NOVEL RADICAL BASED METHODOLOGIES FOR THE DEOXYFUNCTIONALIZATION OF ALCOHOLS & THE SYNTHESIS OF UNNATURAL α-AMINO ACIDS

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Candidate's declaration

This dissertation is submitted in fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry. It constitutes the record of work carried out in the Department of Chemistry at the Faculty of Mathematics and Natural Sciences under the supervision of Dr. Adrián Gómez Suárez and Prof. Stefan Kirsch. I, Francisco José Aguilar Troyano, hereby declare that this thesis has been written by me. Unless specifically indicated in the text, the research described has been carried out by me.

Date..... Signature of Candidate.....

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Author's Contribution

The majority the work reported in this thesis has been published as peer-reviewed journal articles, as described below.

[†] *These authors contributed equally to this work*

Chapter 2:

- *"Light-mediated Formal Radical Deoxyfluorination of Tertiary Alcohols via Selective Single Electron Oxidation with TEDA2^{+}",* Aguilar Troyano, F. J†.; Ballaschk, F.†; Jaschinski, M.†; Özkaya, Y.†; Gómez-Suárez, A.† *Chem.A Eur. J.* **2019**, *25*, 14054–14058.

- "*Selectfluor® Radical Dication (TEDA $^{2+\cdot}$) – A Versatile Species in Modern Synthetic Organic Chemistry*", Aguilar Troyano, F. J.†; Merkens, K.†; Gómez-Suárez, A.† *Asian J. Org. Chem.* **2020**, *9*, 992–1007.

Chapter 3

- "*Radical Deoxyfunctionalisation Strategies*", Anwar, K.†; Merkens, K.†; Aguilar Troyano, F. J.†; Gómez-Suárez, A.† *European J. Org. Chem.* **2022**, *13*, 287–288.

Chapter 5

- "*Synthesis of Unnatural α-Amino Acid Derivatives via Light-Mediated Radical Decarboxylative Processes*", Merkens, K.; Aguilar Troyano, F. J.†; Djossou, J.†; Gómez-Suárez, A.† *Adv. Synth. Catal.* **2020**, *362*, 2354–2359.

- "*Synthesis of γ-Oxo-α-amino Acids via Radical Acylation with Carboxylic Acids*", Merkens, K.†; Aguilar Troyano, F. J.†; Anwar, K.†; Gómez-Suárez, A.† *J. Org. Chem.* **2021**, *86*, 8448–8456.

- "*Radical-Based Synthesis and Modification of Amino Acids*", Aguilar Troyano, F. J.†; Merkens, K.†; Anwar, K.†; Gómez-Suárez, A.† *Angew. Chemie Int. Ed.* **2021**, *60*, 1098–1115.

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1. INTRODUCTION

1.1. Radical Chemistry & Photochemistry

Historically, the synthetic use of radical chemistry has been traditionally overlooked, and ionic chemistry has become the leading actor in both academia and industry.[1,2] The inherent highly reactive nature of radical intermediates led to the misconception that these species were unpredictable and difficult to control. Consequently, the aim of exploiting them to develop new and reliable methodologies represented a difficult if not nearly impossible task. However, it only takes a brief look into the scientific literature to makes a case against these beliefs.[3,4] There are indeed notorious examples worth mentioning. For example, the pinacol coupling reaction invented by Fittig in the last part of the 19th century,[5] or the Wohl-Ziegler reaction at the down of the 20th century.[6] Another key contribution was the "peroxide effect" defined by Kharasch.[7] This helped scientists improve our understanding of the rules proposed by Markovnikov 60 years before,[8] in which radicals were proposed as being the main cause of the *anti*-addition in the presence of peroxides species. The Birch reduction granted straightforward access to substituted 1,4-cyclohexadienes,[9–14] and the thiol-catalyzed methodology developed by Waters in the 50s promoted the homolytic cleavage of aldehydes, allowing the formation of acyl radicals.[15,16] The list continues with even greater transformations like the Minisci reaction,[17] the Barton-McCombie reaction,[18] the SmI_2 chemistry invented by Kagan[19] or the Giese reaction.[20] (**Figure 1**)

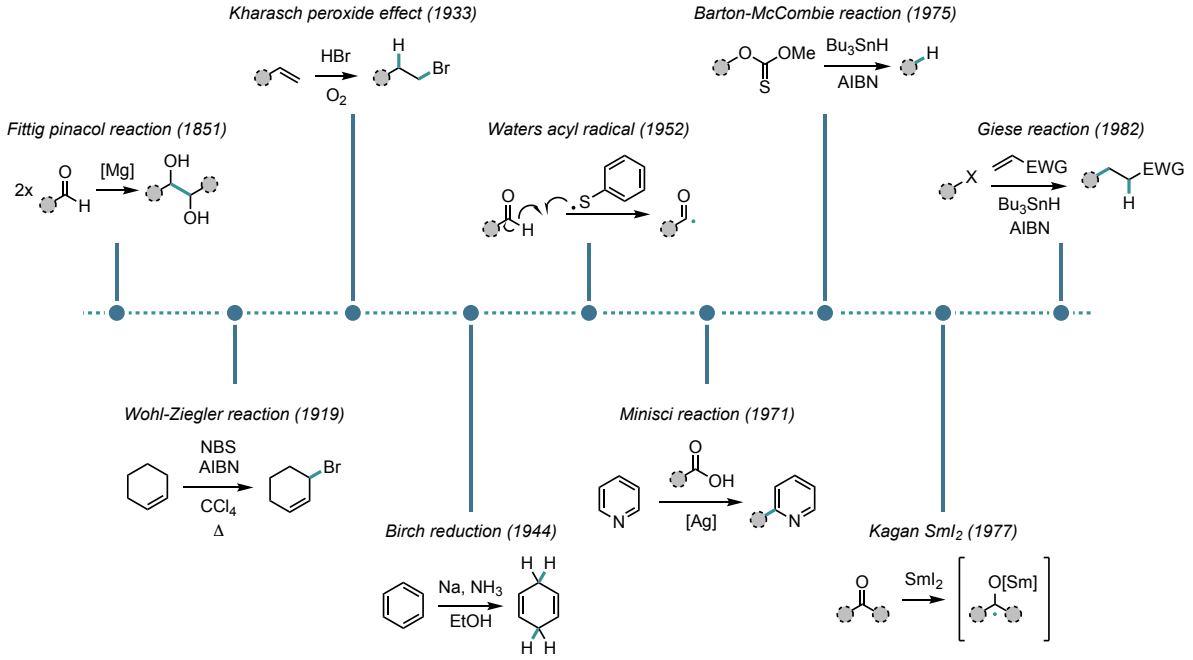


Figure 1. Selected radical chemistry contributions during the las century.

Since the beginning of the 21st century, the number of radical based methodologies with broad applications in synthetic organic chemistry has been increasing almost exponentially. This radical rush

is driven by the development of new technologies to generate reactive radical intermediates in a controlled fashion leading to greener, milder, and, overall, more efficient transformations.[21] Among these new technologies, photochemistry has gained increased popularity over the last decades, as it allows for remarkably mild conditions for the controlled generation of open-shell species, thus avoiding the need for heating or the use of harsh chemicals that could lead to the decomposition of sensitive reaction components.[22]

1.1.1. Origin and Renaissance of Visible Light as Driving Force

Light has been playing a key role in the development of the human history since the discovery of fire to the definition of the photosynthetic mechanisms which governs the plants. Therefore, the aim of transforming such an abundant energy source into useful chemical energy has become one of the most important goals for scientists over the last century.[23,24] One of the very first examples of these efforts in the organic chemistry field was presented by Giacomo Ciamician and Paolo Silber at the beginning of the 20th century.[25] They documented one of the first photochemical organic transformation using ultra-violet (UV) light as main energy source. Despite of how innovative this technology was, there were a couple of drawbacks which could not be ignored:

- Around 40% of the sunlight irradiance is filtered by the atmosphere, being considerably lower at the sea level. In addition, UV light represents only the 4-7% of the content of the sunlight,[26] thus restraining the possible development of industrial applications.
- Most of the organic molecules absorb in the UV region (100-365 nm), meaning a lack of selectivity in molecules with sensitive functional groups, weak bonds, or high complexity. This is due to the high energy profile of the UV photons which prompt a considerable number of decomposition side-reactions (**Figure 2**).

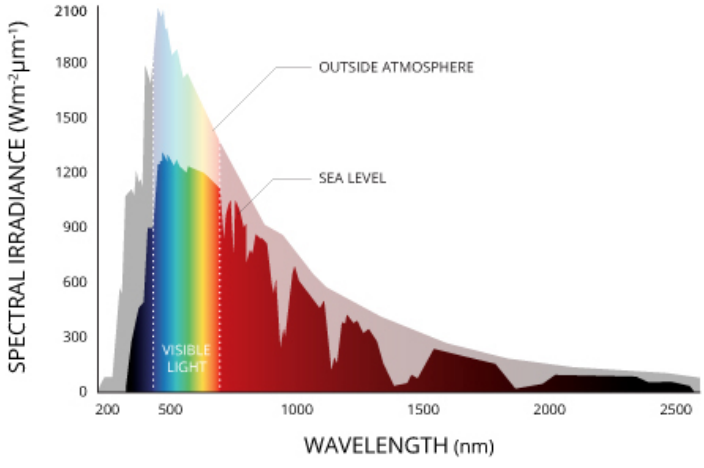
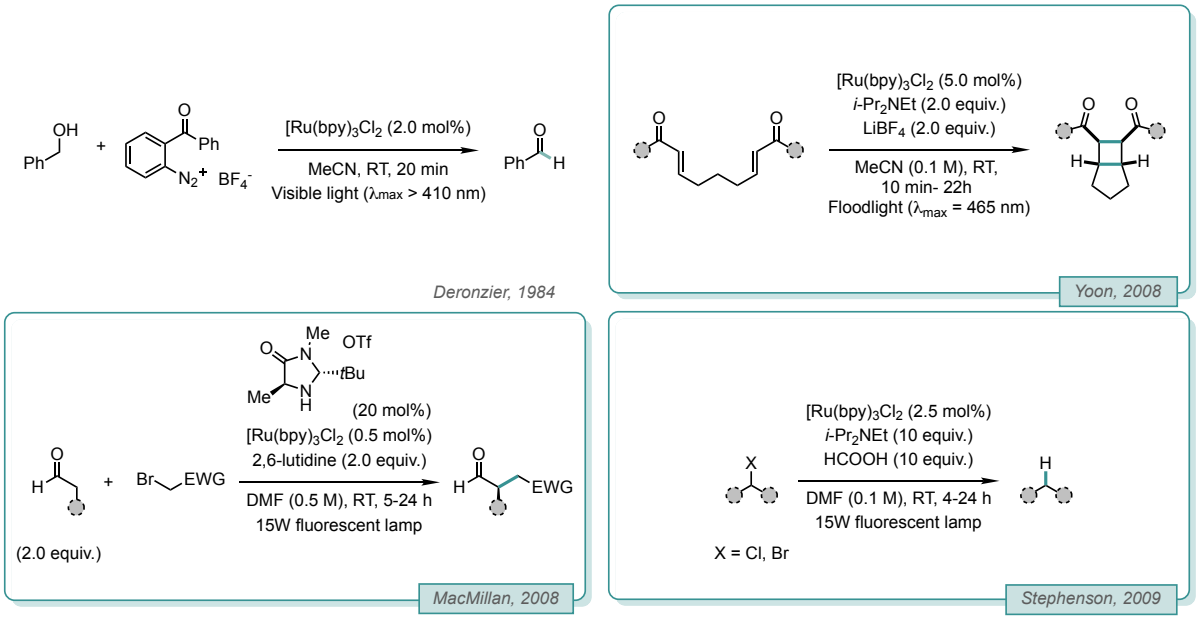


Figure 2. Solar emission spectrum. Measurements. [Card, A., Fitch, K., Kelly, D., Kemker, C., & Rose, K. (2014, March 21) *Fondriest*. Retrieved from Environmental Leading Center: https://www.fondriest.com/environmental-measurements/parameters/weather/photosynthetically-active-radiation/]

These limitations helped to direct the scientists' attention into a different frequency window of the sunlight: the visible light region (365-750 nm). Compared to the UV region, visible light constitutes around 44% of the sun irradiation, and its broad wavelength spectrum corresponds to specific energies (≈70-115 kcal/mol) necessary to break a wide range of chemical bonds. Therefore, applying the right wavelength with the correct amount of energy could solve the selectivity problem.[26] However, the challenge was how take advantage of this region of the sunlight emission knowing, as mentioned above, that the absorption profile of most of the organic molecules corresponds to the UV region. To overcome this challenge, it is necessary to make use of chromophores or sensitizers which can absorb in the visible regium of the spectrum, and channel all that energy to ultimately perform the desired transformations.

1.1.2. Photoredox Catalysis: From Ruthenium until today

Nowadays, visible light photoredox catalysis represents one significant segment of photochemistry. It has become a wide branch which embraces all the methodologies that employ metal complexes and organic dyes as photosensitizers to perform otherwise energetically disfavored reactions.[27–29] Such photocatalysts – in particular Ru-based polypyridyl complexes – have played an important role during the last 50 years in the development of new technologies for artificial photosynthesis, water splitting, and solar energy storage.[30–34] Despite these advances, there had only been sporadic examples of the application of these complexes as photocatalysts in synthetic transformations.[35–38] It was not until 2008 when this scenario changed dramatically with the publication of the seminal works by Yoon,[39] MacMillan[40] and Stephenson[41] (**Scheme 1**).



Scheme 1. Early example & seminal works in photoredox catalysis.

In these key publications one specific metal-polypyridyl complex, **$Ru(bpy)_3Cl_2$** (bpy= 2,2'-bipyridine), was used to promote three distinct transformations: a light-mediated intramolecular [2+2] cycloaddition, the asymmetric alkylation of aldehydes, and a reductive dehalogenation of alkyl halides. The variety of transformations shown in these representative examples highlights the versatile reactivity of this metal complex. The metal center of such complex can be replaced by other atoms, being iridium the most utilized one. Together, these two metals have played a key role in the development of a vast number of photochemical transformations during the last decades.

To fully understand the mechanisms that govern these transformations, first we must consider the underlying photophysical properties of these metal-based catalysts (**Figure 3**). An iridium-based complex will be considered for this purpose, specifically **$[Ir(dF(CF_3)_2ppy)_2(dtbbpy)]PF_6$** ,(ppy=phenyl pyridine), (dtbbpy= diterbutyl bis-pyridine) due to its versatility as good oxidant and reductant and its use in subsequent chapter(s) of this thesis.

Excitation is understood as the process where a molecule absorbs light in its ground state (**S_0**). The photons from this light have a higher energy than the energy gap (**E_g**) between the highest occupied molecular orbital (**HOMO**) and the lowest unoccupied molecular orbital (**LUMO**), therefore promoting the jump of one electron from the **HOMO** – in this case the t_{2g} of the metal center – to the **LUMO**, the π^* of the ligand in this example. This transition, known as a metal to ligand charge transfer (**MLCT**), switches the catalyst into its single excited state (**S_1**) from which the electron has two different pathways for further reactivity:

- Because the electron's spin is paired with the one remaining in the ground state (**S_0**), the former can return to **S_0** via radiative (fluorescence) or via non-radiative transitions (internal conversion).
- The second possibility contemplates the spin change of the electron by an intersystem crossing (**ISC**) event which produces the low energy triplet excited state (**T_1**).

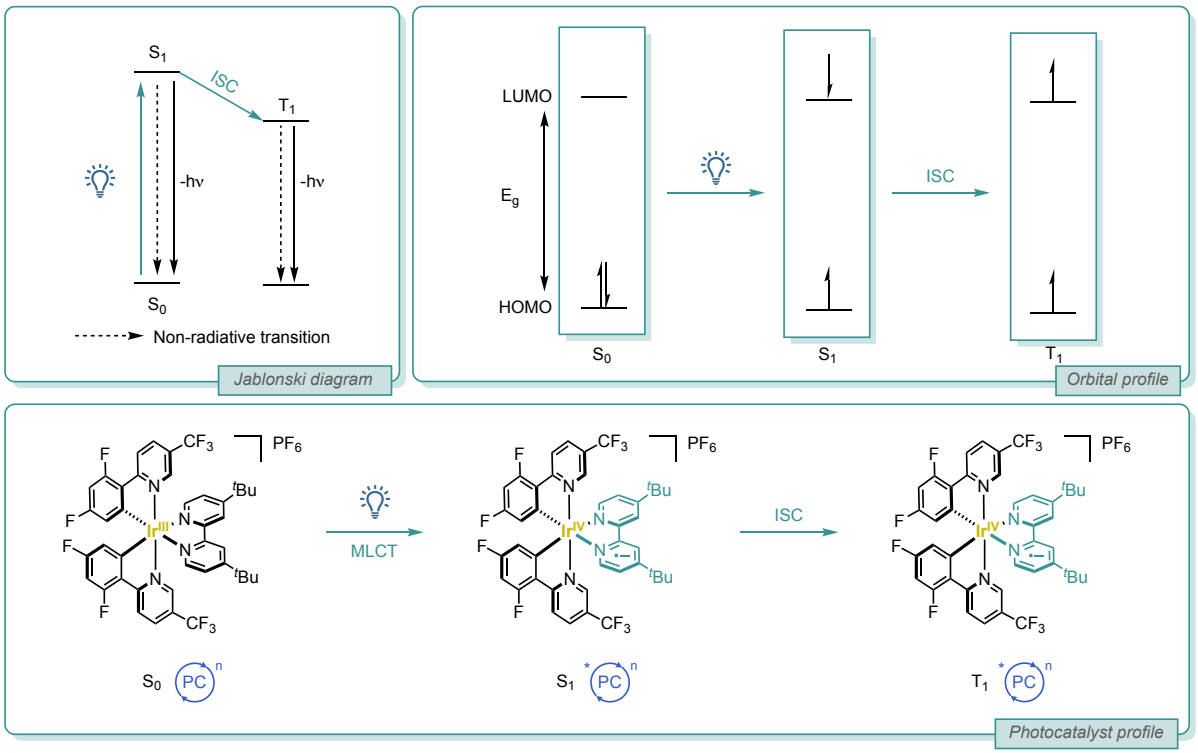


Figure 3. Jablonski diagram and photocatalyst orbital profile.

In the latter case, the excited triplet state is long-lived compared with **S_1.** The alteration of the spin makes impossible the decay into **S_0**,[28,29] resulting **T_1** in the perfect platform to perform single electron transfer (SET) interactions with other substrates. The nature of this SET event depends on the role of the substrate introduced in the chemical environment: if the substrate is an acceptor (**A**), oxidative quenching process will take place ($*PC^n \rightarrow PC^{n+1}$), while if the substrate is a donor (**D**), a reductive quenching route will be favored ($*PC^n \rightarrow PC^{n-1}$). In addition, a third possibility contemplates that the decay of the photocatalyst from its **T_1** excited state to its **S_0** ground state promotes the excitation of a second molecule **A** from **S_0** to **T_1** ($*PC^n \rightarrow PC^n$), in a process termed triplet-triplet energy transfer (**TTET**). These three modes of action are summarized in the **Figure 4**. Both pathways generate a highly oxidized (PC^{n+1}) or reduced species (PC^{n-1}) which needs a further single electron reduction or oxidation step, respectively, to regenerate the ground state of the photocatalyst (PC^n).[29] This ambivalence is why these catalysts are powerful mediators in a myriad of redox systems.

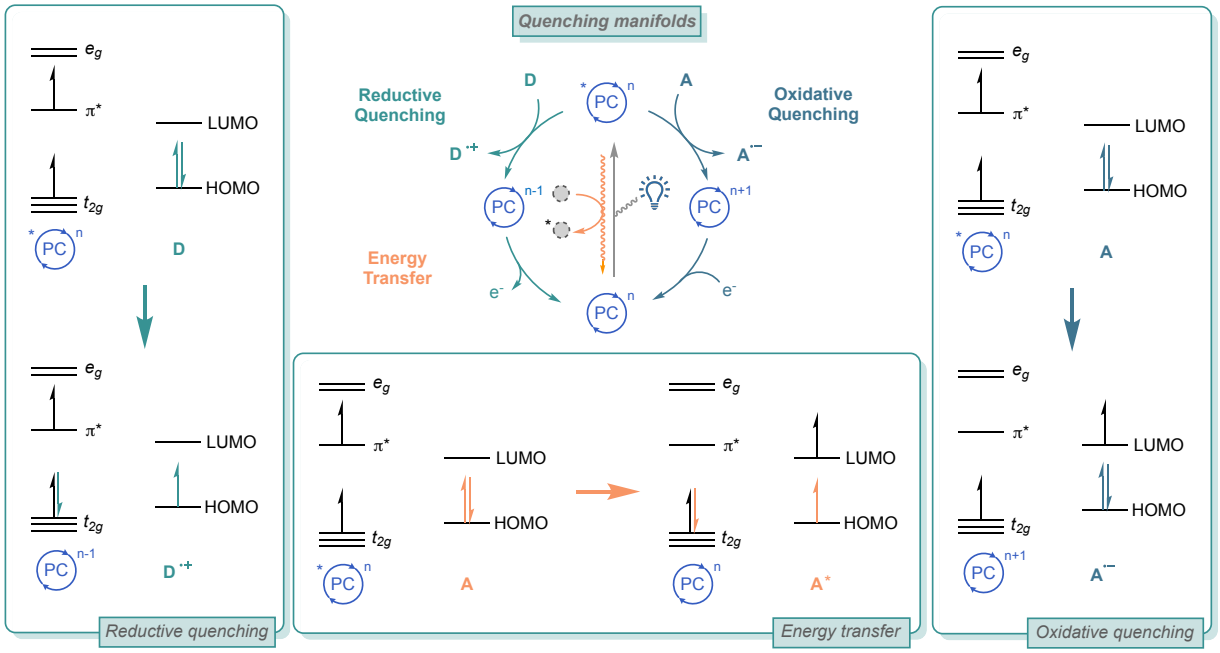


Figure 4. Photocatalyst quenching cycles.

The properties of these metal complexes can be adjusted by modification of certain parts of their structures.[42–44] The nature of the metal center plays a key role in such properties by electing ruthenium or iridium. On one hand, ruthenium usually forms homoleptic (same ligands) polypyridyl complexes, e.g. **Ru(bpy)**$_3$Cl$_2$, where the HOMO orbital is located in the complex metal center. The bipyridine moiety is a π-acceptor neutral ligand which provides the LUMO orbital of the complex.[45] On the other hand, iridium trends to form cyclometalated complexes, being 2-phenylpyridine (ppy) the main ligand in these organometallic compounds. Despite bpy and ppy both being π-acceptor ligands, the former is a monoanionic ligand which has a profound impact in the final properties of the complex. The anionic carbons bonded with the iridium possess a higher σ-donation character, which translates into a delocalization of the HOMO orbital as displayed in **Figure 5** for the case of *fac*-[Ir(ppy)3].[46–48] It is easy to highlight that this orbital delocalization represents a huge advantage of the Ir-based complexes over the Ru ones in terms of tunability, considering that further modification of the ligands leads to more changes in their final properties. As a general rule, addition of electron-donating substituents to the ligand increases the reducing profile of the complex due to a poor stabilization of the electrons involved in the system, while adding electron-withdrawing substituents increases its oxidizing profile due to a better electron stabilization.[29] This tunability is even superior in the case of the heteroleptic (different ligands) iridium-based complex as it has the ability of separate completely HOMO and LUMO spatially for its straightforward modification (**Figure 5**).[49] This ability from the iridium to form heteroleptic complexes is because during their synthesis iridium trends to form dimeric structures in the first step, which can be isolated and then mixed with a different ligand.

Finally, metal-free photocatalyst have been gaining attention during the last decade, displaying similar properties and reactivities than their metal-based counter parts. Organophotocatalyst as 9-mesityl-mehtyl-acridinium (**Mes-Acr-Me**),[50] organic dyes as **eosin Y**,[51,52] or 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (**4CzIPN**)[53] and its derivatives are worth highlighting and could potentially decrease the dependance on precious metals.[54]

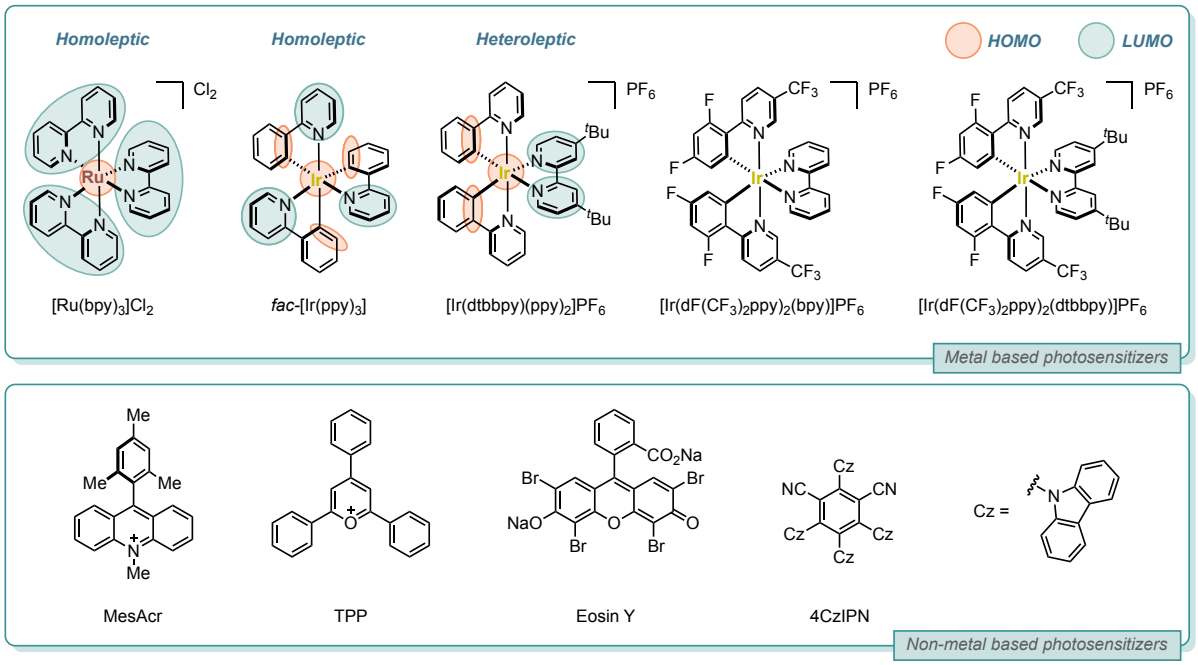


Figure 5. Selected examples of transition metal-based and organophotocatalysts.

1.2. Deoxyfunctionalization Technologies

1.2.1. Alcohols: Advantages & Challenges

Alcohols represent one of the most ubiquitous functionalities in organic molecules. They can be typically found in nature in the form of sugars, steroids, and proteins, while synthetic variants are found across a broad range of pharmaceuticals and agrochemicals.[55] This natural abundance, as well as the myriad of methodologies to introduce hydroxyl moieties into organic molecules, make alcohols excellent starting materials for further functionalizations. In this regard, they present three distinctive modes of action, [56–59] functioning as:

- Oxygen-centered nucleophiles, via their lone pairs.
- Source of protons, due to the extensive polarization of O–H bonds.
- Leaving groups in substitution reactions.

However, in the latter case the intrinsic strength of the C–OH bond makes the hydroxyl moiety a very poor leaving group. Therefore, to perform interesting functional group interconversions (**FGI**) on alcohols it is necessary to derivatize the original alcohol into a more suitable leaving group. In this

field, one of the most useful transformations is the Mitsunobu reaction (**Figure 6**).[60,61] Although very powerful, this reaction presents several disadvantages, such as the use of stoichiometric amounts of triphenylphosphine and diethylazodicarboxylate (**DEAD**) to activate the OH group, thus generating large amounts of triphenylphosphine oxide as side product.

An alternative to the Mitsunobu reaction is the conversion of the hydroxyl group into halides or pseudo-halides, which are better leaving groups than the hydroxyl moiety, enabling further functionalization reactions. These processes generally proceed through nucleophilic substitution reactions via S_N1 or S_N2 pathways. However, while these strategies grant access to a wide range of useful and complex molecules, they present some limitations. For example, S_N2 reactions often require the use of acidic conditions, which can promote the formation of olefinic side products via HX (X = halogen, OTs, OMs, etc.) elimination. Furthermore, reactions proceeding via a S_N2 pathway are highly sensitive towards steric hindrance around the reactive center, so they proceed with difficulty in sterically demanding primary and secondary systems, and with extreme difficulty in tertiary systems. In the case of nucleophilic substitutions via S_N1 mechanism, the main problems are related to the stabilization of the required intermediate carbocation, thus limiting the scope of their application to stabilized tertiary systems and highly activated alcohols (**Figure 6**).[62] Moreover, by-product formation via proton elimination to form olefins, or hydride and alkyl rearrangements can also occur.

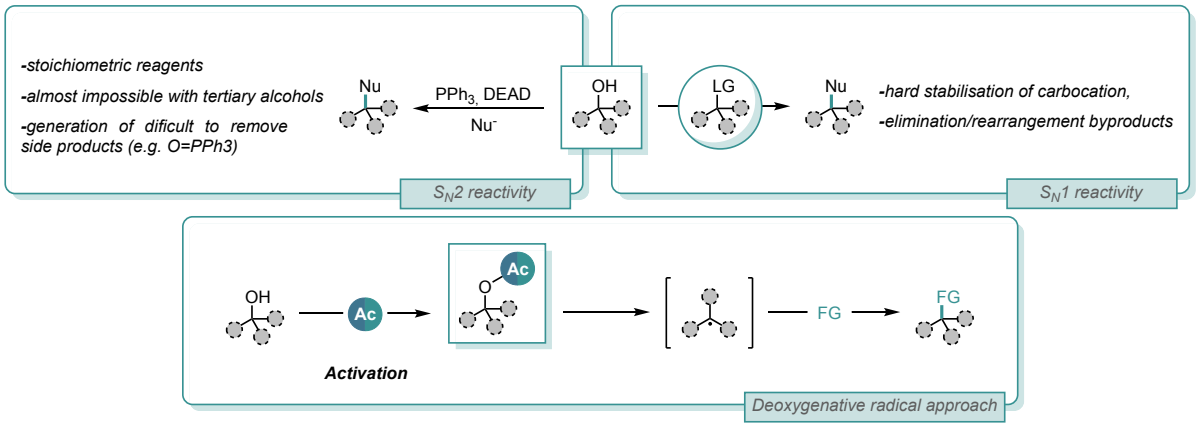


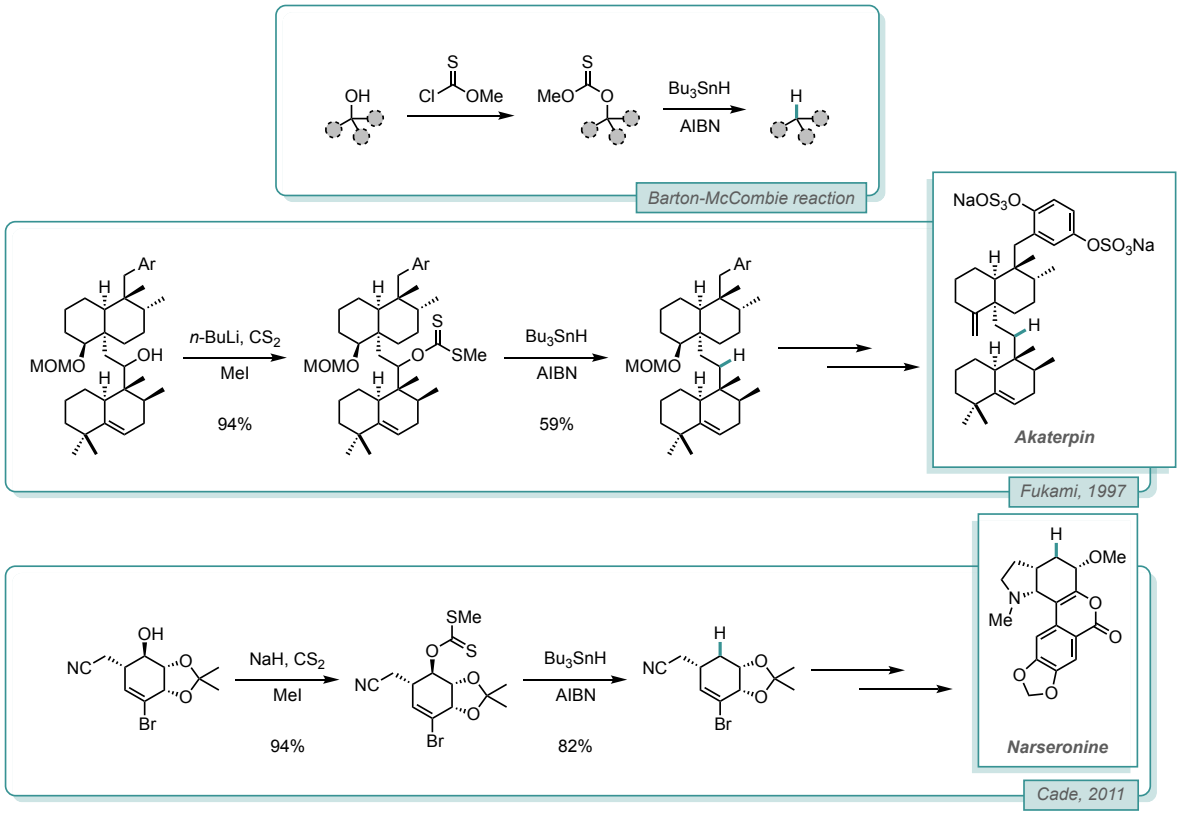
Figure 6. S_N1 vs S_N2 reactivity.

Deoxygenative radical substitution reactions have arisen as an attractive alternative to overcome all limitations associated with S_N1 or S_N2 reactivities.[63] The core idea behind these deoxygenative radical methodologies is the conversion of the hydroxyl group into a good leaving group, which can undergo facile mesolysis in the presence of a suitable radical initiator to generate a primary, secondary or tertiary open-shell species that can engage in further functionalization reactions (**Scheme 2**). This approach would overcome the steric limitations present in traditional nucleophilic

reactions, while also reducing the possibility of byproduct formation due to elimination reactions or rearrangements.

1.2.2. Barton-McCombie reaction: Pioneering work

The pioneers in the field of radical deoxyfunctionalization chemistry were Barton and McCombie. The authors published in 1975 their seminal deoxygenative method for the reduction of C–OH to C–H bonds, a process that replaces a hydroxyl group with hydrogen at a saturated carbon exploiting a free-radical chain reaction between *O*-thioacyl derivatives of secondary alcohols and Bu_3SnH (**Scheme 2**).[18] Arguably, this is one of the most employed technologies to perform this challenging transformation, being present in the total synthesis of numerous complex systems[64–66].



Scheme 2. Barton-McCombie reaction & examples in total synthesis.

1.2.3. Activating the OH group

Although powerful hydride sources, stannanes are toxic and difficulty to remove from the reaction mixture, making their application in the Life Sciences particularly challenging. During the last decades the Barton-McCombie reaction has been improved resulting in novel protocols using more environmentally benign reductants,[67] and more efficient activators. Naturally, the latter have also been adapted to the emergent field of light-mediated deoxyfunctionalizations and can be classified

based on their role in the catalytic cycle as electron acceptors (**A**) or electron donors (**D**). Representative examples of the main types of activating groups are shown in **Figure 7**.

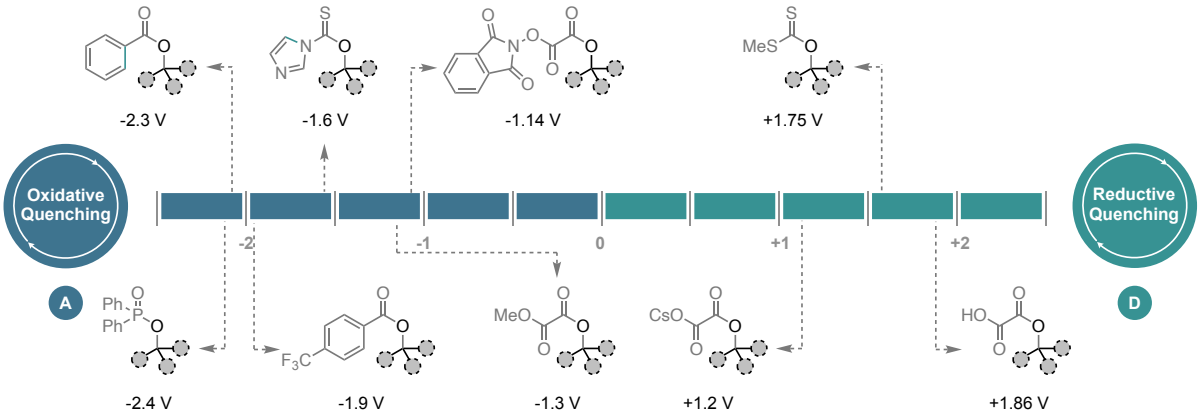


Figure 7. Common activators for radical deoxyfunctionalization reactions.

The way to determine the role of these species is to know their standard reduction potentials, which give us a clue about the thermodynamic viability of the single-electron transfer (**SET**) reaction with a given photocatalyst.[54] Cyclic voltammetry (**CV**) is the most employed technique to measure these values, which are given in volts against a known reference electrode in an specific solvent, usually the saturated calomel electrode (**SCE**) in acetonitrile.[68] As a result, $E_{1/2}^{ox/red}$ are obtained and both represent the electrochemical reduction potential of the half reaction written in the direction of the reduction. This last detail should be taken into consideration to prevent confusion and misinterpretation.

The potentials associated to the different stages of many well-known photocatalysts complexes during the catalytic cycle (PC^n, $*PC^n$, PC^{n-1} or PC^{n+1}) can be readily calculated, and they are considered as the main reference to compare with the rest of the components involved in the mechanism.[29] Since the redox potentials for the photocatalyst and the substrates can be calculated, a qualitative estimation of the photoinduced electron transfer (**PET**) can be measured using the simplified version of "the Gibs energy of photoinduced electron transfer" equation (**eq 1-2**), where $\mathcal{F}$ is the Faraday constant (23.061 kcal V^{-1} mol^{-1}). A more negative value of ΔG_{PET} translates into a more thermodynamically favorable electron transfer event.[54]

$$\Delta G_{PET} = -F\left(E^*_{red}\left(\frac{cat^*}{cat^{\bullet-}}\right) - E_{ox}\left(\frac{sub^{\bullet+}}{sub}\right)\right) \quad \textit{Eq. 1}$$

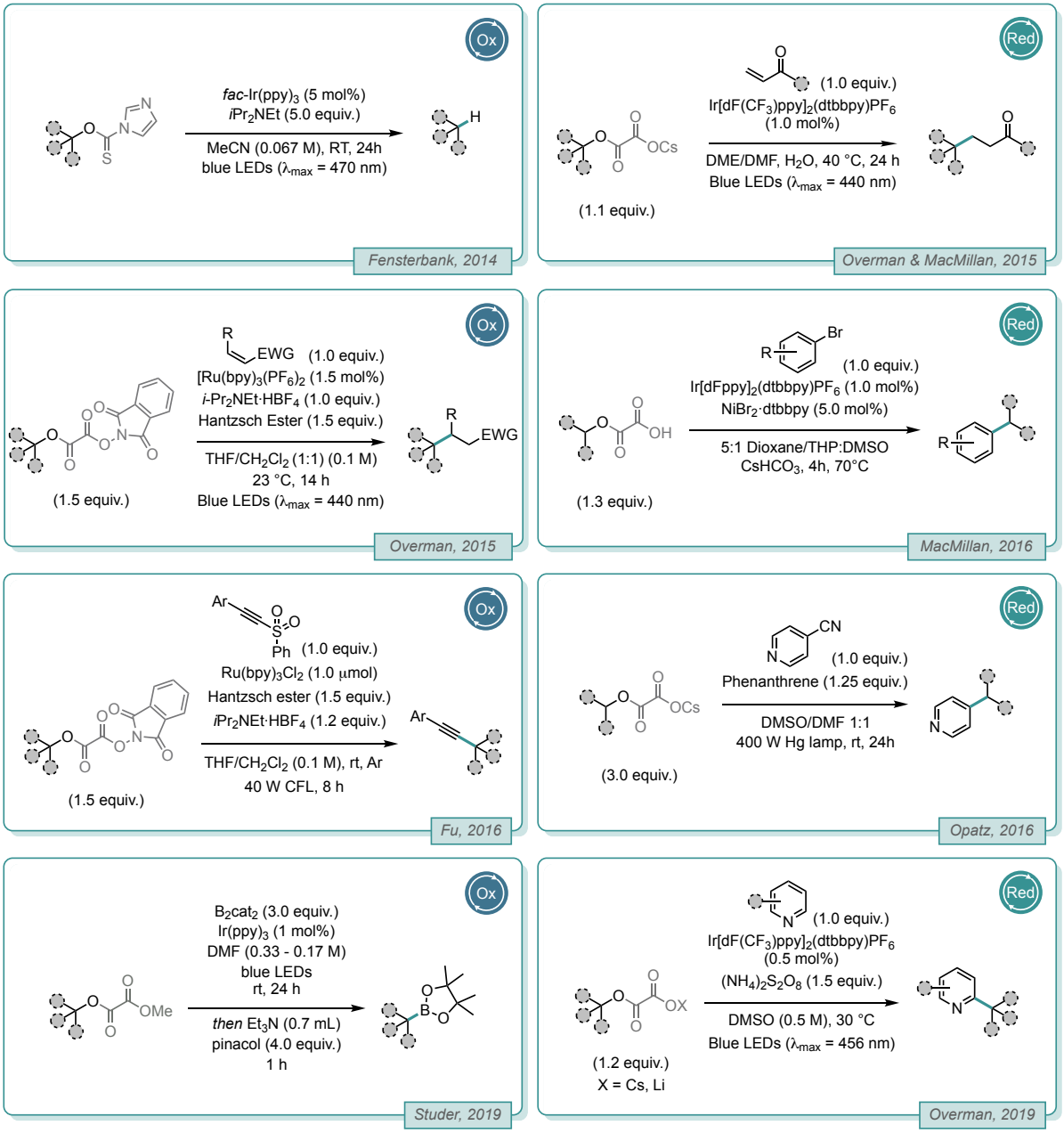
$$\Delta G_{PET} = -F\left(E_{red}\left(\frac{sub}{sub^{\bullet-}}\right) - E^*_{ox}\left(\frac{cat^{\bullet+}}{cat^*}\right)\right) \quad \textit{Eq. 2}$$

Equation 1-2. Gibbs energy of photoinduced electron transfer.

With all this information, many authors have explored the implementation of these activators for the development of novel photoredox-mediated deoxyfunctionalization methodologies. **Scheme 3** illustrates some of the most representative examples of this strategy in the last decade, employing both oxidative and reductive quenching cycles.

Considering the oxidative quenching cycle, in 2014 Fensterbank presented a Barton-McCombie deoxygenation method that avoids the use of toxic tin reagents, using thiocarbamates as activators and Hünig's base as hydrogen source.[69] In 2015, Overman reported a convenient method for the direct construction of quaternary carbons from tertiary alcohols by visible-light photoredox coupling of *tert*-alkyl *N*-phthalimidoyl oxalate redox-active ester (**RAE)** intermediates with electron-deficient alkenes (Michael acceptors).[70] Similarly, Fu and coworkers have reported a novel and efficient visible-light photoredox method for the synthesis of internal alkynes containing quaternary carbons.[71] Recently, Studer reported the deoxygenative borylation of tertiary alcohols,[72] which were activated through the formation of methyl oxalates. In addition, this methodology was employed for the conversion of tertiary propargylic alcohols into allenyl boronic esters – the first radical approach reported towards these structures.

Although synthetically useful, the methods reported by Overman and Fu specifically present one main drawback: *N*-phthalimidoyl oxalates can be difficult to synthesize and isolate due to their instability during aqueous workup or flash chromatography.[73] With the aim of solving this problem, Overman, in collaboration with MacMillan, developed the use of simple cesium oxalate salts as radical precursors under photoredox conditions for the coupling of tertiary alkyl radicals with electron-deficient alkenes.[73] Furthermore, McMillan has expanded the use of these cesium oxalates as carbon radical fragments in metallaphotoredox catalysis for cross-coupling with a broad range of aryl halides.[74] Similarly, Opatz has shown that these oxalates can be used in transition-metal-free decarboxylative photoredox coupling with aromatic nitriles.[75] Finally, Overman has applied the use of cesium oxalate salt activators for the alkylation of basic heteroarenes via a Minisci-type reaction.[76] All these methodologies mechanistically work via reductive quenching cycle.



Scheme 3. Representative examples of photoredox deoxyfunctionalization methodologies.

In summary, all these representative examples show that radical deoxyfunctionalizations have arisen as a promising and advantageous technology to approach the development of novel and exciting functional group interconversion methodologies.

1.3. Amino Acids

Over the 500 amino acids (**AAs**) founded in nature, the human body codes for only 20 and they are known as the natural or canonical **AAs**.[77] This means that every protein in our bodies is made up by a combination of these 20 **AAs**, which are classified in two sub-groups: on one hand, non-essential **AAs** are the ones that the body is able to synthesize and on the other hand, essential **AAs** are the ones which are impossible to synthesize in the human body and they have to be introduced through the diet (**Figure 8**).

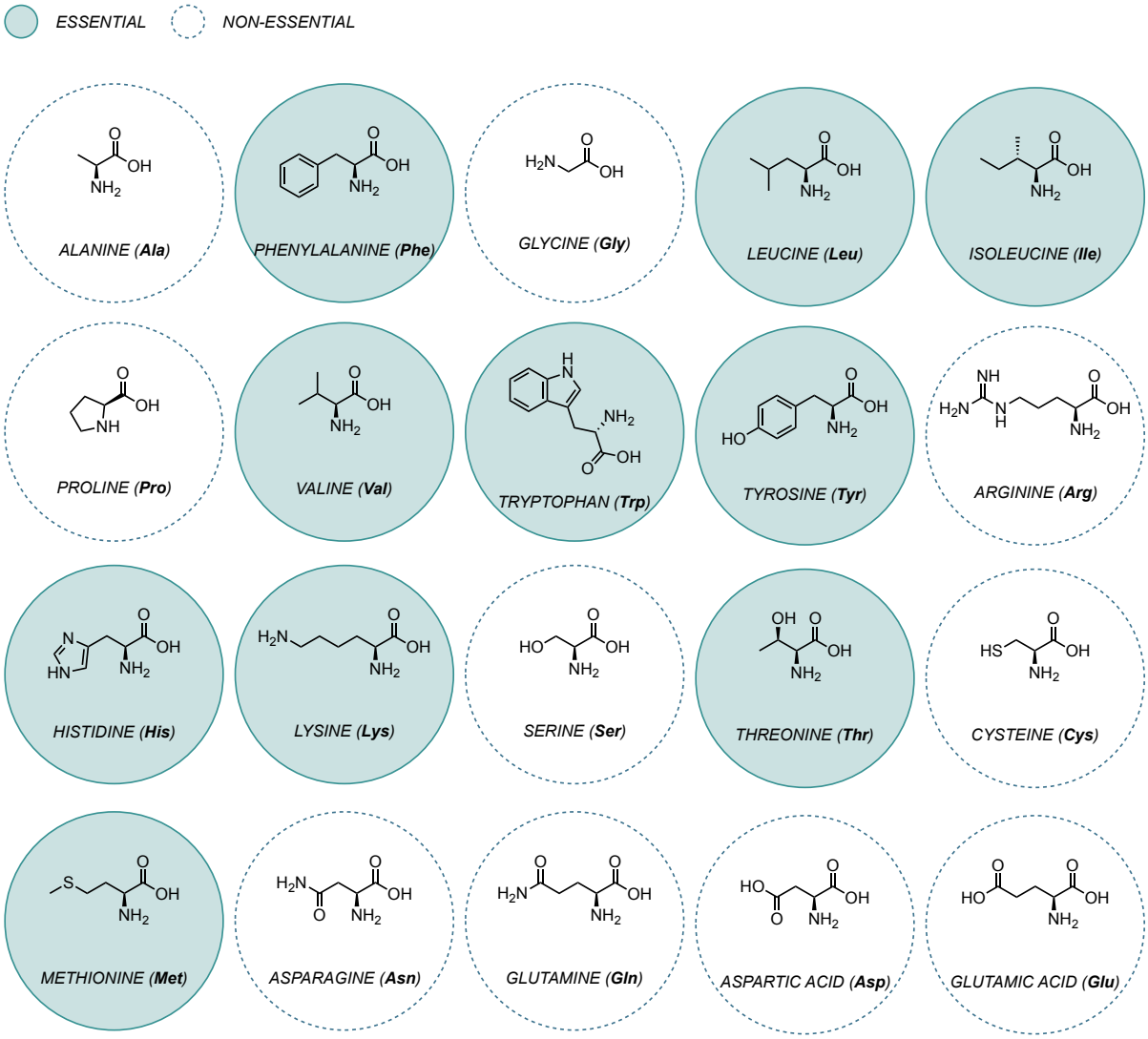


Figure 8. Proteogenic amino acids.

AAs constitute one of the most versatile building blocks for chemical and biological syntheses, as demonstrated by their application in the synthesis of wide range of bioactive molecules, *e.g.* peptidomimetic drugs.[77] Furthermore, they represent an important group of ligands in transition-metal catalysis[78] and key building blocks in polymers and materials.[79]

However, **AAs** suffer from a facile degradation under biological conditions and, their unfavorable physical properties at the time of peptides design and construction, restrain their direct application in pharma. Thus, modification of the **AAs** side chains represents a potent strategy to improve their characteristics and implementation, opening the door to the development of new synthetic methodologies capable of granting rapid access to this fascinating family of compounds.

As a result, such methodologies lead us to another class of these key structural motifs, not found in nature and only obtained through a synthetic pathway; unnatural amino acids (**UAAs**). **UAAs** are particularly important, as they often display distinct and improved properties when compared to their proteogenic counterparts. Between the strategies developed during the last decades, it is worth highlighting the use of enzymatic, and transition-metal-catalyzed processes[80–83] or radical based strategies. [84,85] This last pathway gained value due to all the advantages that radical chemistry offers, including milder conditions, and a plethora of synthetic precursors available to generate open-shell species providing rapid access to libraries of novel **UAAs** and for the site-selective modification of peptides and proteins. All these methodologies will be discussed exhaustively during Chapter 5.

1.4. Goals of the thesis

Light-mediated methodologies have become very popular in the field of radical chemistry during the last decades due to the mild and controlled conditions that these strategies offer to generate open-shell species. The projects described in this thesis represent a modest contribution to this fascinating field, along with a better understanding and development of its applications in two main transformations: selective deoxyfunctionalizations of congested systems, and diastereoselective synthesis of novel unnatural amino acids (**UAAs**) structures. Chapter 2,3, and 4 focus on the former, whereas chapter 5 on the latter.

Regarding deoxyfucntionalizations technologies, chapters 2 and 3 highlight the natural abundance of the hydroxyl moiety, which allows for the development of two straightforward functional group transformations: firstly, the formal deoxyfluorination of tertiary alcohols (Chapter 2), and secondly, the synthesis of novel saccharide based polycyclic scaffolds by using an intramolecular Minisci-type reaction (Chapter 3). Chapter 4 describes the synthesis and potential applications of a novel hypervalent iodine (III) reagent light-mediated radical deoxycyanation and electrophilic cyanations strategies. All these transformations were performed via oxalic or oxalate pre-activation of the corresponding alcohol substrates.

Finally, chapter 5 stands out the advantages of photoredox catalysis in the synthesis of novel unnatural amino acids structures, with two novel methodologies via radical alkylation and acylation in a diastereoselective way.

2. FORMAL RADICAL DEOXYFLUORINATION OF TERTIARY ALCOHOLS

2.1. The Fluorine Atom: Importance & Impact

Despite the nonexistence of organofluoride compounds in Nature, the importance of the fluorine atom in organic molecules is a fact that has been well stablished during the last 60 years.[86] Its presence and implementation on a large number of agrochemicals,[87] organic dyes for new displays and solar cells,[88] and pharmaceuticals[89,90] supports such statement (**Figure 9**). In the case of pharmaceuticals, fluorine atoms play a significant role tuning the electronic and pharmacokinetic properties of potential drug candidates. The introduction of fluorinated motifs on a bioactive molecule often leads to the modification of its ADME (Administration, Distribution, Metabolism, Excretion) profile without disturbing the general characteristics of such molecules.

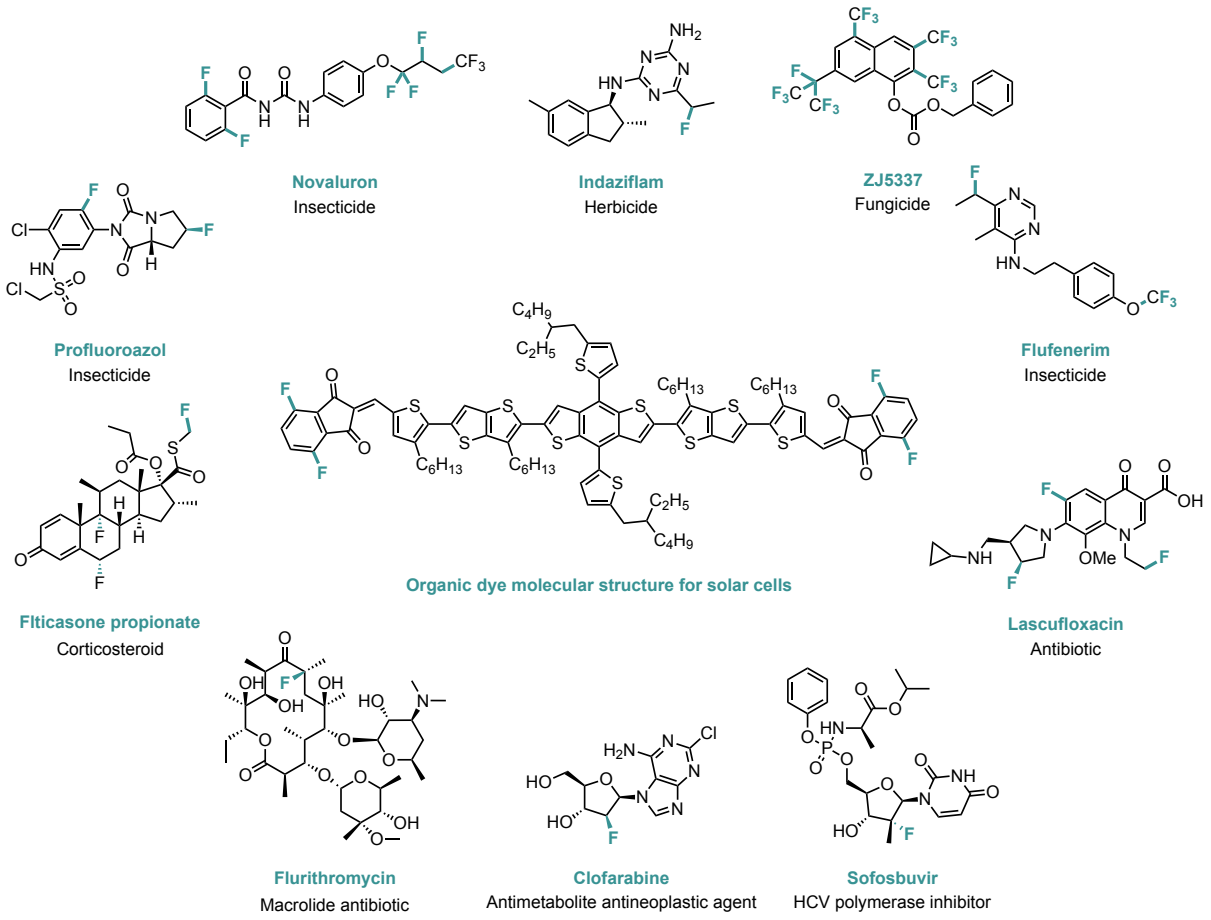


Figure 9. Selected key fluorinated compounds with applications across several research fields

2.1.1. Strategies to introduce F atoms in organic molecules

The direct consequence of this distinct fluorine effect has been the invention of a large number of strategies for the introduction of this privileged atom in organic molecules. Among them, nucleophilic deoxyfluorination methodologies have arisen as one of the most prominent strategies. This is mostly due to the natural abundance, as well as the unique reactivity of alcohols, which were already discussed in Chapter 1. The first known deoxyfluorination reagent was the gaseous SF_4 developed by Smith during the 1970s.[91,92] Despite constituting an excellent reagent for deoxyfluorination reactions, SF_4 is a toxic gas and difficult to manipulate, needing the use of metal autoclaves as reaction vessels. To solve this issue, in 1972 Middleton developed a novel, bench-stable reagent for nucleophilic deoxyfluorinations, diethylaminosulfur trifluoride (**DAST**).[93] Traditionally, this has been the main reagent for deoxyfluorination of primary, secondary and tertiary alcohols. However, its inherent reactivity represents a drawback in terms of functional-group tolerance. Many other reagents have been developed during the subsequent decades, being worth highlighting the PyFluor developed by Doyle,[94,95] or PhenoFluor[96–100] and AlkylFluor by Ritter.[101] These reagents represent a milder and more effective deoxyfluorination option, overcoming the limited functional-group tolerance associated with **DAST** and its derivates (**Figure 10**).

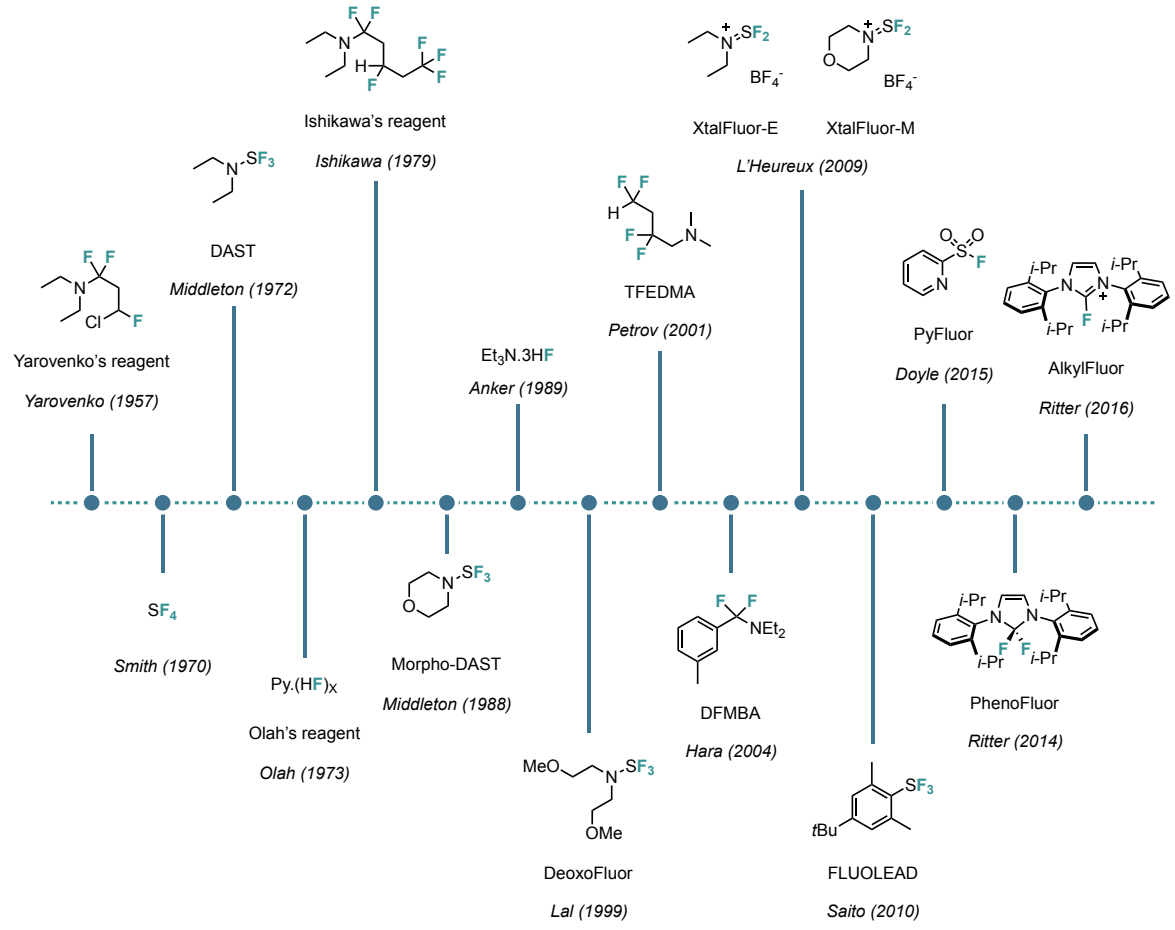


Figure 10. Deoxyfluorination reagents

Although very powerful, these new reagents are ineffective with sterically congested tertiary and neopentyl alcohols, mainly because they react through a S_N2 pathway. Based on the topics discussed in Chapter 1, a radical deoxyfluorination approach might represent a complementing methodology with the potential to overcome the limitations associated to the existing nucleophilic strategies. In terms of radical fluorination methodologies, one reagent stands out over the rest: Selectfluor® (**Figure 11**). Selectfluor® is a non-toxic, air stable, crystalline solid commonly employed in 2-electron processes as an oxidant or as an electrophilic fluorine source.[102] Furthermore, it can also be involved in 1-electron processes, generating *N*-(chloromethyl)triethylenediamine radical dication (**TEDA$^{2+\bullet}$**), a unique species that displays different properties and reactivities than SelectFluor®.[103] Among distinct reactivity modes of **TEDA$^{2+\bullet}$**, its behavior as a single electron oxidant was key to the development of the novel radical deoxyfluorination strategy discussed in this chapter.

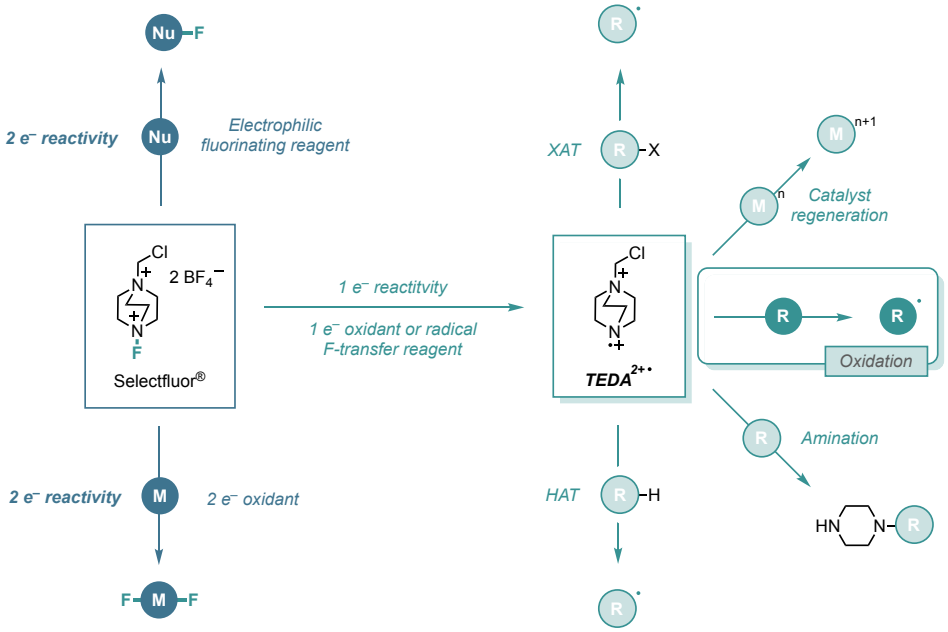
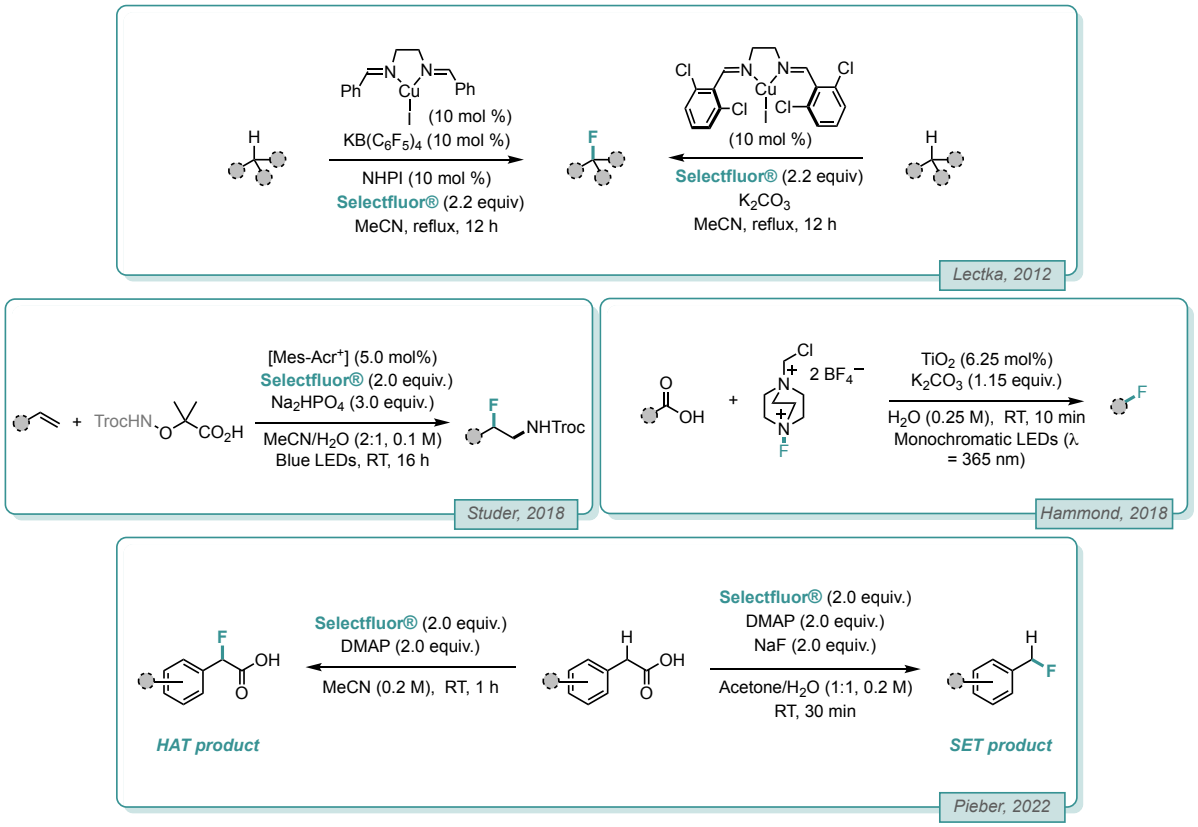


Figure 11. SelectFluor® & TEDA2$^{+\bullet}$

Lectka and co-workers were one of the first group to report the use of **TEDA$^{2+\bullet}$** in a HAT process , using a Cu^{I} catalyst for the straightforward fluorination of aliphatic, allylic or benzylic C–H bonds (**Scheme 4**).[104] Focusing on the oxidation methodologies, Studer and co-workers have accomplished the amidofluorination of unactivated alkenes using α-amido-oxy acids as amidyl radical precursors.[105] Hammond and co-workers have reported the efficient decarboxylative fluorination of aliphatic carboxylic acids using the commercially available and inexpensive heterogeneous catalyst TiO_2.[106–108] Very recently, Pieber and co-workers have reported a divergent benzylic fluorination by N–F activation of Selectfluor® with DMAP.[109] The authors demonstrated that the reaction media played a critical role in the final selectivity of this methodology.



Scheme 4. Radical fluorination examples

2.2. Goals of the project

I joined the Gómez-Suárez group in 2019, being this project the first of my PhD training. All the disclosed information established the bases for the project of this chapter, which consisted in the development of a novel radical-based deoxylfuorination strategy towards tertiary systems (**Figure 12**). Cesium oxalate salts, previously synthesized from the corresponding alcohols motifs, will be employed as suitable radical precursors. These cesium salts demonstrated to possess a great stability, with the possibility of store them for extended periods at room temperature. Moreover, their mild oxidation potentials ($E_{1/2}^{ox}$ = +1.2 V vs SCE) allow their use under visible-light mediated technologies, producing no byproduct other than CO_2. However, Overman and co-workers studies and reported the main reason why the election of these salts was essential for this transformation. [110] The authors confirmed than the decomposition of these salts proceeds via formation of an acyloxy radical intermediate **A**. The latter undergoes under a first decarboxylation event to form an alkoxycarbonyl radical intermediate **B**. Now, **B** experiences a second decarboxylative event, whose rate is dependent of the stability of the resulting radical. This decarboxylation rate is *ca*. 500 times faster in the case of the tertiary alkyl substituents, than for primary substituents, which further supports the choice of cesium salts as radical precursors for the development of a deoxyfluorination protocol for tertiary alcohols.

The combination of these salts with SelectFluor® might generate the open-shell tertiary alkyl radical species **C** via single electron oxidation event mediated by **TEDA2$^{+\bullet}$.** Then, an interaction with a second molecule of SelectFluor® might afford the desired tertiary fluorinated product.

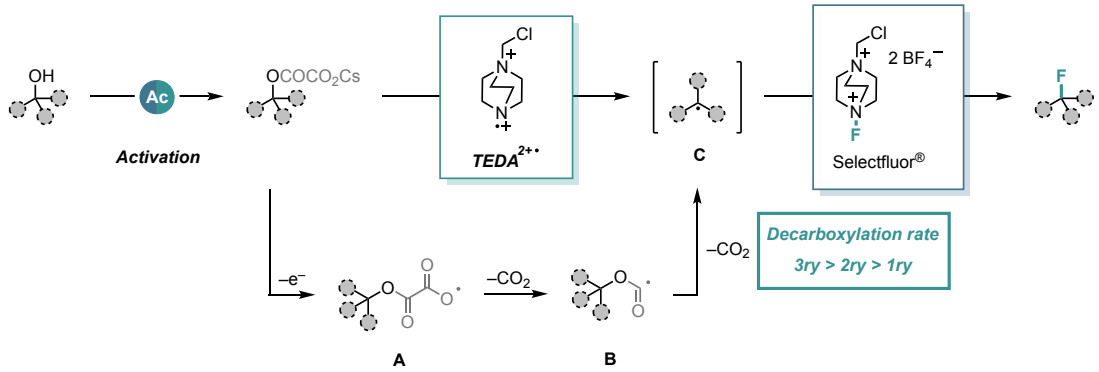
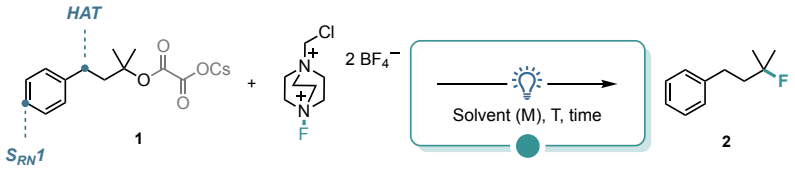


Figure 12. Stages of dexyfluorination method.

During the development of this project, Dr. Frederick Ballaschk, Dr. Marcel Jaschinski, and Dr. Yasemin Özkaya helped me with the synthesis of the starting materials for the first examples of the scope.

2.3. Optimization & scope

To begin with this work, the pertinent optimization studies were carried out, crucial to finding the right conditions for the desired transformation (**Table 1**). The compound chosen as model substrate for such studies was cesium oxalate **1,** as it possesses three potential reactive sites towards **TEDA$^{2+\bullet}$**: 1) the benzylic C–H bond, which is sensible to a hydrogen atom transfer (**HAT**) event,[104,111,112] 2) an aromatic group, which could undergo radical amination in *para* position, and, finally, 3) the oxalate anion, which could undergo the desired single electron oxidation. The first reaction conditions that were tested consisted in the irradiation of **1** and SelectFluor® with a 32 W blue LED (λ_{max}= 440 nm) inside an EvoluChem™ PhotoRedOx Box for 16 h in a 1:1 mixture of 1,4-dioxane/H_2O (**Entry 1**). The yield of the fluorinated product **2** with these initial conditions was 70%, analyzed by ^{19}F-NMR using trifluorotoluene as internal standard. The next logic step was to evaluate the influence of the reaction time, which was reduced to 2.5 h without affecting the yield (**Entry 2**). Further analysis demonstrated that irradiation was essential for the successful outcome of the reaction (**Entry 4**) and heat could not promote this transformation (**Entries 5-6**). A subsequent solvent screening revealed that 1:1 mixture of acetone or acetonitrile with H_2O increased the yield of the reaction up to 80% with only 1 h of irradiation (**Entries 8-9**).



Entry	Selectfluor® (equiv.)	Solvent (ratio, M)	Reaction time (h)	2 (%)[a]
1	2.5	1,4-dioxane:H_2O (1:1, 0.1)	14	70
2	2.5	1,4-dioxane:H_2O (1:1, 0.1)	2.5	73
3[b]	2.5	1,4-dioxane:H_2O (1:1, 0.1)	2.5	71
4[c]	2.5	1,4-dioxane:H_2O (1:1, 0.1)	2.5	0
5[d]	2.5	1,4-dioxane:H_2O (1:1, 0.1)	2.5	0
6[e]	2.5	1,4-dioxane:H_2O (1:1, 0.1)	2.5	4
7	2.5	EtOAc:H_2O (1:1, 0.1)	1	18
8	**2.5**	**Acetone:H_2O (1:1, 0.1)**	**1**	**79**
9	**2.5**	**MeCN:H_2O (1:1, 0.1)**	**1**	**80**
10	2.5	DME:H_2O (1:1, 0.1)	1	43
11	2.5	DMF:H_2O (1:1, 0.1)	1	70
12	2.5	DMA:H_2O (1:1, 0.1)	1	30
13	2.5	DCE:H_2O (1:1, 0.1)	1	61
14	2.5	Acetone (0.1)	1	0
15	2.5	H_2O (0.1)	1	0

a) ^{19}FNMR yields using trifluorotoluene as internal standard; b λ_{max} = 405 nm; c) No light; d) No light, 30 °C; e) No light, 50 °C

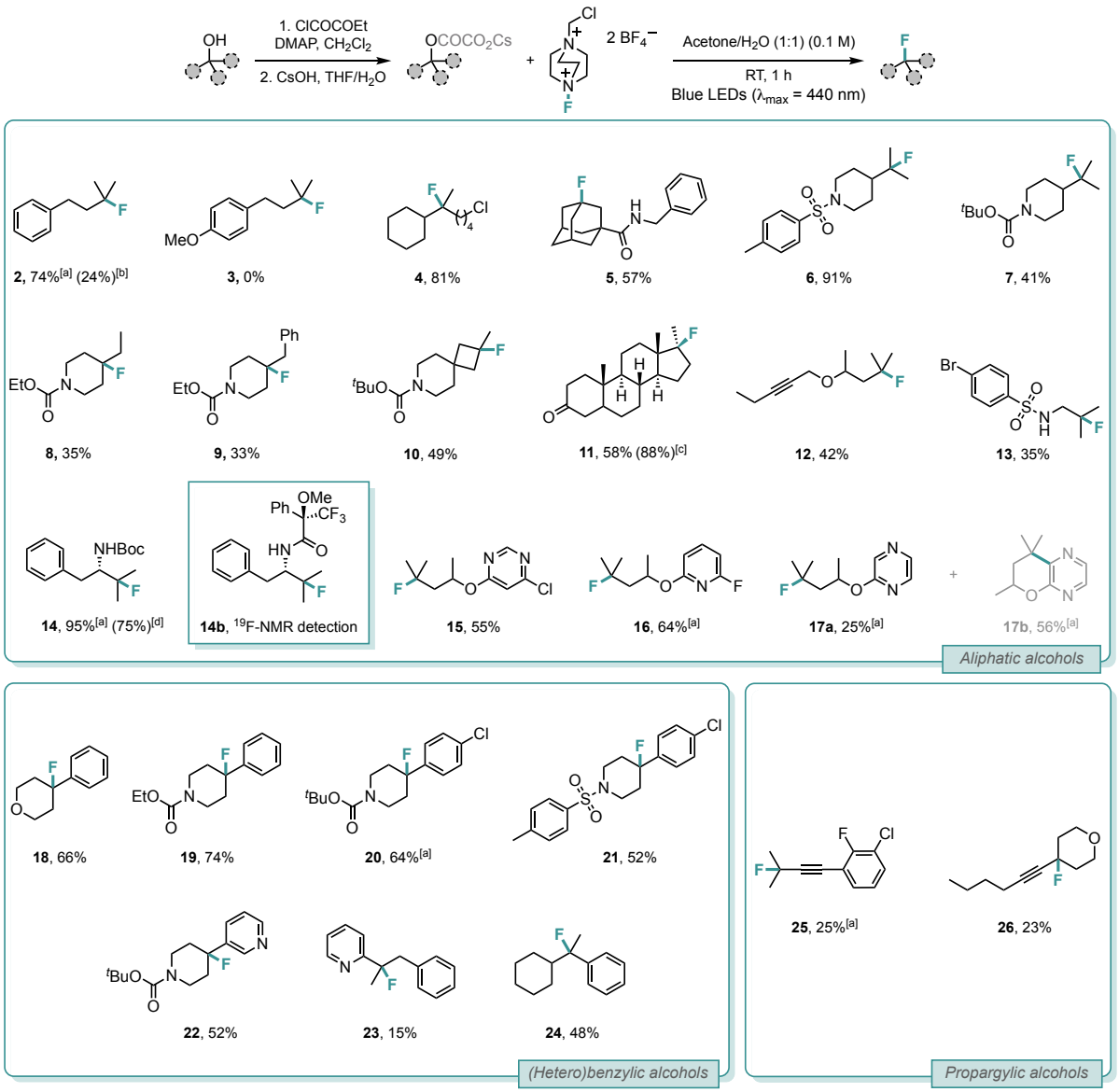
Table 1. Optimization studies.

With the optimal conditions in hand, the scope of this transformation was explored (**Scheme 5**). First, compound **2** was successfully isolated in 74% yield. When an electron rich *p*-methoxy substituent was introduced in the phenyl ring, the reaction failed to afford the desired fluorinated product **3**. The hypothesis behind this lack of reactivity is presumably a competing electron transfer event, where **TEDA$^{2+\bullet}$** oxidizes the electron-rich aromatic ring rather than the oxalate anion. This hypothesis was proven by running the standard reaction with **1** in the presence of 1 equiv. of anisole ($E_{1/2}^{red}$ = +1,79 V vs SCE),[113] which afforded **2** in only 24% yield. Product **4** was isolated 81% high yield bearing a primary chloride. 1-adamantanol derivatives, important motifs in medicinal chemistry and industrial applications,[114–118] also tolerated the deoxyfluorination conditions and product **5** bearing a benzylic amide was obtained in 57% yield. Different piperidine derivatives were also successfully fluorinated, both exocyclic (**6**-**7**) and endocyclic (**8**-**9**) examples bearing different *N*-protecting groups. Other ring sizes (**10**-**11**) and internal alkynes (**12**) were also tolerated, providing the desired products in moderate to good yields (42–58%). It is worth mentioning the excellent functional group tolerance showed in example **11**, where the use of **DAST** would have afforded the corresponding *gem*-difluoride species by attacking the carbonyl position. *ß*-amino alcohol derivates (**13**-**14**) can be also employed as substrates under these fluorination conditions. Moreover, **14** was successfully isolated in 75% yield in a gram-scale reaction after 3 h of irradiation. In addition, the Mosher analysis was employed to demonstrate the stereoretention of this example. Such method was reported by Mosher in 1969, where the author employed enantiopure methoxy(trifluoromethyl)phenylacetyl (MTPA) as a chiral

resolving reagent.[119,120] In the case of **14**, the product was deprotected and the resulting amine was mixed with the enantiopure acyl chloride ®-(+)-MTPA-Cl. ^{19}F NMR of the reaction showed formation of only one diastereoisomer of the desired Mosher's amide **14b**, proving the stereoretention of the reaction (*see SI*). Examples using basic heterocycles, such as pyrimidines (**15)**, pyridines (**16**) and pyrazines (**17a**) were also fluorinated in 55%, 64% and 25% yield respectively. The reason of the low yield in case of the pyrazine example is because **17b** was isolated as the main byproduct in 56% yield. The formation of this fused bicyclic molecule can be explained by a faster intramolecular radical cyclization event, followed by a re-aromatization by oxidation with Selectfluor®.

To further expand the scope of the methodology, several (hetero)benzylic alcohols were also considered as potential substrates. Benzylic tetrahydropyran (**18**), as well as piperidine derivates (**19**-**21**) were all isolated in good yields (52–74%), bearing phenyl and *p*-chloro substituents The change of the phenyl ring for a 3-pyridinil substituent did not affect the outcome of the reaction, obtaining the fluorinated product **22** in 52% yield. Compound **23** bearing a 2-pyridinyl motif was only obtained in 15% yield, while more sterically congested benzylic fluoride **24** was afforded in 48% yield.

Finally, tertiary propargylic alcohols were tested as interesting examples for the scope. The importance of the propargylic fluorides has been well stablished by their presence in biologically important compounds, e.g. insecticides, herbicides, and vitamins.[121,122] Unfortunately, the existing nucleophilic strategies to obtain these substrates present a challenge due to competing elimination processes and 1,2-alkyl shifts.[122] Satisfyingly, examples **25** and **26** were obtained in 25% and 23% yield respectively, demonstrating the versatility of this fluorination method.

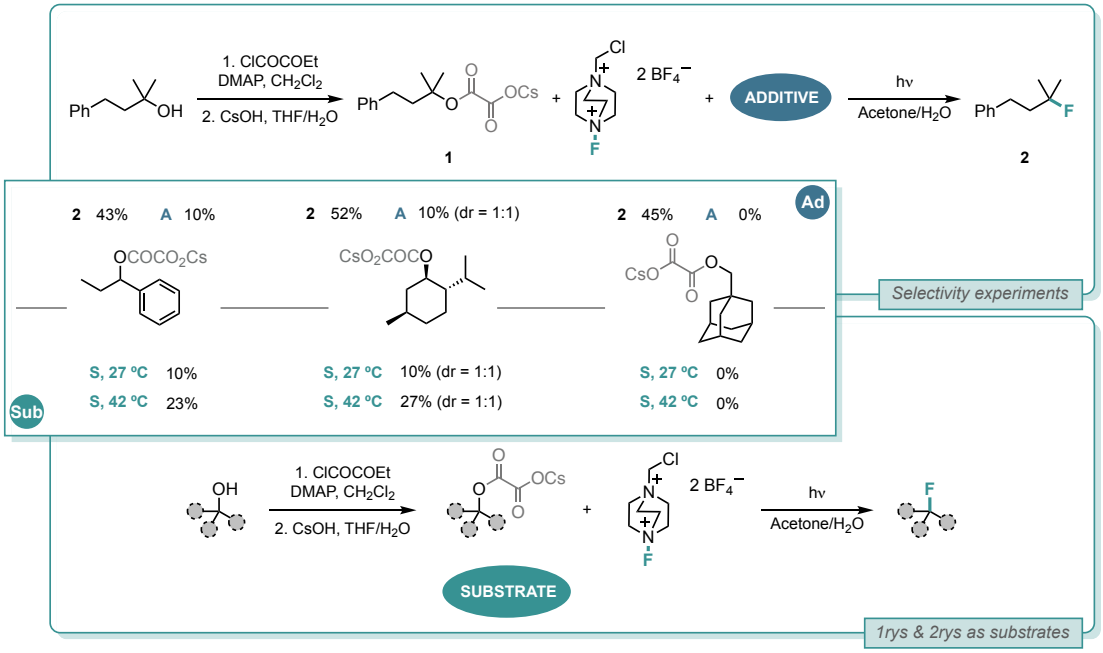


Scheme 5. Scope & limitations of the reaction.

2.4. Control experiments & mechanistic studies

To gain further insight of the factors governing this reaction, control and mechanistic experiments were performed. The selectivity of the reaction was tested by using secondary – both benzylic and aliphatic – and primary oxalates in two different set of experiments. First, the standard reaction with substrate **1** was carried out using 1 equiv. of a primary or secondary oxalate as additive. In all the cases, the tertiary fluoride **2** was the major product of the reaction, with only 10% of the secondary products detected, and with no detection of the corresponding primary fluoride. Afterwards, the deoxyfluorination reaction was conducted using primary and secondary oxalates as substrates. These experiments afforded a similar outcome; secondary fluorides were observed in 10% yields, while no product formation was observed for the primary oxalate. Increasing the reaction

temperature, had only a small effect on the outcome. Therefore, these experiments confirmed the expected high selectivity of this transformation towards tertiary system (**Scheme 6**).



Scheme 6. Selectivity studies.

Once the selectivity of the reaction was verified, I decided to start with the pertinent mechanistic studies. The first stage of such studies was to prove the radical nature of the process. The usual way to perform this experiment is by using a stable radical species as scavenger to trap the possible radicals formed during the reaction. TEMPO ((2,2,6,6-Tetramethylpiperidin-1-yl)oxyl) is the most used radical scavenger. Hence, when TEMPO (1 or 3 equiv.) was introduced as additive under the standard reaction conditions, no fluorinated product was observed, supporting the possibility of the formation of a tertiary alkyl radical (**Scheme 7**). Although some studies suggested the interaction between TEMPO and SelectFluor®,[123] the excess of TEMPO equivalents should ensure the efficient trapping of the radical species formed. The formation of the bicyclic pyrazine **17b** further supports the formation of the key tertiary radical species.

After supporting the possible radical profile of the reaction, the next step was to determine which mechanism is operating in this transformation. The radical species formed during the course of the reaction might react in two different modes, either through a closed catalytic cycle or through a radical chain pathway (**Figure 13**).[124] In the former, both substrate and product interact with the catalytic cycle of the photosensitizer, where one photon produces one molecule of product. In a radical chain pathway, one molecule of the open-shell radical product would interact with another molecule of the substrate in a propagation cycle. Hence, the light irradiation should work as the initiator step for such propagation cycle.

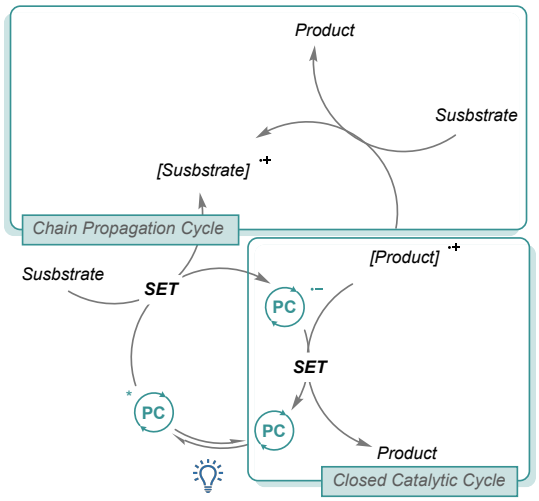


Figure 13. Closed cycle vs. chain propagation cycle.

In the early days of photoredox catalysis, light on/off experiments were used to determine whether a reaction proceeded via a radical chain pathway, assuming that if the reaction did not work in the dark, a radical chain was not possible. However, the lifetime of these processes stands in the range of seconds or nanoseconds, which makes difficult the final labelling of the cycle. Quantum yield (Φ) measurement proved to be a more reliable method for the identification of one or another pathway.[125,126] Φ is defined as the mol of product formed for each mol of photons absorbed, meaning that the reaction would have three possible outcomes:

- A maximum theoretical of Φ = 1 means that the reaction proceeds through a close cycle, where every photon absorbed generates one molecule of product.
- Φ >> 1 would indicate that a self-propagating radical chain is the mechanism in action.
- Φ << 1 does not discard the possibility of a radical chain process, although inefficient. This result is usually inconclusive, and more experiments should be run to clarify the reaction pathway.

With all this information, the quantum yield of the present deoxyfluorination method was measured. Following the procedure described by Yoon,[125] as series of data needs to be determined before performing the final quantum yield calculation. First, the photon flux of the lamps employed in this transformation (λ_{max}= 440 nm) was calculated. The photon flux is defined as the mol of generated photons per second and unit area in a surface. To calculate it, it is necessary to use a reference photochemical transformation. In this case, the well-known ferrioxalate actinometry method was employed as reference, where potassium ferrioxalate (Fe^{III}) is photodecomposed and an Fe^{II} complex is formed in the presence of 1,10-phenanthroline ligand. The moles of Fe^{II} complex formed can be measured using **eq. 3**, and then this data allowed the photon flux calculation using **eq. 4**, where Φ is the quantum yield for the ferrioxalate actinometer (1.01 at λ_{ex} = 437 nm), t is the irradiation time (70

s), and f is the fraction of light absorbed at λ_{ex} = 437 nm by the ferrioxalate actinometer. This value is calculated using **eq. 5** where A(440 nm) is the absorbance of the ferrioxalate solution at 440 nm. An absorption spectrum gave an A(440 nm) value of > 3, indicating that the fraction of absorbed light (f) is > 0.999. The photon flux was thus calculated (average of three experiments) to be 3.15 x 10^{-09} einsteins s^{-1}

$$mol\ Fe^{II} = \frac{V \times \Delta A\ (510\ nm)}{l \times \mathcal{E}} \qquad \textit{Eq. 3}$$

$$Photon\ flux = \frac{mol\ Fe^{II}}{\phi \times t \times f} \qquad \textit{Eq. 4}$$

$$f = 1 - \ 10^{A(440\ nm)} \qquad \textit{Eq. 5}$$

Equation 3-5. Parameters for quantum yield calculation.

After this calculation, the mol of product formed in this equation was calculated by ^{19}F-NMR analysis of a 0.1 mmol scale standard reaction after irradiation at 440 nm for 60 s, affording 8% yield of the product. Finally, the quantum yield of our methodology was measured using **eq. 6**. Where the photon flux corresponds to the one calculated above, *t* is the reaction time (60 s) and f is the fraction of incident light absorbed by the reaction mixture, determined using **eq. 5**. An absorption spectrum of the reaction mixture gave an absorbance value of 0.00847 at 437 nm, thus f is 0.0193. Thus, the quantum yield of the reaction was Φ = 2185.4, showing that a very efficient radical chain mechanism governs this transformation.[126] A further detailed protocol for the calculation of Φ was enclosed in the supporting information of this chapter.

$$\phi = \frac{mol\ of\ product\ formed}{Photon\ flux \times t \times f} \qquad \textit{Eq. 6}$$

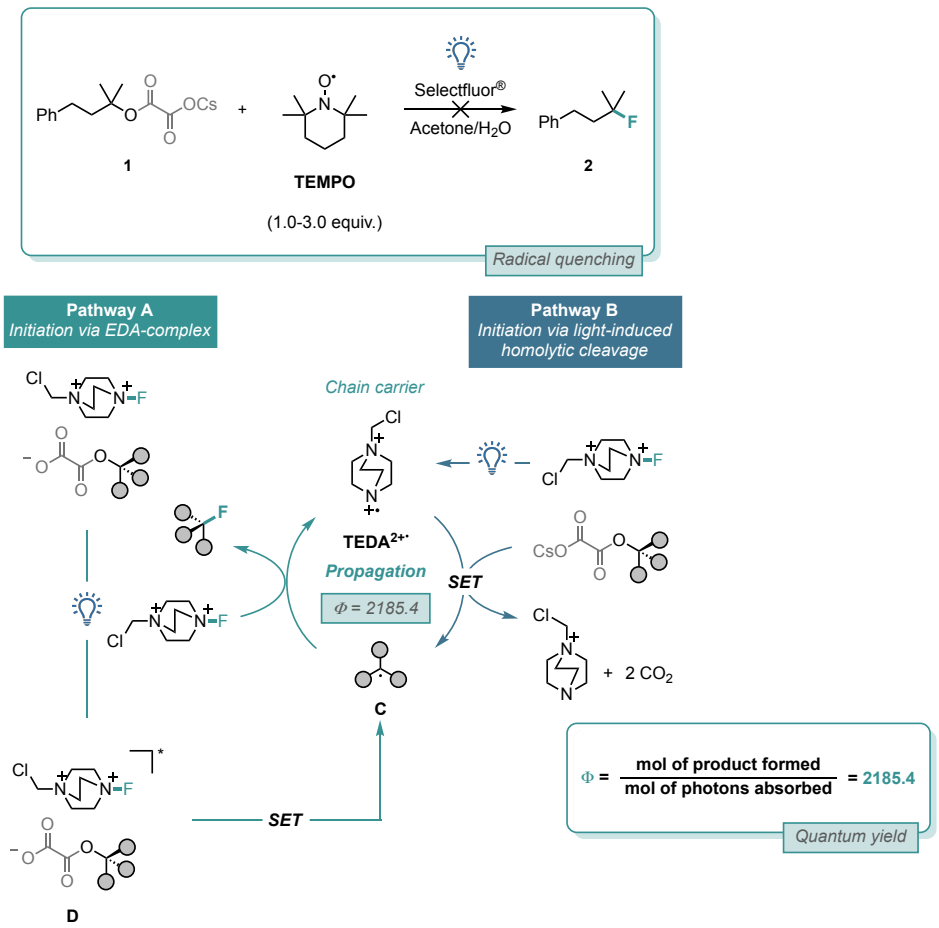
Equation 6. Quantum yield.

This result means that the formation of the aforementioned **TEDA$^{2+\bullet}$** species constitutes the initiation step of the radical chain mechanism, and two possible pathways could be considered for this step (**Scheme 7**):

- **Path A:** Generation of **TEDA2$^{+\bullet}$** via formation of an electron-donor-acceptor (EDA) complex. In spite of EDA-complexes being studied since the 1950s,[127,128] their importance has grown in the last 20 years because of the tendency to find new metal-free photochemical methods.[129] For the deoxyfluorination reaction, the formation of an EDA-complex (**D**) would be favored by the electrostatic interactions between the

corresponding oxalate (electron-rich or donor) and Selectfluor® (electron-poor or acceptor). Irradiation would promote the excitation of the EDA-complex, which under a subsequent **SET** event generates the tertiary alkyl radical species. The latter would be trapped by another molecule of Selectfluor® to afford the desired fluorinated product and **TEDA$^{2+\bullet}$** species. Once **TEDA$^{2+\bullet}$** is formed, it would oxidize a new molecule of the oxalate, stimulating the propagation of the radical-chain.

- **Path B:** Generation of **TEDA$^{2+\bullet}$** via direct irradiation of Selectfluor®. This pathway contemplates the possibility of the homolytic cleavage of the N–F bond caused by the irradiation of Selectfluor® with blue LEDs. Hence, **TEDA$^{2+\bullet}$** would be generated and further react in a single-electron oxidation event with the oxalate species. After a double decarboxylation event, the tertiary radical would been generated and then it would react in the same fashion than in **Path A** to afford the desired fluorinated product and regenerating **TEDA$^{2+\bullet}$.** Reported methodologies by Lei[130,131] and Jin[132] shown the possibility to access **TEDA$^{2+\bullet}$** by direct irradiation of Selectfluor® with blue LEDs to exploit it as a HAT catalyst.



Scheme 7. Proposed mechanism pathways & mechanistic studies.

Further studies were conducted to determine which of these initiation pathways might be in operation in this reaction. One of these studies was the measurement of the UV/Vis spectra of Selectfluor®, **1** and the reaction mixture (**Figure 14**). The rationale behind this experiment is that if a potential EDA-complex would be formed, a new absorption band should appear in the spectrum when all the needed components are mixed. The result of the experiment was the observation of a new band starting at approximately λ = 410 nm which also increase when the concentrations of Selectfluor® versus **1** (from 0.5 to 2.5 equiv.) were increased. This result suggests that the overlap between the absorption spectrum of the reaction mixture and the emission spectrum of blue LEDs with λ_{max} = 405 nm is better, which would boost the outcome of the reaction. Therefore, different wavelengths of irradiation (λ_{max} = 365, 405 and 440 nm) were tested under the standard conditions, revealing that all the reactions were complete after 30 min regardless the λ_{max} employed. However, at shorter reaction times the highest yields were observed when blue LEDs with λ_{max} = 405 nm were employed. All these results point towards **Path A**, proceeding through the formation of the EDA-complex, as the initiation step.

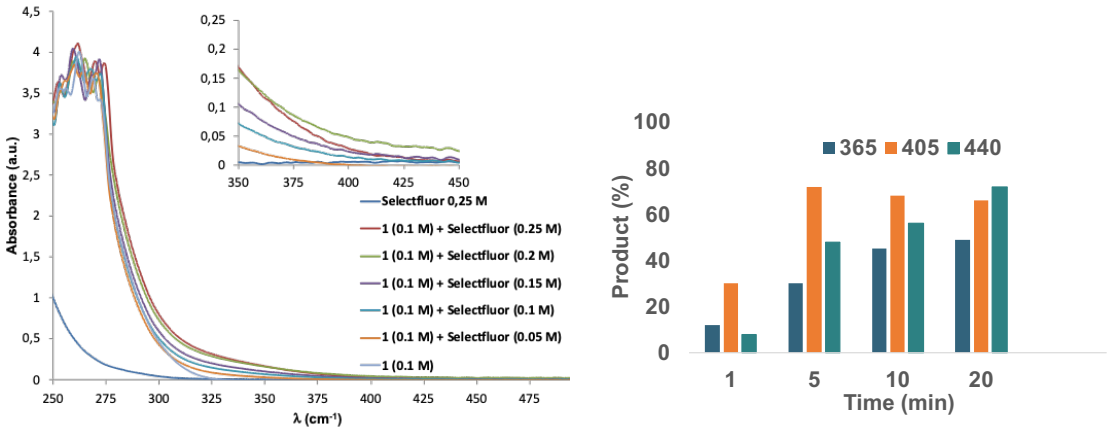


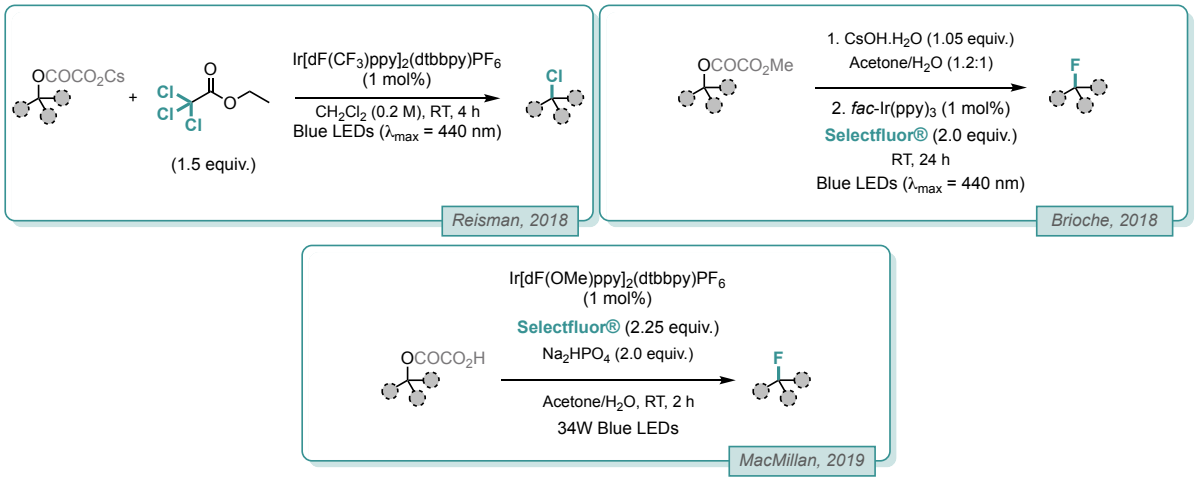
Figure 14. UV/Vis measurements & light sources.

2.5. Summary & conclusions

In summary, a formal and straightforward deoxyfluorination method was developed in the Gómez-Suárez lab. Other deoxychlorination and deoxyfluorination methods were reported by Reisman,[133] Brioche[134], and MacMillan[135] during the preparation of the manuscript for this project (**Scheme 8**). For Reisman's transformation, the main goal of the authors was the development of a novel deoxychlorination methodology. Therefore, all the optimization studies were designed to achieve this goal, showing only preliminary studies in the case of the deoxyfluorination. In the case of Brioche's methodology, the authors reported a two steps, one pot transformation in which the first

step involved the synthesis of tertiary cesium oxalate salt from the corresponding tertiary methyl oxalates. In the subsequent step, the use of the good reductant *fac*-[Ir(ppy)$_3$] photocatalyst in combination with Selectfluor® afforded the desired tertiary fluorinated product. Control reactions without the photocatalyst showed a notorious decrease of yield. My main hypothesis behind these drastically different results is a low concentration of the cesium oxalate salt species in the reaction when the mixture was irradiated, inhibiting the possible formation of the proposed EDA–complex.

For MacMillan's manuscript, the optimization studies were performed using a secondary activated alcohol as model substrate. The latter trends to possess higher oxidation potential and its rate of decarboxylation is considerably lower than in case of tertiary systems (see Section 2.2) , which explains the use of a more oxidant species, concretely the oxidized form of Ir[dF(OMe)ppy]$_2$(dtbbpy)PF$_6$, Ir^{IV} ($E_{1/2}$[Ir^{IV}/Ir^{III}] = –0.89 V vs. SCE).[136]



Scheme 8. Complement deoxychlorination & deoxyfluorination methodologies.

These methodologies further highlight the excellent selectivity towards tertiary alcohols and the metal-free profile of our method. Preliminary mechanistic studies support the formation of an EDA-complex which after irradiation generates the corresponding tertiary alkyl radical and **TEDA$^{2+\bullet}$**, key species of the reaction which affords the desired fluorinated product in a radical-chain mechanism. Nevertheless, generation of **TEDA$^{2+\bullet}$** after direct irradiation of Selectfluor® could not be discarded. Further studies, such as computational investigations using density functional theory (DFT) calculations should be performed to fully differentiate between both initiation pathways.

3. INTRAMOLECULAR MINISCI-TYPE REACTION FOR FUSED HETEROCYCLE SYNTHESIS AND MODIFICATION OF SACCHARIDES

3.1. C–H functionalization of heterocycles

Heterocycles constitute as one of the most ubiquitous frameworks in bioactive organic molecules, as demonstrated by their presence in the most essential living cell architectures, DNA and RNA chains, vitamins, and hormones, as well as in pharmaceuticals, herbicides, pesticides, and dyes (**Figure 13**).[137–141]

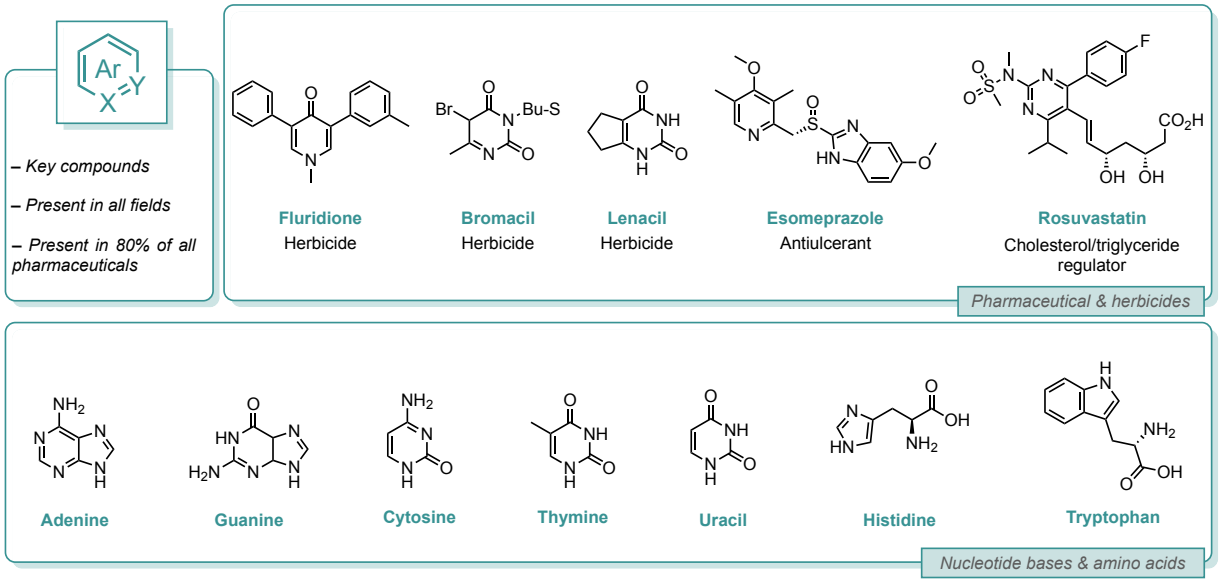
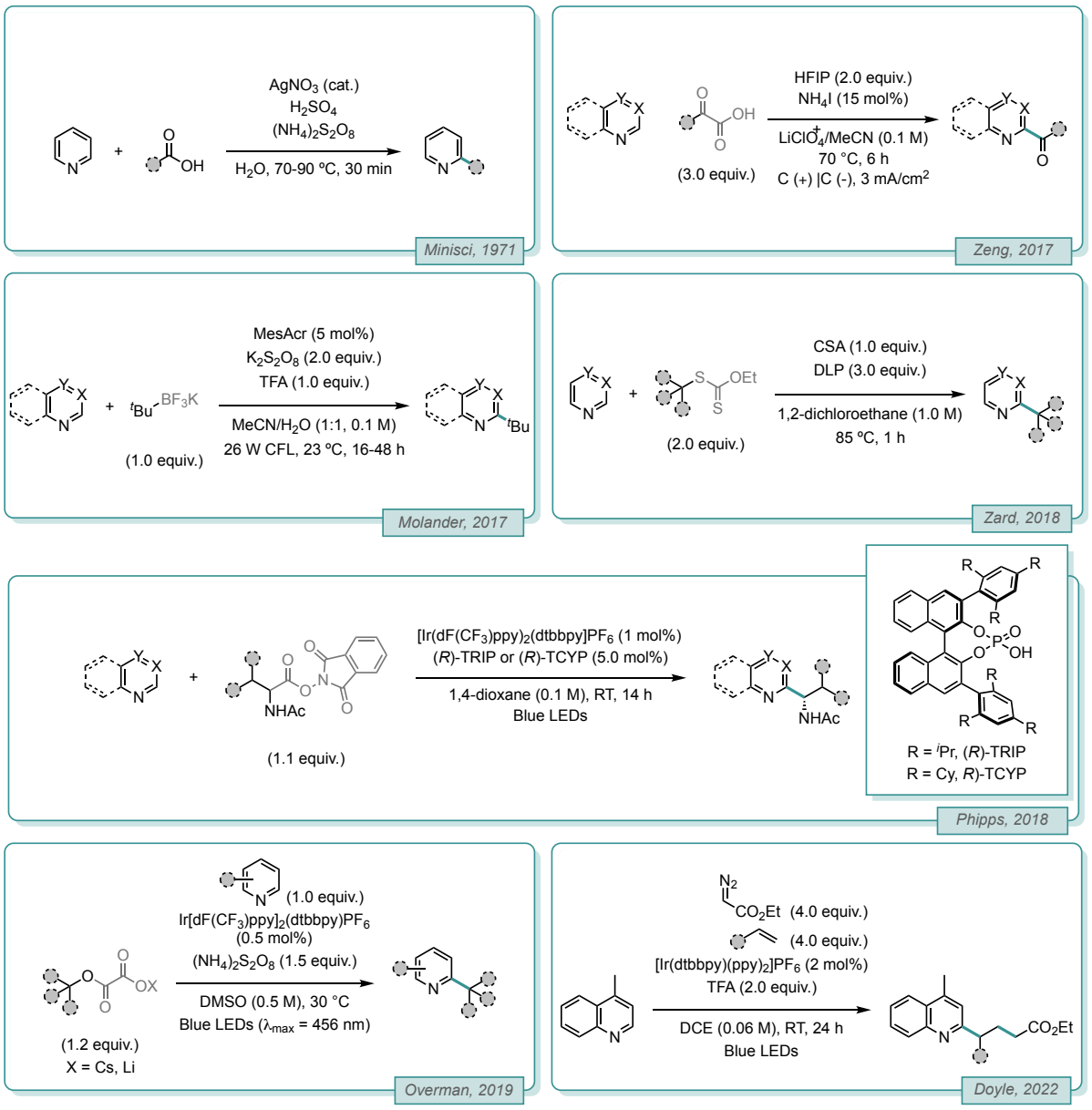


Figure 13. Representative examples of bioactive molecules containing heterocyclic scaffolds.

Therefore, a myriad of methodologies for the synthesis and modification of heterocycles have been developed over the years.[142,143] Among all these protocols, there was one which drastically changed chemists' retrosynthetic mindset for the functionalization of basic *N*-heterocycles. In 1971, Francesco Minisci and co-workers published a protocol which settled the basis for the now known as "Minisci reaction".[17] By combining ammonium persulfate and a catalytic amount of silver nitrate under acidic conditions, the authors were able to perform an oxidative decarboxylation of a alkyl carboxylic acid, affording an alkyl radical species. The latter subsequently attacks an activated basic heteroarene ring, either pyridine or quinoline, in the *C*-2 or *C*-4 position. This innate regioselectivity, previously observed by the authors some years before, [144] was further favored by the extremely acidic conditions employed for this transformation (**Scheme 8**).[145] With this technology, the authors offered an straightforward alternative to the main alkylation methodology available at the time; the Friedel-Craft's alkylation. Although this is a very powerful and useful method, the Friedel-Craft's alkylation is ineffective when using basic heteroarenes as substrates. The reason behind this lack of reactivity is

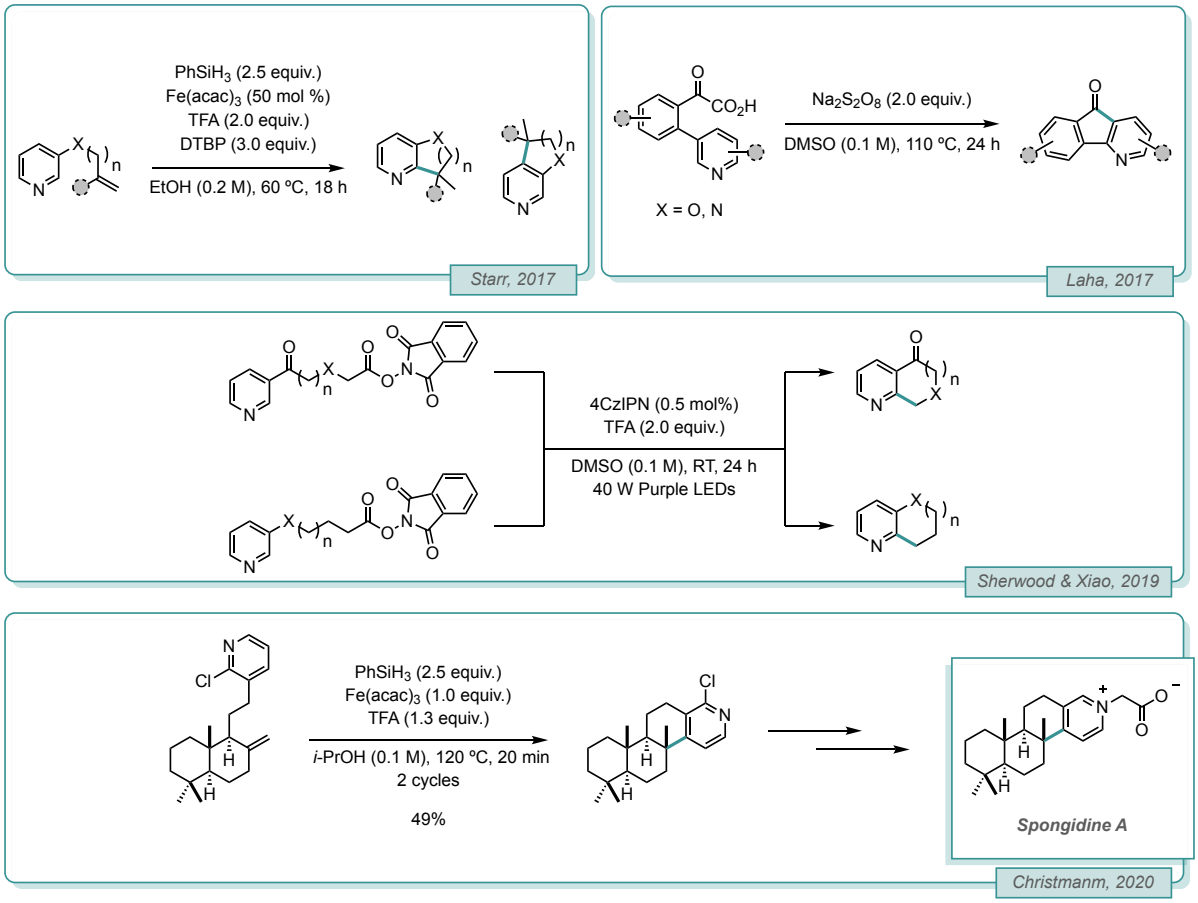
due to their poor nucleophilic character, in combination with the complexation of $AlCl_3$ with the nitrogen atom of the basic heterocycle ring, avoiding the coordination with the alkyl chloride moiety and subsequent formation of the electrophilic carbocation.[146,147] Thus, the Minisci reaction turned into the main methodology for the C–H alkylation of basic heteroarenes and a powerful tool in the medicinal chemistry field.

Several methodologies have been reported since the publication of the original Minisci conditions, substituting carboxylic acids for more efficient radical precursors, and using thermal, electrochemical, and visible-light mediated conditions to promote the radical reaction.[148] In 2017, Zeng and co-workers published one of the first examples using electrochemistry to couple acyl radicals and basic heterocycles using NH_4I as redox catalyst.[149] The same year, Molander and co-workers reported a metal-free and light-mediated Minisci-type reaction using alkyltrifluoroborates as efficient primary, secondary, and tertiary alkyl radical precursors.[150] Later, Zard demonstrated the versatility of dilauroyl peroxide (**DLP**) and tertiary xanthates for the incorporation of quaternary centers into the heteroarene ring.[151] In 2018, Phipps reported the first enantioselective Minisci-type protocols using a phosphorus-based chiral Brønsted acid as inducer of chirality and activator of the heteroarene core.[152] As mentioned in Chapter 1, **Scheme 3**, Overman reported the use of cesium oxalates as alkyl radical precursors in a light-mediated or thermal Minisici-type reaction.[76] Finally, the Minisci reaction has also been implemented in multicomponent processes like the one recently published by Doyle, using diazo compound as efficient radical precursors via a proton-coupled electron transfer (**PCET**) event (**Scheme 9**).[153]



Scheme 9. Original Minisci reaction and state of the art.

While these intermolecular examples illustrate the importance and versatility of Minisci-type reactions, intramolecular versions of this reaction remain highly unexplored. The methodologies reported by Starr (in collaboration with Pfizer),[154] Laha,[155] and Sherwood and Xiao (Merck)[156] constitute the only examples of intramolecular Minisci-type reactions in the synthetic pool (**Scheme 10**). In addition, Christman has recently applied the methodology developed by Starr in the total synthesis of Spongidine A,[157] demonstrating the potential of intramolecular Minisci-type reactions for the synthesis of complex natural products, fused heterocycles, and structure modification of drug candidates.



Scheme 10. Intramolecular Minisci methodologies.

Carbohydrates constitute the most abundant group of natural products. The reason of this abundance relies on the several connections that each of their monosaccharides ring units (pyranose and furanose) can offer.[158,159] Moreover, the anomeric center of these rings further increases the complexity of such connections by differentiation via α and ß isometry. Therefore, carbohydrates play important physiological and pathophysiological roles, being present in many and diverse molecular forms, from glycans and glycoproteins to DNA chain structures. Furthermore, these privilege structures are founded among the most important drugs for the treatment of diabetes,[160] influenza,[161] and thrombosis.[162] Thus, it is easy to highlight the intrinsic potential in the development of strategies for their facile modification, taking advantage of the complexity of their units. In this way, a novel methodology for the synthesis of fused polycyclic systems might open the door to expand three-dimensional chemical space for drug discovery.

3.2. Goals of the project

All this information established the bases for the project of this chapter, which main goal was the development of a straightforward route for the synthesis of novel saccharide scaffolds. This route involves three consecutive synthetic steps; first, a nucleophilic aromatic substitution (S_NAr) event provides the desired alcohol starting materials. Then, a subsequent activation of these alcohols prepares the substrates for the final ring closure via intramolecular Minisci-type reaction. As a result, novel polycyclic structures with potential applications in drug discovery and modification of ADME profile were synthesized following this short "total synthesis" pathway (**Figure 15**).

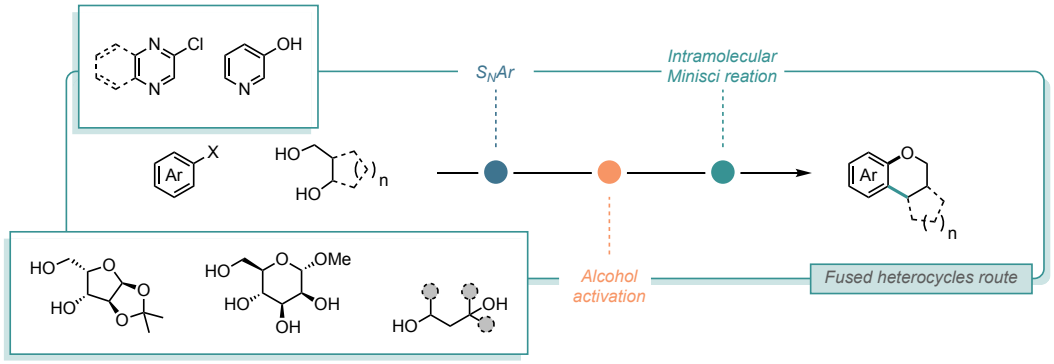
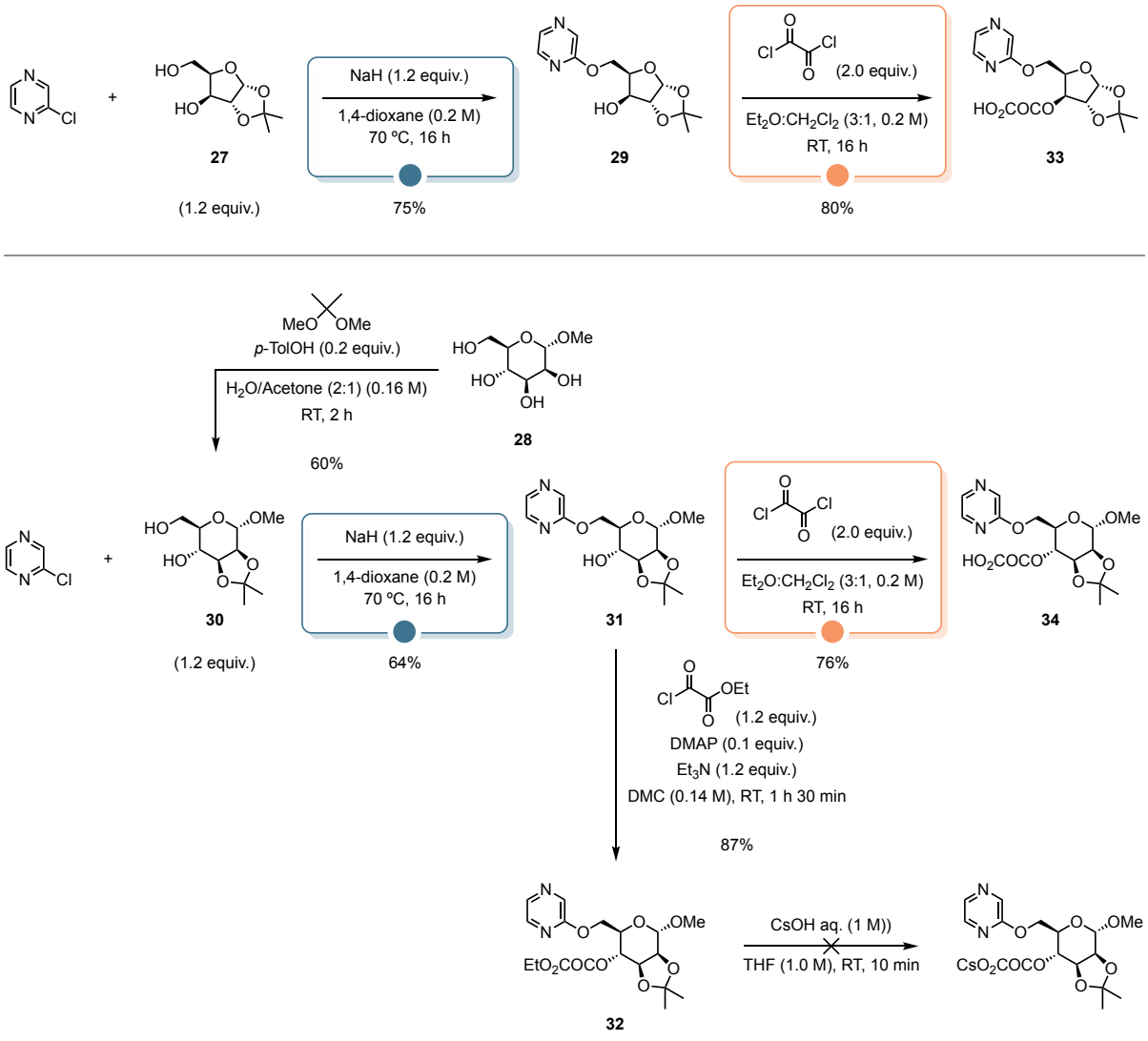


Figure 15. Synthetic strategy to access.

3.3. Optimization & Scope

Furanose **27** and pyranose **28** were the saccharide models chosen to find the optimal conditions of the route showed in **Scheme 11**. In the case of **27**, the pre-installed acetal protection of two of its secondary hydroxyl groups allows for its direct use in the first S_NAr step. By adding sodium hydride (NaH) to a solution of **27** in 1,4-dioxane, the corresponding carbanion was formed after H_2 evolution. Then, chloropyrazine was added to the mixture and after overnight reaction, the corresponding coupled product **29** was obtained in 75% yield. In case of **28**, an extra acetal-protection step was incorporated to the route affording **30**. Once protected, **30** was subjected to the same S_NAr conditions than **29**, in this case using THF as solvent, to obtain **31** in 64% yield. From this point, the activation mode selected for the remained secondary alcohol was via the formation of oxalate species. This idea was based on the previous results obtained during the development of the deoxyfluorination methodology, where **17b** was obtained as the major product due to a faster intramolecular cyclization reaction (see Chapter 2, **Scheme 5**). This result supported the possible development of a visible-light mediated intramolecular Minisci methodology using cesium oxalates. Therefore, **31** was converted to the corresponding ethyl oxalate **32** in 87% yield. Unfortunately, attempts to synthesize the cesium salt species failed due to the basic conditions of the reaction caused the opening of the pyranose ring.

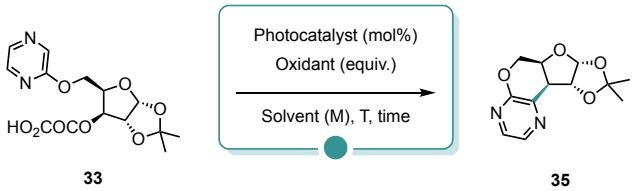
With the aim of surpass this limitation, oxalic acid formation was considered as an alternative activation method of the alcohol moiety. Thus, **29** and **31** reacted with oxalyl chloride in a 3:1 mixture of dichloromethane/ether (CH_2Cl_2/Et_2O) to afford the corresponding oxalic acid species **33** and **34**, respectively. By following this method, the synthetic route was shortened by one-step however no purification of the oxalic acid species was possible, due to their decomposition in column chromatography.



Scheme 11. Polycyclic scaffolds route.

Once **33** and **34** were synthesized, two different pathways were explored to perform the last step of the route: intramolecular Minisci reaction under photochemical, or under thermal conditions.

Considering the conditions reported by Overman,[76] a mixture of **33**, $[Ir(dF(CF_3)_2ppy)_2(dtbbpy)]PF_6$ (0.5 mol%) as photocatalyst, and 1.5 equivalents of ammonium persulfate ($(NH_4)_2S_2O_8$) as oxidant, was irradiated with a 32 W blue LED (λ_{max}= 440 nm) inside an EvoluChem™ PhotoRedOx Box for 2 h at 42 ºC in DMSO (**Table 2, entry 1**), isolating the fused heterocycle **35** in 24% yield. This increase in the temperature should benefit the formation of the secondary alkyl radical species by favoring the decarboxylation rate of the alkoxycarbonyl radical species (see Chapter 2, Section 2.1). Under these conditions, the reaction should proceed through a mechanism similar than the one proposed by Glorius,[163] where $S_2O_8^{2-}$ acts as an efficient oxidative quencher of the photocatalyst ($E_{1/2}(Ir^{IV}/*Ir^{III})$= -0.89 V vs SCE) producing the highly oxidizing sulfate radical anion $SO_4^{-\bullet}$ ($E_{1/2}^{ox}$ = +2.5-3.1 V vs SCE).[164] The later should react via HAT with the oxalic acid **33** affording the desired secondary alkyl radical after double decarboxylation. Thus, the inefficiency and low yield of these conditions might indicate that higher temperatures should be employed to further improve the rate of the second decarboxylation. Therefore, we turned our attention towards the thermal conditions reported by Wang and co-workers.[165] In this case, the authors employed oxalic acids as efficient radical precursors by increasing the time and the temperature of the reaction. Following this principle, a further increase of the temperature should lead to a decrease in reaction time, maintaining or even increasing the yields of the reaction. Hence, **33** was stirred with 1.5 equivalents of $(NH)_4S_2O_8$ in DMSO for 2 h at 100 ºC. Under these thermal conditions, **35** was successfully isolated in 40% yield, being alcohol **29** the only by-product of the reaction (**Table 2, entry 2**). If we compare intermolecular *vs* intramolecular processes, the latter is favored by the formation of a low ring strain six-membered ring. However, the Minisci reaction often requires an excess of the nucleophilic radical source. This feature makes harder the coupling between the parties of the reaction when the stoichiometry between them is 1:1, as in an intramolecular case. This is a common trend in the reported intramolecular Minisci methodologies, and it might explain the reason of the moderate yields obtained. The presence of **29** was probably caused by decomposition of the oxalic acid moiety before the radical generation. Control experiments demonstrated not only that an acid additive was not necessary, but also that it dropped the yield of the reaction (**Table 2, entry 3-5**). An increase in the time of the reaction did not favor this transformation (**Table 2, entry 6-8**). Thus, the thermal conditions of **entry 2** were considered as the optimal for the scope exploration of this intramolecular transformation.

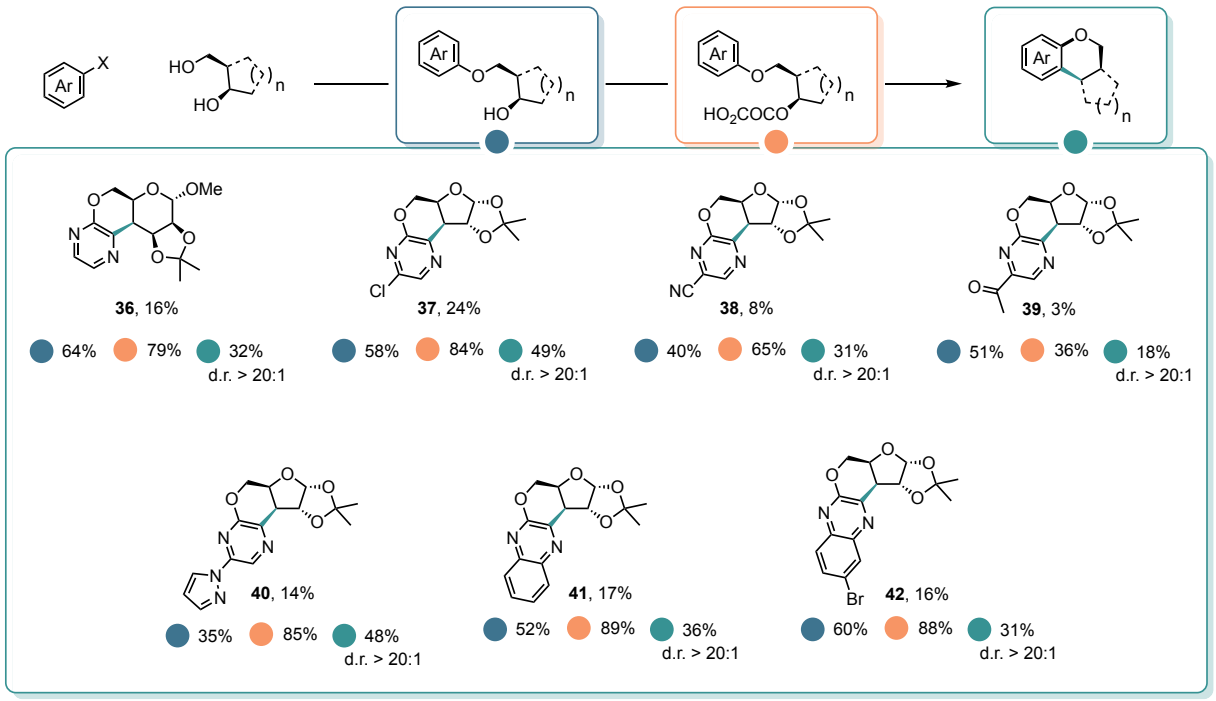


Entry	Catalyst (mol%)	Solvent (M)	Acid (equiv.)	Oxidant (equiv.)	Time (h)	T (ºC)	35 (%)
1	Ir-F (0.5)	DMSO (0.1)	-	$(NH_4)_2S_2O_8$ (1.5)	2	42	24
2	-	DMSO (0.1)	-	$(NH_4)_2S_2O_8$ (1.5)	2	100	40
3[a]	-	DMSO (0.1)	TFA (1.0)	$(NH_4)_2S_2O_8$ (1.5)	2	100	18[a]
4[a]	-	DMSO (0.1)	TFA (3.0)	$(NH_4)_2S_2O_8$ (1.5)	2	100	8[a]
5[a]	-	DMSO (0.1)	TFA (5.0)	$(NH_4)_2S_2O_8$ (1.5)	2	100	5[a]
6	-	DMSO (0.1)	-	$(NH_4)_2S_2O_8$ (1.5)	6	100	22[b]
7[b]	-	DMSO (0.1)	-	$(NH_4)_2S_2O_8$ (1.5)	24	100	22[b]

a) 0.1 mmol scale; b) 3.0 mmol scale

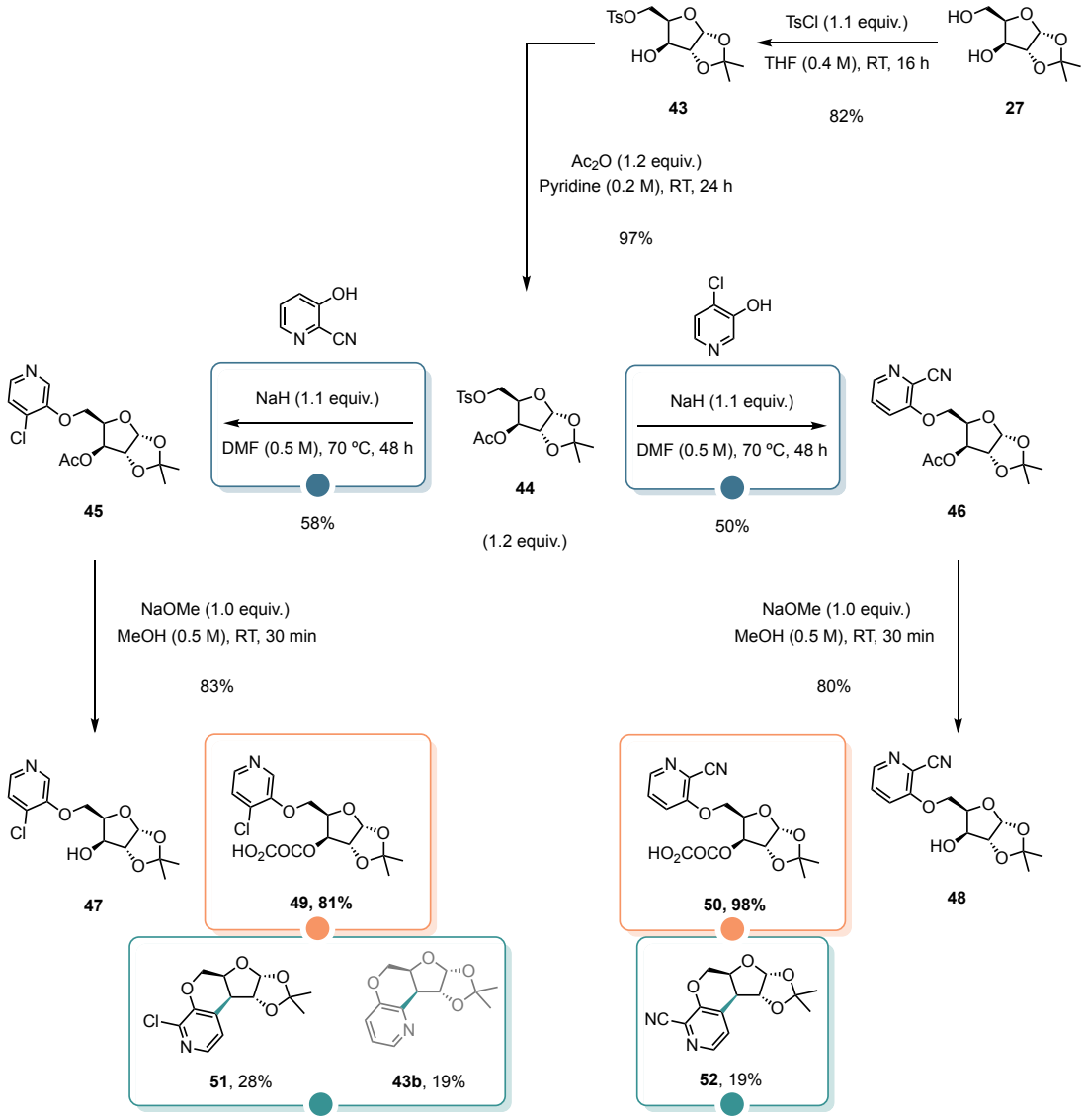
Table 2. Optimization studies.

Scheme 12 displays the scope of the methodology, with the overall yields for the three-step route shown under the synthesized compound, followed by the yields of each step of the route. Fused pyranose-based polycycle **36** was obtained in 32% yield for the intramolecular Minisci stage, in an overall yield of 16%. Several furanose-based oxalic acids were prepared following the same route employed for the synthesis of the saccharide models. Different electron-withdrawing (**37-39**) and electron-donating groups (**40-42**) were installed in the pyrazine core.



Scheme 12. Scope of saccharides.

The pyrazine core was substituted for a pyridine ring bearing different functional groups at the 2-position (**Scheme 13**). In this case, both examples required extra steps to achieve the desired reactivity and regioselectivity, obtaining a six steps route for both examples. Tosylation[166] and subsequent acylation[167] of the free hydroxyl groups in the furanose ring **27** afforded the product **44**. This double protection allows for the differentiation between the primary (OTs) and secondary position (OAc), preventing the formation complex mixtures during the first S_NAr step of the route. As a result, compounds **45** and **46** were obtained in 58% and 50% yield respectively. After deprotection of the secondary hydroxyl moiety, (**47**, **48**) the route continued with the same oxalic activation (**49**, **50**) and final intramolecular Minisci steps employed for the rest of the scope entries. In the case of the 2-chloropyridine ring, the corresponding fused product **51** was isolated in 28% yield, together with 18% of the minor *C2*-substituted regioisomer (**51b**) for the intramolecular Minisci step. The 2-cyanopyrazine product **52** was obtained in 19% yield.



Scheme 13. Scope of pyridine core saccharides.

It is worth highlighting three fundamental aspects of this methodology:

- All the structures isolated following this 3-step route have not been synthesized before, being this the first time that they are reported.
- In all cases, the final intramolecular Minisci conditions proceeded with complete diastereoretention (dr). This was analyzed by proton nuclear magnetic resonance (^{1}H-NMR) using 1,2,4,5-tetramethylbenzene as internal standard to monitor and confirm the yield of the reactions. The crystal structures of **35** and **36** were determined by X-ray analysis to further demonstrate this excellent dr (**Figure 16**).
- The major by-product obtained is the alcohol center via decomposition, giving the possibility of recycling this product via reactivation and subsequent ring-closure reaction.

Bidimensional NMR analyses were also performed to further confirm the structures obtained by single crystal X-ray diffraction analysis (**Figure 16**). After elucidation of the NMR signals of **35** and **36**, NOESY experiments provided the key information to confirm the structure of both compounds. On one hand, the lack of correlation in **35** between the protons of the furanose ring (between 6 and 7 with 8 and 10), along with the correlation between 6 and 7, supported the axial orientation of the position 6. On the other hand, for **36** the correlations observed between all the protons of the pyranose ring (6, 7, 8, and 10), especially between 6 and 7, and the no correlation with 11, demonstrated the equatorial orientation of 11 and the axial orientation of the fused ring bonds.

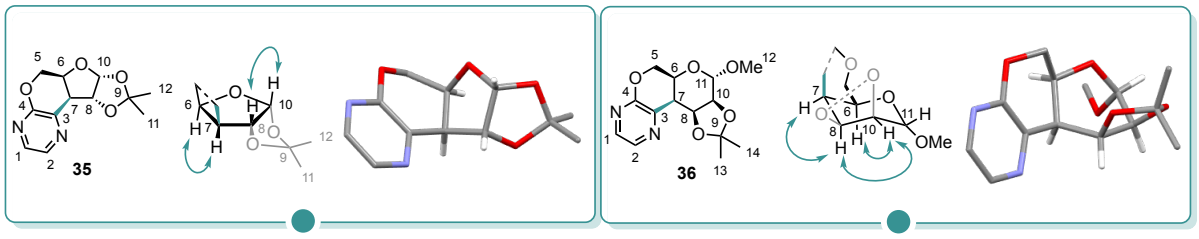
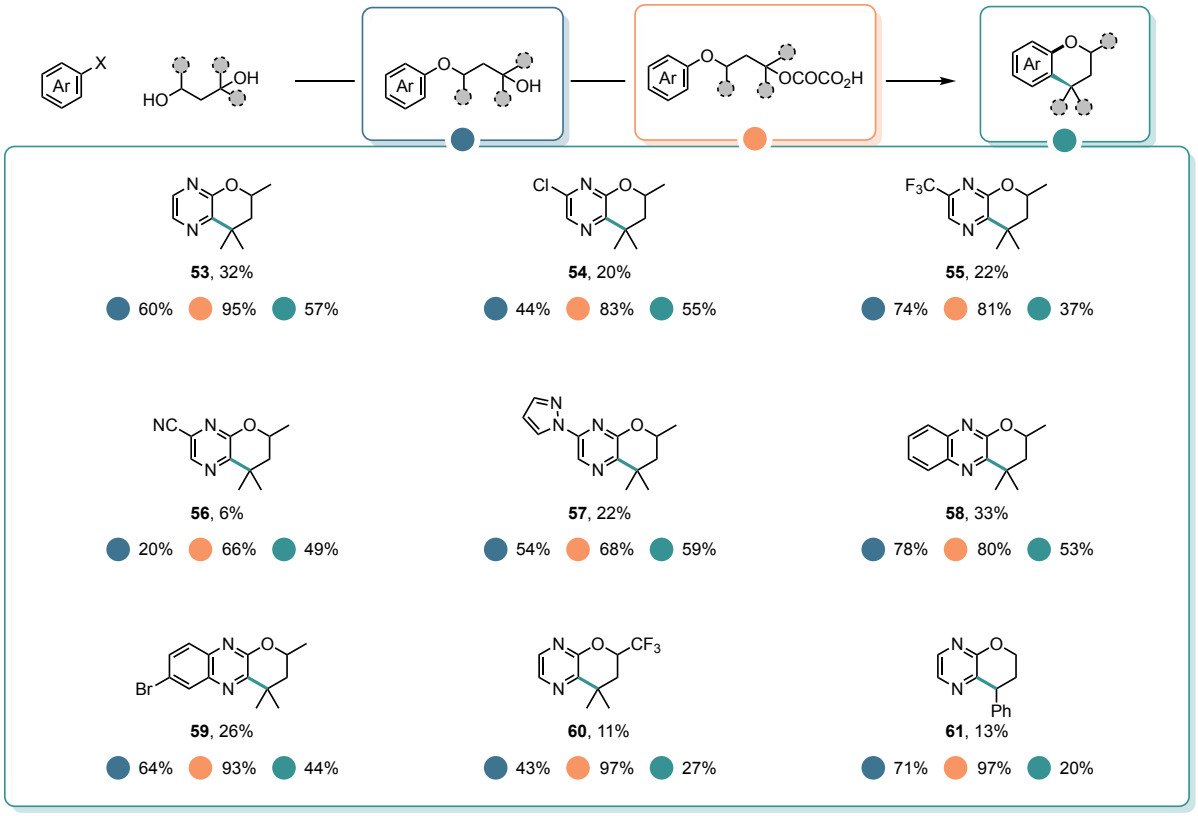


Figure 16. X-ray structures and NMR elucidation of **35** and **36,** & NOESY analysis.

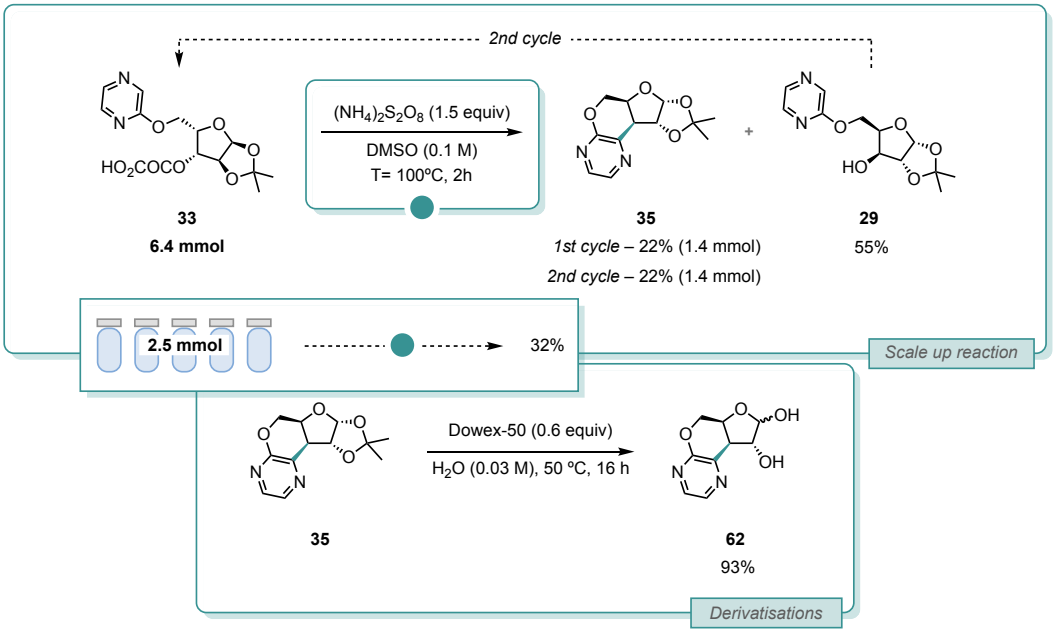
Next, I studied the extension of this protocol for the synthesis of small, fused heterocycles (**Scheme 14**). Different diols systems were employed as starting materials for the route, being coupled with the same pyrazine rings utilized in the synthesis of the saccharides scaffolds. After activation and subsequent intramolecular Minisci reaction, several tertiary systems (**53-60**) afforded the desired fused heterocycle in moderate to good yields for the final Minisci step. A more stable benzylic radical provided **61** in only 20% yield.



Scheme 14. Scope of small rings.

The scalability of this process was tested by synthesizing **35** in gram-scale (2.2 g, 6.4 mmol), affording the desired cyclic product in 22% yield (0.35 g, 1.4 mmol). The alcohol recovered during this scale-up process was used for a second cycle of activation/Intramolecular Minisci steps, increasing the overall yield of the reaction to 44% yield (0.7 g, 2.8 mmol) and confirming the recycling character of the route (**Scheme 15**). It was observed than by decreasing the scale of the reaction higher yields were obtained. Therefore, an extra scale-up reaction was performed, this time dividing the quantity of the substrate in 5 different vials, with 0.5 mmol in each of them (0.85 g, 2.5 mmol). After the reaction took place, the combined crude products of the vials were purified, affording the desired product in slightly increased 32% yield.

Finally, derivatizations of **35** were accomplished to further demonstrate the applicability of these polycyclic structures. The acetal deprotection of the secondary alcohols was possible by using the resin Dowex®50WX8, releasing the unprotected product **62** in 90% isolated yield.

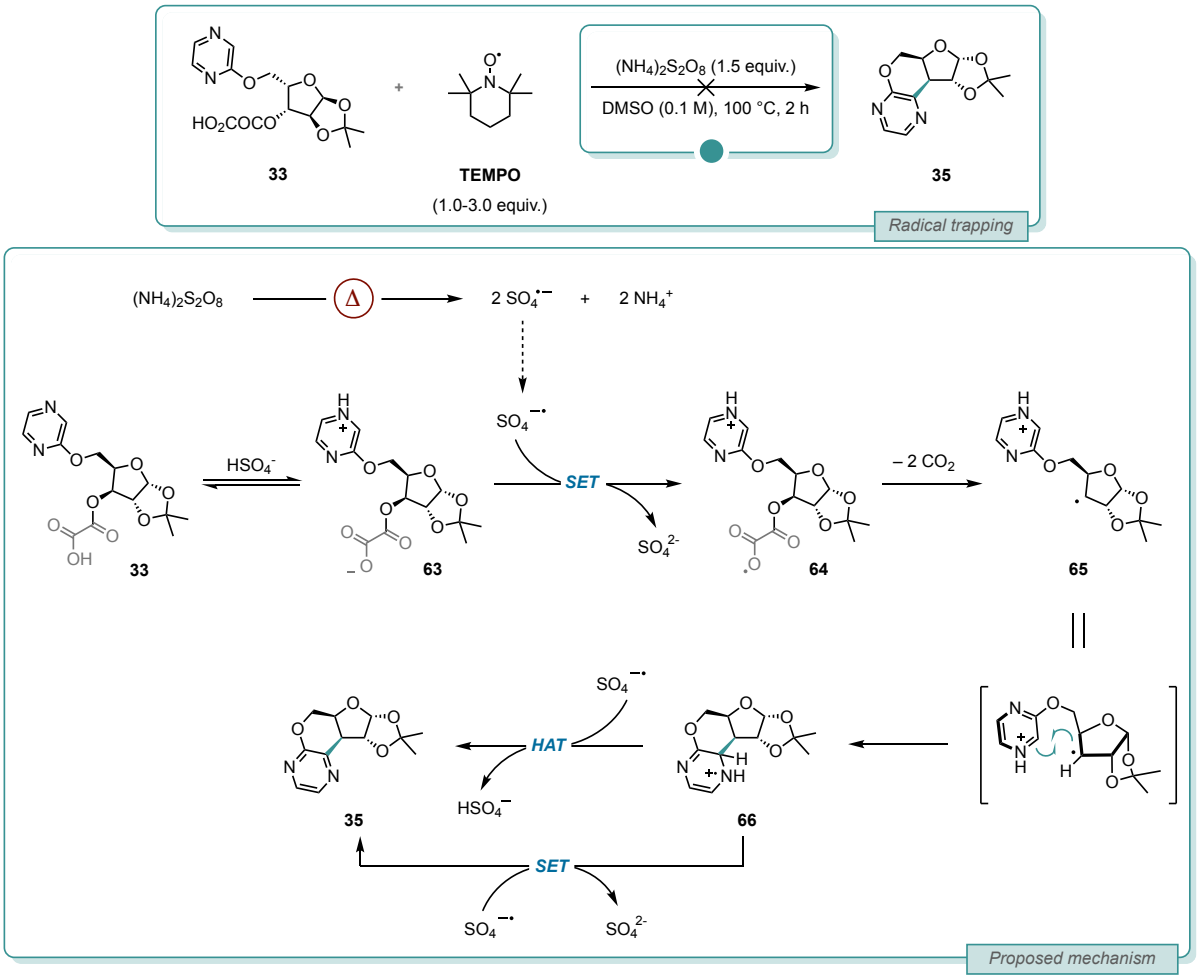


Scheme 15. Scale up & derivatizations.

3.4. Mechanistic studies & biological assays

Having explored the scope of this intramolecular methodology, a series of reactions were carried out to demonstrate the radical character of this transformation and to propose a plausible mechanism. When the radical scavenger **TEMPO** (1.0-3-0 equiv.) was introduced, the formation of the fused cycle product **35** was completely inhibited. On the basis of this experiment and previous literature reports,[76,165] a plausible mechanism was proposed (**Scheme 16**).

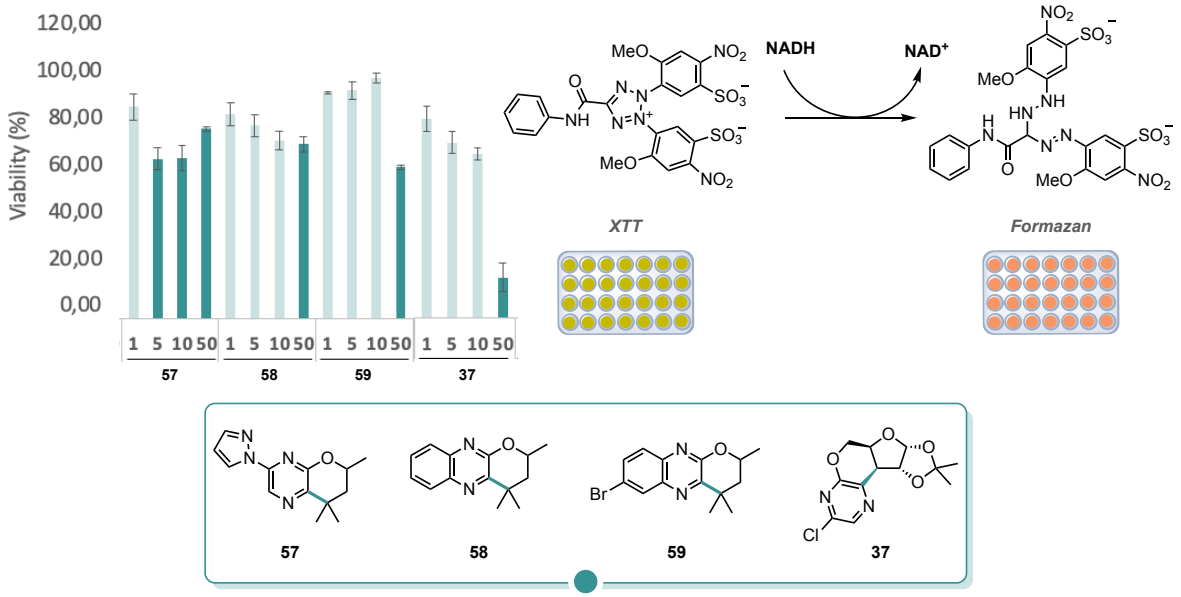
The reaction is initiated by a thermal step, which promotes the decomposition of persulfate $S_2O_8^{2-}$ into the highly oxidizing sulfate radical anion $SO_4^{-\bullet}$ ($E_{1/2}^{ox}$ = +2.5-3.1 V vs SCE). Meanwhile, the heteroarene ring in **33** is activated by the hydrogen sulfate ion (HSO_4^-) present in the reaction media, affording **63.** The latter can participate in a SET event with radical anion $SO_4^{-\bullet}$ to form the radical species **64**, which, after a double decarboxylation, generates the alkyl radical **65** and evolution of CO_2. Subsequent intramolecular addition of **65** to the protonated electron-deficient heteroarene affords the radical cation **66**, which might react either via HAT or via SET event with another molecule of $SO_4^{-\bullet}$ to provide the desired product **35**. In the former, the estimated BDE of the C–H bond α to the nitrogen should be similar to the calculated for the pyrazine core (BDE ≈ 93 kcal/mol).[168] This value represents the energy that should be applied in order to cleavage that bond. In the later, the reduction potential of the sulfate radical anion $SO_4^{-\bullet}$ ($E_{1/2}^{ox}$ = +2.5-3.1 V vs SCE) corresponds to high oxidant species.[164] Based on these data, and despite both steps might be feasible, the HAT pathway seems to be less favored due to the relatively high BDE of the CH bond.



Scheme 16. Radical trapping & proposed mechanism.

Finally, all the novel saccharides scaffolds synthesized were sent to France, to the National Institute of Health and Medical Research (INSERM in French), where they were biologically tested in vitro by the group of Dr. Guillaume Robert (**Scheme 17**). All the compounds were tested against K562 leukemic cells using XTT assay as colorimetric technique. The assay works on the principle that the mitochondrial enzymes of healthy cells convert a yellow XTT dye (2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide) into formazan, which has an orange color.[169,170] This change of color measures the cell viability of the sample, refers to the number of live, healthy cells after an extracellular stimulus. Hence, a lesser change of color means a decrease in the number of live cells, which translates in a better activity of the compound against that type of cells, in this case leukemic cells. The results of this analysis showed that compounds **49, 50,** and **51** decrease the number of live cells moderately after 24 and 48 hours of incubation, while compound **37** exhibited a significant decrease. To further verify these results, the cell cultures were stained with 4',6-diamidino-2-phenylindole (**DAPI**), a fluorescent stain that binds strongly with some regions of the DNA, checking their emission. This last assay corroborates the results obtained for **57**, **58**, and **59** while in the case of

37 was not conclusive. Finally, it is worth highlighting that the concentration of all these results were 50 μM of the tested compounds, which is the highest concentration employed. Therefore, further structural modifications should be carried out in order to reduce possible off-target effects and toxicities in future assays.



Scheme 17. Biological assays.

3.5. Summary & conclusions

In summary, a series of novel fused heterocycles were synthesized following a straightforward three-step route, with a final intramolecular Minisci reaction as focal point. This Minisci step proceeded under thermal conditions, using only the corresponding oxalic acid and $(NH)_4S_2O_8$ as oxidant to afford novel polycyclic scaffolds with an excellent diastereoselectivity. This was further demonstrated by X-ray structure elucidation of compounds **35** and **36**. The scalability and recyclable character of the developed route were tested, as well as the possible biological activity of the final polycyclic compounds. Further experiments would help to improve the results obtained during these experiments, e.g., further structure modification of the novel synthesized structures to boost their biological activity and gain additional insight into their potential biological interactions, or additional optimization studies to find a more scalable method.

4. RADICAL DEOXYCYANATION OF TERTIARY ALCOHOLS USING HYPERVALENT IODINE REAGENTS

4.1. The Nitrile Group: Importance & impact

Nitriles or cyanides represent an outstanding class of compounds both in chemistry and biology, widely used as important intermediates in the synthesis of pharmaceutical and agrochemical compounds.[133-135] Therefore, many different synthetic methodologies have been developed for the introduction of this group into organic compounds. However, since the first synthesis of hydrogen cyanide by Scheele in 1782, by heating Prussian blue with sulfuric acid, the most common approach consists in the nucleophilic substitution of suitable leaving groups with cyanide ions, which usually requires the use of hazardous and highly toxic reagents (e.g. KCN, NaCN, $(Me_3Si)CN$ or $Zn(CN)_2$) with troublesome storage and manipulations (**Figure 17**).[173] Their toxicity relies on the formation of hydrogen cyanide by hydrolysis in the presence of moisture.[174]

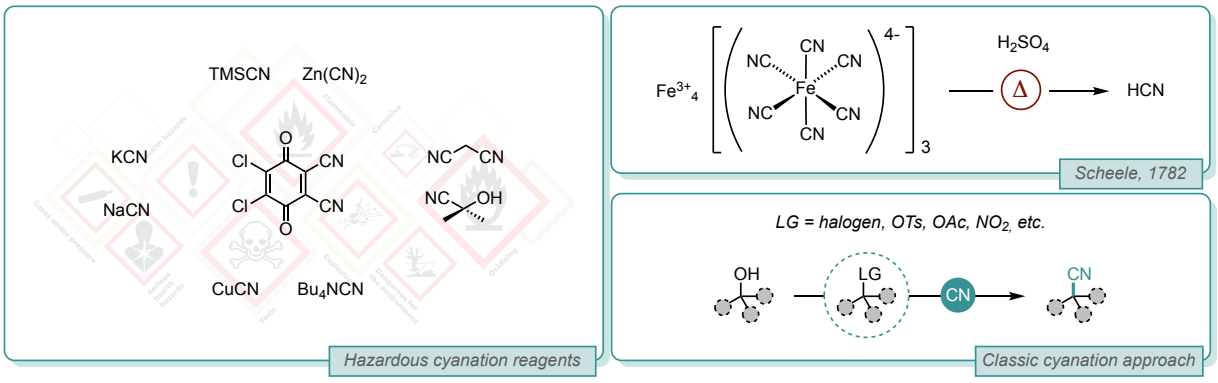
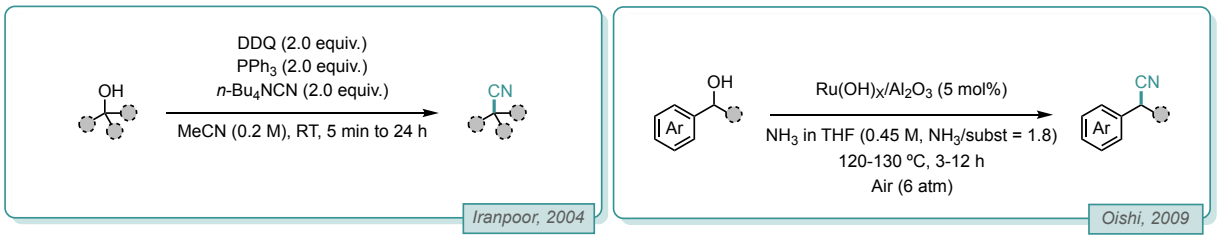


Figure 17. Classic deoxycyanation strategies & reagents.

Although a myriad of leaving groups can be used for this transformation– such as, aryl sulfonates, esters, ethers, nitro and amino motifs, or diazonium salts – alkyl halides and alcohols are the most employed. Regarding alcohols, the transformation of hydroxyl groups into nitriles is an important method for the one carbon elongation of organic molecules. Unfortunately, these reactions suffer the already mentioned limitations associated with S_N1 or S_N2 pathways (see Chapter 1, Section 1.2). In addition to these limitations, this type of reactions frequently requires the conversion of the hydroxyl group to a more easily removable leaving group, such as halides or sulfonates, before the reaction can take place. However, some direct methodologies have been reported during the last decades. Iranpoor and co-workers reported a one-pot deoxycyanation method under Mitsunobu conditions, *i.e.* using HCN/PPh_3/DEAD, to deliver the corresponding nitriles in moderate yields.[175] Oishi and co-workers developed an alternative aerobic oxidative approach using ammonia to achieve this transformation (**Scheme 18**).[176] These two methodologies represent a huge improvement in the direct

cyanation of hydroxyl motifs. However, the use of Mitsunobu-type conditions in the case of Iranpoor's methodology, or the presence of stoichiometric amounts of oxidants and reagents hampers their application towards tertiary systems.



Scheme 18. One-pot deoxycyanation methodologies.

4.2. Hypervalent iodine (III) compounds: Applications & derivates

Hypervalent iodine (III) reagents represent a remarkable group of compounds which has grown in interest during the last decades due to its versatility, being able to act via ionic or radical pathways (**Figure 18**).[173,177] The general structure of these reagents (**67**) presents a characteristic three-atom and 2-electrons pair R–I–X bond, generating by this combination a system considerably longer and weaker than its R–I or I–X equivalents.[178,179] On one hand, the highly polarized system of this reagents enables their use as efficient electrophilic reagents to construct a wide range of systems, including C–CF_3, heteroatom–CF_3, C–R_f (R_f = perfluoroalkyl), heteroatom–R_f, C–N_3,C–CN, S–CN, and C–X bonds (X = halides).[180–182] On the other hand, its use in radical pathways has been achieved through two possibilities. In the first one, the homolytic cleavage of the weak I–X bond applying heat or light irradiation produces a biradical species **A**, which can be employed as efficient HAT reagent in further C–H functionalization strategies. In the second case, a SET reduction of the corresponding hypervalent reagent promotes the formation of the iodanyl radical **B**, which after subsequent degradation affords the anion **C** and the radical species **II**. The later can be then coupled with different acceptors, e.g. (hetero)arenes, alkenes Michael acceptors, or alkynes. In the second case, one of the possible agents which might produce this SET reduction is a photosensitizer. By choosing the right reagent, photosensitizer, light source, and solvent conditions, a wide range of transformations can take place in a mild fashion.[183,184] Some hypervalent iodine (III) reagents worth highlighting include (diacetoxyiodo)benzene (PIDA) (**68**),[185] (bis(trifluoroacetoxy)iodo)benzene (PIFA) (**69**), and the ones developed by Togni in the 2000s for trifluoromethylation methodologies bond formation (**70, 71**),[186,187] and Zhdankin in the 1990s for azidation (**72**) and cyanation (**73**) methodologies.[188,189]

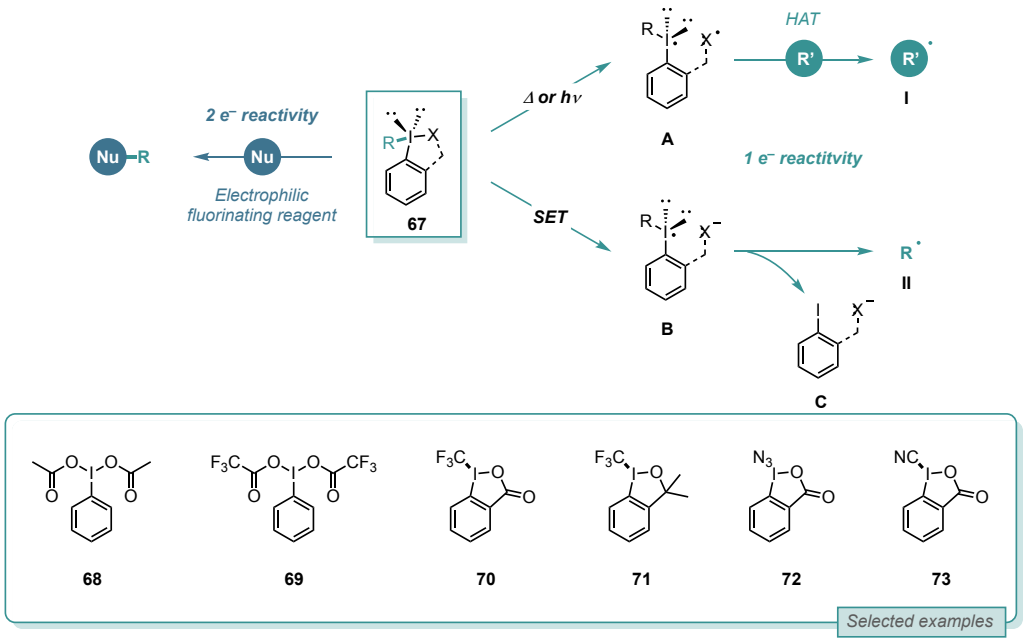
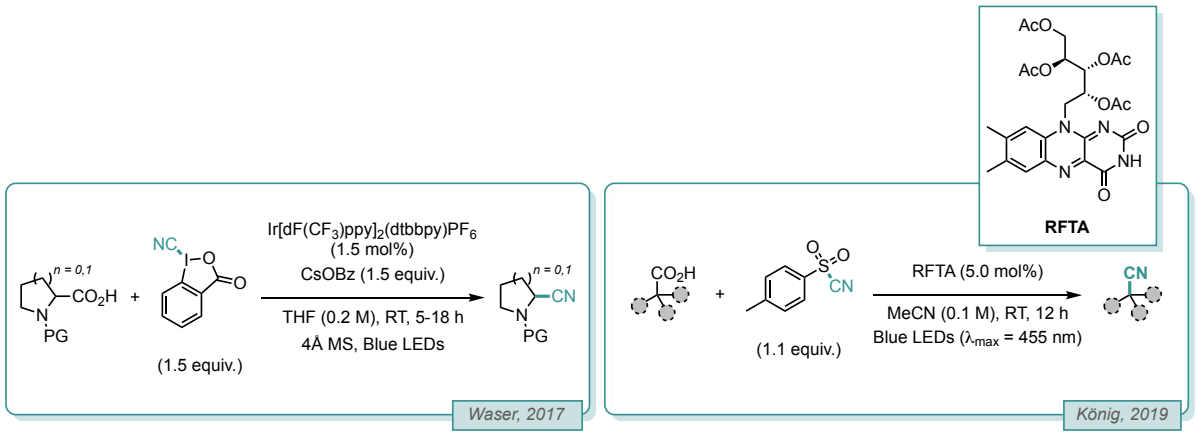


Figure 18. Reactivity of hypervalent iodine (III) reagents.

Regarding cyanation procedures, Waser and co-workers have demonstrated the use of cyanobenziodoxolone (CBX) Zhdankin's reagent (**66**) as an efficient CN transfer reagent in a catalytic photoredox radical decarboxylative process (**Scheme 19**).[190] In 2019, König and co-workers reported a visible-light decarboxylative cyanation method of aliphatic carboxylic acids, using riboflavin tetraacetate (**RFTA**) as photosensitizer.[51] In this case, the reagent employed as cyanide source was tosyl cyanide instead of an hypervalent iodine (III) reagent. **RFTA** plays the role of photosensitizer and base at the same time, avoiding the use of stoichiometric bases to form the corresponding carboxylate species. Although effective methodologies, it is worth noticing that in most of the scope entries the generated radical was in α–position to a heteroatom. Only two examples of using a secondary and a tertiary carboxylic acid were reported in the König's methodology. This reason led me to question that maybe a novel cyanation reagent might open the door to expand the scope of these cyanation methodologies. The structure of this novel reagent could be based on the hypervalent iodine (III) reagents due to their straightforward synthesis and high tunability. Moreover, the potential development of radical–fashion methodologies might translate into the use of milder cyanation conditions, avoiding the generation of toxic intermediates.



Scheme 19. Cyanation and azidation technologies reported by Waser and König.

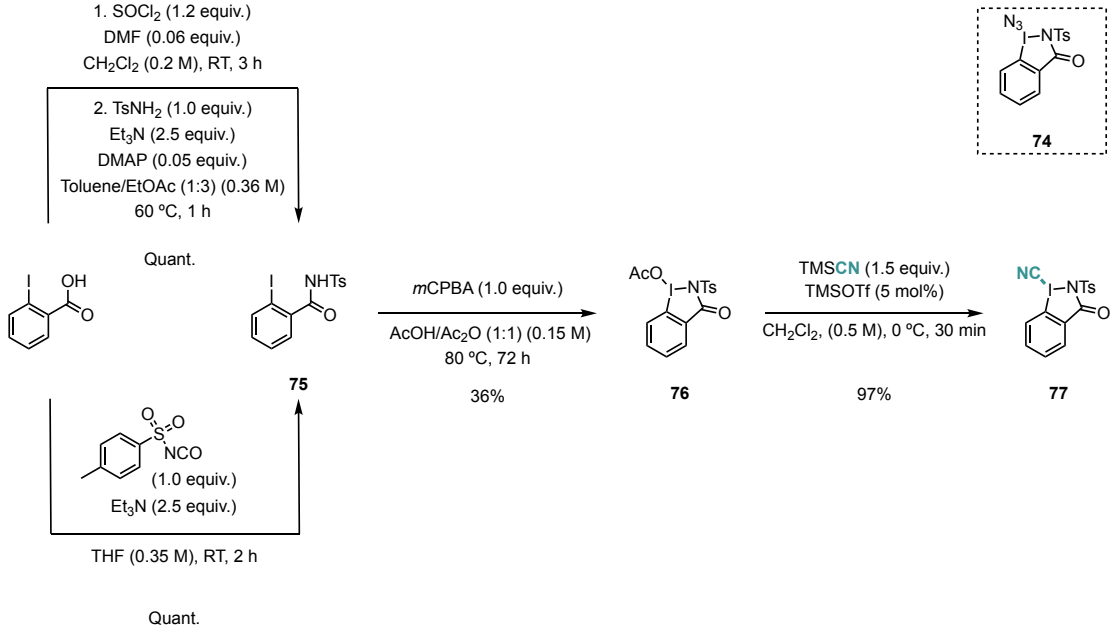
4.3. Goals of the project

Based on this information, a design and synthesis of a novel electrophilic cyanation reagent is highly desirable. With Zhdankin's reagent **65** as model reagent, I envisioned that by replacing the I–O bond for a I–NTs motif might afford a cyanobenziodazolone (CBZ) CN transfer reagent. The higher conjugation apported by the tosyl group might translate into a better stability. Its reactivity will be tested as a potential electrophilic radical CN transfer reagent.

4.4. Synthesis of novel CBZ reagent and optimization of a photoredox deoxycyanation methodology

The first stage to start this project was the synthesis of the novel CBZ reagent. The route chosen to achieve this goal was a modified version of the one utilized by Waser for the synthesis of the ABZ reagent **74** (**Scheme 20**).[190] Commercially available 2-iodobenzoic acid was mixed with thionyl chloride in DMF to promote the formation of the corresponding acyl chloride. After 1 h, the solvent was removed *in vacuo*, and tosyl amine was added to same flask together with 4-dimethylaminopyridine (DMAP) and triethyl amine, affording the tosyl amide **75** in quantitative yield. During the development of this project, Waser and coworkers reported a radical methodology for the azidation of cyclopropenes for the synthesis of quinoline derivatives.[191] In this work, the authors proposed a modified procedure for the synthesis of the ABZ reagent **74**, where the first step was replaced by the use of tosyl isocyanate and triethylamine to obtain the corresponding tosyl amide **75**. This modified protocol was tested in our lab, obtaining **75** as expected in quantitative yield. Although both proposed steps work affording excellent yields, it is worth highlighting the higher simplicity of the second one, which avoids the necessity to pre-form the more reactive acyl chloride species. This advantage, along with the direct use of **75** and in subsequent steps, led me to choose this modified procedure as the preferred protocol for the preparation of **75**. Once **75** was synthesized, it was mixed

with *meta*-chloroperbenzoic acid (*m*CPBA) in a solution of acetic acid and acetic anhydride, obtaining the cyclic compound **76** after 72 h in 36% yield. Finally, in the last step reported by Waser for the synthesis of azidation reagents **74**, the authors mixed **76** with azido(trimethyl)silane ($TMSN_3$) and catalytic amount of trifluoromethanesulfonate (TMSOTf) as Lewis acid activator in dichloromethane (CH_2Cl_2).[192,193] In my case, substituting $TMSN_3$ by trimethylsilyl cyanide (TMSCN) as nucleophilic source afforded the desired cyanating reagent **77** in nearly quantitative yield. Pertinent characterization analyses (NMR, HRMS) were performed to further confirm the structure of compound **77**.

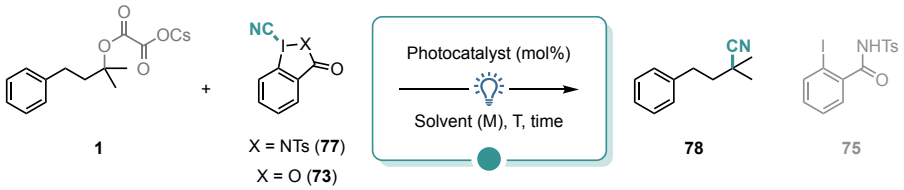


Scheme 20. Route for the synthesis of **77**.

After its synthesis and characterization, I proceeded to investigate the use of **77** as an efficient CN transfer reagent in a straightforward, photoredox-catalyzed deoxycyanating methodology. To develop a selective method towards tertiary hydroxyl systems, cesium oxalates were selected as suitable radical precursors based on their already explained properties and the success obtained with previous methodologies (See Chapter 2)

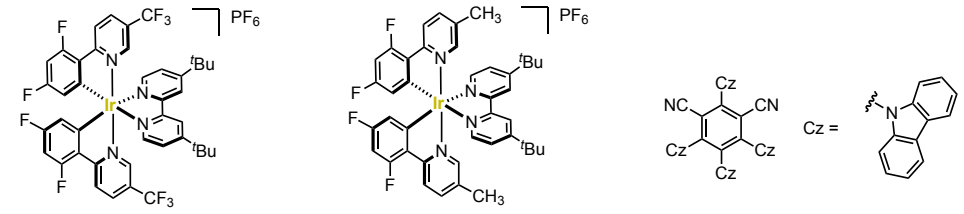
The optimization studies performed to find the best conditions for this transformation are displayed in **Table 3**. All the yields were calculated by gas chromatography with flame ionization detection (GC-FID) using methyl laurate as internal standard. The model substrate chosen for these studies was the same cesium oxalate **1** employed in Chapter 2. Therefore, **1** was irradiated in presence of 1.5 equiv. of **77** with a 32 W blue LED (λ_{max}= 440 nm) inside an EvoluChem™ PhotoRedOx Box for 16 h in acetonitrile (**Entry 1**). Unfortunately, the yield of the desire product **77** under these initial conditions was poor. The lack of reactivity observed could be explained by the poor solubility exhibited by **77** in acetonitrile. As a result, the solvent was replaced for more polar systems (**Entries 2-4**), being DMSO exhibiting the best results (**Entry 4**). An increase of the reaction concentration improved the

yield of **78** to 60%. The use of different photosensitizer revealed that the organophotocatalyst 4CzIPN afforded equal results than the Ir-based photocatalyst Ir-F (**Entry 9**). Iridium is one of the rarest elements in the Earth's crust, therefore its price is considerably high. As explained in Chapter 1, 4CzIPN represents a versatile free metal photosensitizer with similar properties than Ir-F. This free metal character constitutes a tremendous advantage in terms of scalability and industrial applications by decreasing the price of the overall process. By increasing the loading of the photosensitizer and the equivalents of **77** in a 1:1 mixture of DMSO/1,4-dioxane, the cyanated product **78** was successfully isolated in 64% yield (**Entry 10**). These conditions were tested using the CBX Zhdankin reagent **73** as CN transfer reagent, resulting in a decrease of the yield to 19% (**Entry 11**). Next, the ratio between oxalate **1** and CBZ reagent **77** was changed, resulting in 28% yield of **78** when **77** was used as the limiting reagent (**Entry 12**). Control experiments revealed the need of light and photocatalyst for the success of the reaction (**Entry 13-14**).



Entry	Catalyst (mol%)	Solvent (M)	CN reagent (equiv.)	Time (h)	T (ºC)	78 (%)
1	Ir-F (1.0)	MeCN (0.1)	**77** (1.5)	16	25	0
2	Ir-F (1.0)	Acetone (0.1)	**77** (1.5)	16	25	0
3	Ir-F (1.0)	DMF (0.1)	**77** (1.5)	16	25	47
4	Ir-F (1.0)	DMSO (0.1)	**77** (1.5)	16	25	55
5	Ir-F (1.0)	DMSO (0.2)	**77** (1.5)	16	25	60
6	Ir-F (1.0)	DCE (0.2)	**77** (1.5)	16	25	14
7	Ir-F (1.0)	THF (0.2)	**77** (1.5)	16	25	17
8	Ir-Me (1.0)	DMSO (0.2)	**77** (1.5)	16	25	36
9	4 CzIPN (1.0)	DMSO (0.2)	**77** (1.5)	16	25	59
10[a]	4 CzIPN (2.5)	DMSO/1,4-dioxane (1:1) (0.2)	**77** (2.0)	16	25	66 (64)
11	4 CzIPN (2.5)	DMSO/1,4-dioxane (1:1) (0.2)	**73** (2.0)	16	25	19
12[b]	4 CzIPN (2.5)	DMSO/1,4-dioxane (1:1) (0.2)	**77** (1.0)	16	25	28
13	-	DMSO/1,4-dioxane (1:1) (0.2)	**77** (2.0)	16	25	3
14[c]	4 CzIPN (2.5)	DMSO/1,4-dioxane (1:1) (0.2)	**77** (2.0)	16	25	2

a) Isolated yield of 0.5 mmol scale in brackets; b) **78** as limitant reagent; c) No irradiation



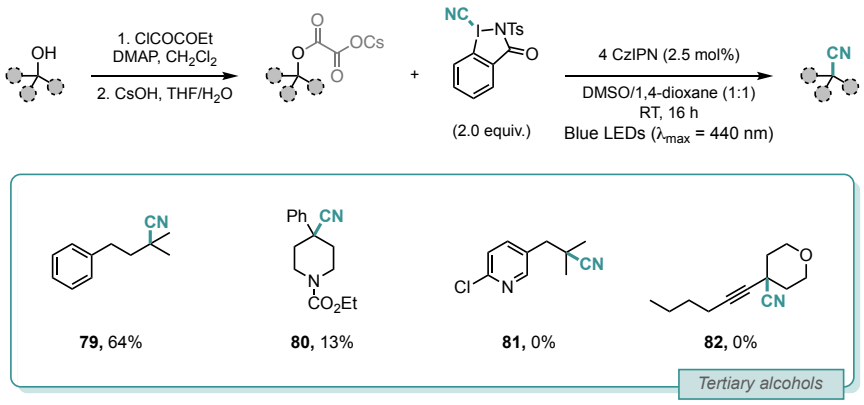
$[Ir(dF(CF_3)_2ppy)_2(dtbbpy)]PF_6$ Ir-F

$[Ir(dF(Me)_2ppy)_2(dtbbpy)]PF_6$ Ir-Me

4CzIPN

Table 3. Optimization studies.

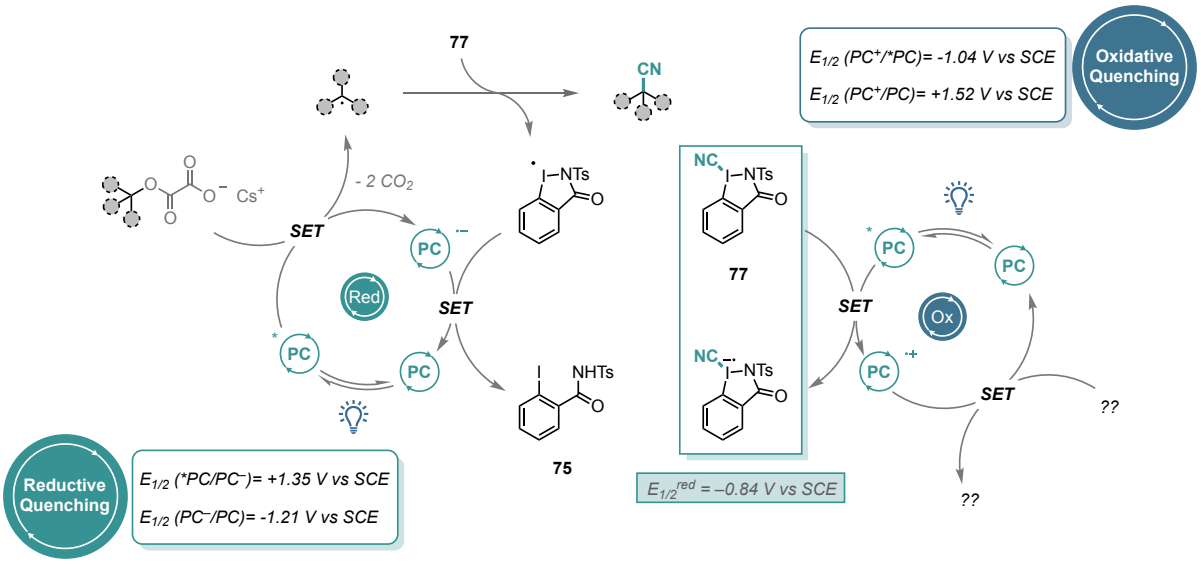
With the optimal conditions in hand, the scope of this transformation was explored (**Scheme 21**). Unfortunately, none of the scopes entries afforded positive results using the conditions selected after the optimization studies. This outcome led me to question which properties of the new compound **77** could affect the reactivity of the process.



Scheme 21. Scope of the reaction

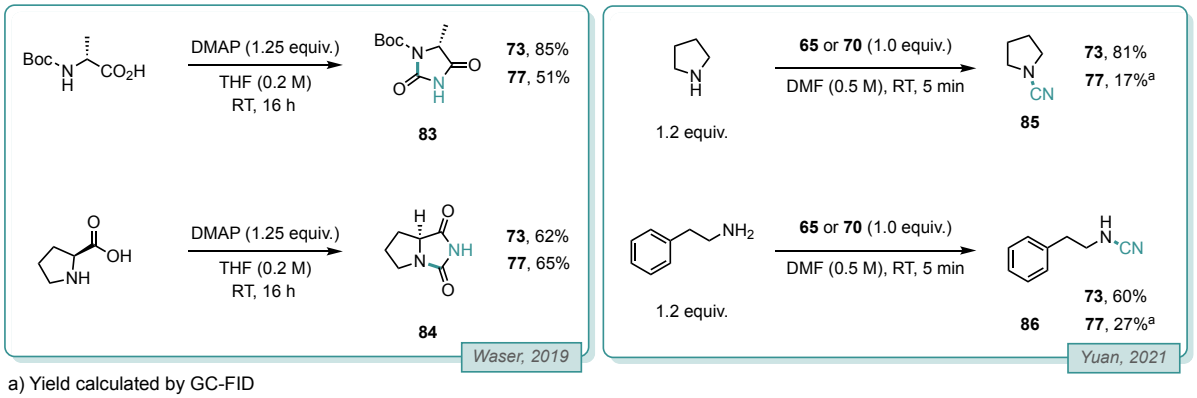
4.5. CV measurements, proposed mechanisms & reactivity tests

To gain further insight of the properties of **77** and the mechanism of the reaction, its reduction potential was measured by cyclic voltammetry. A stock solution of **77** and electrolyte $[NH_4][BF_4]$ in DMSO was placed in a closed vial of an IKA ElectraSyn 2.0 device, using the reference electrode Ag/AgCl in a saturated solution of potassium chloride. The vial was purged with nitrogen and the solvent dry and degassed to prevent oxygen could interfere in the measurement. The result of this experiment determined a value of -0.80 V *vs* Ag/AgCl, which after conversion corresponds to -0.84 *vs* SCE (saturated calomel electrode), for the reduction potential of **77**. This value makes **77** a relatively stronger oxidant than the Zhdankin's reagent **73** ($E_{1/2}^{red}$= −0.92 V vs SCE).[184] With this result in hand, a possible hypothesis was proposed for the reactivity exhibited by this methodology. Compound **77** is oxidant enough to quench the excited state of the 4CzIPN photocatalyst in an oxidative quenching manner ($E_{1/2}$ (PC^-/*PC) = -1.04 V vs SCE).[53] This oxidative quenching cycle might compete with the reductive quenching cycle, where the corresponding cesium oxalate ($E_{1/2}^{ox}$ ≈ +1.2 V vs SCE) is oxidized by the excited state of the photocatalyst ($E_{1/2}$ (*PC/PC^-)= +1.35 V vs SCE). This simultaneous presence of both competing cycles might translate in diminished yields for the final cyanation product. Moreover, changes in the potential of the cesium oxalate substrates employed could further decrease the yield of the reaction, supporting this hypothesis.



Scheme 22. Competing mechanisms.

Despite the unexpected outcome obtained for this radical deoxycyanation methodology, **77** was further employed in non-radical reported methodologies to test its reactivity. In all these methodologies, the authors utilized the Zdhankin's reagent **73** as the main electrophilic source of nitriles (**Scheme 23**). Therefore, replacing **73** for **77** could reveal a hint about its electrophilic character. The first conditions tested were reported by Waser and co-workers in 2019, where the authors reported a novel conditions for the synthesis of hydantoins,[194] different from the ones published by Red and Urech.[195] Hence, the authors discovered that when the light was removed from their previous reported decarboxylative cyanating methodology (see Section 4.2; **Scheme 17)**[190], the resulting product was the hydantoin heterocycle instead of the expected cyanated product. Thus, under these conditions *N*-protected alanine was converted to the hydantoin **83** in a 51% yield when **77** was employed, being the yield obtained lower than the one initially reported. However, the bicyclic hydantoin **84** derived from unprotected *L*-proline was isolated in 65% yield, which constitutes a slight increase of the reported yield. Finally, the last conditions tested were recently reported by Yuan for the *N*-cyanation of primary a secondary amines.[196] The cyanated secondary amine **85** and primary **86** were obtained in 17% and 27% dismissed yields respectively when **78** was employed as cyanating reagent. These results might indicate that **77** possesses a less electrophilic character due to the more electron-rich tosyl amide moiety compared with oxygen.



a) Yield calculated by GC-FID

Scheme 23. Study of the reactivity of **77** as electrophilic cyanating reagent.

4.6. Summary & conclusions

In summary, a new nitrile hypervalent iodine (III) type reagent **77** was synthesized, with potential applications in several chemistry fields. The exploration of a formal photoredox deoxycyanation methodology using **77** cyanation reagent was carried out. Preliminary optimization and mechanistic studies revealed the oxidant profile of this new reagent compare with the Zdhankin's reagent **73**, proposing the existence of a competing cycle which might explain the inefficiency of the conditions employed for this deoxycyanation reaction. Reactivity studies were performed trying to gain more information about the properties of this new reagent. However, further experiments should carried out to obtain a profound insight into the properties and reactivity profile of **77**.

5. RADICAL-BASED SYNTHESIS OF NOVEL UNNATURAL α-AMINO ACID SCAFFOLDS

5.1. Unnatural α-amino acids (UUAs): Importance & main strategies for their synthesis

UAAs, as described in Chapter 1, constitute an important group of molecules present in various fields, such as organic and medicinal chemistry, biology, and materials.[77,197–200] This widespread presence, along with their distinct properties compared to their proteogenic counterparts, boosted the development of novel synthetic methodologies capable of granting rapid access to this fascinating family of compounds. The main retrosynthetic disconnection pathway involves the formation of an α-amino stereocenter by employing a chiral ligands and catalysts able to provide the correct asymmetric conditions (**Figure 19**).[80–82,201–205] Although powerful methodologies, the design and synthesis of such chiral structures have a huge impact in terms of time/resource consuming. Therefore, straightforward methodologies to access UAAs without the necessity of a chiral catalyst are highly sought after.

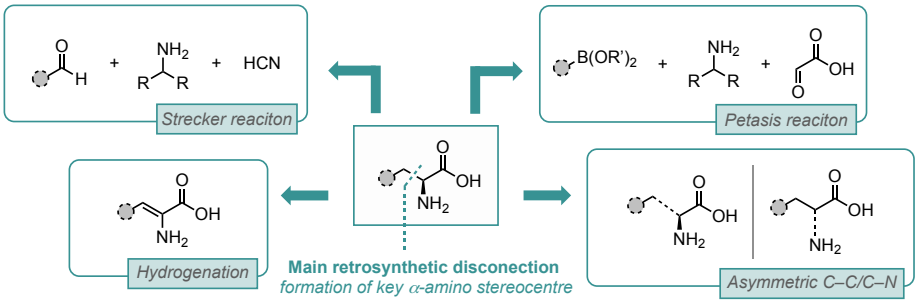
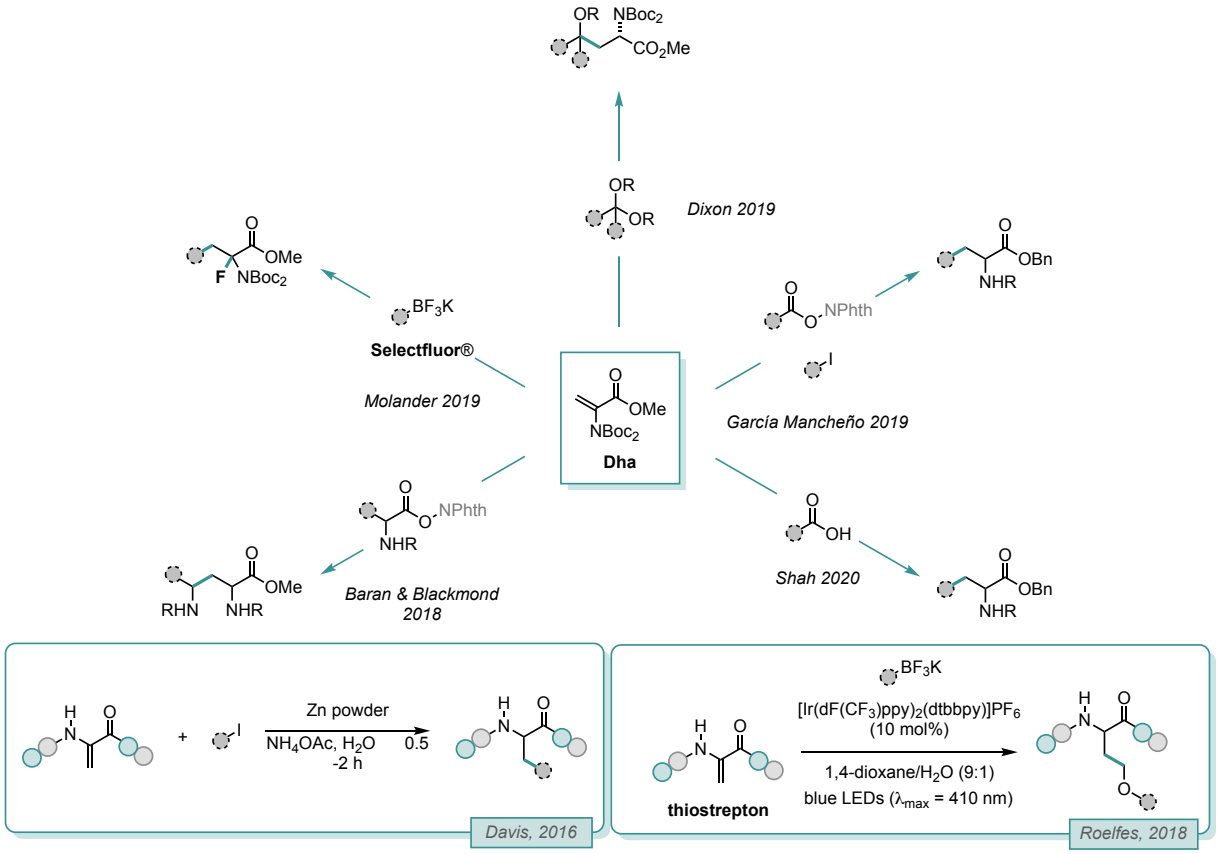


Figure 19. UAAs and main synthesis pathways.

Radical chemistry offers exciting and highly attractive approaches to access new chemical space in a rapid fashion due, in part, to the plethora of synthetic precursors available to generate open-shell species.[3] Thus, it is not surprising that researchers have exploited this versatility by developing strategies for the synthesis and derivatization of amino acids and peptides using radical chemistry.[85] One of the most versatile synthons in these strategies is the dehydroalanine moiety (Dha). Dha exhibits great regioselectivity when is involved in radical addition reactions, acting as a Michael acceptor with the exclusive addition in the *exo*-methylene carbon producing an α-amino radical. Then, the later can be quenched by an efficient HAT reagent to afford β-substituted-α-amino acids in a variety of mild conditions. Methodologies such as those reported by Baran and Blackmond,[206] Molander,[207] Dixon,[208] García-Mancheño,[209] or Shah[210] have illustrated the wide range of possibilities offered by Dha functionalizations (**Schemel 24**). In addition, all these technologies can be applied in

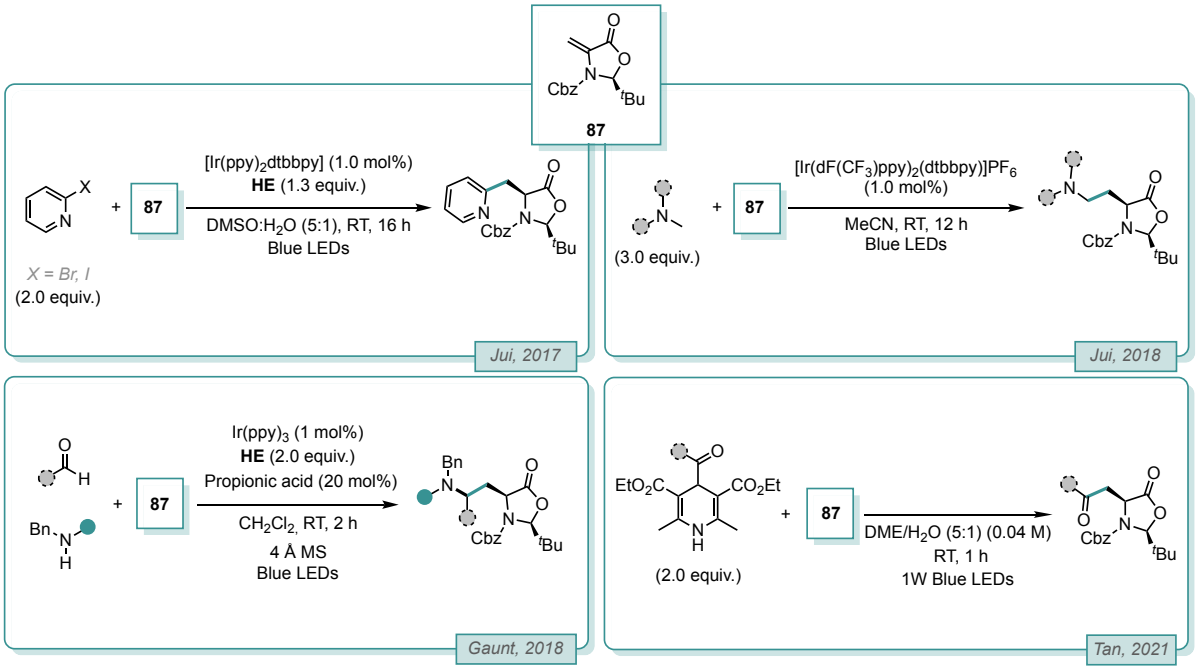
the field of peptide structure modification.[84] During the last years, the objective of this structure modification has been the improvement of the permeability and stability, key characteristic in the design of more efficient peptidic drugs.[211] Davis and co-workers have reported the use of alkyl bromides/iodides as efficient radical precursors for the side-chain modification of proteins.[212] Moreover, Roelfes and co-workers employed organoborates as radical precursors for the alkylation of antimicrobial peptides, and Jui and co-workers generated aminoalkyl radicals for the corresponding tertiary amines for their coupling in peptides structures.[213] All these methodologies showed a perfect chemoselectivity toward the Dha rest present in the peptide structures.



Scheme 24. Radical methodologies with Dha and peptide modification.

The Beckwith-Karady alkene **87** is a chiral dehydroalanine derivative developed in the early 1990s.[214,215] The first syntheses of this oxazolidinone species were reported by Karady in 1984,[216] and by Seebach in 1985,[217] then further described by Beckwith in 1990.[214] The use of **87** during the last years served for the development of highly diastereoselective routes for the synthesis of novel UAAs. (**Scheme 25**). The key for the efficient diasteroselectivity of this substrate is in the bulkiness of the *t*Bu group, which blocks the *si*-face towards possible additions. For example, Jui and co-workers have reported the visible-light heteroarylation and aminoalkylation of **87.**[218,219] Gaunt and co-workers have published a three-component method for the synthesis of UAAs merging dialkyl amines, carbonyl

centers (either ketones or aldehydes), and **87**.[220] Finally, Tan and wo-workers recently reported the use of 4-acyl-1,4-dihydropyridines (acyl-DHPs) as efficient radical precursors for the acylation of **87**.[221] The work of Overman and MacMillan using cesium oxalate salts as radical precursors of tertiary alkyl radicals presented one example in their scope of the efficient coupling with **87** as electron-deficient alkene.[73]



Scheme 25. Diastereoselective syntheses of UAAs using **87**.

5.2. Goals of the projects

All these methodologies served as inspiration for the invention of two novel chemo- and regioselective strategies for the synthesis of UAAs using **87** as a chiral Michael acceptor, which will be presented in this chapter. In one, the use of carboxylic and α-keto acids allowed us to synthesize unnatural α-amino acids via light-mediated radical decarboxylative processes (Project I).[222] In the other, the introduction of triphenylphosphine along with carboxylic acids afforded the corresponding γ-oxo-α-amino acids via radical acylation pathway (Project II) (**Figure 20**).[223] These two projects were developed by all the members of the Gómez-Suárez lab, including Jonas Djossou, who was doing his BSc thesis at that time, my co-workers Kay Merkens, Khadijah Anwar, and me. Therefore, during this chapter I will mostly focus on my side of the performed experiments.

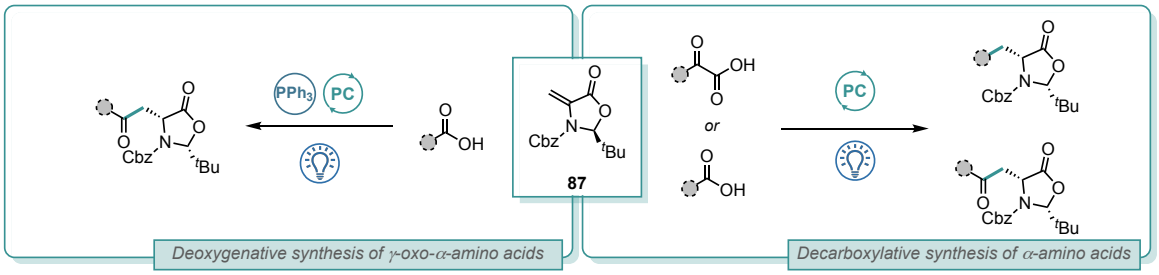
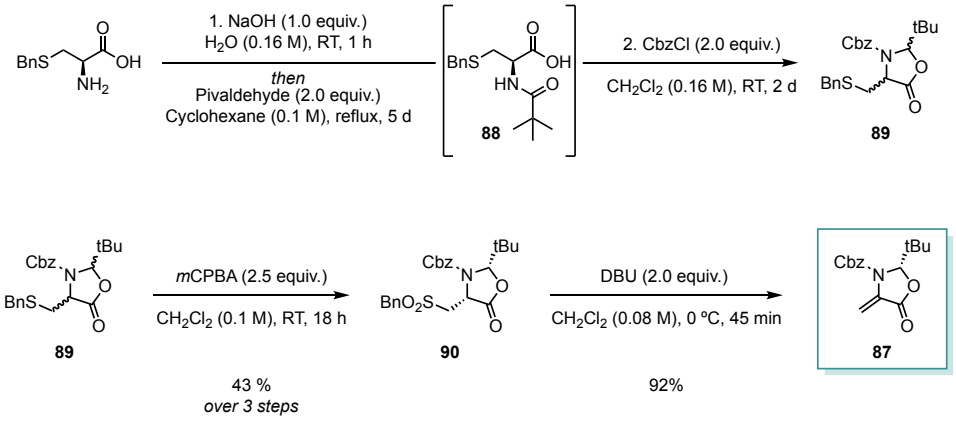


Figure 20. Novel strategies developed for the synthesis of UAAs.

5.3. Synthesis of α-UAAs via radical decarboxylative processes

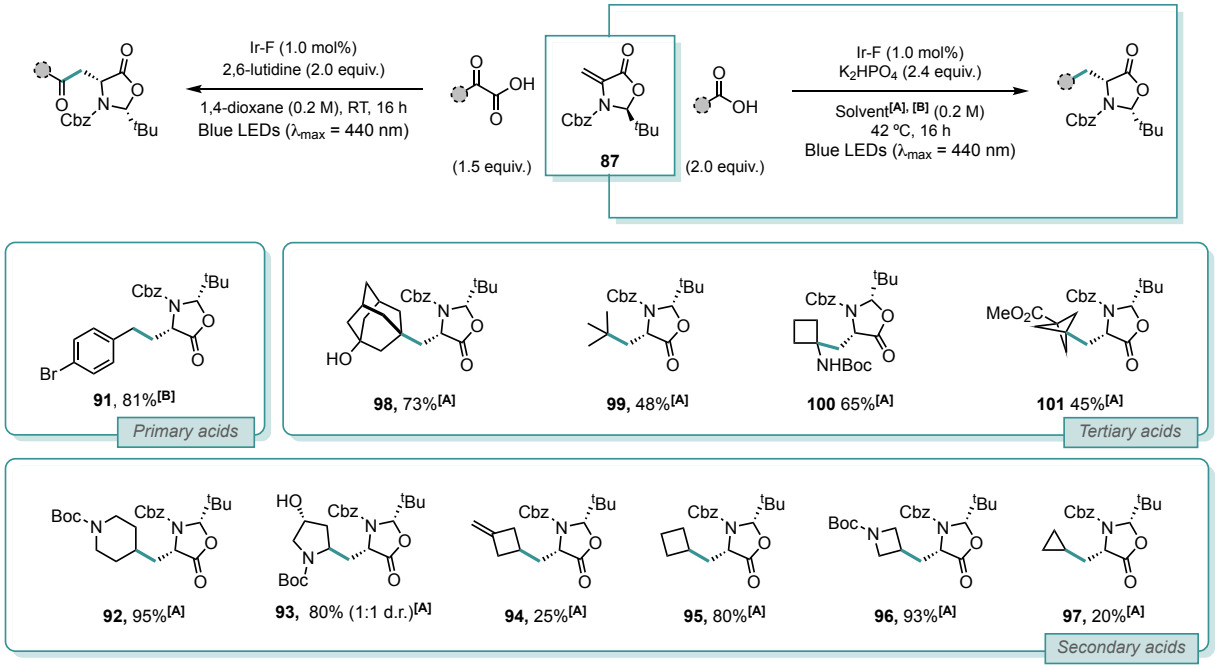
Before starting with any exploration or optimization of conditions, **87** had to be synthesized (**Scheme 26**). A modified version of the route previously reported by Jui was employed to achieve this goal.[218] The first part of the route consisted in two steps performed in one pot, where *S*-benzyl-*L*-cysteine was first treated with a solution of sodium hydroxide in water, followed by a solution of pivaldehyde in cyclohexane to afford the *N*-protected intermediate **88**. The latter was subsequently dissolved in CH_2Cl_2 and mixed with benzyl chloroformate, promoting the formation of the diastereomeric mixture of oxazolidinone intermediate **89**. Subsequent treatment of **89** with *m*CPBA oxidizes the thioether moiety to the corresponding sulfone, obtaining a mixture of diasteroisomers from where the single diastereoisomer **90** was isolated after purification via column chromatography. The last step of the route involves the desulfonylation of **90** using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a non-nucleophilic base to afford the desired alkene **87** in an excellent 92% yield.



Scheme 26. Synthesis of **87**.

With **87** in hand, optimization studies were conducted to obtain the optimal conditions for the decarboxylative acylation and alkylation protocols, using α-keto acids and carboxylic acids, respectively, as radical precursors. As a result, two sets of conditions were identified for the alkylation reaction, and one for the acylation reaction, which are displayed in **Scheme 27** along with the scope entries that I synthesized. While my co-workers were focused on the aromatic and aliphatic α-keto

acids, I was synthesizing the entries corresponding to the carboxylic acids for the alkylation protocol. Primary (**91**), secondary (**92-97**), and tertiary (**98-101**) acids bearing a wide range of functional groups performed well with this transformation in moderate to excellent yields. It is worth highlighting examples like **93**, where *N*-Boc protected *L*-proline was successfully coupled wearing a free hydroxyl group, or the bicyclo[1.1.1]pentane (BCP) example **101**, an important group of saturated bioisosteres of benzenoids in medicinal chemistry and crop science. The diastereoselectivity of the products was calculated via ^{1}H-NMR of the crude reaction mixture.

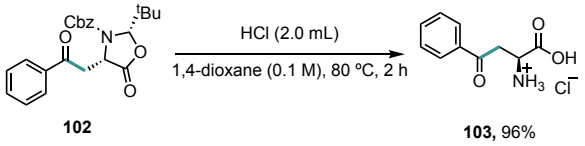


[A] 1,4-dioxane; [B] DMSO

Scheme 27. Scope of the reaction.

5.4. Derivatizations & mechanistic studies

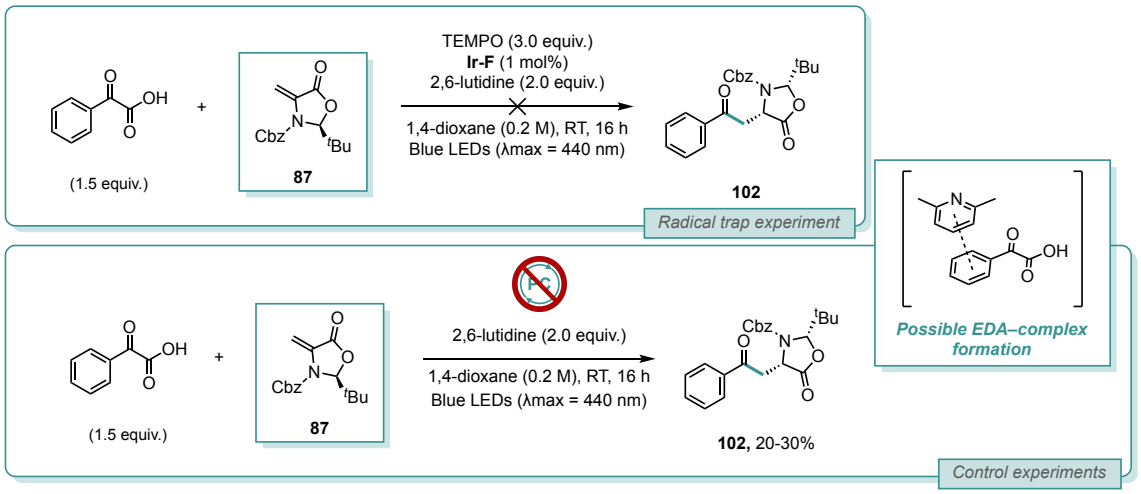
To highlight the utility of this methodology, a series of derivatization reactions were performed. The acidic deprotection of the final products using concentrated HCl in 1,4-dioxane afforded the free acid salts in quantitative yields (**Scheme 28**)



Scheme 28. Acidic deprotection.

To gain further insight of the mechanism of both methodologies, preliminary mechanistic studies were carried out (**Scheme 29**). The introduction of the TEMPO radical scavenger completely inhibited the reaction, supporting the radical nature of these transformations. Control experiments

demonstrated that light and photocatalyst were necessary for the alkylation conditions. However, when phenylglyoxylic acid and 2,6-lutidine as a base were irradiated in absence of photocatalyst, around 20-30% of the desired product was formed. To discover the role played by 2,6-lutidine, a set of test reactions were carried out. First, 2,6-lutidine was replaced for the inorganic base K_2HPO_4, and no product formation was observed after irradiation in absence of photocatalyst. Then, an aliphatic α-keto acid, such as 2-oxo-4-phenylbutanoic acid in combination with 2,6-lutidine, were irradiated in absence of photocatalyst, without formation of the desired product. The combination of these two results suggested the potential formation of an EDA-complex between the phenylglyoxylic acid and 2,6-lutidine by aryl complexation of both molecules



Scheme 29. Derivatizations and control experiments.

This EDA-complex formation hypothesis was tested by measuring the UV/Vis spectra of the reaction mixture, and its components (**Figure 22**). One clear sign of the presence of a possible EDA-complex is that when the suspected involved species are mixed and their UV/Vis spectra are measured, an absorption increase should be observed. Checking the UV/Vis spectra of the reaction mixture using phenylglyoxylic acid and 2,6-lutidine (purple line), this increase was observed. However, when a solution of phenylglyoxylic acid was measured (green line), the same absorption increase was obtained. This last result suggests that the phenylglyoxylic acid is excited after irradiation in the absence of the 2,6-lutidine base. Therefore, the hypothesis of the EDA-complex formation was discarded. In contrast, a possible direct excitation of phenylglyoxylic acid might be the reason of the higher reactivity. This possibility was already described by Kokotos and coworkers in their reported metal-free hydroacylation of unactivated olefins.[224] In this methodology, the authors proposed that phenylglyoxylic acid might act as a photosensitizer and acyl radical source simultaneously. After excitation and ISC event, the excited triplet state of the phenylglyoxilic acid might undergo homolytic cleavage via Norrish Type I event to produce the desired acyl radical center. Quantum yield

measurements supported this last result and proposed that both transformations could procced via radical chain mechanism.

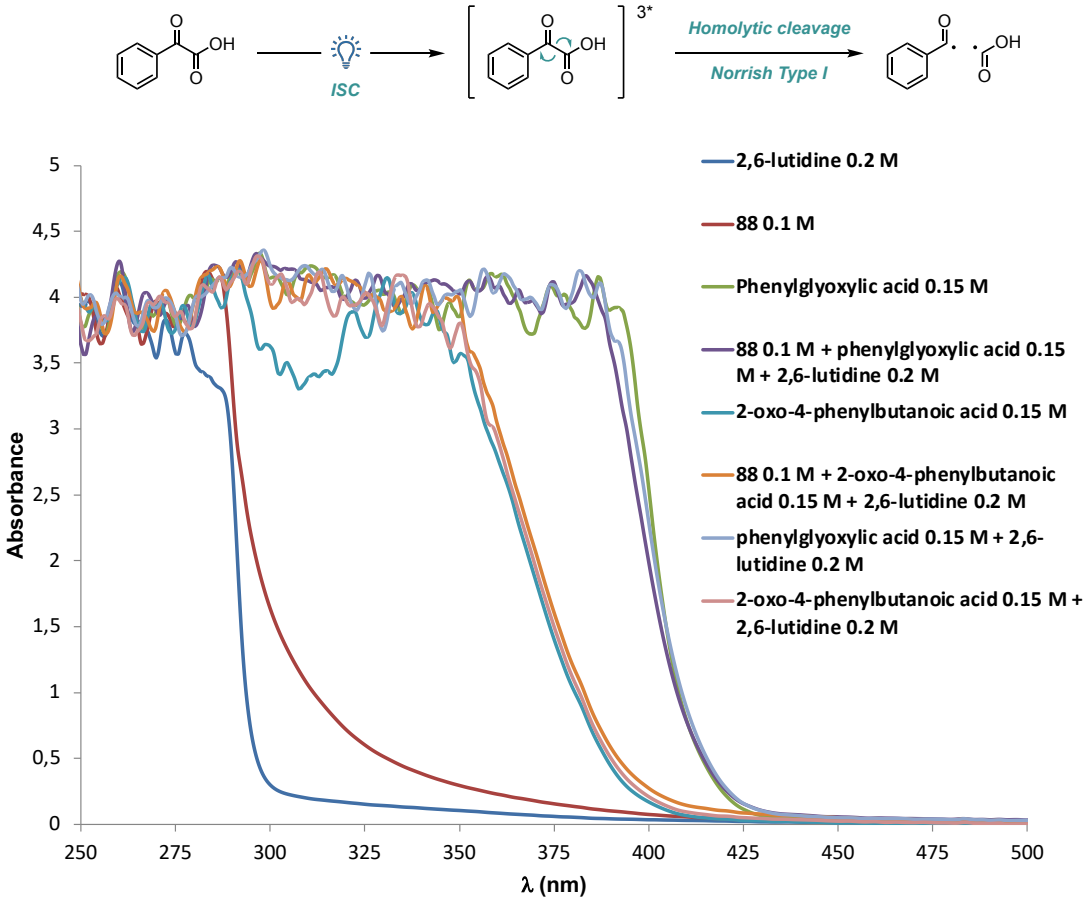
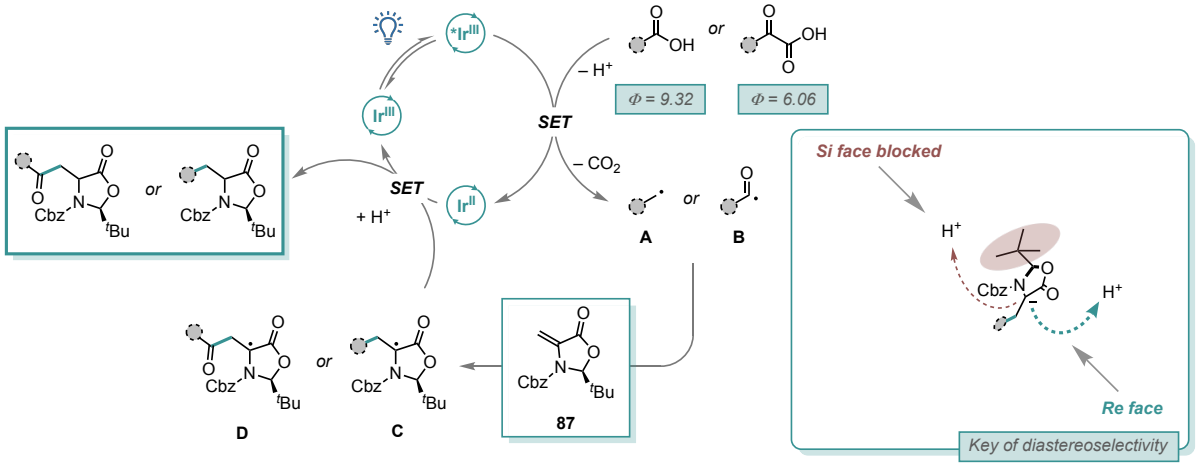


Figure 22. UV/Vis spectra measurements.

With all this information, we proposed a plausible mechanism disclosed in **Scheme 30**. After irradiation, the excited state of the photocatalyst ***Ir^{III}** (*$E_{1/2}$ = +1.21 V vs SCE) is quenched in a reductive manner via SET by the corresponding alkyl or α-keto carboxylate ($E_{1/2}$≈ +1.2–1.5 V vs SCE), forming after decarboxylation the alkyl radical **A** or the acyl radical **B** respectively. Subsequent radical addition of **A/B** to **87** produce the radical species **C/D**, which finally interact with the **Ir^{II}** ($E_{1/2}$ = −1.37 V vs SCE) reduced species, producing the targeted compound in a net redox-neutral cycle. This proposed mechanism is supported by previously reported methodologies for the alkylation of Michael acceptors under photoredox conditions.[225] Unfortunately, we were not able to elucidate the nature of the species involved in the hypothetical radical chain mechanism which the quantum yield measurement suggests, affording values of 9.32 and 6.06 for the carboxylic acids and the α-keto carboxylic acids respectively . Finally, as it was mentioned before, the bulkiness of the ^{t}Bu group constitutes as the reason for the diastereoselectivity of the process, which blocks the *si* face of the

molecule during the protonation event, thus leading to the formation of the syn oxazolidinone species.[214,215,226] NOESY experiments support the conformation of the final products.



Scheme 30. Proposed mechanism for the decarboxylative syntheses of unnatural α-amino acids.

5.5. Synthesis of γ-oxo-α-amino acids via radical acylation process

Among the amino acids, γ-oxo-α-amino acids constitute a polyvalent building blocks due to their widespread use and presence in fields such as organic synthesis or biologically active molecules.[227–230] To synthesize these versatile scaffolds, four classical retrosynthetic pathways can be followed via (**Figure 23**):

- Pathway A: via acylation of *L*- or *D*-aspartic acid, either through Friedel-Crafts acylation or the use of the Weinreb amide.[231,232]
- Pathway B: via asymmetric or diastereoselective Mannich reaction.[233–235]
- Pathway C: via asymmetric Stetter reaction.[236]
- Pathway D: via transition metal-mediated cross- couplings with iodoalanine or β-metalated alanine derivatives.[237–239]

Although powerful, all these methodologies present some limitations. In the case of the first three transformations, they share the already mentioned time/resource consuming drawback. In the case of pathway D, the stoichiometric use of metal-based reductants, e.g. Zn or Mn, is often required. Recently, Rovis and Doyle,[240] and Zhu[241] independently reported seminal studies demonstrating the use of photoredox catalysis to generate acyl and alkyl radical via phosphine radical cations **E**. The later reacts with the corresponding O–center (alcohols or carboxylates) to form the corresponding phosporanyl radical species **F**. This species is key for the success of these methodologies, because of this tetravalent phosphine centered radical can undergo β-scission event to form strong phosphorus–oxygen double bond (130 kcal/mol), which is the driving force of the reaction, and a new carbon–

centered radical species **A** or **B**. (**Figure 23**).[242] Therefore, by using this pathway is possible to avoid extra activation steps and use the readily available alcohols and carboxylic acids motifs as substrates.

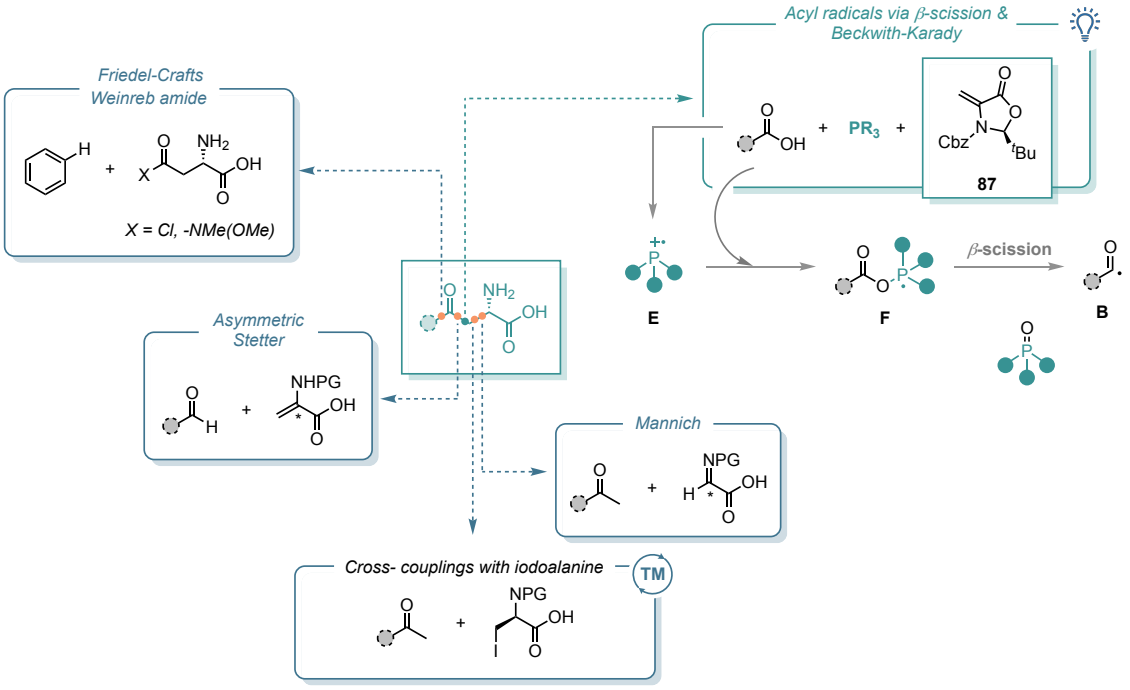
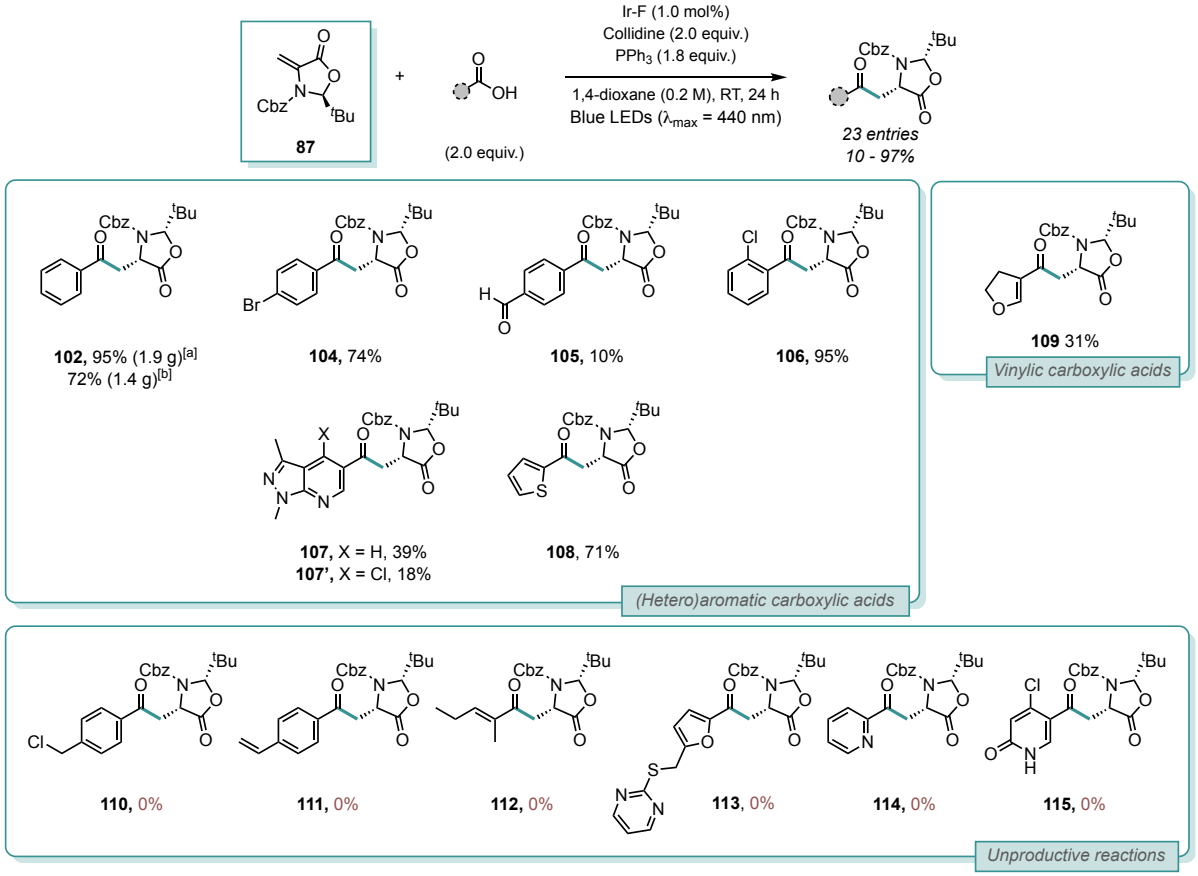


Figure 23. Retrosynthetic pathways for the synthesis of γ-Oxo-α-amino acids.

During the development of our previous methodology, the use of electron deficient or (hetero)aromatic systems did not promote the desired coupling in a very efficient way, affording diminished yields. In addition, α-keto acids are not readily available, and their synthesis often requires the use of hazardous reagents, such SeO_2. Therefore, with the aim of overcome all these drawbacks and inspired by the aforementioned seminal works, we have developed a new retrosynthetic approach using commercially available carboxylic acids as acyl radical precursors, and **87** as chiral radical acceptor. Optimization studies revealed that the best conditions involved the irradiation of **87** in presence of 1.5 equiv. of the corresponding carboxylic acid, Ir-F as photosensitizer, 2.0 equiv. of collidine as base, and 1.8 equiv. of triphenylphosphine with a 32 W blue LED (λ_{max}= 440 nm) inside an EvoluChem™ PhotoRedOx Box for 24 h in 1,4-dioxane. These optimal conditions allowed us to explore the scope and limitations of this transformation (**Scheme 31**). Several (hetero)aromatic carboxylic acids bearing electron rich, and electron poor substituents were coupled successfully with **87**, further improving the reactivity of our previous methodology using electron-poor systems. It is worth highlighting the outcome of the reaction when 4-chloro-1,3-dimethylpyrazolo[3,4-b]pyridine-5-carboxylic acid was employed, being the dechlorinated species **107** (39%) the main product probably because of the basic character of the collidine might abstract the chlorine atom,[243] while the expected product **107'** was isolated only in 18% yield. Cyclic vinylic carboxylic acids were also tested as acyl

coupling partners, obtaining interesting γ-oxo-α-amino acid derivatives bearing 5- and 6-membered heterocycles. The scalability of this methodology was demonstrated by scaling the standard reaction with benzoic acid (**102**) up to 5.0 mmol, affording **1** in 95% (1.9 g) and 73% (1.4 g) yield using 0.5 mol% and 0.25 mol% of **Ir–F**, respectively. Some other substrates were tested to further check the reactivity and limitations of this methodology. The presence of sensitive positions towards radical addition, like the primary chlorine position in **110,** or the alkene position in **111** might explain their lack of reactivity. The lower stabilization of **112** due to a lower conjugated system seems to be an impact factor under this reaction conditions. ^{1}H-NMR analysis of **113** showed a complete decomposition of the pyrimidine core. Attempts to coupling picolinic (**114**), and dihydropyridine derivates (**115**) did not afford positive yields.

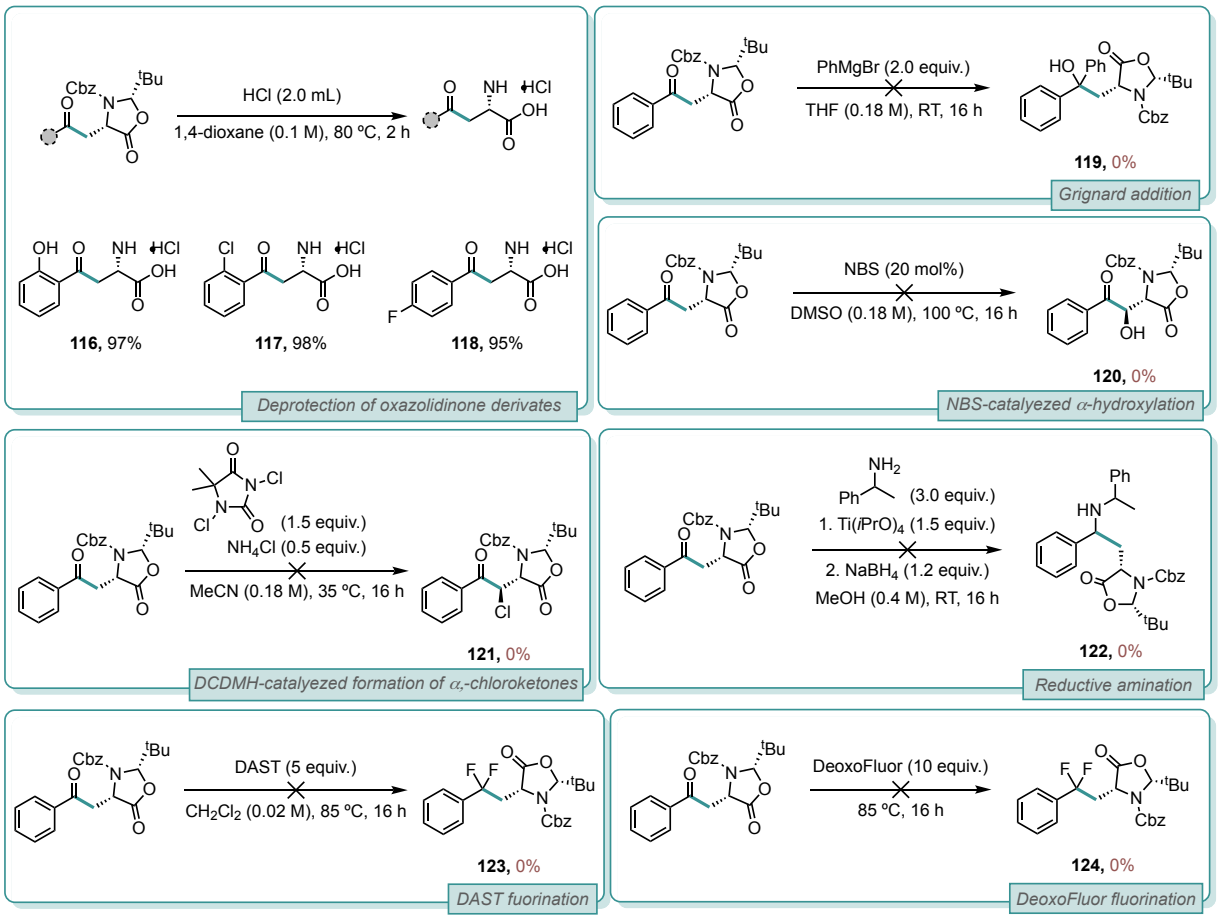


Scheme 31. Scope of the reactions.

5.6. Derivatizations & mechanistic studies

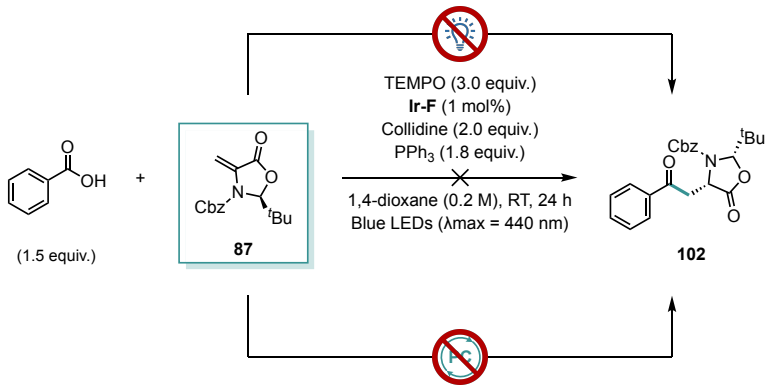
As with the previous project, the acidic deprotection of the final products using concentrated HCl in 1,4-dioxane afforded the free acid salts in quantitative yields. A set of further derivatizations were tested, without obtaining reliable results. When **102** was subjected to some classic chemistry conversions like Grignard addition, reductive amination, or fluorination DAST and DeoxoFluor-mediated fluorinations, no derivatized product was observed. Other transformations were carry out, such as the α-chlorination of ketones using 1,3-Dichloro-5,5-dimethylhydantoin (DCDMH) reported by

Wang,[244] or *N*-bromosuccinimide (NBS)-Catalyzed α-hydroxylation of Ketones in DMSO reported by Jiao.[245] As in the previous cases, no derivatized product was observed (**Scheme 32**). A possible hypothesis might be that the bulkiness of the benzyl chloroformate group produces a high steric hindrance next to the carbonyl position, inhibiting any possible reactivity.



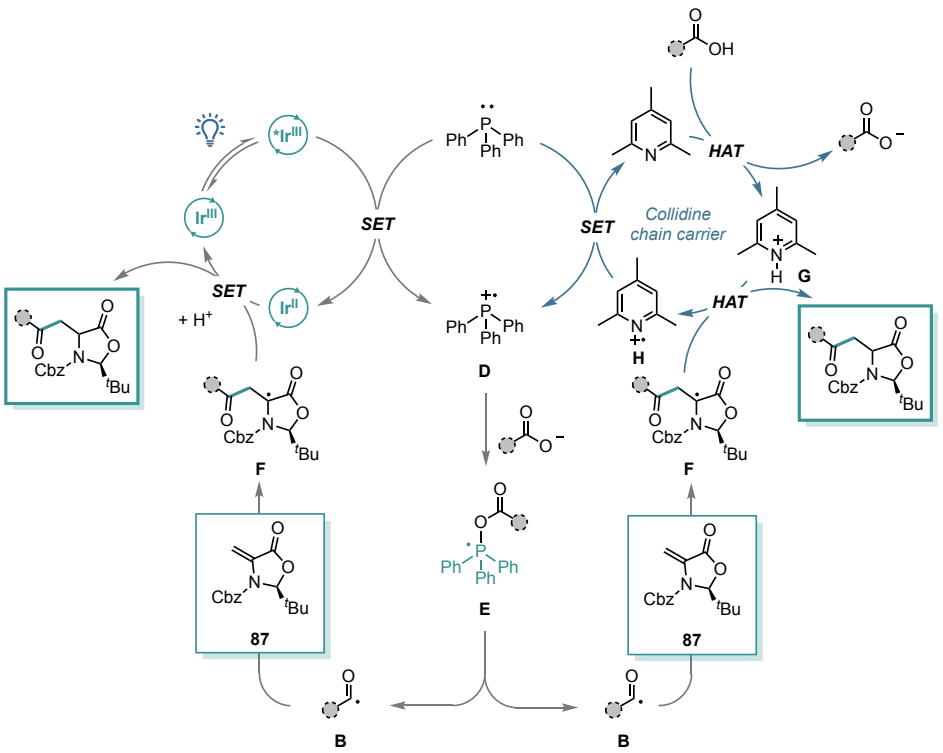
Scheme 32. Derivatization reactions.

The pertinent control experiments showed that the reaction could not proceed in the absence of either light or photocatalyst. Under standard reaction conditions, the presence of TEMPO completely inhibited the formation of the product, supporting the radical nature of this methodology.



Scheme 33. Control experiments.

These results, along with previously reported methodologies,[242] allowed us to suggest a plausible mechanism disclosed in **Scheme 34**. First, PPh_3 ($E_{1/2}$ = +0.98 V vs SCE) is oxidized by the excited photocatalyst ***Ir^{III}** (*$E_{1/2}$ = +1.21 V vs SCE), generating the triphenylphosphine radical cation **D** and **Ir^{II}**. Then, **D** reacts with the corresponding carboxylic acid, affording the phosphoranyl radical cation **E**, which readily undergoes *β*-scission to deliver $OPPh_3$ and the key acyl radical **B**. The latter adds to **87** to afford the radical intermediate **F**, which is subsequently reduced by **Ir^{II}** ($E_{1/2}$ = −1.37 V vs SCE) via SET, delivering the targeted product after final protonation. The results obtained from the measurement of the quantum yield suggested (Φ = 13.5) the possible contribution of a radical chain pathway, where we suspected than 2,4,6-collidine seems to play a crucial role. This hypothesis was based on further analysis, where the reaction was performed using either superstoichiometric amounts of inorganic bases (Cs_2CO_3 or KH_2PO_4) or in the absence of bases, the yield of **102** dropped drastically. However, when the reaction was carried out with catalytic amounts of 2,4,6-collidine (20 mol%), **102** was obtained in 20% yield after 1 h and in 79% yield in 3 h. Despite the fact we were not able to fully disclosed the nature of this radical chain, the information obtained during these last experiments encouraged us to tentatively proposed that a HAT or PCET event between **F** and the pyridinium species **G** would generate a highly oxidizing pyridinium radical cation **H** ($E_{1/2}$ collidine ≥ +2 V vs SCE),[246] which would act as a chain carrier by oxidizing PPh_3 to generate the key phosphoranyl radical cation **D** and regenerate the base.

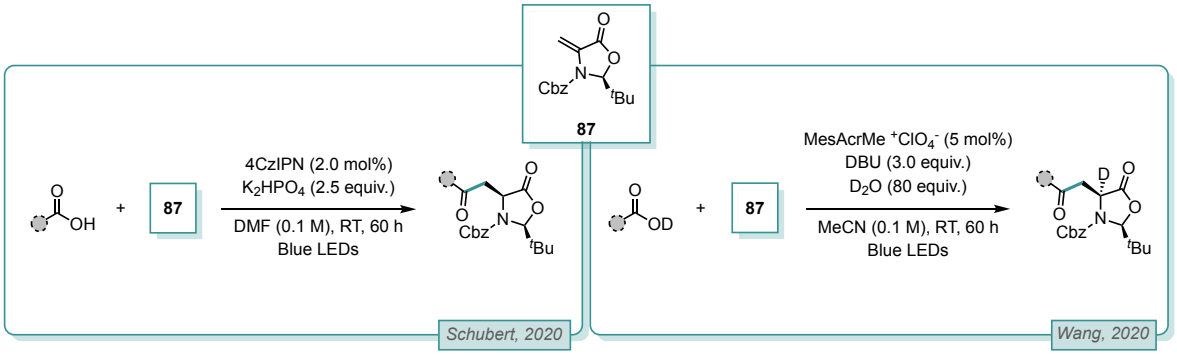


Scheme 34. Proposed mechanism.

5.7. Summary & conclusions

In conclusion, after these two studies we have developed highly efficient, light-mediated methodologies for the radical alkylation and acylation of **87**. Both methods displayed a high functional tolerance in synthetically useful yields with excellent diastereoselectivities for the straightforward construction of a wide range of novel unnatural α-amino acids. Additionally, the synthetic utility and scalability of these protocols was highlighted by a series of derivatization reactions.

During the development of these methodologies, two other transformations using similar conditions were reported by Schubert,[247] and Wang.[248] In the first one, the authors employed the organophotocatalyst 4CzIPN to achieve the alkylation of **87**, using carboxylic acids as alkyl radical precursors. In the second case, deuterated carboxylic acids were used for the synthesis of α-deuterated UAAs (**Scheme 35**).



Scheme 35. Further decarboxylative functionalizations

Finally, both of our methodologies were highlighted in Synfacts,[249,250] and Organic Process Research & Development (OPR&D),[251,252] remarking the mild conditions and low catalyst loading, along with the variety of examples and derivatizations carried out and demonstrating their impact and potential application in the industry.

CONCLUSIONS

The initial aims of the projects here compiled were successfully accomplished, as the ~~with the~~ development of a series of straightforward transformations was achieved. At the beginning, we were able to develop a novel formal radical deoxyfluorination methodology via oxalate salts activation of the corresponding tertiary alcohols. The ambition behind this was to overcome the limitations that the classical deoxyfluorination technologies presented for congested systems. Commercially available Selectfluor® was selected as an efficient fluorinating reagent for this selective metal-free functional group interconversion. Our investigations suggest a potential EDA-complex formation between the corresponding oxalate and Selectfluor® as main mechanistic pathway. Some events during the development of this first project encouraged us to further investigate the potential applications of radical deoxyfunctionalizations methodologies, summarized as follows.

Firstly, the discovery of a major fused heterocycle by-product in a Minisci fashion pathway led us to question the optimization and application of a potential intramolecular Minisci methodology due to the presence of this transformation in the synthetic pool remains scarce. Hence, we have been able to optimize this technology and use it as key step in a three steps straightforward route for the synthesis of novel saccharide based polycyclic structures with perfect diastereoretention. Early biological studies suggested that further modification of these structures, e.g. fused ring size modification, or replacement of the ring heteroatom, might grant access to a wide library of polycyclic compounds.

Secondly, the lack of efficient deoxycyanation methodologies, especially in the case of tertiary examples served to synthesize a novel cyanation hypervalent iodine (III) reagent by replacing the I–O bond of the well-known Zdhankin reagent for a more stable *N*-tosyl group. The reactivity of this novel compound was tested by developing a visible-light mediated deoxycyanation technology using the already employed cesium oxalates. However, preliminary cyclic voltammetry measurements revealed the more oxidant character of this reagent, which could explain the diminished reactivity with our conditions by the presence of competing cycles. Our resulting hypothesis is that the replacement of the carbonyl moiety of the five-membered ring for an imine rest might adjust its reduction potential, avoiding competing pathways.

Furthermore, we have contributed to the field of the synthesis of novel unnatural amino acids (**UUAs**) by developing two novel visible-light protocols for the alkylation and acylation of the Beckwith-Karady chiral dehydroalanine derivative. These two works represent a robust and reproducible pathway for the synthesis of such relevant structures in the development of peptidomimetic drugs.

6. SUPPORTING INFORMATION

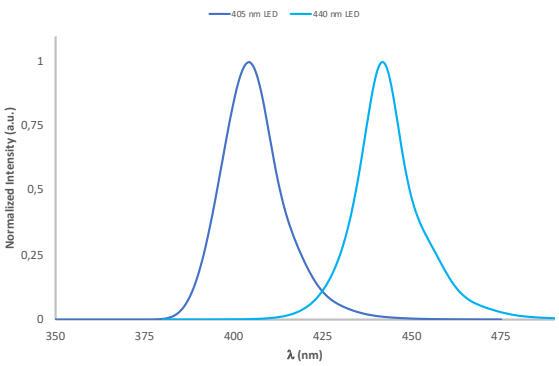
6.1. General information

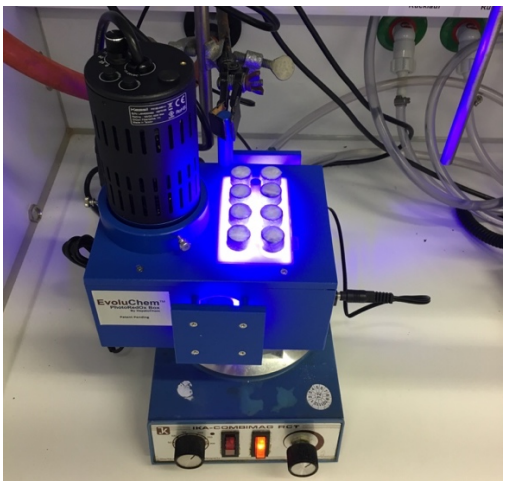
Commercial reagents and solvents were used as purchased. Unless otherwise noted, all reactions were carried out under an atmosphere of N_2 in flame-dried glassware. The solvents used were purified by distillation over standard drying agents and were stored over molecular sieves or transferred under N_2. Visible light from a compact fluorescent lamp (CFL) was provided by a standard household desk lamp fitted with a 23 W fluorescent light bulb. Blue LEDs (32 W, λ_{max} = 440 nm and 18 W, λ_{max} = 405 nm) were used for irradiation, in combination with an EvoluChem™ PhotoRedOx Box. The reaction temperature was kept at 27 °C by the fans incorporated in the reactor.

TLC were conducted with precoated glass-backed plates (silica gel 60 F_{254}) and visualized by exposure to UV light (254 nm) or stained with ceric ammonium molybdate (CAM), basic potassium permanganate ($KMnO_4$), nihydrin, or *p*-anisaldehyde solutions and subsequent heating. Flash column chromatography was performed on silica gel (40-60 µm), the eluent used is reported in the respective experiments. Abbreviations of solvents are as followed: PE: petroleum ether.

^{1}H NMR spectra were recorded with 400 MHz or 600 MHz instruments, ^{13}C NMR spectra at 101 MHz or 151 MHz. Chemical shifts are reported in ppm relative to the solvent signal, coupling constants *J* in Hz. Multiplicities were defined by standard abbreviations. Low-resolution mass spectra (LRMS) were recorded using a LC/MS-combination (ESI). High-resolution mass spectra (HRMS) were obtained using ESI ionization (positive) on a Bruker micrOTOF.

6.2. LED's emission spectra, standard reaction set up & gram-scale reaction set up





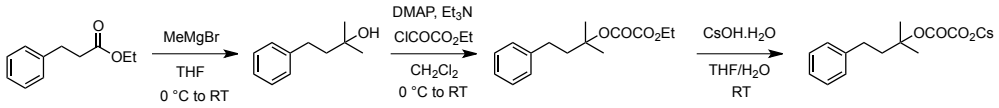
6.3. Chapter 2: Formal Radical Deoxyfluorination of Tertiary Alcohols

6.3.1. General procedures

General procedure for the synthesis of ethyl oxalates (GP1): A round-bottom flask (RBF) was charged with the corresponding tertiary alcohol (1.0 equiv.) and CH_2Cl_2 (0.1 M), followed by addition of triethylamine (1.2 equiv.) and DMAP (0.1 equiv.) and cooled to 0 °C. Next, ethyl chlorooxoacetate (1.2 equiv.) was added dropwise and the reaction was stirred for 1 hour at room temperature and then quenched with saturated NH_4Cl (aq.). Finally, the aqueous phase was extracted with CH_2Cl_2, the combined organic layers dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel.

General procedure for the synthesis of cesium oxalates (GP2): To a RBF containing a solution of the corresponding oxalate in THF (1 M) was added a 1 N aq. solution of CsOH dropwise. The reaction was vigorously stirred at room temperature for 10 min. Afterwards the solvent was evaporated to deliver the corresponding Cs oxalate as a white solid. In certain cases, it was necessary to wash the aqueous phase with EtOAc or dichloromethane to obtain the pure products.

6.3.2. Synthesis & characterization of starting materials



2-methyl-4-phenylbutan-2-ol: MeMgBr (11 mL, 33 mmol, 2.2 equiv.) was added dropwise to a 0 °C solution of ethyl 3-phenylpropanoate (2.7 g, 15 mmol, 1.0 equiv.) in THF (30 mL, 0.5 M). The mixture was stirred at 0 °C for 1 h and then warmed up to room temperature. After 2 h the reaction was quenched with a saturated solution of NH_4Cl (aq.), the product extracted with EtOAc (3 x 50 mL), and the combined organic layers dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by column chromatography using a 2:1 mixture of petrol ether/EtOAc to afford the desired product as a colorless oil in 83% yield (2.0 g, 12 mmol). The characterization matches the reported literature.[253]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 (tt, *J* = 7.9, 1.8 Hz, 2H), 7.24 – 7.21 (m, 2H), 7.21 – 7.18 (m, 1H), 2.76 – 2.69 (m, 2H), 1.83 – 1.79 (m, 2H), 1.31 (s, 6H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 142.6, 128.4, 128.3, 125.7, 70.8, 45.8, 30.8, 29.30.

R_f (PE/EtOAc 2:1) = 0.46 [CAM]

Ethyl(2-methyl-4-phenylbutan-2-yl)oxalate: Synthesized following **GP1** using 2-methyl-4-phenylbutan-2-ol (2.4 g, 18 mmol, 1.0 equiv.). The pure product was isolated as a colorless oil in 78% yield (3.7 g, 14 mmol). The characterization matches the reported literature. [73]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 (t, *J* = 7.2 Hz, 2H), 7.19 (t, *J* = 7.2 Hz, 3H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.73 – 2.67 (m, 2H), 2.18 – 2.12 (m, 2H), 1.61 (s, 6H), 1.38 (t, *J* = 7.2 Hz, 3H).

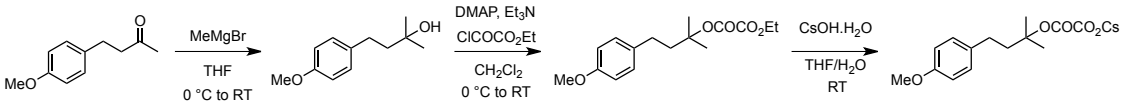
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 158.7, 157.2, 141.7, 128.6, 128.5, 126.1, 86.7, 62.9, 42.6, 30.4, 25.9, 14.1.

R_f (PE/EtOAc 4:1) = 0.36 [CAM]

Cesium 2-((2-methyl-4-phenylbutan-2-yl)oxy)-2-oxoacetate: Synthesized following **GP2** using ethyl(2-methyl-4-phenylbutan-2-yl)oxalate (0.5 g, 1.8 mmol, 1.0 equiv.). The product was isolated as a white solid in 90% yield (0.6 g, 1.6 mmol). The characterization matches the reported literature.[73]

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.31 – 7.23 (m, 2H), 7.20 – 7.14 (m, 3H), 2.63 – 2.56 (m, 2H), 2.04 – 1.96 (m, 2H), 1.41 (s, 6H).

^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 167.4, 163.4, 142.2, 128.2, 128.1, 125.6, 79.9, 42.0, 29.5, 26.0.



Ethyl (4-(4-methoxyphenyl)-2-methylbutan-2-yl) oxalate: To a solution of 4-(4-methoxyphenyl)butan-2-one (1.7 mL, 10 mmol, 1.0 equiv.) in THF (20 mL, 0.5 M) was added dropwise a solution of MeMgBr (3 M in Et_2O, 4.0 mL, 12 mmol, 1.2 equiv.) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then warmed out to room temperature. After 2 h the reaction was quenched with a saturated solution of NH_4Cl (aq.), the product extracted with EtOAc (3 x 50 mL), and the combined organic layers dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was used in the next step without further purification.

Synthesized following **GP1** using 4-(4-methoxyphenyl)-2-methylbutan-2-ol (10 mmol, 1.0 equiv.). The pure product was isolated as a colorless oil in 83% yield (2.44 g, 8.3 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.12 – 7.09 (m, 2H), 6.84 – 6.80 (m, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 2.66 – 2.60 (m, 2H), 2.15 – 2.09 (m, 2H), 1.59 (s, 6H), 1.37 (t, *J* = 6.6 Hz, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 158.7, 158.0, 157.2, 133.7, 129.4, 114.0, 86.7, 62.9, 55.4, 42.8, 29.4, 25.9, 14.1.

GCMS (FI): [m/z] calculated for $C_{16}H_{22}O_5$ ([M]): 294.14672; found 294.14519.

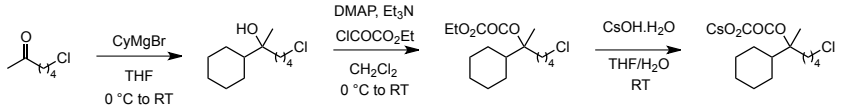
R_f (PE/EtOAc 4:1) = 0.4 [CAM]

Cesium 2-((4-(4-methoxyphenyl)-2-methylbutan-2-yl)oxy)-2-oxoacetate: Synthesized following **GP2** using ethyl (4-(4-methoxyphenyl)-2-methylbutan-2-yl) oxalate (1.0 g, 3.4 mmol, 1.0 equiv.).The product was isolated as a white solid in 94% yield (1.3 g, 3.2 mmol).

^{1}H NMR (600 MHz, DMSO-d_6): δ 7.09 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 3.71 (s, 3H), 2.55 – 2.50 (m, 2H), 2.00 – 1.93 (m, 2H), 1.41 (s, 6H).

^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 167.5, 163.4, 157.3, 134.0, 129.0, 113.7, 80.0, 54.9, 42.3, 28.6, 26.1.

HRMS (ESI-neg): [m/z] calculated for $C_{14}H_{17}O_5$ ([M-Cs]$^-$): 265,1076; found 265.1081.



6-chloro-2-cyclohexylhexan-2-ol: CyMgBr (1 M in Et_2O, 12 mL, 12 mmol, 1.2 equiv.) was added dropwise to a 0 °C solution of 6-chlorohexan-2-one (1.3 mL, 10 mmol, 1.0 equiv.) in THF (20 mL, 0.5 M). The mixture was stirred at 0 °C for 1 h and then warmed up to room temperature. After 2 h the reaction was quenched with a saturated solution of NH_4Cl (aq.), the product extracted with EtOAc (3 x 50 mL), and the combined organic layers dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by column chromatography to afford the desired product as a colorless oil in 33% yield (0.73 g, 3.3 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.55 (t, *J* = 6.7 Hz, 2H), 1.84 – 1.75 (m, 5H), 1.75 – 1.70 (m, 1H), 1.70 – 1.64 (m, 1H), 1.54 – 1.44 (m, 4H), 1.32 (tt, *J* = 12.0, 2.9 Hz, 1H), 1.27 – 1.18 (m, 2H), 1.16 – 1.10 (m, 1H), 1.10 (s, 3H), 1.01 (dqd, *J* = 28.4, 12.2, 3.1 Hz, 2H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 74.5, 47.5, 45.1, 39.1, 33.4, 27.7, 27.0, 26.9, 26.9, 26.7, 24.1, 20.9.

GCMS (FI): [m/z] calculated for $C_{12}H_{23}ClO$ ([M]): 218.14374; found 218.14374.

R_f (PE/EtOAc 10:1) = 0.25 [CAM]

6-chloro-2-cyclohexylhexan-2-yl ethyl oxalate: Synthesized following **GP1** with 6-chloro-2-cyclohexylhexan-2-ol (0.65 g, 3.0 mmol, 1.0 equiv.). The product was isolated as a colorless oil in 51% yield (0.48 g, 1.5 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.31 (q, *J* = 7.1 Hz, 2H), 3.54 (td, *J* = 6.6, 1.1 Hz, 2H), 2.10 – 2.03 (m, 1H), 2.02 – 1.95 (m, 1H), 1.88 – 1.82 (m, 1H), 1.81 – 1.73 (m, 4H), 1.71 – 1.62 (m, 2H), 1.50 – 1.47 (m, 2H), 1.46 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.29 – 1.19 (m, 2H), 1.17 – 1.01 (m, 4H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 158.8, 157.2, 92.3, 62.8, 44.9, 44.5, 34.8, 32.8, 27.4, 27.2, 26.6, 26.6, 20.8, 20.7, 14.1.

HRMS (ESI): [m/z] calculated for $C_{16}H_{27}ClNaO_4$ ([M+Na]$^+$): 341,1496; found 341.1490.

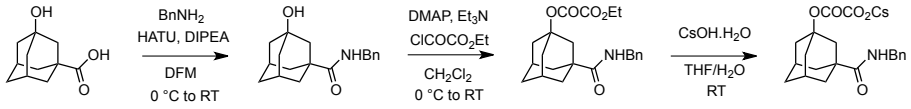
R_f (PE/EtOAc 4:1) = 0.37 [CAM]

Cesium 2-((6-chloro-2-cyclohexylhexan-2-yl)oxy)-2-oxoacetate: Synthesized following **GP2** with 6-chloro-2-cyclohexylhexan-2-yl ethyl oxalate (0.43 g, 1.3 mmol, 1.0 equiv.), the product was obtained as a colorless solid (0.55 g, 1.3 mmol, 96%).

^{1}H NMR (600 MHz, DMSO-d_6): δ 3.61 (t, *J* = 6.7 Hz, 2H), 2.00 (tt, *J* = 11.9, 2.9 Hz, 1H), 1.86 (ddd, *J* = 13.7, 9.3, 7.6 Hz, 1H), 1.75 – 1.56 (m, 8H), 1.38 (dq, *J* = 9.5, 7.4 Hz, 2H), 1.24 (s, 3H), 1.20 – 0.92 (m, 5H).

^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 167.4, 163.5, 45.3, 44.2, 34.7, 32.5, 26.7, 26.4, 26.3, 26.2, 26.1, 20.6, 20.1.

HRMS (ESI-*neg*): [m/z] calculated $C_{14}H_{22}ClO_4$ ([M-Cs]$^-$): 289,1207, found 289.1212.



***N*-benzyl-3-hydroxyadamantane-1-carboxamide:** 3-hydroxyadamantane-1-carboxylic acid (1.2 g, 6.0 mmol, 1 equiv.) and benzyl amine (0.85 mL, 7.8 mmol, 1.3 equiv.) were dissolved in DMF (0.4 M, 15 mL). At 0 °C, HATU (3.4 g, 9.0 mmol, 1.5 equiv.) and DIPEA (2.1 mL, 12 mmol, 2.0 equiv.) were added slowly. The reaction was stirred at room temperature for 18 h. Ethyl acetate and sat. sodium bicarbonate solution were added and the resulting phases were separated. The aqueous phase was extracted with ethyl acetate once and the combined organics were washed with aqueous hydrochloric acid (1 M) and brine, then dried over sodium sulfate, filtrated and the solvent removed under reduced pressure. The crude product was purified by column flash chromatography to yield the desired product as a yellow solid in 91% yield (1.5 g, 5.4 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 – 7.31 (m, 2H), 7.29 – 7.23 (m, 3H), 5.88 (s, 1H), 4.43 (d, J = 5.6 Hz, 2H), 2.33 – 2.23 (m, 2H), 1.83 (s, 2H), 1.82 – 1.75 (m, 4H), 1.74 – 1.67 (m, 4H), 1.61 – 1.58 (m, 2H), 1.44 (dd, J = 22.2, 6.6 Hz, 1H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 176.4, 138.6, 128.9, 127.8, 127.6, 68.6, 47.0, 44.5, 43.6, 38.3, 35.2, 30.5, 17.4.

HRMS (ESI): [m/z] calculated for $C_{18}H_{23}NNaO_2$ ([M+Na]$^+$): 308.1621; Found: 308.1622

R_f (DCM/MeOH 95:5) = 0.24 [UV]

3-(benzylcarbamoyl)adamantan-1-yl ethyl oxalate: Synthesized following **GP1** and using *N*-benzyl-3-hydroxyadamantane-1-carboxamide (1.7 g, 6.0 mmol, 1.0 equiv.). The pure product was isolated as a white solid in 83% yield (1.9 g, 5.0 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 – 7.31 (m, 2H), 7.29 – 7.26 (m, 1H), 7.25 – 7.22 (m, 2H), 5.86 (s, 1H), 4.42 (d, *J* = 5.6 Hz, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 2.38 – 2.33 (m, 2H), 2.30 (s, 2H), 2.24 (d, *J* = 11.4 Hz, 2H), 2.15 (d, *J* = 10.8 Hz, 2H), 1.85 (d, *J* = 2.5 Hz, 4H), 1.71 – 1.62 (m, 2H), 1.35 (t, *J* = 7.2 Hz, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 175.6, 158.5, 156.8, 138.4, 128.9, 127.8, 127.7, 84.5, 63.0, 44.5, 43.7, 42.5, 40.1, 38.2, 35.0, 30.7, 14.1.

HRMS (ESI): [m/z] calculated for $C_{22}H_{27}NNaO_5$ ([M+Na]$^+$): 408.1781; Found: 408.1783.

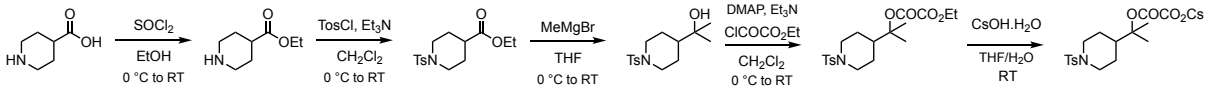
R_f (PE:EA) 70:30) = 0.14 [UV]

Cesium 2-((3-(benzylcarbamoyl)adamantan-1-yl)oxy)-2-oxoacetate: Synthesized following **GP2** using 3-(benzylcarbamoyl)adamantan-1-yl ethyl oxalate (0.77 mg, 2.0 mmol, 1.0 equiv.). The pure compound was isolated as white solid in 85% yield (0.83 g, 1.7 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.09 (t, J = 5.9 Hz, 1H), 7.30 (t, J = 7.7 Hz, 2H), 7.20 (t, J = 7.7 Hz, 3H), 4.25 (d, J = 5.9 Hz, 2H), 2.20 (s, 2H), 2.12 (s, 2H), 2.01 (s, 4H), 1.74 (s, 4H), 1.63 – 1.51 (m, 2H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 175.5, 167.2, 163.1, 140.0, 128.1, 126.7, 126.4, 78.3, 43.3, 42.5, 41.9, 40.2, 37.7, 34.8, 29.9.

HRMS (ESI): [m/z] calculated for $C_{20}H_{22}NO_5$ ([M-Cs]$^-$): 356.1503; Found: 356.1503.



Ethyl piperidine-4-carboxylate: Isonipecotic acid (2.6 g, 20 mmol, 1.0 equiv.) was dissolved in ethanol (abs., 50 mL). The solution was cooled to 0 °C and thionyl chloride (5.84 mL, 80.0 mmol, 4.0 equiv.) was added dropwise. Then the reaction mixture stirred and refluxed for 48 h. The solvent was removed *in vacuo* yielding a yellow oil, which was dissolved in EtOAc and washed with 10% NaOH (aq.). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to afford ethyl piperidine-4-carboxylate as a yellow oil in 74% yield (2.3 g,15 mmol). The characterization matches the reported literature.[254]

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.12 (q, *J* = 7.1 Hz, 2H), 3.08 (dt, *J* = 12.6, 3.7 Hz, 2H), 2.63 (td, *J* = 12.2, 2.7 Hz, 2H), 2.39 (tt, *J* = 11.2, 3.9 Hz, 1H), 1.90 – 1.84 (m, 3H), 1.65 – 1.56 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 175.2, 60.4, 46.0, 41.7, 29.4, 14.4.

R_f (PE/EtOAc 8:2) = 0.19 [UV] [$KMnO_4$].

Ethyl 1-tosylpiperidine-4-carboxylate: To a solution of ethyl piperidine-4-carboxylate (0.94 mg, 6.0 mmol, 1.0 equiv.) and triethylamine (1.2 mL, 9.0 mmol, 1.5 equiv.) in DCM (20 mL, abs.), tosyl chloride (1.7 g, 9.0 mmol, 1.5 equiv.) was added portionwise at 0 °C. The reaction was stirred 15 min at 0 °C and then 4 h at room temperature. 1 N HCl (aq.) was added to the reaction mixture and was stirred

vigorously. The aqueous layer was extracted with DCM (3 x 20 mL). Then, the combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a colorless oil. The residue was purified by chromatography over silica to obtain the desired product as a white solid in 97% yield (1.8 g, 5.8 mmol). The characterization matches the reported literature.[255]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.63 – 3.58 (m, 2H), 2.45 (td, *J* = 11.4, 3.0 Hz, 2H), 2.42 (s, 3H), 2.22 (tt, *J* = 10.6, 4.0 Hz, 1H), 1.98 – 1.91 (m, 2H), 1.84 – 1.75 (m, 2H), 1.20 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 173.9, 143.7, 133.4, 129.8, 127.8, 60.7, 45.5, 40.2, 27.6, 21.6, 14.2.

R_f (PE/EtOAc, 6:4) = 0.51 [$KMnO_4$].

2-(1-tosylpiperidin-4-yl)propan-2-ol: The ester (1.6 g, 5.0 mmol, 1.0 equiv.) was dissolved in THF (25 mL, abs.), followed by addition of MeMgBr (5.0 mL, 3 M in Et_2O, 15 mmol, 3.0 equiv.) dropwise at 0 °C under Ar. The reaction mixture was stirred 15 min at 0 °C and was then allowed to warm up to room temperature overnight. 1M HCl (aq.) was added slowly to the reaction mixture. The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were neutralized with saturated $NaHCO_3$ (aq.), washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel (PE/EtOAc 1:1) to give the desired tertiary alcohol as a white solid in 96% yield (1.4 g, 4.8 mmol). The characterization matches the reported literature.[255]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 3.93 – 3.80 (m, 2H), 2.42 (s, 3H), 2.17 (td, *J* = 12.1, 2.5 Hz, 2H), 1.78 (d, *J* = 13.0 Hz, 2H), 1.45 – 1.35 (m, 3H), 1.17 (tt, *J* = 12.4, 3.4 Hz, 1H), 1.12 (s, 6H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 143.5, 133.3, 129.7, 127.8, 72.1, 46.8, 46.8, 27.0, 26.4, 21.6.

R_f (PE/EtOAc, 1:1) = 0.25 [CAM].

1-cyclohexyl-2-((3,3-diethoxypropyl)amino)-2-oxo-1-phenylethyl ethyl oxalate: Synthesized following **GP1** using 2-(1-tosylpiperidin-4-yl)propan-2-ol (0.89 mg, 3.0 mmol, 1.0 equiv.). The product was obtained as a white solid in 84% yield (1.0 g, 2.5 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 – 7.59 (m, 2H), 7.33 – 7.30 (m, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.91 – 3.82 (m, 2H), 2.43 (s, 3H), 2.17 (td, *J* = 12.1, 2.5 Hz, 2H), 1.86 (tt, *J* = 12.2, 3.3 Hz, 1H), 1.76 – 1.69 (m, 2H), 1.56 – 1.47 (m, 2H), 1.46 (s, 6H), 1.34 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.5, 157.1, 143.7, 133.0, 129.7, 127.9, 88.6, 77.2, 63.0, 46.6, 44.1, 26.1, 23.0, 21.6, 14.0.

HRMS (ESI): (*m/z*) $[M+Na]^+$ calculated for $C_{19}H_{27}NNaO_6S$, 420.1451; found, 420.1455.

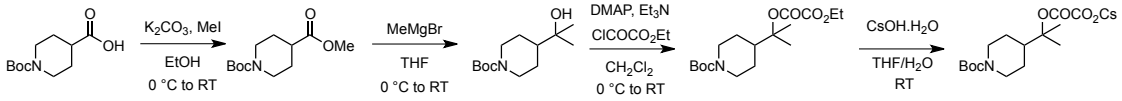
R_f (PE/EtOAc 1:1) = 0.49 [$KMnO_4$].

Cesium 2-((2-methyl-4-(tosyloxy)pentan-2-yl)oxy)-2-oxoacetate: Synthesized following **GP2** using 1-cyclohexyl-2-((3,3-diethoxypropyl)amino)-2-oxo-1-phenylethyl ethyl oxalate (0.95 mg, 2.4 mmol, 1.0 equiv.). The product was isolated as a white solid in 90% yield (1.1 g, 2.1 mmol).

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.61 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 3.70 (d, *J* = 11.6 Hz, 2H), 2.40 (s, 3H), 2.07 (td, *J* = 12.3, 2.4 Hz, 2H), 1.81 (tt, *J* = 12.2, 3.3 Hz, 1H), 1.67 (d, *J* = 12.5 Hz, 2H), 1.34 – 1.19 (m, 8H).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 167.3, 163.2, 143.4, 132.4, 129.7, 127.4, 81.8, 46.3, 43.1, 25.2, 23.2, 21.0.

HRMS (ESI): [*m/z*] calculated for $C_{17}H_{22}CsNO_6S$ ([M-Cs]$^-$): 368.1173; found, 368.1177.



***tert*-Butyl 4-methyl piperidine-1,4-dicarboxylate:** To a solution of 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (2.0 g, 8.7 mmol, 1.0 equiv.) in DMF (38 mL) was added potassium carbonate (1.2 g, 8.7 mmol, 1.0 equiv.) and iodomethane (0.65 mL, 10 mmol, 1.2 equiv.). The reaction mixture was stirred for three hours at room temperature. The reaction was poured into 10% aqueous potassium carbonate (100 mL). The aqueous solution was extracted with EtOAc (3 x 50). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified via column chromatography to afford the desired product as a yellow liquid in 93% yield (1.9 g, 8.1 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.99 (s, 2H), 3.67 (s, 3H), 2.82 (t, *J* = 12.4 Hz, 2H), 2.43 (tt, *J* = 11.0, 3.9 Hz, 1H), 1.88 – 1.81 (m, 1H), 1.70 – 1.55 (m, 2H), 1.44 (s, 9H)

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 174.9, 154.6, 79.5, 51.7, 41.0, 28.4, 27.9.

R_f (PE/EtOAc 8:2)= 0.23 [Ninhydrin])

***tert*-Butyl 4-(2-hydroxypropan-2-yl)piperidine-1-carboxylate:** The ester (1.1 g, 4.3 mmol, 1.0 equiv.) was dissolved in THF (22 mL, 0.2 M), followed by addition of MeMgBr (4.3 mL, 3 M in Et_2O, 13 mmol, 3.0 equiv.) dropwise at 0 °C under Ar. The reaction mixture was stirred 15 min at 0 °C and was then allowed to warm up to room temperature overnight. 1 M HCl (aq.) was added slowly to the reaction mixture. The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were neutralized with saturated $NaHCO_3$ (aq.), washed with brine, dried over Na_2SO_4, filtered and

concentrated under reduced pressure. The product was isolated as a colorless liquid in 99% yield (1.0 g, 4.3 mmol, 99%) without further purification.

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.29 (q, *J* = 7.1 Hz, 2H), 4.22 – 4.12 (m, 2H), 2.65 (d, *J* = 10.4 Hz, 2H), 2.04 (tt, *J* = 12.2, 3.3 Hz, 1H), 1.71 – 1.61 (m, 2H), 1.50 (s, 6H), 1.44 (s, 9H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.27 (qd, *J* = 12.7, 4.4 Hz, 2H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 158.6, 157.1, 154.8, 89.0, 79.6, 62.9, 45.1, 44.0, 28.6, 26.6, 23.1, 14.1.

HRMS (ESI): [m/z] calculated $[C_{13}H_{25}NNaO_3][M+Na]^+$ 266.1727, found 266.1734.

R_f (PE/EtOAc 6:4) = 0.16 [Ninhydrin]

2-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)propan-2-yl ethyl oxalate: Synthesized following **GP1** using *tert*-butyl-4-(2-hydroxypropan-2-yl)piperidine-1-carboxylate (0.53 g, 2.2 mmol, 1.0 equiv.). The product was isolated as a colorless liquid in 69% yield (0.51 g, 1.5 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.29 (q, *J* = 7.1 Hz, 2H), 4.22 – 4.12 (m, 2H), 2.65 (d, *J* = 10.4 Hz, 2H), 2.04 (tt, *J* = 12.2, 3.3 Hz, 1H), 1.71 – 1.61 (m, 2H), 1.50 (s, 6H), 1.44 (s, 9H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.27 (qd, *J* = 12.7, 4.4 Hz, 2H)

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 158.6, 157.1, 154.8, 89.0, 79.6, 62.9, 45.1, 44.0, 28.6, 26.6, 23.1, 14.1

HRMS (ESI): [m/z] calculated $[C_{17}H_{29}NNaO_6][M+Na]^+$ 366.1887, found 366.1889.

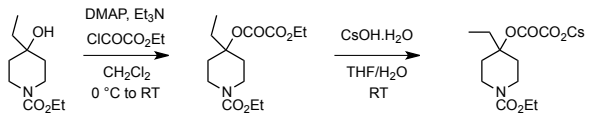
R_f (PE/EtOAc 4:1) = 0.21 [Ninhydrin]

Cesium 2-((2-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)propan-2-yl)oxy)-2-oxoacetate: Synthesized following **GP2** with 2-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)propan-2-yl ethyl oxalate (496 mg, 1.44 mmol, 1.0 equiv.). The product was isolated as a white solid in 89% yield (576 mg, 1.29 mmol).

^{1}H NMR (600 MHz, DMSO-d_6): δ 4.01 (d, *J* = 13.9 Hz, 2H), 2.63 – 2.59 (m, 2H), 2.03 (tt, *J* = 12.2, 3.2 Hz, 1H), 1.62 (dt, *J* = 13.4, 2.8 Hz, 2H), 1.39 (s, 9H), 1.32 (s, 6H), 1.09 (qd, *J* = 12.6, 4.3 Hz, 2H).

^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 167.3, 163.4, 153.7, 82.1, 78.4, 44.1, 40.1, 28.1, 26.0, 23.2

HRMS (ESI-*neg*): [m/z] calculated $C_{15}H_{24}NO_6$ ($[M-Cs]^-$): 314.1609, found 314.1613.

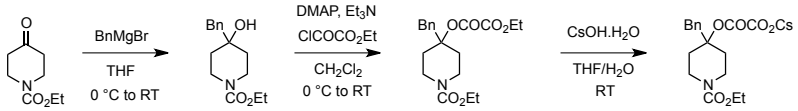


Cesium 2-((2-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)propan-2-yl)oxy)-2-oxoacetate: First, 1-(ethoxycarbonyl)-4-ethylpiperidin-4-yl ethyl oxalate was synthesized following **GP1** with (0.5 g, 2.5 mmol, 1.0 equiv.). The crude product was used in the next step without further purification.

Following **GP2** with 2-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)propan-2-yl ethyl oxalate (496 mg, 1.44 mmol, 1.0 equiv.), the desired cesium oxalate salt was isolated as a white solid in 40% yield (400 mg, 1.0 mmol).

^{1}H NMR (600 MHz, DMSO-d_6): δ 4.02 (q, *J* = 7.1 Hz, 2H), 3.73 (d, *J* = 13.2 Hz, 2H), 2.10 (d, *J* = 13.3 Hz, 2H), 1.86 (q, *J* = 7.5 Hz, 2H), 1.40 (ddd, *J* = 13.7, 11.8, 4.6 Hz, 2H), 1.17 (t, *J* = 7.1 Hz, 3H), 0.80 (t, *J* = 7.5 Hz, 3H).

^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 167.4, 163.1, 154.6, 79.5, 60.5, 40.1, 33.1, 29.4, 14.6, 6.9.



Ethyl 4-benzyl-4-hydroxypiperidine-1-carboxylate: BnMgCl (2 M, 3 mL, 15 mmol, 3 equiv.) was added dropwise to a 0 ºC solution of ethyl 4-oxopiperidine-1-carboxylate (0.75 mL, 5 mmol, 1 equiv.) in THF (15 mL, 0.5 M). The mixture was stirred at 0 ºC for 30 min and then warmed up to 50 ºC. After 20 h the reaction was quenched with a saturated solution of NH4Cl (aq.), the product was extracted with EtOAc (3 x 20 mL), and the combined organic layers dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel using a 1:1 mixture of EtOAc/Cyclohexane to afford the desired product as a white solid in 36% yield (0.48 g, 1.8 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (ddt, *J* = 8.0, 6.5, 1.2 Hz, 2H), 7.29 – 7.24 (m, 1H), 7.21 – 7.16 (m, 2H), 4.12 (qd, *J* = 7.2, 1.2 Hz, 2H), 3.91 (s, 2H), 3.14 (t, *J* = 12.7 Hz, 2H), 2.76 (s, 2H), 2.04 (s, 1H), 1.66 – 1.57 (m, 2H), 1.54 – 1.46 (m, 2H), 1.26 (td, *J* = 7.1, 1.9 Hz, 3H), 1.22 (d, *J* = 0.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7, 136.0, 130.7, 128.6, 127.0, 69.5, 61.4, 60.5, 49.4, 39.9, 36.8, 14.9, 14.3.

HRMS (ESI): [*m/z*] calculated for $C_{15}H_{21}NNaO_3$ [M+Na]$^+$], 286.1419, found 286.1418.

R_f (CH/EtOAc 1:1) = 0.41 [CAM]

4-benzyl-1-(ethoxycarbonyl)piperidin-4-yl ethyl oxalate: Synthesized following **GP1** using ethyl 4-benzyl-4-hydroxypiperidine-1-carboxylate (0.48 g, 1.8 mmol, 1.0 equiv.). The pure product was isolated as a colorless oil in 25% yield (0.19 g, 0.53 mmol).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (ddt, *J* = 8.0, 6.5, 1.2 Hz, 2H), 7.27 – 7.24 (m, 2H), 7.15 – 7.11 (m, 2H), 4.32 (q, *J* = 7.2 Hz, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.98 (s, 2H), 3.30 (s, 2H), 3.02 (s, 2H), 2.34 (dq, *J* = 14.6, 2.8 Hz, 2H), 1.43 (s, 2H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.31, 157.63, 155.58, 135.08, 130.58, 128.53, 127.22, 86.02, 63.11, 61.55, 43.34, 39.47, 33.53, 27.08, 14.82, 14.10.

HRMS (ESI): [*m/z*] calculated for $C_{19}H_{25}NNaO_6$ [M+Na]$^+$], 386.1580, found 386.1574.

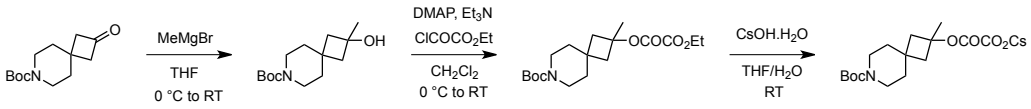
R_f (CH/EtOAc 4:1) = 0.24 [CAM]

Cesium 2-((4-benzyl-1-(ethoxycarbonyl)piperidin-4-yl)oxy)-2-oxoacetate: Synthesized following **GP2** with 4-benzyl-1-(ethoxycarbonyl)piperidin-4-yl ethyl oxalate (0.26 g, 0.7 mmol, 1.0 equiv.). The product was isolated as a white solid in 67 % yield (0.25 g, 0.53 mmol).

^{1}H NMR (600 MHz, DMSO-d_6) δ 7.29 – 7.16 (m, 5H), 4.07 – 3.93 (m, 2H), 3.81 – 3.71 (m, 2H), 3.20 (s, 2H), 2.96 (s, 2H), 2.05 (d, *J* = 15.1 Hz, 2H), 1.46 (ddd, *J* = 13.7, 12.0, 4.6 Hz, 2H), 1.15 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (151 MHz, DMSO) δ 167.6, 162.9, 154.6, 136.2, 130.5, 127.9, 127.5, 126.2, 79.3, 60.5, 42.1, 33.3, 14.6.

HRMS (ESI): [*m/z*] calculated for $C_{17}H_{21}CsNO_6$ [M+], 468.0423, found 468.0418.



***tert*-Butyl 2-hydroxy-2-methyl-7-azaspiro[3.5]nonane-7-carboxylate:** MeMgBr (3 M in Et_2O, 2.0 mL, 6.0 mmol, 3.0 equiv.) was added dropwise to a 0 °C solution of tert-butyl-2-oxo-7-azaspiro[3.5]nonan-7 carboxylate (0.48 g, 2.0 mmol, 1.0 equiv.) in THF (10 mL, 0.2 M). The mixture was stirred at 0 °C for 1 h and then warmed up to room temperature. After 2 h the reaction was quenched with a saturated solution of NH_4Cl (aq.), the product extracted with EtOAc (3 x 25 mL), and the combined organic layers dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by column chromatography to afford the desired product as a white solid in 80% yield (0.41 mg, 1.6 mmol).

^{1}H NMR (600 MHz, CDCl3): 3.44 – 3.11 (m, 1H), 1.93 (q, J = 12.6 Hz, 4H), 1.71 (s, 1H), 1.61 – 1.59 (m, 2H), 1.51 – 1.46 (m, 2H), 1.44 (s, 9H), 1.38 (s, 3H).

^{13}C{^{1}H} NMR (151 MHz, CDCl3): 155.1, 79.4, 69.0, 47.0, 39.1, 37.4, 31.1, 28.6, 28.4.

LCMS (ESI): [m/z] calculated $C_{14}H_{26}NO_3$ ([M+H$^+$]): 256.1913, found 256.2668

R_f (PE/EtOAc 7:3) = 0.27 [CAM]

7-(*tert*-butoxycarbonyl)-2-methyl-7-azaspiro[3.5]nonan-2-yl ethyl oxalate: Synthesized following **GP1** with *tert*-Butyl-2-hydroxy-2-methyl-7-azaspiro[3.5]nonan-7 carboxylate (0.39 g, 1.5 mmol, 1.0 equiv.). The product was obtained as a colorless liquid in 99% yield (0.54 g, 1.5 mmol).

^{1}H-NMR (600 MHz, $CDCl_3$): δ 4.33 (q, *J* = 7.1 Hz, 2H), 3.30 (ddd, *J* = 10.8, 5.9, 3.2 Hz, 4H), 2.29 (d, *J* = 14.4 Hz, 2H), 2.18 – 2.12 (m, 2H), 1.63 (s, 3H), 1.55 (ddd, *J* = 18.9, 6.6, 4.0 Hz, 4H), 1.43 (s, 9H), 1.37 (t, *J* = 7.2 Hz, 3H)

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 158.3, 156.8, 155.0, 80.4, 79.5, 63.1, 60.5, 44.9, 39.0, 37.0, 30.3, 28.6, 26.3, 21.1, 14.3, 14.1.

HRMS (ESI): [m/z] calculated $C_{18}H_{29}NNaO_6$ ([M+Na]$^+$) 378.1887, found 378.1885.

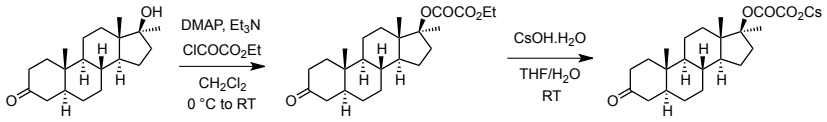
R_f (PE/EtOAc 8:2) = 0.4 [CAM]

Cesium 2-((7-(*tert*-butoxycarbonyl)-2-methyl-7-azaspiro[3.5]nonan-2-yl)oxy)-2-oxoacetate: Synthesized following **GP2** with 7-(*tert*-butoxycarbonyl)-2-methyl-7-azaspiro[3.5]nonan-2-yl ethyl oxalate (0.53 mg, 1.5 mmol, 1.0 equiv.). The product was obtained as a colorless solid in 87% yield (0.59 mg, 1.3 mmol).

^{1}H-NMR (600 MHz, DMSO-*d_6*): □ 3.24 – 3.03 (m, 4H), 2.06 (d, *J* = 13.8 Hz, 2H), 1.99 (d, *J* = 13.7 Hz, 2H), 1.47 (s, 3H), 1.47 – 1.44 (m, 3H), 1.38 (s, 9H);

^{13}C{^{1}H} NMR (151 MHz, DMSO-*d_6*): □ 166.6, 163.0, 153.9, 78.4, 74.5, 44.5, 29.9, 28.1, 26.5;

HRMS (ESI-*neg*): [m/z] calculated $C_{16}H_{24}NO_6$ ([M-Cs]$^-$) 326.1609, found 326.1608.



Ethyl ((5S,8R,9S,10S,13S,14S)-10,13,17-trimethyl-3-oxohexadecahydro-1H-cyclopenta[a]phenanthren-17-yl) oxalate: Synthesized following **GP1** using 17a-mehtylandostran-17b-ol-3-one (0.5 g, 1.6 mmol, 1.0 equiv.). The pure product was isolated as a white solid in 77% yield (0.5 g, 1.24 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (q, *J* = 7.1 Hz, 2H), 2.45 – 2.29 (m, 2H), 2.29 – 2.22 (m, 1H), 2.20 – 2.13 (m, 4H), 2.12 – 1.99 (m, 2H), 1.78 – 1.60 (m, 4H), 1.53 (dd, *J* = 4.2, 1.7 Hz, 1H), 1.50 (s, 4H), 1.45 – 1.38 (m, 3H), 1.38 – 1.33 (m, 5H), 1.33 – 1.25 (m, 2H), 1.23 – 1.12 (m, 1H), 1.06 – 1.00 (m, 3H), 0.92 (s, 4H), 0.76 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 211.9, 158.8, 157.5, 95.0, 62.8, 53.8, 49.3, 47.9, 46.9, 44.8, 38.7, 38.3, 36.4, 36.1, 35.9, 32.1, 31.6, 31.0, 28.9, 23.7, 21.3, 21.1, 14.5, 14.1, 11.6.

HRMS (APCI): [*m/z*] calculated for $C_{24}H_{37}O_5$ [M+], 405.2641, found 405.2721.

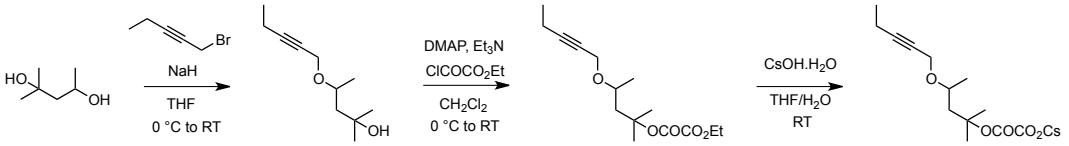
R_f (CH/EtOAc 3:2) = 0.55 [CAM]

Cesium 2-oxo-2-(((5S,8R,9S,10S,13S,14S)-10,13,17-trimethyl-3-oxohexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)oxy)acetate: Synthesized following **GP2** using ethyl ((5S,8R,9S,10S,13S,14S)-10,13,17-trimethyl-3-oxohexadecahydro-1H-cyclopenta[a]phenanthren-17-yl) oxalate (0.5 g, 1.24 mmol, 1.0 equiv.). The product was isolated as a white solid in 93% yield (0.58 g, 1.16 mmol).

^{1}H NMR (600 MHz, DMSO-*d_6*) δ 2.45 – 2.37 (m, 1H), 2.30 (t, *J* = 14.4 Hz, 1H), 2.09 (ddt, *J* = 15.2, 4.5, 2.1 Hz, 1H), 1.99 – 1.91 (m, 3H), 1.89 (ddd, *J* = 14.8, 3.8, 2.2 Hz, 1H), 1.67 – 1.50 (m, 5H), 1.49 – 1.35

(m, 3H), 1.33 (s, 3H), 1.30 – 1.26 (m, 3H), 1.25 – 1.19 (m, 2H), 1.15 (ddd, *J* = 12.3, 10.3, 7.0 Hz, 1H), 0.99 (s, 3H), 0.89 (tdd, *J* = 12.1, 9.3, 3.5 Hz, 1H), 0.79 (s, 3H), 0.76 – 0.68 (m, 1H).

^{13}C NMR (101 MHz, DMSO) δ 210.4, 167.3, 163.6, 88.6, 52.9, 48.6, 46.1, 46.0, 44.1, 37.9, 37.6, 36.5, 35.4, 35.3, 31.7, 31.0, 28.3, 23.2, 21.2, 20.6, 14.0, 11.1.



2-methyl-4-(pent-2-yn-1-yloxy)pentan-2-ol: 2-methylpentane-2,4-diol (1.92 mL, 15.0 mmol, 3.0 equiv.) was added dropwise to a suspension of sodium hydride (400 g, 10.0 mmol, 2.0 equiv.) in THF (10.0 mL, 0.5 M) at 0 °C . The reaction mixture stirred for 30 min and then 1-bromopent-2-yne (511 µL, 5.0 mmol, 1.0 equiv.) was added and the reaction mixture stirred for 4 h at room temperature. The reaction was quenched with water, the product extracted with EtOAc (3 x 25 mL), and the combined organic layers dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by column chromatography (PE:EtOAc 4:1) to afford the desired product as a colorless oil in 68% yield (630 mg, 3.4 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.23 (dt, *J* = 15.5, 2.2 Hz, 1H), 4.15 – 4.03 (m, 2H), 3.35 (bs, 1H), 2.21 (qt, *J* = 7.5, 2.2 Hz, 2H), 1.79 (ddd, *J* = 14.8, 10.7, 0.7 Hz, 1H), 1.50 (dd, *J* = 14.7, 2.6 Hz, 1H), 1.30 (s, 3H), 1.20 (s, 3H), 1.15 (d, *J* = 6.0 Hz, 3H), 1.12 (t, *J* = 7.5 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 88.7, 75.3, 72.1, 70.4, 55.5, 49.0, 31.1, 28.4, 19.5, 13.8, 12.5.

GCMS (FI): [m/z] calculated $C_{11}H_{19}O_2$ ([M-H$^+$]): 183.13850; found 183.13867

R_f (PE/EtOAc 4:1) = 0.29 [$KMnO_4$]

Ethyl (2-methyl-4-(pent-2-yn-1-yloxy)pentan-2-yl) oxalate: Synthesized following **GP1** with 2-methyl-4-(pent-2-yn-1-yloxy)pentan-2-ol (0.60 mg, 3.2 mmol, 1.0 equiv.). The product was isolated as a colorless oil in 51% yield (0.69 g, 2.4 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.30 (q, *J* = 7.1 Hz, 2H), 4.21 – 3.99 (m, 2H), 3.84 (dqd, *J* = 8.0, 6.1, 3.3 Hz, 1H), 2.20 (qt, *J* = 7.5, 2.2 Hz, 2H), 2.10 (dd, *J* = 14.9, 8.0 Hz, 1H), 1.96 (dd, *J* = 14.8, 3.3 Hz, 1H), 1.61 (s, 3H), 1.591 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.18 (d, *J* = 6.2 Hz, 3H), 1.12 (t, *J* = 7.5 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 158.7, 157.2, 87.9, 86.6, 70.7, 62.8, 55.8, 47.1, 27.2, 25.8, 20.4, 14.1, 13.9, 12.5.

GCMS (FI): [m/z] calculated $C_{15}H_{24}O_5$ ([M]): 284,16237; found 284.16237

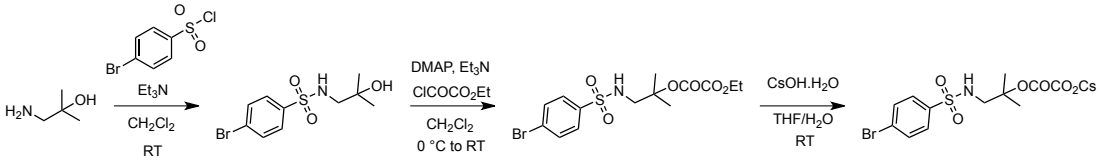
R_f (PE/EtOAc 4:1) = 0.5 [$KMnO_4$]

Cesium 2-((2-methyl-4-(pent-2-yn-1-yloxy)pentan-2-yl)oxy)-2-oxoacetate: Synthesized following **GP2** with ethyl (2-methyl-4-(pent-2-yn-1-yloxy)pentan-2-yl) oxalate (0.60 g, 2.1 mmol, 1.0 equiv.). The product was isolated as a white solid in 92% yield (0.75 g, 1.9 mmol).

^{1}H NMR (400 MHz, DMSO-d_6): δ 4.13 – 3.99 (m, 2H), 3.78 – 3.60 (m, 1H), 2.20 (qt, *J* = 7.5, 2.2 Hz, 2H), 1.92 (dd, *J* = 14.4, 4.0 Hz, 1H), 1.82 (dd, *J* = 14.4, 7.2 Hz, 1H), 1.42 (s, 3H), 1.40 (s, 3H), 1.09 (d, *J* = 6.1 Hz, 3H), 1.06 (t, *J* = 7.5 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 167.4, 163.3, 87.2, 79.8, 76.6, 70.5, 55.0, 46.8, 27.2, 25.9, 20.5, 13.6, 11.6.

HRMS (ESI-*neg*): [m/z] calculated $C_{13}H_{19}O_5$ ([M-Cs]$^-$): 255,1232, found 255.1238.



1-(4-bromophenylsulfonamido)-2-methylpropan-2-yl ethyl oxalate: In a round-bottomed flask under N_2 atmosphere, 4-bromobenzenesulfonyl chloride (1.3 g, 5.0 mmol, 1.0 equiv.) was slowly added to a mixture of triethylamine (0.8 mL, 6.0 mmol, 1.2 equiv.) and 1-amino-2-methylpropan-2-ol (0.4 g, 5.0 mmol, 1.0 equiv.) in CH_2Cl_2 (10.0 mL, 0.5 M). The reaction was stirred at room temperature overnight, and then quenched with a saturated solution of NH_4Cl (aq.). Upon extraction with CH_2Cl_2 (3 x 50 mL) and the combined organic layers dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude product, which was used in the next step without further purification.

Synthesized following **GP1** using 4-bromo-N-(2-hydroxy-2-methylpropyl)benzenesulfonamide (5 mmol, 1.0 equiv.). The pure product was isolated as yellowish oil in 32% yield (0.9 g, 2.2 mmol).

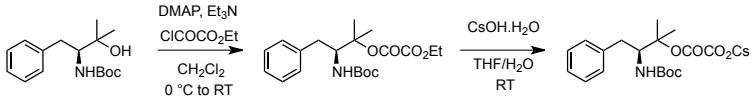
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 – 7.70 (m, 2H), 7.68 – 7.63 (m, 2H), 5.20 (t, *J* = 6.7 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 3.20 (d, *J* = 6.8 Hz, 2H), 1.56 (s, 6H), 1.36 (t, *J* = 7.2 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 157.9, 156.8, 139.3, 132.6, 128.6, 127.9, 85.3, 63.4, 51.9, 23.5, 14.0.

Cesium 2-((1-(4-bromophenylsulfonamido)-2-methylpropan-2-yl)oxy)-2-oxoacetate: Synthesized following **GP2** using ethyl 1-(4-bromophenylsulfonamido)-2-methylpropan-2-yl ethyl oxalate (0.8 g, 1.9 mmol, 1.0 equiv.).The product was isolated as a white solid in 88% yield (1.0 g, 1.9 mmol).

^{1}H NMR (400 MHz, D_2O): δ 7.81 (m, 4H), 3.27 (s, 2H), 1.53 (s, 6H).

^{13}C{^{1}H} NMR (101 MHz, D_2O): δ 166.2, 165.3, 139.6, 134.5, 130.1, 129.5, 85.4, 52.4, 24.5.



(*S*)-3-((*tert*-butoxycarbonyl)amino)-2-methyl-4-phenylbutan-2-yl ethyl oxalate: Synthesized following **GP1** using (*S*)-*tert*-butyl (3-hydroxy-3-methyl-1-phenylbutan-2-yl)carbamate (7.9 mmol, 1.0 equiv.). The pure product was isolated as white solid in 62% yield (1.8 g, 4.7 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, 2H), 7.20 (dd, *J* = 7.6, 2.3 Hz, 3H), 4.73 (d, *J* = 10.3 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 4.05 (td, *J* = 10.7, 3.7 Hz, 1H), 3.15 (dd, *J* = 14.3, 3.6 Hz, 1H), 2.56 (dd, *J* = 14.2, 11.1 Hz, 1H), 1.68 (s, 3H), 1.63 (s, 3H), 1.39 (t, *J* = 7.2 Hz, 3H), 1.26 (s, 9H).

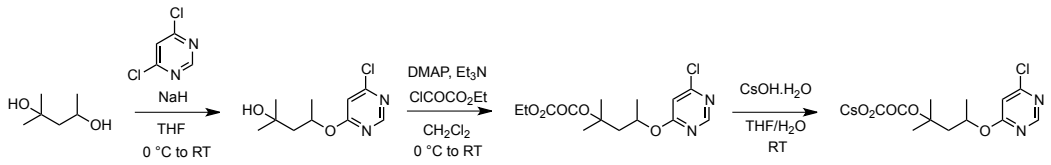
R_f (1:1 Cyclohexane/EtOAc) = 0.54 [*p*-Anisalaldehyde]

Cesium (*S*)-2-((3-((*tert*-butoxycarbonyl)amino)-2-methyl-4-phenylbutan-2-yl)oxy)-2-oxoacetate: Synthesized following **GP2** using (*S*)-3-((*tert*-butoxycarbonyl)amino)-2-methyl-4-phenylbutan-2-yl ethyl oxalate (4.7 mmol, 1.0 equiv.). The pure product was isolated as white solid in 98% yield (2.2 g, 4.6 mmol).

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.33 – 7.15 (m, 5H), 6.68 (d, *J* = 9.8 Hz, 1H), 4.18 (ddd, *J* = 11.9, 9.8, 2.3 Hz, 1H), 2.96 – 2.90 (m, 1H), 2.49 – 2.43 (m, 1H), 1.43 (s, 3H), 1.31 (s, 3H), 1.23 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 167.2, 163.2, 155.6, 139.7, 129.1, 128.9, 127.7, 127.7, 125.5, 82.3, 77.4, 57.3, 34.0, 28.1, 23.8, 21.6.

HRMS (ESI): [m/z] calculated for [$C_{18}H_{25}CsNO_6$] ([M]): 484.0731; Found: 484.0732.



4-((6-chloropyrimidin-4-yl)oxy)-2-methylpentan-2-ol: 2-methylpentane-2,4-diol (637 µL, 5.0 mmol, 1.0 equiv.) was dissolved in THF (15 mL, 0.15 M) and sodium hydride (0.44 g, 11 mmol, 2.2 equiv.) was added slowly at 0 °C. The reaction mixture stirred for 20 min at room temperature, then 4,6-dichloropyrimidine (0.75 g, 5.00 mmol, 1.0 equiv.) was added and the reaction mixture stirred for 4 h at room temperature. The reaction was quenched with water, the aqueous phase was extracted with EtOAc (3 x 10 mL), the organic phase was washed with brine, dried with Na_2SO_4 and evaporated in vacuo. The residue was purified by chromatography over silica to afford the desired product as a pale yellow oil in 20% yield (0.24 g, 1.0 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (d, *J* = 0.9 Hz, 1H), 6.72 (d, *J* = 0.9 Hz, 1H), 5.56 (ddd, *J* = 8.1, 6.2, 3.6 Hz, 1H), 2.21 (bs, 1H), 2.04 (dd, *J* = 15.0, 8.1 Hz, 1H), 1.75 (dd, *J* = 14.9, 3.6 Hz, 1H), 1.38 (d, *J* = 6.2 Hz, 3H), 1.25 (s, 3H), 1.22 (s, 3H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 169.8, 161.2, 158.3, 108.5, 72.1, 70.2, 49.2, 30.1, 30.1, 21.6.

HRMS (ESI): [*m/z*] calculated for $C_{10}H_{15}ClN_2NaO_2$ ([M+Na]$^+$), 253.0714; found, 253.0720.

4-((6-chloropyrimidin-4-yl)oxy)-2-methylpentan-2-yl ethyl oxalate: Synthesized following **GP1** using 4-((6-chloropyrimidin-4-yl)oxy)-2-methylpentan-2-ol (0.24 g, 1.0 mmol, 1.0 equiv.). The pure product was isolated as a colorless oil in 49% yield (0.17 g, 0.5 mmol).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 (d, *J* = 0.9 Hz, 1H), 6.68 (d, *J* = 0.9 Hz, 1H), 5.60 (dqd, *J* = 9.2, 6.2, 3.0 Hz, 1H), 4.28 (qd, *J* = 7.2, 1.1 Hz, 2H), 2.51 (dd, *J* = 15.3, 8.8 Hz, 1H), 2.10 – 2.01 (m, 1H), 1.58 (s, 3H), 1.56 (s, 3H), 1.36 (d, *J* = 6.2 Hz, 4H), 1.34 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.6, 160.9, 158.4, 158.3, 157.1, 108.4, 85.3, 70.7, 63.0, 45.6, 26.9, 26.2, 21.2, 14.1.

HRMS (ESI): [*m/z*] calculated for $C_{14}H_{19}ClN_2NaO_5$ [M+Na]$^+$], 353.0880, found 353.0886.

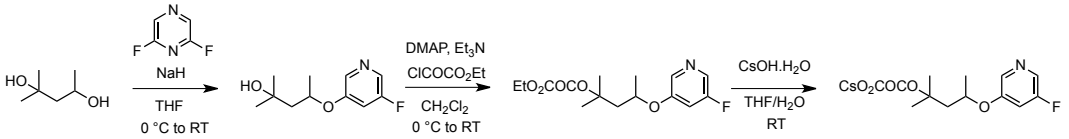
R_f (CH/EtOAc 1:1) = 0.56 [CAM]

Cesium 2-((4-((6-chloropyrimidin-4-yl)oxy)-2-methylpentan-2-yl)oxy)-2-oxoacetate: Synthesized following GP2 using 4-((6-chloropyrimidin-4-yl)oxy)-2-methylpentan-2-yl ethyl oxalate (0.17 g, 0.5 mmol, 1.0 equiv.). The product was isolated as a white solid in 76% yield (0.16 g, 0.4 mmol).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, *J* = 0.9 Hz, 1H), 7.16 (d, *J* = 0.9 Hz, 1H), 5.43 (dddd, *J* = 8.1, 6.1, 4.1, 2.3 Hz, 1H), 2.25 (dd, *J* = 14.9, 8.2 Hz, 1H), 2.12 (dd, *J* = 14.9, 3.7 Hz, 1H), 1.38 (s, 3H), 1.36 (s, 3H), 1.30 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (101 MHz, DMSO) δ 169.30, 167.36, 163.08, 159.80, 158.35, 108.15, 78.93, 70.93, 45.09, 26.85, 26.13, 20.71.

HRMS (APCI): [*m/z*] calculated for $C_{12}H_{14}ClN_2O_5$ ([M-Cs]-), 301,7030, found 303.0764.



4-((6-fluoropyridin-2-yl)oxy)-2-methylpentan-2-ol: 2-methylpentane-2,4-diol (140 µL, 1.0 mmol, 1.1 equiv.) was dissolved in DMSO (1 mL, abs.) and sodium hydride (3.1 g, 16.5 mmol, 1.1 equiv.) was added slowly at room temperature. The reaction mixture stirred for 20 min at room temperature, then 2,6-difluoropyridine (90.8 µL, 1.00 mmol, 1.0 equiv.) was added and the reaction mixture stirred for 30 min at room temperature. The reaction was quenched with water, the aqueous phase was extracted with EtOAc (3 x 10 mL), the organic phase was washed with brine, dried with Na_2SO_4 and evaporated in vacuo. The residue was purified by chromatography over silica to afford the desired product as a pale yellow oil in 87% yield (0.19 g, 0.87 mmol).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (q, *J* = 8.1 Hz, 1H), 6.56 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.46 (dd, *J* = 7.8, 2.4 Hz, 1H), 5.42 – 5.35 (m, 1H), 2.66 (s, 3H), 2.04 (dd, *J* = 14.9, 9.0 Hz, 1H), 1.72 (dd, *J* = 14.9, 3.3 Hz, 1H), 1.35 (d, *J* = 6.1 Hz, 3H), 1.25 (s, 3H), 1.24 (s, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 162.7 (d, J_{C-F} = 147.0 Hz), 161.9 (d, J_{C-F} = 107.1 Hz), 142.9 (d, J_{C-F} = 8.1 Hz), 108.0 (d, J_{C-F} = 5.2 Hz) 100.3 (d, J_{C-F} = 35.5 Hz) 70.8, 70.4, 49.2, 30.5, 29.5, 21.6.

HRMS (ESI): [*m/z*] calculated for $C_{11}H_{16}FNNaO_2$ ([M+Na]$^+$), 236.1057; found, 236.1061.

R_f (PE/EtOAc, 1:1) = 0.51 [UV] [$KMnO_4$].

Ethyl (4-((6-fluoropyridin-2-yl)oxy)-2-methylpentan-2-yl) oxalate: According to **GP1** using 4-((6-fluoropyridin-2-yl)oxy)-2-methylpentan-2-ol (0.85 g, 4.0 mmol, 1.0 equiv.). The product was isolated as a pale yellow liquid in 90% yield (1.1 g, 3.6 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.56 (m, 1H), 6.50 (ddd, *J* = 8.0, 1.7, 0.6 Hz, 1H), 6.42 (ddd, *J* = 7.8, 2.6, 0.6 Hz, 1H), 5.44 – 5.34 (m, 1H), 4.27 (qd, *J* = 7.1, 1.5 Hz, 2H), 2.45 (dd, *J* = 15.1, 8.7 Hz, 1H), 2.08 (dd, *J* = 15.1, 3.2 Hz, 1H), 1.59 (s, 3H), 1.57 (s, 3H), 1.35 (d, *J* = 2.4 Hz, 3H), 1.33 (d, *J* = 3.4 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 162.9 (d, J_{C-F} = 137.3 Hz), 161.7 (d, J_{C-F} = 116.2 Hz), 158.6, 157.2, 142.7 (d, J_{C-F} = 8.0 Hz), 107.8 (d, J_{C-F} = 5.1 Hz), 99.9 (d, J_{C-F} = 35.8 Hz), 85.9, 69.1, 62.9, 45.9, 27.0, 26.1, 21.3, 14.0.

HRMS (ESI): [*m/z*] calculated for $C_{15}H_{20}FNO_5$ ([M+Na]$^+$), 336.1218; found, 336.1219.

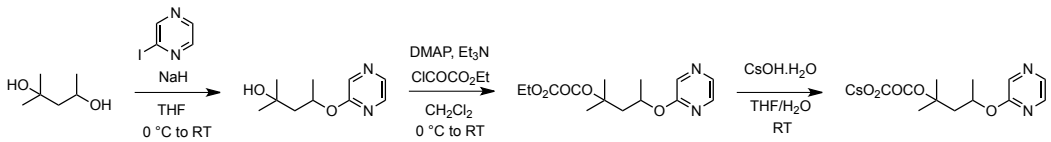
R_f (PE/EtOAc, 8:2) = 0.34 [UV] [$KMnO_4$].

Cesium 2-((4-((6-fluoropyridin-2-yl)oxy)-2-methylpentan-2-yl)oxy)-2-oxoacetate: According to **GP2** using ethyl (4-((6-fluoropyridin-2-yl)oxy)-2-methylpentan-2-yl) oxalate (0.63 g, 2.0 mmol, 1.0 equiv.). The product was isolated as a white solid in 85% yield (0.71 g, 1.7 mmol).

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.90 – 7.77 (m, 1H), 6.71 (ddd, *J* = 8.0, 1.8, 0.6 Hz, 1H), 6.65 (ddd, *J* = 7.8, 2.4, 0.6 Hz, 1H), 5.21 – 5.07 (m, 1H), 2.17 – 2.08 (m, 2H), 1.41 (s, 3H), 1.35 (s, 3H), 1.27 (d, *J* = 6.1 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, DMSO- d_6): δ 167.3, 162.7, 162.47 (d, *J* = 140.5 Hz), 161.0 (d, *J* = 134.6 Hz), 143.9 (d, *J* = 8.3 Hz), 107.9 (d, *J* = 4.8 Hz), 99.8 (d, *J* = 35.3 Hz), 79.3, 69.4, 45.7, 26.9, 25.9, 20.9.

HRMS (ESI-neg): [*m/z*] calculated for $C_{13}H_{15}CsFNO_5$ ([M-Cs]$^-$), 284.0940; found, 284.0952.



Ethyl (2-methyl-4-(pyrazin-2-yloxy)pentan-2-yl) oxalate: 2-methylpentane-2,4-diol (1.4 mL, 11 mmol, 1.1 equiv.) was dissolved in THF (1.0 mL) and sodium hydride (3.1 g, 16 mmol, 1.1 equiv., 60%) was added slowly at 0 °C. The reaction mixture was stirred for 1 h at room temperature, then 2-iodopyrazine (987 µL, 10 mmol, 1.0 equiv.) was added dropwise and the reaction mixture stirred for 2 h at room temperature followed by stirring at 50 °C for 12 h. After being cooled to room temperature, the reaction mixture was poured on ice and water and extracted with EtOAc (3 x 10 mL). The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification by column chromatography over silica gel gave 2-methyl-4-(pyrazin-2-yloxy)pentan-2-ol in 70% purity. This was used in the next step without further purification.

According to **GP1** using 2-methyl-4-(pyrazin-2-yloxy)pentan-2-ol (1.6 g, 5.6 mmol, 70%, 1.0 equiv.). The product was obtained as a colorless oil in 25% yield (0.73 g, 2.5 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 1.4 Hz, 1H), 8.08 (d, J = 2.8 Hz, 1H), 8.05 (dd, J = 2.8, 1.4 Hz, 1H), 5.55 – 5.42 (m, 1H), 4.27 (q, J = 7.1 Hz, 2H), 2.50 (dd, J = 15.2, 8.7 Hz, 1H), 2.10 (dd, J = 15.2, 3.1 Hz, 1H), 1.59 (s, 3H), 1.58 (s, 3H), 1.36 (d, J = 6.2 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 159.6, 158.5, 157.2, 140.7, 136.6, 136.5, 85.7, 69.0, 62.9, 45.9, 27.0, 26.1, 21.1, 14.1.

HRMS (ESI): [m/z] calculated for $C_{14}H_{20}N_2NaO_5$ ([M+Na]$^+$), 319.1265; found, 319.1264.

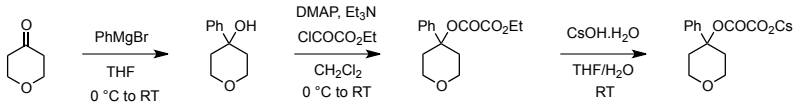
R_f (PE/EtOAc 8:2) = 0.28 [UV] [KMnO4].

Cesium 2-((2-methyl-4-(pyrazin-2-yloxy)pentan-2-yl)oxy)-2-oxoacetate: Synthesized according to **GP2** using ethyl (2-methyl-4-(pyrazin-2-yloxy)pentan-2-yl)-oxalate (0.59 mg, 2.0 mmol, 1.0 equiv.). The product was isolated as white solid in 86% yield (0.69 mg, 1.7 mmol).

^{1}H NMR (400 MHz, DMSO-d^6): δ 8.24 (d, J = 1.4 Hz, 1H), 8.19 (dd, J = 2.8, 1.4 Hz, 1H), 8.15 (d, J = 2.8 Hz, 1H), 5.40 – 5.22 (m, 1H), 2.26 – 2.12 (m, 2H), 1.40 (s, 3H), 1.36 (s, 3H), 1.29 (d, J = 6.2 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d^6): δ 167.3, 163.2, 159.1, 140.7, 136.4, 135.9, 79.4, 69.1, 45.5, 26.9, 26.0, 20.8.

HRMS (ESI): (m/z) calculated for $C_{12}H_{15}CsN_2O_5$ ([M-Cs]$^-$): 267.0986; found, 267.1013.



4-phenyltetrahydro-2H-pyran-4-ol: PhMgBr (6.0 mL, 18.0 mmol, 1.8 equiv.) was added dropwise to a 0 °C solution of dihydro-2H-pyran-4(3H)-one (1.0 mL, 10 mmol, 1.0 equiv.) in THF (25 mL, 0.4 M). The mixture was stirred at 0 °C for 1 h and then warmed up to room temperature. After 2 h, the reaction was quenched with a saturated solution of NH_4Cl (aq.), the product extracted with EtOAc (3 x 50 mL), and the combined organic layers dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by column chromatography using a 4:1 mixture of petrol ether/EtOAc to afford the desired product as a white solid in 73% yield (1.3 g, 7.3 mmol). The characterization matches the reported literature.[256]

^{1}H NMR (400 MHz, CDCl3): δ 7.53 – 7.48 (m, 2H), 7.42 – 7.35 (m, 2H), 7.32 – 7.26 (m, 1H), 3.95 (td, *J* = 11.7, 2.2 Hz, 2H), 3.90 – 3.79 (m, 2H), 2.19 (ddd, *J* = 13.7, 12.0, 5.3 Hz, 2H), 1.75 – 1.67 (m, 2H), 1.65 (bs, 1H).

^{13}C{^{1}H} NMR (600 MHz, CDCl3): δ 148.0, 128.5, 127.3, 124.4, 70.7, 63.9, 38.8.

R_f (PE/EtOAc 3:1) = 0.36 [CAM]

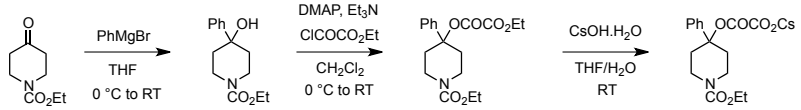
Cesium 2-oxo-2-((4-phenyltetrahydro-2*H*-pyran-4-yl)oxy)acetate: Synthesized following **GP1** using 4-phenyltetrahydro-2*H*-pyran-4-ol (1.0 g, 5.6 mmol, 1.0 equiv.), ethyl oxalyl chloride (0.93 mL, 8.5 mmol, 1.2 equiv.), Et_3N (1.2 mL, 8.5 mmol, 1.2 equiv.) and DMAP (17 mg, 0.14 mmol, 2.5 mol%). The pure product was isolated as colorless oil in 54% yield (0.85 g, 3.0 mmol) after column chromatography using a 10:1 mixture of PE/EtOAc.

Synthesized following **GP2** using ethyl (4-phenyltetrahydro-2H-pyran-4-yl) oxalate (0.85 g, 3.0 mmol, 1.0 equiv.). The product was isolated as a white solid in 86% yield (0.98 g, 2.6 mmol).

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.39 – 7.36 (m, 2H), 7.35 – 7.28 (m, 2H), 7.27 – 7.19 (m, 1H), 3.82 – 3.63 (m, 4H), 2.28 – 2.18 (m, 2H), 2.00 (ddd, *J* = 13.7, 11.2, 5.5 Hz, 2H).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 166.2, 162.8, 144.9, 128.0, 126.6, 124.3, 77.9, 62.6, 36.2.

HRMS (ESI-neg): [m/z] calculated for $C_{13}H_{13}O_5$ ([M-Cs]$^-$): 249.0763; Found: 249.0768.



Ethyl 4-hydroxy-4-phenylpiperidine-1-carboxylate: PhMgBr (6.0 mL, 18 mmol, 1.8 equiv.) was added dropwise to a 0 °C solution of ethyl 4-oxopiperidine-1-carboxylate (2.2 mL, 15 mmol, 1.0 equiv.) in THF (50 mL, 0.3 M). The mixture was stirred at 0 °C for 1 h and then warmed up to room temperature. After 2 h the reaction was quenched with a saturated solution of NH_4Cl (aq.), the product extracted with EtOAc (3 x 50 mL), and the combined organic layers dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by column chromatography to afford the desired product as a white solid in 43% yield (1.6 g, 6.4 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.46 (m, 2H), 7.41 – 7.35 (m, 2H), 7.32 – 7.26 (m, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.09 (d, *J* = 13.6 Hz, 2H), 3.30 (td, *J* = 13.0, 2.7 Hz, 2H), 2.02 (td, *J* = 13.3, 4.9 Hz, 2H), 1.79 – 1.71 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 155.7, 148.0, 128.7, 127.5, 124.5, 71.7, 61.4, 40.1, 38.2, 14.9.

HRMS (ESI): [m/z] calculated for $C_{18}H_{23}NNaO_6$ ([M+Na]$^+$): 372,1423; Found: 372.1429

R_f (2:1 PE/EtOAc) = 0.36 [CAM]

1-(ethoxycarbonyl)-4-phenylpiperidin-4-yl ethyl oxalate: Synthesized following **GP1** using ethyl 4-hydroxy-4-phenylpiperidine-1-carboxylate (1.5 g, 5.9 mmol, 1.0 equiv.). The pure product was isolated as colorless oil in 38% yield (0.75 g, 2.2 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 – 7.37 (m, 4H), 7.35 – 7.30 (m, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.97 – 3.91 (m, 2H), 3.87 (td, *J* = 11.6, 2.1 Hz, 2H), 2.57 (dq, *J* = 14.7, 2.6 Hz, 2H), 2.24 (ddd, *J* = 14.2, 11.4, 5.2 Hz, 2H), 1.39 (t, *J* = 7.2 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 158.1, 156.5, 155.7, 142.0, 128.9, 128.4, 124.8, 84.5, 63.2, 61.6, 39.8, 35.2, 27.1, 14.9, 14.1.

HRMS (ESI): [m/z] calculated for $C_{18}H_{23}NNaO_6$ ([M+Na]$^+$): 372.1419; Found: 372.1418.

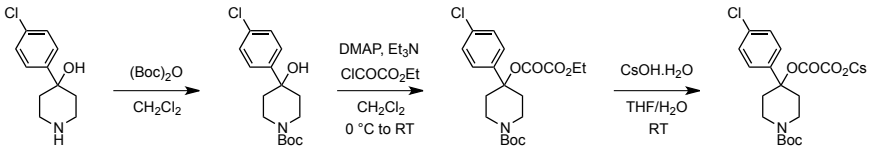
R_f (4:1 PE/EtOAc) = 0.3

Cesium 2-((1-(ethoxycarbonyl)-4-phenylpiperidin-4-yl)oxy)-2-oxoacetate: Synthesized following **GP2** using ethyl (4-phenyltetrahydro-2H-pyran-4-yl) oxalate (0.52 g, 1.5 mmol, 1.0 equiv.). The product was isolated as a white solid in 92% yield (0.62 g, 0.47 mmol).

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.39 – 7.34 (m, 2H), 7.32 (dd, *J* = 8.0, 7.2 Hz, 2H), 7.27 – 7.19 (m, 1H), 4.06 (q, *J* = 7.0 Hz, 2H), 3.96 – 3.88 (m, 2H), 3.10 (s, 2H), 2.40 – 2.24 (m, 2H), 1.94 – 1.80 (m, 2H), 1.20 (t, *J* = 7.1 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO) δ 166.1, 162.7, 154.7, 144.7, 128.0, 126.7, 124.3, 78.4, 60.6, 35.20, 30.63, 14.57.

HRMS (ESI): [m/z] calculated for $C_{16}H_{18}CsNNaO_6$ ([M+Na]$^+$): 476.0081; Found: 476.0114.



***tert*-Butyl 4-(4-chlorophenyl)-4-hydroxypiperidine-1-carboxylate**: 4-(4-chlorophenyl)piperidin-4-ol was dissolved in dichloromethane (0.1 M, 100 mL). DIPEA (1.9 mL, 11 mmol, 1.1 equiv.) and $(Boc)_2O$ (2.5 g, 11 mmol, 1.1 equiv.) was added and the reaction was stirred at room temperature for 18 h. NH_4Cl solution (25%) was added and the phases were separated. The aqueous phase was extracted with dichloromethane and the combined organics were washed with water and brine. Drying over sodium sulfate, filtration and evaporation of the solvent afforded the crude product, which was purified by column chromatography to yield the desired compound as white foam in 82% yield (2.5 g, 8.2 mmol). The characterization matches the reported literature.[257]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42 – 7.38 (m, 2H), 7.34 – 7.29 (m, 2H), 4.01 (br s, 2H), 3.21 (br s, 2H), 1.94 (br s, 2H), 1.69 (dd, J = 14.1, 2.3 Hz, 2H), 1.47 (s, 9H).

$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 155.0, 146.8, 133.2, 128.7, 126.2, 79.8, 71.5, 38.3, 38.2, 28.6.

R_f (PE/EtOAc 1:1) = 0.49 [UV]

1-(*tert*-butoxycarbonyl)-4-(4-chlorophenyl)piperidin-4-yl ethyl oxalate: Synthesized following **GP1** using tert-butyl 4-(4-chlorophenyl)-4-hydroxypiperidine-1-carboxylate (1.6 g, 5.0 mmol, 1.0 equiv.). The pure product was isolated as a white solid in 97% yield (2.0 g, 4.8 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 – 7.33 (m, 4H), 4.35 (q, J = 7.2 Hz, 2H), 4.08 (br s, 2H), 3.19 (br s, 2H), 2.58 (d, J = 13.1 Hz, 2H), 2.05 – 1.97 (m, 2H), 1.49 (s, 9H), 1.38 (t, J = 7.2 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 157.9, 156.4, 154.8, 140.6, 134.3, 129.0, 126.4, 83.9, 80.1, 63.2, 39.4, 35.1, 28.5, 14.0.

HRMS (ESI): [m/z] calculated for $C_{20}H_{26}ClNNaO_6$ ([M+Na]$^+$): 434.1341; Found: 434.1361.

R_f (PE:EA 9:1)= 0.18 [UV]

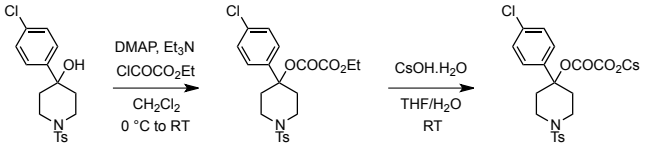
Cesium-2-((1-(*tert*-butoxycarbonyl)-4-(4-chlorophenyl)piperidin-4-yl)oxy)-2-oxoacetate:

Synthesized according to **GP2** using 1-(*tert*-butoxycarbonyl)-4-(4-chlorophenyl)piperidin-4-yl ethyl oxalate (577 mg, 1.4 mmol, 1 equiv.). The product was isolated as white solid in 64% yield (462 mg, 0.90 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 (s, 4H), 3.87 (br s, 2H), 3.03 (br s, 2H), 2.28 (d, J = 12.8 Hz, 2H), 1.83 (td, J = 13.2, 4.4 Hz, 2H), 1.41 (s, 9H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 166.1, 162.5, 154.0, 143.7, 131.4, 128.0, 126.4, 78.7, 77.9, 40.0, 35.0, 28.0.

HRMS (ESI-neg): [m/z] calculated for $C_{18}H_{21}ClNO_6$ ([M-Cs]$^-$): 382.1063; Found: 382.1074.



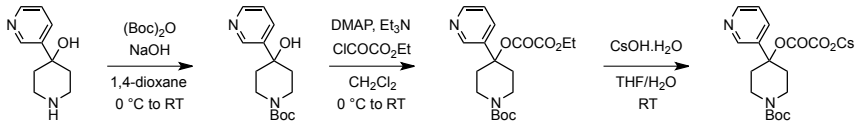
Cesium 2-((4-(4-chlorophenyl)-1-tosylpiperidin-4-yl)oxy)-2-oxoacetate: First, 4-(4-chlorophenyl)-1-tosylpiperidin-4-yl ethyl oxalate was synthesized following **GP1** using 4-(4-chlorophenyl)-1-tosylpiperidin-4-ol (1.1 g, 3.1 mmol, 1.0 equiv.). The crude product was used in the next reaction without further purification.

Cesium 2-((4-(4-chlorophenyl)-1-tosylpiperidin-4-yl)oxy)-2-oxoacetate was synthesized according to the **GP2** using 4-(4-chlorophenyl)-1-tosylpiperidin-4-yl ethyl oxalate (3.1 mmol, 1.0 equiv.). After evaporation of the solvent, the crude solid was dissolved in H_2O and washed with dichloromethane. The product was isolated as a white solid in 89% yield (1.5 g, 2.7 mmol).

^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.48 – 7.43 (m, 2H), 7.39 – 7.33 (m, 4H), 3.68 – 3.59 (m, 2H), 2.61 (td, *J* = 12.2, 2.2 Hz, 2H), 2.43 (s, 3H), 2.41 – 2.33 (m, 2H), 2.07 – 1.94 (m, 2H).

^{13}C{^{1}H} NMR (101 MHz, DMSO-*d*^{6}): δ 165.8, 162.1, 143.5, 143.3, 133.2, 131.5, 129.9, 128.0, 127.3, 126.3, 77.0, 41.7, 34.7, 21.0.

HRMS (ESI-pos): [m/z] calculated for $C_{20}H_{19}ClCsNNaO_6S$ ([M+Na]+): 591.9568; found 591.9565



1-(*tert*-butoxycarbonyl)-4-(pyridin-3-yl)piperidin-4-yl ethyl oxalate: In a round-bottomed flask, 4-(pyridin-3-yl)piperidin-4-ol (0.53 g, 3.0 mmol, 1.0 equiv.) and NaOH (0.15 g, 3.7 mmol, 1.2 equiv.) were dissolved in a 1:1 mixture of 1,4-dioxane (2.0 mL) and water (2.0 mL) and cooled down to 0 °C. Then, $(Boc)_2O$ (1.0 g, 4.6 mmol, 1.5 equiv.) was added in one portion. The reaction was stirred at 0 °C for 2 h and then diluted with 10 mL of water. The organic phase was extracted with EtOAc (3 x 30 mL), the combined organic layers dried over Na_2SO_4, filtered and concentrated to afford the crude product, *tert*-butyl 4-hydroxy-4-(pyridin-3-yl)piperidine-1-carboxylate, as a light orange solid, which was used in the next step without further purification.

1-(*tert*-butoxycarbonyl)-4-(pyridin-3-yl)piperidin-4-yl ethyl oxalate was synthesized following **GP1** using tert-butyl 4-hydroxy-4-(pyridin-3-yl)piperidine-1-carboxylate (3.0 mmol). The pure product was isolated as a sticky yellow oil in 53% yield (0.60 mg, 1.6 mmol) after column chromatography using a 2:1 mixture of EtOAc/DCM, and basic work up with $NaHCO_3$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (d, *J* = 2.6 Hz, 1H), 8.57 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.70 (ddd, *J* = 8.1, 2.5, 1.6 Hz, 1H), 7.31 (ddd, *J* = 8.1, 4.8, 0.9 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 4.17 – 4.00 (m, 2H), 3.19 (t, *J* = 12.8 Hz, 2H), 2.66 – 2.56 (m, 2H), 2.12 – 1.96 (m, 2H), 1.47 (s, 9H), 1.37 (t, *J* = 7.1 Hz, 3H).

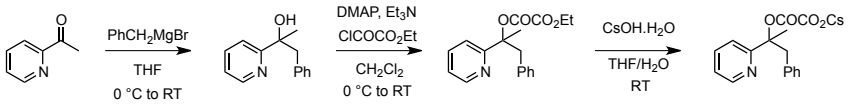
HRMS (ESI): [m/z] calculated for $[C_{19}H_{27}N_2O_6]^+$ ($[M+H]^+$): 379,1869; Found, 379.1864.

R_f (2:1 EtOAc/DCM) = 0.4

Cesium 2-((1-(*tert*-butoxycarbonyl)-4-(pyridin-3-yl)piperidin-4-yl)oxy)-2-oxoacetate: Synthesized according to the **GP2** using 1-(*tert*-butoxycarbonyl)-4-(pyridin-3-yl)piperidin-4-yl ethyl oxalate (600 mg, 1.6 mmol, 1.0 equiv.). After evaporation of the solvent, the crude solid was dissolved in H_2O and washed with dichloromethane. The product was isolated as a white solid in 92% yield (0.70 g, 1.5 mmol).

^{1}H NMR (600 MHz, DMSO-d_6): δ 8.59 (dd, *J* = 2.5, 0.8 Hz, 1H, CH_{Ar}), 8.45 (dd, *J* = 4.7, 1.6 Hz, 1H, CH_{Ar}), 7.74 (ddd, *J* = 8.0, 2.5, 1.6 Hz, 1H, CH_{Ar}), 7.36 (ddd, *J* = 8.0, 4.7, 0.8 Hz, 1H, CH_{Ar}), 3.89 (s, 2H, CH_2), 3.04 (s, 2H, CH_2), 2.35 – 2.31 (m, 2H, CH_2), 1.96 – 1.86 (m, 2H, CH_2), 1.42 (s, 9H, CH_3).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 166.1, 162.5, 154.0, 147.9, 146.0, 139.9, 132.2, 123.1, 78.8, 77.2, 58.1, 34.84, 28.06.



Ethyl (1-phenyl-2-(pyridin-2-yl)propan-2-yl) oxalate: Benzylmagnesium bromide (12.0 mL, 12 mmol, 1.2 equiv.) was added dropwise to a 0 °C solution of ethyl 2-acetylpyridine (1.1 mL, 10 mmol, 1.0 equiv.) in THF (20 mL, 0.5 M). The mixture was stirred at 0 °C for 1 h and then warmed up to room temperature. After 2 h the reaction was quenched with a saturated solution of NH_4Cl (aq.), the product extracted with EtOAc (3 x 50 mL), and the combined organic layers dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was used in the next step without further purification.

Ethyl (1-phenyl-2-(pyridin-2-yl)propan-2-yl) oxalate was synthesized following **GP1** using 1-phenyl-2-(pyridin-2-yl)propan-2-ol (10 mmol, 1.0 equiv.). The pure product was isolated as yellow oil in 34% yield (1.1 g, 3.5 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H), 7.58 (td, *J* = 7.7, 1.8 Hz, 1H), 7.22 – 7.13 (m, 5H), 6.98 – 6.91 (m, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.49 (d, *J* = 13.8 Hz, 1H), 3.42 (d, *J* = 13.8 Hz, 1H), 1.96 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H).

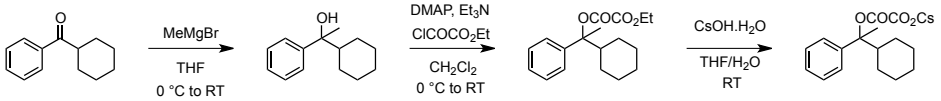
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 160.9, 158.1, 156.6, 149.0, 136.4, 135.7, 130.7, 128.0, 126.9, 122.5, 120.3, 88.4, 63.1, 47.0, 23.4, 14.1.

GCMS (FI): [m/z] calculated for $C_{18}H_{19}NO_4$ ([M]): 313.13141; Found, 313.12870.

Cesium 2-oxo-2-((1-phenyl-2-(pyridin-2-yl)propan-2-yl)oxy)acetate: Synthesized according to the **GP2** using ethyl (1-phenyl-2-(pyridin-2-yl)propan-2-yl) oxalate (1.06 g, 3.4 mmol, 1.0 equiv.). The crude product was washed with Et_2O to afford the desired product as a white solid in 70% yield (1.0 g, 2.3 mmol).

^{1}H NMR (400 MHz, D_2O) δ 8.53 (ddd, *J* = 5.1, 1.8, 0.9 Hz, 1H), 7.86 (td, *J* = 7.8, 1.8 Hz, 1H), 7.45 (ddd, *J* = 7.6, 5.0, 1.1 Hz, 1H), 7.39 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.29 (dq, *J* = 8.8, 4.1, 3.4 Hz, 3H), 7.01 – 6.97 (m, 2H), 3.47 (s, 2H), 1.94 (s, 3H).

HRMS (ESI-pos): [m/z] calculated for $C_{16}H_{14}CsNNaO_4$ ([M+Na]+): 439.9870; Found, 439.9879.



1-Cyclohexyl-1-phenylethanol: MeMgBr (6.0 mL, 18.0 mmol, 1.2 equiv.) was added dropwise to a 0 °C solution of cyclohexyl(phenyl)methanone (2.8 mL, 15 mmol, 1.0 equiv.) in THF (50 mL, 0.3 M). The mixture was stirred at 0 °C for 1 h and then warmed up to room temperature. After 2 h the reaction was quenched with a saturated solution of NH_4Cl (aq.), the product extracted with EtOAc (3 x 50 mL), and the combined organic layers dried over Na_2SO_4 and concentrated *in vacuo*. The pure product was isolated without further purification in quantitative yield. The characterization matches the reported literature.[258]

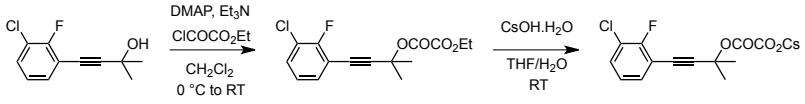
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.38 (m, 2H), 7.36 – 7.28 (m, 2H), 7.25 – 7.20 (m, 1H), 1.79 – 1.66 (m, 3H), 1.60 (m, 4H), 1.53 (s, 3H), 1.25 – 0.90 (m, 5H).

Cesium 2-(1-cyclohexyl-1-phenylethoxy)-2-oxoacetate: First, 1-cyclohexyl-1-phenylethyl ethyl oxalate was synthesized following **GP1** using 1-cyclohexyl-1-phenylethanol (0.62 g, 3.0 mmol, 1.0 equiv.). After workup with CH_2Cl_2 (15 mL x3) and H_2O, the product was used in the next step without further purification.

Cesium 2-(1-cyclohexyl-1-phenylethoxy)-2-oxoacetate was Synthesized following **GP2** using 1-cyclohexyl-1-phenylethyl ethyl oxalate (0.91 mg, 3.0 mmol, 1.0 equiv.). The product was isolated as a white solid in 66% (0.81 g, 2.0 mmol) yield after dissolving the solid in water, washing it with EtOAc and evaporating the solvent.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.21 (m, 4H), 7.22 – 7.16 (m, 1H), 1.76 (s, 3H), 1.75 – 1.51 (m, 5H), 1.44 – 1.34 (m, 1H), 1.18 – 0.77 (m, 5H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 166.4, 144.2, 127.3, 126.0, 125.2, 83.7, 49.5, 26.9, 26.3, 26.0, 26.0, 25.9, 20.5.



4-(3-chloro-2-fluorophenyl)-2-methylbut-3-yn-2-yl ethyl oxalate: Synthesized following **GP1** with 4-(3-Chloro-2-fluorophenyl)-2-methylbut-3-yn-2-ol (0.49 g, 2.2 mmol, 1.0 equiv.), the product was obtained as a colorless oil in 93% yield (0.67 g, 2.2 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): □ 7.35 (ddd, *J* = 8.3, 6.9, 1.7 Hz, 1H), 7.32 (ddd, *J* = 7.8, 6.1, 1.7 Hz, 1H), 7.01 (td, *J* = 7.9, 1.1 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 1.86 (s, 6H), 1.38 (t, *J* = 7.2 Hz, 3H).

$^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): □ 158.55 (d, J_{C-F} = 254.3 Hz), 158.0, 156.2, 132.0, 131.2, 124.4 (d, J_{C-F} = 4.9 Hz), 121.6 (d, J_{C-F} = 17.2 Hz), 112.6 (d, J_{C-F} = 15.8 Hz), 94.7 (d, J_{C-F} = 3.9 Hz), 78.3, 75.9, 63.2, 28.7, 14.1.

HRMS (ESI): [m/z] calculated $C_{15}H_{14}ClFNaO_4$ ($[M+Na]^+$) 355.0457, found 355.0472.

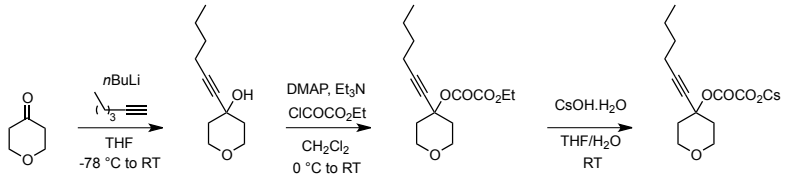
R_f (PE:EtOAc 8:2) = 0.59 [UV]

Cesium 2-((4-(3-chloro-2-fluorophenyl)-2-methylbut-3-yn-2-yl)oxy)-2-oxoacetate: Synthesized following the general procedure **D** with 4-(3-Chloro-2-fluorophenyl)-2-methylbut-3-yn-2-yl ethyl oxalate (0.54 mg, 1.6 mmol, 1.0 equiv.), the product was obtained as a white solid in 80% yield (0.55 g, 1.3 mmol).

^1H NMR (600 MHz, DMSO-d_6): □ 7.62 (ddd, *J* = 8.5, 7.2, 1.6 Hz, 1H), 7.44 (ddd, *J* = 7.9, 6.4, 1.6 Hz, 1H), 7.23 (td, *J* = 8.0, 1.0 Hz, 1H), 1.69 (s, 6H).

$^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6): δ 165.5, 162.1, 157.2 (d, *J* = 250.9 Hz), 132.2, 131.1, 125.6 (d, *J* = 4.9 Hz), 120.1 (d, *J* = 17.1 Hz), 112.1 (d, *J* = 15.4 Hz), 97.9 (d, *J* = 3.8 Hz), 75.4, 70.0, 28.5.

HRMS (ESI-*neg*): [m/z] calculated $C_{13}H_9ClFO_4$ ($[M-Cs]^-$): 283.0179, found 283.0190.



Ethyl (4-(hex-1-yn-1-yl)tetrahydro-2*H*-pyran-4-yl) oxalate: *n*BuLi (2.5 M in hexane, 6.8 mL, 17.0 mmol, 1.3 equiv.) was added dropwise to a -78 °C solution of dihydro-2H-pyran-4(3H)-one (1.4 mL, 15 mmol, 1.0 equiv.) in THF (25 mL, 0.6 M). The mixture was stirred at -78 °C for 1 h and then warmed up to room temperature. After 2 h the reaction was quenched with a saturated solution of NH_4Cl (aq.), the product extracted with EtOAc (3 x 50 mL), and the combined organic layers dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was used in the next step without further purification.

Synthesized following **GP1** using 4-(hex-1-yn-1-yl)tetrahydro-2*H*-pyran-4-ol (15 mmol, 1.0 equiv.). The pure product was isolated as colorless oil in 89% yield (3.8 g, 13 mmol).

^1H NMR (400 MHz, $CDCl_3$): δ 4.34 (q, *J* = 7.1 Hz, 2H), 3.87 (dt, *J* = 11.9, 4.3 Hz, 2H), 3.72 (ddd, *J* = 12.0, 9.4, 2.8 Hz, 2H), 2.31 – 2.20 (m, 4H), 2.09 (ddd, *J* = 13.3, 9.5, 4.1 Hz, 2H), 1.47 (m, 2H), 1.47 – 1.41 (m, 2H), 1.38 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 158.0, 156.0, 89.9, 77.5, 77.3, 77.2, 77.0, 76.8, 64.7, 63.2, 37.8, 30.6, 22.1, 18.5, 14.1, 13.7.

GCMS (FI): [m/z] calculated for $C_{15}H_{22}O_5$: 282.14672; Found: 282.14672.

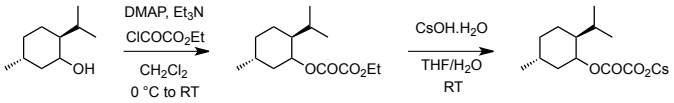
R_f (4:1 PE/EtOAc) = 0.45

Cesium 2-((4-(hex-1-yn-1-yl)tetrahydro-2*H*-pyran-4-yl)oxy)-2-oxoacetate: Synthesized following **GP2** using ethyl (4-(hex-1-yn-1-yl)tetrahydro-2*H*-pyran-4-yl) oxalate (1.4 g, 5.0 mmol, 1.0 equiv.).The product was isolated as a white solid in 98% yield (1.9 g, 4.9 mmol).

^{1}H NMR (600 MHz, DMSO-d_6): δ 3.74 (dt, *J* = 11.8, 4.3 Hz, 2H), 3.55 (ddd, *J* = 11.8, 9.4, 2.7 Hz, 2H), 2.23 (t, *J* = 6.8 Hz, 2H), 2.09 – 1.96 (m, 2H), 1.86 (ddd, *J* = 13.2, 9.4, 4.0 Hz, 2H), 1.48 – 1.34 (m, 4H), 0.88 (t, *J* = 7.2 Hz, 3H).

^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 165.4, 162.3, 86.7, 79.7, 71.0, 63.6, 37.6, 30.2, 21.2, 17.6, 13.4.

HRMS (ESI-neg): [m/z] calculated for [$C_{13}H_{17}O_5$] ([M-Cs]$^-$): 253.1076; Found: 253.1081.



Ethyl ((2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl) oxalate: Synthesized following **GP1** using 2-(4-chlorophenyl)oct-3-yn-2-ol (0.78 g, 5.0 mmol, 1.0 equiv.). The pure product was isolated as colorless oil in >95% (1.3 g, 5.0 mmol) without purification.

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.85 (td, *J* = 11.0, 4.5 Hz, 1H), 4.34 (qd, *J* = 7.1, 0.9 Hz, 2H), 2.08 – 2.03 (m, 1H), 1.89 (pd, *J* = 7.0, 2.8 Hz, 1H), 1.71 (dtd, *J* = 12.8, 6.1, 5.5, 3.0 Hz, 2H), 1.57 – 1.48 (m, 2H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.26 – 1.03 (m, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.78 (d, *J* = 7.0 Hz, 3H).

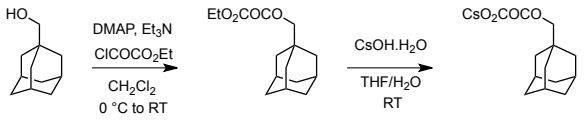
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 158.4, 157.8, 77.9, 63.1, 46.9, 40.4, 34.2, 31.6, 26.4, 23.6, 22.1, 20.8, 16.4, 14.1.

GCMS (FI): [m/z] calculated for $C_{14}H_{24}O_4$: 256.17240; Found: 256.16746.

Cesium 2-(((2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoacetate: Synthesized following **GP2** using ethyl ((2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl) oxalate (0.77 mg, 3.0 mmol, 1.0 equiv.). The product was isolated as a white solid in 93% yield (1.0 g, 2.8 mmol). The characterization matches the reported literature.[133]

^{1}H NMR (400 MHz, DMSO-d_6): δ 4.50 (td, *J* = 10.9, 4.3 Hz, 1H), 1.94 – 1.75 (m, 2H), 1.62 (ddd, *J* = 13.7, 9.9, 3.3 Hz, 2H), 1.49 – 1.37 (m, 1H), 1.35 – 1.25 (m, 1H), 1.09 – 0.90 (m, 2H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 7.1 Hz, 3H), 0.70 (d, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 167.1, 1628, 71.21, 46.6, 40.7, 33.8, 30.9, 25.4, 23.0, 21.9, 20.5, 16.3.



Adamantan-1-ylmethyl ethyl oxalate: Synthesized following **GP1** using adamantan-1-ylmethanol (830 mg, 5.0 mmol, 1.0 equiv.). The pure product was isolated as colorless oil in quantitative yield (1.33 g, 5 mmol) without purification.

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.36 (qd, *J* = 7.2, 0.8 Hz, 2H), 3.88 (s, 2H), 2.00 (t, *J* = 3.0 Hz, 3H), 1.79 – 1.71 (m, 3H), 1.69 – 1.63 (m, 3H), 1.57 (d, *J* = 2.9 Hz, 6H), 1.39 (dd, *J* = 7.2, 0.7 Hz, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 158.5, 158.2, 100.1, 76.3, 63.1, 39.2, 36.8, 33.6, 28.1, 14.1.

GCMS (FI): [m/z] calculated for $C_{15}H_{22}O_4$: 266.15636; Found: 266.15181.

Cesium 2-(((2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoacetate: Synthesized following **GP2** using ethyl ((2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl) oxalate (0.8 mg, 3.0 mmol, 1.0 equiv.). The product was isolated as a white solid in 90% yield (1.0 g, 2.7 mmol).

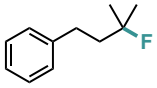
^{1}H NMR (400 MHz, DMSO-d_6): δ 3.53 (s, 2H), 1.99 – 1.90 (m, 3H), 1.68 (d, *J* = 12.4 Hz, 3H), 1.60 (d, *J* = 12.0 Hz, 3H), 1.49 (s, 6H).

^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 167.7, 162.8, 71.4, 58.0, 40.1, 38.7, 36.5, 32.8, 27.4, 14.2.

HRMS (ESI-neg): [m/z] calculated for $C_{13}H_{17}O_4$ ([M-Cs]$^-$): 237.1132; Found: 237.1167.

6.3.3. Synthesis & characterization of tertiary fluorides

General procedure for the fluorination of tertiary cesium oxalates (GP3): An 8 mL Biotage® microwave vial was charged with the corresponding cesium oxalate (0.50 mmol, 1 equiv.) and Selecfluor® (0.44 g, 1.2 mmol, 2.5 equiv.) and sealed with a septum cap. The vial was put under vacuum for 5 min and refilled with N_2. Afterwards, degassed H_2O (2.5 mL) and acetone (2.5 mL) were added subsequently. The reaction mixture was then sparged with N_2 for 2-5 min and irradiated with blue LEDs (λ_{max} = 440 nm) for 2 h. Afterwards, the reaction was combined with a mixture of H_2O and a saturated brine solution (ca. 15 mL) and the organic phase extracted with EtOAc (ca. 3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent evaporated. The crude product was purified by column chromatography over silica gel to afford the desired tertiary fluoride.



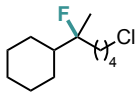
(3-fluoro-3-methylbutyl)benzene (2): Synthesized following **GP3** using cesium 2-((2-methyl-4-phenylbutan-2-yl)oxy)-2-oxoacetate (0.18 g, 0.50 mmol, 1.0 equiv.). The reaction was performed twice, and the combined crude products purified by column chromatography. The product was isolated as a colorless oil in 76% yield (0.13 g, 0.76 mmol). The characterization data matches the reported literature.[259]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.26 (m, 2H), 7.23 – 7.16 (m, 3H), 2.77 – 2.70 (m, 2H), 2.00 – 1.88 (m, 2H), 1.44 (s, 3H), 1.39 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 142.2, 128.6, 128.4, 126.0, 95.4 (d, *J* = 165.6 Hz), 43.5 (d, *J* = 23.0 Hz), 30.4 (d, *J* = 5.4 Hz), 26.8 (d, *J* = 24.7 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ -138.80.

R_f (PE/EtOAc, 10:1) = 0.5 [CAM]



(6-chloro-2-fluorohexan-2-yl)cyclohexane (4): Synthesized following **GP3** using cesium 2-((6-chloro-2-cyclohexylhexan-2-yl)oxy)-2-oxoacetate (0.21 g, 0.50 mmol, 1.0 equiv.). The product was isolated as a colorless oil in 81% yield (90 mg, 0.41 mmol).

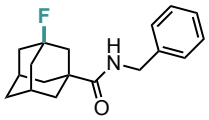
^{1}H NMR (400 MHz, CD_3CN): δ 3.60 (t, *J* = 6.7 Hz, 2H), 1.83 – 1.45 (m, 12H), 1.30 – 1.10 (m, 5), 1.21 (d, *J* = 22.2 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 100.00 (d, *J* = 167.9 Hz), 46.97 (d, *J* = 21.8 Hz), 46.08, 37.47 (d, *J* = 23.3 Hz), 33.67, 28.26 (d, *J* = 6.9 Hz), 27.62 (d, *J* = 5.4 Hz), 27.29, 27.21, 21.63 (d, *J* = 25.3 Hz), 21.26 (d, *J* = 4.6 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ -149.56.

GCMS (FI): [m/z] calculated for $C_{12}H_{22}ClF$ ([M]): 220.13941; Found: 220.13720.

R_f (PE/EtOAc, 10:1) = 0.62 [CAM]



(1*r*,3*s*,5*R*,7*S*)-*N*-benzyl-3-fluoroadamantane-1-carboxamide (5): Synthesized following **GP3** using cesium 2-(((1*s*,3*r*,5*R*,7*S*)-3-(benzylcarbamoyl)adamantan-1-yl)oxy)-2-oxoacetate (0.24 g, 0.50 mmol, 1.0 equiv.). The product was isolated as a white solid in 57% yield (81 mg, 0.28 mmol).

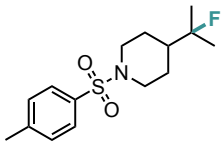
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.30 (m, 2H), 7.30 – 7.22 (m, 3H), 5.91 (s, 1H), 4.43 (d, *J* = 5.5 Hz, 2H), 2.37 (q, *J* = 3.5 Hz, 2H), 2.01 (d, *J* = 5.8 Hz, 2H), 1.88 (dd, *J* = 5.7, 3.1 Hz, 4H), 1.80 (t, *J* = 2.8 Hz, 4H), 1.60 (d, *J* = 3.1 Hz, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 175.7 (d, *J* = 1.9 Hz), 138.5, 128.9, 127.7, 127.6, 92.4 (d, *J* = 184.5 Hz), 45.2 (d, *J* = 9.6 Hz), 44.4, 44.2, 43.6, 42.1, 41.9, 38.2 (d, *J* = 1.9 Hz), 35.0 (d, *J* = 2.0 Hz), 31.1 (d, *J* = 9.9 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ -132.07.

GCMS (FI): [m/z] calculated for $C_{18}H_{22}FNO$ ([M]): 287.16854; Found: 287.17377.

R_f (PE/EtOAc, 2:1) = 0.28 [CAM]



4-(2-fluoropropan-2-yl)-1-tosylpiperidine (6): Synthesized following **GP3** using cesium 2-oxo-2-((2-(1-tosylpiperidin-4-yl)propan-2-yl)oxy)acetate (0.27 g, 0.50 mmol, 1.0 equiv.). The product was isolated as a white solid in 91% yield (0.15 g, 0.45 mmol).

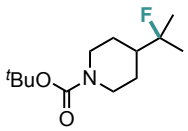
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 – 7.62 (m, 2H), 7.34 – 7.29 (m, 2H), 3.91 – 3.83 (m, 2H), 2.43 (s, 3H), 2.19 (td, *J* = 11.4, 2.3 Hz, 2H), 1.82 – 1.71 (m, 2H), 1.52 – 1.37 (m, 3H), 1.28 (s, 3H), 1.23 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 143.60, 133.32, 129.72, 127.86, 96.71 (d, *J* = 167.2 Hz), 46.58, 45.38 (d, *J* = 22.8 Hz), 26.25 (d, *J* = 6.3 Hz), 24.33 (d, *J* = 25.0 Hz), 21.64.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ -140.51.

GCMS (FI): [m/z] calculated for $C_{15}H_{22}NO_2FS$ ([M]): 299.13553; Found: 299.13363.

R_f (PE/EtOAc, 4:1) = 0.4 [CAM]



***tert*-butyl 4-(2-fluoropropan-2-yl)piperidine-1-carboxylate (7):** Synthesized following **GP3** using cesium 2-((2-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)propan-2-yl)oxy)-2-oxoacetate (0.22 g, 0.5 mmol, 1.0 equiv.). The product was isolated as a colorless oil in 41% yield (56 mg, 0.2 mmol). The characterization matches the reported literature.[259]

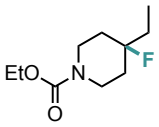
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.19 (d, *J* = 13.6 Hz, 2H), 2.64 (td, *J* = 12.9, 2.5 Hz, 2H), 1.70 (ddd, *J* = 12.6, 3.2, 1.7 Hz, 2H), 1.45 (s, 9H), 1.32 (s, 3H), 1.27 (s, 3H), 1.26 – 1.18 (m, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 154.9, 97.0 (d, *J* = 166.7 Hz), 79.5, 46.2 (d, *J* = 22.4 Hz), 44.1, 28.6, 26.8 (d, *J* = 6.1 Hz), 24.6, 24.3.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ -140.74.

GCMS (FI): [m/z] calculated for $C_{13}H_{24}FNO_2$: 245.17911; Found: 245.18312.

R_f (PE/EtOAc, 4:1) = 0.5 [CAM]



Ethyl 4-ethyl-4-fluoropiperidine-1-carboxylate (8): Synthesized following **GP3** using cesium 2-((1-(ethoxycarbonyl)-4-ethylpiperidin-4-yl)oxy)-2-oxoacetate (0.20 g, 0.50 mmol, 1.0 equiv.). The product was isolated as a colorless oil in 35% yield (70 mg, 0.17 mmol).

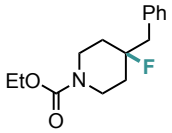
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.19 – 4.09 (m, 2H), 3.98 (d, *J* = 12.7 Hz, 2H), 3.16 – 3.06 (m, 2H), 1.80 (td, *J* = 10.6, 9.2, 4.7 Hz, 2H), 1.70 – 1.41 (m, 4H), 1.25 (td, *J* = 7.1, 0.6 Hz, 3H), 1.00 – 0.91 (m, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 155.7, 94.2 (d, *J* = 171.0 Hz), 61.4, 39.9 (d, *J* = 2.5 Hz), 34.1 (d, *J* = 22.2 Hz), 33.1 (d, *J* = 22.9 Hz), 14.8, 7.2 (d, *J* = 5.6 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ -164.71.

GCMS (FI): [m/z] calculated for $C_{10}H_{18}NO_2F$ ([M]): 203.13216; Found: 203.13221.

R_f (PE/EtOAc, 4:1) = 0.37 [CAM]



Ethyl 4-benzyl-4-fluoropiperidine-1-carboxylate (9): Synthesized following **GP3** using cesium cesium 2-((4-benzyl-1-(ethoxycarbonyl)piperidin-4-yl)oxy)-2-oxoacetate (0.23 g, 0.50 mmol, 1.0 equiv.). The product was isolated as a colorless oil in 33% yield (44 mg, 0.16 mmol).

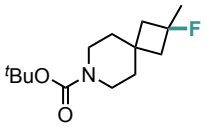
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (s, 3H), 7.22 – 7.17 (m, 2H), 4.11 (q, J = 7.1 Hz, 2H), 3.98 (m, 2H), 3.15 – 3.02 (m, 2H), 2.91 (d, J_{H-F} = 22.0 Hz, 2H), 1.75 (m, 2H), 1.67 – 1.49 (m, 3H), 1.24 (t, *J* = 7.1 Hz, 4H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 155.6, 135.6 (d, J_{C-F} = 2.8 Hz), 130.5, 129.4, 128.7, 128.3, 127.0, 93.7 (d, J_{C-F} = 174.1 Hz), 61.5, 46.8 (d, J_{C-F} = 22.1 Hz), 46.7, 39.8 (d, J_{C-F} = 2.5 Hz), 34.6 (d, J_{C-F} = 21.8 Hz), 31.0, 14.8.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ -161.44.

GCMS (FI): [m/z] calculated for $C_{15}H_{20}NO_2F$ ([M]): 265.14781; Found: 265.14930.

R_f (PE/EtOAc, 4:1) = 0.37 [CAM]



***tert*-butyl 2-fluoro-2-methyl-7-azaspiro[3.5]nonane-7-carboxylate (9):** Synthesized following **GP3** using cesium 2-((7-(*tert*-butoxycarbonyl)-2-methyl-7-azaspiro[3.5]nonan-2-yl)oxy)-2-oxoacetate (0.23 g, 0.50 mmol, 1.0 equiv.). The product was isolated as a colorless oil in 49% yield (62 mg, 0.24 mmol).

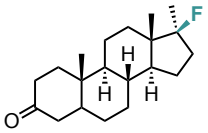
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.36 – 3.27 (m, 4H), 2.16 (m, 2H), 2.04 – 1.89 (m, 2H), 1.66 – 1.59 (m, 2H), 1.50 – 1.42 (m, 14H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 155.1, 92.9 (d, *J* = 199.6 Hz), 79.5, 45.0, 44.8, 41.0, 40.8, 38.6, 37.1 (d, *J* = 4.5 Hz), 29.0 (d, *J* = 7.0 Hz), 28.6, 27.4 (d, *J* = 25.8 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ -125.18.

GCMS (FI): [m/z] calculated for $C_{14}H_{24}FNO_2$ ([M]): 257.17911; Found: 257.18694.

R_f (PE/EtOAc, 4:1) = 0.53 [CAM]



(5S,8R,9S,10S,13S,14S)-17-fluoro-10,13,17-trimethylhexadecahydro-3H-cyclopenta[a]phenanthren-3-one (11): Synthesized following **GP3** using cesium 2-oxo-2-(((5S,8R,9S,10S,13S,14S)-10,13,17-trimethyl-3-oxohexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)oxy)acetate (0.25 g, 0.50 mmol, 1.0 equiv.). The product was isolated as a white solid in 58% yield (88 mg, 0.28 mmol). It was observed that the product decomposes in $CDCl_3$, presumably due to traces of HCl, therefore the NMR spectra were recorded in CD_3CN.

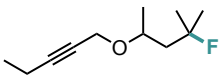
^{1}H NMR (400 MHz, CD_3CN): δ 2.41 (dddd, *J* = 15.1, 14.0, 6.6, 0.9 Hz, 1H), 2.30 (ddd, *J* = 14.8, 13.8, 0.9 Hz, 1H), 2.19 – 2.09 (m, 2H), 2.05 – 1.99 (m, 1H), 1.97 (dd, *J* = 3.9, 2.4 Hz, 1H), 1.91 – 1.79 (m, 1H), 1.76 – 1.62 (m, 4H), 1.59 – 1.45 (m, 4H), 1.40 – 1.30 (m, 4H), 1.26 (d, *J* = 22.7 Hz, 3H), 1.23 – 1.15 (m, 1H), 1.04 (s, 3H), 1.02 – 0.92 (m, 1H), 0.83 – 0.73 (m, 1H), 0.70 (d, *J* = 0.7 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, CD_3CN): δ 211.8, 107.3 (d, *J* = 173.5 Hz), 54.7, 51.1, 47.6, 45.3, 39.3, 38.7, 37.0, 36.8, 36.6, 36.5, 32.7, 30.6 (d, *J* = 5.0 Hz), 29.7, 24.4 (d, *J* = 1.0 Hz), 21.6, 19.3 (d, *J* = 27.7 Hz), 15.7 (d, *J* = 5.6 Hz), 11.7.

^{19}F{1H} NMR (376 MHz, CD_3CN): δ -142.10.

HRMS(ESI): [*m/z*] calculated for $C_{20}H_{31}FNaO$ ([M+Na]$^+$): 329.2257; found 329.2253.

R_f(CH/EtOAc 6:1) = 0.14 [CAM]



1-((4-fluoro-4-methylpentan-2-yl)oxy)pent-2-yne (10): Synthesized following **GP3** using cesium 2-((2-methyl-4-(pent-2-yn-1-yloxy)pentan-2-yl)oxy)-2-oxoacetate (0.25 g, 0.64 mmol, 1.0 equiv.). The product was isolated as a white solid in 42% yield (50 mg, 0.27 mmol).

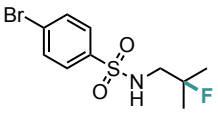
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.19 – 4.04 (m, 2H), 3.89 – 3.79 (m, 1H), 2.22 (qt, *J* = 7.5, 2.2 Hz, 2H), 1.89 (ddd, *J* = 24.7, 14.8, 7.4 Hz, 1H), 1.74 (td, *J* = 14.7, 4.0 Hz, 1H), 1.43 (d, *J* = 10.3 Hz, 3H), 1.38 (d, *J* = 10.6 Hz, 3H), 1.19 (dd, *J* = 6.1, 0.6 Hz, 3H), 1.14 (t, *J* = 7.5 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 95.24 (d, *J* = 164.2 Hz), 87.90, 70.80 (d, *J* = 5.5 Hz), 55.87, 48.27 (d, *J* = 22.5 Hz), 28.68 (d, *J* = 24.4 Hz), 26.28 (d, *J* = 24.8 Hz), 20.49, 13.90, 12.57.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ -133.73.

GCMS (FI): [m/z] calculated for $C_{11}H_{18}FO$ ([M-H$^+$]): 185.13417; Found: 185.13542.

R_f (PE/EtOAc, 2:1) = 0.77 [CAM]



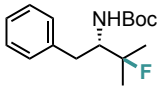
4-bromo-*N*-(2-fluoro-2-methylpropyl)benzenesulfonamide (13): Synthesized following **GP3** using cesium 2-((1-(4-bromophenylsulfonamido)-2-methylpropan-2-yl)oxy)-2-oxoacetate (0.26 g, 0.5 mmol, 1.0 equiv.). The product was isolated as a white solid in 35% yield (55 mg, 0.17 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 – 7.70 (m, 2H), 7.69 – 7.64 (m, 2H), 4.76 (t, *J* = 6.5 Hz, 1H), 3.07 (dd, *J* = 19.8, 6.5 Hz, 2H), 1.37 (d, J_{H-F} = 21.4 Hz, 7H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 139.21, 132.64, 128.66, 127.89, 94.61 (d, J_{C-F} = 168.3 Hz), 51.81 (d, J_{C-F} = 22.5 Hz), 24.53 (d, J_{C-F} = 23.9 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ -145.15.

R_f (PE/EtOAc, 4:1) = 0.37 [CAM]



(*S*)-*tert*-butyl (3-fluoro-3-methyl-1-phenylbutan-2-yl)carbamate (14): Synthesized following **GP3** using cesium (*S*)-2-((3-((*tert*-butoxycarbonyl)amino)-2-methyl-4-phenylbutan-2-yl)oxy)-2-oxoacetate (0.24 g, 0.5 mmol, 1.0 equiv.). The reaction was performed twice and the combined crude products purified by column chromatography. The product was isolated as a white solid in 95% yield (133 mg, 0.47 mmol).

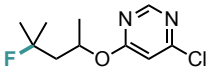
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 3H), 7.23 – 7.15 (m, 3H), 4.47 (d, *J* = 10.1 Hz, 1H), 4.06 – 3.81 (m, 1H), 3.15 (dd, *J* = 14.3, 3.8 Hz, 1H), 2.57 (t, *J* = 12.7 Hz, 1H), 1.44 (dd, *J* = 23.1, 21.7 Hz, 6H), 1.26 (s, 10H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.7, 138.4, 129.3, 128.4, 126.4, 97.2 (d, *J* = 171.1 Hz), 79.3, 58.0 (d, *J* = 23.0 Hz), 36.1, 28.3, 25.1 (d, *J* = 24.2 Hz), 24.3 (d, *J* = 24.3 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -152.54.

HRMS(ESI): [*m/z*] calculated for $C_{16}H_{24}FNNaO_2$ ($[M+Na]^+$), 304.1689, found 304.1683.

R_f(Cyclohexane/EtOAc 4:1) = 0.5 [Ninhydrin]



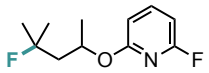
4-chloro-6-((4-fluoro-4-methylpentan-2-yl)oxy)pyrimidine (15): Synthesized following **GP3** using cesium 2-((4-((6-chloropyrimidin-4-yl)oxy)-2-methylpentan-2-yl)oxy)-2-oxoacetate (86 mg, 0.20 mmol, 1.0 equiv.). The product was isolated as a colorless oil in 55 % yield (24 mg, 0.11 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, *J* = 0.9 Hz, 1H), 6.69 (d, *J* = 0.9 Hz, 1H), 5.57 (dqd, *J* = 7.8, 6.2, 4.0 Hz, 1H), 2.12 (ddd, *J* = 25.0, 15.0, 7.8 Hz, 1H), 1.92 (td, *J* = 15.3, 4.1 Hz, 1H), 1.40 (d, *J* = 6.6 Hz, 3H), 1.37 (dd, *J* = 6.2, 0.7 Hz, 3H), 1.34 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 161.0, 158.4, 108.3, 94.4 (d, J_{C-F} = 166.3 Hz), 70.9 (d, J_{C-F} = 4.2 Hz), 47.1 (d, J_{C-F} = 22.7 Hz), 28.3 (d, J_{C-F} = 24.5 Hz), 26.4 (d, *J* = 24.9 Hz), 21.2 (d, J_{C-F} = 1.4 Hz).

^{19}F{1H} NMR (376 MHz, $CDCl_3$) δ -136.52.

R_f(Cyclohexan/EtOAc 4:1) = 0.54 [CAM]



2-fluoro-6-((4-fluoro-4-methylpentan-2-yl)oxy)pyridine (16): Synthesized following **GP3** using cesium 2-((4-((6-fluoropyridin-2-yl)oxy)-2-methylpentan-2-yl)oxy)-2-oxoacetate (0.21 g, 0.50 mmol, 1.0 equiv.). The reaction was performed twice and the combined crude products purified by column chromatography. The product was isolated as a colorless oil in 64% yield (0.14 g, 0.64 mmol).

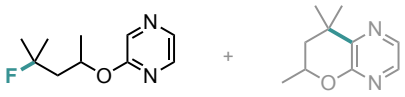
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 (dt, *J* = 8.5, 7.9 Hz, 1H), 6.53 (ddd, *J* = 8.0, 1.7, 0.6 Hz, 1H), 6.42 (ddd, *J* = 7.7, 2.6, 0.6 Hz, 1H), 5.36 (dqd, *J* = 7.9, 6.1, 4.0 Hz, 1H), 2.11 (ddd, *J* = 24.5, 14.8, 7.9 Hz, 1H), 1.91 (td, *J* = 14.9, 4.1 Hz, 1H), 1.42 (s, 3H), 1.39 – 1.32 (m, 6H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.41 (d, *J* = 240.0 Hz), 162.4 (d, *J* = 13.6 Hz), 142.7 (d, *J* = 8.1 Hz), 107.7 (d, *J* = 5.2 Hz), 99.8 (d, *J* = 35.8 Hz), 94.9 (d, *J* = 165.3 Hz), 69.4 (d, *J* = 5.0 Hz), 47.4 (d, *J* = 22.8 Hz), 28.4 (d, *J* = 24.5 Hz), 26.4 (d, *J* = 24.8 Hz), 21.3 (d, *J* = 1.2 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ -69.92, -134.61.

GCMS (FI): [m/z] calculated for $C_{11}H_{15}F_2NO$ ([M]): 215.11217; Found: 215.11180.

R_f (PE/EtOAc, 10:1) = 0.66 [CAM]



2-((4-fluoro-4-methylpentan-2-yl)oxy)pyrazine (17a) and 6,8,8-trimethyl-7,8-dihydro-6*H*-pyrano[2,3-*b*]pyrazine (17b): Synthesized following **GP3** using cesium 2-((2-methyl-4-(pyrazin-2-yloxy)pentan-2-yl)oxy)-2-oxoacetate (0.20 g, 0.50 mmol, 1.0 equiv.). The reaction was performed twice and the combined crude products purified by column chromatography. The products were isolated as colorless oils in 25% (50 mg, 0.25 mmol) and 56% yield (100 mg, 0.25 mmol) respectively.

2-((4-fluoro-4-methylpentan-2-yl)oxy)pyrazine (17a)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 1.3 Hz, 1H), 8.08 (d, *J* = 2.9 Hz, 1H), 8.06 (dd, *J* = 2.8, 1.4 Hz, 1H), 5.45 (dqd, *J* = 7.8, 6.2, 4.0 Hz, 1H), 2.14 (ddd, *J* = 25.4, 14.9, 7.8 Hz, 1H), 1.94 (td, *J* = 14.9, 4.1 Hz, 1H), 1.41 (d, *J* = 6.5 Hz, 3H), 1.39 – 1.33 (m, 6H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 159.8, 140.8, 136.5, 136.4, 94.7 (d, *J* = 165.6 Hz), 69.2 (d, *J* = 4.6 Hz), 47.3 (d, *J* = 22.7 Hz), 28.5 (d, *J* = 24.5 Hz), 26.3 (d, *J* = 24.9 Hz), 21.1 (d, *J* = 1.4 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ -135.60.

GCMS (FI): [m/z] calculated for $C_{10}H_{15}FN_2O$ ([M]): 198.11684; Found: 198.11724.

R_f (PE/EtOAc, 4:1) = 0.39 [CAM]

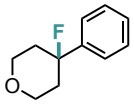
2-((4-fluoro-4-methylpentan-2-yl)oxy)pyrazine (17b)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 2.5 Hz, 1H), 7.98 (d, *J* = 2.5 Hz, 1H), 4.48 (dqd, *J* = 10.5, 6.2, 3.2 Hz, 1H), 1.91 – 1.76 (m, 2H), 1.48 (d, *J* = 6.2 Hz, 3H), 1.38 (s, 3H), 1.36 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 157.0, 147.5, 140.5, 137.2, 70.7 44.5, 34.7, 30.1, 28.4, 21.5.

GCMS (FI): [m/z] calculated for $C_{10}H_{14}N_2O$ ([M]): 178.11061; Found: 178.10993.

R_f (PE/EtOAc, 4:1) = 0.18 [CAM]



4-fluoro-4-phenyltetrahydro-2*H*-pyran (18): Synthesized following **GP3** using cesium 2-oxo-2-((4-phenyltetrahydro-2*H*-pyran-4-yl)oxy)acetate (0.19 g, 0.50 mmol, 1.0 equiv.). The product was isolated as a white solid in 66% yield (60 mg, 0.33 mmol). It was observed that the product decomposes in $CDCl_3$, presumably due to traces of HCl, therefore the NMR spectra were recorded in toluene-d_8.

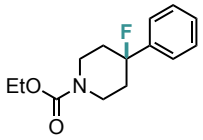
^{1}H NMR (400 MHz, Tol-d_8): δ 7.21 – 7.17 (m, 2H), 7.15 – 7.12 (m, 2H), 7.07 – 7.02 (m, 1H), 3.81 – 3.66 (m, 4H), 1.92 – 1.70 (m, 2H), 1.62 – 1.52 (m, 2H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, Tol-d_8): δ 144.9 (d, *J* = 21.8 Hz), 137.5, 128.5 (d, *J* = 1.0 Hz), 124.2 (d, *J* = 9.0 Hz), 93.5 (d, *J* = 174.9 Hz), 63.7, 37.5 (d, *J* = 23.0 Hz).

$^{19}F\{^{1}H\}$ NMR (376 MHz, Tol-d_8): δ -160.94.

GCMS (FI): [m/z] calculated for $C_{11}H_{13}FO$ ([M]): 180.09504; Found: 180.09244.

R_f (PE/EtOAc, 4:1) = 0.47 [CAM]



Ethyl 4-fluoro-4-phenylpiperidine-1-carboxylate (19): Synthesized following **GP3** using cesium 2-((1-(ethoxycarbonyl)-4-phenylpiperidin-4-yl)oxy)-2-oxoacetate (0.23 g, 0.50 mmol, 1.0 equiv.). The product was isolated as a colorless oil in 73% yield (92 mg, 0.36 mmol).

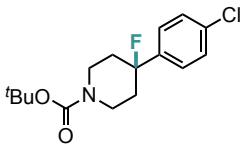
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.33 (m, 4H), 7.36 – 7.28 (m, 1H), 4.18 (m, 4H), 3.29 – 3.19 (m, 2H), 2.13 – 1.88 (m, 4H), 1.29 (t, *J* = 7.1 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 155.7, 144.1 (d, *J* = 21.4 Hz), 128.6 (d, *J* = 1.2 Hz), 127.9 (d, *J* = 1.4 Hz), 124.0 (d, *J* = 9.2 Hz), 94.3 (d, *J* = 174.8 Hz), 61.6, 40.0 (d, *J* = 2.1 Hz), 36.7 (d, *J* = 22.9 Hz), 14.9.

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ -162.66.

GCMS (FI): [m/z] calculated for $C_{14}H_{18}NO_2F$ ([M]): 251.13216; Found: 251.13094.

R_f (PE/EtOAc, 4:1) = 0.50 [CAM]



***tert*-butyl 4-(4-chlorophenyl)-4-fluoropiperidine-1-carboxylate (20):** Synthesized following **GP3** using cesium 2-((1-(*tert*-butoxycarbonyl)-4-(4-chlorophenyl)piperidin-4-yl)oxy)-2-oxoacetate (0.26 g, 0.50 mmol, 1.0 equiv.). The reaction was performed twice and the combined crude products purified by column chromatography. The product was isolated as a colorless oil in 64% yield (0.21 g, 0.64 mmol).

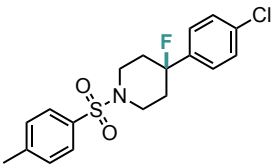
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.32 (m, 2H), 7.32 – 7.27 (m, 2H), 4.20 – 4.04 (m, 2H), 3.16 (t, *J* = 12.2 Hz, 2H), 2.08 – 1.83 (m, 4H), 1.49 (s, 9H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 154.9, 142.7 (d, *J* = 22.1 Hz), 133.8, 128.8, 125.5 (d, *J* = 9.2 Hz), 94.1 (d, *J* = 175.3 Hz), 80.0, 39.8, 36.66 (d, *J* = 22.5 Hz), 28.6.

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ -162.50.

GCMS (FI): [m/z] calculated for $C_{16}H_{21}ClFNO_2$ ([M]): 313.12448; Found: 313.12968.

R_f (PE/EtOAc, 10:1) = 0.35 [CAM]



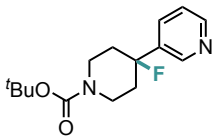
4-(4-chlorophenyl)-4-fluoro-1-tosylpiperidine (21): Synthesized following **GP3** using cesium 2-((4-(4-chlorophenyl)-1-tosylpiperidin-4-yl)oxy)-2-oxoacetate (0.28 g, 0.50 mmol, 1.0 equiv.). The product was isolated as a white solid in 52% yield (95 mg, 0.26 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (m, 2H), 7.40 – 7.31 (m, 4H), 7.26 (m, 2H), 3.82 (ddt, *J* = 11.9, 4.8, 1.9 Hz, 2H), 2.69 (td, *J* = 12.2, 2.7 Hz, 2H), 2.46 (s, 3H), 2.16 (dtd, *J* = 39.5, 13.5, 13.0, 5.1 Hz, 2H), 2.05 – 1.95 (m, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 143.9, 133.4, 129.9, 128.9, 127.9, 125.4 (d, *J* = 9.4 Hz), 93.1 (d, *J* = 176.1 Hz), 42.4 (d, *J* = 1.6 Hz), 36.4 (d, *J* = 22.5 Hz), 21.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -162.17 (tt, J_{H-F} = 39.7, 10.2 Hz).

R_f (Cyclohexane/EtOAc, 4:1) = 0.5 [CAM]



***tert*-butyl 4-fluoro-4-(pyridin-3-yl)piperidine-1-carboxylate (22):** Synthesized following **GP3** using cesium 2-((1-(*tert*-butoxycarbonyl)-4-(pyridin-3-yl)piperidin-4-yl)oxy)-2-oxoacetate (0.24 g, 0.50 mmol, 1.0 equiv.). The product was isolated as a colorless oil in 52% yield (73.5 mg, 0.26 mmol).

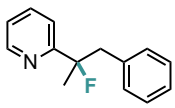
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.63 (d, *J* = 2.4 Hz, 1H), 8.56 (dd, *J* = 4.9, 1.6 Hz, 1H), 7.69 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.31 (dd, *J* = 8.0, 4.8 Hz, 1H), 4.16 – 4.12 (m, 2H), 3.17 (s, 2H), 2.03 – 1.86 (m, 4H), 1.48 (s, 9H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 154.83, 149.21, 145.85 (d, *J* = 9.2 Hz), 139.57 (d, *J* = 21.6 Hz), 131.98 (d, *J* = 9.6 Hz), 123.42, 93.32 (d, *J* = 175.8 Hz), 80.06, 39.92, 39.47, 36.61, 36.47, 28.58.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ -164.27.

GCMS (FI): [m/z] calculated for $C_{15}H_{21}FN_2O_2$ ([M]): 280.15871; Found: 280.16511.

R_f (EtOAc) = 0.35 [CAM]



2-(2-fluoro-1-phenylpropan-2-yl)pyridine (23): Synthesized following **GP3** using cesium 2-oxo-2-((1-phenyl-2-(pyridin-2-yl)propan-2-yl)oxy)acetate (0.21 g, 0.50 mmol, 1.0 equiv.). The product was isolated as a colorless oil in 15% yield (15 mg, 0.07 mmol).

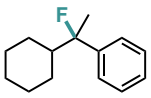
^{1}H NMR (400 MHz, $CDCl_3$):δ 8.61 (ddt, *J* = 4.8, 1.9, 1.0 Hz, 1H), 7.62 (td, *J* = 7.7, 1.8 Hz, 1H), 7.35 (ddt, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.23 – 7.19 (m, 3H), 7.19 – 7.16 (m, 1H), 7.08 (ddd, *J* = 6.4, 2.4, 1.1 Hz, 2H), 3.43 – 3.24 (m, 2H), 1.72 (d, *J* = 22.4 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 163.06 (d, J_{C-F} = 27.2 Hz), 148.7 (d, J_{C-F} = 2.6 Hz), 136.6 (d, J_{C-F} = 2.0 Hz), 136.3, 130.7, 127.9, 126.6, 122.2, 119.2 (d, J_{C-F} = 10.7 Hz), 99.29 (d, J_{C-F} = 171.4 Hz), 46.9 (d, J_{C-F} = 21.8 Hz), 26.0 (d, J_{C-F} = 23.8 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -153.90.

GCMS (FI): [m/z] calculated for $C_{14}H_{14}NF$ ([M]): 215.11103; Found: 215.11435.

R_f (PE/EtOAc, 4:1) = 0.39 [CAM]



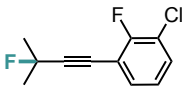
(**1-cyclohexyl-1-fluoroethyl)benzene (24):** Synthesized following **GP3** using cesium 2-(1-cyclohexyl-1-phenylethoxy)-2-oxoacetate (0.20 g, 0.50 mmol, 1.0 equiv.). The product was isolated as a colorless oil in 48% yield (50 mg, 0.24 mmol). It was observed that the product decomposes in $CDCl_3$, presumably due to traces of HCl, therefore the NMR spectra were recorded in acetone-d_6.

^{1}H NMR (400 MHz, Acetone-d_6): δ 7.39 – 7.31 (m, 4H), 7.30 – 7.23 (m, 1H), 1.85 – 1.61 (m, 4H), 1.59 (s, 3H), 1.29 – 0.96 (m, 5H).

^{13}C{^{1}H} NMR (101 MHz, Acetone-d_6): δ 145.6 (d, *J* = 21.9 Hz), 128.7 (d, *J* = 1.7 Hz), 127.8 (d, *J* = 1.2 Hz), 125.5 (d, *J* = 10.0 Hz), 100.0 (d, *J* = 173.8 Hz), 48.6 (d, *J* = 23.2 Hz), 28.0 (d, *J* = 4.5 Hz), 27.6 (d, *J* = 4.5 Hz), 27.1 (d, *J* = 3.5 Hz), 27.0, 24.6, 24.4.

^{19}F{^{1}H} NMR (376 MHz, Acetone-d_6): δ -154.19.

R_f (PE/EtOAc, 10:1) = 0.62 [CAM]



1-chloro-2-fluoro-3-(3-fluoro-3-methylbut-1-yn-1-yl)benzene (25): Synthesized following **GP3** using 4-(3-chloro-2-fluorophenyl)-2-methylbut-3-yn-2-yl ethyl oxalate (0.21 g, 0.50 mmol, 1.0 equiv.). The reaction was performed twice and the combined crude products purified by column chromatography. The product was isolated as a colorless oil in 25% yield (55.0 mg, 0.25 mmol).

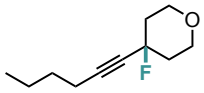
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.29 (m, 2H), 7.04 (td, *J* = 7.9, 1.2 Hz, 1H), 1.78 (s, 3H), 1.73 (s, 3H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 158.6 (d, *J* = 252.2 Hz), 131.9 (d, *J* = 2.6 Hz), 131.3, 124.44 (d, *J* = 5.0 Hz), 121.7 (d, *J* = 17.3 Hz), 112.6 (d, *J* = 19.1 Hz), 95.8 (d, *J* = 29.7 Hz), 87.6 (d, *J* = 165.2 Hz), 77.6 (d, *J* = 8.9 Hz), 29.4, 29.11.

$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ -111.45 (d, *J* = 1.6 Hz), -127.20 (d, *J* = 1.1 Hz).

GCMS (FI): [m/z] calculated for $C_{11}H_9ClF_2$ ([M]): 214.03608; Found: 214.03409.

R_f (PE/EtOAc, 4:1) = 0.52 [CAM]



4-fluoro-4-(hex-1-yn-1-yl)tetrahydro-2*H*-pyran (26): Synthesized following **GP3** using cesium 2-((4-(hex-1-yn-1-yl)tetrahydro-2*H*-pyran-4-yl)oxy)-2-oxoacetate (0.19 g, 0.50 mmol, 1.0 equiv.). The product was isolated as a colorless oil in 23% yield (21.0 mg, 0.11 mmol). It was observed that the product decomposes in $CDCl_3$, presumably due to traces of HCl, therefore the NMR spectra were recorded in toluene-d_8.

^{1}H NMR (400 MHz, Tol-d_8): δ 3.71 – 3.62 (m, 2H), 3.51 (ddd, *J* = 12.0, 6.0, 4.7 Hz, 2H), 1.96 (td, *J* = 6.9, 5.8 Hz, 2H), 1.89 – 1.79 (m, 4H), 1.39 – 1.17 (m, 4H), 0.82 – 0.72 (m, 3H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, Tol-d_8): δ 137.47, 88.08 (d, *J* = 9.3 Hz), 87.09 (d, *J* = 172.2 Hz), 80.14 (d, *J* = 30.3 Hz), 38.73 (d, *J* = 22.6 Hz), 30.82 (d, *J* = 2.3 Hz), 22.18, 18.42 (d, *J* = 2.7 Hz), 13.60.

$^{19}F\{^{1}H\}$ NMR (376 MHz, Tol-d_8): δ -135.98 (bs).

GCMS (FI): [m/z] calculated for $C_{11}H_{17}OF$ ([M]): 184.12634; Found: 184.12814.

R_f (PE/EtOAc, 4:1) = 0.62 [CAM]

6.3.4. Determination of enantiomeric purity

100 mg (0.35 mmol) of **14** were stirred in a 1:1 mixture of TFA/CH_2Cl_2 (1 mL, 0.35 M) and the reaction monitored by TLC. After ~ 2 h, the reaction was quenched with a saturated solution of K_2HCO_3 (5 mL) and the organic phase extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent evaporated. The ^{1}H NMR of the crude product showed clean **14a** (63%, 40 mg, 0.22 mmol). Next, in an NMR tube, the crude product (25 mg, 0.13 mmol, 1.0 equiv.) was reacted with (R)-(+)-MTPA-Cl (28 µL, 0.11 mmol, 1.1 equiv.) and Et_3N (15 µL, 0.11 mmol, 1.1 equiv.) in CD_3CN. After 20 min the ^{19}F NMR of the reaction showed formation of only diastereoisomer of the desired Mosher's amide **14b**, thus supporting that the deoxyfluorination reaction proceeds with stereoretention on the α-amino stereocenter.

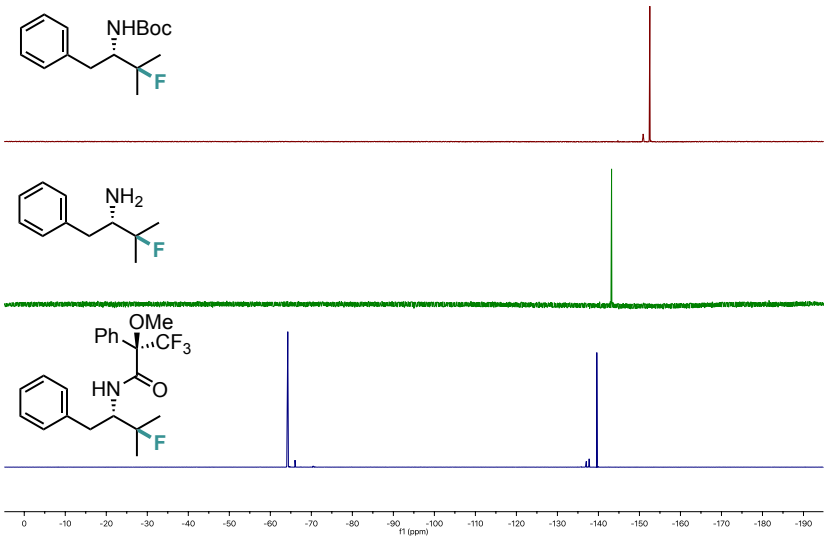


Figure S1. ^{19}F NMR spectra of 14, 14a and 14b.

6.3.5. Competition experiments

Tertiary vs primary & secondary oxalates: A 4 mL vial was charged with **1** (37 mg, 0.10 mmol, 1 equiv.), Selectfluor® (88 mg, 0.25 mmol, 2.5 equiv.) and 0.1 mmol (1.0 equiv.) of the corresponding primary or secondary oxalate, and sealed with a septum cap. The vial was put under vacuum for 5 min and refilled with N_2. Afterwards, degassed H_2O (0.50 mL) and acetone (0.50 mL) were added subsequently. The reaction mixture was then sparged with N_2 for 2-5 min and irradiated with blue LEDs (λ_{max} = 440 nm) for 1 h. Afterwards, the reaction was diluted with EtOAc (1 mL) and trifluorotoluene (12.5 µL, 0.1 mmol, 1.0 equiv.) were added. The organic phase was transferred to an NMR tube containing $CDCl_3$ (0.2 mL) and the ^{19}F NMR of the mixture was recorded with a relaxation time of 20 sec, to accurately calculate the yield.

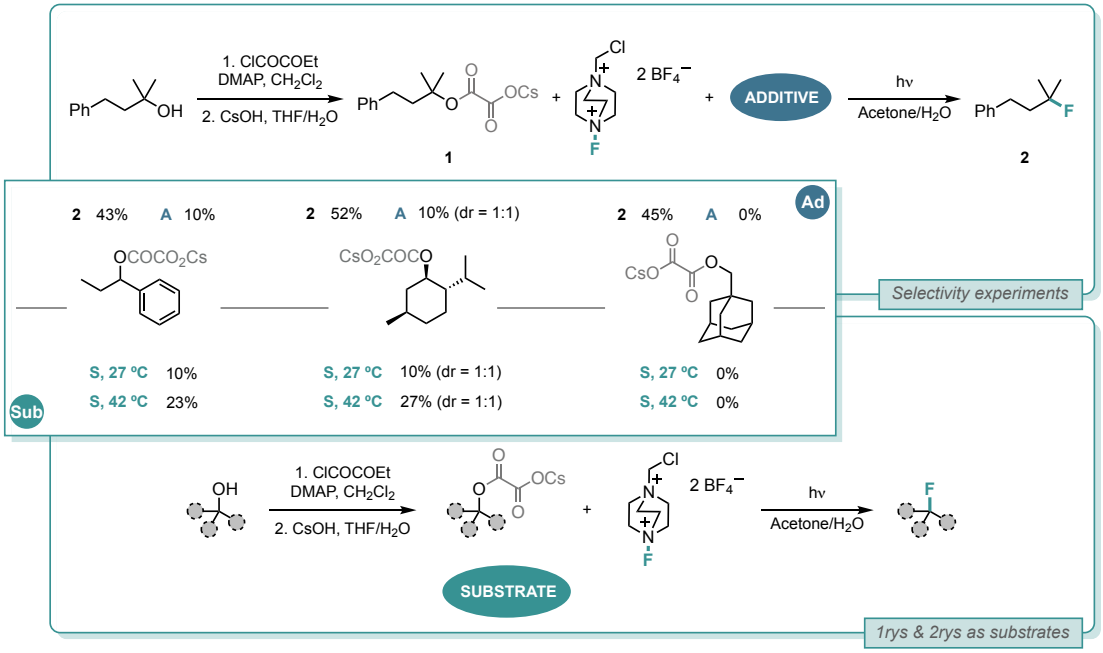


Figure S2. Selectivity studies.

Reaction with primary and secondary oxalates in isolation: A 4 mL vial was charged with the corresponding oxalate (0.10 mmol, 1 equiv.), Selectfluor® (88 mg, 0.25 mmol, 2.5 equiv.) and sealed with a septum cap. The vial was put under vacuum for 5 min and refilled with N_2. Afterwards, degassed H_2O (0.50 mL) and acetone (0.50 mL) were added subsequently. The reaction mixture was then sparged with N_2 for 2-5 min and irradiated with blue LEDs (λ_{max} = 440 nm) for 1 h. Afterwards, the reaction was diluted with EtOAc (1 mL) and trifluorotoluene (12.5 µL, 0.1 mmol, 1.0 equiv.) were added. The organic phase was transferred to an NMR tube containing $CDCl_3$ (0.2 mL) and the ^{19}F NMR of the mixture was recorded with a relaxation time of 20 sec, to accurately calculate the yield. For the reactions at 42 °C the fan of the EvoluChem™ PhotoRedOx Box was turn off.

6.3.6. Reactions in presence of TEMPO

A 4 mL vial was charged with **1** (37 mg, 0.10 mmol, 1 equiv.), Selectfluor® (88 mg, 0.25 mmol, 2.5 equiv.) and TEMPO (0.1 or 0.3 mmol, 1.0 or 3.0 equiv.) and then sealed with a septum cap. The vial was put under vacuum for 5 min and refilled with N_2. Afterwards, degassed H_2O (0.50 mL) and acetone (0.50 mL) were added subsequently. The reaction mixture was then sparged with N_2 for 2-5 min and irradiated with blue LEDs (λ_{max} = 440 nm) for 1 h. Afterwards, the reaction was diluted with EtOAc (1 mL) and trifluorotoluene (12.5 µL, 0.1 mmol, 1.0 equiv.) were added. The organic phase was transferred to an NMR tube containing $CDCl_3$ (0.2 mL) and the ^{19}F NMR of the mixture was recorded with a relaxation time of 20 sec, to accurately calculate the yield. No product formation was observed in both experiments.

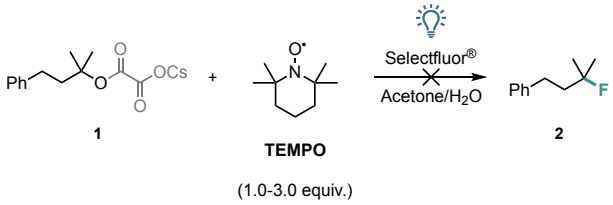


Figure S3. Scheme of reaction in the presence of TEMPO

6.3.7. UV/Vis absorption spectra

UV/vis absorption spectra were recorded using a Mettler Toledo UV5 spectrophotometer. The samples were measured in UV quartz cuvettes (chamber volume = 1.4 mL, H × W × D = 46 mm × 12.5 mm, 12.5 mm) fitted with a PTFE stopper. Stock solutions of oxalate **1** and Selectfluor®, were prepared with the same concentration used in the reaction in the presence of air using 1,4-dioxane/H_2O (1:1). as solvent.

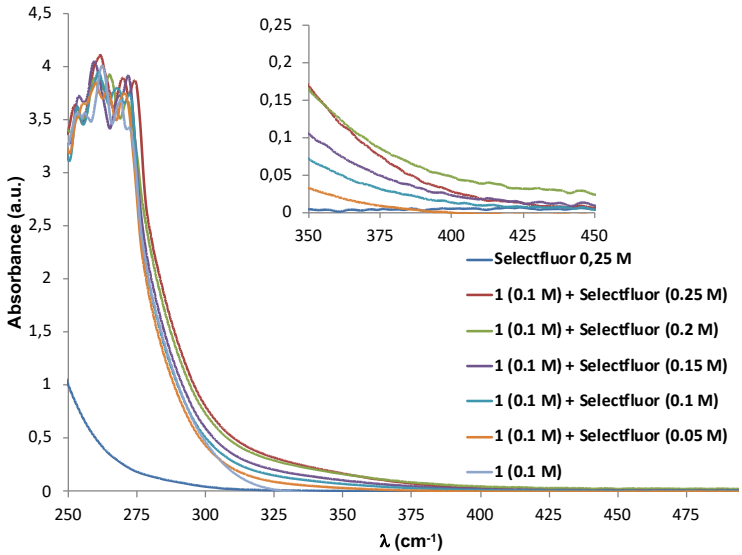


Figure S4. UV/Vis absorption spectra at different concentrations of Selectfluor®

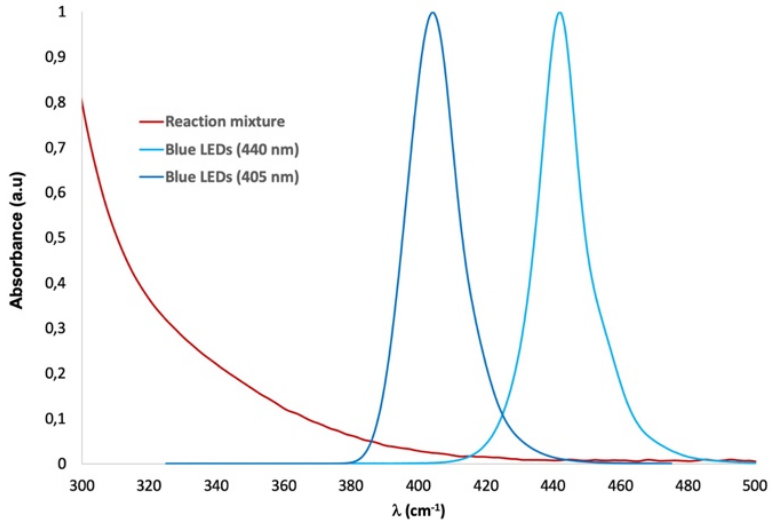


Figure S5. Overlap between the absorption spectra of the reaction mixture and the emission spectra of blue LEDs of λ_{max} = 405 and 440 nm.

6.1.1. *Influence of light source*

The influence of the wavelength of irradiation over the reaction was investigated by irradiating the reaction mixture with blue LEDs of λ_{max} = 365, 405 and 440 nm. 4 independent reactions were performed under the standard reaction conditions – **1** (0.1 mmol), Selectfluor® (0.25 mmol), acetone (0.5 mL), water (0.5 mL) – and stopped at regular intervals, i.e., 1, 5, 10 and 20 min reaction time. Once the reactions were stopped, EtOAc (1 mL) and trifluorotoluene (12.5 µL, 0.1 mmol) were added and the reaction yield measured by ^{19}F NMR with a relaxation time of 20 sec.

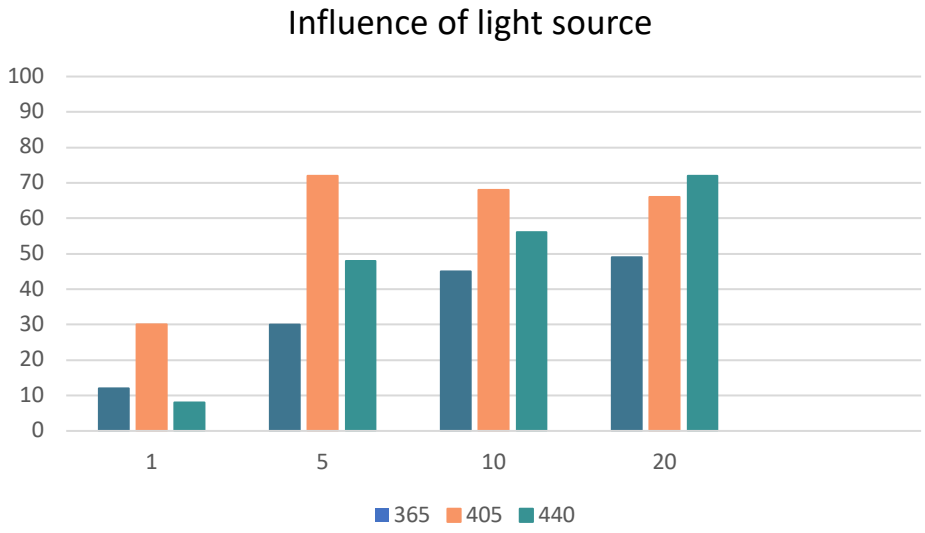


Figure S6. Influence of the wavelength of irradiation on the reaction

6.3.8. *Light ON/OFF Experiments*

The reaction was carried out in an NMR tube using **1** (37 mg, 0.10 mmol, 1.0 equiv.), Selectfluor® (88 mg, 0.25 mmol, 2.5 equiv.) in a dry and degassed acetone-d_6/D_2O mixture (1 mL, 1:1, 0.1 M). The NMR was irradiated with an 18 W blue LED (λ_{max} = 405 nm). The experiment shows that without irradiation, the reaction does not proceed.

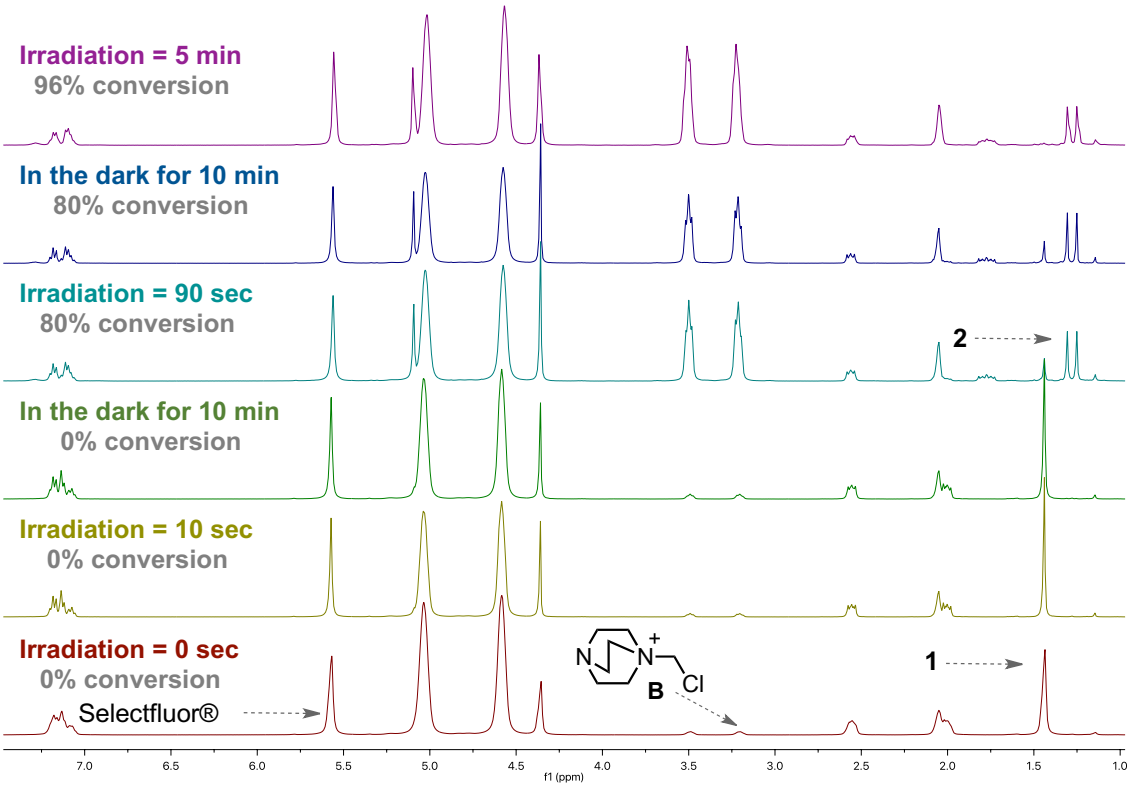


Figure S7. Light ON/OFF experiments with irradiation from 18 W blue LED (λ_{max} = 405 nm).

6.1.2. *Quantum yield determination*

According to the procedure of Yoon,[125] the photon flux of the LED (λ_{max} = 440 nm) was determined by standard ferrioxalate actinometry.[260,261] A 0.15 M solution of ferrioxalate was prepared by dissolving potassium ferrioxalate trihydrate (0.73 g) in H_2SO_4 (10 mL of a 0.05 M solution). A buffered solution of 1,10-phenanthroline was prepared by dissolving 1,10-phenanthroline (25 mg) and sodium acetate (5.6 g) in H_2SO_4 (25 mL of a 0.50 M solution). Both solutions were stored in the dark. To determine the photon flux of the LED, the ferrioxalate solution (1.0 mL) was placed in a cuvette and irradiated for 70 seconds at λ_{max} = 440 nm. After irradiation, the phenanthroline solution (175 µL) was added to the cuvette and the mixture was allowed to stir in the dark for 1.0 h to allow the ferrous ions to completely coordinate to the phenanthroline. The absorbance of the solution was measured at 510 nm. A non-irradiated sample was also prepared and the absorbance at 510 nm was measured. Conversion was calculated using eq. 1.

$$\text{mol Fe}^{2+} = \frac{V \bullet \Delta A(510\ \text{nm})}{l \bullet \varepsilon} \quad \text{(eq. 3)}$$

where V is the total volume (0.001175 L) of the solution after addition of phenanthroline, ΔA is the difference in absorbance at 510 nm between the irradiated and non-irradiated solutions, l is the path length (1.00 cm), and ε is the molar absorptivity of the ferrioxalate actinometer at 510 nm (11,100 $Lmol^{-1}cm^{-1}$). With this data, the photon flux can be calculated using eq. 2.

$$\text{Photon flux} = \frac{\text{mol } Fe^{2+}}{\Phi \bullet t \bullet f} \quad \text{(eq. 4)}$$

where Φ is the quantum yield for the ferrioxalate actinometer (1.01 at λ_{ex} = 437 nm),[260] t is the irradiation time (70 s), and f is the fraction of light absorbed at λ_{ex} = 437 nm by the ferrioxalate actinometer. This value is calculated using eq. 3 where A (440 nm) is the absorbance of the ferrioxalate solution at 440 nm. An absorption spectrum gave an A (440 nm) value of > 3, indicating that the fraction of absorbed light (f) is > 0.999.

$$f = 1 - 10^{A(440\ nm)} \quad \text{(eq. 5)}$$

The photon flux was thus calculated (average of three experiments) to be 3.15 x 10^{-09} einsteins s^{-1}

Determination of the reaction quantum yield

A reaction under the standard conditions using **1** (37 mg, 0.1 mmol, 1 equiv.) and Selectfluor® (88 mg, 0.25 mmol, 2.5 equiv.) was irradiated at 440 nm for 60 sec. Afterwards, the reaction was diluted with EtOAc (1 mL) and trifluorotoluene (12.5 µL, 0.1 mmol, 1.0 equiv.) were added. The organic phase was transferred to an NMR tube containing $CDCl_3$ (0.2 mL) and the ^{19}F NMR of the mixture was recorded with a relaxation time of 20 sec, to accurately calculate the yield. This afforded **2** in 8% yield (8 x 10^{-6} mol). The reaction quantum yield (Φ) was determined using eq. 4 where the photon flux is 3.15 x 10^{-09} einsteins s^{-1} (determined by actinometry as described above), t is the reaction time (60 s) and f is the fraction of incident light absorbed by the reaction mixture, determined using eq. 3. An absorption spectrum of the reaction mixture gave an absorbance value of 0.00847 at 437 nm, thus f is 0.0193.

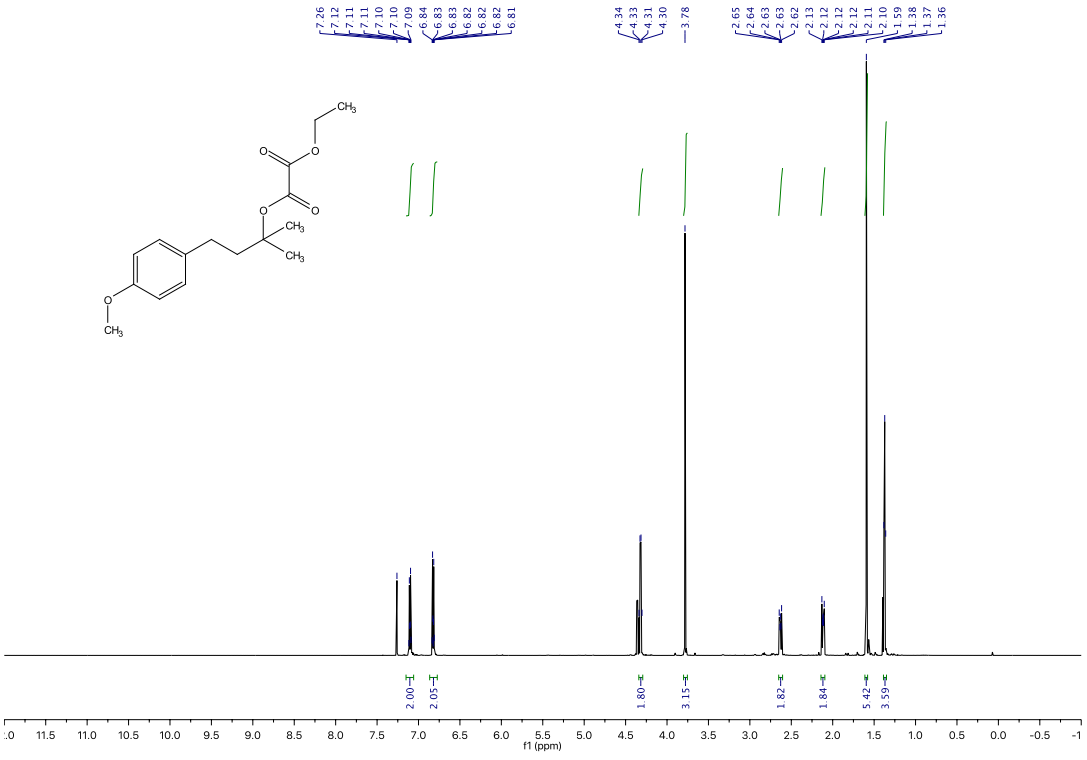
$$\Phi = \frac{\text{mol of product formed}}{\text{Photon flux} \bullet t \bullet f} \quad \text{(eq. 6)}$$

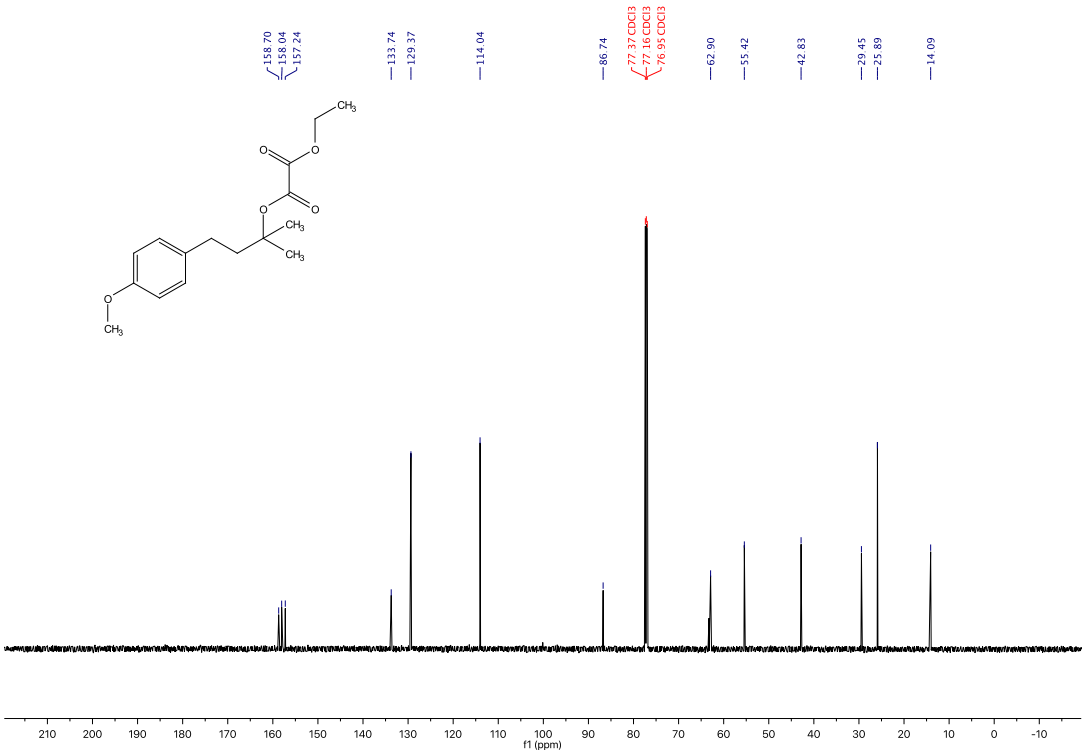
The reaction quantum yield (Φ) was thus determined to be 2185.4.

6.3.9. ^{1}H, ^{13}C and ^{19}F NMR Spectra

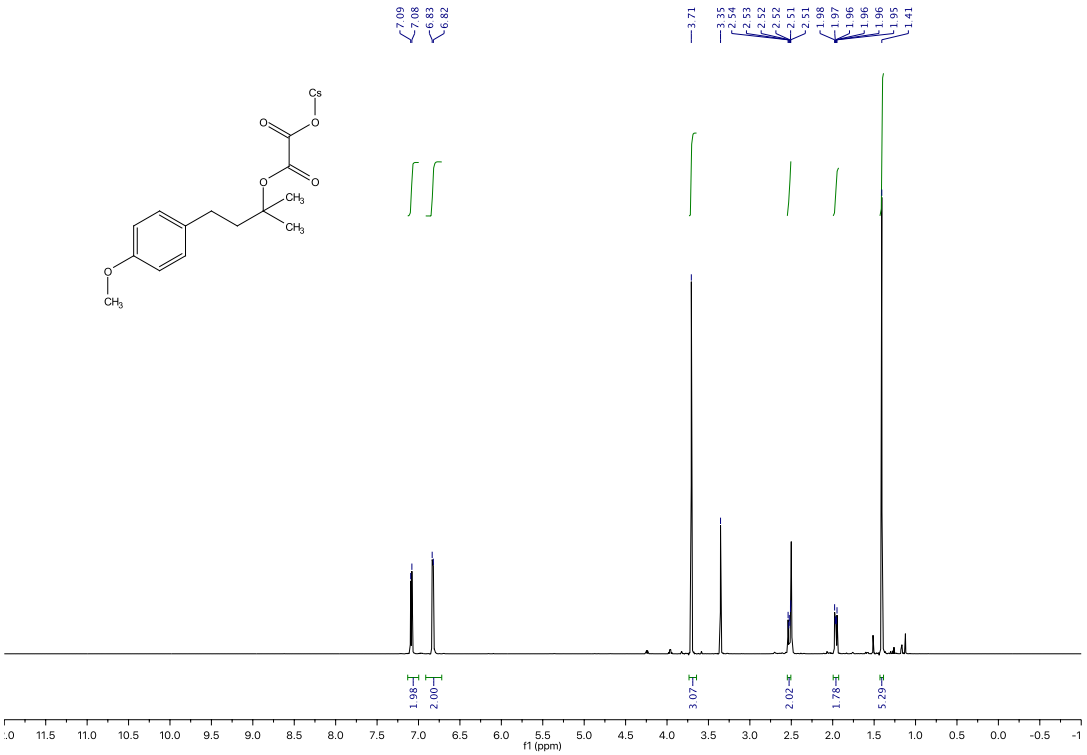
6.3.9.1. Starting materials

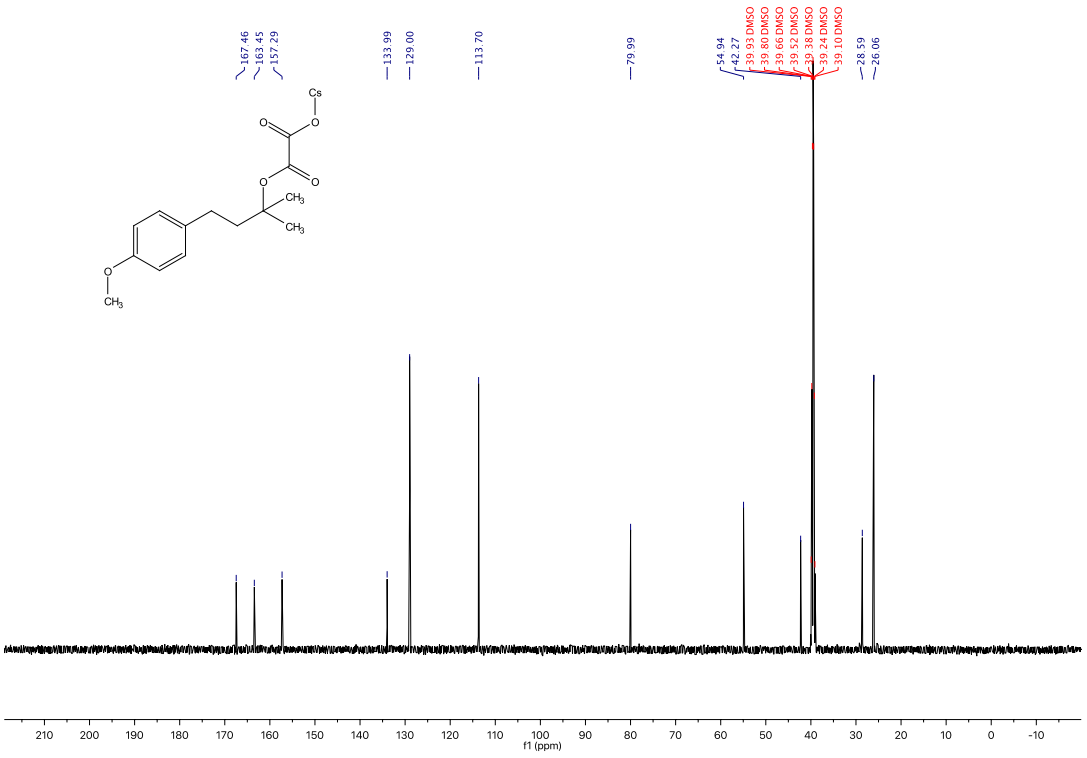
Ethyl (4-(4-methoxyphenyl)-2-methylbutan-2-yl) oxalate



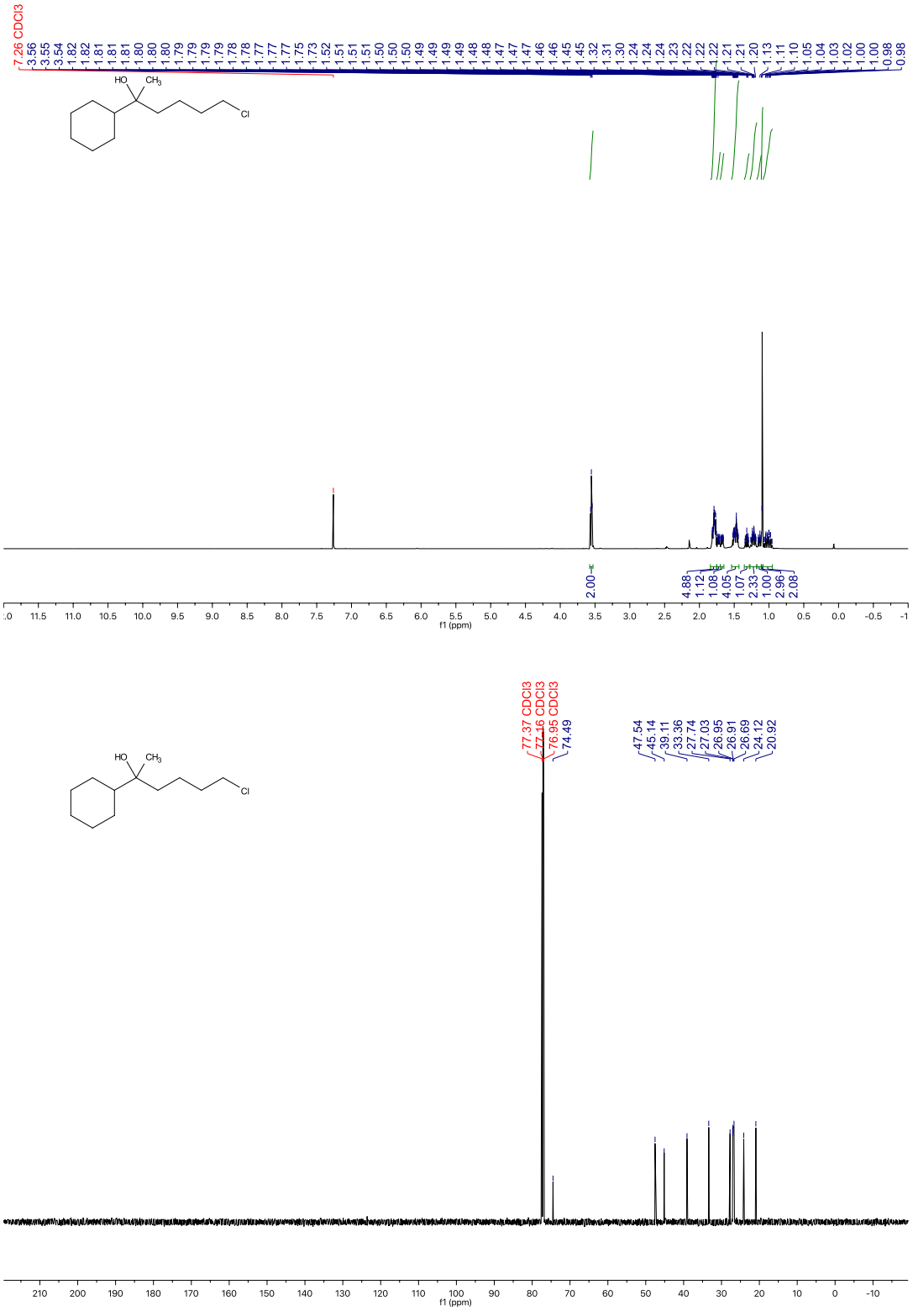


Cesium 2-((4-(4-methoxyphenyl)-2-methylbutan-2-yl)oxy)-2-oxoacetate

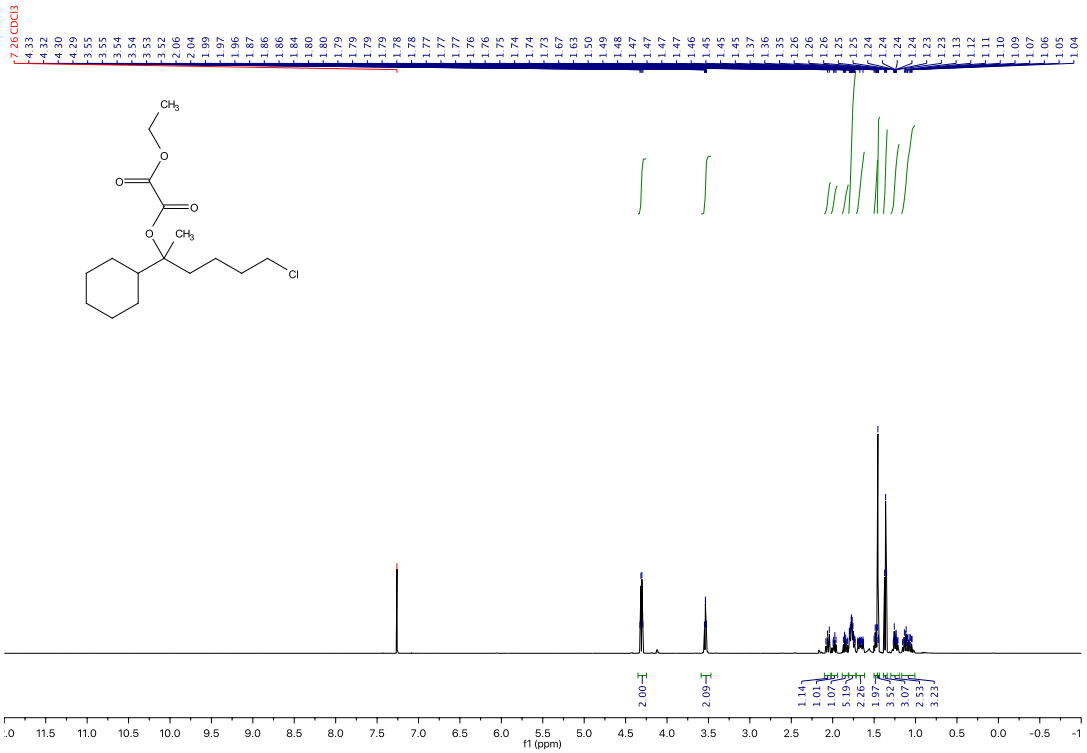


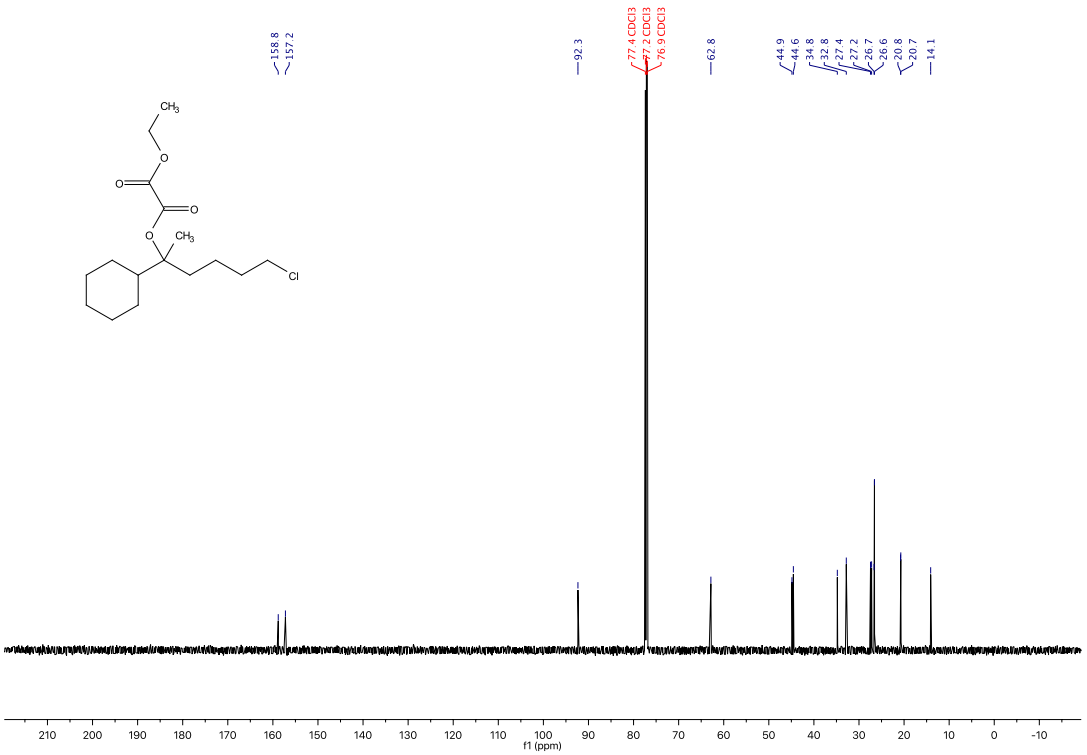


6-chloro-2-cyclohexylhexan-2-ol

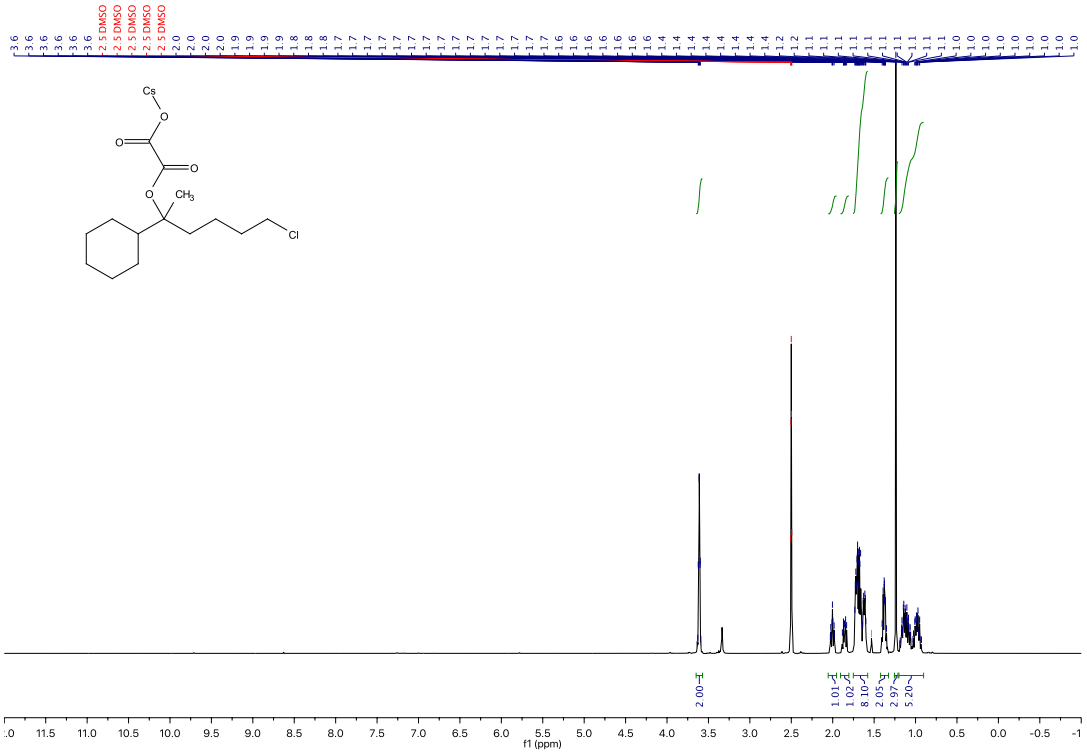


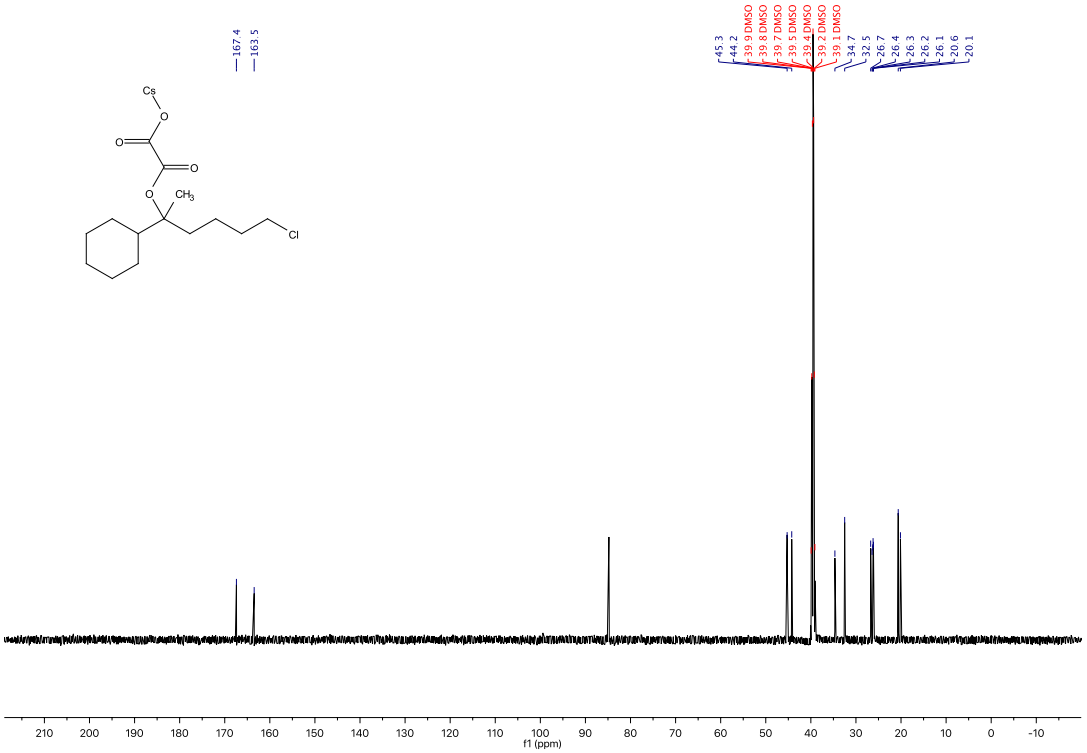
6-chloro-2-cyclohexylhexan-2-yl ethyl oxalate



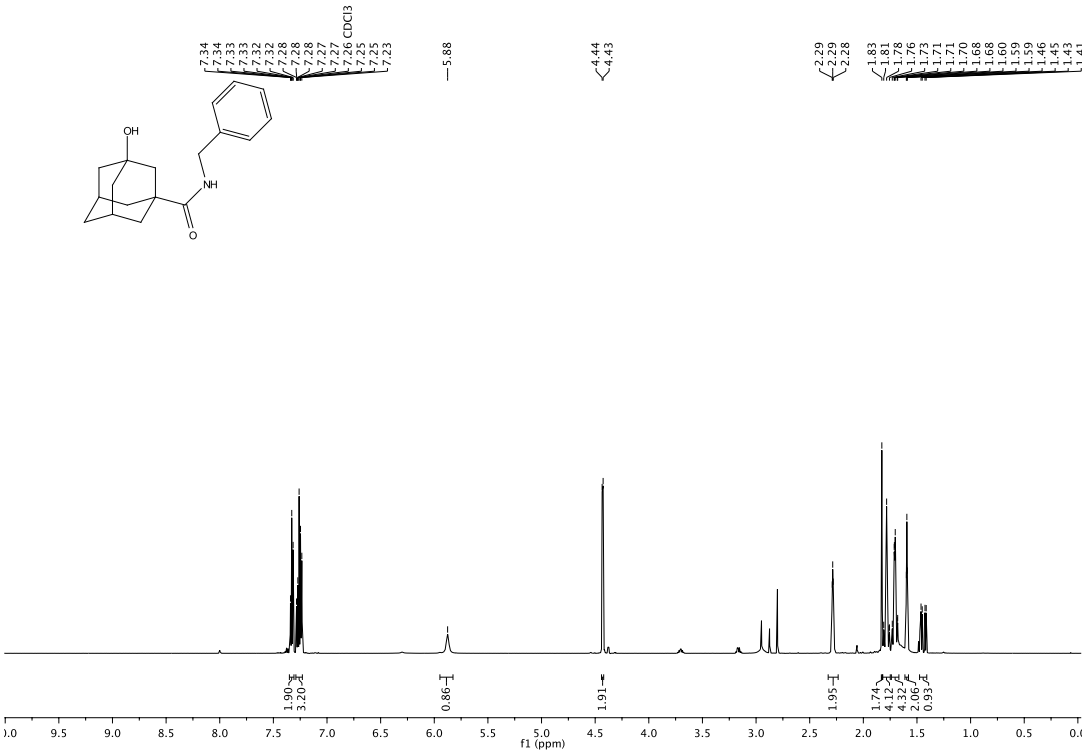


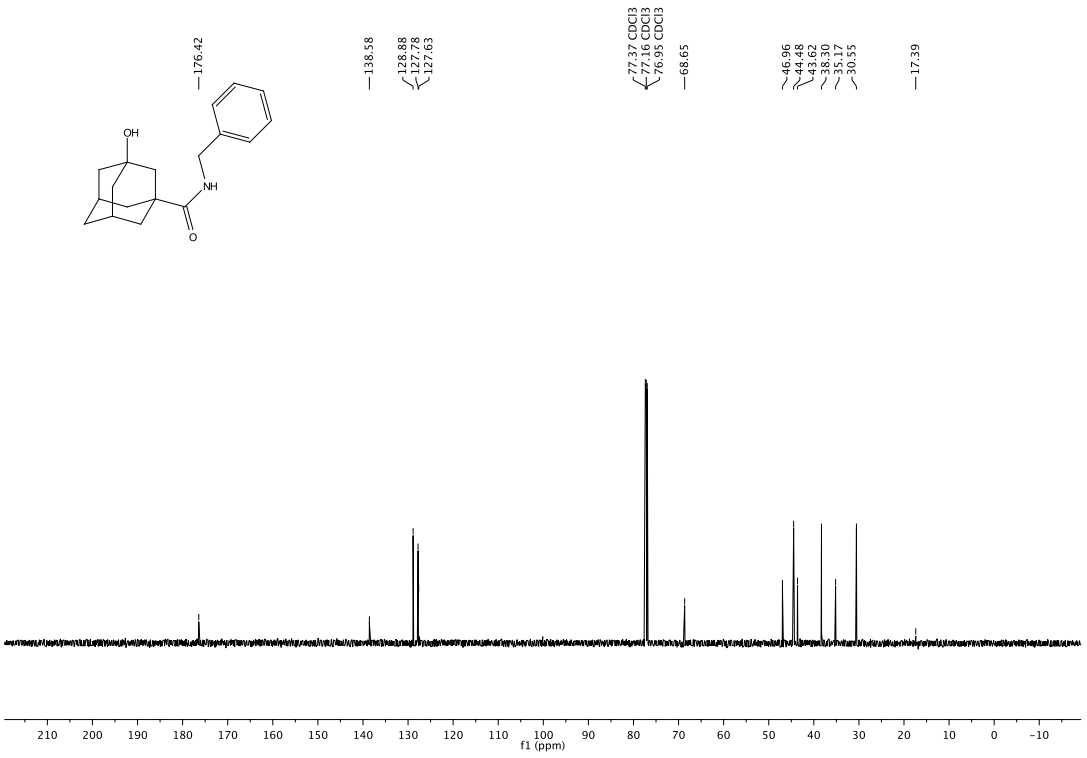
Cesium 2-((6-chloro-2-cyclohexylhexan-2-yl)oxy)-2-oxoacetate



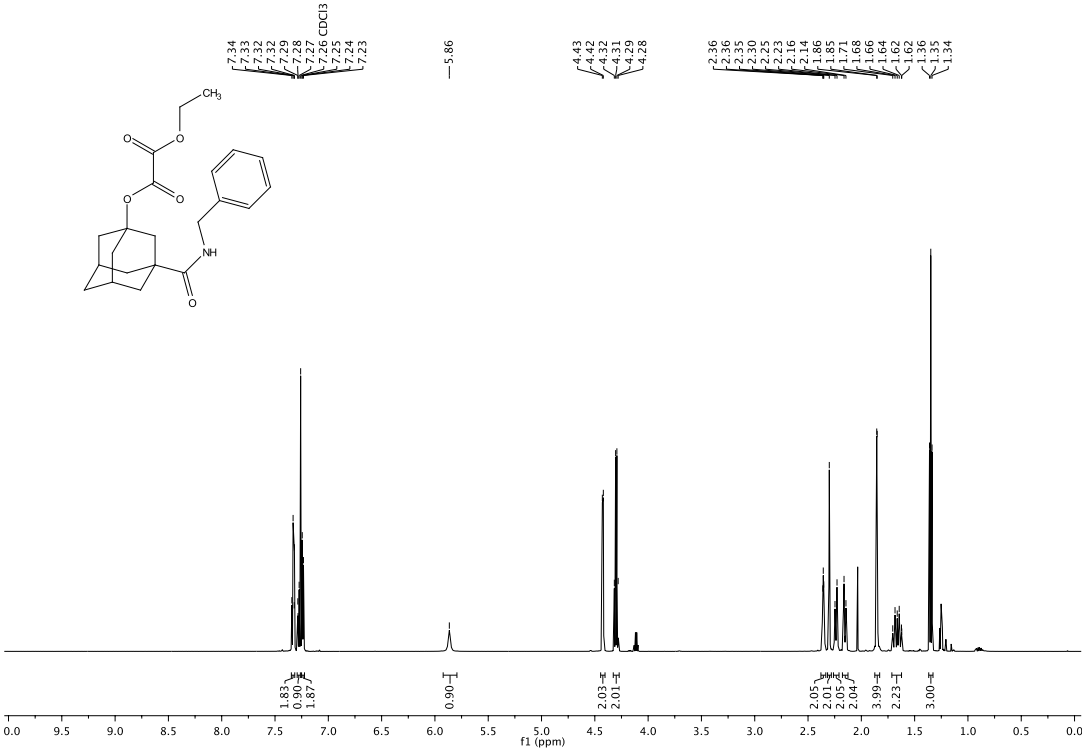


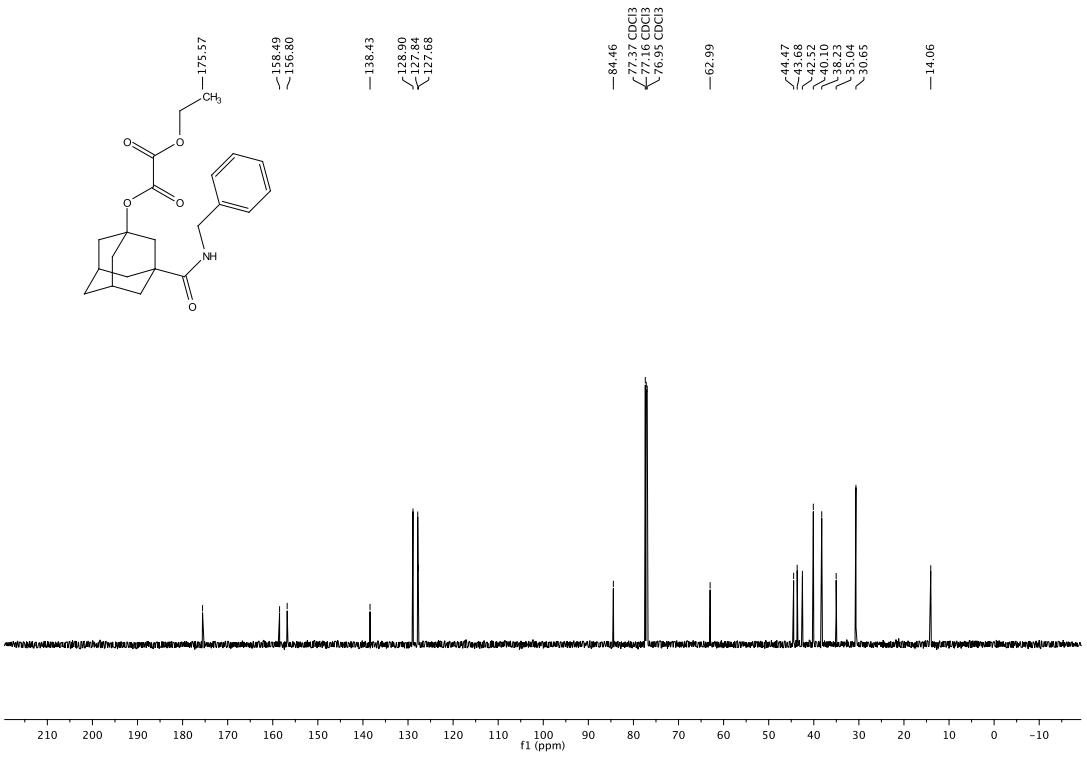
_N_-benzyl-3-hydroxyadamantane-1-carboxamide



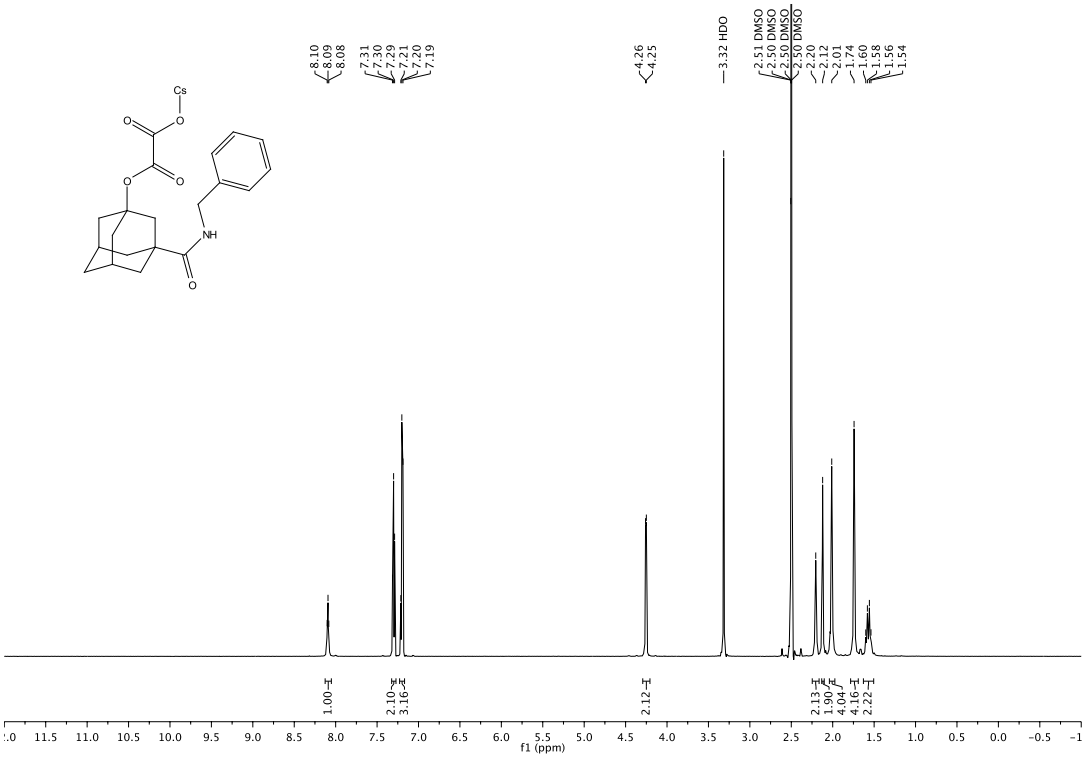


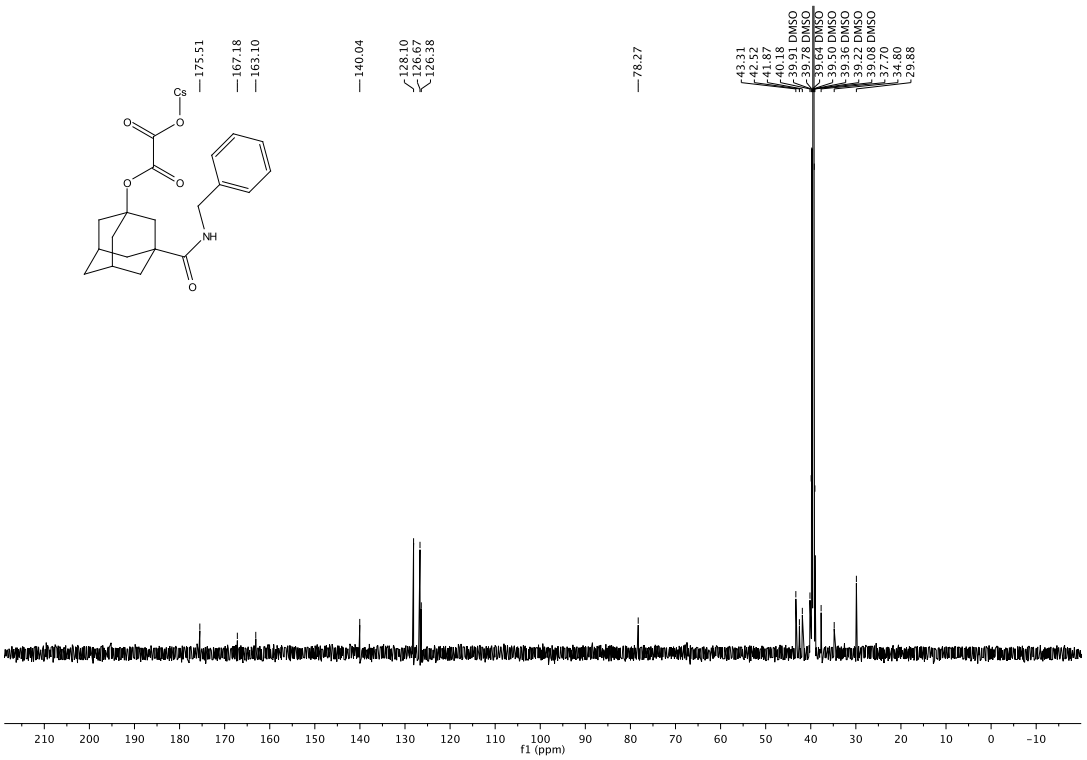
3-(benzylcarbamoyl)adamantan-1-yl ethyl oxalate



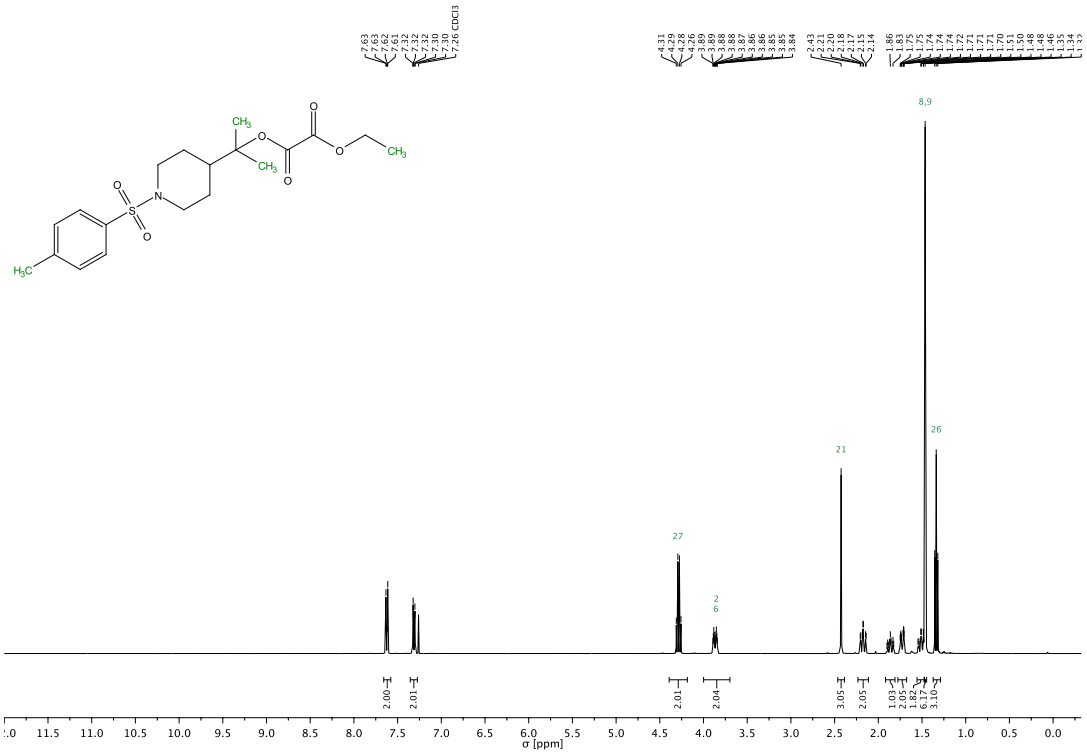


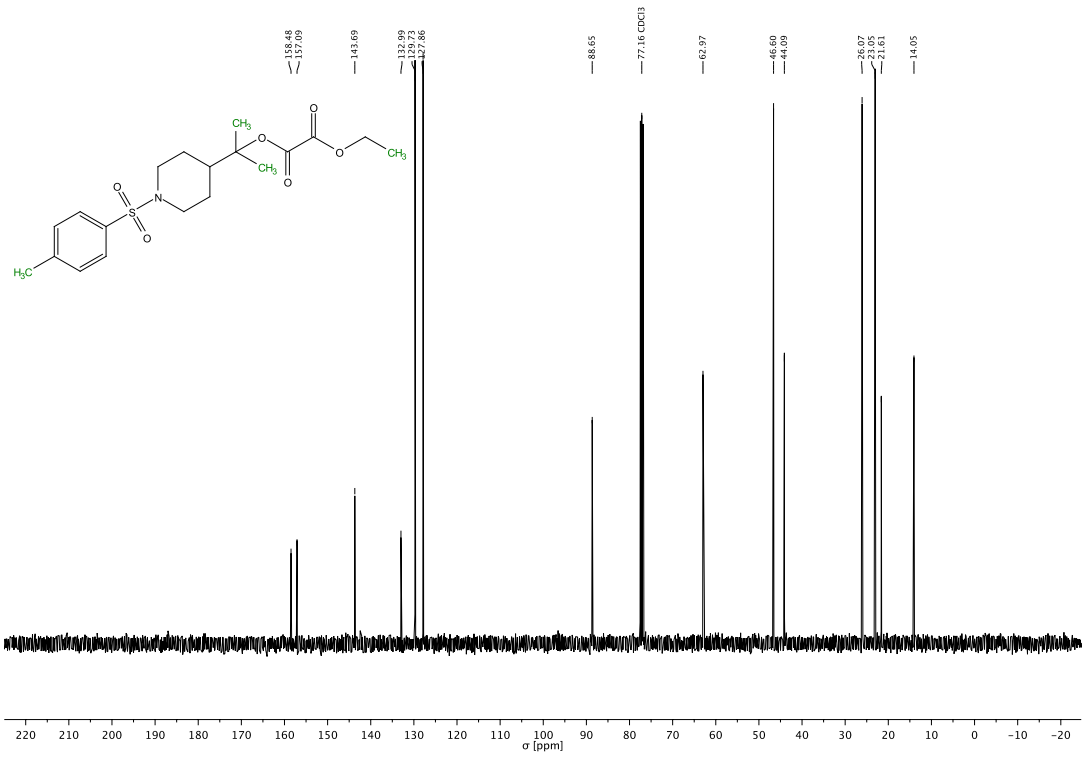
Cesium 2-((3-(benzylcarbamoyl)adamantan-1-yl)oxy)-2-oxoacetate



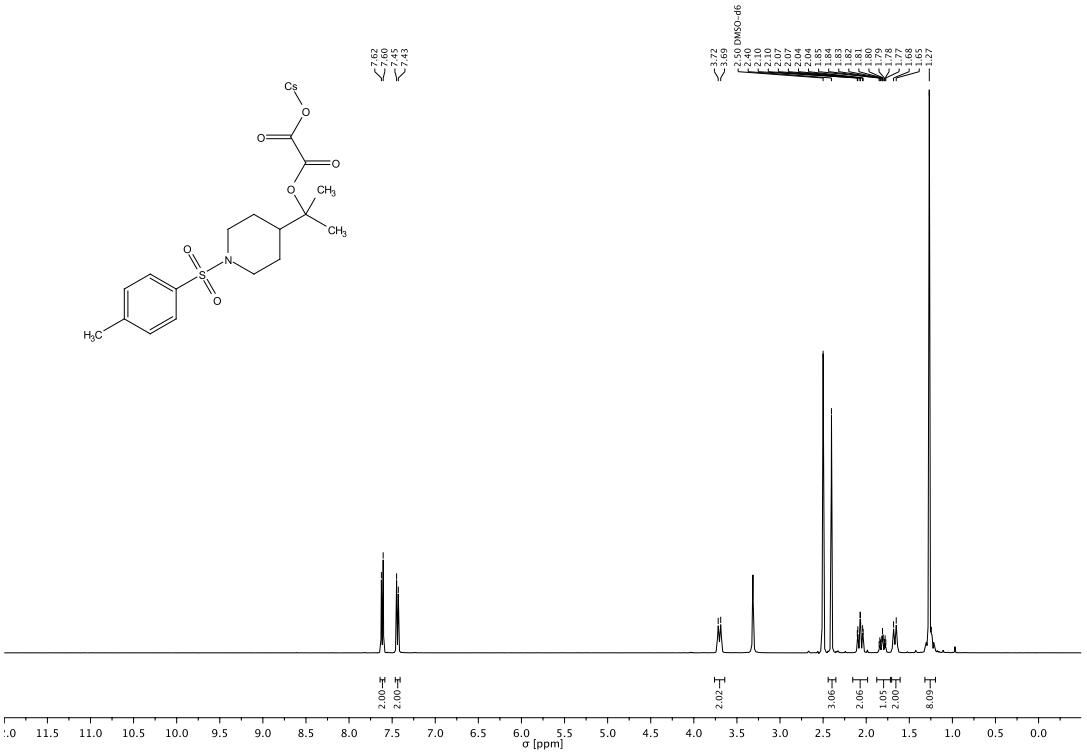


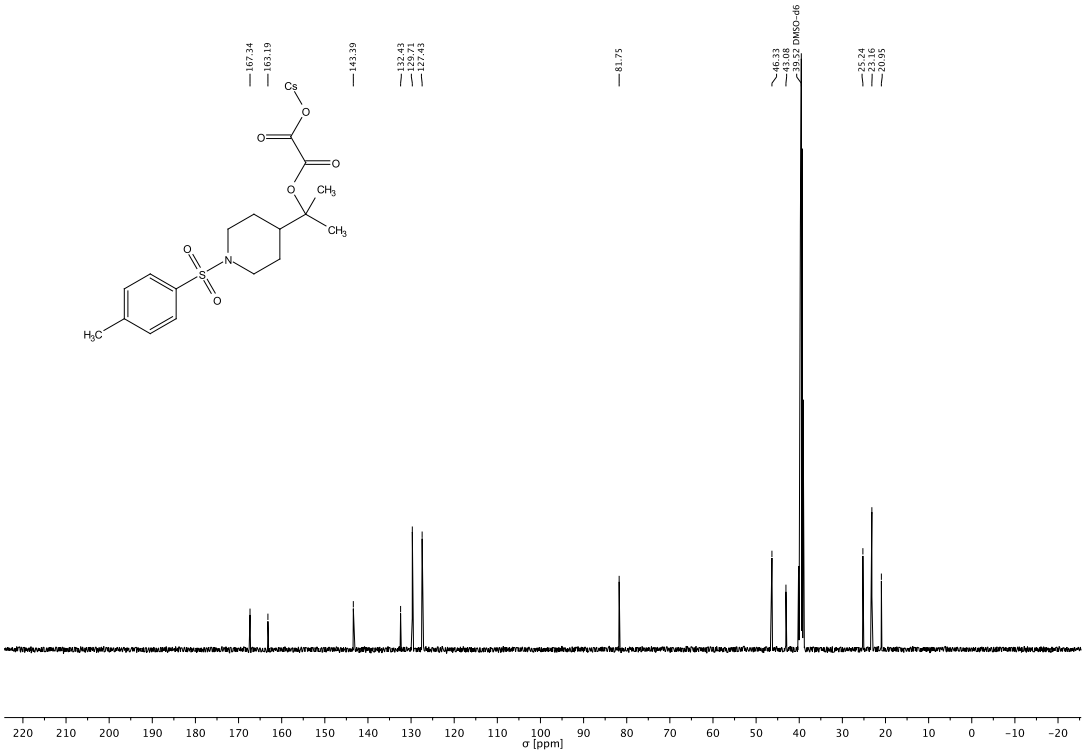
1-cyclohexyl-2-((3,3-diethoxypropyl)amino)-2-oxo-1-phenylethyl ethyl oxalate



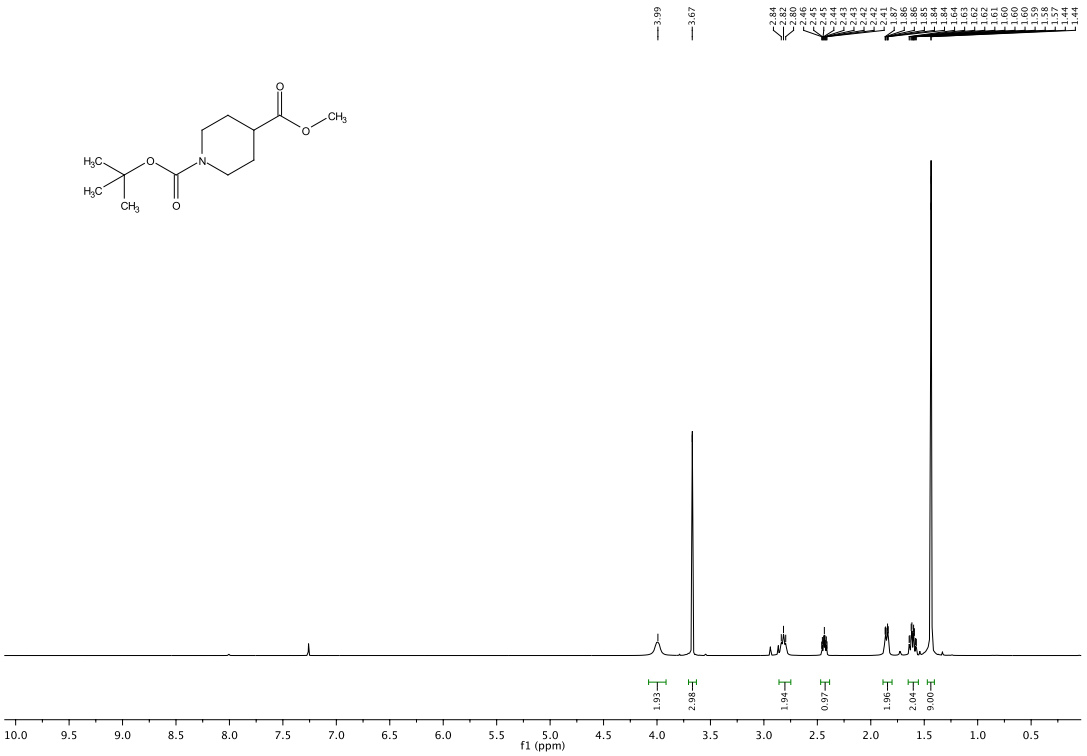


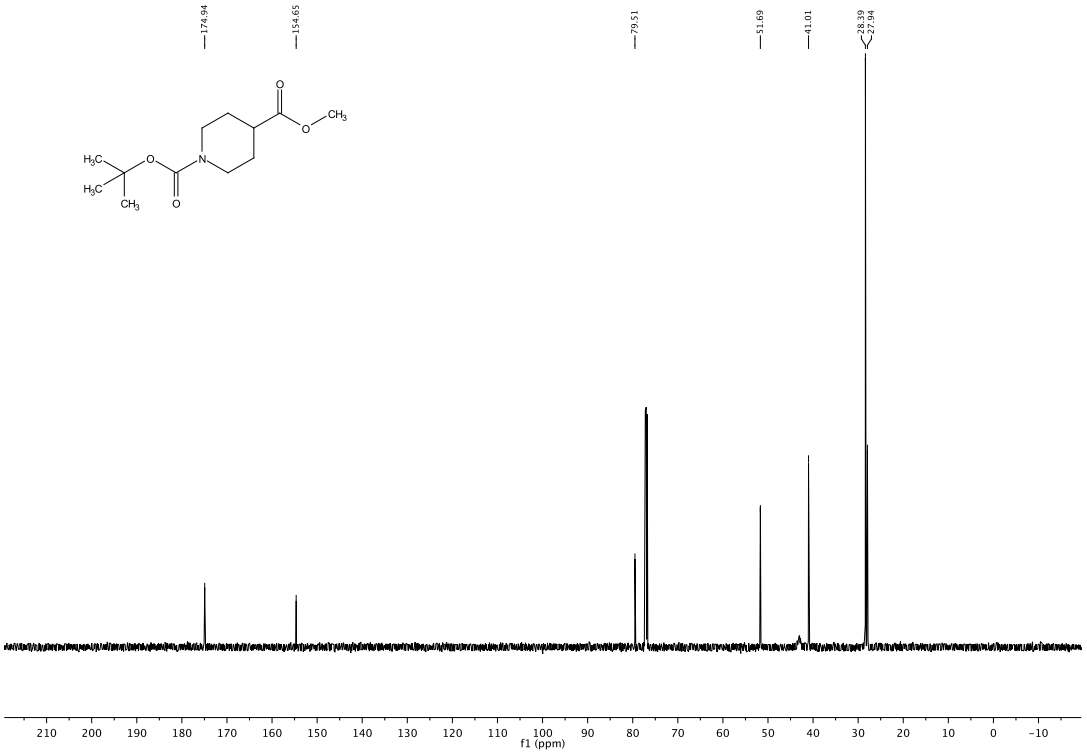
Cesium 2-((2-methyl-4-(tosyloxy)pentan-2-yl)oxy)-2-oxoacetate



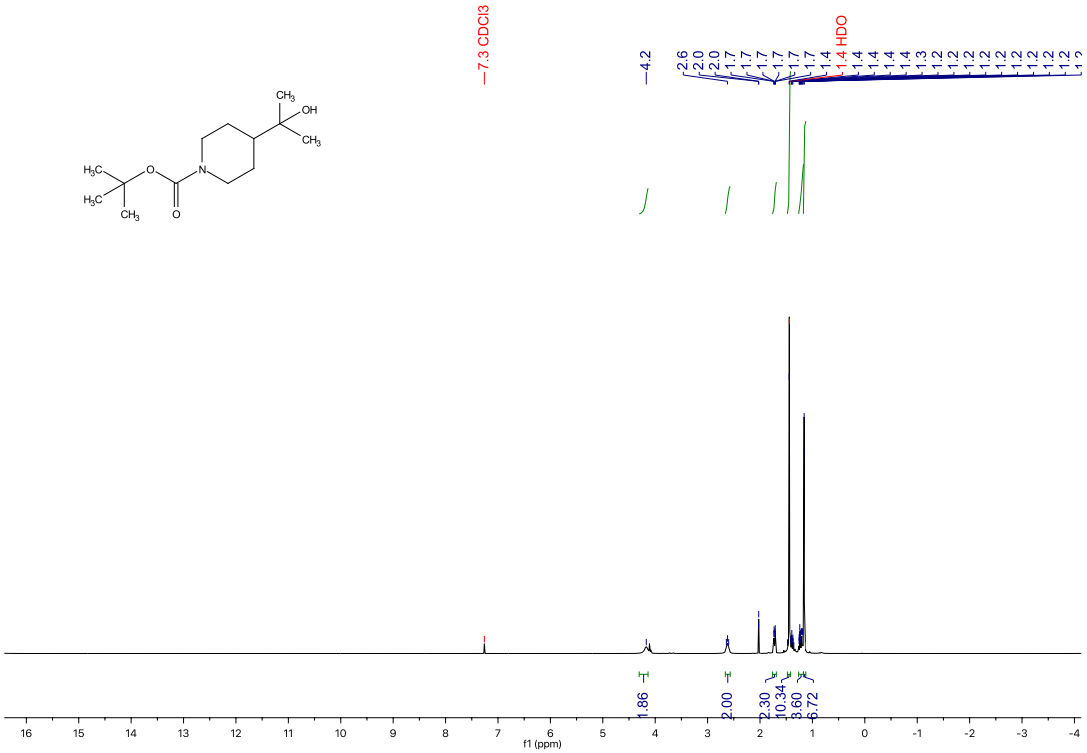


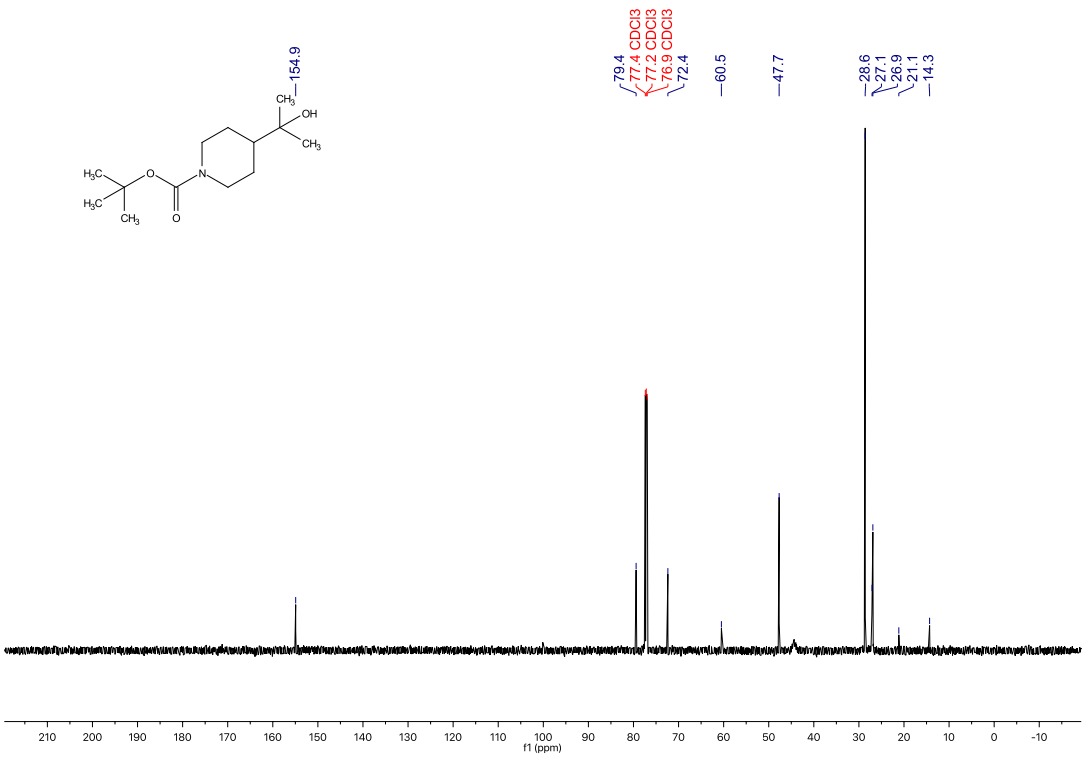
tert-Butyl 4-methyl piperidine-1,4-dicarboxylate



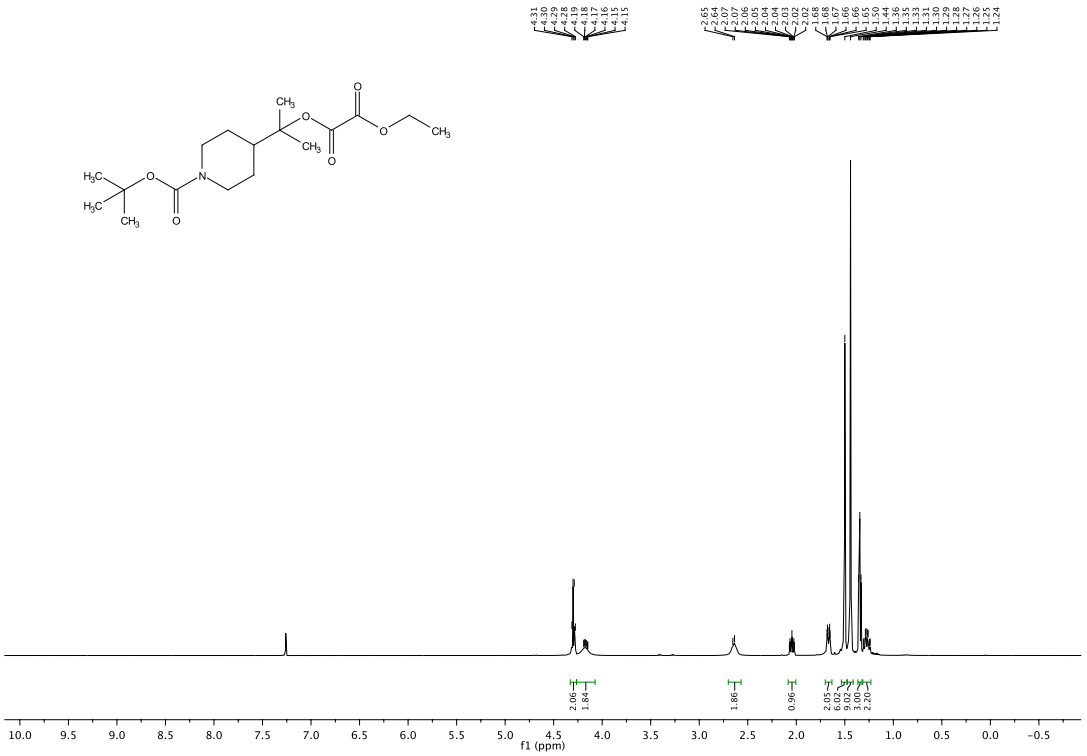


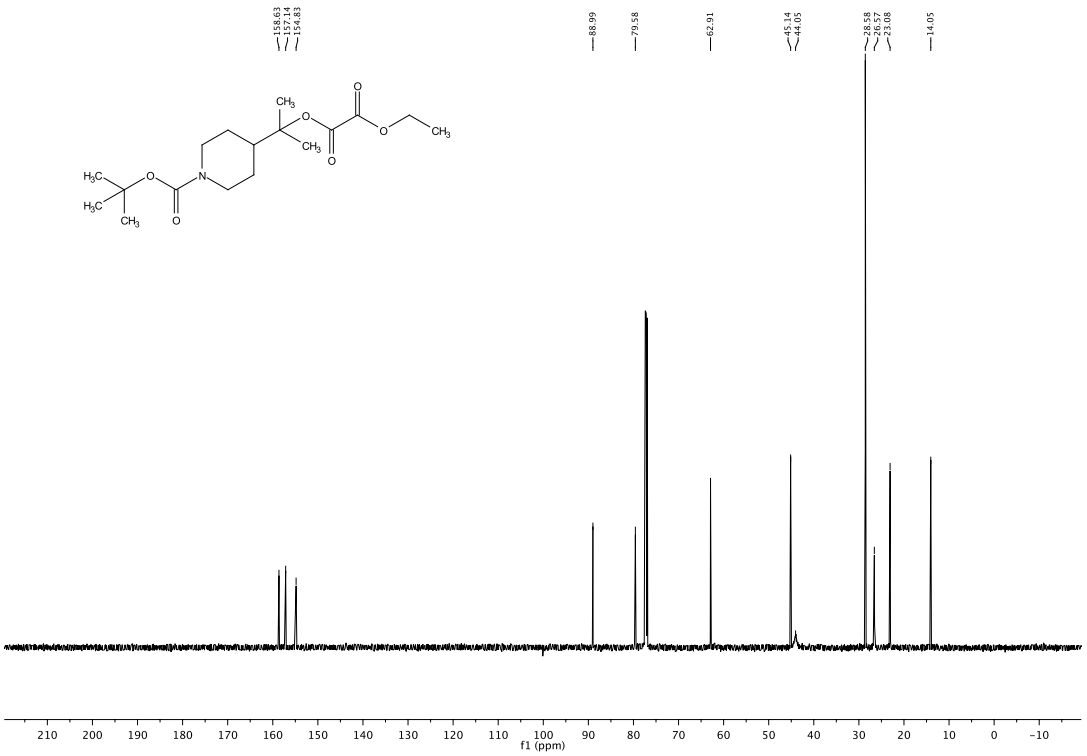
tert-Butyl 4-(2-hydroxypropan-2-yl)piperidine-1-carboxylate



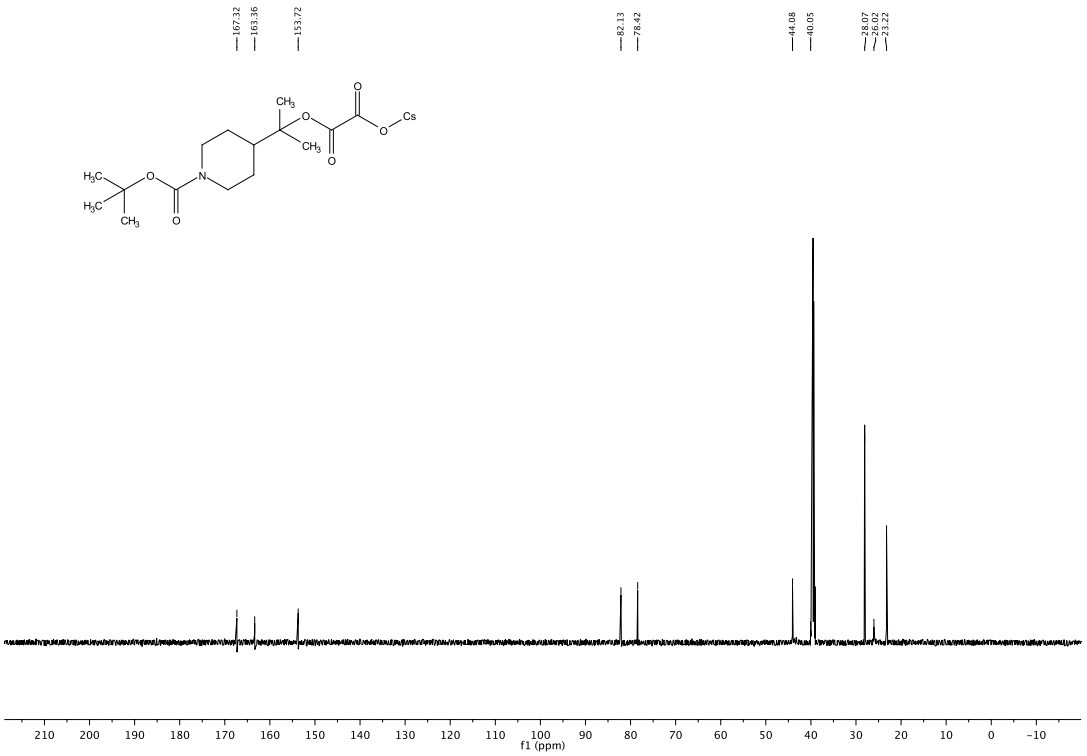


2-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)propan-2-yl ethyl oxalate

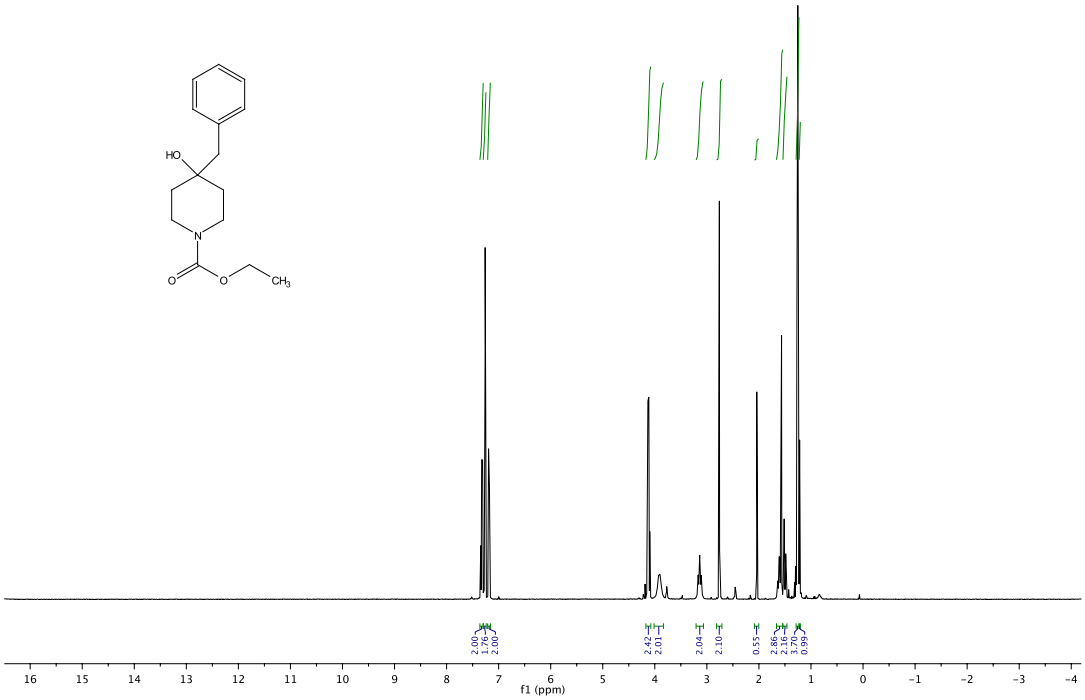


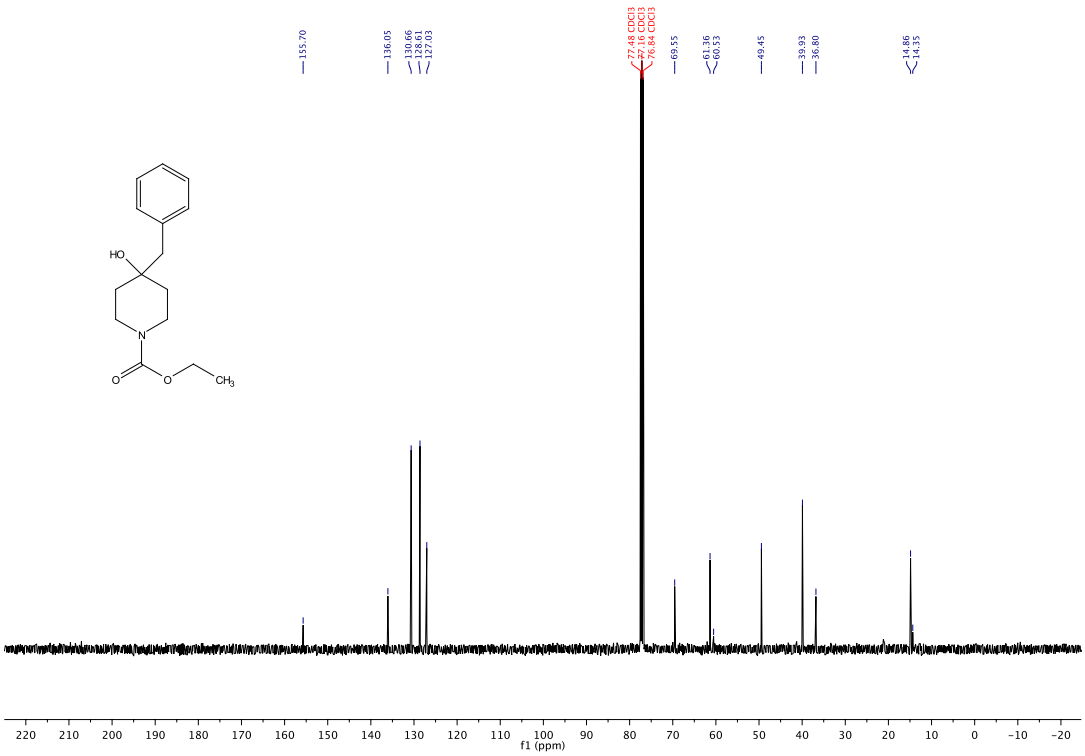


Cesium 2-((2-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)propan-2-yl)oxy)-2-oxoacetate

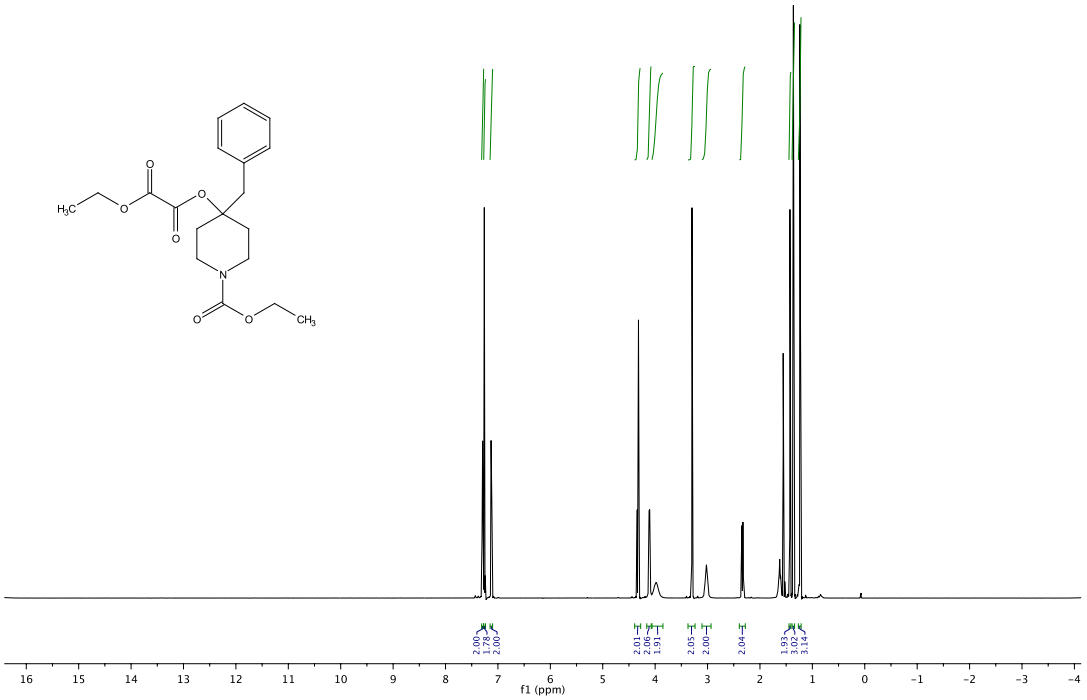


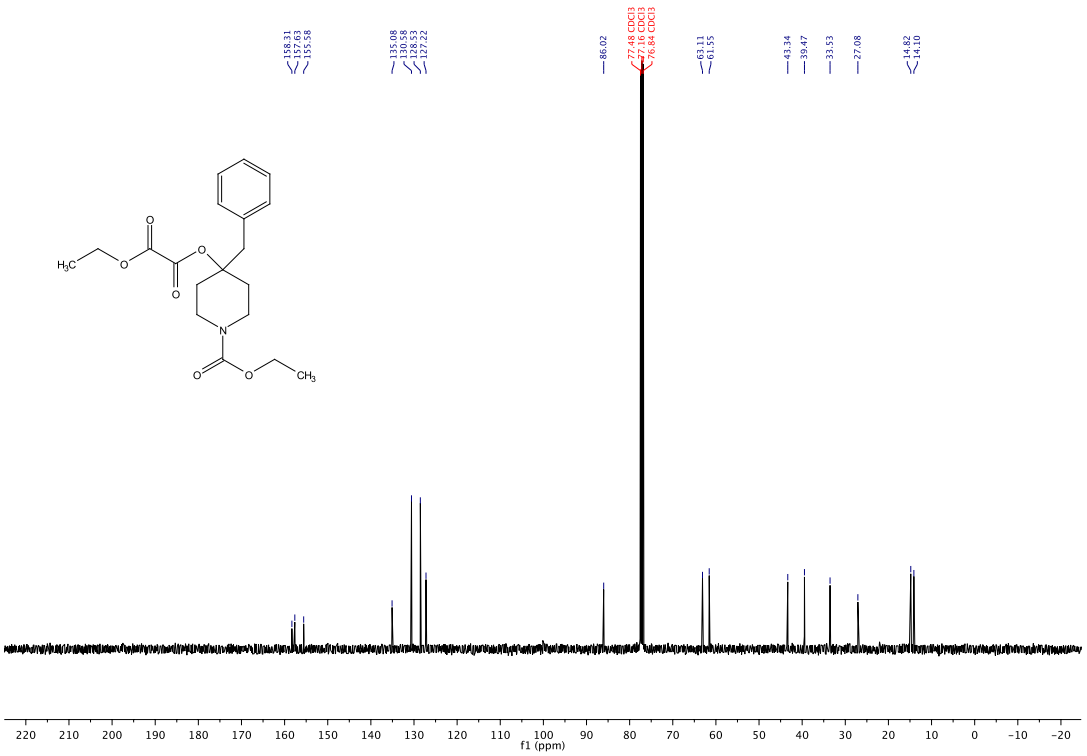
Ethyl 4-benzyl-4-hydroxypiperidine-1-carboxylate



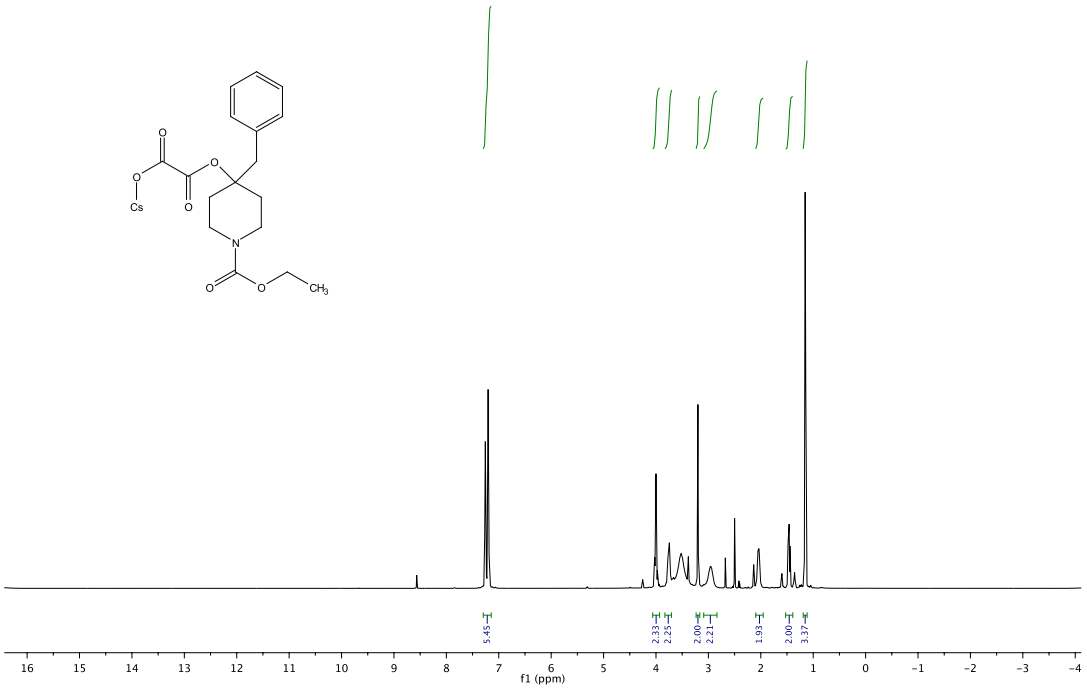


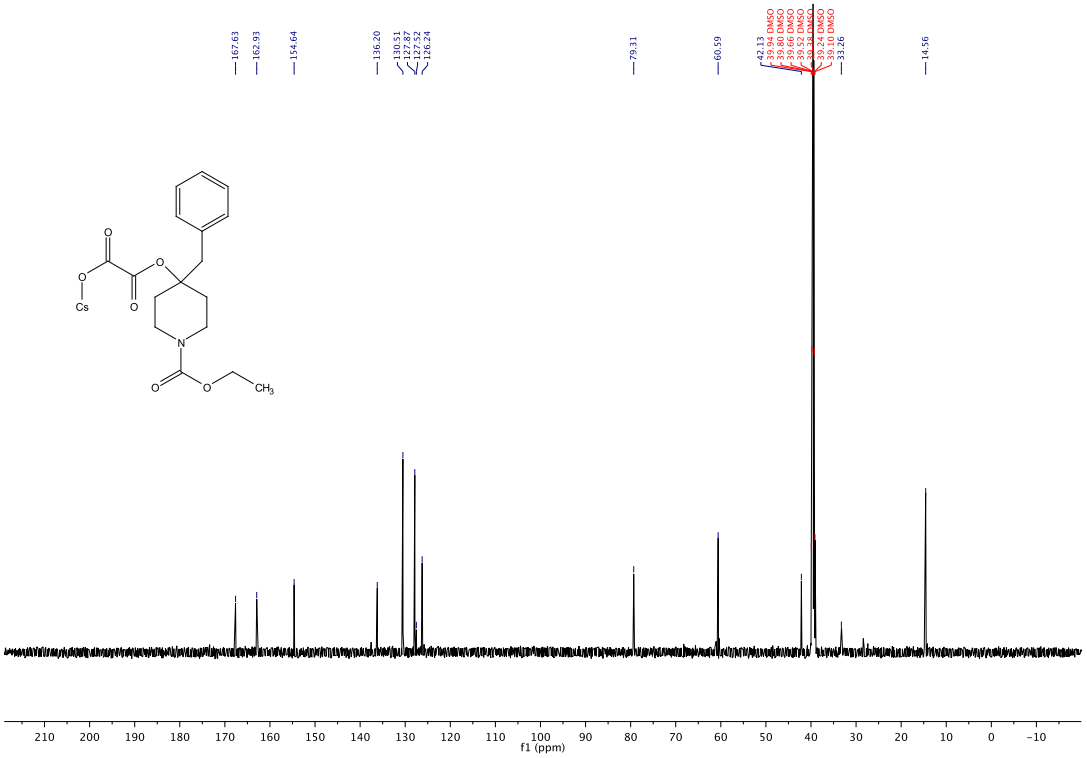
4-benzyl-1-(ethoxycarbonyl)piperidin-4-yl ethyl oxalate



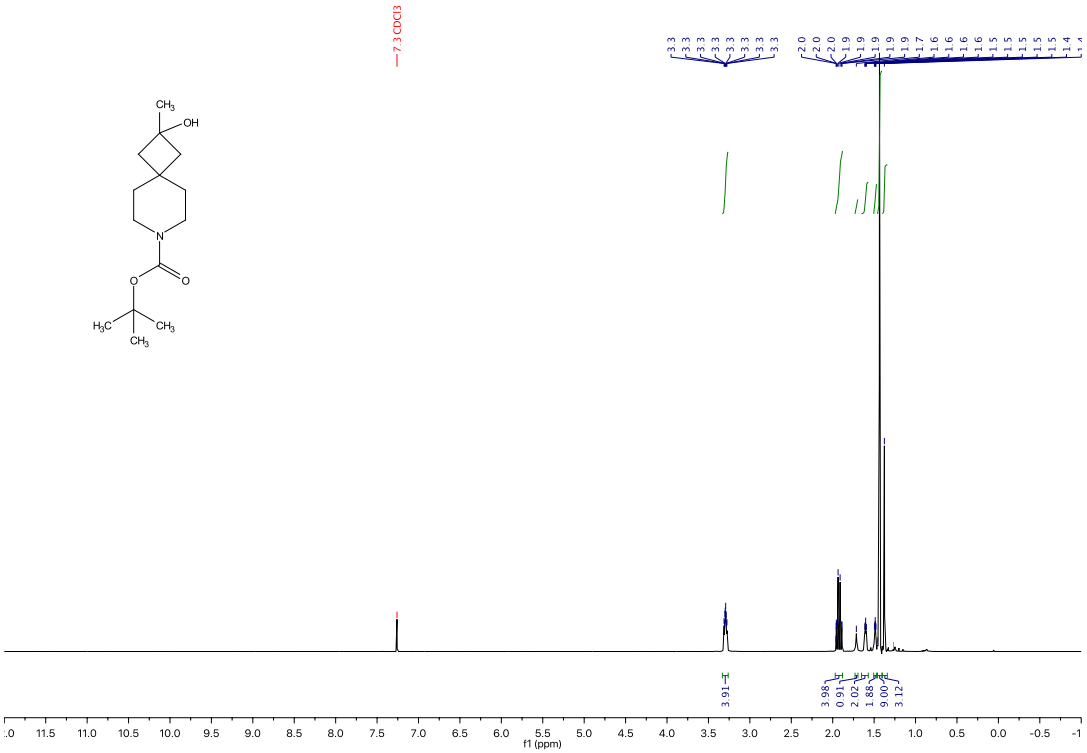


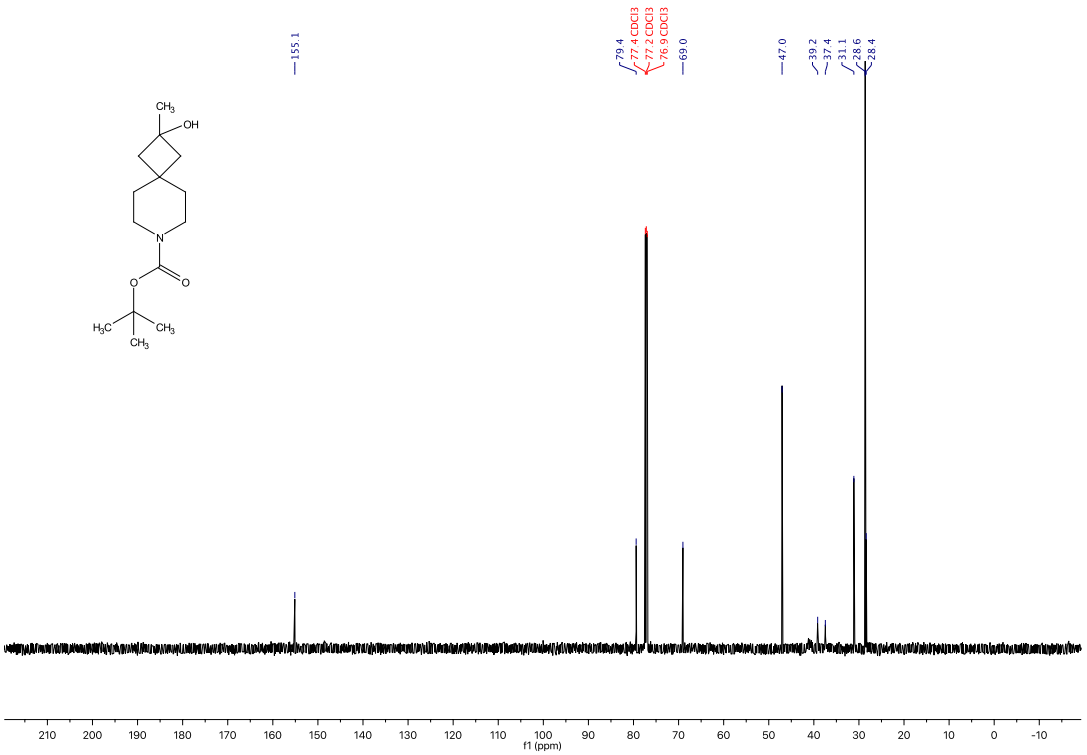
Cesium 2-((4-benzyl-1-(ethoxycarbonyl)piperidin-4-yl)oxy)-2-oxoacetate



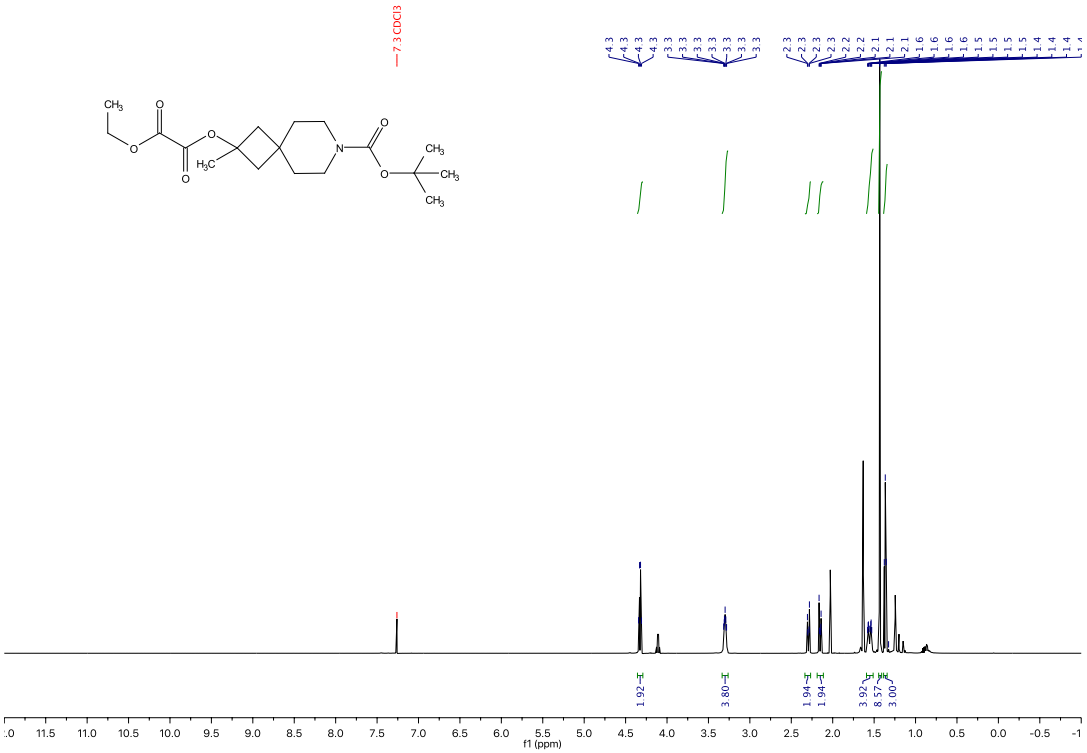


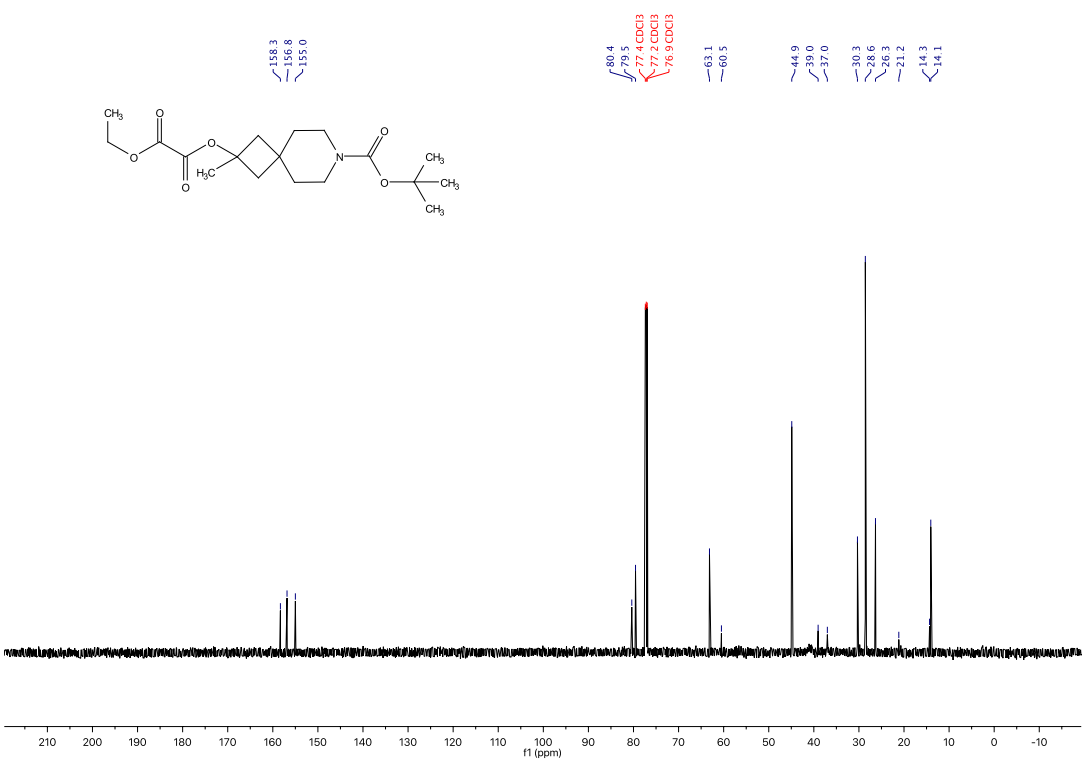
tert-Butyl 2-hydroxy-2-methyl-7-azaspiro[3.5]nonane-7-carboxylate



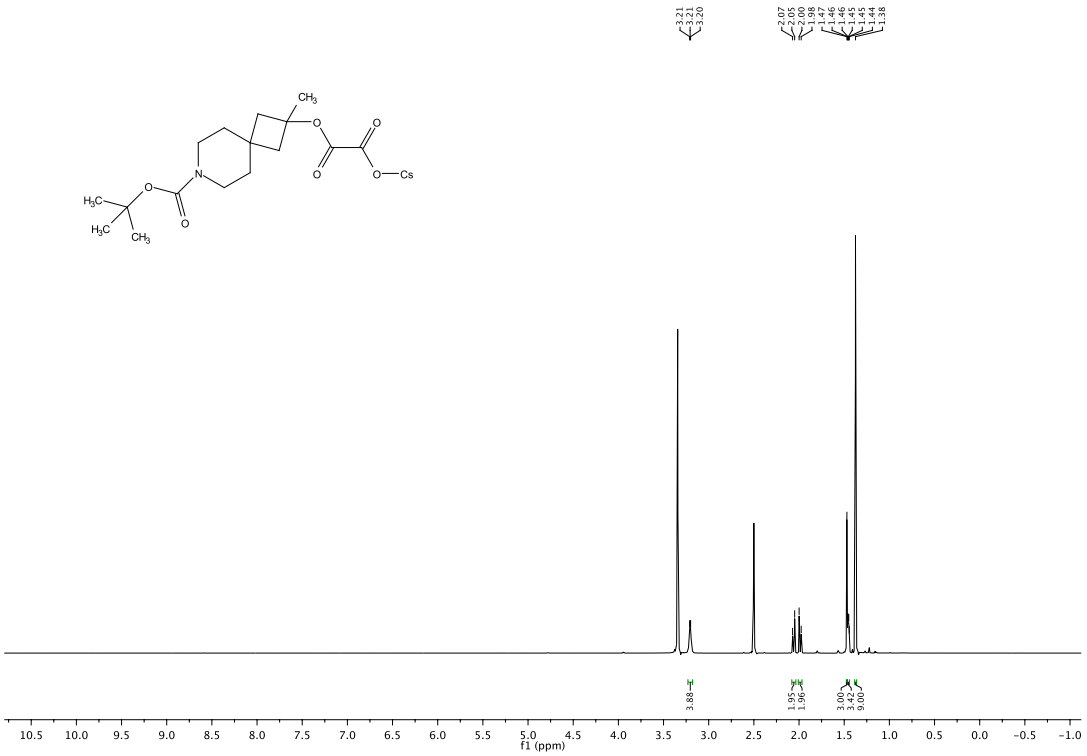


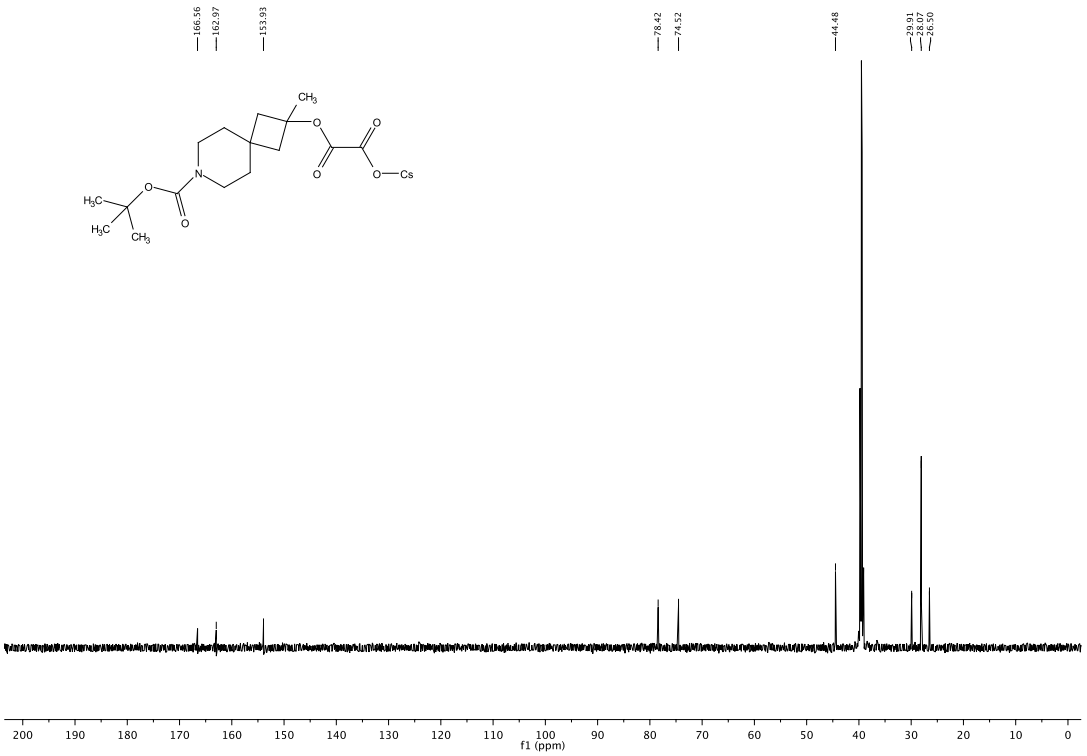
7-(*tert*-butoxycarbonyl)-2-methyl-7-azaspiro[3.5]nonan-2-yl ethyl oxalate



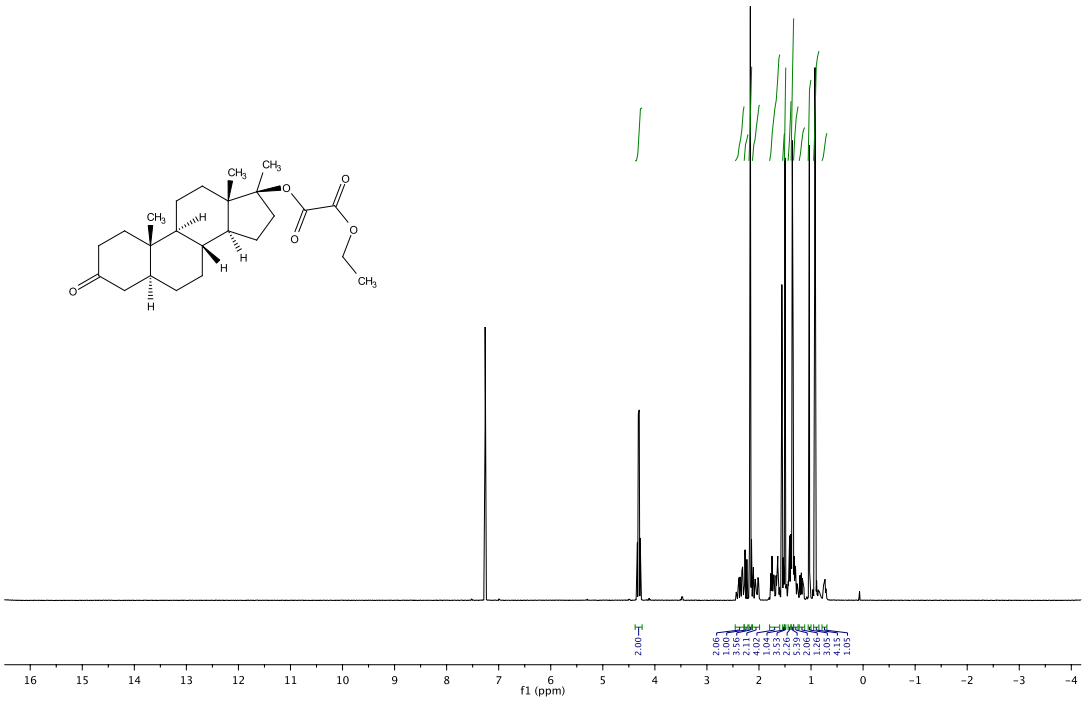


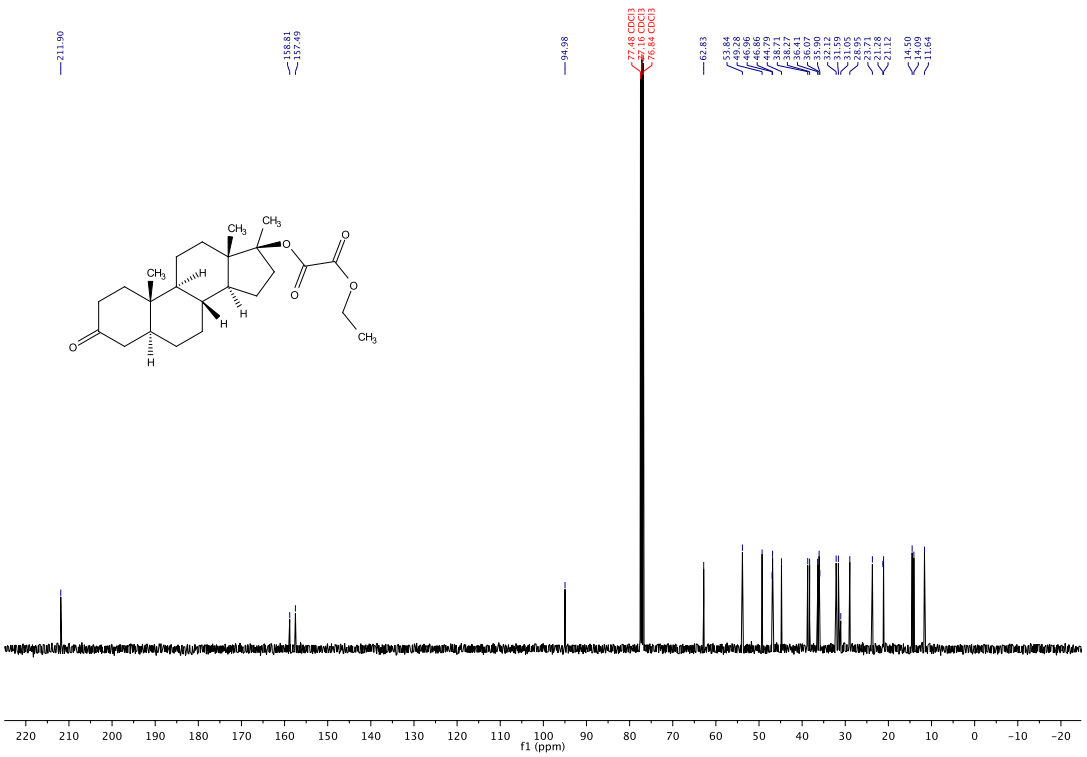
Cesium 2-((7-(*tert*-butoxycarbonyl)-2-methyl-7-azaspiro[3.5]nonan-2-yl)oxy)-2-oxoacetate



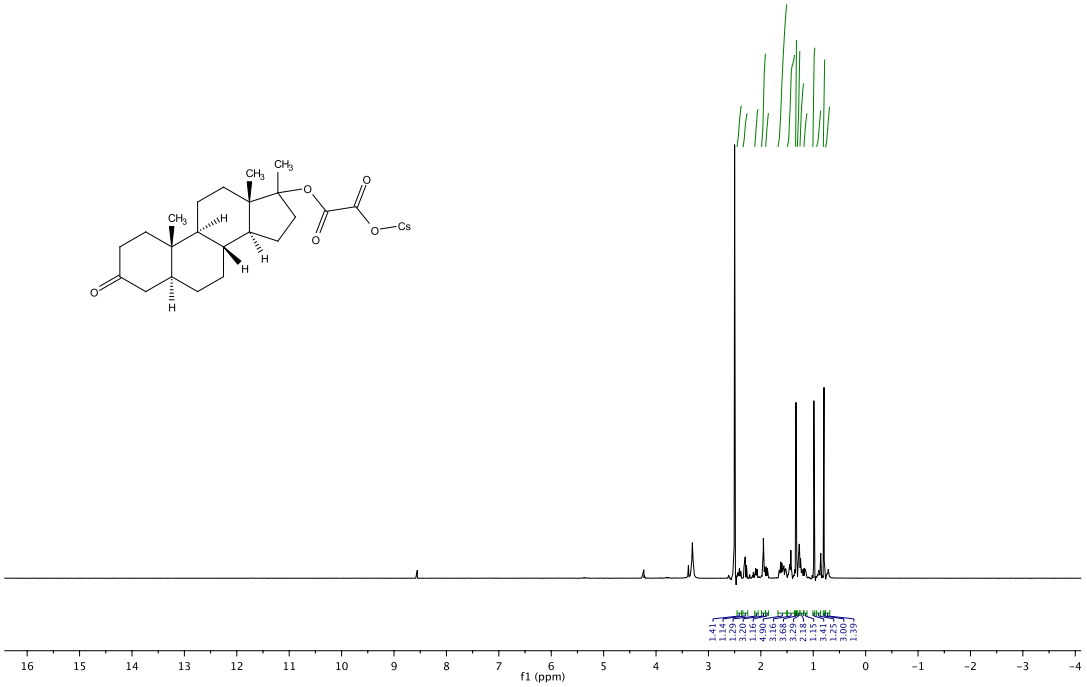


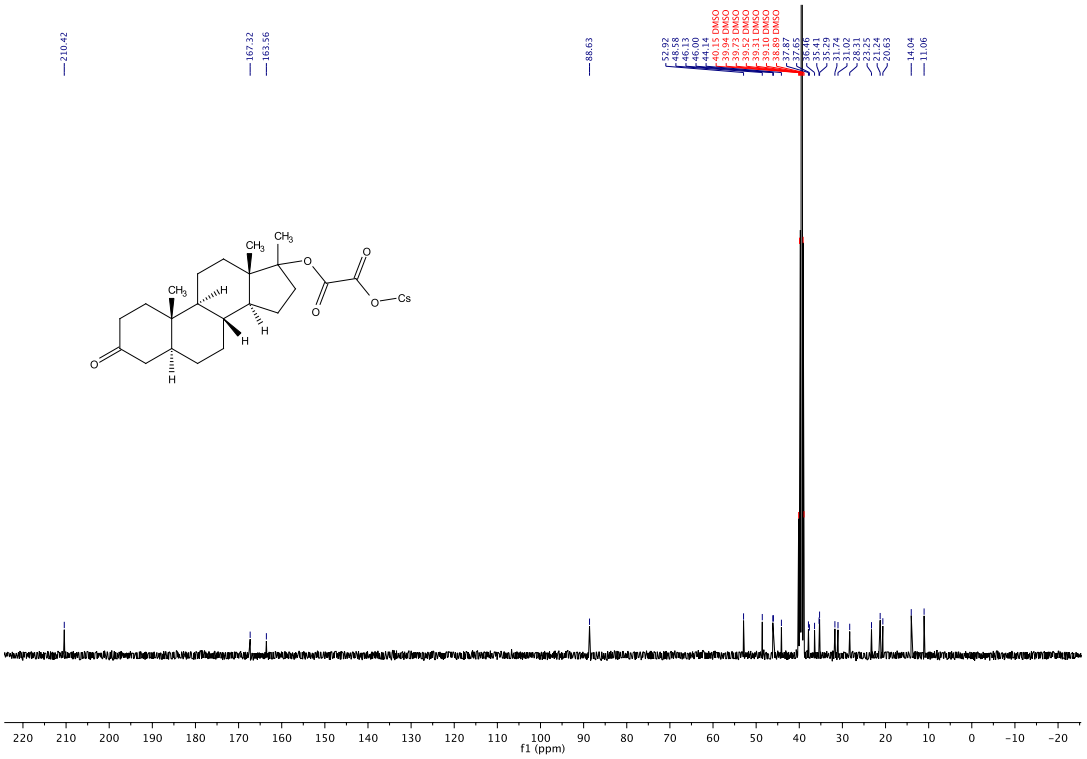
Ethyl ((5S,8R,9S,10S,13S,14S)-10,13,17-trimethyl-3-oxohexadecahydro-1H-cyclopenta[a]phenanthren-17-yl) oxalate



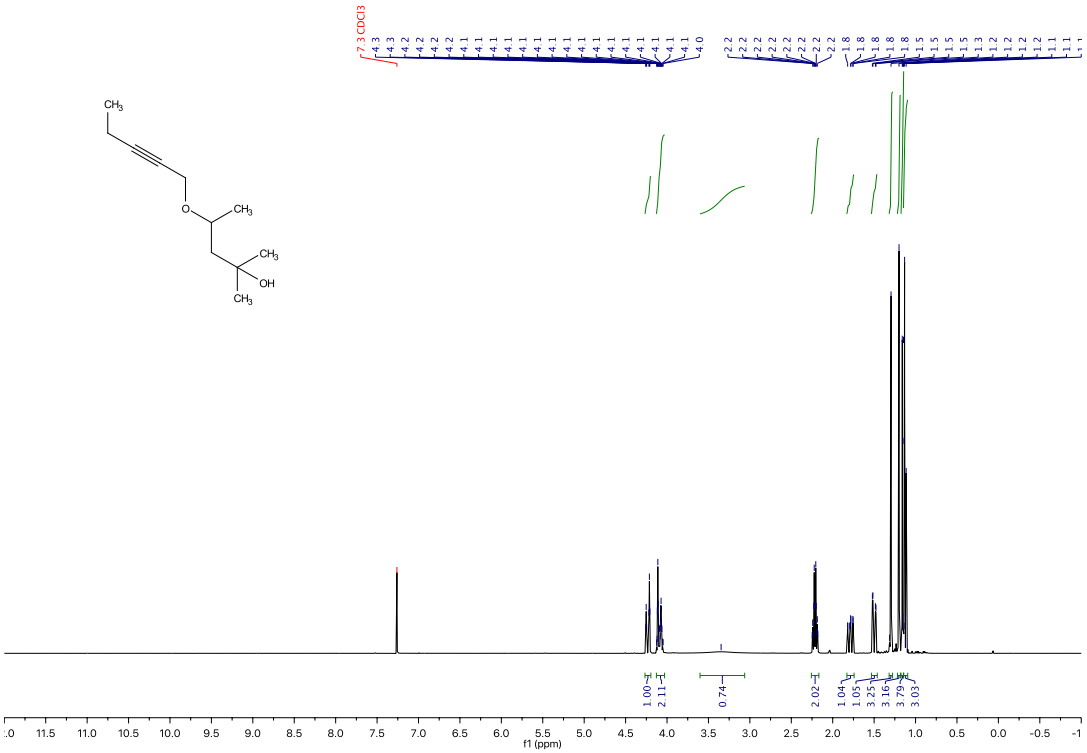


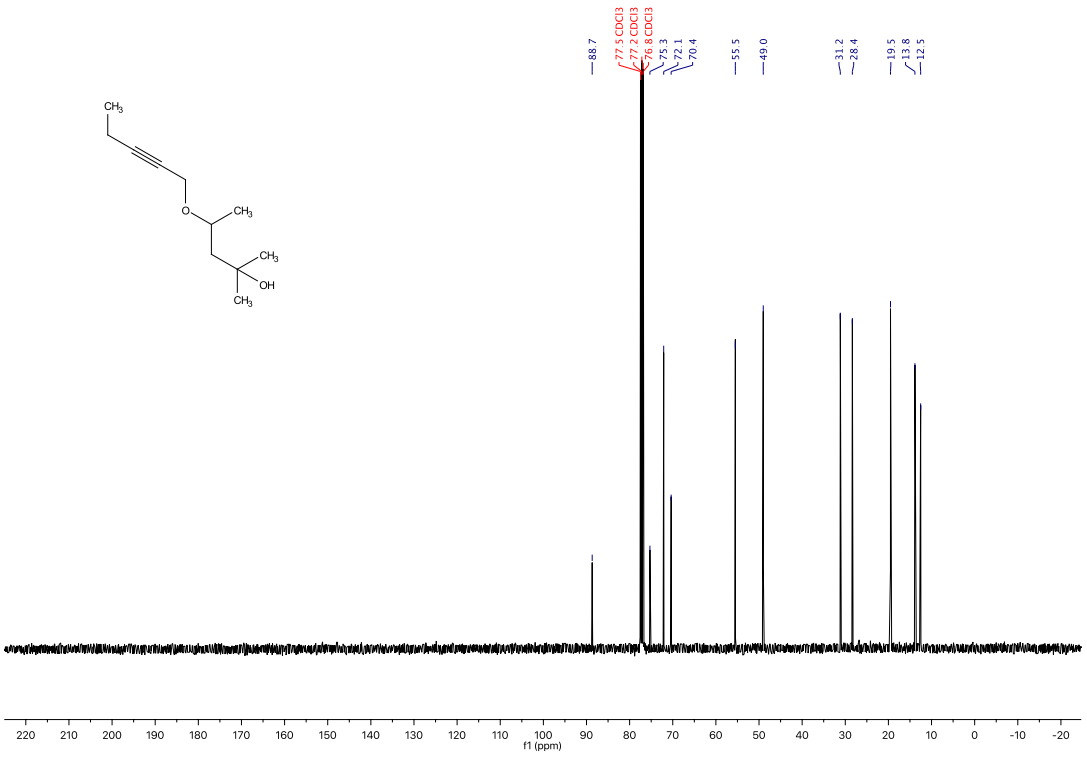
cesium 2-oxo-2-(((5S,8R,9S,10S,13S,14S)-10,13,17-trimethyl-3-oxohexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)oxy)acetate



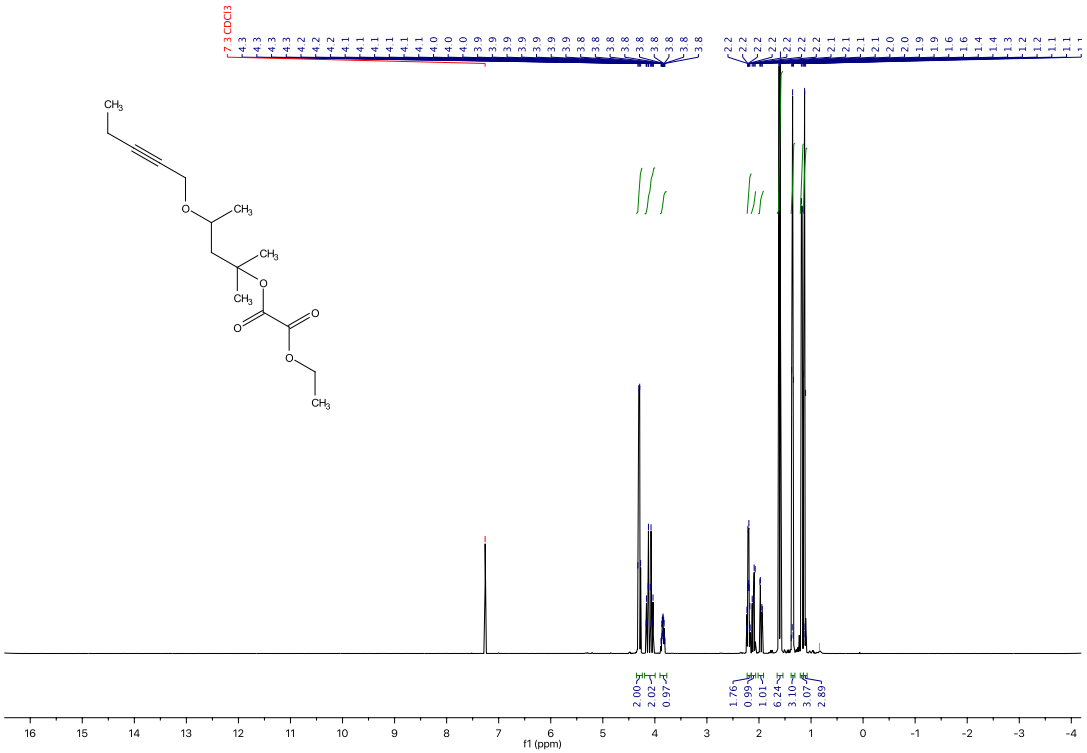


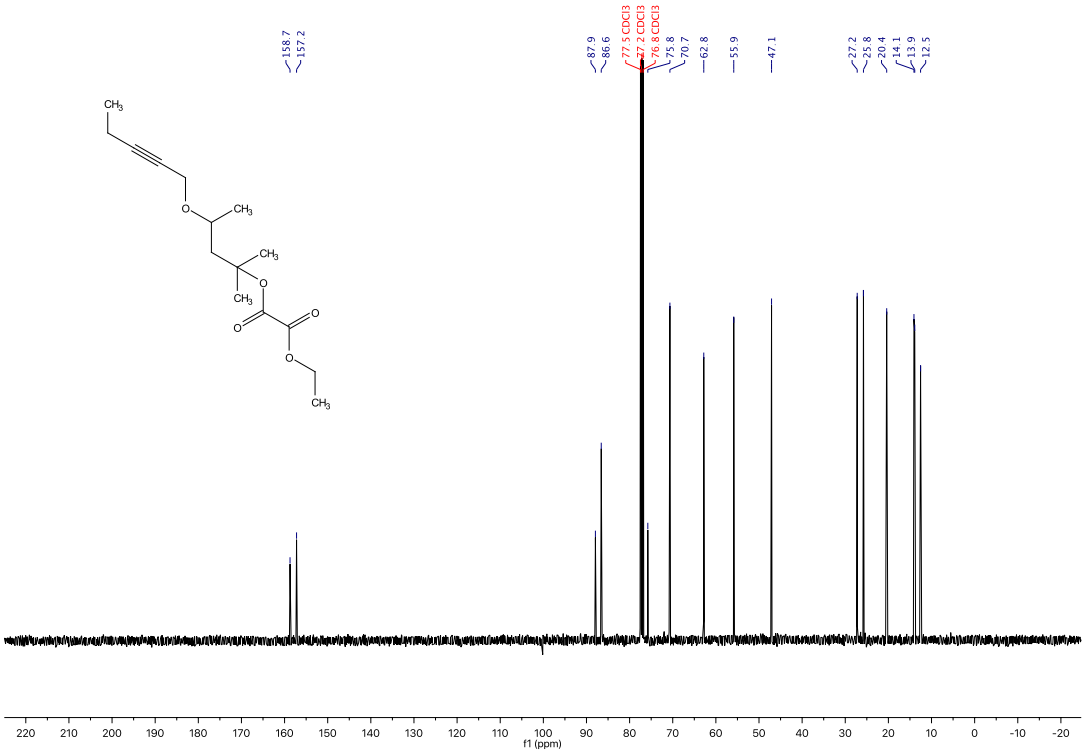
2-methyl-4-(pent-2-yn-1-yloxy)pentan-2-ol



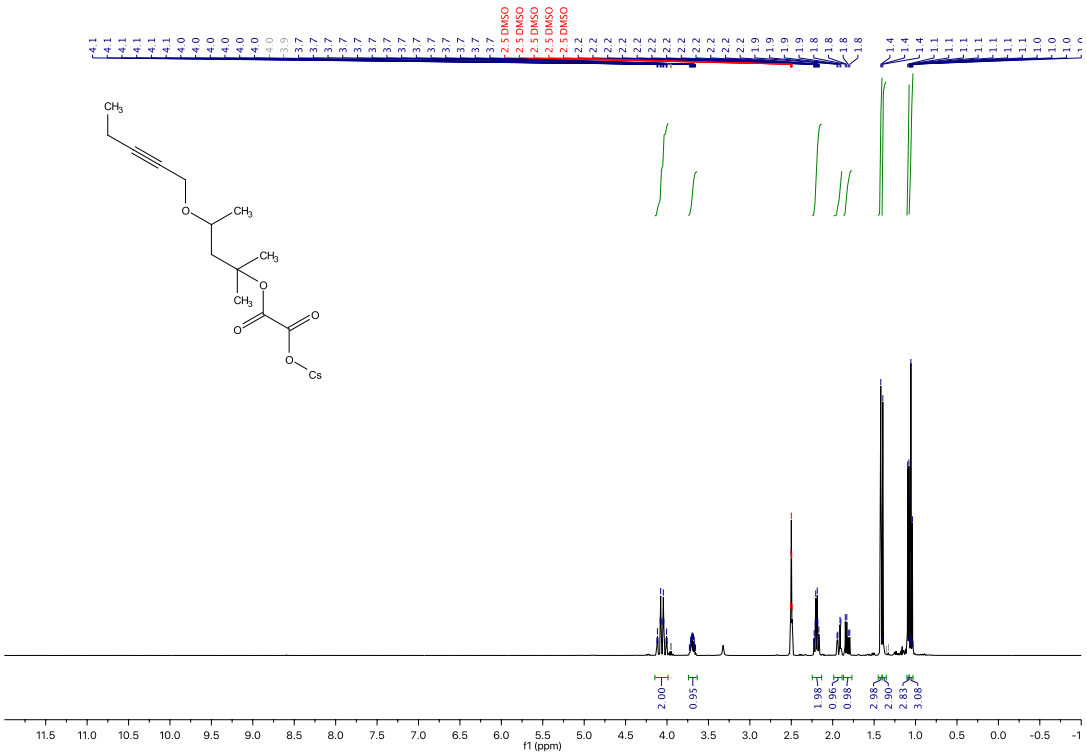


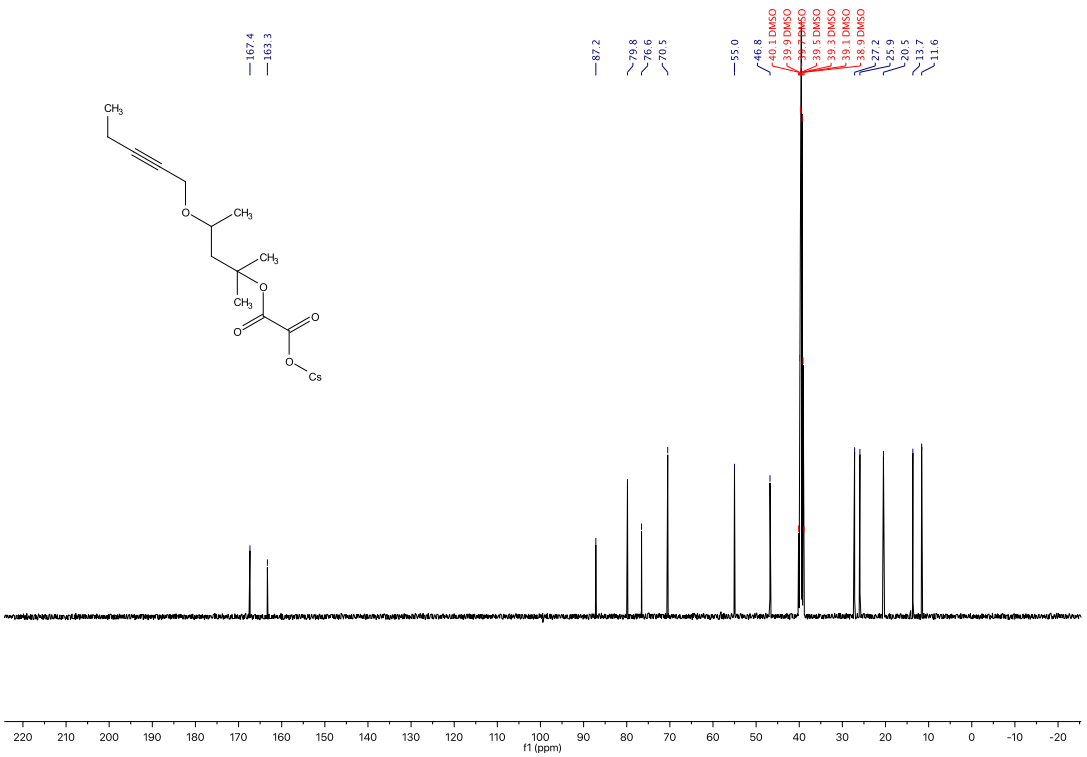
Ethyl (2-methyl-4-(pent-2-yn-1-yloxy)pentan-2-yl) oxalate



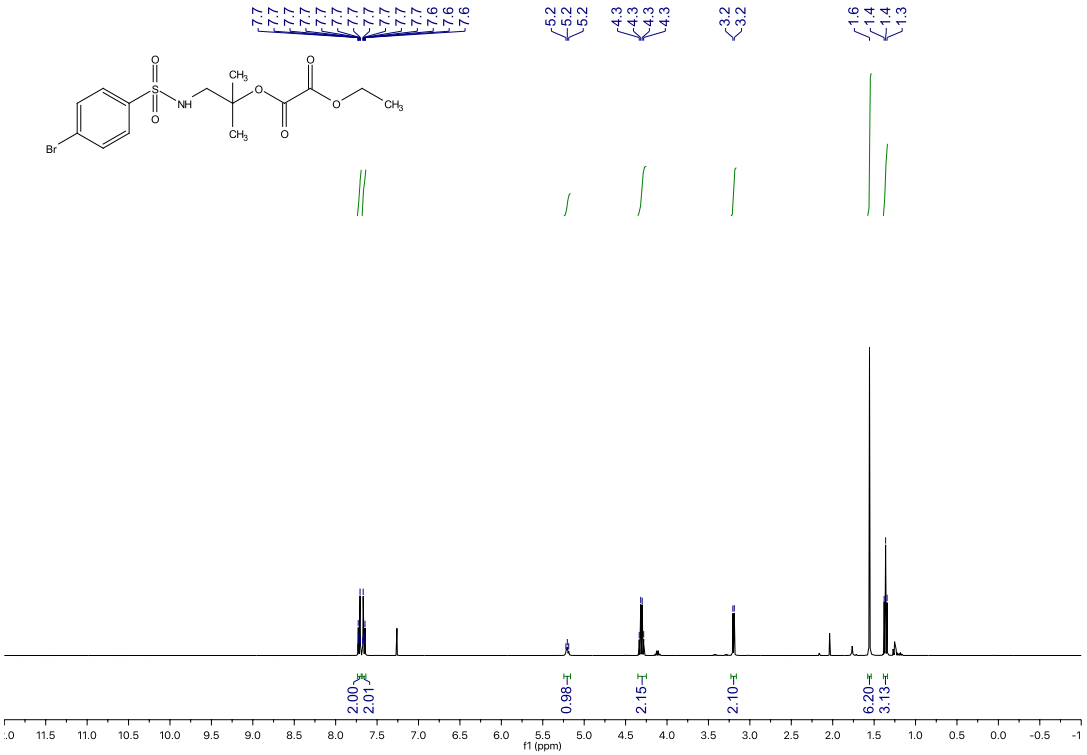


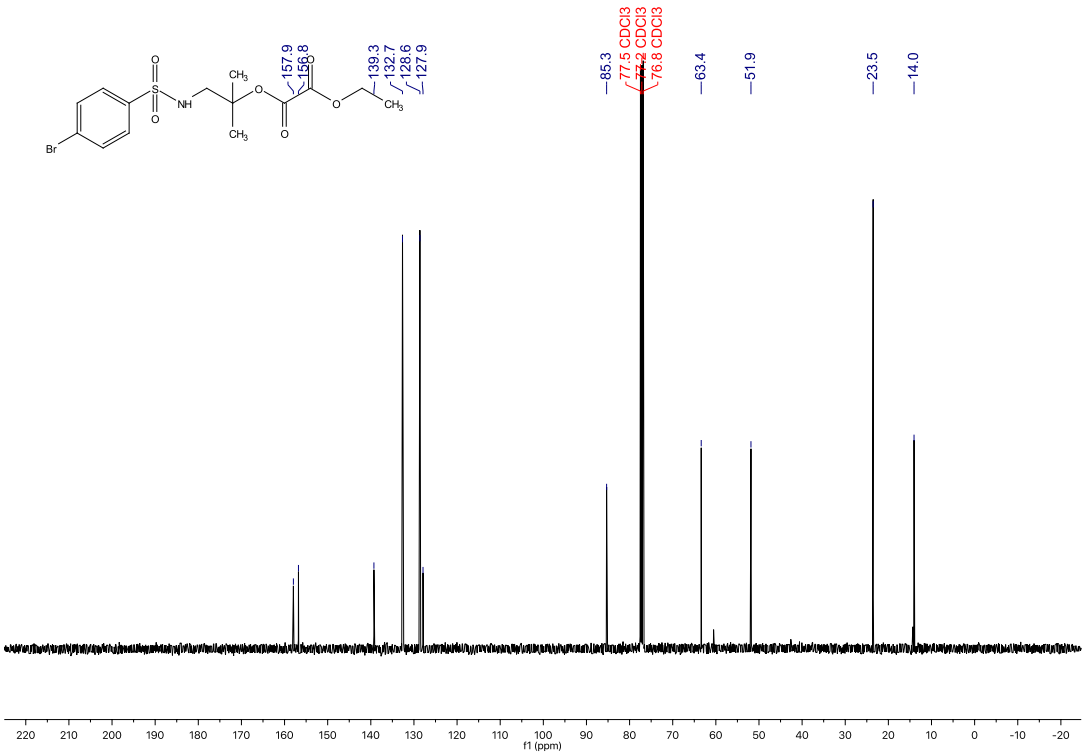
Cesium 2-((2-methyl-4-(pent-2-yn-1-yloxy)pentan-2-yl)oxy)-2-oxoacetate



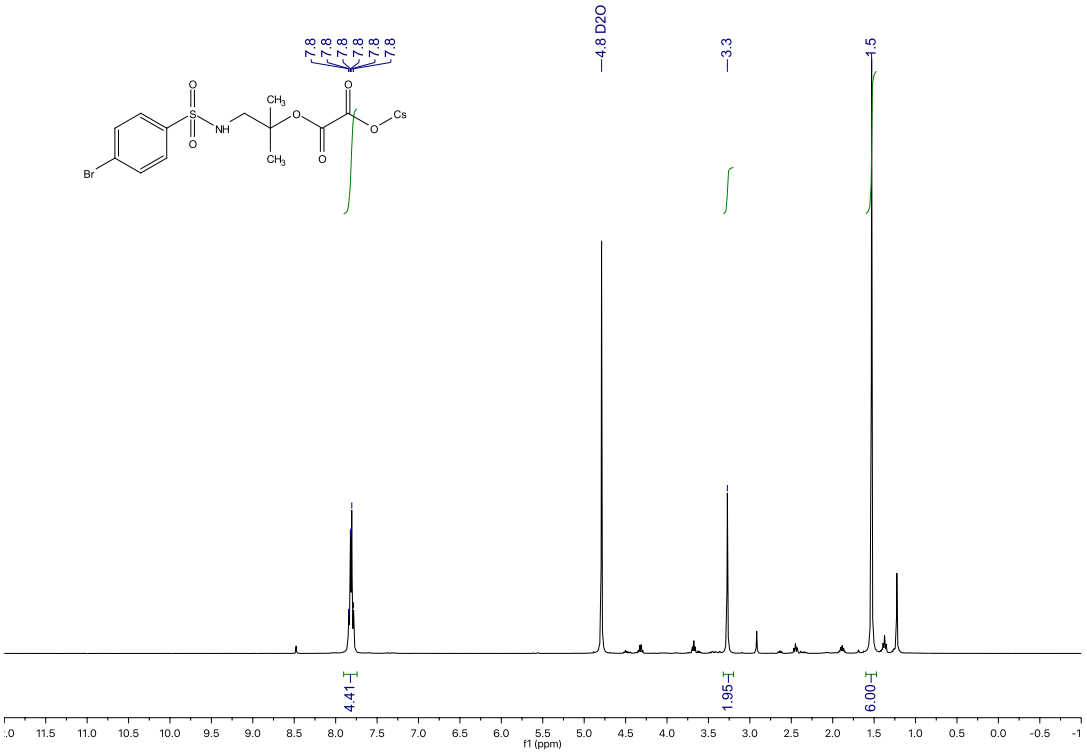


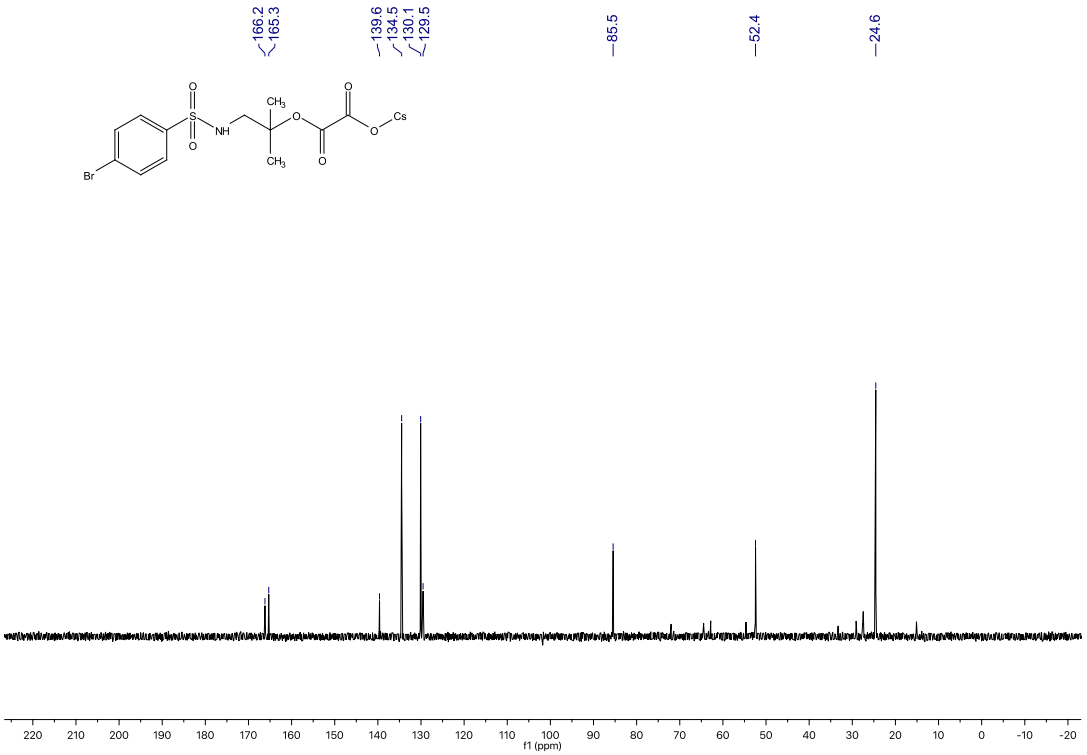
1-(4-bromophenylsulfonamido)-2-methylpropan-2-yl ethyl oxalate



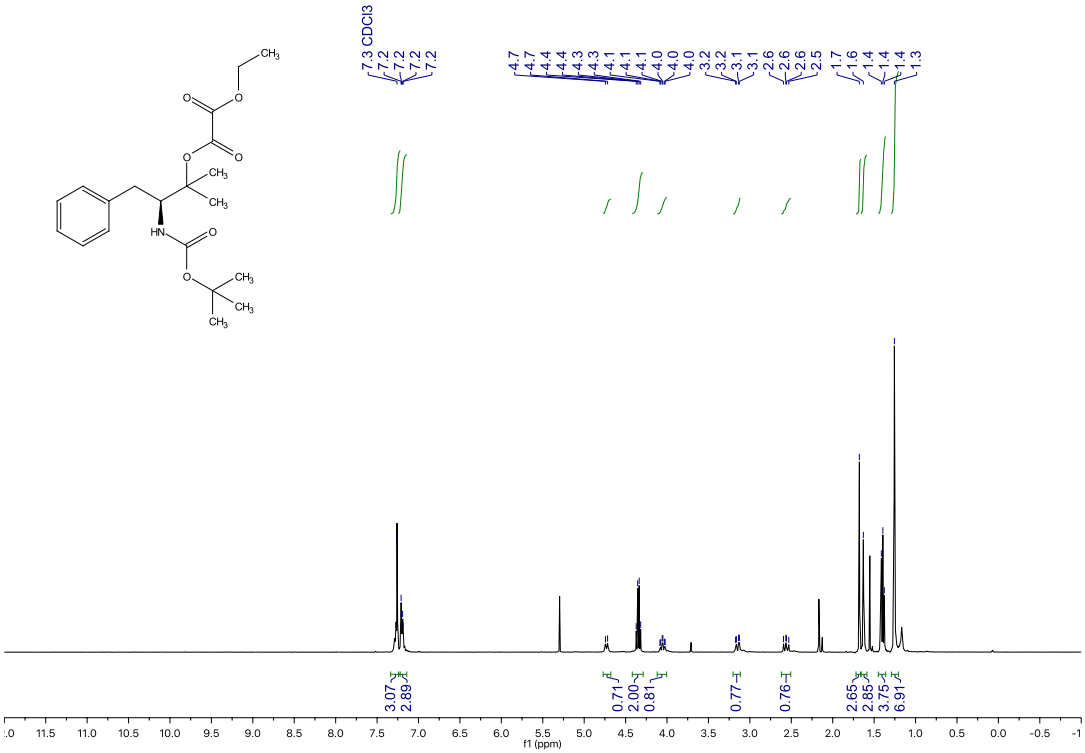


Cesium 2-((1-(4-bromophenylsulfonamido)-2-methylpropan-2-yl)oxy)-2-oxoacetate

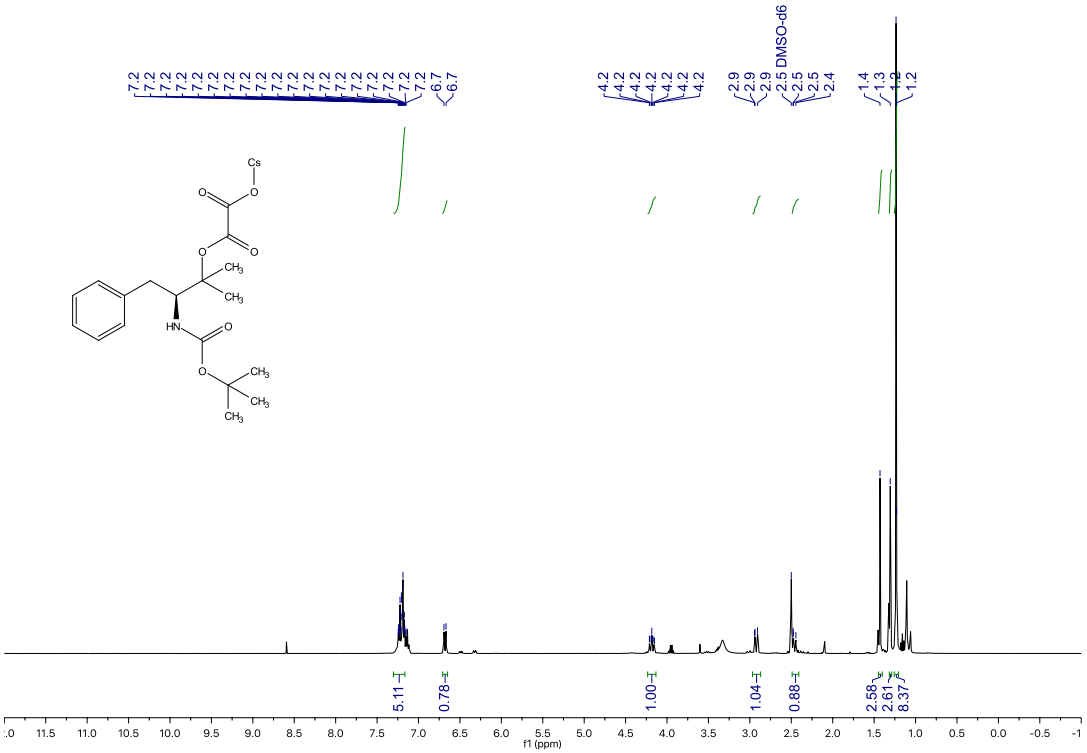


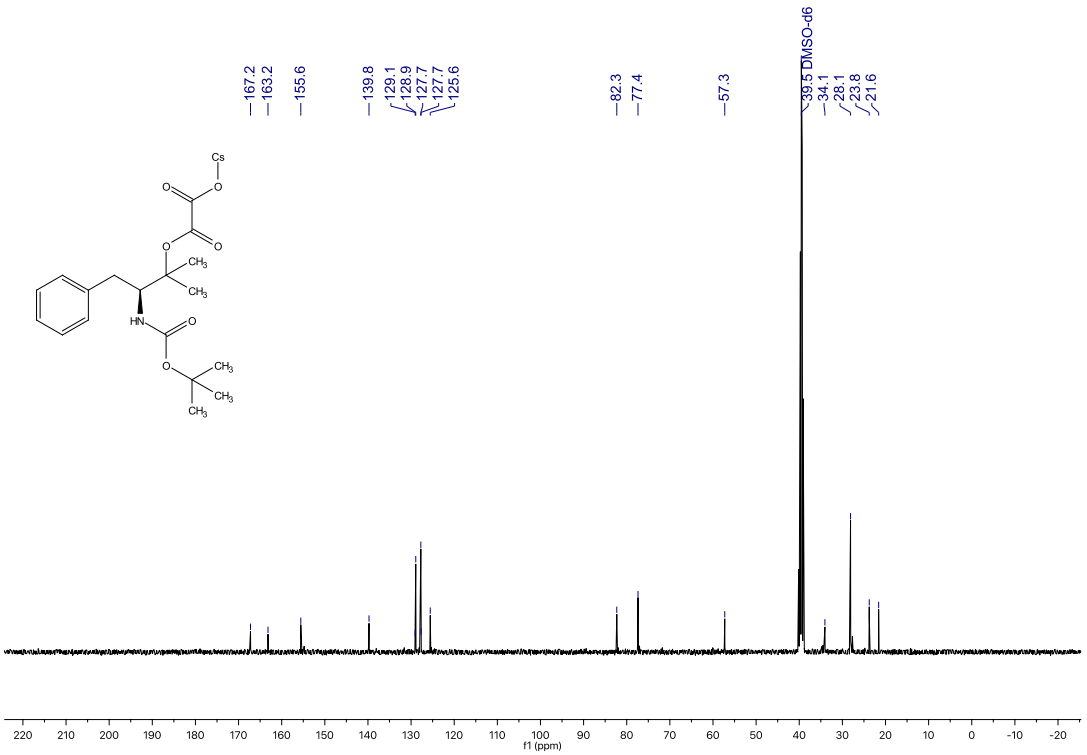


(*S*)-3-((*tert*-butoxycarbonyl)amino)-2-methyl-4-phenylbutan-2-yl ethyl oxalate

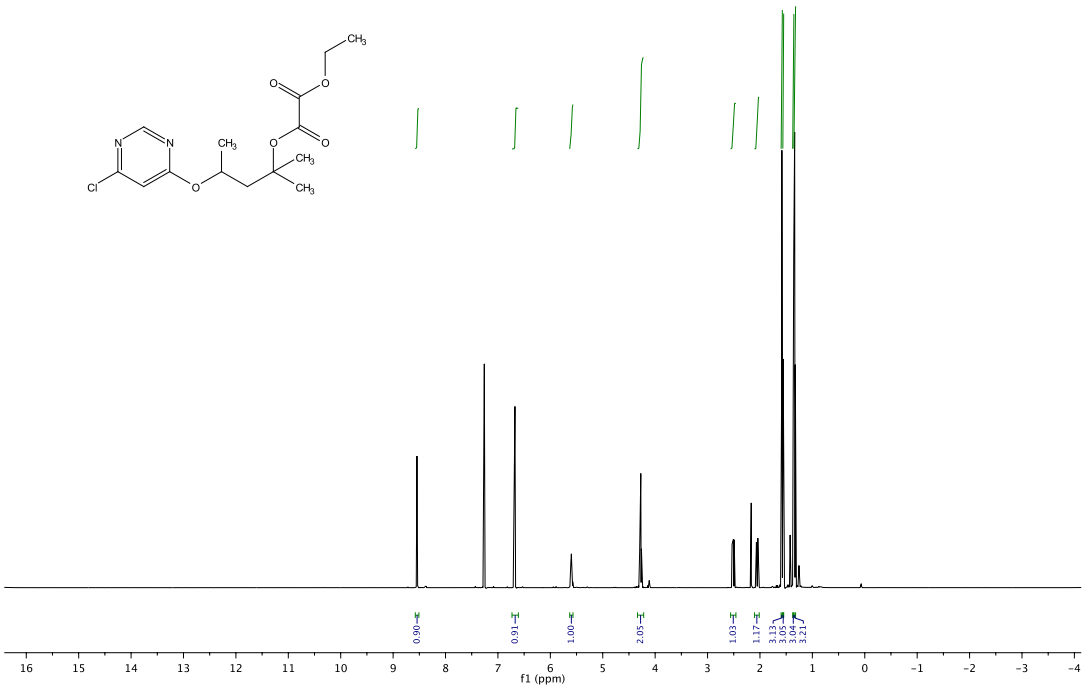


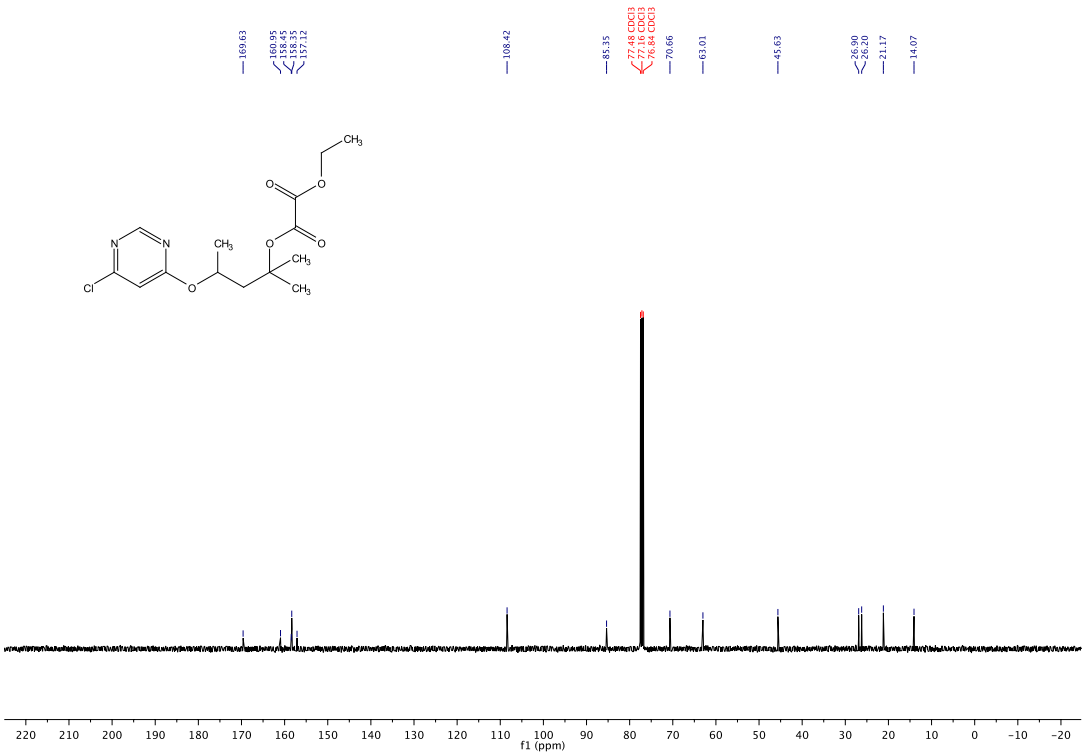
cesium (*S*)-2-((3-((*tert*-butoxycarbonyl)amino)-2-methyl-4-phenylbutan-2-yl)oxy)-2-oxoacetate



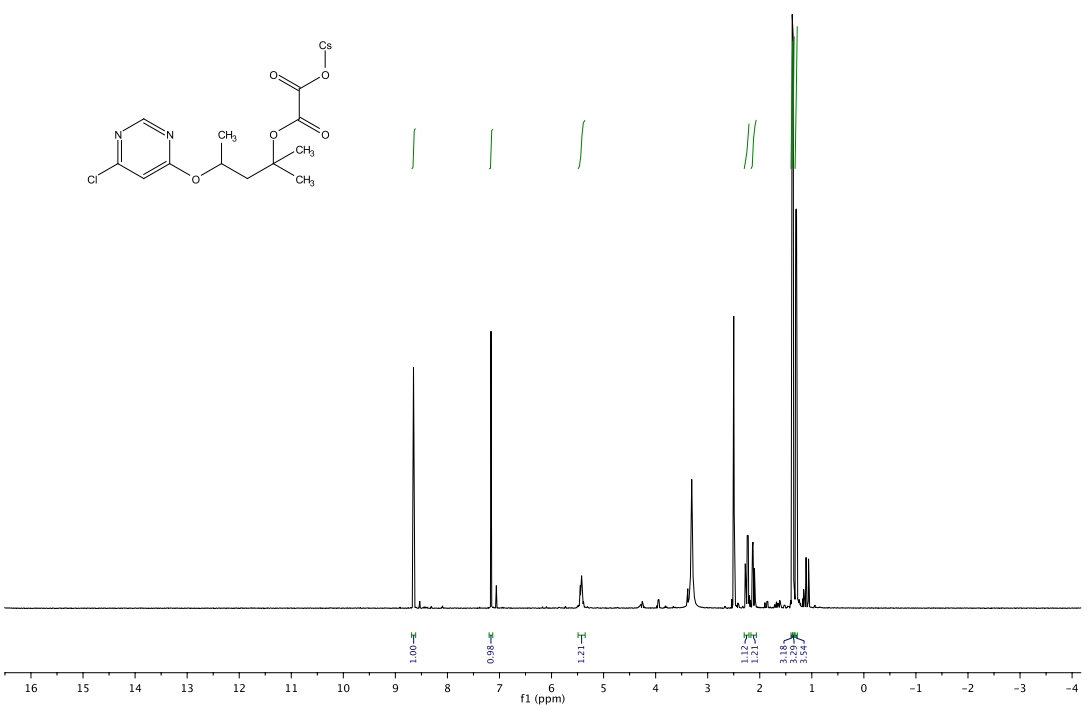


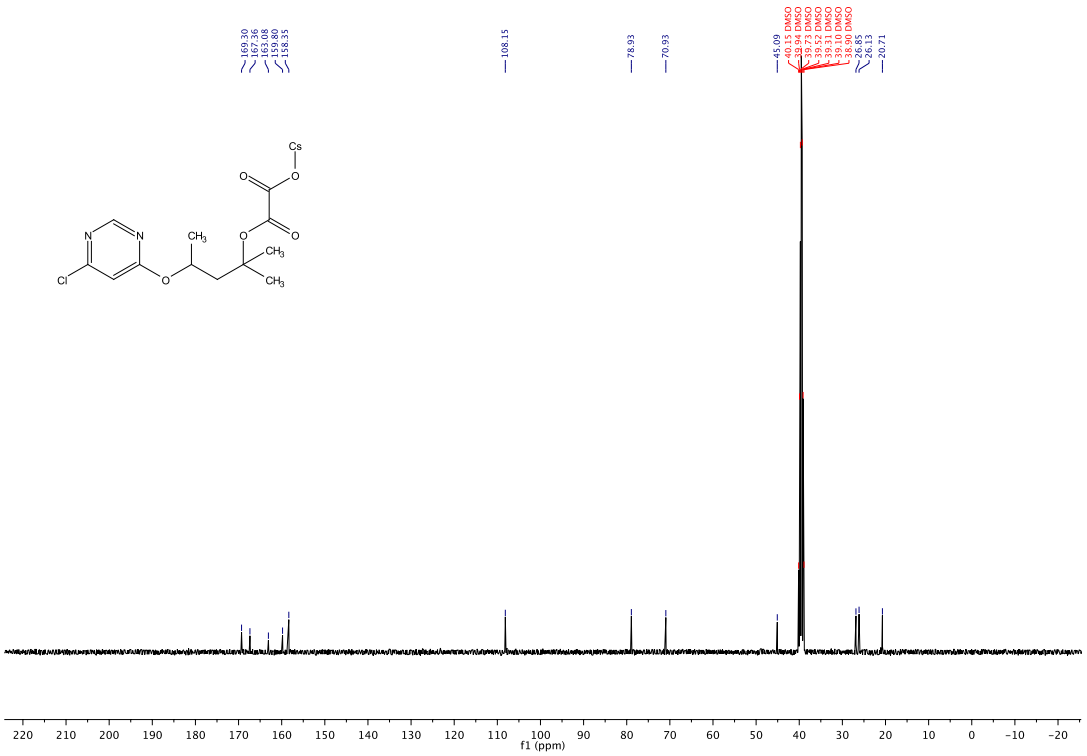
4-((6-chloropyrimidin-4-yl)oxy)-2-methylpentan-2-yl ethyl oxalate



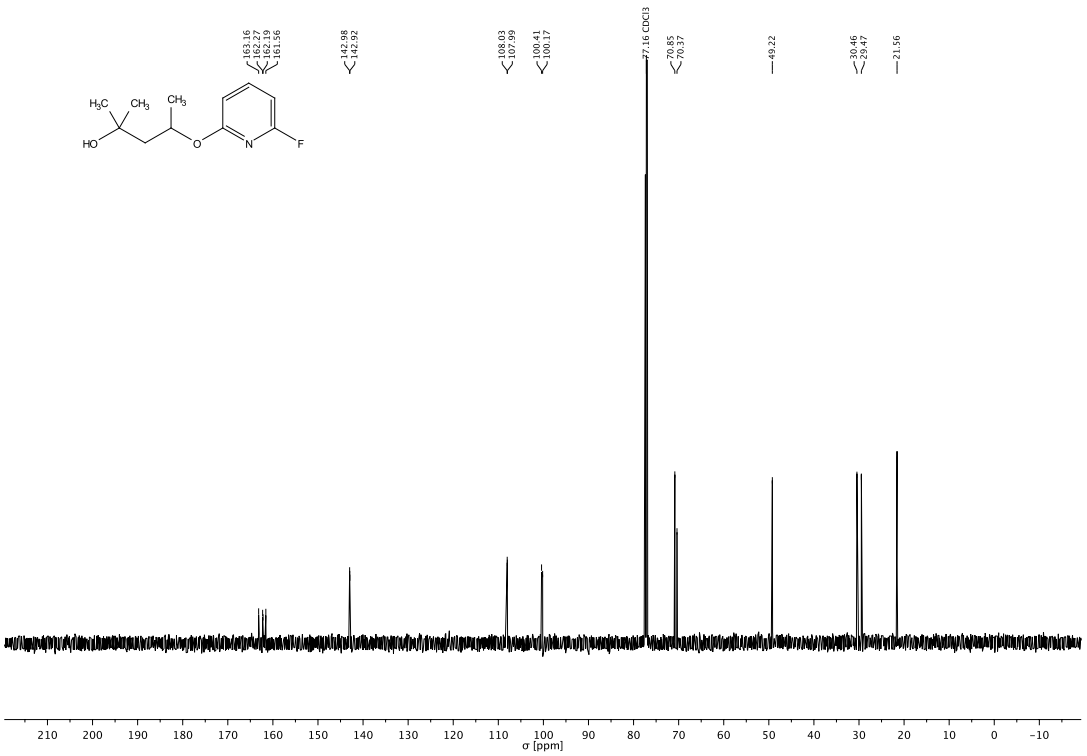


Cesium 2-((4-((6-chloropyrimidin-4-yl)oxy)-2-methylpentan-2-yl)oxy)-2-oxoacetate

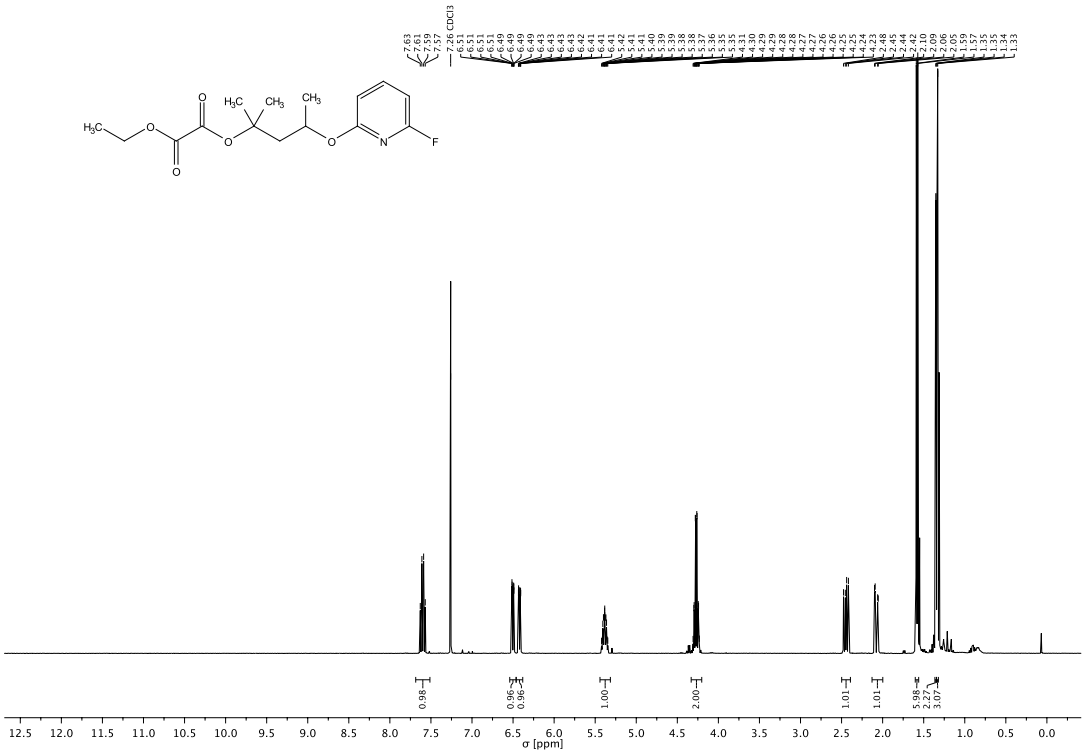


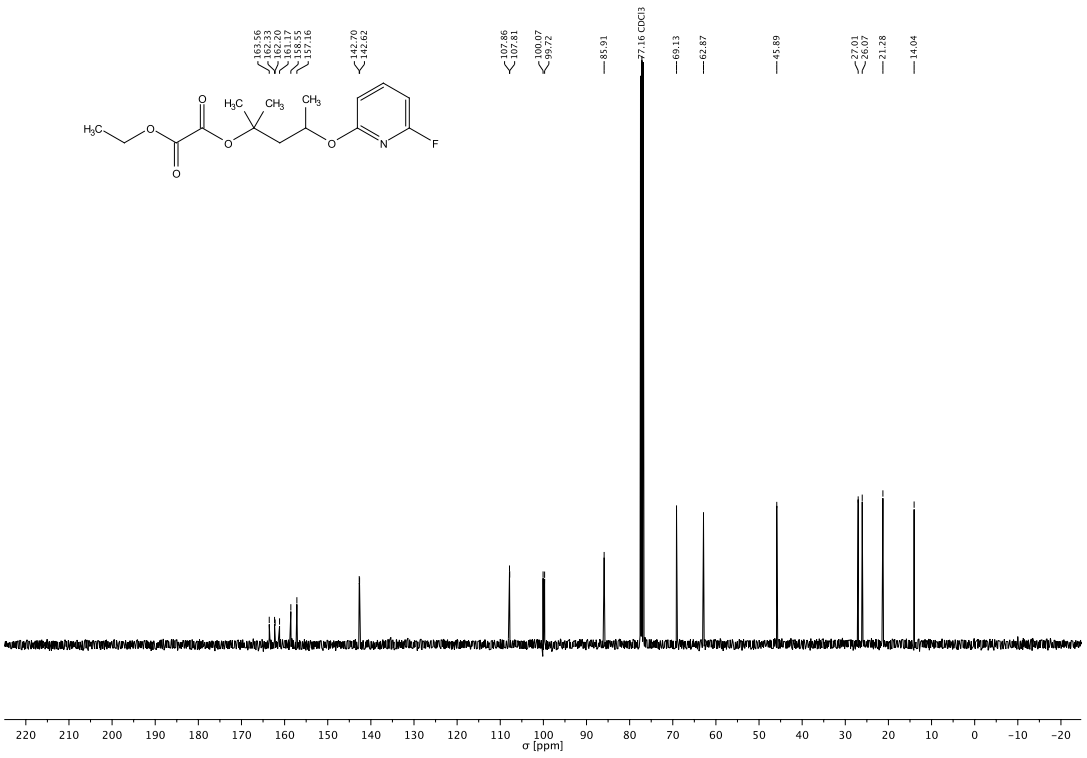


4-((6-fluoropyridin-2-yl)oxy)-2-methylpentan-2-ol

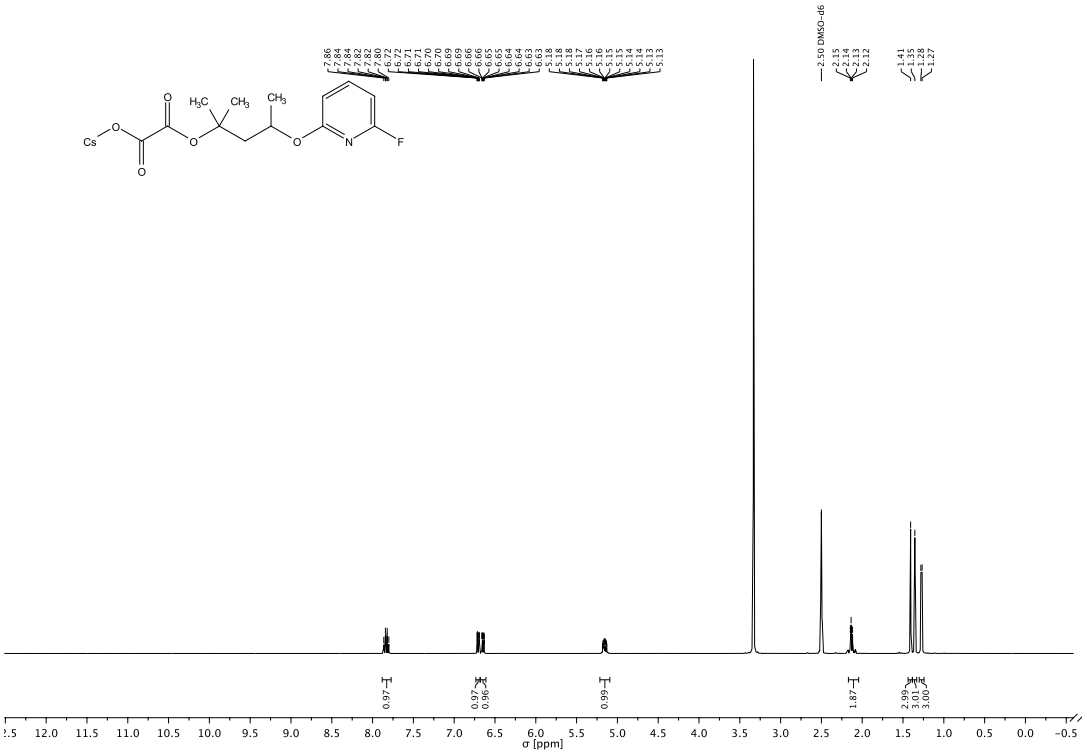


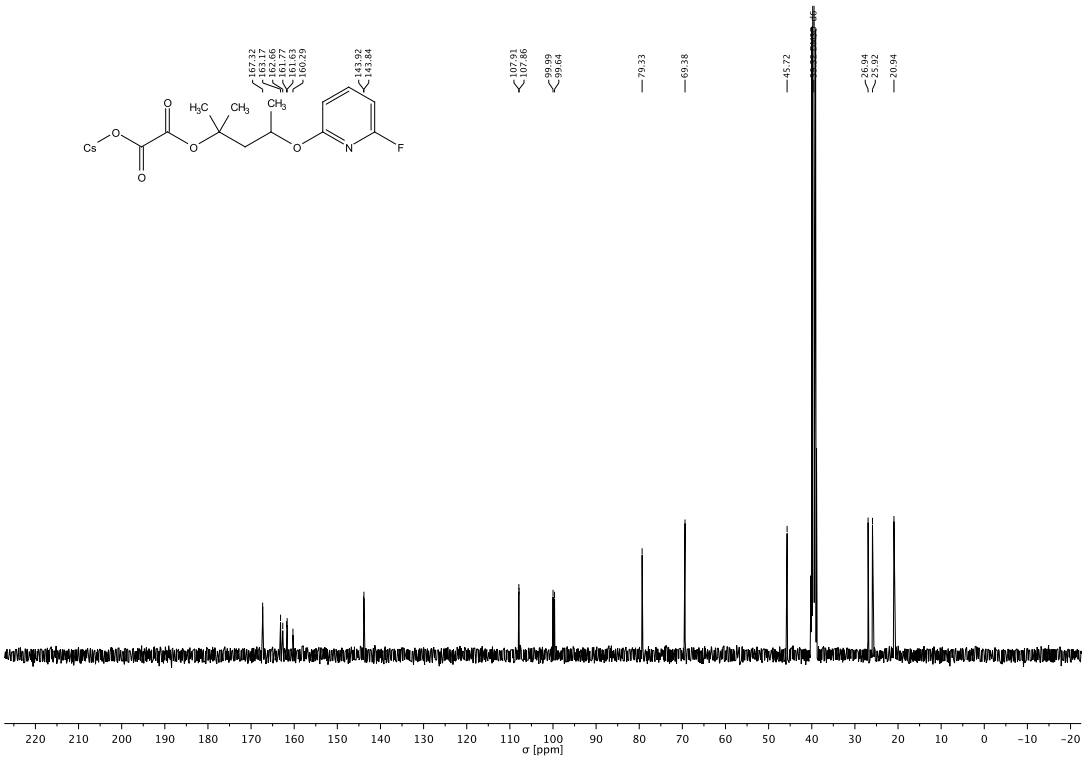
Ethyl (4-((6-fluoropyridin-2-yl)oxy)-2-methylpentan-2-yl) oxalate



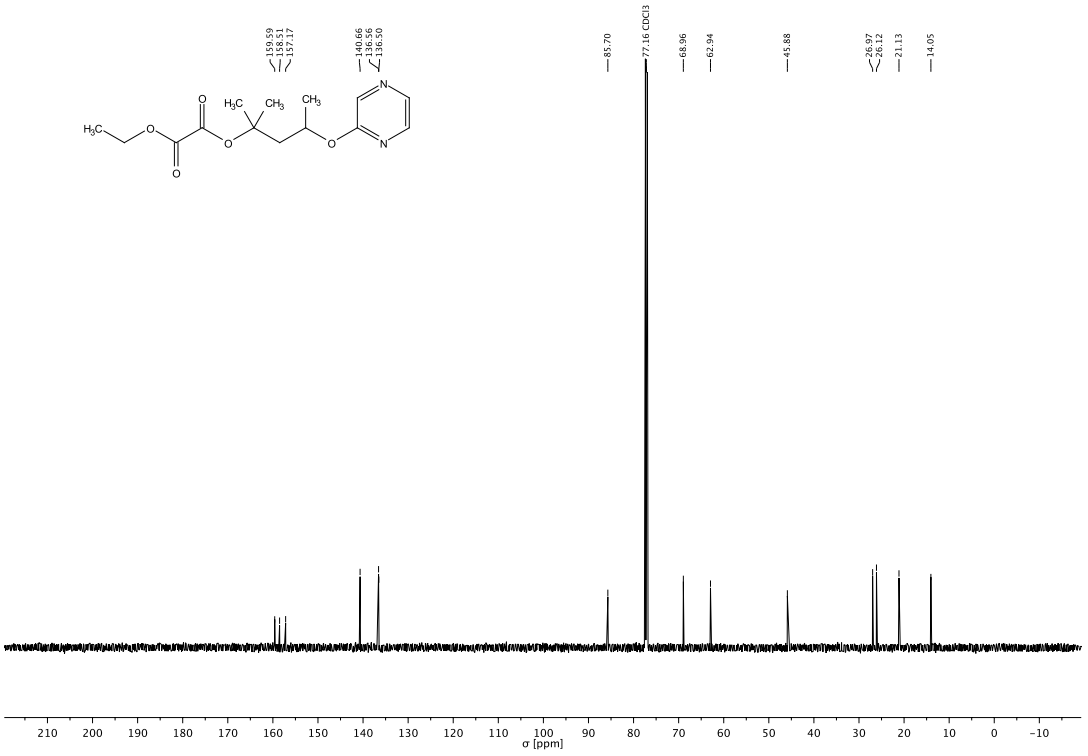


Cesium 2-((4-((6-fluoropyridin-2-yl)oxy)-2-methylpentan-2-yl)oxy)-2-oxoacetate

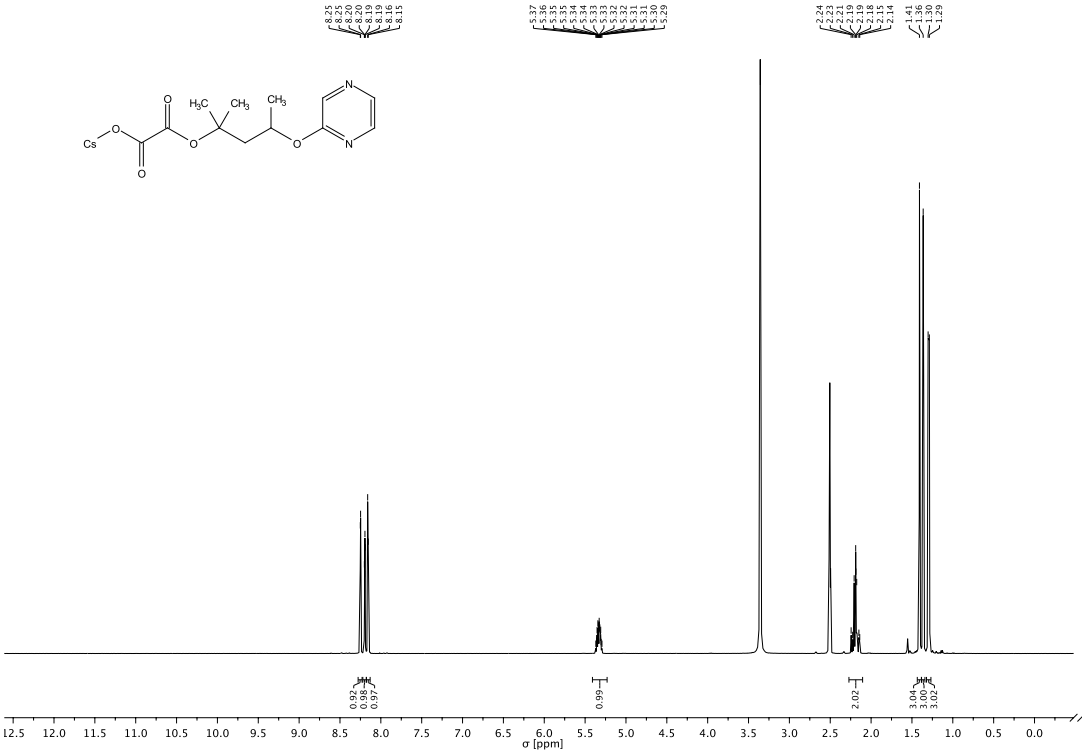


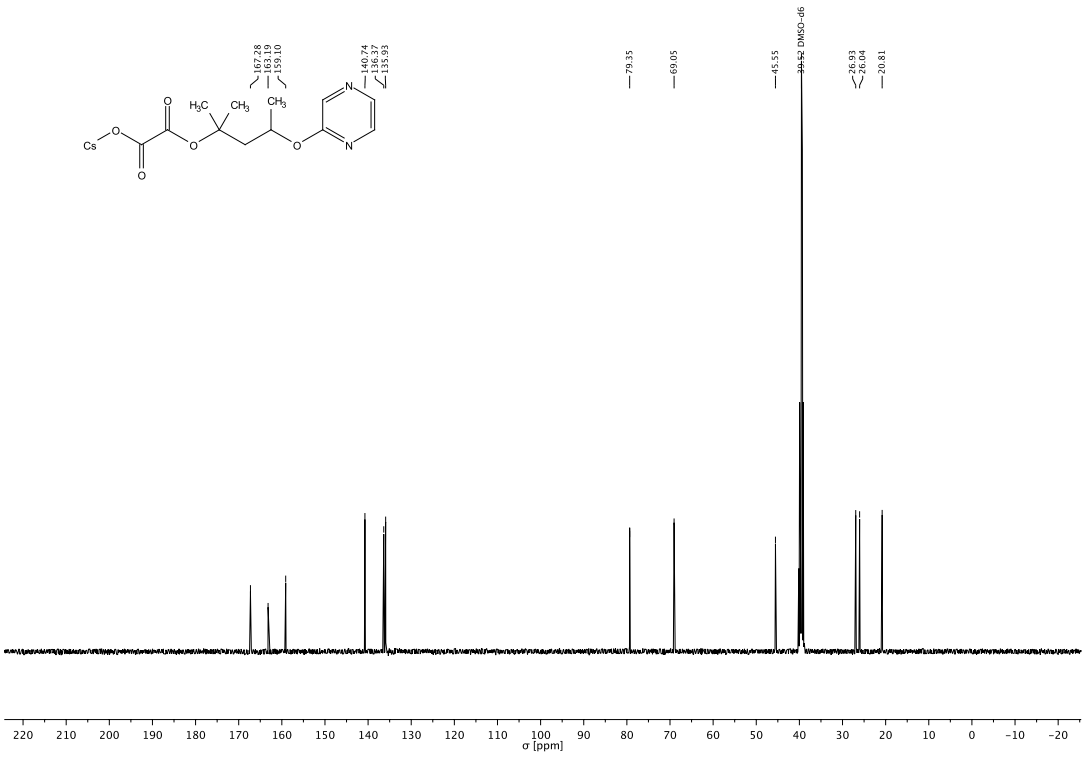


Ethyl (2-methyl-4-(pyrazin-2-yloxy)pentan-2-yl) oxalate

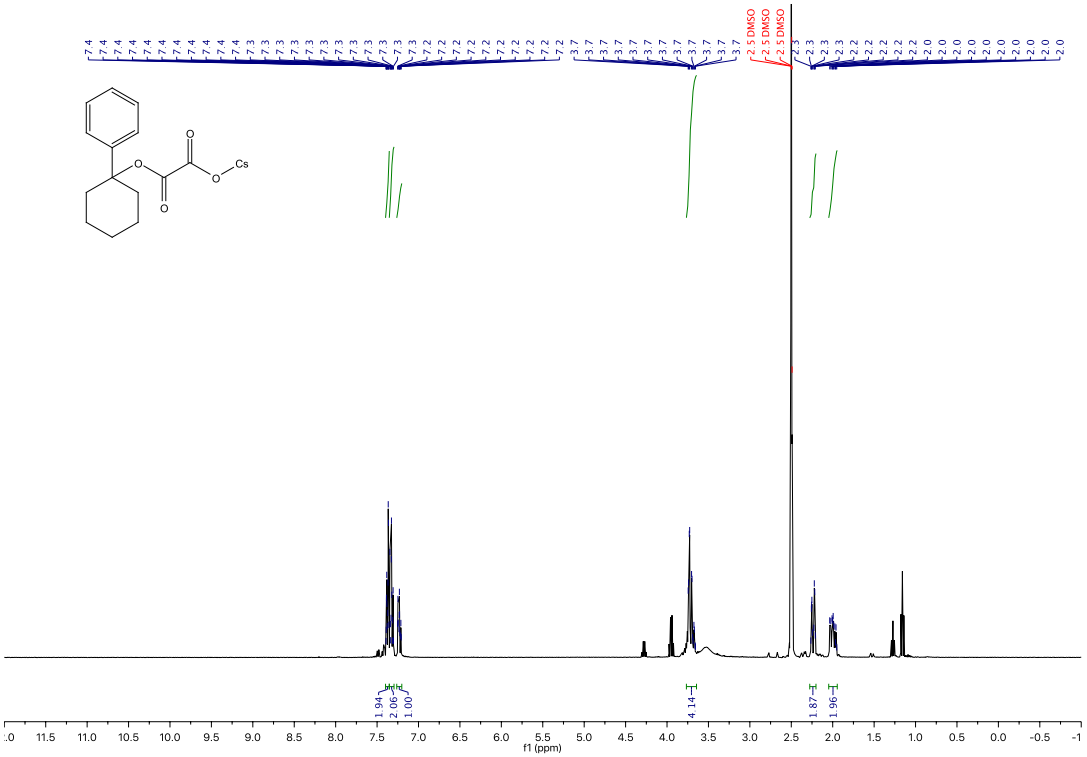


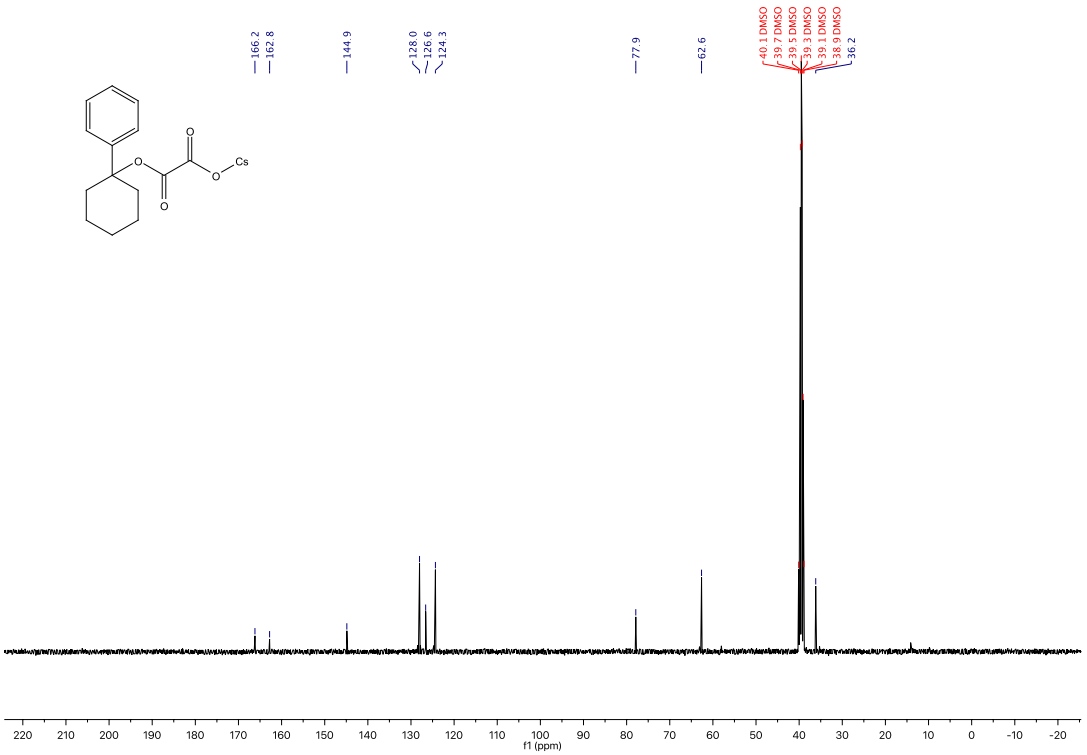
Cesium 2-((2-methyl-4-(pyrazin-2-yloxy)pentan-2-yl)oxy)-2-oxoacetate



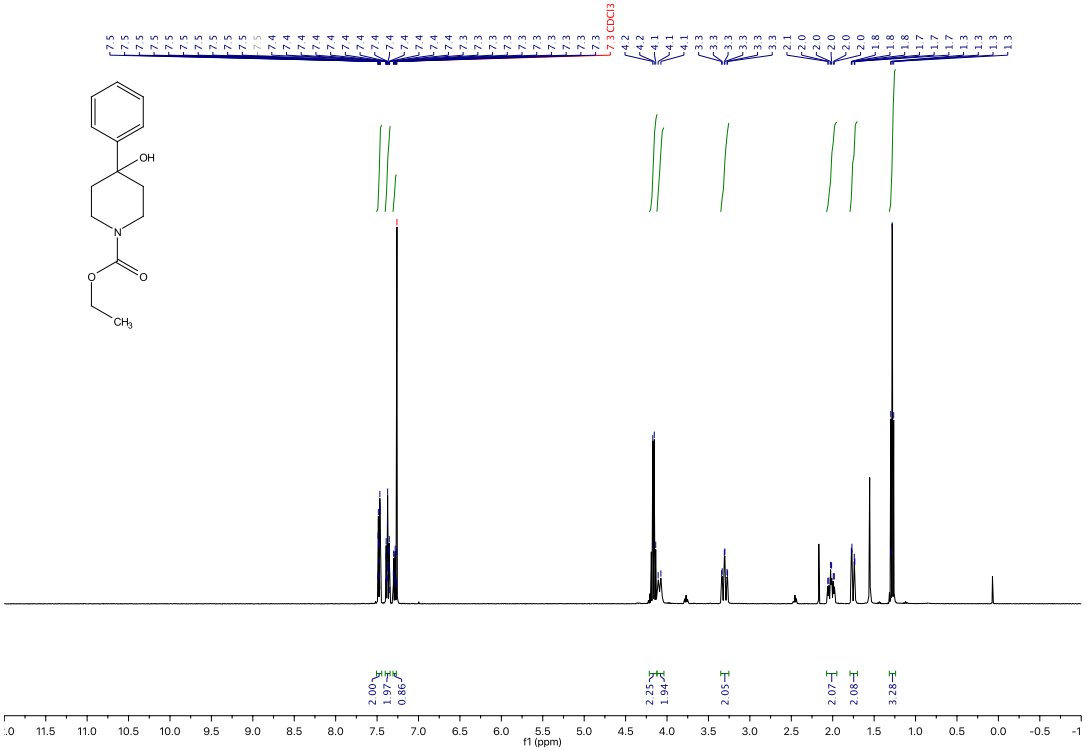


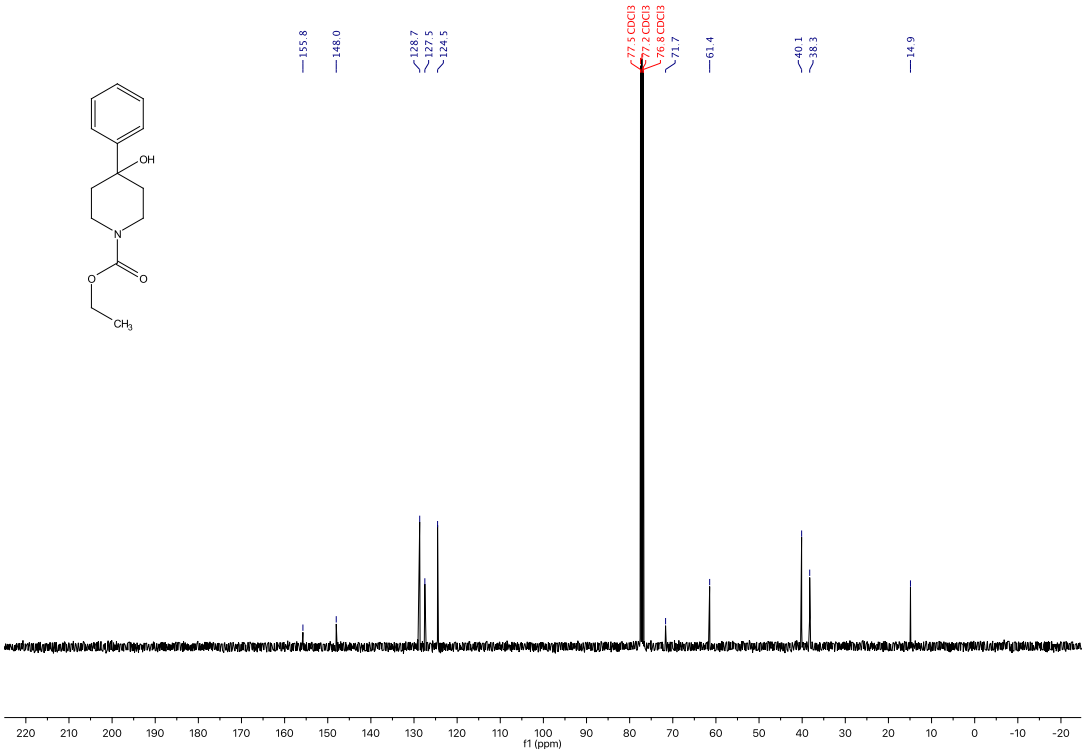
Cesium 2-oxo-2-((4-phenyltetrahydro-2*H*-pyran-4-yl)oxy)acetate



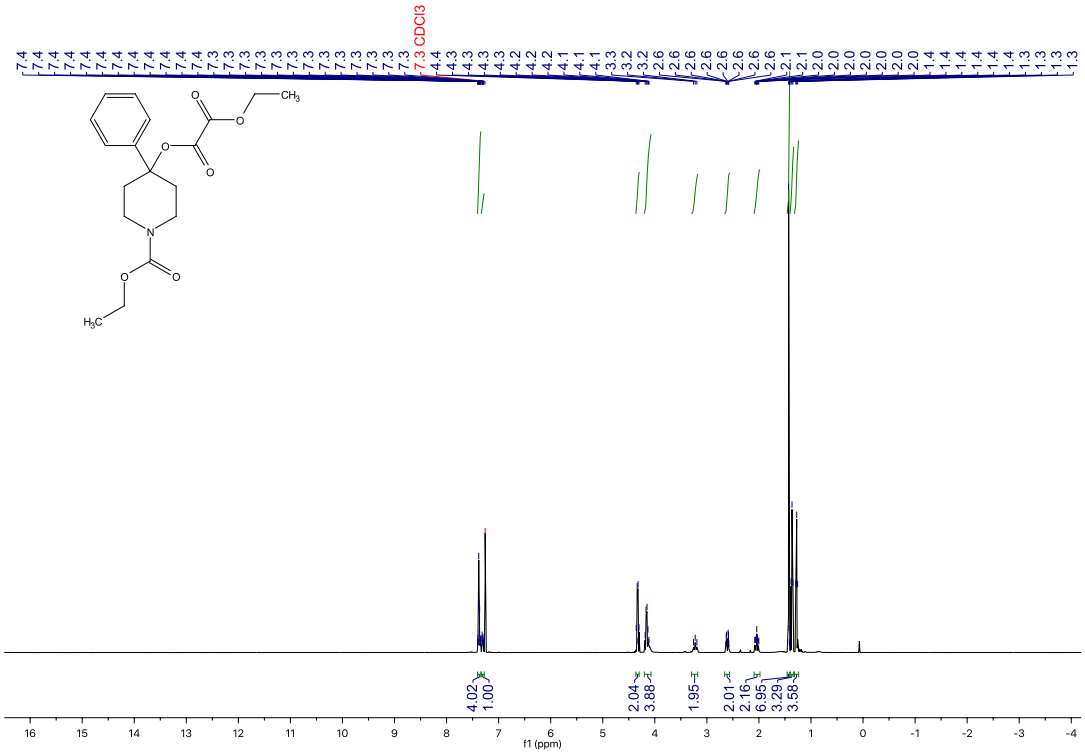


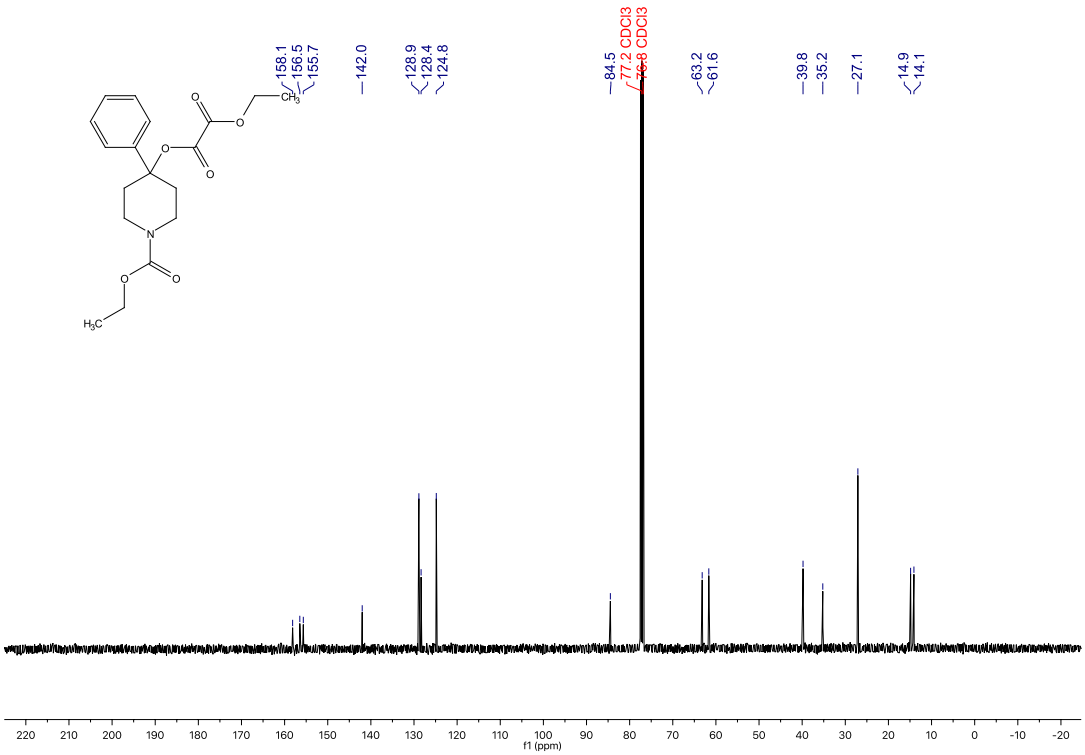
Ethyl 4-hydroxy-4-phenylpiperidine-1-carboxylate



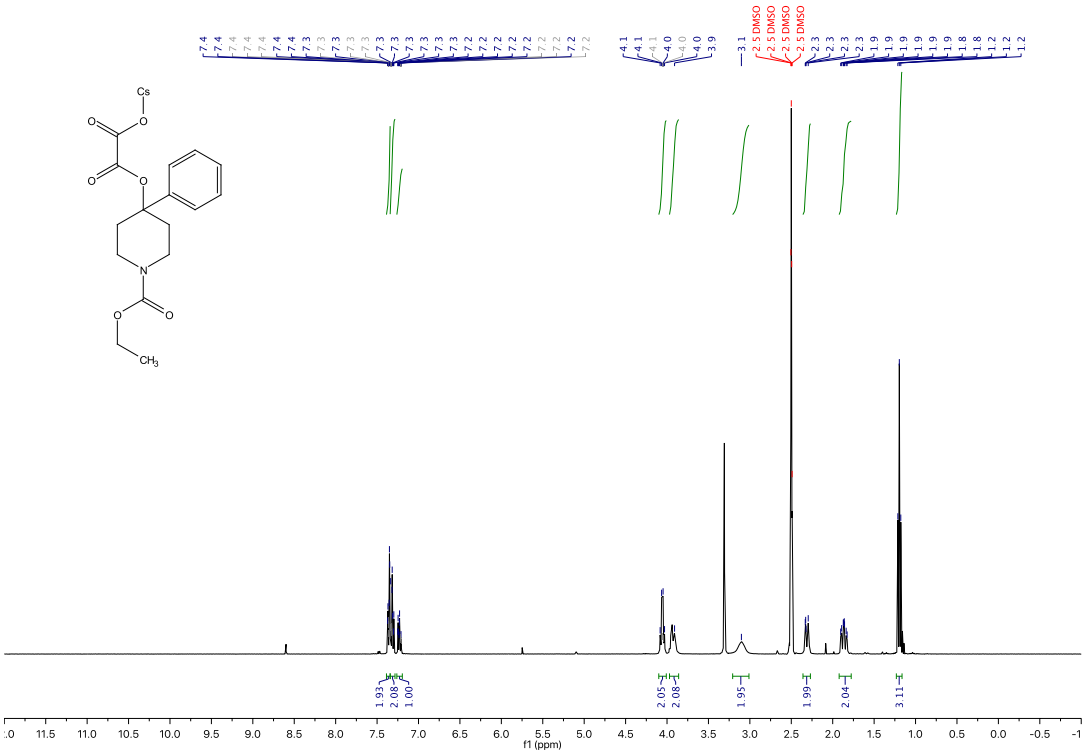


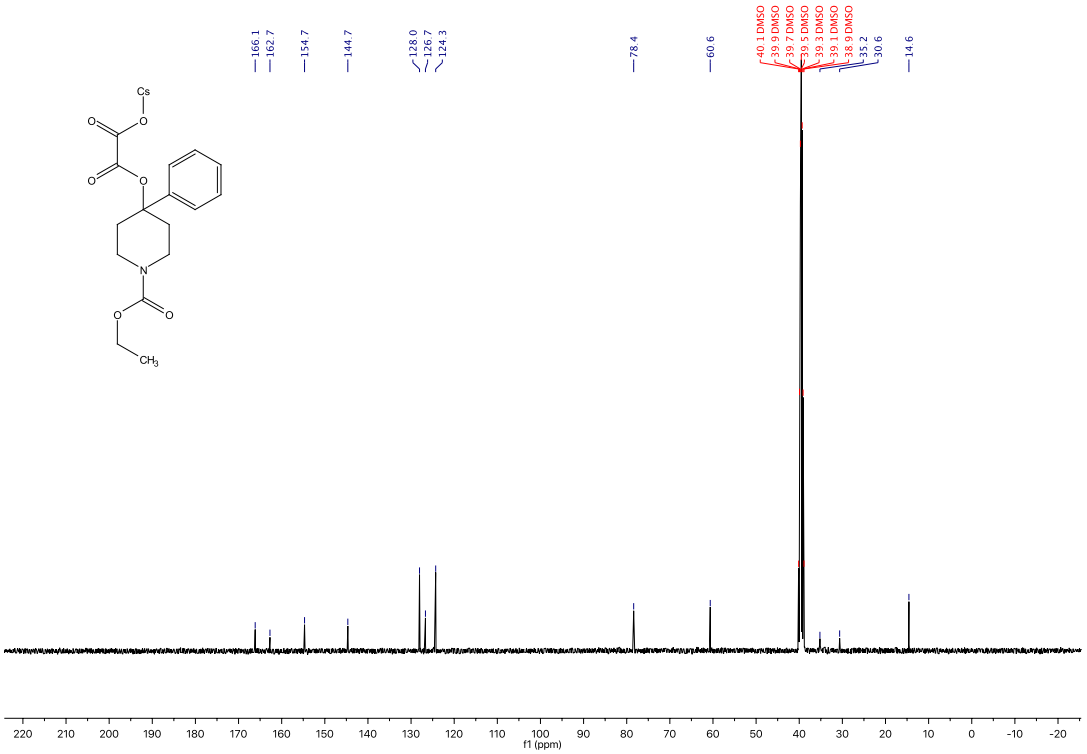
1-(ethoxycarbonyl)-4-phenylpiperidin-4-yl ethyl oxalate



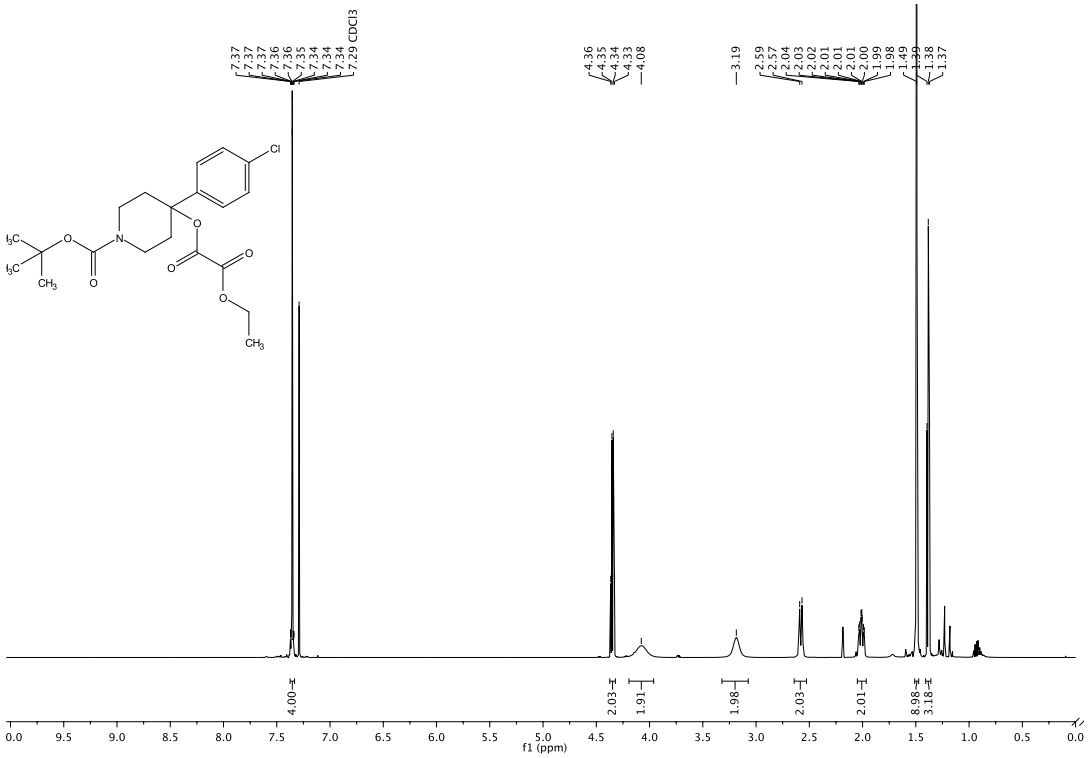


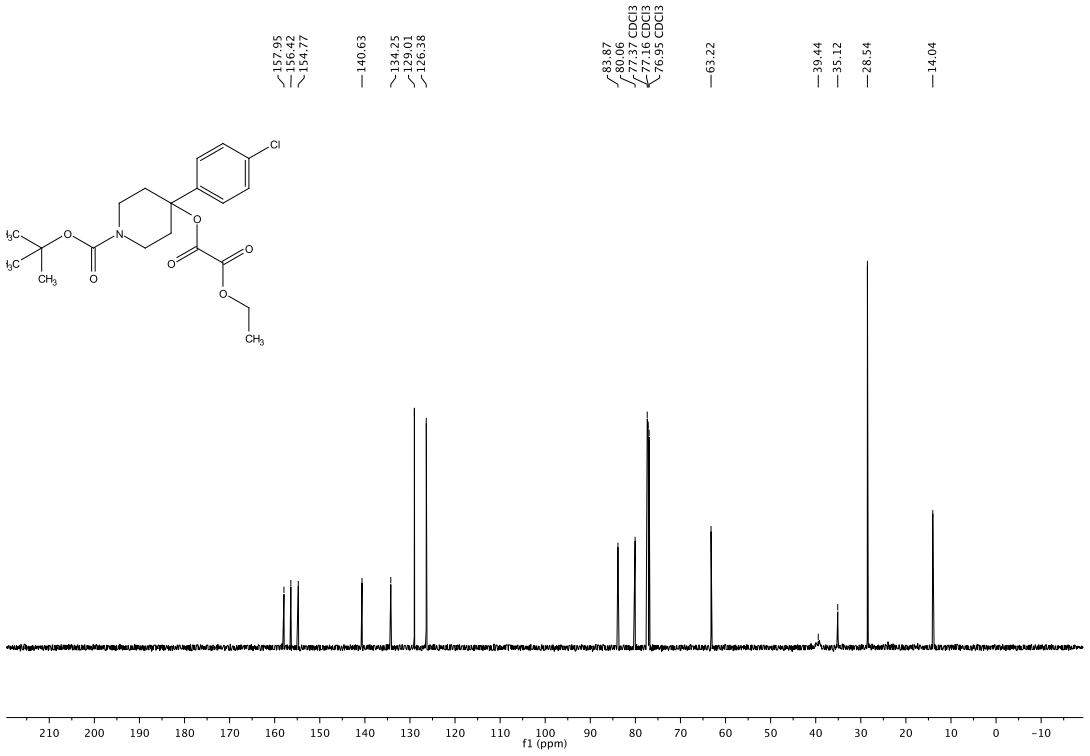
Cesium 2-((1-(ethoxycarbonyl)-4-phenylpiperidin-4-yl)oxy)-2-oxoacetate



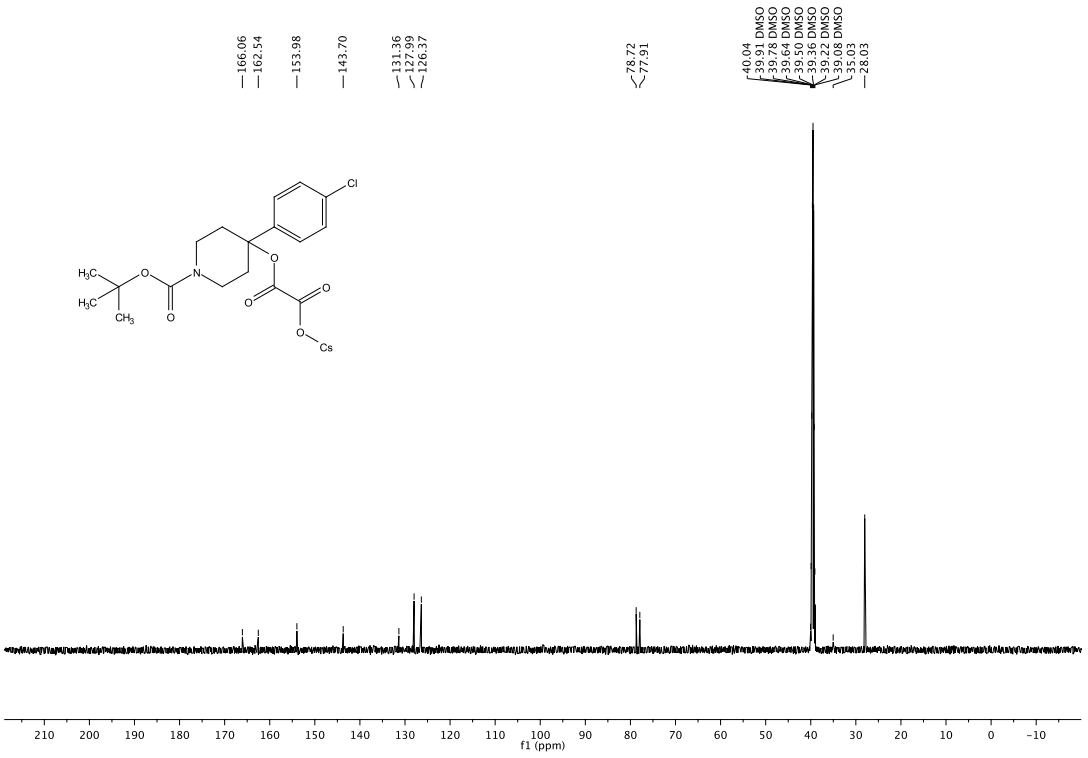


1-(*tert*-butoxycarbonyl)-4-(4-chlorophenyl)piperidin-4-yl ethyl oxalate

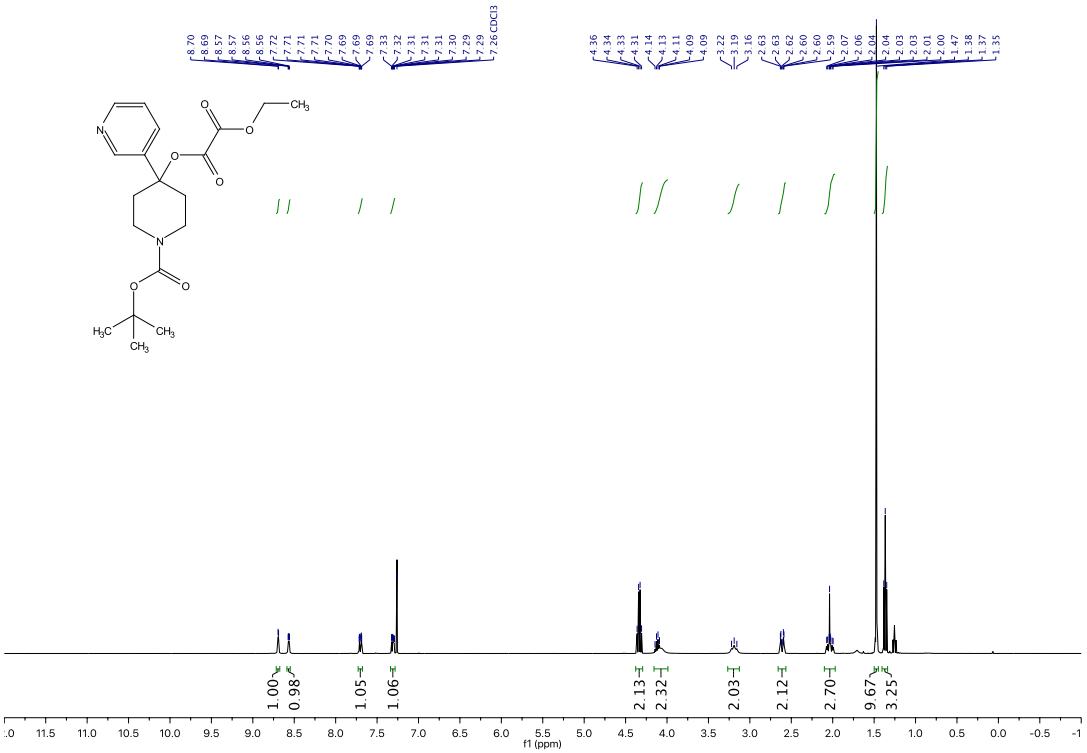




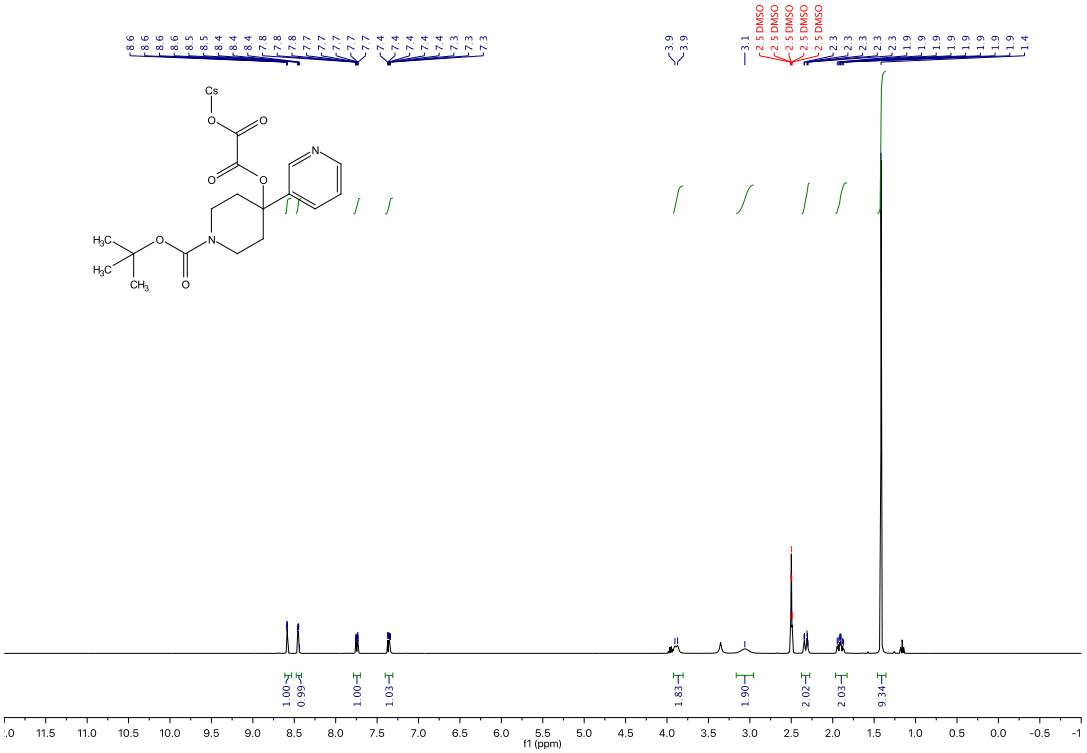
Cesium 2-((1-(*tert*-butoxycarbonyl)-4-(4-chlorophenyl)piperidin-4-yl)oxy)-2-oxoacetate

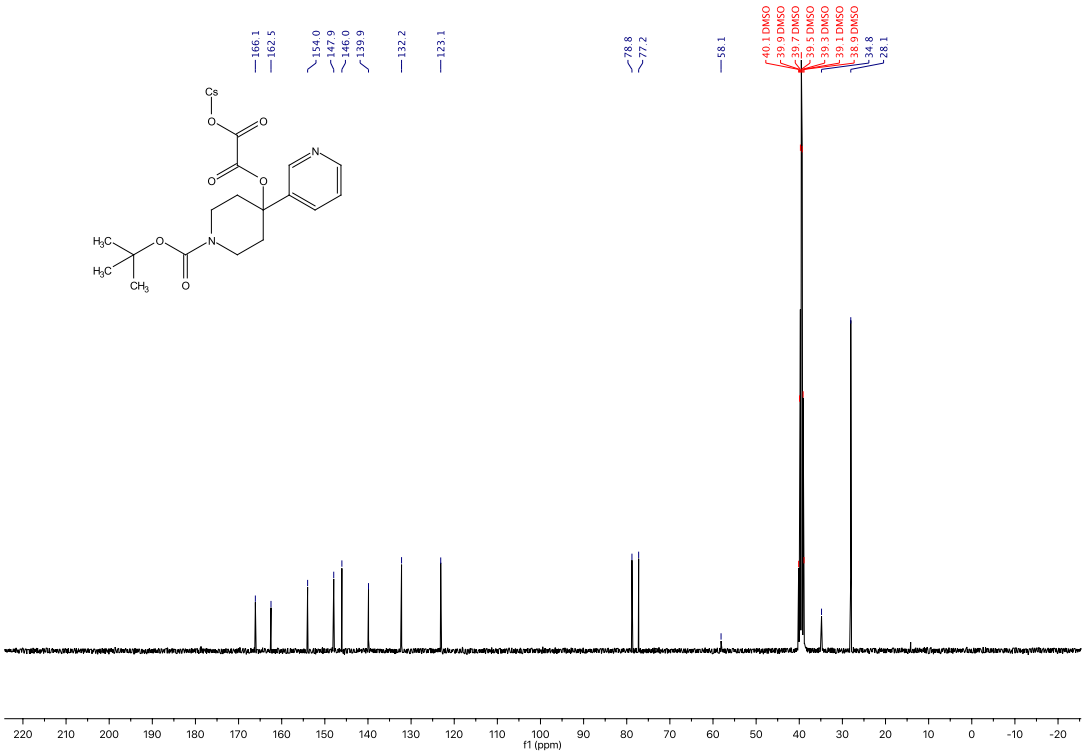


1-(*tert*-butoxycarbonyl)-4-(pyridin-3-yl)piperidin-4-yl ethyl oxalate

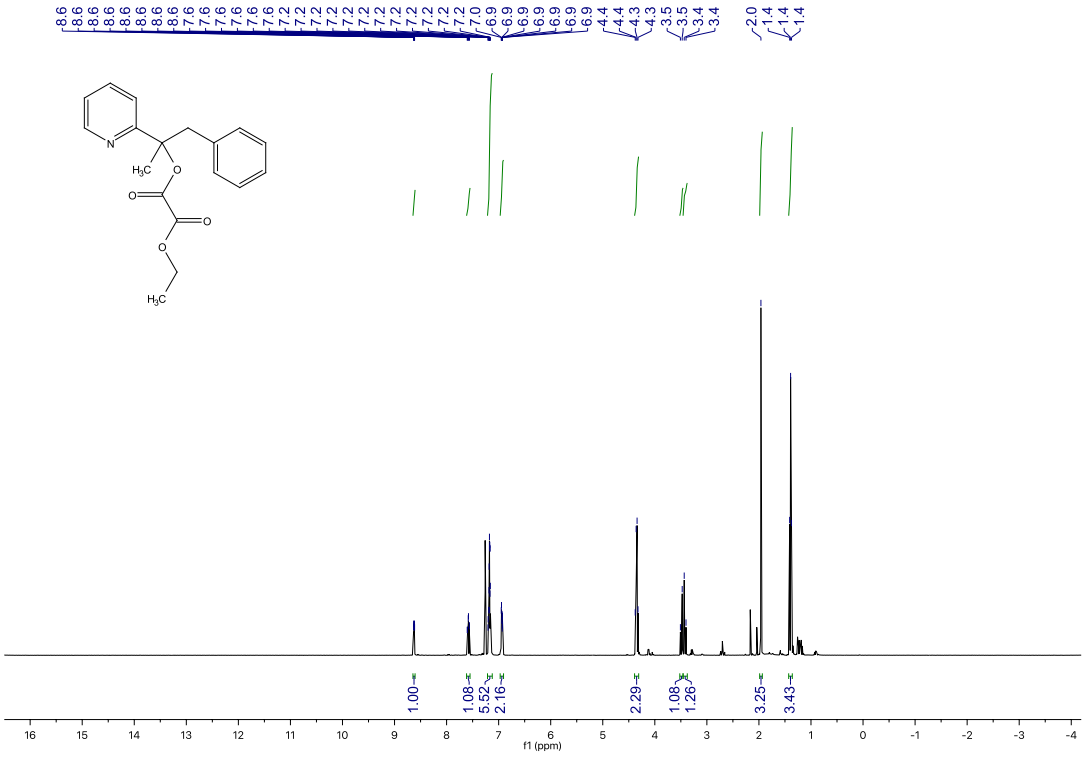


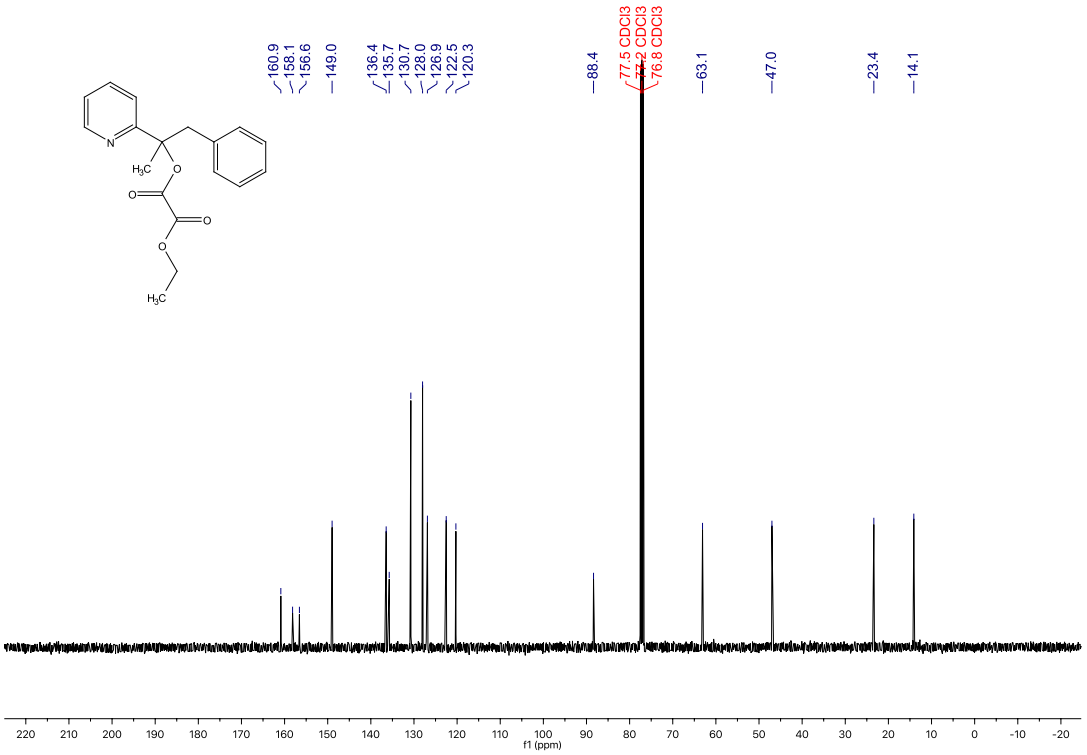
Cesium 2-((1-(*tert*-butoxycarbonyl)-4-(pyridin-3-yl)piperidin-4-yl)oxy)-2-oxoacetate



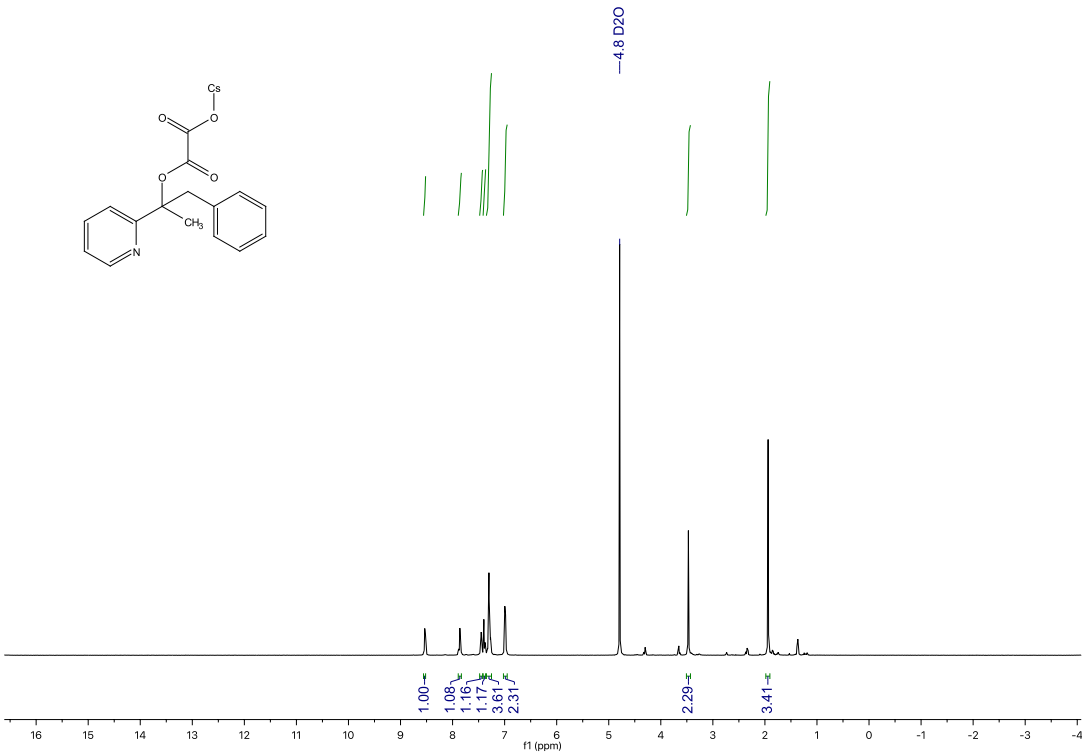


Ethyl (1-phenyl-2-(pyridin-2-yl)propan-2-yl) oxalate

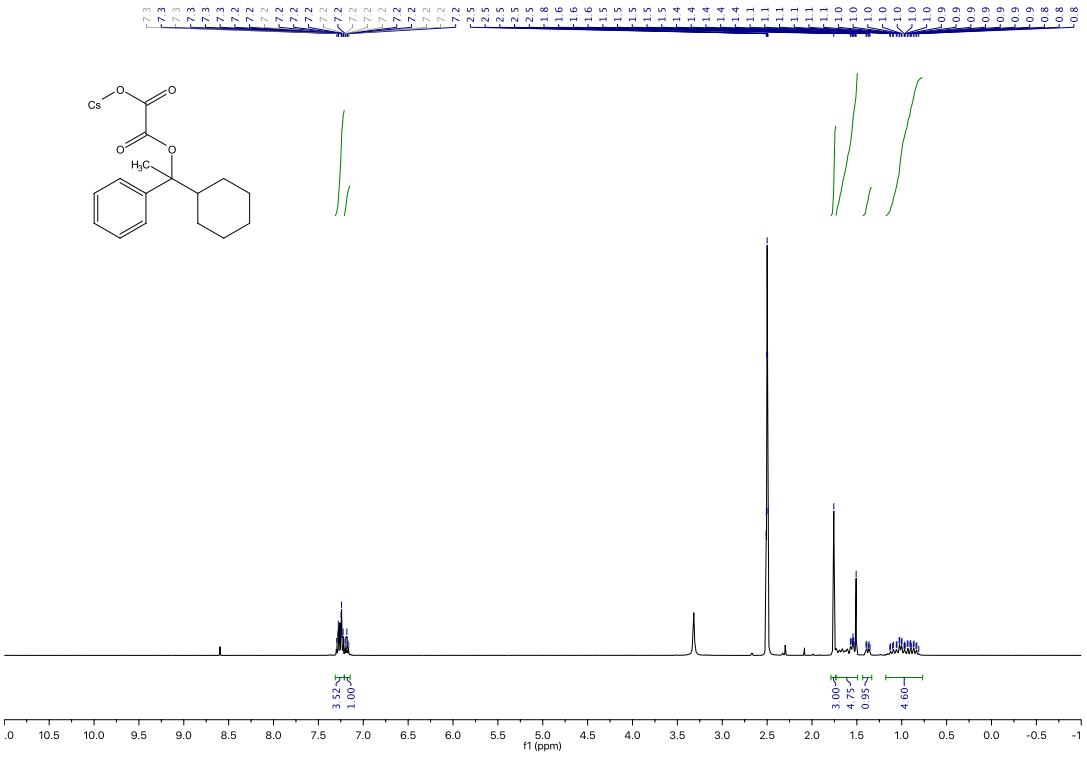


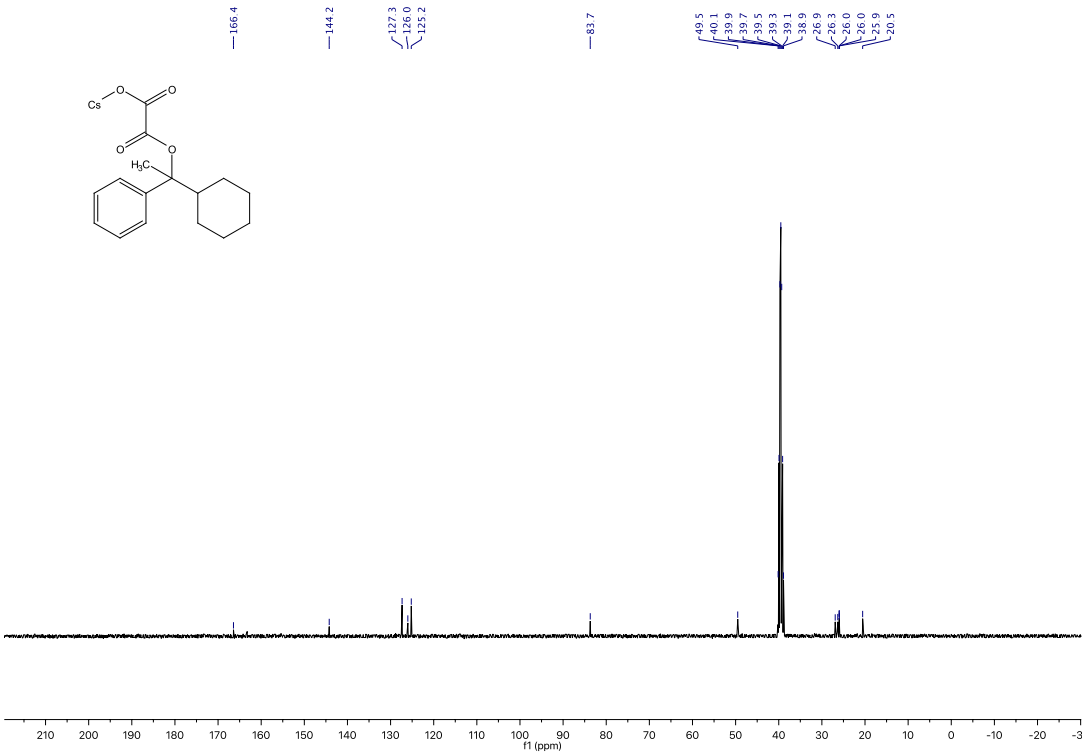


Cesium 2-oxo-2-((1-phenyl-2-(pyridin-2-yl)propan-2-yl)oxy)acetate

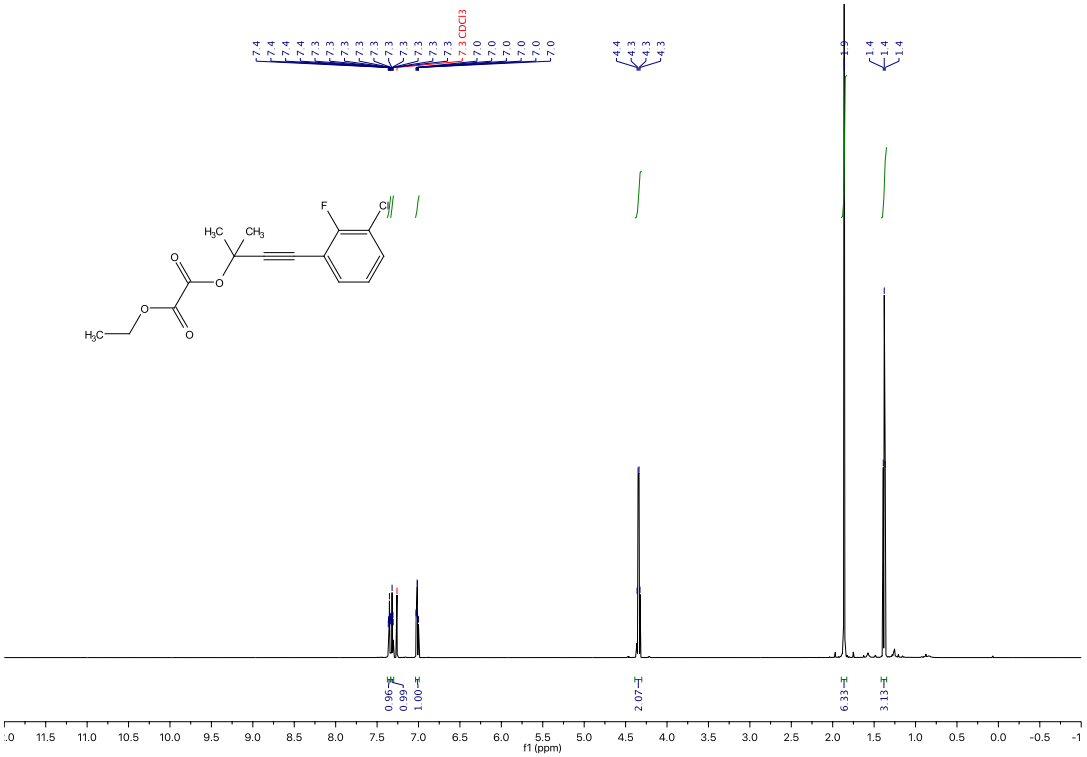


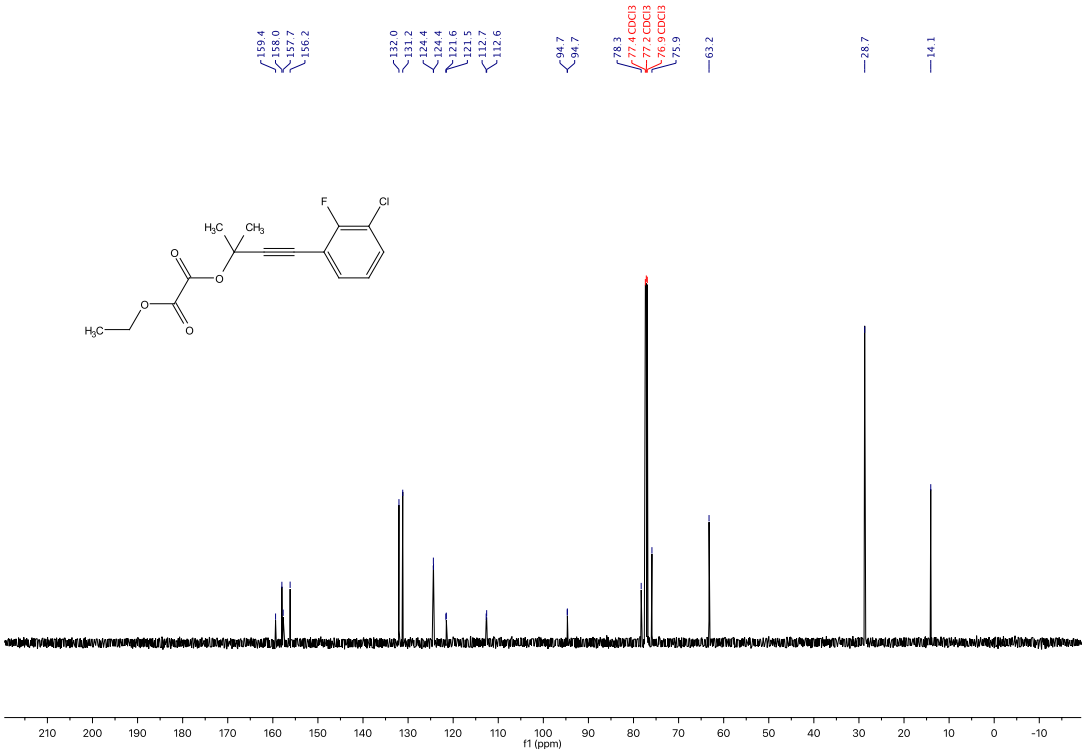
Cesium 2-(1-cyclohexyl-1-phenylethoxy)-2-oxoacetate



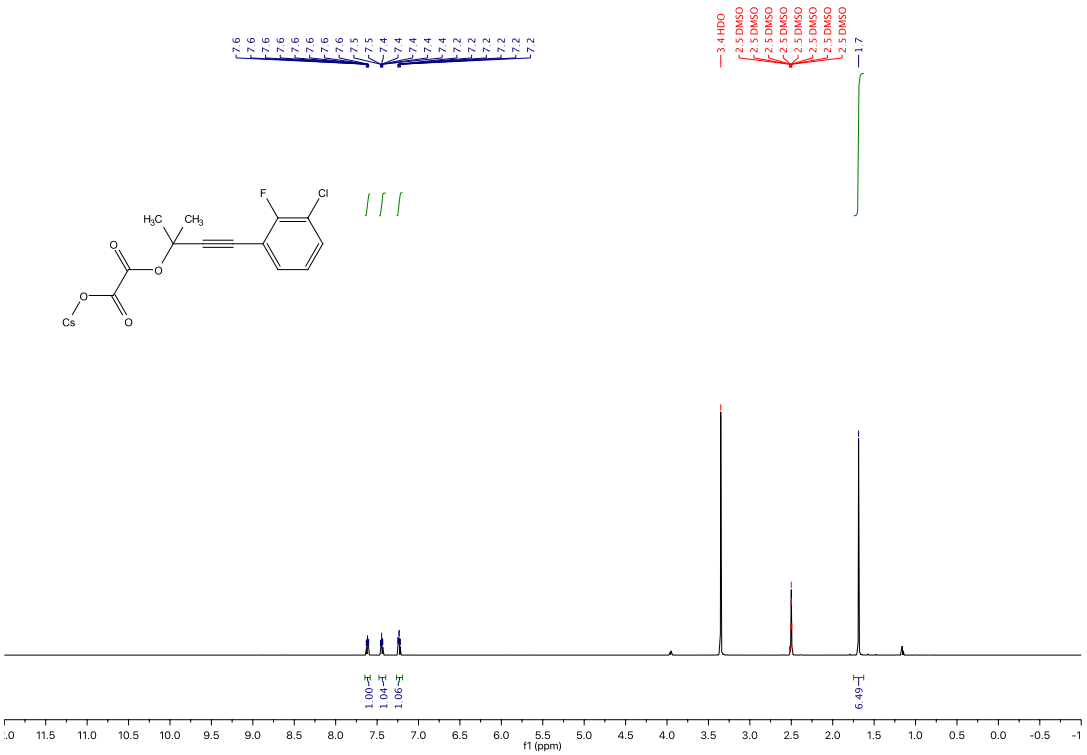


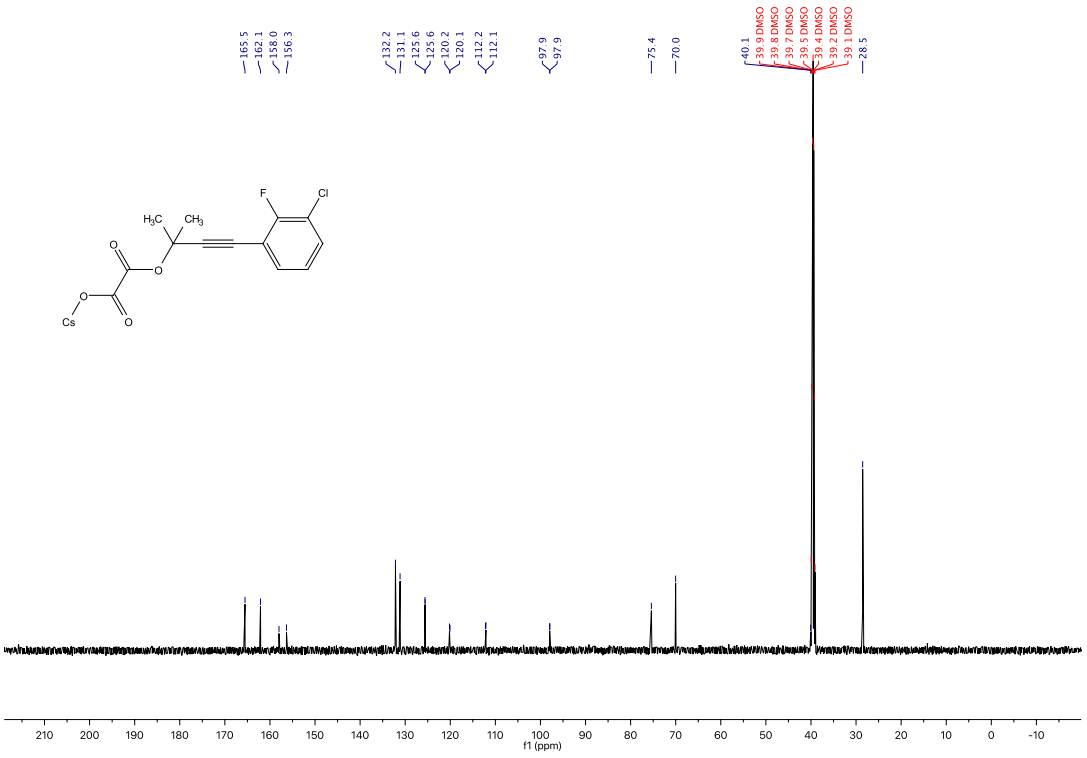
4-(3-chloro-2-fluorophenyl)-2-methylbut-3-yn-2-yl ethyl oxalate



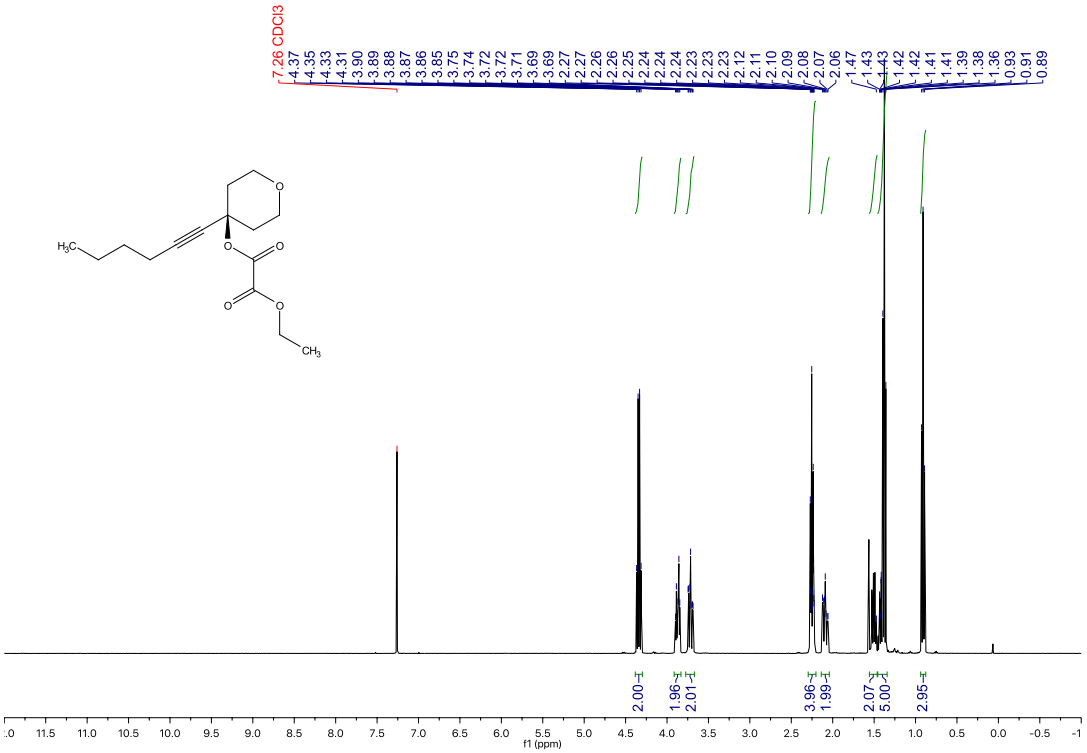


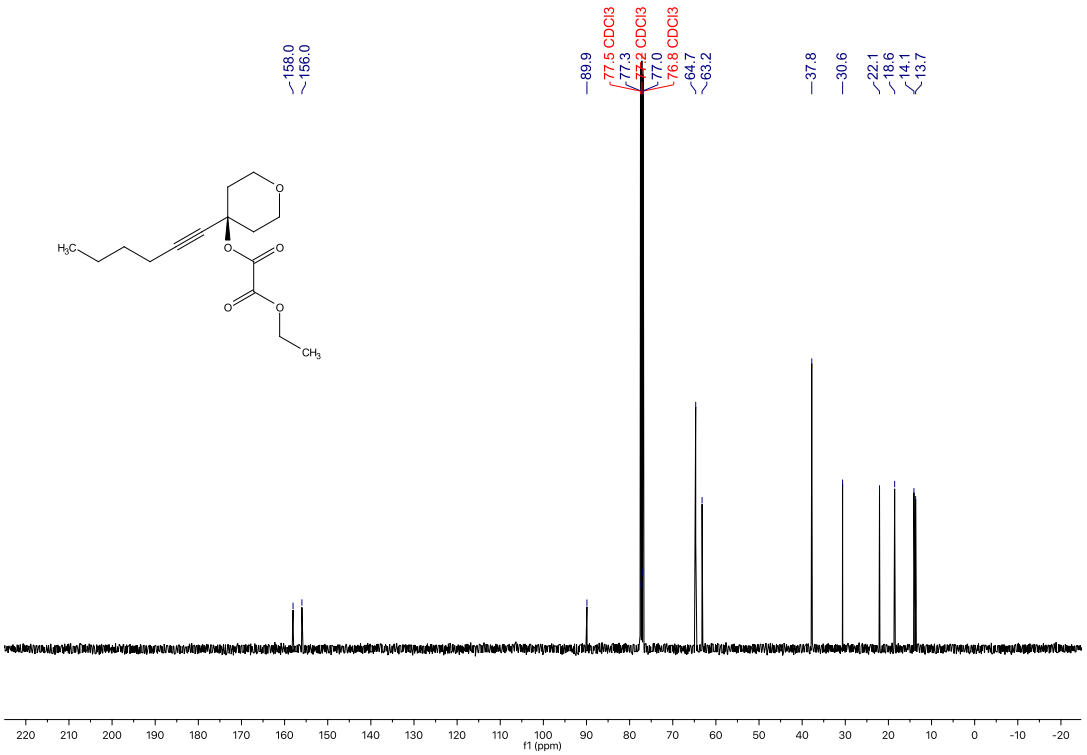
Cesium 2-((4-(3-chloro-2-fluorophenyl)-2-methylbut-3-yn-2-yl)oxy)-2-oxoacetate



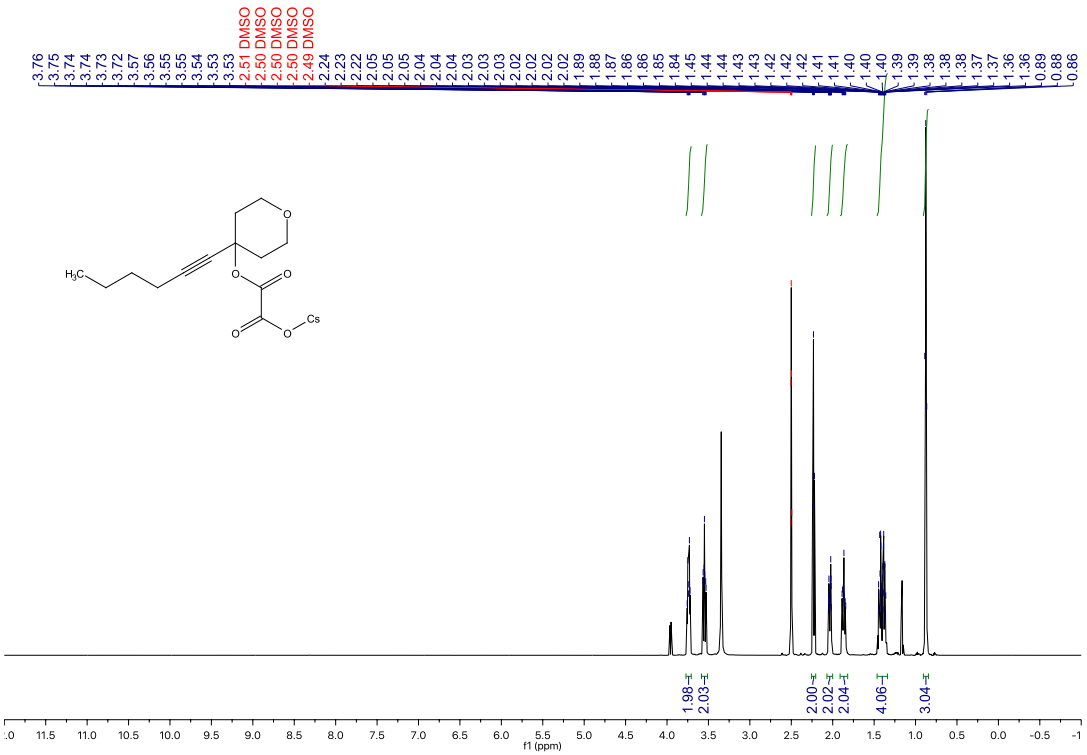


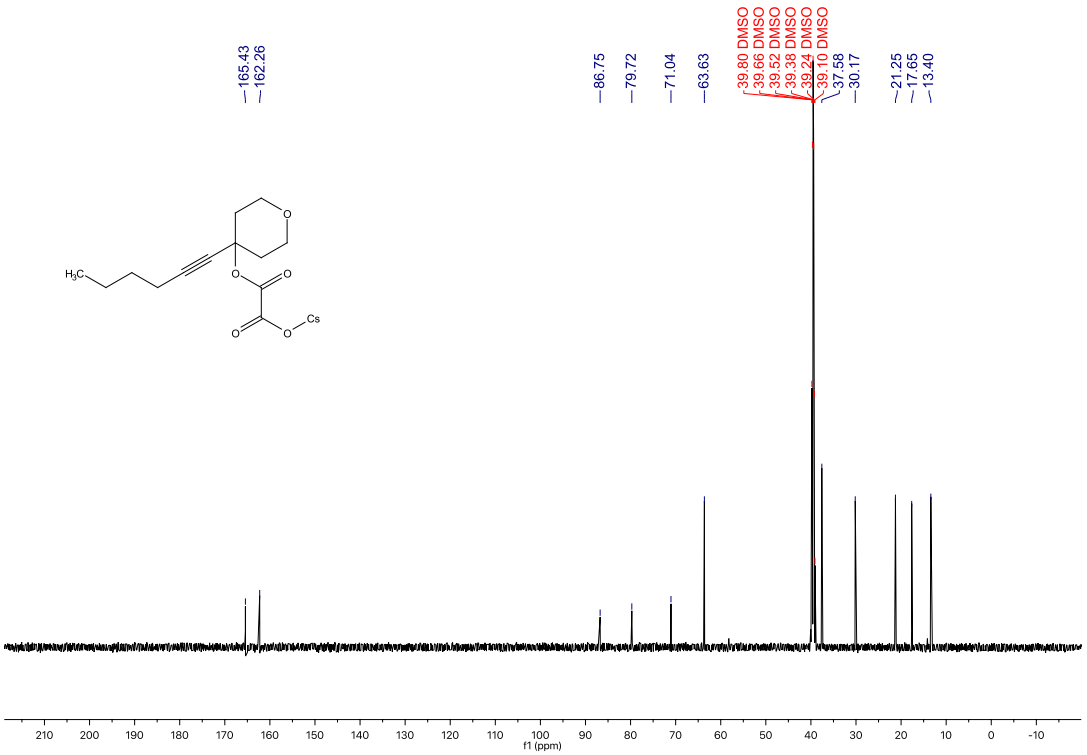
Ethyl (4-(hex-1-yn-1-yl)tetrahydro-2*H*-pyran-4-yl) oxalate



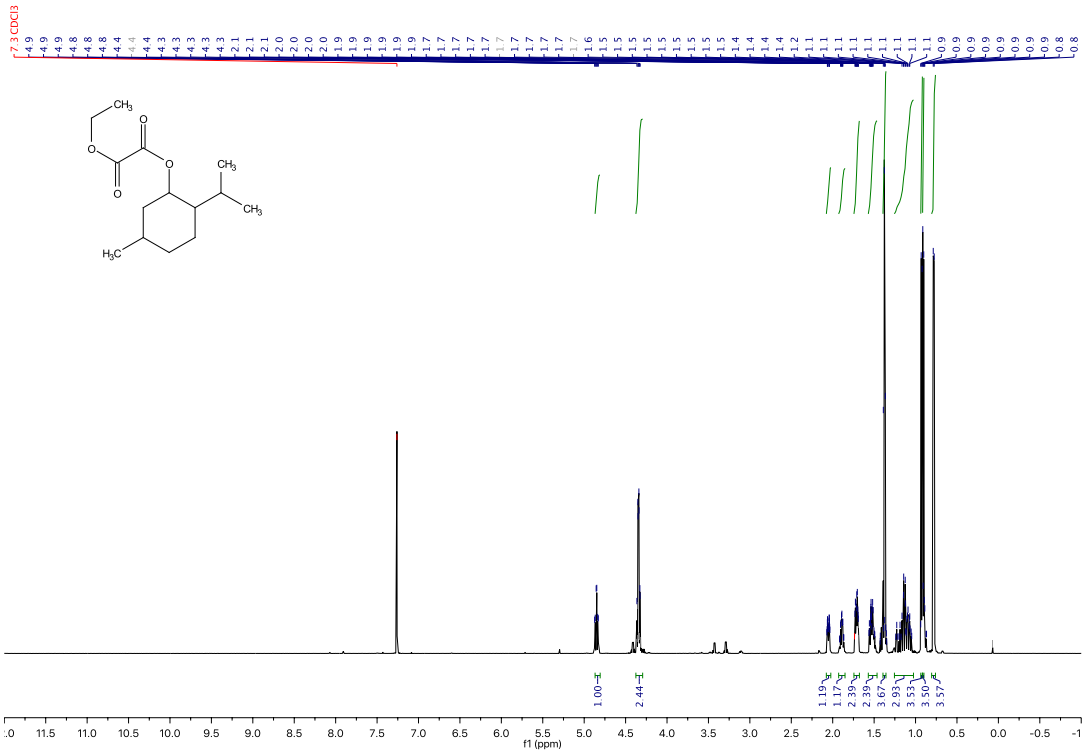


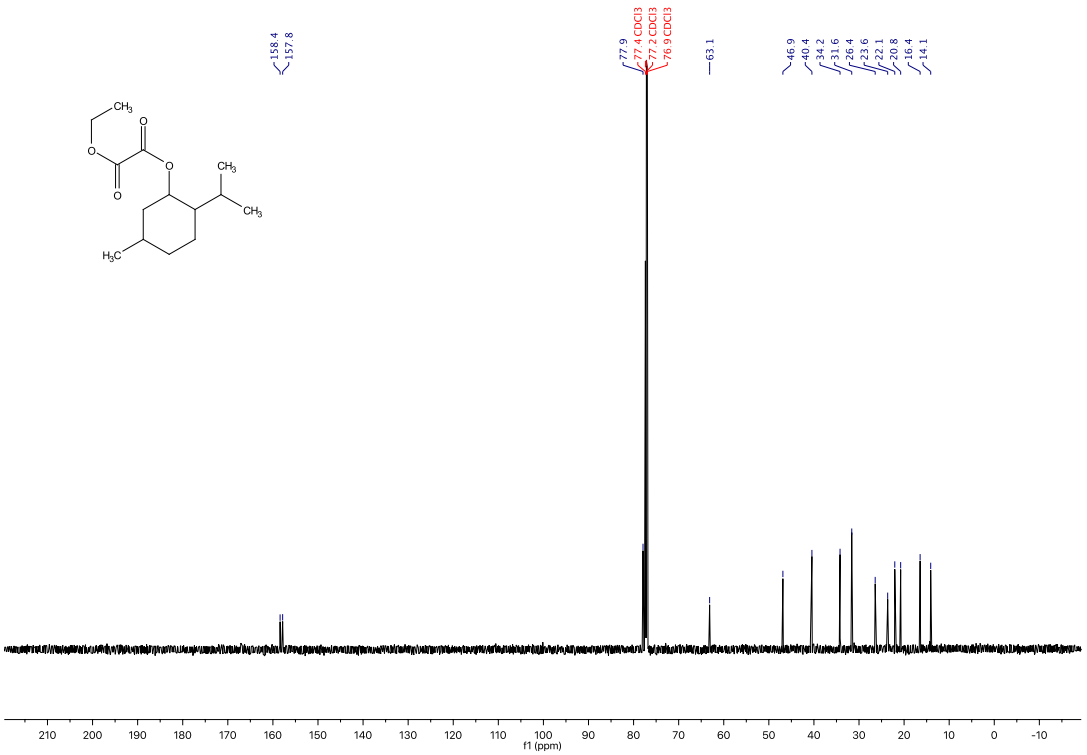
Cesium 2-((4-(hex-1-yn-1-yl)tetrahydro-2*H*-pyran-4-yl)oxy)-2-oxoacetate



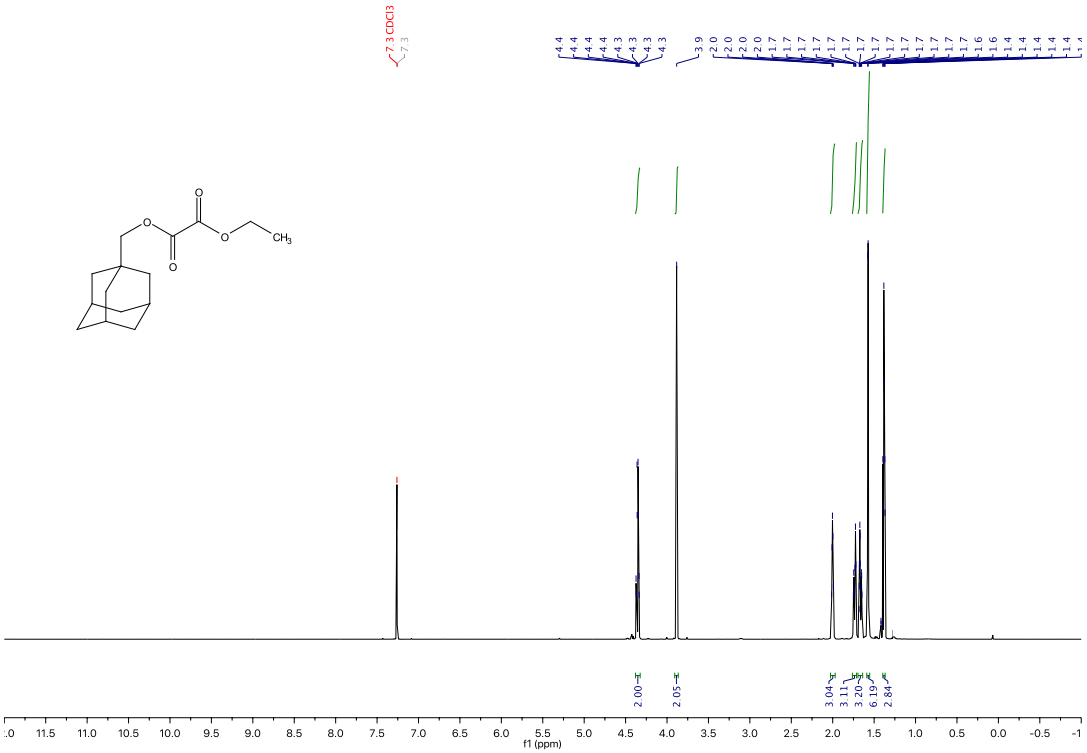


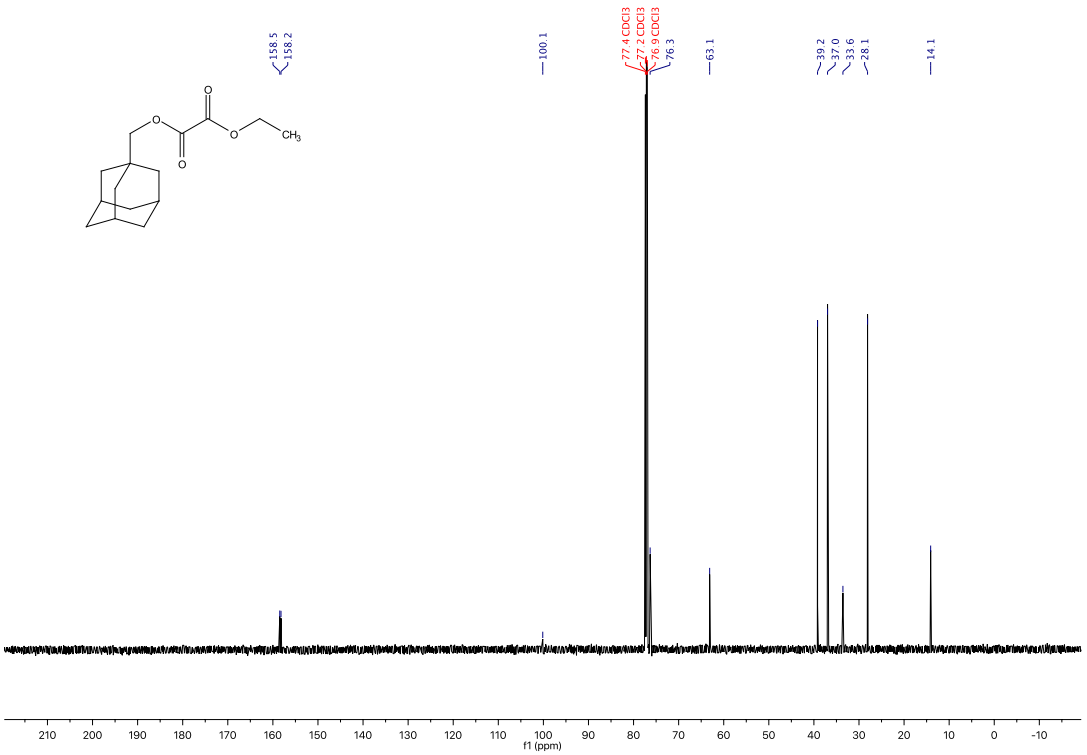
Ethyl ((2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl) oxalate



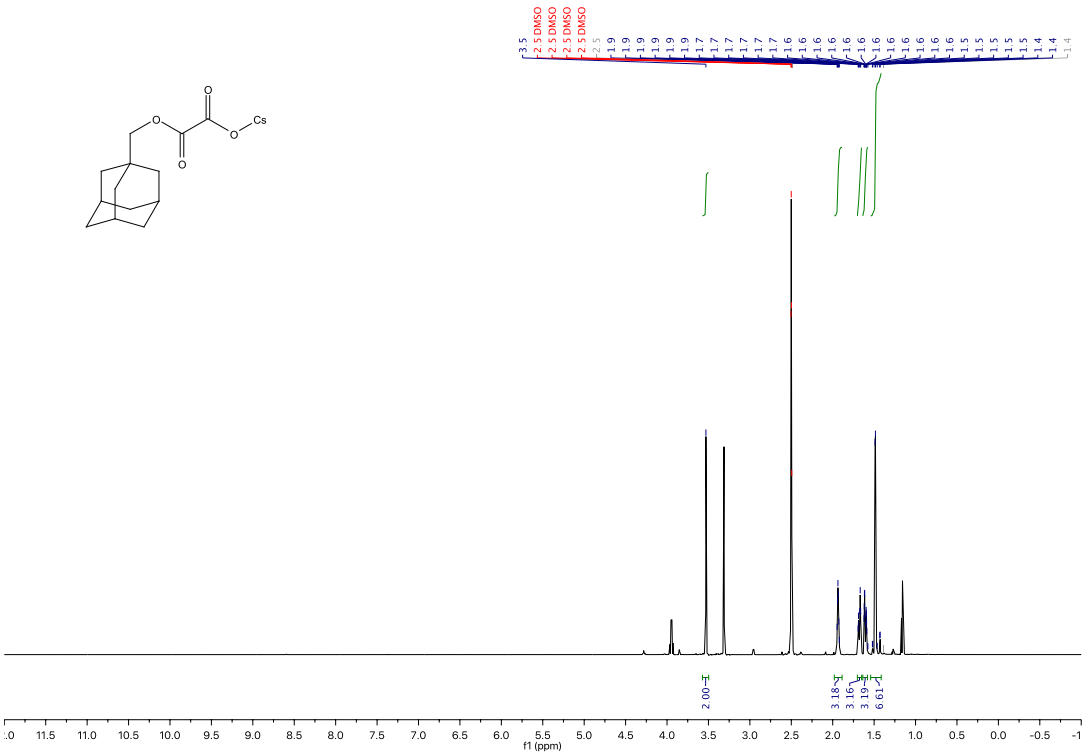


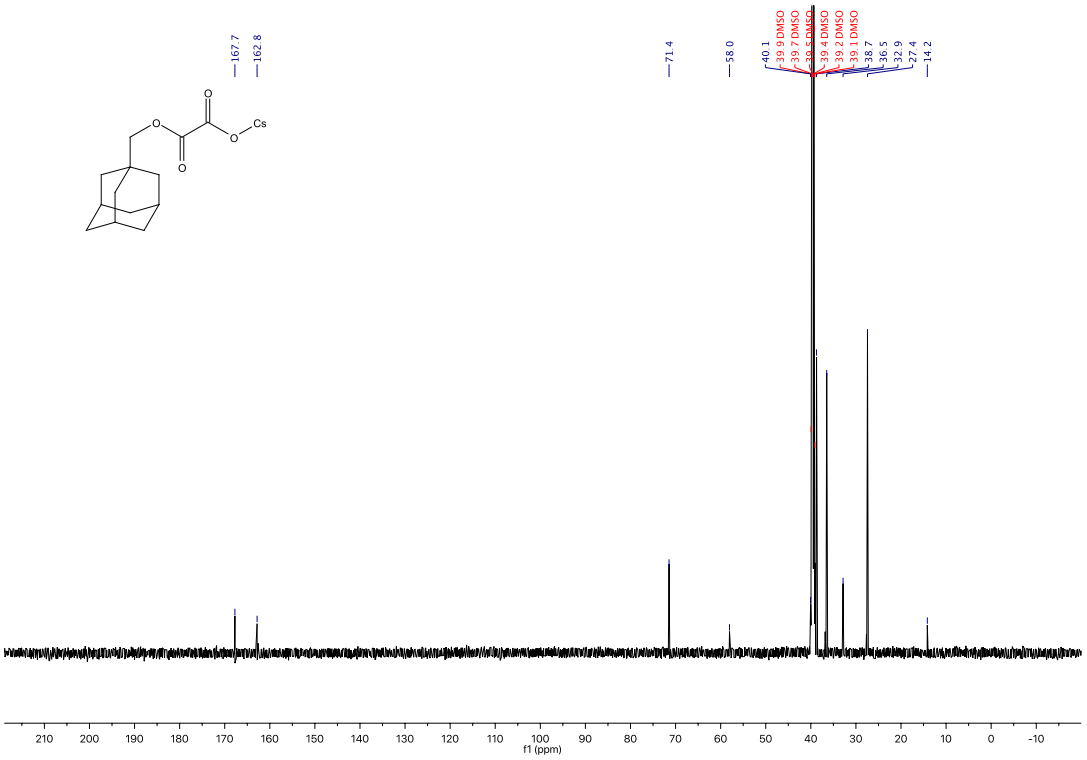
Adamantan-1-ylmethyl ethyl oxalate





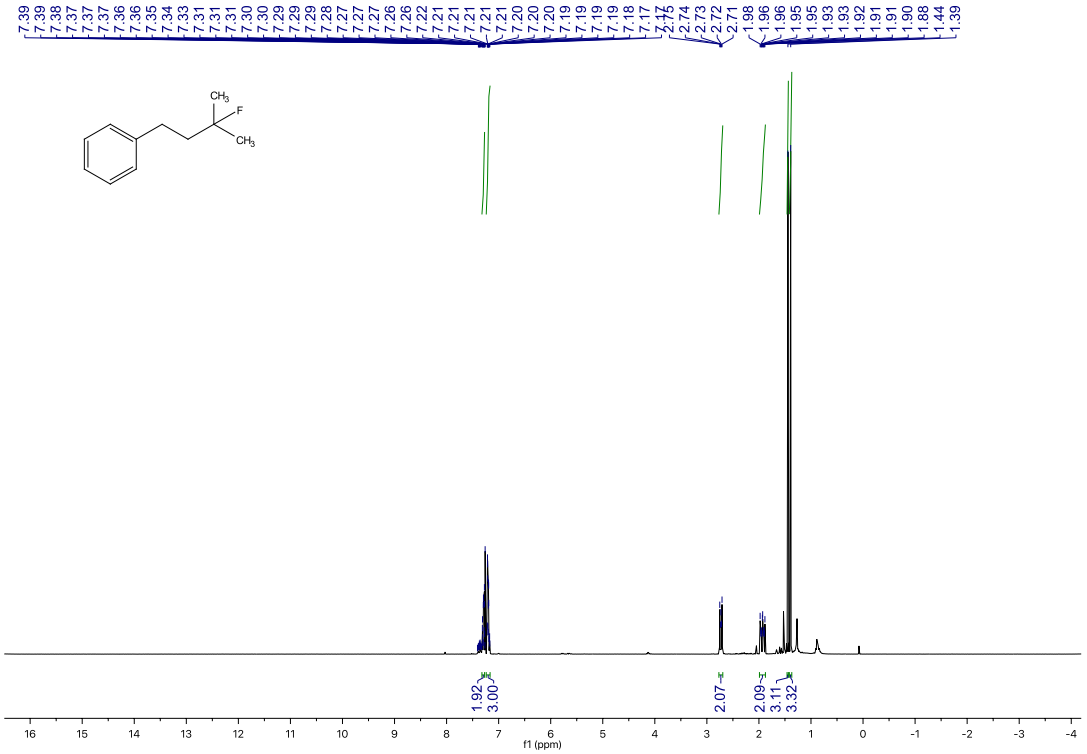
Cesium 2-(((2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoacetate

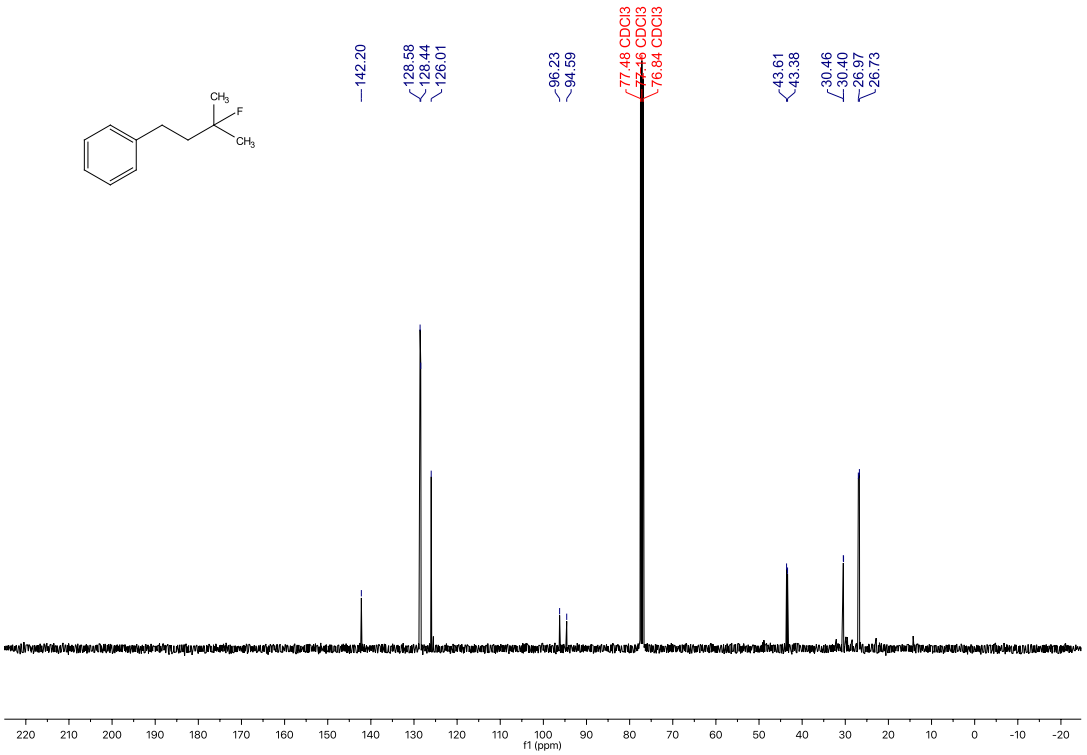


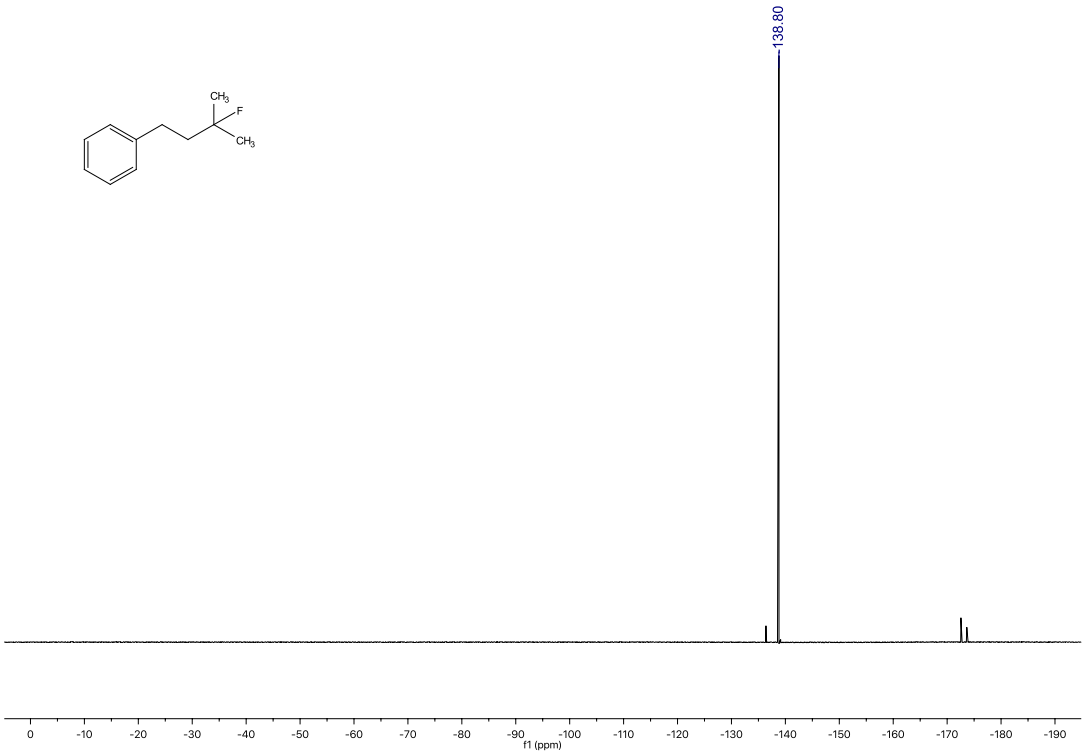


6.3.9.2. Products

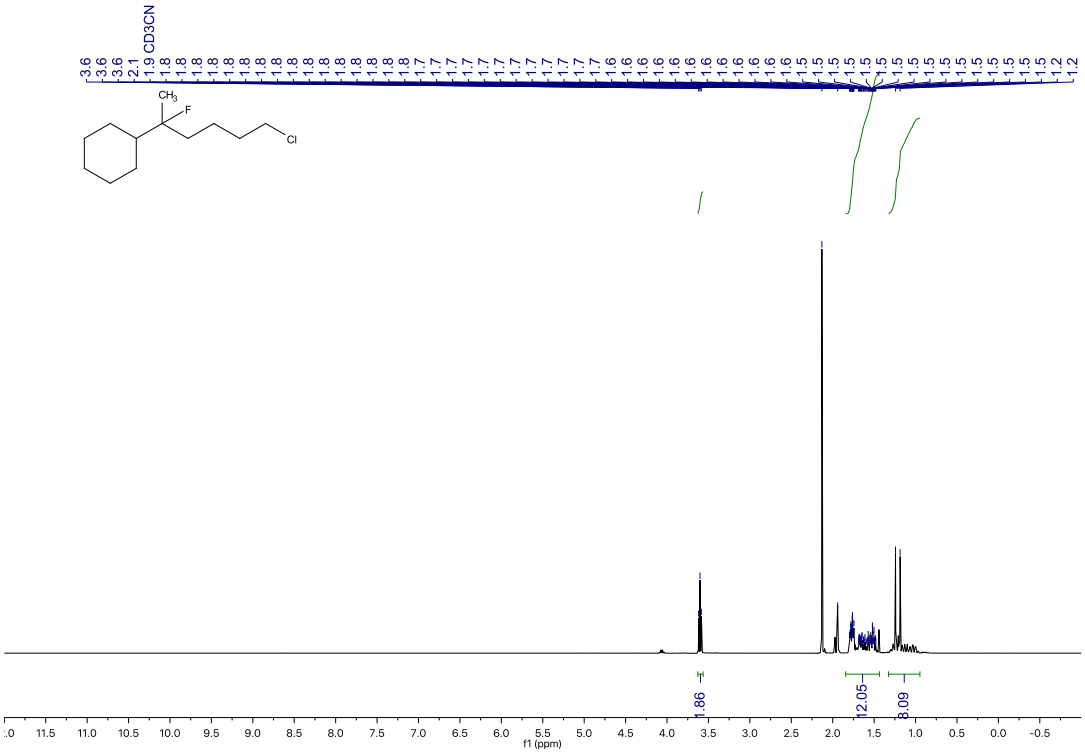
(3-fluoro-3-methylbutyl)benzene (2)

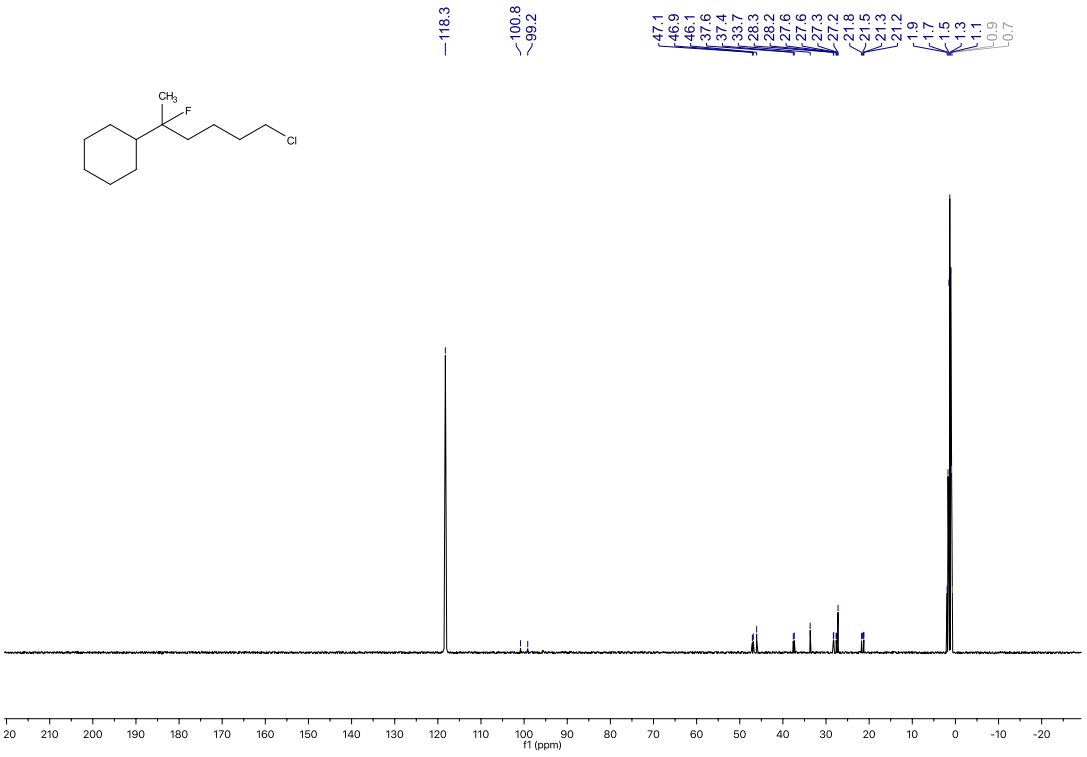






(6-chloro-2-fluorohexan-2-yl)cyclohexane (4)

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27.3
27.2
21.8
21.5
21.3
21.2
1.9
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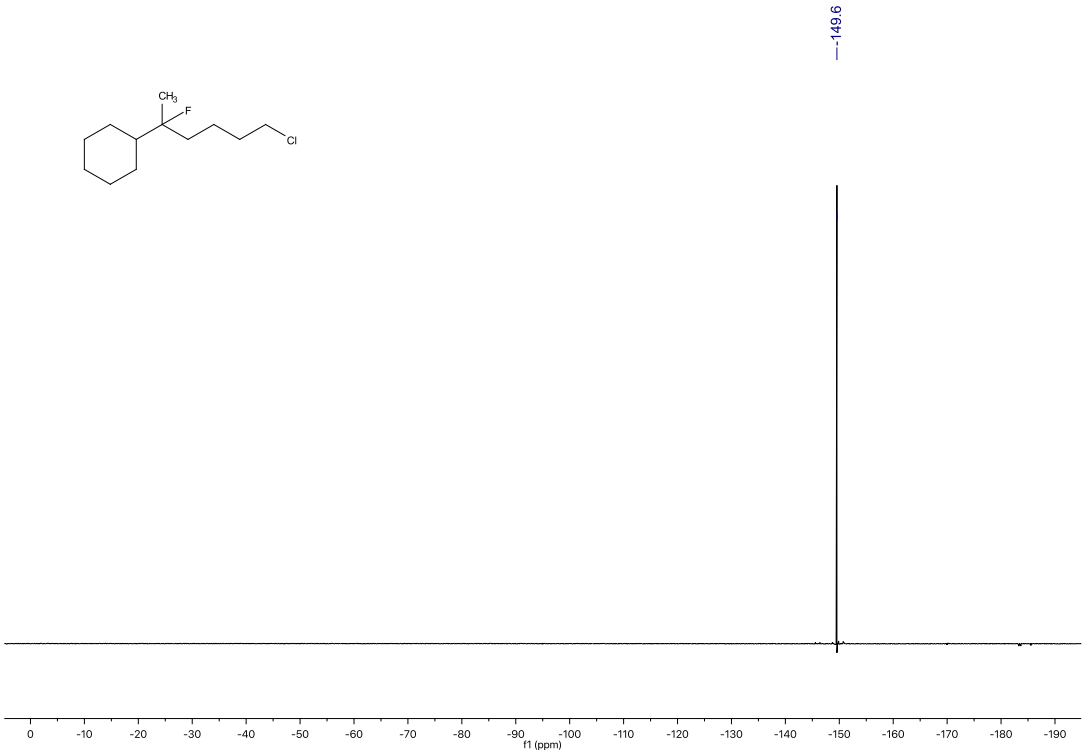
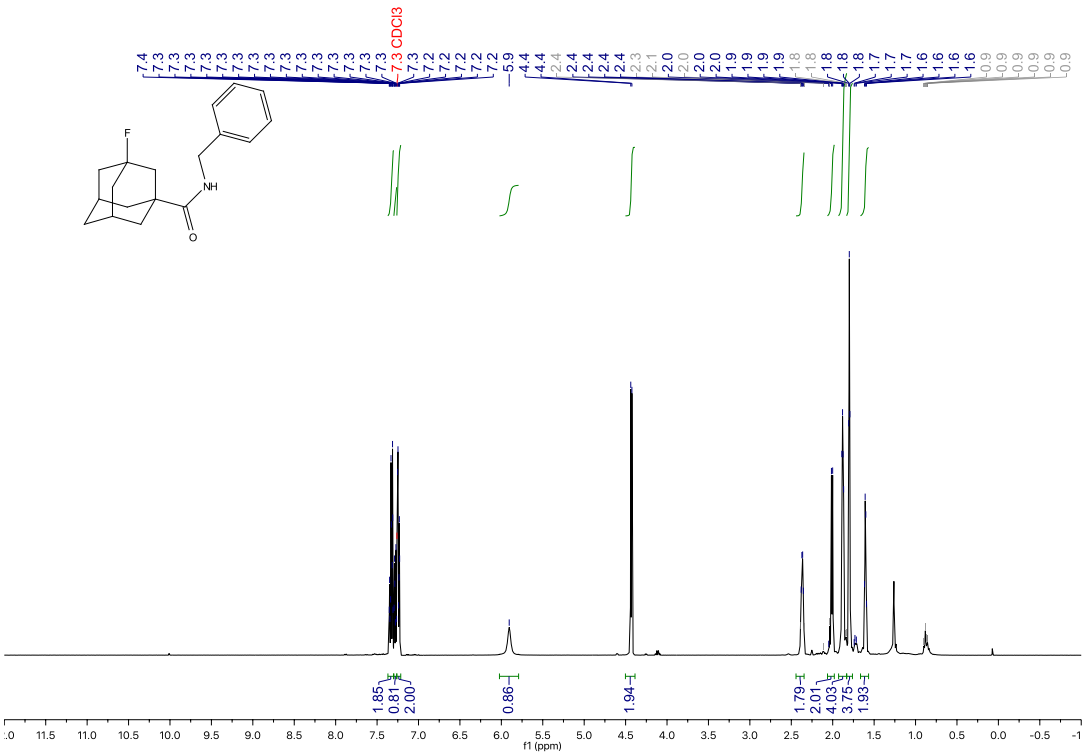
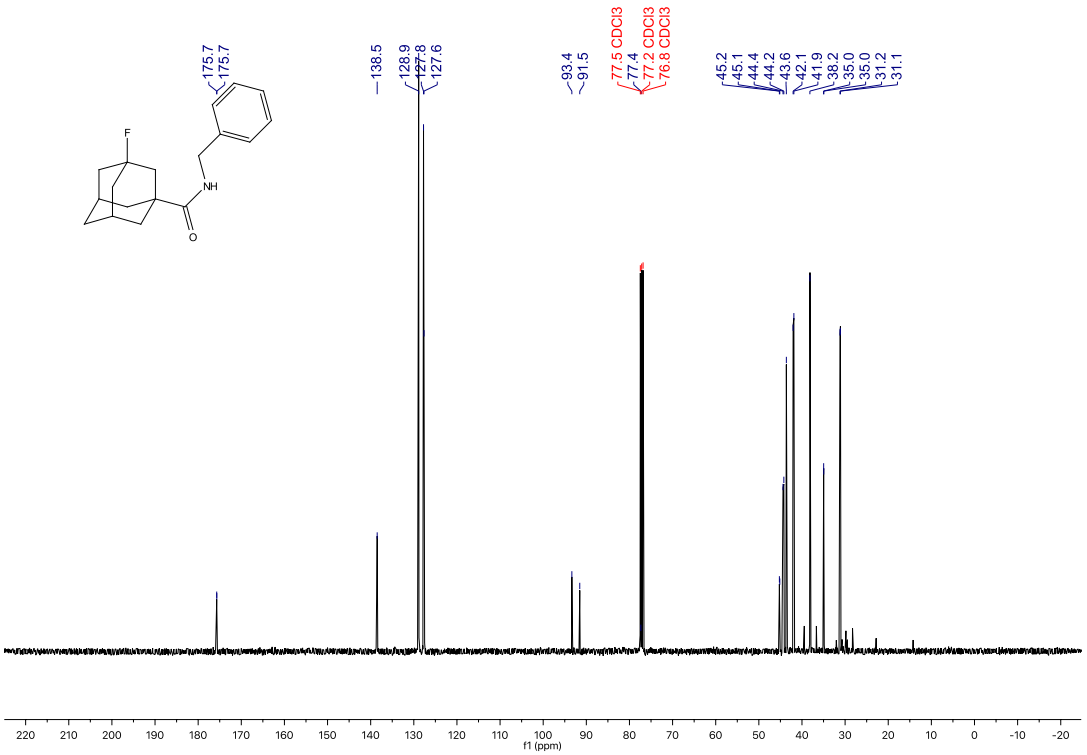
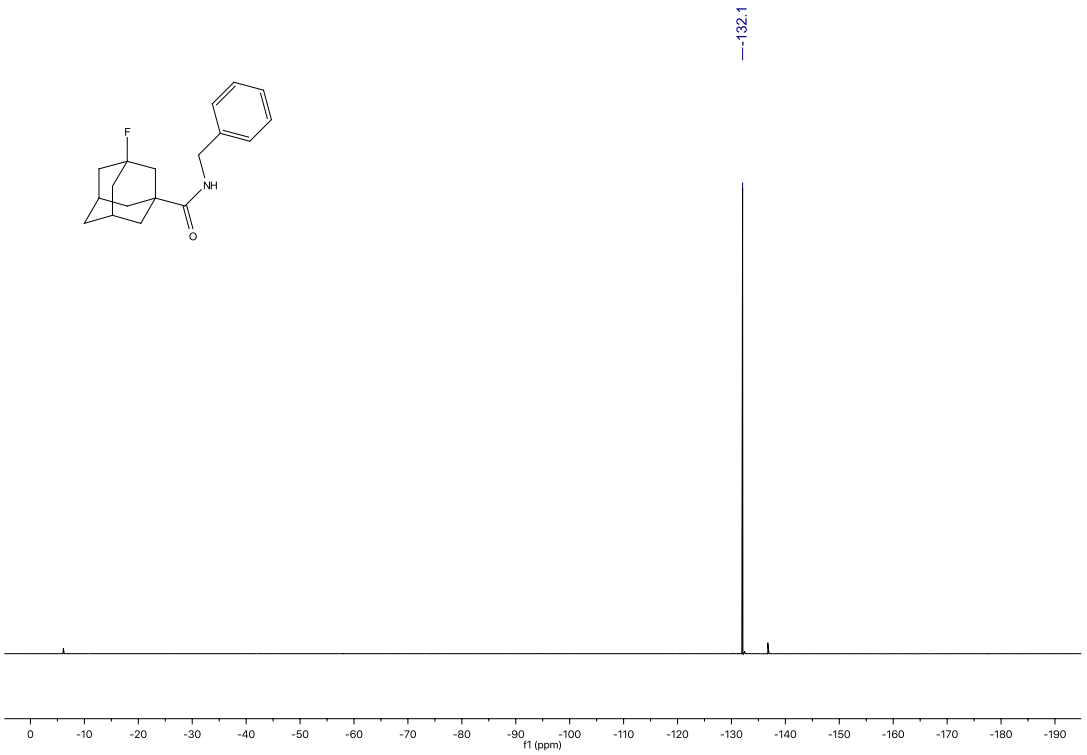
1.5
1.3
1.1
0.9
0.7
CH3
F
Cl
f1 (ppm)


149.6
CH3
F
Cl
f1 (ppm)

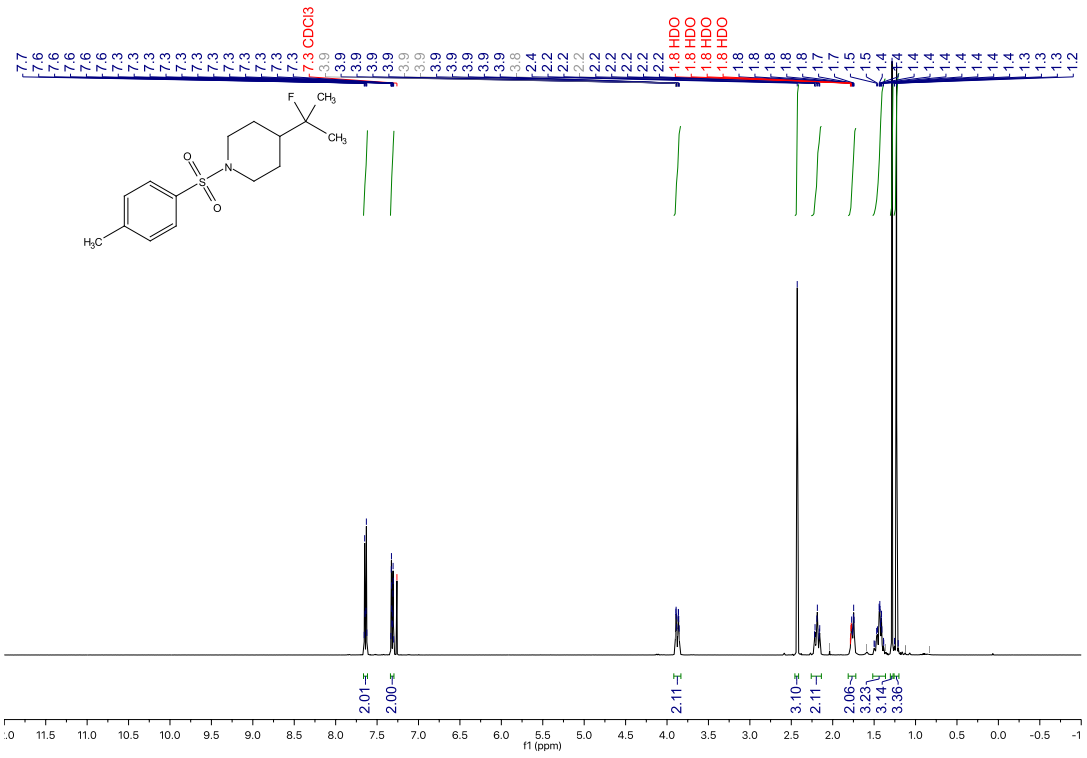
(1*r*,3*s*,5*R*,7*S*)-*N*-benzyl-3-fluoroadamantane-1-carboxamide (5)

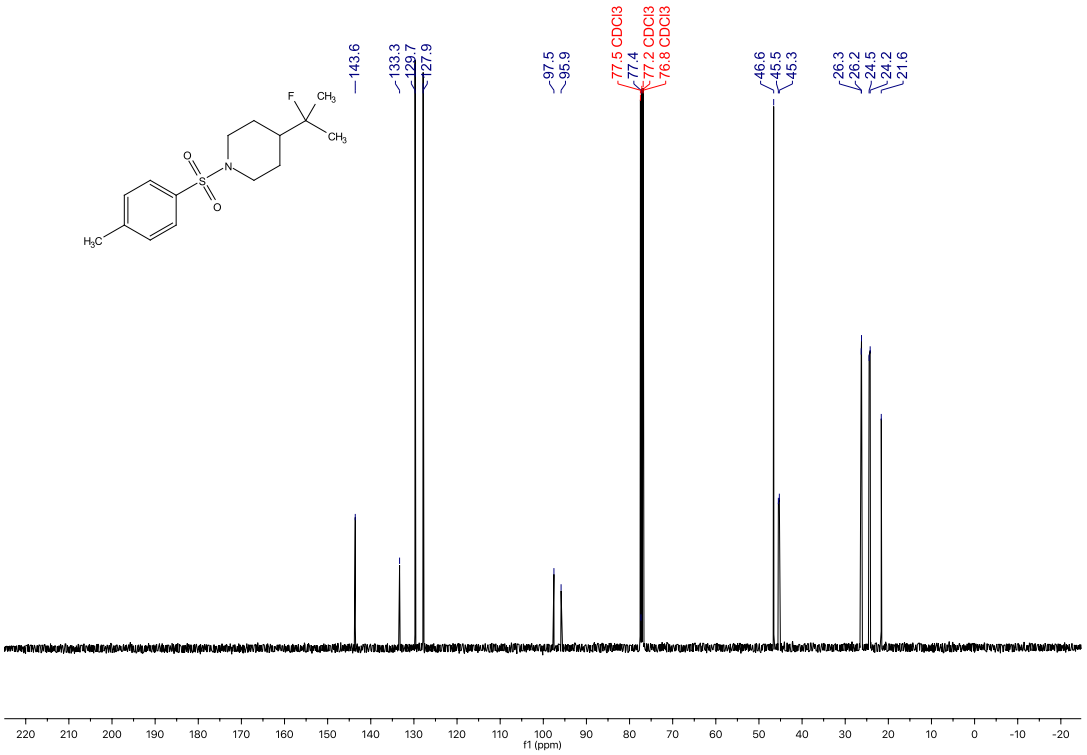


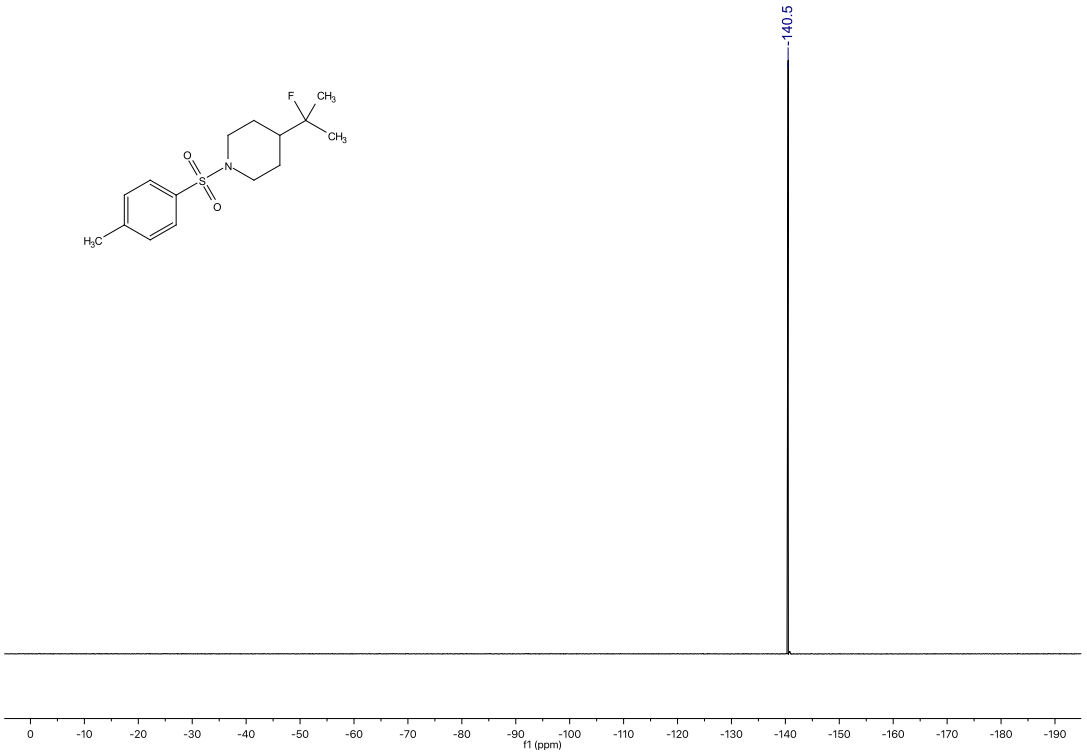




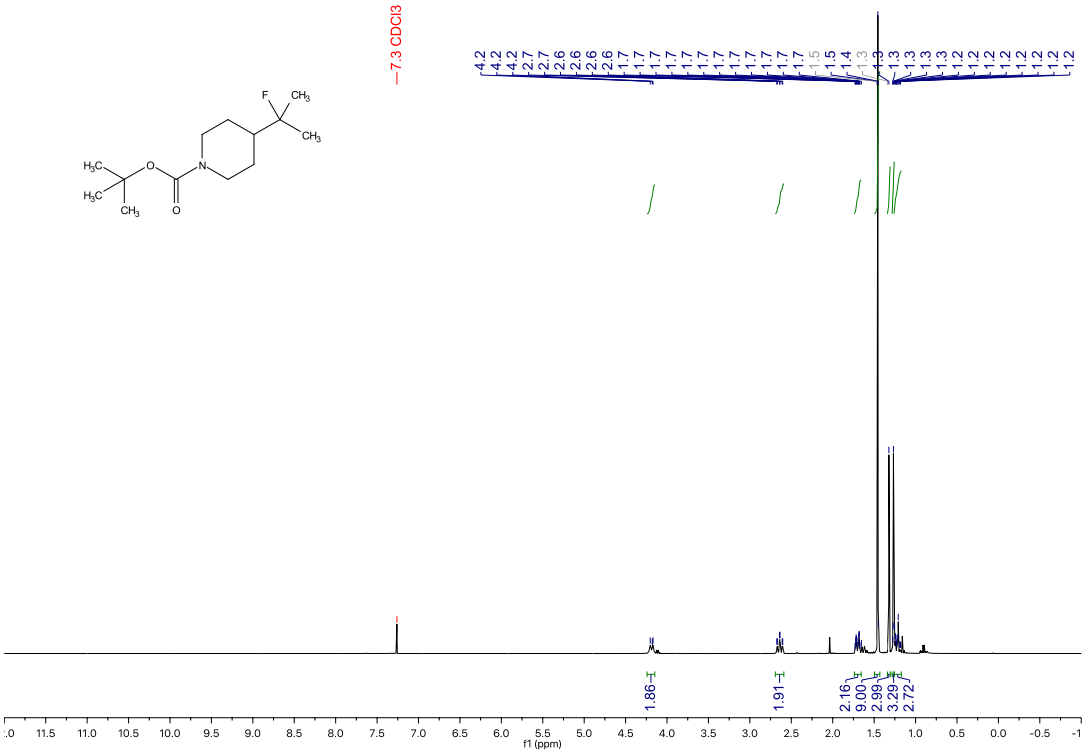
4-(2-fluoropropan-2-yl)-1-tosylpiperidine (6)

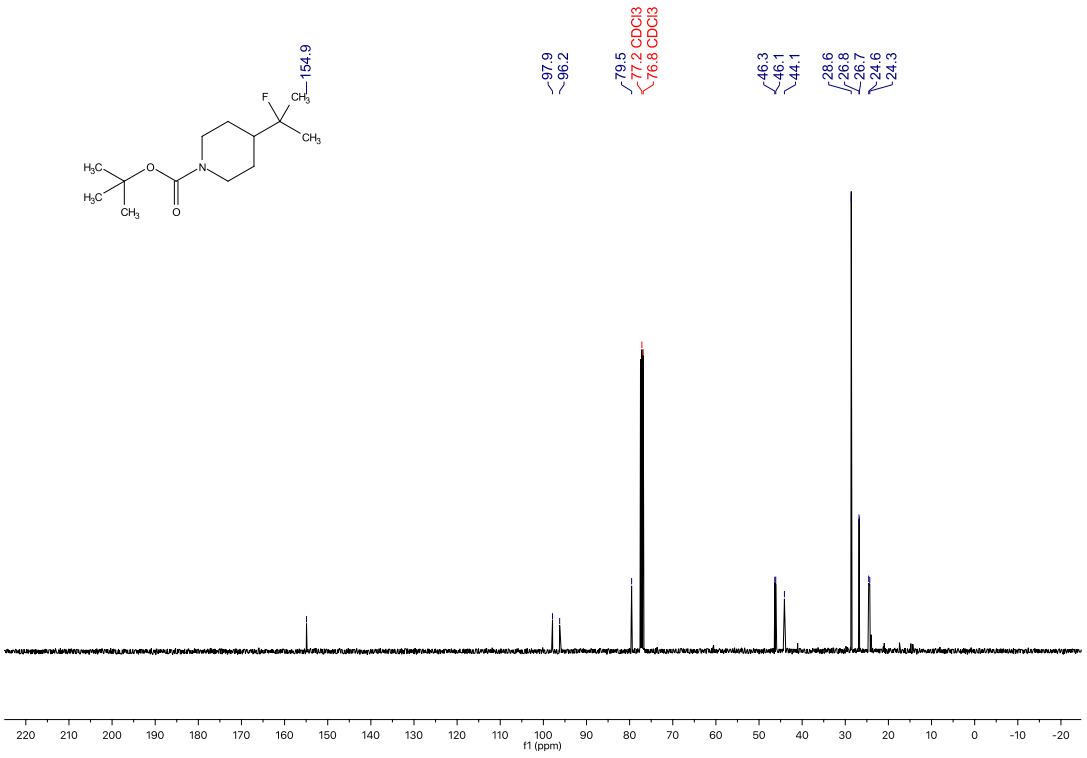


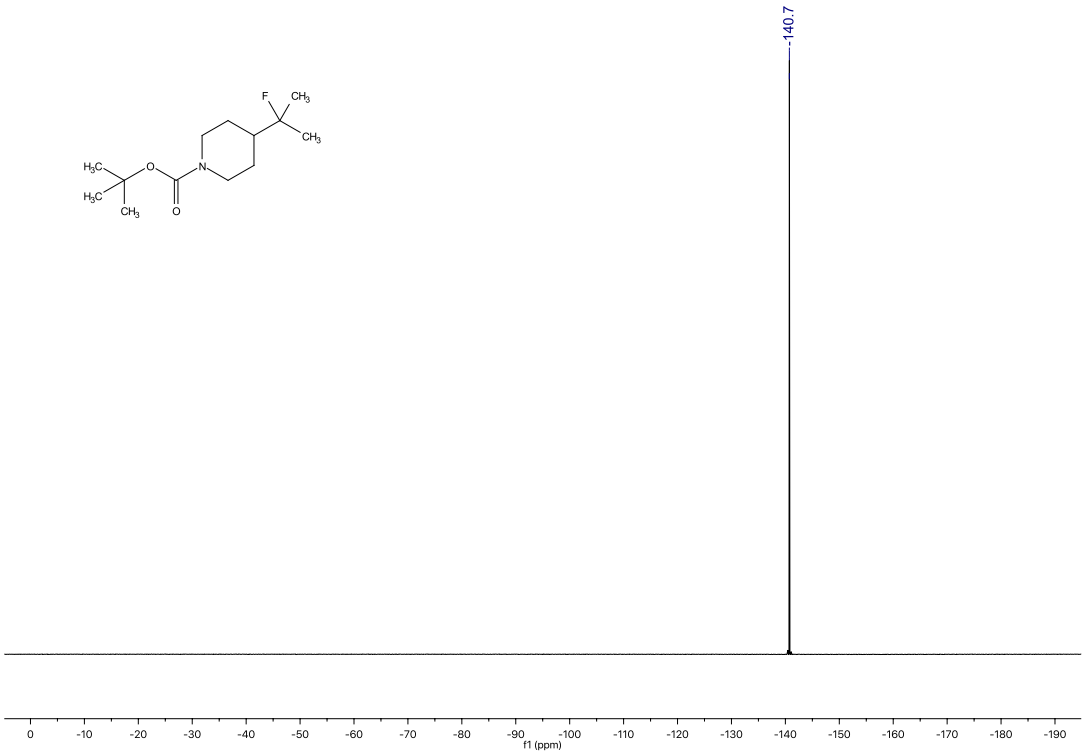

143.6
133.3
129.7
127.9
97.5
95.9
77.5 CDCl3
77.4
77.2 CDCl3
76.8 CDCl3
46.6
45.5
45.3
26.3
26.2
24.5
24.2
21.6
F
CH3
CH3
O
S
O
N
H3C
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


140.5
F
CH3
CH3
O
S
O
N
H3C
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

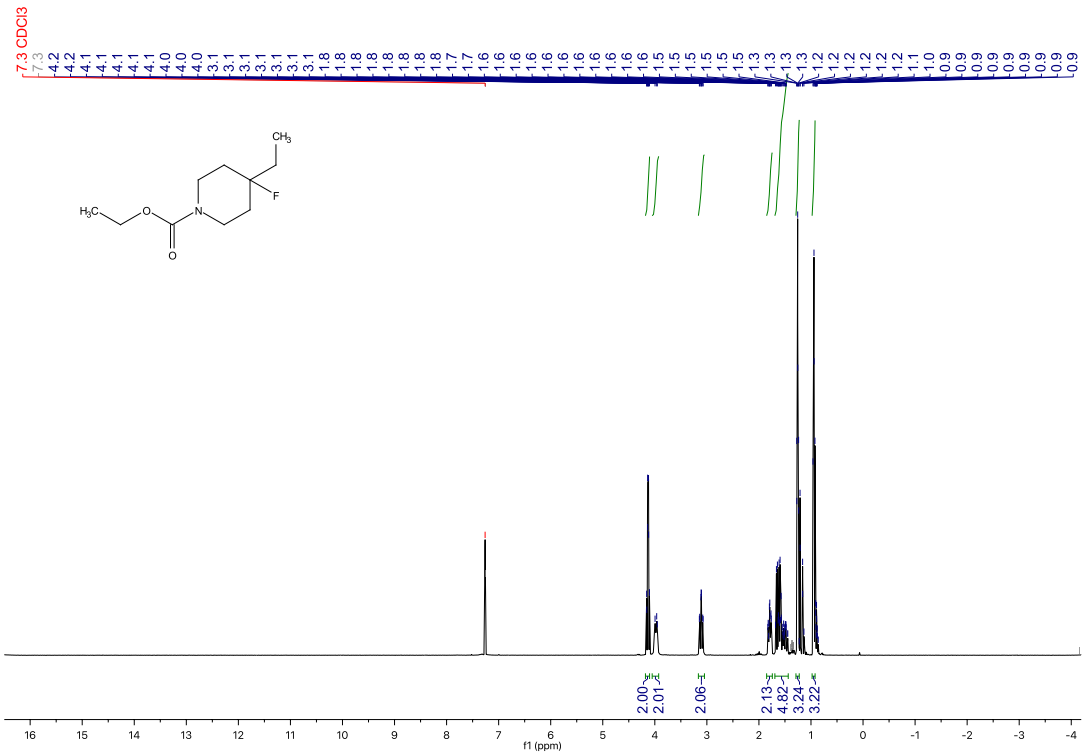
tert-butyl 4-(2-fluoropropan-2-yl)piperidine-1-carboxylate (7)

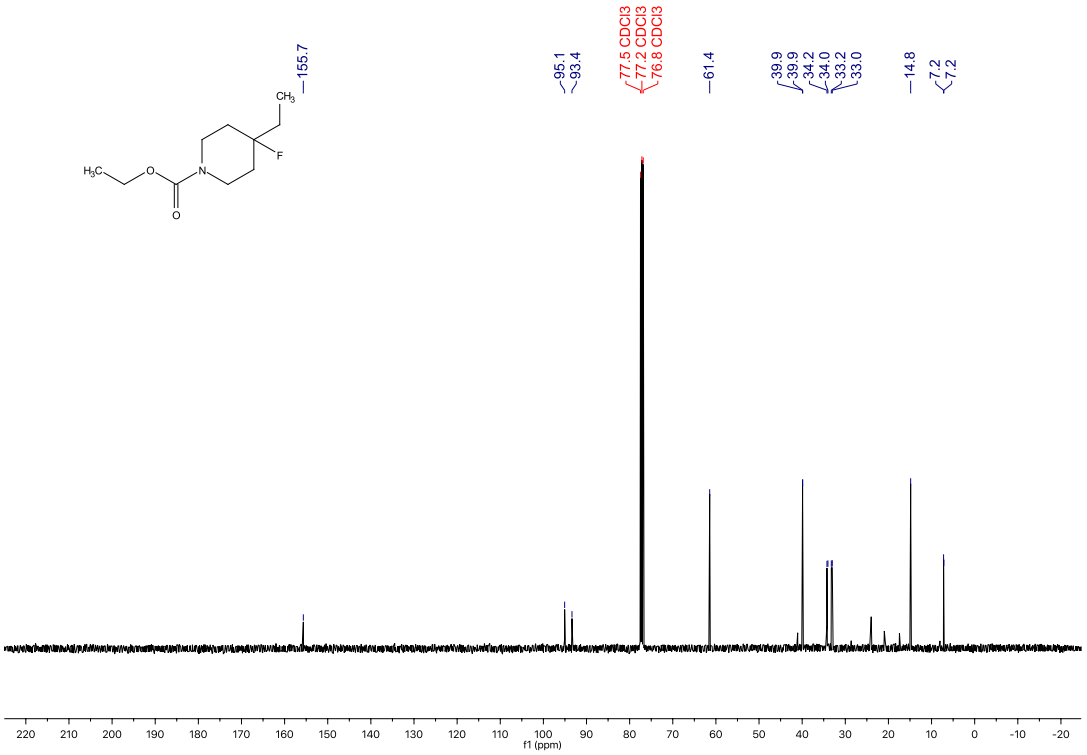


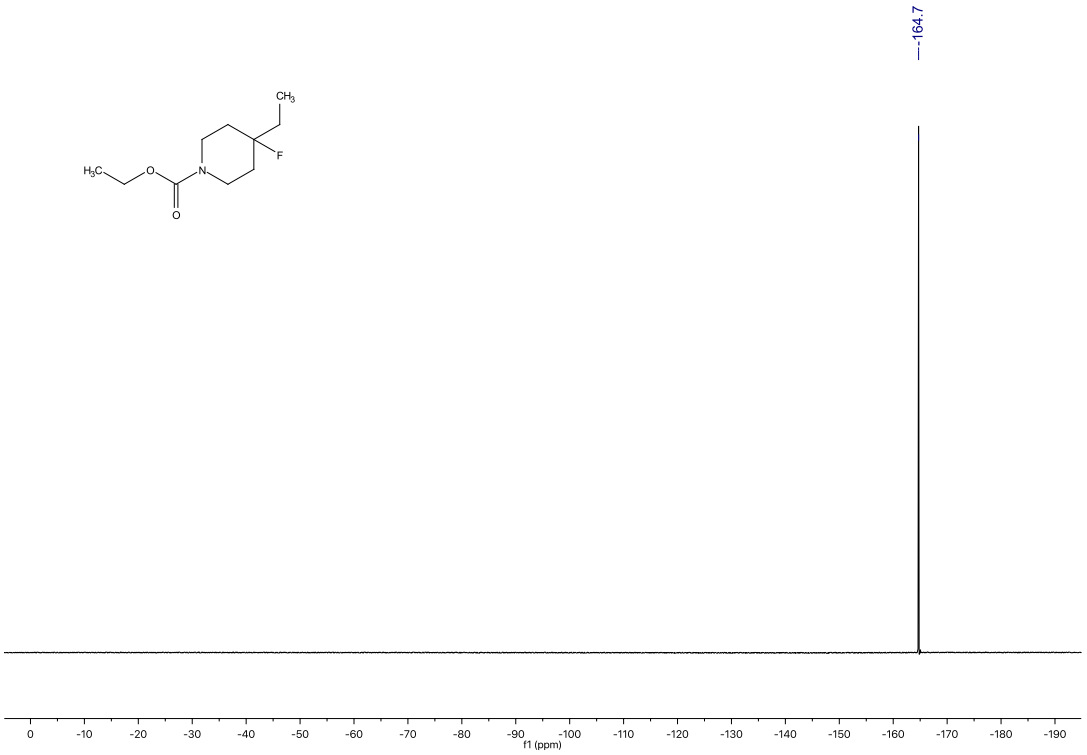




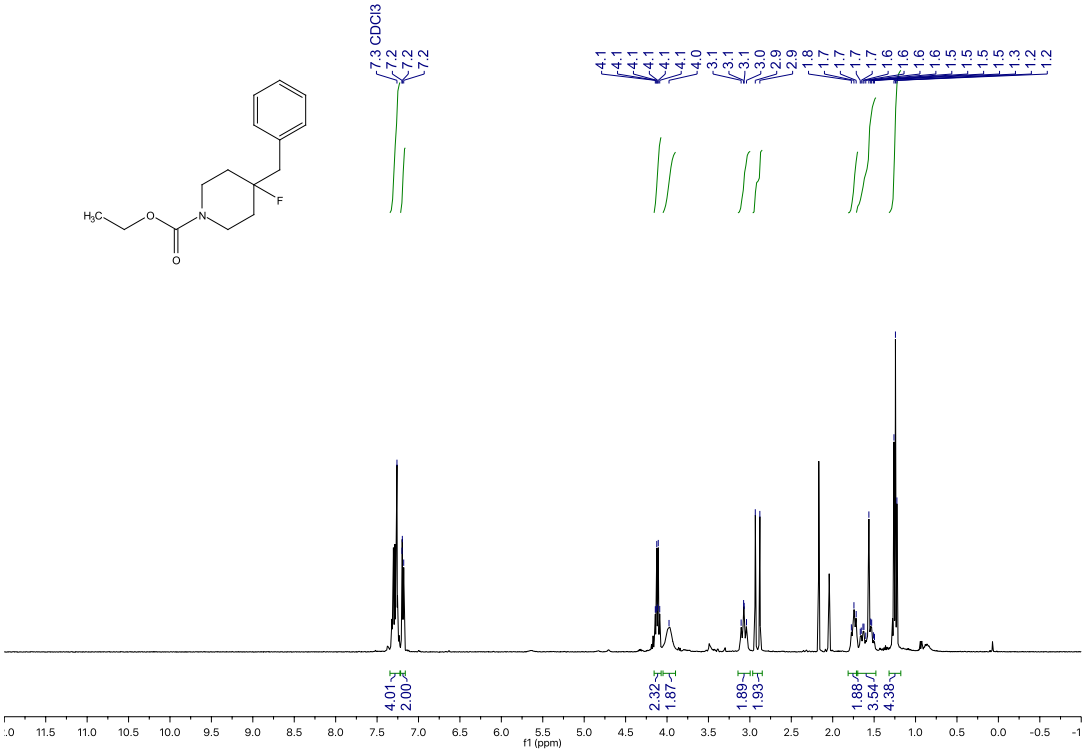
Ethyl 4-ethyl-4-fluoropiperidine-1-carboxylate (8)

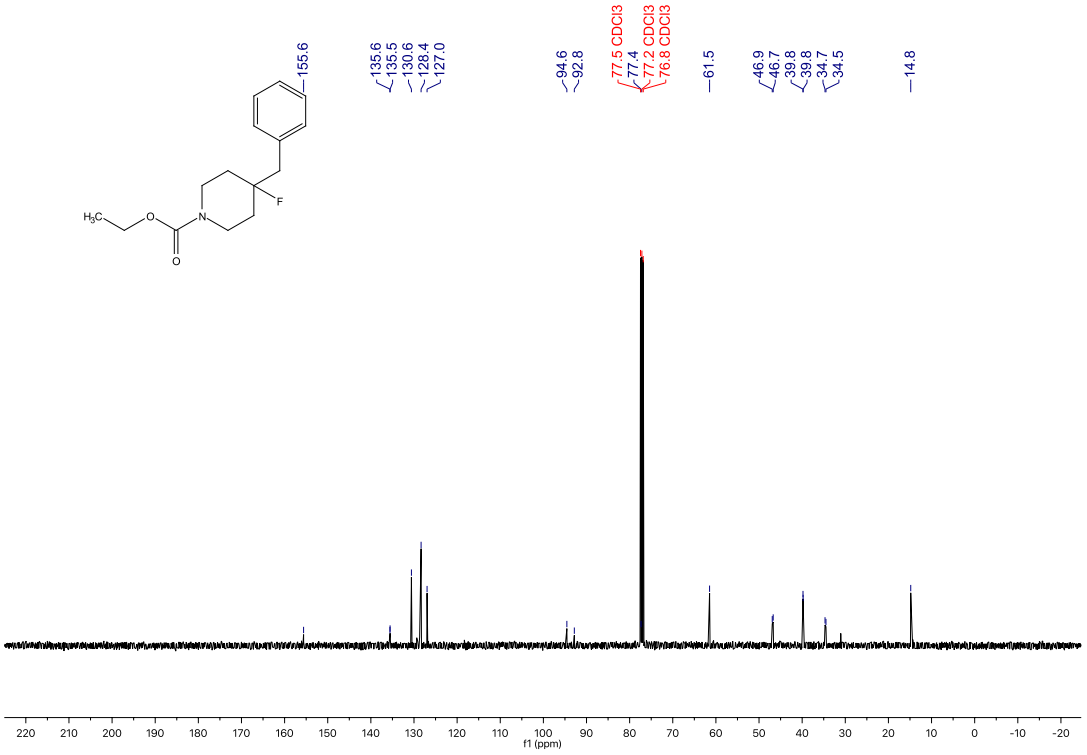


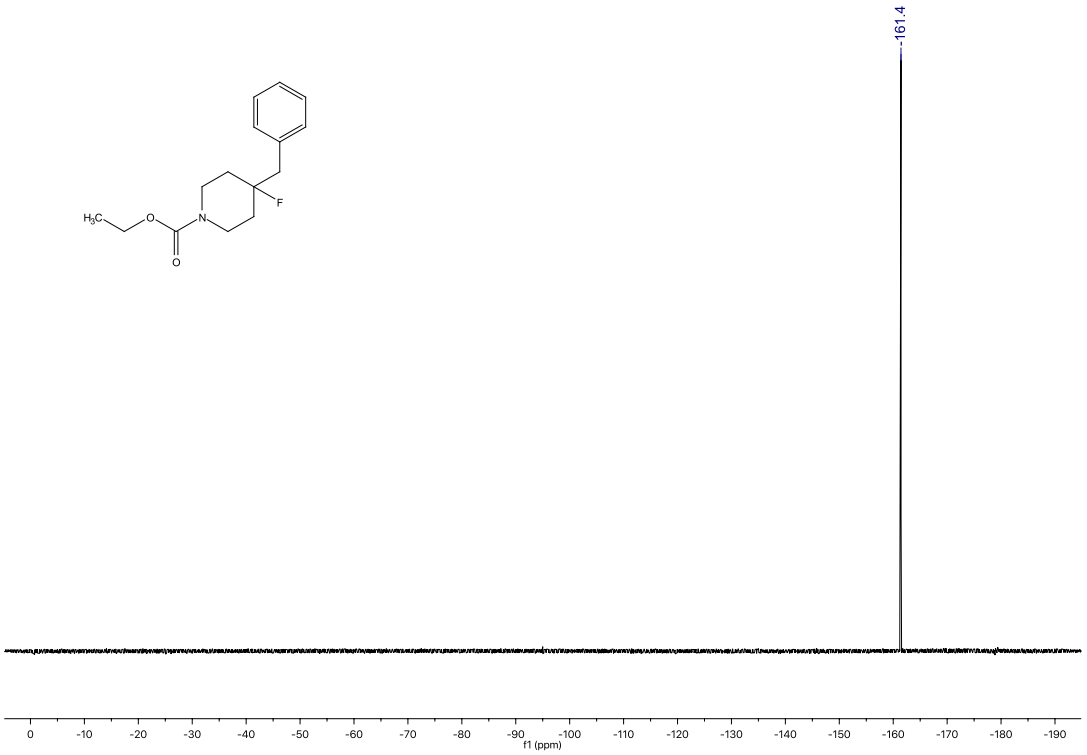

155.7
95.1
93.4
77.5 CDCl3
77.2 CDCl3
76.8 CDCl3
61.4
39.9
39.9
34.2
34.0
33.2
33.0
14.8
7.2
7.2
CH3
F
H3C
O
N
O
f1 (ppm)


164.7
CH3
F
H3C
O
N
O
f1 (ppm)

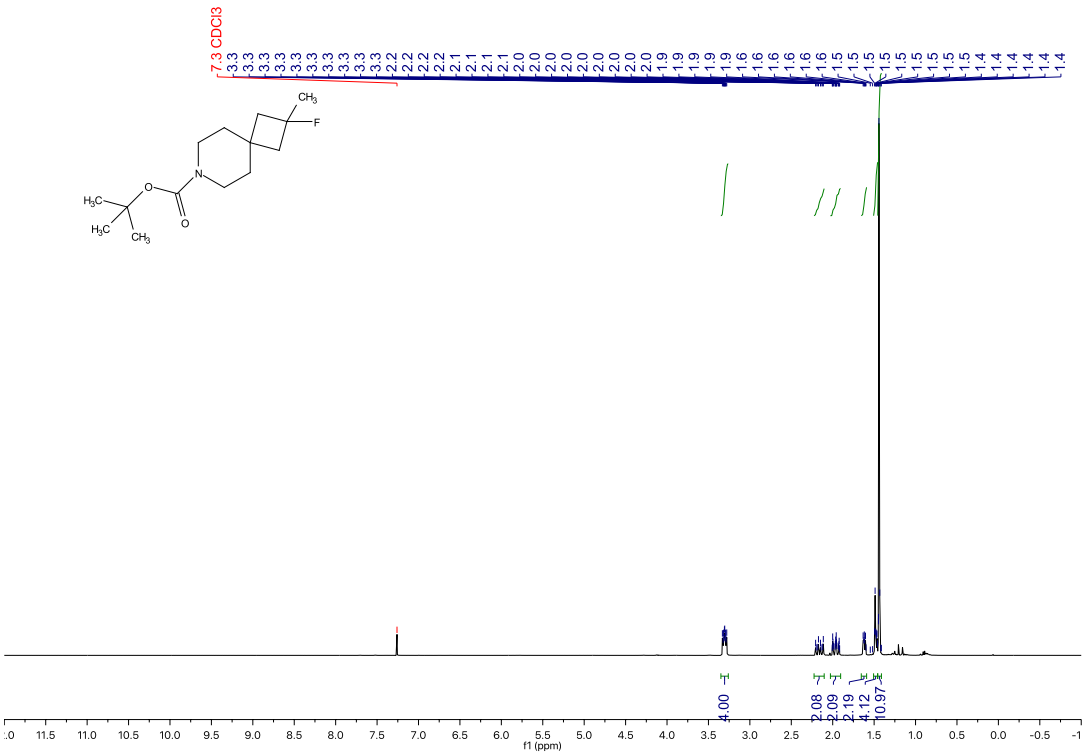
ethyl 4-benzyl-4-fluoropiperidine-1-carboxylate (9)

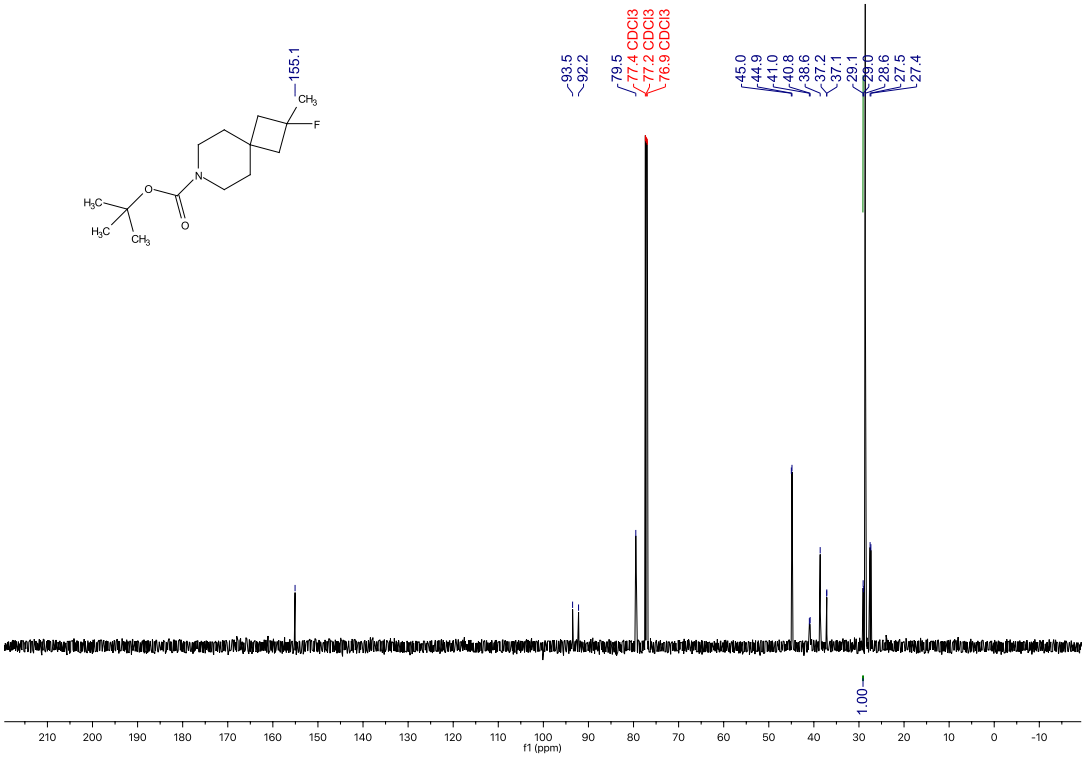


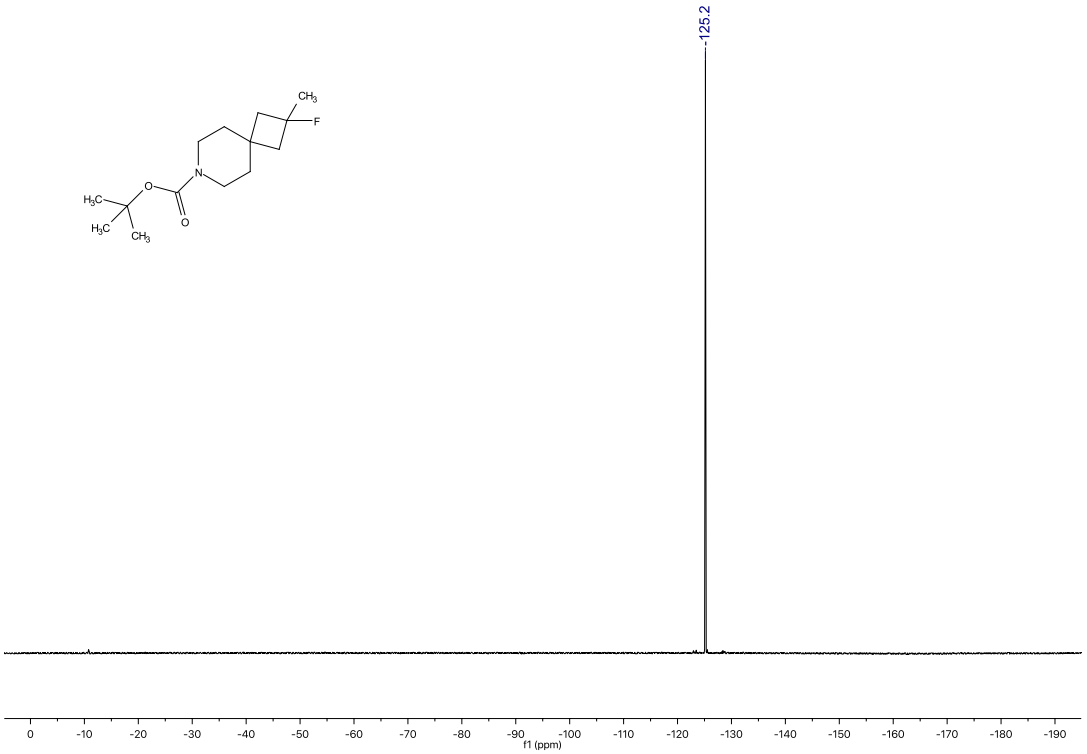




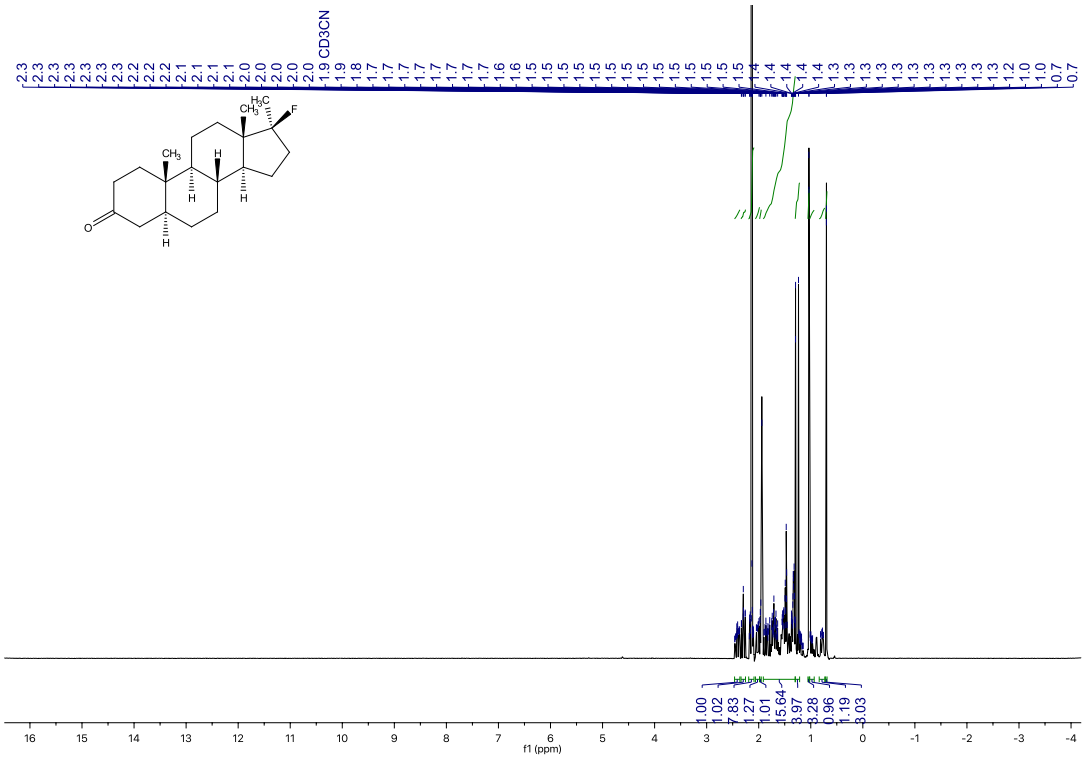
tert-butyl 2-fluoro-2-methyl-7-azaspiro[3.5]nonane-7-carboxylate (10)

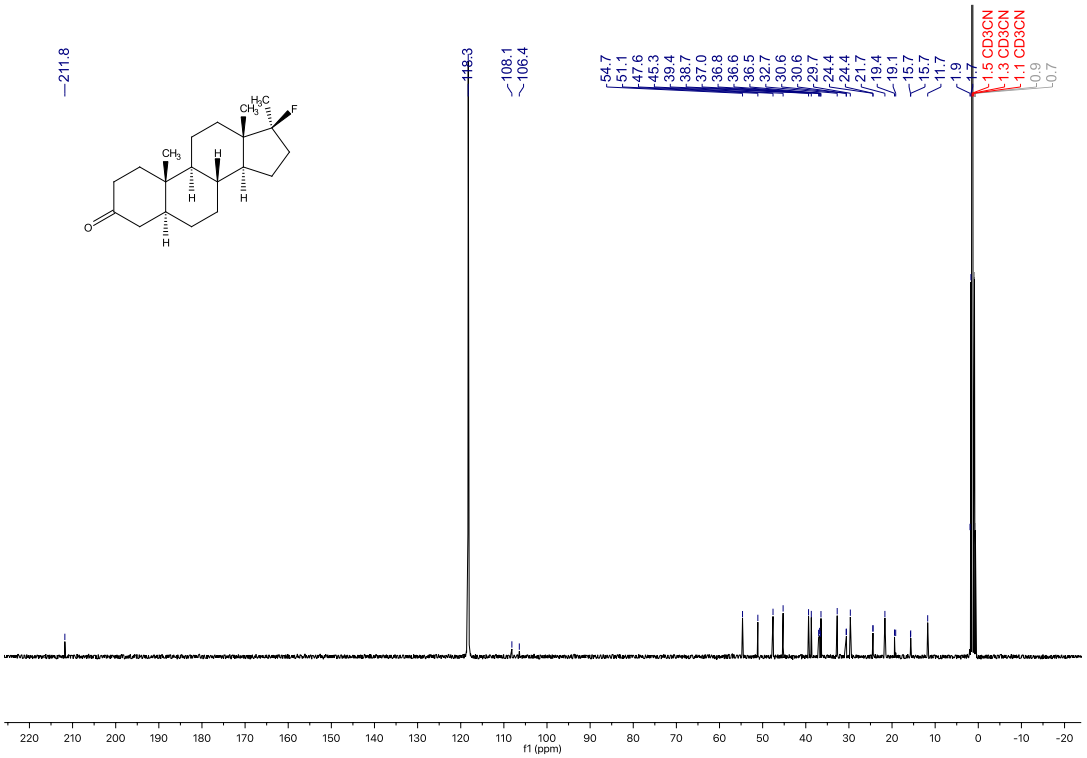


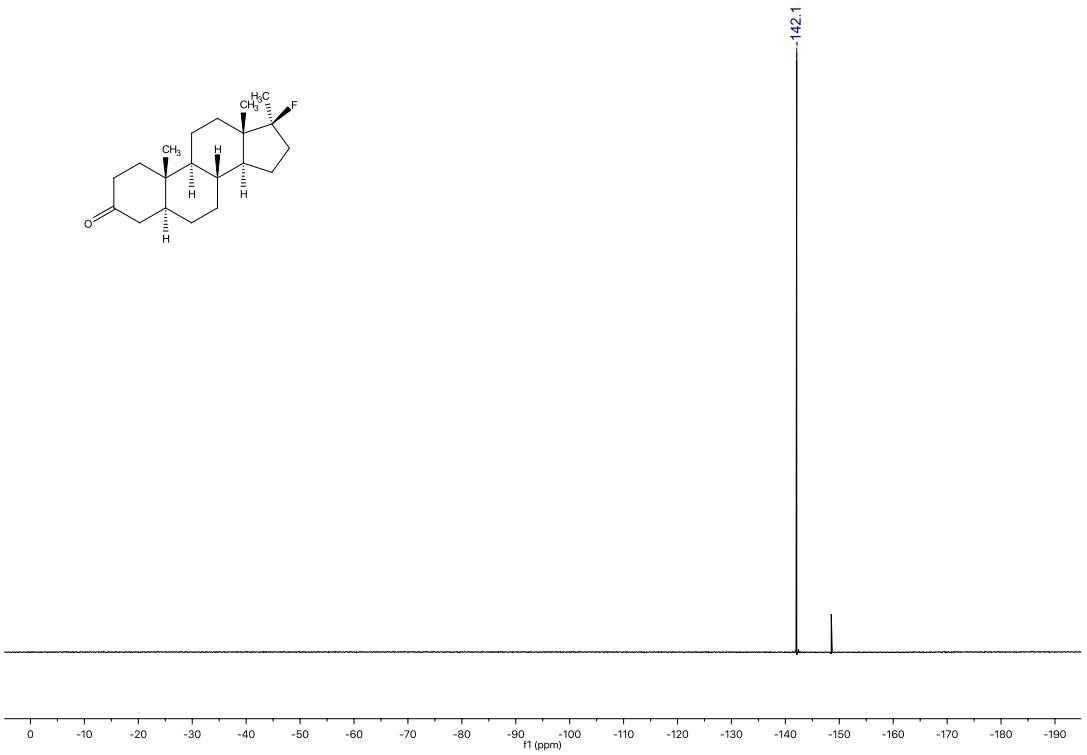

155.1
93.5
92.2
79.5
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
45.0
44.9
41.0
40.8
38.6
37.2
37.1
29.1
29.0
28.6
27.5
27.4
1.00
f1 (ppm)


-125.2
f1 (ppm)

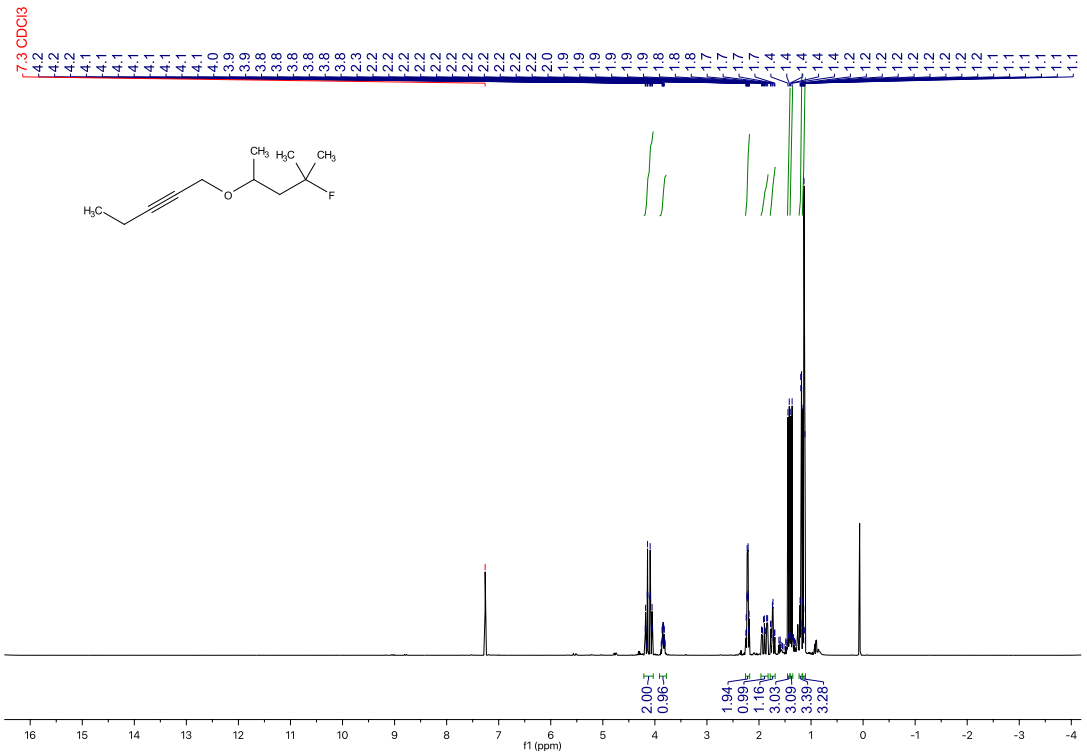
(5S,8R,9S,10S,13S,14S)-17-fluoro-10,13,17-trimethylhexadecahydro-3H-cyclopenta[a]phenanthren-3-one (11)

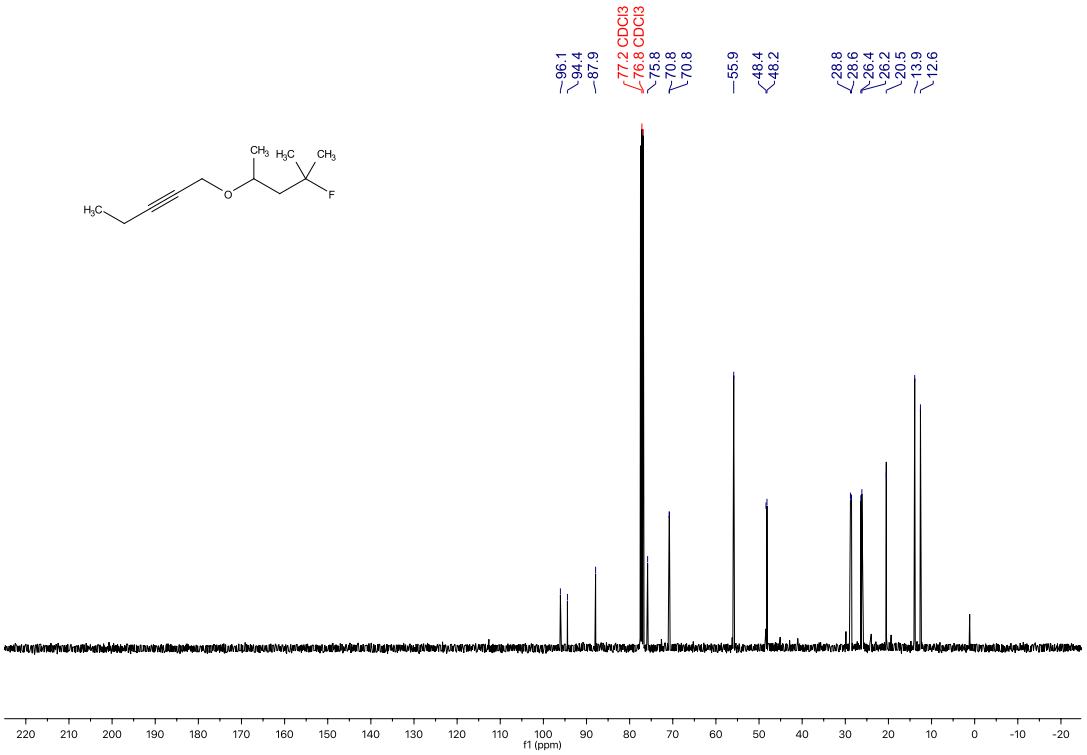


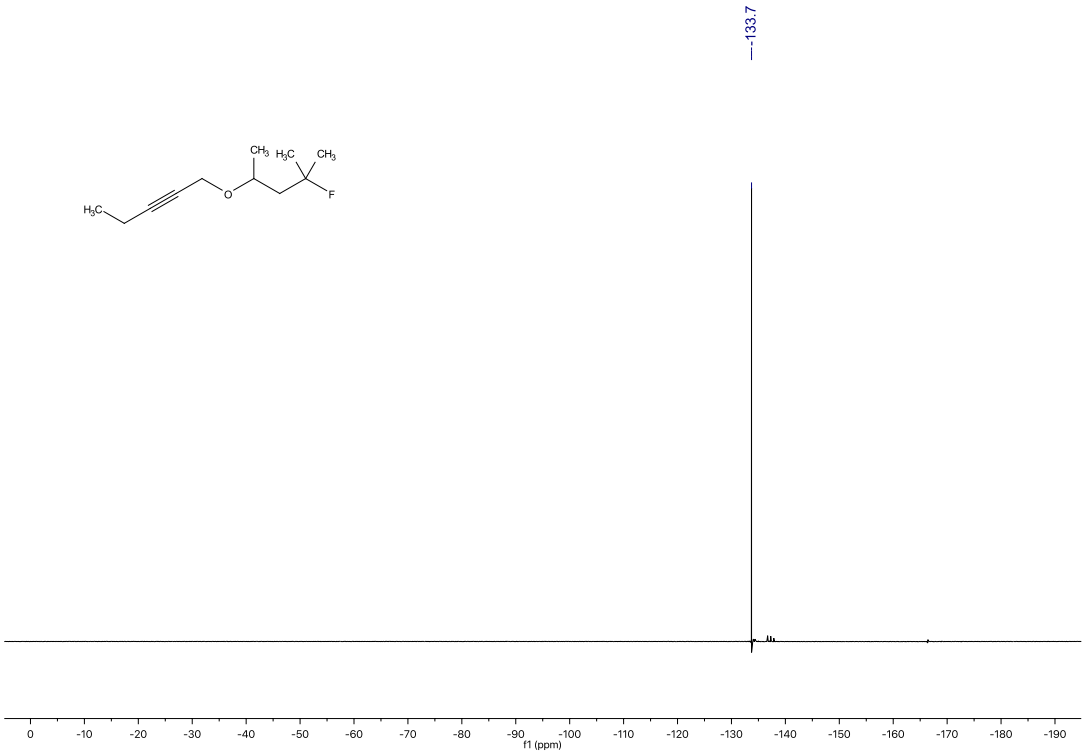




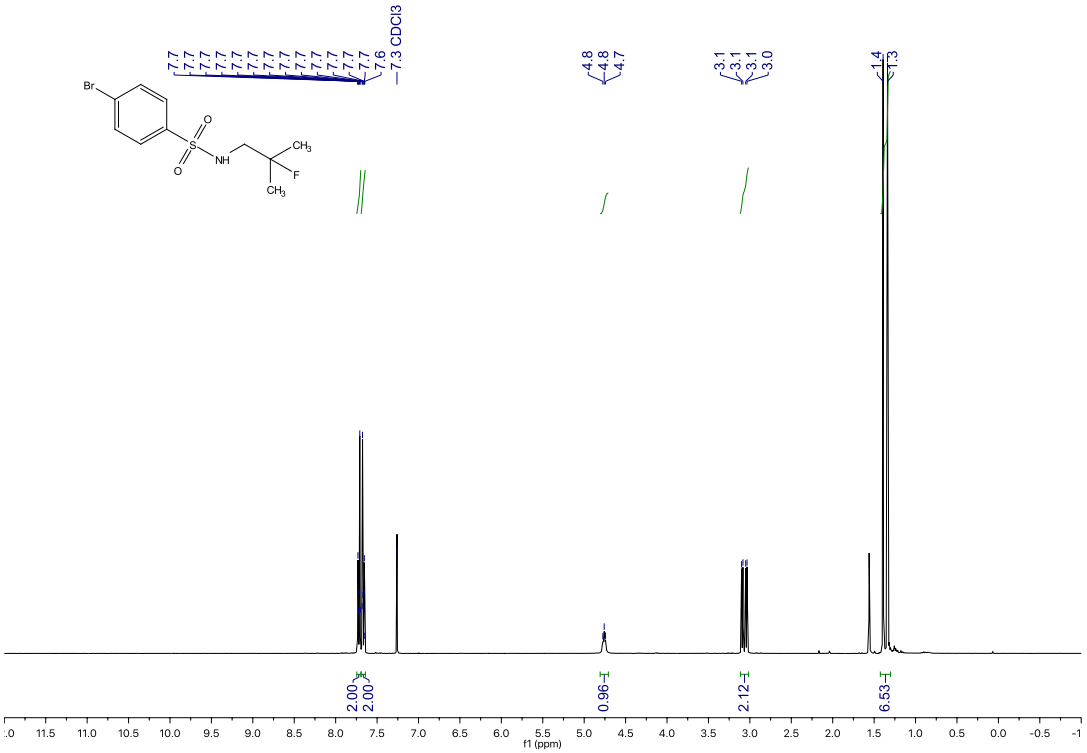
1-((4-fluoro-4-methylpentan-2-yl)oxy)pent-2-yne (12)

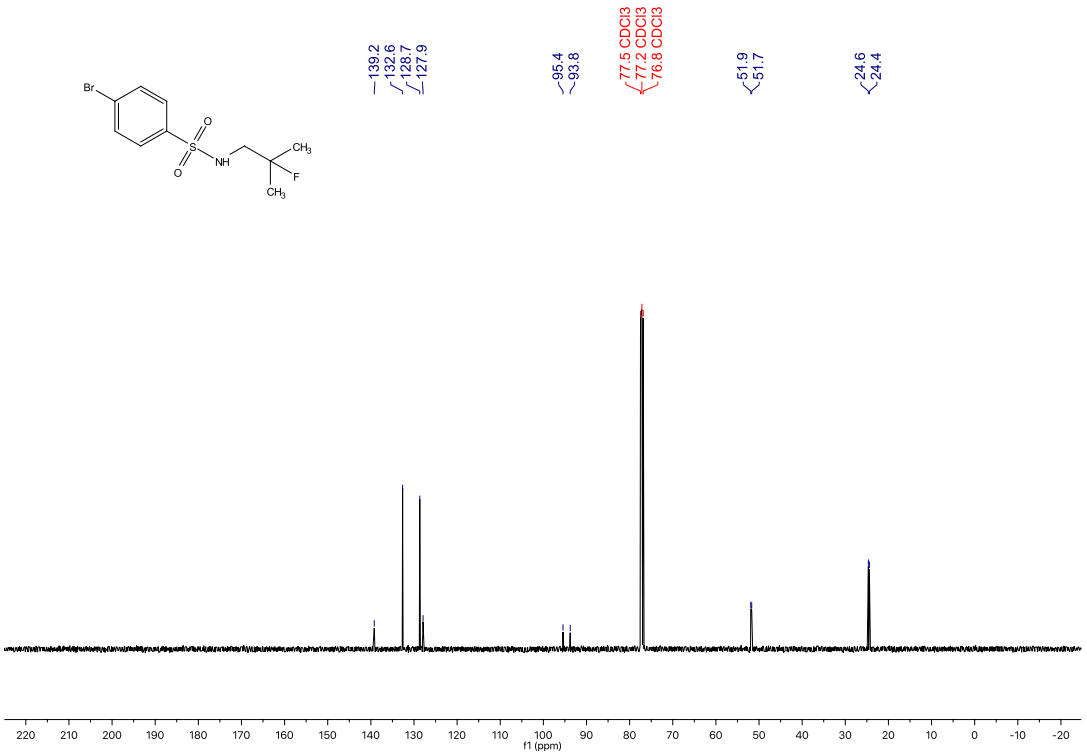


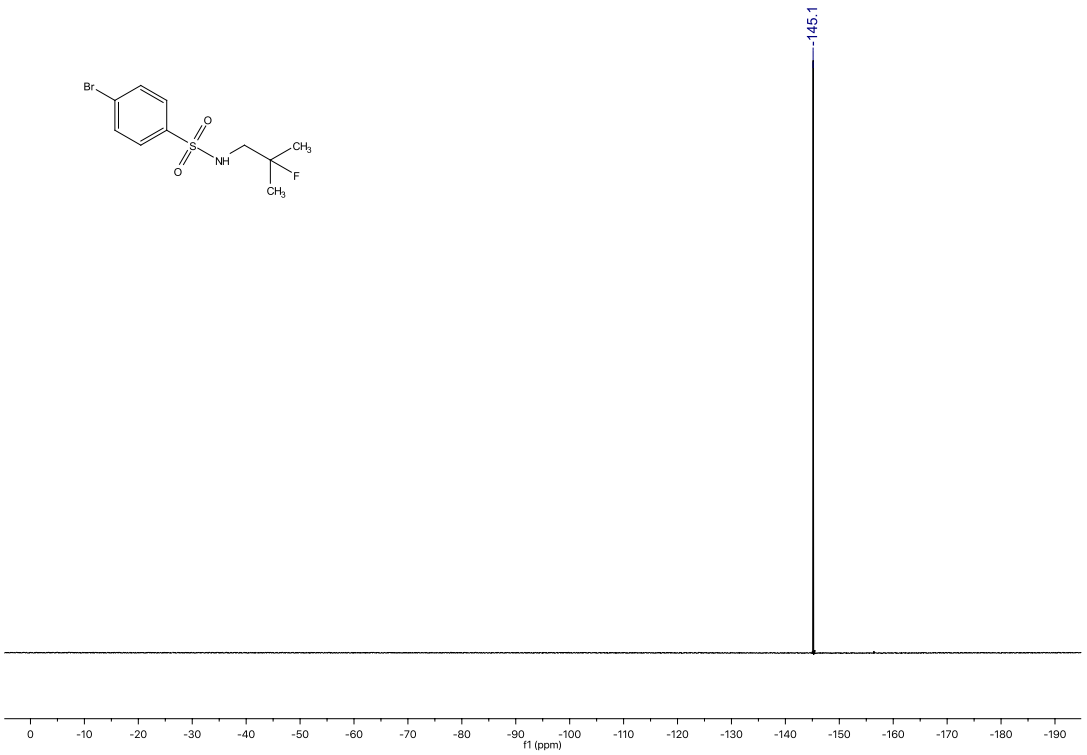

96.1
94.4
87.9
77.2 CDCl3
76.8 CDCl3
75.8
70.8
70.8
55.9
48.4
48.2
28.8
28.6
26.4
26.2
20.5
13.9
12.6
CH3 H3C CH3
H3C
O
F
f1 (ppm)


133.7
CH3 H3C CH3
H3C
O
F
f1 (ppm)

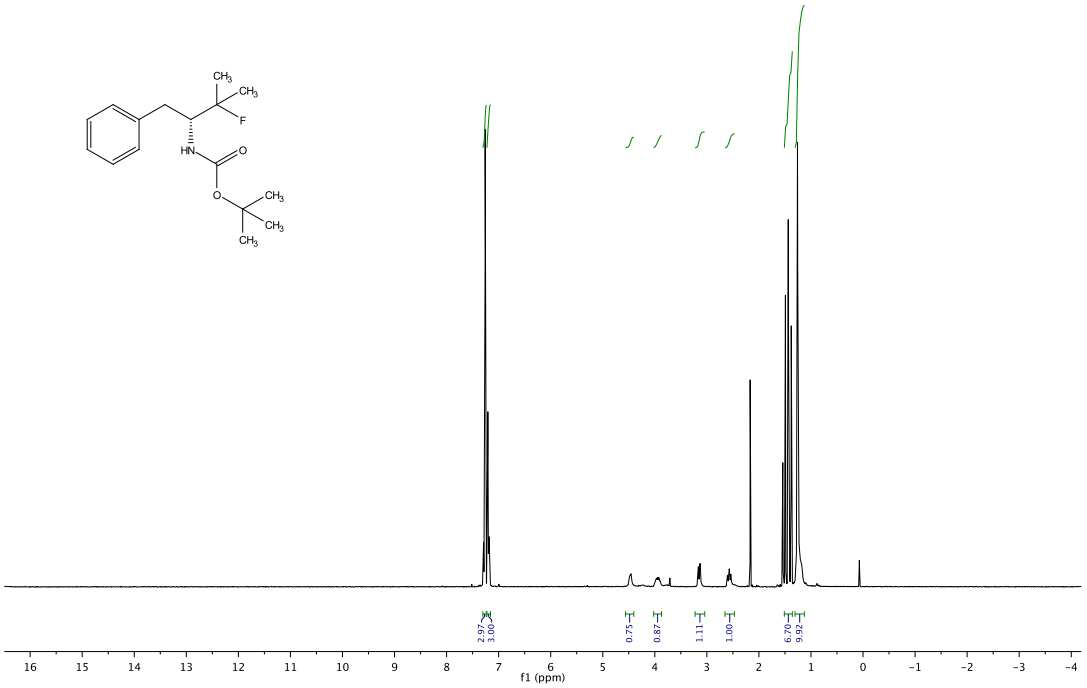
4-bromo-*N*-(2-fluoro-2-methylpropyl)benzenesulfonamide (13):

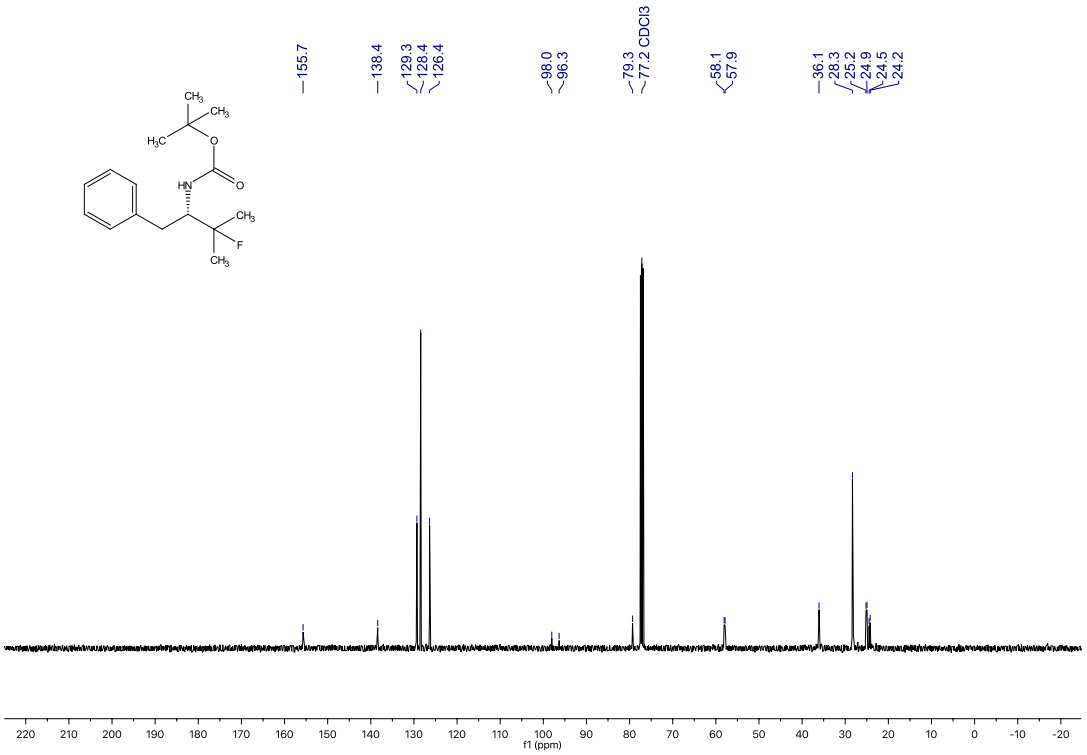


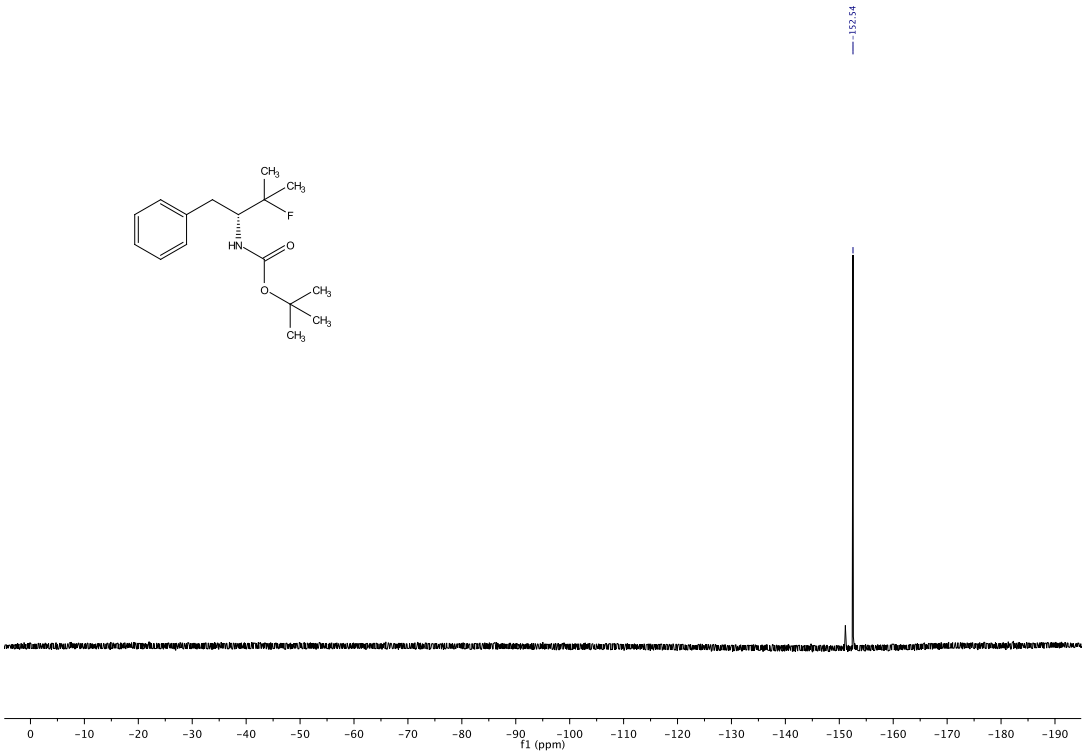




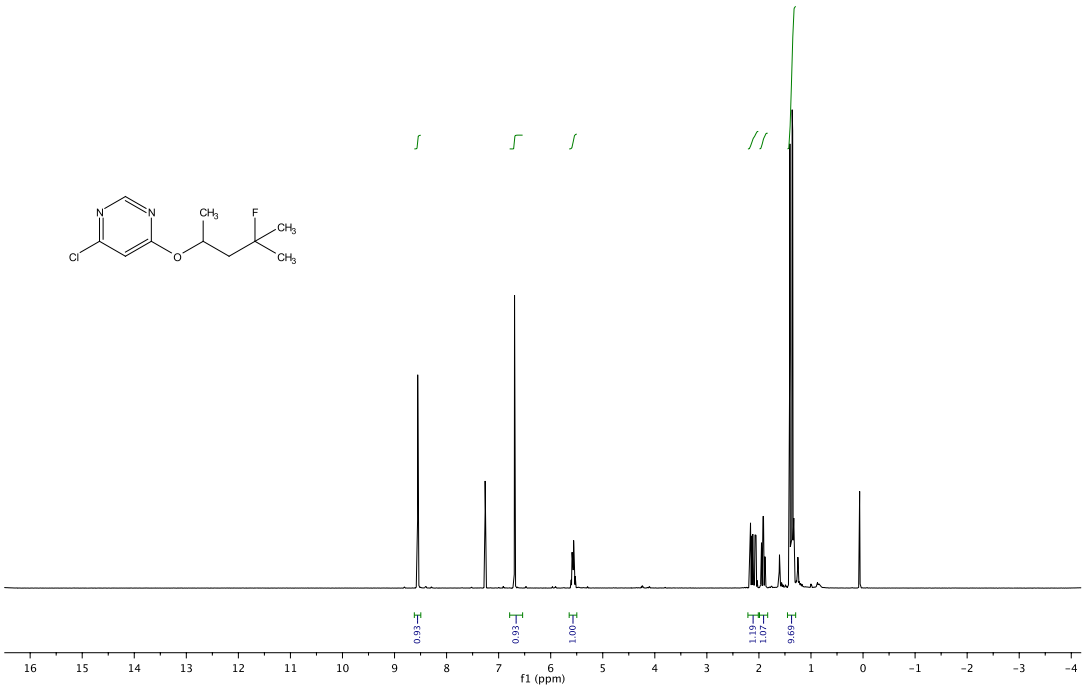
tert-butyl (*S*)-(3-fluoro-3-methyl-1-phenylbutan-2-yl)carbamate (14):

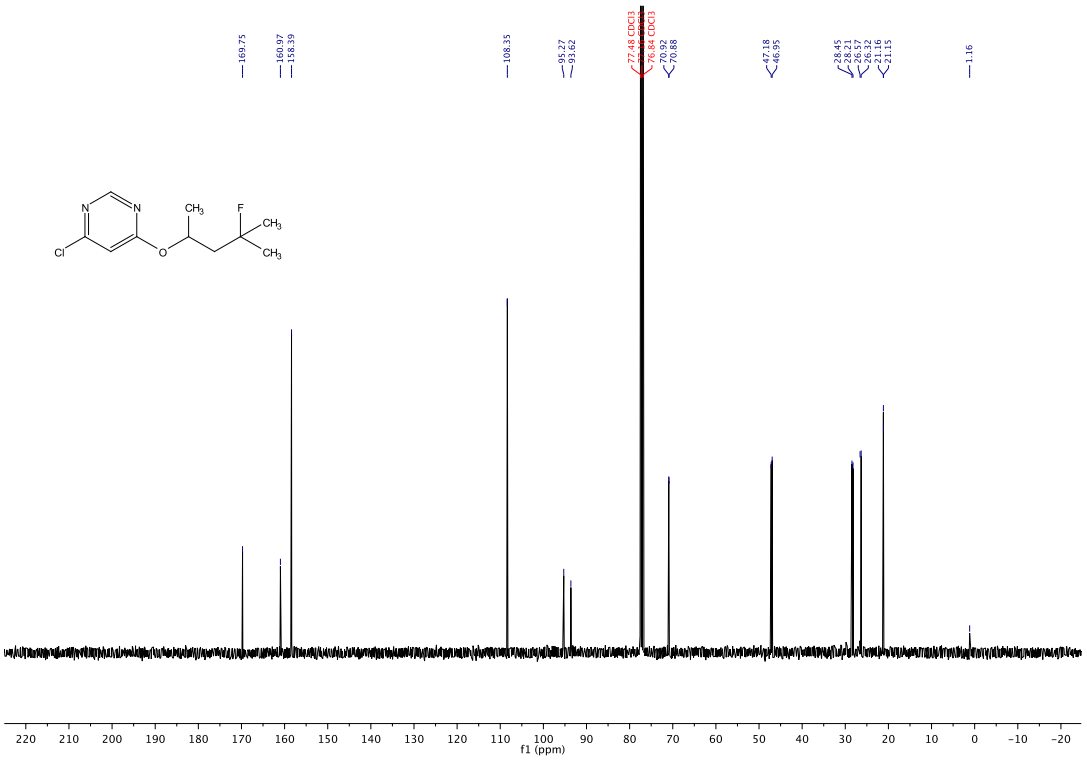


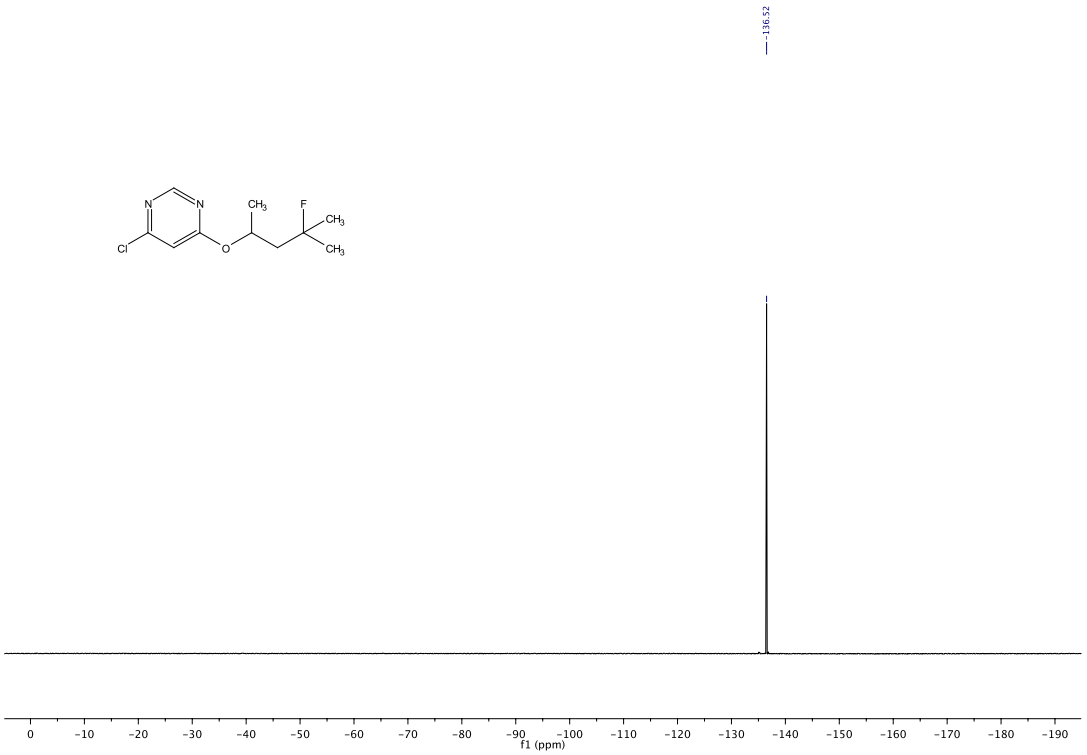

155.7
138.4
129.3
128.4
126.4
98.0
96.3
79.3
77.2 CDCl3
58.1
57.9
36.1
28.3
25.2
24.9
24.5
24.2
f1 (ppm)


152.54
f1 (ppm)

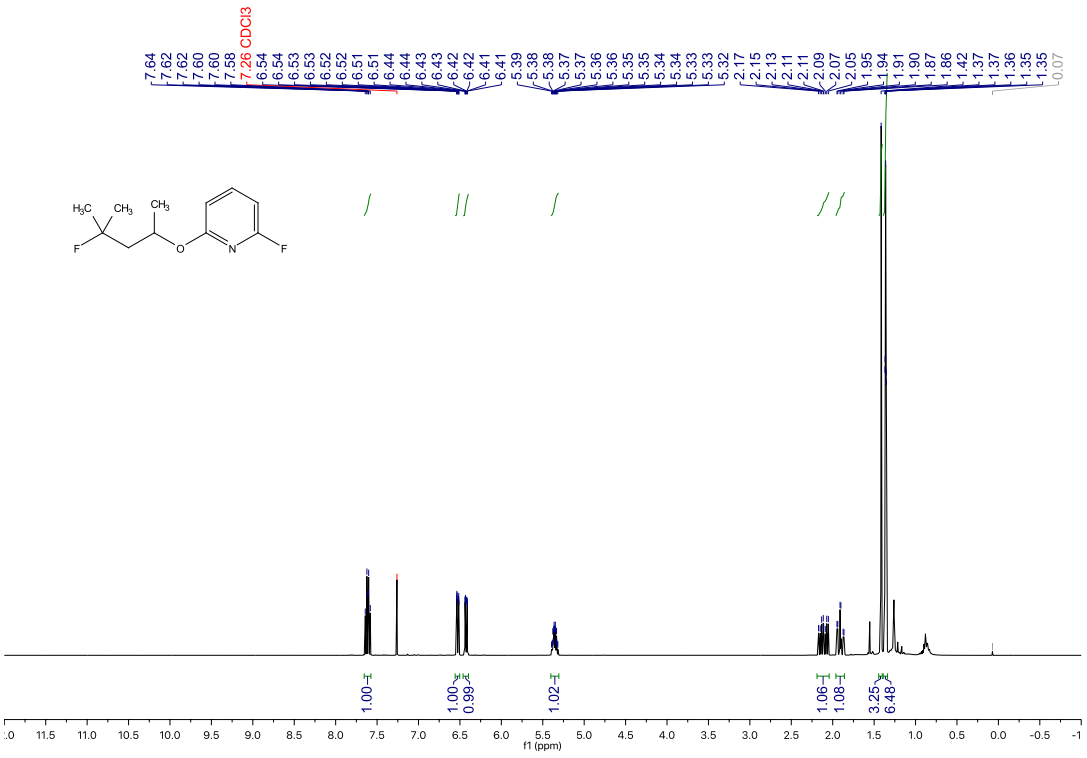
4-chloro-6-((4-fluoro-4-methylpentan-2-yl)oxy)pyrimidine (15)

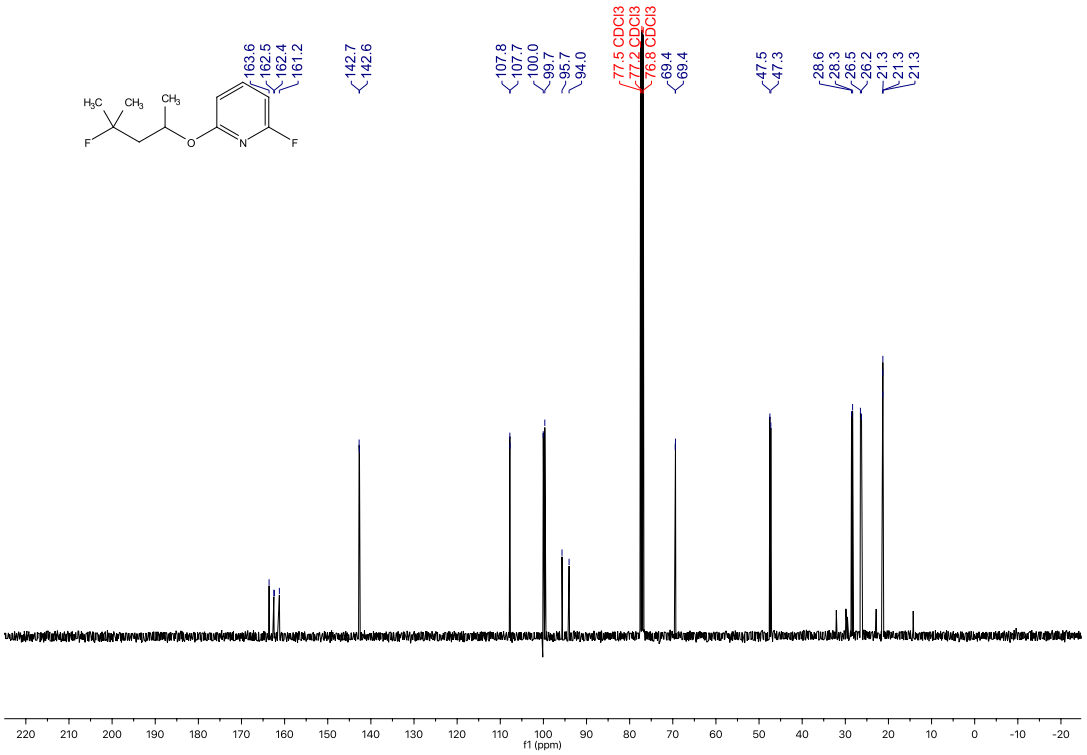






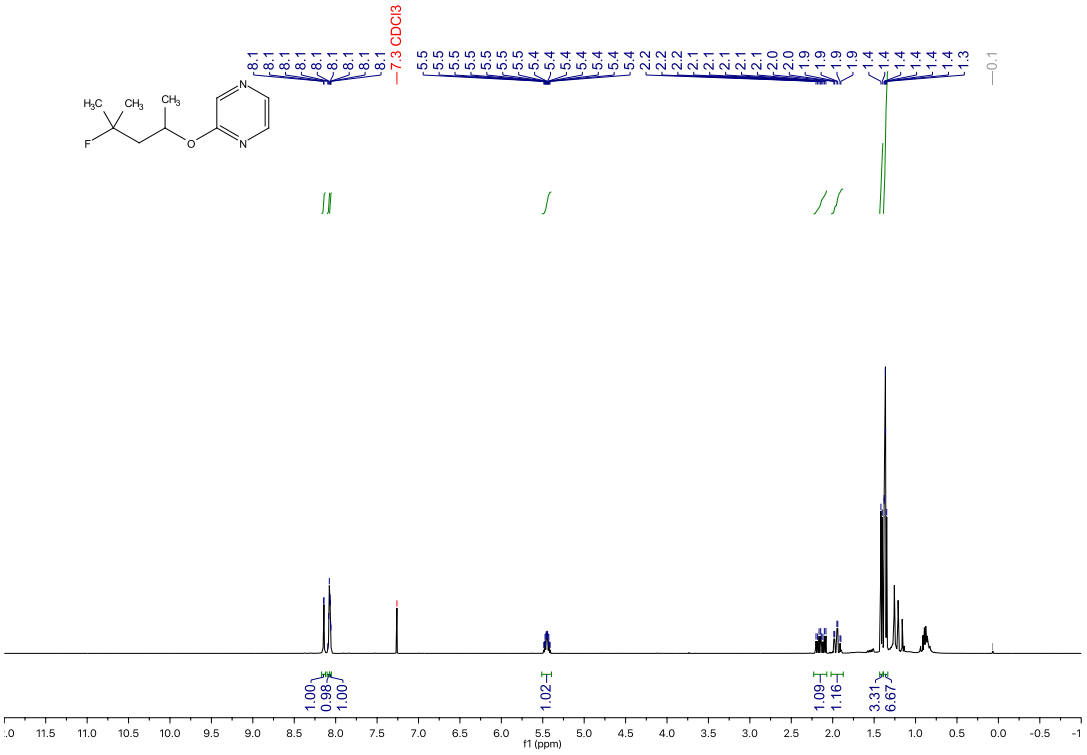
2-fluoro-6-((4-fluoro-4-methylpentan-2-yl)oxy)pyridine (16):

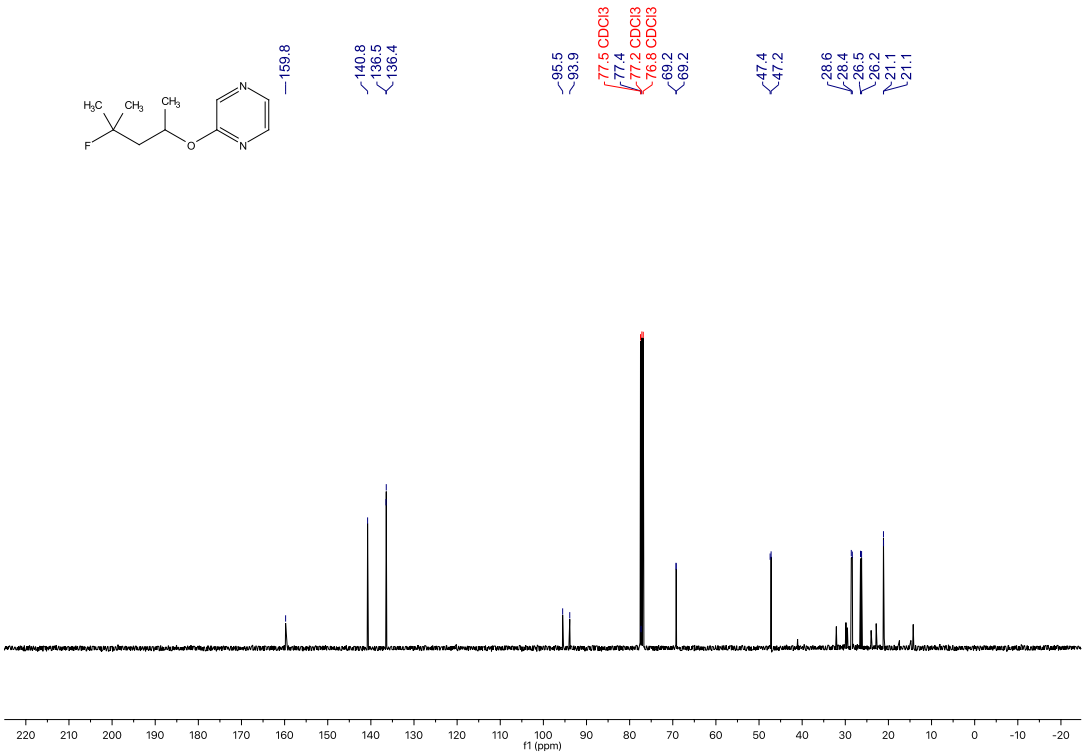


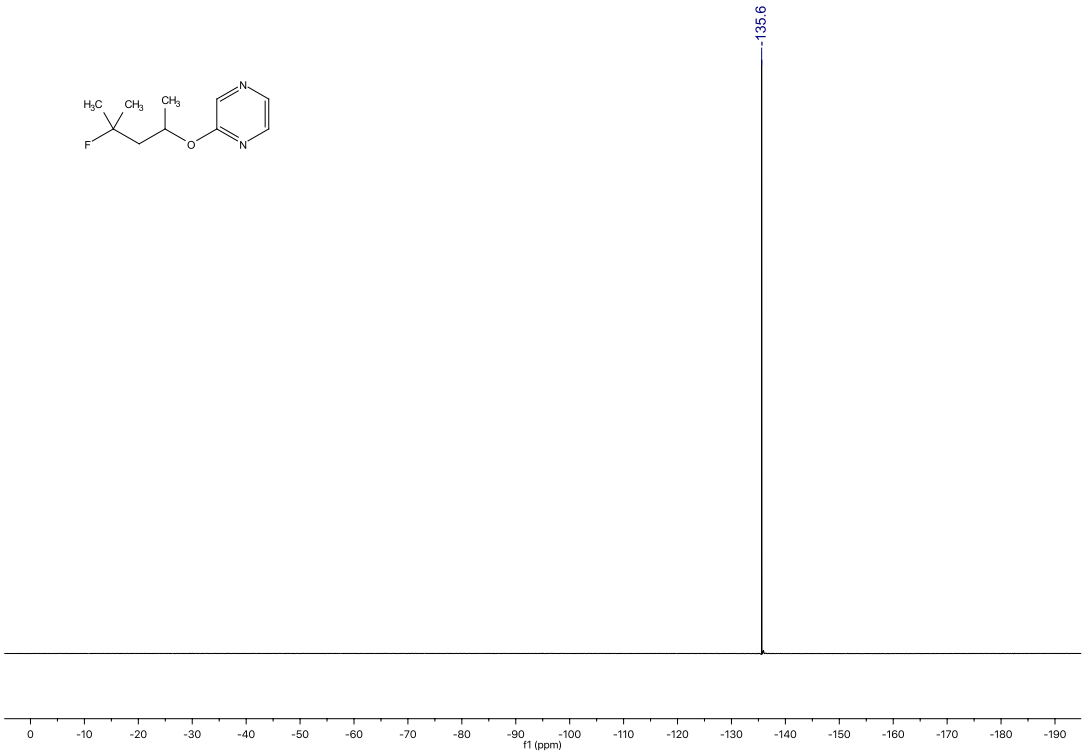

163.6
162.5
162.4
161.2
142.7
142.6
107.8
107.7
100.0
99.7
95.7
94.0
77.5 CDCl3
77.2 CDCl3
76.8 CDCl3
69.4
69.4
47.5
47.3
28.6
28.3
26.5
26.2
21.3
21.3
21.3
H3C
CH3
CH3
F
O
N
F
f1 (ppm)


-69.92
134.61
H3C
CH3
CH3
F
O
N
F
f1 (ppm)

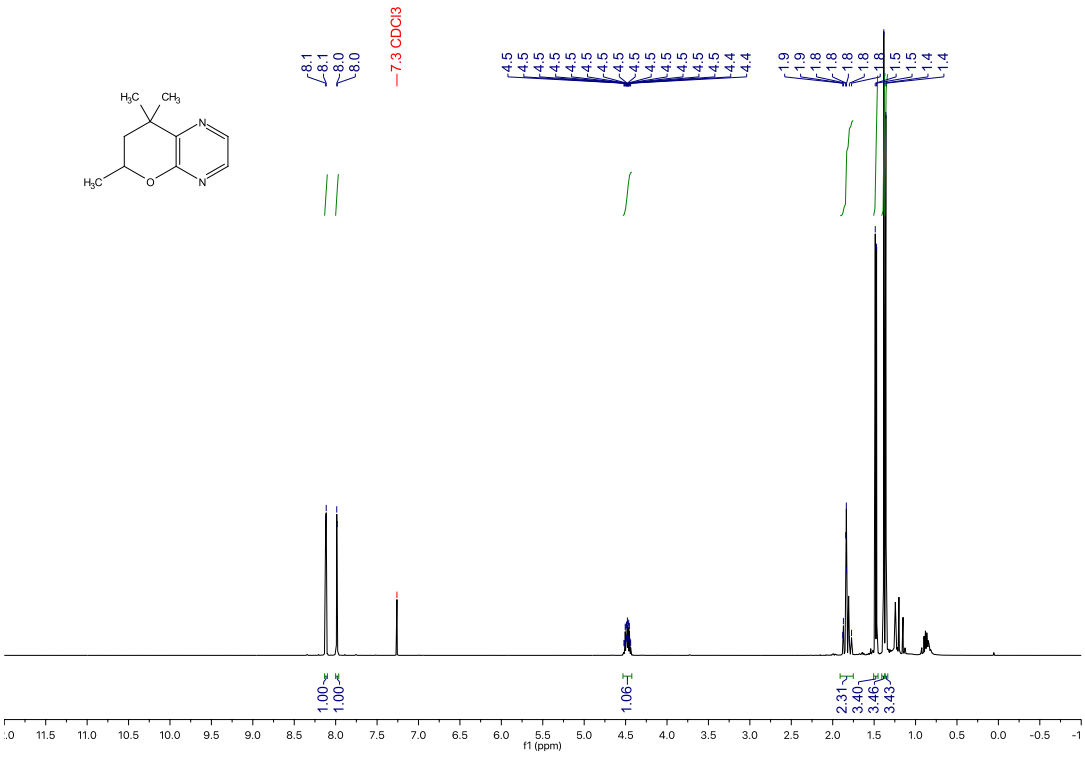
2-((4-fluoro-4-methylpentan-2-yl)oxy)pyrazine (17a)

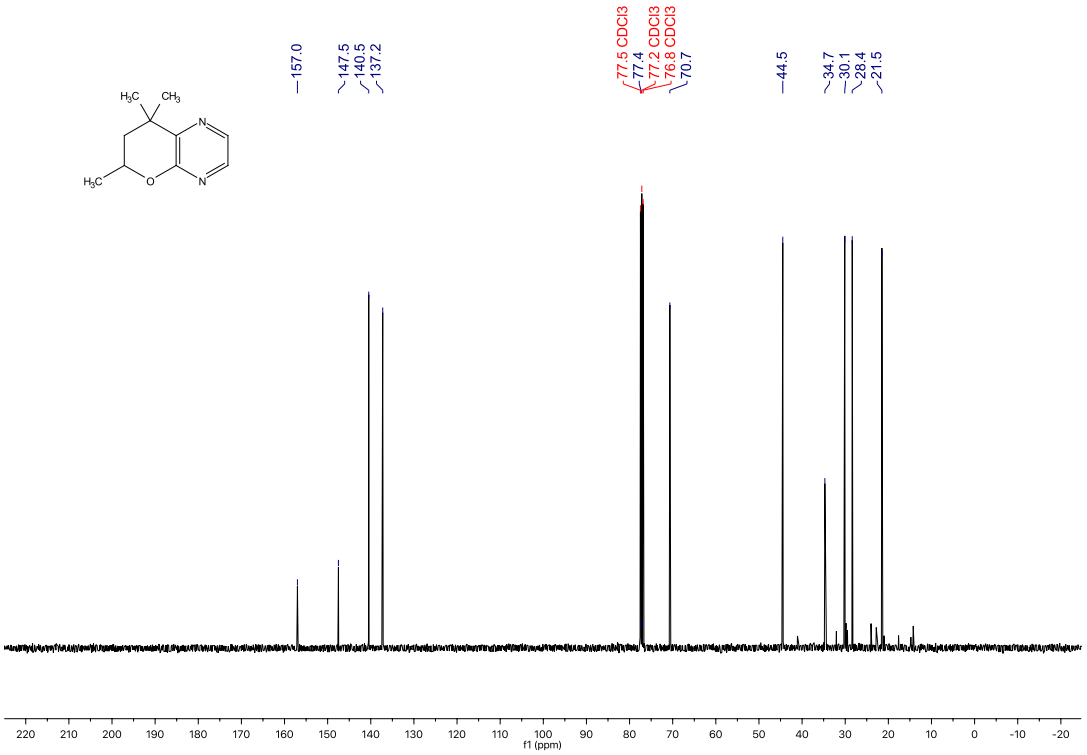




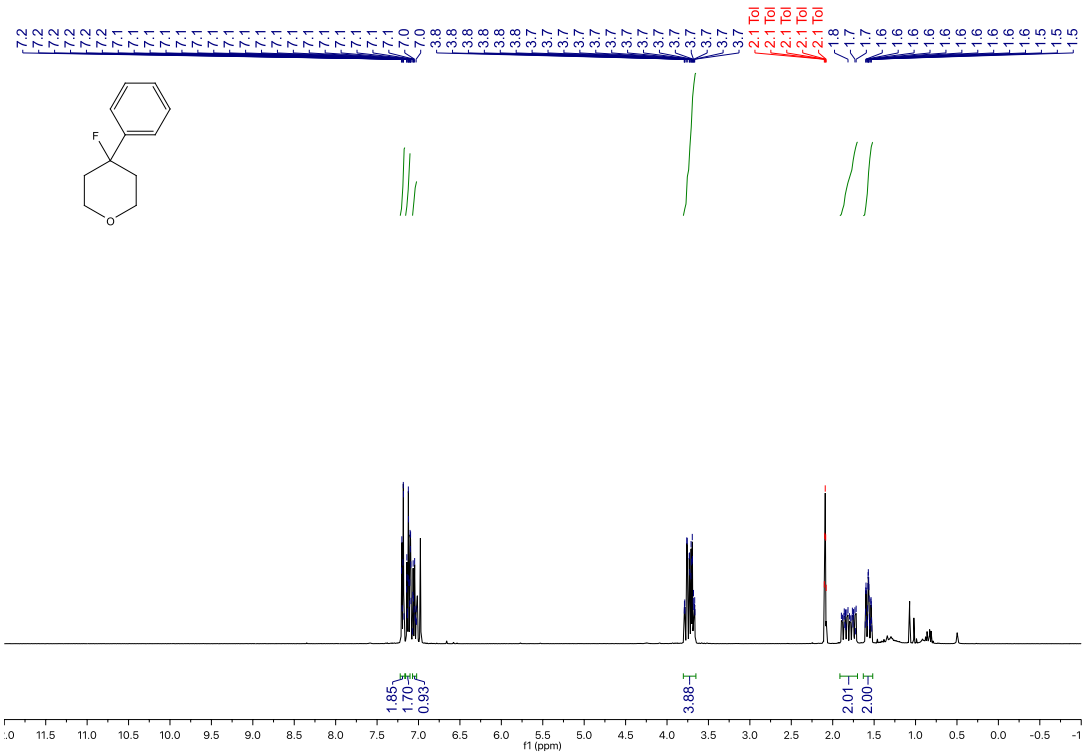


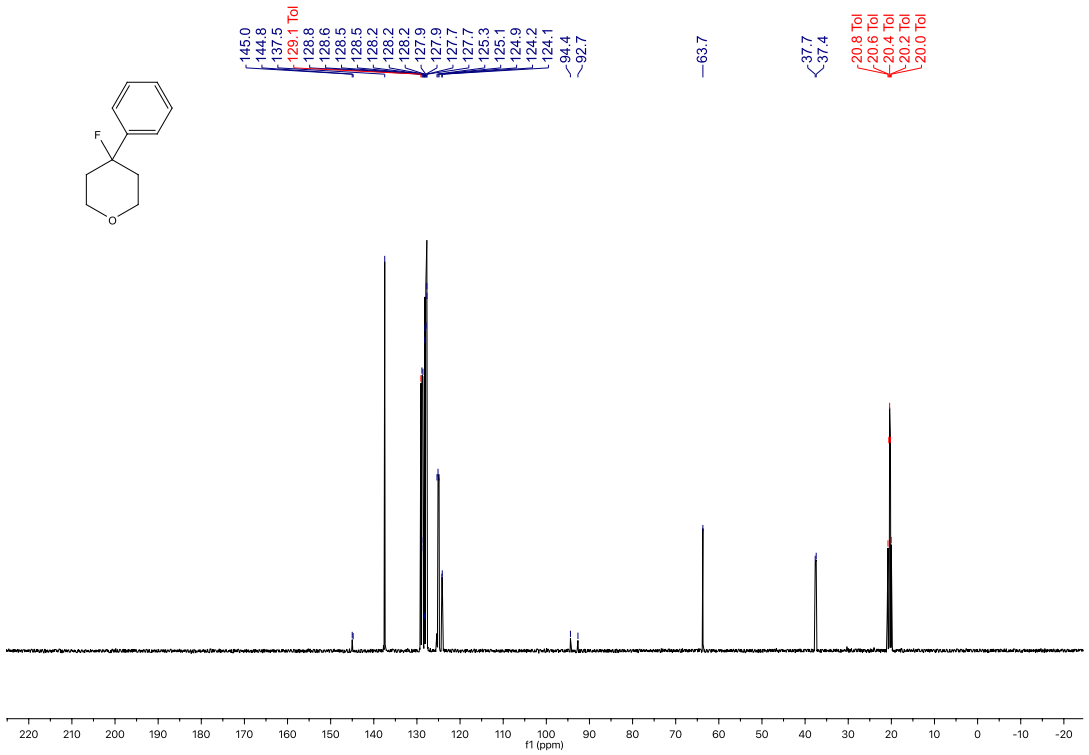
2-((4-fluoro-4-methylpentan-2-yl)oxy)pyrazine (17b)

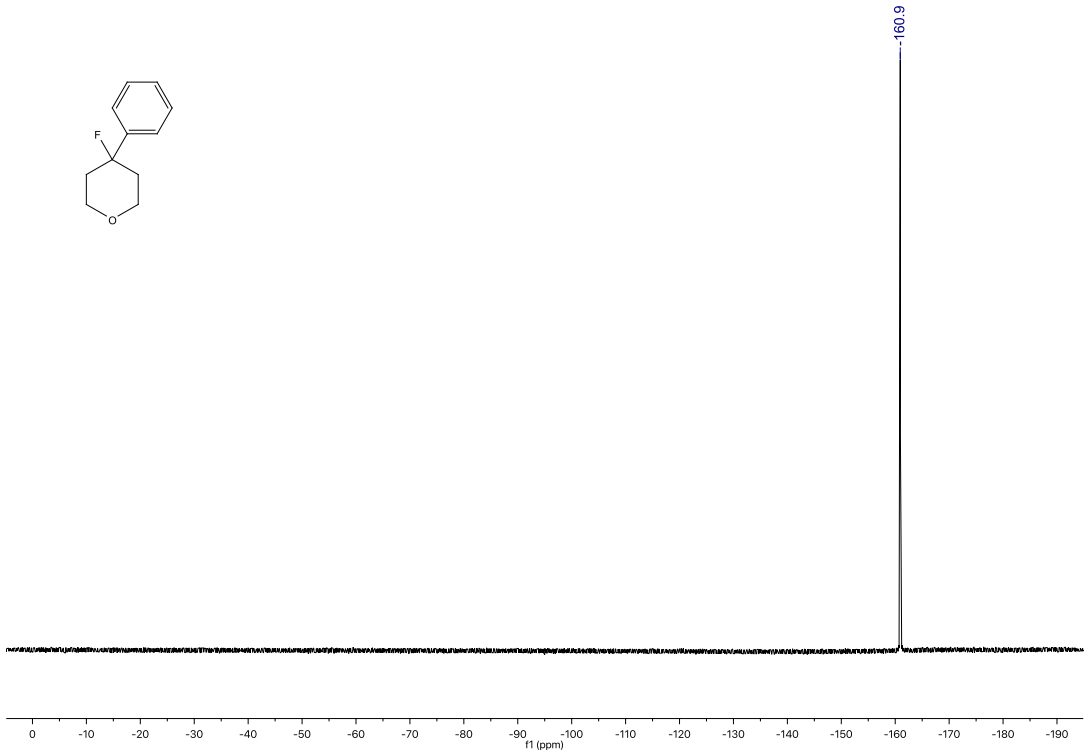




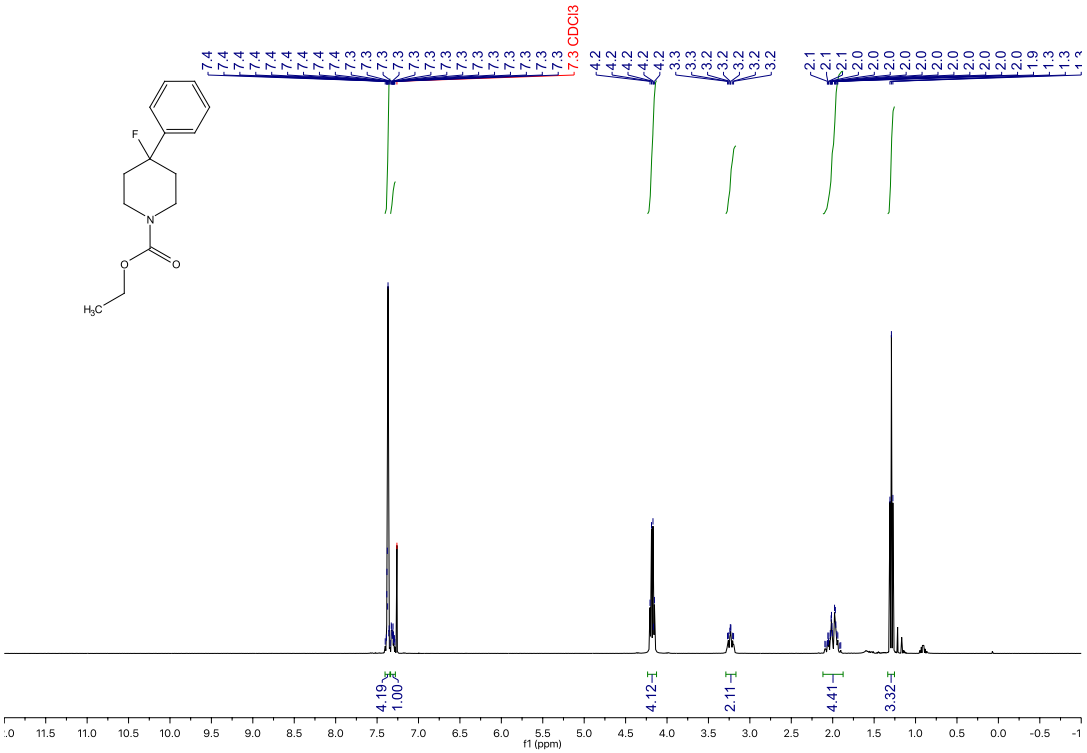
4-fluoro-4-phenyltetrahydro-2*H*-pyran (18)

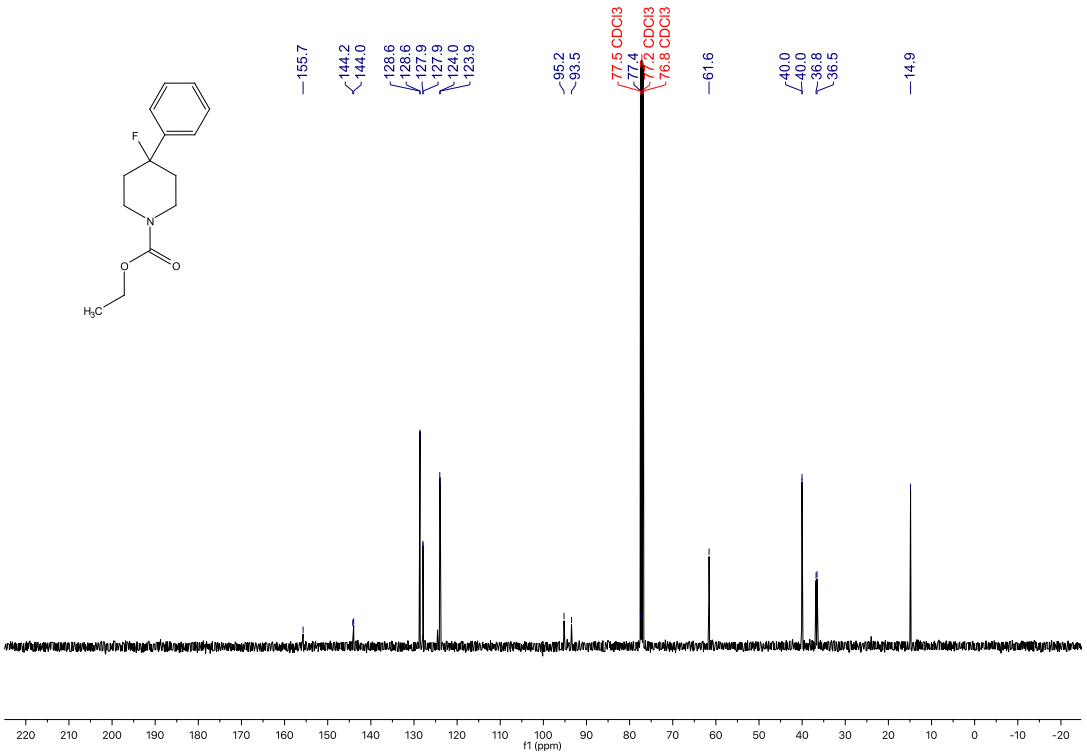


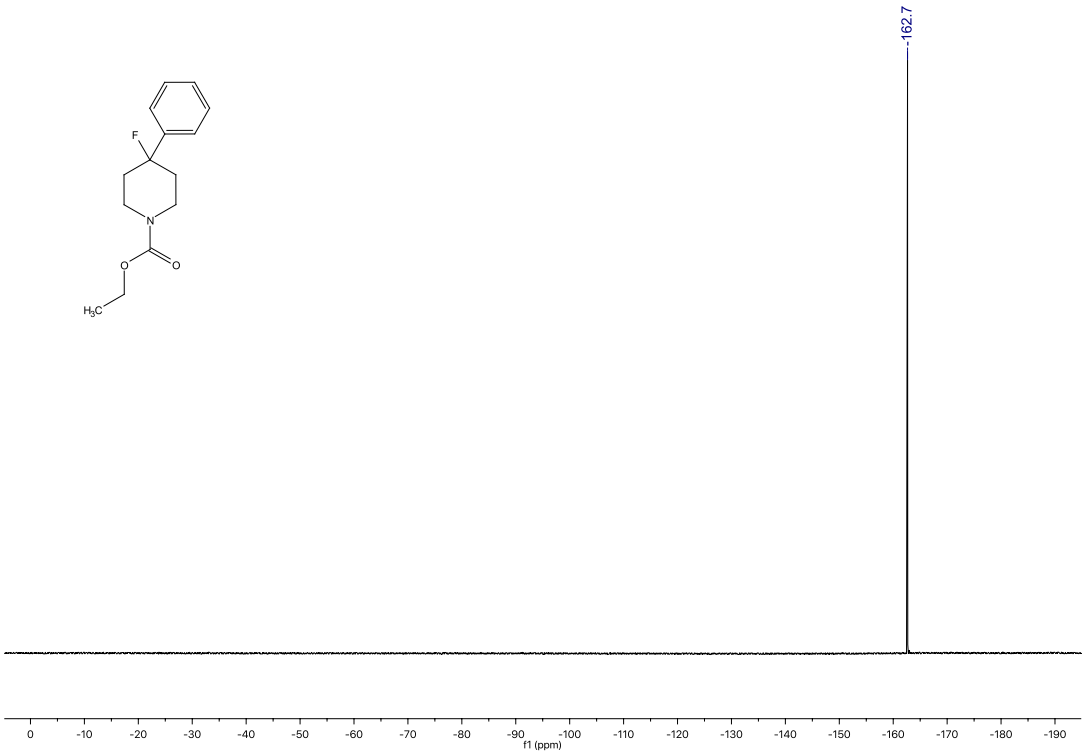

145.0
144.8
137.5
129.1 Tol
128.8
128.6
128.5
128.5
128.2
128.2
128.2
127.9
127.9
127.7
127.7
125.3
125.1
124.9
124.2
124.1
94.4
92.7
63.7
37.7
37.4
20.8 Tol
20.6 Tol
20.4 Tol
20.2 Tol
20.0 Tol
F
O
f1 (ppm)


160.9
F
O
f1 (ppm)

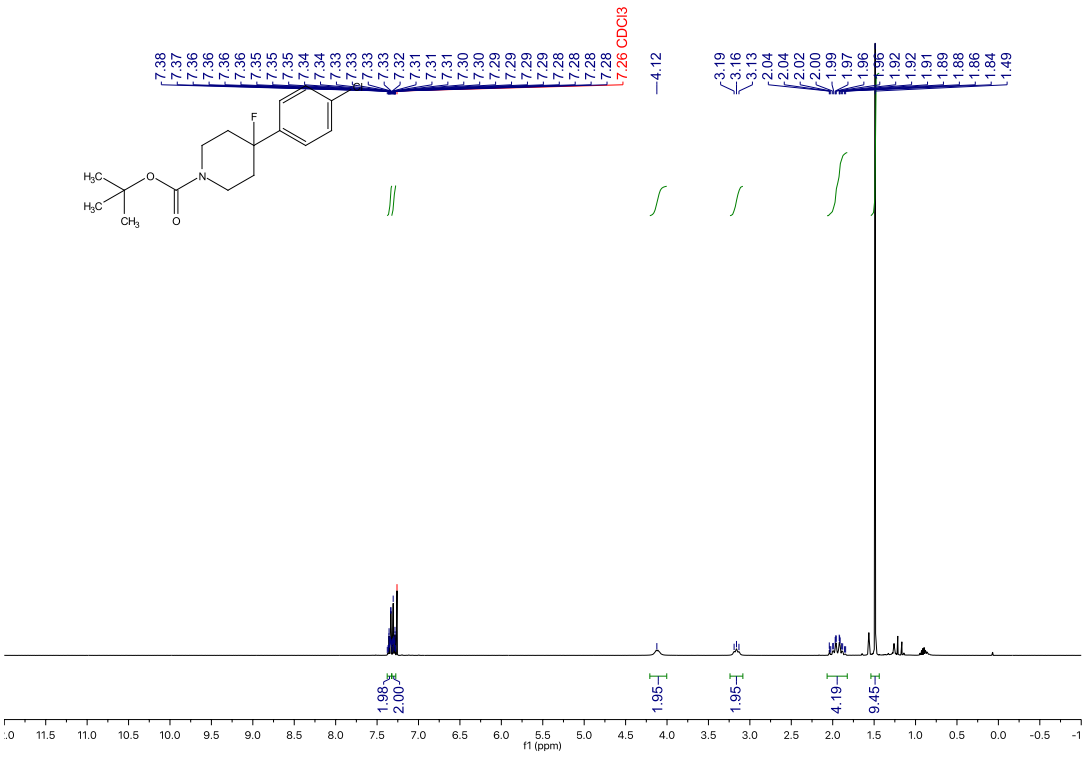
Ethyl 4-fluoro-4-phenylpiperidine-1-carboxylate (19)

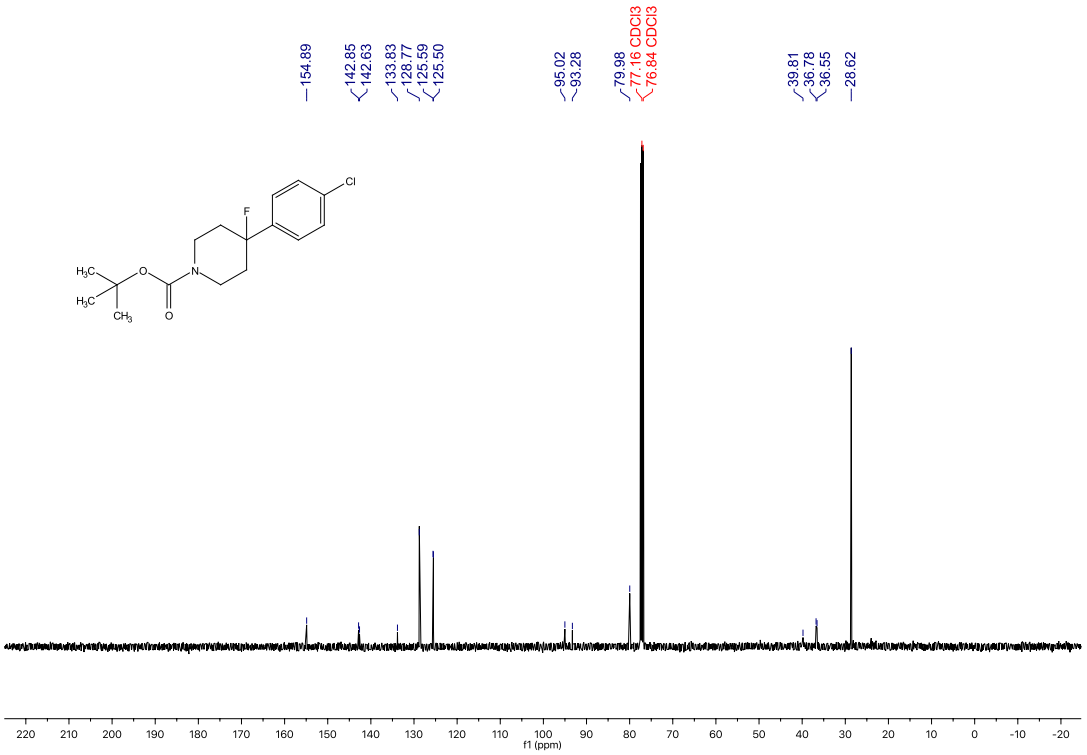


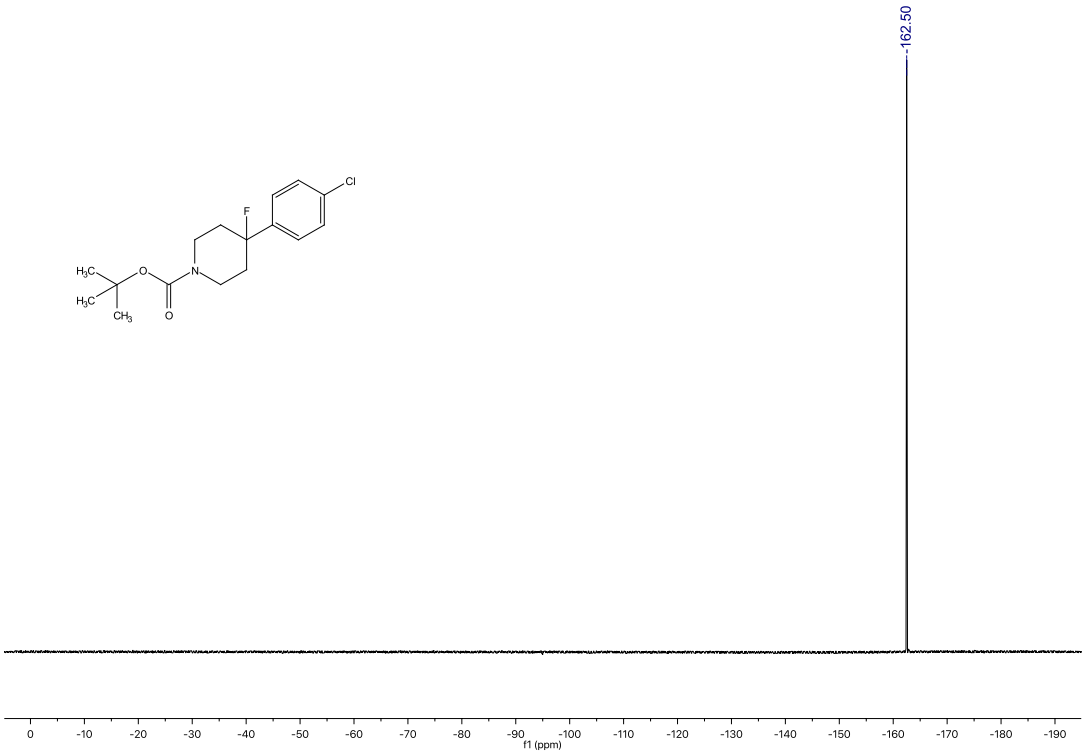




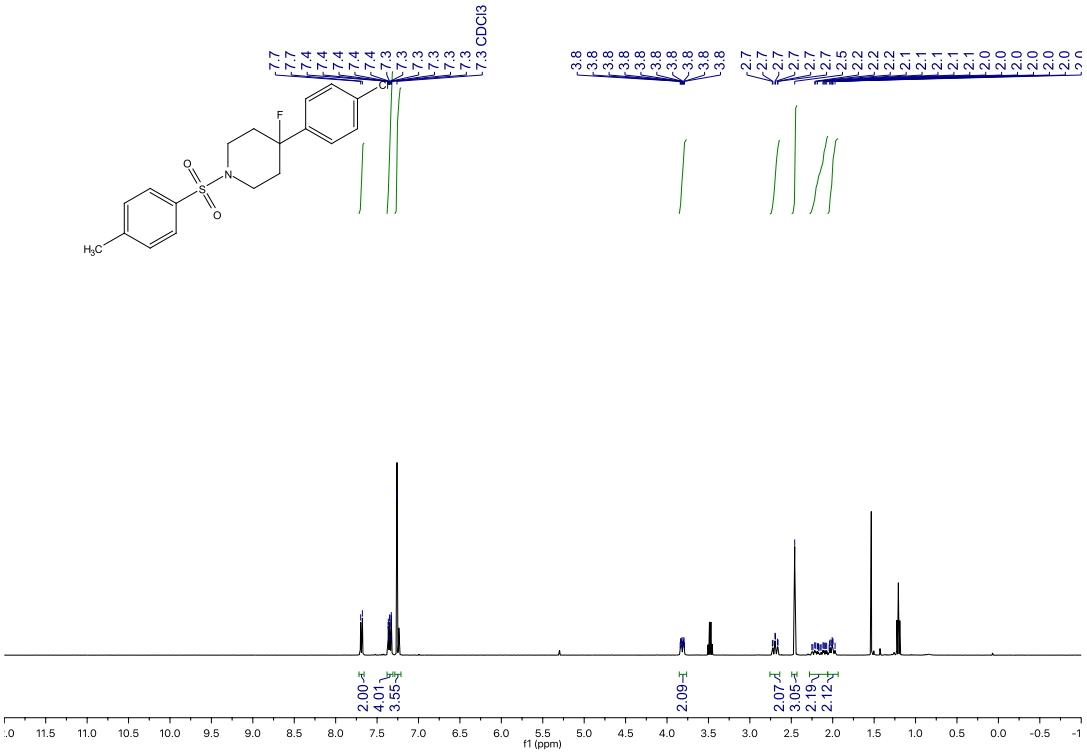
tert-butyl 4-(4-chlorophenyl)-4-fluoropiperidine-1-carboxylate (20)

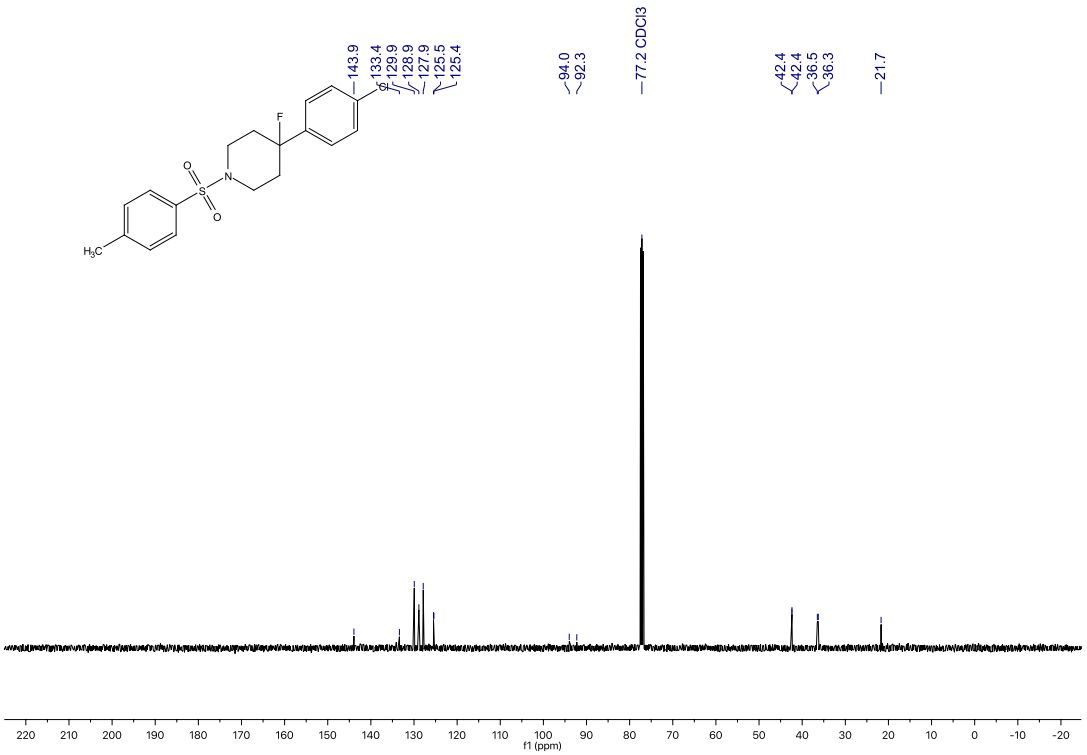


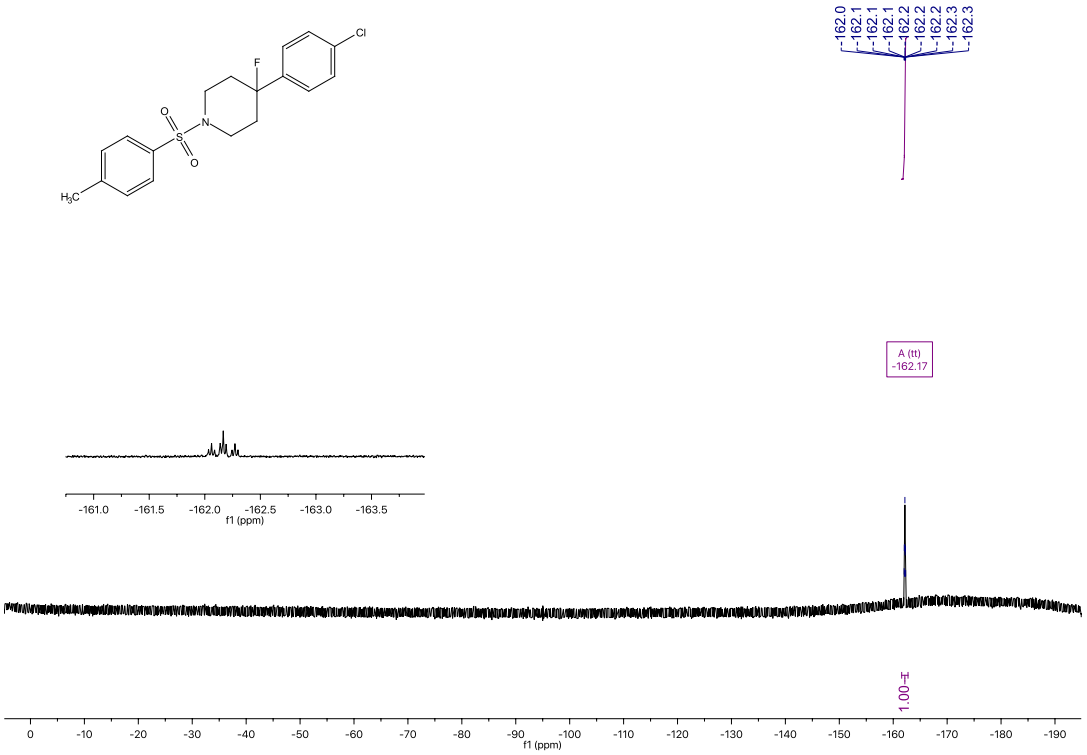

154.89
142.85
142.63
133.83
128.77
125.59
125.50
95.02
93.28
79.98
77.16 CDCl3
76.84 CDCl3
39.81
36.78
36.55
28.62
Cl
F
N
O
H3C
CH3
f1 (ppm)


162.50
Cl
F
N
O
H3C
CH3
f1 (ppm)

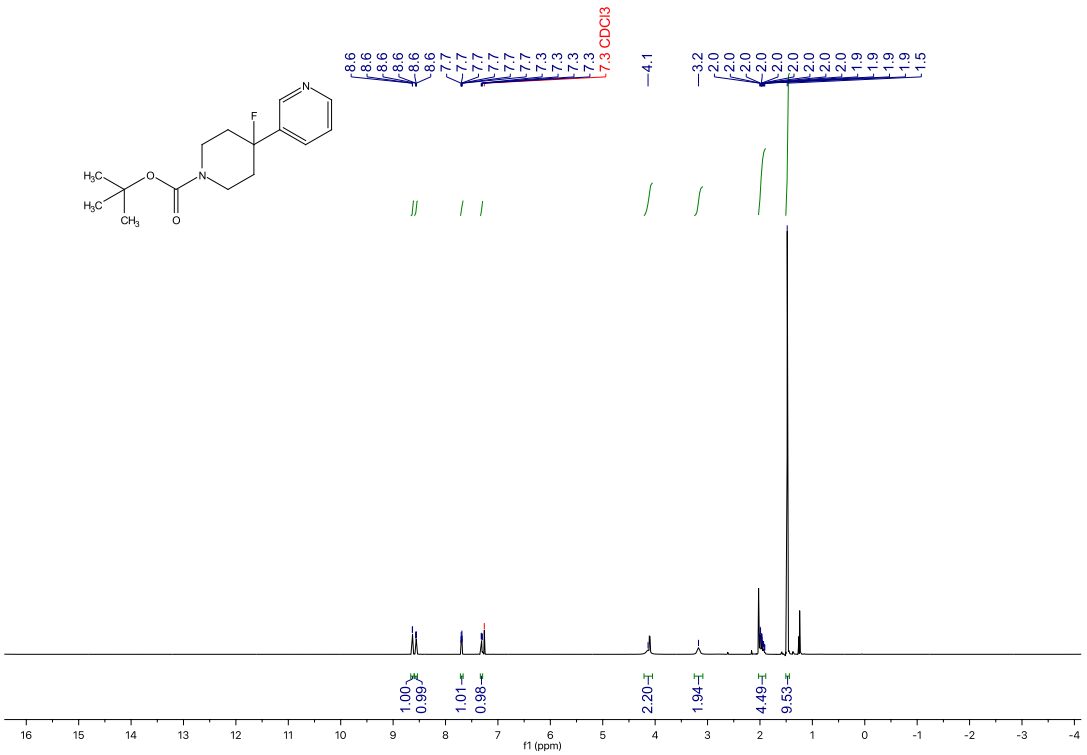
4-(4-chlorophenyl)-4-fluoro-1-tosylpiperidine (21)

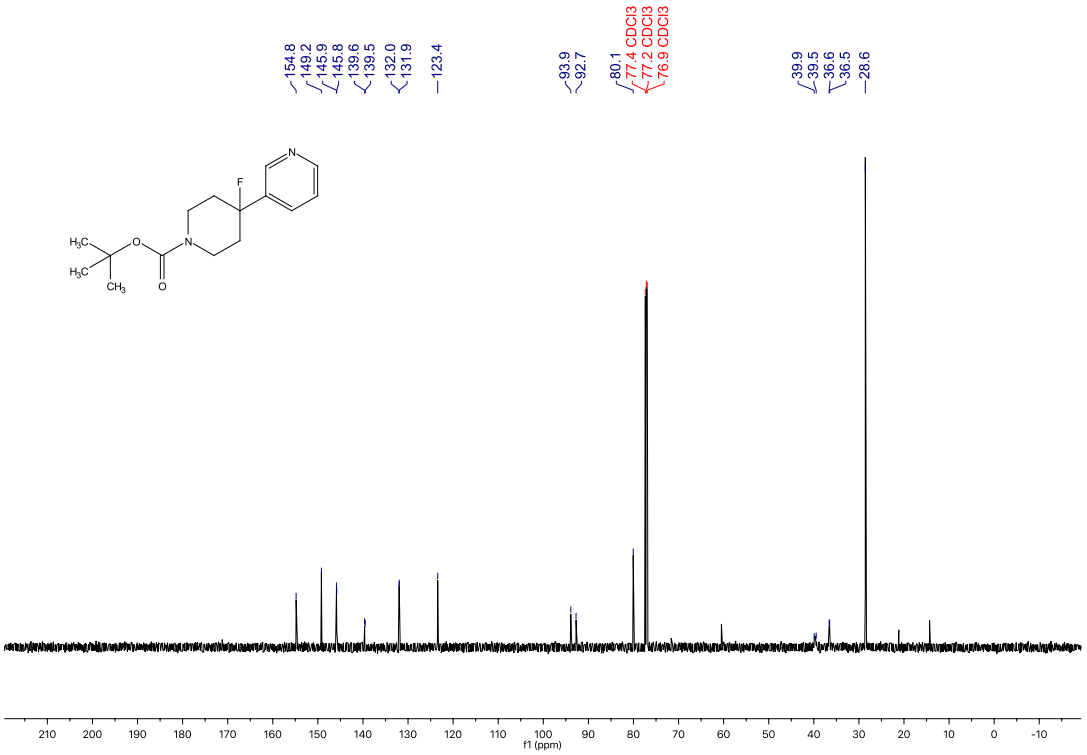


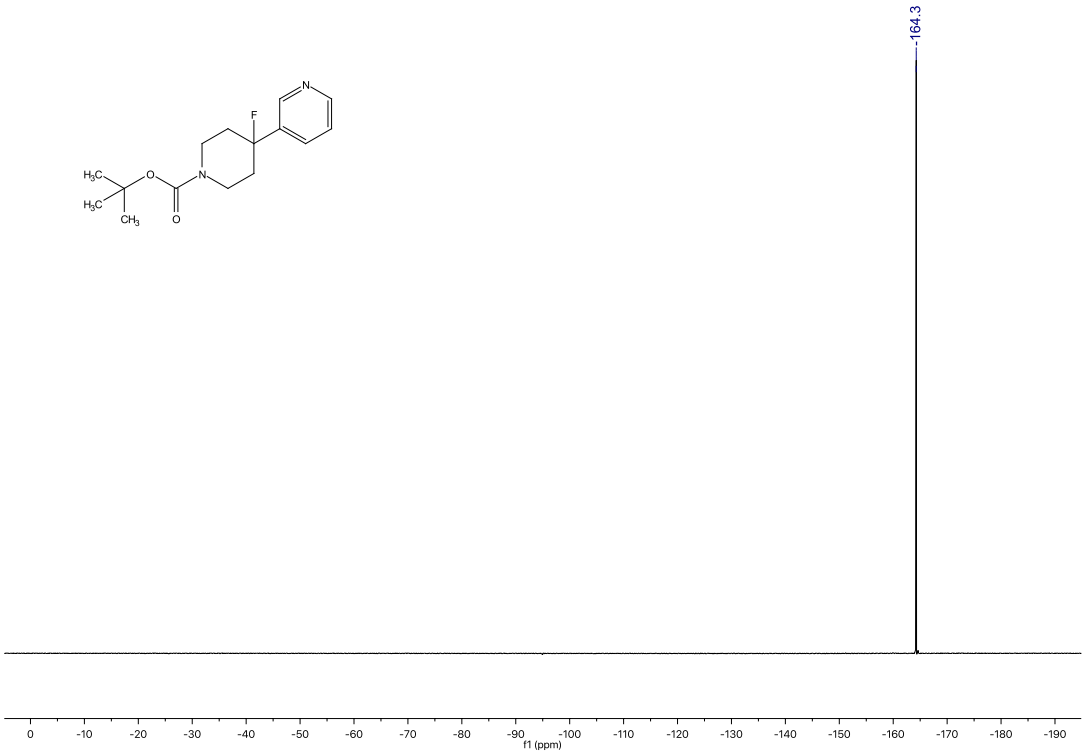




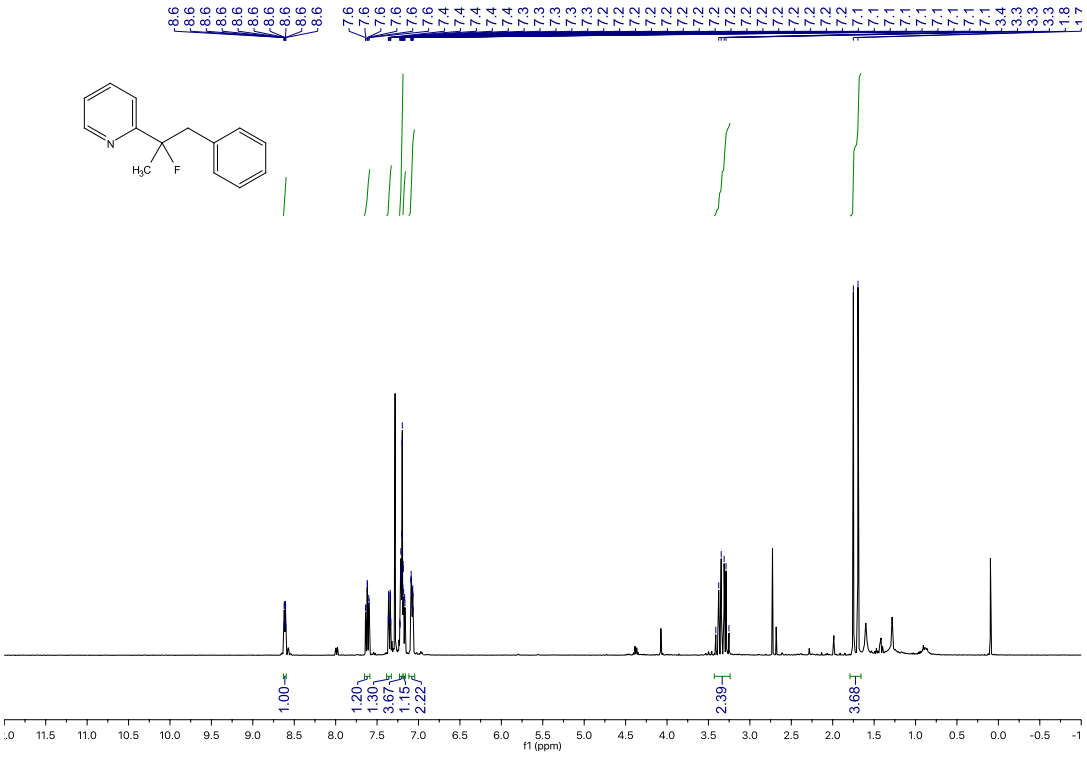
tert-butyl 4-fluoro-4-(pyridin-3-yl)piperidine-1-carboxylate (22)

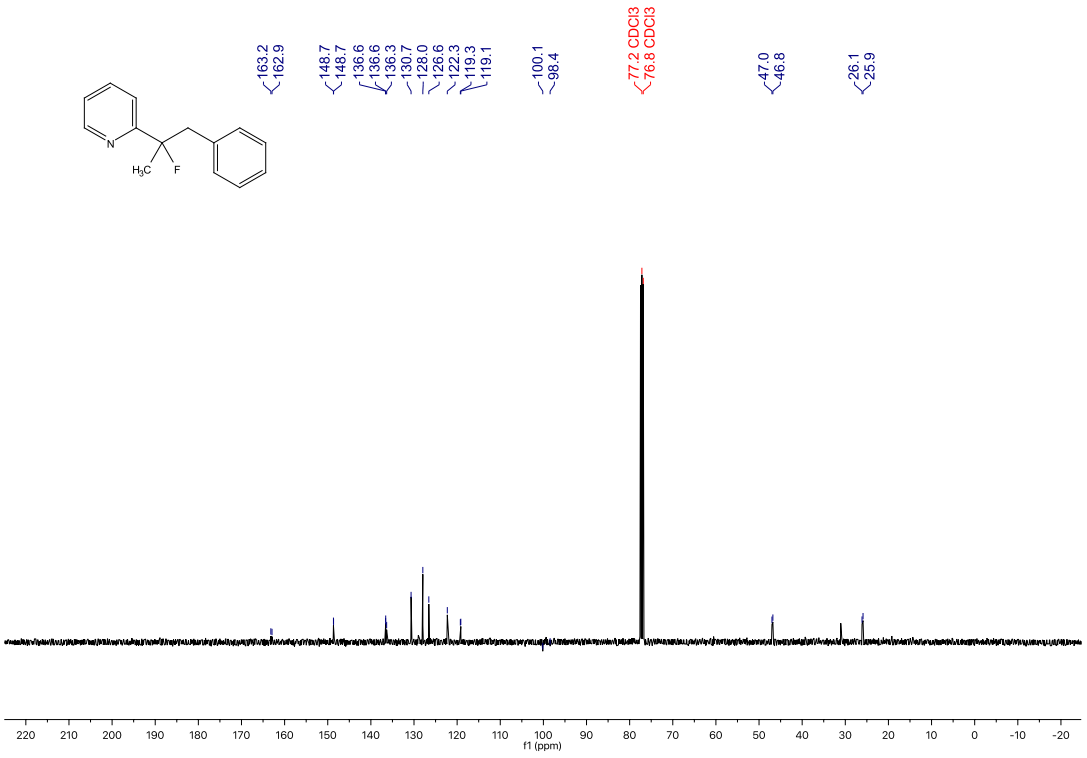



154.8
149.2
145.9
145.8
139.6
139.5
132.0
131.9
123.4
93.9
92.7
80.1
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
39.9
39.5
36.6
36.5
28.6
f1 (ppm)

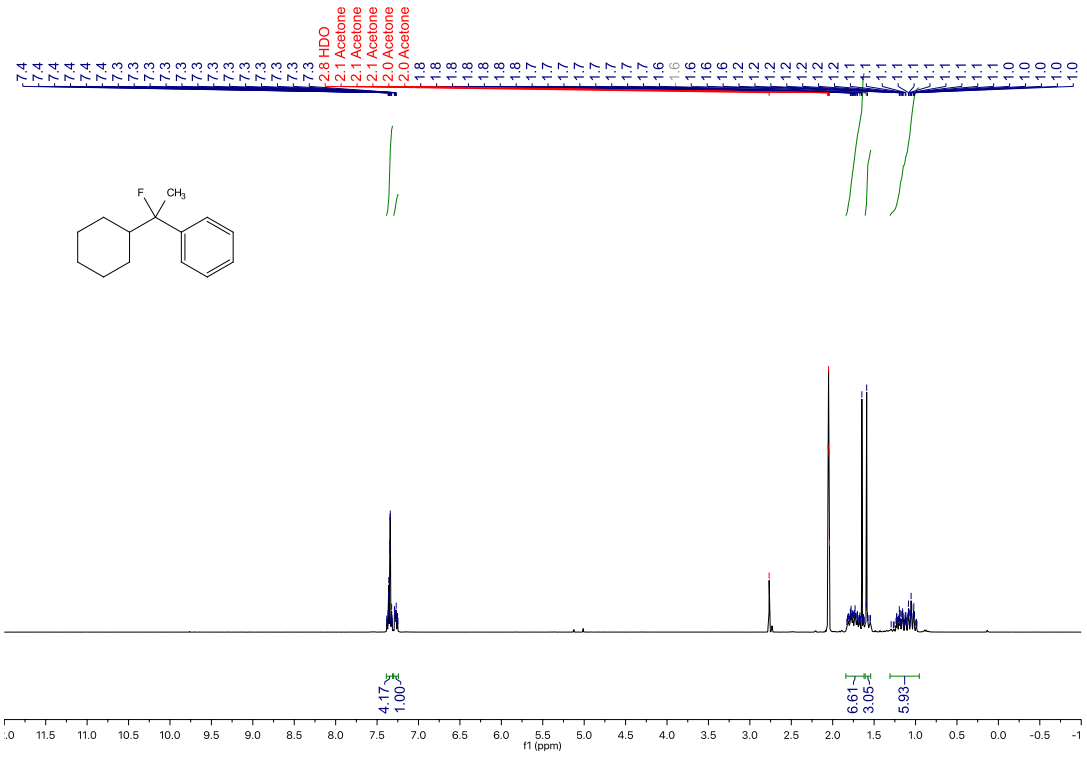

164.3
f1 (ppm)

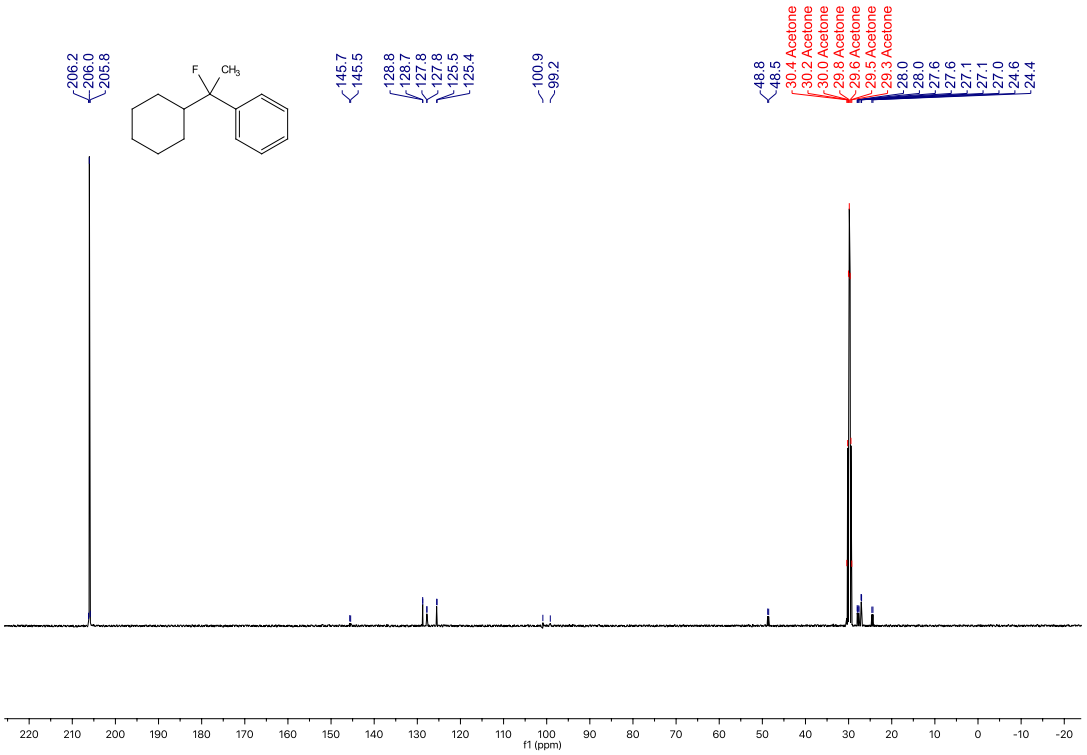
2-(2-fluoro-1-phenylpropan-2-yl)pyridine (23)

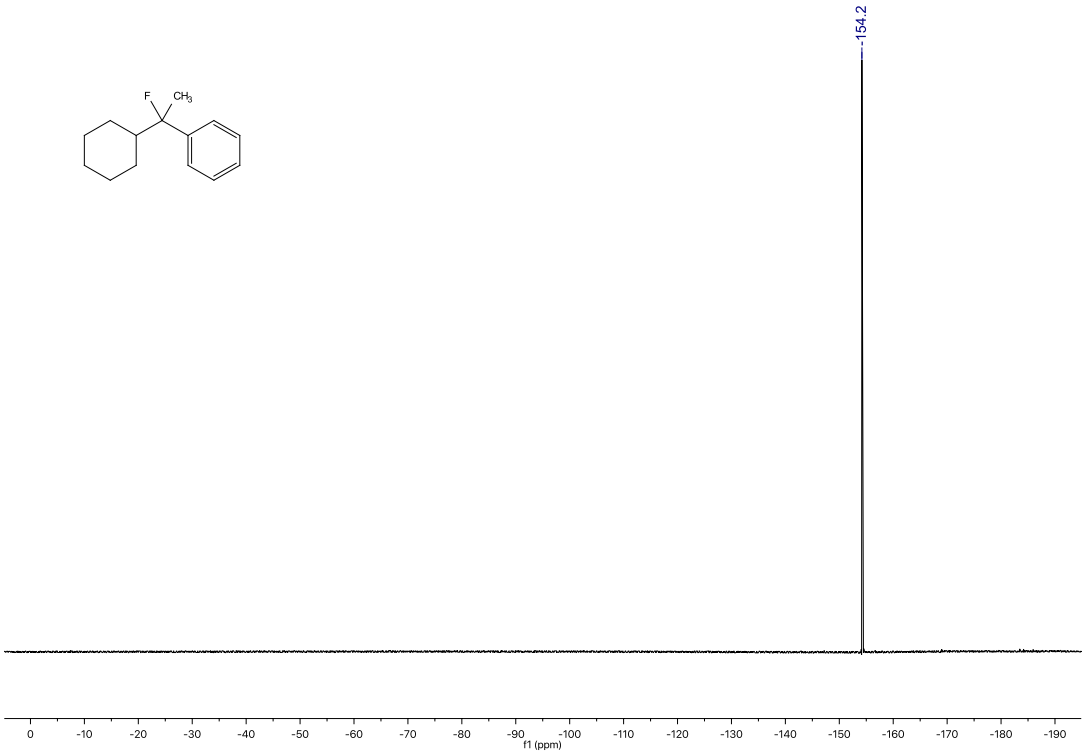




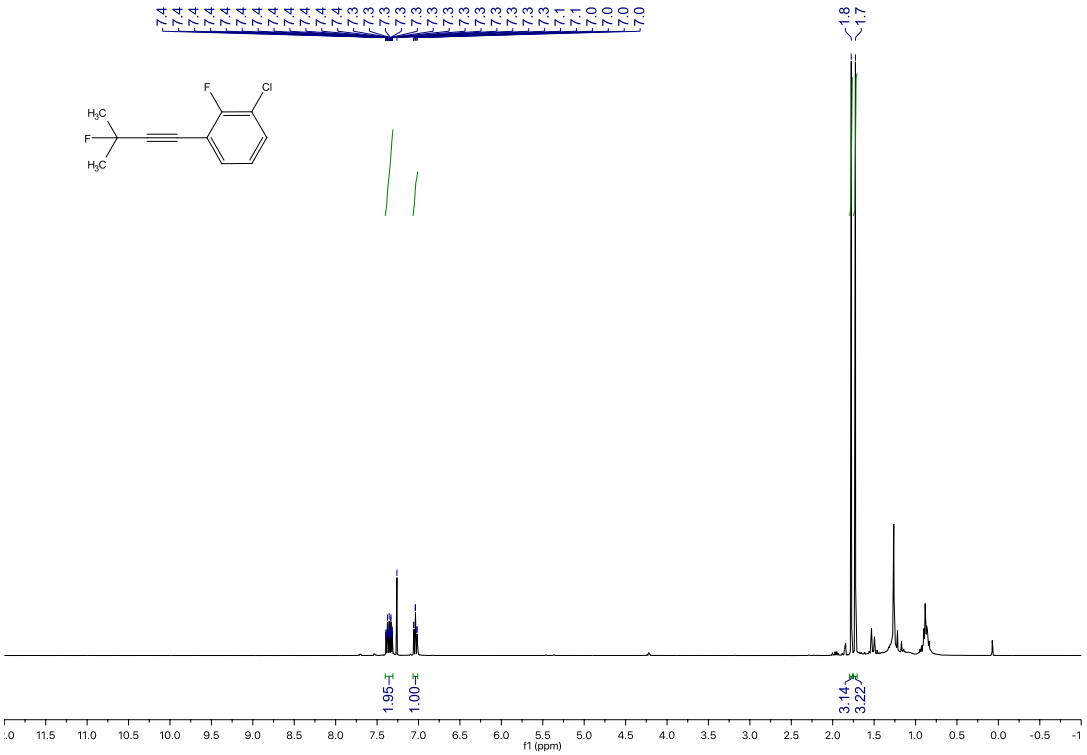
(1-cyclohexyl-1-fluoroethyl)benzene (24):

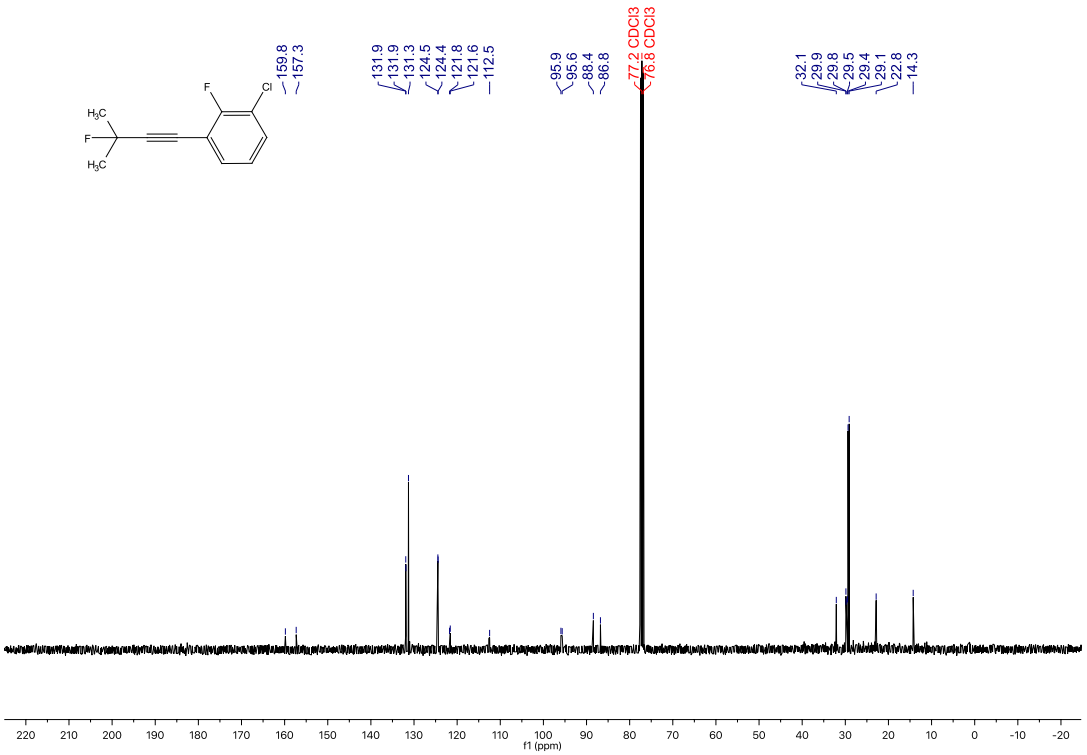



206.2
206.0
205.8
145.7
145.5
128.8
128.7
127.8
127.8
125.5
125.4
100.9
99.2
48.8
48.5
30.4 Acetone
30.2 Acetone
30.0 Acetone
29.8 Acetone
29.6 Acetone
29.5 Acetone
29.3 Acetone
28.0
28.0
27.6
27.6
27.1
27.1
27.0
24.6
24.4
F
CH3
f1 (ppm)

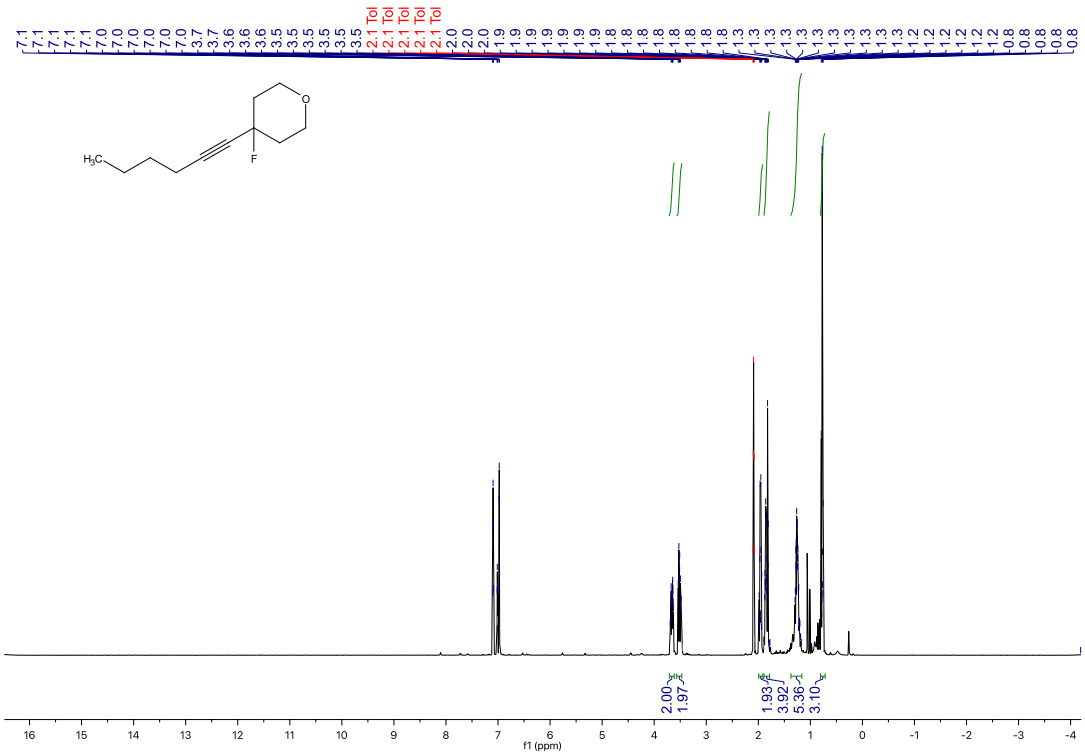

154.2
F
CH3
f1 (ppm)

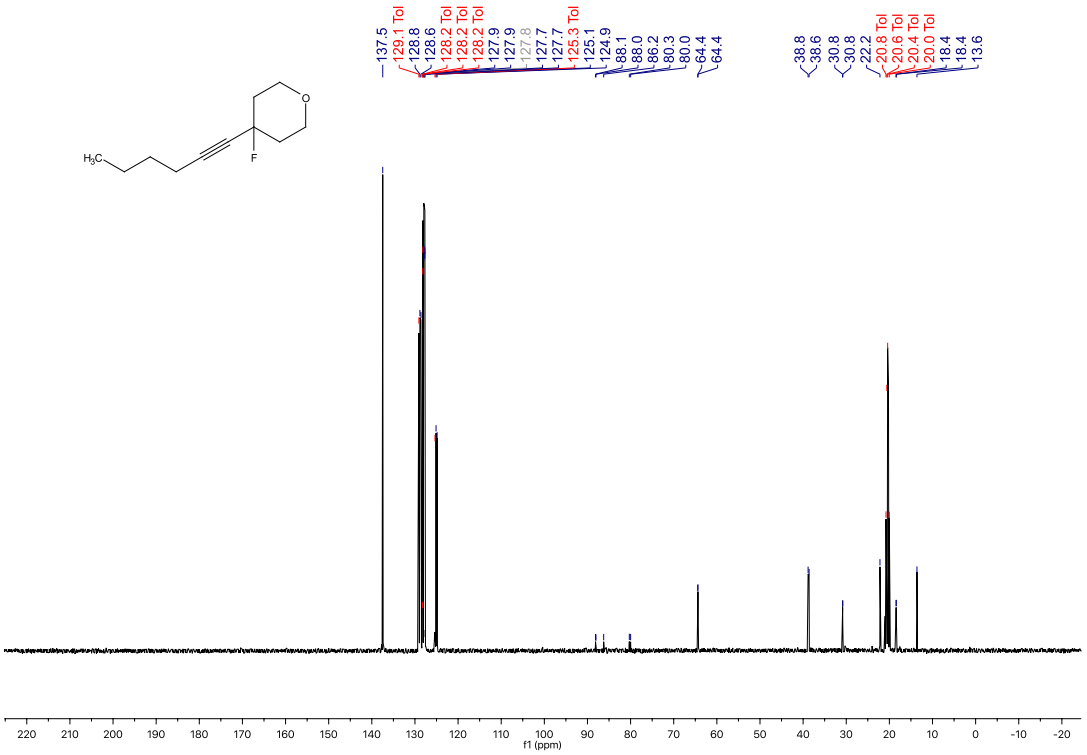
1-chloro-2-fluoro-3-(3-fluoro-3-methylbut-1-yn-1-yl)benzene (25)

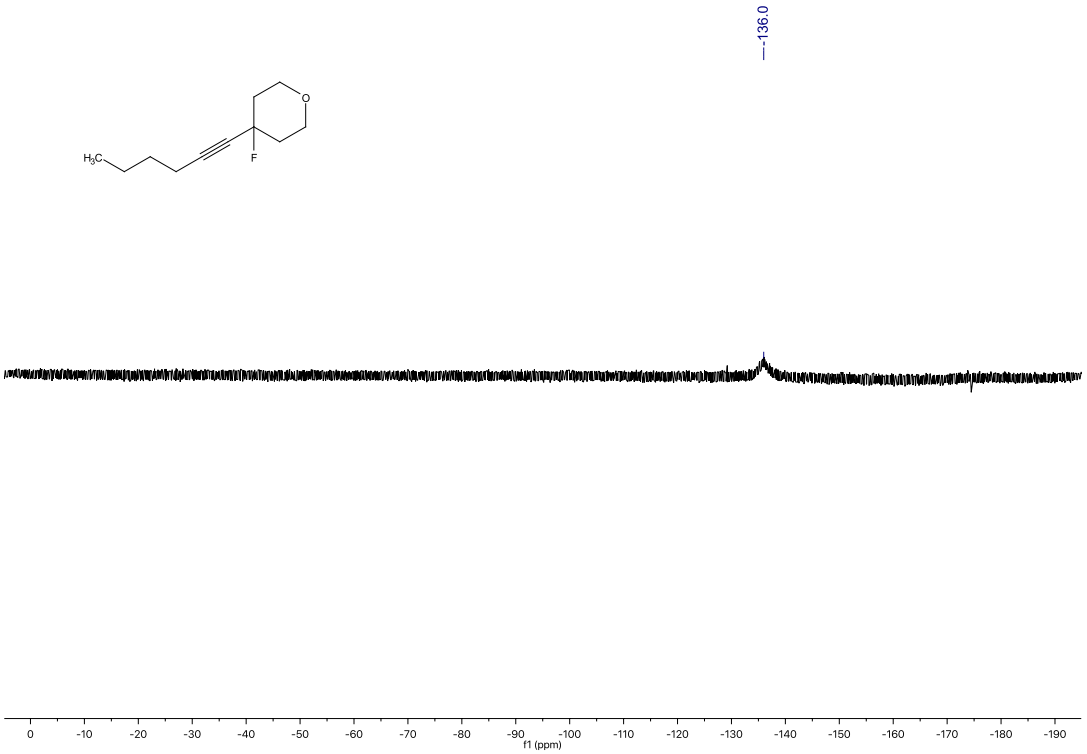




4-fluoro-4-(hex-1-yn-1-yl)tetrahydro-2*H*-pyran (26)




137.5
129.1 Tol
128.8
128.6
128.2 Tol
128.2 Tol
128.2 Tol
127.9
127.9
127.8
127.7
127.7
125.3 Tol
125.1
124.9
88.1
88.0
86.2
80.3
80.0
64.4
64.4
38.8
38.6
30.8
30.8
22.2
20.8 Tol
20.6 Tol
20.4 Tol
20.0 Tol
18.4
18.4
13.6
O
H3C
F
f1 (ppm)


136.0
O
H3C
F
f1 (ppm)

6.4. Chapter 3: Intramolecular Minisci-Type Reaction for Fused Heterocycle Synthesis and Modification of Saccharides

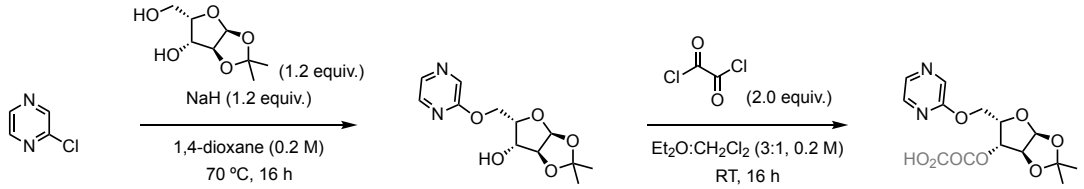
6.4.1. General procedures

General procedure for the nucleophilic aromatic substitution (S_NAr) with saccharides (GP4): A round-bottom flask (RBF) was charged with the corresponding alcohol (1.2 equiv.) was dissolved in 1,4-dioxane (0.2 M) and cooled to 15 °C. NaH (1.2 equiv.) was added portion-wise and the reaction was stirred at room temperature (RT) for 1 h (H_2 evolution). The reaction was cooled to 15 °C and the corresponding chloro-*N*-heteroaromatic ring (1.0 equiv.) was added dropwise. The reaction was stirred at RT for 16h, then quenched with H_2O (10 mL). The crude product was extracted with EtOAc (20 mL × 3), and the organic layer was dried over Na_2SO_4. Purification by column chromatography over silica gel afforded the desired product.

General procedure for the nucleophilic aromatic substitution (S_NAr) with small alcohols (GP5): A round-bottom flask (RBF) was charged with the corresponding alcohol (2.0 equiv.) was dissolved in DMSO (0.4 M) and cooled to 15 °C. NaH (2.0 equiv.) was added portion-wise and the reaction was stirred at room temperature (RT) for 1 h (H_2 evolution). The reaction was cooled to 15 °C and the corresponding chloro-*N*-heteroaromatic ring (1.0 equiv.) was added dropwise. The reaction was stirred at RT for 16h, then quenched with H_2O (10 mL). The crude product was extracted with EtOAc (20 mL × 3), and the organic layer was dried over Na_2SO_4. Purification by column chromatography over silica gel afforded the desired product.

General procedure for the synthesis of oxalic acids (GP6): Under N_2, a RBF was charged with the corresponding tertiary alcohol (1.0 equiv.) and Et_2O:CH_2Cl_2 (3:1, 0.2 M). Next, oxalyl chloride (2.0 equiv.) was added dropwise and the reaction was stirred at RT for 16 h. H_2O (10 mL each 3 mmol) was added slowly, and the mixture was stirred at 0 ºC for 40 min. Finally, the aqueous phase was extracted with EtOAc (15 mL x 3), the combined organic layers dried over Na2SO4 and concentrated under reduced pressure. The crude material was used in the next step without any further purification.

6.4.2. Synthesis & characterization of oxalic acids



(3aS,5S,6R,6aS)-2,2-dimethyl-5-((pyrazin-2-yloxy)methyl)tetrahydrofuro[2,3-d][1,3]dioxol-6-ol: Synthesized following **GP4** using 2-chloropyrazine (1.0 equiv., 3 mmol, 0.27 mL) to afford the desired product as a white solid in 78% yield (0.62 g, 2.34 mmol).

^{1}HNMR(400 MHz, Chloroform-*d*) δ 8.31 (d, *J* = 1.4 Hz, 1H), 8.19 (d, *J* = 2.9 Hz, 1H), 8.05 (dd, *J* = 2.9, 1.4 Hz, 1H), 5.96 (d, *J* = 3.6 Hz, 1H), 4.77 (dd, *J* = 11.5, 8.0 Hz, 1H), 4.60 (d, *J* = 3.7 Hz, 1H), 4.52 – 4.46 (m, 1H), 4.43 (ddd, *J* = 8.0, 4.7, 2.4 Hz, 1H), 4.12 (d, *J* = 2.5 Hz, 1H), 1.54 – 1.48 (m, 3H), 1.33 (d, *J* = 0.7 Hz, 3H).

^{13}C NMR(101 MHz, Chloroform-*d*) δ 159.7, 139.8, 137.3, 136.7, 112.0, 104.9, 85.3, 78.8, 74.5, 63.0, 27.0, 26.4.

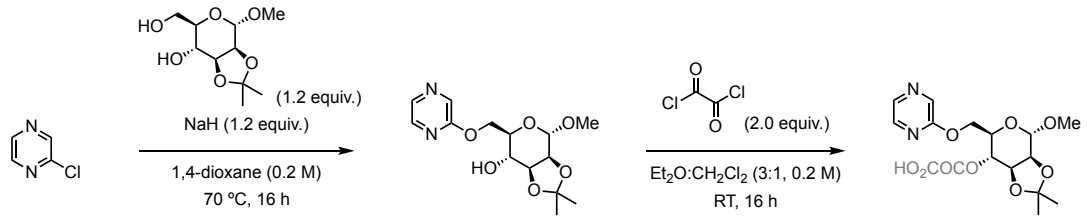
HRMS(ESI): [m/z] calculated for$C_{12}H_{16}N_2NaO_5$ ([M+Na]$^+$): 291.0951; Found: 291.0949.

R_f (CH_2Cl_2/EtOAc, 1:1) = 0.4 [CAM]

2-(((3aS,5S,6R,6aS)-2,2-dimethyl-5-((pyrazin-2-yloxy)methyl)tetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)-2-oxoacetic acid: Synthesized following **GP6** using (3aS,5S,6R,6aS)-2,2-dimethyl-5-((pyrazin-2-yloxy)methyl)tetrahydrofuro[2,3-d][1,3]dioxol-6-ol (1.0 equiv., 2.34 mmol, 0.62 g) to afford the desired product as a white solid in 90% yield (0.70 g, 2.11 mmol). The product was used in the next sept with any further purification.

^{1}HNMR(600 MHz, Chloroform-*d*) δ 8.23 (dd, *J* = 3.0, 1.4 Hz, 1H), 8.15 (d, *J* = 1.4 Hz, 1H), 8.05 (d, *J* = 2.9 Hz, 1H), 5.69 (dqd, *J* = 10.3, 6.2, 1.8 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 1H), 2.97 (dd, *J* = 15.7, 10.3 Hz, 1H), 1.70 (dd, *J* = 15.6, 1.8 Hz, 1H), 1.55 (s, 3H), 1.37 (d, *J* = 6.2 Hz, 3H)

HRMS(ESI): [m/z] calculated for C14H17N2O8 ([M]$^+$): 341.0983; Found: 341.0979.



(3aS,4S,6R,7R,7aS)-4-methoxy-2,2-dimethyl-6-((pyrazin-2-yloxy)methyl)tetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-7-ol: Synthesized following **GP4** using 2-chloropyrazine (1.0 equiv., 3 mmol, 0.27 mL) to afford the desired product as a white solid in 64% yield (0.56 g, 1.92 mmol).

^{1}HNMR(600 MHz, Chloroform-*d*) δ 8.33 (d, *J* = 1.4 Hz, 1H), 8.17 (d, *J* = 2.9 Hz, 1H), 8.08 (dd, *J* = 2.9, 1.4 Hz, 1H), 4.96 (s, 1H), 4.79 (dd, *J* = 12.1, 4.4 Hz, 1H), 4.56 (dd, *J* = 12.1, 2.6 Hz, 1H), 4.21 – 4.13 (m, 2H), 3.84 (ddd, *J* = 9.7, 4.4, 2.6 Hz, 1H), 3.65 – 3.60 (m, 1H), 3.42 (s, 3H), 1.46 (s, 3H), 1.35 – 1.33 (m, 3H).

^{13}C NMR(151 MHz, Chloroform-*d*) δ 160.4, 140.5, 136.8, 136.3, 109.8, 98.9, 78.0, 75.6, 69.0, 68.9, 66.0, 55.3, 28.1, 26.2.

HRMS(ESI): [m/z] calculated for$C_{14}H_{20}N_2NaO_6$ ([M+Na]$^+$): 335.1219; Found: 335.1214.

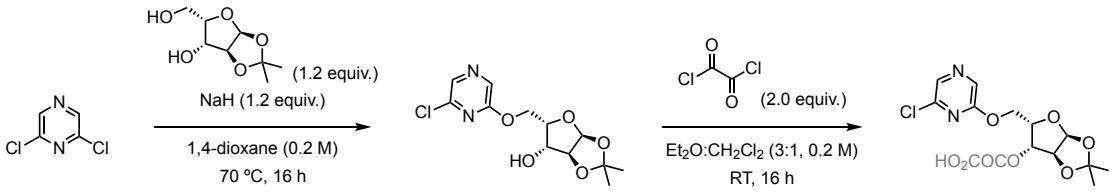
R_f (CH_2Cl_2/EtOAc, 1:1) = 0.22 [CAM]

2-(((3aS,4S,6R,7R,7aS)-4-methoxy-2,2-dimethyl-6-((pyrazin-2-yloxy)methyl)tetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-7-yl)oxy)-2-oxoacetic acid: Synthesized following **GP6** using (3aS,4S,6R,7R,7aS)-4-methoxy-2,2-dimethyl-6-((pyrazin-2-yloxy)methyl)tetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-7-ol (1.0 equiv., 1.92 mmol, 0.56 g) to afford the desired product as a pale white solid in 79% yield (0.58 g, 1.52 mmol).

^{1}HNMR(600 MHz, Chloroform-*d*) δ 8.27 (s, 1H), 8.22 (d, *J* = 2.7 Hz, 1H), 8.11 (d, *J* = 2.9 Hz, 1H), 5.30 (dd, *J* = 10.3, 7.7 Hz, 1H), 5.01 (s, 1H), 4.64 (dd, *J* = 11.4, 4.2 Hz, 1H), 4.45 (dd, *J* = 11.4, 6.0 Hz, 1H), 4.39 (dd, *J* = 7.8, 5.4 Hz, 1H), 4.20 (s, 1H), 4.15 (ddt, *J* = 17.3, 14.3, 6.3 Hz, 2H), 3.44 (s, 3H), 1.60 (s, 3H), 1.37 (s, 3H).

^{13}C NMR(151 MHz, Chloroform-*d*) δ 160.3, 158.5, 142.2, 134.4, 134.2, 110.5, 98.4, 75.9, 75.3, 74.6, 66.2, 64.6, 55.4, 27.9, 26.5.

HRMS(ESI): [m/z] calculated for $C_{16}H_{21}N_2O_9$ ([M+]$^+$): 385.1270; Found: 385.1242.



(3aS,5S,6R,6aS)-5-(((6-chloropyrazin-2-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol: Synthesized following **GP4** using 2,6-dichloropyrazine (1.0 equiv., 3 mmol, 0.45 g) to afford the desired product as a yellowish solid in 58% yield (0.53 g, 1.74 mmol).

^{1}HNMR(600 MHz, Chloroform-*d*) δ 8.19 (d, *J* = 1.6 Hz, 2H), 5.97 (d, *J* = 3.6 Hz, 1H), 4.72 (dd, *J* = 11.5, 6.7 Hz, 1H), 4.59 (d, *J* = 3.6 Hz, 1H), 4.52 (dd, *J* = 11.5, 5.4 Hz, 1H), 4.45 (ddd, *J* = 6.7, 5.3, 2.5 Hz, 1H), 4.23 (d, *J* = 2.6 Hz, 1H), 1.51 (s, 3H), 1.33 (d, *J* = 0.7 Hz, 3H).

^{13}C NMR(151 MHz, Chloroform-*d*) δ 158.8, 145.2, 136.0, 133.6, 112.1, 104.9, 85.4, 78.4, 74.9, 64.2, 26.9, 26.3.

HRMS(ESI): [m/z] calculated for $C_{12}H_{15}ClN_2NaO_5$ ([M+Na]$^+$): 325.0571 ; Found: 325.0562 .

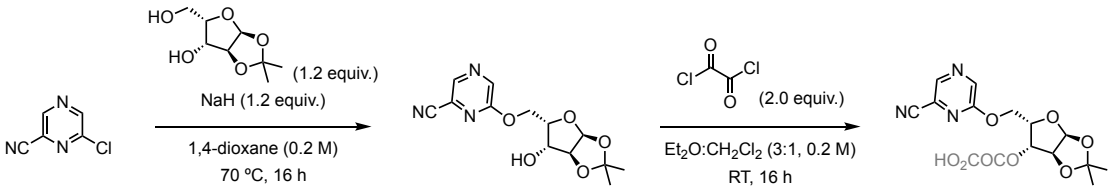
R_f (cyclohexane /EtOAc, 1:3) = 0.53 [CAM]

2-(((3a*S*,5*S*,6*R*,6a*S*)-5-(((6-chloropyrazin-2-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl)oxy)-2-oxoacetic acid: Synthesized following **GP6** using (3aS,5S,6R,6aS)-5-(((6-chloropyrazin-2-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol (1.0 equiv., 1.74 mmol, 0.53 g) to afford the desired product as a pale white solid in 84% yield (0.55 g, 1.46 mmol).

^{1}HNMR (600 MHz, Chloroform-*d*) δ 8.21 (s, 1H), 8.13 (s, 1H), 6.05 (d, *J* = 3.7 Hz, 1H), 5.48 (d, *J* = 2.8 Hz, 1H), 4.76 (dd, *J* = 11.6, 4.7 Hz, 1H), 4.70 – 4.59 (m, 3H), 1.55 (s, 3H), 1.35 (s, 3H).

^{13}C NMR(151 MHz, Chloroform-*d*) δ 159.3, 157.9, 157.8, 134.4, 132.2, 112.8, 104.9, 83.2, 78.8, 66.1, 63.7, 26.8, 26.4, 26.3, 15.1.

HRMS(ESI): [m/z] calculated for $C_{14}H_{15}ClN_2NaO_8$ ([M+Na]$^+$): 397.0414; Found: 397.0409.



6-(((3aS,5S,6R,6aS)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methoxy)pyrazine-2-carbonitrile: Synthesized following **GP4** using 6-chloropyrazine-2-carbonitrile (1.0 equiv., 3 mmol, 0.42 g) to afford the desired product as a white solid in 40% yield (0.35 g, 1.2 mmol).

^{1}HNMR (600 MHz, Chloroform-*d*) δ 8.49 (d, *J* = 11.0 Hz, 2H), 6.00 (d, *J* = 3.7 Hz, 1H), 4.71 (dd, *J* = 11.6, 5.2 Hz, 1H), 4.60 (dd, *J* = 11.6, 6.6 Hz, 1H), 4.57 (d, *J* = 3.6 Hz, 1H), 4.52 (ddd, *J* = 6.6, 5.1, 2.8 Hz, 1H), 1.52 (s, 3H), 1.34 – 1.33 (m, 3H).

^{13}C NMR(151 MHz, Chloroform-*d*) δ 159.3, 140.8, 140.5, 125.9, 115.3, 112.3, 105.1, 85.5, 78.1, 75.4, 65.2, 26.9, 26.3.

HRMS(ESI): [m/z] calculated for $C_{13}H_{15}N_3NaO_5$ ([M+Na]$^+$): 316.0912; Found: 316.0904.

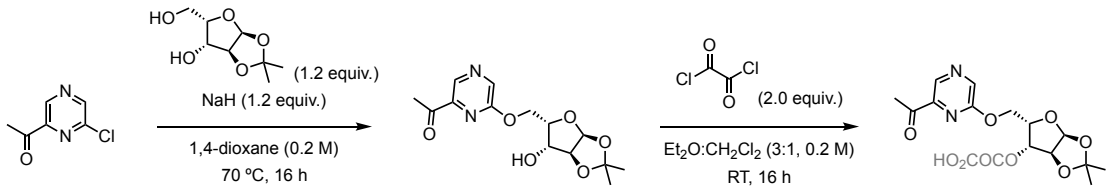
R_f (cyclohexane /EtOAc, 1:3) = 0.45 [CAM]

2-(((3aS,5S,6R,6aS)-5-(((6-cyanopyrazin-2-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)-2-oxoacetic acid: Synthesized following **GP6** using 6-(((3aS,5S,6R,6aS)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methoxy)pyrazine-2-carbonitrile (1.0 equiv., 1.2 mmol, 0.42 g) to afford the desired product as a brownish solid in 65% yield (0.28 g, 0.76 mmol).

^{1}HNMR (600 MHz, Chloroform-*d*) δ 8.48 (d, *J* = 6.5 Hz, 2H), 6.05 (d, *J* = 3.7 Hz, 1H), 5.47 (d, *J* = 2.7 Hz, 1H), 4.71 (ddd, *J* = 18.5, 6.6, 3.3 Hz, 3H), 4.63 – 4.59 (m, 1H), 1.56 (s, 3H), 1.35 (s, 3H).

^{13}C NMR(151 MHz, Chloroform-*d*) δ 157.4, 157.3, 140.4, 140.1, 112.9, 105.0, 83.1, 78.8, 76.5, 66.1, 64.0, 26.8, 26.3, 15.1, 1.2.

HRMS(ESI): [m/z] calculated for $C_{15}H_{15}N_3NaO_8$ ([M+Na]$^+$): 388.0750; Found: 388.0751.



1-(6-(((3aS,5S,6R,6aS)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methoxy)pyrazin-2-yl)ethan-1-one: Synthesized following **GP4** using 1-(6-chloropyrazin-2-yl)ethan-1-one (1.0 equiv., 3 mmol, 0.47 g) to afford the desired product as a yellow solid in 51% yield (0.47 g, 1.53 mmol).

^{1}HNMR(600 MHz, Chloroform-*d*) δ 8.78 (d, *J* = 1.3 Hz, 1H), 8.28 (d, *J* = 1.3 Hz, 1H), 5.98 (d, *J* = 3.6 Hz, 1H), 4.83 (dd, *J* = 11.7, 7.1 Hz, 1H), 4.59 (d, *J* = 3.8 Hz, 2H), 4.47 (ddd, *J* = 7.0, 5.4, 2.5 Hz, 1H), 4.18 (d, *J* = 2.5 Hz, 1H), 2.66 (s, 3H), 1.51 (s, 3H), 1.33 (d, *J* = 0.8 Hz, 3H).

^{13}C NMR(151 MHz, Chloroform-*d*) δ 198.1, 161.3, 142.4, 140.9, 134.9, 112.1, 104.9, 85.3, 78.5, 74.8, 64.1, 27.0, 26.3, 26.1.

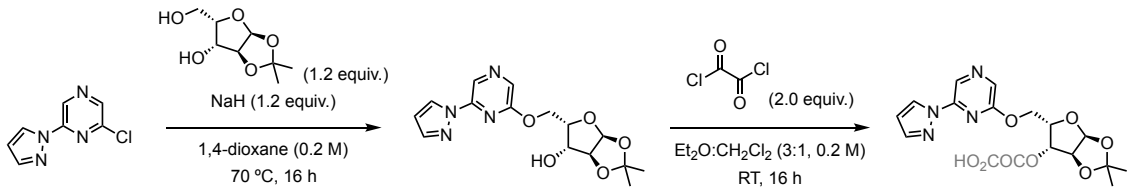
HRMS(ESI): [m/z] calculated for $C_{14}H_{18}N_2NaO_6$ ([M+Na]$^+$): 333.1057; Found: 333.1057.

R_f (cyclohexane /EtOAc, 1:3) = 0.49 [*p*-Anisaldehyde]

2-(((3aS,5S,6R,6aS)-5-(((6-acetylpyrazin-2-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)-2-oxoacetic acid: Synthesized following **GP6** using 1-(6-(((3aS,5S,6R,6aS)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methoxy)pyrazin-2-yl)ethan-1-one (1.0 equiv., 1.53 mmol, 0.47 g) to afford the desired product as an orange solid in 36% yield (0.21 g, 0.55 mmol).

^{1}HNMR(600 MHz, Chloroform-*d*) δ 8.74 (d, *J* = 1.3 Hz, 1H), 8.45 (d, *J* = 1.3 Hz, 1H), 5.99 (d, *J* = 3.9 Hz, 1H), 5.26 (d, *J* = 2.6 Hz, 1H), 4.72 (d, *J* = 3.9 Hz, 1H), 4.68 – 4.63 (m, 2H), 4.53 (d, *J* = 4.1 Hz, 1H), 2.58 (s, 3H), 1.45 (s, 3H), 1.27 (s, 3H).

^{13}C NMR(151 MHz, Chloroform-*d*) δ 197.4, 141.6, 140.6, 134.4, 111.4, 104.5, 85.0, 82.3, 78.1, 78.0, 76.3, 64.2, 26.3, 26.0, 25.8, 14.1.



(3aS,5S,6R,6aS)-5-(((6-(1H-pyrazol-1-yl)pyrazin-2-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol: Synthesized following **GP4** using 2-chloro-6-(1H-pyrazol-1-yl)pyrazine (1.0 equiv., 3 mmol, 0.53 g) to afford the desired product as a white solid in 35% yield (0.35 g, 1.05 mmol).

^{1}HNMR(400 MHz, Chloroform-*d*) δ 8.97 (s, 1H), 8.43 (dd, *J* = 2.6, 0.7 Hz, 1H), 7.76 (dd, *J* = 1.7, 0.7 Hz, 1H), 6.47 (dd, *J* = 2.7, 1.6 Hz, 1H), 5.72 (d, *J* = 3.6 Hz, 1H), 5.13 (dd, *J* = 3.6, 1.0 Hz, 1H), 4.82 – 4.75 (m, 2H), 4.38 – 4.32 (m, 1H), 3.69 (d, *J* = 4.4 Hz, 1H), 1.59 (s, 3H), 1.38 – 1.32 (m, 3H).

^{13}C NMR(101 MHz, Chloroform-*d*) δ 154.8, 144.9, 143.3, 131.8, 128.5, 127.8, 112.1, 108.7, 105.1, 85.7, 73.4, 66.3, 46.9, 26.9, 26.2.

HRMS(ESI): [m/z] calculated for $C_{15}H_{18}N_4NaO_5$ ([M+Na]$^+$): 357.1169; Found: 357.1165.

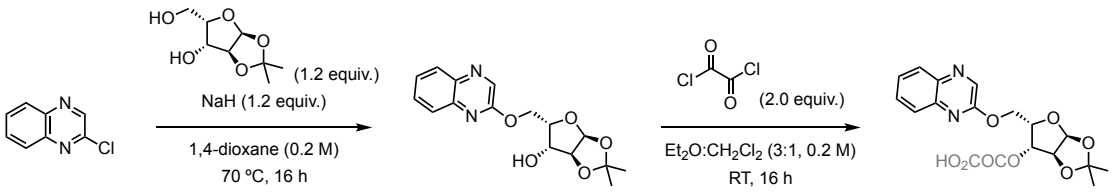
R_f (cyclohexane /EtOAc, 1:3) = 0.4 [*p*-Anisaldehyde]

2-(((3aS,5S,6R,6aS)-5-(((6-(1H-pyrazol-1-yl)pyrazin-2-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)-2-oxoacetic acid:

Synthesized following **GP6** using (3aS,5S,6R,6aS)-5-(((6-(1H-pyrazol-1-yl)pyrazin-2-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol (1.0 equiv., 1.05 mmol, 0.36 g) to afford the desired product as an orangish solid in 85% yield (0.21 g, 0.90 mmol).

^{1}HNMR(600 MHz, Chloroform-*d*) δ 8.74 (s, 1H), 8.37 (d, *J* = 2.6 Hz, 1H), 8.18 (s, 1H), 7.77 (d, *J* = 1.5 Hz, 1H), 6.49 (t, *J* = 2.1 Hz, 1H), 6.08 (d, *J* = 3.7 Hz, 1H), 5.54 (d, *J* = 2.9 Hz, 1H), 4.85 (dd, *J* = 11.4, 5.1 Hz, 1H), 4.74 – 4.70 (m, 2H), 4.67 (dd, *J* = 11.4, 4.3 Hz, 1H), 1.56 (s, 3H), 1.36 (s, 3H).

^{13}C NMR(151 MHz, Chloroform-*d*) δ 158.6, 158.2, 145.4, 143.5, 130.7, 127.9, 124.5, 112.7, 108.9, 105.0, 83.3, 78.7, 76.7, 63.2, 26.8, 26.3.



(3aS,5S,6R,6aS)-2,2-dimethyl-5-((quinoxalin-2-yloxy)methyl)tetrahydrofuro[2,3-d][1,3]dioxol-6-ol: Synthesized following **GP4** using 2-chloroquinoxaline (1.0 equiv., 3 mmol, 0.49 g) to afford the desired product as a yellowidh solid in 52% yield (0.59 g, 1.56 mmol).

^{1}HNMR (400 MHz, Chloroform-*d*) δ 8.54 (s, 1H), 8.06 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.82 – 7.76 (m, 1H), 7.74 – 7.68 (m, 1H), 7.62 (ddd, *J* = 8.4, 7.0, 1.5 Hz, 1H), 5.99 (d, *J* = 3.6 Hz, 1H), 5.00 (dd, *J* = 11.6, 8.7 Hz, 1H), 4.64 (d, *J* = 3.6 Hz, 1H), 4.56 (dd, *J* = 11.6, 4.3 Hz, 1H), 4.47 (ddd, *J* = 8.7, 4.4, 2.4 Hz, 1H), 4.12 (d, *J* = 2.4 Hz, 1H), 1.52 (s, 3H), 1.33 (d, *J* = 0.7 Hz, 3H).

^{13}C NMR(101 MHz, Chloroform-*d*) δ 156.9, 139.8, 139.1, 131.0, 129.3, 127.5, 126.5, 112.0, 104.8, 85.3, 79.0, 74.3, 62.9, 27.1, 27.0, 26.3.

HRMS(ESI): [m/z] calculated for $C_{16}H_{18}N_2NaO_5$ ([M+Na]$^+$): 341.1119; Found: 341.1108.

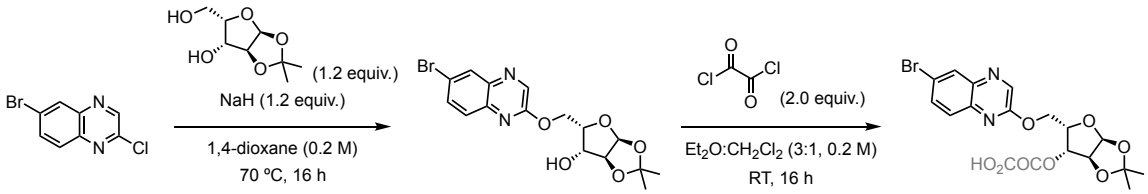
R_f (cyclohexane /EtOAc, 1:3) = 0.5 [*p*-Anisaldehyde]

2-(((3aS,5S,6R,6aS)-2,2-dimethyl-5-((quinoxalin-2-yloxy)methyl)tetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)-2-oxoacetic acid: Synthesized following **GP6** using (3aS,5S,6R,6aS)-2,2-dimethyl-5-((quinoxalin-2-yloxy)methyl)tetrahydrofuro[2,3-d][1,3]dioxol-6-ol (1.0 equiv., 1.56 mmol, 0.59 g) to afford the desired product as an yellowish solid in 89% yield (0.53 g, 1.4 mmol).

^{1}HNMR (600 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 7.97 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.87 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.71 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H), 7.55 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H), 6.11 (d, *J* = 3.8 Hz, 1H), 5.59 (d, *J* = 2.9 Hz, 1H), 5.06 (dd, *J* = 12.3, 4.5 Hz, 1H), 4.81 (dd, *J* = 12.3, 3.1 Hz, 1H), 4.76 (d, *J* = 3.8 Hz, 1H), 4.71 (dt, *J* = 4.6, 3.0 Hz, 1H), 1.57 (s, 3H), 1.37 (s, 3H).

^{13}C NMR(151 MHz, Chloroform-*d*) δ 157.3, 140.8, 138.2, 131.2, 127.8, 127.6, 127.0, 112.6, 104.8, 83.5, 79.0, 63.0, 26.9, 26.3.

HRMS(ESI): [m/z] calculated for C18H19N2O8 ([M]$^+$): 391.1137; Found: 391.1136.



(3aS,5S,6R,6aS)-5-(((6-bromoquinoxalin-2-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol: Synthesized following **GP4** using 6-bromo-2-chloroquinoxaline (1.0 equiv., 3 mmol, 0.73 g) to afford the desired product as a white solid in 60% yield (0.71 g, 1.8 mmol).

^{1}HNMR(400 MHz, Chloroform-*d*) δ 8.52 (s, 1H), 7.98 (d, *J* = 2.1 Hz, 1H), 7.90 (d, *J* = 8.8 Hz, 1H), 7.69 (dd, *J* = 8.8, 2.1 Hz, 1H), 5.99 (d, *J* = 3.6 Hz, 1H), 4.95 (dd, *J* = 11.6, 8.1 Hz, 1H), 4.63 (d, *J* = 3.7 Hz, 1H), 4.61 – 4.56 (m, 1H), 4.49 (ddd, *J* = 8.2, 4.7, 2.5 Hz, 1H), 4.15 (d, *J* = 2.5 Hz, 1H), 1.52 (s, 3H), 1.34 (d, *J* = 0.7 Hz, 3H).

^{13}C NMR(151 MHz, Chloroform-*d*) δ 157.3, 140.1, 140.1, 138.0, 131.0, 130.5, 129.1, 125.1, 112.1, 104.9, 85.3, 78.7, 74.5, 63.3, 27.0, 26.3.

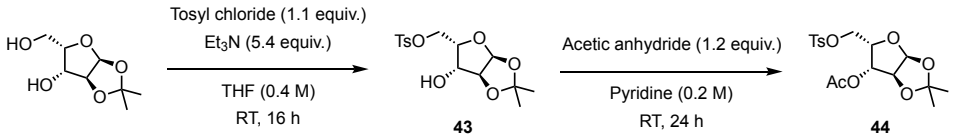
HRMS(ESI): [m/z] calculated for $C_{16}H_{18}BrN_2O_5$ ([M+]$^+$): 397.0394; Found: 397.0394.

R_f (cyclohexane /EtOAc, 1:1) = 0.33 [UV/CAM]

2-(((3aS,5S,6R,6aS)-5-(((6-bromoquinoxalin-2-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)-2-oxoacetic acid: Synthesized following **GP6** using (3aS,5S,6R,6aS)-5-(((6-bromoquinoxalin-2-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol (1.0 equiv., 1.8 mmol, 0.71 g) to afford the desired product as an brown solid in 88% yield (0.75 g, 1.6 mmol).

^{1}HNMR(600 MHz, Chloroform-*d*) δ 8.61 (s, 1H), 8.03 (d, *J* = 2.1 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.62 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.10 (d, *J* = 3.8 Hz, 1H), 5.57 (d, *J* = 2.9 Hz, 1H), 4.99 (dd, *J* = 12.1, 4.6 Hz, 1H), 4.78 – 4.73 (m, 2H), 4.71 (dt, *J* = 4.6, 3.4 Hz, 1H), 1.57 (s, 3H), 1.36 (s, 3H).

^{13}C NMR(151 MHz, Chloroform-*d*) δ 158.3, 158.1, 157.6, 141.4, 140.8, 138.9, 135.7, 131.2, 130.8, 130.1, 128.5, 125.3, 112.9, 112.7, 104.9, 83.4, 79.3, 79.0, 76.8, 63.2, 26.8, 26.8, 26.3.

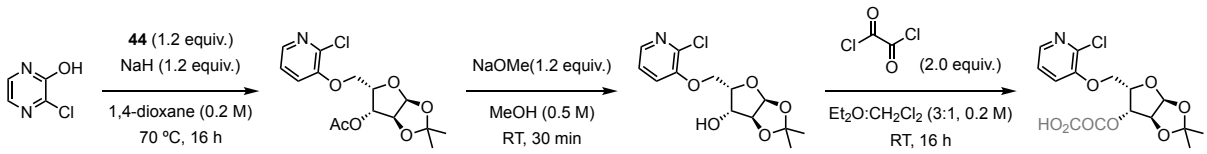


((3aS,5S,6R,6aS)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methyl 4-methylbenzenesulfonate: To a RBF containing a solution of furanose saccharide **27** (1.0 equiv., 10 mmol, 1.9 g), Et_3N (5.4 equiv., 54 mmol, 7.5 mL) in THF (10 mL) a solution of tosyl chloride (1.1 equiv., 11 mmol, 2.1 g) in THF (15 ml) was added slowly at 0 ºC. Then, the reaction mixture was stirred at RT for 16 h. Afterwards, the reaction was dried under vacuum and solved in EtOAc. The resulting mixture was washed with H_2O, saturated solution of $NaHCO_3$ and brine. The organic phase extracted with EtOAc (ca. 3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent evaporated to afford the desired product **43** as a white solid in 82% yield (2.8 g, 8.2 mmol). The product was used in the next step with any further purification. The spectroscopic data are consistent with those previously reported.[166]

^{1}HNMR (400 MHz, Chloroform-*d*) δ 7.81 (s, 2H), 7.36 (dd, *J* = 8.6, 0.8 Hz, 2H), 5.87 (d, *J* = 3.6 Hz, 1H), 4.50 (d, *J* = 3.6 Hz, 1H), 4.38 – 4.28 (m, 3H), 4.14 (d, *J* = 5.2 Hz, 1H), 2.45 (s, 3H), 1.46 (s, 3H), 1.30 (s, 3H).

(3aS,5S,6R,6aS)-2,2-dimethyl-5-((tosyloxy)methyl)tetrahydrofuro[2,3-d][1,3]dioxol-6-yl acetate: To a RBF containing a solution of ((3aS,5S,6R,6aS)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methyl 4-methylbenzenesulfonate (1.0 equiv., 8.2 mmol, 2.8 g) in anhydrous pyridine (41 mL), acetic anhydride (1.2 equiv., 9.8 mmol, .92 mL) was added under N_2 at 0 ºC. The reaction mixture was stirred at RT for 24 h. Afterwards, the solvent was removed under vacuo and the resulting crude was solve in EtOAc (30 ml). This organic phase was washed with $NaHCO_3$, and brine, and then it was separated. The solvent was removed in vacuo to afford the product **44** as a yellow oil in 97% yield (3.12 g, 8.05 mmol). The product was used in subsequent steps with any further purification. The spectroscopic data are consistent with those previously reported.[167]

^{1}HNMR(600 MHz, Chloroform-*d*) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.35 (dt, *J* = 8.0, 0.8 Hz, 2H), 5.85 (d, *J* = 3.6 Hz, 1H), 5.19 (d, *J* = 3.1 Hz, 1H), 4.48 (d, *J* = 3.7 Hz, 1H), 4.43 (td, *J* = 6.1, 3.1 Hz, 1H), 4.26 – 4.14 (m, 2H), 2.45 (s, 3H), 2.03 (s, 3H), 1.46 (s, 3H), 1.29 (d, *J* = 0.7 Hz, 3H).



(3aS,5S,6R,6aS)-5-(((2-chloropyridin-3-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl acetate: Synthesized following **GP4** using 3-chloropyrazin-2-ol (1.0 equiv., 2.6 2 mmol, 0.24 g) and **44** (1.2 equiv., 2.2 mmol, 0.85 g) to afford the desired product as an oily yellowish solid in 57% yield (0.49 g, 1.5 mmol).

^{1}HNMR(600 MHz, Chloroform-*d*) δ 8.34 (s, 1H), 8.19 (d, *J* = 5.1 Hz, 1H), 7.35 (d, *J* = 5.1 Hz, 1H), 5.98 (d, *J* = 3.7 Hz, 1H), 5.36 (d, *J* = 3.2 Hz, 1H), 4.73 (td, *J* = 5.9, 3.2 Hz, 1H), 4.58 (d, *J* = 3.7 Hz, 1H), 4.36 (dd, *J* = 9.9, 6.0 Hz, 1H), 4.30 (dd, *J* = 9.9, 5.9 Hz, 1H), 2.06 (s, 3H), 1.55 (s, 3H), 1.34 (s, 3H).

^{13}C NMR(151 MHz, Chloroform-*d*) δ 169.8, 151.5, 143.2, 136.3, 133.8, 125.5, 112.7, 105.1, 83.5, 76.5, 67.6, 26.9, 26.4, 20.8.

R_f (cyclohexane /EtOAc, 1:3) = 0.41 [UV/*p*-Anisaldehyde]

(3aS,5S,6R,6aS)-5-(((2-chloropyridin-3-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol: To a RBF, a solution of (3aS,5S,6R,6aS)-5-(((2-chloropyridin-3-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl acetate (1. Equiv.,1.55 mmol, 0.49 g) in methanol (2.1 mL) sodium methoxide (1 equiv., 1 mmol, 54 mg) was added. The reaction mixture was stirred at RT for 30 min, afterwards the solvent was removed in vacuo and H_2O (20 mL) and CH_2Cl_2 were added. The organic layer was extracted with CH_2Cl_2 (3 x 15 mL) and the solvent was removed in vacuo to afford the desired product as a white solid in 83% yield (0.36 g, 1.28 mmol). The product was used in the next step with any further purification.

^{1}HNMR (400 MHz, Chloroform-*d*) δ 8.33 (s, 1H), 8.16 (d, *J* = 5.1 Hz, 1H), 7.31 (d, *J* = 5.1 Hz, 1H), 6.01 (d, *J* = 3.6 Hz, 1H), 4.60 (d, *J* = 3.7 Hz, 1H), 4.58 – 4.53 (m, 1H), 4.51 – 4.40 (m, 3H), 1.53 (s, 3H), 1.35 (d, *J* = 0.8 Hz, 3H).

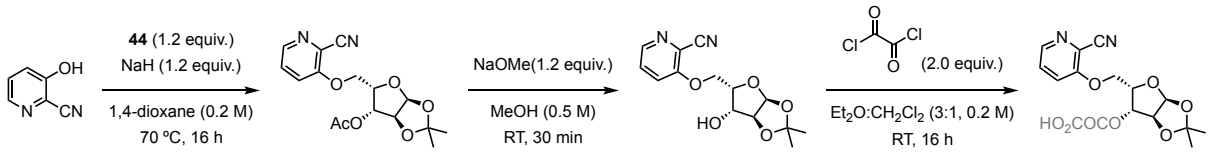
^{13}C NMR(101 MHz, Chloroform-*d*) δ 151.2, 143.2, 135.9, 133.2, 125.3, 112.2, 105.2, 85.5, 78.1, 75.4, 67.7, 27.0, 26.4.

HRMS(ESI): [m/z] calculated for $C_{13}H_{17}ClNO_5$ ($[M]^+$): 302.0790; Found: 302.0790.

2-(((3aS,5S,6R,6aS)-5-(((2-chloropyridin-3-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)-2-oxoacetic acid: Synthesized following **GP6** using (3aS,5S,6R,6aS)-5-(((2-chloropyridin-3-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol (1.0 equiv., 1.28 mmol, 0.36 g) to afford the desired product as an yellowish solid in 81% yield (0.35 g, 1.03 mmol).

^{1}HNMR (400 MHz, Chloroform-*d*) δ 7.93 (dd, *J* = 4.7, 1.5 Hz, 1H), 7.21 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.14 (dd, *J* = 8.2, 4.7 Hz, 1H), 5.99 (d, *J* = 3.6 Hz, 1H), 4.60 (d, *J* = 3.6 Hz, 1H), 4.58 – 4.53 (m, 1H), 4.49 (d, *J* = 2.8 Hz, 1H), 4.31 (qd, *J* = 9.5, 5.8 Hz, 2H), 1.53 (s, 3H), 1.33 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 150.7, 140.9, 123.5, 120.8, 112.2, 105.1, 85.4, 78.1, 74.9, 66.4, 27.0, 26.3.



(3aS,5S,6R,6aS)-5-(((2-chloropyridin-3-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl acetate: Synthesized following **GP4** using 3-hydroxypyrazine-2-carbonitrile (1.0 equiv., 2 mmol, 0.24 g) and **44** (1.2 equiv., 2.2 mmol, 0.85 g) to afford the desired product as an oily yellowish solid in 50% yield (0.33 g, 1 mmol).

^{1}HNMR(600 MHz, Chloroform-*d*) δ 8.32 (dd, *J* = 3.9, 1.9 Hz, 1H), 7.48 – 7.43 (m, 2H), 5.97 (d, *J* = 3.7 Hz, 1H), 5.36 (d, *J* = 3.2 Hz, 1H), 4.71 (td, *J* = 5.4, 3.3 Hz, 1H), 4.60 (d, *J* = 3.7 Hz, 1H), 4.35 (d, *J* = 5.4 Hz, 2H), 2.09 (s, 3H), 1.54 (s, 3H), 1.33 (d, *J* = 1.0 Hz, 3H).

^{13}C NMR(151 MHz, Chloroform-*d*) δ 169.8, 157.8, 143.5, 127.8, 124.4, 121.1, 114.9, 112.8, 105.0, 83.5, 76.7, 67.1, 38.6, 26.9, 26.4, 20.9.

HRMS(ESI): [m/z] calculated for $C_{16}H_{18}N_2NaO_6$ ([M+Na]$^+$): 357.1063; Found: 357.1057.

R_f (cyclohexane /EtOAc, 1:3) = 0.33 [UV/*p*-Anisaldehyde]

3-(((3aS,5S,6R,6aS)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methoxy)picolinonitrile: To a RBF, a solution of ((3aS,5S,6R,6aS)-5-(((2-chloropyridin-3-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl acetate (1. Equiv.,1. mmol, 0.33 g) in methanol (2.1 mL) sodium methoxide (1 equiv., 1 mmol, 54 mg) was added. The reaction mixture was stirred at RT for 30 min, afterwards the solvent was removed in vacuo and H_2O (20 mL) and CH_2Cl_2 were added. The organic layer was extracted with CH_2Cl_2 (3 x 15 mL) and the solvent was removed in vacuo to afford the desired product as a white solid in 80% yield (0.26 g, 0.8 mmol). The product was used in the next step with any further purification.

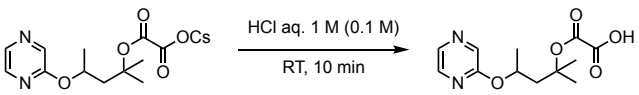
^{1}HNMR (400 MHz, Chloroform-*d*) δ 8.31 (t, *J* = 2.9 Hz, 1H), 7.48 (d, *J* = 2.9 Hz, 2H), 5.99 (d, *J* = 3.6 Hz, 1H), 4.62 – 4.56 (m, 2H), 4.49 (t, *J* = 3.7 Hz, 1H), 4.42 (dd, *J* = 6.0, 1.5 Hz, 2H), 1.54 – 1.51 (m, 3H), 1.34 (d, *J* = 0.7 Hz, 3H).

^{13}C NMR(101 MHz, Chloroform-*d*) δ 157.9, 143.5, 128.0, 124.2, 120.9, 115.1, 112.4, 105.2, 85.5, 78.1, 77.5, 77.2, 76.8, 75.0, 66.8, 27.0, 26.4.

HRMS(ESI): [m/z] calculated for $C_{14}H_{16}N_2NaO_5$ ([M+Na]$^+$): 315.0950; Found: 315.0951.

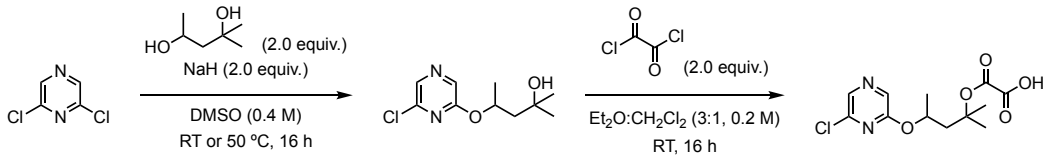
2-(((3aS,5S,6R,6aS)-5-(((2-cyanopyridin-3-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)-2-oxoacetic acid: Synthesized following **GP6** using 3-(((3aS,5S,6R,6aS)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methoxy)picolinonitrile (1.0 equiv., 0.8 mmol, 0.26 g) to afford the desired product as an orange solid in quantitative yield (0.29 g, 0.8 mmol). The product was used in the next step with any further purification

^{1}HNMR (400 MHz, Chloroform-*d*) δ 8.34 (dt, *J* = 4.3, 2.2 Hz, 1H), 7.49 (q, *J* = 1.7, 1.1 Hz, 2H), 6.04 (d, *J* = 3.8 Hz, 1H), 5.54 (d, *J* = 3.2 Hz, 1H), 4.79 (dd, *J* = 5.5, 3.1 Hz, 1H), 4.70 (d, *J* = 3.7 Hz, 1H), 4.46 (ddd, *J* = 14.2, 9.2, 5.1 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 1H), 1.57 (s, 3H), 1.36 (s, 3H).



2-((2-methyl-4-(pyrazin-2-yloxy)pentan-2-yl)oxy)-2-oxoacetic acid: To a RBF containing cesium 2-((2-methyl-4-(pyrazin-2-yloxy)pentan-2-yl)oxy)-2-oxoacetate (1.0 equiv., 1 mmol, 0.4 g), aqueous HCl (1 M, 10 mL) was added and the reaction was stirred vigorously. After 10 min, the reaction mixture was extracted with EtOAc (10 mL x 3). The organic layer was separated, dried over Na_2SO_4 and the solvent was removed *in vacuo* to afford the desired product as a yellow solid in 95% yield (0.26 g, 0.95 mmol) The product was used in the next step with any further purification.

^{1}HNMR(600 MHz, Chloroform-*d*) δ 8.23 (dd, *J* = 3.0, 1.4 Hz, 1H), 8.15 (d, *J* = 1.4 Hz, 1H), 8.05 (d, *J* = 2.9 Hz, 1H), 5.69 (dqd, *J* = 10.3, 6.2, 1.8 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 1H), 2.97 (dd, *J* = 15.7, 10.3 Hz, 1H), 1.70 (dd, *J* = 15.6, 1.8 Hz, 1H), 1.55 (s, 3H), 1.37 (d, *J* = 6.2 Hz, 3H)



4-((6-chloropyrazin-2-yl)oxy)-2-methylpentan-2-ol: Synthesized following **GP5** using 2,6-dichloropyrazine (1.0 equiv., 3.0 mmol, 0.45 g), 2-methyl-2,4-pentandiol (1.2 equiv., 3.6 mmol, 0.46 mL) and NaH (1.2 equiv., 3.6 mmol, 86.4 mg) at 50 °C for 16 h. The crude product was purified by flash column chromatography (cyclohexane/EtOAc, 1:1 to afford the desired product as a pale-yellow oil in 44% yield (0.3 g, 1.32 mmol).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.13 (d, *J* = 0.6 Hz, 1H), 8.07 (d, *J* = 0.6 Hz, 1H), 5.47 – 5.37 (m, 1H), 2.06 (dd, *J* = 14.9, 8.2 Hz, 1H), 1.77 (dd, *J* = 14.9, 3.6 Hz, 1H), 1.39 (d, *J* = 6.1 Hz, 3H), 1.26 (d, *J* = 5.7 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 158.73, 145.57, 135.32, 133.71, 71.83, 70.30, 49.25, 30.18, 30.08, 21.44.

HRMS (ESI): [m/z] calculated for $C_{10}H_{15}ClN_2NaO_2$ ([M+Na]$^+$): 253.0714; Found: 253.0714.

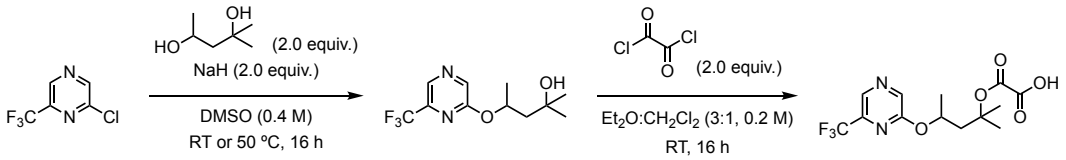
R_f (Cyclohexane/EtOAc, 1:1) = 0.4 [CAM]

2-((4-((6-chloropyrazin-2-yl)oxy)-2-methylpentan-2-yl)oxy)-2-oxoacetic acid: Synthesized following **GP6** using 4-((6-chloropyrazin-2-yl)oxy)-2-methylpentan-2-ol (1.0 equiv., 1.32 mmol, 0.31 g) to afford the desired product 2B as an off-yellow solid in 83% yield (0.33 g, 1.1 mmol).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.07 (s, 1H), 8.03 (s, 1H), 5.60 (ddd, *J* = 10.0, 6.1, 2.1 Hz, 1H), 2.87 (ddd, *J* = 15.6, 10.0, 1.7 Hz, 1H), 1.79 (dt, *J* = 15.7, 1.8 Hz, 1H), 1.66 (s, 3H), 1.57 (s, 3H), 1.38 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.30, 158.97, 157.88, 146.47, 133.17, 132.43, 85.13, 70.57, 45.01, 26.94, 26.41, 21.03.

HRMS (ESI): [m/z] calculated for $C_{12}H_{16}ClN_2O_5$ ([M+Na]$^+$): 303.0734; Found: 303.0742.



2-methyl-4-((5-(trifluoromethyl)pyrazin-2-yl)oxy)pentan-2-ol:

Synthesized following **GP5** using 5-chloro-2-trifluoromethylpyrazine (1.0 equiv., 3.0 mmol, 0.27 mL) and 2-methyl-2,4-pentandiol (2.0 equiv., 6.0 mmol, 0.77 mL) at RT for 16 h. The crude product was purified by flash column chromatography (cyclohexane/EtOAc, 4:1) to afford the desired product as a yellow oil in 74% yield (0.58 g, 2.2 mmol).

^{1}HNMR (600 MHz, Chloroform-*d*) δ 8.45 (s, 1H), 8.21 (d, *J* = 1.3 Hz, 1H), 5.55 (dqd, *J* = 12.2, 6.2, 3.5 Hz, 1H), 2.09 (dd, *J* = 15.0, 8.2 Hz, 1H), 1.80 (dd, *J* = 15.0, 3.5 Hz, 1H), 1.40 (d, *J* = 6.2 Hz, 3H), 1.26 (d, *J* = 14.5 Hz, 6H)**.**

^{13}C NMR(151 MHz, Chloroform-*d*) δ 138.83, 138.80, 136.50, 71.90, 70.27, 49.22, 30.25, 30.07, 21.42.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -66.76.

HRMS (ESI): [m/z] calculated for $C_{11}H_{15}F_3N_2NaO_2$ ([M+Na]$^+$): 287.0982; Found: 287.0978

R_f Cyclohexane/EtOAc, 4:1) = 0.29 [CAM].

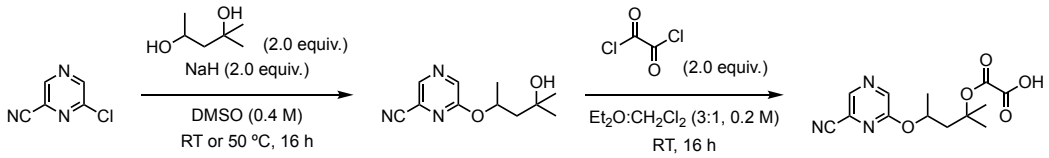
2-((2-methyl-4-((5-(trifluoromethyl)pyrazin-2-yl)oxy)pentan-2-yl)oxy)-2-oxoacetic acid: Synthesized following **GP6** using 2-methyl-4-((5-(trifluoromethyl)pyrazin-2-yl)oxy)pentan-2-ol (1.0 equiv., 2.2 mmol, 0.58 g) to afford the desired product as a yellow oil in 81% yield (0.6 g, 1.78 mmol).

^{1}HNMR (600 MHz, Chloroform-*d*) δ 8.44 (s, 1H), 8.19 (d, *J* = 1.3 Hz, 1H), 5.59 (ddt, *J* = 9.1, 6.1, 3.1 Hz, 1H), 2.56 (dd, *J* = 15.4, 8.6 Hz, 1H), 2.09 (dd, *J* = 15.4, 3.2 Hz, 1H), 1.62 (d, *J* = 11.2 Hz, 6H), 1.40 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR(151 MHz, Chloroform-*d*) δ 161.01, 157.94, 157.26, 138.99, 136.35, 122.69, 120.88, 86.42, 70.48, 45.76, 26.56, 26.26, 21.04.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -66.57.

HRMS(ESI): [m/z] calculated for $C_{13}H_{15}F_3N_2NaO_5$ ([M+Na]$^+$): 359.0827; Found: 359.0825.



6-((4-hydroxy-4-methylpentan-2-yl)oxy)pyrazine-2-carbonitrile: Synthesized following **GP5** using 6-chloropyrazine-2-carbonitrile (1.0 equiv., 3.0 mmol, 0.29 mL) and 2-methyl-2,4-pentandiol (2.0 equiv., 6.0 mmol, 0.77 mL) at rt for 16 h. The crude product was purified by flash column chromatography (cyclohexane/EtOAc, 4:1) to afford the desired product as a pale yellow oil in 20% yield (0.13 g, 0.59 mmol).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.44 (d, *J* = 0.6 Hz, 1H), 8.33 (d, *J* = 0.6 Hz, 1H), 5.49 (dtt, *J* = 12.2, 6.2, 3.1 Hz, 1H), 2.08 (dd, *J* = 14.9, 8.3 Hz, 1H), 1.79 (dd, *J* = 15.0, 3.5 Hz, 1H), 1.40 (d, *J* = 6.1 Hz, 3H), 1.27 (d, *J* = 4.9 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.17, 140.72, 140.19, 126.26, 115.58, 72.27, 70.33, 49.09, 30.39, 29.98, 21.17.

HRMS (ESI): [m/z] calculated for $C_{11}H_{15}N_3NaO_2$ ([M+Na]$^+$): 244.1061; Found: 244.1056.

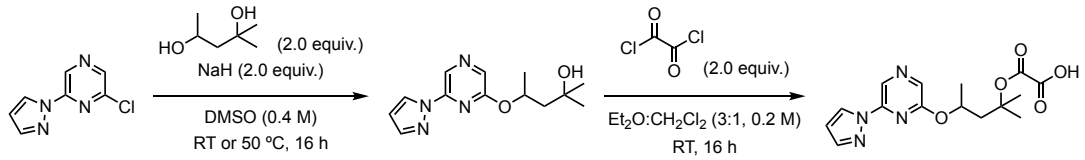
R_f Cyclohexane/EtOAc, 1:1) = 0.35 [CAM].

2-((4-((6-cyanopyrazin-2-yl)oxy)-2-methylpentan-2-yl)oxy)-2-oxoacetic acid: Synthesized following **GP6** using 6-((4-hydroxy-4-methylpentan-2-yl)oxy)pyrazine-2-carbonitrile (1.0 equiv., 0.54 mmol, 0.12 g) to afford the desired product as an off-white solid in 66% yield (103 mg, 0.35 mmol).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.41 (d, *J* = 0.6 Hz, 1H), 8.32 (d, *J* = 0.5 Hz, 1H), 5.51 (ddd, *J* = 9.0, 6.1, 2.9 Hz, 1H), 2.58 (dd, *J* = 15.4, 8.9 Hz, 1H), 2.05 (dd, *J* = 15.4, 3.0 Hz, 1H), 1.59 (d, *J* = 14.2 Hz, 6H), 1.38 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.04, 158.05, 140.80, 139.97, 126.14, 115.60, 84.95, 70.91, 45.57, 26.73, 26.42, 20.88.

HRMS (ESI): [m/z] calculated for $C_{13}H_{15}N_3NaO_5$ ([M+Na]$^+$): 316.0892; Found: 316.0904.



4-((6-(1H-pyrazol-1-yl)pyrazin-2-yl)oxy)-2-methylpentan-2-ol: Synthesized following **GP5** using 2-chloro-6- (1H-pyrazol-1-yl)pyrazine (1.0 equiv., 3.0 mmol, 0.54 g) and 2-methyl-2,4-pentandiol (2.0 equiv., 6.0 mmol, 0.77 mL) at rt for 16 h. The crude product was purified by flash column chromatography (cyclohexane/EtOAc, 4:1) to afford the desired product as a pale yellow oil in 54% yield (0.43 g, 1.63 mmol).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.81 (d, *J* = 0.6 Hz, 1H), 8.39 (dd, *J* = 2.6, 0.7 Hz, 1H), 8.05 (d, *J* = 0.6 Hz, 1H), 7.76 (dd, *J* = 1.7, 0.7 Hz, 1H), 6.48 (dd, *J* = 2.7, 1.7 Hz, 1H), 5.54 – 5.44 (m, 1H), 2.09 (dd, *J* = 14.9, 8.8 Hz, 1H), 1.78 (dd, *J* = 14.9, 3.3 Hz, 1H), 1.42 (d, *J* = 6.1 Hz, 3H), 1.26 (d, *J* = 7.7 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.80, 144.74, 143.05, 132.46, 127.43, 125.57, 108.41, 71.15, 70.27, 49.12, 30.33, 29.94, 21.25.

HRMS (ESI): [m/z] calculated for $C_{13}H_{18}N_4NaO_2$ ([M+Na]$^+$): 285.1319; Found: 285.1322.

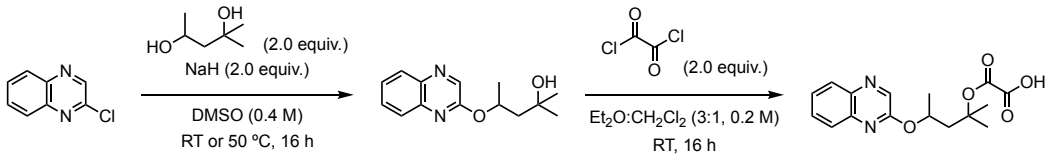
R_f (Cyclohexane/EtOAc, 1:1) = 0.45 [CAM]

2-((4-((6-(1H-pyrazol-1-yl)pyrazin-2-yl)oxy)-2-methylpentan-2-yl)oxy)-2-oxoacetic acid: Synthesized following **GP6** using 4-((6-(1H-pyrazol-1-yl)pyrazin-2-yl)oxy)-2-methylpentan-2-ol (1.0 equiv., 1.63 mmol, 0.43 g) to afford the desired product as an off-yellow solid in 68% yield (0.37 g, 1.11 mmol).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.73 (s, 1H), 8.38 (dd, *J* = 2.7, 0.7 Hz, 1H), 8.05 (s, 1H), 7.77 (dd, *J* = 1.6, 0.7 Hz, 1H), 6.51 (dd, *J* = 2.7, 1.7 Hz, 1H), 5.69 – 5.60 (m, 1H), 2.95 – 2.85 (m, 1H), 1.85 (dd, *J* = 15.6, 1.9 Hz, 1H), 1.67 (s, 3H), 1.59 (s, 3H), 1.43 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 158.66, 158.15, 145.76, 143.44, 130.76, 127.47, 123.32, 108.80, 100.15, 84.73, 70.07, 45.12, 26.95, 26.60, 21.08.

HRMS (ESI): [m/z] calculated for $C_{15}H_{19}N_4O_5$ ([M+Na]$^+$): 335.1343; Found: 335.1350.



2-methyl-4-(quinoxalin-2-yloxy)pentan-2-ol: Synthesized following **GP5** using 2-chloroquinoxaline (1.0 equiv., 3.0 mmol, 0.49 g) and 2-methyl-2,4-pentandiol (2.0 equiv., 6.0 mmol, 0.77 mL) at 50 °C for 16 h. The crude product was purified by flash column chromatography (cyclohexane/EtOAc, 4:1) to afford the desired product as a red oil in 78% yield (0.58 g, 2.35 mmol).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 – 7.94 (m, 1H), 7.82 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.61 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.53 (ddd, *J* = 8.3, 6.9, 1.5 Hz, 1H), 4.68 (do, *J* = 8.0, 6.2 Hz, 1H), 1.97 – 1.93 (m, 2H), 1.55 (d, *J* = 6.3 Hz, 6H), 1.45 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.78, 150.85, 140.52, 139.45, 129.71, 128.47, 127.20, 126.77, 71.12, 44.44, 35.72, 29.75, 28.51, 21.76.

HRMS (ESI): [m/z] calculated for $C_{14}H_{18}N_2NaO_2$ ([M+Na]$^+$): 269.1268; Found: 269.1260.

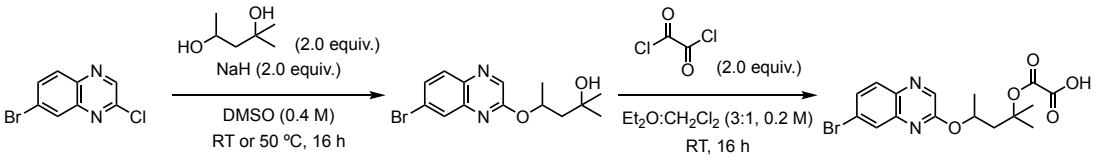
R_f (Cyclohexane/EtOAc, 1:1) = 0.32 [CAM].

2-((2-methyl-4-(quinoxalin-2-yloxy)pentan-2-yl)oxy)-2-oxoacetic acid: Synthesized following **GP6** using 2-methyl-4-(quinoxalin-2-yloxy)pentan-2-ol (1.0 equiv., 2.35 mmol, 0.58 g) to afford the desired product as an off-yellow solid in 80% yield (0.60 g, 1.88 mmol).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.48 (s, 1H), 7.84 (dd, *J* = 8.4, 4.6 Hz, 2H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 1H), 5.88 (td, *J* = 6.3, 3.0 Hz, 1H), 3.01 (dd, *J* = 15.7, 10.3 Hz, 1H), 1.80 (d, *J* = 15.7 Hz, 1H), 1.70 (s, 3H), 1.61 (s, 3H), 1.45 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 159.78, 158.35, 157.22, 141.02, 139.12, 136.40, 130.77, 127.38, 127.16, 127.09, 84.84, 69.42, 45.03, 27.15, 26.40, 21.08.

HRMS (ESI): [m/z] calculated for $C_{16}H_{19}N_2O_5$ ([M+Na]$^+$): 319.1286; Found: 319.1288.



4-((7-bromoquinoxalin-2-yl)oxy)-2-methylpentan-2-ol: Synthesized following **GP5** using 7-bromo-2-chloroquinoxaline (1.0 equiv., 3.0 mmol, 0.73 g) and 2-methyl-2,4-pentandiol (2.0 equiv., 6.0 mmol, 0.77 mL) at 50 °C for 48 h. The crude product was purified by flash column chromatography (cyclohexane/EtOAc, 4:1) to afford the desired product as a red oil in 64% yield (0.62 g, 1.9 mmol).

^{1}H NMR 400 MHz, Chloroform-*d*) δ 8.42 (s, 1H), 8.00 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.80 (ddd, *J* = 8.3, 1.4, 0.6 Hz, 1H), 7.65 (ddd, *J* = 8.3, 7.0, 1.5 Hz, 1H), 7.55 (ddd, *J* = 8.3, 7.0, 1.4 Hz, 1H), 5.64 – 5.54 (m, 1H), 2.13 (dd, *J* = 14.9, 6.9 Hz, 1H), 1.82 (dd, *J* = 14.9, 4.2 Hz, 1H), 1.47 (d, *J* = 6.2 Hz, 3H), 1.29 (s, 3H), 1.24 (s, 3H).

^{13}C NMR(101 MHz, Chloroform-d) δ 157.18, 140.57, 137.64, 130.32, 130.27, 129.51, 124.45, 71.15, 70.28, 54.04, 49.51, 30.43, 29.86, 21.85.

HRMS (ESI): [m/z] calculated for $C_{14}H_{17}BrN_2NaO_2$ ([M+Na]$^+$): 347.0366; Found: 347.0366.

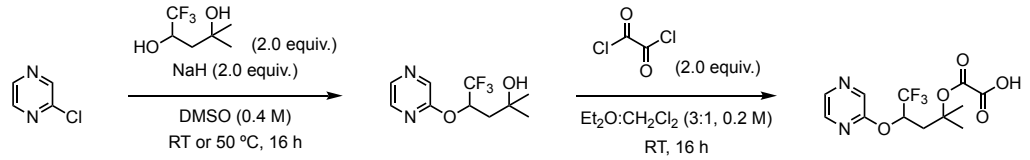
R_f (Cyclohexane/EtOAc, 1:1) = 0.4 [CAM].

2-((4-((7-bromoquinoxalin-2-yl)oxy)-2-methylpentan-2-yl)oxy)-2-oxoacetic acid: Synthesized following **GP_2** using 4-((7-bromoquinoxalin-2-yl)oxy)-2-methylpentan-2-ol (1.0 equiv., 1.9 mmol, 0.62 g) to afford the desired product as a black solid in 93% yield (0.7 g, 1.76 mmol).

^{1}H NMR(600 MHz, Chloroform-*d*) δ 8.42 (s, 1H), 8.02 (d, *J* = 2.1 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 1H), 7.53 (dd, *J* = 8.8, 2.1 Hz, 1H), 5.83 (dqd, *J* = 12.3, 6.1, 1.9 Hz, 1H), 2.91 (dd, *J* = 15.7, 9.9 Hz, 1H), 1.86 (dd, *J* = 15.7, 2.0 Hz, 1H), 1.69 (s, 3H), 1.61 (s, 3H), 1.44 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR(151 MHz, Chloroform-*d*) δ 159.20, 157.95, 157.53, 141.71, 139.77, 130.50, 129.86, 128.73, 124.85, 85.31, 69.79, 45.18, 26.92, 26.45, 21.05.

HRMS (ESI): [m/z] calculated for $C_{16}H_{18}BrN_2O_5$ ([M+Na] $^+$): 397.0389; Found: 397.0394.



5,5,5-trifluoro-2-methyl-4-(pyrazin-2-yloxy)pentan-2-ol: Synthesized following **GP5** using 5-chloro-2-trifluoromethylpyrazine (1.0 equiv., 3.0 mmol, 0.27 mL) and 1,1,1-trifluoro-4-methylpentane-2,4-diol (2.0 equiv., 6.0 mmol, 1.03 g) at rt for 16 h. The crude product was purified by flash column chromatography (cyclohexane/EtOAc, 4:1) to afford the desired product as a yellow oil in 43% yield (0.32 g, 1.28 mmol).

^{1}HNMR (400 MHz, Chloroform-*d*) δ 8.32 (d, *J* = 1.5 Hz, 1H), 8.25 (d, *J* = 2.7 Hz, 1H), 8.12 (dd, *J* = 2.8, 1.4 Hz, 1H), 6.10 – 6.01 (m, 1H), 2.14 (dd, *J* = 15.2, 9.4 Hz, 1H), 2.04 (dd, *J* = 15.2, 2.0 Hz, 1H), 1.32 (s, 3H), 1.22 (s, 3H).

^{13}C NMR(151 MHz, Chloroform-*d*) δ 158.85, 140.37, 138.44, 136.15, 41.27, 40.31, 32.15, 30.57, 29.68, 27.70.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -78.55.

HRMS(ESI): [m/z] calculated for $C_{10}H_{14}F_3N_2O_2$ ([M+Na]$^+$): 251.1002; Found: 251.1002.

R_f (Cyclohexane/EtOAc, 1:1) = 0.3

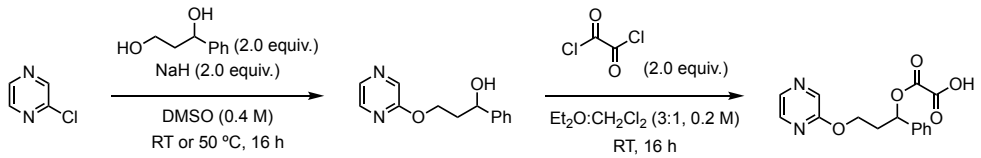
2-oxo-2-((5,5,5-trifluoro-2-methyl-4-(pyrazin-2-yloxy)pentan-2-yl)oxy)acetic acid: Synthesized following **GP6** using 5,5,5-trifluoro-2-methyl-4-(pyrazin-2-yloxy)pentan-2-ol (1.0 equiv., 1.28 mmol, 0.32 g) to afford the desired product as a yellow solid in 97% yield (0.4 g, 1.24 mmol).

^{1}HNMR(600 MHz, Chloroform-*d*) δ 8.25 (dd, *J* = 2.9, 1.4 Hz, 1H), 8.21 (d, *J* = 1.4 Hz, 1H), 8.11 (d, *J* = 2.9 Hz, 1H), 6.31 (dd, *J* = 10.7, 6.3 Hz, 1H), 2.98 (dd, *J* = 15.7, 10.5 Hz, 1H), 1.96 (d, *J* = 15.6 Hz, 1H), 1.71 (s, 3H), 1.67 (s, 3H).

^{13}C NMR(151 MHz, Chloroform-*d*) δ 159.28, 159.25, 157.60, 141.97, 135.07, 133.92, 124.89, 123.02, 83.34, 38.09, 26.98, 25.52.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -77.71.

HRMS(ESI): [m/z] calculated for $C_{12}H_{14}F_3N_2O_5$ ([M+Na]$^+$): 323.0853; Found: 323.0849.



1-phenyl-3-(pyrazin-2-yloxy)propan-1-ol: Synthesized following **GP5** using 2-chloropyrazine (1.0 equiv., 3.6 mmol, 0.32 mL) and 1-phenyl-3-(pyrazin-2-yloxy)propan-1-ol (1.2 equiv., 4.3 mmol, 0.65 g) at rt for 16 h. The crude product was purified by flash column chromatography (cyclohexane/EtOAc, 4:1) to afford the desired product as a yellow oil in 74% yield (0.59 g, 2.6 mmol).

^{1}**HNMR** (400 MHz, Chloroform-*d*) δ 8.24 (d, *J* = 1.4 Hz, 1H), 8.13 (d, *J* = 2.8 Hz, 1H), 8.07 (dd, *J* = 2.8, 1.4 Hz, 1H), 7.42 – 7.32 (m, 4H), 7.32 – 7.27 (m, 1H), 4.90 (d, *J* = 6.9 Hz, 1H), 4.63 (ddd, *J* = 11.0, 7.1, 6.1 Hz, 1H), 4.39 (dt, *J* = 11.0, 5.5 Hz, 1H), 2.27 – 2.16 (m, 2H), 1.56 (s, 1H).

R$_f$ (Cyclohexane/EtOAc, 1:1) = 0.3 [UV/CAM]

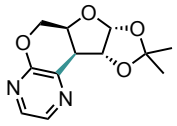
2-oxo-2-(1-phenyl-3-(pyrazin-2-yloxy)propoxy)acetic acid: Synthesized following **GP6** using 1-phenyl-3-(pyrazin-2-yloxy)propan-1-ol (1.0 equiv., 2.6 mmol, 0.59 g) to afford the desired product as an orange solid in 97% yield (0.69 g, 2.5 mmol). The product was used in the next step with any further purification.

^{1}**HNMR** (400 MHz, Chloroform-*d*) δ 8.29 (d, *J* = 1.3 Hz, 1H), 8.19 – 8.15 (m, 1H), 8.11 (d, *J* = 2.9 Hz, 1H), 7.43 (d, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.33 (dd, *J* = 8.8, 5.9 Hz, 1H), 6.19 (dd, *J* = 8.8, 4.3 Hz, 1H), 4.55 (ddd, *J* = 11.2, 7.1, 4.2 Hz, 1H), 4.47 (ddd, *J* = 11.3, 7.4, 4.1 Hz, 1H), 2.60 (ddt, *J* = 15.7, 7.7, 4.0 Hz, 1H), 2.39 (ddd, *J* = 15.3, 7.5, 3.9 Hz, 1H).

6.4.3. Synthesis & characterization of polycyclic scaffolds

General procedure for the intramolecular Minisci reaction (GP7): An 8 mL BiotageR microwave vial was charged with the corresponding oxalic acid (0.50 mmol, 1 equiv.), $(NH_4)_2S_2O_8$ (171.15 mg, 0.75 mmol, 1.5 equiv.) and sealed with a septum cap. The vial was put under vacuum for 5 min and refilled with N2. Afterwards, dry DMSO (5 mL) was added. The reaction mixture was then sparged with N2 for 2-5 min and stirred at 100 ºC for 2 h. Afterwards, the reaction was quenched carefully at RT with $NaHCO_3$ (aq.) (ca. 15 mL) and the organic phase extracted with EtOAc (ca. 3 x15 mL). The combined organic layers were washed with brine, dried over Na2SO4 and the solvent evaporated. The crude product was purified by column chromatography over silica gel to afford the desired fused heterocycle.

(6aS,7aR,10aR,10bS)-9,9-dimethyl-6a,7a,10a,10b-tetrahydro-6H-[1,3]dioxolo [4'',5'':4',5'] furo[3',2':4,5]pyrano[2,3-b]pyrazine (35):



Synthesized following **GP7** using 2-(((3aR,5R,6S,6aR)-2,2-dimethyl-5-((pyrazin-2-yloxy)methyl)tetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)-2-oxoacetic acid (1.0 equiv., 0.5 mmol, 102.6 mg). The product was isolated as a yellowish solid in 40% yield (40.1 mg, 0.2 mmol)

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.24 (d, *J* = 2.5 Hz, 1H), 8.14 – 8.08 (m, 1H), 5.72 (d, *J* = 3.6 Hz, 1H), 5.14 – 5.06 (m, 1H), 4.78 (ddd, *J* = 4.7, 2.1, 1.2 Hz, 1H), 4.77 – 4.73 (m, 1H), 4.37 – 4.24 (m, 1H), 3.67 (d, *J* = 4.6 Hz, 1H), 1.59 (s, 3H), 1.34 (d, *J* = 0.7 Hz, 3H).

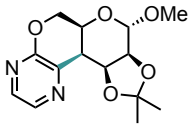
^{13}C NMR (151 MHz, Chloroform-*d*) δ 157.2, 141.9, 138.7, 136.3, 112.1, 105.2, 86.0, 73.5, 65.9, 47.3, 27.0, 26.3.

HRMS (ESI): [m/z] calculated for $C_{12}H_{15}N_2O_4$ ($[M+Na]^+$): 251.1026; Found: 251.1026.

IR ṽ [cm^{-1}] 2977.70 (m), 2942.62 (m), 2896.16 (m) ,1727.27 (m), 1426.54 (s), 1373.85 (s), 1284.08 (s), 1208.94 (s), 1165.32 (s), 1100.80 (s), 1059.46 (s), 1012.77 (s), 906.97 (s), 861.85 (s), 823.34 (s), 727.99 (s), 558.45 (s), 522.92 (s), 469.06 (s).

R_f (CH_2Cl_2/EtOAc, 1:1) = 0.4 [UV/CAM]

3a*S*,4*S*,5a*S*,11b*S*,11c*S*)-4-methoxy-2,2-dimethyl-3a,4,5a,6,11b,11c-hexahydro-[1,3] dioxolo[4'',5'':4',5']pyrano[3',2':4,5]pyrano[2,3-*b*]pyrazine (36):



Synthesized following **GP7** using 2-(((3aS,4S,6R,7R,7aS)-4-methoxy-2,2-dimethyl-6-((pyrazin-2-yloxy)methyl)tetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-7-yl)oxy)-2-oxoacetic acid (1.0 equiv., 0.5 mmol, 147.1 mg). The product was isolated as a yellowish solid in 31% yield (47.3 mg, 0.15 mmol).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.26 (d, *J* = 2.5 Hz, 1H), 8.12 (dd, *J* = 2.5, 0.9 Hz, 1H), 5.08 (ddd, *J* = 7.4, 3.4, 0.9 Hz, 1H), 4.67 (s, 1H), 4.50 – 4.41 (m, 2H), 4.37 – 4.31 (m, 1H), 4.23 (d, *J* = 7.5 Hz, 1H), 3.69 (ddt, *J* = 7.6, 3.2, 1.0 Hz, 1H), 3.49 (s, 3H), 1.46 – 1.41 (m, 3H), 1.29 – 1.26 (m, 3H).

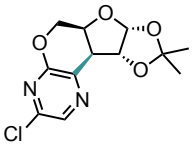
^{13}C NMR (151 MHz, Chloroform-*d*) δ 158.3, 150.7, 141.2, 138.6, 138.3, 110.3, 99.9, 74.4, 73.1, 67.9, 63.5, 56.4, 35.2, 26.4, 24.6.

HRMS (ESI): [m/z] calculated for $C_{16}H_{21}N_2O_9$ ([M]$^+$): 385.1242; Found: 385.1036.

IR ṽ [cm^{-1}] 3330.92 (w), 2969.64 (s), 2931.65 (m), 2883.09 (m), 1466.14 (m), 1408.10 (m), 1377.76 (s), 1307.22 (m), 1159.44 (s), 1127.76 (s), 950.20 (s), 816.39 (s),633.45 (s), 487.41 (m), 425.24 (m).

R$_f$ (CH_2Cl_2/EtOAc, 1:1) = 0.49 [UV/CAM]

(6aS,7aR,10aR,10bS)-3-chloro-9,9-dimethyl-6a,7a,10a,10b-tetrahydro-6H-[1,3]dioxolo [4'',5'':4',5']furo[3',2':4,5]pyrano[2,3-b]pyrazine (37):



Synthesized following **GP7** using 2-(((3aR,5R,6aR)-5-(((6-chloropyrazin-2-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)-2-oxoacetic acid (1.0 equiv., 0.5 mmol, 138.1 mg). The product was isolated as a yellowish solid in 49% yield (67.3 mg, 0.24 mmol).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.24 (s, 1H), 5.72 (d, *J* = 3.6 Hz, 1H), 5.07 (d, *J* = 3.6 Hz, 1H), 4.80 – 4.74 (m, 2H), 4.32 (d, *J* = 12.6 Hz, 1H), 3.64 (d, *J* = 4.5 Hz, 1H), 1.58 (s, 3H), 1.34 (s, 3H).

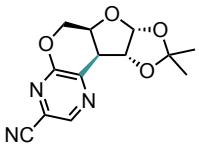
^{13}C NMR (151 MHz, Chloroform-*d*) δ 156.2, 145.9, 137.9, 134.0, 112.4, 105.3, 85.9, 73.3, 66.5, 47.1, 27.1, 26.5.

HRMS (ESI): [m/z] calculated for $C_{12}H_{14}ClN_2O_4$ ([M+Na]$^+$): 285.0638; Found: 285.0637.

IR ṽ [cm^{-1}] 3329.57 (w), 2969.62 (s), 2931.84 (m), 2883.03 (m), 1465.99 (m), 1377.72 (s), 1307.00 (m), 1159.50 (s), 1127.78 (s), 950.20 (s), 816.35 (s), 638.90 (m), 487.25 (m), 424.50 (m).

R$_f$ (CH_2Cl_2/EtOAc, 1:1) = 0.65 [UV/CAM]

(6aS,7aR,10aR,10bS)-9,9-dimethyl-6a,7a,10a,10b-tetrahydro-6H-[1,3]dioxolo [4'',5'':4',5'] furo[3',2':4,5]pyrano[2,3-b]pyrazine-3-carbonitrile (38):



Synthesized following **GP7** using 2-(((3aR,5R,6aR)-5-(((6-cyanopyrazin-2-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)-2-oxoacetic acid (1.0 equiv., 0.5 mmol, 137.6 mg). The product was isolated as a yellow foam in 31% yield (43 mg, 0.15 mmol).

^{1}H NMR (600 MHz, Chloroform-*d)* δ 8.54 (s, 1H), 5.72 (d, *J* = 3.6 Hz, 1H), 5.11 (d, *J* = 3.6 Hz, 1H), 4.86 – 4.77 (m, 2H), 4.40 (d, *J* = 12.9 Hz, 1H), 3.70 (d, *J* = 4.5 Hz, 1H), 1.59 (s, 3H), 1.35 (s, 3H).

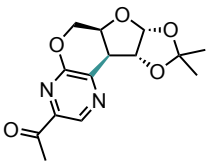
^{13}C NMR (151 MHz, Chloroform-*d*) δ 156.8, 141.5, 126.9, 115.0, 112.4, 105.0, 85.8, 72.6, 66.4, 60.5, 47.8, 26.8, 26.3..

HRMS (ESI): [m/z] calculated for $C_{13}H_{13}N_3NaO_4$ ([M+Na]$^+$): 298.0804; Found: 298.0798.

IR ṽ [cm^{-1}] 3332.50 (w), 2969.66 (s), 2932.14 (m), 2883.21 (m), 1466.10 (m), 1408.33 (s), 1377.76 (m), 1307.22 (s), 1159.45 (s), 1127.74 (s), 950.19 (s), 816.35 (m), 632.52 (m), 487.45 (m), 424.24 (m).

R_f (CH_2Cl_2/EtOAc, 1:1) = 0.5 [UV/*p*-anisaldehyde]]

1-((6aS,7aR,10aR,10bS)-9,9-dimethyl-6a,7a,10a,10b-tetrahydro-6H-[1,3]dioxolo [4'',5'':4',5'] furo[3',2':4,5]pyrano[2,3-b]pyrazin-3-yl)ethan-1-one (39):



Synthesized following **GP7** using 2-(((3aR,5R,6aR)-5-(((6-acetylpyrazin-2-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)-2-oxoacetic acid (1.0 equiv., 0.5 mmol, 146.1 mg). The product was isolated as a yellowish solid in 18% yield (25.7 mg, 0.095 mmol).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.81 (d, *J* = 1.0 Hz, 1H), 5.75 (d, *J* = 3.6 Hz, 1H), 5.14 (d, *J* = 3.7 Hz, 1H), 4.89 – 4.79 (m, 2H), 4.43 – 4.36 (m, 1H), 3.72 – 3.67 (m, 1H), 2.68 (s, 3H), 2.66 – 2.64 (m, 1H), 1.61 (s, 3H), 1.39 (s, 3H).

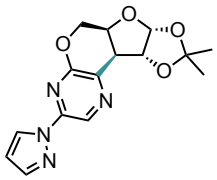
^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.1, 143.1, 142.2, 134.4, 112.3, 105.1, 86.0, 73.0, 66.3, 47.3, 26.9, 26.4, 26.0.

HRMS (ESI): [m/z] calculated for$C_{14}H_{16}N_2NaO_5$ ([M+Na]$^+$): 315.0957; Found: 315.0951.

IR ṽ [cm^{-1}] 3333.41 (w), 2969.68 (s), 2931.84 (m), 2883.04 (m), 1466.12 (m), 1408.03 (m), 1377.82 (s), 1340.12 (m), 1306.75 (m), 1159.48 (s), 1127.75 (s), 1107.98 (s), 950.17 (s), 816.35 (s), 637.96 (m), 487.45 (m), 424.78 (m).

R_f (CH_2Cl_2/EtOAc, 1:1) = 0.47 [UV/*p*-anisaldehyde]]

(6aS,7aR,10aR,10bS)-9,9-dimethyl-3-(1H-pyrazol-1-yl)-6a,7a,10a,10b-tetrahydro-6H-[1,3] dioxolo[4'',5'':4',5']furo[3',2':4,5]pyrano[2,3-b]pyrazine (40):



Synthesized following **GP7** using 2-(((3aR,5R,6aR)-5-(((6-(1H-pyrazol-1-yl)pyrazin-2-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)-2-oxoacetic acid (1.0 equiv., 0.5 mmol, 158.2 mg). The product was isolated as a yellowish solid in 48% yield (76.1 mg, 0.24 mmol).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.98 (s, 1H), 8.44 (dd, *J* = 2.7, 0.7 Hz, 1H), 7.77 (dd, *J* = 1.7, 0.7 Hz, 1H), 6.48 (dd, *J* = 2.7, 1.7 Hz, 1H), 5.73 (d, *J* = 3.6 Hz, 1H), 5.13 (dd, *J* = 3.6, 1.0 Hz, 1H), 4.84 – 4.75 (m, 2H), 4.36 (d, *J* = 12.2 Hz, 1H), 3.69 (d, *J* = 4.5 Hz, 1H), 1.60 (s, 3H), 1.37 – 1.33 (m, 3H).

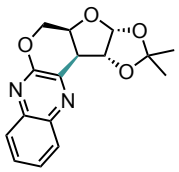
^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.8, 143.3, 131.9, 128.5, 127.9, 112.2, 108.7, 105.2, 85.8, 73.4, 66.3, 47.0, 27.0, 26.3..

HRMS (ESI): [m/z] calculated for$C_{15}H_{16}N_4NaO_4$ ($[M+Na]^+$): 339.1069; Found: 339.1064

IR ṽ [cm^{-1}] 3329.97(w), 2969.65 (s), 2931.98 (m), 2883.19 (m), 1466.12 (m), 1377.71(s), 1307.25 (s), 1159.47 (s), 1127.74 (s), 950.20 (s), 816.39 (s), 635.94 (m), 486.98 (m), 424.47 (m).

R_f (CH_2Cl_2/EtOAc, 1:1) = 0.56 [UV/*p*-anisaldehyde]]

(3aR,4aS,12bS,12cR)-2,2-dimethyl-3a,4a,12b,12c-tetrahydro-5H-[1,3]dioxolo[4'',5'':4',5'] furo[3',2':4,5]pyrano[2,3-b]quinoxaline (41):



Synthesized following **GP7** using 2-(((3aS,5S,6aS)-2,2-dimethyl-5-((quinoxalin-2-yloxy)methyl)tetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)-2-oxoacetic acid (1.0 equiv., 0.5 mmol, 150.2 mg). The product was isolated as a yellowish solid in 54% yield (54.1 mg, 0.27 mmol).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.99 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.87 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.69 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.63 – 7.58 (m, 1H), 5.74 (d, *J* = 3.6 Hz, 1H), 5.31 (d, *J* = 3.6 Hz, 1H), 4.92 – 4.82 (m, 2H), 4.47 (dd, *J* = 13.2, 1.6 Hz, 1H), 3.83 (d, *J* = 4.4 Hz, 1H), 1.62 (s, 3H), 1.38 (s, 3H).

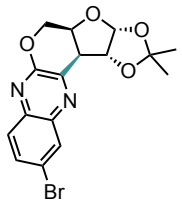
^{13}C NMR (151 MHz, Chloroform-*d*) δ 141.0, 140.1, 139.8, 130.7, 128.4, 127.8, 127.6, 112.2, 105.2, 86.7, 73.3, 66.0, 48.4, 27.0, 26.4.

HRMS (ESI): [m/z] calculated for $C_{16}H_{17}N_2O_4$ ($[M]^+$): 301.1183; Found: 301.1177.

IR ṽ [cm^{-1}] 3332.89 (w), 2969.64 (s), 2931.80 (m), 2883.13 (m), 1466.14 (m), 1408.33(m), 1377.74 (m), 1339.94 (s), 1307.23 (s), 1159.46 (s), 1127.75 (s), 1108.09 (s), 950.20 (s), 816.38 (s), 633.91 (m), 487.35 (m), 424.08 (m).

R_f (CH_2Cl_2/EtOAc, 1:1) = 0.51 [UV/CAM]

(3aR,4aS,12bS,12cR)-10-bromo-2,2-dimethyl-3a,4a,12b,12c-tetrahydro-5H-[1,3]dioxolo [4'',5'':4',5']furo[3',2':4,5]pyrano[2,3-b]quinoxaline (42):



Synthesized following **GP7** using 2-(((3aS,5S,6aS)-5-(((6-bromoquinoxalin-2-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)-2-oxoacetic acid (1.0 equiv., 0.5 mmol, 189.6 mg). The product was isolated as a yellow solid in 33% yield (63.1 mg, 0.16 mmol).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.03 (d, *J* = 2.1 Hz, 1H), 7.84 (d, *J* = 8.9 Hz, 1H), 7.68 (dd, *J* = 8.9, 2.1 Hz, 1H), 5.74 (d, *J* = 3.8 Hz, 1H), 5.28 (d, *J* = 3.6 Hz, 1H), 4.90 – 4.83 (m, 2H), 4.48 (d, *J* = 12.6 Hz, 1H), 3.78 (d, *J* = 4.3 Hz, 1H), 1.61 (s, 3H), 1.37 (s, 3H)

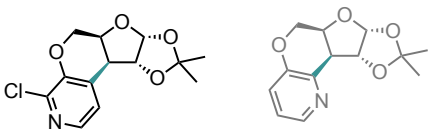
^{13}C NMR (151 MHz, Chloroform-*d*) δ 154.8, 141.7, 140.2, 138.8, 131.2, 130.0, 129.6, 124.8, 112.3, 105.1, 86.6, 73.0, 66.1, 48.3, 26.9, 26.3.

HRMS (ESI): [m/z] calculated for $C_{16}H_{16}BrN_2O_4$ ($[M+Na]^+$): 379.0289; Found: 379.0288

IR ṽ [cm^{-1}] 3333.07 (w), 2969.64 (s), 2932.08 (m), 2883.10 (m), 1466.13 (m), 1408.20 (s), 1377.73 (m), 1339.95 (s), 1159.48 (s), 1127.74 (s), 950.20 (s), 816.38 (s), 634.27 (w), 487.40 (m), 424.64 (m).

R_f (CH_2Cl_2/EtOAc, 1:1) = 0.6 [*p*-anisaldehyde]

(6aS,7aR,10aR,10bS)-4-chloro-9,9-dimethyl-6a,7a,10a,10b-tetrahydro-6H-[1,3] dioxolo[4'',5'':4',5']furo[3',2':4,5]pyrano[2,3-c]pyridine (51):



Synthesized following **GP7** using 2-(((3aR,5R,6aR)-5-(((2-chloropyridin-3-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)-2-oxoacetic acid (1.0 equiv., 0.5 mmol, 141.9 mg). The product was isolated as yellowish solid in 28% yield (39.4 mg, 0.14 mmol).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.97 (d, *J* = 5.0 Hz, 1H), 7.13 (dd, *J* = 5.0, 0.9 Hz, 1H), 5.77 (d, *J* = 3.6 Hz, 1H), 4.72 (dd, *J* = 12.0, 2.8 Hz, 3H), 4.10 (d, *J* = 12.2 Hz, 1H), 3.51 (d, *J* = 4.9 Hz, 1H), 1.58 (s, 3H), 1.35 (s, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 147.2, 140.9, 140.7, 128.8, 123.2, 112.4, 105.3, 87.0, 73.3, 66.0, 43.6, 27.0, 26.4.

HRMS (ESI): [m/z] calculated for $C_{13}H_{15}ClNO_4$ ([M+Na]$^+$): 284.0684; Found: 284.0684.

IR ṽ [cm^{-1}] 3333.65 (w), 2969.65 (s), 2932.04 (m), 2883.12 (m), 1466.15 (m), 1408.15 (s), 1377.77 (m), 1340.01 (s), 1307.07 (s), 1159.48 (s), 1127.74 (s), 1108.12 (s), 950.20 (s), 816.37 (s), 637.33 (w), 487.49 (m), 424.02 (m).

R$_f$ (CH_2Cl_2/EtOAc, 1:1) = 0.5 [UV/*p*-anisaldehyde]]

Spectroscopic data for 51':

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.02 (dd, *J* = 4.7, 1.5 Hz, 1H), 7.29 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.21 (dd, *J* = 8.2, 4.7 Hz, 1H), 6.01 (d, *J* = 3.6 Hz, 1H), 4.60 (d, *J* = 3.6 Hz, 1H), 4.56 (ddd, *J* = 5.9, 5.0, 2.8 Hz, 1H), 4.48 (dd, *J* = 4.8, 2.8 Hz, 1H), 4.38 (dd, *J* = 5.5, 2.7 Hz, 2H), 2.60 (d, *J* = 4.9 Hz, 1H), 1.53 (s, 3H), 1.35 (d, *J* = 0.7 Hz, 3H).

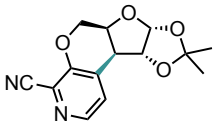
^{13}C NMR (101 MHz, Chloroform-*d*) δ 150.7, 141.5, 123.4, 121.0, 112.2, 105.1, 85.5, 75.5, 66.8, 27.0, 26.4.

HRMS (ESI): [m/z] calculated for C16H16BrN2O4 ([M]$^+$): 379.0289; Found: 379.0288.

IR ṽ [cm^{-1}] 3329.92 (w), 2969.65 (s), 2932.07 (m), 2883.43 (m), 1466.05(m), 1377.71 (s), 1303.61(m), 1159.54 (s), 1127.76 (s), 950.21 (s), 816.43 (s), 616.38 (w), 487.07 (m), 424.65 (m).

R$_f$ (CH_2Cl_2/EtOAc, 1:1) = 0.32 [UV/*p*-anisaldehyde]]

(6aS,7aR,10aR,10bS)-9,9-dimethyl-6a,7a,10a,10b-tetrahydro-6H-[1,3]dioxolo [4'',5'':4',5'] furo[3',2':4,5]pyrano[2,3-c]pyridine-4-carbonitrile (52):



Synthesized following **GP7** using 2-(((3aR,5R,6S,6aR)-5-(((2-cyanopyridin-3-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)-2-oxoacetic acid (1.0 equiv., 0.5 mmol, 145 mg). The product was isolated as a pale-yellow solid in 19% yield (21 mg, 0.095 mmol).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.26 (d, *J* = 4.8 Hz, 1H), 7.40 (dd, *J* = 4.9, 1.1 Hz, 1H), 5.77 (d, *J* = 3.6 Hz, 1H), 4.80 – 4.71 (m, 3H), 4.18 (dd, *J* = 12.4, 1.0 Hz, 1H), 3.52 (d, *J* = 4.8 Hz, 1H), 1.58 (s, 3H), 1.37 – 1.35 (m, 3H).

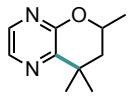
^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.2, 143.2, 129.1, 127.5, 123.5, 114.8, 112.5, 105.1, 86.9, 77.5, 77.2, 76.8, 72.6, 66.1, 42.9, 26.9, 26.4.

HRMS (ESI): [m/z] calculated for $C_{14}H_{14}N_2NaO_4$ ([M+Na]$^+$): 297.0846; Found: 297.0846.

IR ṽ [cm^{-1}] 3333.20 (w), 2969.65 (s), 2931.82 (m), 2883.23 (m), 1466.18 (m), 1408.17 (s), 1377.74 (m), 1307.23 (s), 1159.45 (s), 1127.75 (s), 950.21 (s), 816.38 (s), 632.53 (w), 487.23 (m), 424.31 (m).

R$_f$ (CH_2Cl_2/EtOAc, 1:1) = 0.47 [UV/CAM]

6,8,8-trimethyl-7,8-dihydro-6H-pyrano[2,3-b]pyrazine (53):



Synthesized following **GP7** using 2-((2-methyl-4-(pyrazin-2-yloxy)pentan-2-yl)oxy)-2-oxoacetic acid (1.0 equiv., 0.5 mmol, 134.1 mg). The product was isolated as a yellow oil in 57% yield (51.2 mg, 0.28 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 2.5 Hz, 1H), 7.98 (d, *J* = 2.5 Hz, 1H), 4.48 (dqd, *J* = 10.5, 6.2, 3.2 Hz, 1H), 1.91 – 1.76 (m, 2H), 1.48 (d, *J* = 6.2 Hz, 3H), 1.38 (s, 3H), 1.36 (s, 3H).

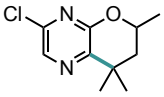
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 157.0, 147.5, 140.5, 137.2, 70.7 44.5, 34.7, 30.1, 28.4, 21.5.

HRMS (ESI): [m/z] calculated for$C_{10}H_{15}N_2O$ ([M]$^+$): 179.1179; Found: 179.1175.

IR ṽ [cm^{-1}] 3334.90 (w), 2969.52 (s), 2932.07 (m), 2882.93(m), 1465.72 (m), 1410.04 (m), 1377.88 (s), 1308.70 (m), 1159.64 (s), 1127.91 (s), 950.14 (s), 816.38 (s), 627.40 (w), 487.10 (m), 425.15 (m).

R$_f$ (Cyclohexane/EtOAc, 4:1) = 0.18 [CAM]

2-chloro-6,8,8-trimethyl-7,8-dihydro-6H-pyrano[2,3-b]pyrazine (54):



Synthesized following **GP7** using 2-((4-((6-chloropyrazin-2-yl)oxy)-2-methylpentan-2-yl)oxy)-2-oxoacetic acid (1.0 equiv., 0.5 mmol, 151.4 mg). The product was isolated as a pale yellow oil in 55% yield (59.6 mg, 0.28 mmol).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.12 (s, 1H), 4.50 (dqd, *J* = 11.4, 6.2, 2.5 Hz, 1H), 1.87 (dd, *J* = 14.2, 2.4 Hz, 1H), 1.82 – 1.75 (m, 1H), 1.48 (d, *J* = 6.2 Hz, 3H), 1.37 (s, 3H), 1.35 (s, 3H).

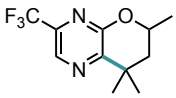
^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.76, 145.15, 144.04, 135.97, 71.50, 44.22, 34.54, 29.96, 28.27, 21.32.

HRMS (ESI): [m/z] calculated for $C_{10}H_{14}ClN_2O$ ([M+Na]$^+$): 213.0793; Found: 213.0789.

IR ṽ [cm^{-1}] 2975 (w), 2933 (w), 2870 (w), 1737 (m), 1703 (m), 1536 (s), 1370 (s), 1245 (s), 1224 (s), 1201 (s), 1162 (s), 1084 (s), 1038 (s), 982 (s), 960 (m), 900 (m), 877 (m), 689 (m), 529 (m).

R$_f$ (Cyclohexane/EtOAc, 1:1) = 0.5 [CAM].

6,8,8-trimethyl-3-(trifluoromethyl)-7,8-dihydro-6H-pyrano[2,3-b]pyrazine (55):



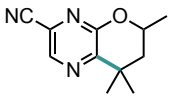
Synthesized following **GP7** using 2-((2-methyl-4-((5-(trifluoromethyl)pyrazin-2-yl)oxy)pentan-2-yl)oxy)-2-oxoacetic acid (1.0 equiv., 0.5 mmol, 168.2 mg). The product was isolated as a pale yellow oil in 37% yield (45.5 mg, 0.19 mmol).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.36 (s, 1H), 4.59 (dqd, *J* = 12.4, 6.2, 2.2 Hz, 1H), 1.93 (dd, *J* = 14.2, 2.2 Hz, 1H), 1.85 (dd, *J* = 14.3, 11.6 Hz, 1H), 1.53 (d, *J* = 6.2 Hz, 3H), 1.43 (s, 3H), 1.39 (s, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 158.63, 147.79, 138.14, 136.44, 136.21, 71.76, 43.98, 35.02, 29.89, 28.04, 21.42.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -67.76.

6,8,8-trimethyl-7,8-dihydro-6H-pyrano[2,3-b]pyrazine-2-carbonitrile (56):



Synthesized following **GP7** using 2-((4-((6-cyanopyrazin-2-yl)oxy)-2-methylpentan-2-yl)oxy)-2-oxoacetic acid (1.0 equiv., 0.5 mmol, 146.7 mg). The product was isolated as a pale yellow oil in 49% yield (50.8 mg, 0.25 mmol).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.43 (s, 1H), 4.83 – 4.34 (m, 1H), 2.12 – 1.73 (m, 2H), 1.66 – 1.16 (m, 10H).

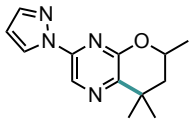
^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.62, 152.78, 140.48, 125.54, 115.52, 71.87, 43.67, 35.57, 29.85, 27.97, 21.33.

HRMS (ESI): [m/z] calculated for $C_{11}H_{13}N_3NaO$ ($[M+Na]^+$): 226.0947; Found: 226.0951.

IR $\tilde{\nu}$ [cm^{-1}] 2976 (m), 2936 (m), 2871 (m), 2236 (m), 1726 (w), 1539 (s), 1472 (m), 1434 (m), 1400 (m), 1321 (m), 1261 (s), 1193 (s), 1094 (s), 1043 (s), 931 (s), 905 (m), 861 (m), 664 (s), 533 (s), 462 (s).

R_f (Cyclohexane/EtOAc, 1:1) = 0.33 [CAM].

6,8,8-trimethyl-2-(1H-pyrazol-1-yl)-7,8-dihydro-6H-pyrano[2,3-b]pyrazine (57):



Synthesized following **GP7** using 2-((4-((6-(1H-pyrazol-1-yl)pyrazin-2-yl)oxy)-2-methylpentan-2-yl)oxy)-2-oxoacetic acid (1.0 equiv., 0.5 mmol, 167.2 mg). The product was isolated as a pale yellow oil in 59% yield (73.3 mg, 0.30 mmol).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.88 (s, 1H), 8.46 (dd, *J* = 2.6, 0.7 Hz, 1H), 7.74 (dd, *J* = 1.6, 0.7 Hz, 1H), 6.45 (dd, *J* = 2.7, 1.7 Hz, 1H), 4.56 (dqd, *J* = 10.7, 6.2, 2.9 Hz, 1H), 1.91 – 1.88 (m, 1H), 1.87 – 1.79 (m, 1H), 1.54 (d, *J* = 6.2 Hz, 3H), 1.43 (s, 3H), 1.40 (s, 3H).

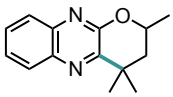
^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.62, 144.23, 143.63, 142.80, 127.62, 126.76, 108.19, 71.46, 44.62, 34.58, 30.03, 28.53, 21.49.

HRMS (ESI): [m/z] calculated for $C_{13}H_{16}N_4NaO$ ($[M+Na]^+$): 267.1216; Found: 267.1216.

IR ṽ [cm^{-1}] 2973 (m), 2930 (m), 1553 (m), 1522 (m), 1429 (m), 1394 (s), 1324 (m), 1262 (m), 1184 (s), 1137 (s), 1064 (s), 1034 (s), 933 (m), 889 (m), 756 (s), 649 (s), 604 (s), 529 (s).

R_f (Cyclohexane/EtOAc, 1:1) = 0.5 [CAM].

2,4,4-trimethyl-3,4-dihydro-2H-pyrano[2,3-b]quinoxaline (58):



Synthesized following **GP7** using 2-((2-methyl-4-(quinoxalin-2-yloxy)pentan-2-yl)oxy)-2-oxoacetic acid (1.0 equiv., 0.5 mmol, 159.2 mg). The product was isolated as a pale yellow oil in 53% yield (60.5 mg, 0.27 mmol).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 – 7.94 (m, 1H), 7.82 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.61 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.53 (ddd, *J* = 8.3, 6.9, 1.5 Hz, 1H), 4.68 (do, *J* = 8.0, 6.2 Hz, 1H), 1.97 – 1.93 (m, 2H), 1.55 (d, *J* = 6.3 Hz, 6H), 1.45 (s, 3H).

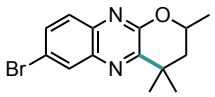
^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.78, 150.85, 140.52, 139.45, 129.71, 128.47, 127.20, 126.77, 71.12, 44.44, 35.72, 29.75, 28.51, 21.76.

HRMS (ESI): [m/z] calculated for $C_{14}H_{17}N_2O$ ($[M+Na]^+$): 229.1336; Found: 229.1335.

IR ṽ [cm^{-1}] 2980 (m), 2956 (m), 2931 (m), 2898 (m), 2865 (m), 1694 (s), 1570 (m), 1459 (m), 1405 (s), 1305 (s), 1269 (m), 1219 (m), 1126 (m), 1083 (s), 975 (m), 767 (s), 603 (s), 523 (m).

R_f (Cyclohexane/EtOAc, 1:1) = 0.35 [CAM].

7-bromo-2,4,4-trimethyl-3,4-dihydro-2H-pyrano[2,3-b]quinoxaline (59):



Synthesized following **GP7** using 2-((4-((7-bromoquinoxalin-2-yl)oxy)-2-methylpentan-2-yl)oxy)-2-oxoacetic acid (1.0 equiv., 0.5 mmol, 198.6 mg). The product was isolated as a red oil in 44% yield (67.6 mg, 0.22 mmol).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.94 (d, *J* = 2.2 Hz, 1H), 7.79 (d, *J* = 8.8 Hz, 1H), 7.59 (dd, *J* = 8.9, 2.2 Hz, 1H), 4.67 (ddd, *J* = 10.1, 6.3, 3.9 Hz, 1H), 1.98 – 1.88 (m, 2H), 1.53 (d, *J* = 6.3 Hz, 3H), 1.50 (s, 3H), 1.42 (s, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 155.27, 151.28, 141.44, 138.12, 130.21, 129.76, 129.46, 123.50, 71.33, 44.17, 35.76, 29.60, 28.36, 21.69.

HRMS (ESI): [m/z] calculated for $C_{14}H_{16}BrN_2O$ ([M+Na]$^+$): 307.0434; Found: 307.0441.

IR ṽ [cm^{-1}] 2976 (m), 2960 (m), 2934 (m), 2857 (m), 1572 (s), 1469 (m), 1404 (s), 1348 (s), 1319 (s). 1203 (s), 1139 (s), 1087 (s), 1041 (s), 911 (s), 867 (m), 819 (s), 784 (s), 677 (s), 586 (m), 516 (s).

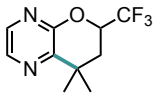
R$_f$ (Cyclohexane/EtOAc, 1:1) = 0.3 [CAM].

HRMS (ESI): [m/z] calculated for $C_{11}H_{14}F_3N_2O$ ([M+Na]$^+$): 247.1047; Found: 247.1053.

IR ṽ [cm^{-1}] 2969 (m), 2935 (m), 2871 (m), 1783 (s), 1723 (s), 1574 (s), 1552 (s), 1456 (s), 1400 (s), 1331 (s), 1287 (s), 1210 (m), 1124 (m), 1101 (m), 1036 (m), 933 (m), 717 (s), 635 (s), 521 (s).

R$_f$ (Cyclohexane/EtOAc, 1:1) = 0.45 [CAM]

8,8-dimethyl-6-(trifluoromethyl)-7,8-dihydro-6H-pyrano[2,3-b]pyrazine (60):



Synthesized following **GP7** using 2-oxo-2-((5,5,5-trifluoro-2-methyl-4-(pyrazin-2-yloxy)pentan-2-yl)oxy)acetic acid (1.0 equiv., 0.5 mmol, 161.1 mg). The product was isolated as a pale yellow oil in 27% yield (32.5 mg, 0.14 mmol).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.24 (d, *J* = 2.4 Hz, 1H), 8.09 (dd, *J* = 2.6, 1.2 Hz, 1H), 4.76 – 4.64 (m, 1H), 2.13 – 2.06 (m, 2H), 1.50 (d, *J* = 1.3 Hz, 3H), 1.41 (d, *J* = 1.3 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 154.84, 146.47, 141.10, 138.80, 71.82, 35.10, 34.04, 29.39, 27.78.

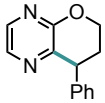
^{19}F NMR (376 MHz, Chloroform-*d*) δ -78.56 (d, *J* = 5.7 Hz).

HRMS (ESI): [m/z] calculated for $C_{10}H_{12}F_3N_2O$ ([M+Na]$^+$): 233.0889; Found: 233.0896.

IR ṽ [cm^{-1}] 3054 (m), 2966 (m), 2931 (m), 2870 (m), 1540 (s), 1476 (s), 1453 (m), 1401 (m), 1291 (m), 1267 (m), 1159 (m), 1128 (m), 1104 (s), 1027 (s), 905 (m), 852 (m), 731 (s), 676 (s), 519 (s).

R$_f$ (Cyclohexane/EtOAc, 1:1) = 0.4 [CAM]

(*S*)-8-phenyl-7,8-dihydro-6*H*-pyrano[2,3-*b*]pyrazine (61):



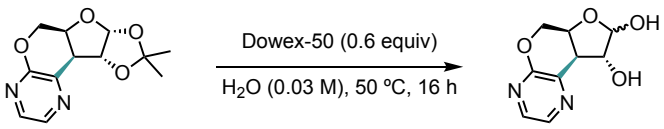
Synthesized following **GP7** using 2-oxo-2-(1-phenyl-3-(pyrazin-2-yloxy)propoxy)acetic acid (1.0 equiv., 0.5 mmol, 151.1 mg). The product was isolated as a pale-yellow oil in 19% yield (20 mg, 0.095 mmol).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.17 (d, *J* = 2.5 Hz, 1H), 8.10 (dd, *J* = 2.5, 0.9 Hz, 1H), 7.35 – 7.26 (m, 3H), 7.08 – 7.04 (m, 2H), 4.43 – 4.38 (m, 3H), 2.54 – 2.39 (m, 1H), 2.32 – 2.21 (m, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 158.5, 143.1, 142.0, 141.5, 138.0, 128.9, 128.5, 128.5, 127.1, 65.0, 44.2, 31.0.

R_f (CH_2Cl_2/EtOAc, 4:1) = 0.35 [UV/CAM]

6.4.4. Derivatization reactions: Deprotection:



35 **62**

In a 20 mL microwave vial, the **35** (111.4 mg, 0.45 mmol, 1.0 equiv.) was dissolved in H_2O (15 mL) and resin Dowex-50 (100 mg, 0.27 mmol, 0.6 equiv.) (previously washed with 10% HCl, H_2O, EtOH, and Et_2O) was added. The reaction was stirred at 50 ºC for 16 h. After this time, the resin was filtered off and washed with NH_4OH (3 mL). The solvent was removed *in vacuo* afford the desired deprotected product **62** as an orange solid in quantitative yield as 2:1 diasteromeric mixture (92.8 mg, 0.45 mmol).

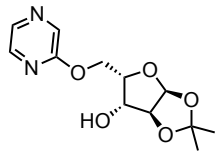
^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.25 (d, *J* = 2.5 Hz, 1H), 8.14 (dd, *J* = 2.5, 0.9 Hz, 1H), 8.08 (dd, *J* = 2.6, 1.0 Hz, 1H), 5.37 (d, *J* = 4.0 Hz, 1H), 4.88 (ddd, *J* = 5.8, 3.2, 2.1 Hz, 1H), 4.52 (dd, *J* = 12.6, 3.2 Hz, 1H), 4.49 (t, *J* = 3.6 Hz, 1H), 4.25 (dd, *J* = 12.5, 2.2 Hz, 1H), 4.23 – 4.19 (m, 1H), 3.66 (dd, *J* = 6.2, 3.1 Hz, 1H).

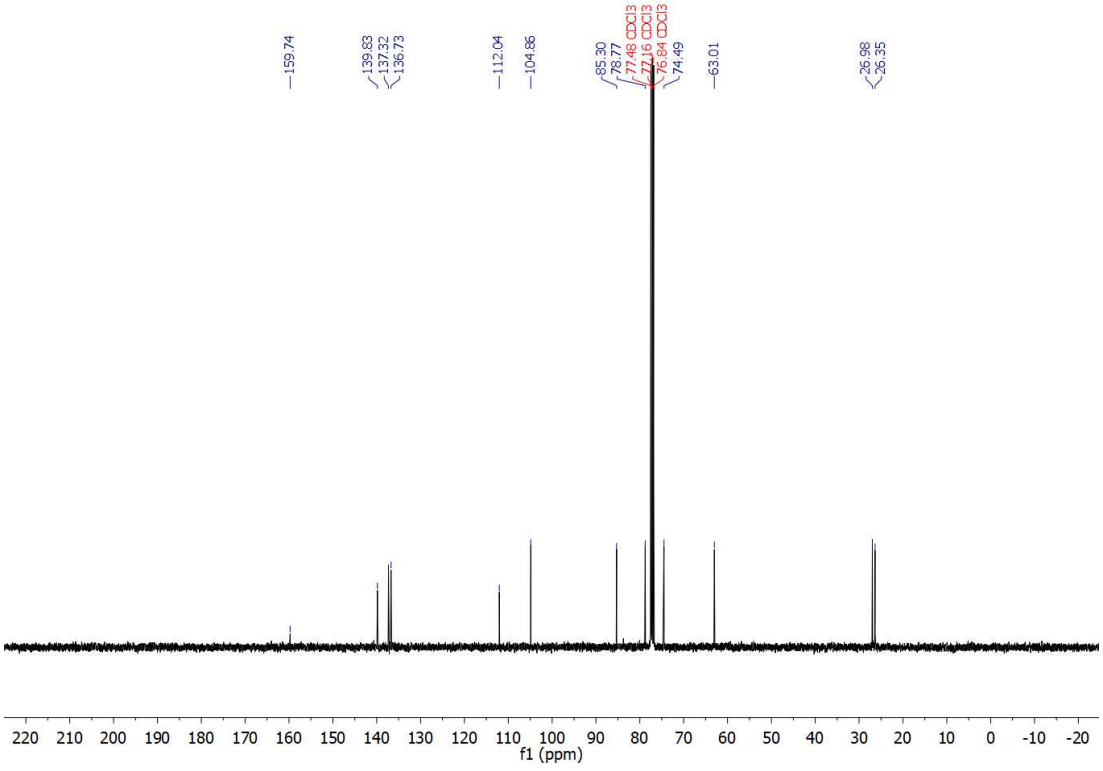
HRMS (ESI): [m/z] calculated for $C_9H_{10}N_2NaO_4$ ($[M+Na]^+$): 233.0533; Found: 233.0531.

6.4.5. ^{1}H and ^{13}C–NMR Spectra

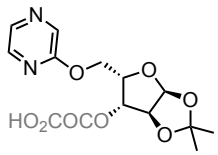
6.4.5.1. Starting materials

(3aS,5S,6R,6aS)-2,2-dimethyl-5-((pyrazin-2-yloxy)methyl)tetrahydrofuro[2,3-d][1,3]dioxol-6-ol:

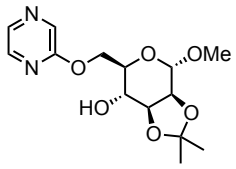


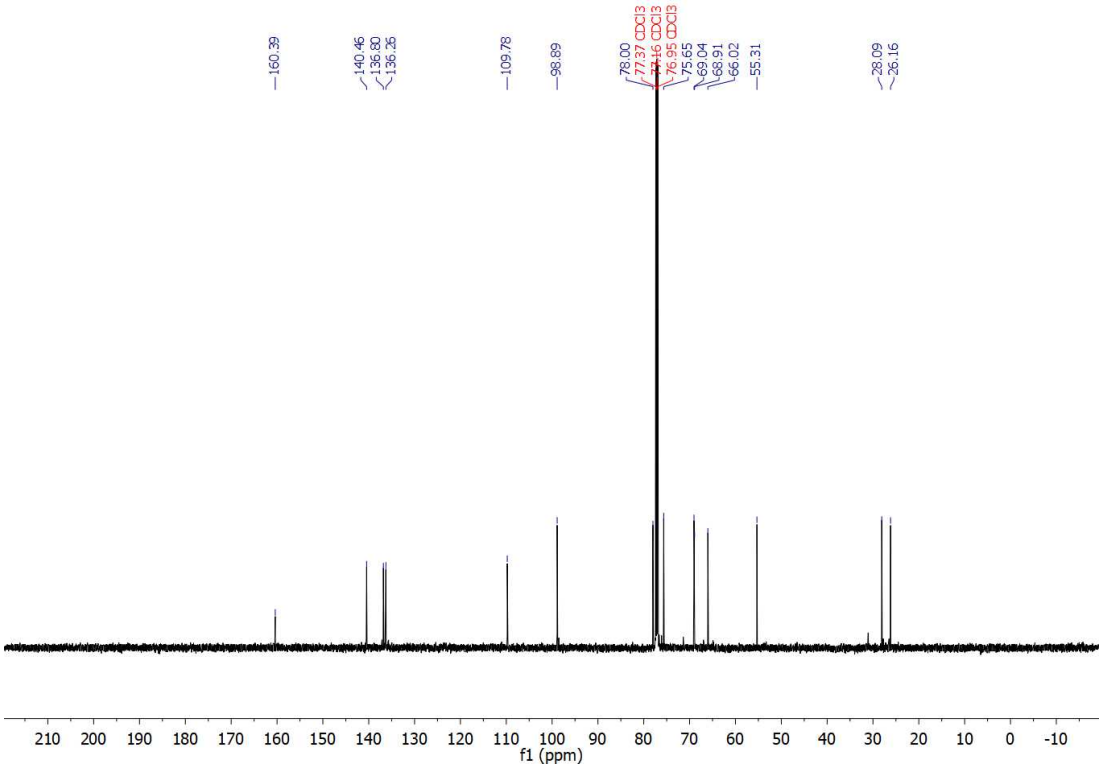


2-(((3aS,5S,6R,6aS)-2,2-dimethyl-5-((pyrazin-2-yloxy)methyl)tetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)-2-oxoacetic acid:

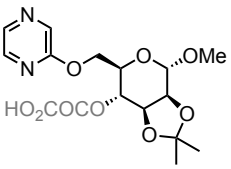


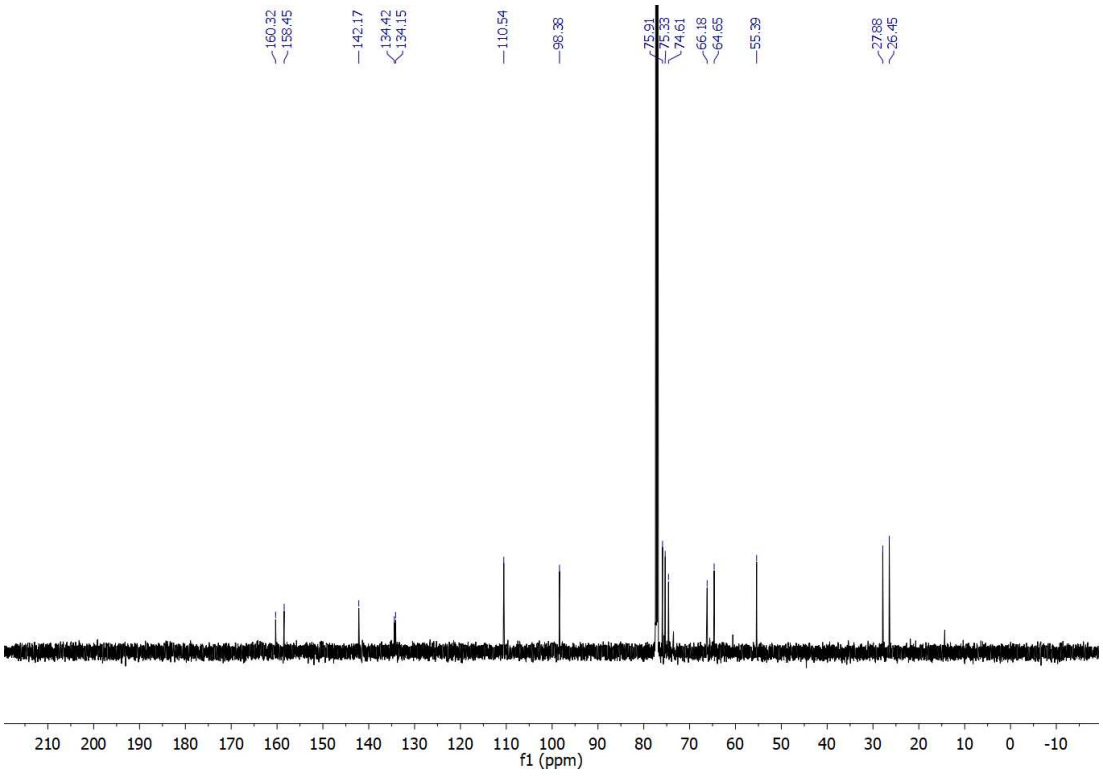
(3aS,4S,6R,7R,7aS)-4-methoxy-2,2-dimethyl-6-((pyrazin-2-yloxy)methyl)tetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-7-ol:



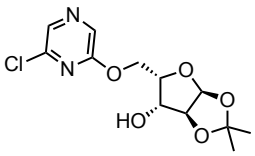


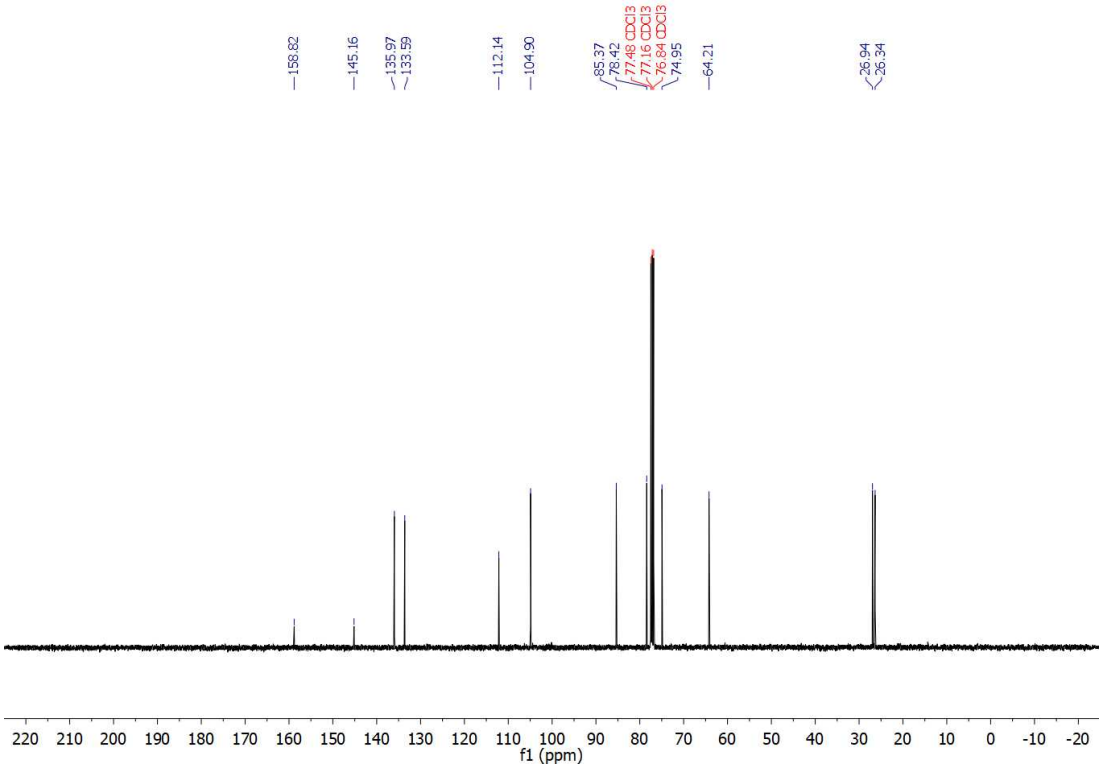
2-(((3aS,4S,6R,7R,7aS)-4-methoxy-2,2-dimethyl-6-((pyrazin-2-yloxy)methyl)tetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-7-yl)oxy)-2-oxoacetic acid:



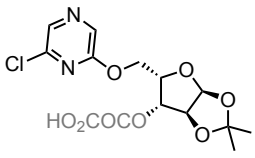


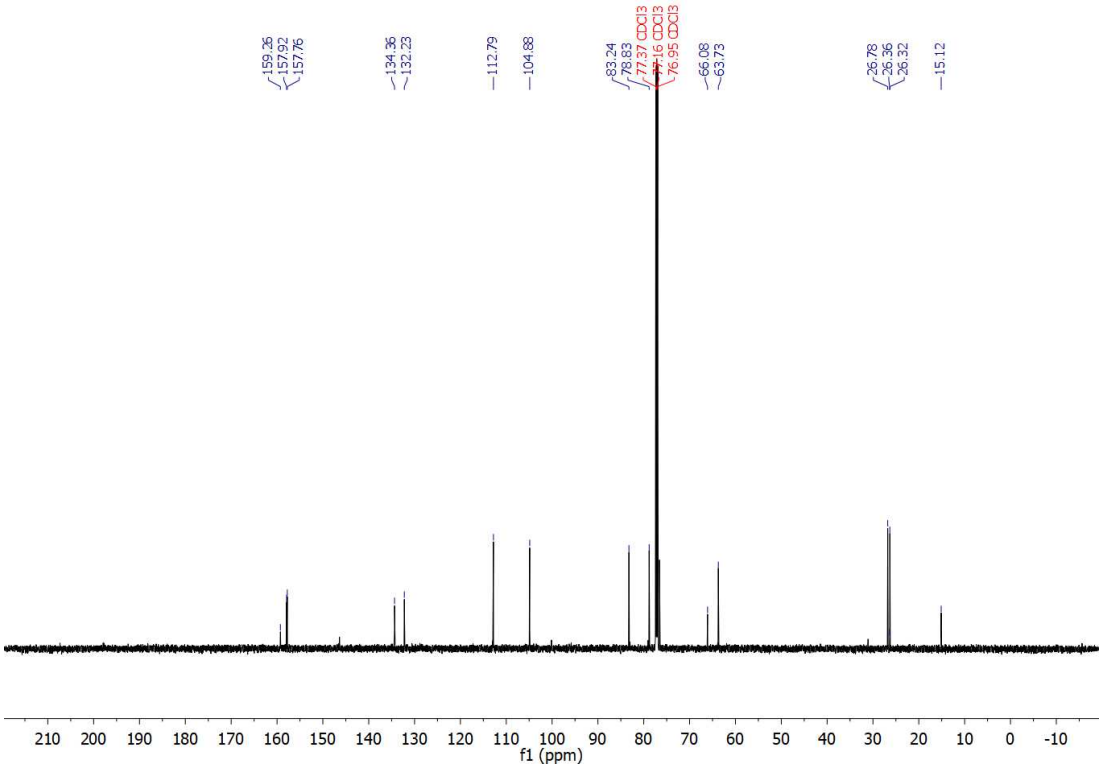
3aS,5S,6R,6aS)-5-(((6-chloropyrazin-2-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol:



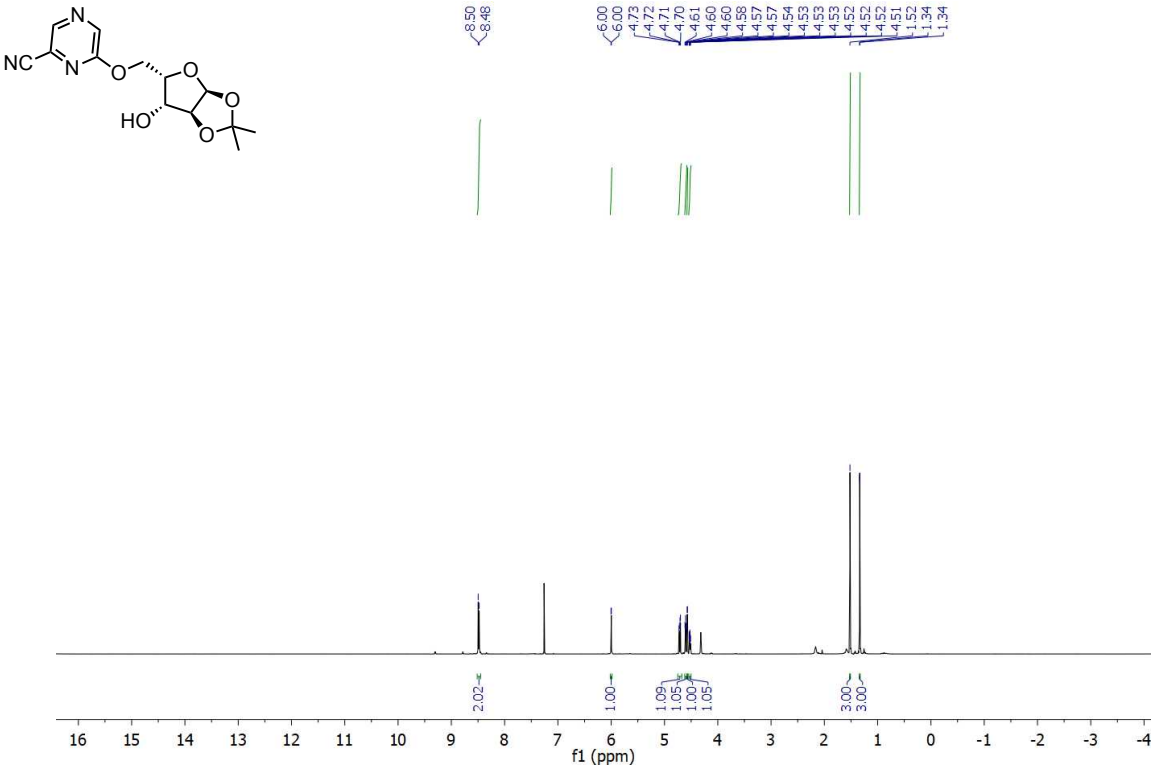


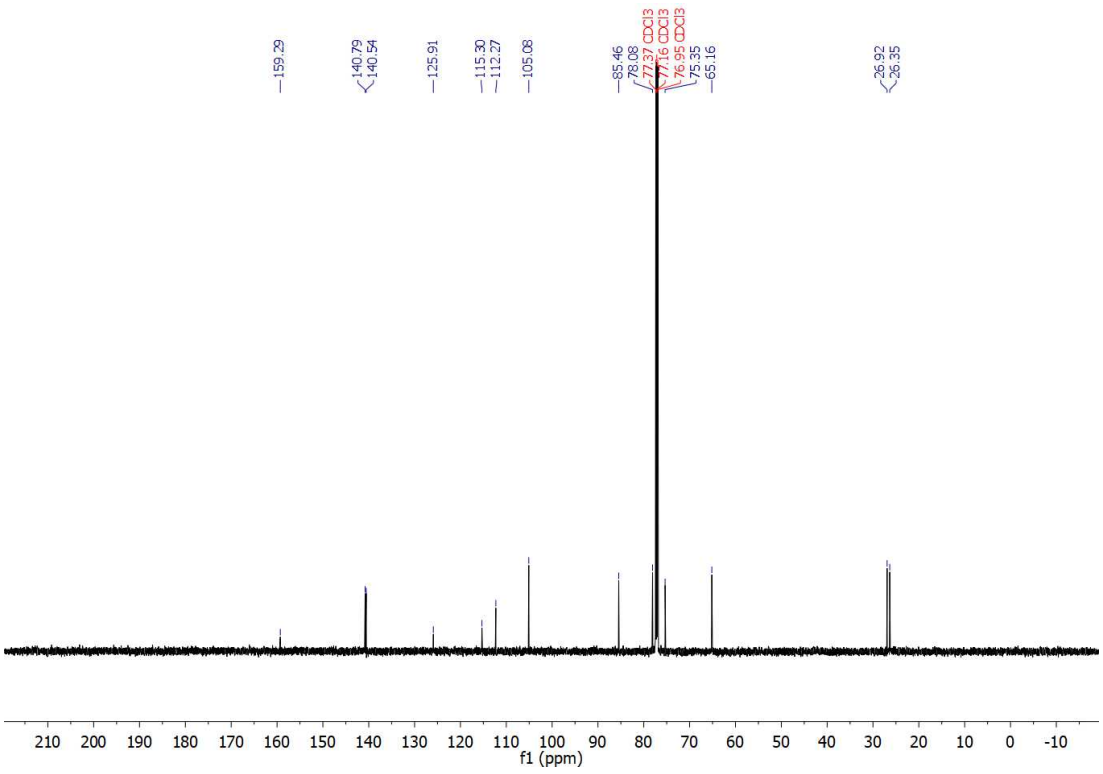
2-(((3a*S*,5*S*,6*R*,6a*S*)-5-(((6-chloropyrazin-2-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl)oxy)-2-oxoacetic acid:



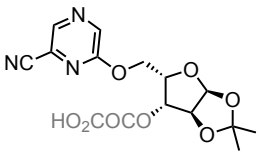


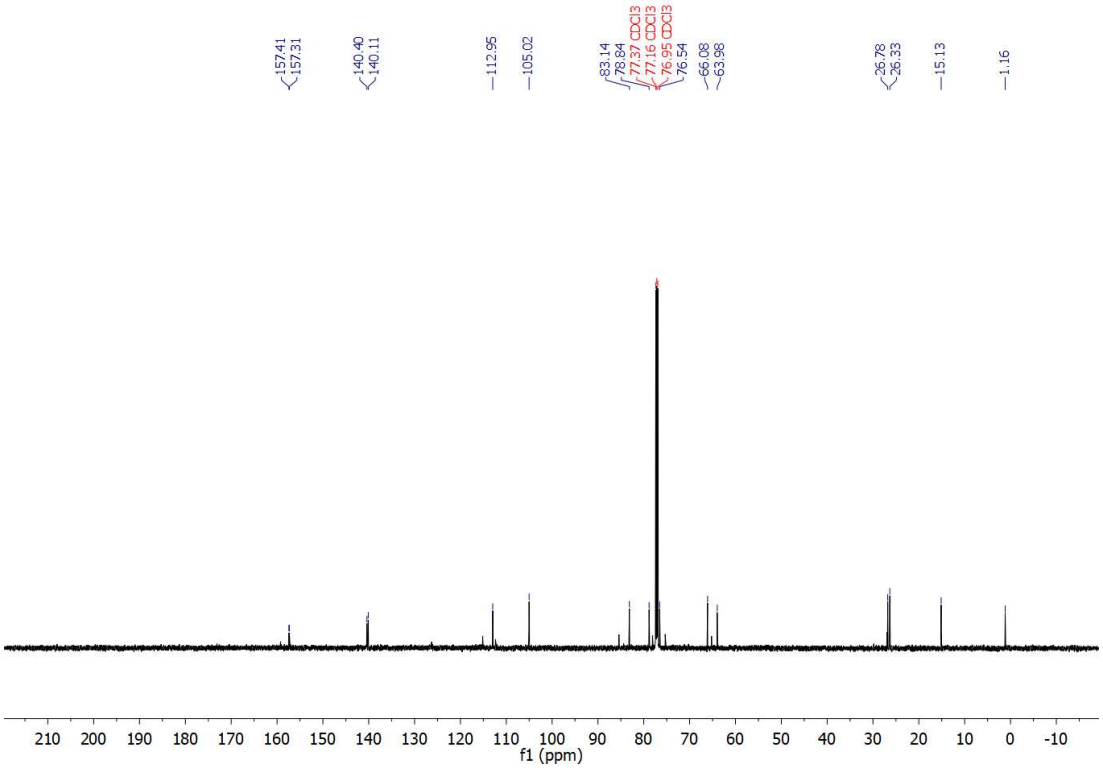
6-(((3aS,5S,6R,6aS)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methoxy)pyrazine-2-carbonitrile:



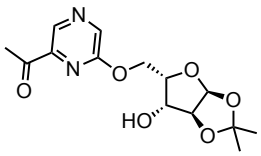


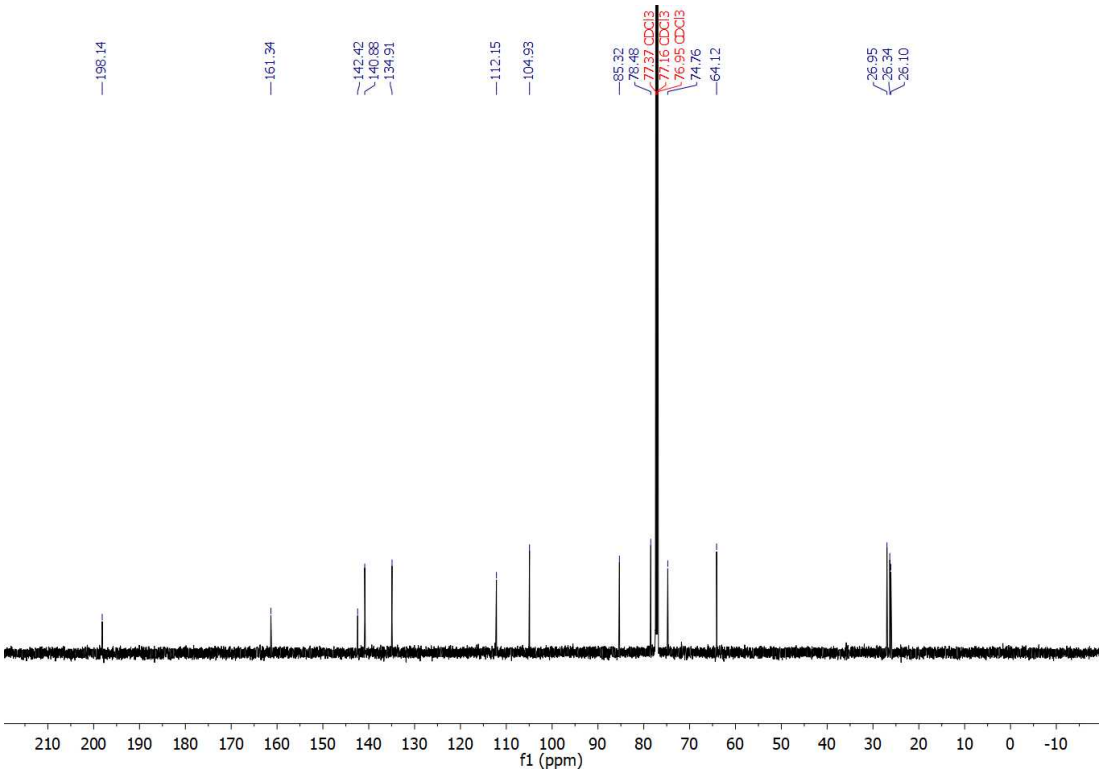
2-(((3aS,5S,6R,6aS)-5-(((6-cyanopyrazin-2-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)-2-oxoacetic acid:



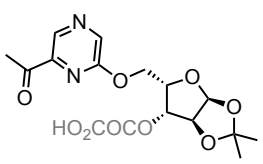


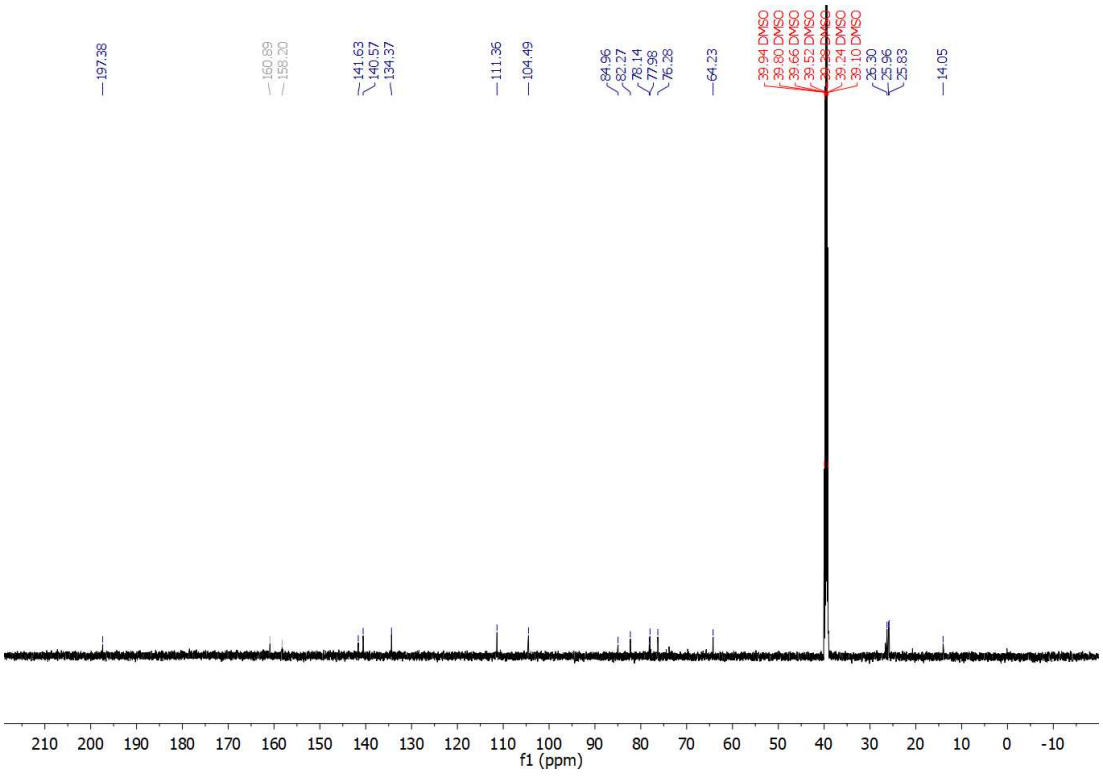
1-(6-(((3aS,5S,6R,6aS)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methoxy)pyrazin-2-yl)ethan-1-one:



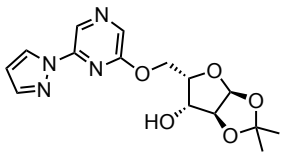


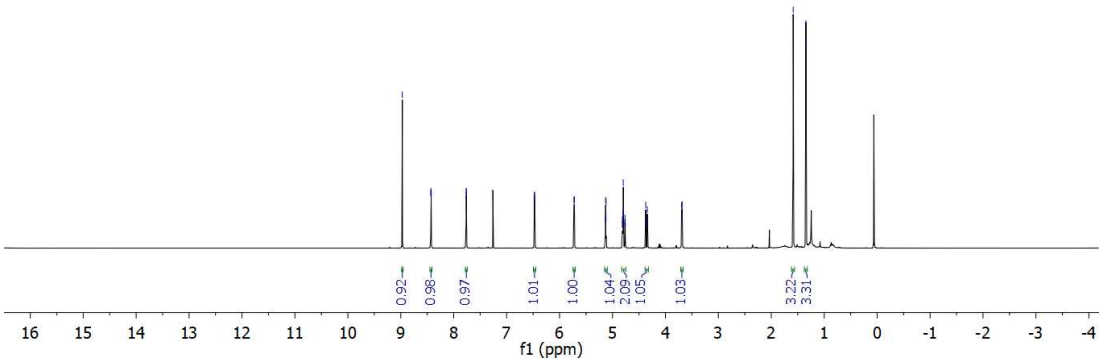
2-(((3aS,5S,6R,6aS)-5-(((6-acetylpyrazin-2-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)-2-oxoacetic acid:

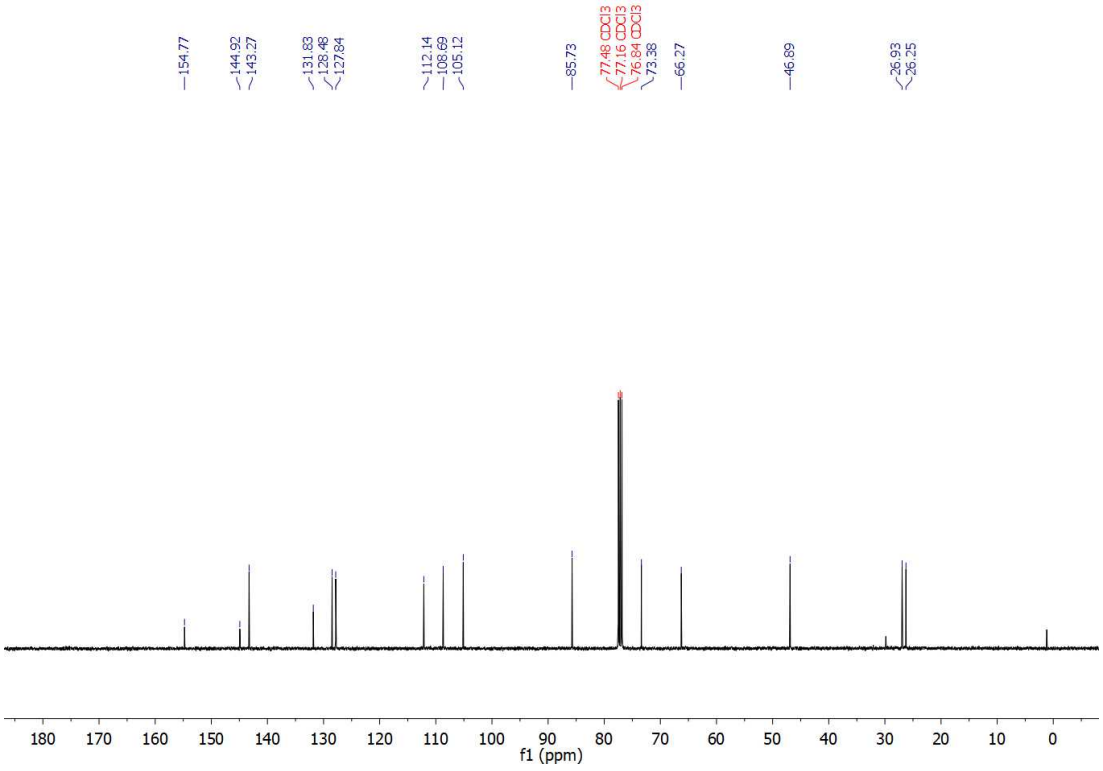




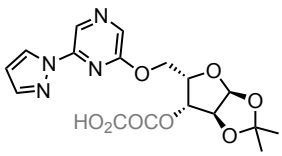
(3aS,5S,6R,6aS)-5-(((6-(1H-pyrazol-1-yl)pyrazin-2-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol:

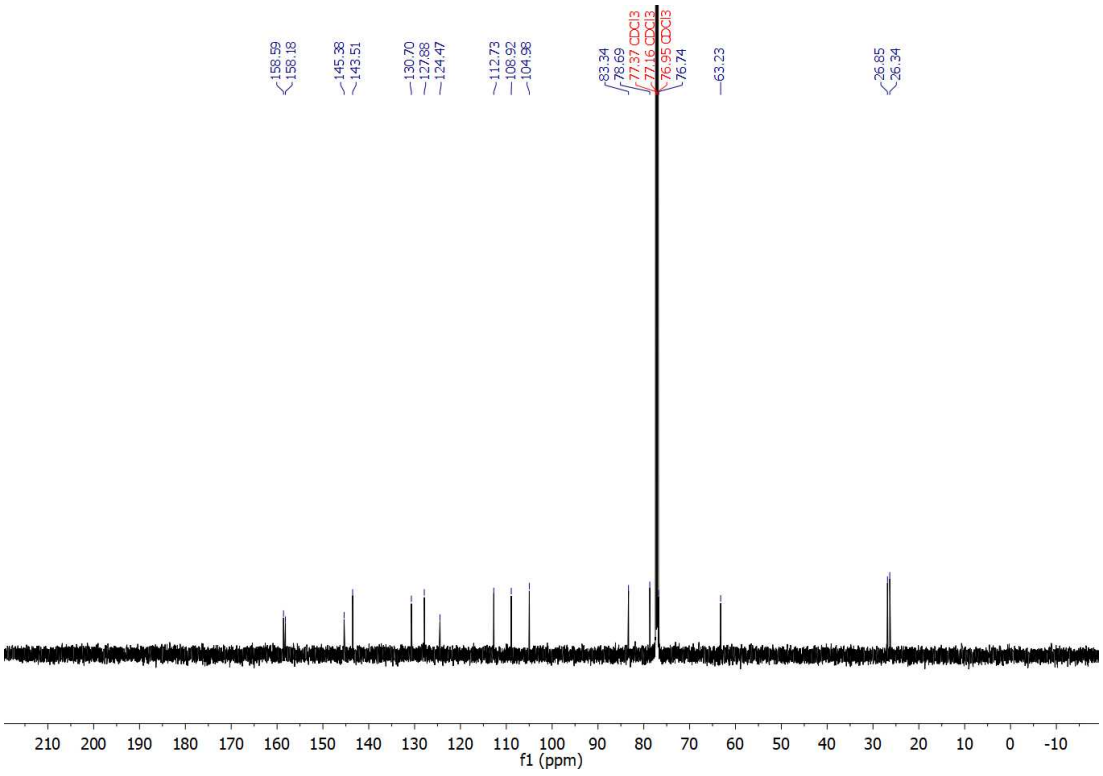




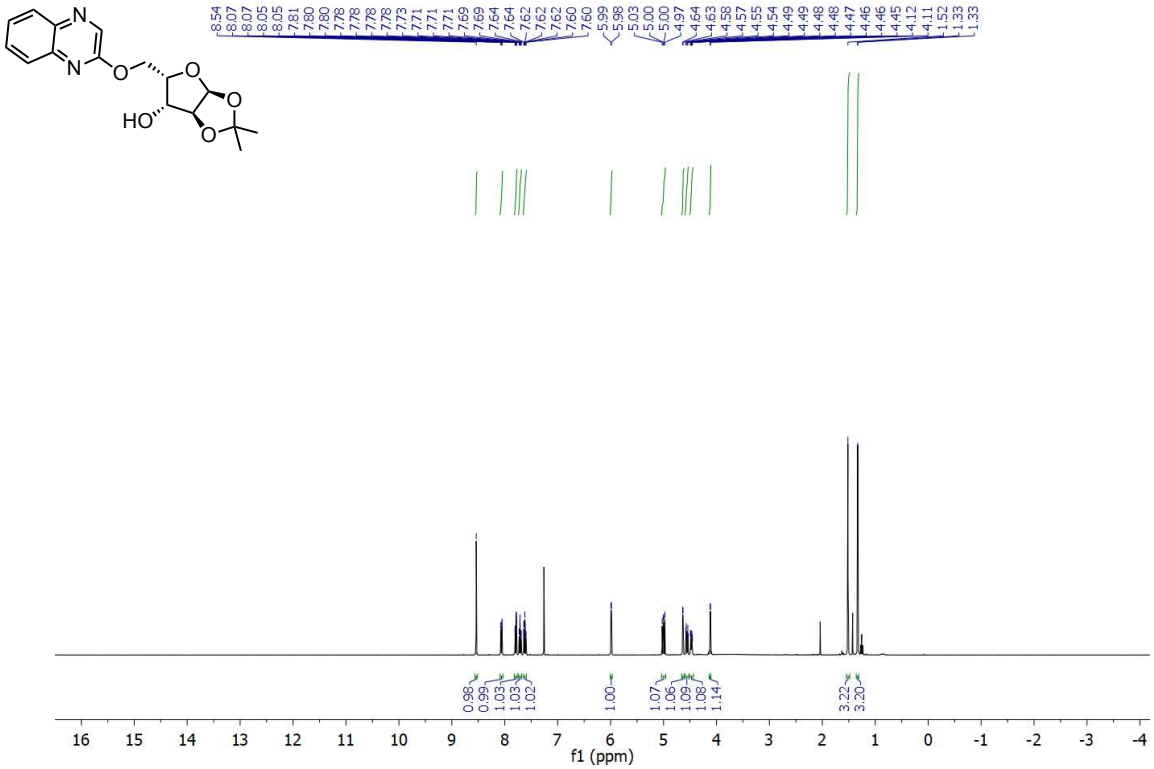


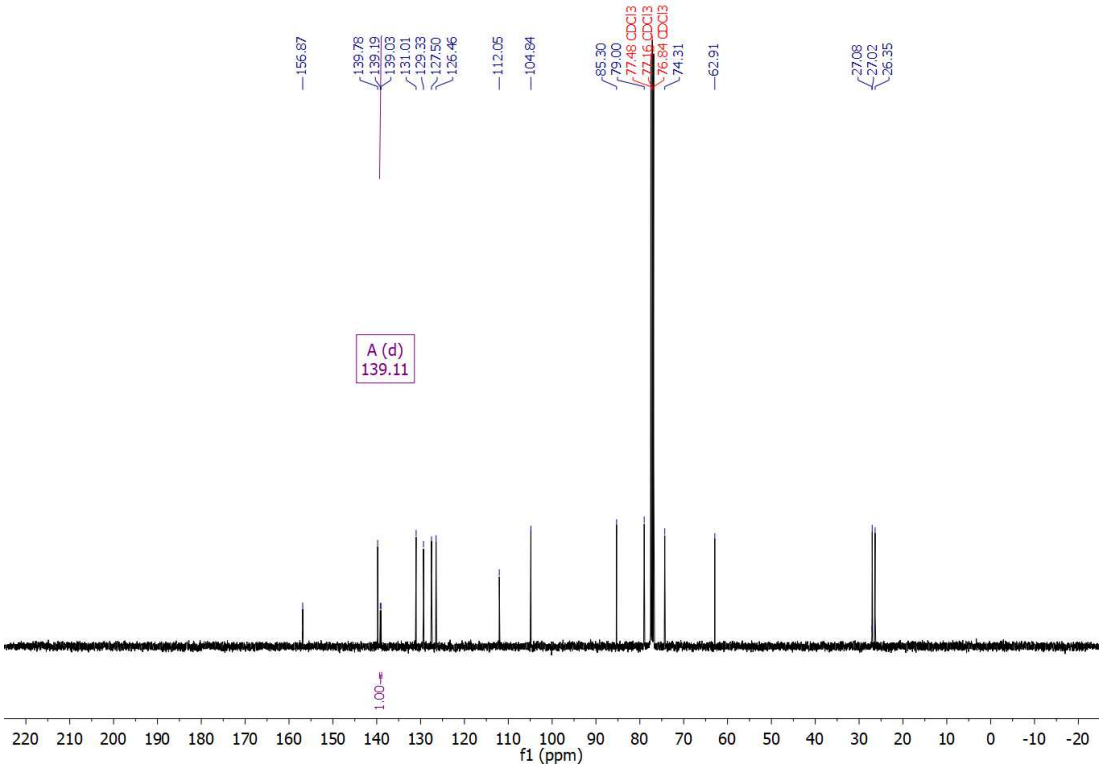
2-(((3aS,5S,6R,6aS)-5-(((6-(1H-pyrazol-1-yl)pyrazin-2-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)-2-oxoacetic acid:



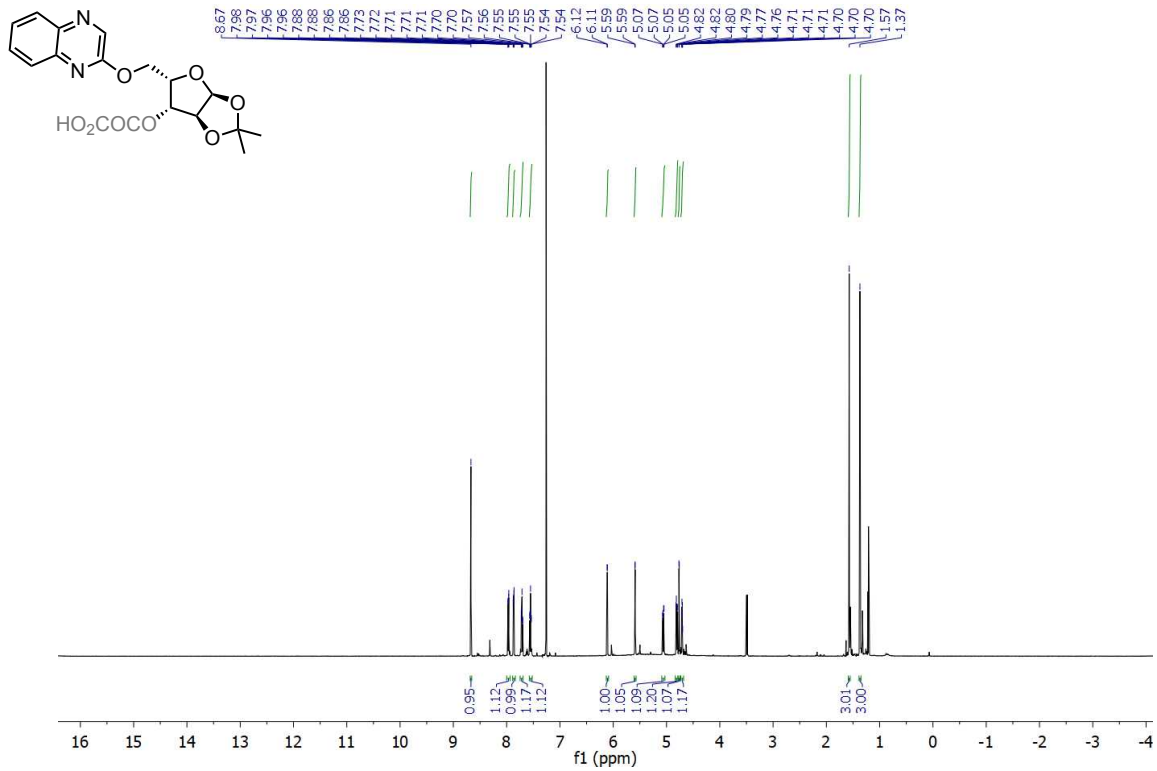


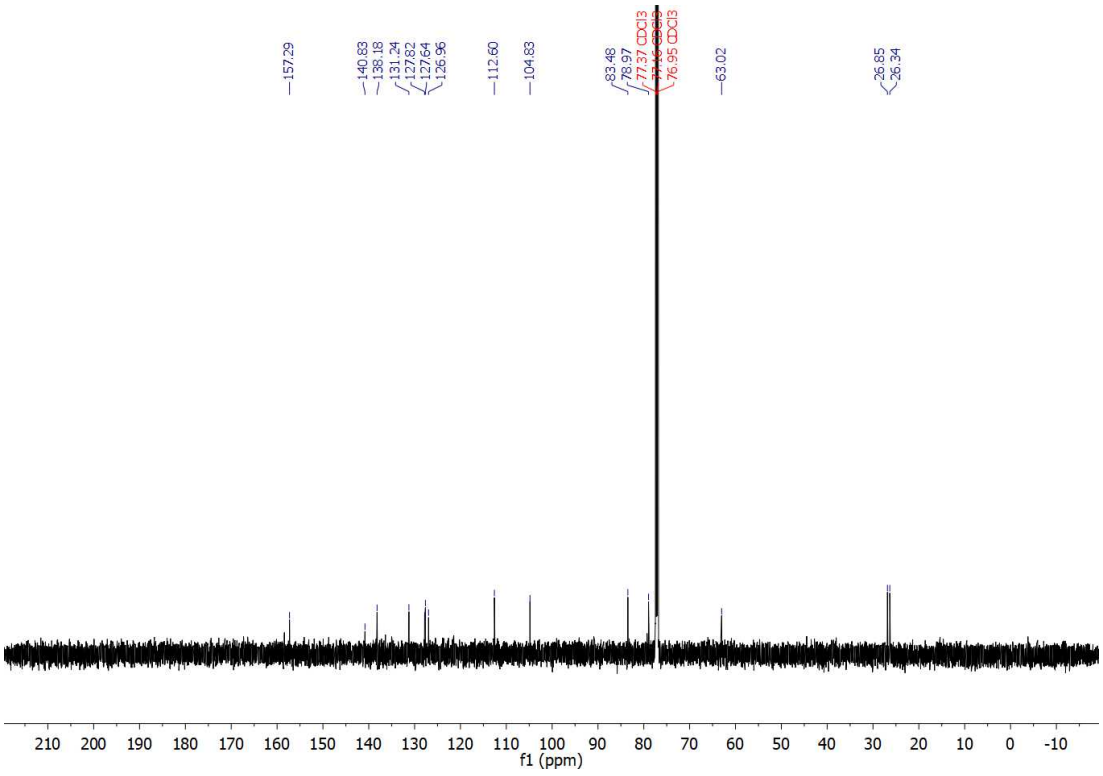
(3aS,5S,6R,6aS)-2,2-dimethyl-5-((quinoxalin-2-yloxy)methyl)tetrahydrofuro[2,3-d][1,3]dioxol-6-ol:



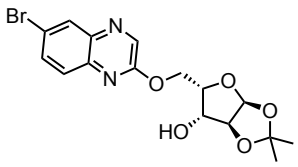


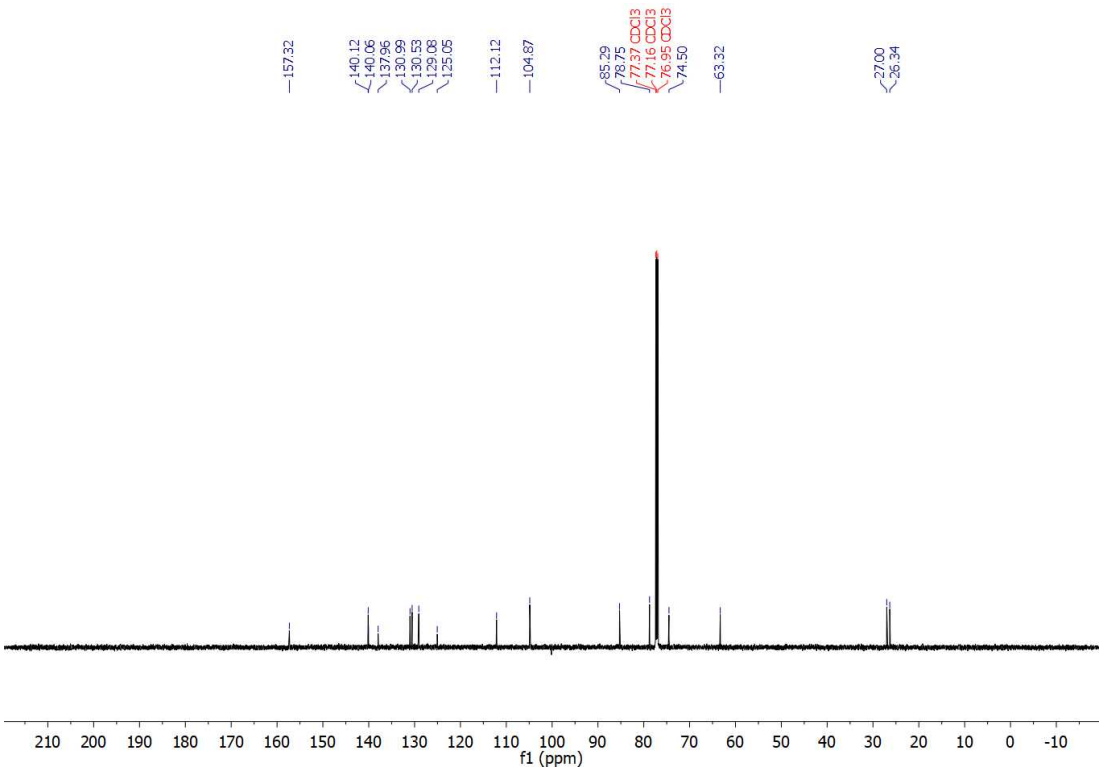
2-(((3aS,5S,6R,6aS)-2,2-dimethyl-5-((quinoxalin-2-yloxy)methyl)tetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)-2-oxoacetic acid:



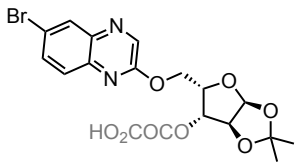


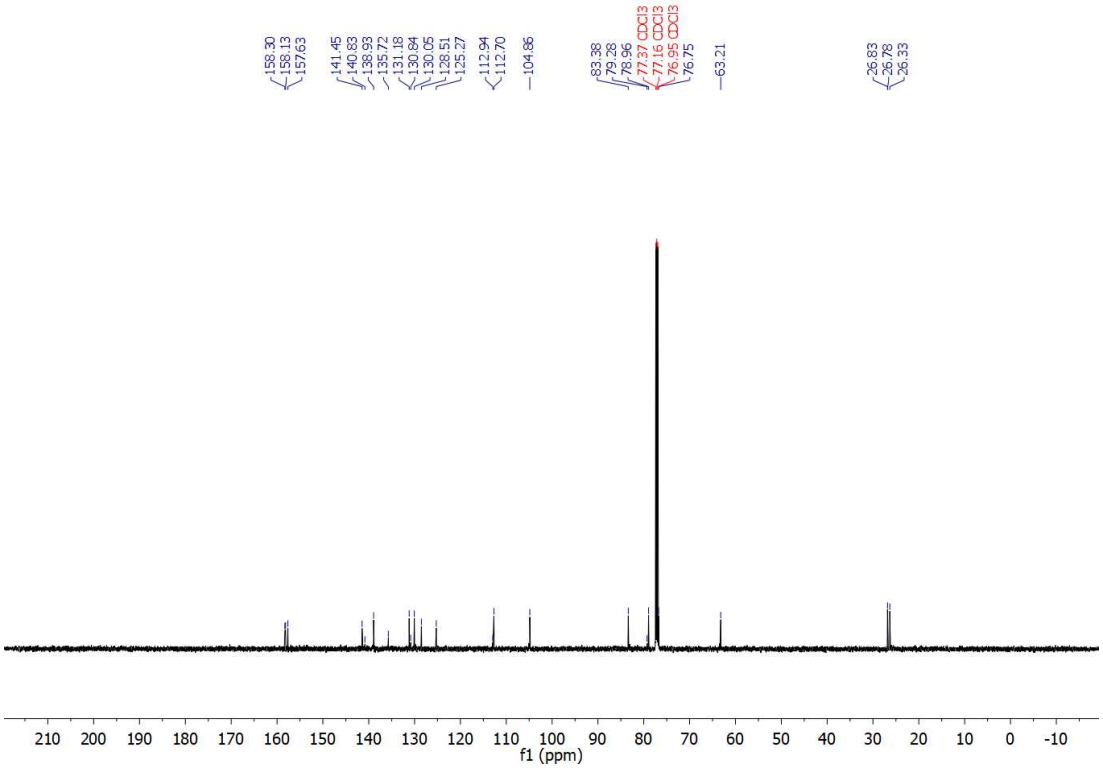
(3aS,5S,6R,6aS)-5-(((6-bromoquinoxalin-2-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol:



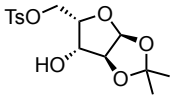


2-(((3aS,5S,6R,6aS)-5-(((6-bromoquinoxalin-2-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)-2-oxoacetic acid:

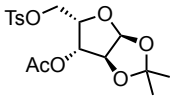




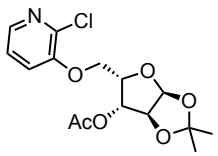
((3aS,5S,6R,6aS)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methyl 4-methylbenzenesulfonate:

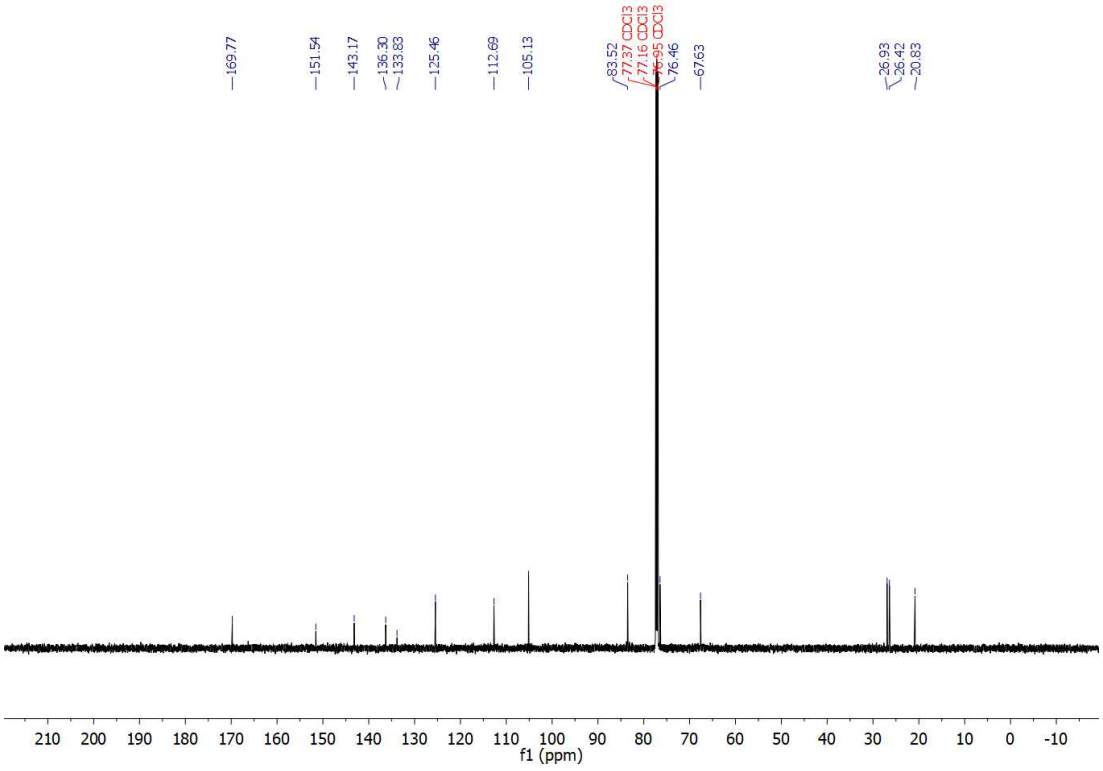


(3aS,5S,6R,6aS)-2,2-dimethyl-5-((tosyloxy)methyl)tetrahydrofuro[2,3-d][1,3]dioxol-6-yl acetate:

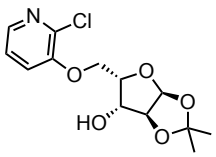


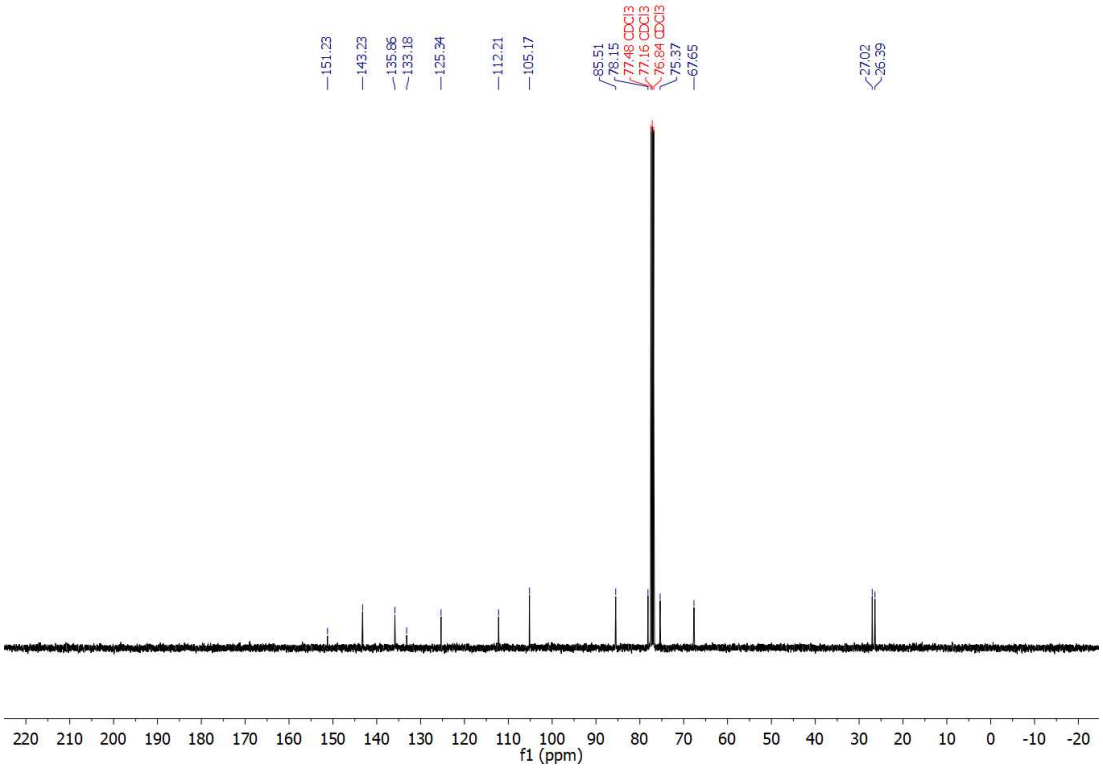
(3aS,5S,6R,6aS)-5-(((2-chloropyridin-3-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl acetate:



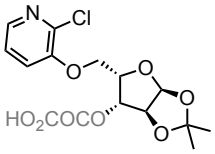


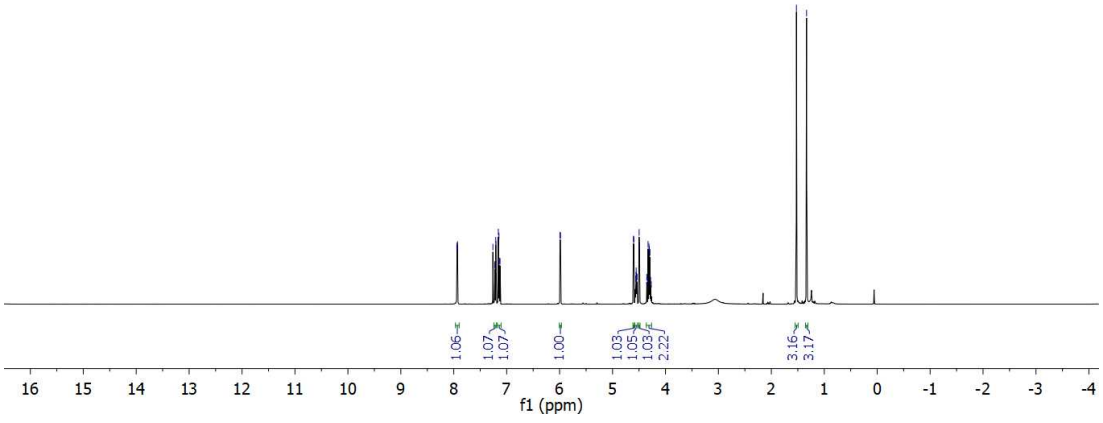
(3aS,5S,6R,6aS)-5-(((2-chloropyridin-3-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol:

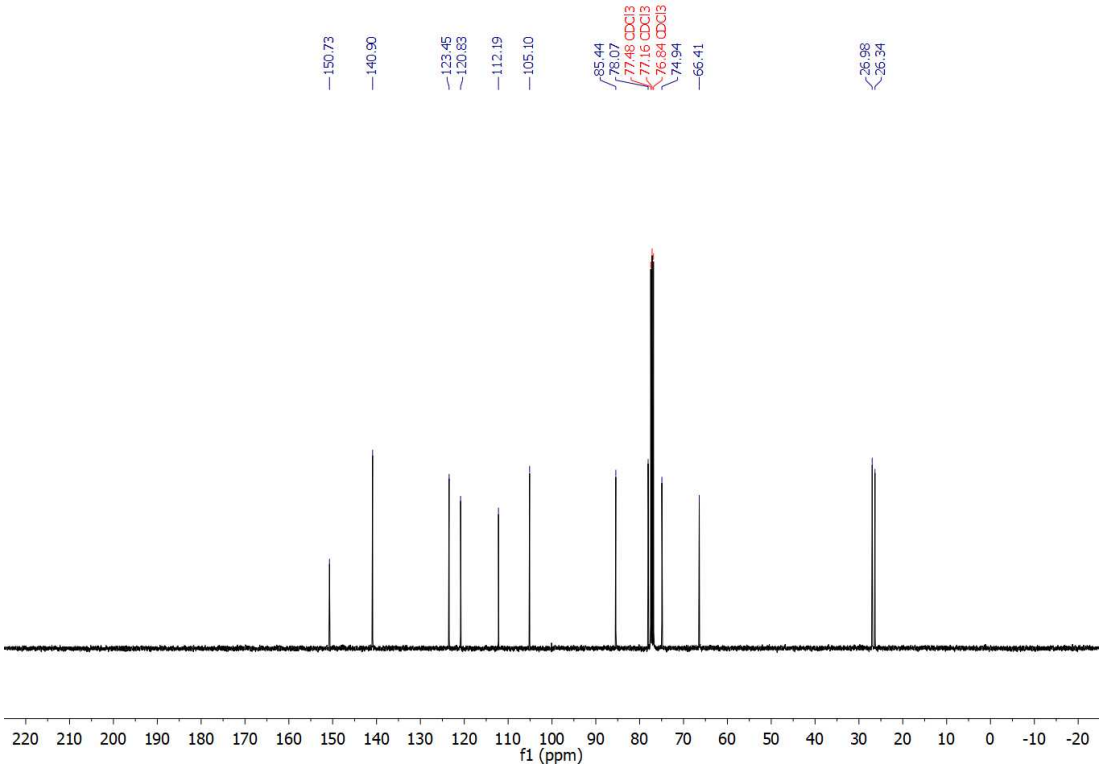




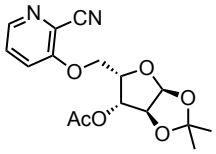
2-(((3aS,5S,6R,6aS)-5-(((2-chloropyridin-3-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)-2-oxoacetic acid:

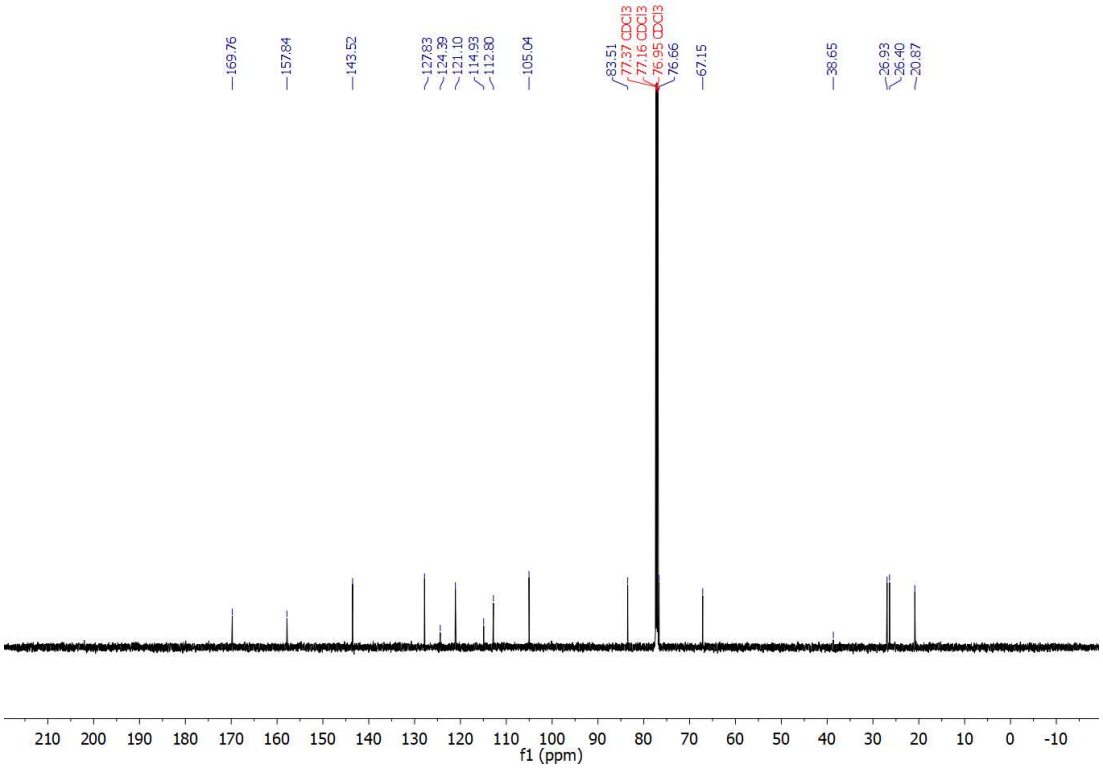




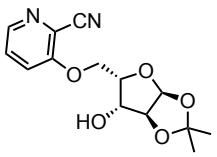


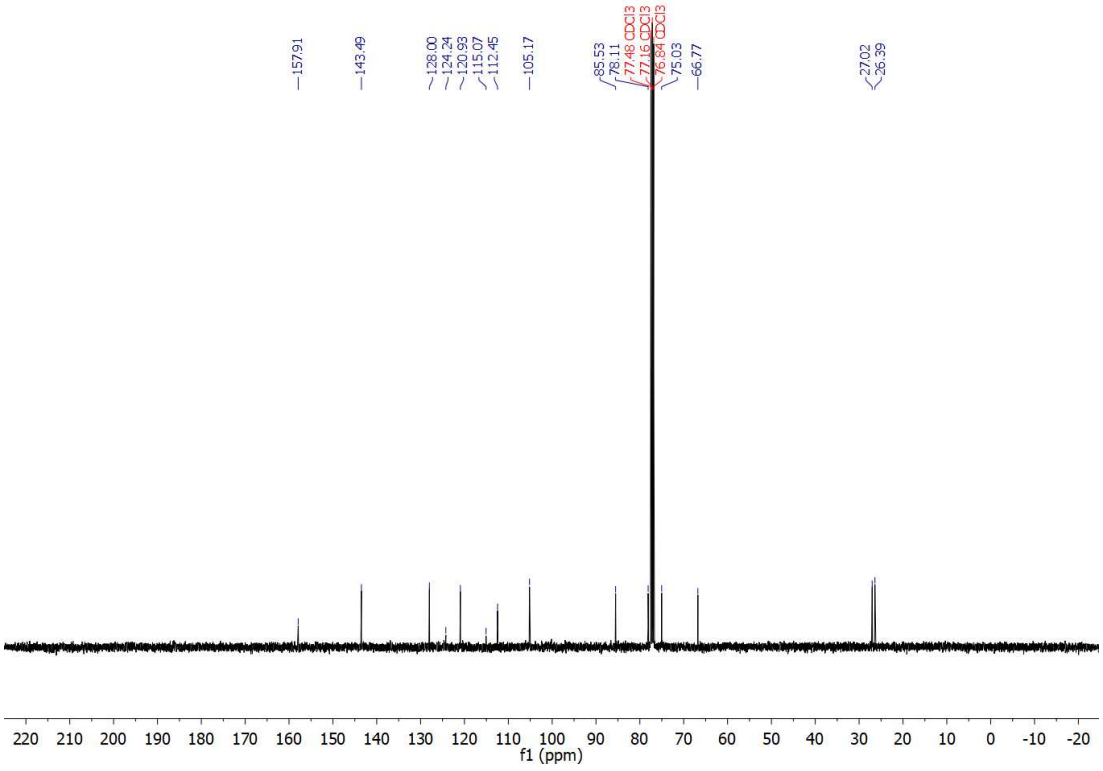
(3aS,5S,6R,6aS)-5-(((2-chloropyridin-3-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl acetate:



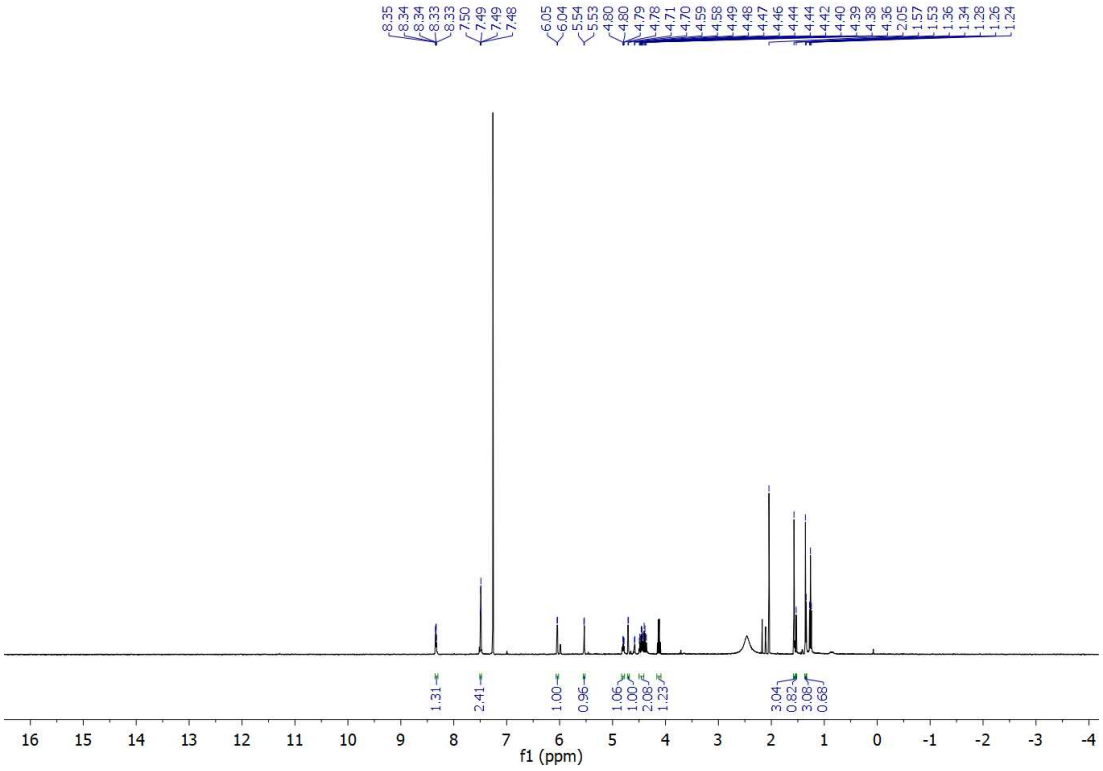


3-(((3aS,5S,6R,6aS)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methoxy)picolinonitrile:

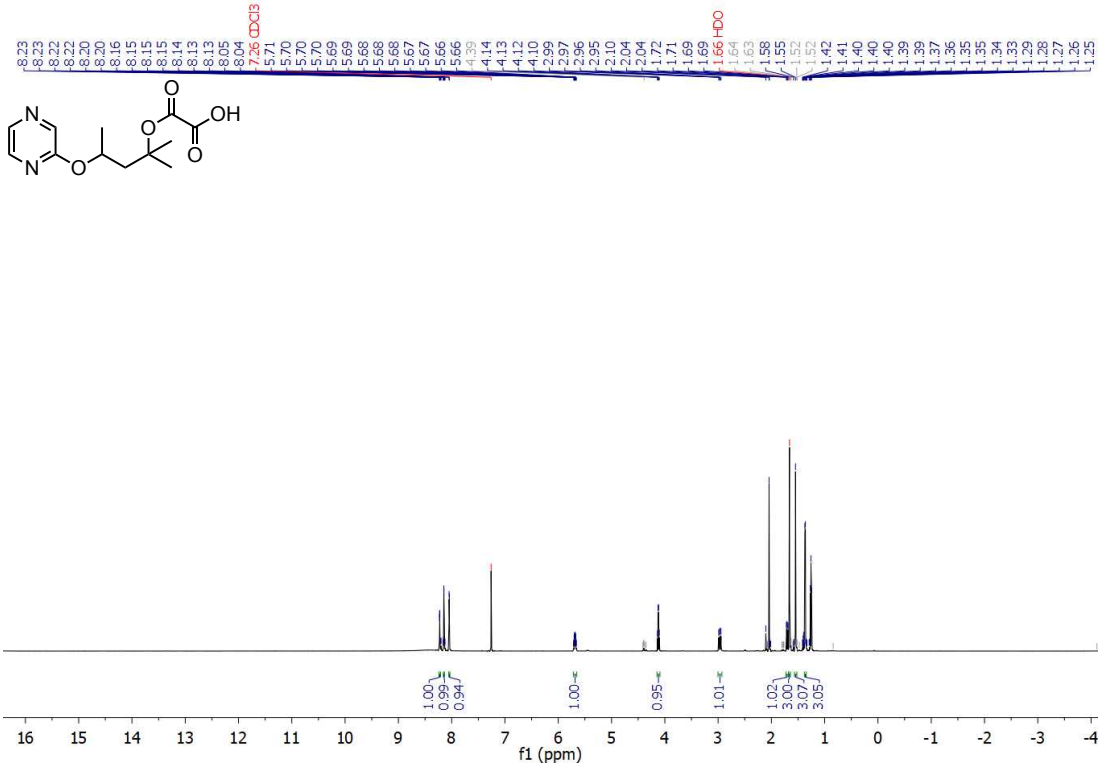




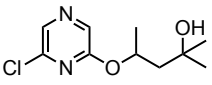
2-(((3aS,5S,6R,6aS)-5-(((2-cyanopyridin-3-yl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)-2-oxoacetic acid:

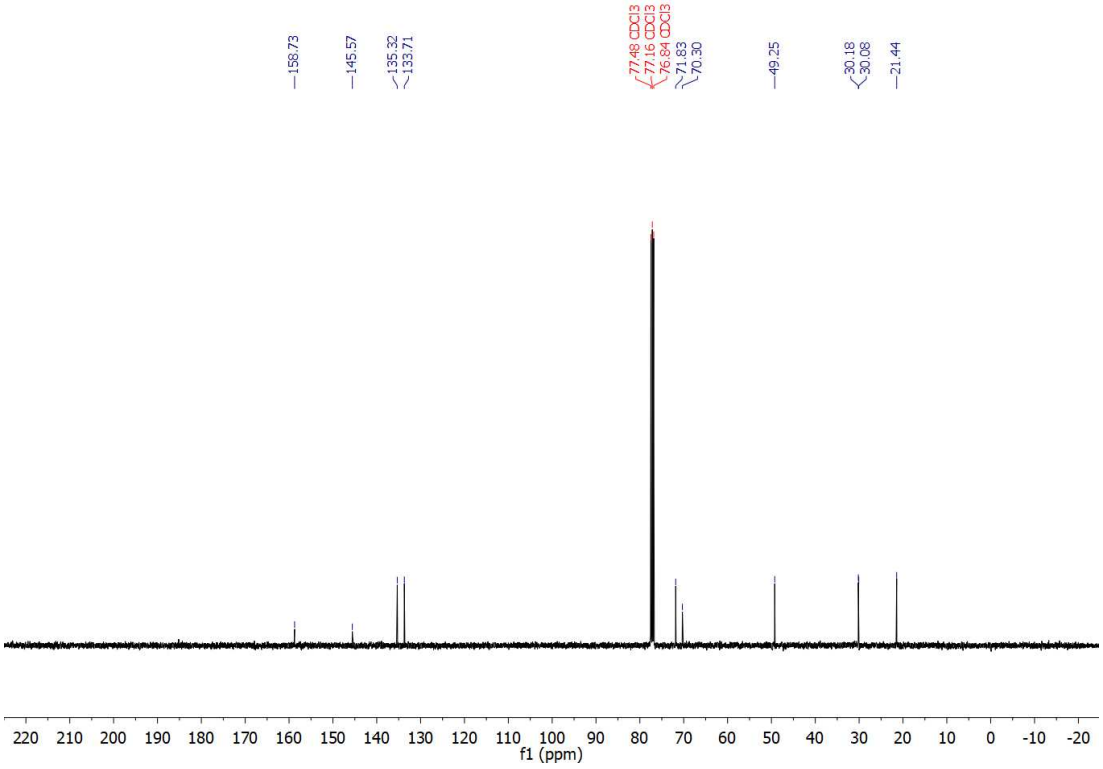


2-((2-methyl-4-(pyrazin-2-yloxy)pentan-2-yl)oxy)-2-oxoacetic acid:

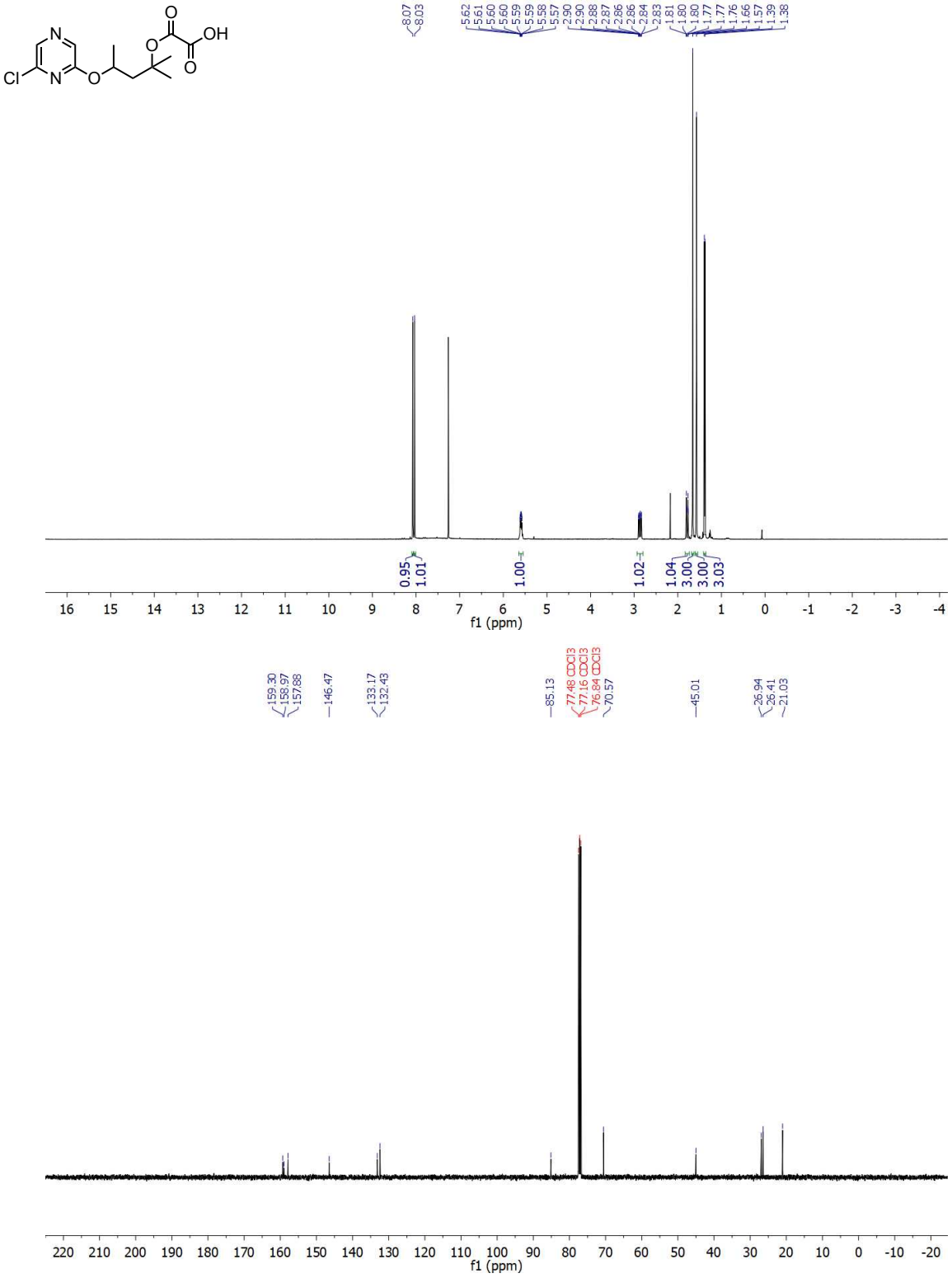


4-((6-chloropyrazin-2-yl)oxy)-2-methylpentan-2-ol:

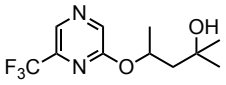


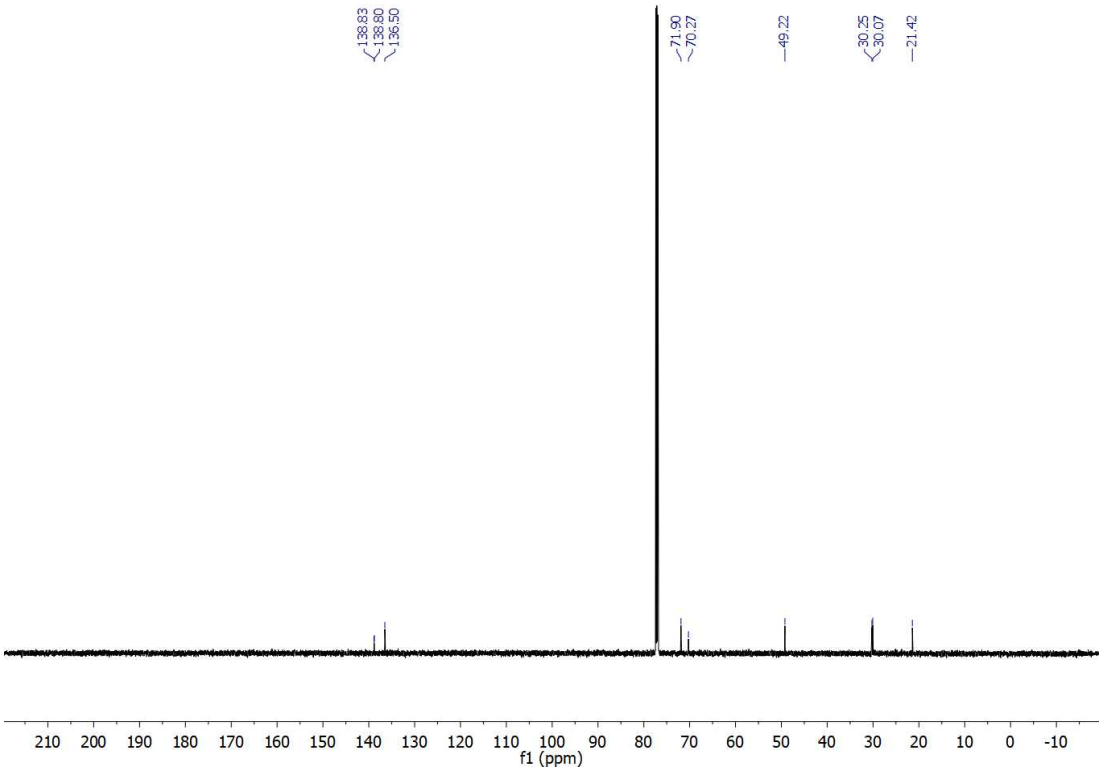


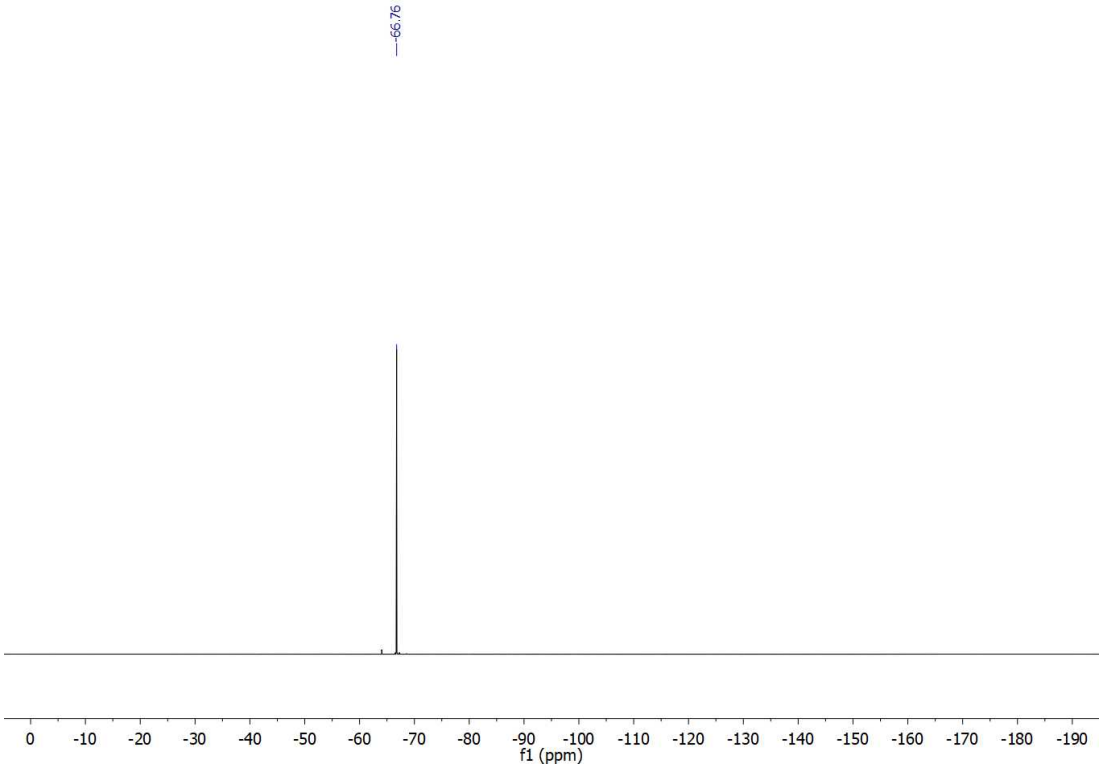
2-((4-((6-chloropyrazin-2-yl)oxy)-2-methylpentan-2-yl)oxy)-2-oxoacetic acid:



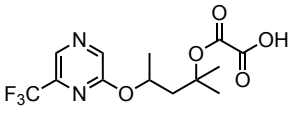
2-methyl-4-((5-(trifluoromethyl)pyrazin-2-yl)oxy)pentan-2-ol:

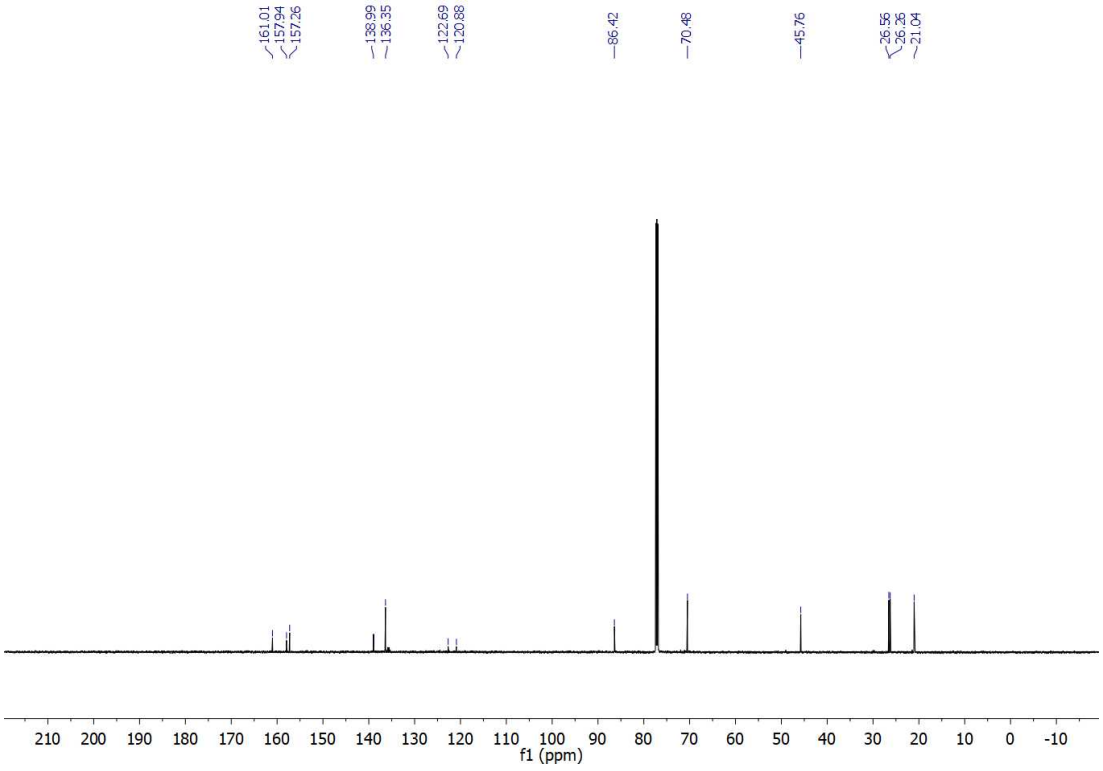






2-((2-methyl-4-((5-(trifluoromethyl)pyrazin-2-yl)oxy)pentan-2-yl)oxy)-2-oxoacetic acid:

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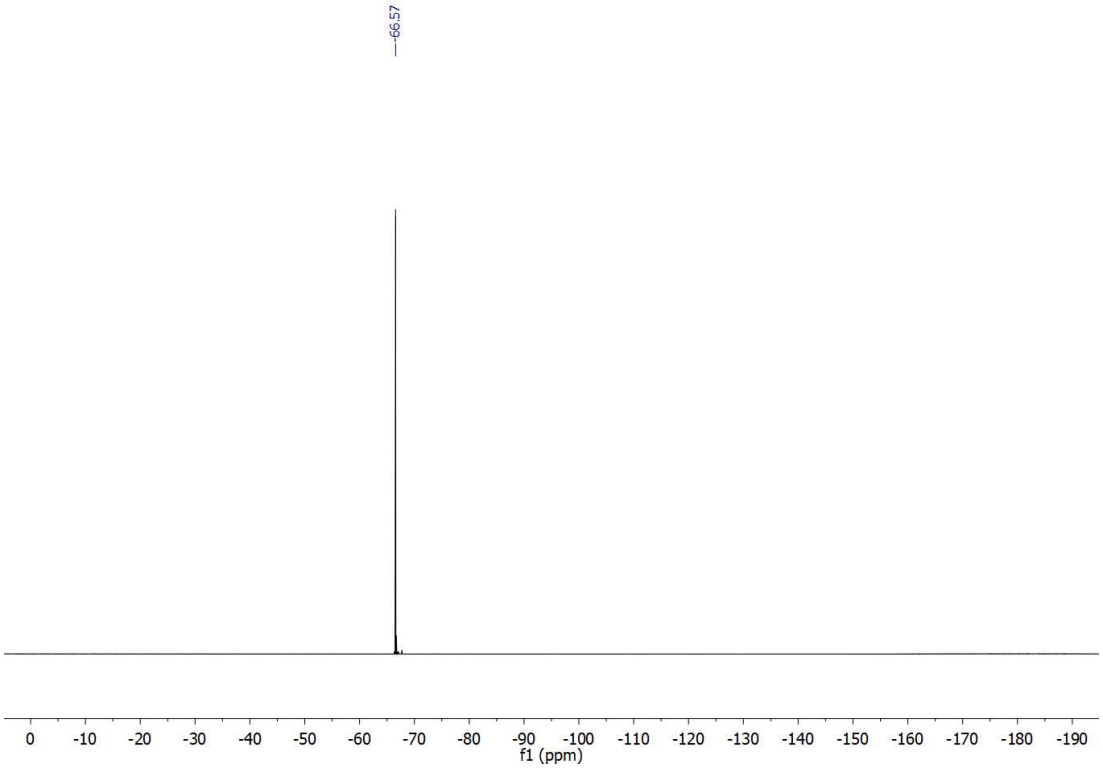
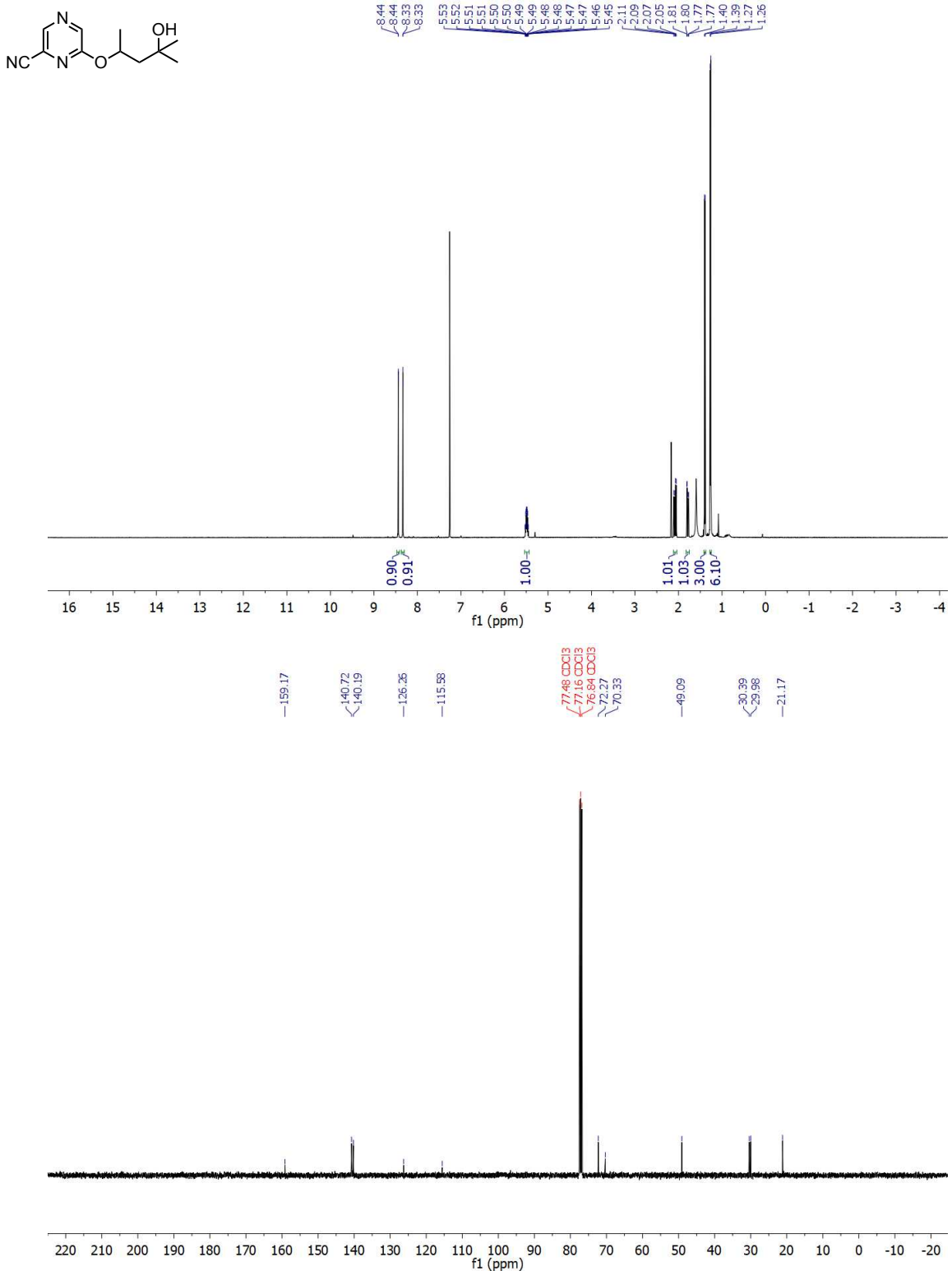
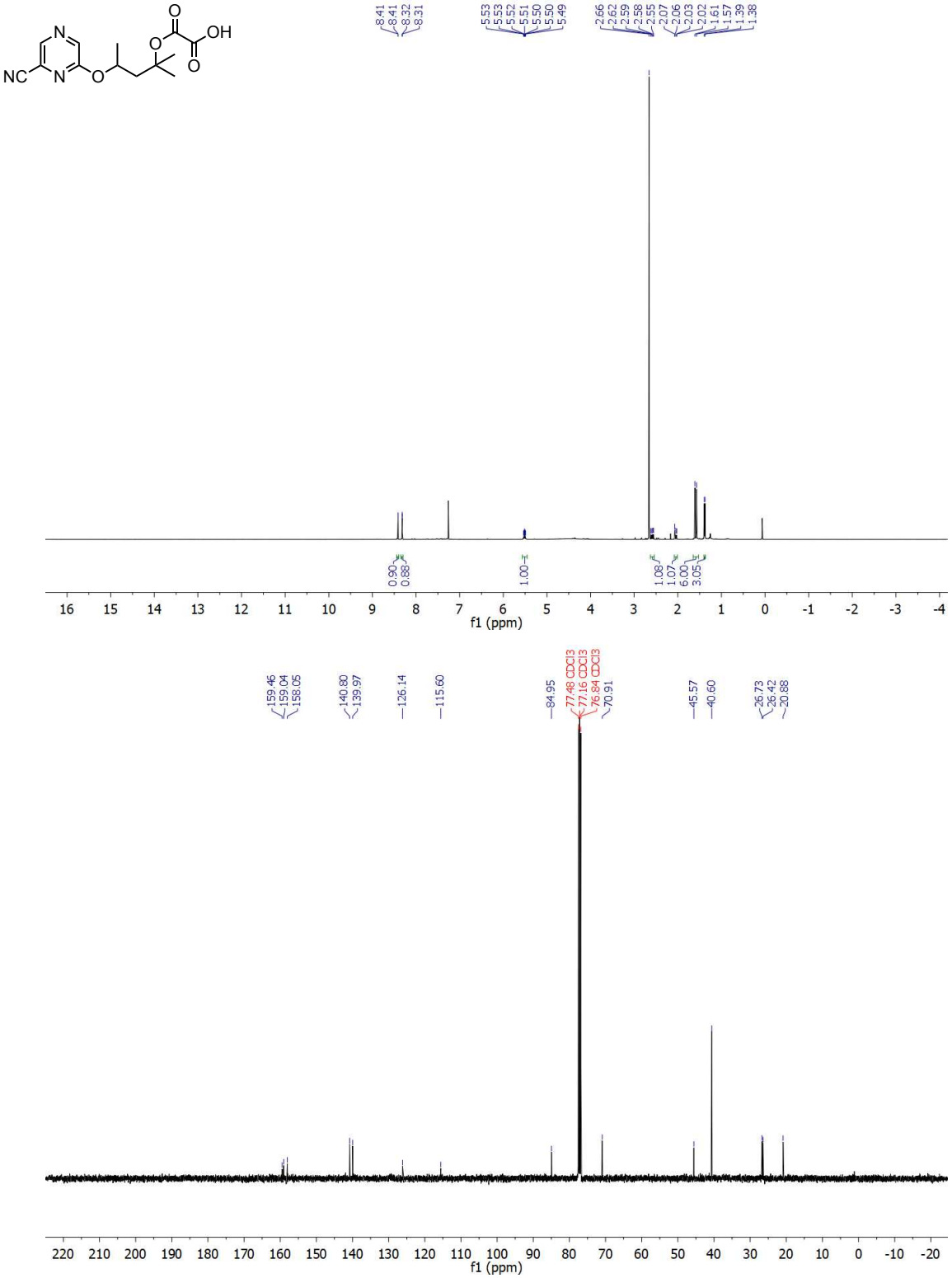
157.94
157.26
138.99
136.35
122.69
120.88
86.42
70.48
45.76
26.56
26.26
21.04
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


66.57
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

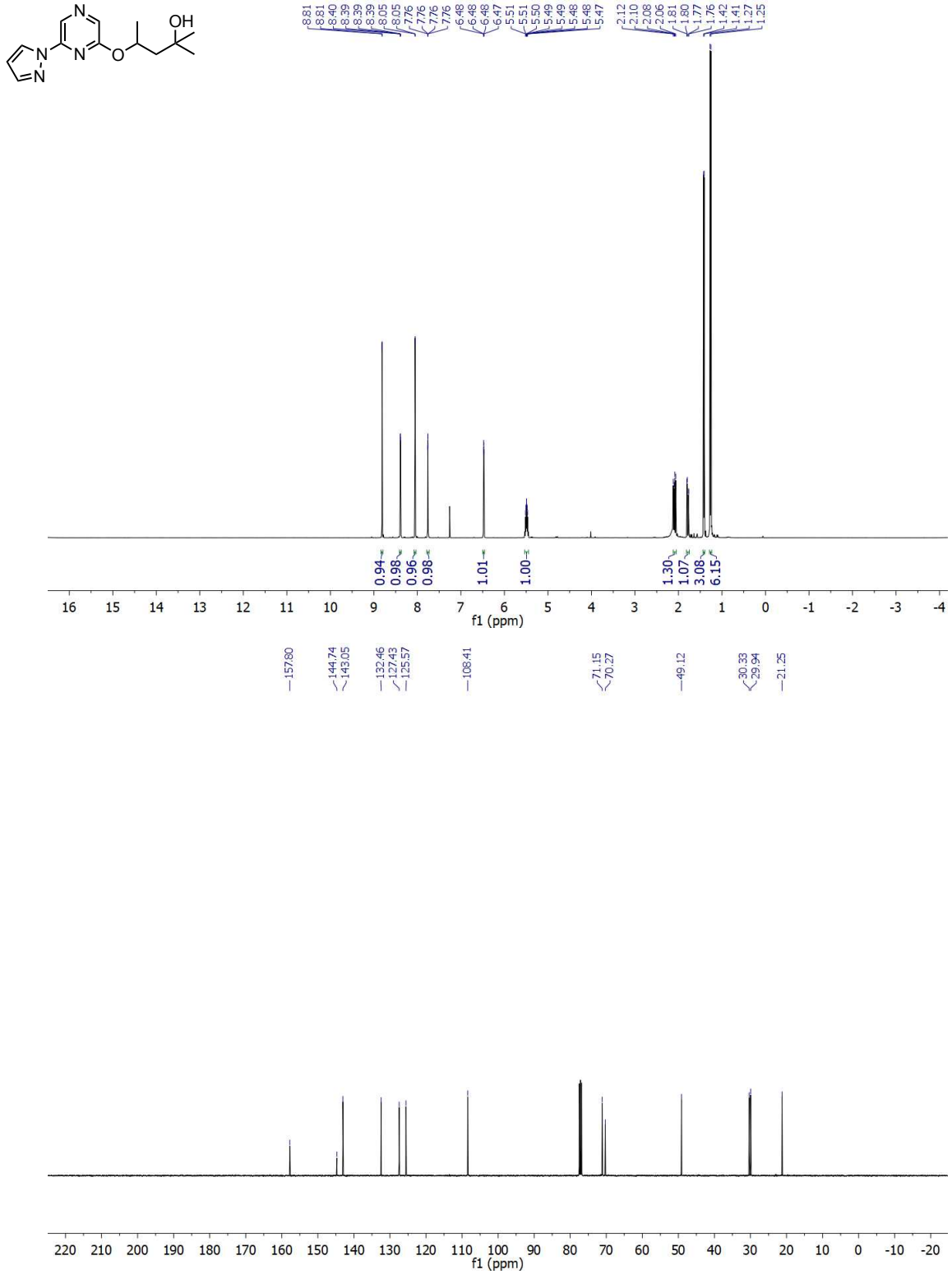
6-((4-hydroxy-4-methylpentan-2-yl)oxy)pyrazine-2-carbonitrile:



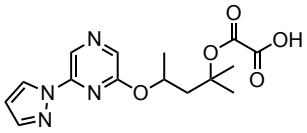
2-((4-((6-cyanopyrazin-2-yl)oxy)-2-methylpentan-2-yl)oxy)-2-oxoacetic acid:

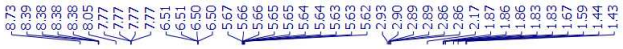


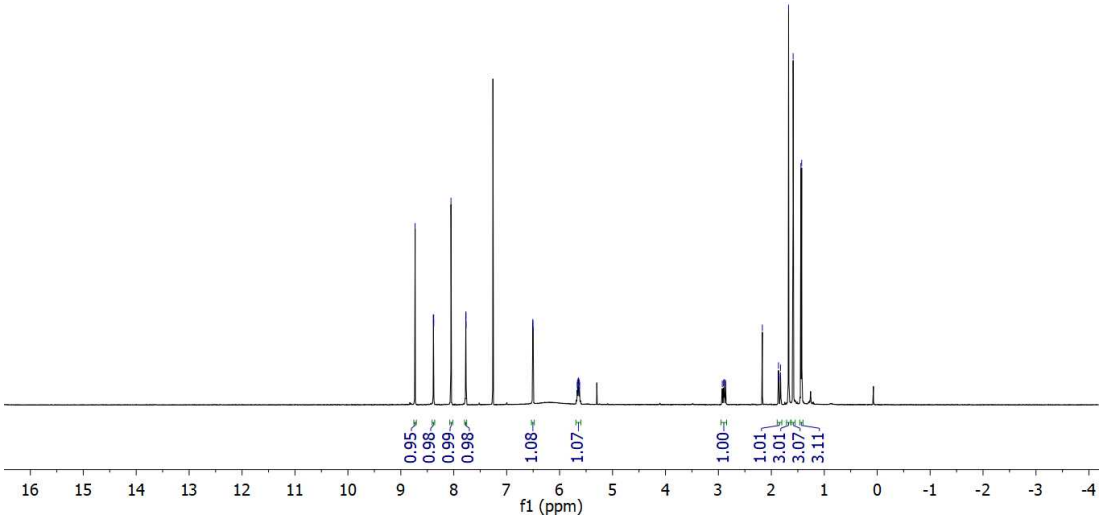
((6-(1H-pyrazol-1-yl)pyrazin-2-yl)oxy)-2-methylpentan-2-ol:

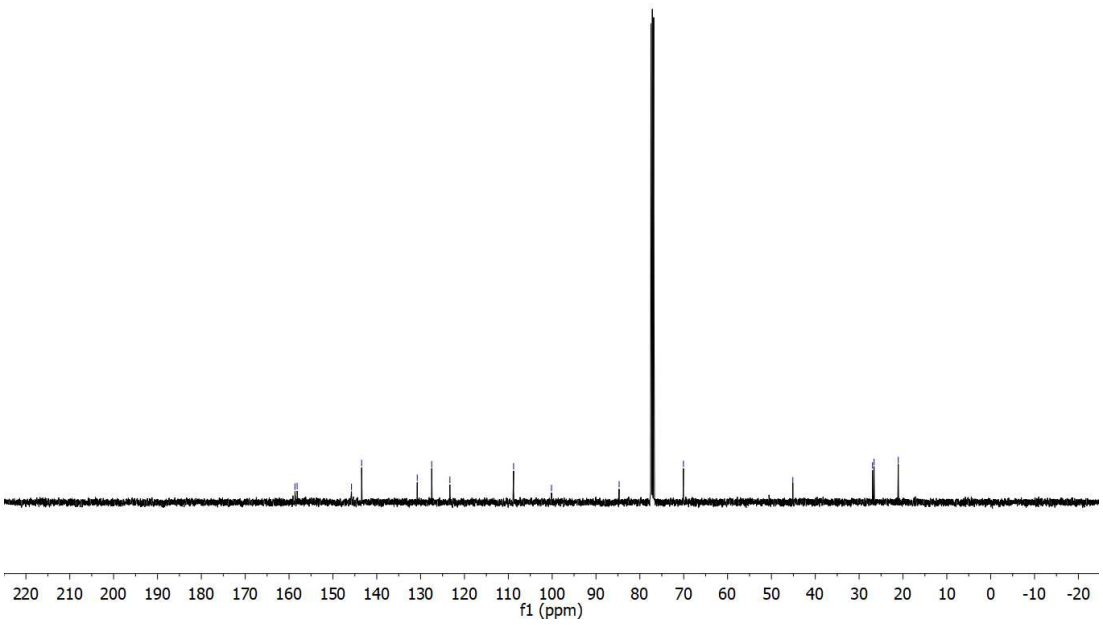


2-((4-((6-(1H-pyrazol-1-yl)pyrazin-2-yl)oxy)-2-methylpentan-2-yl)oxy)-2-oxoacetic acid:

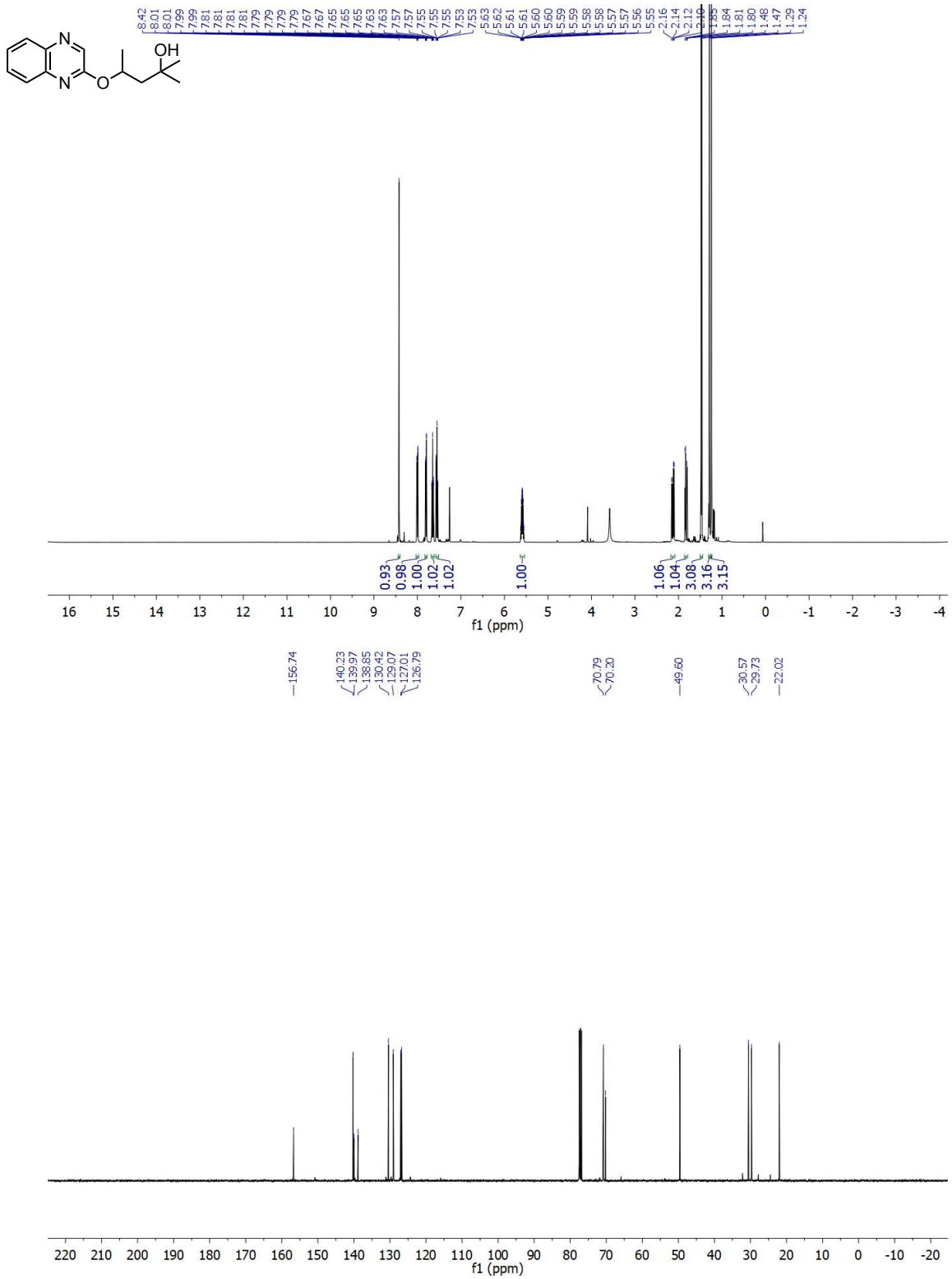




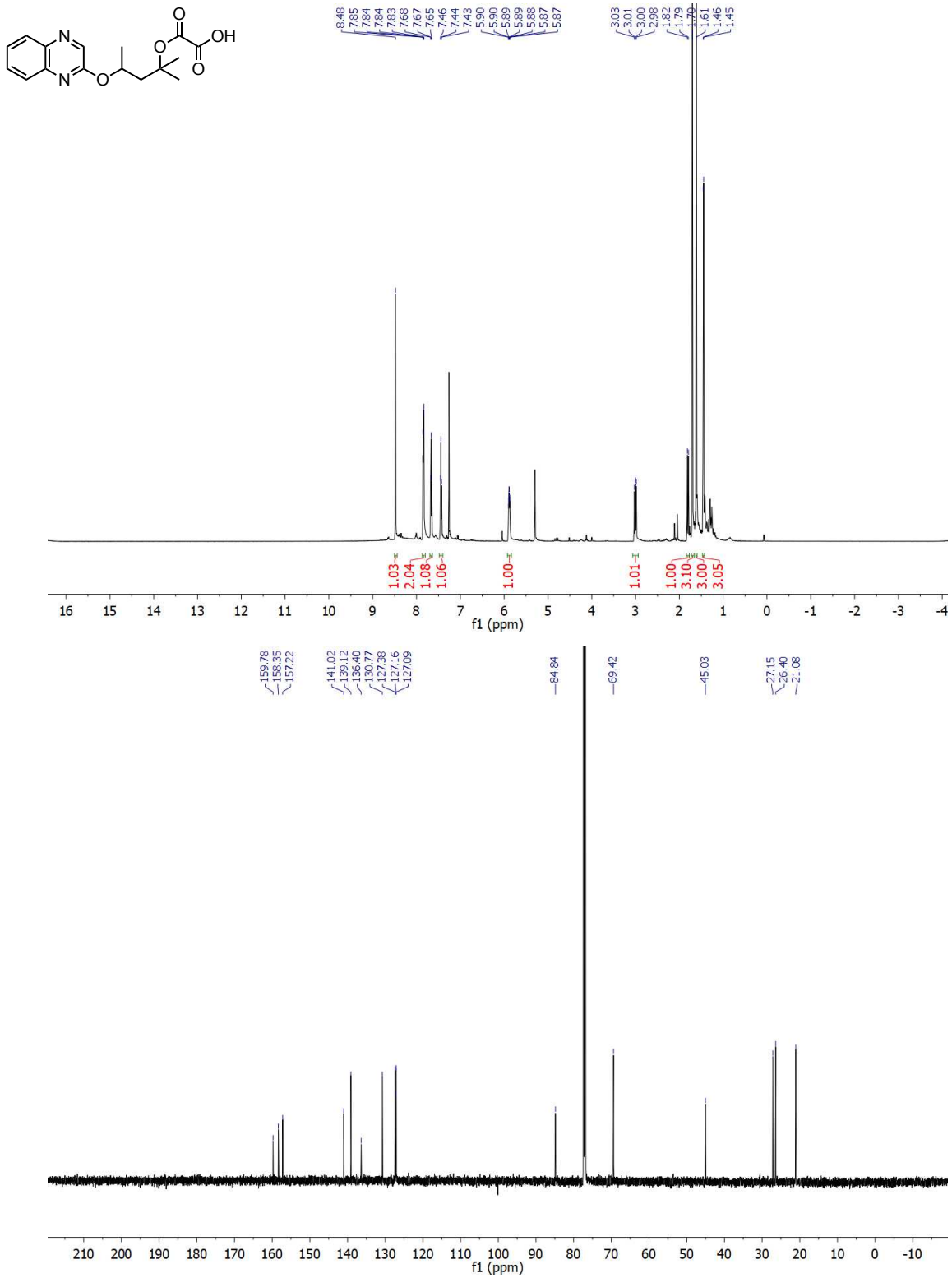




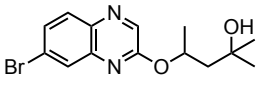
2-methyl-4-(quinoxalin-2-yloxy)pentan-2-ol:

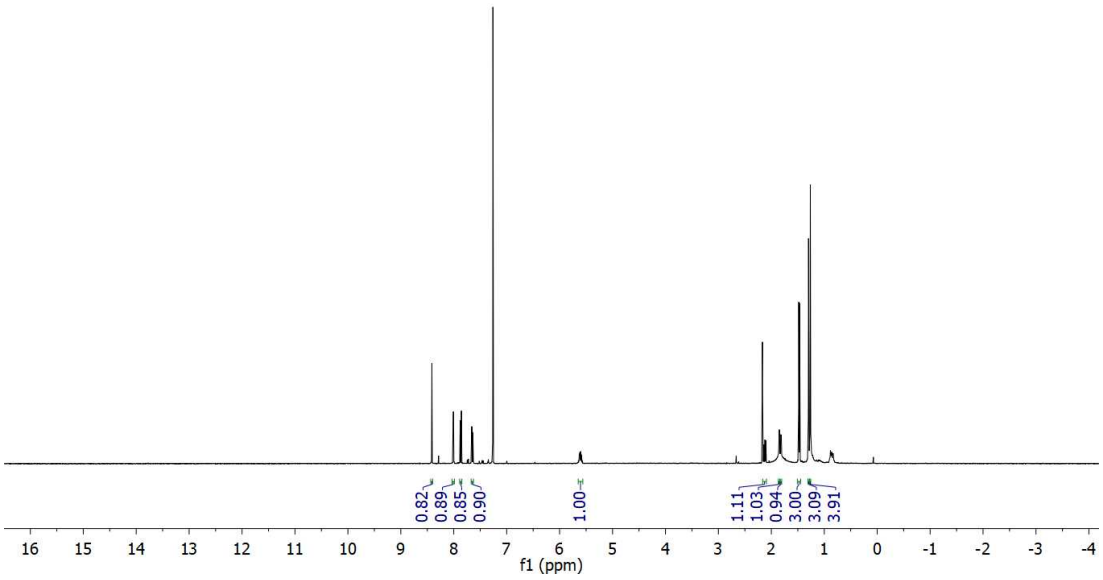


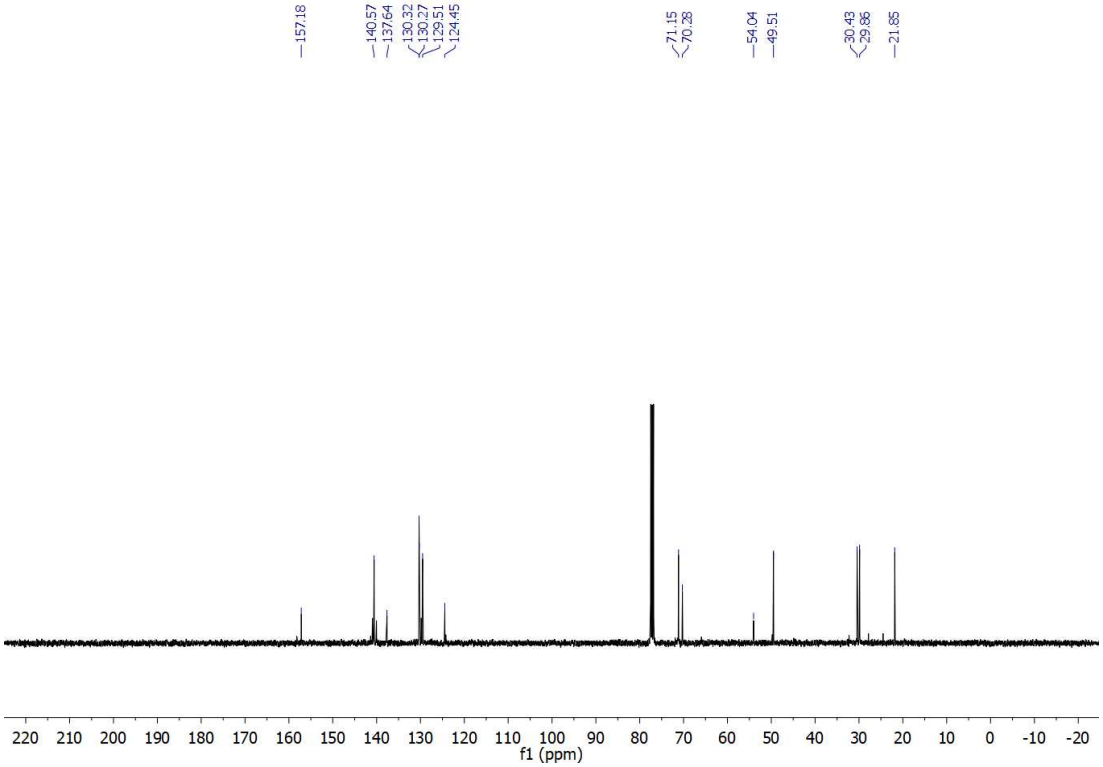
2-((2-methyl-4-(quinoxalin-2-yloxy)pentan-2-yl)oxy)-2-oxoacetic acid:



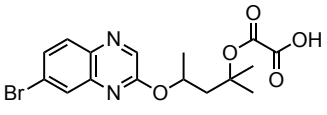
4-((7-bromoquinoxalin-2-yl)oxy)-2-methylpentan-2-ol:

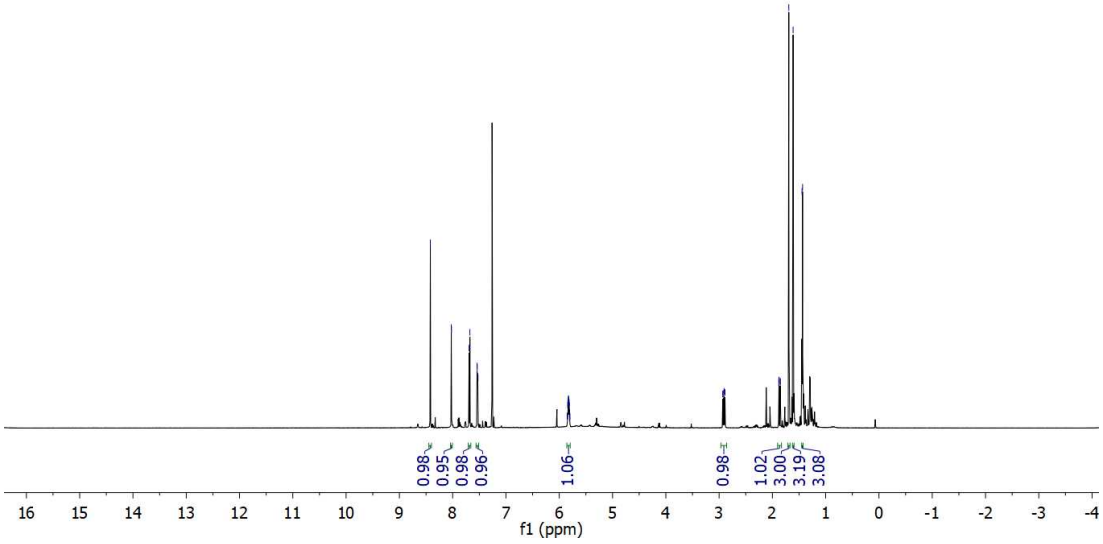


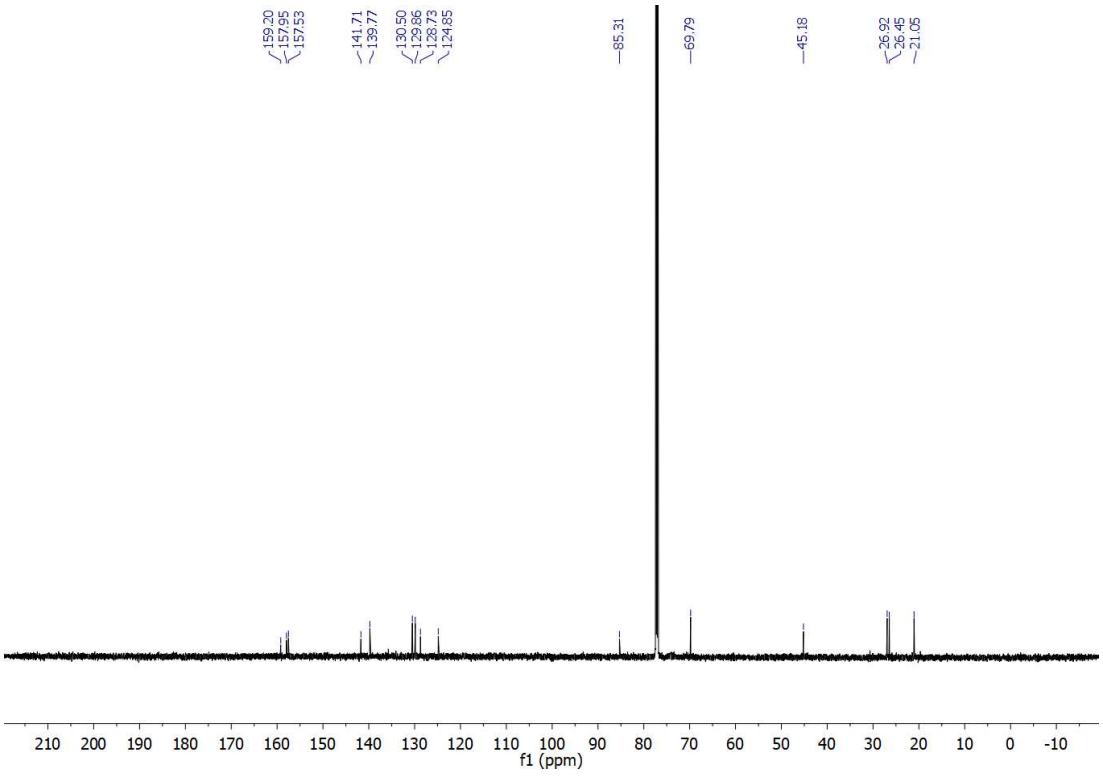




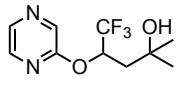
2-((4-((7-bromoquinoxalin-2-yl)oxy)-2-methylpentan-2-yl)oxy)-2-oxoacetic acid:

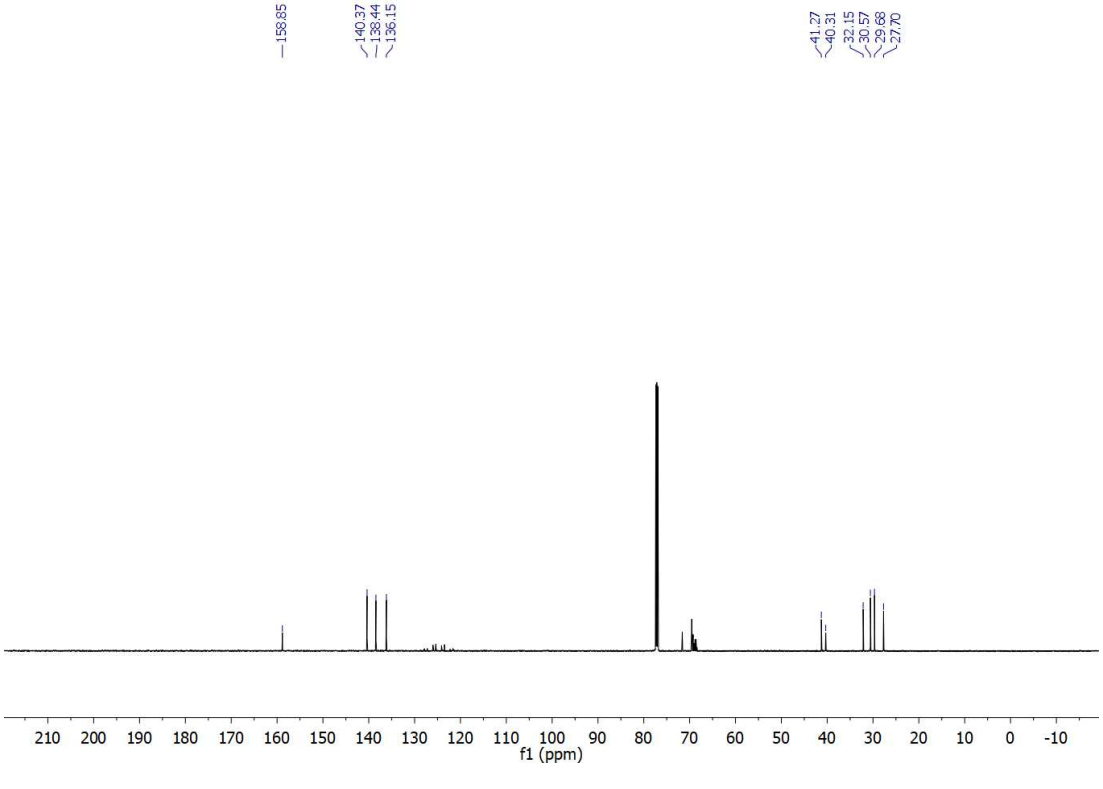


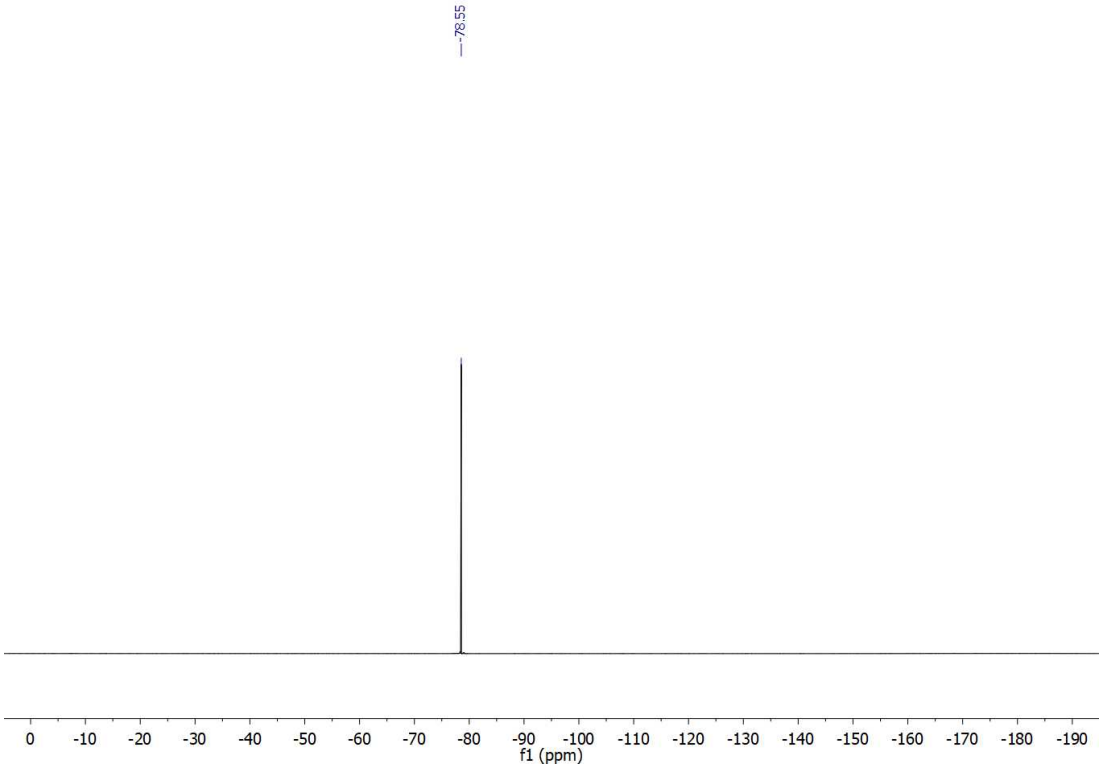




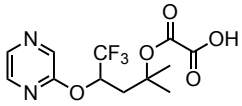
5,5,5-trifluoro-2-methyl-4-(pyrazin-2-yloxy)pentan-2-ol:

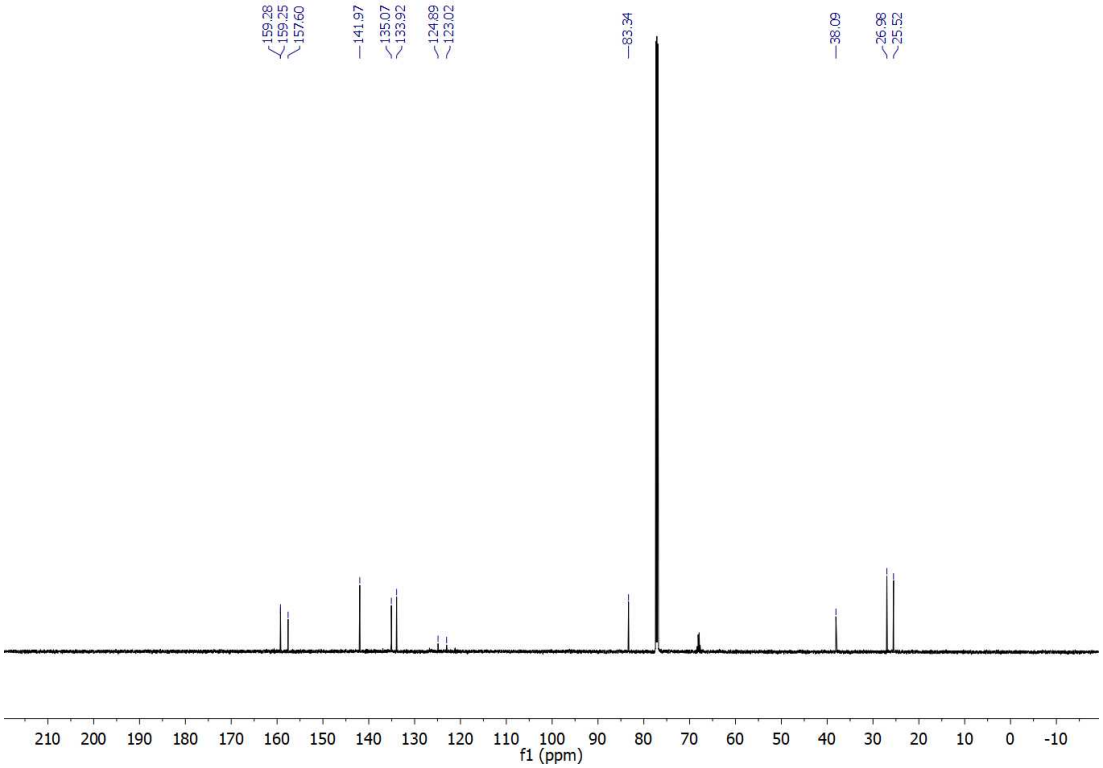


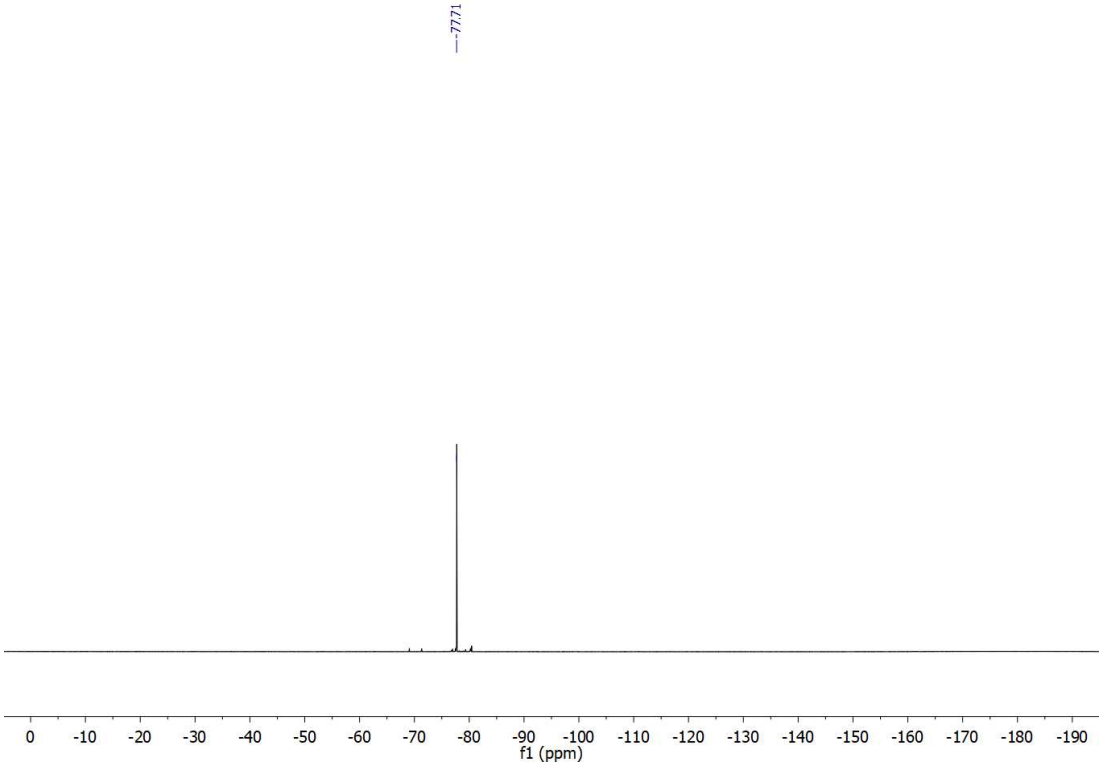




2-oxo-2-((5,5,5-trifluoro-2-methyl-4-(pyrazin-2-yloxy)pentan-2-yl)oxy)acetic acid:

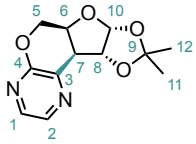


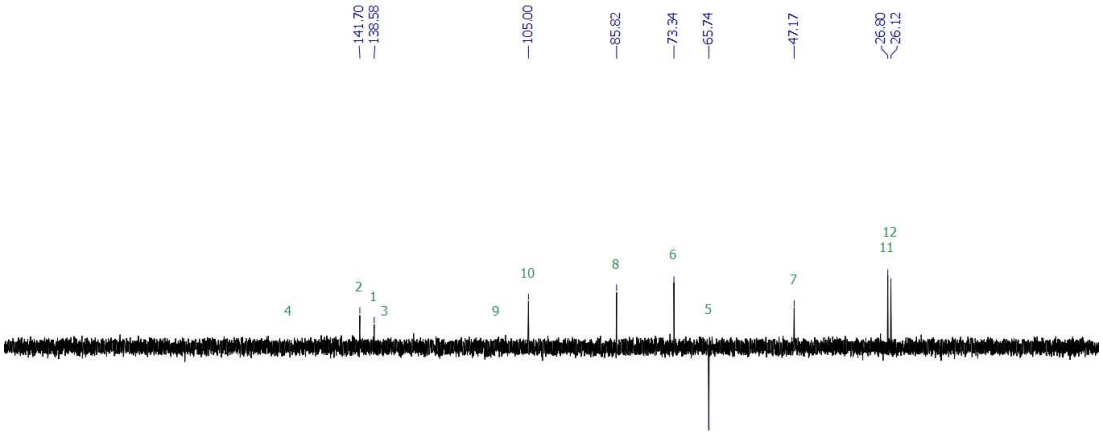

159.28
159.25
157.60
141.97
135.07
133.92
124.89
123.02
83.34
38.09
26.98
25.52
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

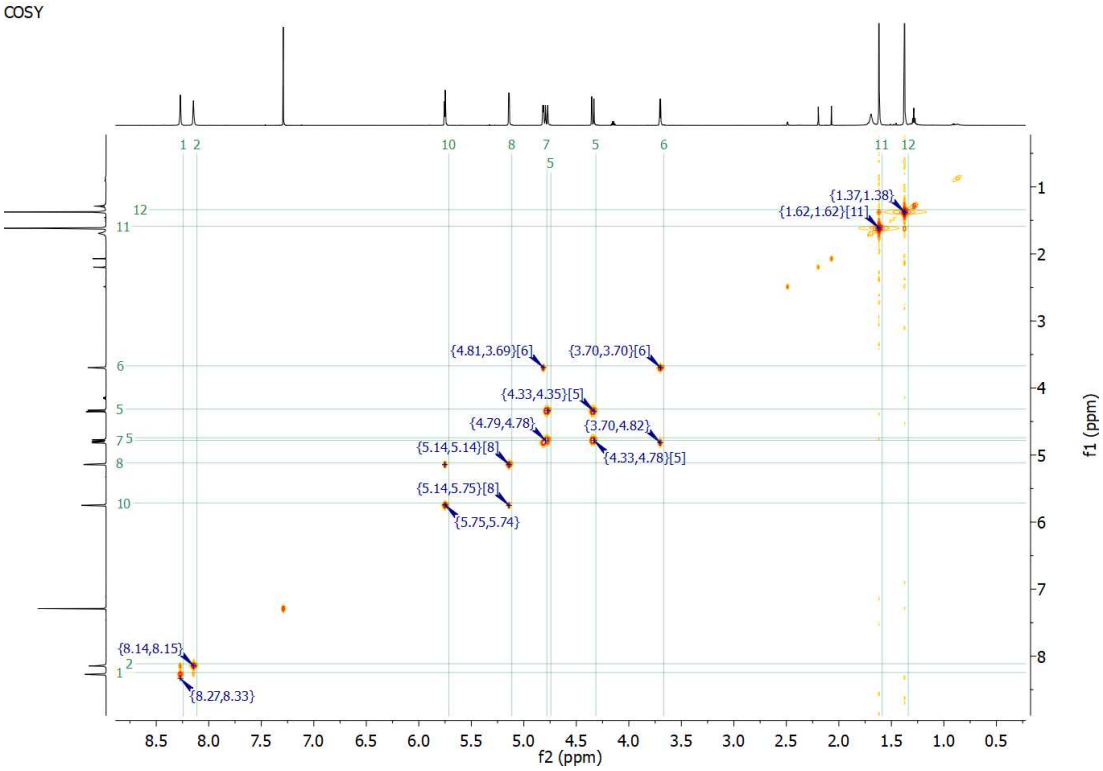

77.71
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

6.4.5.2. Products

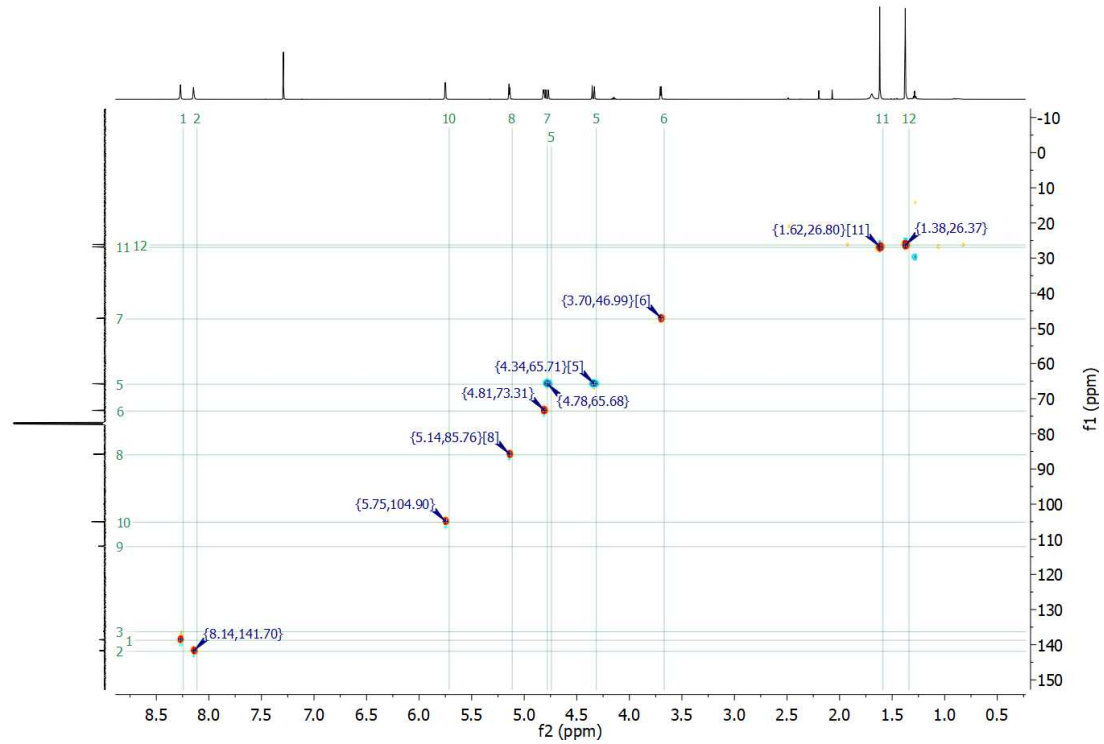
(6aS,7aR,10aR,10bS)-9,9-dimethyl-6a,7a,10a,10b-tetrahydro-6H-[1,3]dioxolo [4'',5'':4',5'] furo[3',2':4,5]pyrano[2,3-b]pyrazine (35):



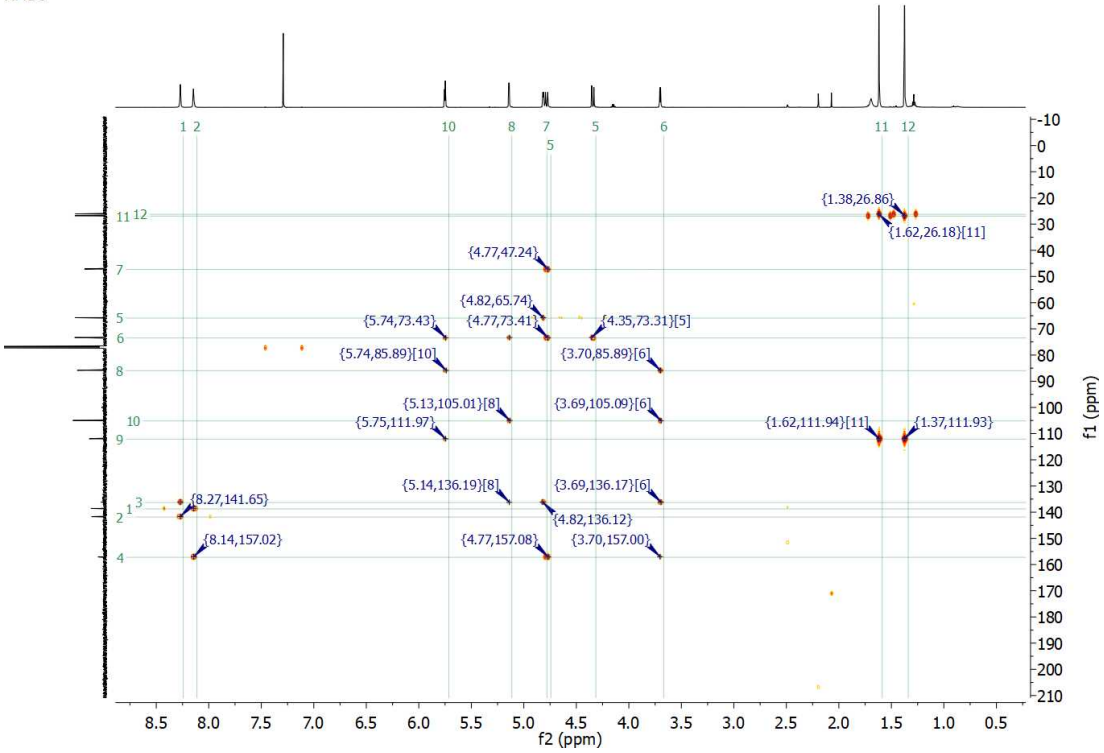

141.70
138.58
105.00
85.82
73.34
65.74
47.17
26.80
26.12
f1 (ppm)

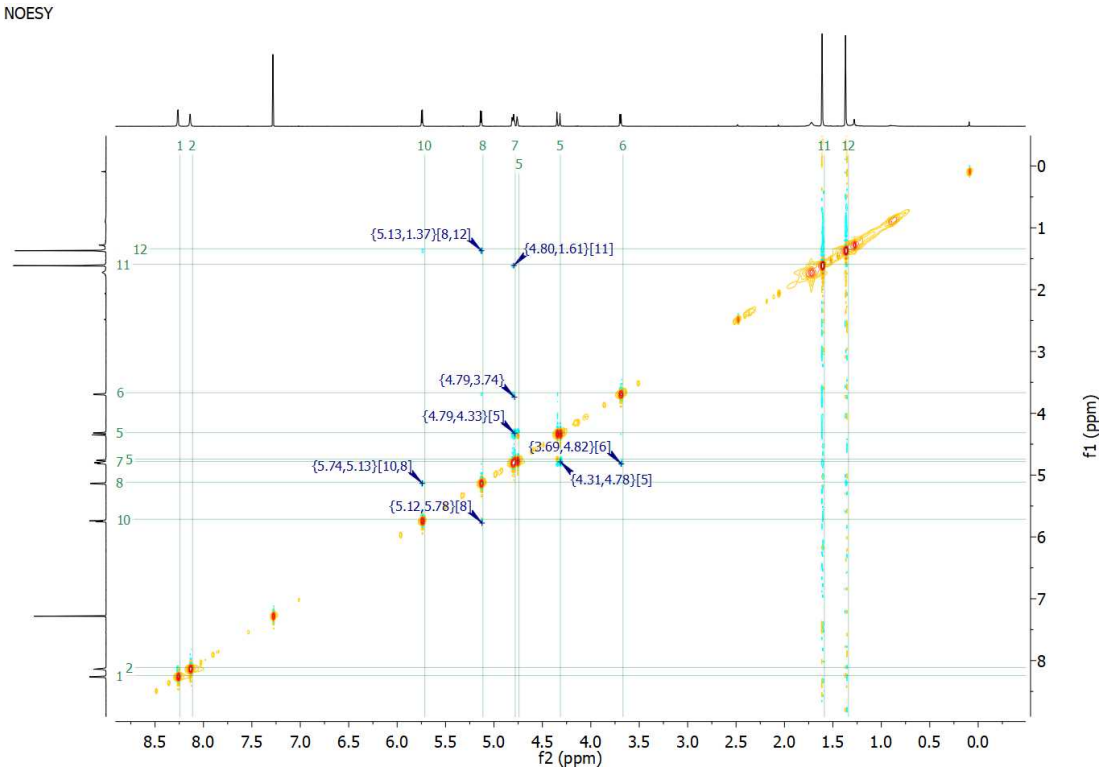

COSY
{1.37,1.38}
{1.62,1.62}[11]
{4.81,3.69}[6]
{3.70,3.70}[6]
{4.33,4.35}[5]
{4.79,4.78}
{3.70,4.82}
{4.33,4.78}[5]
{5.14,5.14}[8]
{5.14,5.75}[8]
{5.75,5.74}
{8.14,8.15}
{8.27,8.33}
f2 (ppm)
f1 (ppm)

HSQC

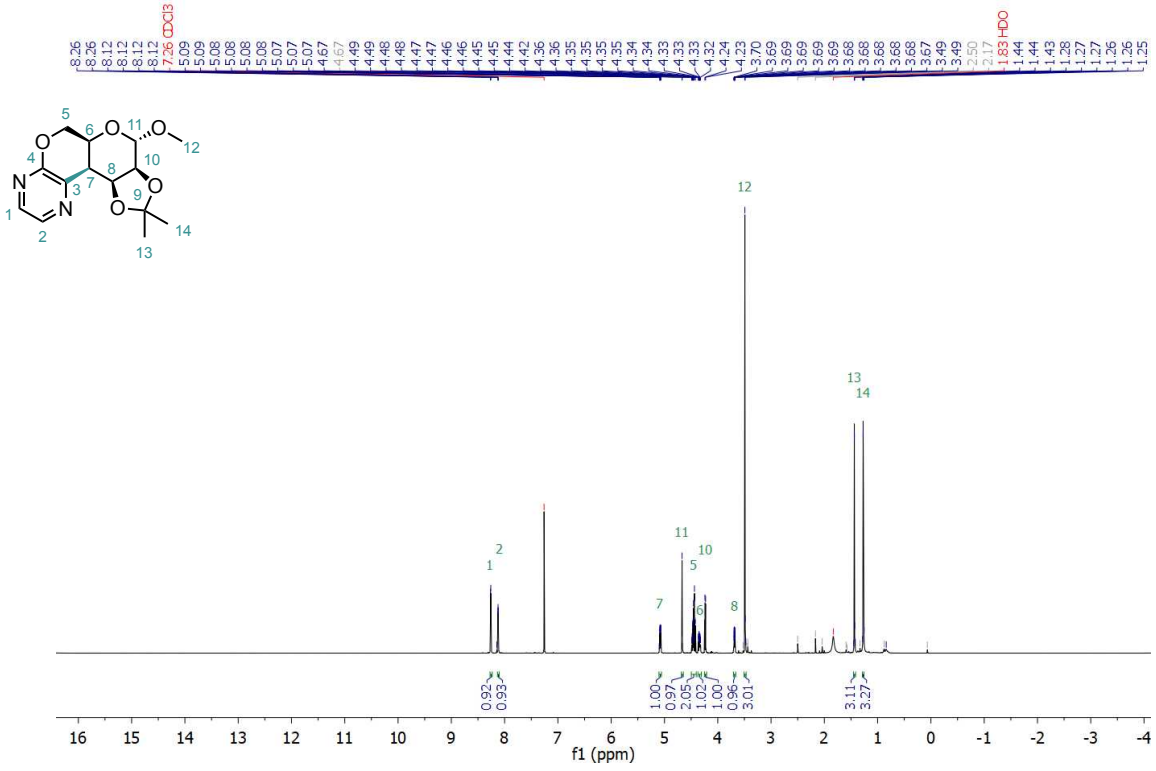

{1.62,26.80}[11]
{1.38,26.37}
{3.70,46.99}[6]
{4.34,65.71}[5]
{4.81,73.31}
{4.78,65.68}
{5.14,85.76}[8]
{5.75,104.90}
{8.14,141.70}
f2 (ppm)
f1 (ppm)

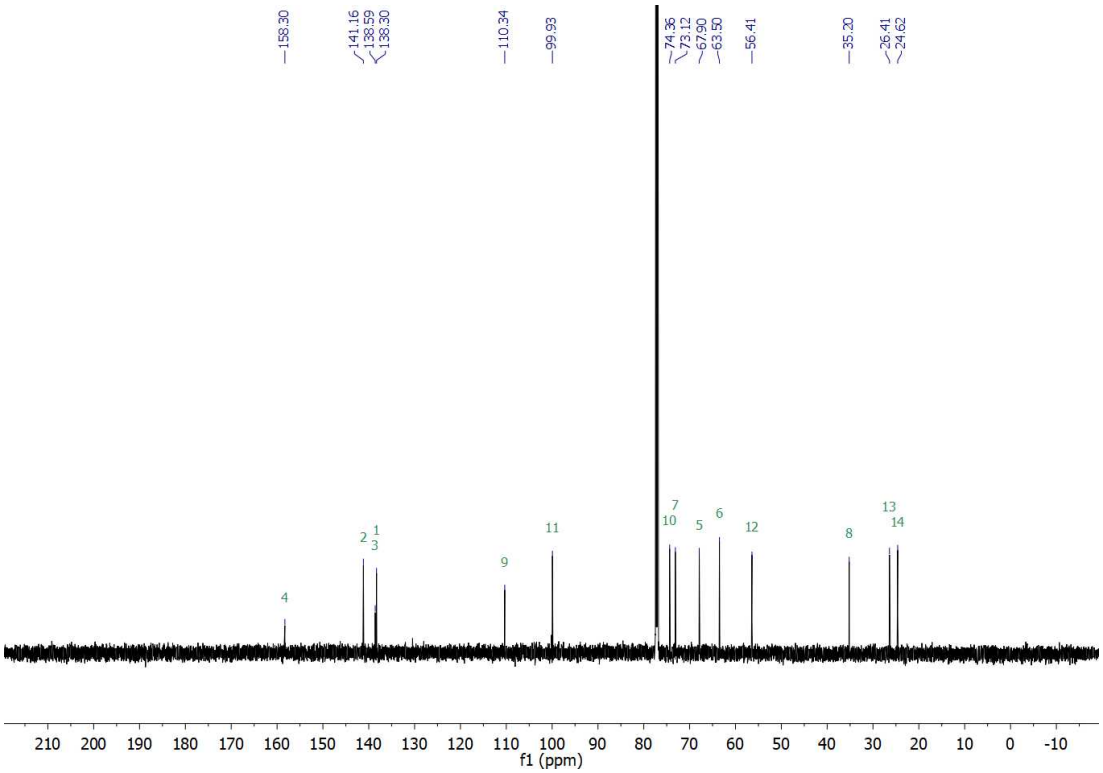
HMBC

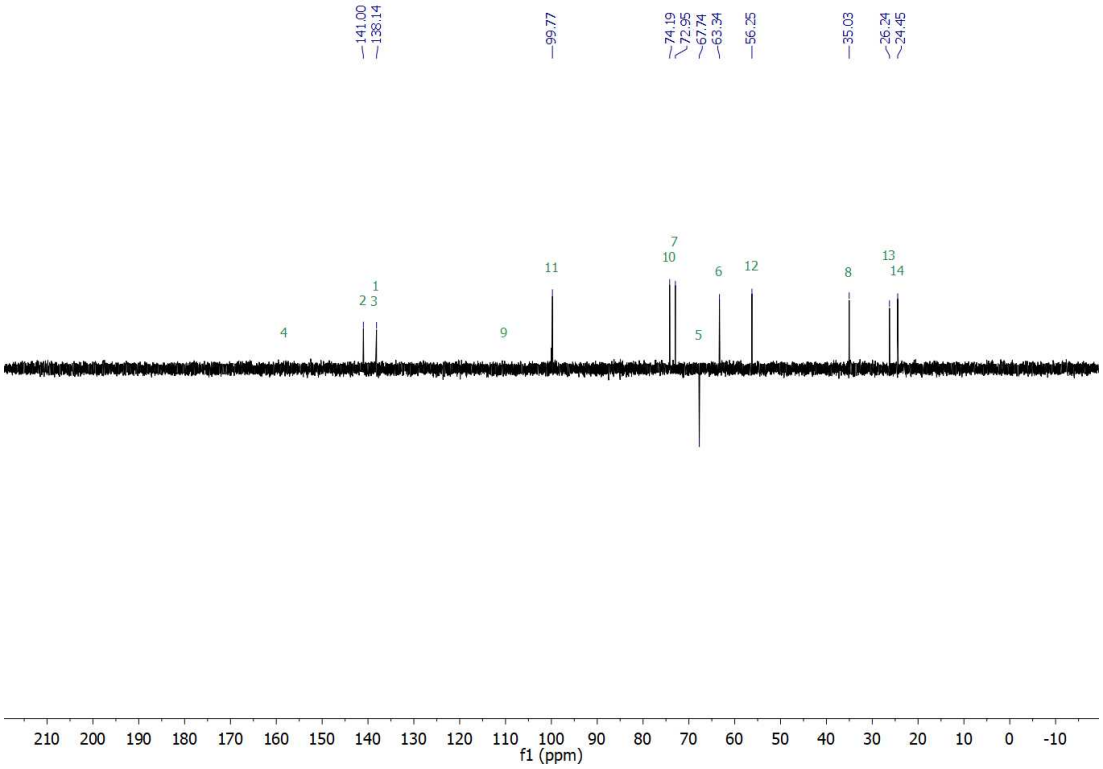

{1.38,26.86}
{1.62,26.18}[11]
{4.77,47.24}
{4.82,65.74}
{5.74,73.43}
{4.77,73.41}
{4.35,73.31}[5]
{5.74,85.89}[10]
{3.70,85.89}[6]
{5.13,105.01}[8]
{3.69,105.09}[6]
{5.75,111.97}
{1.62,111.94}[11]
{1.37,111.93}
{5.14,136.19}[8]
{3.69,136.17}[6]
{8.27,141.65}
{4.82,136.12}
{8.14,157.02}
{4.77,157.08}
{3.70,157.00}
f2 (ppm)
f1 (ppm)



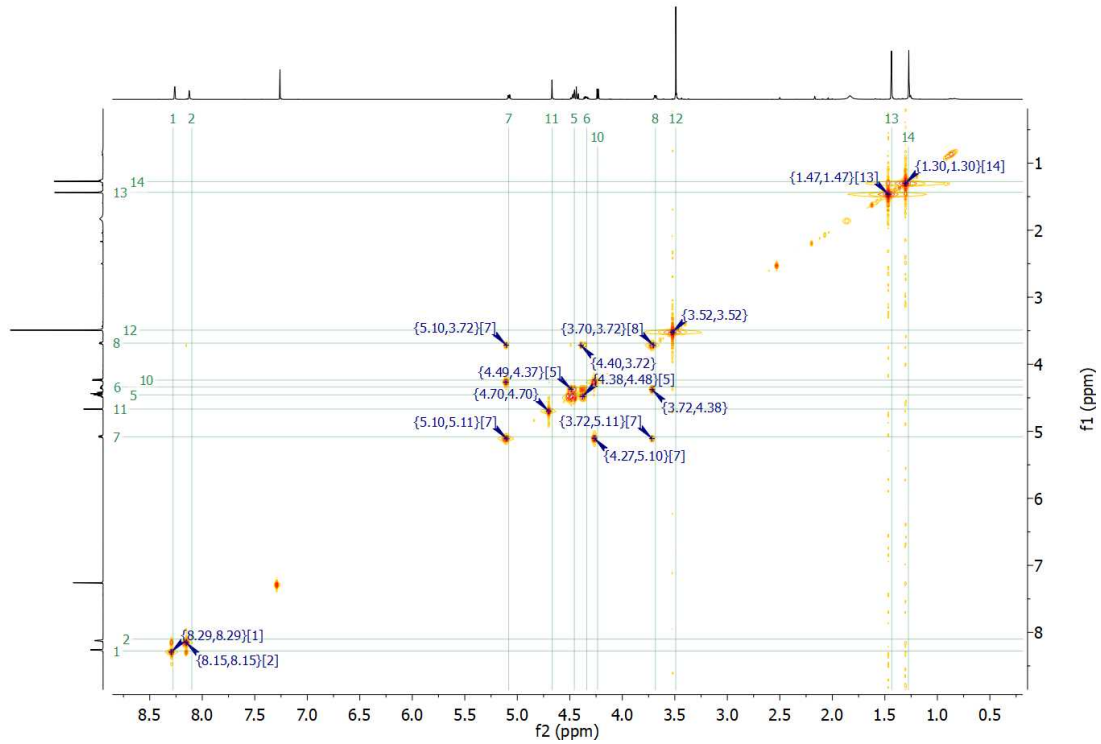
3a*S*,4*S*,5a*S*,11b*S*,11c*S*)-4-methoxy-2,2-dimethyl-3a,4,5a,6,11b,11c-hexahydro-[1,3] dioxolo[4'',5'':4',5']pyrano[3',2':4,5]pyrano[2,3-*b*]pyrazine (36):



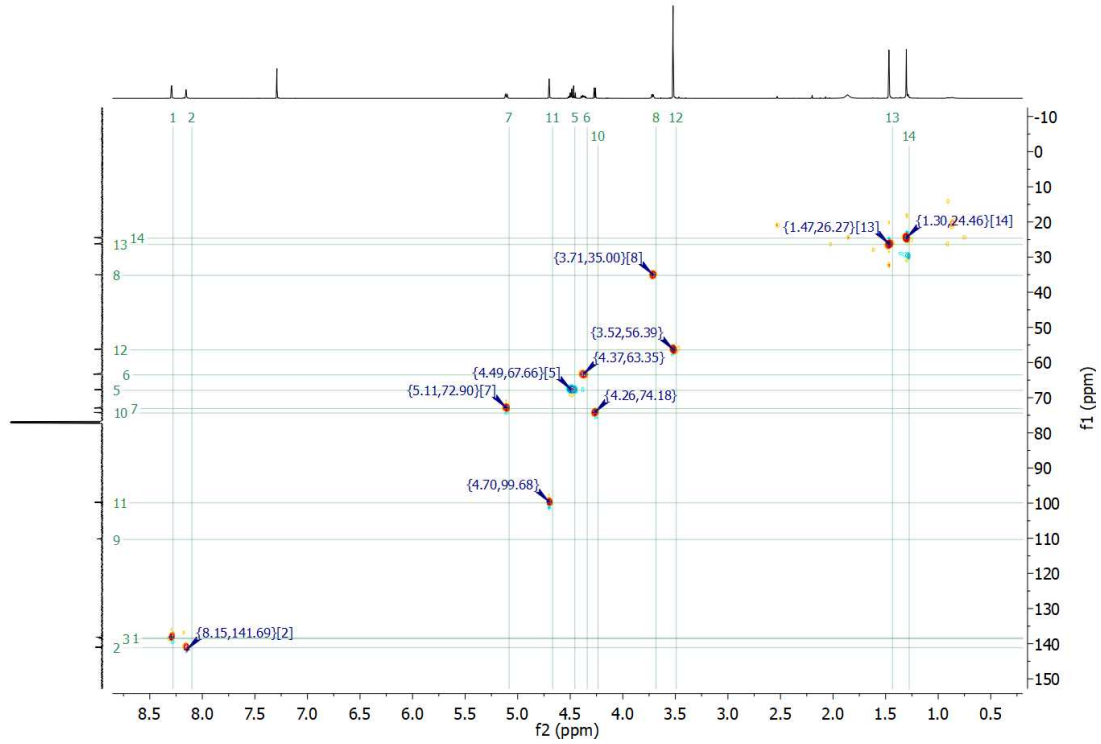

158.30
141.16
138.59
138.30
110.34
99.93
74.36
73.12
67.90
63.50
56.41
35.20
26.41
24.62
4
2
1
3
9
11
7
10
5
6
12
8
13
14
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


141.00
138.14
99.77
74.19
72.95
67.74
63.34
56.25
35.03
26.24
24.45
4
2
1
3
9
11
7
10
5
6
12
8
13
14
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

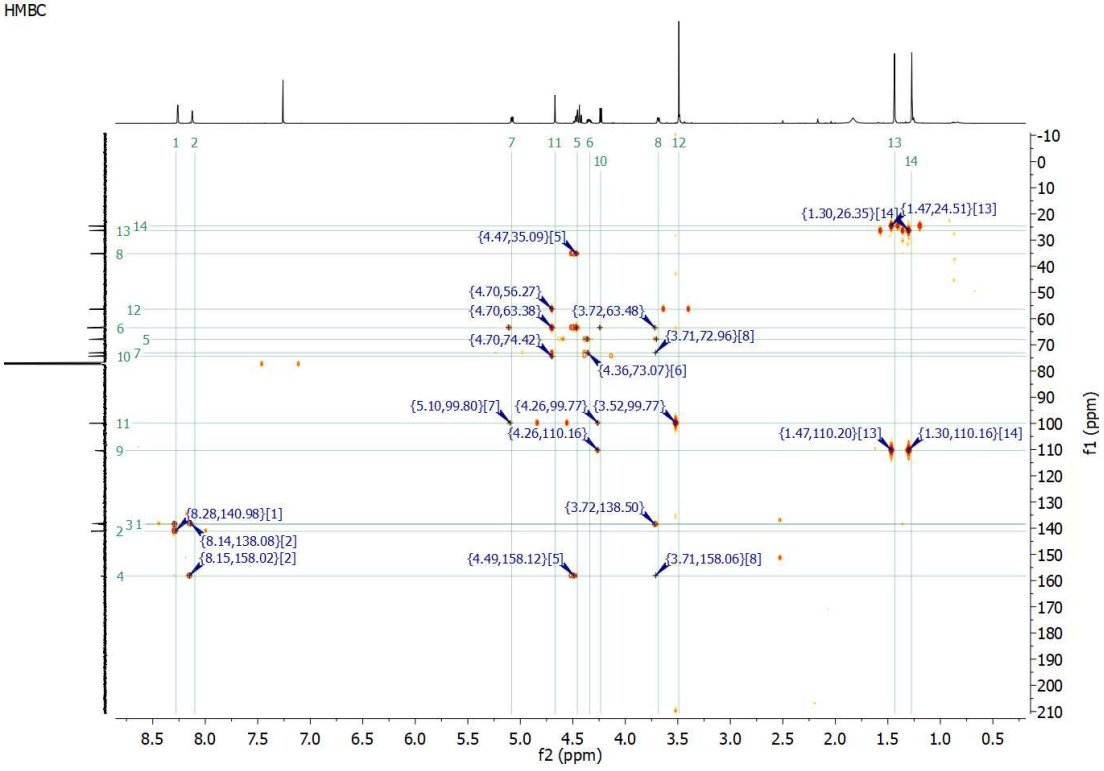
COSY


{1.47,1.47}[13]
{1.30,1.30}[14]
{5.10,3.72}[7]
{3.70,3.72}[8]
{3.52,3.52}
{4.40,3.72}
{4.49,4.37}[5]
{4.38,4.48}[5]
{4.70,4.70}
{3.72,4.38}
{5.10,5.11}[7]
{3.72,5.11}[7]
{4.27,5.10}[7]
{8.29,8.29}[1]
{8.15,8.15}[2]
f2 (ppm)
f1 (ppm)

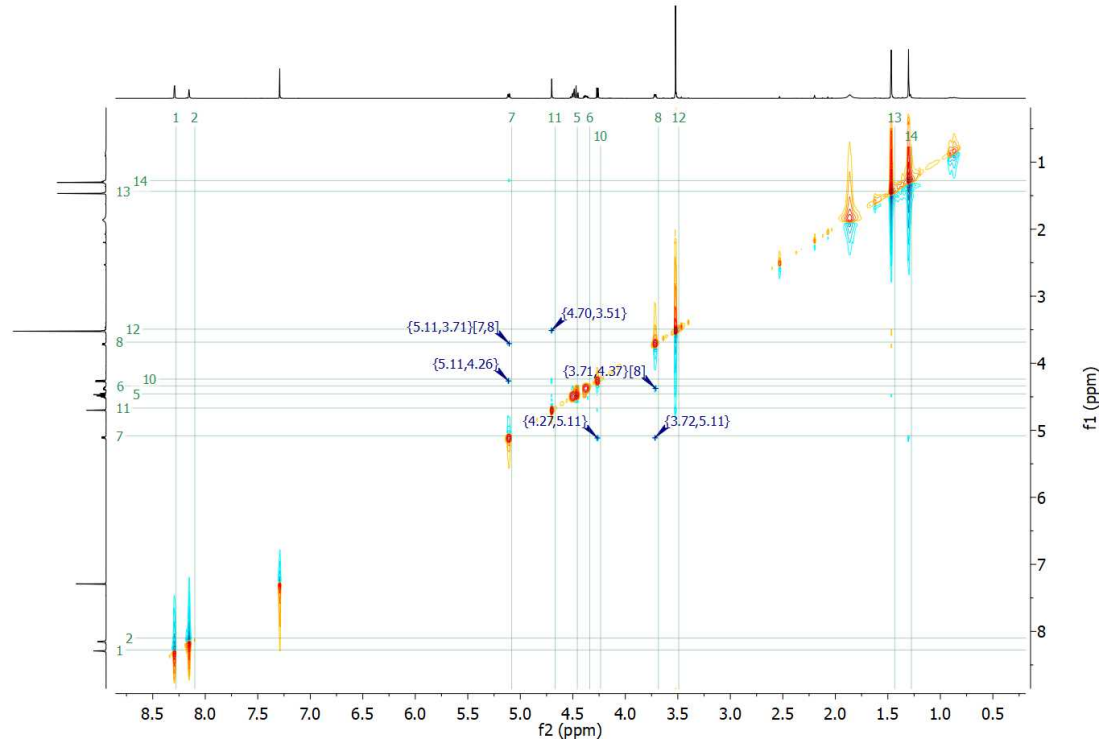
HSQC


{1.47,26.27}[13]
{1.30,24.46}[14]
{3.71,35.00}[8]
{3.52,56.39}
{4.37,63.35}
{4.49,67.66}[5]
{5.11,72.90}[7]
{4.26,74.18}
{4.70,99.68}
{8.15,141.69}[2]
f2 (ppm)
f1 (ppm)

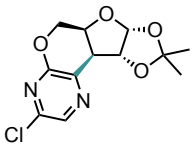
HMBC

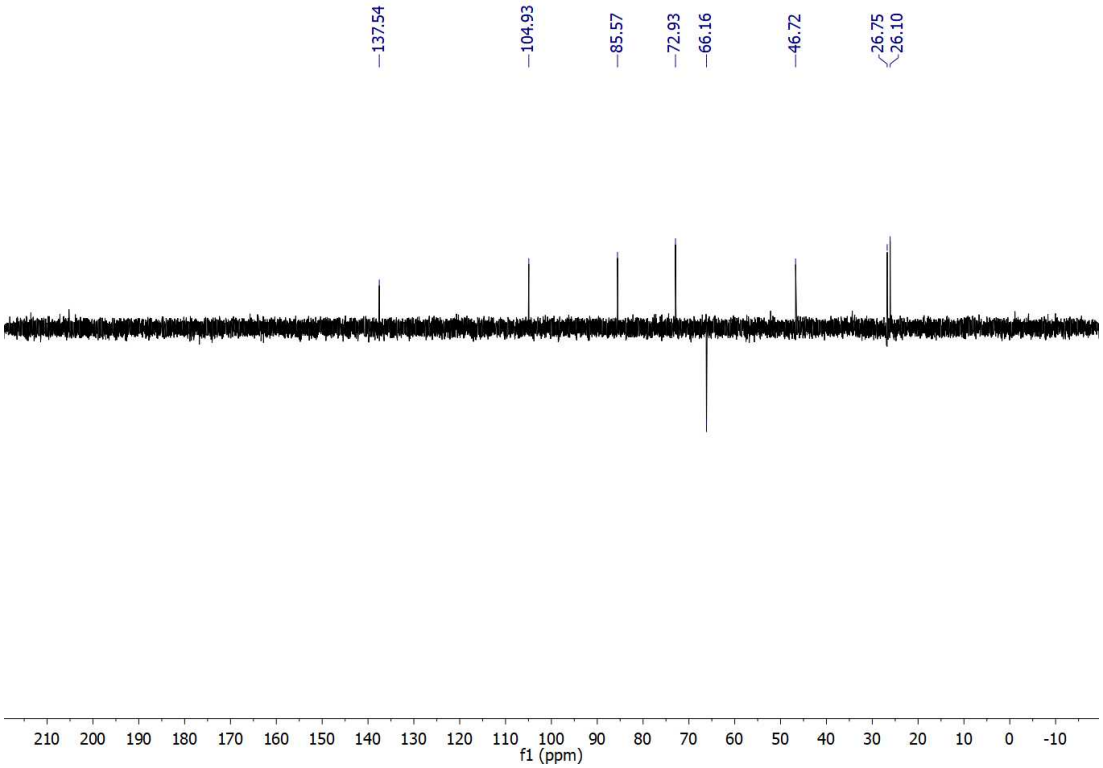

{1.30,26.35}[14]
{1.47,24.51}[13]
{4.47,35.09}[5]
{4.70,56.27}
{4.70,63.38}
{3.72,63.48}
{4.70,74.42}
{3.71,72.96}[8]
{4.36,73.07}[6]
{5.10,99.80}[7]
{4.26,99.77}
{3.52,99.77}
{4.26,110.16}
{1.47,110.20}[13]
{1.30,110.16}[14]
{8.28,140.98}[1]
{3.72,138.50}
{8.14,138.08}[2]
{8.15,158.02}[2]
{4.49,158.12}[5]
{3.71,158.06}[8]
f2 (ppm)
f1 (ppm)

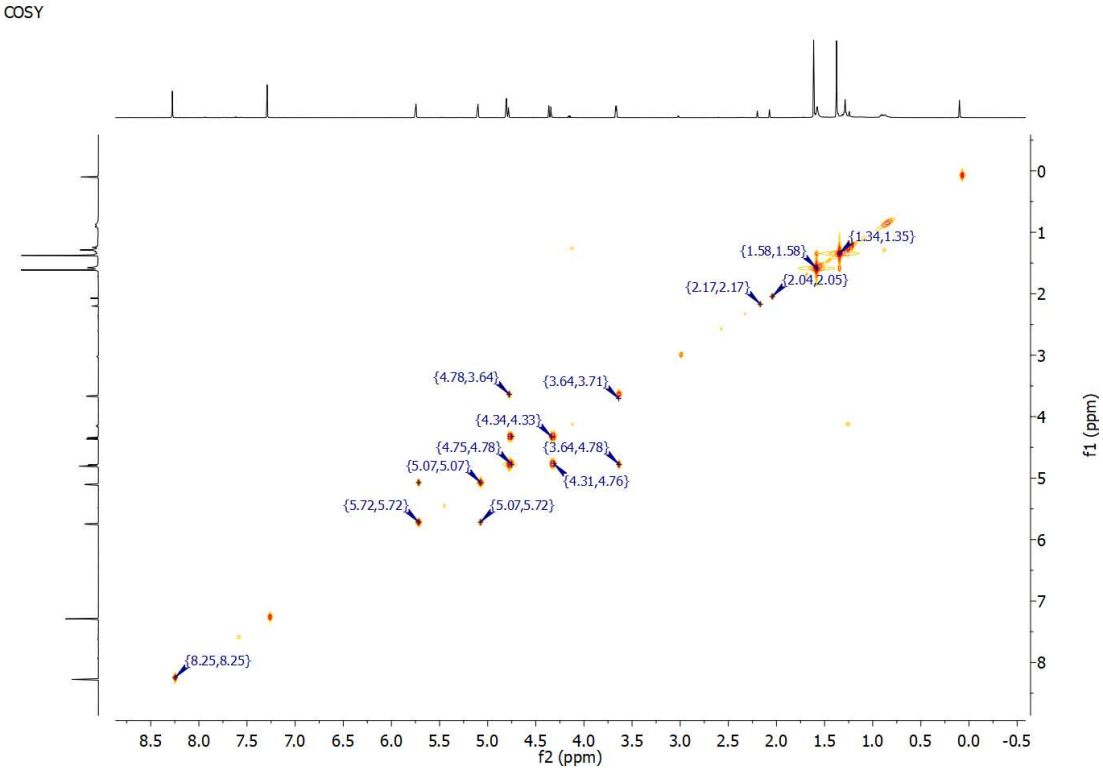
NOESY


{5.11,3.71}[7,8]
{4.70,3.51}
{5.11,4.26}
{3.71,4.37}[8]
{4.27,5.11}
{3.72,5.11}
f2 (ppm)
f1 (ppm)

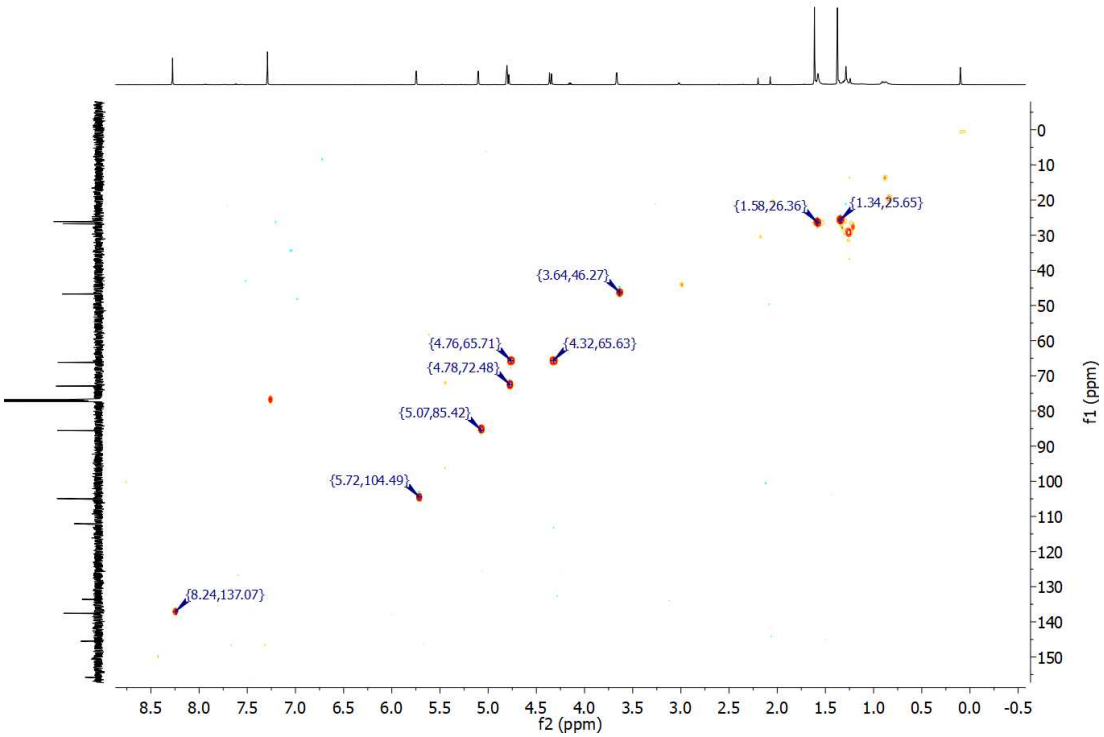
(6aS,7aR,10aR,10bS)-3-chloro-9,9-dimethyl-6a,7a,10a,10b-tetrahydro-6H-[1,3]dioxolo [4'',5'':4',5']furo[3',2':4,5]pyrano[2,3-b]pyrazine (37):



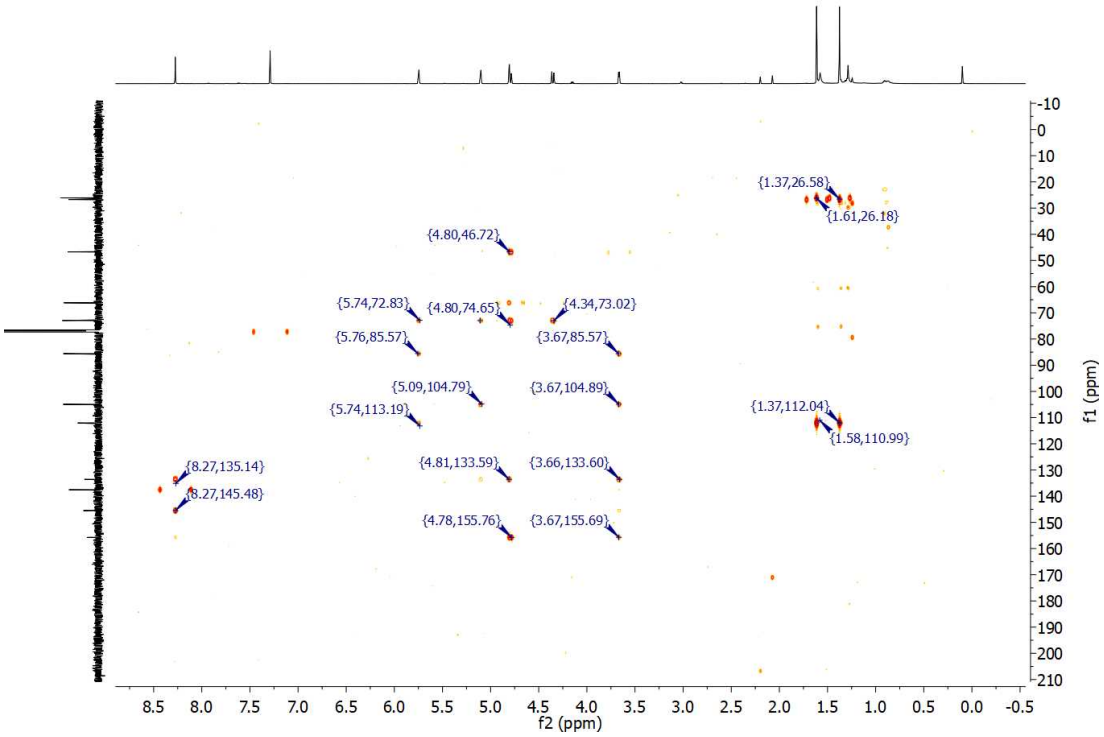

137.54
104.93
85.57
72.93
66.16
46.72
26.75
26.10
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

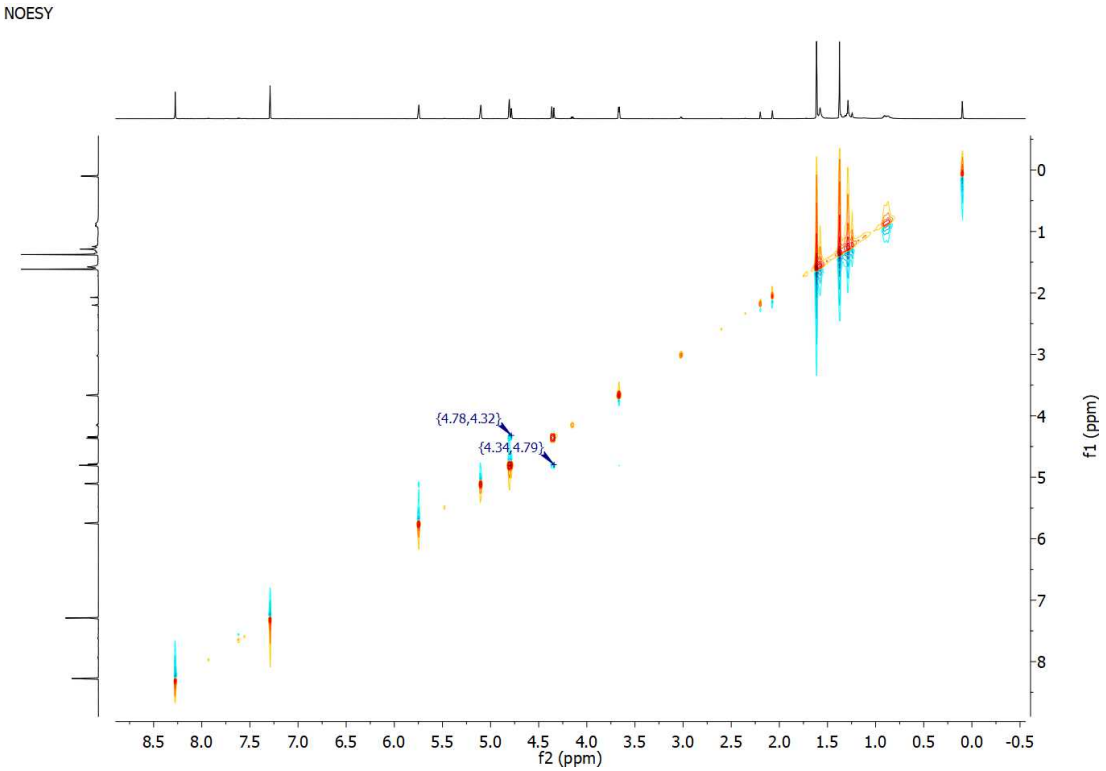

COSY
{1.34,1.35}
{1.58,1.58}
{2.04,2.05}
{2.17,2.17}
{4.78,3.64}
{3.64,3.71}
{4.34,4.33}
{4.75,4.78}
{3.64,4.78}
{5.07,5.07}
{4.31,4.76}
{5.72,5.72}
{5.07,5.72}
{8.25,8.25}
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f2 (ppm)
0 1 2 3 4 5 6 7 8
f1 (ppm)

HSQC

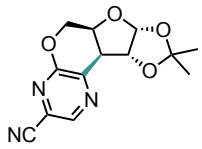

{1.58,26.36}
{1.34,25.65}
{3.64,46.27}
{4.76,65.71}
{4.32,65.63}
{4.78,72.48}
{5.07,85.42}
{5.72,104.49}
{8.24,137.07}
f1 (ppm)
f2 (ppm)

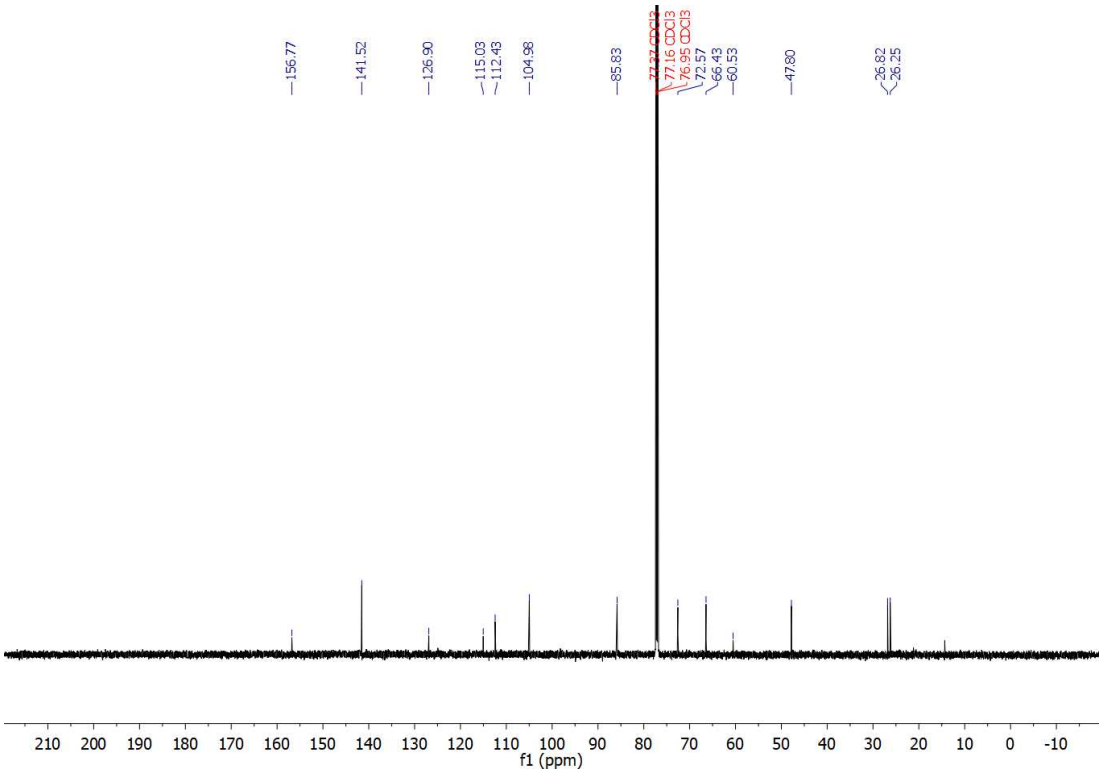
HMBC

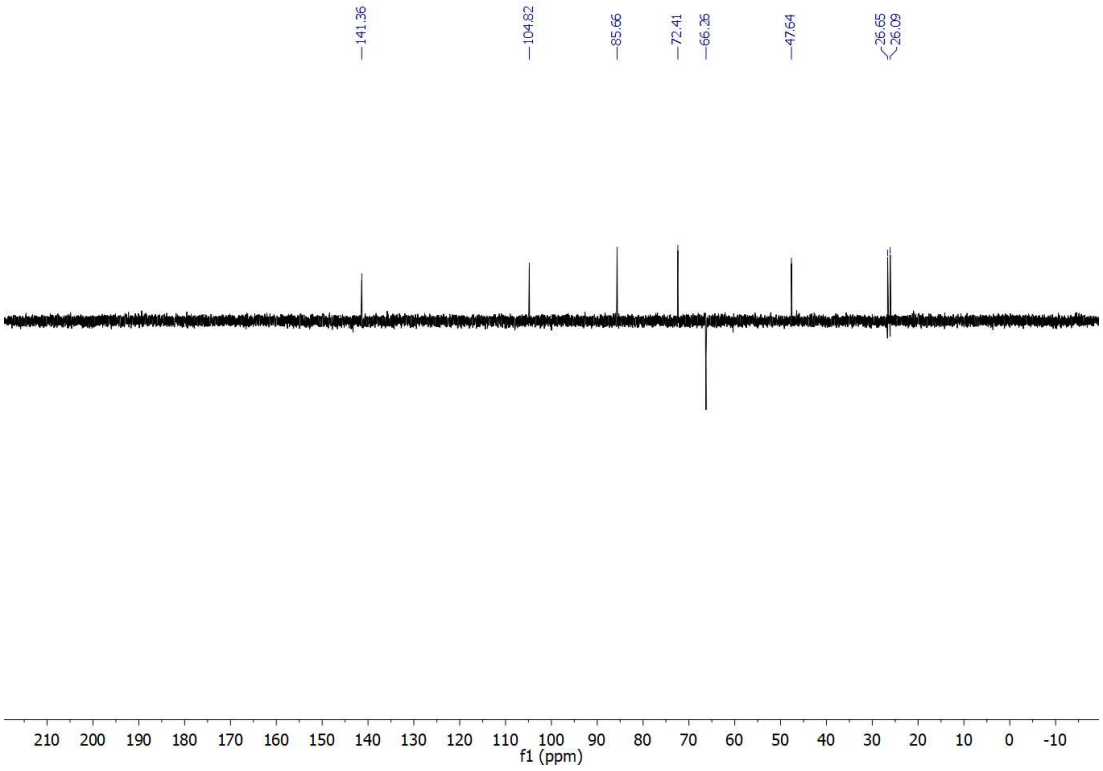

{1.37,26.58}
{1.61,26.18}
{4.80,46.72}
{5.74,72.83}
{4.80,74.65}
{4.34,73.02}
{5.76,85.57}
{3.67,85.57}
{5.09,104.79}
{3.67,104.89}
{5.74,113.19}
{1.37,112.04}
{1.58,110.99}
{8.27,135.14}
{4.81,133.59}
{3.66,133.60}
{8.27,145.48}
{4.78,155.76}
{3.67,155.69}
f1 (ppm)
f2 (ppm)



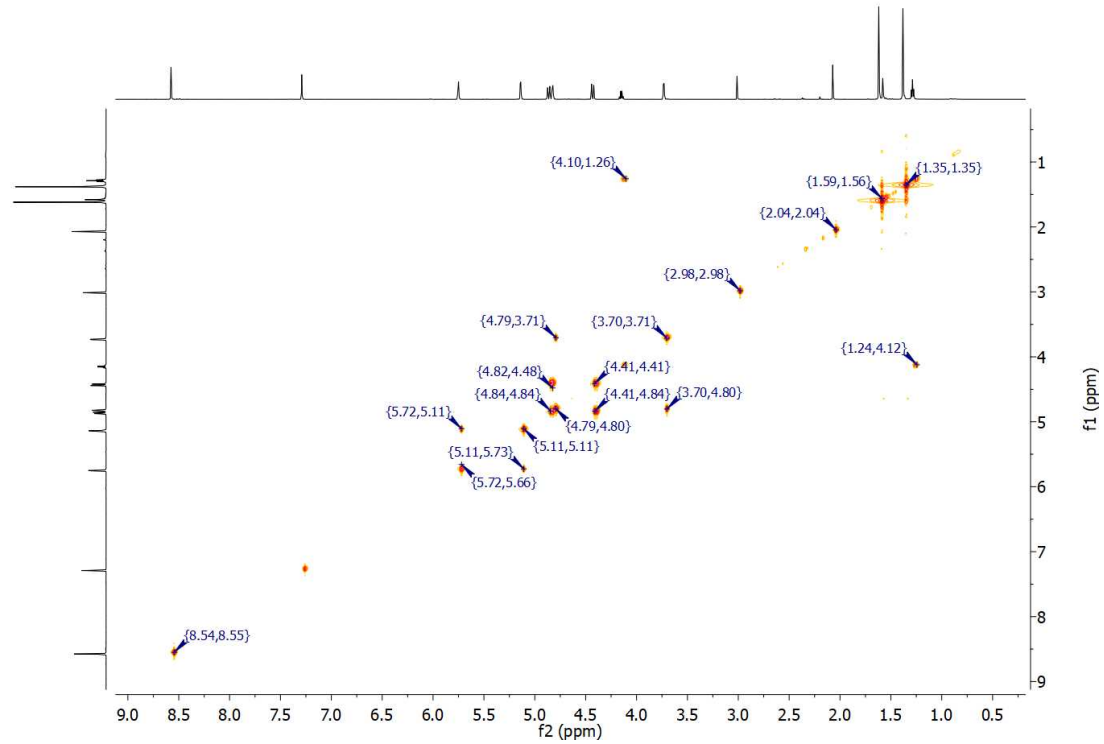
(6aS,7aR,10aR,10bS)-9,9-dimethyl-6a,7a,10a,10b-tetrahydro-6H-[1,3]dioxolo [4'',5'':4',5'] furo[3',2':4,5]pyrano[2,3-b]pyrazine-3-carbonitrile (38):



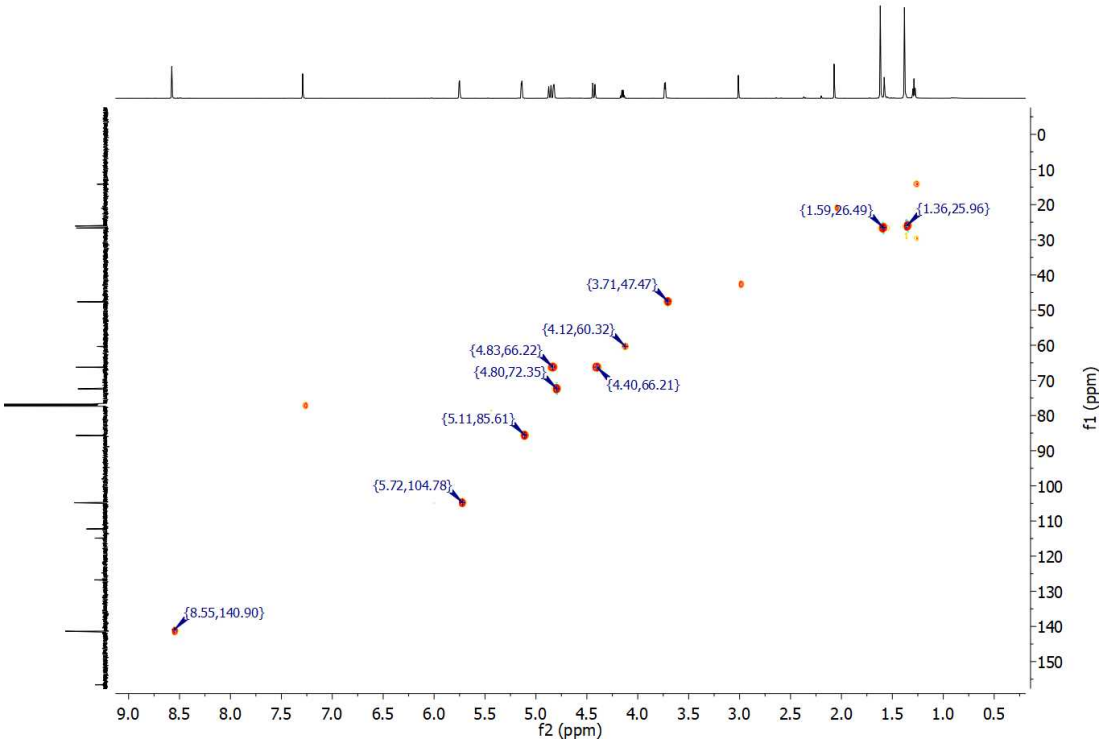

156.77
141.52
126.90
115.03
112.43
104.98
85.83
77.16 CDCl3
76.95 CDCl3
72.57
66.43
60.53
47.80
26.82
26.25
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


141.36
104.82
85.66
72.41
66.26
47.64
26.65
26.09
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

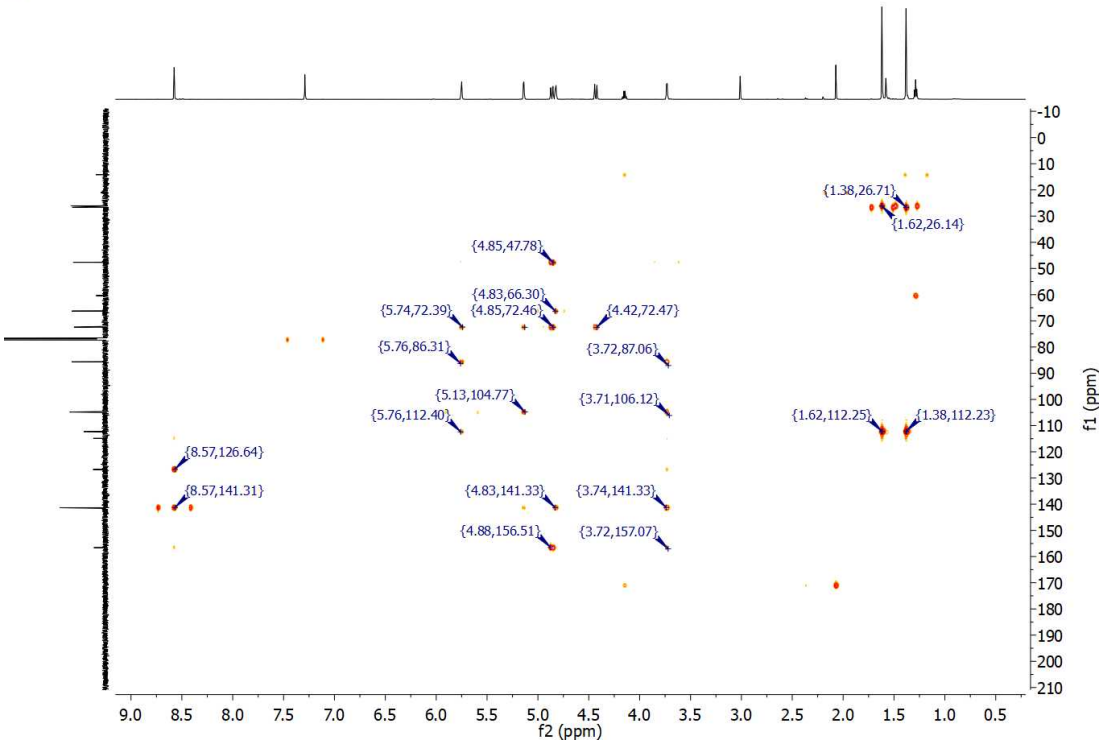
COSY


{4.10,1.26}
{1.59,1.56}
{1.35,1.35}
{2.04,2.04}
{2.98,2.98}
{4.79,3.71}
{3.70,3.71}
{1.24,4.12}
{4.82,4.48}
{4.41,4.41}
{4.84,4.84}
{4.41,4.84}
{3.70,4.80}
{5.72,5.11}
{4.79,4.80}
{5.11,5.11}
{5.11,5.73}
{5.72,5.66}
{8.54,8.55}
f2 (ppm)
f1 (ppm)

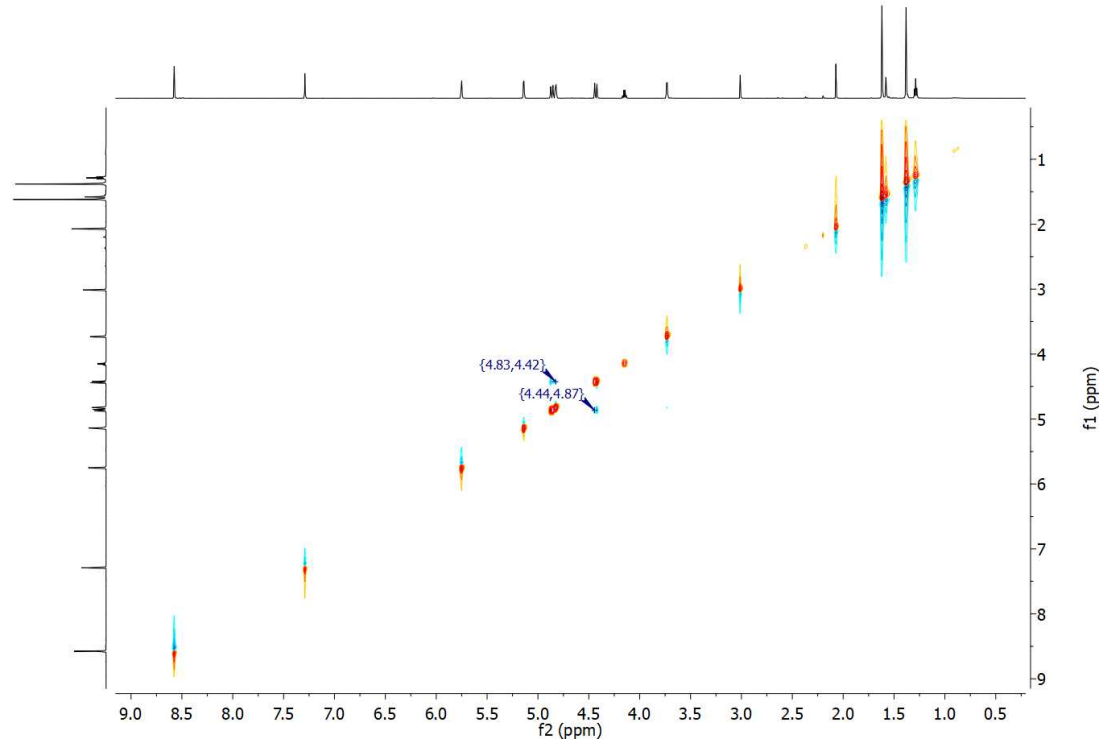
HSQC


{1.59,26.49}
{1.36,25.96}
{3.71,47.47}
{4.12,60.32}
{4.83,66.22}
{4.80,72.35}
{4.40,66.21}
{5.11,85.61}
{5.72,104.78}
{8.55,140.90}
f2 (ppm)
f1 (ppm)

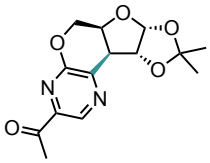
HMBC

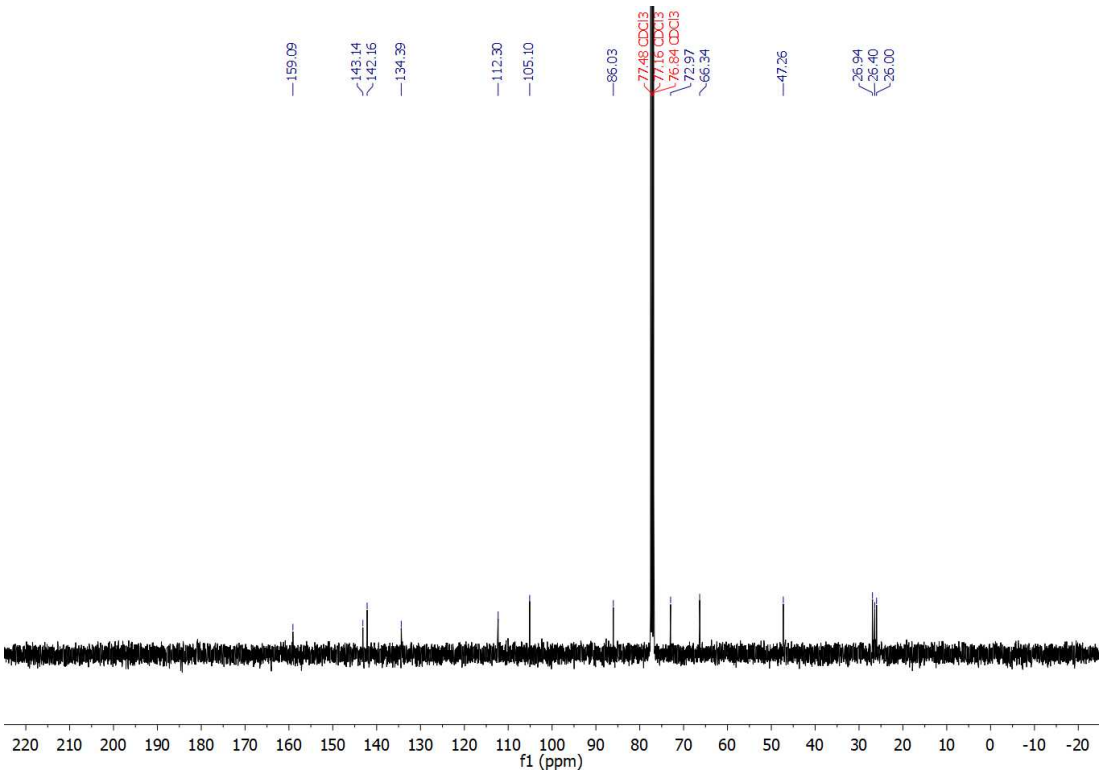

{1.38,26.71}
{1.62,26.14}
{4.85,47.78}
{4.83,66.30}
{5.74,72.39}
{4.85,72.46}
{4.42,72.47}
{5.76,86.31}
{3.72,87.06}
{5.13,104.77}
{3.71,106.12}
{5.76,112.40}
{1.62,112.25}
{1.38,112.23}
{8.57,126.64}
{8.57,141.31}
{4.83,141.33}
{3.74,141.33}
{4.88,156.51}
{3.72,157.07}
f2 (ppm)
f1 (ppm)

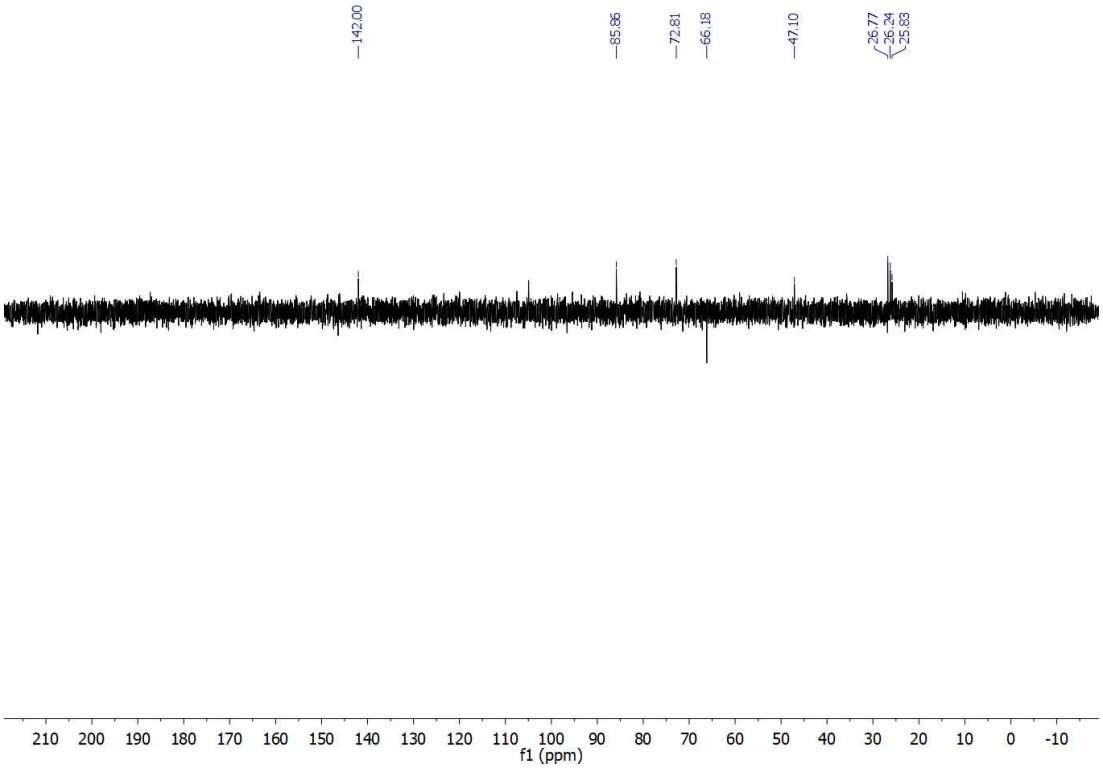
NOESY

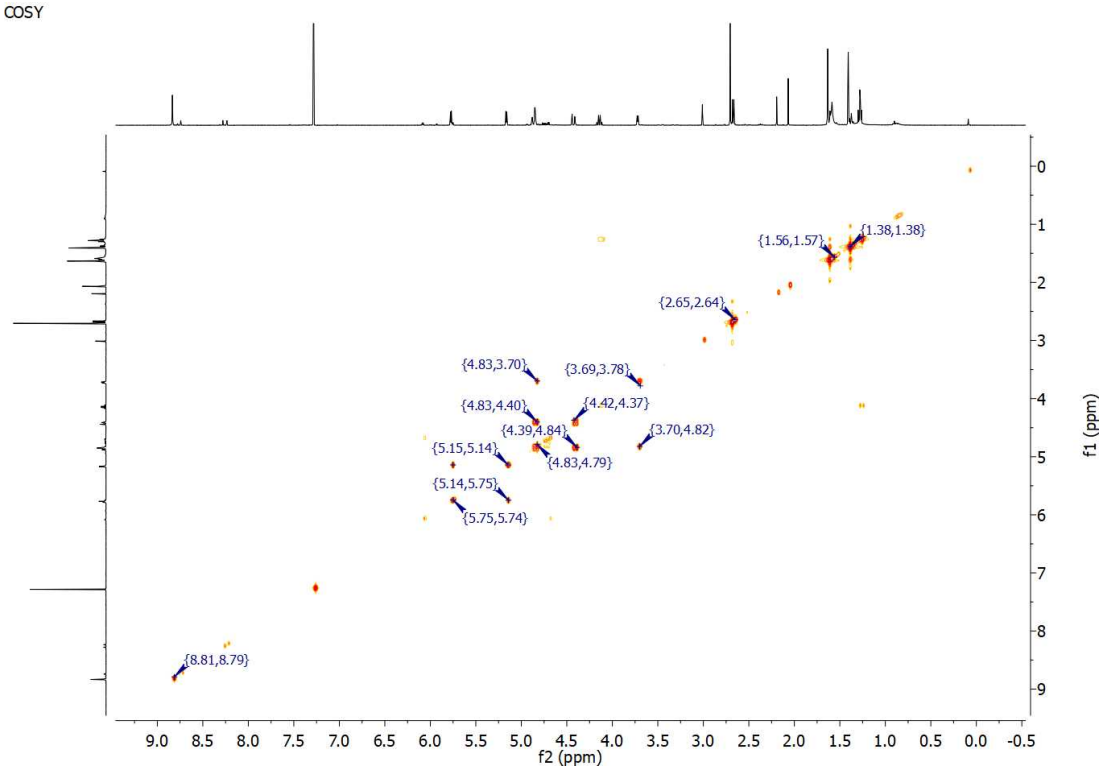

{4.83,4.42}
{4.44,4.87}
f2 (ppm)
f1 (ppm)

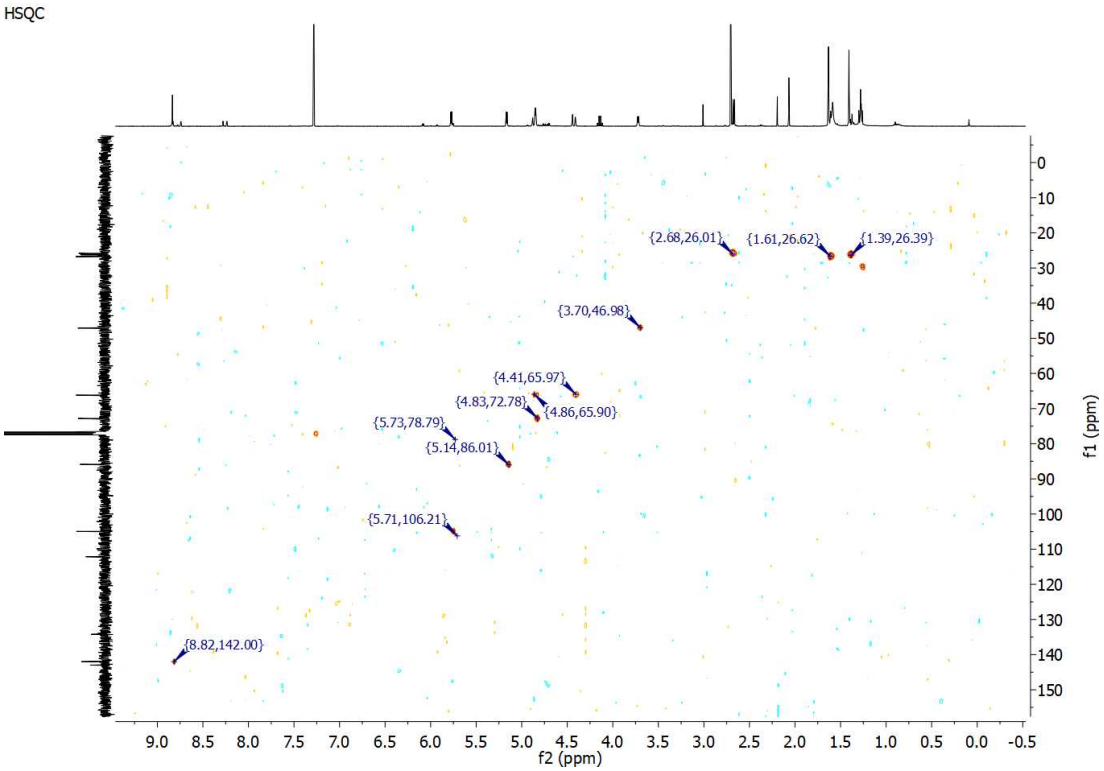
1-((6aS,7aR,10aR,10bS)-9,9-dimethyl-6a,7a,10a,10b-tetrahydro-6H-[1,3]dioxolo [4'',5'':4',5'] furo[3',2':4,5]pyrano[2,3-b]pyrazin-3-yl)ethan-1-one (39):

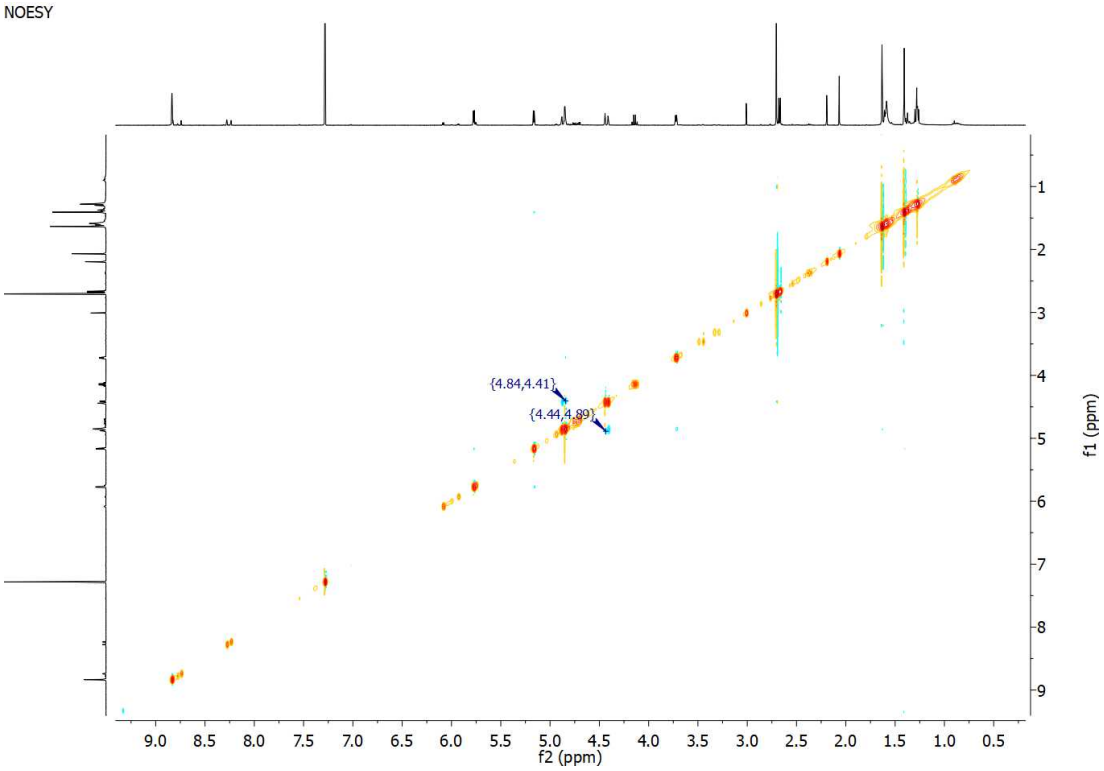




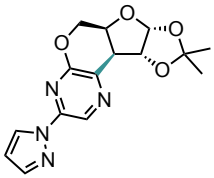

142.00
85.86
72.81
66.18
47.10
26.77
26.24
25.83
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

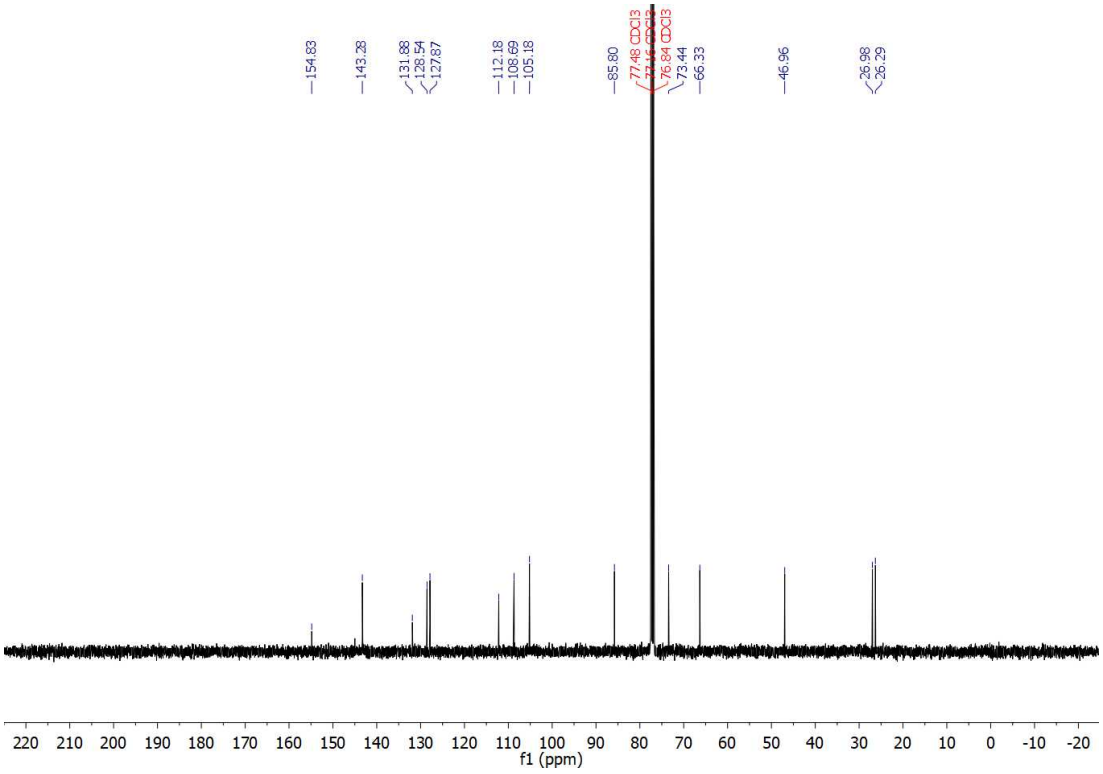

COSY
{1.38,1.38}
{1.56,1.57}
{2.65,2.64}
{4.83,3.70}
{3.69,3.78}
{4.83,4.40}
{4.42,4.37}
{4.39,4.84}
{3.70,4.82}
{5.15,5.14}
{4.83,4.79}
{5.14,5.75}
{5.75,5.74}
{8.81,8.79}
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f2 (ppm)
0 1 2 3 4 5 6 7 8 9
f1 (ppm)

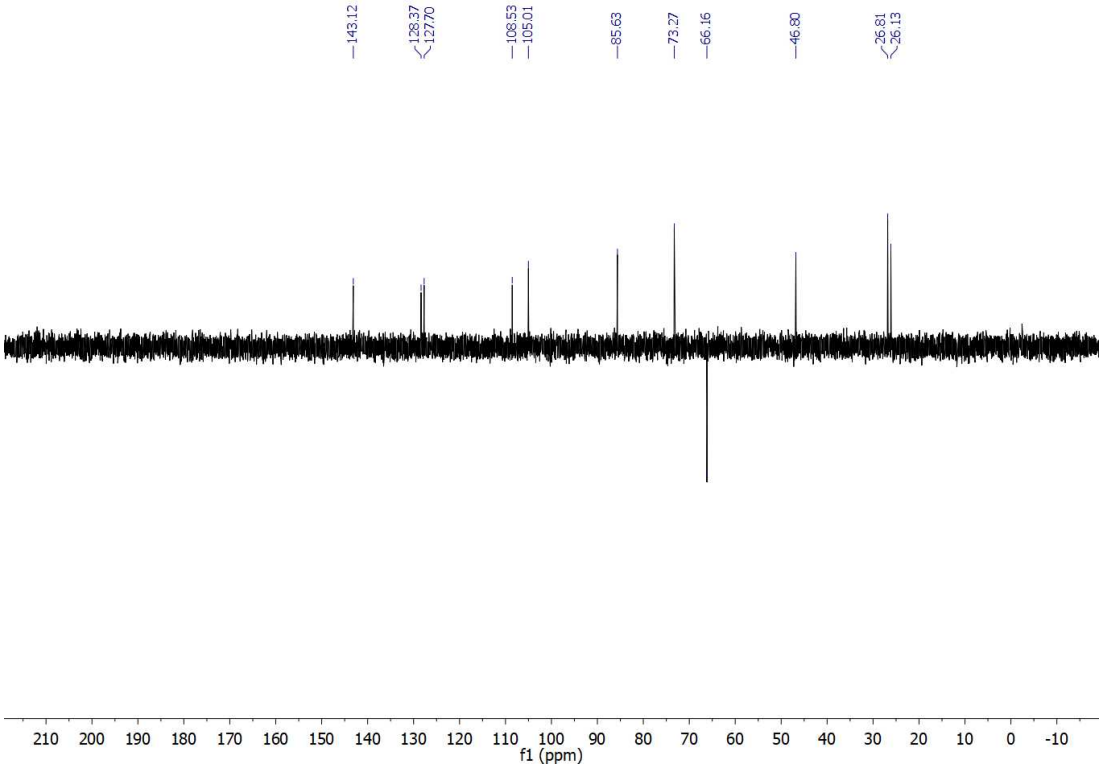

HSQC
{2.68,26.01}
{1.61,26.62}
{1.39,26.39}
{3.70,46.98}
{4.41,65.97}
{4.83,72.78}
{4.86,65.90}
{5.73,78.79}
{5.14,86.01}
{5.71,106.21}
{8.82,142.00}
f2 (ppm)
f1 (ppm)

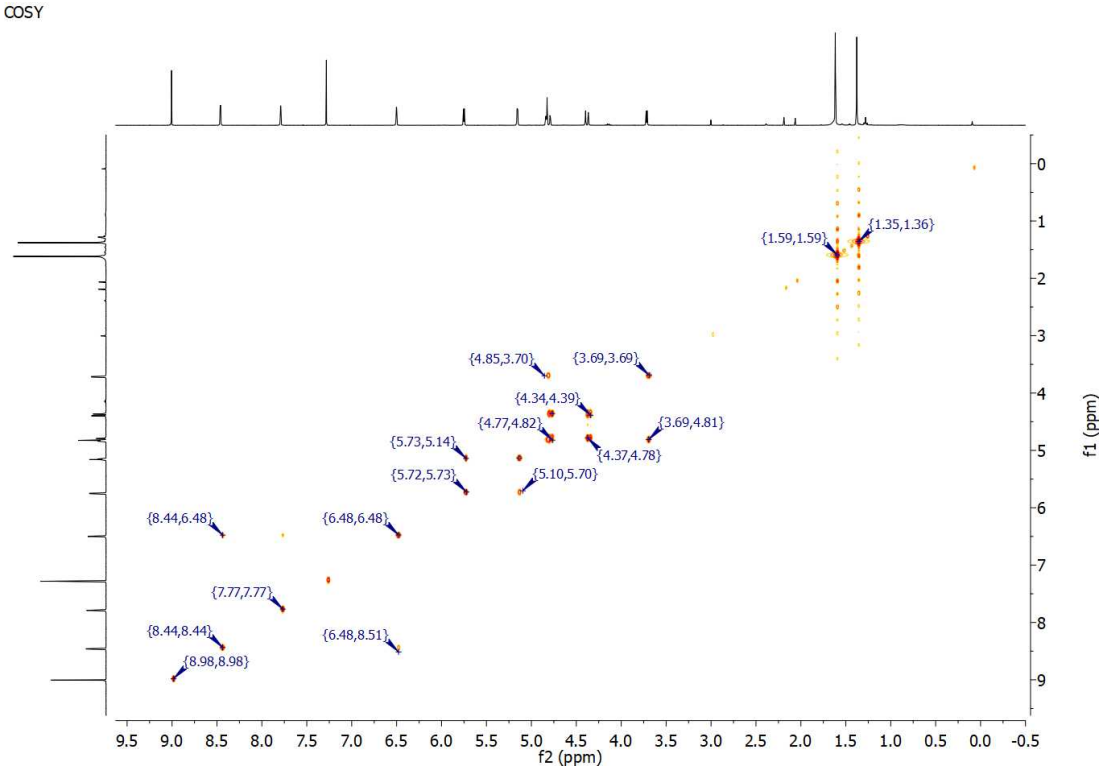

NOESY
{4.84,4.41}
{4.44,4.89}
f2 (ppm)
f1 (ppm)

(6aS,7aR,10aR,10bS)-9,9-dimethyl-3-(1H-pyrazol-1-yl)-6a,7a,10a,10b-tetrahydro-6H-[1,3] dioxolo[4'',5'':4',5']furo[3',2':4,5]pyrano[2,3-b]pyrazine (40):

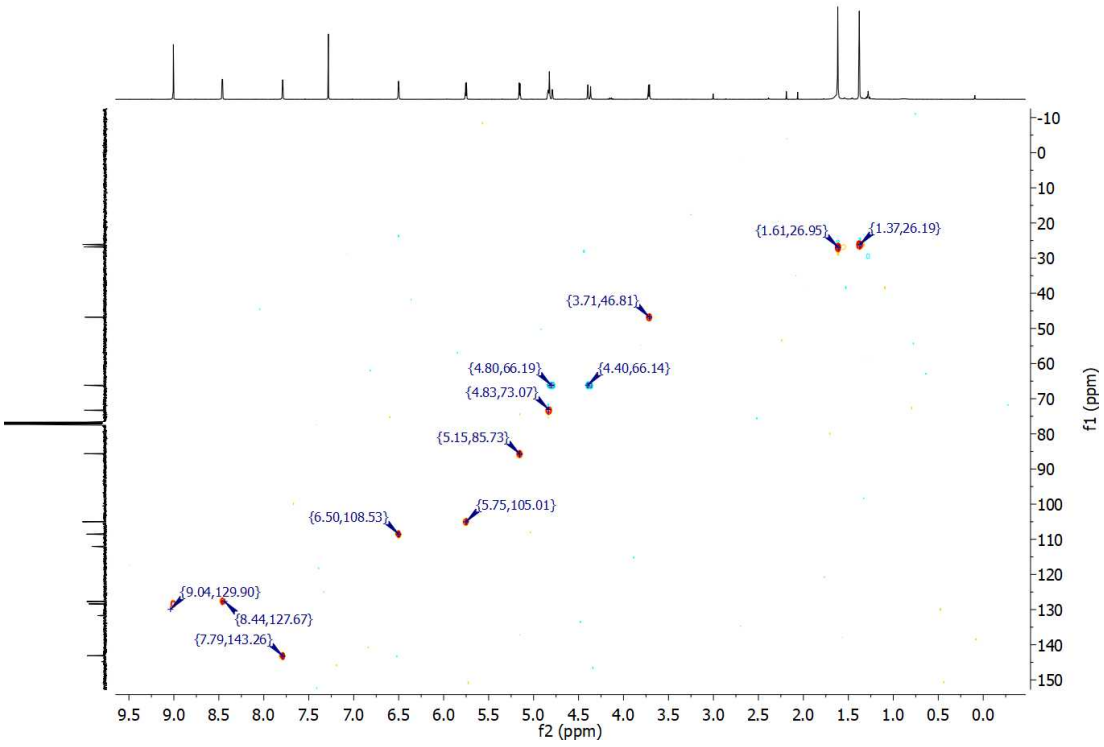




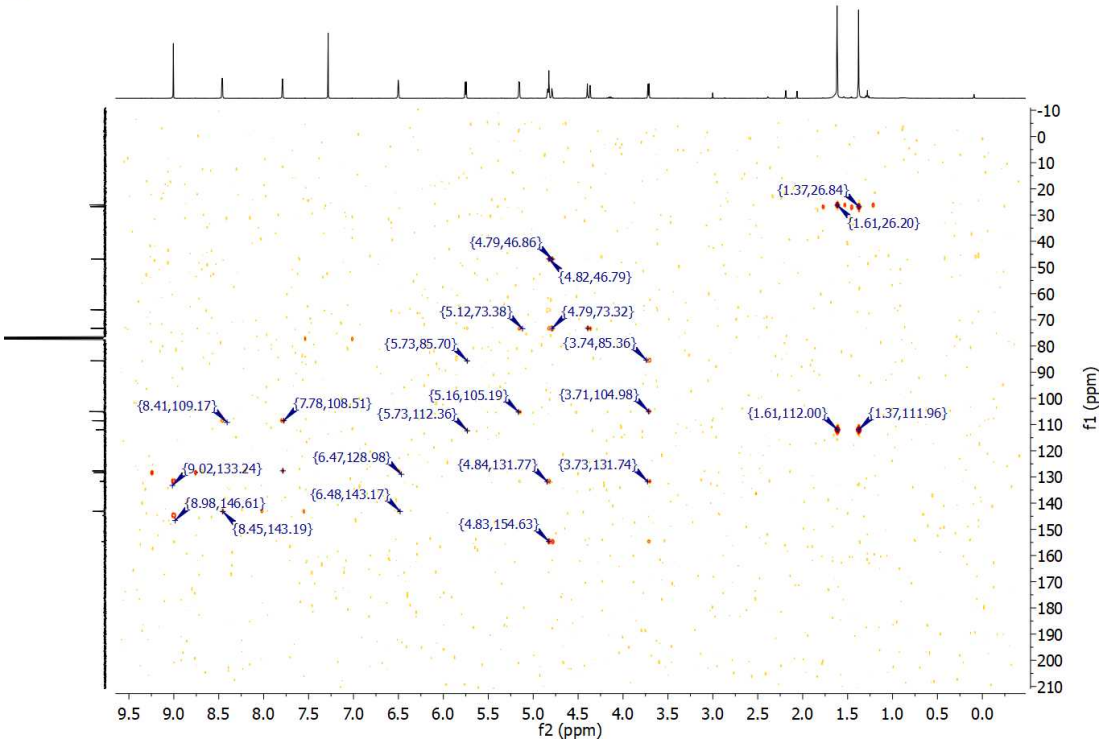

143.12
128.37
127.70
108.53
105.01
85.63
73.27
66.16
46.80
26.81
26.13
f1 (ppm)

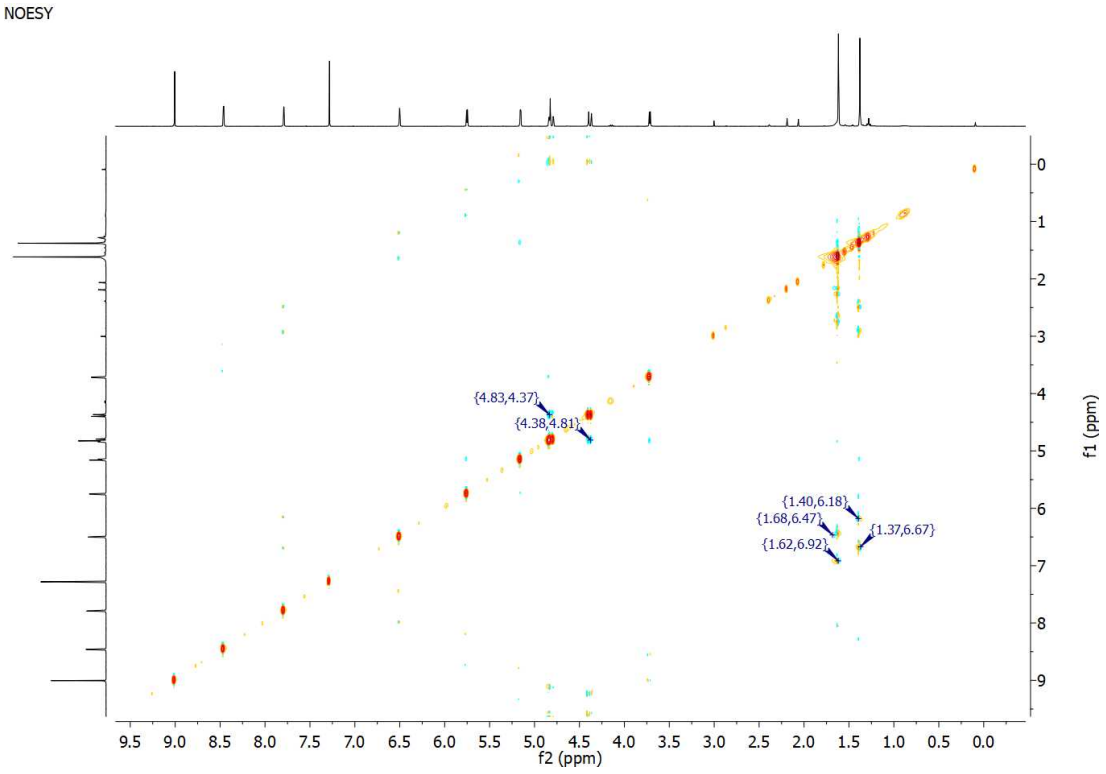

COSY
{1.59,1.59}
{1.35,1.36}
{4.85,3.70}
{3.69,3.69}
{4.34,4.39}
{4.77,4.82}
{3.69,4.81}
{5.73,5.14}
{4.37,4.78}
{5.72,5.73}
{5.10,5.70}
{8.44,6.48}
{6.48,6.48}
{7.77,7.77}
{8.44,8.44}
{6.48,8.51}
{8.98,8.98}
f2 (ppm)
f1 (ppm)

HSQC

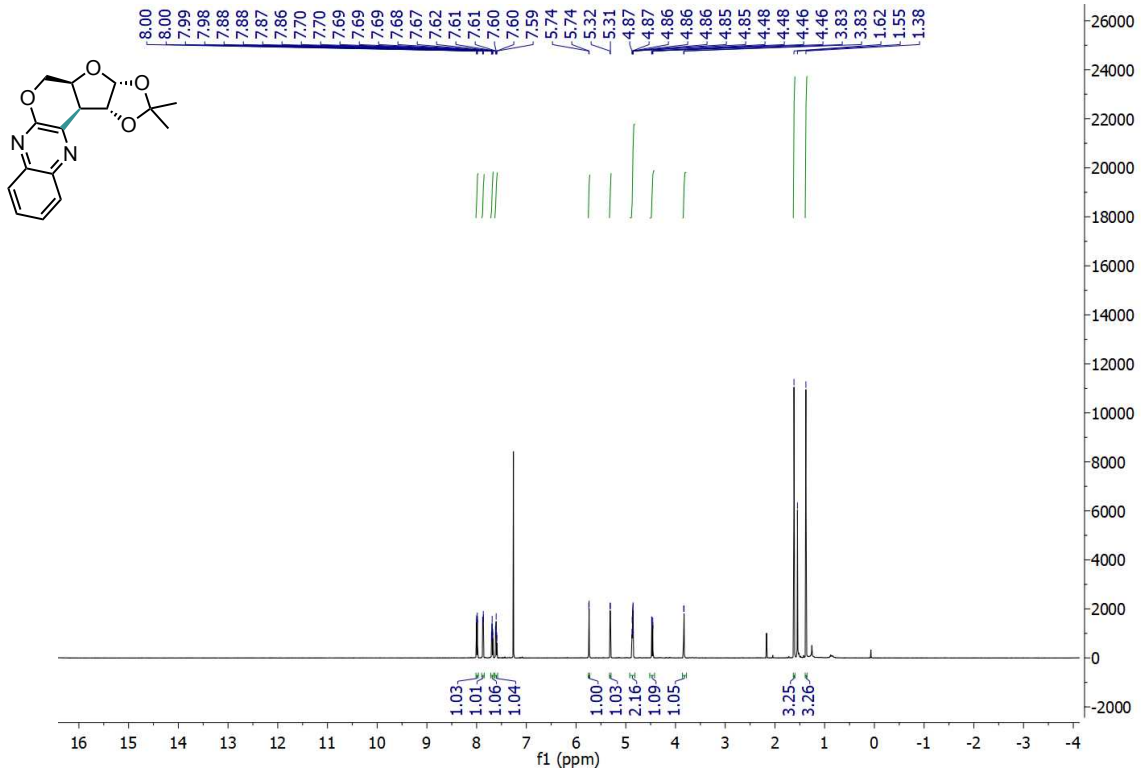

{1.61,26.95}
{1.37,26.19}
{3.71,46.81}
{4.80,66.19}
{4.40,66.14}
{4.83,73.07}
{5.15,85.73}
{6.50,108.53}
{5.75,105.01}
{9.04,129.90}
{8.44,127.67}
{7.79,143.26}
f2 (ppm)
f1 (ppm)

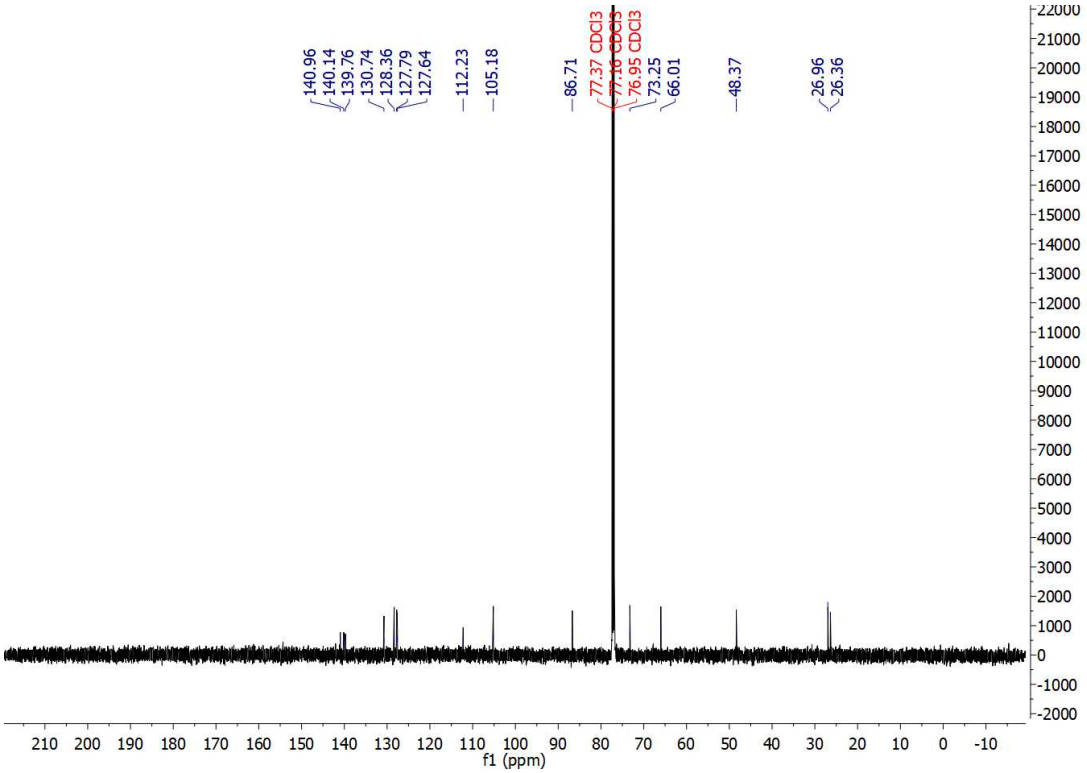
HMBC

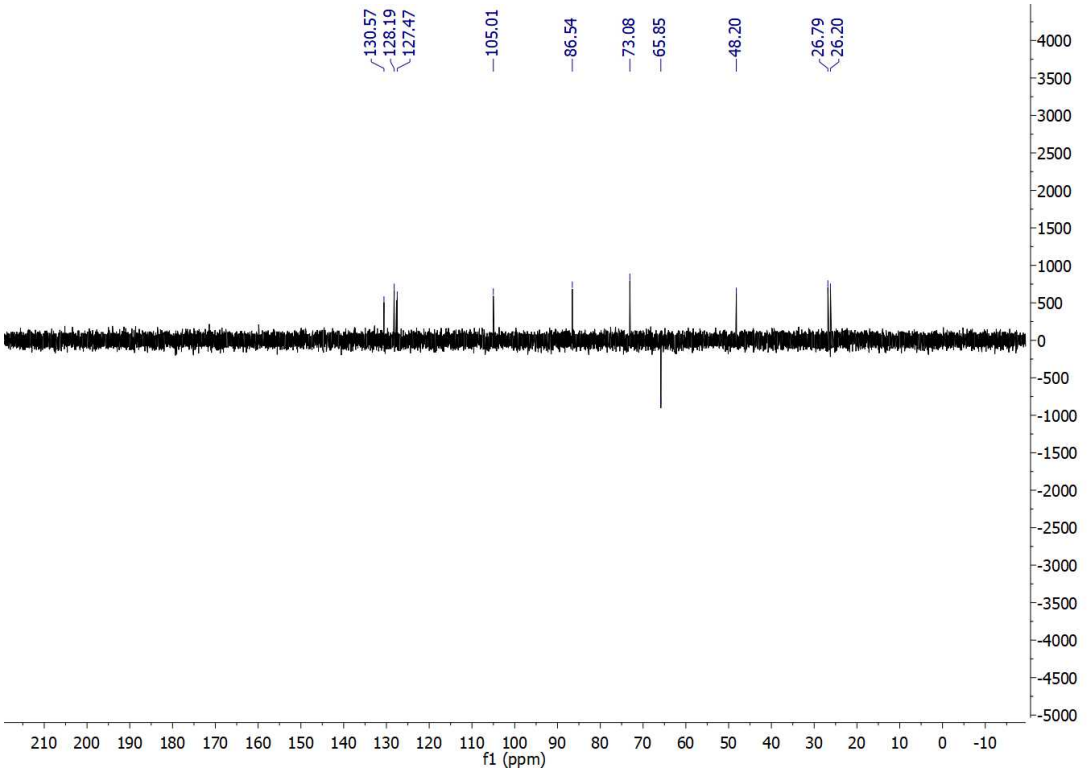

{1.37,26.84}
{1.61,26.20}
{4.79,46.86}
{4.82,46.79}
{5.12,73.38}
{4.79,73.32}
{5.73,85.70}
{3.74,85.36}
{8.41,109.17}
{7.78,108.51}
{5.16,105.19}
{3.71,104.98}
{5.73,112.36}
{1.61,112.00}
{1.37,111.96}
{6.47,128.98}
{9.02,133.24}
{4.84,131.77}
{3.73,131.74}
{6.48,143.17}
{8.98,146.61}
{8.45,143.19}
{4.83,154.63}
f2 (ppm)
f1 (ppm)



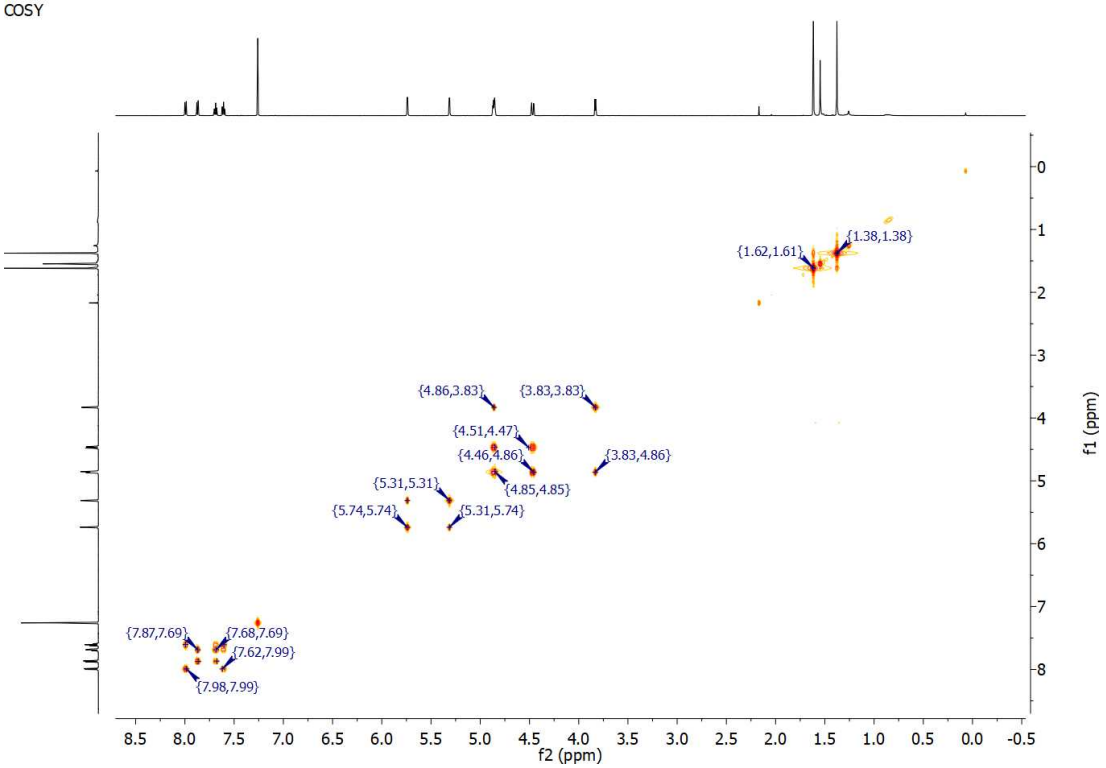
(3aR,4aS,12bS,12cR)-2,2-dimethyl-3a,4a,12b,12c-tetrahydro-5H-[1,3]dioxolo[4'',5'':4',5'] furo[3',2':4,5]pyrano[2,3-b]quinoxaline (41):



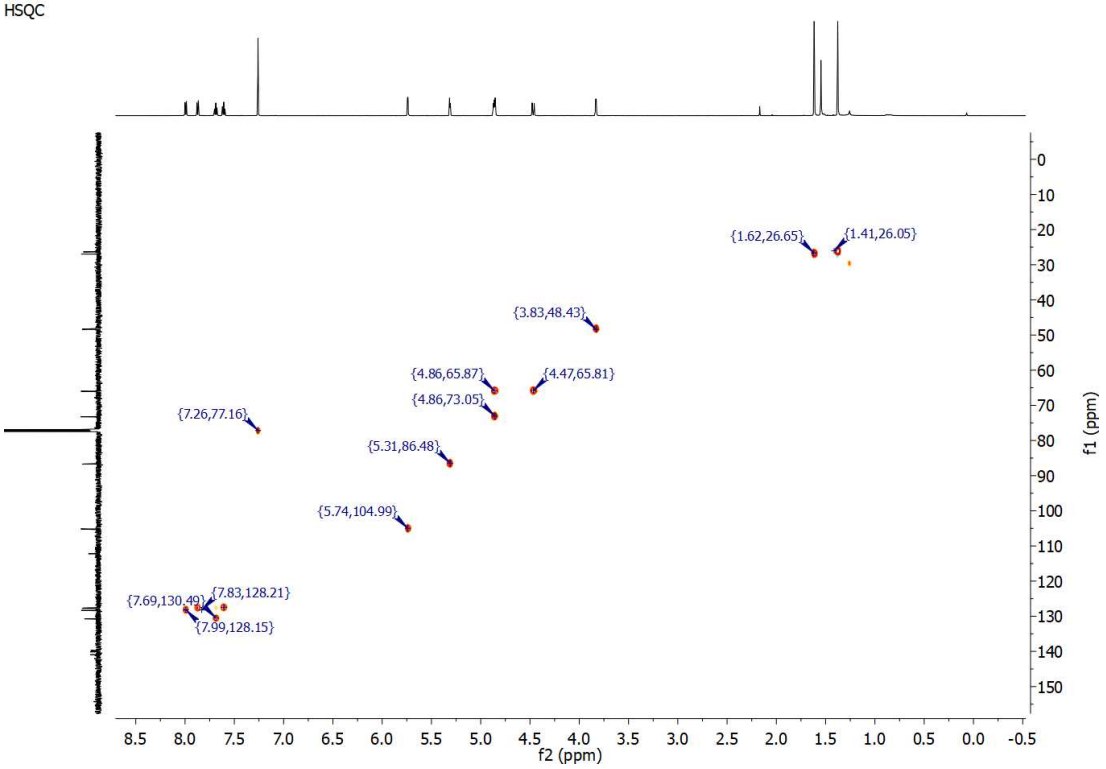

140.96
140.14
139.76
130.74
128.36
127.79
127.64
112.23
105.18
86.71
77.37 CDCl3
77.16 CDCl3
76.95 CDCl3
73.25
66.01
48.37
26.96
26.36
f1 (ppm)


130.57
128.19
127.47
105.01
86.54
73.08
65.85
48.20
26.79
26.20
f1 (ppm)

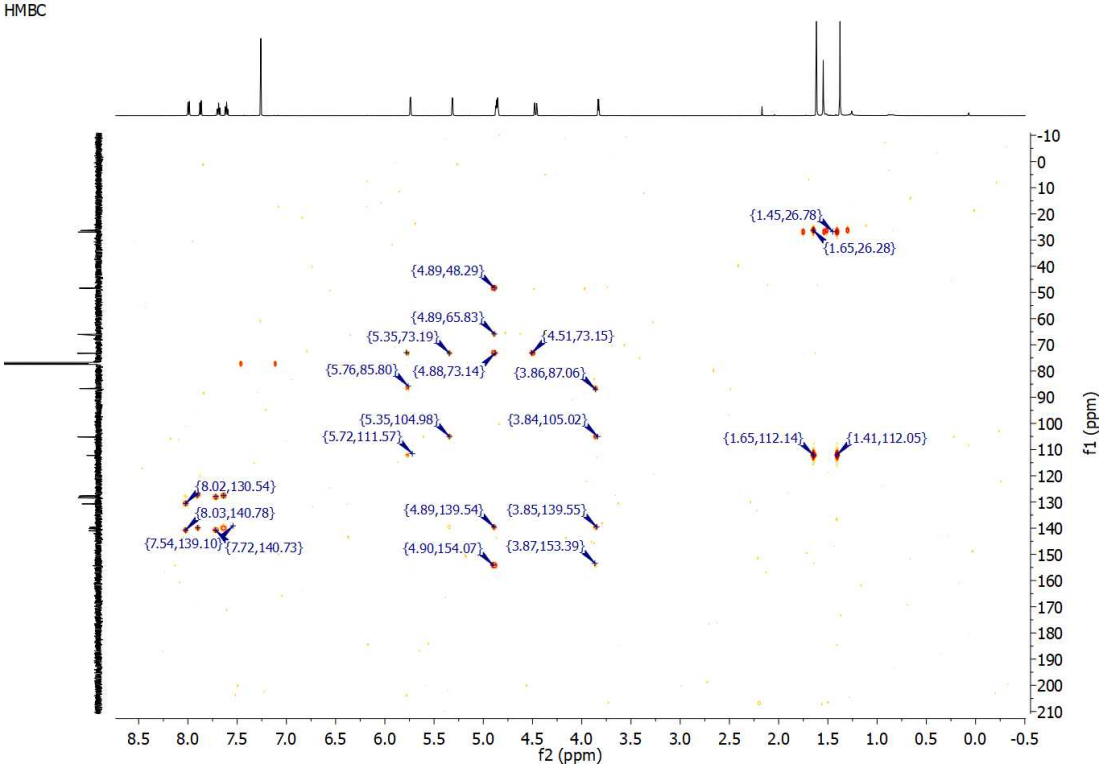
COSY


{1.62,1.61}
{1.38,1.38}
{4.86,3.83}
{3.83,3.83}
{4.51,4.47}
{4.46,4.86}
{3.83,4.86}
{4.85,4.85}
{5.31,5.31}
{5.74,5.74}
{5.31,5.74}
{7.87,7.69}
{7.68,7.69}
{7.62,7.99}
{7.98,7.99}
f2 (ppm)
f1 (ppm)

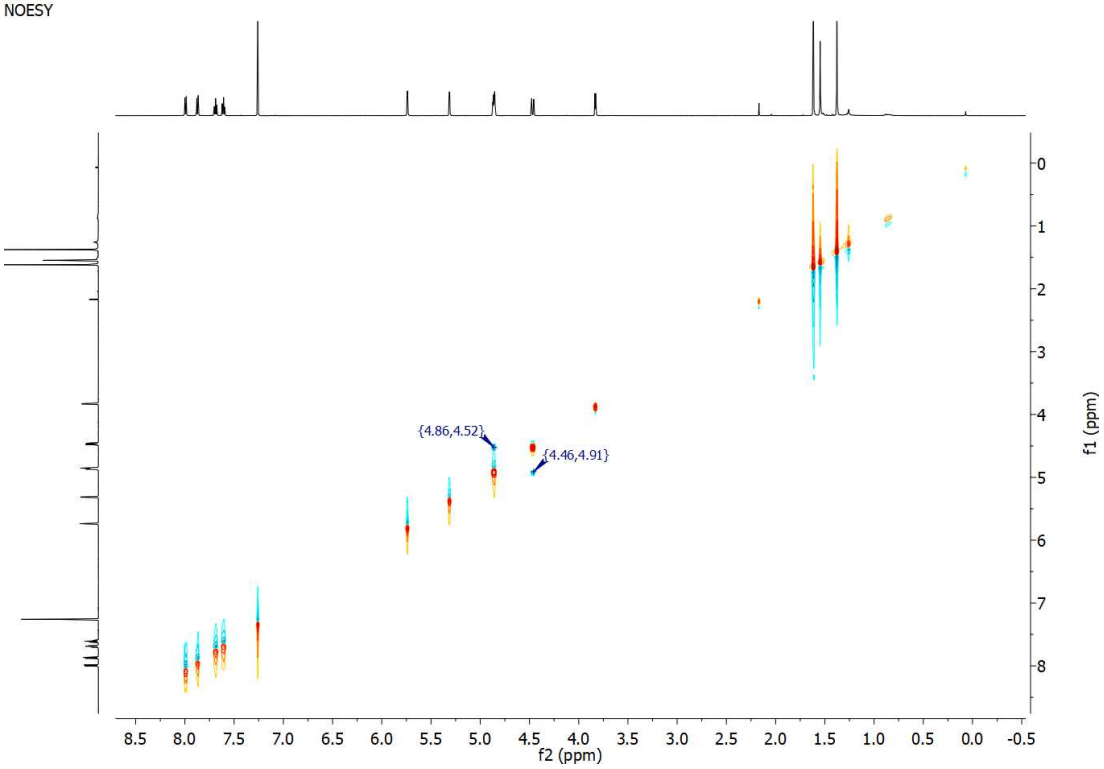
HSQC


{1.62,26.65}
{1.41,26.05}
{3.83,48.43}
{4.86,65.87}
{4.47,65.81}
{4.86,73.05}
{7.26,77.16}
{5.31,86.48}
{5.74,104.99}
{7.69,130.49}
{7.83,128.21}
{7.99,128.15}
f2 (ppm)
f1 (ppm)

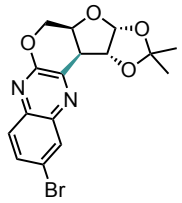
HMBC

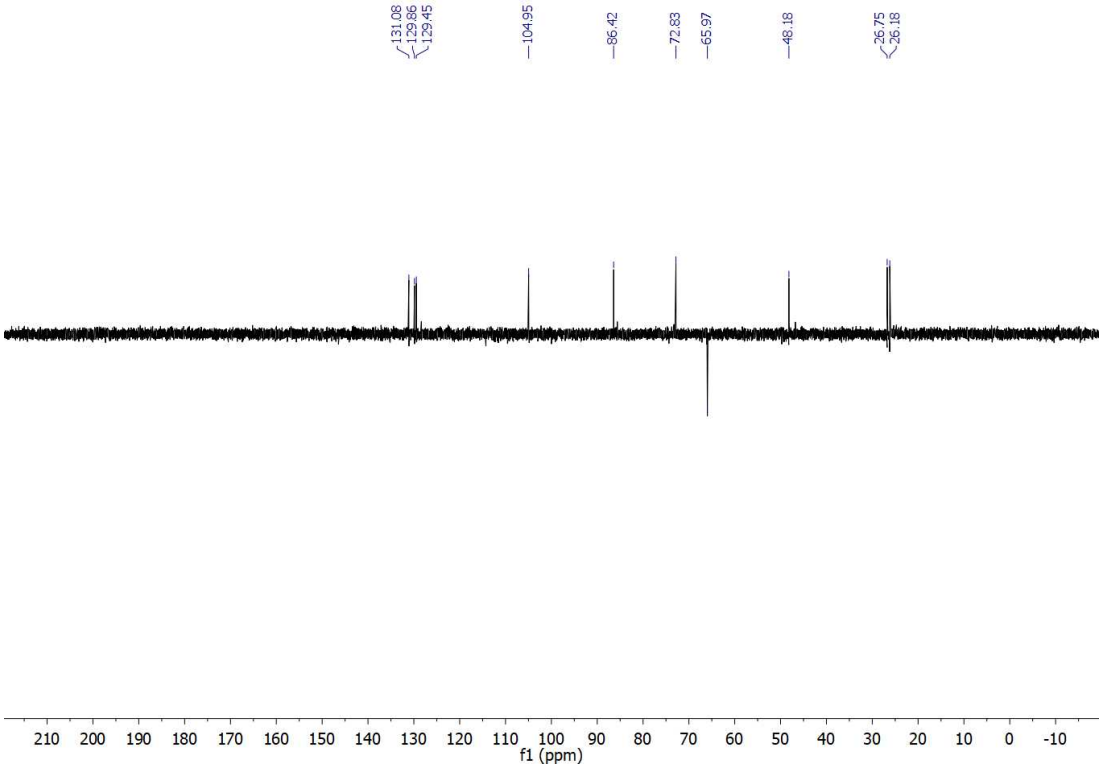

{1.45,26.78}
{1.65,26.28}
{4.89,48.29}
{4.89,65.83}
{5.35,73.19}
{4.51,73.15}
{5.76,85.80}
{4.88,73.14}
{3.86,87.06}
{5.35,104.98}
{3.84,105.02}
{5.72,111.57}
{1.65,112.14}
{1.41,112.05}
{8.02,130.54}
{8.03,140.78}
{4.89,139.54}
{3.85,139.55}
{7.54,139.10}
{7.72,140.73}
{4.90,154.07}
{3.87,153.39}
f2 (ppm)
f1 (ppm)

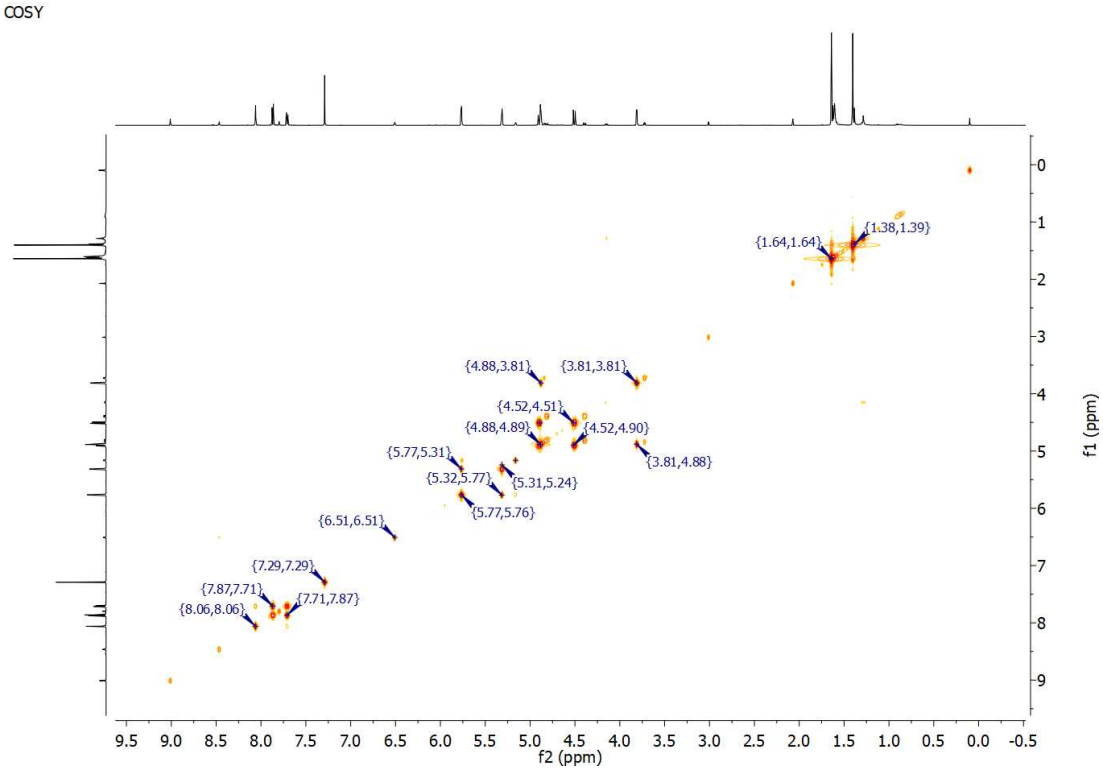
NOESY


{4.86,4.52}
{4.46,4.91}
f2 (ppm)
f1 (ppm)

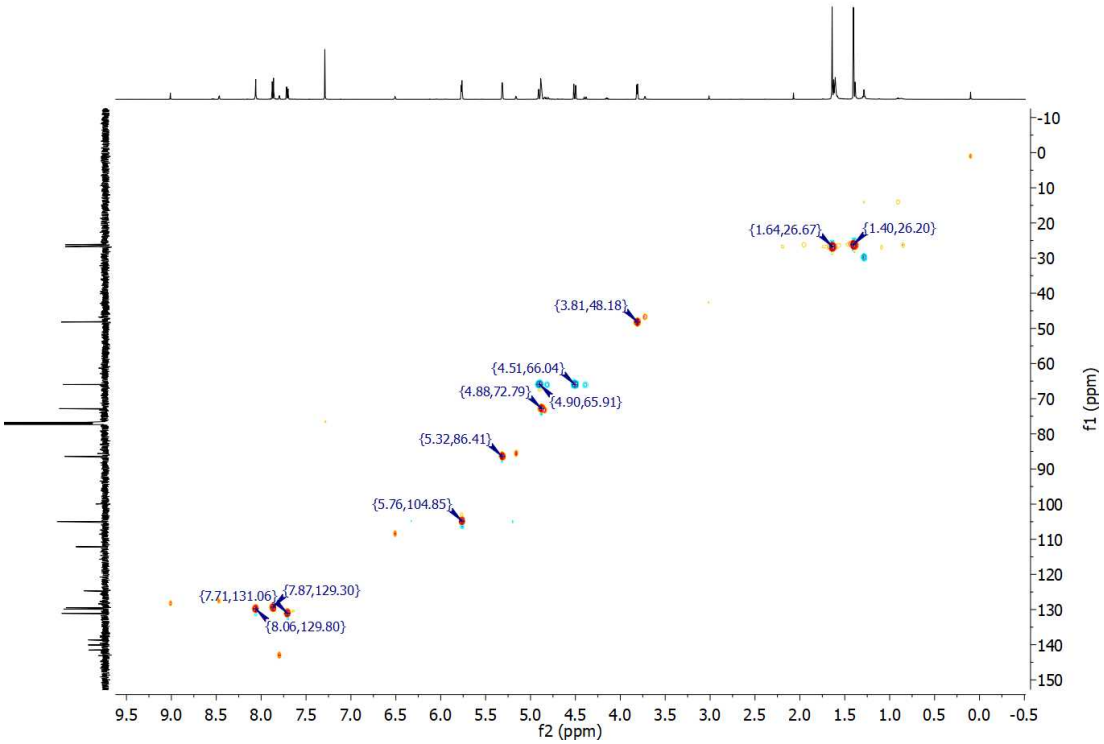
(3aR,4aS,12bS,12cR)-10-bromo-2,2-dimethyl-3a,4a,12b,12c-tetrahydro-5H-[1,3]dioxolo [4'',5'':4',5']furo[3',2':4,5]pyrano[2,3-b]quinoxaline (42):



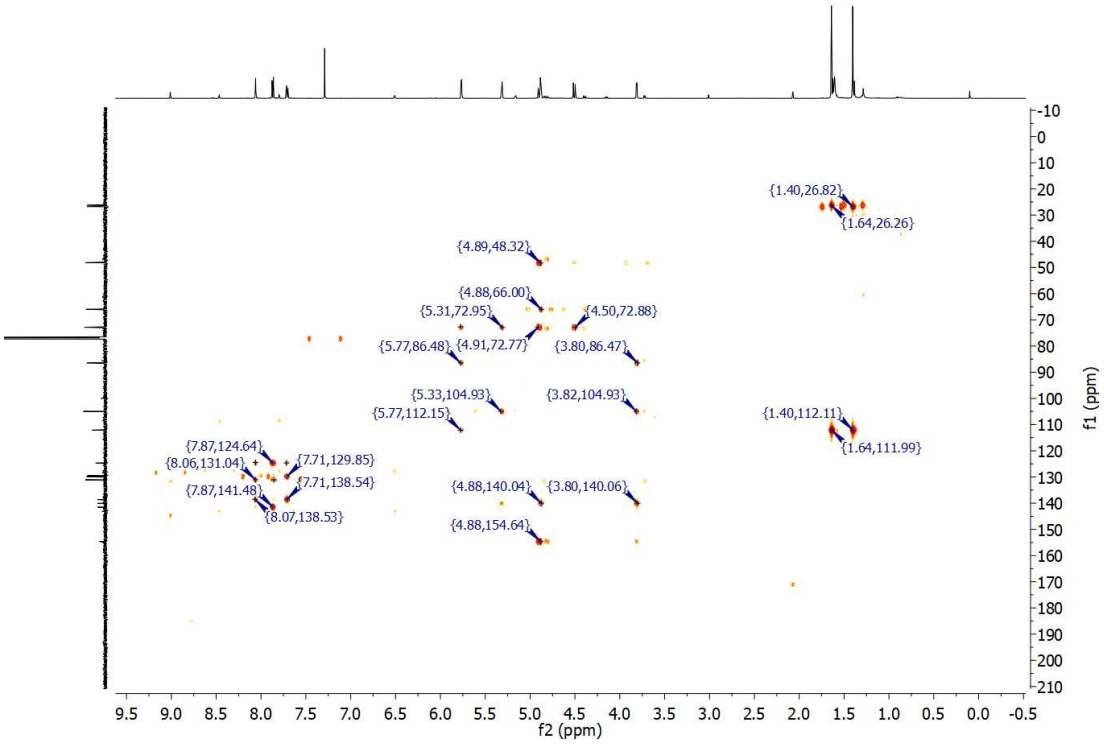

131.08
129.86
129.45
104.95
86.42
72.83
65.97
48.18
26.75
26.18
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

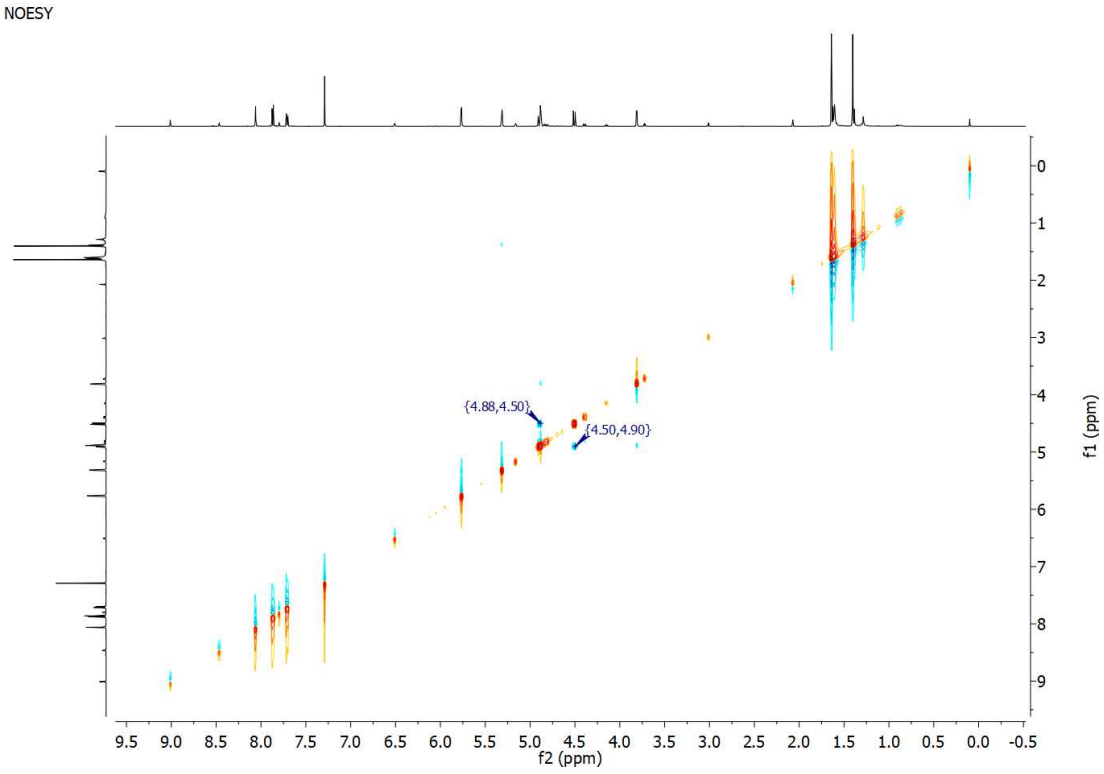

COSY
{1.64,1.64}
{1.38,1.39}
{4.88,3.81}
{3.81,3.81}
{4.52,4.51}
{4.88,4.89}
{4.52,4.90}
{5.77,5.31}
{3.81,4.88}
{5.32,5.77}
{5.31,5.24}
{5.77,5.76}
{6.51,6.51}
{7.29,7.29}
{7.87,7.71}
{7.71,7.87}
{8.06,8.06}
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f2 (ppm)
0 1 2 3 4 5 6 7 8 9
f1 (ppm)

HSQC

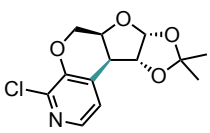

{1.64,26.67}
{1.40,26.20}
{3.81,48.18}
{4.51,66.04}
{4.88,72.79}
{4.90,65.91}
{5.32,86.41}
{5.76,104.85}
{7.71,131.06}
{7.87,129.30}
{8.06,129.80}
f1 (ppm)
f2 (ppm)

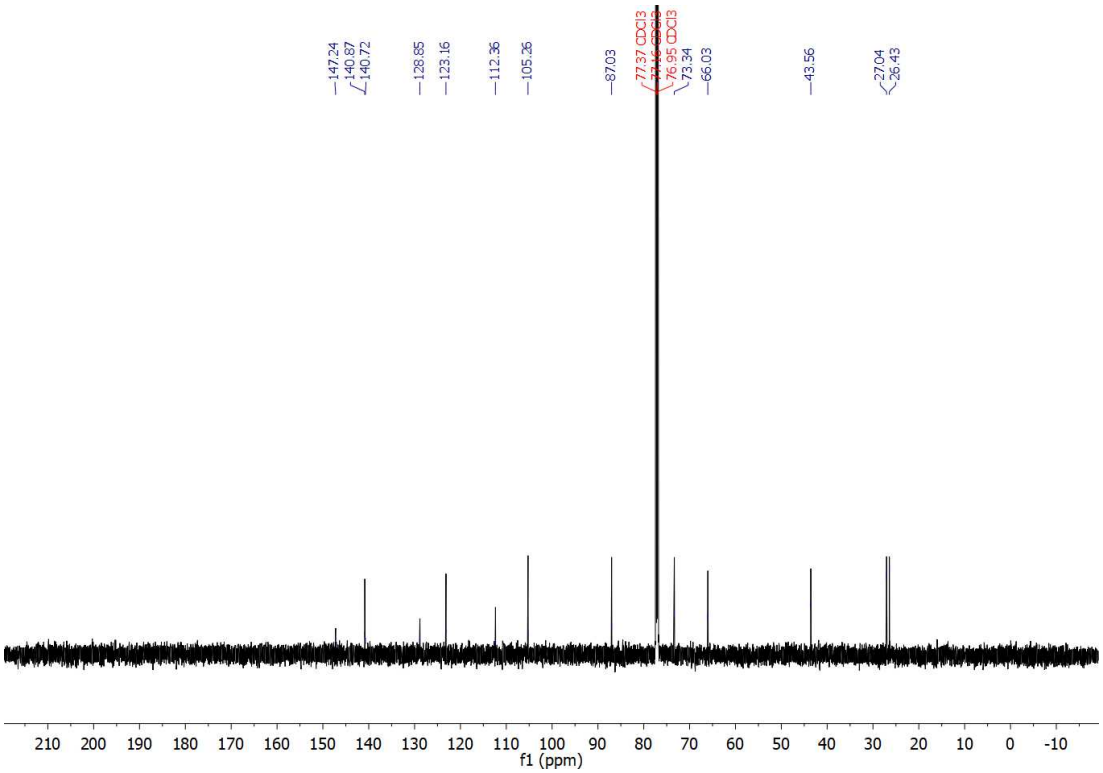
HMBC

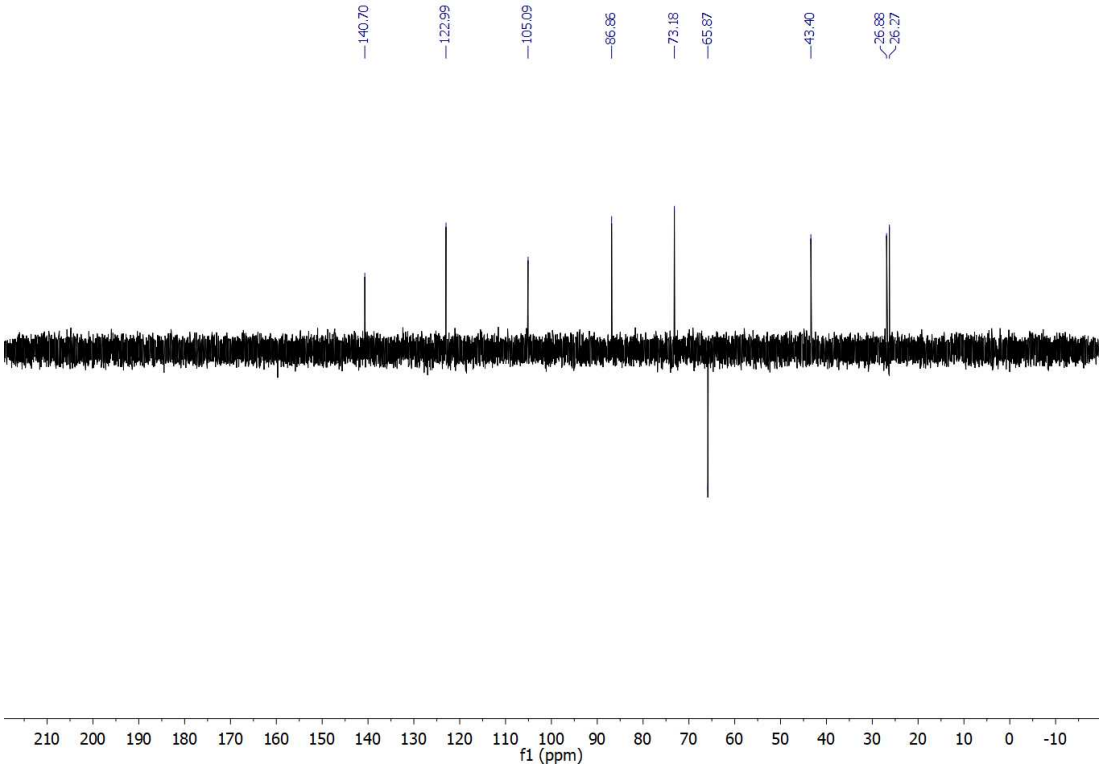

{1.40,26.82}
{1.64,26.26}
{4.89,48.32}
{4.88,66.00}
{5.31,72.95}
{4.50,72.88}
{5.77,86.48}
{4.91,72.77}
{3.80,86.47}
{5.33,104.93}
{3.82,104.93}
{5.77,112.15}
{1.40,112.11}
{1.64,111.99}
{7.87,124.64}
{8.06,131.04}
{7.71,129.85}
{7.71,138.54}
{7.87,141.48}
{8.07,138.53}
{4.88,140.04}
{3.80,140.06}
{4.88,154.64}
f1 (ppm)
f2 (ppm)



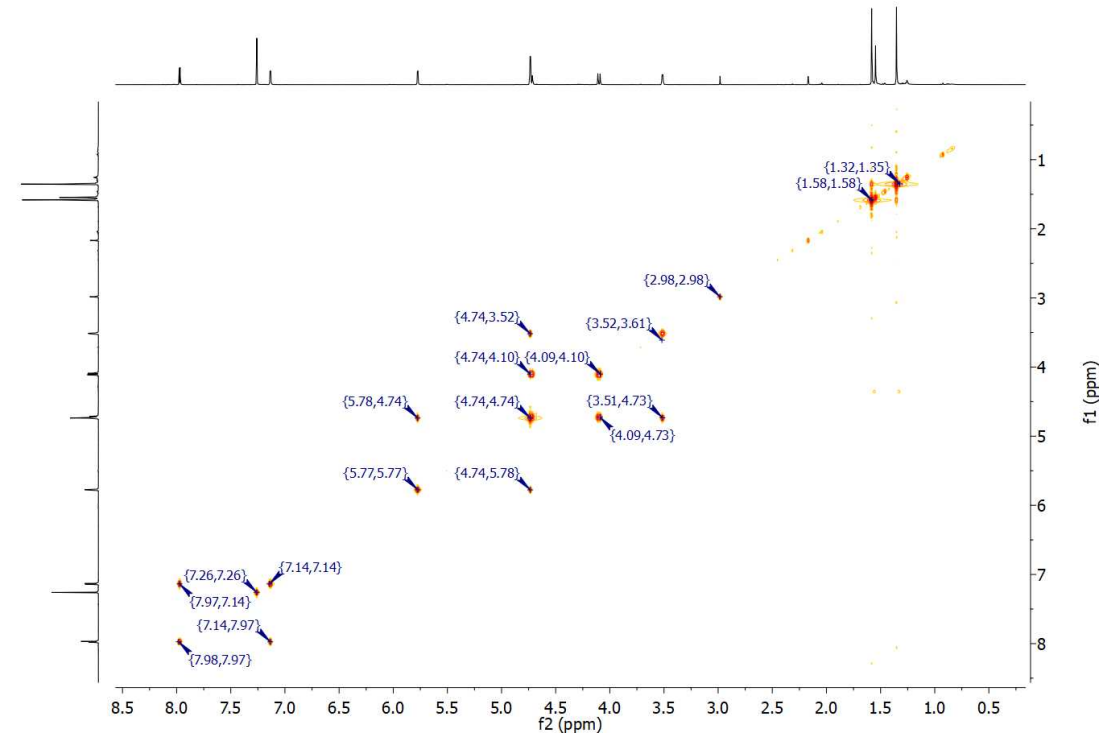
(6aS,7aR,10aR,10bS)-4-chloro-9,9-dimethyl-6a,7a,10a,10b-tetrahydro-6H-[1,3] dioxolo[4'',5'':4',5']furo[3',2':4,5]pyrano[2,3-c]pyridine (51):



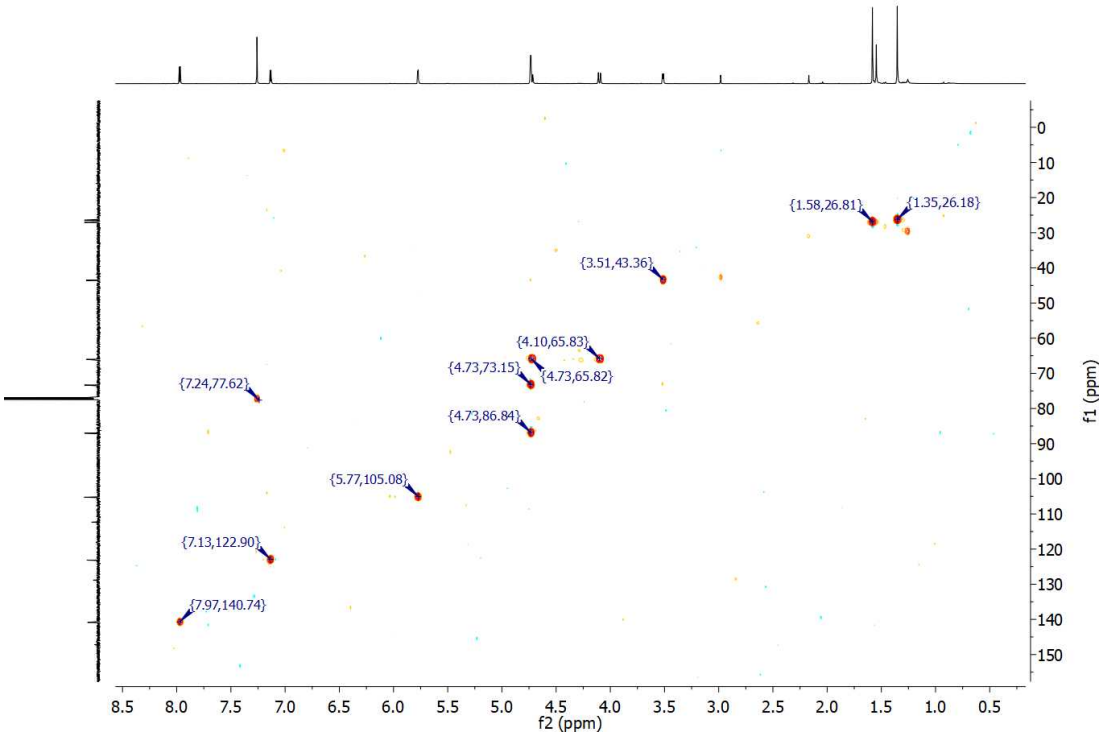

147.24
140.87
140.72
128.85
123.16
112.36
105.26
87.03
77.37 CDCl3
76.95 CDCl3
73.34
66.03
43.56
27.04
26.43
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


140.70
122.99
105.09
86.86
73.18
65.87
43.40
26.88
26.27
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

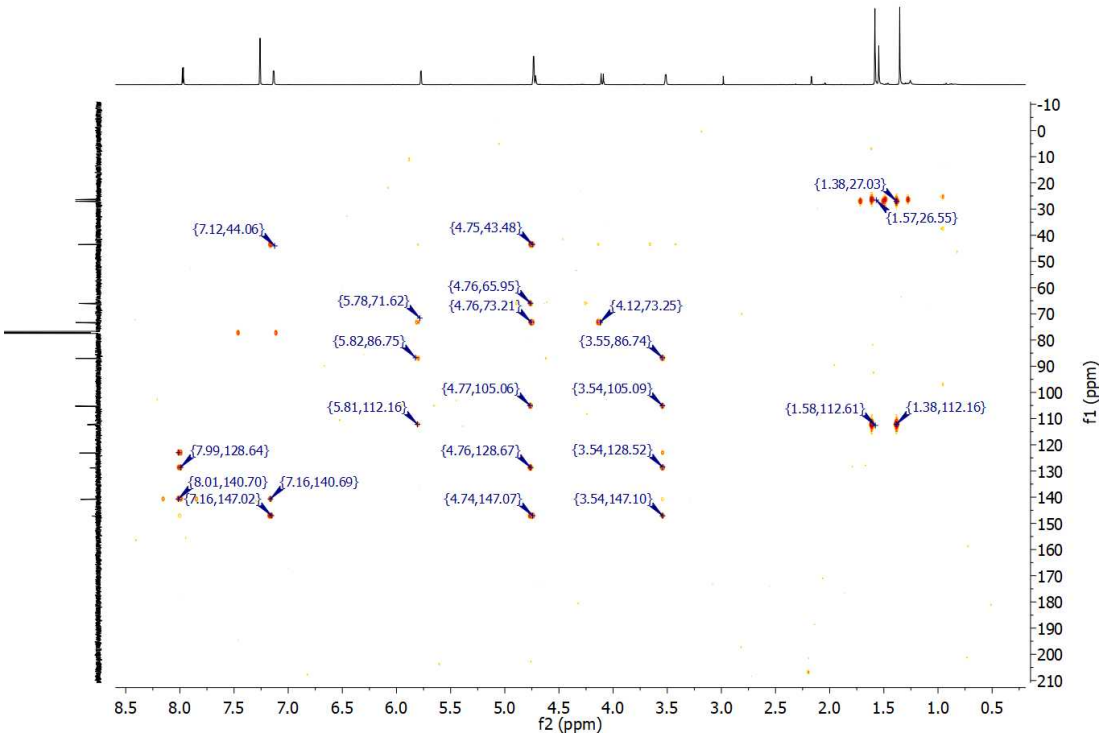
COSY


{1.32,1.35}
{1.58,1.58}
{2.98,2.98}
{4.74,3.52}
{3.52,3.61}
{4.74,4.10}
{4.09,4.10}
{5.78,4.74}
{4.74,4.74}
{3.51,4.73}
{4.09,4.73}
{5.77,5.77}
{4.74,5.78}
{7.26,7.26}
{7.14,7.14}
{7.97,7.14}
{7.14,7.97}
{7.98,7.97}
f1 (ppm)
f2 (ppm)

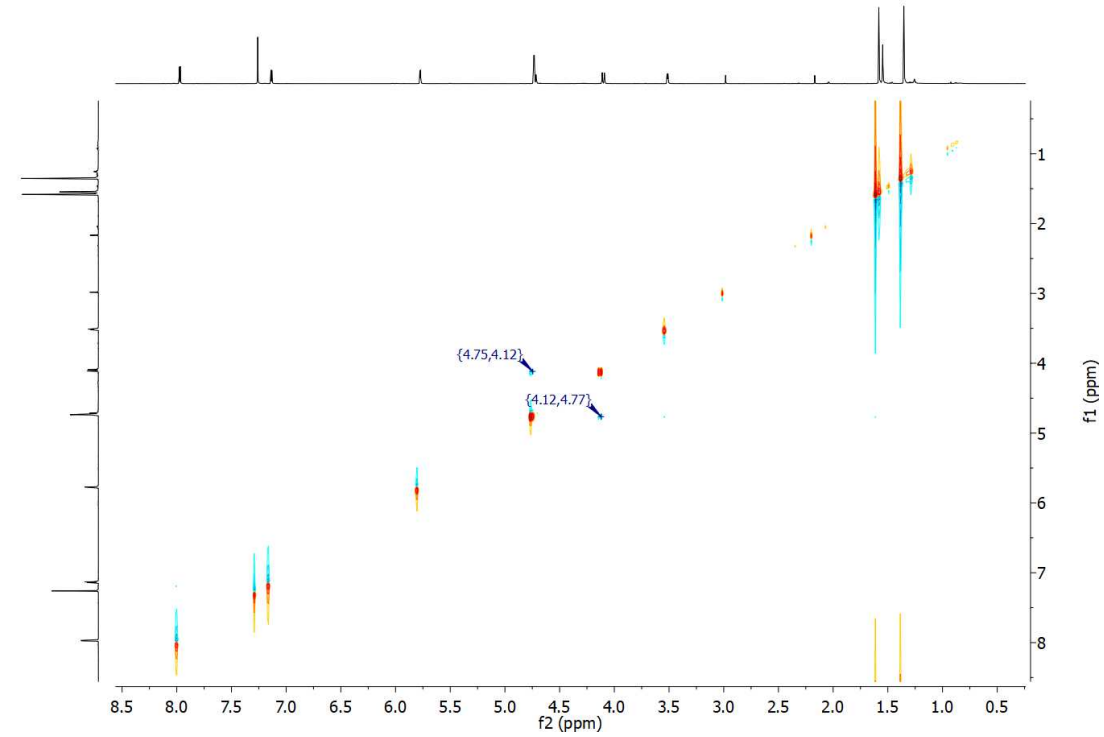
HSQC


{1.58,26.81}
{1.35,26.18}
{3.51,43.36}
{4.10,65.83}
{4.73,73.15}
{4.73,65.82}
{7.24,77.62}
{4.73,86.84}
{5.77,105.08}
{7.13,122.90}
{7.97,140.74}
f1 (ppm)
f2 (ppm)

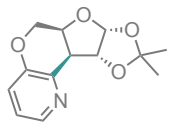
HMBC

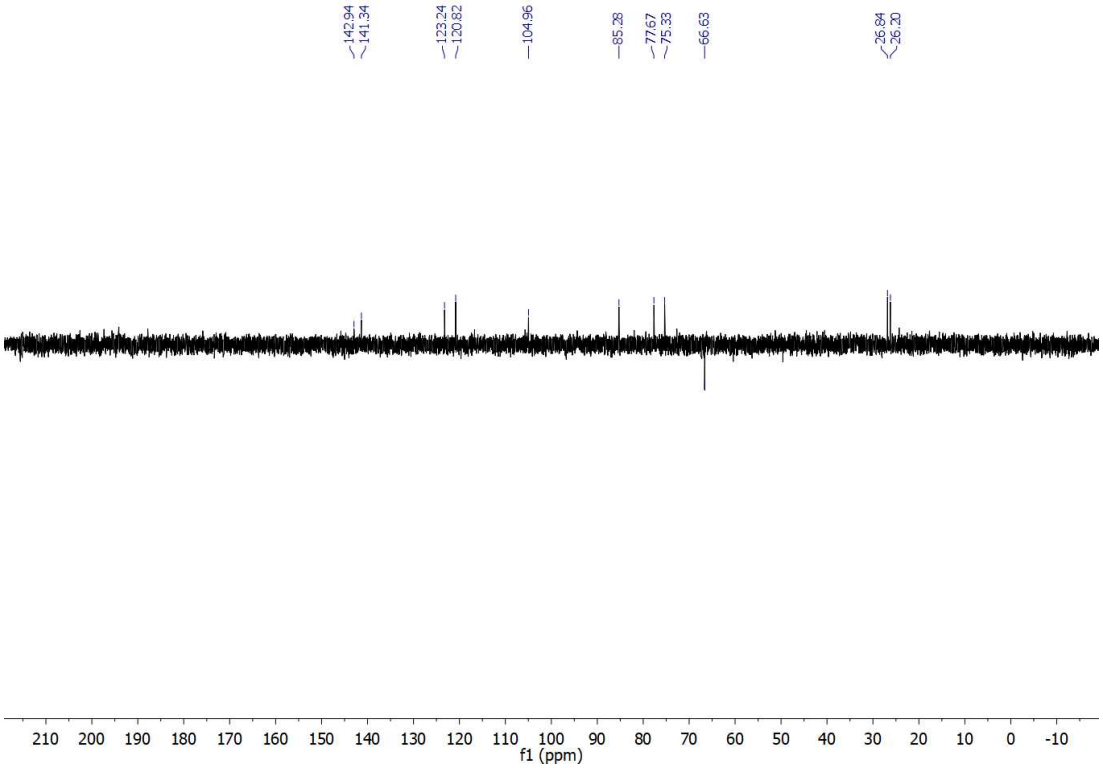

{1.38,27.03}
{1.57,26.55}
{7.12,44.06}
{4.75,43.48}
{4.76,65.95}
{5.78,71.62}
{4.76,73.21}
{4.12,73.25}
{5.82,86.75}
{3.55,86.74}
{4.77,105.06}
{3.54,105.09}
{5.81,112.16}
{1.58,112.61}
{1.38,112.16}
{7.99,128.64}
{4.76,128.67}
{3.54,128.52}
{8.01,140.70}
{7.16,140.69}
{7.16,147.02}
{4.74,147.07}
{3.54,147.10}
f2 (ppm)
f1 (ppm)

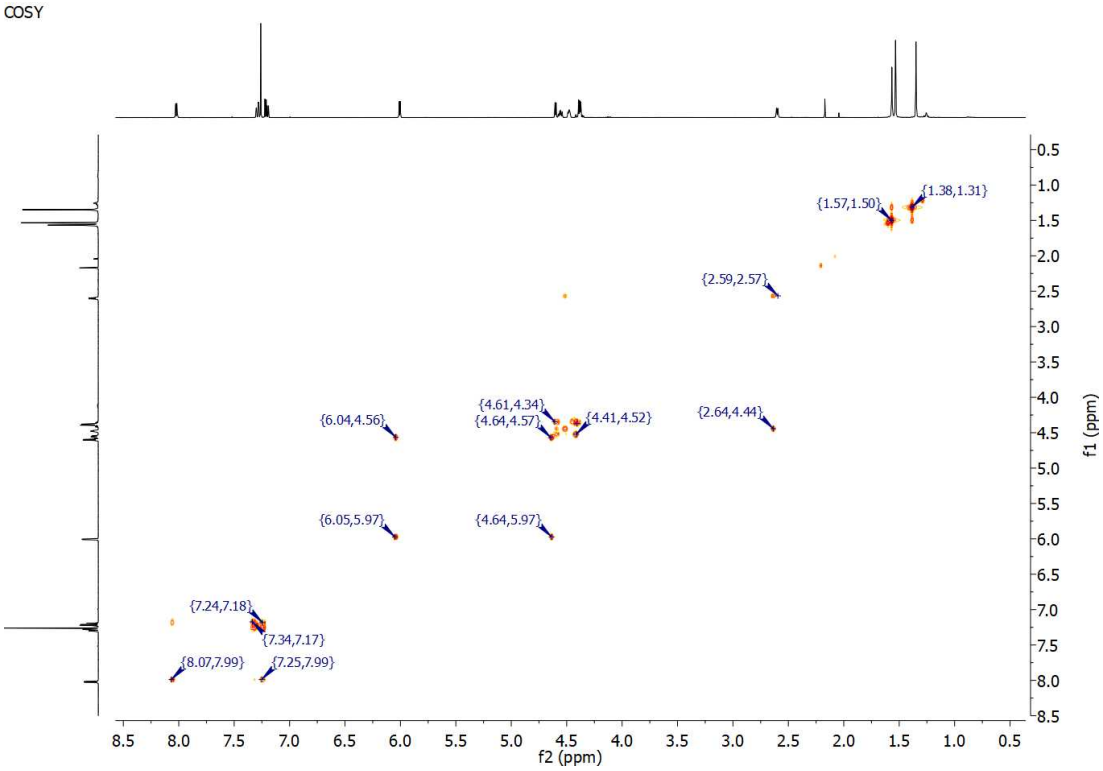
NOESY

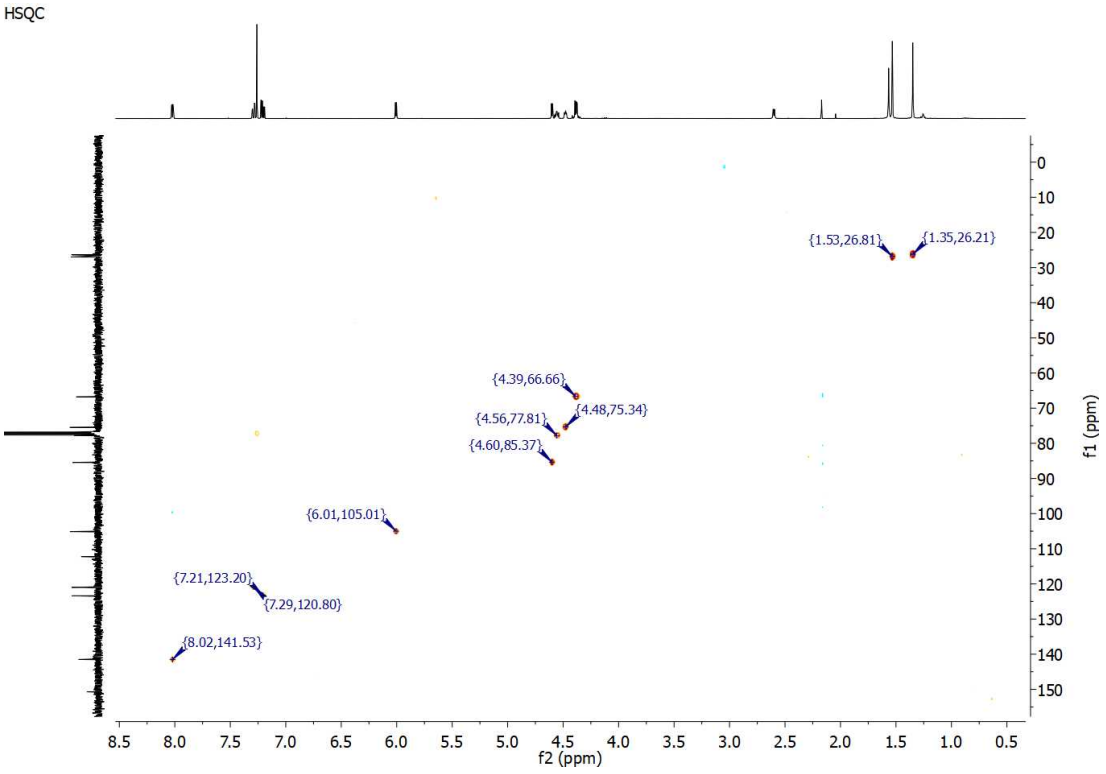

{4.75,4.12}
{4.12,4.77}
f2 (ppm)
f1 (ppm)

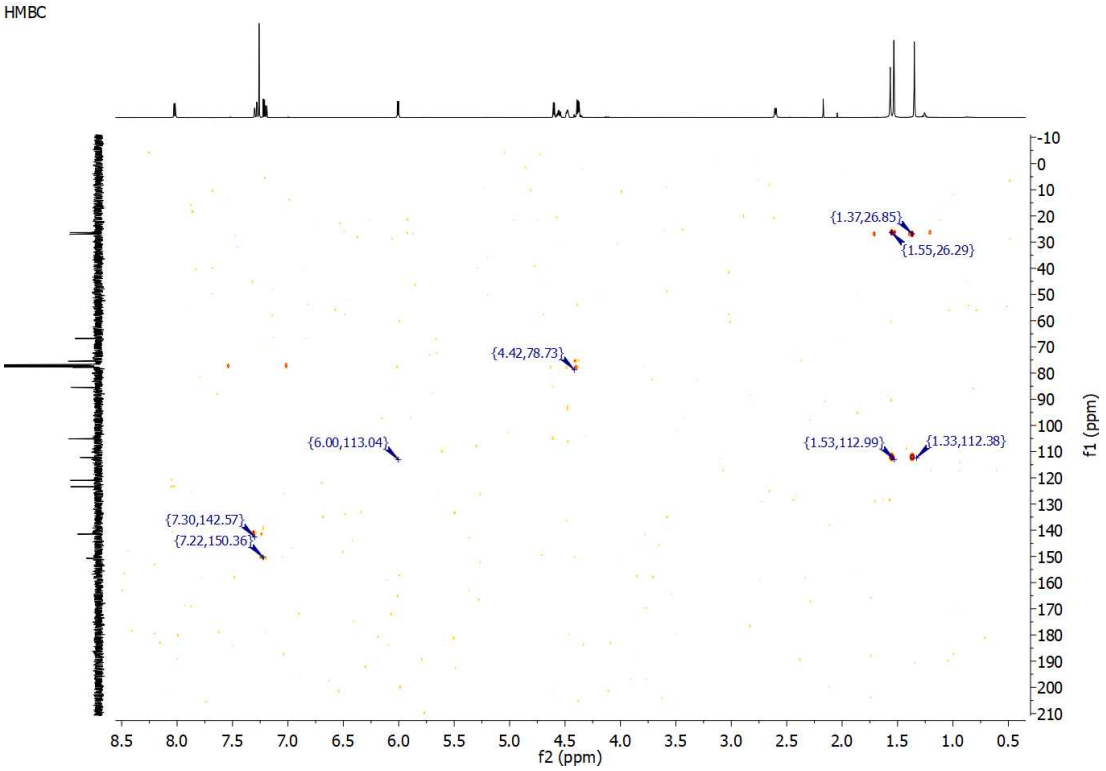
(6a*S*,7a*R*,10a*R*,10b*S*)-9,9-dimethyl-6a,7a,10a,10b-tetrahydro-6*H*-[1,3]dioxolo[4'',5'':4',5']furo[3',2':4,5]pyrano[3,2-*b*]pyridine (51'):

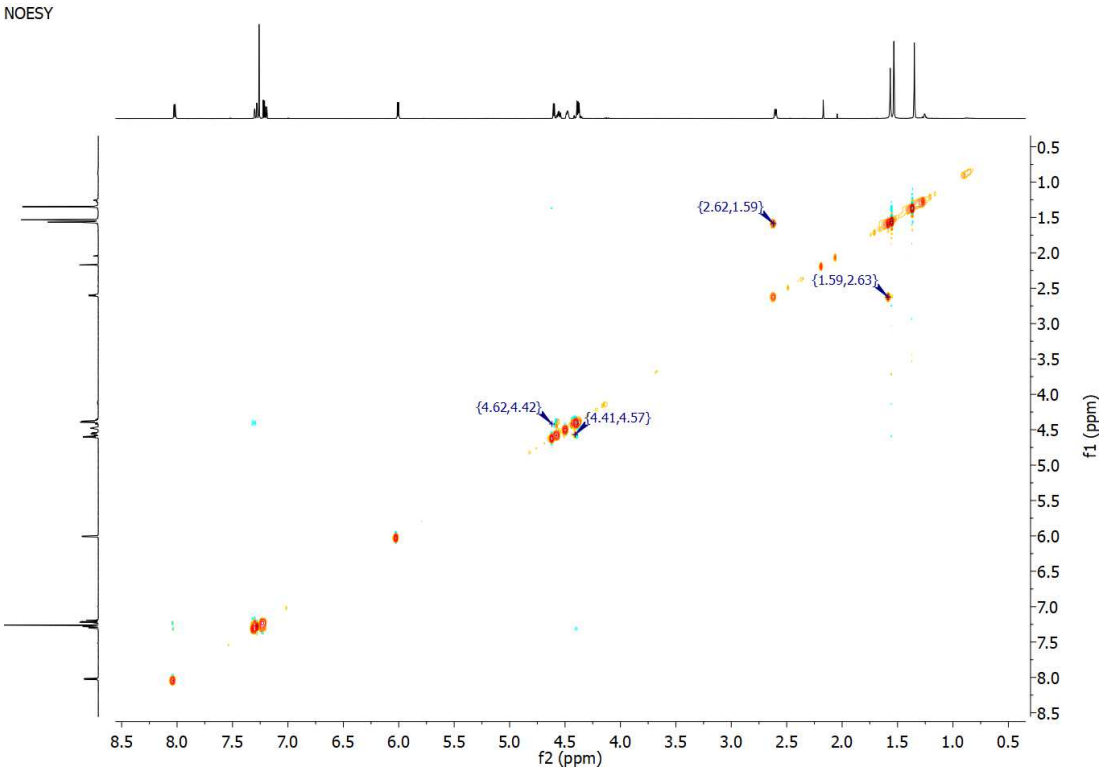



142.94
141.34
123.24
120.82
104.96
85.28
77.67
75.33
66.63
26.84
26.20
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

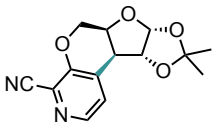

COSY
{1.57,1.50}
{1.38,1.31}
{2.59,2.57}
{6.04,4.56}
{4.61,4.34}
{4.64,4.57}
{4.41,4.52}
{2.64,4.44}
{6.05,5.97}
{4.64,5.97}
{7.24,7.18}
{7.34,7.17}
{8.07,7.99}
{7.25,7.99}
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f2 (ppm)
0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5
f1 (ppm)

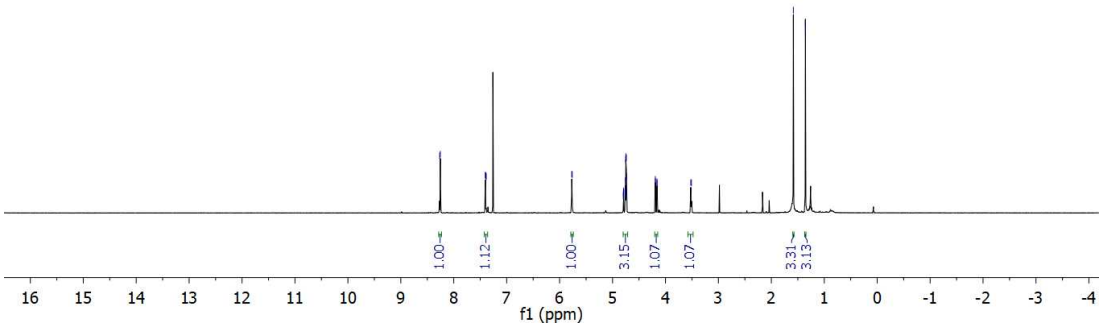

HSQC
{1.53,26.81}
{1.35,26.21}
{4.39,66.66}
{4.48,75.34}
{4.56,77.81}
{4.60,85.37}
{6.01,105.01}
{7.21,123.20}
{7.29,120.80}
{8.02,141.53}
f2 (ppm)
f1 (ppm)

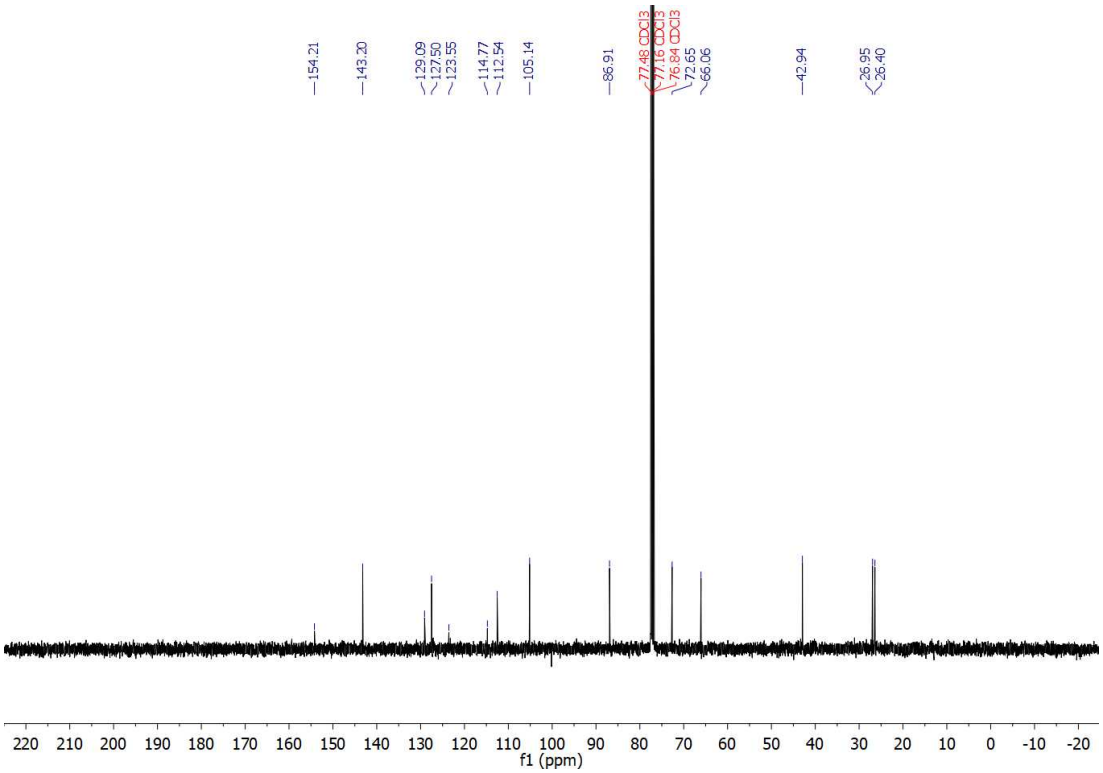

HMBC
{1.37,26.85}
{1.55,26.29}
{4.42,78.73}
{6.00,113.04}
{1.53,112.99}
{1.33,112.38}
{7.30,142.57}
{7.22,150.36}
f2 (ppm)
f1 (ppm)

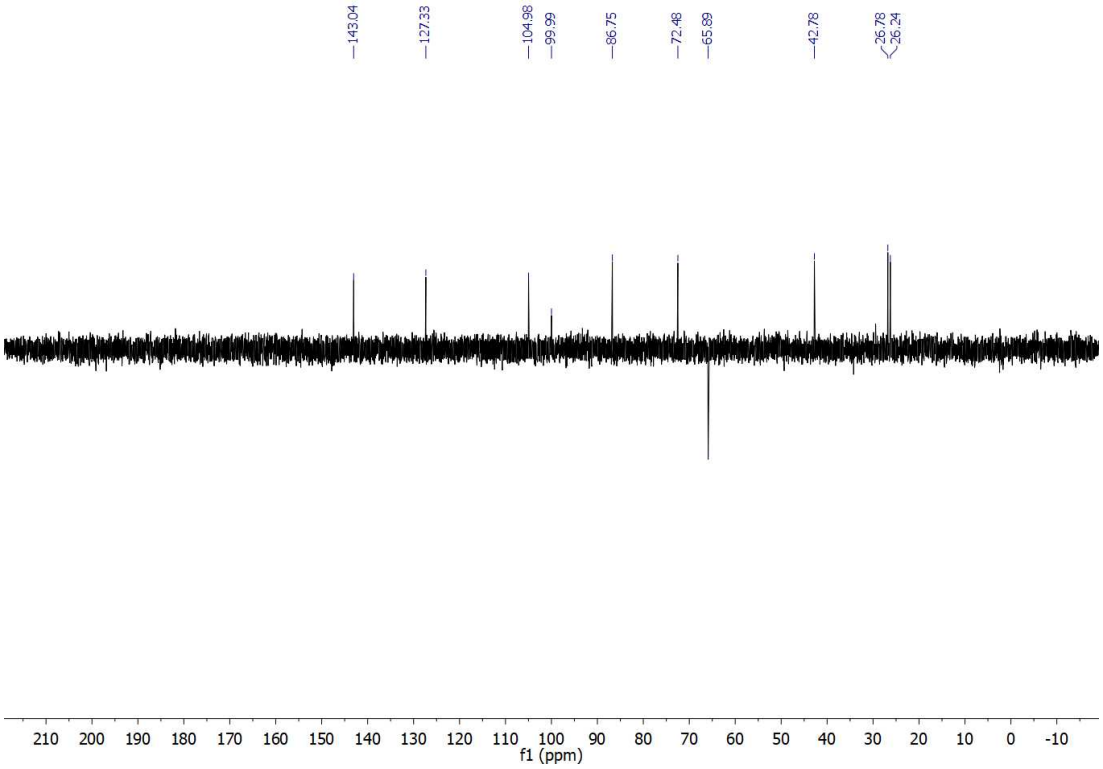


(6aS,7aR,10aR,10bS)-9,9-dimethyl-6a,7a,10a,10b-tetrahydro-6H-[1,3]dioxolo [4'',5'':4',5'] furo[3',2':4,5]pyrano[2,3-c]pyridine-4-carbonitrile (52):

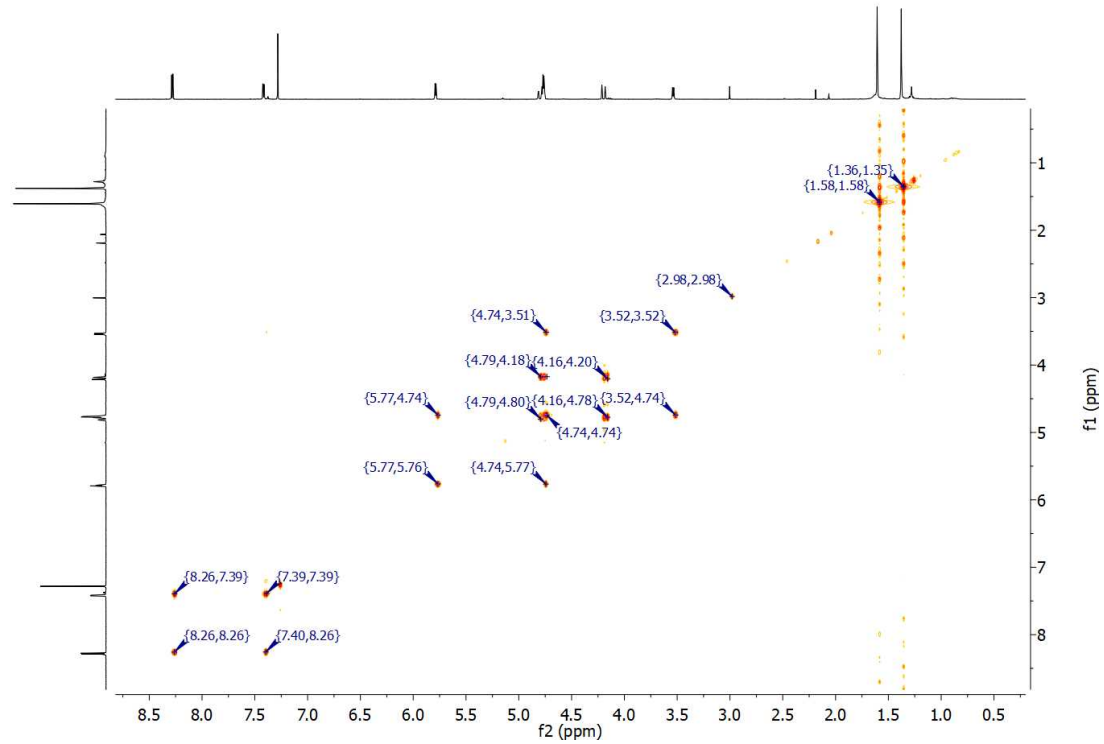




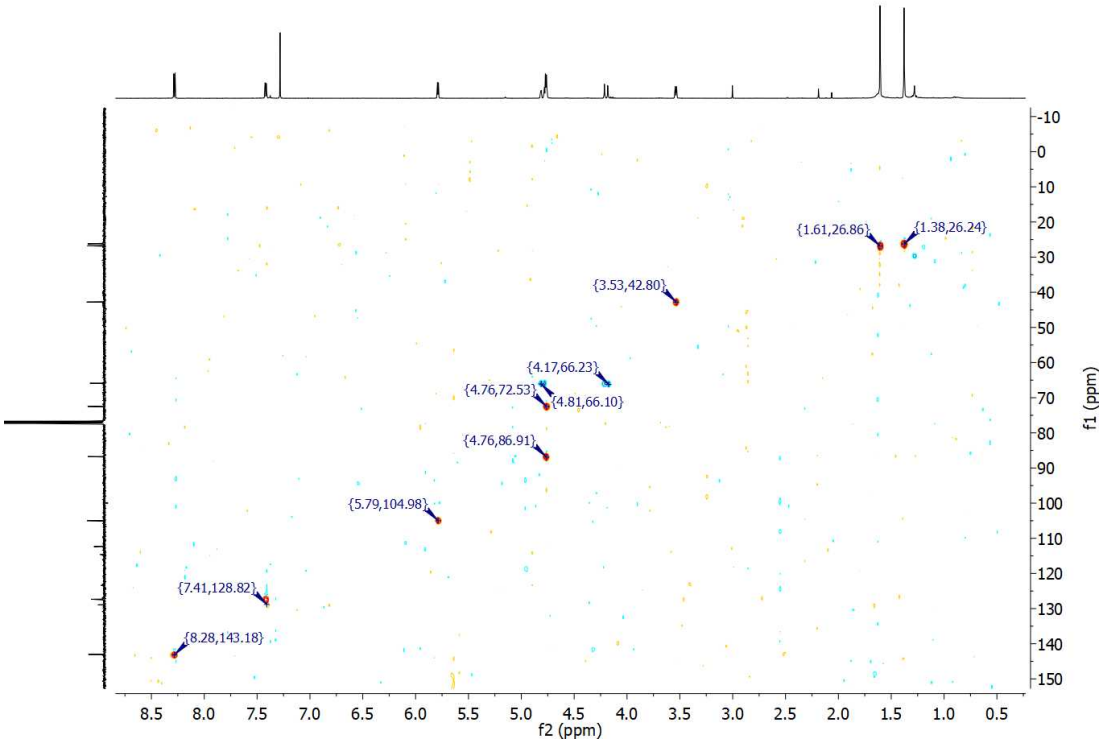

154.21
143.20
129.09
127.50
123.55
114.77
112.94
105.14
86.91
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
72.65
66.06
42.94
26.95
26.40
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


143.04
127.33
104.98
99.99
86.75
72.48
65.89
42.78
26.78
26.24
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

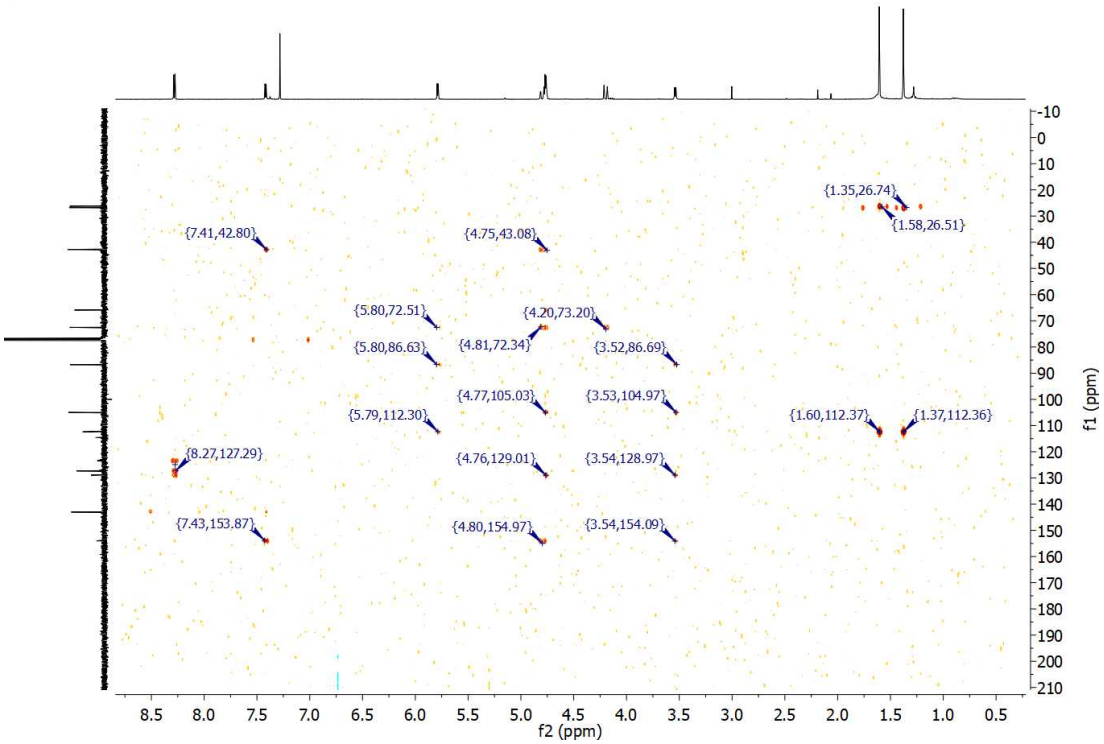
COSY


{1.36,1.35}
{1.58,1.58}
{2.98,2.98}
{4.74,3.51}
{3.52,3.52}
{4.79,4.18}
{4.16,4.20}
{5.77,4.74}
{4.79,4.80}
{4.16,4.78}
{3.52,4.74}
{4.74,4.74}
{5.77,5.76}
{4.74,5.77}
{8.26,7.39}
{7.39,7.39}
{8.26,8.26}
{7.40,8.26}
f2 (ppm)
f1 (ppm)

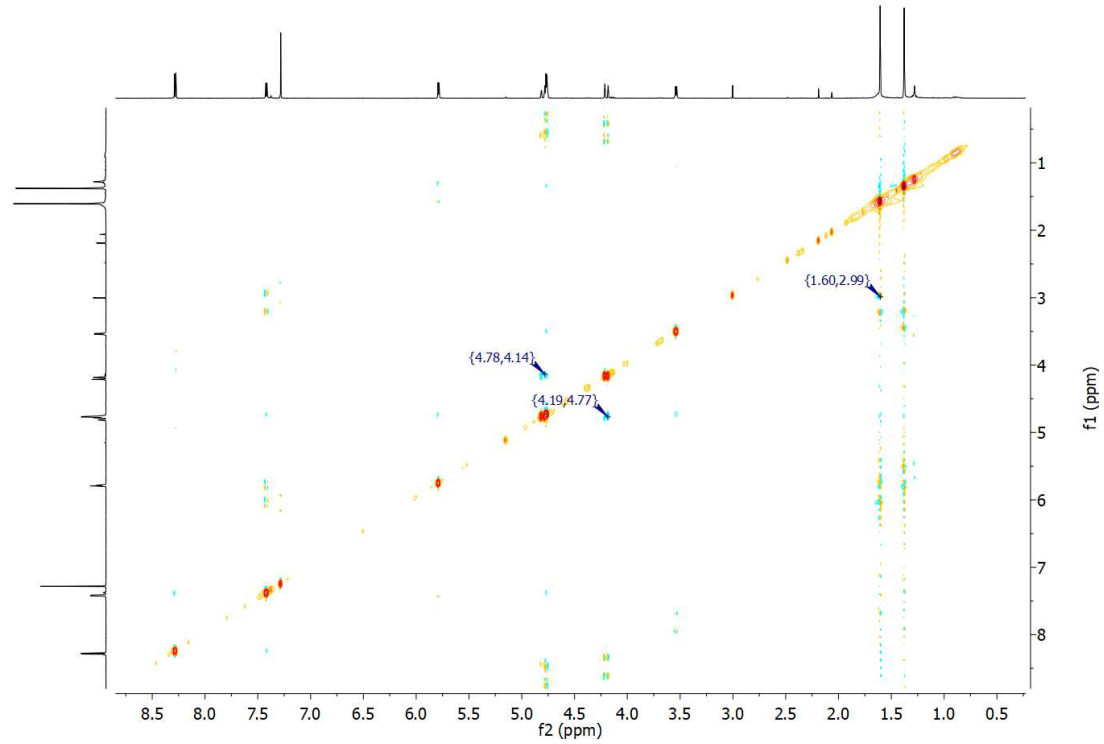
HSQC


{1.61,26.86}
{1.38,26.24}
{3.53,42.80}
{4.17,66.23}
{4.76,72.53}
{4.81,66.10}
{4.76,86.91}
{5.79,104.98}
{7.41,128.82}
{8.28,143.18}
f2 (ppm)
f1 (ppm)

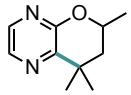
HMBC

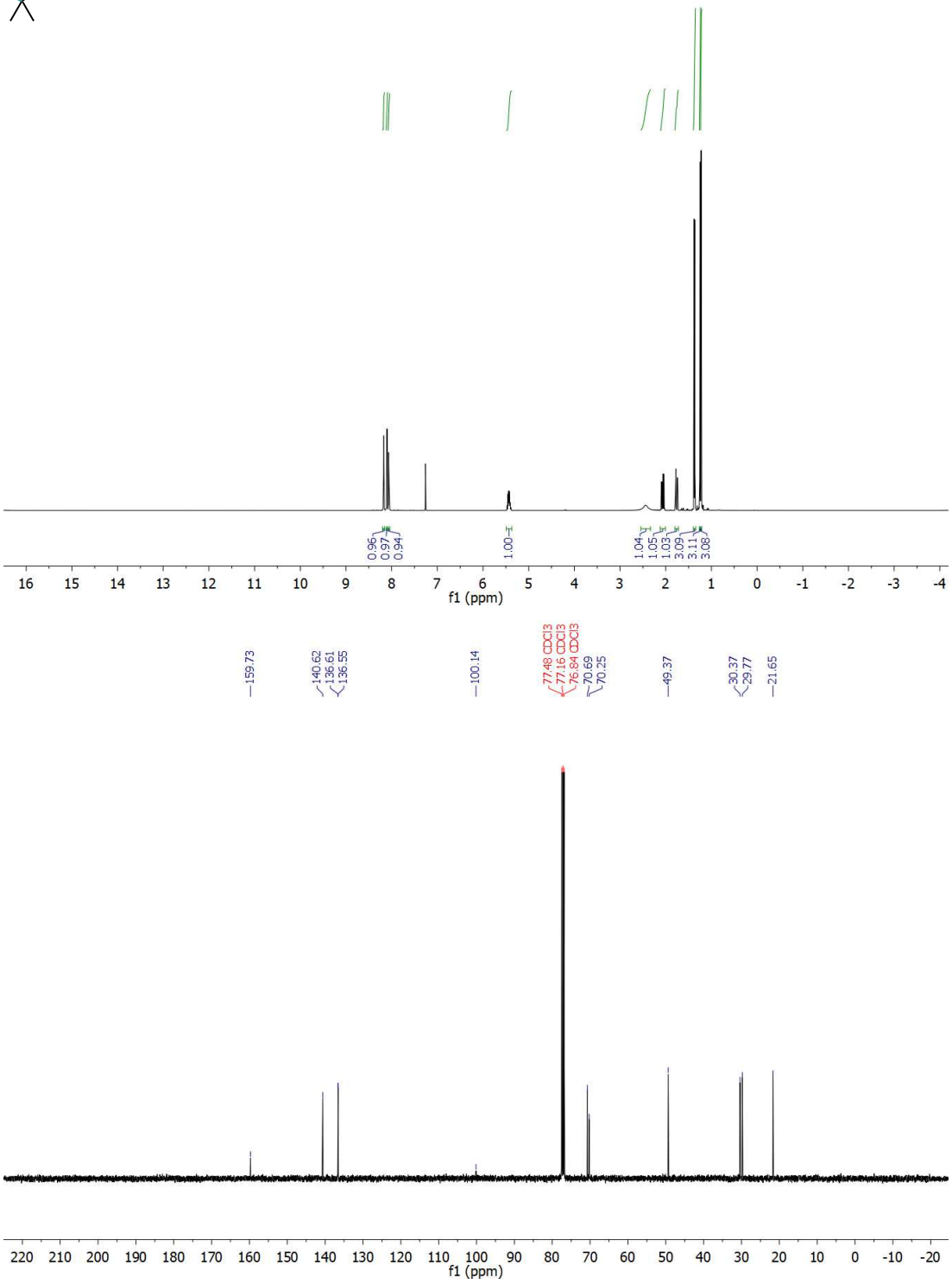

{1.35,26.74}
{1.58,26.51}
{7.41,42.80}
{4.75,43.08}
{5.80,72.51}
{4.20,73.20}
{5.80,86.63}
{4.81,72.34}
{3.52,86.69}
{4.77,105.03}
{3.53,104.97}
{5.79,112.30}
{1.60,112.37}
{1.37,112.36}
{8.27,127.29}
{4.76,129.01}
{3.54,128.97}
{7.43,153.87}
{4.80,154.97}
{3.54,154.09}
f2 (ppm)
f1 (ppm)

NOESY

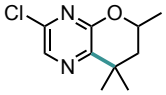

{1.60,2.99}
{4.78,4.14}
{4.19,4.77}
f2 (ppm)
f1 (ppm)

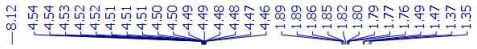
6,8,8-trimethyl-7,8-dihydro-6H-pyrano[2,3-b]pyrazine (53):

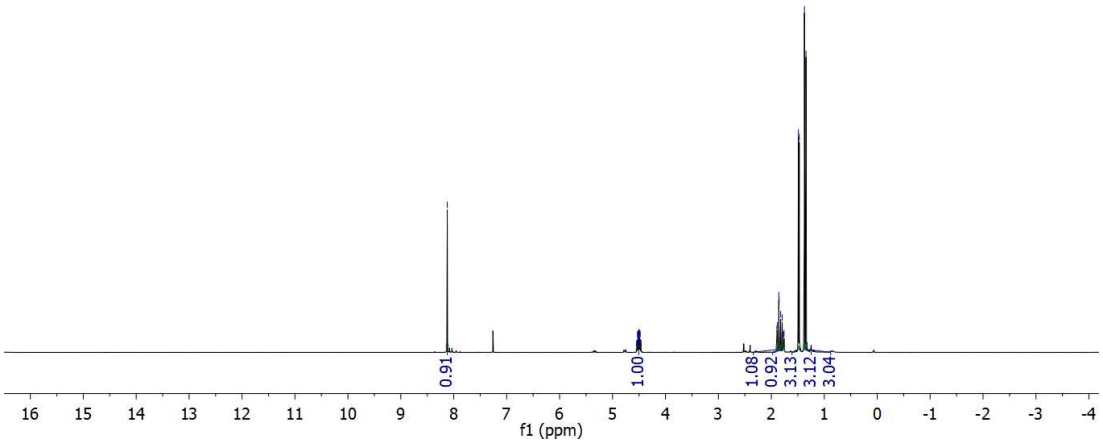


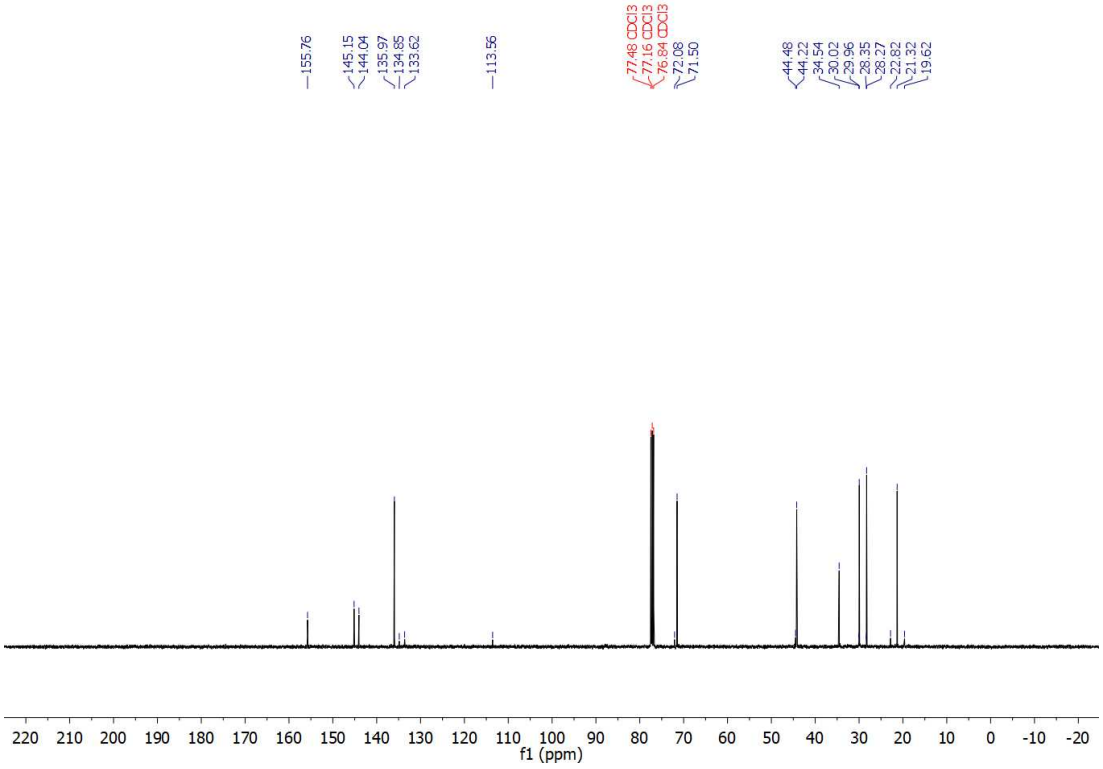


2-chloro-6,8,8-trimethyl-7,8-dihydro-6H-pyrano[2,3-b]pyrazine (54):

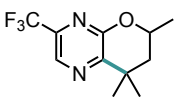


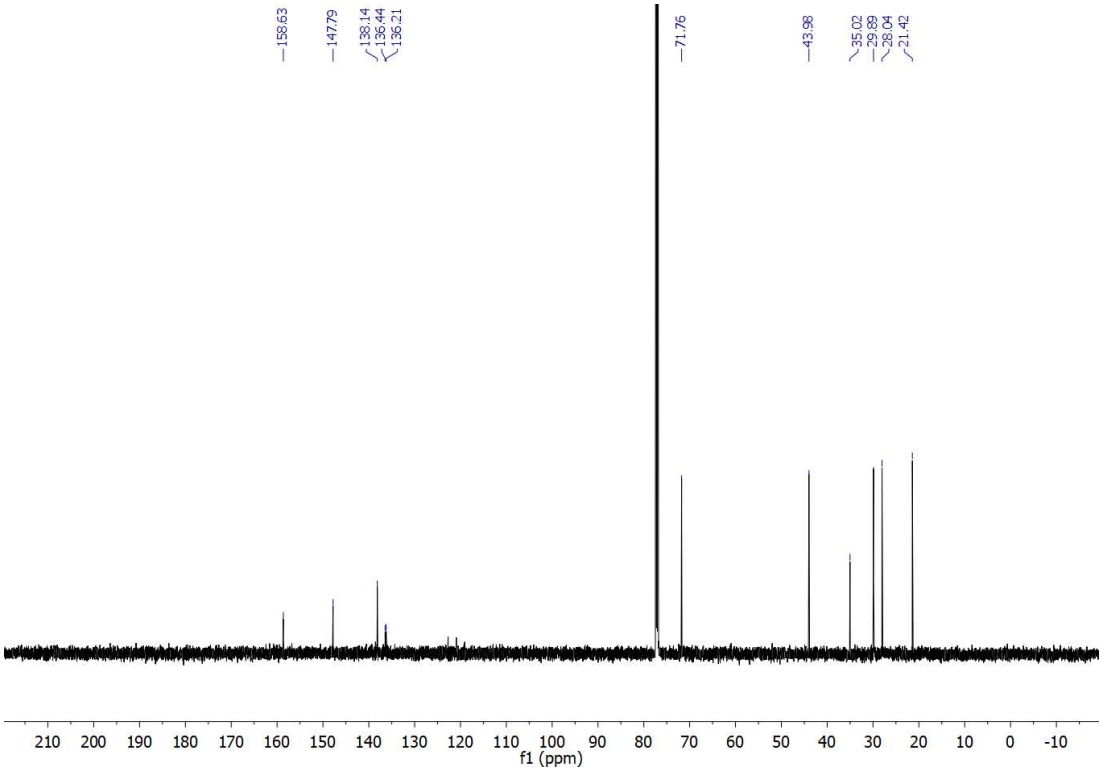


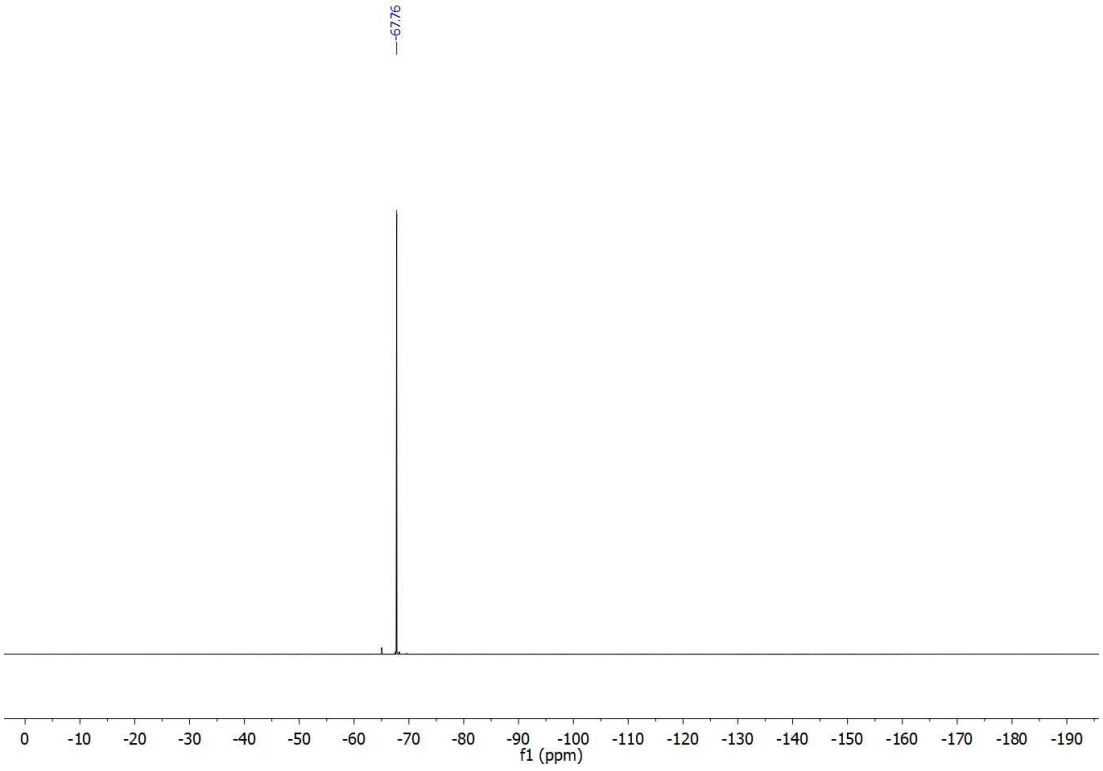




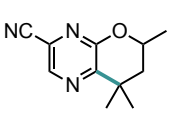
6,8,8-trimethyl-3-(trifluoromethyl)-7,8-dihydro-6H-pyrano[2,3-b]pyrazine (55):

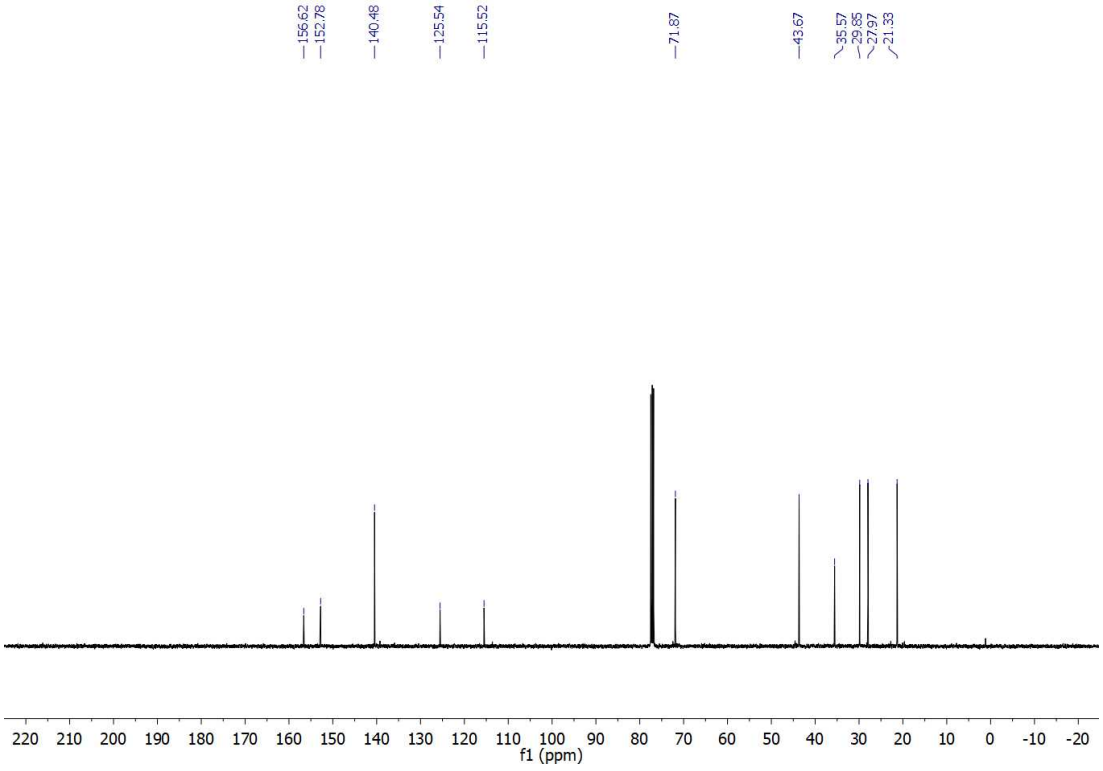




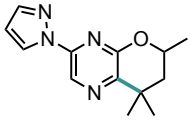


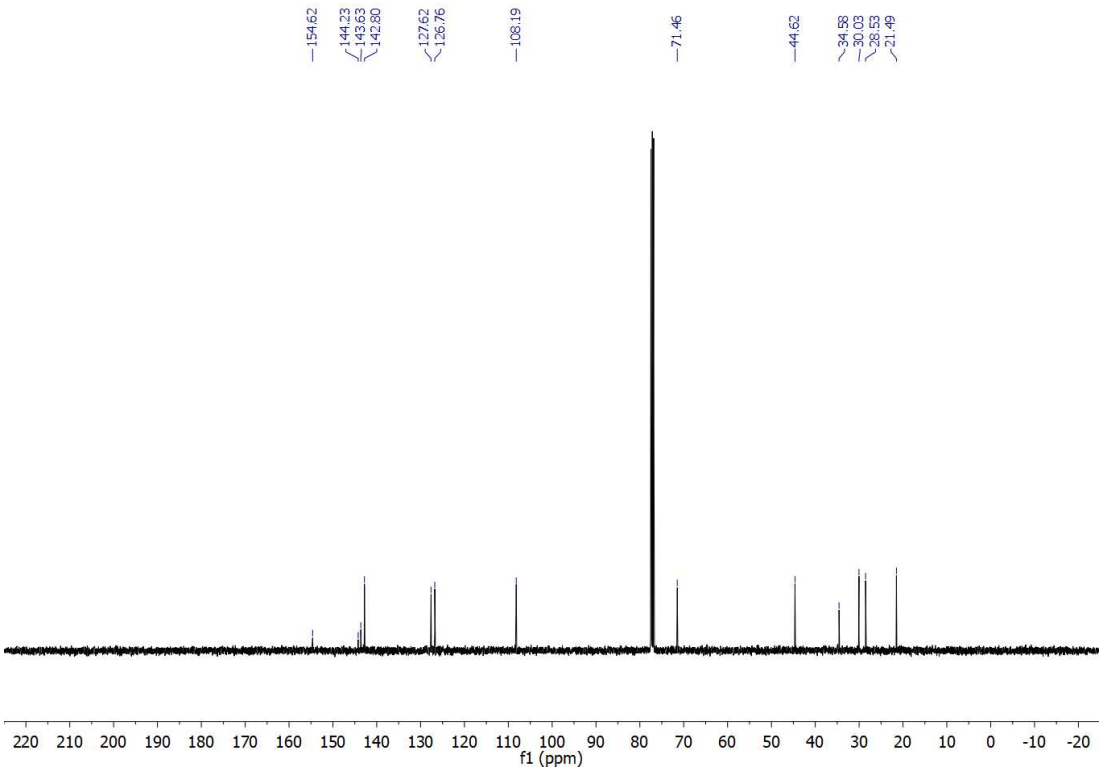
6,8,8-trimethyl-7,8-dihydro-6H-pyrano[2,3-b]pyrazine-2-carbonitrile (56):



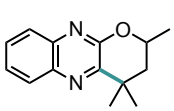


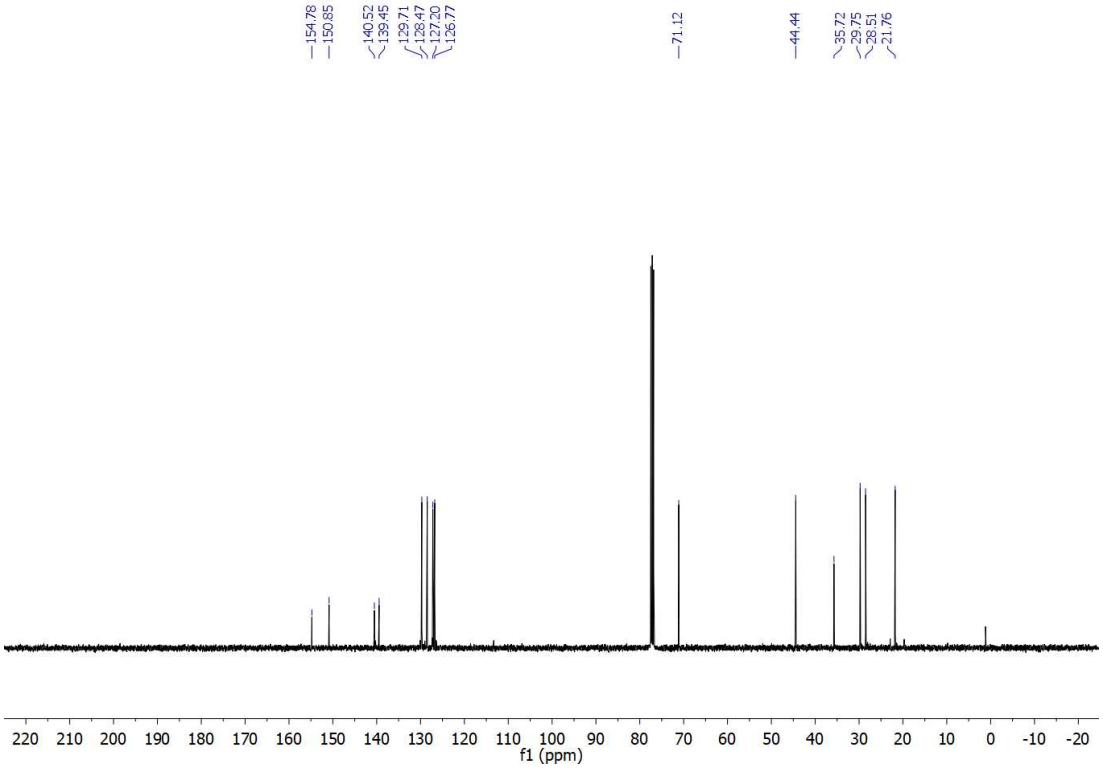
6,8,8-trimethyl-2-(1H-pyrazol-1-yl)-7,8-dihydro-6H-pyrano[2,3-b]pyrazine (57):



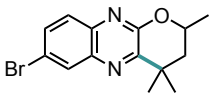


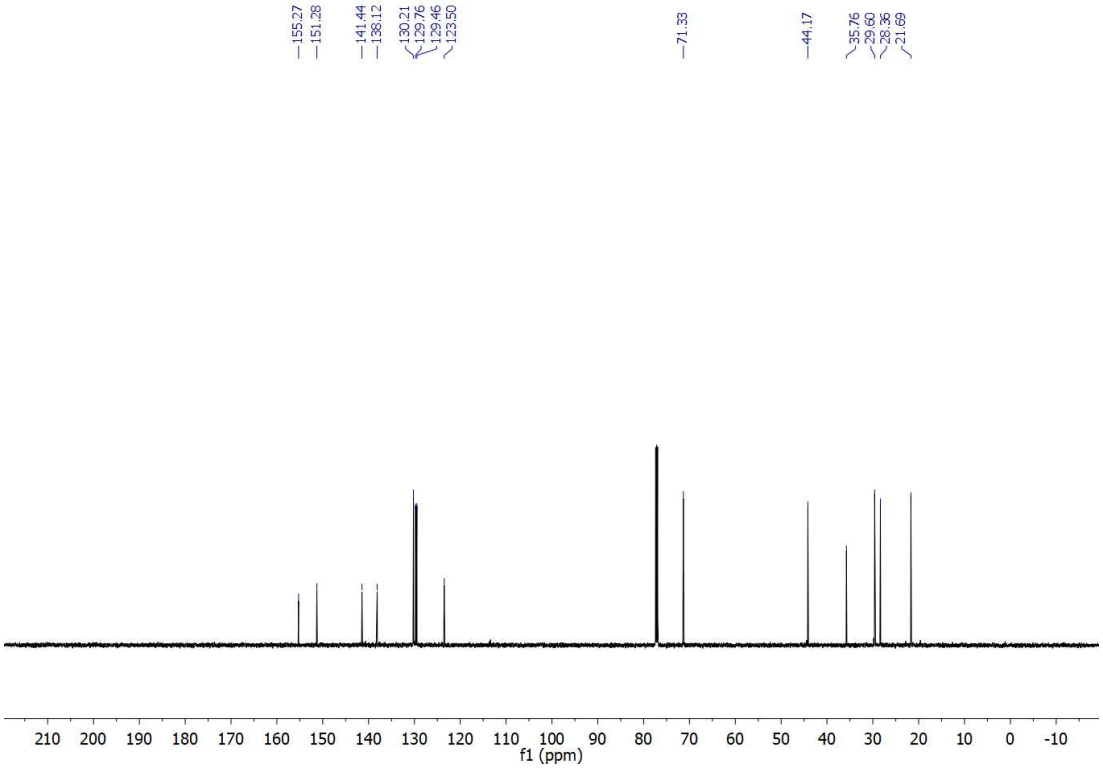
2,4,4-trimethyl-3,4-dihydro-2H-pyrano[2,3-b]quinoxaline (58):



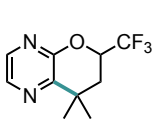


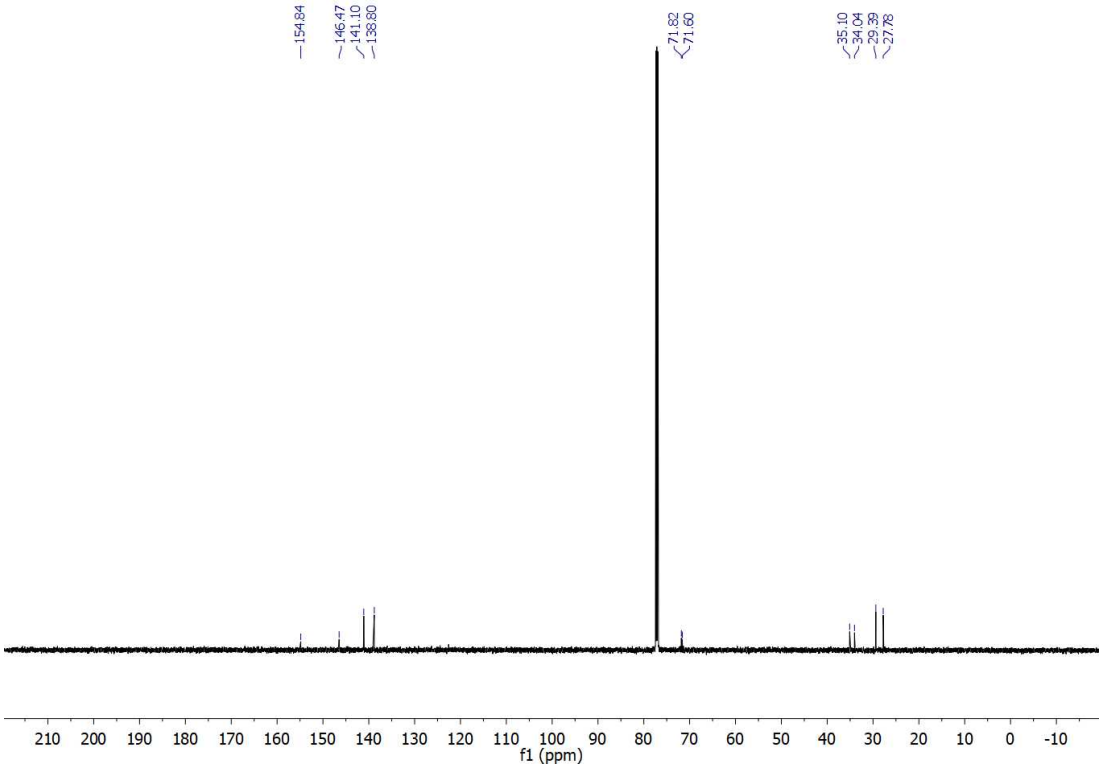
7-bromo-2,4,4-trimethyl-3,4-dihydro-2H-pyrano[2,3-b]quinoxaline (59):

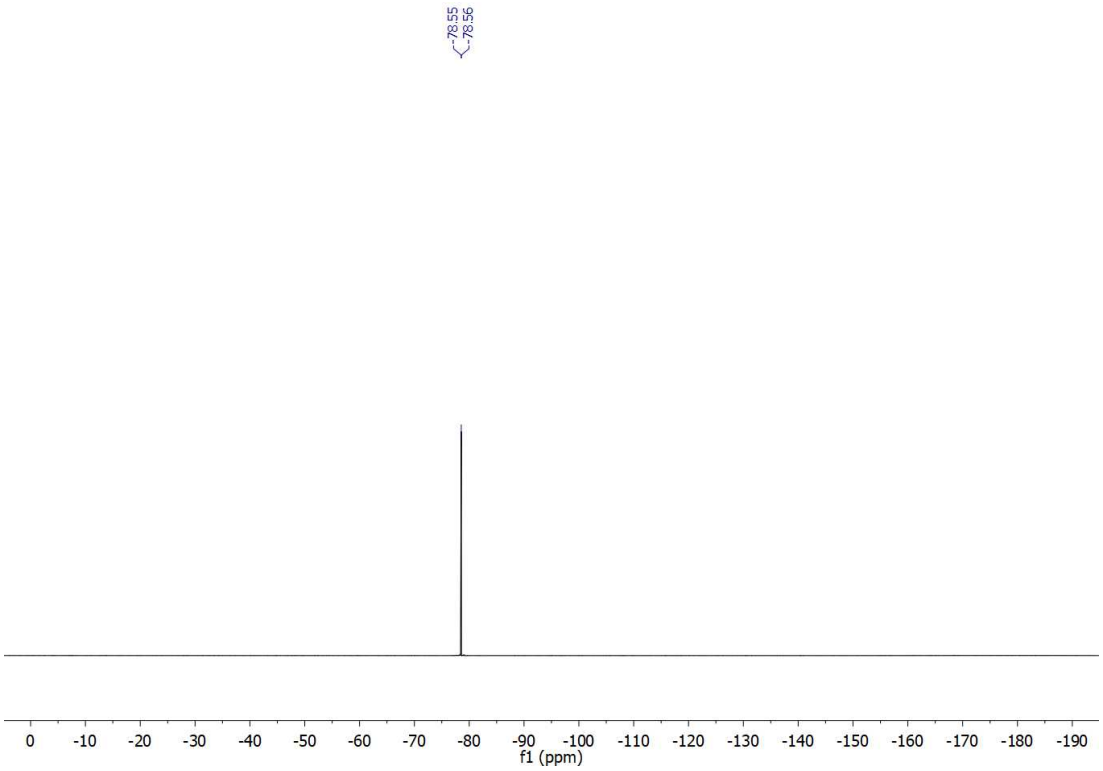




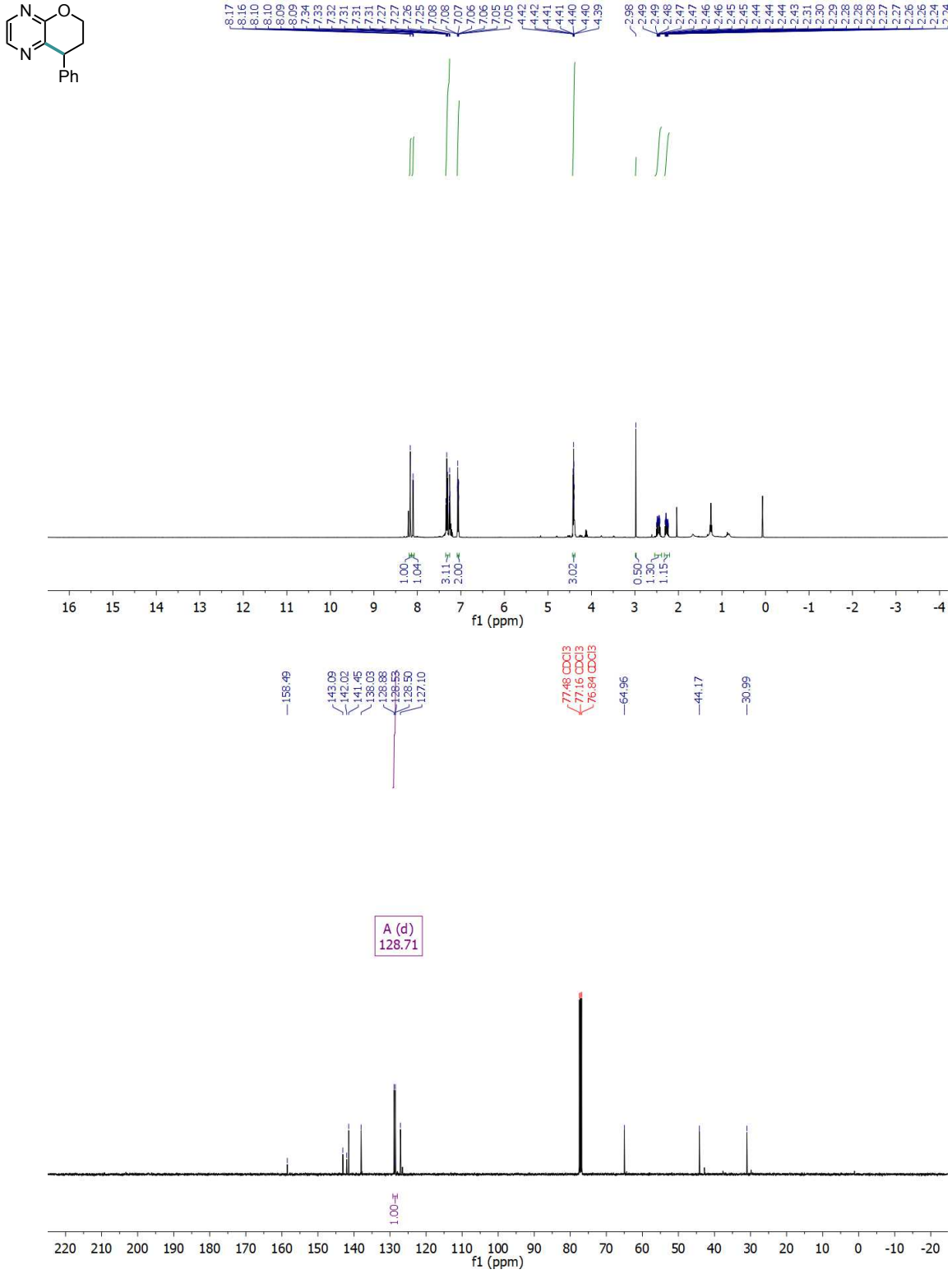
8,8-dimethyl-6-(trifluoromethyl)-7,8-dihydro-6H-pyrano[2,3-b]pyrazine (60):




154.84
146.47
141.10
138.80
71.82
71.60
35.10
34.04
29.39
27.78
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


78.55
78.56
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

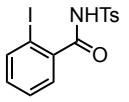
(*S*)-8-phenyl-7,8-dihydro-6*H*-pyrano[2,3-*b*]pyrazine (61):



6.5. Chapter 4: Radical Deoxycyanation of Tertiary Alcohols using Hypervalent Iodine Reagents

*6.5.1. Synthesis of CBZ reagent **78**.*

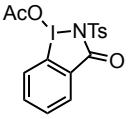
2-iodo-*N*-tosylbenzamide (75):



Following the procedure reported by Waser,[184] To a solution of 2-iodobenzoic acid (4.96 g, 20 mmol, 1.0 equiv.) and tosyl isocyanate (3.05 mL, 20 mmol, 1.0 equiv.) in THF (57 mL) Et_3N (2.8 mL, 20 mmol, 1.0 equiv.) was added dropwise. The reaction mixture was diluted with EtOAc (86 mL) and washed with HCl (1N) (2x35 mL) and brine (50 mL). The organic layer was dried over MgSO4, filtered and concentrated under vacuum to afford 2-iodo-N-tosylbenzamide (**75)** in quantitative yield (8.02 g, 19.9 mmol) as a yellow thick solid. The compound was used without further purification. The spectroscopic data are consistent with those previously reported.[191]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.12 – 7.97 (m, 2H), 7.84 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.44 – 7.35 (m, 4H), 7.15 (ddd, *J* = 8.0, 6.8, 2.4 Hz, 1H), 2.46 (s, 3H).

3-oxo-2-tosyl-2,3-dihydro-1*H*-1λ^3-benzo[*d*][1,2]iodazol-1-yl acetate (76):



A solution of 22-iodo-N-tosylbenzamide (**75)** (8.02 g, 19.9 mmol) and 3-chloroperbenzoic acid (4.6 g, 20 mmol, 1equiv, ca 75% purity) in acetic acid (67 mL) and acetic anhydride (67 mL) was heated at 80°C for 72h. The reaction mixture was diluted with ether (63 mL), cooled to -20°C. The formed solid was filtered off, washed with ether and dried under vacuum to give 3-oxo-2-tosyl-2,3-dihydro-1*H*-1λ^3-benzo[*d*][1,2]iodazol-1-yl acetate **(76)** (3.31 g, 7.2 mmol) as a white solid. The compound was used without further purification. The spectroscopic data are consistent with those previously reported.[191]

^{1}H NMR (600 MHz, DMSO-d_6) δ 8.01 – 7.96 (m, 2H), 7.95 – 7.90 (m, 2H), 7.87 (dd, *J* = 8.9, 1.0 Hz, 1H), 7.76 (td, *J* = 7.4, 0.9 Hz, 1H), 7.46 – 7.42 (m, 2H), 2.39 (s, 3H), 2.26 (s, 3H).

3-oxo-2-tosyl-2,3-dihydro-1*H*-1λ^3-benzo[*d*][1,2]iodazole-1-carbonitrile (78):

Caution: For safety reasons, the reaction was carried out behind an antiblast shield. To a solution of **76** (3.0 g, 6.5 mmol, 1.0 equiv.) in dichloromethane (13 mL), cooled to 0°C cyano(trimethyl)silane (1.22 mL, 9.75 mmol, 1.5 equiv) was added dropwise, followed by 1 drop of trimethylsilyl trifluoromethanesulfonate (5.8 µL, 32.0 µmol, 0.005 equiv.). The reaction mixture was stirred at 0°C for 30 minutes. The formed solid was filtered off, washed with cold dichloromethane and ether and dried under vacuum to afford the CBZ reagent **78** in 97% yield (2.68 g, 6.3 mmol, 90% purity) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 – 8.41 (m, 1H), 8.06 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.99 (ddd, *J* = 8.4, 7.3, 1.8 Hz, 1H), 7.91 – 7.81 (m, 3H), 7.43 – 7.37 (m, 2H), 2.38 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.6, 143.7, 137.1, 136.8, 133.1, 132.0, 131.2, 129.4, 128.7, 127.6, 117.3, 92.8, 21.0.

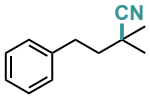
HRMS (ESI): [*m/z*] calculated for $C_{15}H_{11}IN_2NaO_3S$ [M+Na]$^+$], 448.9427, found 448.9420.

6.5.2. Synthesis & characterization of products

General procedure for the cyanation of tertiary cesium oxalates (GP8)

An 8 mL Biotage® microwave vial was charged with the corresponding cesium salt (0.5 mmol, 1.0 equiv.), **78** (426,2 mg, 1.0 mmol, 2.0 equiv.)**4CzIPN** (9.9 mg, 2.5 µmol, 2.5 mol%), and sealed with a septum cap. The vial was put under vacuum for 1 min and refilled with N_2 (x 3). Afterwards, a 1:1 mixture of degassed DMSO:1,4-dioxane (2.5 mL, 0.2 M) was added. The reaction mixture was then sparged with N_2 for 2-5 min and irradiated with blue LEDs (λ_{max} = 440 nm) at RT for 16 h. Afterwards, the reaction was combined with a mixture of H_2O and a saturated brine solution (ca. 10 mL) and the organic phase extracted with EtOAc (ca. 3 x 10 mL). The combined organic layers were dried over Na_2SO_4, and the solvent evaporated. The crude product was purified by column chromatography over silica gel to afford the desired product.

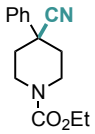
2,2-dimethyl-4-phenylbutanenitrile (80):



Synthesized following **GP8** using cesium 2-((2-methyl-4-phenylbutan-2-yl)oxy)-2-oxoacetate **1** (184 mg, 0.5 mmol, 1.0 equiv.). The pure product was isolated as a pale-yellow oil in 64% yield (55,4 mg, 0.32 mmol). The spectroscopic data are consistent with those previously reported.[262]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 8.6, 6.6 Hz, 2H), 7.24 – 7.18 (m, 3H), 2.83 – 2.77 (m, 2H), 1.87 – 1.79 (m, 2H), 1.41 (s, 6H).

ethyl 4-cyano-4-phenylpiperidine-1-carboxylate (81):



Synthesized following **GP8** using cesium 2-((1-(ethoxycarbonyl)-4-phenylpiperidin-4-yl)oxy)-2-oxoacetate (227 mg, 0.5 mmol, 1.0 equiv.). The pure product was isolated as a yellow oil in 13% yield (16.7 mg, 0.065 mmol). The spectroscopic data are consistent with those previously reported.[263]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 5H), 4.22 – 4.16 (m, 2H), 4.13 (q, *J* = 2.8 Hz, 2H), 3.69 (t, *J* = 5.7 Hz, 2H), 2.55 (s, 2H), 1.30 (d, *J* = 7.1 Hz, 3H), 1.26 (d, *J* = 1.5 Hz, 2H).

*6.5.3. Cyclic voltammetry measurements of **78**.*

An IKA ElectraSyn 2.0 electrochemical reactor was employed with a 3-electrode cell configuration: glassy carbon (working electrode), Pt wire as (control electrode), and Ag/AgCl (KCl, 3 M aq.) as (reference electrode) was used for the measures. Tetrabutyl ammonium tetrafluoroborate (0.1 M in DMSO) was used as an electrolyte. CBZ reagent **78** (25.6 mg, 0.06 mmol) was dissolved in a stock solution of tetrabutyl ammonium tetrafluoroborate (0.01 M, 6 mL in DMSO) and was degassed by bubbling N_2 directly before measuring.

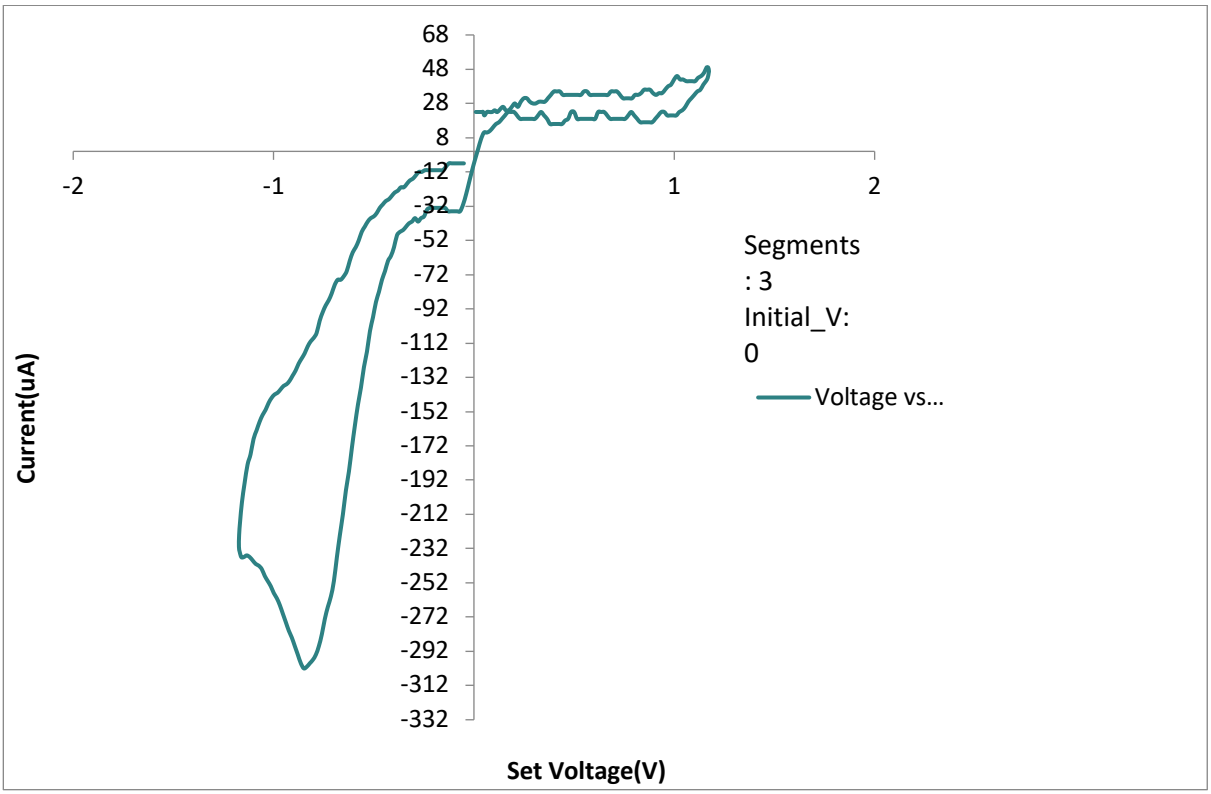
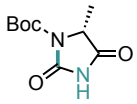


Figure S8. Cyclic voltammogram of **78**.

The result of this experiment determined a value of -0.80 V *vs* Ag/AgCl, which after conversion corresponds to -0.84 *vs* SCE (saturated calomel electrode), for the reduction potential of **78**

6.5.4. Reactivity test reactions.

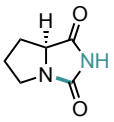
tert-butyl (R)-5-methyl-2,4-dioxoimidazolidine-1-carboxylate (83):



A 5 mL Biotage® microwave vial was charged with (tert-butoxycarbonyl)-D-alanine (57 mg, 0.3 mmol, 1.0 equiv.), **78** (192 mg, 0.45 mmol, 1.5 equiv.), DMAP (46 mg, 0.375 mmol, 1.25 equiv.), and sealed with a septum cap. The vial was put under vacuum for 1 min and refilled with N_2 (x 3). Afterwards, degassed THF (1.5 mL, 0.2 M) was added. The reaction mixture was then sparged with N_2 for 2-5 min and stirred at room temperature for 16 h. After this time, the solvent was *in vacuo* and the crude product was purified by column chromatography over silica gel to afford **83** as a yellow solid in 51% yield and 82% purity (41 mg, 0.15 mmol). The product contains ~18% of by-product **75**. The spectroscopic data are consistent with those previously reported.[194]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.44 (q, *J* = 6.9 Hz, 1H), 2.44 (d, *J* = 15.4 Hz, 1H), 1.61 (d, *J* = 6.9 Hz, 3H), 1.56 (d, *J* = 0.9 Hz, 9H).

(S)-tetrahydro-1H-pyrrolo[1,2-c]imidazole-1,3(2H)-dione (84):

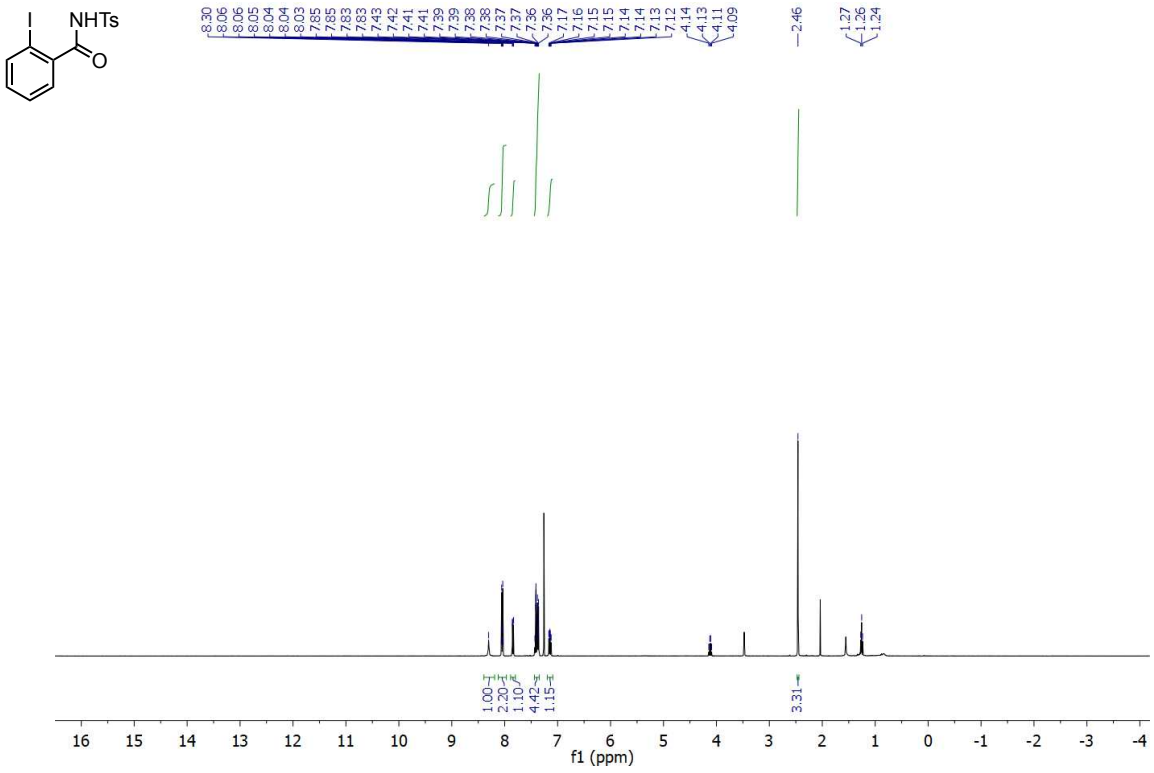


Synthesized following the same procedure employed for **83** using *L*-proline (34.5 mg, 0.3 mmol, 1.0 equiv.). The pure product was isolated as white solid in 65% yield and 81% purity (34.2 mg, 0.19 mmol). The product contains ~18% of by-product **75**. The spectroscopic data are consistent with those previously reported.[194]

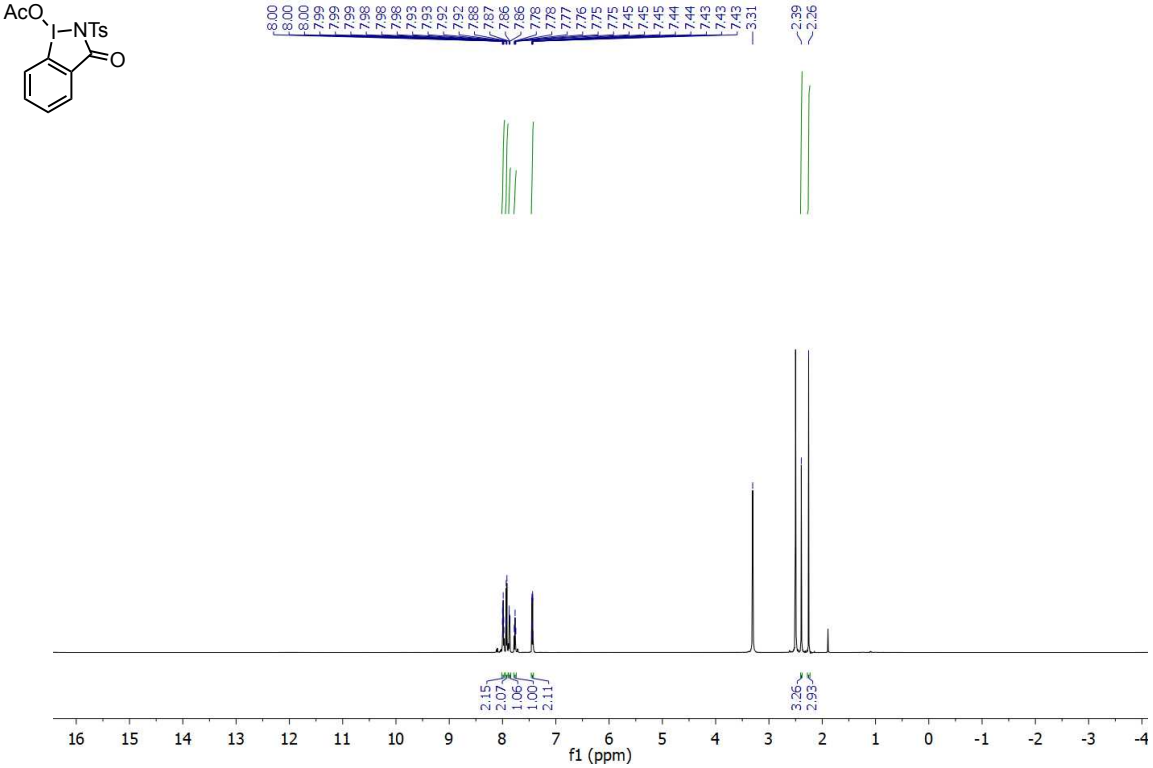
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 – 4.08 (m, 1H), 3.70 (dt, *J* = 11.3, 7.7 Hz, 1H), 3.23 (ddd, *J* = 11.3, 8.3, 4.6 Hz, 1H), 2.46 (s, 1H), 2.30 – 2.21 (m, 1H), 2.20 – 2.02 (m, 2H), 1.86 – 1.72 (m, 1H).

6.5.5. ^{1}H and ^{13}C–NMR Spectra

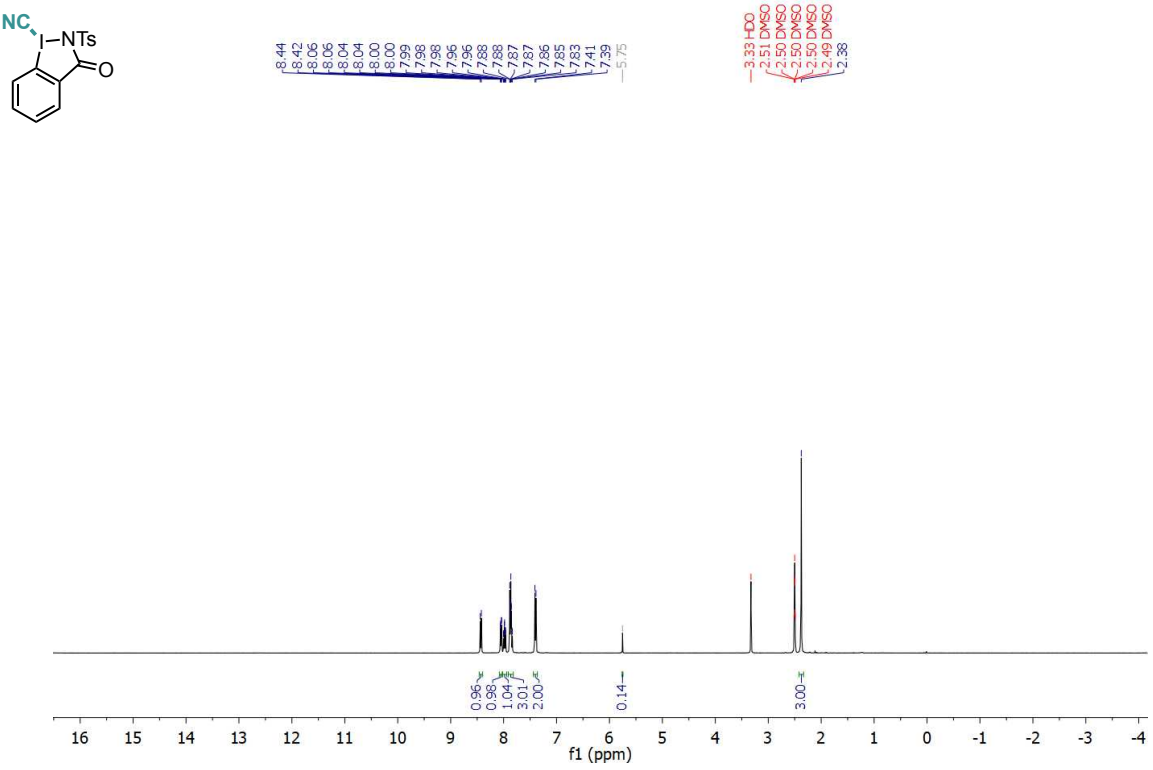
2-iodo-*N*-tosylbenzamide (75):

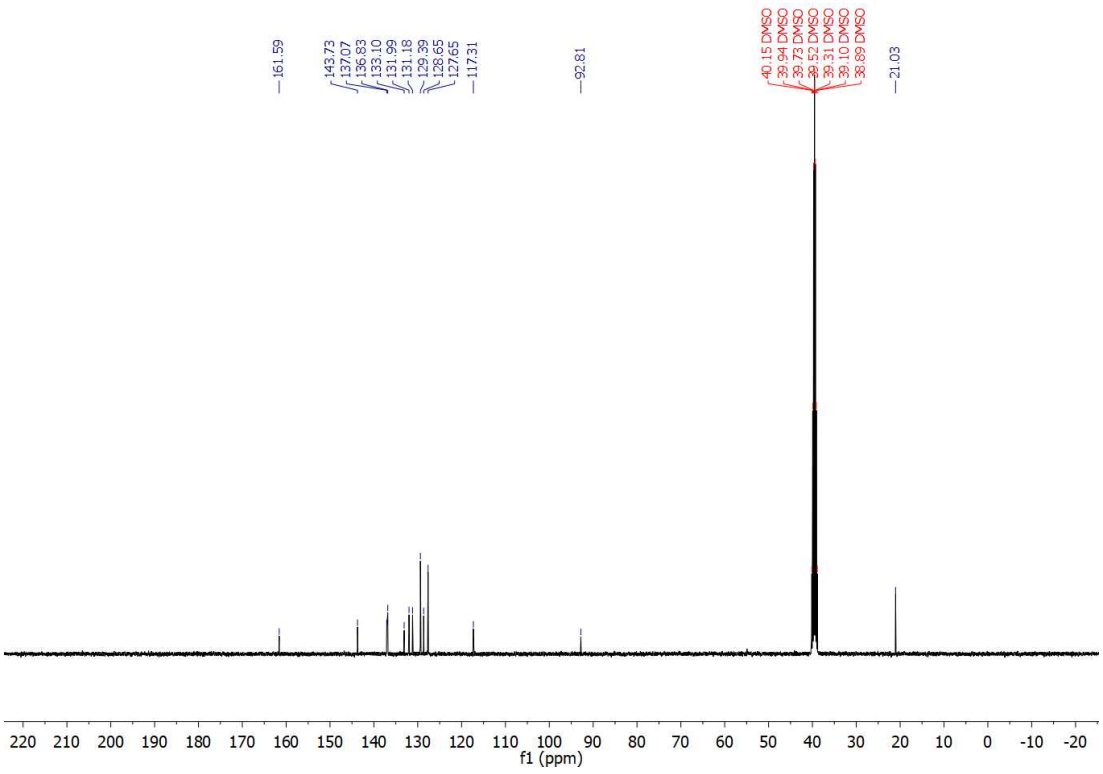


3-oxo-2-tosyl-2,3-dihydro-1*H*-1λ^3-benzo[*d*][1,2]iodazol-1-yl acetate (76):

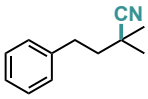


3-oxo-2-tosyl-2,3-dihydro-1*H*-1λ^3-benzo[*d*][1,2]iodazole-1-carbonitrile (78):

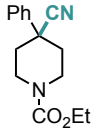


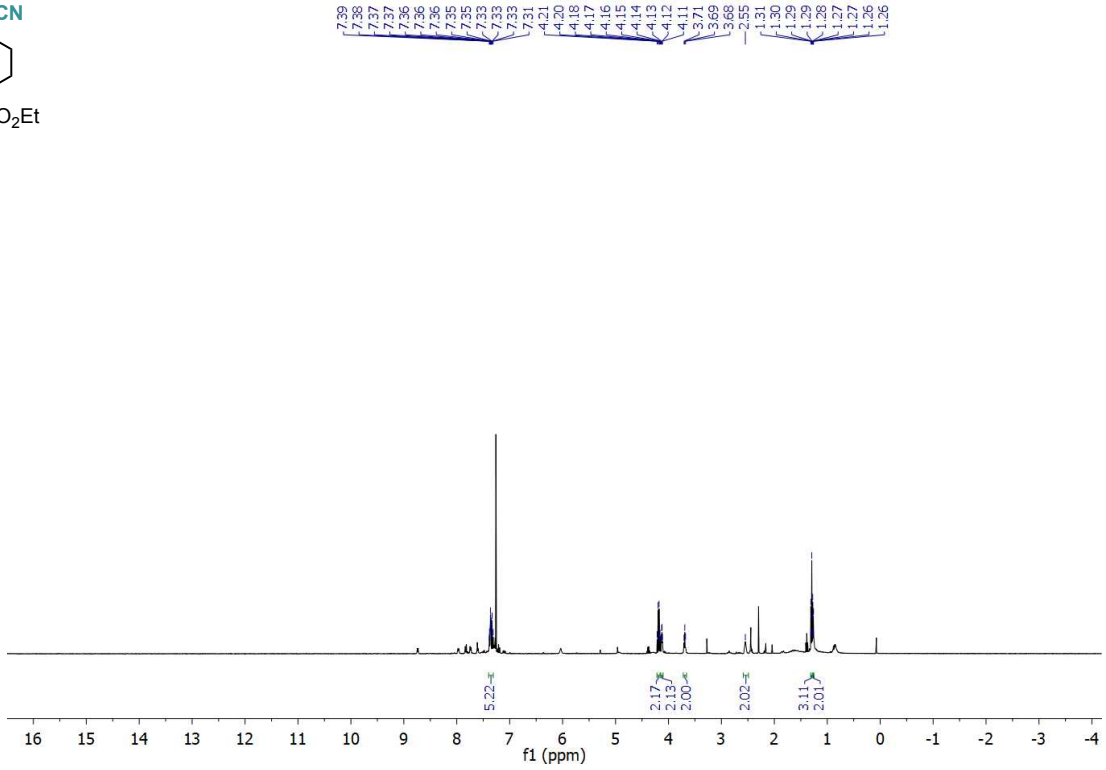


2,2-dimethyl-4-phenylbutanenitrile (80):

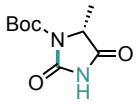


ethyl 4-cyano-4-phenylpiperidine-1-carboxylate (81):

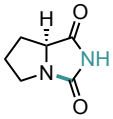




tert-butyl (R)-5-methyl-2,4-dioxoimidazolidine-1-carboxylate (83):



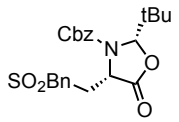
(S)-tetrahydro-1H-pyrrolo[1,2-c]imidazole-1,3(2H)-dione (84):



6.6. Chapter 5.3: Synthesis of α-UAAs via radical decarboxylative processes

*6.6.1. Synthesis of Beckwith-Karady alkene **87***

Benzyl (2S,4R)-4-((benzylsulfonyl)methyl)-2-(tert-butyl)-5-oxo-oxazolidine-3-carboxylate



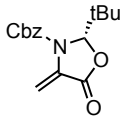
S-benzyl-*L*-cysteine (10.0 g, 48.0 mmol, 1 eq.) was treated with a solution of sodium hydroxide (1.9 g, 48.0 mmol, 1 equiv.) in water (300 mL) and evaporated until dryness via rotary evaporation leaving a white solid. A solution of pivalaldehyde (10.5 mL, 96 mmol, 2 equiv.) in cyclohexane (500 mL) was added to the solid and the mixture stirred and refluxed in presence of a Dean-Stark separator for 5 days (the reaction was followed by ^{1}H NMR). The reaction mixture was then cooled down and evaporated to dryness to achieve the crude imine as a pale-yellow gum. The crude was suspended in anh. CH_2Cl_2 (300 mL) and treated with benzyl chloroformate (13.7 mL, 96 mmol, 2 equiv.) at 0 °C. After stirring for 2 days, the reaction was quenched with 1 M NaOH (1 x 250 mL), the organic phase was dried over Na_2SO_4 and filtered. The solvent was removed via rotary evaporation, afterwards the concentrate was quickly filtered through a silica column (cyclohexane/EtOAc 1:1) to achieve the corresponding diastereomeric mixture of oxazolidinone intermediate (26 g; R_f = 0.25, Cyclohexane:EtOAc, 4:1) as a brown oil after concentration in vacuo, which was used in the next step without further purification. The crude was dissolved in CH_2Cl_2 (500 mL), treated with *m*CPBA (≥77%, 35.2 g, 157.18 mmol, 2.5 equiv.) and stirred for 18 h at room temperature. The reaction was washed with 1M NaOH (3 x 200 mL), then the organic phase was dried over $Na_2SO_4$and concentrated in vacuo. Purification via flash column chromatography (cyclohexane:EtOAc, 20:1 – 2.3:1) afforded the desired product as a pale yellow oil in 43 % yield (9.26 g, 20.78 mmol) over three steps. The spectroscopic data are consistent with those previously reported.[218]

^{1}H NMR (600 MHz, $CDCl_3$) δ =7.44 – 7.32 (m, 10H), 5.62 (s, 1H), 5.28 (d, *J*=12.0, 1H), 5.21 (d, *J*=12.0, 1H), 5.08 (dd, *J*=8.0, 4.1, 1H), 4.66 (d, *J*=14.1, 1H), 4.42 (d, *J*=14.1, 1H), 3.44 (dd, *J*=15.3, 8.0, 1H), 3.15 (ddd, *J*=15.3, 4.1, 1.5, 1H), 0.89 (s, 9H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ =170.8, 155.4, 135.0, 131.1, 129.3, 129.2, 129.0, 128.9, 128.9, 128.1, 97.0, 69.1, 60.6, 53.8, 52.9, 37.3, 24.7.

R_f (cyclohexane/EtOAc, 4:1) = 0.14 [*p*-Anisaldehyde]

benzyl (S)-2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (88)



Benzyl (*2S,4R*)-4-((benzylsulfonyl)methyl)-2-(tert-butyl)-5-oxo-oxazolidine-3-carboxylate (9.26 g, 20.78 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (260 mL) and cooled in an ice bath, then DBU (6.20 mL, 41.57 mmol, 2 equiv.) was added dropwise via syringe. The mixture was stirred for 45 min at 0 °C and quenched with sat. aq. NH_4Cl (100 mL) while still in the ice bath. The organic phase was extracted with sat. aq. NH_4Cl (3 x 200 mL), dried over Na_2SO_4 and the solvent was removed via rotary evaporation. The crude was quickly filtered through a silica column (cyclohexane /EtOAc 1:1) to provide **87** in 92 % yield (5.54 g, 19.14 mmol) as a yellowish solid after concentration in vacuo. The spectroscopic data are consistent with those previously reported.[218]

^{1}H NMR (600 MHz, $CDCl_3$) δ =7.42 – 7.34 (m, 5H), 5.72 (s, 1H), 5.69 (s, 1H), 5.31 - 5.21 (m, 2H), 0.93 (s, 9H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ =164.7, 134.9, 130.3, 129.0, 128.9, 128.8, 104.5, 94.2, 77.4, 68.9, 38.8, 24.5.

R_f (cyclohexane /EtOAc, 4:1) = 0.45 [*p*-Anisaldehyde]

6.6.2. Synthesis & characterization of products

General procedure 9 (GP9) – *Alkylation*

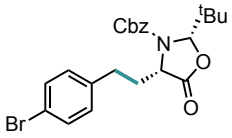
An 8 mL Biotage® microwave vial was charged with the corresponding acid (1.0 mmol, 2.0 equiv.), Dha **1** (145 mg, 0.50 mmol, 1.0 equiv.), **Ir-F** (5.5 mg, 5µmol, 2 mol%), K_2HPO_4 (209 mg, 1.2 mmol, 2.4 equiv.), and sealed with a septum cap. The vial was put under vacuum for 1 min and refilled with N_2 (x 3). Afterwards, degassed 1,4-dioxane (5.0 mL, 0.1 M) was added. The reaction mixture was then sparged with N_2 for 2-5 min and irradiated with blue LEDs (λ_{max} = 440 nm) at 42 °C for 16 h. Afterwards, the reaction was combined with a mixture of H_2O and a saturated brine solution (ca. 15 mL) and the organic phase extracted with EtOAc (ca. 3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent evaporated. The crude product was purified by column chromatography over silica gel to afford the desired product.

General procedure 10 (GP10) – *Alkylation*

An 8 mL Biotage® microwave vial was charged with the corresponding acid (1.0 mmol, 2.0 equiv.), Dha **1** (145 mg, 0.50 mmol, 1.0 equiv.), **Ir-F** (5.5 mg, 5µmol, 2 mol%), K_2HPO_4 (209 mg, 1.2 mmol, 2.4 equiv.), and sealed with a septum cap. The vial was put under vacuum for 1 min and refilled with N_2 (x 3). Afterwards, degassed DMSO (2.5 mL, 0.2 M) was added. The reaction mixture was then sparged with

N_2 for 2-5 min and irradiated with blue LEDs (λ_{max} = 440 nm) at 42 °C for 16 h. Afterwards, the reaction was combined with a mixture of H_2O and a saturated brine solution (ca. 15 mL) and the organic phase extracted with EtOAc (ca. 3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent evaporated. The crude product was purified by column chromatography over silica gel to afford the desired product.

Benzyl (2S,4S)-4-(4-bromophenethyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate (91)



Synthesized following **GP9** using 4-bromophenylacetic acid (215 mg, 1.0 mmol, 2.0 equiv.). The pure product was isolated as a yellow oil in 81% yield (187 mg, 0.41 mmol)

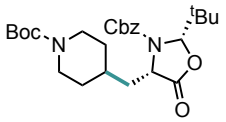
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.33 (m, 5H), 7.29 (dd, *J* = 7.3, 2.2 Hz, 2H), 7.04 (d, *J* = 7.9 Hz, 2H), 5.54 (s, 1H), 5.13 (s, 2H), 4.23 (s, 1H), 2.95 – 2.78 (m, 2H), 2.23 – 2.07 (m, 2H), 0.96 (s, 10H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 172.5, 156.0, 135.3, 131.7, 130.4, 128.9, 128.7, 120.2, 96.4, 68.5, 37.2, 34.6, 31.7, 25.1.

HRMS (ESI): [*m/z*] calculated for $C_{23}H_{26}BrNNaO_4$ [M+Na]$^+$], 482.0937, found 482.0936.

R_f (Cyclohexane /EtOAc 6:1) = 0.27 [UV]

Benzyl (2S,4S)-4-((1-(tert-butoxycarbonyl)piperidin-4-yl)methyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate (92)



Synthesized following **GP9** using 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (215 mg, 1.0 mmol, 2.0 equiv.). The pure product was isolated as a yellow oil in 95% yield (231 mg, 0.49 mmol)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 – 7.32 (m, 6H), 5.56 (s, 1H), 5.20 – 5.10 (m, 2H), 4.33 (d, *J* = 7.8 Hz, 1H), 3.99 (d, *J* = 13.2 Hz, 2H), 2.60 (dd, *J* = 28.2, 15.0 Hz, 2H), 1.86 – 1.75 (m, 2H), 1.69 (p, *J* = 6.6, 6.2 Hz, 2H), 1.46 (s, 10H), 1.12 – 0.99 (m, 2H), 0.96 (s, 10H).

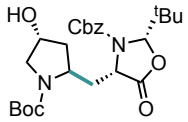
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 172.9, 156.1, 154.9, 135.2, 129.0, 128.9, 96.5, 79.4, 68.7, 55.0, 43.8, 40.4, 37.1, 33.0, 32.4, 31.9, 28.6, 27.6, 25.1.

HRMS (ESI): [*m/z*] calculated for $C_{26}H_{38}N_2NaO_6$ [M+Na]$^+$], 497.2622, found 497.2623.

$[\alpha]_D^{20}$: + 18.2 (ρ = 1.01, CH_2Cl_2)

R_f (Cyclohexane /EtOAc 4:1) = 0.13 [p-anisaldehyde]

(2S,4S)-benzyl 4-(((4R)-1-(tert-butoxycarbonyl)-4-hydroxypyrrolidin-2-yl)methyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate (93):



Synthesized following **GP9** using (4R)-1-(tert-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (231 mg, 1.0 mmol, 2.0 equiv.). Product **30** was obtained as a 1:1 diastereomeric mixture – calculated from the ^{1}H NMR of the crude reaction mixture. The mixture of diastereoisomers was isolated as a white solid in 80% yield (190 mg, 0.40 mmol).

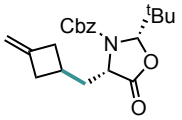
^{1}H NMR (400 MHz, $CDCl_3$ – *both isomers*): δ 7.44 – 7.33 (m, 7H), 5.58 (s, 0.47H), 5.55 (s, 1H), 5.22 – 5.12 (m, 3H), 4.52 – 4.16 (m, 4.29 H), 3.53 (dd, *J* = 12.1, 5.0 Hz, 1.46 H), 3.35 (q, *J* = 10.9, 7.5 Hz, 1.46 H), 2.66-2.40 (m, 1.26 H), 2.32 – 2.17 (m, 1H), 2.13 – 1.95 (m, 1.91 H), 1.94-1.78 (s, 1.68 H), 1.43 (s, 14H), 1.03 – 0.91 (m, 14H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$ – *both isomers*) δ 172.95, 172.34, 156.14, 155.82, 154.88, 154.76, 154.38, 135.29, 129.13, 129.03, 129.01, 128.94, 128.92, 96.88, 96.41, 79.84, 77.36, 70.65, 69.87, 68.79, 55.19, 55.10, 54.78, 54.41, 53.81, 40.21, 37.88, 37.61, 37.30, 37.18, 28.66, 28.54, 25.03, 24.97.

HRMS (ESI): [*m/z*] calculated for $C_{25}H_{36}N_2NaO_7$ [M+Na]$^{+}$], 499.2415, found 499.2426.

R_f (Cyclohexane /EtOAc 1:1) = 0.18 [CAM]

Benzyl (2S,4S)-2-(tert-butyl)-4-((3-methylenecyclobutyl)methyl)-5-oxooxazolidine-3-carboxylate (94)



Synthesized following **GP9** using 3-methylenecyclobutanecarboxylic acid (112 mg, 1.0 mmol, 2.0 equiv.). The pure product was isolated as a yellow oil in 25% yield (44.1 mg, 0.12 mmol)

^{1}H NMR(400 MHz, $CDCl_3$) δ 7.42 – 7.33 (m, 5H), 5.55 (s, 1H), 5.24 – 5.09 (m, 2H), 4.72 (dp, *J* = 7.2, 2.3 Hz, 2H), 4.18 (q, *J* = 6.8 Hz, 1H), 2.84 – 2.69 (m, 2H), 2.68 – 2.57 (m, 1H), 2.39 – 2.25 (m, 2H), 2.10 (ddd, *J* = 14.1, 7.7, 6.7 Hz, 1H), 1.96 (ddd, *J* = 13.7, 8.7, 6.6 Hz, 1H), 0.97 (s, 9H).

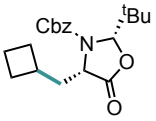
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.8, 156.1, 146.4, 135.3, 128.9, 128.9, 128.8, 106.4, 96.6, 68.6, 56.1, 39.7, 37.7, 37.1, 37.0, 27.4, 25.1

HRMS (ESI): [*m/z*] calculated for C21H27NNaO4 [M+Na]$^{+}$], 380.1832, found 380.1833.

$[\alpha]_D^{20}$: + 21.8 º (□ = 1.04, CH_2Cl_2)

R_f (Cyclohexane /EtOAc 6:1) = 0.35 [p-anisaldehyde]

Benzyl (2S,4S)-2-(tert-butyl)-4-(cyclobutylmethyl)-5-oxooxazolidine-3-carboxylate (95)



Synthesized following **GP9** using cyclobutanecarboxylic acid (100 mg, 1.0 mmol, 2.0 equiv.). The pure product was isolated as a yellow oil in 80% yield (137 mg, 0.40 mmol)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.33 (m, 5H), 5.54 (s, 1H), 5.17 (d, *J* = 2.2 Hz, 2H), 4.16 (dd, *J* = 7.7, 6.6 Hz, 1H), 2.65 (hept, *J* = 8.0 Hz, 1H), 2.11 – 1.97 (m, 3H), 1.94 – 1.74 (m, 3H), 1.67 – 1.58 (m, 2H), 0.96 (s, 9H).

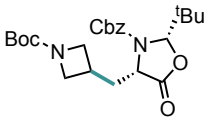
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.0, 156.1, 135.4, 128.8, 128.8, 96.5, 68.5, 55.7, 40.3, 37.1, 32.8, 28.3, 27.7, 25.1, 18.4.

HRMS (ESI): [*m/z*] calculated for $C_{20}H_{27}NNaO_4$ $[M+Na]^+$], 368.1832, found 368.1851.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: + 19.8 (ρ = 1.04, CH_2Cl_2)

$\mathbf{R}_f$ (Cyclohexane /EtOAc 6:1) = 0.38 [UV]

Benzyl (2S,4S)-4-((1-(tert-butoxycarbonyl)azetidin-3-yl)methyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate (96)



Synthesized following **GP9** using 1-Boc-azetidine-3-carboxylic acid (201 mg, 1.0 mmol, 2.0 equiv.). The pure product was isolated as a yellow oil in 93% yield (207 mg, 0.46 mmol)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.32 (m, 5H), 5.56 (s, 1H), 5.25 – 5.10 (m, 2H), 4.19 (t, *J* = 7.3 Hz, 1H), 4.00 (t, *J* = 8.2 Hz, 2H), 3.57 (dt, *J* = 9.1, 4.7 Hz, 2H), 2.21 (dt, *J* = 14.4, 7.3 Hz, 1H), 2.15 – 2.00 (m, 1H), 1.44 (s, 9H), 0.96 (s, 9H).

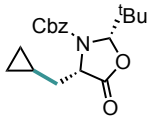
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.2, 156.1, 135.1, 129.0, 129.0, 128.8, 96.7, 79.5, 68.8, 55.9, 54.6, 54.0, 37.7, 37.10, 28.6, 26.5, 25.1.

HRMS (ESI): [*m/z*] calculated for $C_{24}H_{34}N_2NaO_6$ $[M+Na]^+$], 469.2309, found 469.2318.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: + 15.5 (ρ = 1.07, CH_2Cl_2)

$\mathbf{R}_f$ (Cyclohexane /EtOAc 4:1) = 0.32 [Ninhydrin]

Benzyl (2S,4S)-2-(tert-butyl)-4-(cyclopropylmethyl)-5-oxooxazolidine-3-carboxylate (97)



Synthesized following **GP9** using cyclopropanecarboxylic acid (215 mg, 2.5 mmol, 5.0 equiv.). The pure product was isolated as a yellow oil in 20% yield (33.3 mg,0.20 mmol)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.32 (m, 5H), 5.56 (s, 1H), 5.22 – 5.10 (m, 2H), 4.40 (dd, *J* = 8.2, 5.9 Hz, 1H), 2.07 – 1.96 (m, 1H), 1.49 (ddd, *J* = 14.3, 8.6, 5.9 Hz, 1H), 1.12 – 1.00 (m, 1H), 0.96 (s, 9H), 0.44 (dd, *J* = 8.0, 1.3 Hz, 2H), 0.09 (dd, *J* = 8.9, 3.7 Hz, 2H).

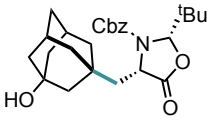
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 156.2, 135.4, 128.8, 128.7, 96.4, 68.5, 57.9, 38.6, 37.2, 25.1, 8.4, 5.7, 4.6.

HRMS (ESI): [*m/z*] calculated for $C_{19}H_{25}NNaO_4$ $[M+Na]^+$], 354.1676, found 354.1688.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: + 27.6 (ρ = 1.04, CH_2Cl_2)

R_f (Cyclohexane /EtOAc 6:1) = 0.36 [*p*-anisaldehyde]

Benzyl (2S,4S)-2-(tert-butyl)-4-(((1s,3S)-3-hydroxyadamantan-1-yl)methyl)-5-oxooxazolidine-3-carboxylate (98)



Synthesized following **GP9** using 3-hydroxyadamantane-1-carboxylic acid (196 mg, 1.0 mmol, 2.0 equiv.). The pure product was isolated as a yellow solid in 73% yield (162 mg, 0.38 mmol)

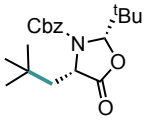
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.31 (m, 5H), 5.55 (s, 1H), 5.22 – 5.10 (m, 2H), 4.47 – 4.38 (m, 1H), 1.90 (s, 3H), 1.75 (dd, *J* = 14.3, 8.5 Hz, 1H), 1.68 (s, 1H), 1.65 (s, 2H), 1.59 – 1.52 (m, 6H), 1.52 – 1.47 (m, 3H), 0.96 (s, 10H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 155.8, 135.3, 129.1, 128.9, 128.8, 96.1, 68.5, 52.8, 49.4, 42.5, 37.1, 37.0, 32.9, 28.7, 25.1.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: + 27.8 º (ρ = 1.00, CH_2Cl_2)

R_f (Cyclohexane/EtOAc 6:1) = 0.45 [p-anisaldehyde/CAM]

Benzyl (2S,4S)-2-(tert-butyl)-4-neopentyl-5-oxooxazolidine-3-carboxylate (99)



Synthesized following **GP9** using pivalic carboxylic acid (102 mg, 1.0 mmol, 2.0 equiv.). The pure product was isolated as a yellow oil in 48% yield (83.5 mg, 0.24 mmol)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42 – 7.32 (m, 5H), 5.55 (s, 1H), 5.23 – 5.12 (m, 2H), 4.37 (dd, *J* = 8.2, 3.0 Hz, 1H), 1.90 (dd, *J* = 14.2, 8.1 Hz, 1H), 1.67 (dd, *J* = 14.3, 3.1 Hz, 1H), 0.99 (s, 9H), 0.96 (s, 9H).

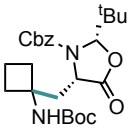
^{13}C{^{1}H} NMR (101 MHz, CDCl3) δ = 173.5, 155.9, 135.4, 129.0, 128.8, 128.8, 96.2, 68.5, 54.5, 48.4, 37.1, 31.0, 29.8, 25.2.

HRMS (ESI): [m/z] calculated for $C_{20}H_{29}NNaO_4$ = 370.1989; found: 370.1989

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: + 30.06 (ρ = 1.15, CH_2Cl_2)

R_f (Cyclohexane/EtOAc, 4:1) = 0.38 [*p*-Anisaldehyde]

Benzyl (2S,4S)-4-((1-((tert-butoxycarbonyl)amino)cyclobutyl)methyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate (100)



Synthesized following **GP9** using 1-N-Boc-amino-cyclobutanecarboxylic acid (215.3 mg, 1.0 mmol, 2.0 equiv.). The pure product was isolated as a yellow oil in 65% yield (150 mg, 0.33 mmol).

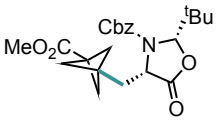
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.32 (m, 5H), 5.58 (s, 1H), 5.18 (d, *J* = 4.6 Hz, 2H), 4.41 (s, 1H), 2.42 – 2.18 (m, 4H), 2.06 (d, *J* = 9.2 Hz, 2H), 1.87 (s, 2H), 1.43 (s, 9H), 0.96 (s, 9H).

HRMS (ESI): [*m/z*] calculated for $C_{25}H_{36}N_2NaO_6$ [M+Na]$^+$], 483.2466, found 483.2475.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: + 21.0 º (ρ = 1.02, CH_2Cl_2)

R_f (CH/EtOAc 6:1) = 0.29 [UV/Ninhydrin]

Benzyl (2S,4S)-2-(tert-butyl)-4-((3-(methoxycarbonyl)bicyclo[1.1.1]pentan-1-yl)methyl)-5-oxooxazolidine-3-carboxylate (102)



Synthesized following **GP9** using 3-(Methoxycarbonyl)bicyclo[1.1.1)pentane-1-carboxylic acid (170 mg, 1.0 mmol, 2.0 equiv.). The pure product was isolated as a yellow solid in 45% yield (92.8 mg, 0.22 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.32 (m, 5H), 5.53 (s, 1H), 5.17 (d, *J* = 2.7 Hz, 2H), 4.25 (dd, *J* = 9.2, 3.6 Hz, 1H), 3.66 (s, 3H), 2.12 (dd, *J* = 14.5, 9.2 Hz, 1H), 2.01 (d, *J* = 9.5 Hz, 7H), 0.94 (s, 9H).

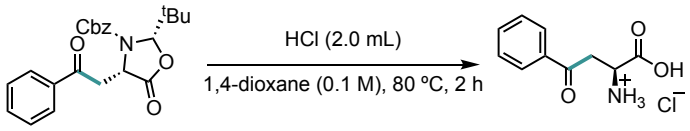
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.5, 155.7, 135.3, 128.9, 128.9, 128.8, 96.4, 68.6, 55.1, 52.4, 51.7, 38.4, 37.8, 37.2, 35.8, 25.0.

HRMS (ESI): [*m/z*] calculated for $C_{23}H_{29}NNaO_6$ [M+Na]$^+$], 438.1887, found 438.1879.

$[\alpha]_D^{20}$: + 15.0 (ρ = 1.05, CH_2Cl_2)

R_f (Cyclohexane /EtOAc 4:1) = 0.28 [CAM]

6.6.3. Derivatization reactions: deprotection:



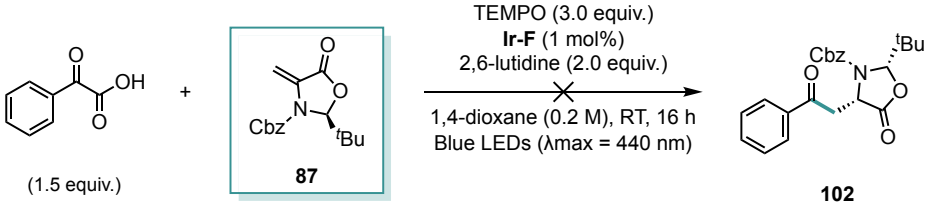
102 **103**

Deprotection under acidic conditions: In a 4 mL vial, **102** (35.0 mg, 0.09 mmol) was dissolved in a mixture of 1,4-dioxane (1.0 mL) and conc. HCl (2.0 mL) and stirred at 80 °C for 2 h. The reaction was monitored by TLC. Afterwards, the solvent was evaporated in the rotavapor. Then cyclohexane was added to resulting solid (3 x 2.0 mL) and evaporated in the rotavapor to azeotrope any water residues to afford the desired α-amino acid salt **103** as an off-white solid in 96% yield (20.0 mg, 0.087 mmol). The characterization data matches the reported literature.[227]

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (s, 3H), 8.02 – 7.97 (m, 2H), 7.73 – 7.67 (m, 1H), 7.57 (t, *J* = 7.7 Hz, 2H), 4.33 (t, *J* = 5.0 Hz, 1H), 3.80 – 3.68 (m, 2H).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 196.0, 170.2, 135.4, 133.9, 128.9, 128.0, 47.8, 38.4.

6.6.4. Reactions in presence of TEMPO



102

A 4 mL vial was charged with phenylglyoxylic acid (22.5 mg, 0.15 mmol, 1.5 equiv.), Dha **1** (29 mg, 0.1 mmol, 1.0 equiv.), **Ir-F** (1.1 mg, 1 µmol, 1 mol%), TEMPO (46.8 mg, 0.3 mmol, 3.0 equiv.) ,and sealed with a septum cap. The vial was put under vacuum for 1 min and refilled with N_2 (x 3). Afterwards, 2,6-lutidine (23 µL, 0.2 mmol, 2.0 equiv.) and degassed 1,4-dioxane (0.5 mL, 0.2 M) were added. The reaction mixture was then sparged with N_2 for 2-5 min and irradiated with blue LEDs (λmax = 440 nm) for 16 h. Afterwards, the reaction was diluted with EtOAc (1 mL) and methyl laureate (25 µL, 0.1 mmol,

1.0 equiv.) was added as internal standard. An aliquot of the mixture was then analyzed by GC-FID. No product formation was observed.

6.6.5. Quantum yield determination

According to the procedure of Yoon,[125] the photon flux of the LED (λ_{max} = 440 nm) was determined by standard ferrioxalate actinometry.[260,261] A 0.15 M solution of ferrioxalate was prepared by dissolving potassium ferrioxalate trihydrate (0.73 g) in H_2SO_4 (10 mL of a 0.05 M solution). A buffered solution of 1,10-phenanthroline was prepared by dissolving 1,10-phenanthroline (25 mg) and sodium acetate (5.6 g) in H_2SO_4 (25 mL of a 0.50 M solution). Both solutions were stored in the dark. To determine the photon flux of the LED, the ferrioxalate solution (1.0 mL) was placed in a cuvette and irradiated for 70 seconds at λ_{max} = 440 nm. After irradiation, the phenanthroline solution (175 µL) was added to the cuvette and the mixture was allowed to stir in the dark for 1.0 h to allow the ferrous ions to completely coordinate to the phenanthroline. The absorbance of the solution was measured at 510 nm. A non-irradiated sample was also prepared and the absorbance at 510 nm was measured. Conversion was calculated using eq. 1.

$$\text{mol Fe}^{2+} = \frac{V \bullet \Delta A(510\text{ nm})}{l \bullet \varepsilon} \quad \text{(eq. 3)}$$

where V is the total volume (0.001175 L) of the solution after addition of phenanthroline, ΔA is the difference in absorbance at 510 nm between the irradiated and non-irradiated solutions, l is the path length (1.00 cm), and ε is the molar absorptivity of the ferrioxalate actinometer at 510 nm (11,100 $Lmol^{-1}cm^{-1}$).[261] With this data, the photon flux can be calculated using eq. 2.

$$\text{Photon flux} = \frac{\text{mol } Fe^{2+}}{\Phi \bullet t \bullet \text{f}} \quad \text{(eq. 4)}$$

where Φ is the quantum yield for the ferrioxalate actinometer (1.01 at λ_{ex} = 437 nm),[260] t is the irradiation time (120 s), and f is the fraction of light absorbed at λ_{ex} = 437 nm by the ferrioxalate actinometer. This value is calculated using eq. 3 where A(440 nm) is the absorbance of the ferrioxalate solution at 440 nm. An absorption spectrum gave an A(440 nm) value of > 3, indicating that the fraction of absorbed light (f) is > 0.999.

$$\text{f} = 1 - 10^{A(440\,nm)} \quad \text{(eq. 5)}$$

The photon flux was thus calculated (average of three experiments) to be $1{,}1917E^{-09}$ einsteins s^{-1}

Determination of the reaction quantum yield

Using GP-9: A reaction under the standard conditions using **1** (29 mg, 0.1 mmol, 1 equiv.) and phenylglyoxylic acid (22.5 mg, 0.15 mmol, 1.5 equiv.) was irradiated at 440 nm for 3600 sec. Afterwards, the reaction was diluted with EtOAc (1 mL) and methyl laureate (25 µL, 0.1 mmol, 1.0 equiv.) was added as internal standard. An aliquot of the mixture was then analyzed by GC-FID and the yield or conversion calculated from the corresponding calibration curve. This afforded **2** in 26% yield (3 x 10^{-5} mol). The reaction quantum yield (Φ) was determined using eq. 4 where the photon flux is 1.44 x 10^{-07} einsteins s^{-1} (determined by actinometry as described above), t is the reaction time (3600 s) and f is the fraction of incident light absorbed by the reaction mixture, determined using eq. 3. An absorption spectrum of the reaction mixture gave an absorbance value of 4.18468 at 437 nm, thus f is 0.9999.

$$\Phi = \frac{\text{mol of product formed}}{\text{Photon flux} \bullet t \bullet \text{f}} \quad \text{(eq. 4)}$$

The reaction quantum yield (Φ) was thus determined to be 6.06.

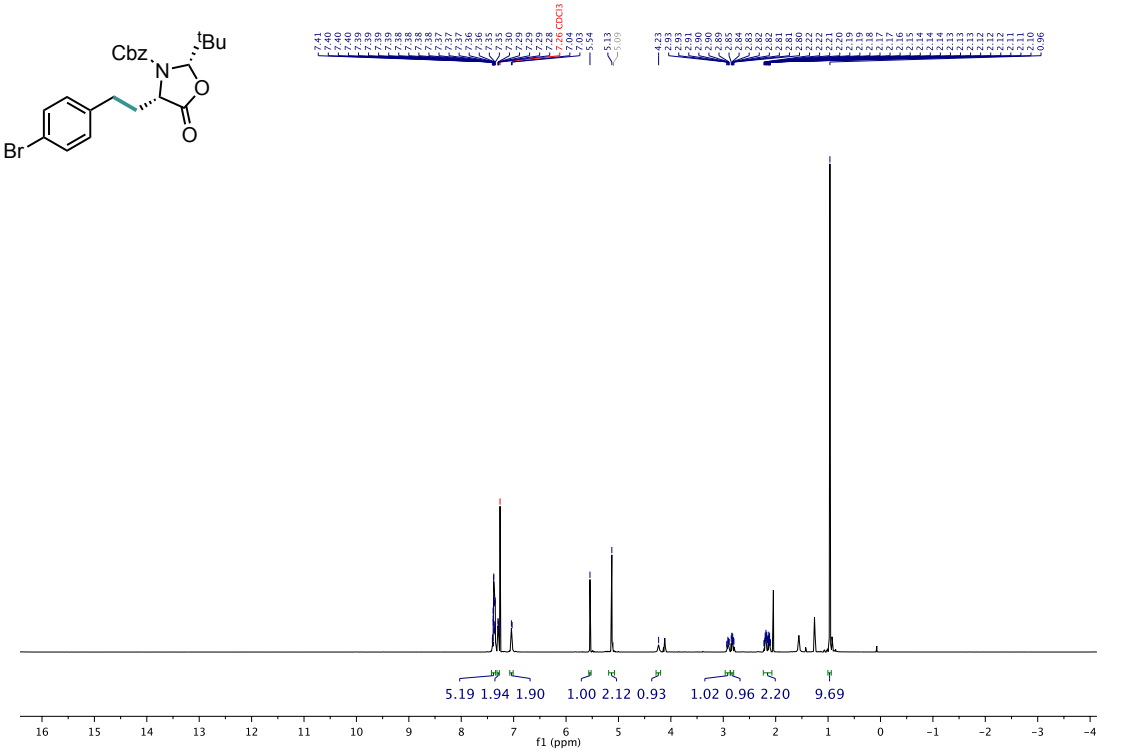
Using GP-10: A reaction under the standard conditions using **1** (29 mg, 0.1 mmol, 1 equiv.) and 4-bromophenyl acetic acid (43 mg, 0.20 mmol, 2.0 equiv.) was irradiated at 440 nm for 3600 sec. Afterwards, the reaction was diluted with EtOAc (1 mL) and methyl laureate (25 µL, 0.1 mmol, 1.0 equiv.) was added as internal standard. An aliquot of the mixture was then analyzed by GC-FID and the yield or conversion calculated from the corresponding calibration curve. This afforded **17** in 40% yield (4 x 10^{-5} mol). The reaction quantum yield (Φ) was determined using eq. 4 where the photon flux is 1.44 x 10^{-07} einsteins s^{-1} (determined by actinometry as described above), t is the reaction time (3600 s) and f is the fraction of incident light absorbed by the reaction mixture, determined using eq. 3. An absorption spectrum of the reaction mixture gave an absorbance value of 4.09989 at 437 nm, thus f is 0.9999.

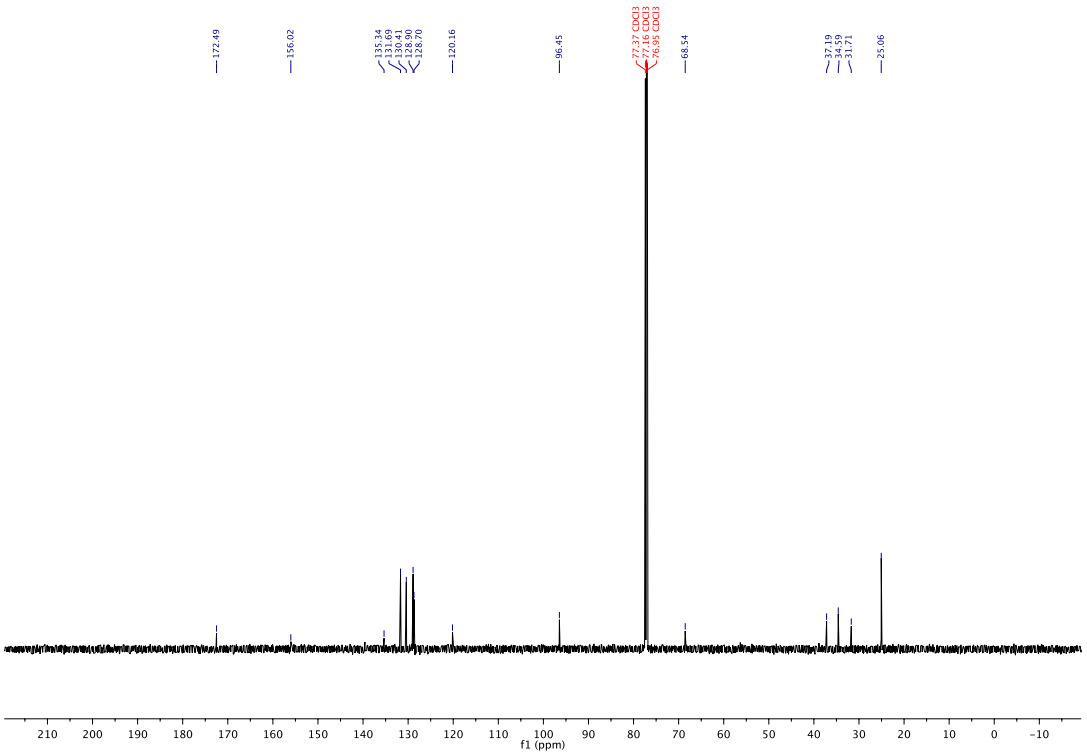
$$\Phi = \frac{\text{mol of product formed}}{\text{Photon flux} \bullet t \bullet \text{f}} \quad \text{(eq. 6)}$$

The reaction quantum yield (Φ) was thus determined to be 9.32.

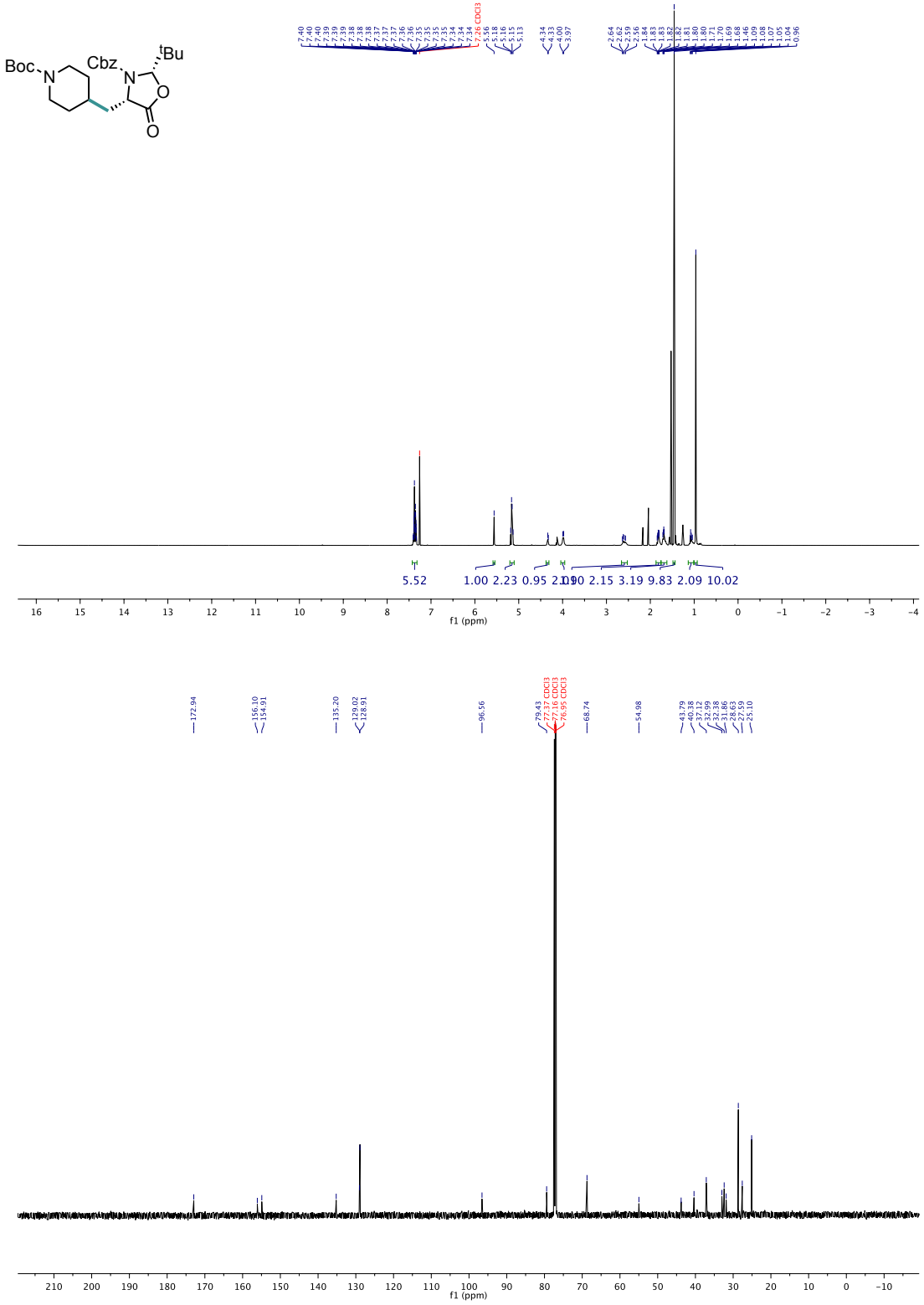
6.6.6. ^{1}H and ^{13}C–NMR Spectra

Benzyl (2S,4S)-4-(4-bromophenethyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate (91)

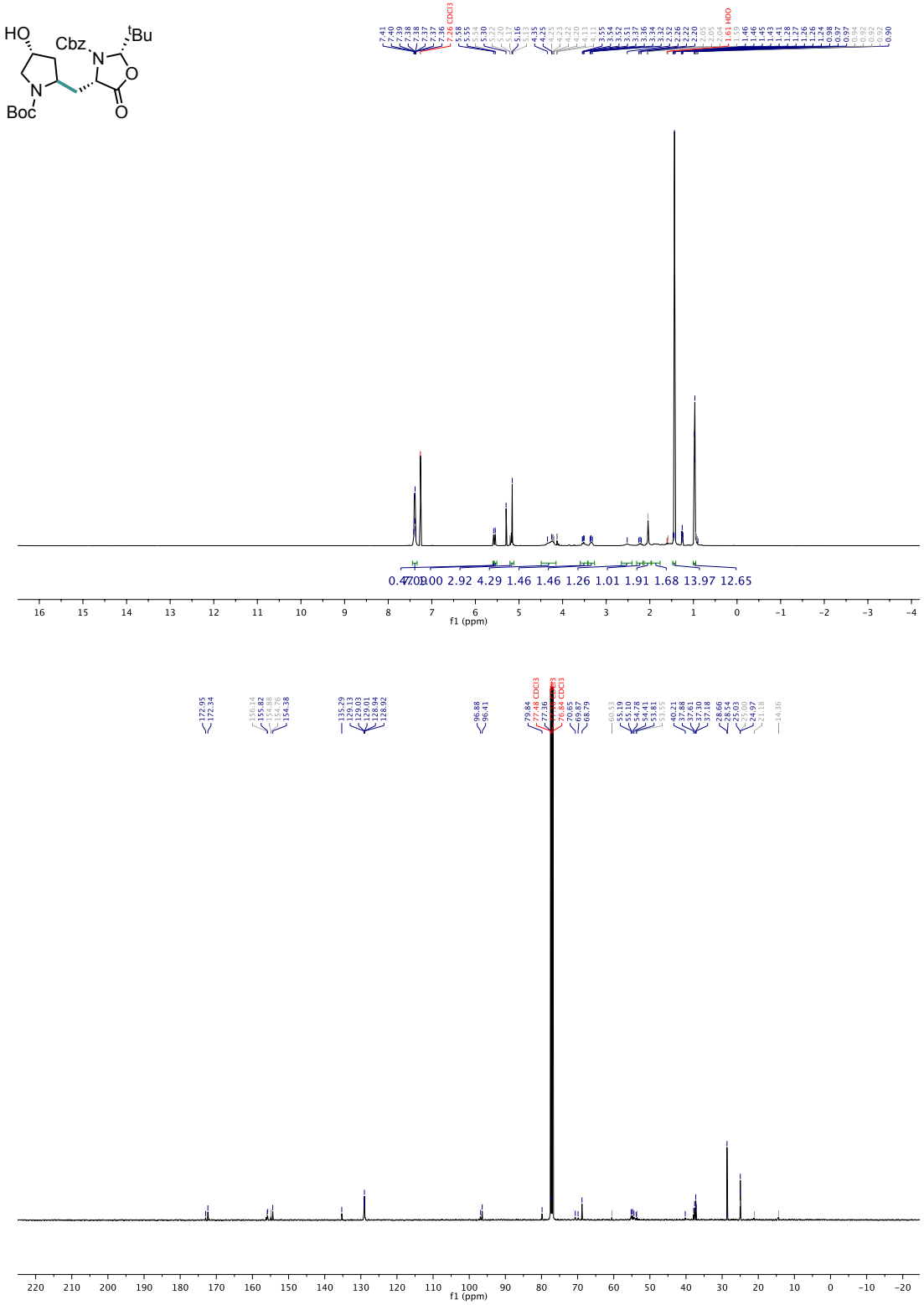




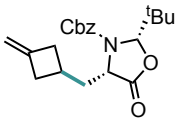
Benzyl (2S,4S)-4-((1-(tert-butoxycarbonyl)piperidin-4-yl)methyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate (92)

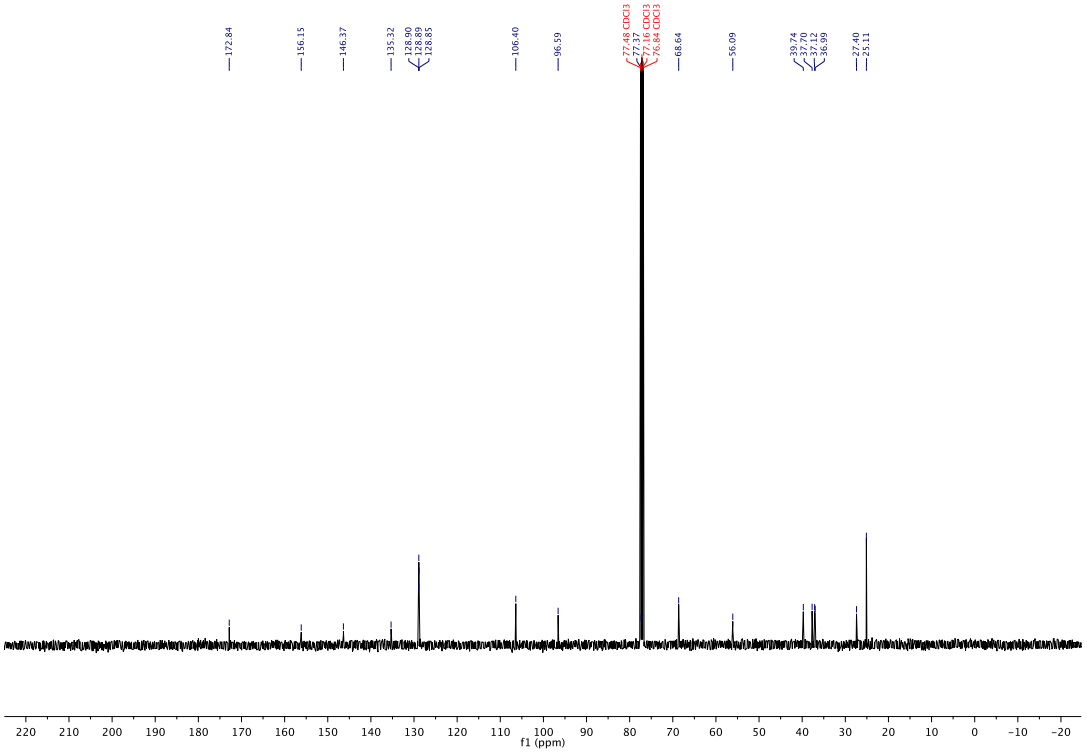


(2S,4S)-benzyl 4-(((4R)-1-(tert-butoxycarbonyl)-4-hydroxypyrrolidin-2-yl)methyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate (93):

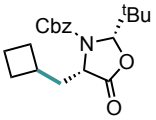


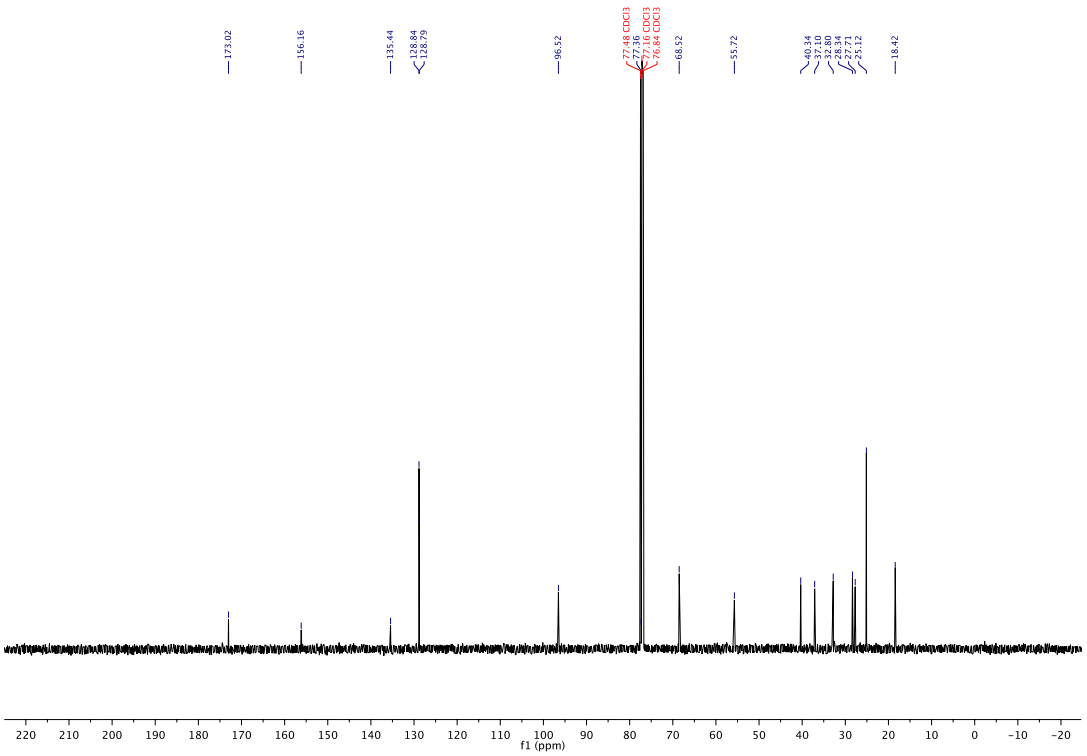
Benzyl (2S,4S)-2-(tert-butyl)-4-((3-methylenecyclobutyl)methyl)-5-oxooxazolidine-3-carboxylate (94)



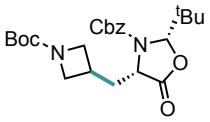


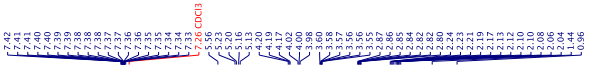
Benzyl (2S,4S)-2-(tert-butyl)-4-(cyclobutylmethyl)-5-oxooxazolidine-3-carboxylate (95)

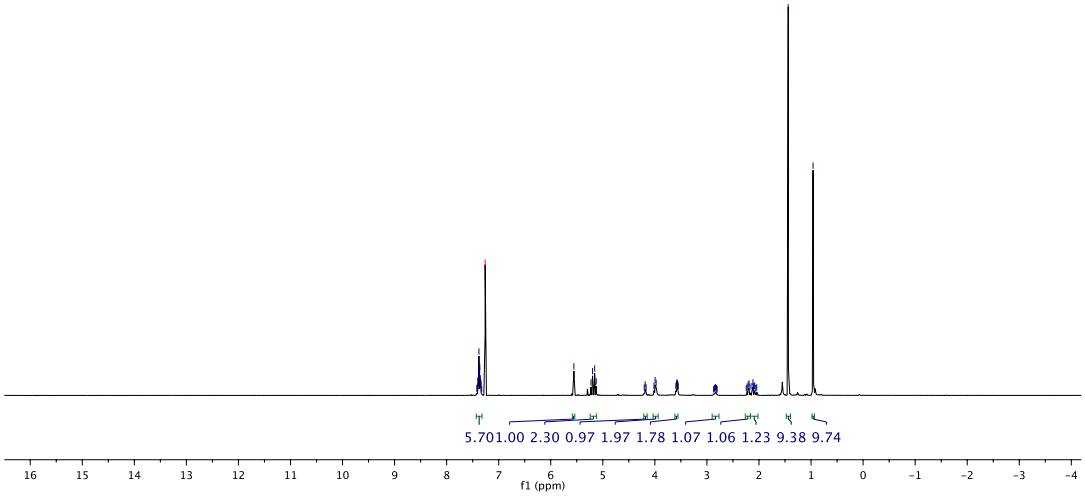


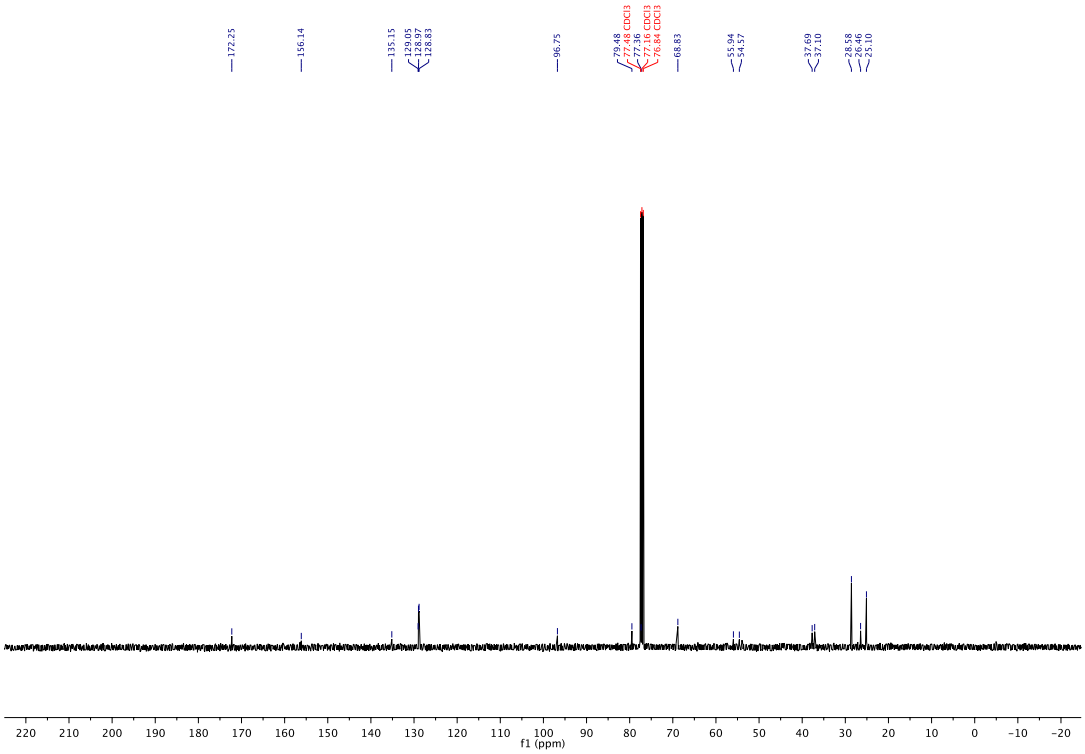


Benzyl (2S,4S)-4-((1-(tert-butoxycarbonyl)azetidin-3-yl)methyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate (96)

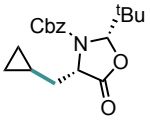


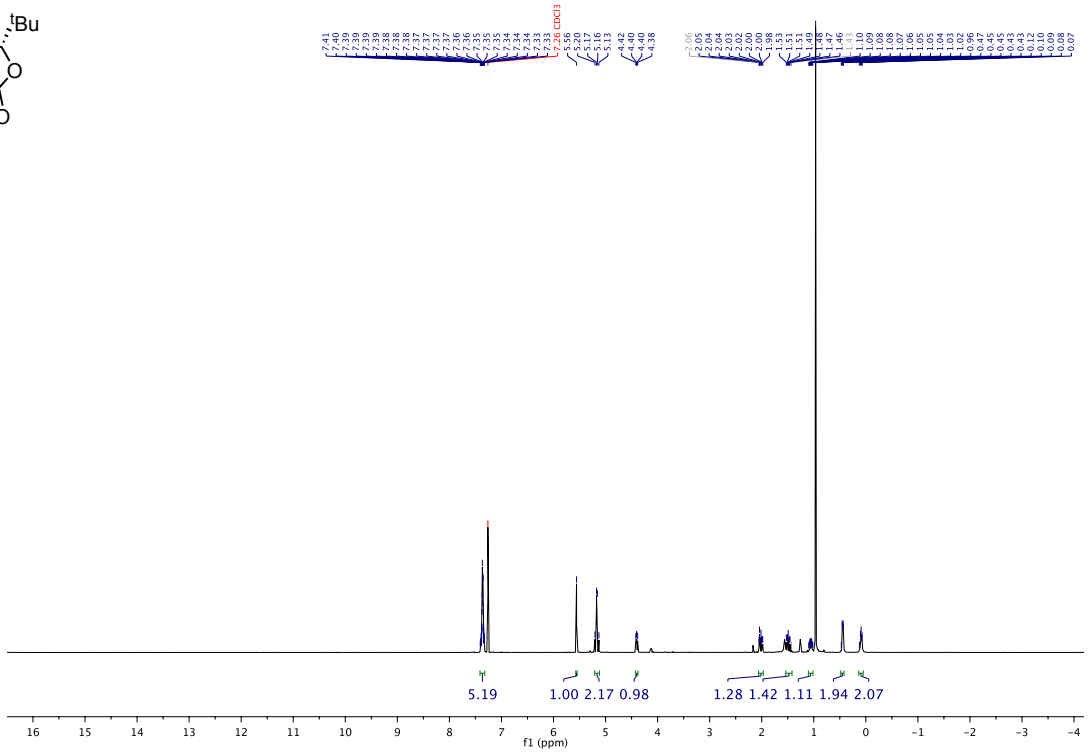


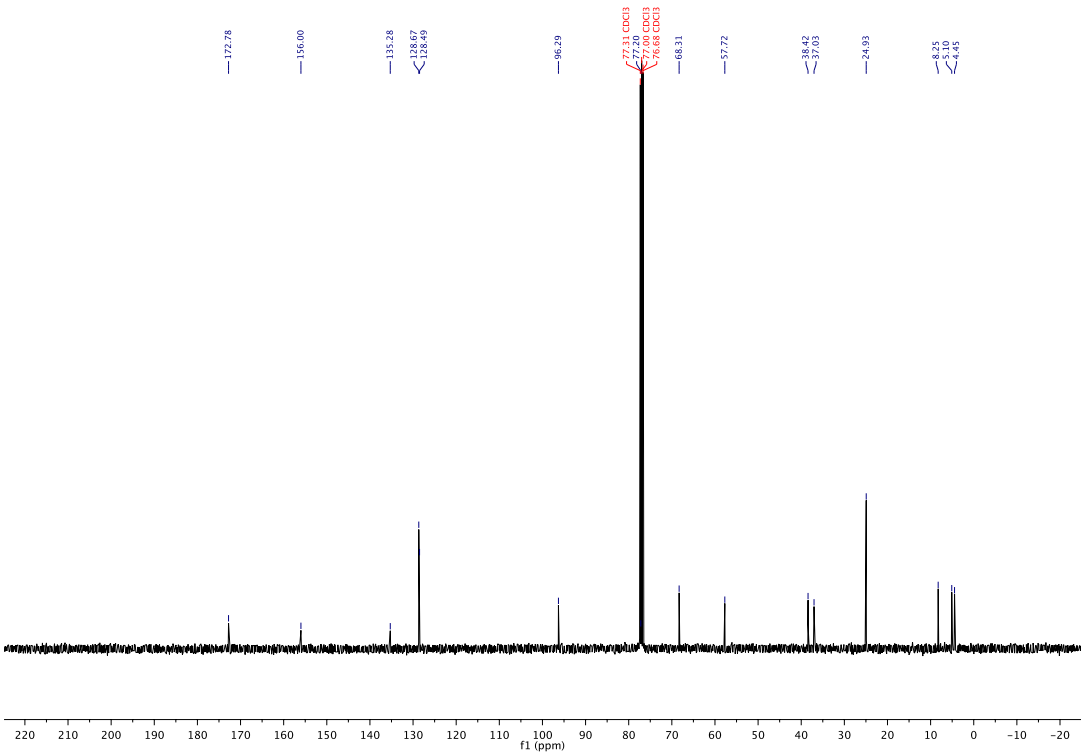




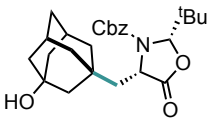
Benzyl (2S,4S)-2-(tert-butyl)-4-(cyclopropylmethyl)-5-oxooxazolidine-3-carboxylate (97)

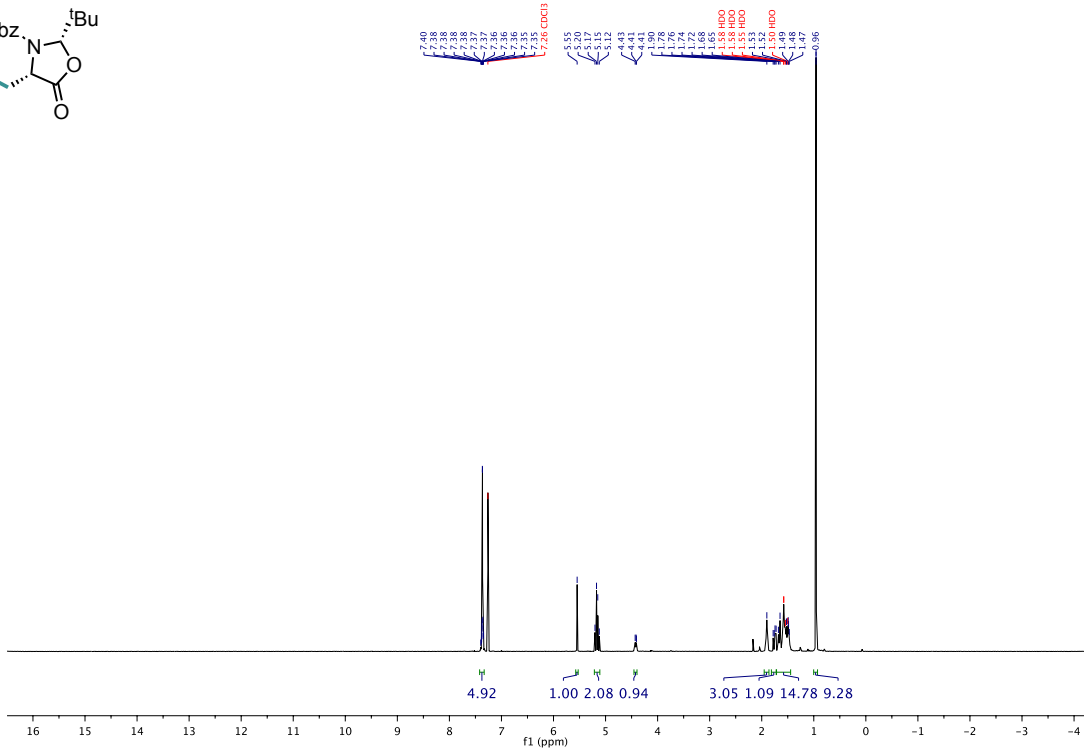


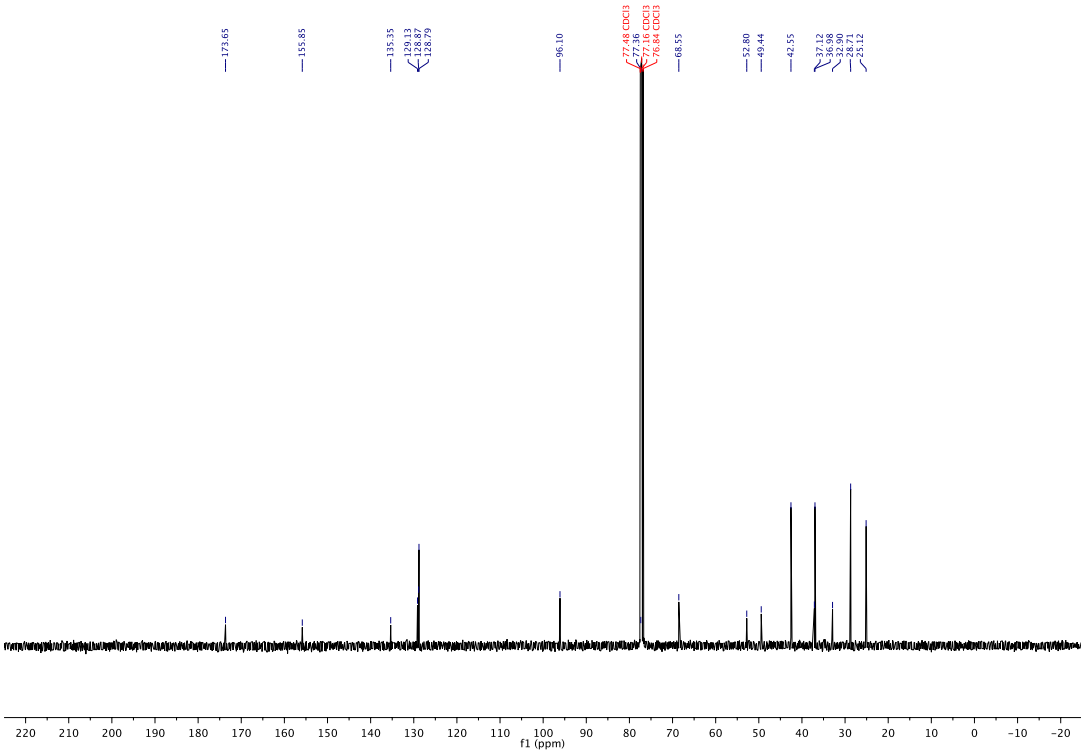




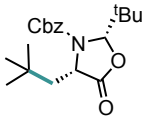
Benzyl (2S,4S)-2-(tert-butyl)-4-(((1s,3S)-3-hydroxyadamantan-1-yl)methyl)-5-oxooxazolidine-3-carboxylate (98)

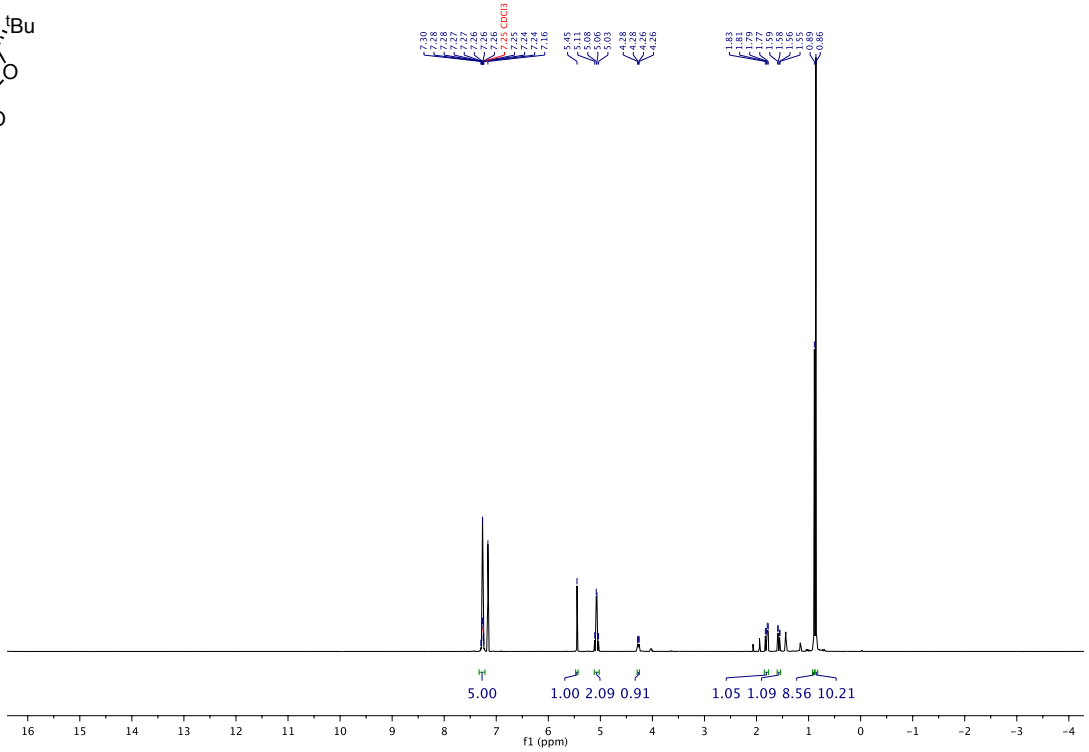


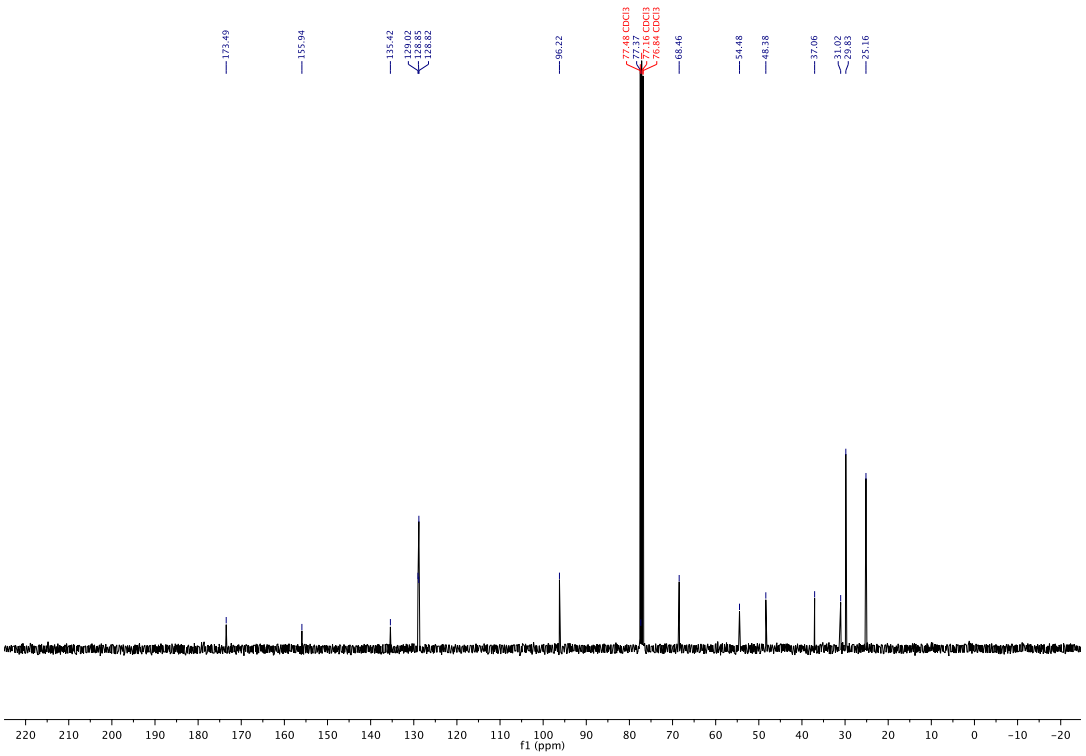




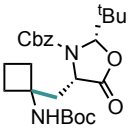
Benzyl (2S,4S)-2-(tert-butyl)-4-neopentyl-5-oxooxazolidine-3-carboxylate (99)

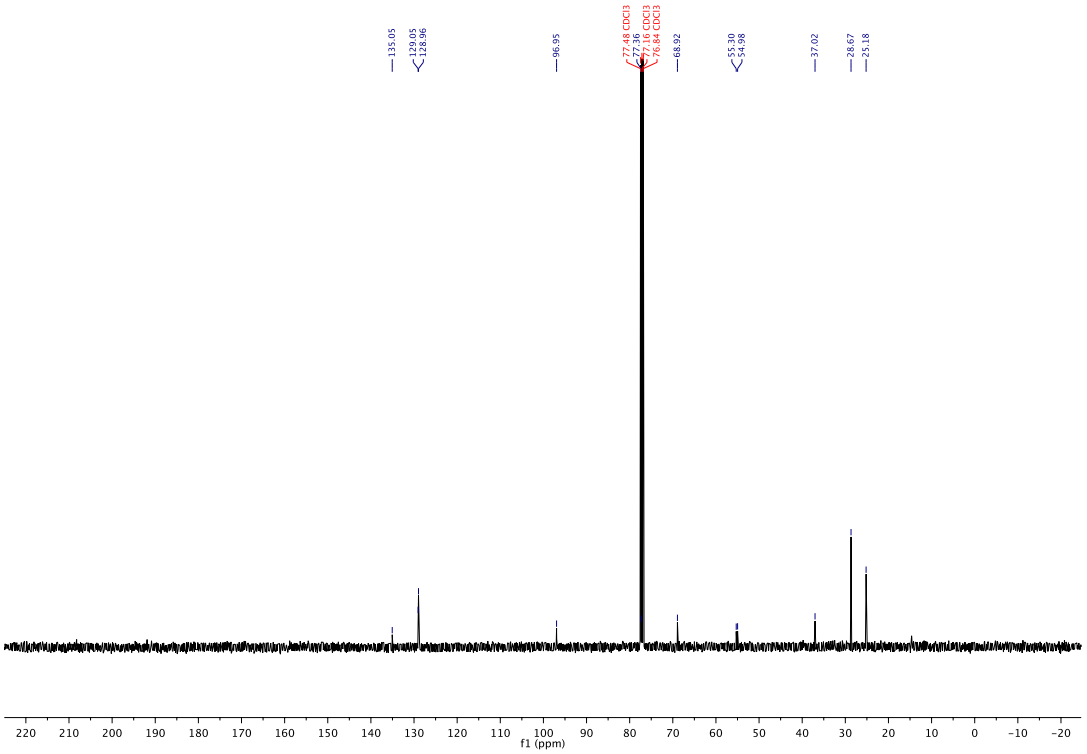




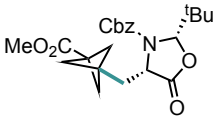


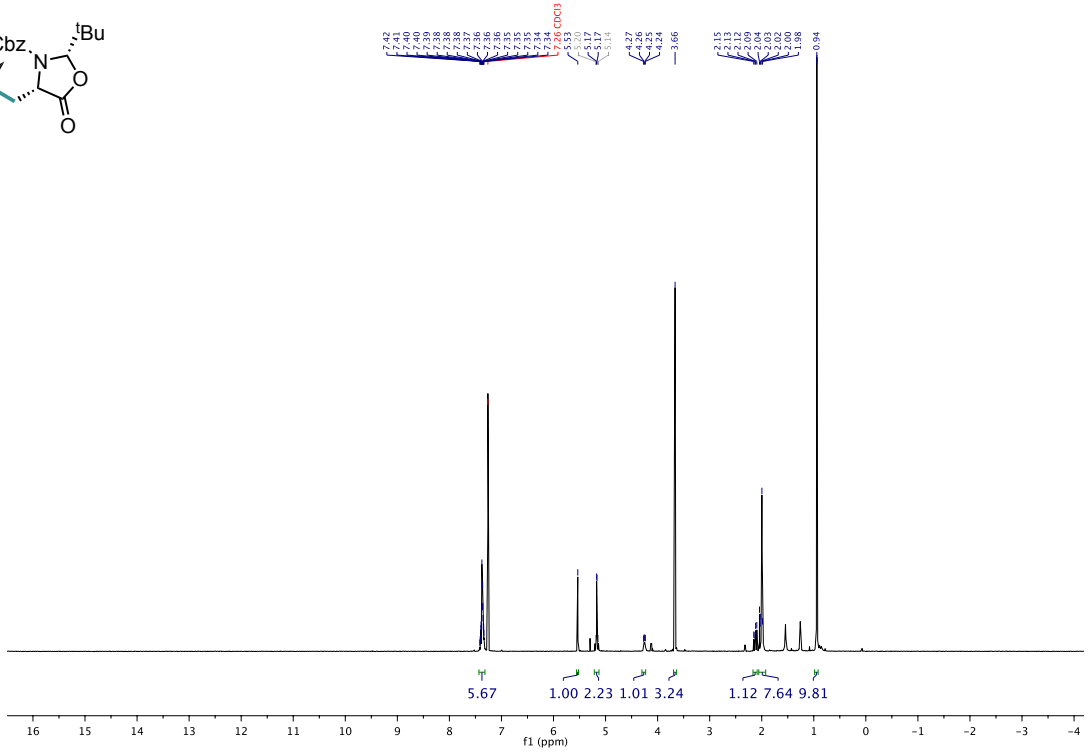
Benzyl (2S,4S)-4-((1-((tert-butoxycarbonyl)amino)cyclobutyl)methyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate (100)

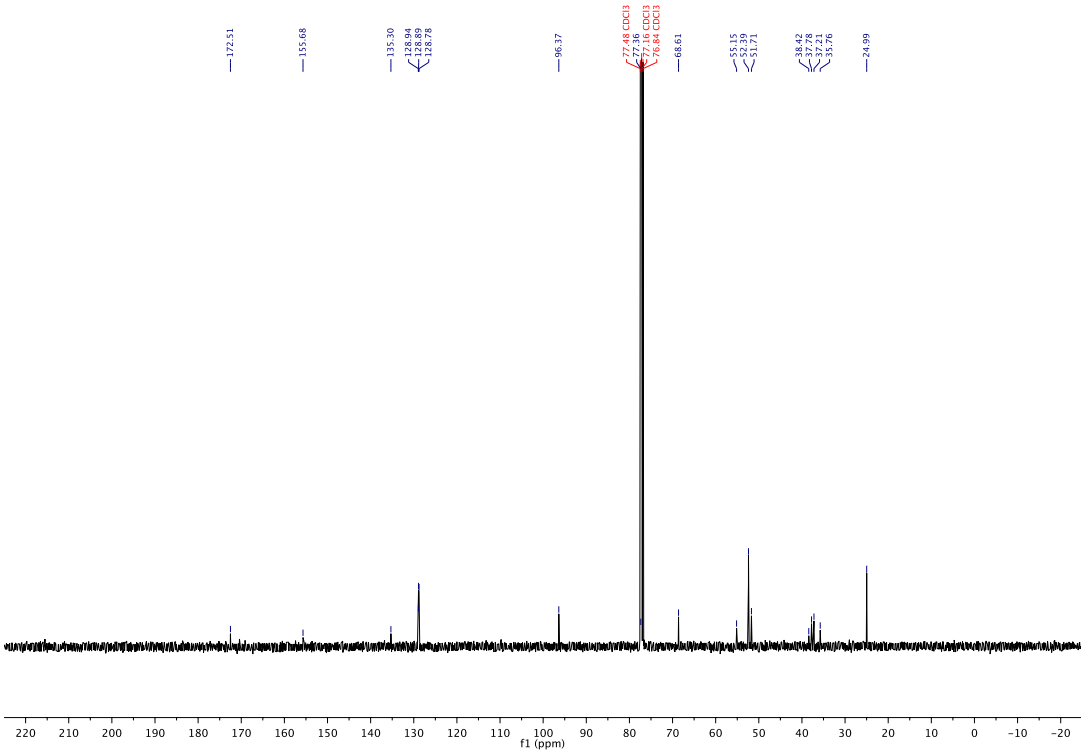




Benzyl (2S,4S)-2-(tert-butyl)-4-((3-(methoxycarbonyl)bicyclo[1.1.1]pentan-1-yl)methyl)-5-oxooxazolidine-3-carboxylate (101)







6.7. Chapter 5.5: Synthesis of γ-Oxo-α-amino acids via radical acylation process

6.7.1. Synthesis & characterization of products

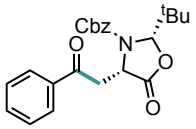
General Procedure 11 (GP11).

An 8 mL Biotage microwave vial was charged with the corresponding carboxylic acid (0.75 mmol, 1.5 equiv.), **88** (145 mg, 0.50 mmol, 1.0 equiv.), PPh_3 (235 mg, 0.9 mmol, 1.8 equiv.), Ir−F (5.5 mg, 5 µmol, 1 mol%), and sealed with a septum cap. The vial was put under a vacuum for 1 min and refilled with N_2 (× 3). Afterward, 2,4,6-collidine (132 μL, 1.0 mmol, 2.0 equiv.) and degassed 1,4-dioxane (2.5 mL, 0.2 M) were added. The reaction mixture was then sparged with N2 for 2−5 min and irradiated with blue LEDs (λ_{max} = 440 or 450 nm) in an EvoluChem PhotoRedOx Box for 24 h. Finally, the solvent was evaporated, and the crude reaction mixture was purified by column chromatography over silica gel to afford the desired product.

General Procedure 12 (GP12).

An 8 mL Biotage microwave vial was charged with the corresponding carboxylic acid (0.75 mmol, 1.5 equiv.), **88** (145 mg, 0.50 mmol, 1.0 equiv.), PPh_3 (235 mg, 0.9 mmol, 1.8 equiv.), Ir−F (5.5 mg, 5 µmol, 1 mol%), and sealed with a septum cap. The vial was put under a vacuum for 1 min and refilled with N_2 (× 3). Afterward, 2,4,6-collidine (132 μL, 1.0 mmol, 2.0 equiv.) and degassed DMF (2.5 mL, 0.2 M) were added. The reaction mixture was then sparged with N2 for 2−5 min and irradiated with blue LEDs (λ_{max} = 440 or 450 nm) in an EvoluChem PhotoRedOx Box for 24 h. Finally, the solvent was evaporated, and the crude reaction mixture was purified by column chromatography over silica gel to afford the desired product.

(2S,4S)-2-(tert-Butyl)-5-oxo-4-(2-oxo-2- phenylethyl)oxazolidine-3-carboxylate (102):



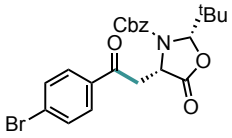
In 0.5 mmol scale: Synthesized following **GP11** using benzoic acid (90 mg, 0.75 mmol 1.5 equiv.). The crude product was purified by flash column chromatography (cyclohexane/EtOAc, 4:1) to provide 1 as a yellow oil in 95% yield (190 mg, 0.48 mmol). The spectroscopic data are consistent with those previously reported.[222]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94−7.88 (m, 2H), 7.62−7.55 (m, 1H), 7.49−7.42 (m, 2H), 7.32−7.27 (m, 3H), 7.24−7.20 (m, 2H), 5.61 (s, 1H), 5.24 (dd, J = 6.9, 5.0 Hz, 1H), 5.11 (d, J = 12.1 Hz, 1H), 5.00 (d, J = 12.1 Hz, 1H), 3.56 (dd, J = 16.4, 6.9 Hz, 1H), 3.38 (dd, J = 16.4, 5.0 Hz, 1H), 1.02 (s, 9H).

In 5.0 mmol scale: Synthesized following **GP11** using benzoic acid (916 mg, 7.5 mmol 1.5 equiv.) and Ir−F (28 mg, 25 µmol, 0.5 mol%). The crude product was purified by flash column chromatography (cyclohexane/EtOAc, 4:1) to provide 1 as a yellow oil in 97% yield (1.9 g, 4.8 mmol).

In 5.0 mmol scale: Synthesized following **GP11** using benzoic acid (916 mg, 7.5 mmol 1.5 equiv.) and Ir−F (14 mg, 12.5 µmol, 0.25 mol %) for 72 h. The crude product was purified by flash column chromatography (cyclohexane/EtOAc, 4:1) to provide 1 as a yellow oil in 73% yield (1.4 g, 3.6 mmol).

Benzyl (2S,4S)-4-(2-(4-bromophenyl)-2-oxoethyl)-2-(tert-butyl)- 5-oxooxazolidine-3-carboxylate (104):



Synthesized following **GP11** using 4-bromobenzoic acid (151 mg, 0.75 mmol, 1.5 equiv.). The crude product was purified by flash column chromatography (cyclohexane/EtOAc, 10:1) to provide **106** as a yellow oil in 74% yield (175 mg, 0.37 mmol).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 8.6 Hz, 2H), 7.31 (d, J = 1.5 Hz, 3H), 7.24−7.17 (m, 2H), 5.61 (s, 1H), 5.18 (dd, J = 6.9, 5.1 Hz, 1H), 5.10 (d, J = 12.0 Hz, 1H), 5.01 (d, J = 12.0 Hz, 1H), 3.49 (dd, J = 16.2, 6.9 Hz, 1H), 3.33 (dd, J = 16.2, 5.1 Hz, 1H), 1.01 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 193.9, 172.0, 155.6, 135.1, 135.1, 132.2, 129.8, 128.8, 128.8, 128.8, 128.6, 110.0, 96.5, 68.5, 53.8, 41.9, 37.6, 24.9.

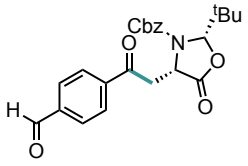
IR ṽ [cm^{-1}] = 2963 (w), 2874 (w), 1791 (s), 1719 (m), 1688 (m), 1584 (s), 1581 (m), 1457 (m), 1393 (m), 1343 (m), 1286 (m), 1235 (m), 1173 (m), 1120 (m), 1068 (m), 1042 (m), 989 (w), 823 (m), 733 (m), 697 (s), 509 (s), 453 (s).

HRMS (ESI): [*m/z*] calculated for $C_{23}H_{24}BrNNaO_5$ ([M + Na]+) 496.0729, found 496.0730.

$[\alpha]_D^{20}$: +40.5 (ρ = 0.93, CH_2Cl_2).

R_f (cyclohexane/EtOAc, 4:1) = 0.62 [p-Anisaldehyde].

Benzyl (2S,4S)-2-(tert-butyl)-4-(2-(4-formylphenyl)-2-oxoethyl)- 5-oxooxazolidine-3-carboxylate (105):



Synthesized following **GP11** using 4-formylbenzoic acid (113 mg, 0.75 mmol 1.5 equiv.). The crude product was purified by flash column chromatography (cyclohexane/EtOAc, 4:1) to provide **107** as a yellow oil in 10% yield (21.2 mg, 0.05 mmol).

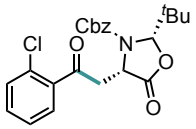
^{1}H NMR (600 MHz, $CDCl_3$) δ 10.10 (s, 1H), 8.01 (t, J = 8.1 Hz, 2H), 7.94 (d, J = 8.4 Hz, 2H), 7.30 (dd, J = 5.1, 2.1 Hz, 3H), 7.25−7.20 (m, 2H), 5.63 (s, 1H), 5.21 (dd, J = 7.0, 5.0 Hz, 1H), 5.11 (d, J = 12.0 Hz, 1H), 5.03 (d, J = 12.1 Hz, 1H), 3.57 (dd, J = 16.3, 7.0 Hz, 1H), 3.41 (dd, J = 16.3, 5.0 Hz, 1H), 1.02 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 194.4, 191.5, 171.9, 155.6, 140.5, 139.4, 135.1, 130.0, 128.8, 128.8, 128.6, 96.5, 68.6, 53.8, 42.4, 37.6, 27.1, 24.9.

HRMS (ESI): [*m/z*] calculated for $C_{24}H_{25}NNaO_6$ ([M + Na]+) 446.1574, found 446.1573.

R_f (cyclohexane/EtOAc, 4:1) = 0.16 [p-Anisaldehyde].

Benzyl (2S,4S)-2-(tert-butyl)-4-(2-(2-chlorophenyl)-2-oxoethyl)- 5-oxooxazolidine-3-carboxylate (106):



Synthesized following **GP11** using 2-chlorobenzoic acid (117.4 mg, 0.75 mmol, 1.5 equiv.). The crude product was purified by flash column chromatography (cyclohexane/EtOAc, 10:1) to provide **108** as a yellow oil in 95% yield (203 mg, 0.47 mmol).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (d, J = 7.7 Hz, 1H), 7.41−7.39 (m, 2H), 7.33 (s, 5H), 7.32−7.28 (m, 1H), 5.61 (s, 1H), 5.22 (t, J = 6.1 Hz, 1H), 5.20−5.12 (m, 2H), 3.51−3.48 (m, 2H), 0.97 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 197.4, 172.1, 155.6, 138.5, 135.3, 132.4, 131.3, 130.7, 130.0, 128.8, 128.7, 128.6, 127.2, 96.4, 68.5, 53.7, 45.8, 37.6, 24.9.

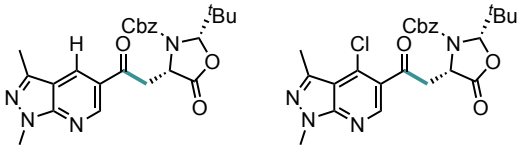
HRMS (ESI): [*m/z*] calculated for $C_{23}H_{24}ClNNaO_5$ ([M + Na]+) 452.1215, found 452.1235.

IR $\tilde{\nu}$ [cm^{-1}] = 2968 (w), 1791 (s), 1716 (s), 1589 (s), 1392 (m), 1345 (m), 1284 (m), 1176 (m), 1120 (m), 1076 (m), 1040 (m), 976 (m), 757 (m), 697 (m), 697 (s), 633 (m).

$[\alpha]_D^{20}$ = +47.2 (*ρ* = 1.03, CH_2Cl_2).

R_f (cyclohexane/EtOAc, 4:1) = 0.45 [p-Anisaldehyde].

Benzyl (2S,4S)-2-(tert-butyl)-4-(2-(1,3-dimethyl-1H-pyrazolo[3,4- b]pyridin-5-yl)-2-oxoethyl)-5-oxooxazolidine-3-carboxylate (107) and Benzyl (2S,4S)-2-(tert-butyl)-4-(2-(4-chloro-1,3-dimethyl-1H- pyrazolo[3,4-b]pyridin-5-yl)-2-oxoethyl)-5-oxooxazolidine-3-car- boxylate (107'):



Synthesized following **GP12** using 4-Chloro-1,3- dimethylpyrazolo[3,4-b]pyridine-5-carboxylic acid (169 mg, 0.75 mmol 1.5 equiv.), and irradiating for 48 h. The crude product was purified by flash column chromatography (cyclohexane/EtOAc, 2:1) to provide **100** a yellow foam in 39% (98 mg, 0.20 mmol) and **100'** as a yellow solid in 18% yield (45 mg, 0.10 mmol).

Spectroscopic data for 107:

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.05 (d, J = 2.0 Hz, 1H), 8.49 (d, J = 2.0 Hz, 1H), 7.23 (q, J = 2.9 Hz, 3H), 7.19 (dd, J = 6.8, 3.1 Hz, 2H), 5.64 (s, 1H), 5.26 (dd, J = 6.8, 5.2 Hz, 1H), 5.11−5.01 (m, 2H), 4.11 (s, 3H), 3.59 (dd, J = 16.0, 6.8 Hz, 1H), 3.43 (dd, J = 16.0, 5.2 Hz, 1H), 2.59 (s, 3H), 1.04 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 193.2, 172.0, 155.7, 152.2, 149.5, 143.2, 135.0, 130.8, 128.7, 128.6, 128.5, 125.1, 114.8, 96.5, 68.5, 54.0, 42.0, 37.6, 33.9, 24.9, 12.6.

HRMS (ESI): [*m/z*] calculated for $C_{25}H_{28}N_4NaO_5$ ([M + Na]+) 487.1957, found 487.1952.

IR ṽ [cm^{-1}] = 2961 (s), 2926 (s), 1790 (w), 1719 (w), 1678 (w), 1599 (w), 1564 (m), 1520 (m), 1478 (m), 1392 (w), 1281 (w), 1177 (w), 1121 (m), 1041 (w), 983 (w), 748 (m), 697 (w), 578 (m), 503 (m), 456 (m), 428 (m).

$[\alpha]_D^{20}$ = +40.1 (ρ = 0.92,CH_2Cl_2).

R_f (cyclohexane/ EtOAc, 1:1) = 0.33 [p-Anisaldehyde].

Spectroscopic data for 107':

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s,1H), 7.40−7.29 (m, 1H), 7.27 (tdd, J = 4.6, 3.4, 2.0 Hz, 4H), 5.63 (s, 1H), 5.23 (dd, J = 6.9, 5.4 Hz, 1H), 5.14 (d, J = 1.0 Hz, 2H), 4.07 (s, 3H), 3.60 (dd, J = 16.3, 6.9 Hz, 1H), 3.53 (dd, J = 16.3, 5.5 Hz, 1H), 2.73 (s, 3H), 1.00 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 195.0, 171.9, 155.6, 152.3, 151.0, 142.9, 138.0, 135.1, 128.7, 128.7, 128.6, 126.1, 113.2, 96.5, 68.6, 54.2, 45.9, 37.6, 34.0, 24.9, 15.1.

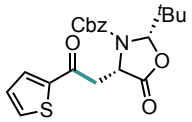
HRMS (ESI): [*m/z*] calculated for $C_{25}H_{27}ClN_4NaO_5$. ([M + Na]+) 521.1562, found 521.1560.

IR ṽ [cm^{-1}] = 2962 (s), 2874 (s), 1791 (m), 1717 (w), 1582 (s), 1547 (m), 1515 (w), 1456 (w), 1391 (m), 1332 (w), 1285 (w), 1234 (w), 1175 (w), 1117 (m), 1038 (w), 729 (w), 697 (w), 582 (m), 503 (m).

$[\alpha]_D^{20}$ = +38.1 (ρ = 0.96, CH_2Cl_2).

R_f (cyclohexane/EtOAc, 1:1) = 0.43 [p-Anisaldehyde].

Benzyl (2S,4S)-2-(tert-butyl)-5-oxo-4-(2-oxo-2-(thiophen-2-yl)- ethyl)oxazolidine-3-carboxylate (108):



Synthesized following **GP11** using thiophene-2-carboxylic acid (96 mg, 0.75 mmol 1.5 equiv.). The crude product was purified by flash column chromatography (cyclohexane/EtOAc, 4:1) to provide **110** as a yellow oil in 71% yield (134 mg, 0.35 mmol).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71− 7.64 (m, 2H), 7.33−7.27 (m, 3H), 7.24 (dd, J = 6.7, 2.9 Hz, 2H), 7.12 (dd, J = 4.9, 3.8 Hz, 1H), 5.61 (s, 1H), 5.18−5.09 (m, 2H), 5.00 (d, J = 12.1 Hz, 1H), 3.47 (dd, J = 15.7, 6.6 Hz, 1H), 3.30 (dd, J = 15.6, 5.6 Hz, 1H), 1.01 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 187.6, 171.9, 155.7, 143.7, 135.3, 134.5, 132.3, 128.8, 128.7, 128.5, 128.4, 96.5, 68.4, 54.1, 42.6, 37.6, 24.9.

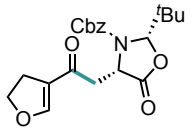
HRMS (ESI): [*m/z*] calculated for $C_{21}H_{23}NNaO_5S$ ([M + Na]+) 424.1190, found 424.1189.

IR ṽ [cm^{-1}] = 2962 (s), 2874 (s), 1791 (m), 1717 (w), 1582 (s), 1547 (m), 1515 (w), 1456 (w), 1391 (m), 1332 (w), 1285 (w), 1234 (w), 1175 (w), 1117 (m), 1038 (w), 729 (w), 697 (w), 582 (m), 503 (m).

$[\alpha]_D^{20}$ = +26.6 (ρ= 0.93, CH_2Cl_2).

R_f (cyclohexane/EtOAc, 4:1) = 0.20 [p-Anisaldehyde].

Benzyl 2-(tert-butyl)-4-(2-(4,5-dihydrofuran-3-yl)-2-oxoethyl)-5- oxooxazolidine-3-carboxylate (109):



Synthesized following **GP11** using 4,5-dihydro-furan-3-carboxylic acid (86 mg, 0.75 mmol 1.5 equiv.), and irradiating for 48 h. The crude product was purified by flash column chromatography (cyclohexane/EtOAc, 2:1) to provide **112** as a yellow oil in 31% yield (60 mg, 0.15 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.31 (m, 5H), 7.26−7.25 (m, 1H), 5.59 (s, 1H), 5.15 (s, 2H), 5.08 (dd, J = 7.1, 5.3 Hz, 1H), 4.56−4.46 (m, 2H), 3.08 (dd, J = 15.2, 7.1 Hz, 1H), 2.95 (dd, J = 15.2, 5.3 Hz, 1H), 2.87− 2.70 (m, 2H), 0.98 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 189.6, 172.1, 158.5, 155.8, 135.5, 128.8, 128.7, 128.5, 120.4, 96.4, 73.8, 68.4, 54.2, 42.4, 37.5, 27.4, 24.9.

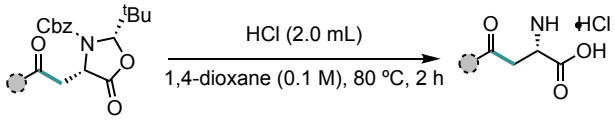
HRMS (ESI): [*m/z*] calculated for $C_{21}H_{25}NNaO_6$ ([M + Na]+) 410.1585, found 410.1574. IR ṽ [cm−1] = 2968 (s), 1790 (w), 1716 (w), 1648 (m), 1604 (w), 1392 (m), 1334 (m), 1291 (m), 1178 (m), 1129 (w), 1042 (m), 910 (m), 728 (w), 697 (w), 456 (m).

$[\alpha]_D^{20}$ = +35.2 (ρ = 1.05, CH_2Cl_2).

R_f (cyclohexane/EtOAc, 1:1) = 0.33 [p- Anisaldehyde].

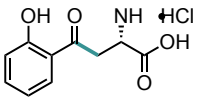
6.7.2. Derivatization reactions: deprotection:

General Procedure 13 (GP13):



In a 4mL vial, the corresponding oxazolidinone was dissolved in a mixture of 1,4-dioxane (1.0 mL) and conc. HCl (2.0 mL) and stirred at 80 °C in an oil bath for 2 h, monitoring by TLC. Afterwards, the reaction was concentrated in vacuo. To the resulting solid, cyclohexane (3 × 2.0 mL) was added and evaporated in vacuo to azeotrope any water residues, affording the desired α-amino acid salts.

(S)-2-Amino-4-(2-hydroxyphenyl)-4-oxobutanoic acid hydrochloride salt (116):



Synthesized following **GP13** to afford the desired α-amino acid salt **119** as an off-yellow solid in 97% yield (35.5 mg, 0.136 mmol).

^{1}H NMR (400 MHz, D_2O) δ 7.98 (dd, J = 8.1, 1.6 Hz, 1H), 7.70 (ddd, J = 8.4, 7.3, 1.6 Hz, 1H), 7.18−7.07 (m, 2H), 4.53 (t, J = 5.3 Hz, 1H), 3.98 (d, J = 5.3 Hz, 2H).

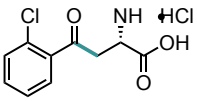
^{13}C{^{1}H} NMR (101 MHz, D_2O) δ 204.5, 173.9, 162.1, 139.4, 132.5, 122.0, 120.8, 119.6, 50.9, 40.2.

HRMS (ESI) [m/z] calculated for C10H11ClNO4

([M]−) 244.0383, found 244.0382.

$[\alpha]_D^{20}$ = +26.7(ρ = 0.30, MeOH).

(S)-2-Amino-4-(2-chlorophenyl)-4-oxobutanoic acid hydrochloride salt (117):

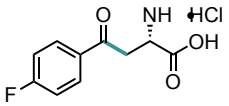


Synthesized following **GP13** to afford the desired α-amino acid salt **120** as an off-brown solid in quantitative yield (27.0 mg, 0.11 mmol).

^{1}H NMR (400 MHz, D_2O) δ 7.80 (dt, J = 7.7, 1.1 Hz, 1H), 7.69−7.61 (m, 2H), 7.55 (dt, J = 7.7, 4.3 Hz, 1H), 4.50 (t, J = 5.3 Hz, 1H), 3.90 (d, J = 5.3 Hz, 2H).

The characterization data matches the reported literature.[264]

(S)-2-Amino-4-oxo-4-(pyridin-3-yl) butanoic acid hydrochloride salt (118):

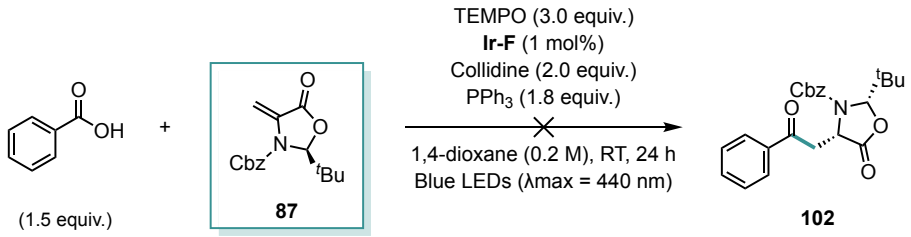


Synthesized following **GP13** to afford the desired α-amino acid salt **121** as an off-brown solid in 95% yield (45.0 mg, 0.18 mmol).

^{1}H NMR (400 MHz, D_2O) δ 8.15−8.09 (m, 2H), 7.37−7.29 (m, 2H), 4.45 (dd, J = 5.8, 4.7 Hz, 1H), 3.93−3.83 (m, 2H).

The characterization data matches the reported literature.[231]

6.7.3. Reactions in presence of TEMPO



A 4 mL vial was charged with benzoic acid (22.5 mg, 0.15 mmol, 1.5 equiv.), **88** (29 mg, 0.1 mmol, 1.0 equiv.), PPh_3 (47 mg, 0.27 mmol, 1.8 equiv.), **Ir-F** (1.1 mg, 1 µmol, 1 mol%), and TEMPO (46.8 mg, 0.3 mmol, 3.0 equiv.), and sealed with a septum cap. The vial was put under vacuum for 1 min and refilled with N_2 (x 3). Afterwards, 2,4,6-collidine (25 µL, 0.2 mmol, 2.0 equiv.) and degassed 1,4-dioxane (0.5 mL, 0.2 M) were added. The reaction mixture was then sparged with N_2 for 2-5 min and irradiated with blue LEDs (λ_{max} = 440 nm) for 16 h. Afterwards, the reaction was diluted with EtOAc (1 mL) and methyl laureate (25 µL, 0.1 mmol, 1.0 equiv.) was added as internal standard. An aliquot of the mixture was then analysed by GC-FID. No product formation was observed.

6.7.4. Quantum yield determination

Following the procedure of Yoon,[125] the photon flux of the LED (λ_{max} = 440 nm) was determined by standard ferrioxalate actinometry.[260,261] A 0.15 M solution of ferrioxalate was prepared by dissolving potassium ferrioxalate trihydrate (0.73 g) in H_2SO_4 (10 mL of a 0.05 M solution). A buffered solution of 1,10-phenanthroline was prepared by dissolving 1,10-phenanthroline (25 mg) and sodium acetate (5.6 g) in H_2SO_4 (25 mL of a 0.50 M solution). Both solutions were stored in the dark. To determine the photon flux of the LED, the ferrioxalate solution (1.0 mL) was placed in a cuvette and irradiated for 120 seconds at λ_{max} = 440 nm. After irradiation, the phenanthroline solution (175 µL) was added to the cuvette and the mixture was allowed to stir in the dark for 1 h to allow the ferrous ions to fully coordinate to the phenanthroline. The absorbance of the solution was measured at 510 nm. A non-

irradiated sample was also prepared, and the absorbance was measured at 510 nm. Conversion was calculated using eq. 1.

$$\text{mol } Fe^{2+} = \frac{V\Delta A(510\text{ nm})}{l\varepsilon} \quad \text{(eq. 3)}$$

where V is the total volume (0.001175 L) of the solution after addition of phenanthroline, ΔA is the difference in absorbance at 510 nm between the irradiated and non-irradiated solutions, l is the path length (1.00 cm), and ε is the molar absorptivity of the ferrioxalate actinometer at 510 nm (11,100 $Lmol^{-1}cm^{-1}$). With this data, the photon flux was calculated using eq. 2.

$$\text{Photon flux} = \frac{\text{mol } Fe^{2+}}{\Phi t f} \quad \text{(eq. 4)}$$

where Φ is the quantum yield for the ferrioxalate actinometer (1.01 at λ_{ex} = 437 nm), t is the irradiation time (120 s), and f is the fraction of light absorbed at λ_{ex} = 437 nm by the ferrioxalate actinometer. This value was calculated using eq. 3 where A (440 nm) is the absorbance of the ferrioxalate solution at 440 nm. An absorption spectrum gave an A (440 nm) value of > 3, indicating that the fraction of absorbed light (f) is > 0.999.

$$f = 1 - 10^{-A(440\,nm)} \quad \text{(eq. 5)}$$

The photon flux was thus calculated (as an average of three experiments) to be 8.24081 x 10^{-10} einsteins s^{-1}

Determination of the reaction quantum yield

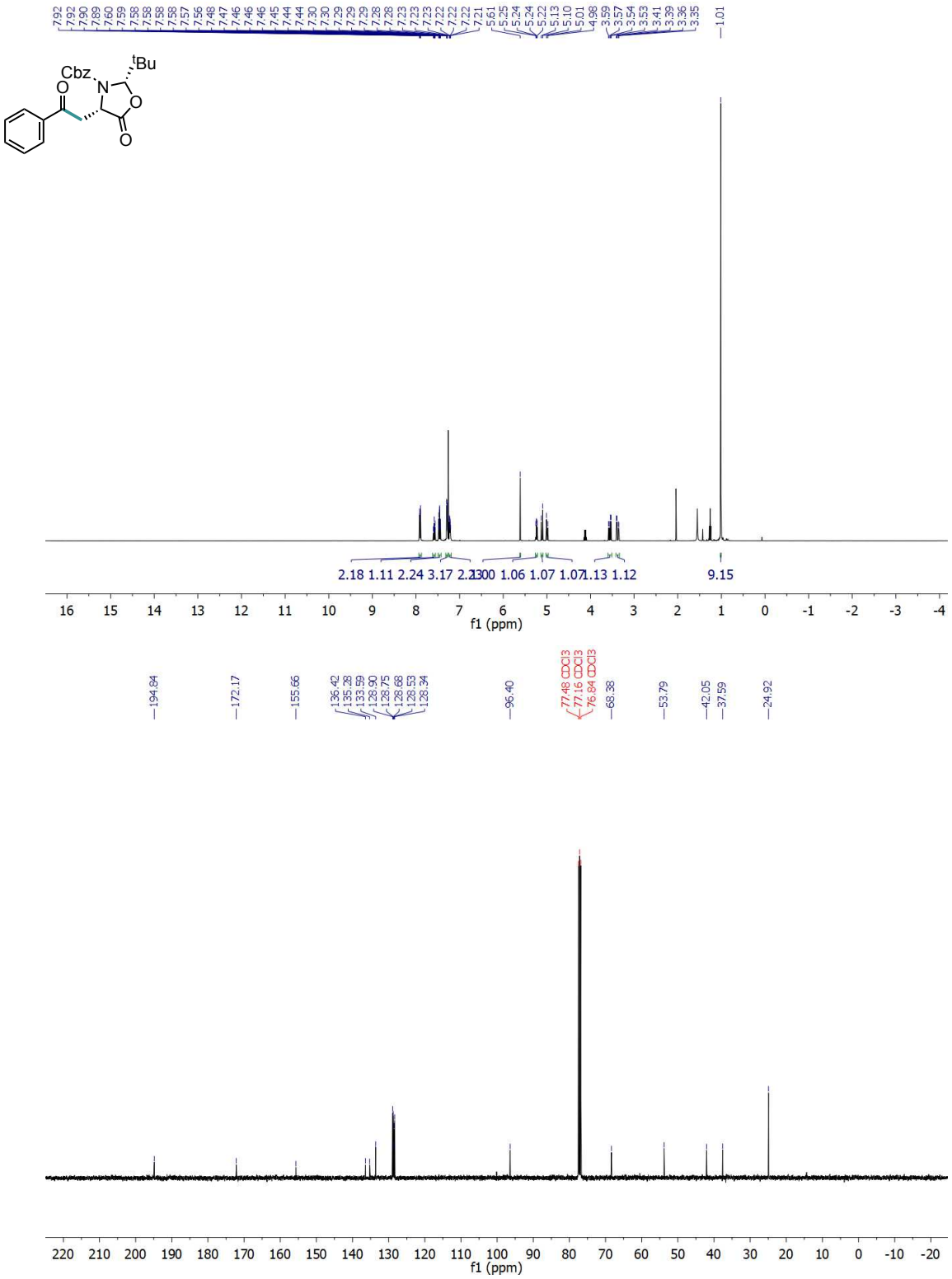
Using GP11: A reaction under the standard conditions using **1** (29 mg, 0.1 mmol, 1 equiv.) and benzoic acid (18.3 mg, 0.15 mmol, 1.5 equiv.) was irradiated at 440 nm for 3600 sec. Afterwards, the reaction was diluted with EtOAc (1 mL) and methyl laureate (25 µL, 0.1 mmol, 1.0 equiv.) was added as internal standard. An aliquot of the mixture was then analysed by GC-FID and the yield/conversion was calculated from the corresponding calibration curve. This afforded **2** in 40 % yield (4 x 10^{-5} mol). The reaction quantum yield (Φ) was determined using eq. 4, where the photon flux 8.24081 x 10^{-10} einsteins s^{-1} (determined by actinometry as described above), t is the reaction time (3600 s) and f is the fraction of incident light absorbed by the reaction mixture, determined using eq. 3. An absorption spectrum of the reaction mixture gave an absorbance value of 2.19444 at 437 nm, thus f was determined to be a value of 0.9936.

$$\Phi = \frac{\text{mol of product formed}}{\text{Photon flux}tf} \quad \text{(eq. 6)}$$

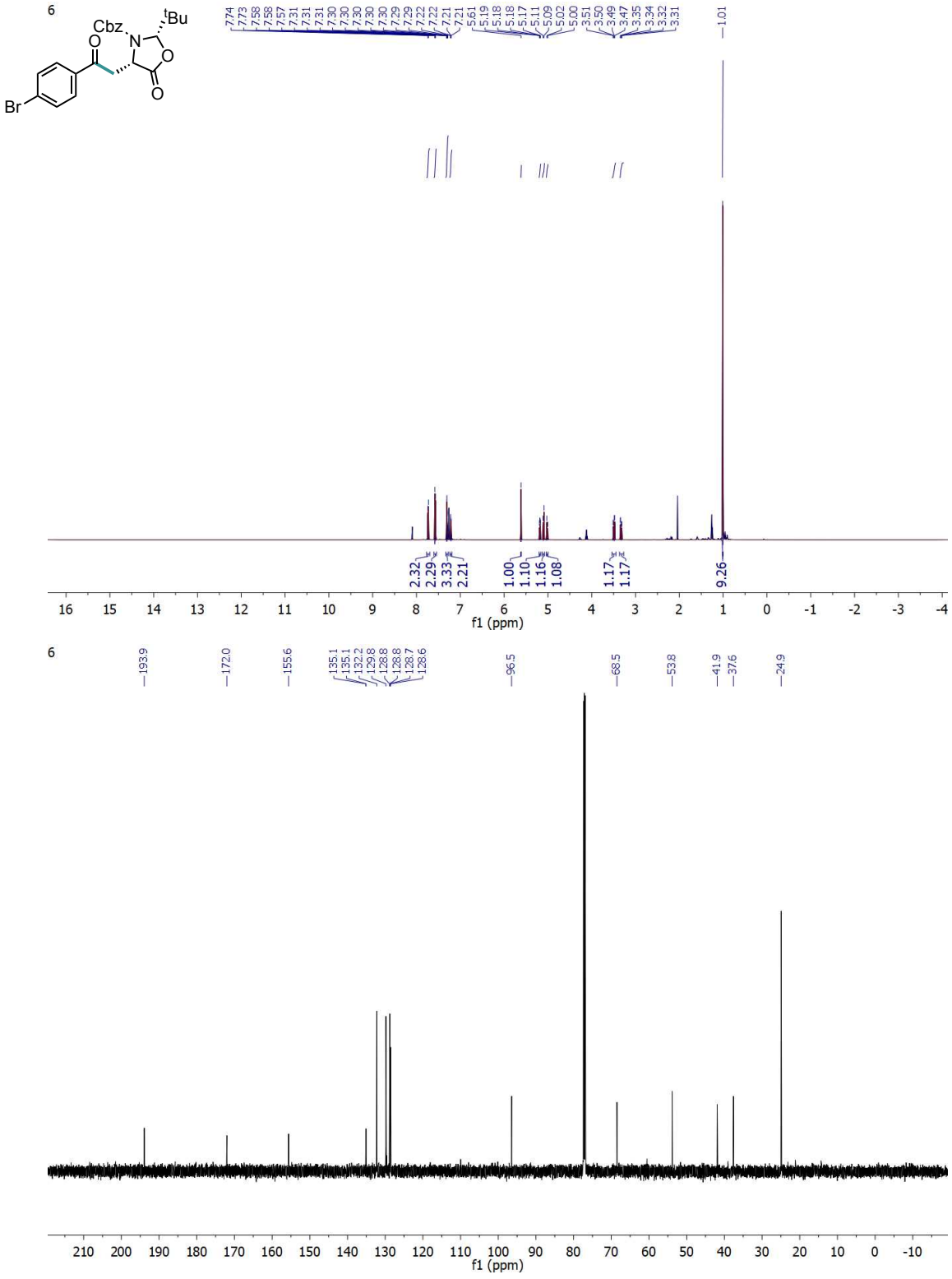
Hence, the reaction quantum yield (Φ) was thus determined to be 13.57.

6.7.5. ^{1}H and ^{13}C–NMR Spectra

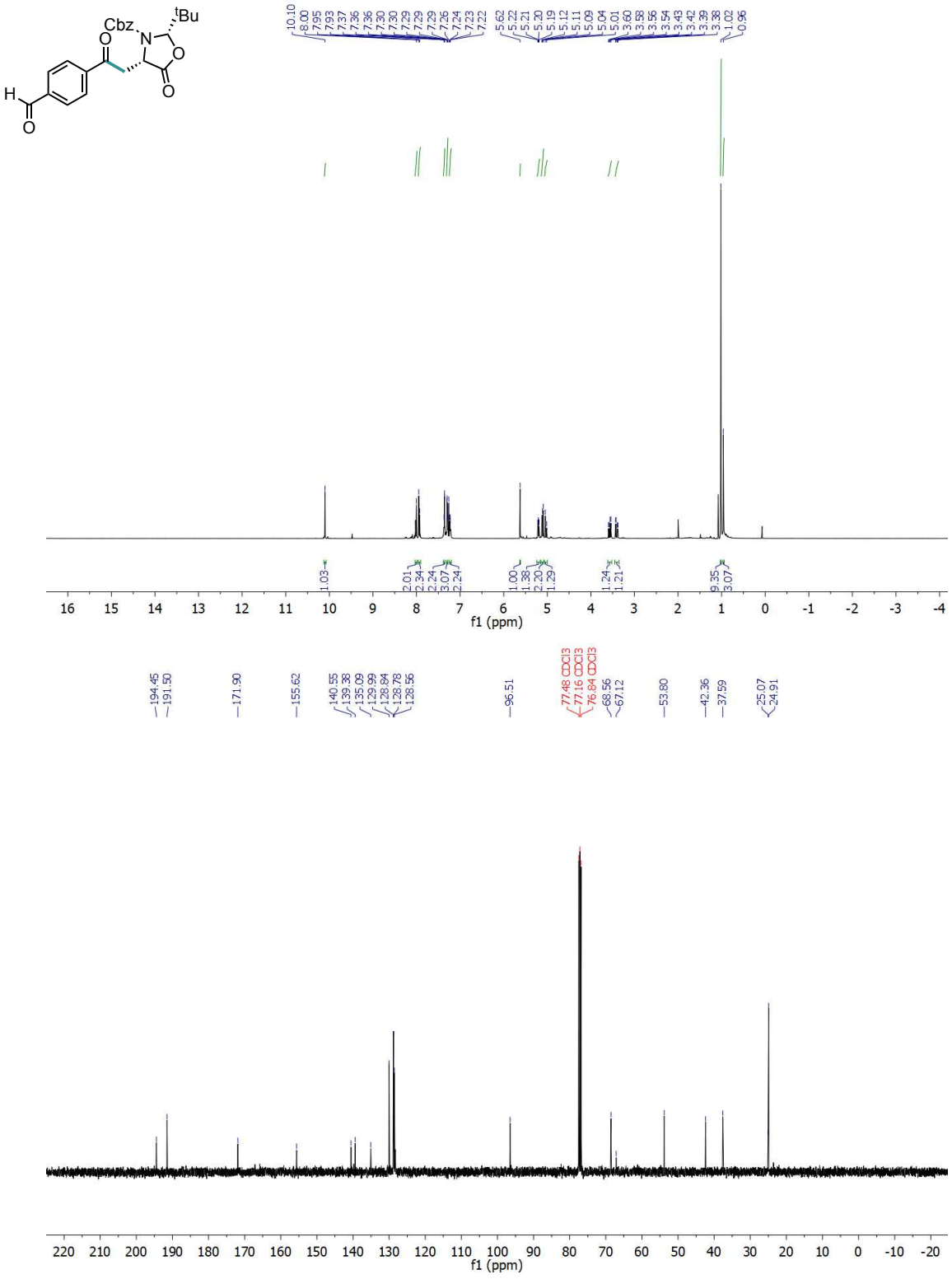
(2S,4S)-2-(tert-Butyl)-5-oxo-4-(2-oxo-2- phenylethyl)oxazolidine-3-carboxylate (102):



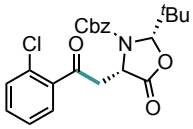
Benzyl (2S,4S)-4-(2-(4-bromophenyl)-2-oxoethyl)-2-(tert-butyl)- 5-oxooxazolidine-3-carboxylate (104):

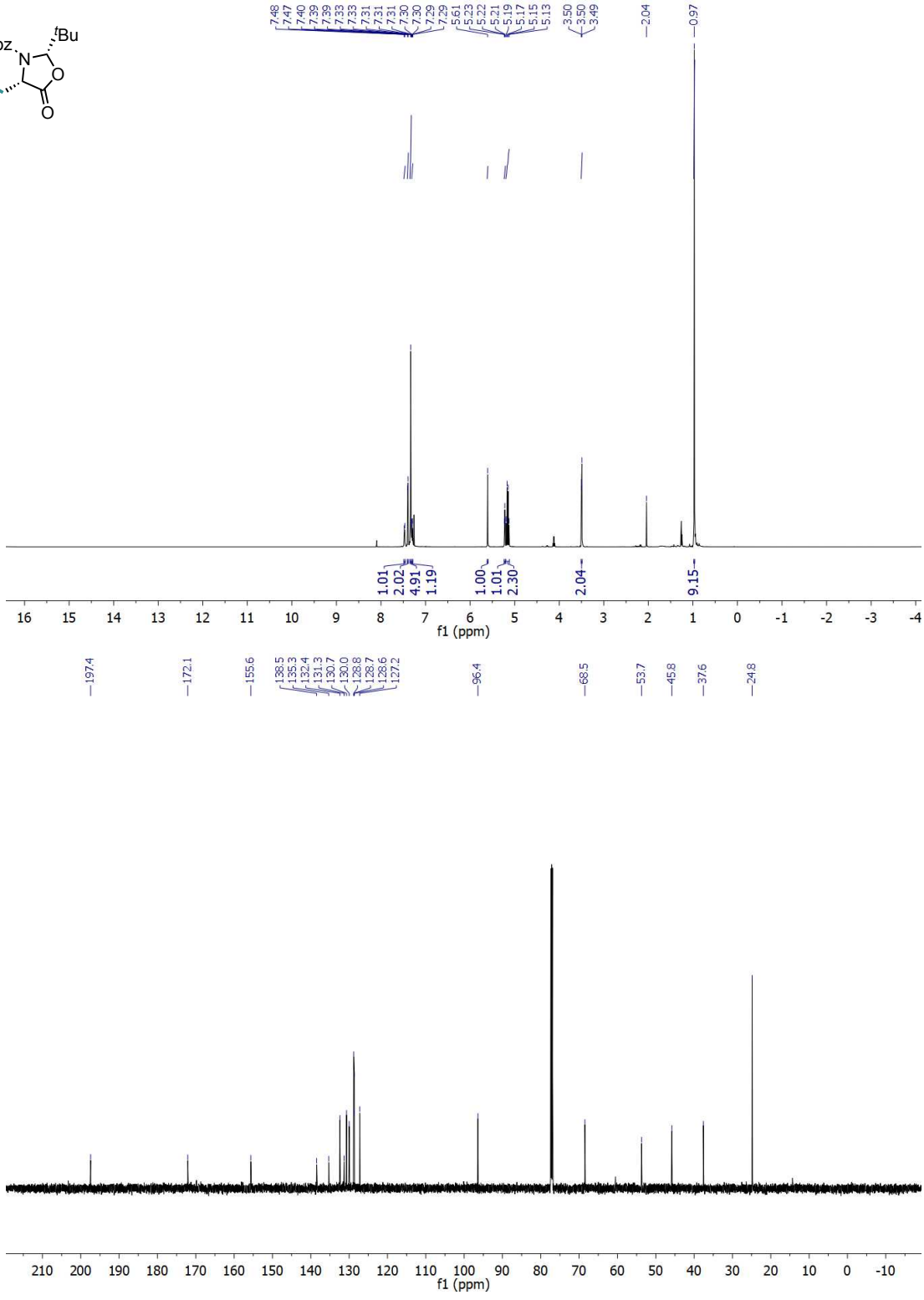


Benzyl (2S,4S)-2-(tert-butyl)-4-(2-(4-formylphenyl)-2-oxoethyl)- 5-oxooxazolidine-3-carboxylate (105):

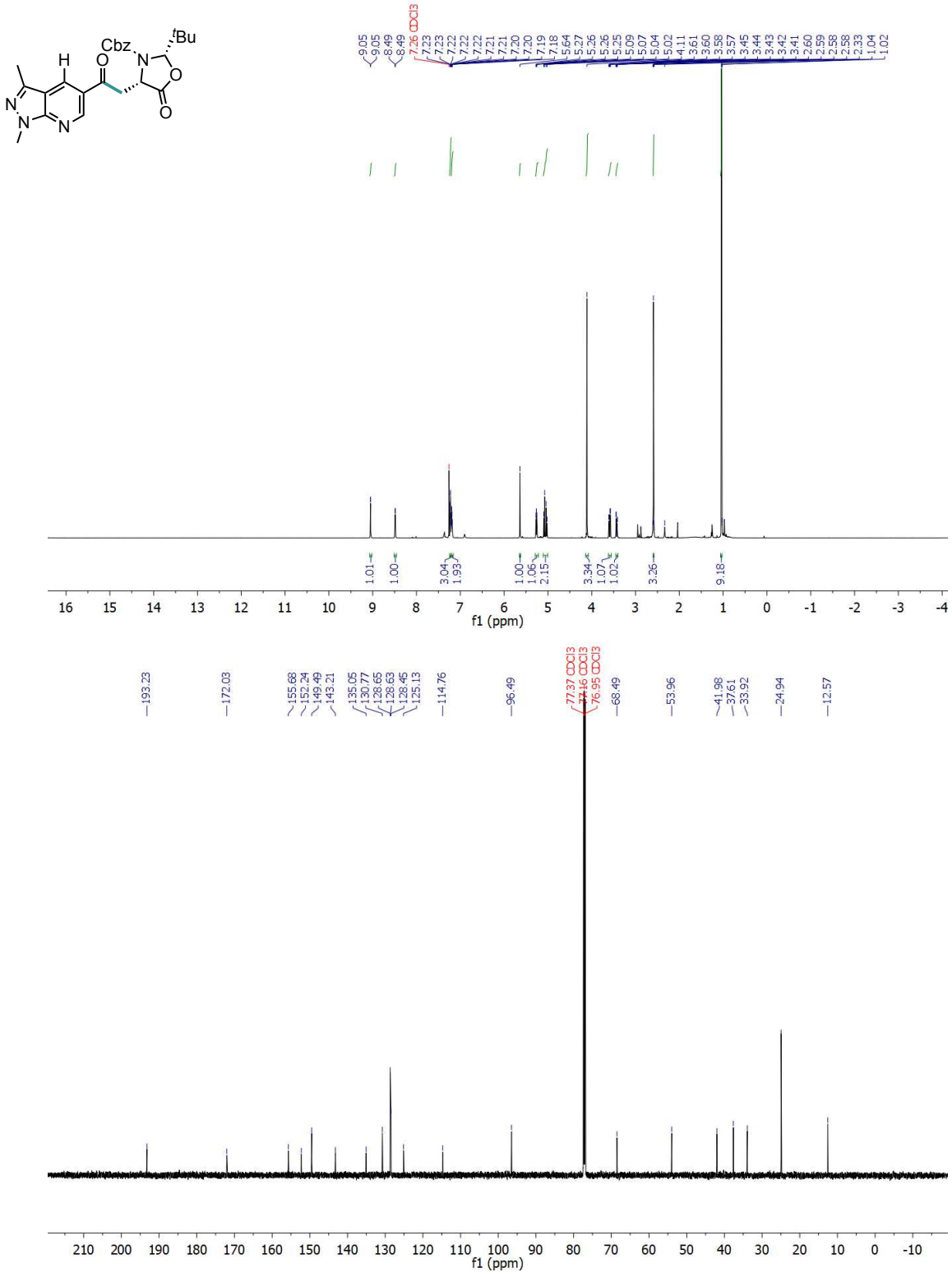


Benzyl (2S,4S)-2-(tert-butyl)-4-(2-(2-chlorophenyl)-2-oxoethyl)- 5-oxooxazolidine-3-carboxylate (106):

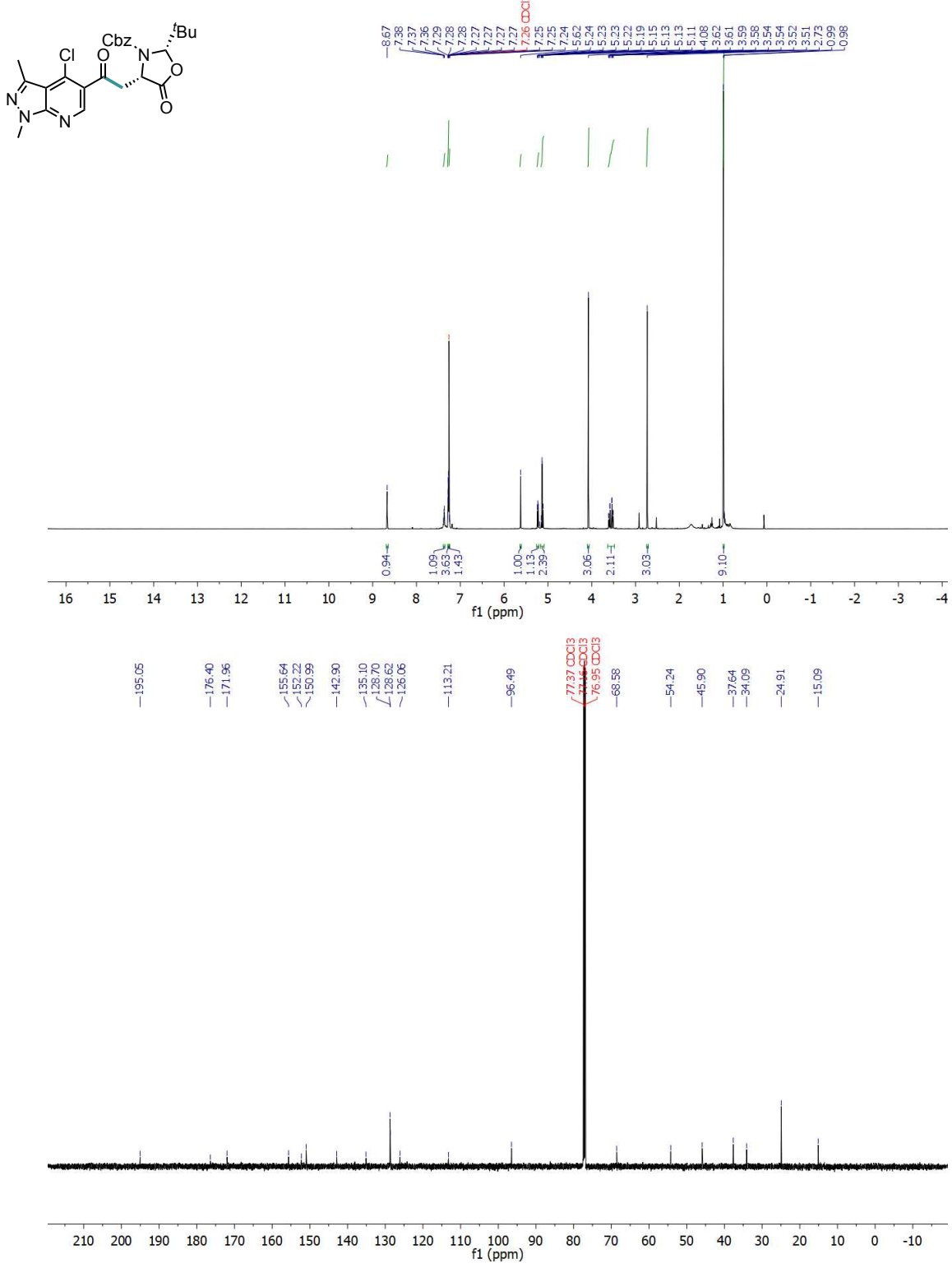




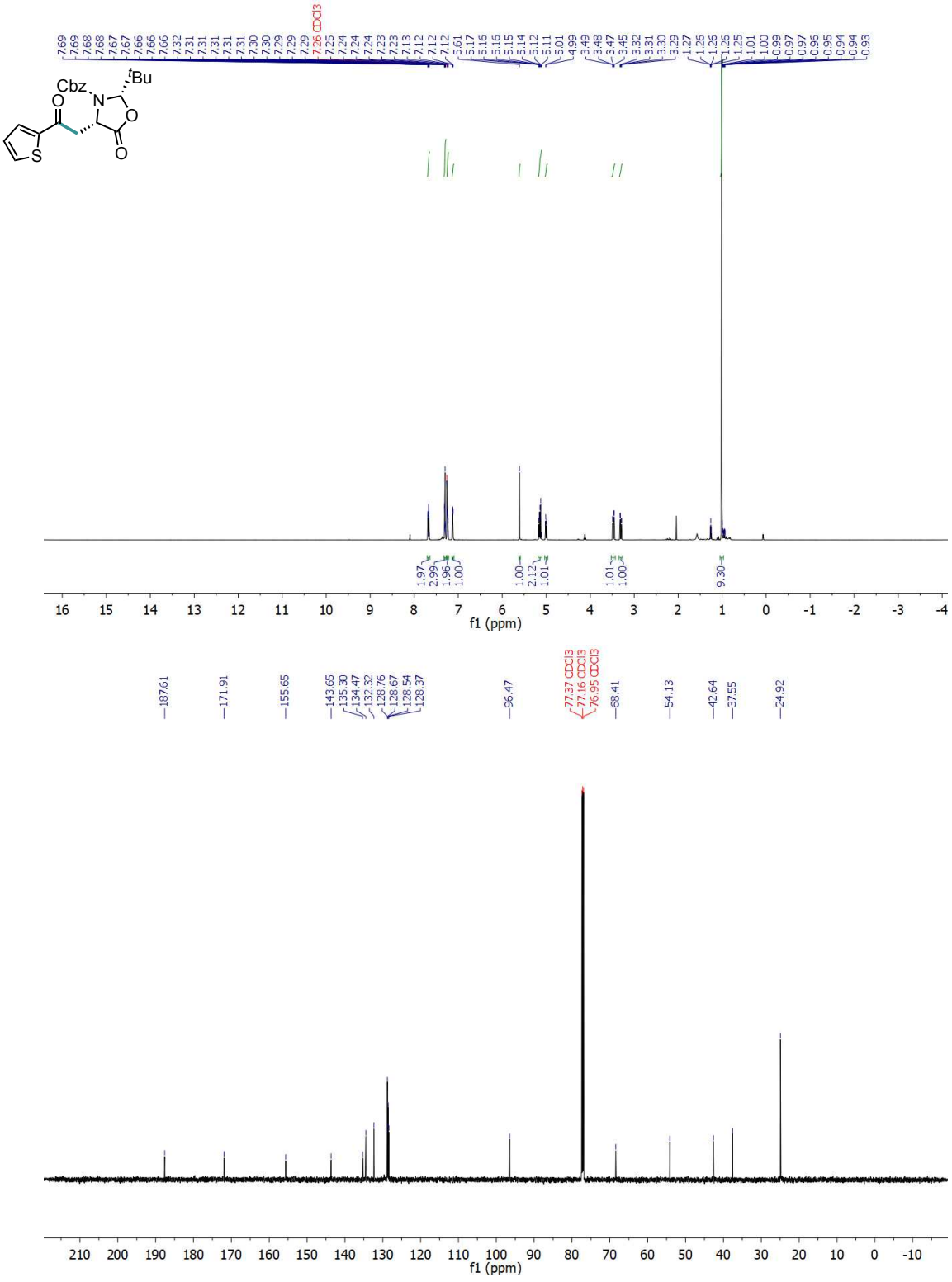
Benzyl (2S,4S)-2-(tert-butyl)-4-(2-(1,3-dimethyl-1H-pyrazolo[3,4- b]pyridin-5-yl)-2-oxoethyl)-5-oxooxazolidine-3-carboxylate (107):



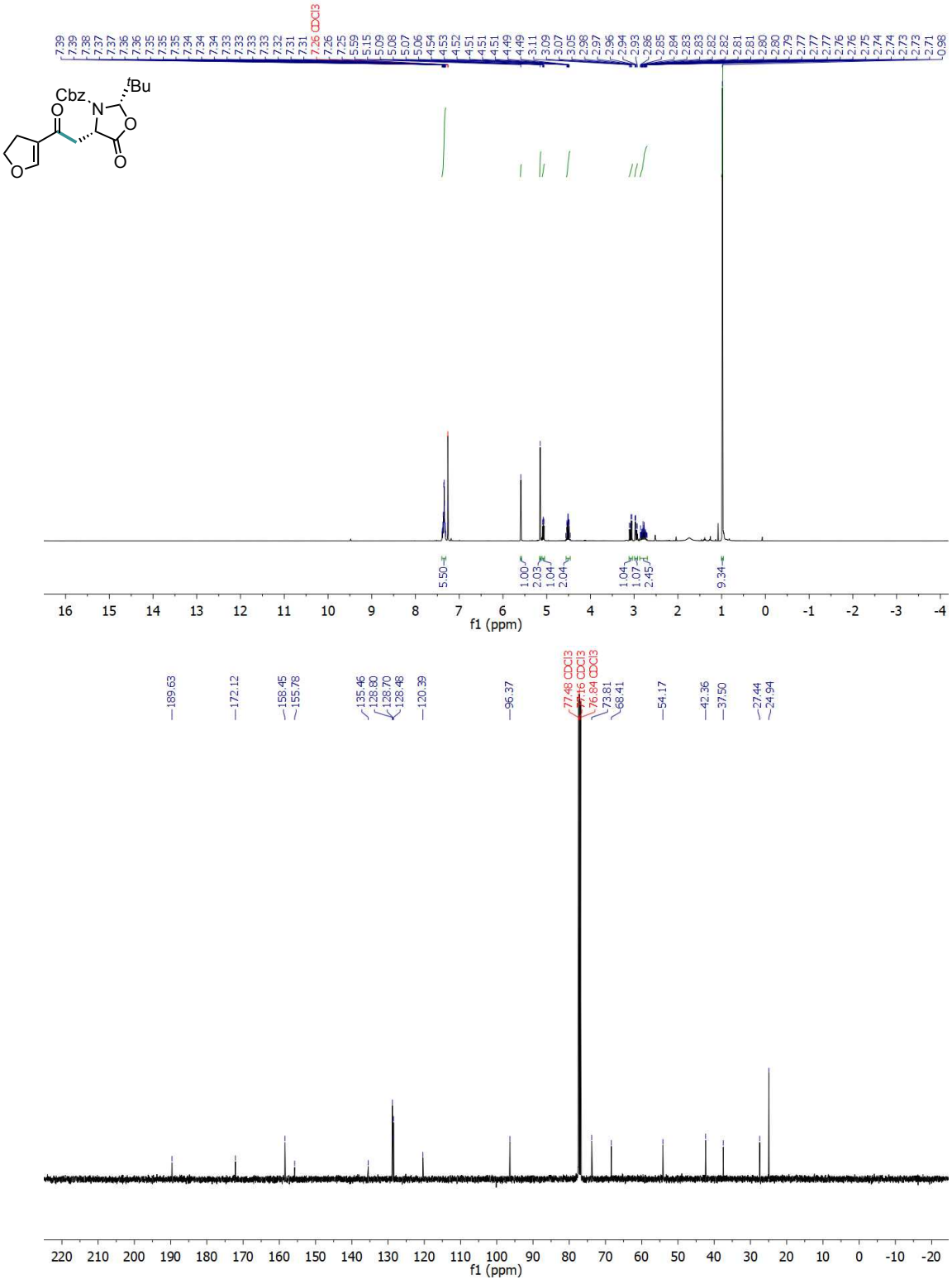
Benzyl (2S,4S)-2-(tert-butyl)-4-(2-(4-chloro-1,3-dimethyl-1H- pyrazolo[3,4-b]pyridin-5-yl)-2-oxoethyl)-5-oxooxazolidine-3-car- boxylate (107'):



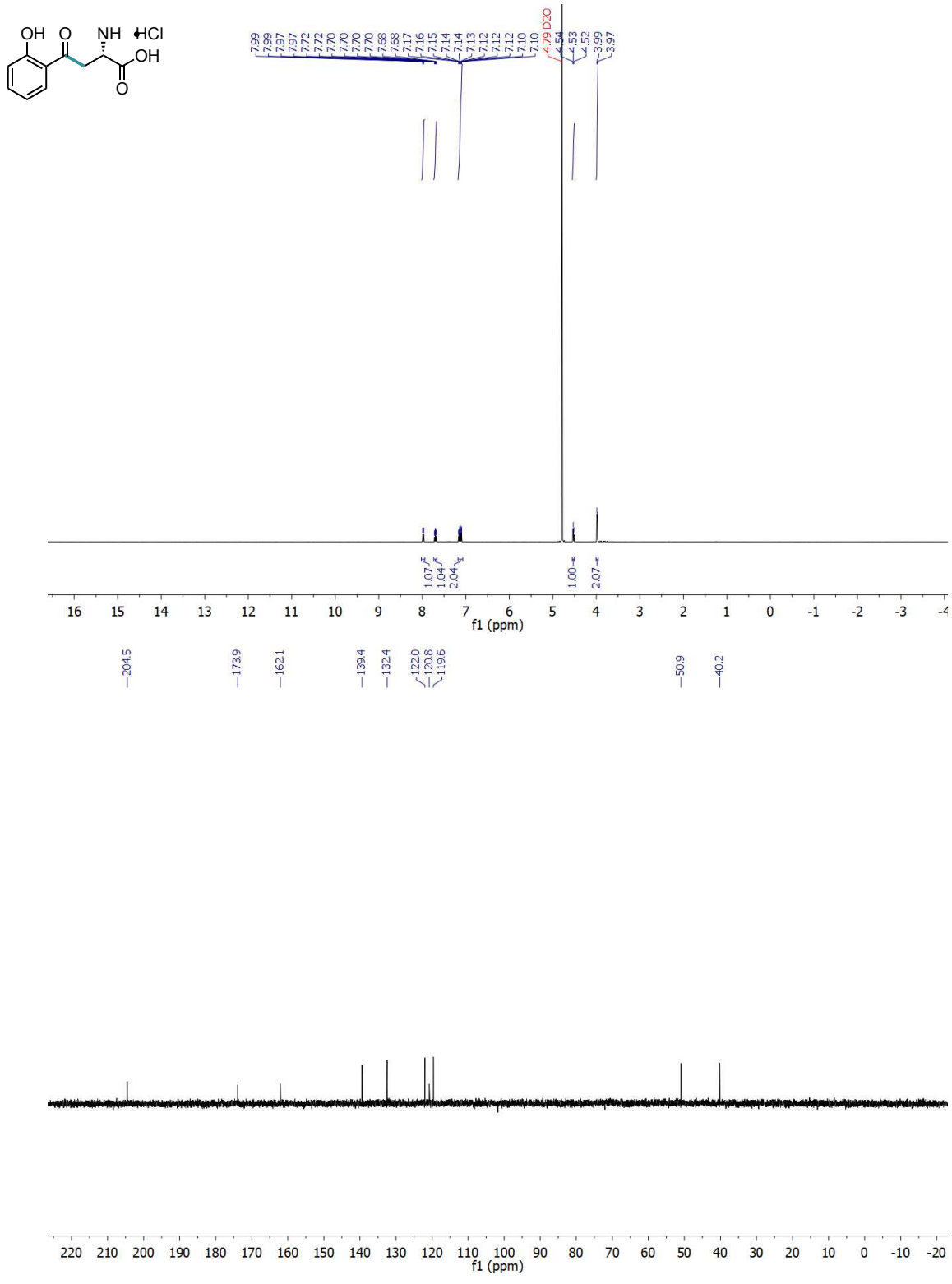
Benzyl (2S,4S)-2-(tert-butyl)-5-oxo-4-(2-oxo-2-(thiophen-2-yl)- ethyl)oxazolidine-3-carboxylate (108):



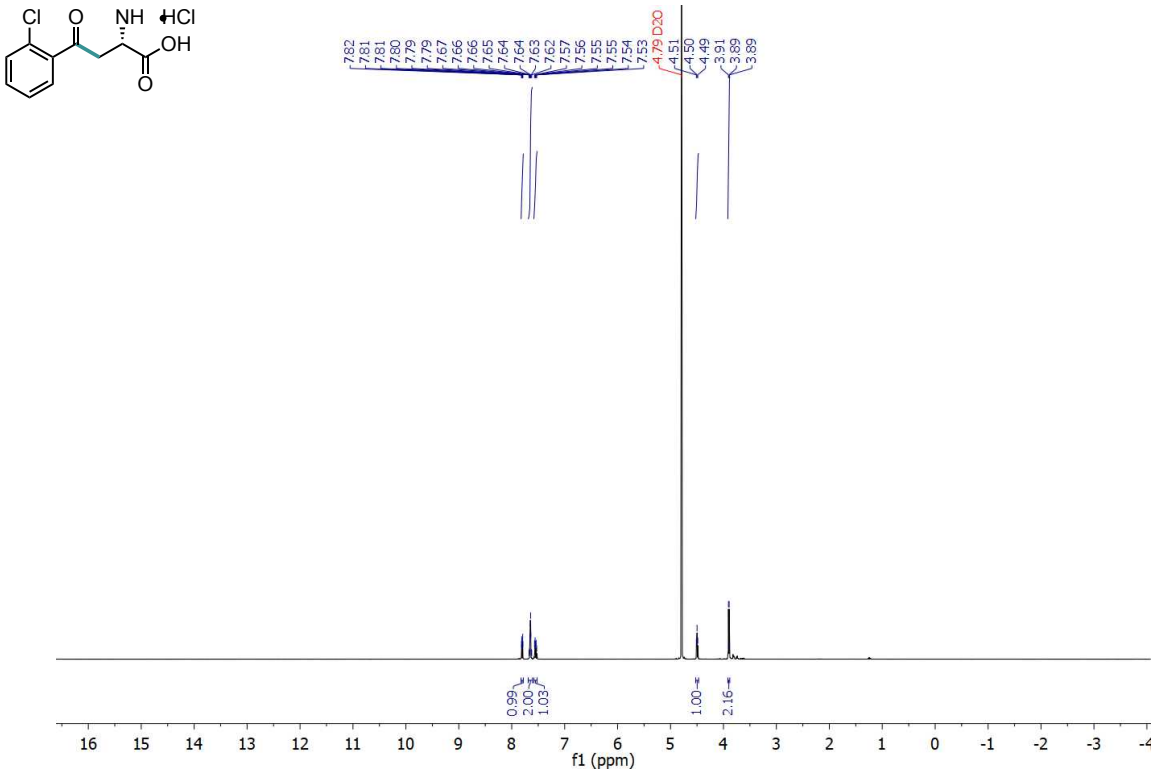
Benzyl 2-(tert-butyl)-4-(2-(4,5-dihydrofuran-3-yl)-2-oxoethyl)-5- oxooxazolidine-3-carboxylate (109):



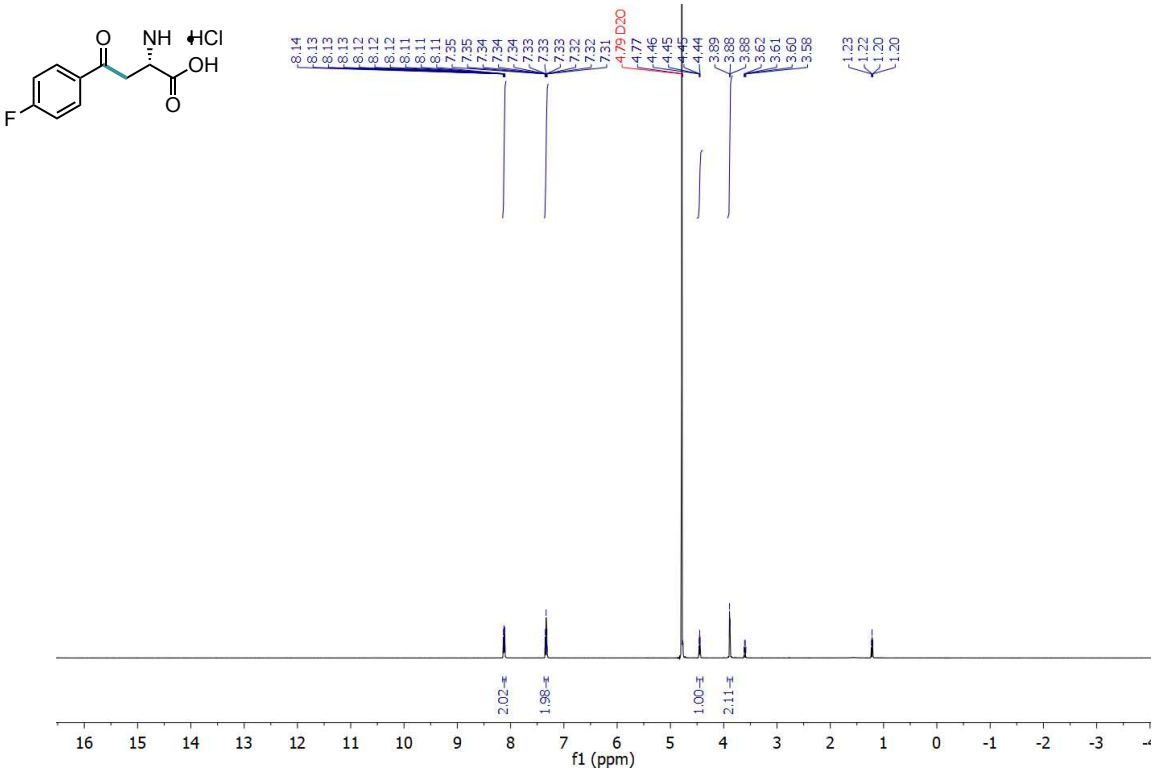
(S)-2-Amino-4-(2-hydroxyphenyl)-4-oxobutanoic acid hydrochloride salt (116):



(S)-2-Amino-4-(2-chlorophenyl)-4-oxobutanoic acid hydrochloride salt (117):



S)-2-Amino-4-oxo-4-(pyridin-3-yl)butanoic acid hydrochloridesalt (118):



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