ARENOPHILE-MEDIATED DEAROMATIVE FUNCTIONALIZATION OF UNACTIVATED ARENES

BY

WILLIAM CHARLES WERTJES

THESIS

Submitted in partial fulfillment of the requirements
for the degree of Master of Science in Chemistry
in the Graduate College of the
University of Illinois at Urbana-Champaign, 2020

Urbana, Illinois

Adviser:

Professor David Sarlah

Abstract:

Two photomediated dearomative methods are reported using an "arenophile" called MTAD. Arene-arenophile cycloadducts are formed by irradiation of mixtures of unactivated arenes and MTAD at cryogenic temperatures with visible light. These cycloadducts are subsequently used as substrates in metal-catalyzed transformations.

In chapter one a palladium-catalyzed dearomative *syn*- 1,4-diamination of unactivated arenes is presented using simple amine nucleophiles. An enantioselective variant and a number of elaborations of the resulting products are exhibited. In chapter two a concise two-step procedure to access oxepines from simple arenes is disclosed, enabled by a manganese(II)-catalyzed epoxidation of the arene-arenophile cycloadducts. Studies toward utilizing this method in concise syntheses of natural products perilloxin and fortimicin A are also reported.

Table of Contents:

Introduction:

Aromatic molecules belong to one of the most fundamental and abundant classes of organic compounds and are widely used across all areas of molecular sciences. Not surprisingly, the chemistry of these molecules is an exceptionally rich field and is distinctive due to their unique reactivity patterns and inherent stability. One area of particular interest for synthetic organic chemists is that of dearomatizations, transformations capable of disturbing the aromatic π-system and providing unsaturated, and often functionalized, products (Figure 1a). By utilizing arenes as starting materials, dearomative strategies offer rapid access to more complex, value-added, and synthetically versatile intermediates from readily available sources of hydrocarbons.[1] This direct, simplicity-to-complexity synthetic logic is becoming increasingly popular in the fields of natural product synthesis and small-molecule medicinal chemistry, where a high degree of functionality and structural diversity (sp^3-content) is often desired.[2] Consequently, the number of reports on the development and application of dearomatization processes has steadily increased in recent decades, and will likely continue to grow, especially with recent advances in transition metal catalysis,[3] asymmetric catalysis,[4] and biocatalysis.[5]

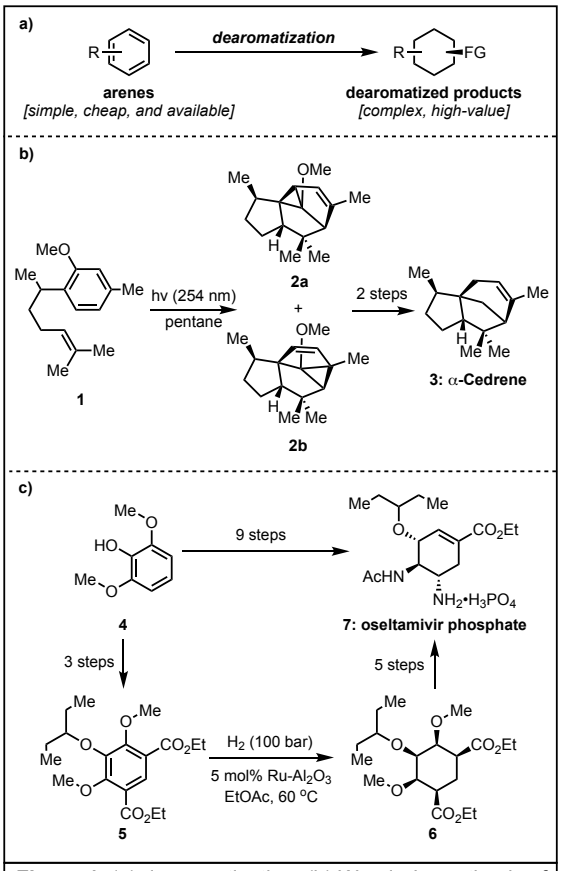


Figure 1: (a) dearomatization; (b) Wender's synthesis of α-Cedrene; (c) La Roche's dearomative synthesis of oseltamivir phosphate

Dearomative transformations have been used extensively for the synthesis of natural products and other biologically active compounds. For example, Wender's synthesis of α-Cedrene[6] and La Roche's synthesis of oseltamivir[7] are landmark examples in their use of dearomative transformations. The core of α-Cedrene is constructed efficiently by an alkene-arene meta-photocycloaddition of a simple arene starting material, and the synthesis can be completed in two more steps (Figure 1b). In addition, the cyclohexane core of oseltamivir (**7**, Tamiflu®) is formed

through Rh/Al_2O_3-catalyzed hydrogenation of an easily constructed pyrogallol derivative (Figure 1c). Other classes of dearomative transformations have been employed in natural product synthesis including reductions, oxidations, and transition-metal mediated additions.[1]

Chapter 1: Palladium-Catalyzed Dearomative *syn* 1,4-Diamination

Despite the recent growth of interest in dearomative transformations there is dearth of research on dearomative reactions that directly incorporate amines into the final products. A notable exception is a collection of transformations developed by Lautens using azabenzonorbornadiene substrates, which can be synthesized via dearomative cycloadditions between **8** and protected pyrroles.[8] These systems synthesize formally 1,2-aminofunctionalized dearomatized naphthalene products through transition-metal catalysis (Figure 2). The reactions yield exclusively 1,2-functionalized products and either exclusively *syn* (Figure 2a) or *anti* (Figure 2b) stereochemistry based upon the catalyst and nucleophile. The stereochemistry can be rationalized based upon two distinct mechanisms: ***(1)*** *exo*-face migratory insertion of a metal-carbon bond across the olefin of **9** followed by beta-elimination (carbon-based nucleophiles; Figure 2a), or ***(2)*** *exo*-face oxidative addition between **12** and a rhodium catalyst to generate **13**, followed by SN2' displacement with a heteroatom nucleophile (Figure 2b). There are a number of systems that employ this approach and a variety of types of products can be readily accessed, many of them with very high levels of enantioselectivity.[9] Although elegant, this approach has several limitations: ***(1)*** these reactions have not been used to synthesize the analogous 1,2-aminofunctionalized dearomatized mononuclear arenes, ***(2)*** other stereo- and constitutional isomers of these products can generally not be accessed using these systems, and ***(3)*** the starting materials (**9**/**12**) have to be synthesized from benzyne precursors such as **8**. Thus, due to the limitations of this work, additional methods for synthesizing amino-functionalized dearomatized products with a larger substrate scope and varying stereochemistry is desired. One focus of our research group is the development of new dearomative strategies that leads to a large diversity of highly functionalized small molecules containing amines. These

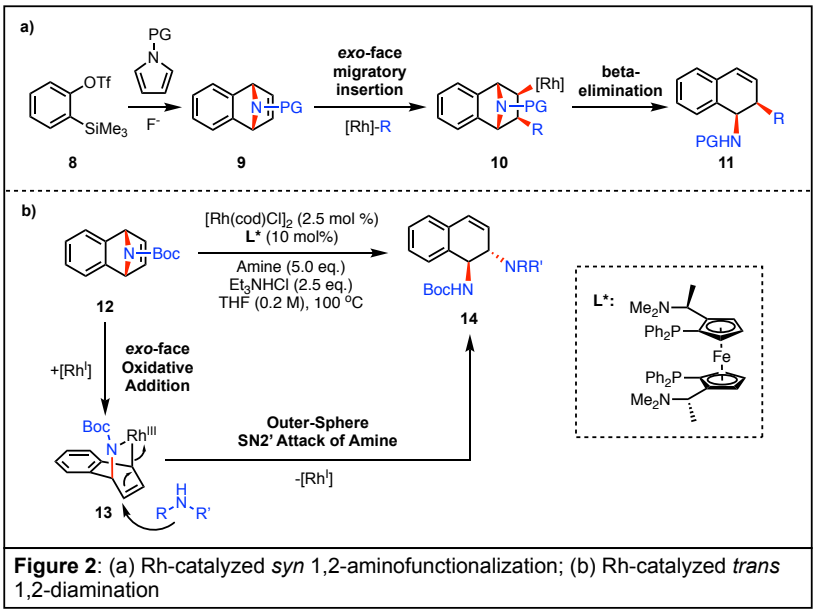


Figure 2: (a) Rh-catalyzed *syn* 1,2-aminofunctionalization; (b) Rh-catalyzed *trans* 1,2-diamination

amine-containing cyclohexyl derivatives represent common motifs used by medicinal chemists in developing lead compounds as well as the cores of natural products.[10-12]

In particular, over the past several years our research group has developed multiple strategies for incorporating amines in the dearomatization of non-activated arenes (Figure 3a). Our recent studies established that arenophile 4-methyl-1,2,4-triazoline-3,5-dione (MTAD, **15**) can perform a *para*-photocycloaddition on simple arenes such as naphthalene (**16**) and *in situ* OsO_4 catalyzed dihydroxylation[13] or diimide reduction[14] of the resulting cycloadducts (e.g. **17**), followed by urazole cleavage yielded a variety of previously inaccessible functionalized *syn*-1,4 diamines (**18**, **19**). Following these reports, we realized *in situ* transition-metal catalyzed allylic substitution reactions of the MTAD-arene cycloadducts with carbon nucleophiles to give formal *anti* 1,2-carboamination[15] (**20**) or *syn* 1,4-carboamination[16] of arenes (**21**) with nickel or palladium catalysts, respectively. Notably, the nickel-catalyzed *anti* 1,2-carboamination of benzene (**23**) to cyclohexadiene **24** was used by our group to achieve the asymmetric synthesis of natural products 7-deoxypancratistatin (**25**) and pancratistatin (**26**) on gram scale (Figure 3b).

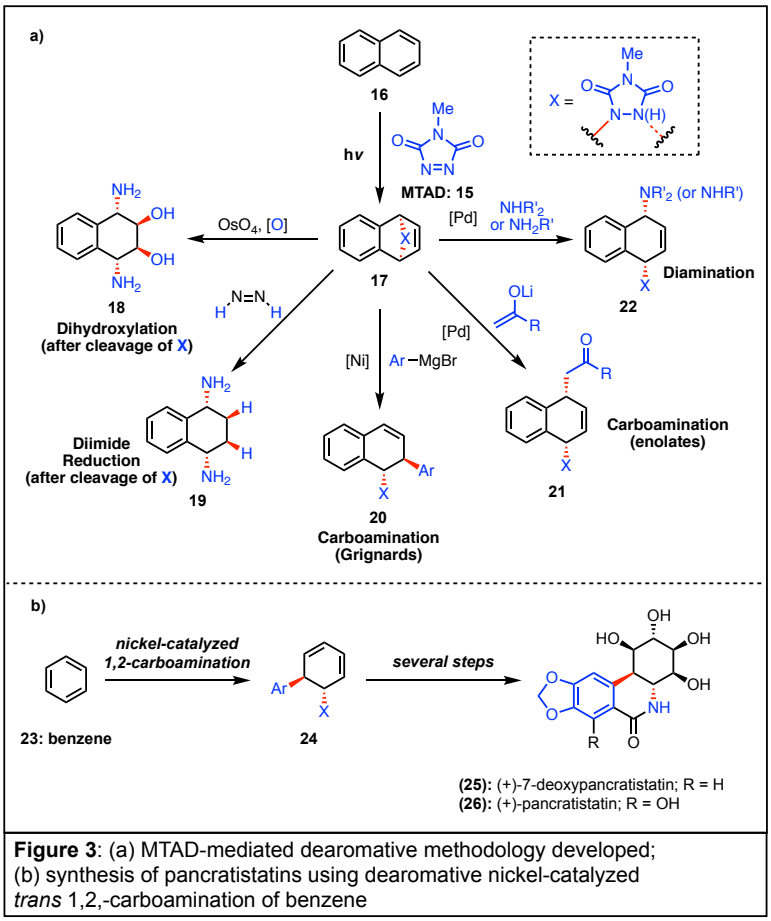
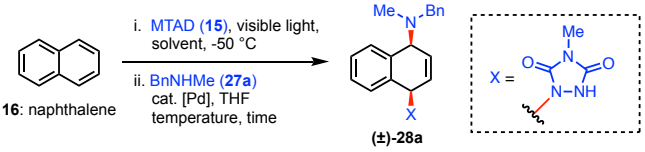


Figure 3: (a) MTAD-mediated dearomative methodology developed; (b) synthesis of pancratistatins using dearomative nickel-catalyzed *trans* 1,2,-carboamination of benzene

With these prior results in mind, we turned toward developing a method using amines as nucleophiles to accomplish palladium-catalyzed *syn* 1,4-diamination of simple arenes. The instability of the arene-arenophile cycloadducts (**17** begins rapidly cycloreverting above -10 °C) necessitates a highly reactive catalytic system. Accordingly, our preliminary investigations commenced by subjecting a solution of naphthalene (**16**) and MTAD (**15**) to visible-light until cycloaddition was completed, followed by addition of a solution of amine **27a** and Pd catalyst in THF. Thus, using CH_2Cl_2 as a solvent and complex from $Pd_2(dba)_3$ and PPh_3, product **28a** was obtained in 52% yield and as a single diastereo- and constitutional isomer (entry 1, Table 1). Importantly, this initial result demonstrated the feasibility of catalytic dearomative *syn* 1,4-diamination at the low temperatures required for this transformation. Next, we turned our attention toward the evaluation of reaction parameters. Probing the steric and electronic properties of monodentate phosphines P(*o*-$MeC_6H_4)_3$, P(*p*-$FC_6H_4)_3$, P(*p*-$MeOC_6H_4)_3$, PPh_2Cy, $PPhCy_2$ (entries 2-6), as well as bidentate dppf (entry 7), typically used in palladium-catalyzed allylic substitution reactions, did not increase the yield of the desired product. Use of alternative Pd sources (entries 8-12) revealed that $Pd(PPh_3)_4$ gave a slight increase in yield and indicated that a Pd^0 species was most likely required for the reaction to progress. However, in all cases significant amounts of MTAD-naphthalene cycloadduct were observed after analyzing crude reaction mixtures. Therefore, increasing the temperature of the ring-opening step to –20° C and longer reaction times proved highly beneficial for product formation (entries 13–15), and with EtOAc as a solvent provided the highest yield of the product (72%, entry 15).



entry	[Pd] source	ligand	solvent	temp (°C)	time (h)	yield (%)
1	$Pd_2(dba)_3$	PPh_3	CH_2Cl_2		5	52
2	$Pd_2(dba)_3$	P(*p*-$MeOC_6H_4)_3$	CH_2Cl_2		5	44
3	$Pd_2(dba)_3$	P(*p*-$FC_6H_4)_3$	CH_2Cl_2		5	10
4	$Pd_2(dba)_3$	P(*o*-$MeC_6H_4)_3$	CH_2Cl_2	-50 to 0	5	<5
5	$Pd_2(dba)_3$	PPh_2Cy	CH_2Cl_2		5	48
6	$Pd_2(dba)_3$	$PPhCy_2$	CH_2Cl_2		5	22
7	$Pd_2(dba)_3$	dppf	CH_2Cl_2		5	36
8	$Pd(dba)_2$	PPh_3	CH_2Cl_2		5	55
9	$[Pd(allyl)Cl]_2$	PPh_3	CH_2Cl_2		5	51
10	$Pd(MeCN)_2Cl_2$	PPh_3	CH_2Cl_2	-50 to 0	5	<5
11	$Pd(OAc)_2$	PPh_3	CH_2Cl_2		5	<5
12	$Pd(PPh_3)_4$	—	CH_2Cl_2		5	57
13	$Pd(PPh_3)_4$	—	CH_2Cl_2		20	70
14	$Pd(PPh_3)_4$	—	EtCN	-20	20	70
15	$Pd(PPh_3)_4$	—	EtOAc		20	72 (62)

Table 1: Optimization of palladium-catalyzed *syn* 1,4-diamination starting from naphthalene (**16**)

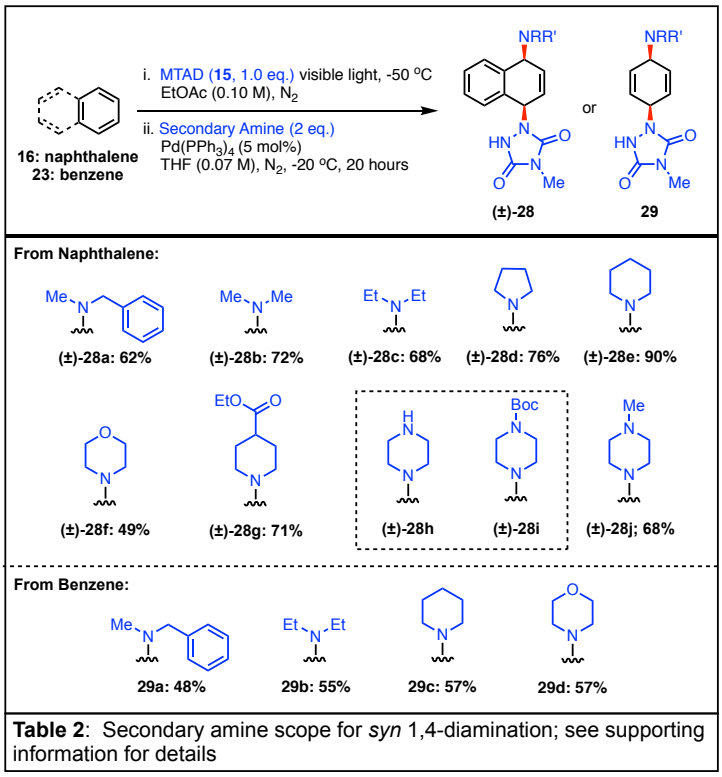


Table 2: Secondary amine scope for *syn* 1,4-diamination; see supporting information for details

With optimized conditions in hand (Table 1, entry 15), we examined the amine scope for this protocol using naphthalene (**16**) and benzene (**23**, Table 2). Thus, besides methylbenzylamine (**27a**), other acyclic secondary amines proved to be compatible with naphthalene (**16**), as exemplified with dimethylamine and diethylamine, which gave products with similar yields (**28b** and **28c**). Moreover, cyclic secondary amines, such as pyrrolidine, piperidine, and morpholine, proved to be good substrates for this transformation (**28d**–**28f**). It should be noted that products **28d**, **28e**, and **28f** were remarkably unstable and had to be purified and characterized within hours of warming the reaction to room temperature. Piperazine derived amines (**28h**–**28j**) were competent nucleophiles. However, piperazine (**28h**) produced varying amounts of C–N bond formation at both nitrogen atoms (Table 2, inset). Moreover, while 1-Boc-piperazine (**28i**) proceeded to incomplete conversion of the cycloadduct, the analogous reaction with 1-Me-piperazine (**28j**), proceeded to full conversion as determined by NMR analysis of the crude reaction mixture. In addition to naphthalene (**16**), benzene (**23**) also showed the desired reactivity, delivering products **29a**–**29d** with a representative set of linear (**29a** and **29b**) and cyclic (**29c** and **29d**) secondary amines.

Next, we explored the dearomative diamination process with primary amines as substrates. Unfortunately, with catalyst $Pd(PPh_3)_4$ significant erosion in yields were observed. Gratifyingly, after performing an additional screen, we found that utilizing the same protocol, except changing the catalyst to [$Pd_2(dba)_3$/dppf] (2.5/6.0 mol%), resulted in a more efficient process with these substrates. Thus, a range of aliphatic amines, such as linear *n*propyl-, *n*penty-, and benzylamine (**28k**–**28m**), or branched *i*propyl-, cyclohexyl-, and *t*butylamine (**28n**–**28p**), all gave products

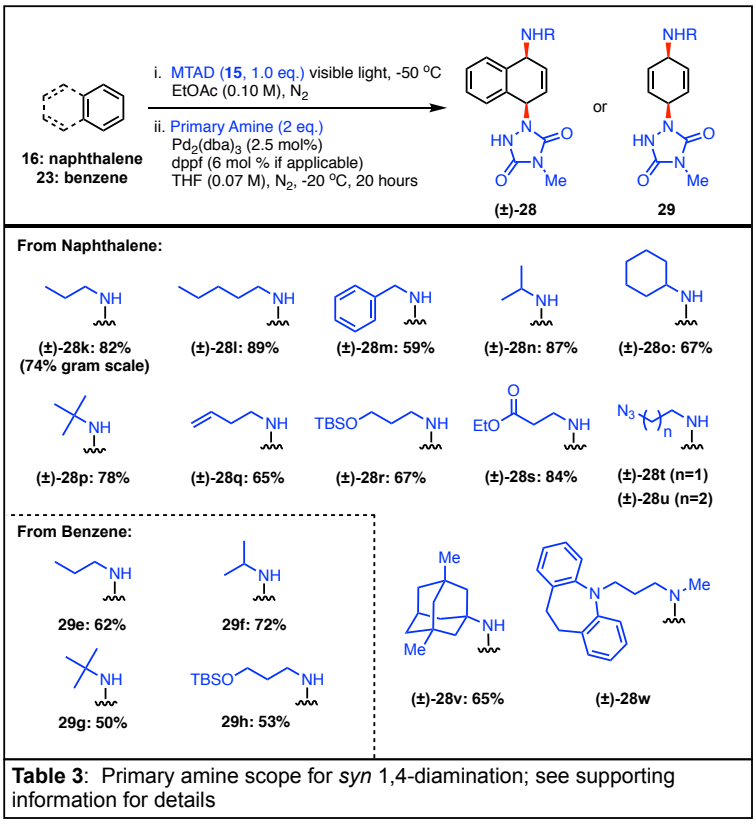
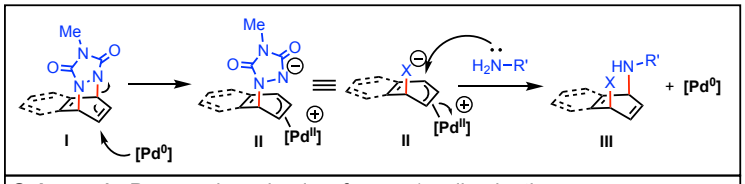


Table 3: Primary amine scope for *syn* 1,4-diamination; see supporting information for details

with naphthalene (**16**) in good yields. Importantly, this dearomative difunctionalization is mild enough to tolerate a variety of functionality as exemplified with products derived from amines incorporating alkene (**28q**), silyl-protected alcohol (**28r**), and ester groups (**28g** and **28s**). The ester of beta alanine (**28s**) illustrates the tolerance for certain additives in the reaction, as it was formed *in situ* from the corresponding HCl salt via addition of NEt_3 to the reaction mixture. Amines containing a free alcohol or cyano group were not well tolerated in this transformation, and proceeded to the desired products with only trace yield. Furthermore, azide-containing amines produced desired products **28t** or **28u** in significant amounts as identified by NMR analysis of the crude reaction mixtures. However, these products were too unstable to be cleanly isolated and decomposed both thermally and on SiO_2 gel. Notably, anilines were not competent nucleophiles in this reaction, and efforts to screen reaction parameters to support anilines including changes to the temperature, solvent, or catalyst were unsuccessful. Although we lack definitive proof for this, anilines' non-reactivity can be attributed to their decreased nucleophilicity.

For dearomative aminofunctionalization to be a practical way to access our desired compounds, we need to be able to synthesize appreciable amounts of them. We tested the scalability of this transformation by conducting the above-described reaction of naphthalene with *n*propylamine on gram scale. Accordingly, we obtained **28k** in 74% yield on a 10 mmol scale, showcasing the practicability of this process. Finally, benzene (**23**) also reacted successfully with primary amines, albeit with slightly lower yields of products **29e**–**29h** compared to naphthalene. Importantly, throughout these experiments we have always observed disubstituted products

formed as single diastereo- and constitutional isomers (see Supporting Information for representative X-ray structures of **28a**, **29d**, **28k**, and **29f**).



Scheme 1: Proposed mechanism for *syn* 1,4-diamination

Prior studies on allylic substitution[16] indicate that this transformation most likely proceeds through the following double inversion, net retention mechanism (Scheme 1): ***(1)*** oxidative addition of a Pd^0 species into the MTAD-arene cycloadduct (**I**) to form a cationic π-allyl Pd^{II} complex (**II**), followed by ***(2)*** outer sphere substitution of the Pd^{II} metal center in **II** to reform the Pd^0 catalyst and the desired product **(III)**. Preliminary low temperature NMR studies using stoichiometric palladium species in combination with the MTAD-naphthalene cycloadduct (**17**) indicate a possible π-allyl intermediate. Additionally, a compound with the exact mass of cationic palladium species **II** was identified by high resolution mass spectroscopy by premixing $Pd(PPh_3)_4$ with the naphthalene cycloadduct at -78 °C with or without the amine nucleophile.

We next investigated the scope of arenes using *n*$PrNH_2$ as the amine source (Table 3). While benzene worked well, substituted derivatives unfortunately proved not to be good substrates for this reaction and proceeded to the desired products in very low yields. This can be attributed to at least four possible factors, assuming a mechanism discussed above: an inability of the palladium catalyst to form a π-allyl intermediate of type **II**, the amine nucleophile not displacing the palladium catalyst in **II**, off-cycle intermediates that lead to catalyst death (i.e. coordination of amines to palladium), or the degradation of the desired product prior to analysis or isolation. Low temperature NMR studies using stoichiometric palladium are required to rule out one or more of these explanations.

In contrast to mononuclear arenes, polynuclear arenes delivered desired products **30**–**37**, albeit mixtures of constitutional isomers were obtained in case of **31**–**34**, resulting from the lack of regioselectivity of the formation of the Pd π-allyl intermediate from the non-symmetrical arene-arenophile cycloadducts. Moreover, polynuclear heteroarenes were amenable to dearomative *syn* 1,4-aminofunctionalization, providing products **34**–**37**. Compared to naphthalene-derived

products, most of these compounds were obtained with noticeably higher selectivities. A number of other polynuclear arenes, many of them heteroarenes, proceeded to the desired products as determined by NMR analysis of the crude reaction mixtures, but the presumed products underwent significant decomposition and could not be isolated or characterized. In addition, a variety of polyarenes with varying substituents did not form significant amounts of the desired products. Regardless of the yield or conversion, dearomative cycloaddition with polynuclear arenes always proceeded in a highly site-selective manner, and functionalization was observed only at the terminal, non-substituted ring.

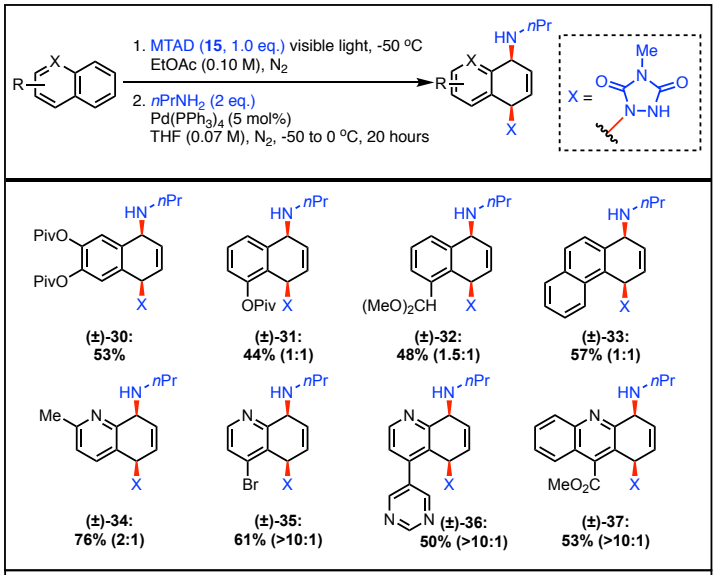


Table 4: Scope of dearomative *syn* 1,4-diamination of polyarenes with *n*PrNH$_2$; see supporting information for details

While the developed process can produce the desired products in very good yields and with exquisite selectivity, we also wanted to provide an enantioselective variant of this transformation, in cases where arene-arenophile cycloadducts are amenable to desymmetrization (Table 5). Thus, in a brief screen of chiral ligands, we found that high enantioselectivities could be achieved with [$Pd_2(dba)_3$] and (S,S_p)-*t*Bu-Phosferrox (**L1**, 2.5/6.0 mol%), which also was used for the previously reported asymmetric variant of the palladium-catalyzed *syn*-1,4 carboamination (significantly lower enantioselectivities were observed with Phosferrox ligands with different substituents on the oxazoline ring). Accordingly, a variety of amine-naphthalene

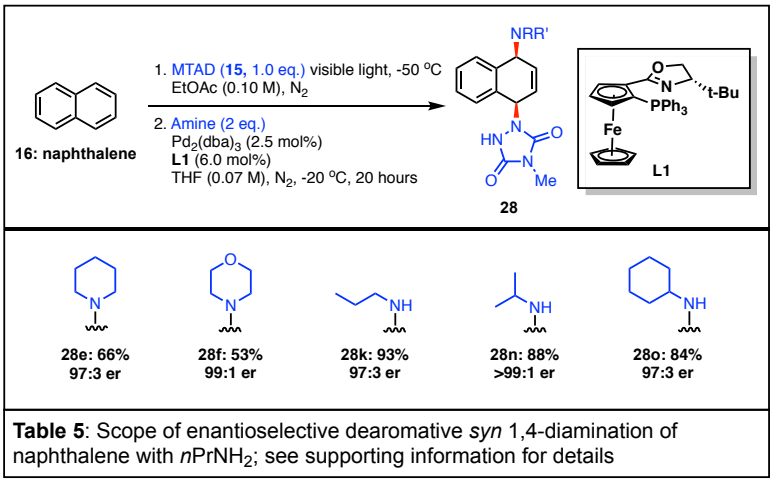
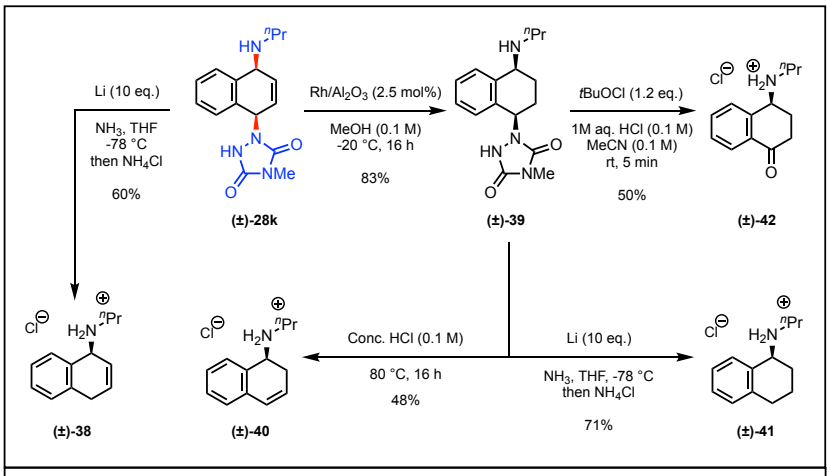


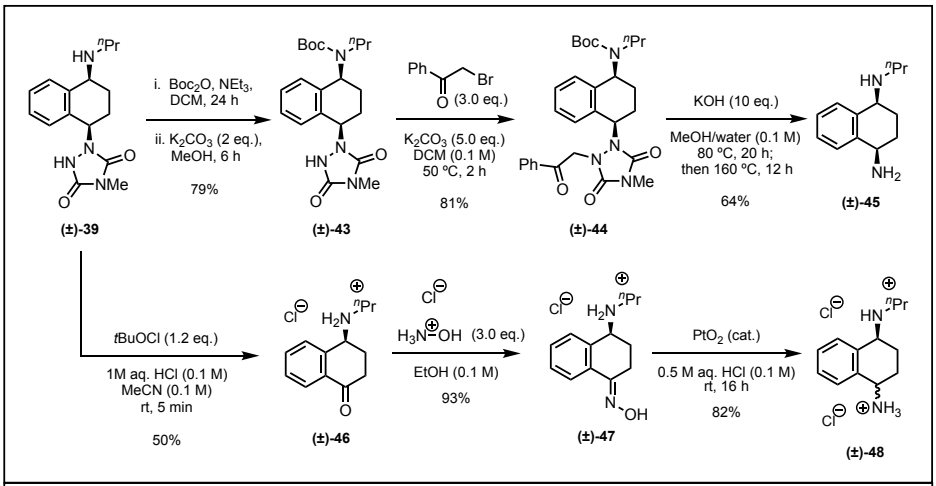
Table 5: Scope of enantioselective dearomative *syn* 1,4-diamination of naphthalene with *n*PrNH$_2$; see supporting information for details

adducts was obtained from secondary (**28e** and **28f**) and primary amines (**28k**, **28n**, and **28o**) with selectivities ranging from 97:3 to >99:1 er.

The dearomative transformation described above allows for rapid molecular elaboration, as well as incorporation and modification of amine-containing drugs. For example, representative product **(±)-28k** contains several handles for further functionalization (Scheme 2). Accordingly, unsaturated amine **(±)-38** could be synthesized through single electron reduction with Li/NH_3 of the urazole moiety in **(±)-28k** to achieve a formal 1,4-hydroaminated product in good yield. In addition, amine **(±)-39** was synthesized by first Rh/Al_2O_3-catalyzed hydrogenation of the double bond in **(±)-28k** followed by elimination of the urazole with concentrated HCl to yield the formally 1,2- hydroaminated product **(±)-40**. The styrenyl olefin in **(±)-40** represents a powerful functional group handle for further elaboration. Similar single electron conditions as described above reduced **(±)-39** to **(±)-41**. Alternatively, aminoketone **(±)-42** could be isolated as the HCl salt after oxidation of the urazole in **(±)-39** with *t*BuOCl. A differentially substituted diamine **(±)-45** was obtained from **(±)-39** in several steps using chemistry developed by developed by Adam *et al* (Scheme 3).[17] This involved selective boc-protection of the amine to **(±)-43**, followed the appending of α-bromo acetophenone to **(±)-44**. Treatment with KOH under elevated temperatures led to **(±)-45** in 64% yield. Moreover, a single diastereomer of diamine **(±)-48** could also be synthesized from aminoketone **(±)-46** through condensation with hydroxylamine to oxime **(±)-47** and ensuing PtO_2-catalyzed hydrogenation. However, the diastereoselectivity of the resulting di-HCl salt **(±)-48** was unable to be determined by 2D NMR spectroscopy and crystals for X-ray crystallographic analysis were not obtained. Nevertheless, a similar approach could potentially be used in the future to synthesize a range of stereochemically-defined 1,4-diamines.

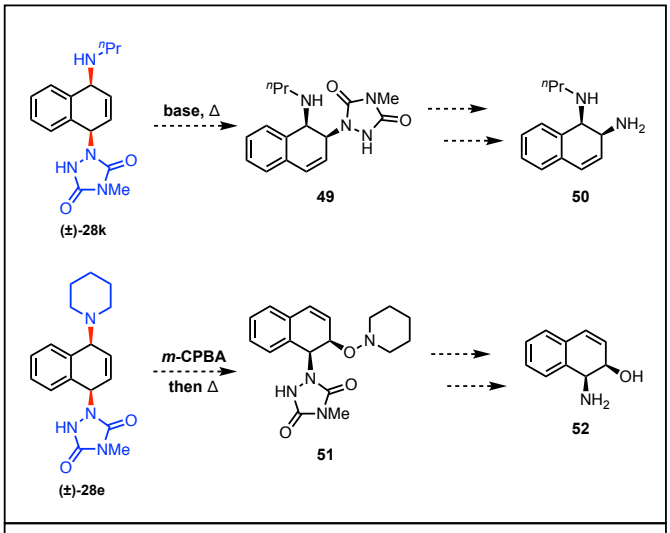


Scheme 2: Derivatizations of **(±)-28k**; see supporting information for details

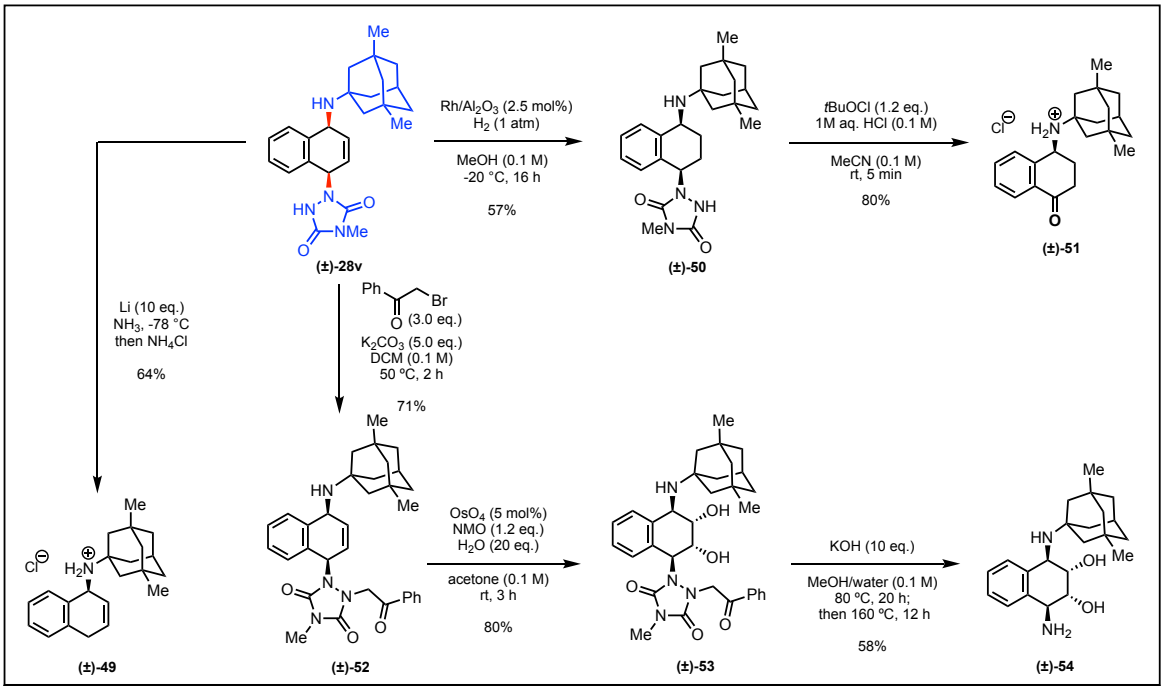


Scheme 3: Derivatizations of **(±)-28k** to diamines; see supporting information for details

Further attempts to elaborate either the previously described products were unsuccessful, including efforts to use either the allylic urazole or amine motifs in sigmatropic rearrangements (Scheme 4). There is precedent for a 2,3-sigmatropic rearrangements of allylic urazoles to the thermodynamically more stable product.[18] However, subjecting **(±)-28k** to similar reaction conditions failed to produce the styrene product **49** and potentially access products such as **50**. Similarly, oxidation of **(±)-28e** to the corresponding amine oxide for a Meisenheimer rearrangement only led to decomposition of the starting materials. The fact that this is a cyclic allylic system may contribute for the lack of desired reactivity for both transformations by restricting the conformation needed for correct orbital alignment. Similarly, attempts to perform allylic substitution on the allylic urazole motif in **(±)-28k** and its derivatives proved unsuccessful, with the existing benzylic/allylic urazole C–N bond resistant to further transition-metal-mediated manipulations.



Scheme 4: Failed derivatizations of **(±)-28k and (±)-28e**



Scheme 5: Derivatizations of **(±)-28v**; see supporting information for details

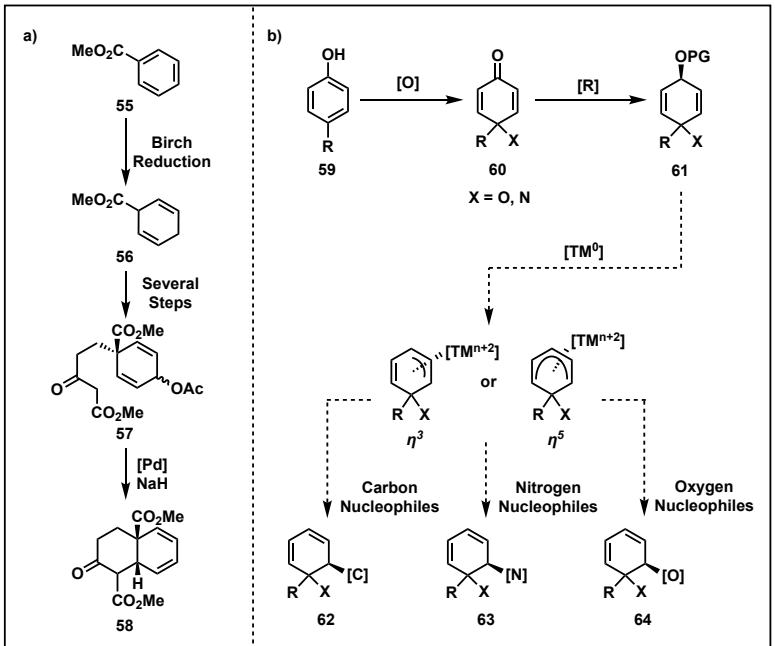
We were also interested to probe this dearomative diamination protocol as a tool for diversification of medicinally-relevant amines. Accordingly, memantine, an FDA-approved drug used for treatment of dementia associated with Alzheimer's disease, was appended onto naphthalene (**16**) using standard conditions to give the dearomatized product in 66% yield (**(±)-28v**, Table 3). This intermediate was further diversified to alkene **(±)-49** under dissolving metal reduction conditions (Scheme 5). Furthermore, after the olefin in **(±)-28v** was reduced with Rh/Al_2O_3, saturated ketone **(±)-51** was synthesized by oxidation of the urazole with *t*BuOCl. Finally, diol-diamine **(±)-54** was obtained involving Upjohn hydroxylation combined by a two-step unmasking of the urazole to the diamine (**(±)-52** and **(±)-53**). Together these reactions showcase the diverse functionalization opportunities this chemistry provides. Attempts to synthesize enantioenriched **(±)-28v** using the asymmetric conditions described above failed to produce any product. Separately, desipramine, an FDA-approved drug used to treat depression was used also applied in the racemic variant of this transformation (**(±)-28w**, Table 3). The desired product was identified by analysis of the crude NMR analysis in good yields, but could not be isolated due to significant instability. Development of *in situ* functionalization of the

olefin in **(±)-28w** prior to isolation would provide one possible solution to the issues regarding stability.

In summary, we have reported a dearomative aminofunctionalization strategy. This process involves a visible-light-mediated *para*-cycloaddition of arenes with an arenophile and subsequent Pd-catalyzed ring-opening of the resulting cycloadducts with amines as nucleophiles. A variety of amines and arenes provided products with exclusive *syn*-1,4-selectivity, and high enantioselectivity was observed with naphthalene. However, in general less nucleophilic amines proceeded to the desired products in lower yields. The corresponding dearomatized products offer unique access to functionalized small molecules as they contain unsaturation and the arenophile motif, both of which could be used for further functionalization. The synthetic value of this method has also been demonstrated by rapid and selective elaboration of memantine into new analogs as well as the dearomative incorporation of desipramine onto naphthalene. Finally, from a practical perspective, it is noteworthy that this methodology could be conducted on a gram scale without significant loss of efficiency.

Future Directions:

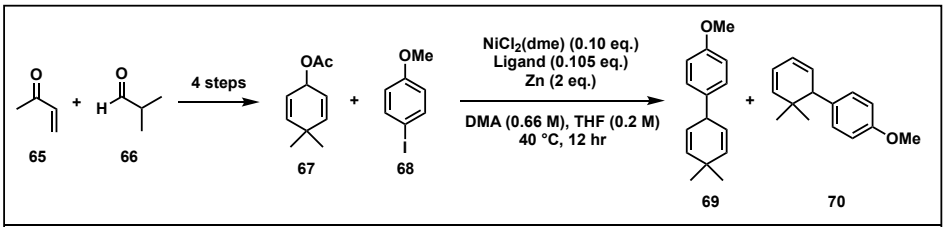
In addition to our palladium catalyzed *syn*-1,4 carboamination and now *syn*-1,4 diamination, our group has published an analogous *syn*-1,4 oxyamination with alcohols or oximes as nucleophiles. Furthermore, apart from transition-metal catalyzed ring-opening of arene-arenophile cycloadducts, we are also interested in utilizing, in different contexts, similar vinyl transition-metal π-allyl intermediates that are presumably accessed in the above-



Scheme 6: (a) Precedent from Shibasaki; (b) Future plans for the development of metal-catalyzed transformations

described chemistry. A single report from Shibasaki showcased the use of one such intermediate (Scheme 5a), which starts with the birch reduction of methyl benzoate (**55**) to 1,4-cyclohexadiene **56**.[19] Over several steps **56** is converted to bis-allylic acetate **57**, which undergoes intramolecular allylic substitution with a malonate functional group under palladium catalysis to afford 1,3-cyclohexadiene **58** with high levels of enantioselectivity. Efforts were initially focused on accessing similar motifs more readily through a several step protocol from phenols (**59**) involving their oxidation to dienones (**60**) and reduction to the bis-allylic alcohol derivatives (**61**). These bis-allylic substrates would then be applied in the synthesis of natural products and value added compounds for medicinal chemistry through transition-metal catalyzed C–C (**62**), C–N (**63**), and C–O (**64**) bond formation (Scheme 5b). However, upon investigation the starting materials (**61**) for these reactions were too unstable to be synthesized. Upon reduction of the carbonyl to obtain **61**, the products rearomatize back to the phenol derivatives (**59**).

Nevertheless, a positive result was observed in the reaction outlined in Table 6 using nickel catalysis. Acetate **67** was not derived from phenols, but instead from methyl vinyl ketone and an alpha-substituted aldehyde in a four-step procedure. Using reductive coupling conditions modified from conditions developed by Weix, we were able to couple 4-iodoanisole to bis-allylic acetate **67** in 11% yield and and 3:1 ratio of the two diene products (**69** and **70**). Only ligand neocuproine generated any of the desired product. Moving forward, the



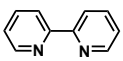
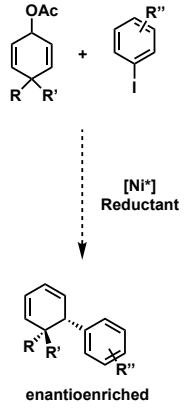
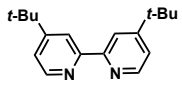
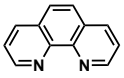
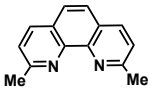
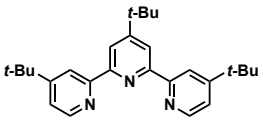
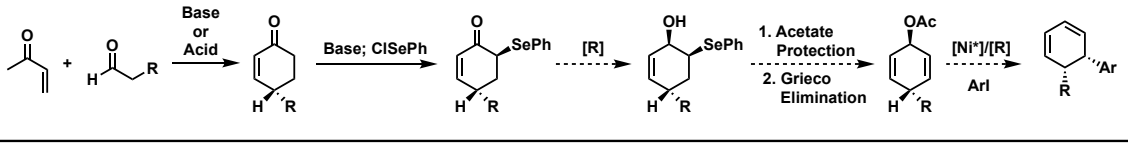
Ligand:	Result:	Goal:
	homocoupling of allylic substrate	
	no conversion	
	no conversion	
	full conversion (11% yield — 3:1 (**69**:**70**))	
	no conversion	

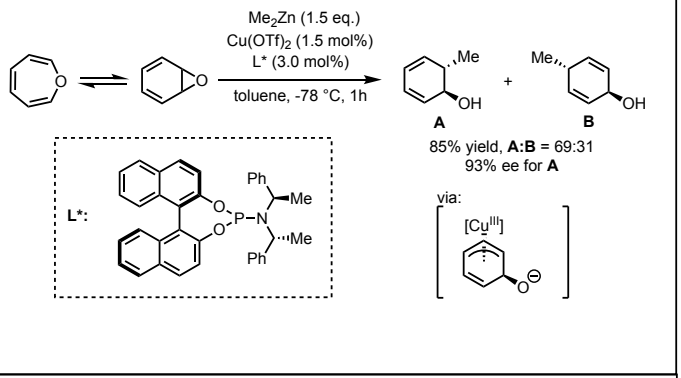
Table 6: Initial results for nickel catalysis

goal would be to: 1) increase the yield of the reaction, 2) enhance and understand the selectivity for either product, 3) develop stereoselective variants. If successful this project would provide a method to access enantioenriched trisubstituted 1,3-dienes using η-5 transition-metal catalysis. Furthermore, one could synthesize substrates as shown in Scheme 7, potentially allowing the synthesis of *syn* disubstituted 1,3-dienes when subjected to transition-metal catalysis.[20]



Scheme 7: Proposed synthesis of starting materials and ensuing nickel-catalyzed reaction

In addition, arene oxides could be used as substrates in this allylic substitution chemistry to access trans-substituted 1,3-dienes. Moreover, this reaction generates the same type of trans-substituted 1,3-dienes that nature synthesizes from arene oxides. There is only one example of such a reaction using copper catalysis, and it is non-selective (Scheme 8).[21] A novel two-step method for access to arene oxides from mononuclear arenes is presented in the second portion of this thesis.



Scheme 8: Precedent for arene oxides in allylic substitution reactions

References:

1. Roche, S.P.; Porco Jr., J.A. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068–4093.
2. Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752–6756.
3. Zheng, C.; You, S.-L. *Chem* **2016**, *1*, 830–857.
4. Zhuo, C.-X.; Zhang, W.; You, S.-L.; *Angew. Chem., Int. Ed.* **2012**, *51*, 12662–12686.
5. Boyd, D.R.; Bugg, T.D.H. *Org. Biomol. Chem.* **2006**, *4*, 181–192.
6. Wender, P.A.; Howbert, J.J. *J. Am. Chem. Soc.*, **1981**, 688-690.
7. Zutter, U.; Iding, H.; Spurr, P.; Wirz, B. *J. Org. Chem.*, **2008**, *73*, 4895–4902.
8. For selected reviews, see: (a) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48. (b) Rayabarapu, D.K.; Cheng, C.-H. *Acc. Chem. Res.* **2007**, *40*, 971. (c) Woo, S.; Keay, B. A. (d) Chiu, P.; Lautens, M. *Top. Curr. Chem.* **1997**, *190*, 1.
9. For selected examples of formal dearomative 1,2-diamination, see: (a) Cho, Y.; Zunic, V.; Senboku, H.; Olsen, M.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 6837. (b) Cho, Y.-H.;

Fayol, A.; Lautens, M. *Tetrahedron: Asymmetry* **2006**, *17*, 416. (c) Lautens, M.; Fagnou, K.; Zunic, V. *Org. Lett.* **2002**, *4*, 3465.
10. Nara, T.; Yamamoto, M.; Kawamoto, I.; Takayama, K.; Okaci, R.; Takasawa, S.; Sato, T.; Sato, S. *J. Antibiot.* **1977**, *30*, 533.
11. Ho, W.-B.; Broka, C. *J. Org. Chem.* **2000,** *65,* 6743.
12. Bruhn, J.A.; Pasteris, R. J. WO 2008091594, **2008**.
13. Southgate, E.H.; Pospech, J.; Fu, J.; Holycross, D.R.; Sarlah, D. *Nat. Chem.* **2016**, *8*, 922.
14. Okumura, M.; Nakamata Huynh, S.M.; Pospech, J.; Sarlah, D. *Angew. Chem., Int. Ed.* **2016**, *55*, 15910–15914
15. (a) Hernandez, L.W.; Klöckner, U.; Pospech, J.; Hauss, L.; Sarlah, D. *J. Am. Chem. Soc.* **2018**, *140*, 4503. (b) Okumura, M.; Shved, A.S.; Sarlah, D. *J. Am. Chem. Soc.* **2017**, *139*, 17787.
16. For reviews on Pd-catalyzed allylic substitution, see: (a) Trost, B.M.; Van Vranken, D.L. *Chem. Rev.* **1996**, *96*, 395. (b) Trost, B.M.; Crawley, M.L. *Chem. Rev.* **2003**, *103*, 2921. (c) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258. (d) Weaver, J.D.; Recio, A., III; Grenning, A.J.; Tunge, J.A. *Chem. Rev.* **2011**, *111*, 1846.
17. Adam, W. Pastor, A. Wirth, T. *Org. Lett*., **2000** *2*, 1295-1297.
18. Fortner, K. C.; Kato, D.; Tanaka, Y.; Shair, M. D. *J. Am. Chem. Soc.* **2010**, 132, 275-280.
19. (a) Takemoto, T.; Nishikimi, Y. Sodeoka, M. Shibasaki, M. *Tet. Lett.* **1992**, *33*, 3531-3532. (b) Takemoto, T.; Nishikimi, Y. Sodeoka, M. Shibasaki, M. *Tet. Lett.* **1992**, *33*, 3527-3530.
20. Hagiwara, H.; Okabe, T.; Ono, H.; Kamat, V.P.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Chem. Soc., Perkin Trans. 1*, **2002**, 895–900.
21. Bertozzi, F.; Crotti, P.; Del Moro, F.; Feringa, B.L.; Macchiaa, F.; Mauro, P. *Chem. Commun.* **2001**, 2606-2607.

Chapter 2: Synthesis of Oxepines

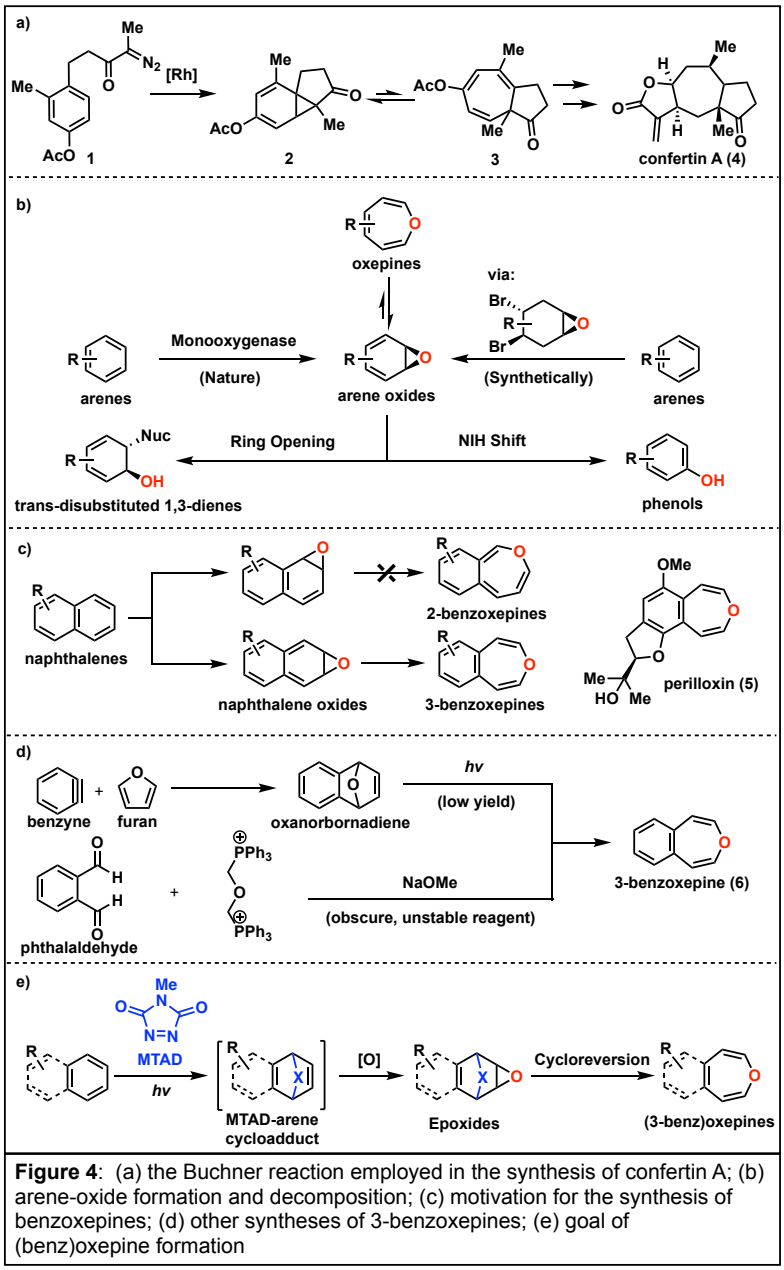


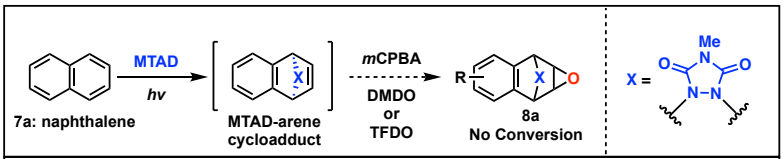
Figure 4: (a) the Buchner reaction employed in the synthesis of confertin A; (b) arene-oxide formation and decomposition; (c) motivation for the synthesis of benzoxepines; (d) other syntheses of 3-benzoxepines; (e) goal of (benz)oxepine formation

The Buchner reaction is an important reaction that expands aromatic rings into cycloheptatrienes, and many developments and applications of this transformation to the synthesis of natural products have been documented.[1] One such example is shown in Figure 4a, where alpha-diazo **1** forms cyclopropane **2** under rhodium catalysis. Cycloheptatriene **3**, which is in equilibrium with the **2**, is trapped and carried on to form the seven-membered core of natural product confertin A. In contrast to the synthetically useful Buchner reaction, the analogous transformation for the epoxidation of arenes and ensuing electrocyclic ring-opening of the arene-oxide to afford oxepines has several synthetic limitations. 1) For mononuclear substrates, there is an equilibrium between the oxepine and the arene-oxide. Moreover, arene oxides readily undergo NIH shifts to afford phenols (Figure 4b).[2] Nature employs this NIH shift, but can also take advantage of the high reactivity of monocyclic arene oxides to achieve a variety of ring-opening reactions, with the resulting cyclohexanes forming the core to numerous classes of natural products. 2) Synthetically, arene oxides have been formed in four steps from benzene

derivatives, with the first step being a Birch reduction, while nature directly oxidizes monocyclic arenes using monooxygenases.

In contrast to monocyclic oxepines, benzoxepines are more stable and do not readily undergo degradation under synthetic conditions. Synthetic epoxidation of polyarenes often form oxidation 1-2-oxidation products (Figure 4c), which do not undergo electrocyclic ring-openings to form 2-benzoxepines.[2] Nature can also oxidize the terminal "olefin" in polyarenes, which form 3-benzoxepines through electrocyclization. Since oxidation of polyarenes is presumed to be involved in the metabolism of small-molecule drugs that contain such motifs, there is a strong desire to readily access 3-benzoxepines to understand their biological activity and more easily elucidate certain drugs' metabolic fate. Furthermore, a method to generate 3-benzoxepines could allow access to several classes of natural products that include perilloxin[3] (**5**, Figure 4c), a cyclooxygenase inhibitor. Despite these motivations, there is no general method for the generation of 3-benzoxepines, hereafter referred to as benzoxepines. The only known ways to access benzoxepines involve very low-yielding steps or unstable and obscure compounds (Figure 4d).[4]

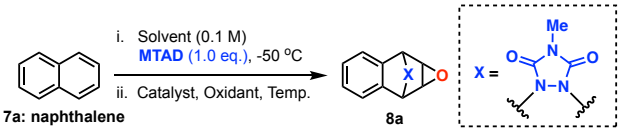
Alternatively, we envisioned that our MTAD-arene cycloadduct chemistry may facilitate a rapid synthesis of monocyclic arene oxides and benzoxepines through epoxidation of *in situ* formed cycloadducts followed by cycloreversion of the urazole motif (Figure 4e). Our proposed method would generate the desired products in two steps directly from arenes, with precedent for the cycloreversion.[5a-c] We directed our attention initially toward polycyclic arenes due to the relative stability of the proposed benzoxepine products compared to monocyclic oxepines.[5d]



Scheme 9: Initial attempts to epoxidize MTAD-naphthalene cycloadduct

Unfortunately, the electron-deficiency of the arene-arenophile cycloadduct olefin and restraints in the temperature by the facile cyclo-reversion of the cycloadduct posed a significant challenge in the epoxidation of the cycloadduct olefin. We quickly discovered that organic oxidants such as *meta*-chloroperoxybenzoic acid (*m*CPBA), dimethyldioxarane (DMDO), and trifluoromethyl-

methyldioxirane (TFDO) did not convert the MTAD-naphthalene cycloadduct into **8a** at the necessary cryogenic temperatures (Scheme 9). With this in mind, our attention turned to metal-catalyzed epoxidation reactions, and particularly systems that are considered robust or proceed at low temperatures.



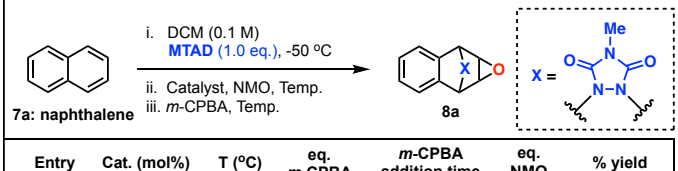
Entry	Catalyst/mol%	Oxidant/eq.	Solvent	Temp. (°C)	% yield
1	MTO/10 + 1 eq. pyridine	H_2O_2/1.0	DCM	-20	none
2	Fe(PDP)/2.5	*m*CPBA/1.2	DCM	-20	none
3	Fe(PDP)/5.0	*m*CPBA/1.2	EtCN	-78	none
4	$Cu(MeCN)_4PF_6$/10	*m*CPBA/2.0	DCM	-78	none
5	$Cu(MeCN)_4PF_6$/20	*m*CPBA/4.0	DCM	-78	none

Table 7: Initial optimization for the epoxidation of MTAD-naphthalene cycloadduct

Accordingly, to begin our screening we explored using substoichiometric methyltrioxorhenium (MTO) with urea hydrogen peroxide as the oxidant. However, these conditions failed to convert *in situ* formed MTAD-naphthalene cycloadduct into **8a** at -20 °C (Table 7, Entry 1). Similarly, using Fe(PDP) with *m*CPBA as the oxidant was unsuccessful, yielding none of the desired epoxide and only remaining starting material at two different temperatures (Table 7, Entries 2 and 3). Although tetrakis(acetonitrile)copper(I) hexafluorophosphate is capable of epoxidizing a wide range of electronically differentiated olefins at -78 °C,[6] no product was observed with two different loadings of that catalyst with *m*CPBA (Table 7, Entry 4-5). These reactions were run under nitrogen atmosphere in degassed methylene chloride. Other systems failed to produce any product as well.[7]

We next turned toward the use of manganese salen catalysts, which are known to have exceptional activity, even at temperatures as low as -78 °C.[8] To our delight, initial studies of the catalytic activity of **A** (Table 8) showed the first sign of epoxidation of arene-arenophile cycloadduct. The reaction of the arene-arenophile cycloadduct with 10 mol % catalytic loading of catalyst A and two equivalents of *m*CPBA led to epoxide **4** in 10% yield as a single diastereomer (Table 8, Entry 1). X-ray crystallography later revealed the diastereomer to be the trans isomer. Interestingly, the reaction indicated no significant dependence on temperature (Table 8, Entries 2-4) and only a slight dependence on catalyst loading. Turning to older literature, we found that nitro substituents on the aromatic rings of salen complexes increase their reactivity. However, after synthesizing and testing **B** we found a sharp decrease in reactivity,

which could not be recovered through higher catalyst loading (Entries 6-8). Undeterred, we recognized that the cyclohexane backbone of the catalyst might be susceptible to oxidation by a strongly oxidizing catalyst and switched to the analogous complex **C**, with a tetramethyl backbone. This catalyst proved to superior to both catalyst **A** and **B** in terms of yield (Entry 9). However, further optimizing of the reaction parameters (Entries 10-16) including temperature, oxidant loading, oxidant addition time, and equivalents of additive *N*-methyl morpholine *N*-oxide (NMO) only led to an optimized yield of 29% (Entry 12). To test the importance of the nitro groups in complex **C**, we next employed unsubstituted complex **D** and tetra-nitro complex **E** in the reaction (Entries 17 and 18), both of which only produced minimal amounts of the desired product (**4**). It should be noted that **E** appeared to be completely insoluble in DCM, which may have contributed to its low reactivity.



Entry	Cat. (mol%)	T (°C)	eq. *m*-CPBA	*m*-CPBA addition time	eq. NMO	% yield
1	A (10%)	-78	2	2 min.	5	10
2	A (10%)	-50	2	2 min.	5	7
3	A (10%)	-20	2	2 min.	5	10
4	A (10%)	0	2	2 min.	5	12
5	A (20%)	-78	2	2 min.	5	16
6	B (10%)	-78	2	2 min.	5	4
7	B (20%)	-78	2	2 min.	5	5
8	B (50%)	-78	2	2 min.	5	5
9	C (10%)	-78	2	2 min.	5	22
10	C (10%)	-78	2	1 hr.	5	21
11	C (10%)	-78	4	2 min.	8	23
12	C (10%)	-78	4	2 min.	2	29
13	C (10%)	-78	4	2 min.	0	15
14	C (10%)	-78	4	2 min.	10	25
15	C (10%)	-50	4	2 min.	10	14
16	C (10%)	-20	4	2 min.	10	11
17	D (10%)	-78	4	2 min.	10	2
18	E (10%)	-78	4	2 min.	10	Trace

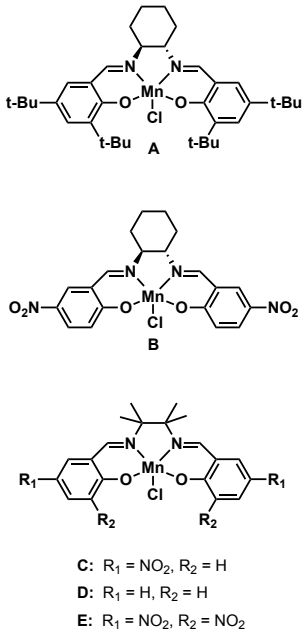
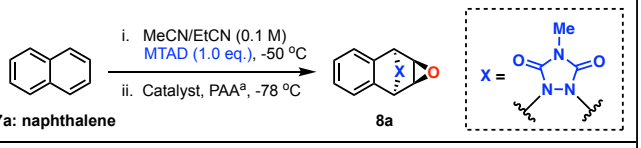


Table 8: Optimization for the epoxidation of MTAD-naphthalene cycloadduct using Mn-salen complexes

With an apparent limit to the optimization of manganese-salen complexes for the epoxidation of the MTAD-naphthalene cycloadduct, we turned our attention to the use of manganese salts in the presence of picolinic acid, a system originally reported by Stack.[9] In this original report, highly electron deficient, but non-conjugated, olefins were epoxided at cryogenic temperatures. While the ligand sphere of the manganese catalyst is unknown, the active oxidizing species is presumed



7a: naphthalene 8a

Entry	Mn Source/mol%	eq. Picolinic Acid	eq. PAA[a]	% yield[b]
1	$Mn(OAc)_2$/2	0.15	1.1	Trace
2	$MnCl_2$/2	0.15	1.1	Trace
3	$Mn(OAc)_2$/10	0.5	4	Trace
4	$MnCl_2$/10	0.5	4	Trace
5	$Mn(OTf)_2$/10	0.5	2	17
6	$Mn(OTf)_2$/100	5	2	82
7	$Mn(ClO_4)_2$•H_2O/5	0.25	4	84

[a] PAA = peracetic acid
[b] 1.6:1 mixture of diastereomers. Major diastereomer is the trans isomer

Table 9: Optimization for the epoxidation of MTAD-naphthalene cycloadduct with Mn/picolinic acid as the catalyst

to be a high-valent manganese-oxo species. *In situ* epoxidation of the MTAD-naphthalene cycloadduct with $Mn(OAc)_2$ or $MnCl_2$ mixed with picolinic acid and peracetic acid as the oxidant resulted in trace amounts of **8a** (Table 9, Entries 1-4). However, switching to strongly electrophilic Mn(II) sources such as $Mn(OTf)_2$ or $Mn(ClO_4)_2$ eventually resulted in yields above 80% (Entries 5-7). Also, in contrast to the manganese-salen complexes the diastereomeric ratio of **8a** under all the conditions in Table 9 was 1.6:1, favoring the trans diastereomer. It should be noted that considering the yield of the cycloaddition (determined in NMR studies) these yields are essentially quantitative.

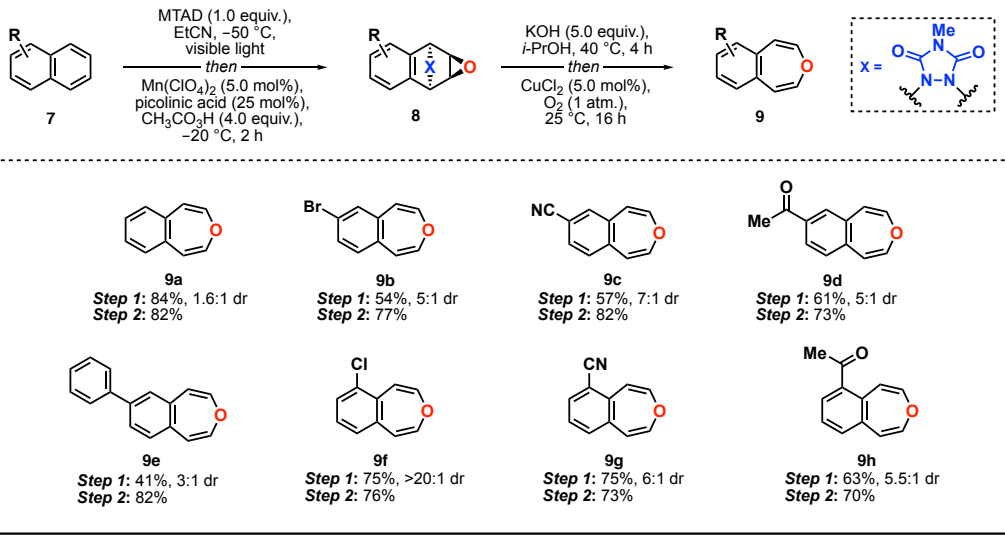


Table 10: Scope of Naphthalenes

Next, we turned toward optimizing a base-promoted cycloreversion of the epoxidized products (**8**, Table 10) to furnish the desired benzoxepines (**9**).[5a-c] Treatment of **8** with KOH in *i*-PrOH or EtOH, neutralizing workup, and addition of $CuCl_2$ under air resulted in the desired benzoxepines in good yield. The copper presumably oxidizes the semi-carbazide, which is revealed under basic conditions. Application of this two-step method to a variety of naphthalenes, quinolones and

isoquinolines (**7a-7u**, Tables 10-11) resulted in good yields of the desired benzoxepine products. Notably, only functional groups on starting materials **7o**, **7p**, and **7q** were modified: to amide, ether-substituted quinolone, and pyridone functional groups, respectively.

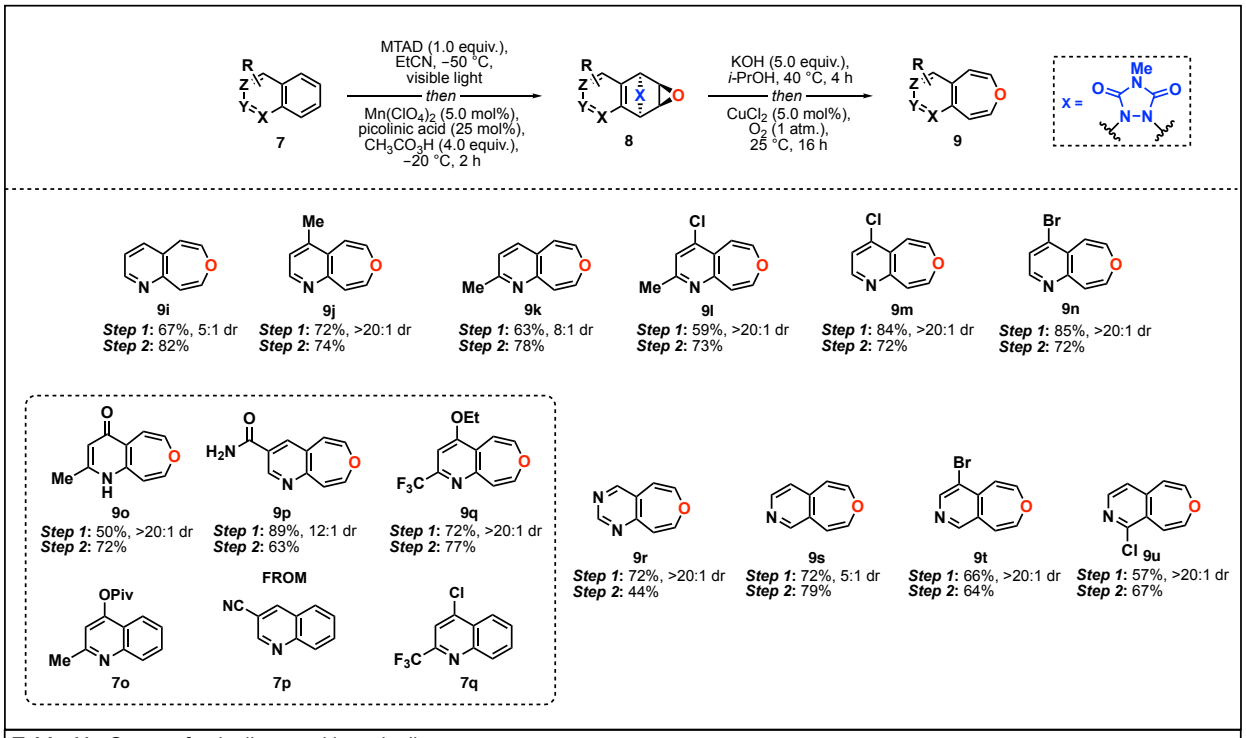


Table 11: Scope of quinolines and isoquinolines

With these results in hand, our attention turned to the application of our oxidation method to monocyclic arenes. Unfortunately, our manganese/picolinic acid system did not produce any of the desired product when applied to monocyclic arene-MTAD cycloadducts. A modified procedure was optimized using benzene as the model substrate with phenanthroline instead of picolinic

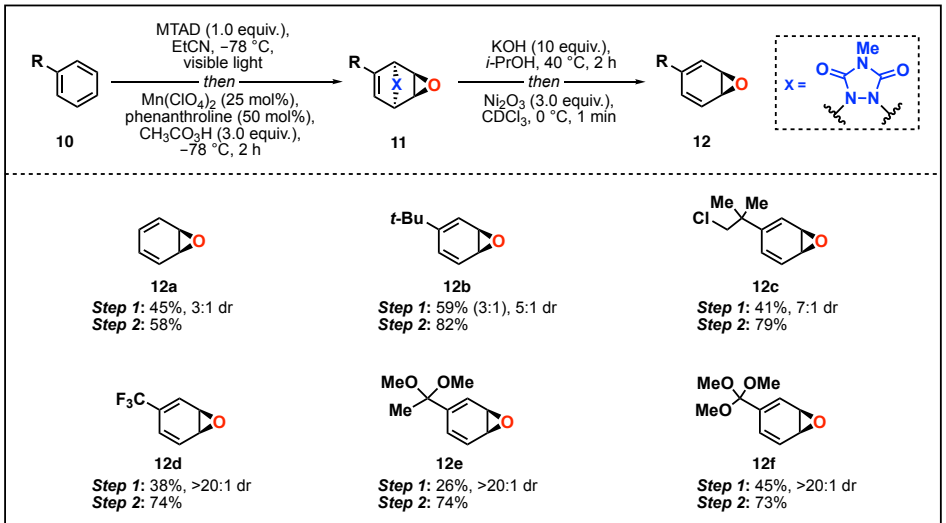
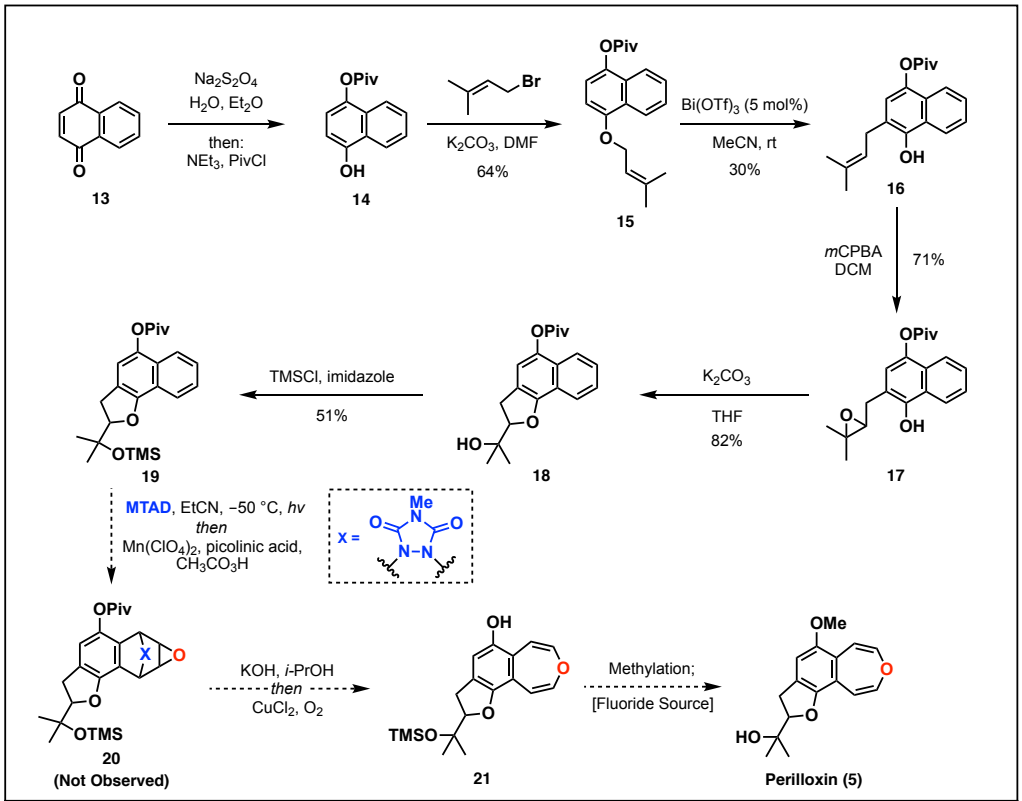


Table 12: Scope of mononuclear arenes

acid as the manganese ligand in the oxidation of the cycloadduct (Table 12). In addition, freshly prepared peracetic acid was used without trace amounts of H_2SO_4. In turn, this method was applied to a number of mono-substituted benzene derivatives (**10a-10f**) and the desired epoxidized cycloadduct was obtained in good yields. The cycloreverted arene oxides (**12a-12f**) were obtained using a basic alcohol solution followed by neutralization with acetic acid and treatment with Ni_2O_3 instead of $CuCl_2$. Due to their high instability, yields of the arene oxide products were determined by NMR spectroscopy using nitromethane as the internal standard.

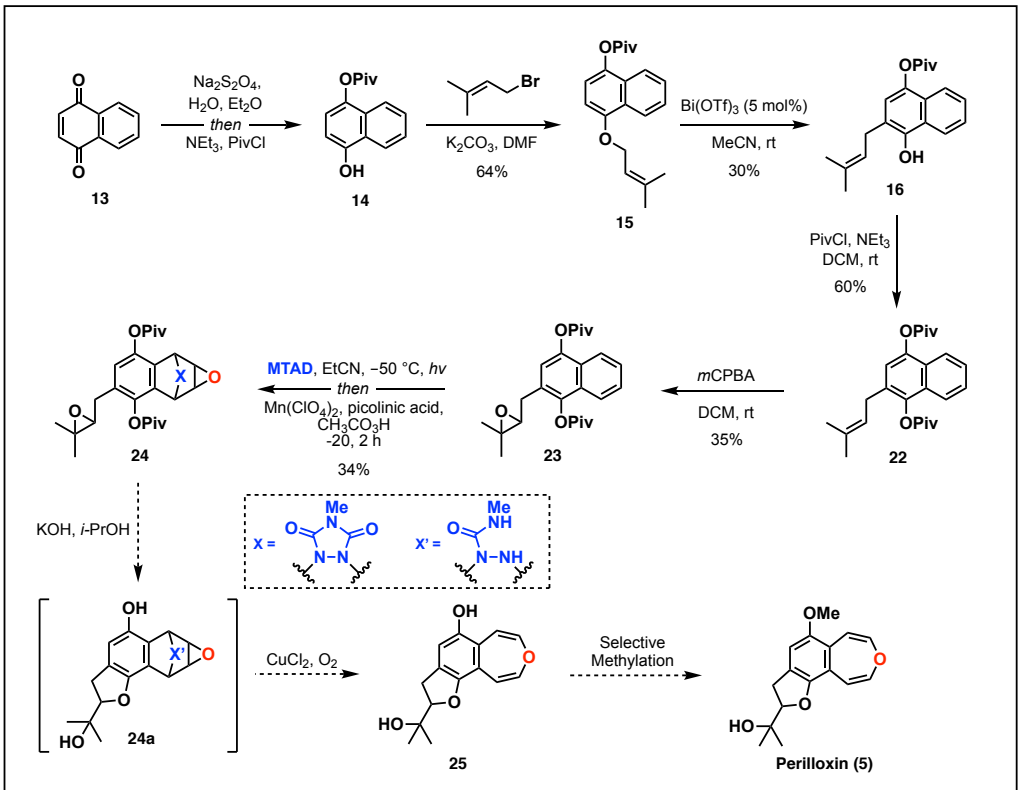
Next, a route to perilloxin (**5**), a benzoxepine containing natural product and cyclooxygenase inhibitor, was investigated (Scheme 10). We envisioned late stage formation of the benzoxepine to avoid over-oxidation of the vinyl ether functionality. To begin the synthesis quinone **13** was converted into mono-pivalate protected hydroquinone **14** using a known procedure. Prenylation followed by a bismuth-catalyzed isomerization/Claisen rearrangement sequence resulted in **15** in 19% yield over two steps. Epoxidation with *m*CPBA was followed by a base-promoted ring-closing reaction in good yield. Silyl protection of the resulting tertiary alcohol **18** yielded an



Scheme 10: Initial route to perilloxin

intermediate we envisioned could be used in our MTAD/epoxidation method to generate the desired epoxide en route to the benzoxepine core of the natural product. However, treatment of **19** with MTAD followed by manganese/picolinic acid epoxidation conditions resulted in a single side-product. Moreover, no desired product or incorporation of MTAD was observed upon workup of the reaction. We concluded that **19** was not a suitable starting material for the photomediated cycloaddition with MTAD and abandoned this route.

With these results in mind, a modified synthesis of perilloxin was developed (Scheme 11). Starting from common prenylated intermediate **16**, pivalate protection and epoxidation resulted in bis-pivalate protected epoxide **23**. We identified this intermediate as ideal for testing with our cycloaddition chemistry. Treatment with MTAD followed by addition of a solution of manganese/picolinic acid catalyst and peracetic acid resulted in a mixture of diastereomers of the desired product in 34% yield. Epoxide opening and cycloreversion of the urazole motif through



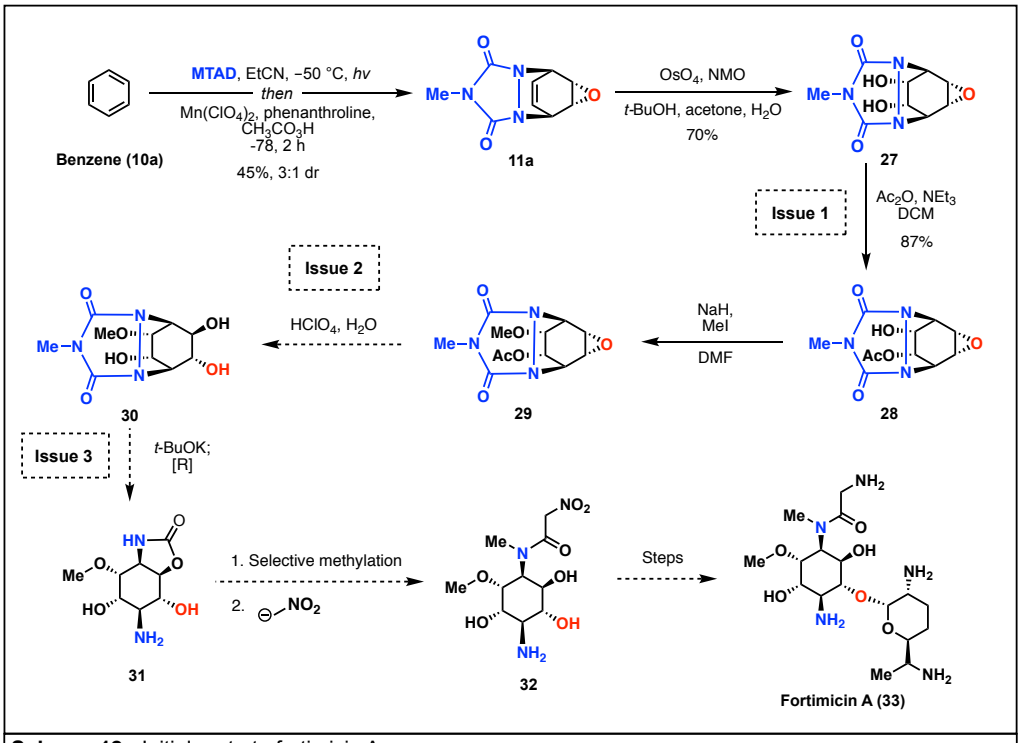
Scheme 11: Revised route to perilloxin

treatment with alcoholic base and oxidant would presumably yield **25**. Selective methylation of the hydroquinone oxygen would produce perilloxin (**5**). These last two steps have not been attempted.

In summary, we have developed a method for the *in situ* formation and epoxidation of arene-arenophile cycloadducts to generate epoxides for both mono- and polynuclear arenes. The developed system produced the desired product in good yields, but with poor diastereoselectivity using electron-deficient Mn(II) sources combined with picolinic acid or phenanthroline at low temperatures. In addition, two routes to the benzoxepine natural product Perilloxin have been investigated.

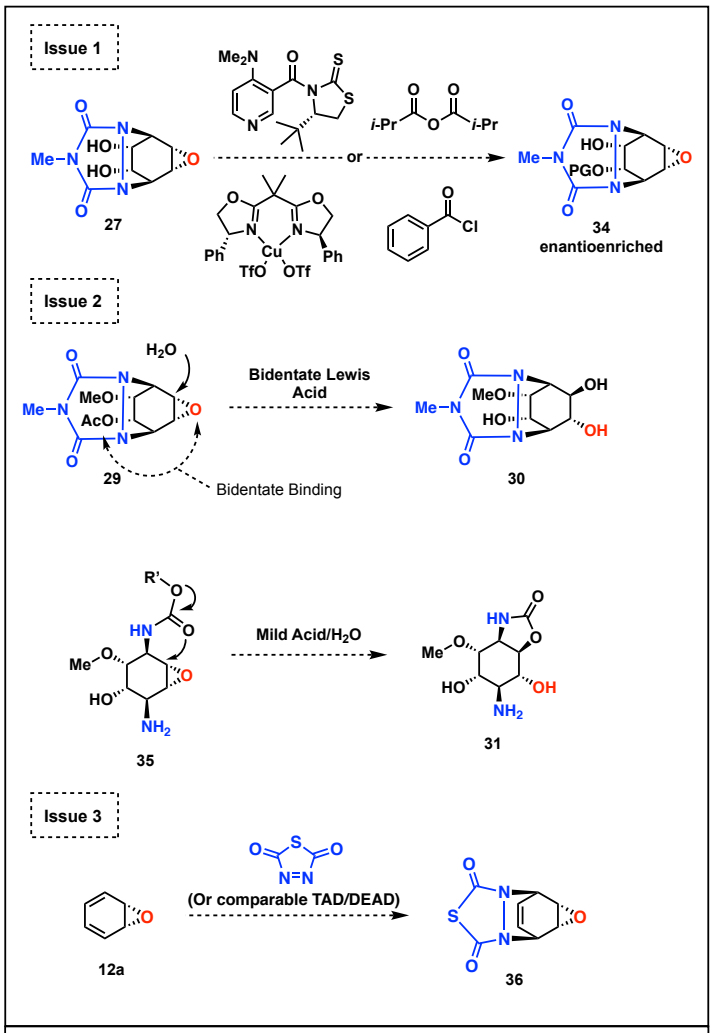
Future Directions:

With the rise of antibiotic resistance there is a search for underutilized antimicrobial agents and efficient ways to synthesize them and their analogues.[10] Fortimicin A is an aminoglycoside with similar antimicrobial activity as antibiotics akimicin and gentamicin.[11] A route to the core of fortimicin A was briefly investigated employing the epoxidation method described above. Fortimicin A contains a cyclohexane core with 1,4-*syn* nitrogens. A proposed route is presented



Scheme 12: Initial route to fortimicin A

in Scheme 12, which begins from benzene. Photo-mediated cycloaddition between MTAD and benzene followed by oxidation yields epoxide **26**. Dihydroxylation of the resulting olefin and mono-acetate protection produces racemic mono-protected alcohol **28**. Methylation of the



Scheme 13: Potential solutions to issues highlighted in Scheme 3

unprotected alcohol in DMF gave **29**. For the remaining aspects of the synthesis, there are three critical obstacles to accomplish it without multiple protection/deprotection sequences. All three of these issues could require significant experimentation and understanding of the conformation of various intermediates. These concerns are highlighted in Scheme 12 with possible solutions presented in Scheme 13:

1) An enantioselective synthesis of the cyclohexane core of fortimicin is needed to append the chiral diamine sugar. The desymmetrization could come in the acetate protection to generate **28**. The use of chiral catalysts to desymmetrize mixtures of *meso*-diols is well precedented (Scheme 13).[12] An alternative method for desymmetrization would involve a chiral lewis acid to open the epoxide.[13] However, desymmetrizing the molecule to generate a tetra-ol could complicate the selective installation of a single methyl group on one of the product's four alcohols.

2) The next unprecedented step in the synthesis would be a selective opening of the epoxide. Treatment with HCl likely would produce a mixture of chlorohydrins while perchloric or sulfuric acid in water may open epoxide **29** non-stereoselectively. All acids may result in substitution at the bridging urazole as well. Potentially the dihydroxylation of the olefin would ameloriate chemoselectivity concerns. Other options for opening the epoxide include using a bidentate lewis acid or intramolecular addition of a carbonyl group derived from the urazole (Scheme 13). The

resulting conformation of the prospective intermediates will play a critical role in determining their reactivity.

3) Fragmentation and differentiation of the two nitrogen atoms that are part of the bridging urazole are critical for the completion of this synthesis. Intramolecular attack of the alcohol *syn* to the bridging urazole in **30** would result in formation of a cyclic carbamate (Scheme 12). For more facile manipulation of the two nitrogens, replacing the MTAD urazole with another triazoline dione or dieneophile with a more electron-deficient group on the nitrogen (through cycloaddition with the corresponding arene oxide) may result in easier manipulation of the two amine groups originating from the urazole (Scheme 13).

References:

1. Reisman, S.E.; Nani, R.R.; Levin, S. *Synlett* **2011**, 2437–2442.
2. (a) Boyd, D.R.; Sharma, N.D. *Chem. Soc. Rev.* **1996**, *25*, 289-296. (b) Guroff, G.; Renson, J.; Udenfriend, S.; Daly, J.W.; Jerina, D.M.; Witkop, B. *Science* **1967**, *157*, 1524−1530. (c) Jerina, D.M.; Daly, J.W. *Science* **1974**, *185*, 573−582.
3. (a) Liu, J.-h.; Steigel, A.; Reininger, E.; Bauer, R. *J. Nat. Prod.* **2000**, *63*, 403-405. (b) Ulubelen, A.; Tuzlacia, E.; Atilan, N. *Phytochemistry* **1989**, *28*, 649-650.
4. von Angerer, S. *Science of Synthesis* **2004**, *17*, 653-703.
5. (a) Okumura, M.; Nakamata Huynh, S.M.; Pospech, J.; Sarlah, D. *Angew. Chem., Int. Ed.* **2016**, *55*, 15910−15914. (b) Heyman, M.; Bandurco, V.T.; Snyder, J.P. *J. Chem. Soc. D* **1971**, 297−298. (b) Jösel, R.; Schröder, G. *Liebigs Annalen der Chemie* **1980**, 1428−1437. (c) Jain, R.; Sponsler, M.B.; Coms, F.D.; Dougherty, D.A. *J. Am. Chem. Soc.* **1988**, *110*, 1356−1366. (d) Siddiqi, Z.; Wertjes, W.C.; Sarlah, D. *J. Am. Chem. Soc.* **2020**, *142*, 10125−10131.
6. Andrus, M.B.; Poehlein, B.W. *Tetrahedron Lett.* **2000**, 41, 1013-1014.
7. (a) De Vos, D.E.; Sels, B.F.; Reynaers, M.; Subba Rao, Y.V.; Jacobs, P.A. *Tetrahedron Lett.* **1998**, 39, 3221-3224. (b) Berkessel, A.; Sklorz, C.A. *Tetrahedron Lett.* **1999**, 40, 7965-7968. (c) De Vos, D.E.; Bein, T. *Chem. Comum.* **1996**, 917-918. (d) De Vos, D.E.; Bein, T. *J. Organomet. Chem.* **1996**, 520, 195-200.
8. (a) Zhang, W.; Loeabach, J.L.; Wilson, S.R.; Jacobsen, E.N. *J. Am. Chem. Soc.* **1990**, 112, 2801. (b) Palucki, M.; Pospisil, P.J.; Zhang, W.; Jacobsen, E.N. *J. Am. Chem. Soc.* **1994**, 116, 9333.
9. (a) Moretti, R.A.; Du Bois, J.; Stack, T.D.P *Org. Lett.* **2016**, 18, 2528-2531. (b) Murphy, A.; Stack, T.D.P. *J. Mol. Catal. A.* **2006**, 251 (1-2), 78. (c) Murphy, A.; Du Bois, G.; Stack, T.D.P. *J. Am. Chem Soc.* **2003**, 125 (18), 5250.
10. Aslam, B.; Wang, W.; Arshad, M.I.; Khurshid, M.; Muzammil, S.; Rasool, M.H.; Nisar, M.A.; Alvi, R.F.; Aslam, M.A.; Qamar, M.U.; Salamat, M.K.F.; Baloch, Z. *Infect. Drug Resist.* **2018**, *11*, 1645–1658.

11. Jones, R.N.; Barry, A.L.; Fuchs, P.C.; Gavan, T.L.; Sommers, H.M.; Gerlach, E.H. *Antimicrob Agents Chemother.* **1979**, *16*, 823–828.
12. (a) Enriquez-Garcia, A.; Kundig, E.P. *Chem. Soc. Rev.*, **2012**, *41*, 7803–7831. (b) Wurz, R.P. *Chem. Rev.* **2007**, *107*, 5570−5595.
13. Yus, M.; Pastor, I.M. *Curr. Org. Chem.* **2005**, *9*, 1-29.

SUPPLEMENTARY INFORMATION: CHAPTER 1

TABLE OF CONTENTS

1. General Experimental

Unless otherwise noted, all reactions were carried out under an ambient atmosphere. All chemicals were purchased from commercial suppliers and used as received. Tris(dibenzylideneacetone)dipalladium(0) (Pd_2dba_3) was purchased from Acros Organics, and tetrakis(triphenylphosphinie)palladium(0) ($Pd(PPh_3)_4$) was purchased from Strem Chemicals, Inc. 1,1'-Bis(diphenylphosphino)ferrocene (dppf) was purchased from Oakwood Chemical. *N*-methyl-1,2,4-triazoline-3,5-dione (MTAD) was prepared based on the literature procedures[1,2] and was sublimed before use. (*S*, S_p)-*t*Bu-phosferrox was prepared based on the literature procedure from the corresponding L-*tert*-leucinol, and the ^{1}H and ^{13}C spectra were in accordance with the reported values.[3,4] Naphthalen-2,3-yl-bispivalate and naphthalen-1-yl-pivalate were synthesized based on the literature procedure from corresponding commercially available naphthols.[5,6] 1-(Dimethoxymethyl)naphthalene was synthesized based on the literature procedure.[7] 4-(5-Pyrimidyl)quinolone was synthesized based on the literature procedure from 4-bromoquinoline and pyrimidine-5-boronic acid.[8,9] Methyl-acridine-9-carboxylate was synthesized based on the literature procedure from acridine-9-carboylic acid.[10] *Tert*-butyl hypochlorite was prepared based on the literature procedure.[11] Ethyl acetate (EtOAc) was purchased from Sigma Aldrich, and freshly distilled over CaH, then degassed with nitrogen gas before use. Propionitrile (EtCN) was obtained from Alfa Aesar and acetonitrile (MeCN) was obtained from Fisher Scientific and both were dried before use. Dry dichloromethane (CH_2Cl_2) and tetrahydrofuran (THF) were obtained by passing commercially available anhydrous, oxygen-free formulations through activated alumina columns. For methanol, acetone, and acetonitrile commercially available anhydrous solvents were used without further purification. Analytical thin-layer chromatography was performed on Merck silica gel 60 F_{254} glass plates. Visualization was accomplished with UV light and/or potassium permanganate ($KMnO_4$) solutions. Retention factor (R_f) values reported were measured using a 5 × 2 cm TLC plate in a developing chamber containing the solvent system described. Flash column chromatography was performed using Silicycle SiliaFlash® P60 (SiO_2, 40-63 μm particle size, 230-400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on Varian Unity Inova 500 (500 MHz, ^{1}H; 125 MHz, ^{13}C) MHz or Bruker 500 (500 MHz, ^{1}H; 125 MHz, ^{13}C) spectrometers. Spectra are referenced to residual chloroform (δ = 7.26 ppm, ^{1}H; 77.16 ppm, ^{13}C) or residual methanol (δ = 3.31 ppm, ^{1}H; 49.0 ppm, ^{13}C). Chemical shifts are reported in parts per million (ppm). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling constants *J* are reported in Hertz (Hz). Mass spectrometry (MS) was performed by the University of Illinois

Mass Spectrometry Laboratory. Electron Impact (EI^+) spectra were performed at 70 eV using methane as the carrier gas, with time-of-flight (TOF) mass analyzer. Chemical Ionization (CI^+) spectra were performed with methane reagent gas, with either a double focusing sector field (DFSF) or time-of-flight (TOF) mass analyzer. Electrospray ionization (ESI^+) spectra were performed using a time-of-flight (TOF) mass analyzer. Data are reported in the form of m/z (intensity relative to the base peak = 100). For several compounds, Waters Q-TOF Ultima ESI and Agilent 6230 ESI TOF LC/MS spectrometers were used to obtain the high resolution mass spectra. Infrared spectra were measured neat on a Perkin-Elmer spectrum BX FT-IR spectrometer. Peaks are reported in cm^{-1} with indicated relative intensities: s (strong, 0–33% T); m (medium, 34–66% T), w (weak, 67–100% T), and br (broad). Visible-light spectrum of LED was recorded using an Avantes Sensline Avaspec-ULS TEC Spectrometer. Melting points were measured on a Buchi B-540 melting point apparatus and are uncorrected. Optical rotations were recorded on a Jasco P-2000 polarimeter at 589 nm, and are reported in units of 10^{-1} (deg cm^2 g^{-1}). HPLC was performed on a Shimadzu Prominence HPLC system with SPD-M20A UV/VIS Photodiode array detector. The x-ray diffraction experiments were conducted using Bruker D8 Venture/Photon 100 diffractometer or Bruker APEX-II CCD diffractometer. Using Olex2,[12] the structure was solved with ShelXT[13] structure solution program using Intrinsic Phasing solution method, and the XL[14] refinement package using Least Squares minimization.

2. Experimental Procedures

2-1. LED light source

Generic cool white light LED corn bulbs were used for the photochemical experiments. These can be obtained from several manufactures over amazon.com and proved to give consistent results as well as identical visible spectra. Detailed info:

Socket: G4

LED Chip: 48 LEDs SMD 2835

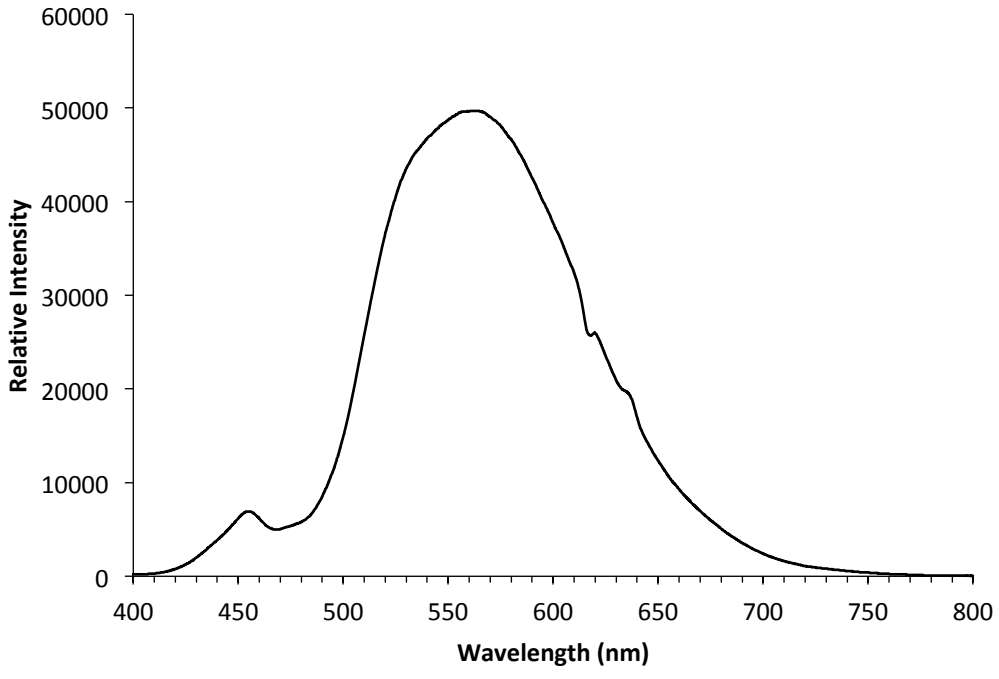
Consume wattage: 4W

Input voltage: AC / DC 12V

Beam degree: 360 degrees

Color temperature: 6500K (Cool White)

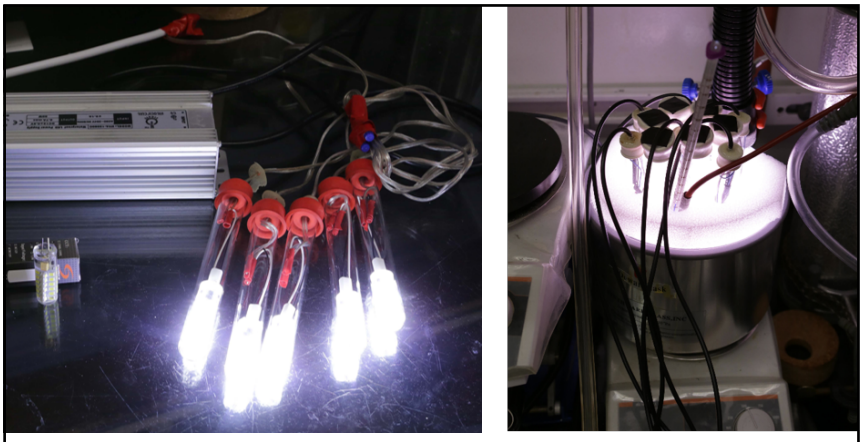
Initial Lumens (lm): 290



Supplementary Spectra 1: Spectrum of an LED bulb used

2-2. Set-up for small scale reactions (up to 2.0 mmol scale)

Five 4 W LED corn bulbs (12V, cool white light 6500K) were wired to a suitable 12V power supply, then sealed into test tubes and capped with septa (Picture S1). Lights and reaction tubes were arranged in a merry-go-round fashion for maximal exposure of each reaction vessel to light source and were submerged in a −78 °C bath. Generally, up to four 0.2-2.0 mmol scale reactions can be run in the same bath using five 4 W lamps positioned around them.



Supplementary Picture 1:
Assembly of LED bulbs for small-scale photochemical reactions.

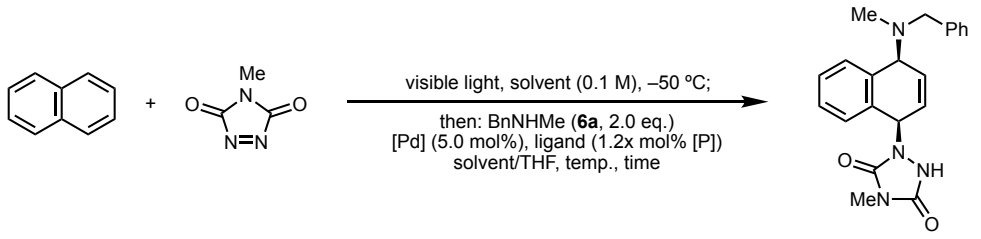
2-3. Set-up for large scale reactions (up to 10 mmol scale)

Eight 4 W LED corn bulbs (12V, cool white light 6500K) were wired to a suitable 12V power supply, then sealed into test tubes and capped with septa (see Picture S1). Lights were arranged in a merry-go-round fashion around a 500 mL clear borosilicate glass bottle (Picture S2). A normal reagent or media bottle can be used. The whole set-up was kept submerged in a −50 °C bath during the photochemical reaction.

Supplementary Picture 2:
Photochemical set-up for large scale reactions.

3. Experimental Procedures

3-1. Optimization for dearomative *syn*-1,4-diamination of naphthalene and *N*-benzylmethylamine



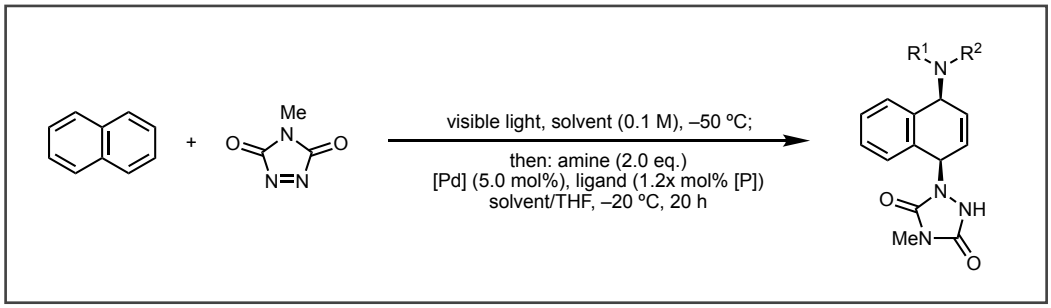
Supplementary Table 1: Optimization of reaction conditions

Entry	Solvent	[Pd]	Ligand	Temp. (ºC)	Time (h)	Yield (%)[a]
1	CH_2Cl_2	$Pd_2(dba)_3$	PPh_3		5	52
2	CH_2Cl_2	$Pd_2(dba)_3$	$P(p\text{-}MeOC_6H_4)_3$		5	44
3	CH_2Cl_2	$Pd_2(dba)_3$	$P(p\text{-}FC_6H_4)_3$		5	10
4	CH_2Cl_2	$Pd_2(dba)_3$	$P(o\text{-}MeC_6H_4)_3$	–50 to 0	5	<5
5	CH_2Cl_2	$Pd_2(dba)_3$	PPh_2Cy		5	48
6	CH_2Cl_2	$Pd_2(dba)_3$	$PPhCy_2$		5	22
7	CH_2Cl_2	$Pd_2(dba)_3$	dppf		5	36
8	CH_2Cl_2	$Pd(dba)_2$	PPh_3		5	55
9	CH_2Cl_2	$[Pd(allyl)Cl]_2$	PPh_3		5	51
10	CH_2Cl_2	$Pd(MeCN)_2Cl_2$	PPh_3	–50 to 0	5	<5
11	CH_2Cl_2	$Pd(OAc)_2$	PPh_3		5	<5
12	CH_2Cl_2	$Pd(PPh_3)_4$	–		5	57
13	CH_2Cl_2	$Pd(PPh_3)_4$	–		20	70
14	EtCN	$Pd(PPh_3)_4$	–	–20	20	70
15	EtOAc	$Pd(PPh_3)_4$	–		20	72 (62)

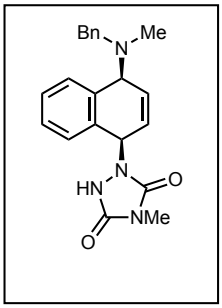
a) Determined by ^1H NMR analysis using nitromethane as the internal standard. Isolated yield shown in parenthesis.

3-2. Dearomative *syn*-1,4-diamination of naphthalene and benzene with amine

General procedure A for the dearomative *syn*-1,4-diamination of naphthalene with amines (Table 2)



MTAD (**15**, 56.7 mg, 0.50 mmol, 1.0 eq.) was combined with naphthalene (**16**, 128 mg, 1.0 mmol) and a stir bar in a test tube with a septum as the cap under nitrogen atmosphere. Ethyl acetate (5.0 mL, 0.1 M) was added to the test tube at rt, the contents were stirred until completely dissolved and then cooled to –50 ºC. The resulting pink solution was stirred under irradiation with LED lights at –50 ºC until the solution became colorless (approximately 6 h). After turning off the lights, to this solution at –50 ºC were added an amine (2.0 mmol, 2.0 eq.) and a solution of a Pd complex in THF (2.0 mL) [primary amines: $Pd_2(dba)_3$ (11.4 mg, 0.0125 mmol, 2.5 mol%) and dppf (16.6 mg, 0.03 mmol, 6.0 mol%); secondary amines: $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol, 5.0 mol%)], and the resulting mixture was stirred at –20 ºC for 20 h. The reaction was then warmed up to rt, concentrated under reduced pressure, and purified by flash column chromatography (SiO_2, CH_2Cl_2:MeOH mixture).



Synthesis of (±)-28a (Table 2): Following the general procedure A, the title compound was isolated by flash chromatography (SiO_2, CH_2Cl_2 to CH_2Cl_2:MeOH = 50:1) as a white solid (112.3 mg, 62%).

R_f = 0.43 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

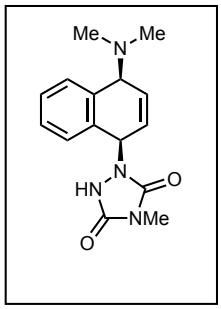
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.41 (dd, *J* = 7.1, 1.8 Hz, 1H), 7.36-7.27 (m, 7H), 6.62 (ddd, *J* = 10.0, 4.4, 0.8 Hz, 1H), 6.21 (ddd, *J* = 10.0, 4.4, 0.8 Hz, 1H), 5.89 (t, *J* = 3.8 Hz 1H), 4.07 (t, *J* = 3.8 Hz 1H), 3.80 (d, *J* = 12.9, 1H), 3.73 (d, *J* = 12.9 Hz, 1H), 3.09 (s, 3H), 2.20 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 153.9, 153.4, 137.7, 137.0, 133.2, 132.2, 130.2, 129.3, 128.7, 128.48, 128.47, 128.3, 127.7, 127.5, 59.5, 59.2, 51.9, 38.6, 25.3.

HRMS: (ESI-TOF, m/z) calcd. For $C_{21}H_{23}N_4O_2$ $[M+H]^+$ calc.: 363.1816; found: 363.1834.

IR: (ATR, neat, cm^{-1}): 3466 (w), 3029 (w), 2842 (w), 1763 (m), 1691 (s), 1476 (m), 1453 (m), 1019 (m), 753 (m), 700 (m).

m.p.: 135–136 ºC.



Synthesis of (±)-28b (Table 2): Following the general procedure A (except that dichloromethane was used in replace of ethyl acetate), the title compound was isolated by flash chromatography (SiO_2, EtOAc then CH_2Cl_2:MeOH = 19:1 to 4:1) as a yellow solid (102.5 mg, 72%).

R_f = 0.11 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

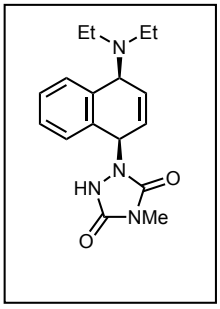
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.4 Hz, 1H), 7.34 (td, *J* = 7.4, 1.4 Hz, 1H), 7.30 (td, *J* = 7.4, 1.4 Hz, 1H), 7.25 (t, *J* = 9.6, 1H), 6.62 (dd, J = 9.5, 5.5 Hz, 1H), 6.37 (dd, *J* = 9.5, 6.0 Hz, 1H), 5.92 (d, *J* = 6.0 Hz, 1H), 3.71 (d, *J* = 5.5 Hz, 1H), 3.02 (s, 3H), 2.46 (s, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 153.1, 152.6, 136.1, 135.2, 134.5, 130.5, 130.0, 129.8, 129.1, 127.8, 62.1, 51.2, 43.0, 25.1.

HRMS: (ESI-TOF, m/z) calcd. For $C_{15}H_{19}N_4O_2$ $[M+H]^+$ calc.: 287.1503; found: 287.1512.

IR: (ATR, neat, cm^{-1}): 3397 (w), 3054 (w), 1686 (s), 1602 (s), 1464 (s), 1392 (m), 1278 (m), 1149 (m), 1017 (s), 914 (s), 756 (s), 634 (m), 537 (m).

m.p.: 49–51 ºC decomposed.



Synthesis of (±)-28c (Table 2): Following the general procedure A (except that dichloromethane was used in place of ethyl acetate), the title compound was isolated by flash chromatography (SiO_2, CH_2Cl_2:MeOH (sat. with NH_3) = 19:1 to 4:1) as a white solid (106.5 mg, 68%).

R_f = 0.21 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

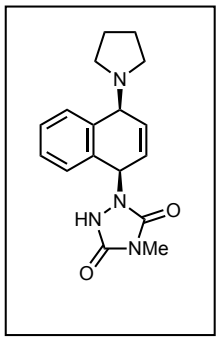
^{1}H NMR: 7.46 (d, *J* = 7.2 Hz, 1H), 7.34 (td, *J* = 7.3, 1.7 Hz, 1H), 7.30 (td, *J* = 7.5, 1.6 Hz, 1H), 7.27 (d, *J* = 7.3 Hz, 1H), 6.58 (dd, *J* = 9.6, 5.4 Hz, 1H), 6.39 (dd, *J* = 9.6, 5.8 Hz, 1H), 5.91 (d, *J* = 5.8, 1H), 4.14 (d, *J* = 5.4, 1H), 3.02 (s, 3H), 2.93-2.82 (m, 4H), 1.15 (t, *J* = 7.2 Hz, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 153.2 (Overlap of 2 peaks), 135.9, 135.8, 133.6, 130.6, 130.3, 129.8, 129.0, 127.7, 56.4, 51.1, 42.2, 25.1, 9.5.

HRMS: (ESI-TOF, m/z) calcd. For $C_{17}H_{23}N_4O_2$ $[M+H]^+$ calc.: 315.1816; found: 315.1820.

IR: (ATR, neat, cm^{-1}): 3412 (w), 2985 (w), 1694 (s), 1605 (s), 1463 (s), 1392 (m), 1280 (m), 758 (s).

m.p.: 75–76 ºC decomposed.



Synthesis of (±)-28d (Table 2): Following the general procedure A, the title compound was isolated by flash chromatography (SiO_2, EtOAc then CH_2Cl_2:MeOH = 19:1 to 4:1) as a yellow solid (118.9 mg, 76%).

R_f = 0.23 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

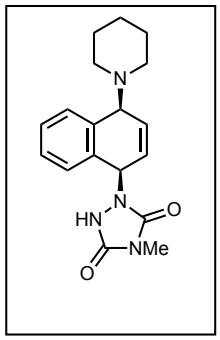
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.30 (td, *J* = 7.4, 1.6 Hz, 1H), 7.26 (td, *J* = 7.4, 1.6 Hz, 1H), 7.20 (dd, *J* = 7.4, 1.7 Hz, 1H), 6.55 (dd, *J* = 9.4, 5.7 Hz, 1H), 6.34 (dd, *J* = 9.4, 6.1 Hz, 1H), 5.88 (d, *J* = 6.0 Hz, 1H), 3.84 (dd, *J* = 5.9, 1.7 Hz, 1H), 2.94 (s, 3H), 2.89-2.86 (m, 2H), 2.65-2.62 (m, 2H), 1.93-1.85 (m, 4H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 152.8, 152.7, 136.2, 135.2, 134.1, 129.9, 129.6, 129.3, 129.0, 127.9, 60.1, 51.9, 50.8, 24.9, 22.8.

HRMS: (ESI-TOF, m/z) calcd. For $C_{17}H_{21}N_4O_2$ $[M+H]^+$ calc.: 313.1659; found: 313.1656

IR: (ATR, neat, cm^{-1}): 3406 (w), 2886 (w), 1683 (s), 1614 (s), 1459 (s), 1391 (m), 1275 (m), 1146 (m), 922 (m), 755 (s), 726 (s), 631 (m), 530 (m).

m.p.: 84–86 ºC.



Synthesis of (±)-28e (Table 2): Following the general procedure A, the title compound was isolated by flash chromatography (C_{18} reverse phase SiO_2, H_2O:MeOH = 9:1 to 1:1) as a yellow solid (146.1 mg, 90%).

R_f = 0.26 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

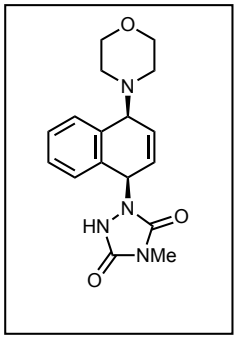
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.35 (td, *J* = 7.5, 1.4 Hz, 1H), 7.29 (td, *J* = 7.5, 1.4 Hz, 1H), 7.19 (d, *J* = 7.4 Hz, 1H), 6.67 (dd, *J* = 9.5, 5.7 Hz, 1H), 6.40 (dd, *J* = 9.5, 6.2 Hz, 1H), 5.94 (d, *J* = 6.2 Hz, 1H), 3.73 (d, *J* = 5.7 Hz, 1H), 3.03 (s, 3H), 2.84 (br, 2H), 2.66 (br, 2H), 1.75 (p, *J* = 5.7 Hz, 4H), 1.54 (br, 2H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 152.7, 152.5, 135.8, 135.7, 135.0, 131.0, 130.2, 130.1, 129.1, 127.5, 61.6, 52.5, 50.9, 25.0, 24.9, 23.9.

HRMS: (ESI-TOF, m/z) calcd. For $C_{18}H_{23}N_4O_2$ $[M+H]^+$ calc.: 327.1816; found: 327.1834.

IR: (ATR, neat, cm^{-1}): 3401 (w), 2942 (w), 1688 (m), 1598 (s), 1461 (m), 1390 (m), 760 (m).

m.p.: 85–87 ºC decomposed.



Synthesis of (±)-28f (Table 2): Following the general procedure A, the title compound was isolated by flash chromatography (SiO_2, CH_2Cl_2:MeOH = 19:1 to 9:1) as a white solid (80.3 mg, 49%).

R_f = 0.35 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

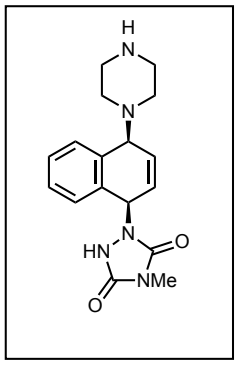
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.36 (td, *J* = 7.4, 1.5 Hz, 1H), 7.32 (td, *J* = 7.4, 1.5 Hz, 1H), 7.23 (dd, *J* = 7.6, 1.3 Hz, 1H), 6.66 (dd, *J* = 9.6, 5.5 Hz, 1H), 6.38 (dd, *J* = 9.6, 6.0 Hz, 1H), 5.94 (d, *J* = 6.0 Hz, 1H), 3.80-3.76 (m, 5H) 3.05 (s, 3H), 2.84 (br, 2H), 2.67 (dt, *J* = 10.7, 4.7 Hz, 2H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 152.8, 152.1, 135.4, 135.0, 134.7, 130.9, 130.0, 129.7, 129.2, 127.8, 66.3, 61.4, 51.8, 51.3, 25.1.

HRMS: (ESI-TOF, m/z) calcd. For $C_{17}H_{21}N_4O_3$ $[M+H]^+$ calc.: 329.1608; found: 329.1620.

IR: (ATR, neat, cm^{-1}): 3471 (w), 2853 (w), 1768 (w), 1699 (s), 1474 (m), 1115 (m), 758 (m).

m.p.: 122–124 ºC decomposed.



Synthesis of (±)-28h (Table 2): Following the general procedure A, the title compound was isolated by flash chromatography (C_{18} reverse phase SiO_2, H_2O:MeOH = 100:0 to 70:30) as a white solid (156.8 mg, 96%).

R_f = 0.36 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

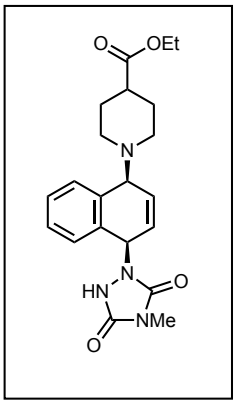
^{1}H NMR: (500 MHz, D_2O) δ 7.72 (d, *J* = 7.7 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.34 (t, *J* = 7.4 Hz, 1H), 7.09 (d, *J* = 7.7 Hz, 1H), 6.35 (d, *J* = 10.4 Hz, 1H), 6.10 (d, *J* = 10.4 Hz, 1H), 5.70 – 5.69 (m, 1H), 4.37 (br, 1H), 3.27 – 3.19 (m, 4H), 3.07 (s, 3H), 2.93 – 2.85 (m, 4H).

^{13}C NMR: (125 MHz, D_2O) δ 157.5, 154.2, 133.9, 133.7, 129.0, 128.7, 128.4, 128.2, 127.4, 126.7, 58.9, 50.5, 45.7, 43.8, 25.2.

HRMS: (ESI-TOF, m/z) calcd. For $C_{17}H_{22}N_5O_2$ $[M+H]^+$ calc.: 328.1768; found: 328.1765.

IR: (ATR, neat, cm^{-1}): 3456 (w), 3056 (w), 1704 (s), 1472 (m), 1438 (m), 1179 (m), 1120 (m), 755 (m), 722 (s), 695 (m), 541 (s).

m.p.: 145–147 ºC decomposed.



Synthesis of (±)-28g (Table 2): Following the general procedure A, the title compound was isolated by flash chromatography (SiO_2, CH_2Cl_2:EtOAc:MeOH (sat. with NH_3) = 5:4:1 to 9:0:1) as a white solid (142.0 mg, 71%).

R_f = 0.31 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 7.4, 0.9 Hz, 1H), 7.33 (td, *J* = 7.4, 1.5 Hz, 1H), 7.29 (td, *J* = 7.4, 1.5 Hz, 1H), 7.22 (dd, *J* = 7.4, 0.9 Hz,

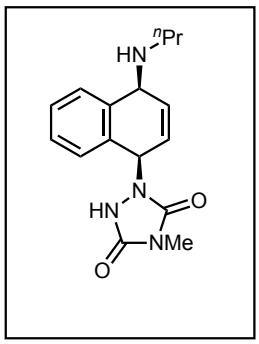
1H), 6.62 (dd, *J* = 9.6, 5.4 Hz, 1H), 6.33 (dd, *J* = 9.6, 5.9 Hz, 1H), 5.89 (d, *J* = 5.9 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.75 (d, *J* = 5.4 Hz, 1H), 3.02 – 3.00 (m, 4H), 2.86 (br, 1H), 2.65 (br, 1H), 2.47-2.44 (m, 4H), 2.01-1.89 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 174.1, 152.9, 152.4, 135.9, 135.0, 134.6, 130.8, 129.7, 129.4, 128.9, 127.7, 61.0, 60.6, 51.2, 50.4, 49.8, 39.5 (br), 27.1, 25.0, 14.3.

HRMS: (ESI-TOF, m/z) calcd. For $C_{21}H_{27}N_4O_4$ $[M+H]^+$ calc.: 399.2027; found: 399.2035.

IR: (ATR, neat, cm^{-1}): 3451 (w), 2947 (w), 1702 (s), 1627 (m), 1472 (m), 1192 (m), 1045 (w), 1021 (w), 757 (m).

m.p.: 90–94 ºC decomposed.



Synthesis of (±)-28k (Table 2): Following the general procedure A, the title compound was isolated by flash chromatography (SiO_2, EtOAc then CH_2Cl_2:MeOH = 19:1 to 4:1) as a white solid (123.1 mg, 82%).

Gram-scale synthesis of (±)-7i (Table 2): MTAD (1.0 g, 8.8 mmol, 1.0 eq.) and naphthalene (2.3 g, 17.7 mmol, 2.0 eq.) were placed in a 500 mL clear borosilicate glass bottle (see Picture S2) with a septum as the cap under nitrogen atmosphere. Ethyl acetate (100 mL, 0.088 M) was added to the bottle at rt, and the mixture was stirred until both MTAD and the naphthalene were completely dissolved. Then the resulting pink solution was stirred under irradiation with LED lights at –50 ºC until the solution became a white suspension (about 48 hours). Following this discoloration, a solution of $Pd_2(dba)_3$ (202 mg, 0.221 mmol, 2.5 mol%) and dppf (294 mg, 0.531 mmol, 6.0 mol%) in THF (50 mL) was added and the resulting mixture was stirred at –20 ºC for 20 h. The reaction was then warmed up to rt, concentrated under reduced pressure, and isolated by flash column chromatography (SiO_2, CH_2Cl_2:MeOH = 19:1 to 4:1) as a white solid (1.97 g, 74%).

R_f = 0.11 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

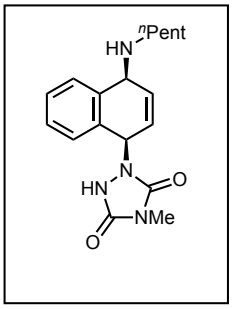
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.6 Hz, 1H), 7.33 (dt, *J* = 7.7, 4.5 Hz, 1H), 7.244-7.235 (m, 2H), 6.39-6.32 (m, 2H), 5.95 – 5.87 (m, 1H), 4.43 – 4.36 (m, 1H), 3.08 (s, 3H), 2.69-2.58 (m, 2H), 1.54-1.40 (m, 2H), 0.77 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 155.9, 152.9, 136.9, 134.1, 132.5, 129.77, 129.74, 129.5, 128.4, 127.8, 52.6, 49.6, 47.1, 25.4, 19.8, 11.6.

HRMS: (ESI-TOF, m/z) calcd. For $C_{16}H_{21}N_4O_2$ $[M+H]^+$ calc.: 301.1659; found: 301.1666.

IR: (ATR, neat, cm^{-1}): 3411 (w), 2967 (w), 1685 (s), 1614 (s), 1461 (s), 1390 (m), 1146 (m), 923 (m), 777 (m), 753 (s), 729 (s), 634 (m).

m.p.: 139–140 ºC.



Synthesis of (±)-28l (Table 2): Following the general procedure A, the title compound was isolated by flash chromatography (SiO_2, EtOAc then CH_2Cl_2:MeOH = 19:1 to 16:4) as a white solid (145.8 mg, 89%).

R_f = 0.37 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

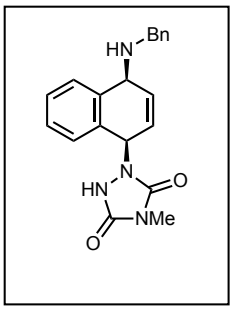
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.5 Hz, 1H), 7.33 – 7.30 (m, 1H), 7.24 - 7.21 (m, 2H), 6.34 (br, 2H), 5.91 – 5.87 (m, 1H), 4.42 – 4.38 (m, 1H), 3.07 (s, 3H), 2.71 - 2.54 (m, 2H), 1.57-1.46 (m, 2H), 1.20-1.12 (m, 4H), 0.82 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR: (125 MHz, CDCl3) δ 155.9, 152.9, 136.9, 134.2, 132.3, 129.8, 129.7, 129.4, 128.2, 127.7, 52.1, 49.6, 45.1, 29.1, 25.6, 25.3, 22.2, 14.0.

HRMS: (ESI-TOF, m/z) calcd. For $C_{18}H_{25}N_4O_2$ $[M+H]^+$ calc.: 329.1972; found: 329.1973.

IR: (ATR, neat, cm^{-1}): 3430 (w), 2957 (w), 1690 (s), 1623 (m), 1465 (m), 1390 (w), 1285 (w), 1146 (w) 755 (m).

m.p.: 144–145 ºC.



Synthesis of (±)-28m (Table 2): Following the general procedure A, the title compound was isolated by flash chromatography (SiO_2, CH_2Cl_2:MeOH (sat. with NH_3) = 98:2 to 90:10) as a white solid (102.4 mg, 59%).

R_f = 0.37 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.39 – 7.36 (m, 3H), 7.31 – 7.28 (m, 3H), 7.26 - 7.17 (m, 3H), 6.39 (dd, *J* = 9.5, 5.4 Hz, 1H), 6.33 (dd, *J* = 9.5, 5.7 Hz, 1H), 5.88 (d, *J* = 5.7

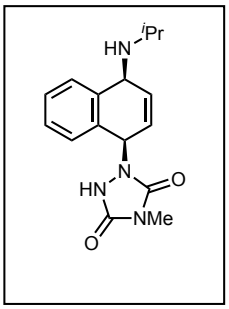
Hz, 1H), 4.38 (d, *J* = 5.4 Hz, 1H), 3.65 (d, *J* = 13.5 Hz, 1H), 3.61 (d, *J* = 13.5 Hz, 1H), 3.08 (s, 3 H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 154.3, 152.7, 135.8, 134.2, 134.0, 132.4, 130.1, 129.6, 129.5, 129.19, 129.18, 129.1, 128.6, 128.1, 52.3, 50.1, 49.8, 25.3.

HRMS: (ESI-TOF, m/z) calcd. For $C_{20}H_{21}N_4O_2$ $[M+H]^+$ calc.: 349.1659; found: 349.1664.

IR: (ATR, neat, cm^{-1}): 3417 (w), 3035 (w), 1690 (s), 1618 (s), 1467 (s), 1392 (w), 920 (w), 732 (m), 753 (m).

m.p.: 94–95 ºC.



Synthesis of (±)-28n (Table 2): Following the general procedure A, the title compound was isolated by flash chromatography (SiO_2, EtOAc then CH_2Cl_2:MeOH = 19:1 to 9:1) as a white solid (130.0 mg, 87%).

R_f = 0.23 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

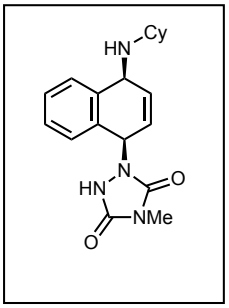
^{1}H NMR: (500 MHz, $CDCl_3$) 7.45 (d, *J* = 7.5 Hz, 1H), 7.37 - 7.28 (m, 2H), 7.25 - 7.22 (m, 1H), 6.52 - 6.46 (m, 2H), 5.97 (d, *J* = 5.5 Hz, 1H), 4.59 (d, *J* = 5.0 Hz, 1H), 3.12 – 2.99 (m, 4H), 1.14 – 1.13 (m, 3H), 0.81 (br, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$) 155.7, 152.9, 137.4, 134.3, 132.3, 129.9, 129.8, 128.6, 128.0, 50.0, 49.6, 46.8, 25.4, 19.4, 18.2.

HRMS: (ESI-TOF, m/z) calcd. For $C_{16}H_{21}N_4O_2$ $[M+H]^+$ calc.: 301.1659; found: 301.1663.

IR: (ATR, neat, cm^{-1}): 3407 (w), 2977 (w), 2423 (s), 1688 (m), 1612 (s), 1455 (s), 1388 (m), 1143 (m), 945 (w), 751 (s), 520 (m).

m.p.: 120–125 ºC.



Synthesis of (±)-28o (Table 2): Following the general procedure A, the title compound was isolated by flash chromatography (SiO_2, CH_2Cl_2:MeOH (sat. with NH_3) = 19:1 to 17:3) as a pale yellow solid (114.4 mg, 67%).

R_f = 0.39 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.5 Hz, 1H), 7.35 – 7.25 (m,

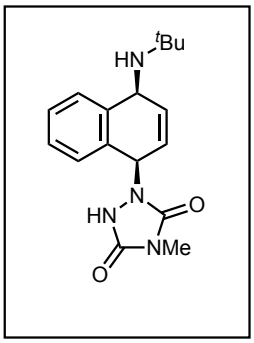
3H), 6.40 (br, 2H), 5.95 – 5.94 (m, 1H), 4.63 – 4.62 (m, 1H), 3.07 (s, 3H), 2.76 – 2.72 (m, 1H), 1.90 – 1.54 (m, 5H), 1.22 – 0.81 (m, 5H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 155.7, 152.9, 137.4, 134.3, 132.4, 129.8 (2 overlapping peaks as determined by HSQC and HMBC), 129.5, 128.4, 127.9, 54.2, 49.6, 49.2, 29.3, 28.7, 25.4, 25.3, 24.9.

HRMS: (ESI-TOF, m/z) calcd. For $C_{19}H_{25}N_4O_2$ $[M+H]^+$ calc.: 341.1972; found: 341.1984.

IR: (ATR, neat, cm^{-1}): 3268 (w), 2926 (m), 2853 (m), 1682 (m), 1585 (s), 1450 (m), 1389 (m), 1286 (m), 1150 (w), 912 (m), 754 (m), 728 (s), 640 (m).

m.p.: 141–142 ºC.



Synthesis of (±)-28p (Table 2): Following the general procedure A, the title compound was isolated by flash chromatography (SiO_2, CH_2Cl_2:MeOH (sat. with NH_3) = 19:1 to 17:3) as a white solid (114.4 mg, 73%).

R_f = 0.27 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

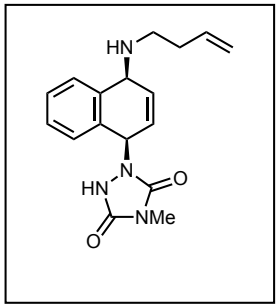
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.44 – 7.42 (m, 1H), 7.35 – 7.28 (m, 3H), 7.06 (br, 2H), 6.54 (dd, *J* = 9.6, 5.6 Hz, 1H), 6.29 (dd, *J* = 9.6, 6.1 Hz, 1H), 5.91 (d, *J* = 6.1 Hz, 1H), 4.54 (d, *J* = 5.6 Hz, 1H), 3.03 (s, 3H), 1.22 (s, 9H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 153.1, 152.9, 138.1, 135.7, 134.7, 129.6, 129.4, 128.9, 128.70, 128.65, 54.4, 50.5, 50.1, 29.3, 25.1.

HRMS: (ESI-TOF, m/z) calcd. For $C_{17}H_{23}N_4O_2$ $[M+H]^+$ calc.: 315.1816; found: 315.1820.

IR: (ATR, neat, cm^{-1}): 3412 (w), 2974 (w), 1684 (m), 1617 (s), 1465 (m), 792 (w), 754 (m).

m.p.: 142–143 ºC.



Synthesis of (±)-28q (Table 2): General procedure A with the following modifications was used to synthesize the title compound: during the setup 3-butenylamine hydrochloride was dissolved in 2.5 mL of degassed CH_2Cl_2 and added as the amine source and then 2.0 eq. (1.0

mmol) of triethylamine was added. This was followed by the addition of the palladium catalyst. **7o** was isolated by flash chromatography (SiO_2, CH_2Cl_2:EtOAc:MeOH = 5:4:1 to 9:0:1) as a pale yellow solid (101.2 mg, 65%).

R_f = 0.26 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

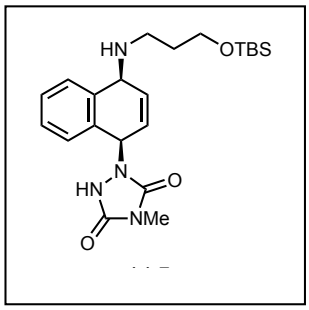
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.4 Hz, 1H), 7.34 (td, *J* = 7.4, 1.6 Hz, 1H), 7.28 (td, *J* = 7.3, 1.2 Hz, 1H), 7.25 (d, *J* = 7.3 Hz, 1H) 6.46 (dd, *J* = 9.5, 5.5 Hz, 1H), 6.36 (dd, *J* = 9.5, 5.9 Hz, 1H), 5.94 (d, *J* = 5.8 Hz, 1H), 5.64 (ddt, *J* = 17.1, 10.6, 6.8 Hz, 1H), 5.07 – 5.03 (m, 2H), 4.38 (d, *J* = 5.5 Hz, 1H), 3.07 (s, 3H), 2.84 – 2.73 (m, 2H), 2.34 – 2.21 (m, 2H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 154.4, 152.8, 135.9, 134.1, 133.7, 132.4, 130.4, 129.8, 129.7, 129.2, 128.2, 118.2, 53.0, 50.2, 45.1, 31.5, 25.3.

HRMS: (ESI-TOF, m/z) calcd. For $C_{17}H_{21}N_4O_2$ $[M+H]^+$ calc.: 313.1659; found: 313.1667.

IR: (ATR, neat, cm^{-1}): 3397 (w), 2969 (w), 1681 (m), 1592 (s), 1464 (s), 1391 (m), 1286 (w), 1146 (w), 923 (w), 774 (m), 755 (s), 641 (w).

m.p.: 70–72 ºC decomposed.



Synthesis of (±)-28r (Table 2): Following the general procedure A, the title compound was isolated by flash chromatography (SiO_2, EtOAc until most impurities had been removed and then switched to a gradient of CH_2Cl_2:MeOH = 19:1 to 9:1) as a white solid (143.0 mg, 66%).

R_f = 0.33 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

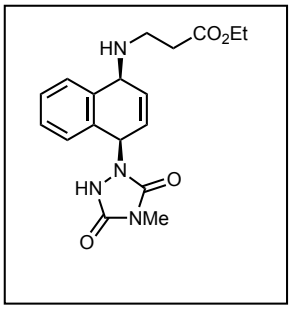
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.6 Hz, 1H), 7.33 (td, *J* = 7.6, 2.1 Hz, 1H), 7.28 – 7.24 (m, 2H), 6.43 (dd, *J* = 9.5, 5.5 Hz, 1H), 6.36 (dd, *J* = 9.5, 5.9 Hz, 1H), 5.92 (d, *J* = 5.9 Hz, 1H), 4.40 (d, *J* = 5.5 Hz, 1H), 3.50 – 3.43 (m, 2H), 3.06 (s, 3H), 2.84 (td, *J* = 10.7, 9.6, 5.9 Hz, 1H), 2.77 (td, *J* = 11.8, 10.7, 5.9 Hz, 1H), 1.62 – 1.57 (m, 2H), 0.83 (s, 9H), -0.01 (s, 3H), -0.03 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 155.3, 152.8, 136.7, 133.4, 133.3, 129.7, 129.64, 129.60, 129.4, 127.9, 60.6, 52.8, 49.8, 43.4, 29.4, 26.0, 25.3, 18.3, -5.3, -5.4.

HRMS: (ESI-TOF, m/z) calcd. For $C_{22}H_{35}N_4O_3Si$ $[M+H]^+$ calc.: 431.2473; found: 431.2475.

IR: (ATR, neat, cm^{-1}): 3456 (w), 2960 (w), 2861 (w), 1743 (m), 1694 (m), 1625 (s), 1460 (m), 1376 (m), 1217 (w), 835 (m), 780 (m), 755 (m).

m.p.: 83–85 ºC decomposed.



Synthesis of (±)-28s (Table 2): Following the general procedure A, the title compound was isolated by flash chromatography (SiO_2, CH_2Cl_2:EtOAc:MeOH = 5:4:1) as a white solid (151.3 mg, 84%).

R_f = 0.22 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.29 (br, 2H), 7.44 – 7.42 (m, 1H), 7.32 (td, *J* = 7.5, 1.5 Hz, 1H), 7.28 (td, *J* = 7.5, 1.5 Hz, 1H), 7.23 (dd, *J* = 7.5, 1.2 Hz, 1H), 6.51 (dd, *J* = 9.6, 5.5 Hz, 1H), 6.31 (dd, *J* = 9.6, 5.8 Hz, 1H), 5.90 (d, *J* = 5.8 Hz, 1H), 4.35 (d, *J* = 5.5 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.04 – 2.92 (m, 2H), 3.02 (s, 3H), 2.66 – 2.53 (m, 2H), 1.22 (t, *J* = 7.2 Hz, 3H).

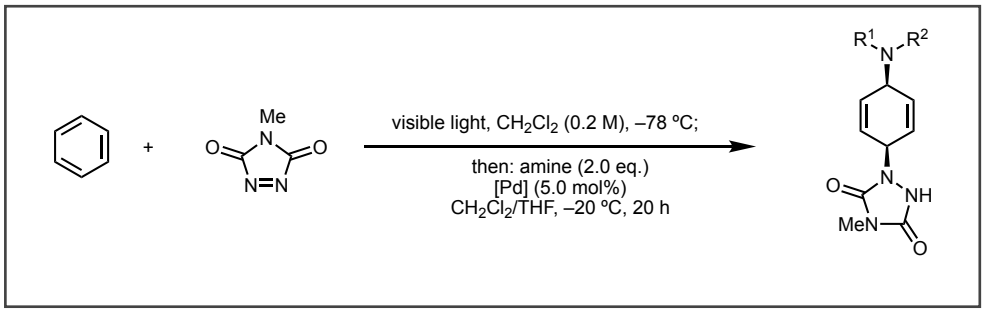
^{13}C NMR: (125 MHz, $CDCl_3$) δ 171.4, 153.9, 152.7, 135.4, 134.7, 131.5, 131.4, 129.7, 129.4, 129.2, 128.2, 61.1, 53.3, 50.4, 41.4, 32.1, 25.2, 14.2.

HRMS: (ESI-TOF, m/z) calcd. For $C_{18}H_{23}N_4O_4$ $[M+H]^+$ calc.: 359.1714; found: 359.1716.

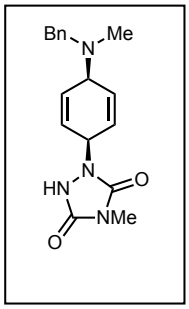
IR: (ATR, neat, cm^{-1}): 3432 (w), 2972 (w), 1760 (m), 1696 (m), 1622 (s), 1469 (m), 1265 (m), 1111 (s), 1030 (m), 784 (m), 757 (m).

m.p.: 101–103 ºC decomposed.

General procedure B for the dearomative *syn*-1,4-diamination of benzene with amines (Table 2)



MTAD (**4**, 113 mg, 1.0 mmol, 1.0 eq.) was placed in a test tube with a septum as the cap under nitrogen atmosphere. Dichloromethane (5.0 mL, 0.2 M) was added to the test tube at rt, and cooled to –78 ºC. Benzene (0.89 mL, 10 mmol, 10 eq.) was added dropwise at –78 ºC, and the resulting pink solution was stirred under irradiation with LED lights at –78 ºC until the solution became colorless (approximately 12 h). To this solution were added an amine (2.0 mmol, 2.0 eq.) and a solution of Pd complex in THF (2.0 mL) [primary amine: $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol, 2.5 mol%) and dppf (33.3 mg, 0.06 mmol, 6.0 mol%), pre-stirred at rt in THF for 30 min; secondary amine: $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol, 5.0 mol%)], and the resulting mixture was stirred at –20 ºC for 20 h. The reaction was then warmed up to rt, filtered through a pad of celite, and concentrated under reduced pressure. The product was purified by flash column chromatography (SiO_2, CH_2Cl_2:MeOH mixture).



Synthesis of 29a (Table 2): Following the general procedure B, the title compound was isolated by flash chromatography (SiO_2, CH_2Cl_2:MeOH (sat. with NH_3) = 5:1 to 3:1) as a white solid (149.4 mg, 48%).

R_f = 0.27 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

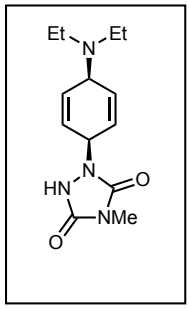
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.33 – 27 (m, 4H), 7.26 – 7.24 (m, 1H), 6.18 (ddd, *J* = 10.4, 3.2, 1.9 Hz, 2H), 5.77 (ddd, *J* = 10.4, 3.2, 1.9 Hz, 2H), 5.16 – 5.12 (m, 1H), 3.76 – 3.73 (m, 1H), 3.58 (s, 2H), 3.02 (s, 3H), 2.25 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 155.5, 154.5, 139.6, 132.0, 128.8, 128.4, 127.3, 125.1, 57.7, 56.0 50.9, 38.8, 25.2.

HRMS: (ESI-TOF, m/z) calcd. For $C_{17}H_{20}N_4NaO_2$ $[M+Na]^+$ calc.: 335.1478; found: 335.1486.

IR: (ATR, neat, cm^{-1}): 3100 (w), 2831 (w), 1694 (s), 1593 (s), 1488 (s), 1453 (s), 1371 (m), 1138 (m), 750 (s), 739 (s), 695 (s), 666 (m), 633 (m), 539 (m), 468 (m).

m.p.: 120–121 ºC.



Synthesis of 29b (Table 2): Following the general procedure B, the title compound was isolated by flash chromatography (SiO_2, CH_2Cl_2:MeOH = 10:1 to 5:1) as a white solid (144.2 mg, 55%).

R_f = 0.18 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

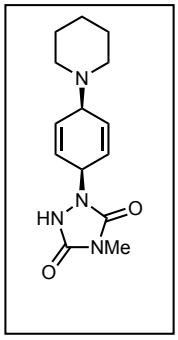
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.14 (br, 1H), 6.14 (ddd, *J* = 10.3, 3.2, 1.7 Hz, 2H), 5.84 (ddd, *J* = 10.3, 3.3, 1.7 Hz, 2H), 5.19 – 5.15 (m, 1H), 3.86 – 3.83 (m, 1H), 3.08 (s, 3H), 2.63 (q, *J* = 7.2 Hz, 4H), 1.09 (t, *J* = 7.2 Hz, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 155.1, 154.6, 132.4, 125.6, 53.1, 50.4, 44.5, 25.4, 13.6.

HRMS: (ESI-TOF, m/z) calcd. For $C_{13}H_{21}N_4O_2$ $[M+H]^+$ calc.: 265.1665; found: 265.1676.

IR: (ATR, neat, cm^{-1}): 1693 (m), 1584 (s), 1464 (s), 1455 (s), 1389 (w), 1370 (w), 1286 (w), 795 (w), 768 (m), 755 (m), 665 (w), 536 (w).

m.p.: 122–123 ºC.



Synthesis of 29c (Table 2): Following the general procedure B, the title compound was isolated by flash chromatography (SiO_2, CH_2Cl_2:MeOH = 10:1 to 5:1) as a white solid (156.7 mg, 57%).

R_f = 0.40 (CH_2Cl_2:MeOH = 5:1, UV, $KMnO_4$).

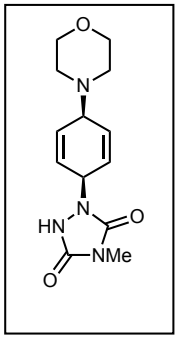
^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.22 (ddd, *J* = 10.4, 3.6, 1.6 Hz, 2H), 5.91 (ddd, *J* = 10.4, 2.7, 1.6 Hz, 2H), 5.22 – 5.19 (m, 1H), 3.58 – 3.56 (m, 1H), 3.08 (s, 3H), 2.64 – 2.62 (m, 4H), 1.67 – 1.62 (m, 4H), 1.49 – 1.45 (m, 2H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 155.5, 155.1, 130.8, 124.6, 57.9 50.50, 50.46, 25.4, 23.6, 22.7.

HRMS: (ESI-TOF, m/z) calcd. For $C_{14}H_{21}N_4O_2$ $[M+H]^+$ calc.: 277.1665; found: 277.1667.

IR: (ATR, neat, cm^{-1}): 1695 (s), 1586 (m), 1466 (m), 1454 (m), 1413 (w), 1389 (w), 1370 (w), 1032 (w), 800 (w), 748 (s), 692 (w), 664 (w), 624 (w), 593 (w).

m.p.: 100–101ºC.



Synthesis of 29d (Table 2): Following the general procedure B, the title compound was isolated by flash chromatography (SiO_2, CH_2Cl_2:MeOH = 15:1 to 9:1) as a white solid (172.6 mg, 62%).

R_f = 0.27 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

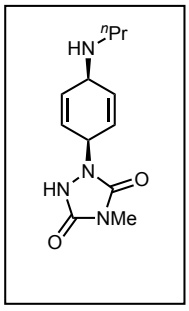
^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.15 (ddd, *J* = 10.3, 3.2, 1.7 Hz, 2H), 5.87 (ddd, *J* = 10.3, 3.4, 1.7 Hz, 2H), 5.19 – 5.15 (m, 1H), 3.72 – 3.70 (m, 4H), 3.64 – 3.62 (m, 1H), 3.08 (s, 3H), 2.63 – 2.61 (m, 4H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 155.2, 154.7, 131.7, 126.0, 67.4, 57.1, 50.6, 49.7, 25.4.

HRMS: (ESI-TOF, m/z) calcd. For $C_{13}H_{18}KN_4O_3$ $[M+K]^+$ calc.: 317.1010; found: 317.1009.

IR: (ATR, neat, cm^{-1}): 2950 (w), 2810 (w), 1690 (s), 1484 (m), 1403 (w), 1224 (w), 1112 (s), 1036 (m), 1016 (m), 941 (w), 886 (w), 771 (s), 731 (m), 637 (m), 551 (m), 461 (m).

m.p.: 148–149 ºC.



Synthesis of 29e (Table 2): Following the general procedure B, the title compound was isolated by flash chromatography (SiO_2, CH_2Cl_2:MeOH (sat. with NH_3) = 5:1 to 3:1) as a white solid (155.0 mg, 62%).

R_f = 0.27 (CH_2Cl_2:MeOH = 5:1, UV, $KMnO_4$).

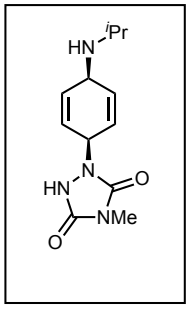
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.05 (br, 1H), 6.13 (ddd, *J* = 10.5, 3.7, 1.7 Hz, 2H), 6.03 (dd, *J* = 10.2, 2.7 Hz, 2H), 5.36 – 5.33 (m, 1H), 3.94 – 3.89 (m, 1H), 3.06 (s, 3H), 2.93 (t, *J* = 7.5 Hz, 2H), 1.76 (tq, *J* = 7.5, 7.4 Hz, 2H), 1.00 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 156.4, 152.8, 131.8, 124.3, 49.7, 47.4, 46.4, 25.4, 20.7, 11.5.

HRMS: (ESI-TOF, m/z) calcd. For $C_{12}H_{19}N_4O_2$ $[M+H]^+$ calc.: 251.1503; found: 251.1497.

IR: (ATR, neat, cm^{-1}): 2968 (w), 1698 (s), 1597 (s), 1462 (m), 1406 (w), 1375 (m), 1283 (w), 1155 (w), 1022 (w), 850 (w), 781 (s), 758 (s), 693 (w), 640 (m), 562 (w), 479 (m).

m.p.: 100–101 ºC.



Synthesis of 29f (Table 2): Following the general procedure B, the title compound was isolated by flash chromatography (SiO_2, CH_2Cl_2:MeOH = 9:1 to 5:1) as a white solid (180.0 mg, 72%).

R_f = 0.27 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

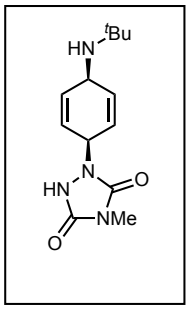
^{1}H NMR: (500 MHz, $CDCl_3$) δ 9.75 (br, 2H), 6.23 (dd, *J* = 9.8, 4.6 Hz, 2H), 6.18 (dd, *J* = 9.8, 4.8 Hz, 2H), 5.36 (td, *J* = 4.8, 2.8 Hz, 1H), 4.06 (td, *J* = 4.6, 2.8 Hz, 1H), 3.26 (hept, *J* = 6.5 Hz, 1H) , 3.04 (s, 3H), 1.22 (d, *J* = 6.5 Hz, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 156.2, 153.1, 133.2, 126.4, 46.9, 45.9, 45.6, 25.4, 19.8.

HRMS: (ESI-TOF, m/z) calcd. For $C_{12}H_{19}N_4O_2$ $[M+H]^+$ calc.: 251.1503; found: 251.1513.

IR: (ATR, neat, cm^{-1}): 3242 (w), 2850 (w), 1677 (m), 1599 (s), 1473 (w), 1396 (w), 1376 (w), 1148 (w), 799 (w), 780 (m), 759 (w), 710 (w), 691 (w), 639 (m), 572 (w), 536 (m).

m.p.: 129–130ºC.



Synthesis of 29g (Table 2): Following the general procedure B, the title compound was isolated by flash chromatography (SiO_2, CH_2Cl_2:MeOH = 9:1 to 5:1) as a white solid (131.0 mg, 50%).

R_f = 0.27 (CH_2Cl_2:MeOH = 5:1, $KMnO_4$).

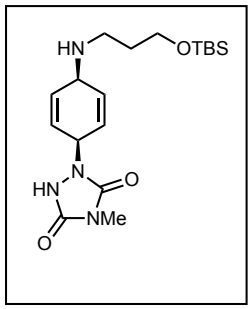
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.12 (br, 2H), 6.15 (ddd, *J* = 10.3, 3.6, 1.6 Hz, 2H), 5.88 (ddd, *J* = 10.3, 3.6, 1.4 Hz, 2H), 5.23 (dtt, *J* = 5.4, 3.6, 1.6 Hz, 1H), 3.97 – 3.91 (m, 1H), 3.06 (s, 3H), 1.30 (s, 9H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 155.4, 153.8, 130.8, 127.4, 54.1, 47.6, 45.5, 28.8, 25.3.

HRMS: (ESI-TOF, m/z) calcd. For $C_{13}H_{20}N_4NaO_2$ $[M+Na]^+$ calc.: 287.1478; found: 287.1466.

IR: (ATR, neat, cm^{-1}): 3320 (w), 2974 (w, br), 1692 (s), 1464 (m), 1393 (w), 1234 (w), 1005 (w), 828 (m), 764 (m), 739 (m), 623 (w), 491 (m).

m.p.: 153–155 ºC.



Synthesis of 29h (Table 2): Following the general procedure B, the title compound was isolated by flash chromatography (SiO_2, CH_2Cl_2:MeOH (sat. with NH_3) = 20:1 to 10:1) as a white solid (202.9 mg, 53%).

R_f = 0.54 (CH_2Cl_2:MeOH = 5:1, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.54 (br, 2H), 6.20 (dd, *J* = 9.8, 4.4 Hz, 2H), 6.03 (dd, *J* = 9.8, 4.4 Hz, 2H), 5.29 (dt, *J* = 4.5, 4.4 Hz, 1H), 3.86 (dt, *J* = 4.5, 4.4 Hz, 1H), 3.66 (t, *J* = 6.0 Hz, 2H), 3.05 (s, 3H), 2.92 (t, *J* = 6.8 Hz, 2H), 1.78 (tt, *J* = 6.0, 6.8 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 155.8, 153.6, 130.4, 128.4, 60.7, 49.1, 47.3, 43.5, 30.8, 26.0, 25.3, 18.3, –5.3.

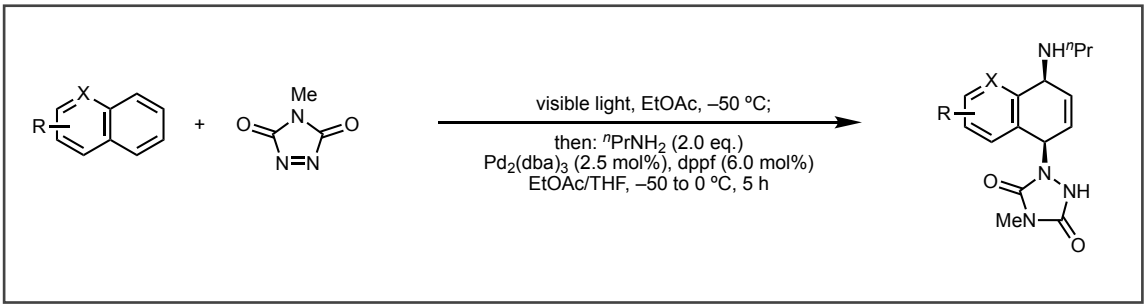
HRMS: (ESI-TOF, m/z) calcd. For $C_{18}H_{33}N_4O_3Si$ $[M+H]^+$ calc.: 381.2316; found: 381.2333.

IR: (ATR, neat, cm^{-1}): 2928 (w), 2856 (w), 1683 (w), 1591 (s), 1575 (s), 1500 (m), 1458 (m), 1373 (m), 1252 (w), 1095 (s), 833 (s), 773 (s), 751 (s), 689 (m), 665 (s), 634 (m), 508 (w).

m.p.: 143–146 ºC.

3-3. Dearomative *syn*-1,4-diamination of arenes with *n*-propylamine

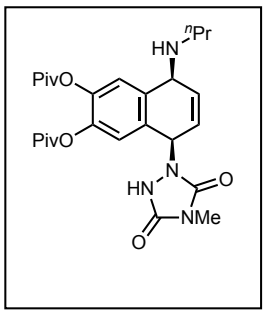
General procedure C for the dearomative *syn*-1,4-diamination of naphthalene derivatives with *n*-propylamine (Table 4)



For solid arene: MTAD (**15**, 113 mg, 1.0 mmol, 1.0 eq.) and arene (2.0 mmol, 1.0 eq.) were placed in a test tube with a septum as the cap under nitrogen atmosphere. Ethyl acetate (10.0 mL, 0.1 M) was added to the test tube at rt, and the mixture was stirred until both MTAD and the naphthalene were completely dissolved.

For liquid arene: MTAD (**15**, 113 mg, 1.0 mmol, 1.0 eq.) was dissolved in ethyl acetate (8.0 mL) at rt under nitrogen atmosphere. Then a solution of arene (2.0 mmol, 1.0 eq.) in ethyl acetate (2.0 mL) was added.

The resulting pink solution was stirred under irradiation with LED lights at –50 ºC until the solution became white suspension or colorless solution. To this solution were added an amine (2.0 mmol, 2.0 eq.) and a solution of $Pd_2(dba)_3$ (28.8 mg, 0.025 mmol, 2.5 mol%) and dppf (33.2 mg, 0.060 mmol, 6.0 mol%) in THF (2.0 mL, pre-stirred at rt in THF for 30 min) and the resulting mixture was slowly warmed up from –50 to 0 ºC over 5 h. The reaction was then filtered through a pad of celite, and concentrated under reduced pressure. The product was purified by flash column chromatography (SiO_2, CH_2Cl_2:MeOH mixture).



Synthesis of (±)-30 (Table 3): The reaction was conducted following the general procedure C, except the substitution step was done by stirring the mixture at –20 ºC for 20 h. The title compound was isolated by flash chromatography (SiO_2, CH_2Cl_2:MeOH = 30:1 to 15:1) as a light-red solid (257.7 mg, 53%).

R_f = 0.34 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

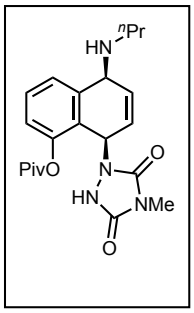
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.28 (s, 1H), 7.26 (s, 1H), 7.11 (br, 1H), 6.41 (dd, *J* = 9.4, 5.6 Hz, 1H), 6.34 (dd, *J* = 94, 5.7 Hz, 1H), 5.91 (d, *J* = 5.7 Hz, 1H), 4.35 (d, *J* = 5.6 Hz, 1H), 3.05 (s, 3H), 2.71 – 2.61 (m, 2H), 1.52 – 1.45 (m, 2H), 1.32 (s, 18H), 0.82 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 175.7, 175.4, 155.7, 152.8, 143.3, 142.0, 135.1, 133.3, 130.5, 128.6, 124.9, 124.7, 52.0, 49.1, 47.2, 39.3, 39.2, 27.31, 27.25, 25.3, 19.8, 11.4.

HRMS: (ESI-TOF, m/z) calcd. For $C_{26}H_{37}N_4O_6$ $[M+H]^+$ calc.: 501.2729; found: 501.2713.

IR: (ATR, neat, cm^{-1}): 2973 (w), 1703 (m), 1622 (s), 1479 (w), 1458 (m), 1387 (w), 1262 (w), 1114 (s), 1093 (s), 1029 (w), 782 (m), 757 (w), 631 (w).

m.p.: 143–144 ºC (recrystallized from CH_2Cl_2/diethyl ether).



Synthesis of (±)-31 (Table 3): The reaction was conducted following the general procedure C, except the reaction was run in dichloromethane (10 mL, 0.1 M) with 10 mol% of Pd_2dba_3 and 12 mol% dppf. The title compound was isolated as a mixture of **31** and **31'** by flash chromatography (SiO_2, CH_2Cl_2:MeOH = 15:1 to 9:1) as a light-yellow solid (174.3 mg, 44%). The isomers were further separated by careful flash chromatography (SiO_2, CH_2Cl_2:MeOH = 15:1 to 9:1).

R_f = 0.34 (CH_2Cl_2:MeOH = 5:1, UV, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 8.0, 7.7 Hz, 1H), 7.19 (d, *J* = 7.7 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.40 – 6.34 (m, 2H), 5.98 (d, *J* = 5.4 Hz, 1H), 4.42 (d, *J* = 5.0 Hz, 1H), 3.05 (s, 3H), 2.68 – 2.65 (m, 2H), 1.56 – 1.47 (m, 2H), 1.43 (s, 9H), 0.81 (t, *J* = 7.4 Hz, 3H).

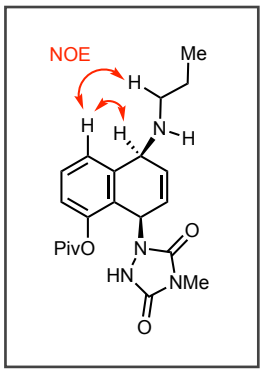
^{13}C NMR: (125 MHz, $CDCl_3$) δ 177.5, 155.1, 152.3, 149.4, 136.0, 133.3, 128.8, 128.5, 128.3, 127.0, 123.4, 52.5, 47.6, 44.4, 39.6, 27.3, 25.2, 20.4, 11.6.

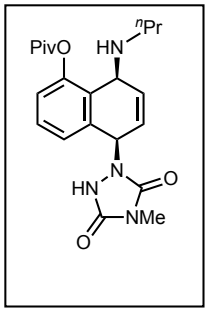
HRMS: (ESI-TOF, m/z) calcd. For $C_{21}H_{29}N_4O_4$ $[M+H]^+$ calc.: 401.2189; found: 401.2180.

IR: (ATR, neat, cm^{-1}): 2965 (w), 2341 (w), 1752 (w), 1703 (m), 1623 (s), 1456 (m), 1390 (w), 1236 (w), 1100 (s), 980 (w), 871 (w), 785 (w), 758 (w), 746 (m), 635 (w).

m.p.: 181–182 ºC.

Observed NOE correlation:





(±)-31'

R_f = 0.53 (CH_2Cl_2:MeOH = 5:1, UV, $KMnO_4$).

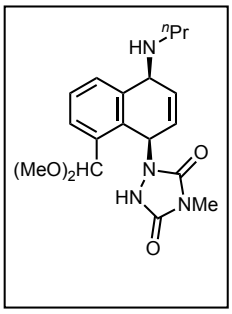
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 2H), 7.02 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.53 (dd, *J* = 9.4, 5.7 Hz, 1H), 6.34 (dd, *J* = 9.4, 6.0 Hz, 1H), 5.99 (d, *J* = 6.0 Hz, 1H), 4.40 (d, *J* = 5.7 Hz, 1H), 3.03 (s, 3H), 2.81 – 2.76 (m, 1H), 2.65 – 2.59 (m, 1H), 1.60 – 1.49 (m, 2H), 1.41 (s, 9H), 0.89 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 177.1, 153.6, 152.6, 148.6, 137.6, 131.6, 131.1, 130.2, 128.0, 127.5, 122.2, 50.2, 48.7, 47.5, 39.5, 27.3, 25.2, 21.5, 11.8.

HRMS: (ESI-TOF, m/z) calcd. For $C_{21}H_{29}N_4O_4$ $[M+H]^+$ calc.: 401.2189; found: 401.2182.

IR: (ATR, neat, cm^{-1}): 2963 (w), 2320 (w), 1700 (m), 1617 (m), 1468 (m), 1446 (m), 1386 (w), 1279 (w), 1233 (w), 1104 (s), 1027 (w), 950 (w), 784 (s), 754 (s), 635 (w).

m.p.: 145–146 ºC.



Synthesis of (±)-32 (Table 3): The reaction was conducted following the general procedure C, except the reaction in dichloromethane (10 mL, 0.1 M). The title compound was isolated as a mixture of **32** and **32'** by flash chromatography (SiO_2, CH_2Cl_2:MeOH = 15:1 to 9:1) as a light-yellow solid (179.8 mg, 48%). The isomers were further separated by careful flash chromatography (SiO_2, CH_2Cl_2:MeOH = 9:1 to 5:1).

R_f = 0.45 (CH_2Cl_2:MeOH = 5:1, UV, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.5 Hz, 1H), 7.32 (dd, *J* = 7.6, 7.5 Hz, 1H), 7.27 – 7.25 (m, 1H), 6.35 – 6.32 (m, 2H), 6.29 – 6.27 (m, 1H), 5.76 (s, 1H), 4.44 – 4.42 (m, 1H), 3.42 (s, 3H), 3.39 (s, 3H), 3.10 (s, 3H), 2.68 – 2.56 (m, 2H), 1.49 – 1.44 (m, 2H), 0.77 (t, *J* = 7.5 Hz, 3H).

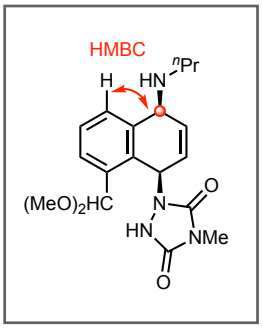
^{13}C NMR: (125 MHz, $CDCl_3$) δ 155.4, 152.2, 138.1, 134.2, 133.8, 133.7, 130.2, 128.3, 127.9, 127.7, 100.9, 55.7, 53.8, 53.3, 47.5, 45.4, 25.4, 20.2, 11.6.

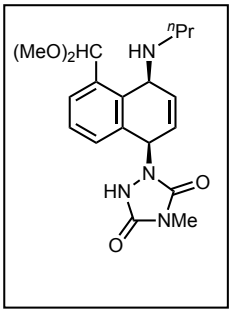
HRMS: (ESI-TOF, m/z) calcd. For $C_{19}H_{27}N_4O_4$ $[M+H]^+$ calc.: 375.2032; found: 375.2024.

IR: (ATR, neat, cm^{-1}): 3491 (w), 2958 (w), 1681 (m), 1615 (s), 1571 (m), 1462 (w), 1444 (w), 1103 (w), 1026 (s), 991 (w), 867 (w), 784 (m), 756 (m), 749 (m), 670 (w), 563 (w), 525 (w).

m.p.: 192–193 ºC.

Observed HMBC correlation:





(±)-32'

R_f = 0.55 (CH_2Cl_2:MeOH = 5:1, UV, $KMnO_4$).

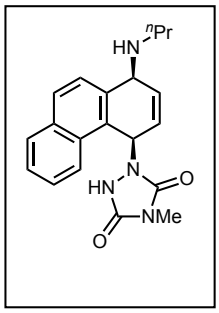
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.51 – 7.48 (m, 1H), 7.37 – 7.32 (m, 2H), 6.55 (dd, *J* = 9.5, 5.8 Hz, 1H), 6.44 (dd, *J* = 9.5, 6.1 Hz, 1H), 5.99 (d, *J* = 6.1 Hz, 1H), 5.28 (s, 1H), 4.96 (d, *J* = 5.8 Hz, 1H), 3.55 (s, 3H), 3.31 (s, 3H), 2.99 (s, 3H), 2.98 – 2.94 (m, 1H), 2.76 (ddd, *J* = 11.6, 8.3, 6.6 Hz, 1H), 1.875 – 1.66 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 153.3, 152.8, 137.3, 135.5, 135.4, 132.2, 131.2, 130.7, 128.8, 128.4, 106.7, 56.5, 54.1, 50.8, 49.1, 48.7, 25.0, 22.0, 11.8.

HRMS: (ESI-TOF, m/z) calcd. For $C_{19}H_{27}N_4O_4$ $[M+H]^+$ calc.: 375.2032; found: 375.2024.

IR: (ATR, neat, cm^{-1}): 3442 (w), 2938 (w), 2226 (w), 1684 (m), 1618 (s), 1459 (m), 1389 (w), 1353 (w), 1192 (w), 1112 (w), 1044 (m), 1031 (w), 998 (w), 912 (w), 895 (w), 780 (m), 773 (m), 759 (w), 723 (s), 637 (w).

m.p.: 146–147 ºC.



Synthesis of (±)-33 (Table 3): Following the general procedure C, the title compound was isolated as a mixture of **33** and **33'** by flash chromatography (SiO_2, CH_2Cl_2:MeOH = 15:1 to 9:1) as a light-yellow solid (199.3 mg, 57%). The isomers were further separated by careful flash chromatography (SiO_2, CH_2Cl_2:MeOH = 15:1 to 9:1).

$\mathbf{R_f}$ = 0.54 (CH_2Cl_2:MeOH = 5: 1, UV, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.64 – 7.61 (m, 1H), 7.57 – 7.54 (m, 2H), 6.77 (dd, *J* = 9.5, 5.7 Hz, 1H), 6.47 (dd, *J* = 9.5, 5.8 Hz, 1H), 6.08 (d, *J* = 5.8 Hz, 1H), 5.18 (d, *J* = 5.7 Hz, 1H), 3.03 (s, 3H), 2.95 – 2.88 (m, 1H), 2.84 – 2.77 (m, 2H), 1.69 – 1.55 (m, 2H), 0.80 (t, *J* = 6.7 Hz, 3H).

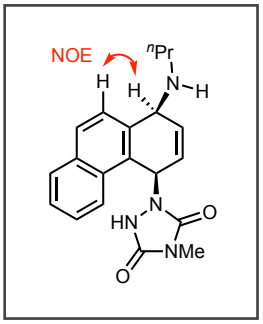
^{13}C NMR: (125 MHz, $CDCl_3$) δ 153.9, 152.8, 134.2, 133.3, 131.8, 131.3, 130.9, 130.6, 130.0, 129.3, 127.5, 127.0, 126.6, 121.9, 51.1, 48.8, 48.1, 25.3, 21.4, 11.7.

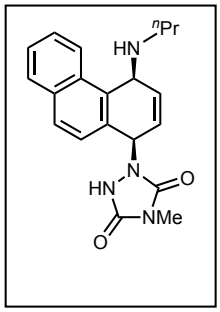
HRMS: (ESI-TOF, m/z) calcd. For $C_{20}H_{23}N_4O_2$ $[M+H]^+$ calc.: 351.1821; found: 351.1833.

IR: (ATR, neat, cm^{-1}): 3052 (w), 2965 (w), 1692 (m), 1616 (s), 1461 (m), 1387 (w), 1283 (w), 1197 (w), 1092 (w), 802 (w), 782 (s), 757 (m), 737 (w), 710 (w), 655 (w), 629 (m), 607 (w), 491 (w).

m.p.: 128–129 ºC.

Observed NOE correlations:





(±)-33'

R_f = 0.45 (CH_2Cl_2:MeOH = 5:1, UV, $KMnO_4$).

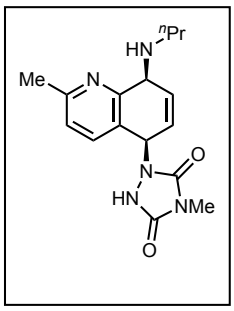
^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.51 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.63 (ddd, *J* = 8.4, 6.8, 1.3 Hz, 1H), 7.51 (dd, *J* = 8.2, 6.8 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 6.51 (d, *J* = 5.8 Hz, 1H), 6.27 (br, 1H), 6.08 (br, 1H), 4.49 (d, *J* = 5.4 Hz, 1H), 3.10 (s, 3H), 2.58 (br, 1H), 2.47 (br, 1H), 1.41 – 1.17 (m, 2H), 0.45 (br, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 155.9, 152.1, 134.6, 133.6, 133.1, 131.0, 130.7, 128.6, 128.5, 127.8, 127.3, 127.0, 126.5, 124.3, 53.2, 47.2, 45.6, 25.4, 19.6, 11.1.

HRMS: (ESI-TOF, m/z) calcd. For $C_{20}H_{23}N_4O_2$ $[M+H]^+$ calc.: 351.1821; found: 351.1833.

IR: (ATR, neat, cm^{-1}): 3412 (w), 2968 (w), 1686 (w), 1622 (s), 1573 (w), 1470 (w), 1373 (w), 1141 (w), 1025 (w), 819 (m), 783 (m), 754 (m), 655 (w), 634 (w), 618 (w), 574 (w).

m.p.: 168–169 ºC.



Synthesis of (±)-34 (Table 3): Following the general procedure C, the title compound was isolated as a mixture of **34** and **34'** by flash chromatography (SiO_2, CH_2Cl_2:MeOH = 15:1 to 9:1) as a light-yellow solid (240.1 mg, 76%). The isomers were further separated by careful flash chromatography (SiO_2, CH_2Cl_2:MeOH = 9:1 to 5:1).

R_f = 0.46 (CH_2Cl_2:MeOH = 5:1, UV, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.9 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 6.51 (dd, *J* = 9.6, 5.4 Hz, 1H), 6.28 (dd, *J* = 9.6, 5.7 Hz, 1H), 5.95 (d, *J* = 5.7 Hz, 1H), 4.42 (d, *J* = 5.4 Hz, 1H), 3.04 (s, 4H), 2.81 (t, *J* = 7.8 Hz, 2H), 2.55 (s, 4H), 1.73 – 1.66 (m, 1H), 1.57 – 1.50 (m, 1H), 0.91 (t, *J* = 7.4 Hz, 3H).

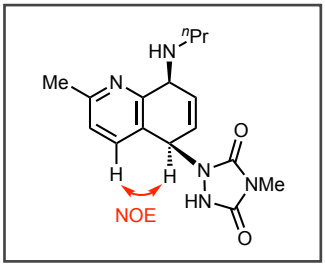
^{13}C NMR: (125 MHz, $CDCl_3$) δ 158.3, 154.8, 153.1, 152.9, 137.6, 130.9, 130.6, 128.5, 124.0, 54.9, 49.9, 48.1, 25.3, 24.4, 21.0, 11.7.

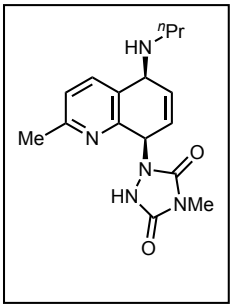
HRMS: (ESI-TOF, m/z) calcd. For $C_{16}H_{22}N_5O_2$ $[M+H]^+$ calc.: 316.1774; found: 316.1779.

IR: (ATR, neat, cm^{-1}): 2890 (w), 1694 (m), 1615 (m), 1589 (s), 1574 (m), 1453 (s), 1408 (w), 1381 (m), 1372 (m), 1300 (w), 1283 (w), 1142 (w), 802 (m), 777 (s), 756 (s), 643 (m), 602 (w), 561 (w).

m.p.: 119–120 ºC.

Observed NOE correlation:





(±)-34'

R_f = 0.32 (CH_2Cl_2:MeOH = 5:1, UV, $KMnO_4$).

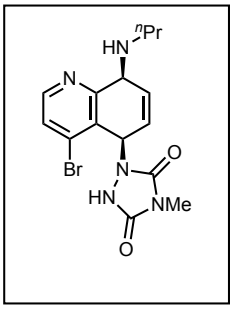
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.9 Hz, 1H), 7.09 (d, *J* = 7.9 Hz, 1H), 6.42 – 6.36 (m, 2H), 5.90 – 5.89 (m, 1H), 4.38 (d, *J* = 4.3 Hz, 1H), 3.08 (s, 3H), 2.63 – 2.59 (m, 2H), 2.55 (s, 3H), 1.47 – 1.39 (m, 2H), 0.80 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$) 159.6, 155.0, 153.7, 153.4, 137.3, 132.5, 129.3, 126.7, 122.6, 53.0, 52.7, 47.7, 25.4, 24.5, 20.9, 11.6.

HRMS: (ESI-TOF, m/z) calcd. For $C_{16}H_{22}N_5O_2$ $[M+H]^+$ calc.: 316.1774; found: 316.1764.

IR: (ATR, neat, cm^{-1}): 3390 (w), 2967 (w), 1694 (m), 1620 (s), 1600 (w), 1473 (m), 1448 (m), 1372 (w), 1146 (w), 1022 (w), 831 (w), 778 (m), 757 (s), 637 (m), 566 (w).

m.p.: 131–132 ºC.



Synthesis of (±)-35 (Table 3): The reaction was conducted following the general procedure C, except the reaction was run with MTAD (**15**, 0.5 mmol, 1.0 eq.) in EtOAc (10 mL, 0.05 M). Single constitutional- and diastereoisomer was observed in crude ^{1}H NMR. The title compound was isolated by flash chromatography (SiO_2, CH_2Cl_2:MeOH = 9:1 to 5:1) as a light-yellow solid (115.3 mg, 61%).

R_f = 0.44 (CH_2Cl_2:MeOH = 5:1, UV, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 5.2 Hz, 1H), 7.58 (d, *J* = 5.2 Hz, 1H), 6.39 (dd, *J* = 9.5, 5.5 Hz, 1H), 6.31 (dd, *J* = 9.5, 5.9 Hz, 1H), 6.16 (d, *J* = 5.9 Hz, 1H), 4.50 (d, *J* = 5.5 Hz, 1H), 3.12 (s, 3H), 2.88 – 2.77 (m, 2H), 1.7 – 1.63 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H).

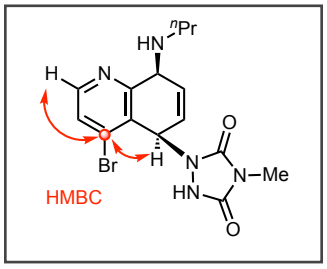
^{13}C NMR: (125 MHz, $CDCl_3$) δ 155.3, 154.9, 152.2, 149.1, 135.1, 132.6, 131.4, 128.8, 128.4, 54.9, 49.7, 47.7, 25.4, 20.6, 11.6.

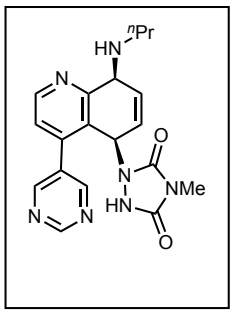
HRMS: (ESI-TOF, m/z) calcd. For $C_{15}H_{19}BrN_5O_2$ $[M+H]^+$ calc.: 380.0710; found: 380.0722.

IR: (ATR, neat, cm^{-1}): 3030 (w), 1705 (m), 1613 (s), 1455 (s), 1386 (m), 1279 (w), 1239 (w), 1019 (w), 827 (m), 791 (s), 760 (s), 710 (w), 654 (w), 635 (m), 608 (m), 493 (m).

m.p.: 136–137 ºC.

Observed HMBC correlations:





Synthesis of (±)-36 (Table 3): The reaction was conducted following the general procedure C, except the reaction was run with MTAD (**15**, 0.5 mmol, 1.0 eq.) in dichloromethane (5 mL, 0.1 M). The title compound was isolated by flash chromatography (SiO_2, CH_2Cl_2:MeOH = 10:1 to 5:1) as a off-white solid (94.9 mg, 50%).

R_f = 0.21 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.65 (d, *J* = 4.9 Hz, 1H), 8.61 (s, 2H), 7.24 (d, *J* = 4.9 Hz, 1H), 6.48 (dd, *J* = 9.5, 5.6 Hz, 1H), 6.20 (dd, *J* = 9.5, 5.9 Hz, 1H), 5.77 (d, *J* = 5.9 Hz, 1H), 4.61 (d, *J* = 5.6 Hz, 1H), 3.02 (s, 3H), 2.93 – 2.82 (m, 2H), 1.74 – 1.70 (m, 1H), 1.68 – 1.63 (m, 1H), 0.94 (t, *J* = 7.4 Hz, 3H).

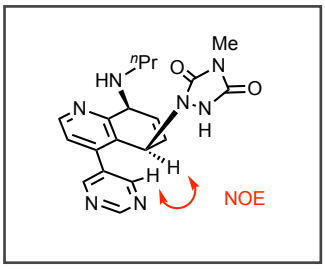
^{13}C NMR: (125 MHz, $CDCl_3$) δ 159.2, 157.0, 155.9, 155.8, 154.5, 152.0, 149.3, 144.2, 131.0, 130.9, 130.3, 129.2, 125.2, 55.5, 48.4, 47.6, 25.3, 21.3, 11.7.

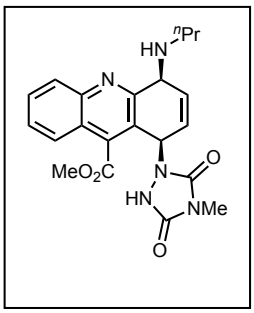
HRMS: (ESI-TOF, m/z) calcd. For $C_{19}H_{22}N_7O_2$ $[M+H]^+$ calc.: 380.1835; found: 380.1846.

IR: (ATR, neat, cm^{-1}): 1703 (m), 1612 (s), 1587 (w), 1453 (w), 1417 (m), 1381 (w), 1285 (w), 1036 (w), 853 (w), 791 (w), 774 (w), 762 (w), 729 (m), 634 (s), 531 (w).

m.p.: 138–139 ºC.

Observed NOE correlation:





Synthesis of (±)-37 (Table 3): The reaction was conducted following the general procedure C, except the reaction was run with MTAD (**2**, 0.5 mmol, 1.0 eq.) in dichloromethane (5 mL, 0.1 M). The title compound was isolated by flash chromatography (SiO_2, CH_2Cl_2:MeOH = 15:1 to 9:1) as a light-red solid (108.8 mg, 53%).

$\mathbf{R_f}$ = 0.53 (CH_2Cl_2:MeOH = 5:1, UV, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.4 Hz, 1H), 7.83 – 7.78 (m, 2H), 7.64 (ddd, *J* = 8.4, 7.0, 1.2 Hz, 1H), 6.53 (dd, *J* = 9.5, 5.7 Hz, 1H), 6.34 (d, *J* = 6.1 Hz, 1H), 6.27 (dd, *J* = 9.5, 6.1 Hz, 1H), 4.69 (d, *J* = 5.7 Hz, 1H), 4.16 (s, 3H), 3.06 (s, 3H), 2.86 (ddd, *J* = 11.9, 9.9, 5.7 Hz, 1H), 2.76 (ddd, *J* = 11.9, 9.8, 5.7 Hz, 1H), 1.69 – 1.65 (m, 1H), 1.55 – 1.51 (m, 1H), 0.84 (t, *J* = 7.4 Hz, 3H).

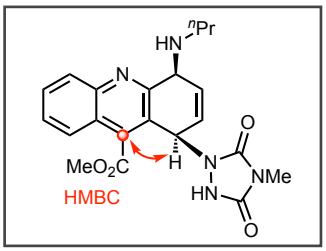
^{13}C NMR: (125 MHz, $CDCl_3$) δ 166.4, 154.9, 153.2, 152.2, 146.8, 140.1, 132.0, 131.1, 129.7, 129.1, 128.7, 125.2, 125.0, 123.9, 55.5, 53.9, 47.7, 46.7, 25.3, 20.6, 11.5.

HRMS: (ESI-TOF, m/z) calcd. For $C_{21}H_{24}N_5O_4$ $[M+H]^+$ calc.: 410.1828; found: 410.1812.

IR: (ATR, neat, cm^{-1}): 2980 (w), 1743 (m), 1702 (m), 1688 (m), 1625 (s), 1471 (m), 1456 (m), 1228 (m), 1213 (m), 785 (s), 770 (s), 747 (s), 728 (m), 624 (m).

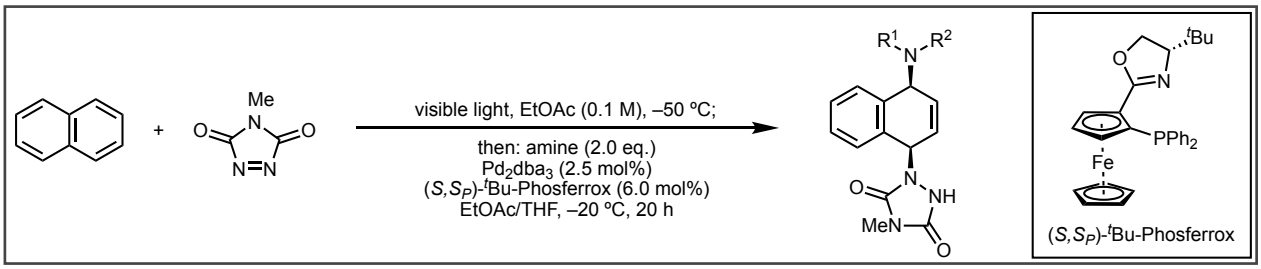
m.p.: 100–101 ºC.

Observed HMBC correlation:

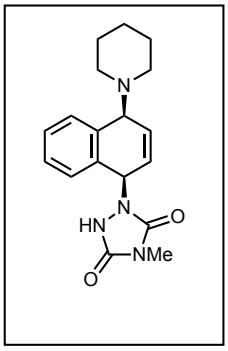


3-4. Asymmetric dearomative *syn*-1,4-diamination of naphthalene

General procedure D for the asymmetric dearomative *syn*-1,4-diamination of naphthalene (Table 4)

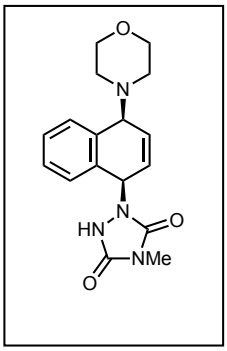


MTAD (**4**, 56.7 mg, 0.50 mmol, 1.0 eq.) was combined with naphthalene (**5**, 128 mg, 1.0 mmol, 2.0 eq.) and a stir bar in a test tube with a septum as the cap under nitrogen atmosphere. Ethyl acetate (5.0 mL, 0.1 M) was added to the test tube at rt, the contents were stirred until completely dissolved and then cooled to –50 ºC. The resulting pink solution was stirred under irradiation with LED lights at –50 ºC until the solution became colorless (approximately 5 h). After turning off the lights, to this solution at –50 ºC were added an amine (2.0 mmol, 2.0 eq.) and a solution of $Pd_2(dba)_3$ (11.4 mg, 0.0125 mmol, 2.5 mol%) and (*S*,*Sp*)-*t*Bu-Phosferrox (14.9 mg, 0.03 mmol, 6.0 mol%) in THF (2.0 mL), and the resulting mixture was stirred at –20 ºC for 20 h. The reaction was then warmed up to rt, concentrated under reduced pressure, and purified by flash column chromatography (SiO_2, CH_2Cl_2:MeOH mixture).

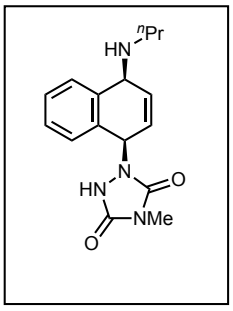


Synthesis of 28e (Table 5): Following the general procedure D, the title compound was isolated by flash chromatography (SiO_2, CH_2Cl_2:MeOH (saturated with NH_3) = 95:5 to 85:15) as a white solid (107.5 mg, 66%). Enantiomeric excess was determined with HPLC analysis using Diacel Chiracel® OD-3 column, 25% ^{i}PrOH in *n*-hexane, 0.8 mL/min. 97:3 er, ^{t}R(major) = 11.2 min, ^{t}R(minor) = 7.9 min.

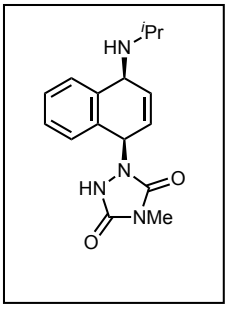
$[\alpha]D^{20}$ = +204.4 (c = 0.50 in $CHCl_3$)



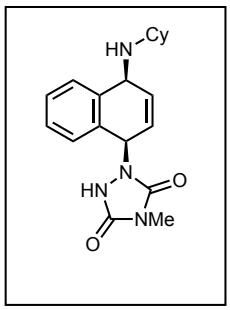
Synthesis of 28f (Table 5): Following the general procedure D, the title compound was isolated by flash chromatography (SiO_2, CH_2Cl_2:MeOH (saturated with NH_3) = 95:5 to 85:15) as a white solid (86.5 mg, 53%). Enantiomeric excess was determined with HPLC analysis using Diacel Chiracel® IA-3 column, 50% ^{i}PrOH in *n*-hexane, 0.8 mL/min. 99:1 er, ^{t}R(major) = 6.1 min, ^{t}R(minor) = 4.3 min. $[\alpha]D^{20}$ = +952.0 (c = 0.10 in $CHCl_3$)



Synthesis of 28k (Table 5): Following the general procedure D, the title compound was isolated by flash chromatography (SiO_2, CH_2Cl_2:MeOH (saturated with NH_3) = 98:2 to 85:15) as a white solid (140.2 mg, 93%). Both the free N–H bonds in **7i** were acetylated prior to HPLC analysis and taking optical rotation. Enantiomeric excess was determined with HPLC analysis using Diacel Chiracel® IA-3 column, 10% ^{i}PrOH in *n*-hexane, 0.8 mL/min. 97:3 er, ^{t}R(major) = 10.4 min, ^{t}R(minor) = 8.5 min. $[\alpha]D^{20}$ = -363.9 (c = 0.50 in $CHCl_3$)

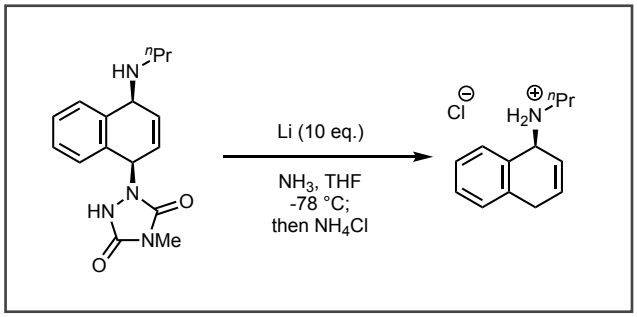


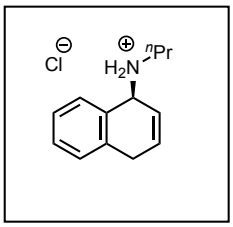
Synthesis of 28n (Table 5): Following the general procedure D, the title compound was isolated by flash chromatography (SiO_2, *n*-hexane:EtOAc = 2:1 to 1:1) as a white solid (131.8 mg, 88%). The double bond was hydrogenated and both the free N–H bonds in **7l** were acetylated prior to HPLC analysis and taking optical rotations. Enantiomeric excess was determined with HPLC analysis using Diacel Chiracel® OD-3 column, 20% ^{i}PrOH in *n*-hexane, 0.8 mL/min. >99:1 er, ^{t}R(major) = 10.0 min, ^{t}R(minor) = 11.6 min. $[\alpha]D^{20}$ = +64.3 (c = 1.00 in $CHCl_3$)



Synthesis of 28o (Table 5): Following the general procedure D, the title compound was isolated by flash chromatography (SiO_2, *n*-hexane:EtOAc = 2:1 to 1:1) as a white solid (142.6 mg, 84%). Both the free N–H bonds in **7m** were acetylated prior to HPLC analysis and taking optical rotation. Enantiomeric excess was determined with HPLC analysis using Diacel Chiracel® IA-3 column, 25% ^{i}PrOH in *n*-hexane, 0.8 mL/min. 97:3 er, ^{t}R(major) = 6.4 min, ^{t}R(minor) = 4.8 min. $[\alpha]D^{20}$ = -397.6 (c = 0.50 in $CHCl_3$)

3-5. Derivatizations





Synthesis of (±)-38 (Figure 2): **(±)-28k** (75 mg, 0.25 mmol, 1.0 eq.) was added to a 100 mL three-necked flask charged with a stir bar. To the flask was then attached a bubbler and purged thoroughly with nitrogen gas, and the flask was cooled in an acetone/dry ice bath. Next, ammonia was introduced as a gas into the flask, and approximately 10 mL of liquid ammonia was allowed to condense in the flask. After turning off the ammonia and putting the flask back under nitrogen pressure, small chunks of lithium metal (approximately 17.4 mg, 10 eq., 2.5 mmol) were added to the reaction and allowed to stir until the whole solution became dark blue. At this point ammonium chloride was added to quench the remaining lithium and then the reaction was poured over a saturated ammonium chloride solution (100 mL), extracted with dichloromethane (3 X 100 mL), dried over Magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (SiO_2, CH_2Cl_2:MeOH = 99:1 to 9:1) as a yellow solid (33.6 mg, 60%).

R_f = 0.23 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

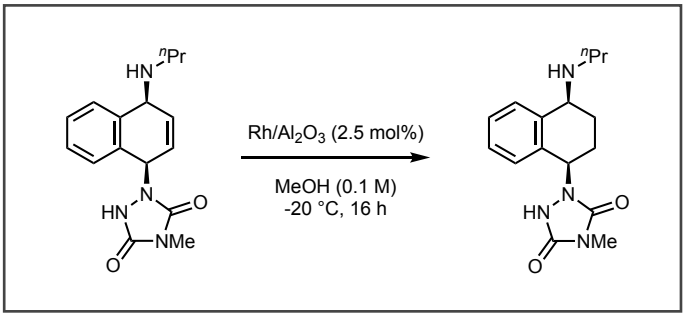
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.5 Hz, 1H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.20 (t, *J* = 6.8 Hz, 1H), 7.15 (d, *J* = 7.3 Hz, 1H), 6.10 (dt, *J* = 10.1, 3.4 Hz, 1H), 6.03 (ddd, *J* = 10.1, 3.7, 1.7 Hz, 1H), 4.38 (q, *J* = 3.8 Hz, 1H), 3.46 – 3.41 (m, 1H), 3.36 – 3.31 (m, 1H), 2.53 (dt, *J* = 11.1, 7.1 Hz, 1H), 2.39 (dt, *J* = 11.1, 7.3 Hz, 1H), 1.46 (hex, *J* = 7.0 Hz, 2H), 0.88 (t, *J* = 7.4 Hz, 3H).

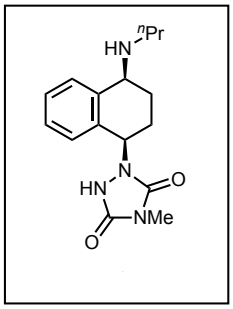
^{13}C NMR: (125 MHz, $CDCl_3$) δ 136.9, 135.2, 128.4, 128.3, 128.2, 127.1, 126.6, 126.3, 53.9, 46.9, 30.0, 23.8, 12.0.

HRMS: (ESI-TOF, m/z) calcd. For $C_{13}H_{18}N$ $[M+H]^+$ calc.: 188.1434; found: 188.1436.

IR: (ATR, neat, cm^{-1}): 3392 (w), 3024 (m), 2949 (s), 1742 (s), 1604 (m), 1460 (m), 1374 (m), 1217 (w), 750 (s).

m.p.: 205–207 ºC.





Synthesis of (±)-39: To a 250 mL round bottom flask charged with a stir bar was added **(±)-28k** (1.96 g, 6.5 mmol, 1.0 eq.) and 5% Rh on Alumina (336 mg, 0.16 mmol, 0.025 eq.) and MeOH (65 mL, 0.10 M). The flask was thoroughly purged by bubbling nitrogen gas through the resulting suspension at room temperature. Then a hydrogen-containing balloon was used to bubble hydrogen gas through the suspension at room temperature for approximately five minutes before cooling to -20 °C and stirring under a hydrogen atmosphere until complete conversion was observed (as monitored by NMR; usually about 16 hours). After complete conversion, the reaction was warmed up to room temperature, purged with nitrogen atmosphere, and filtered over a pad of celite using MeOH. The resulting filtrate was concentrated under reduced pressure and purified by flash chromatography (SiO_2, EtOAc then CH_2Cl_2/MeOH = 9:1 to 4:1) as a white solid (1.64 g, 83%).

R_f = 0.19 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

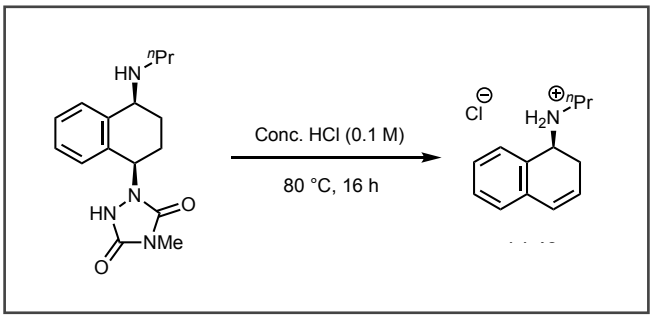
^{1}H NMR: (500 MHz, $CDCl_3$) δ 10.42 (br, 2H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.34 (td, *J* = 7.6, 1.2 Hz, 1H), 7.21 (td, *J* = 7.5, 1.1 Hz, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 5.63 (dd, *J* = 10.2, 3.5 Hz, 1H), 4.02-4.01 (m, 1H), 3.03 (s, 3H), 2.68 (td, *J* = 11.7, 5.4 Hz, 1H), 2.61 (td, *J* = 11.7, 5.4 Hz, 1H), 2.28 – 2.22 (m, 1H), 2.16 – 2.15 (m, 1H), 1.97 – 1.67 (m, 4H), 0.87 (t, *J* = 7.4 Hz, 3H).

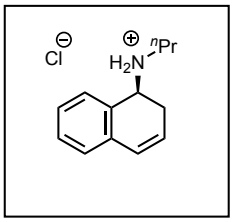
^{13}C NMR: (125 MHz, $CDCl_3$) δ 155.8, 152.2, 137.0, 132.7, 131.3, 130.6, 129.6, 127.8, 54.8, 48.4, 46.8, 25.6, 25.3, 21.3, 19.8, 11.6.

HRMS: (ESI-TOF, m/z) calcd. For $C_{16}H_{23}N_4O_2$ $[M+H]^+$ calc.: 303.1816; found: 303.1813.

IR: (ATR, neat, cm^{-1}): 3383 (w), 2966 (w), 1682 (m), 1595 (s), 1467 (m), 1389 (w), 1288 (w), 1159 (w), 758 (w), 732 (w), 650 (w).

m.p.: 116–118 ºC.





Synthesis of (±)-40 (Figure 2): **(±)-39** (20 mg, 0.066 mmol) was dissolved in concentrated aqueous HCl (0.66 mL, 0.1 M) in a 4 mL vial. The vial was sealed without any exclusion of air and heated to 80 °C for 16 hours. Upon cooling, the contents of the vial were concentrated under reduced pressure. The resulting residue was purified by flash chromatography (SiO_2 CH_2Cl_2:MeOH = 99:1 to 9:1) as a yellow solid (7.1 mg, 48%).

R_f = 0.29 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

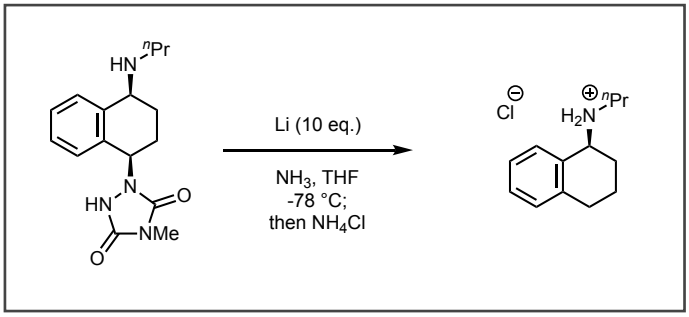
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.4 Hz, 1H), 7.37 (td, *J* = 7.5, 1.1 Hz, 1H), 7.30 (td, *J* = 7.5, 1.1 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 6.61 (dd, *J* = 9.7, 2.9 Hz, 1H), 6.03 (ddd, *J* = 8.9, 5.7, 2.4 Hz, 1H), 4.52 (d, *J* = 6.2 Hz, 1H), 3.15 (ddd, *J* = 19.2, 5.7, 1.4 Hz, 1H), 2.78 – 2.73 (m, 2H), 2.62 – 2.56 (m, 1H), 1.85 – 1.76 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H).

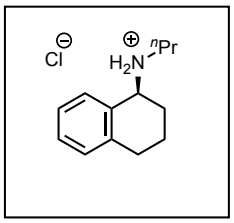
^{13}C NMR: (125 MHz, $CDCl_3$) δ 134.4, 130.5, 130.4, 128.2, 128.1, 127.3, 126.2, 125.0, 53.1, 45.3, 26.8, 20.0, 11.5.

HRMS: (ESI-TOF, m/z) calcd. For $C_{13}H_{18}N$ $[M+H]^+$ calc.: 188.1434; found: 188.1437**.**

IR: (ATR, neat, cm^{-1}): 3397 (w), 2965 (w), 1687 (s), 1590 (m), 1472 (m), 1266 (w), 980 (w), 761 (s), 731 (s), 698 (m), 517 (m).

m.p.: 70–72 ºC decomposed.





Synthesis of (±)-41 (Figure 2): **(±)-39** (75 mg, 1.0 eq., 0.25 mmol) was added to a 100 mL three-necked flask charged with a stir bar. Next, the flask and attached bubbler were purged thoroughly with nitrogen gas, and THF (10 mL, 0.025 M) was added to dissolve the substrate. The flask was cooled in an acetone/dry ice bath. Next, ammonia was introduced as a gas into the flask, and approximately 10 mL of liquid ammonia was allowed to condense in the flask. After turning off the ammonia and putting the flask back under nitrogen pressure, small chunks of lithium metal (approximately 17.4 mg, 10 eq., 2.5 mmol) were added to the reaction and allowed to stir until the whole solution became dark blue. At this point ammonium chloride was added to quench the remaining lithium and then the reaction was poured over a saturated ammonium chloride solution (100 mL), extracted with CH_2Cl_2 (3 x 100 mL), dried over Magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (SiO_2 CH_2Cl_2:MeOH = 99:1 to 9:1) as a yellow solid (39.7 mg, 71%).

R_f = 0.29 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

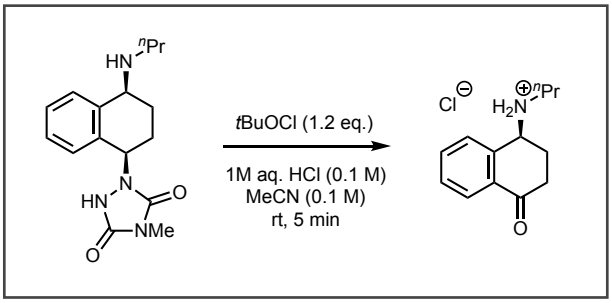
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.34 (m, 1H), 7.17 – 7.12 (m, 2H), 7.09 – 7.07 (m, 1H), 3.77 (t, *J* = 4.9 Hz, 1H), 2.81 (dt, *J* = 11.2, 5.6 Hz, 1H), 2.75 – 2.61 (m, 3H), 2.00 – 1.91 (m, 1H), 1.89 – 1.85 (m, 2H), 1.77 – 1.70 (m, 1H), 1.54 (hex, *J* = 7.3 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).

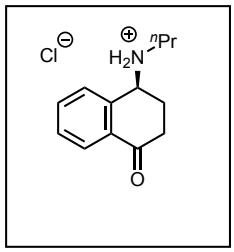
^{13}C NMR: (125 MHz, $CDCl_3$) δ 139.4, 137.4, 129.2, 128.8, 126.7, 125.8, 55.5, 49.4, 29.5, 28.5, 23.7, 19.1, 12.1.

HRMS: (ESI-TOF, m/z) calcd. For $C_{13}H_{20}N$ $[M+H]^+$ calc.: 190.1590; found: 190.1600.

IR: (ATR, neat, cm^{-1}): 3018 (w), 2928 (s), 2862 (m), 1489 (w), 1451 (m), 1107 (w), 739 (s).

m.p.: 160–162 ºC.





Synthesis of (±)-42 (Figure 2): The title compound was synthesized by dissolving **(±)-39** (36 mg, 0.12 mmol, 1.0 eq.) in 1 M aqueous HCl (1.2 mL, 0.1 M). Following dissolution, *t*BuOCl (16 uL, 0.14 mmol) in MeCN (1.2 mL, 0.1 M) was added dropwise to the aqueous solution containing the substrate. Upon waiting five minutes, the contents of the vial were concentrated under reduced pressure and isolated by flash chromatography (SiO_2, *n*-hexanes:EtOAc = 9:1 to EtOAc) as a white solid (14.4 mg, 50%).

R_f = 0.37 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

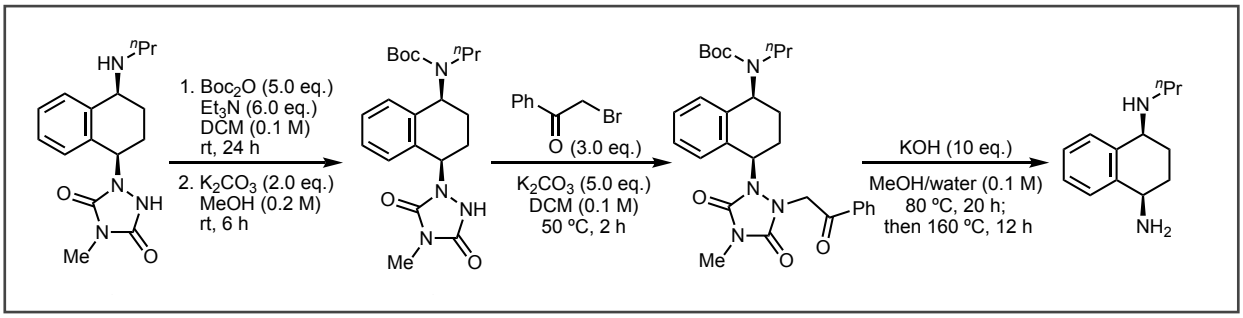
^{1}H NMR: (500 MHz, $CDCl_3$) δ 9.97 (br, 2H), 8.07 (d, *J* = 7.7 Hz, 1H), 7.79 (d, *J* = 7.7 Hz, 1H), 7.61 (t, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 4.58 (b, 1H), 3.17 (dt, *J* = 17.5, 6.7 Hz, 1H), 2.85 (t, *J* = 7.7 Hz, 2H), 2.67 (dt, *J* = 17.5, 5.7 Hz, 1H), 2.57 – 2.54 (m, 2H), 1.90 – 1.89 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H).

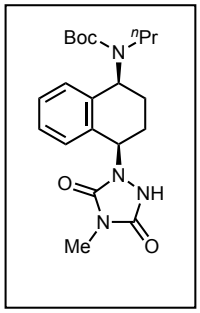
^{13}C NMR: (125 MHz, $CDCl_3$) δ 195.3, 135.5, 134.2, 133.0, 130.0, 129.3, 128.1, 54.9, 46.2, 34.6, 24.9, 19.8, 11.5.

HRMS: (ESI-TOF, m/z) calcd. For $C_{13}H_{18}NO$ $[M+H]^+$ calc.: 204.1383; found: 204.1386.

IR: (ATR, neat, cm^{-1}): 3387 (w), 2967 (w), 2791 (w), 1685 (s), 1604 (m), 1451 (m), 1287 (w), 767 (m), 733 (m).

m.p.: 105–107 ºC decomposed.





Synthesis of (±)-43: The title compound was synthesized by dissolving **(±)-39** (100 mg, 0.33 mmol, 1.0 eq.) in CH_2Cl_2 (3.3 mL, 0.10 M) and then triethyl amine (276 µL, 1.98 mmol, 6.0 eq.) and di-*tert*-butyl dicarbonate (334 µL, 1.65 mmol, 5.0 eq.) was added at 0 ^oC. The reaction was allowed to stir for 24 hours at room temperature (or until complete conversion by TLC). Then, NaOMe (25% weight solution in MeOH, 2 mL) was added dropwise to the mixture and the reaction was allowed to stir for five more minutes at room temperature. The contents were then diluted with 50 mL of CH_2Cl_2 and 1 M HCl was added until the pH = 1. The aqueous layer was then extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The desired compound was isolated by flash chromatography (SiO_2, EtOAc) as a white solid (105 mg, 79%).

R_f = 0.20 (EtOAc, UV, $KMnO_4$).

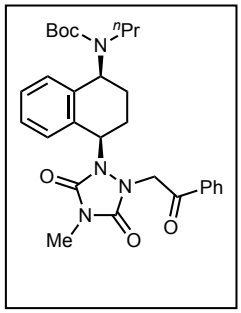
^{1}H NMR: (500 MHz, $CDCl_3$) 7.30 - 7.15 (m, 4H), 5.35 – 5.34 (m, 1H), 4.28 (br, 1H), 3.43 – 3.33 (m, 2H), 3.08 (s, 3H), 2.44 - 2.42 (m, 1H), 2.28 – 2.25 (m, 1H), 2.07 – 1.95 (m, 2H), 1.74 – 1.67 (m, 2H), 1.39 (s, 9H), 0.97 (t, *J* = 6.5 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 154.7 (overlap of 2 peaks detected by HSQC and HMBC), 152.2, 139.1, 131.5, 130.6, 129.4, 127.4, 126.0, 81.0, 57.9, 52.8 (overlap of 2 peaks detected by HSQC), 28.6, 28.3, 25.1, 23.25, 23.17, 11.5.

HRMS: (ESI-TOF, m/z) calcd. For $C_{21}H_{30}N_4NaO_4$ $[M+Na]^+$ calc.: 425.2159; found: 425.2156.

IR: (ATR, neat, cm^{-1}): 3137 (w), 2968 (w), 1767 (w), 1687 (s), 1474 (m), 1410 (m), 1366 (m), 1148 (m), 742 (m).

m.p.: 73-74 ºC.



Synthesis of (±)-44 (Figure 2): The title compound was synthesized by combining **(±)-43** (500 mg, 1.2 mmol, 1.0 eq.) with K_2CO_3 (858 mg, 6.2 mmol, 5.0 eq.) in 12 mL of CH_2Cl_2 and then 2-bromoacetophenone (371 mg, 1.9 mmol, 1.5 eq.) was added as a solid. The reaction was allowed to stir at room temperature for 24 hours and then 50 mL of water was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The desired compound was isolated by flash chromatography (SiO_2, *n*-hexane:EtOAc = 4:1 to 1:1) as a white solid (523 mg, 81%).

R_f = 0.36 (*n*-hexane:EtOAc = 2:1, UV, $KMnO_4$).

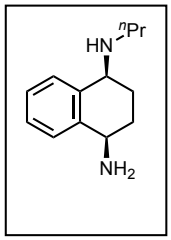
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.55 – 7.41 (m, 3H), 7.23 – 7.15 (m, 4H) 6.90 (t, *J* = 7.7 Hz, 1H), 6.60 (t, *J* = 7.3 Hz, 1H), 5.46 – 5.40 (m, 1H), 5.03 (d, *J* = 18.9 Hz, 1H), 4.68 (d, *J* = 18.9 Hz, 1H), 4.24 (br, 1H), 3.36 – 3.29 (m, 2H), 3.24 (s, 3H), 2.60 (d, *J* = 14.7 Hz, 1H), 2.27 – 2.04 (m, 2H), 2.01 – 1.90 (m, 1H), 1.78 – 1.61 (m, 2H), 1.50 (s, 9H), 0.97 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 193.1, 158.0, 156.0, 154.6, 138.3, 134.3, 133.6, 132.9, 129.4, 128.3 (overlap of 2 peaks detected by HSQC), 127.9, 127.3, 125.6, 79.6, 58.7, 53.6, 52.7, 51.9, 28.6, 26.7, 26.0, 24.5, 23.2, 11.6.

HRMS: (ESI-TOF, m/z) calcd. For $C_{29}H_{37}N_4O_5$ $[M+H]^+$ calc.: 521.2764; found: 521.2755.

IR: (ATR, neat, cm^{-1}): 2967 (w), 1711 (m), 1684 (s), 1364 (w), 1246 (w), 1151 (s), 769 (w), 741 (m), 687 (w), 594 (w), 552 (w).

m.p.: 80–81 ºC.



Synthesis of (±)-45 (Figure 2): A degassed mixture of compound **(±)-44** (100 mg, 0.192 mmol, 1.0 eq.) and 40% aq. potassium hydroxide (0.40 mL, 2.88 mmol, 15 eq.) in methanol (1.0 mL, 0.2 M) in a pressure tube was heated at 80 ºC for 30 h and then at 160 ºC for 20 h under nitrogen atmosphere. After cooling the reaction to rt, volatiles were removed under reduced pressure. The crude residue

was purified by flash column chromatography (SiO_2, CH_2Cl_2:MeOH = 5:1, then CH_2Cl_2:MeOH(sat. with NH_3) = 4:1) to afford the compound **(±)-15** as a colorless oil (25.0 mg, 64%).

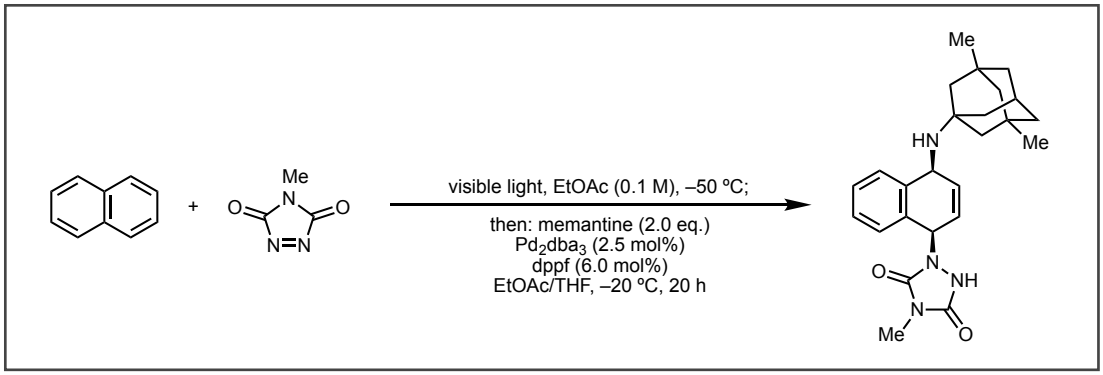
R_f = 0.40 (CH_2Cl_2:MeOH(sat. with NH_3) = 4:1, $KMnO_4$).

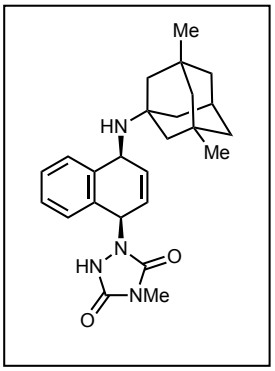
^{1}H NMR: (500 MHz, CD_3OD) δ 7.49 – 7.42 (m, 3H), 7.32 – 7.27 (m, 1H), 4.48 (dd, *J* = 5.7, 3.9 Hz, 1H), 4.24 (dd, *J* = 4.9, 3.2 Hz, 1H), 2.81 (ddd, *J* = 11.8, 8.9, 6.0 Hz, 1H), 2.58 (ddd, *J* = 11.8, 8.9, 6.4 Hz, 1H), 2.38 – 2.26 (m, 1H), 2.26 – 1.97 (m, 3H), 1.71 – 1.51 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR: (125 MHz, CD_3OD) δ 141.2, 139.0, 129.8, 129.3, 128.9, 128.4, 74.5, 56.7, 50.4, 28.4, 26.0, 23.6, 12.1.

HRMS: (ESI-TOF, m/z) calcd. For $C_{13}H_{21}N_2$ $[M+H]^+$ calc.: 205.1705; found: 205.1707.

IR: (ATR, neat, cm^{-1}): 2930 (w), 1594 (m), 1493 (w), 1450 (w), 1366 (m), 1281 (w), 1056 (w), 1027 (w), 953 (w), 757 (m), 734 (w), 698 (s), 530 (w).





Synthesis of (±)-28v (Figure 2b): **(±)-28v** was synthesized following the general procedure A, with the following modifications: the reaction was run on a 1.50 mmol (MTAD, **15**) scale and the other reagents were scaled accordingly; memantine was prepared from dissolving 5 mmol of Memantine•HCl salt in 100 mL of H_2O and 100 mL of CH_2Cl_2 and increasing the pH of the aqueous layer to at least 12 with KOH, stirred rapidly until everything was dissolved, and then extracted with 3:1 $CHCl_3$:*i*PrOH (3 x 100 mL). The title compound was

isolated by flash column chromatography (two columns: (SiO_2, CH_2Cl_2:MeOH = 19:1 to 9:1) and (C_{18} reverse phase SiO_2, H_2O:MeOH = 19:1 to 9:1) as a white solid (416.3 mg, 66%).

R_f = 0.39 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

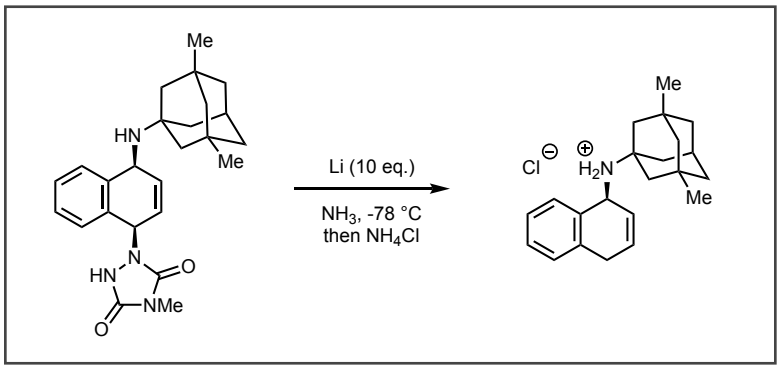
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.42 – 7.41 (m, 1H), 7.31 – 7.27 (m, 2H), 7.21 – 7.20 (m, 1H), 6.51 (dd, *J* = 9.7, 5.4 Hz, 1H), 6.17 (dd, *J* = 9.6, 5.9 Hz, 1H), 5.86 (d, *J* = 5.8 Hz, 1H), 4.55 (d, *J* = 5.3, 1H), 2.99 (s, 3H), 2.15 (m, 1H), 1.63 (q, *J* = 11.5 Hz, 2H), 1.50 (d, *J* = 11.6 Hz, 1H), 1.43 – 1.27 (m, 7H), 1.16 – 1.10 (m, 2H), 0.85 (s, 6H).

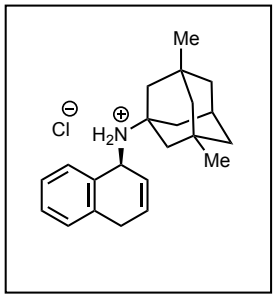
^{13}C NMR: (125 MHz, $CDCl_3$) δ 152.6, 152.2, 139.4, 136.0, 134.7, 129.5, 128.8, 128.5, 128.1, 127.3, 55.5, 50.7, 50.6, 49.1, 48.1, 42.55, 42.52, 41.7, 32.75, 32.74, 30.27, 30.23, 30.21, 25.0.

HRMS: (ESI-TOF, m/z) calcd. For $C_{25}H_{33}N_4O_2$ $[M+H]^+$ calc.: 421.2598; found: 421.2588.

IR: (ATR, neat, cm^{-1}): 3402 (w), 2945 (w), 2904 (m), 2843 (w), 1691 (s), 1611 (s), 1461 (m), 754 (m).

m.p.: 120–121 ºC.





Synthesis of (±)-49 (Scheme 5): **(±)-28v** (100 mg, 1.0 eq., 0.237 mmol) was added to a 100 mL three-necked flask charged with a stir bar. Next, the flask and attached bubbler were purged thoroughly with nitrogen gas, and then the flask was cooled in an acetone/dry ice bath. Next, ammonia was released as a gas into the flask, and approximately 10 mL of liquid ammonia was allowed to condense in the flask. After turning off the ammonia and putting the flask back under nitrogen pressure, very small chunks of lithium metal were added to the reaction and allowed to stir until the whole solution became dark blue. At this point half a scoop of ammonium chloride was added to quench the remaining lithium and then the reaction was poured over a saturated ammonium chloride solution (100 mL), extracted with CH_2Cl_2 (3 X 100 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (SiO_2, *n*-hexane:EtOAc = 100:0 to 1:1) as a white solid (52.4 mg, 64%).

R_f = 0.30 (*n*-hexane:EtOAc = 1:1, UV, $KMnO_4$).

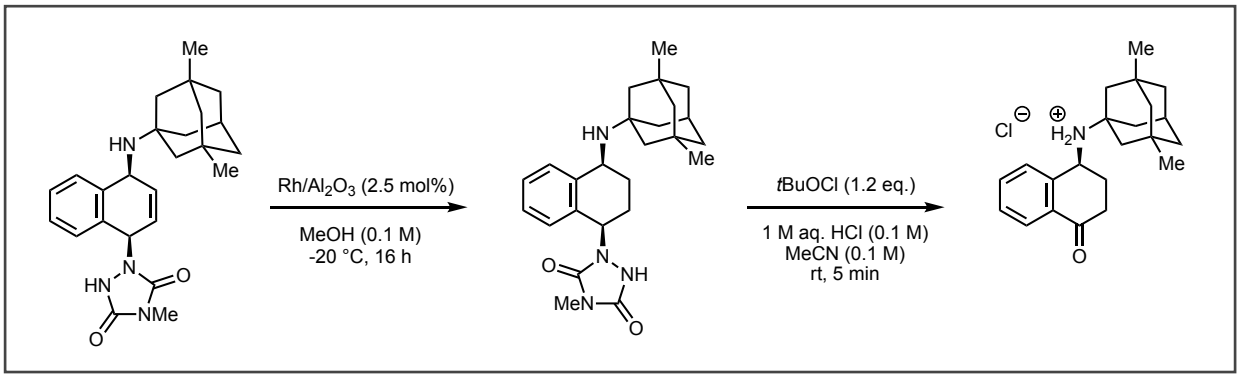
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.7 Hz, 1H), 7.22 (td, *J* = 7.4, 1.3 Hz, 1H), 7.14 (td, *J* = 7.4, 1.3 Hz, 1H), 7.09 (d, *J* = 7.7 Hz, 1H), 5.98 – 5.91 (m, 2H), 4.37 (q, *J* = 4.4, 3.7 Hz, 1H), 3.45 - 3.39 (m, 1H), 3.31 – 3.24 (m, 1H), 2.18 (dt, *J* = 6.1, 3.1 Hz, 1H), 1.65 – 1.15 (m, 12H), 0.88 (s, 6H).

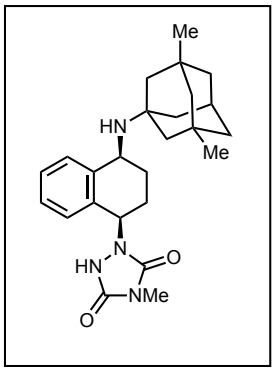
^{13}C NMR: (125 MHz, $CDCl_3$) δ 139.6, 134.5, 131.6, 129.2, 128.1, 126.5, 126.2, 124.6, 53.4, 51.1, 50.62, 50.60, 46.7, 43.1, 42.9, 32.7, 30.60, 30.57, 29.7.

HRMS: (ESI-TOF, m/z) calcd. For $C_{22}H_{30}N$ $[M+H]^+$ calc.: 308.2373; found: 308.2379.

IR: (ATR, neat, cm^{-1}): 2907 (s), 2841 (m), 1740 (m), 1454 (m), 1355 (w), 1196 (w), 746 (m).

m.p.: 68–69 ºC.





Synthesis of (±)-50: To a 250 mL round bottom flask charged with a stir bar was added **(±)-28v** (40 mg, 0.095 mmol, 1.0 eq.) and 5% Rh on Alumina (5 mg 0.0024 mmol, 0.025 eq.), and 1 mL (0.1 M) of MeOH. The flask was thoroughly purged by bubbling nitrogen gas through the resulting suspension at room temperature. Then a hydrogen-containing balloon was used to bubble hydrogen gas through the suspension at room temperature for approximately five minutes before cooling to -20 °C and stirring under a hydrogen atmosphere until complete conversion was observed (as monitored by NMR; usually about 16 hours). After complete conversion, the reaction was warmed up to room temperature, purged with nitrogen atmosphere, and filtered over a pad of celite using MeOH. The resulting filtrate was concentrated under reduced pressure and purified by flash chromatography (SiO_2, CH_2Cl_2:MeOH = 99:1 to 9:1) as a white solid (23.0 mg, 57%).

R_f = 0.41 (CH_2Cl_2:MeOH = 9:1, UV, $KMnO_4$).

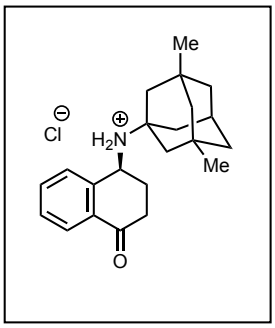
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.22 – 7.17 (m, 4H), 6.27 (br, 2H), 5.41 (t, *J* = 7.9 Hz, 1H), 4.24 (br, 1H), 3.02 (s, 3H), 2.42 – 2.39 (m, 1H), 2.22 – 2.19 (m, 2H), 2.06 (br, 1H), 1.91 (t, *J* = 13.2 Hz, 1H), 1.74 (d, *J* = 10.9 Hz, 1H), 1.67 (d, *J* = 10.9 Hz, 1H), 1.59 – 1.44 (m, 4H), 1.32 (s, 4H), 1.15 (q, *J* = 12.6 Hz, 2H), 0.87 (s, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 154.9, 153.4, 137.2, 136.4, 129.4, 129.2, 128.8, 127.8, 57.6, 51.5, 50.5, 48.8, 47.5, 47.4, 42.5, 40.2, 32.76, 32.75, 30.3, 30.2, 28.7, 25.3, 22.5.

HRMS: (ESI-TOF, m/z) calcd. For $C_{25}H_{35}N_4O_2$ $[M+H]^+$ calc.: 423.2755; found: 423.2764.

IR: (ATR, neat, cm^{-1}): 2912 (m), 2846 (w), 1694 (s), 1610 (m), 1468 (m), 1020 (w), 731 (w).

m.p.: 121–124 ºC decomposed.



Synthesis of (±)-51 (Figure 2): The title compound was synthesized by dissolving **(±)-50** (38 mg, 0.090 mmol, 1.0 eq.) in 1M aqueous HCl (0.90 mL, 0.1 M). Following dissolution, *t*BuOCl (24 uL, 0.22 mmol, 2.4 eq.) in MeCN (1.2 mL, 0.1 M) was added dropwise to the aqueous solution containing the substrate. Upon waiting five minutes, the contents of the vial were concentrated under reduced pressure and isolated by flash chromatography (SiO_2, *n*-hexane:EtOAc = 9:1 to EtOAc) as a white solid (25.8 mg, 80%).

R_f = 0.24 (*n*-hexane:EtOAc = 1:1, UV, $KMnO_4$).

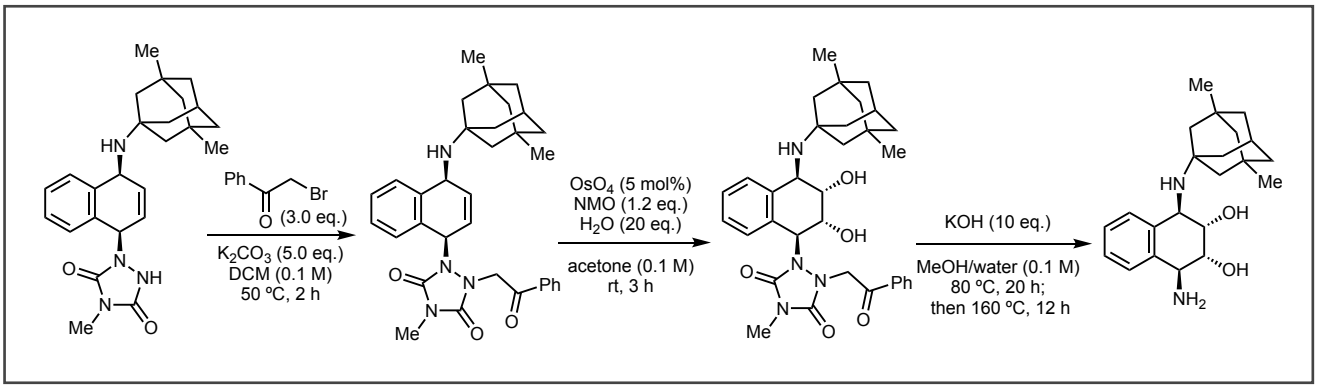
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 4.14 (dd, *J* = 6.8, 3.4 Hz, 1H), 3.07 (ddd, *J* = 17.1, 8.4, 4.2 Hz, 1H), 2.57 (ddd, *J* = 17.2, 8.5, 4.4 Hz, 1H), 2.24 (ddt, *J* = 12.6, 8.2, 3.9 Hz, 1H), 2.18 (dt, *J* = 5.5, 2.7 Hz, 1H), 2.03 – 1.96 (m, 1H), 1.64 – 1.05 (m, 12H), 0.88 (s, 6H).

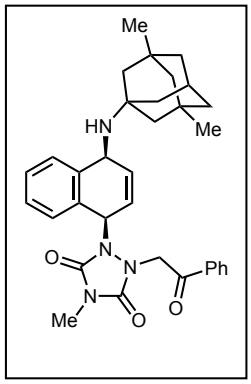
^{13}C NMR: (125 MHz, $CDCl_3$) δ 198.7, 148.7, 133.9, 132.1, 128.5, 127.3, 127.1, 53.4, 51.1, 50.5, 48.5, 43.1, 42.8, 36.0, 33.2, 32.7, 30.5, 29.9.

HRMS: (ESI-TOF, m/z) calcd. For $C_{22}H_{30}NO$ $[M+H]^+$ calc.: 324.2322; found: 324.2321.

IR: (ATR, neat, cm^{-1}): 3384 (w), 3035 (m), 2921 (m), 2313 (w), 1685 (s), 1500 (m), 1401 (m), 1117 (m), 1069 (m), 760 (m).

m.p.: 114–116 ºC decomposed.





Synthesis of (±)-52 (Figure 2): A mixture of compound **(±)-28v** (50.0 mg, 0.12 mmol, 1.0 eq.), 2'-bromoacetophenone (71.0 mg, 0.36 mmol, 3.0 eq.), and K_2CO_3 (82.2 mg, 0.60 mmol, 5.0 eq.) in dichloromethane (1.2 mL, 0.1 M) was stirred at 50 ºC for 2 h. After cooling to rt, water (2.0 mL) was added, and the organic phase was separated. The aqueous layer was extracted with dichloromethane (3 × 2.0 mL), the combined organic extracts were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, *n*-hexane:EtOAc = 4:1) to afford the compound **(±)-52** as a colorless oil (45.2 mg, 71%).

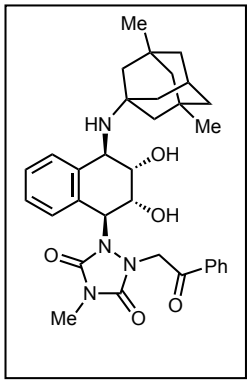
R_f = 0.63 (*n*-hexane:EtOAc = 1:4, UV, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.60 – 7.58 (m, 2H), 7.54 (td, *J* = 7.5, 1.3 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.36 – 7.33 (m, 2H), 7.13 – 7.08 (m, 2H), 6.91 (t, *J* = 7.5 Hz, 1H), 6.14 (ddd, *J* = 10.2, 3.9, 2.0 Hz, 1H), 5.86 – 5.84 (m, 1H), 5.72 (dd, *J* = 10.2, 3.6 Hz, 1H), 4.96 (d, *J* = 18.4 Hz, 1H), 4.45 (d, *J* = 18.4 Hz, 1H), 4.40 – 4.32 (m, 1H), 3.25 (s, 3H), 2.25 – 2.22 (m, 1H), 1.71 – 1.66 (m, 1H), 1.63 – 1.60 (m, 1H), 1.54 – 1.31 (m, 8H), 1.23 – 1.16 (m, 2H), 0.92 (s, 6H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 192.1, 156.9, 155.7, 139.3, 135.6, 134.3, 133.9, 131.4, 129.3, 128.6, 128.5, 128.1, 127.9, 127.4, 122.4, 53.8, 52.8, 52.5, 51.0, 50.5, 45.8, 43.0, 42.8, 32.8, 32.7, 30.5, 26.0.

HRMS: (ESI-TOF, m/z) calcd. For $C_{33}H_{39}N_4O_3$ $[M+H]^+$ calc.: 539.3022; found: 539.3029.

IR: (ATR, neat, cm^{-1}): 2899 (w), 1770 (w), 1708 (s), 1693 (s), 1598 (w), 1469 (m), 1449 (m), 1397 (w), 1355 (w), 1225 (m), 1192 (w), 1002 (w), 963 (w), 790 (s), 728 (m), 686 (m), 649 (w), 592 (m).



Synthesis of (±)-53 (Figure 2): Compound **(±)-52** (90.0 mg, 0.167 mmol, 1.0 eq.) and 4-methylmorpholine *N*-oxide (25.4 mg, 0.217 mmol, 1.3 eq.) were dissolved in acetone (1.7 mL, 0.1 M) and water (60.0 μL, 3.34 mmol, 20 eq.). To this solution was dropwise added osmium tetroxide (42 μL, 0.2 M solution in acetonitrile, 0.0084 mmol, 5.0 mol%) and the resulting solution was stirred at rt for 3 h. Then the reaction was quenched with saturated aqueous sodium thiosulfate solution (0.3 mL), and diluted with EtOAc (3.0 mL) and water (3.0 mL). The organic phase was separated, then the aqueous layer was extracted with EtOAc (3 × 3.0 mL), the combined organic extracts were washed with saturated aqueous sodium chloride solution (3.0 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, *n*-hexane:EtOAc = 1:4) to afford the compound **(±)-53** as a colorless oil (76.5 mg, 80%).

R_f = 0.44 (CH_2Cl_2:MeOH = 5:1, UV, $KMnO_4$).

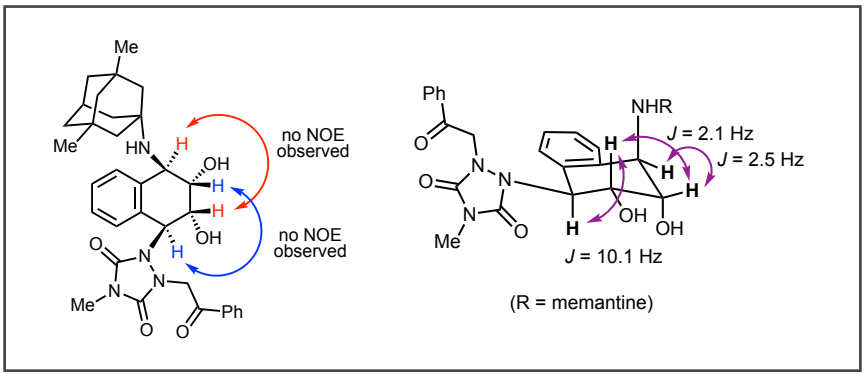
^{1}H NMR: (500 MHz, CD_3OD) δ 7.60 – 7.56 (m, 3H), 7.40 – 7.37 (m, 2H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.09 (d, *J* = 7.8 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.67 (t, *J* = 7.6 Hz, 1H), 5.44 (d, *J* = 10.1 Hz, 1H), 4.98 (d, *J* = 18.6 Hz, 1H), 4.63 (dd, *J* = 10.1, 2.1 Hz, 1H), 4.35 (d, *J* = 18.6 Hz, 1H), 4.10 – 4.05 (d, *J* = 2.5 Hz, 1H), 4.08 – 4.04 (m, 1H), 3.21 (s, 3H), 2.23 – 2.21 (m, 1H), 1.77 (d, *J* = 11.4 Hz, 1H), 1.62 (d, *J* = 11.7 Hz, 1H), 1.56 – 1.34 (m, 8H), 1.20 – 1.17 (m, 2H), 0.92 (s, 6H).

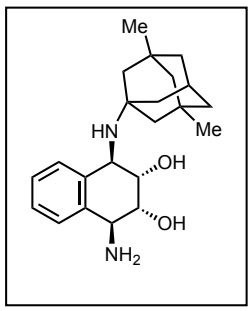
^{13}C NMR: (125 MHz, CD_3OD) δ 194.1, 159.1, 158.9, 139.3, 135.5, 135.2, 135.1, 131.9, 129.7, 129.4, 128.9, 128.5, 127.3, 76.8, 67.7, 60.4, 56.4, 55.0, 54.3, 52.0, 51.0, 50.9, 43.99, 43.97, 43.2, 33.6, 33.5, 31.9, 30.9, 26.1.

HRMS: (ESI-TOF, m/z) calcd. For $C_{33}H_{41}N_4O_5$ $[M+H]^+$ calc.: 573.3077; found: 573.3068.

IR: (ATR, neat, cm^{-1}): 2903 (w), 1770 (w), 1692 (s), 1477 (m), 1450 (w), 1226 (m), 753 (w), 686 (w).

Observed NOE correlations and *J* couplings:





Synthesis of (±)-54 (Figure 2): A degassed mixture of compound **(±)-53** (100 mg, 0.175 mmol, 1.0 eq.) and 40% aq. potassium hydroxide (0.24 mL, 1.75 mmol, 10 eq.) in methanol (1.7 mL, 0.1 M) in a pressure tube was heated at 80 ºC for 24 h and then at 160 ºC for 12 h under nitrogen atmosphere. After cooling the reaction to rt, volatiles were removed under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, CH_2Cl_2:MeOH = 10:1) to afford the compound **(±)-54** as a colorless oil (36.3 mg, 58%).

R_f = 0.44 (CH_2Cl_2:MeOH = 5:1, UV, $KMnO_4$).

^{1}H NMR: (500 MHz, CD_3OD) δ 7.46 – 7.31 (m, 4H), 4.32 – 4.21 (m, 2H), 4.14 – 4.06 (m, 1H), 4.01 – 3.98 (m, 1H), 2.20 (s, 1H), 1.72 (d, *J* = 12.7 Hz, 1H), 1.57 (d, *J* = 11.9 Hz, 1H), 1.53 – 1.43 (m, 8H), 1.21 – 1.15 (m, 2H), 0.90 (s, 6H).

^{13}C NMR: (125 MHz, CD_3OD) δ 139.3, 134.5, 132.1, 129.9, 128.7, 126.8, 76.2, 70.2, 56.2, 54.8, 53.4, 51.9, 51.0, 50.9, 44.0, 43.2, 33.52, 33.51, 31.9, 30.9.

HRMS: (ESI-TOF, m/z) calcd. For $C_{22}H_{33}N_2O_2$ $[M+H]^+$ calc.: 357.2542; found: 357.2540.

IR: (ATR, neat, cm^{-1}): 2898 (br), 2839 (m), 2454 (w), 1559 (w), 1453 (s), 1336 (w), 1066 (m), 977 (w), 757 (m), 630 (w).

4. References

(1) Breton, G. W.; Turlington, M. Alternative synthetic routes to *N*-methyl-1,2,4-triazoline-3,5-dione (MeTAD) and other triazolinedione derivatives, *Tetrahedron Lett.* **2014***, 55*, 4661.

(2) Cookson, R. C.; Gupte, S. S.; Stevens, I. D. R.; Watts, C. T. 4-Phenyl-1,2,4-triazoline-3.5-dione, *Org. Synth.* **1971**, *51*, 121.

(3) Richards, C. J.; Mulvaney, A. W. Synthesis of phosphinoferrocenyloxazolines. New ligands for asymmetric catalysis, *Tetrahedron: Asymmetry*, **1996**, *7*, 1419.

(4) Arthurs, R. A.; Richards, C. J. Deuterium as a Stereochemically Invisible Blocking Group for Chiral Ligand Synthesis, *Org. Lett.*, **2017**, *19*, 702.

(5) Correa, A.; León, T.; Martin R. Ni-Catalyzed Carboxylation of $C(sp^2)$– and $C(sp^3)$–O Bonds with CO_2, *J. Am. Chem. Soc.,* **2014***, 136*, 1062.

(6) (a) Rao, C. B.; Chinnabubu, B.; Venkateswarlu, Y. An Efficient Protocol for Alcohol Protection Under Solvent- and Catalyst-Free Conditions, *J. Org. Chem.,* **2009***, 74*, 8856. (b) Xu, G.; Fu, W.; Liu, G.; Senanayake, C. H.; Tang, W. Efficient Syntheses of Korupensamines A, B and Michellamine B by Asymmetric Suzuki-Miyaura Coupling Reactions, *J. Am. Chem. Soc.,* **2014***, 136*, 570.

(7) Li, Z.; Lian, M.; Yang, F.; Meng, Q.; Gao, Z. K. Diterpenoid Alkaloid Lappaconine Derivative Catalyzed Asymmetric α‐Hydroxylation of β‐Dicarbonyl Compounds with Hydrogen Peroxide, *Eur. J. Org. Chem.*, **2014**, *16*, 3491.

(8) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. Chiral Brønsted Acid Catalyzed Enantioselective Hydrophosphonylation of Imines: Asymmetric Synthesis of α-Amino Phosphonates, *Org. Lett.,* **2005**, *7*, 2583.

(9) Koyama, T.; Hirota, T.; Bashou, C.; Nanba, T.; Ohmori, S.; Yamato, M. Polycyclic N-Hetero Compounds. XIV. Reactions of Methylpyridines with Formamide, *Chem. Pharm. Bull.,* **1977**, *25*, 1923.

(10) Trzybiński, D.; Zadykowicz, B.; Wera, M.; Serdiuk, I.; Sieradzan, A.; Sikorski, A.; Storoniak, P.; Krzymiński, K. Structure, formation, thermodynamics and interactions in 9-carboxy-10-methylacridinium-based molecular systems, *New J. Chem.*, **2016**, *40*, 7359.

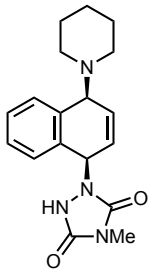
(11) Mintz, M. J.; Walling, C. *t*-Butyl hypochlorite, *Org. Synth.*, **1969**, *49*, 9.

(12) Dolomanov,O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. OLEX2: a complete structure solution, refinement and analysis program, *J. Appl. Cryst.* **2009**, *42*, 339.

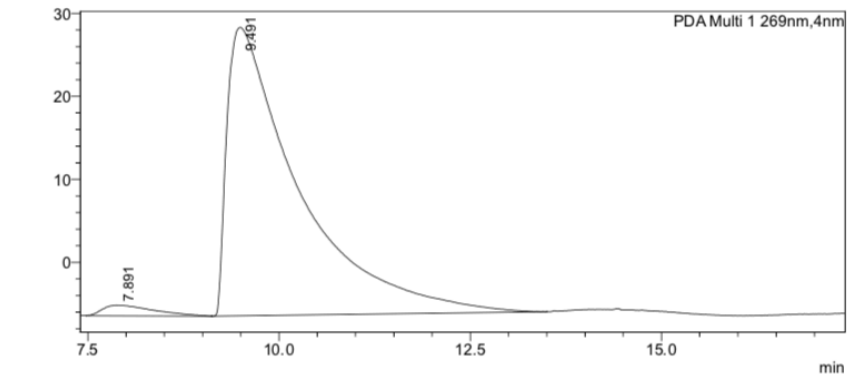
(13) Sheldrick, G. M. SHELXT – Integrated space-group and crystal-structure determination, *Acta Cryst.* **2015**, *A71*, 3.

(14) Sheldrick, G. M. A short history of SHELX, *Acta Cryst.* **2008**, *A64*, 112.

5. HPLC traces



<Chromatogram>



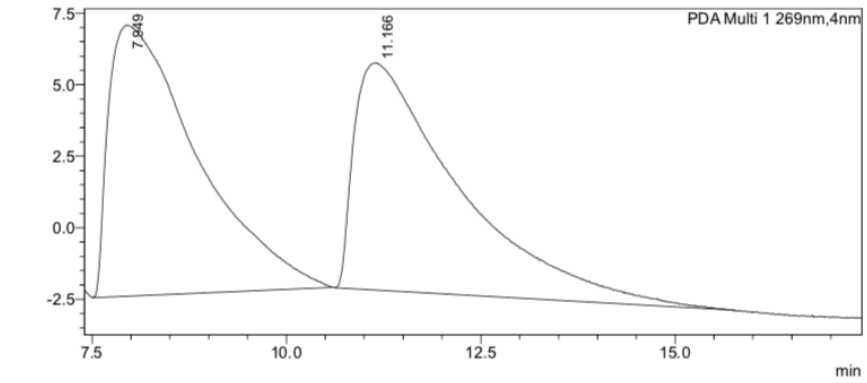
<Peak Table>

PDA Ch1 269nm

Peak#	Ret. Time	Area	Height	Conc.	Area%	Height%
1	7.891	58885	1270	0.000	2.532	3.528
2	9.491	2266868	34733	0.000	97.468	96.472
Total		2325754	36003		100.000	100.000

Racemic

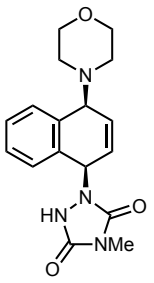
<Chromatogram>



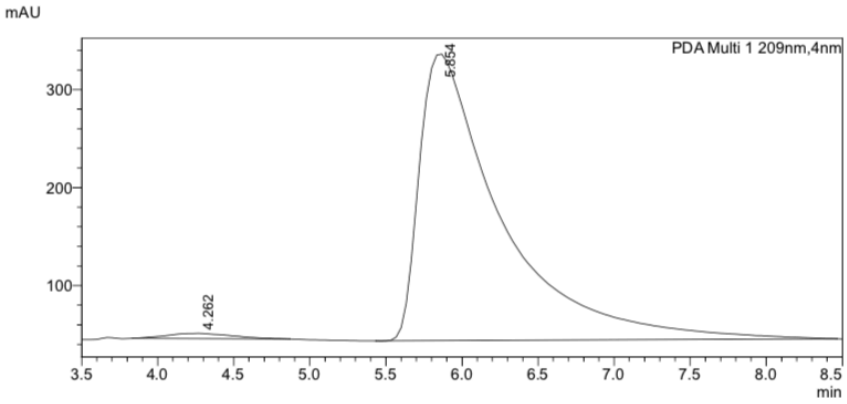
<Peak Table>

PDA Ch1 269nm

Peak#	Ret. Time	Area	Height	Conc.	Area%	Height%
1	7.949	749546	9475	0.000	50.174	54.409
2	11.166	744361	7940	0.000	49.826	45.591
Total		1493907	17415		100.000	100.000



<Chromatogram>



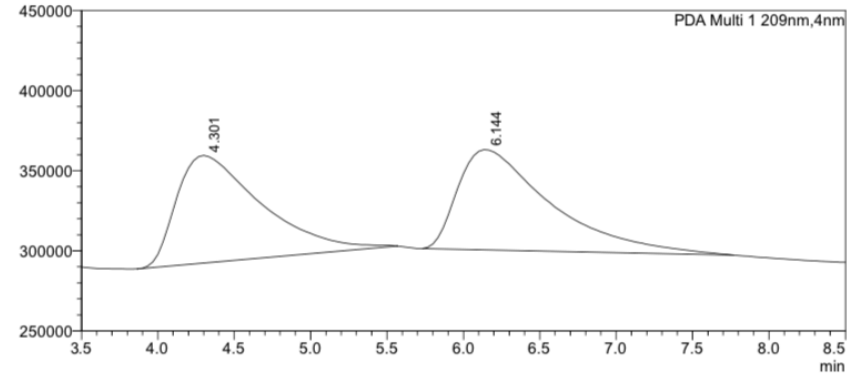
<Peak Table>

PDA Ch1 209nm

Peak#	Ret. Time	Area	Height	Conc.	Area%	Height%
1	4.262	161268	5406	0.000	1.447	1.816
2	5.854	10980408	292212	0.000	98.553	98.184
Total		11141676	297618		100.000	100.000

Racemic

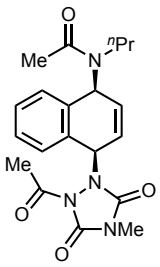
<Chromatogram>



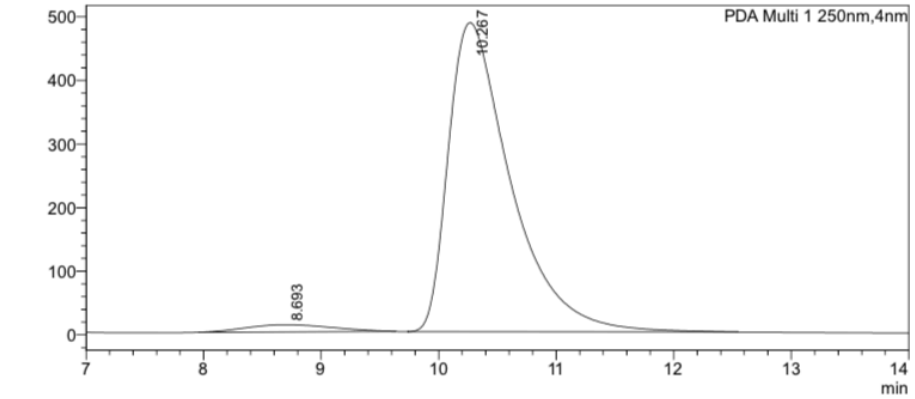
<Peak Table>

PDA Ch1 209nm

Peak#	Ret. Time	Area	Height	Conc.	Area%	Height%
1	4.301	2593062	67152	0.000	49.637	51.769
2	6.144	2630980	62562	0.000	50.363	48.231
Total		5224041	129714		100.000	100.000



<Chromatogram>



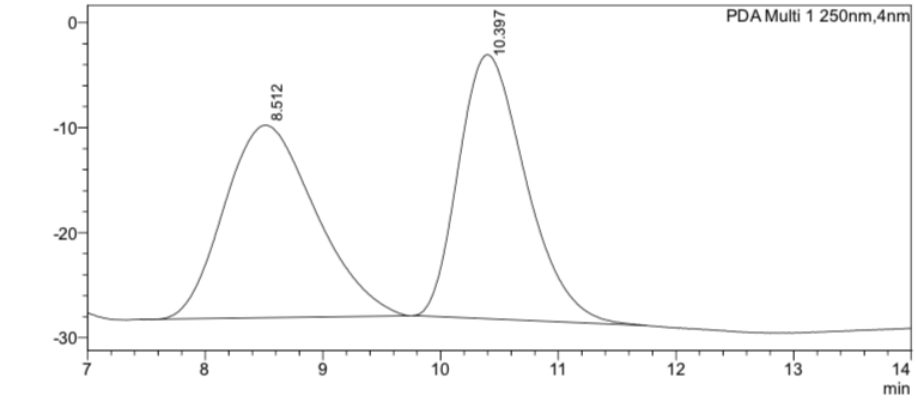
<Peak Table>

PDA Ch1 250nm

Peak#	Ret. Time	Area	Height	Conc.	Area%	Height%
1	8.693	583617	11312	0.000	3.148	2.276
2	10.267	17953330	485797	0.000	96.852	97.724
Total		18536947	497108		100.000	100.000

Racemic

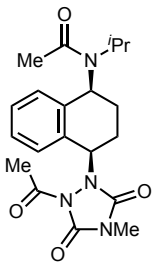
<Chromatogram>



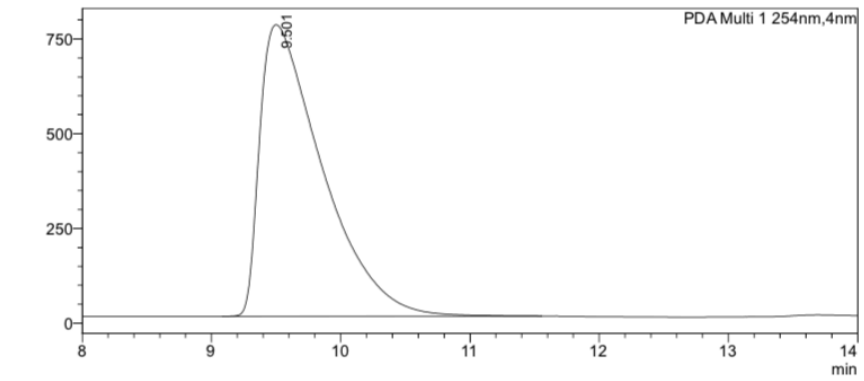
<Peak Table>

PDA Ch1 250nm

Peak#	Ret. Time	Area	Height	Conc.	Area%	Height%
1	8.512	990075	18328	0.000	49.752	42.168
2	10.397	999946	25137	0.000	50.248	57.832
Total		1990021	43465		100.000	100.000



<Chromatogram>



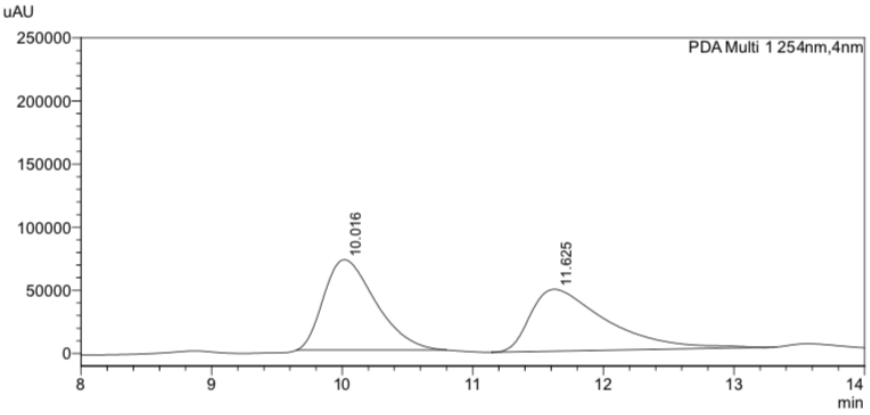
<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Area%	Height%
1	9.501	25860139	769241	0.000	100.000	100.000
Total		25860139	769241		100.000	100.000

Racemic

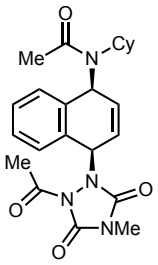
<Chromatogram>



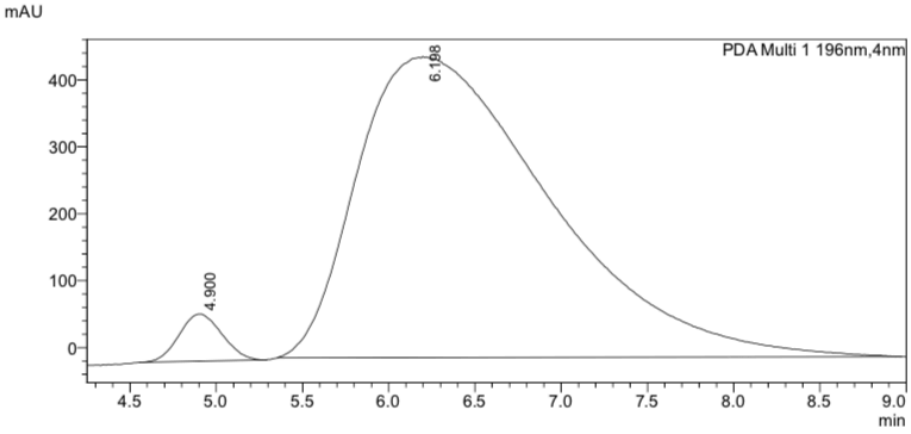
<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Area%	Height%
1	10.016	1980518	71601	0.000	50.041	59.377
2	11.625	1977254	48987	0.000	49.959	40.623
Total		3957772	120589		100.000	100.000



<Chromatogram>



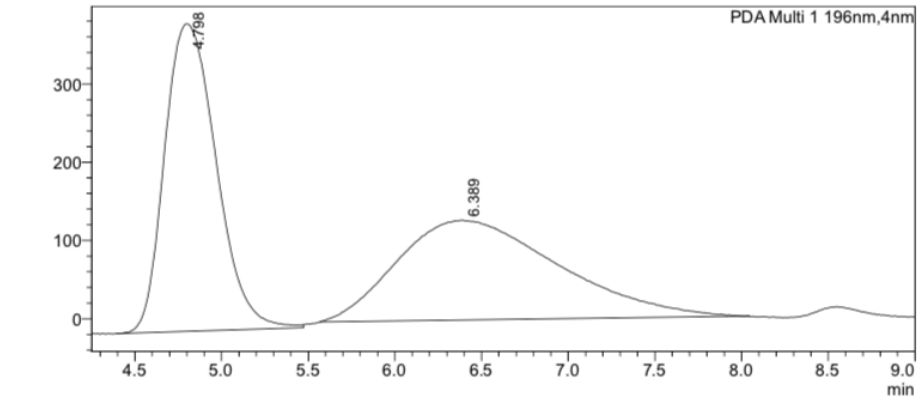
<Peak Table>

PDA Ch1 196nm

Peak#	Ret. Time	Area	Height	Conc.	Area%	Height%
1	4.900	1216791	70277	0.000	3.367	13.515
2	6.198	34921391	449736	0.000	96.633	86.485
Total		36138181	520013		100.000	100.000

Racemic

<Chromatogram>



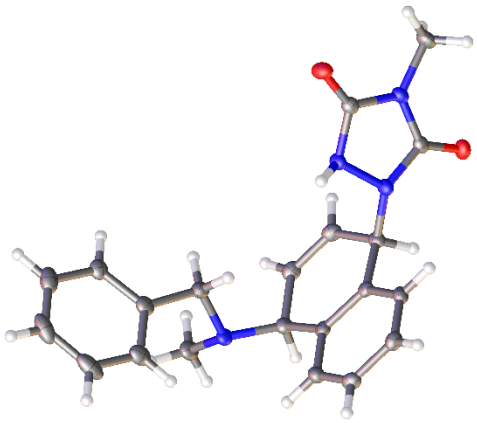
<Peak Table>

PDA Ch1 196nm

Peak#	Ret. Time	Area	Height	Conc.	Area%	Height%
1	4.798	8153484	392943	0.000	49.729	75.479
2	6.389	8242271	127658	0.000	50.271	24.521
Total		16395754	520601		100.000	100.000

6. Crystallographic data

Crystallographic Data for compound (±)-28a

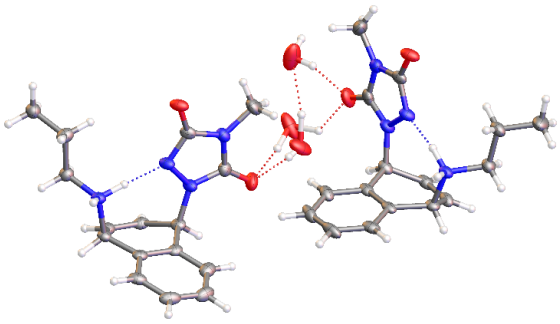


Single crystals of compound **(±)-28a** were obtained by slow recrystallization from *n*-hexanes/ethyl acetate mixtures. A suitable crystal was selected and diffraction data were collected on a Bruker D8 Venture/Photon 100 diffractometer. The crystal was kept at 100.03 K during data collection.

Supplementary Table 2: Crystal data and structure refinement for compound (±)-28a

Identification code	CCDC 1877219
Empirical formula	$C_{21}H_{22}N_4O_2$
Formula weight	362.42
Temperature/K	100.03
Crystal system	triclinic
Space group	P-1
a/Å	9.5948(2)
b/Å	12.3669(3)
c/Å	16.3965(4)
α/°	99.9720(10)
β/°	104.3150(10)
γ/°	91.5190(10)
Volume/Å^3	1851.78(8)
Z	4
ρ_{calc}g/cm^3	1.300
μ/mm^{-1}	0.692
F(000)	768.0
Crystal size/mm^3	0.143 × 0.129 × 0.048
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	5.66 to 136.796
Index ranges	$-11 \leq h \leq 11$, $-14 \leq k \leq 14$, $-19 \leq l \leq 19$
Reflections collected	27751
Independent reflections	6678 [R_{int} = 0.0355, R_{sigma} = 0.0293]
Data/restraints/parameters	6678/0/498
Goodness-of-fit on F^2	1.068
Final R indexes [I>=2σ (I)]	R_1 = 0.0365, wR_2 = 0.0805
Final R indexes [all data]	R_1 = 0.0449, wR_2 = 0.0851
Largest diff. peak/hole / e Å^{-3}	0.21/-0.21

Crystallographic Data for compound (±)-28k

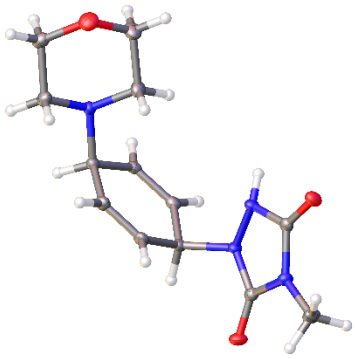


Twin crystals of compound **(±)-28k** were obtained by slow recrystallization from CH_2Cl_2/diethyl ether mixtures. A suitable crystal was selected and diffraction data were collected on a Bruker D8 Venture/Photon 100 diffractometer. The crystal was kept at 100.01 K during data collection.

Supplementary Table 3: Crystal data and structure refinement for compound (±)-28k

Identification code	CCDC 1877220
Empirical formula	$C_{16}H_{21.31}N_4O_{2.66}$
Formula weight	312.20
Temperature/K	100.01
Crystal system	triclinic
Space group	P-1
a/Å	9.8206(4)
b/Å	11.1581(5)
c/Å	15.3236(7)
α/°	101.9240(10)
β/°	100.7390(10)
γ/°	100.1540(10)
Volume/Å^3	1573.33(12)
Z	4
ρ_{calc}g/cm^3	1.318
μ/mm^{-1}	0.092
F(000)	666.0
Crystal size/mm^3	0.561 × 0.39 × 0.238
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.33 to 56.72
Index ranges	$-13 \le h \le 13$, $-14 \le k \le 14$, $-20 \le l \le 20$
Reflections collected	117799
Independent reflections	117799 [R_{int} = ?, R_{sigma} = 0.0645]
Data/restraints/parameters	117799/1/463
Goodness-of-fit on F^2	1.028
Final R indexes [I>=2σ (I)]	R_1 = 0.0550, wR_2 = 0.1245
Final R indexes [all data]	R_1 = 0.0798, wR_2 = 0.1374
Largest diff. peak/hole / e Å^{-3}	0.47/-0.29

Crystallographic Data for compound 29d



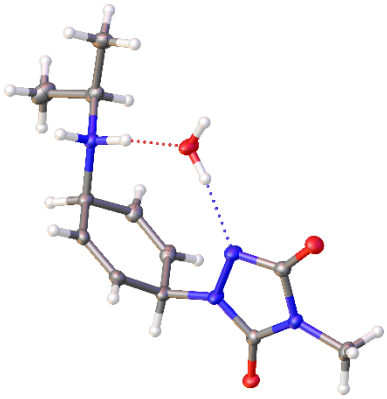
Single crystals of compound **29d** were obtained by slow recrystallization from dichloromethane/diethyl ether mixtures. A suitable crystal was selected and diffraction data were collected on a Bruker D8 Venture/Photon 100 diffractometer. The crystal was kept at 99.95 K during data collection.

Supplementary Table 4: Crystal data and structure refinement for compound 29d

Identification code	CCDC 1877221
Empirical formula	$C_{13}H_{18}N_4O_3$
Formula weight	278.31
Temperature/K	99.95
Crystal system	monoclinic
Space group	C2/c
a/Å	22.4136(10)
b/Å	6.0223(3)
c/Å	19.9058(8)
α/°	90
β/°	94.244(2)
γ/°	90
Volume/Å^3	2679.5(2)
Z	8
ρ_{calc}g/cm^3	1.380
μ/mm^{-1}	0.101
F(000)	1184.0
Crystal size/mm^3	0.404 × 0.222 × 0.128
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.284 to 54.372
Index ranges	$-28 \leq h \leq 28$, $-7 \leq k \leq 7$, $-25 \leq l \leq 25$
Reflections collected	28276
Independent reflections	2980 [R_{int} = 0.0367, R_{sigma} = 0.0170]
Data/restraints/parameters	2980/0/196
Goodness-of-fit on F^2	1.050
Final R indexes [I>=2σ (I)]	R_1 = 0.0376, wR_2 = 0.0947
Final R indexes [all data]	R_1 = 0.0402, wR_2 = 0.0969
Largest diff. peak/hole / e Å^{-3}	0.27/-0.29

Crystallographic Data for compound 29f

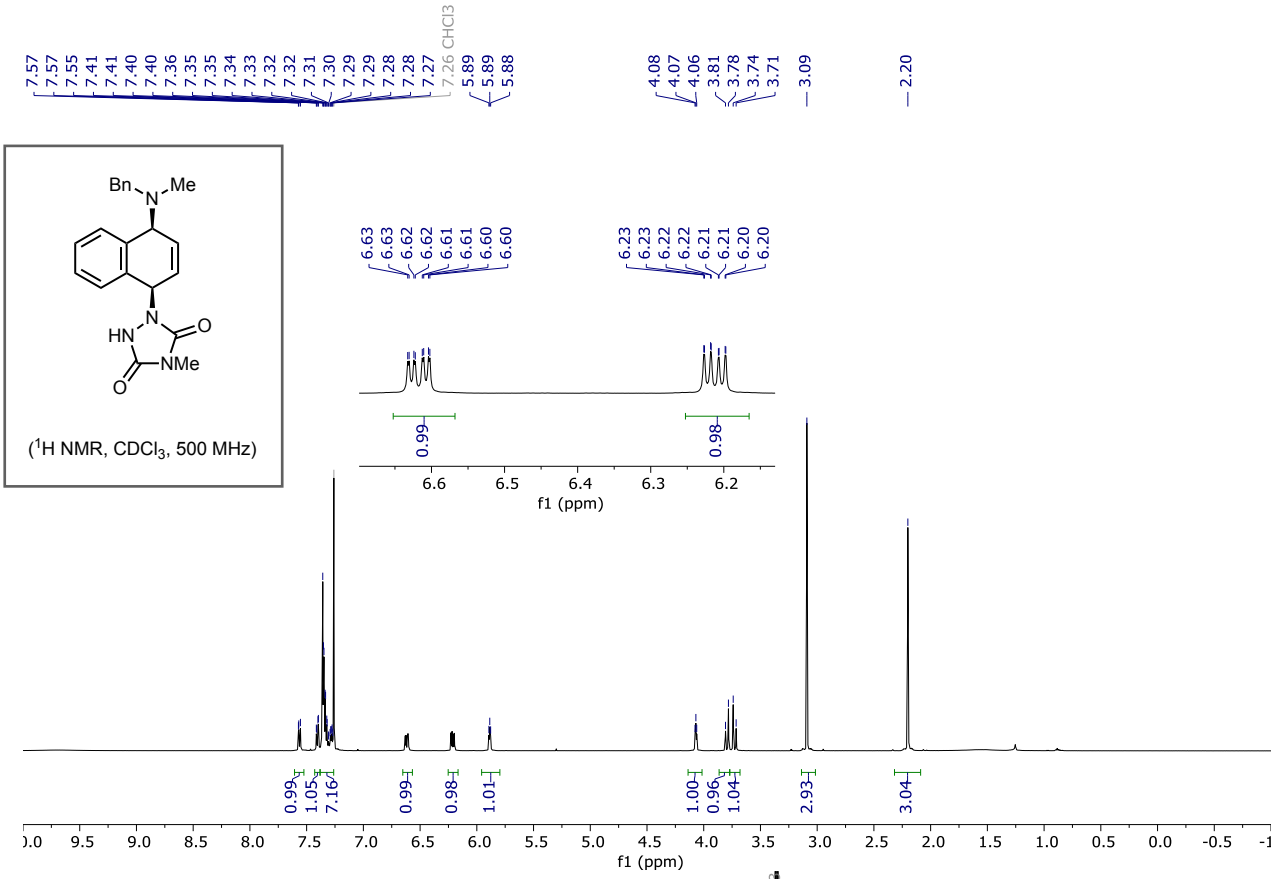
Single crystals of compound **29f** were obtained by slow recrystallization from dichloromethane/diethyl ether mixtures. A suitable crystal was selected and diffraction data were collected on a Bruker D8 Venture/Photon 100 diffractometer. The crystal was kept at 99.99 K during data collection.

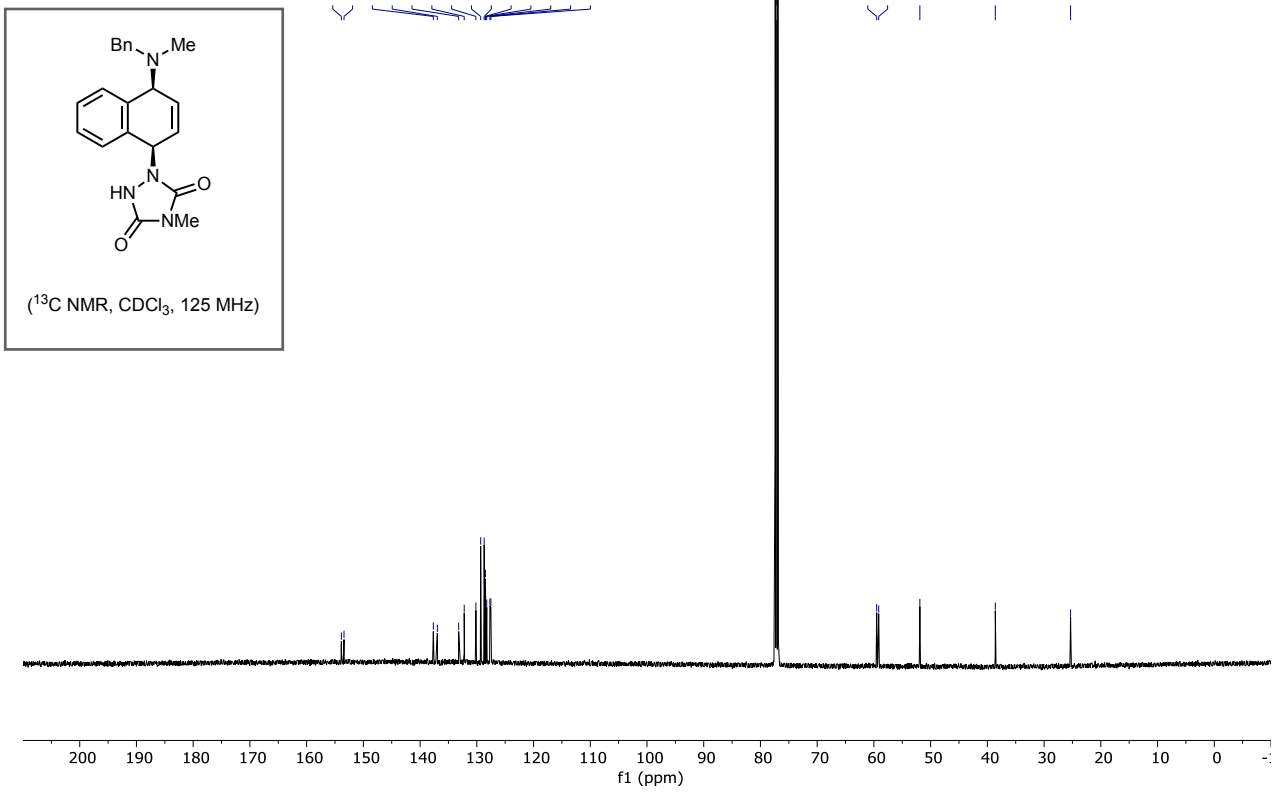


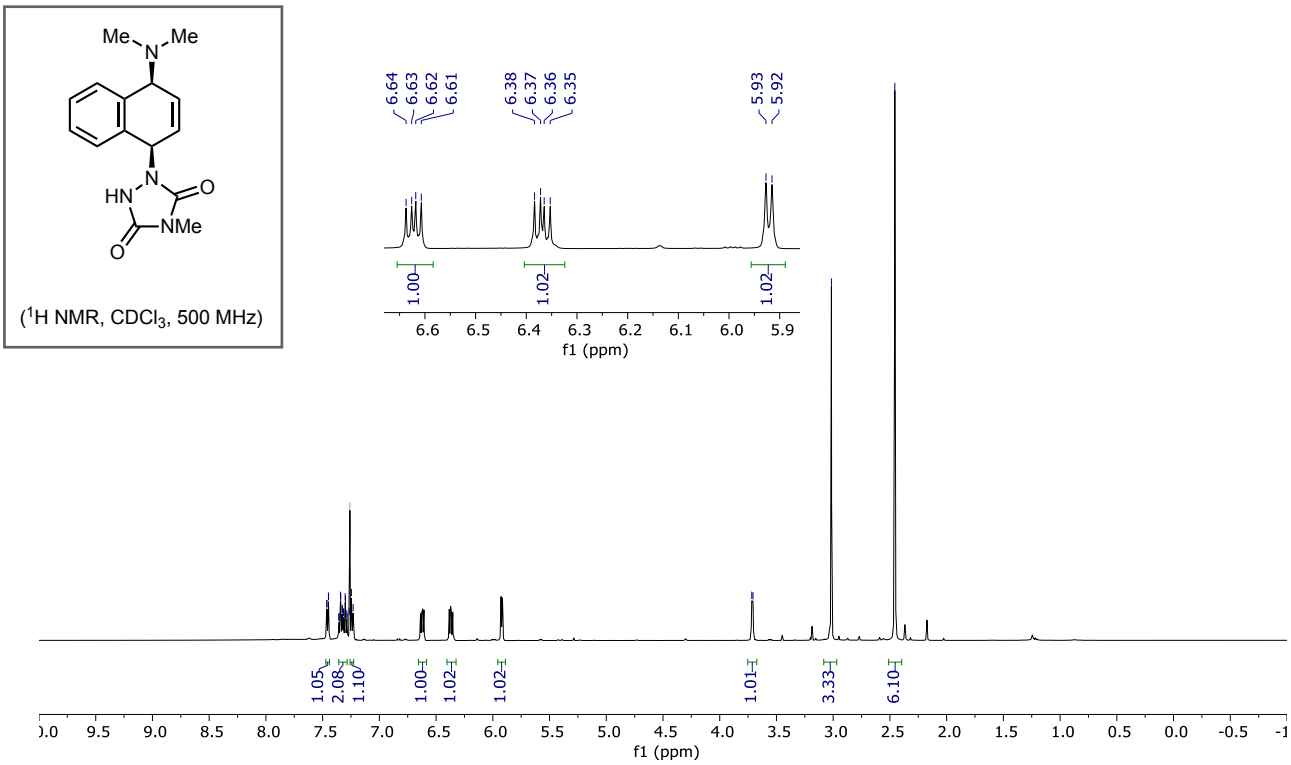
Supplementary Table 5: Crystal data and structure refinement for compound 29f

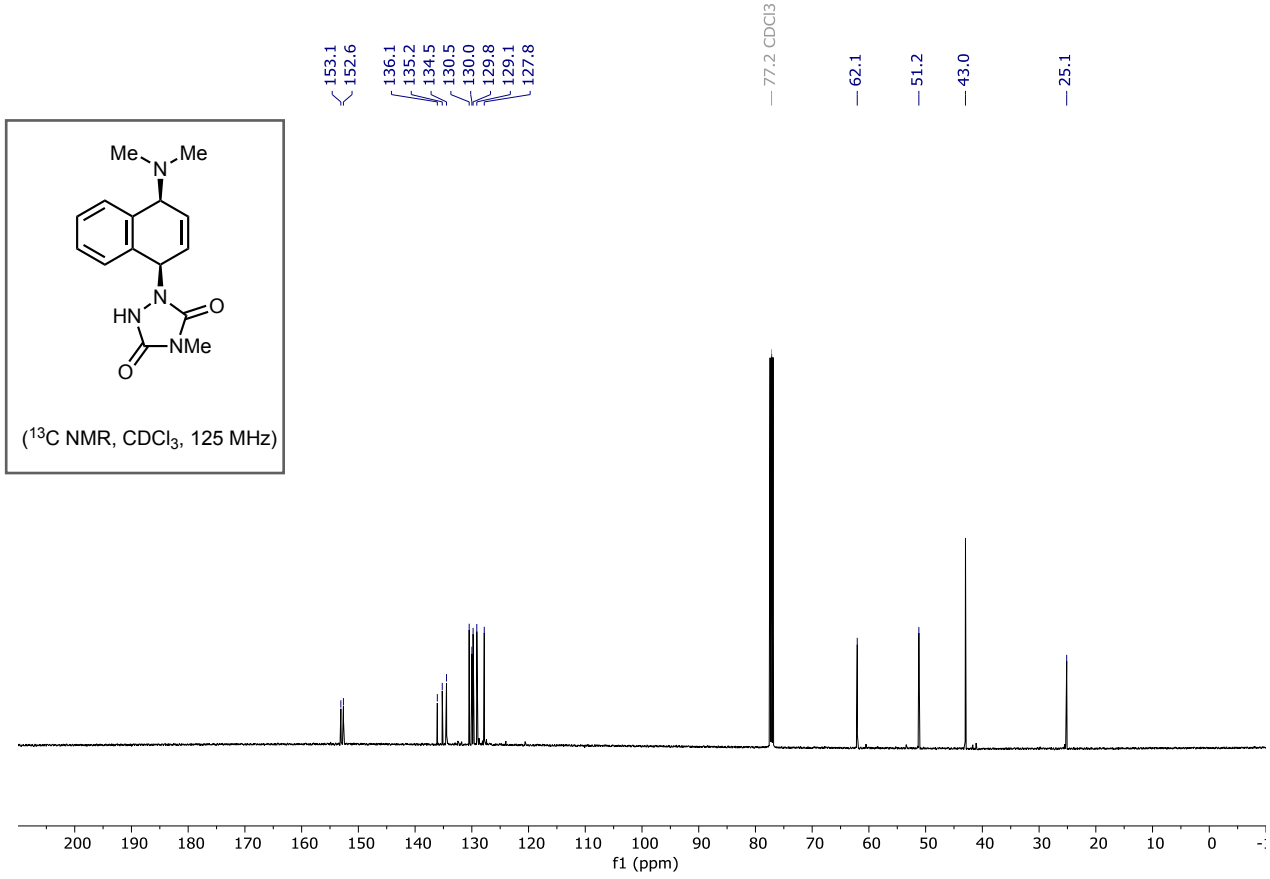
Identification code	CCDC 1877222
Empirical formula	$C_{12}H_{20}N_4O_3$
Formula weight	268.32
Temperature/K	99.99
Crystal system	triclinic
Space group	P-1
a/Å	8.0480(3)
b/Å	8.8580(4)
c/Å	10.9924(5)
α/°	69.1109(16)
β/°	76.8504(17)
γ/°	68.7540(16)
Volume/Å^3	678.01(5)
Z	2
ρ_{calc}g/cm^3	1.314
μ/mm^{-1}	0.096
F(000)	288.0
Crystal size/mm^3	0.317 × 0.154 × 0.08
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.176 to 52.886
Index ranges	-10 ≤ h ≤ 10, -11 ≤ k ≤ 11, -13 ≤ l ≤ 13
Reflections collected	5557
Independent reflections	2779 [R_{int} = 0.0192, R_{sigma} = 0.0255]
Data/restraints/parameters	2779/0/188
Goodness-of-fit on F^2	1.107
Final R indexes [I>=2σ (I)]	R_1 = 0.0472, wR_2 = 0.0940
Final R indexes [all data]	R_1 = 0.0584, wR_2 = 0.0980
Largest diff. peak/hole / e Å^{-3}	0.28/-0.23

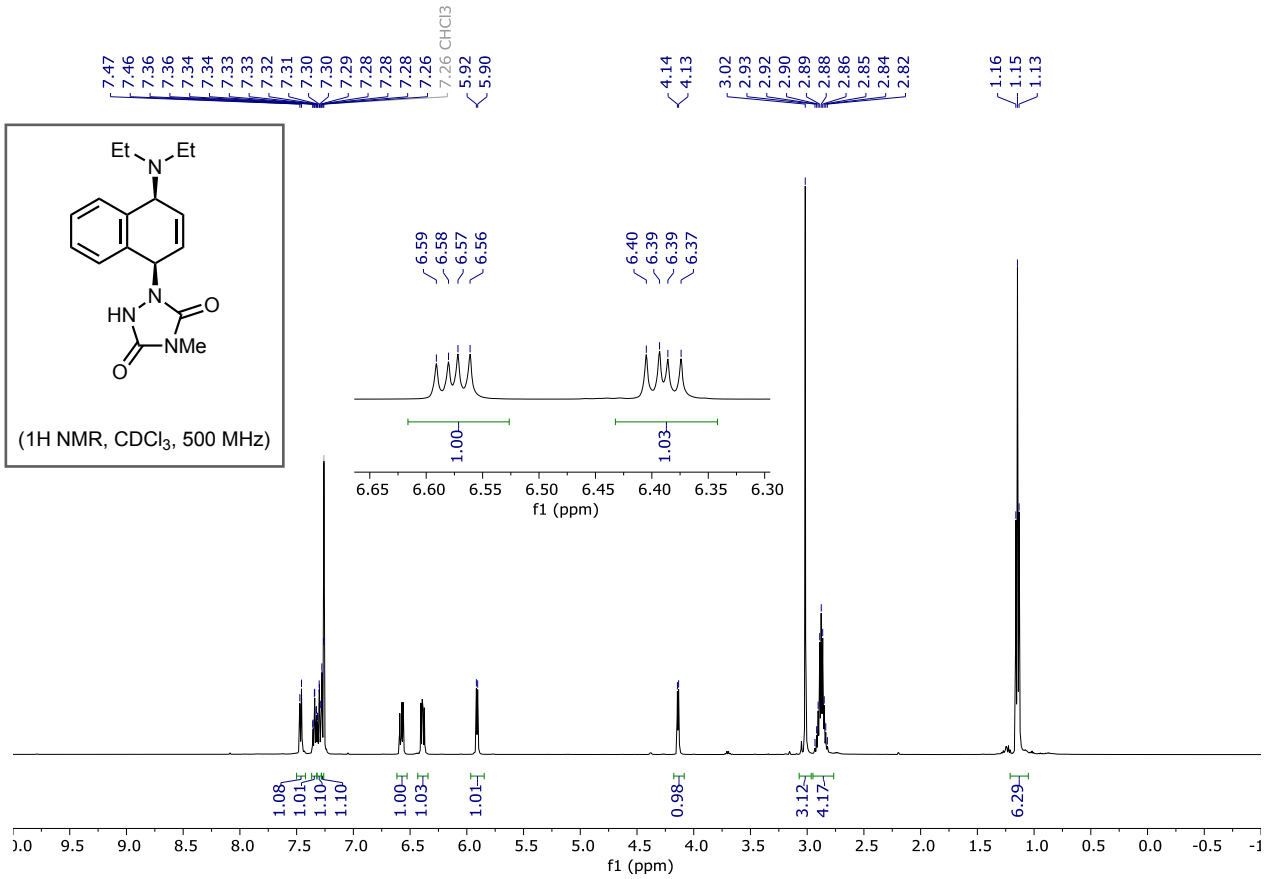
7. ^{1}H and ^{13}C NMR Spectra

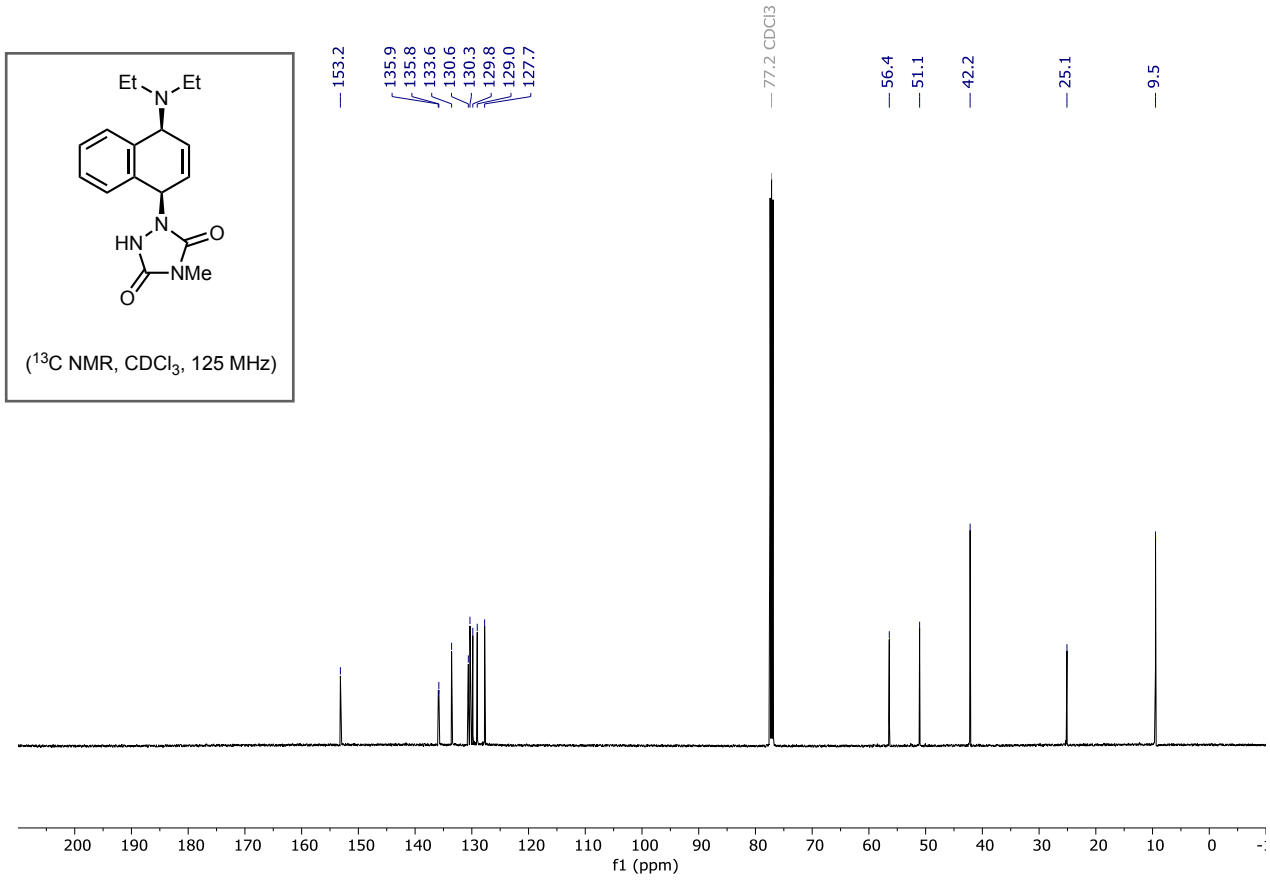


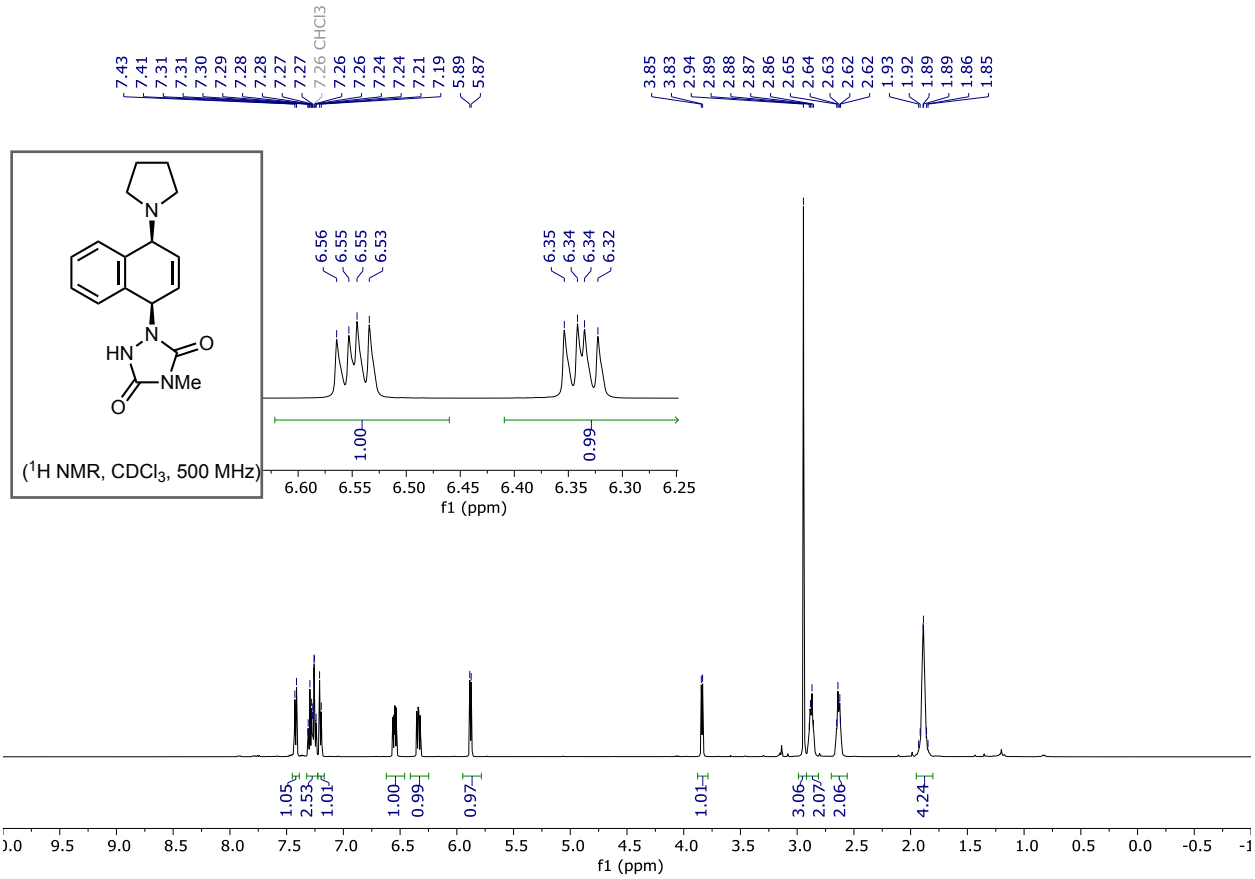


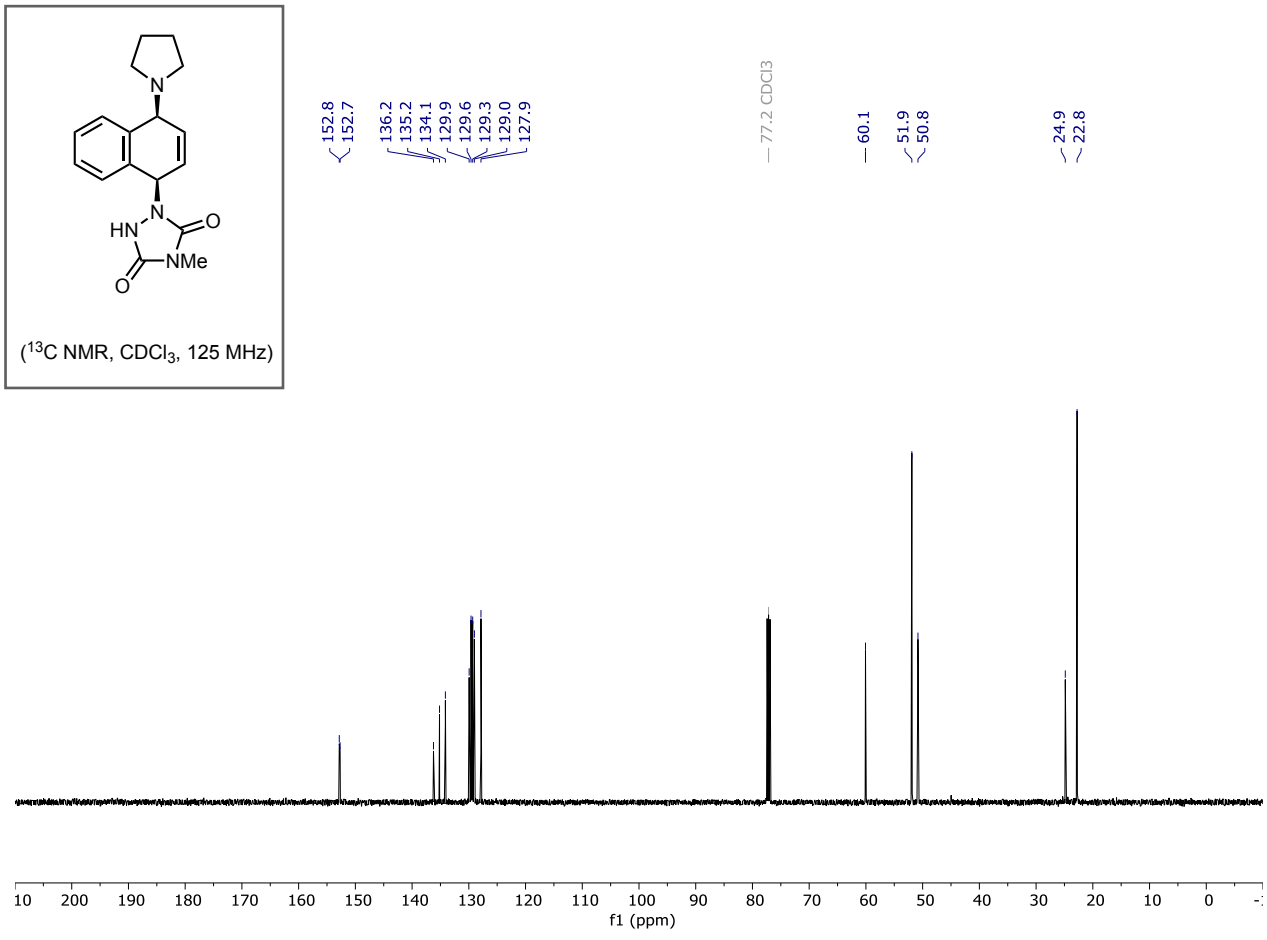

Me
N
Me
HN
O
NMe
O
(1H NMR, CDCl3, 500 MHz)
7.46
7.46
7.45
7.45
7.36
7.35
7.34
7.34
7.33
7.33
7.32
7.31
7.30
7.30
7.29
7.28
7.27
7.26 CHCl3
7.25
7.23
3.72
3.71
3.02
2.46
6.64
6.63
6.62
6.61
6.38
6.37
6.36
6.35
5.93
5.92
1.00
1.02
1.02
f1 (ppm)
1.05
2.08
1.10
1.00
1.02
1.02
1.01
3.33
6.10
f1 (ppm)

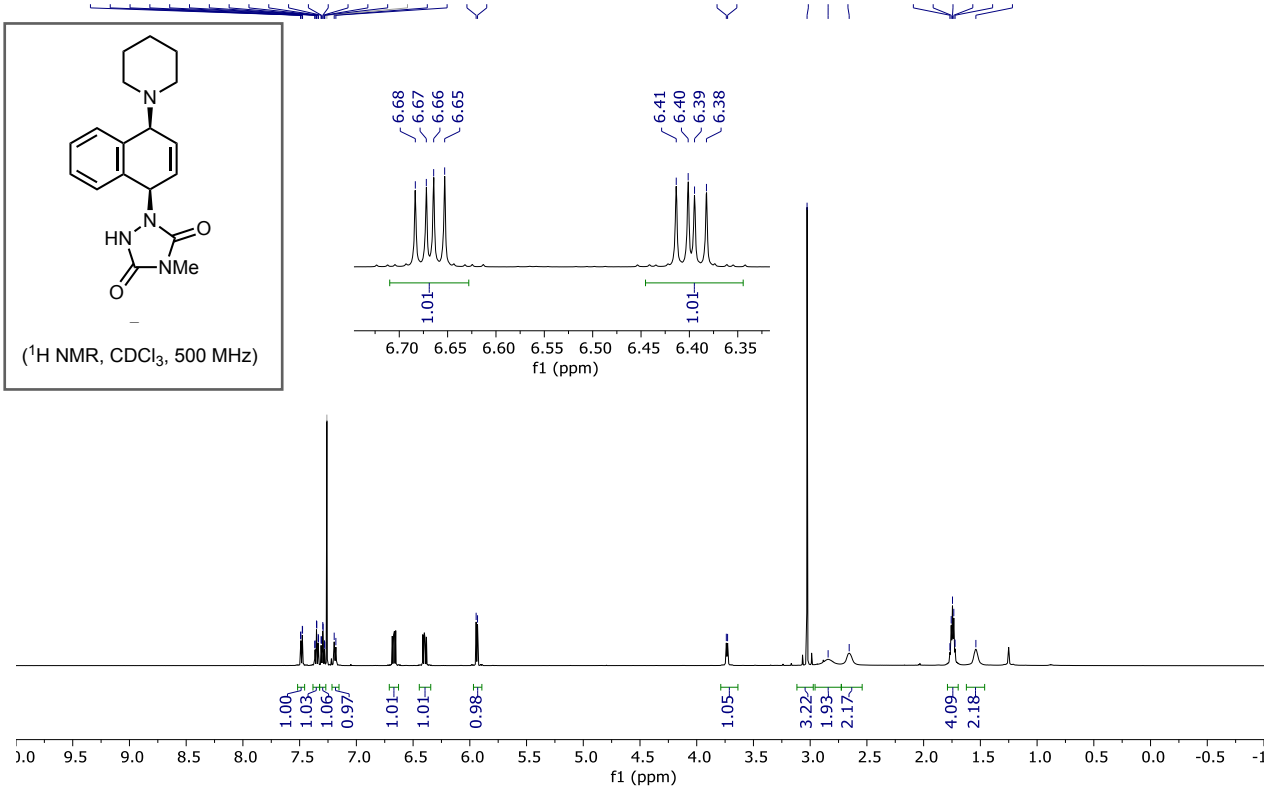

Me
N
Me
HN
O
NMe
O
(13C NMR, CDCl3, 125 MHz)
153.1
152.6
136.1
135.2
134.5
130.5
130.0
129.8
129.1
127.8
77.2 CDCl3
62.1
51.2
43.0
25.1
f1 (ppm)

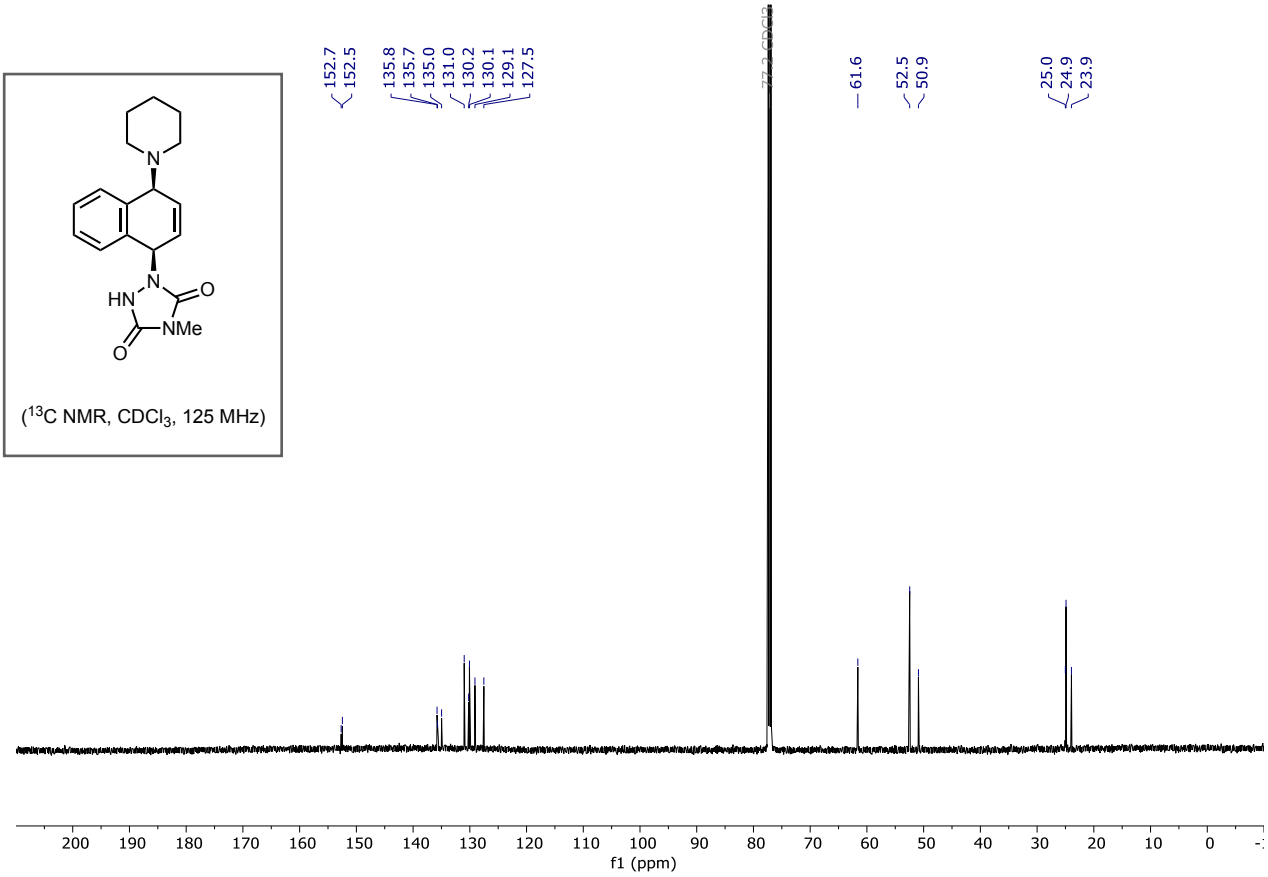

Et
N
Et
HN
N
O
NMe
O
(1H NMR, CDCl3, 500 MHz)
7.47 7.46 7.36 7.36 7.34 7.34 7.33 7.33 7.32 7.31 7.30 7.30 7.29 7.28 7.28 7.28 7.26 7.26 CHCl3
5.92 5.90
4.14 4.13
3.02 2.93 2.92 2.90 2.89 2.88 2.86 2.85 2.84 2.82
1.16 1.15 1.13
6.59 6.58 6.57 6.56
6.40 6.39 6.39 6.37
1.00 1.03
6.65 6.60 6.55 6.50 6.45 6.40 6.35 6.30
f1 (ppm)
1.08 1.01 1.10 1.10 1.00 1.03 1.01 0.98 3.12 4.17 6.29
f1 (ppm)

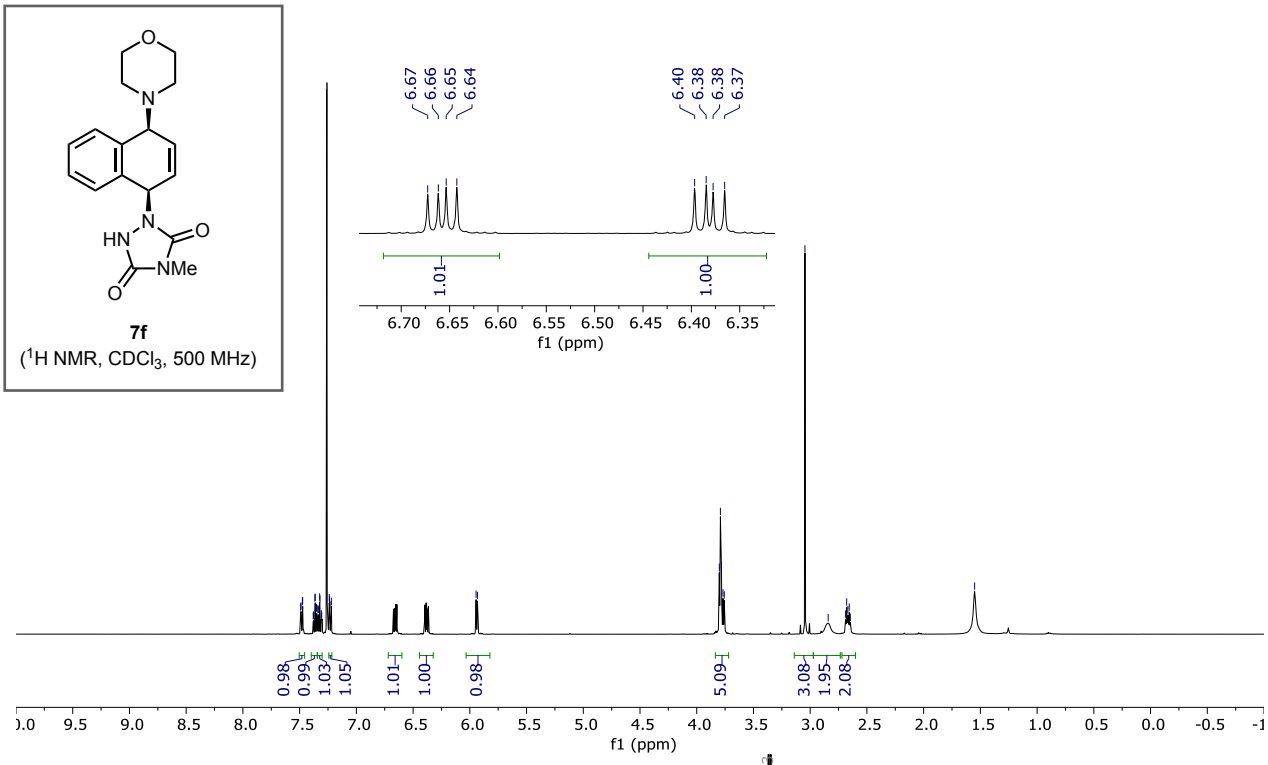

Et
N
Et
HN
N
O
NMe
O
(13C NMR, CDCl3, 125 MHz)
153.2
135.9 135.8 133.6 130.6 130.3 129.8 129.0 127.7
77.2 CDCl3
56.4
51.1
42.2
25.1
9.5
f1 (ppm)


7.43 7.41 7.31 7.31 7.30 7.29 7.28 7.28 7.27 7.27 7.26 CHCl3 7.26 7.26 7.24 7.24 7.21 7.19 5.89 5.87
3.85 3.83 2.94 2.89 2.88 2.87 2.86 2.65 2.64 2.63 2.62 2.62 1.93 1.92 1.89 1.89 1.86 1.85
6.56 6.55 6.55 6.53 6.35 6.34 6.34 6.32
1.00 0.99
6.60 6.55 6.50 6.45 6.40 6.35 6.30 6.25
f1 (ppm)
1.05 2.53 1.01 1.00 0.99 0.97 1.01 3.06 2.07 2.06 4.24
f1 (ppm)
HN N O NMe O
(^{1}H NMR, $CDCl_3$, 500 MHz)


152.8 152.7 136.2 135.2 134.1 129.9 129.6 129.3 129.0 127.9
77.2 CDCl3
60.1 51.9 50.8 24.9 22.8
f1 (ppm)
HN N O NMe O
(^{13}C NMR, $CDCl_3$, 125 MHz)

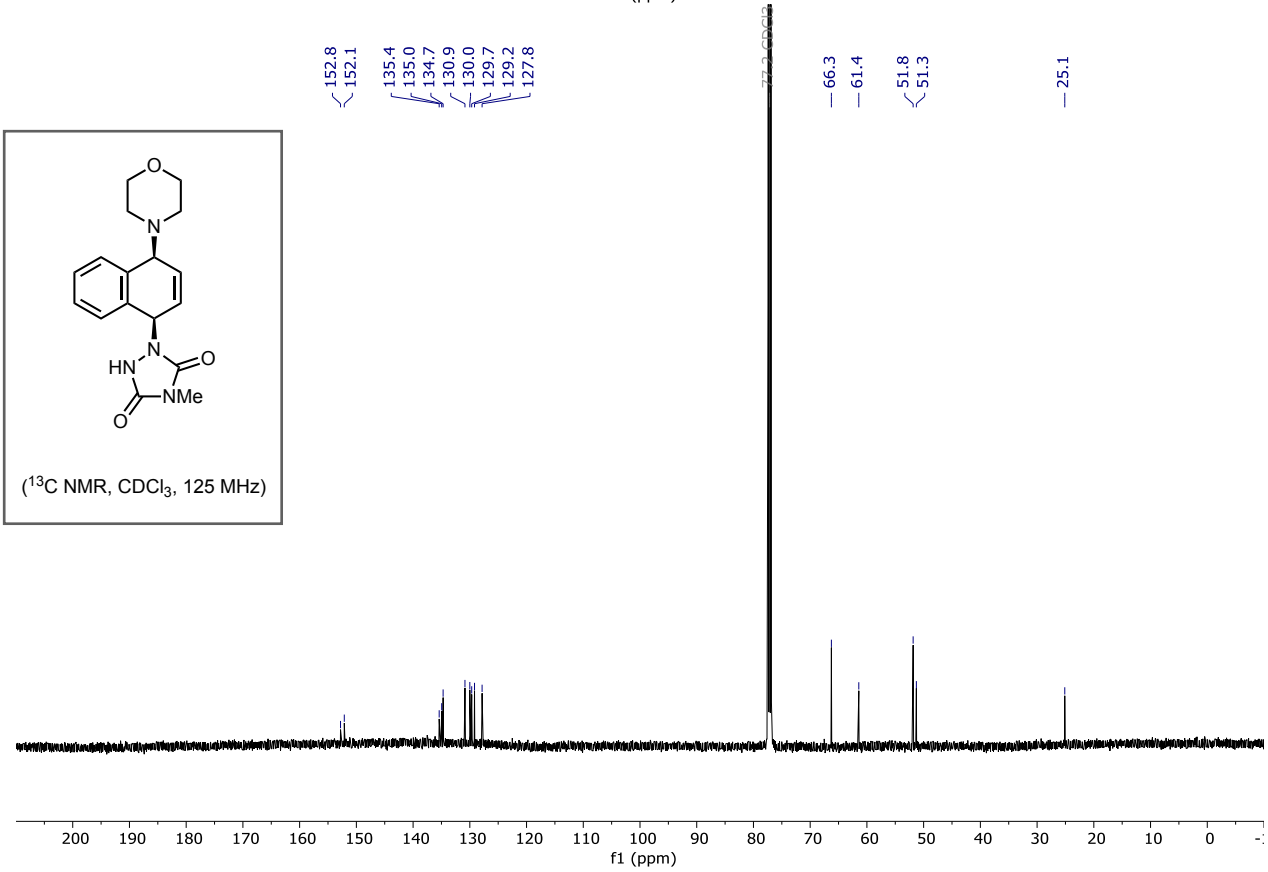

7.49
7.49
7.48
7.47
7.37
7.36
7.35
7.35
7.34
7.33
7.31
7.31
7.30
7.29
7.28
7.28
7.26 CHCl3
7.20
7.18
5.94
5.93
3.74
3.73
3.03
2.84
2.66
1.77
1.76
1.75
1.73
1.72
1.54
6.68
6.67
6.66
6.65
6.41
6.40
6.39
6.38
1.01
1.01
6.70 6.65 6.60 6.55 6.50 6.45 6.40 6.35
f1 (ppm)
HN
N
O
NMe
O
(^{1}H NMR, $CDCl_3$, 500 MHz)
1.00
1.03
1.06
0.97
1.01
1.01
0.98
1.05
3.22
1.93
2.17
4.09
2.18
f1 (ppm)


152.7
152.5
135.8
135.7
135.0
131.0
130.2
130.1
129.1
127.5
77.2 CDCl3
61.6
52.5
50.9
25.0
24.9
23.9
HN
N
O
NMe
O
(^{13}C NMR, $CDCl_3$, 125 MHz)
f1 (ppm)

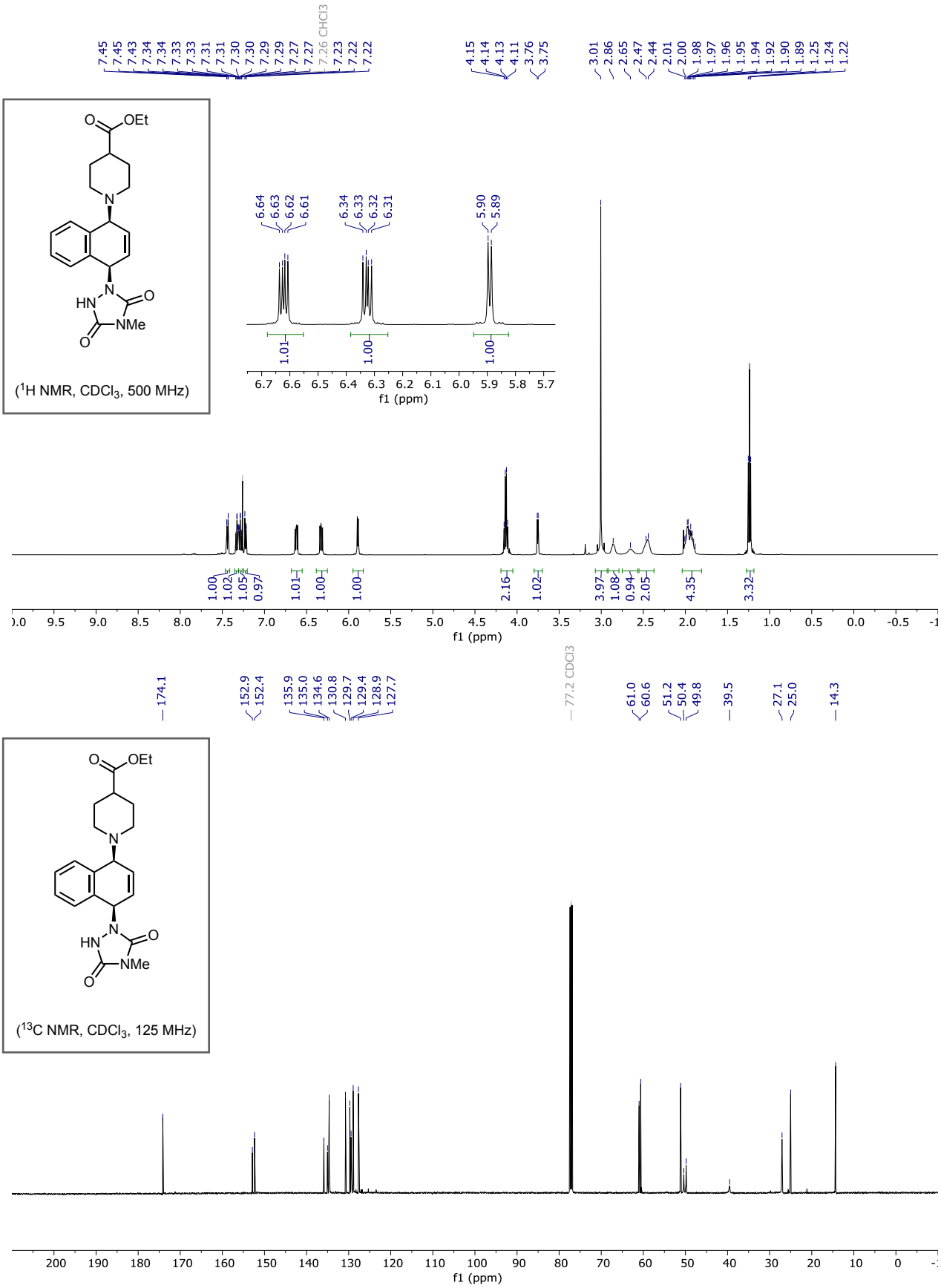


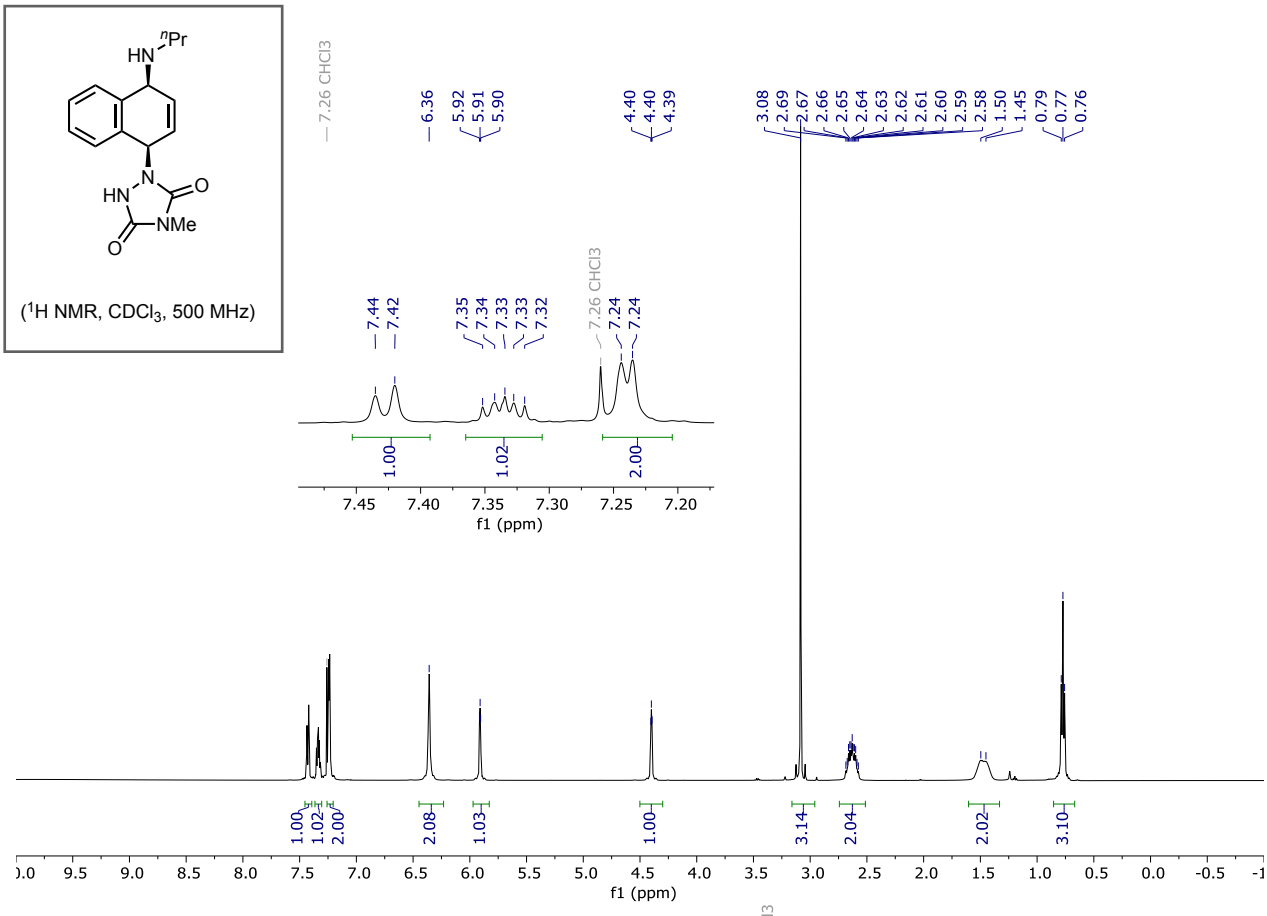
7f

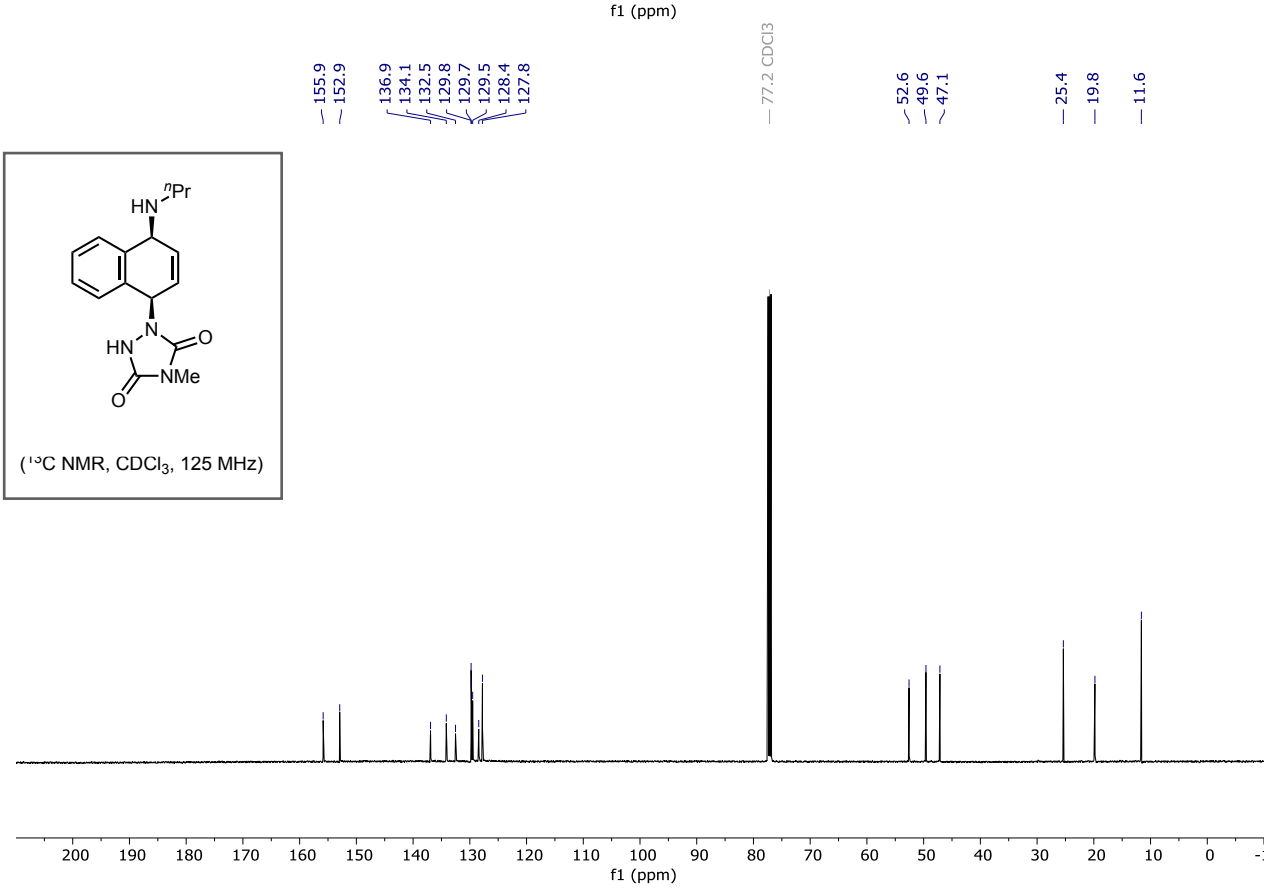
(^{1}H NMR, $CDCl_3$, 500 MHz)

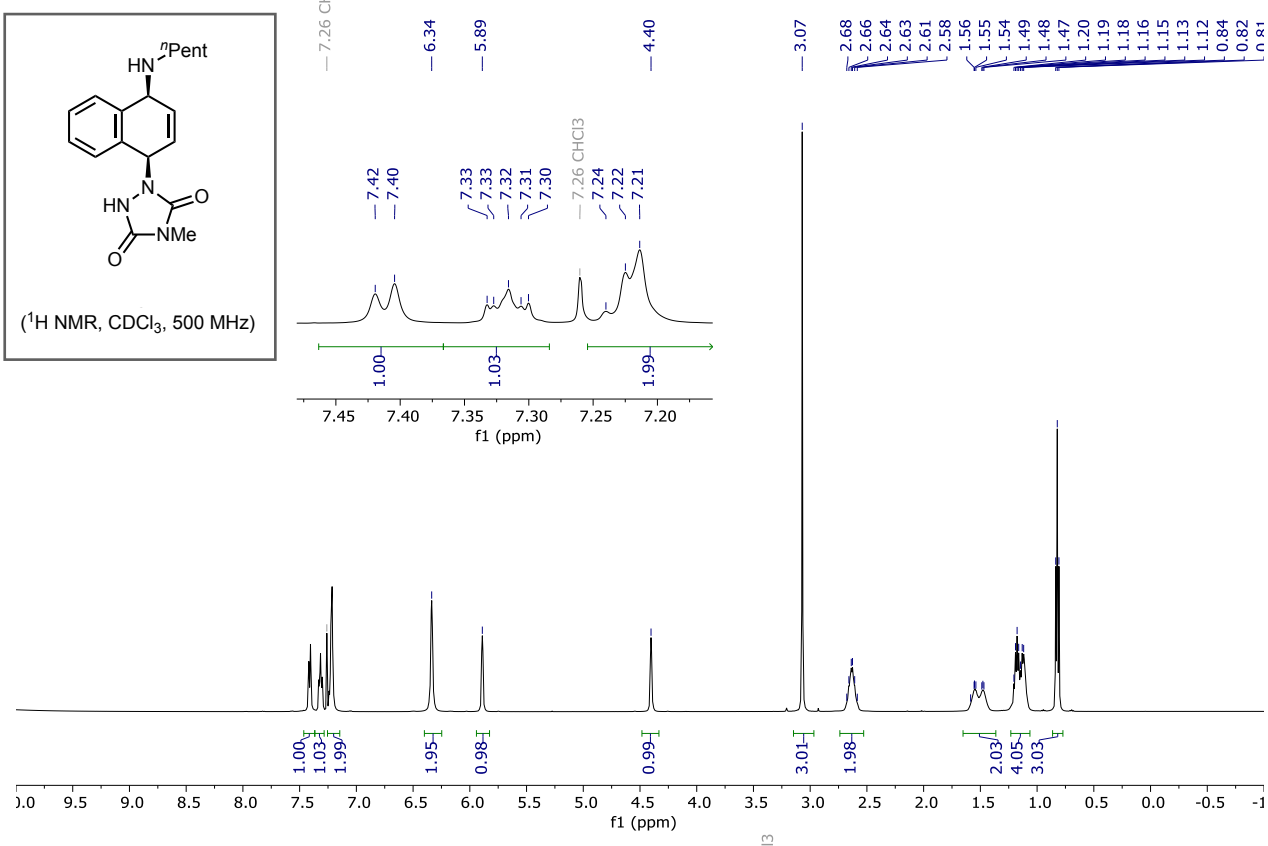


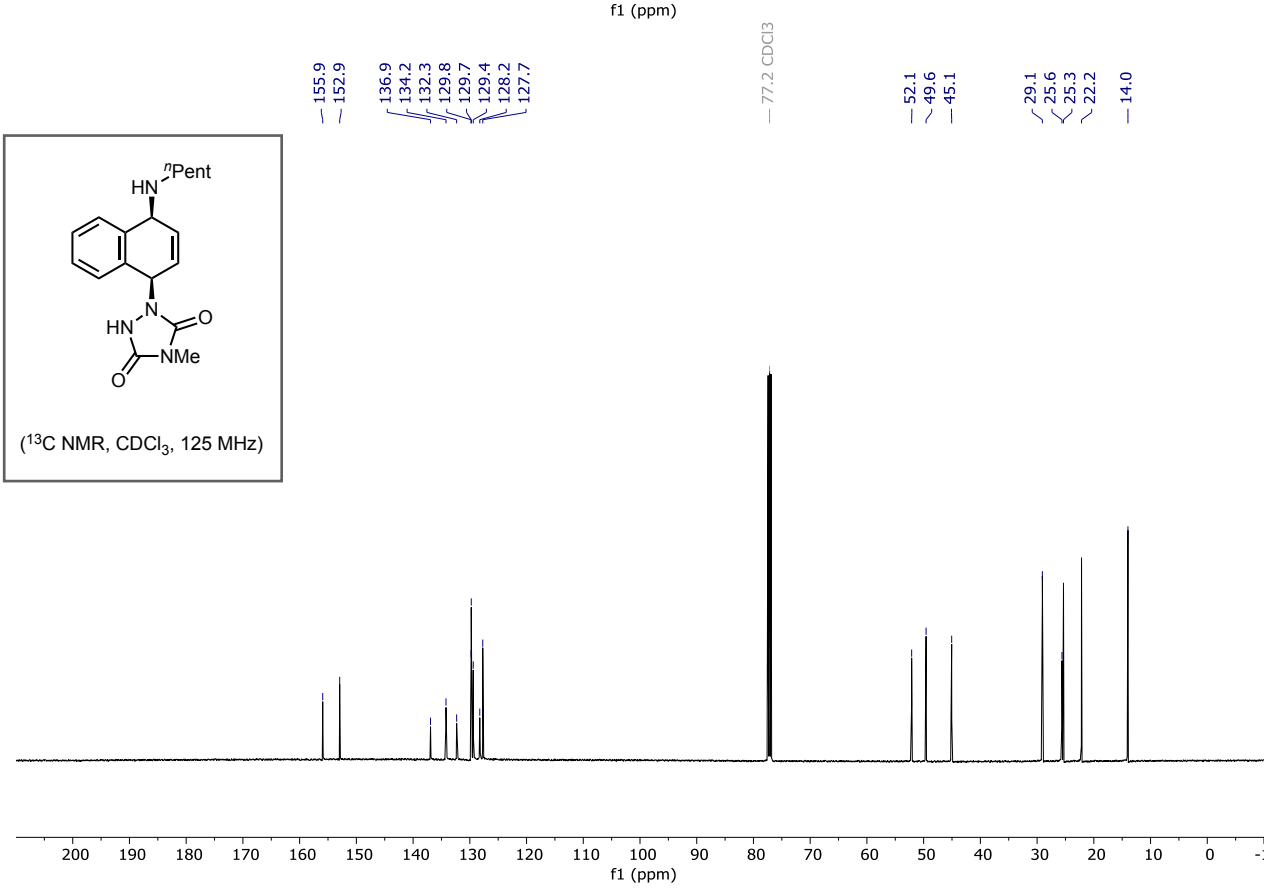
(^{13}C NMR, $CDCl_3$, 125 MHz)

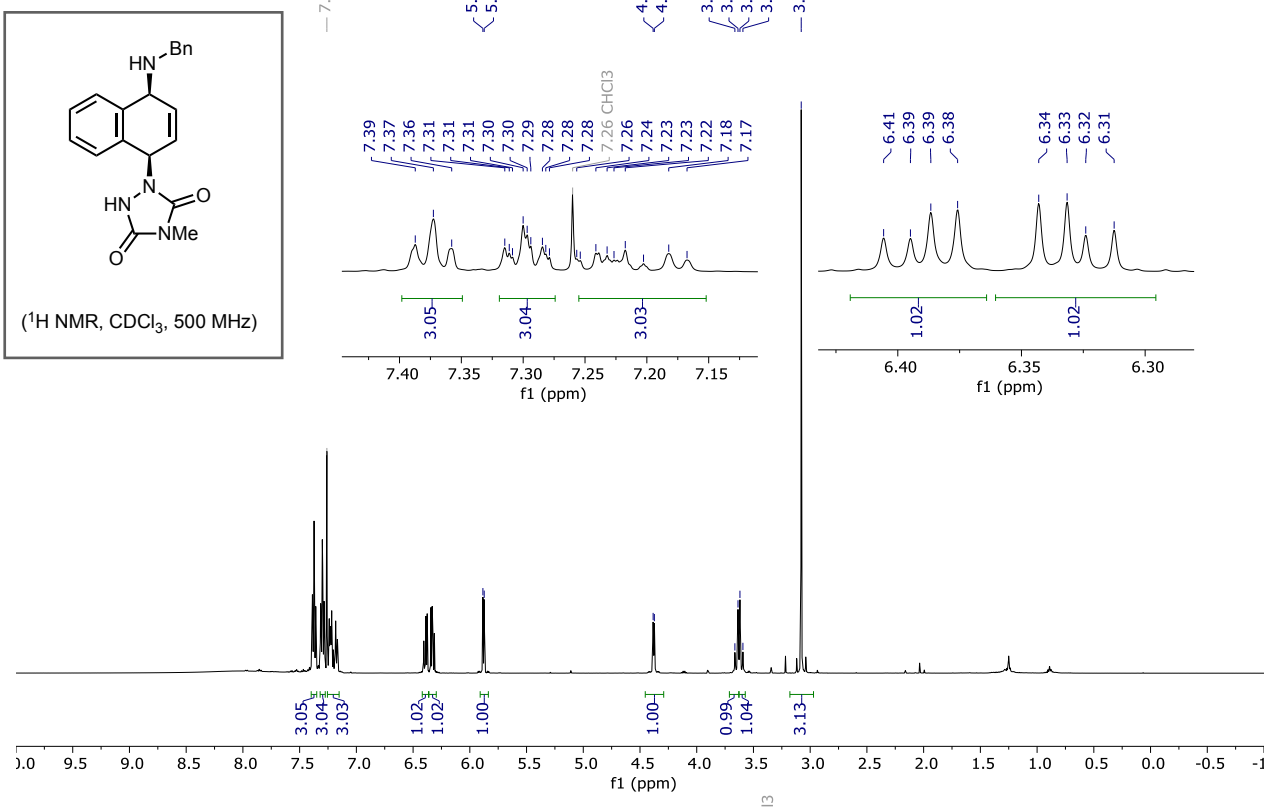

7.45 7.45 7.43 7.34 7.34 7.33 7.33 7.31 7.31 7.30 7.30 7.29 7.29 7.27 7.27 7.26 CHCl3 7.23 7.22 7.22
4.15 4.14 4.13 4.11 3.76 3.75
3.01 2.86 2.65 2.47 2.44 2.01 2.00 1.98 1.97 1.96 1.95 1.94 1.92 1.90 1.89 1.25 1.24 1.22
O OEt
N
N
HN
O
NMe
O
(1H NMR, CDCl3, 500 MHz)
6.64 6.63 6.62 6.61 6.34 6.33 6.32 6.31 5.90 5.89
1.01 1.00 1.00
6.7 6.6 6.5 6.4 6.3 6.2 6.1 6.0 5.9 5.8 5.7
f1 (ppm)
1.00 1.02 1.05 0.97 1.01 1.00 1.00 2.16 1.02 3.97 1.08 0.94 2.05 4.35 3.32
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
f1 (ppm)
174.1
152.9 152.4
135.9 135.0 134.6 130.8 129.7 129.4 128.9 127.7
77.2 CDCl3
61.0 60.6 51.2 50.4 49.8 39.5 27.1 25.0 14.3
O OEt
N
N
HN
O
NMe
O
(13C NMR, CDCl3, 125 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

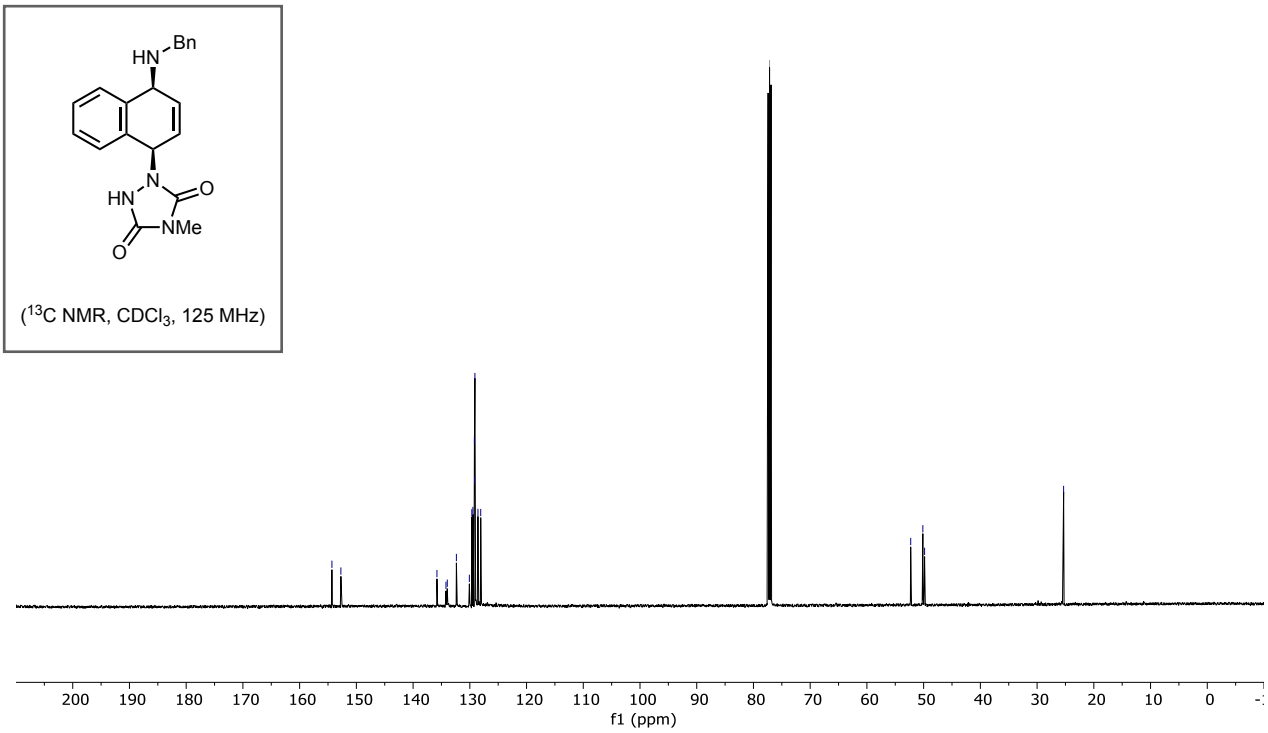

HN
nPr
HN
N
O
NMe
O
(1H NMR, CDCl3, 500 MHz)
7.26 CHCl3
6.36
5.92
5.91
5.90
4.40
4.40
4.39
3.08
2.69
2.67
2.66
2.65
2.64
2.63
2.62
2.61
2.60
2.59
2.58
1.50
1.45
0.79
0.77
0.76
7.44
7.42
7.35
7.34
7.33
7.33
7.32
7.26 CHCl3
7.24
7.24
1.00
1.02
2.00
7.45 7.40 7.35 7.30 7.25 7.20
f1 (ppm)
1.00
1.02
2.00
2.08
1.03
1.00
3.14
2.04
2.02
3.10
f1 (ppm)

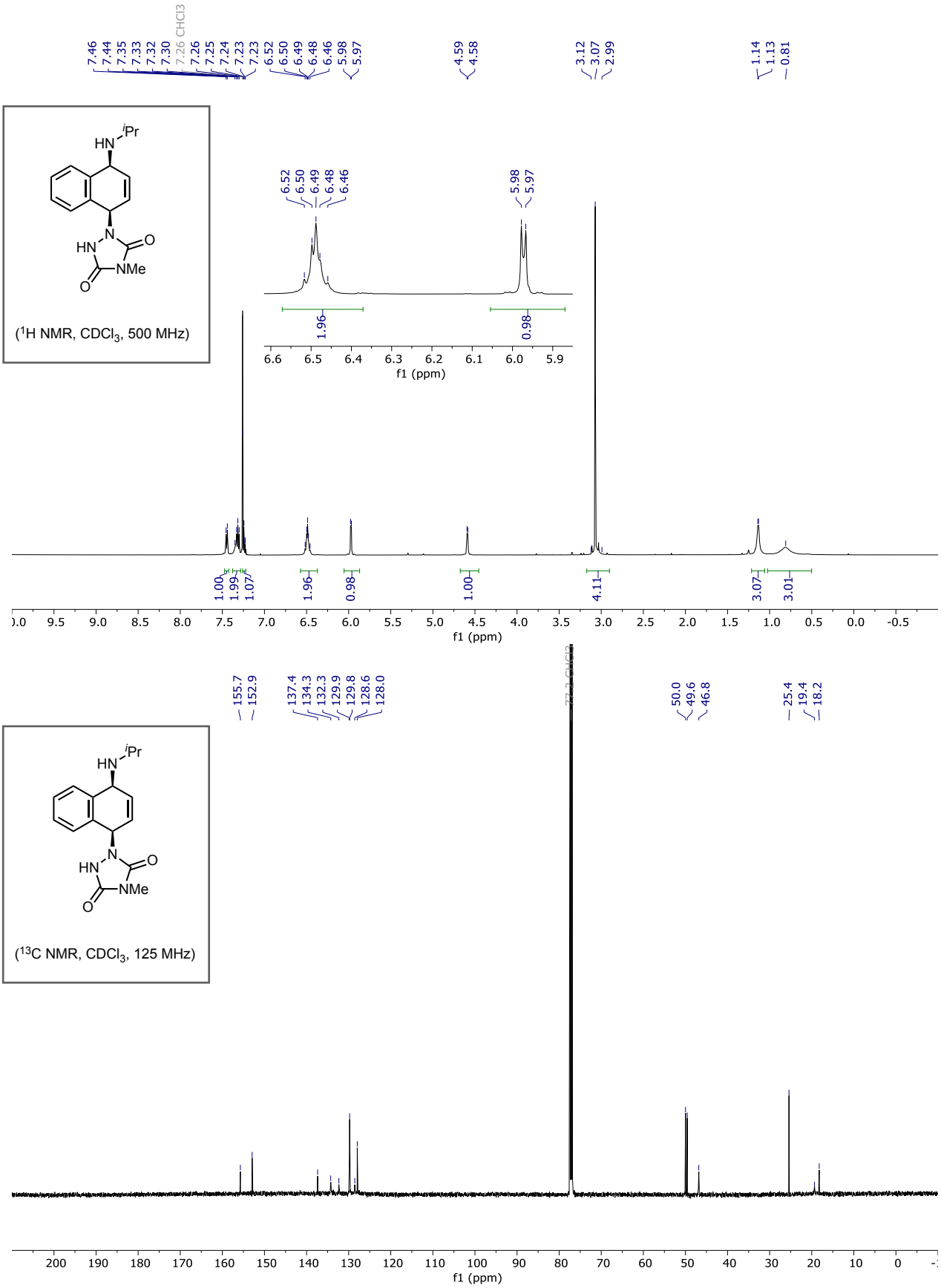

HN
nPr
HN
N
O
NMe
O
(13C NMR, CDCl3, 125 MHz)
155.9
152.9
136.9
134.1
132.5
129.8
129.7
129.5
128.4
127.8
77.2 CDCl3
52.6
49.6
47.1
25.4
19.8
11.6
f1 (ppm)

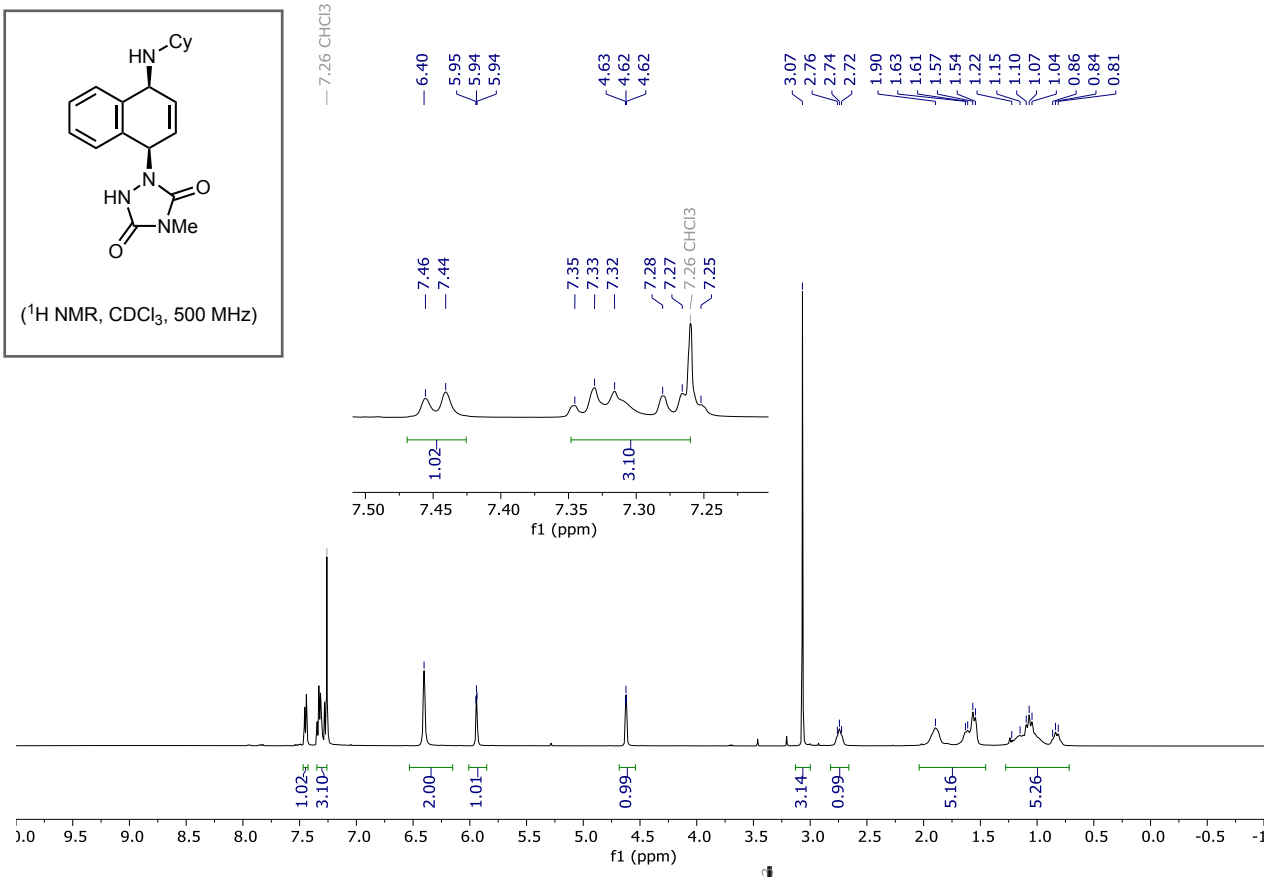

HN
nPent
HN
N
O
NMe
O
(1H NMR, CDCl3, 500 MHz)
7.26 CHCl3
6.34
5.89
4.40
3.07
7.42
7.40
7.33
7.33
7.32
7.31
7.30
7.26 CHCl3
7.24
7.22
7.21
1.00
1.03
1.99
7.45
7.40
7.35
7.30
7.25
7.20
f1 (ppm)
1.00
1.03
1.99
1.95
0.98
0.99
3.01
1.98
2.03
4.05
3.03
f1 (ppm)

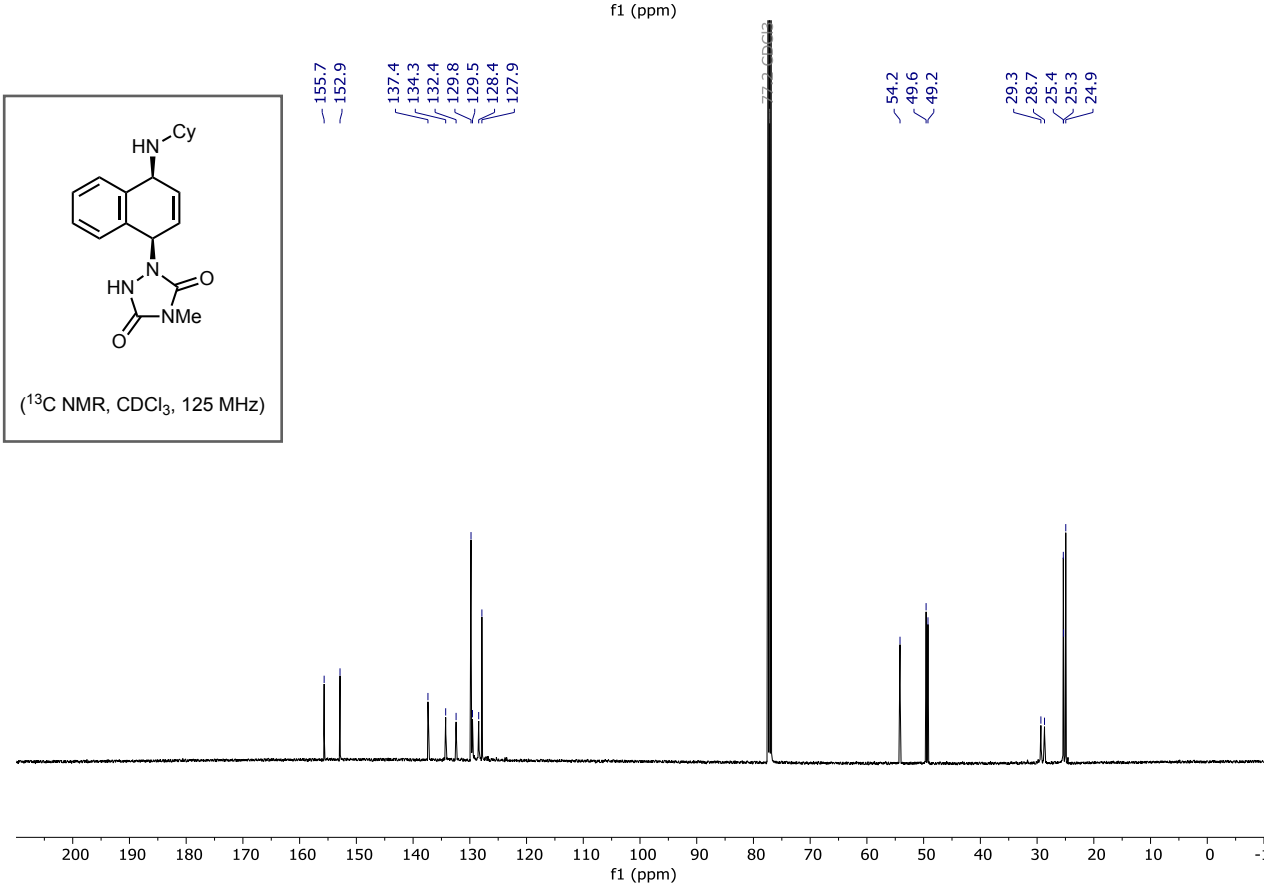

HN
nPent
HN
N
O
NMe
O
(13C NMR, CDCl3, 125 MHz)
155.9
152.9
136.9
134.2
132.3
129.8
129.7
129.4
128.2
127.7
77.2 CDCl3
52.1
49.6
45.1
29.1
25.6
25.3
22.2
14.0
f1 (ppm)

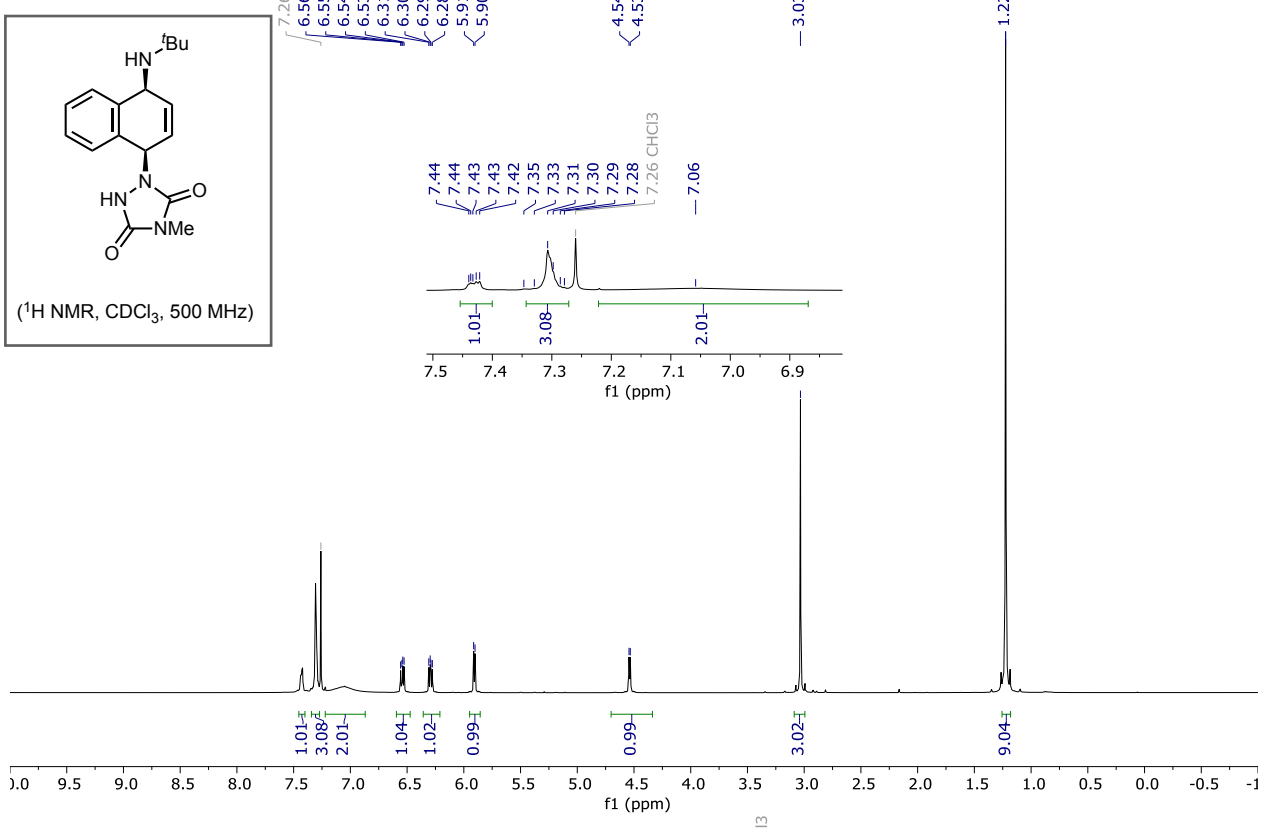

HN
Bn
HN
N
O
NMe
O
(^{1}H NMR, $CDCl_3$, 500 MHz)
7.26 CHCl3
5.88
5.87
4.38
4.37
3.66
3.64
3.62
3.59
3.08
7.39
7.37
7.36
7.31
7.31
7.31
7.30
7.30
7.29
7.28
7.28
7.28
7.26
7.24
7.23
7.23
7.22
7.18
7.17
6.41
6.39
6.39
6.38
6.34
6.33
6.32
6.31
3.05
3.04
3.03
1.02
1.02
1.00
1.00
0.99
1.04
3.13
f1 (ppm)

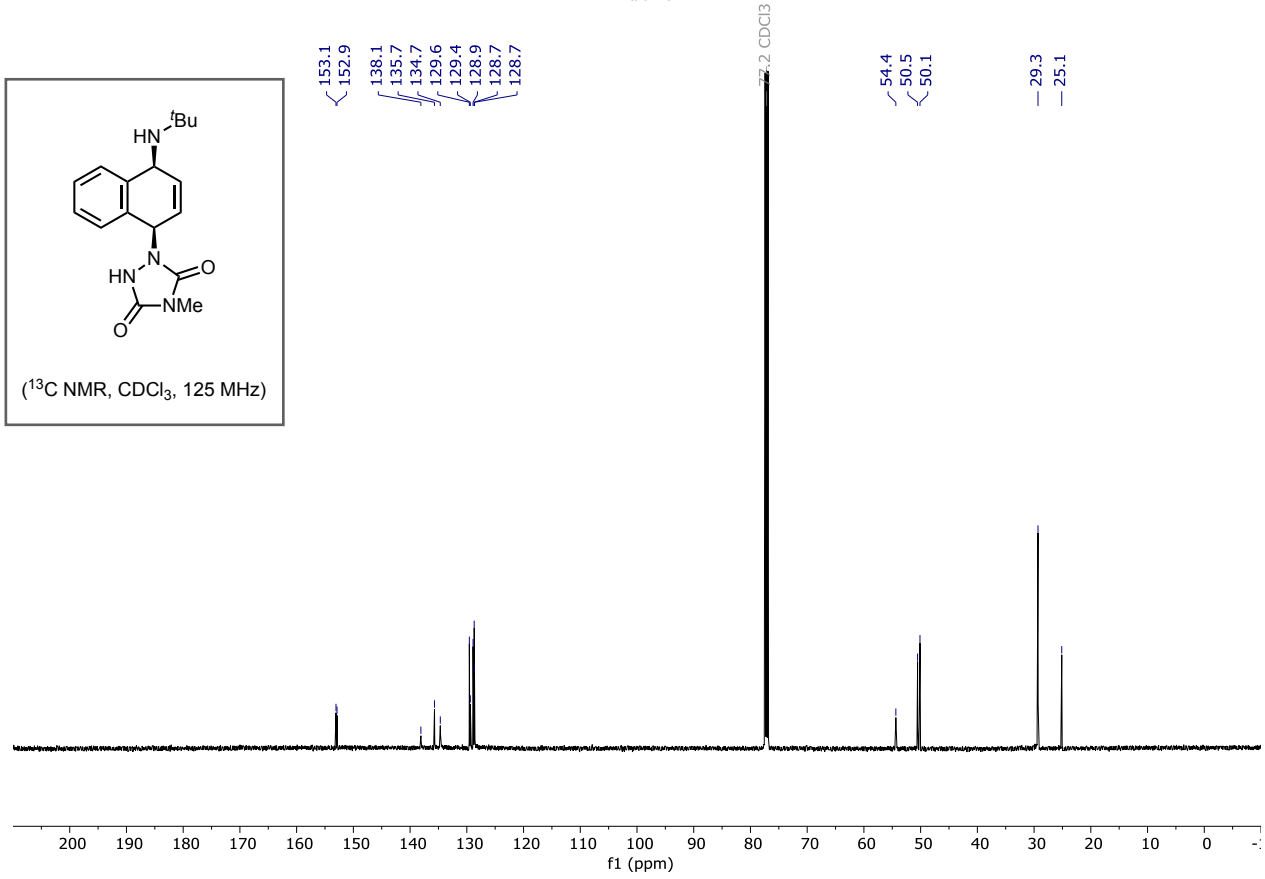

HN
Bn
HN
N
O
NMe
O
(^{13}C NMR, $CDCl_3$, 125 MHz)
154.3
152.7
135.8
134.2
134.0
132.4
130.1
129.6
129.5
129.2
129.2
129.1
128.6
128.1
77.2 CDCl3
52.3
50.1
49.8
25.3
f1 (ppm)

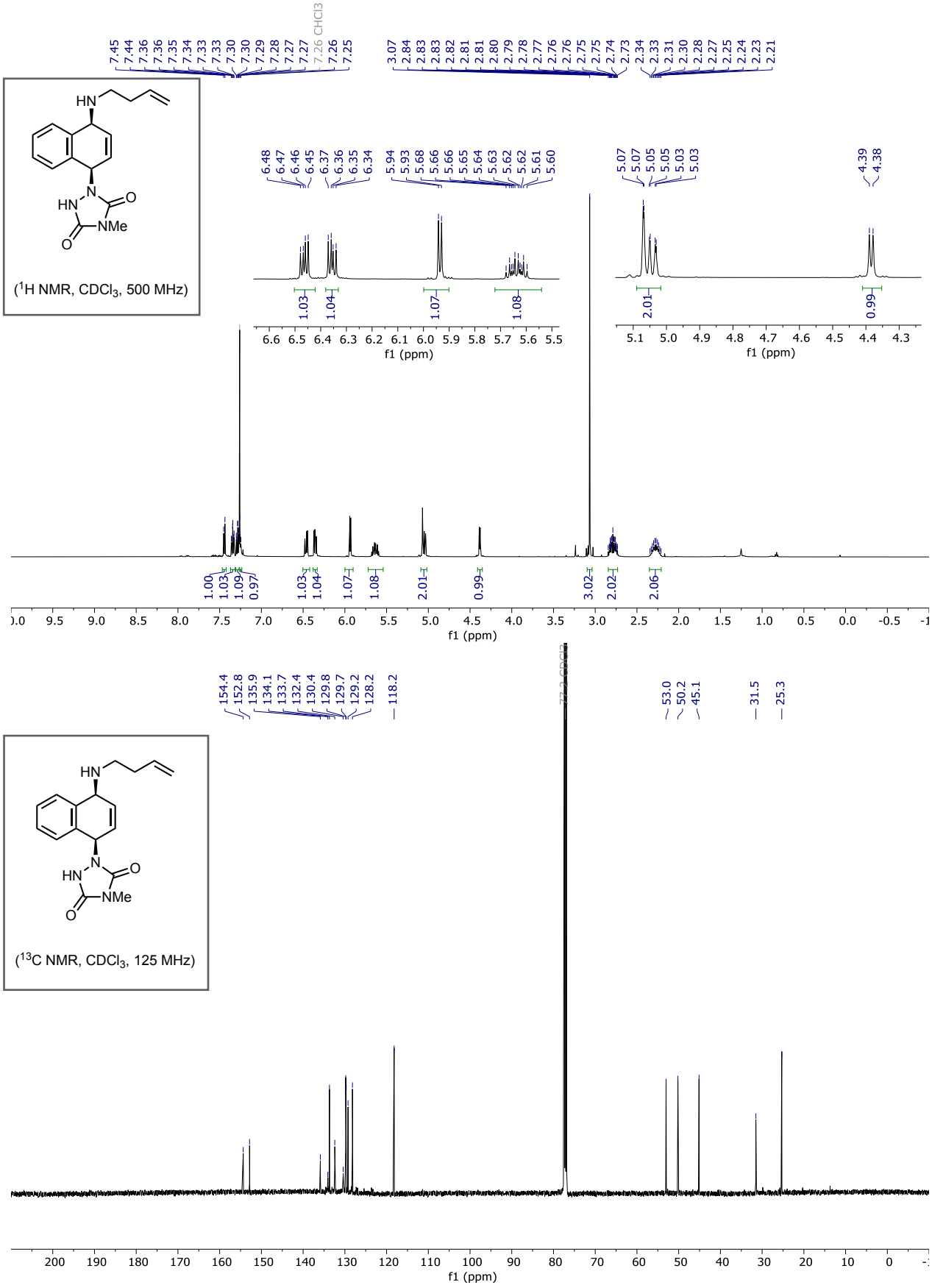

7.46
7.44
7.35
7.33
7.32
7.30
7.26 CHCl3
7.26
7.25
7.24
7.23
7.23
6.52
6.50
6.49
6.48
6.46
5.98
5.97
4.59
4.58
3.12
3.07
2.99
1.14
1.13
0.81
HN
iPr
HN
N
O
NMe
O
(1H NMR, CDCl3, 500 MHz)
1.96
0.98
f1 (ppm)
1.00
1.99
1.07
1.96
0.98
1.00
4.11
3.07
3.01
f1 (ppm)
155.7
152.9
137.4
134.3
132.3
129.9
129.8
128.6
128.0
77.2 CHCl3
50.0
49.6
46.8
25.4
19.4
18.2
(13C NMR, CDCl3, 125 MHz)
f1 (ppm)

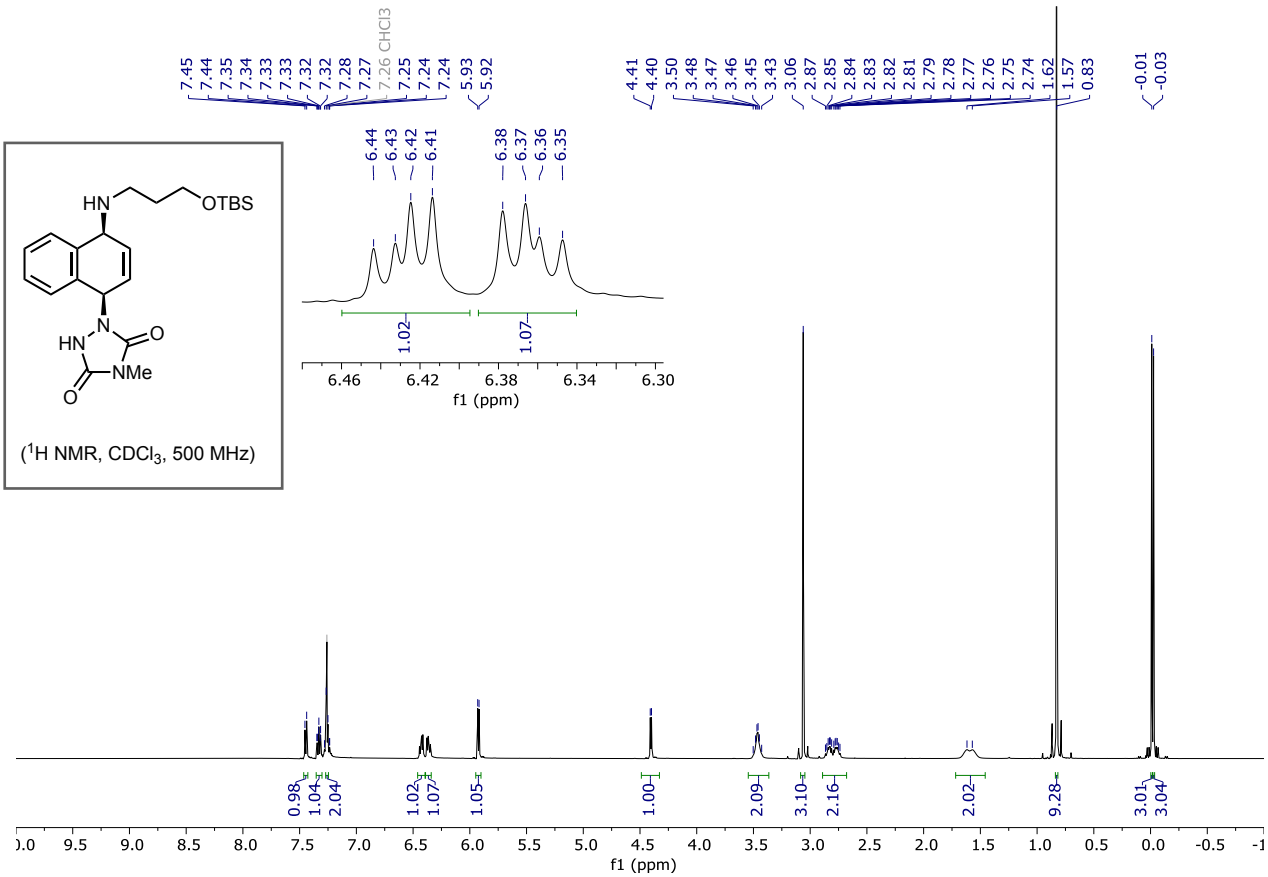

HN
Cy
HN
N
O
NMe
O
(^{1}H NMR, $CDCl_3$, 500 MHz)
7.26 CHCl3
6.40
5.95
5.94
5.94
4.63
4.62
4.62
3.07
2.76
2.74
2.72
1.90
1.63
1.61
1.57
1.54
1.22
1.15
1.10
1.07
1.04
0.86
0.84
0.81
7.46
7.44
7.35
7.33
7.32
7.28
7.27
7.26 CHCl3
7.25
1.02
3.10
f1 (ppm)
1.02
3.10
2.00
1.01
0.99
3.14
0.99
5.16
5.26
f1 (ppm)

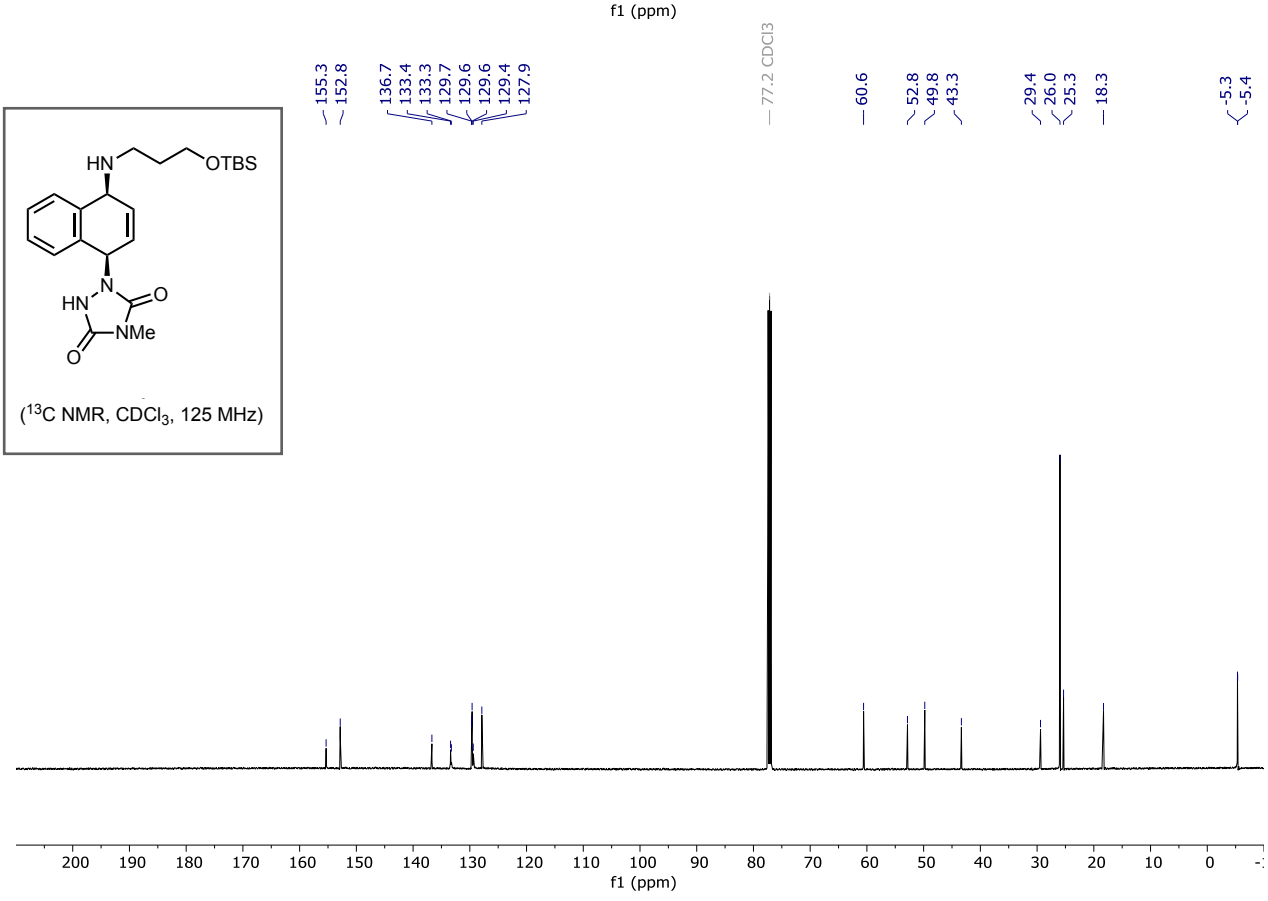

HN
Cy
HN
N
O
NMe
O
(^{13}C NMR, $CDCl_3$, 125 MHz)
155.7
152.9
137.4
134.3
132.4
129.8
129.5
128.4
127.9
77.2 CDCl3
54.2
49.6
49.2
29.3
28.7
25.4
25.3
24.9
f1 (ppm)

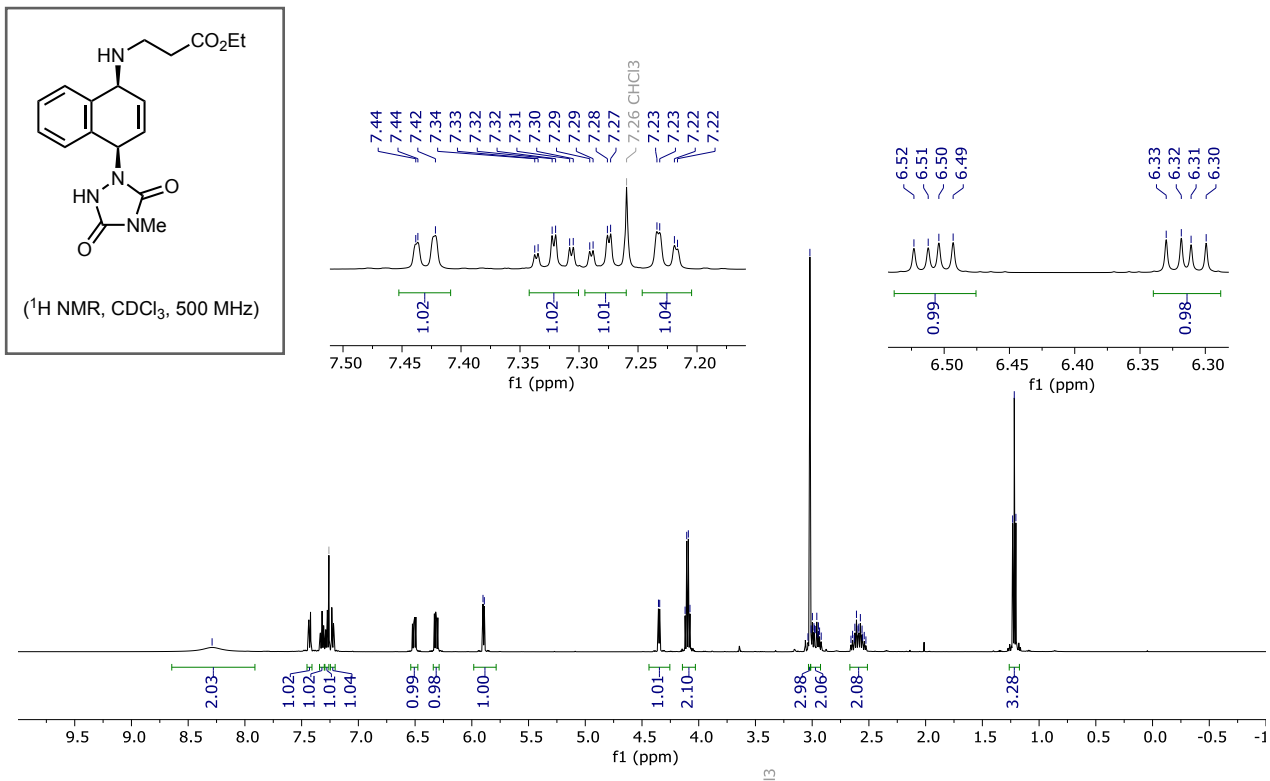

HN
tBu
HN
N
O
NMe
O
(1H NMR, CDCl3, 500 MHz)
7.26 CHCl3
6.56
6.55
6.54
6.53
6.31
6.30
6.29
6.28
5.91
5.90
4.54
4.53
3.03
1.22
7.44
7.44
7.43
7.43
7.42
7.35
7.33
7.31
7.30
7.29
7.28
7.26 CHCl3
7.06
1.01
3.08
2.01
7.5
7.4
7.3
7.2
7.1
7.0
6.9
f1 (ppm)
1.01
3.08
2.01
1.04
1.02
0.99
0.99
3.02
9.04
f1 (ppm)

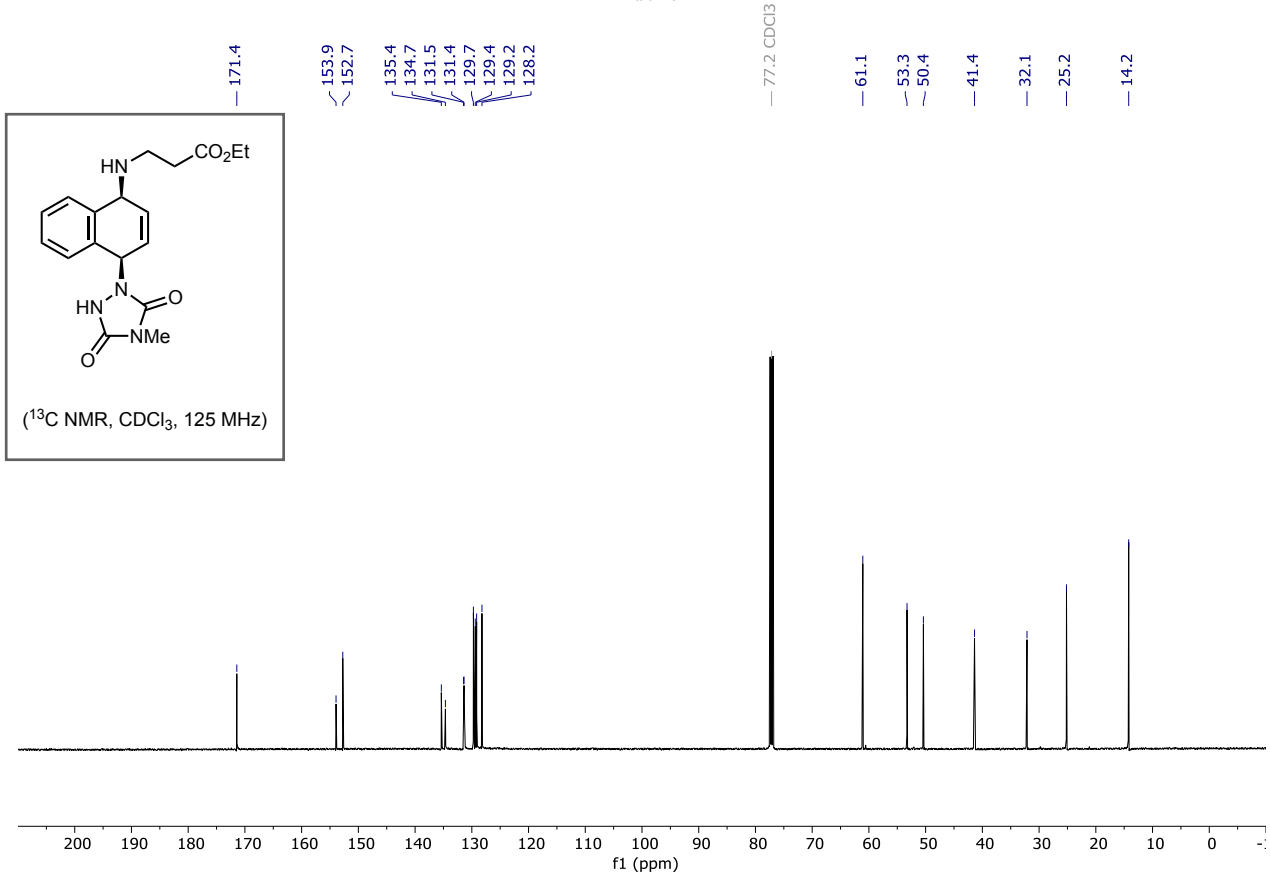

HN
tBu
HN
N
O
NMe
O
(13C NMR, CDCl3, 125 MHz)
153.1
152.9
138.1
135.7
134.7
129.6
129.4
128.9
128.7
128.7
77.2 CDCl3
54.4
50.5
50.1
29.3
25.1
f1 (ppm)

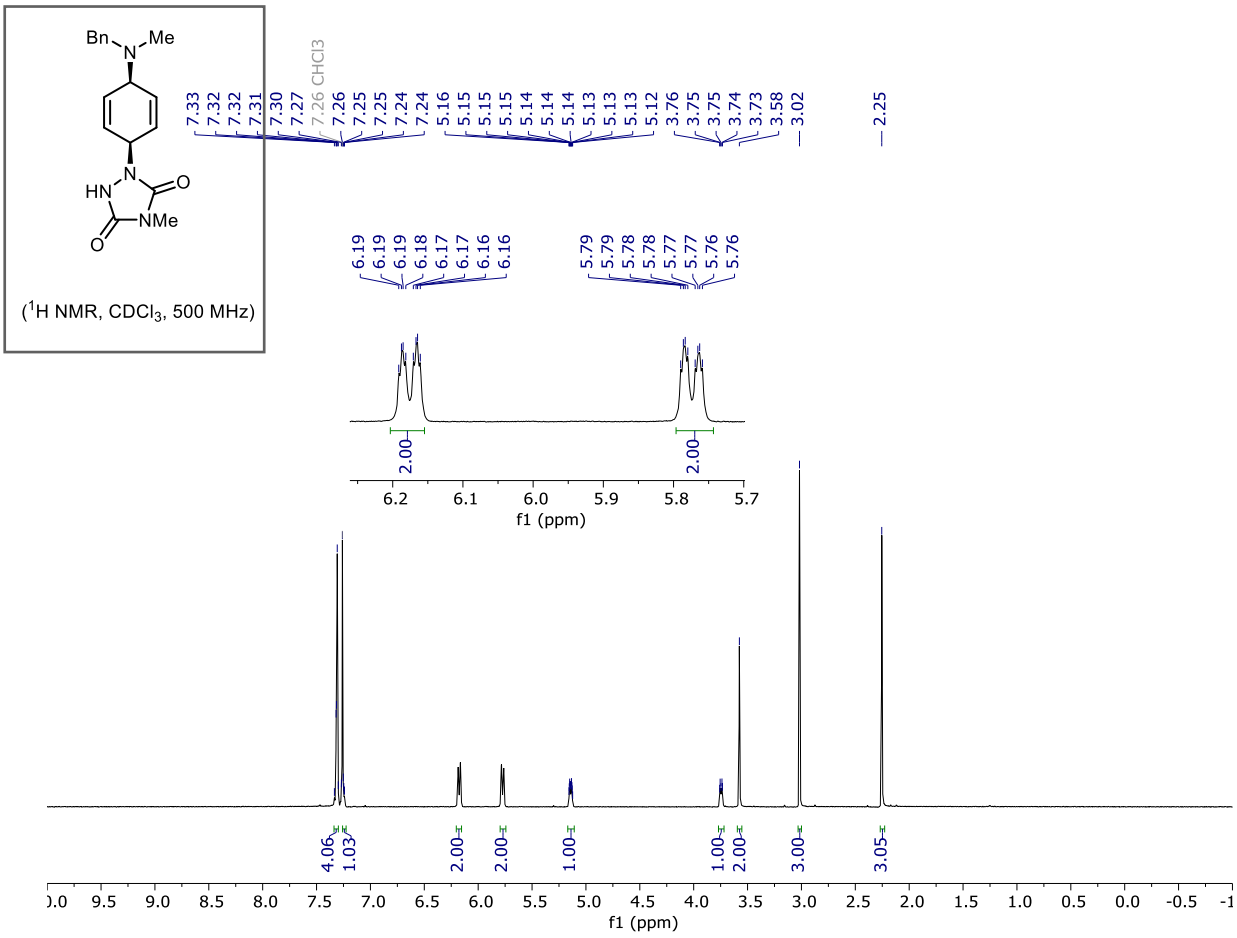

HN
HN
N
O
NMe
O
(^{1}H NMR, $CDCl_3$, 500 MHz)
7.45 7.44 7.36 7.36 7.35 7.34 7.33 7.33 7.30 7.30 7.29 7.28 7.27 7.27 7.26 CHCl3 7.26 7.25
3.07 2.84 2.83 2.83 2.82 2.81 2.81 2.80 2.79 2.78 2.77 2.76 2.76 2.75 2.75 2.74 2.73 2.34 2.33 2.31 2.30 2.28 2.27 2.25 2.24 2.23 2.21
6.48 6.47 6.46 6.45 6.37 6.36 6.35 6.34 5.94 5.93 5.68 5.66 5.66 5.65 5.64 5.63 5.62 5.62 5.61 5.60
5.07 5.07 5.05 5.05 5.03 5.03 4.39 4.38
1.03 1.04 1.07 1.08
2.01 0.99
f1 (ppm)
1.00 1.03 1.09 0.97 1.03 1.04 1.07 1.08 2.01 0.99 3.02 2.02 2.06
f1 (ppm)
HN
HN
N
O
NMe
O
(^{13}C NMR, $CDCl_3$, 125 MHz)
154.4 152.8 135.9 134.1 133.7 132.4 130.4 129.8 129.7 129.2 128.2 118.2
77.3 CDCl3
53.0 50.2 45.1 31.5 25.3
f1 (ppm)

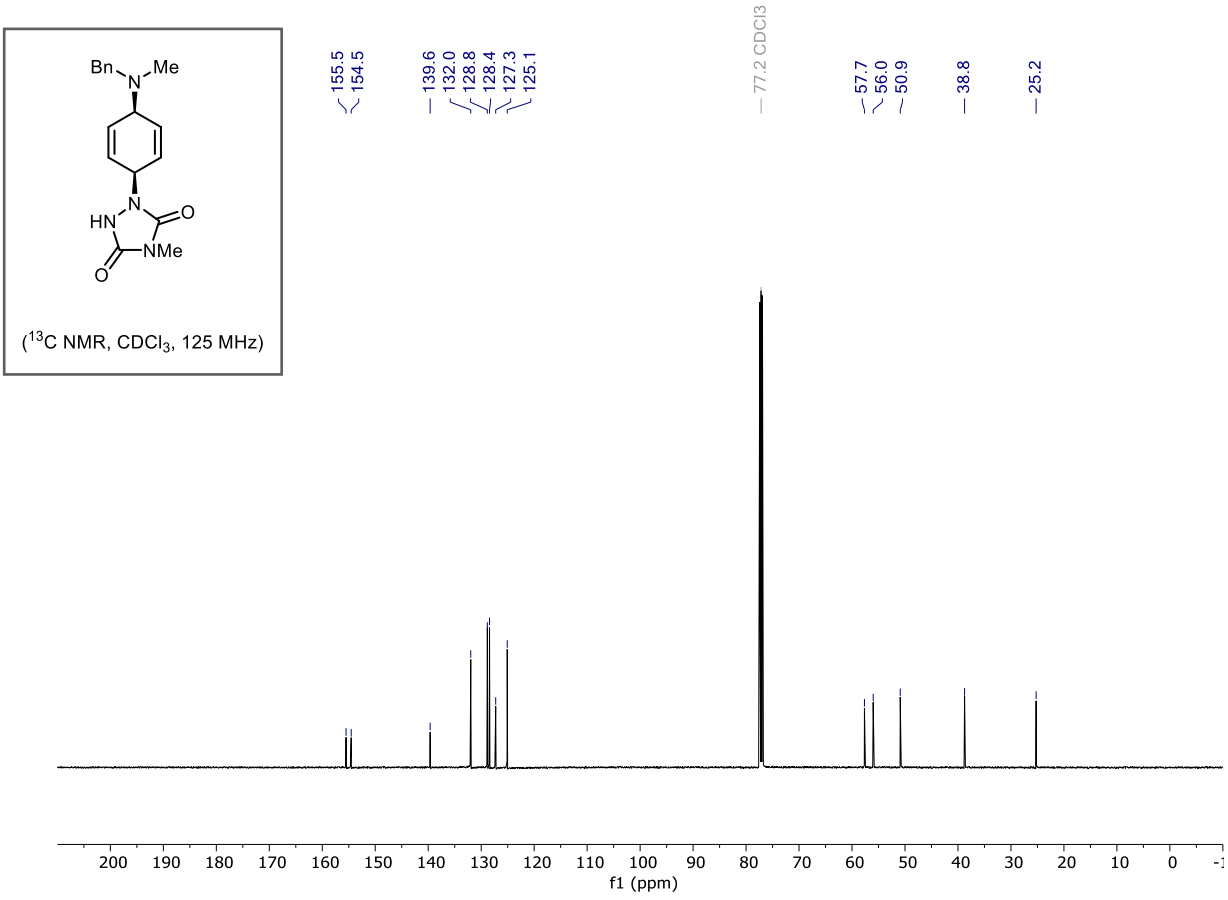

HN
OTBS
HN
N
O
NMe
O
(1H NMR, CDCl3, 500 MHz)
7.45
7.44
7.35
7.34
7.33
7.33
7.32
7.32
7.28
7.27
7.26 CHCl3
7.25
7.24
7.24
5.93
5.92
4.41
4.40
3.50
3.48
3.47
3.46
3.45
3.43
3.06
2.87
2.85
2.84
2.83
2.82
2.81
2.79
2.78
2.77
2.76
2.75
2.74
1.62
1.57
0.83
-0.01
-0.03
6.44
6.43
6.42
6.41
6.38
6.37
6.36
6.35
1.02
1.07
6.46
6.42
6.38
6.34
6.30
f1 (ppm)
0.98
1.04
2.04
1.02
1.07
1.05
1.00
2.09
3.10
2.16
2.02
9.28
3.01
3.04
f1 (ppm)

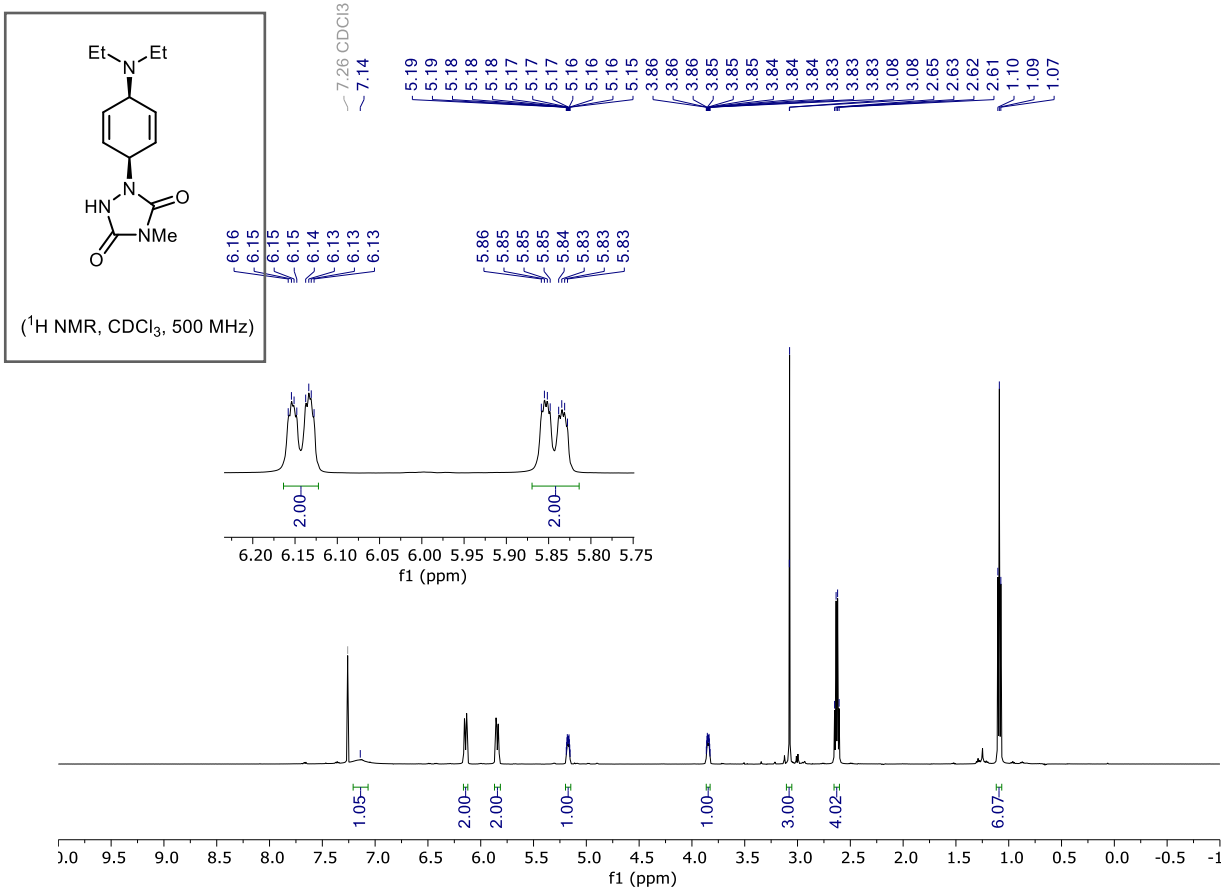

HN
OTBS
HN
N
O
NMe
O
(13C NMR, CDCl3, 125 MHz)
155.3
152.8
136.7
133.4
133.3
129.7
129.6
129.6
129.4
127.9
77.2 CDCl3
60.6
52.8
49.8
43.3
29.4
26.0
25.3
18.3
-5.3
-5.4
f1 (ppm)

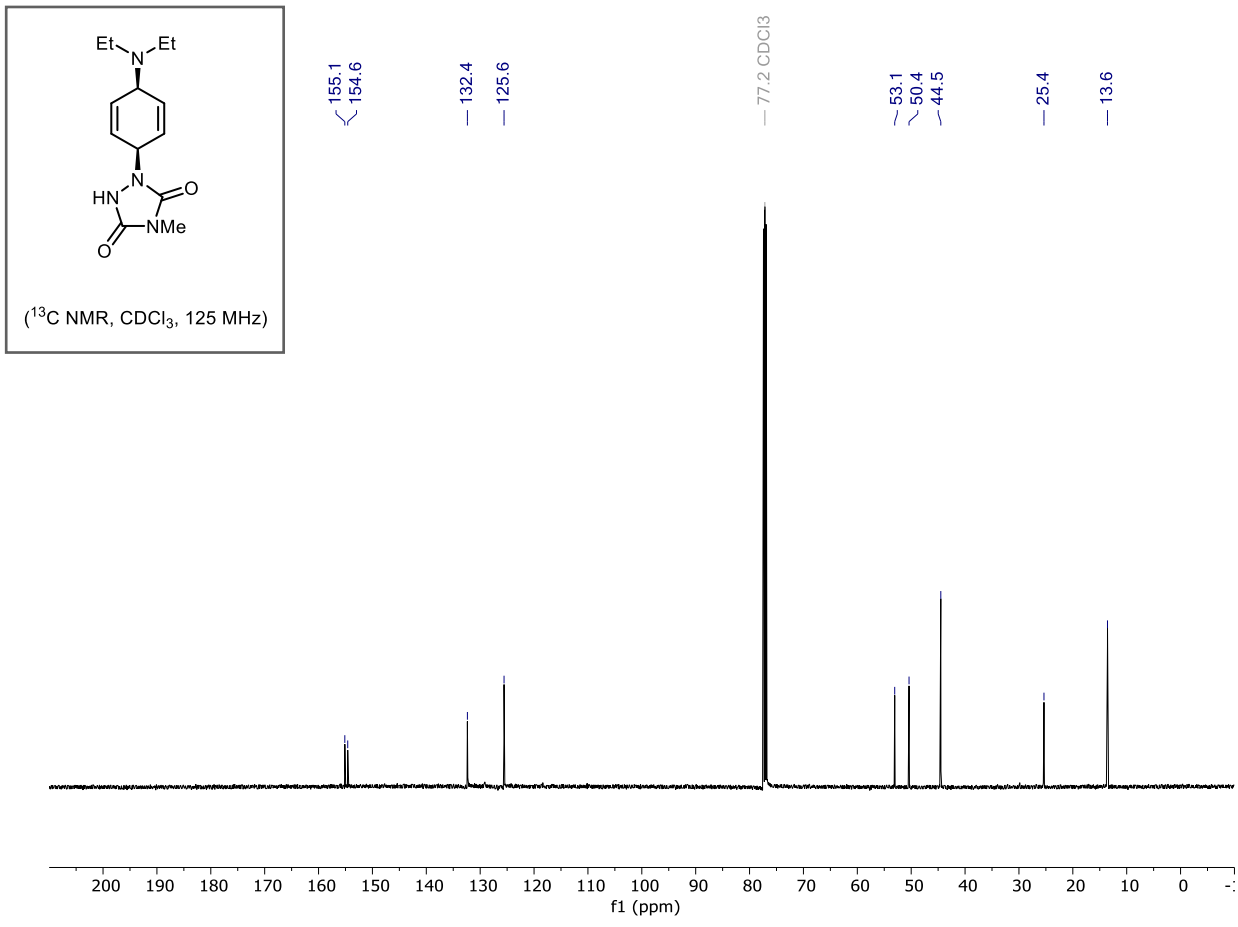

HN
CO2Et
HN
N
O
NMe
O
(1H NMR, CDCl3, 500 MHz)
8.29
7.26 CHCl3
5.90
5.89
4.35
4.34
4.12
4.11
4.09
4.08
3.04
3.02
3.01
3.00
2.98
2.98
2.97
2.96
2.95
2.94
2.93
2.92
2.66
2.64
2.63
2.62
2.61
2.60
2.59
2.58
2.56
2.55
2.54
1.23
1.22
7.44
7.44
7.42
7.34
7.33
7.32
7.32
7.31
7.30
7.29
7.29
7.28
7.27
7.26 CHCl3
7.23
7.23
7.22
7.22
6.52
6.51
6.50
6.49
6.33
6.32
6.31
6.30
1.02
1.02
1.01
1.04
0.99
0.98
f1 (ppm)
2.03
1.02
1.02
1.01
1.04
0.99
0.98
1.00
1.01
2.10
2.98
2.06
2.08
3.28
f1 (ppm)

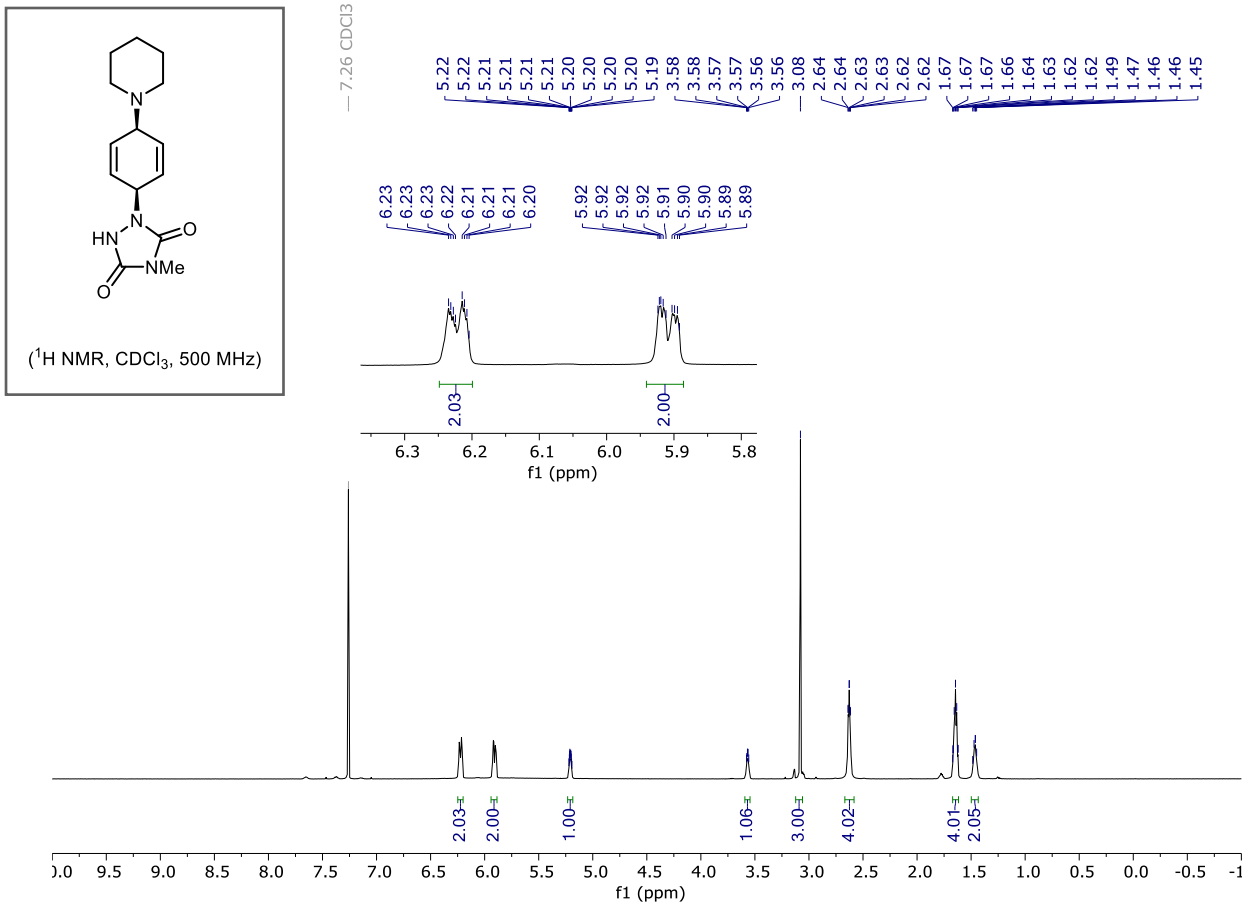

HN
CO2Et
HN
N
O
NMe
O
(13C NMR, CDCl3, 125 MHz)
171.4
153.9
152.7
135.4
134.7
131.5
131.4
129.7
129.4
129.2
128.2
77.2 CDCl3
61.1
53.3
50.4
41.4
32.1
25.2
14.2
f1 (ppm)

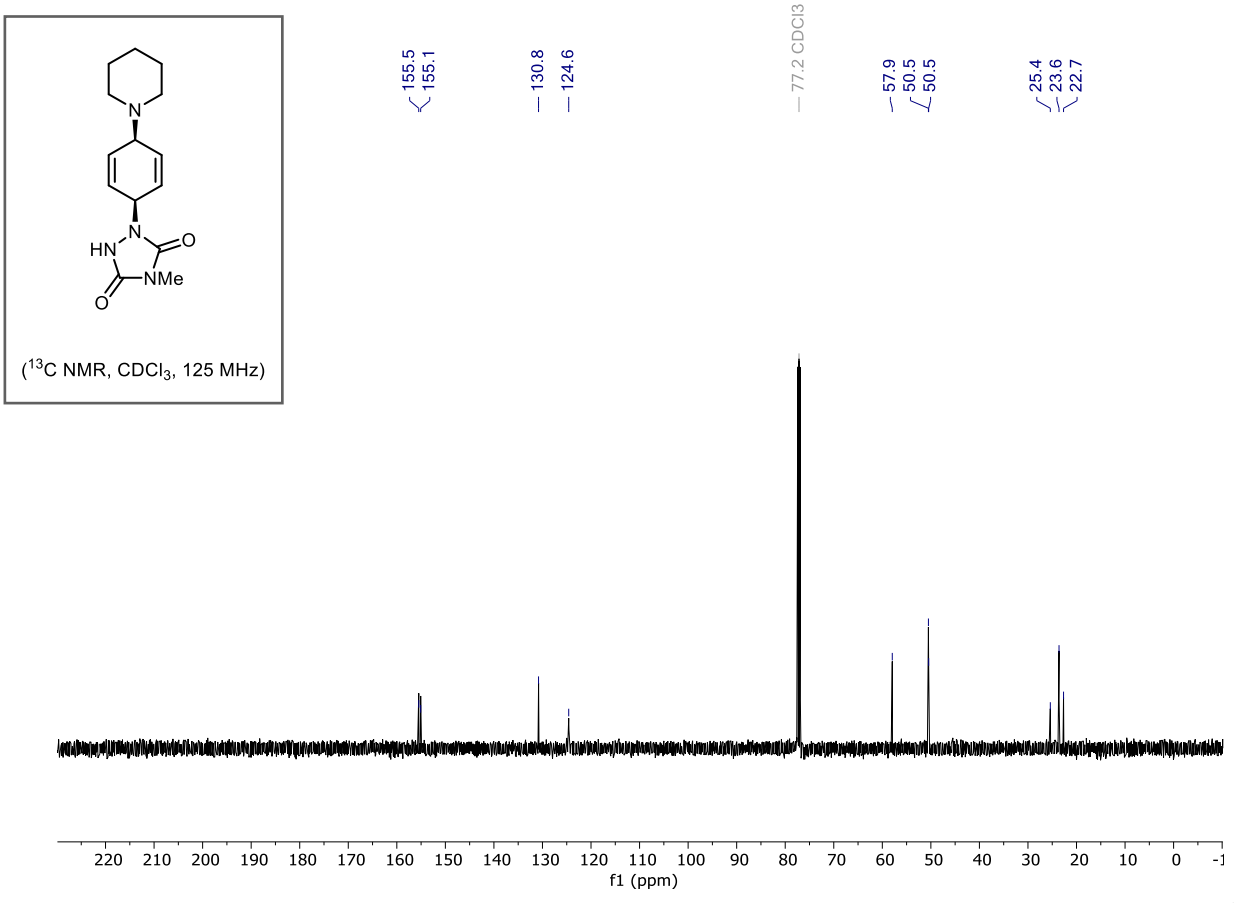

Bn
N
Me
HN
N
O
NMe
O
(1H NMR, CDCl3, 500 MHz)
7.33
7.32
7.32
7.31
7.30
7.27
7.26 CHCl3
7.26
7.25
7.25
7.24
7.24
5.16
5.15
5.15
5.15
5.14
5.14
5.14
5.13
5.13
5.13
5.12
3.76
3.75
3.75
3.74
3.73
3.58
3.02
2.25
6.19
6.19
6.19
6.18
6.17
6.17
6.16
6.16
5.79
5.79
5.78
5.78
5.77
5.77
5.76
5.76
2.00
2.00
6.2
6.1
6.0
5.9
5.8
5.7
f1 (ppm)
4.06
1.03
2.00
2.00
1.00
1.00
2.00
3.00
3.05
f1 (ppm)

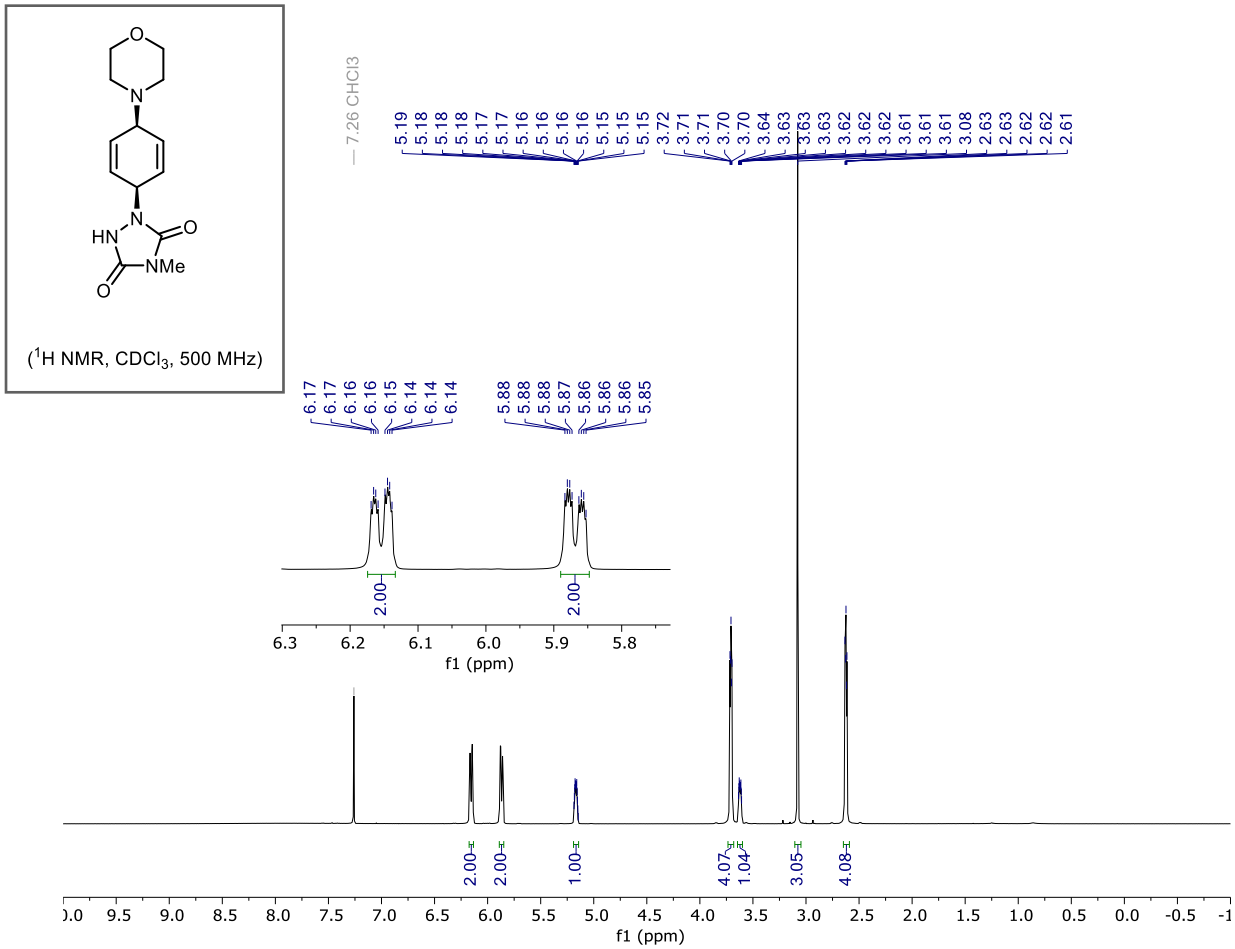

Bn
N
Me
HN
N
O
NMe
O
(13C NMR, CDCl3, 125 MHz)
155.5
154.5
139.6
132.0
128.8
128.4
127.3
125.1
77.2 CDCl3
57.7
56.0
50.9
38.8
25.2
f1 (ppm)

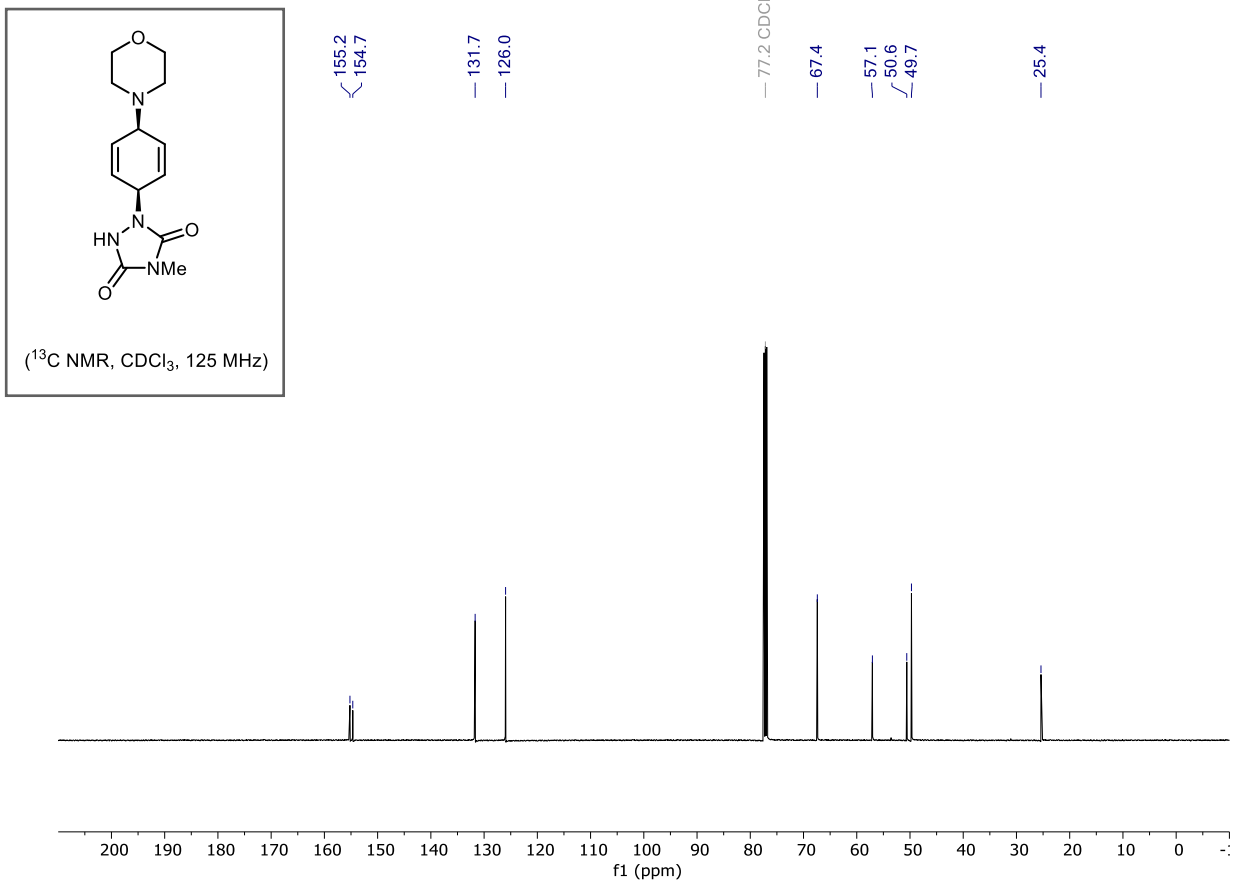

Et
N
Et
HN
N
O
NMe
O
(1H NMR, CDCl3, 500 MHz)
7.26 CDCl3
7.14
5.19 5.19 5.18 5.18 5.17 5.17 5.16 5.16 5.15
3.86 3.86 3.85 3.85 3.85 3.84 3.84 3.84 3.83 3.83 3.83 3.08 3.08 2.65 2.63 2.62 2.61 1.10 1.09 1.07
6.16 6.15 6.15 6.15 6.14 6.13 6.13 6.13
5.86 5.85 5.85 5.85 5.84 5.83 5.83 5.83
2.00
2.00
6.20 6.15 6.10 6.05 6.00 5.95 5.90 5.85 5.80 5.75
f1 (ppm)
1.05
2.00
2.00
1.00
1.00
3.00
4.02
6.07
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
f1 (ppm)

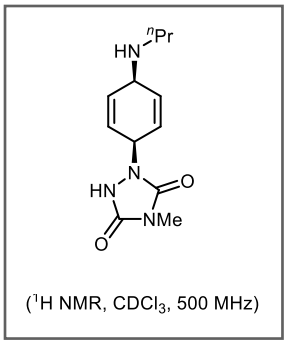

Et
N
Et
HN
N
O
NMe
O
(13C NMR, CDCl3, 125 MHz)
155.1
154.6
132.4
125.6
77.2 CDCl3
53.1
50.4
44.5
25.4
13.6
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


(^{1}H NMR, $CDCl_3$, 500 MHz)
7.26 CDCl3
5.22 5.22 5.21 5.21 5.21 5.21 5.20 5.20 5.20 5.20 5.19
3.58 3.58 3.57 3.57 3.56 3.56
3.08
2.64 2.64 2.63 2.63 2.62 2.62
1.67 1.67 1.67 1.66 1.64 1.63 1.62 1.62 1.49 1.47 1.46 1.46 1.45
6.23 6.23 6.23 6.22 6.21 6.21 6.21 6.20
5.92 5.92 5.92 5.92 5.91 5.90 5.90 5.89 5.89
2.03
2.00
6.3 6.2 6.1 6.0 5.9 5.8
f1 (ppm)
2.03 2.00 1.00 1.06 3.00 4.02 4.01 2.05
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
f1 (ppm)

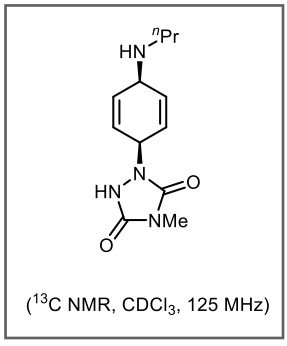

(^{13}C NMR, $CDCl_3$, 125 MHz)
155.5
155.1
130.8
124.6
77.2 CDCl3
57.9
50.5
50.5
25.4
23.6
22.7
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


(1H NMR, CDCl3, 500 MHz)
7.26 CHCl3
f1 (ppm)

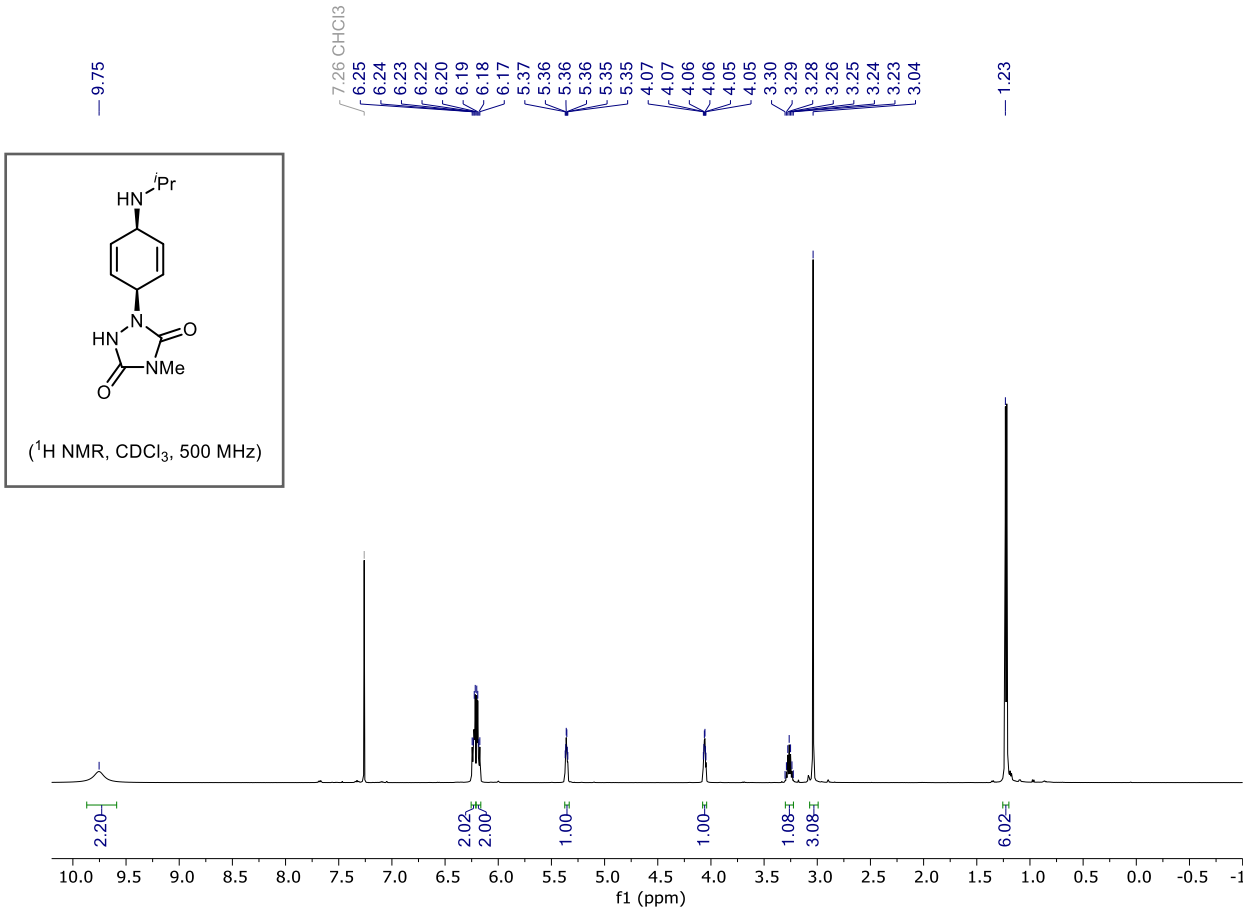

(13C NMR, CDCl3, 125 MHz)
77.2 CDCl3
f1 (ppm)

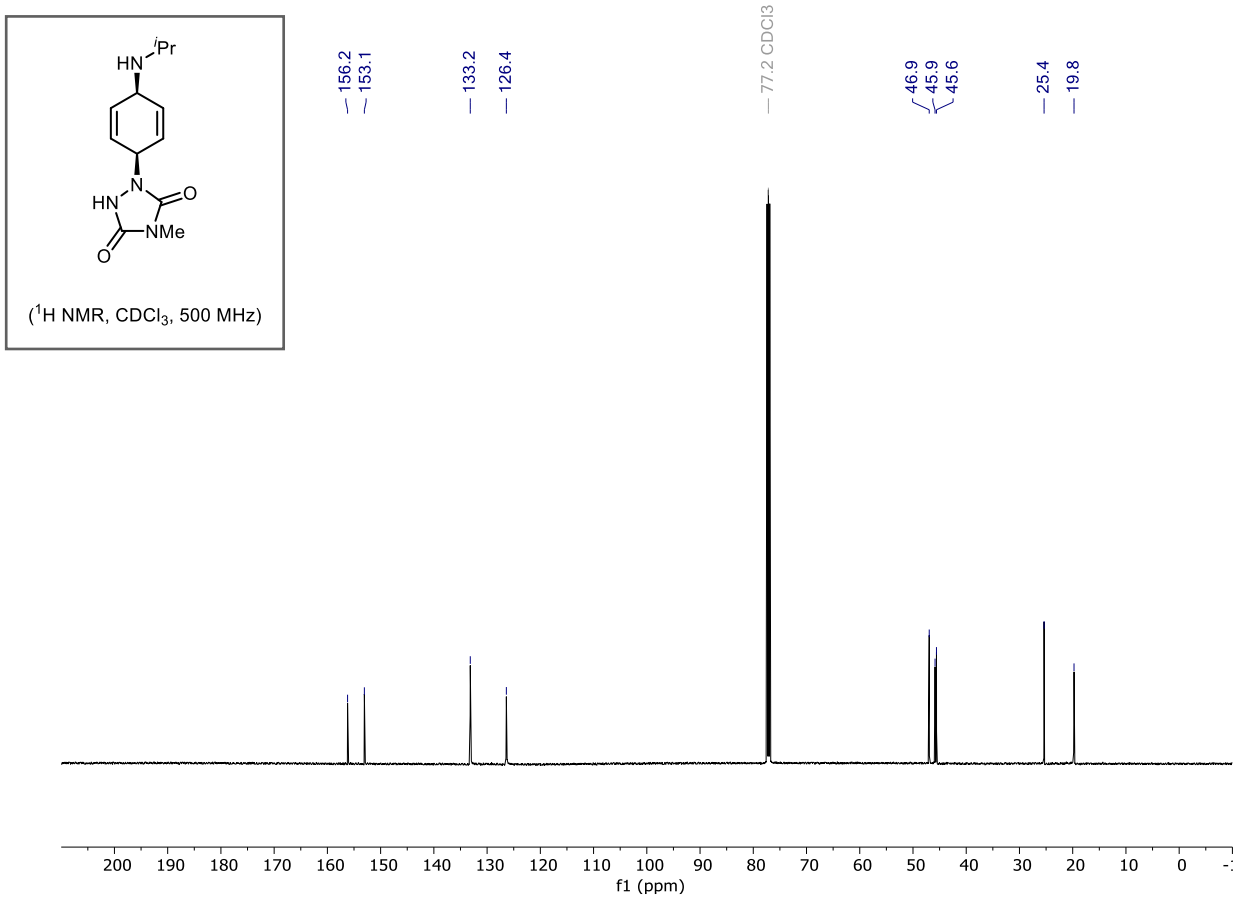


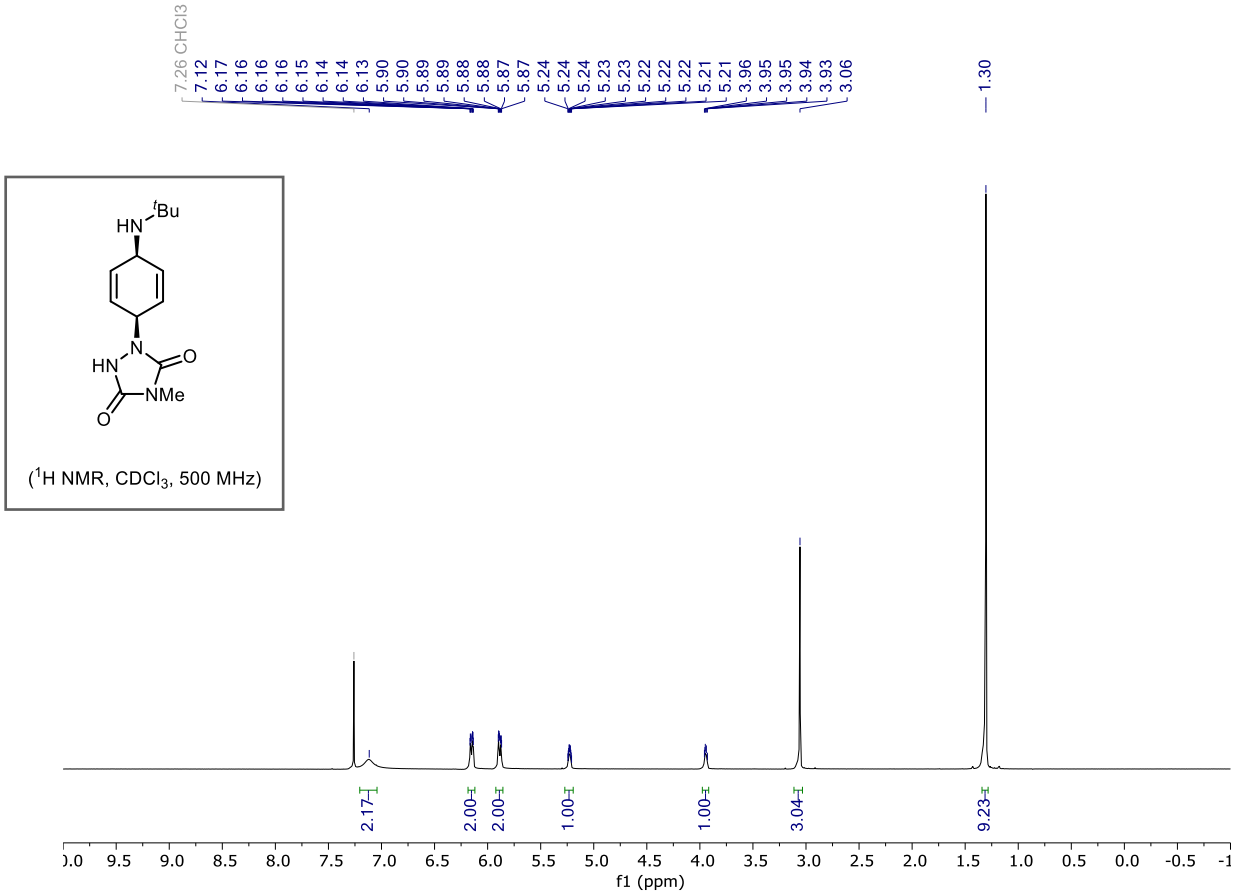
(^{1}H NMR, $CDCl_3$, 500 MHz)

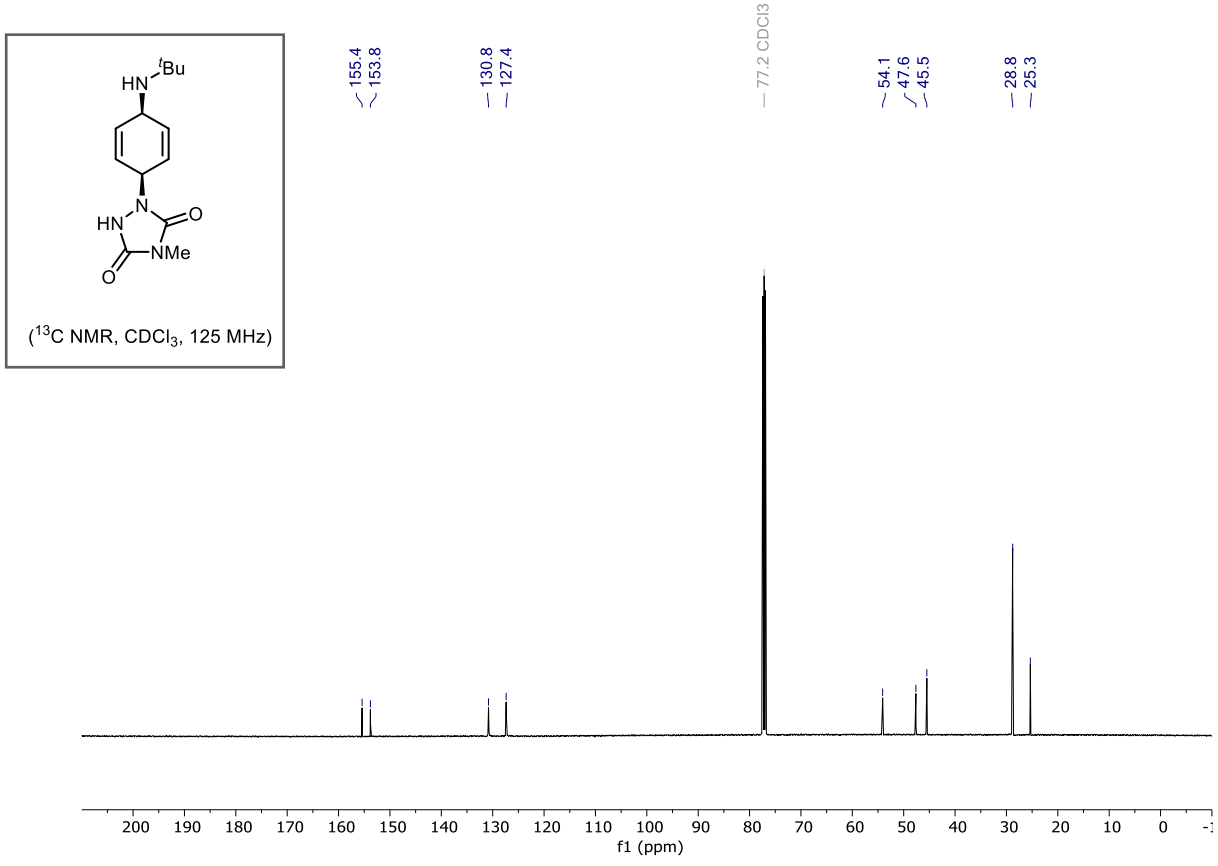


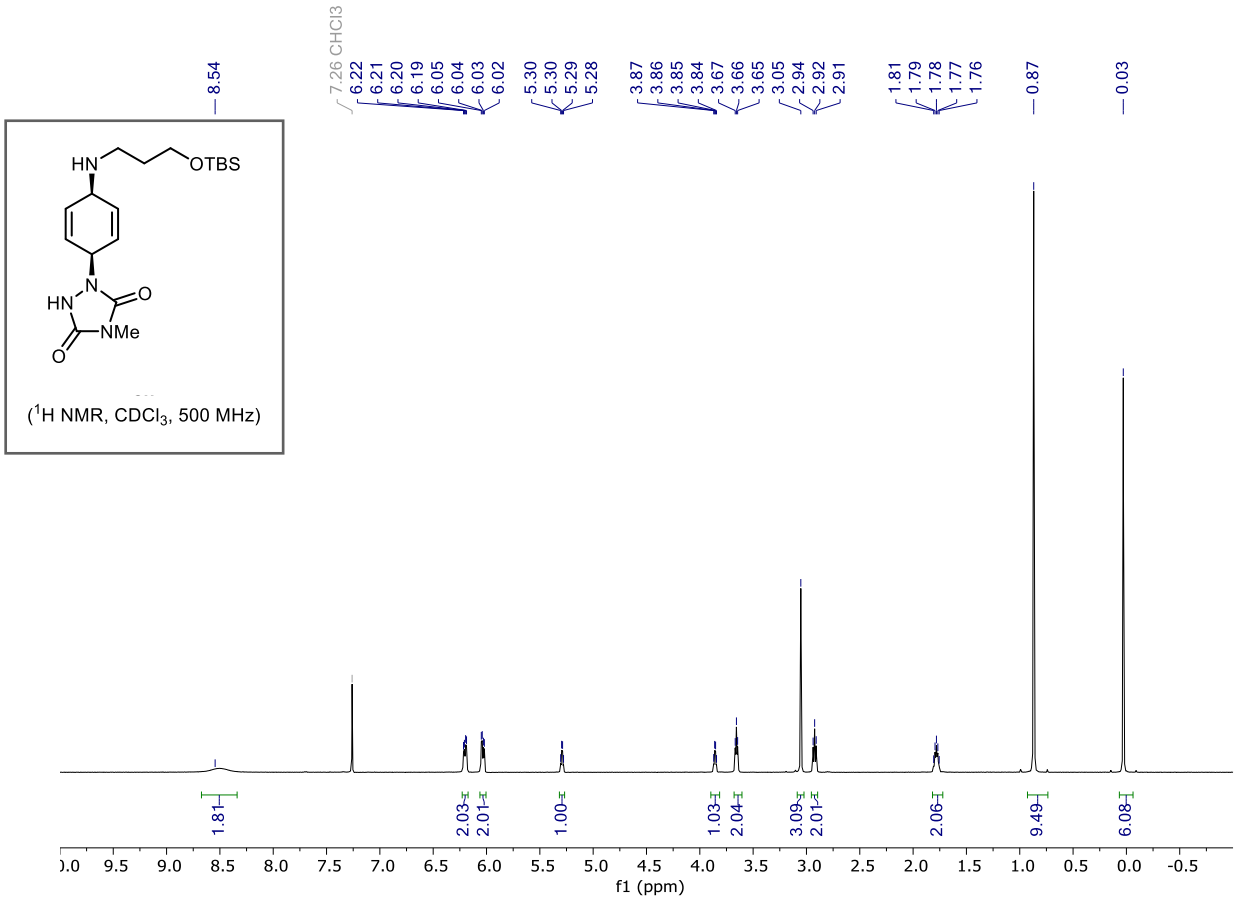
(^{13}C NMR, $CDCl_3$, 125 MHz)

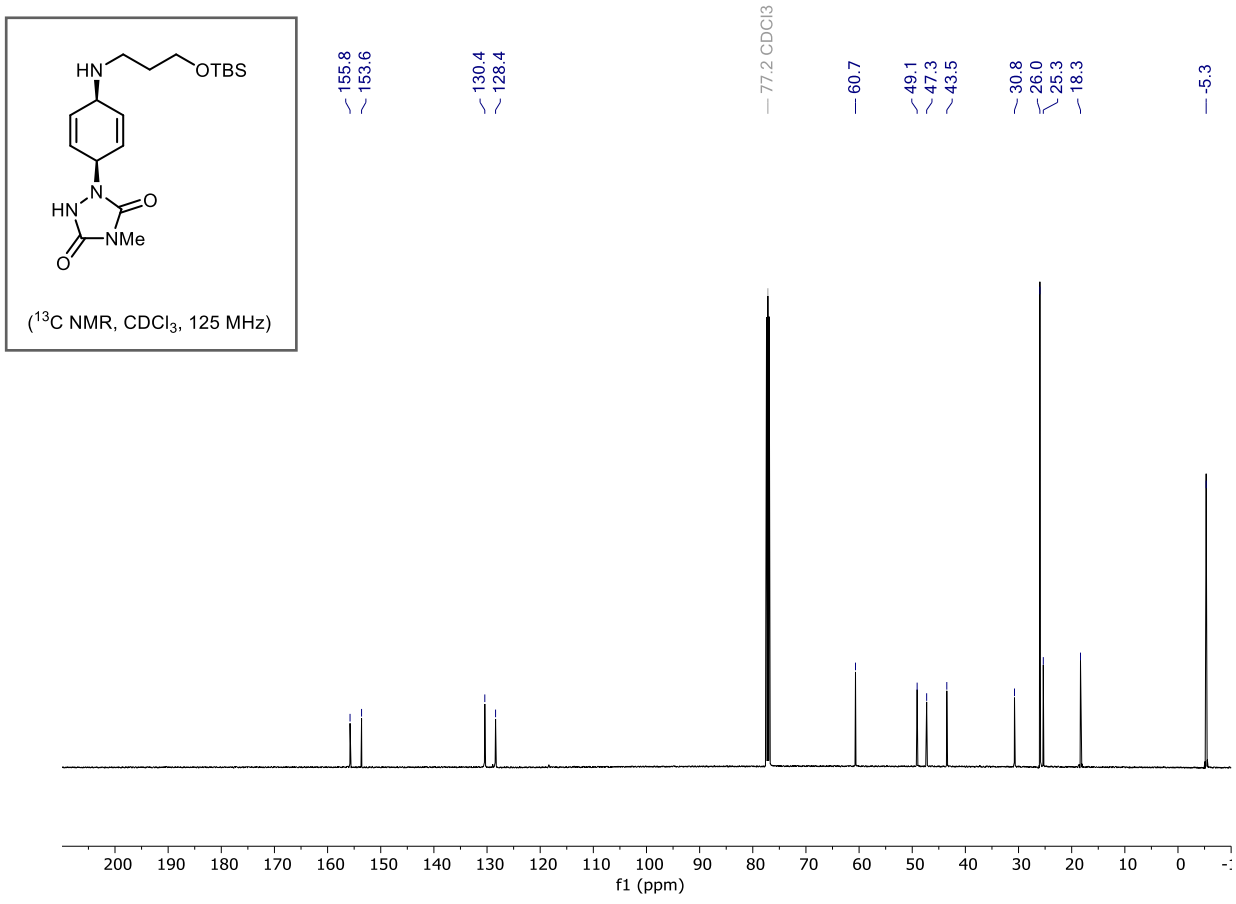

9.75
7.26 CHCl3
6.25
6.24
6.23
6.22
6.20
6.19
6.18
6.17
5.37
5.36
5.36
5.36
5.35
5.35
4.07
4.07
4.06
4.06
4.05
4.05
3.30
3.29
3.28
3.26
3.25
3.24
3.23
3.04
1.23
HN
iPr
HN
N
O
NMe
O
(1H NMR, CDCl3, 500 MHz)
2.20
2.02
2.00
1.00
1.00
1.08
3.08
6.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

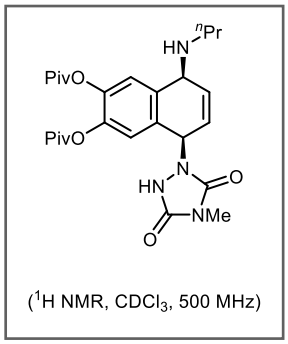

HN
iPr
HN
N
O
NMe
O
(1H NMR, CDCl3, 500 MHz)
156.2
153.1
133.2
126.4
77.2 CDCl3
46.9
45.9
45.6
25.4
19.8
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.26 CHCl3
7.12
6.17
6.16
6.16
6.16
6.15
6.14
6.14
6.13
5.90
5.90
5.89
5.89
5.88
5.88
5.87
5.87
5.24
5.24
5.24
5.23
5.23
5.22
5.22
5.22
5.21
5.21
3.96
3.95
3.95
3.94
3.93
3.06
1.30
HN
tBu
HN
N
O
NMe
O
(^{1}H NMR, CDCl$_3$, 500 MHz)
2.17
2.00
2.00
1.00
1.00
3.04
9.23
f1 (ppm)

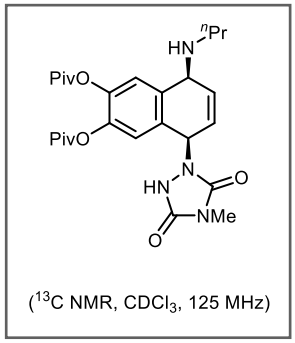

155.4
153.8
130.8
127.4
77.2 CDCl3
54.1
47.6
45.5
28.8
25.3
HN
tBu
HN
N
O
NMe
O
(^{13}C NMR, CDCl$_3$, 125 MHz)
f1 (ppm)


HN
OTBS
HN
N
O
NMe
O
(1H NMR, CDCl3, 500 MHz)
8.54
7.26 CHCl3
6.22
6.21
6.20
6.19
6.05
6.04
6.03
6.02
5.30
5.30
5.29
5.28
3.87
3.86
3.85
3.84
3.67
3.66
3.65
3.05
2.94
2.92
2.91
1.81
1.79
1.78
1.77
1.76
0.87
0.03
1.81
2.03
2.01
1.00
1.03
2.04
3.09
2.01
2.06
9.49
6.08
f1 (ppm)

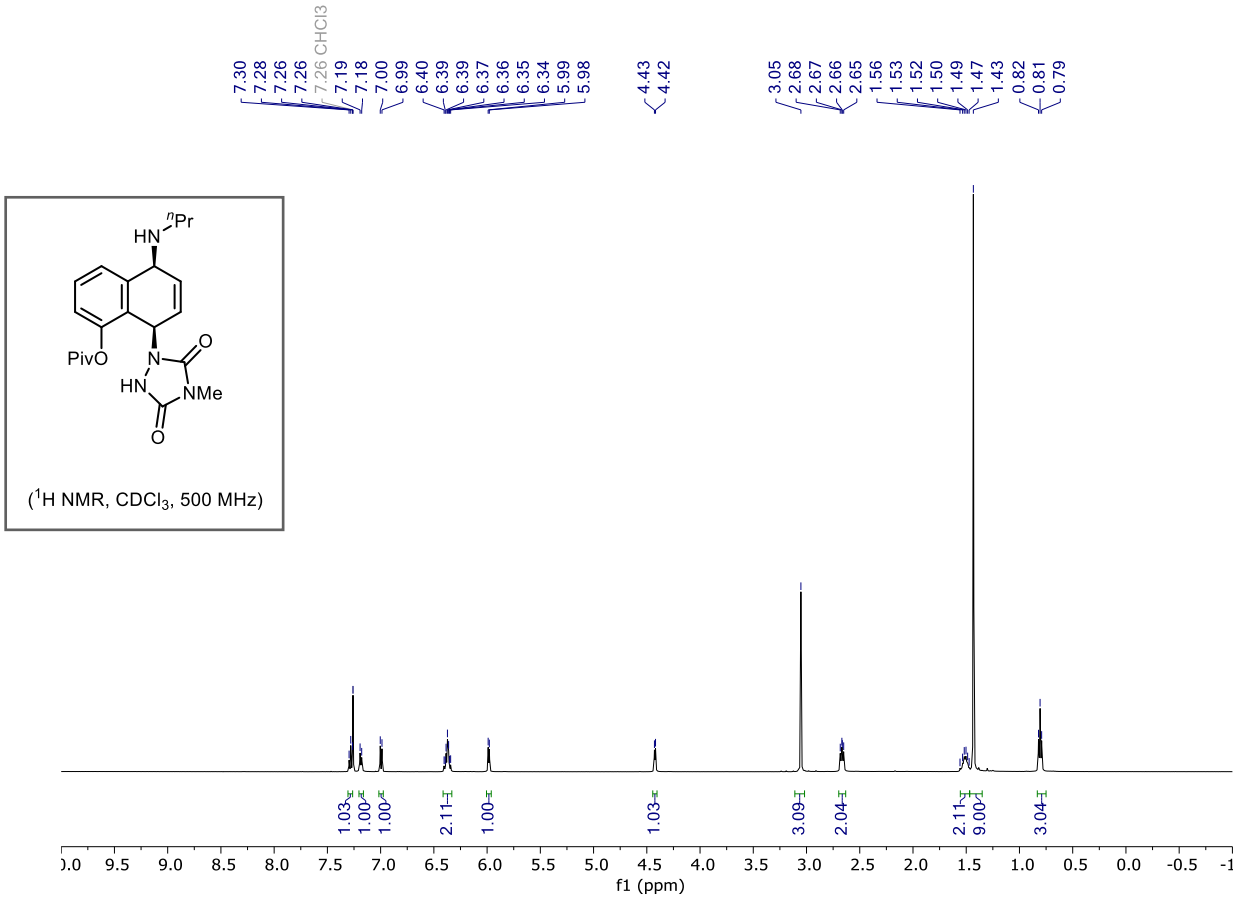

HN
OTBS
HN
N
O
NMe
O
(13C NMR, CDCl3, 125 MHz)
155.8
153.6
130.4
128.4
77.2 CDCl3
60.7
49.1
47.3
43.5
30.8
26.0
25.3
18.3
-5.3
f1 (ppm)

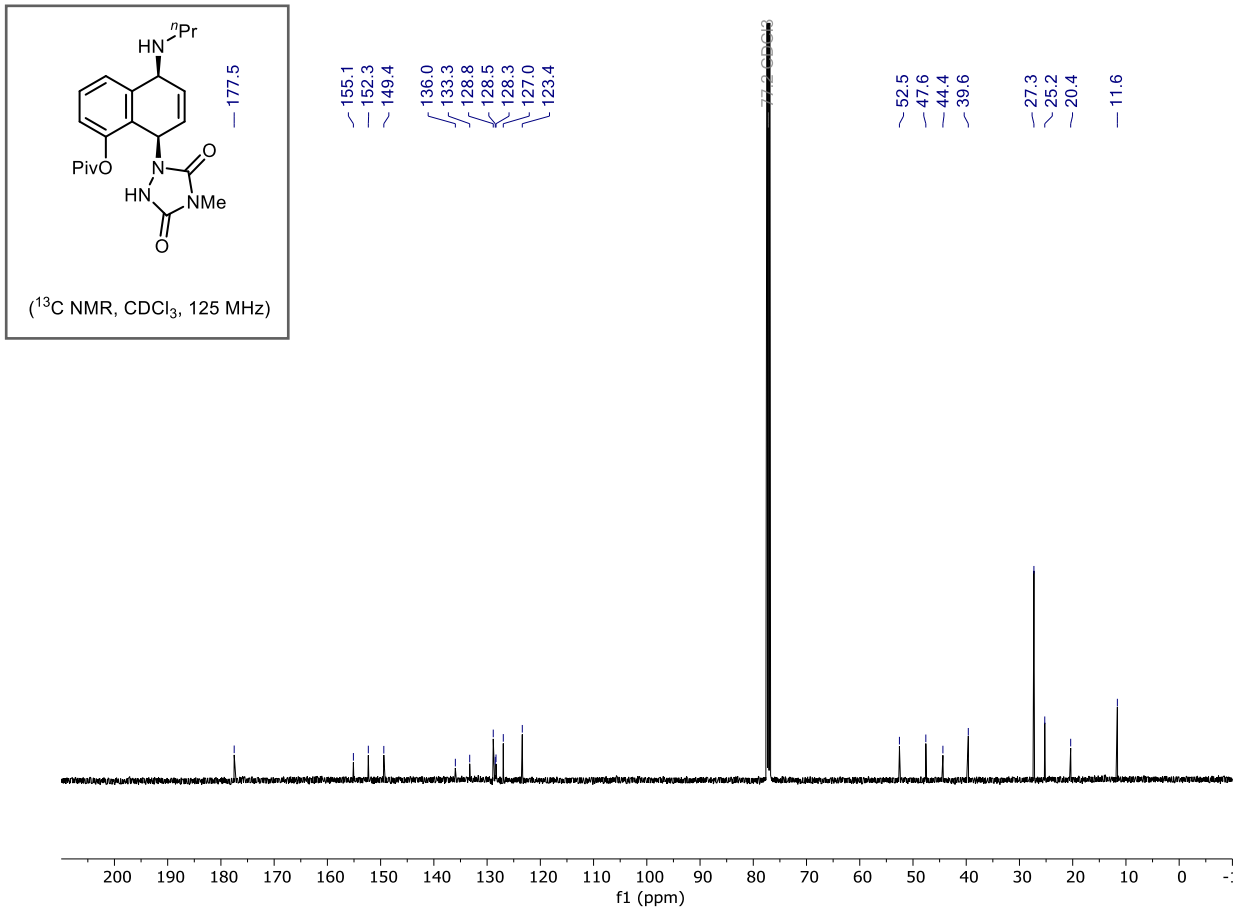


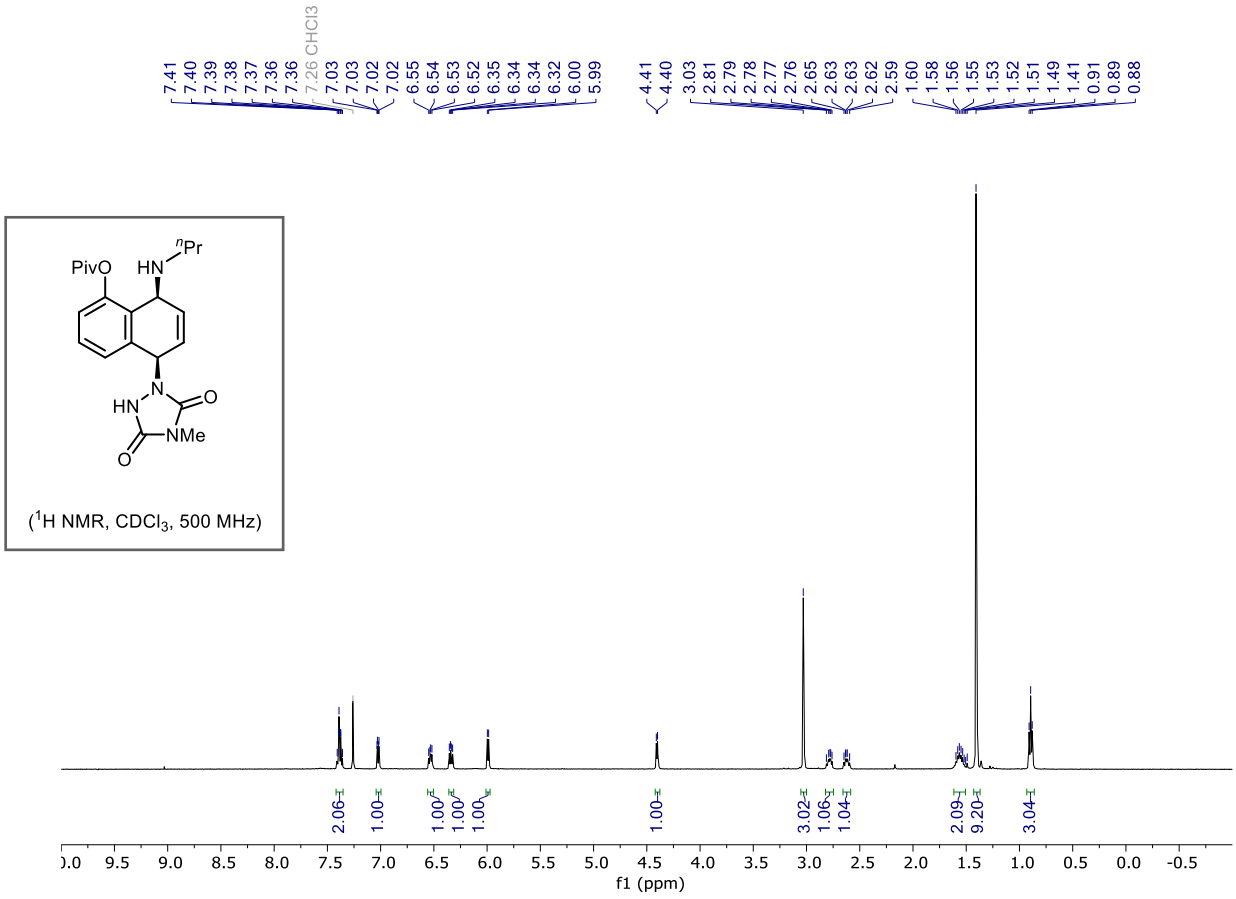
(^{1}H NMR, $CDCl_3$, 500 MHz)

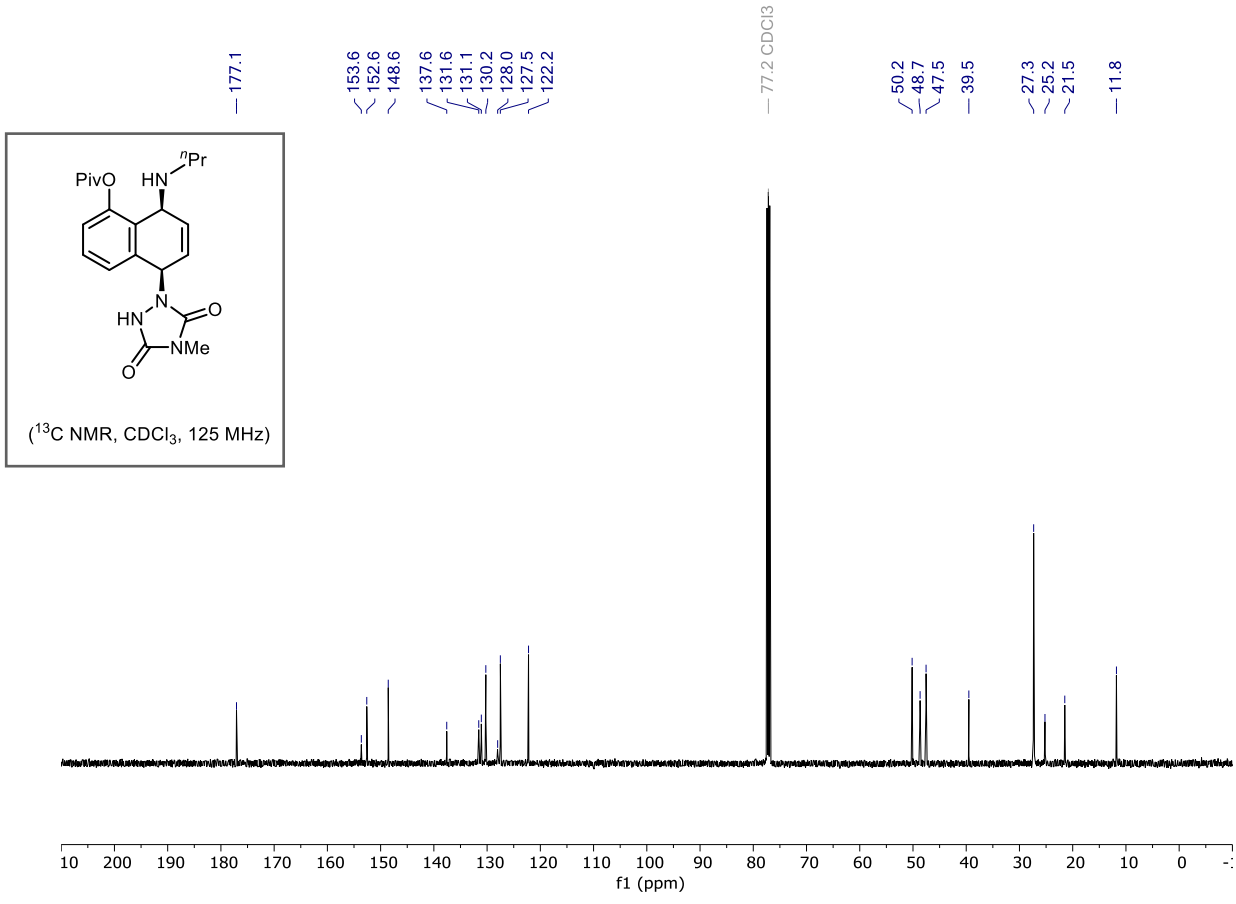


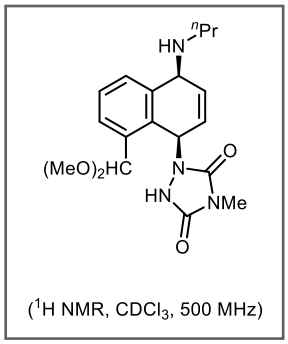
(^{13}C NMR, $CDCl_3$, 125 MHz)


7.30
7.28
7.26
7.26
7.26 CHCl3
7.19
7.18
7.00
6.99
6.40
6.39
6.39
6.37
6.36
6.35
6.34
5.99
5.98
4.43
4.42
3.05
2.68
2.67
2.66
2.65
1.56
1.53
1.52
1.50
1.49
1.47
1.43
0.82
0.81
0.79
HN
nPr
PivO
O
N
HN
NMe
O
(1H NMR, CDCl3, 500 MHz)
1.03
1.00
1.00
2.11
1.00
1.03
3.09
2.04
2.11
9.00
3.04
f1 (ppm)

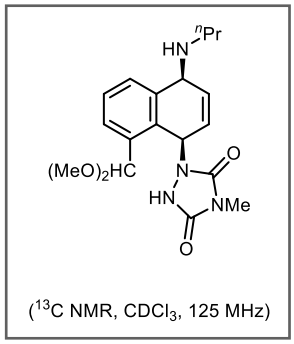

HN
nPr
PivO
O
N
HN
NMe
O
177.5
(13C NMR, CDCl3, 125 MHz)
155.1
152.3
149.4
136.0
133.3
128.8
128.5
128.3
127.0
123.4
77.2 CDCl3
52.5
47.6
44.4
39.6
27.3
25.2
20.4
11.6
f1 (ppm)


7.41
7.40
7.39
7.38
7.37
7.36
7.36
7.26 CHCl3
7.03
7.03
7.02
7.02
6.55
6.54
6.53
6.52
6.35
6.34
6.34
6.32
6.00
5.99
4.41
4.40
3.03
2.81
2.79
2.78
2.77
2.76
2.65
2.63
2.63
2.62
2.59
1.60
1.58
1.56
1.55
1.53
1.52
1.51
1.49
1.41
0.91
0.89
0.88
PivO
HN
nPr
HN
N
O
NMe
O
(^{1}H NMR, $CDCl_3$, 500 MHz)
2.06
1.00
1.00
1.00
1.00
1.00
3.02
1.06
1.04
2.09
9.20
3.04
f1 (ppm)

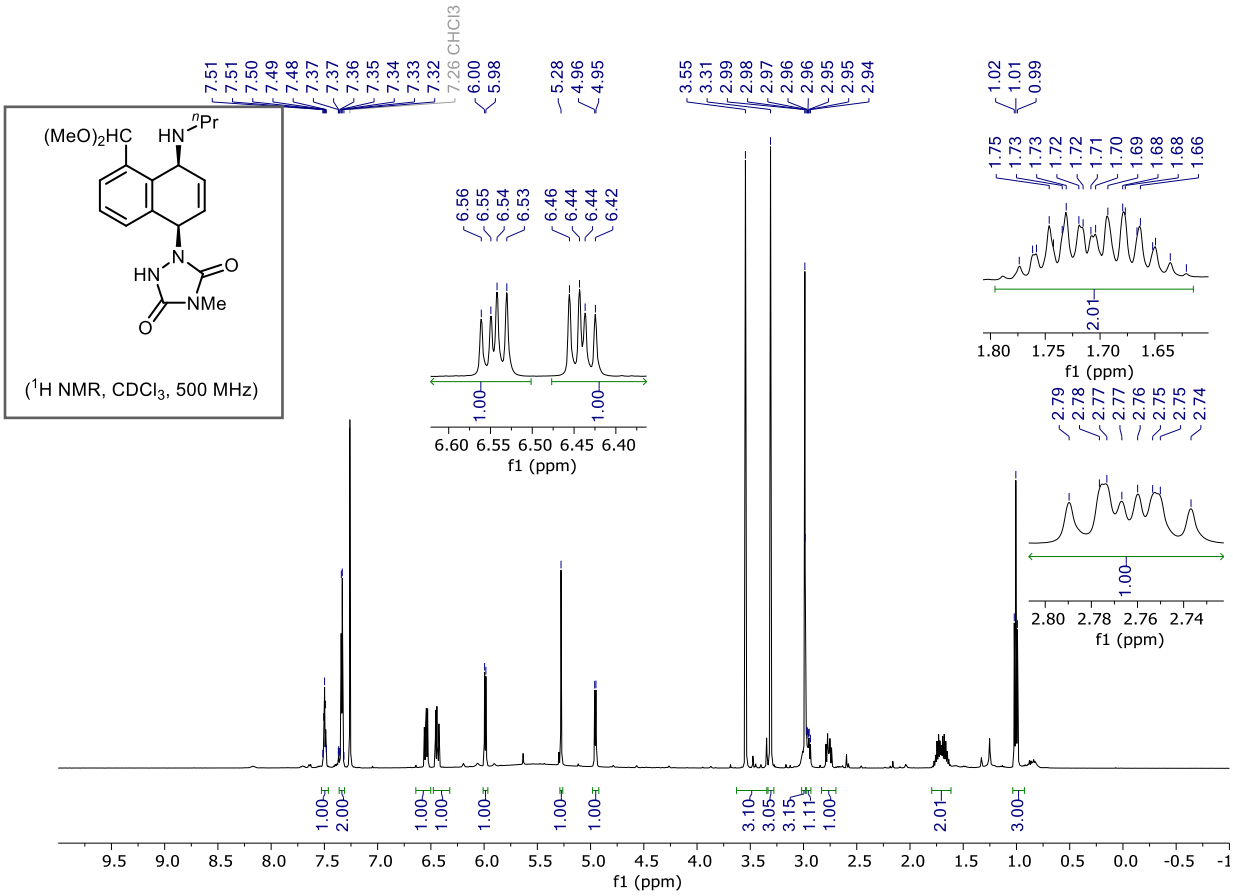

177.1
153.6
152.6
148.6
137.6
131.6
131.1
130.2
128.0
127.5
122.2
77.2 CDCl3
50.2
48.7
47.5
39.5
27.3
25.2
21.5
11.8
PivO
HN
nPr
HN
N
O
NMe
O
(^{13}C NMR, $CDCl_3$, 125 MHz)
f1 (ppm)

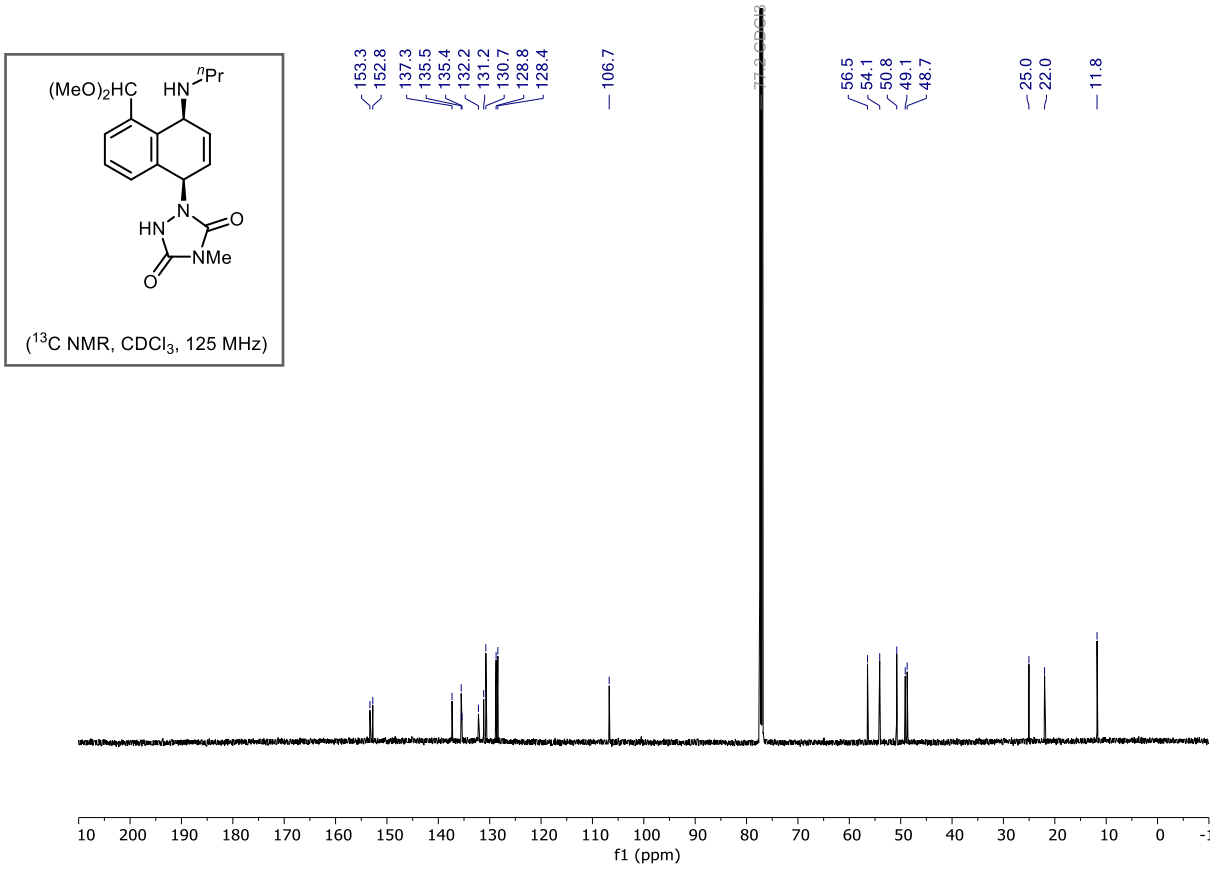


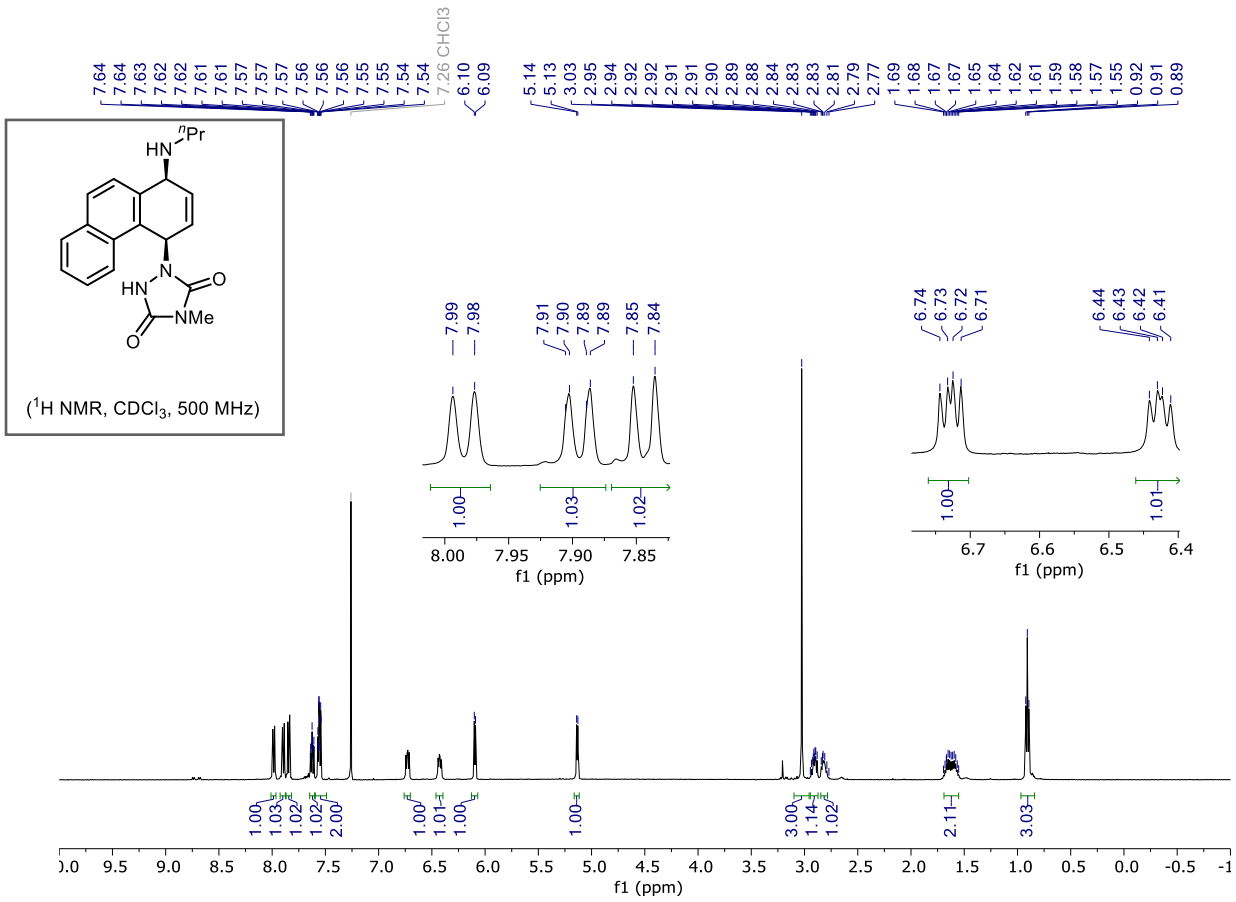
(^{1}H NMR, $CDCl_3$, 500 MHz)

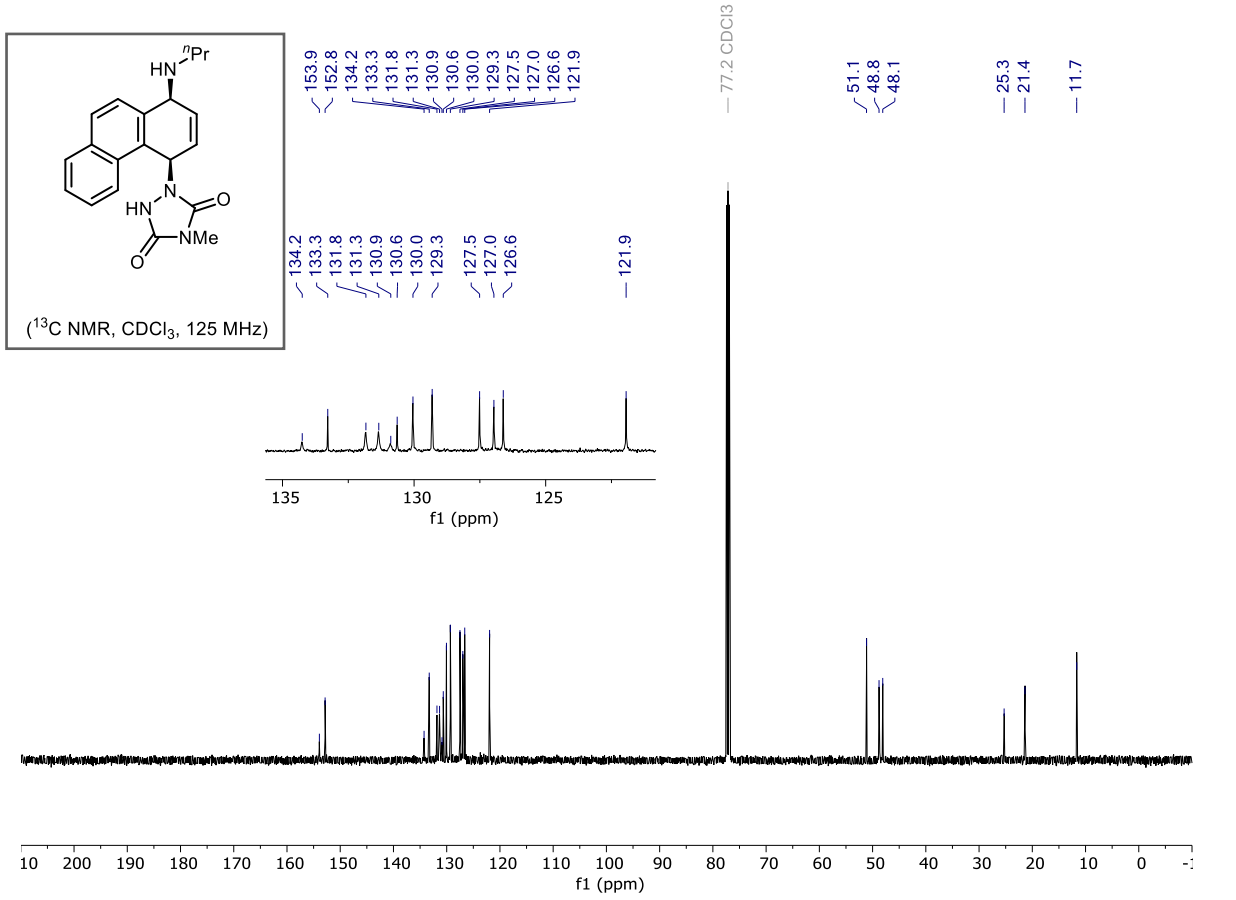


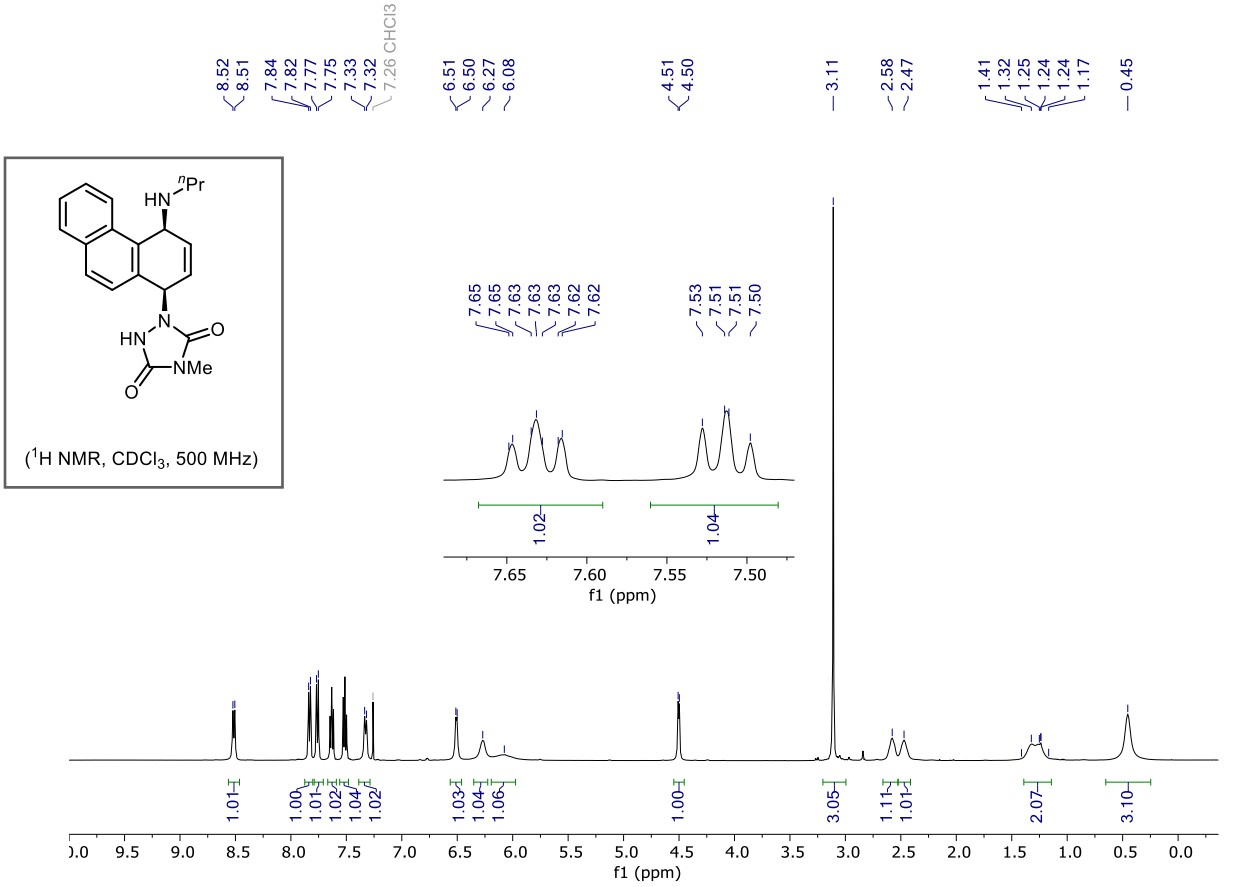
(^{13}C NMR, $CDCl_3$, 125 MHz)

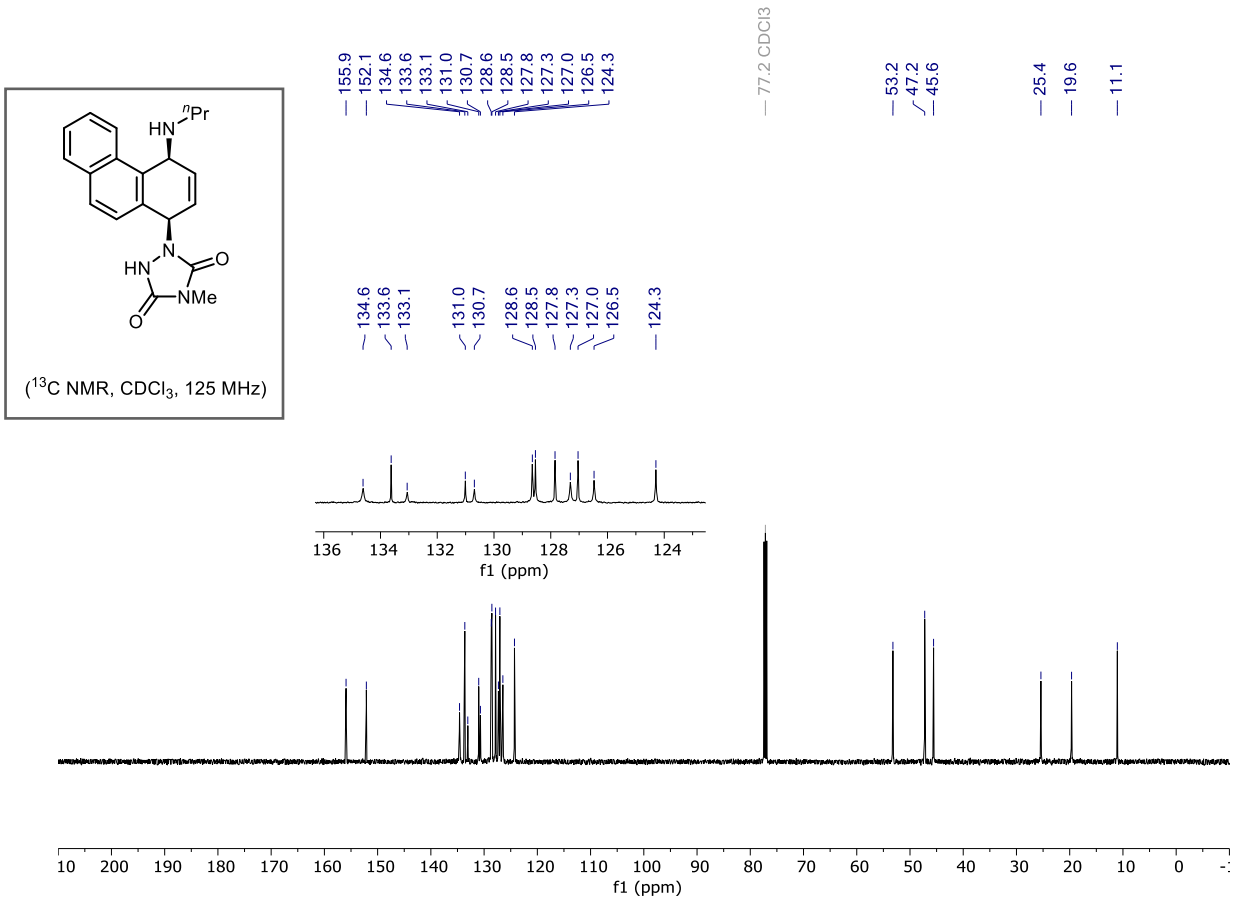

(MeO)2HC
HN
nPr
HN
N
O
NMe
O
O
(1H NMR, CDCl3, 500 MHz)
7.51 7.51 7.50 7.49 7.48 7.37 7.37 7.36 7.35 7.34 7.33 7.32
7.26 CHCl3
6.00 5.98
5.28 4.96 4.95
3.55 3.31 2.99 2.98 2.97 2.96 2.96 2.95 2.95 2.94
1.02 1.01 0.99
6.56 6.55 6.54 6.53 6.46 6.44 6.44 6.42
1.00 1.00
6.60 6.55 6.50 6.45 6.40
f1 (ppm)
1.75 1.73 1.73 1.72 1.72 1.71 1.70 1.69 1.68 1.68 1.66
2.01
1.80 1.75 1.70 1.65
f1 (ppm)
2.79 2.78 2.77 2.77 2.76 2.75 2.75 2.74
1.00
2.80 2.78 2.76 2.74
f1 (ppm)
1.00 2.00 1.00 1.00 1.00 1.00 1.00 3.10 3.05 3.15 1.11 1.00 2.01 3.00
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 -1
f1 (ppm)

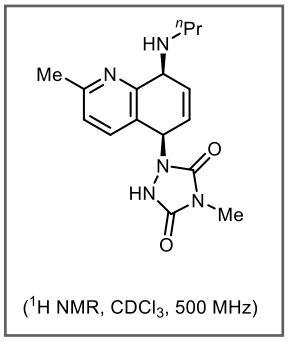

(MeO)2HC
HN
nPr
HN
N
O
NMe
O
O
(13C NMR, CDCl3, 125 MHz)
153.3 152.8 137.3 135.5 135.4 132.2 131.2 130.7 128.8 128.4 106.7
77.2 (CDCl3)
56.5 54.1 50.8 49.1 48.7 25.0 22.0 11.8
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


HN
nPr
HN
N
O
NMe
O
(^{1}H NMR, $CDCl_3$, 500 MHz)
7.64 7.64 7.63 7.62 7.62 7.61 7.61 7.57 7.57 7.57 7.56 7.56 7.56 7.55 7.55 7.54 7.54
7.26 CHCl3
6.10 6.09
5.14 5.13 3.03 2.95 2.94 2.92 2.92 2.91 2.91 2.90 2.89 2.88 2.84 2.83 2.83 2.81 2.79 2.77
1.69 1.68 1.67 1.67 1.65 1.64 1.62 1.61 1.59 1.58 1.57 1.55 0.92 0.91 0.89
7.99 7.98 7.91 7.90 7.89 7.89 7.85 7.84
6.74 6.73 6.72 6.71 6.44 6.43 6.42 6.41
1.00 1.03 1.02 1.02 2.00 1.00 1.01 1.00 1.00 3.00 1.14 1.02 2.11 3.03
f1 (ppm)

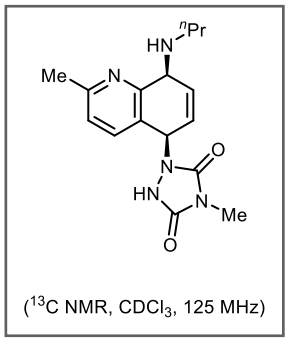

HN
nPr
HN
N
O
NMe
O
(^{13}C NMR, $CDCl_3$, 125 MHz)
153.9 152.8 134.2 133.3 131.8 131.3 130.9 130.6 130.0 129.3 127.5 127.0 126.6 121.9
77.2 CDCl3
51.1 48.8 48.1
25.3 21.4 11.7
f1 (ppm)


8.52
8.51
7.84
7.82
7.77
7.75
7.33
7.32
7.26 CHCl3
6.51
6.50
6.27
6.08
4.51
4.50
3.11
2.58
2.47
1.41
1.32
1.25
1.24
1.24
1.17
0.45
7.65
7.65
7.63
7.63
7.63
7.62
7.62
7.53
7.51
7.51
7.50
1.02
1.04
7.65
7.60
7.55
7.50
f1 (ppm)
1.01
1.00
1.01
1.02
1.04
1.02
1.03
1.04
1.06
1.00
3.05
1.11
1.01
2.07
3.10
f1 (ppm)
HN
nPr
HN
N
O
NMe
O
(1H NMR, CDCl3, 500 MHz)

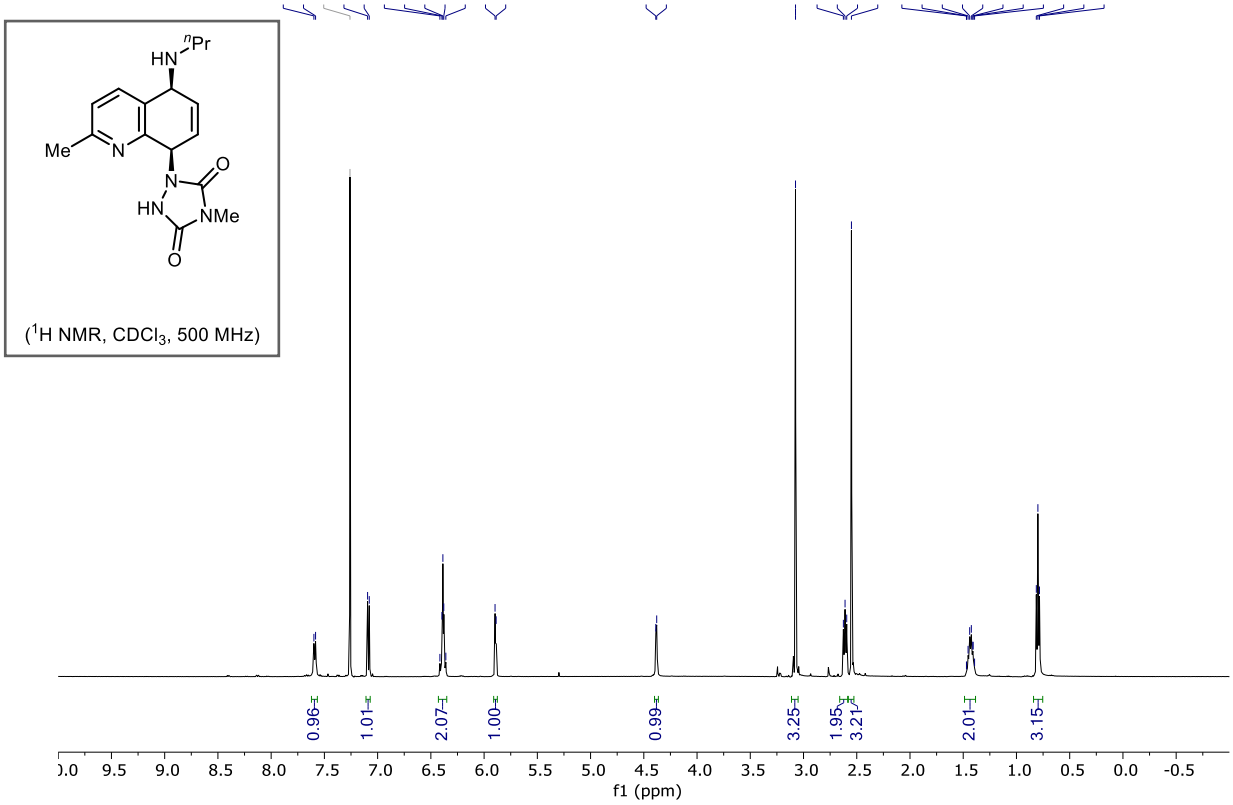

155.9
152.1
134.6
133.6
133.1
131.0
130.7
128.6
128.5
127.8
127.3
127.0
126.5
124.3
77.2 CDCl3
53.2
47.2
45.6
25.4
19.6
11.1
134.6
133.6
133.1
131.0
130.7
128.6
128.5
127.8
127.3
127.0
126.5
124.3
136
134
132
130
128
126
124
f1 (ppm)
f1 (ppm)
HN
nPr
HN
N
O
NMe
O
(13C NMR, CDCl3, 125 MHz)



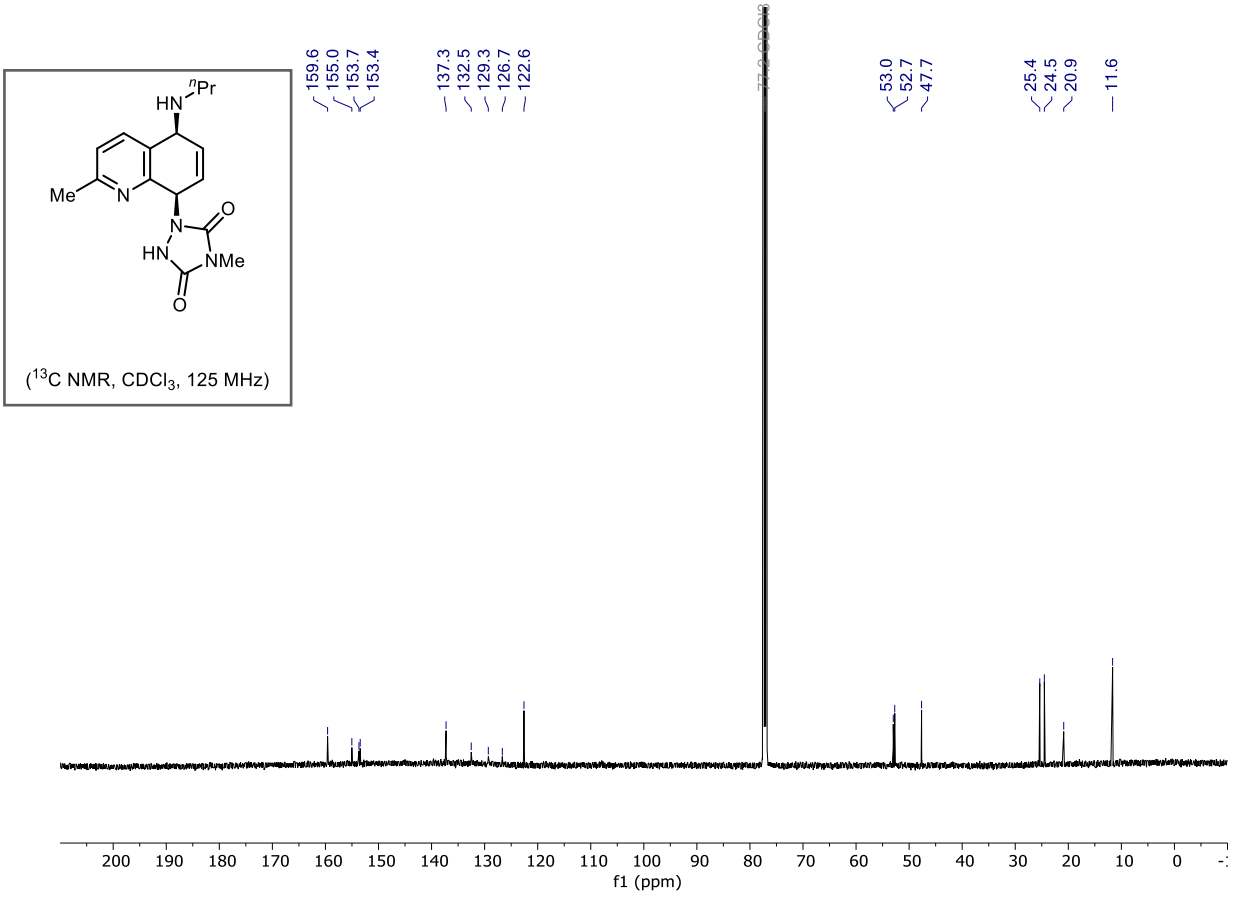
(^{1}H NMR, $CDCl_3$, 500 MHz)



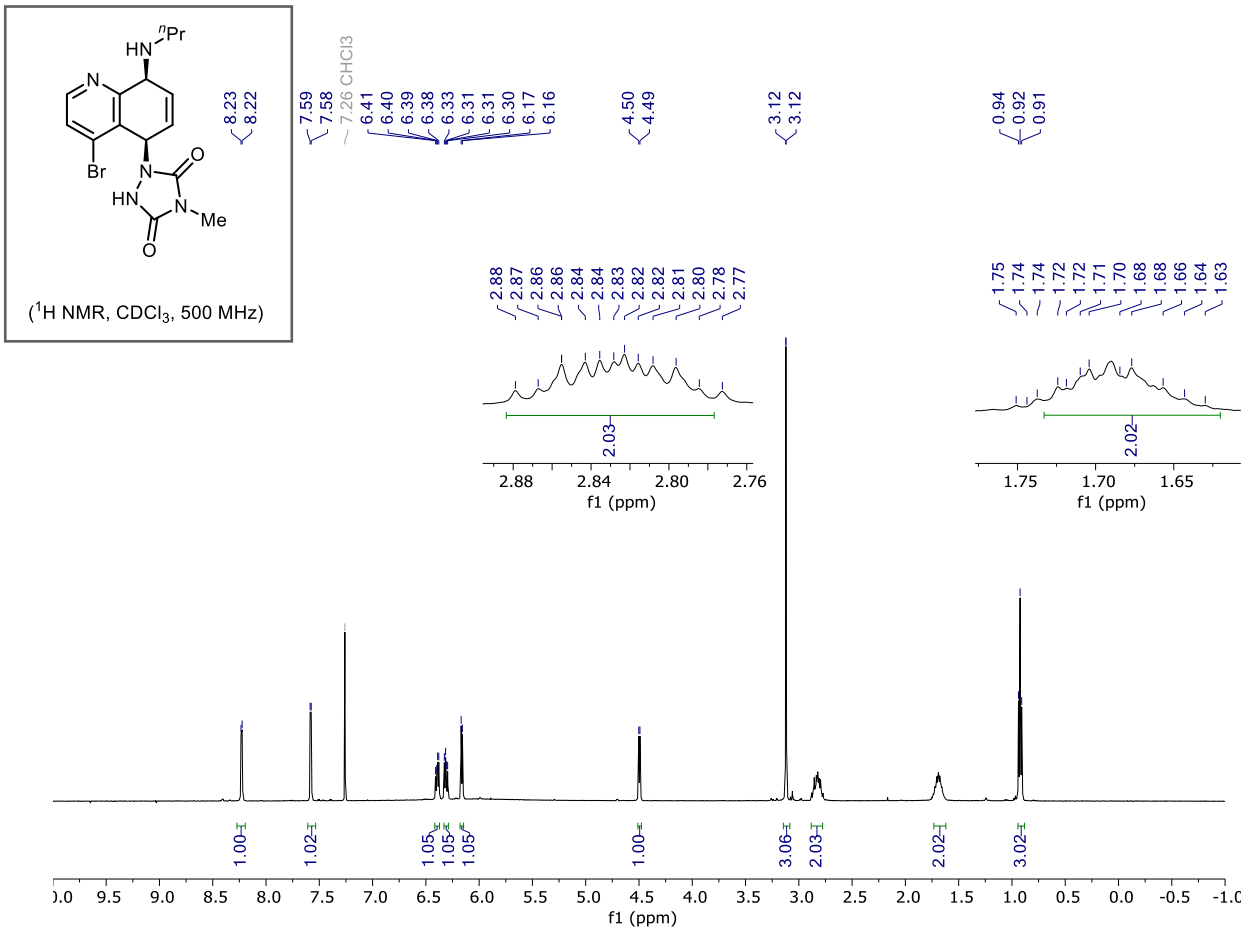
(^{13}C NMR, $CDCl_3$, 125 MHz)

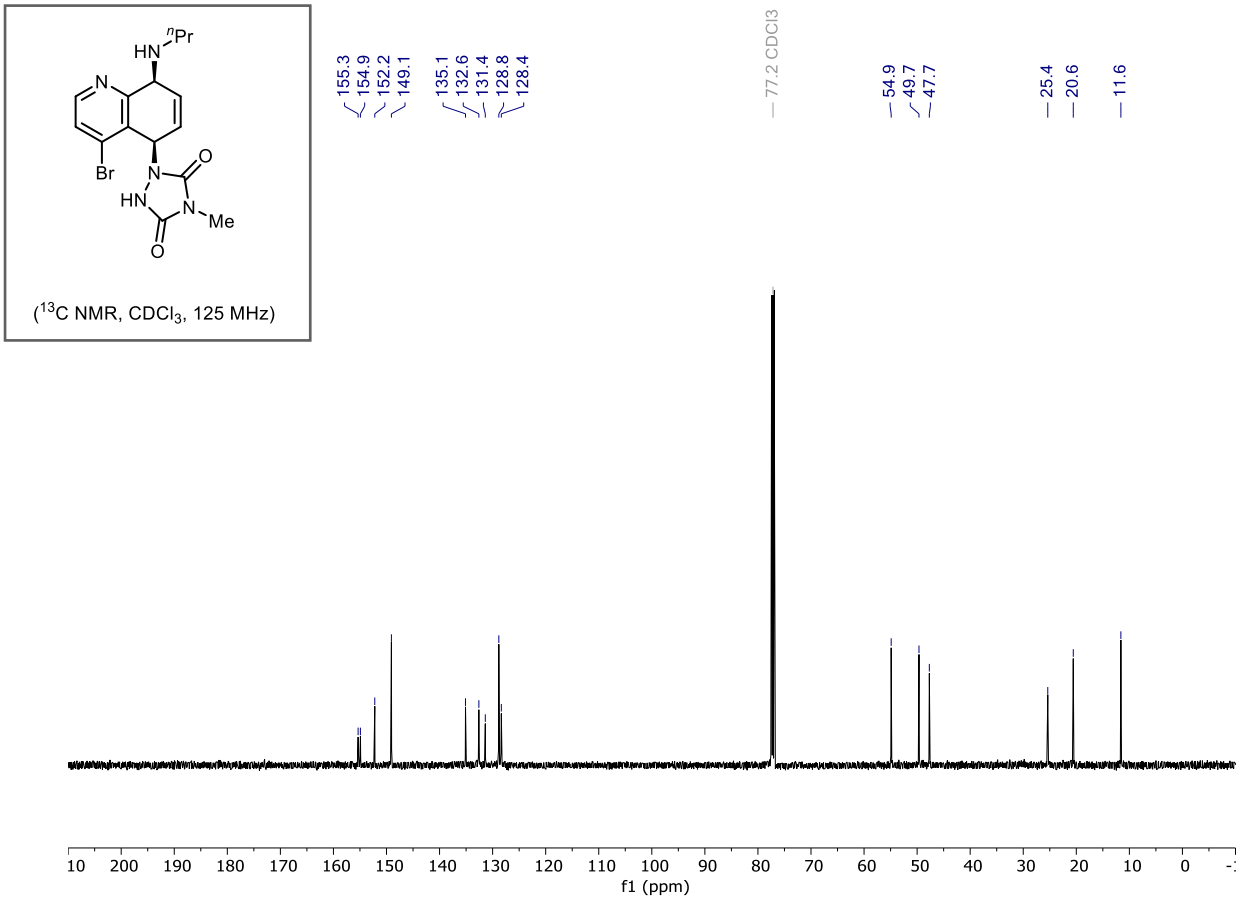


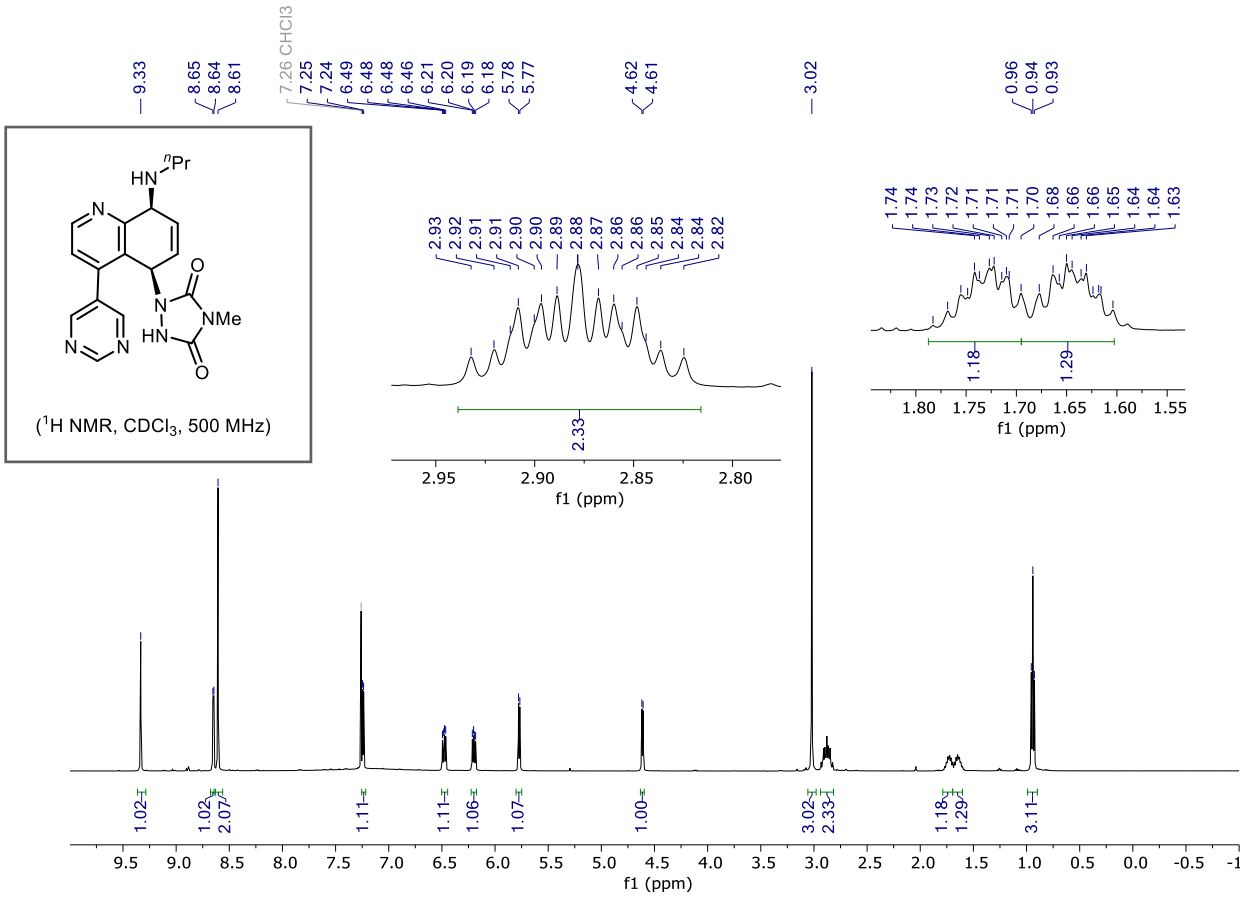
(^{1}H NMR, $CDCl_3$, 500 MHz)

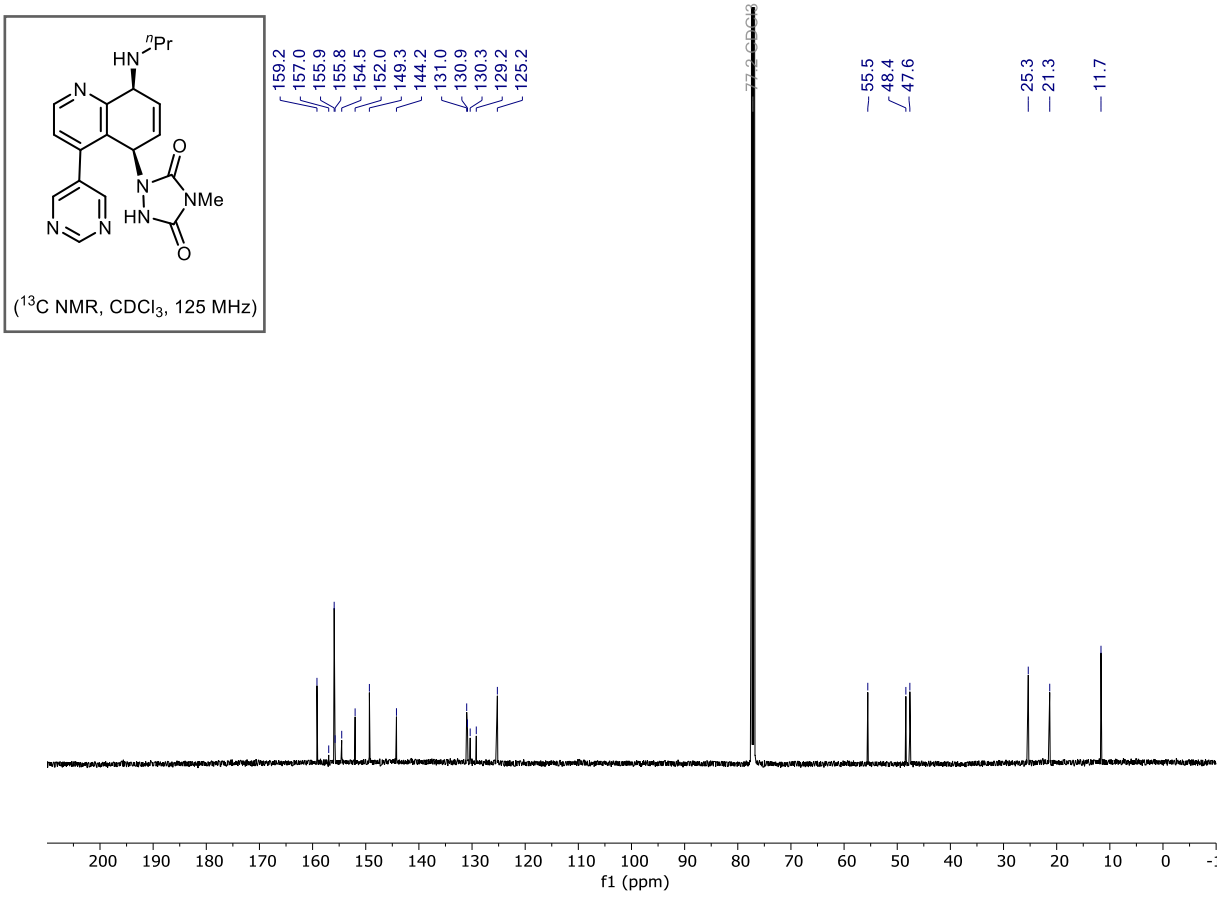


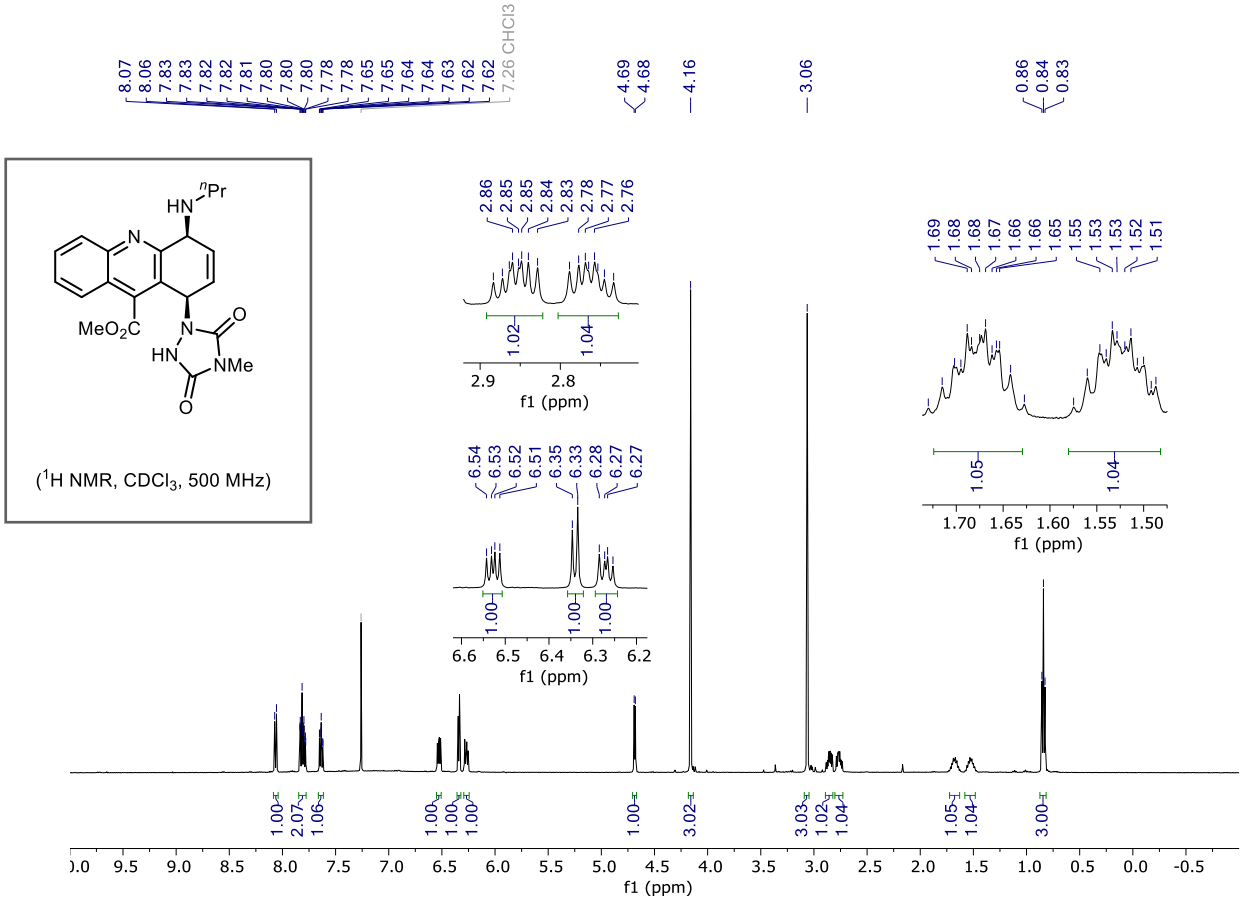
(^{13}C NMR, $CDCl_3$, 125 MHz)

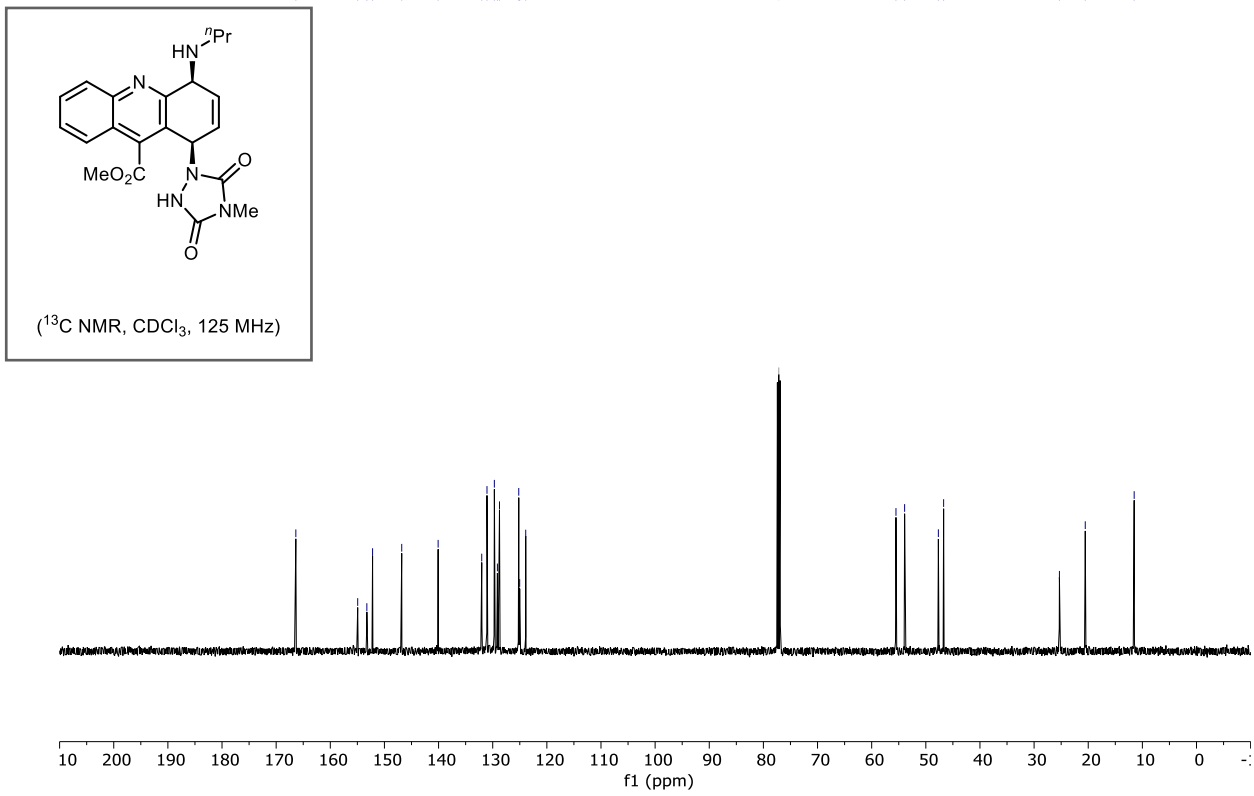

HN
nPr
N
Br
N
O
HN
N
Me
O
(1H NMR, CDCl3, 500 MHz)
8.23
8.22
7.59
7.58
7.26 CHCl3
6.41
6.40
6.39
6.38
6.33
6.31
6.31
6.30
6.17
6.16
4.50
4.49
3.12
3.12
0.94
0.92
0.91
2.88
2.87
2.86
2.86
2.84
2.84
2.83
2.82
2.82
2.81
2.80
2.78
2.77
2.03
1.75
1.74
1.74
1.72
1.72
1.71
1.70
1.68
1.68
1.66
1.64
1.63
2.02
f1 (ppm)
1.00
1.02
1.05
1.05
1.05
1.00
3.06
2.03
2.02
3.02
f1 (ppm)

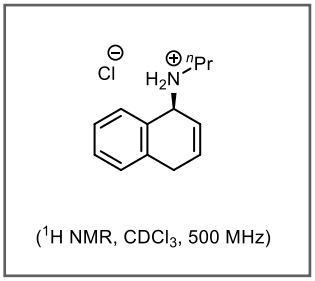

HN
nPr
N
Br
N
O
HN
N
Me
O
(13C NMR, CDCl3, 125 MHz)
155.3
154.9
152.2
149.1
135.1
132.6
131.4
128.8
128.4
77.2 CDCl3
54.9
49.7
47.7
25.4
20.6
11.6
f1 (ppm)


(1H NMR, CDCl3, 500 MHz)
f1 (ppm)

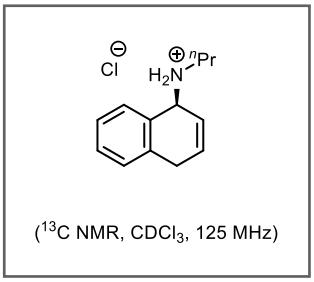

(13C NMR, CDCl3, 125 MHz)
f1 (ppm)


8.07 8.06 7.83 7.83 7.82 7.82 7.81 7.80 7.80 7.80 7.78 7.78 7.65 7.65 7.64 7.64 7.63 7.62 7.62
7.26 CHCl3
4.69 4.68
4.16
3.06
0.86 0.84 0.83
2.86 2.85 2.85 2.84 2.83 2.78 2.77 2.76
1.02 1.04
2.9 2.8
f1 (ppm)
1.69 1.68 1.68 1.67 1.66 1.66 1.65 1.55 1.53 1.53 1.52 1.51
1.05 1.04
1.70 1.65 1.60 1.55 1.50
f1 (ppm)
6.54 6.53 6.52 6.51 6.35 6.33 6.28 6.27 6.27
1.00 1.00 1.00
6.6 6.5 6.4 6.3 6.2
f1 (ppm)
1.00 2.07 1.06 1.00 1.00 1.00 1.00 3.02 3.03 1.02 1.04 1.05 1.04 3.00
f1 (ppm)

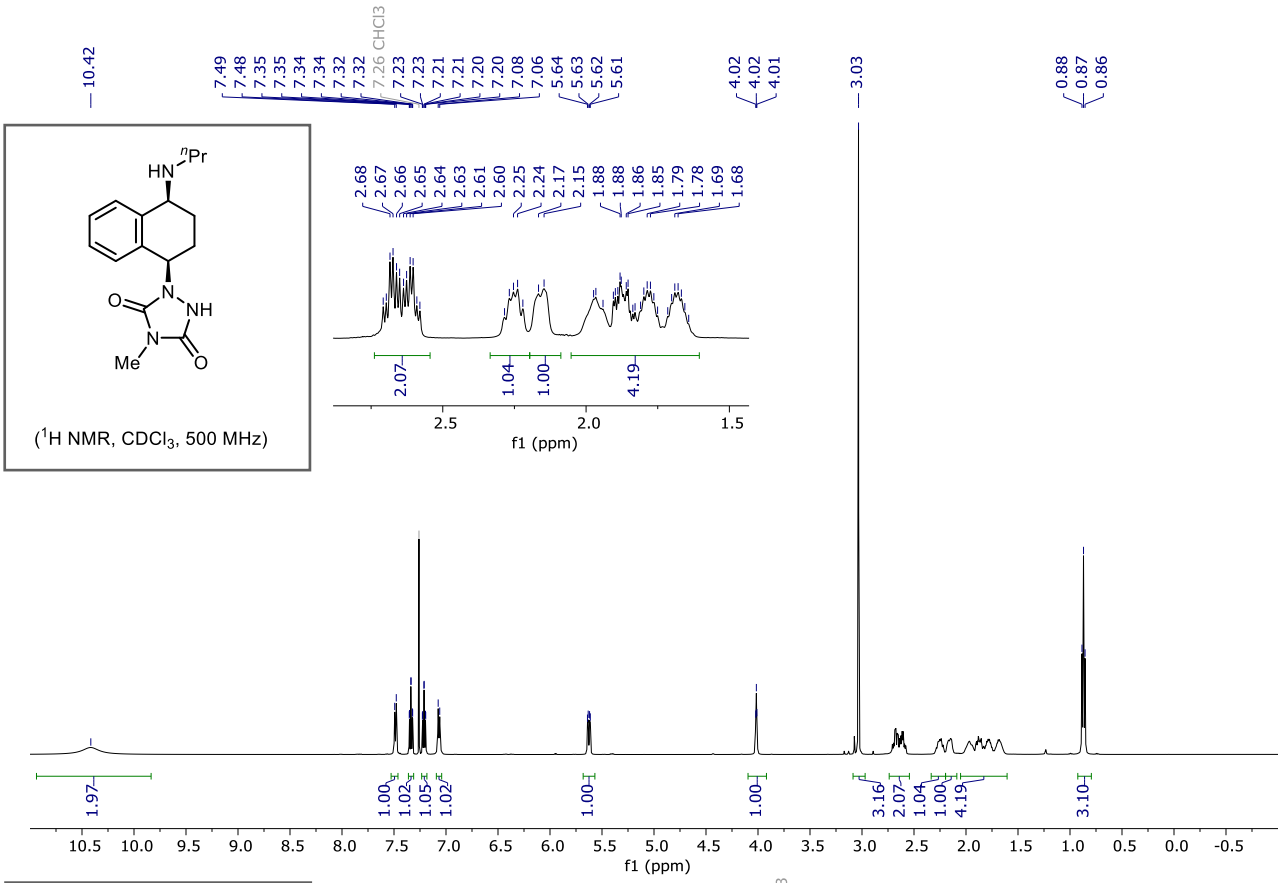

166.4
154.9 153.2 152.2 146.8 140.1 132.0 131.1 129.7 129.1 128.7 125.2 125.0 123.9
77.2 CDCl3
55.5 53.9 47.7 46.7
25.3 20.5 11.5
f1 (ppm)

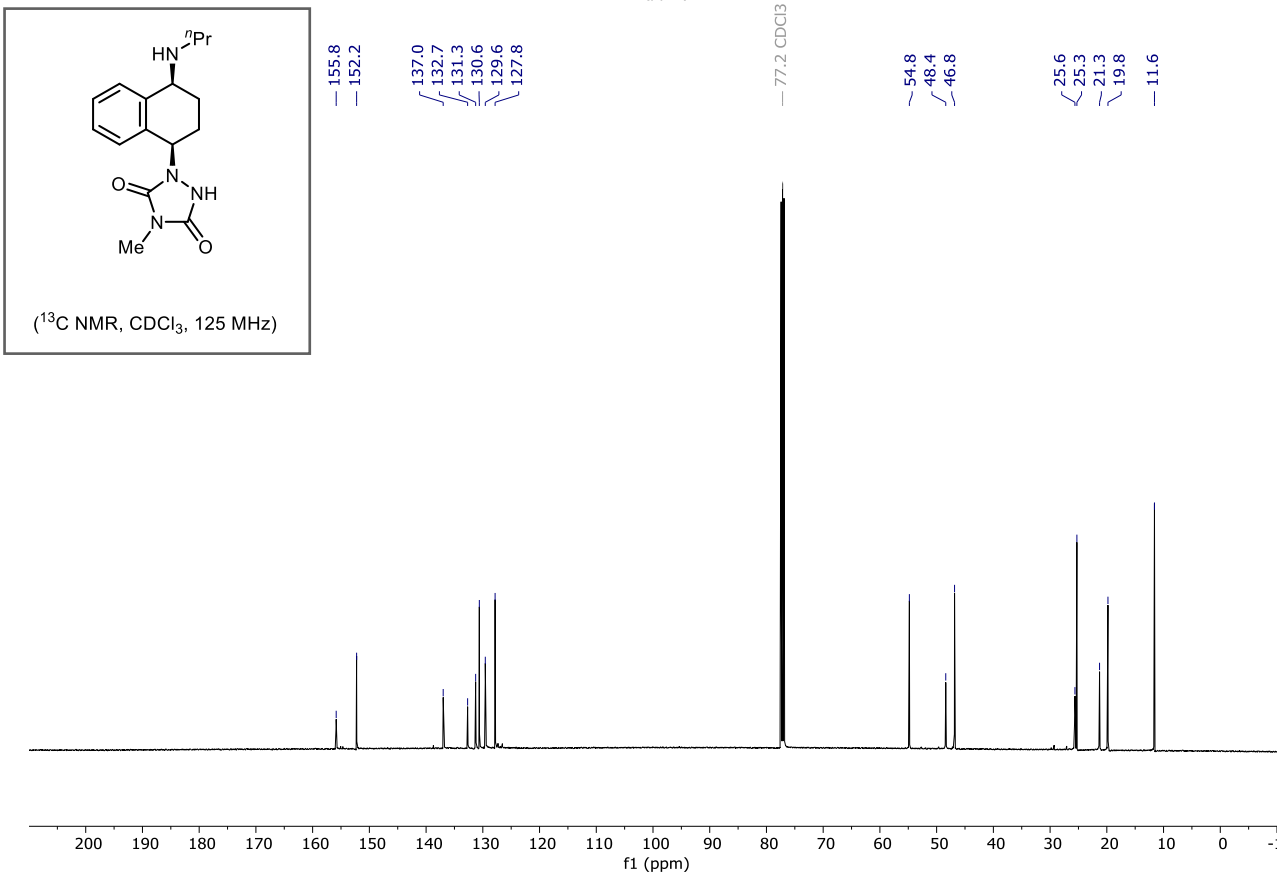


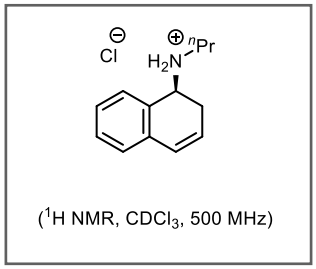
(^{1}H NMR, $CDCl_3$, 500 MHz)



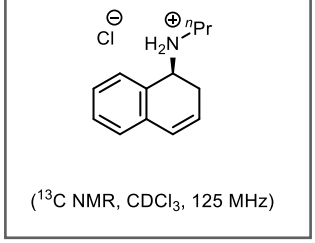
(^{13}C NMR, $CDCl_3$, 125 MHz)


HN
nPr
O
N
NH
N
Me
O
(1H NMR, CDCl3, 500 MHz)
f1 (ppm)

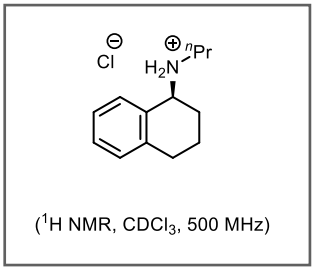

HN
nPr
O
N
NH
N
Me
O
(13C NMR, CDCl3, 125 MHz)
f1 (ppm)



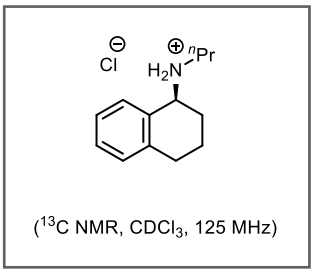
(^{1}H NMR, $CDCl_3$, 500 MHz)



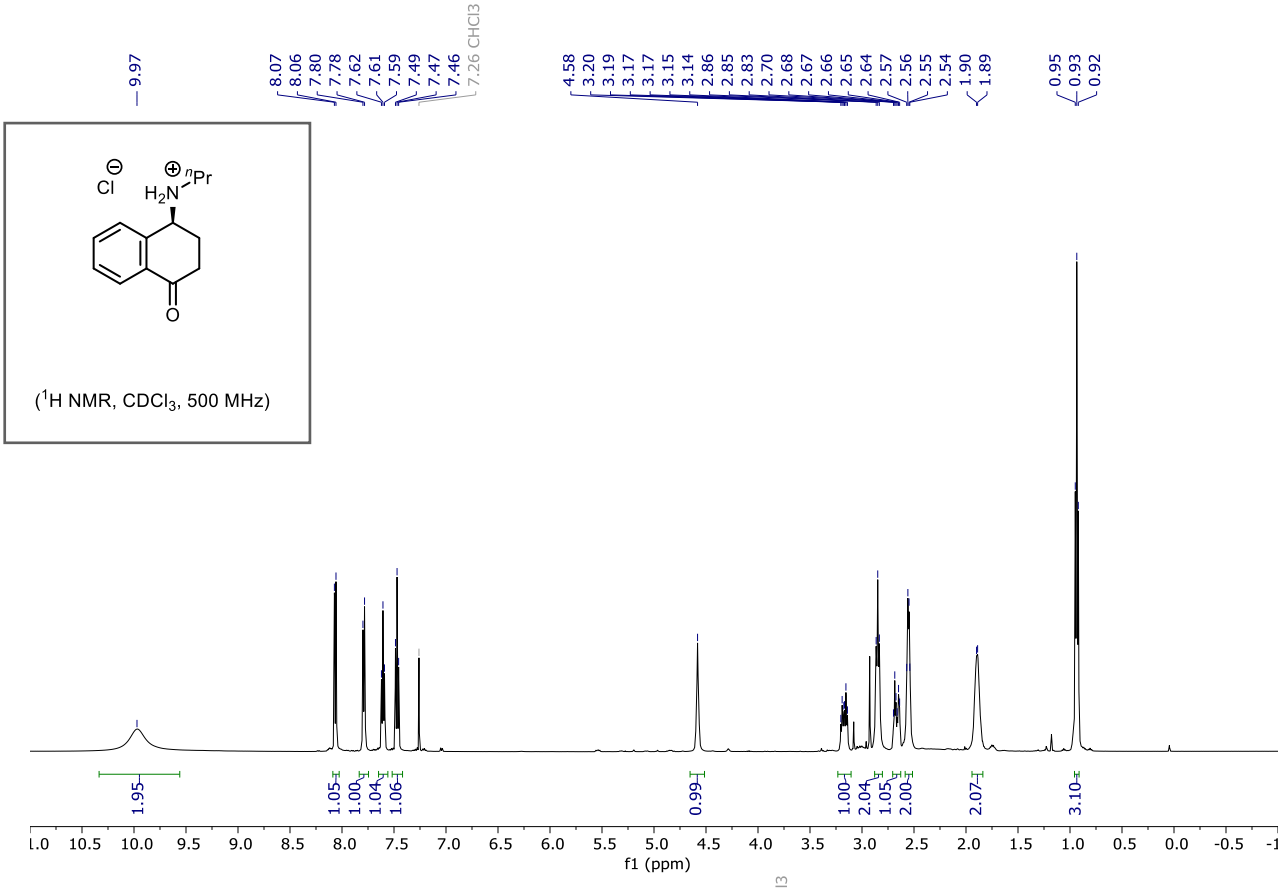
(^{13}C NMR, $CDCl_3$, 125 MHz)

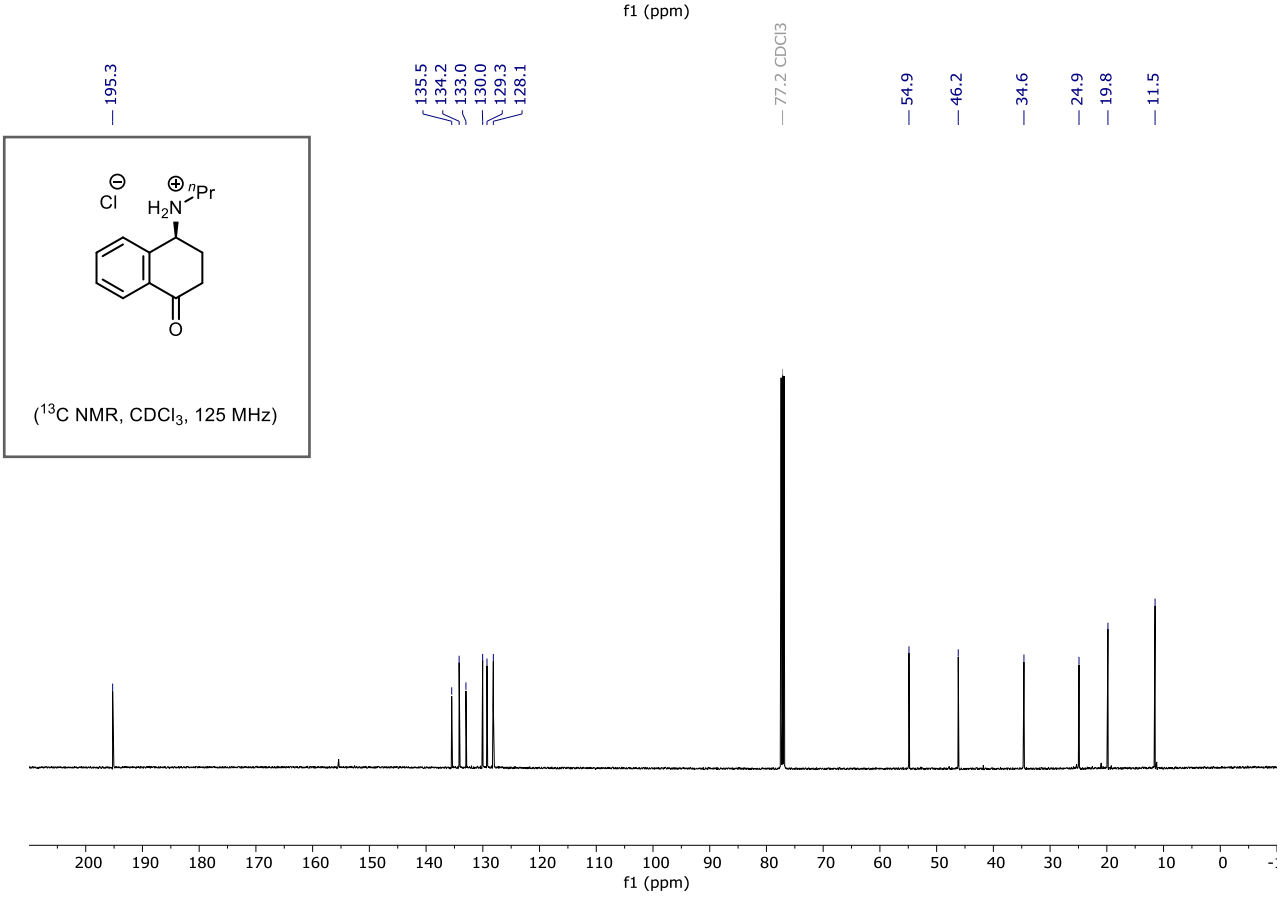


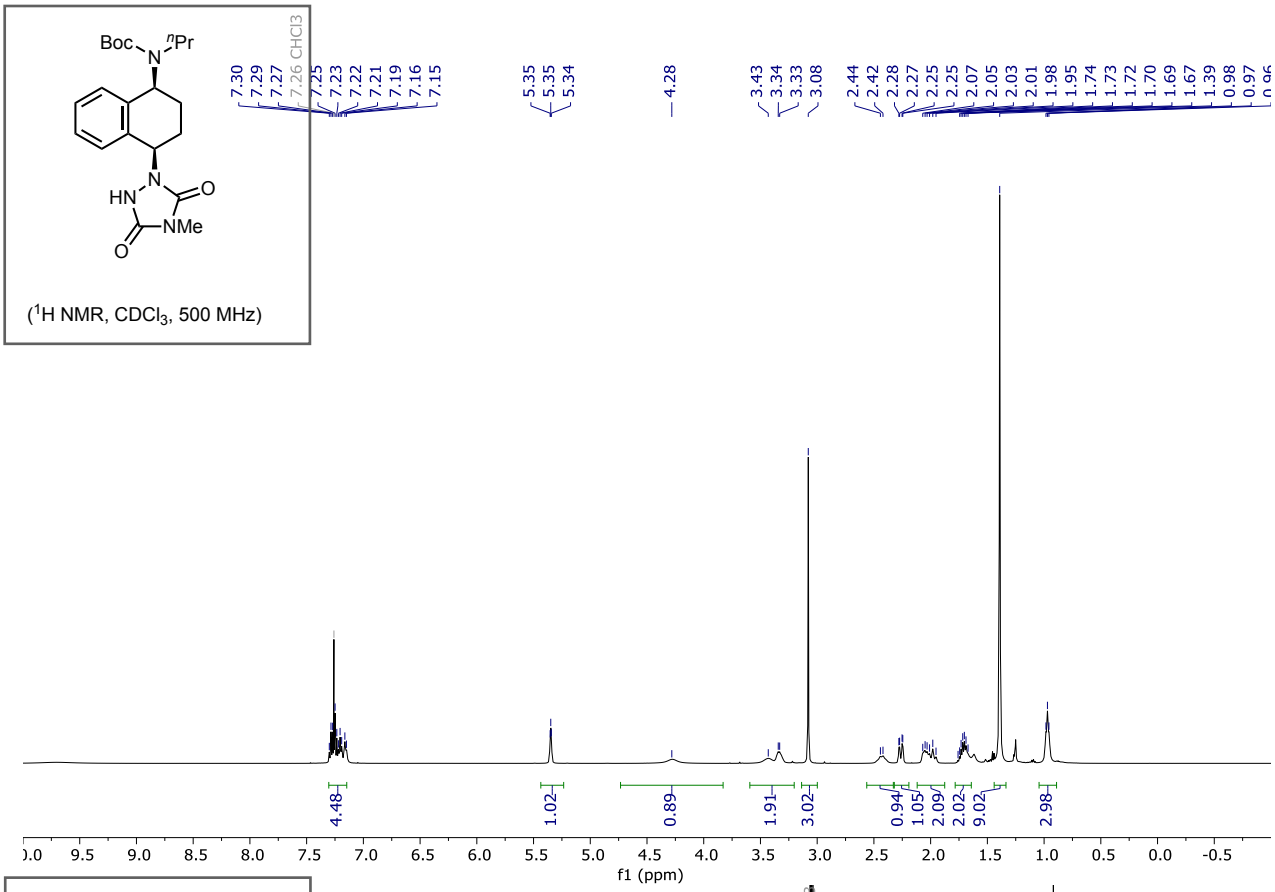
(^{1}H NMR, $CDCl_3$, 500 MHz)



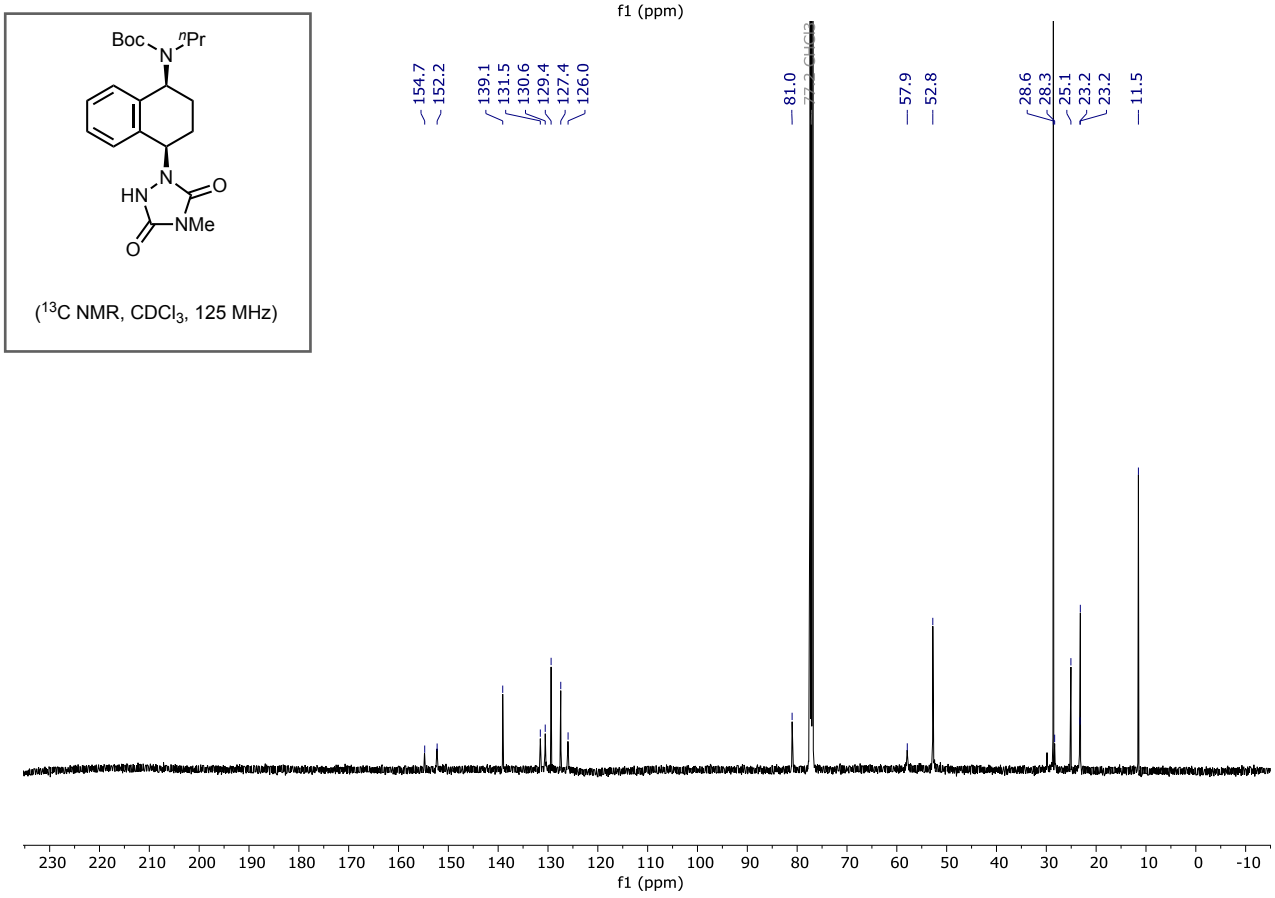
(^{13}C NMR, $CDCl_3$, 125 MHz)


9.97
8.07
8.06
7.80
7.78
7.62
7.61
7.59
7.49
7.47
7.46
7.26 CHCl3
4.58
3.20
3.19
3.17
3.17
3.15
3.14
2.86
2.85
2.83
2.70
2.68
2.67
2.66
2.65
2.64
2.57
2.56
2.55
2.54
1.90
1.89
0.95
0.93
0.92
Cl
nPr
H2N
O
(1H NMR, CDCl3, 500 MHz)
1.95
1.05
1.00
1.04
1.06
0.99
1.00
2.04
1.05
2.00
2.07
3.10
f1 (ppm)

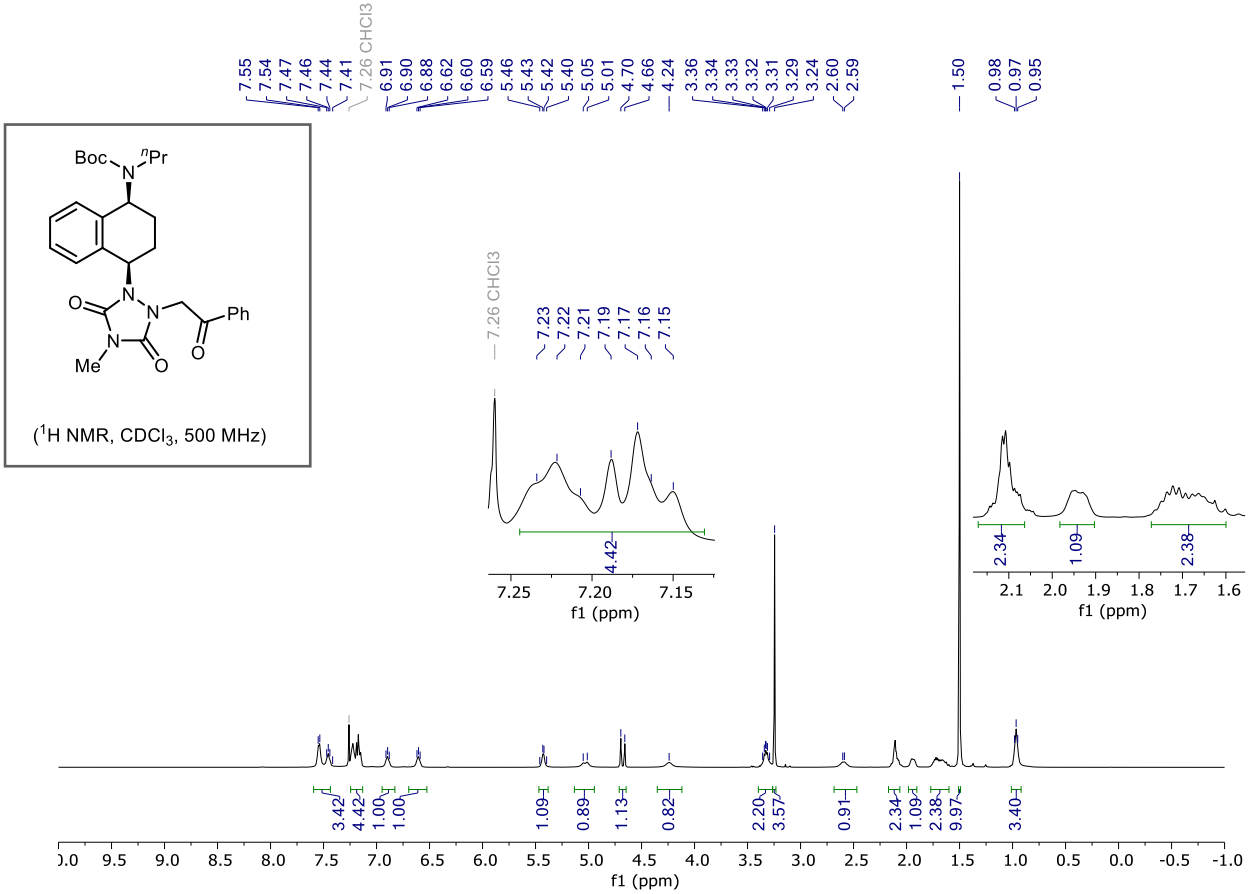

195.3
135.5
134.2
133.0
130.0
129.3
128.1
77.2 CDCl3
54.9
46.2
34.6
24.9
19.8
11.5
Cl
nPr
H2N
O
(13C NMR, CDCl3, 125 MHz)
f1 (ppm)

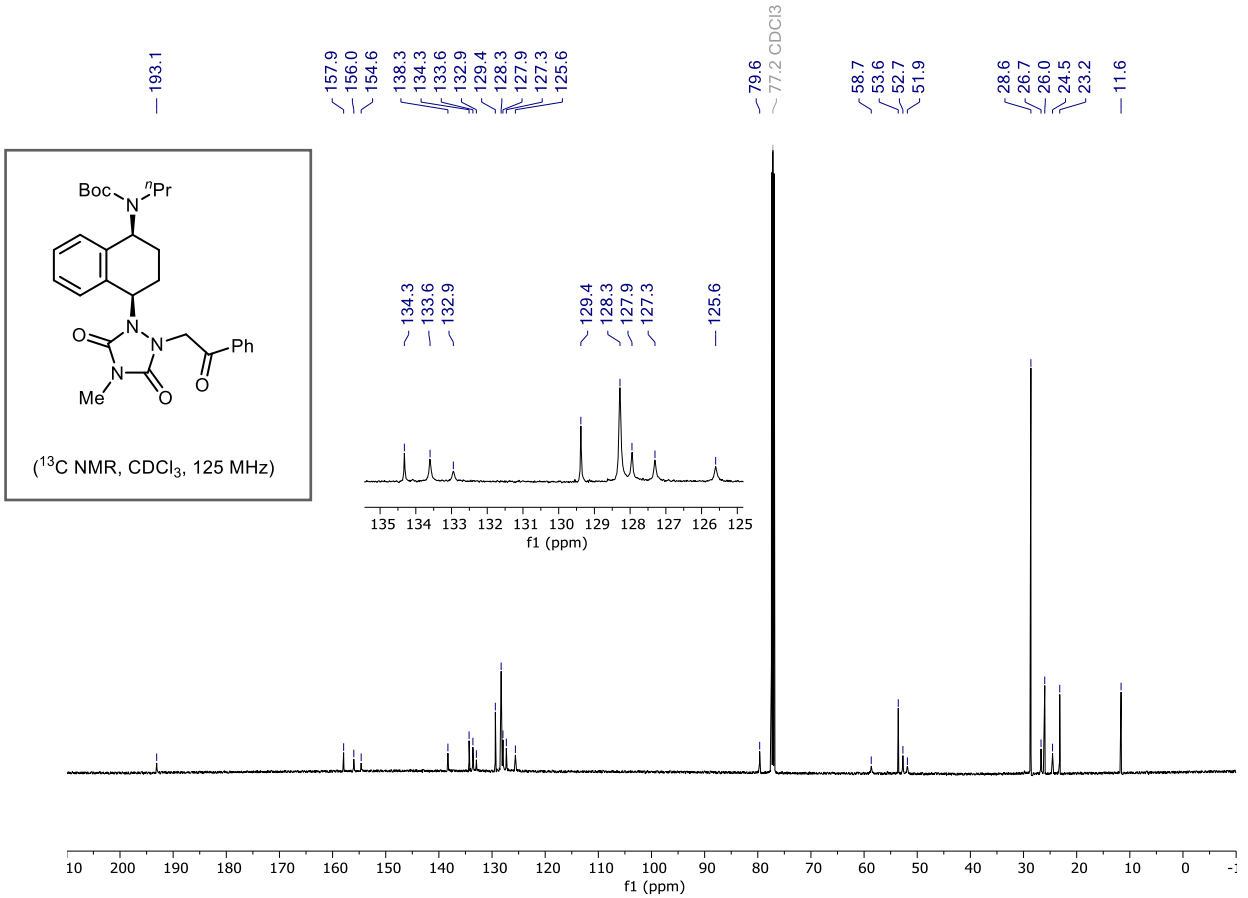


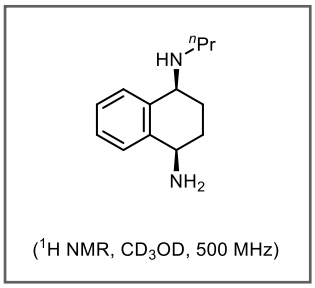
(^{1}H NMR, $CDCl_3$, 500 MHz)



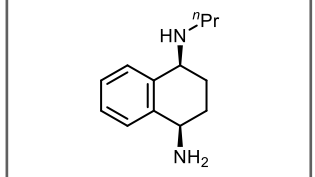
(^{13}C NMR, $CDCl_3$, 125 MHz)


Boc
nPr
N
O
N
N
Ph
O
Me
N
O
(^{1}H NMR, $CDCl_3$, 500 MHz)
7.55
7.54
7.47
7.46
7.44
7.41
7.26 CHCl3
6.91
6.90
6.88
6.62
6.60
6.59
5.46
5.43
5.42
5.40
5.05
5.01
4.70
4.66
4.24
3.36
3.34
3.33
3.32
3.31
3.29
3.24
2.60
2.59
1.50
0.98
0.97
0.95
7.26 CHCl3
7.23
7.22
7.21
7.19
7.17
7.16
7.15
4.42
7.25
7.20
7.15
f1 (ppm)
2.34
1.09
2.38
2.1
2.0
1.9
1.8
1.7
1.6
f1 (ppm)
3.42
4.42
1.00
1.00
1.09
0.89
1.13
0.82
2.20
3.57
0.91
2.34
1.09
2.38
9.97
3.40
f1 (ppm)

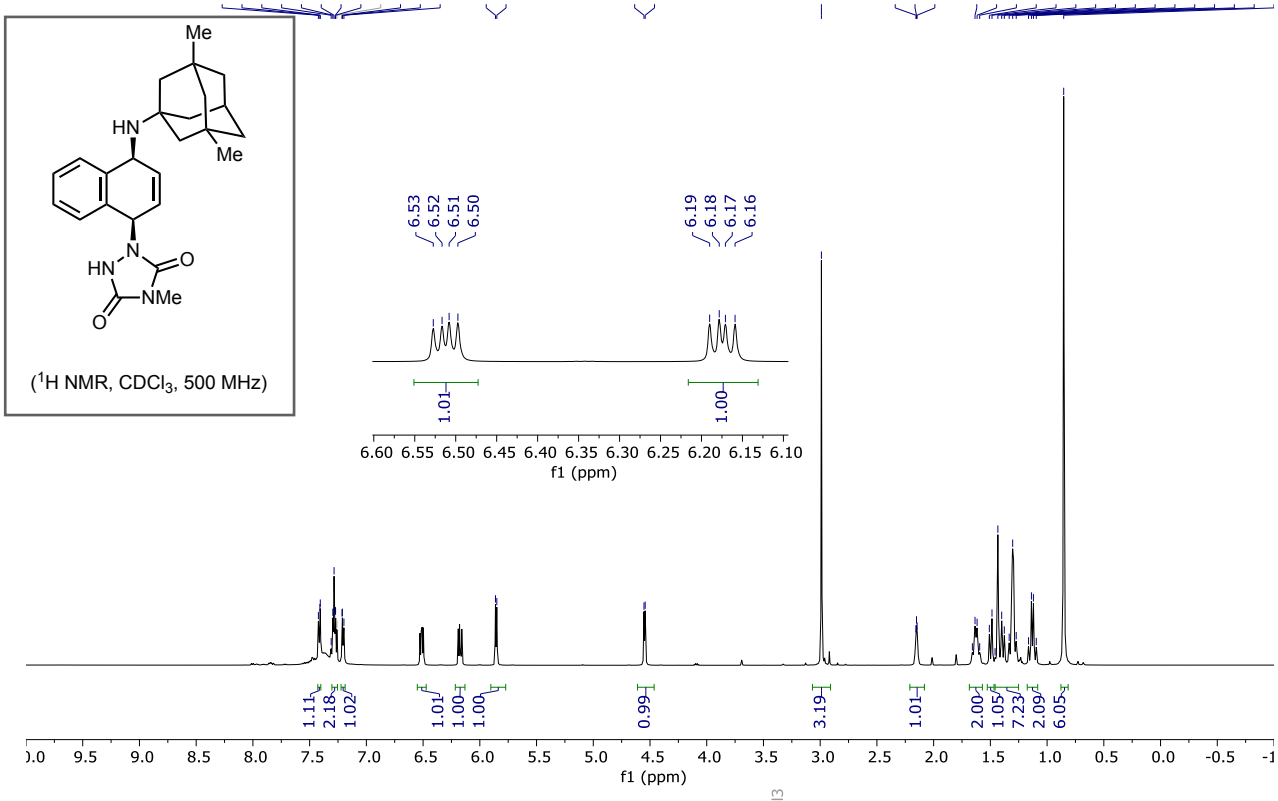

Boc
nPr
N
O
N
N
Ph
O
Me
N
O
(^{13}C NMR, $CDCl_3$, 125 MHz)
193.1
157.9
156.0
154.6
138.3
134.3
133.6
132.9
129.4
128.3
127.9
127.3
125.6
79.6
77.2 CDCl3
58.7
53.6
52.7
51.9
28.6
26.7
26.0
24.5
23.2
11.6
134.3
133.6
132.9
129.4
128.3
127.9
127.3
125.6
f1 (ppm)
f1 (ppm)

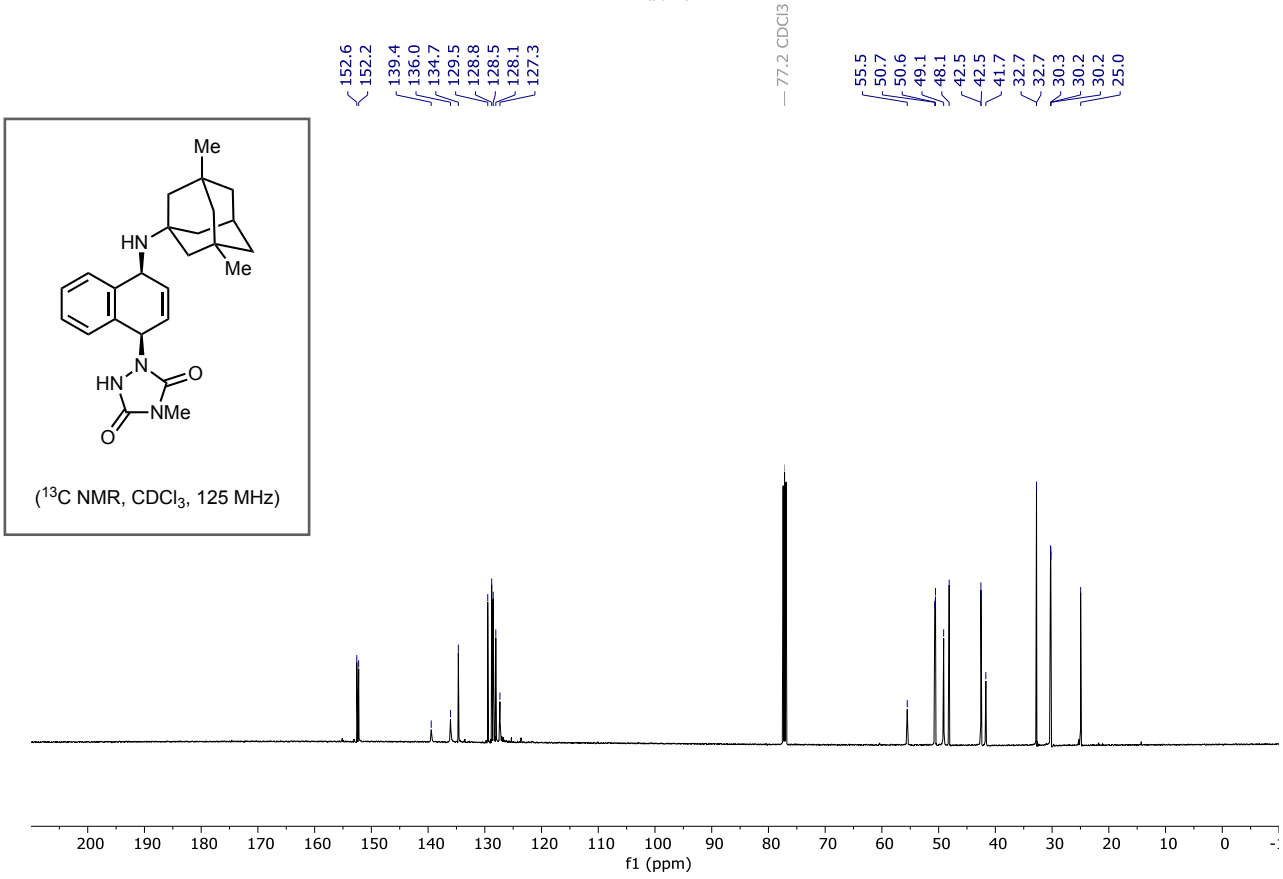


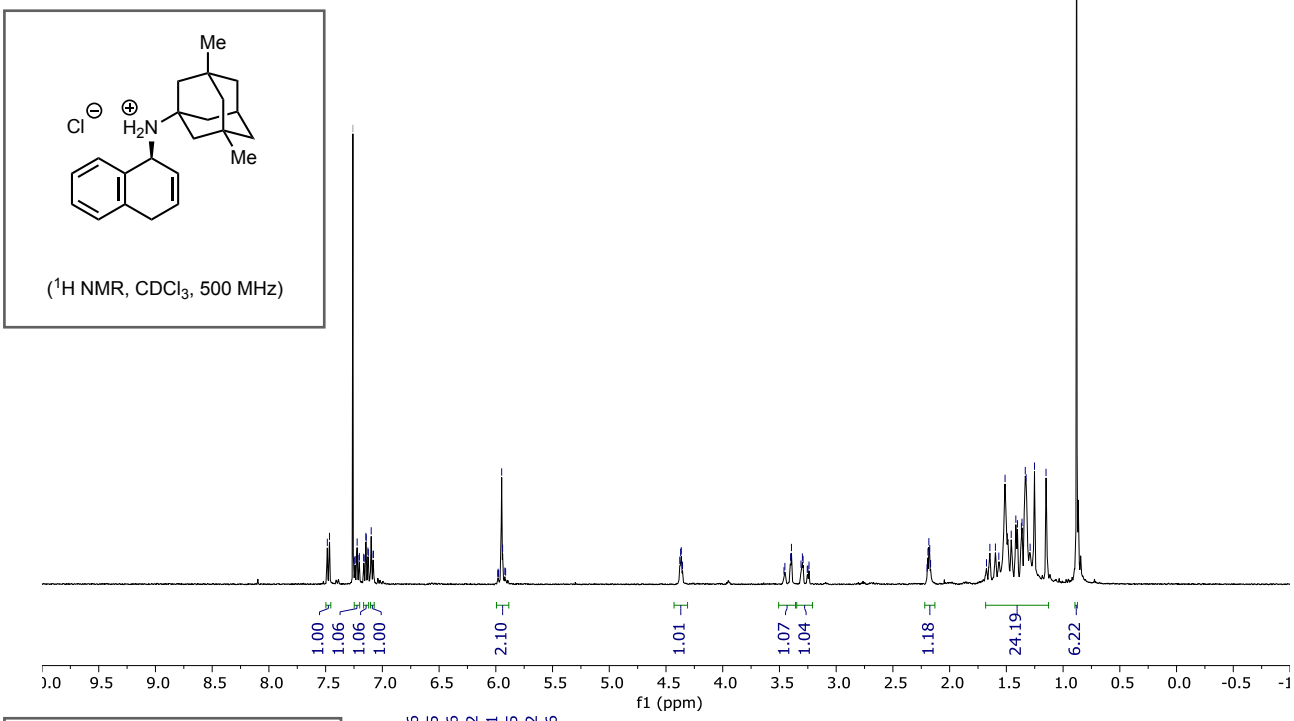
(^{1}H NMR, CD_3OD, 500 MHz)



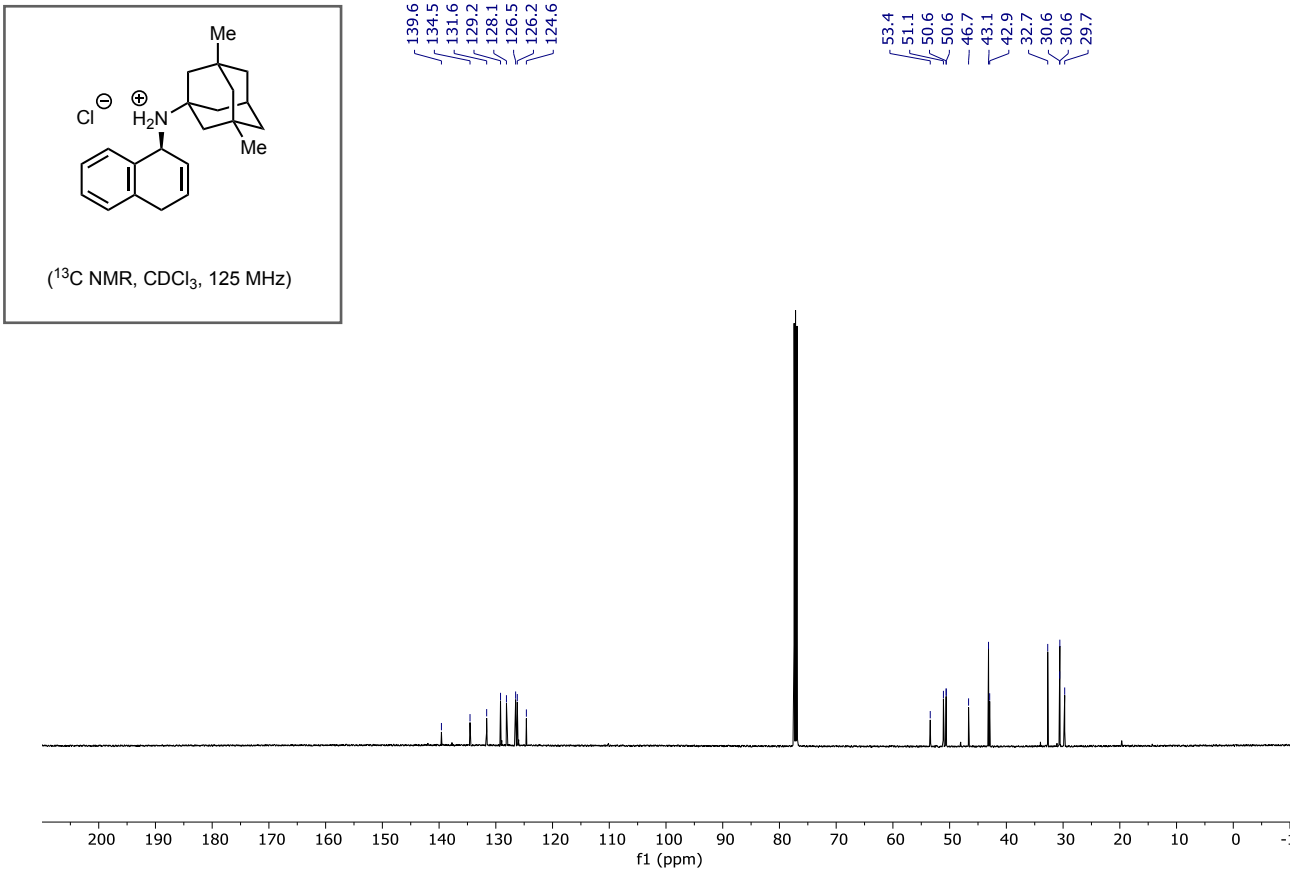
(^{13}C NMR, CD_3OD, 125 MHz)


Me
HN
Me
HN
N
O
NMe
O
(^{1}H NMR, $CDCl_3$, 500 MHz)
7.42 7.41 7.41 7.31 7.30 7.28 7.27 7.27 7.26 CHCl3 7.21 7.21 7.20
5.86 5.85
4.55 4.54
2.99
2.16 2.15 2.15
1.64 1.62 1.59 1.51 1.49 1.43 1.40 1.38 1.33 1.30 1.27 1.16 1.14 1.12 1.10
6.53 6.52 6.51 6.50
6.19 6.18 6.17 6.16
1.01
1.00
6.60 6.55 6.50 6.45 6.40 6.35 6.30 6.25 6.20 6.15 6.10
f1 (ppm)
1.11 2.18 1.02 1.01 1.00 1.00 0.99 3.19 1.01 2.00 1.05 7.23 2.09 6.05
f1 (ppm)

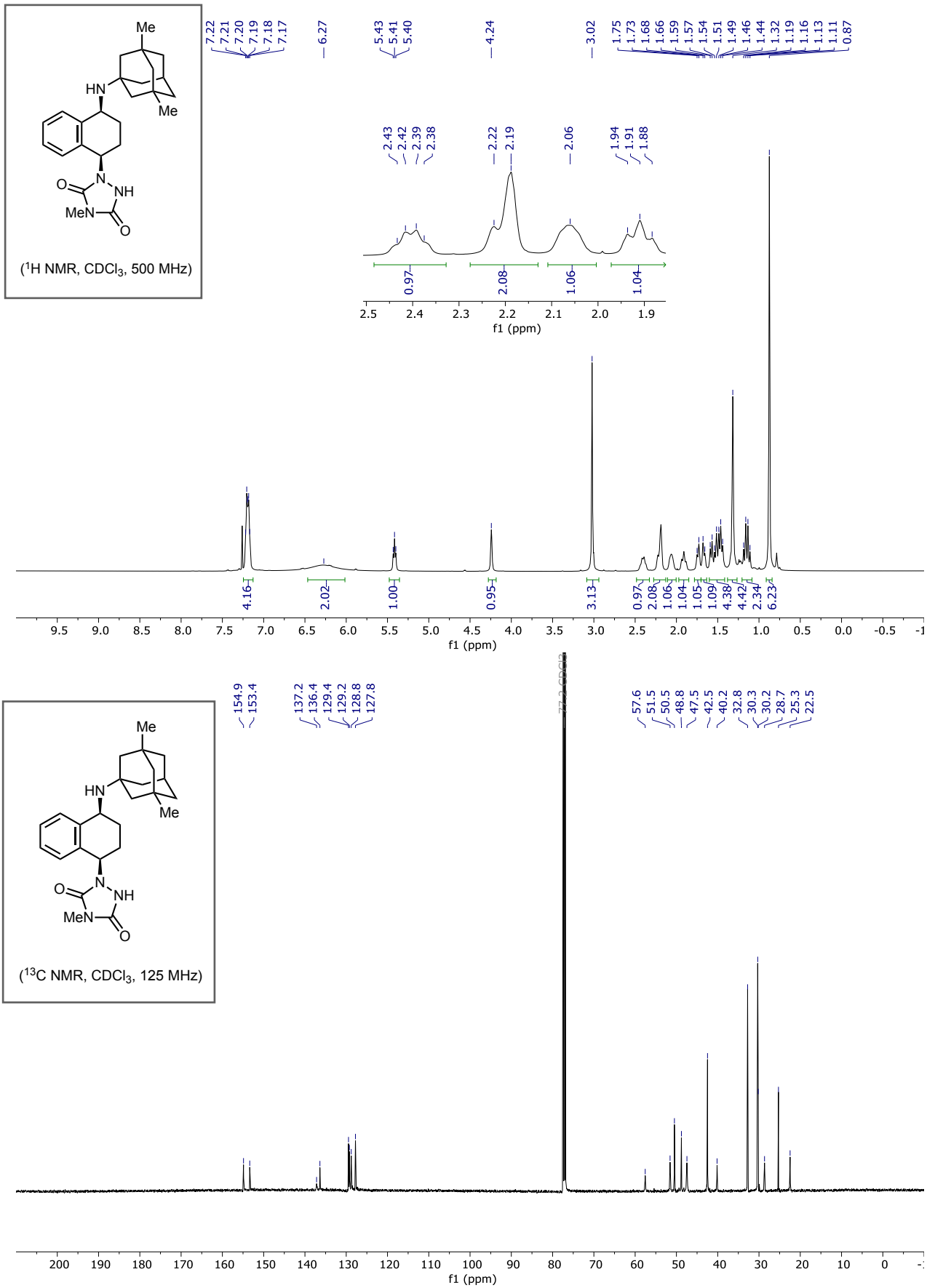

Me
HN
Me
HN
N
O
NMe
O
(^{13}C NMR, $CDCl_3$, 125 MHz)
152.6 152.2 139.4 136.0 134.7 129.5 128.8 128.5 128.1 127.3
77.2 CDCl3
55.5 50.7 50.6 49.1 48.1 42.5 42.5 41.7 32.7 32.7 30.3 30.2 30.2 25.0
f1 (ppm)

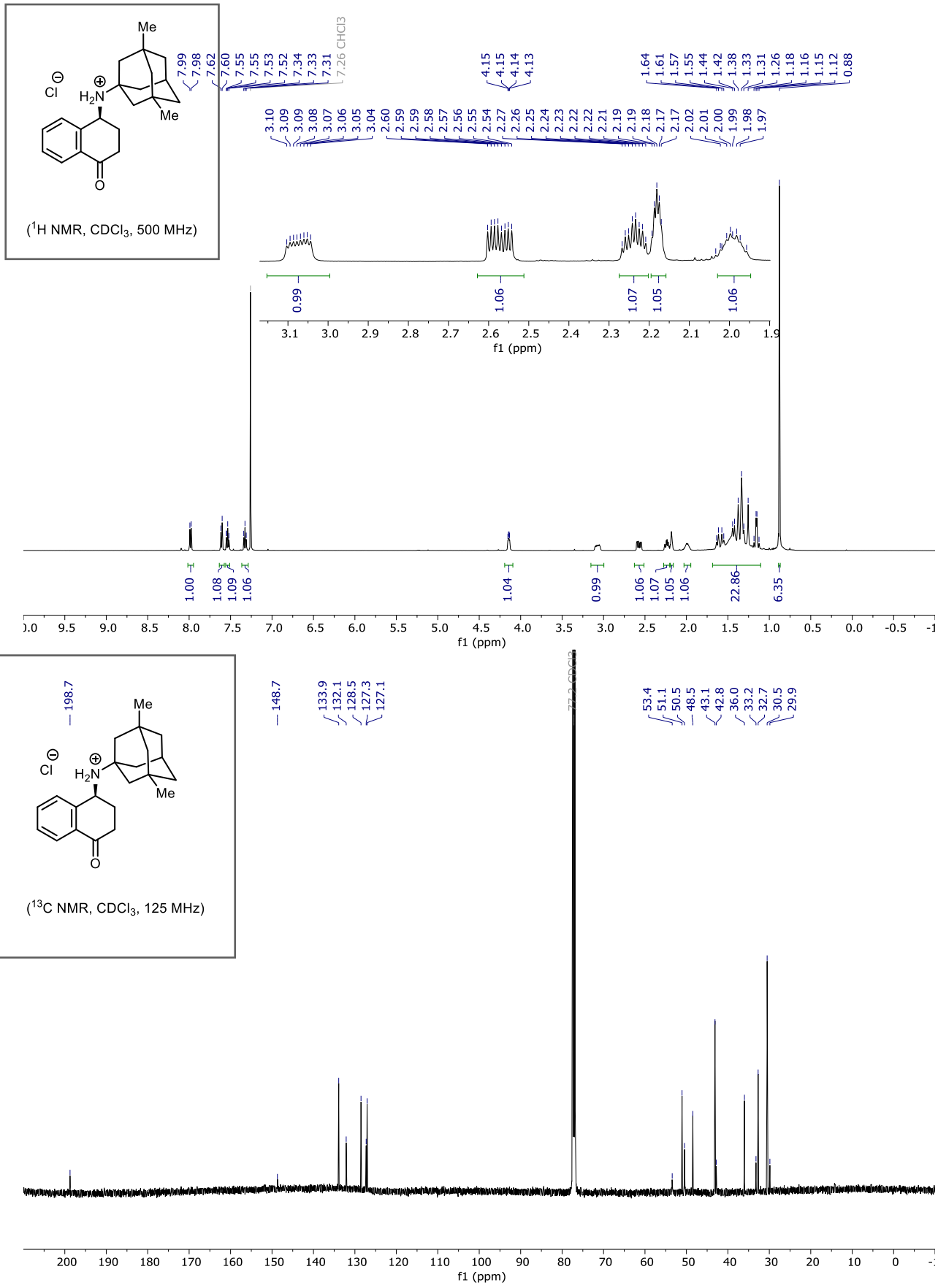


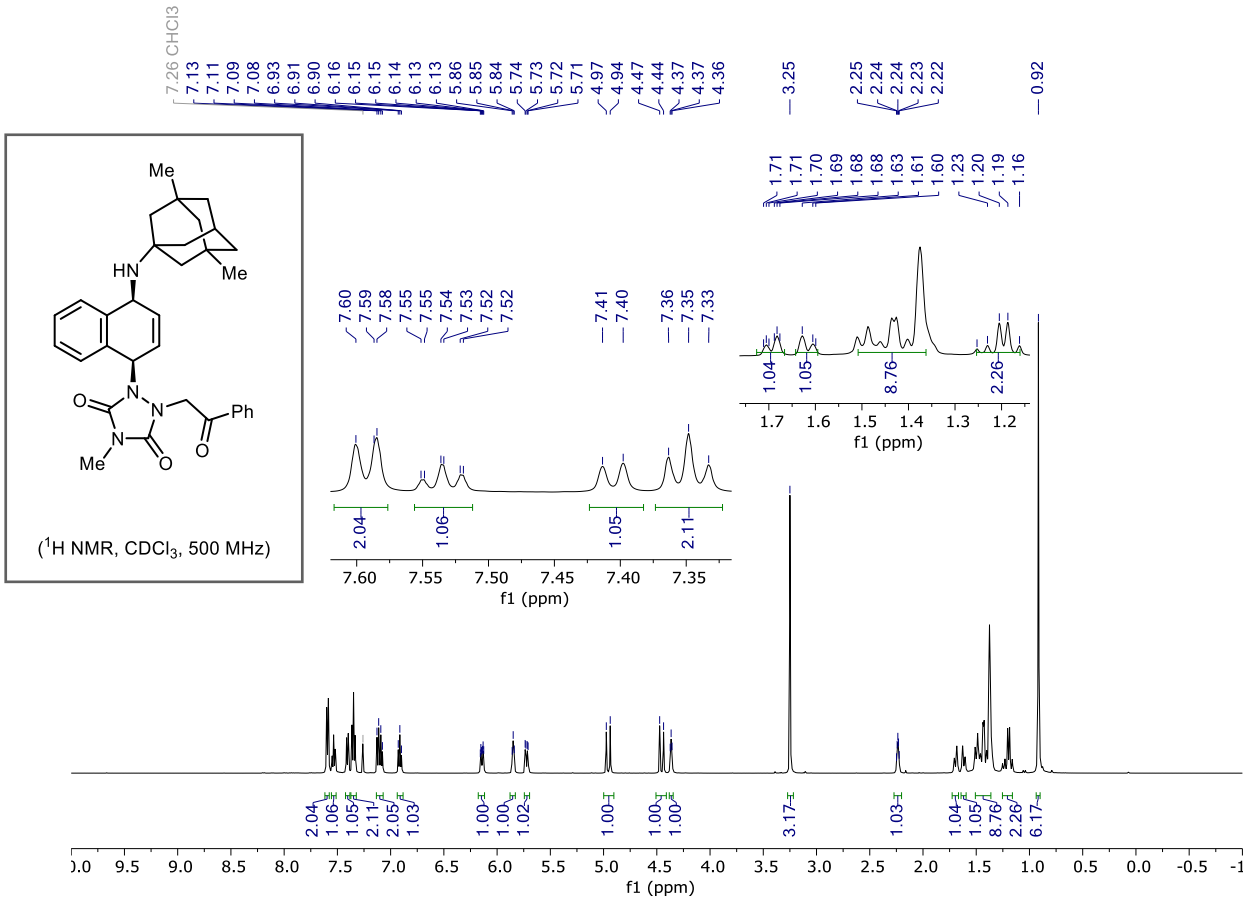
(^{1}H NMR, $CDCl_3$, 500 MHz)

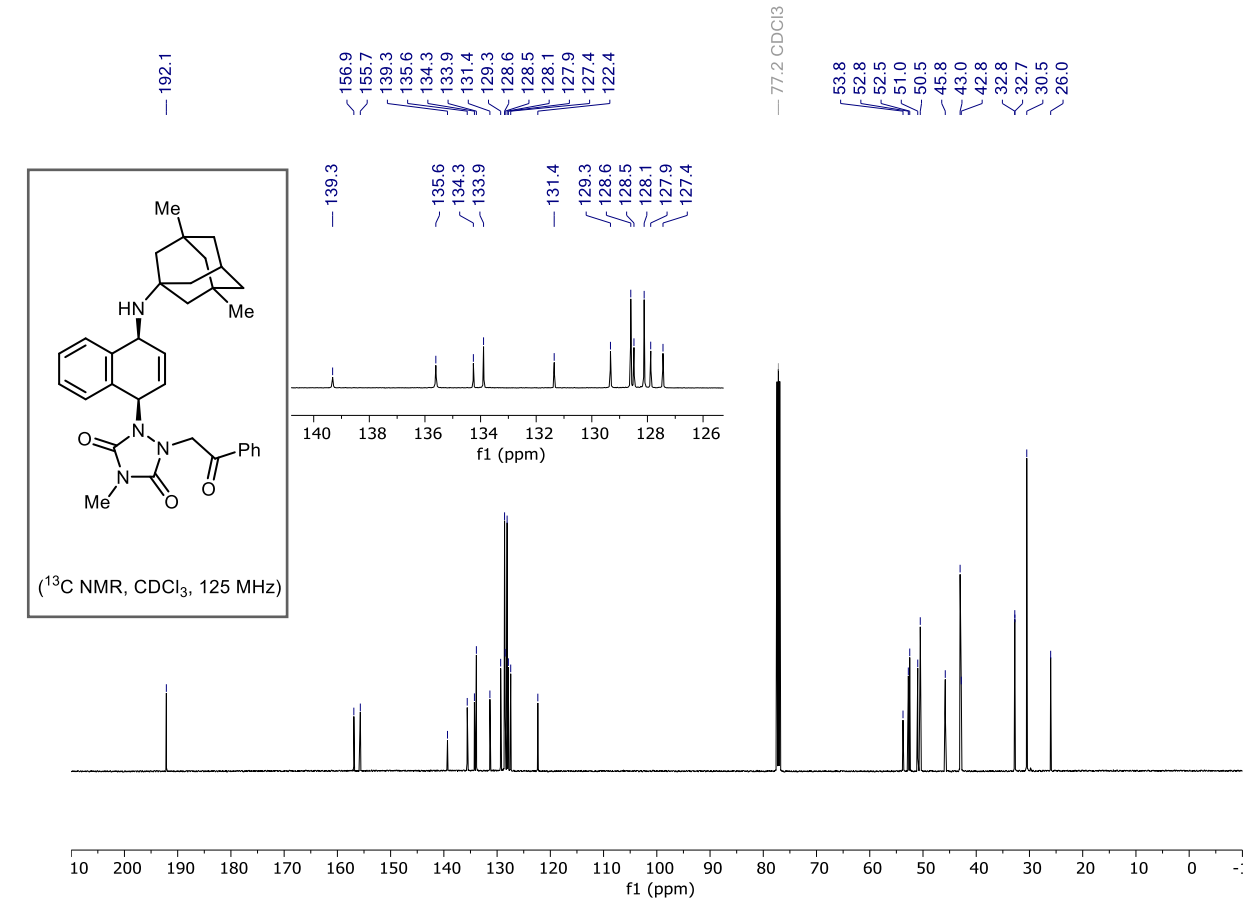


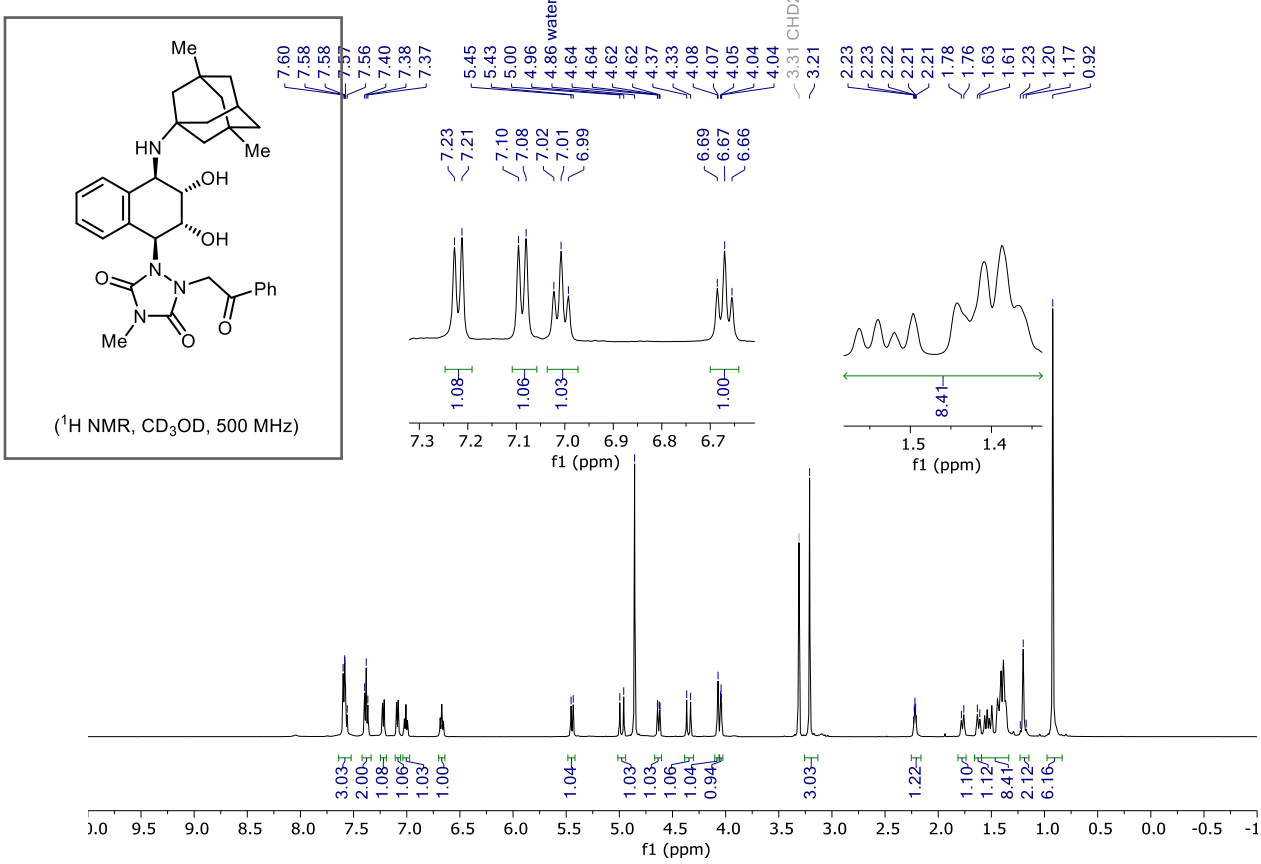
(^{13}C NMR, $CDCl_3$, 125 MHz)

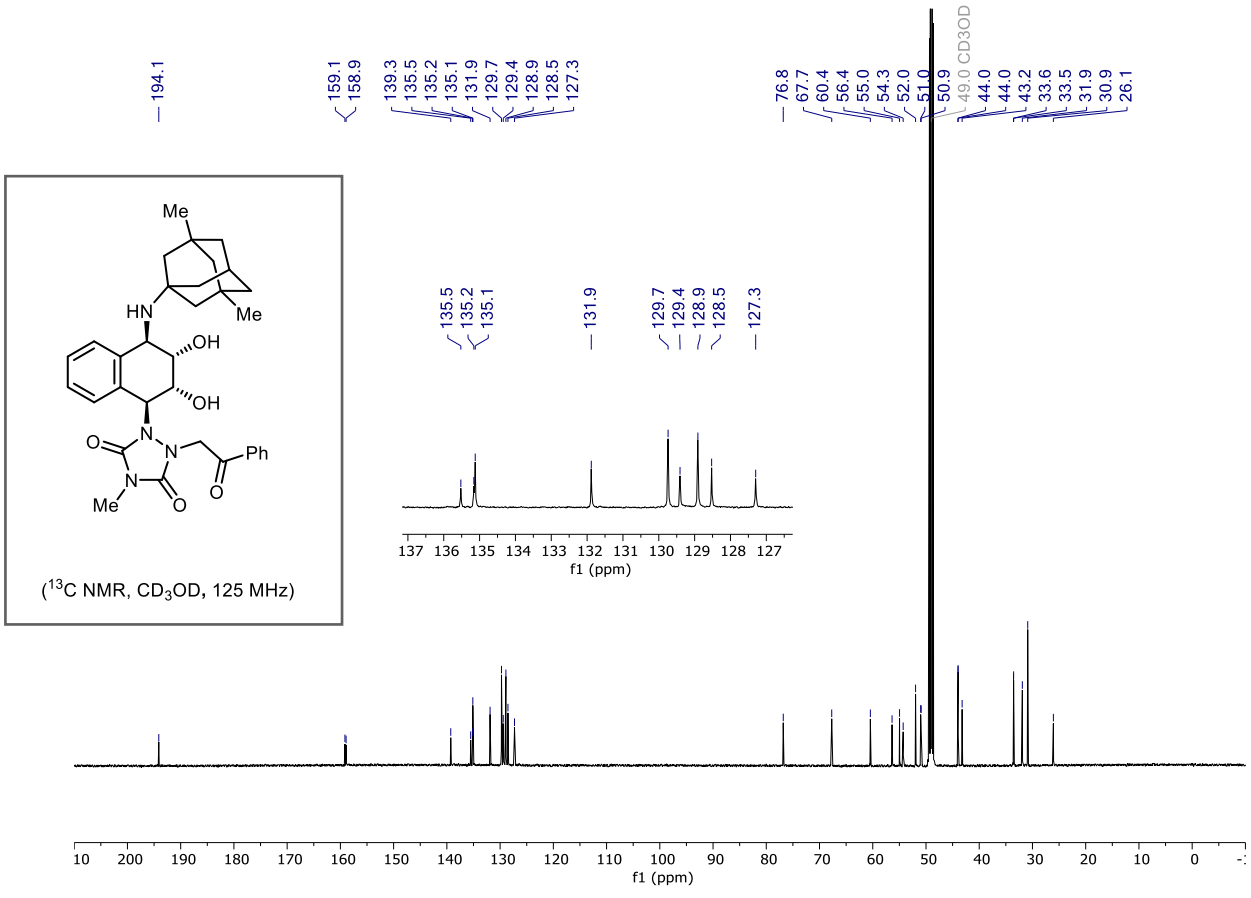

Me
HN
Me
N
NH
O
MeN
O
(^{1}H NMR, $CDCl_3$, 500 MHz)
7.22
7.21
7.20
7.19
7.18
7.17
6.27
5.43
5.41
5.40
4.24
3.02
1.75
1.73
1.68
1.66
1.59
1.57
1.54
1.51
1.49
1.46
1.44
1.32
1.19
1.16
1.13
1.11
0.87
2.43
2.42
2.39
2.38
2.22
2.19
2.06
1.94
1.91
1.88
0.97
2.08
1.06
1.04
f1 (ppm)
4.16
2.02
1.00
0.95
3.13
0.97
2.08
1.06
1.04
1.05
1.09
4.38
4.42
2.34
6.23
f1 (ppm)
Me
HN
Me
N
NH
O
MeN
O
(^{13}C NMR, $CDCl_3$, 125 MHz)
154.9
153.4
137.2
136.4
129.4
129.2
128.8
127.8
77.3
57.6
51.5
50.5
48.8
47.5
42.5
40.2
32.8
30.3
30.2
28.7
25.3
22.5
f1 (ppm)

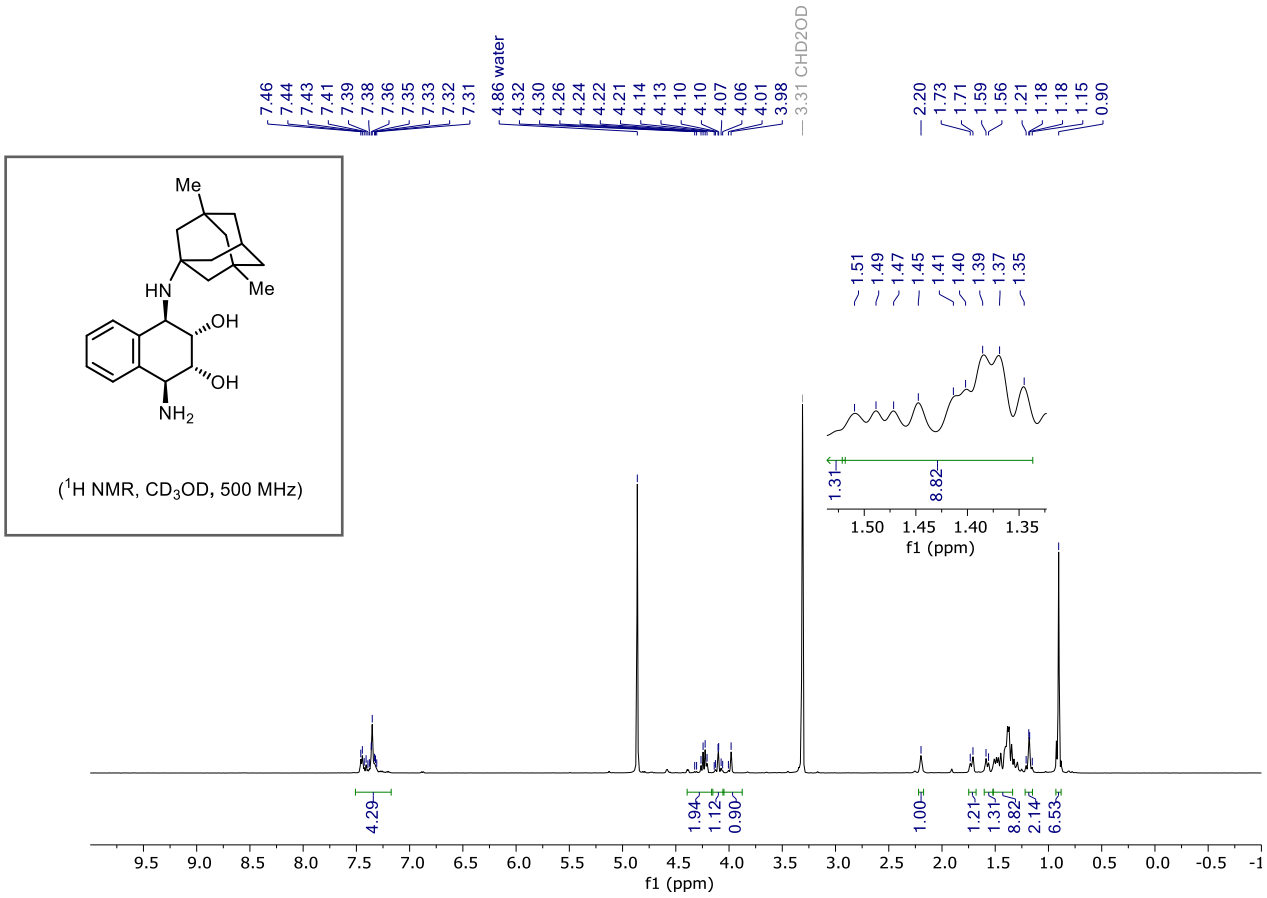

Me
Cl
H2N
Me
O
(1H NMR, CDCl3, 500 MHz)
7.99
7.98
7.62
7.60
7.55
7.55
7.53
7.52
7.34
7.33
7.31
7.26 CHCl3
4.15
4.15
4.14
4.13
1.64
1.61
1.57
1.55
1.44
1.42
1.38
1.33
1.31
1.26
1.18
1.16
1.15
1.12
0.88
3.10
3.09
3.09
3.08
3.07
3.06
3.05
3.04
2.60
2.59
2.59
2.58
2.57
2.56
2.55
2.54
2.27
2.26
2.25
2.24
2.23
2.22
2.22
2.21
2.19
2.19
2.18
2.17
2.17
2.02
2.01
2.00
1.99
1.98
1.97
0.99
1.06
1.07
1.05
1.06
f1 (ppm)
1.00
1.08
1.09
1.06
1.04
0.99
1.06
1.07
1.05
1.06
22.86
6.35
f1 (ppm)
198.7
Me
Cl
H2N
Me
O
(13C NMR, CDCl3, 125 MHz)
148.7
133.9
132.1
128.5
127.3
127.1
77.3 CDCl3
53.4
51.1
50.5
48.5
43.1
42.8
36.0
33.2
32.7
30.5
29.9
f1 (ppm)

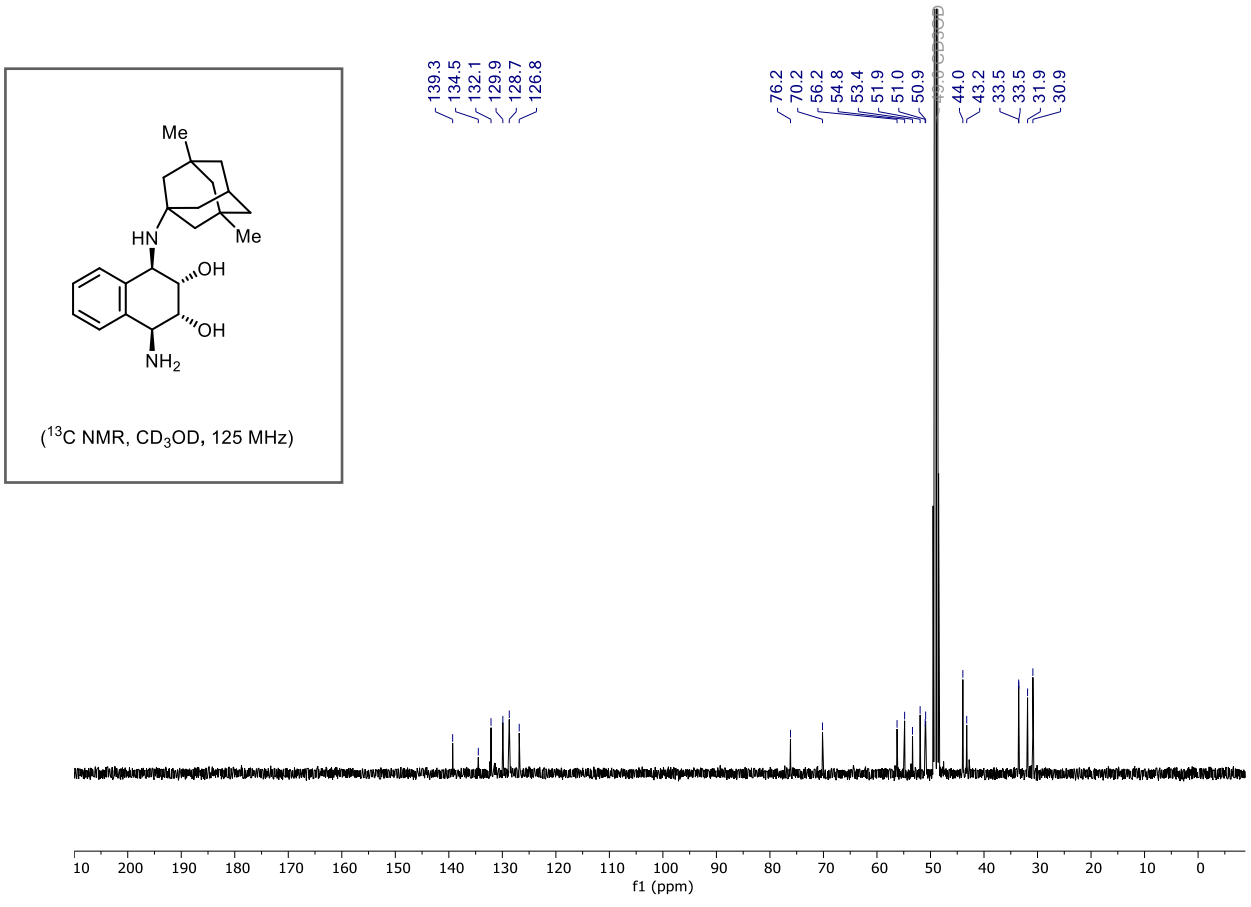

7.26 CHCl3
3.25
2.25
2.24
2.24
2.23
2.22
0.92
1.71
1.71
1.70
1.69
1.68
1.68
1.63
1.61
1.60
1.23
1.20
1.19
1.16
7.60
7.59
7.58
7.55
7.55
7.54
7.53
7.52
7.52
7.41
7.40
7.36
7.35
7.33
Me
HN
Me
O
N
N
Ph
O
N
Me
O
(1H NMR, CDCl3, 500 MHz)
1.04
1.05
8.76
2.26
1.7 1.6 1.5 1.4 1.3 1.2
f1 (ppm)
2.04
1.06
1.05
2.11
7.60 7.55 7.50 7.45 7.40 7.35
f1 (ppm)
2.04
1.06
1.05
2.11
2.05
1.03
1.00
1.00
1.02
1.00
1.00
1.00
3.17
1.03
1.04
1.05
8.76
2.26
6.17
f1 (ppm)


192.1
156.9
155.7
139.3
135.6
134.3
133.9
131.4
129.3
128.6
128.5
128.1
127.9
127.4
122.4
77.2 CDCl3
53.8
52.8
52.5
51.0
50.5
45.8
43.0
42.8
32.8
32.7
30.5
26.0
139.3
135.6
134.3
133.9
131.4
129.3
128.6
128.5
128.1
127.9
127.4
Me
HN
Me
O
N
N
Ph
O
N
Me
O
(13C NMR, CDCl3, 125 MHz)
140 138 136 134 132 130 128 126
f1 (ppm)
f1 (ppm)


Me
HN
Me
OH
OH
O
N
N
Ph
O
Me
N
O
(^{1}H NMR, CD_3OD, 500 MHz)
7.60 7.58 7.58 7.57 7.56 7.40 7.38 7.37
5.45 5.43 5.00 4.96 4.86 water 4.64 4.64 4.62 4.62 4.37 4.33 4.08 4.07 4.05 4.04 4.04 3.31 CHD2OD 3.21
2.23 2.23 2.22 2.21 2.21 1.78 1.76 1.63 1.61 1.23 1.20 1.17 0.92
7.23 7.21 7.10 7.08 7.02 7.01 6.99 6.69 6.67 6.66
1.08 1.06 1.03 1.00
8.41
f1 (ppm)
3.03 2.00 1.08 1.06 1.03 1.00 1.04 1.03 1.03 1.06 1.04 0.94 3.03 1.22 1.10 1.12 8.41 2.12 6.16
f1 (ppm)


Me
HN
Me
OH
OH
O
N
N
Ph
O
Me
N
O
(^{13}C NMR, CD_3OD, 125 MHz)
194.1
159.1 158.9 139.3 135.5 135.2 135.1 131.9 129.7 129.4 128.9 128.5 127.3
76.8 67.7 60.4 56.4 55.0 54.3 52.0 51.0 50.9 49.0 CD3OD 44.0 44.0 43.2 33.6 33.5 31.9 30.9 26.1
135.5 135.2 135.1 131.9 129.7 129.4 128.9 128.5 127.3
f1 (ppm)
f1 (ppm)


Me
HN
Me
OH
OH
NH2
(1H NMR, CD3OD, 500 MHz)
7.46 7.44 7.43 7.41 7.39 7.38 7.36 7.35 7.33 7.32 7.31
4.86 water
4.32 4.30 4.26 4.24 4.22 4.21 4.14 4.13 4.10 4.10 4.07 4.06 4.01 3.98
3.31 CHD2OD
2.20 1.73 1.71 1.59 1.56 1.21 1.18 1.18 1.15 0.90
1.51 1.49 1.47 1.45 1.41 1.40 1.39 1.37 1.35
1.31
8.82
1.50 1.45 1.40 1.35
f1 (ppm)
4.29
1.94
1.12
0.90
1.00
1.21
1.31
8.82
2.14
6.53
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 -1
f1 (ppm)


Me
HN
Me
OH
OH
NH2
(13C NMR, CD3OD, 125 MHz)
139.3
134.5
132.1
129.9
128.7
126.8
76.2
70.2
56.2
54.8
53.4
51.9
51.0
50.9
49.0 CD3OD
44.0
43.2
33.5
33.5
31.9
30.9
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

SUPPLEMENTARY INFORMATION: CHAPTER 2

TABLE OF CONTENTS

1. General Experimental

Unless otherwise noted, all reactions were carried out under inert atmosphere. N-Methyl-1,2,4-triazoline 3,5-dione (MTAD) was prepared according to the literature procedure, sublimed, and stored in a −40 °C freezer.[1] $Mn(ClO_4)_2 \cdot 6H_2O$ and picolinic acid were purchased from Acros Organics. Peracetic Acid (32wt% in dilute acetic acid) was purchased from Sigma Aldrich. Acetonitrile and propionitrile were stored over 4Å molecular sieves. Nickel oxide,[2] peracetic acid (8-10% in acetic acid),[3] hydroxycarbonimidic dibromide,[4] and 2-methylquinolin-4-yl pivalate,[5] were synthesized according to literature procedures. All other chemicals were purchased from commercial vendors and used without further purification.

Analytical thin-layer chromatography was performed on Merck silica gel 60 F254 glass plates. Visualization was accomplished with UV light and/or potassium permanganate ($KMnO_4$). Retention factor (R_f) values reported were measured using a 5 × 2 cm TLC plate in a developing chamber containing the solvent system described. Flash column chromatography was performed using Silicycle SiliaFlash® P60 (SiO_2, 40-63 μm particle size, 230-400 mesh).

^1H and ^{13}C NMR spectra were recorded on Varian Unity 500 (500 MHz, ^1H; 126 MHz, ^{13}C) MHz or Bruker 500 (500 MHz, 1H; 126 MHz, 13C) spectrometers. Spectra are referenced to residual chloroform (δ = 7.26 ppm, ^1H; 77.16 ppm, ^{13}C) or residual methanol (δ = 3.31 ppm, ^1H; 49.0 ppm, ^{13}C). Chemical shifts are reported in parts per million (ppm). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constants J are reported in Hertz (Hz).

Mass spectrometry (MS) was performed by the University of Illinois Mass Spectrometry Laboratory. Electron Impact (EI^+) spectra were performed at 70 eV using methane as the carrier gas, with time-of-flight (TOF) mass analyzer. Chemical Ionization (CI^+) spectra were performed with methane reagent gas, with either a double focusing sector field (DFSF) or time-of-flight (TOF) mass analyzer. Electrospray Ionization (ESI^+) spectra were performed using a time-of-flight (TOF) mass analyzer. Data are reported in the form of m/z (intensity relative to the base peak = 100).

Infrared spectra were measured neat on a Perkin-Elmer spectrum BX FT-IR spectrometer. Peaks are reported in cm^{-1} with indicated relative intensities: s (strong, 0–33% T), m (medium, 34–66% T), w (weak, 67–100% T), and br (broad).

Visible-light spectrum of LED was recorder using Avantes Sensline Avaspec-ULS TEC Spectrometer.

Melting points were measured on a Buchi B-540 melting point apparatus and are uncorrected.

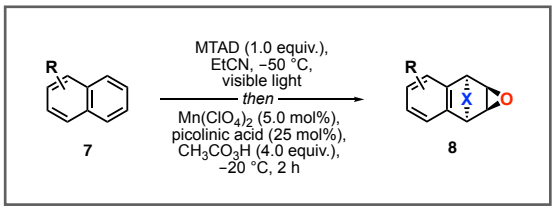
2. Experimental Set-up

The general experimental set-up was identical to that used in Chapter 1.

3. Experimental Procedures

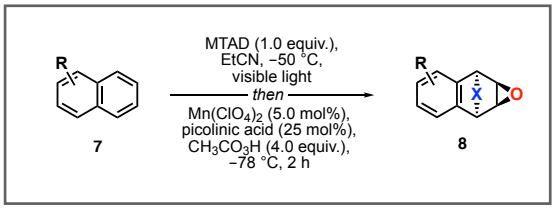
3-1. General procedures for dearomative epoxidation with polycyclic arenes

General Procedure A (at −20 °C)

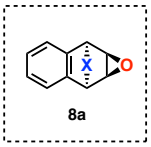


A solution of N-methyl-1,2,4-triazoline-3,5-dione (7, MTAD, 113.4 mg, 1.0 mmol, 1.0 equiv.) and arene (1.5 mmol, 1.5 equiv.) in propionitrile (10.0 mL) was irradiated with LED lights at −78 °C under a nitrogen atmosphere (see Section 2-2.). Upon decolorization, which generally proceeds within 3 – 12 hours with the described setup, the reaction vessel was transferred to a −20 °C bath under high stirring (600 rpm). A suspension of $Mn(ClO_4)_2 \cdot 6H_2O$ (18.1 mg, 0.05 mmol, 0.05 equiv., 5 mol%) and picolinic acid (31 mg, 0.25 mmol, 0.25 equiv., 25 mol%) in acetonitrile (4 mL, sonicated for 1 minute), was added to the reaction mixture over the course of 10 seconds, being careful to ensure proper mixing. To this solution was added peracetic acid (32 wt% in dilute acetic acid, 0.84 mL, 4.0 equiv.) over the course of 10 seconds. The reaction was then left to stir for 2 hours at −20 °C. Afterwards, a 10% sodium thiosulfate solution (20 mL) was added and the aqueous phase was separated. The organic phase was extracted with ethyl acetate (3 × 15 mL), then the organic extracts were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The product was immediately isolated by flash chromatography (SiO_2, hexanes: ethyl acetate mixtures).

General Procedure B (at −78 °C)



This procedure was modified from the literature protocol. 6 A solution of N-methyl-1,2,4-triazoline-3,5-dione (7, MTAD, 113.4 mg, 1.0 mmol, 1.0 equiv.) and arene (1.5 mmol, 1.5 equiv.) in propionitrile (10.0 mL) was irradiated with LED lights at −78 °C under a nitrogen atmosphere (see Chapter 1 Section 2.). Upon decolorization, which generally proceeds within 8 – 12 hours with the described setup, the reaction was then transferred to a bath at −78 °C under high stirring (600 rpm). A suspension of $Mn(ClO_4)_2 \cdot 6H_2O$ (72.4 mg, 0.20 mmol, 0.20 equiv.) and picolinic acid (123.1 mg, 1.0 mmol, 1.0 equiv.) in acetonitrile (8 mL, sonicated for 1 minute), was added over the course of 10 seconds, being careful to ensure proper mixing. To this solution was added peracetic acid (32 wt% in dilute acetic acid, 1.3 mL, 6.0 equiv.) over the course of 1 hour in 6 evenly spaced portions and left to stir for another hour at −78 °C. The reaction was warmed to room temperature, upon which a 10% sodium thiosulfate solution (20 mL) was added and the organic phase was separated. The aqueous phase was extracted with ethyl acetate (3 × 15 mL). The organic extracts were combined and filtered through a plug of silica gel, which was washed with CH_2Cl_2 (15 mL). The organic phase was then dried over $MgSO_4$ and concentrated under reduced pressure. The product was immediately isolated by flash chromatography (SiO2, hexanes: ethyl acetate mixtures).



2-methyl-5,10-dihydro-1H-5,10-[2,3]epoxireno[1,2,4]triazolo[1,2-*b*]phthalazine1,3(2H)-dione (8a):

Following General Procedure A (1.0 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 5:1 to 1:1) as a white solid (217 mg, 1.6:1 d.r., 84%).

R_f = 0.3 (SiO_2, hexanes:ethyl acetate = 1:1, UV)

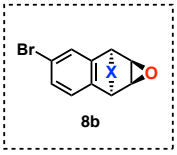
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.41 (dd, J = 5.4, 3.2 Hz, 2H), 7.30 – 7.23 (m, 2H), 5.66 (dd, J = 3.2, 1.7 Hz, 2H), 3.89 (dd, J = 3.2, 1.7 Hz, 2H), 2.82 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 157.1, 129.87, 129.83, 124.4, 57.8, 44.4, 25.5

HRMS: (ESI-TOF, m/z) calcd. for $C_{13}H_{12}N_3O_3$ $[M+H]^+$, 258.0873; found: 258.0887

IR: (ATR, neat, cm^{-1}) = 3014 (w), 1761 (m), 1701 (s), 1467(m), 1447(m), 1395 (m), 1227 (w), 1214 (w), 1170 (w), 1037 (w), 964 (m), 923 (w), 864 (m), 755 (m), 701 (w), 662 (w), 552 (m), 502 (w)

m.p. = 244 – 245 °C



8b

7-bromo-2-methyl-5,10-dihydro-1H-5,10-[2,3]epoxireno[1,2,4]triazolo[1,2-*b*]phthalazine-1,3(2H)-dione (8b):

Following General Procedure A (1.0 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 5:1 to 1:1) as a white solid (183 mg, 5:1 d.r., 54%).

R_f = 0.3 (SiO_2, hexanes:ethyl acetate = 1:1, UV)

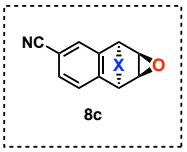
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.59 – 7.52 (m, 1H), 7.44 – 7.38 (m, 1H), 7.14 (d, J = 7.9 Hz, 1H), 5.62 (dd, J = 9.7, 3.4 Hz, 2H), 3.89 (d, J = 3.4 Hz, 2H), 2.85 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 157.0, 156.9, 132.9, 131.6, 128.7, 127.7, 126.1, 123.7, 57.3, 57.2, 44.3, 44.2, 25.7

HRMS: (ESI-TOF, m/z) calculated for $C_{13}H_{11}N_3O_3$ $[M+H]^+$, 335.9978; found: 335.9989 S16

IR: (ATR, neat, cm^{-1}) 1771 (m), 1705 (s), 1453 (m), 1394 (w), 1199 (w), 963 (w), 851 (w), 767 (w), 730 (w), 571 (w), 523 (m)

m.p. = 194 – 196 °C



2-methyl-1,3-dioxo-2,3,5,10-tetrahydro-1H-5,10-[2,3]epoxireno[1,2,4]triazolo[1,2-*b*]phthalazine-7-carbonitrile (8c):

Following General Procedure A (1.0 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 10:1 to 1:1) as a colorless oil (160.2 mg, 7:1 d.r., 57%).

R_f = 0.3 (SiO_2, hexanes:ethyl acetate = 1:1, UV)

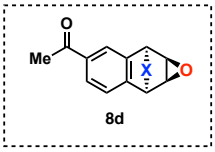
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.73 (dd, J = 7.7, 1.6 Hz, 1H), 7.55 (d, J = 1.6 Hz, 1H), 7.39 (d, J = 7.7 Hz, 1H), 5.71 (m, 2H), 4.02 – 3.89 (m, 2H), 2.84 (s, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 156.78*, 134.4, 134.0, 131.1, 127.9, 125.4, 117.8, 113.9, 57.2, 57.0, 44.2, 44.1, 25.7 (*2 peaks overlapping)

HRMS: (ESI-TOF, m/z) calculated for $C_{14}H_{11}N_4O_3$ $[M+H]^+$, 283.0826; found: 283.0835

IR: (ATR, neat, cm^{-1}) 3055 (w), 2231 (w), 1772 (m), 1701 (s), 1451 (m), 1394 (w), 1197 (w), 1033 (m), 964 (m), 911 (m), 852 (m), 728 (m), 590 (w), 539 (m)

m.p. = 97 – 100 °C



7-acetyl-2-methyl-5,10-dihydro-1H-5,10-[2,3]epoxireno[1,2,4]triazolo[1,2-*b*]phthalazine-1,3(2H)-dione (8d):

Following General Procedure A (1.0 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 5:1 to 1:1) as a white solid (183 mg, 5:1 d.r., 61%).

R_f = 0.2 (SiO2, hexanes:ethyl acetate = 1:1, UV)

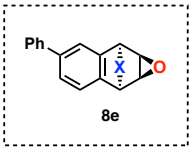
^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.02 (dd, J = 7.8, 1.7 Hz, 1H), 7.84 (d, J = 1.7 Hz, 1H), 7.37 (d, J = 7.8 Hz, 1H), 5.76 – 5.69 (m, 2H), 3.97 – 3.90 (m, 2H), 2.82 (s, 3H), 2.60 (s, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 196.9, 156.88*, 138.4, 134.4, 130.4, 130.0, 124.8, 124.3, 57.7, 57.3, 44.4, 44.3, 26.8, 25.6 (*2 peaks overlapping)

HRMS: (ESI-TOF, m/z) calculated for $C_{15}H_{14}N_3O_4$ $[M+H]^+$, 300.0979; found: 300.0995.

IR: (ATR, neat, cm^{-1}) 3006 (w), 2954 (w), 2252 (w), 1771 (m), 1704 (s), 1454 (m), 1394 (m), 1359 (m), 1270 (w), 1194 (w), 1031 (w), 913 (w), 852 (w), 766 (w), 729 (m), 655 (w), 603 (w), 562 (m), 523 (w).

m.p. = 176.5 °C (decomp.)



2-methyl-7-phenyl-5,10-dihydro-1H-5,10-[2,3]epoxireno[1,2,4]triazolo[1,2-*b*]phthalazine-1,3(2H)-dione (8e):

Following General Procedure A (1.0 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 10:1 to 1:1) as a colorless gel (136 mg, 3:1 d.r., inseperable, 41%).

R_f = 0.3 (SiO_2, hexanes:ethyl acetate = 1:1, UV)

Major diastereomer (excluding aromatic region for ^{1}H NMR):

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.74 – 5.67 (m, 2H), 3.97 – 3.87 (m, 2H), 2.85 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 157.1, 157.0, 142.9, 140.0, 130.4, 129.2, 129.0, 128.4, 128.0, 127.3, 124.8, 123.2, 57.9, 57.6, 44.6, 44.6, 25.6.5

Minor diastereomer (excluding aromatic region for ^{1}H NMR):

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.56 (ddd, J = 9.1, 3.1, 1.1 Hz, 2H), 3.73 (dt, J = 2.9, 1.4 Hz, 2H), 3.10 (s, 3H)

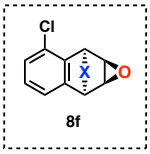
^{13}C NMR: (126 MHz, $CDCl_3$) δ 156.98, 156.97, 142.8, 140.0, 136.6, 134.7, 128.7, 128.2, 128.0, 127.4, 126.2, 124.8, 57.8, 57.7, 54.3, 53.9, 25.7

Complete ^{1}H NMR (including aromatic region):

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.67 (d, J = 1.7 Hz, 0.4H), 7.62 (m, 1.3H), 7.59 – 7.51 (m, 3.4H), 7.50 – 7.34 (m, 5.3H), 7.32 (d, J = 7.7 Hz, 1H), 5.71 (ddt, J = 7.3, 5.0, 2.7 Hz, 2H), 5.56 (ddd, J = 9.1, 3.1, 1.1 Hz, 0.8H), 3.96 – 3.88 (m, 2H), 3.73 (dt, J = 2.9, 1.4 Hz, 0.8H), 3.10 (s, 1H), 2.85 (s, 3H)

HRMS: (ESI-TOF, m/z) calculated for $C_{19}H_{16}N_3O_3$ $[M+H]^+$, 334.1186; found: 334.1191.

IR: (ATR, neat, cm^{-1}) 3497 (w), 1760 (m), 1682 (s, br), 1451 (m), 1387 (m), 1217 (m), 1026 (w), 917 (w), 837 (w), 758 (m), 711 (m)



8f

6-chloro-2-methyl-5,10-dihydro-1H-5,10-[2,3]epoxireno[1,2,4]triazolo[1,2-*b*]phthalazine-1,3(2H)-dione (8f):

Following General Procedure B (1.0 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 5:1 to 1:1) as a white solid (219 mg, >20:1 d.r., 75%).

R_f = 0.3 (SiO_2, hexanes:ethyl acetate = 1:1, UV)

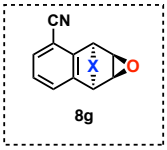
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.42 (dd, J = 8.3, 1.0 Hz, 1H), 7.33 (t, J = 7.8 Hz, 1H), 7.19 – 7.10 (m, 1H), 6.14 (d, J = 4.6 Hz, 1H), 5.64 (d, J = 4.5 Hz, 1H), 3.93 (t, J = 4.5 Hz, 1H), 3.88 (t, J = 4.4 Hz, 1H), 2.84 (s, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 157.0, 156.9, 131.7, 130.7, 130.32, 130.30, 128.20, 122.94, 57.5, 54.6, 44.13, 44.11, 25.7

HRMS: (ESI-TOF, m/z) calcd. for $C_{13}H_{11}N_3O_3Cl$ $[M+H]^+$, 292.0484; found: 292.0489

IR: (ATR, neat, cm^{-1}) = 1771 (m), 1708 (s), 1451 (m), 1394 (w), 1269 (w), 1234 (w), 1200 (w), 1171 (w), 1033 (w), 963 (m), 852 (m), 769 (w), 734 (w), 720 (w), 705 (w), 580 (m), 456 (w)

m.p. = 195 – 196 °C



2-methyl-1,3-dioxo-2,3,5,10-tetrahydro-1H-5,10-[2,3]epoxireno[1,2,4]triazolo[1,2-*b*]phthalazine-6-carbonitrile (8g):

Following General Procedure B (1.0 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 5:1 to 1:1) as a white solid (212 mg, 6:1 d.r., 75%).

R_f = 0.3 (SiO_2, hexanes:ethyl acetate = 1:1, UV)

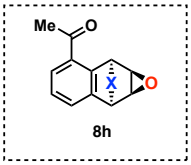
^1H NMR: (500 MHz, $CDCl_3$) δ 7.71 (dd, J = 7.7, 1.4 Hz, 1H), 7.58 – 7.44 (m, 2H), 6.05 (d, J = 4.5 Hz, 1H), 5.72 (d, J = 4.5 Hz, 1H), 3.97 (dt, J = 23.8, 4.4 Hz, 2H), 2.84 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 157.0, 156.7, 133.2, 133.0, 131.2, 130.3, 128.8, 115.6, 109.2, 57.2, 55.6, 44.0, 43.9, 25.7

HRMS: (ESI-TOF, m/z) calculated for $C_{14}H_{11}N_4O_3$ $[M+H]^+$, 283.0826; found: 283.0833

IR: (ATR, neat, cm^{-1}) = 3021 (w), 2231 (w), 1713 (s), 1448 (s), 1392 (s), 1272 (w), 1243 (w), 1196 (m), 1178 (m), 1113 (w), 1032 (w), 965 (m), 849 (m), 764 (s), 702 (m), 598 (m), 533 (m)

m.p. = 212 °C (decomp.)



6-acetyl-2-methyl-5,10-dihydro-1H-5,10-[2,3]epoxireno[1,2,4]triazolo[1,2-*b*]phthalazine-1,3(2H)-dione (8h):

Following General Procedure B (1.0 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 5:1 to 1:1) as a white solid (189 mg, 5.5:1 d.r., 63%).

R_f = 0.2 (SiO_2, hexanes:ethyl acetate = 1:1, UV)

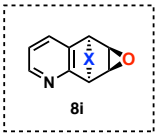
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.86 (dd, J = 8.0, 1.1 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.40 (dd, J = 7.6, 1.1 Hz, 1H), 6.91 (d, J = 4.4 Hz, 1H), 5.67 (d, J = 4.4 Hz, 1H), 3.96 (t, J = 4.4 Hz, 1H), 3.90 (t, J = 4.4 Hz, 1H), 2.82 (d, J = 0.8 Hz, 3H), 2.63 (d, J = 0.8 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 199.4, 157.1, 156.5, 133.4, 131.5, 130.39, 130.35, 129.3, 128.5, 57.5, 53.6, 44.0, 43.9, 28.7, 25.6

HRMS: (ESI-TOF, m/z) calculated for $C_{15}H_{14}N_3O_4$ $[M+H]^+$, 300.0979; found: 300.0974

IR: (ATR, neat, cm^{-1}) 3051 (w), 2954 (w), 2253 (w), 1771 (m), 1702 (s), 1587 (w), 1447 (m), 1394 (m), 1358 (w), 1261 (m) 1201 (m), 1131 (w), 1034 (w), 1018 (w), 962 (m), 912 (m), 853 (m), 709 (m), 727 (s), 647 (w), 600 (w), 509 (w)

m.p. = 159 – 161 °C



8i

8-methyl-5,11-dihydro-7H-5,11-[2,3]epoxirenopyrido[2,3-*d*][1,2,4]triazolo[1,2-*a*]pyridazine-7,9(8H)-dione (8l):

Following General Procedure A (1.0 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 3:1 to 1:2) as an off-white solid (172 mg, 5:1 d.r., 67%).

R_f = 0.2 (SiO_2, hexanes:ethyl acetate = 1:2, UV)

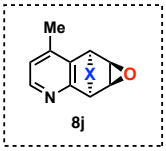
^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.58 (d, J = 5.1 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.35 (dd, J = 7.6, 5.1 Hz, 1H), 5.84 (dd, J = 4.6, 1.1 Hz, 1H), 5.73 (dd, J = 4.6, 1.1 Hz, 1H), 4.07 – 3.86 (m, 2H), 2.85 (s, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 156.9, 156.4, 150.6, 150.2, 132.2, 125.1, 124.8, 59.2, 56.7, 44.4, 44.0, 25.7.

HRMS: (ESI-TOF, m/z) calculated for $C_{12}H_{11}N_4O_3$ $[M+H]^+$, 259.0826 found: 259.0826.

IR: (ATR, neat, cm^{-1}): 1764 (m), 1694 (s), 1577 (w), 1448 (m), 1395 (m), 1209 (w), 1118 (w), 1035 (w), 964 (w), 809 (w), 757 (m), 556 (m).

m.p. = 189 – 191 °C



4,8-dimethyl-5,11-dihydro-7H-5,11-[2,3]epoxirenopyrido[2,3-d][1,2,4]triazolo[1,2-*a*]pyridazine-7,9(8H)-dione (8j):

Following General Procedure A (1.0 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 3:1 to 1:2) as an off-white solid (197 mg, >20:1 d.r., 72%).

R_f =0.3 (SiO_2, hexanes:ethyl acetate = 1:2, UV)

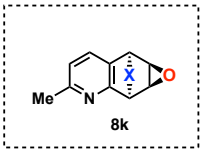
^1H NMR: (500 MHz, $CDCl_3$) δ 8.40 (d, J = 5.3 Hz, 1H), 7.16 (d, J = 5.3 Hz, 1H), 5.94 (d, J = 4.3 Hz, 1H), 5.79 (d, J = 4.3 Hz, 1H), 3.98 – 3.91 (m, 2H), 2.85 (s, 3H), 2.43 (s, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 157.4, 156.6, 150.0, 149.7, 142.6, 126.3, 124.4, 59.6, 53.4, 44.4, 43.9, 25.7, 17.6.

HRMS: (ESI-TOF, m/z) calculated for $C_{13}H_{13}N_4O_3$ $[M+H]^+$, 273.0982 found: 273.0986.

IR: (ATR, neat, cm^{-1}) 1764 (m), 1698 (s), 1593 (m), 1447 (m), 1400 (m), 1204 (w), 1032 (w), 963 (m), 921 (w), 870 (w), 851 (m), 766 m), 754 (m), 710 (w), 634 (w), 591 (w), 517 (w), 490 (w).

m.p. = 220 – 223 °C



2,8-dimethyl-5,11-dihydro-7H-5,11-[2,3]epoxirenopyrido[2,3-*d*][1,2,4]triazolo[1,2-*a*]pyridazine-7,9(8H)-dione (8k):

Following General Procedure A (1.0 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 3:1 to 1:2) as an off-white solid (171 mg, 8:1 d.r., 63%).

R_f = 0.4 (SiO_2, hexanes:ethyl acetate = 1:2, UV)

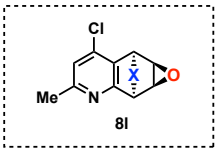
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.44 (d, J = 7.7 Hz, 1H), 7.16 (d, J = 7.7 Hz, 1H), 5.75 (d, J = 4.5 Hz, 1H), 5.68 (d, J = 4.5 Hz, 1H), 3.92 (t, J = 4.4 Hz, 1H), 3.88 (t, J = 4.4 Hz, 1H), 2.83 (s, 3H), 2.53 (s, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 159.9, 156.8, 156.3, 149.5, 132.3, 124.1, 122.0, 59.2, 56.4, 44.4, 43.9, 25.6, 24.5.

HRMS: (ESI-TOF, m/z) calculated for $C_{13}H_{13}N_4O_3$ $[M+H]^+$, 273.0982 found: 273.0986.

IR: (ATR, neat, cm^{-1}) 1772 (m), 1702 (s), 1599 (m), 1448 (w), 1394 (w), 1273 (w), 1196 (w), 1032 (w), 986 (w), 960 (m), 911 (m), 870 (w), 766 (w), 725 (m), 546 (m), 526 (w).

m.p. = 214 – 216 °C



4-chloro-2,8-dimethyl-5,11-dihydro-7H-5,11-[2,3]epoxirenopyrido[2,3-*d*][1,2,4]triazolo[1,2-*a*]pyridazine-7,9(8H)-dione (8l):

Following General Procedure A (1.0 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 3:1 to 1:2) as an off-white solid (180 mg, >20:1 d.r., 59%).

R_f = 0.5 (SiO_2, hexanes:ethyl acetate = 1:2, UV)

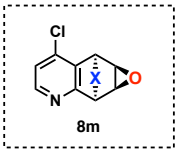
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.22 (s, 1H), 6.11 – 6.07 (m, 1H), 5.78 – 5.74 (m, 1H), 3.97 – 3.92 (m, 2H), 2.89 (s, 3H), 2.54 (s, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 161.1, 156.6, 156.2, 150.7, 140.2, 124.5, 120.9, 59.0, 53.5, 44.3, 43.8, 25.8, 24.4.

HRMS: (ESI-TOF, m/z) calculated for $C_{13}H_{12}N_4O_3Cl$ $[M+H]^+$, 307.0592 found: 307.0601.

IR: (ATR, neat, cm^{-1}) 1774 (m), 1710 (s), 1591 (m), 1566 (m), 1452 (m), 1395 (w), 1269 (w), 1231 (w), 1193 (m), 1034 (w), 962 (w), 898 (w), 854 (w), 768 (w), 753 (w), 706 (w), 646 (w), 602 (w).

m.p. = 269 – 270 °C (decomp.)



4-chloro-8-methyl-5,11-dihydro-7H-5,11-[2,3]epoxirenopyrido[2,3-*d*][1,2,4]triazolo[1,2-*a*]pyridazine-7,9(8H)-dione (**8m**):

Following General Procedure A (1.0 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 3:1 to 1:2) as an off-white solid (246 mg, >20:1 d.r., 84%)

R_f =0.5 (SiO_2, hexanes:ethyl acetate = 1:2, UV)

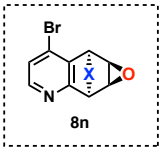
^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.46 (d, J = 5.5 Hz, 1H), 7.38 (d, J = 5.5 Hz, 1H), 6.15 (dq, J = 3.0, 1.1 Hz, 1H), 5.93 – 5.75 (m, 1H), 4.04 – 3.90 (m, 2H), 2.89 (s, 3H) S21

^{13}C NMR: (126 MHz, $CDCl_3$) δ 156.6, 156.3, 151.5, 151.0, 140.3, 125.4, 124.0, 59.0, 53.6, 44.2, 43.8, 25.8.

HRMS: (ESI-TOF, m/z) calculated for $C_{12}H_{10}N_4O_3Cl$ $[M+H]^+$, 293.0436 found: 293.0448.

IR: (ATR, neat, cm^{-1}) 1768 (m), 1705 (s), 1578 (w), 1446 (m), 1403 (m), 1227 (w), 1201 (m), 1039 (w), 978 (w), 964 (m), 921 (w), 852 (m), 766 (m), 722 (m), 591 (w), 591 (m).

m.p. = 218 – 221 °C (decomp.)



4-bromo-8-methyl-5,11-dihydro-7H-5,11-[2,3]epoxirenopyrido[2,3-*d*][1,2,4]triazolo[1,2-*a*]pyridazine-7,9(8H)-dione (**8n**):

Following General Procedure A (1.0 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 3:1 to 1:2) as an off-white solid (285 mg, >20:1 d.r., 85%).

R_f =0.5 (SiO_2, hexanes:ethyl acetate = 1:2, UV)

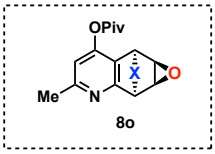
^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.36 (d, J = 5.5 Hz, 1H), 7.54 (d, J = 5.5 Hz, 1H), 6.14 – 6.09 (m, 1H), 5.84 – 5.79 (m, 1H), 4.01 – 3.95 (m, 2H), 2.89 (s, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 156.6, 156.3, 151.1, 150.9, 130.2, 128.5, 126.3, 59.1, 55.8, 44.2, 43.8, 25.8.

HRMS: (ESI-TOF, m/z) calculated for $C_{12}H_{10}N_4O_3Br$ $[M+H]^+$, 336.9931 found: 336.9948.

IR: (ATR, neat, cm^{-1}) 1771(m), 1711(s), 1556 (m), 1456 (m), 1396 (m), 1229 (m), 1200 (m), 1035 (w), 963(m), 851(w), 765(m), 706 (w), 586 (w), 522(w).

m.p. = 253 – 254 °C with decomposition



8o

2,8-dimethyl-7,9-dioxo-5,8,9,11-tetrahydro-7H-5,11-[2,3]epoxirenopyrido[2,3-*d*][1,2,4]triazolo[1,2-*a*]pyridazin-4-yl pivalate (8o):

Following general procedure A (1.0 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 3:1 to 1:2) as an off-white solid (185 mg, 0.568 mmol, >20:1 d.r., 50%).

R_f =0.5 (SiO_2, hexanes:ethyl acetate = 1:2, UV)

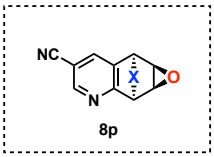
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.06 (s, 1H), 5.80 – 5.73 (m, 2H), 3.97 – 3.90 (m, 2H), 2.87 (s, 3H), 2.56 (s, 3H), 1.42 (s, 9H).

^{13}C NMR: (126 MHz, CDCl3) δ 175.6, 161.6, 156.8, 156.4, 153.0, 151.5, 117.4, 114.5, 59.0, 51.9, 44.4, 43.9, 39.8, 27.2, 25.8, 24.7.

IR: (ATR, neat, cm^{-1}) 2977 (w), 1764 (m), 1714 (s), 1587 (m), 1454 (m), 1396 (w), 1344 (w), 1095 (m), 961 (w), 731 (w), 533 (w), 498 (w).

HRMS: (ESI-TOF, m/z) calculated for C18H21N4O5 $[M+H]^+$, 373.1507 found: 373.1506.

m.p. = 237 – 238 °C



8p

8-methyl-7,9-dioxo-5,8,9,11-tetrahydro-7H-5,11-[2,3]epoxirenopyrido[2,3-*d*][1,2,4]triazolo[1,2-*a*]pyridazine-3-carbonitrile (8p):

Following General Procedure A (1.0 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 3:1 to 1:2) as an off-white solid (253 mg, 12:1 d.r., 89%).

R_f =0.5 (SiO_2, hexanes:ethyl acetate = 1:2, UV)

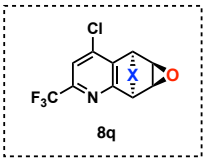
^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.86 (d, J = 1.9 Hz, 1H), 7.86 (d, J = 1.9 Hz, 1H), 5.89 (d, J = 4.6 Hz, 1H), 5.79 (d, J = 4.6 Hz, 1H), 4.03 (m, 2H), 2.88 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 156.5, 156.0, 153.7, 153.6, 135.0, 125.4, 115.8, 111.2, 58.8, 55.9, 44.3, 43.8, 25.9.

HRMS: (ESI-TOF, m/z) calculated for $C_{13}H_{10}N_5O_3$ $[M+H]^+$, 284.0778 found: 284.0784.

IR: (ATR, neat, cm^{-1}) 2236 (w), 1776(m), 1710 (s), 1456 (m), 1394 (m), 1210(w), 1035 (w), 967 (w), 914 (w), 848 (w), 766 (w), 728 (m), 646 (w), 593 (w), 544 (w), 525 (w).

m.p. = 239 – 241 °C (decomp.)



8q

4-chloro-8-methyl-2-(trifluoromethyl)-5,11-dihydro-7H-5,11-[2,3]epoxirenopyrido[2,3-*d*][1,2,4]triazolo[1,2-*a*]pyridazine-7,9(8H)-dione (8q):

1.05 equivalents (243 mg, 1.05 mmol) of arene was used. With a slight modification to General Procedure A (1.0 mmol), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 3:1 to 1:2) as an off-white solid (277 mg, >20:1 d.r., 72%).

R_f =0.7 (SiO_2, hexanes:ethyl acetate = 1:2, UV)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.77 (s, 1H), 6.19 (dd, J = 3.4, 1.7 Hz, 1H), 5.91 (dd, J = 3.4, 1.7 Hz, 1H), 4.03 (m, 2H), 2.91 (s, 3H)

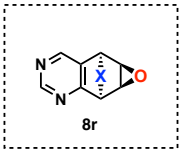
^{13}C NMR: (126 MHz, $CDCl_3$) δ 156.2, 155.7, 152.0, 149.6 (q, J = 36.0), 141.7, 127.0, 122.7 (q, J = 2.9 Hz), 120.6 (q, J = 275.0 Hz), 58.4, 53.1, 44.1, 43.7, 25.9.

^{19}F NMR: (471 MHz, $CDCl_3$) δ -67.65.

HRMS: (ESI-TOF, m/z) calculated for $C_{13}H_9N_4O_3F_3Cl$ $[M+H]^+$, 361.0310 found: 361.0310.

IR: (ATR, neat, cm^{-1}) 1779 (m), 1707 (s), 1578 (w), 1452 (m), 1394 (w), 1347 (m), 1192 (m), 1108 (w), 964 (w), 866 (w), 845 (w), 767 (w), 754 (w), 735 (m), 723 (m).

m.p. = 223 – 225 °C



8r

8-methyl-5,11-dihydro-7H-5,11-[2,3]epoxirenopyrimido[4,5-d][1,2,4]triazolo[1,2-*a*]pyridazine-7,9(8H)-dione (8r):

Following General Procedure A (1.0 mmol scale), the title compound was isolated by flash chromatography (SiO2, hexanes:ethyl acetate = 3:1 to 1:2) as an off-white solid (186 mg, >20:1 d.r., 72%).

R_f=0.3 (SiO_2, hexanes:ethyl acetate = 1:2, UV)

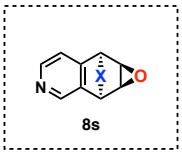
^{1}H NMR: (500 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.64 (s, 1H), 5.80 (m, 2H), 4.06 – 3.97 (m, 2H), 2.88 (s, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 160.2, 158.1, 156.6, 156.0, 151.5, 122.9, 58.2, 54.4, 44.4, 43.5, 25.9.

HRMS: (ESI-TOF, m/z) calculated for $C_{11}H_{10}N_5O_3$ $[M+H]^+$, 260.0778 found: 260.0784.

IR: (ATR, neat, cm^{-1}) 1774 (m), 1709 (s), 1594 (w), 1568 (m), 1458 (w), 1395 (w), 1218 (w), 965 (w), 848 (w), 766 (w), 677 (w), 565 (w).

m.p. = 217 – 218 °C



8s

2-methyl-5,10-dihydro-1H-5,10-[2,3]epoxirenopyrido[3,4-d][1,2,4]triazolo[1,2-*a*]pyridazine-1,3(2H)-dione (8s):

Following General Procedure A (1.0 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 3:1 to 1:2) as an off-white solid (187mg, 5:1 d.r., 72%).

R_f = 0.2 (SiO_2, hexanes:ethyl acetate = 1:2, UV)

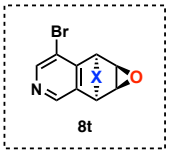
^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.52 (s, 1H), 7.21 (d, J = 4.7 Hz, 1H), 5.74 (d, J = 4.4 Hz, 1H), 5.67 (d, J = 4.4 Hz, 1H), 3.93 (m, 2H), 2.82 (s, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 156.8, 156.7, 151.8, 144.7, 137.9, 125.4, 119.0 56.5, 55.4, 44.3, 43.8, 25.7.

HRMS: (ESI-TOF, m/z) calculated for $C_{12}H_{11}N_4O_3$ $[M+H]^+$, 259.0826 found: 259.0828.

IR: (ATR, neat, cm^{-1}): 3059 (w), 1709 (s), 1609 (w), 1456 (m), 1395 (m), 1269 (w), 1207 (w), 1097 (w), 692 (w), 766 (w), 733 (w), 560 (w)

m.p. = 226 °C (decomp.)



8t

9-bromo-2-methyl-5,10-dihydro-1H-5,10-[2,3]epoxirenopyrido[3,4-*d*][1,2,4]triazolo[1,2-*a*]pyridazine-1,3(2H)-dione (8t):

Following General Procedure A (1.0 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 3:1 to 1:2) as an off-white solid (223 mg, >20:1 d.r., 66%).

R_f = 0.4 (SiO_2, hexanes:ethyl acetate = 1:2, UV)

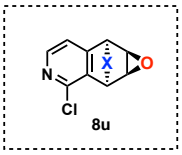
^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.42 (s, 1H), 6.06 (d, J = 4.5 Hz, 1H), 5.73 (d, J = 4.5 Hz, 1H), 3.97 (m, 2H), 2.87 (s, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 156.7, 156.5, 153.2, 143.2, 138.2, 126.8, 117.3, 55.8, 55.2, 44.1, 43.6, 25.8.

HRMS: (ESI-TOF, m/z) calculated for $C_{12}H_{10}N_4O_3Br$ $[M+H]^+$, 336.9931 found: 336.9940.

IR: (ATR, neat, cm^{-1}) 1775 (m), 1706 (s), 1595 (w), 1553 (w), 1449 (m), 1393 (w), 1192 (m), 1159 (w), 1101 (w), 1034 (w), 963 (w), 909 (w), 847 (w), 766 (w), 727 (m), 576 (m), 512(w).

m.p. = 243 °C (decomp.)



8u

6-chloro-2-methyl-5,10-dihydro-1H-5,10-[2,3]epoxirenopyrido[3,4-*d*][1,2,4]triazolo[1,2-*a*]pyridazine-1,3(2H)-dione (**8u**):

Following General Procedure A (1.0 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 3:1 to 1:2) as an off-white solid (166 mg, >20:1 d.r., 57%).

R_f =0.4 (SiO_2, hexanes:ethyl acetate = 1:2, UV)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.45 (d, J = 5.6 Hz, 1H), 7.38 (d, J = 5.6 Hz, 1H), 6.24 – 5.99 (m, 1H), 5.85 – 5.77 (m, 1H), 4.07 – 3.89 (m, 2H), 2.89 (s, 3H)

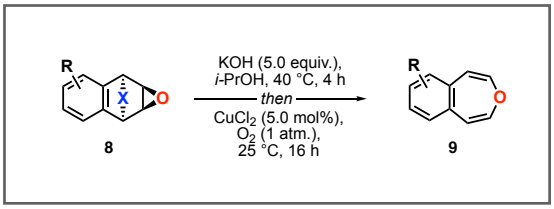
^{13}C NMR: (126 MHz, $CDCl_3$) δ 156.7, 156.6, 151.3, 146.9, 140.8, 124.5, 118.3, 56.4, 54.7, 44.0, 43.5, 25.9.

HRMS: (ESI-TOF, m/z) calculated for $C_{12}H_{10}N_4O_3Cl$ $[M+H]^+$, 293.0436 found: 293.0437.

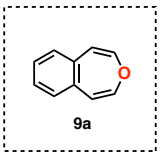
IR: (ATR, neat, cm^{-1}): 1773 (w), 1710 (s) , 1601 (w), 1560 (w), 1452 (m), 1412 (w), 1395 (w), 1189 (w), 964 (w), 855 (w), 767 (w), 733 (w), 585 (w), 519 (w).

m.p. = 238 – 239 °C

3-2. General procedure for the cycloreversion to benzoxepines



To a vial containing finely ground KOH (156 mg, 5.0 equiv., 90 wt%), and substrate (0.500 mmol, 1.0 equiv.) under nitrogen was added *i*-PrOH (5.0 mL, 0.1 M) and degassed with nitrogen/sonication for 15 min. The reaction was heated to 40 °C with vigorous stirring (700 rpm) and progress was monitored by TLC in 30 min intervals. Upon completion, the reaction was cooled in an ice bath and H_2O (5.0 mL) were added. AcOH is then carefully added dropwise until pH = 5, upon which gas evolution is observed. $CuCl_2$ dihydrate (4.3 mg, 25 μmol, 0.05 mol%). was then added as a solid, followed by sparging with oxygen, and the reaction was stirred for 10-16 h under an atmosphere of oxygen (balloon). Work-up for hydrocarbon arene-derived benzoxepines: Upon completion, the reaction was partitioned between diethyl ether (10 mL) and saturated brine (10 mL) and the organic layer was extracted with ether (3 × 10 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum and isolated by flash chromatography (SiO_2, hexanes:ethyl acetate mixtures). Compounds are volatile; thus, execute caution when putting the compound under vacuum. Work-up for heteroarene-derived benzoxepines: Upon completion, the reaction was poured into saturated aqueous $_{NaHCO3}$ (10 mL). The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organics were then washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum and isolated by flash chromatography (SiO_2, hexanes:ethyl acetate mixtures). Compounds are volatile; thus, caution is needed upon drying the compound under reduced pressure.



3-Benzoxepin (benzo[d]oxepine, 9a):

Following the general procedure (0.5 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 1 to 10:1) as a bright yellow solid (59 mg, 82%).

R_f = 0.4 (SiO_2, hexanes, UV)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.90 (dd, J = 5.6, 3.3 Hz, 2H), 6.63 (dd, J = 5.5, 3.4 Hz, 2H), 5.67 (d, J = 7.4 Hz, 2H), 5.06 (d, J = 7.4 Hz, 2H).

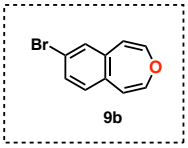
^{13}C NMR: (126 MHz, $CDCl_3$) δ 146.1, 136.0, 129.1, 127.8, 113.3.

HRMS: (EI-TOF, m/z) calcd. For $C_{10}H_8O$ $[M]^+$, 144.05697; found: 144.05719. S26

IR: (ATR, neat, cm^{-1}) = 3050 (w), 2926 (w), 1658 (m), 1635 (m), 1496 (m), 1438 (m), 1316 (s), 1254 (m), 1211 (m), 1118 (m), 1049 (s), 921 (m), 847 (m), 770 (s).

m.p. = 81 – 82 °C

The analytical data were in accordance with previously reported values.



9b

7-bromobenzo[d]oxepine (9b):

Following the general procedure (0.5 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 1:0 to 10:1) as a yellow solid (86 mg, 77%).

R_f = 0.3 (SiO_2, hexanes:ethyl acetate = 9:1, UV)

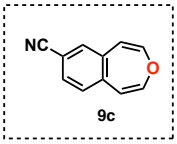
^{1}H NMR: (500 MHz, CD_3CN) δ 7.08 (dd, J = 8.1, 2.1 Hz, 1H), 6.86 (d, J = 2.1 Hz, 1H), 6.59 (d, J = 8.1 Hz, 1H), 5.73 (m, 2H), 5.10 (m, 2H)

^{13}C NMR: (126 MHz, CD_3CN) δ 148.2, 147.4, 139.0, 135.9, 132.4, 131.7, 131.4, 121.8, 113.0, 112.5

HRMS: (EI, m/z) calcd. For $C_{10}H_7OBr$ $[M]^+$, 221.9675; found: 221.9674

IR: (ATR, neat, cm^{-1}) 1670 (m), 1634 (m), 1576 (w), 1491 (m), 1397 (m), 1367 (m), 1318 (m), 1254 (w), 1211 (m), 1130 (w), 1089 (w), 1049 (s), 888(w), 872 (w), 873 (m), 828 (m), 762 (m), 733 (w), 583 (w)

m.p. = 69 – 71 °C



Benzo[d]oxepine-7-carbonitrile (9c):

Following the general procedure (0.5 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 1 to 10:1) as a yellow solid (69 mg, 82%).

R_f = 0.5 (SiO2, hexanes:ethyl acetate = 9:1, UV)

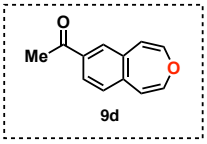
^{1}H NMR: (500 MHz, CD_3CN) δ 7.24 (dd, J = 7.9, 1.7 Hz, 1H), 6.94 (d, J = 1.7 Hz, 1H), 6.75 (d, J = 7.9 Hz, 1H), 5.73 (m, 2H), 5.10 (m, 2H)

^{13}C NMR: (126 MHz, CD_3CN) δ 149.6, 148.5, 141.8, 138.0, 132.8, 132.6, 130.4, 119.2, 112.5, 112.1, 111.8

HRMS: (ESI-TOF, m/z) calcd. For $C_{11}H_8NO$ $[M+H]^+$, 170.600; found: 170.0606

IR: (ATR, neat, cm^{-1}): 3073 (w), 2227 (m), 1671 (m), 1591 (m), 1498 (w), 1326 (m), 1257 (w), 1205 (w), 1053 (s), 901 (w), 844 (w), 651 (m)

m.p. = 83 – 84 °C



1-(benzo[d]oxepin-7-yl)ethan-1-one (9d):

Following the general procedure (0.5 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 1 to 10:1) as a yellow solid (68 mg, 73%).

R_f = 0.3 (SiO_2, hexanes:ethyl acetate = 9:1, UV)

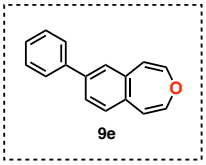
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.48 – 7.40 (m, 1H), 7.14 (d, J = 1.8 Hz, 1H), 6.64 (d, J = 7.8 Hz, 1H), 5.66 (m, 2H), 5.01 (m, 2H), 2.48 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 197.0, 148.0, 146.4, 141.1, 136.4, 136.3, 129.1, 128.51, 128.48, 112.4, 112.0, 25.6

HRMS: (ESI-TOF, m/z) calcd. For $C_{12}H_{11}O_2$ $[M+H]^+$, 187.0754 found: 187.0756

IR: (ATR, neat, cm^{-1}) 3346 (w), 1730 (w), 1675 (s), 1593 (m), 1566 (w), 1406 (w), 1356 (m), 1311 (m), 1273 (m), 1192 (w), 1147 (w), 1082 (w), 1049 (m), 972 (w), 933 (w), 838 (m), 763 (m), 636 (w), 570 (m).

m.p. = 71 – 74 °C (decomp.)



7-phenylbenzo[d]oxepine (9e):

Following the general procedure (0.5 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 1 to 10:1) as a yellow solid (90 mg, 82%).

R_f = 0.5 (SiO2, hexanes, UV)

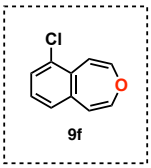
^1H NMR: (500 MHz, $CDCl_3$) δ 7.53 – 7.48 (m, 2H), 7.40 (m, 2H), 7.35 – 7.30 (m, 1H), 7.13 (dd, J = 7.8, 2.0 Hz, 1H), 6.87 (d, J = 2.0 Hz, 1H), 6.70 (d, J = 7.8 Hz, 1H), 5.70 (m, 2H), 5.10 (m, 2H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 146.20, 146.17, 140.6, 140.2, 136.4, 135.0, 129.6, 128.9, 128.0, 127.6, 126.7, 126.3, 113.1, 112.8

HRMS (ESI-TOF, m/z) calcd. For $C_{16}H_{13}O$ $[M+H]^+$, 221.0961; found: 221.0956

IR (ATR, neat, cm^{-1}): 3057 (w), 3037 (w), 1667 (m), 1562 (w), 1485(w), 1325 (m), 1264 (w), 1201 (w), 1051 (s), 892 (w), 849 (w), 691 (s)

m.p. = 91 – 92 °C



6-chlorobenzo[d]oxepine (9f):

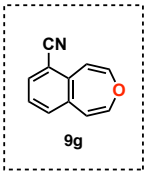
Following the general procedure (0.5 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 1 to 10:1) as a yellow oil (68 mg, 76%).

R_f = 0.3 (SiO_2, hexanes:ethyl acetate = 9:1, UV)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.04 (dd, J = 7.8, 1.3 Hz, 1H), 6.90 (t, J = 7.8 Hz, 1H), 6.63 (dd, J = 7.8, 1.3 Hz, 1H), 5.91 (d, J = 7.3 Hz, 1H), 5.85 (d, J = 7.0 Hz, 1H), 5.74 (d, J = 7.3 Hz, 1H), 5.25 (d, J = 7.0 Hz, 1H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 148.0, 147.9, 137.9, 133.3, 133.0, 128.6, 128.6, 127.8, 113.9, 110.5. HRMS: (EI-TOF, m/z) calcd. For $C_{10}H_7OCl$ $[M]^+$, 178.01799; found: 178.01804.

IR: (ATR, neat, cm^{-1}) = 3060 (w), 1667 (m), 1636 (m), 1466 (w), 1433 (s), 1299 (w), 1223 (w), 1080 (m), 1053 (s), 938 (m), 893 (w), 851 (w), 826 (w), 803 (w), 762 (s).



9g

Benzo[d]oxepine-6-carbonitrile (9g):

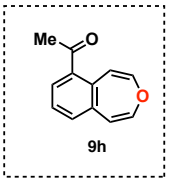
Following the general procedure (0.5 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 1 to 10:1) as a yellow solid (62 mg, 73%).

R_f = 0.5 (SiO_2, hexanes:ethyl acetate = 9:1, UV)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.19 (dd, J = 7.7, 1.4 Hz, 1H), 6.97 (t, J = 7.7 Hz, 1H), 6.80 (dd, J = 7.7, 1.4 Hz, 1H), 5.84 (d, J = 7.5 Hz, 1H), 5.73 (d, J = 7.3 Hz, 1H), 5.53 (d, J = 7.5 Hz, 1H), 5.09 (d, J = 7.3 Hz, 1H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 149.9, 148.0, 139.5, 137.4, 132.8, 131.4, 128.1, 117.5, 112.7, 111.5, 109.8. HRMS: (ESI-TOF, m/z) calcd. For $C_{11}H_8NO$ $[M+H]^+$, 170.0600; found: 170.0603.

IR: (ATR, neat, cm^{-1}) = 3077 (w), 3010 (w), 2226 (m), 1672(s), 1634 (m), 1466 (m), 1449(m), 1312 (s), 1241 (m), 1093 (m), 1066 (m), 957 (m), 922 (m), 851 (m), 803(m), 767 (m). m.p. = 81 – 84 °C



9h

1-(benzo[d]oxepin-6-yl)ethan-1-one (9h):

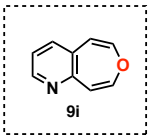
Following the general procedure (0.5 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 1 to 10:1) as a yellow oil (65 mg, 70%).

R_f = 0.5 in (SiO_2, hexanes:ethyl acetate = 9:1, UV)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.25 (d, J = 5.7 Hz, 1H), 7.08 (t, J = 7.7 Hz, 1H), 6.89 (dd, J = 7.7, 1.3 Hz, 1H), 5.95 (m, 2H), 5.82 (d, J = 7.0 Hz, 1H), 5.40 (d, J = 7.0 Hz, 1H), 2.52 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 202.9, 148.6, 147.9, 139.0, 137.7, 133.9, 131.9, 127.3, 127.1, 114.5, 112.3, 30.6 HRMS: (ESI-TOF, m/z) calcd. For $C_{12}H_{10}O$ $[M]^+$, 186.06753; found: 186.06801

IR: (ATR, neat, cm^{-1}) 3066 (w), 1678 (s), 1633 (m), 1444 (w), 1352 (m), 1260 (s), 1056(s), 1014 (m), 980 (m), 938 (m), 896 (w), 852 (w), 815 (m), 766 (s), 592 (w)



9i

Oxepino[4,5-b]pyridine (9i):

Following the general procedure (0.5 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 10:1 to 2:1) as a yellow solid (90 mg, 82%).

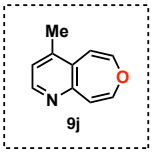
R_f = 0.5 (SiO_2, hexanes:ethyl acetate = 1:1, UV)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.05 (s, 1H), 6.84 (dd, J = 7.7, 1.5 Hz, 1H), 6.77 (dd, J = 7.7, 4.8 Hz, 1H), 5.81 (d, J = 7.7 Hz, 1H), 5.68 (d, J = 7.5 Hz, 1H), 5.28 (d, J = 7.7 Hz, 1H), 4.93 (d, J = 7.5 Hz, 1H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 155.9, 149.0, 147.4, 147.1, 135.2, 132.9, 122.0, 114.9, 110.6.

HRMS: (ESI-TOF, m/z) calcd. For C_9H_8O $[M+H]^+$, 146.0600; found: 146.0600

IR: (ATR, neat, cm^{-1}) 3046 (w), 1671 (m), 1634 (m), 1571 (m), 1451 (s), 1303 (w), 1271 (w), 1228 (w), 1121 (m), 1044 (w), 873 (w), 789 (w), 575 (w).



9j

4-methyloxepino[4,5-b]pyridine (9j):

Following the general procedure (0.5 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 10:1 to 2:1) as a yellow oil (59 mg, 74%).

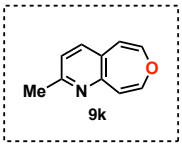
R_f = 0.3 (SiO_2, hexanes:ethyl acetate = 1:1, UV)

^1H NMR: (500 MHz, $CDCl_3$) δ 8.04 (d, J = 5.0 Hz, 1H), 6.72 (d, J = 5.0 Hz, 1H), 6.02 (d, J = 7.2 Hz, 1H), 5.95 (d, J = 7.2 Hz, 1H), 5.55 (d, J = 7.2 Hz, 1H), 5.36 (d, J = 7.2 Hz, 1H), 2.14 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 155.4, 150.1, 147.9, 147.5, 144.0, 131.3, 123.8, 116.5, 109.0, 19.3

HRMS: (ESI-TOF, m/z) calcd. For $C_{10}H_{10}NO$ $[M+H]^+$, 160.0757; found: 160.0776

IR: (ATR, neat, cm^{-1}) 3052 (w), 2979 (w), 1668 (m), 1633 (m), 1581 (m), 1496 (s), 1264 (w), 1218 (w), 1109 (m), 1019 (w), 833 (w), 765 (w), 681 (w)



9k

2-methyloxepino[4,5-b]pyridine (9k):

Following the general procedure (0.5 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 10:1 to 2:1) as a yellow oil (62 mg, 78%).

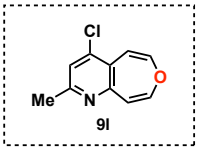
R_f = 0.3 (SiO_2, hexanes:ethyl acetate = 1:1, UV)

^1H NMR: (500 MHz, $CDCl_3$) δ 6.78 (d, J = 7.7 Hz, 1H), 6.65 (d, J = 7.7 Hz, 1H), 5.84 (dd, J = 7.6, 1.8 Hz, 1H), 5.69 (dd, J = 7.4, 1.8 Hz, 1H), 5.31 (dd, J = 7.6, 2.0 Hz, 1H), 4.98 (dd, J = 7.4, 1.8 Hz, 1H), 2.35 (d, J = 1.8 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 156.3, 155.1, 148.9, 146.4, 135.8, 129.8, 121.3, 115.4, 110.9, 24.0

HRMS: (ESI-TOF, m/z) calcd. For $C_{10}H_{10}NO$ $[M+H]^+$, 160.0757; found: 160.0763

IR: (ATR, neat, cm^{-1}) 3052 (w), 1670 (m), 1634 (m), 1587 (m), 1469 (s), 1284 (w), 1213 (w), 1129 (m), 1044 (w), 835 (w), 759 (w), 614(w), 557 (w)



4-chloro-2-methyloxepino[4,5-b]pyridine (9l):

Following the general procedure (0.5 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 10:1 to 2:1) as a yellow oil (70.2 mg, 0.36 mmol, 73%).

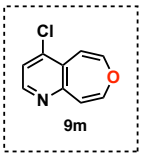
R_f = 0.5 (SiO_2, hexanes:ethyl acetate = 1:1, UV)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.79 (s, 1H), 5.98 (d, J = 7.4 Hz, 1H), 5.89 (d, J = 7.3 Hz, 1H), 5.57 (d, J = 7.3 Hz, 1H), 5.44 (d, J = 7.4 Hz, 1H), 2.35 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 157.2, 156.4, 150.6, 148.1, 141.4, 127.6, 122.0, 115.6, 107.6, 23.9

HRMS: (ESI-TOF, m/z) calculated for $C_{10}H_9NOCl$ $[M+H]^+$, 194.0367 found: 194.0373

IR: (ATR, neat, cm^{-1}): 3006 (w), 2921 (w), 1669(m), 1634 (m), 1572 (m), 1538 (m),1443 (w), 1262 (w), 1048 (s), 955 (w), 808 (w)



4-chlorooxepino[4,5-b]pyridine (9m):

Following the general procedure (0.5 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 10:1 to 2:1) as a yellow solid (65 mg, 72%).

R_f= 0.7 (SiO_2, hexanes:ethyl acetate = 1:1, UV)

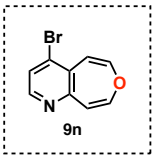
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.98 (d, J = 5.4 Hz, 1H), 6.89 (d, J = 5.4 Hz, 1H), 5.96 (d, J = 7.5 Hz, 1H), 5.89 (d, J = 7.5 Hz, 1H), 5.56 (d, J = 7.5 Hz, 1H), 5.43 (d, J = 7.5 Hz, 1H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 157.3, 150.7, 148.9, 147.9, 141.1, 130.8, 122.9, 115.4, 107.2

HRMS: (ESI-TOF, m/z) calcd. For C_9H_7ClO $[M+H]^+$, 180.0211; found: 180.0198

IR: (ATR, neat, cm^{-1}) 3083 (w), 1670 (m), 1634 (m), 1552 (w), 1438 (s), 1389 (w), 1302 (m), 1262 (w), 1199 (w), 1098 (m), 900 (w), 853 (w), 786 (w), 760 (w), 567 (w)

m.p. = 67 – 71 °C (decomp.)



9n

4-bromooxepino[4,5-b]pyridine (9n):

Following the general procedure (0.5 mmol scale), the title compound was isolated by flash chromatography (SiO2, hexanes:ethyl acetate = 10:1 to 2:1) as a yellow solid (81 mg, 72%).

R_f = 0.7 (SiO_2, hexanes:ethyl acetate = 1:1, UV)

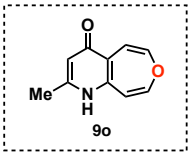
^{1}H NMR: (500 MHz, CD_3CN) δ 7.90 (d, J = 5.3 Hz, 1H), 7.20 (d, J = 5.3 Hz, 1H), 6.07 (d, J = 7.4 Hz, 1H), 6.01 (d, J = 7.3 Hz, 1H), 5.63 (dd, J = 7.3, 0.8 Hz, 1H), 5.48 (d, J = 7.4 Hz, 1H)

^{13}C NMR: (126 MHz, CD_3CN) δ 157.5, 152.0, 150.2, 149.0, 132.92, 132.88, 127.1, 116.3, 111.0

HRMS: (ESI-TOF, m/z) calculated for C_9H_7NOBr $[M+H]^+$, 223.9706 found: 223.9711

IR: (ATR, neat, cm^{-1}) 3057 (w), 1751 (m), 1668 (m), 1633 (m), 1545 (w), 1494 (s), 1387 (w), 1259 (w), 1223 (w), 1197 (m), 1095 (w), 888 (w), 765 (w), 651 (w)

m.p. = 61 – 64 °C (decomp.)



9o

2-methyl-4a,9a-dihydrooxepino[4,5-b]pyridin-4(1H)-one (9o):

Following the general procedure (0.5 mmol scale), the title compound was isolated by flash chromatography (SiO2, MeOH in ethyl acetate, 0 to 30%) as a yellow oil (63 mg, 72%).

R_f = 0.8 (SiO_2, methanol, UV)

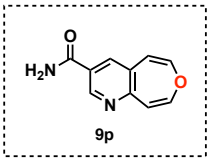
^{1}H NMR: (500 MHz, MeOD) δ 6.23 (d, J = 6.7 Hz, 1H), 6.12 (s, 1H), 5.89 (d, J = 6.5 Hz, 1H), 5.83 (d, J = 6.5 Hz, 1H), 5.46 (d, J = 6.7 Hz, 1H), 2.26 (s, 3H)

^{13}C NMR: (126 MHz, MeOD) δ 178.2, 154.3, 149.3, 147.1, 145.8, 122.7, 115.1, 110.5, 109.5, 18.8

HRMS: (ESI-TOF, m/z) calculated for $C_{10}H_{10}NO_2$ $[M+H]^+$, 176.0706 found: 176.0713

IR: (ATR, neat, cm^{-1}) 3281 (m, b), 1642 (m), 1602 (m), 1494 (s), 1250 (w), 1214 (w), 1167 (w), 968 (w), 760 (w)

m.p. = color change from yellow to grey (onset at 131 °C, assumed decomposition) took place slowly and no melting was observed up to 250 °C



9p

Oxepino[4,5-b]pyridine-3-carboxamide (9p):

Following the general procedure (0.5 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 10:1 to 2:1) as a yellow solid (60 mg, 63%).

R_f = 0.2 (SiO_2, hexanes:ethyl acetate = 1:3, UV)

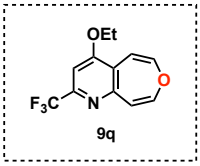
^{1}H NMR: (500 MHz, MeOD) δ 8.40 (d, J = 2.1 Hz, 1H), 7.40 (d, J = 2.1 Hz, 1H), 5.94 (d, J = 7.9 Hz, 1H), 5.76 (d, J = 7.7 Hz, 1H), 5.23 (d, J = 7.9 Hz, 1H), 5.09 (d, J = 7.7 Hz, 1H)

^{13}C NMR: (126 MHz, MeOD) δ 169.2, 159.8, 152.2, 148.8, 147.2, 135.8, 134.4, 129.3, 113.9, 110.6

HRMS: (ESI-TOF, m/z) calculated for $C_{10}H_9N_2O_2$ $[M+H]^+$, 189.0659 found: 189.0657

IR: (ATR, neat, cm^{-1}) 3288 (m, br), 2980 (w), 1673 (m), 1629 (s), 1630 (s), 1458 (m), 1399 (w), 1234 (s), 927 (w).

m.p. = 122 °C (decomp.)



9q

4-ethoxy-2-(trifluoromethyl)oxepino[4,5-b]pyridine (9q):

Ethanol was used instead of i-PrOH. Following the general procedure (0.5 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 10:1 to 2:1) as a yellow solid (99 mg, 77%).

R_f = 0.6 (SiO_2, hexanes:ethyl acetate = 1:1, UV)

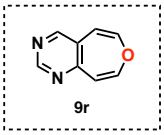
^1H NMR: (500 MHz, $CDCl_3$) δ 6.76 (s, 1H), 5.95 (d, J = 7.4 Hz, 1H), 5.86 (d, J = 7.4 Hz, 1H), 5.55 (d, J = 7.4 Hz, 1H), 5.46 (dd, J = 7.4, 0.9 Hz, 1H), 4.07 (q, J = 7.0 Hz, 2H), 1.43 (td, J = 7.0, 0.9 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 161.1, 157.1, 150.9, 148.4, 147.6 (q, J = 34.3 Hz), 123.7, 121.3 (q, J = 274.1 Hz), 115.3, 104.7, 102.7 (q, J = 3.0 Hz), 64.8, 14.5

HRMS: (ESI-TOF, m/z) calcd. For $C_{12}H_{11}NO_2F_3$ $[M+H]^+$, 258.0736; found: 258.0746

IR: (ATR, neat, cm^{-1}): 2988 (w), 2944 (w), 1740 (m), 1591 (m), 1419 (s), 1386 (w), 1244 (w), 1181 (w), 1093 (s), 911 (w), 768 (w)

m.p. = 128 – 131 °C (decomp.)



9r

Oxepino[4,5-d]pyrimidine (9r):

Extraction from 4:1 chloroform:isopropanol (3 x 15mL) Following the general procedure (0.5 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 3:1 to 1:2) as a yellow oil (32 mg, 44%).

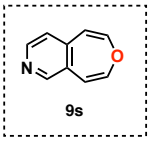
R_f = 0.24 (SiO_2, hexanes:ethyl acetate = 1:2, UV)

^{1}H NMR: (500 MHz, CD_3OD) δ 8.46 (s, 1H), 7.80 (s, 1H), 5.99 (d, J = 7.9 Hz, 1H), 5.74 (d, J = 7.7 Hz, 1H), 5.05 (d, J = 7.9 Hz, 1H), 5.01 (d, J = 7.7 Hz, 1H)

^{13}C NMR: (126 MHz, CD_3OD) δ 165.2, 158.2, 155.6, 154.5, 149.9, 132.0, 112.7, 107.6

HRMS: (ESI-TOF, m/z) calculated for $C_8H_7N_2O$ $[M+H]^+$, 147.0553 found: 147.0560

IR: (ATR, neat, cm^{-1}) 1672 (m), 1563 (m), 1456 (s), 1391 (w), 1309 (w), 1049 (m), 767 (w)



9s

Oxepino[4,5-c]pyridine (9s):

Following the general procedure (0.5 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 10:1 to 2:1) as a yellow oil (58 mg, 79%).

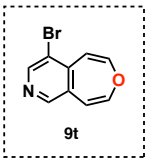
R_f = 0.4 (SiO_2, hexanes:ethyl acetate = 2:1, UV)

^{1}H NMR: (500 MHz, CD_3CN) δ 8.07 (s, 1H), 7.76 (s, 1H), 6.54 (d, J = 4.8 Hz, 1H), 5.78 (d, J = 7.5 Hz, 1H), 5.72 (d, J = 7.5 Hz, 1H), 5.10 (d, J = 7.5 Hz, 1H), 5.03 (d, J = 7.6 Hz, 1H)

^{13}C NMR: (126 MHz, CD_3CN) δ 151.2, 151.1, 149.6, 148.6, 144.3, 131.8, 123.4, 111.5, 110.6

HRMS: (ESI-TOF, m/z) calculated for C_9H_8NO $[M+H]^+$, 146.0600 found: 146.0601

IR: (ATR, neat, cm^{-1}) 3028 (w), 1667 (m), 1634 (w), 1582 (m), 1495 (w), 1404 (s), 1327 (w), 1220 (w), 1045 (s), 842 (m), 760 (m)



4-bromooxepino[4,5-c]pyridine (9t):

Following the general procedure (0.5 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 10:1 to 2:1) as a yellow oil (72 mg, 64%).

R_f = 0.2 (SiO_2, hexanes:ethyl acetate = 1:1, UV)

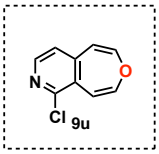
^1H NMR: (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.69 (s, 1H), 5.89 (d, J = 7.6 Hz, 1H), 5.78 (d, J = 7.3 Hz, 1H), 5.49 (d, J = 7.6 Hz, 1H), 5.11 (d, J = 7.3 Hz, 1H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 151.9, 151.8, 149.4, 147.5, 142.5, 132.7, 120.6, 110.5, 110.1

HRMS: (ESI-TOF, m/z) calculated for C_9H_7BrNO $[M+H]^+$, 223.9706 found: 223.9696

IR: (ATR, neat, cm^{-1}): 3038 (w), 3001 (w), 1669 (m), 1629 (m), 1564 (s), 1531 (w), 1247 (s), 1211 (w), 1196 (w), 1055 (s), 936 (w), 760 (w)

m.p. = 81 °C (decomp.)



1-chlorooxepino[4,5-c]pyridine (9u):

Following the general procedure (0.5 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 10:1 to 2:1) as a yellow oil (60 mg, 67%).

R_f = 0.5 (SiO_2, hexanes:ethyl acetate = 2:1, UV)

^1H NMR: (500 MHz, $CDCl_3$) δ 7.94 (d, J = 4.9 Hz, 1H), 6.50 (d, J = 4.9 Hz, 1H), 5.89 (m, 2H), 5.62 (d, J = 7.3 Hz, 1H), 5.14 (d, J = 7.3 Hz, 1H)

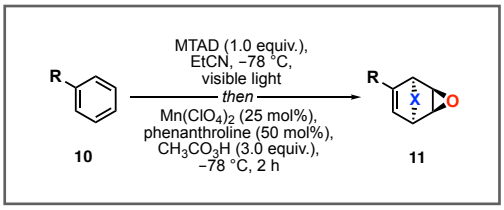
^{13}C NMR: (126 MHz, $CDCl_3$) δ 152.1, 149.7, 149.4, 149.0, 146.8, 129.4, 122.3, 111.6, 109.9 S34

HRMS: (ESI-TOF, m/z) calculated for C_9H_7NOCl $[M+H]^+$, 180.0211 found: 180.0219

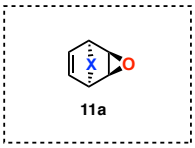
IR: (ATR, neat, cm^{-1}) 3053 (w), 1668 (m), 1631 (m), 1466 (s), 1392 (w), 1288 (w), 1185 (w), 1057 (m), 901 (w), 763 (w)

3-3. Dearomative epoxidation of monocyclic arenes

General procedure for dearomative epoxidation with arenes



This procedure was modified from the literature protocol. 3 N-Methyl-1,2,4-triazoline-3,5-dione (7, MTAD, 113.4 mg, 1.0 mmol, 1.0 equiv.) was placed in a test tube and propionitrile (10 mL, 0.1 M) was added at room temperature and placed in a −78 °C chiller. Arene (10.0 mmol, 10 equiv.) was added slowly and the solution was stirred under irradiation with LED lights at −78 °C until the solution had become colorless, which took about 12 hours with the described set up (see Section 2-2.). Upon decolorization, a solution of $Mn(ClO_4)_2 \cdot 6H_2O$ (90.3 mg, 0.25 mmol, 25mol%) and 1,10-phenanthroline (90.1 mg, 0.5 mmol, 50 mol%) in acetonitrile (3 mL, sonicated for 1 minute), was added over the course of 10 seconds, being careful to ensure proper mixing. To this solution, was quickly added freshly-prepared peracetic acid (8-10 wt% in acetic acid, 3.0 equiv.) and left to stir for two hours at −78 °C. Afterwards, a 10% sodium thiosulfate solution (20 mL) was added and the organic phase was separated. The aqueous phase was extracted with ethyl acetate (3 × 15 mL). The organic extracts were combined and passed through a silica plug which was washed with CH_2Cl_2 (15 mL). The organic phase was then dried over $MgSO_4$ and concentrated under reduced pressure. The compound was isolated by flash chromatography (SiO_2, hexanes: ethyl acetate mixtures).



5-methyl-1a,2,8,8a-tetrahydro-4H-2,8-ethenooxireno[2,3-d][1,2,4]triazolo[1,2-a]pyridazine-4,6(5H)-dione (11a):

Following the general procedure (1.0 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 5:1 to 1:1) as a white solid (93 mg, 3:1 d.r., 45%).

R_f = 0.3 (SiO_2, hexanes:ethyl acetate = 1:1, UV)

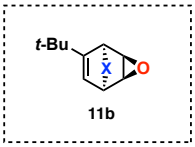
^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.16 – 6.00 (m, 2H), 5.20 (dd, J = 4.8, 3.2, 1.6 Hz, 2H), 3.67 (dd, J = 3.2, 1.6 Hz, 2H), 3.01 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 158.2, 125.0, 54.6, 42.1, 25.7

HRMS: (ESI-TOF, m/z) calcd. For $C_9H_{10}N_3O_3$ $[M+H]^+$, 208.0717; found: 208.0722

IR: (ATR, neat, cm^{-1}) 2923 (w), 1761 (m), 1708 (s), 1605 (m), 1511 (m), 1456 (m), 1401 (m), 1389 (m), 1373 (w), 1196 (m), 1080 (w), 1029 (w), 1011 (w), 955 (w), 930 (w), 529 (w)

m.p.= 188 – 191 °C



9-(tert-butyl)-5-methyl-1a,2,8,8a-tetrahydro-4H-2,8-ethenooxireno[2,3-d][1,2,4]triazolo[1,2-a]pyridazine-4,6(5H)- dione (11b):

Following the general procedure (1.0 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 5:1 to 1:1) as a yellow oil (155 mg, 5:1 d.r., 3:1 r.r., 59%). where the major diastereomer was inseparable from the constitutional isomer (3:1).

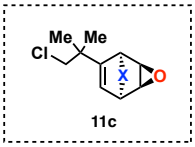
Rf = 0.4 (SiO_2, hexanes:ethyl acetate = 1:1, UV)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.63 (ddd, J = 6.2, 2.3, 1.0 Hz, 1H), 5.22 (dd, J = 4.5, 2.3 Hz, 1H), 5.12 (dd, J = 6.2, 4.2 Hz, 1H), 3.62 (t, J = 4.5 Hz, 1H), 3.58 (td, J = 4.2, 1.0 Hz, 1H), 2.98 (d, J = 1.3 Hz, 3H), 1.03 (s, 9H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 158.3, 157.8, 157.4, 156.9, 148.6, 127.1, 123.9, 113.3, 57.0, 55.2, 55.1, 54.2, 46.5, 42.7, 41.9, 33.1, 31.8, 27.9, 25.9, 25.6, 25.6

HRMS: (ESI-TOF, m/z) calcd. For $C_{13}H_{18}N_3O_3$ $[M+H]^+$, 264.1343; found: 264.1353

IR: (ATR, neat, cm^{-1}) 2964 (w), 2872 (w), 1773 (m), 1703 (s), 1632 (m), 1453 (m), 1394 (m), 1366 (w), 1201 (m), 1092 (w), 1009 (w), 957 (m), 768 (w)



11c

9-(1-chloro-2-methylpropan-2-yl)-5-methyl-1a,2,8,8a-tetrahydro-4H-2,8-ethenooxireno[2,3-d][1,2,4]triazolo[1,2-a]pyridazine-4,6(5H)-dione (11c):

Following the general procedure (1.0 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 5:1 to 1:1) as an off-white oil (123 mg, 7:1 d.r., 41%)

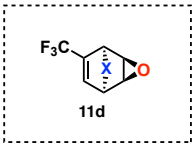
Rf = 0.4 (SiO_2, hexanes:ethyl acetate = 1:1, UV)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.76 (dd, J = 6.2, 2.3 Hz, 1H), 5.18 (m, 2H), 3.66 (t, J = 4.3 Hz, 1H), 3.62 (t, J = 4.3 Hz, 1H), 3.49 (d, J = 11.1 Hz, 1H), 3.36 (d, J = 11.1 Hz, 1H), 2.97 (s, 3H), 1.15 (s, 3H), 1.13 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 158.1, 157.5, 142.6, 118.0, 54.8, 54.3, 52.4, 42.5, 42.0, 38.4, 25.7, 24.5, 23.4

HRMS: (ESI-TOF, m/z) calcd. For $C_{13}H_{17}N_3O_3$ $[M+H]^+$, 298.0953; found: 298.0959

IR: (ATR, neat, cm^{-1}) 2970 (w), 1706 (s), 1455 (m), 1394 (w), 1229 (m), 1205 (m), 954 (w), 769 (w), 527 (w)



11d

5-methyl-9-(trifluoromethyl)-1a,2,8,8a-tetrahydro-4H-2,8-ethenooxireno[2,3-d][1,2,4]triazolo[1,2-a]pyridazine-4,6(5H)-dione (11d):

Following the general procedure (1.0 mmol scale), the title compound was isolated by flash chromatography (SiO_2, hexanes:ethyl acetate = 5:1 to 1:1) as a yellow oil (105 mg, >20:1 d.r., 38%).

R_f = 0.4 (SiO_2, hexanes:ethyl acetate = 1:1, UV)

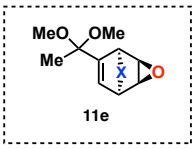
^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.60 – 6.44 (m, 1H), 5.39 (dd, J = 4.4, 2.3 Hz, 1H), 5.34 (dd, J = 6.1, 4.4 Hz, 1H), 3.79 (t, J = 4.3 Hz, 1H), 3.75 (td, J = 4.3, 0.9 Hz, 1H), 3.02 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 157.7, 157.1, 127.9 (q, J = 36.57) , 125.9 (q, J = 5.78) ,120.0 (q, J = 120.24), 53.5, 53.3, 42.0, 41.4, 25.9

^{19}F NMR: (471 MHz, $CDCl_3$) δ -67.37

HRMS: (ESI-TOF, m/z) calcd. For $C_{10}H_9N_3O_3F_3$ $[M+H]^+$, 276.0591; found: 276.0594

IR: (ATR, neat, cm^{-1}) 2970 (w), 1718 (s), 1455 (m), 1375 (m), 1266 (w), 1216 (m), 768 (w), 527 (w)



11e

9-(1,1-dimethoxyethyl)-5-methyl-1a,2,8,8a-tetrahydro-4H-2,8-ethenooxireno[2,3-d][1,2,4]triazolo[1,2-a]pyridazine-4,6(5H)-dione (11e):

The work-up is modified from the general procedure as follows: The reaction was quenched with a 10% sodium thiosulfate solution (20 mL) and saturated NaHCO3 (40 mL) and the organic phase was separated. The aqueous phase was extracted with ethyl acetate (3 × 15 mL). The organic extracts were combined and passed through a silica plug and flushed with CH2Cl2 (15 mL). The organic phase was then dried over MgSO4 and concentrated under reduced pressure. The title compound was isolated by column chromatography (SiO2, hexanes:ethyl acetate (SiO2, 5:1 to 1:1 with 1% Et3N) as a light yellow oil (77 mg, >20:1 d.r., 26%).

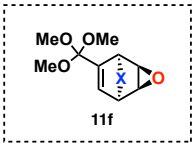
R_f = 0.3 (SiO_2, hexanes:ethyl acetate = 1:1, UV)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.06 (ddd, J = 6.2, 2.2, 1.0 Hz, 1H), 5.30 (dd, J = 4.2, 2.2 Hz, 1H), 5.23 (dd, J = 6.2, 4.2 Hz, 1H), 3.66 (m, 2H), 3.17 (s, 3H), 3.13 (s, 3H), 2.99 (s, 3H), 1.31 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 157.6, 157.1, 140.4, 120.0, 99.1, 54.8, 54.2, 49.5, 49.2, 42.9, 42.1, 25.6, 22.8

HRMS: (ESI-TOF, m/z) calcd. For $C_{13}H_{17}N_3O_5Na$ $[M+Na]^+$, 318.1066; found: 318.1073

IR: (ATR, neat, cm^{-1}) 2956 (w), 1777 (m), 1708 (s), 1455 (m), 1397 (m), 1190 (m), 1144 (m), 1040 (s), 917(w), 732 (w), 732 (m)



5-methyl-9-(trimethoxymethyl)-1a,2,8,8a-tetrahydro-4H-2,8-ethenooxireno[2,3-d][1,2,4]triazolo[1,2-a]pyridazine-4,6(5H)-dione (11f):

The work-up is modified from the general procedure as follows: The reaction was quenched with a 10% sodium thiosulfate solution (20mL) and saturated $NaHCO_3$ (40 mL) and the organic phase was separated. The aqueous phase was extracted with ethyl acetate (3 × 15 mL). The organic extracts were combined and passed through a silica plug and flushed with CH_2Cl_2 (15 mL). The organic phase was then dried over MgSO4 and concentrated under reduced pressure. The title compound was isolated by column chromatography (SiO_2, hexanes:ethyl acetate (SiO_2, 5:1 to 1:1 with 1% Et3N) as an off-white solid (141 mg, >20:1 d.r., 45%).

R_f = 0.3 (SiO_2, hexanes:ethyl acetate = 1:1, UV)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.18 (dd, J = 6.1, 2.1 Hz, 1H), 5.37 – 5.21 (m, 2H), 3.74 – 3.62 (m, 2H), 3.12 (d, J = 0.9 Hz, 9H), 2.97 (s, 3H)

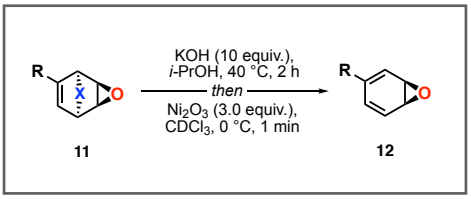
^{13}C NMR: (126 MHz, $CDCl_3$) δ 157.2, 156.3, 134.3, 123.6, 112.3, 54.4, 53.7, 49.9, 42.7, 42.1, 25.6

HRMS: (ESI-TOF, m/z) calcd. For $C_{13}H_{17}N_3O_6Na$ $[M+Na]^+$, 334.1001; found: 334.1030

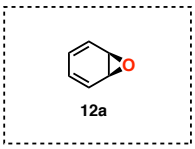
IR: (ATR, neat, cm^{-1}) 2949 (w), 1778 (m), 1704 (s), 1451 (m), 1394 (m), 1242 (m), 1181 (m), 1094 (s), 1065 (s), 768 (w), 529 (w)

m.p. = 162 – 164 °C

3-4. General procedure for the synthesis of arene oxides/oxepines



To a vial containing finely ground KOH (120 mg, 10 equiv., 90 wt%), and substrate (0.20 mmol, 1.0 equiv.) under nitrogen was added *i*-PrOH (2 mL, 0.1 M) and degassed with sonication and nitrogen for 15 min. The reaction was heated to 40 °C with vigorous stirring (1000 rpm) for 2 hours or until complete conversion by TLC. Upon completion, the reaction was cooled in an ice bath and H_2O (2 mL) was added. AcOH was then carefully added dropwise until pH 5. The semicarbazide intermediate was then extracted out with ethyl acetate (3 × 5 mL). The organic layers were combined, dried with $NaHCO_3$ and concentrated under reduced pressure. This mixture containing the semicarbazide was added to vial, followed by $CDCl_3$ (2.0 mL, 0.1 M), and sparged with nitrogen for 15 minutes. Next, nickel oxide (Ni_2O_3, 30% active basis, 330 mg, 3.0 equiv.) was added as a solid under a stream of nitrogen (note: vigorous gas evolution was observed). The solution was agitated manually for 1 minute, filtered through a celite plug, and the celite was washed thoroughly with $CDCl_3$ to yield the resulting arene-oxide as a solution. Due to the pronounced instability and volatility of these arene-oxides, further purification was impractical and yields were determined by ^{1}H-NMR internal standard ($MeNO_2$). MeNCO was observed as a byproduct after filtering through celite in all cases. IR spectra were not acquired due to the instability of these compounds upon sample preparation. Note: Arene oxides are suspected carcinogens. Caution in the handling of these compounds should be used. Note: In many instances, due to the valence tautomerization of arene-oxide/oxepins, ^{13}C signals corresponding to the carbon next to oxygen can be severely broadened. In these cases, it was necessary to assign these peaks via HSQC/HMBC.



Benzene-Oxide (7-oxabicyclo[4.1.0]hepta-2,4-diene, 12a):

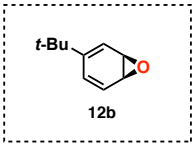
Following the general procedure (0.20 mmol scale), the title compound was obtained as a yellow solution in $CDCl_3$ using $MeNO_2$ as internal standard (58% yield). See ^{1}H NMR spectra of **12a** for graphical visualization of internal standard.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.26 (dd, J = 5.1, 2.9 Hz, 2H), 5.94 (td, J = 4.8, 2.9 Hz, 2H), 5.09 (d, J = 4.8 Hz, 2H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 129.5, 121.5, 105.3

HRMS: (EI, m/z) calcd. For C_6H_6O $[M]^+$, 94.04132; found: 94.04195

The analytical data were in accordance with previously reported values.



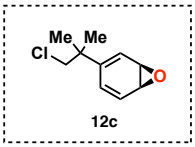
3-(tert-butyl)-7-oxabicyclo[4.1.0]hepta-2,4-diene (**12b**):

Since the undesirable constitutional isomer (**11b'**) was inseperable from **11b**, the resultant semicarbazides were separated after KOH hydrolysis utilizing a silica plug (ethyl acetate, 100%). The title compound was obtained as a yellow solution in $CDCl_3$ using $MeNO_2$ as internal standard (82% yield).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.32 (dt, J = 8.5, 1.5 Hz, 1H), 6.12 (dd, J = 8.5, 4.3 Hz, 1H), 6.01 (ddd, J = 4.7, 1.5, 0.8 Hz, 1H), 4.71 (dd, J = 4.7, 2.5 Hz, 1H), 4.65 (ddd, J = 4.0, 2.5, 1.2 Hz, 1H), 1.13 (s, 9H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 150.4, 126.6, 123.7, 118.0, 84.6*, 85.6*, 35.0, 29.5 (*detected by HSQC)

HRMS: (ESI-TOF, m/z) calcd. For $C_{10}H_{15}O$ $[M+H]^+$, 151.1117; found: 151.1124



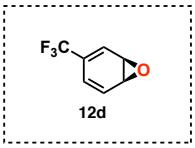
3-(1-chloro-2-methylpropan-2-yl)-7-oxabicyclo[4.1.0]hepta-2,4-diene (12c):

Following the general procedure (0.20 mmol scale), the title compound was obtained as a yellow solution in $CDCl_3$ using MeNO2 as internal standard (79% yield).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.28 (d, J = 8.3 Hz, 1H), 6.12 (dd, J = 8.3, 4.4 Hz, 1H), 6.01 (d, J = 4.8 Hz, 1H), 4.82 (dd, J = 4.8, 2.2 Hz, 1H), 4.79 – 4.75 (m, 1H), 3.49 (s, 2H), 1.23 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 145.57, 126.7, 123.6, 119.7, 89.8*, 89.3*, 54.3, 40.2, 25.2 (*detected by HMBC)

HRMS: (ESI-TOF, m/z) calcd. For $C_{10}H_{14}OCl$ $[M+H]^+$, 185.0728; found: 185.0740



12d

3-(trifluoromethyl)-7-oxabicyclo[4.1.0]hepta-2,4-diene (12d):

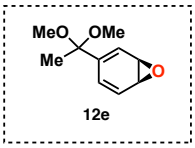
Following the general procedure (0.20 mmol scale), the title compound was obtained as a yellow solution in $CDCl_3$ using $MeNO_2$ as internal standard (74% yield).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.59 (d, J = 7.1 Hz, 1H), 6.04 (d, J = 5.0 Hz, 1H), 5.94 (dd, J = 6.9, 5.0 Hz, 1H), 5.40 (m, 2H)

^{13}C NMR: (500 MHz, $CDCl_3$) δ 131.5 (q, J = 31.3 Hz), 128.4 (q, J = 4.9 Hz), 123.1 (q, J = 272.5 Hz), 119.5, 118.5, 117.2*, 117.1 (q, J = 3.6 Hz) (*signal detected by HSQC)

^{19}F NMR: (471 MHz, $CDCl_3$) δ -67.38

HRMS: (ESI-TOF, m/z) calcd. For $C_7H_6OF_3$ $[M+H]^+$, 163.0365; found: 163.0373



12e

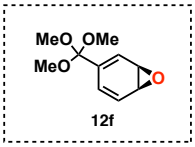
3-(1,1-dimethoxyethyl)-7-oxabicyclo[4.1.0]hepta-2,4-diene (12e):

Following the general procedure (0.20 mmol scale), the title compound was obtained as a yellow solution in $CDCl_3$ using $MeNO_2$ as internal standard (74% yield).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.41 (dt, J = 8.0, 1.2 Hz, 1H), 6.17 – 6.12 (m, 1H), 6.04 (dd, J = 8.0, 4.5 Hz, 1H), 4.93 (dd, J = 4.8, 1.7 Hz, 1H), 4.90 (dt, J = 4.5, 1.7 Hz, 1H), 3.15 (s, 6H), 1.39 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 142.5, 127.4, 122.3, 120.4, 100.8, 96.3, 96.2, 49.0, 23.8

HRMS: (EI, m/z) calcd. For $C_{10}H_{14}O_3$ $[M]^+$, 182.0937; found: 182.0949



12f

3-(trimethoxymethyl)-7-oxabicyclo[4.1.0]hepta-2,4-diene (12f):

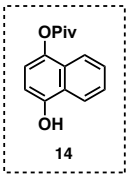
Following the general procedure (0.20 mmol scale), the title compound was obtained as a yellow solution in $CDCl_3$ using $MeNO_2$ as internal standard (73% yield).

^1H NMR: (500 MHz, $CDCl_3$) δ 6.48 (d, J = 7.7 Hz, 1H), 6.11 (d, J = 4.5 Hz, 1H), 5.98 (dd, J = 7.7, 4.5 Hz, 1H), 5.09 (m, 2H), 3.15 (s, 9H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 136.8, 129.1, 121.1, 120.9, 113.9, 104.9, 104.2, 49.7

HRMS: (ESI-TOF, m/z) calcd. For $C_{10}H_{14}O_4Na$ $[M+Na]^+$, 221.0790; found: 221.0799

3-5. Initial route to perilloxin

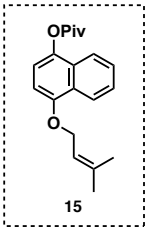


14

4-hydroxynaphthalen-1-yl pivalate (14):

A mixture of 1,4-naphthoquinone (4.0 g, 25.4 mmol, 1.0 eq.) and sodium dithionite (17.6 g, 101.6 mmol, 4.0 eq.) in degassed diethyl ether (126 mL) and water (126 mL) were vigorously stirred at rt for 1 h under nitrogen atmosphere. Phases were separated and the organic phase was washed with water (2 × 30 mL), then brine (30 mL), and dried over anhydrous magnesium sulfate. After removing the solvent under reduced pressure, the crude material was dissolved in dichloromethane (126 mL) at 0 ºC. Pivaloyl chloride (3.1 mL, 25.3 mmol, 1.0 eq.), triethylamine (5.3 mL, 37.9 mmol, 1.5 eq.). The reaction was then quenched with saturated aqueous NaHCO3 (30 mL) and water (30 mL). The organic phase was separated, and the aqueous phase was extracted with dichloromethane (3 × 50 mL), and the combined organic extracts were washed with saturated aqueous sodium chloride solution (50 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The product was taken on without further purification (approximately 1.5 g of crude product was generated).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.3 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.42 (ddd, *J* = 8.3, 6.7, 1.3 Hz, 1H), 7.38 – 7.33 (m, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 6.65 (d, *J* = 8.1 Hz, 1H), 1.43 (s, 9H).

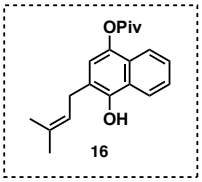


15

4-((3-methylbut-2-en-1-yl)oxy)naphthalen-1-yl pivalate (15):

Impure compound **14** (1.0 g, 4.1 mmol, 1.0 eq.) was dissolved in degassed DMF (41 mL). bromide (0.71 mL, 6.1 mmol, 1.5 eq.) was added dropwise followed by finely ground K_2CO_3 (0.57 g, 4.1 mmol, 1.0 eq.). The reaction was monitored until full consumption of the starting materials was observed. The reaction was quenched with water (82 mL) and extracted with ether (3 X 100 mL). The title compound was purified by flash chromatography (SiO_2: gradient of hexanes and ethyl acetate). (821.2 mg, 64% yield, 2.6 mmol)

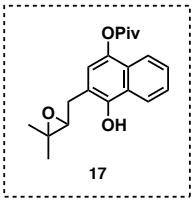
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.36 – 8.22 (m, 1H), 7.82 – 7.71 (m, 1H), 7.59 – 7.40 (multiple peaks, 2H), 7.08 (d, *J* = 8.2 Hz, 1H), 6.78 (d, *J* = 8.3 Hz, 1H), 5.61 (ddq, *J* = 6.7, 5.1, 1.4 Hz, 1H), 4.69 (d, *J* = 6.6 Hz, 2H), 1.83 (s, 3H), 1.78 (s, 3H), 1.49 (s, 9H).



4-hydroxy-3-(3-methylbut-2-en-1-yl)naphthalen-1-yl pivalate (16):

Compound **15** (452 mg, 1.45 mmol, 1.0 eq.) was dissolved in dry, degassed MeCN (14.5 mL). $Bi(OTf)_3$ (48 mg, 0.072 mmol, 0.050 eq.) was added as a solid. The reaction was stirred at room temperature and monitored until full consumption of the starting materials was observed. The reaction was quenched with silica gel and concentrated under reduced pressure. The title compound was purified by flash chromatography (SiO_2: gradient of hexanes and ethyl acetate). (328 mg, 73% yield, 1.05 mmol)

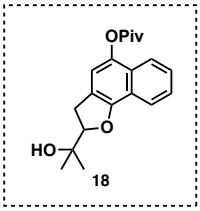
^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.19 – 8.14 (m, 1H), 7.75 – 7.69 (m, 1H), 7.49 – 7.43 (multiple peaks, 2H), 6.96 (s, 1H), 5.79 (s, 1H), 5.41 (tt, *J* = 7.2, 1.4 Hz, 1H), 3.50 (d, *J* = 7.2 Hz, 2H), 1.86 (s, 3H), 1.82 (s, 3H), 1.48 (s, 9H).



3-((3,3-dimethyloxiran-2-yl)methyl)-4-hydroxynaphthalen-1-yl pivalate (17):

Compound **16** (100 mg, 0.32 mmol, 1.0 eq.) was dissolved in dichloromethane (3.2 mL). Meta-chloroperoxybenzoic acid (79 mg, 0.35 mmol, 1.1 eq., 77 wt%) was added as a solid and stirred at room temperature until complete consumption of the starting material was observed. The reaction was concentrated under reduced pressure and the title compound was purified by flash chromatography (SiO_2: gradient of hexanes and ethyl acetate). (14.1 mg, 13% yield, 43 mmol)

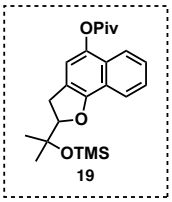
^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.29 (d, *J* = 6.5 Hz, 1H), 7.91 (s, 1H), 7.76 – 7.69 (m, 1H), 7.51 – 7.45 (multiple peaks, 2H), 6.98 (s, 1H), 3.15 (t, *J* = 6.3 Hz, 1H), 3.01 (d, *J* = 6.3 Hz, 2H), 1.57 (s, 3H), 1.48 (s, 9H), 1.40 (s, 3H).



2-(2-hydroxypropan-2-yl)-2,3-dihydronaphtho[1,2-*b*]furan-5-yl pivalate (18):

Compound **17** (62 mg, 0.189 mmol, 1.0 eq.) was dissolved in tetehydrofuran (1.9 mL). K_2CO_3 (26 mg, 0.189 mmol, 1.0 eq.) was added as a solid and stirred at room temperature until complete consumption of the starting material was observed. The reaction was quenched with silica gel and concentrated under reduced pressure. The title compound was purified by flash chromatography (SiO_2: gradient of hexanes and ethyl acetate). (53 mg, 82% yield, 0.155 mmol)

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.04 – 7.90 (m, 1H), 7.83 – 7.68 (m, 1H), 7.54 – 7.37 (multiple peaks, 2H), 7.06 (s, 1H), 4.81 (dd, J = 9.7, 8.9 Hz, 1H), 3.42 – 3.22 (multiple peaks, 2H), 1.49 (s, 9H), 1.40 (s, 3H), 1.26 (s, 3H).

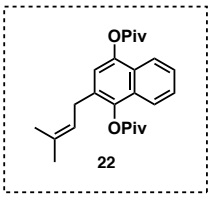


2-(2-((trimethylsilyl)oxy)propan-2-yl)-2,3-dihydronaphtho[1,2-*b*]furan-5-yl pivalate (19):

Compound **18** (12.6 mg, 0.038 mmol, 1.0 eq.) was dissolved in dichloromethane (0.38 mL). Imidazole (7.8 mg, 0.115 mmol, 3.0 eq.) and trimethylchlorosilane (10 uL, 0.077 mmol, 2 eq.) were added and stirred until complete consumption of the starting material was observed. The reaction was loaded onto silica gel and concentrated under reduced pressure. The title compound was purified by flash chromatography (SiO_2: gradient of hexanes and ethyl acetate). (8.2 mg, 53% yield, 0.020 mmol)

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.98 – 7.91 (m, 1H), 7.77 – 7.69 (m, 1H), 7.48 – 7.38 (multiple peaks, 2H), 7.05 (s, 1H), 4.75 (dd, J = 9.8, 8.0 Hz, 1H), 3.32 (qd, J = 15.8, 8.9 Hz, 2H), 1.48 (s, 9H), 1.37 (s, 3H), 1.29 (s, 3H), 0.09 (s, 9H).

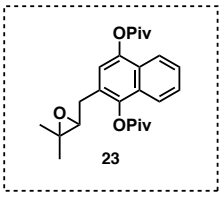
3-6. Revised route to perilloxin



2-(3-methylbut-2-en-1-yl)naphthalene-1,4-diyl bis(2,2-dimethylpropanoate) (22):

Compound **16** (235 mg, 0.752 mmol, 1.0 eq.) was dissolved in dichloromethane (7.5 mL). Pivaloyl chloride (0.10 mL, 0.827 mmol, 1.1 eq.) and triethylamine (0.16 mL, 1.1 mmol, 1.5 eq.) were added and the mixture was stirred at room temperature until complete consumption of the starting material was observed. The reaction was concentrated under reduced pressure and purified by flash chromatography (SiO_2: gradient of hexanes and ethyl acetate). (180 mg, 60%, 0.454 mmol)

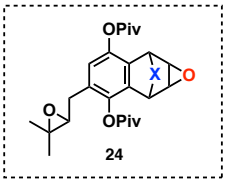
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.55 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.34 (td, *J* = 7.9, 1.4 Hz, 2H), 6.92 (s, 1H), 5.17 – 5.08 (m, 1H), 3.23 – 3.14 (m, 2H), 1.60 (d, *J* = 1.6 Hz, 3H), 1.57 (d, *J* = 1.4 Hz, 3H), 1.34 (s, 18H).



2-((3,3-dimethyloxiran-2-yl)methyl)naphthalene-1,4-diyl bis(2,2-dimethylpropanoate) (23):

Compound **22** (200 mg, 0.50 mmol, 1.0 eq.) was dissolved in dichloromethane (5.0 mL). Meta-chloroperoxybenzoic acid (113 mg, 0.50, 1.0 eq., 77 wt%) was added as a solid and stirred until complete consumption of the starting material was observed. The reaction was concentrated on silica gel under reduced pressure and purified by flash chromatography (SiO_2: gradient of hexanes and ethyl acetate). (73mg, 35% yield, 0.177 mmol)

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.88 – 7.81 (m, 1H), 7.74 – 7.68 (m, 1H), 7.56 – 7.46 (multiple peaks, 2H), 7.22 (s, 1H), 3.02 (t, *J* = 6.0 Hz, 1H), 2.95 – 2.80 (multiple peaks, 2H), 1.53 (s, 9H), 1.49 (s, 9H), 1.40 (s, 3H), 1.34 (s, 3H).

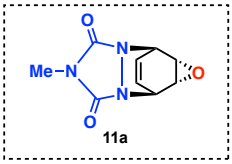


24

7-((3,3-dimethyloxiran-2-yl)methyl)-2-methyl-1,3-dioxo-2,3,5,10-tetrahydro-1*H*-5,10-[2,3]epoxireno[1,2,4]triazolo[1,2-*b*]phthalazine-6,9-diyl bis(2,2-dimethylpropanoate) (24):

Compound **23** was obtained using general procedure B described above. The title compound was purified by flash chromatography (SiO_2: gradient of hexanes and ethyl acetate). (52 mg, 34% yield, 0.097 mmol)

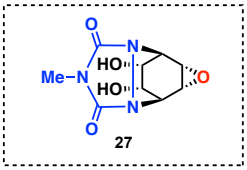
3-7. Route to fortimicin A



11a

5-methyl-1a,2,8,8a-tetrahydro-4*H*-2,8-ethenooxireno[2,3-*d*][1,2,4]triazolo[1,2-*a*]pyridazine-4,6(5*H*)-dione (11a):

The title compound was synthesized using the general procedure described in section **3-3**.

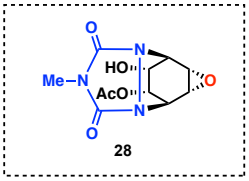


27

9,10-dihydroxy-5-methyltetrahydro-4*H*-2,8-ethanooxireno[2,3-*d*][1,2,4]triazolo[1,2-*a*]pyridazine-4,6(5*H*)-dione (27):

Compound **26** (10.0 mg, 0.50 mmol, 1.0 eq.) and 4-methylmorpholine N-oxide (11.0 mg, 0.10 mmol, 2.0 eq.) were dissolved in acetone (0.50 mL) and water (17 µL, 1.0 mmol, 20 eq.). To this solution was dropwise added osmium tetroxide (12 µL, 0.2 M solution in acetonitrile, 0.005 mmol, 5.0 mol%) and the resulting solution was stirred at room temperature until complete consumption of the starting material. Then the reaction was quenched with sodium thiosulfate and concentrated on SiO_2 gel. The title compound was isolated by flash chromatography (SiO_2: gradient of CH_2Cl_2 and MeOH). (8.2 mg, 70% yield, 0.034 mmol)

^{1}H NMR: (500 MHz, CD_3OD) δ 4.73 (m, 2H), 4.02 (m, 2H), 3.79 (m, 2H), 3.05 (s, 3H)

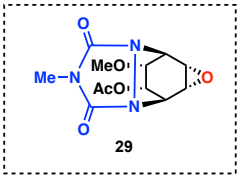


28

10-hydroxy-5-methyl-4,6-dioxohexahydro-4*H*-2,8-ethanooxireno[2,3-*d*][1,2,4]triazolo[1,2-*a*]pyridazin-9-yl acetate (28):

Compound **27** (55 mg, 0.23 mmol, 1.0 eq.) was dissolved in dichloromethane (2.3 mL). Acetic anhydride (0.022 mL, 0.23 mmol, 1.0 eq.) and triethylamine (0.047 mL, 0.34 mmol, 1.5 eq.) were added and the mixture was stirred at room temperature until complete consumption of the starting material was observed. The reaction was concentrated under reduced pressure and the title compound was purified by flash chromatography (SiO_2: gradient of CH_2Cl_2 and MeOH).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 4.96 (dd, J = 8.0, 2.4 Hz, 1H), 4.92 – 4.87 (m, 1H), 4.86 – 4.78 (m, 1H), 4.29 (dd, J = 8.0, 2.6 Hz, 1H), 3.75 (multiple peaks, 2H), 3.11 (s, 3H), 2.08 (s, 3H), 1.99 (s, 3H)



29

10-methoxy-5-methyl-4,6-dioxohexahydro-4*H*-2,8-ethanooxireno[2,3-*d*][1,2,4]triazolo[1,2-*a*]pyridazin-9-yl acetate (29):

Compound **28** (50 mg, 0.18 mmol, 1.0 eq.) was dissolved in DMF (0.90 mL) and added dropwise to a suspension of NaH (8.5 mg, 0.21 mmol, 1.2 eq.) in DMF (0.90 mL) at 0 °C. After addition was complete, methyl iodide (0.018 mL, 0.28 mmol, 1.6 eq.) was added quickly and stirred at room temperature until complete consumption of the starting material was observed. The reaction was quenched at 0 °C with methanol. The title compound was purified by flash chromatography (SiO_2: gradient of CH_2Cl_2 and MeOH; a limited amount of pure CH_2Cl_2 was first flushed through the column to remove residual DMF).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 4.99 (dd, J = 8.1, 2.3 Hz, 1H), 4.91 (dd, J = 4.7, 2.5 Hz, 1H), 4.84 (dd, J = 4.7, 2.3 Hz, 1H), 3.77 (multiple peaks, 2H), 3.72 (dd, J = 8.1, 2.4 Hz, 1H), 3.29 (s, 3H), 3.09 (s, 3H), 2.02 (s, 3H)

4. References

(1) Breton, G. W.; Turlington, M. *Tetrahedron Lett.* **2014**, *55*, 4661.

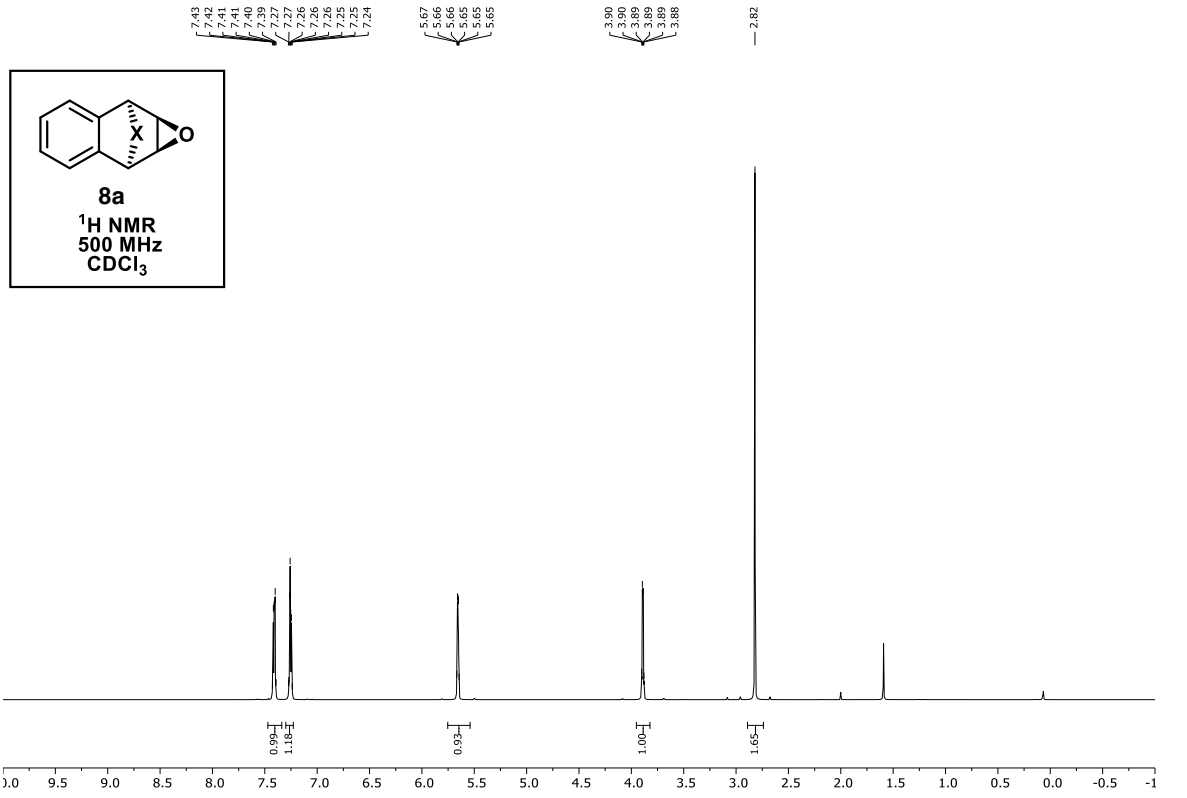
(2) Nakagawa, K.; Konaka, R.; Nakata, T. J. Org. Chem. **1962**, *27*, 1597.

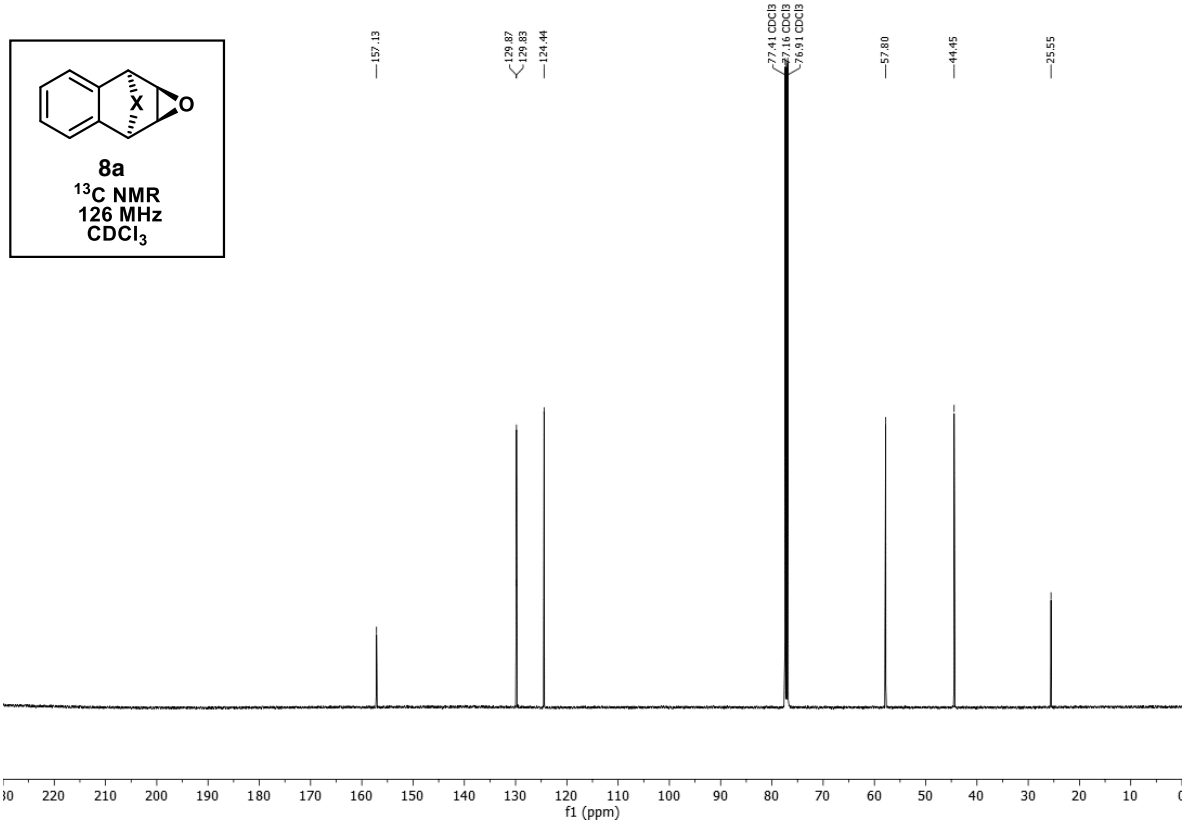
(3) Murphy, A.; Stack, T.D.P. *J. Mol. Catal.* A **2006**, *251*, 78.

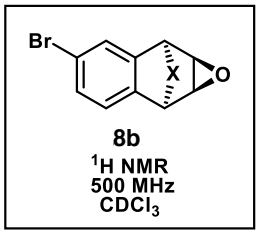
(4) Vyas, D.M.; Chiang, Y.; Doyle, T.W. *Tetrahedron Lett.* **1984**, *25*, 487.

(5) Zarate, C.; Martin, R. *J. Am. Chem. Soc.* **2014**, *136*, 2236−2239.

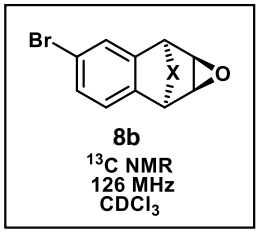
5. ^{1}H and ^{13}C NMR Spectra



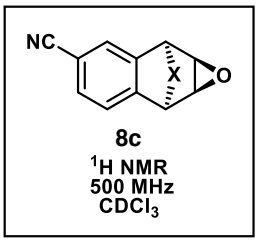




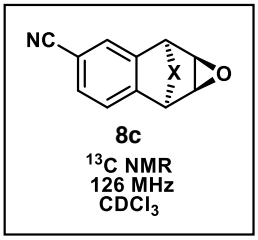
8b
^{1}H NMR
500 MHz
$CDCl_3$



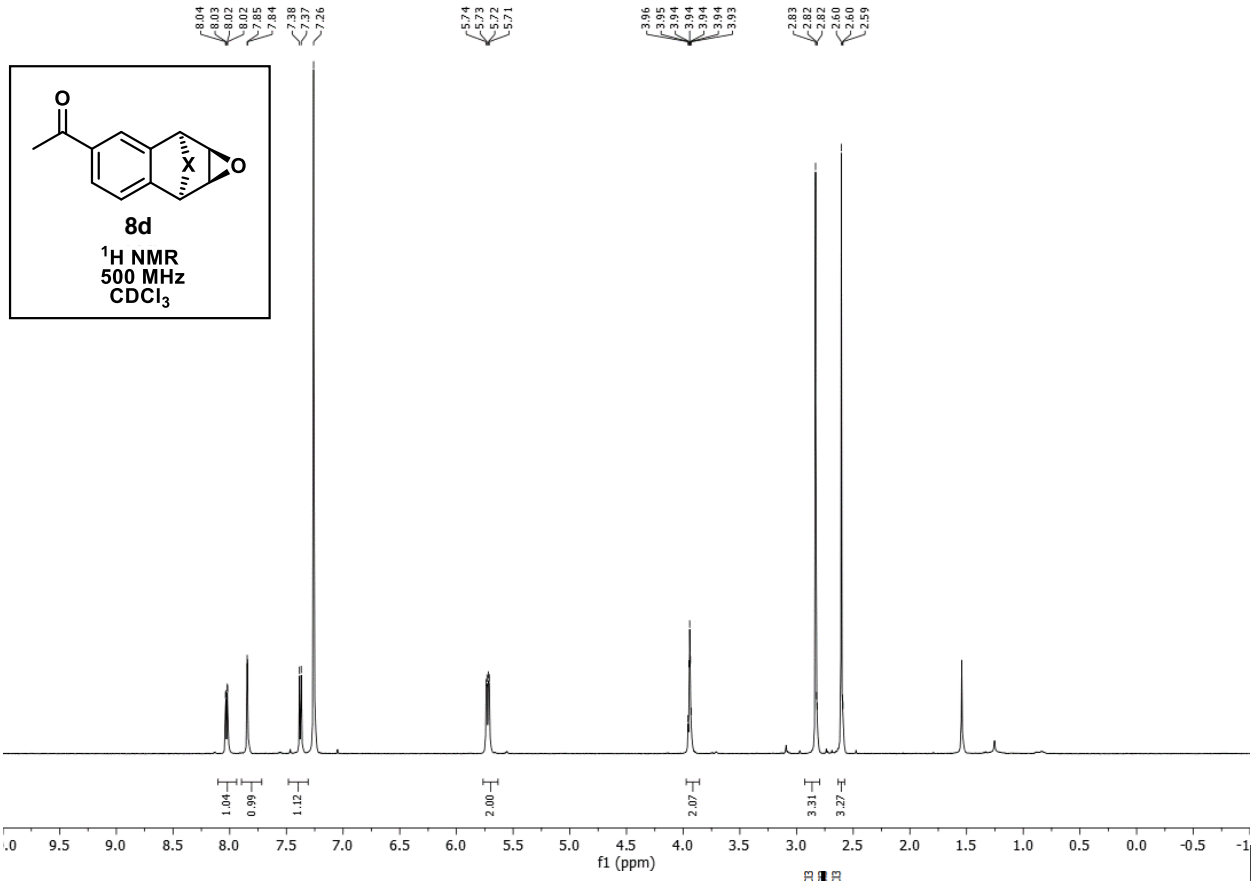
8b
^{13}C NMR
126 MHz
$CDCl_3$

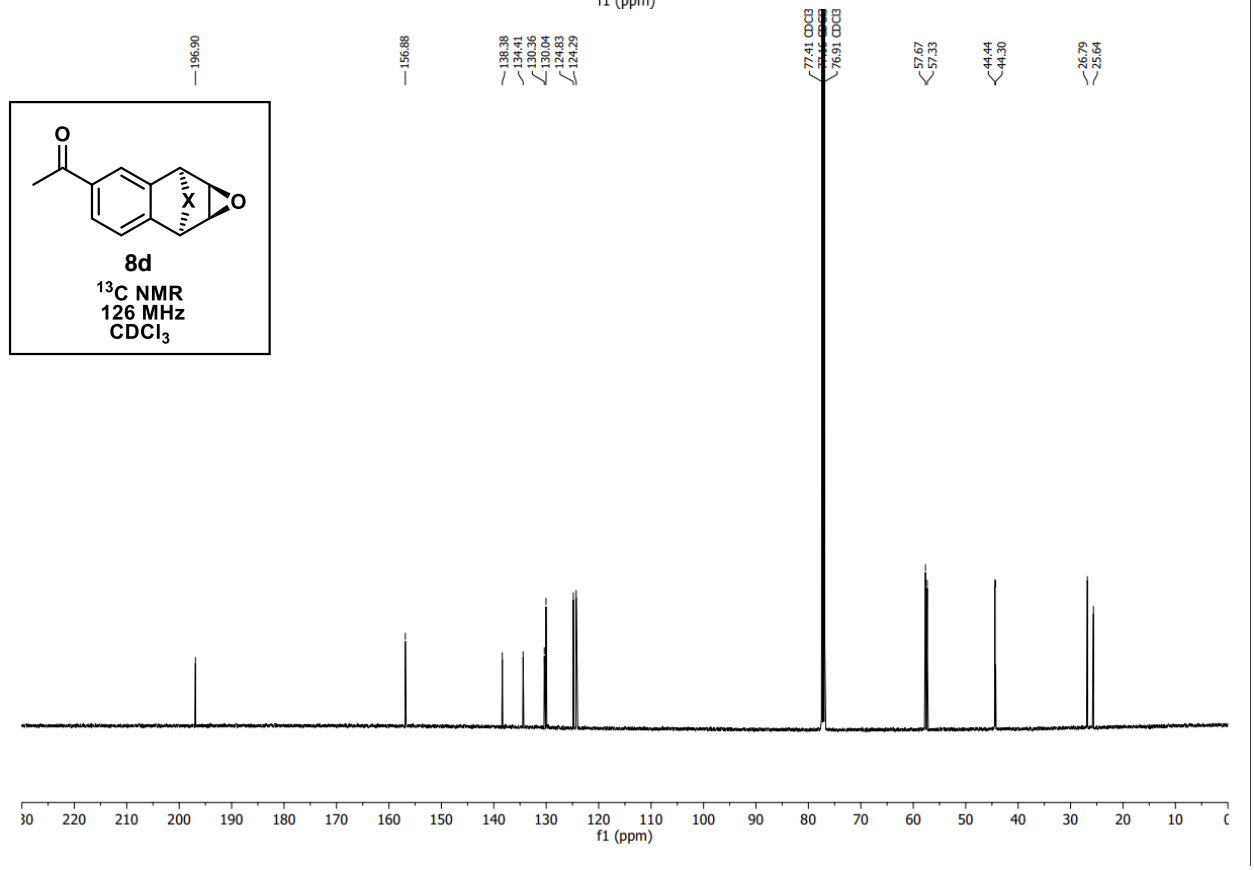


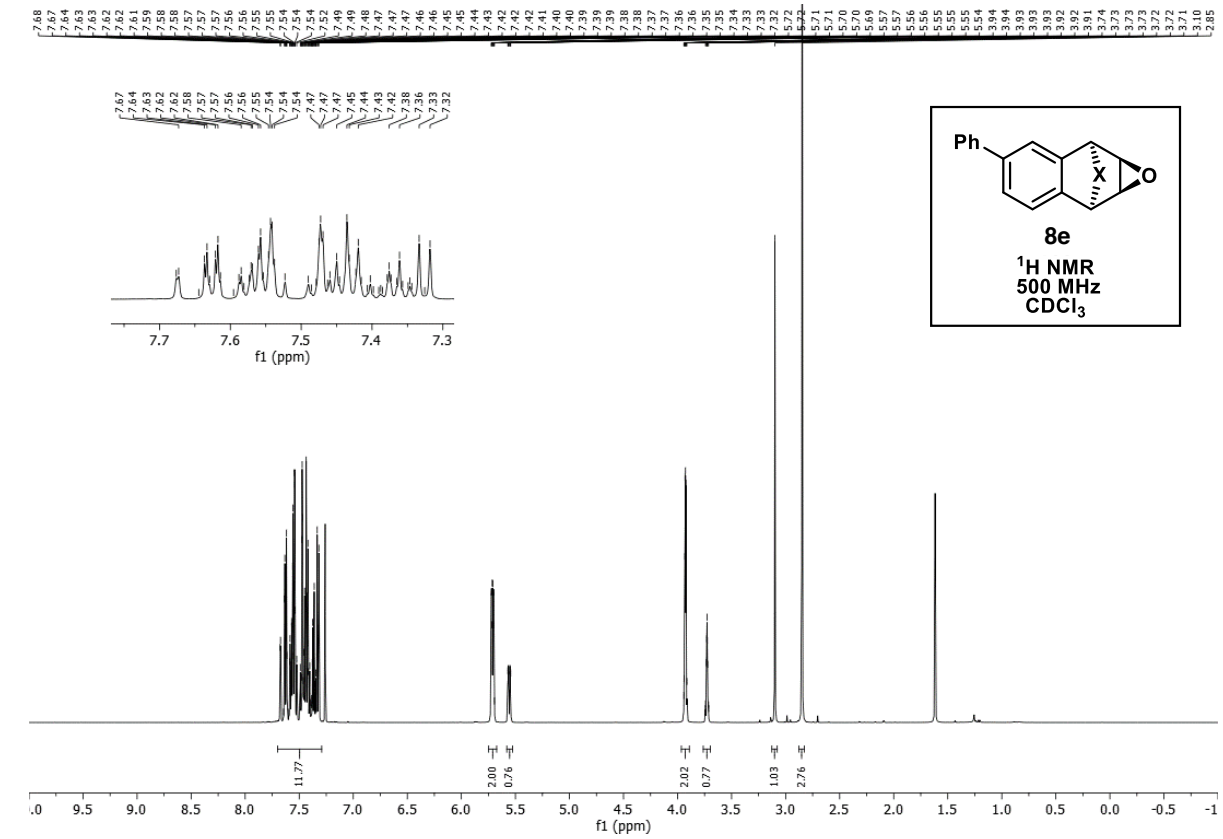
8c
^{1}H NMR
500 MHz
$CDCl_3$

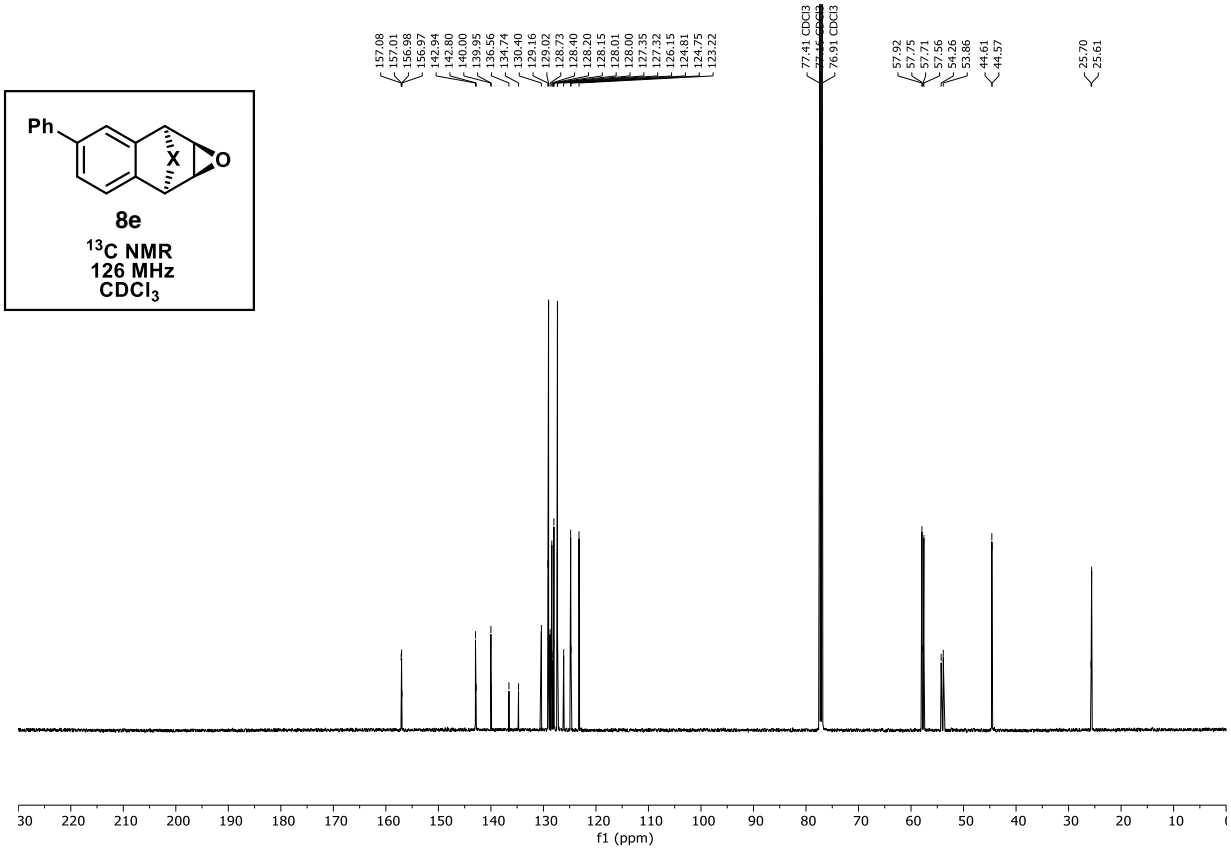


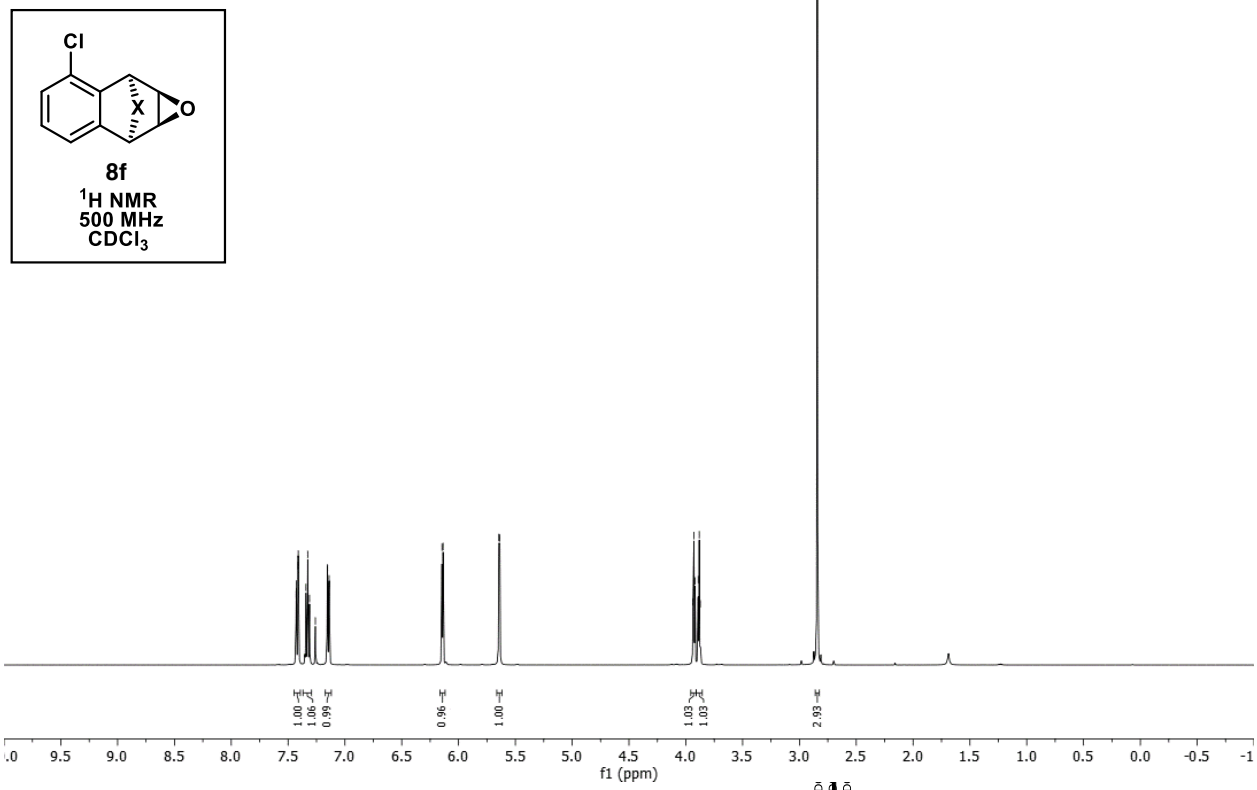
8c
^{13}C NMR
126 MHz
$CDCl_3$

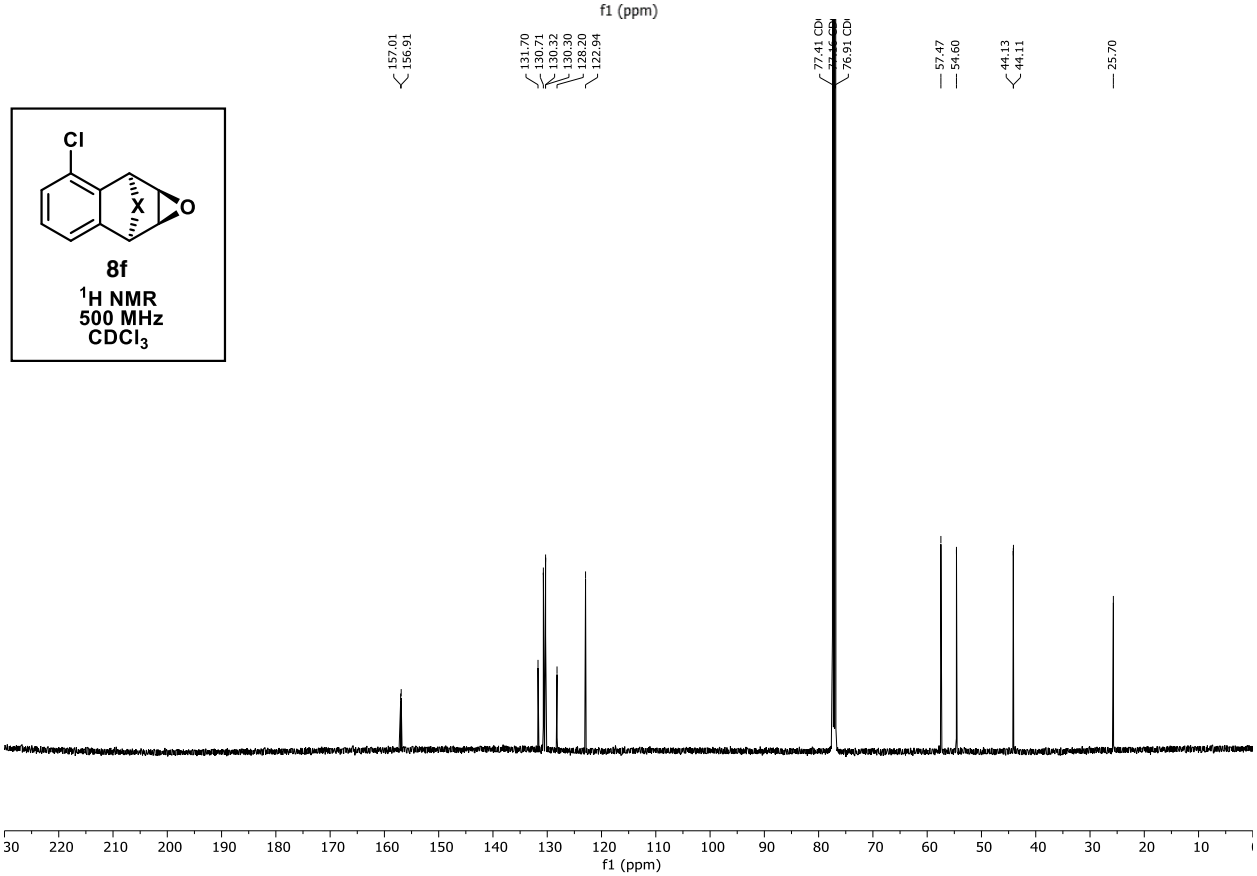

8d
1H NMR
500 MHz
CDCl3
f1 (ppm)

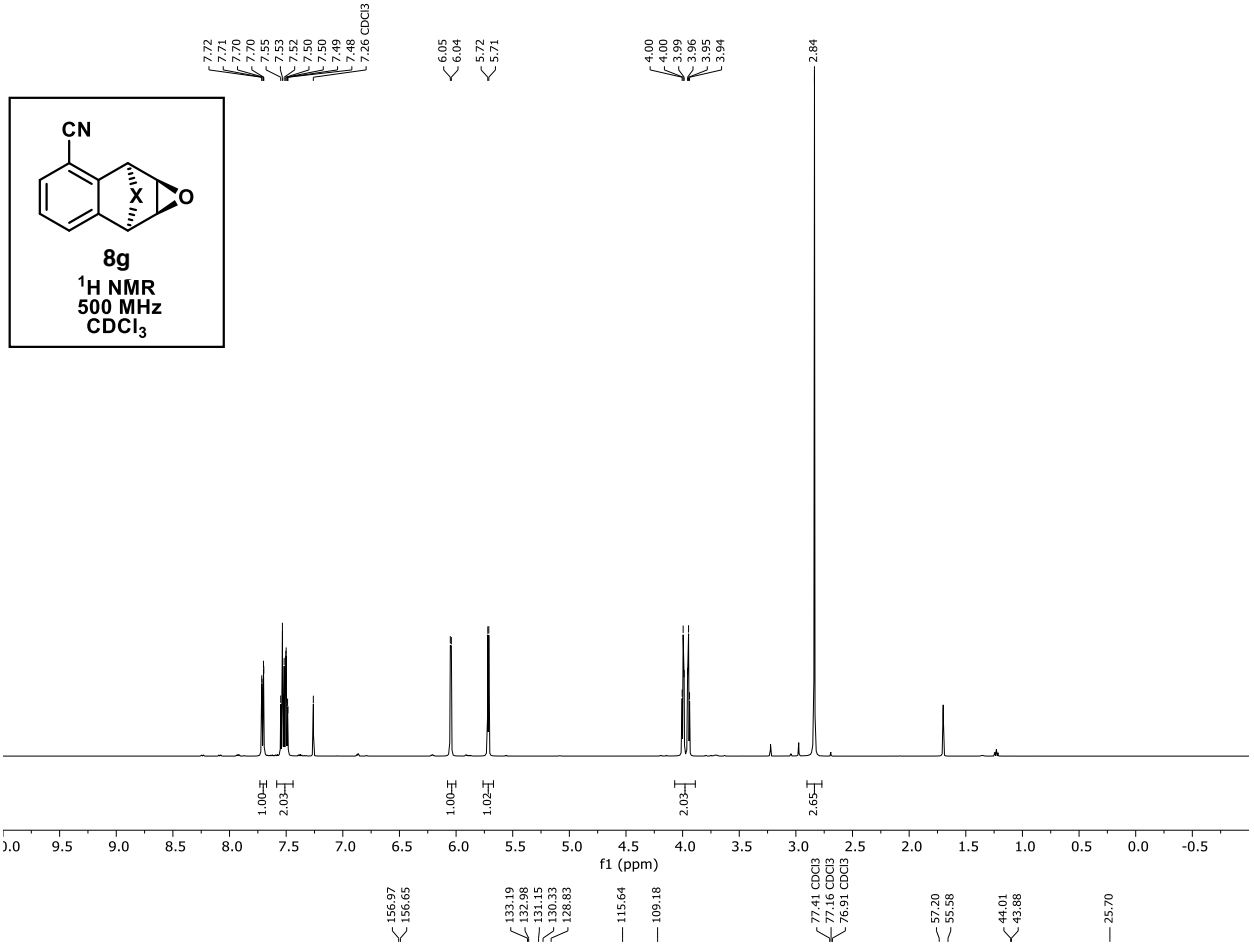

8d
13C NMR
126 MHz
CDCl3
f1 (ppm)

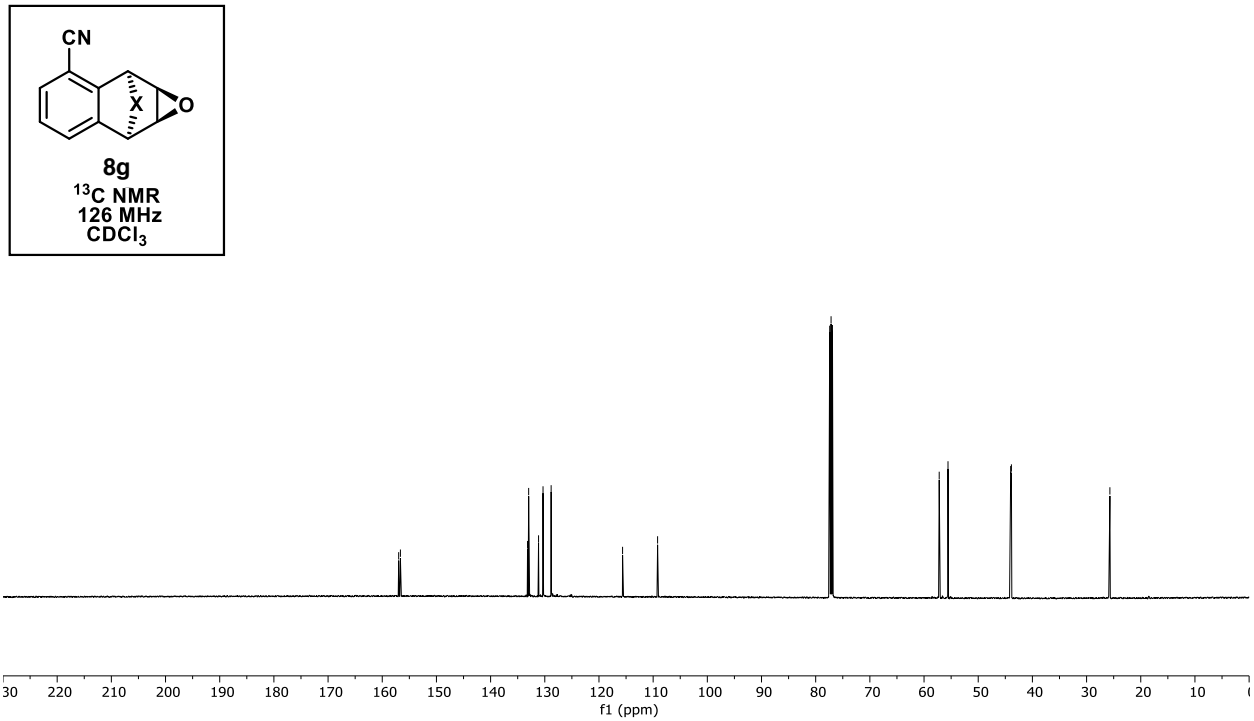

Ph
X
O
8e
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

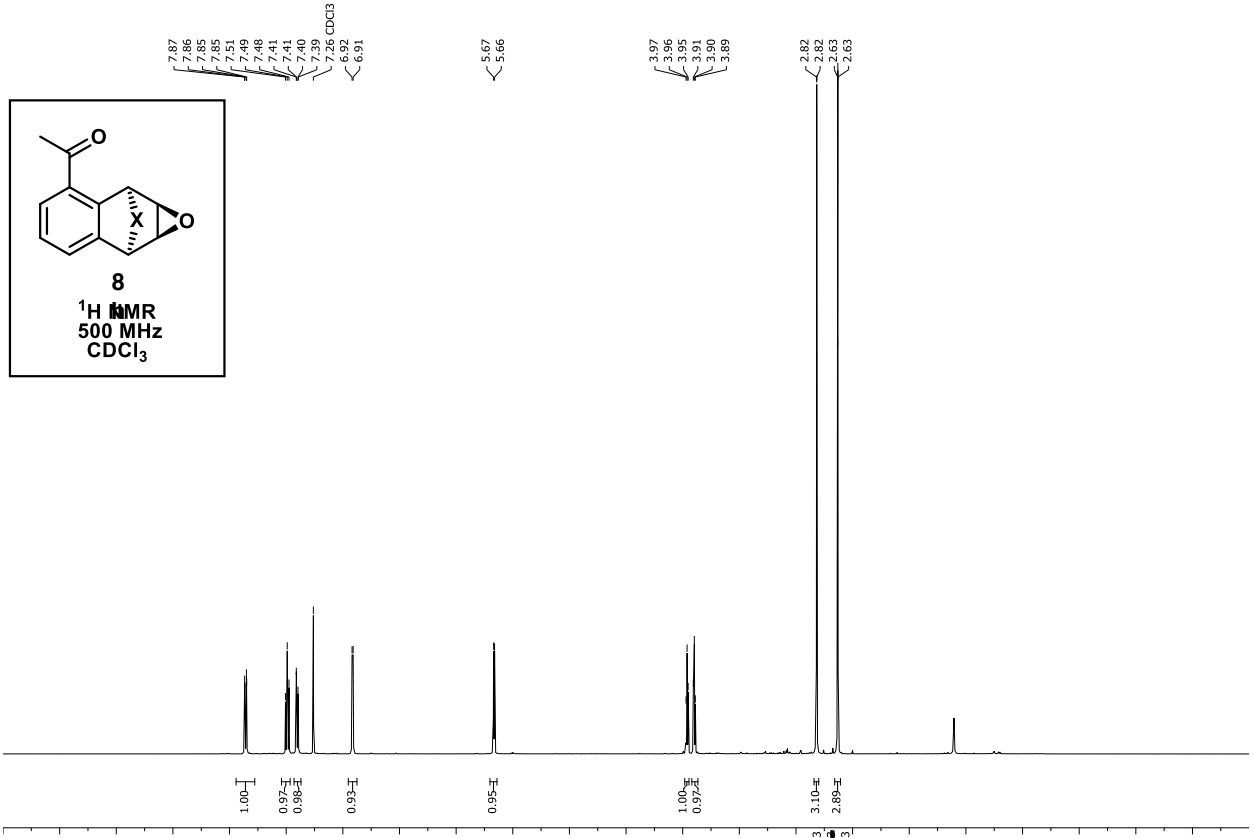

Ph
X
O
8e
^{13}C NMR
126 MHz
$CDCl_3$
f1 (ppm)

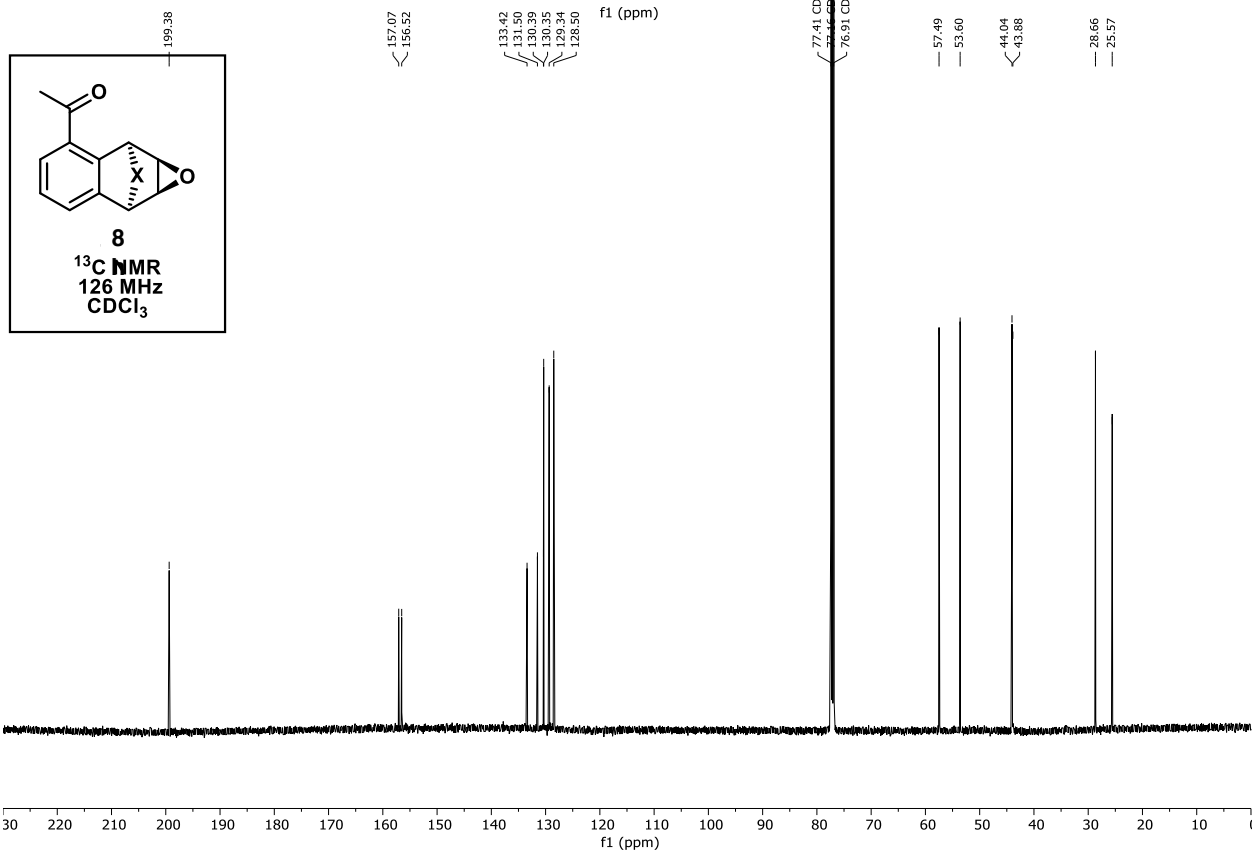

Cl
X
O
8f
1H NMR
500 MHz
CDCl3
7.43
7.43
7.41
7.41
7.34
7.33
7.31
7.26 CDCl3
7.15
7.15
7.14
7.14
6.15
6.14
5.65
5.64
3.94
3.93
3.92
3.89
3.88
3.87
2.84
1.00
1.06
0.99
0.96
1.00
1.03
1.03
2.93
f1 (ppm)

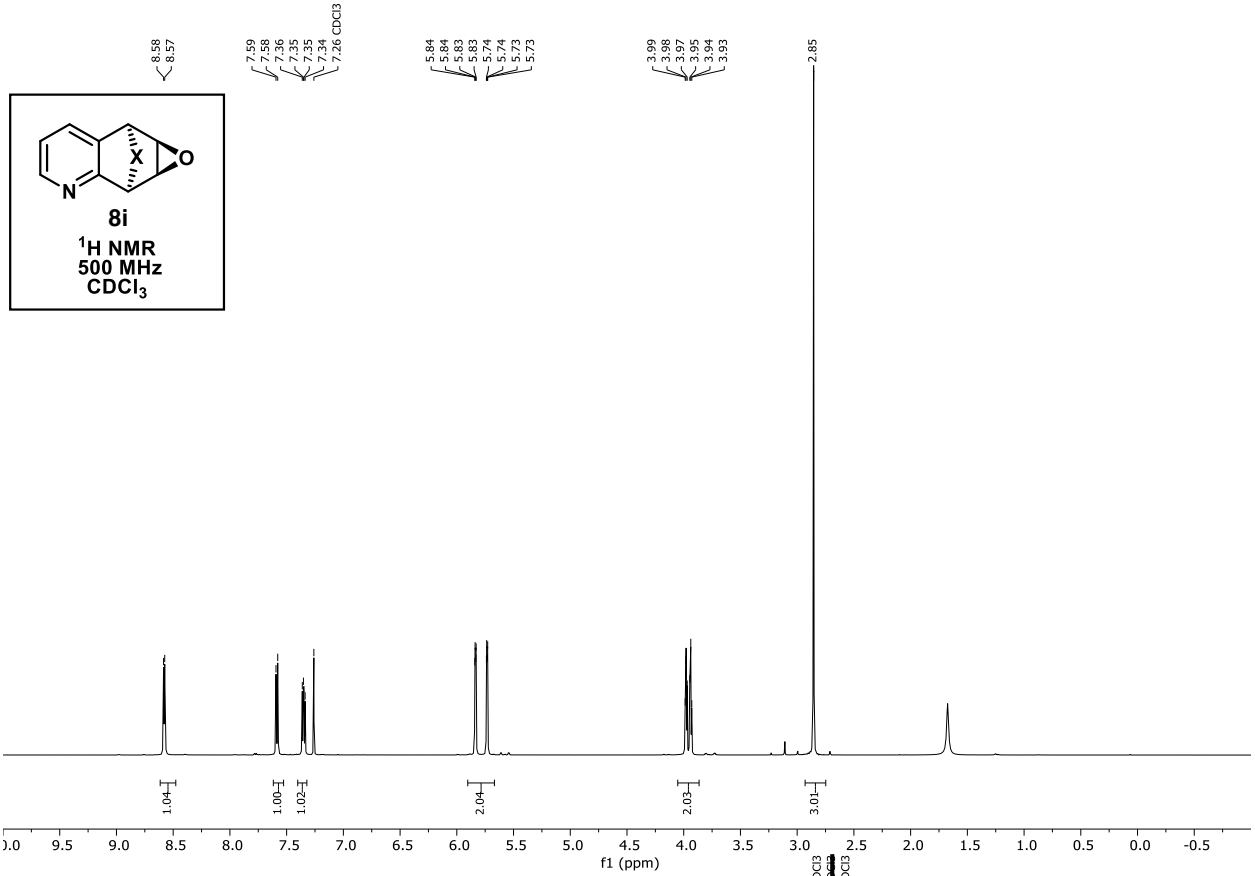

Cl
X
O
8f
1H NMR
500 MHz
CDCl3
157.01
156.91
131.70
130.71
130.32
130.30
128.20
122.94
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
57.47
54.60
44.13
44.11
25.70
f1 (ppm)

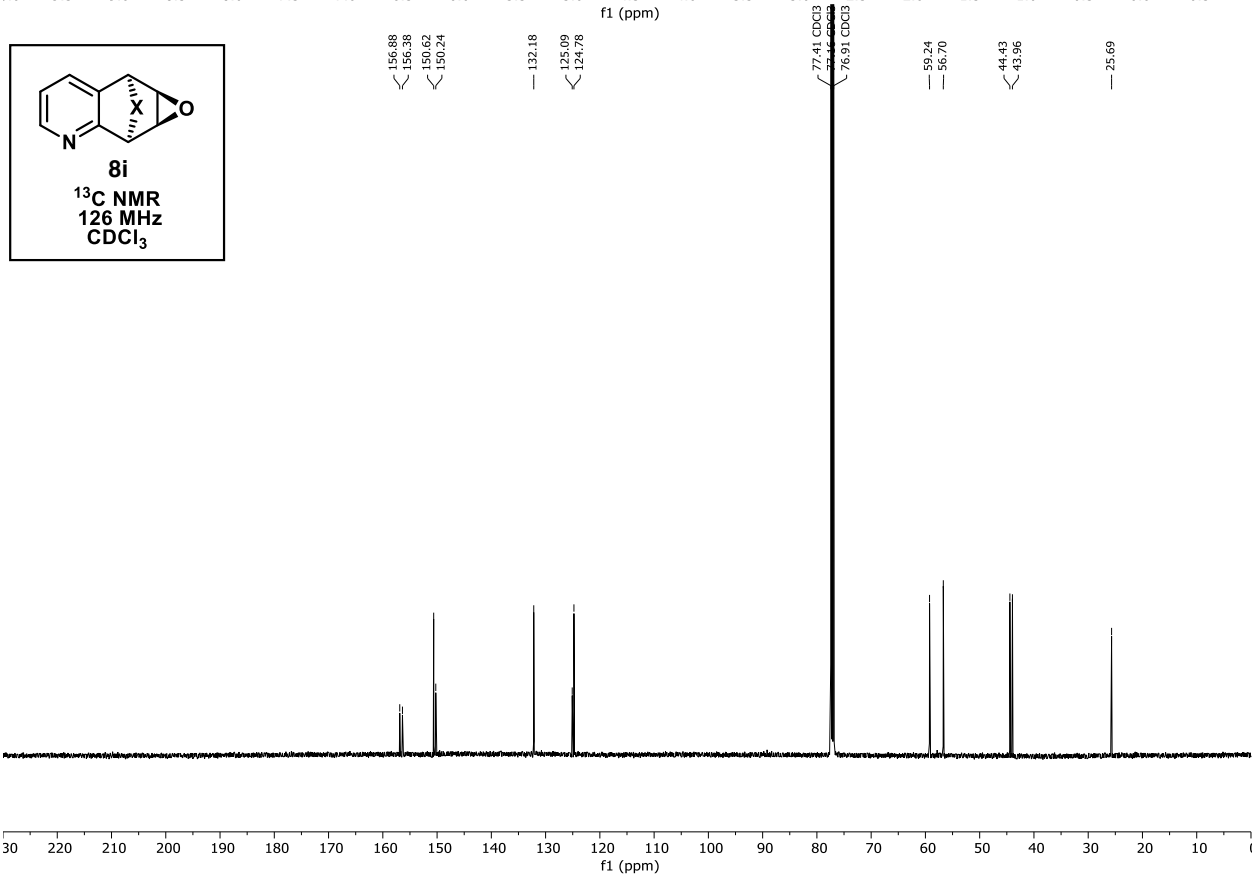

CN
X
O
8g
1H NMR
500 MHz
CDCl3
7.72
7.71
7.70
7.70
7.55
7.53
7.52
7.50
7.50
7.49
7.48
7.26 CDCl3
6.05
6.04
5.72
5.71
4.00
4.00
3.99
3.96
3.95
3.94
2.84
1.00
2.03
1.00
1.02
2.03
2.65
f1 (ppm)
156.97
156.65
133.19
132.98
131.15
130.33
128.83
115.64
109.18
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
57.20
55.58
44.01
43.88
25.70

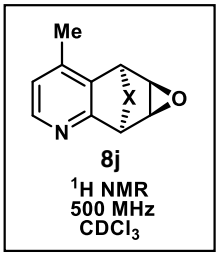

CN
X
O
8g
13C NMR
126 MHz
CDCl3
f1 (ppm)


8
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)


8
^{13}C NMR
126 MHz
$CDCl_3$
f1 (ppm)

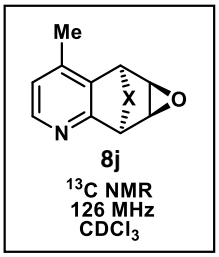

8.58
8.57
7.59
7.58
7.36
7.35
7.35
7.34
7.26 CDCl3
5.84
5.84
5.83
5.83
5.74
5.74
5.73
5.73
3.99
3.98
3.97
3.95
3.94
3.93
2.85
X
O
N
8i
1H NMR
500 MHz
CDCl3
1.04
1.00
1.02
2.04
2.03
3.01
f1 (ppm)


156.88
156.38
150.62
150.24
132.18
125.09
124.78
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
59.24
56.70
44.43
43.96
25.69
X
O
N
8i
13C NMR
126 MHz
CDCl3
f1 (ppm)



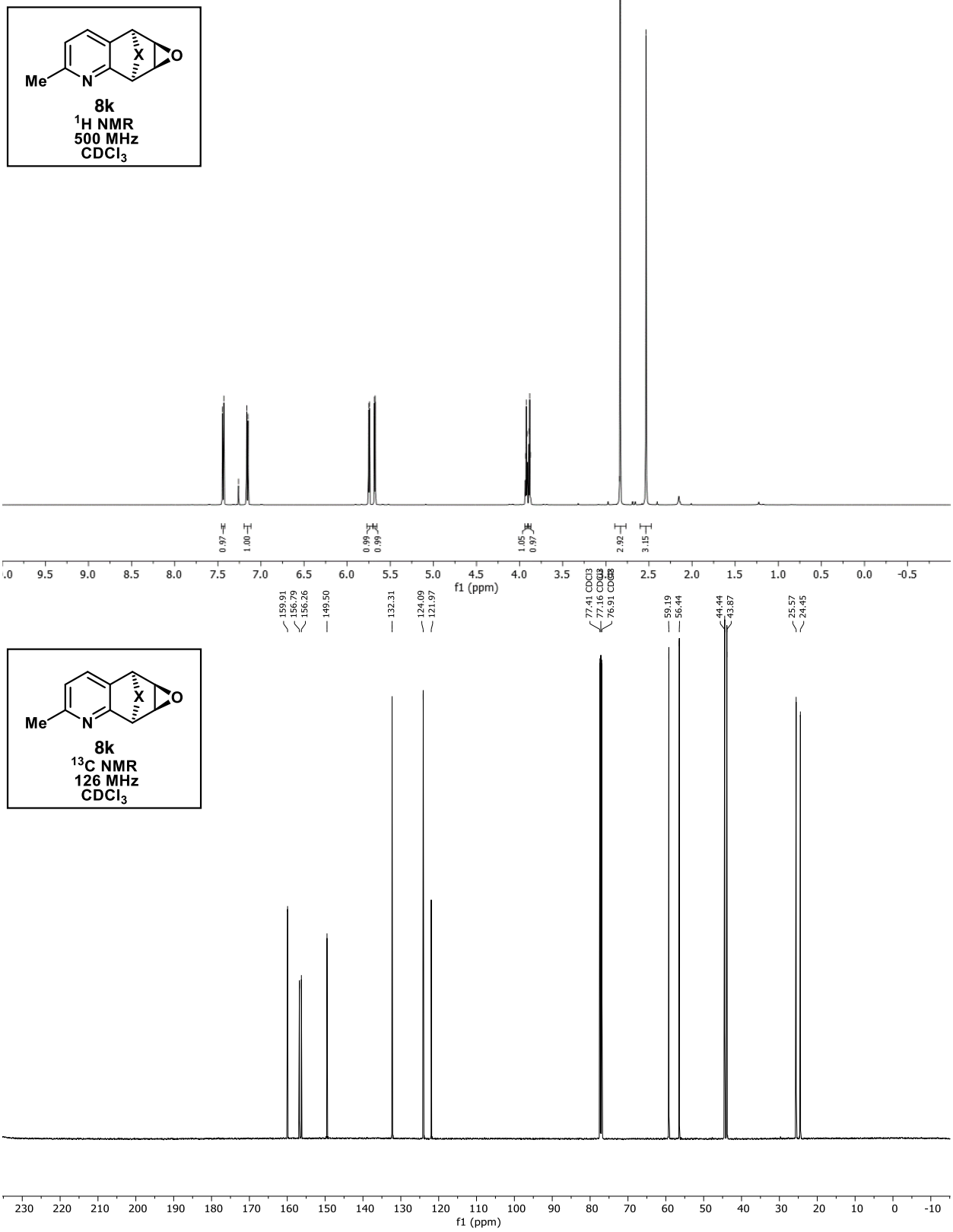
8j

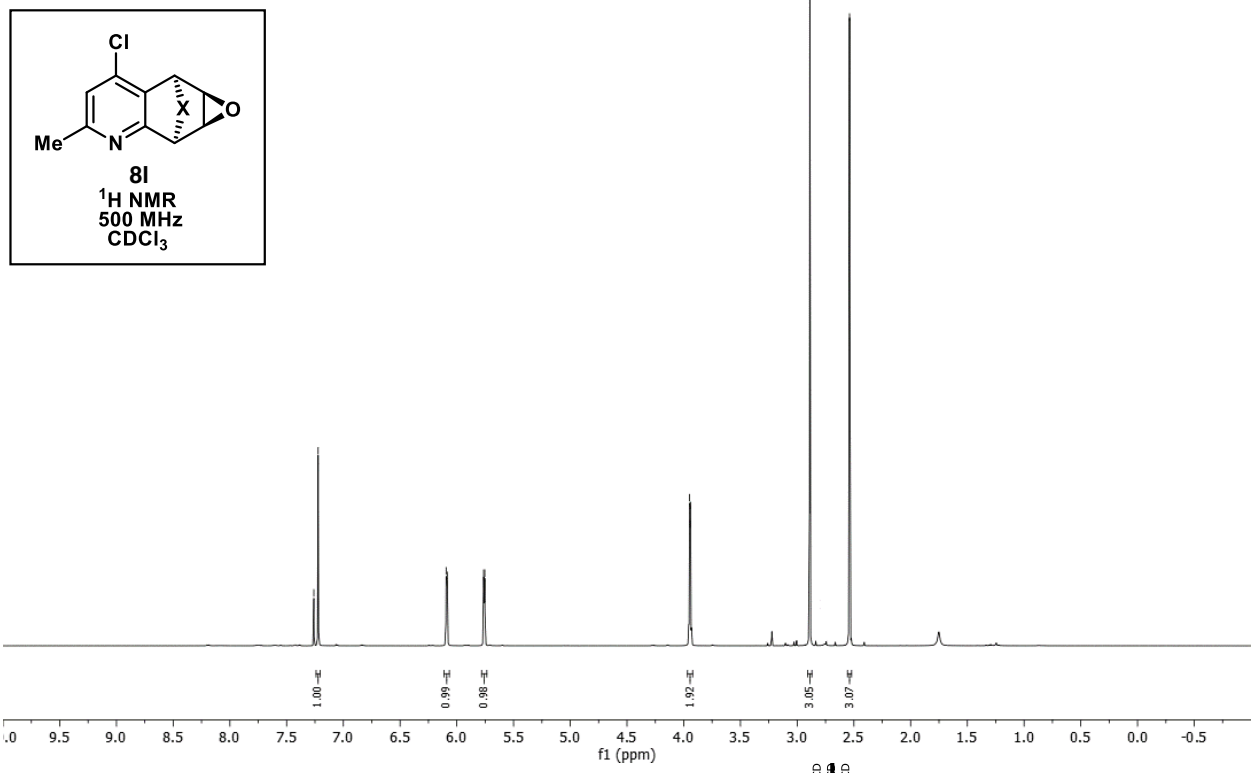
^{1}H NMR
500 MHz
$CDCl_3$

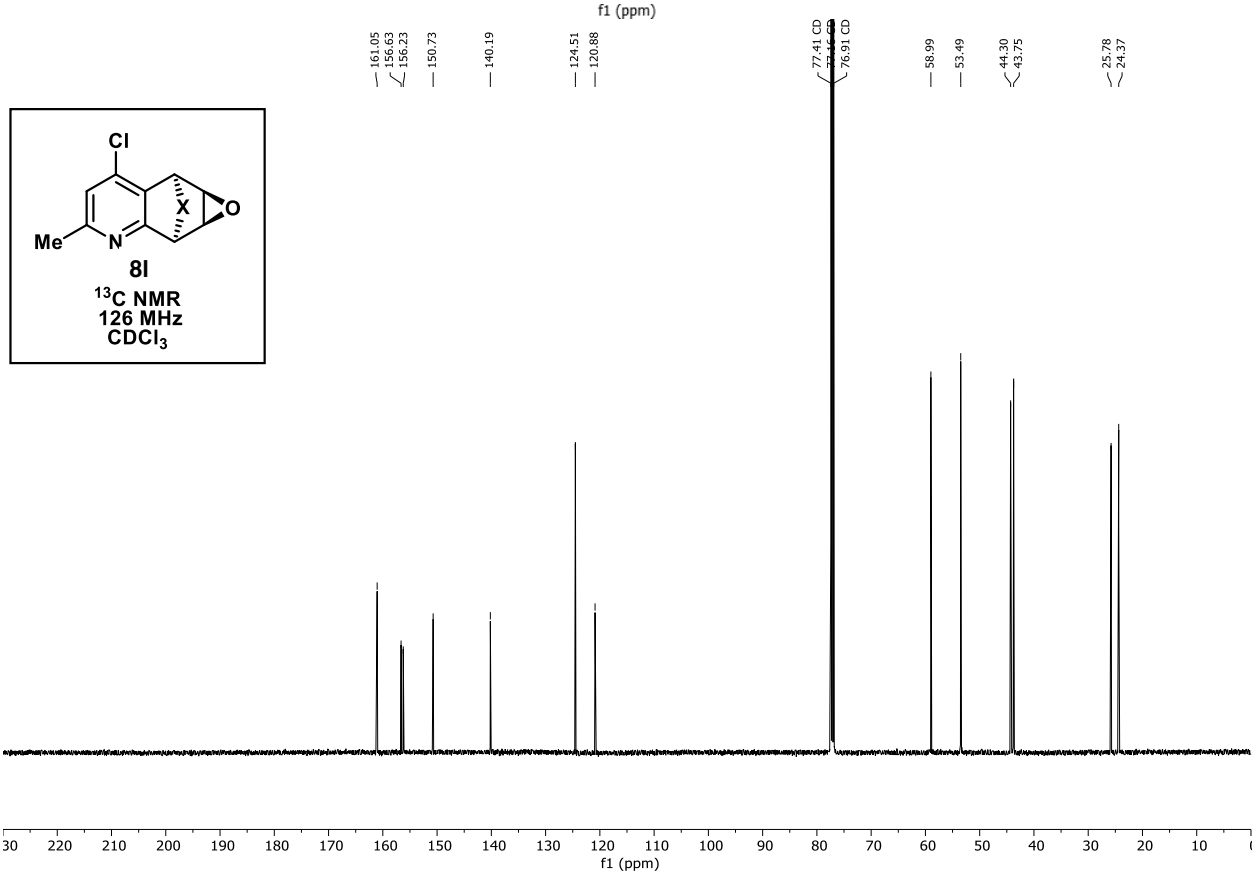


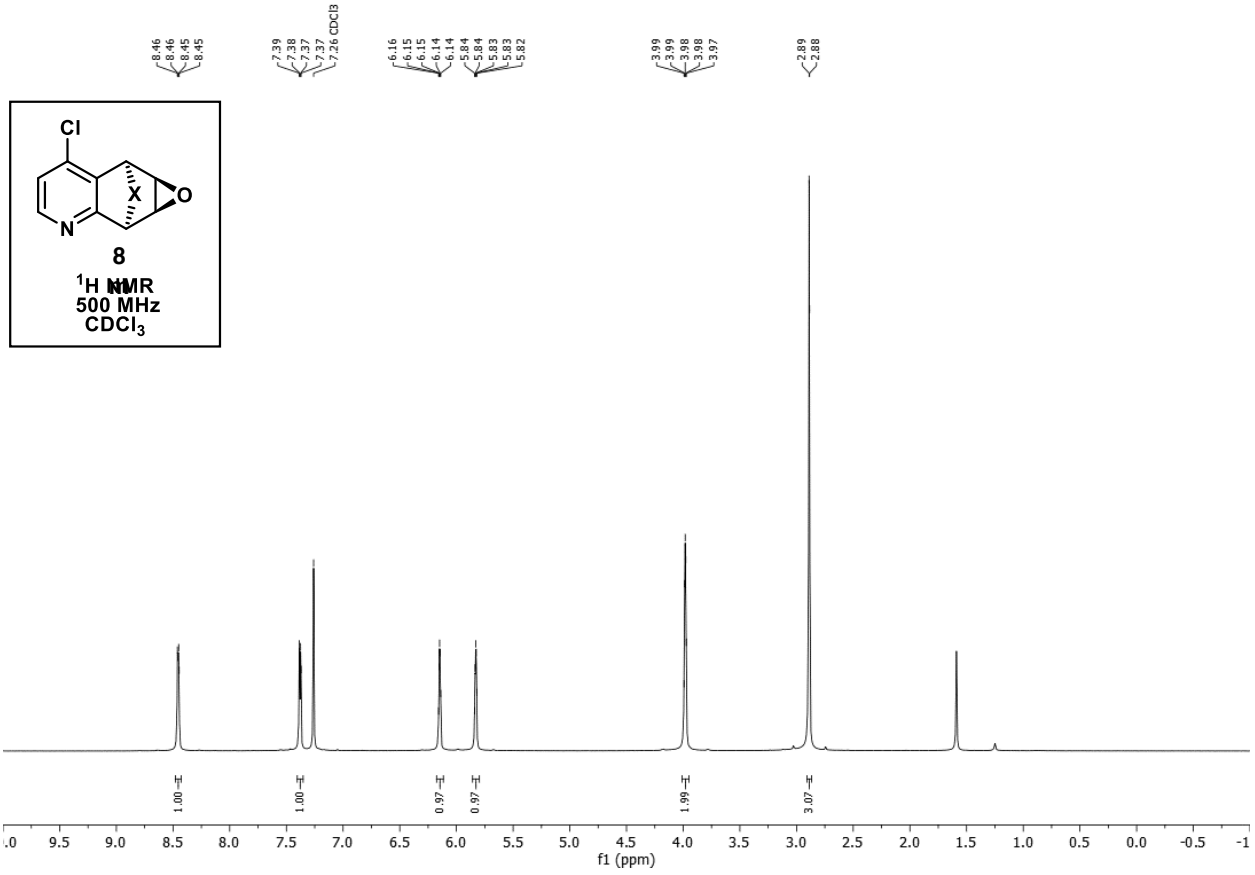
8j

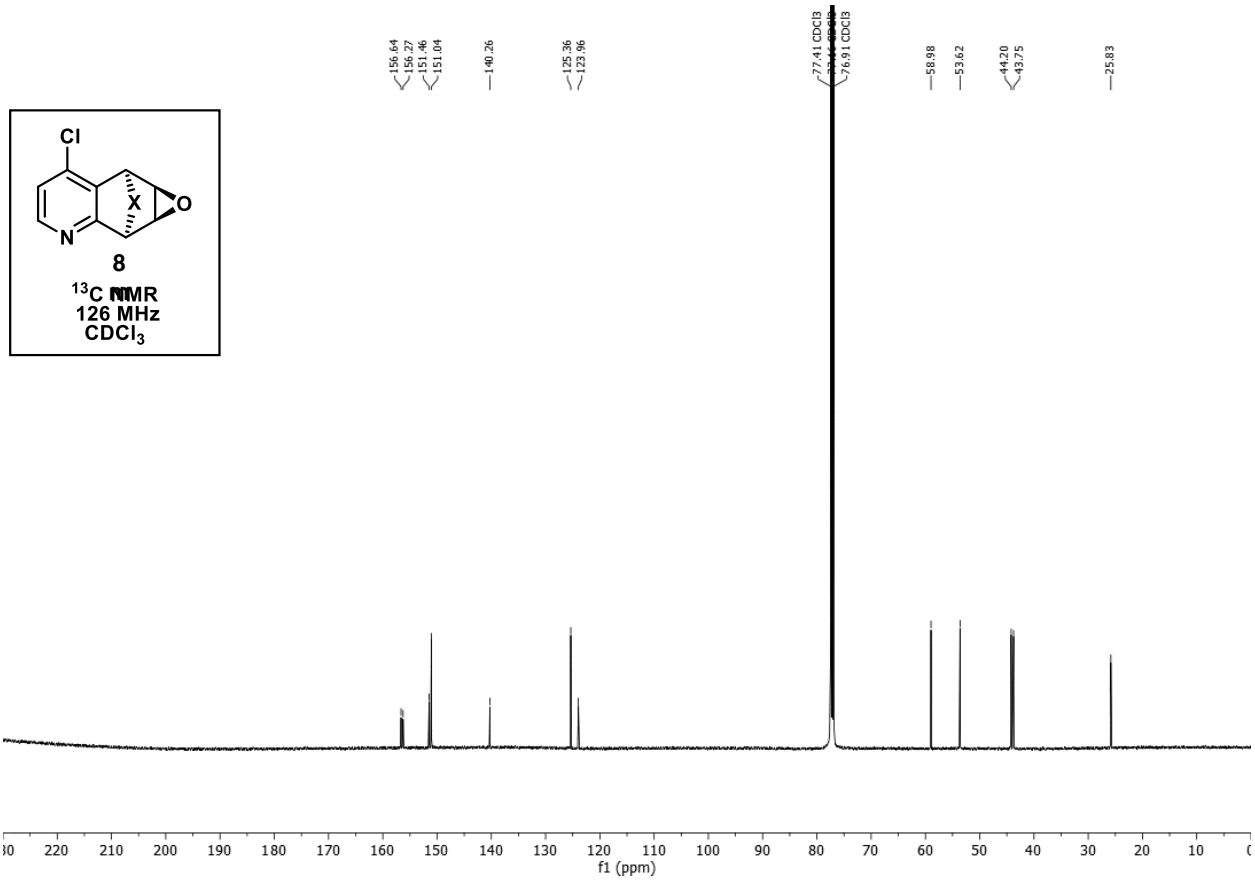
^{13}C NMR
126 MHz
$CDCl_3$

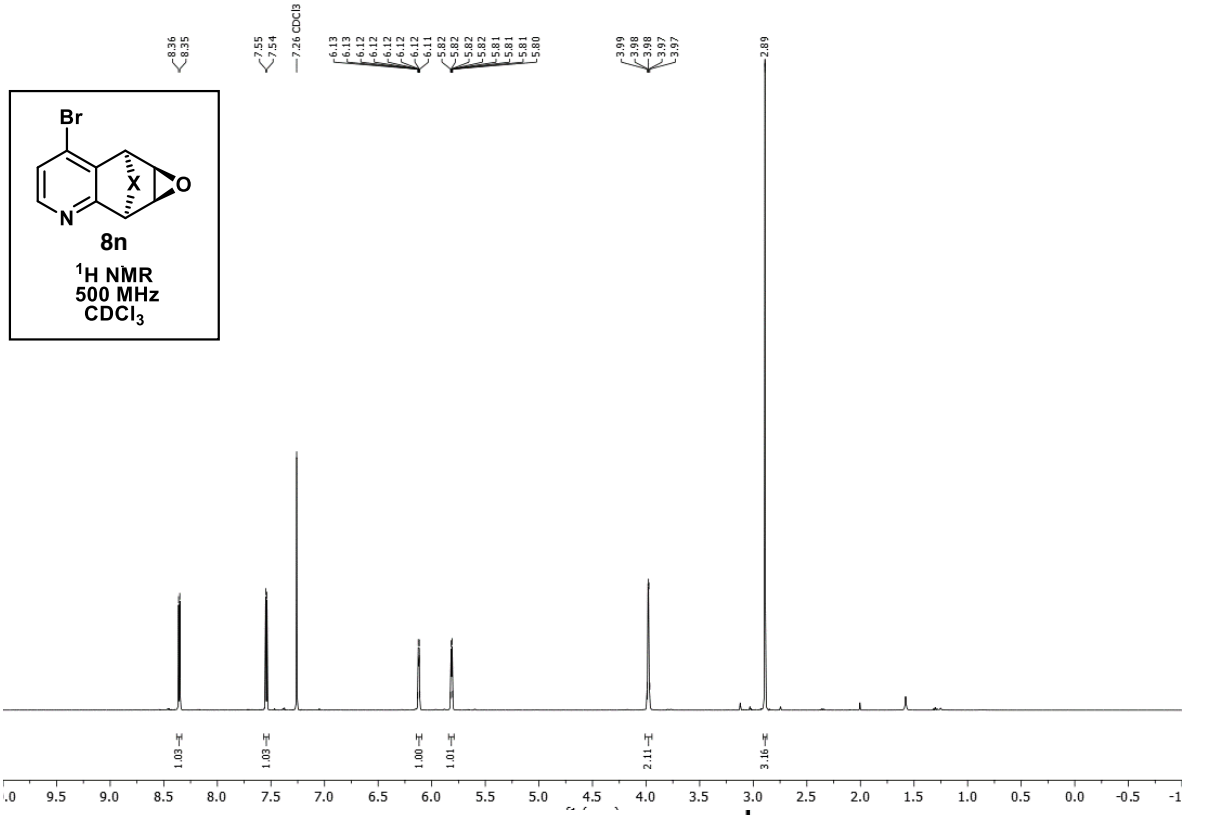

7.45
7.43
7.26 CDCl3
7.17
7.15
5.75
5.74
5.68
5.67
3.93
3.92
3.91
3.89
3.88
3.87
2.84
2.83
2.53
Me
N
X
O
8k
1H NMR
500 MHz
CDCl3
0.97
1.00
0.99
0.99
1.05
0.97
2.92
3.15
f1 (ppm)
159.91
156.79
156.26
149.50
132.31
124.09
121.97
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
59.19
56.44
44.44
43.87
25.57
24.45
8k
13C NMR
126 MHz
CDCl3
f1 (ppm)

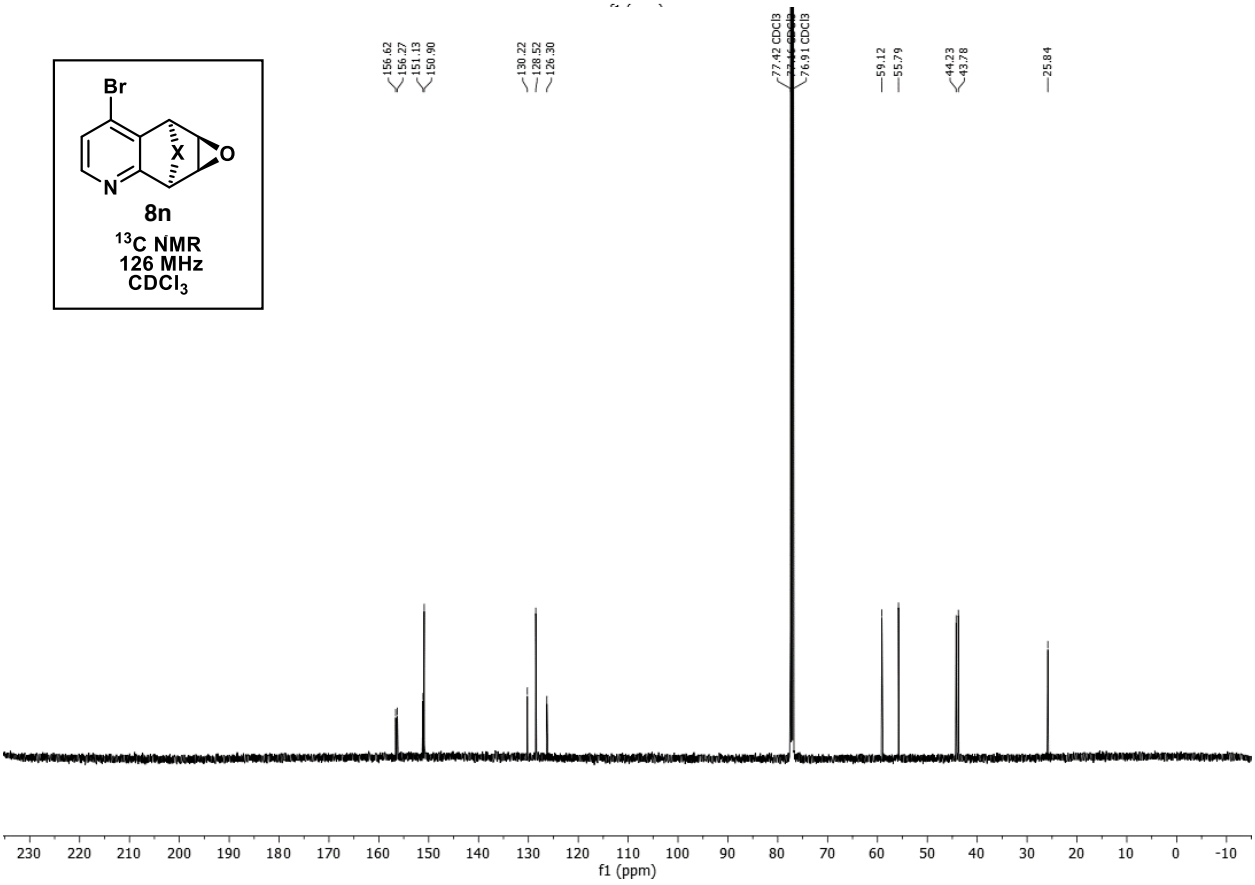

Cl
X
O
Me
N
8l
^{1}H NMR
500 MHz
$CDCl_3$
7.26 CDCl3
7.22
6.09
6.09
6.08
5.76
5.76
5.75
3.95
3.94
3.94
2.89
2.54
1.00
0.99
0.98
1.92
3.05
3.07
f1 (ppm)

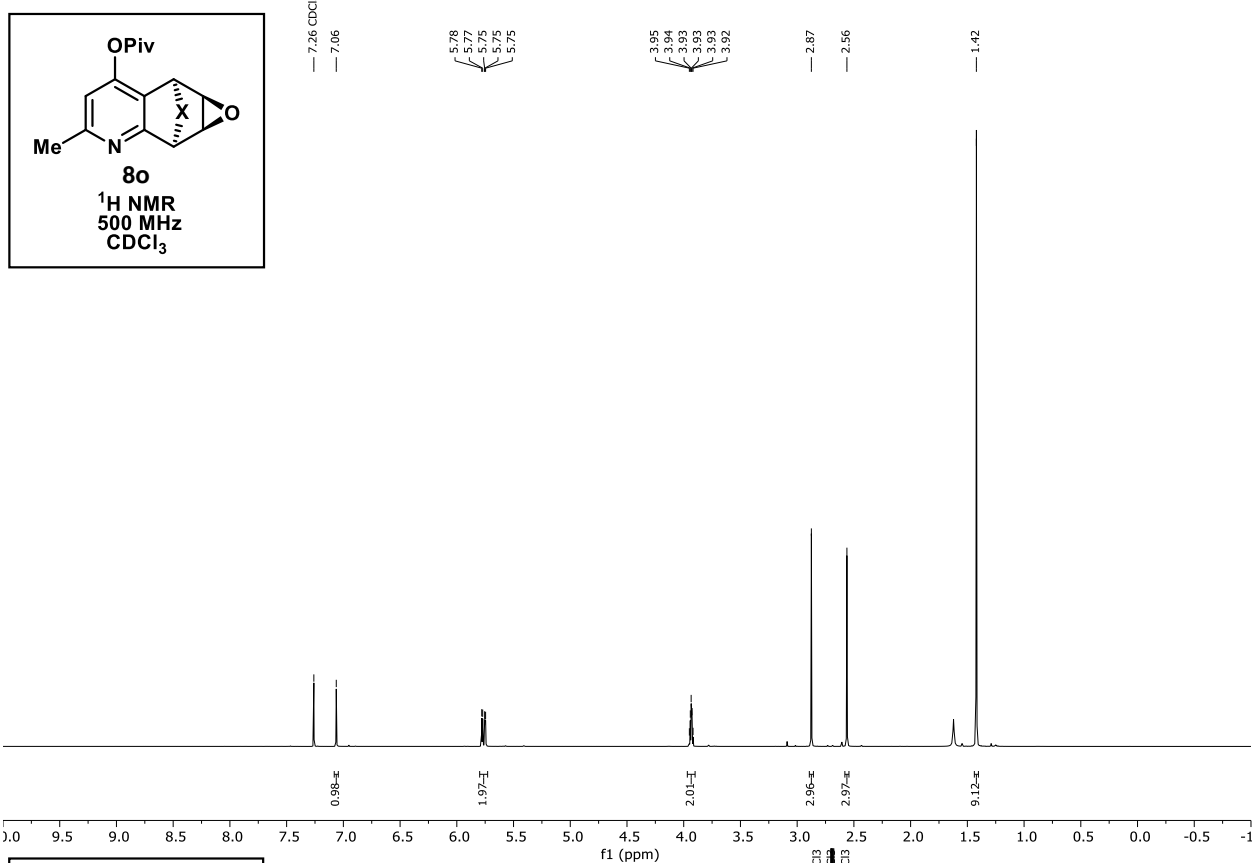

Cl
X
O
Me
N
8l
^{13}C NMR
126 MHz
$CDCl_3$
161.05
156.63
156.23
150.73
140.19
124.51
120.88
77.41 CD
76.91 CD
58.99
53.49
44.30
43.75
25.78
24.37
f1 (ppm)

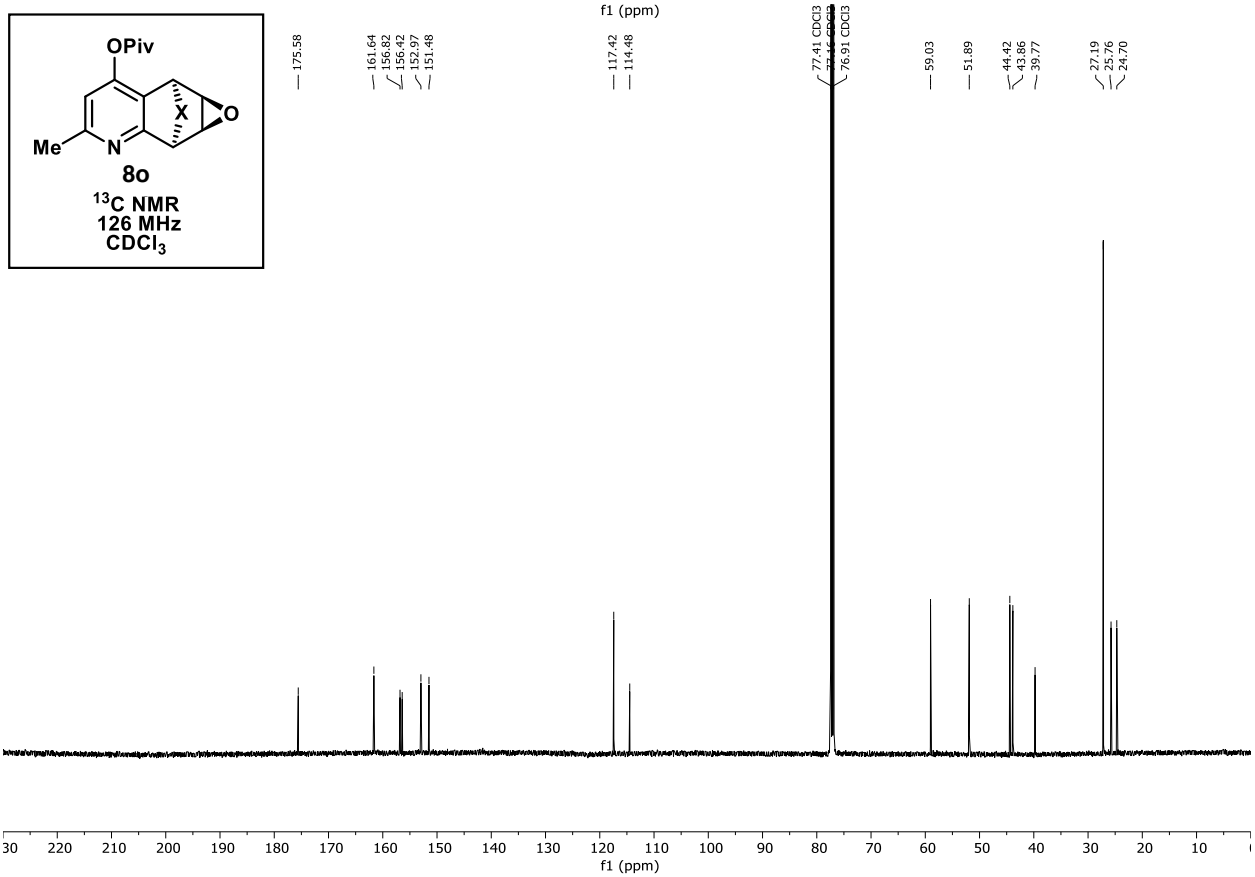

8.46
8.46
8.45
8.45
7.39
7.38
7.37
7.37
7.26 CDCl3
6.16
6.15
6.15
6.14
6.14
5.84
5.84
5.83
5.83
5.82
3.99
3.99
3.98
3.98
3.97
2.89
2.88
Cl
X
O
N
8
1H NMR
500 MHz
CDCl3
1.00
1.00
0.97
0.97
1.99
3.07
f1 (ppm)

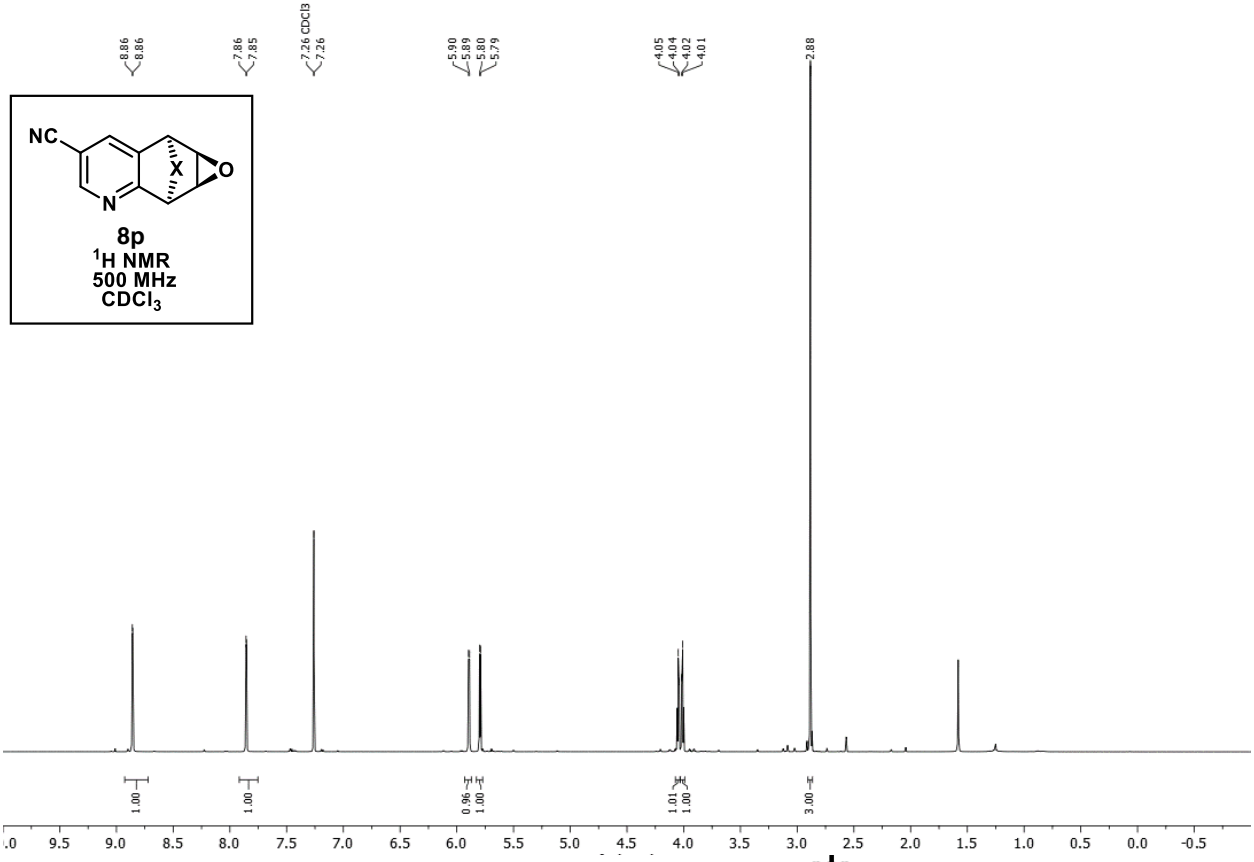

156.64
156.27
151.46
151.04
140.26
125.36
123.96
77.41 CDCl3
76.91 CDCl3
58.98
53.62
44.20
43.75
25.83
Cl
X
O
N
8
13C NMR
126 MHz
CDCl3
f1 (ppm)

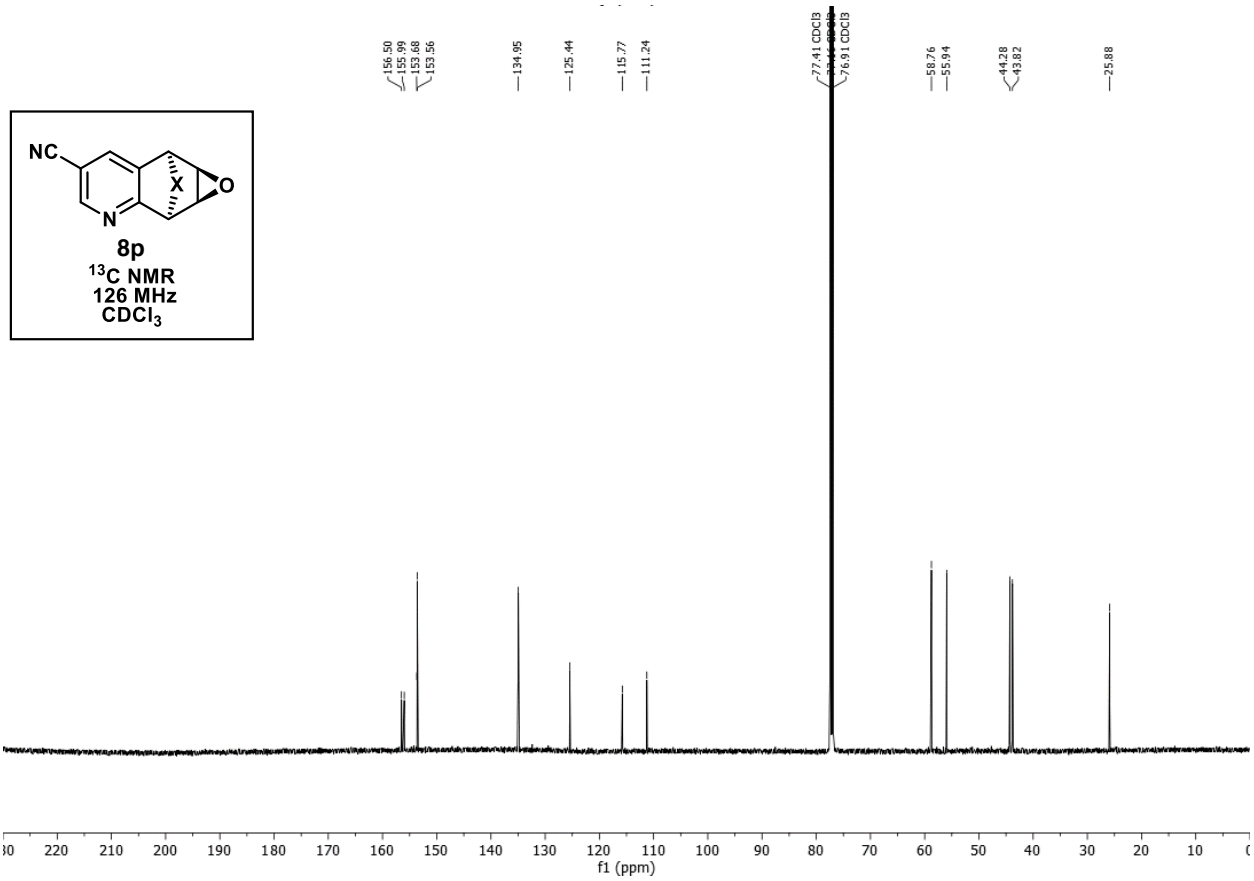

Br
X
O
N
8n
^{1}H NMR
500 MHz
$CDCl_3$
8.36
8.35
7.55
7.54
7.26 CDCl3
6.13
6.13
6.12
6.12
6.12
6.12
6.12
6.11
5.82
5.82
5.82
5.82
5.81
5.81
5.81
5.80
3.99
3.98
3.98
3.97
3.97
2.89
1.03
1.03
1.00
1.01
2.11
3.16
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

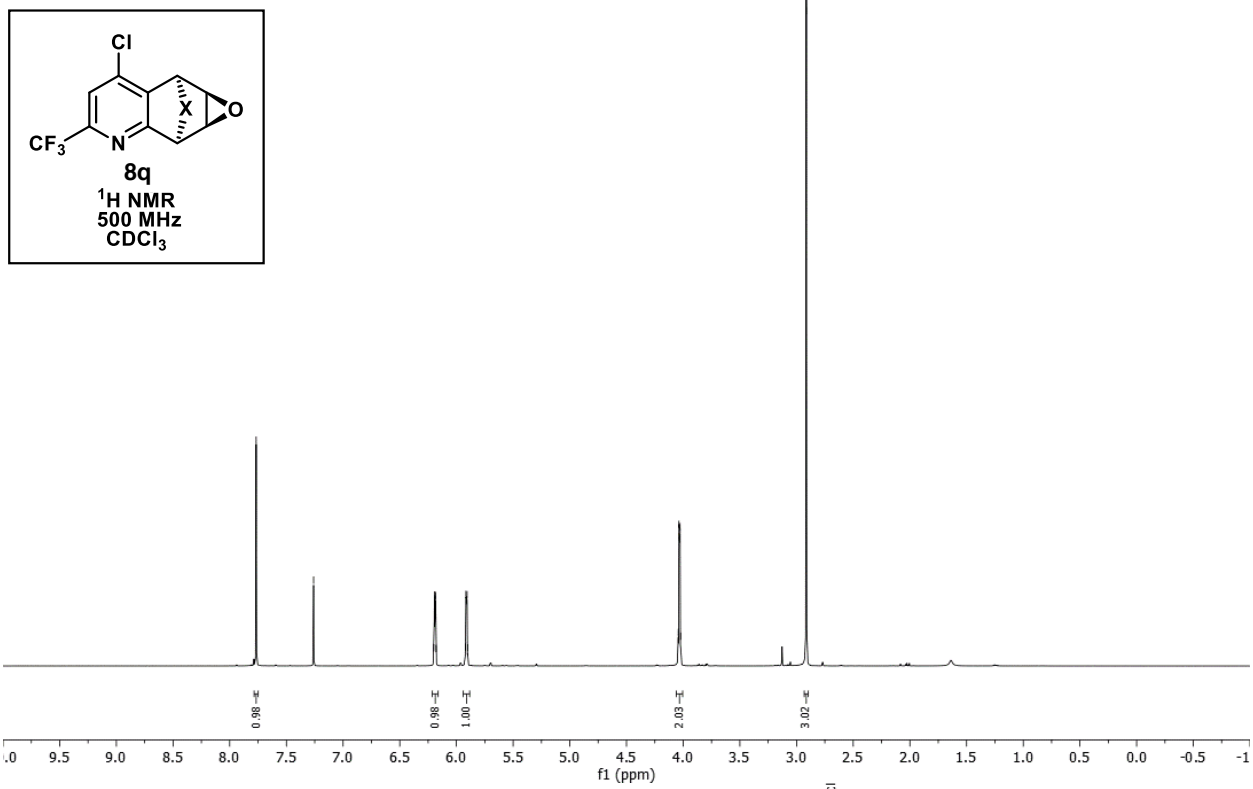

Br
X
O
N
8n
^{13}C NMR
126 MHz
$CDCl_3$
156.62
156.27
151.13
150.90
130.22
128.52
126.30
77.42 CDCl3
76.91 CDCl3
59.12
55.79
44.23
43.78
25.84
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

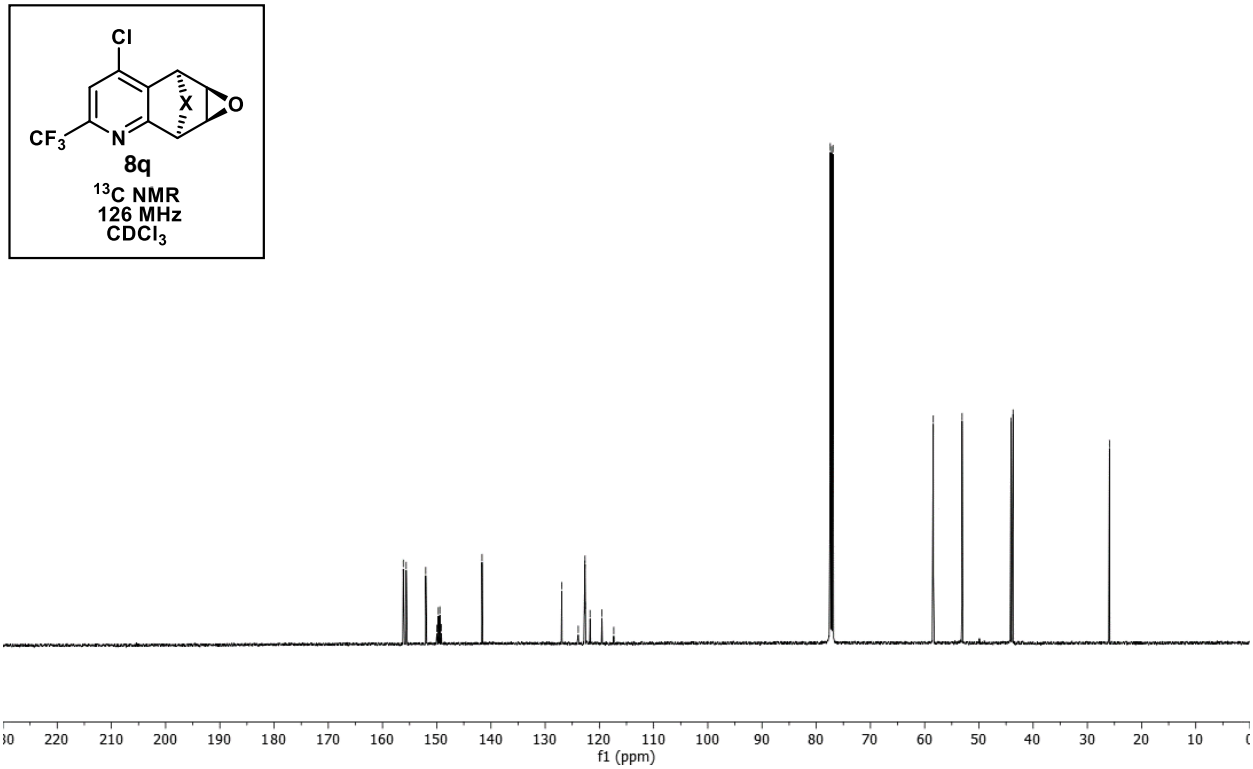

OPiv
X
O
Me
N
8o
^{1}H NMR
500 MHz
$CDCl_3$
7.26 CDCl3
7.06
5.78
5.77
5.75
5.75
5.75
5.75
3.95
3.94
3.93
3.93
3.93
3.93
3.92
2.87
2.56
1.42
0.98
1.97
2.01
2.96
2.97
9.12
f1 (ppm)

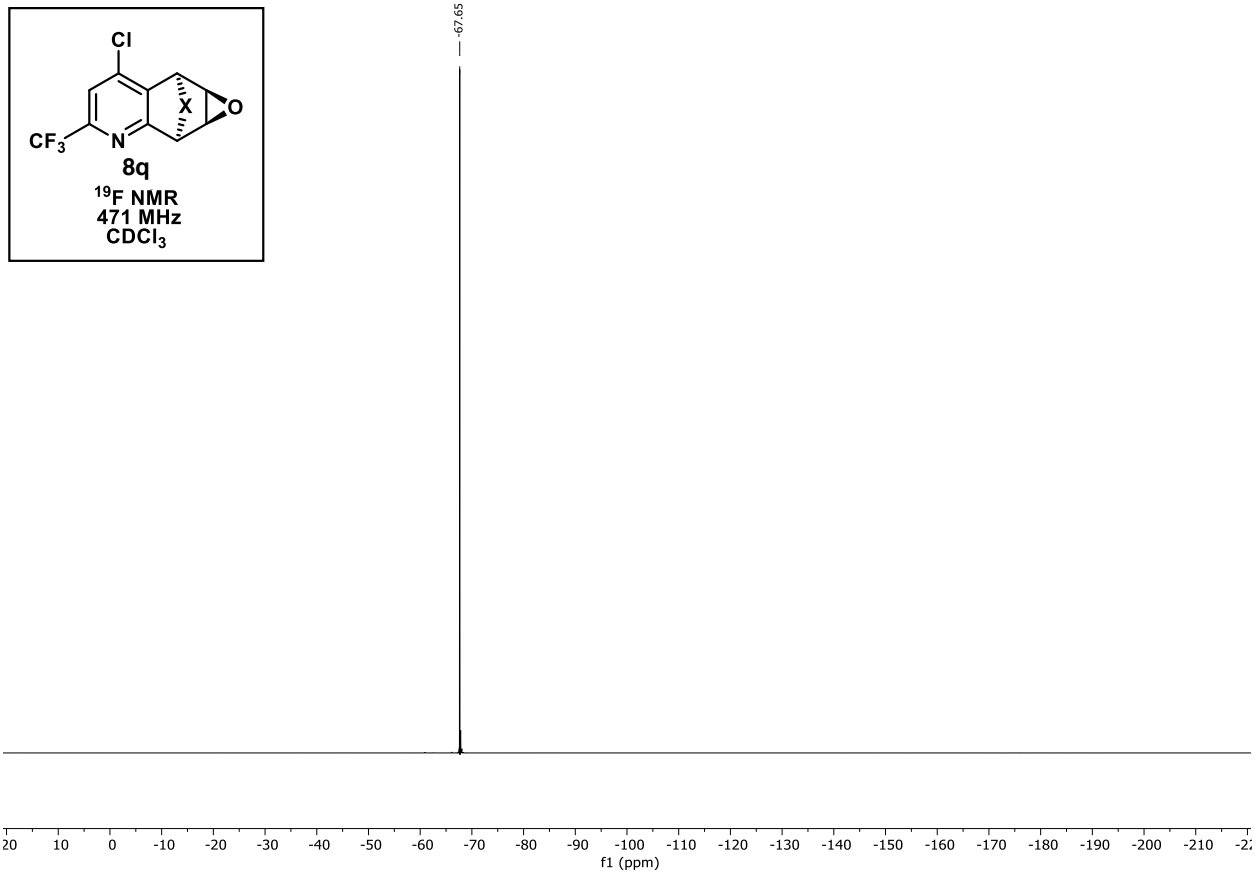

OPiv
X
O
Me
N
8o
^{13}C NMR
126 MHz
$CDCl_3$
175.58
161.64
156.82
156.42
152.97
151.48
117.42
114.48
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
59.03
51.89
44.42
43.86
39.77
27.19
25.76
24.70
f1 (ppm)

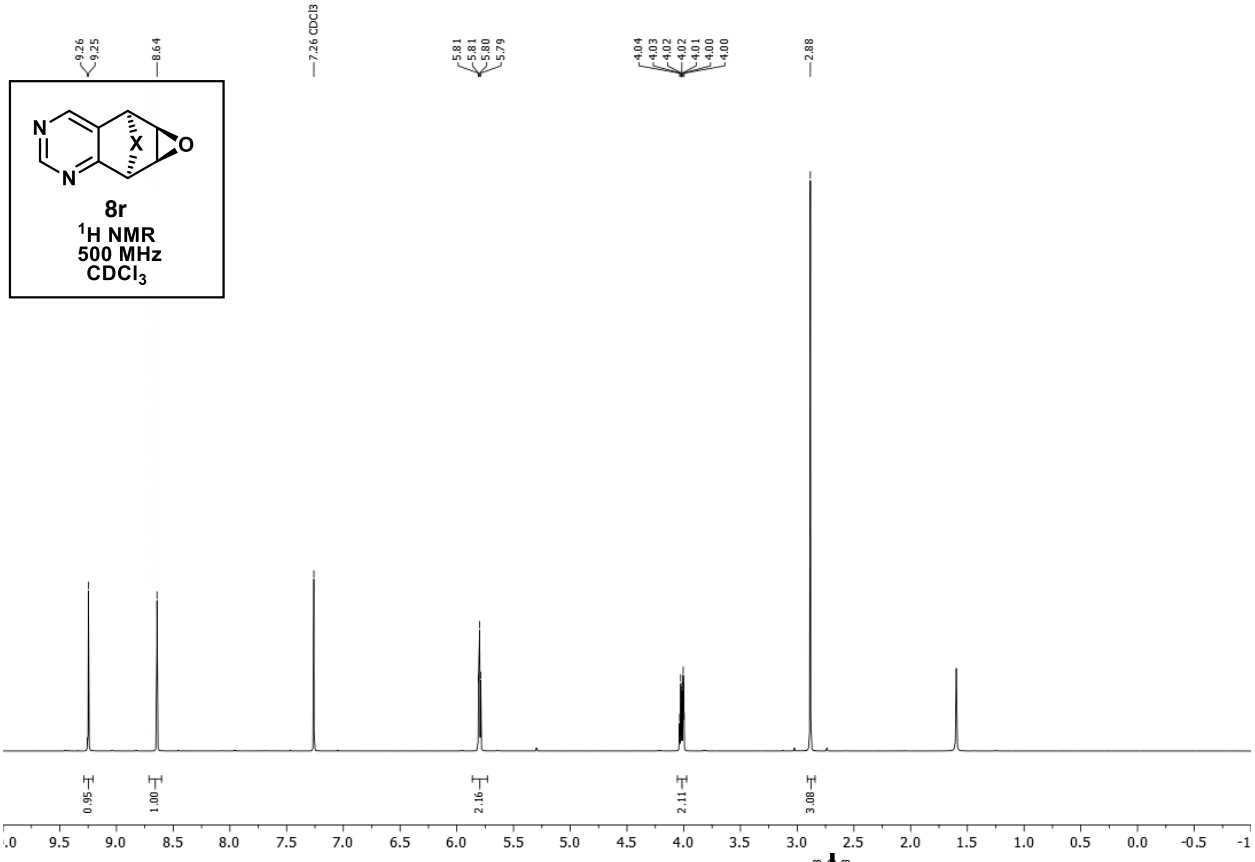

8.86
8.86
7.86
7.85
7.26 CDCl3
7.26
5.90
5.89
5.80
5.79
4.05
4.04
4.02
4.01
2.88
NC
X
O
N
8p
1H NMR
500 MHz
CDCl3
1.00
1.00
0.96
1.00
1.01
1.00
3.00
f1 (ppm)

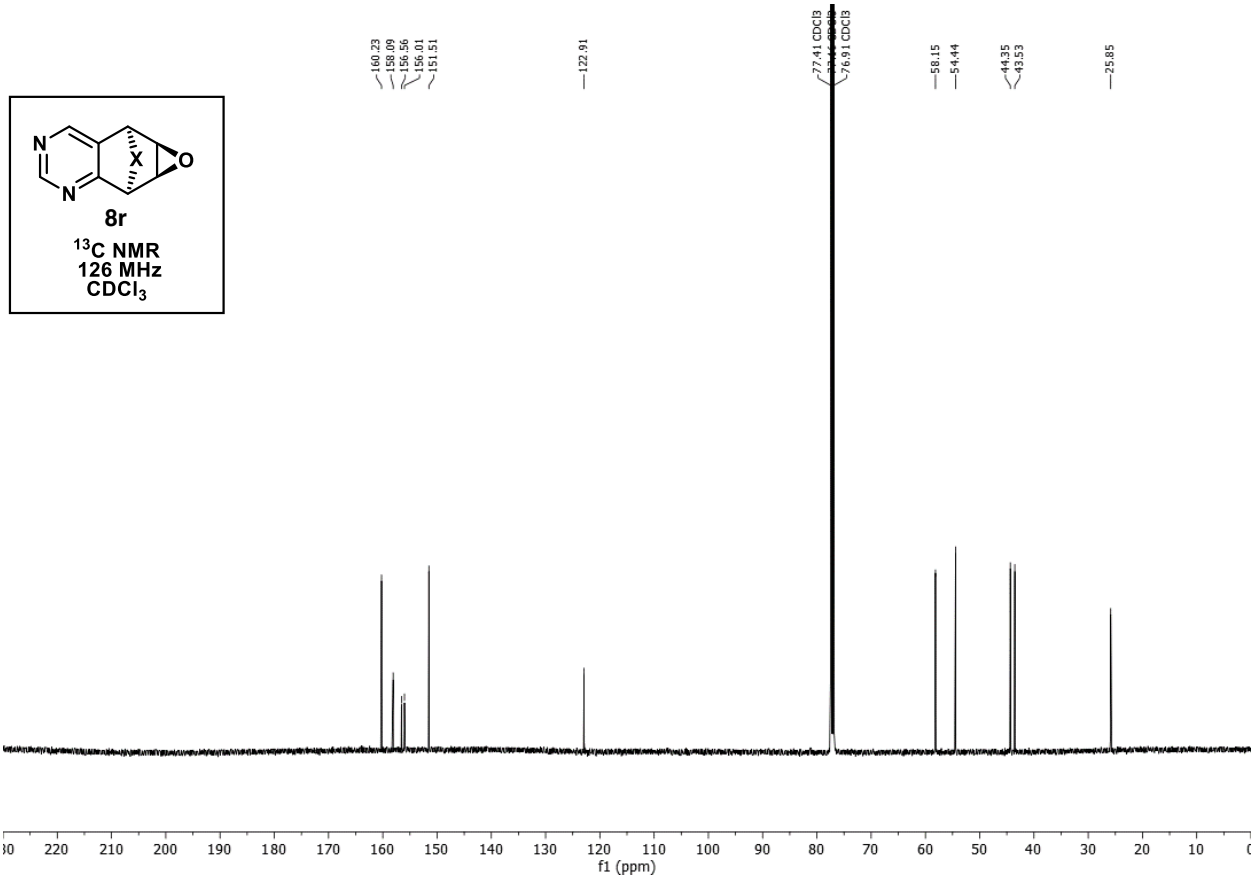

156.50
155.99
153.68
153.56
134.95
125.44
115.77
111.24
77.41 CDCl3
76.91 CDCl3
58.76
55.94
44.28
43.82
25.88
NC
X
O
N
8p
13C NMR
126 MHz
CDCl3
f1 (ppm)

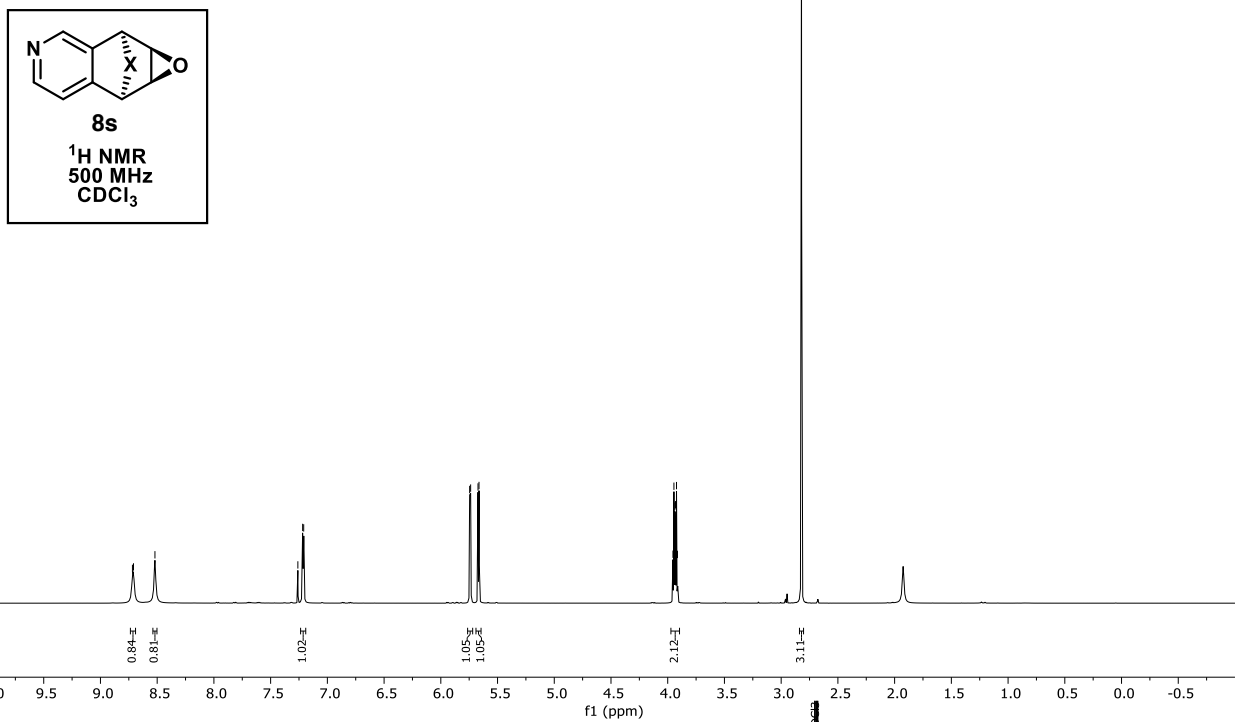

Cl
X
O
CF3
N
8q
1H NMR
500 MHz
CDCl3
7.77
7.26 CDCl3
6.20
6.19
6.19
6.19
6.18
6.18
5.92
5.92
5.91
5.91
5.91
5.90
4.04
4.04
4.03
4.03
4.03
4.02
2.91
0.98
0.98
1.00
2.03
3.02
f1 (ppm)

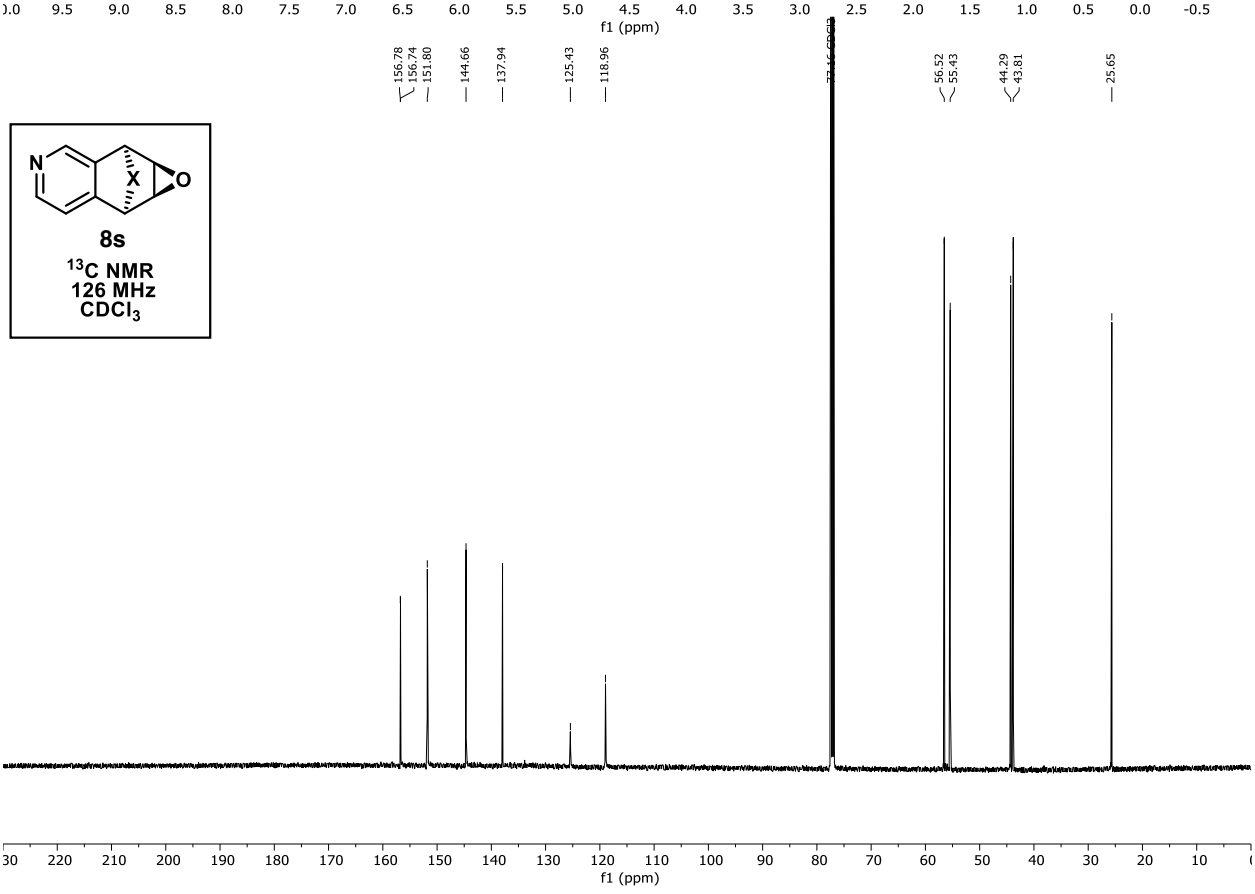

Cl
X
O
CF3
N
8q
13C NMR
126 MHz
CDCl3
156.16
155.64
152.03
149.99
149.70
149.42
149.13
141.65
126.94
123.90
122.70
122.68
122.65
122.63
121.72
119.53
117.35
77.41
77.16 CDCl
76.91
58.41
53.10
44.05
43.69
25.92
f1 (ppm)

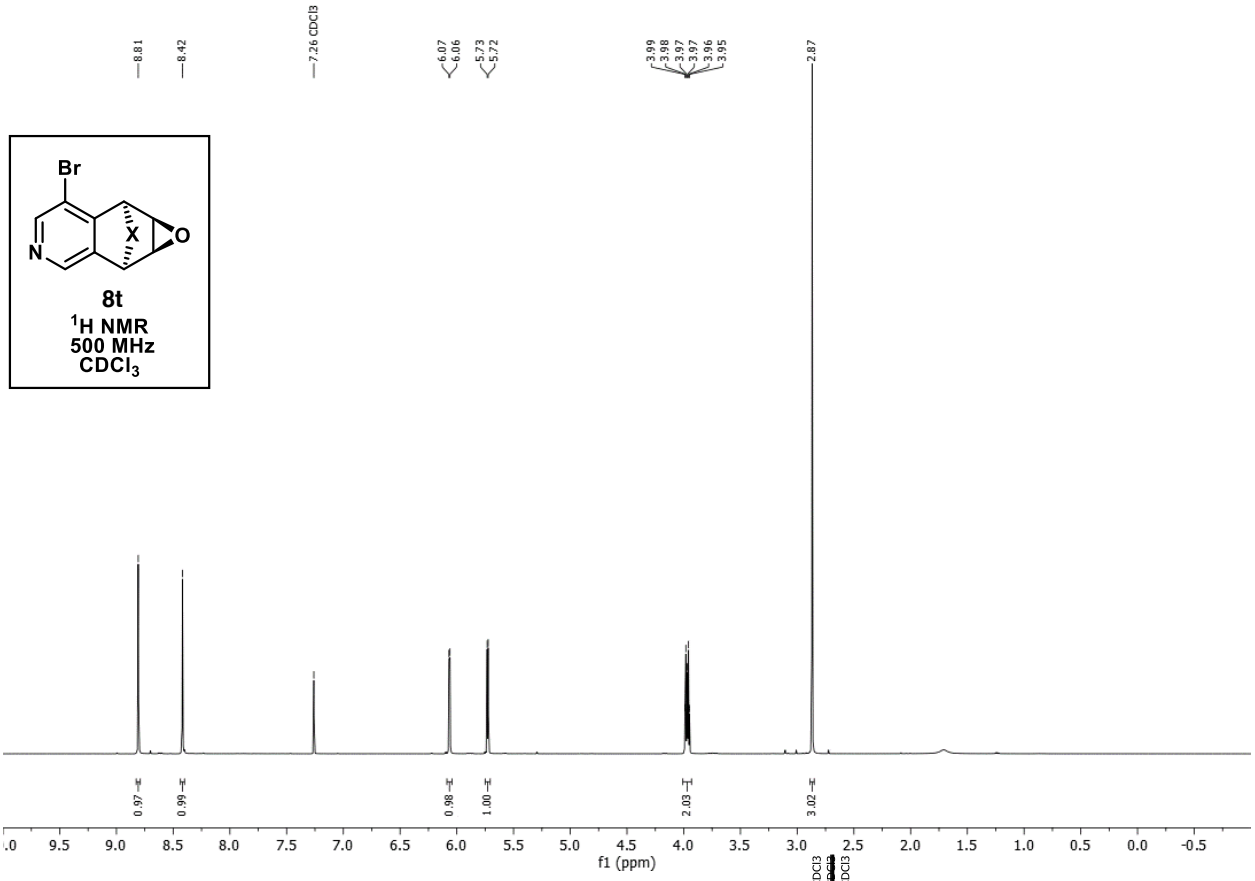

Cl
X
O
CF3
N
8q
19F NMR
471 MHz
CDCl3
-67.63
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

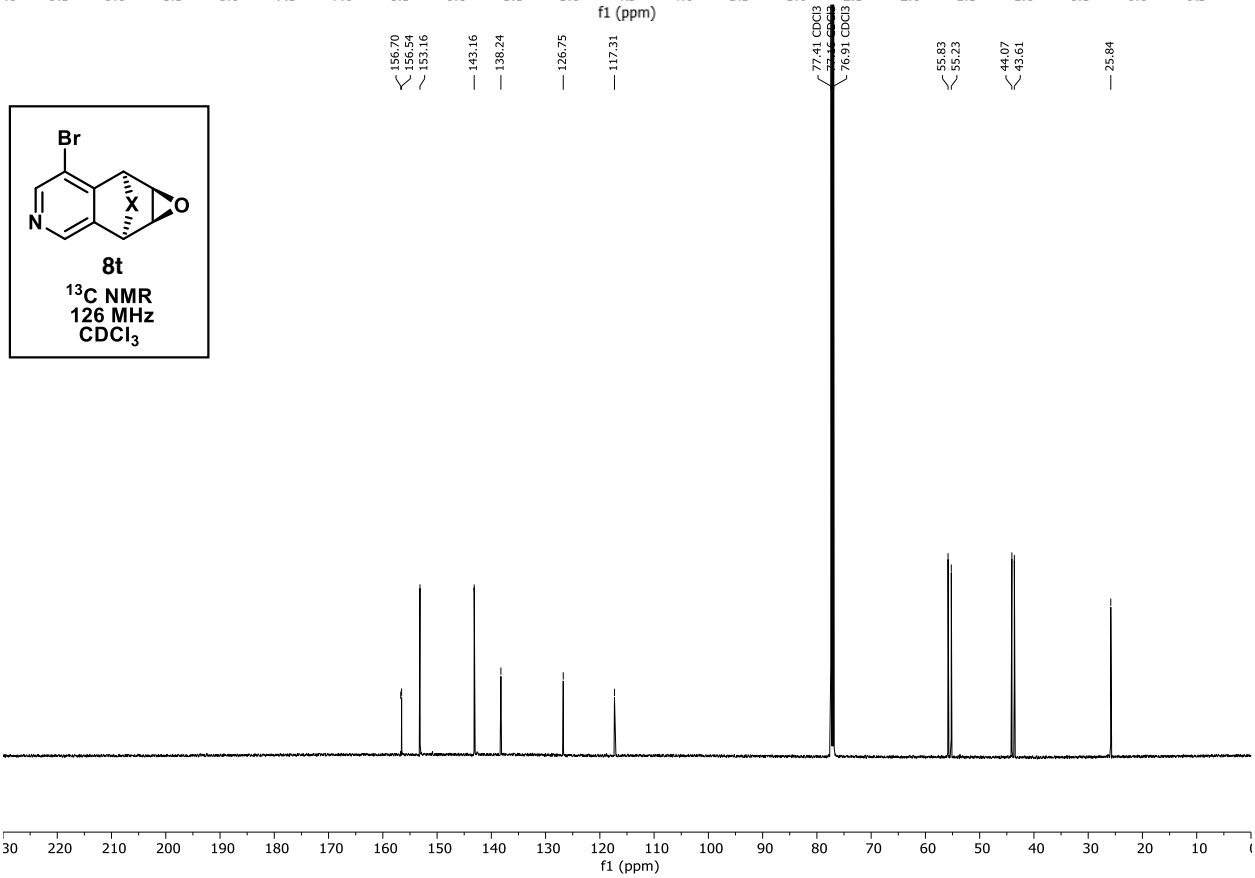

9.26
9.25
8.64
7.26 CDCl3
5.81
5.81
5.80
5.79
4.04
4.03
4.02
4.02
4.01
4.00
4.00
2.88
0.95
1.00
2.16
2.11
3.08
8r
1H NMR
500 MHz
CDCl3

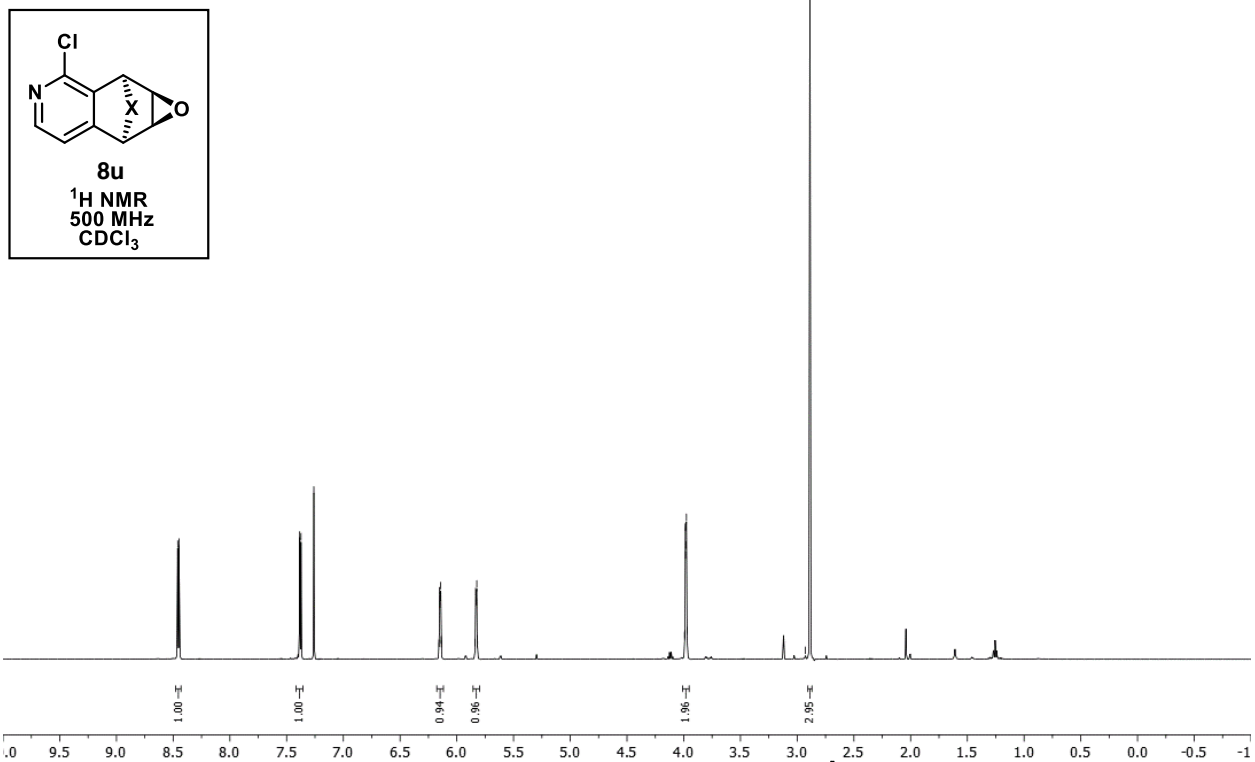

160.23
158.09
156.56
156.01
151.51
122.91
77.41 CDCl3
76.91 CDCl3
58.15
54.44
44.35
43.53
25.85
8r
13C NMR
126 MHz
CDCl3
f1 (ppm)

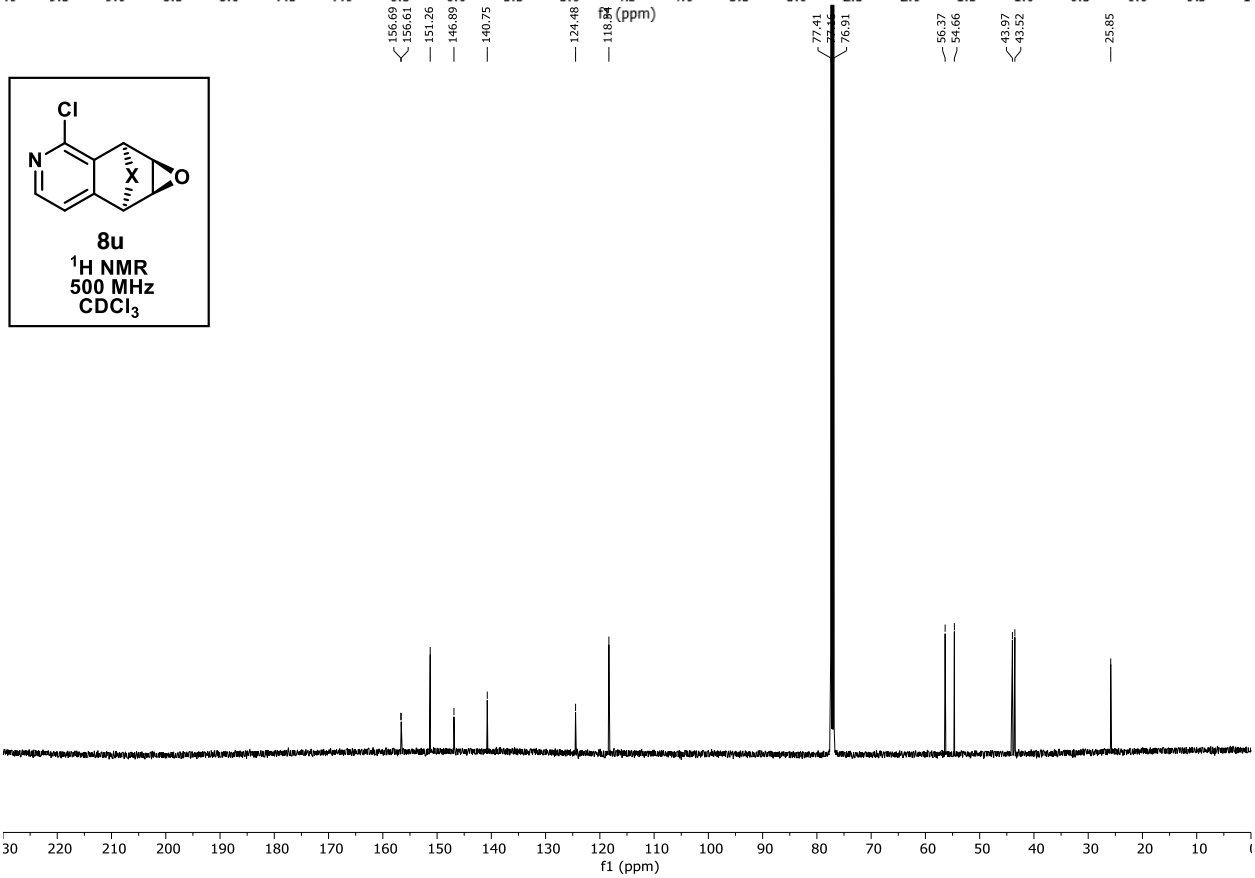

8.72
8.71
8.52
7.26 CDCl3
7.22
7.21
5.75
5.74
5.67
5.66
3.95
3.95
3.94
3.93
3.92
3.91
2.82
N
X
O
8s
1H NMR
500 MHz
CDCl3
0.84
0.81
1.02
1.05
1.05
2.12
3.11
f1 (ppm)

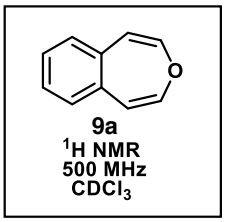

156.78
156.74
151.80
144.66
137.94
125.43
118.96
77.16 CDCl3
56.52
55.43
44.29
43.81
25.65
N
X
O
8s
13C NMR
126 MHz
CDCl3
f1 (ppm)


8.81
8.42
7.26 CDCl3
6.07
6.06
5.73
5.72
3.99
3.98
3.97
3.97
3.97
3.96
3.95
2.87
Br
X
O
N
8t
1H NMR
500 MHz
CDCl3
0.97
0.99
0.98
1.00
2.03
3.02
f1 (ppm)

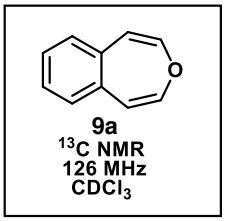

156.70
156.54
153.16
143.16
138.24
126.75
117.31
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
55.83
55.23
44.07
43.61
25.84
Br
X
O
N
8t
13C NMR
126 MHz
CDCl3
f1 (ppm)


Cl
N
X
O
8u
1H NMR
500 MHz
CDCl3
8.46
8.45
7.38
7.37
7.26 CDCl3
6.16
6.15
6.15
6.15
6.14
6.14
6.14
6.14
5.84
5.83
5.83
5.83
5.83
5.82
5.82
5.82
3.99
3.99
3.99
3.98
3.98
3.98
3.98
3.97
2.93
2.89
1.00
1.00
0.94
0.96
1.96
2.95
f2 (ppm)

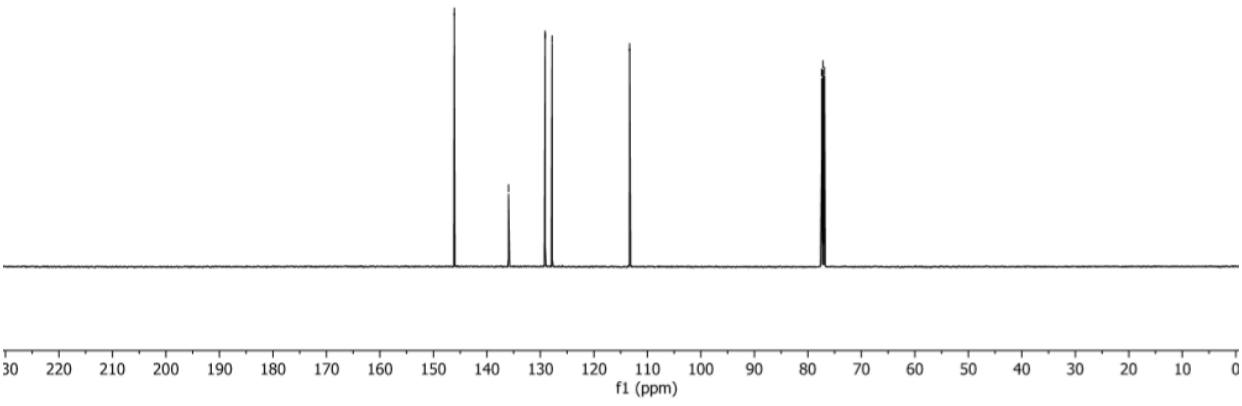

Cl
N
X
O
8u
1H NMR
500 MHz
CDCl3
156.69
156.61
151.26
146.89
140.75
124.48
118.84
77.41
77.16
76.91
56.37
54.66
43.97
43.52
25.85
f1 (ppm)

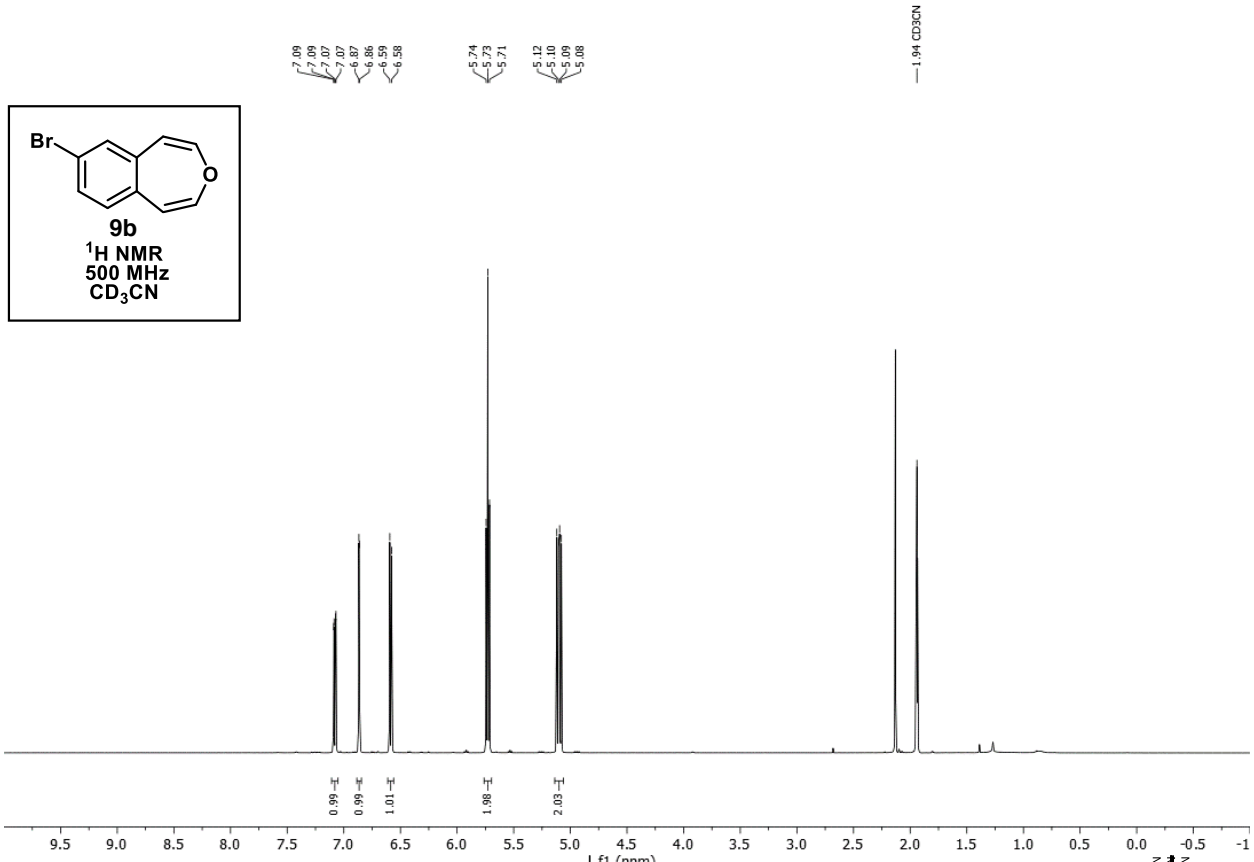


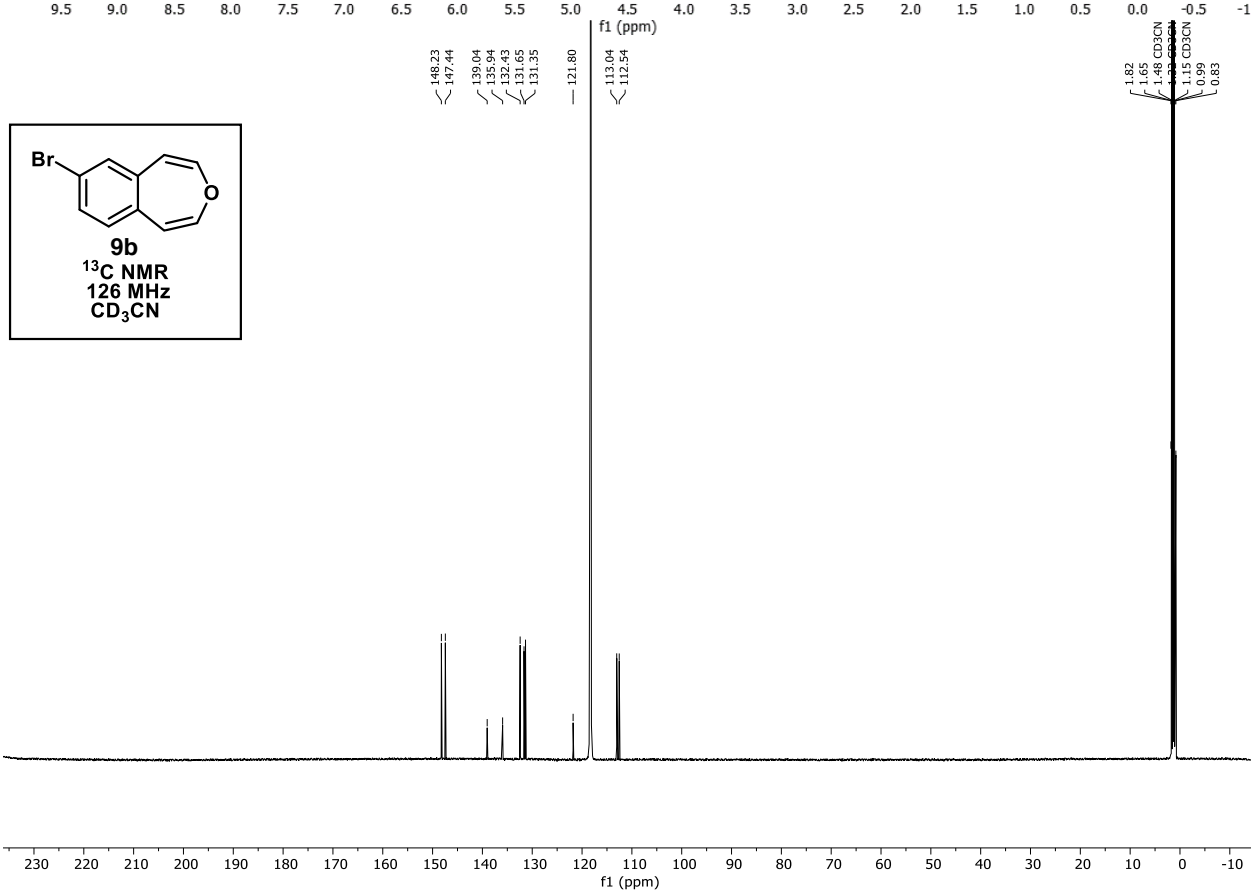
9a
^{1}H NMR
500 MHz
$CDCl_3$

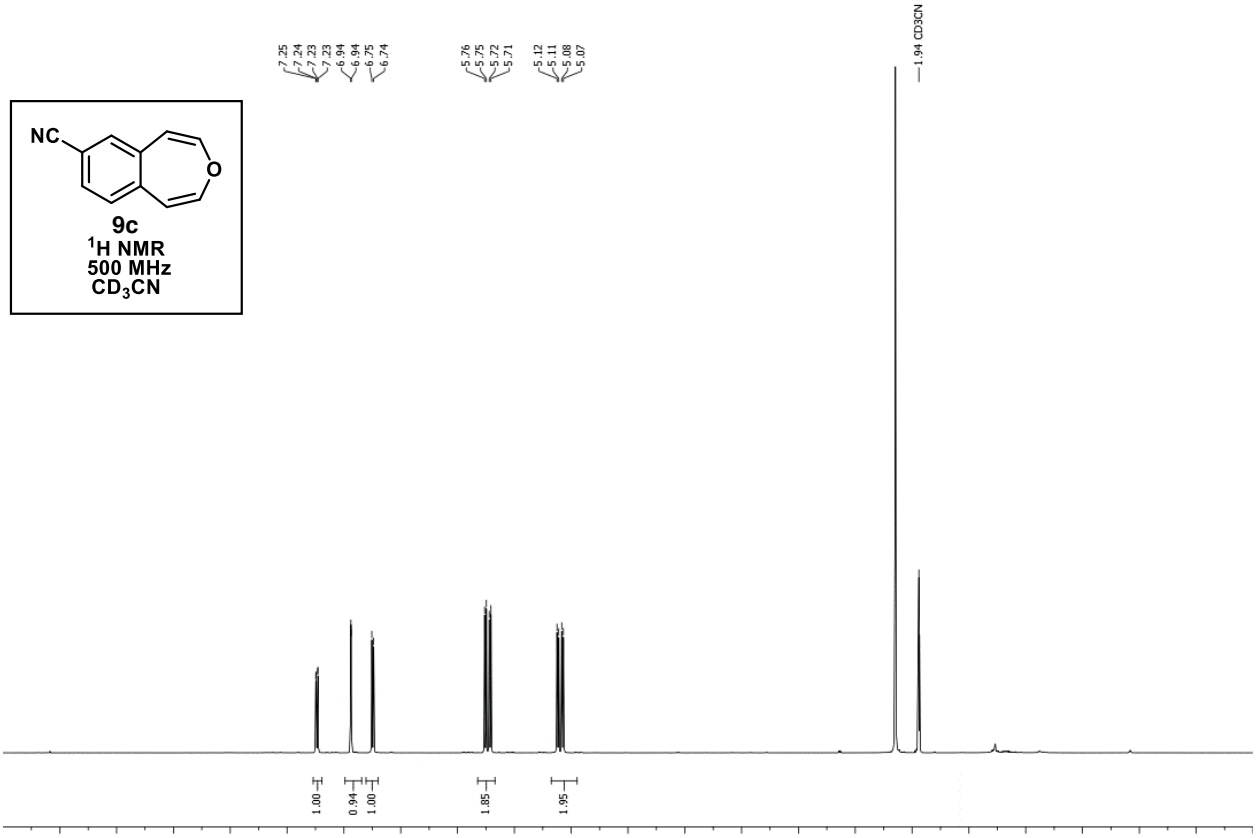


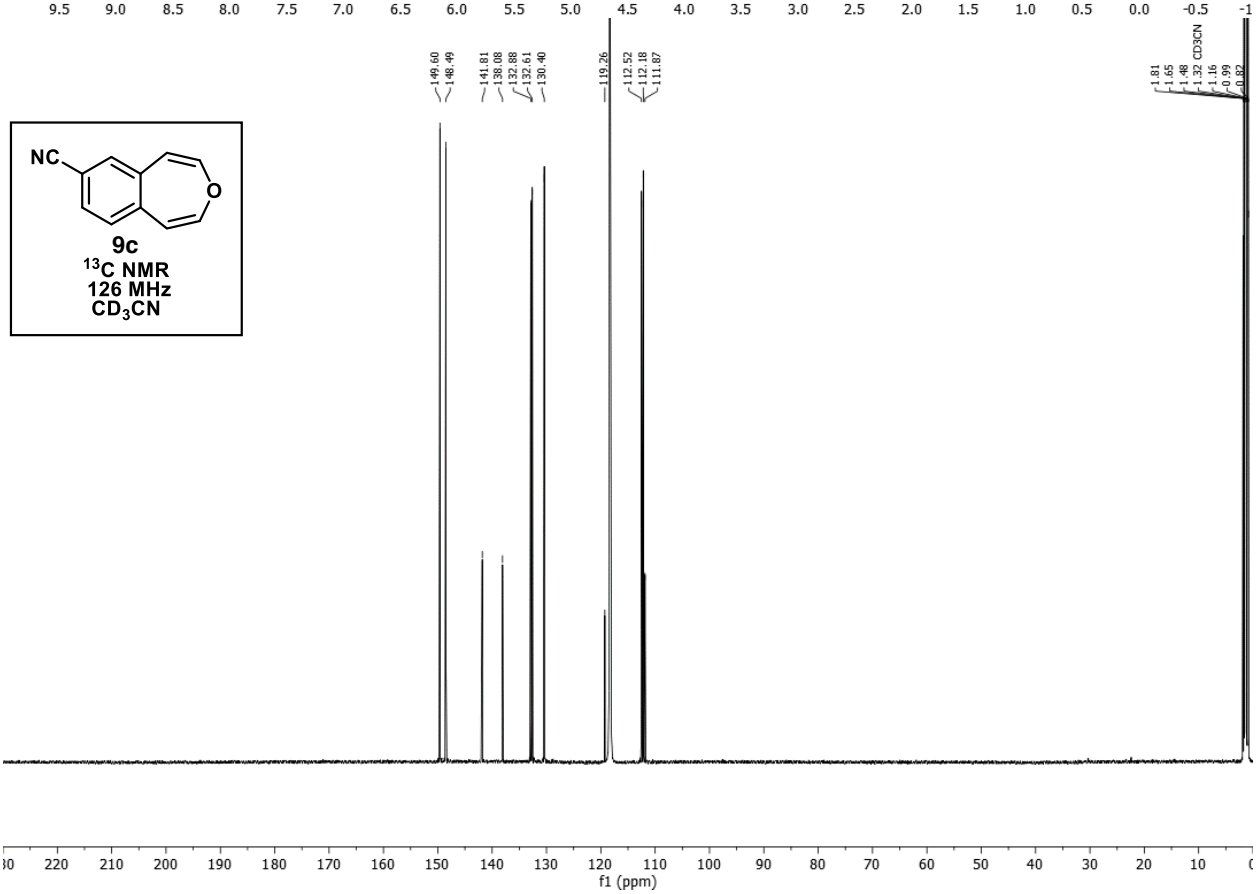
9a
^{13}C NMR
126 MHz
$CDCl_3$

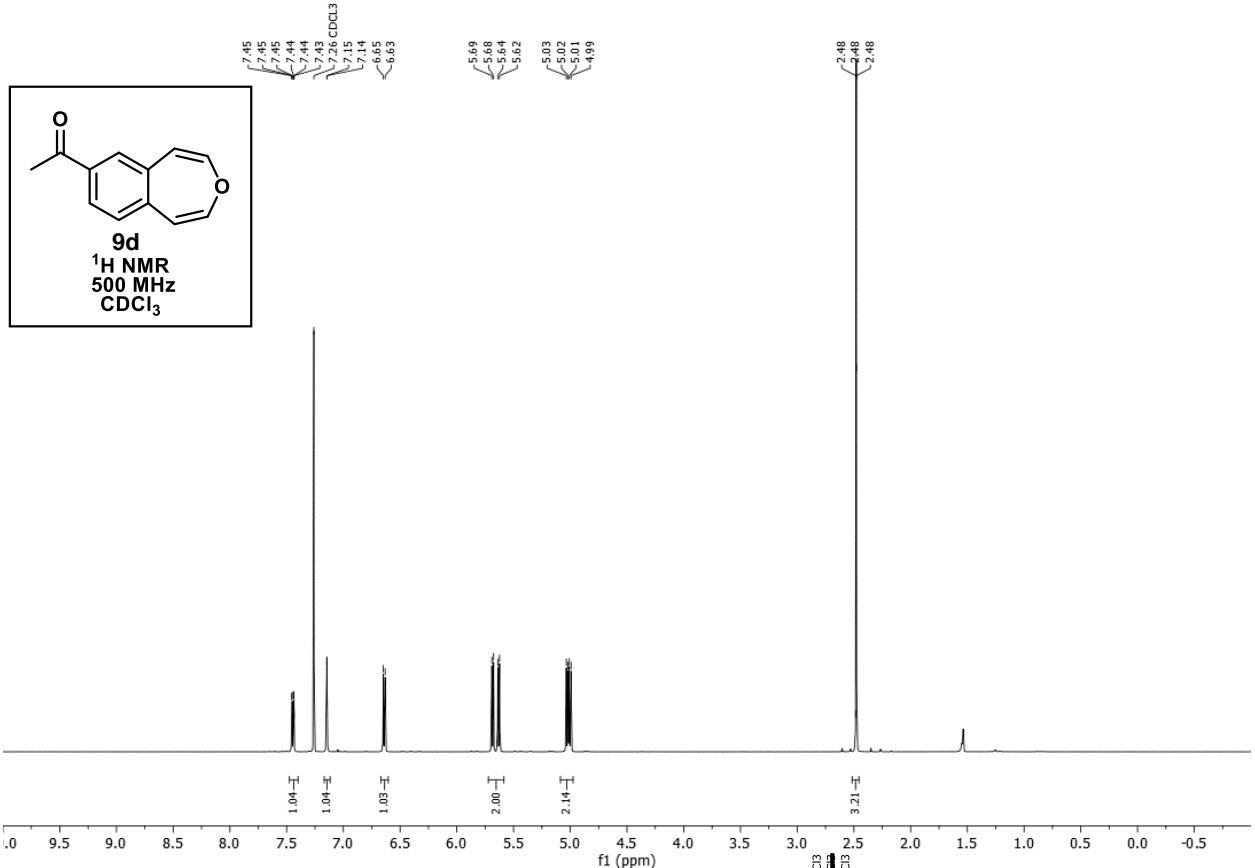


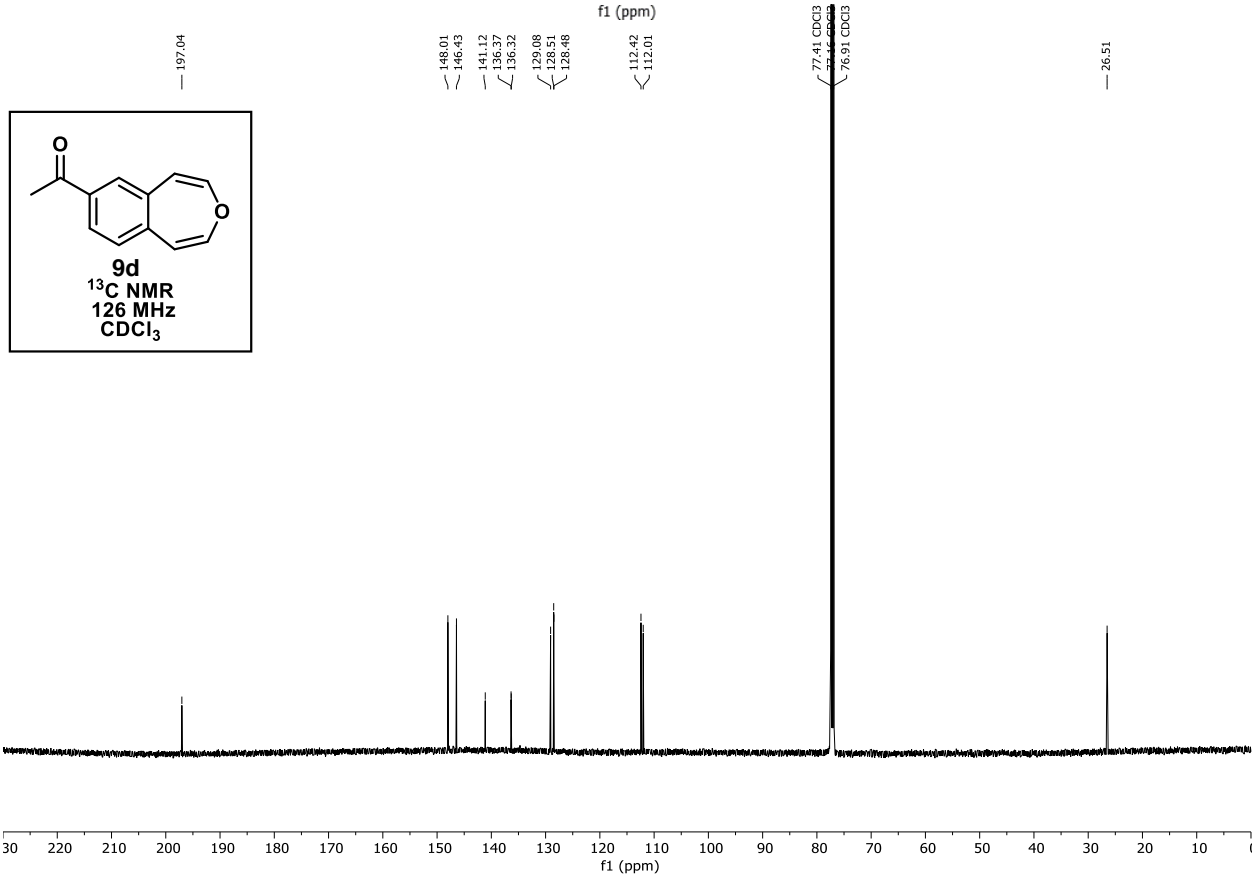

Br
O
9b
1H NMR
500 MHz
CD3CN
7.09
7.09
7.07
7.07
6.87
6.86
6.59
6.58
5.74
5.73
5.71
5.12
5.10
5.09
5.08
1.94 CD3CN
0.99
0.99
1.01
1.98
2.03
f1 (ppm)

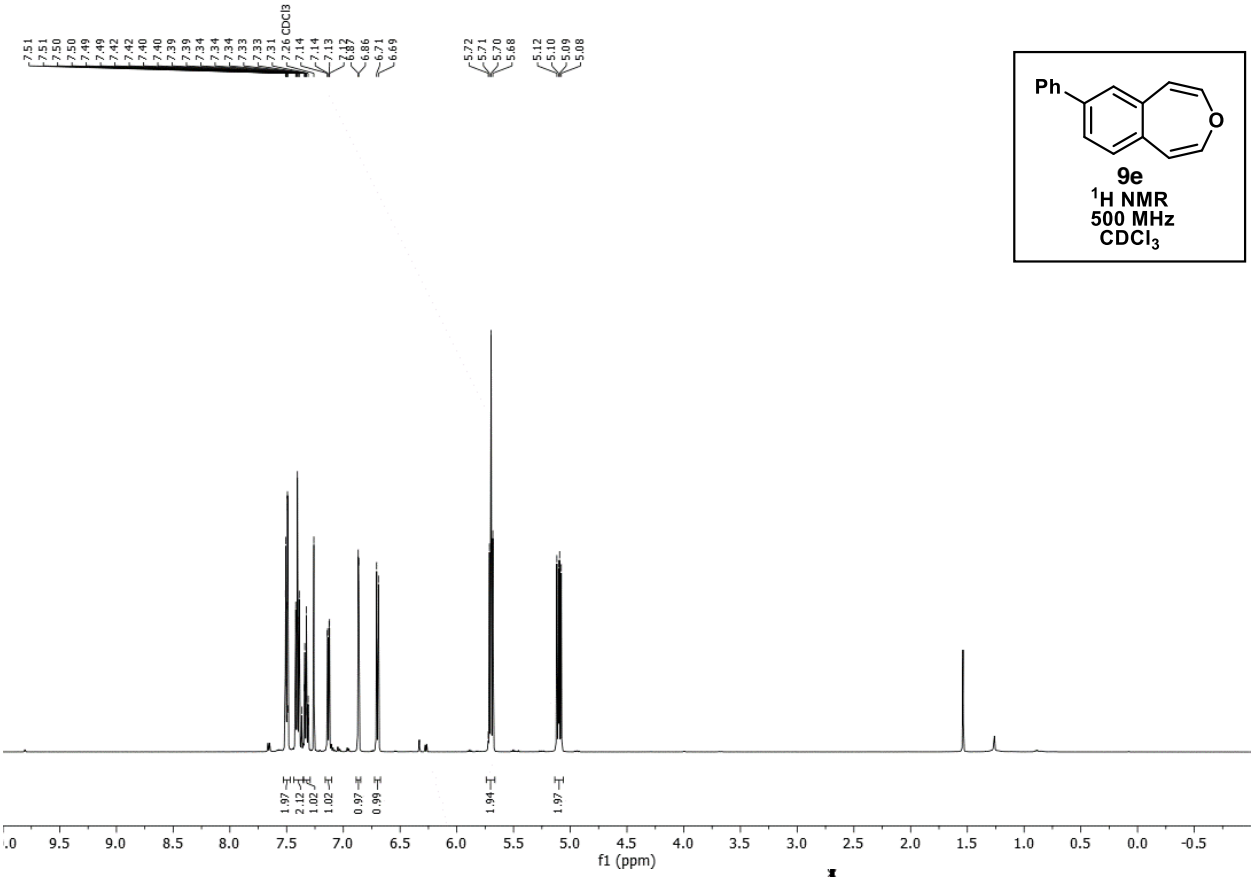

Br
O
9b
13C NMR
126 MHz
CD3CN
148.23
147.44
139.04
135.94
132.43
131.65
131.35
121.80
113.04
112.54
1.82
1.65
1.48 CD3CN
1.15 CD3CN
0.99
0.83
f1 (ppm)

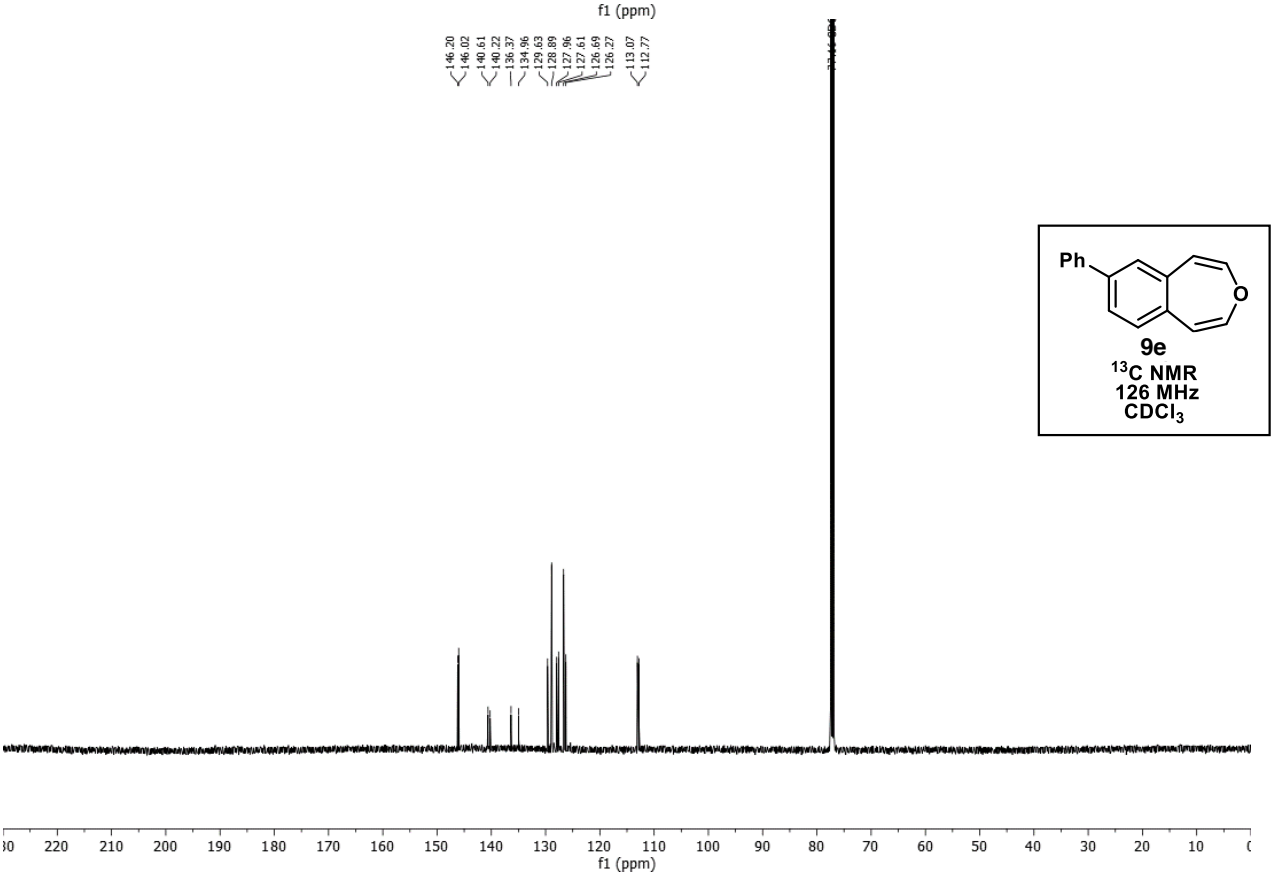

NC
O
9c
1H NMR
500 MHz
CD3CN
7.25
7.24
7.23
7.23
6.94
6.94
6.75
6.74
5.76
5.75
5.72
5.71
5.12
5.11
5.08
5.07
1.94 CD3CN
1.00
0.94
1.00
1.85
1.95
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

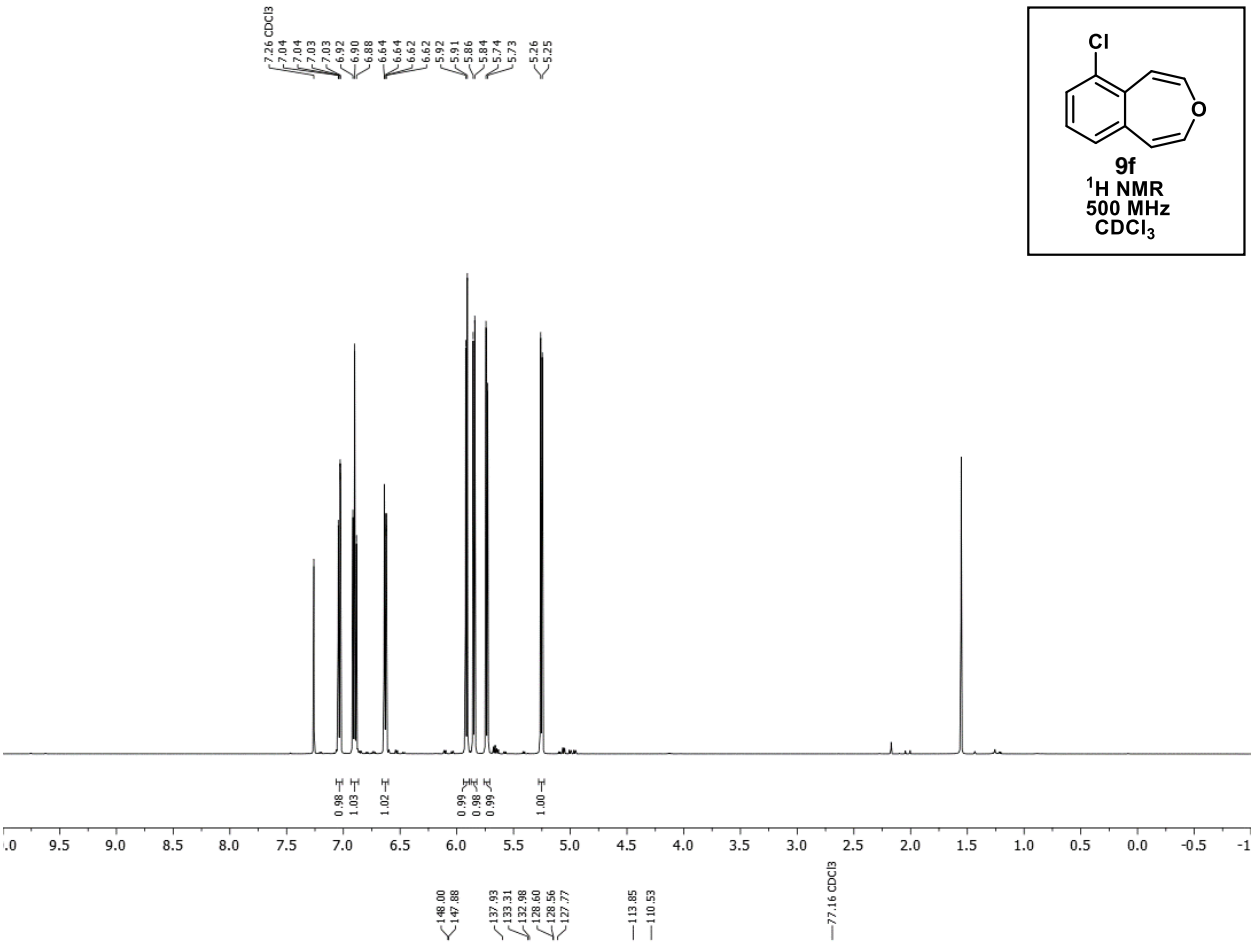

NC
O
9c
13C NMR
126 MHz
CD3CN
149.60
148.49
141.81
138.08
132.88
132.61
130.40
119.26
112.52
112.18
111.87
1.81
1.65
1.40
1.32 CD3CN
1.16
0.99
0.82
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

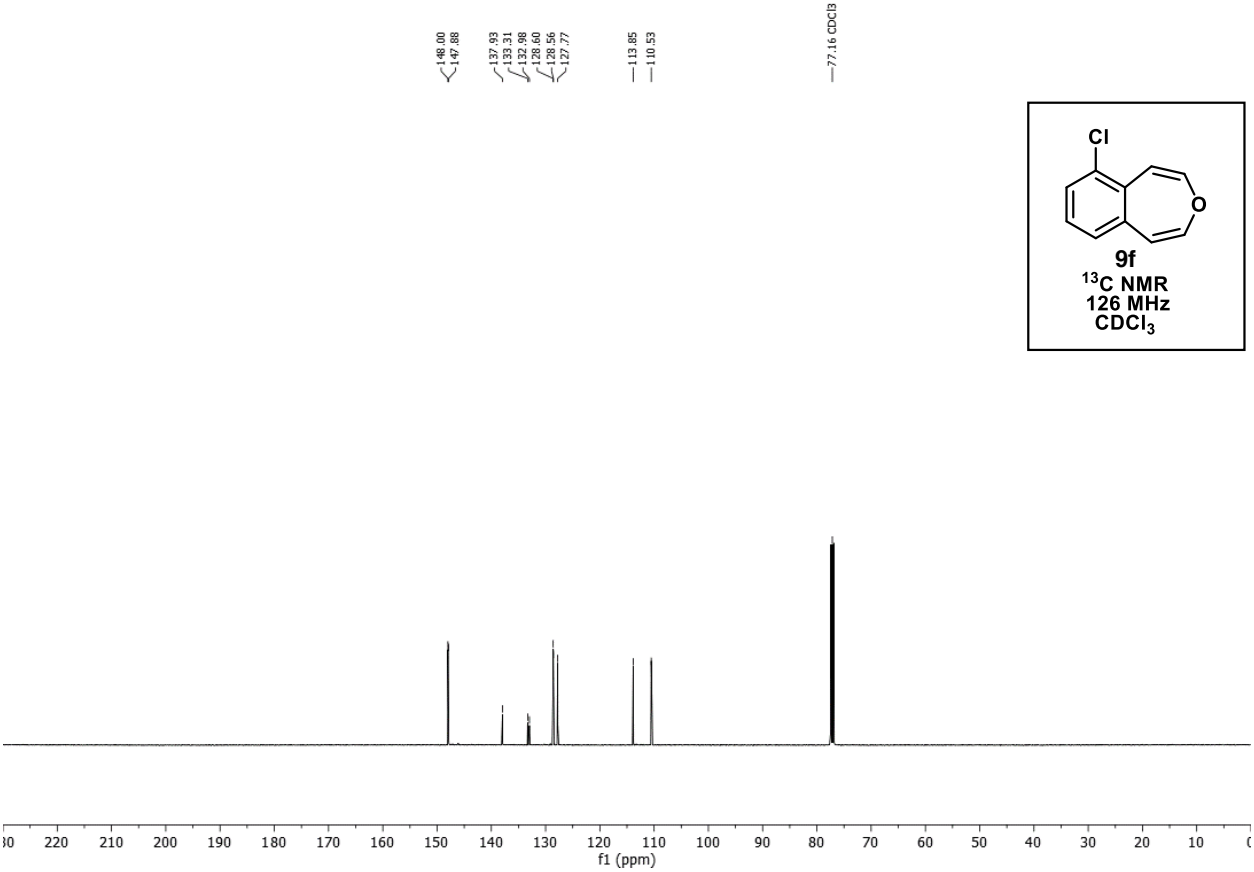

9d
1H NMR
500 MHz
CDCl3
f1 (ppm)

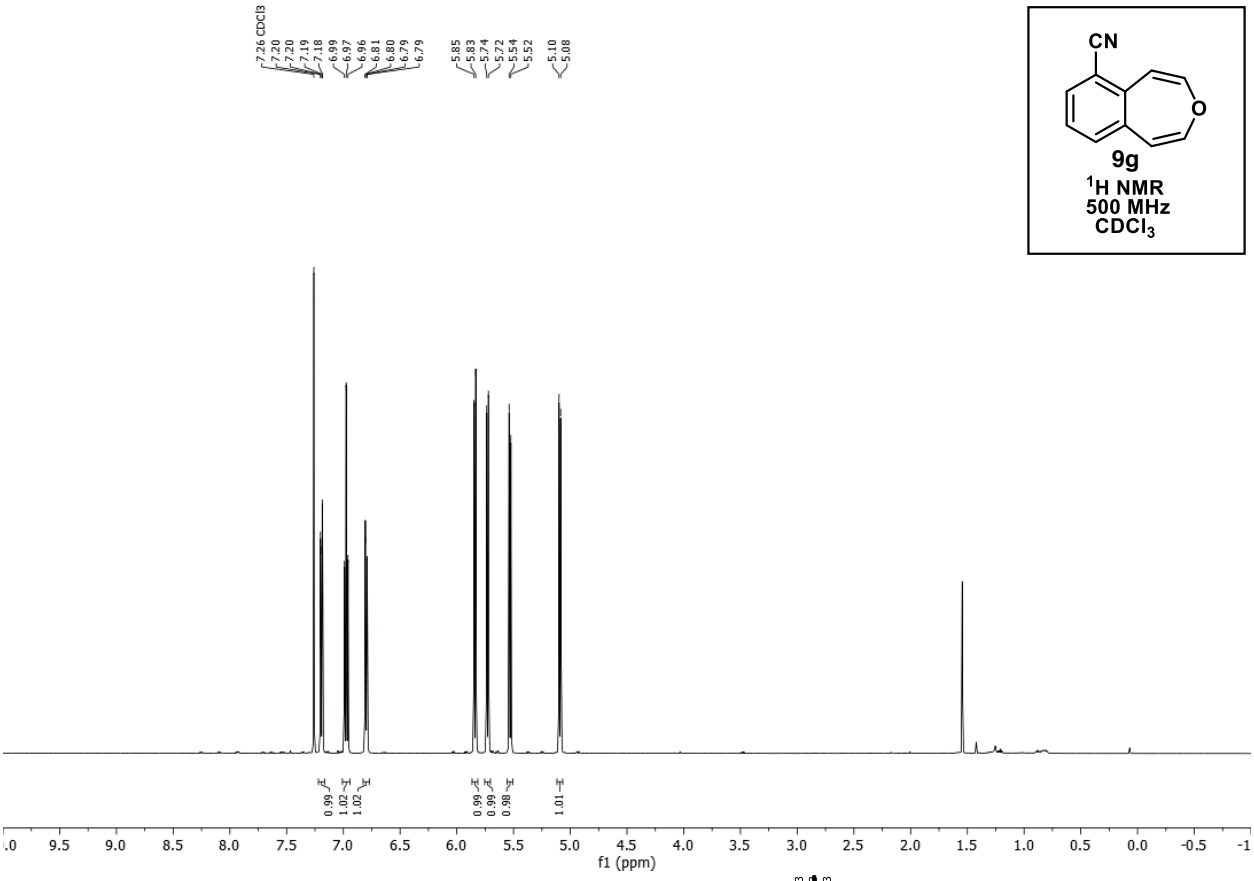

9d
13C NMR
126 MHz
CDCl3
f1 (ppm)

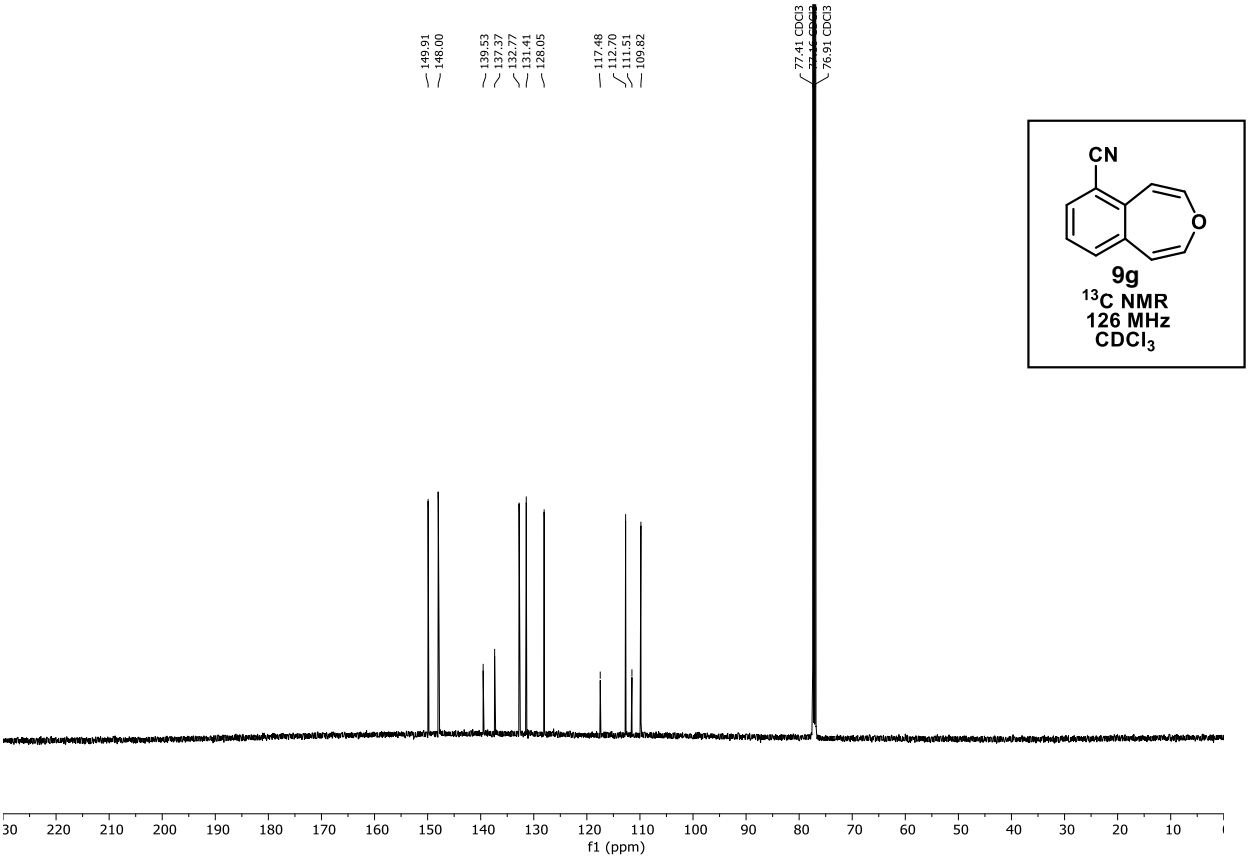

Ph
O
9e
1H NMR
500 MHz
CDCl3
f1 (ppm)

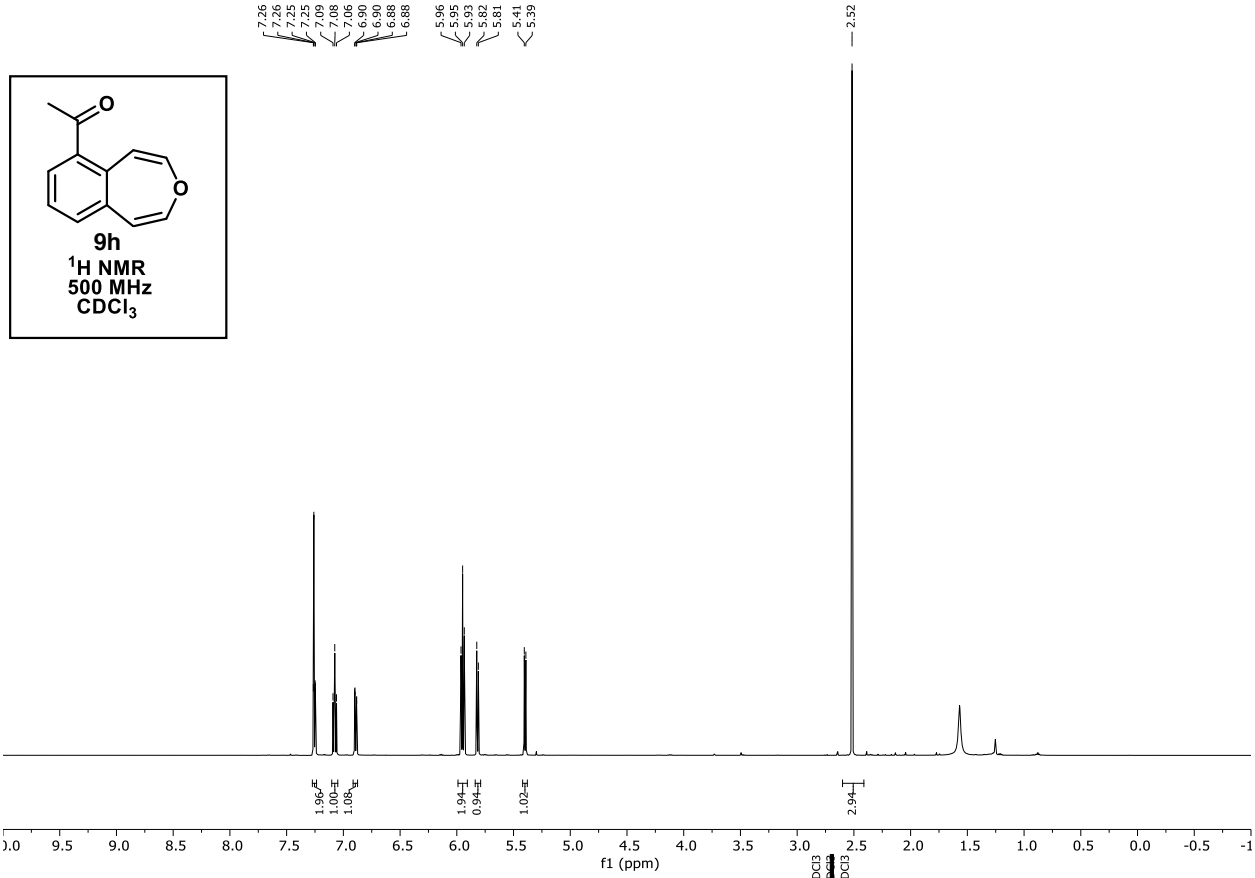

Ph
O
9e
13C NMR
126 MHz
CDCl3
f1 (ppm)

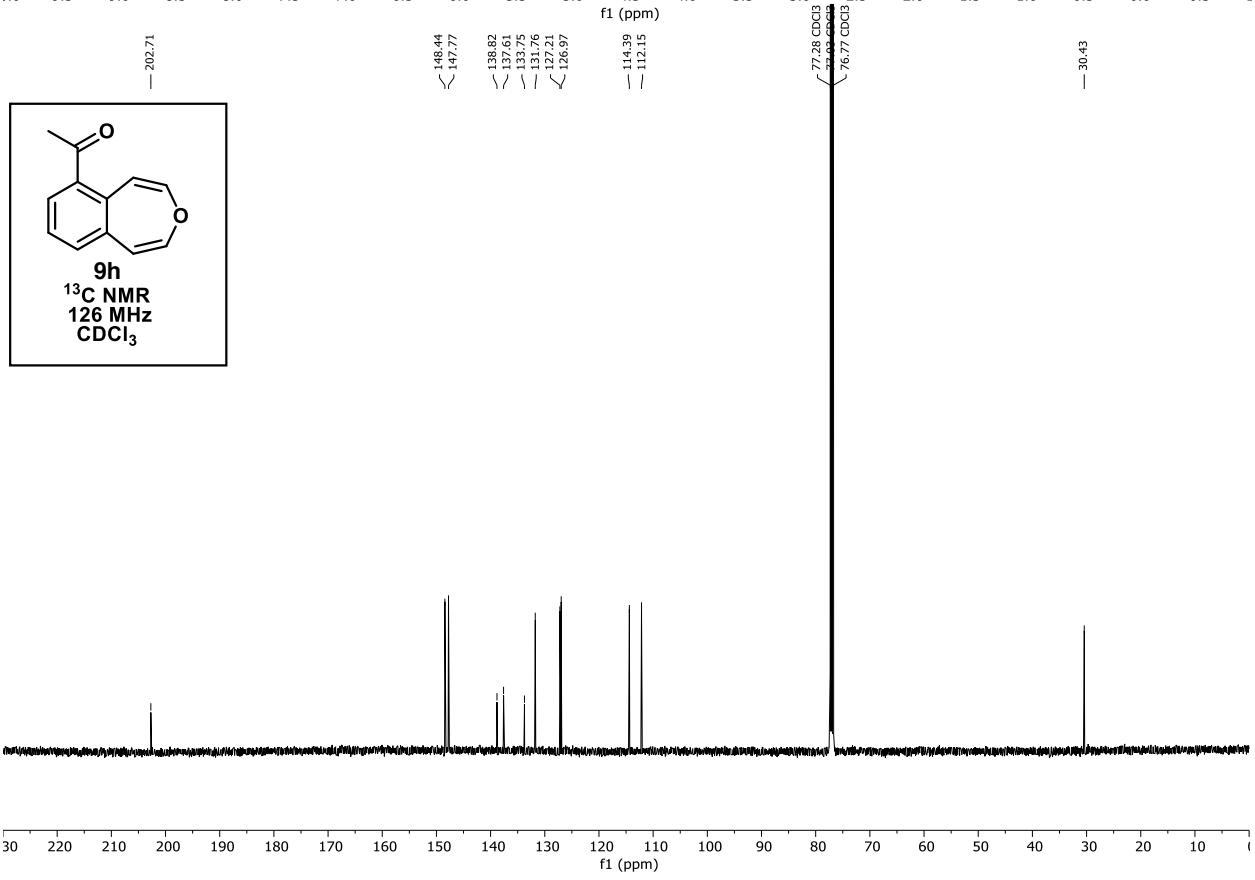

7.26 CDCl3
7.04
7.04
7.03
7.03
7.03
6.92
6.90
6.88
6.64
6.64
6.62
6.62
5.92
5.91
5.86
5.84
5.74
5.73
5.26
5.25
Cl
O
9f
1H NMR
500 MHz
CDCl3
0.98
1.03
1.02
0.99
0.98
0.99
1.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

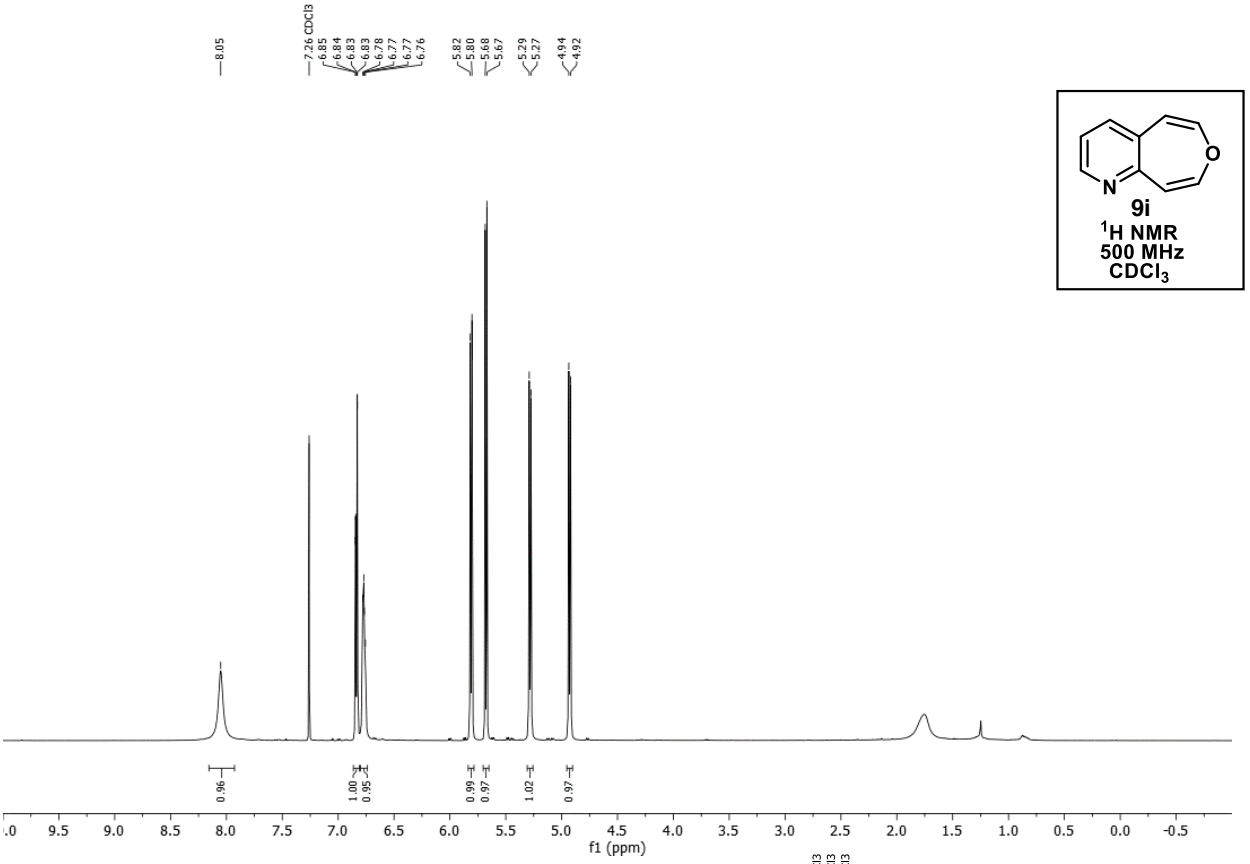

148.00
147.88
137.93
133.31
132.98
128.60
128.56
127.77
113.85
110.53
77.16 CDCl3
Cl
O
9f
13C NMR
126 MHz
CDCl3
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

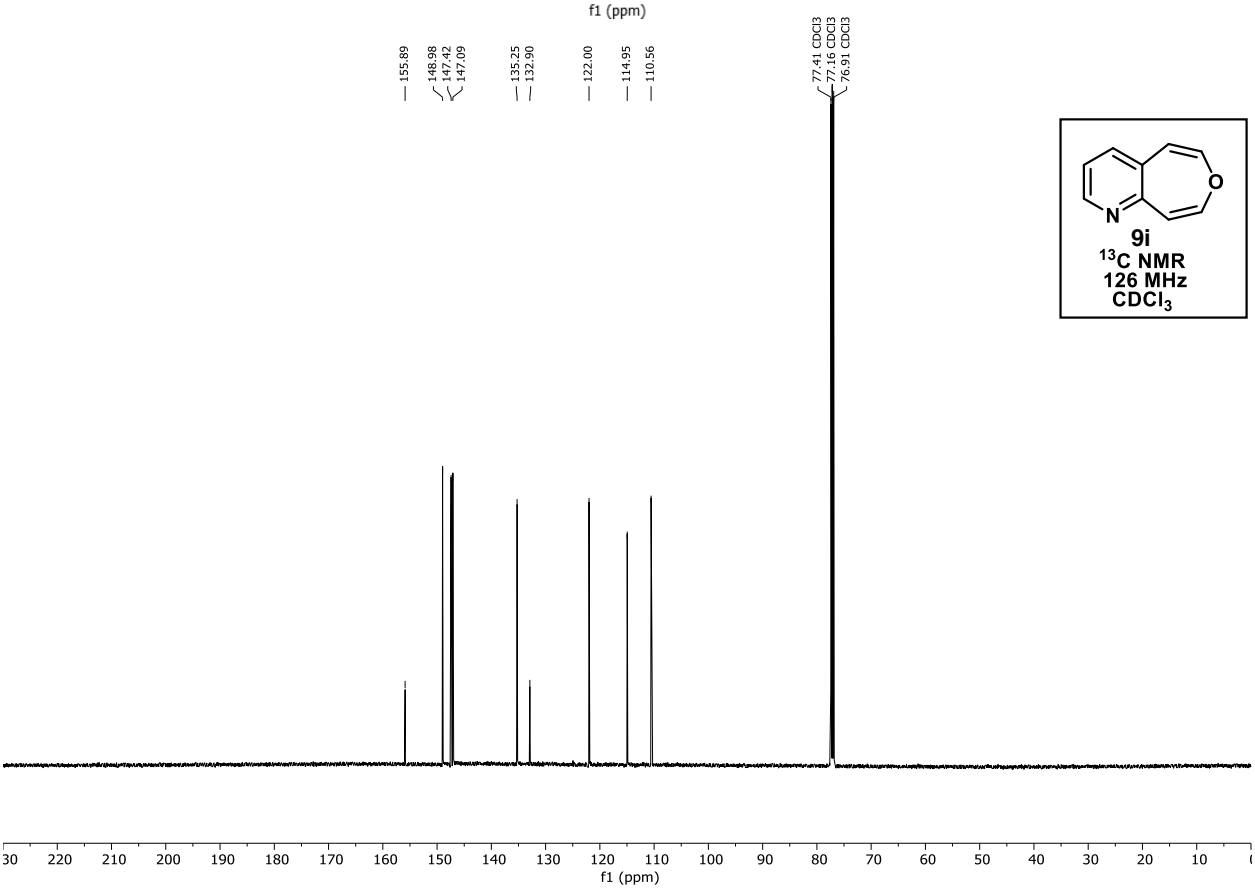

7.26 CDCl3
7.20
7.20
7.19
7.18
6.99
6.97
6.96
6.81
6.80
6.79
6.79
5.85
5.83
5.74
5.72
5.54
5.52
5.10
5.08
CN
O
9g
1H NMR
500 MHz
CDCl3
0.99
1.02
1.02
0.99
0.99
0.98
1.01
f1 (ppm)

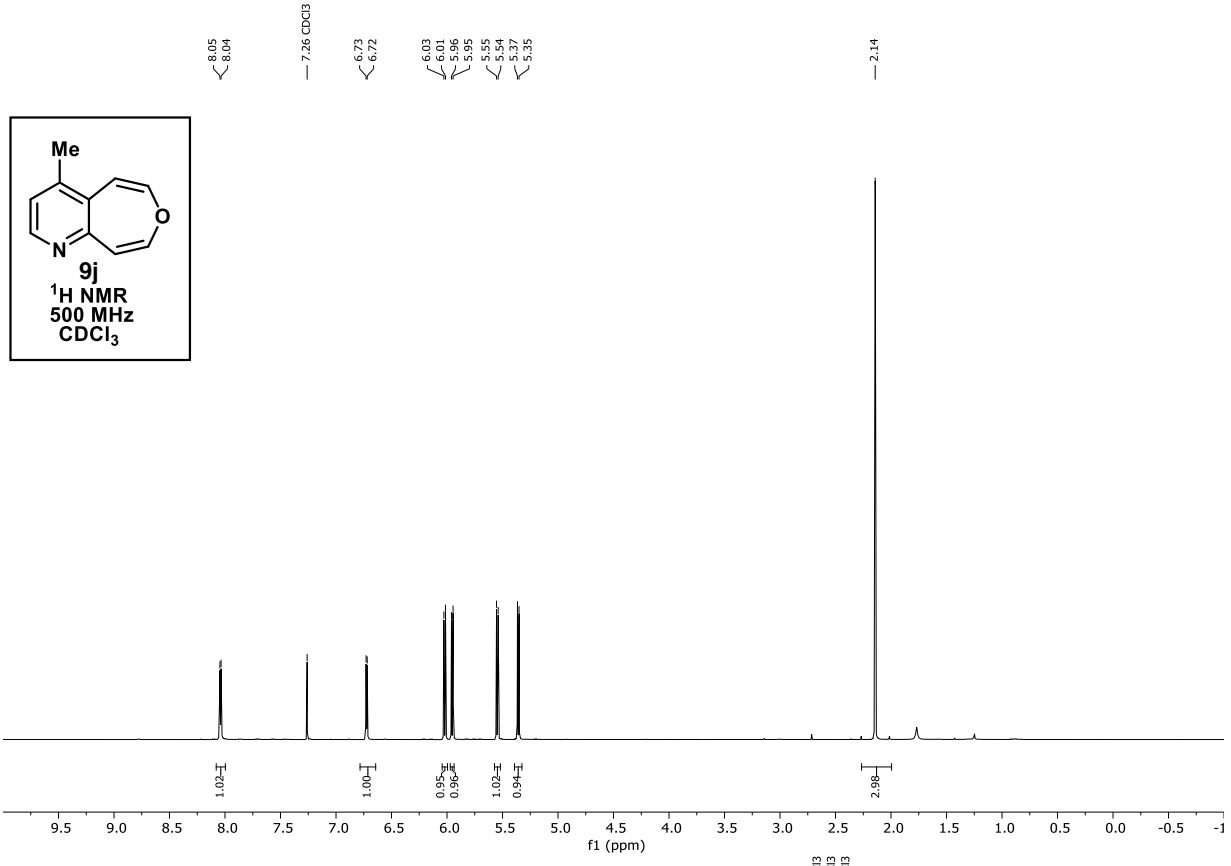

149.91
148.00
139.53
137.37
132.77
131.41
128.05
117.48
112.70
111.51
109.82
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
CN
O
9g
13C NMR
126 MHz
CDCl3
f1 (ppm)

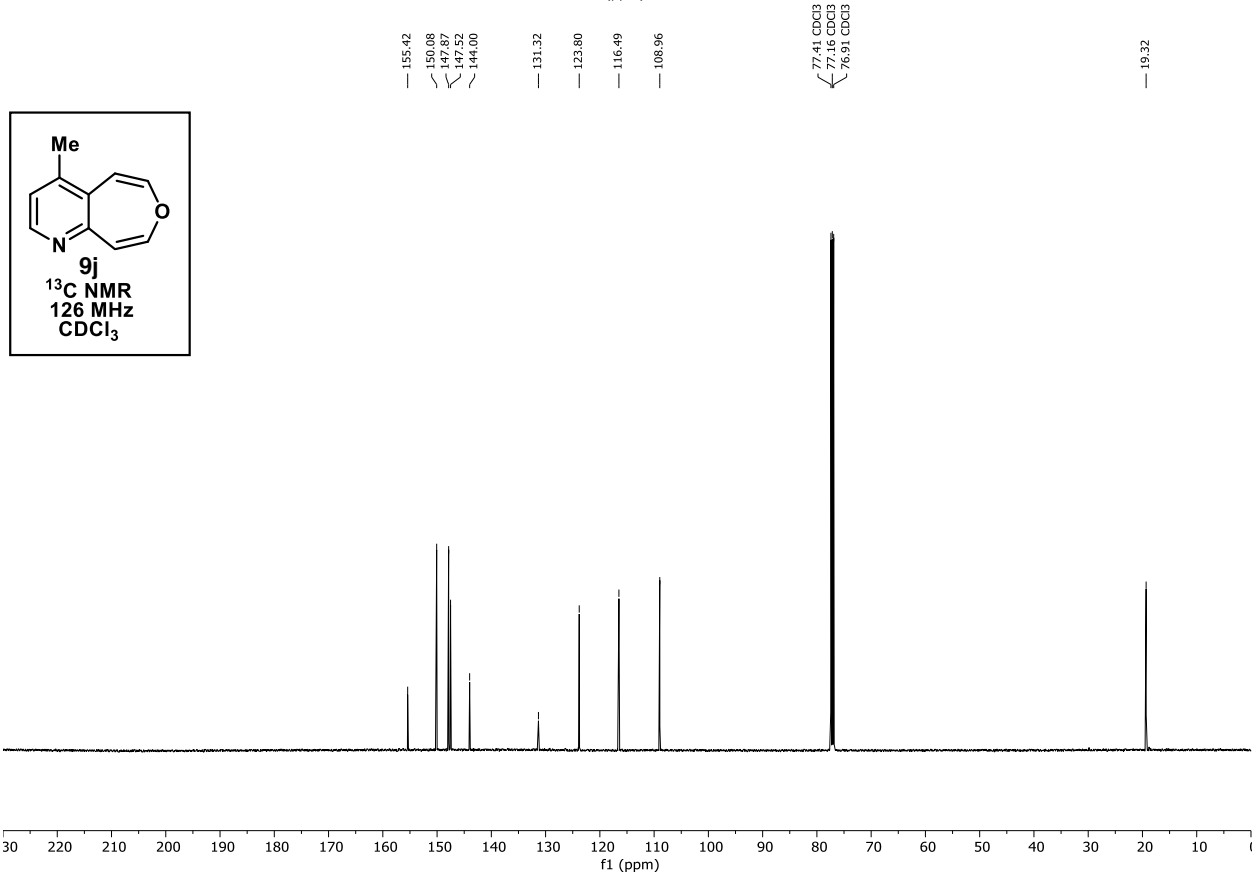

9h
1H NMR
500 MHz
CDCl3
7.26
7.26
7.25
7.25
7.09
7.08
7.06
6.90
6.90
6.88
6.88
5.96
5.95
5.93
5.82
5.81
5.41
5.39
2.52
1.96
1.00
1.08
1.94
0.94
1.02
2.94
f1 (ppm)

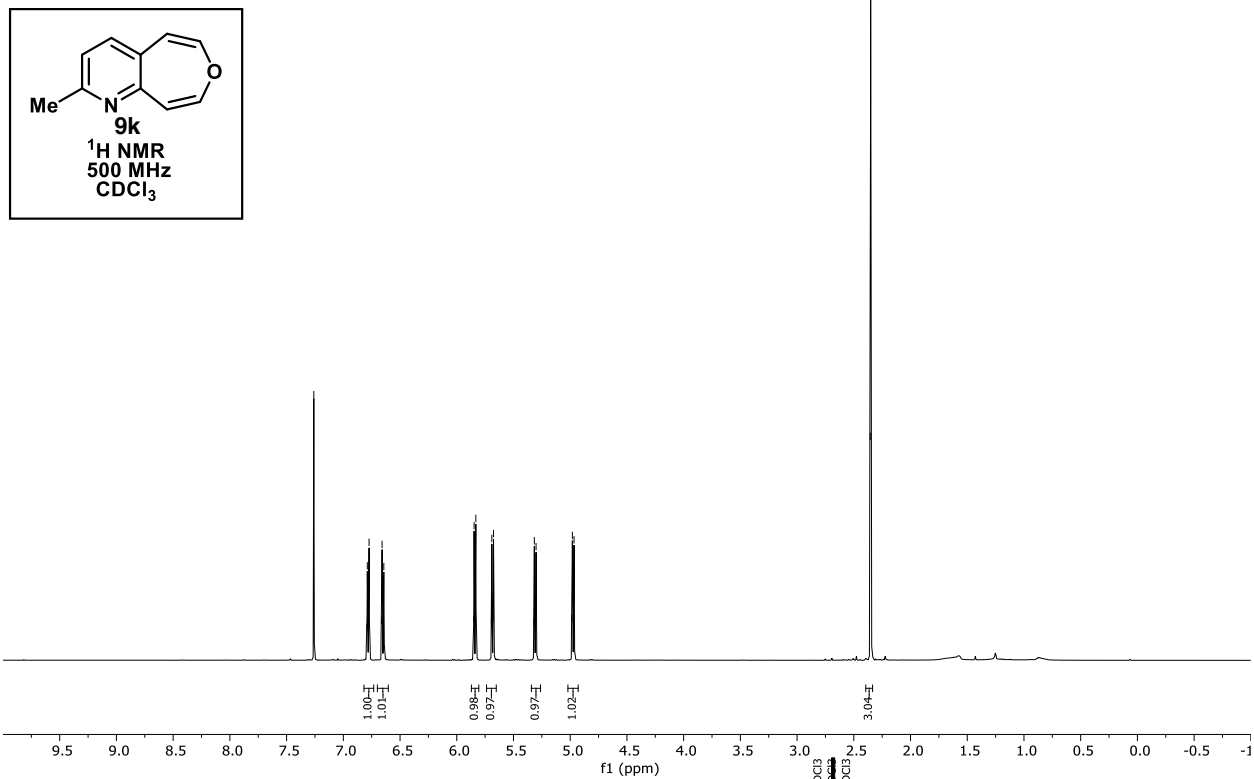

9h
13C NMR
126 MHz
CDCl3
202.71
148.44
147.77
138.82
137.61
133.75
131.76
127.21
126.97
114.39
112.15
77.28 CDCl3
77.02 CDCl3
76.77 CDCl3
30.43
f1 (ppm)

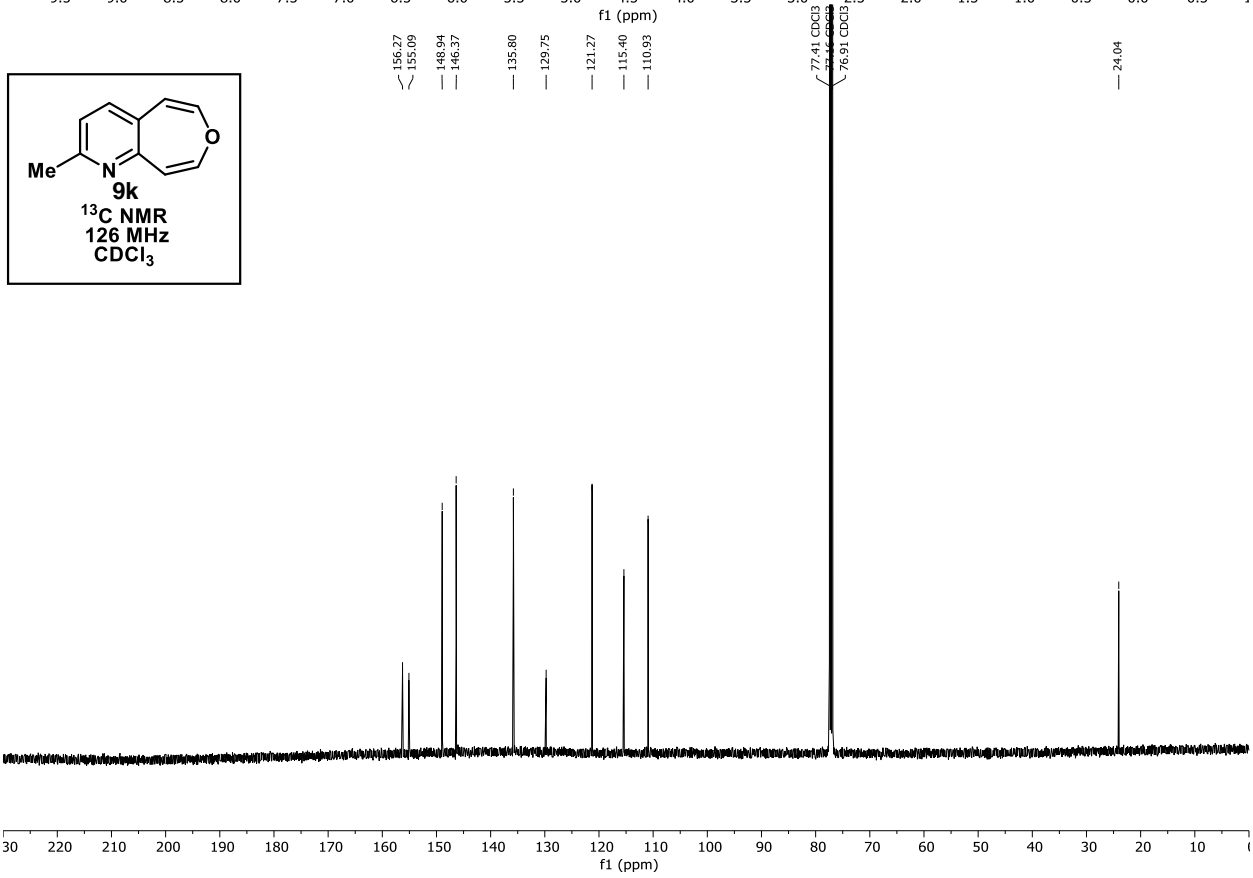

8.05
7.26 CDCl3
6.85
6.84
6.83
6.83
6.78
6.77
6.77
6.76
5.82
5.80
5.68
5.67
5.29
5.27
4.94
4.92
0.96
1.00
0.95
0.99
0.97
1.02
0.97
f1 (ppm)
9i
1H NMR
500 MHz
CDCl3

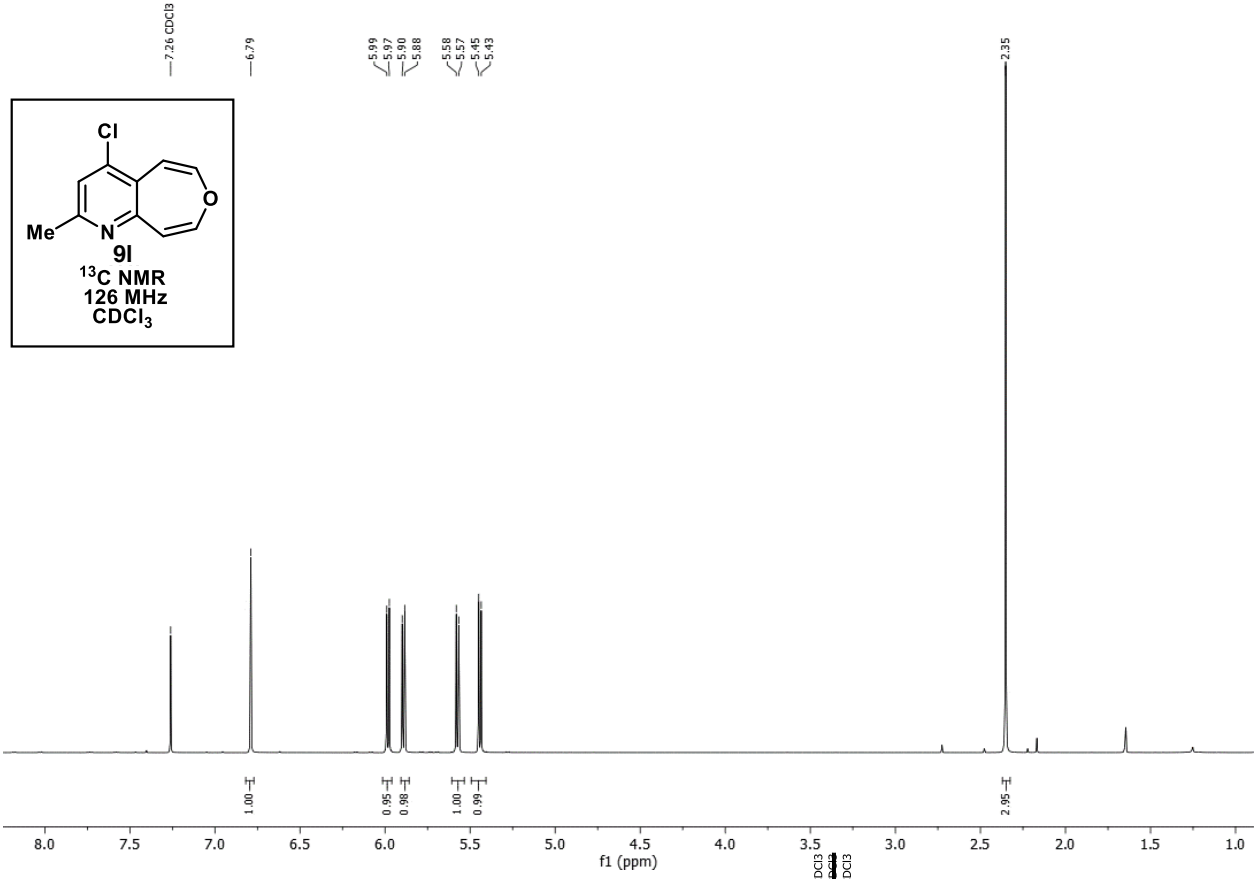

155.89
148.98
147.42
147.09
135.25
132.90
122.00
114.95
110.56
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
f1 (ppm)
9i
13C NMR
126 MHz
CDCl3

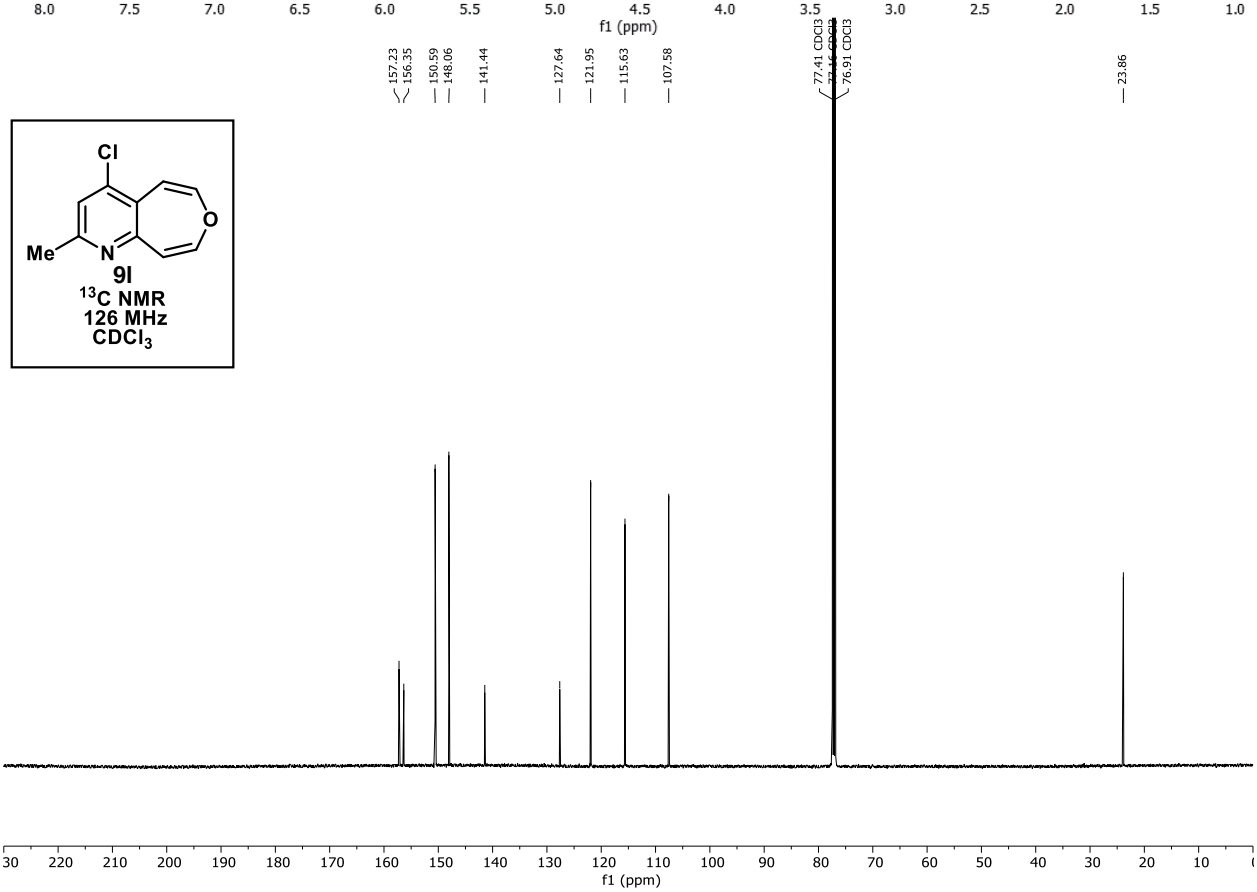

Me
O
N
9j
1H NMR
500 MHz
CDCl3
8.05
8.04
7.26 CDCl3
6.73
6.72
6.03
6.01
5.96
5.95
5.55
5.54
5.37
5.35
2.14
1.02
1.00
0.95
0.96
1.02
0.94
2.98
f1 (ppm)

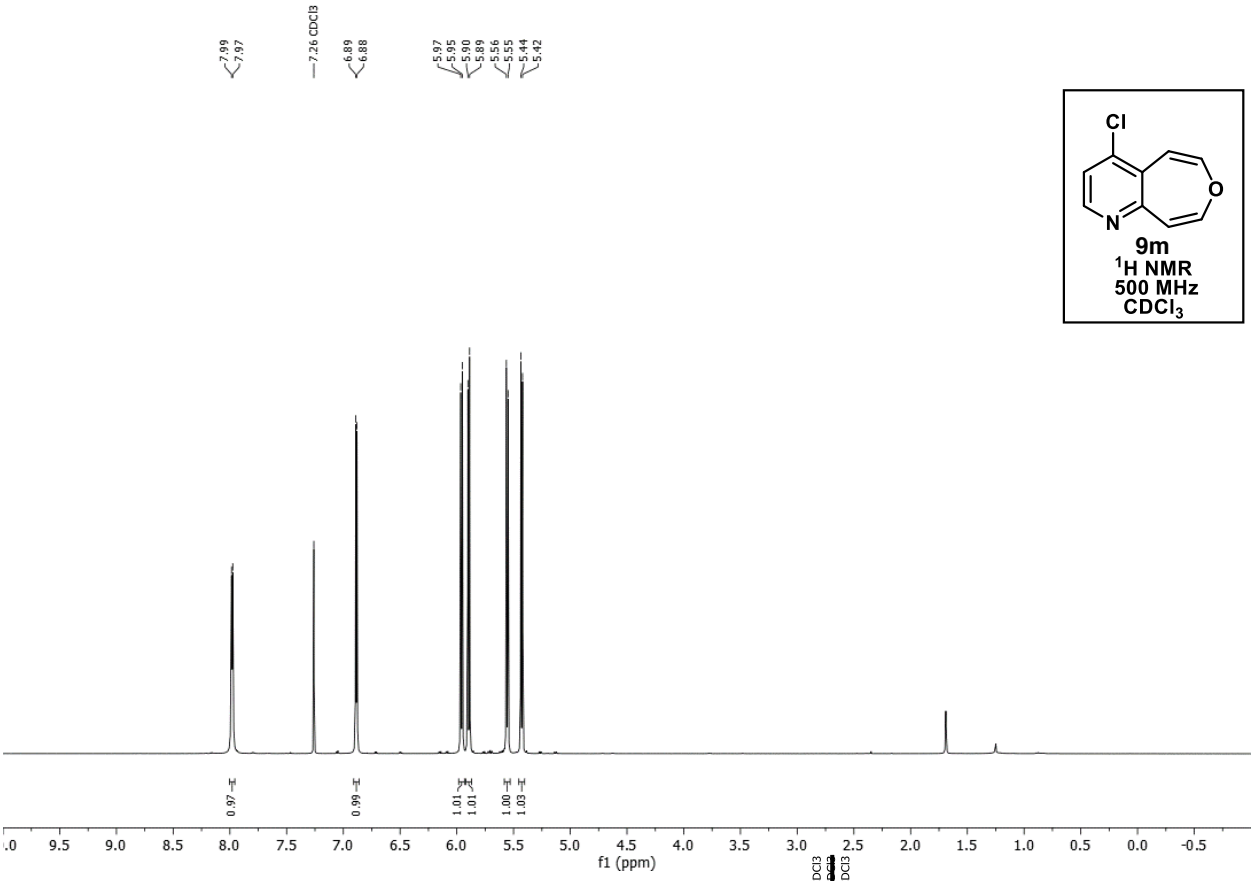

Me
O
N
9j
13C NMR
126 MHz
CDCl3
155.42
150.08
147.87
147.52
144.00
131.32
123.80
116.49
108.96
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
19.32
f1 (ppm)

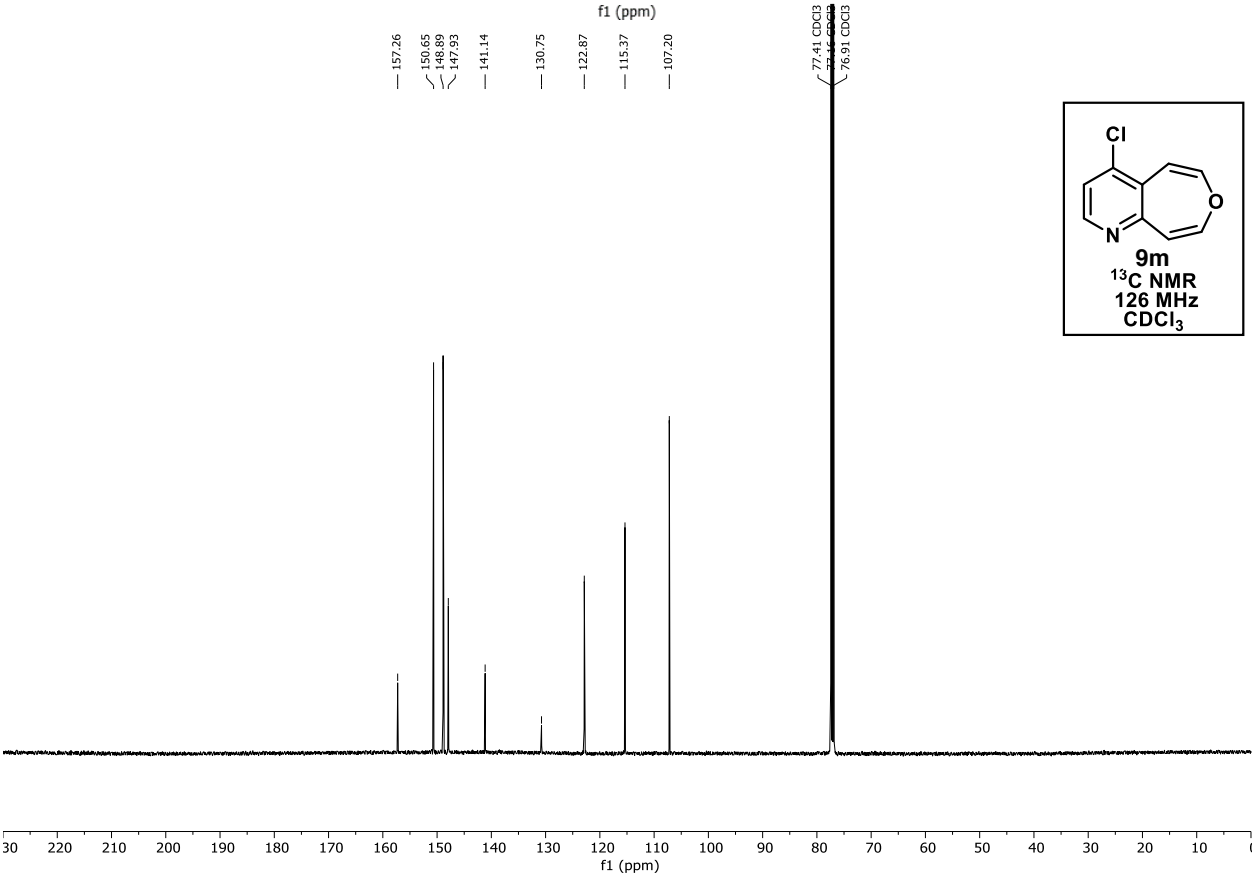

Me
N
O
9k
1H NMR
500 MHz
CDCl3
7.26 CDCl3
6.79
6.78
6.77
6.66
6.65
6.64
5.85
5.84
5.83
5.69
5.68
5.32
5.30
4.98
4.97
2.36
2.35
1.00
1.01
0.98
0.97
0.97
1.02
3.04
f1 (ppm)

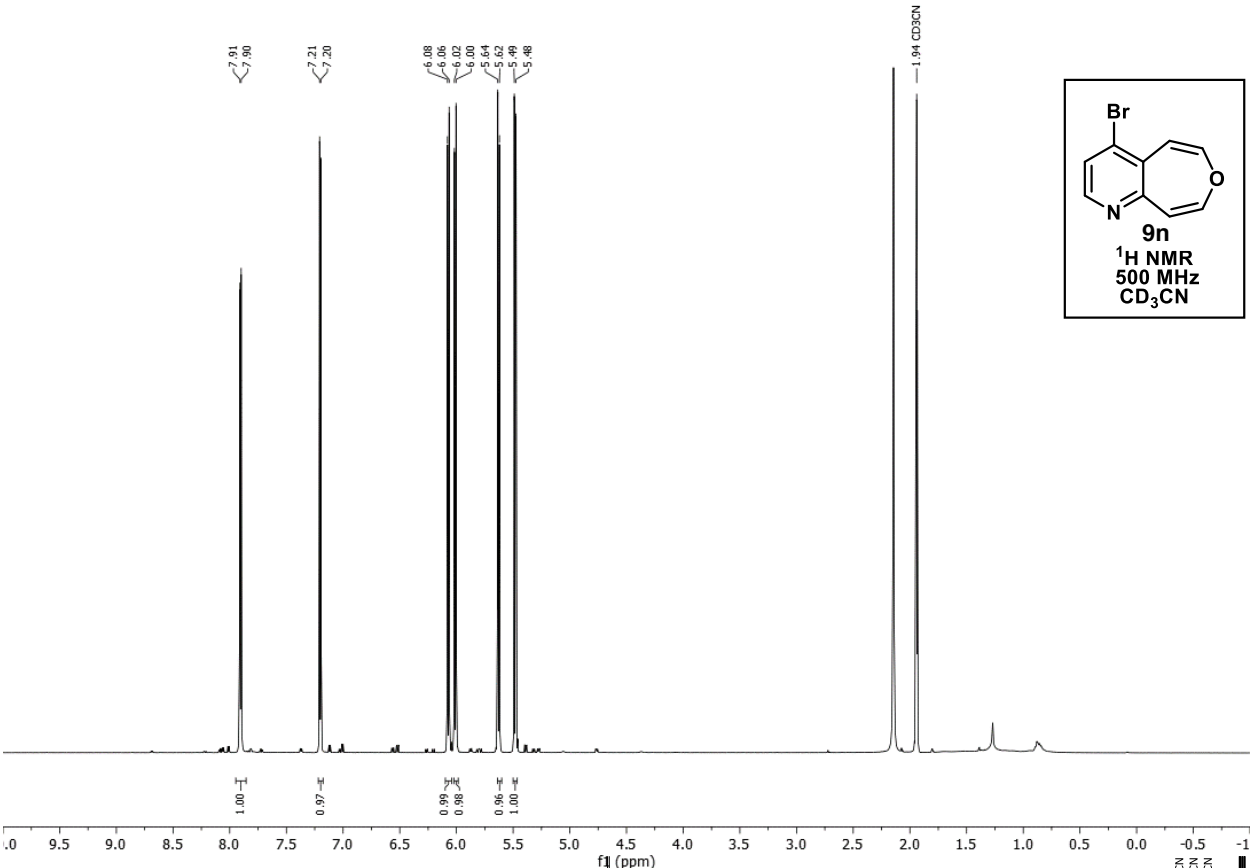

Me
N
O
9k
13C NMR
126 MHz
CDCl3
156.27
155.09
148.94
146.37
135.80
129.75
121.27
115.40
110.93
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
24.04
f1 (ppm)

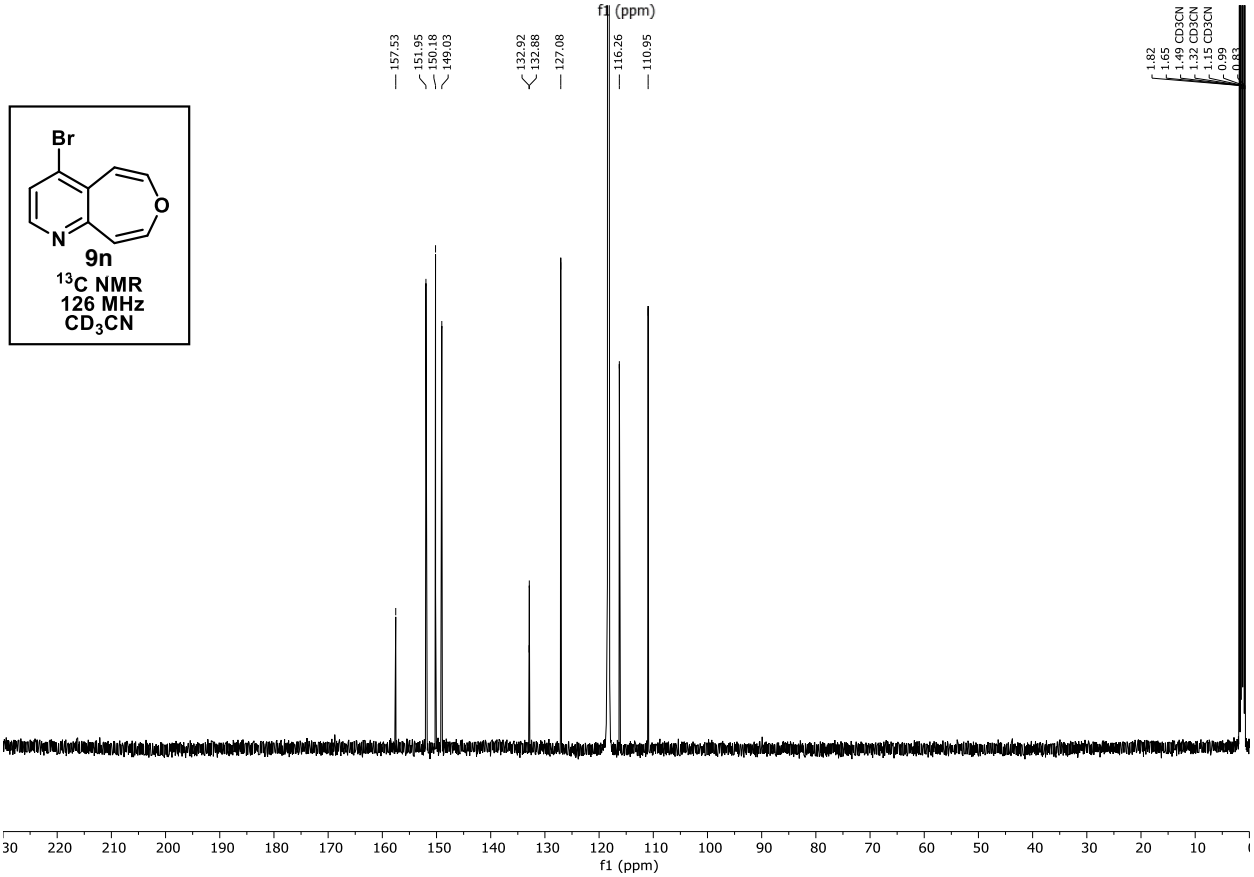

Cl
Me
N
O
9l
^{13}C NMR
126 MHz
$CDCl_3$
7.26 CDCl3
6.79
5.99
5.97
5.90
5.88
5.58
5.57
5.45
5.43
2.35
1.00
0.95
0.98
1.00
0.99
2.95
f1 (ppm)

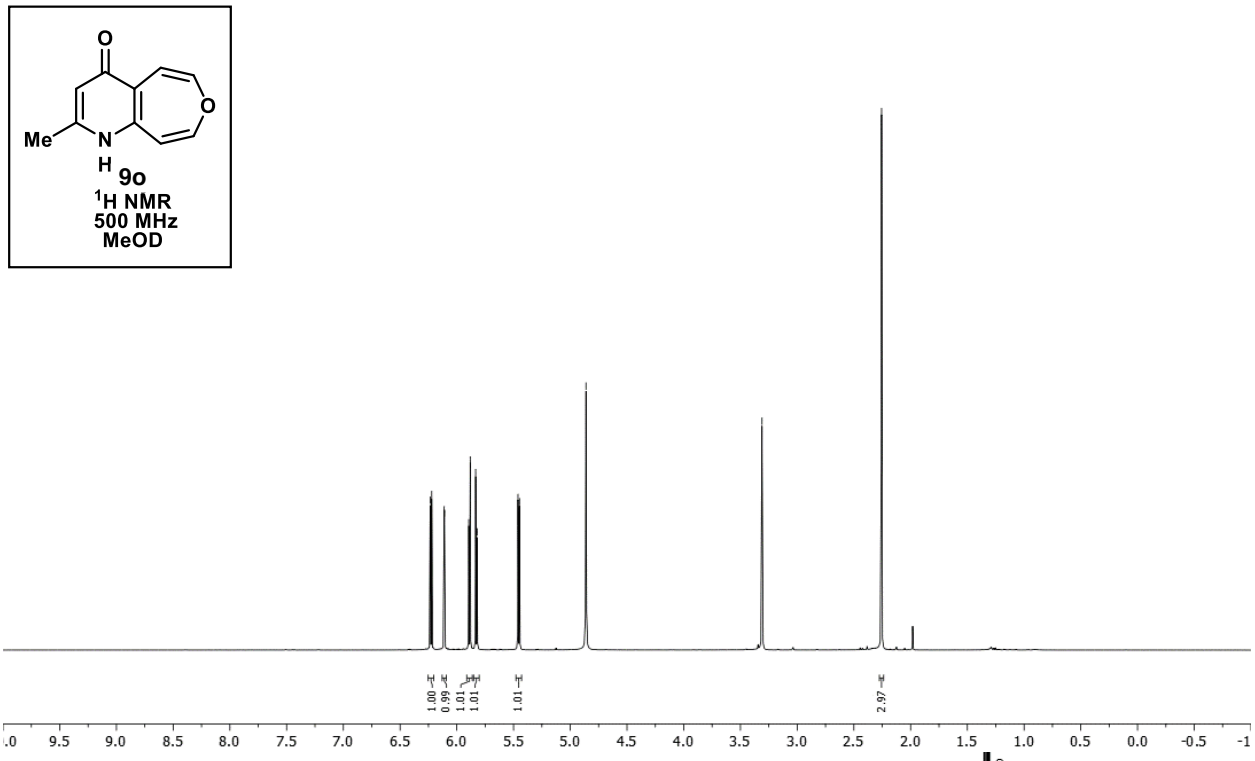

Cl
Me
N
O
9l
^{13}C NMR
126 MHz
$CDCl_3$
157.23
156.35
150.59
148.06
141.44
127.64
121.95
115.63
107.58
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
23.86
f1 (ppm)

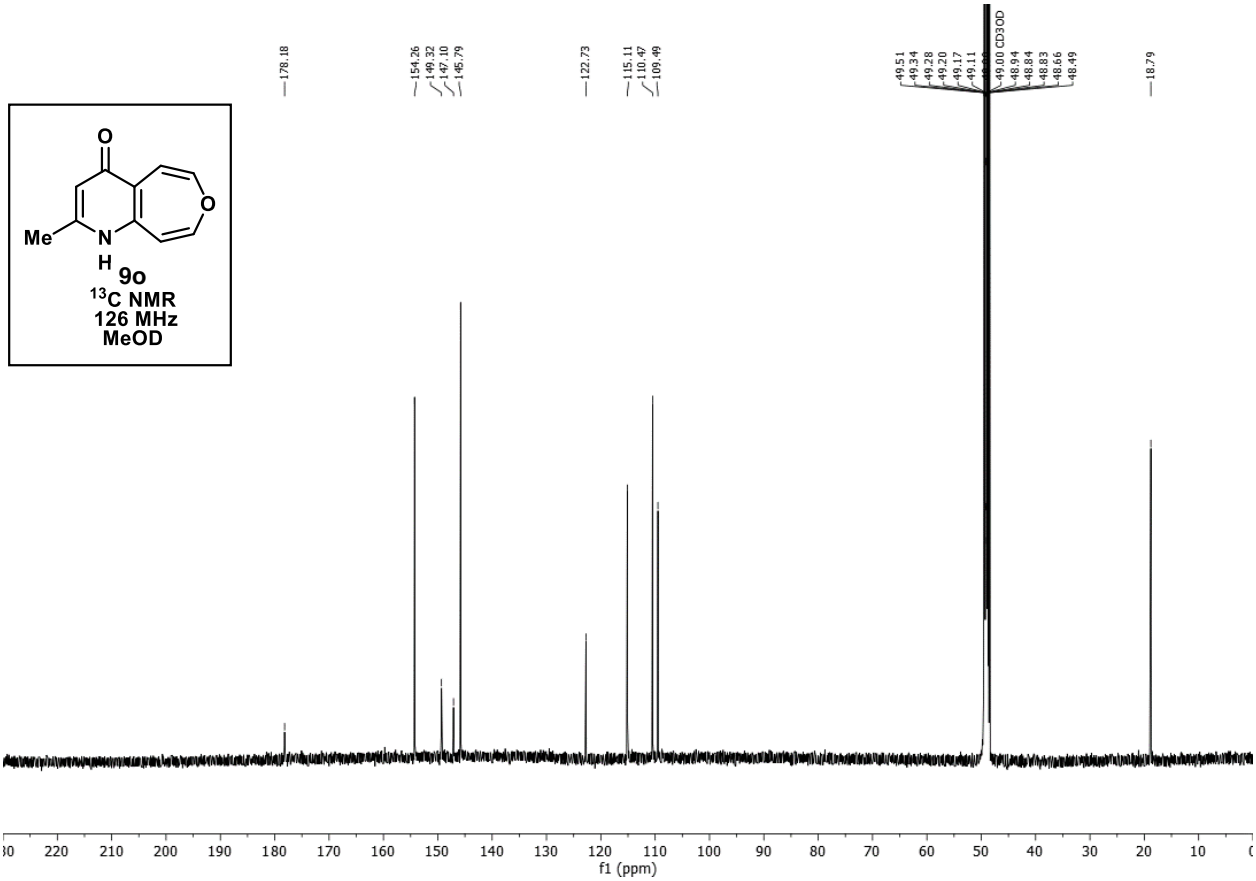

7.99
7.97
7.26 CDCl3
6.89
6.88
5.97
5.95
5.90
5.89
5.56
5.55
5.44
5.42
Cl
O
N
9m
1H NMR
500 MHz
CDCl3
0.97
0.99
1.01
1.01
1.00
1.03
f1 (ppm)

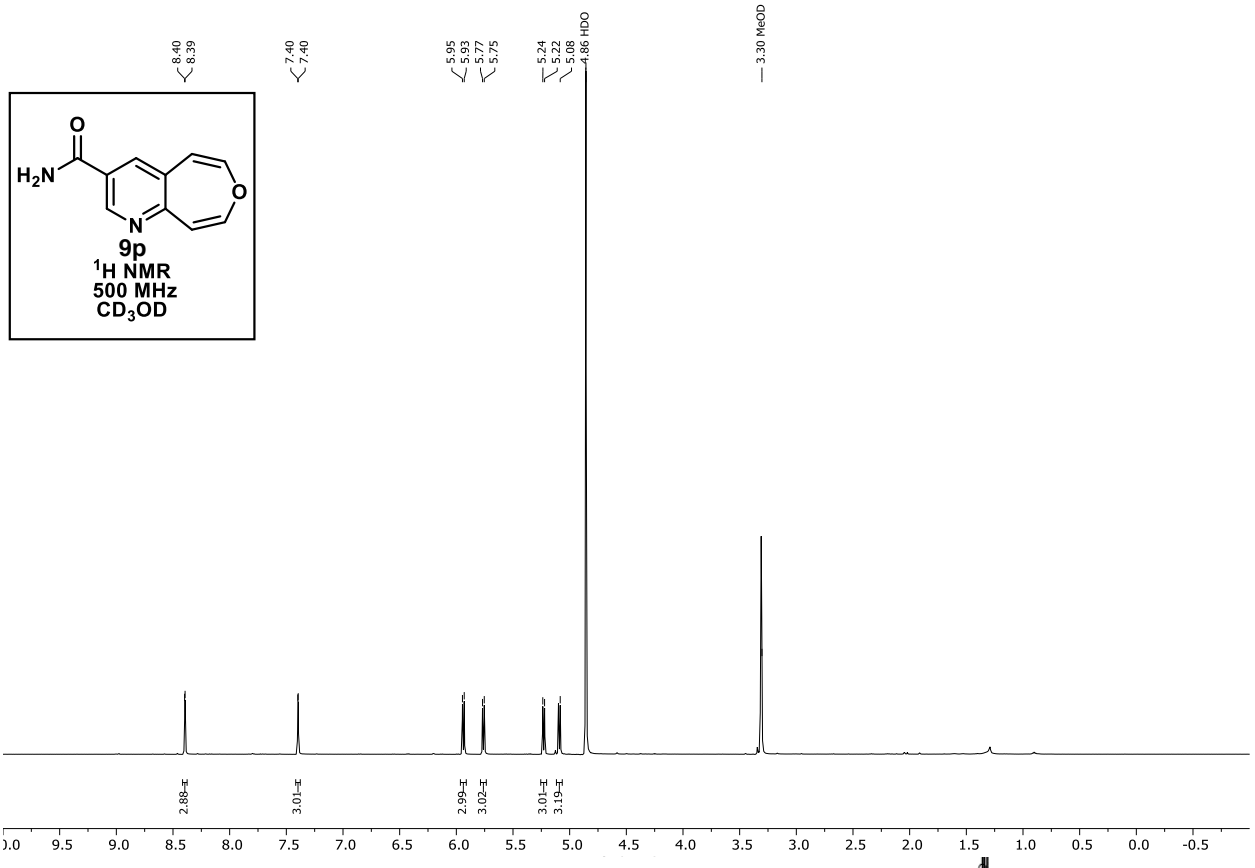

157.26
150.65
148.89
147.93
141.14
130.75
122.87
115.37
107.20
77.41 CDCl3
76.91 CDCl3
Cl
O
N
9m
13C NMR
126 MHz
CDCl3
f1 (ppm)

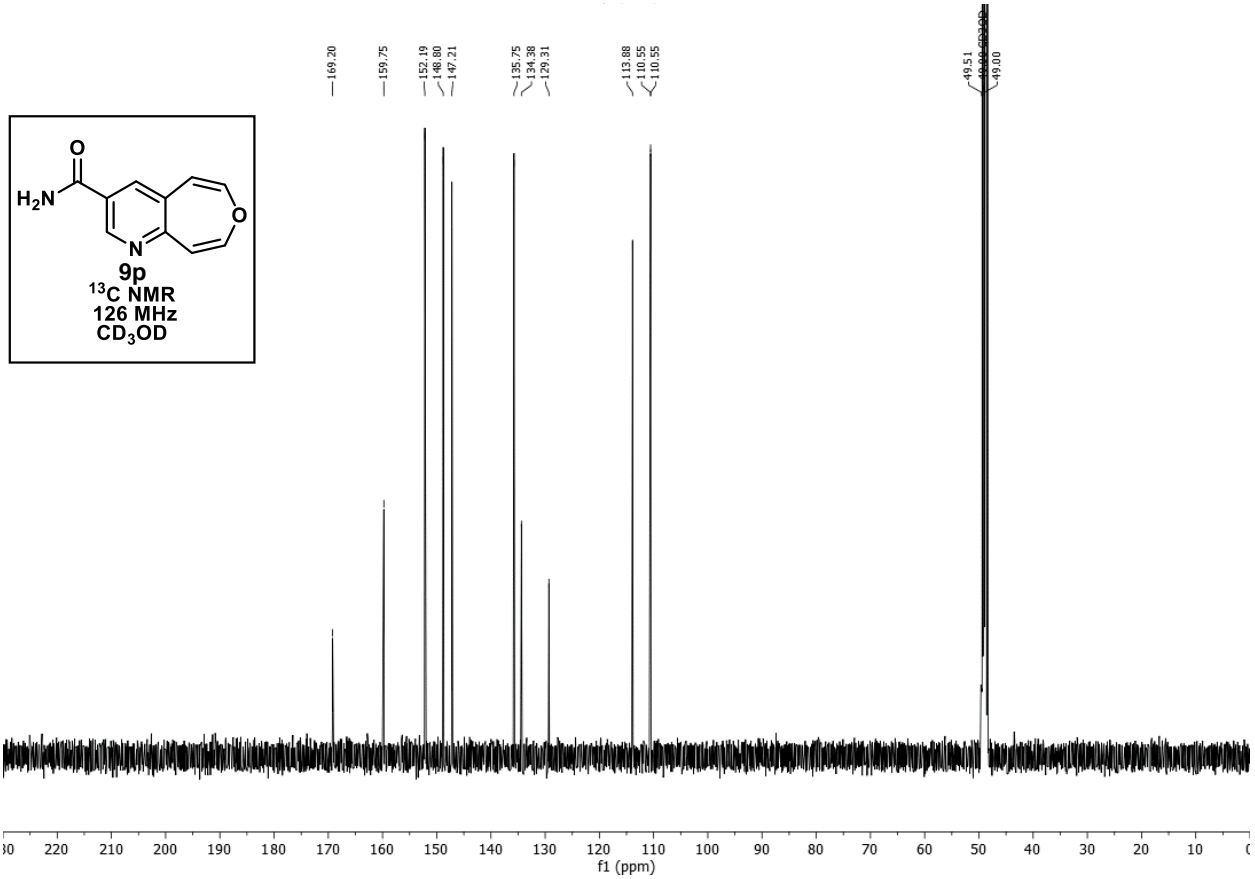

7.91
7.90
7.21
7.20
6.08
6.06
6.02
6.00
5.64
5.62
5.49
5.48
1.94 CD3CN
1.00
0.97
0.99
0.98
0.96
1.00
f1 (ppm)
Br
O
N
9n
1H NMR
500 MHz
CD3CN

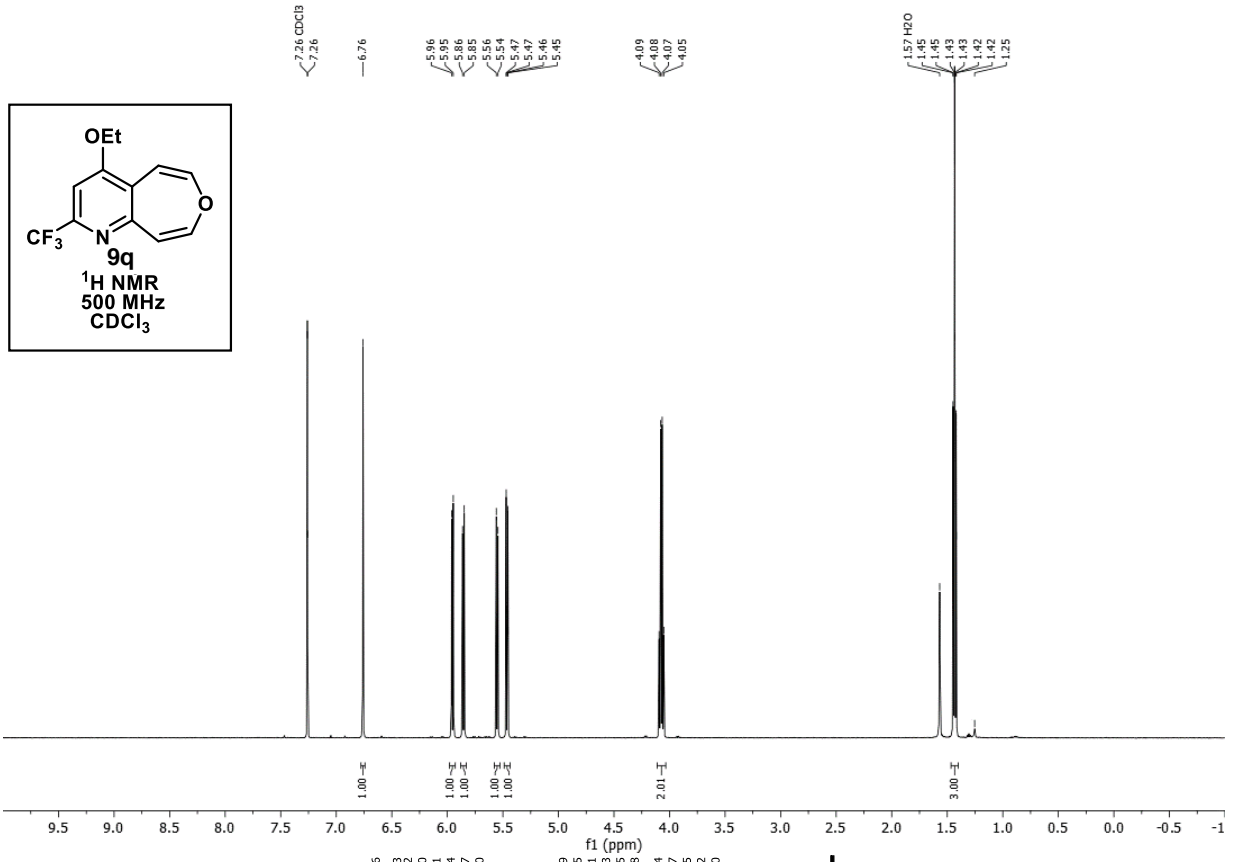

157.53
151.95
150.18
149.03
132.92
132.88
127.08
116.26
110.95
1.82
1.65
1.49 CD3CN
1.32 CD3CN
1.15 CD3CN
0.99
0.83
f1 (ppm)
Br
O
N
9n
13C NMR
126 MHz
CD3CN

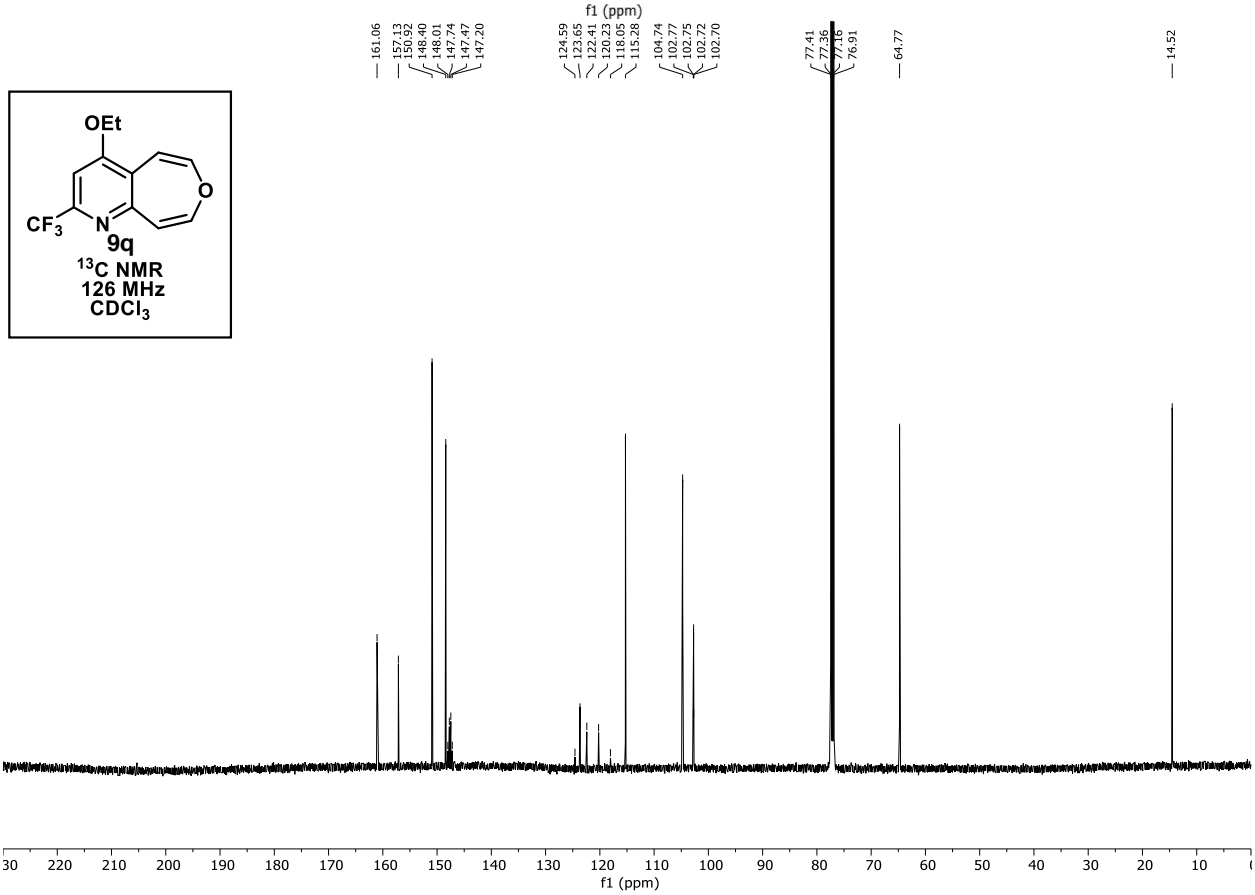

6.23
6.22
6.11
6.11
5.89
5.88
5.83
5.82
5.46
5.45
4.86 HDO
3.31 CD3OD
2.26
O
Me
N
H
O
1.00
0.99
1.01
1.01
1.01
2.97
9o
1H NMR
500 MHz
MeOD

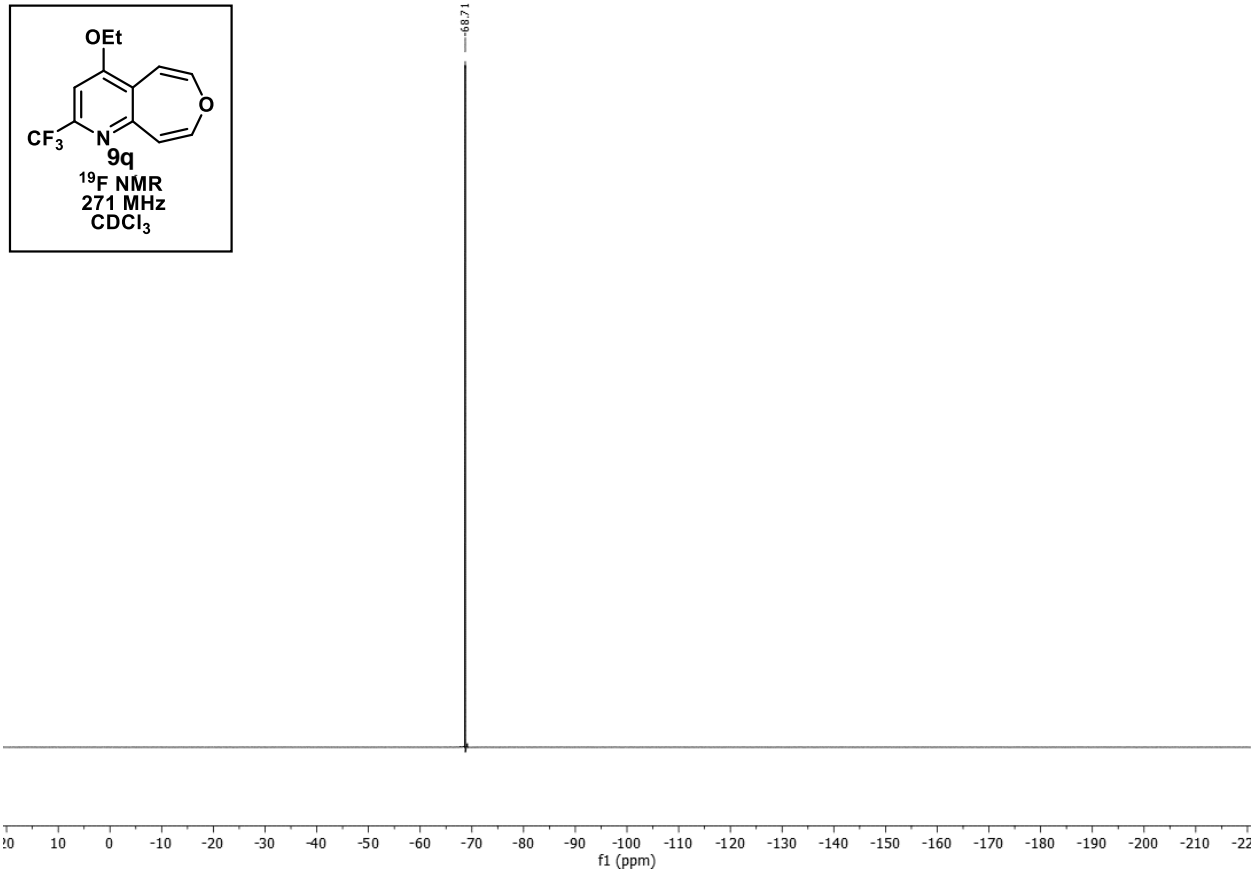

178.18
154.26
149.32
147.10
145.79
122.73
115.11
110.47
109.49
49.51
49.34
49.28
49.20
49.17
49.11
49.00 CD3OD
48.94
48.84
48.83
48.66
48.49
18.79
O
Me
N
H
O
9o
13C NMR
126 MHz
MeOD
f1 (ppm)

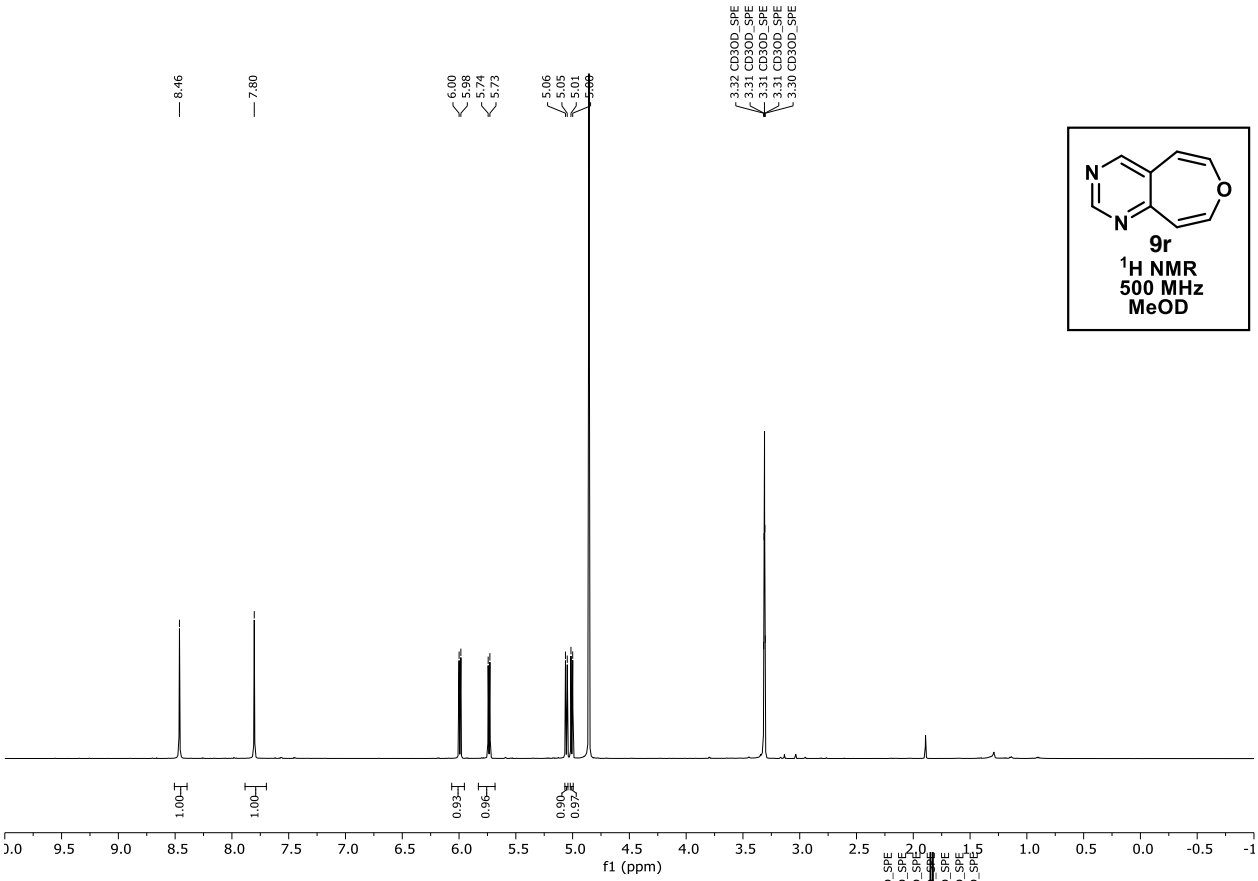

8.40
8.39
7.40
7.40
5.95
5.93
5.77
5.75
5.24
5.22
5.08
4.86 HDO
3.30 MeOD
O
H2N
O
N
9p
1H NMR
500 MHz
CD3OD
2.88
3.01
2.99
3.02
3.01
3.19
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

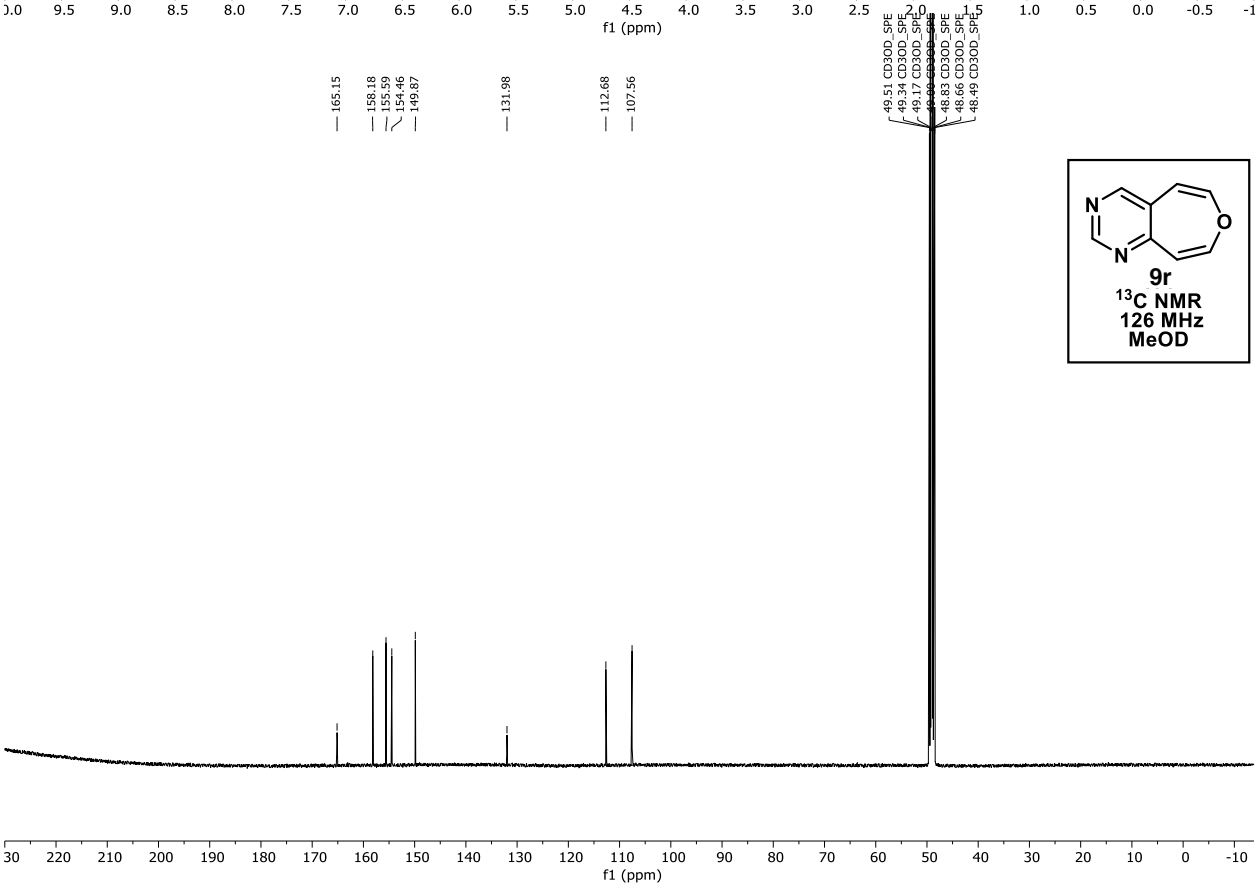

169.20
159.75
152.19
148.80
147.21
135.75
134.38
129.31
113.88
110.55
110.55
49.51
49.00
O
H2N
O
N
9p
13C NMR
126 MHz
CD3OD
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

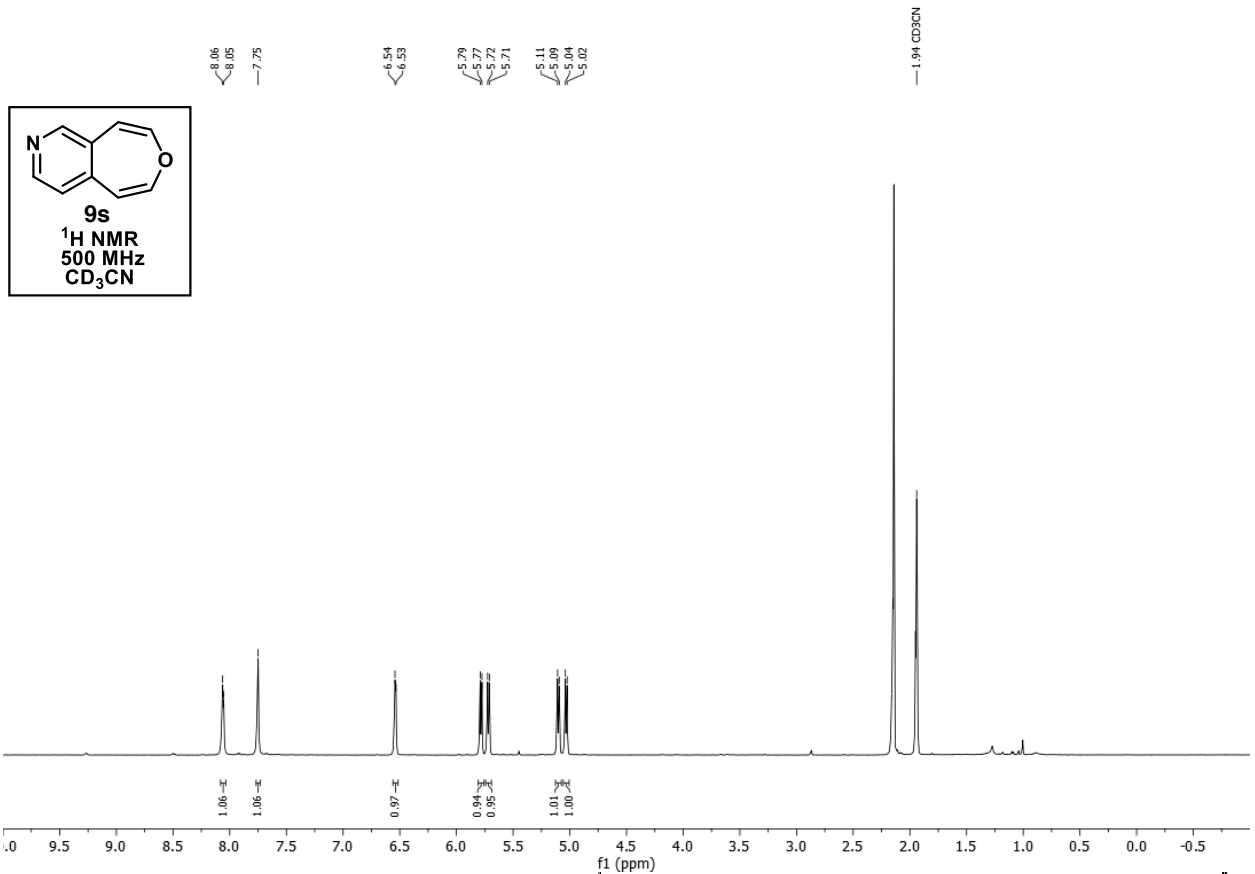

OEt
O
CF3
N
9q
1H NMR
500 MHz
CDCl3
7.26 CDCl3
7.26
6.76
5.96
5.95
5.86
5.85
5.56
5.54
5.47
5.47
5.46
5.45
4.09
4.08
4.07
4.05
1.57 H2O
1.45
1.45
1.43
1.43
1.42
1.42
1.25
1.00
1.00
1.00
1.00
1.00
2.01
3.00
f1 (ppm)

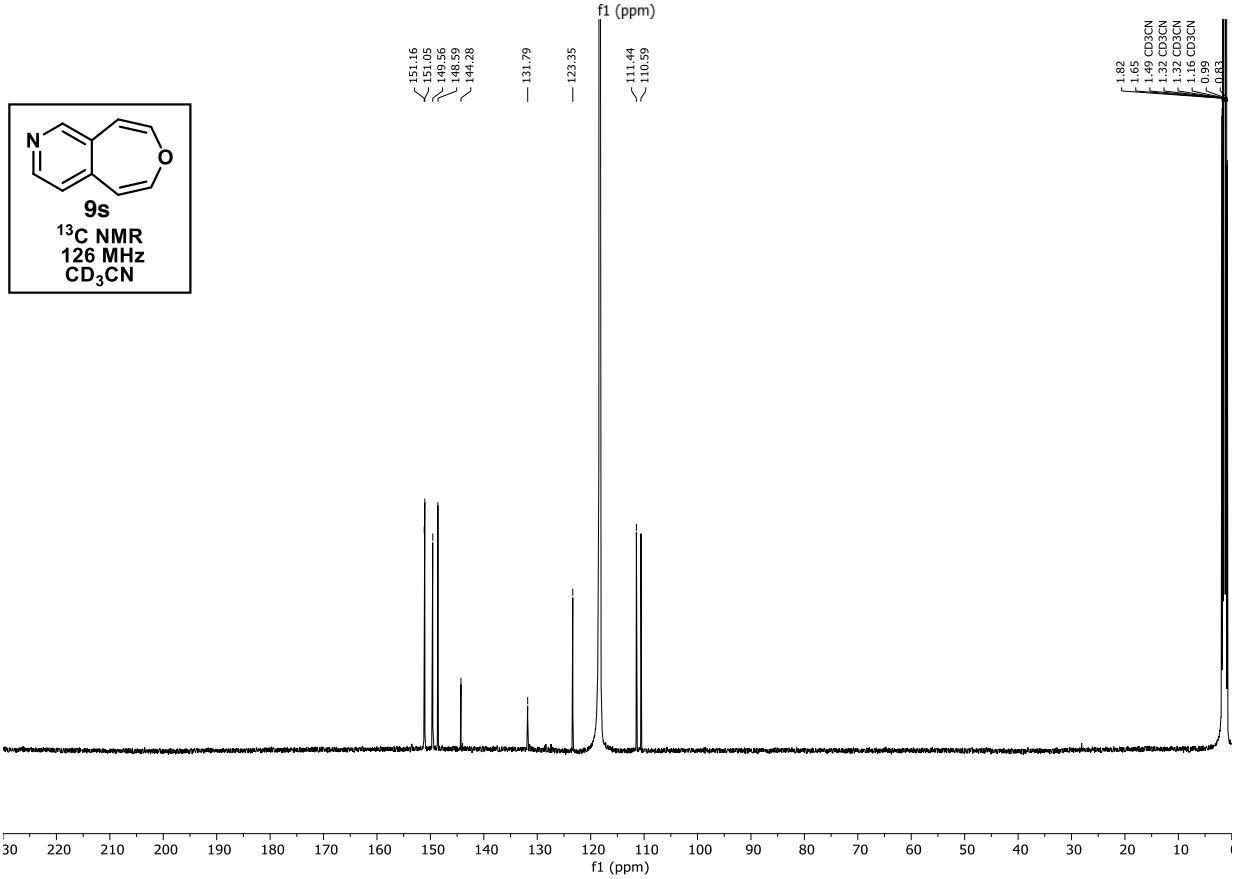

OEt
O
CF3
N
9q
13C NMR
126 MHz
CDCl3
161.06
157.13
150.92
148.40
148.01
147.74
147.47
147.20
124.59
123.65
122.41
120.23
118.05
115.28
104.74
102.77
102.75
102.72
102.70
77.41
77.36
77.16
76.91
64.77
14.52
f1 (ppm)

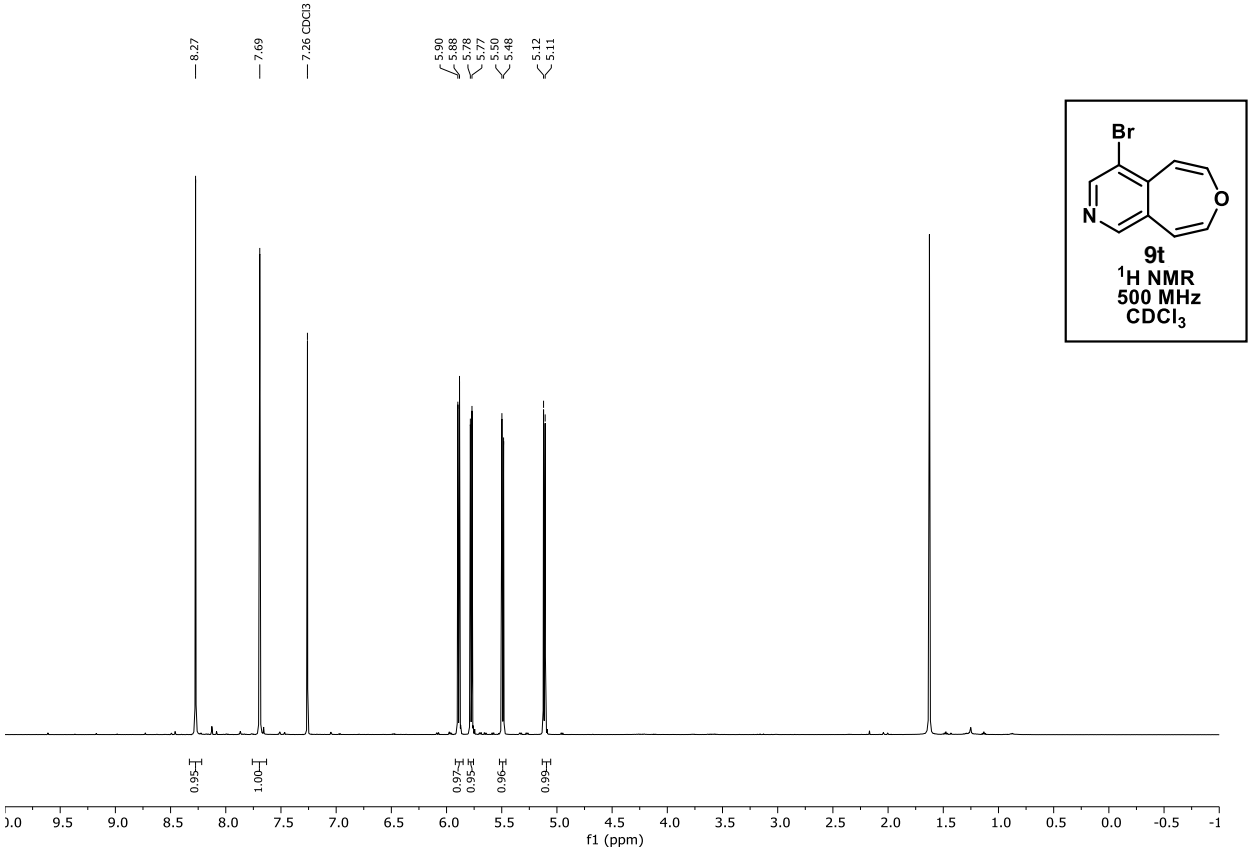

OEt
O
CF3
N
9q
19F NMR
271 MHz
CDCl3
-68.71
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

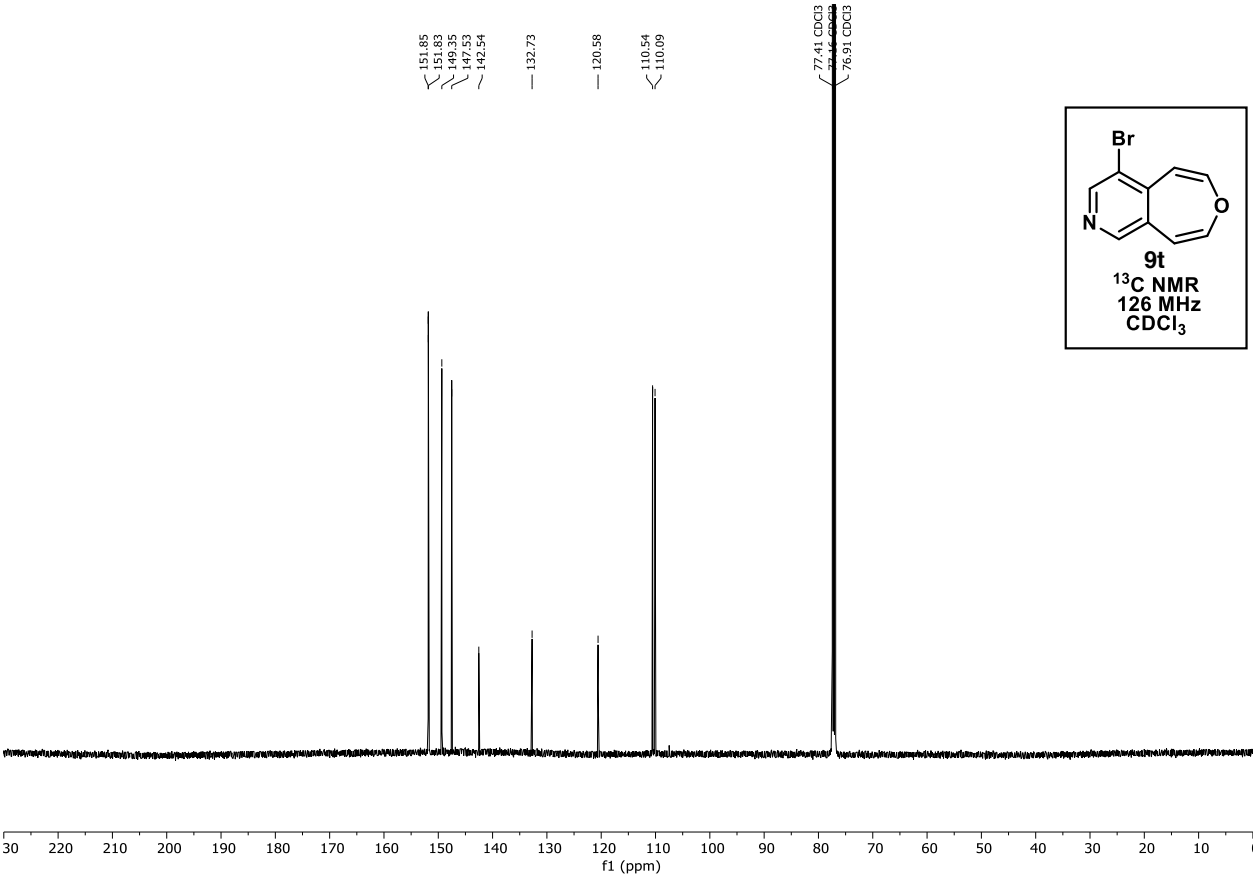

8.46
7.80
6.00
5.98
5.74
5.73
5.06
5.05
5.01
5.00
3.32 CD3OD_SPE
3.31 CD3OD_SPE
3.31 CD3OD_SPE
3.31 CD3OD_SPE
3.30 CD3OD_SPE
1.00
1.00
0.93
0.96
0.90
0.97
f1 (ppm)
9r
1H NMR
500 MHz
MeOD

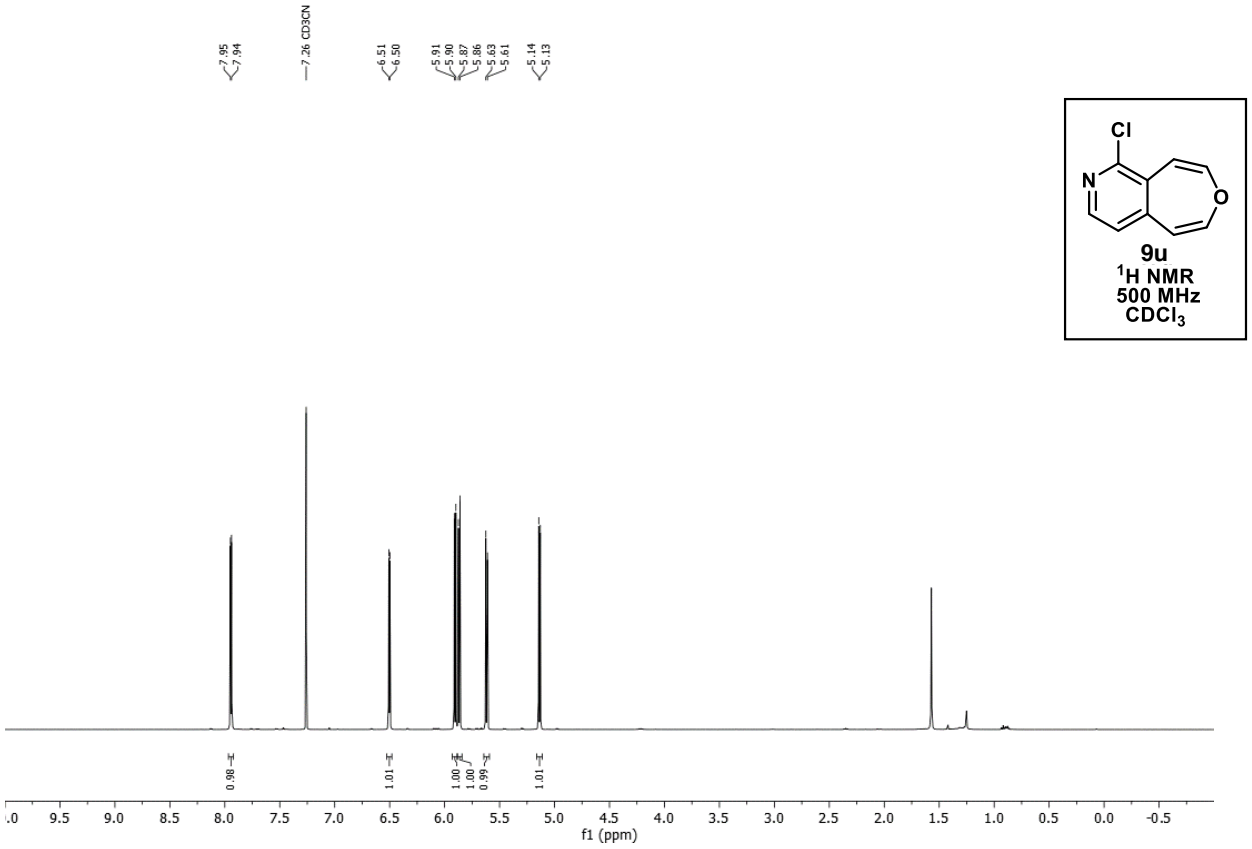

165.15
158.18
155.59
154.46
149.87
131.98
112.68
107.56
49.51 CD3OD_SPE
49.34 CD3OD_SPE
49.17 CD3OD_SPE
48.83 CD3OD_SPE
48.66 CD3OD_SPE
48.49 CD3OD_SPE
f1 (ppm)
9r
13C NMR
126 MHz
MeOD

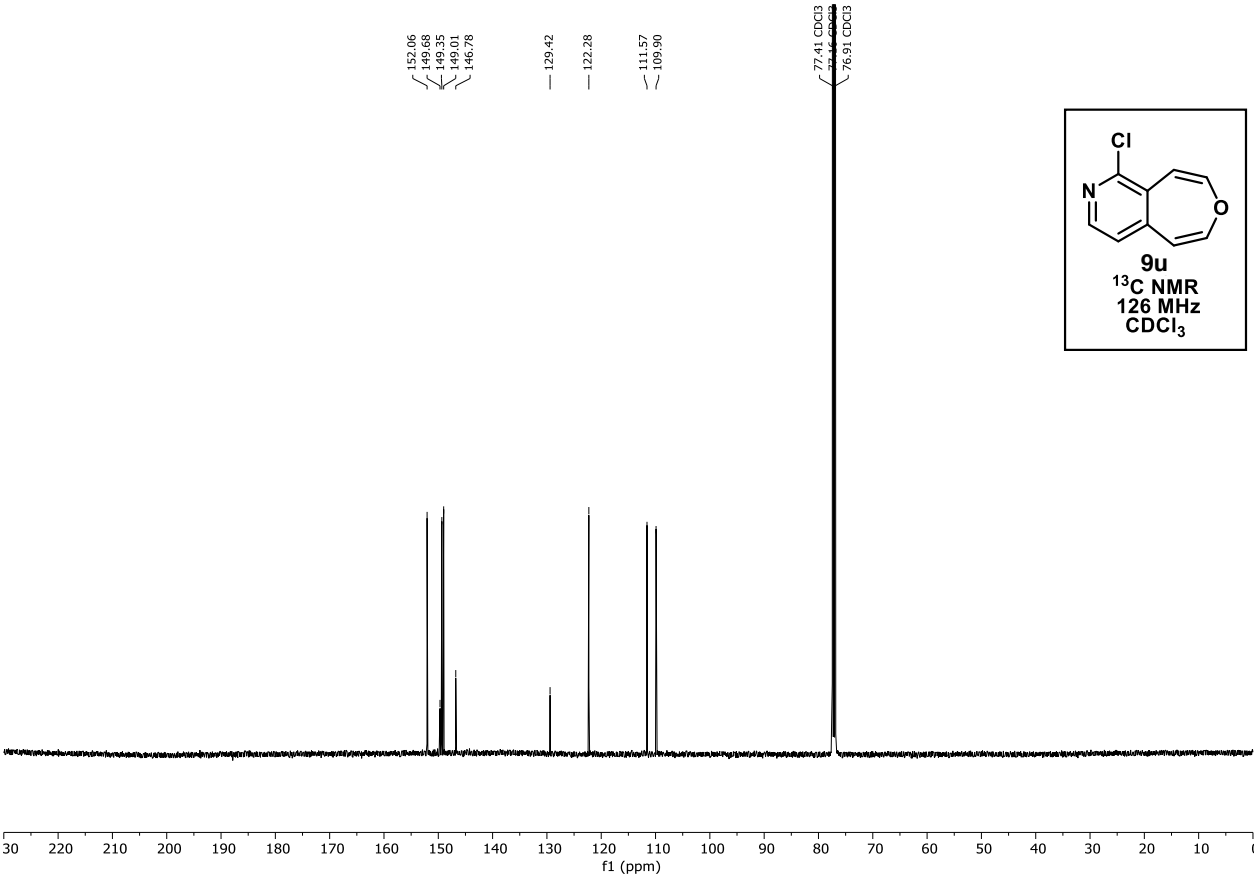

9s
1H NMR
500 MHz
CD3CN
8.06
8.05
7.75
6.54
6.53
5.79
5.77
5.72
5.71
5.11
5.09
5.04
5.02
1.94 CD3CN
1.06
1.06
0.97
0.94
0.95
1.01
1.00
f1 (ppm)

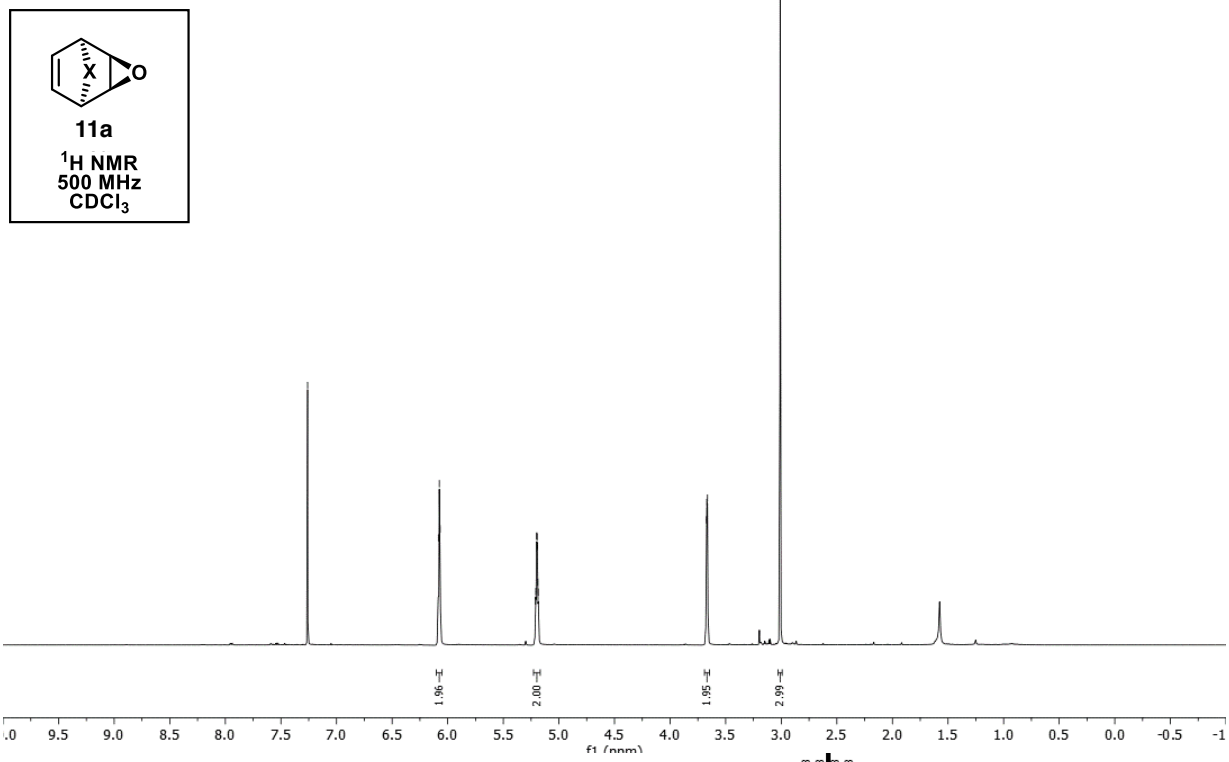

9s
13C NMR
126 MHz
CD3CN
151.16
151.05
149.56
148.59
144.28
131.79
123.35
111.44
110.59
1.82
1.65
1.49 CD3CN
1.32 CD3CN
1.32 CD3CN
1.16 CD3CN
0.99
0.83
f1 (ppm)

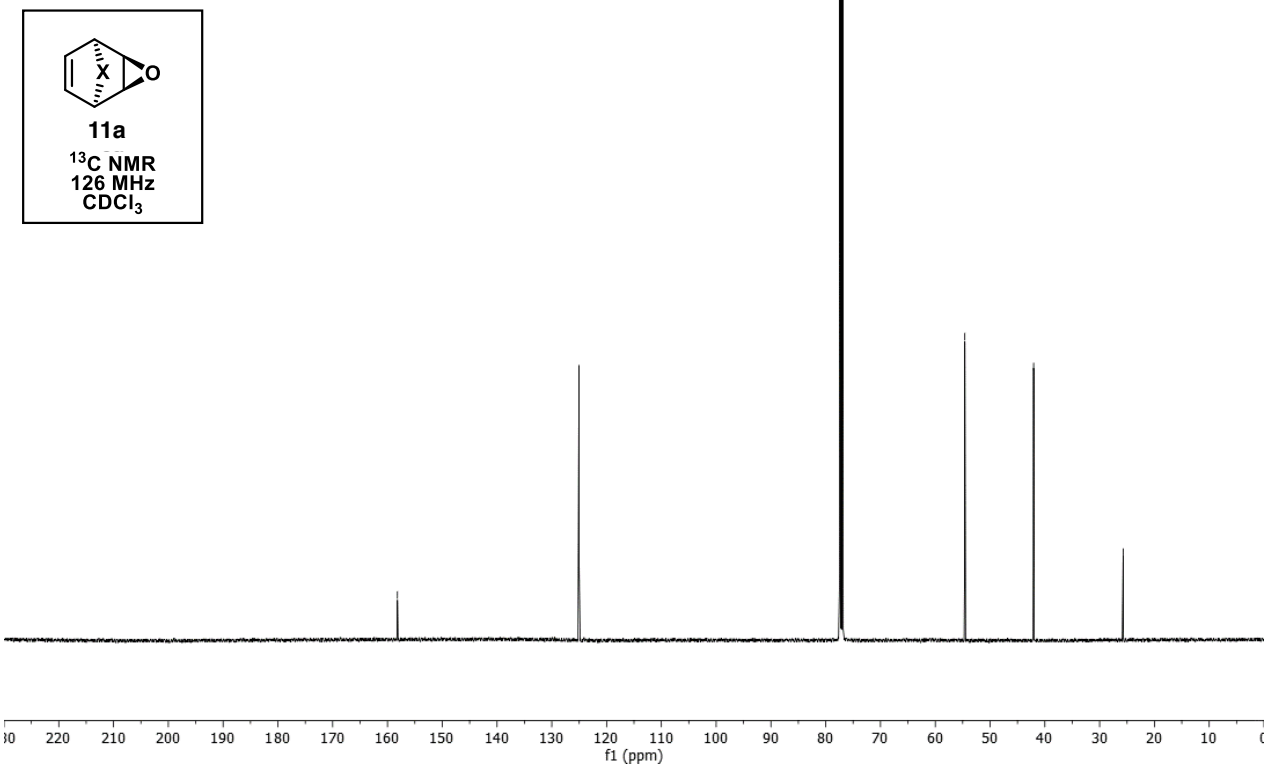

8.27
7.69
7.26 CDCl3
5.90
5.88
5.78
5.77
5.50
5.48
5.12
5.11
0.95
1.00
0.97
0.95
0.96
0.99
f1 (ppm)
Br
N
O
9t
1H NMR
500 MHz
CDCl3

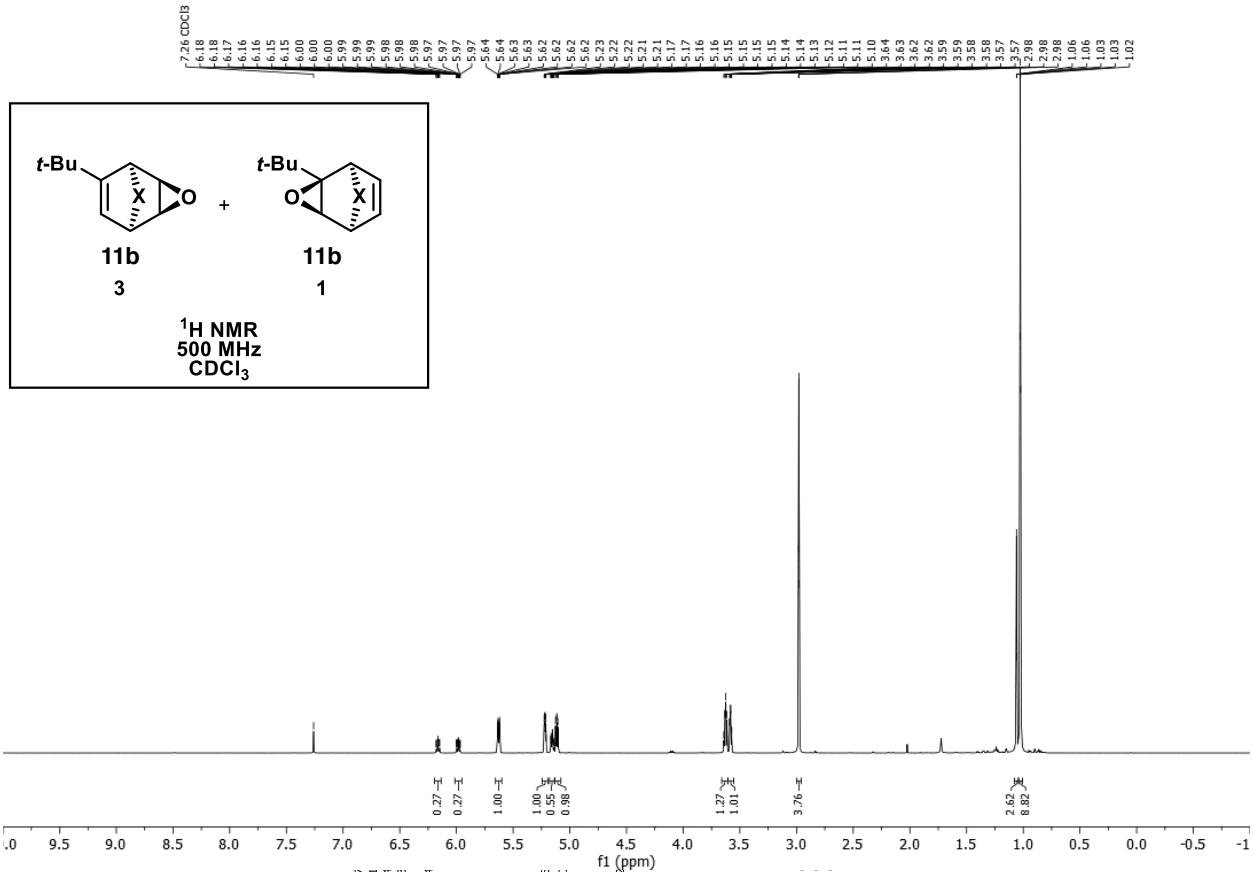

151.85
151.83
149.35
147.53
142.54
132.73
120.58
110.54
110.09
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
f1 (ppm)
Br
N
O
9t
13C NMR
126 MHz
CDCl3

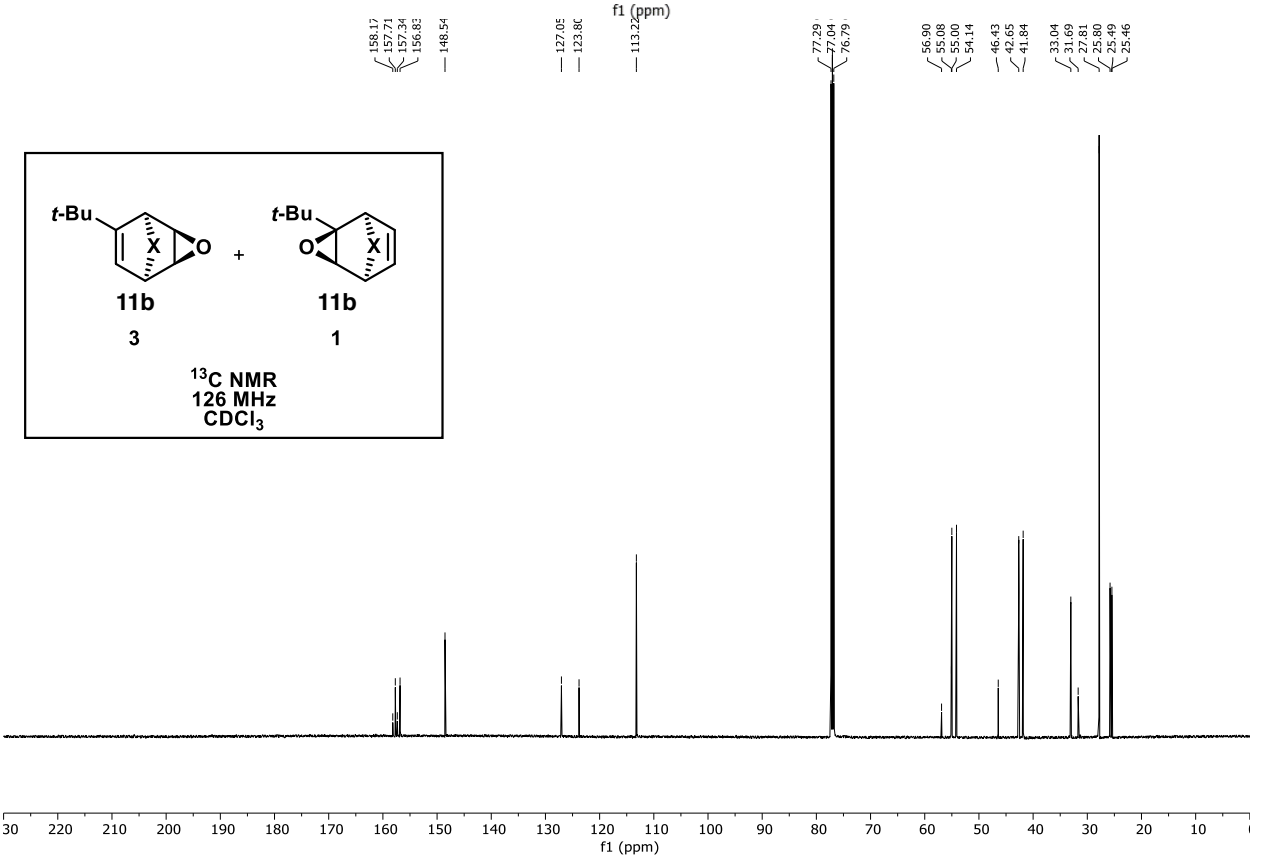

7.95
7.94
7.26 CD3CN
6.51
6.50
5.91
5.90
5.87
5.86
5.63
5.61
5.14
5.13
Cl
N
O
9u
1H NMR
500 MHz
CDCl3
0.98
1.01
1.00
1.00
0.99
1.01
f1 (ppm)

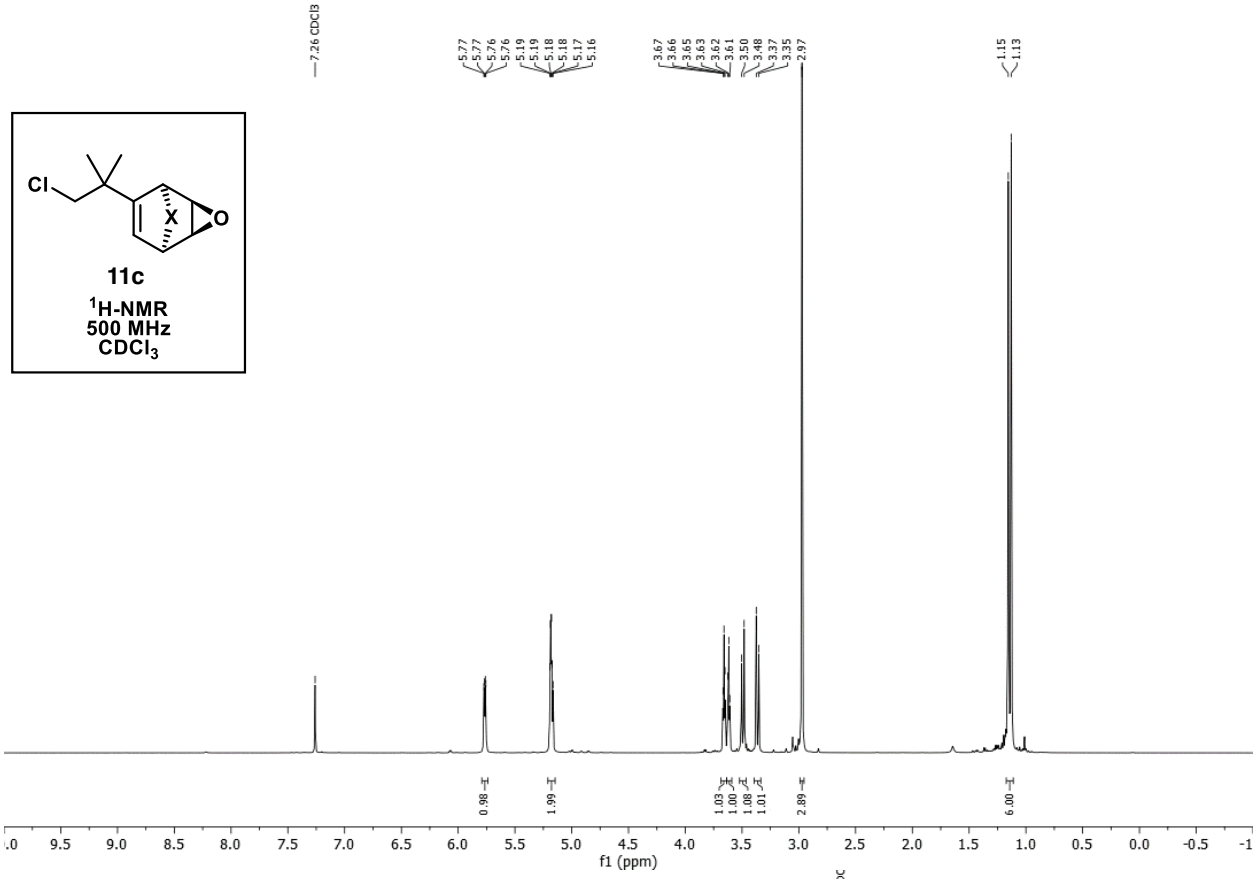

152.06
149.68
149.35
149.01
146.78
129.42
122.28
111.57
109.90
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
Cl
N
O
9u
13C NMR
126 MHz
CDCl3
f1 (ppm)

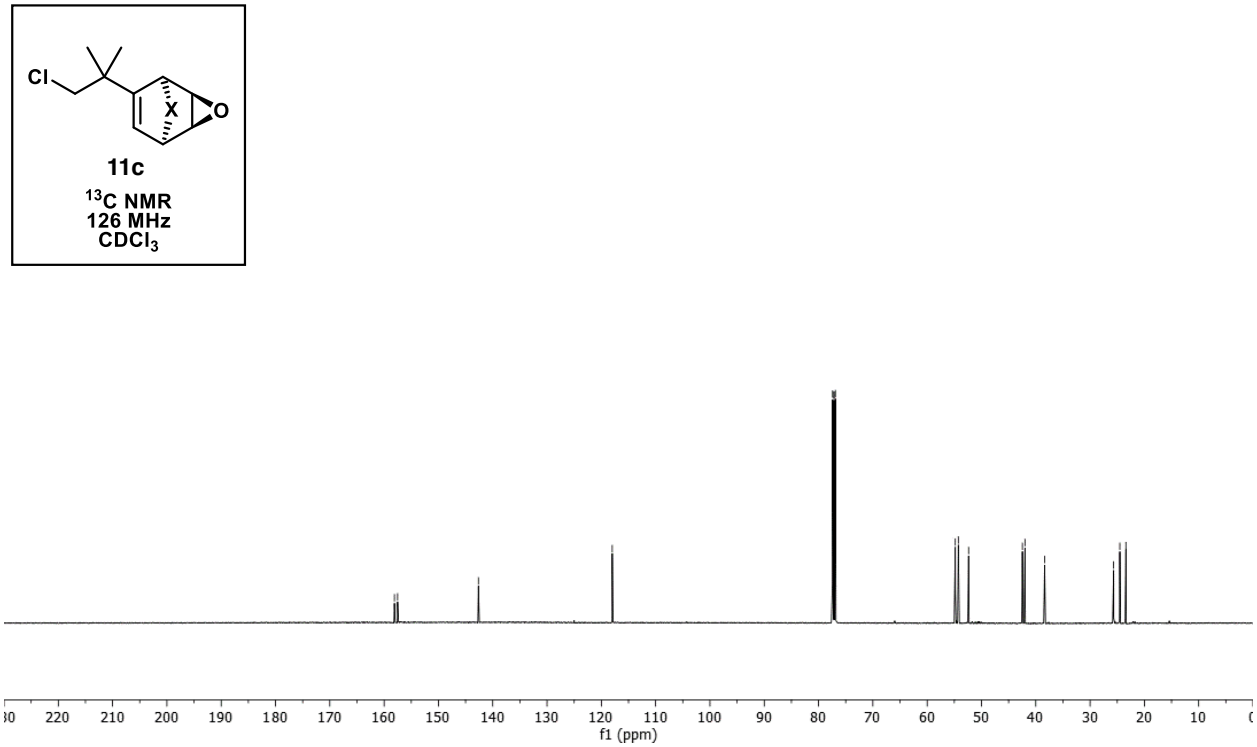

11a
1H NMR
500 MHz
CDCl3

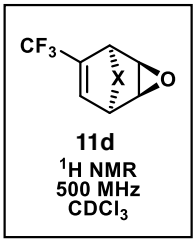

11a
13C NMR
126 MHz
CDCl3
f1 (ppm)


t-Bu
X
O
+
t-Bu
O
X
11b
3
11b
1
1H NMR
500 MHz
CDCl3
f1 (ppm)

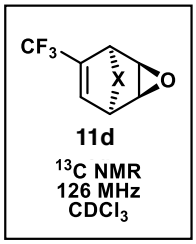

t-Bu
X
O
+
t-Bu
O
X
11b
3
11b
1
13C NMR
126 MHz
CDCl3
f1 (ppm)


Cl
X
O
11c
1H-NMR
500 MHz
CDCl3
7.26 CDCl3
5.77
5.77
5.76
5.76
5.19
5.19
5.18
5.18
5.17
5.16
3.67
3.66
3.65
3.63
3.62
3.61
3.50
3.48
3.37
3.35
2.97
1.15
1.13
0.98
1.99
1.03
1.00
1.08
1.01
2.89
6.00
f1 (ppm)

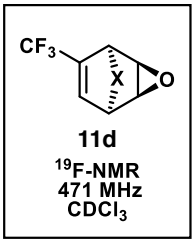

Cl
X
O
11c
13C NMR
126 MHz
CDCl3
158.10
157.52
142.64
117.99
77.41
77.16
77.16 CDC
76.91
54.82
54.26
52.37
42.47
41.99
38.37
25.66
24.52
23.40
f1 (ppm)



11d
^{1}H NMR
500 MHz
$CDCl_3$

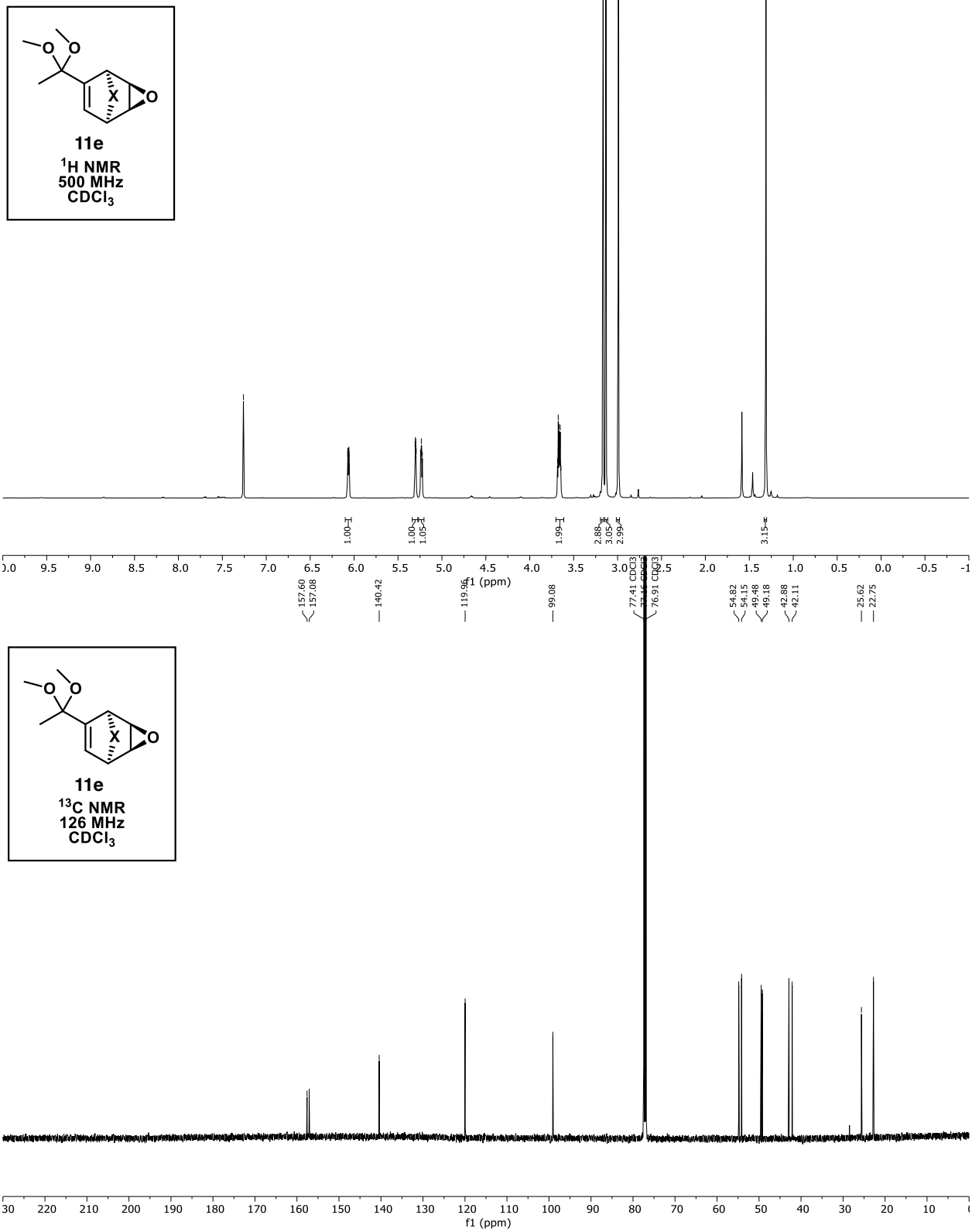


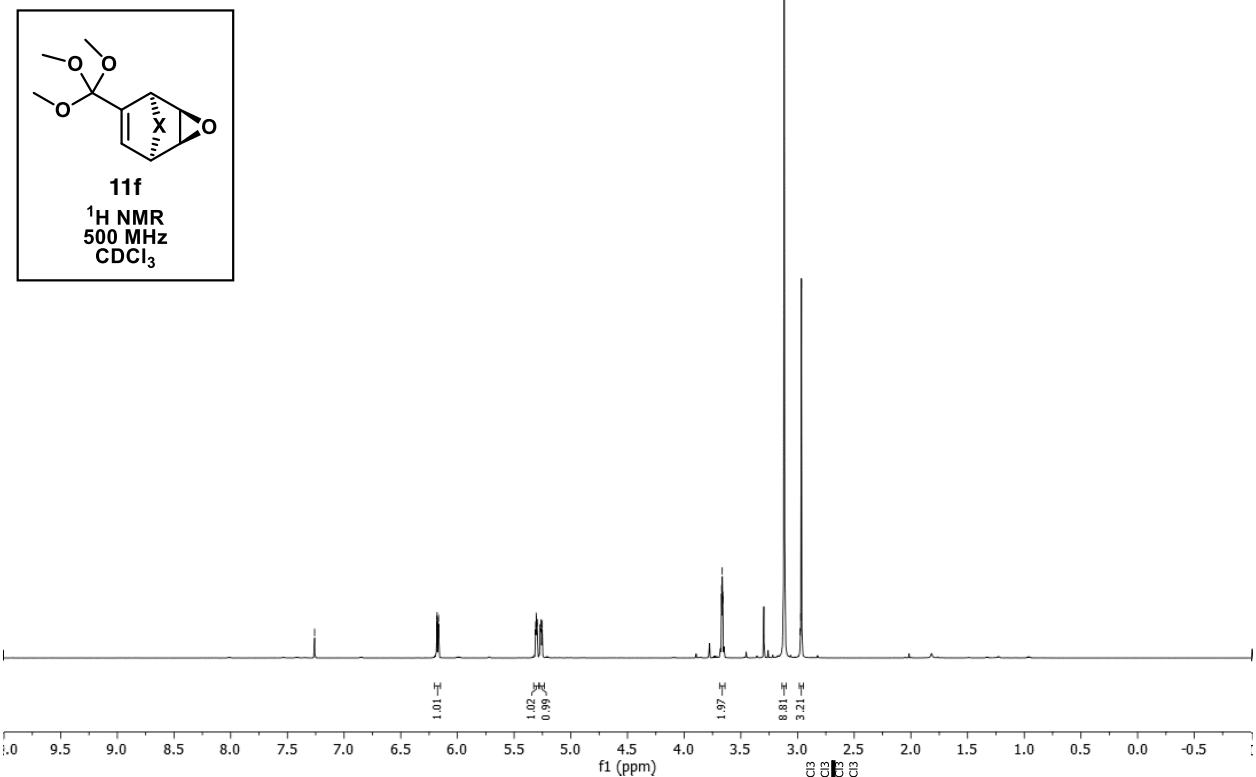
11d
^{13}C NMR
126 MHz
$CDCl_3$



11d

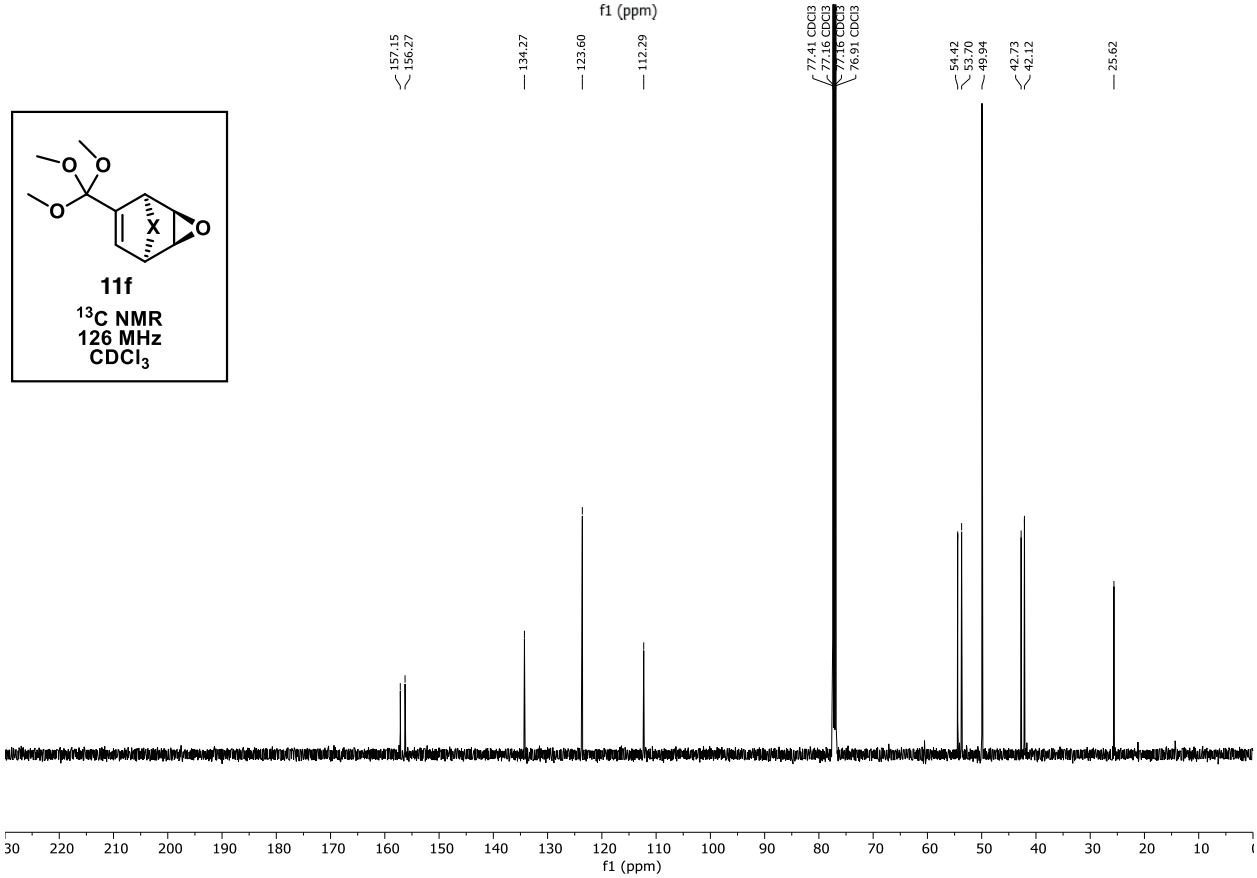
^{19}F-NMR
471 MHz
$CDCl_3$


11e
1H NMR
500 MHz
CDCl3
11e
13C NMR
126 MHz
CDCl3
f1 (ppm)



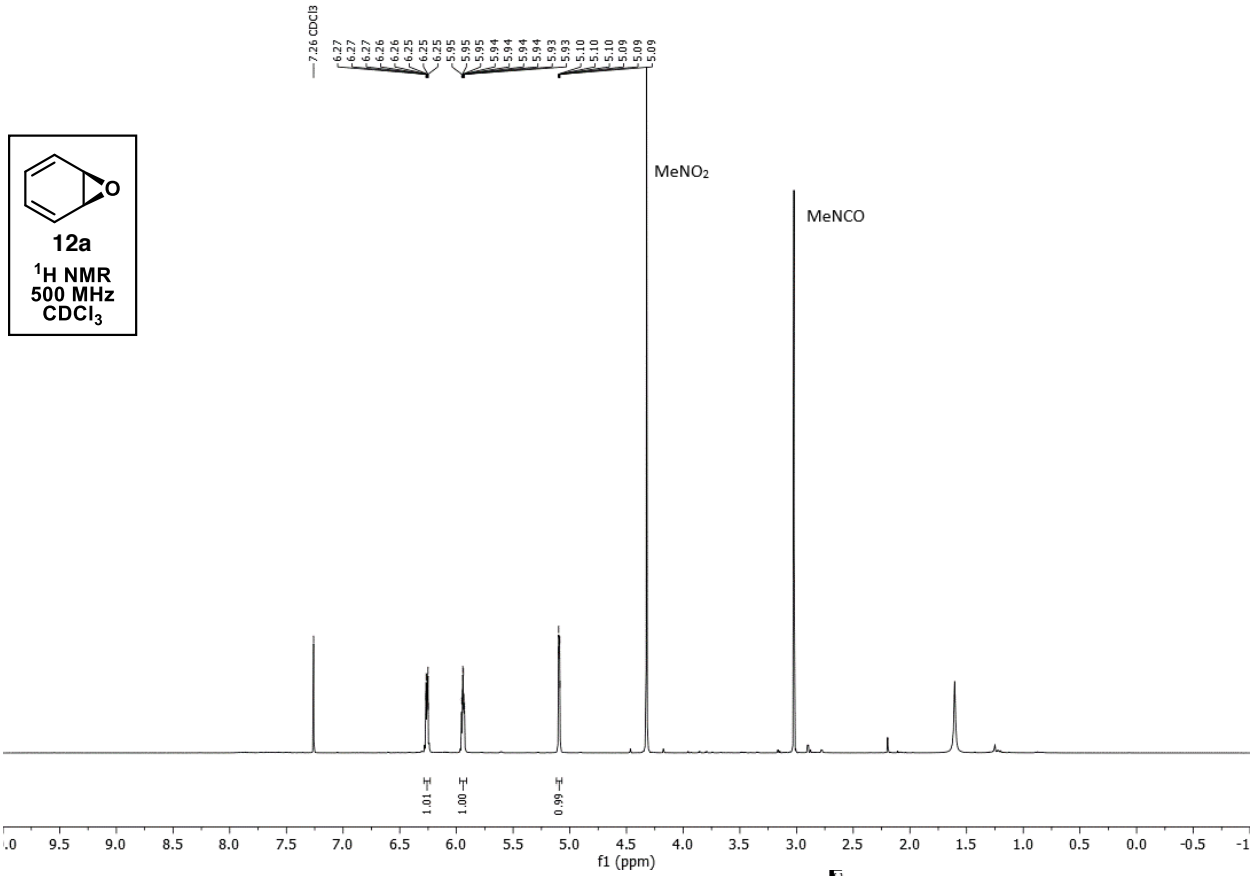
11f

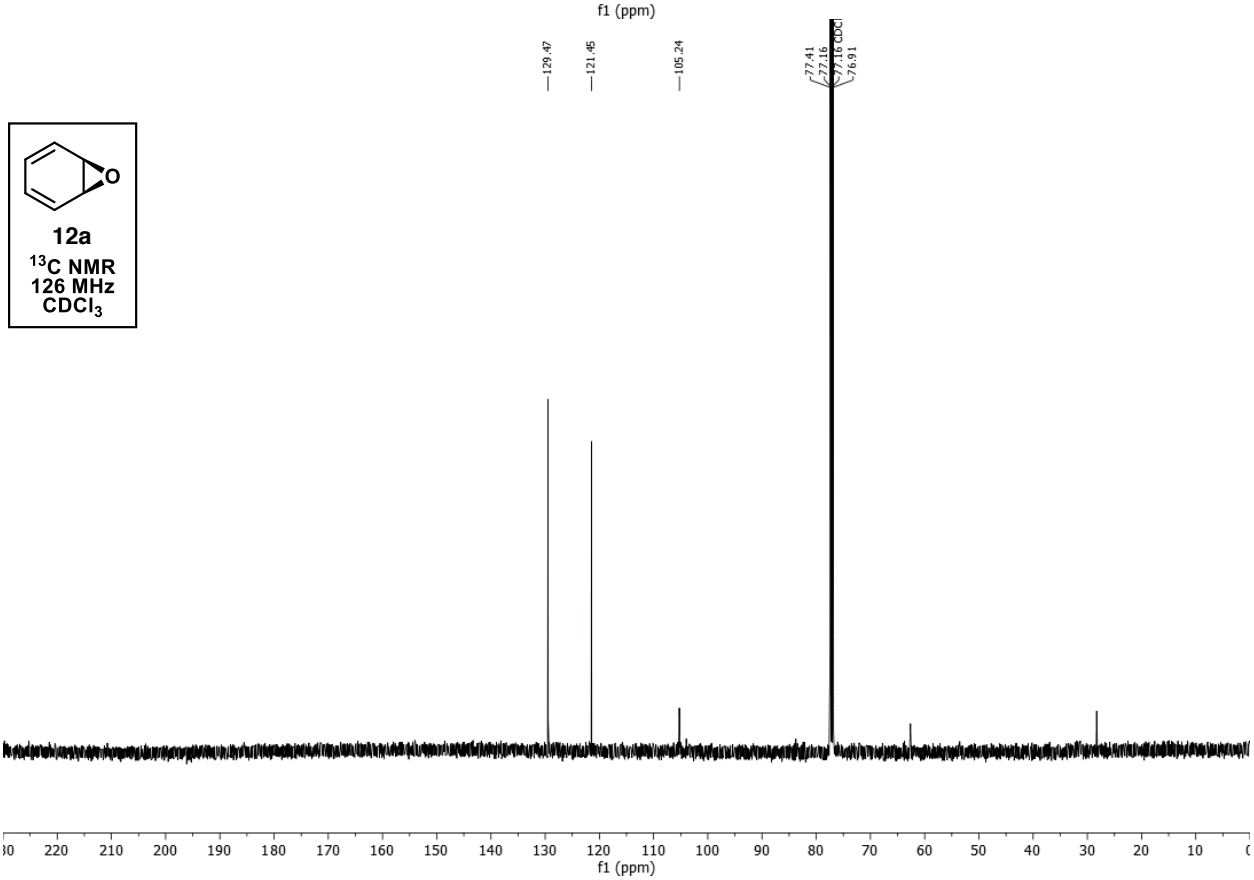
^{1}H NMR
500 MHz
$CDCl_3$

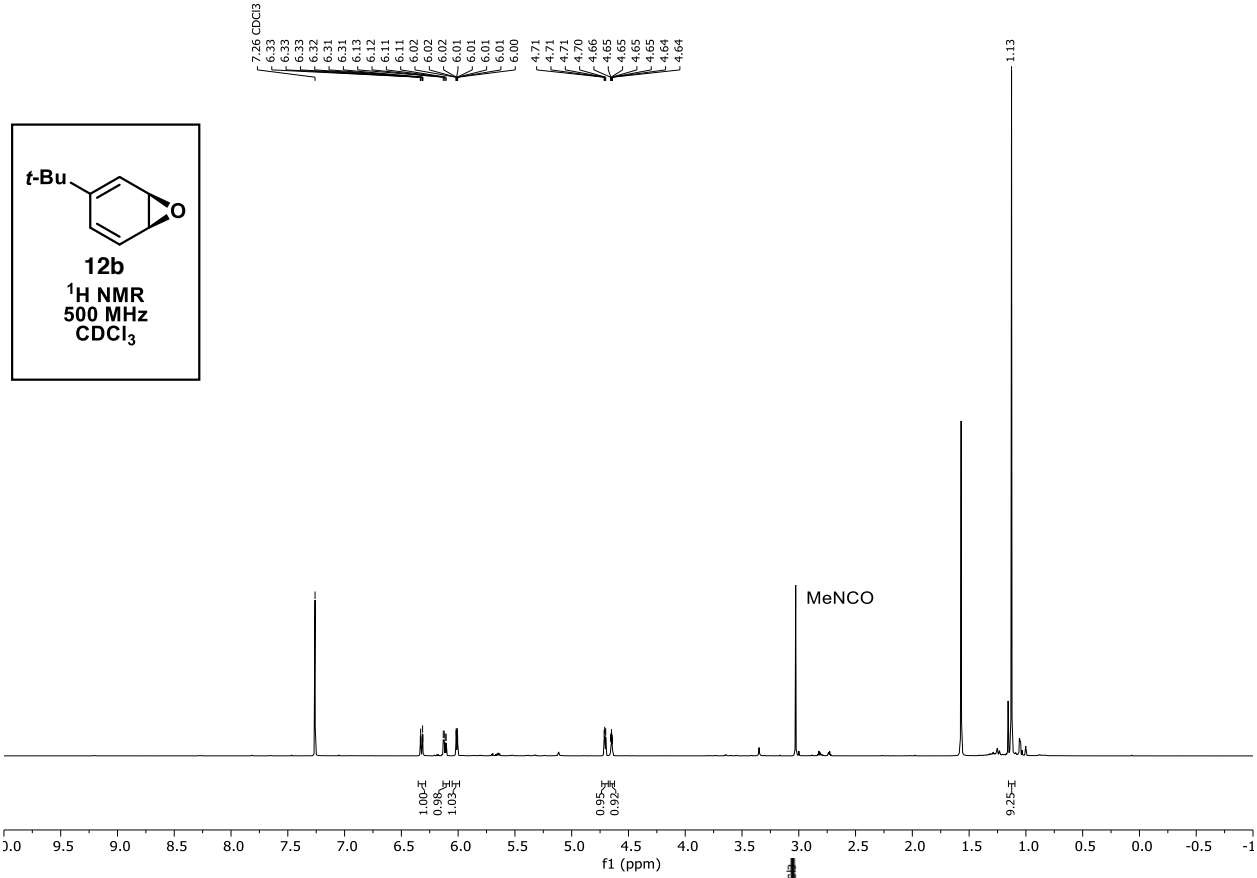


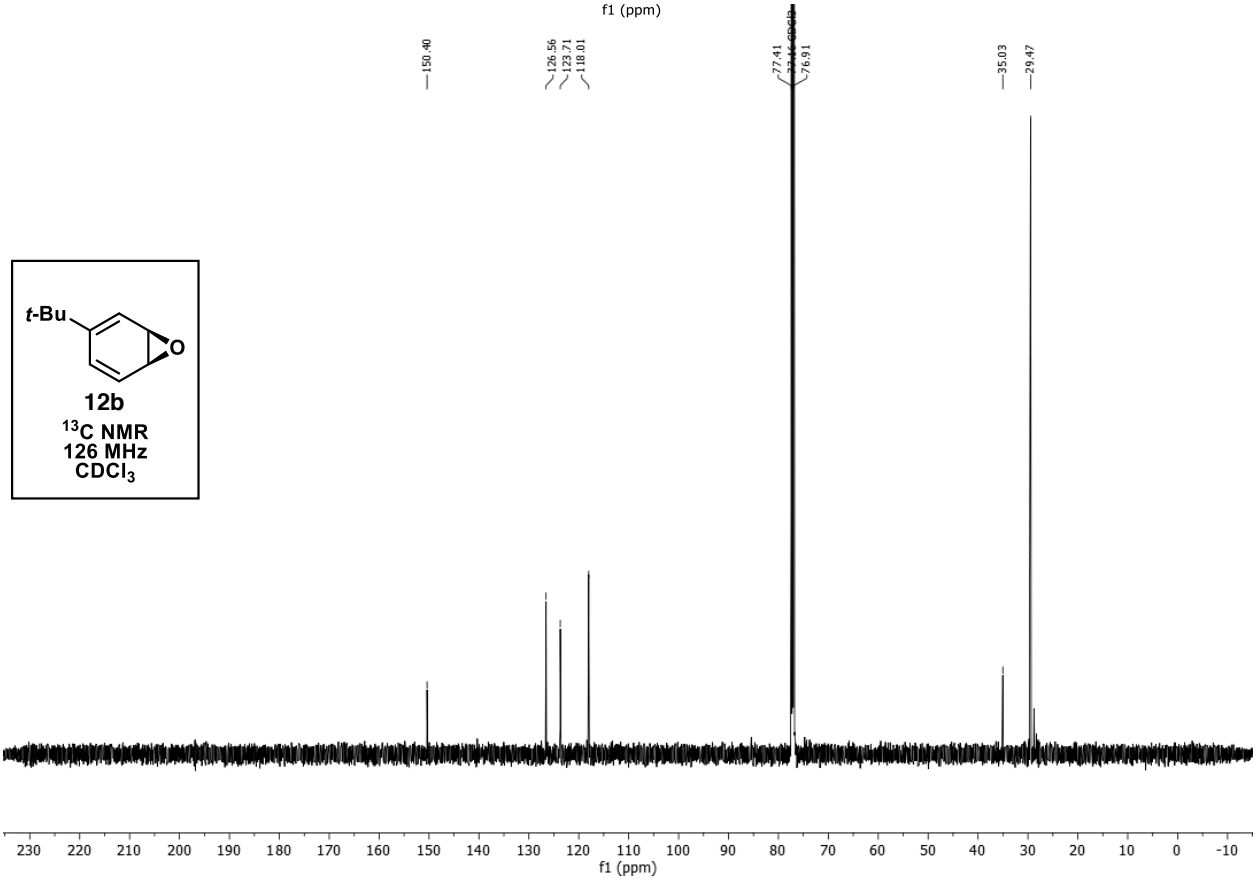
11f

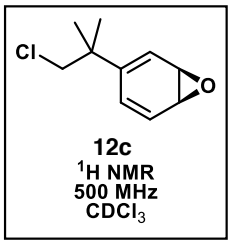
^{13}C NMR
126 MHz
$CDCl_3$


12a
1H NMR
500 MHz
CDCl3
MeNO2
MeNCO
f1 (ppm)

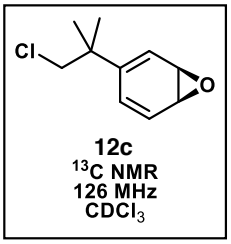

12a
13C NMR
126 MHz
CDCl3
f1 (ppm)


t-Bu
O
12b
1H NMR
500 MHz
CDCl3
MeNCO
f1 (ppm)

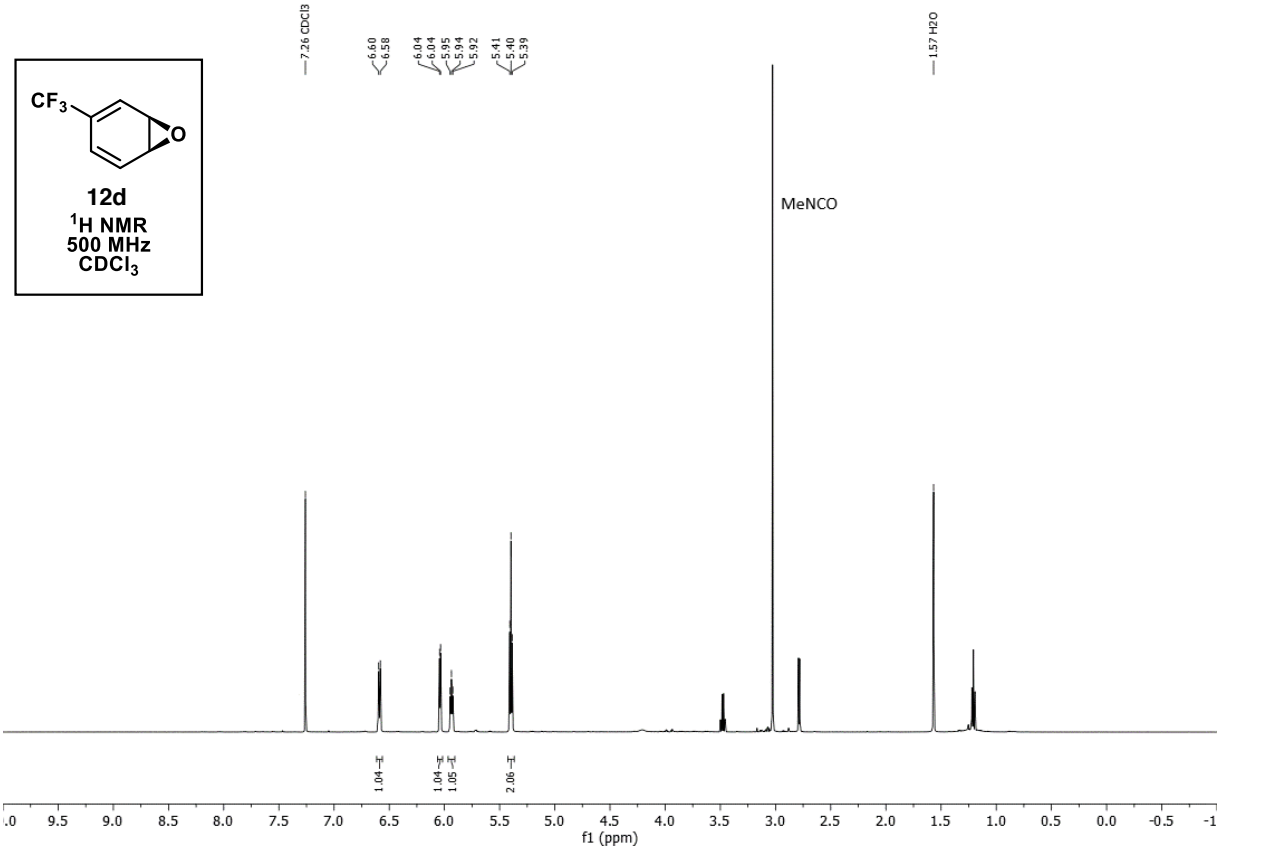

t-Bu
O
12b
13C NMR
126 MHz
CDCl3
f1 (ppm)

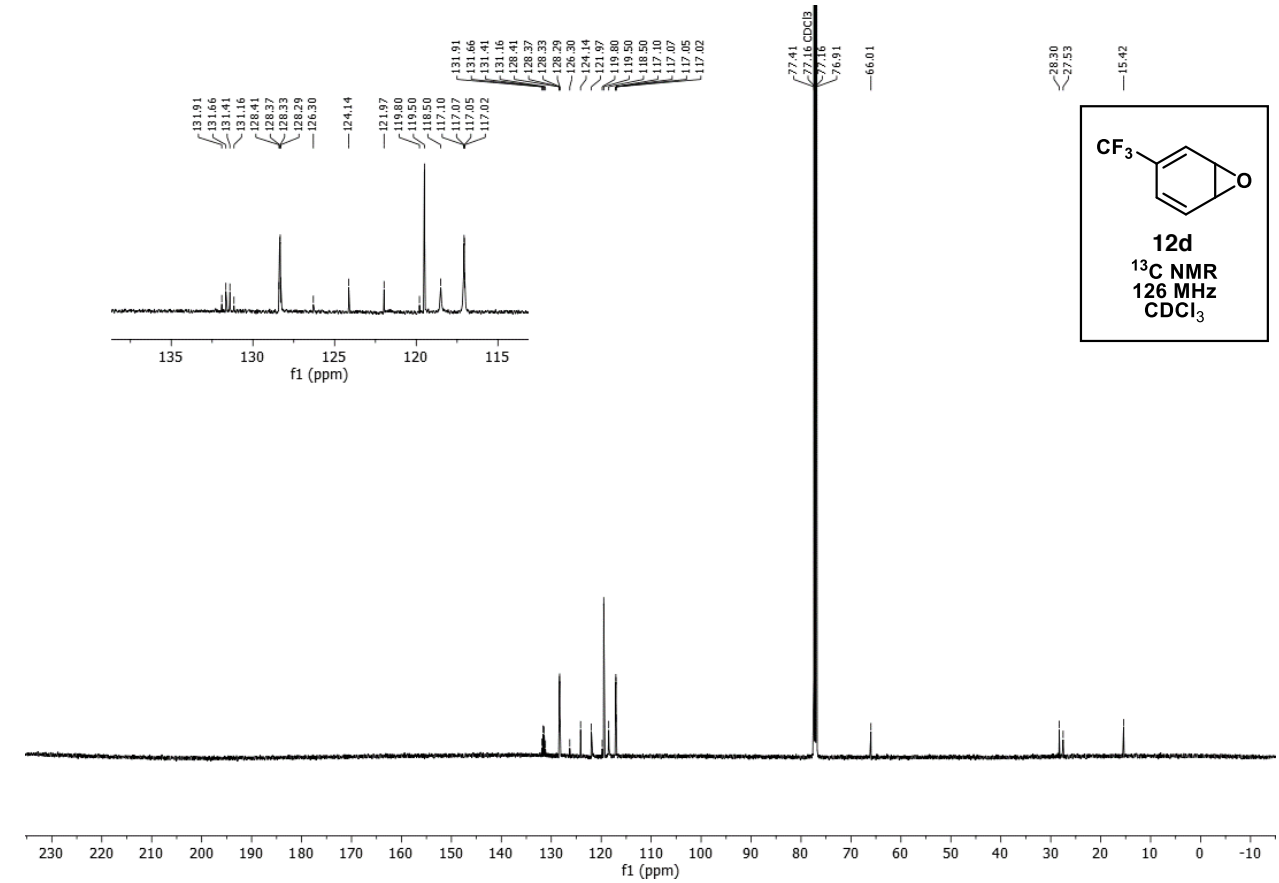


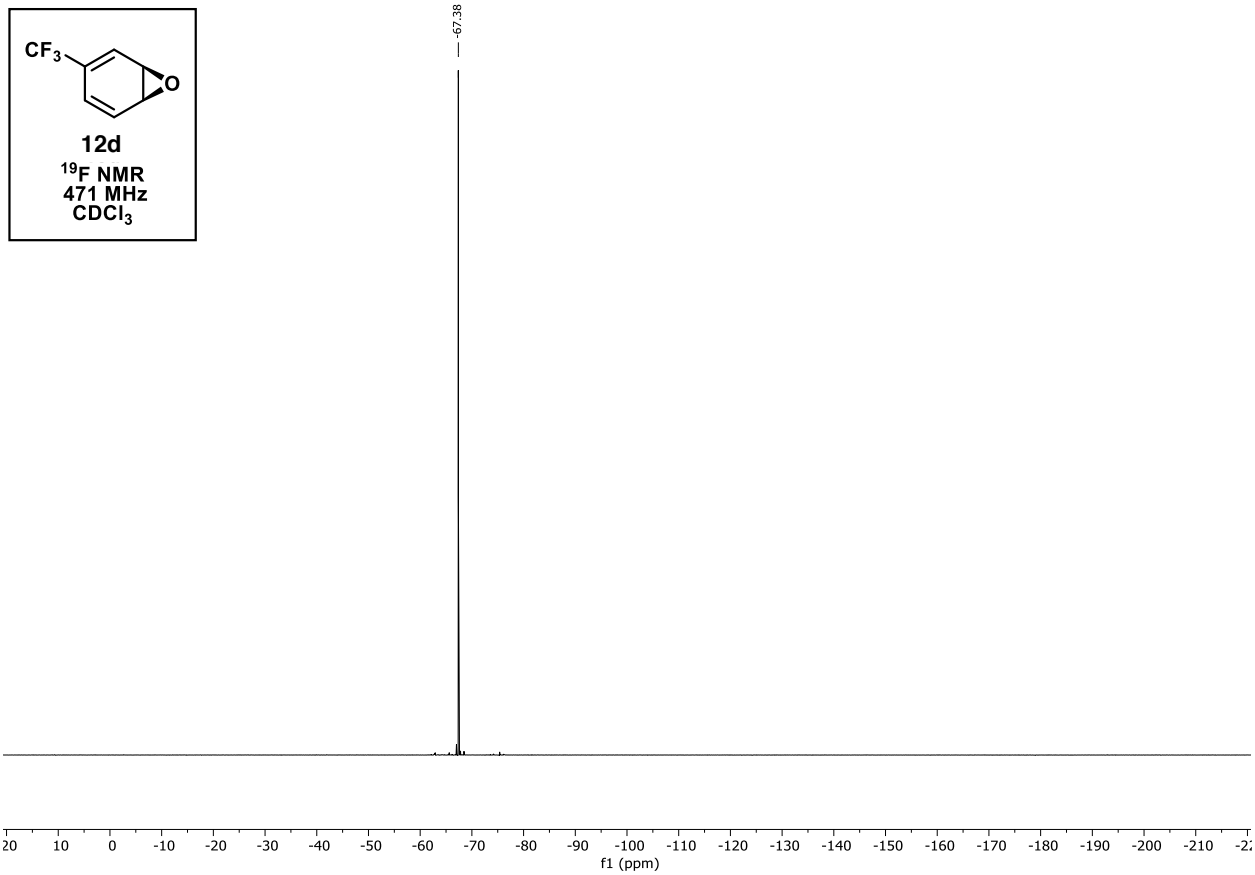
12c
^{1}H NMR
500 MHz
$CDCl_3$

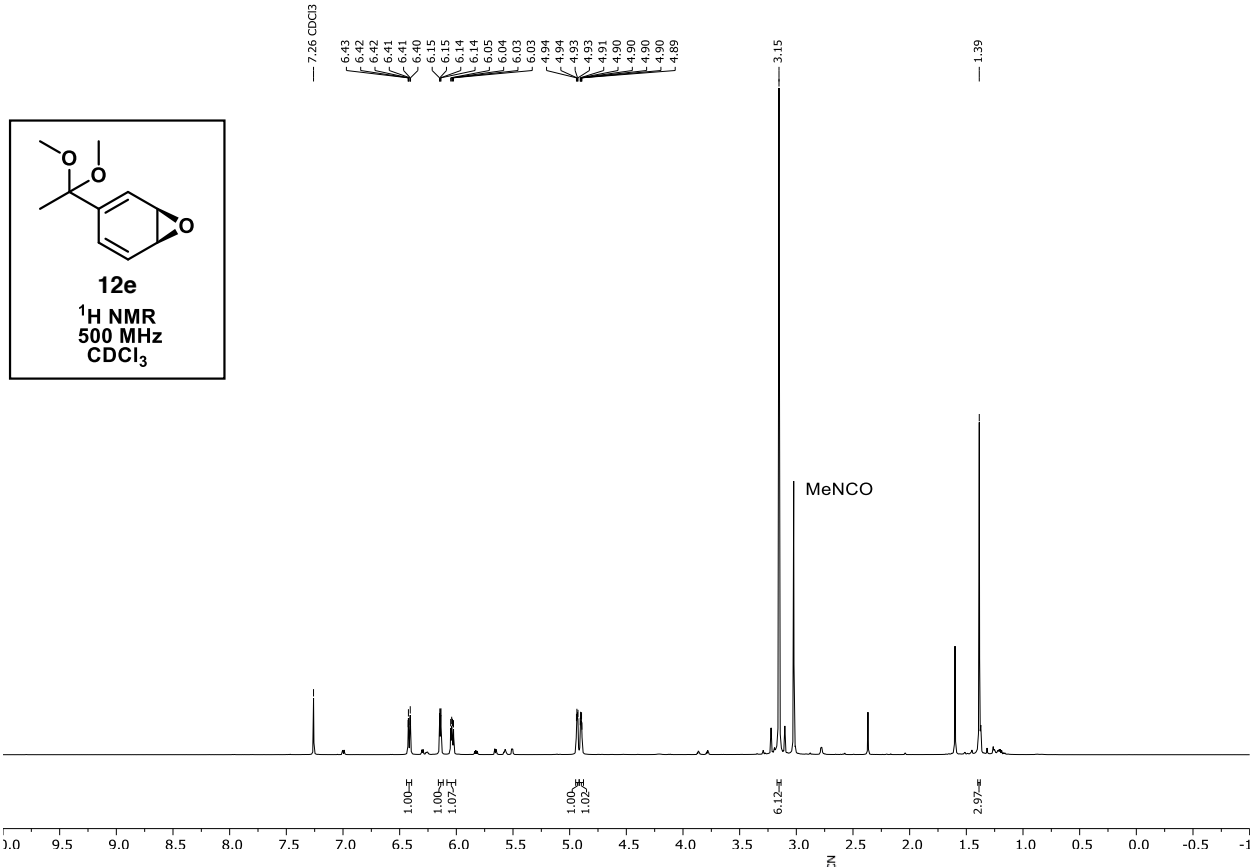


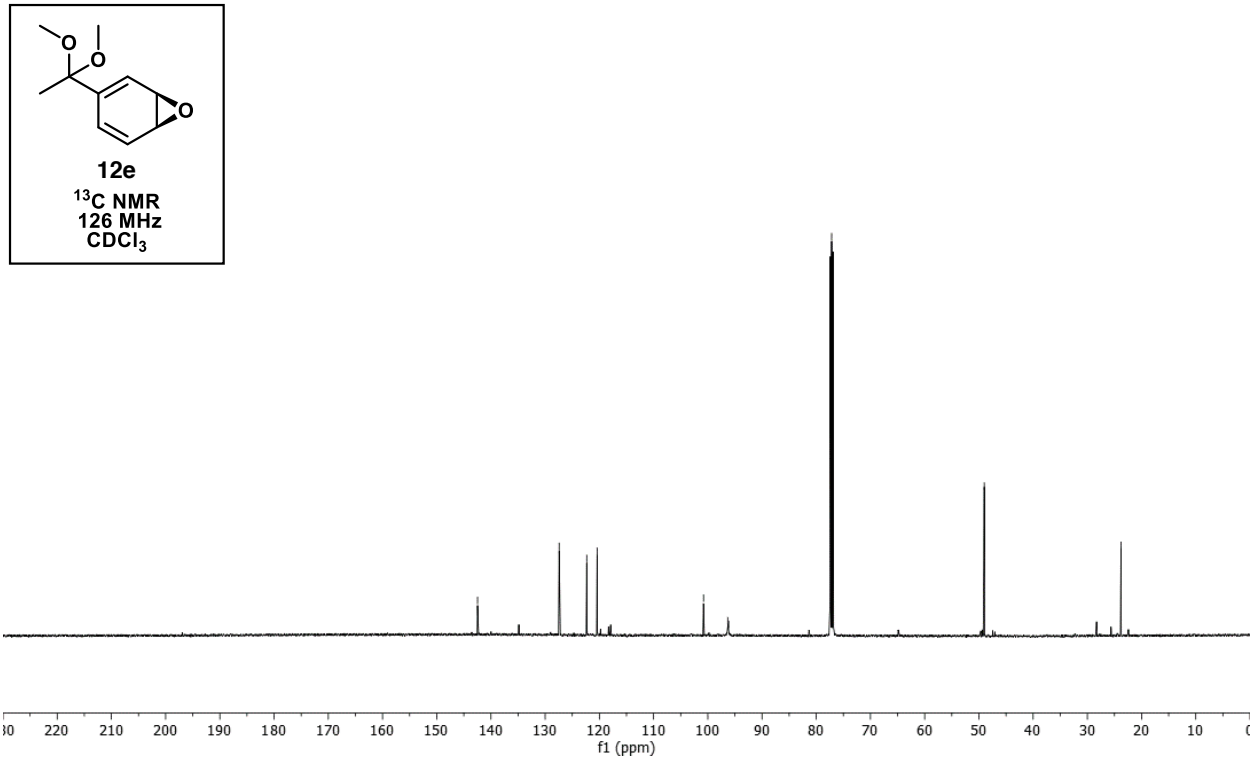
12c
^{13}C NMR
126 MHz
$CDCl_3$

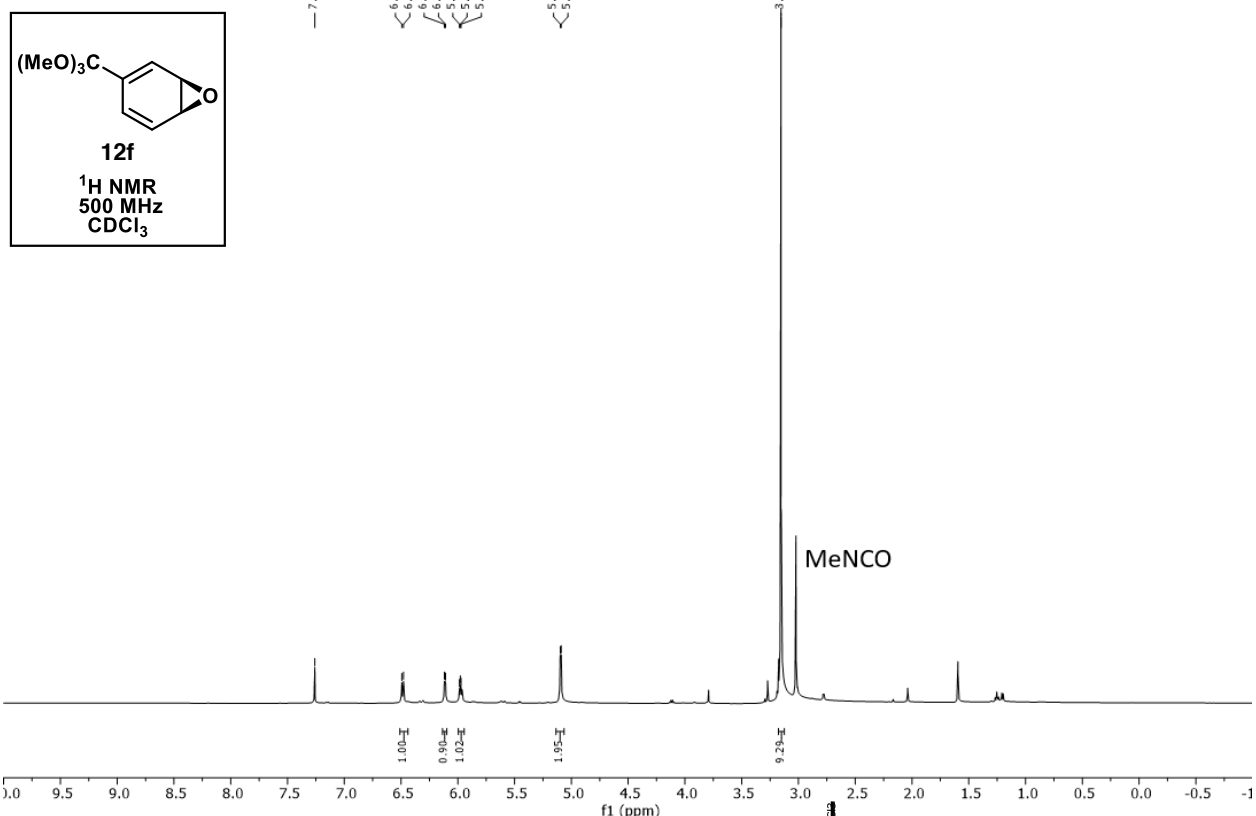

12d
1H NMR
500 MHz
CDCl3
MeNCO
f1 (ppm)

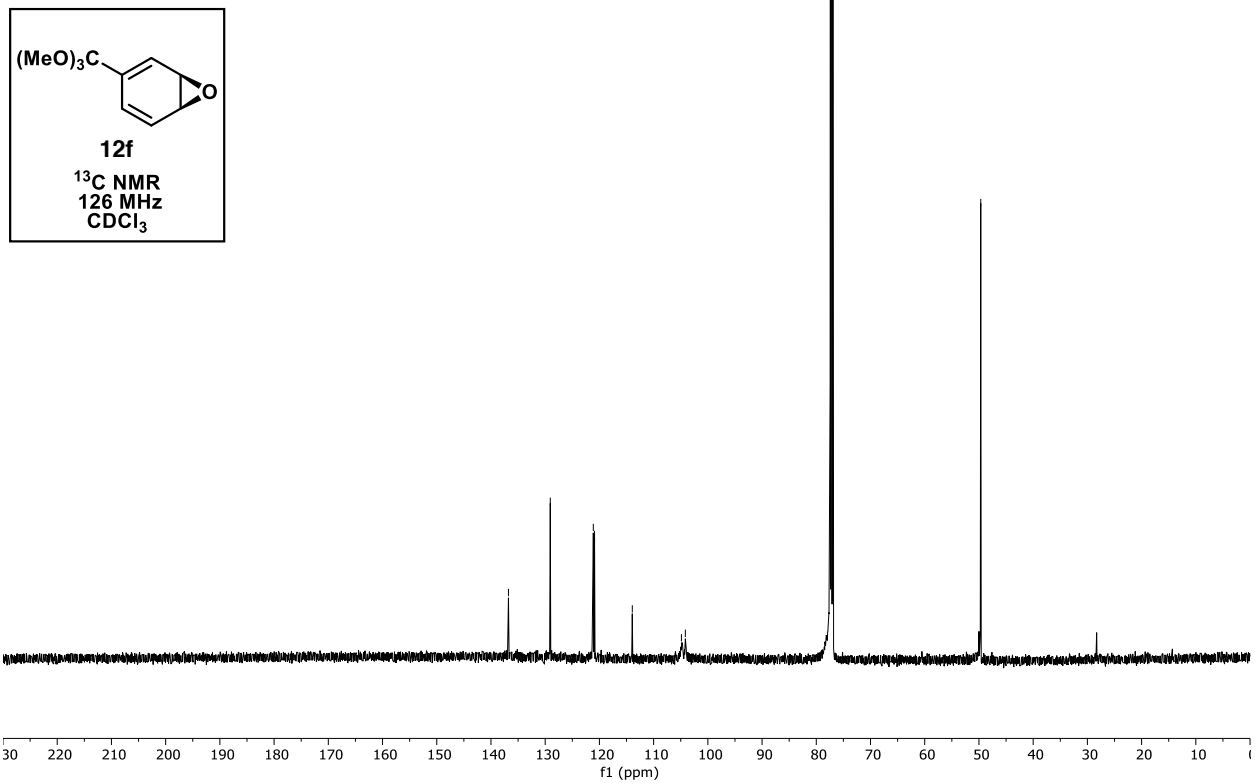

12d
13C NMR
126 MHz
CDCl3
f1 (ppm)


CF3
O
12d
19F NMR
471 MHz
CDCl3
-67.38
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)


12e
1H NMR
500 MHz
CDCl3
MeNCO


12e
13C NMR
126 MHz
CDCl3
f1 (ppm)


(MeO)3C
O
12f
1H NMR
500 MHz
CDCl3
7.26 CDCl3
6.49
6.48
6.12
6.11
5.99
5.98
5.97
5.10
5.09
3.15
MeNCO
1.00
0.90
1.02
1.95
9.29
f1 (ppm)


(MeO)3C
O
12f
13C NMR
126 MHz
CDCl3
136.77
129.06
121.13
120.90
113.93
104.87
104.15
77.16 CDCl3
49.67
f1 (ppm)