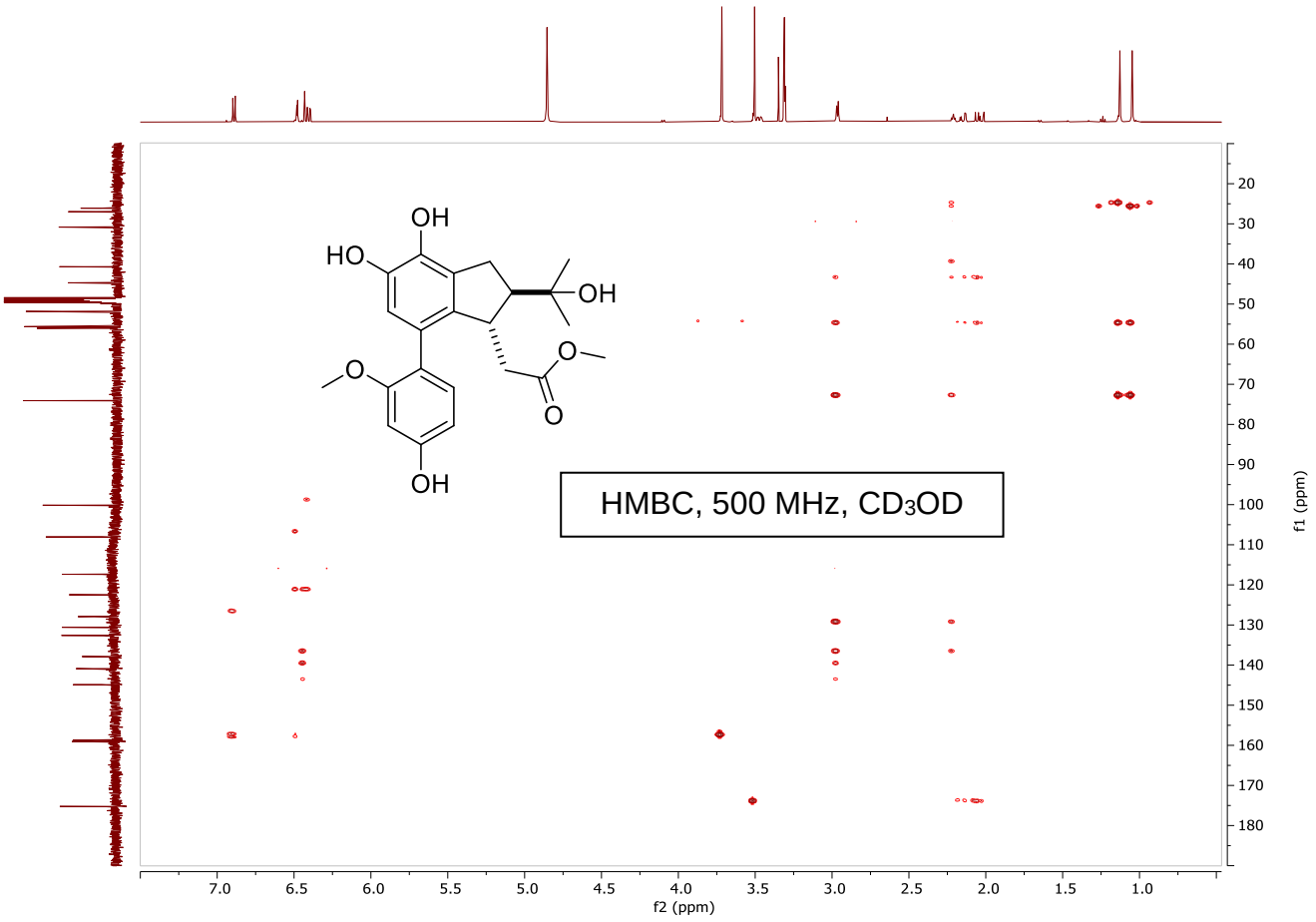




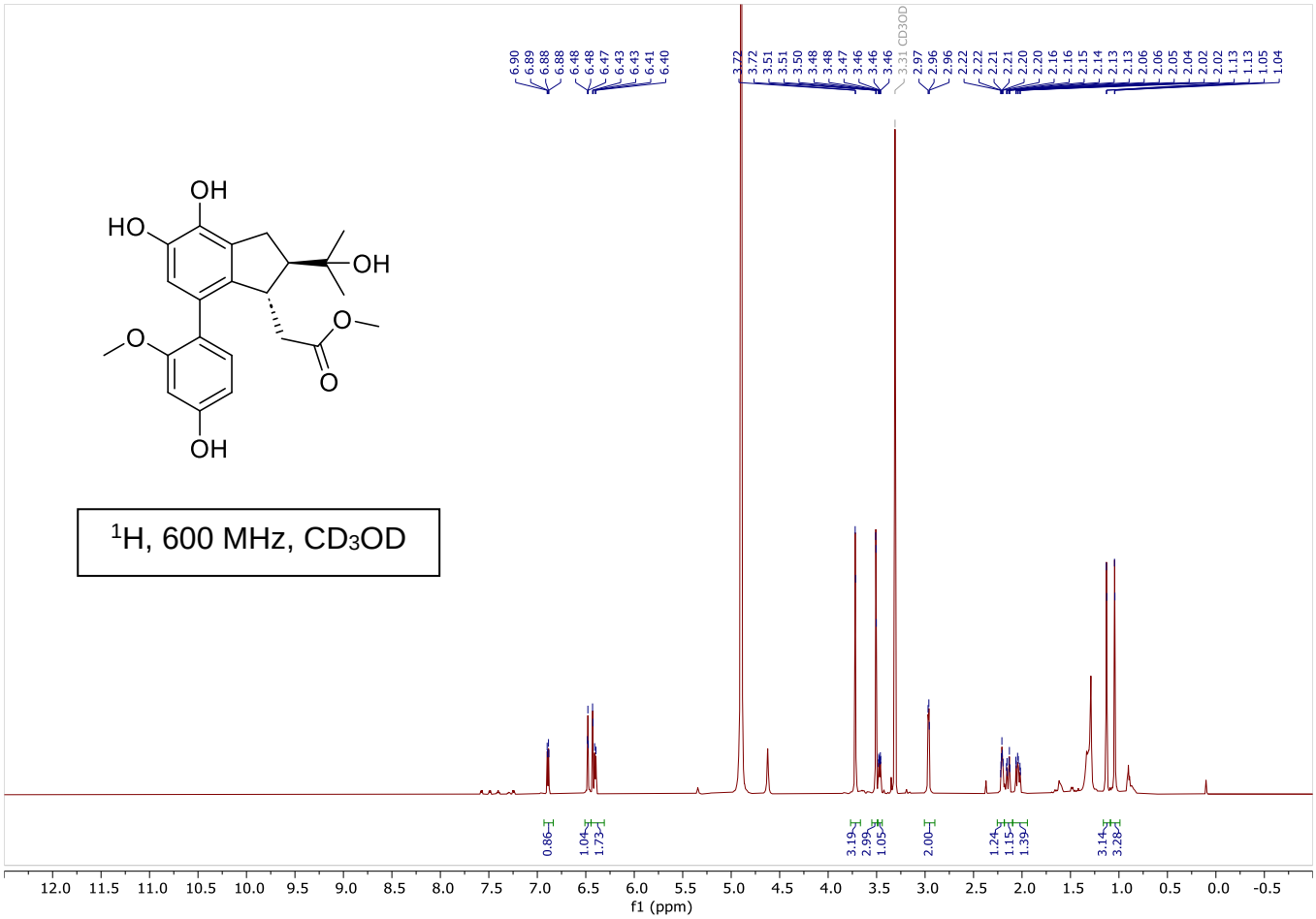

COSY, 500 MHz, CD3OD
OH
HO
OH
O
O
O
OH
f2 (ppm)
f1 (ppm)

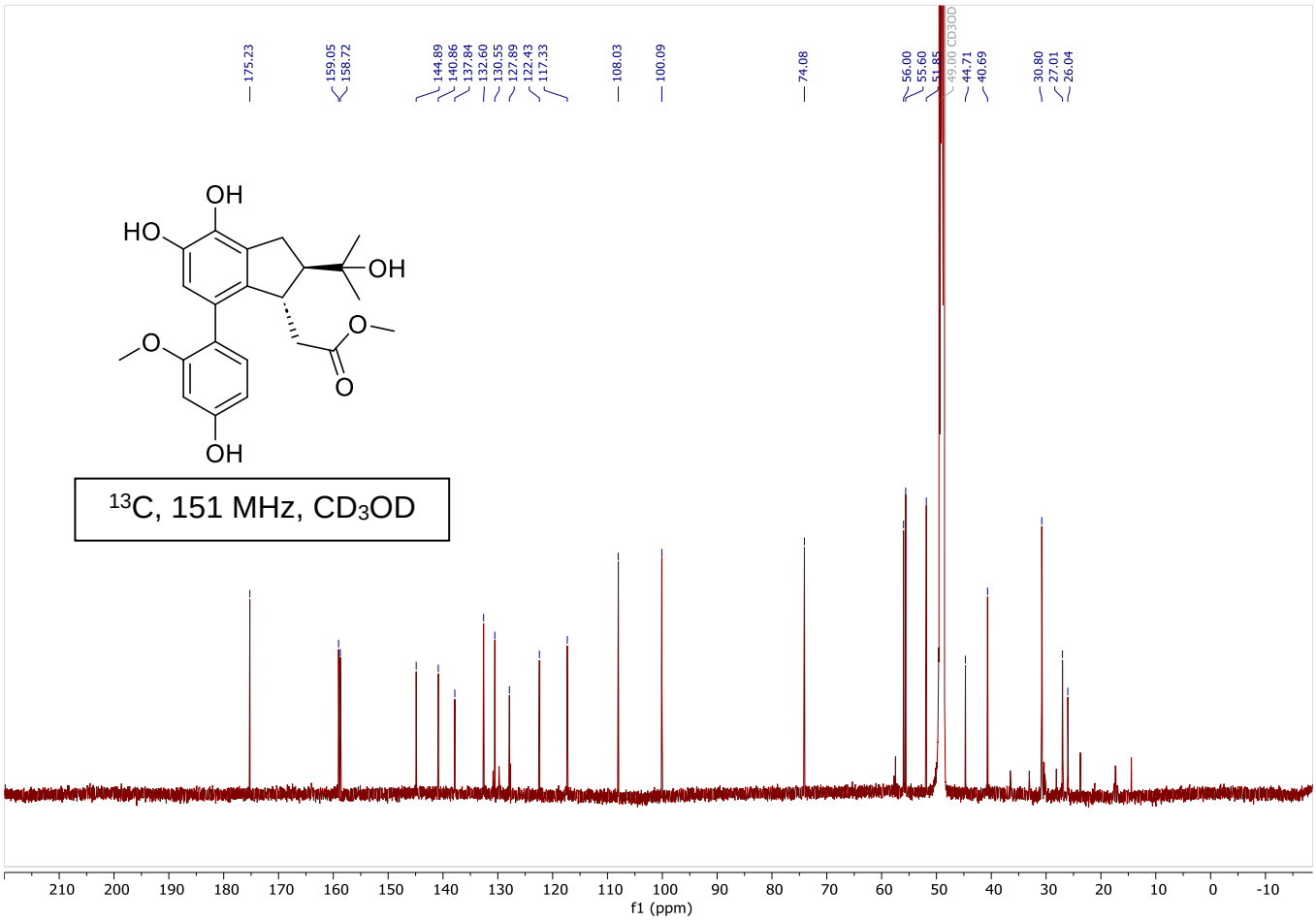

NOESY, 500 MHz, CD3OD
OH
HO
OH
H
O
H H
O
OH
f2 (ppm)
f1 (ppm)


OH
HO
OH
O
O
OH
HMQC, 500 MHz, CD3OD
f2 (ppm)
f1 (ppm)


OH
HO
OH
O
O
OH
HMBC, 500 MHz, CD3OD
f2 (ppm)
f1 (ppm)

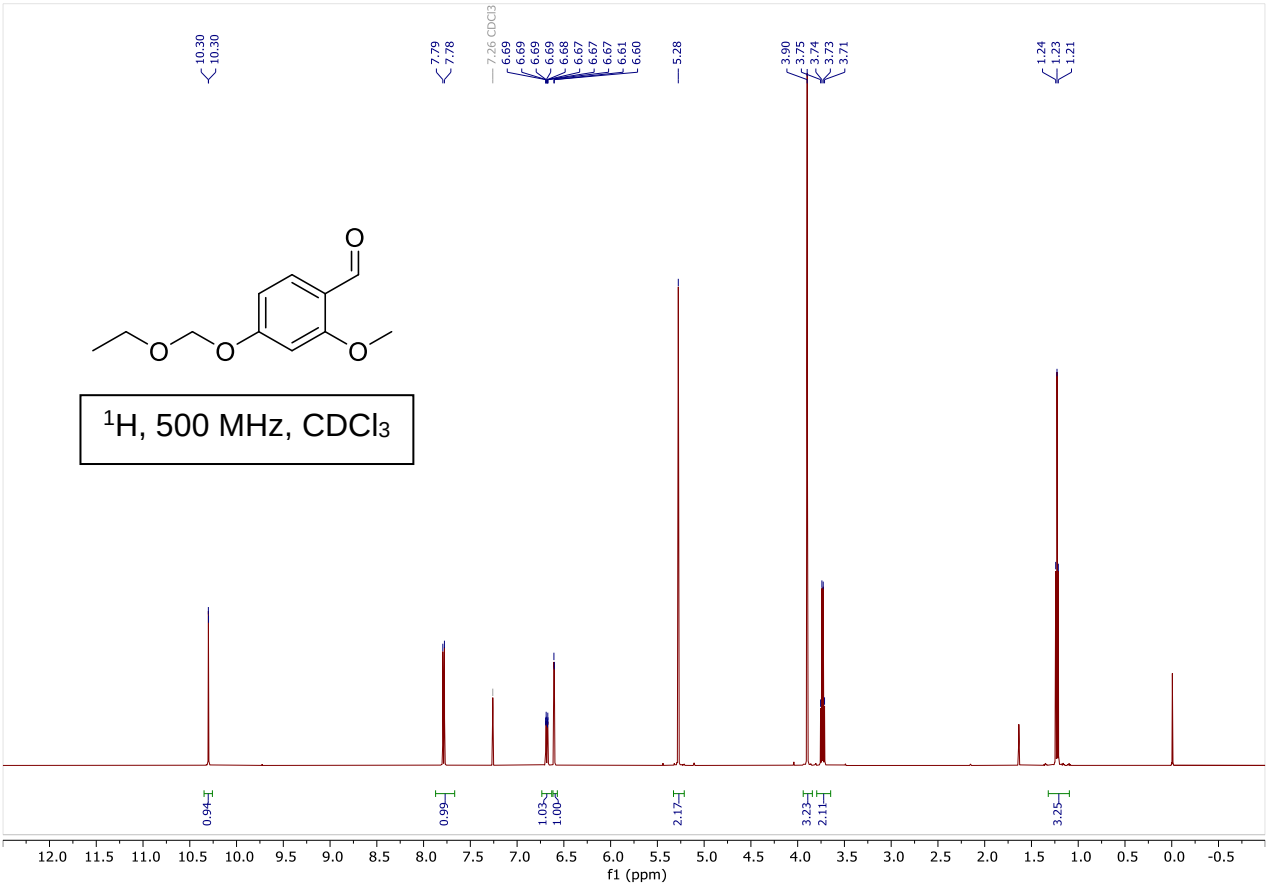
(*S*,*R*)–Indidene C ((*S*,*R*)-2)



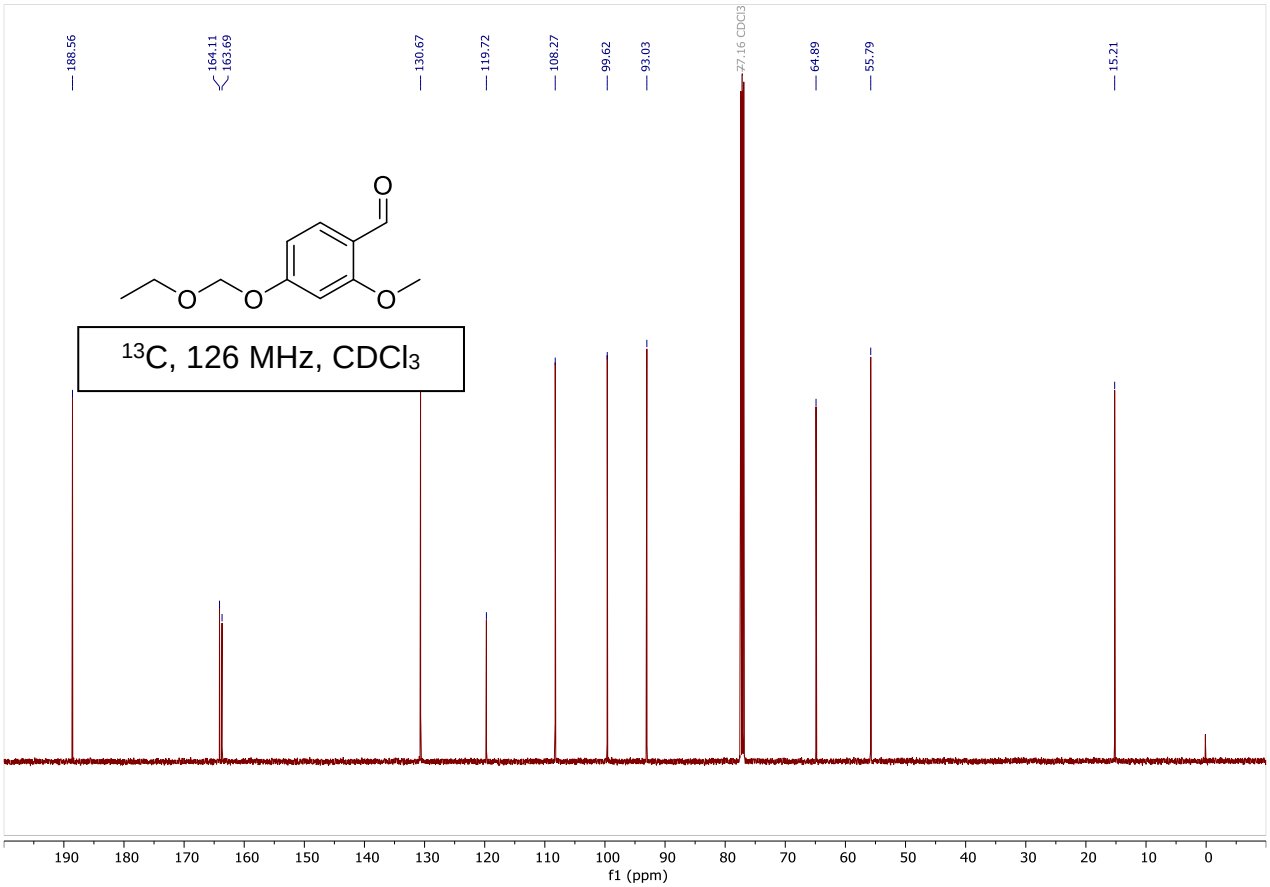


7.4 Divergence towards Indidene A

4-(ethoxymethoxy)-2-methoxybenzaldehyde (aldehyde 26)

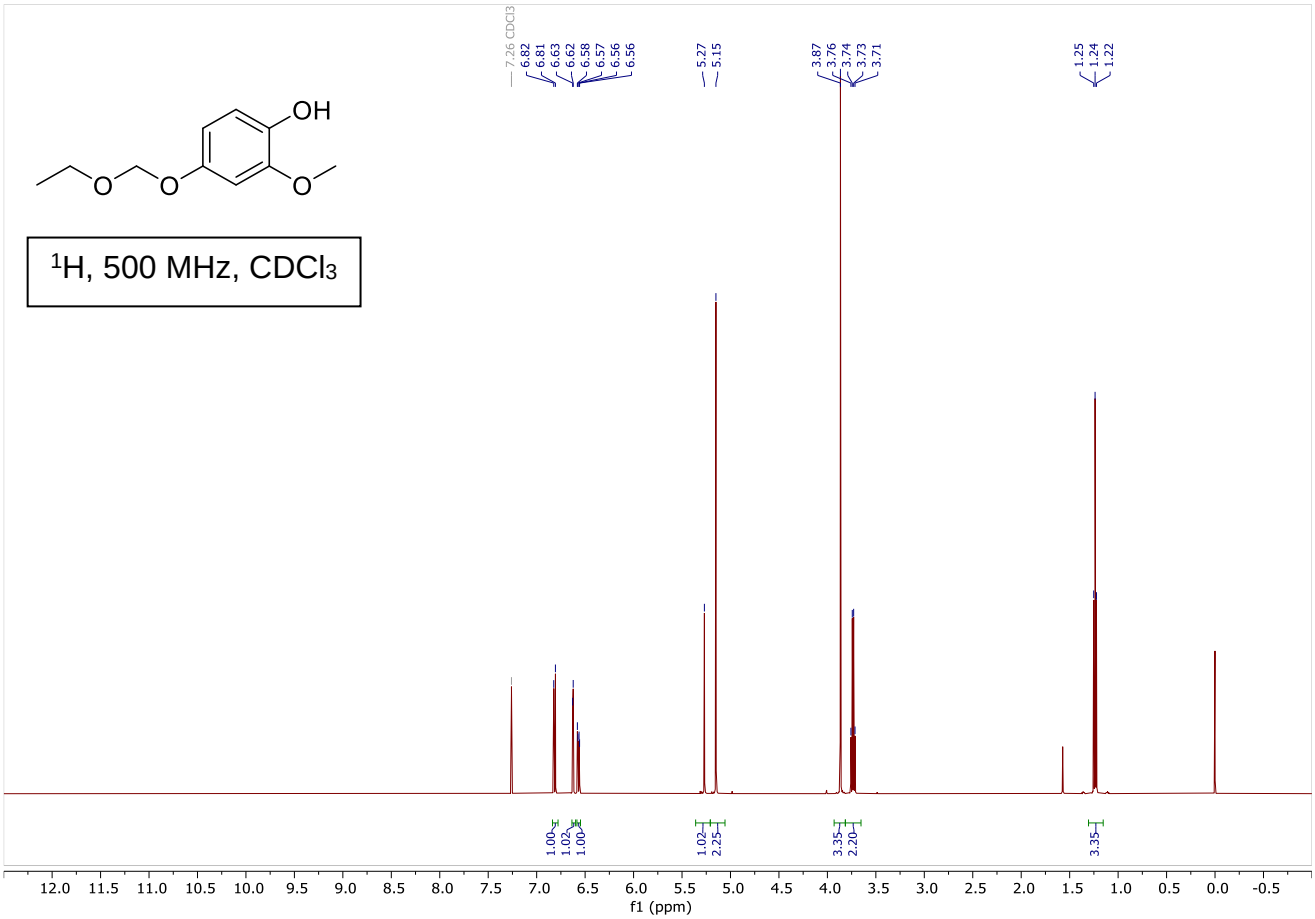


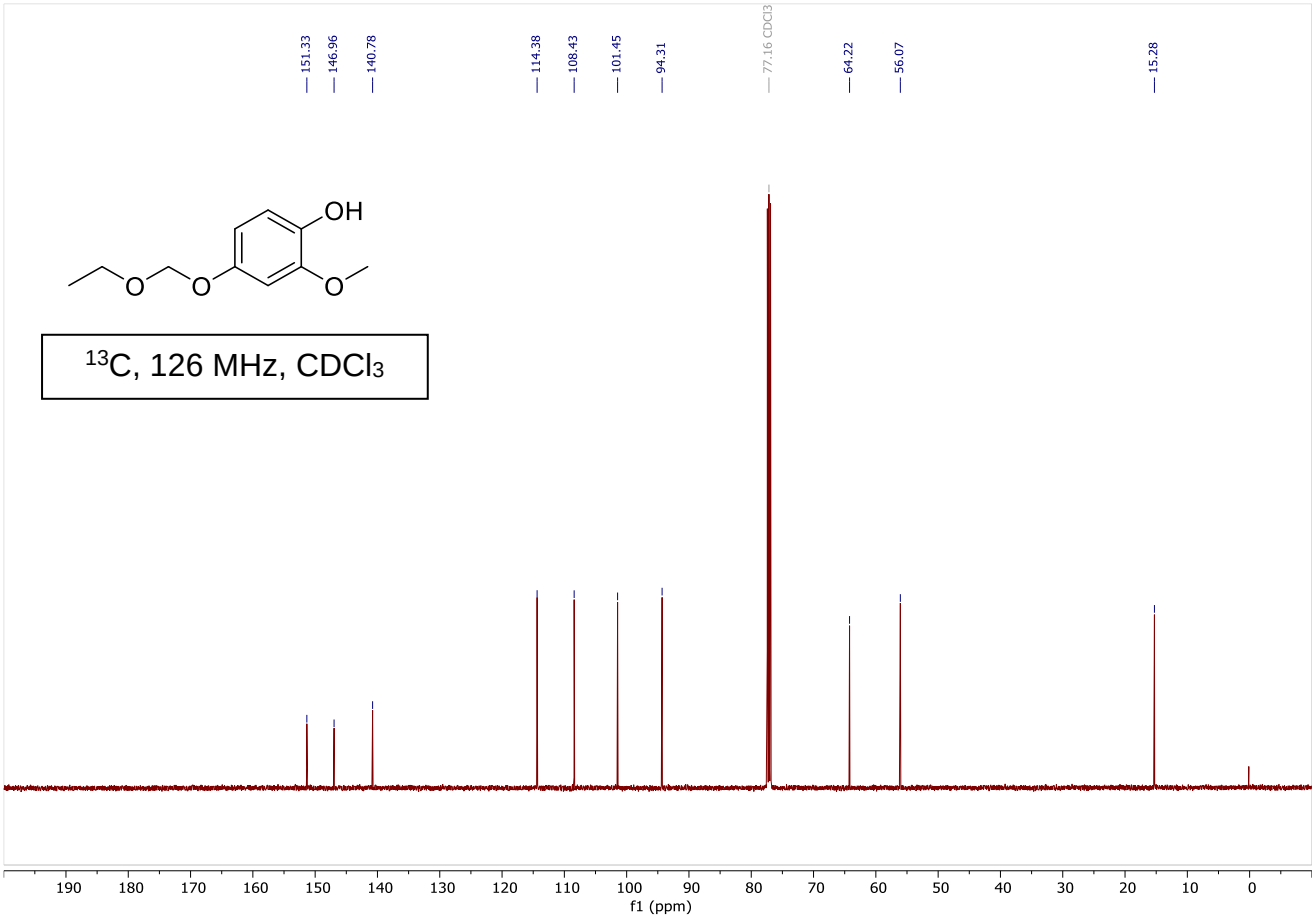
^{1}H, 500 MHz, $CDCl_3$



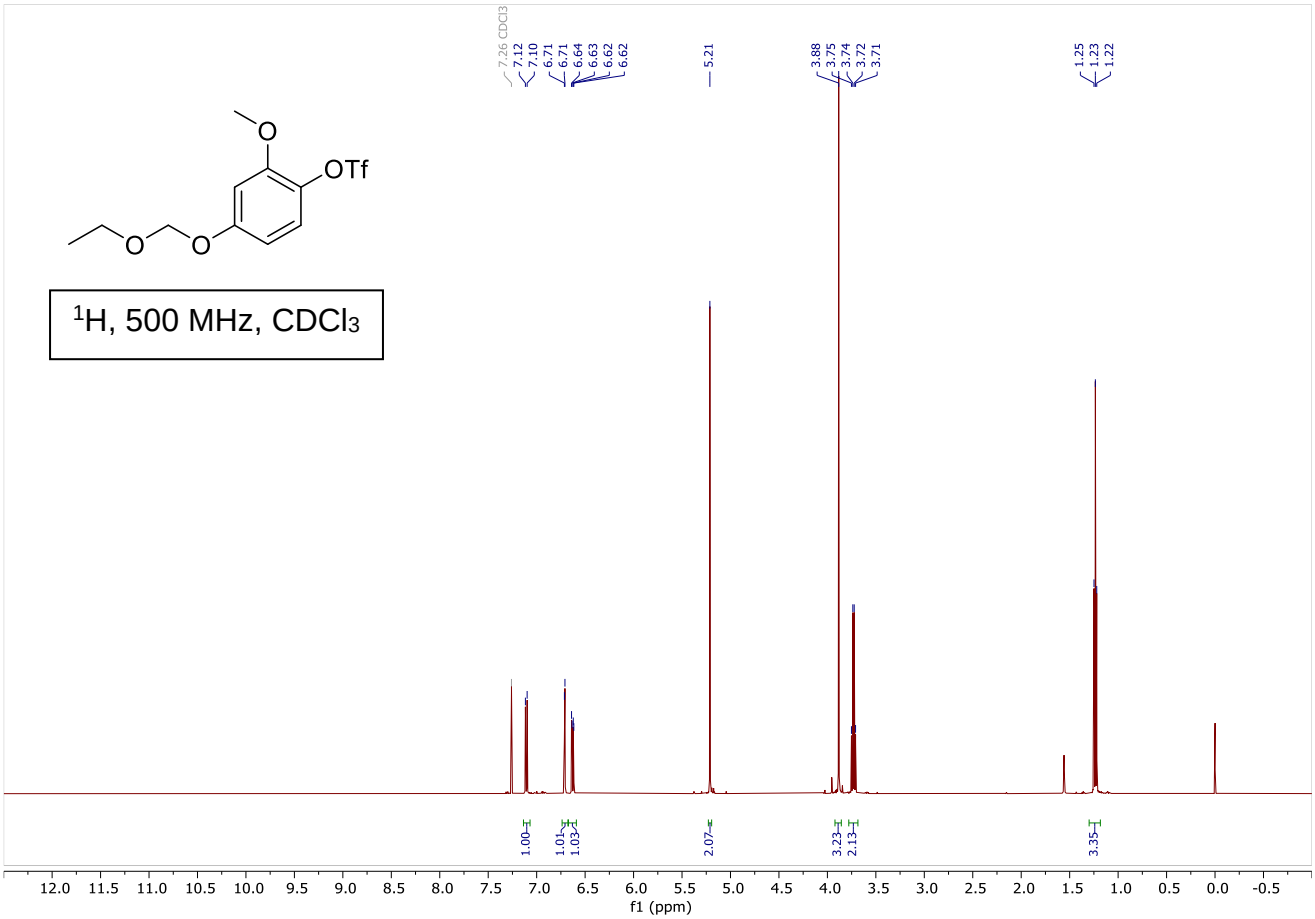
^{13}C, 126 MHz, $CDCl_3$

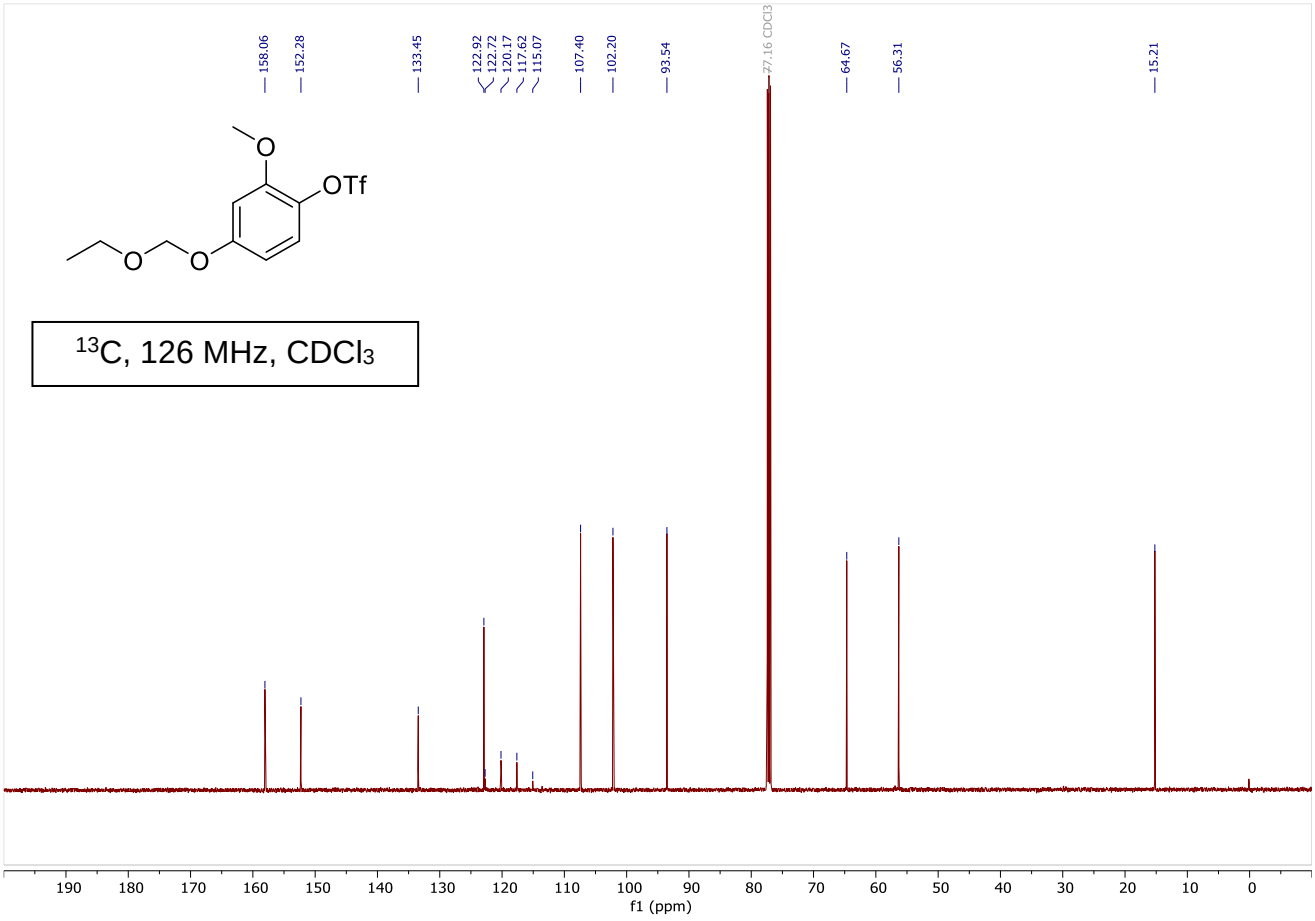
4-(ethoxymethoxy)-2-methoxyphenol (monophenol 28)



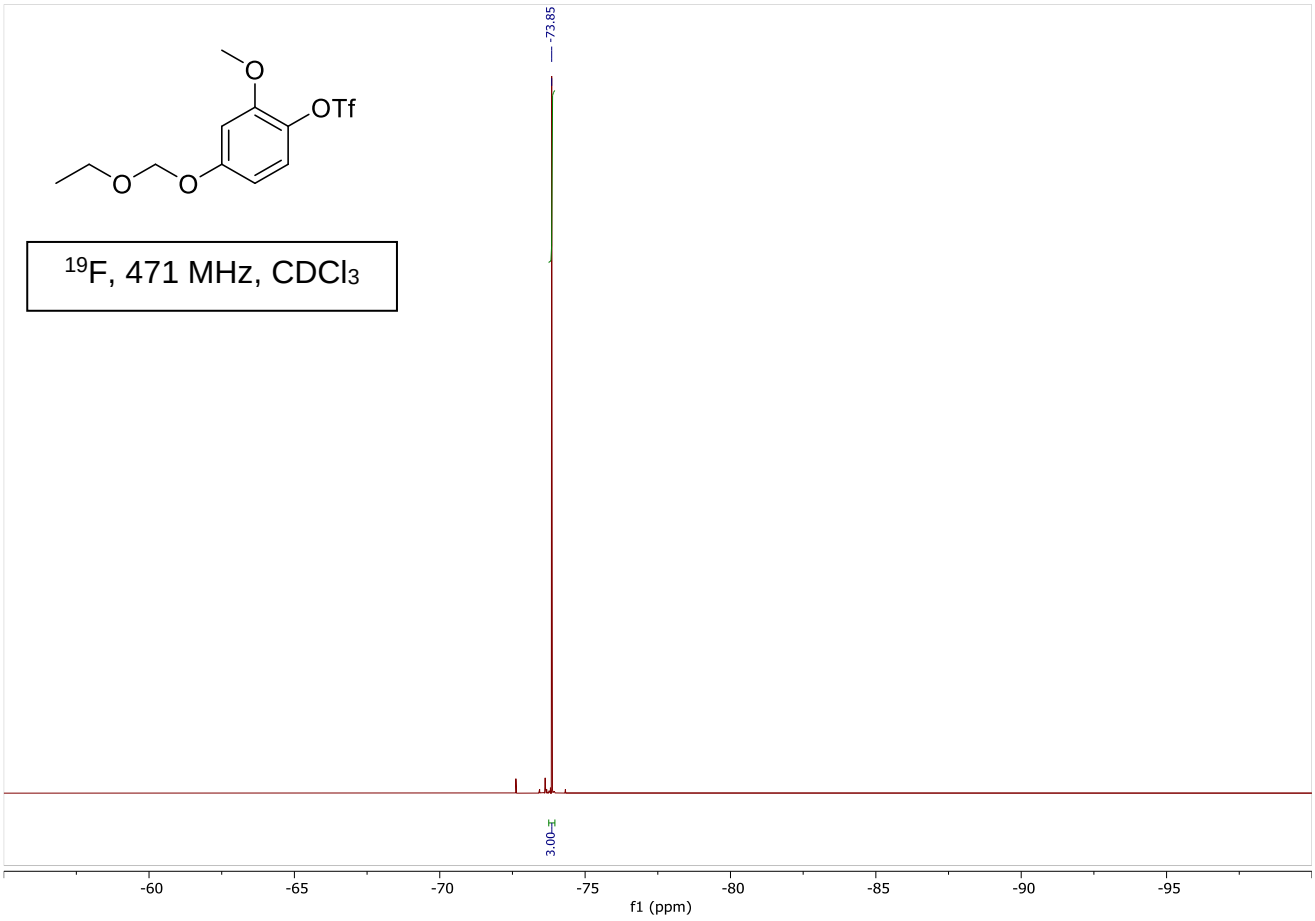


4-(ethoxymethoxy)-2-methoxyphenyl trifluoromethanesulfonate (triflate 17)

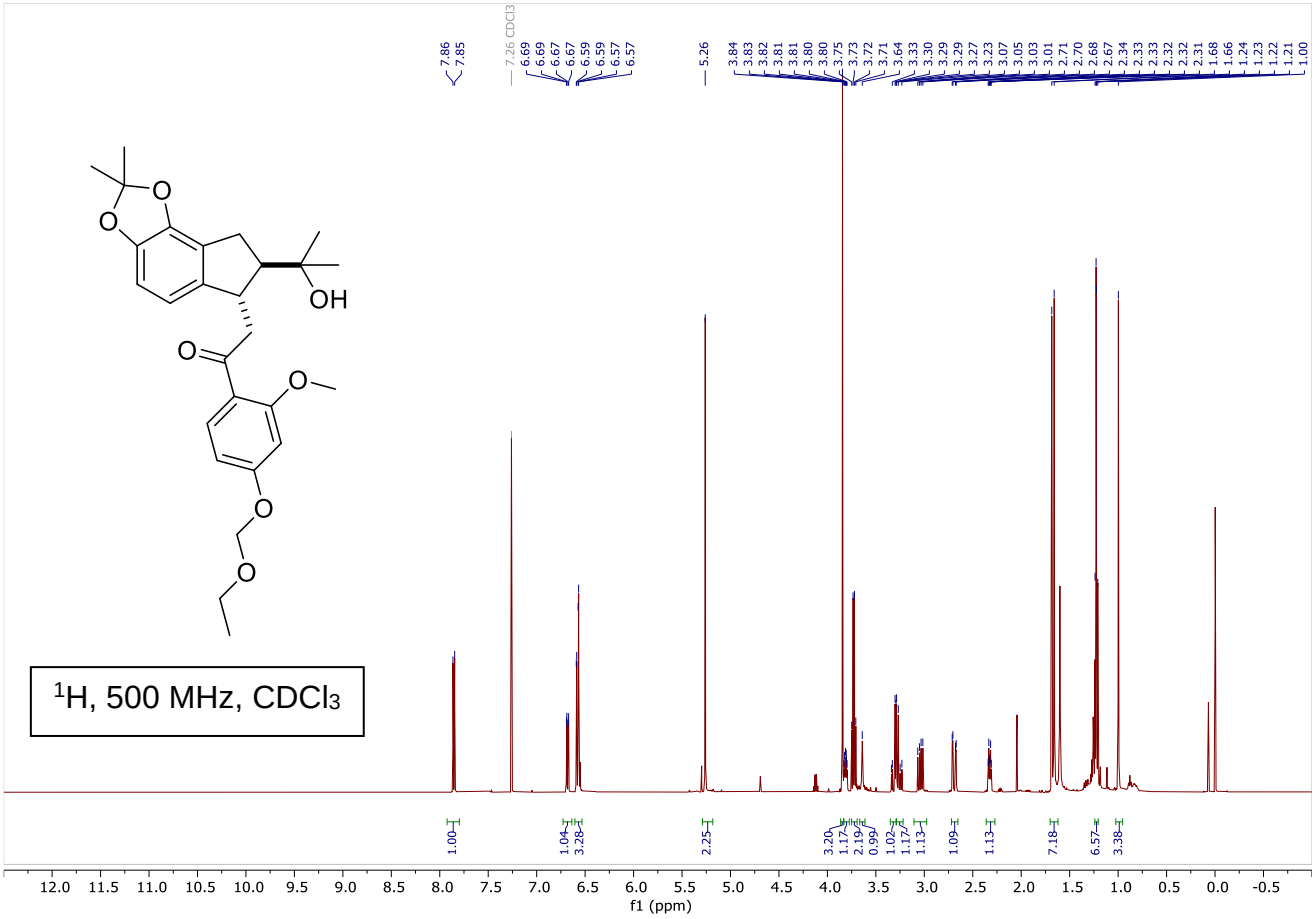


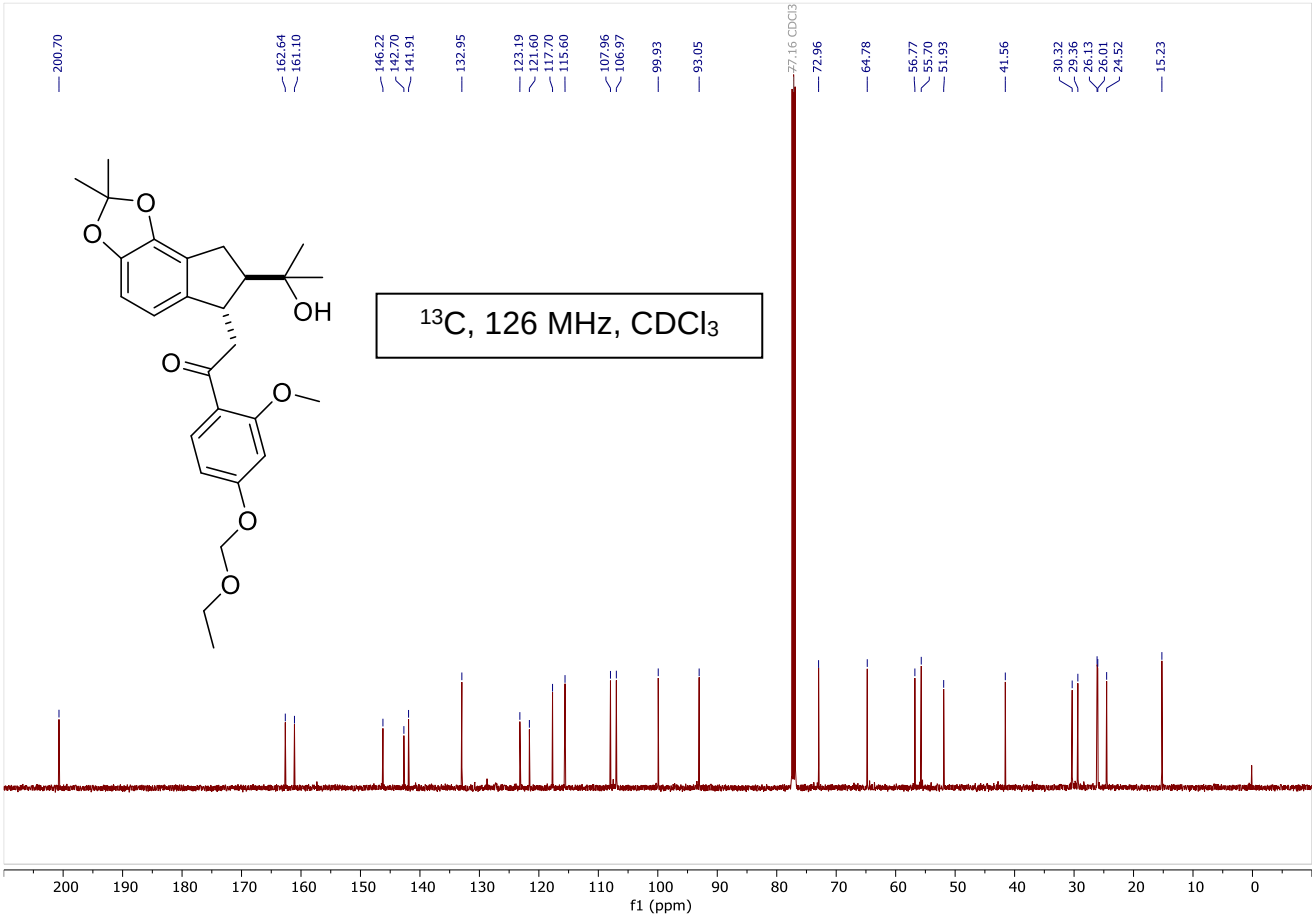


4-(ethoxymethoxy)-2-methoxyphenyl trifluoromethanesulfonate (triflate 17)

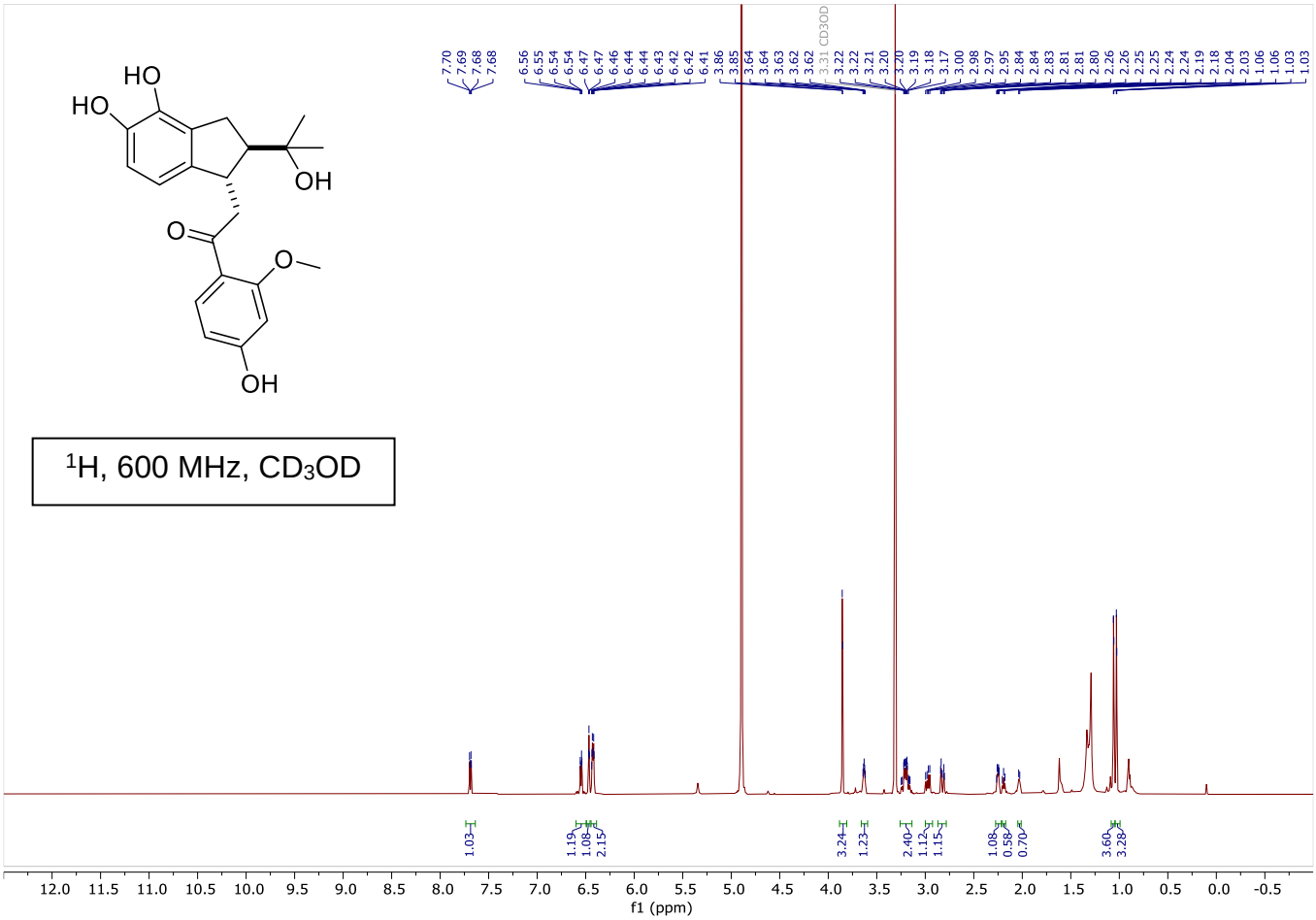


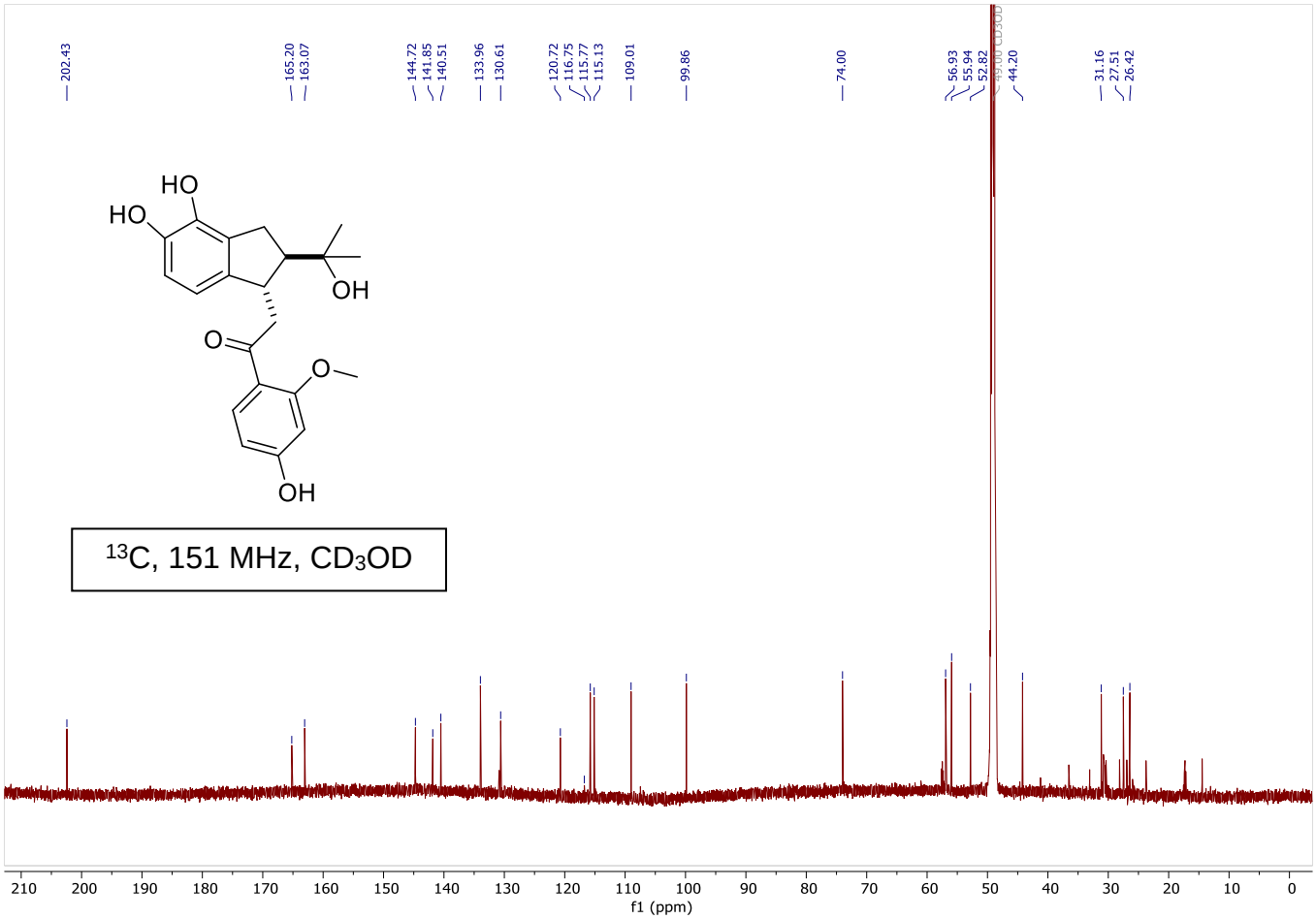
1-(4-(ethoxymethoxy)-2-methoxyphenyl)-2-((6S,7R)-7-(2-hydroxypropan-2-yl)-2,2-dimethyl-7,8-dihydro-6H-indeno[4,5-d][1,3]dioxol-6-yl)ethan-1-one (ketone 16)

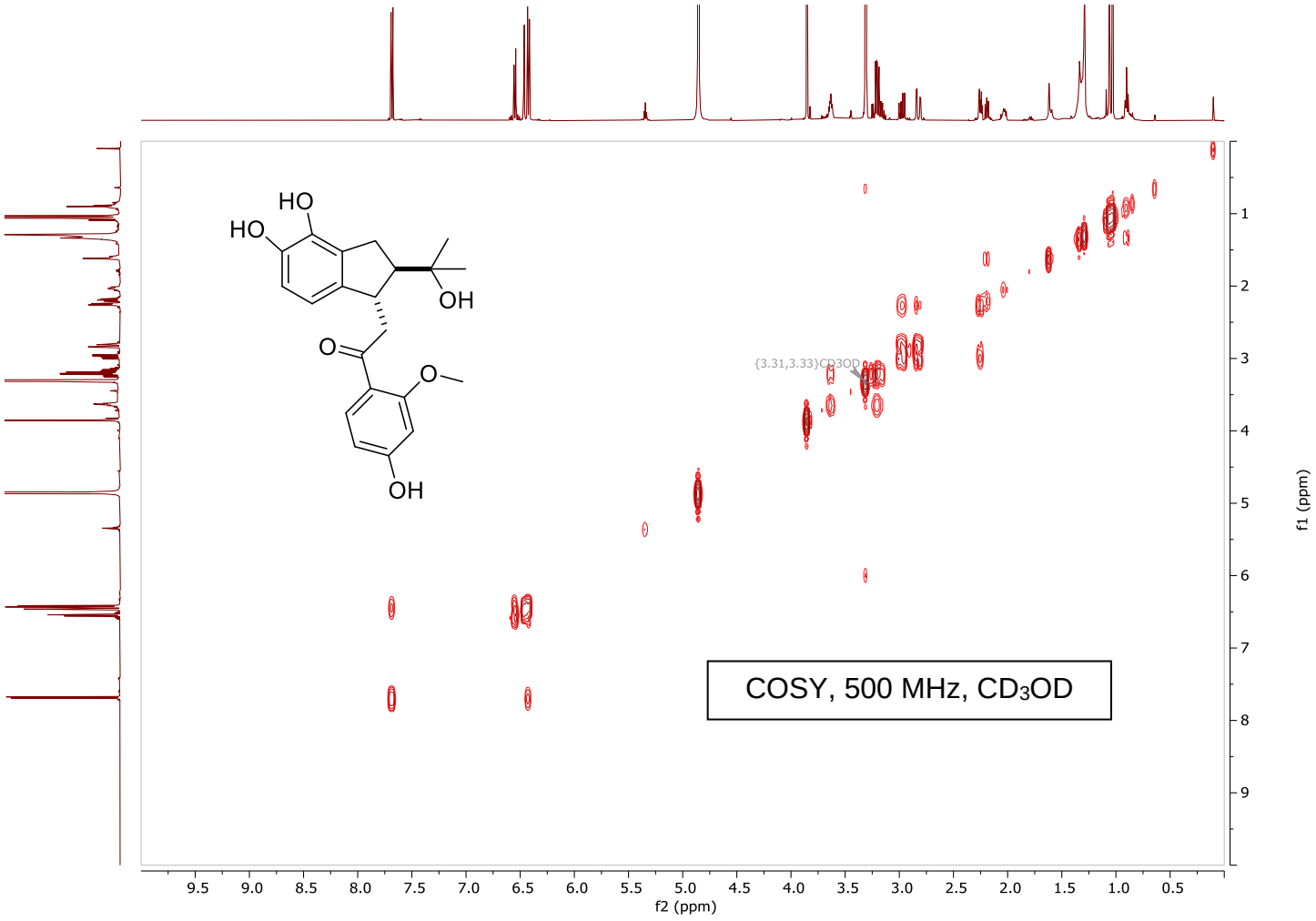


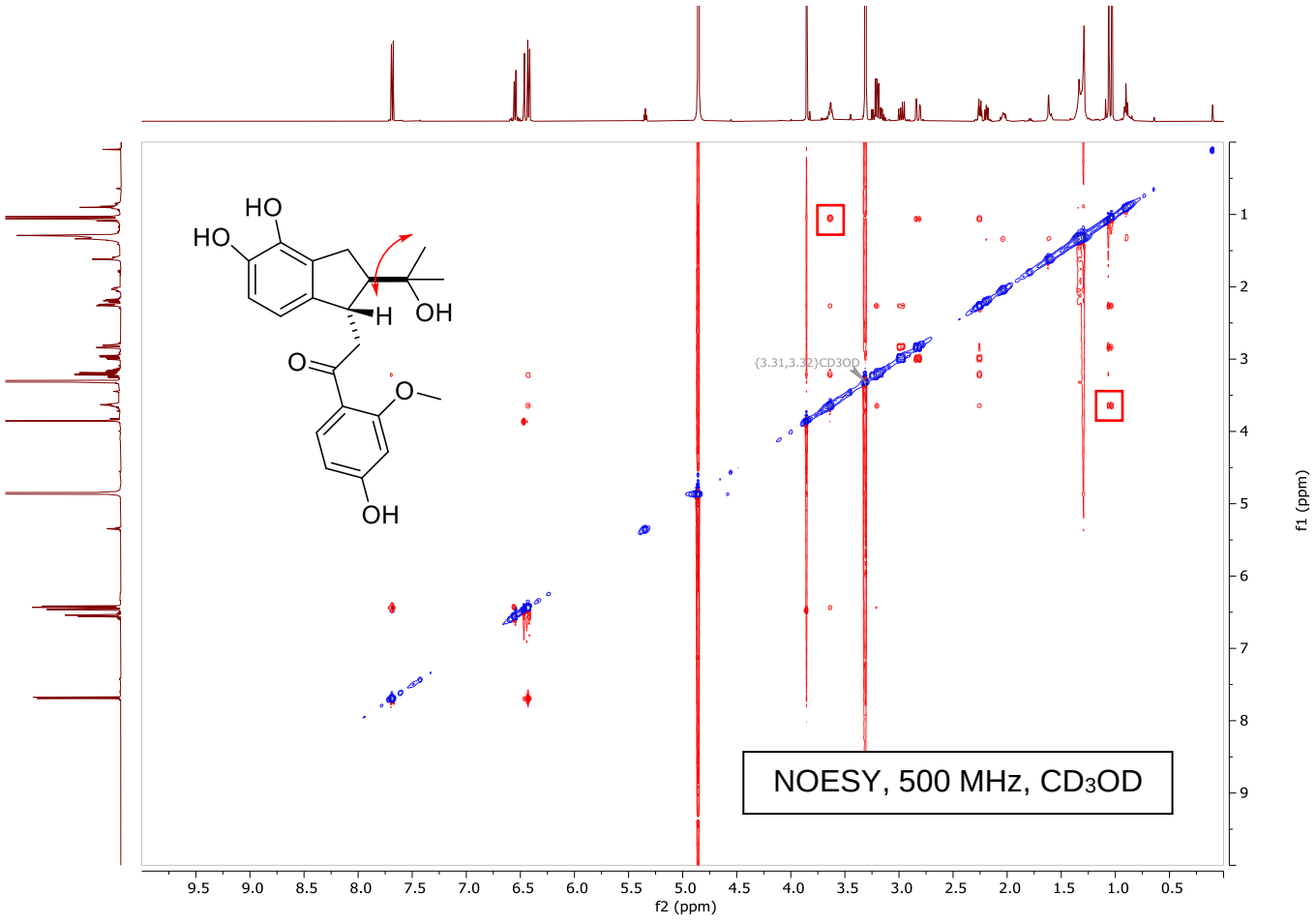


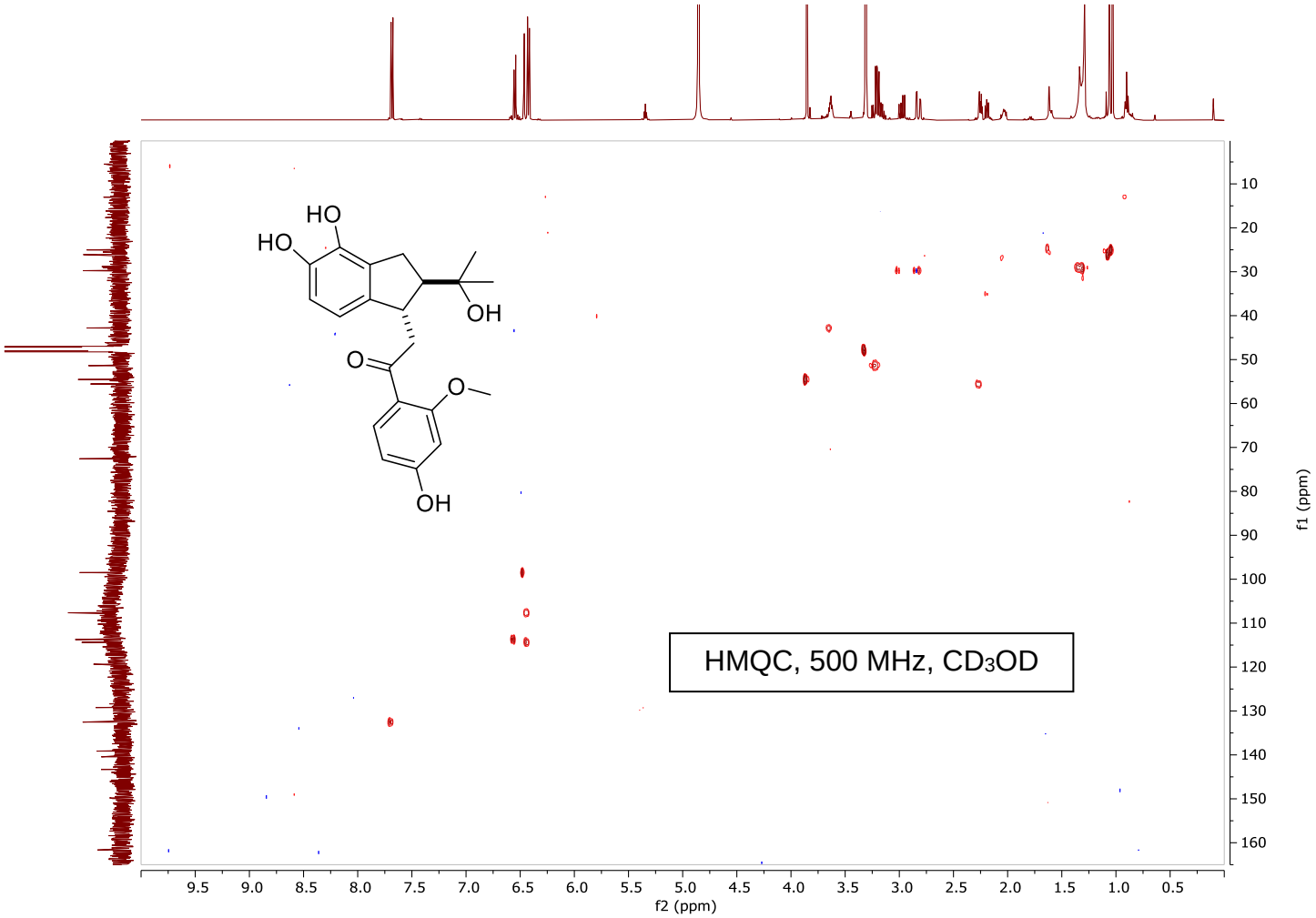
(±)-Indidene A (1)

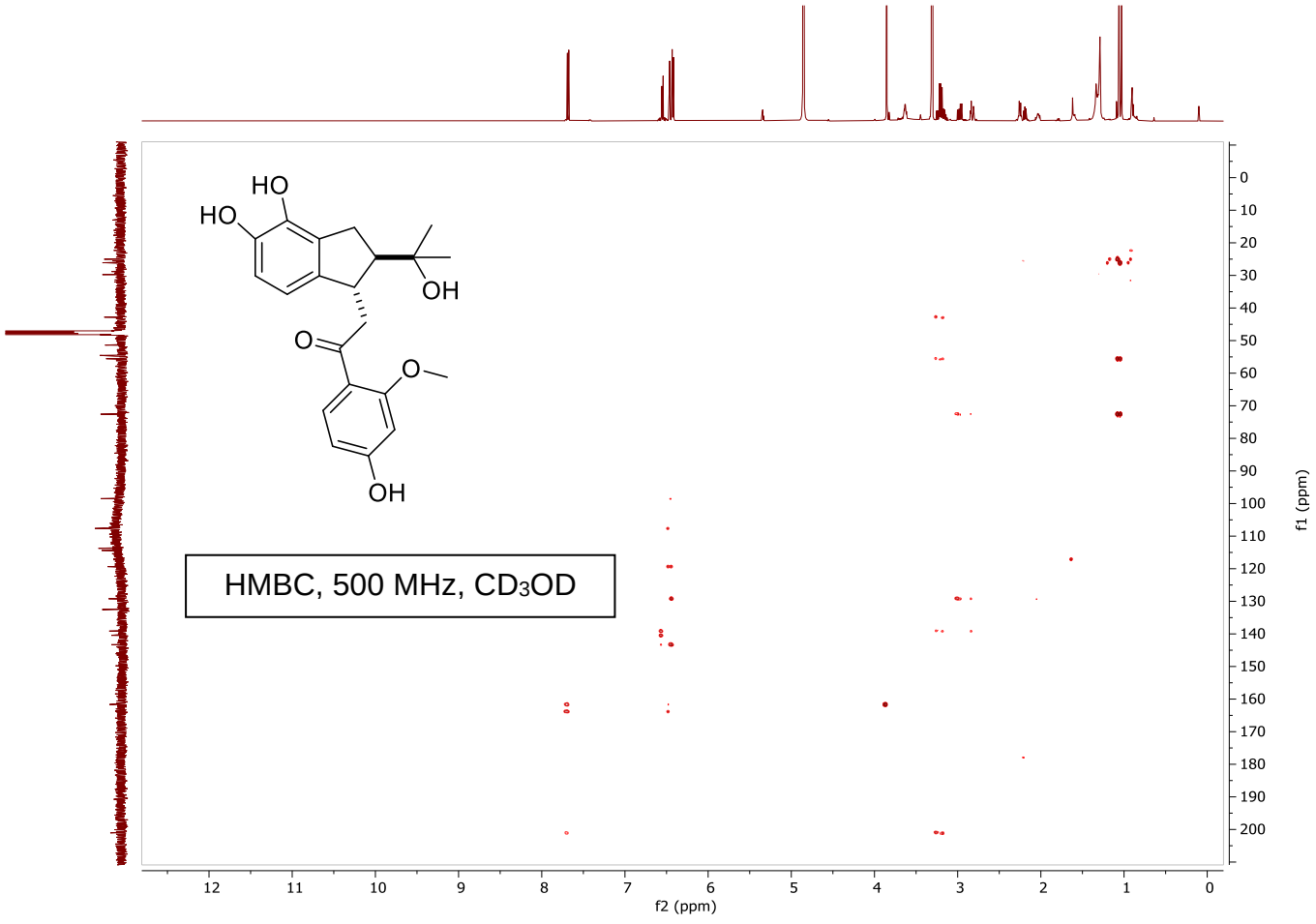

HO
HO
OH
O
O
OH
1H, 600 MHz, CD3OD
f1 (ppm)


HO
HO
OH
O
O
OH
13C, 151 MHz, CD3OD
f1 (ppm)


HO
HO
OH
O
O
OH
{3.31,3.33}CD3OD
COSY, 500 MHz, CD3OD
f1 (ppm)
f2 (ppm)

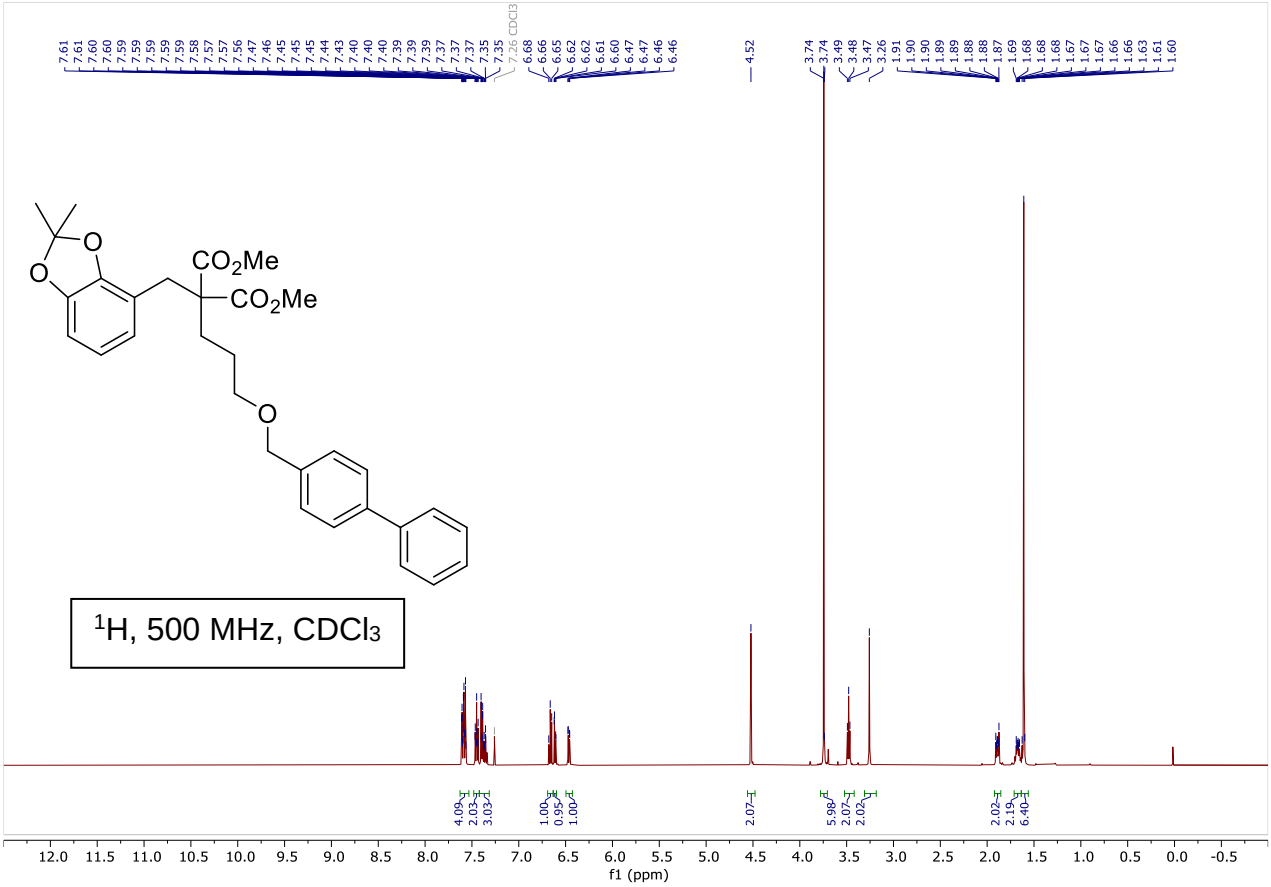

HO
HO
H
OH
O
O
OH
{3.31,3.32}CD3OD
NOESY, 500 MHz, CD3OD
f1 (ppm)
f2 (ppm)

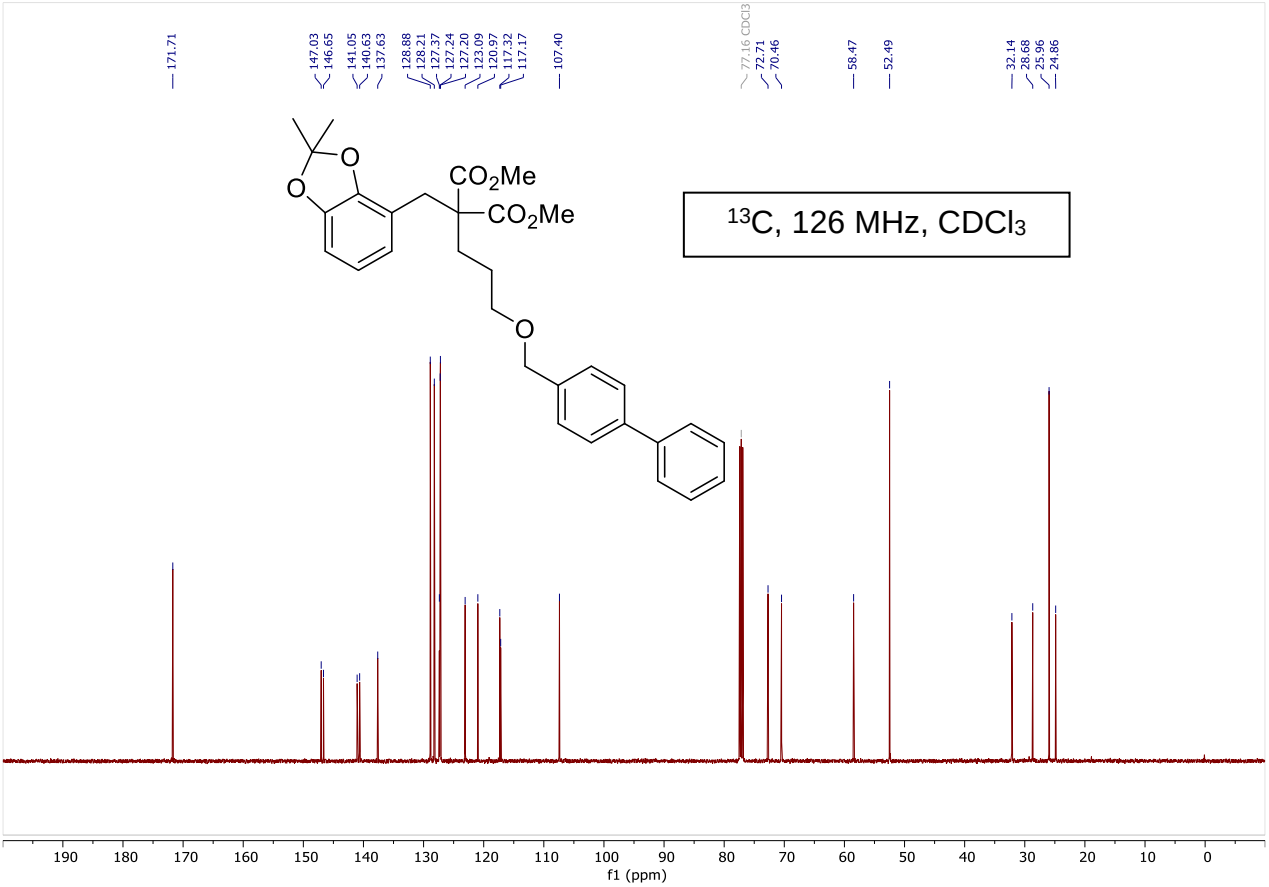

HO
HO
OH
O
O
OH
HMQC, 500 MHz, CD3OD
f2 (ppm)
f1 (ppm)


HO
HO
OH
O
O
OH
HMBC, 500 MHz, CD3OD
f2 (ppm)
f1 (ppm)

7.5 Other compounds

dimethyl 2-(3-([1,1'-biphenyl]-4-ylmethoxy)propyl)-2-((2,2-dimethylbenzo[d][1,3]dioxol-4-yl)methyl)malonate (dehalo 11a)





Curriculum vitae

Anton Kudashev

Born: 26.07.1996 in Kyiv, Ukraine
⚑ Ukraine
Signalstrasse 35a, 4058 Basel, CH
anton.kudashev@unibas.ch
antonkudashevUA@gmail.com
Anton Kudashev

Industry-oriented chemist with a good balance of academic and industrial CRO experience. Strong knowledge of synthetic organic chemistry and related techniques. Deeply involved in professional networks with strong presentation, communication, and organizational skills.

Professional experience

2019 - now Basel, Switzerland

Ph.D. researcher – *University of Basel* – Group of Prof. Dr. O. Baudoin

- **Oversaw end to end execution** of scientific projects with full disclosure in scientific journals in the form of articles.
- **Supervised Master and Bachelor level students**, assisted in teaching undergraduate courses, 528 hours total.
- **Communicated results** through oral and graphical presentations at conferences, seminars and public forums.
- **Coordinated general and niche events** with up to 100 participants.

2014 – 2019 Kyiv, Ukraine

Synthetic chemist – *Enamine Ltd.*

- Completed **more than 100 synthetic projects** on gram-scale.
- **Client engagement** through project progress communication.
- **Collaborated interdepartmentally** on synthetic projects.

Education

2018 – 2019 Kyiv, Ukraine

M. Sc. (Organic Chemistry) – *Igor Sikorsky Kyiv Polytechnic Institute*

2014 – 2018 Kyiv, Ukraine

B. Sc. (Chemical Engineering) – *Igor Sikorsky Kyiv Polytechnic Institute*

Degree focused on **technology of organic compounds** with strong background in **engineering** and **enterprise management and economics**.

Volunteering experience

2022 – now ***youngSCS*** network – Representative in Basel cluster

2022 – now ***PhD Chemistry Community (PCC)*** – Social Activities

2020 – 2021 Co-author to ***Swiss Science Concentrates*** *(Chimia)*

Core skills

Analytical techniques
Supervision
Communication
Management
Equipment use
Scientific writing

Languages

UKR, RUS: native
ENG: proficient (C1)
DE: beginner (A2)

Honors and awards

Travel Grant Award (2022)
Finalist of FameLab Switzerland (2023)

Interests

Drawing (digital + graphical)
Writing
Sewing
Programming (Python)

Publications

1. **A. Kudashev**, S. Vergura, M. Zuccarello, T. Bürgi, O. Baudoin, Methylene C(sp^3)−H Arylation Enables the Stereoselective Synthesis and Structure Revision of Indidene Natural Products, *Angew. Chem. Int. Ed.* **2023**, e202316103
2. **A. Kudashev**, O. Baudoin, Site-Selective Pd-Catalyzed C(sp^3)−H Arylation of Heteroaromatic Ketones. *Chem. Eur. J.*, **2021**, *27*, 17688-17694.
3. O. Vyhivskyi, **A. Kudashev**, T. Miyakoshi, O. Baudoin, Chiral Catalysts for Pd^0-Catalyzed Enantioselective C–H Activation. *Chem. Eur. J.* **2021**, *27*, 1231-1257.