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Santa Barbara

Efforts Towards the Total Synthesis of (–)-Lycopodine

A thesis submitted in partial satisfaction of the

requirements for the degree Master of Science in Chemistry

by

Cristian Ramirez

Committee in charge:

Professor Armen Zakarian, Chair

Professor Javier Read de Alaniz

Professor Yang Yang

September 2024

The thesis of Cristian Ramirez is approved.

Yang Yang

Javier Read de Alaniz

Armen Zakarian, Committee Chair

September 2024

Efforts Towards the Total Synthesis of (–)-Lycopodine

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Cristian Ramirez

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I could not have accomplished what I have without the love and support of my family and friends. Thank you.

ABSTRACT

Efforts Towards the Total Synthesis of (–)-Lycopodine

by

Cristian Ramirez

The total synthesis of (–)-lycopodine, a member of the Lycopodium alkaloid family, has been a longstanding challenge in synthetic organic chemistry, with many previous efforts yielding primarily racemic mixtures. In this thesis, I present a novel synthetic approach that introduces a chiral center at the very first step, thereby steering the synthesis towards enantioselectivity from the outset. A key feature of our methodology is an unprecedented Grignard addition, which plays a critical role in constructing the core framework of (–)-lycopodine. Our synthesis has progressed to an advanced intermediate, positioned just one step away from the final product. This work represents a significant advance in the stereocontrolled synthesis of *Lycopodium* alkaloids, providing new insights and strategies for the total synthesis of complex natural products.

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Chapter 1: Introduction and Background

1.1 Introduction

The genus *Lycopodium* comprises over 450 species inhabiting diverse environments such as marshlands, coniferous forests, and mountainous regions. These plants are characterized by their flowerless, extensively branched stems with small, needle-like or scale-like leaves. Known as clubmosses, lycopods reproduce asexually via spores and possess an underground sexual phase that produces gametes, alternating with the spore-producing plant phase. As remnants of prehistoric ferns, lycopods have fossil records dating back to the early Devonian Period, over 300 million years ago[1-4].

Given their ancient origins and broad distribution, it is unsurprising that various *Lycopodium* species were utilized in traditional folk medicine. In European medicine, these plants were considered nontoxic and were sometimes prepared as a tea to treat liver inflammation, nosebleeds, intestinal irritation, and kidney disorders. Specifically, a mixture of *Lycopodium clavatum* and couch grass was used to create a tea for addressing skin irritations and acne.

Native American tribes also highly valued lycopods as herbal remedies. The Blackfoot used them to treat pulmonary diseases, while the Iroquois believed in the plant's ability to induce pregnancy. The Upper Tanana Indians employed the whole plant of *Lycopodium selago* for headache relief[5].

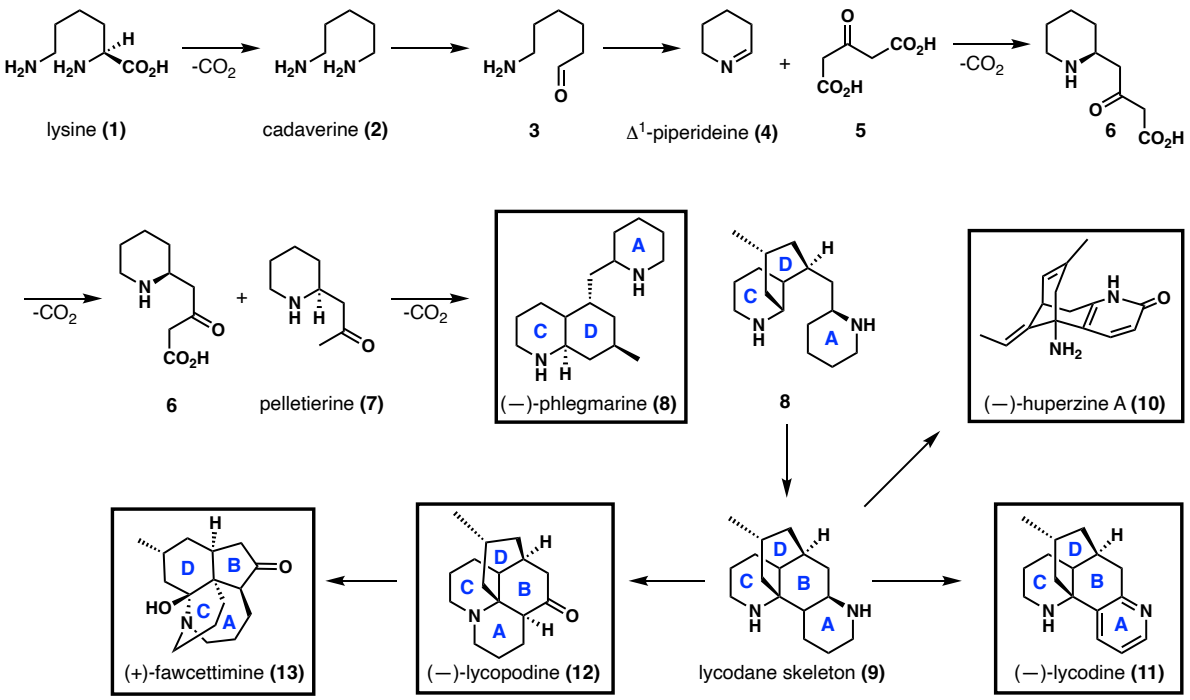
Despite their historical use, lycopods are no longer commonly employed as herbal remedies, as their side effects often outweigh their benefits. However, the genus remains of significant interest in various scientific fields. Biologists are intrigued by lycopods as ancient

relics from the Carboniferous period, offering insights into prehistoric times. Phytochemists are fascinated by the isolation of biologically and structurally complex alkaloids from these seemingly simple plants, raising questions about their synthesis of such diverse metabolites. Medicinally active constituents, such as huperzine A—a compound you might find in local grocery stores—attract attention from the pharmaceutical community. Finally, synthetic chemists are drawn to the complex structural features of the alkaloids isolated from these clubmosses[6-9].

1.2 Background

Lycopodium alkaloids are comprised of structurally diverse natural products with complex polycyclic skeletons. They are nitrogen-containing heterocyclic compounds with either a tricyclic or tetracyclic body composed of the basic skeletons C11N, C15N2, and to a lesser extent C11N, C15N2, C22N2 and C27N3 alkaloids. Different levels of oxidation on these polycyclic cores are what differentiates the various natural products within this family[10].

The chemical interest in these alkaloids started after the isolation of lycopodine from *L. complanatum* by Bödeker in 1881[11]. Later the likes of Orechoff, Muszynski, Achematowicz, Uzieblo, Marion and Manske furthered the investigation into the isolation and characterization of these alkaloids within the *Lycopodium* family[12]. Over the next decades, interest in the isolation, characterization, and biological evaluation of these alkaloids increased with many chemists, particularly coming from the Canadian laboratory of W. A Ayer, pursued the total synthesis of these alkaloids. Ayer divided the *Lycopodium* alkaloids into four structural classes according to their characteristics: Lycopodine class, Lycodine class, fawcettimine class, and the miscellaneous group. Lycopodine, lycodine, fawcettimine



Scheme 1.1. Proposed biosynthetic pathway of *Lycopodium* alkaloids

and phlegmarine are the representative compounds within this division of classes[13].

During the 1980s, research on the *Lycopodium* family focused largely on isolating new metabolites, leading to the identification of several structurally intriguing natural products. However, detailed information on the biosynthetic pathways of *Lycopodium* alkaloids remained scarce, primarily due to the challenges associated with cultivating clubmosses. Spenser and colleagues conducted feeding studies using ^{13}C- and ^{14}C-labeled substrates and alkaloid precursors on lycopods in their natural habitats, analyzing the isotope content of the alkaloids. While they could not definitively identify the enzymes involved in the biosynthetic pathways, their work remains significant for guiding future investigations[14-19].

Although the focus of the thesis rests on the chemical synthesis of lycopodine, I will briefly talk about the proposed biosynthetic pathway. **Scheme 1.1** shows the proposed biosynthetic pathway in its abbreviated form. The route starts with the decarboxylation of

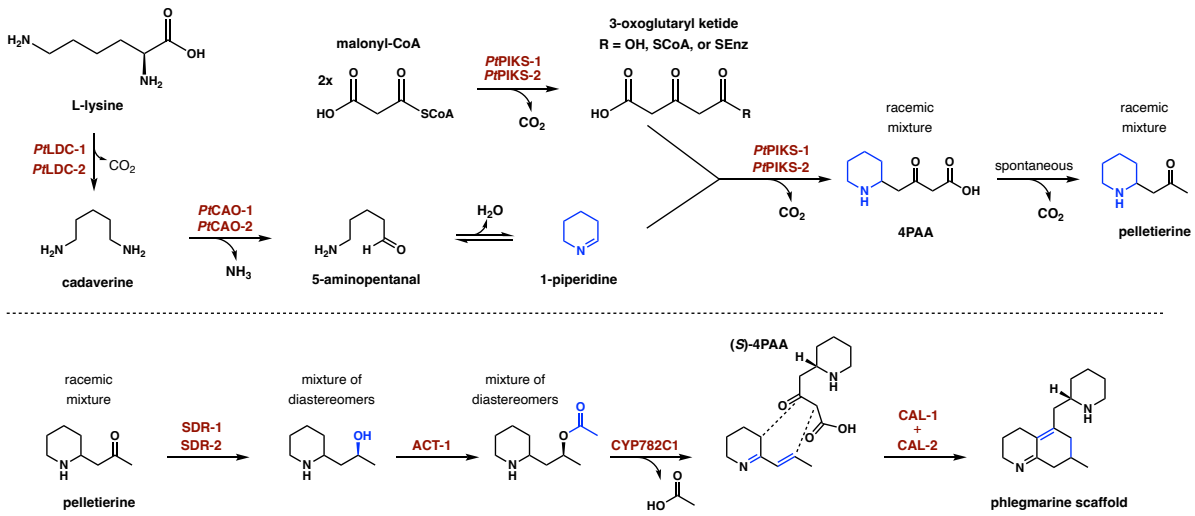


Figure 1.2. Biosynthetic proposal for the early chemical transformations in Lycopodium alkaloid biosynthesis.

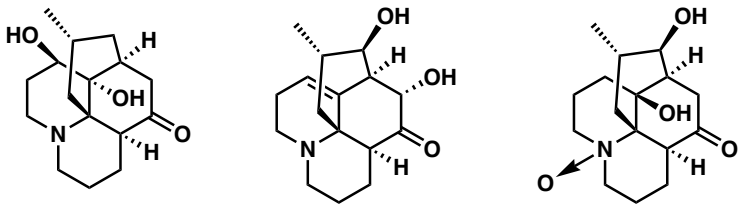
lysine **(1)** to give cadaverine **(2)**. Δ^1-piperideine **(4)** is generated from the 5-aminopentanal **(3)**, likely via the enzyme diamine oxidase. Next, the imine is converted to pelletierine **(7)** via the coupling to acetonedicarboxylic acid **(5)**, or the corresponding CoA derivative, followed by the decarboxylation of the intermediary beta-ketoester **(6)**. Pelletierine then reacts with **(6)** and generates a general intermediate, phlegmarine **(8)**, in the biosynthesis of all *Lycopodium* alkaloids. The stage is then set for the formation of all structurally diverging alkaloids after the cyclization of phlegmarine to the tetracyclic lycodine skeleton **(9)**.

More recently, the Sattely lab at Stanford recently investigated the biosynthesis of huperzine and related natural products to gain a deeper understanding of the largely unexplored mechanisms by which clubmosses produce these lysine-derived alkaloids[34,35]. By integrating metabolic profiling with transcriptomics, they identified a developmentally regulated set of biosynthetic genes responsible for the production of lycopodium alkaloids. This work enabled the biosynthetic reconstruction and functional characterization of key enzymes involved in both the initiation and termination of medicinal alkaloid biosynthesis.

Their findings, summarized in **Scheme 1.2**, culminate in the formation of a phlegmarine scaffold.

1.3 Previous Total Synthesis of Lycopodine

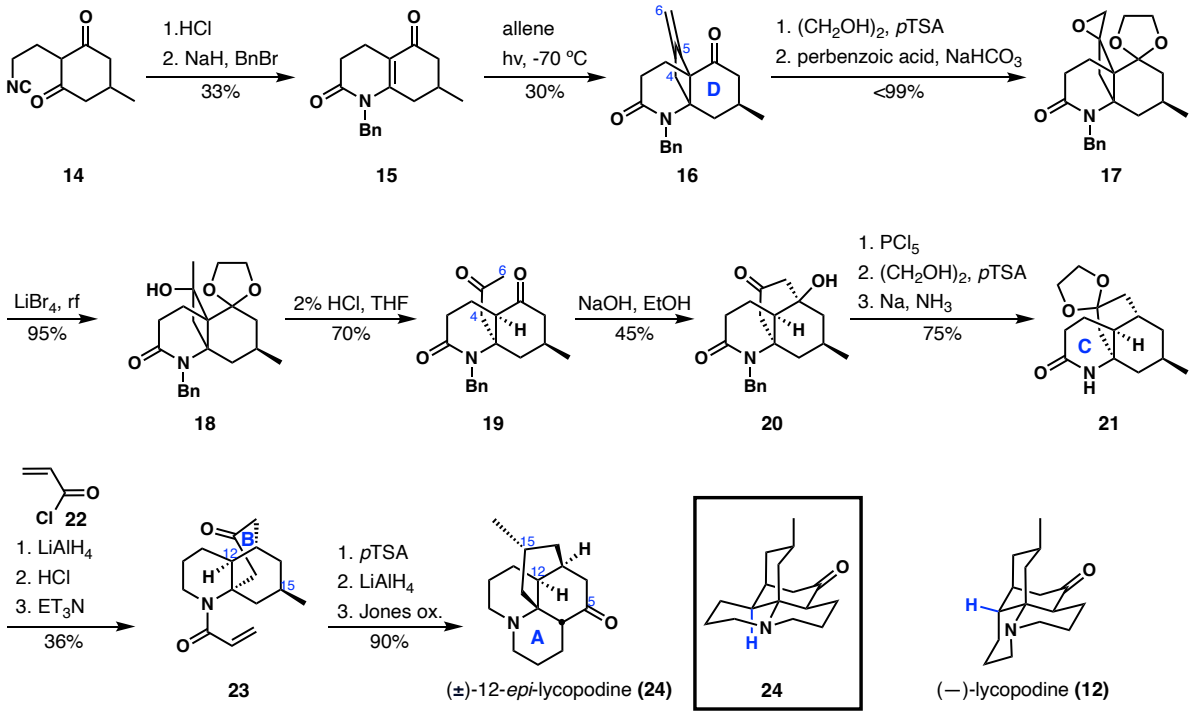
The lycopodine class is the largest and most widely spread group of known *Lycopodium* alkaloids with over 156 alkaloids isolated from the whole plant. The constituents are characterized by four connected six-membered rings, with rings A and C being a *cis* quinolizidine ring system (connections at C-4 and C-13). The carbonyl groups that decorate the alkaloids are typically found on the B ring at C-5 and C-6. Lycopodine, the representative compound of the class, possessed a few key features. Its C-4 and C-6 positions alpha to the carbonyl as well as the H atoms at the tertiary C-7 are easily oxidized to hydroxyl groups such is the case with 11-beta-hydroxy-12-epilycodoline **(97)** and 8-beta-hydroxylycoposerramine K **(98)**. Its N atom is highly nucleophilic and easily oxidized as such is the case with miyoshianine C **(99)**.



97 **98** **99**

Figure 1.1. Lycopodine alkaloids

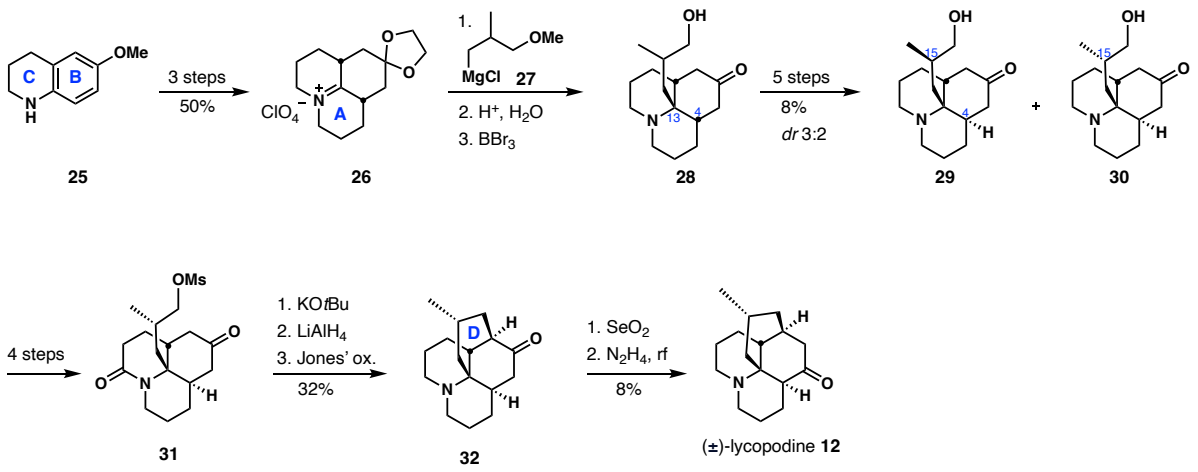
Several key milestones are noteworthy in the study of *Lycopodium* alkaloids. The first significant achievement occurred in 1967 when Wiesner reported the synthesis of 12-*epi*-lycopodine, marking the first successful preparation of the tetracyclic skeleton of this important natural product. This seminal work was followed in 1968 by Stork and Ayer, who completed the first total syntheses of racemic lycopodine. **Scheme 1.3** describes the synthesis of 12-*epi*-lycopodine. This epimer of the natural product was first described by Ayer, who



Scheme 1.3. Wiesner's synthesis of (±)-12-*epi*-lycopodine

isolated the unnatural alkaloid along with the natural product lycopodine **(12)** upon catalytic hydrogenation of anhydrolycodoline[22].

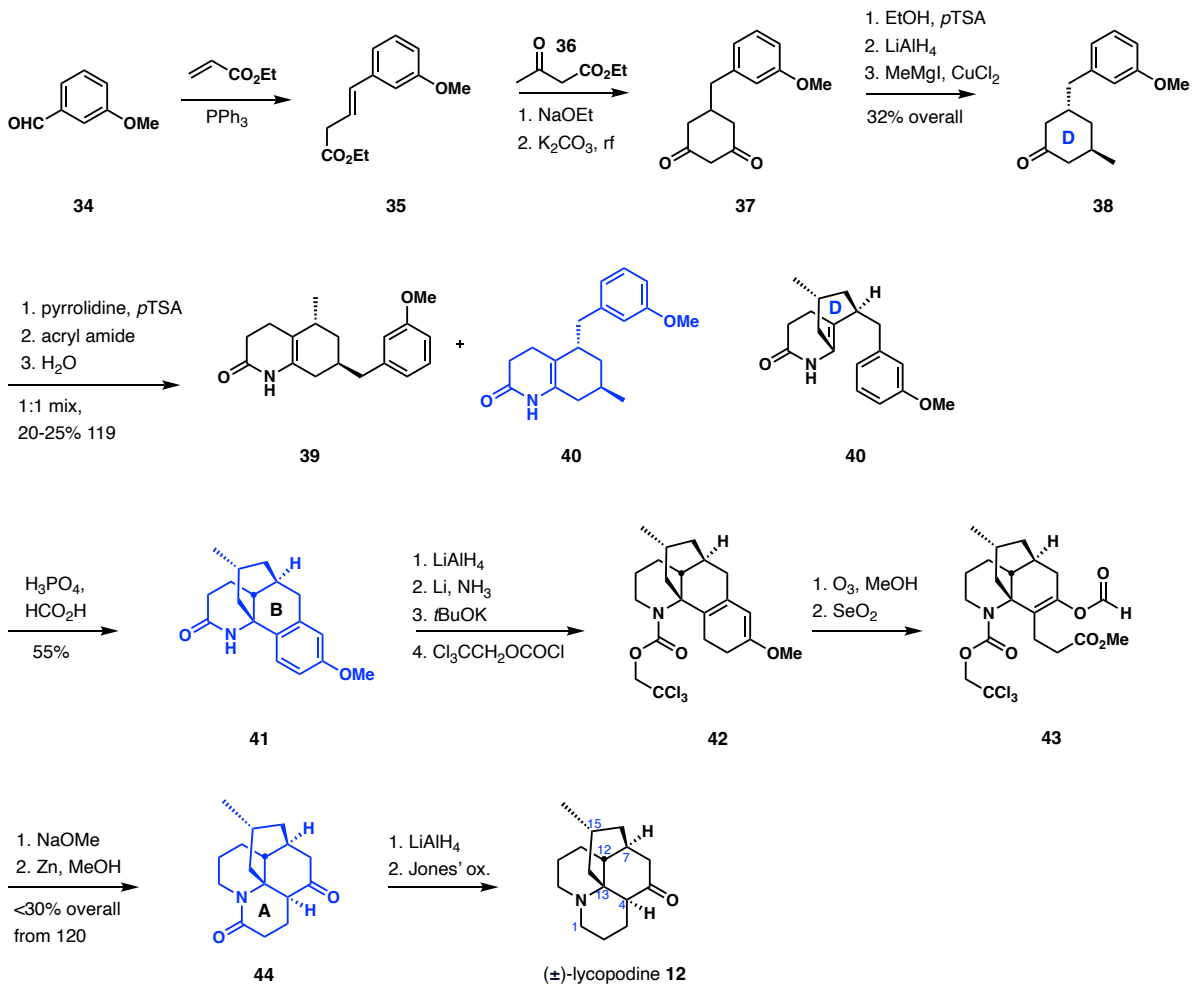
The route begins with the bicyclic enone **(15)** being generated via hydrolysis and a subsequent condensation reaction of the cyanoethylation product of dihydrooricinol **(14)** and *N*-benzylation of the amide. Then a [2+2]-photocyclization reaction with allene and the unsaturated ketone gives rise to the bridged tricyclic ring system **(16)**. The *exo*-methylene functionality **(17)** was introduced via ketalization followed by epoxidation. Lithium borohydride reduction was utilized to introduce the tertiary alcohol **(18)**. With the precursor for the retro-aldol addition in hand, **(18)** was exposed to acidic conditions wherein liberation of the ketone and simultaneous mediated retro-aldol addition gave compound **(19)**. This intermediate was then treated with a dilute solution of sodium hydroxide in ethanol to construct the B-ring of the alkaloid. To access lactam **(21)**, the bridgehead hydroxy in **(20)**



Scheme 1.4. Ayer's synthesis of (±)-lycopodine

was converted into the corresponding chloride then ketalization and reduction with sodium in a mixture of ether and liquid ammonia were performed. A reaction with lithium aluminum hydride followed by exposure to dilute hydrochloric acid yielded the corresponding amine, which was then reacted with acryloyl chloride **(22)** to give the compound **(23)**. The reaction between the enolized ketone in **(23)** with the Michael acceptor gave the lycopodine skeleton. Finally, a reduction with lithium aluminum hydride and reoxidation of the secondary alcohol resulted in the formation of 12-*epi*-lycopodine **(24)**.

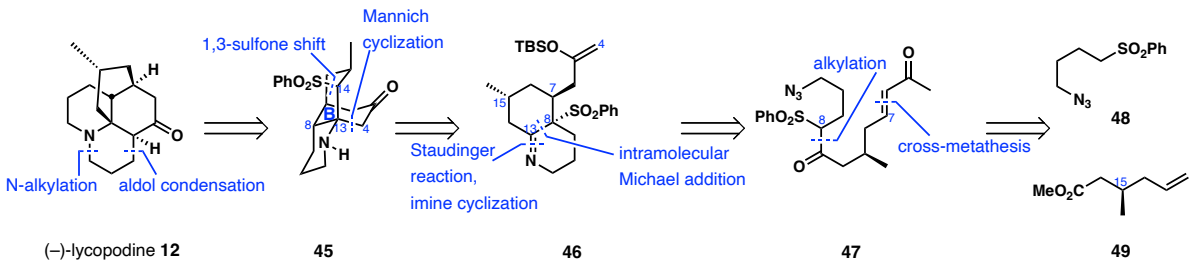
Next we will explore Ayer's synthesis (1968) of lycopodine[23] which is outlined in **Scheme 1.4**. The route begins with the conversion of thallin **(25)** to the tricyclic iminium salt **(26)** in three synthetic operations. This iminium salt was then treated with the Grignard reagent **(27)** to afford a stereoselective addition and yield the intermediate **(28)** possessing a quaternary carbon handle. Epimerization at C4 was achieved in 5 steps after which the C15 epimers **(29)** and **(30)** were successfully separated. The alcohol **(30)** was converted to the lactam **(31)** before being exposed to basic conditions to induce the desired intramolecular attack of the enolate anion onto the mesylate completing the construction of the final ring in



Scheme 1.5. Stork's synthesis of (±)-lycopodine

lycopodine. With the four rings set, the lactam was reduced and the newly generated C-6 hydroxy was reoxidized to the ketone **(32)**. Finally, racemic lycopodine **(33)** was isolated after selenium dioxide-mediated oxidation of C-5 followed by the reduction with hydrazine hydrate in diethylene glycol.

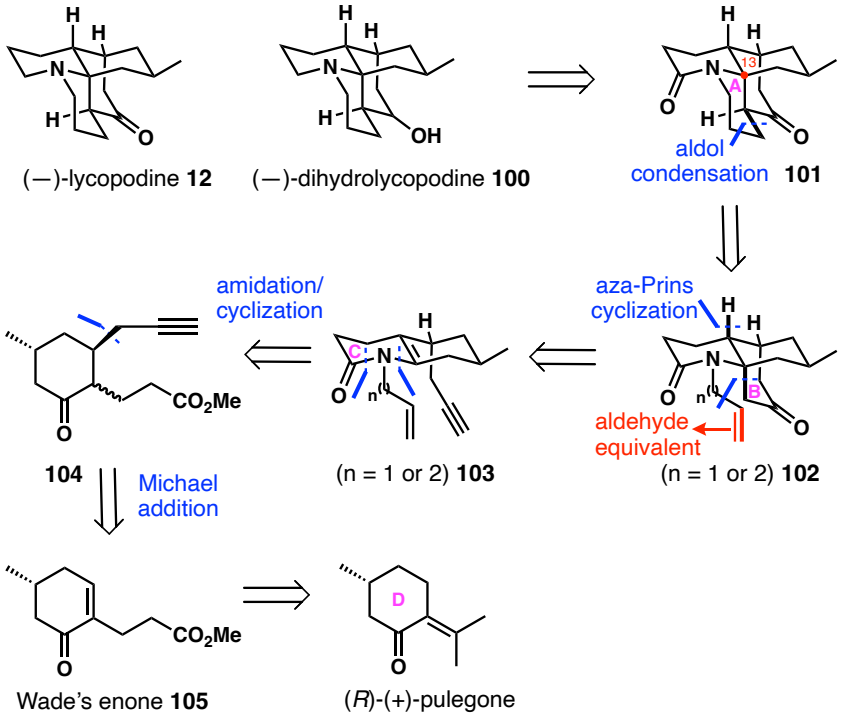
Stork's route towards lycopodine[24] begins (**Scheme 1.5**) with the reaction between *m*-methoxybenzaldehyde **(34)** and ethyl acrylate in the presence of triphenylphosphine to yield the beta,gamma-unsaturated ester **(35)**. After isomerization of the double bond a Michael addition of ethyl acetoacetate **(36)** and intramolecular acylation, hydrolysis, and



Scheme 1.6. (–)-Lycopodine, Carter, 2008

decarboxylation yielded the D-ring as the 1,3-diketone intermediate **(37)**. Formylation of the vinylogous ethyl ester followed by reduction with lithium aluminum hydride and conjugate cuprate addition onto the unsaturated enone afforded cyclohexanone **(38)**. An annelation reaction of the corresponding enamine followed by a Micheal addition to acrylamide gave hexahydroquinolone (**39)** along with the regioisomer **(40)** in a 1:1 mixture. Cyclization of **(40)** with a mixture of phosphoric acid and formic acid gave lactam **(41)**. The construction of the final ring began with the reduction of the amide to the corresponding amine. A Birch reduction followed by a base-catalyzed isomerization of the double bond, and a protection of the amine as the carbamate gave the advanced intermediate **(42)**. Ozonolysis gave the corresponding aldehyde ester which was then converted into the enol formate **(43)** after a Baeyer-Villiger-type oxidation with selenium dioxide and hydrogen peroxide. Hydrolysis of the enol formate with sodium methoxide releases the carbonyl at C-5 and a zinc-mediated reductive cleavage of the carbamate-protecting group delivers the free amine. This amine spontaneously cyclized to yield the desired lactam **(44)**. Similar to Ayer's route, racemic lycopodine **(12)** was accessed after the reduction of the lactam and subsequent reoxidation of the C-5 hydroxyl to the corresponding ketone.

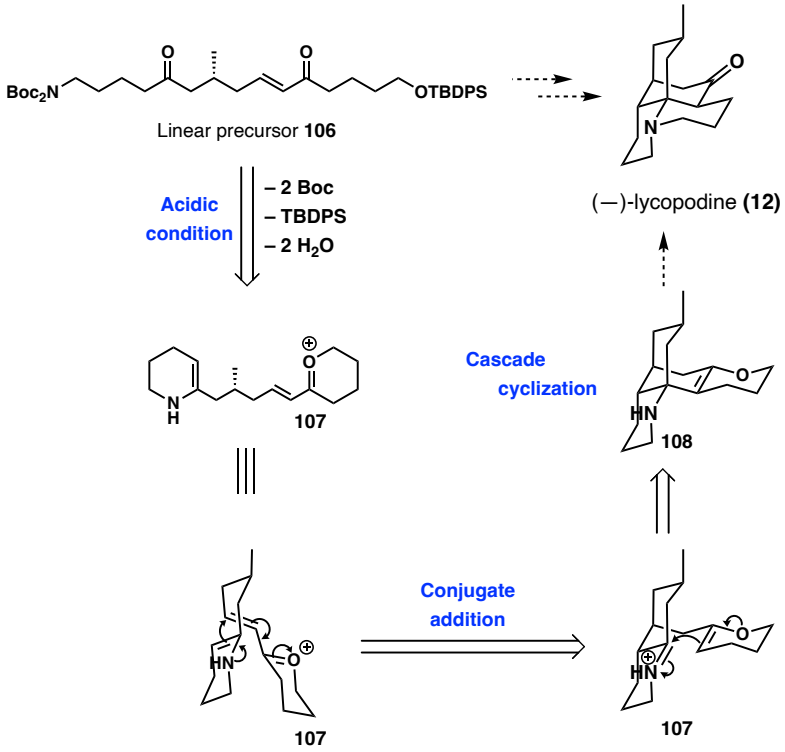
Many racemic syntheses of lycopodine have since been published but in 2008, the first enantioselective synthesis was published by Carter[25,26]. **Scheme 1.6** depicts the retrosynthetic



Scheme 1.7. (–)-Lycopodine, She, 2016

analysis. An intramolecular Michael addition and Staudinger reaction followed by an imine cyclization for the construction of rings B and C. The core of the alkaloid was then afforded via a Mannich cyclization where a 1,3-sulfone shift is displayed as a key step. The final ring closure of A afforded the natural product. In 2016, She, published the second assymetric total synthesis of (–)-lycopodine via a key aza-Prins cyclization reacton[36].

Scheme 1.7 illustrates the retrosynthetic analysis of the target molecule (**12**). The synthetic strategy envisions accessing (**12**) from the tetracyclic intermediate (**101**) through final-stage functional group interconversion, which would also allow for the simultaneous synthesis of (–)-dihydrolycopodine (**100**). The A-ring in lactam (**101**) would be constructed through an aldol/elimination/hydrogenation sequence starting from the pivotal tricyclic ketone (**102**). A key step involves the formation of the B-ring via an aza-Prins cyclization from alkyne-enamide (**103**). The C-ring of (**103**) could be generated from alkyne-ketone (**104**) through a one-pot amidation and cyclization. Compound (**104**) can be derived from Wade's



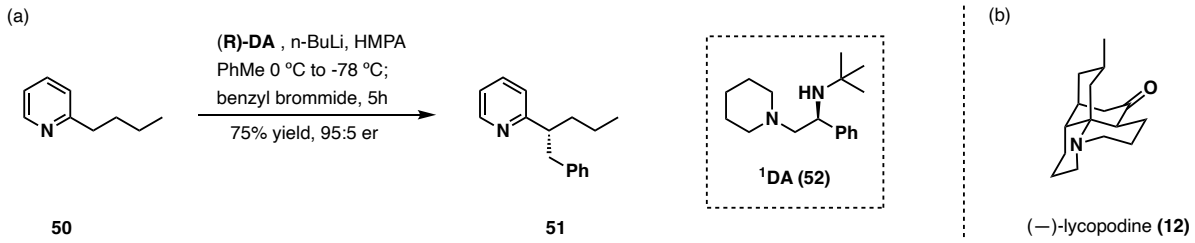
Scheme 1.8. (–)-Lycopodine, Takayama, 2016

fawcettimine enone (**105**) and propargyl bromide through a Michael addition. Notably, Wade's fawcettimine enone (**105**) is readily accessible from (R)-(+)-pulegone.

In 2019, Takayama published the third and most recent asymmetric total synthesis of (–)-lycopodine (**12**) using a cascade cyclization reaction of a linear precursor (**106**)[37]. **Scheme 1.8** illustrates the group's synthetic approach toward lycopodine. This work features a bioinspired cascade reaction that the group had previously employed for the synthesis of Lycodoline. They hypothesized that the dihydropyran ring in compound (**108**), an advanced intermediate in Heathcock's synthesis of lycopodine, would be formed through the conjugate addition of the oxonium intermediate (**107**). Intermediate (**107**) would be generated by exposing the linear precursor (**106**) to acidic conditions. The linear substrate (**106**) would be synthesized via a previously established route, starting from commercially available crotonamide.

Chapter 2: Efforts Towards the Total Synthesis of (–)-Lycopodine

2.1 Identifying the Koga Base that can be used to install a stereocenter as the first step



Scheme 2.1. a) General reaction scheme of asymmetric alkylation of 2-alkylpyridines. b) structure of (–)-lycopodine

Much of the issues surrounding the successful total synthesis of natural products lie in the ability to form asymmetric carbon-carbon bonds. It comes as no surprise that a variety of enantioselective alkylation methods have been published since the dawn of synthetic chemistry and are widely utilized in the subfield of total synthesis. For enolate-based carbanions, these methods generally rely on the use of chiral covalent directing groups, which require additional steps for their attachment, removal, and subsequent recovery[28]. Our group has previously demonstrated that chiral lithium amides (CLAs), as non-covalent, traceless stereodirecting groups, enable highly enantioselective transformations of dianionic enediolates derived from carboxylic acids via enolate or carbanion aggregation in solution[29,30,31]. Applying CLAs to transformations of non-enolate derived carbanions, we developed a general method for the direct asymmetric alkylation of C2-alkylpyridines[32] (**Scheme 2.1a**). To demonstrate the

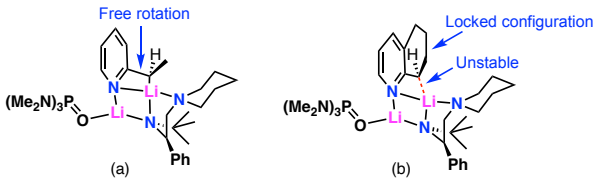
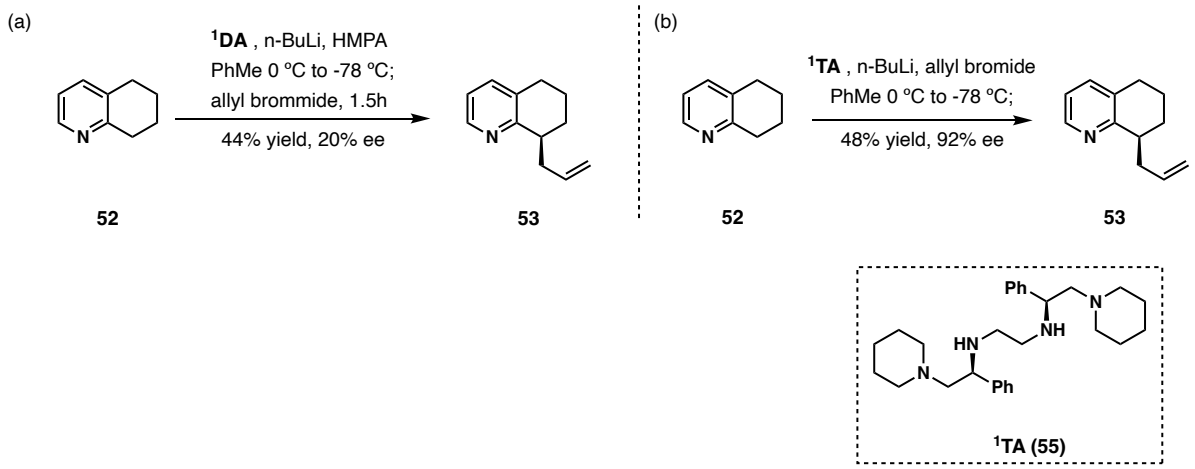


Figure 1. 2. a) Reactive mixed aggregate obtained for 2-ethylpyridine. b) Proposed unreactive and unstable aggregate with **52**



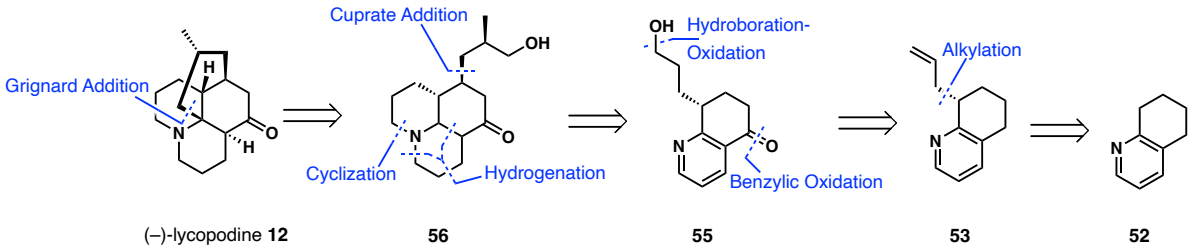
Scheme 2.2. a) Alkylation of **52** using **[1]DA**, *n*-BuLi, HMPA, and allyl bromide. b) Alkylation of **52** using **[1]TA**, *n*-BuLi, and allyl bromide.

synthetic utility of this method, we propose to use CLAs for the enantioselective total synthesis of (–)-lycopodine (**Scheme 2.1b**).

Our synthesis of lycopodine commenced with the allylation of **52** using our reported procedure with **[1]DA**, *n*-butyllithium, hexamethylphosphoramide (HMPA), and allyl bromide. The previously optimized reaction conditions resulted in only 44% yield of **53** and 20% enantiomeric excess (ee) (**Scheme 2.2a**). Efforts to optimize the reaction conditions by varying equivalents of HMPA, **[1]DA**, or *n*-BuLi resulted in only minimal improvements to the enantioselectivity of the reaction (<30% ee). Based on the crystal structure obtained from the lithiation of 2-ethylpyridine (**Figure 1.2. a**), the mechanism of stereocontrol for this method is achieved by mixed aggregation between the deprotonated substrate and chiral amine, providing a chiral environment for the approach by the electrophile. A possible explanation for the low enantioselectivity with **52** is likely due to the limited bond rotation in rigid cyclic pyridine **52** (**Figure 1.2. b**), resulting in destabilization of the chiral aggregate. Thus, a thorough chiral amine screen was performed to find the optimum reaction conditions for the allylation of **52**. Delightedly, preliminary results have shown that 2.0 equivalents of C_2-

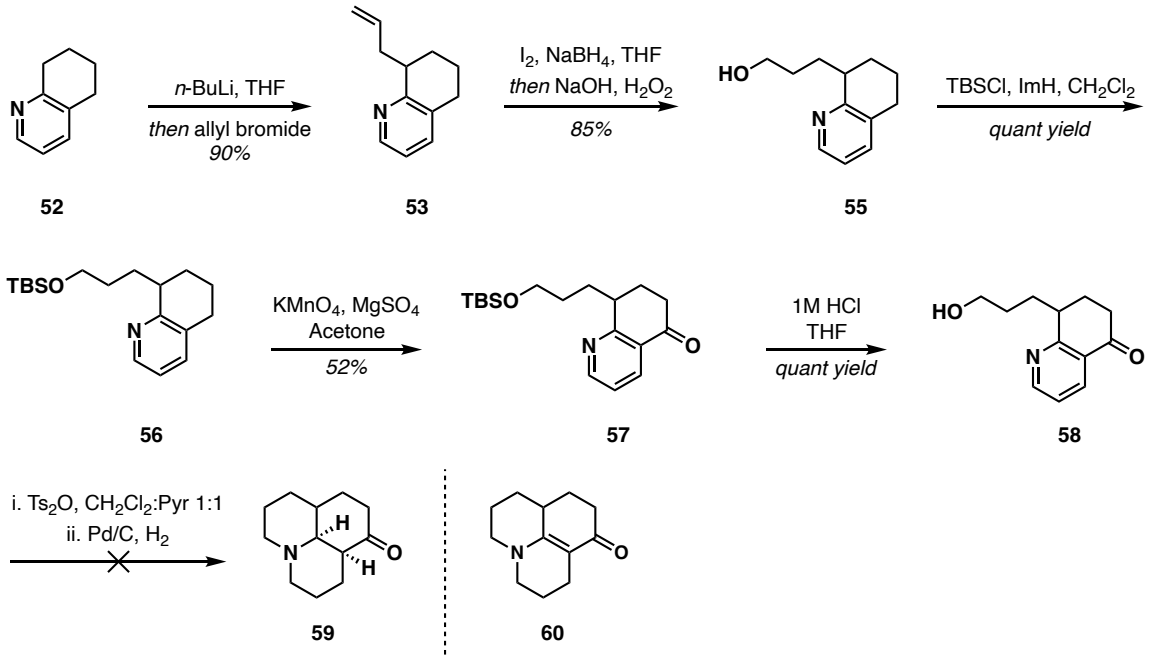
symmetric tetraamine (**^{1}TA**)[33], 4.0 equivalents of *n*-BuLi, and no HMPA provided **53** in 48% yield and 92% ee (**Scheme 2.2b**). Deviation from 2.0 equiv. of ^{1}**TA** and 4.0 equiv. of *n*-BuLi resulted in significant loss of enantioselectivity. Although further optimization of reaction yield is needed, these efforts demonstrate the viability of using our enantioselective alkylation methodology for our synthetic strategy. We envision that by installing a stereogenic center at the beginning of the synthesis, the diastereoselectivity of subsequent transformations could be controlled without the introduction of a synthetic handle or the use of expensive chiral catalysts. As efforts towards the optimization of the alkylation continue, I subsequently focused on the racemic synthesis of lycopodine.

2.2 Retrosynthetic Analysis and Forward Synthesis (1st generation)



Scheme 3.1. 1st Generation Retrosynthetic Analysis

Scheme 3.1 illustrates the initial retrosynthetic analysis proposed to carry out the synthesis of lycopodine. The construction of ring D was envisioned to occur through a Grignard addition into a newly formed imine. The tricyclic A, B, C ring system would be assembled following an *N*-cyclization, hydrogenation of the pyridine ring, and a subsequent cuprate addition to intermediate **55**. Access to intermediate **55** was planned via hydroboration-oxidation, followed by benzylic oxidation of precursor **53** to introduce the ketone functionality. Precursor **53** would be synthesized through an alkylation reaction with **52**.

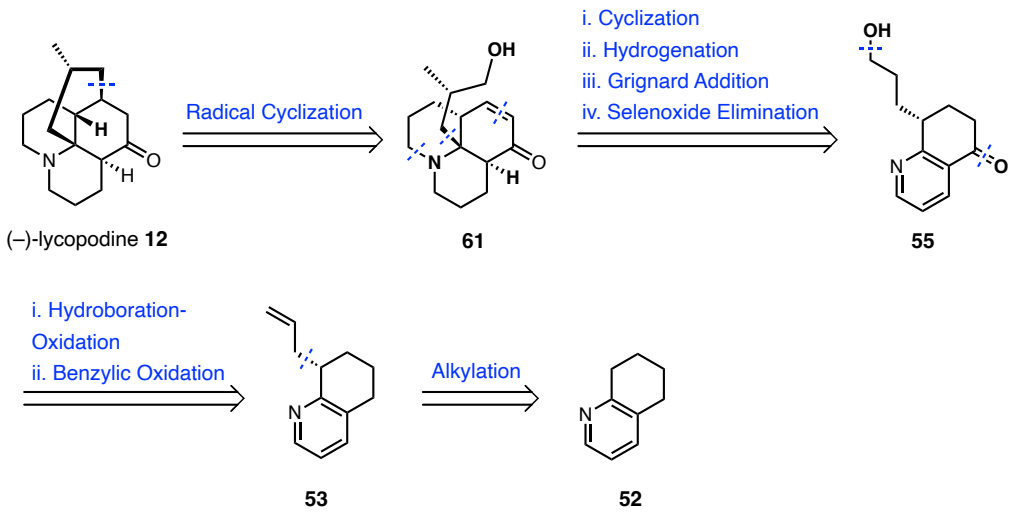


Scheme 3.2. 1st Generation Racemic Forward Synthesis

The racemic synthesis commenced with the alkylation of 5,6,7,8-tetrahydroquinoline to generate the allylated species **53** using *n*-butyllithium in THF, followed by allyl bromide addition. Alcohol **55** was obtained through hydroboration-oxidation and was subsequently protected as the silyl enol ether using *tert*-butyldimethylsilyl chloride. The following step involved the challenging benzylic oxidation of intermediate **56**, where various silver salts and oxidants—such as cobalt catalysts, IBX, and $KMnO_4$—were screened for their effectiveness in forming the ketone. Ultimately, a mixture of $KMnO_4$ and 15% aqueous $MgSO_4$ in acetone and water afforded the ketone in a 52% yield, after recovering and resubmitting the starting material to the oxidation conditions. Deprotection was carried out with 1M HCl, as TBAF led to the formation of an undesired phenol species under basic conditions. With intermediate **58** in hand, the synthesis progressed towards the key intermediate **59**, which contains the lycopodine skeleton comprising rings A, B, and C. After screening various conditions, tosyl

anhydride was identified as the optimal reagent for inducing *N*-cyclization. The final step envisioned was a hydrogenation reaction using 10% Pd/C to obtain advanced intermediate **59**. However, the expected intermediate was not formed upon treatment with 10% Pd/C. Analysis of the ^{1}H NMR and ^{13}C NMR spectra revealed that the partially hydrogenated species **60** was instead produced. Efforts to drive the reaction to completion by increasing catalyst loading, reaction time, and pressure consistently resulted in **60** as the sole product. At this juncture, the viability of the synthetic route was reconsidered, including the possibility of reversing the sequence of introduction and cyclization of the functional group intended to form ring D.

2.4 Retrosynthetic Analysis and Forward Synthesis (2nd generation)



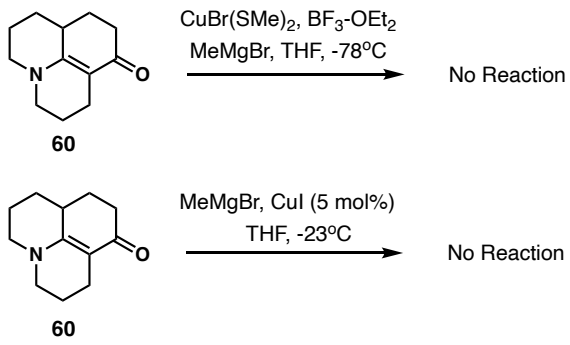
Scheme 4.1. 2nd Generation Retrosynthetic Analysis

Initially, I hypothesized that the vinylogous amide could undergo conjugate addition via an organocuprate reagent; however, as will be discussed later, this approach proved unsuccessful. I subsequently hypothesized that the vinylogous amide might be activated by a Lewis acid or electrophile, facilitating the addition of an organolithium species or Grignard

reagent. This shift in strategy necessitated revisions to the latter stages of the synthesis, specifically the cyclization of ring D. Instead of using a Grignard reagent for the final ring closure, I proposed employing a radical cyclization to the newly generated unsaturated ketone (Scheme 4.1). With this revised approach, I proceeded to test the forward synthetic route using racemic material.

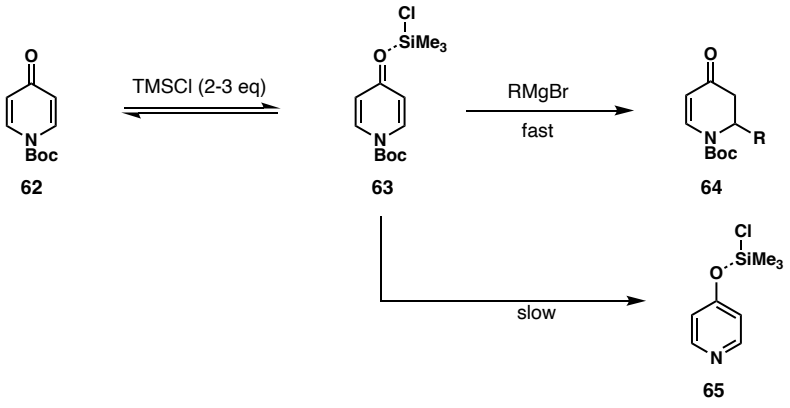
2.5 Forward Synthesis and problems solved

The exploration of a forward synthetic route to lycopodine began with the evaluation of standard conditions typically employed for organocuprate additions. Initially, the tricyclic intermediate was exposed to $CuBr(SMe)_2$, $BF_3 \cdot OEt_2$, followed by MeMgBr; however, no reaction was observed, and the starting material was recovered quantitatively (Scheme 5.1). A subsequent attempt to introduce the desired functional group involved treating the tricyclic intermediate with MeMgBr and 5 mol% CuI. As with the previous conditions, no reaction occurred, and the starting material was again recovered in quantitative yield. Following these outcomes, I revised my approach, exploring the potential for addition using organolithium species or a Grignard reagent. While concerns about addition to the existing carbonyl group arose, this issue was further investigated through experimental data.



Scheme 5.1. Attempts at conjugate addition into advanced intermediate **60**

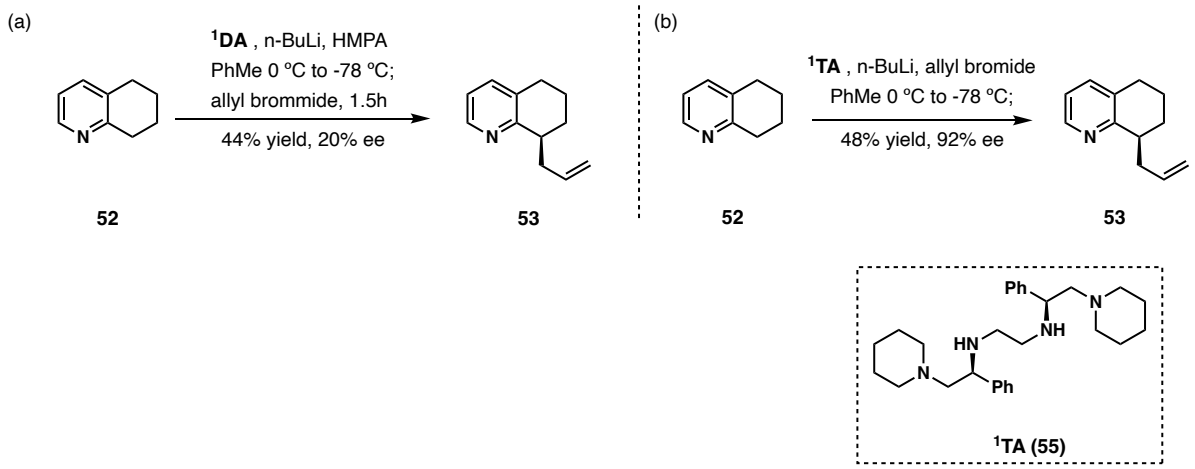
The general strategy involves activating the vinylogous amide to convert it into an electrophilic imine species, thereby making it susceptible to nucleophilic attack by an



Scheme 5.2. TMSCl is used to activate enones and allow for the fast addition of Grignard reagents

organometallic reagent. Literature reports suggest that vinylogous amides can be activated by exposure to 2-3 equivalents of TMSCl, resulting in the formation of a reactive imine intermediate, which can subsequently undergo nucleophilic addition. Specifically, the addition of Grignard reagents to this intermediate is expected to proceed rapidly, as illustrated in **Scheme 5.2**[35]. **Scheme 5.3** illustrates Yang's work from Novartis, San Diego, which elegantly demonstrates the utility of this methodology. In his published paper, Yang successfully employed TMSCl to activate a vinylogous amide, allowing for the addition of a Grignard reagent. Similar to my results, his attempts with organocuprates to facilitate nucleophilic attack yielded less favorable outcomes. Building on this approach, I exposed the tricyclic intermediate to TMSCl and MeMgBr, obtaining the desired compound with an 81% yield. Encouraged by this success, I proceeded to test other Grignard reagents, which were successfully incorporated. This led to the development of a method for introducing the appropriate methyl-containing handle (see **Scheme 5.4**).

2-Methylpropane-1,3-diol was subjected to *mono*-methylation to yield compound **74**. This compound was subsequently brominated using standard Appel conditions to produce bromide **75**. Following the preparation of the halide, the Grignard reagent was generated and titrated to determine its concentration before being applied to the vinylogous amide. Under the

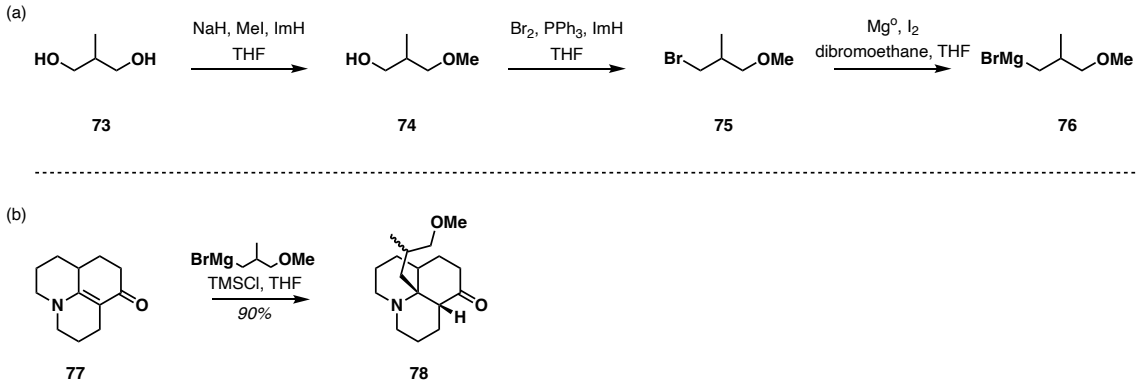


Scheme 2.2. a) Alkylation of **52** using **[1]DA**, *n*-BuLi, HMPA, and allyl bromide. b) Alkylation of **52** using **[1]TA**, *n*-BuLi, and allyl bromide.

established conditions for Grignard addition, the newly synthesized compound **76** reacted exceptionally well (see **Scheme 5.4b**).

To synthesize the alpha,beta-unsaturated ketone, I initially employed Saegusa-Ito oxidation conditions. Although the formation of the enol was successful, the subsequent oxidation with palladium resulted in a complex mixture, likely due to side reactions with the amine. I then explored an alternative classical method found in the literature: selenoxide elimination. My initial trials used diphenyl diselenide and m-CPBA as the oxidant, which yielded the phenyl selenium intermediate. However, the desired product was not obtained. Instead, I observed complete consumption of the phenyl selenium species and the formation of a new, highly polar compound, as evidenced by TLC with a 10% MeOH:90% dichloromethane mobile phase.

Curious whether hydrogen peroxide, another traditional oxidant for selenoxide elimination, would yield different results, I replaced m-CPBA with H_2O_2. The results were identical. This led me to hypothesize that the highly polar compound observed on TLC was likely the *N*-oxide forming before the selenoxide elimination. Upon isolation and characterization, it was confirmed that the N-oxide was indeed forming. To prevent this, I

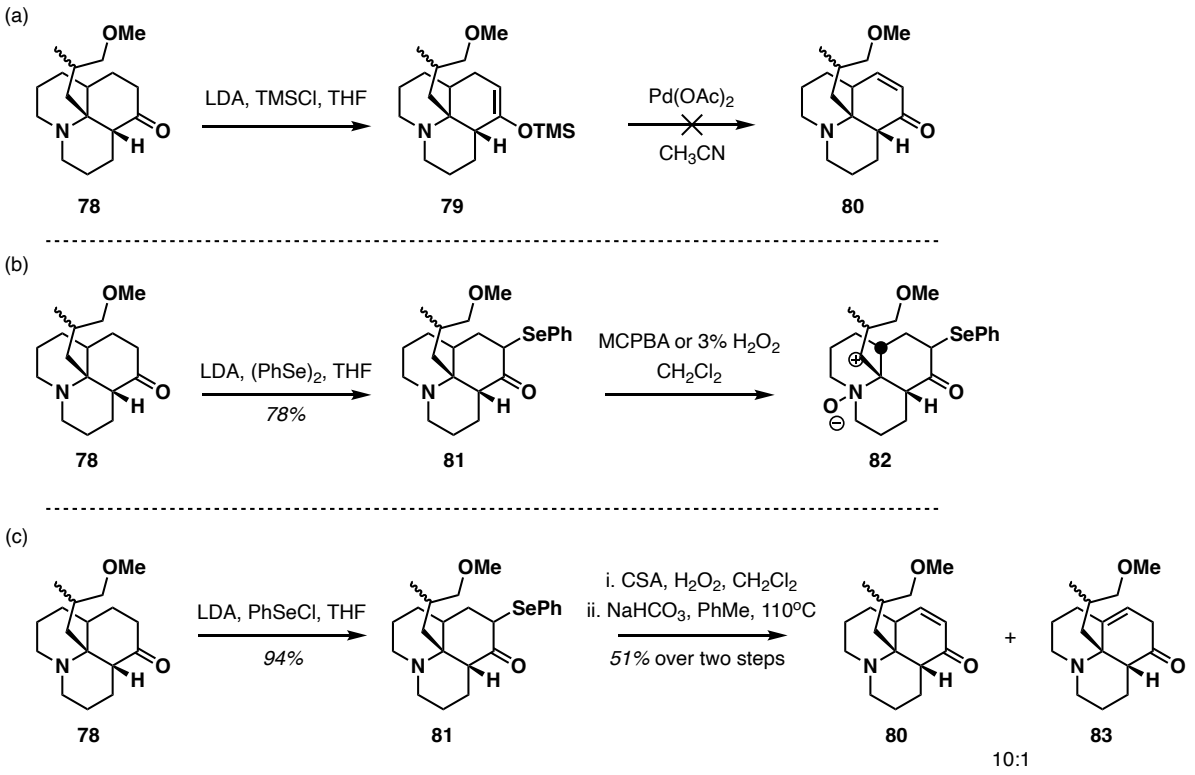


Scheme 5.4. (a) Racemic synthesis of potential D-Ring handle containing a methoxy protecting group (b) Addition of Grignard reagent into the vinylogous amide

introduced CSA before adding the oxidant, successfully obtaining the desired alpha,beta-unsaturated ketone along with regioisomer **83** in a 10:1 ratio (as determined by ^{1}H NMR). The reaction worked optimally with hydrogen peroxide, so I proceeded with these conditions.

Attempts to minimize regioisomer formation by reducing the reaction time proved ineffective. However, lowering the temperature to 0 ºC resulted in trace amounts of **83**, as detected by ^{1}H NMR. Additionally, while troubleshooting selenoxide formation, I tested PhSeCl instead of $(PhSe)_2$, achieving an increased yield from 78% to 94%.

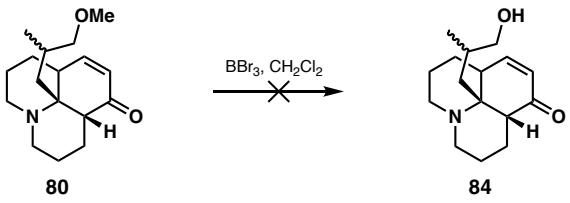
For the final cyclization, deprotection of the primary alcohol was required. Using BBr_3 led to a complex mixture (see **Scheme 5.6)**. After several troubleshooting attempts, I focused on developing a new Grignard reagent with a different protecting group, which could be removed under milder conditions. I explored -OTBS and -OMOM as protecting groups but was unsuccessful in forming the Grignard reagents. During the synthesis of the silyl ether protecting group I observed the Retro-Brook rearrangement product. The methyoxymethyl ether successfully formed the bromo intermediate but did not react with magnesium. Ultimately, I utilized PMB as a protecting group, which allowed me to successfully form the Grignard reagent (**Scheme 5.7a**), perform the reaction with **77**, and proceed through the the



Scheme 5.5. (a) The failed attempt at constructing the unsaturated ketone via Saegua-Ito oxidation (b) Initial attempts at forming the selenoxide species (c) successful synthesis of enone

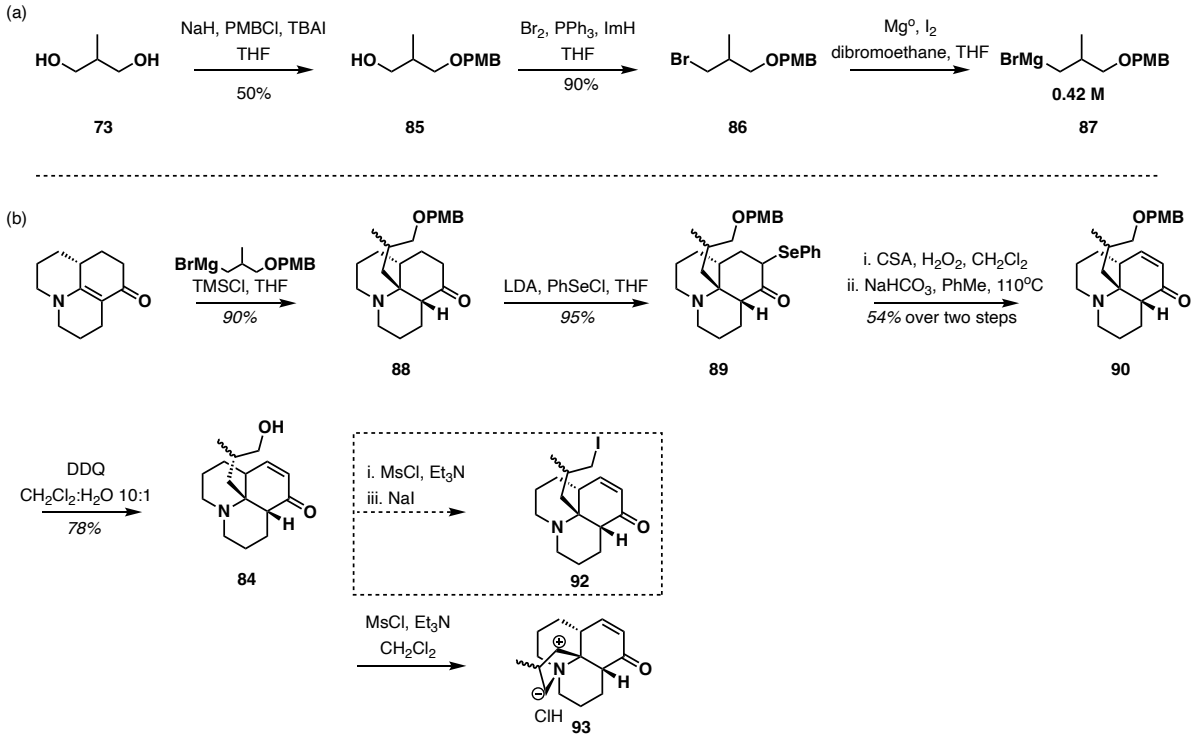
sequence until deprotection. Using DDQ for deprotection yielded the primary alcohol **84**. The final cyclization stage, initially envisioned as a radical cyclization, was approached using the Gueise reaction as a potential candidate. I attempted to convert the primary alcohol to the iodide species but was unsuccessful. TLC indicated complete consumption of the starting material and the formation of a more polar compound. After isolating the baseline spot from the crude material via a silica plug, the resulting ^{1}H NMR spectrum was too complex for analysis, even after a second silica plug purification.

Subsequently, I attempted to prepare the iodine species through a two-step process involving mesylation followed by iodination with NaI. However, the mesylation step yielded a similar TLC profile to that observed during the Appel reaction. Isolating the material

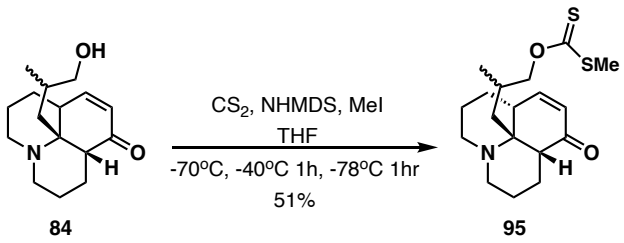


Scheme 5.6. BBr_3 deprotection attempt

provided a clearer spectrum, which revealed that the nitrogen was too nucleophilic, leading to intramolecular attacks on the electrophilic intermediates and resulting in *N*-cyclized quaternary ammonium salts as the sole products (see **Scheme 5.7b**). This indicated that the high nucleophilicity of the nitrogen posed a significant challenge to achieving the desired cyclization. Literature on the direct generation of primary radical species from primary alcohols is scarce. The few reports available often involve in-situ generation of species that are too electrophilic for the nitrogen. For instance, a recent study demonstrated the direct conversion of a primary alcohol to a primary radical using Tf_2O; however, under these conditions, my substrate still underwent *N*-cyclization. I eventually found conditions



Scheme 5.7. (a) Synthesis of potential D-Ring handle containing a PMB protecting group (b) Synthetic sequence starting from the vinylogous amide to the formation of the quaternary ammonium salt via internal ring closure on the nitrogen



Scheme 5.8. Conditions to access the Xanthate

describing the formation of a xanthate species from a primary alcohol in the presence of a nucleophilic amine, with the reaction performed at -40 ºC. Although initially skeptical due to the requirement of MeI to form the xanthate, I proceeded with the experiment and successfully obtained the xanthate species (see **Scheme 5.8.**). The remaining challenge was to generate the radical species and facilitate the final ring closure. Attempts using classical conditions to generate the radical species yielded no reaction, as indicated by TLC.

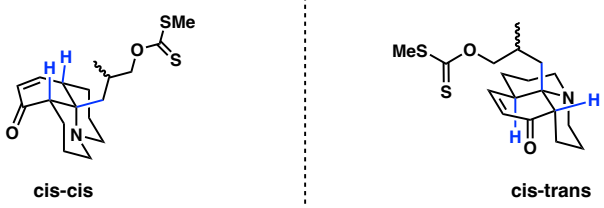
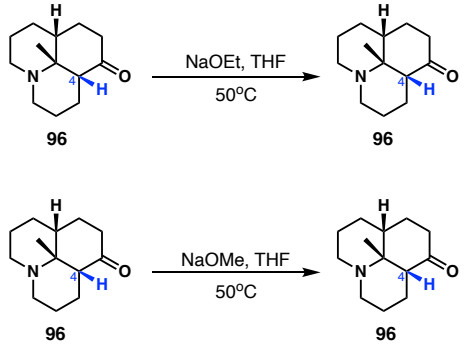


Figure 5.1. Cis-Cis vs Cis-Trans conformation of intermediate **95**

Despite rigorous efforts to isolate any hidden spots, it became apparent that there was no conversion of the starting material, as confirmed by the ^{1}H NMR spectrum. Reviewing 3D models and previously obtained 2D NMR spectra provided insight into the reaction's outcome. It appears that the proton at C4 needs to be inverted to bring the radical and unsaturated ketone into close proximity, facilitating cyclization. In its current cis-cis conformation with respect to the bridgehead (**Figure 5.1**), the spatial separation between the radical and unsaturated ketone rendered cyclization virtually impossible. Using the methyl derivative **96** as a model compound, I attempted to invert the hydrogen using

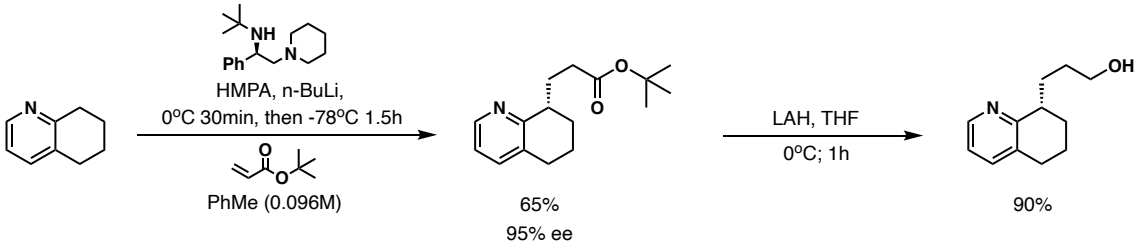


Scheme 5.9. Attempts to epimerize C4 of **96**

NaOEt and NaOMe but was unsuccessful, recovering the starting material in quantitative yield (**Scheme 5.9**). This concludes my efforts toward the total synthesis of (–)-lycopodine.

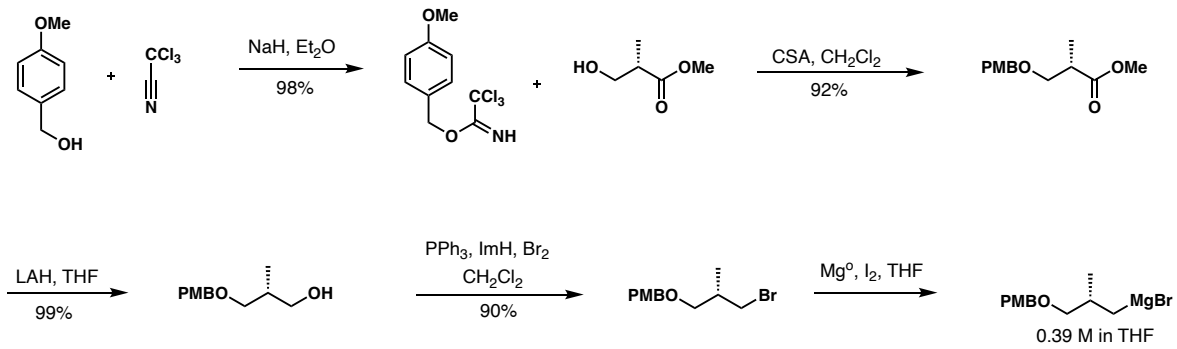
2.5 Future Plans and Conclusion

In conclusion, I have developed a viable synthetic route to (–)-lycopodine, reaching a stage just one intermediate away from completion. This route involves the initial installation of a key chiral center, the construction of rings A, B, and C, and the preparation and introduction of the handle necessary for ring D formation. The future progress of this project hinges on achieving the successful cyclization of ring D and optimizing several lower-yielding reactions, including the enantioselective alkylation and $KMnO_4$ oxidation.



Scheme 5.10. Preliminary results towards 2nd generation enantioselective alkylation.

I have obtained promising preliminary results for a second generation enantioselective alkylation (see **Scheme 5.10**), which may become the conditions used in the final total synthesis. Additionally, I have executed literature procedures for constructing the enantioselective handle of ring D, starting from the corresponding Roche ester (see **Scheme 5.11**).



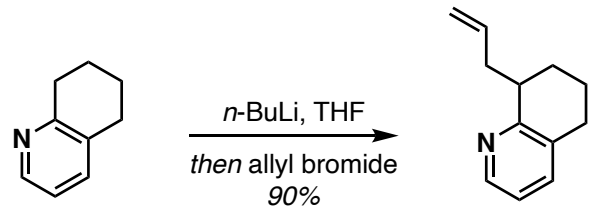
Scheme 5.11. Enantiopure handle for the construction of ring D.

Supporting Information

General Information

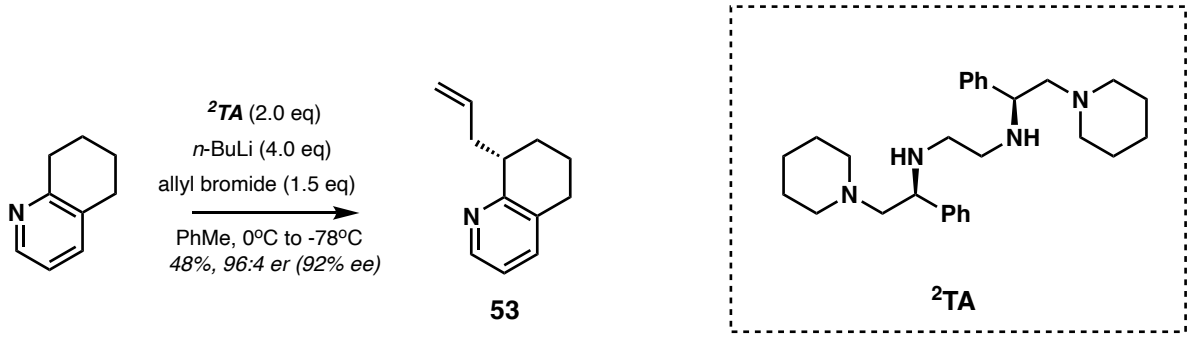
All reactions were carried out under an atmosphere of dry argon in oven and flame-dried glassware, unless the reaction procedure states otherwise. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium-benzophenone in a continuous still under an atmosphere of nitrogen. Dichloromethane, *N*,*N*-diisopropylethylamine, and acetonitrile were distilled from calcium hydride in a continuous still under an atmosphere of nitrogen. Methanol was distilled from magnesium turnings and iodine in a continuous still under an atmosphere of nitrogen. Reaction temperatures were controlled by IKA ETS-D4 fuzzy thermocouples. Analytical normal-phase thin-layer chromatography (TLC) was performed using pre-coated TLC plates with Silica Gel 60 F254 (EMD no. 5715-7) and visualized using combinations of UV, anisaldehyde, and potassium permanganate staining. Normal-phase flash column chromatography was performed using 40-63 μm silica gel (EMD, Geduran, no. 11567-1) as the stationary phase. Proton nuclear magnetic resonance spectra were recorded at 400, 500, 600 MHz on a Bruker Avance NEO spectrometer or Varian Unity Inova spectrometer. Carbon nuclear magnetic resonance spectra were recorded at 125 MHz on a Bruker Avance NEO spectrometer and 100, 125, and 150 MHz on Varian Unity Inova spectrometers. All chemical shifts were reported in δ units relative to tetramethylsilane.

Experimental Procedures

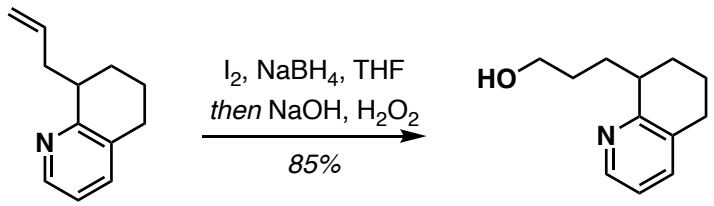


52 **53**

8-allyl-5,6,7,8-tetrahydroquinoline. A solution of *n*-butyllithium (17.6 mL, 2.50 M in hexane, 39.4 mmol, 1.05 eq) was added dropwise to 5,6,7,8-tetrahydroquinoline (5.0 g, 37.5 mmol) in THF (75.0 mL) at -78 ºC and stirred for 15 minutes. The reaction was then warmed to 0 ºC and stirred for 15 minutes before being cooled back to -78 ºC. Allyl bromide (4.54 g, 37.5 mmol, 1.0 eq) was added dropwise to the mixture and stirred for 3 hours. Upon completion, the reaction was quenched with MeOH at -78 ºC and brought to room temperature, where the mixture was diluted with H_2O and EtOAc. The organics were extracted with EtOAc, washed with brine, and dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (30% ethyl acetate in hexane) to afford 8-allyl-5,6,7,8-tetrahydroquinoline (5.85 g, 33.75 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 – 8.37 (m, 1H), 7.37 – 7.30 (m, 1H), 7.01 (dd, *J* = 7.6, 4.7 Hz, 1H), 5.85 (dddd, *J* = 17.1, 10.1, 8.1, 6.2 Hz, 1H), 5.12 – 4.99 (m, 2H), 2.95 (dq, *J* = 10.1, 5.7 Hz, 1H), 2.83 (dddt, *J* = 14.0, 6.6, 3.5, 1.5 Hz, 1H), 2.74 (qd, *J* = 5.7, 3.1 Hz, 2H), 2.38 – 2.25 (m, 1H), 1.99 – 1.64 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.92, 147.03, 137.66, 136.86, 132.57, 121.03, 116.29, 40.41, 39.72, 29.37, 27.15, 19.86.

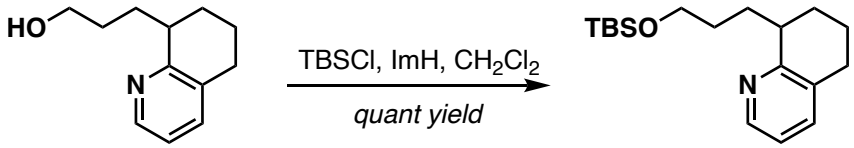


(*S*)-8-allyl-5,6,7,8-tetrahydroquinoline (53). ^{2}TA was added to a flame dried round bottom flask and backfilled with argon (3x). 5,6,7,8-tetrahydroquinoline (1.0 g, 7.51 mmol) and toluene (78.0 mL) were added to the flask and the mixture was cooled to 0 ºC where *n*-butyllithium (12.0 mL, 2.50 M in hexane, 30.04 mmol, 4.0 eq) was added dropwise and stirred for 15 minutes. The solution was cooled to -78 ºC and stirred for 15 minutes before the addition of allyl bromide (1.36 g, 11.27 mmol). The reaction was stirred for 4 hours then quenched with MeOH (1.5 M) and stirred for 15 minutes. The mixture was brought to room temperature and diluted with H_2O (0.09 M) and EtOAc (0.2 M) and the organics were collected, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (30% ethyl acetate in hexane) to afford (*S*)-8-allyl-5,6,7,8-tetrahydroquinoline (625 mg, 3.60 mmol, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 – 8.37 (m, 1H), 7.37 – 7.30 (m, 1H), 7.01 (dd, *J* = 7.6, 4.7 Hz, 1H), 5.85 (dddd, *J* = 17.1, 10.1, 8.1, 6.2 Hz, 1H), 5.12 – 4.99 (m, 2H), 2.95 (dq, *J* = 10.1, 5.7 Hz, 1H), 2.83 (dddt, *J* = 14.0, 6.6, 3.5, 1.5 Hz, 1H), 2.74 (qd, *J* = 5.7, 3.1 Hz, 2H), 2.38 – 2.25 (m, 1H), 1.99 – 1.64 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.92, 147.03, 137.66, 136.86, 132.57, 121.03, 116.29, 40.41, 39.72, 29.37, 27.15, 19.86.



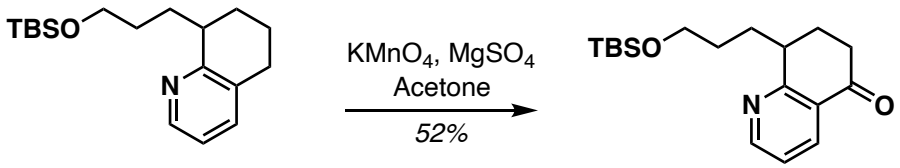
53 **55**

(*S*)-3-(5,6,7,8-tetrahydroquinolin-8-yl)propan-1-ol (55). Sodium borohydride (4.40 g, 115.24 mmol, 4.0 eq) was suspended in THF (86.0 mL) and cooled to -10 ºC. Iodine (14.6 g, 57.62 mmol, 2.0 eq) was added, dropwise, as a solution in THF (10.0 mL) according to the disappearance of color. The mixture was stirred for 30 minutes before (*S*)-8-allyl-5,6,7,8-tetrahydroquinoline (5.0 g, 28.81 mmol) was added dropwise. The solution was warmed to 0 ºC and stirred for 15 minutes, then brought to room temperature and stirred for 1.5 hours. The reaction was cooled to 0 ºC and 3.0M aq. NaOH (193.0 mL, 576.2 mmol, 20 eq) was added followed by 30% aq. H_2O_2 (200.0 mL, 1959.08 mmol, 68 eq). The reaction was stirred overnight at room temperature and an extraction was preformed twice using EtOAc (0.5 M). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (5% MeOH in dichloromethane) to afford (*S*)-3-(5,6,7,8-tetrahydroquinolin-8-yl)propan-1-ol (4.66 g, 24.36 mmol, 86%). ^{1}H NMR (400 MHz, CDCl3) δ 8.39 – 8.33 (m, 1H), 7.39 – 7.32 (m, 1H), 7.03 (dd, *J* = 7.7, 4.7 Hz, 1H), 3.72 (dd, *J* = 6.8, 5.0 Hz, 2H), 2.96 (p, *J* = 6.0 Hz, 1H), 2.85 – 2.68 (m, 2H), 2.10 – 1.96 (m, 2H), 1.94 – 1.84 (m, 1H), 1.84 – 1.61 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.92, 147.03, 137.66, 136.86, 132.57, 121.03, 116.29, 40.41, 39.72, 29.37, 27.15, 19.86.



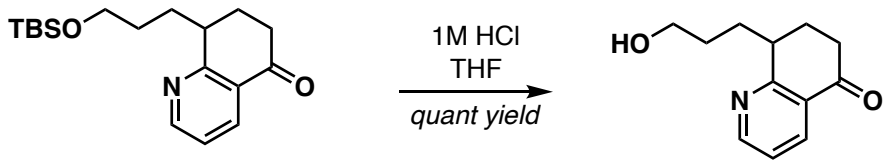
55 **56**

(*S*)-8-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-5,6,7,8-tetrahydroquinoline (56). (*S*)-3-(5,6,7,8-tetrahydroquinolin-8-yl)propan-1-ol (3.8 g, 19.67 mmol) was dissolved in dichloromethane (66.0 mL) and stirred at room temperature. tert-Butyldimethylsilyl chloride (3.2 g, 21.64 mmol, 1.1 eq) and imidazole (2.0 g, 29.51 mmol, 1.5 eq) were added to the solution and the mixture was stirred for 1.5 hours before being quenched with saturated aq. $NaHCO_3$. The organics were extracted twice with dichloromethane (0.5 M) and washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (100% hexanes then 50% EtOAc in hexanes) to afford (*S*)-8-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-5,6,7,8-tetrahydroquinoline (19.67 mmol, 100%). ^{1}H NMR (400 MHz, CDCl3) δ 8.41 – 8.35 (m, 1H), 7.37 – 7.29 (m, 1H), 7.00 (dd, *J* = 7.7, 4.7 Hz, 1H), 3.69 (ddd, *J* = 10.0, 7.6, 5.6 Hz, 1H), 3.60 (dt, *J* = 10.0, 6.9 Hz, 1H), 2.87 (dt, *J* = 9.2, 5.1 Hz, 1H), 2.74 (q, *J* = 5.7 Hz, 2H), 1.97 (ddt, *J* = 11.7, 10.1, 5.7 Hz, 2H), 1.87 (ddt, *J* = 11.5, 9.5, 6.4 Hz, 1H), 1.80 – 1.53 (m, 5H), 0.88 (s, 9H), 0.04 (d, *J* = 2.4 Hz, 6H).



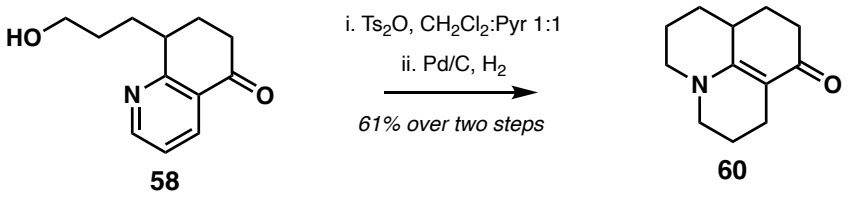
56 **57**

(*R*)-8-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-7,8-dihydroquinolin-5(6*H*)-one (57). Potassium permanganate (9.0 g, 56.94 mmol, 3.0 eq) was added to a solution of (*S*)-8-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-5,6,7,8-tetrahydroquinoline (5.8 g, 18.98 mmol) in a 6:1 mixture of acetone:water (0.05 M). 15% aq. $MgSO_4$ (47.0 mL, 0.40 M) was added and the mixture was stirred for 48 hours before being passed through celite and concentrated under reduced pressure. The residue was resuspended in EtOAc (0.5M) and saturated aq. $NaCO_3$, where the organics were collected, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (10% EtOAc in hexanes) to afford (*R*)-8-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-7,8-dihydroquinolin-5(6*H*)-one (10.23 mmol, 53% after recycling starting material 2x). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (dd, *J* = 4.7, 1.9 Hz, 1H), 8.26 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.29 – 7.27 (m, 1H), 3.77 – 3.60 (m, 2H), 3.10 (dq, *J* = 10.8, 5.2 Hz, 1H), 2.81 (ddd, *J* = 17.5, 10.2, 4.7 Hz, 1H), 2.62 (ddd, *J* = 17.5, 7.3, 4.7 Hz, 1H), 2.38 – 2.25 (m, 1H), 2.14 – 1.97 (m, 2H), 1.86 – 1.60 (m, 3H), 0.88 (s, 9H), 0.04 (d, *J* = 3.0 Hz, 6H). ^{13}C NMR (151 MHz, $cdcl_3$) δ 198.00, 166.54, 153.36, 135.08, 127.47, 122.08, 63.20, 40.50, 35.23, 30.70, 29.39, 25.93, 25.74, 18.30, -5.31.

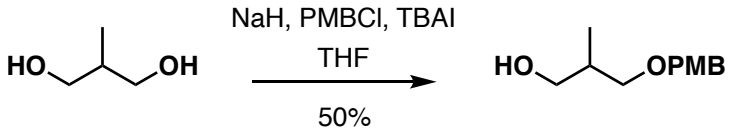


57 **58**

(*R*)-8-(3-hydroxypropyl)-7,8-dihydroquinolin-5(6*H*)-one (58). (*R*)-8-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-7,8-dihydroquinolin-5(6*H*)-one (1.56 g, 4.88 mmol) was dissolved in THF (24.0 mL) and 1M HCl (24.0 mL). The mixture was allowed to stir for 1 hour before being poured into a separatory funnel containing saturated aq. $NaHCO_3$ (60.0 mL) and extracted with EtOAc. The organics were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (5% MeOH in dichloromethane) to afford (*R*)-8-(3-hydroxypropyl)-7,8-dihydroquinolin-5(6*H*)-one (0.95 g, 4.62 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (dd, *J* = 4.8, 1.9 Hz, 1H), 8.29 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.30 (ddd, *J* = 7.8, 4.8, 0.6 Hz, 1H), 3.78 – 3.69 (m, 2H), 3.17 (h, *J* = 5.5 Hz, 1H), 2.83 (ddd, *J* = 17.5, 9.4, 4.6 Hz, 1H), 2.75 (t, *J* = 5.5 Hz, 1H), 2.64 (ddd, *J* = 17.5, 8.1, 4.7 Hz, 1H), 2.33 (ddt, *J* = 14.1, 9.4, 4.7 Hz, 1H), 2.22 – 2.00 (m, 2H), 1.90 – 1.64 (m, 3H). ^{13}C NMR (151 MHz, $cdcl_3$) δ 197.90, 166.40, 153.22, 135.51, 127.80, 122.39, 62.35, 40.11, 35.67, 30.41, 29.57, 26.61.

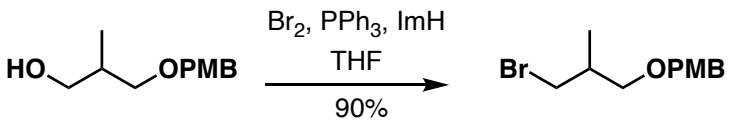


(*R*)-2,3,5,6,7,9,10,10a-octahydro-1*H*,8*H*-pyrido[3,2,1-*ij*]quinolin-8-one (60). i. (*R*)-8-(3-hydroxypropyl)-7,8-dihydroquinolin-5(6*H*)-one was dissolved in a 1:1 mixture of dichloromethane:pyridine (36.0 mL). p-Toluenesulfonic anhydride (3.85 g, 11.79 mmol, 1.1 eq) was then added and the mixture was stirred for 1 hour at room temperature. Upon completion, the reaction was concentrated and submitted crude to the next step. ii. The crude mixture was dissolved in methanol (107.0 mL) and 10% Pd/C (3.22 mmol, 10 mol%) was added. The mixture was sparged with H_2 for 1 hour before being left under 1atm of H_2 overnight. Upon completion, the reaction was passed through celite and basified to a pH of 7 with saturated aq. $NaHCO_3$ then concentrated. The residue was resuspended in EtOAc and the organics were dried over Na_2SO_4 and concentrated under reduced pressure. Purification was preformed by column chromatography on silica gel (5% MeOH in dichloromethane) to afford (*R*)-2,3,5,6,7,9,10,10a-octahydro-1*H*,8*H*-pyrido[3,2,1-*ij*]quinolin-8-one (1.3 g, 6.80 mmol, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 – 3.07 (m, 4H), 2.56 – 2.43 (m, 1H), 2.38 (ddd, *J* = 16.7, 4.8, 2.3 Hz, 1H), 2.33 – 2.16 (m, 3H), 1.97 – 1.67 (m, 6H), 1.59 (dtd, *J* = 13.6, 12.5, 4.8 Hz, 1H), 1.37 – 1.20 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.81, 161.10, 104.81, 50.96, 50.93, 36.68, 36.09, 29.86, 28.32, 23.07, 20.71, 19.85.



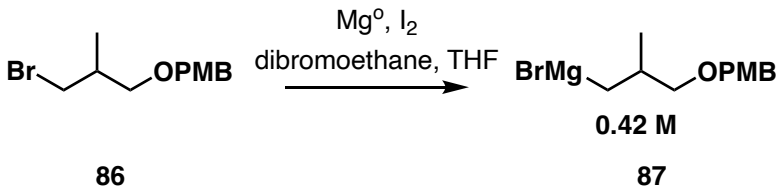
73 **85**

3-((4-methoxybenzyl)oxy)-2-methylpropan-1-ol. 2-methylpropane-1,3-diol (5.0g, 55.48 mmol) was dissolved in THF (37 mL) and cooled to 0 ºC. NaH (1.33 g, 55.48 mmol, 1.0 eq) was added, portion wise, and the resulting pale yellow suspension was stirred for 30 minutes. PMBCl (8.69 g, 55.48 mmol, 1.0 eq) was made fresh and added to the reaction followed by TBAI (2.05 g, 5.55 mmol, 0.1 eq) and the reaction was warmed to 55 ºC for 16 hours. Upon completion the reaction was cooled to room temperatre and quenched with water (1.5 M). The organics were extracted three times with EtOAc (1.5 M). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. Purification was preformed by column chromatography on silica gel (25% EtOAc in hexanes) to afford 3-((4-methoxybenzyl)oxy)-2-methylpropan-1-ol (5.8 g, 27.74 mmol, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 9.5 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.45 (s, 2H), 3.81 (s, 3H), 3.60 (td, *J* = 7.1, 4.0 Hz, 2H), 3.53 (ddd, *J* = 9.1, 4.7, 0.7 Hz, 1H), 3.39 (dd, *J* = 9.1, 8.1 Hz, 1H), 2.57 (dd, *J* = 7.0, 4.2 Hz, 1H), 2.13 – 1.99 (m, 1H), 0.87 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $cdcl_3$) δ 159.42, 129.40, 114.01, 75.42, 73.22, 68.19, 55.43, 35.68, 13.60.

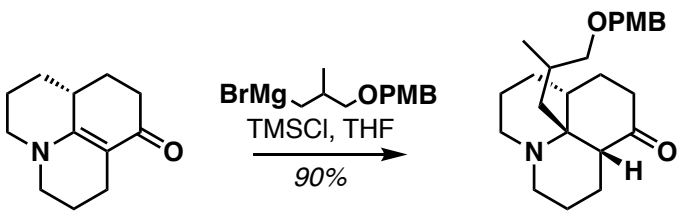


85 **86**

1-((3-bromo-2-methylpropoxy)methyl)-4-methoxybenzene. To a solution of PPh_3 (15.72 g, 59.92 mmol, 2.0 eq) and imidazole (6.12 g, 89.88, 3.0 eq) in dichloromethane (130 mL) was added Br_2 (2.76 mL, 53.93 mmol, 1.8 eq) at 0 ºC. After 15 minutes of stirring, 3-((4-methoxybenzyl)oxy)-2-methylpropan-1-ol (6.3 g, 29.96 mmol) was added and stirred for 30 minutes. Upon completion, the suspension was quenched with 3% H_2O_2 (1.17 M). The organics were extracted with EtOAc (0.5 M, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification was performed by column chromatography on silica gel (4:1 Hexane:Et_2O) to afford 1-((3-bromo-2-methylpropoxy)methyl)-4-methoxybenzene (). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.45 (s, 2H), 3.81 (s, 3H), 3.55 – 3.44 (m, 2H), 3.48 – 3.32 (m, 2H), 2.11 (dtdd, *J* = 12.1, 6.9, 5.3, 1.5 Hz, 1H), 1.02 (d, *J* = 6.8 Hz, 3H).

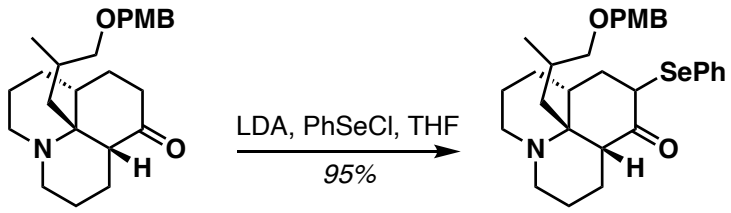


(3-((4-methoxybenzyl)oxy)-2-methylpropyl)magnesium bromide. A round bottom flask was charged with a Teflon stir bar, magnesium turnings (193 mg, 8.03 mmol, 1.1 eq), a crystal of iodine, and THF (7.3 mL). At reflux, a small portion of 1-((3-bromo-2-methylpropoxy)methyl)-4-methoxybenzene (0.20 g) was added dropwise and the brown color of the reaction was allowed to turn dark gray and cloudy. The additional 1-((3-bromo-2-methylpropoxy)methyl)-4-methoxybenzene (1.8 g) was added while maintaining a gentle reflux. The mixture was stirred for 2 hours to afford a 0.42 M solution of (3-((4-methoxybenzyl)oxy)-2-methylpropyl)magnesium bromide in THF.



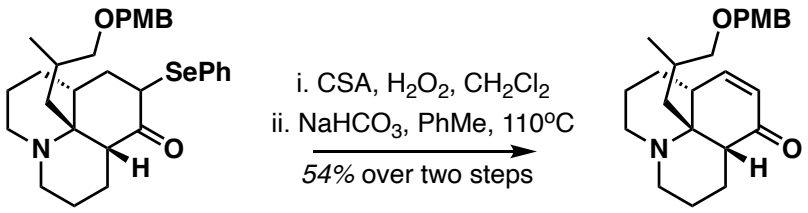
88

(4^1*R*,7a*R*,10a*R*)-4^1-(3-((4-methoxybenzyl)oxy)-2-methylpropyl)decahydro-1*H*,8*H*-pyrido[3,2,1-*ij*]quinolin-8-one (88). (*R*)-2,3,5,6,7,9,10,10a-octahydro-1*H*,8*H*-pyrido[3,2,1-*ij*]quinolin-8-one (29.0 mg, 0.152 mmol) was dissolved in THF (1.3 mL) and trimethylsilyl chloride (0.06 mL, 49.54 mmol, 3.0 eq) was added at 0 ºC. The mixture was allowed to stir for 10 minutes before being brought to room temperature for 1 hour. The mixture was cooled to 0 ºC and the Grignard reagent was added. The reaction was allowed to stir overnight at room temperature. Upon completion, the reaction was quenched with saturated aq. NH_4Cl and extracted three times EtOAc (0.5 M). The organics were collected, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (5% MeOH in dichloromethane) to afford (4^1*R*,7a*R*,10a*R*)-4^1-(3-((4-methoxybenzyl)oxy)-2-methylpropyl)decahydro-1*H*,8*H*-pyrido[3,2,1-*ij*]quinolin-8-one (53.0 mg, 0.137 mmol, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 13.4, 8.5 Hz, 2H), 6.87 (dd, *J* = 8.7, 2.3 Hz, 2H), 4.41 (dd, *J* = 16.2, 6.6 Hz, 2H), 3.80 (s, 3H), 3.24 (dd, *J* = 9.0, 5.5 Hz, 1H), 3.15 (ddd, *J* = 8.6, 6.5, 1.8 Hz, 1H), 2.68 – 2.52 (m, 2H), 2.49 – 2.35 (m, 4H), 2.30 (dd, *J* = 12.0, 3.8 Hz, 1H), 2.00 – 1.89 (m, 1H), 1.87 – 1.63 (m, 8H), 1.65 – 1.41 (m, 4H), 1.40 – 1.20 (m, 1H), 0.95 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.00, 159.11, 129.23, 76.00, 72.48, 61.81, 59.52, 55.33, 48.43, 48.23, 47.25, 40.64, 29.37, 28.93, 27.82, 26.54, 25.84, 25.68, 25.13, 21.06, 20.72, 19.45, 19.17.



(4^1*R*,7a*R*,10a*R*)-4^1-(3-((4-methoxybenzyl)oxy)-2-methylpropyl)-9-(phenylselanyl)decahydro-1*H*,8*H*-pyrido[3,2,1-*ij*]quinolin-8-one. To a round bottom flask was added THF (0.67 mL) and diisopropylamine (0.09 mL, 0.67 mmol, 10 eq). *n*-butyllithium (0.2 mL, 2.50 M in hexane, 0.536 mmol, 8.0 eq) was added at -78 ºC and the reaction was allowed to stir for 10 minutes before being warmed to 0 ºC for 10 minutes. At -78 ºC, (4^1*R*,7a*R*,10a*R*)-4^1-(3-((4-methoxybenzyl)oxy)-2-methylpropyl)decahydro-1*H*,8*H*-pyrido[3,2,1-*ij*]quinolin-8-one (26 mg, 0.067 mmol) was added and the mixture was stirred for 30 minutes before phenyl selenium chloride (38.5 mg, 0.201 mmol, 3.0 eq) in THF (0.5 M) was added dropwise. The solution was stirred for 15 minutes then warmed to room temperature and stirred for 1 hour. The reaction was quenched with saturated aq. NH_4Cl and extracted with Et_2O (0.5 M), dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography was used for purification (2% MeOH in dichloromethane) to afford (4^1*R*,7a*R*,10a*R*)-4^1-(3-((4-methoxybenzyl)oxy)-2-methylpropyl)-9-(phenylselanyl)decahydro-1*H*,8*H*-pyrido[3,2,1-*ij*]quinolin-8-one (34.4 mg ,0.064 mmol, 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 – 7.53 (m, 2H), 7.32 – 7.22 (m, 5H), 6.88 (d, *J* = 8.1 Hz, 2H), 4.47 – 4.33 (m, 2H), 3.82 (s, 3H), 3.17 (dtd, *J* = 12.4, 8.9, 6.4 Hz, 2H), 2.71 – 2.54 (m, 2H), 2.51 – 2.32 (m, 3H), 2.31 – 2.19 (m, 1H), 2.06 – 1.91 (m, 1H), 1.89 – 1.49 (m, 10H), 1.48 – 1.09 (m, 4H), 0.92 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.24, 159.20, 134.70, 134.65, 129.29, 129.27, 129.26, 128.43, 113.79, 76.70, 75.97, 72.72, 72.58,

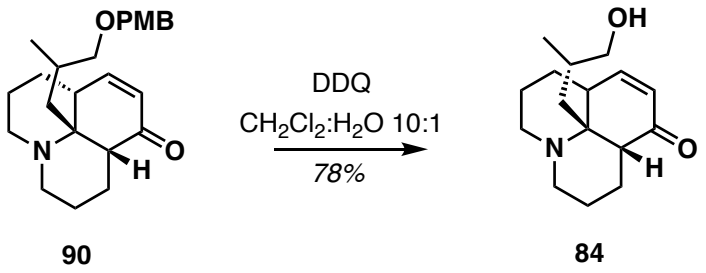
55.38, 49.01, 48.49, 48.09, 44.06, 35.01, 34.93, 29.65, 29.17, 25.77, 25.66, 25.58, 21.12, 20.74, 19.63, 19.50.



89 **90**

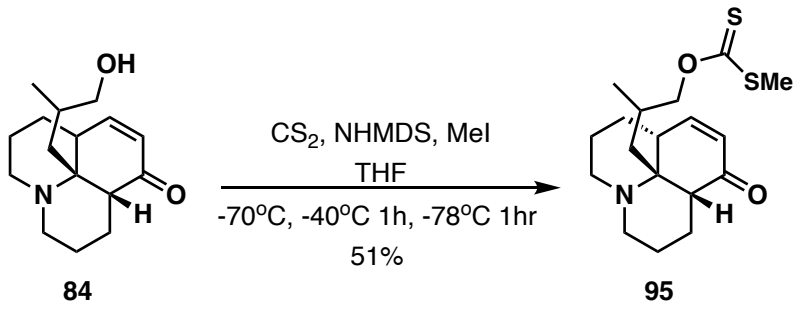
(4^1*R*,7a*R*,10a*R*)-4^1-(3-((4-methoxybenzyl)oxy)-2-methylpropyl)-2,3,4^1,5,6,7,7a,10a-octahydro-1*H*,8*H*-pyrido[3,2,1-*ij*]quinolin-8-one (90). i. (4^1*R*,7a*R*,10a*R*)-4^1-(3-((4-methoxybenzyl)oxy)-2-methylpropyl)-9-(phenylselanyl)decahydro-1*H*,8*H*-pyrido[3,2,1-*ij*]quinolin-8-one (17 mg, 0.030 mmol) was dissolved in dichloromethane (0.68 mL) and CSA (36.38 mg, 0.138 mmol, 5.0 eq) was added at room temperature. The reaction was allowed to stir for 10 minutes then cooled to 0 ºC and 3% aq. H_2O_2 (0.15 mL, 0.156 mmol, 5.0 eq) was added. Upon completion, the reaction was quenched with $Na_2S_2O_3$ and poured into a separatory funnel with saturated aq. $NaHCO_3$ and brine. Dichloromethane (0.5 M) was used to extract the organics which were dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was moved to the next step. ii. The crude was dissolved in toluene (0.5 mL) and $NaHCO_3$ (8.5mg, 0.100 mmol, 3.3 eq) was added. The reaction was stirred at 110 ºC for 1 hour. The reaction was diluted with saturated aq. $NaHCO_3$. Dichloromethane (0.5 M) was used to extract the organics which were dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography was used for purification (5% MeOH in dichloromethane) to afford (4^1*R*,7a*R*,10a*R*)-4^1-(3-((4-methoxybenzyl)oxy)-2-methylpropyl)-2,3,4^1,5,6,7,7a,10a-octahydro-1*H*,8*H*-pyrido[3,2,1-*ij*]quinolin-8-one (6.29 mg, 0.017 mmol, 54%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 5.8 Hz, 2H), 6.87 (d, *J* = 7.7 Hz, 2H), 6.71 – 6.56 (m, 1H), 5.99 – 5.90 (m, 1H), 4.45 – 4.30 (m, 2H), 3.81 (s, 3H), 3.22 – 3.04 (m, 2H), 2.69 – 2.49 (m, 5H), 1.85 – 1.69 (m, 5H), 1.63

(d, J = 12.2 Hz, 3H), 1.34 – 1.17 (m, 4H), 0.83 (d, J = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.73, 159.10, 129.19, 113.71, 76.26, 75.93, 72.65, 72.36, 55.29, 53.44, 47.62, 47.52, 47.43, 36.01, 30.55, 29.75, 19.75, 19.35.

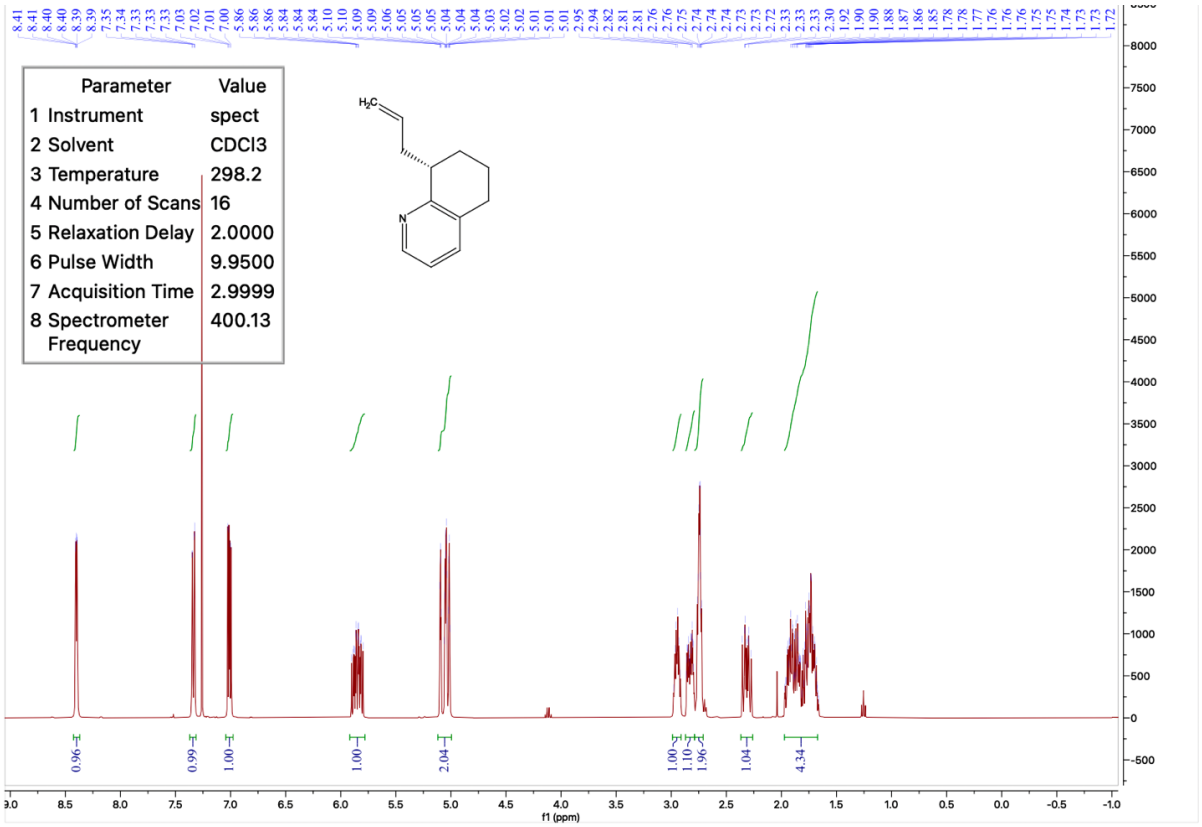


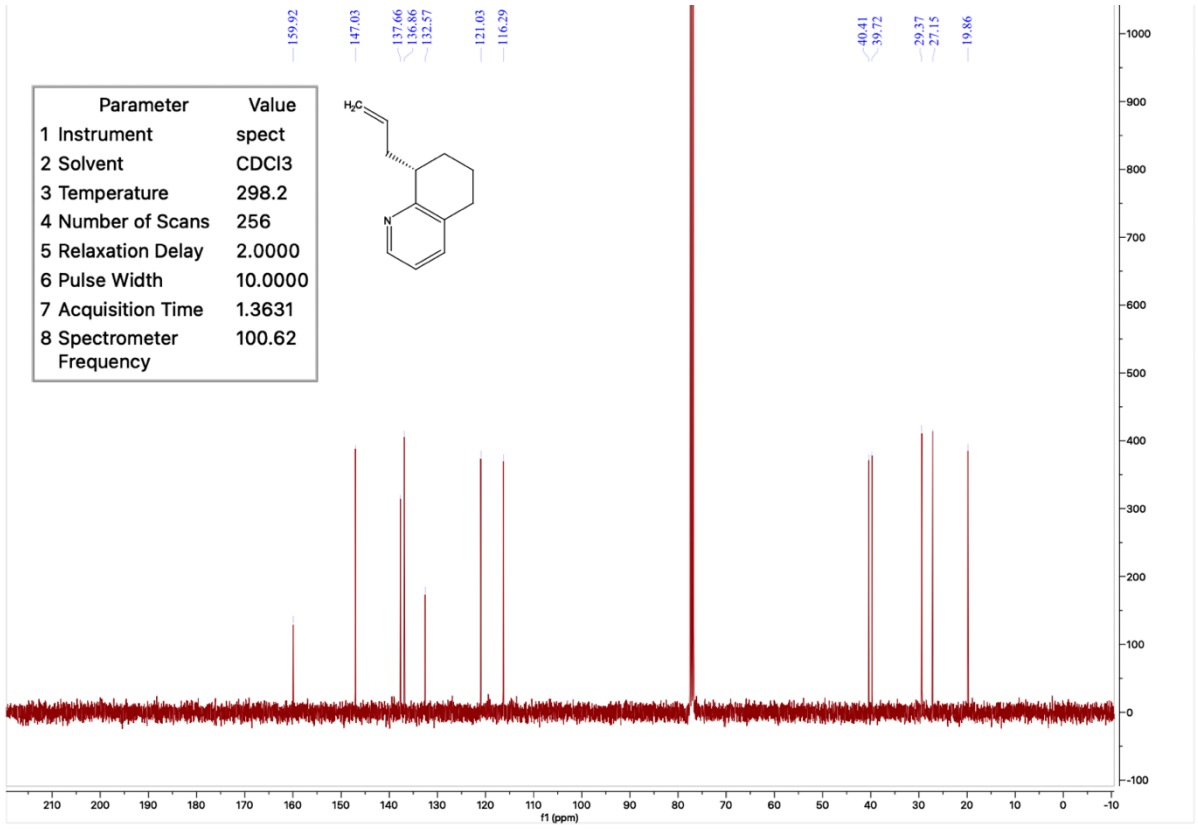
90 **84**

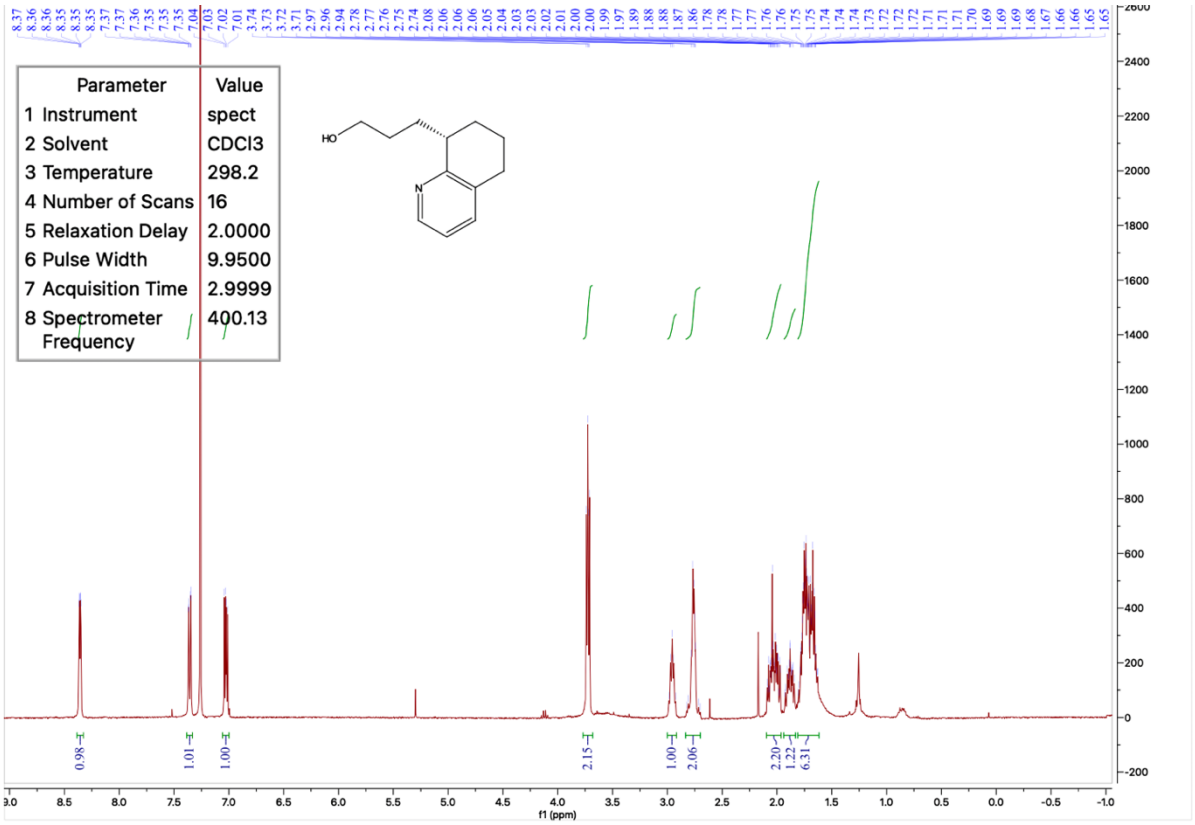
(4^1*R*,7a*R*)-4^1-((*S*)-3-hydroxy-2-methylpropyl)-2,3,4^1,5,6,7,7a,10a-octahydro-1*H*,8*H*-pyrido[3,2,1-*ij*]quinolin-8-one (84). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (53.1 mg, 0.234 mmol, 22.0 eq) was added to a solution of (4^1*R*,7a*R*,10a*R*)-4^1-(3-((4-methoxybenzyl)oxy)-2-methylpropyl)-2,3,4^1,5,6,7,7a,10a-octahydro-1*H*,8*H*-pyrido[3,2,1-*ij*]quinolin-8-one (6.0 mg, 0.0156 mmol) in a 10:1 solution of dichloromethane:water (0.24 mL). Upon completion, the reaction was diluted with dichloromethane and water. Three extractions with dichloromethane (0.5 M) were preformed and the organics were dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography was used for purification (10% MeOH in dichloromethane) to afford (4^1*R*,7a*R*)-4^1-((*S*)-3-hydroxy-2-methylpropyl)-2,3,4^1,5,6,7,7a,10a-octahydro-1*H*,8*H*-pyrido[3,2,1-*ij*]quinolin-8-one (5.1 mg, 0.0134 mmol, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.75 (d, *J* = 10.1 Hz, 1H), 6.02 (dd, *J* = 9.9, 3.3 Hz, 1H), 3.43 (dd, *J* = 10.5, 4.6 Hz, 1H), 3.21 (dd, *J* = 10.6, 7.3 Hz, 1H), 2.95 – 2.71 (m, 5H), 2.43 – 2.34 (m, 1H), 2.17 (td, *J* = 13.9, 5.6 Hz, 2H), 1.98 – 1.79 (m, 6H), 1.72 (dd, *J* = 14.5, 9.0 Hz, 1H), 1.49 (td, *J* = 15.4, 7.1 Hz, 2H), 1.27 (s, 1H), 0.86 (d, *J* = 6.1 Hz, 3H).

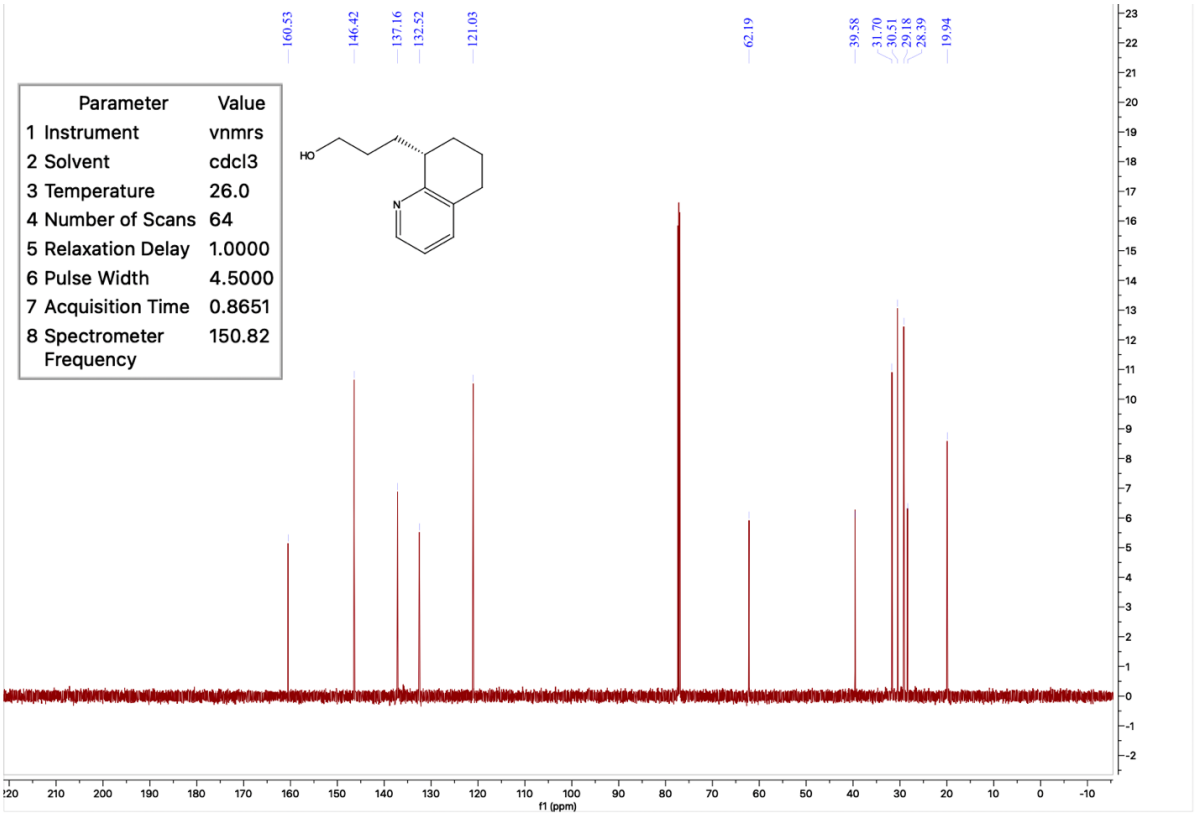


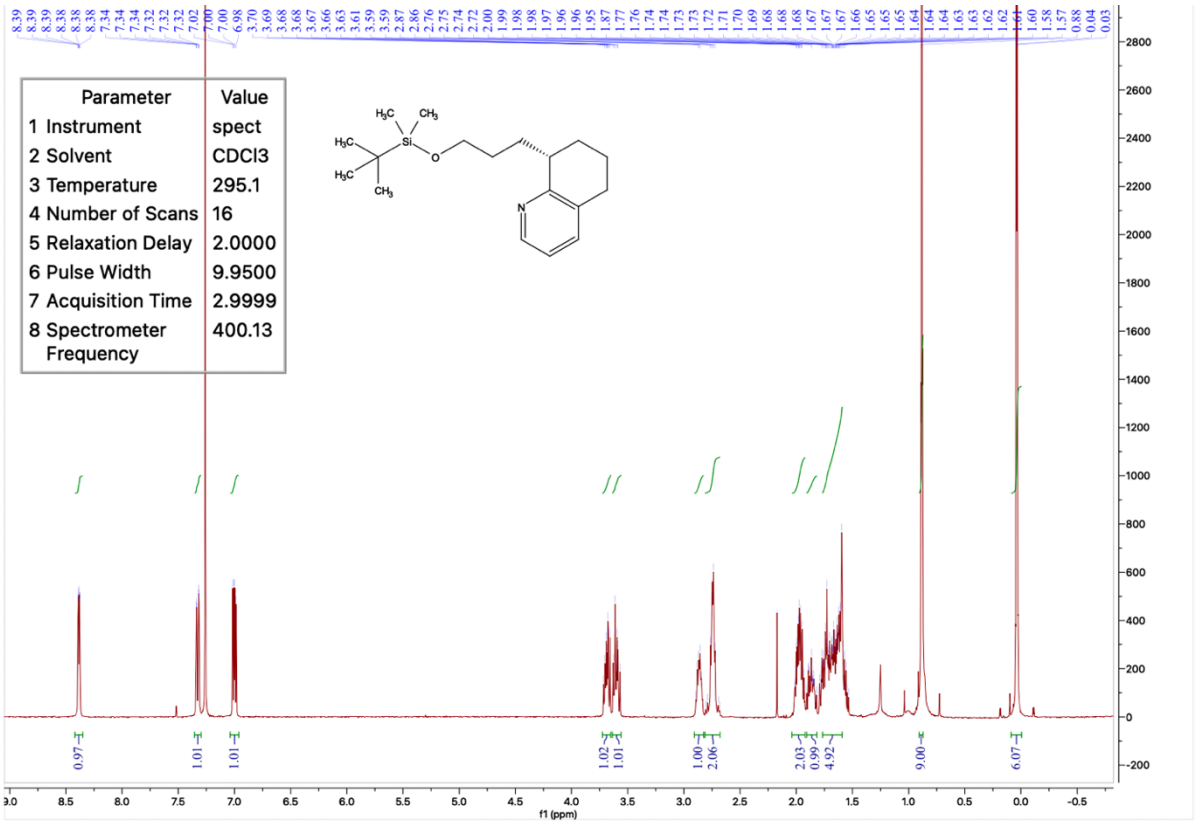
***S*-methyl *O*-(2-methyl-3-((4^1*R*,7a*R*,10a*R*)-8-oxo-2,3,5,6,7,7a,8,10a-octahydro-1*H*,4^1*H*-pyrido[3,2,1-*ij*]quinolin-4^1-yl)propyl) carbonodithioate (95)**. Carbon disulfide (0.07 mL, 0.114 mmol, 20 eq) was added to a solution of (4^1*R*,7a*R*,10a*R*)-4^1-(3-hydroxy-2-methylpropyl)-2,3,4^1,5,6,7,7a,10a-octahydro-1*H*,8*H*-pyrido[3,2,1-*ij*]quinolin-8-one (3.0 mg, 0.014 mmol) in THF (0.6 mL). The reaction was cooled to -78 ºC and 1 M NHMDS (0.014 mL, 0.014 mmol, 1.2 eq) was added and the reaction was gradually warmed to -40 ºC and stirred for 1 hour. Methyl iodide (0.006 mL, 0.014 mmol, 1.2 eq) was added at -78 ºC and the reaction was stirred for 1 hour. The reaction was quenched with saturated aq. NH_4Cl and extracted with EtOAc (0.5 M). The organics were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography was used for purification (2% MeOH in dichloromethane) to afford *S*-methyl *O*-(2-methyl-3-((4^1*R*,7a*R*,10a*R*)-8-oxo-2,3,5,6,7,7a,8,10a-octahydro-1*H*,4^1*H*-pyrido[3,2,1-*ij*]quinolin-4^1-yl)propyl) carbonodithioate (2.5 mg, 0.0071 mmol, 51%).^{1}H NMR (500 MHz, $CDCl_3$) δ 6.75 (dd, *J* = 10.1, 2.3 Hz, 1H), 6.00 (dd, *J* = 10.0, 3.5 Hz, 1H), 4.34 – 4.23 (m, 2H), 2.58 (s, 3H), 2.52 – 2.42 (m, 2H), 2.40 – 2.29 (m, 1H), 2.20 – 2.06 (m, 2H), 2.06 – 1.61 (m, 8H), 1.63 – 1.41 (m, 2H), 1.36 (d, *J* = 6.8 Hz, 1H), 1.27 (s, 2H), 0.94 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 216.13, 199.72, 151.66, 129.24, 128.34, 79.53, 62.53, 57.93, 48.12, 47.76, 47.49, 29.24, 25.98, 24.94, 24.39, 24.20, 19.08, 18.45.

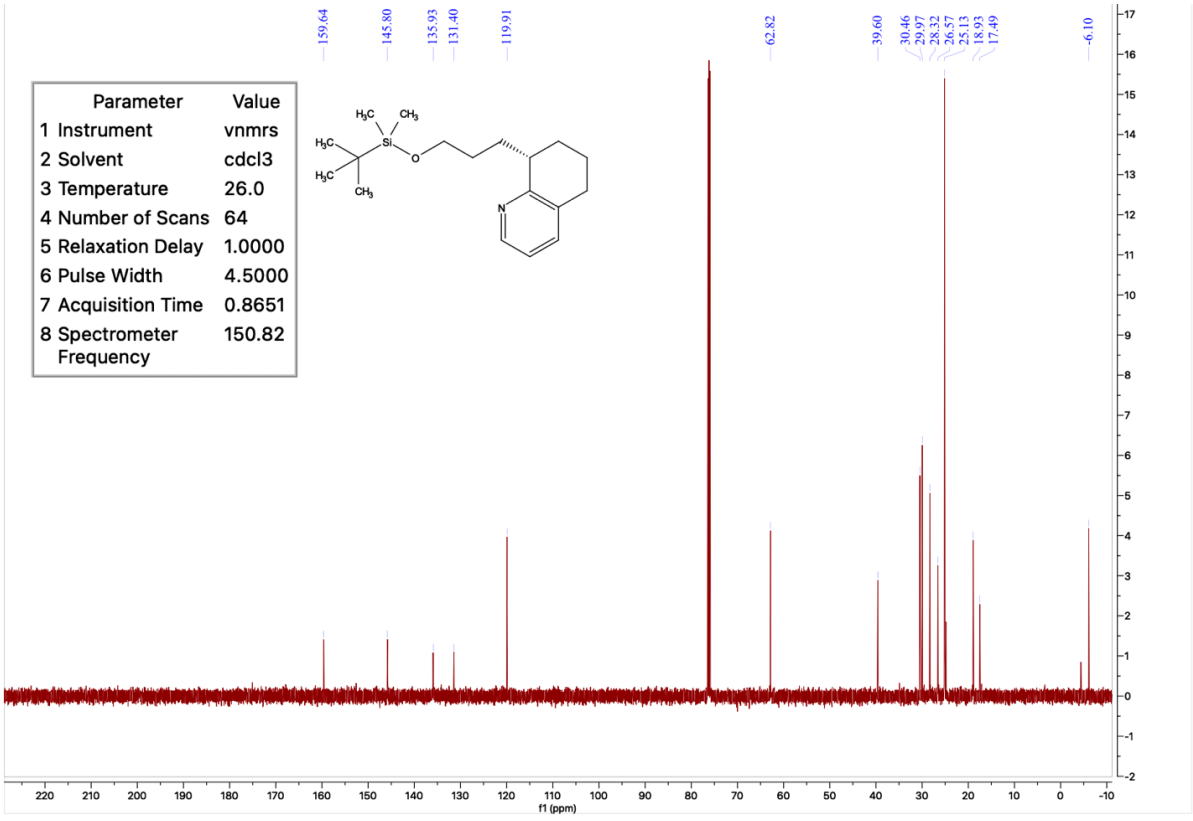

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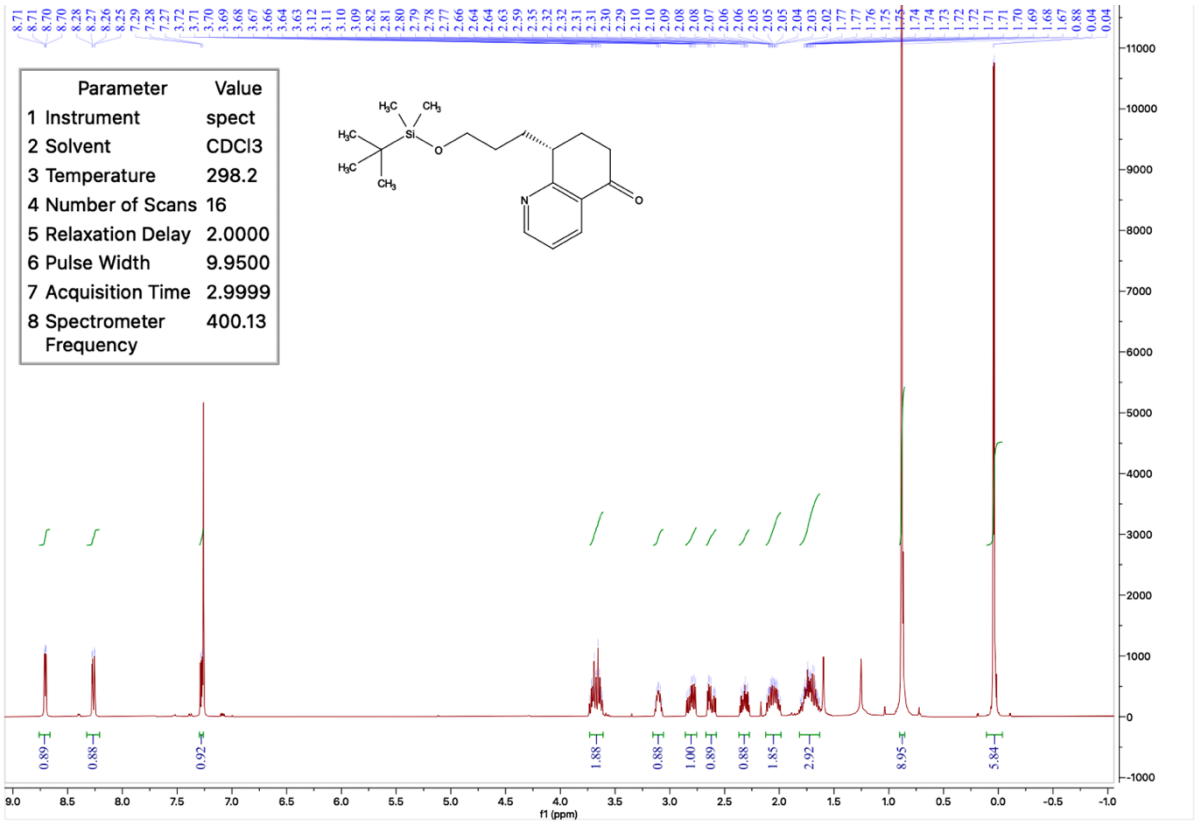

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6 Pulse Width 10.0000
7 Acquisition Time 1.3631
8 Spectrometer Frequency 100.62
f1 (ppm)

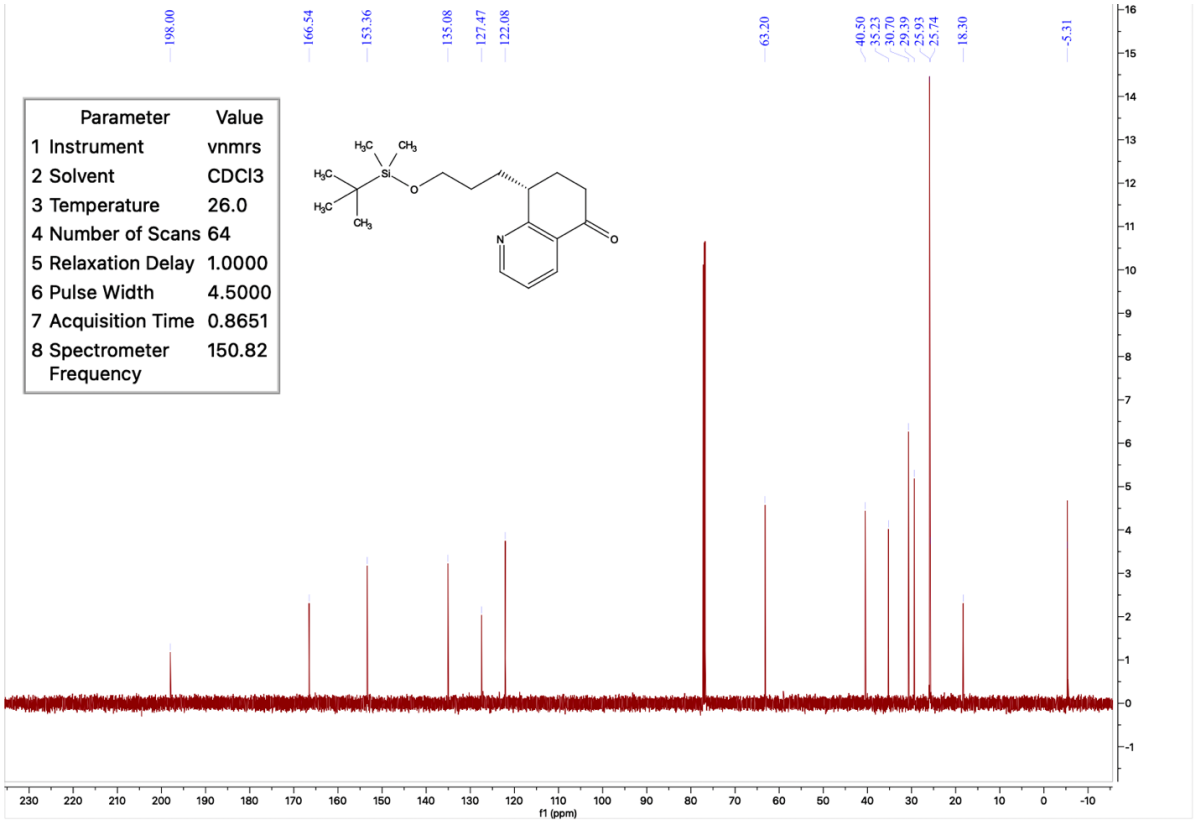

Parameter Value
1 Instrument spect
2 Solvent CDCl3
3 Temperature 298.2
4 Number of Scans 16
5 Relaxation Delay 2.0000
6 Pulse Width 9.9500
7 Acquisition Time 2.9999
8 Spectrometer Frequency 400.13
HO
N
0.98
1.01
1.00
2.15
1.00
2.06
2.20
1.22
6.31
f1 (ppm)

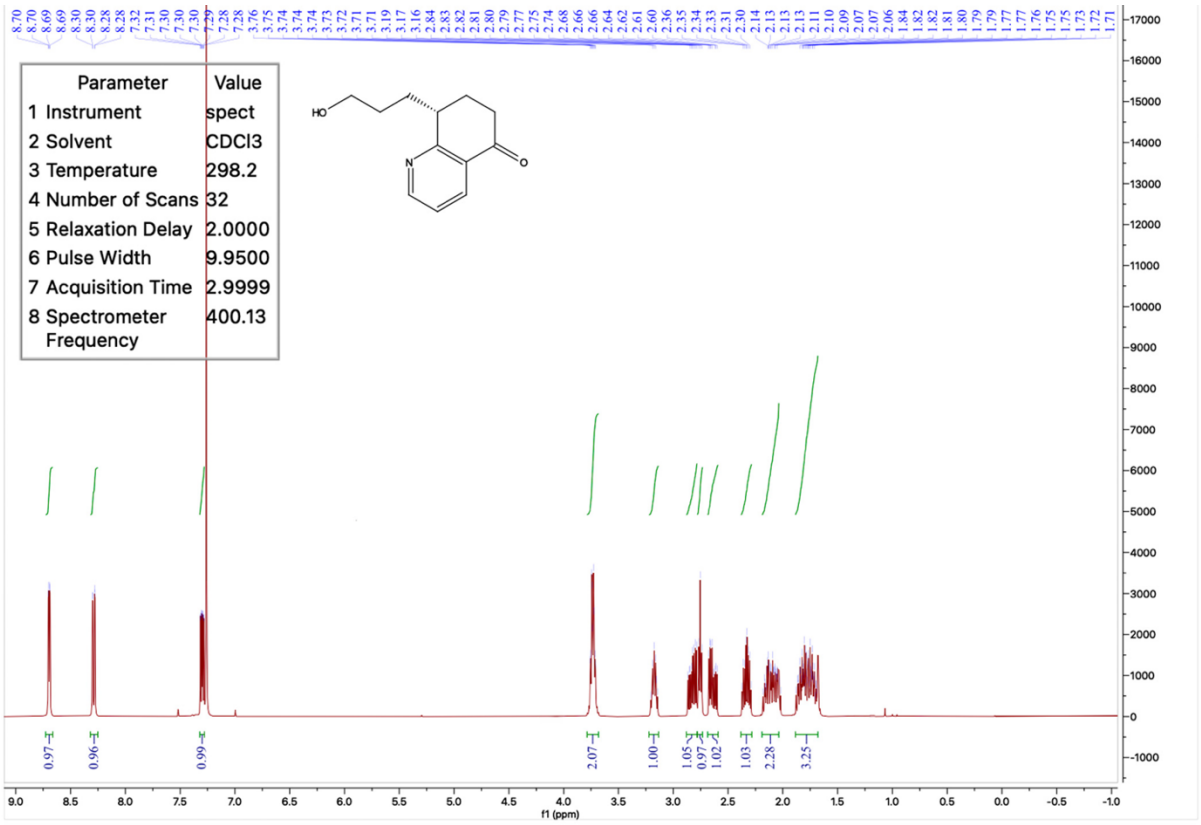

160.53
146.42
137.16
132.52
121.03
62.19
39.58
31.70
30.51
29.18
28.39
19.94
Parameter Value
1 Instrument vnmrs
2 Solvent cdcl3
3 Temperature 26.0
4 Number of Scans 64
5 Relaxation Delay 1.0000
6 Pulse Width 4.5000
7 Acquisition Time 0.8651
8 Spectrometer Frequency 150.82
HO
N
f1 (ppm)

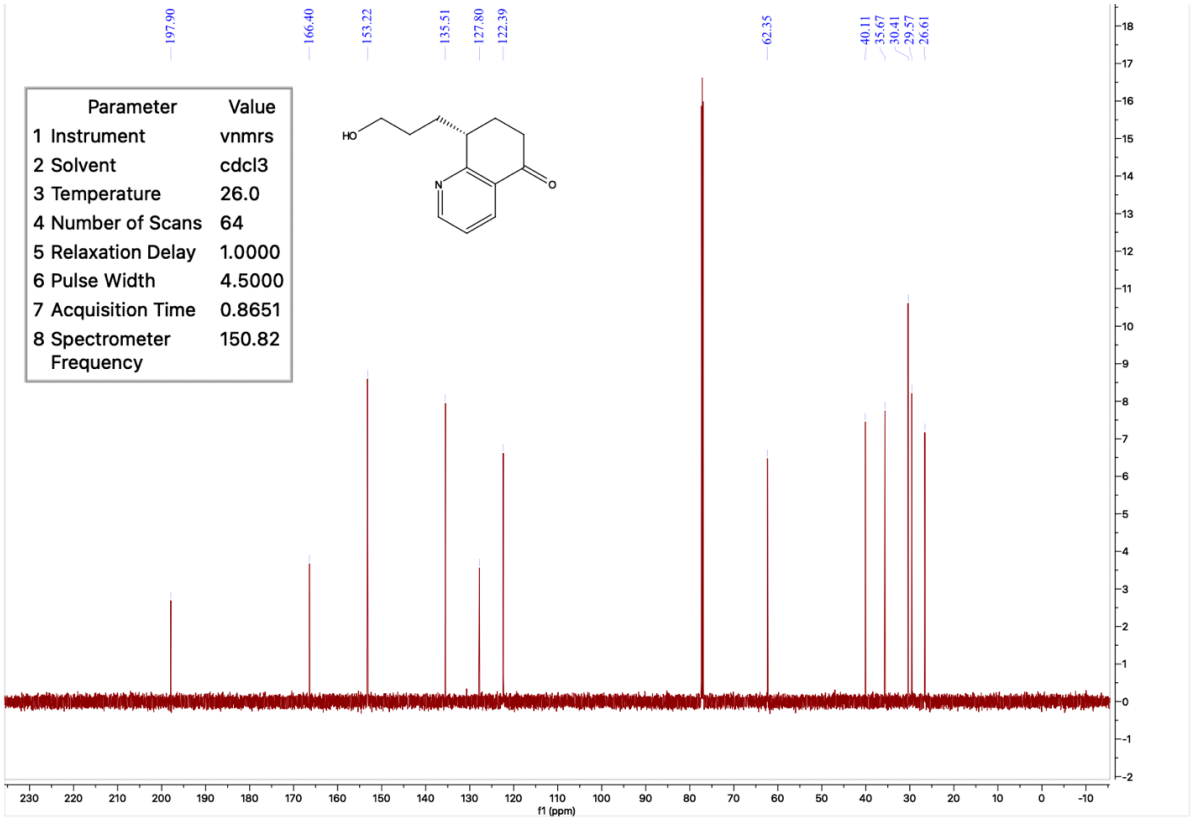

Parameter Value
1 Instrument spect
2 Solvent CDCl3
3 Temperature 295.1
4 Number of Scans 16
5 Relaxation Delay 2.0000
6 Pulse Width 9.9500
7 Acquisition Time 2.9999
8 Spectrometer Frequency 400.13
f1 (ppm)

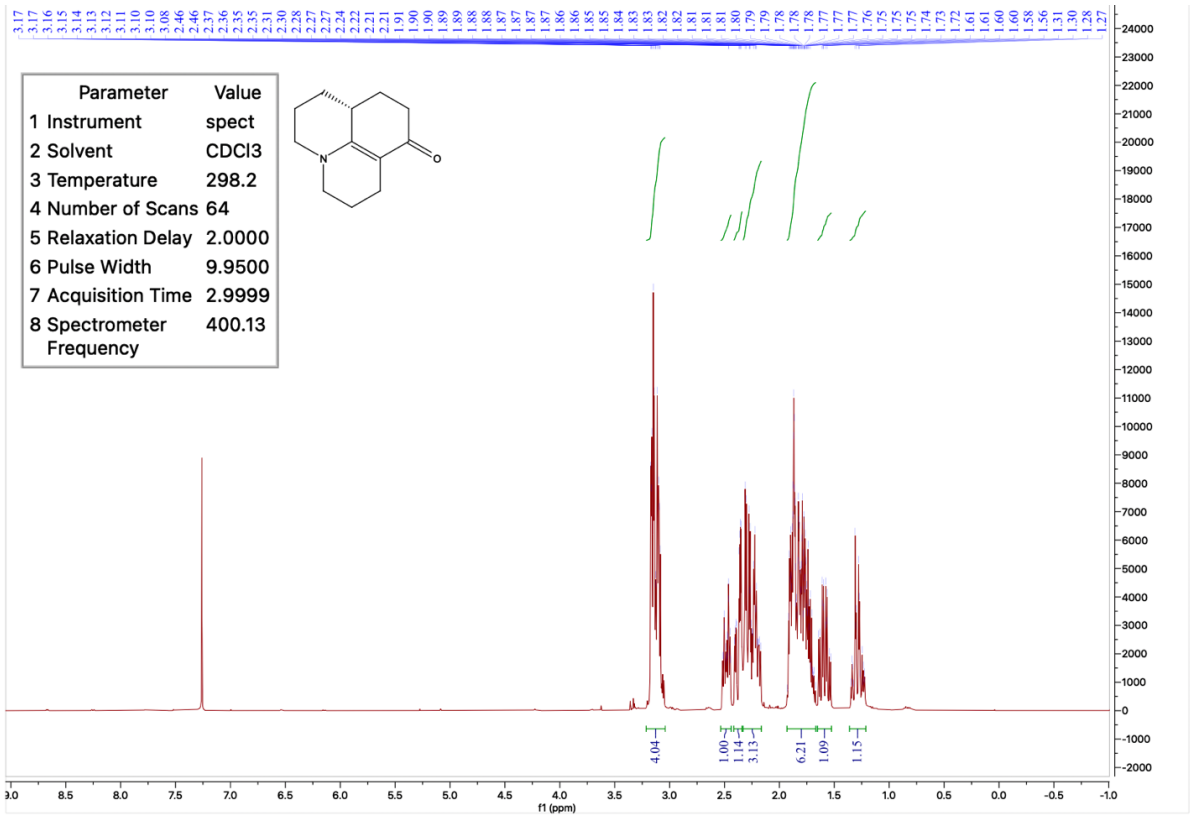

Parameter Value
1 Instrument vnmrs
2 Solvent cdcl3
3 Temperature 26.0
4 Number of Scans 64
5 Relaxation Delay 1.0000
6 Pulse Width 4.5000
7 Acquisition Time 0.8651
8 Spectrometer Frequency 150.82
f1 (ppm)

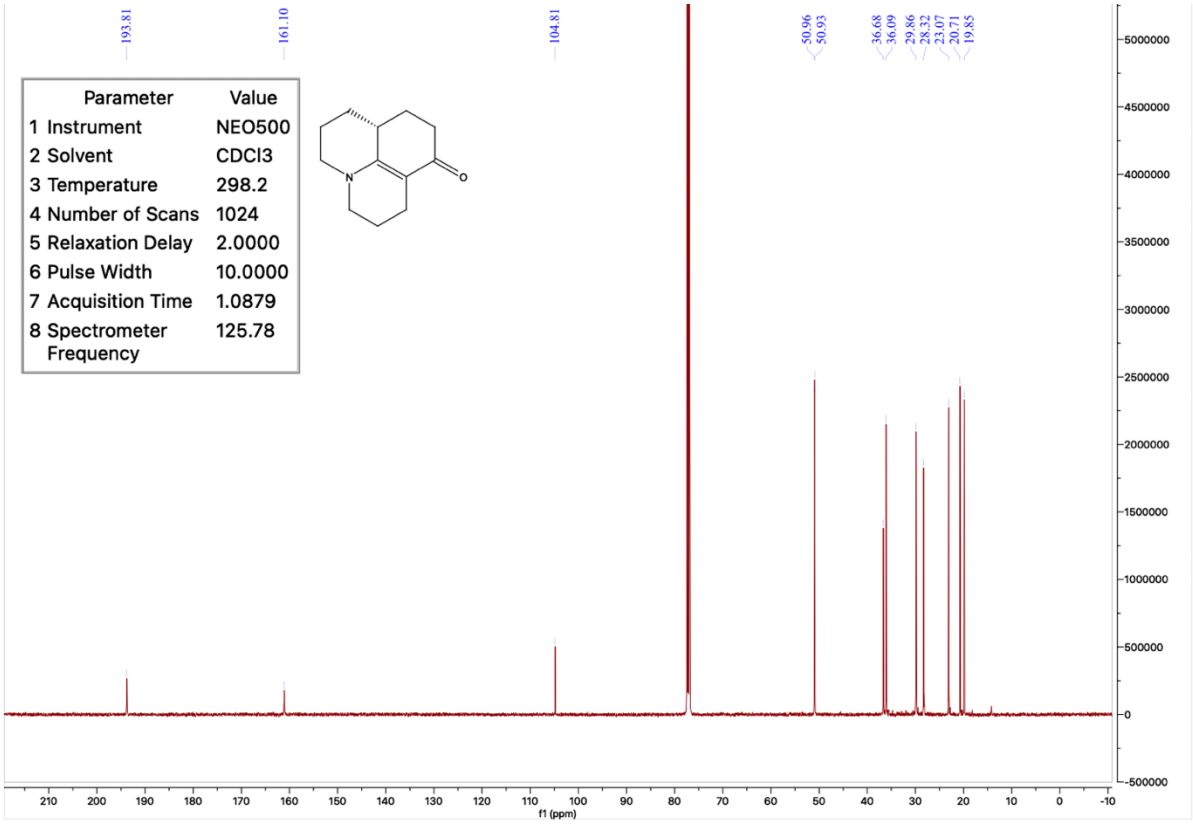

Parameter Value
1 Instrument spect
2 Solvent CDCl3
3 Temperature 298.2
4 Number of Scans 16
5 Relaxation Delay 2.0000
6 Pulse Width 9.9500
7 Acquisition Time 2.9999
8 Spectrometer Frequency 400.13
f1 (ppm)

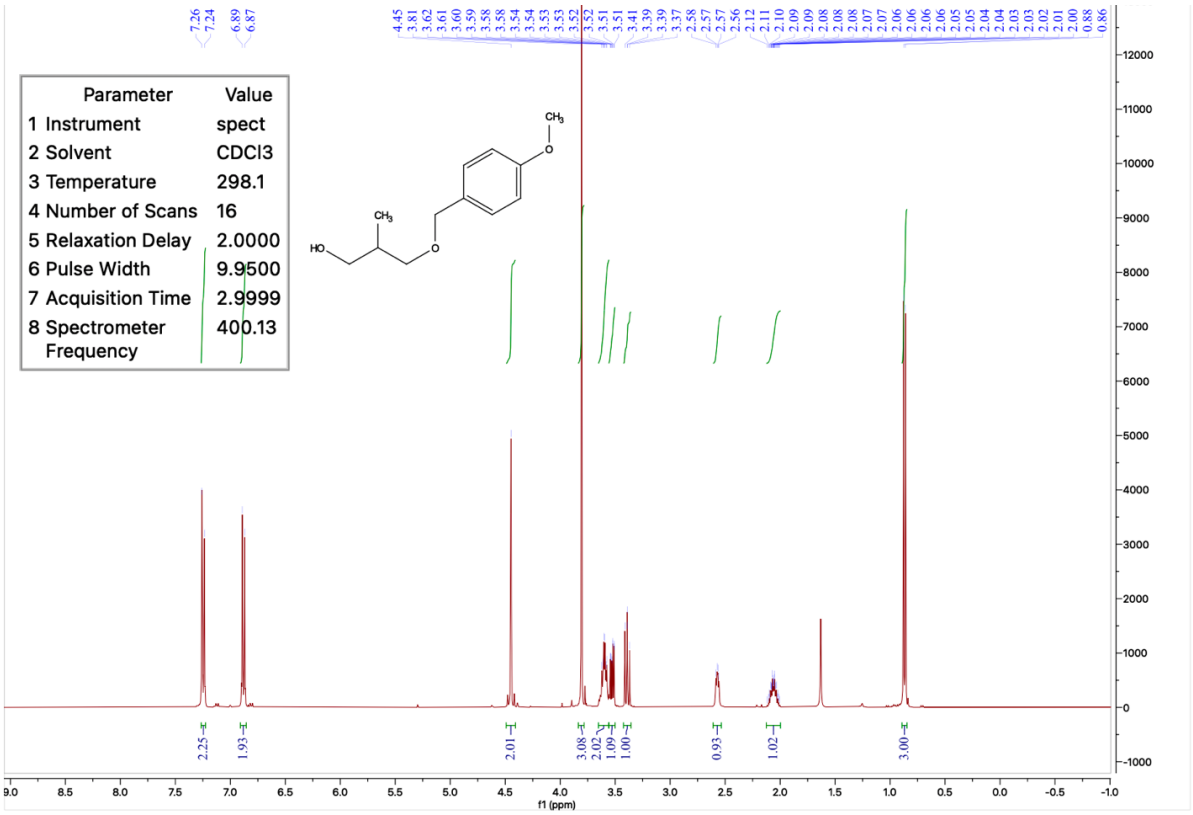

Parameter Value
1 Instrument vnmrs
2 Solvent CDCl3
3 Temperature 26.0
4 Number of Scans 64
5 Relaxation Delay 1.0000
6 Pulse Width 4.5000
7 Acquisition Time 0.8651
8 Spectrometer Frequency 150.82
198.00
166.54
153.36
135.08
127.47
122.08
63.20
40.50
35.23
30.70
29.39
25.93
25.74
18.30
-5.31
f1 (ppm)

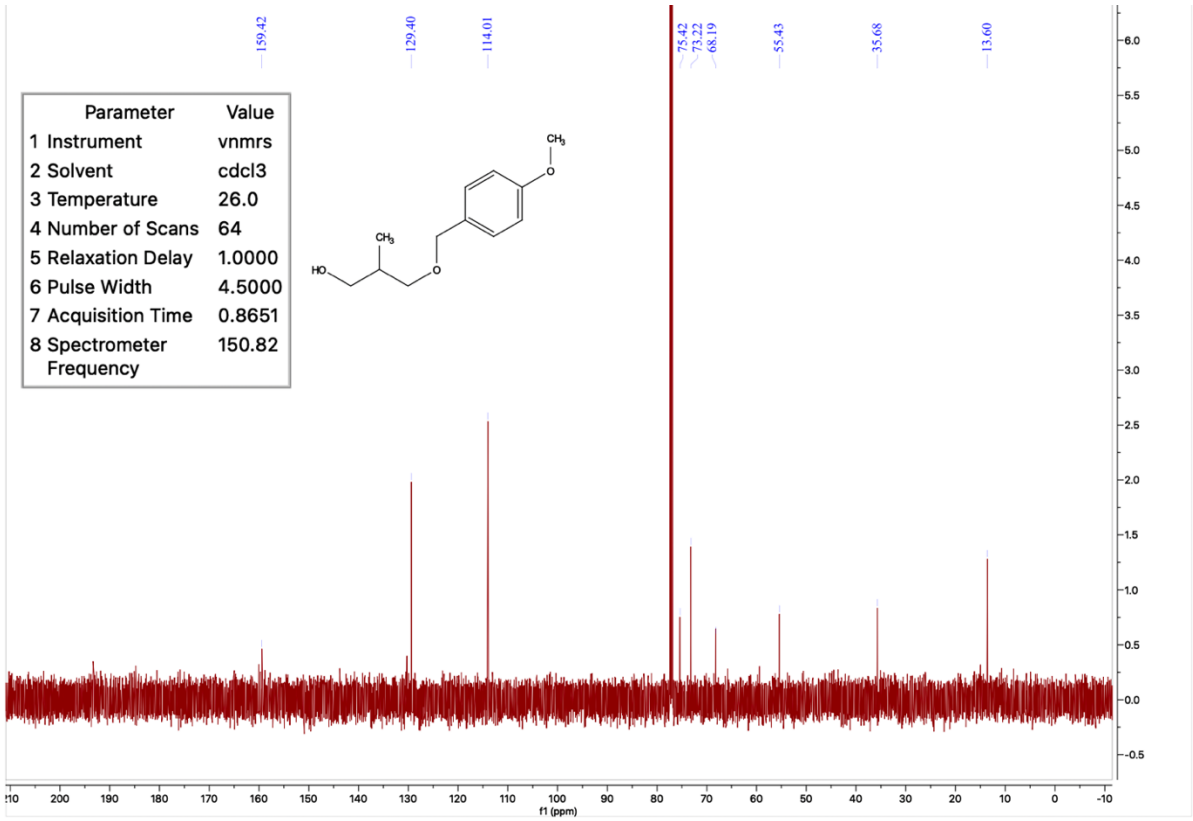

Parameter Value
1 Instrument spect
2 Solvent CDCl3
3 Temperature 298.2
4 Number of Scans 32
5 Relaxation Delay 2.0000
6 Pulse Width 9.9500
7 Acquisition Time 2.9999
8 Spectrometer Frequency 400.13
HO
N
O
f1 (ppm)

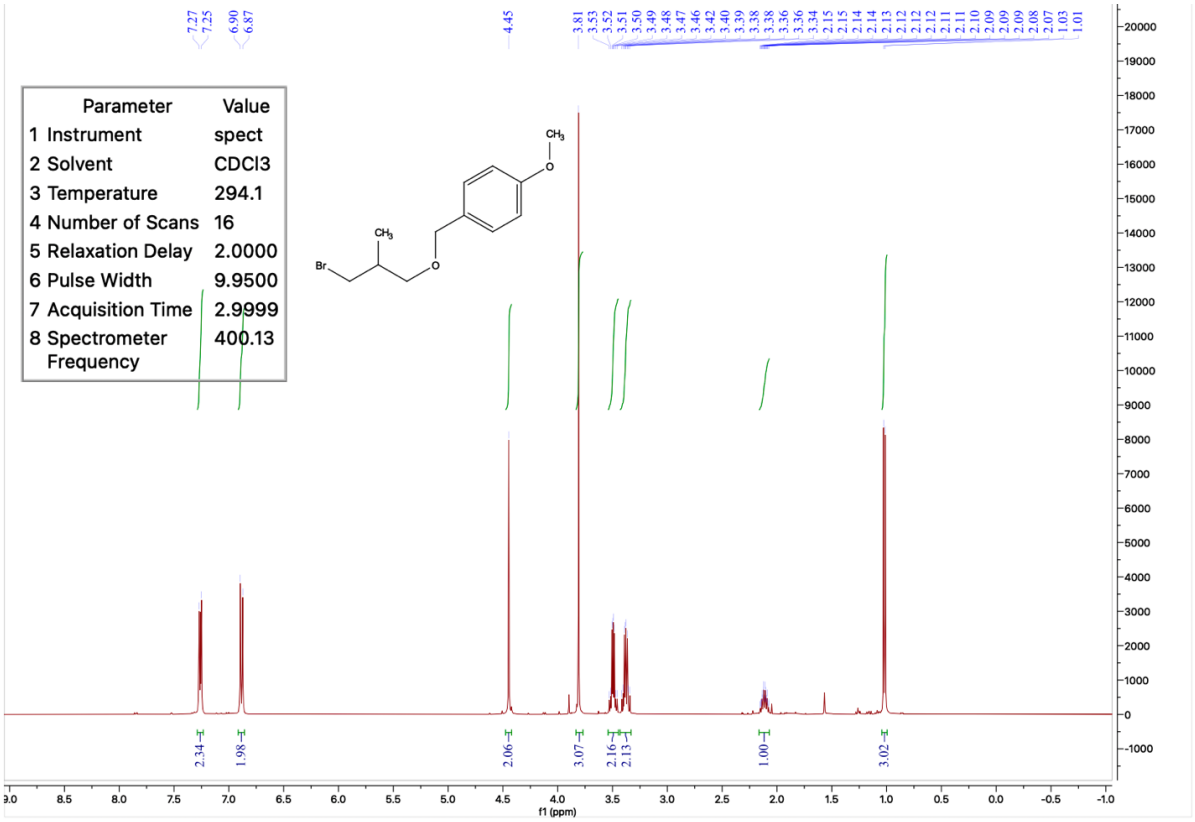

197.90
166.40
153.22
135.51
127.80
122.39
62.35
40.11
35.67
30.41
29.57
26.61
Parameter Value
1 Instrument vnmrs
2 Solvent cdcl3
3 Temperature 26.0
4 Number of Scans 64
5 Relaxation Delay 1.0000
6 Pulse Width 4.5000
7 Acquisition Time 0.8651
8 Spectrometer Frequency 150.82
HO
N
O
f1 (ppm)

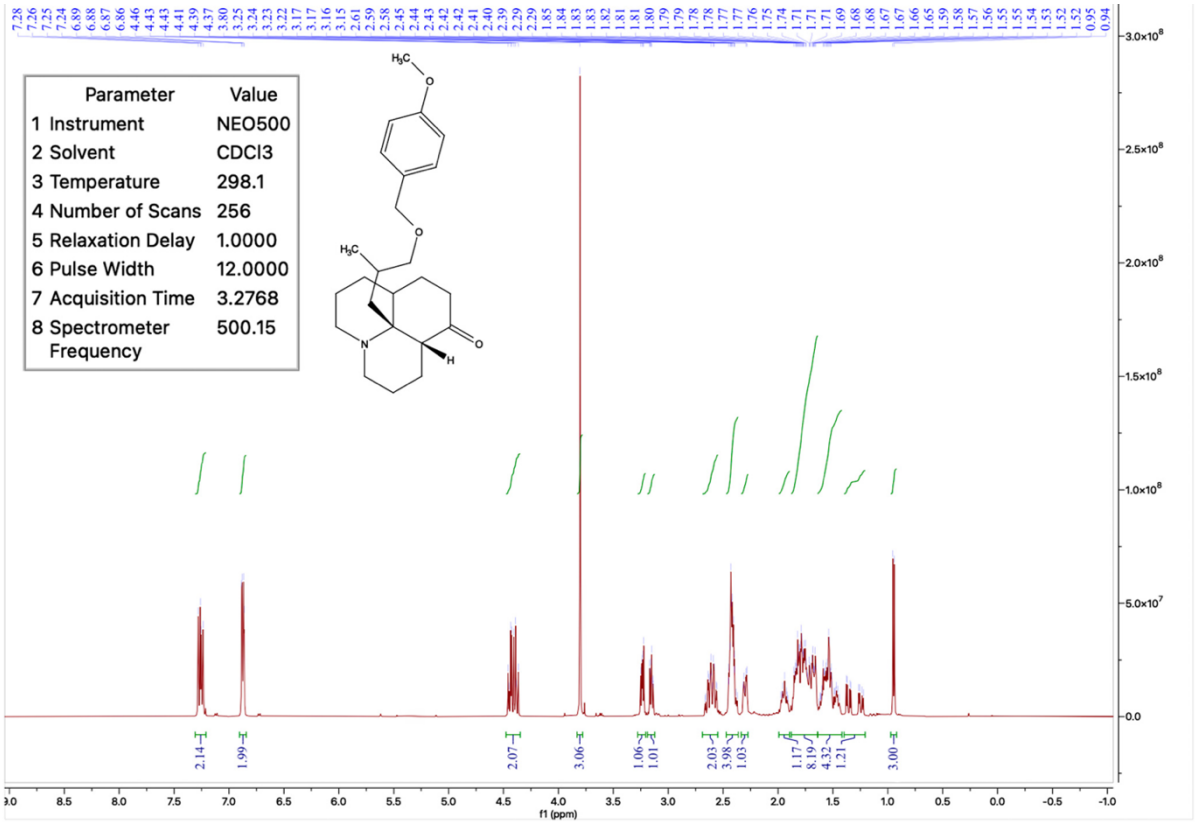

Parameter Value
1 Instrument spect
2 Solvent CDCl3
3 Temperature 298.2
4 Number of Scans 64
5 Relaxation Delay 2.0000
6 Pulse Width 9.9500
7 Acquisition Time 2.9999
8 Spectrometer Frequency 400.13
4.04
1.00
1.14
3.13
6.21
1.09
1.15
f1 (ppm)

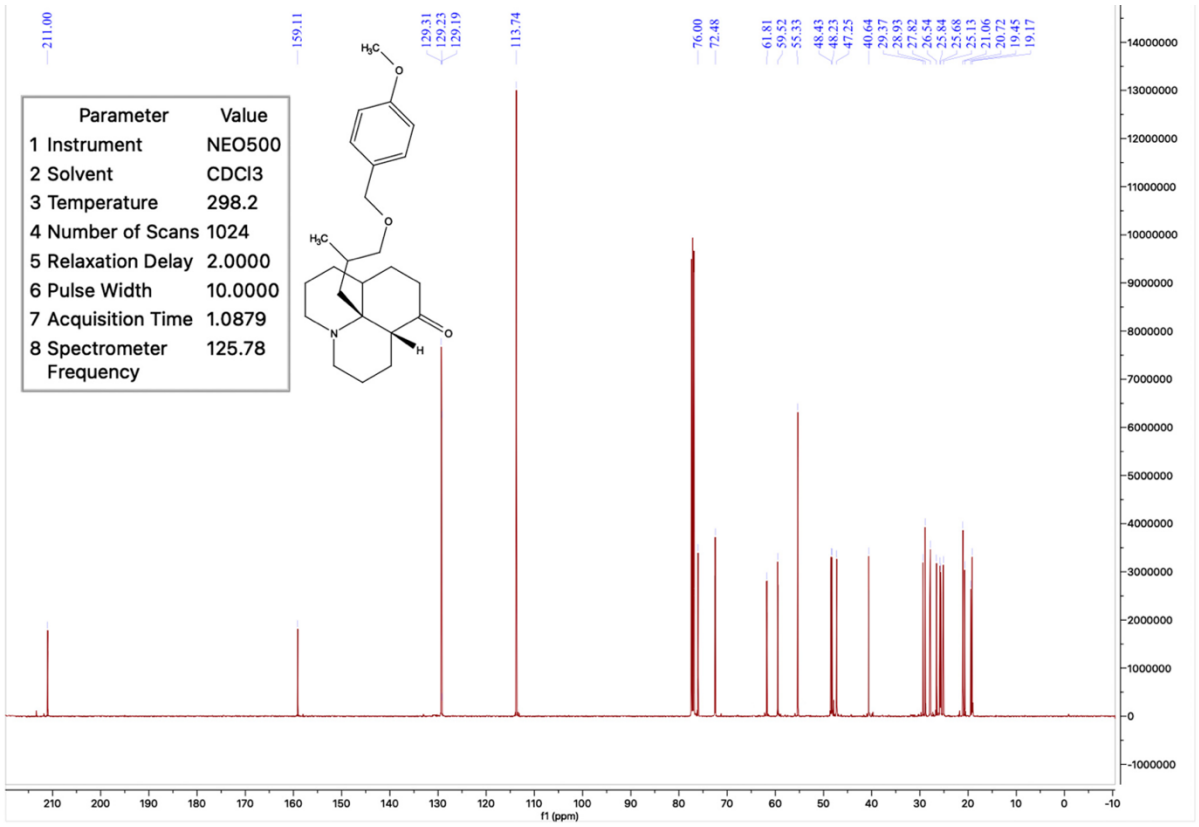

193.81
161.10
104.81
50.96
50.93
36.68
36.09
29.86
28.32
23.07
20.71
19.85
Parameter Value
1 Instrument NEO500
2 Solvent CDCl3
3 Temperature 298.2
4 Number of Scans 1024
5 Relaxation Delay 2.0000
6 Pulse Width 10.0000
7 Acquisition Time 1.0879
8 Spectrometer Frequency 125.78
f1 (ppm)

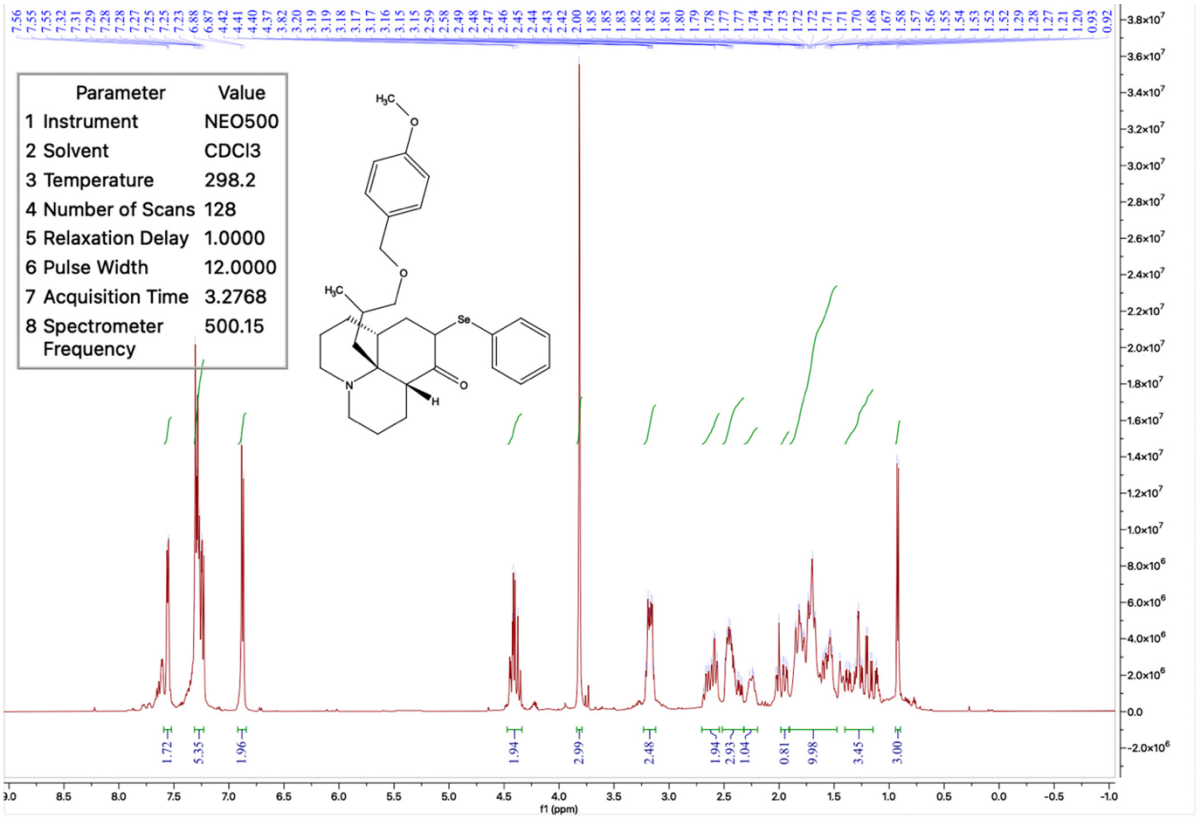

Parameter Value
1 Instrument spect
2 Solvent CDCl3
3 Temperature 298.1
4 Number of Scans 16
5 Relaxation Delay 2.0000
6 Pulse Width 9.9500
7 Acquisition Time 2.9999
8 Spectrometer Frequency 400.13
f1 (ppm)

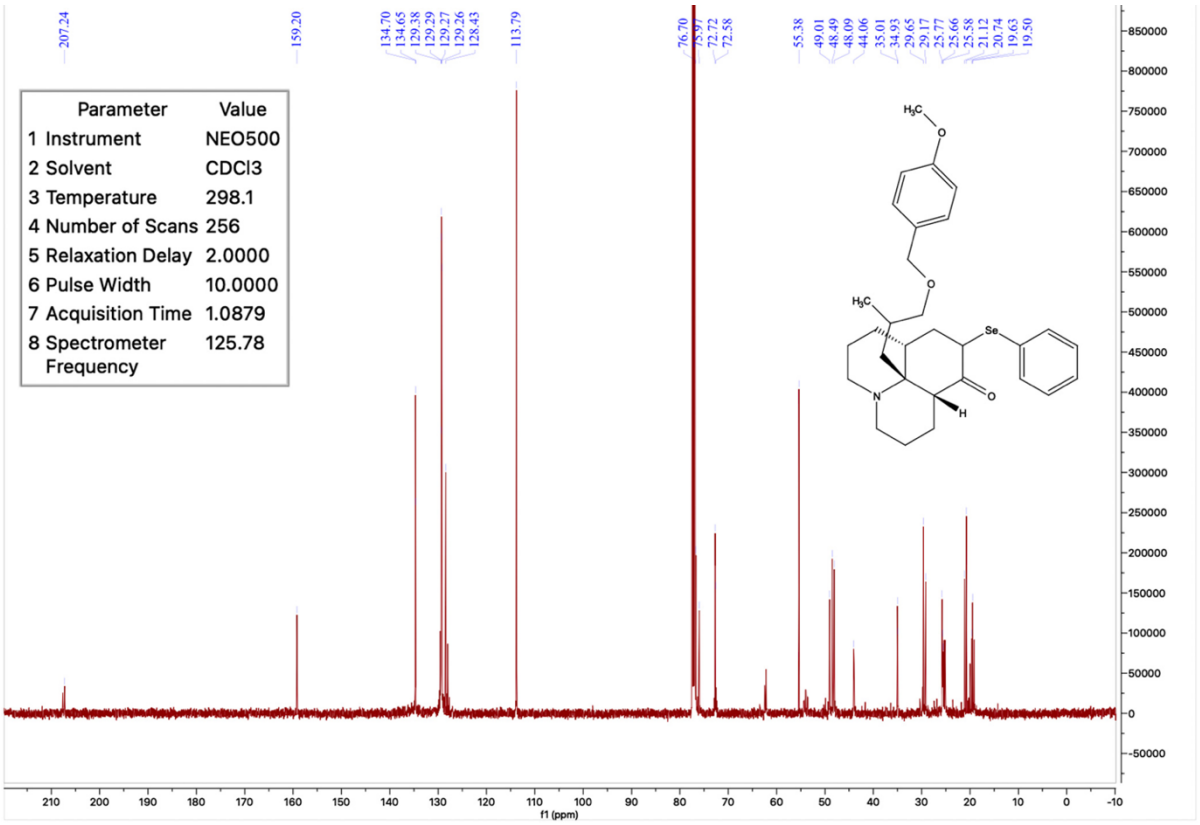

Parameter Value
1 Instrument vnmrs
2 Solvent cdcl3
3 Temperature 26.0
4 Number of Scans 64
5 Relaxation Delay 1.0000
6 Pulse Width 4.5000
7 Acquisition Time 0.8651
8 Spectrometer Frequency 150.82
f1 (ppm)

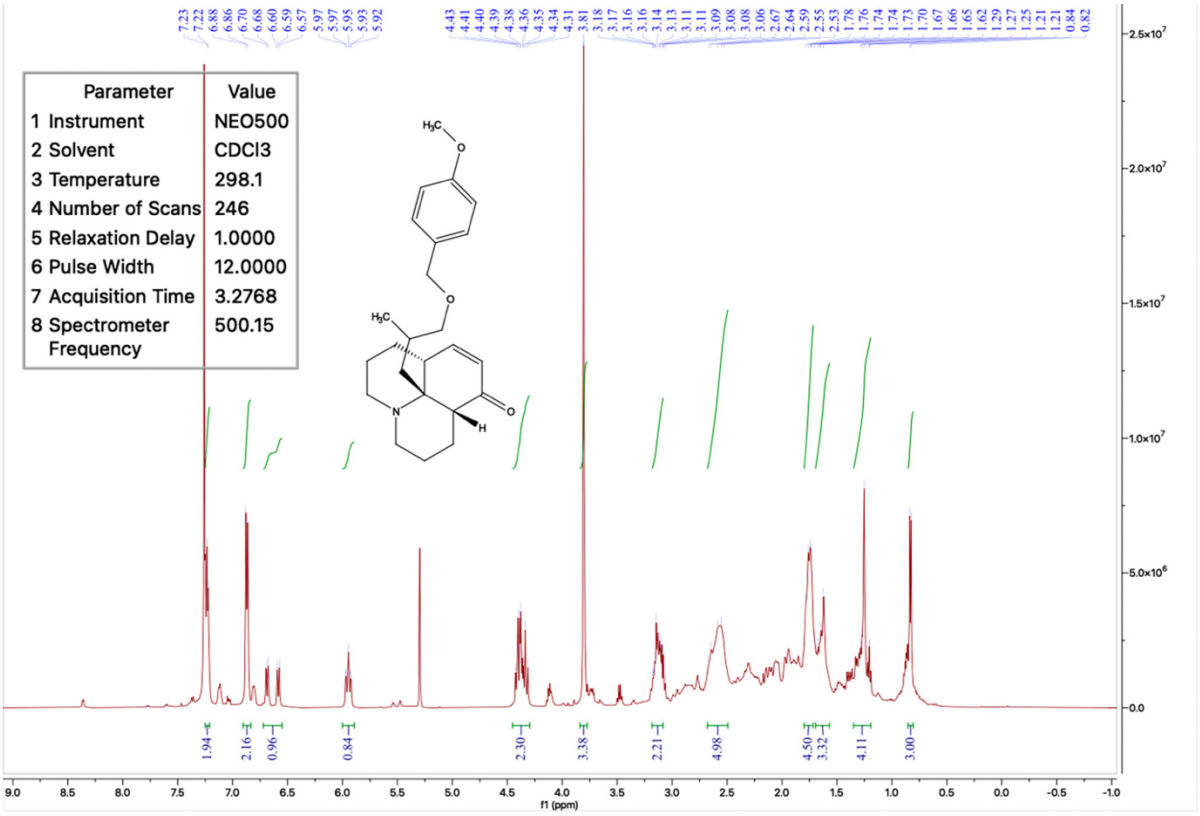

Parameter Value
1 Instrument spect
2 Solvent CDCl3
3 Temperature 294.1
4 Number of Scans 16
5 Relaxation Delay 2.0000
6 Pulse Width 9.9500
7 Acquisition Time 2.9999
8 Spectrometer Frequency 400.13
f1 (ppm)

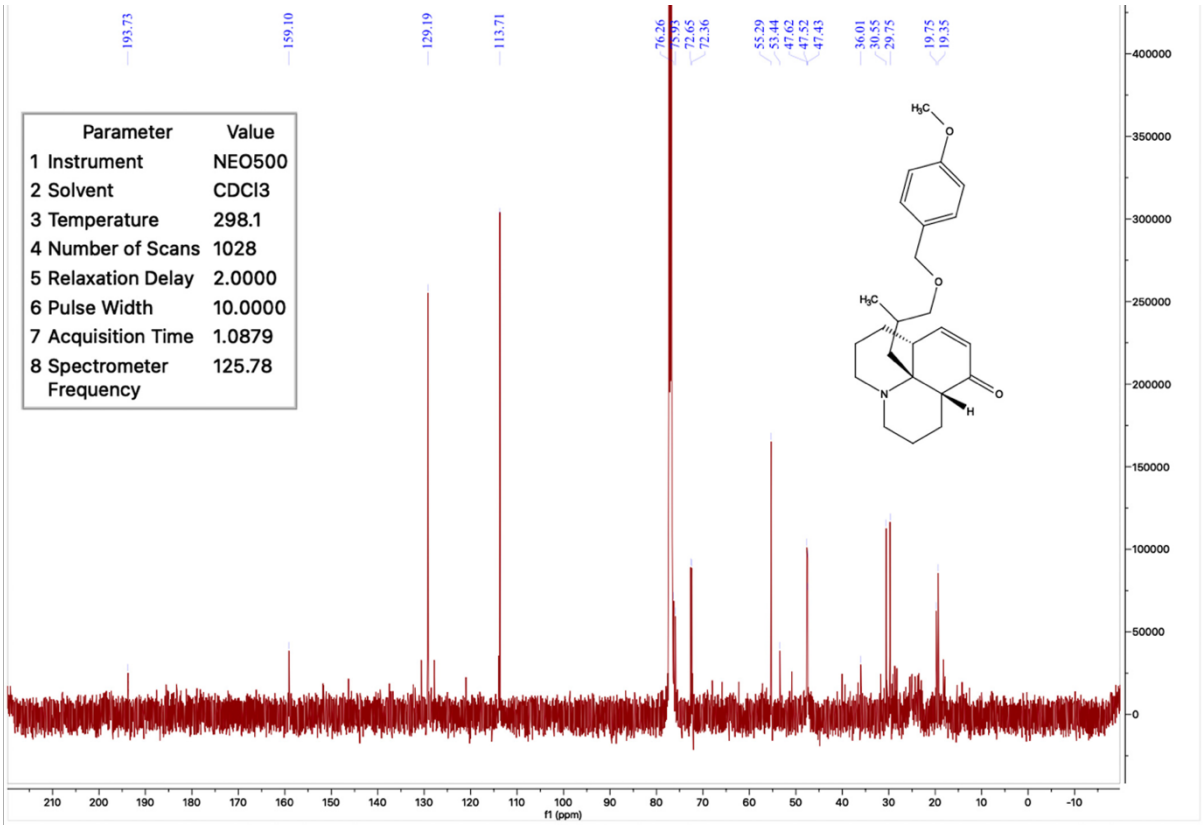

Parameter Value
1 Instrument NEO500
2 Solvent CDCl3
3 Temperature 298.1
4 Number of Scans 256
5 Relaxation Delay 1.0000
6 Pulse Width 12.0000
7 Acquisition Time 3.2768
8 Spectrometer Frequency 500.15
f1 (ppm)

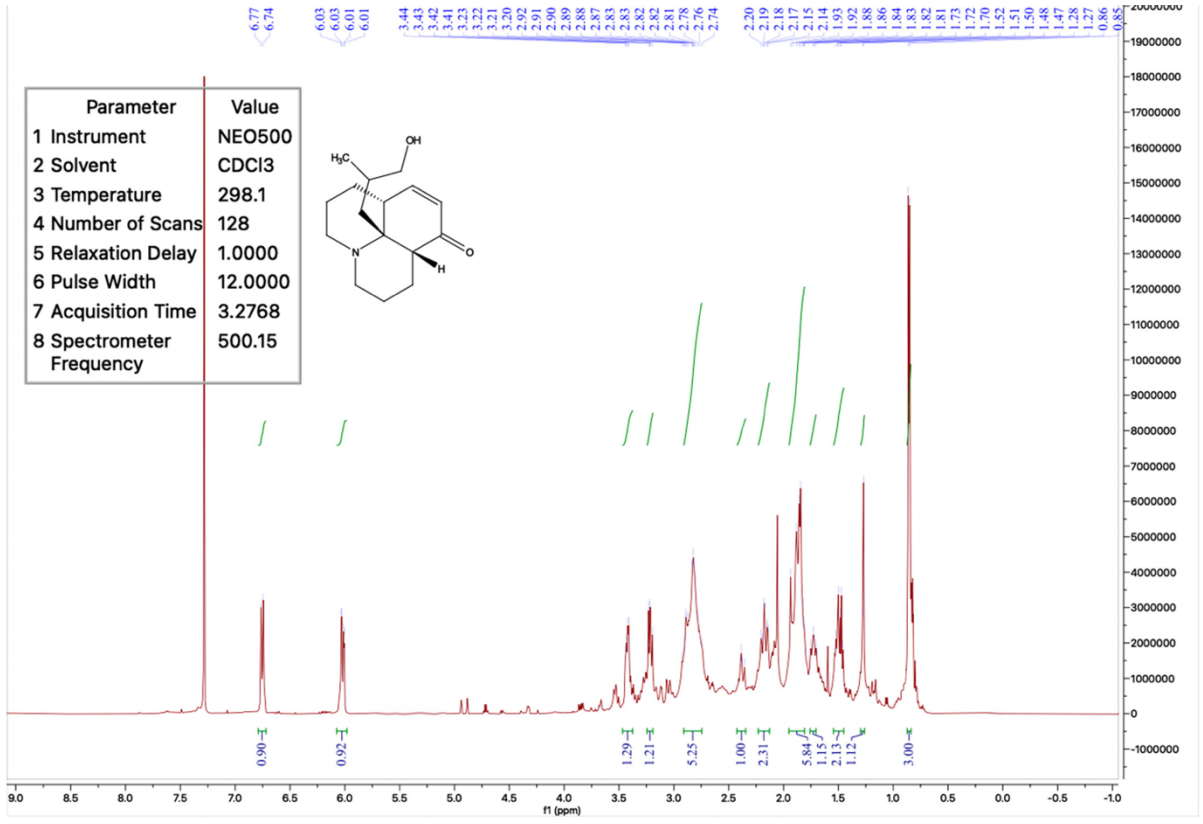

211.00
159.11
129.31
129.23
129.19
113.74
76.00
72.48
61.81
59.52
55.33
48.43
48.23
47.25
40.64
29.37
28.93
27.82
26.54
25.84
25.68
25.13
21.06
20.72
19.45
19.17
Parameter Value
1 Instrument NEO500
2 Solvent CDCl3
3 Temperature 298.2
4 Number of Scans 1024
5 Relaxation Delay 2.0000
6 Pulse Width 10.0000
7 Acquisition Time 1.0879
8 Spectrometer Frequency 125.78
f1 (ppm)

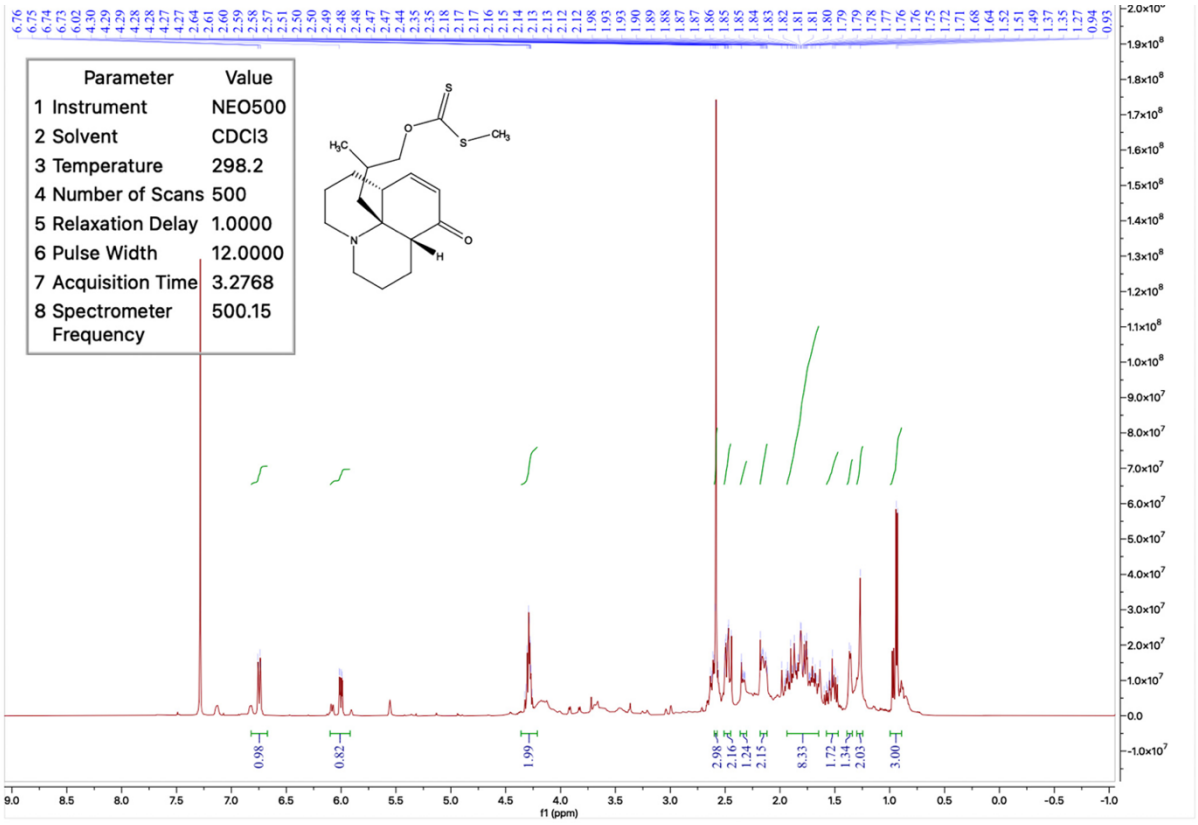

Parameter Value
1 Instrument NEO500
2 Solvent CDCl3
3 Temperature 298.2
4 Number of Scans 128
5 Relaxation Delay 1.0000
6 Pulse Width 12.0000
7 Acquisition Time 3.2768
8 Spectrometer Frequency 500.15
1.72
5.35
1.96
1.94
2.99
2.48
1.94
2.93
1.04
0.81
9.98
3.45
3.00
f1 (ppm)

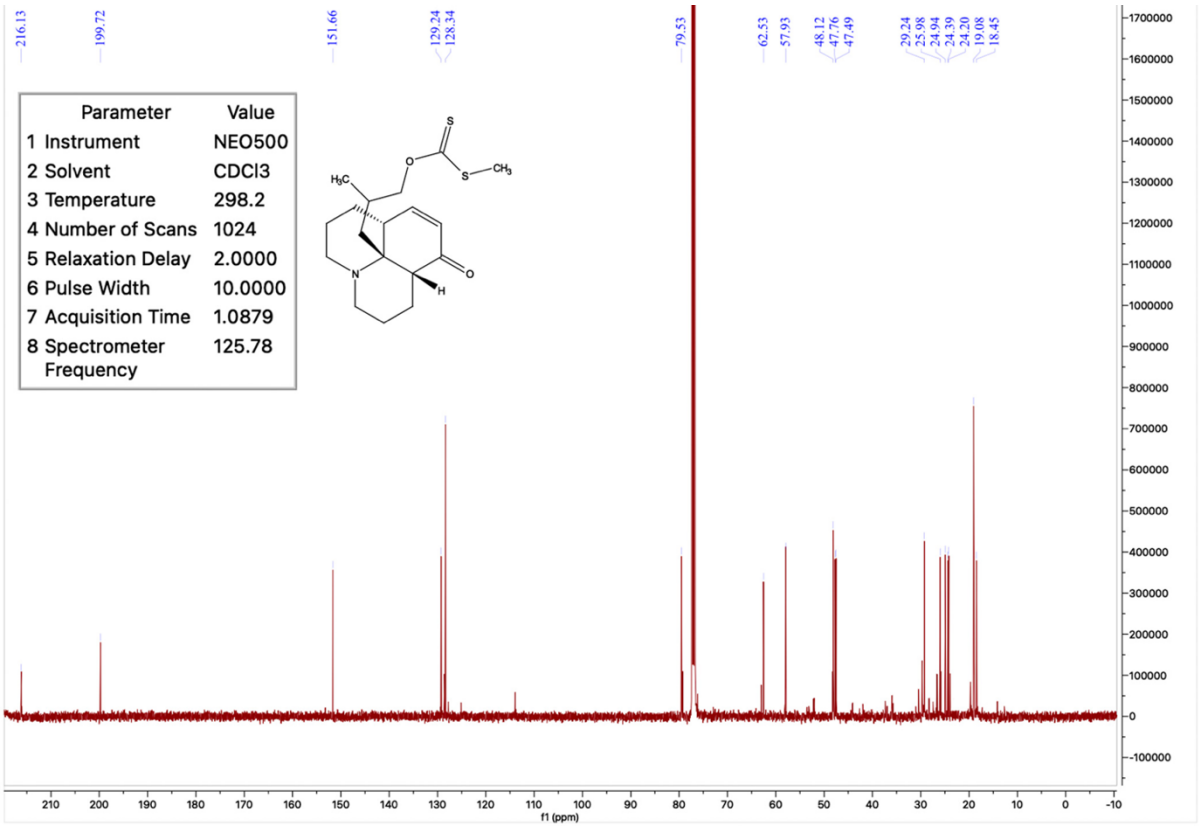

207.24
159.20
134.70
134.65
129.38
129.29
129.27
129.26
128.43
113.79
76.70
25.97
72.72
72.58
55.38
49.01
48.49
48.09
44.06
35.01
34.93
29.65
29.17
25.77
25.66
25.58
21.12
20.74
19.63
19.50
Parameter Value
1 Instrument NEO500
2 Solvent CDCl3
3 Temperature 298.1
4 Number of Scans 256
5 Relaxation Delay 2.0000
6 Pulse Width 10.0000
7 Acquisition Time 1.0879
8 Spectrometer Frequency 125.78
f1 (ppm)


Parameter Value
1 Instrument NEO500
2 Solvent CDCl3
3 Temperature 298.1
4 Number of Scans 246
5 Relaxation Delay 1.0000
6 Pulse Width 12.0000
7 Acquisition Time 3.2768
8 Spectrometer Frequency 500.15
1.94
2.16
0.96
0.84
2.30
3.38
2.21
4.98
4.50
3.32
4.11
3.00
f1 (ppm)


193.73
159.10
129.19
113.71
76.26
75.93
72.65
72.36
55.29
53.44
47.62
47.52
47.43
36.01
30.55
29.75
19.75
19.35
Parameter Value
1 Instrument NEO500
2 Solvent CDCl3
3 Temperature 298.1
4 Number of Scans 1028
5 Relaxation Delay 2.0000
6 Pulse Width 10.0000
7 Acquisition Time 1.0879
8 Spectrometer Frequency 125.78
f1 (ppm)


6.77
6.74
6.03
6.03
6.01
6.01
3.44
3.43
3.42
3.41
3.23
3.22
3.21
3.20
2.92
2.91
2.90
2.89
2.88
2.87
2.83
2.83
2.82
2.82
2.81
2.78
2.76
2.74
2.20
2.19
2.18
2.17
2.15
2.14
1.93
1.92
1.88
1.86
1.84
1.83
1.82
1.81
1.73
1.72
1.70
1.52
1.51
1.50
1.48
1.47
1.28
1.27
0.86
0.85
Parameter Value
1 Instrument NEO500
2 Solvent CDCl3
3 Temperature 298.1
4 Number of Scans 128
5 Relaxation Delay 1.0000
6 Pulse Width 12.0000
7 Acquisition Time 3.2768
8 Spectrometer Frequency 500.15
0.90
0.92
1.29
1.21
5.25
1.00
2.31
5.84
1.15
2.13
1.12
3.00
f1 (ppm)


Parameter Value
1 Instrument NEO500
2 Solvent CDCl3
3 Temperature 298.2
4 Number of Scans 500
5 Relaxation Delay 1.0000
6 Pulse Width 12.0000
7 Acquisition Time 3.2768
8 Spectrometer Frequency 500.15
f1 (ppm)


Parameter Value
1 Instrument NEO500
2 Solvent CDCl3
3 Temperature 298.2
4 Number of Scans 1024
5 Relaxation Delay 2.0000
6 Pulse Width 10.0000
7 Acquisition Time 1.0879
8 Spectrometer Frequency 125.78
f1 (ppm)

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