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Submitted date: 27/05/2020 • Posted date: 28/05/2020

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Citation information: Greve, Eric; Lindeman, Sergey; Dockendorff, Chris (2020): Route Exploration and Synthesis of the Reported Pyridone-Based PDI Inhibitor STK076545. ChemRxiv. Preprint.

<https://doi.org/10.26434/chemrxiv.12376469.v1>

The enzyme protein disulfide isomerase (PDI) is essential for the correct folding of proteins and the activation of certain cell surface receptors, and is a promising target for the treatment of cancer and thrombotic conditions. A previous high-throughput screen identified the commercial compound STK076545 as a promising PDI inhibitor. To confirm its activity and support further biological studies, a resynthesis was pursued of the reported β -keto-amide with an N-alkylated pyridone at the α -position. Numerous conventional approaches were complicated by undesired fragmentations or rearrangements. However, a successful 5-step synthetic route was achieved using an aldol reaction with an α -pyridone allyl ester as a key step. An X-ray crystal structure of the final compound confirmed that the reported structure of STK076545 was achieved, however its lack of PDI activity and inconsistent spectral data suggest that the commercial structure was misassigned.

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Route exploration and synthesis of the reported pyridone-based PDI inhibitor STK076545

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KEYWORDS: PDI, STK076545, aldol, β -keto-amide, pyridone, retro-Claisen

ABSTRACT: The enzyme protein disulfide isomerase (PDI) is essential for the correct folding of proteins and the activation of certain cell surface receptors, and is a promising target for the treatment of cancer and thrombotic conditions. A previous high-throughput screen identified the commercial compound STK076545 as a promising PDI inhibitor. To confirm its activity and support further biological studies, a resynthesis was pursued of the reported β -keto-amide with an N-alkylated pyridone at the α -position. Numerous conventional approaches were complicated by undesired fragmentations or rearrangements. However, a successful 5-step synthetic route was achieved using an aldol reaction with an α -pyridone allyl ester as a key step. An X-ray crystal structure of the final compound confirmed that the reported structure of STK076545 was achieved, however its lack of PDI activity and inconsistent spectral data suggest that the commercial structure was misassigned.

INTRODUCTION

Protein disulfide isomerase (PDI) is an enzyme primarily localized in the endoplasmic reticulum that catalyzes the oxidation-reduction and isomerization of disulfide bonds and serves as a necessary chaperone for protein folding.¹ In addition, PDI can be released onto the surface of endothelial and platelet cells, where they act to promote effective coagulation via mechanisms presently under study. For these reasons, PDI inhibitors are of significant interest both for the treatment of cancer² and the prevention of thrombosis.³ Several animal models of thrombosis have demonstrated that targeting cell surface PDI with antibodies or small molecules blocks both platelet accumulation and fibrin generation.⁴⁻⁸ Previously reported PDI antagonists suffer from poor selectivity, irreversibility, and/or low potency. In an effort to identify novel inhibitors of PDI with more suitable therapeutic properties, a high-throughput screen was performed by Flaumenhaft and co-workers on approximately 5,000 bioactive small molecules.⁶ They identified a class of flavonoids called quercertins, found in high abundance in various fruits and vegetables, that inhibit PDI. From this class, isoquercetin was found to decrease D-dimer plasma concentrations, a biomarker for venous thromboembolic disease, by a median of 22% in a phase II clinical trial.⁹ However, the high dose and highly variable patients responses are drawbacks of isoquercetin.

To seek additional PDI inhibitors, a second high-throughput screen was performed on 348,505 compounds from the Molecular Libraries Small Molecule Repository.¹⁰ Two series of PDI inhibitors, represented by bepristats 1a and 2a (Figure 1) were found to bind to the hydrophobic pocket of the b' domain.⁸ A commercial compound called STK076545 was also identified from the high-throughput screen to be a reasonably potent hit for the inhibition of PDI, and had an attractive structure for medicinal chemistry studies relative to other hits. The commercial supply of STK076545 was soon depleted, and we were unable to secure additional quantities, so we immediately endeavored to synthesize it. Its structure proved to be deceptively simple, and this manuscript describes several pitfalls that were encountered prior to its successful synthesis.

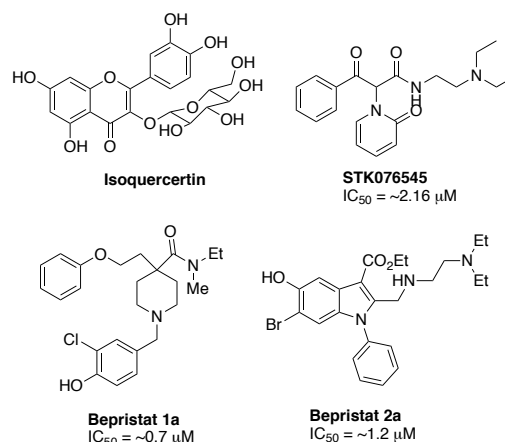


Figure 1. Select inhibitors of PDI

Methods for preparing β -keto amides have been pursued for at least a century.¹¹ The most obvious approach to β -keto amides is via amide couplings between β -keto acids and amines, which also permits late stage diversification for medicinal chemistry studies (Figure 2, approach 'a'). However, this approach may be complicated by the limited stability of the β -keto acid starting materials, which can undergo decarboxylation (step 'c'). Alternatively, Meldrum's acid can be C-acylated, then aminolysis affords a β -keto amide, but limited to α -unsubstituted substrates.¹² Direct aminolysis of β -keto esters¹³ or β -keto thioesters¹⁴ at high temperature is possible (approach 'd'), but can be compromised by competing enamine formation. Aminolysis reactions catalyzed with DMAP,¹⁵ enzymes,¹⁶ or transition metals¹⁷⁻¹⁸ have also been reported. Alternatively, addition of a ketone or enamine to an isocyanate have also been reported (approach 'e'). Cross Claisen-like condensations of esters with amide enolates have been reported (approach 'f'),¹⁹⁻²⁰ or alternatively an aldol reaction between a pyridone-containing amide and a benzaldehyde (Ar = Ph for STK076545) could be envisaged (step 'g'), followed by alcohol oxidation (step 'h').

Other approaches involving a late stage addition of the pyridone are possible, but these were not initially considered since we were first interested in exploring amide structure-activity relationships (SARs), and the presence of a basic tertiary amine on the amide side chain of STK076045 could complicate a late

stage halogenation/pyridone N-alkylation reaction. It remained to be determined how the presence of an α -pyridone could affect the steps outlined in Figure 2. Herein, we report our explorations of these routes, culminating in a successful 5-step synthesis of the reported structure of STK076545.

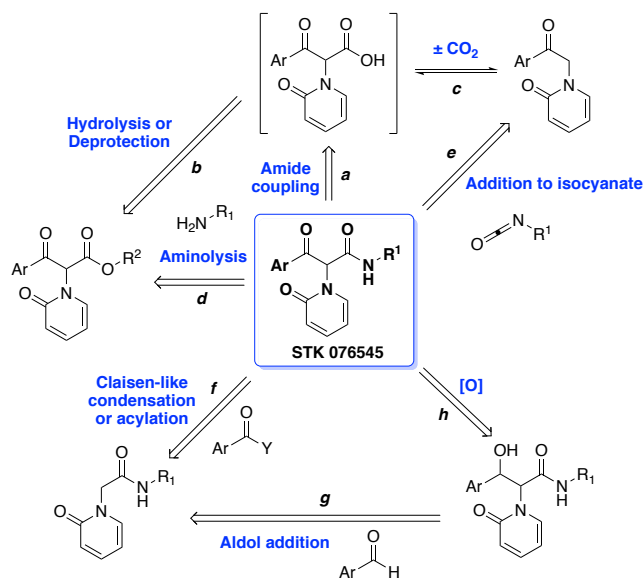
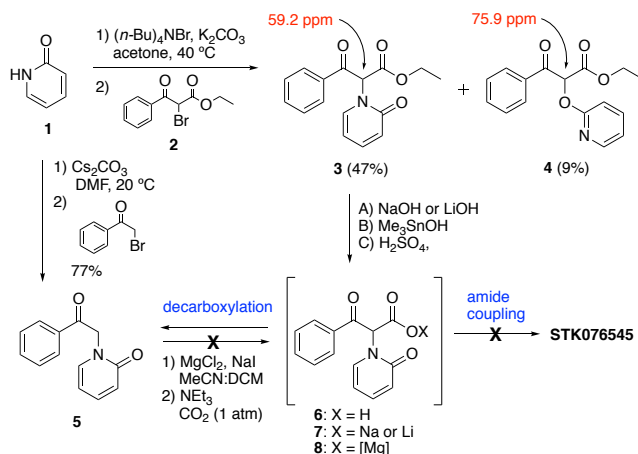


Figure 2. Retrosynthetic strategies for accessing the β -keto amide in STK076545 (Ar = Ph, R¹ = -CH₂CH₂NEt₂).

RESULTS AND DISCUSSION

Scheme 1. Ester hydrolysis and carboxylate formation

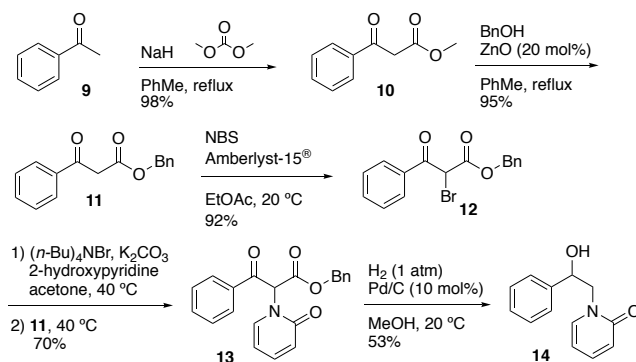


β -Keto Carboxylic Acid. The initial synthetic route we envisioned to access STK076545 involved N-alkylation of 2-pyridone with bromo- β -keto ester **2**, followed by ester hydrolysis and peptide coupling (Scheme 1). Alkylation of 2-pyridone with **2** proceeded smoothly using conditions previously reported using a bromomalonate.²¹ Both the N-alkylated **3** and O-alkylated **4** products were isolated, in 47% and 9% yield respectively. **3** and **4** were readily distinguishable based on their ¹³C NMR chemical shifts for the α -carbon, with the O-alkylated product **4** being assigned based on the more downfield α -carbon peak at 75.9 ppm. In this paper, all alkylations of 2-pyridone gave N-alkylation as the major product, though the O-alkylated products were sometimes observed in trace amounts. Unfortunately, the hydrolysis of ester **3** under acidic (H₂SO₄) or basic

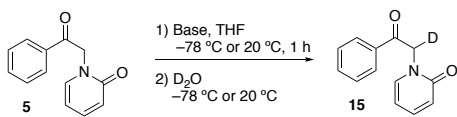
conditions (NaOH, LiOH, or Me₃SnOH²²) all resulted in decarboxylation of carboxylic acid intermediate **6** to yield ketone **5**, despite careful attempted isolations using buffered aqueous media. Direct coupling of alkali metal carboxylate salts has been shown by Batey and coworkers to be a useful strategy with unstable carboxylic acids.²³ Attempts at a tandem ester hydrolysis of **3** with NaOH or LiOH followed by peptide coupling with carboxylate **7** were not fruitful. Alternatively, the decarboxylation product **5** was synthesized on a larger scale via N-alkylation of 2-pyridone with 2-bromoacetophenone. Subsequent carboxylation using MgCl₂ and NaI with CO₂ also gave no detectable amount of carboxylate **8** or carboxylic acid **6** after an acidic workup.²⁴

In an effort to access carboxylic acid **6** under milder conditions, the analogous benzyl ester intermediate **13** was synthesized in four steps (Scheme 2). First, 1,3-dicarbonyl **10** was prepared from acetophenone and dimethylcarbonate using NaH in 98% yield.²⁵ ZnO-catalyzed transesterification of **10** afforded benzyl alcohol **11**.²⁶ Next, monohalogenation of **11** with NBS catalyzed by Amberlyst-15[®], followed by reaction with 2-pyridone yielded α -substituted- β -keto ester **13** in 66% yield over two steps.²⁷ Benzyl removal from ester **13** via palladium-catalyzed hydrogenation also resulted in decarboxylation. In addition, ¹H NMR analysis of the crude product indicated the ketone was reduced to afford benzyl alcohol **14**. Efforts to reduce the ketone prior to ester hydrolysis were not successful (Scheme 7).

Scheme 2. Synthesis and deprotection of benzyl ester **13**



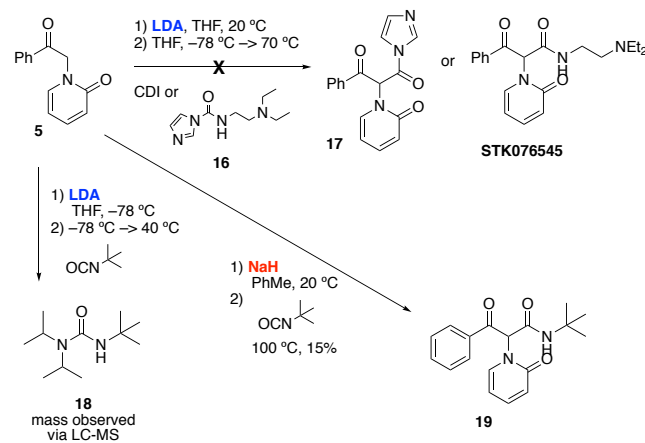
Enolate Formation and Reactivity on Ketone **5.** Instead of proceeding through a carboxylic acid intermediate, we envisioned installation of the amide via reaction of an enolate with a suitable isocyanate, or CDI followed by addition of an amine to the intermediate acylimidazole. To identify suitable conditions for enolate formation with ketone **5**, LDA, LiHMDS, and NaH were screened as bases (Table 1). Reactions were quenched at -78 °C or 20 °C using D₂O, and crude samples were analyzed via ¹H NMR. Based on our screen, it was found that all reactions occurring at 20 °C facilitated enolate formation (entries 3-5), while no deuterium incorporation occurred when quenching the samples at -78 °C (entries 1-2).

Table 1. Enolate formation from ketone **5**


Entry	Base	T (°C) Addition of Base	T (°C) Addition of D ₂ O	% Deuterium Incorporation ^a
1	LDA	-78	-78	0
2	LiHMDS	-78	-78	0
3	LDA	-78	20	117
4	LiHMDS	-78	20	92
5	NaH	20	20	134

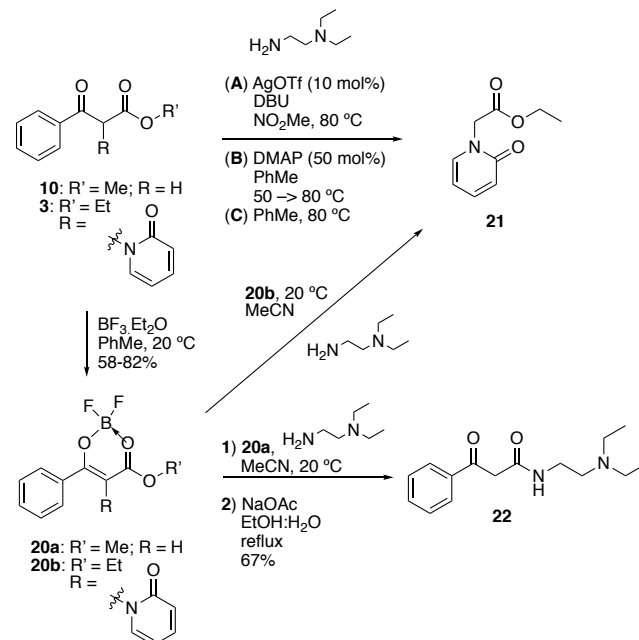
^a Deuterium incorporation was determined via ¹H NMR.

The enolate from ketone **5** was next formed using LDA at 20 °C and reacted with CDI or urea intermediate **16**, synthesized from CDI and *N,N*-diethylethylenediamine (Scheme 3). There was no observable reaction with either electrophile, even after heating at 70 °C. We then tested commercially available *tert*-butyl isocyanate as a model isocyanate for reaction screening. When LDA was used as a base, no desired product was observed. Rather, urea byproduct **18** formed from the addition of diisopropylamine to *tert*-butyl isocyanate was detected via LC-MS. Switching to NaH as the base and heating the reaction at 100 °C for 2 h in toluene yielded amide **19** in 15% yield. Efforts to synthesize the desired isocyanate from *N,N*-diethylethylenediamine and triphosgene, or reacting diethylamine with 2-bromoethyl isocyanate, were both troublesome. With this synthetic route being low yielding and having the limitation of only producing secondary amides, we chose to seek an alternative route.

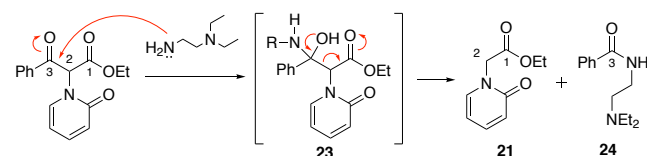
Scheme 3. Enolate reactions with ketone **5**

Direct Aminolysis of β -Keto Ester. Another common synthetic approach to access amides is via direct aminolysis of esters. Starting from β -keto ester **3**, we first tested a Ag(I)-catalyzed aminolysis (Scheme 4).¹⁸ Rather than observing conversion to the desired β -keto amide, reaction monitoring via LC-MS when using condition A showed masses associated with ester **21** and amide **24** (Scheme 5). Similarly, when heating ester **3** with *N,N*-diethylethylenediamine in toluene at 80 °C with or without DMAP, the same decomposition peaks were present. Ester **21** was isolated when using conditions B and correlated with the mass peak observed via LC-MS. Ag(I)/DBU and

DMAP were found to both accelerate the conversion to **21** in a few hours, in comparison to the reaction heated in toluene that proceeded slowly over 24 h. We hypothesize that the β -keto ester decomposes via a retro Claisen-like condensation mechanism. The amine (or nucleophilic catalyst) could add to the ketone, followed by collapse of the tetrahedral intermediate **22** and cleavage of the C-C bond to produce ester **21** (Scheme 5).

Scheme 4. Direct aminolysis attempts with β -keto esters

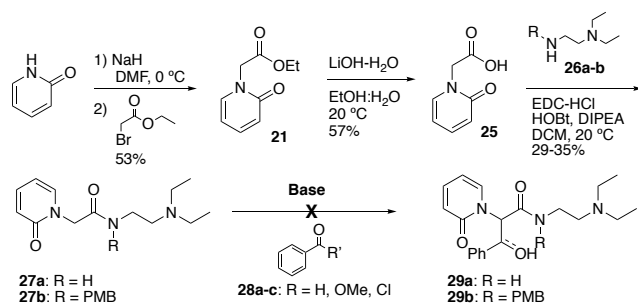
Stefane and Polanc reported a method to prepare β -keto amides from β -keto esters that proceeds via a 1,3,2-dioxaborinane intermediate.²⁸ Reacting β -keto ester **3** with boron trifluoride etherate afforded the boron complex **20b** in 82% yield (Scheme 4). Unfortunately, subsequent treatment of **20b** with *N,N*-diethylethylenediamine also resulted in decomposition to ester **21** after only 1 h, and complete decomposition after 24 h. Interestingly, when starting from β -keto ester **10** which does not have the pyridone substituent in the α position, the preparation of the boron complex **20a** and treatment with *N,N*-diethylethylenediamine cleanly afforded β -keto amide **22**.

Scheme 5. Proposed retro Claisen-like Condensation decomposition

Late Stage C2-C3 Coupling Route. Inspired by our observed retro Claisen-like reaction that occurred with a β -keto ester substrate, we examined the feasibility of performing an aldol addition, Claisen-like condensation, or acylation with intermediates **27a-b** (Scheme 6). Thus, installation of the C2-C3 bond would occur after amide formation and minimize the possibility of decarboxylation. Synthesis of **27a-b** began with *N*-alkylation of 2-pyridone with ethyl bromoacetate followed by ester hydrolysis, affording the previously reported carboxylic

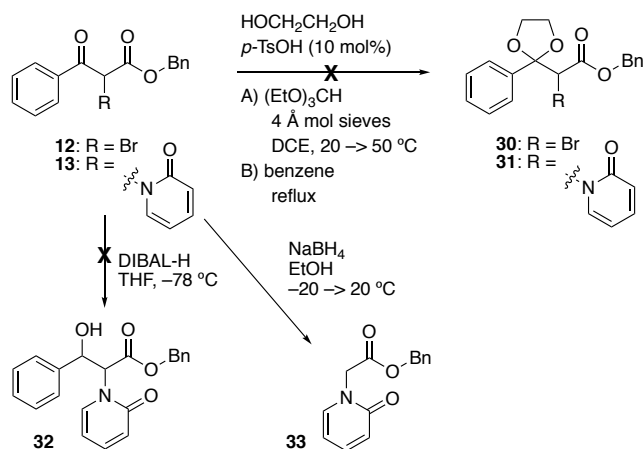
acid **25**.²⁹ Amide coupling with either *N,N*-diethylethylenediamine **25a** or PMB-protected amine **26b** yielded amides **27a-b**. We prepared the PMB-protected amide **26b** in an effort to avoid competitive deprotonation of the amide proton during enolization reactions. Extensive efforts with various electrophiles (aldehyde, ester, or acid chloride **28a-c**) bases (NaOMe, NaH, and LDA), and temperatures (0–160 °C) were all unfruitful.

Scheme 6. C2-C3 coupling attempts on amide 26a-b



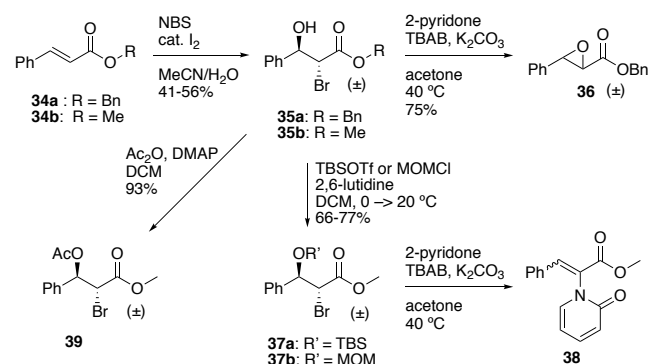
Identification of the aldol adduct as a possible intermediate provided inspiration to access alcohol **32**, which would not undergo decarboxylation during ester hydrolysis (Scheme 7). Starting from benzyl esters **12** or **13**, we attempted to either protect or reduce the benzylic ketone. Efforts to protect the ketone using ethylene glycol and catalytic *p*-TsOH with triethyl orthoformate and 4 Å mol sieves or a Dean–Stark trap resulted in no conversion. Alternatively, an attempt to reduce the ketone with DIBAL-H resulted in pyridone reduction, as suggested by the crude ¹H NMR spectrum. Switching to NaBH₄ produced benzyl ester **33**, which we presume proceeds via a similar retroaldol reaction as observed previously.

Scheme 7. Attempted protection and reduction reactions of benzylic ketone 12 and 13



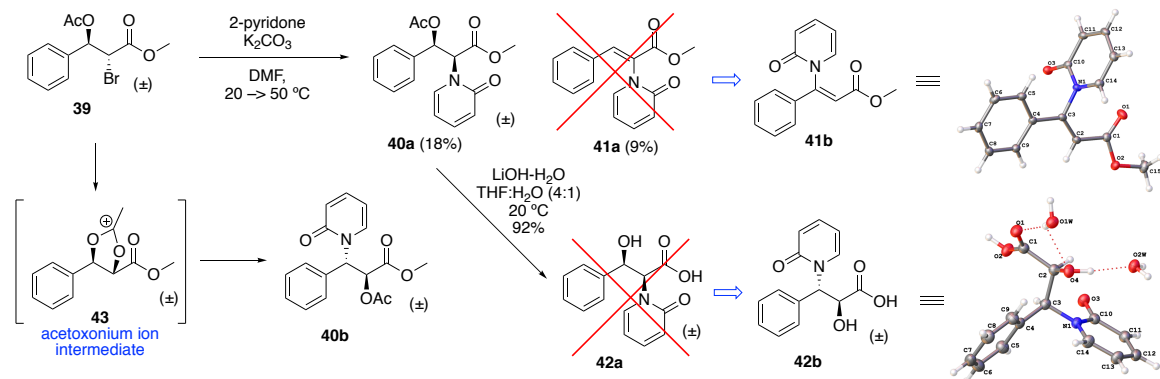
Protected Benzylic Alcohol Route. To access benzylic alcohols that could be converted to ketones late in the synthesis, we prepared bromohydrins **35a-b** from the respective methyl and benzyl cinnamates using NBS and I₂ as a catalyst (Scheme 8).³⁰ This also installed alpha halides for pyridone alkylations. Under standard 2-pyridone alkylation conditions, epoxide **36** was exclusively formed. To circumvent this issue, the TBS- or MOM-protected bromohydrins **37a-b** were synthesized. It was found that the use of 2,6-lutidine as base was critical, as alternative bases such as DIPEA favored epoxidation over alcohol protection. However, subjecting the TBS- or MOM-protected bromohydrin to pyridone alkylation conditions afforded only alkene **38** in <20% yield. Alternatively, the acetyl-protected alcohol **39** was synthesized using acetic anhydride and catalytic DMAP. *N*-alkylation of 2-pyridone using **39** afforded what was initially presumed to be the desired product **40** and alkene **41** in 18% and 9% yield respectively (Scheme 9). Due to the low yields, we screened alternative solvents (acetone) and bases (Cs₂CO₃) in an effort to increase the yield and selectivity; however, the yield of **40** was not improved.

Scheme 8. Preparation of bromohydrin intermediates

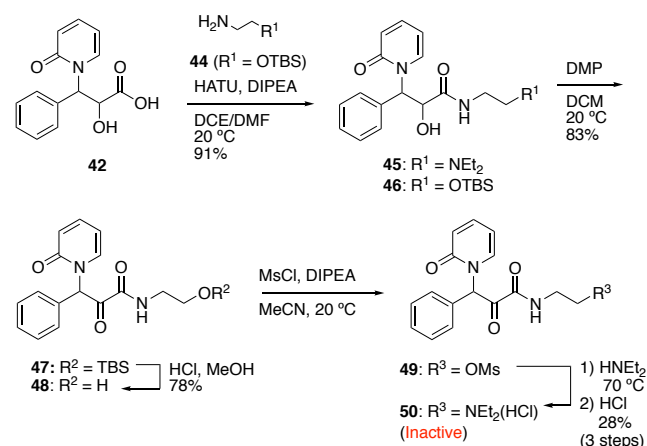


Moving forward with the synthesis, methyl ester and acetate hydrolysis proceeded smoothly to yield the presumed carboxylic acid **42a** (Scheme 9). At that time, we did not suspect any issues and completed the synthetic sequence to yield **50**, which was initially thought to be STK076545 (Scheme 10). *N,N*-diethylethylenediamine was used directly for the peptide coupling to prepare **45**; however, the subsequent alcohol oxidation was unsuccessful when using DMP, PDC, IBX, or Bobbitt's salt under basic (2,6-lutidine) or acidic (silica gel) conditions.³¹ Instead, ethanolamine was TBS-protected to afford **44** and then used in an amide coupling using HATU with carboxylic acid **42** to yield **46** in 91% yield. DMP oxidation of the alcohol proceeded smoothly to afford ketone **47**, followed by TBS removal using HCl. In a one-pot reaction, alcohol **48** underwent a methylation followed by a substitution with diethylamine. The final product was treated with HCl to furnish the HCl salt **50** in 28% yield over 2 steps.

Scheme 9. N-alkylation of 2-pyridone with acetyl-protected bromohydrin



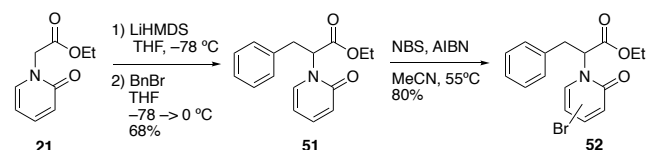
Scheme 10. Synthesis of the incorrect regioisomer of STK076545



However, analogs **48** and **50** were both found to be inactive in a PDI activity assay measuring the reduction of insulin (cleavage of its disulfide bonds). Obtained X-ray crystal structures of **41b** and **42b** revealed that the pyridone was in the benzylic position (Scheme 9). A distinct difference between **42a** and the X-ray structure of **42b** is the relative stereochemistry between the hydroxyl and pyridone substituents. We propose that cyclic acetoxonium ion intermediate **43** is formed, similar to that proposed for the Prévost³² and Woodward³³ dihydroxylation reactions, and 2-pyridone then attacks the benzylic carbon. Since we started with (*E*)-methyl cinnamate, the *anti* addition of water to the intermediate *rac*-bromonium ion results in a racemic mixture of bromohydrins **39**. Formation of the proposed acetoxonium ion intermediate **43** and subsequent pyridone alkylation would result in inversion of both stereocenters and generate

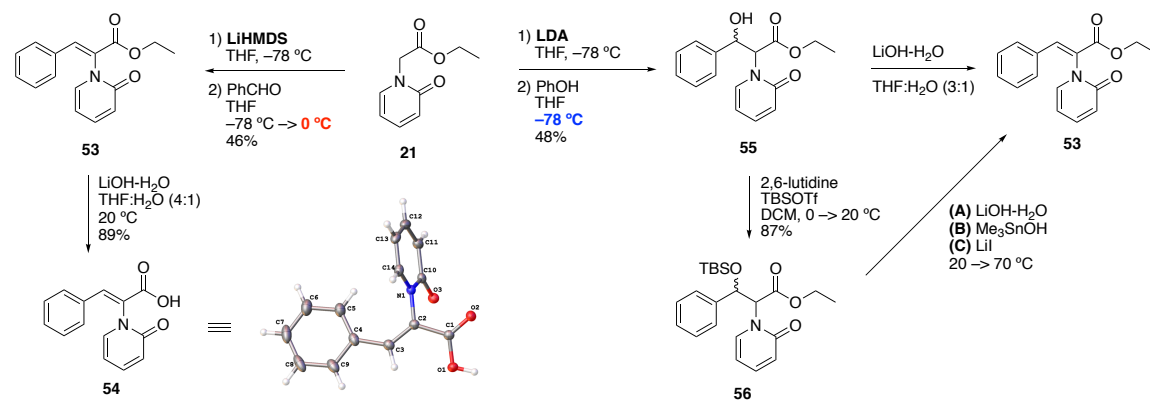
40b. Ester hydrolysis of **40b** then yielded acid **42b**, with its relative stereochemistry confirmed by the X-ray crystal structure (Scheme 9).

Scheme 11. Alkylation and attempted benzylic bromination



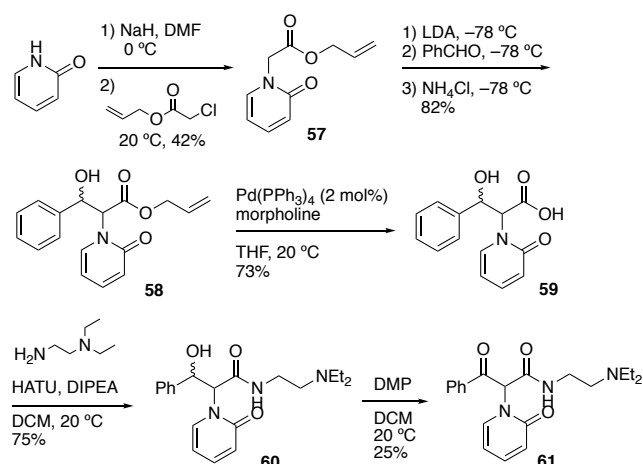
Aldol Addition Route. To circumvent the unexpected rearrangement through the acetoxonium ion intermediate, we planned to perform the N-alkylation prior to installation of the alcohol/ketone functionality. Inspired by Easton and co-workers' use of NBS and $AgNO_3$ to generate hydroxy- α -amino acid derivatives,³⁴ we sought to access a benzylic bromide intermediate from **51** (Scheme 11). Ester **21** was reacted with $LiHMDS$ to generate an enolate, followed by alkylation with benzyl bromide to afford **51**. Subsequent treatment with NBS and $AIBN$ in $MeCN$ yielded no bromination at the benzylic position. The m/z peak observed in the LC-MS trace confirmed the presence of a brominated product, but the crude 1H NMR spectrum suggested that bromination occurred on the pyridone. Alternatively, benzaldehyde was used instead of benzyl bromide to react with the enolate generated from ester **21** to access the benzylic alcohol directly (Scheme 12). Using identical conditions ($LiHMDS$ and 0 $^\circ C$), the elimination product **53** was generated. Hydrolysis of ester **53** yielded carboxylic acid **54**, which X-ray crystallography confirmed to be the alkene to be the *Z* alkene.

Scheme 12. Aldol reactions with α -pyridone ester 21



With LDA being more commonly used in the literature for aldol addition reactions with esters, we switched our base to LDA (Scheme 12). Quenching the reaction at $-78\text{ }^{\circ}\text{C}$ was found to be critical to avoid generation of the elimination product and give the desired alcohol **55**. Unfortunately, ester hydrolysis with LiOH yielded the elimination product **53** again. In an effort to avoid generation of this undesired alkene, we synthesized the TBS-protected alcohol **56**. This route was unfruitful as ester hydrolysis or cleavage using LiOH, Me_3SnOH , or LiI all resulted in the generation of **53**.

Scheme 13. Successful allyl ester route to STK076545



In order to access the carboxylic acid under milder conditions, we instead synthesized allyl ester **57** (Scheme 13). First, 2-pyridone was alkylated with allyl chloroacetate to yield allyl ester **57**, and subsequent aldol addition using benzaldehyde afforded alcohol **58**. By increasing the amount of benzaldehyde from 1 to 2 equivalents, we were able to nearly double the yield to 82% for this reaction. Allyl removal with $\text{Pd}(\text{PPh}_3)_4$ produced carboxylic acid **59**. Amide coupling and subsequent DMP oxidation of alcohol **60** successfully produced the final β -keto-amide product **61** with the reported structure of STK076545. Alcohol analog **60** and the final compound **61** were both tested in the insulin reduction assay and found to be inactive. We obtained an X-ray crystal structure corroborating the structure of **61** (Figure 3). Interestingly, the ^1H and ^{13}C NMR spectra do not match that of the batch received from the commercial supplier. This confirms that the structure of the active PDI-inhibiting compound was misassigned.

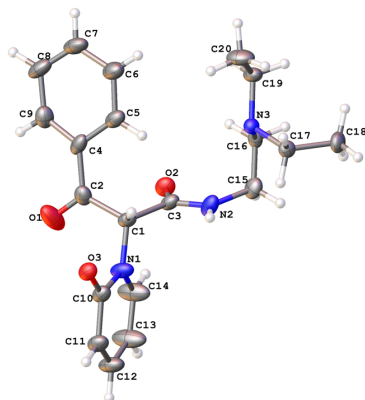


Figure 3. X-ray structure of amide **61**.

CONCLUSION

Several conventional methods for forming β -keto amides resulted in fragmentation of pyridone-containing intermediates, such as retro-Claisen-like and retro-aldol reactions. Efforts to instead proceed via an acetyl protected bromohydrin resulted in a rearrangement that we propose proceeds via an acetoxonium ion intermediate. Alternatively, we successfully synthesized the reported structure of STK076545 via a 5-step synthetic route proceeding through allyl ester **58**. This strategy should prove to be broadly useful in accessing β -keto amides, particularly with an electron-withdrawing α -substituent such as N-pyridone.

Unexpectedly, neither the final compound (**61**) nor several of its precursors were found to inhibit protein disulfide isomerase, and its ^1H and ^{13}C NMR spectra do not match those of the active commercial compound STK076545. It is not uncommon for complex natural products to have misassigned structures which require correction after more detailed synthetic and spectroscopic studies.³⁵ However, it is often taken for granted that simpler commercial small molecules are provided in high purity and with structures as advertised, which is not always the case.³⁶ Our results here highlights the importance of resynthesis and structure validation of active compounds prior to embarking on medicinal chemistry campaigns. Current efforts in our lab are ongoing to elucidate the correct structure of the commercially supplied compound that may have useful PDI inhibitory activity.

EXPERIMENTAL SECTION

General information.

All reagents and solvents were purchased from commercial vendors and used as received, except for diethylamine, which was distilled and stored over 4 Å mol sieves prior to use. Reactions were performed in ventilated fume hoods with magnetic stirring and oil bath heating, unless otherwise noted. Deionized water was purified by charcoal filtration and used for reaction workups and in reactions with water. NMR spectra were recorded on Varian 300 MHz or 400 MHz spectrometers as indicated. Proton and carbon chemical shifts are reported in parts per million (ppm; δ) relative to tetramethylsilane, CDCl_3 , or CD_3OD (^1H δ 0, ^{13}C δ 77.16, or ^1H δ 3.31, ^{13}C δ 49.0, respectively). NMR data are reported as follows: chemical shifts, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet); coupling constant(s) in Hz; integration. Unless otherwise indicated, NMR data were collected at $25\text{ }^{\circ}\text{C}$. NMR data were processed using MestReNova software. Flash chromatography was performed using Biotage SNAP cartridges filled with 40–60 μm silica gel on Biotage Isolera systems, with photodiode array UV detectors. Analytical thin layer chromatography (TLC) was performed on Agela Technologies glass plates with 0.25 mm silica gel with F254 indicator. Visualization was accomplished with UV light (254 nm) and aqueous potassium permanganate (KMnO_4) stain followed by heating, unless otherwise noted. Tandem liquid chromatography/mass spectrometry (LC-MS) was performed on a Shimadzu LCMS-2020 with autosampler, photodiode array detector, and single-quadrupole MS with ESI and APCI dual ionization, using a Peak Scientific nitrogen generator. Unless otherwise noted, a standard LC-MS method was used to analyze reactions and reaction products: Phenomenex Gemini C18 column (100 x 4.6 mm, 3 μm particle size, 110 Å pore size); column temperature $40\text{ }^{\circ}\text{C}$; 5 μL of sample in MeOH or CH_3CN at a nominal concentration of 1 mg/mL was injected, and peaks were eluted with a gradient of 25–95% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (both with 0.1% formic acid) over 5 min., then 95% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ for 2 min.

Synthetic protocols.

Ethyl 3-oxo-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanoate (3); **ethyl 3-oxo-3-phenyl-2-(pyridin-2-yl)oxypropanoate (4)**. A suspension of 2-hydroxypyridone (163 mg, 1.72 mmol), tetrabutylammonium bromide (59.5 mg, 0.184 mmol), and potassium carbonate (765 mg, 55.3 mmol) in acetone (6.0 mL) was heated to 40 °C and stirred for 30 min. Ethyl-2-bromo-3-oxo-3-phenylpropanoate (500 mg, 1.84 mmol) was added and the suspension was stirred at 40 °C for 30 min before being cooled to 20 °C. A solution of acetic acid (160 μ L, 2.79 mmol) in water (2.0 mL) was added slowly, and the mixture was stirred for 15 min. The resulting mixture was diluted with H₂O (2.0 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude orange oil was dissolved in DCM and purified via flash chromatography (25 g SiO₂ column, 0–60% EtOAc/hexanes) to yield pyridone **3** as a yellow oil (229 mg, 47%) and **4** as a yellow oil (44 mg, 9%). **3**: $R_f = 0.25$ (50:50 EtOAc:hexanes); ¹H NMR (CDCl₃, 400 MHz) δ 8.09 (d, $J = 7.3$ Hz, 2H), 7.64–7.58 (m, 2H), 7.51–7.46 (m, 3H), 7.37–7.33 (m, 1H), 6.62 (d, $J = 8.7$ Hz, 1H), 6.22–6.18 (m, 1H), 4.31–4.28 (m, 2H), 1.27 (t, $J = 7.1$ Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 191.9, 166.6, 161.4, 140.6, 136.4, 134.8, 134.0, 129.4, 129.2, 120.2, 106.4, 62.8, 59.2, 14.1; LC-MS $t_R = 3.96$; $m/z = 285.75$ (M+H); **4**: ¹H NMR (CDCl₃, 400 MHz) δ 8.06–7.96 (m, 3H), 7.60–7.48 (m, 5H), 6.95–6.92 (m, 1H), 4.26–4.11 (m, 2H), 1.22–1.20 (m, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 191.7, 166.6, 161.3, 146.5, 139.3, 133.9, 129.4, 128.7, 118.3, 111.4, 76.0, 62.2, 14.1; LC-MS $t_R = 2.86$; $m/z = 285.75$ (M+H).

1-(2-Oxo-2-phenylethyl)-1,2-dihydropyridin-2-one (5). 2-hydroxypyridine (0.263 g, 2.76 mmol) and Cs₂CO₃ (1.63 g, 5.02 mmol) were added to a 15 mL oven-dried flask with stir bar and sealed under N₂. Anhydrous DMF (5.0 mL) was added and the suspension was stirred at 20 °C for 30 min before 2-bromoacetophenone (0.500 g, 2.51 mmol) was added and the suspension was stirred for an additional 1 h at 20 °C. A solution of glacial acetic acid (210 μ L, 3.77 mmol) in H₂O (2 mL) was slowly added and the mixture was stirred until it turned clear and stopped bubbling (~10 min). The mixture was diluted with H₂O (5 mL) and EtOAc (40 mL) and the layers were separated. The organic layer was washed with water (3 x 15 mL) and the combined aqueous layers were extracted with EtOAc (10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude yellow solid was dissolved in DCM and purified via flash chromatography (50 g SiO₂ column, 0–100% EtOAc/hexanes) to yield pyridone **5** as a white crystalline solid (0.411 g, 77%). This compound has been previously reported and characterized (CAS# 952-75-0).³⁷ ¹H NMR (CDCl₃, 400 MHz) δ 8.02–8.00 (m, 2H), 7.62 (tt, $J = 7.4, 1.2$ Hz, 1H), 7.51–7.47 (m, 1H), 7.40–7.35 (m, 1H), 7.23–7.21 (m, 1H), 6.59 (d, $J = 9.2$ Hz, 1H), 6.21 (td, $J = 6.7, 1.3$ Hz, 1H), 2.21 (s, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ 192.4, 162.5, 140.2, 138.4, 134.7, 134.1, 129.0, 128.2, 120.8, 106.1, 54.4.

Methyl 3-oxo-3-phenylpropanoate (10). NaH (3.7 g, 60% in mineral oil, 92 mmol) and dimethyl carbonate (5.9 g, 66 mmol) were added to a 250 mL oven-dried flask with stir bar. A reflux condenser and addition funnel were attached, the apparatus was sealed and flushed with N₂, and anhydrous toluene (33 mL) was added under N₂. After the mixture was heated to reflux, a solution of acetophenone (3.80 mL, 32.4 mmol) in tol-

uene (17 mL) was added dropwise over 0.5 h. The reaction solution turned orange with the formation of a white precipitate. After the evolution of hydrogen ceased (~15 min), the reaction was cooled to room temperature. Glacial acetic acid (10 mL) was added dropwise and a heavy pasty solid separated. Ice-cold water was slowly added until the solid dissolved completely, and the reaction mixture was diluted with EtOAc (200 mL). The organic layer was separated, washed with H₂O (200 mL) and brine (200 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was dissolved in DCM and purified via flash chromatography (100 g SiO₂ column, 0–25% EtOAc/hexanes) to yield ester **10** as an orange oil (5.65 g, 98%). This compound has been previously reported and characterized (CAS# 614-27-7). ¹H NMR (300 MHz, CDCl₃) δ 12.51 (s, 0.22 H), 7.94 (m, 2H), 7.78 (m, 0.44 H), 7.76–7.58 (m, 0.44 H), 7.62–7.58 (m, 1 H), 7.50–7.40 (m, 2.7 H), 5.68 (s, 0.22 H), 4.01 (s, 2H), 3.80 (s, 0.65 H), 3.75 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 192.5, 173.6, 171.6, 168.0, 136.0, 133.9, 133.4, 131.4, 128.9, 128.64, 128.6, 126.2, 87.1, 52.6, 51.5, 45.8.

Benzyl 3-oxo-3-phenylpropanoate (11). A 25 mL round bottom flask was charged with methyl 3-oxo-3-phenylpropanoate (1.05 g, 5.91 mmol), benzyl alcohol (6.10 mL, 59.1 mmol), ZnO (96.0 mg, 1.18 mmol) and anhydrous toluene (5 mL). The flask was fitted with a short-path distillation head and heated in an oil bath set at 110 °C, distilling the methanol formed during the reaction. After 24 h, LC-MS analysis of the reaction mixture showed complete consumption of the starting material. The reaction mixture was filtered through a plug of Celite and concentrated. The crude residue was dissolved in DCM and purified via flash chromatography (100 g SiO₂ column, 0–20% EtOAc/hexanes) to give benzyl ester **11** as a light orange oil (1.43 g, 95%). This compound has been previously reported and characterized (CAS# 63888-22-2).³⁸ This compound exists as a mixture of tautomers in CDCl₃ (10:1 keto:enol). ¹H NMR (300 MHz, CDCl₃) δ 12.50 (s, enol), 7.94 (d, $J = 8.0$ Hz, enol), 7.90 (d, $J = 8.0$ Hz, 2H), 7.77 (d, $J = 7.9$ Hz, enol), 7.59 (t, $J = 7.5$ Hz, 1H), 7.48–7.28 (m, 7H), 5.73 (s, enol), 5.25 (s, enol), 5.19 (s, 2H), 4.04 (s, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 192.4, 167.5, 135.4, 133.9, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 67.3, 46.1.

Benzyl 2-bromo-3-oxo-3-phenylpropanoate (12). In a 100 mL flask with stir bar, ester **11** (1.00 g, 3.93 mmol), *N*-bromosuccinimide (0.735 g, 4.13 mmol), and Amberlyst-15 (2.89 g) in ethyl acetate (30 mL) were stirred at 20 °C for 2.5 h. After completion of the reaction, as indicated by LC-MS, the reaction mixture was filtered and washed with EtOAc (2 x 20 mL). The combined organic filtrates were dried over anhydrous Na₂SO₄, and concentrated. The crude product was dissolved in DCM and purified via flash chromatography (50 g SiO₂ column, 0–20% EtOAc/hexanes) to yield alkyl bromide **12** as a light yellow oil (1.20 g, 92%). This compound has been previously reported and characterized (CAS# 845733-96-2).²⁷ ¹H NMR (400 MHz, CDCl₃) δ 7.94–7.92 (m, 2H), 7.58 (m, 1H), 7.43 (m, 2H), 7.30–7.23 (m, 5H) ¹³C NMR (100 MHz, CDCl₃) δ 188.0, 165.1, 134.6, 134.3, 133.3, 129.2, 128.9, 128.6, 128.6, 128.4, 68.8, 46.4.

Benzyl 3-oxo-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanoate (13). A suspension of 2-hydroxypyridone (212 mg, 2.23 mmol), tetrabutylammonium bromide (65.4 mg, 0.203 mmol), and potassium carbonate (0.841 g, 6.09 mmol) in acetone (4.0 mL) was heated to 40 °C and stirred for 30 min. Then, bromide **12** (676 mg, 2.03 mmol) in acetone (0.5 mL) was added. The suspension was stirred at 40 °C for 30 min and cooled to room temperature before a solution of acetic acid (232

uL, 4.06 mmol) in water (2.0 mL) was added slowly. The resulting mixture was stirred for 15 min before it was diluted with H₂O (5.0 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude dark orange oil was dissolved in DCM and purified via flash chromatography (50 g SiO₂, 0–50% EtOAc/hexanes) to yield pyridone **13** as a colorless oil (496 mg, 70%). ¹H NMR (400 MHz, CDCl₃) δ 8.07–8.04 (m, 2H), 7.64 (s, 1H), 7.60 (tt, *J* = 7.4, 1.2 Hz, 1H), 7.48–7.44 (m, 3H), 7.35–7.26 (m, 6H), 6.61 (d, *J* = 9.2 Hz, 1H), 6.18 (td, *J* = 6.8 Hz, 1.3 Hz, 1H), 5.25 (s, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 191.7, 166.5, 161.4, 140.7, 136.4, 134.8, 134.6, 133.9, 129.4, 129.2, 128.7, 128.7, 128.4, 120.3, 106.4, 68.3, 59.4; LC-MS *t*_R = 3.72; *m/z* = 348.10 (M+H).

1-(2-Hydroxy-2-phenylethyl)-1,2-dihydropyridin-2-one (14). To a 15 mL flask with stir bar, **13** (33.5 mg, 0.096 mmol) and MeOH (3.0 mL) were added. The flask headspace was flushed with N₂ before 10% Pd/C (10.3, 0.0096 mmol) was added. The flask was flushed with H₂ and stirred under H₂ (1 atm) at 20 °C for 1 h. After 1 h, the reaction mixture was filtered through Celite, condensed under vacuum and analyzed via LC-MS and ¹H NMR, which indicated conversion to alcohol **14**. ¹H NMR of the crude product showed signals for alkyl protons at 4.36, 3.89, and 5.01 ppm, consistent with published data. This compound has been previously reported and characterized (CAS# 69914-21-2). ¹H NMR (400 MHz, CD₃OD) δ 7.43–7.39 (m, 2H), 7.39–7.33 (m, 3H), 7.29–7.26 (m, 2H), 6.56 (d, *J* = 8.5 Hz, 1H), 6.30 (td, *J* = 6.7, 1.2 Hz, 1H), 5.01 (dd, *J* = 8.8, 3.8 Hz, 1H), 4.36 (dd, *J* = 13.1, 3.8 Hz, 1H), 3.89 (dd, *J* = 13.1, 8.8 Hz, 1H). 215.75; LC-MS *t*_R = 1.68; *m/z* = 215.75 (M+H).

***N*-[2-(Diethylamino)ethyl]-1*H*-imidazole-1-carboxamide (16).** 1,1-carbonyldiimidazole (205 mg, 1.26 mmol) was added to a 4 mL oven-dried vial with stir bar and sealed under N₂. Anhydrous THF (1.2 mL) was added and the solution was cooled to 0 °C in an ice bath. A solution of *N,N*-diethylethylenediamine (97.9 mg, 0.842 mmol) in anhydrous DCM (0.6 mL) was added dropwise over 10 min and the solution was stirred at 20 °C for 1.5 h. Next, the solvent was removed via vacuum and the crude product was loaded on to Celite and purified via flash chromatography (12 g C18, MeOH/H₂O gradient) to yield urea **16** as a yellow oil (93.7 mg, 53%). This compound has been previously reported (CAS# 698388-51-1). ¹H NMR (300 MHz, CDCl₃) δ 8.18 (s, 1H), 7.45–7.42 (m, 1H), 7.09–7.07 (m, 2H), 3.46 (t, *J* = 6.1 Hz, 2H), 2.66 (t, *J* = 5.6 Hz, 2H), 2.61–2.51 (m, 4H), 1.06–0.97 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 149.1, 136.1, 130.3, 130.1, 116.1, 51.3, 46.8, 38.2, 11.8; LC-MS *t*_R = 1.01; *m/z* = 210.80 (M+H).

***N-Tert*-butyl-3-oxo-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenyl propanamide (19).** In a 4 mL oven-dried vial with a stir bar, *t*-butylisocyanate (7.0 mg, 0.071 mmol) and NaH (60% w/w in mineral oil, 4.7 mg, 0.118 mmol) were mixed in anhydrous toluene (0.5 mL) under N₂ at 20 °C. Then, ketone **5** (10.0 mg, 0.047 mmol) was added in one portion and the mixture was heated at 100 °C for 2 h. After 2 h, the reaction was quenched by the addition of saturated ammonium chloride. The aqueous layer was extracted with DCM (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and condensed to a yellow residue. The crude product was purified via flash chromatography (10 g SiO₂, 0–100% EtOAc/hexanes) to afford amide **19** as a yellow oil (2.2 mg, 15%) and recovered ketone **5** (8.0 mg, 80%). ¹H NMR (300 MHz, CDCl₃) δ 7.98 (d, *J* = 8.0 Hz, 2H), 7.74–7.72 (m, 1H), 7.56–7.52 (m, 1H) 7.43–7.36 (m, 3H), 7.31 (s, 1H),

6.85 (br. s., 1H), 6.61 (d, *J* = 9.0 Hz, 1H), 6.29 (t, *J* = 6.8 Hz, 1H). LC-MS *t*_R = 2.96; *m/z* = 313.15 (M+H).

2,2-Difluoro-6-methoxy-4-phenyl-2*H*-1λ³,3,2λ⁴-dioxaborinine (20a). To an oven-dried 20 mL vial, **10** (0.420 g, 2.36 mmol) and a stir bar were added and the vial was purged with N₂ for 10 min. Then, anhydrous toluene (10 mL) and boron trifluoride etherate (0.58 mL, 4.71 mmol) were sequentially added. The reaction mixture was stirred at 20 °C for 20 h. The reaction mixture was then concentrated to ~1/3 of its volume and cooled to –30 °C in a dry ice MeOH/H₂O cooling bath. The precipitated material was filtered off and washed with 5:1 petroleum ether/EtOAc (5 mL), yielding the boron complex **20a** as a yellow solid (307 mg, 58%). ¹H NMR (300 MHz, CDCl₃) δ 7.96–7.92 (m, 2H), 7.63–7.57 (m, 1H), 7.51–7.46 (2H), 6.03 (s, 1H), 4.12 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 179.6, 176.3, 134.0, 132.0, 129.0, 127.9, 83.2, 56.1.

Ethyl 2-(2-oxo-1,2-dihydropyridin-1-yl)acetate (21). To an oven-dried 1.0 L round bottom flask charged with a stir bar, NaH (60% in mineral oil, 1.99 g, 49.9 mmol) was suspended in anhydrous DMF (100 mL) and cooled to 0 °C in an ice bath under N₂. To the NaH suspension, a solution of 2-hydroxypyridine (4.07 g, 42.1 mmol) in anhydrous DMF (200 mL) was slowly added. The resulting solution was stirred for 1 h at 0 °C before ethyl bromoacetate (4.3 mL, 38 mmol) was added and the mixture was stirred at room temperature for 1.5 h. The reaction was quenched with saturated NH₄Cl (40 mL) and the product was extracted with DCM (3 x 150 mL). The combined organic extracts were washed with water (7 x 200 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude product was dissolved in DCM and purified via flash chromatography (100 g SiO₂, 0–100 % EtOAc/hexanes) to yield ester **21** as a pale yellow oil (3.62 g, 53%). This compound has been previously reported and characterized (CAS# 80056-43-5).²⁹ *R*_f = 0.74 (DCM/MeOH 9:1). ¹H NMR (300 MHz, CDCl₃) δ 1.29 (t, 3H, *J* = 7.1 Hz), 4.24 (q, 2H, *J* = 7.1 Hz), 4.64 (s, 2H), 6.18–6.23 (m, 1H), 6.58–6.61 (m, 1H), 7.21–7.24 (m, 1H), 7.34–7.40 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 14.15, 50.52, 61.91, 106.22, 120.97, 121.01, 138.04, 140.27, 162.47, 167.78.

***N*-[2-(Diethylamino)ethyl]-3-oxo-3-phenylpropanamide (22).** *N,N*-diethylethylenediamine (167.0 mg, 1.438 mmol) was added to a 15 mL oven-dried flask with stir bar and sealed under N₂. Anhydrous MeCN (5.0 mL) and **20a** (250 mg, 1.11 mmol) were added, and the reaction mixture was stirred at 20 °C for 4 h. After 4 h, an aliquot was removed, condensed under reduced pressure, and dissolved in CDCl₃ to monitor the reaction via ¹H NMR. The reaction mixture was condensed under vacuum, dissolved in EtOAc (30 mL), washed with H₂O (2 x 10 mL), dried over MgSO₄, filtered, and condensed under vacuum to yield complex **22** as a pale yellow oil (283 mg, 82%). The crude oil (259 mg, 0.834 mmol), sodium acetate (0.342 g, 4.17 mmol), ethanol (5.0 mL), and H₂O (5.0 mL) were refluxed for 8 h. TLC analysis (10% MeOH/DCM) of the reaction mixture indicated the starting material was consumed. The solvent was removed under reduced pressure, and the residue was dissolved in EtOAc (30 mL) and washed with water (2 x 10 mL). The combined aqueous layers were saturated with NaCl and extracted with 9:1 DCM:MeOH (5 x 10 mL). The combined organics were dried over magnesium sulfate, filtered, and concentrated. The crude oil was purified by flash chromatography (10 g SiO₂, 0–10% MeOH/DCM) to yield amide **22** as a pale yellow oil (147 mg, 67%). *R*_f = 0.50 (9:1 DCM:MeOH); ¹H NMR (300 MHz, CDCl₃) δ 7.99 (d, *J* = 7.4 Hz, 2H), 7.61–7.57 (m, 1H) 7.50–7.45 (m, 2H), 3.96 (s, 2H), 3.48 (q, *J* = 5.5 Hz, 2H), 2.79–2.73 (m, 6H), 1.14 (t, *J* = 7.1 Hz, 6H); ¹³C NMR (300 MHz, CDCl₃) δ

195.16, 178.19, 136.43, 133.82, 128.84, 128.70, 51.54, 47.03, 46.53, 36.49, 10.50; LC-MS t_R = 1.06; m/z = 263.15 (M+H).

2-(2-Oxo-1,2-dihydropyridin-1-yl)acetic acid (25). Ester **21** (3.59 g, 19.8 mmol) and EtOH:H₂O (1:1, 60 mL) were added to a 250 mL oven-dried flask with stir bar and cooled to 0 °C. A 1 N aqueous solution of LiOH (40 mL, 40 mmol) was added and the solution was stirred for 2 h at 20 °C. After 2 h, ethanol was removed under vacuum and 2 M HCl was added to the aqueous solution to reach a pH ~ 6. Next, the solution was concentrated down to dryness and the crude solid was dissolved with DCM and purified via flash chromatography (50 g SiO₂, 0–10% MeOH/DCM w/ 0.1% formic acid) to afford **25** as a white powder (2.04 g, 67%). This compound has been previously reported and characterized (CAS# 56546-36-2).²⁹ ¹H NMR (400 MHz, acetone-*d*₆) δ 7.62–7.60 (m, 1H), 7.46–7.42 (m, 1H), 6.41–6.25 (m, 1H), 6.26–6.21 (m, 1H), 4.71 (s, 2H).

[2-(Diethylamino)ethyl][(4-methoxyphenyl)methyl]amine (26b). *N,N*-diethylethylenediamine (1.25 g, 10.6 mmol) was added to a 100 mL oven-dried flask with stir bar and sealed under N₂. *i*-PrOH (25 mL) was added and the flask was cooled to 0 °C. Then, *p*-anisaldehyde (1.58 mL, 12.8 mmol) was added dropwise, and the reaction was slowly warmed to 20 °C and stirred for 16 h. MeOH (20 mL) was added, the solution was cooled to 0 °C, and NaBH₄ (1.69 g, 44.7 mmol) was added in portions over 1 h. The solution was stirred for an additional 1 h, while warmed to 20 °C. A solution of 10% NaOH in H₂O (25 mL) was added and the resulting mixture was extracted with DCM (3 x 40 mL). The combined organic layers were washed with a 10% aqueous solution of NaI (50 mL). The organic layers were dried over Na₂SO₄, filtered, and concentrated. The resulting crude yellow oil was dissolved in DCM (5 mL) and ether (10 mL), cooled to 0 °C, and a 4 M HCl solution in 1,4-dioxane (5.6 mL, 22.4 mmol) was added dropwise. The white precipitate was filtered and washed with DCM and diethyl ether to yield an off-white solid. This was dissolved in water (30 mL), cooled to 0 °C, and the solution was basified with NaOH (to pH ~ 9). The resulting mixture was extracted with DCM (3 x 40 mL). The combined organics were dried over Na₂SO₄, filtered, and concentrated to yield amine **26b** as a yellow oil (1.86 g, 74% yield). This compound has been previously reported (CAS# 65875-40-3). R_f = 0.57 (9:1 DCM:MeOH); ¹H NMR (300 MHz, CDCl₃) δ 7.23 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 3.79 (s, 3H), 3.74 (s, 2H), 2.66 (t, J = 6.2 Hz, 2H), 2.55 (t, J = 6.2 Hz, 2H), 2.49 (q, J = 7.1 Hz, 4H), 0.99 (t, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 158.56, 132.83, 129.31, 113.75, 55.31, 53.53, 52.71, 47.08, 46.93, 11.93; LC-MS t_R = 0.89; m/z = 236.90 (M+H).

***N*-[2-(Diethylamino)ethyl]-2-(2-oxo-1,2-dihydropyridin-1-yl)acetamide (27a).** Carboxylic acid **25** (37.0 mg, 0.242 mmol) was added to an oven-dried 50 mL flask with stir bar and sealed under N₂. To the suspension, anhydrous DCM (4.0 mL), HOBt (69.4 mg, 0.363 mmol), DIPEA (62.0 μL, 0.362 mmol), and *N,N*-diethylethylenediamine (33.7 mg, 0.290 mmol) were sequentially added. The reaction mixture was stirred for 5 min at 20 °C before EDC-HCl (69.4 mg, 0.362 mmol) was added in one portion. The reaction mixture was stirred at 20 °C for 48 h. Monitoring via LC-MS showed conversion to the desired product. The solvent was removed under vacuum and the residue was dry loaded using Celite and purified via flash chromatography (12 g C18, 0–95% MeOH/H₂O gradient w/ 0.1% NH₄OH) to yield amide **27a** as a pale yellow oil (21 mg, 35%). ¹H NMR (300 MHz, CDCl₃) δ 7.38–7.38 (m, 2H), 6.61 (d, J = 9.0 Hz, 1H), 6.24 (td, J = 1.3, 6.7 Hz, 1H), 4.56 (s, 2H), 3.30 (q, J = 5.7 Hz, 2H), 2.57–2.50 (m, 7H), 0.99 (t, J = 7.1 Hz, 6H); ¹³C NMR

(75 MHz, CD₃OD) δ 168.1, 163.6, 141.5, 139.8, 139.7, 119.3, 107.2, 52.0, 51.2, 46.9, 36.6, 10.3; LC-MS t_R = 0.99; m/z = 251.80 (M+H).

***N*-[2-(Diethylamino)ethyl]-*N*-[(4-methoxyphenyl)methyl]-2-(2-oxo-1,2-dihydropyridin-1-yl)acetamide (27b).** Carboxylic acid **25** (0.300 g, 19.6 mmol) was added to an oven dried 50 mL flask with stir bar and sealed under N₂. Anhydrous DCE (20.0 mL) was added, and the resulting mixture was cooled to 0 °C using an ice bath before EDC-HCl (0.563, 29.4 mmol), amine **27b** (0.300 g, 19.6 mmol), and DMAP (23.9 mg, 1.96 mmol) were added. The reaction was allowed to warm up to 20 °C and stirred under N₂ for 16 h. The resulting solution was washed with 1 M NaOH (10 mL). The aqueous layer was extracted with DCM (2 x 5 mL), and the combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude yellow oil was dissolved with DCM and purified via flash chromatography (12 g C18, 0–95% MeOH/H₂O with 0.1% NH₄OH) to yield amide **27b** as a colorless oil (213 mg, 29%). The ¹H and ¹³C NMR are complicated due to rotamers. ¹H NMR (300 MHz, CDCl₃) δ 7.39–7.24 (m, 3H), 7.20–7.18 (m, 1H), 6.93–6.91 (m, 1H), 6.85–6.82 (m, 1H), 6.58–6.54 (m-1H), 6.22–6.16 (m, 1H), 4.89 (s, 1H), 4.73 (s, 1H), 4.66 (s, 1H), 4.59 (s, 1H), 3.80–3.77 (s, 3H), 3.46–3.37 (m, 2H), 2.64–2.45 (m, 6H), 1.03–0.95 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 167.0, 166.7, 162.5, 162.4, 159.2, 159.0, 140.0, 140.0, 138.9, 138.7, 129.5, 129.1, 128.2, 127.9, 120.4, 114.3, 114.0, 105.8, 105.7, 55.3, 55.2, 51.5, 51.3, 50.3, 49.7, 49.4, 48.9, 47.5, 47.4, 45.6, 45.3, 45.2, 12.0; LC-MS t_R = 1.43; m/z = 371.95 (M+H).

Benzyl 2-bromo-3-hydroxy-3-phenylpropanoate (35a). To a 25 mL flask with stir bar, benzyl cinnamate (477 mg, 2.00 mmol), NBS (427 mg, 2.40 mmol) and MeCN:H₂O (4:1) (10 mL) were added and the solution was cooled to 0 °C. Iodine (50.8 mg, 0.200 mmol) was added and the mixture was stirred for 72 h. The reaction mixture was washed with 10 % aq. sodium thiosulfate (20 mL) and extracted with EtOAc (3 x 40 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude product was dissolved in DCM and purified by flash chromatography (50 g SiO₂, 0–100% EtOAc/hexanes) to afford bromohydrin **35a** as a colorless liquid (276 mg, 41%). This compound has been previously reported (CAS# 1332928-50-3). R_f = 0.47 (50:50 EtOAc:hexanes); ¹H NMR (300 MHz, CDCl₃) δ 7.23-7.37 (m, 10H), 5.20 (s, 2H), 5.07 (dd, J = 5.5, 8.2 Hz, 1H), 4.41 (d, J = 8.2 Hz, 1H), 3.26 (br d, J = 5.5 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 169.3, 139.0, 134.9, 128.9, 128.7, 128.7, 128.3, 127.0, 75.3, 68.0, 47.8.

Methyl 2-bromo-3-hydroxy-3-phenylpropanoate (35b). The procedure for the synthesis of bromohydrin **35a** was used with the following modifications: methyl *trans*-cinnamate (1.62 g, 10.0 mmol) was used instead of benzyl *trans*-cinnamate, NBS (2.14 g, 12.0 mmol), MeCN:H₂O (4:1) (50 mL), and iodine (254 mg, 1.00 mmol). The crude product was dissolved in DCM and purified by flash chromatography (100 g SiO₂, 0–40% EtOAc/hexanes) to afford bromohydrin **35b** as an off-white solid (1.45 g, 56%). This compound has been previously reported (CAS# 90841-69-3).³⁰ R_f = 0.38 (70:30 hexanes:EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 7.35–7.38 (m, 5H), 5.06 (dd, J = 5.3, 8.4 Hz, 1H), 4.37 (d, J = 8.4 Hz, 1H), 3.79 (s, 3H), 3.28 (d, J = 5.3 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 170.0, 139.0, 128.9, 128.7, 127.1, 75.3, 53.3, 47.5.

Benzyl 3-phenyloxirane-2-carboxylate (36). In a 4 mL oven-dried vial with stir bar, a suspension of 2-hydroxypropidone (6.8 mg, 0.072 mmol), tetrabutylammonium bromide (1.9 mg, 0.0060 mmol), and ground potassium carbonate (24.7 mg,

0.179 mmol) in acetone (0.5 mL) was heated at 40 °C for 30 min. A solution of the bromohydrin **35a** (20.0 mg, 0.0597 mmol) in acetone (0.2 mL) was added dropwise over 5 min and the mixture was stirred at 40 °C for 30 min. The reaction mixture was monitored via LCMS and TLC (50:50 EtOAc:hexanes) and stained with PAA. Saturated NH₄Cl (1 mL) and H₂O (1 mL) were added the solution was stirred for 10 min. The resulting solution was diluted with H₂O (5 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude pale yellow oil was dissolved in DCM and purified by flash chromatography (5 g SiO₂, 0–100% EtOAc/hexanes) to yield pyridone **36** as a colorless oil (11.4 mg, 75%). This compound has been previously reported and synthesized (CAS# 144667-57-2). ¹H NMR (300 MHz, CDCl₃) δ 3.55 (d, *J* = 1.7 Hz, 1H), 4.11 (d, *J* = 1.7 Hz, 1H), 5.25 (m, 2H), 7.25–7.40 (m, 10H); ¹³C NMR (75 MHz, CDCl₃) δ 168.2, 135.1, 135.0, 129.2, 128.8, 128.8, 128.7, 126.0, 67.6, 58.2, 56.9.

Methyl 2-bromo-3-[(tert-butyl)dimethylsilyloxy]-3-phenylpropanoate (37a). Bromohydrin **35a** (70.0 mg, 0.209 mmol) was added to a 4 mL oven-dried vial with stir bar and sealed under N₂. Anhydrous DCM (1.0 mL), 2,6-lutidine (92.0 μL, 0.794 mmol) and TBSOTf (72.0 μL, 0.314 mmol) were sequentially added and the solution was stirred at 20 °C for 2 h. TLC analysis (50:50 EtOAc:hexanes) indicated consumption of starting material. The reaction was quenched with the slow addition of saturated NaCl (2 mL), and the mixture was stirred for 15 min. The aqueous layer was extracted with ether (2 x 10 mL), and the organic layer was washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered, and condensed. The crude yellow oil was dissolved in DCM and purified by flash chromatography (25 g SiO₂, 0–20% EtOAc/hexanes) to yield **37a** as a pale yellow oil (277 mg, 77%). This compound has been previously reported and synthesized (CAS# 175722-72-2). *R*_f = 0.68 (70:30 hexanes:EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 7.31–7.38 (m, 5H), 4.98 (d, *J* = 9.8 Hz, 1H), 4.21 (d, *J* = 9.8 Hz, 1H), 3.81 (s, 3H), 0.79 (s, 9H), 0.01 (s, 3H), –0.29 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 169.6, 140.1, 128.7, 127.7, 76.7, 53.0, 49.4, 25.6, 18.0, –4.7, –3.3.

Methyl 2-bromo-3-(methoxymethoxy)-3-phenylpropanoate (37b). Bromohydrin **35a** (100 mg, 0.386 mmol) was added to a 4 mL oven-dried vial with stir bar and sealed under N₂. Anhydrous DCM (1.0 mL) was added and the solution was cooled to 0 °C. Then, 2,6-lutidine (67.4 μL, 0.579 mmol) was added followed by dropwise addition of methoxychloromethane (44 μL, 0.579 mmol). The solution was stirred at 0 °C for 1 h and allowed to warm up to room temperature, then stirred at room temperature for 16 h under N₂. After 16 h, the reaction was diluted with EtOAc (15 mL) and washed with saturated aq. NaHCO₃ (10 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL), and the combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude yellow oil was dissolved in DCM and purified by flash chromatography (5 g SiO₂, 0–40% EtOAc/hexanes) to yield **37b** as a colorless oil (78 mg, 66%). *R*_f = 0.59 (70:30 hexanes:EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 7.40–7.35 (m, 5H), 5.00 (d, *J* = 10.1 Hz, 1H), 4.54–4.45 (m, 2H), 4.33 (d, *J* = 10.1 Hz, 1H), 3.85 (s, 3H), 3.25 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 169.4, 136.9, 129.1, 128.7, 128.6, 128.4, 128.4, 127.1, 94.8, 78.7, 56.1, 53.1, 47.3.

Methyl 3-(acetyloxy)-2-bromo-3-phenylpropanoate (39). Bromohydrin **35b** (3.28 g, 12.6 mmol) was added to a 50 mL oven-dried flask with stir bar and sealed under N₂. Anhydrous DCM (20.0 mL), acetic anhydride (1.34 mL, 14.3 mmol) and

DMAP (61.8 mg, 0.506 mmol) were sequentially added. The solution was stirred at 20 °C for 16 h. TLC analysis (50:50 hexanes:EtOAc) confirmed consumption of starting material. The reaction mixture was poured into ice cold H₂O (100 mL), and extracted with DCM (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude pale yellow oil was dissolved in DCM and purified by flash chromatography (100 g SiO₂, 0–20% EtOAc/hexanes) to yield **39** as a colorless oil (3.55 g, 93%). This compound has been previously reported and synthesized (CAS# 59339-56-9). *R*_f = 0.73 (50:50 EtOAc:hexanes); ¹H NMR (300 MHz, CDCl₃) δ 7.43–7.35 (m, 5H), 6.11 (d, *J* = 9.9 Hz, 1H), 4.50 (d, *J* = 9.9 Hz, 1H), 3.81 (s, 3H), 2.02 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 168.8, 168.3, 136.0, 129.3, 128.6, 128.0, 75.6, 53.3, 46.1, 20.9.

Methyl 2-(acetyloxy)-3-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanoate (40b). 2-Hydroxypyridine (3.55 g, 37.4 mmol) and Cs₂CO₃ (8.11 g, 24.9 mmol) were added to a 250 mL oven-dried flask with stir bar and sealed under N₂. Anhydrous DMF (75 mL) was added and the suspension was heated at 50 °C for 1 h, then cooled to 20 °C. A solution of alkyl bromide **39** (7.50 g, 24.9 mmol) in anhydrous DMF (20 mL) was added and the reaction mixture was stirred at 20 °C for 16 h. The reaction was quenched with saturated aq. NH₄Cl (75 mL), diluted with EtOAc (500 mL), and washed with H₂O (6 x 200 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated. The resulting crude yellow oil was dissolved in DCM and purified by flash chromatography (100 g SiO₂, 0–100% EtOAc/hexanes) to yield **40b** as a waxy off-white solid (1.98 g, 25%) and **41b** as an off-white solid (0.60 g, 9%). **40b**: ¹H NMR (400 MHz, CDCl₃) δ 7.49–7.47 (m, 2H), 7.39–7.38 (m, 3H), 7.27–7.25 (m, 1H), 7.05 (d, *J* = 7.1 Hz, 1H), 6.87 (d, *J* = 5.1 Hz, 1H), 6.60 (d, *J* = 9.7 Hz, 1H), 6.02 (t, *J* = 6.7 Hz, 1H), 5.89 (d, *J* = 7.1 Hz, 1H), 3.65 (s, 3H), 2.14 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 169.4, 167.9, 162.2, 139.4, 135.9, 134.6, 129.5, 129.3, 129.1, 120.7, 105.8, 71.3, 57.2, 53.0, 20.7; LC-MS *t*_R = 5.50; *m/z* = 255.75 (M+H). **41b**: ¹H NMR (400 MHz, CDCl₃) δ 7.50–7.37 (m, 7H), 7.12 (ddd, *J* = 6.8, 2.1, 0.7 Hz, 1H), 6.68–6.65 (m, 1H), 6.65 (s, 1H), 6.28 (td, *J* = 6.8, 1.2 Hz, 1H), 3.69 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 164.0, 161.8, 151.1, 140.6, 137.5, 131.2, 129.5, 129.2, 126.6, 122.1, 115.8, 105.9, 52.0; LC-MS *t*_R = 4.25; *m/z* = 255.75 (M+H).

2-Hydroxy-3-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanoic acid (42b). To a 50 mL flask with stir bar, acetate **40b** (1.98 g, 6.28 mmol), THF (48 mL), H₂O (12 mL), and LiOH·H₂O (580 mg, 13.8 mmol) were sequentially added and the reaction was stirred at 20 °C for 30 min. Analysis via LC-MS indicated complete conversion. THF was removed under vacuum before a 1M HCl solution was added dropwise until the pH reached ~ 1. The solution was concentrated, the crude product was dry loaded using Celite, and purified via flash chromatography (12 g C18, 0–95% 0.5 N NH₃ in MeOH/H₂O) to afford carboxylic acid **42b** as an off-white solid (1.49 g, 92%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.49–7.47 (m, 3H), 7.37–7.29 (m, 4H), 6.43–6.40 (m, 2H), 6.15 (t, *J* = 6.7 Hz, 1H), 4.66 (d, *J* = 5.0 Hz, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 173.2, 161.2, 139.7, 137.6, 136.8, 129.3, 128.6, 128.1, 119.2, 105.0, 70.4, 58.2; LC-MS *t*_R = 3.34; *m/z* = 258.05 (M–H).

(2-Aminoethoxy)(tert-butyl)dimethylsilane (44). Ethanolamine (2.07 g, 33.9 mmol) was added to a 25 mL oven-dried flask with stir bar and sealed under N₂. Imidazole (4.61 g, 67.8 mmol) and anhydrous DCM (30 mL) were added before a solution of TBSCl (5.11 g, 33.9 mmol) in anhydrous DCM (5 mL) was added dropwise over 10 min via syringe pump at 20 °C.

The solution was allowed to stir at room temperature for 1 h. Next, the solution was diluted with DCM (150 mL) and washed with water (3 x 50 mL) and brine (50 mL). The organic layer was dried over MgSO₄, filtered, and concentrated to give amine **44** as a pale yellow oil (4.77 g, 80%). This compound has been previously reported and synthesized (CAS# 101711-55-1). ¹H NMR (CDCl₃, 400 MHz) δ 3.63 (t, *J* = 5.2 Hz, 2H), 2.77 (t, *J* = 5.2 Hz, 2H), 1.47, (br s, 2H), 0.91 (s, 9H), 0.07 (s, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 65.5, 44.5, 26.1, 18.5, -5.2.

N-{2-[(*Tert*-butyldimethylsilyloxy)ethyl]-2-hydroxy-3-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanamide (**46**). To an oven-dried 50 mL round bottom flask, acid **42** (420 mg, 1.62 mmol), amine **44** (568 mg, 3.24), anhydrous DMF (10 mL), and anhydrous DCE (10 mL) were added. Next, NMM (356 μL, 3.24 mmol) was added via syringe and HATU (739 mg, 1.94 mmol) was added in one portion. The reaction mixture was stirred at 20 °C for 16 h under N₂. After 16 h, the reaction mixture was diluted with EtOAc (200 mL) and washed with H₂O (2 x 50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered, and condensed under vacuum to yield a crude yellow oil. The crude oil was purified by flash chromatography (25 g SiO₂, 0–100% EtOAc/hexanes) to afford amide **46** as a colorless oil (620 mg, 91%). ¹H NMR (400 MHz, CDCl₃) δ 7.44–7.40 (m, 1H), 7.35–7.30 (m, 7H), 6.81 (br s, 1H), 6.68 (d, *J* = 9.1 Hz, 1H), 6.25 (t, *J* = 7.3 Hz, 1H), 6.00 (s, 1H), 4.84 (s, 1H), 3.66–3.53 (m, 2H), 3.42–3.30 (m, 2H), 0.87 (s, 9H), 0.02 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 170.9, 164.9, 140.6, 139.2, 135.0, 128.7, 128.6, 128.4, 121.6, 107.7, 74.5, 61.8, 41.6, 31.6, 26.0, 18.4, -5.3; LC-MS *t*_R = 5.74; *m/z* = 417.00 (M+H).

N-{2-[(*Tert*-butyldimethylsilyloxy)ethyl]-2-oxo-3-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanamide (**47**). Alcohol **46** (205 mg, 0.492 mmol) was added to a 20 mL oven-dried vial with stir bar and sealed under N₂. Anhydrous DCM (10 mL) and DMP (251 mg, 0.592 mmol) were added and the reaction was stirred at 20 °C for 2 h under N₂. A 10% Na₂S₂O₃ aqueous solution (10 mL) was added and the biphasic mixture was stirred for 20 min until the two layers became clear. The aqueous layer was separated and the organic layer was washed with saturated NaHCO₃ (2 x 5 mL). The combined aqueous layers were extracted with EtOAc (1 x 10 mL) and the combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude oil was dissolved in DCM and purified via flash chromatography (25 g SiO₂, 0–80% EtOAc/hexanes) to afford ketone **47** as an off-white solid (170 mg, 83%). ¹H NMR (400 MHz, CDCl₃) δ 7.38–7.26 (m, 7H), 6.93 (d, *J* = 7.0 Hz, 1H), 6.85 (s, 1H), 6.52 (d, *J* = 9.1 Hz, 1H), 6.08 (t, *J* = 6.7 Hz, 1H), 3.64–3.60 (m, 2H), 3.43–3.25 (m, 2H), 0.80 (s, 9H), -0.04 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 189.76, 162.43, 159.43, 140.19, 135.48, 130.69, 130.21, 129.95, 129.71, 119.70, 106.46, 64.34, 61.33, 41.51, 25.87, 18.24, -5.35; LC-MS *t*_R = 6.09; *m/z* = 414.95 (M+H).

N-(2-Hydroxyethyl)-2-oxo-3-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanamide (**48**). To a 100 mL flask charged with a stir bar, silyl ether **47** (100 mg, 0.241 mmol) and MeOH (10.0 mL) were added. Then a 2% aqueous HCl in MeOH solution (10.0 mL) was added, and the reaction was stirred for 1 h at 20 °C. The solution was concentrated, dry loaded on to Celite, and purified via flash chromatography (12 g C18, 0–40% MeOH/H₂O) to afford alcohol **48** as a colorless oil (56.7 mg, 78%). LC-MS *t*_R = 3.64; *m/z* = 300.85 (M+H). This intermediate was used directly in the next step.

Diethyl({2-[2-oxo-3-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanamido]ethyl})azanium chloride (**50**). Alcohol

48 (40.0 mg, 0.133 mmol) was added to a 20 mL oven-dried vial with stir bar and sealed under Ar. Anhydrous MeCN (4.0 mL), DIPEA (22.8 μL, 0.133 mmol), and MsCl (30.9 μL, 0.400 mmol) were respectively added and the solution was stirred at 20 °C for 24 h. Analysis via TLC confirmed conversion to the mesylate. Diethylamine (275 μL, 2.66 mmol) was added and the reaction was heated at 70 °C for 16 h under Ar. The reaction was concentrated, dry loaded using Celite, and purified via flash chromatography (10 g C18, MeOH/H₂O gradient w/ 0.1% formic acid) to afford the free base of amine **50** as an off-white powder (11.0 mg, 28%). *R*_f = 0.61 (95:5 DCM:MeOH); ¹H NMR (400 MHz, CDCl₃) δ 8.61 (s, 1H), 8.03 (s, 1H), 7.51–7.49 (m, 3H), 7.41 (ddd, *J* = 8.8, 6.6, 1.9 Hz, 1H), 7.37–7.35 (m, 2H), 6.90 (dd, *J* = 7.1, 1.7 Hz, 1H), 6.55 (d, *J* = 8.8 Hz, 1H), 6.15 (td, *J* = 6.6, 1.2 Hz, 1H), 6.07 (s, 1H), 4.73–4.70 (m, 1H), 4.26–4.22 (m, 1H), 3.86–3.58 (m, 6H), 1.36–1.24 (m, 6H). This compound had poor solubility in chloroform and MeOH. The HCl salt was formed prior to ¹³C NMR analysis. The product was taken up into minimal H₂O and 0.5 mL of 1M HCl was added. The solution was lyophilized to afford a yellow oil. ¹³C NMR (75 MHz, D₂O) δ 170.4, 164.2, 155.1, 143.0, 136.5, 131.0, 131.0, 130.4, 129.9, 129.8, 118.9, 109.2, 64.83, 64.63, 49.67, 45.54, 41.91, 13.3, 10.6; LC-MS *t*_R = 1.61; *m/z* = 356.40 (M+H).

Ethyl 2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanoate (**51**). In a 20 mL oven-dried vial with stir bar, HMDS (1.90 mL, 9.11 mmol) and anhydrous THF (9.0 mL) were added under N₂. The solution was cooled to 0 °C in an ice bath before *n*-butyl lithium (5.43 mL of a 1.6 M solution in hexanes, 8.69 mmol) was added dropwise over 10 min. The solution was cooled to -78 °C before a solution of ester **21** (1.50 g, 8.28 mmol) in anhydrous THF (25.0 mL) was added dropwise. The solution was stirred at -78 °C for 1 h under N₂ before benzylbromide (985 μL, 8.28 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 1 h, allowed to warm up to 0 °C, quenched with saturated NH₄Cl (10 mL), and diluted with EtOAc (50 mL). The organic layer was separated, washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude material was dissolved in DCM and purified via flash chromatography (100 g SiO₂, 0–40% EtOAc/hexanes) to afford **51** as a colorless oil (1.52 g, 68%). ¹H NMR (300 MHz, CDCl₃) δ 7.28–7.18 (m, 4H), 7.11–7.08 (m, 2H), 7.03 (dd, *J* = 6.9, 1.5 Hz, 1H), 6.50 (d, *J* = 9.2 Hz, 1H), 6.03 (td, *J* = 6.8, 1.3 Hz, 1H), 5.41 (dd, *J* = 9.7, 5.6 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.50 (m, 1H), 3.33 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 169.46, 162.16, 139.64, 136.50, 136.11, 129.12, 128.69, 127.09, 120.75, 105.64, 61.92, 61.16, 36.33, 14.12; LC-MS *t*_R = 4.67; *m/z* = 271.90 (M+H).

Ethyl (2*Z*)-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylprop-2-enoate (**53**). The procedure for the synthesis of **51** was followed using HMDS (392 mg, 2.43 mmol), anhydrous THF (9.0 mL), *n*-butyl lithium (1.45 mL of a 1.6 M solution in hexanes, 2.32 mmol), **21** (400 mg, 2.21 mmol) in anhydrous THF (3.0 mL), and benzaldehyde (0.247 mL, 2.43 mmol) instead of benzylbromide. After workup, the product was dissolved in DCM and purified via flash chromatography (25 g SiO₂, 0–50% EtOAc/hexanes) to afford alkene **53** as an off-white solid (272 mg, 46%). ¹H NMR (400 MHz, CDCl₃) δ 7.83 (s, 1H), 7.43 (ddd, *J* = 9.0, 6.6, 2.0 Hz, 1H), 7.33–7.26 (m, 3H), 7.20–7.18 (m, 2H), 6.96 (dd, *J* = 6.7, 1.8 Hz, 1H), 6.67 (d, *J* = 8.7 Hz, 1H), 6.18 (td, *J* = 6.7, 1.0 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 163.4, 162.4, 140.8, 137.7, 137.4, 131.4, 130.5, 130.2, 129.9, 128.9, 121.8, 106.8, 62.0, 14.1. LC-MS *t*_R = 6.06; *m/z* = 269.80 (M+H).

(2Z)-2-(2-Oxo-1,2-dihydropyridin-1-yl)-3-phenylprop-2-enoic acid (54). To a 15 mL flask with stir bar, ester **53** (136 mg, 0.504 mmol), THF (6.0 mL), H₂O (1.5 mL), and LiOH·H₂O (25.4 mg, 0.604 mmol) were added and the solution was stirred at 20 °C for 12 h. THF was removed under vacuum before a 1M HCl solution was added dropwise until the pH reached ~ 1. The solution was concentrated under vacuum and the crude product was dry loaded using Celite and purified via flash chromatography (12 g C18, 0–75% MeOH/H₂O w/ 0.1% formic acid) to afford carboxylic acid **54** as an off-white solid (108 mg, 89%). ¹H NMR (400 MHz, CD₃OD) δ 7.94 (s, 1H), 7.65 (ddd, *J* = 9.1, 6.7, 2.0 Hz, 1H), 7.39–7.30 (m, 4H), 7.20–7.18 (m, 2H), 6.67 (d, *J* = 9.1 Hz, 1H), 6.42 (td, *J* = 6.7, 1.0 Hz, 1H); ¹³C NMR (100 MHz, CD₃OD) δ 166.2, 164.8, 143.6, 140.0, 139.0, 133.1, 131.7, 131.6, 130.9, 130.1, 121.6, 109.4; LC-MS *t*_R = 4.17; *m/z* = 241.75 (M+H).

Ethyl 3-hydroxy-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanoate (55). In a 100 mL oven-dried flask with stir bar, diisopropylamine (309 μL, 2.21 mmol) and anhydrous THF (35.0 mL) were added via syringe under N₂. The solution was cooled to –78 °C in a dry ice/acetone bath before *n*-butyl lithium (1.38 mL of a 1.6 M solution in hexanes, 2.21 mmol) was added dropwise over 10 min. The solution was allowed to stir for 30 min before a solution of **21** (400 mg, 2.21 mmol) in anhydrous THF (3.0 mL) was added dropwise over 5 min. The heterogeneous solution was stirred at –78 °C for 1 h before benzaldehyde (0.247 mL, 2.43 mmol) was added, and the solution was stirred at –78 °C for 2 h. The reaction was quenched at –78 °C via the addition saturated aq. NH₄Cl (15 mL) and diluted with EtOAc (75 mL). The organic layer was separated, washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude material was dissolved in DCM and purified via flash chromatography (50 g SiO₂, 0–100% EtOAc/hexanes) to afford alcohol **55** as a colorless oil (307 mg, 48%). The NMR spectra are complex due to diastereomers. ¹H NMR (300 MHz, CDCl₃) δ 7.59 (dd, *J* = 6.8, 1.3 Hz, 1H), 7.26–7.15 (m, 12H), 6.80 (dd, *J* = 6.8, 1.5 Hz, 1H), 6.39 (d, *J* = 9.1 Hz, 1H), 6.28 (d, *J* = 9.1 Hz, 1H), 6.05 (td, *J* = 6.7, 1.2 Hz, 1H), 5.86 (td, *J* = 6.7 Hz, 1.2 Hz, 1H), 5.81 (d, *J* = 4.3 Hz, 1H), 5.63 (d, *J* = 4.3 Hz, 1H), 5.45 (d, *J* = 7.5 Hz, 1H), 4.74 (d, *J* = 7.5 Hz, 1H), 4.22–4.16 (m, 4H), 1.24–1.19 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 169.4, 168.2, 162.9, 162.3, 140.2, 140.1, 139.5, 138.9, 138.5, 137.9, 128.4, 128.3, 127.8, 126.4, 125.9, 120.3, 119.7, 105.9, 105.6, 73.5, 72.1, 67.5, 63.5, 62.1, 62.1, 60.4, 21.1, 14.2, 14.1, 14.0; LC-MS *t*_R = 4.78, 4.92; *m/z* = 287.80 (M+H).

Ethyl 3-[(*tert*-butyldimethylsilyloxy]-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanoate (56). The procedure for the synthesis of **37a** was used with the following modifications: **55** (153 mg, 0.533 mmol), DCM (6.0 mL), 2,6-lutidine (74.4 μL, 0.639 mmol) and TBSOTf (147 μL, 0.639 mmol) were used. The crude oil was dissolved in DCM and purified via flash chromatography (25 g SiO₂, 0–50% EtOAc/hexanes) to yield **56** as a pale yellow oil (187 mg, 87%). ¹H NMR (300 MHz, CDCl₃) δ 8.20 (dd, *J* = 6.9, 1.4 Hz, 1H), 7.87 (dd, *J* = 6.9, 1.4 Hz, 1H), 7.56–7.38 (m, 11H), 6.62 (d, *J* = 9.2 Hz, 1H), 6.53 (d, *J* = 9.2 Hz, 1H), 6.44–6.39 (m, 1H), 6.33–6.28 (m, 1H), 6.12 (d, *J* = 7.2 Hz, 1H), 5.87 (d, *J* = 3.9 Hz, 1H), 5.44 (d, *J* = 7.2 Hz, 1H), 4.59–4.51 (m, 1H), 4.45–4.33 (m, 3H), 1.53 (t, *J* = 7.1 Hz, 3H), 1.46 (t, *J* = 7.1 Hz, 3H), 1.13 (s, 9H), 1.11 (s, 9H), 0.29 (s, 3H), 0.25 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 169.0, 168.5, 162.2, 161.8, 139.6, 139.5, 139.4, 139.3, 138.7, 136.6, 128.3, 128.2, 128.2, 128.2, 127.0, 126.4, 120.4, 119.7, 105.4, 104.5, 75.6, 75.4, 62.1, 61.9, 61.7, 61.5, 25.8, 25.8, 18.1, 18.1, 14.2, 14.1, –4.4, –4.6, –5.3, –5.5; LC-MS *t*_R = 6.95; *m/z* = 401.95 (M+H).

Prop-2-en-1-yl 2-(2-oxo-1,2-dihydropyridin-1-yl)acetate (57). NaH (60% dispersion in mineral oil, 1.77 g, 46.3 mmol) was added to a 500 mL oven-dried flask with stir bar and sealed under N₂. Anhydrous DMF (125 mL) was added and the suspension was cooled to 0 °C in an ice bath. A solution of 2-hydroxypyridine (4.00 g, 42.1 mmol) in anhydrous DMF (25.0 mL) was slowly added and stirred for 1 h at 0 °C. Allyl chloroacetate (5.98 mL, 50.5 mmol) was added and the mixture was stirred at 20 °C for 12 h. The reaction was quenched with saturated NH₄Cl (200 mL) and diluted with EtOAc (750 mL). The organic layer was washed with water (6 x 200 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude product was dissolved in DCM and purified via flash chromatography (100 g SiO₂, 0–85% EtOAc/hexanes) to afford pyridone **57** as a pale yellow oil (3.40 g, 42%). ¹H NMR (400 MHz, CDCl₃) δ 7.30 (ddd, *J* = 9.2, 6.7, 2.1 Hz, 1H), 7.20 (ddd, *J* = 6.7, 2.1, 0.7 Hz, 1H), 6.49 (ddd, *J* = 9.2, 1.4, 0.7 Hz, 1H), 6.13 (td, *J* = 6.7, 1.4 Hz, 1H), 5.82 (ddt, *J* = 17.2, 10.5, 5.7 Hz, 1H), 5.25 (dq, *J* = 17.2 1.5 Hz, 1H), 5.17 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.60 (s, 2H), 4.58 (dt, *J* = 5.7, 1.4 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 167.5, 162.4, 140.3, 138.0, 131.3, 121.0, 119.0, 106.2, 66.3, 50.5. LC-MS *t*_R = 2.30; *m/z* = 181.90 (M+H).

Prop-2-en-1-yl 3-hydroxy-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanoate (58). In an oven-dried 100 mL flask with stir bar, anhydrous THF (50.0 mL) and diisopropylamine (1.55 mL, 11.0 mmol) were added via syringe under N₂. The solution was cooled to –78 °C before *n*-butyl lithium (6.90 mL of a 1.6 M solution in hexanes, 11.0 mmol) was added dropwise over 5 min. The solution was stirred for 30 min before a solution of ester **57** (1.94 g, 10.0 mmol) in anhydrous THF (8.0 mL) was added dropwise over 5 min and stirred at –78 °C for 1 h. Benzaldehyde (1.53 mL, 15.1 mmol) was added and the resulting solution was stirred at –78 °C for 2 h. The reaction was quenched at –78 °C with saturated aq. NH₄Cl and diluted with EtOAc (200 mL) and H₂O (10 mL). The layers were separated and the organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated. The crude yellow oil was dissolved in DCM and purified via flash chromatography (100 g SiO₂, 0–70% EtOAc/hexanes) to afford alcohol **58** as a yellow oil (2.45 g, 82%). ¹H NMR (400 MHz, CDCl₃) δ 7.43 (d, *J* = 7.9 Hz, 1H), 7.27–7.22 (m, 13H), 6.71 (dd, *J* = 6.8, 1.5 Hz, 1H), 6.46 (d, *J* = 9.1 Hz, 1H), 6.40 (d, *J* = 8.8 Hz, 1H), 6.09 (td, *J* = 6.8, 1.3 Hz, 1H), 5.94–5.81 (m, 3H), 5.73 (s, 2H), 5.57 (d, *J* = 7.9 Hz, 1H), 5.34–5.20 (m, 4H), 4.72–4.64 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 169.2, 167.9, 163.1, 162.4, 140.3, 140.2, 139.4, 138.7, 138.5, 137.9, 131.4, 131.3, 128.5, 128.4, 128.4, 128.0, 126.4, 125.9, 120.5, 120.0, 119.1, 119.0, 106.0, 105.8, 73.7, 72.1, 68.0, 66.6, 66.6, 64.0; LC-MS *t*_R = 4.40, 4.53; *m/z* = 299.75 (M+H).

3-Hydroxy-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanoic acid (59). Alcohol **58** (1.90 g, 0.264 mmol) and Pd(PPh₃)₄ (12.2 mg, 0.0106 mmol) were added to a 500 mL oven-dried flask with stir bar and sealed under N₂. Anhydrous THF (6.0 mL) and morpholine (24.2 μL, 0.277 mmol) were added via syringe and the reaction was stirred at 20 °C for 30 min. After 30 min, analysis via LC-MS indicated consumption of starting material. The reaction mixture was concentrated, dry loaded using Celite, and purified using flash chromatography (30 g C18, 0–95% MeOH/H₂O w/ 0.1% formic acid) to afford carboxylic acid **59** as a yellow oil (1.20 g, 73%). ¹H NMR (400 MHz, CD₃OD) δ 8.10 (d, *J* = 6.5 Hz, 1H), 7.44 (d, *J* = 6.5 Hz, 1H), 7.36–7.15 (m, 10H), 6.37 (d, *J* = 9.0 Hz, 1H), 6.30–6.27 (m, 1H), 6.14–6.10 (m, 1H), 5.73 (d, *J* = 3.8 Hz, 1H), 5.45 (d, *J* = 7.9 Hz, 1H), 5.30 (d, *J* = 7.9 Hz, 1H). LC-MS *t*_R = 3.74, 3.88; *m/z* = 259.75 (M+H).

N-[2-(Diethylamino)ethyl]-3-hydroxy-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanamide (60). Carboxylic acid **59** (886 mg, 3.42 mmol) was added to a 500 mL oven-dried flask with stir bar and sealed under N₂. Anhydrous DCM (150 mL), HATU (1.95 g, 5.13 mmol), DIPEA (655 μ L, 3.76 mmol), and *N,N*-diethylethylenediamine (624 μ L, 4.44 mmol) were sequentially added and the solution was stirred at 20 °C for 12 h. After 12 h, the reaction was concentrated under vacuum, dry loaded using Celite, and purified via flash chromatography (30 g C18, 0–95% MeOH/H₂O w/ 0.1% formic acid) to afford amide **60** as an off-white waxy solid (918 mg, 75%). ¹H NMR (400 MHz, CD₃OD) δ 7.44 (dd, *J* = 6.9, 1.5 Hz, 1H), 7.34 (ddd, *J* = 9.0, 6.7, 2.0 Hz, 1H), 7.28–7.26 (m, 2H), 7.24–7.19 (m, 3H), 6.36 (dd, *J* = 9.0, 0.6 Hz, 1H), 6.14 (td, *J* = 6.7, 1.3 Hz, 1H), 5.39 (d, *J* = 9.5 Hz, 1H), 5.19 (d, *J* = 9.5 Hz, 1H), 3.79–3.73 (m, 1H), 3.64–3.57 (m, 1H), 3.38–3.22 (m, 6H), 1.31 (t, *J* = 7.3 Hz, 6H); ¹³C NMR (100 MHz, CD₃OD) δ 171.8, 164.4, 142.5, 141.1, 140.0, 129.5, 129.4, 128.0, 120.5, 108.4, 73.4, 67.3, 53.0, 49.1, 35.7, 9.2. LC-MS *t*_R = 1.07, 1.32; *m/z* = 357.95 (M+H).

N-[2-(Diethylamino)ethyl]-3-oxo-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanamide (61). Alcohol **60** (47.5 mg, 0.133 mmol) was added to a 20 mL oven-dried vial with stir bar and sealed under N₂. Anhydrous DCM (6.0 mL) and DMP (84.5 mg, 0.199 mmol) were sequentially added and the reaction mixture was stirred at 20 °C for 1 h. After 1 h, H₂O (2.7 μ L, 0.15 mmol) was added via microsyringe. The reaction solution was stirred at room temperature for 48 h before being quenched with saturated Na₂S₂O₃ (3 mL). The product was extracted with DCM (3 x 10 mL) and concentrated. The crude product was dissolved in DCM and purified via flash chromatography (12 g SiO₂, 0–20% MeOH/DCM) to afford ketone **61** as an off-white solid (11.7 mg, 25%). *R*_f = 0.71 (80:20 DCM:MeOH). ¹H NMR (400 MHz, CDCl₃) δ 8.01 (d, *J* = 7.1 Hz, 2H), 7.65 (dd, *J* = 6.8, 1.7 Hz, 1H), 7.60–7.56 (m, 1H), 7.48–7.44 (m, 1H), 7.40–7.34 (m, 2H), 6.60 (d, *J* = 9.2 Hz, 1H), 6.24 (td, *J* = 6.8, 1.3 Hz, 1H), 3.39–3.28 (m, 2H), 2.57–2.48 (m, 6H), 0.96 (t, *J* = 7.2 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 192.0, 165.2, 162.0, 140.7, 137.4, 135.0, 134.3, 129.1, 128.8, 119.9, 106.2, 61.6, 51.1, 46.7, 37.4, 11.5; LC-MS *t*_R = 1.57; *m/z* = 356.20 (M+H).

Crystallographic Data

CCDC 2004020 and 2004021 (Scheme 10), 2004022 (Scheme 13), and 2004023 (Figure 3) contain the supplementary crystallographic data for this paper. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via <https://www.ccdc.cam.ac.uk>.

ASSOCIATED CONTENT

Supporting Information

¹H and ¹³C NMR spectra; Additional X-ray crystallography figures and discussion.

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Funding Sources

We thank the Foundation for Women's Wellness for supporting this project in part. E.G. thanks Arthur J. Schmitt and Marquette University for a graduate fellowship.

ACKNOWLEDGMENTS

We thank Prof. Robert Flaumenhaft and colleagues (Beth Israel Deaconess Medical Center) for testing the PDI activity of compounds in this paper. We also thank Dr. Sheng Cai for assistance with LC-MS, GC-MS, and NMR instruments, and ChemAxon Ltd. for access to chemical property and structure prediction software.

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Supporting Information

Synthesis of STK076545: A Reported Protein Disulfide Isomerase Inhibitor

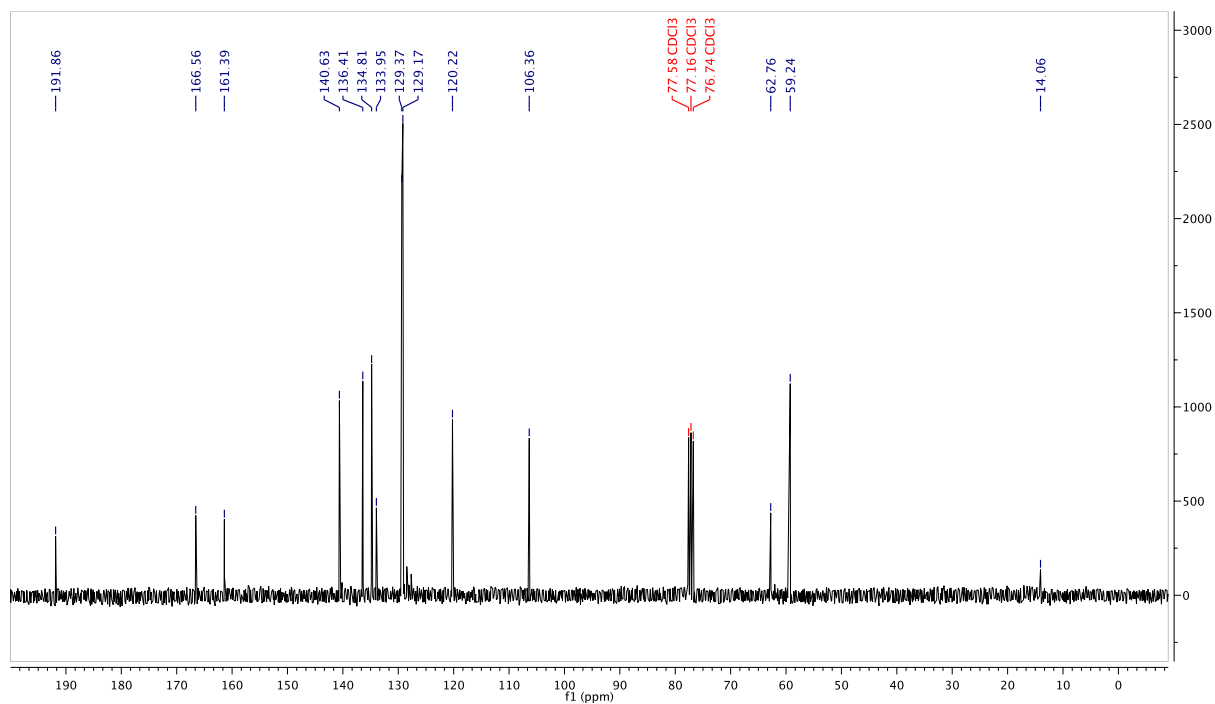
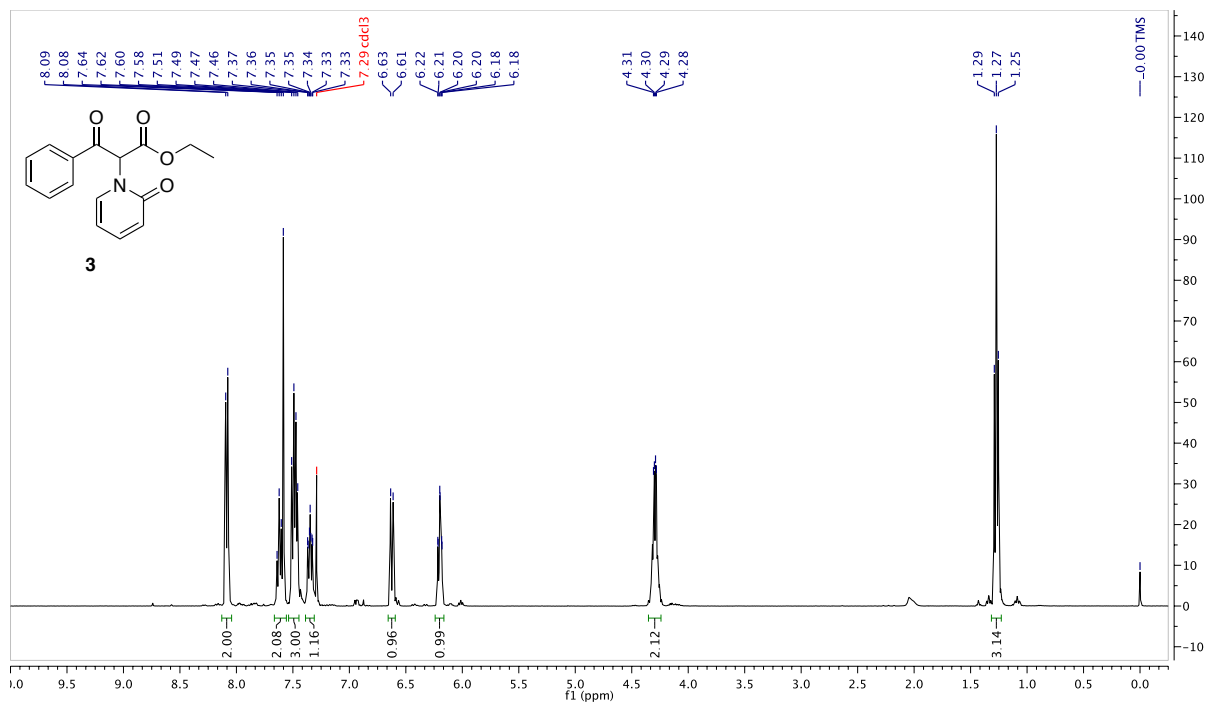
Eric Greve, Sergey V Lindeman, and Chris Dockendorff*

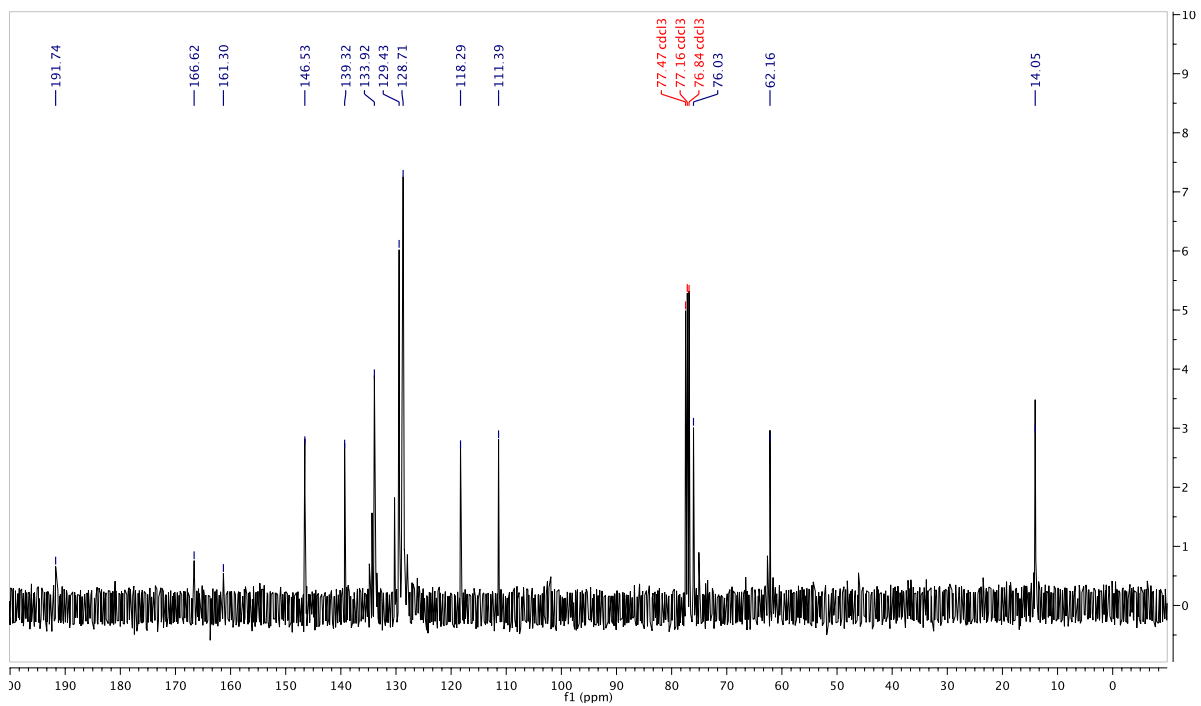
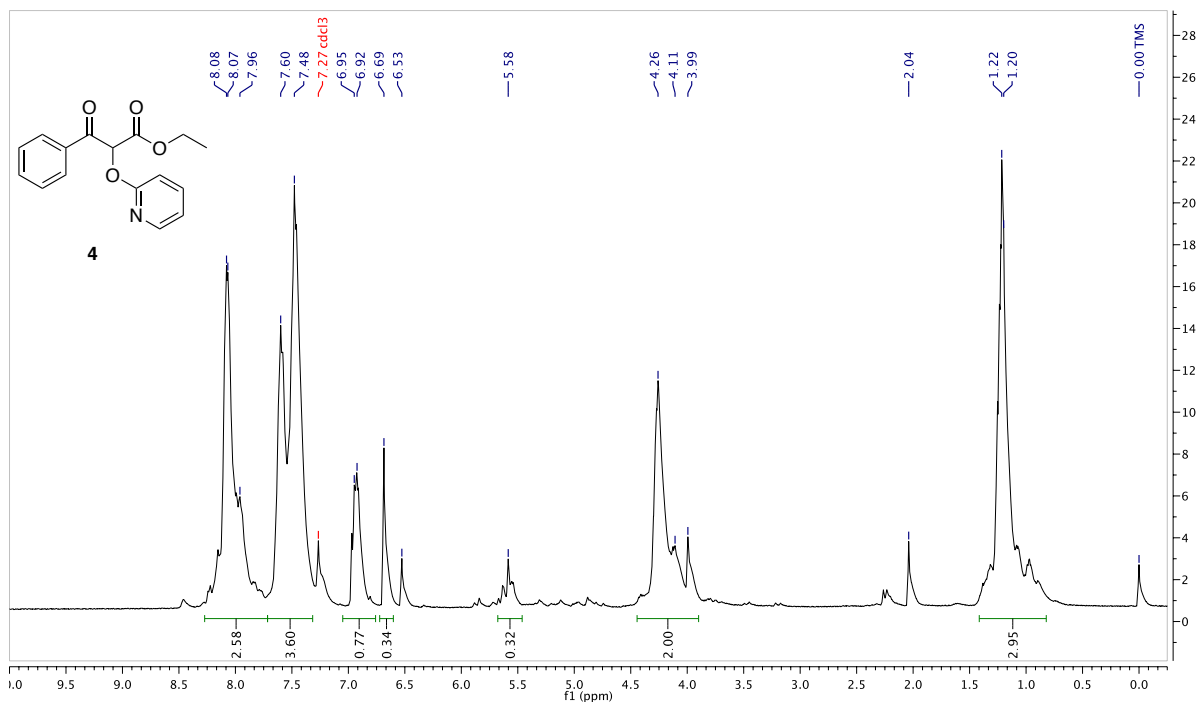
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Email: christopher.dockendorff@mu.edu

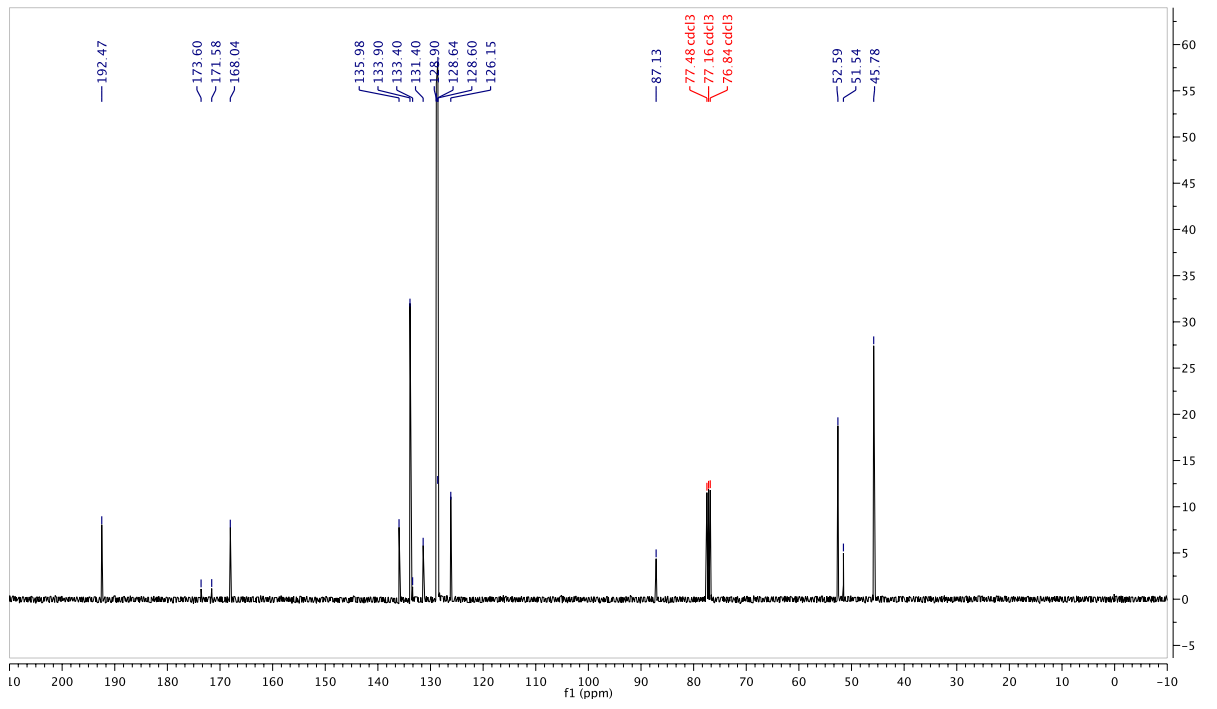
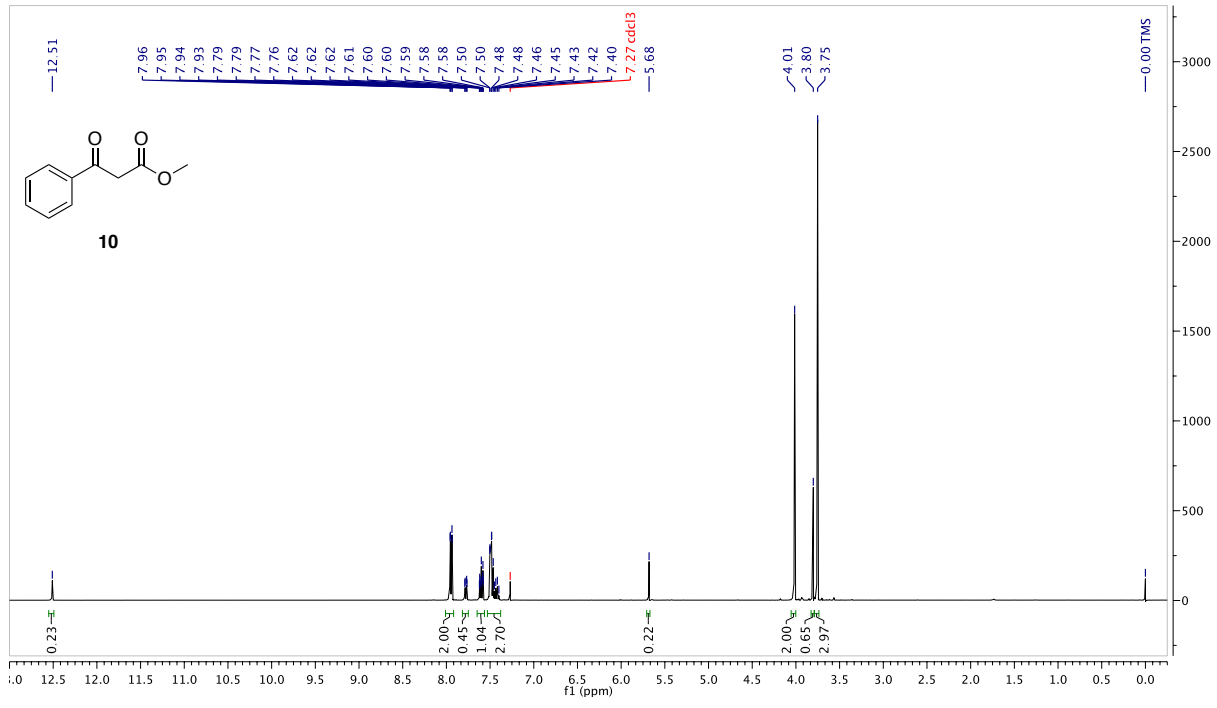
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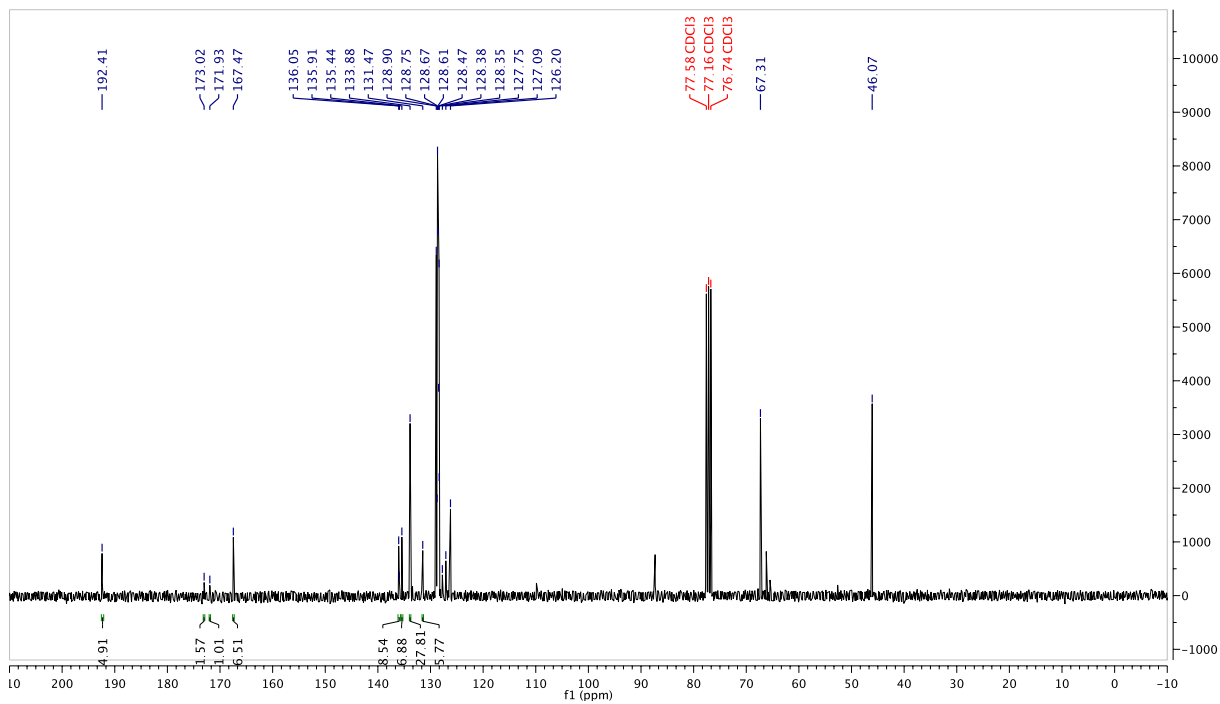
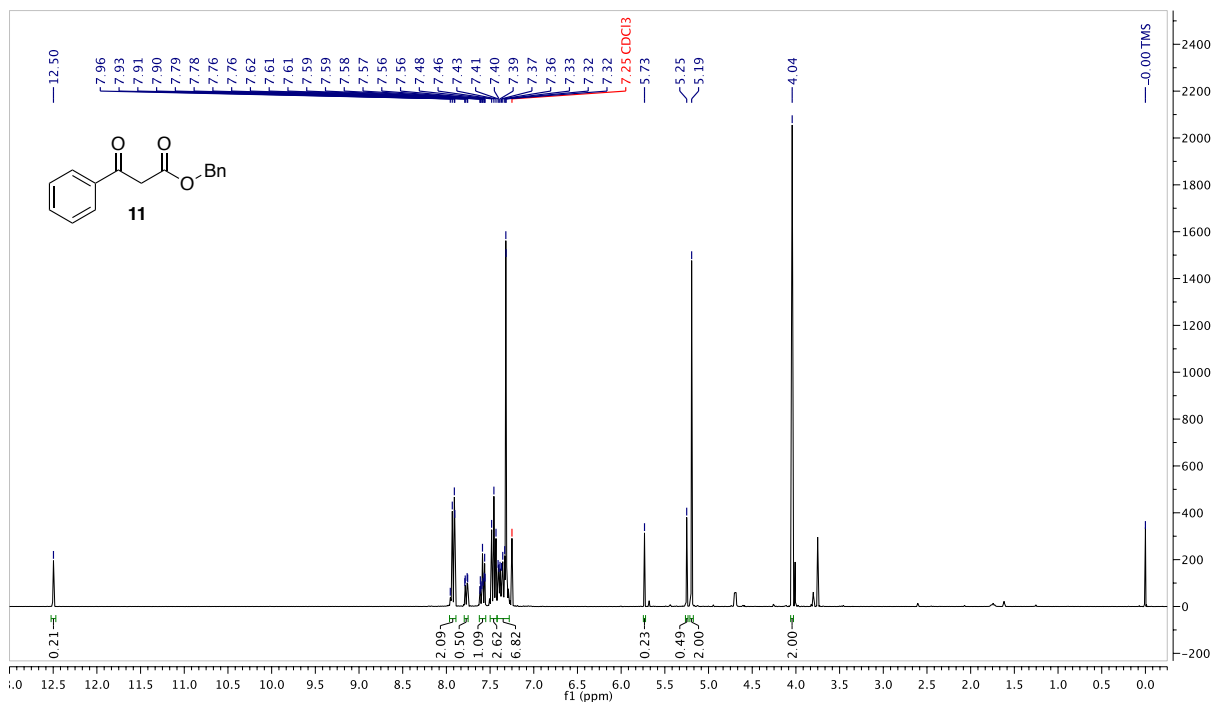
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2. X-ray crystallographic structures and sample preparation.....	S43

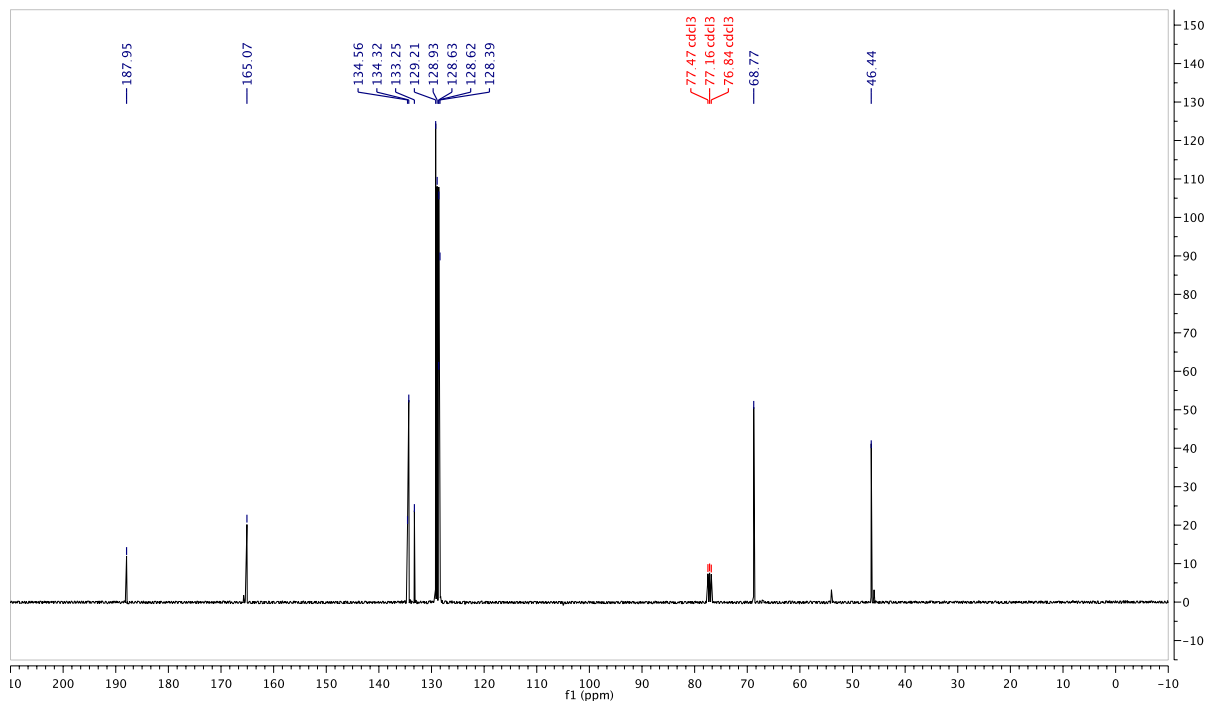
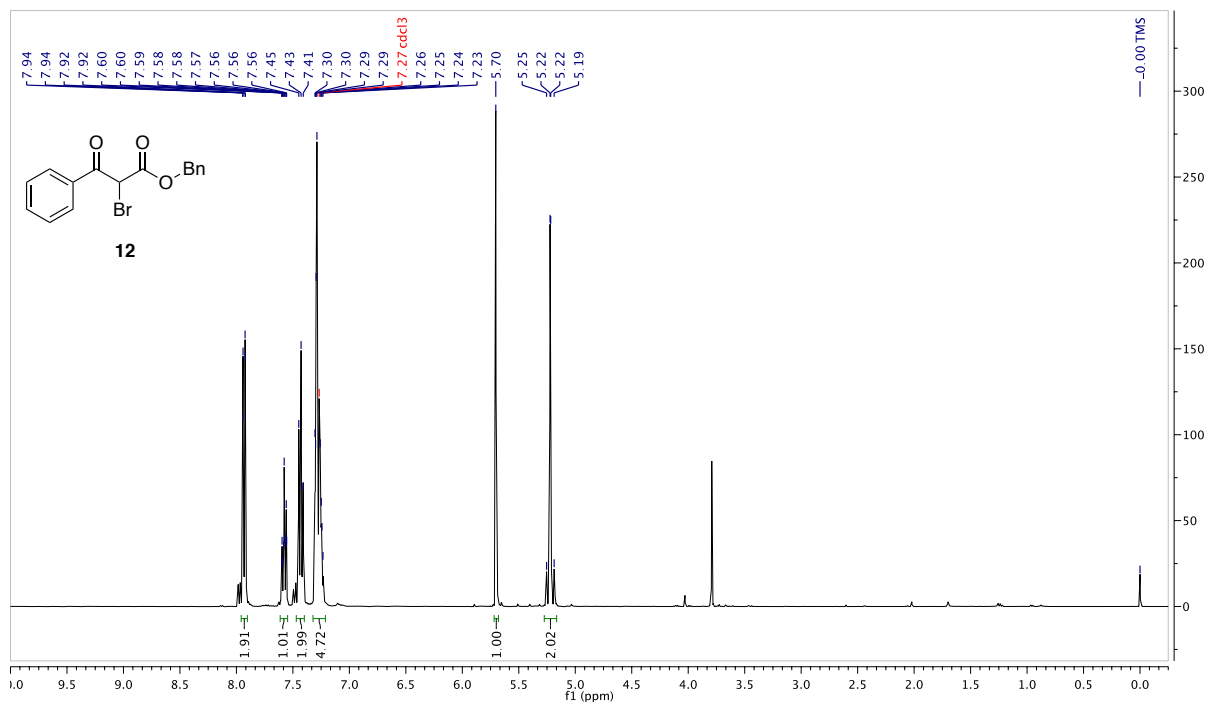
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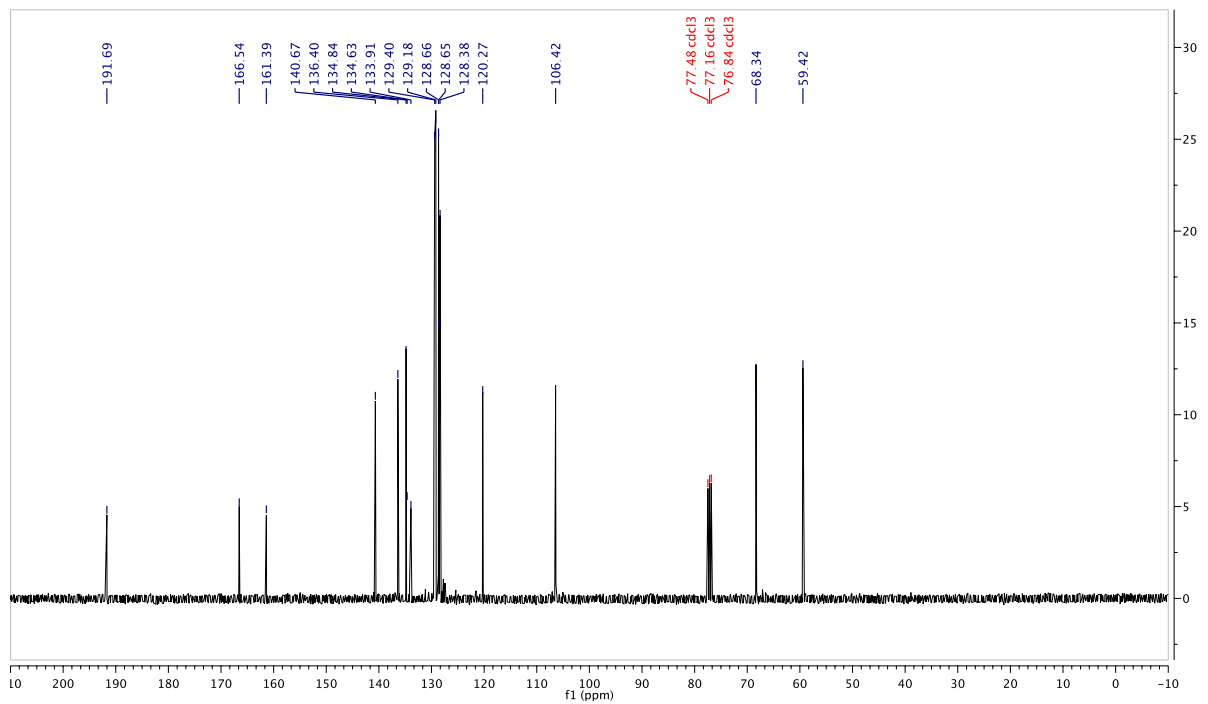
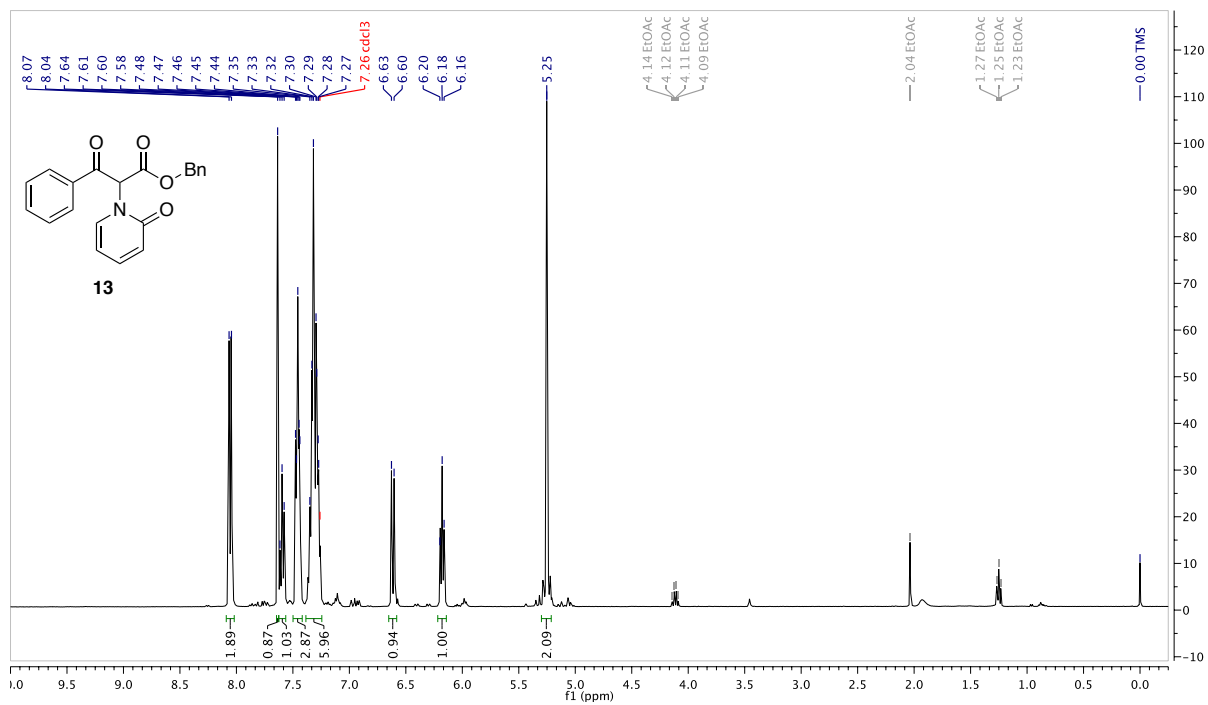


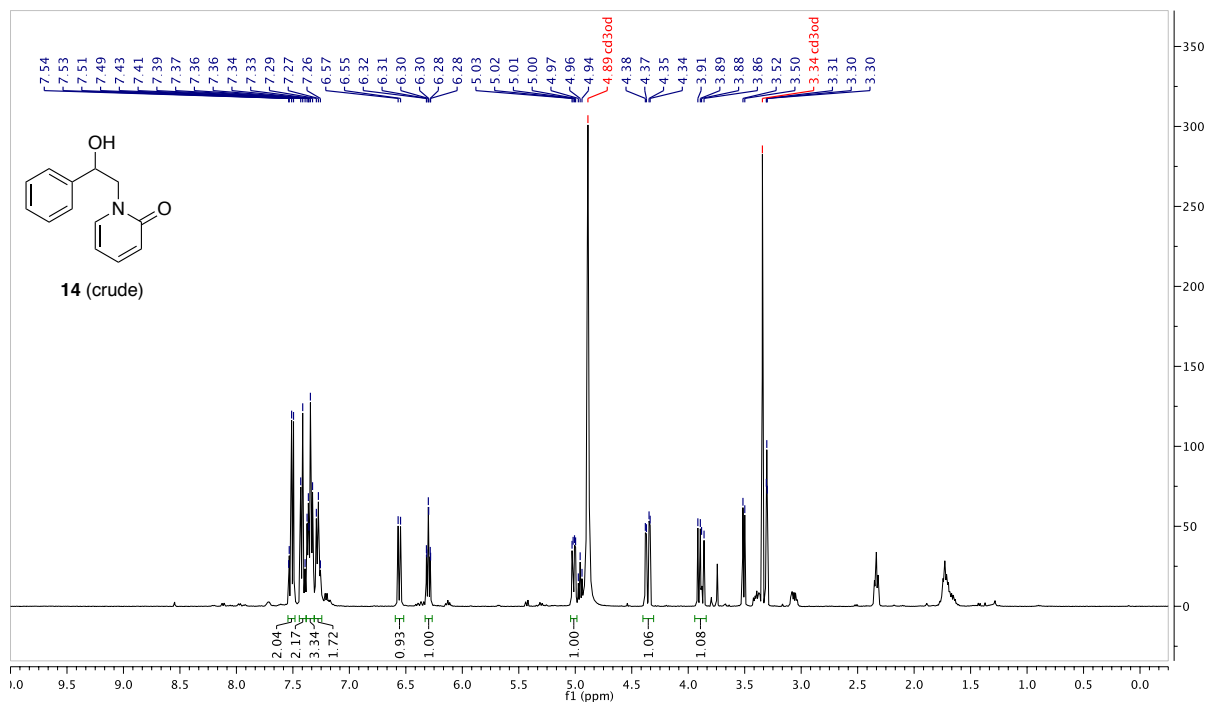


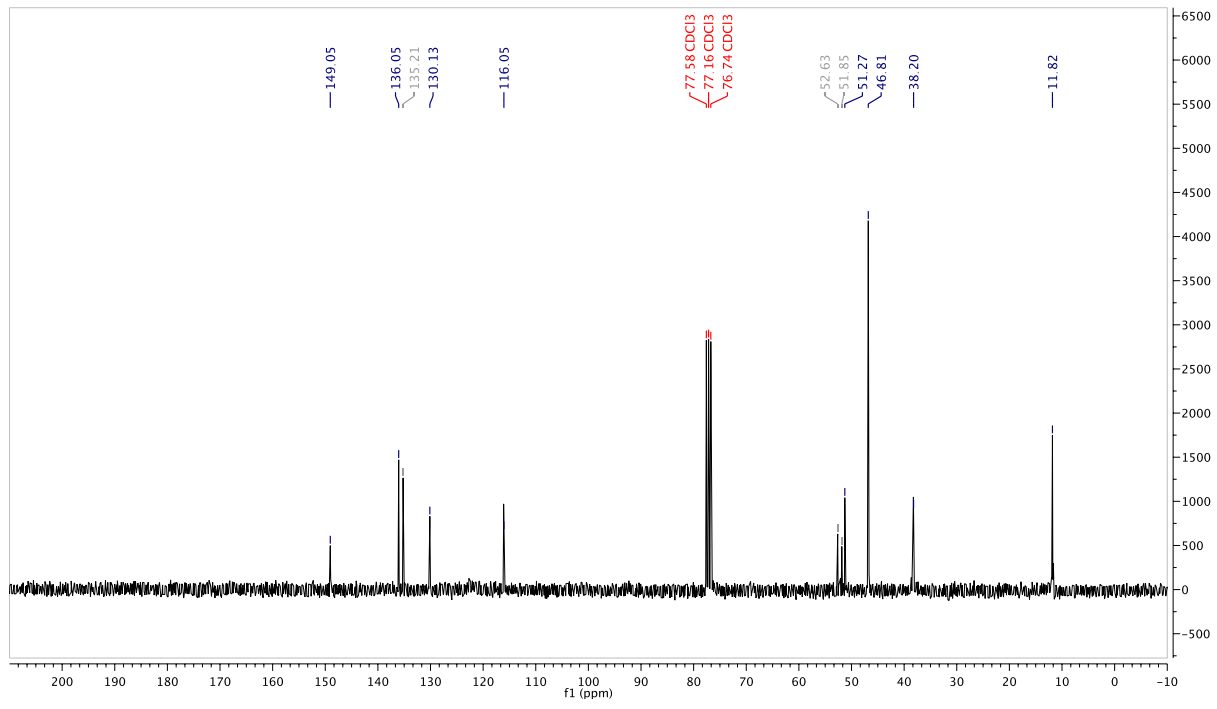
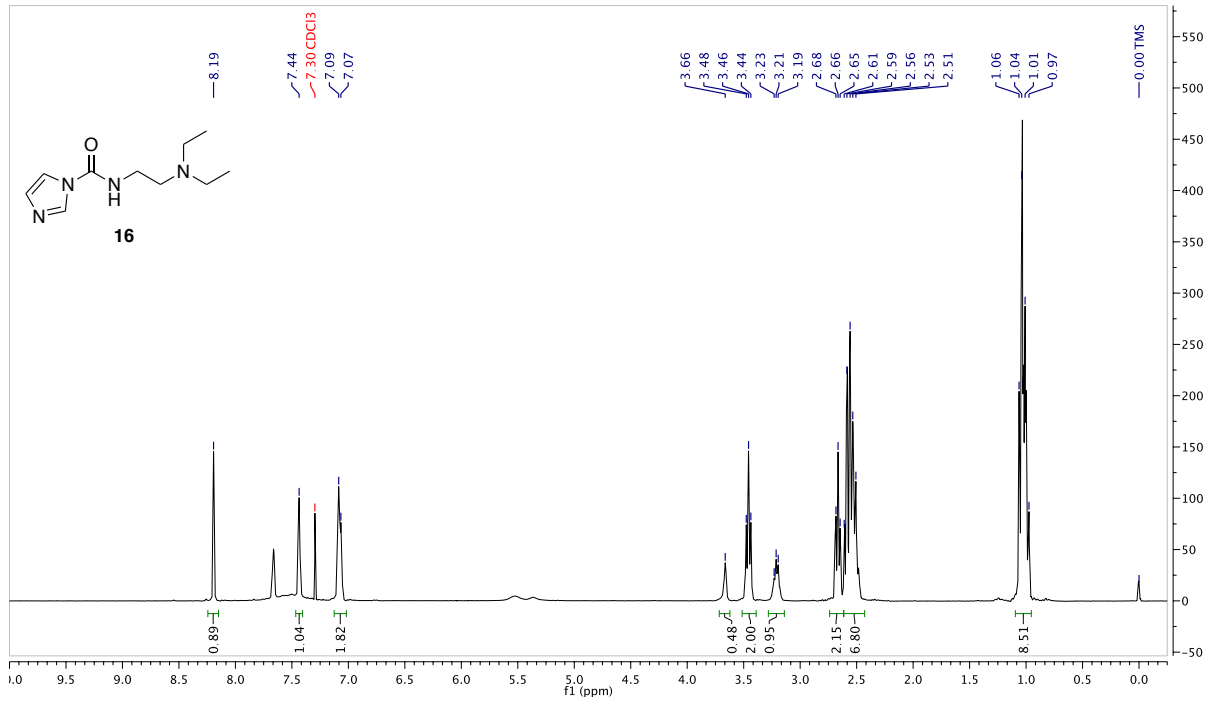


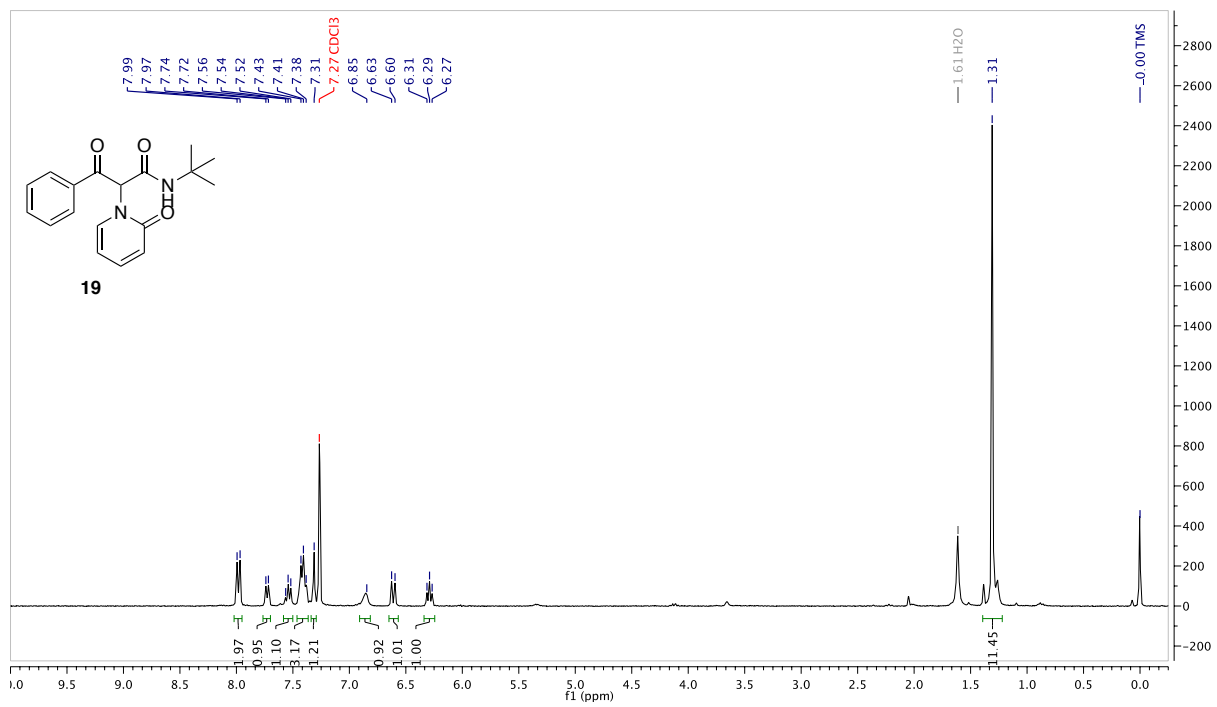


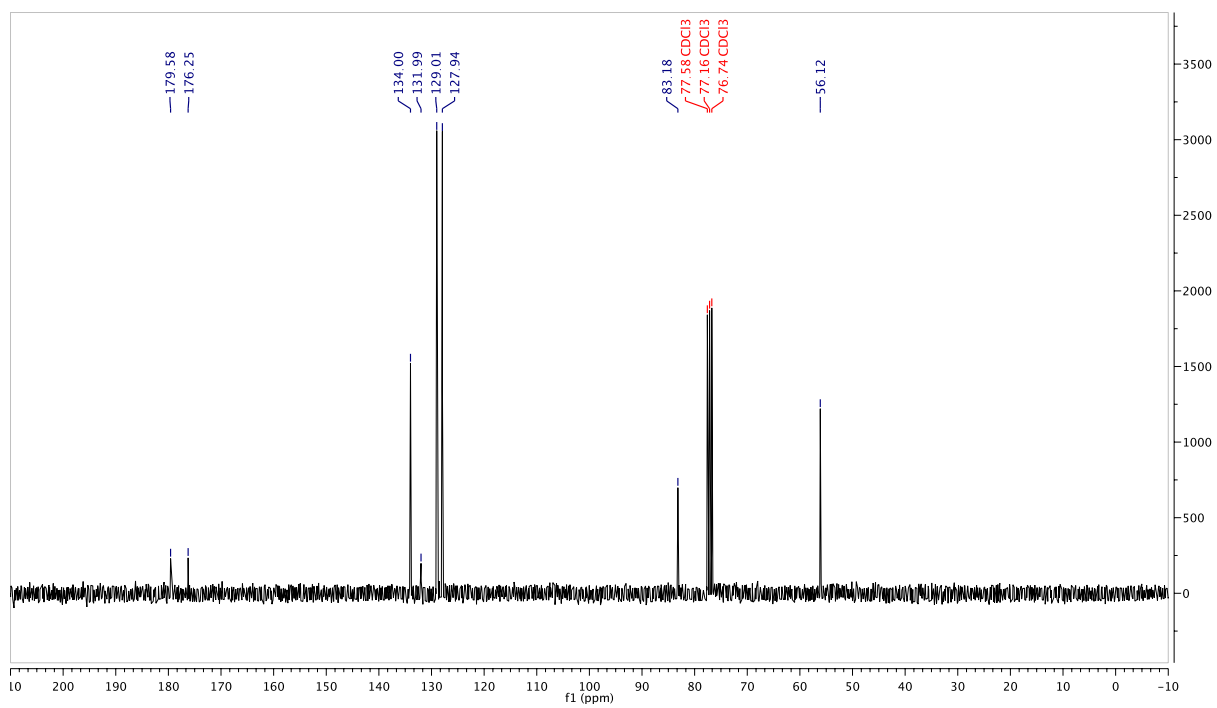
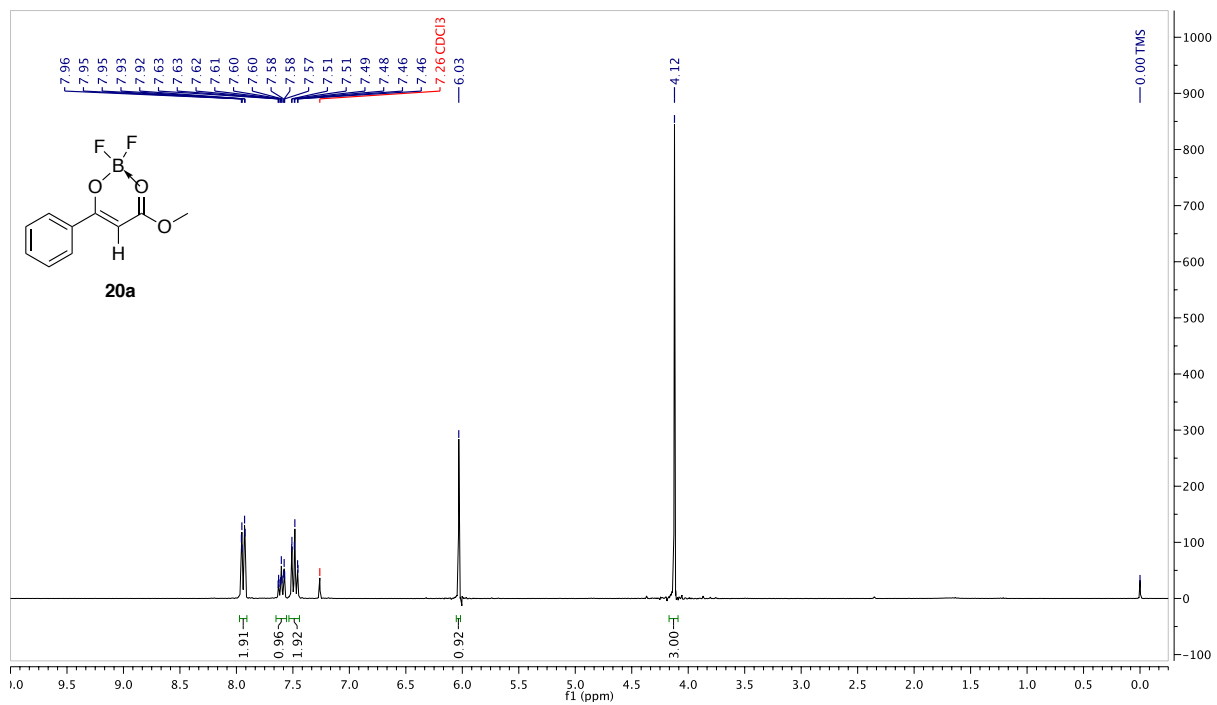


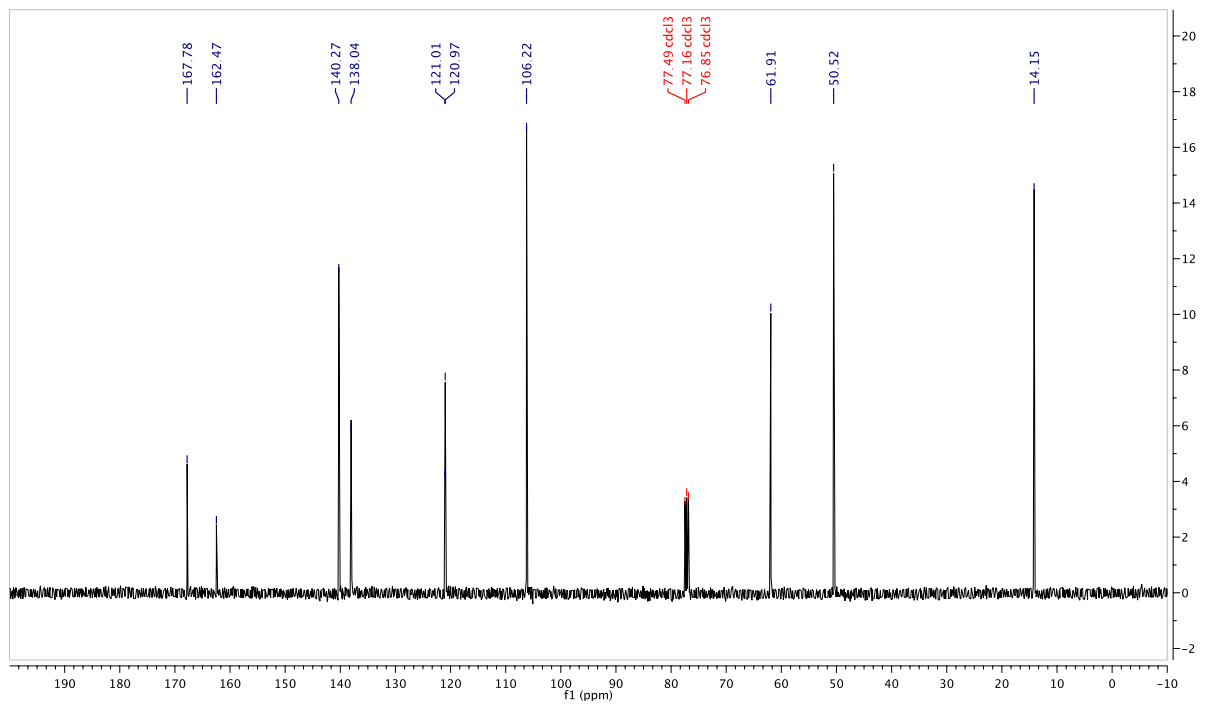
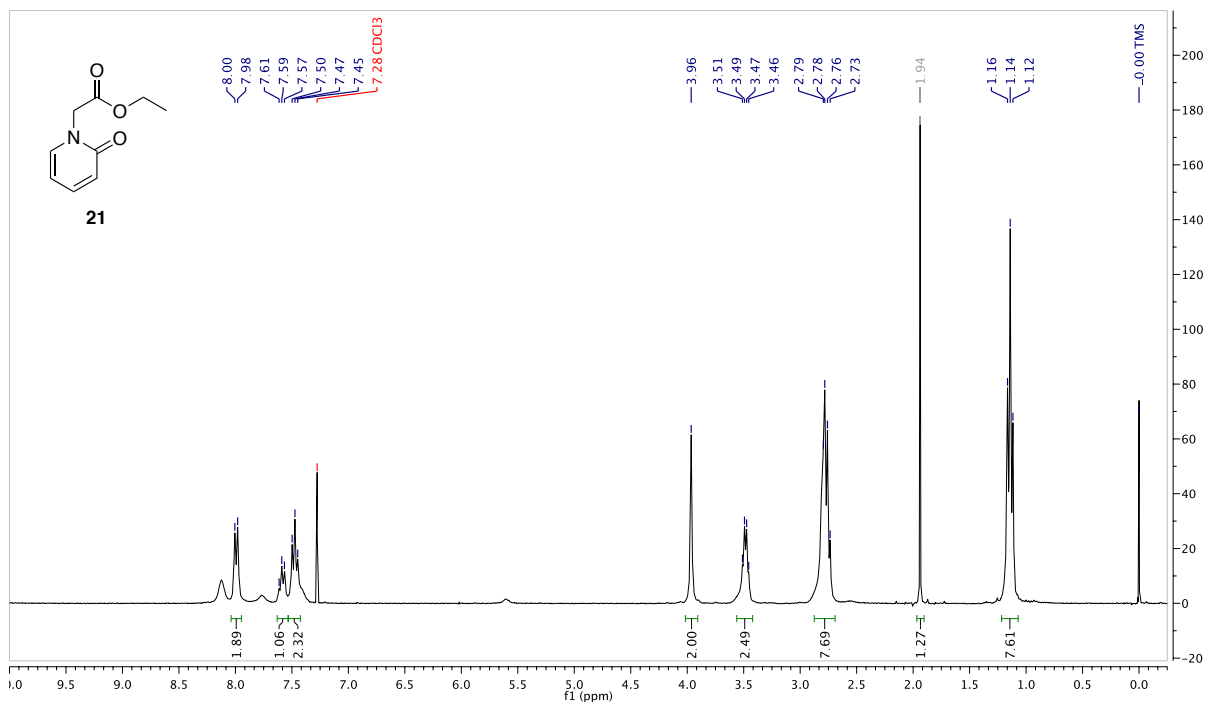


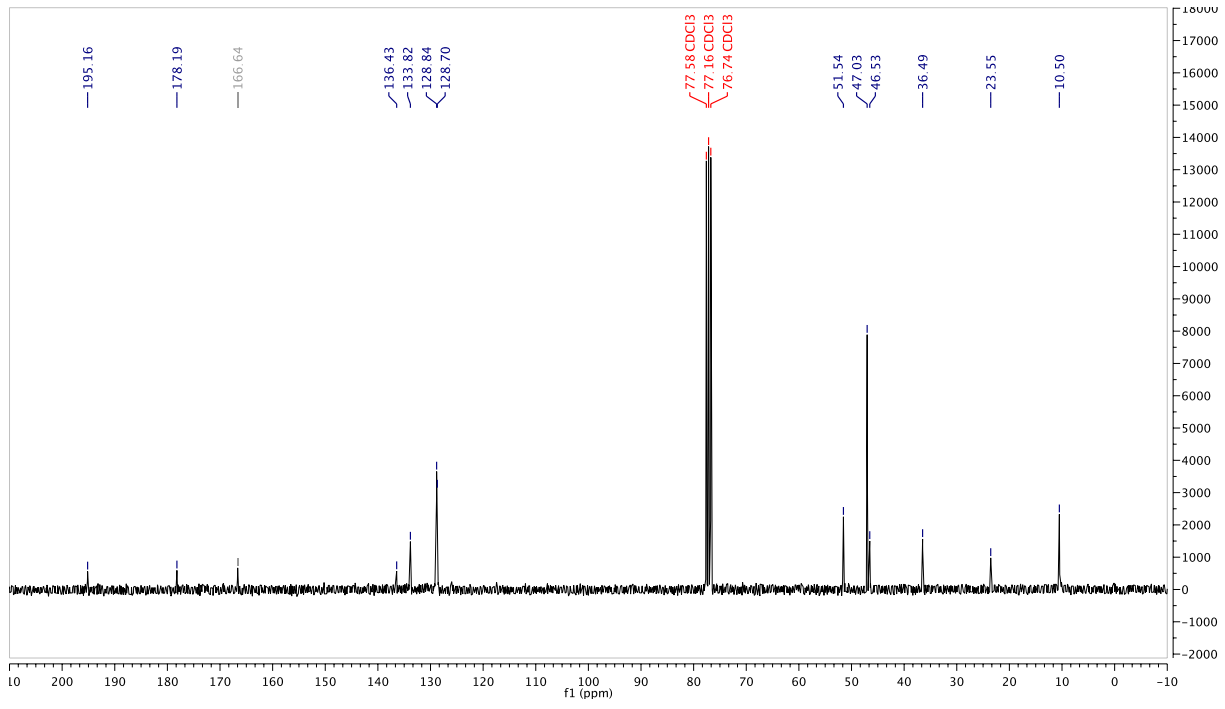
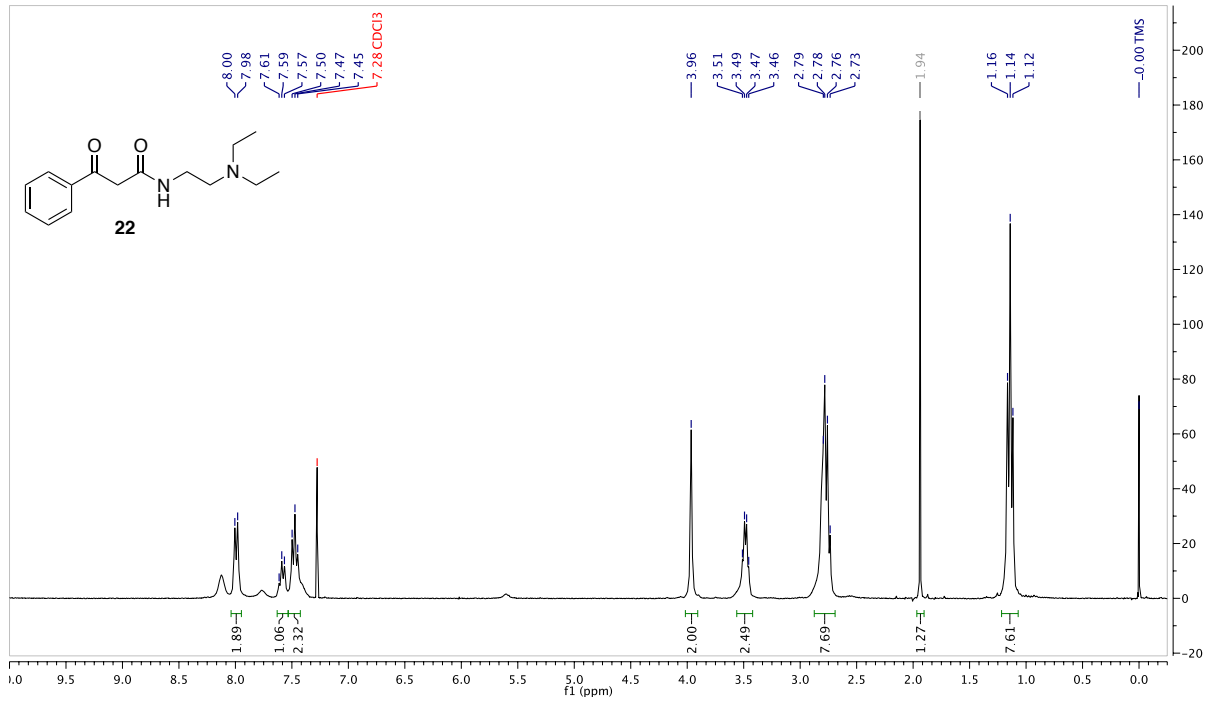


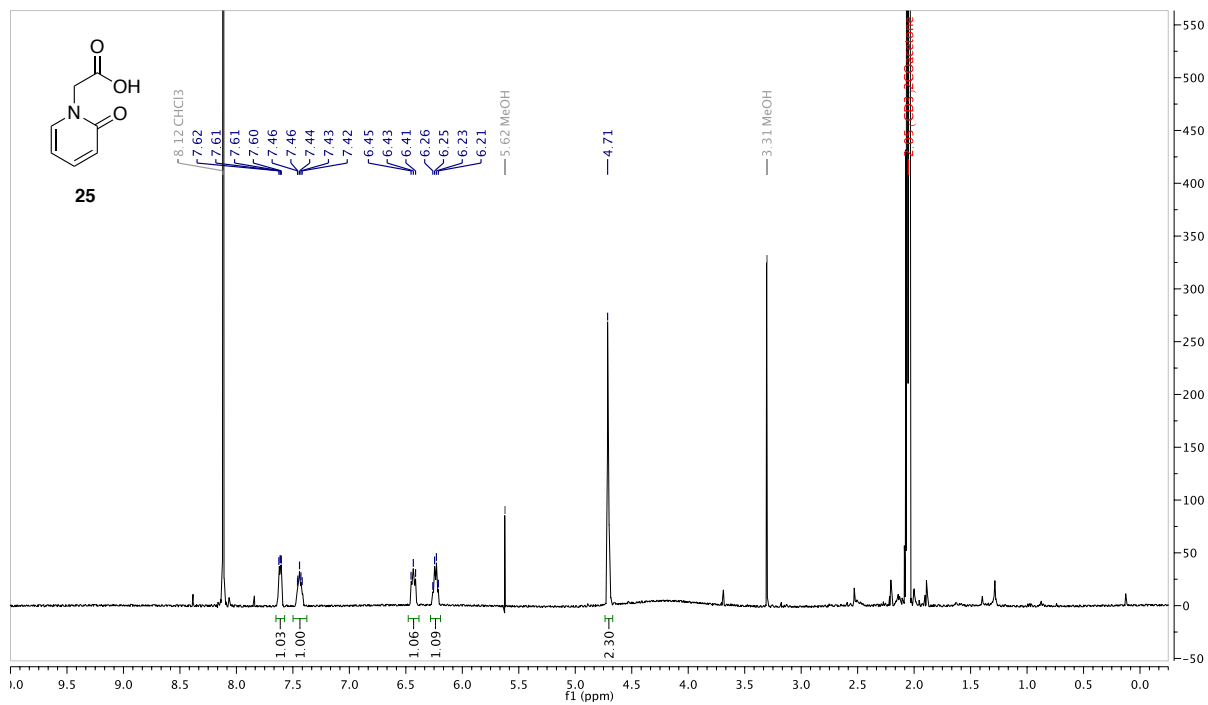


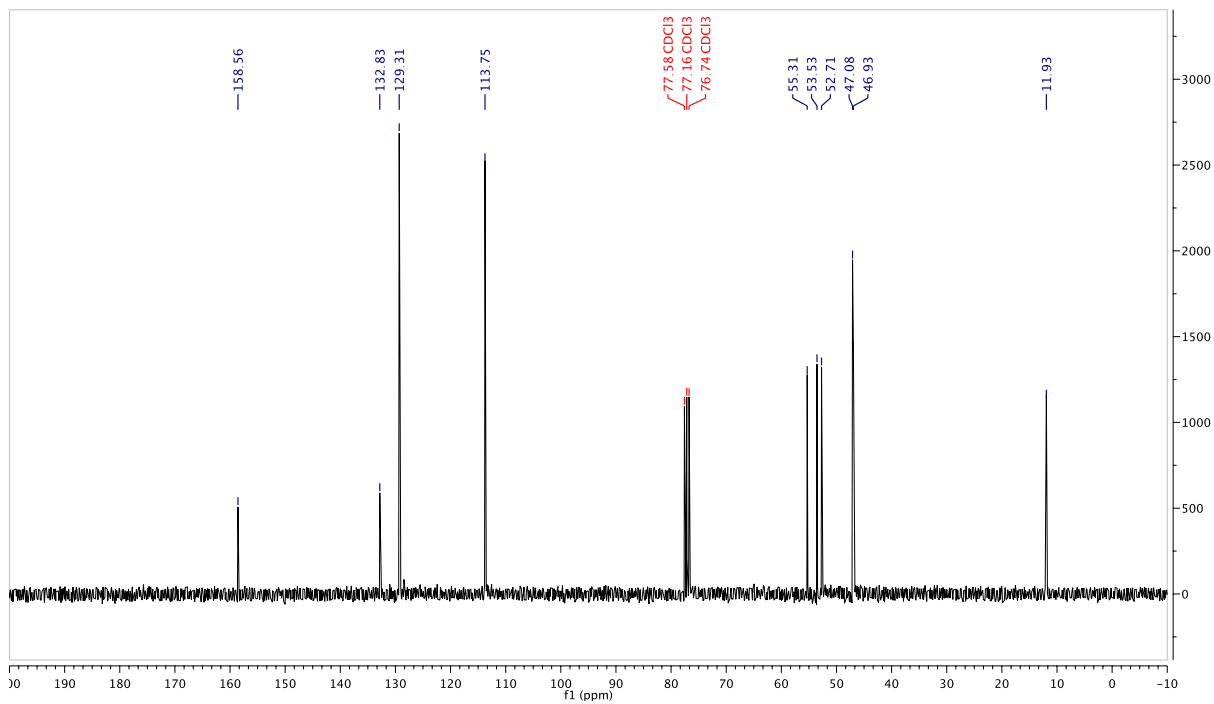
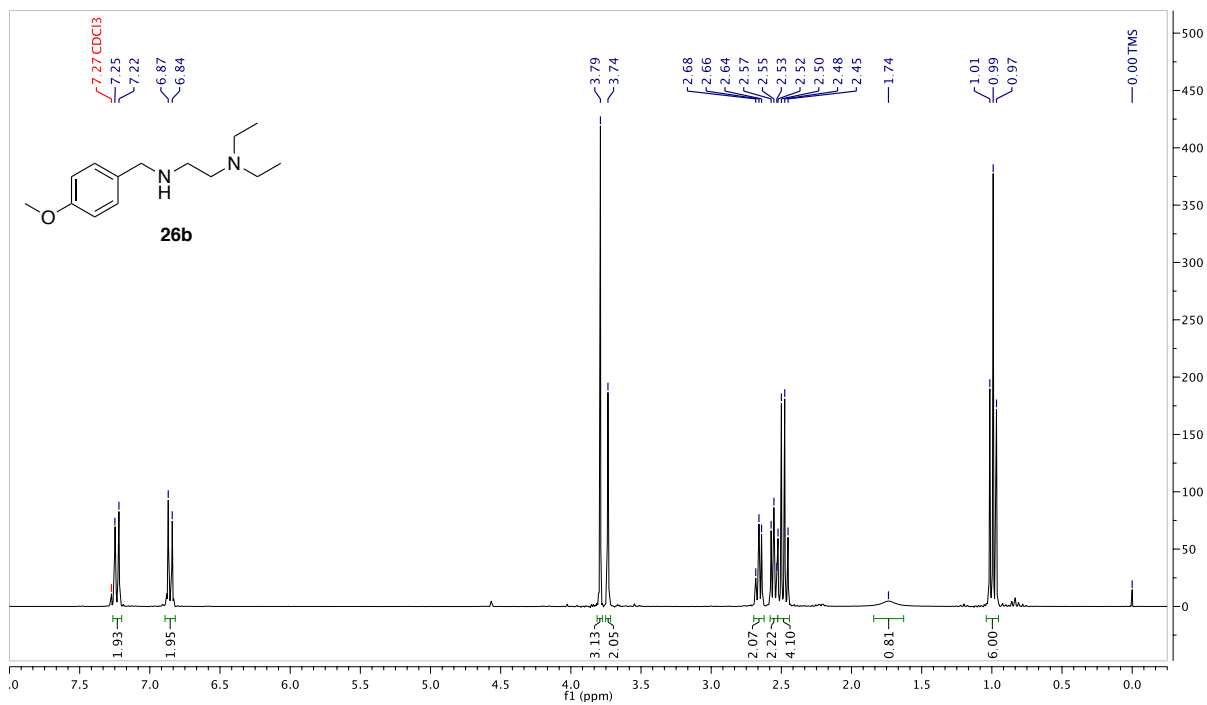


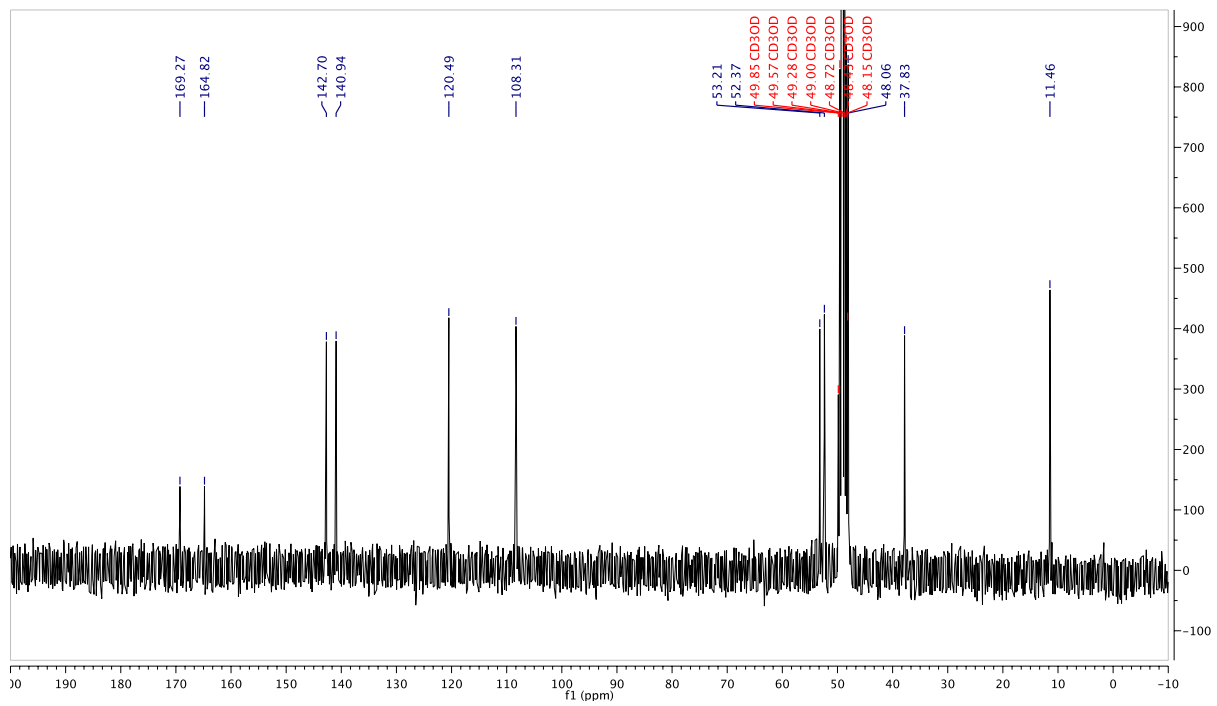
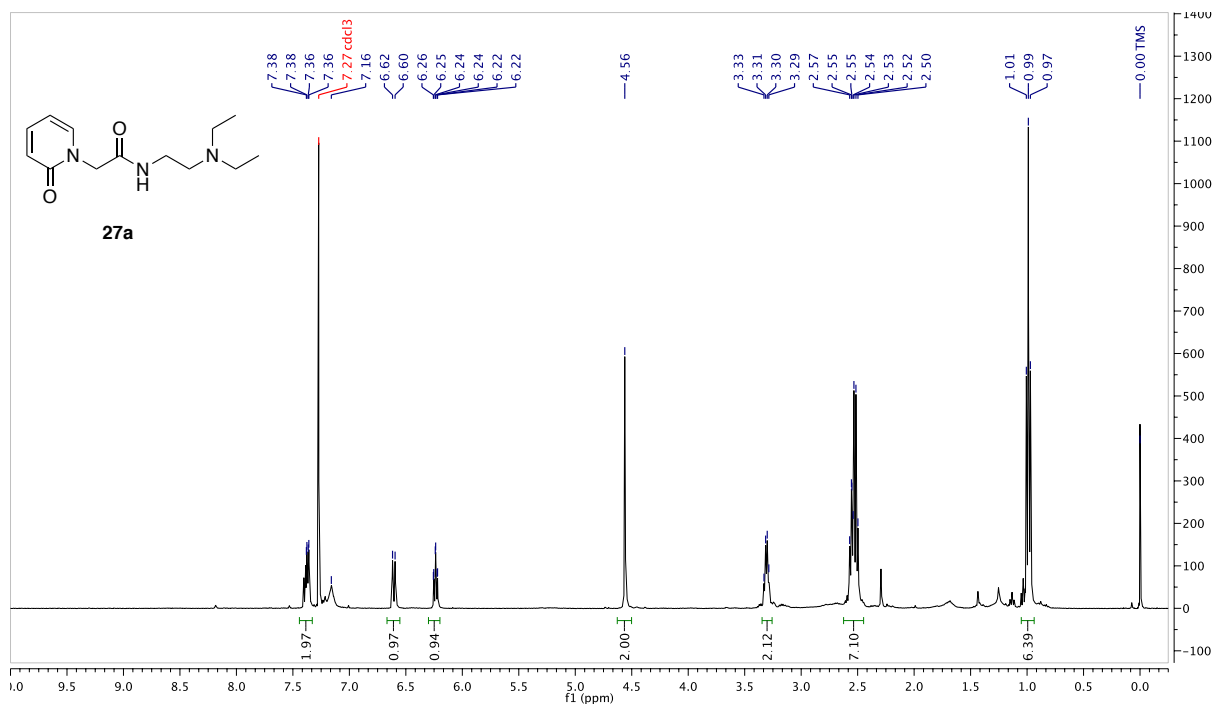


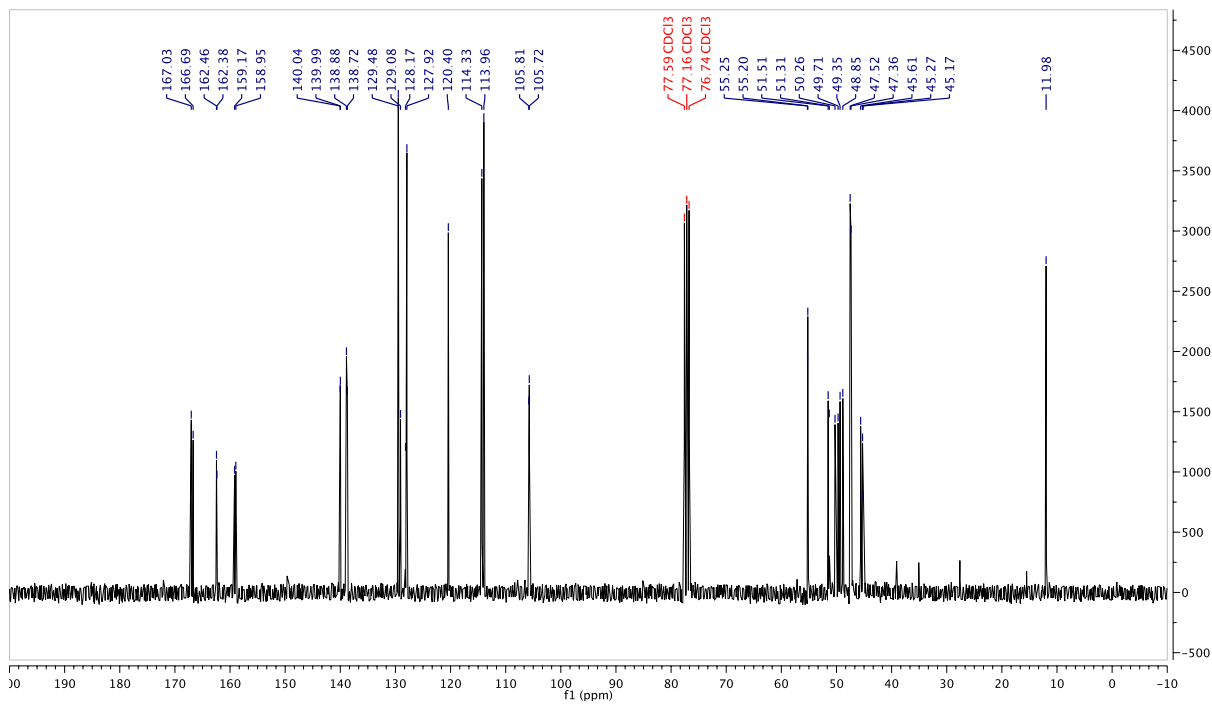
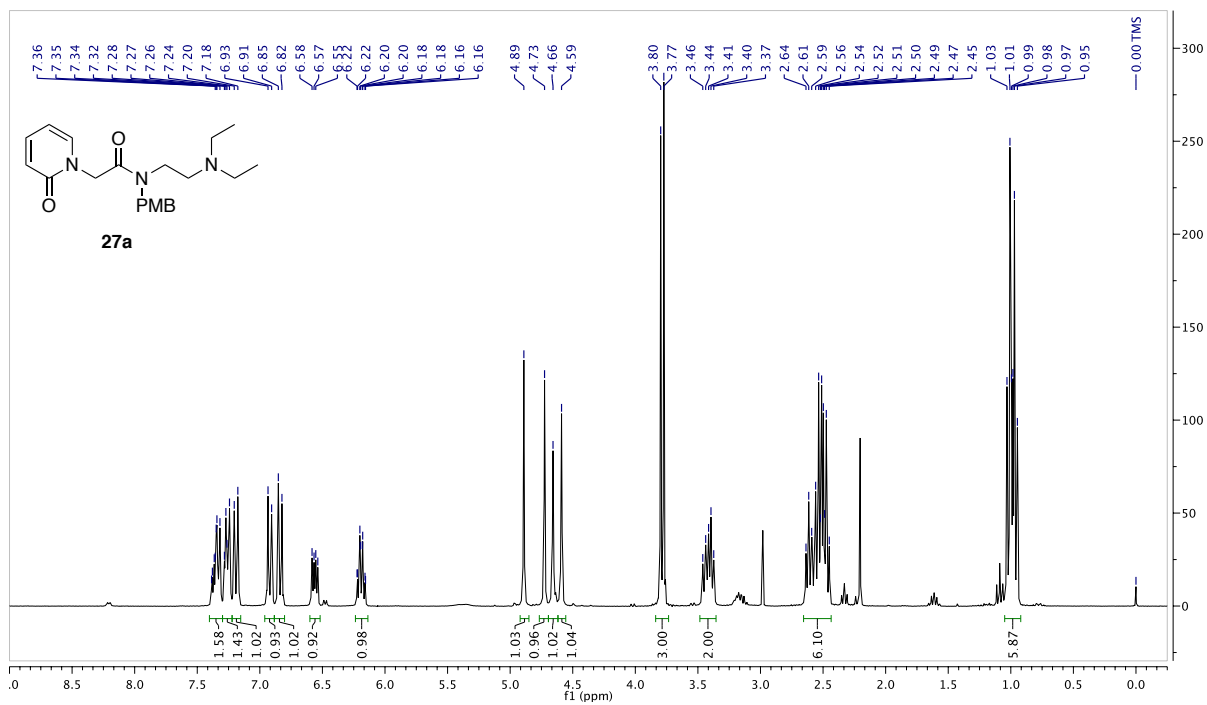


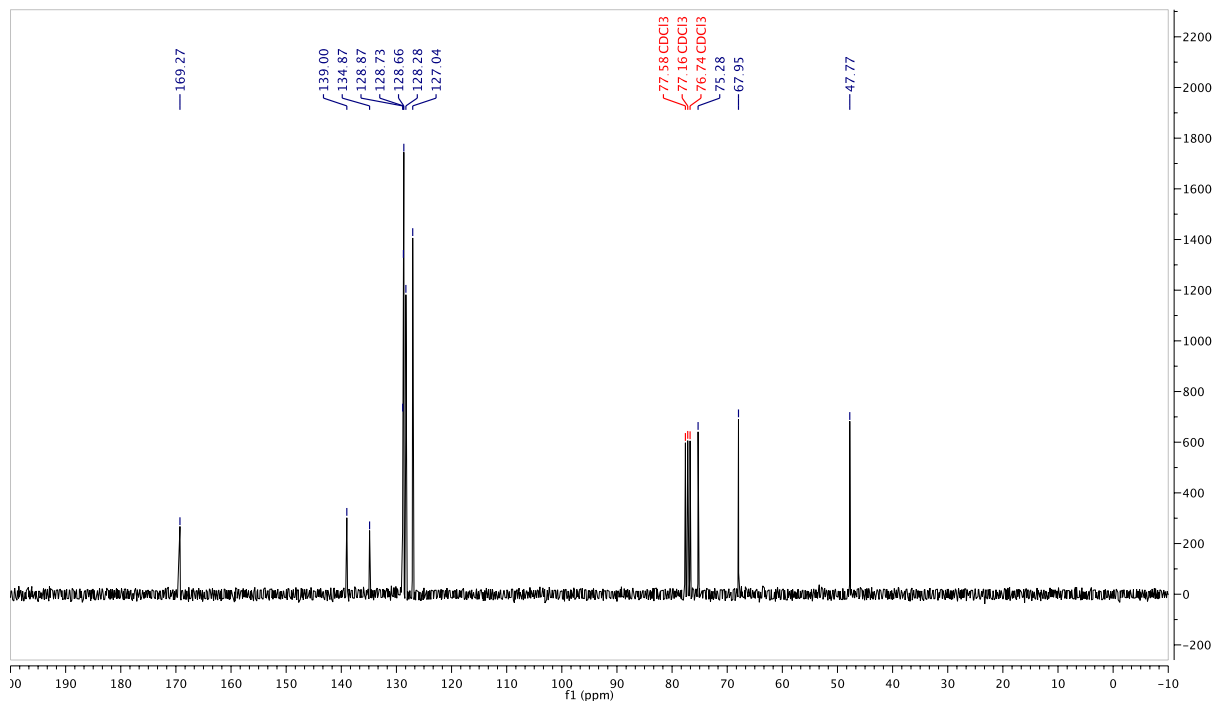
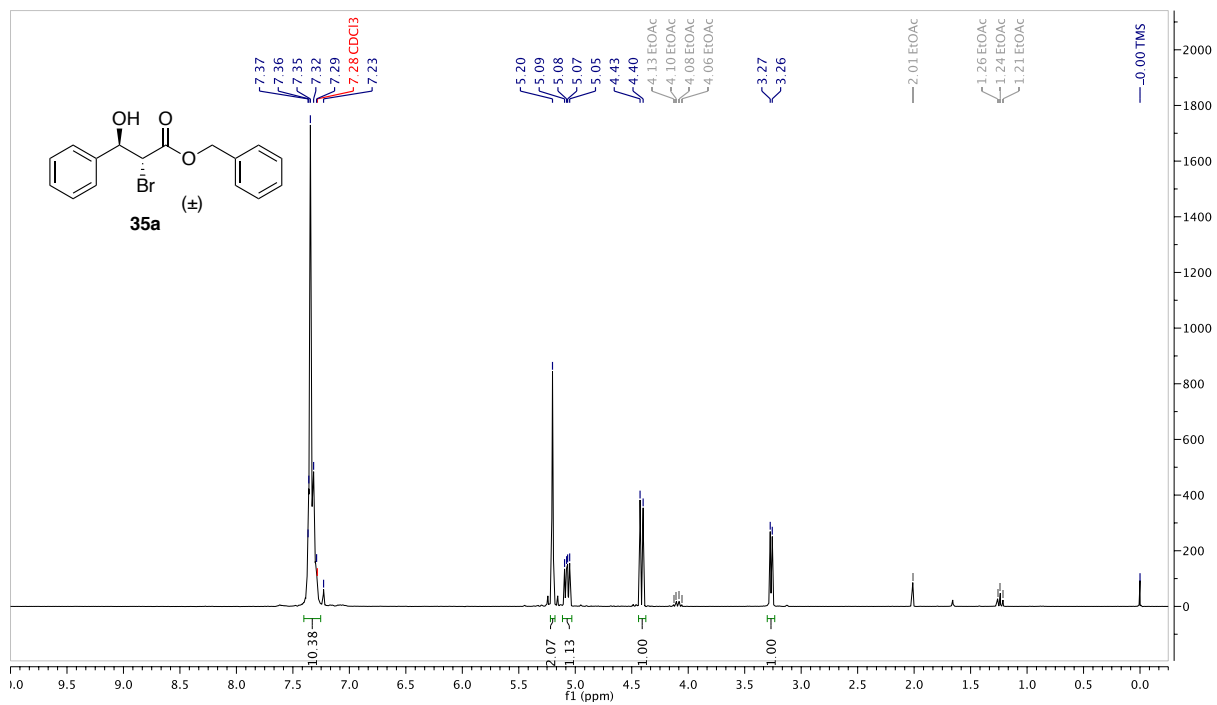


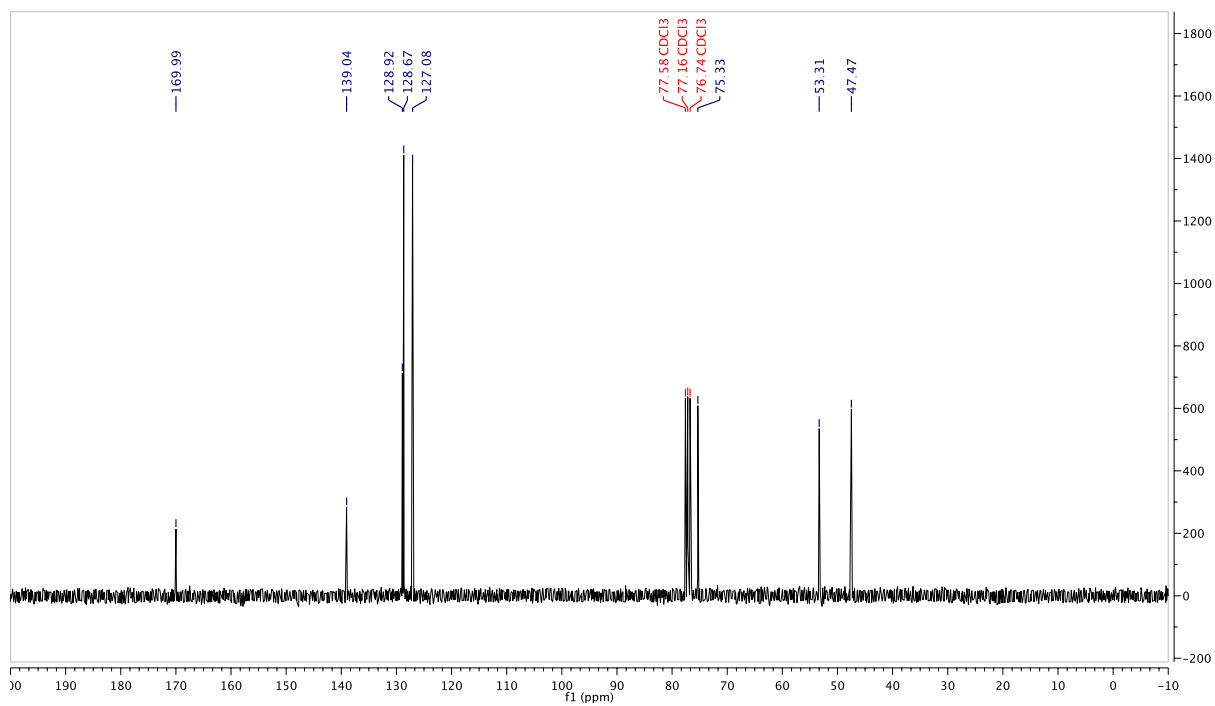
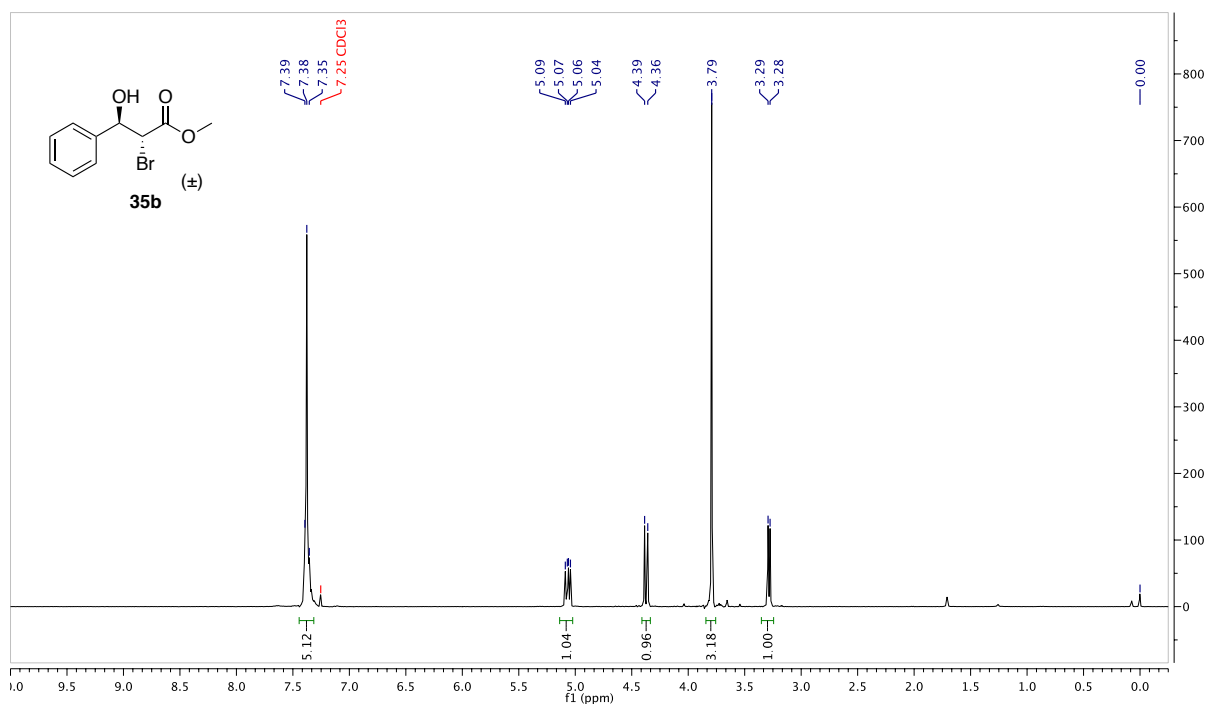


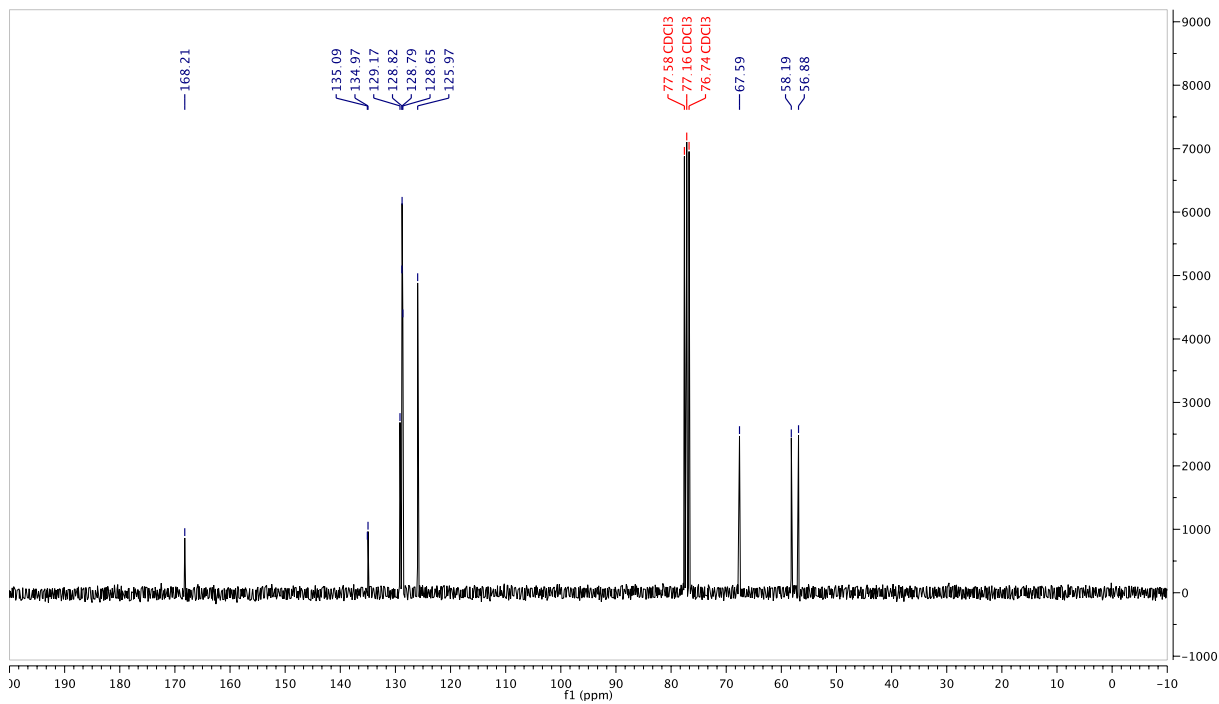
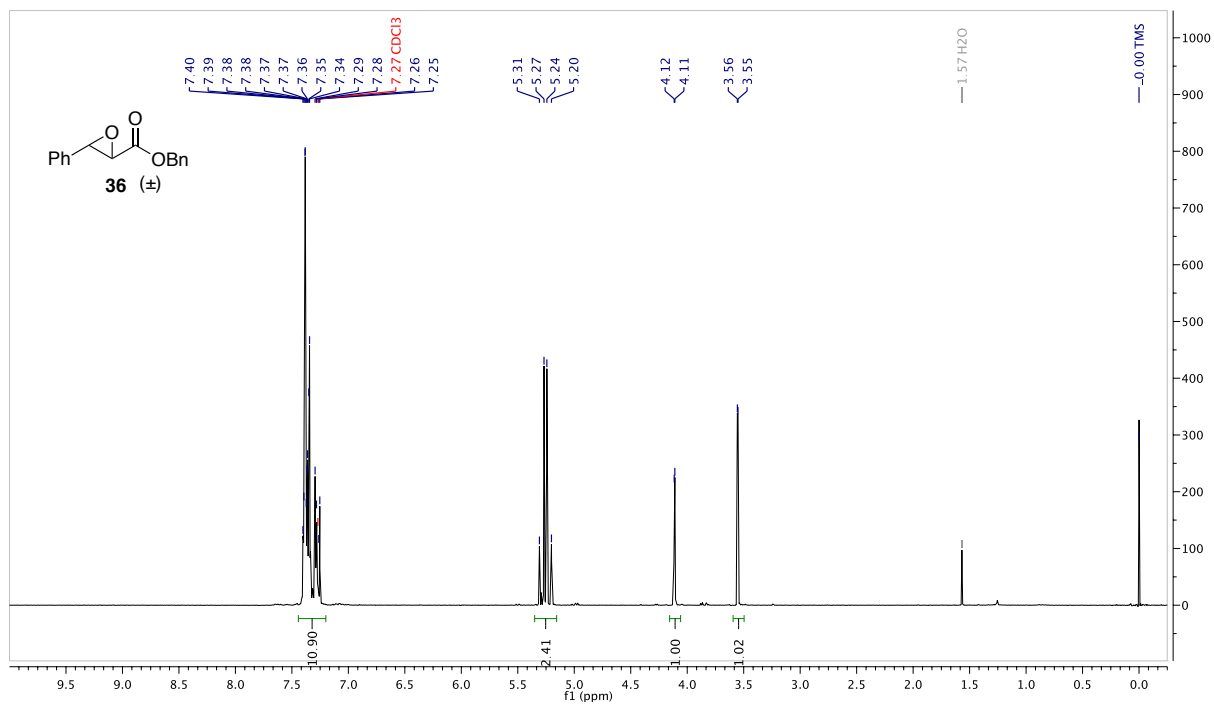


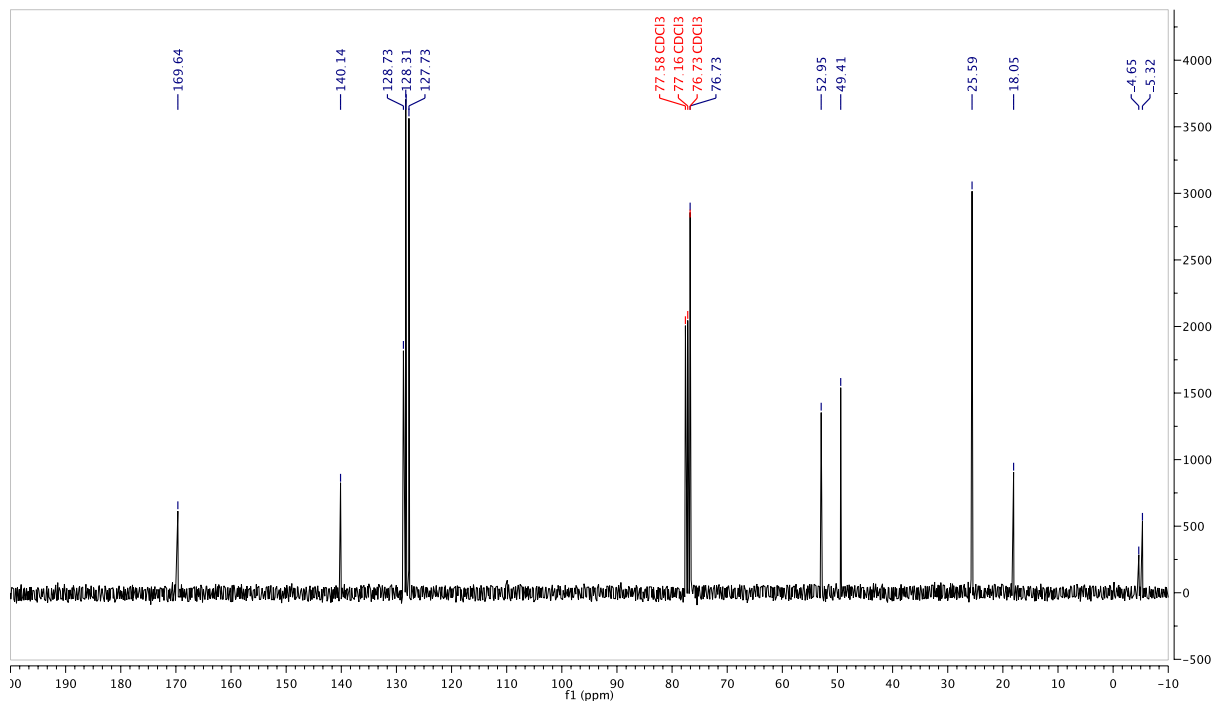
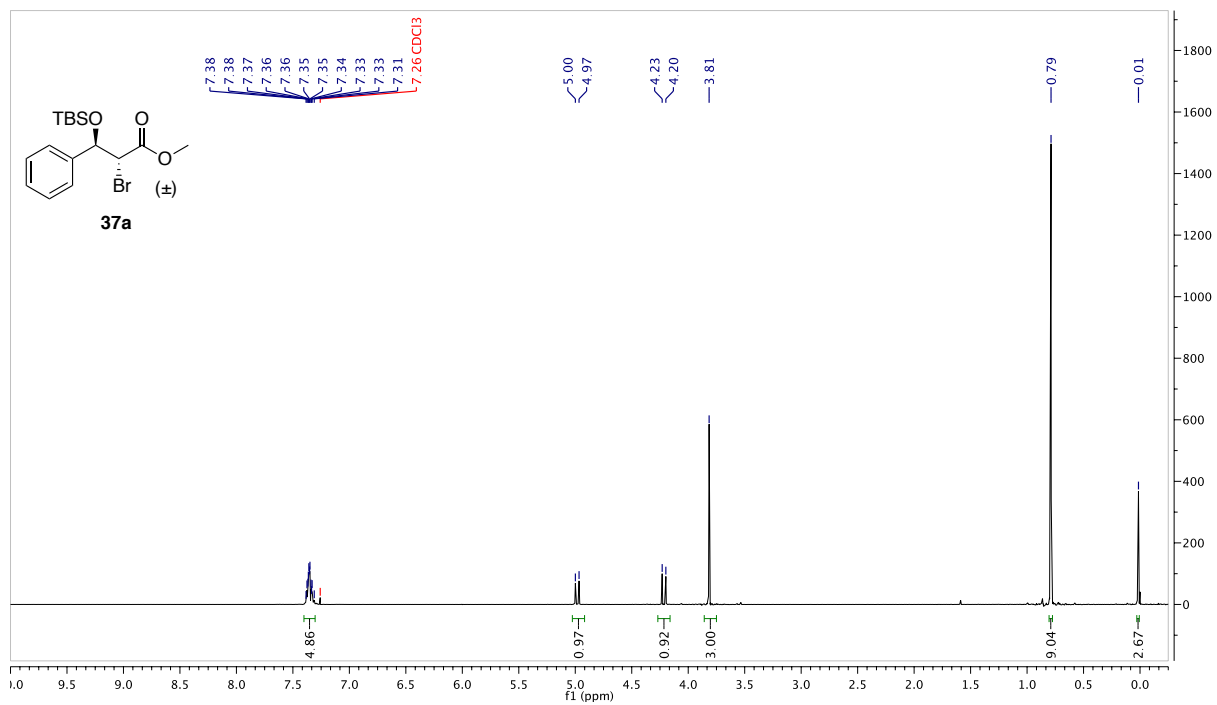


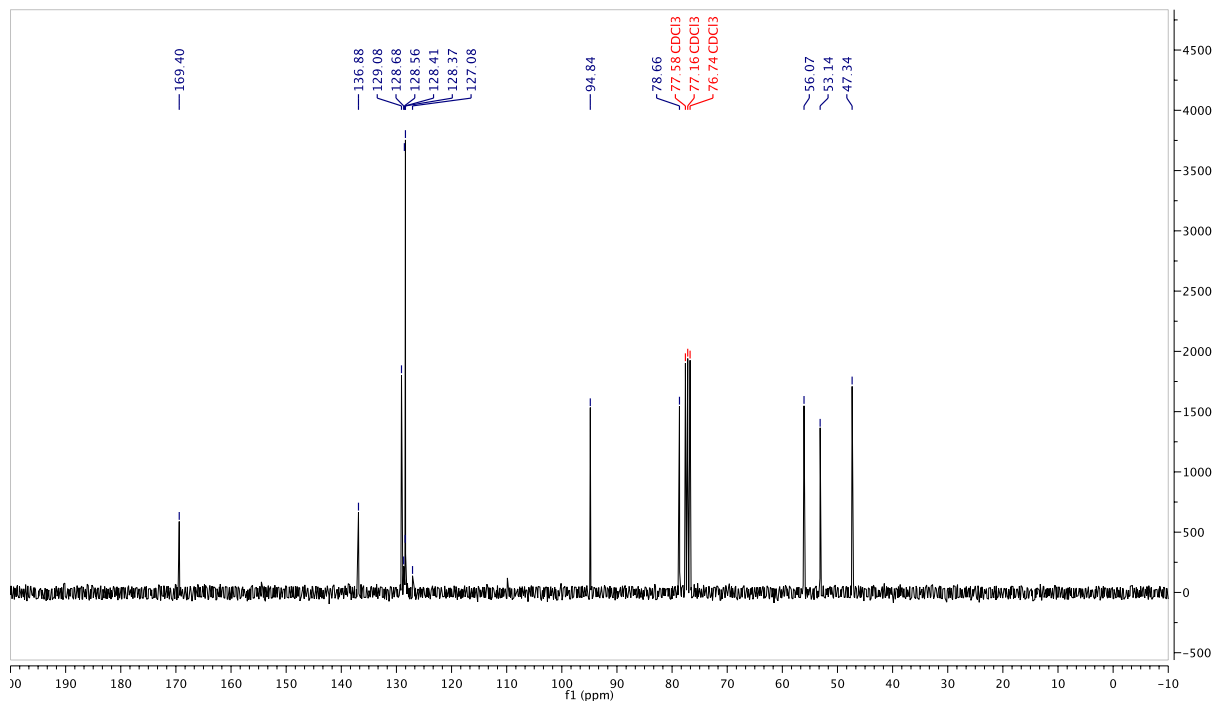
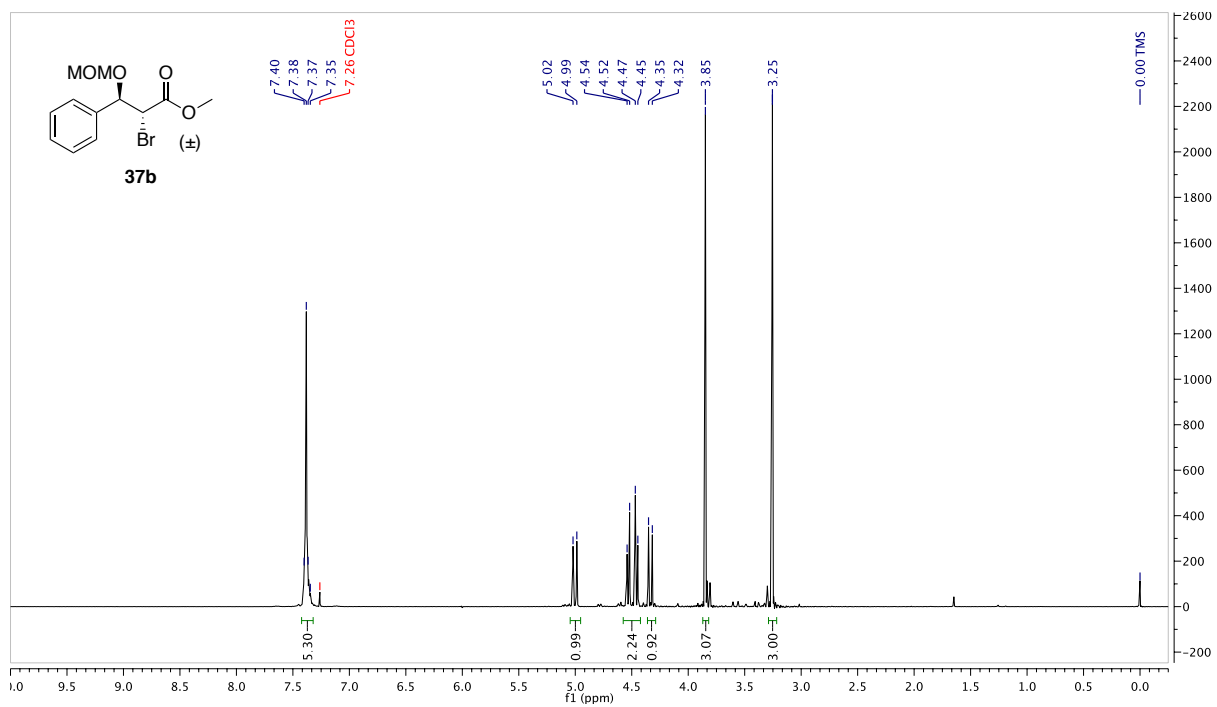


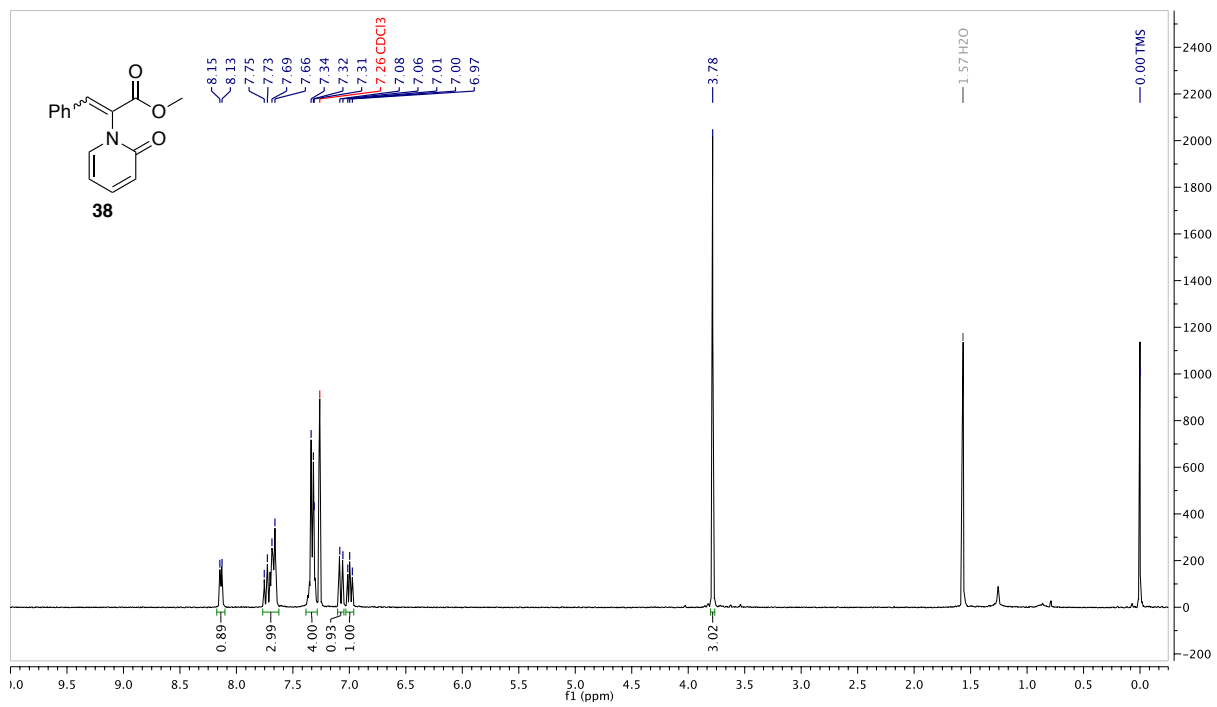


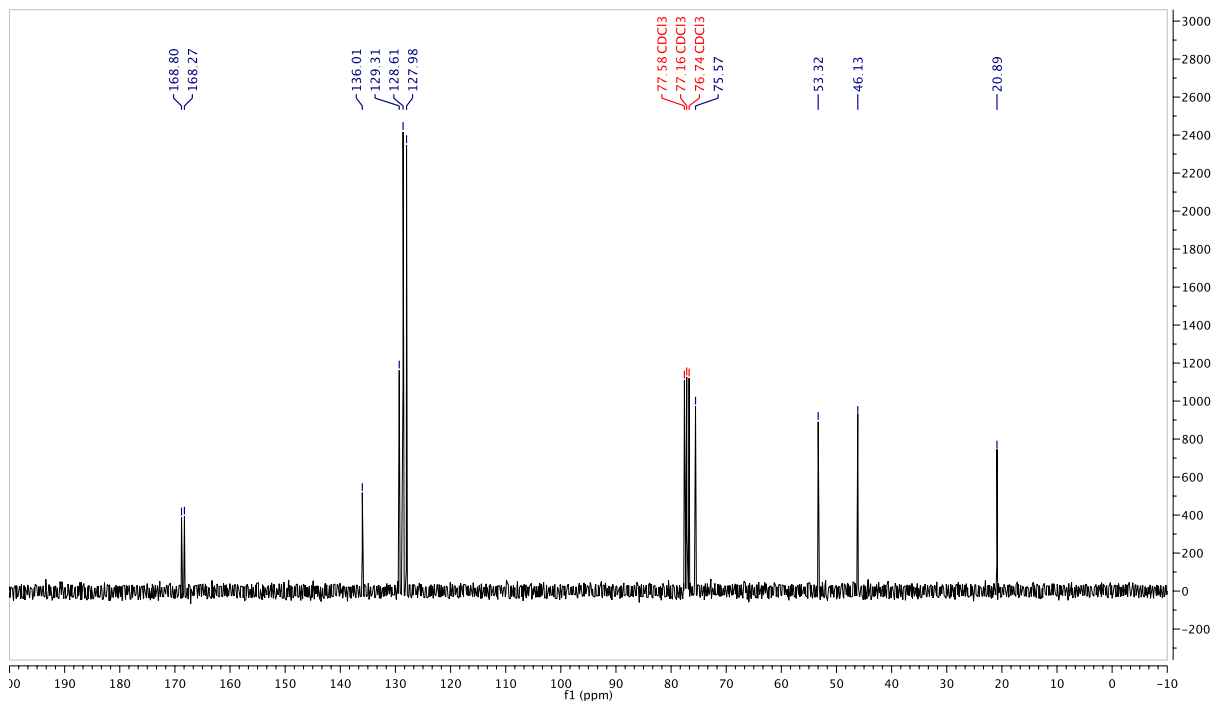
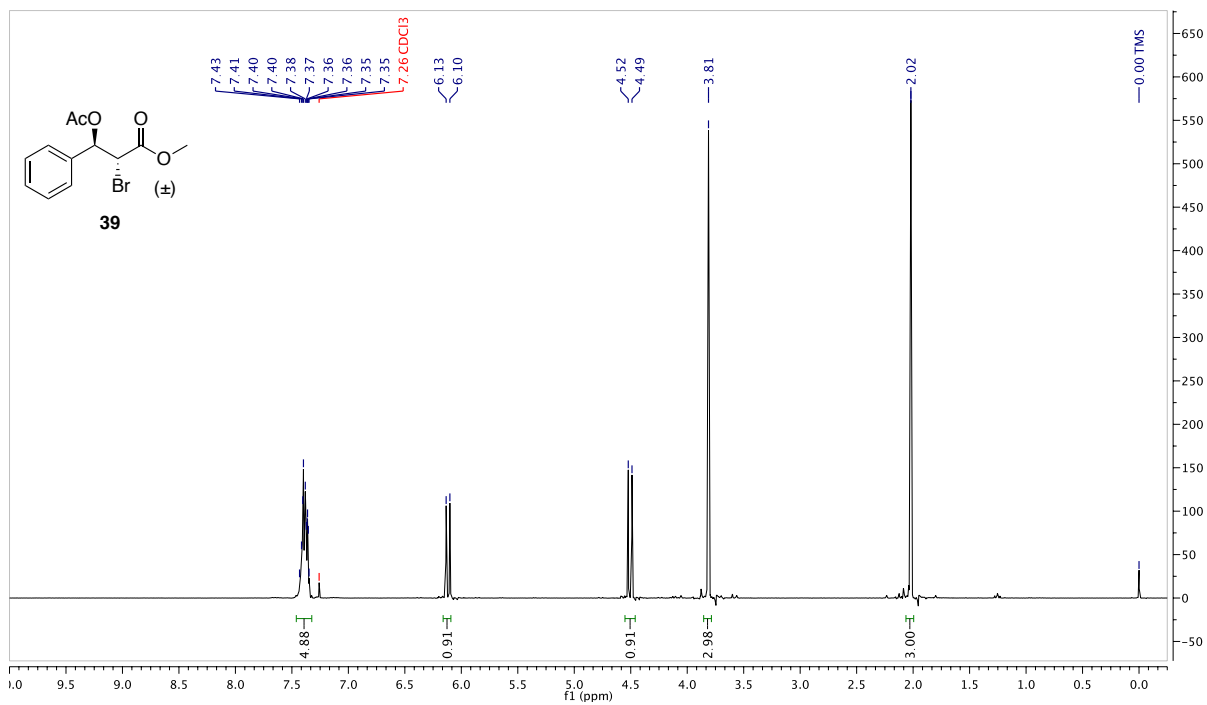


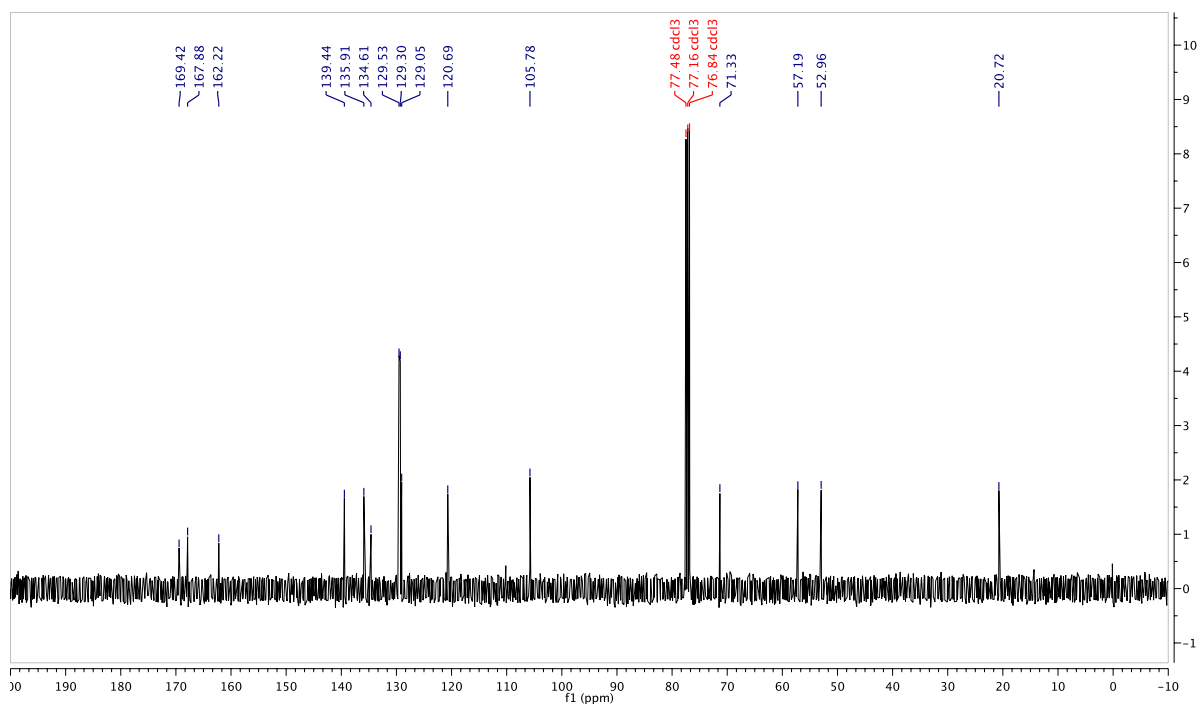
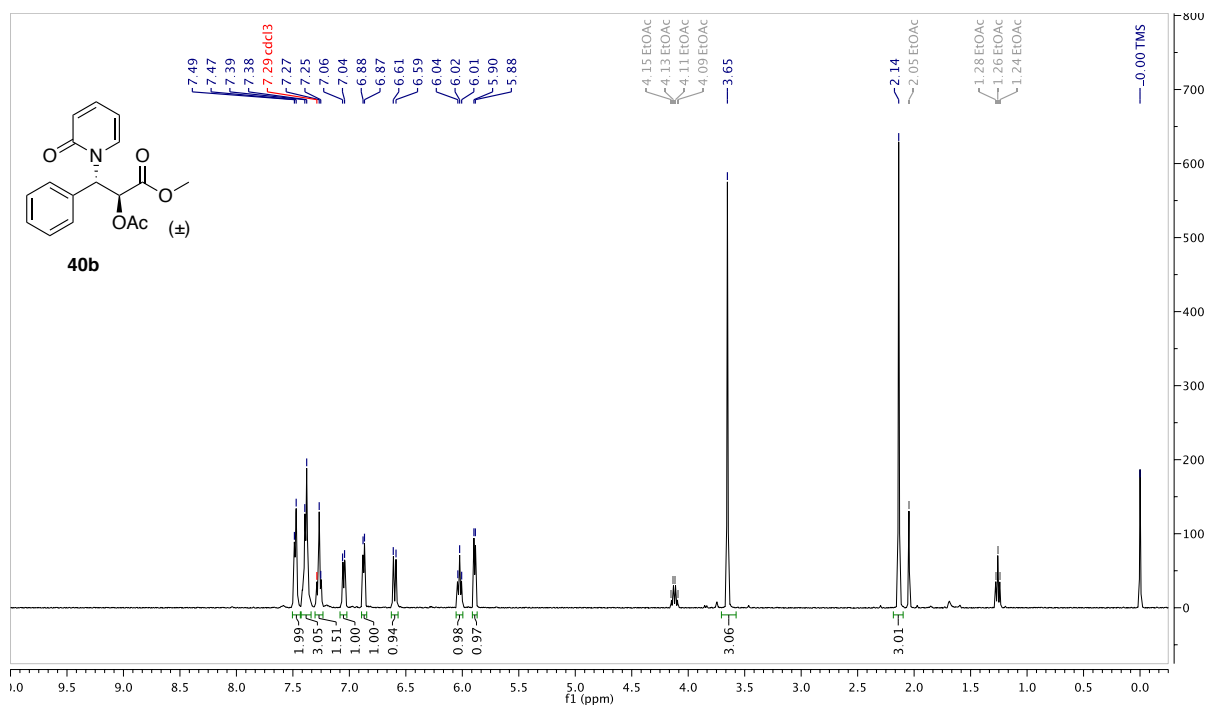


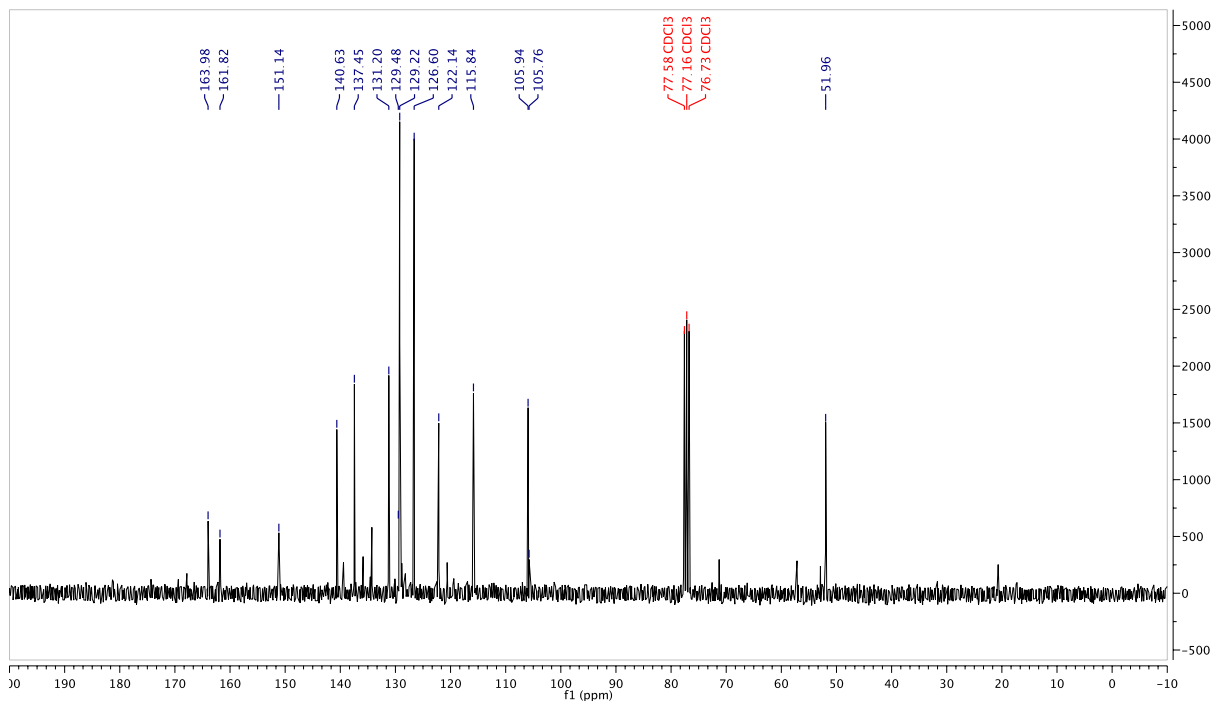
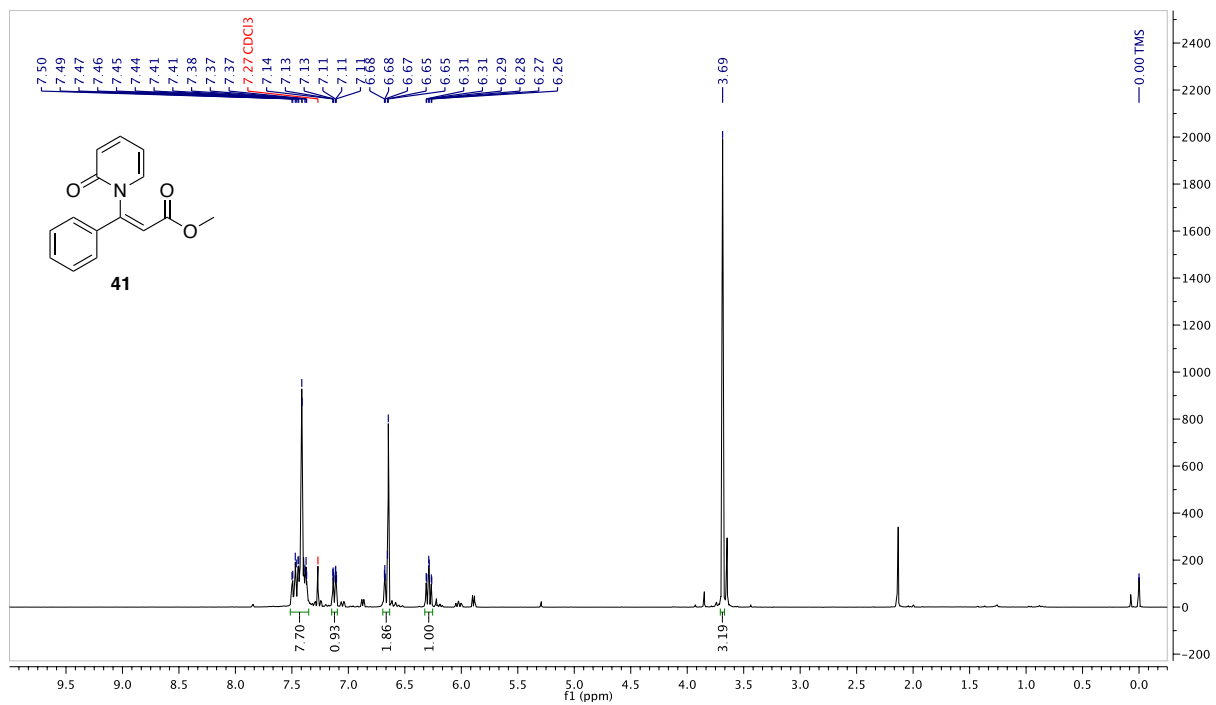


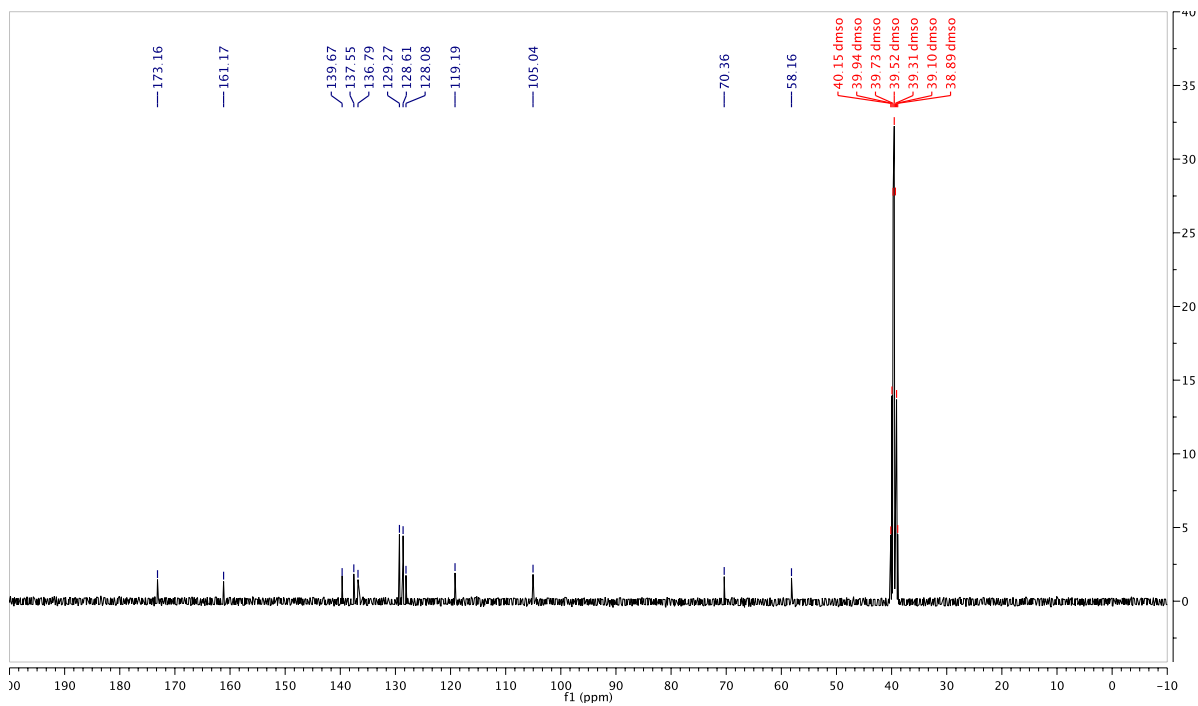
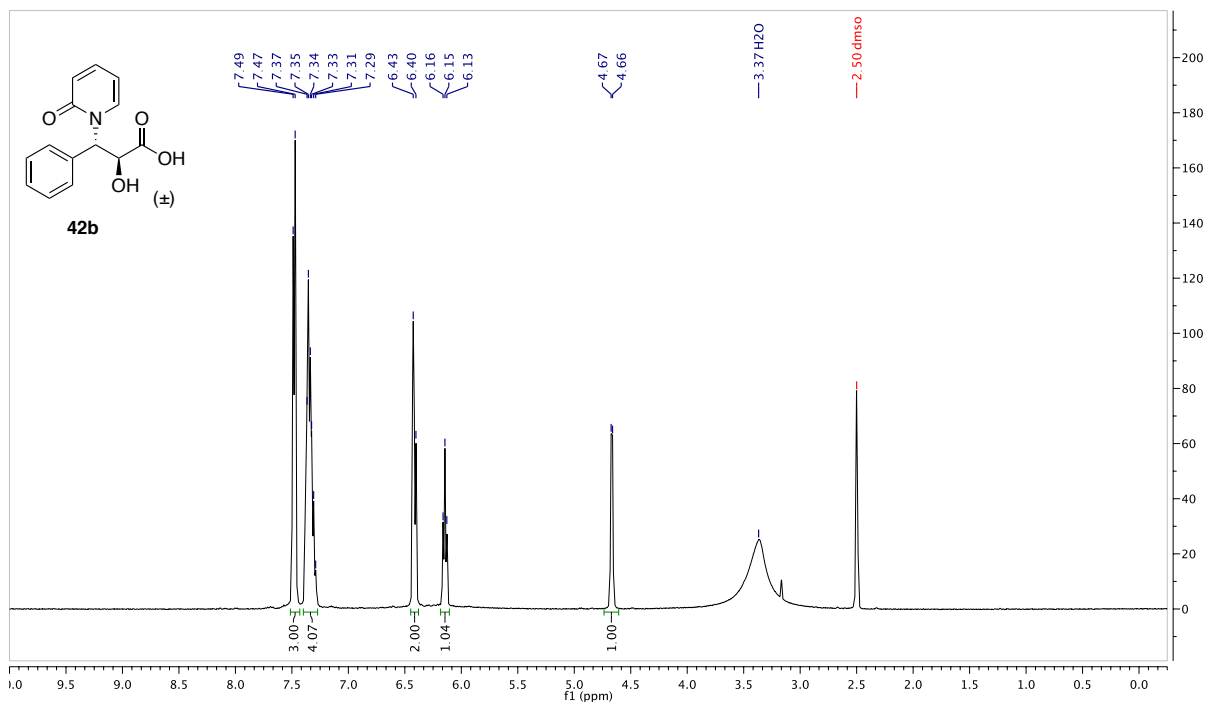


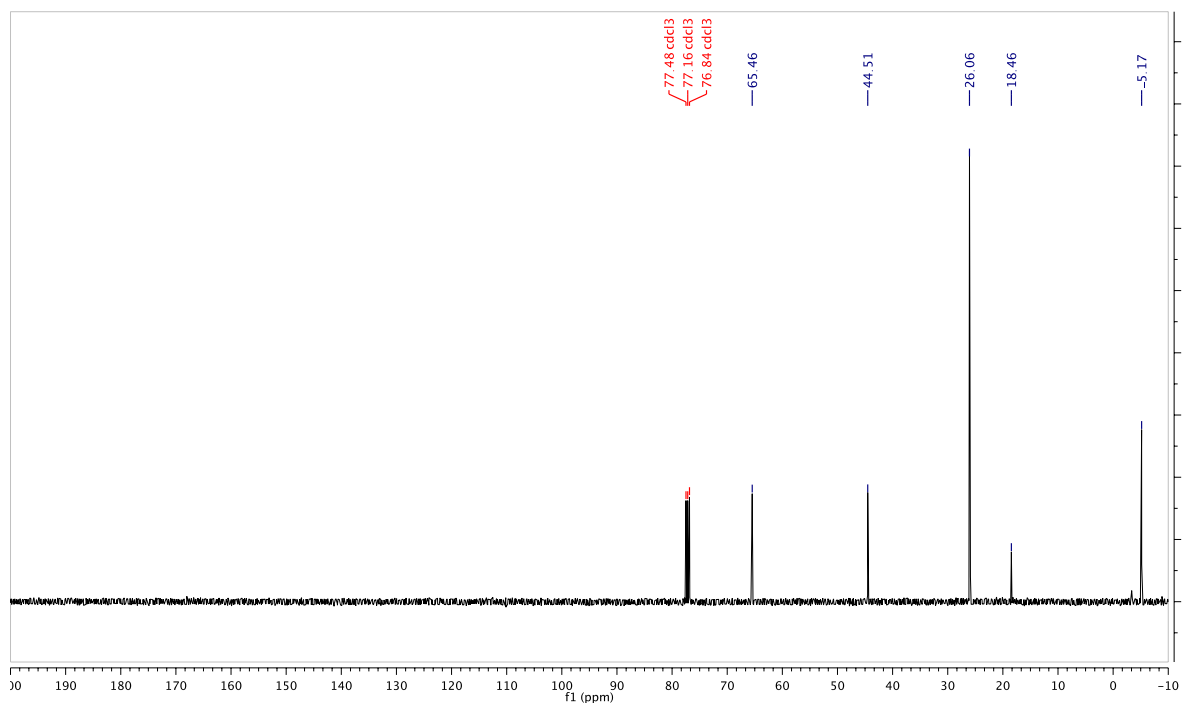
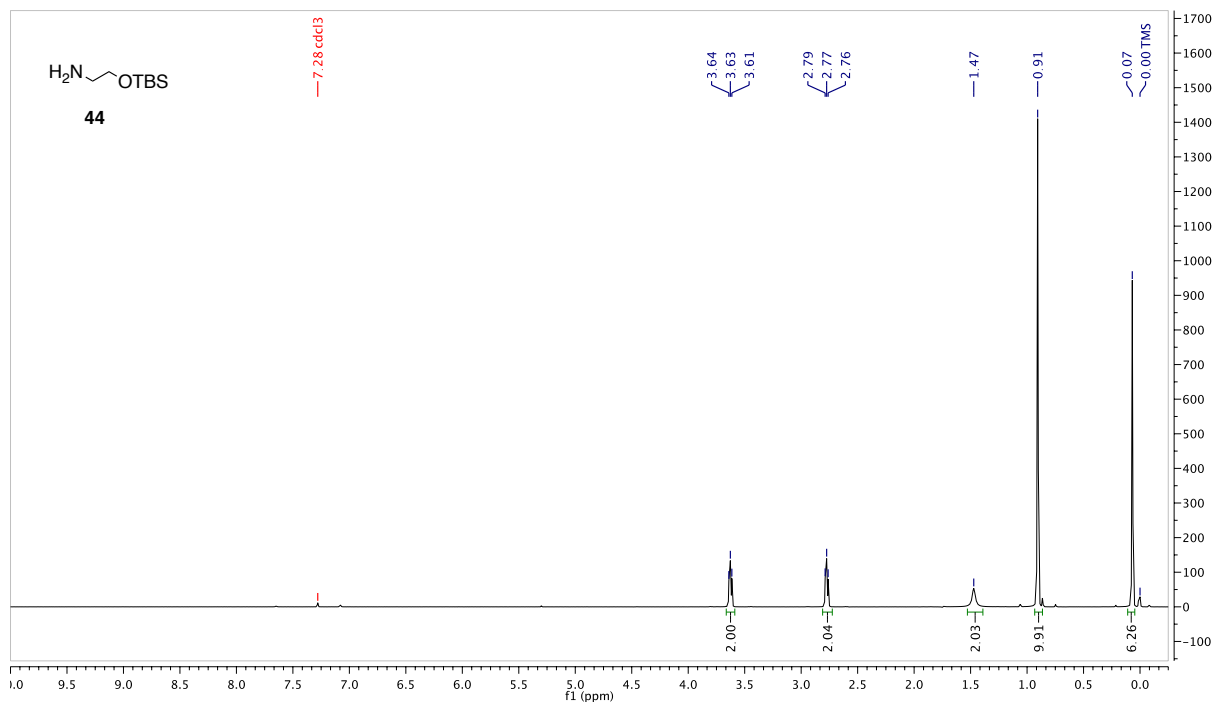


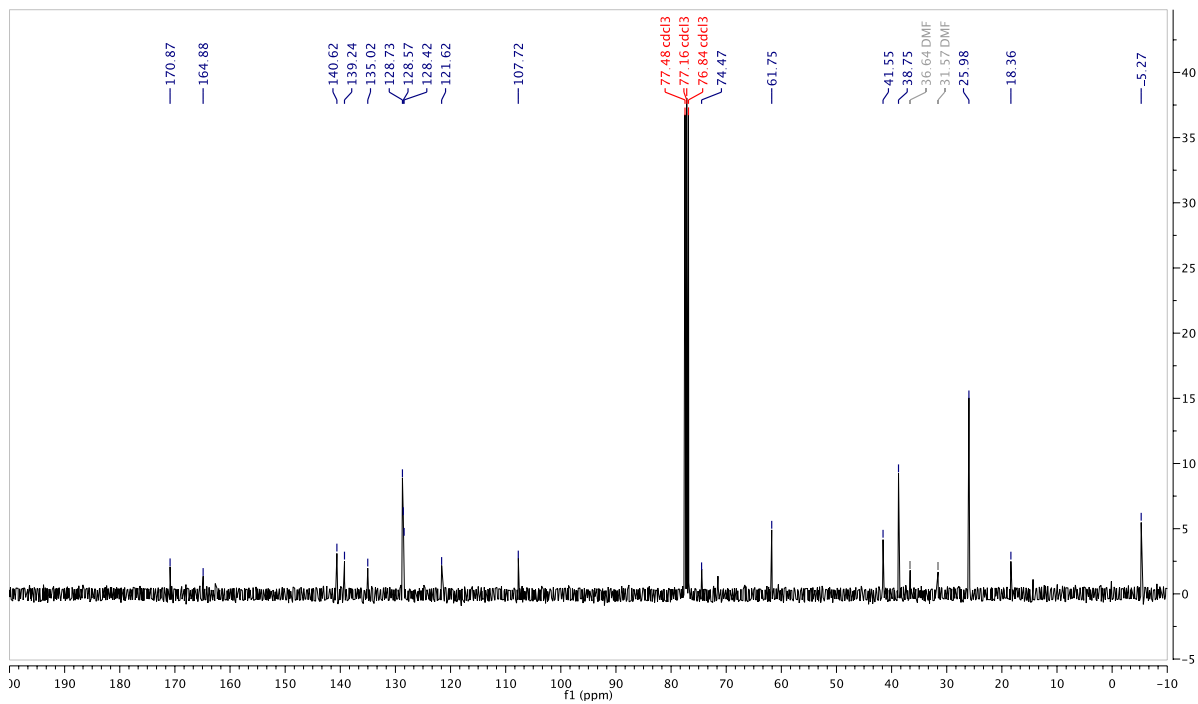
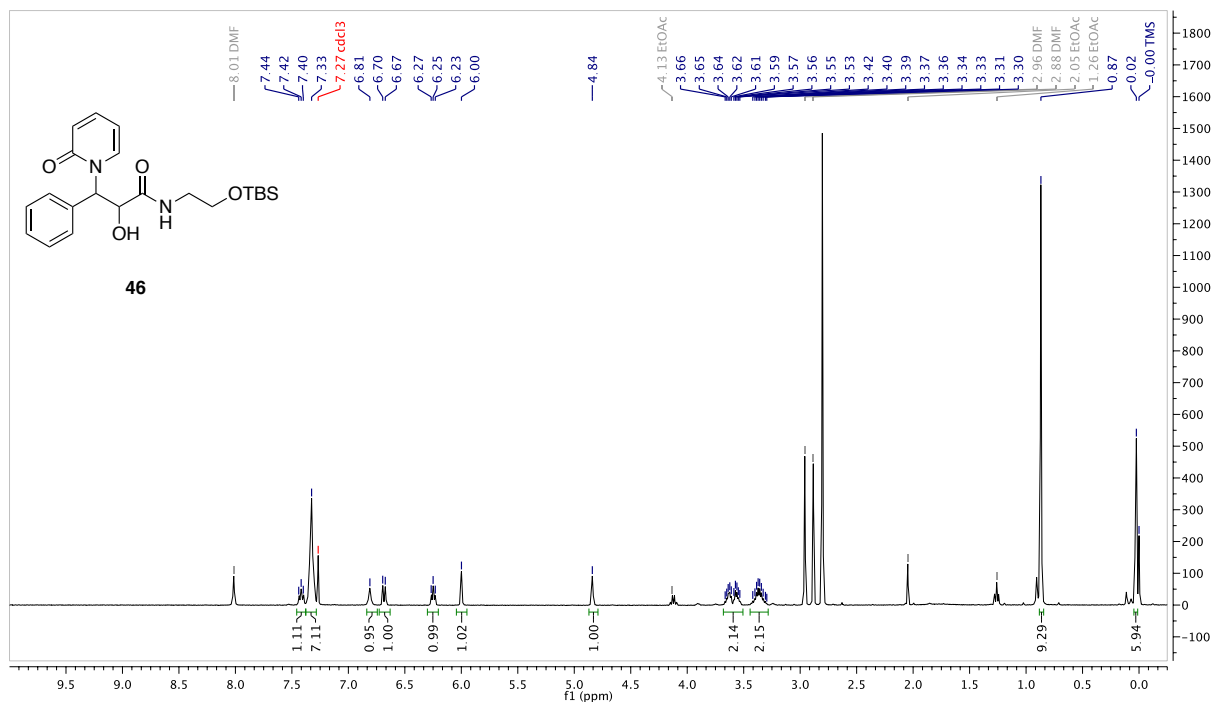


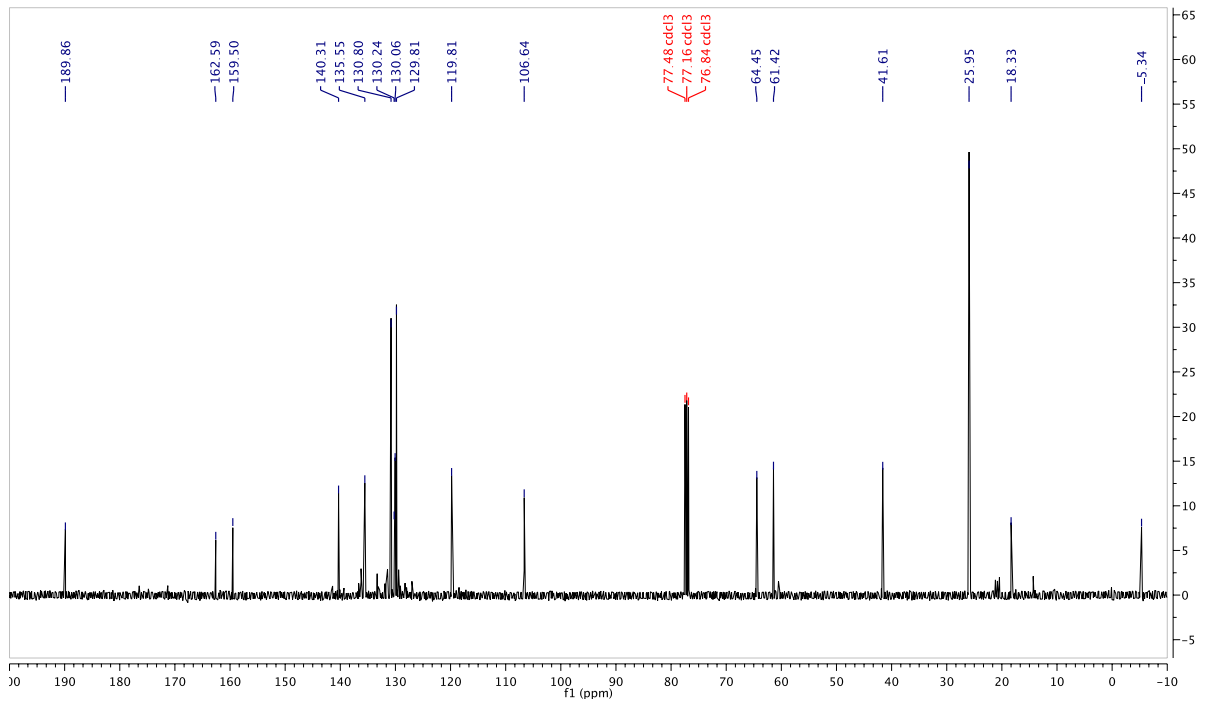
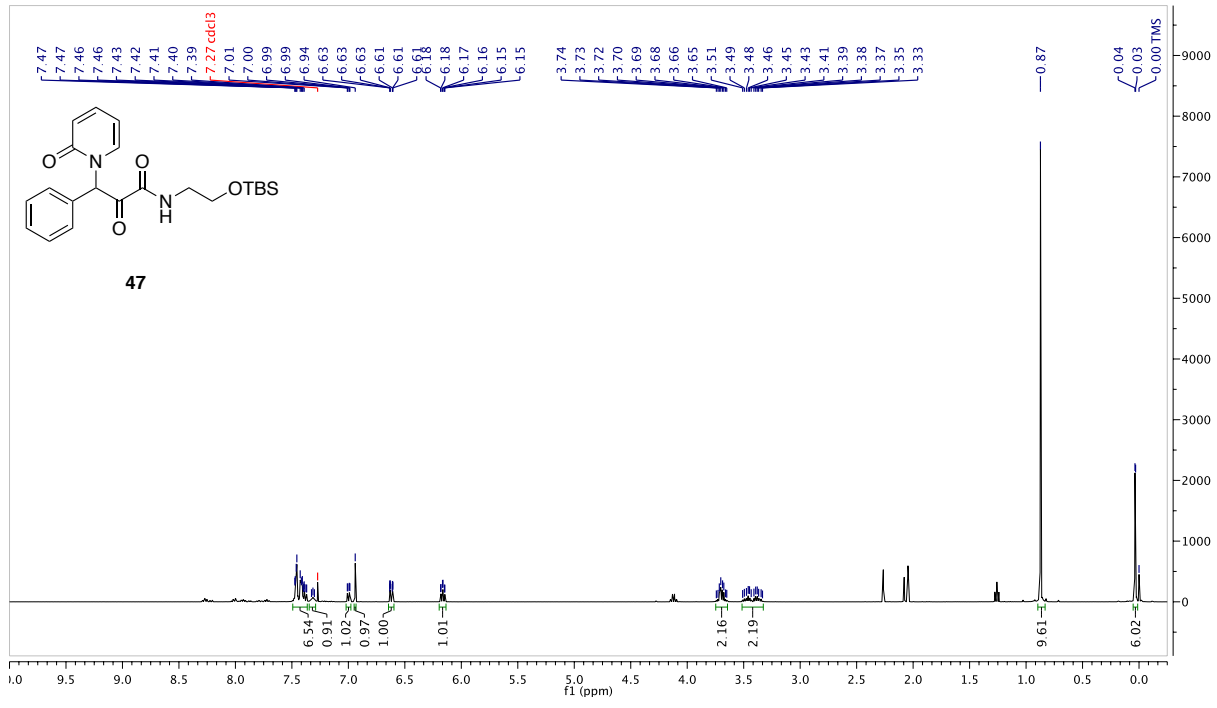


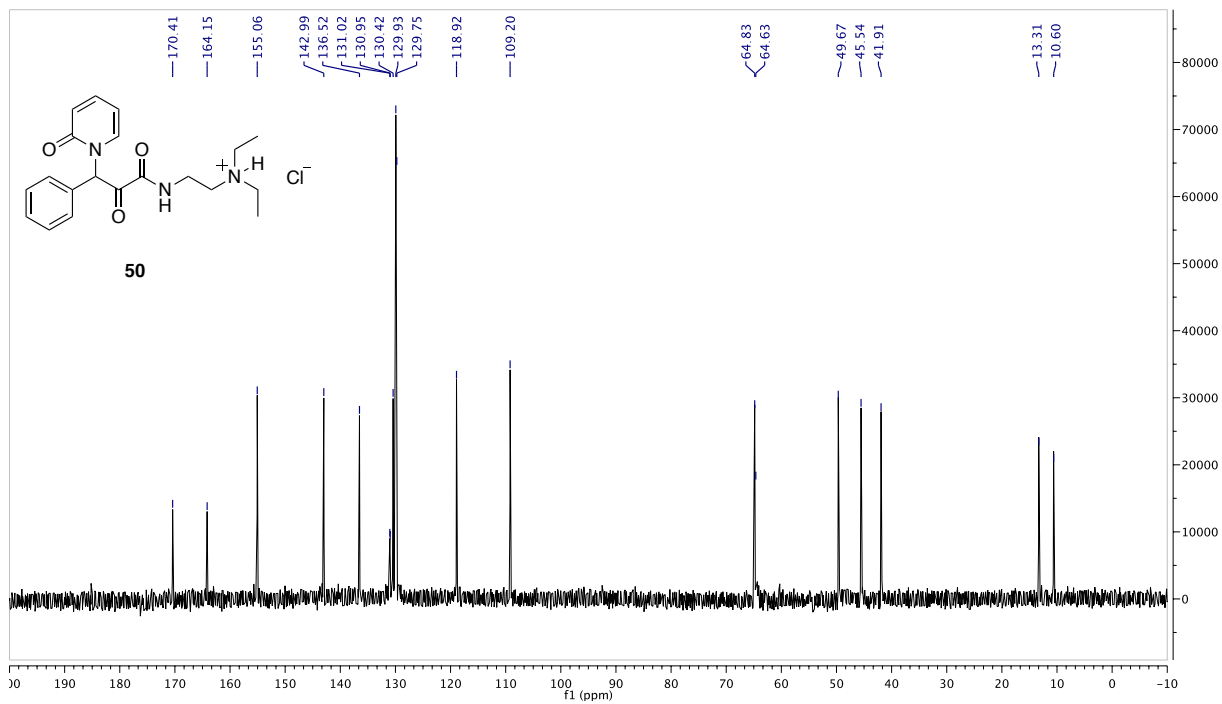
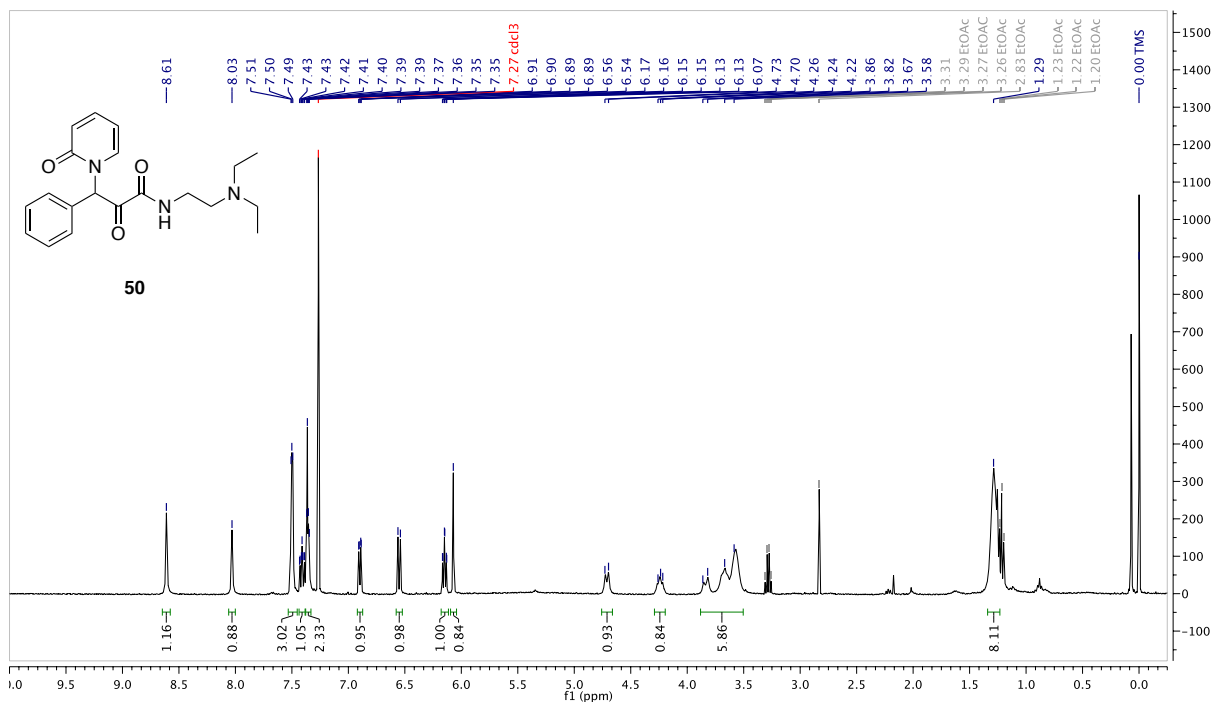


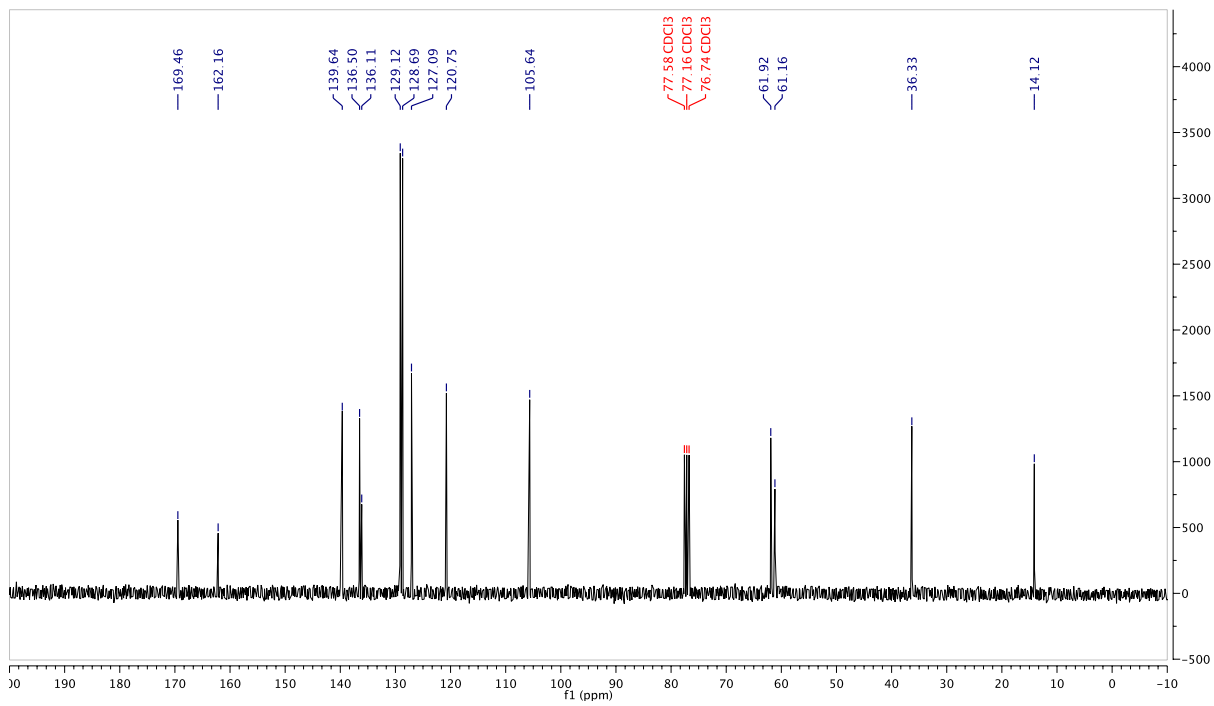
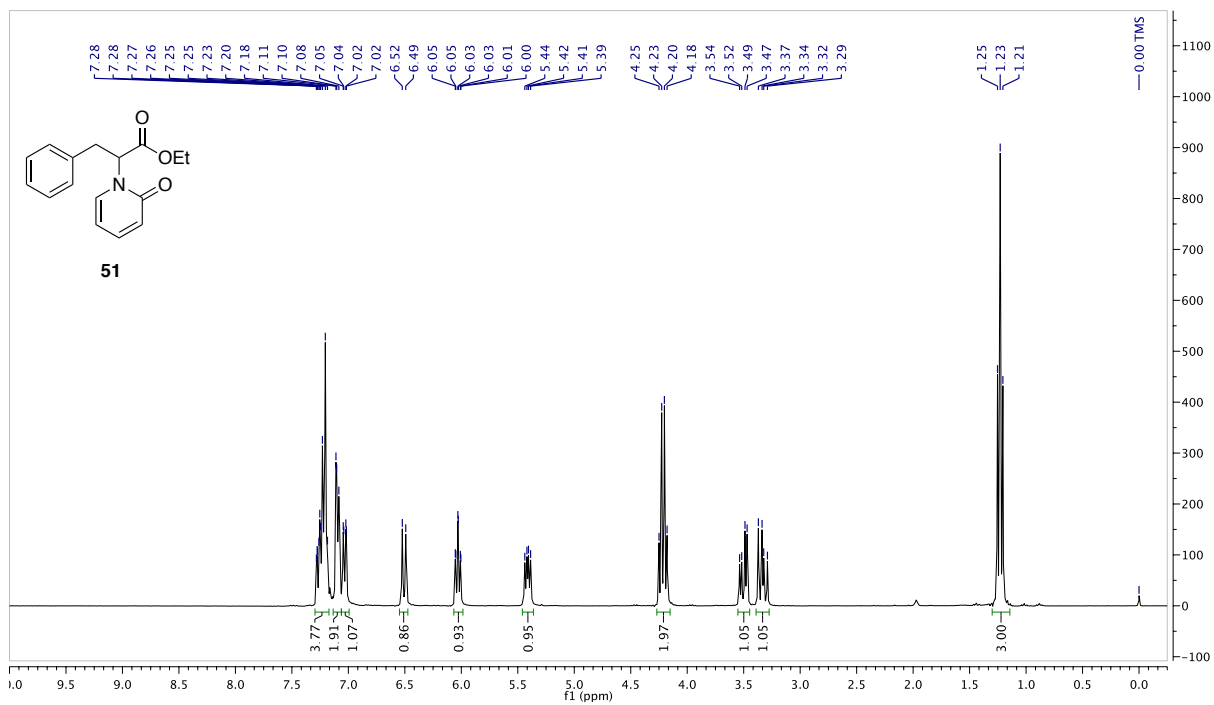


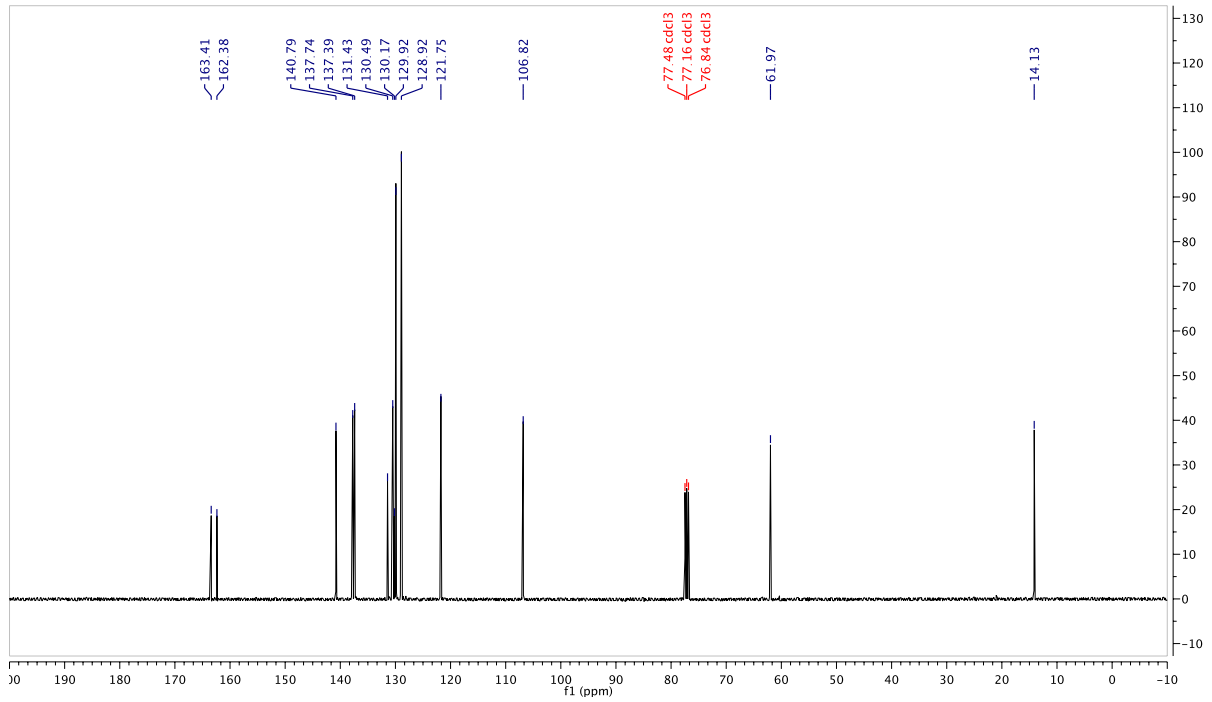
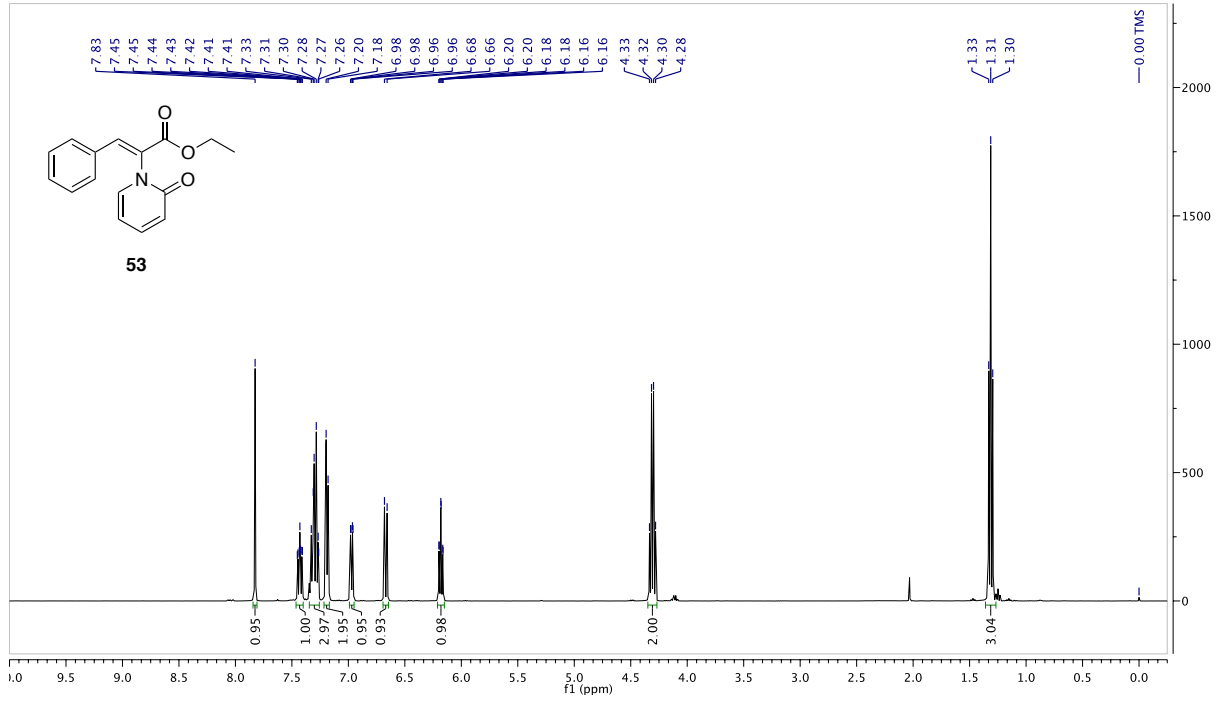


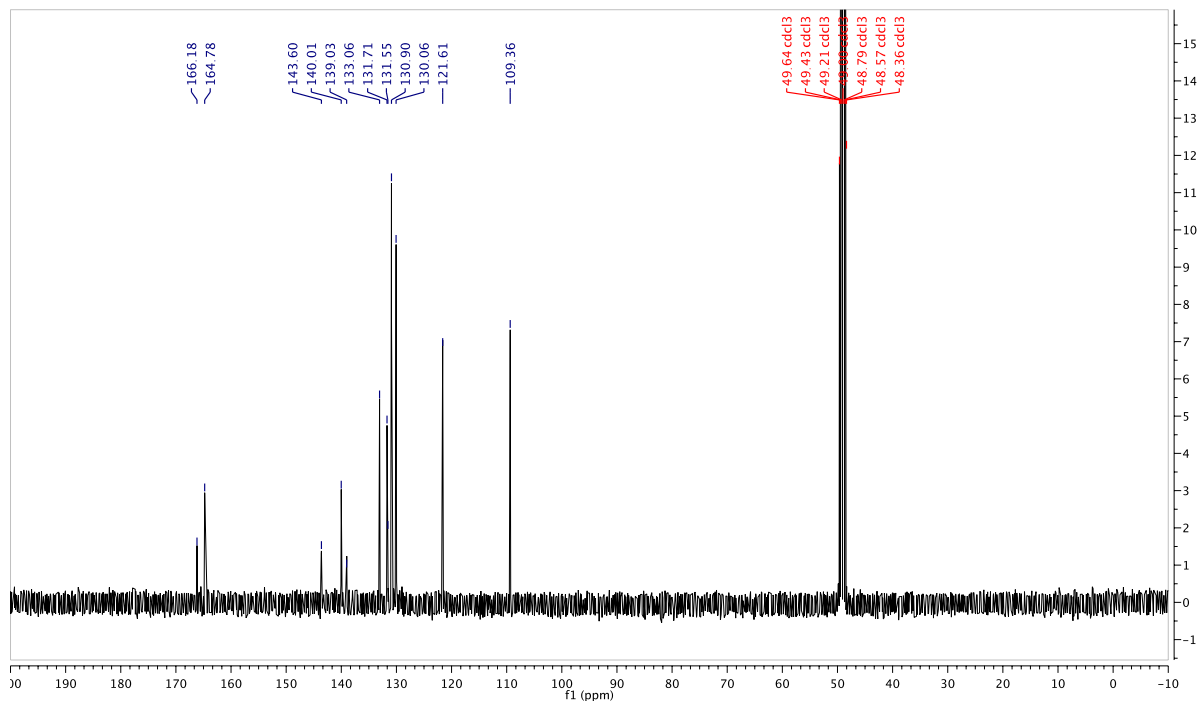
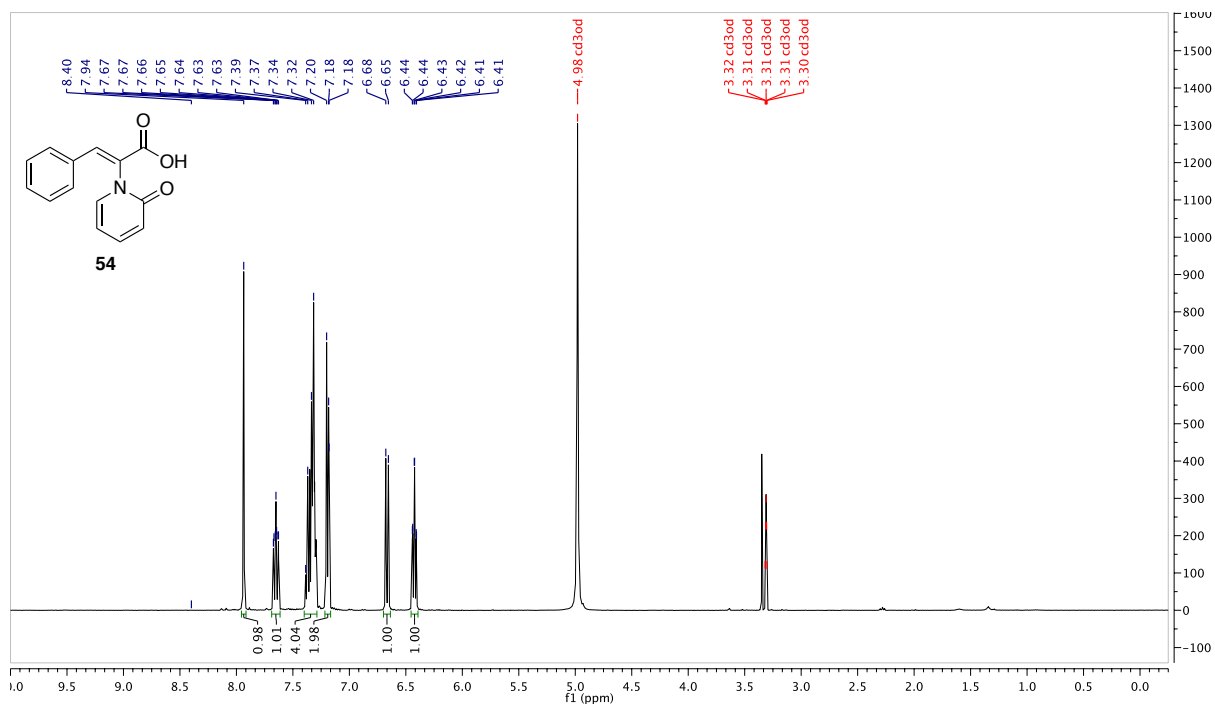


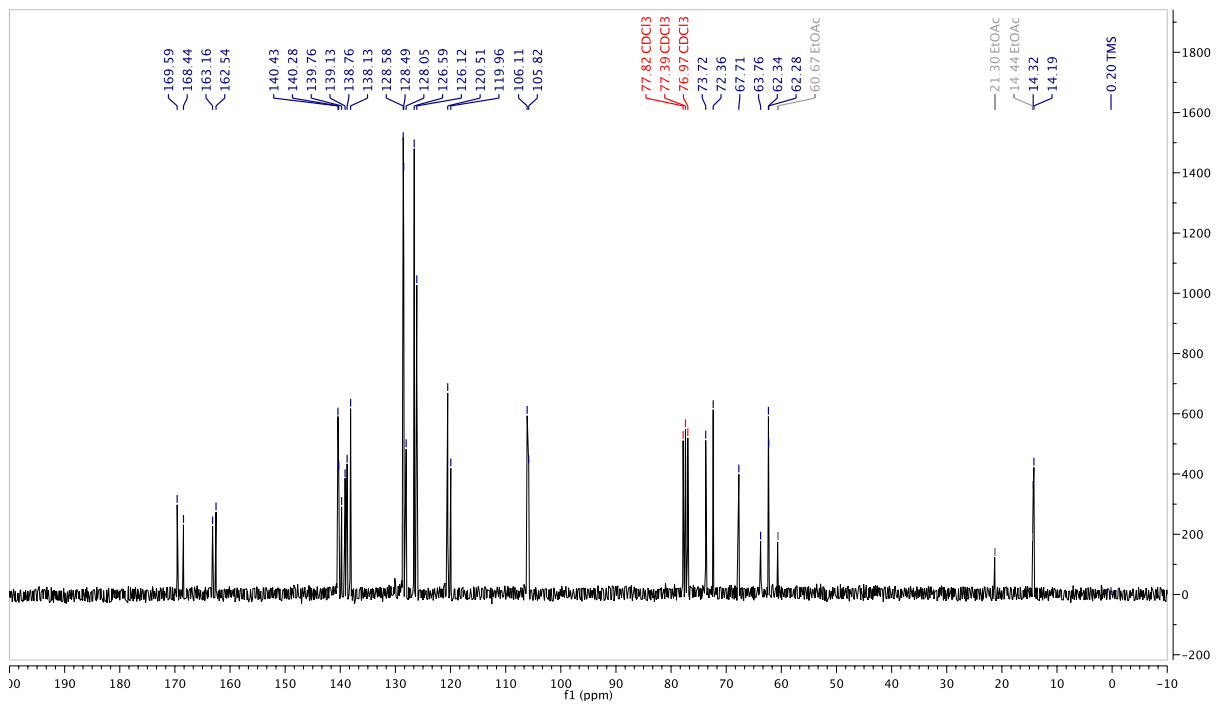
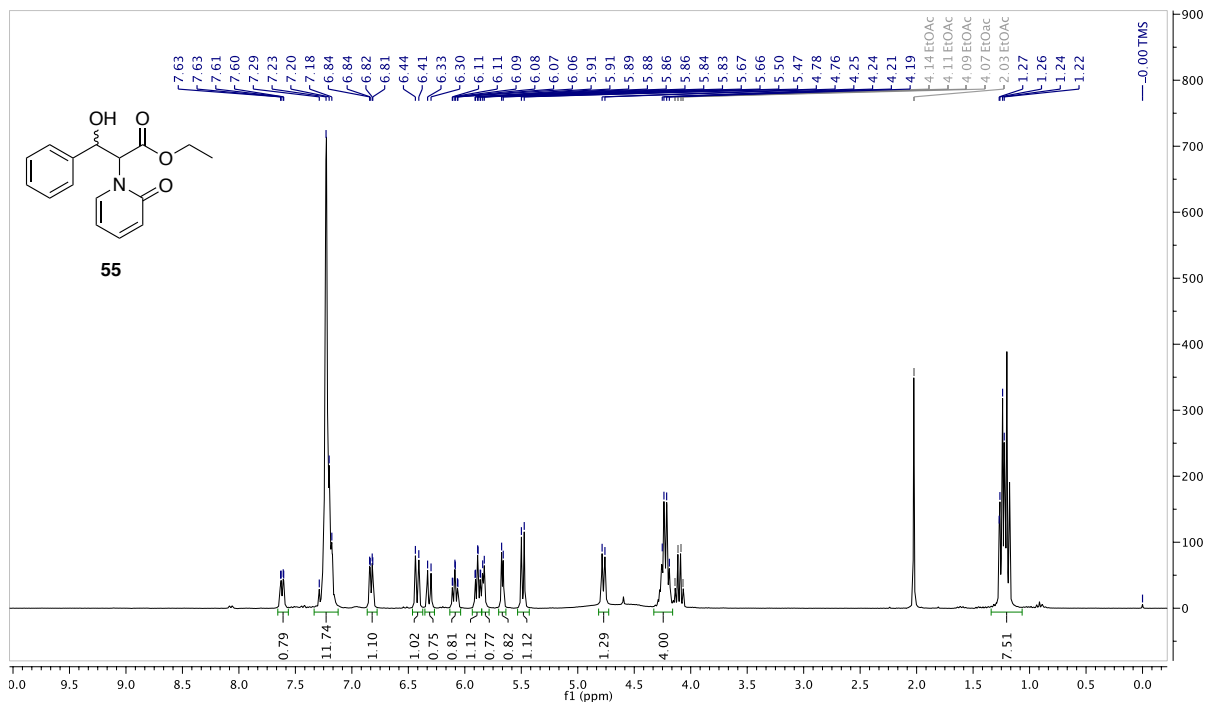


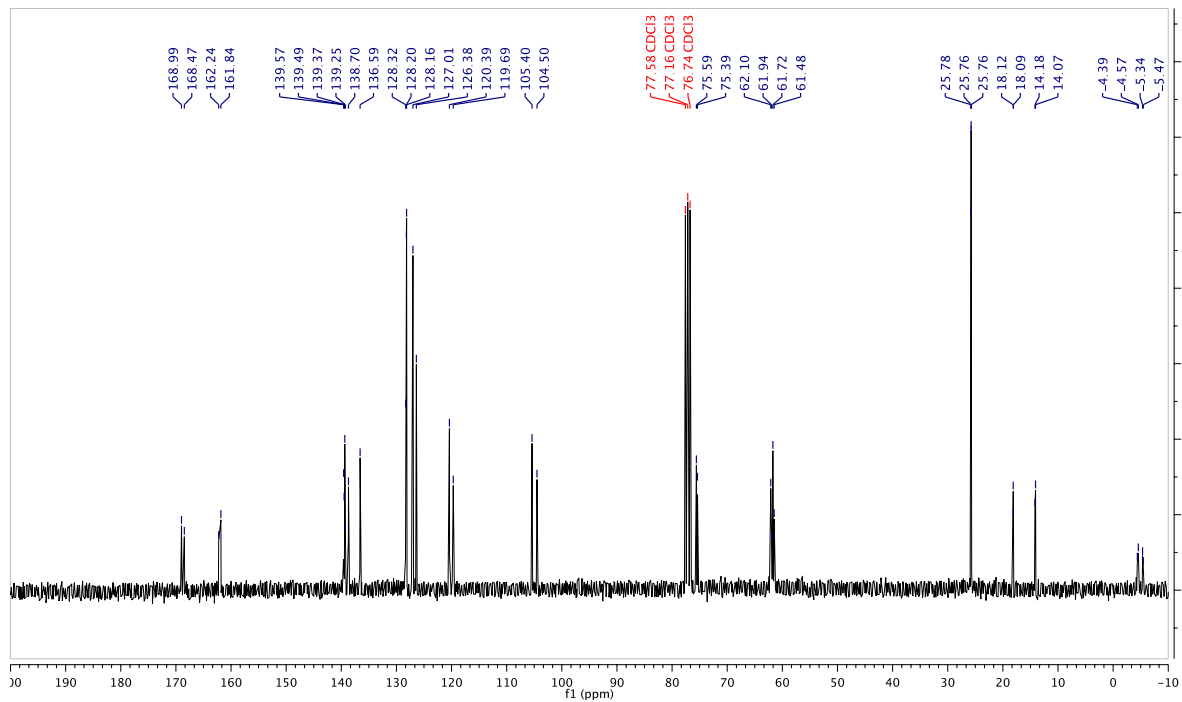
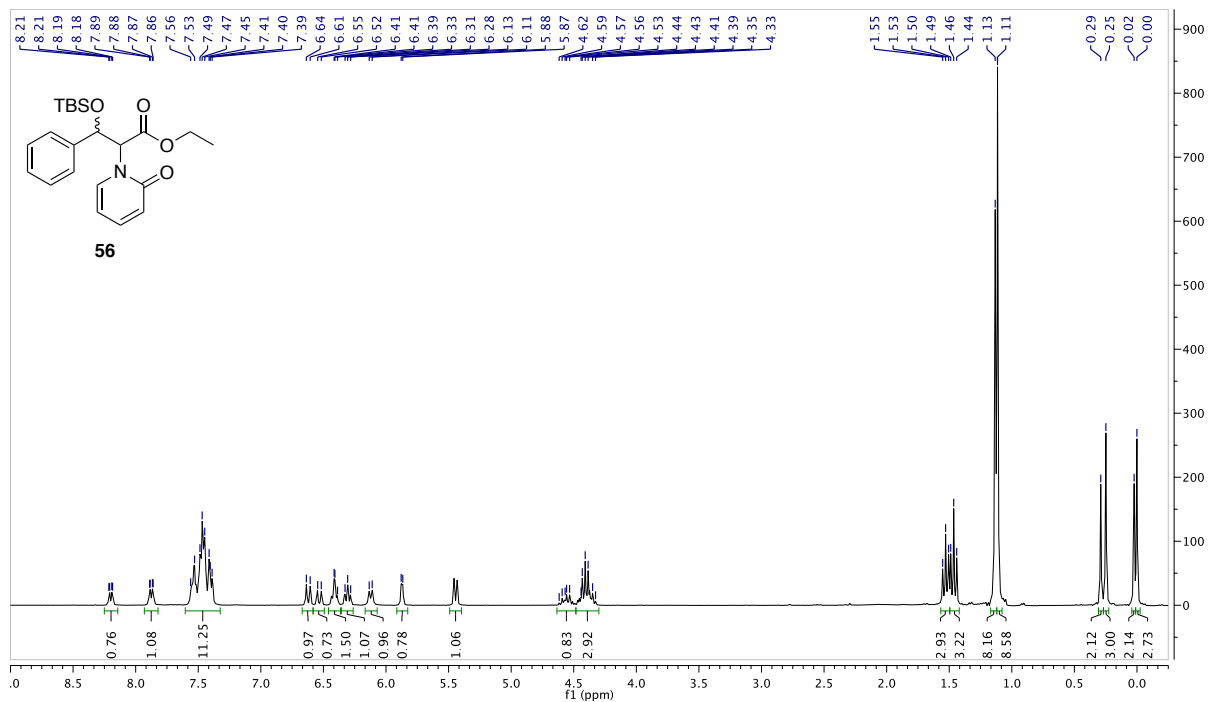


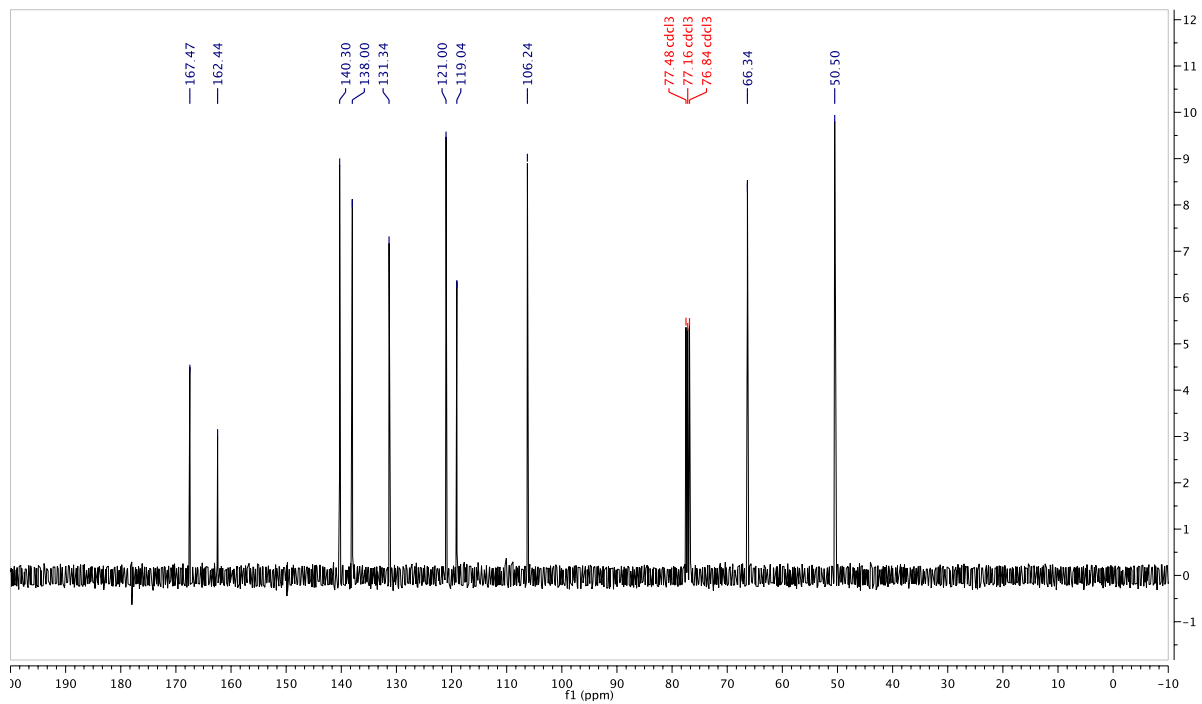
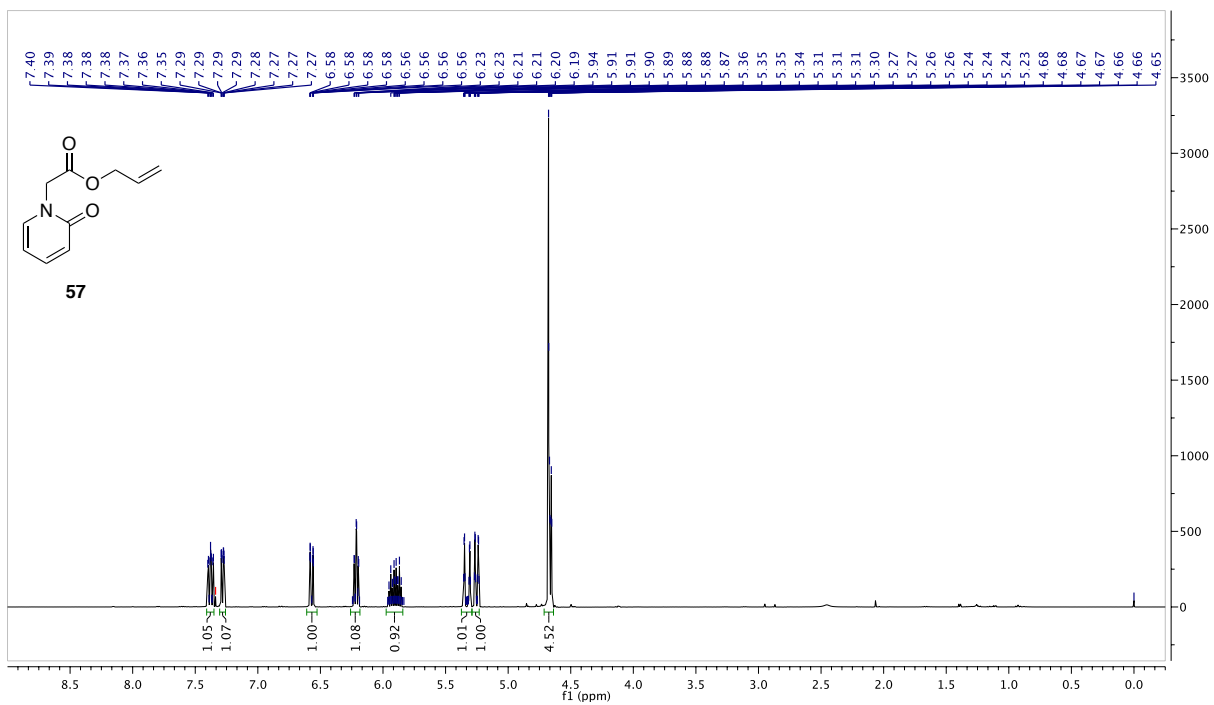


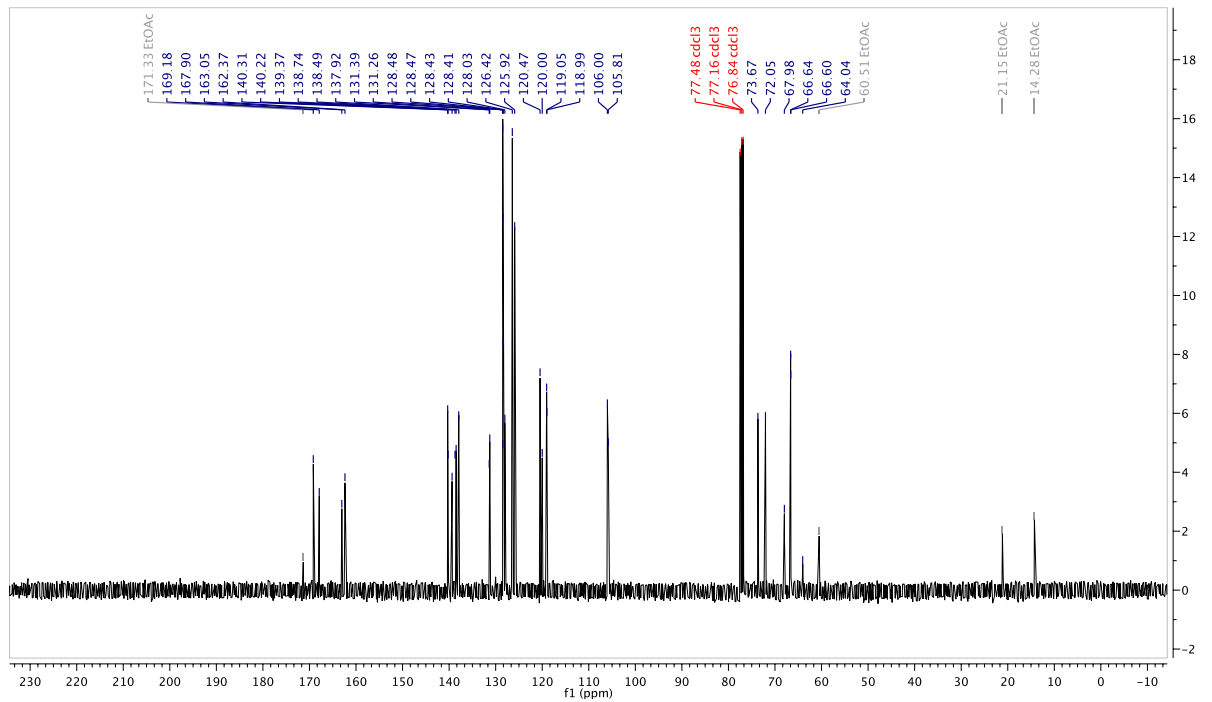
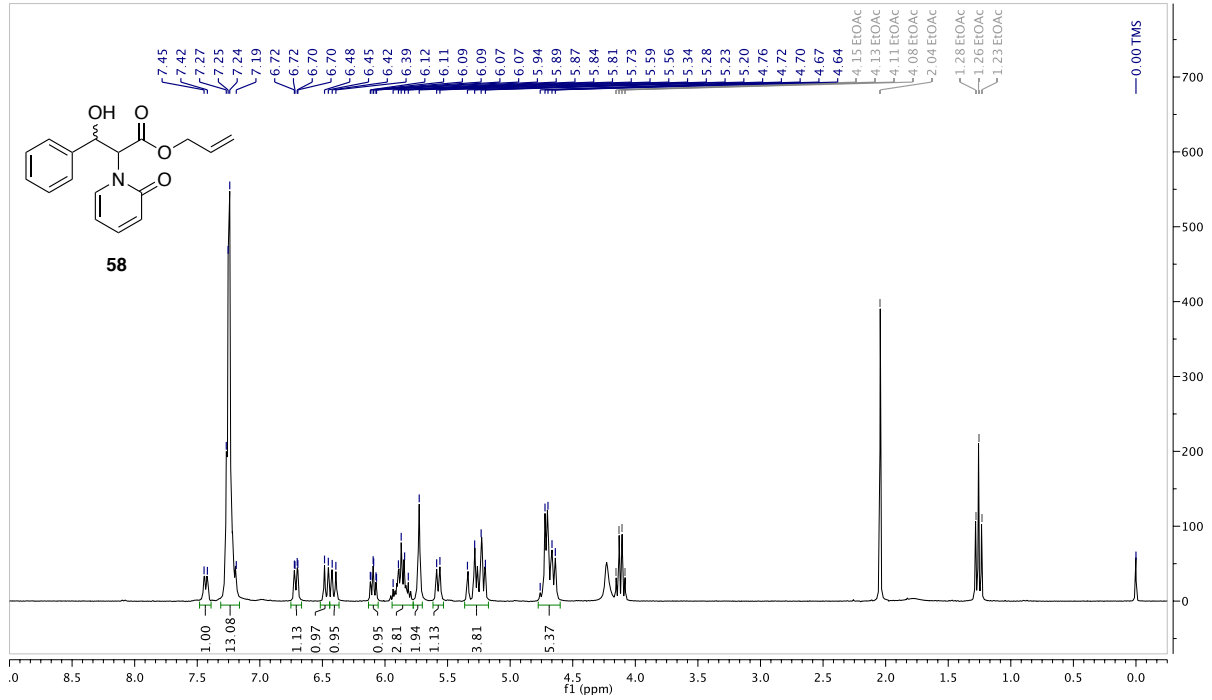


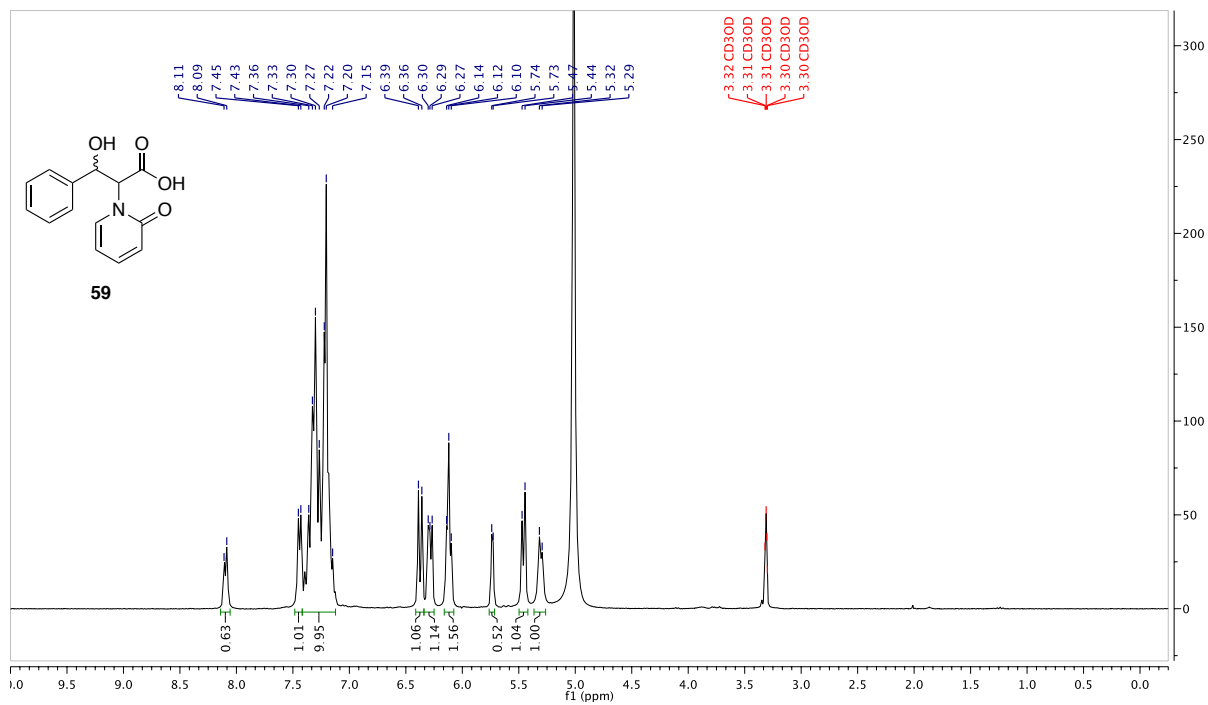


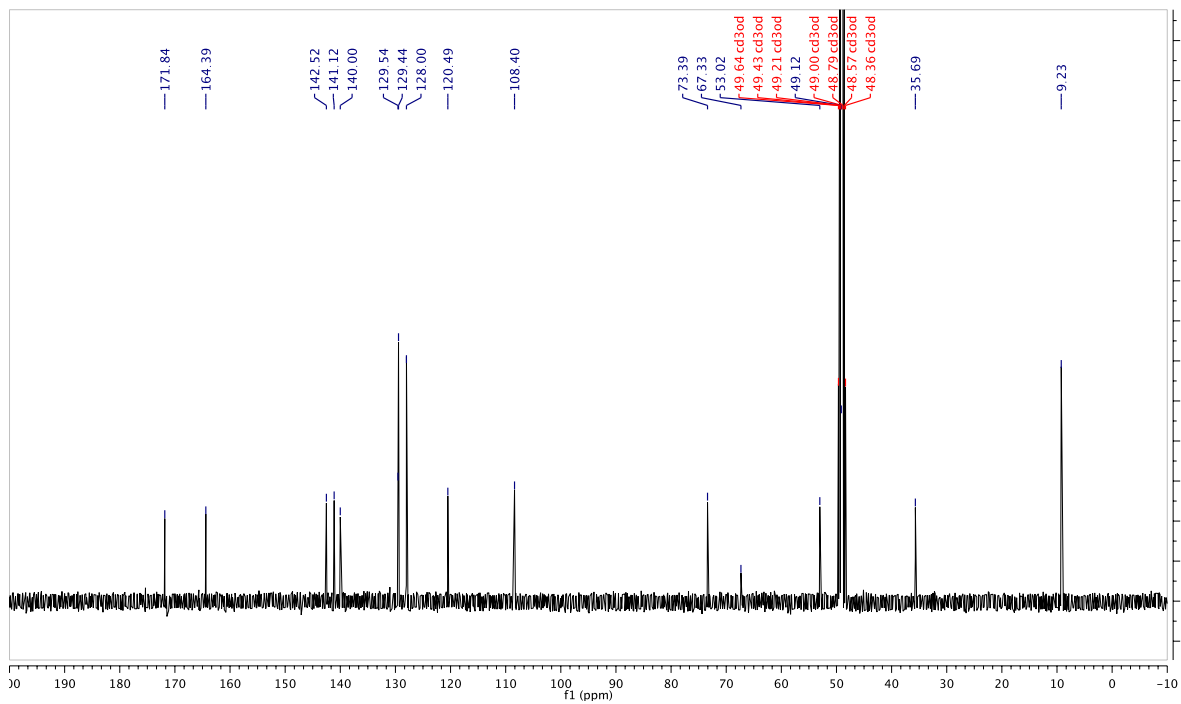
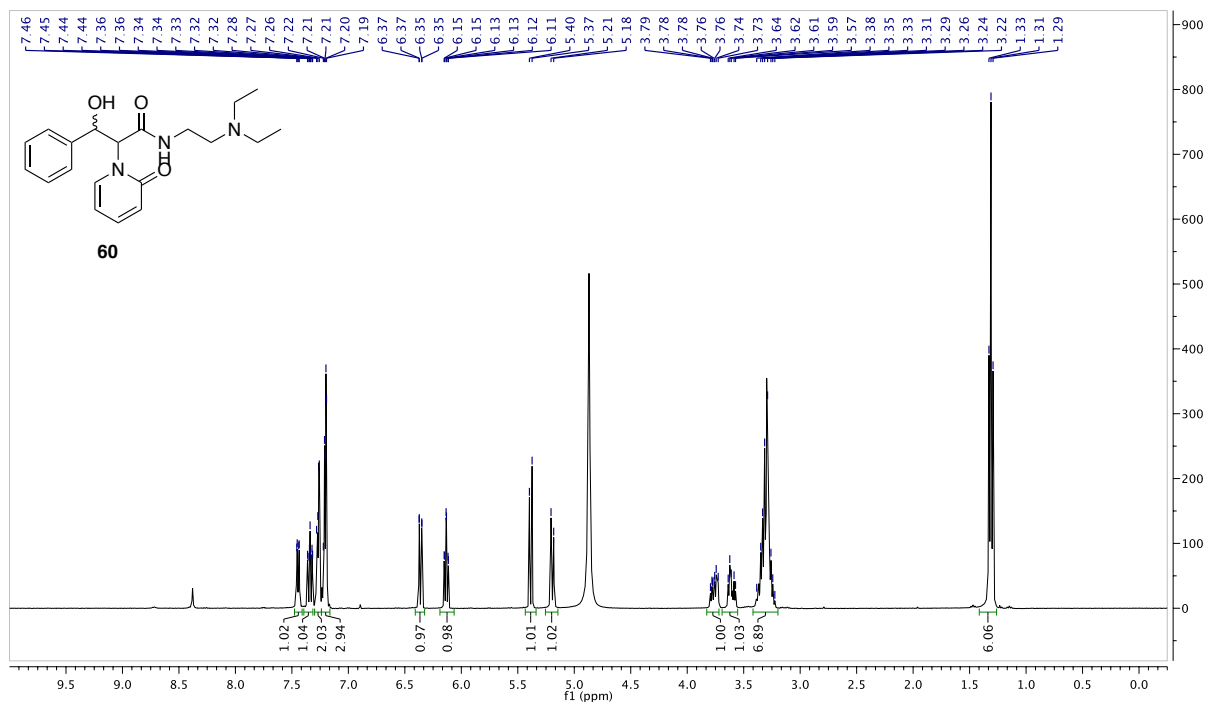


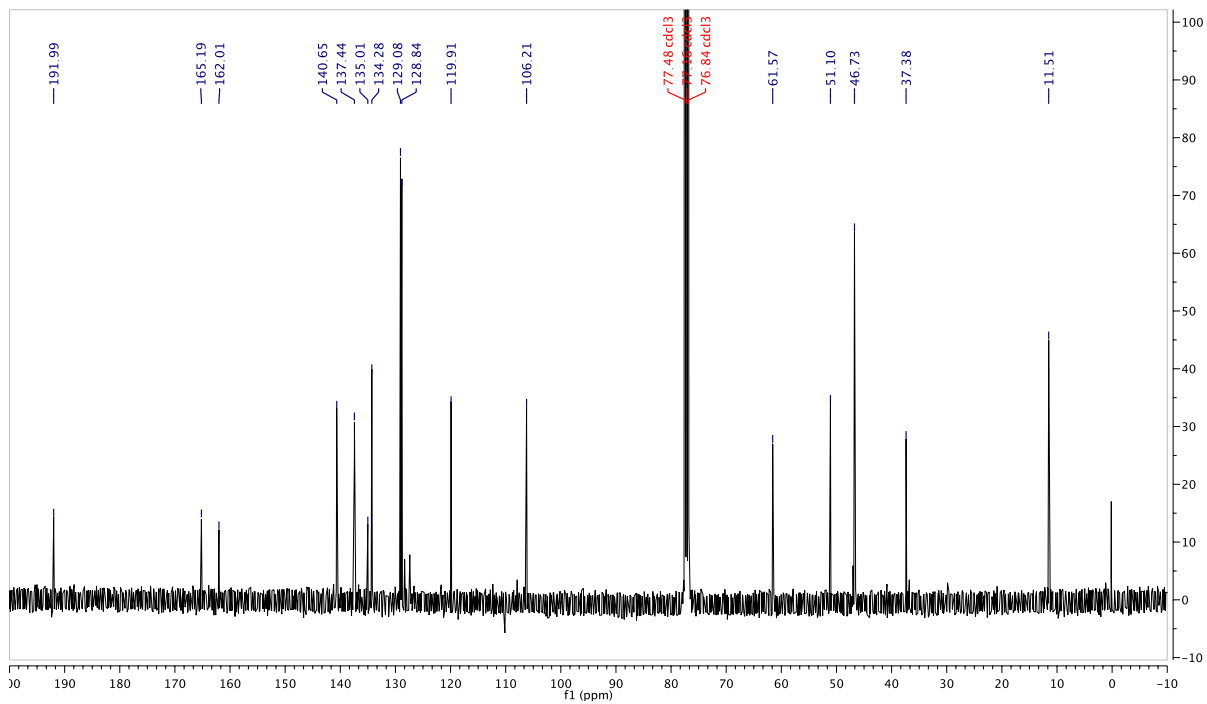
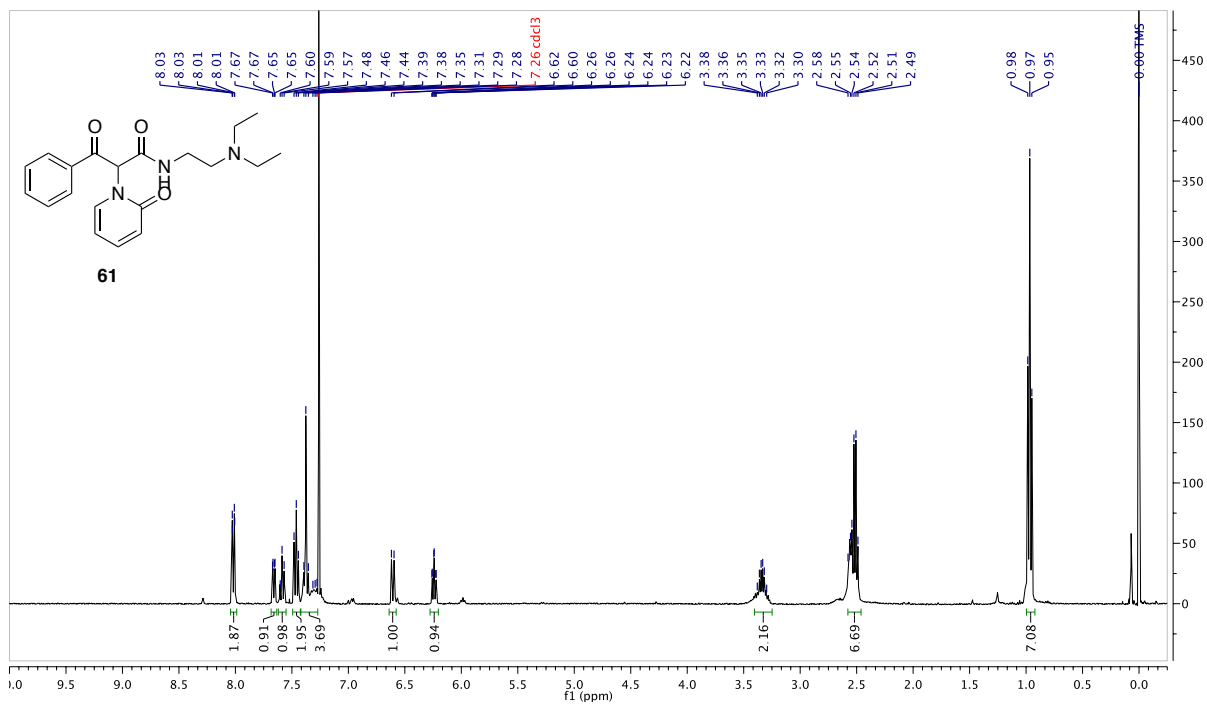




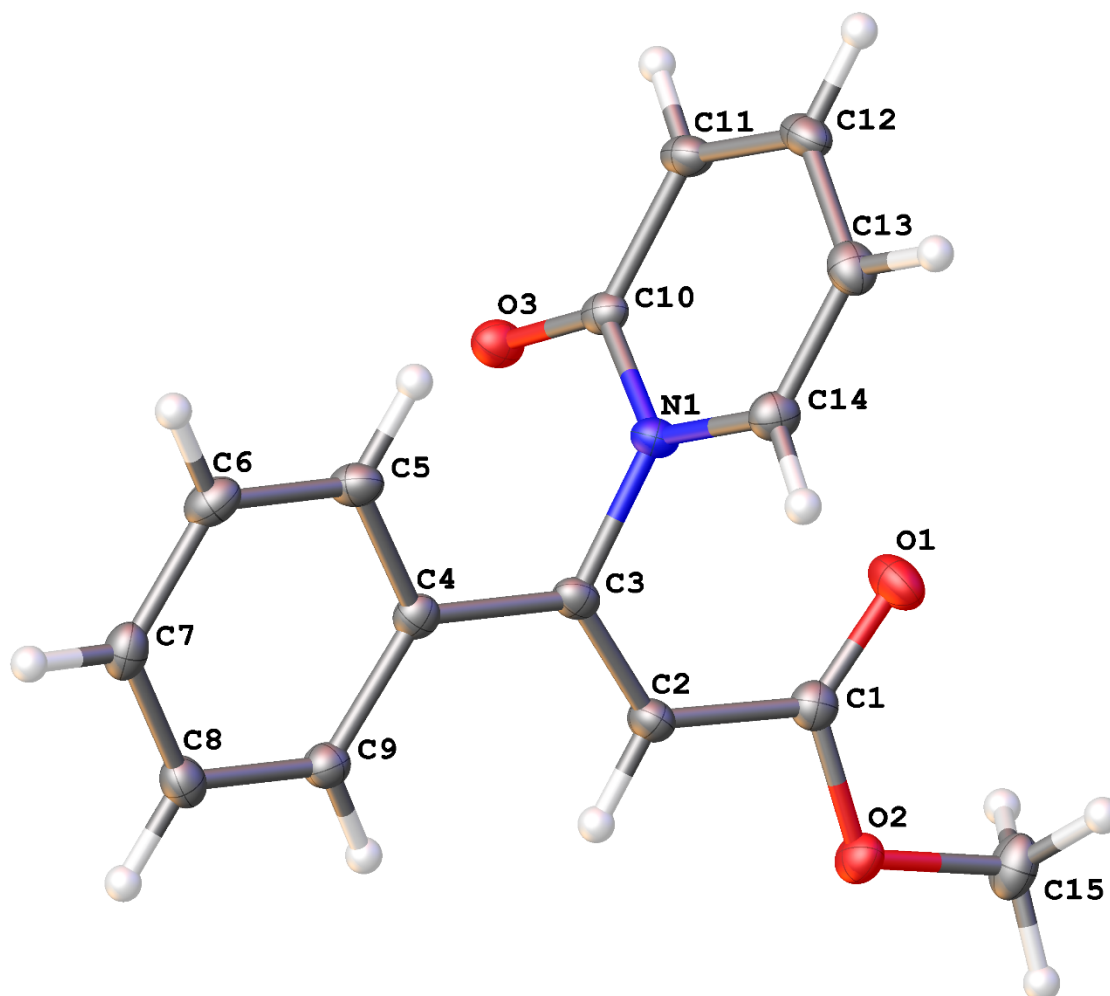






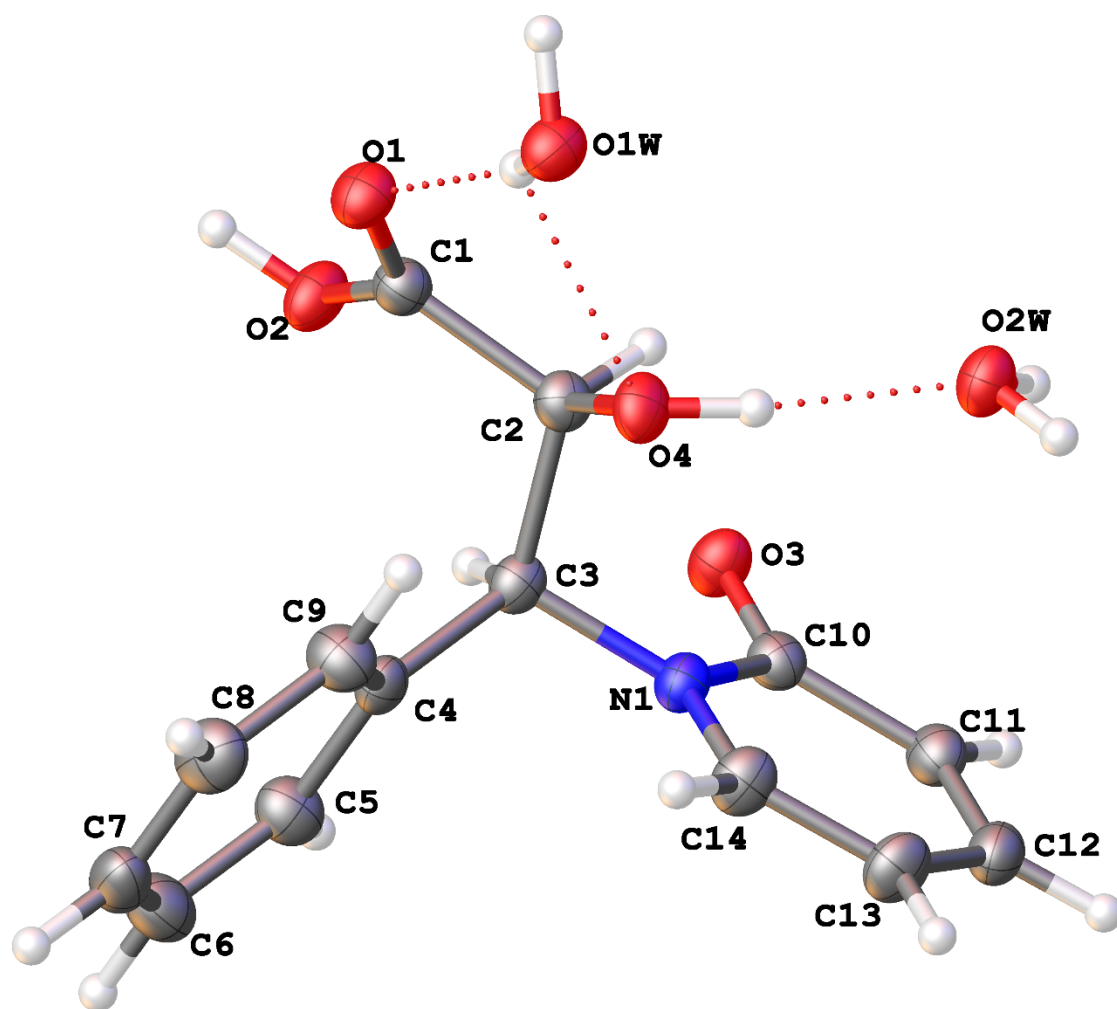


2. X-ray crystallographic structures and sample preparation



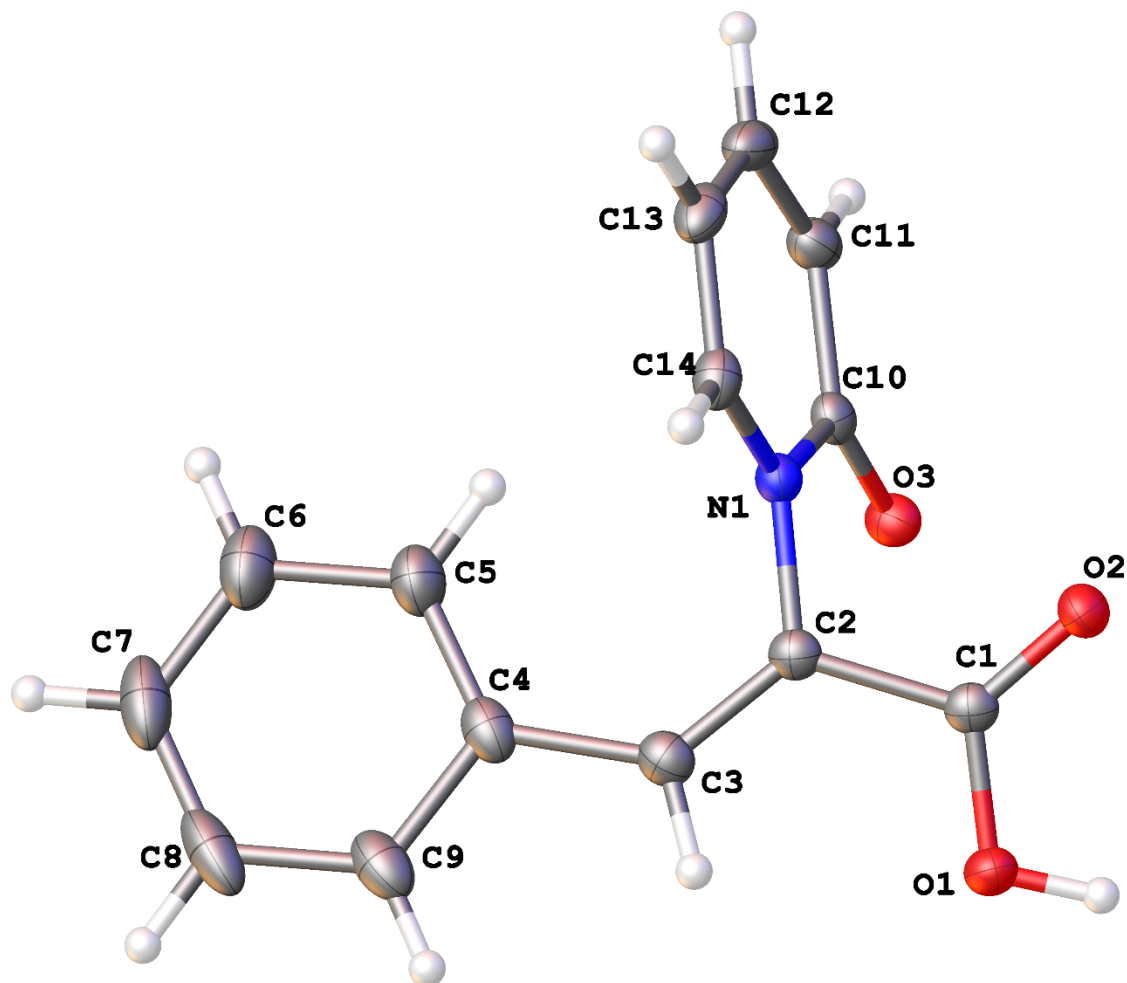
41b Structure Description:

Colorless prism crystals were obtained via slow evaporation in a saturated EtOAc solution. The dataset was collected with an Oxford SuperNova diffractometer using Mo(K α) radiation at 100K. The trans-cinnamic acid residue is essentially planar with 2-pyridinone group almost perpendicular (dihedral angle 85°) to it.



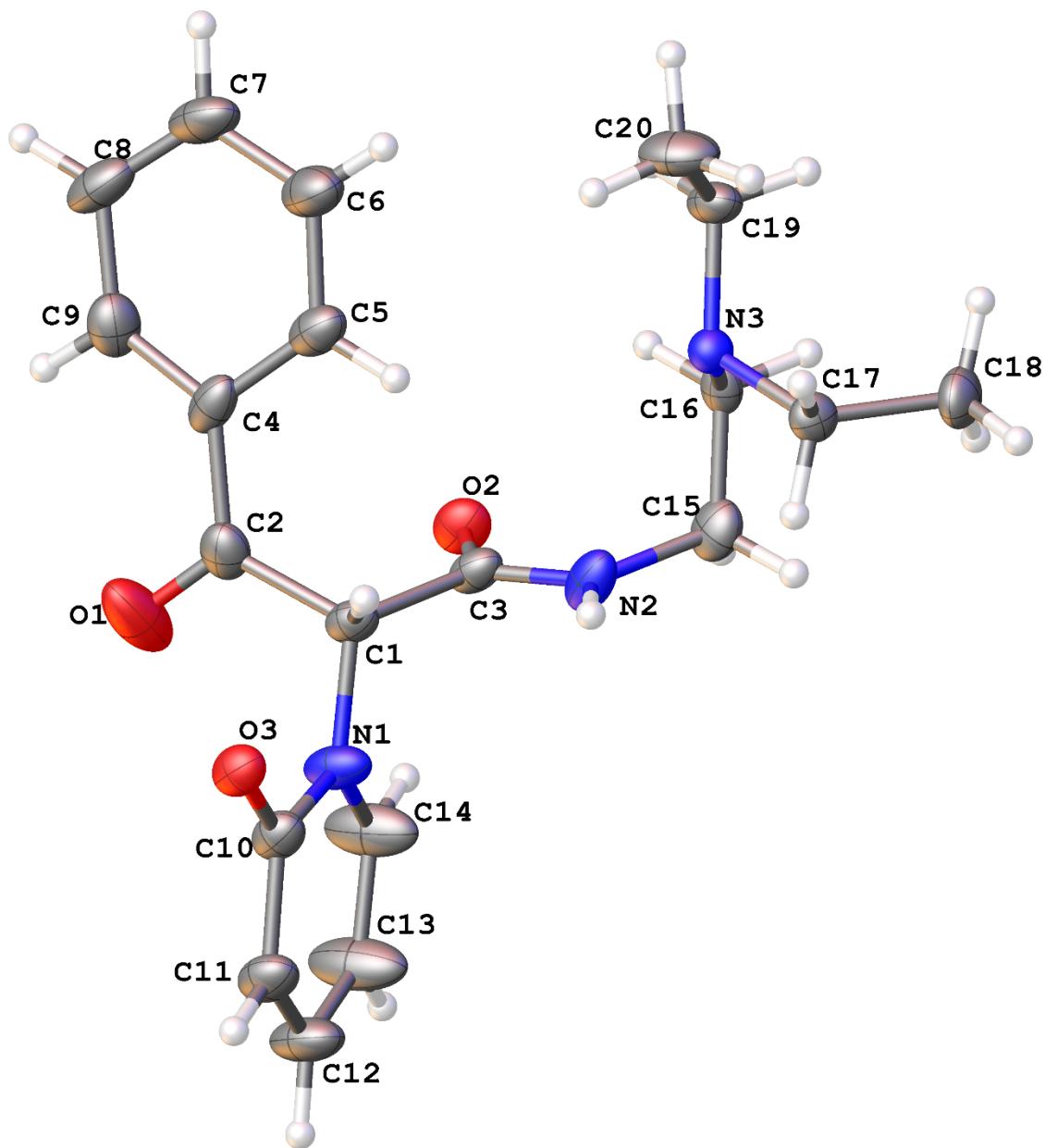
42b Structure Description:

Colorless thin plates were obtained via slow cooling **42b** (30 mg) in MeOH (0.5 mL). The compound represents a C2(S),C3(S) diastereomer (crystallizing as a racemate). The molecule has a staggered conformation along the bond C2-C3.



54 Structure Description:

Colorless tablets were obtained via slow cooling **54** (40 mg) in MeOH (0.5 mL). The cinnamic acid residue has trans-configuration with the double bond and carboxy groups well-conjugated (dihedral angle O=C-C=C 169.6°). The styrene moiety is also conjugated (dihedral angle between benzene ring and double bond 8.1°). The pyridinone group is rotated out of conjugation (dihedral angle C-N-C=C 74.8°).



61 Structure Description:

Colorless prisms were obtained by slow evaporation of **61** (3 mg) in DCE:Dioxane (300 μ L). The groups around the central tertiary carbon atom are arranged in a propeller-like order, with two α -carbonyl groups oriented *anti* relative to C-H bond and pyridinone carbonyl – *syn* (possibly – because of attraction between the carbonyl and acidic C-H group, although modern rules do not recognize 5-membered H-bonded rings). The amide group is in trans-conformation. The terminal NEt₂ group is orientationally disordered over two positions with equal population. The nearby phenyl group is also disordered, as a consequence. It is possible that the disorder is a result of averaging of more complex supersymmetric structure, but corresponding extra reflections were too weak to explore this possibility.

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