THE UNIVERSITY OF CHICAGO

THE DEVELOPMENT OF STRATEGIES, REACTIONS, AND TACTICS FOR THE TOTAL SYNTHESES OF CHILOCORINE C AND DANKASTERONE B

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$(BzO)_2$	benzoyl peroxide
(*S*)-Me-CBS	(*S*)-2-Me-Corey-Bakshi-Shibata oxazaborolidine catalyst
Ac	acyl
Ar	aryl
Bn	benzyl
Bz	benzoyl
CIDR	crystallization-induced dynamic resolution
COSY	correlated spectroscopy
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DCE	1,2-dichloroethene
DIBAL	lithium bis(trimethylsilyl)amide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
Hantzsch ester	diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate
HBpin	4,4,5,5-tetramethyl-1,3,2-dioxaborolane
HMPA	hexamethylphosphoramide

IBX	2-iodoxybenzoic acid
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
*m*CPBA	*meta*-chloroperoxybenzoic acid
$Mn(dpm)_3$	tris(2,2,6,6-tetramethyl-3,5-heptanedionato)manganese(III)
MVK	methyl vinyl ketone
NaHMDS	sodium bis(trimethylsilyl)amide
NBD	norbornadiene
NHC	N-heterocyclic carbenes
NOESY	nuclear Overhauser effect spectroscopy
PES	potential energy surface
p-TsOH	*para*-toluenesulfonic acid
TBAF	tetra-*n*-butylammonium fluoride
TBSCl	*tert*-butylchlorodimethylsilane
TFA	trifluoroacetic acid
TMSCl	trimethylsilyl chloride
TS	transition state

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Abstract

The Development of Strategies, Reactions, and Tactics for the Total Syntheses of Chilocorine C and Dankasterone B

Vladislav G. Lisnyak

Chapter 1. Mannich-type Reactions of Cyclic Nitrones: Syntheses of (–)-Lobeline and (–)-Sedinone.

Piperidine is a very common structural motif of numerous classes of alkaloids and important pharmaceuticals. A particularly common structural feature found in these molecules is the presence of a β-aminocarbonyl or β-aminoalcohol moiety. We have developed an enantioselective Mannich-type addition of methyl ketones to nitrones producing the resulting hydroxylamines with high yields and enantioslectivity. The substrate scope of this reaction is broad and includes different 2,3,4-substituted and heterocyclic nitrones, as well as different electron rich- and -deficient acetophenones and alkyl methyl ketones. Additionally, we developed a nitrone variant of Robinson-Schöpf reaction that further expanded the scope to 5- and 7-membered ring and acyclic nitrones, albeit in racemic format. The combination of two developed methodologies provided a powerful tool for the unified approach towards total synthesis of two 2,6-disubstituted piperidine alkaloids: (–)-lobeline and (–)-sedinone.

Chapter 2. Enantiospecific Total Synthesis of Chilocorine C.

Chilocorine C is a very structurally unique defensive hexacyclic alkaloid that was isolated from ladybug beetles (Coccinellidae). It belongs to a class of "dimeric alkaloids" and is present as a minor component in *Chilocorus cacti*. We have successfully completed the first total synthesis of chilocorine C via a convergent strategy. Our overall approach includes a carefully orchestrated

sequence with several chemoselective transformations, including a specifically designed cascade that accomplishes nine distinct chemical reactions in one-pot, can smoothly forge that domain and ultimately enable a 15-step, 11-pot enantiospecific synthesis of the natural product. Mechanistic studies, density functional theory calculations, and the delineation of several other unsuccessful approaches highlight its unique elements.

Chapter 3. Enantiospecific Total Synthesis of Dankasterone B.

Dankasterone B represents a unique biologically active cystostatic steroid that was isolated from *Halichondria* sponge-derived fungus *Gymnascella dankaliensis*. Structurally, it contains a very rare 13(14→8)*abeo*-8-ergostane steroid core, that is believed to be a result of a 1,2-migration of the C13–C14 bond to the C8 position. We have successfully accomplished a 20 step total synthesis of dankasterone B as well as formal total synthesis of dankasterone A and periconiastone A, starting from commercially available (*R*)-carvone using a convergent strategy. Our synthesis combines several unique elements like Zweifel olefination, diastereospecific intramolecular Heck reaction, diastereoselective Claisen rearrangement to install the ergosterol sidechain and SmI_2-promoted late-stage 6-*exo*-*trig* cyclization.

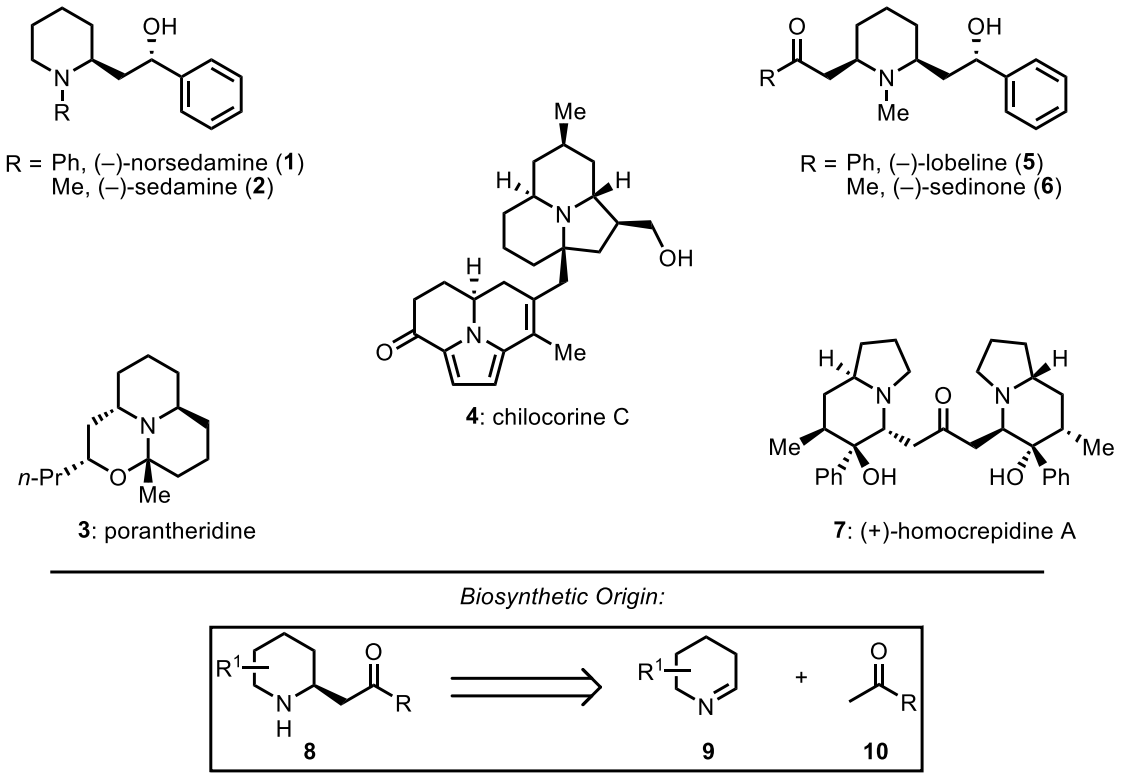
Chapter 1

Mannich-type Reactions of Cyclic Nitrones: Syntheses of (–)-Lobeline and (–)-Sedinone

1.1. Introduction.

Piperidine is a very common structural motif of numerous classes of alkaloids and important pharmaceuticals.[1] A particularly common structural feature found in these molecules is the presence of a β-aminocarbonyl or β-aminoalcohol moiety. Representative examples (drawn in Figure 1.1) of alkaloids containing this moiety include *Sedum* alkaloids (**1**, **2** and **6**), *Lobelia* alkaloids (**5**), porantheridine (**3**), coccinellid alkaloid chilocorine C (**4**), and dimeric alkaloid (+)-homocrepidine A (**7**).[2] Biosynthetically, it is believed that these structural motifs arise from the Mannich-type additions of carbonyl-containing compounds (**10**) and cyclic imines (**9**).[2c,3]

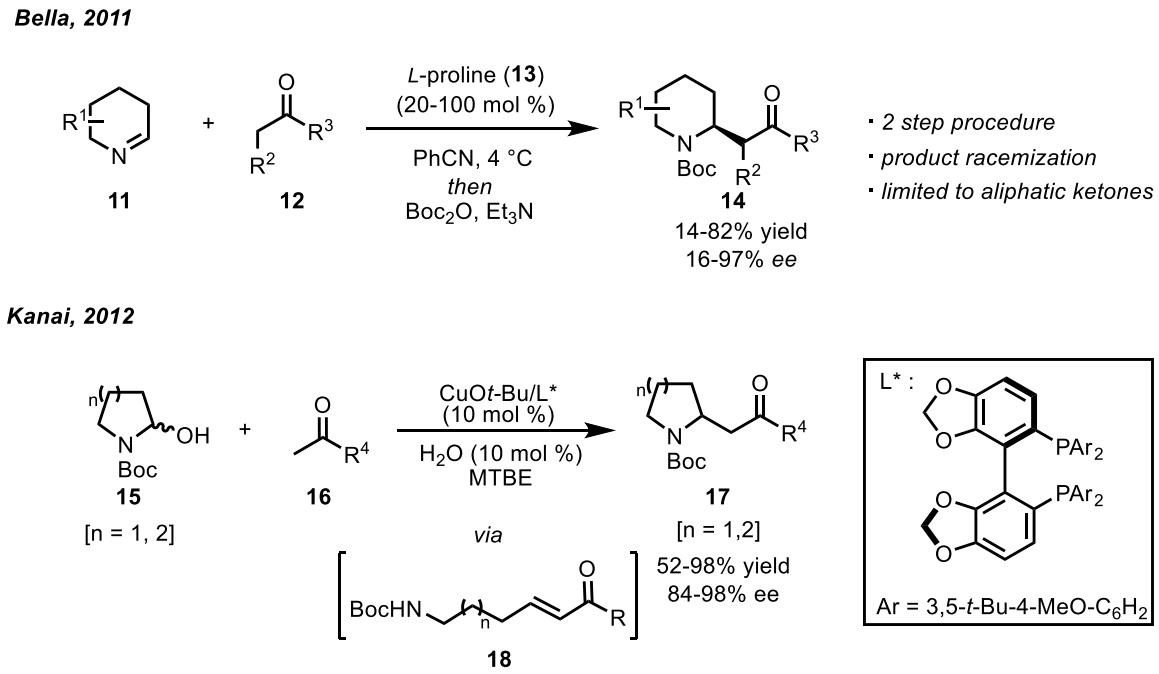
Figure 1.1. Naturally Isolated Alkaloids Containing β-Aminoketone or β-Aminoalcohol Moiety and Their Biosynthetic Origin.



When we initiated this project, only two asymmetric strategies employing this direct Mannich-type addition of ketones to imines/iminium surrogates were known (shown in Scheme

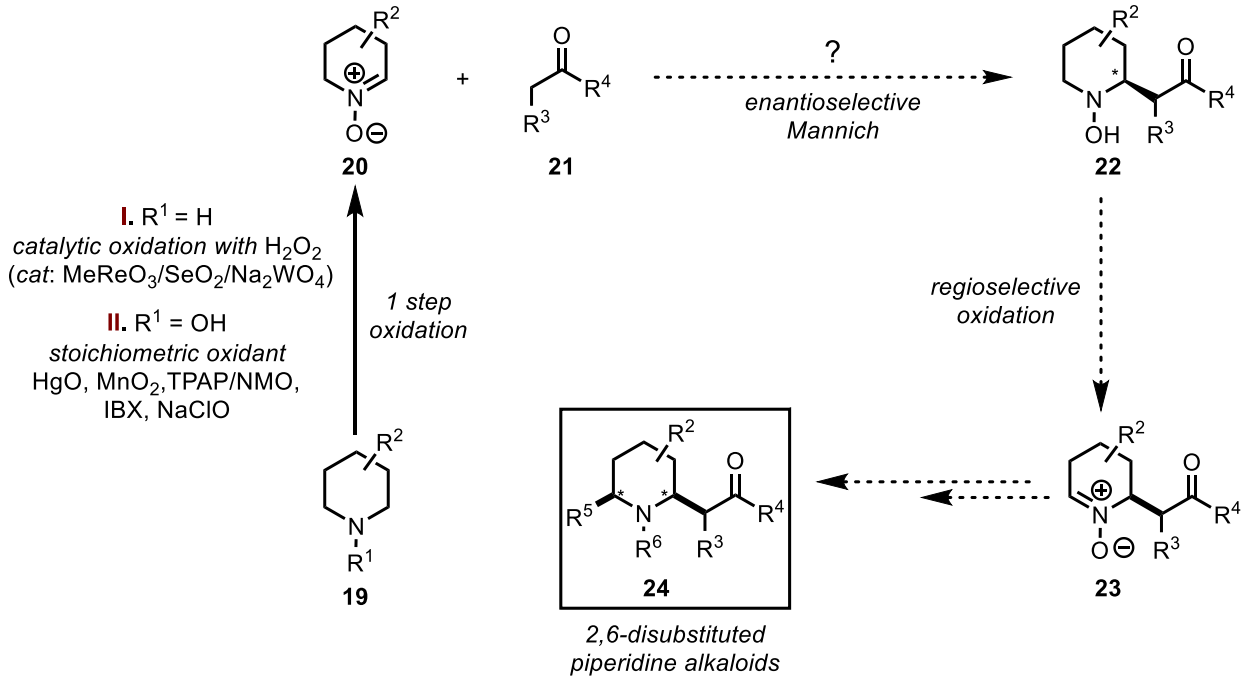
1.1). The first example was reported by Bella,[4] which includes a *L*-proline (**13**) catalyzed direct Mannich-type reaction between cyclic imines (**11**) and various ketones (primarily methyl ketones) (**12**) to produce, after additional Boc-protection, β-aminoketones **14**. The second approach was reported by Kanai,[5] and takes advantage of a chiral copper(I)-conjugated Brønsted base pair to catalyze a stepwise aldol addition-dehydration-Michael cascade between cyclic hemiaminal **15** and methyl ketones **16**, with an *aza*-Michael reaction of intermediate **18** being the stereodefining step of the whole process. However, both methodologies involve unstable and/or step intensive preparation of the cyclic starting material component (i.e.**11** and **15**), resulting in rather limited substrate scopes.

Scheme 1.1. Key Precedents of Direct Addition of Ketones (12, 16) to Imines (11) and Hemiaminals (15).



Although both approaches are powerful in their own way, we wondered whether a complimentary enantioselective method involving cyclic nitrones of type **20** (Scheme 1.2) could lead to enantioenriched β-*N*-hydroxy-amino-ketones **22**. From here, the *N*-hydroxylamine moiety could be utilized in a regioselective oxidation to afford aldonitrones **23** that would eventually lead to various 2,6-disubstituted piperidines (**24**). Cyclic nitrones exclusively exist as *E*-isomers and, as a result, are more reactive than the corresponding linear nitrones, which commonly have a *Z*-configuration of the double bond.[6] They are also easily prepared in one step by the oxidation of the corresponding, readily available secondary amines[7] or by the oxidation of the corresponding hydroxylamines (for more sensitive substrates).[8]

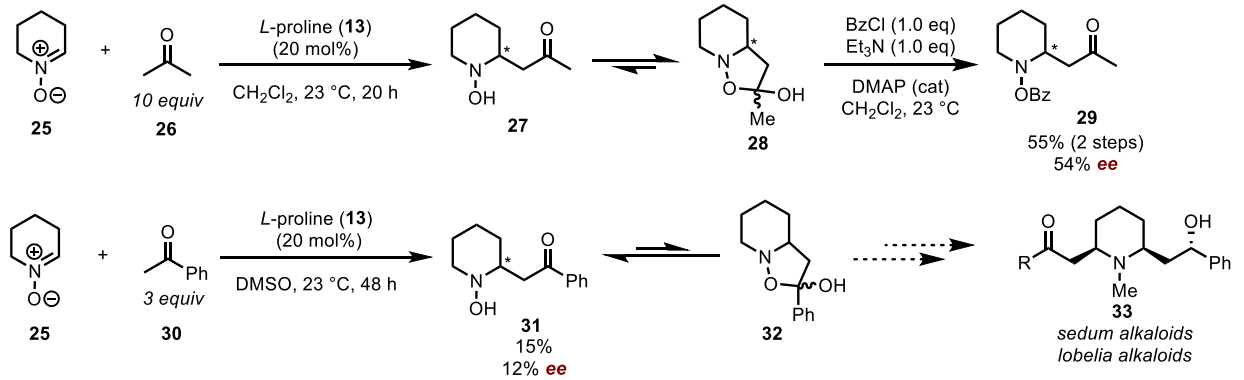
Scheme 1.2. Cyclic Nitrones (20) as Potential Electrophiles in Enantioselective Mannich Reaction.



1.2. Development of the Asymmetric Mannich-type Reaction of Cyclic Nitrones and Methyl Ketones.

To see if the addition of ketones to nitrones was feasible and to study the nature of the addition product, we first tested a simple-piperidine derived cyclic nitrone **25** in the reaction with excess acetone under conditions similar to Bella's report using *L*-proline (**13**) as a catalyst (Scheme 1.3).[4] Gratifyingly, this reaction provided the desired β-*N*-hydroxy-amino-ketone **27** that was found to exist in equilibrium with the cyclic isoxazolidine form **28**. Upon derivatization of this mixture with BzCl, the resulting regioselective Bz-protected hydroxylamine **29** was isolated, exhibiting 54% *ee*. A similar reaction was conducted with acetophenone (**30**) as the nucleophile, but only a low yield (15%) of **31** was observed with poor enantioselectivity (12% *ee*). Since this particular substrate (**31**) is a common precursor for the preparation of many natural products (for example 1, 2, 5, and 6) this reaction was chosen as our model reaction. Of note, all of these reactions could be run open to air, without the need for anhydrous conditions.[2f]

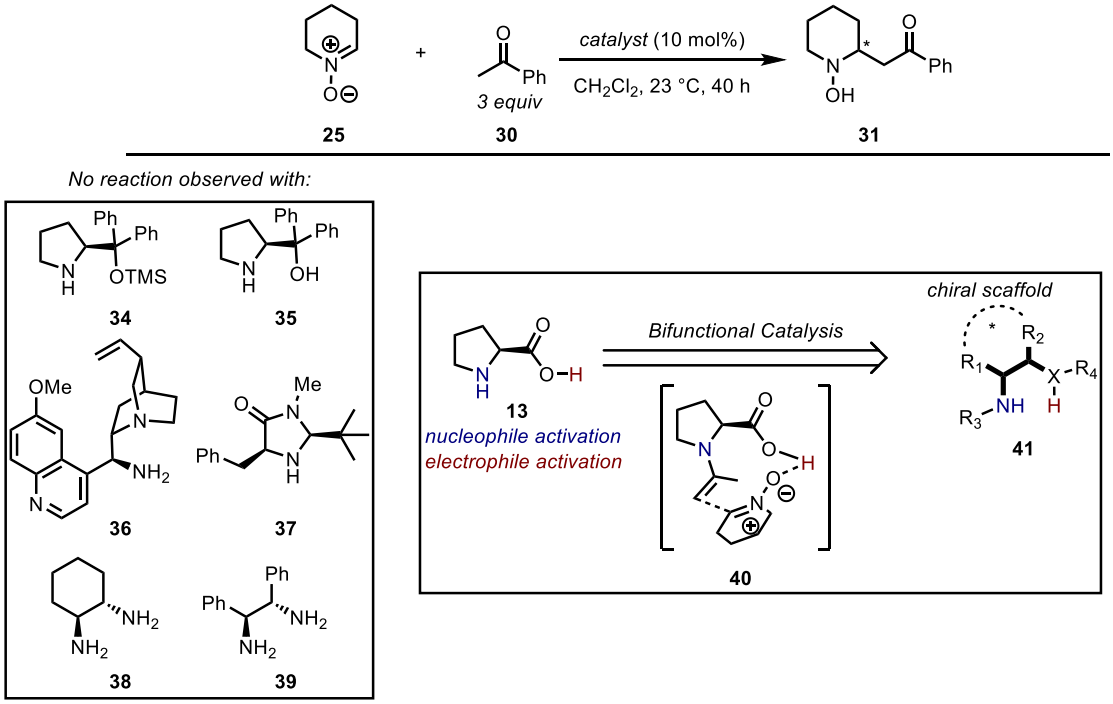
Scheme 1.3. Initial Results in Enantioselective Mannich Reaction between 25 and 26, and 25 and 30.



Our screening began with a search of a suitable catalyst. Since *L*-proline (**13**) was able to catalyze this reaction, albeit poorly, we turned our attention to other proline-based catalysts like

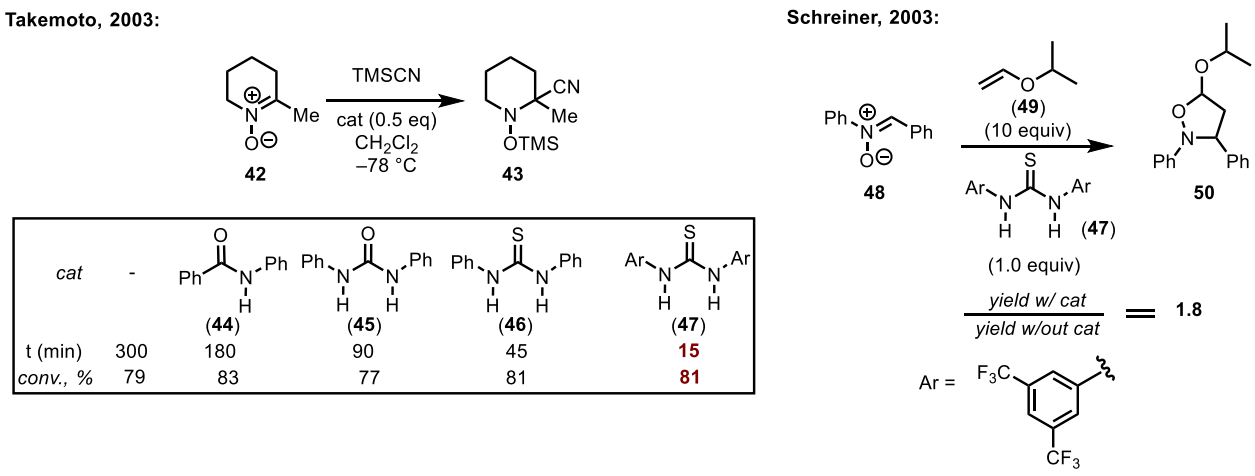
Hayashi-Jørgensen-type catalysts like **34** (Scheme 1.4).[10] Unfortunately, both **34** and **35** were not able to catalyze this reaction. The same outcome was observed for MacMillan catalyst **37**[10] and other primary amine based organocatalysts like **36**, **38** and **39**. However, a key observation that when **36** or **38** were used in the reaction with 10 mol% of BzOH, the product **31** was isolated with 20% and 10% yield (respectively) and 80% and -86% *ee* (respectively). That made us think that both nucleophile activation (via enamine catalysis)[11] and electrophile activation (via hydrogen bonding)[12] was important, with one of the primary amino groups of **38**/**39** acting as a hydrogen bond donor in its protonated state. The same idea applies to *L*-proline (**13**), where the carboxylic group (-CO_2H) acts a hydrogen bond donor (**40**). With that idea in mind, we devised a general catalyst structure for this reaction **41**.[12b]

Scheme 1.4. Initial Catalyst Screening for the Enantioselective Mannich Reaction between 25 and 30 and General Catalyst Structure (41).



In order to find a suitable hydrogen bond donor for nitrones, we looked into the literature and found two early examples from Yamamoto[13] and Schreiner[14] (Scheme 1.5). Yamamoto was able to show that in the presence of amides (**44**), ureas (**45**), or thioureas (**46**, **47**) the addition of TMSCN to cyclic ketonitrone **42** was significantly faster, with catalyst **47** being the most efficient. At the same time, Schreiner identified the same catalyst **47** to be able to almost double the rate of (3+2)-cycloaddition between nitrone **48** and vinyl ether **49**. These reports prompted us to start looking for thioureas as a potential electrophile activation component for our general catalyst structure (**41**).

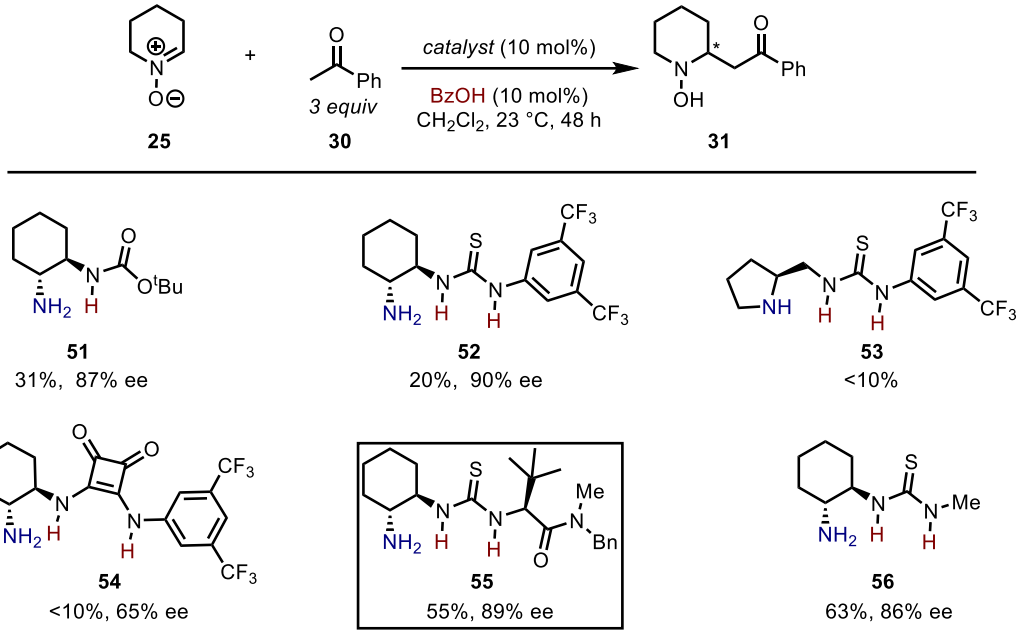
Scheme 1.5. Early Examples of Nitrone Activation with Hydrogen Bond Donors.



Thus, we tested several organocatalysts in our model reaction bearing hydrogen bond donor motifs with selected examples presented in Table 1.1. A simple Boc-protected chiral 1,2-diaminocyclohexane (**51**) was able to produce **31** with 31% yield and significantly improved enantioselectivity (87% *ee*). Employing the thiourea moiety seemed to further improve enantioselectivity in some cases (**52**)[15] or yield (**56**), with a Jacobsen catalyst (**55**)[16] giving the best yield/enantioselectivity balance (55%, 89% *ee*). Addition of BzOH in each case was essential

for an optimal yield, but didn't have a significant effect on enantioselectivity. Interestingly, squaramide catalyst **54**[17] was not able to catalyze this reaction well.

Table 1.1. Selected Examples of Further Catalyst Screening for the Enantioselective Mannich Reaction between 25 and 30.



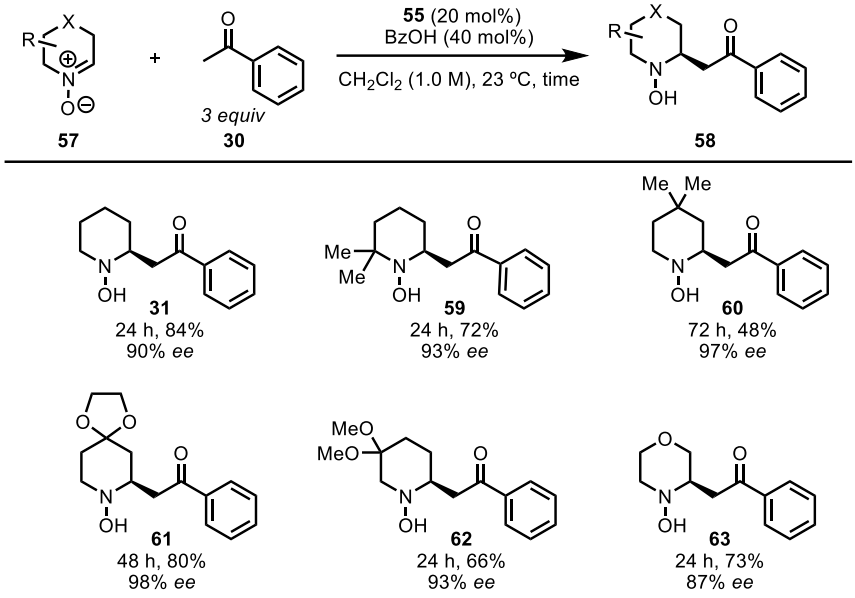
Once the catalyst was selected, we screened several other parameters in our model reaction, such as concentration, temperature, time, solvent, and additives.[18] It was found that when the reaction was conducted in CH_2Cl_2 (1.0 M solution relative to **25**) with 3 equivalents of **30**, 20 mol% of **55**, and 40 mol% BzOH for 24 h at 23 °C (optimal conditions), the addition product **31** could be isolated in 84% yield with 90% *ee*.

Several other 6-membered cyclic nitrones (**57**) were tested with **30** as the nucleophile under the optimal conditions, but with different reaction times (Table 1.2). As can be seen from the table, reaction conditions tolerate different substitution patterns on the nitrone coupling partner, affording various 2,3,4-substituted addition products **59**-**62**. Of particular note, is a "heterocyclic"

nitrone[19] that provided the addition product **63** a good yield and enantioselectivity (73%, 87% *ee*).

In collaboration with Tessa Lynch-Colameta, we screened different electron -rich and -deficient acetophenones in this reaction with a model nitrone **25** affording products **66-81** in good to moderate yields and high enantioselectivity (Table 1.3). The reaction with acetone turned out to

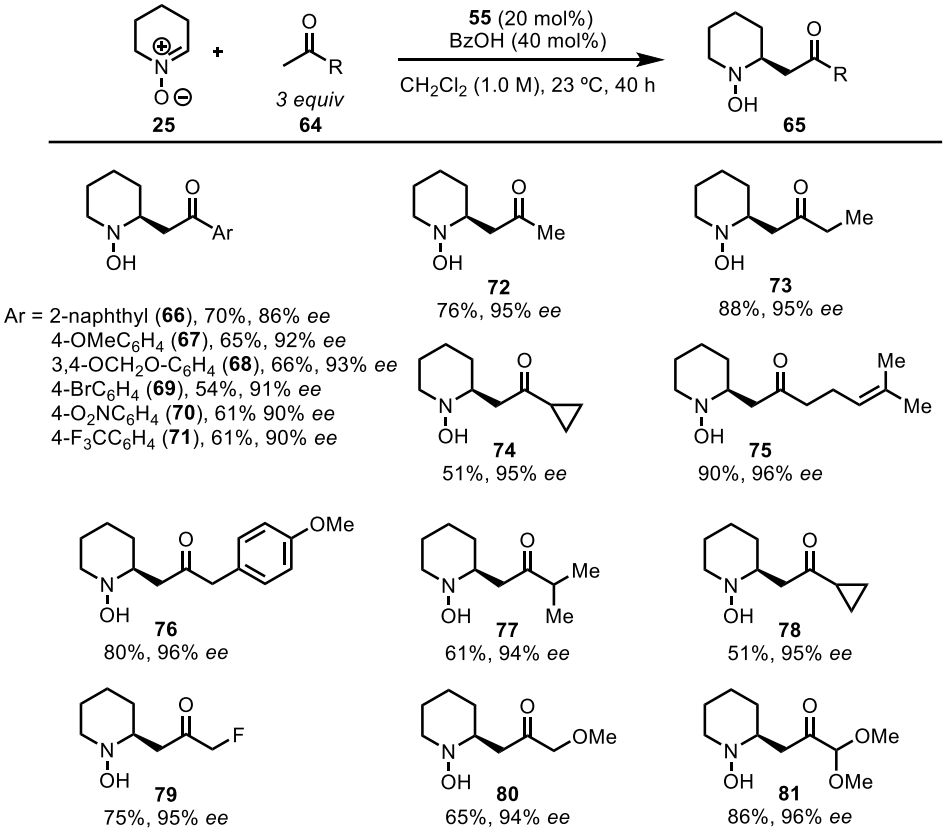
Table 1.2. Nitrone Scope under Optimized Conditions with Catalyst 55.



be highly enantioselective (95% *ee*) providing **72** with a good yield. Parent alkyl methyl ketones performed similarly well producing exclusively linear regioisomers **73-81**. Additionally, although introduction of a substituent at the α-position of the ketone decreases the yield, the enantioselectivity remains high (94-96% *ee*). The use of fluoroacetone provided **79** as a single regioisomer, and methoxyacetone afforded **80**[20] in high regioselectivity and enantioselectivity. Finally, 1,1-dimethoxyacetone delivered **81** as a single regioisomer with high yield and enantioselectivity (95% *ee* and 94% *ee* respectively). Unlike the parent β-aminoketones, β–*N*-hydroxy-amino-ketones **65** are more configurationally stable and do not undergo rapid

epimerization.[21] For example, as for **31** only 3% *ee* was lost after 20 h standing in MeOH at 23 °C, while **72** is configurationally stable for months. Moreover, unlike the parent secondary amines that normally require a further Boc-protection step for purification (due to polarity),[4] **58** and **65** can be chromatographed directly on a normal phase silica gel (hexanes/EtOAc as an eluent). Additionally, as tested with **58** and **65**, the N-OH bond can be readily cleaved with Zn/AcOH to provide the corresponding secondary amines if needed.

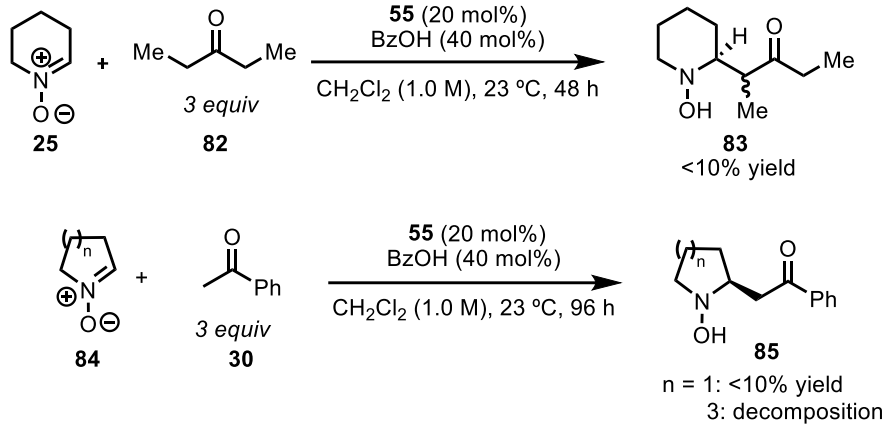
Table 1.3. Methyl Ketone Scope under Optimized Conditions with Catalyst 55.



The developed methodology, however, has its own limitations (Scheme 1.6). For example, any attempt to involve diethyl ketone **82** in the reaction with **25** only provided trace amounts of **83**. Similar observation was made when a five-membered cyclic nitrone **84** (n = 1) was used in the reaction under optimal conditions with **30** as a nucleophile. Additionally, a seven-membered cyclic

nitrone **84** (n = 3) also failed to react in the same reaction due to facile decomposition/polymerization of this nitrone under acidic conditions.[22]

Scheme 1.6. Limitations of the Developed Enantioselective Methodology.

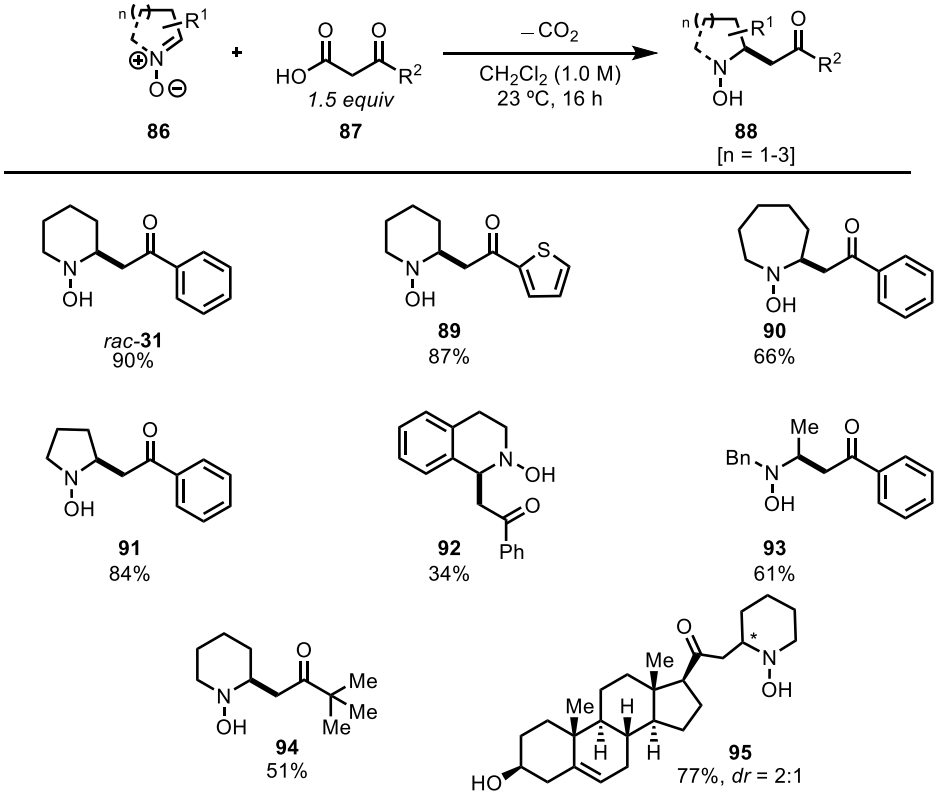


1.3. Development of the Robinson-Schöpf Reaction of Nitrones.

During the development of the enantioselective reaction described above, we were trying to develop a more suitable nucleophile to involve five- and seven-membered nitrones in the reaction that failed to react under the optimized conditions of the asymmetric reaction. That led to a separate discovery, that involved the coupling of nitrones of type **86** (cyclic and acyclic) with β-ketoacids (**87**) (Table 1.4). The analogous reaction of cyclic imines is known in the literature as Robinson-Schöpf reaction.[23] The reaction itself is notoriously known to have long reaction times, limited substrate scope, to be low-yielding, and highly pH-dependent due to the undesirable side reactions.[23, 24] To our delight, we found that replacing the cyclic imine partner with an analogous cyclic nitrone (**86**) allowed this reaction to proceed smoothly without any catalyst[25] at room temperature in CH_2Cl_2, providing **88** in good yields after 2 h under non-optimized conditions. Unlike the previous asymmetric Mannich-type reaction, the substrate scope can be extended to different ring sizes of the nitrone delivering adducts **90** and **91** with good yields (66 and 84%

respectively). Conjugated tetrahydroisoquinoline-derived nitrone afforded the corresponding hydroxylamine **92**, albeit in a low yield. Additionally, the linear *Z*-nitrone was found to participate in this reaction affording corresponding adduct **93** with a moderate yield (61%). We have also tested a small variety of β-ketoacids (**87**) with a model nitrone **25** that are usually challenging to involve in Mannich reactions with imines. Thus, heterocyclic β-ketoacid afforded **89** (87%), sterically hindered β-ketoacid provided **94** (51%) and, finally, pregnenolone-derived β-ketoacid delivered **95** (*dr* = 2:1, 77%), highlighting the ability to use this reaction for late-stage functionalization.

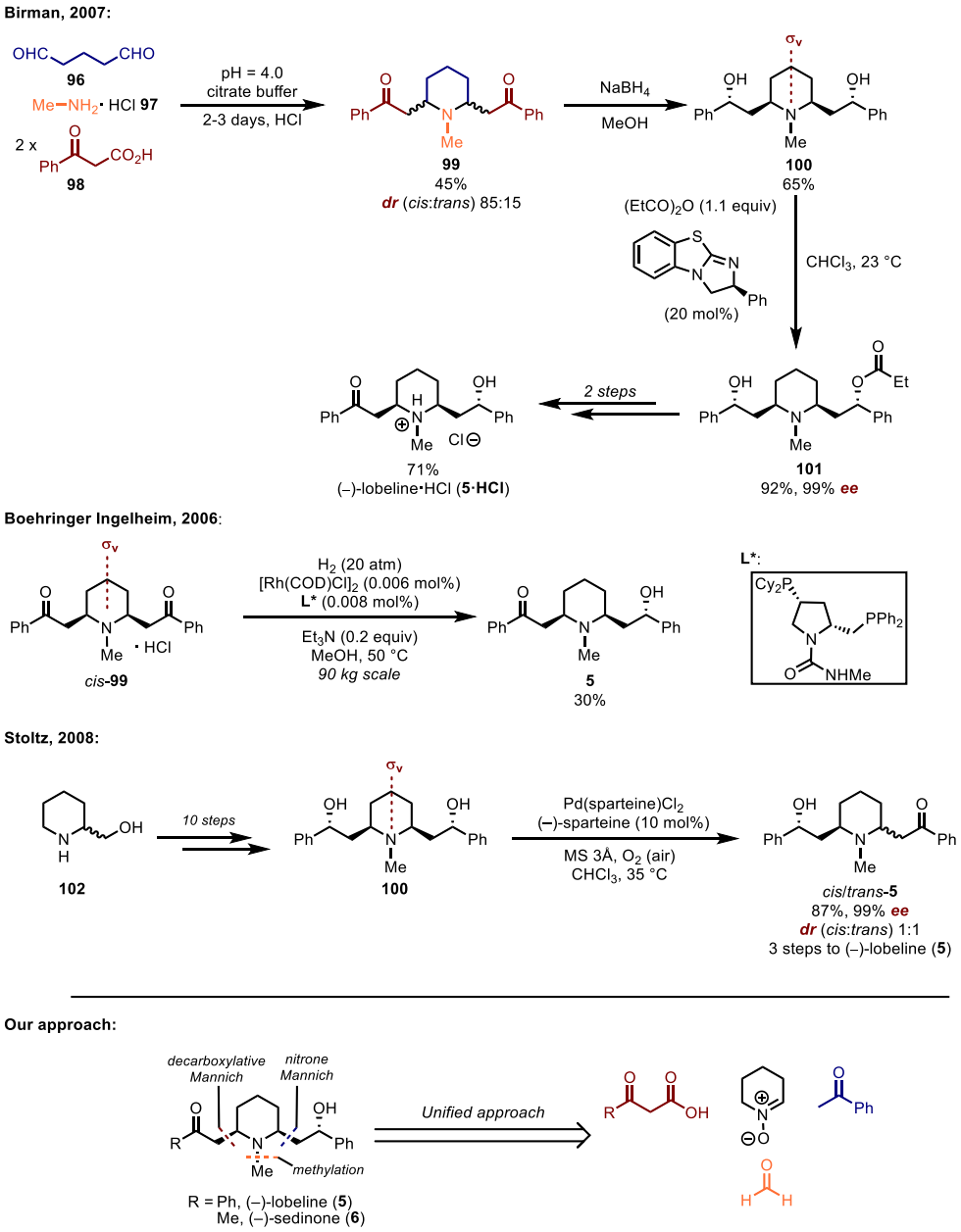
Table 1.4. Substrate Scope of Various Nitrones (86) and β-Ketoacids (87).



1.4. Total Syntheses of (–)-Lobeline and (–)-Sedinone.

To demonstrate the synthetic utility of the two methodologies we developed, we devised the short total syntheses of two alkaloids (–)-lobeline (**5**) and (–)-sedinone (**6**) (Figure 1.1). The total synthesis (–)-lobeline (**5**) has been accomplished by a number of research groups in the past, with the most efficient syntheses highlighted on Scheme 1.7. All of these syntheses take advantage of the inherent symmetry of one of the intermediates in the syntheses. For example, the synthesis by Birman[26] exploits the symmetry of the intermediate **100** (prepared in 2 steps from commercially available materials) to prepare mono-ester **101** that required additional 2 steps to afford **5** HCl. The Stoltz group[27] performed an oxidative desymmetrization, which was developed in their group, on this same intermediate **100** (prepared in 10 steps from **102**) to produce *cis*/*trans*-**5** that was further converted into *cis*-**5** in 3 steps. Synthesis by Boehringer Ingelheim[28] comprises the most efficient synthesis of **5** to date, and also exploits the symmetry of intermediate *cis*-**99** (prepared in the same manner to Birmans' synthesis), that was engaged in reductive desymmetrization to afford (–)-lobeline (**5**) directly. By contrast, non-symmetric (–)-sedinone (**6**) has been synthesized only twice: first, as a racemate in 9 steps; and second as single enantiomer (7 steps) starting from **1** (Figure 1.1).[29] Our own approach, however, was designed to be the first unified solution that was capable of accessing both targets and potentially other analogs for medicinal chemistry purposes, especially given the known therapeutic value of **5** as a potent antagonist at nicotinic acetylcholine receptors.[30]

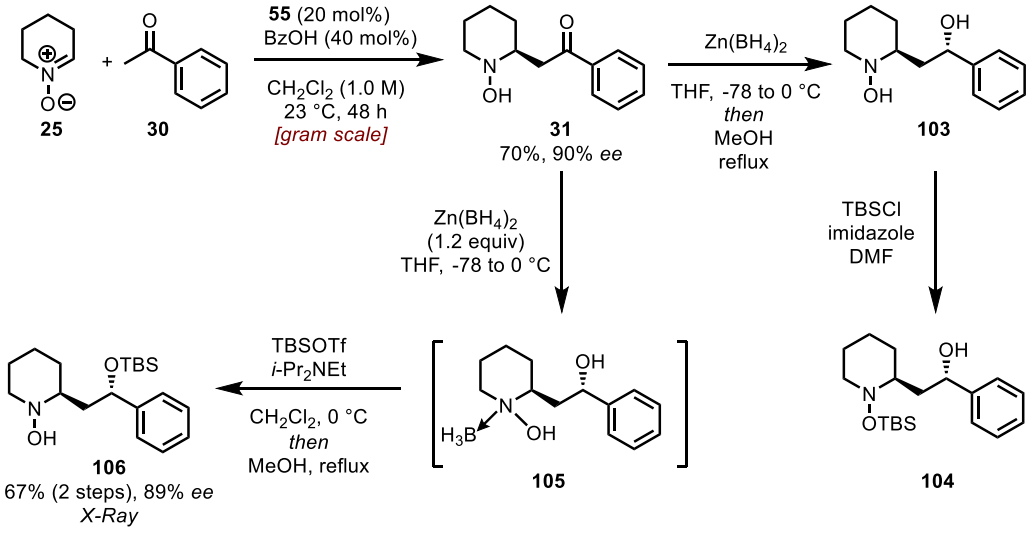
Scheme 1.7. Previous Syntheses of (–)-Lobeline (5) and Our Unified Approach to Access both 5 and 6.



First, we applied the developed catalytic protocol for the preparation of **31** on a gram scale (Scheme 1.8). Although the yield dropped slightly, the enantioselectivity did not change (70%, 90% *ee*). The *syn*-reduction of **31** was achieved by using $Zn(BH_4)_2$[31] in THF (*dr* 9:1) to produce

103 after cleaving the intermediate BH_3-complex **105** by refluxing **105** in methanol. An attempt to put a TBS group selectively on the newly formed alcohol under standard conditions (TBSCl, imidazole, DMF) resulted only in the undesired silylation of the hydroxylamine functionality, giving **104**. However, when we subjected the borane complex **105** to TBSOTf/*i*-Pr_2EtN, we cleanly isolated the desired silylated alcohol **106** (after subsequently removing BH_3 in the same manner described above) in 67% over 2 steps. The absolute configuration of **106** was determined by a single crystal X-Ray analysis, thus also establishing the (*S*)-configuration for all the addition products in our asymmetric method by analogy.

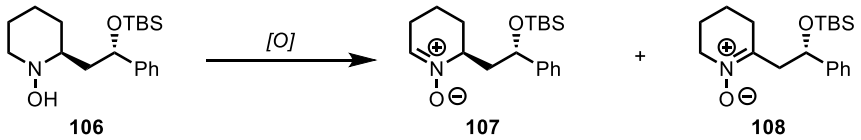
Scheme 1.8. Synthesis of Hydroxylamine 106.



Next, in order to obtain the aldonitrone (**107**) required for a further functionalization of the piperidine core, we screened a set of common oxidation procedure on hydroxylamine **106**. Unfortunately, all of the oxidants screened (HgO, MnO_2, UHP (cat. MTO))[8,32] provided a 1:1 mixture of regioisomers **107**:**108**. Then we turned our attention to a literature report by Goti,[8d] that described oxidation of cyclic 5-membered (**109**) and acyclic hydroxylamines favoring aldonitrones (**110**) by using "commercial" IBX (IBX stabilized with benzoic and isophthalic

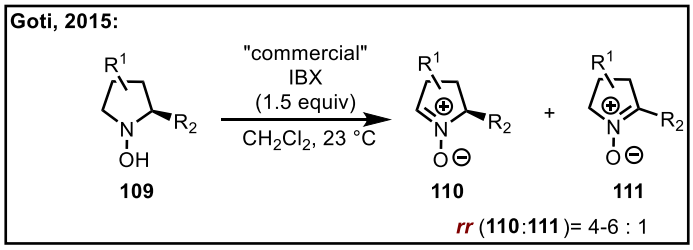
acids). Interestingly, no 6-membered cyclic hydroxylamines were reported. When we tested the exact reported conditions on our substrate **106**, a rapid decomposition was observed. The use of freshly prepared pure IBX provided the same result. However, when we lowered the temperature to 0 °C, we were able to isolate a mixture of **107**:**108** with a 3:1 *rr* with 35% yield among other decomposition products. Excited by this result, we tried to lower the temperature further, and eventually found that at –40 °C we could almost quantitatively generate the mixture of **107**:**108** without any decomposition, and with a good 4:1 *rr* favoring aldonitrone **107**.

Scheme 1.9. Regioselective Oxidation of Hydroxylamine 106 to Access Aldonitrone 107.



conditions:

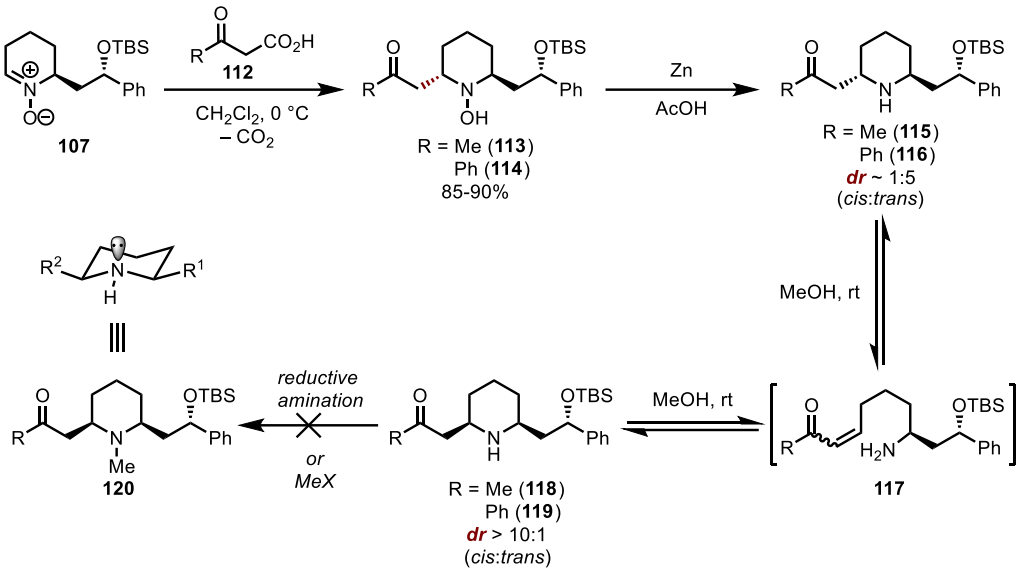
HgO/MnO_2/UHP (cat. MTO)	**1**	:	**1**
IBX (1.5 equiv), CH_2Cl_2, 23 °C		*decomposition*	
IBX (1.5 equiv), CH_2Cl_2, 0 °C, 35%	**3**	:	**1**
IBX (1.5 equiv), CH_2Cl_2, -20 °C, 90%	**3.6**	:	**1**
IBX (1.5 equiv), CH_2Cl_2, -40 °C, 98%	**4**	:	**1**



With **107** in hand, we applied our developed variant of Robinson-Schöpf reaction with the two required β-ketoacids (**112**, R = Me or Ph). Interestingly, the addition of both β-ketoacids afforded **113** and **114** with predominantly *trans* configuration (*dr* ~1:5 for both) (established on the final stage when *epi*-**5** and *epi*-**6** were isolated as a major product). Further N–O cleavage (Zn/AcOH) quantitatively provided two products **115** and **116** bearing the same *dr*. The epimerization to a more thermodynamically stable *cis*-isomers **118** and **119** was achieved by

leaving **115** and **116** (respectively) to stand in methanol overnight.[33] However, attempts to achieve *N*-methylation of **115**/**116** to obtain **120** either via reductive amination or using any electrophilic source of Me was fruitless. A potential explanation for this phenomenon is that the lone pair on nitrogen is too sterically crowded to be accessible by electrophiles. Thus, we needed to find a way to methylate *trans*-diastereomers **115** and **116** while avoiding any extra operations that might lead to epimerization to the useless for alkylation *cis*-isomers.

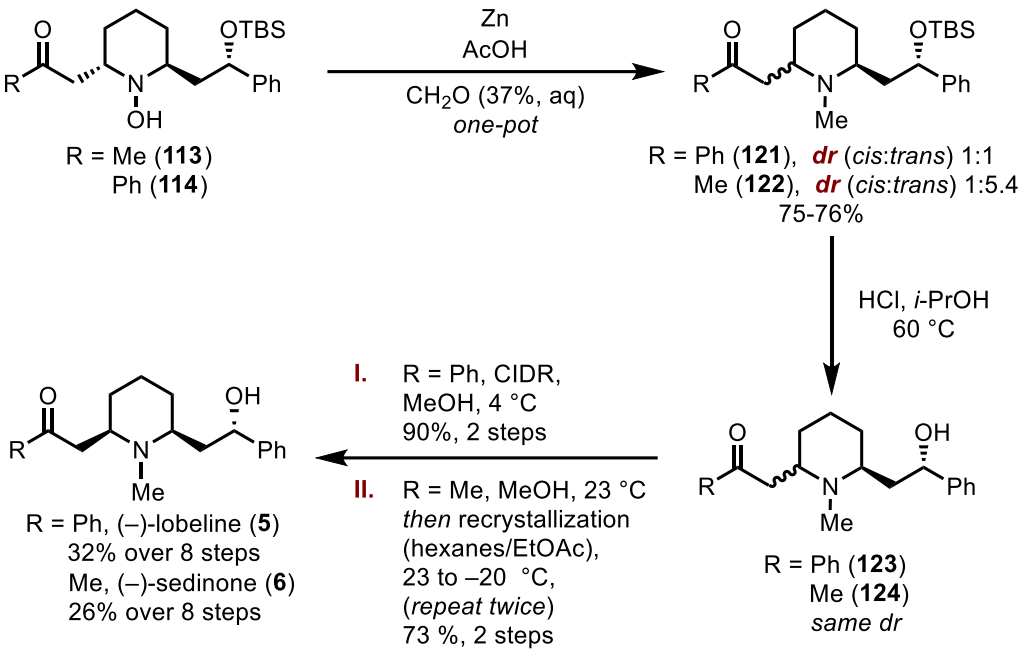
Scheme 1.10. Nucleophilic Addition to 107 and Subsequent Attempt to Access 120.



The solution was found when we realized that N–O cleavage could be combined with reductive amination with formaldehyde using Zn as a reductant for both processes. Thus, when intermediate hydroxylamines **113**/**114** were subjected to Zn powder in AcOH in the presence of aqueous formaldehyde,[34] *N*-methylamines **121** (*dr* (*cis*:*trans*) = 1:1) and **122** (*dr* (*cis*:*trans*) = 1:5.4) were isolated in 75% and 76% yields respectively. The reason that **121** (unlike **122**) was isolated as 1:1 mixture of diastereomers is the rapid epimerization of the *trans*-diastereomer to a thermodynamic equilibrium 1:1 mixture.

After removal of the TBS group under acidic conditions[27] and subsequent basification we obtained **123** as 1:1 mixture of diastereomers and predominantly *epi*-sedinone (**124**) (*dr* (*cis*:*trans*)=1:5.4). Encouraged by the literature precedent on CIDR of the parent lobelanine,[35] we tried to perform a recrystallization of the free base. Thus, slow evaporation of the solution of **123** in MeOH at 4 °C for two weeks afforded exclusively (–)-lobeline (**5**) (90% over 2 steps). The same procedure, however, did not work for (–)-sedinone (**6**), presumably due to the much slower equilibration rate. We found however, that the *cis*- isomer could be selectively precipitated from a

Scheme 1.11. Completion of the Syntheses of 5 and 6.



mixture of hexanes/EtOAc. Hence, after three cycles of equilibration in MeOH followed by crystallization in hexanes/EtOAc, we were able to obtain a pure (–)-sedinone (**6**) (73% over 2 steps). Of note, since it is not totally clear which diastereomer of **6** is present in nature,[29] the current methodology effective provides access to both diastereomers of **6**.

1.5. Conclusion.

In this chapter, we have developed an enantioselective Mannich-type addition of methyl ketones to nitrones producing the resulting hydroxylamines with high yields and enantioselectivity. The substrate scope of this reaction is broad and includes different 2,3,4-substituted and heterocyclic nitrones, as well as different electron rich- and -deficient acetophenones and alkyl methyl ketones. Additionally, we developed a nitrone variant of Robinson-Schöpf reaction that further expanded the scope to 5- and 7-membered ring and acyclic nitrones, albeit in racemic format. The combination of two developed methodologies provided a powerful tool for the unified approach towards total synthesis of two 2,6-disubstituted piperidine alkaloids: (–)-lobeline and (–)-sedinone.

1.6. Experimental Details.

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), diethyl ether (Et_2O), and dichloromethane (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent, and an aqueous solution of potassium permanganate and sodium bicarbonate and heat as a developing agent. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker 400 and 500 MHz instruments and calibrated using residual

solvent as an internal reference (^{1}H, δ 7.26 ppm; ^{13}C, δ 77.16 ppm). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet. IR spectra were recorded on a Nicolet iS5 FT-IR spectrometer using neat thin film technique. High-resolution mass spectra (HRMS) were recorded on Agilent 6244 Tof-MS using ESI (Electrospray Ionization) at the University of Chicago Mass Spectroscopy Core Facility. Chiral high-performance liquid chromatography (HPLC) analysis was performed using a Shimadzu Prominence analytical chromatograph with commercial ChiralPak columns (OD-H, OJ-H, and IA). The X-ray diffraction data were measured on a Bruker D8 VENTURE diffractometer at the University of Chicago X-ray Laboratory.

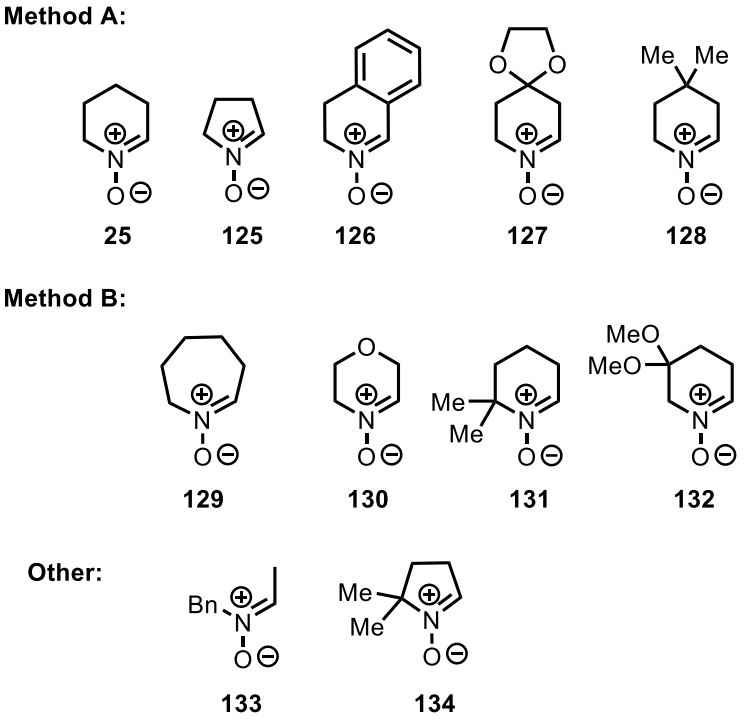
Preparation of Nitrones. Two general literature modified protocols were used in this chapter to prepare cyclic nitrones.[36]

Method A. To a mixture of secondary amine (1.0 equiv) and SeO_2 (5 mol%) in acetone (0.5 M) was added dropwise an aqueous 30% (w/w) H_2O_2 solution (2.2-3.0 equiv) over 10 min at 0 ºC under an argon atmosphere. The resultant mixture was stirred at 0 ºC for 1 h, and then warmed to 23 ºC for 3 h. Upon completion, the acetone was removed under reduced pressure. The remaining aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL/g of starting secondary amine). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. The resultant crude product was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH). The corresponding nitrone was stored as a 1.0 M solution in CH_2Cl_2 at –20 ºC to prevent dimerization.

Method B. To a solution of corresponding hydroxylamine (1.0 equiv) in CH_2Cl_2 (0.5 M) was added yellow HgO (3.0 equiv) in one portion at 23 ºC under an argon atmosphere. The reaction contents were stirred for 1 h and then anhydrous $MgSO_4$ was added. The resulting grey heterogeneous mixture was filtered through a pad of Celite with a layer of $MgSO_4$ on top, washed

with CH_2Cl_2, and concentrated to afford the corresponding the corresponding nitrone that was used without further purification. The resulting nitrone was stored as a 1.0 M solution in CH_2Cl_2 at –20 ºC to prevent dimerization.

Figure 1.2. Nitrones explored in this chapter.



Nitrones **25**,[36a] **125**,[36a] **126**[36a], **133**[37], and **134**[38] were prepared according to the literature procedures. All spectroscopic data matched that reported in Ref. 36-38.

Nitrones **129** and **130** were prepared from corresponding hydroxylamines[39] on a 0.5 mmol scale using a further modified **Method B** to avoid polymerization: upon completion, the reaction was filtered through a frit containing $MgSO_4$, the filter cake was washed with CH_2Cl_2 and the excess CH_2Cl_2 was concentrated (bath set to less than 25 ºC) to afford a 1.0 M solution of **129**/**130** in CH_2Cl_2 (quantitative conversion assumed) that was used immediately after preparation.

1,4-dioxa-8-azaspiro[4.5]dec-7-ene 8-oxide (127): Prepared using **Method A** described above, starting from 4,4-ethylenedioxy-piperidine (0.50 g, 3.49 mmol) using 2.2 equiv of H_2O_2 (0.78 mL), yielding **127** (237 mg, 43%) as a pale-yellow oil. **127**: R_f = 0.56 (silica gel, CH_2Cl_2/MeOH =10/1); IR (film) ν_{max} 3380, 2893, 1620, 1441, 1372, 1191, 1077, 1018, 954, 875, 728 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.00 (t, *J* = 4.0 Hz, 1 H), 4.22–3.81 (m, 6 H), 2.68–2.52 (m, 2 H), 2.08 (t, *J* = 6.4 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.8, 103.4, 65.0, 57.5, 36.1, 32.0. HRMS (ESI) calcd for $C_7H_{12}NO_3^+$ [M + H^+] 158.0812, found 158.0816.

4,4-dimethyl-2,3,4,5-tetrahydropyridine 1-oxide (128): Prepared using **Method A** described above, starting from 4,4-dimethylpiperidine[40] (0.15 g, 1.33 mmol) using 3.0 equiv of H_2O_2 (0.32 mL), yielding **128** (87 mg, 53%) as a clear oil. **128**: R_f = 0.51 (silica gel, CH_2Cl_2/MeOH =10/1); IR (film) ν_{max} 3387, 2956, 2871, 1620, 1454, 1369, 1236, 1167, 1059, 817, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.15–7.04 (m, 1 H), 3.81 (t, *J* = 6.1 Hz, 2 H), 2.28–2.14 (m, 2 H), 1.74 (t, *J* = 6.2 Hz, 2 H), 1.06 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1, 55.4, 39.5, 35.6, 27.8, 26.6; HRMS (ESI) calcd for $C_7H_{14}NO^+$ [M + H^+] 128.1070, found 128.1072.

2,2-dimethyl-2,3,4,5-tetrahydropyridine 1-oxide (131): Prepared using **Method B** described above, starting from 2,2-dimethylpiperidin-1-ol[18] (0.11 g, 0. 88 mmol) using 3.0 equiv of HgO (0.57 g) to afford the nitrone **131** (98 mg, 88%) as a white solid. **S17**: R_f = 0.52 (silica gel, CH_2Cl_2/MeOH = 10/1); IR (film) ν_{max} 3247, 2940, 2874, 1661, 1590, 1460, 1363, 1175, 971, 816 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.95 (t, *J* = 4.1 Hz, 1 H), 2.31 (td, *J* = 6.3, 4.3 Hz, 2 H), 1.85–1.77 (m, 2 H), 1.71–1.60 (m, 2 H), 1.40 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.5, 66.1, 36.9, 26.8, 26.4, 15.2; HRMS (ESI) calcd for $C_7H_{14}NO^+$ [M + H^+] 128.1070, found 128.1075.

3,3-dimethoxy-2,3,4,5-tetrahydropyridine 1-oxide (132): 3,3-dimethoxypiperidin-1-ol[18, 41] (0.16 g, 1.00 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (2 mL, 0.5 M) and cooled to 0 ºC.

Then IBX (0.28 g, 1.0 equiv) was added in one portion and the mixture was stirred for 3 h at 0 ºC. Upon completion, the solution was quickly filtered through Celite, washed with cold CH_2Cl_2, and concentrated to afford a mixture of **132** and **132'** (regioisomer) (1.2:1 according to the crude NMR). The desired nitrone **132** was separated by flash chromatography (CH_2Cl_2/MeOH = 20/1) to afford **132** (55 mg, 31%) as a clear oil. **132**: R_f = 0.30 (silica gel, CH_2Cl_2/MeOH =15/1); IR (film) ν_{max} 3234, 2950, 2833, 1440, 1266, 1114, 1054, 885, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.18–7.10 (m, 1 H), 3.90–3.81 (m, 2 H), 3.21 (s, 6 H), 2.55–2.32 (m, 2 H), 1.86 (t, *J* = 6.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.7, 97.4, 62.9, 48.4, 24.9, 22.6. HRMS (ESI) calcd for $C_7H_{14}NO_3^+$ [M + H^+] 160.0968, found 160.0973. ***Note***: upon the isolation on silica gel the ratio changes to 1:2 (**132**/**132'**).

General Procedure for Enantioselective Mannich-type Reactions between Nitrones 57 and Acetophenone (30). To a vial containing **55** (39.1 mg, 0.10 mmol, 0.2 equiv), BzOH (24.4 mg, 0.20 mmol, 0.4 equiv), and acetophenone **30** (181.4 mg, 1.51 mmol, 3.0 equiv) at 23 ºC under ambient atmosphere was added a solution of nitrone **57** (0.50 mmol, 1.0 equiv) in CH_2Cl_2 (0.50 mL). The reaction mixture was then stirred for 24-72 h. Upon completion, the contents were quenched with saturated aqueous $NaHCO_3$ (2 mL) and extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were then dried ($MgSO_4$), filtered, and concentrated. The resultant crude material was purified by flash column chromatography (silica gel, hexane/EtOAc).

(*S*)-2-(1-hydroxypiperidin-2-yl)-1-phenylethan-1-one (31): Prepared using the general procedure described above with **25** ultimately yielding **33** (93 mg, 84% yield, 90% *ee*) as a pale-yellow oil. **31**: **19**: R_f = 0.45 (silica gel, EtOAc); $[\alpha]_D^{25}$ = –31.2º (*c* = 1.00, $CHCl_3$); IR (film) ν_{max} 3159, 2937, 2856, 1683, 1597, 1448, 1285, 1205, 973, 752, 691 cm^{-1}; acyclic ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.6 Hz, 2 H), 7.53 (t, *J* = 7.2 Hz, 1 H), 7.42 (t, *J* = 7.5 Hz, 2 H), 7.19–6.76

(br s, 1 H, exchangeable), 3.74 (dd, *J* = 15.4, 3.9 Hz, 1 H), 3.32 (d, *J* = 9.7 Hz, 1 H), 3.00–3.09 (m, 1 H), 2.84 (dd, *J* = 15.5, 7.4 Hz, 1 H), 2.57 (t, *J* = 10.8 Hz, 1 H), 1.90 (d, *J* = 11.9 Hz, 1 H), 1.73 (d, *J* = 12.1 Hz, 1 H), 1.64–1.53 (m, 2 H), 1.42–1.16 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 137.4, 133.1, 128.7, 128.4, 64.7, 60.0, 43.6, 32.2, 25.9, 23.6; HRMS (ESI) calcd for $C_{13}H_{18}NO_2^+$ [M + H^+] 220.1332, found 220.1332.

(*S*)-2-(1-hydroxy-6,6-dimethylpiperidin-2-yl)-1-phenylethan-1-one (59): Prepared using the general procedure described above with **131** ultimately yielding **59** (88 mg, 72% yield, 93% *ee*) as a yellow oil. **59**: R_f = 0.75 (silica gel, EtOAc); $[\alpha]_D^{25}$ = -12.1° (*c* = 1.00, $CHCl_3$); IR (film) ν_{max} 3398, 2935, 2869, 1684, 1598, 1449, 1390, 1287, 1211, 1002, 752, 722, 690 cm^{-1}; cyclic:acyclic= 4:1 ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.5 Hz, 1.66 H), 7.67–7.58 (m, 0.34 H), 7.58–7.50 (m, 0.83 H), 7.50–7.41 (m, 1.66 H), 7.40–7.29 (m, 0.51 H), 4.69–4.26 (m, 0.75 H), 3.80–3.26 (m, 1.75 H), 3.04–2.90 (m, 0.20 H), 2.90–2.60 (m, 0.75 H), 2.60–2.48 (m, 0.25 H), 1.91–1.81 (m, 1.30 H), 1.55–1.43 (m, 3 H), 1.38–1.22 (m, 2 H), 1.18 (s, 3 H), 1.09 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1, 137.4, 132.9, 129.9, 128.6, 128.2, 127.0, 125.6, 91.6, 59.6, 57.7, 44.4, 39.0, 37.4, 33.0, 32.5, 30.0, 29.7, 27.3, 19.8, 16.4, 14.9. HRMS (ESI) calcd for $C_{15}H_{22}NO_2^+$ [M + H^+] 248.1645, found 248.1643.

(*S*)-2-(1-hydroxy-4,4-dimethylpiperidin-2-yl)-1-phenylethan-1-one (60): Prepared using the general procedure described above with **128** ultimately yielding **60** (59 mg, 48% yield, 97% *ee*) as a yellow oil. **60**: R_f = 0.44 (silica gel, EtOAc); $[\alpha]_D^{25}$ = –30.7° (*c* = 1.00, $CHCl_3$); IR (film) ν_{max} 2952, 2924, 1684, 1448, 1288, 1207, 1001, 754, 691 cm^{-1}; acyclic ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.6 Hz, 2 H), 7.58–7.48 (m, 1 H), 7.48–7.34 (m, 2 H), 3.68 (dd, *J* = 15.7, 3.8 Hz, 1 H), 3.42–3.22 (m, 1 H), 3.22–3.00 (m, 1 H), 2.97–2.70 (m, 2 H), 1.71–1.48 (m, 2 H), 1.42–1.20 (m, 2 H), 1.01 (s, 3 H), 0.90 (d, *J* = 11.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.7,

137.5, 133.1, 128.7, 128.3, 60.5, 55.7, 45.3, 43.6, 38.6, 32.1, 29.3, 24.4; HRMS (ESI) calcd for $C_{15}H_{22}NO_2^+$ [M + H^+] 248.1645, found 248.1649.

(*R*)-2-(8-hydroxy-1,4-dioxa-8-azaspiro[4.5]decan-7-yl)-1-phenylethan-1-one (61): Prepared using the general procedure described above with **127** ultimately yielding **61** (110 mg, 80% yield, 98% *ee*) as a pale-yellow oil. **61**: R_f = 0.50 (silica gel, EtOAc); $[\alpha]_D^{25}$ = –13.3º (*c* = 1.00, $CHCl_3$); IR (film) ν_{max} 3061, 2960, 2881, 1684, 1448, 1289, 1146, 1055, 929, 753, 691 cm^{-1}; acyclic ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.5 Hz, 2 H), 7.65–7.50 (m, 1 H), 7.50–7.30 (m, 2 H), 6.56–6.07 (br s, 1 H, exchangeable), 4.04–3.79 (m, 4 H), 3.75–3.54 (m, 1 H), 3.49–3.20 (m, 2 H), 3.20–2.99 (m, 1 H), 2.99–2.70 (m, 1 H), 2.27–1.33 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.2, 137.3, 133.2, 128.8, 128.4, 106.2, 64.6, 64.5, 61.8, 56.3, 43.1, 39.9, 34.4; HRMS (ESI) calcd for $C_{15}H_{20}NO_4^+$ [M + H^+] 278.1389, found 278.1388.

(*S*)-2-(1-hydroxy-5,5-dimethoxypiperidin-2-yl)-1-phenylethan-1-one (62): Prepared using the general procedure described above with **132** ultimately yielding **62** (92 mg, 66% yield, 93% *ee*) as a yellow oil. **62**: R_f = 0.64 (silica gel, EtOAc); $[\alpha]_D^{25}$ = –23.1º (*c* = 1.00, $CHCl_3$); IR (film) ν_{max} 3309, 2958, 2831, 1682, 1597, 1448, 1205, 1054, 890, 752, 691 cm^{-1}; acyclic ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.5 Hz, 2 H), 7.60–7.50 (m, 1 H), 7.50–7.39 (m, 2 H), 3.85 (d, *J* = 14.3 Hz, 1 H), 3.68–3.45 (m, 1 H), 3.21 (s, 3 H), 3.17 (s, 3 H), 3.11–2.99 (m, 1 H), 2.98–2.81 (m, 1 H), 2.70–2.44 (m, 1 H), 2.08–1.77 (m, 2 H), 1.55–1.23 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.2, 137.3, 133.2, 128.7, 128.3, 99.3, 63.9, 63.4, 48.2, 48.0, 42.6, 30.1, 27.2; HRMS (ESI) calcd for $C_{15}H_{22}NO_4^+$ [M + H^+] 280.1544, found 280.1543.

(*R*)-2-(4-hydroxymorpholin-3-yl)-1-phenylethan-1-one (63): Prepared using the general procedure described above with **130** ultimately yielding **63** (80 mg, 73% yield, 88% *ee*) as a yellow oil. **63**: R_f = 0.55 (silica gel, EtOAc); $[\alpha]_D^{25}$ = –31.2º (*c* = 1.00, $CHCl_3$); IR (film) ν_{max} 3350, 2857,

1681, 1449, 1280, 1108, 1003, 753, 692 cm^{-1}; acyclic ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 6.3 Hz, 2 H), 7.70–7.51 (m, 1 H), 7.51–7.36 (m, 2 H), 6.63–6.10 (br s, 1 H, exchangeable), 4.16–3.72 (m, 2 H), 3.72–3.42 (m, 2 H), 3.37–3.02 (m, 3 H), 2.97–2.67 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.7, 137.0, 133.4, 128.8, 128.4, 70.6, 66.7, 63.6, 58.9, 39.1; HRMS (ESI) calcd for $C_{12}H_{16}NO_3^+$ [M + H^+] 222.1125, found 222.1124.

General Procedure for Enantioselective Mannich-type Reactions between Nitrone 25 and Methyl Ketones 64. To a vial containing **55** (39.1 mg, 0.10 mmol, 0.2 equiv), BzOH (24.4 mg, 0.20 mmol, 0.4 equiv), and the corresponding methyl ketone **64** (1.51 mmol, 3.0 equiv) at 23 ºC under ambient atmosphere was added a solution of nitrone **25** (49.6 mg, 0.50 mmol, 1.0 equiv) in CH_2Cl_2 (0.50 mL). The reaction mixture was then stirred for 40 h (except **69**-**71**, which were stirred for only 16 h). Upon completion, the contents were quenched with saturated aqueous $NaHCO_3$ (2 mL) and extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were then dried ($MgSO_4$), filtered, and concentrated. The resultant crude material was purified by flash column chromatography (silica gel, hexane/EtOAc).

(*S*)-2-(1-hydroxypiperidin-2-yl)-1-(naphthalen-2-yl)ethan-1-one (66): Prepared using the general procedure described above yielding **66** (95 mg, 70% yield, 86% *ee*) as a yellow oil. 46: R_f = 0.44 (silica gel, EtOAc); $[\alpha]_D^{25}$ = –34.1º (*c* = 1.00, $CHCl_3$); IR (film) ν_{max} 3164, 2936, 2856, 1678, 1627, 1468, 1353, 1292, 1184, 1123, 861, 820, 748 cm^{-1}; acyclic ^1H NMR (500 MHz, $CDCl_3$) δ 8.48 (s, 1 H), 8.03 (d, *J* = 8.6 Hz, 1 H), 7.90–7.80 (m, 3 H), 7.60–7.45 (m, 2 H), 6.86–6.36 (br s, 1 H, exchangeable), 3.87 (dd, *J* = 15.2, 3.7 Hz, 1 H), 3.36 (d, *J* = 9.6 Hz, 1 H), 3.17–3.09 (m, 1 H), 2.98 (dd, *J* = 15.3, 7.0 Hz, 1 H), 2.59 (t, *J* = 10.9 Hz, 1 H), 1.94 (d, *J* = 12.9 Hz, 1 H), 1.79–1.71 (m, 1 H), 1.66–1.58 (m, 2 H), 1.44–1.23 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

199.6, 135.6, 134.6, 132.6, 130.0, 129.7, 128.5, 128.4, 127.7, 126.7, 124.0, 64.8, 60.0, 43.7, 32.3, 25.9, 23.6; HRMS (ESI) calcd for $C_{17}H_{20}NO_2^+$ [M + H^+] 270.1489, found 270.1493.

(*S*)-2-(1-hydroxypiperidin-2-yl)-1-(4-(trifluoromethyl)phenyl) ethan-1-one (71): Prepared using the general procedure described above yielding **71** (89 mg, 61% yield, 90% *ee*) as a white solid. **71**: R_f = 0.55 (silica gel, EtOAc); $[\alpha]_D^{25}$ = –13.0º (*c* = 1.00, $CHCl_3$); IR (film) ν_{max} 3159, 2941, 2858, 1691, 1410, 1326, 1167, 1129, 1067, 1013, 848, 750 cm^{-1}; acyclic:cyclic = 3:1 ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.2 Hz, 1.5 H), 7.82–7.74 (m, 0.5 H), 7.73–7.67 (m, 1.5 H), 7.66–7.55 (m, 0.5 H), 6.97–6.52 (br s, 1 H, exchangeable), 3.76–3.64 (m, 0.75 H), 3.62–3.50 (m, 0.25 H), 3.51–3.38 (m, 0.25 H), 3.34–3.25 (m, 0.75 H), 3.12–3.03 (m, 0.75 H), 3.00–2.89 (m, 0.25 H), 2.88–2.77 (m, 0.75 H), 2.69–2.60 (m, 0.25 H), 2.59–2.49 (m, 0.75 H), 2.42–2.23 (m, 0.25 H), 1.96–1.78 (m, 1 H), 1.77–1.53 (m, 3 H), 1.42–1.23 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 147.3, 140.1, 134.3 (q, *J* = 33.3 Hz), 128.7, 126.2, 125.8, 125.3, 122.4, 119.7, 102.6, 68.2, 64.7, 60.0, 55.0, 52.2, 44.0, 43.5, 32.4, 29.8, 28.7, 25.8, 24.6, 23.6, 22.0; HRMS (ESI) calcd for $C_{14}H_{17}F_3NO_2^+$ [M + H^+] 288.1206, found 288.1212.

(*S*)-2-(1-hydroxypiperidin-2-yl)-1-(4-nitrophenyl)ethan-1-one (70): Prepared using the general procedure described above yielding **70** (81 mg, 61% yield, 90% *ee*) as a yellow solid. **70**: R_f = 0.50 (silica gel, EtOAc); $[\alpha]_D^{25}$ = +1.7º (*c* = 1.00, $CHCl_3$); IR (film) ν_{max} 3110, 2940, 2856, 1691, 1604, 1524, 1347, 1200, 1106, 1012, 856, 746, 703 cm^{-1}; acyclic:cyclic = 1:1, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34–8.25 (m, 1 H), 8.24–8.17 (m, 1 H), 8.17–8.06 (m, 1 H), 7.90–7.72 (m, 1 H), 7.09–6.66 (br s, 1 H, exchangeable), 3.85–3.65 (m, 0.5 H), 3.65–3.35 (m, 0.5 H), 3.33–3.23 (m, 0.5 H), 3.22–3.13 (m, 0.25 H), 3.13–3.03 (m, *J* = 31.0 Hz, 0.5 H), 3.03–2.92 (m, 0.25 H), 2.91–2.75 (m, 0.5 H), 2.75–2.44 (m, 1.5 H), 2.41–2.32 (m, 0.25 H), 1.95–1.84 (m, 1.25 H), 1.81–1.51

(m, 3 H), 1.46–1.35 (m, 1 H), 1.34–1.22 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 150.3, 142.0, 129.4, 126.9, 123.9, 123.5, 102.4, 68.2, 64.7, 59.9, 55.0, 52.3, 44.2, 32.3, 28.7, 25.6, 24.7, 24.6, 23.5; HRMS (ESI) calcd for $C_{13}H_{17}N_2O_4^+$ [M + H^+] 265.1183, found 265.1188.

(*S*)-1-(4-bromophenyl)-2-(1-hydroxypiperidin-2-yl)ethan-1-one (69): Prepared using the general procedure described above yielding **69** (81 mg, 54% yield, 91% *ee*) as a pale-yellow solid. **69**: R_f = 0.45 (silica gel, EtOAc); $[\alpha]_D^{25}$ = –25.8º (*c* = 1.00, $CHCl_3$); IR (film) ν_{max} 3159, 2937, 2856, 1684, 1585, 1396, 1288, 1203, 1071, 1007, 841, 752 cm^{-1}; acyclic ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 14.9 Hz, 2 H), 7.58 (d, *J* = 15.3 Hz, 2 H), 6.56–5.67 (br s, 1 H, exchangeable), 3.65 (dd, *J* = 16.0, 10.2 Hz, 1 H), 3.35–3.27 (m, 1 H), 3.07–2.97 (m, 1 H), 2.78 (dd, *J* = 15.3, 6.4 Hz, 1 H), 2.59–2.51 (m, 1 H), 1.90–1.84 (m, 1 H), 1.76–1.70 (m, 1 H), 1.65–1.57 (m, 2 H), 1.37–1.24 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 136.0, 132.0, 129.9, 128.3, 64.7, 60.0, 43.6, 32.2, 25.8, 23.6; HRMS (ESI) calcd for $C_{13}H_{17}BrNO_2^+$ [M + H^+] 298.0437, found 298.0437.

(*S*)-2-(1-hydroxypiperidin-2-yl)-1-(4-methoxyphenyl)ethan-1-one (67): Prepared using the general procedure described above yielding **67** (82 mg, 65% yield, 92% *ee*) as a pale-yellow oil. **67**: R_f = 0.38 (silica gel, EtOAc); $[\alpha]_D^{25}$ = –32.7º (*c* = 1.00, $CHCl_3$); IR (film) ν_{max} 3176, 2936, 2855, 1673, 1601, 1511, 1258, 1172, 1030, 843, 749 cm^{-1}; acyclic ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.7 Hz, 2 H), 6.90 (d, *J* = 8.7 Hz, 2 H), 3.85 (s, 3 H), 3.68 (dd, *J* = 15.1, 3.6 Hz, 1 H), 3.34 (d, *J* = 9.1 Hz, 1 H), 3.06–2.97 (m, 1 H), 2.79 (dd, *J* = 15.1, 7.4 Hz, 1 H), 2.56 (t, *J* = 10.4 Hz, 1 H), 1.91–1.85 (m, 1 H), 1.77–1.69 (m, 1 H), 1.64–1.55 (m, 2 H), 1.37–1.21 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 163.6, 130.7, 130.5, 113.9, 65.0, 60.0, 55.6, 43.2, 32.3, 26.0, 23.7; HRMS (ESI) calcd for $C_{14}H_{20}NO_3^+$ [M + H^+] 250.1438, found 250.1439.

(*S*)-1-(benzo[d][1,3]dioxol-5-yl)-2-(1-hydroxypiperidin-2-yl)ethan-1-one (68): Prepared using the general procedure described above yielding **68** (88 mg, 66% yield, 93% *ee*) as a clear oil. **68**: R_f = 0.46 (silica gel, EtOAc); $[\alpha]_D^{25}$ = –26.9º (*c* = 1.00, $CHCl_3$); IR (film) ν_{max} 3188, 2936, 2857, 1673, 1604, 1503, 1443, 1354, 1249, 1112, 1038, 933, 809, 736 cm^{-1}; acyclic ^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.1 Hz, 1 H), 7.45 (s, 1 H), 6.81 (d, *J* = 8.1 Hz, 1 H), 6.41–6.22 (br s, 1 H, exchangeable), 6.03 (s, 2 H), 3.62 (dd, *J* = 15.2, 4.2 Hz, 1 H), 3.33 (d, *J* = 9.6 Hz, 1 H), 3.06–2.96 (m, 1 H), 2.75 (dd, *J* = 15.2, 7.2 Hz, 1 H), 2.55 (t, *J* = 10.5 Hz, 1 H), 1.87 (d, *J* = 12.3 Hz, 1 H), 1.73 (d, *J* = 12.2 Hz, 1 H), 1.60 (t, *J* = 13.1 Hz, 2 H), 1.35–1.22 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 151.8, 148.3, 132.2, 124.7, 108.2, 108.0, 101.9, 64.9, 60.0, 43.4, 32.3, 25.9, 23.7; HRMS (ESI) calcd for $C_{14}H_{18}NO_4^+$ [M + H^+] 264.1230, found 264.1242.

(*S*)-1-(1-hydroxypiperidin-2-yl)propan-2-one (72): Prepared using the general procedure described above yielding **72** (60 mg, 76% yield, 95% *ee*) as a pale-yellow oil. **72**: R_f = 0.36 (silica gel, EtOAc); $[\alpha]_D^{25}$ = +8.3º (*c* = 1.00, $CHCl_3$); IR (film) ν_{max} 3158, 2937, 2856, 1713, 1443, 1358, 1226, 1165, 1063, 862, 774 cm^{-1}; acyclic:cyclic = 1:1 ^1H NMR (500 MHz, $CDCl_3$) δ 7.89–7.33 (br s, 0.5 H, exchangeable), 6.16–5.55 (br s, 0.5 H, exchangeable), 3.44–3.33 (m, 0.5 H), 3.31–3.26 (m, 0.5 H), 3.06–2.96 (m, 0.5 H), 2.95–2.86 (m, 0.5 H), 2.59–2.28 (m, 2.5 H), 2.18 (s, 1.5 H), 2.08–1.95 (m, 0.5 H), 1.94–1.52 (m, 4.5 H), 1.45 (s, 1.5 H), 1.34–1.16 (m, 1.5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.3, 102.4, 68.1, 64.1, 60.0, 54.8, 49.4, 49.2, 32.2, 30.5, 28.9, 26.7, 25.7, 24.6, 23.6; HRMS (ESI) calcd for $C_8H_{16}NO_2^+$ [M + H^+] 158.1176, found 158.1173.

(*S*)-1-(1-hydroxypiperidin-2-yl)butan-2-one (73): Prepared using the general procedure described above yielding **73** (76 mg, 88% yield, 95% *ee*) as a clear oil. **73**: R_f = 0.40 (silica gel, EtOAc); $[\alpha]_D^{25}$ = +10.0º (*c* = 1.00, $CHCl_3$); IR (film) ν_{max} 3159, 2937, 2857, 1712, 1444, 1377,

1215, 1113, 952, 897, 767 cm^{-1}; acyclic:cyclic = 1:1 ^1H NMR (500 MHz, $CDCl_3$) δ 7.56–7.33 (br s, 0.5 H, exchangeable), 5.69–5.35 (br s, 0.5 H, exchangeable), 3.45–3.35 (m, 0.5 H), 3.31–3.23 (m, 0.5 H), 3.00 (dd, *J* = 15.5, 5.1 Hz, 0.5 H), 2.95–2.87 (m, 0.5 H), 2.55–2.37 (m, 2.5 H), 2.36–2.23 (m, 1 H), 1.99–1.84 (m, 1 H), 1.83–1.66 (m, 3 H), 1.65–1.52 (m, 1.5 H), 1.50–1.37 (m, 0.5 H), 1.32–1.17 (m, 1.5 H), 1.04 (t, *J* = 7.2 Hz, 1.5 H), 0.98 (t, *J* = 7.2 Hz, 1.5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.8, 104.4, 68.1, 64.2, 60.0, 54.8, 47.8, 47.2, 36.4, 32.2, 29.0, 25.7, 24.6, 23.7, 8.6, 7.9; HRMS (ESI) calcd for $C_9H_{18}NO_2^+$ [M + H^+] 172.1332, found 172.1334.

(*S*)-1-(1-hydroxypiperidin-2-yl)-6-methylhept-5-en-2-one (75): Prepared using the general procedure described above yielding **75** (102 mg, 90% yield, 96% *ee*) as a clear oil. **75**: R_f = 0.53 (silica gel, EtOAc); $[\alpha]_D^{25}$ = +2.9º (*c* = 1.00, $CHCl_3$); IR (film) ν_{max} 3163, 2936, 2857, 1713, 1444, 1377, 1277, 1110, 985, 861, 778 cm^{-1}; acyclic:cyclic = 1.5:1 ^1H NMR (500 MHz, $CDCl_3$) δ 7.23–6.94 (br s, 0.6 H, exchangeable), 5.73–5.34 (br s, 0.4 H, exchangeable), 5.19–5.09 (m, 0.4 H), 5.09–5.00 (m, 0.6 H), 3.44–3.23 (m, 1 H), 3.11–2.80 (m, 1 H), 2.62–2.32 (m, 3 H), 2.32–2.01 (m, 3 H), 2.00–1.71 (m, 3 H), 1.68–1.51 (m, 8 H), 1.50–1.14 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.0, 132.7, 132.0, 124.1, 123.0, 103.9, 68.0, 64.0, 59.9, 54.8, 48.2, 47.9, 43.3, 39.6, 32.3, 28.9, 25.8, 25.7, 24.6, 23.6, 23.0, 22.6, 17.8; HRMS (ESI) calcd for $C_{13}H_{24}NO_2^+$ [M + H^+] 226.1802, found 226.1803.

(*S*)-1-(1-hydroxypiperidin-2-yl)-3-(4-methoxyphenyl)propan-2-one (76): Prepared using the general procedure described above yielding **76** (106 mg, 80% yield, 96% *ee*) as a clear oil. **76**: R_f = 0.51 (silica gel, EtOAc); $[\alpha]_D^{25}$ = +16.0º (*c* = 1.00, $CHCl_3$); IR (film) ν_{max} 3148, 2937, 2836, 1710, 1611, 1513, 1442, 1301, 1248, 1178, 1036, 825 cm^{-1}; acyclic:cyclic = 1:1.7 ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.2 Hz, 1.2 H), 7.11 (d, *J* = 7.8 Hz, 0.8 H), 6.92–6.77 (m, 2 H), 6.77–6.62 (br s, 1 H, exchangeable), 3.84–3.74 (m, 3 H), 3.74–3.60 (m, 0.8 H), 3.48–3.35 (m, 0.6

H), 3.33–3.22 (m, 0.4 H), 3.05–2.85 (m, 2 H), 2.55–2.44 (m, 0.4 H), 2.44–2.31 (m, 1.3 H), 1.96–1.79 (m, 1 H), 1.79–1.68 (m, 2 H), 1.67–1.51 (m, 2 H), 1.38–1.17 (m, 2 H), 1.17–1.04 (m, 0.5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9, 158.7, 158.6, 132.0, 130.7, 128.3, 126.5, 114.2, 114.0, 113.9, 113.5, 103.6, 68.0, 64.1, 60.0, 55.4, 54.8, 49.6, 47.2, 46.9, 44.3, 32.2, 28.8, 26.9, 25.7, 24.6, 23.6; HRMS (ESI) calcd for $C_{15}H_{22}NO_3^+$ [M + H^+] 264.1594, found 264.1593.

(*S*)-1-(1-hydroxypiperidin-2-yl)-3-methylbutan-2-one (77): Prepared using the general procedure described above yielding **77** (57 mg, 61% yield, 94% *ee*) as a clear oil. **77**: R_f = 0.49 (silica gel, EtOAc); $[\alpha]_D^{25}$ = +21.1° (*c* = 1.00, $CHCl_3$); IR (film) ν_{max} 3163, 2938, 2858, 1710, 1468, 1382, 1268, 1149, 1107, 1031, 955, 759 cm^{-1}; acyclic:cyclic = 1:1 ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18–6.83 (br s, 0.5 H, exchangeable), 5.23–4.54 (br s, 0.5 H, exchangeable), 3.43–3.35 (m, 0.5 H), 3.32–3.25 (m, 0.5 H), 3.07 (dd, *J* = 16.1, 4.7 Hz, 0.5 H), 2.93–2.86 (m, 0.5 H), 2.71–2.62 (m, 0.5 H), 2.54–2.35 (m, 2 H), 2.27–2.17 (m, 0.5 H), 1.91–1.84 (m, 1 H), 1.81–1.75 (m, 1 H), 1.74–1.67 (m, 1 H), 1.65–1.56 (m, 1.5 H), 1.47–1.37 (m, 0.5 H), 1.29–1.17 (m, 1.5 H), 1.11–1.05 (m, 3.5 H), 1.02–0.94 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.0, 106.0, 68.2, 64.0, 60.0, 54.8, 45.6, 45.5, 41.1, 35.9, 32.2, 29.1, 25.8, 24.7, 23.7, 23.6, 18.3, 17.8, 17.3; HRMS (ESI) calcd for $C_{10}H_{20}NO_2^+$ [M + H^+] 186.1489, found 186.1492.

(*S*)-1-cyclopropyl-2-(1-hydroxypiperidin-2-yl)ethan-1-one (74): Prepared using the general procedure described above yielding **74** (47 mg, 51% yield, 95% *ee*) as a clear oil. **74**: R_f = 0.36 (silica gel, EtOAc); $[\alpha]_D^{25}$ = –31.1° (*c* = 1.00, $CHCl_3$); IR (film) ν_{max} 3183, 2037, 2857, 1695, 1444, 1389, 1276, 1065, 903, 822, 764 cm^{-1}; acyclic ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14–6.53 (br s, 1 H, exchangeable), 3.30 (d, *J* = 9.9 Hz, 1 H), 3.18 (dd, *J* = 15.5, 4.8 Hz, 1 H), 2.97–2.87 (m, 1 H), 2.59–2.44 (m, 2 H), 1.97 (td, *J* = 7.7, 4.0 Hz, 1 H), 1.86–1.77 (m, 1 H), 1.75–1.68 (m, 1 H), 1.65–1.54 (m, 2 H), 1.31–1.21 (m, 2 H), 1.06–0.98 (m, 2 H), 0.90–0.83 (m, 2 H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 210.5, 64.3, 59.9, 48.8, 32.3, 25.9, 23.7, 21.1, 11.2, 11.0; HRMS (ESI) calcd for $C_{10}H_{18}NO_2^+$ [M + H^+] 184.1332, found 184.1335.

(*S*)-1-fluoro-3-(1-hydroxypiperidin-2-yl)propan-2-one (79): Prepared using the general procedure described above yielding **79** (66 mg, 75% yield, 95% *ee*) as a clear oil. **79**: R_f = 0.54 (silica gel, EtOAc); $[\alpha]_D^{25}$ = +75.5º (*c* = 1.00, $CHCl_3$); IR (film) ν_{max} 3399, 3139, 2941, 2857, 1728, 1445, 1282, 1152, 1109, 1047, 861, 779 cm^{-1}; cyclic, *dr*(cyclic) = 7:1, major *dr*: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.89–4.56 (br s, 1 H, exchangeable), 4.32 (d, *J* = 47.1 Hz, 2 H), 3.52–3.35 (m, 1 H), 2.62–2.45 (m, 2 H), 2.44–2.29 (m, 1 H), 2.14–1.97 (m, 1 H), 1.96–1.86 (m, 1 H), 1.85–1.62 (m, 3 H), 1.55–1.41 (m, 1 H), 1.31–1.19 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 101.3 (d, *J* = 13.7 Hz), 83.7 (d, *J* = 176.0 Hz), 68.2, 55.0, 44.9, 28.8, 24.6, 23.6; HRMS (ESI) calcd for $C_8H_{15}FNO_2^+$ [M + H^+] 176.1081, found 176.1084.

(*S*)-1-(1-hydroxypiperidin-2-yl)-3-methoxypropan-2-one (80): Prepared using the general procedure described above yielding **80** (61 mg (major regioisomer), 65% yield, 94% *ee*; 73 mg (combined, *rr* : 5.4:1), 77% yield) as a yellow oil. **80**: R_f = 0.29 (silica gel, EtOAc); $[\alpha]_D^{25}$ = +59.2º (*c* = 1.00, $CHCl_3$); IR (film) ν_{max} 3401, 3148, 2938, 2857, 1722, 1445, 1261, 1120, 1049, 980, 861, 780 cm^{-1}; cyclic, *dr*(cyclic) = 2.7:1 ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.09–3.99 (m, 0.3 H), 3.61–3.34 (m, 6 H), 2.66–2.52 (m, 0.3 H), 2.51–2.42 (m, 0.7 H), 2.42–2.32 (m, 0.8 H), 2.32–2.25 (m, 0.7 H), 2.20–2.07 (m, 0.2 H), 2.06–1.94 (m, 0.6 H), 1.96–1.83 (m, 1 H), 1.82–1.55 (m, 3 H), 1.53–1.42 (m, 0.9 H), 1.40–1.15 (m, 1.5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 102.1, 101.8, 76.5, 76.3, 68.0, 65.6, 59.8, 59.7, 55.8, 55.2, 45.2, 43.8, 29.0, 28.9, 24.9, 24.6, 23.7; HRMS (ESI) calcd for $C_9H_{18}NO_3^+$ [M + H^+] 188.1281, found 188.1282.

(*S*)-3-(1-hydroxypiperidin-2-yl)-1,1-dimethoxypropan-2-one (81): Prepared using the general procedure described above yielding **81** (94 mg, 86% yield, 96% *ee*) as a clear oil. **81**: R_f = 0.32 (silica gel, EtOAc); $[\alpha]_D^{25}$ = +65.1º (*c* = 1.00, $CHCl_3$); IR (film) ν_{max} 3417, 3149, 2938, 2833, 1729, 1446, 1351, 1262, 1152, 1086, 988, 862 cm^{-1}; cyclic, *dr*(cyclic) = 2:1 ^1H NMR (500 MHz, $CDCl_3$) δ 4.31 (s, 0.33 H), 4.26 (s, 0.67 H), 3.81 (br s, 0.33 H, exchangeable), 3.66 (br s, 0.67 H, exchangeable), 3.58 (s, 1 H), 3.53 (s, 2 H), 3.50 (s, 2 H), 3.45 (s, 1 H), 2.64–2.41 (m, 2 H), 2.35–2.23 (m, 0.67 H), 2.20–2.08 (m, 0.33 H), 2.07–1.91 (m, 1 H), 1.91–1.56 (m, 4 H), 1.56–1.30 (m, 1.67 H), 1.30–1.09 (m, 1.33 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 105.9, 105.3, 103.0, 102.6, 68.0, 65.6, 57.7, 56.8, 56.6, 56.0, 55.5, 55.4, 43.8, 42.6, 29.0, 24.9, 24.7, 23.7, 23.7; HRMS (ESI) calcd for $C_{10}H_{20}NO_4^+$ [M + H^+] 218.1387, found 218.1389.

General Procedure for Decarboxylative Mannich-type Reactions between Nitrones 86 and β-ketoacids 87. To a vial containing β-ketoacid **87** (0.76 mmol, 1.5 equiv) at 23 ºC under an ambient atmosphere was added a solution of nitrone **86** (0.50 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL). The reaction mixture was then stirred for 16 h. Upon completion, the contents were quenched with saturated aqueous $NaHCO_3$ (2 mL) and extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were then dried ($MgSO_4$), filtered, and concentrated. The resultant crude material was purified by flash column chromatography (silica gel, hexane/EtOAc) to yield **88**.

(±)-2-(1-hydroxypiperidin-2-yl)-1-phenylethan-1-one (*rac*-31): Prepared using the general procedure described above with **25** ultimately yielding *rac*-**31** (16 h: 100 mg, 90% yield; 2 h: 88 mg, 80% yield) as a pale-yellow oil.

(±)-2-(1-hydroxypyrrolidin-2-yl)-1-phenylethan-1-one (91): Prepared using the general procedure described above with **125** ultimately yielding **91** (86 mg, 84% yield) as a yellow oil. **91**: R_f = 0.40 (silica gel, EtOAc); IR (film) ν_{max} 3213, 2963, 1681, 1598, 1450, 1259, 1065, 1025, 754,

710 cm^{-1}; acyclic ^1H NMR (500 MHz, $CDCl_3$) δ 8.02–7.87 (m, 2 H), 7.62–7.48 (m, 1 H), 7.48–7.33 (m, 2 H), 3.64–3.45 (m, 1 H), 3.44–3.18 (m, 2 H), 3.12–2.94 (m, 1 H), 2.92–2.76 (m, 1 H), 2.27–2.05 (m, 1 H), 1.89–1.68 (m, 2 H), 1.55–1.31 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.4, 137.2, 133.2, 128.7, 128.3, 65.1, 57.6, 42.6, 27.9, 20.1; HRMS (ESI) calcd for $C_{12}H_{16}NO_2^+$ [M + H^+] 206.1176, found 206.1174. See **S33** for ^1H and ^{13}C NMR data of the *O*-benzoylated adduct.

(±)-2-(1-hydroxyazepan-2-yl)-1-phenylethan-1-one (90): Prepared using the general procedure described above with **129** ultimately yielding **90** (78 mg, 66% yield) as a yellow oil. **90**: R_f = 0.68 (silica gel, EtOAc); IR (film) ν_{max} 3061, 2932, 2857, 1683, 1598, 1450, 1246, 1063, 710 cm^{-1}; acyclic:cyclic = 1:3.4 ^1H NMR (500 MHz, $CDCl_3$) δ 8.07–7.80 (m, 0.5 H), 7.78–7.59 (m, 1.5 H), 7.58–7.08 (m, 3 H), 6.18–4.85 (br s, 1 H, exchangeable), 3.84–3.38 (m, 1.5 H), 3.31–2.84 (m, 1.5 H), 2.84–2.52 (m, 1.2 H), 2.51–2.34 (m, 0.4 H), 2.26–2.02 (m, 0.4 H), 2.01–1.34 (m, 8 H); ^{13}C NMR (100 MHz, MeOD) δ 143.7, 142.0, 132.9, 127.7, 125.6, 103.9, 65.9, 60.8, 57.8, 52.0, 29.6, 29.1, 26.9, 26.2, 25.0, 24.4, 24.3; HRMS (ESI) calcd for $C_{14}H_{20}NO_2^+$ [M + H^+] 234.1489, found 234.1490.

(±)-2-(1-hydroxypiperidin-2-yl)-1-(thiophen-2-yl)ethan-1-one (89): Prepared using the general procedure described above with **25** ultimately yielding **89** (99 mg, 87% yield) as a yellow oil. **89**: R_f = 0.49 (silica gel, EtOAc); IR (film) ν_{max} 3102, 2937, 2856, 1656, 1518, 1415, 1355, 1291, 1235, 1059, 859, 730 cm^{-1}; acyclic ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 3.2 Hz, 1 H), 7.62 (d, *J* = 4.8 Hz, 1 H), 7.18–7.05 (m, 1 H), 6.60–6.07 (br s, 1 H, exchangeable), 3.59 (dd, *J* = 14.9, 4.0 Hz, 1 H), 3.34 (d, *J* = 8.5 Hz, 1 H), 3.09–2.99 (m, 1 H), 2.81 (dd, *J* = 14.9, 7.1 Hz, 1 H), 2.57 (t, *J* = 10.8 Hz, 1 H), 1.95–1.82 (m, 1 H), 1.80–1.67 (m, 1 H), 1.67–1.51 (m, 2 H), 1.42–1.20 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 144.9, 133.8, 132.3, 128.2, 64.9, 59.9, 44.3, 32.2, 25.9, 23.6; HRMS (ESI) calcd for $C_{11}H_{16}NO_2S^+$ [M + H^+] 226.0896, found 226.0899.

(±)-1-(1-hydroxypiperidin-2-yl)-3,3-dimethylbutan-2-one (94): Prepared using the general procedure described above (except using MeOH as the solvent) with **25** ultimately yielding **94** (51 mg, 51% yield) as a white solid. **94**: R_f = 0.59 (silica gel, EtOAc); IR (film) ν_{max} 3166, 2939, 2860, 1704, 1479, 1363, 1271, 1149, 1102, 963, 898, 747 cm^{-1}; acyclic:cyclic = 1:1 ^1H NMR (500 MHz, $CDCl_3$) δ 6.43–5.96 (br s, 0.5 H, exchangeable), 4.35–3.95 (br s, 0.5 H, exchangeable), 3.42–3.35 (m, 0.5 H), 3.34–3.28 (m, 0.5 H), 3.20–3.12 (m, 0.5 H), 2.96–2.85 (m, 0.5 H), 2.62–2.42 (m, 2 H), 2.25–2.13 (m, 0.5 H), 1.91–1.82 (m, 0.5 H), 1.82–1.63 (m, 3 H), 1.63–1.54 (m, 1 H), 1.48–1.37 (m, 0.5 H), 1.33–1.16 (m, 1.5 H), 1.13 (s, 5 H), 1.01 (s, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.1, 107.4, 68.3, 63.9, 60.0, 54.9, 45.0, 44.5, 41.1, 37.3, 31.9, 29.2, 26.4, 26.0, 25.2, 24.7, 23.8, 23.7; HRMS (ESI) calcd for $C_{11}H_{22}NO_2^+$ [M + H^+] 200.1645, found 200.1648. See **S35** for ^1H and ^{13}C NMR data of the *O*-benzoylated adduct.

(±)-3-(benzyl(hydroxy)amino)-1-phenylbutan-1-one (93): Prepared using the general procedure described above with **133** ultimately yielding **93** (82 mg, 61% yield) as a yellow oil. **93**: R_f = 0.42 (silica gel, hexanes/EtOAc = 4/1); IR (film) ν_{max} 3168, 2974, 2875, 1681, 1587, 1449, 1370, 1287, 1210, 1003, 738, 697 cm^{-1}; acyclic:cyclic = 2:1, *dr*(acyclic) = 2:1; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.5 Hz, 1.2 H), 7.67–7.53 (m, 1.4 H), 7.52–7.42 (m, 2 H), 7.41–7.20 (m, 5.4 H), 6.40–6.01 (br s, 1 H, exchangeable), 4.35–4.12 (m, 0.5 H), 3.93 (dd, *J* = 13.4, 9.0 Hz, 0.9 H), 3.76 (d, *J* = 13.0 Hz, 0.7 H), 3.59 (dq, *J* = 12.9, 6.4 Hz, 0.8 H), 3.46 (dd, *J* = 15.9, 4.9 Hz, 0.6 H), 2.96 (dd, *J* = 15.9, 8.0 Hz, 0.9 H), 2.73 (dd, *J* = 12.4, 5.8 Hz, 0.1 H), 2.56 (dd, *J* = 13.3, 7.5 Hz, 0.2 H), 2.27–2.12 (m, 0.1 H), 2.08–1.96 (m, 0.2 H), 1.24 (d, *J* = 6.4 Hz, 1.8 H), 1.16 (d, *J* = 6.1 Hz, 0.4 H), 1.11 (d, *J* = 6.1 Hz, 0.8 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 143.1, 137.7, 137.5, 137.2, 136.1, 133.0, 130.0, 129.8, 129.3, 128.3, 128.3, 128.2, 128.1, 127.9, 127.5, 127.8,

127.4, 127.3, 125.7, 125.6, 104.7, 102.6, 61.8, 61.3, 60.5, 60.0, 58.2, 53.1, 51.9, 42.2, 16.3, 15.1; HRMS (ESI) calcd for $C_{17}H_{20}NO_2^+$ [M + H^+] 270.1489, found 270.1489.

(±)-2-(2-hydroxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-one (92): Prepared using the general procedure described above with **126** ultimately yielding **92** (46 mg, 34% yield) as a yellow oil. **92**: R_f = 0.50 (silica gel, hexane/EtOAc, 1/1); IR (film) ν_{max} 3062, 2929, 2848, 1684, 1597, 1493, 1448, 1354, 1276, 1209, 1002, 912, 748, 690 cm^{-1}; acyclic:cyclic = 1.5:1 ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16–7.81 (m, 1 H), 7.74–6.93 (m, 8 H), 6.93–6.66 (br s, 1 H, exchangeable), 5.16–4.96 (m, 0.4 H), 4.96–4.73 (m, 0.6 H), 3.95–3.63 (m, 0.6 H), 3.53–2.80 (m, 5 H), 2.65–2.35 (m, 0.4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 136.9, 133.7, 133.6, 133.2, 128.6, 128.5, 128.5, 127.4, 127.2, 126.9, 126.7, 126.0, 125.9, 125.7, 104.8, 63.4, 61.9, 52.2, 51.9, 51.7, 50.2, 49.8, 44.1, 28.6, 27.0; HRMS (ESI) calcd for $C_{17}H_{18}NO_2^+$ [M + H^+] 268.1332, found 268.1332.

(±)-1-((3*S*, 8*S*, 9*S*, 10*R*, 13*S*, 14*S*, 17*S*)-3-hydroxy-10,13-dimethyl-2, 3, 4, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)-2-(1-hydroxypiperidin-2-yl)ethan-1-one (95): Prepared using the general procedure described above with **25** (1.5 equiv) ultimately yielding **95** (161 mg, 77% yield, 2:1 *dr*) as a white solid. **95**: R_f = 0.16 (silica gel, hexanes/EtOAc = 1/1); $[\alpha]_D^{25}$ = –19.7º (*c* = 1.00, $CHCl_3$); IR (film) ν_{max} 3307, 2936, 2849, 1701, 1450, 1377, 1266, 1110, 1058, 954, 737 cm^{-1}; acyclic, *dr*(acyclic) = 2:1 ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18–6.86 (br s, 1 H, exchangeable), 5.33 (s, 1 H), 3.63–3.42 (m, 1 H), 3.41–3.20 (m, 1 H), 3.14–2.98 (m, 1 H), 2.97–2.83 (m, 1 H), 2.70–2.58 (m, 1 H), 2.58–2.46 (m, 1 H), 2.41–2.10 (m, 4 H), 2.08–1.93 (m, 2 H), 1.96–1.78 (m, 3 H), 1.79–1.35 (m, 11 H), 1.35–1.05 (m, 5 H), 0.98 (s, 3 H), 0.96–0.88 (m, 1 H), 0.63 (s, 2 H, major), 0.62 (s, 1 H, minor); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.8 (major), 210.5 (minor), 141.0, 121.4, 71.6, 64.4 (minor), 64.2 (major),

63.5 (minor), 63.2 (major), 60.1 (major), 60.0 (minor), 57.2 (minor), 57.2 (major), 50.3 (major), 50.2 (minor), 49.5 (major), 49.2 (minor), 44.4 (minor), 44.3 (major), 42.4, 39.2, 39.0, 37.5, 36.6, 32.3, 32.0, 31.9, 25.9, 25.5, 24.6, 23.7, 23.1, 23.1, 21.3, 19.5, 13.6 (minor), 13.4 (major); HRMS (ESI) calcd for $C_{26}H_{42}NO_3^+$ [M + H^+] 416.3158, found 416.3162.

General Procedure for Benzoylation of Hydroxylamines. To a solution of the corresponding hydroxylamine (1.0 equiv) in CH_2Cl_2 (0.1 M) at 0 ºC were sequentially added 4-DMAP (0.2 equiv), Et_3N (4.0 equiv), and BzCl (2.0 equiv). The mixture was then warmed to 23 ºC and stirred at this temperature for 2 h. Upon completion (monitored by TLC), the contents were quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. The resultant crude product was purified by flash column chromatography (silica gel, hexane/EtOAc, 20/1→1/1) with yields up to 80%. The benzoylated products were then either used for characterization and/or to determine enantiopurity by HPLC.

(±)-2-(2-oxo-2-phenylethyl)pyrrolidin-1-yl benzoate (91'): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10–7.79 (m, 4 H), 7.59–7.46 (m, 2 H), 7.46–7.28 (m, 4 H), 3.84 (ddd, *J* = 17.0, 8.8, 4.2 Hz, 1 H), 3.72–3.62 (m, 1 H), 3.62–3.52 (m, 1 H), 3.13 (dd, *J* = 16.9, 8.8 Hz, 1 H), 3.08–2.93 (m, 1 H), 2.35 (dt, *J* = 20.5, 7.6 Hz, 1 H), 1.99 (dt, *J* = 14.1, 8.4 Hz, 2 H), 1.64–1.50 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 165.5, 136.9, 133.3, 133.2, 129.5, 129.2, 128.7, 128.5, 128.2, 64.5, 56.2, 42.5, 27.7, 20.6.

(±)-2-(2-oxo-2-phenylethyl)azepan-1-yl benzoate (90'): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.3 Hz, 2 H), 7.88 (d, *J* = 7.3 Hz, 2 H), 7.59–7.43 (m, 2 H), 7.43–7.31 (m, 4 H), 4.06–3.77 (m, 1 H), 3.55–3.41 (m, 1 H), 3.41–3.31 (m, 2 H), 3.14 (dd, *J* = 17.0, 8.8 Hz, 1 H), 2.00–1.64

(m, 7 H), 1.64–1.49 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 165.2, 137.0, 133.1, 129.4, 129.4, 128.6, 128.4, 128.2, 64.2, 57.8, 44.3, 30.5, 27.4, 25.9, 24.3.

(±)-2-(3,3-dimethyl-2-oxobutyl)piperidin-1-yl benzoate (94'): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.4 Hz, 2 H), 7.64–7.45 (m, 1 H), 7.49–7.37 (m, 2 H), 3.67–3.53 (m, 1 H), 3.53–3.40 (m, 1 H), 2.90 (dd, *J* = 17.7, 4.1 Hz, 1 H), 2.83–2.70 (m, 1 H), 2.62 (dd, *J* = 17.7, 7.4 Hz, 1 H), 1.96–1.74 (m, 3 H), 1.68 (d, *J* = 12.1 Hz, 1 H), 1.51 (d, *J* = 12.8 Hz, 1 H), 1.38 (d, *J* = 13.0 Hz, 1 H), 1.01 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.2, 165.0, 133.2, 129.6, 129.2, 128.5, 62.3, 58.1, 44.4, 41.3, 32.0, 26.2, 25.6, 23.6.

(±)-1-(2-oxo-2-phenylethyl)-3,4-dihydroisoquinolin-2(1H)-yl benzoate (92'): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.3 Hz, 2 H), 7.84 (d, *J* = 7.3 Hz, 2 H), 7.50 (dd, *J* = 11.3, 7.3 Hz, 2 H), 7.42–7.37 (m, 2 H), 7.37–7.31 (m, 2 H), 7.22–7.05 (m, 4 H), 5.50–5.06 (m, 1 H), 3.78 (dd, *J* = 17.3, 5.0 Hz, 1 H), 3.75–3.66 (m, 1 H), 3.57–3.45 (m, 1 H), 3.40 (dd, *J* = 17.2, 5.8 Hz, 1 H), 3.24–3.12 (m, 1 H), 3.05 (dt, *J* = 16.7, 5.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 164.9, 136.8, 136.5, 133.4, 133.2, 133.2, 129.6, 129.0, 128.7, 128.6, 128.4, 128.4, 127.0, 126.8, 126.7, 61.6, 51.2, 44.8, 26.7.

(*S*)-2-(2-oxopropyl)piperidin-1-yl benzoate (72'): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.4 Hz, 2 H), 7.64–7.49 (m, 1 H), 7.48–7.34 (m, 2 H), 3.65–3.50 (m, 1 H), 3.49–3.33 (m, 1 H), 2.87 (dd, *J* = 17.1, 5.0 Hz, 1 H), 2.74 (t, *J* = 9.5 Hz, 1 H), 2.44 (dd, *J* = 17.1, 6.4 Hz, 1 H), 2.01 (s, 3 H), 1.92–1.62 (m, 4 H), 1.61–1.47 (m, 1 H), 1.44–1.28 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.3, 165.0, 133.3, 129.6, 129.1, 128.6, 62.7, 58.0, 48.1, 32.1, 31.2, 25.5, 23.6.

(*S*)-2-(2-oxobutyl)piperidin-1-yl benzoate (73'): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.2 Hz, 2 H), 7.63–7.49 (m, 1 H), 7.49–7.35 (m, 2 H), 3.58–3.51 (m, 1 H), 3.50–3.36 (m, 1 H), 2.84 (dd, *J* = 16.9, 5.3 Hz, 1 H), 2.75 (t, *J* = 9.9 Hz, 1 H), 2.40 (dd, *J* = 16.9, 5.6 Hz, 1 H), 2.36–2.27 (m, 1 H), 2.27–2.16 (m, 1 H), 1.89–1.64 (m, 4 H), 1.60–1.46 (m, 1 H), 1.43–1.29 (m, 1 H), 0.85 (t, *J* = 6.7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.8, 165.0, 133.3, 129.6, 129.1, 128.6, 62.6, 58.0, 47.0, 37.2, 32.2, 25.5, 23.6, 7.5.

(*S*)-2-(6-methyl-2-oxohept-5-en-1-yl)piperidin-1-yl benzoate (75'): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.0 Hz, 2 H), 7.66–7.50 (m, 1 H), 7.49–7.33 (m, 2 H), 5.03–4.78 (m, 1 H), 3.67–3.53 (m, 1 H), 3.53–3.37 (m, 1 H), 2.84 (dd, *J* = 17.1, 5.0 Hz, 1 H), 2.75 (t, *J* = 9.7 Hz, 1 H), 2.41 (dd, *J* = 17.0, 5.7 Hz, 1 H), 2.36–2.28 (m, 1 H), 2.28–2.18 (m, 1 H), 2.18–2.09 (m, 1 H), 2.07–1.97 (m, 1 H), 1.94–1.64 (m, 4 H), 1.58 (s, 3 H), 1.56-1.50 (m, 1 H), 1.48 (s, 3 H), 1.42–1.30 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2, 165.0, 133.3, 132.8, 129.6, 129.1, 128.6, 122.6, 62.6, 58.1, 47.4, 44.1, 32.2, 25.7, 25.5, 23.6, 22.3, 17.7.

(*S*)-2-(3-methyl-2-oxobutyl)piperidin-1-yl benzoate (77'): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.0 Hz, 2 H), 7.64–7.50 (m, 1 H), 7.49–7.35 (m, 2 H), 3.63–3.51 (m, 1 H), 3.50–3.37 (m, 1 H), 2.89 (dd, *J* = 17.4, 4.5 Hz, 1 H), 2.76 (t, *J* = 9.8 Hz, 1 H), 2.50 (dd, *J* = 17.4, 6.9 Hz, 1 H), 2.48–2.34 (m, 1 H), 1.94–1.61 (m, 4 H), 1.60–1.44 (m, 1 H), 1.36 (d, *J* = 12.7 Hz, 1 H), 1.00 (d, *J* = 6.8 Hz, 3 H), 0.88 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.9, 165.1, 133.3, 129.7, 129.2, 128.6, 62.4, 58.1, 45.0, 41.6, 32.2, 25.6, 23.6, 18.2, 17.7.

(*S*)-2-(2-cyclopropyl-2-oxoethyl)piperidin-1-yl benzoate (78'): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.2 Hz, 2 H), 7.63–7.50 (m, 1 H), 7.50–7.36 (m, 2 H), 3.67–3.51 (m, 1 H), 3.50–3.34 (m, 1 H), 2.99 (dd, *J* = 16.8, 4.5 Hz, 1 H), 2.87–2.65 (m, 1 H), 2.55 (dd, *J* = 16.7, 5.9 Hz, 1 H), 1.91–1.62 (m, 5 H), 1.62–1.49 (m, 1 H), 1.45–1.23 (m, 1 H), 0.97–0.70 (m, 3 H), 0.68–

0.52 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2, 165.1, 133.2, 129.7, 129.2, 128.5, 62.7, 58.1, 47.6, 32.2, 25.5, 23.6, 21.6, 11.1, 10.6.

(*S*)-2-(3-fluoro-2-oxopropyl)piperidin-1-yl benzoate (79'): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 6.4 Hz, 2 H), 7.63–7.53 (m, 1 H), 7.50–7.39 (m, 2 H), 4.64 (d, *J* = 47.6 Hz, 2 H), 3.65–3.57 (m, 1 H), 3.57–3.42 (m, 1 H), 3.02–2.90 (m, 1 H), 2.86–2.68 (m, 1 H), 2.51 (ddd, *J* = 17.1, 6.0, 2.2 Hz, 1 H), 1.95–1.77 (m, 3 H), 1.76–1.68 (m, 1 H), 1.65–1.54 (m, 1 H), 1.44–1.30 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.0 (d, *J* = 18.9 Hz), 164.9, 133.4, 129.6, 129.0, 128.7, 85.0 (d, *J* = 186.0 Hz), 62.1, 58.0, 42.9, 32.2, 25.4, 23.6.

(*S*)-2-(3-methoxy-2-oxopropyl)piperidin-1-yl benzoate (80'): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.0 Hz, 2 H), 7.65–7.51 (m, 1 H), 7.50–7.36 (m, 2 H), 3.94–3.75 (m, 2 H), 3.62–3.55 (m, 1 H), 3.53–3.44 (m, 1 H), 3.17 (s, 3 H), 2.88 (dd, *J* = 16.8, 5.5 Hz, 1 H), 2.75 (t, *J* = 9.8 Hz, 1 H), 2.40 (dd, *J* = 16.6, 4.8 Hz, 1 H), 1.96–1.76 (m, 3 H), 1.75–1.65 (m, 1 H), 1.63–1.53 (m, 1 H), 1.46–1.30 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.7, 164.9, 133.3, 129.6, 129.1, 128.6, 78.0, 62.4, 59.2, 58.0, 43.5, 32.2, 25.5, 23.6.

(*S*)-2-(3,3-dimethoxy-2-oxopropyl)piperidin-1-yl benzoate (81'). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.3 Hz, 2 H), 7.61–7.44 (m, 1 H), 7.44–7.30 (m, 2 H), 4.18 (s, 1 H), 3.51 (d, *J* = 9.8 Hz, 1 H), 3.45–3.31 (m, 1 H), 3.18 (s, 3 H), 3.11 (s, 3 H), 2.99 (dd, *J* = 17.6, 5.2 Hz, 1 H), 2.86–2.55 (m, 1 H), 2.53–2.35 (m, 1 H), 1.87–1.48 (m, 5 H), 1.41–1.19 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 164.9, 133.2, 129.6, 129.3, 128.5, 104.1, 62.3, 58.0, 54.9, 54.7, 42.3, 32.3, 25.5, 23.6.

Gram-scale Preparation of 31. To a flask containing **55** (0.78 g, 2.0 mmol, 0.2 equiv), BzOH (0.49 g, 4.0 mmol, 0.4 equiv), and methyl ketone **30** (3.50 mL, 30.3 mmol, 3.0 equiv) at 23

ºC under an ambient atmosphere was added a solution of nitrone **25** (1.00 g, 10.1 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL). The reaction mixture was then stirred for 48 h at 23 ºC. Upon completion, the contents were quenched with saturated aqueous $NaHCO_3$ (40 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were then dried ($MgSO_4$), filtered, and concentrated. The resultant crude material was purified by flash column chromatography (silica gel, hexanes/EtOAc = 2/1) to yield **31** (1.55 g, 70%, 90% *ee*).

Hydroxylamine 106. To a solution of **31** (0.62 g, 2.83 mmol, 1.0 equiv) in THF (20 mL) at –78 ºC under an argon atmosphere was added $Zn(BH_4)_2$ (6.50 mL, 0.52 M solution in THF, 3.39 mmol, 1.2 equiv) dropwise over 5 min. The resulting solution was stirred for 1 h at –78 ºC and then slowly warmed to 0 ºC over the course of 2 h. After stirring at 0 ºC for an additional 1 h, the reaction was quenched by careful addition of saturated aqueous NH_4Cl (20 mL), keeping the internal temperature at less than 5 ºC. The mixture was then warmed to 23 ºC, the organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Pressing forward without any additional purification, this crude intermediate was dissolved in CH_2Cl_2 (20 mL), *i*-Pr_2NEt (0.99 mL, 5.66 mmol, 2.0 equiv) was added at 0 ºC followed by dropwise addition of TBSOTf (0.72 mL, 3.11 mmol, 1.1 equiv). The resultant mixture was stirred at 0 ºC for 30 min. Upon completion, the mixture was warmed to 23 ºC, diluted with CH_2Cl_2 (40 mL), and successively washed with saturated aqueous $NaHCO_3$ (10 mL), saturated aqueous NH_4Cl (10 mL), and brine (20 mL). The organic phase was then dried ($MgSO_4$), filtered, and concentrated. The resultant crude material was dissolved in MeOH and refluxed for 2 h. The MeOH was then evaporated and the resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 10/1→2/1) to afford **106** (0.64 g, 67% over 2 steps, 89% *ee*) as a white solid. **106**: R_f = 0.35 (silica gel, EtOAc);

$[\alpha]_D^{25}$ = –23.3º (*c* = 1.00, $CHCl_3$); IR (film) ν_{max} 3186, 2931, 2857, 1472, 1361, 1256, 1092, 836, 775, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.25 (m, 4 H), 7.25–7.15 (m, 1 H), 6.38–5.65 (br s, 1 H, exchangeable), 4.76 (dd, *J* = 8.8, 3.8 Hz, 1 H), 3.27 (d, *J* = 10.3 Hz, 1 H), 2.95–2.64 (m, 0.5 H), 2.64–2.28 (m, 2.5 H), 1.98–1.78 (m, 1 H), 1.76–1.40 (m, 4 H), 1.36–1.04 (m, 2 H), 0.87 (s, 9 H), 0.01 (s, 3 H), -0.23 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.7, 128.1, 127.0, 126.3, 125.9, 72.9, 64.5, 59.9, 44.3, 31.4, 25.9, 25.8, 23.7, 18.2, –4.4, –4.9; HRMS (ESI) calcd for $C_{19}H_{34}NO_2Si^+$ [M + H^+] 336.2353, found 336.2352.

Nitrone 107. To a solution of **106** (0.60 g, 1.80 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) at –20 ºC under an argon atmosphere was added IBX (0.55 g, 1.98 mmol, 1.1 equiv) in a single portion. The resultant reaction mixture was stirred vigorously at –20 ºC for 4 h. Upon completion, anhydrous $MgSO_4$ (0.25 g) was added to the reaction solution and the contents were stirred for 30 minutes. The reaction contents were then quickly filtered through a pad of Celite while still cold and concentrated directly to afford **107** (0.59 g, 99%, *rr* of aldonitrone:ketonitrone = 4:1) as a colorless oil, which was used in the next step without any further purification. **107**: $[\alpha]_D^{25}$ = –44.0º (*c* = 1.00, $CHCl_3$); IR (film) ν_{max} 2953, 2856, 1472, 1361, 1257, 1200, 1064, 836, 756, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43–7.34 (m, 2 H), 7.33–7.27 (m, 2 H), 7.25–7.21 (m, 1 H), 7.09 (t, *J* = 3.9 Hz, 0.6 H), 5.50 (dd, *J* = 8.5, 4.9 Hz, 0.2 H), 4.93 (dd, *J* = 8.4, 4.7 Hz, 0.8 H), 3.93–3.70 (m, 1 H), 2.94–2.82 (m, 0.8 H), 2.82–2.77 (m, 0.2 H), 2.68–2.61 (m, 0.2 H), 2.52–2.45 (m, 0.2 H), 2.40–2.36 (m, 1.4 H), 2.04–1.83 (m, 2.6 H), 1.83–1.76 (m, 1 H), 1.76–1.68 (m, 0.8 H), 1.68–1.58 (m, 1.2 H), 0.93–0.80 (m, 9 H), 0.02 (s, 3 H), -0.16 (s, 0.6 H), -0.17–-0.26 (m, 2.4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.6, 145.2, 144.2, 136.1, 128.3, 128.2, 127.5, 127.2, 126.4, 125.6, 72.7, 69.9, 64.3, 58.3, 44.6, 43.0, 31.3, 27.2, 25.9, 25.7, 23.1, 18.8, 18.2, 15.0, – 4.5, – 4.8, – 5.0; HRMS (ESI) calcd for $C_{19}H_{32}NO_2Si^+$ [M + H^+] 334.2197, found 334.2200.

Compound 121. To a solution of **107** (0.27 g, 0.81 mmol, 1 equiv) in CH_2Cl_2 (1 mL) at 0 ºC was added β-ketoacid **112** (R = Ph) (0.20 g, 1.22 mmol, 1.5 equiv) in a single portion under an ambient atmosphere. The resulting mixture was stirred at 0 ºC for 20 h and then for 2 h at 23 ºC. Upon completion, the reaction contents were diluted with CH_2Cl_2 (10 mL), quenched with saturated aqueous $NaHCO_3$ (10 mL), and transferred to a separatory funnel. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 10 mL), brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified via flash column chromatography (silica gel, hexanes/EtOAc, 10/1→2/1) to afford the intermediate hydroxylamine. Pushing forward, to a solution of the above hydroxylamine dissolved in acetic acid (8 mL) was sequentially added CH_2O (0.36 mL, 37 wt. % in H_2O, 4.86 mmol, 6.0 equiv,) and Zn powder (0.56 g, 8.10 mmol, 10 equiv) at 23 ºC under an argon atmosphere. The resulting mixture was vigorously stirred for 4 h at 23 ºC to avoid Zn clumping. Upon completion, the reaction contents were filtered through a pad of Celite, washed with MeOH, and concentrated to dryness. To the resulting solid was sequentially added saturated aqueous $NaHCO_3$ (10 mL) and aqueous NH_3 (10 mL, 30 wt. %). The resulting mixture was diluted with EtOAc (50 mL) and transferred to a separatory funnel. The organic layer was separated and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 × 20 mL), brine (20 mL), dried ($MgSO_4$), filtered, and concentrated to afford **121** (0.27 g, 76%, *cis*:*trans* = 1.3:1) as a pale-yellow oil, which was used without any further purification. **121**: R_f = 0.52 (silica gel, CH_2Cl_2/MeOH = 10:1); $[\alpha]_D^{25}$ = –20.1º (*c* = 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.3 Hz, 1.2 H), 7.95 (d, *J* = 7.3 Hz, 0.8 H), 7.62–7.52 (m, 1 H), 7.52–7.42 (m, 2 H), 7.34–7.16 (m, 5 H), 4.65 (dd, *J* = 11.2, 5.5 Hz, 1 H), 3.43–3.32 (m, 0.4 H), 3.25 (td, *J* = 15.7, 5.0 Hz, 1 H),

3.18–3.09 (m, 0.6 H), 3.03–2.85 (m, 1.4 H), 2.55–2.39 (m, 0.6 H), 2.34 (s, 1.2 H), 2.22 (s, 1.8 H), 2.12–1.96 (m, 1 H), 1.75–1.32 (m, 7 H), 0.89 (s, 3.6 H), 0.86 (s, 5.4 H), 0.02 (s, 1.2 H), –0.00 (s, 1.8 H), –0.21 (s, 1.8 H), –0.22 (s, 1.2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 199.5, 146.0, 145.9, 137.5, 137.4, 137.4, 133.1, 128.8, 128.8, 128.3, 128.2, 128.2, 128.1, 127.1, 127.0, 126.2, 126.1, 77.5, 77.2, 76.9, 72.8, 72.4, 60.1, 59.8, 59.7, 54.8, 54.8, 45.9, 44.7, 40.8, 40.5, 38.8, 31.8, 28.4, 27.3, 26.9, 26.4, 26.0, 24.5, 19.7, 18.3, 6.1, 2.6, 2.6, 1.6, 1.6, –4.3, –4.4, –4.8, –4.9; HRMS (ESI) calcd for $C_{28}H_{42}NO_2Si^+$ [M + H^+] 452.2980, found 452.2973. ***Note***: the ratio *cis*:*trans* is in equilibrium in solution and can vary.

Compound 122. Prepared on the same scale as **121** by analogy with **112** (R = Me). The intermediate hydroxylamine was isolated via column chromatography (silica gel, hexanes/EtOAc, 5/1→1/1). Compound **122** (0.23 g, 75%, *cis*:*trans* = 1:5.4) was isolated as a pale-yellow oil, which was used without any further purification. **122**: R_f = 0.35 (silica gel, CH_2Cl_2/MeOH = 10:1); $[\alpha]_D^{25}$ = –38.1° (*c* = 1.00, $CHCl_3$); IR (film) ν_{max} 2929, 2856, 1714, 1472, 1360, 1251, 1084, 1006, 836, 775, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.27 (m, 4 H), 7.25–7.19 (m, 1 H), 4.63 (dd, *J* = 9.0, 4.1 Hz, 1 H), 3.19–3.11 (m, 0.8 H), 3.00–2.93 (m, 0.1 H), 2.92–2.76 (m, 1 H), 2.68 (dd, *J* = 15.9, 5.5 Hz, 1 H), 2.58–2.48 (m, 0.1 H), 2.39 (dd, *J* = 15.9, 6.8 Hz, 1 H), 2.27 (s, 2.7 H), 2.21–2.11 (m, 3.3 H), 2.02–1.93 (m, 1 H), 1.68–1.22 (m, 7 H), 0.93–0.81 (m, 9 H), 0.00 (s, 3 H), –0.15––0.29 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.0, 145.9, 145.8, 128.2, 128.1, 127.1, 127.1, 126.2, 126.1, 77.4, 77.2, 76.9, 72.8, 72.6, 59.5, 54.8, 54.1, 49.5, 46.3, 45.9, 40.6, 38.3, 31.1, 30.7, 30.4, 27.9, 26.7, 26.2, 25.9, 24.5, 19.7, 18.2, 6.1, 2.6, 2.6, 1.6, 1.6, –4.4, –4.4, –4.9, –5.0; HRMS (ESI) calcd for $C_{23}H_{40}NO_2Si^+$ [M + H^+] 390.2823, found 390.2824. ***Note***: the ratio *cis*:*trans* is in equilibrium in solution and can vary.

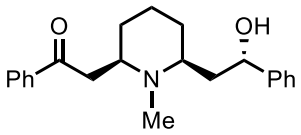
(–)-Lobeline (5): To a solution of **121** (0.25 g, 0.55 mmol, 1.0 equiv) in *i*-PrOH (6 mL) was added concentrated HCl (0.06 mL, 0.70 mmol, 1.3 equiv). The resulting mixture was stirred at 60 ºC for 12 h. Upon completion, the mixture was cooled to 23 ºC and concentrated. The resulting solid was washed with Et_2O (4 × 6 mL, removed by decantation) and dried under high vacuum. Then saturated aqueous $NaHCO_3$ (6 mL) was added, followed by EtOAc (10 mL), and the resulting mixture was transferred to a separatory funnel. The organic layer was separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to afford **3** (0.18 g, 95%, *cis*:*trans* = 1:1) as a yellow oil. Crude **123** was then dissolved in MeOH (1 mL) and the solvent was left to slowly evaporate in a vial with a loosened cap for 2 weeks at 4 ºC to yield yellow crystals. The crystals were washed with cold (0 ºC) hexanes (3 × 0.5 mL) and dried under high vacuum to afford (–)-lobeline (**5**), (0.17 g, 90% over two steps) as a pale-yellow solid exclusively as the *cis*-isomer. **5**: R_f = 0.20 (silica gel, CH_2Cl_2/MeOH = 10:1); $[\alpha]_D^{25}$ = –31.0º (*c* = 1.00, $CHCl_3$) [lit. $[\alpha]_D^{21}$ = –38.2º (*c* = 1.986, $CHCl_3$)];[11] IR (film) ν_{max} 3085, 2936, 1687, 1450, 1302, 1214, 1062, 1002, 951 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.00–7.94 (m, 2 H), 7.61–7.52 (m, 1 H), 7.52–7.41 (m, 2 H), 7.41–7.34 (m, 2 H), 7.34–7.28 (m, 2 H), 7.27–7.19 (m, 1 H), 6.70–6.36 (br s, 1 H, exchangeable), 4.95 (dd, *J* = 10.7, 2.9 Hz, 1 H), 3.63–3.52 (m, 1 H), 3.26–3.15 (m, 2 H), 3.02 (dd, *J* = 16.0, 8.5 Hz, 1 H), 2.35 (s, 3 H), 1.99–1.88 (m, 1 H), 1.86–1.76 (m, 1 H), 1.70–1.40 (m, 5 H), 1.23–1.10 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.3, 145.2, 137.2, 133.2, 128.8, 128.3, 128.2, 127.0, 125.6, 75.8, 64.6, 59.1, 43.9, 40.6, 27.4, 24.9, 23.5, 23.4; HRMS (ESI) calcd for $C_{22}H_{28}NO_2^+$ [M + H^+] 338.2115, found 338.2113.

(–)-Sedinone (6). To a solution of **122** (0.20 g, 0.51 mmol, 1.0 equiv) in *i*-PrOH (6 mL) was added concentrated HCl (0.06 mL, 0.70 mmol, 1.4 equiv). The resulting mixture was stirred

at 60 ºC for 12 h. Upon completion, the mixture was cooled to 23 ºC and concentrated. The resulting solid was washed with Et_2O (4 × 6 mL, removed by decantation) and dried under high vacuum. Then saturated aqueous $NaHCO_3$ (6 mL) was added, followed by EtOAc (10 mL), and the resulting mixture was transferred to a separatory funnel. The organic layer was separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to afford mostly *epi*-sedinone (*epi*-**6** 0.13 g, 93%, *cis*:*trans* = 1:5.4) as a yellow oil. *epi*-**6**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.28 (m, 4 H), 7.27–7.20 (m, 1 H), 7.06–6.52 (br s, 1 H, exchangeable), 4.90 (dd, *J* = 10.7, 2.1 Hz, 1 H), 3.71–3.58 (m, 0.85 H), 3.45–3.35 (m, 0.15 H), 3.25–3.16 (m, 1 H), 2.74–2.51 (m, 2 H), 2.48 (s, 3 H), 2.21 (s, 3 H), 1.88–1.68 (m, 1 H), 1.67–1.17 (m, 7 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.9, 206.8, 145.4, 145.1, 128.3, 127.1, 125.6, 125.6, 77.5, 77.2, 76.8, 76.0, 76.0, 64.7, 61.0, 58.8, 51.1, 49.1, 48.1, 40.4, 38.9, 35.7, 32.4, 30.3, 30.3, 29.8, 26.9, 24.9, 23.5, 23.3, 23.2, 23.1, 20.6. The crude *epi*-**6** was then dissolved in MeOH (1 mL) and left for 12 h at 23 ºC. At this stage, the ratio determined by ^{1}H NMR analysis revealed a 1:1 mixture of diastereomers. The mixture was then concentrated and hexanes (4 mL) was added to the residue, yielding a cloudy yellow solution, which was made transparent by the dropwise addition of EtOAc (~0.8 mL) with stirring. The solution was then placed in the freezer at –20 ºC for 16 h. The precipitated crystals were collected by filtration, washed with cold (–20 ºC) hexanes, and dried under high vacuum. The filtrate was evaporated and the procedure was repeated two additional times, starting from equilibration in MeOH at 23 ºC, followed by crystallization at –20 ºC using scaled amounts of solvents. Combining all the crystal fractions afforded (–)-sedinone (**6**, 0.10 g, 73% over two steps) as a white solid predominantly as the *cis* isomer (*dr* > 97:3 after 1 h in $CDCl_3$, slowly epimerizes). The hydrochloride salt of **6** was obtained by dissolving **6** in Et_2O

and adding HCl (2.0 equiv, 1.0 M in Et_2O), followed by filtration and drying. **6**: R_f = 0.18 (silica gel, CH_2Cl_2/MeOH = 10:1); $[\alpha]_D^{25}$ = –67.8º (*c* = 1.10, MeOH) (hydrochloride) [lit. $[\alpha]_D^{20}$ = –79.4º (*c* = 1.0, MeOH)];[12] IR (film) ν_{max} 3150, 2932, 2858, 1711, 1451, 1359, 1060, 836, 760, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42–7.35 (m, 2 H), 7.35–7.29 (m, 2 H), 7.25–7.18 (m, 1 H), 6.73–6.28 (br s, 1 H, exchangeable), 4.95 (dd, *J* = 10.8, 2.9 Hz, 1 H), 3.48–3.34 (m, 1 H), 3.28–3.16 (m, 1 H), 2.65 (dd, *J* = 16.0, 6.1 Hz, 1 H), 2.49 (dd, *J* = 15.7, 8.3 Hz, 1 H), 2.27 (s, 3 H), 2.18 (s, 3 H), 1.91 (dt, *J* = 14.8, 11.1 Hz, 1 H), 1.85–1.77 (m, 1 H), 1.69–1.43 (m, 4 H), 1.37–1.30 (m, 1 H), 1.20–1.10 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.9, 145.1, 128.4, 127.1, 125.6, 76.1, 64.7, 58.8, 49.1, 40.4, 30.3, 26.9, 24.9, 23.3, 23.2; HRMS (ESI) calcd for $C_{17}H_{26}NO_2^+$ [M + H^+] 276.1958, found 276.1957.

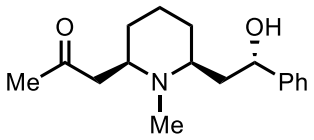
Table 1.5. NMR Comparison between Synthetic 5 and Natural (–)-Lobeline.



(–)-lobeline (**5**)

natural sample ^{1}H δ (ppm)[27]	synthetic ^{1}H δ (ppm)	natural sample ^{13}C δ (ppm)[27]	synthetic ^{13}C δ (ppm)
8.01-7.97 (comp. m, 2H)	8.00–7.94 (m, 2 H),	198.3	198.3
7.64–7.22 (comp m, 8 H)	7.61–7.19 (m, 8 H)	145.2	145.2
4.97 (dd, *J* = 10.8, 2.9 Hz, 1H)	4.95 (dd, *J* = 10.7, 2.9 Hz, 1 H)	137.1	137.2
3.65-3.59 (m, 1H)	3.63–3.52 (m, 1 H)	133.3	133.2
3.26 (dd, J = 16.0, 5.0 Hz, 2H)	3.26–3.15 (m, 2 H),	128.8	128.8
3.00 (dd, *J* = 16.0, 8.5 Hz, 1H)	3.02 (dd, *J* = 16.0, 8.5 Hz, 1 H),	128.3	128.3
2.38 (s, 3H),	2.35 (s, 3 H),	128.2	128.2
2.06-1.46 (comp. m, 7H),	1.99–1.40 (m, 7H)	127.1	127.0
1.29-1.18 (m, 1H)	1.23–1.10 (m, 1 H)	125.6	125.6
		75.8	75.8
		64.6	64.6
		59.1	59.1
		43.8	43.9
		40.5	40.6
		27.4	27.4
		24.8	24.9
		23.5	23.5
		23.4	23.4

Table 1.6. NMR Comparison between Synthetic 6 and Natural (–)-Sedinone.



(–)-sedinone (**6**)

natural sample ^{1}H δ (ppm)[42]	synthetic ^{1}H δ (ppm)	natural sample ^{13}C δ (ppm)[43]	synthetic ^{13}C δ (ppm)
7.4–7.2 (m, 5H)	7.42–7.18 (m, 5 H)	206.6	206.9
4.95 (dd, 1H)	4.95 (dd, *J* = 10.8, 2.9 Hz, 1 H)	75.8	76.1
3.4 (m, 1H)	3.48–3.34 (m, 1 H)	64.5	64.7
3.2 (m, 1H)	3.28–3.16 (m, 1 H)	58.9	58.8
2.65 (dd, 1H)	2.65 (dd, *J* = 16.0, 6.1 Hz, 1 H)	49.0	49.1
2.5 (dd, 1H)	2.49 (dd, *J* = 15.7, 8.3 Hz, 1 H)	40.5	40.4
2.3 (s, 3H)	2.27 (s, 3 H)	30.1	30.3
2.2 (s, 3H)	2.18 (s, 3 H)	27.1	26.9
2.0-1.1 (9H)	1.95-1.10 (8H)	24.8	24.9
		23.4	23.3
		23.4	23.2

1.7. References.

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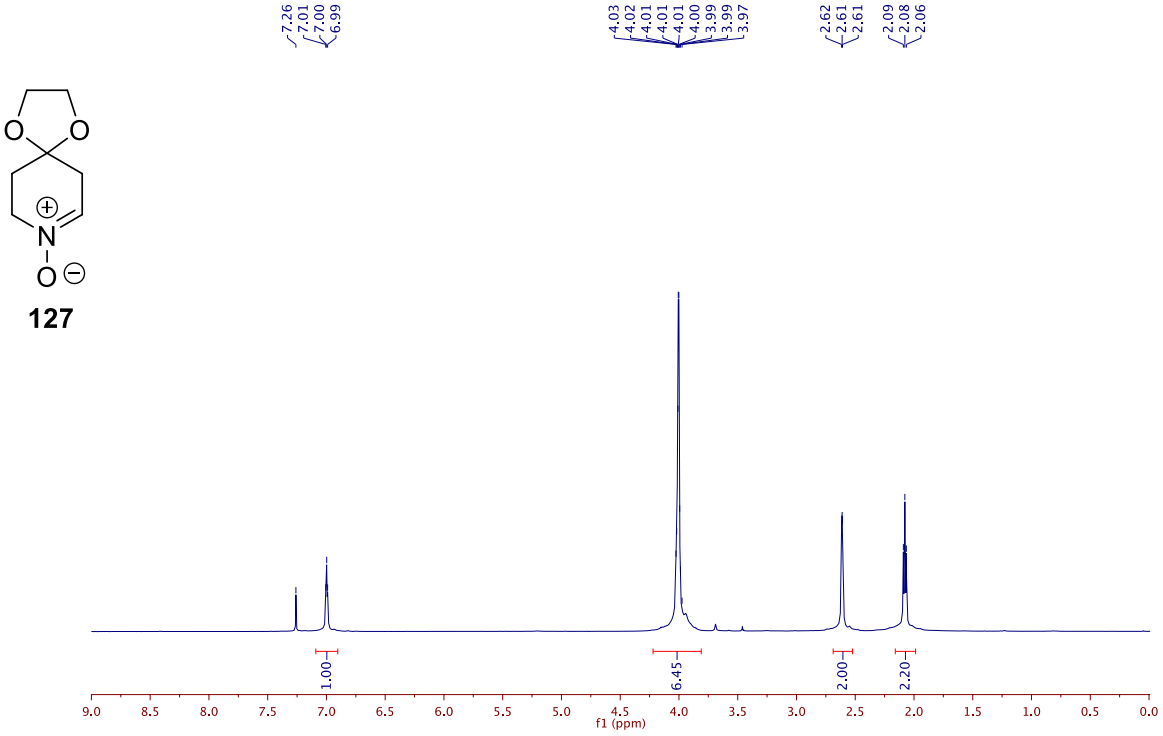
1.8. ^{1}H and ^{13}C NMR Data



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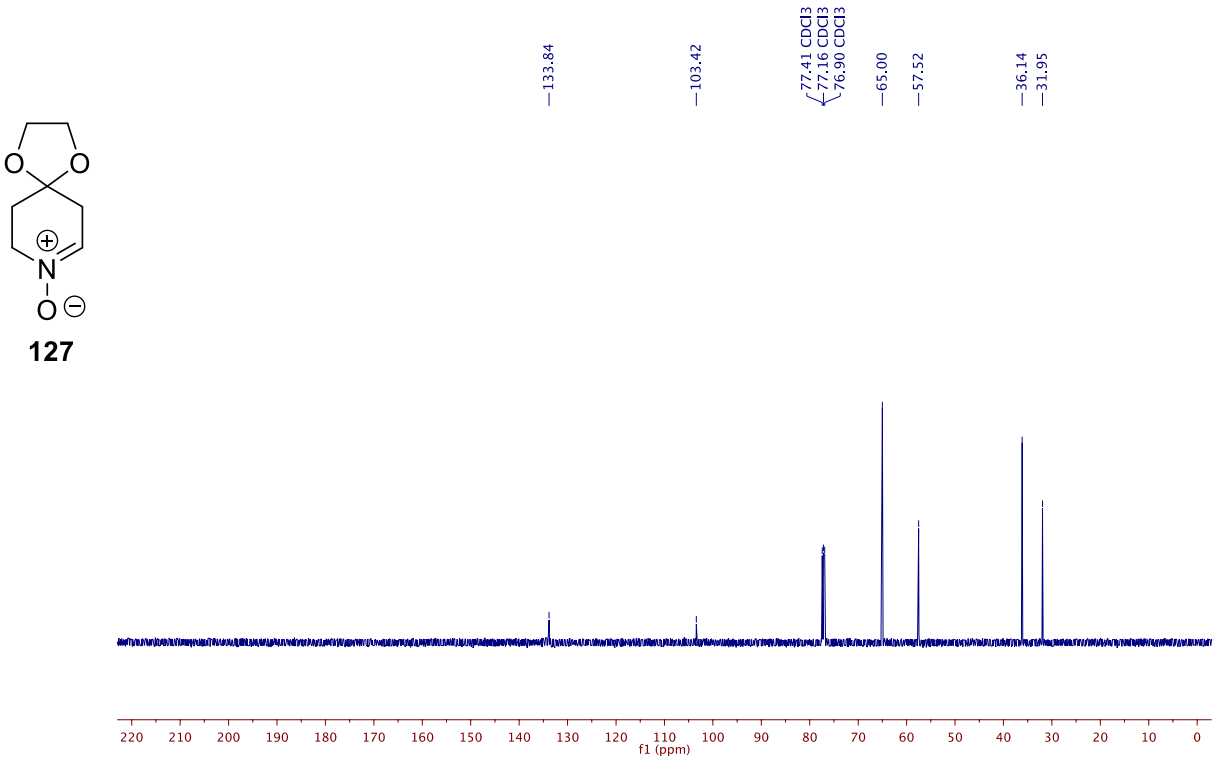

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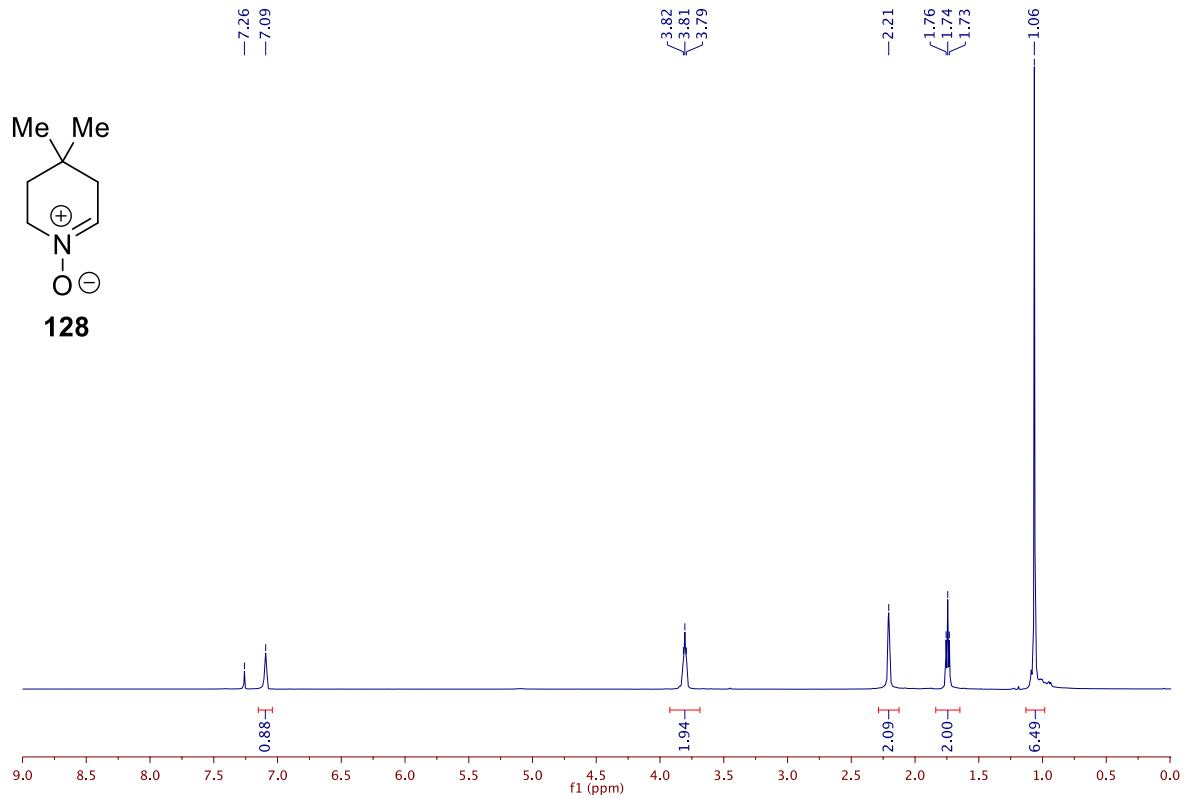
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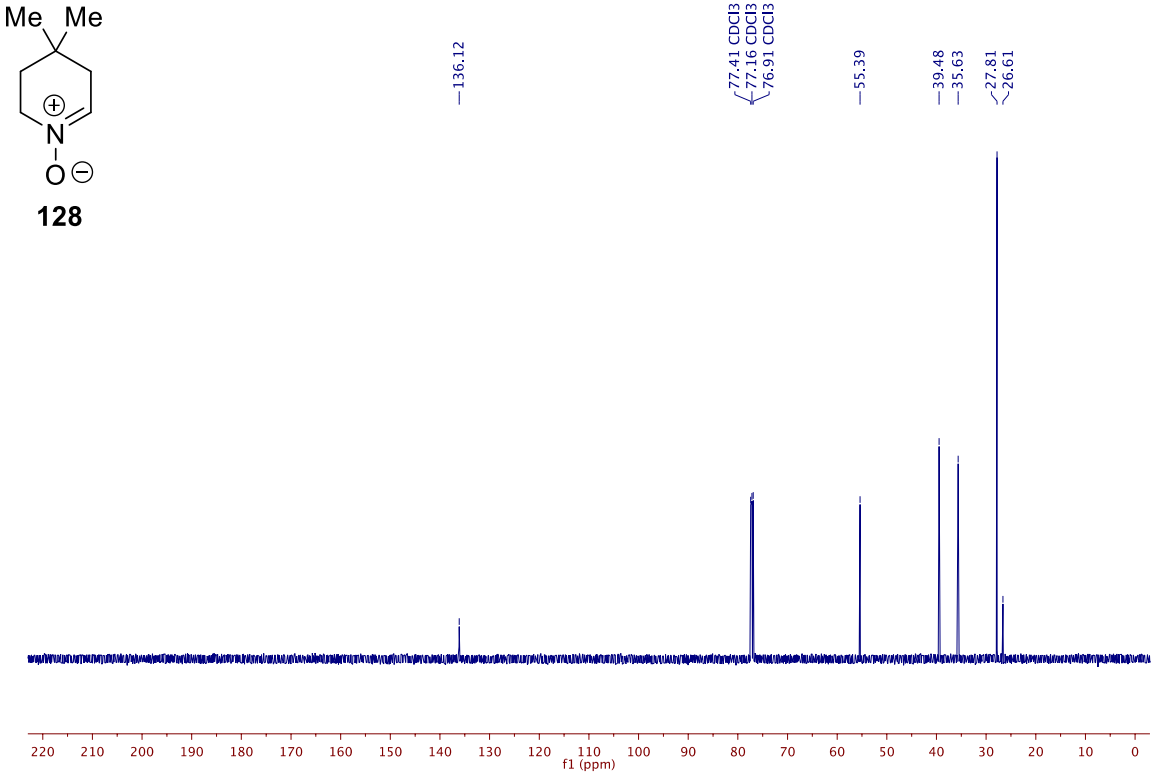
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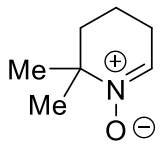
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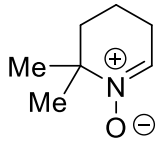
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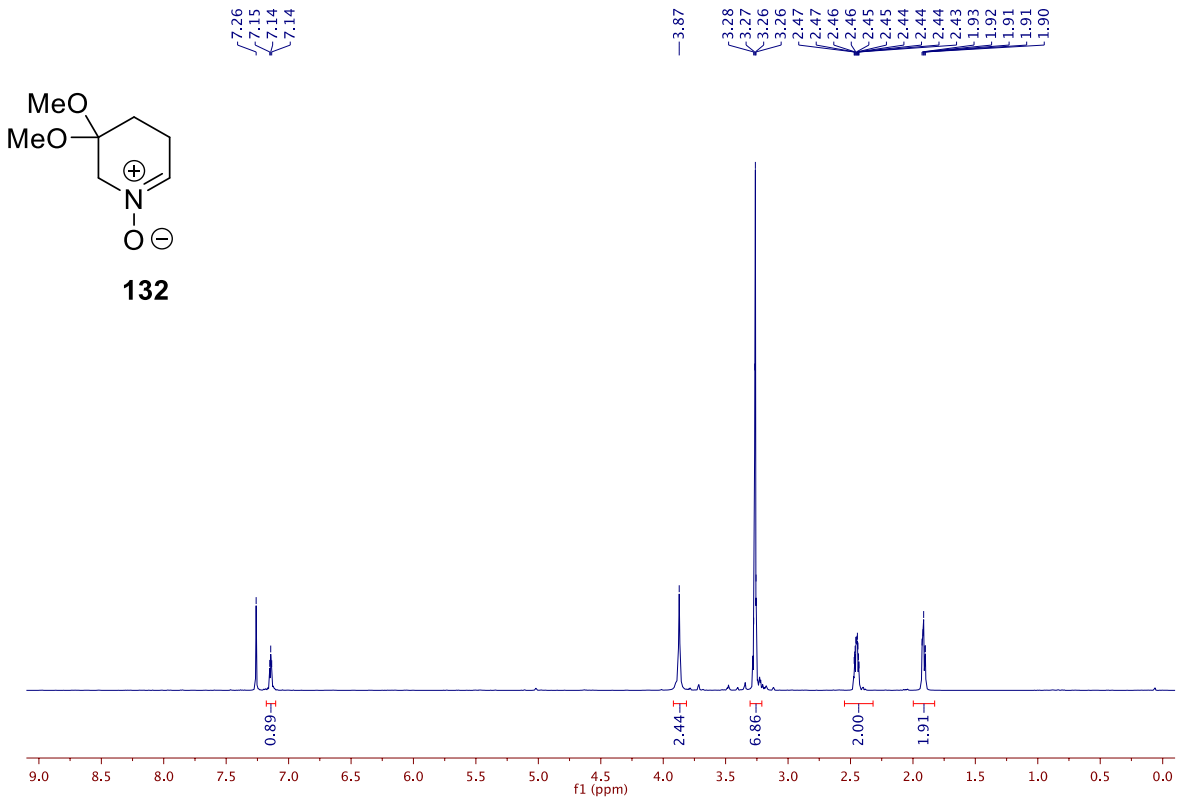
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3.26
3.26
2.47
2.47
2.46
2.46
2.45
2.45
2.44
2.44
2.44
2.43
1.93
1.92
1.91
1.91
1.90
0.89
2.44
6.86
2.00
1.91
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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3.5
3.0
2.5
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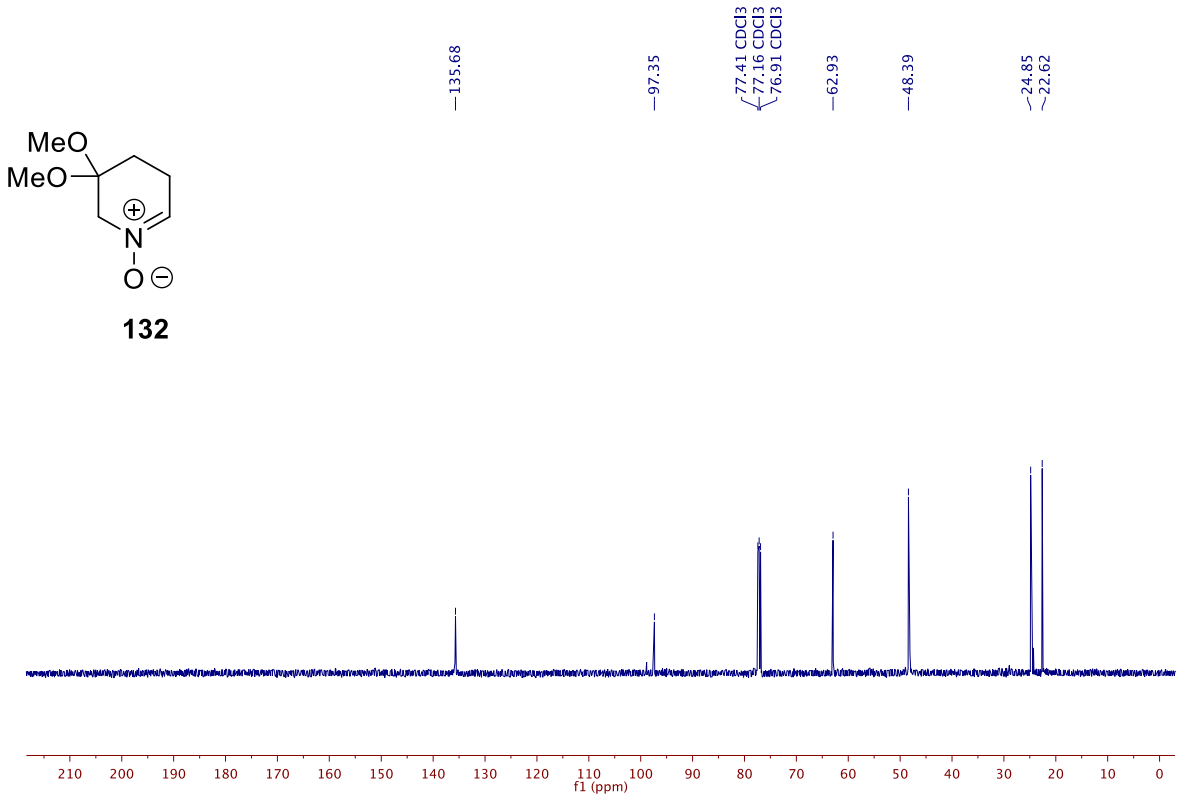
1.0
0.5
0.0
f1 (ppm)


MeO
MeO
N
O
132
135.68
97.35
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77.16 CDCl3
76.91 CDCl3
62.93
48.39
24.85
22.62
210
200
190
180
170
160
150
140
130
120
110
100
90
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70
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50
40
30
20
10
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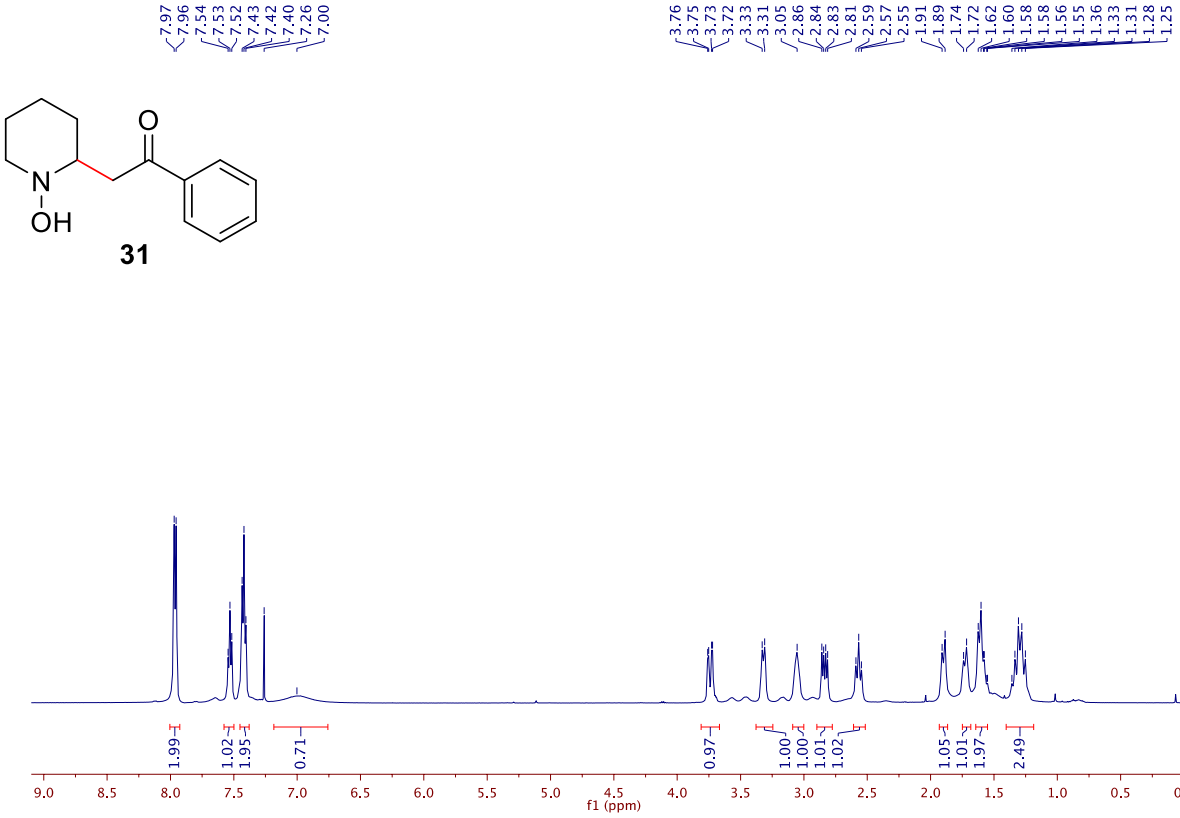
f1 (ppm)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7.54
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7.52
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7.42
7.40
7.26
7.00
3.76
3.75
3.73
3.72
3.33
3.31
3.05
2.86
2.84
2.83
2.81
2.59
2.57
2.55
1.91
1.89
1.74
1.72
1.62
1.60
1.58
1.58
1.56
1.55
1.36
1.33
1.31
1.28
1.25
O
N
OH
31
1.99
1.02
1.95
0.71
0.97
1.00
1.00
1.01
1.02
1.05
1.01
1.97
2.49
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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3.5
3.0
2.5
2.0
1.5
1.0
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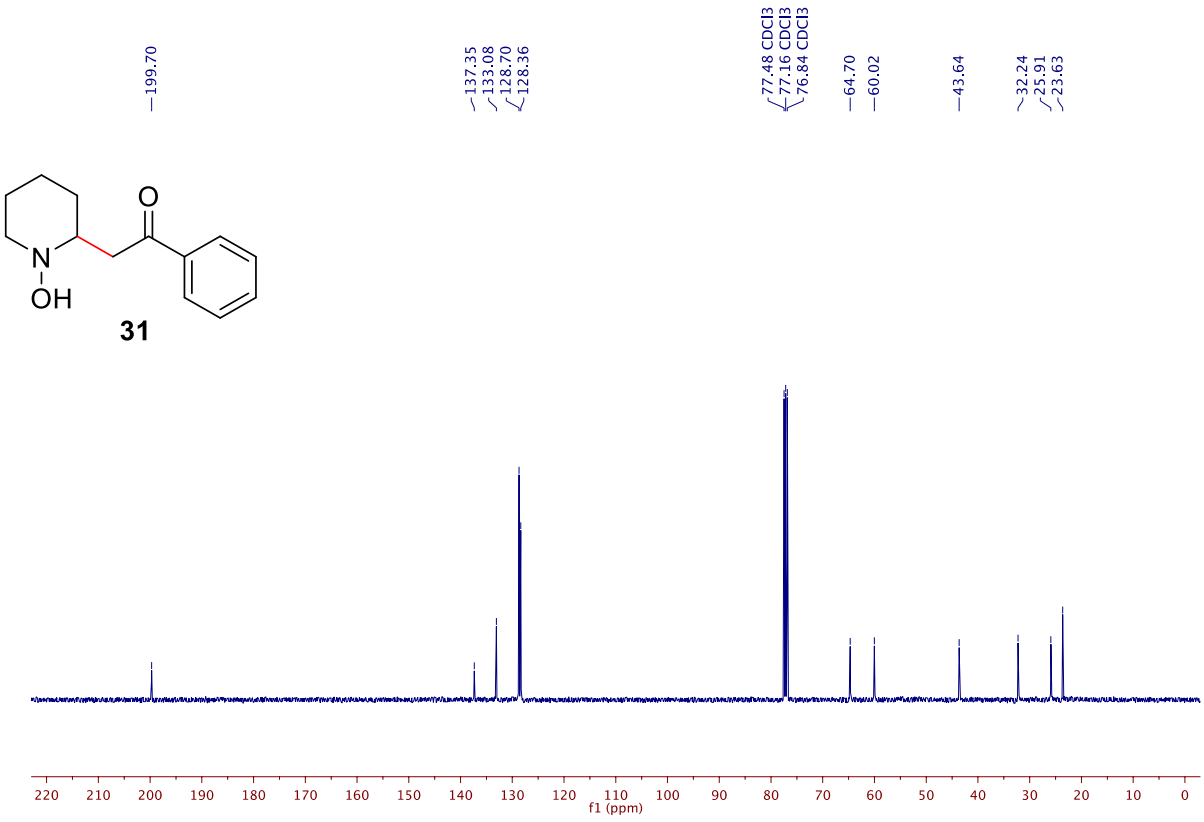
0.0
f1 (ppm)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137.35
133.08
128.70
128.36
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77.16 CDCl3
76.84 CDCl3
64.70
60.02
43.64
32.24
25.91
23.63
O
N
OH
31
220
210
200
190
180
170
160
150
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130
120
110
100
90
80
70
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50
40
30
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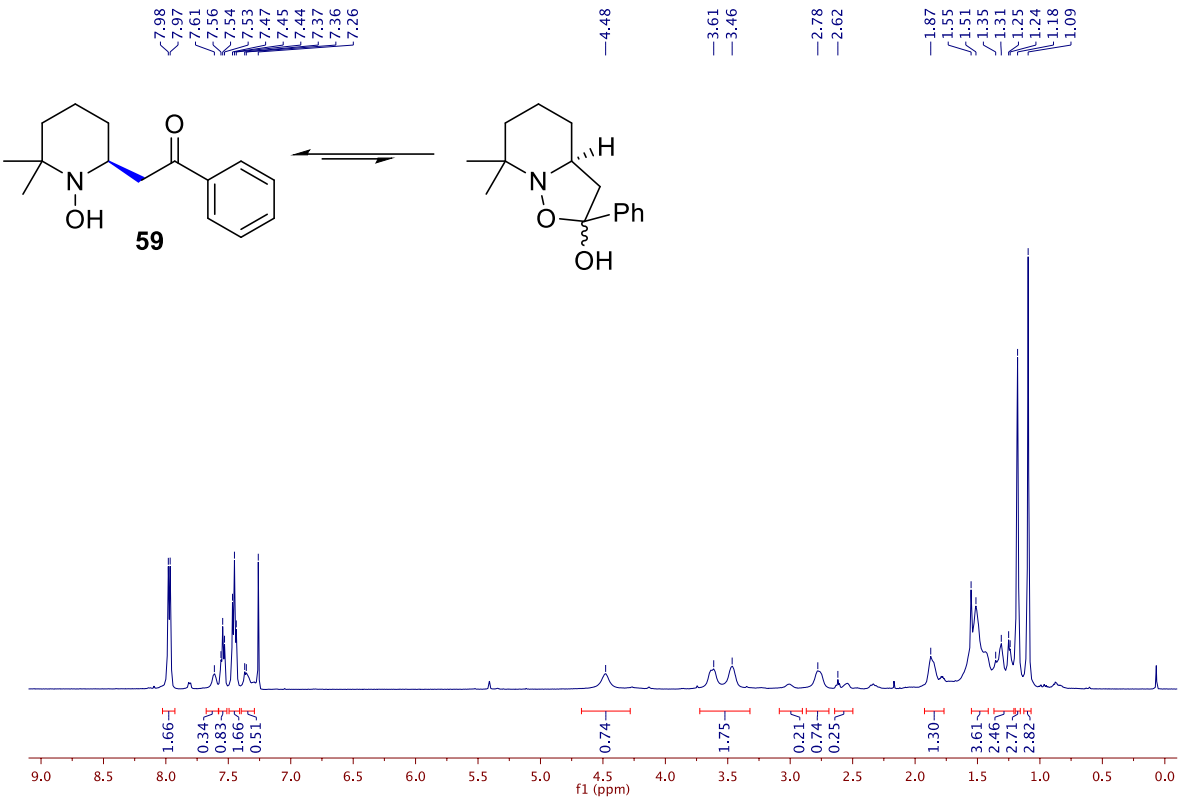
10
0
f1 (ppm)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7.97
7.61
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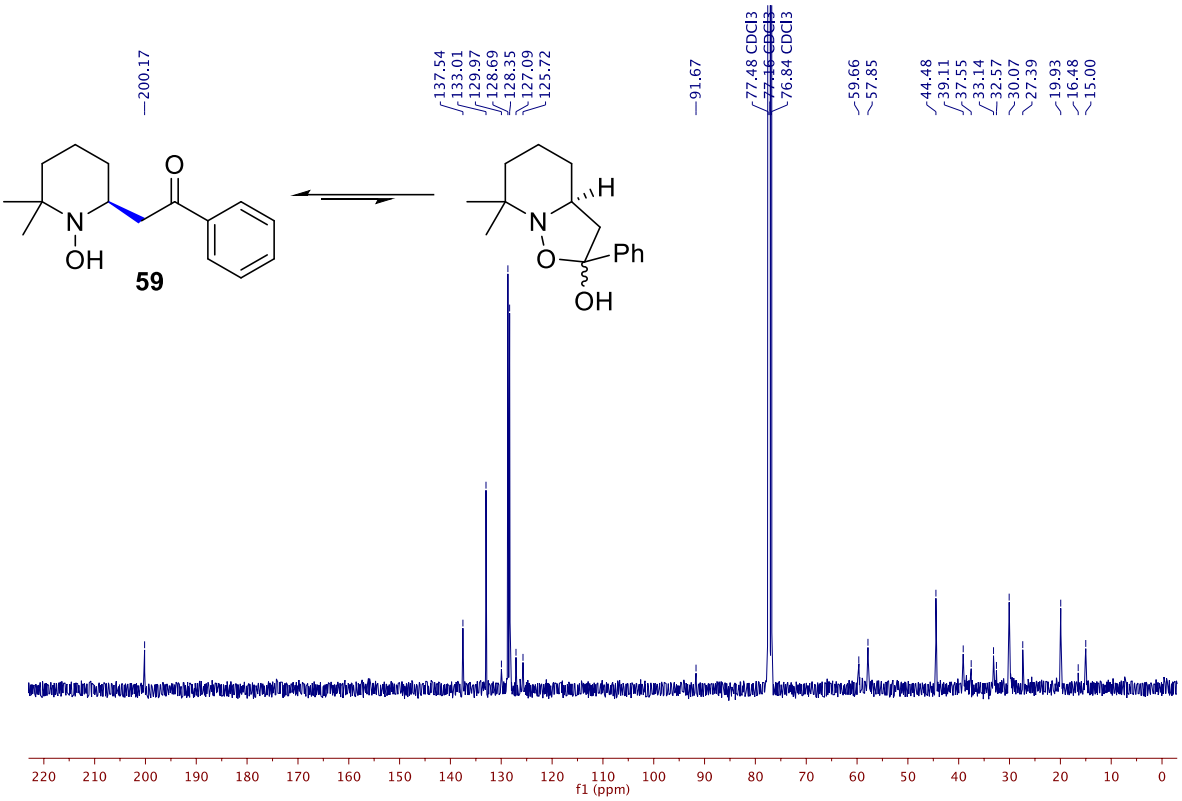
7.54
7.53
7.47
7.45
7.44
7.37
7.36
7.26
4.48
3.61
3.46
2.78
2.62
1.87
1.55
1.51
1.35
1.31
1.25
1.24
1.18
1.09
O
N
OH
59
H
N
O
Ph
OH
1.66
0.34
0.83
1.66
0.51
0.74
1.75
0.21
0.74
0.25
1.30
3.61
2.46
2.71
2.82
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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133.01
129.97
128.69
128.35
127.09
125.72
91.67
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
59.66
57.85
44.48
39.11
37.55
33.14
32.57
30.07
27.39
19.93
16.48
15.00
O
N
OH
59
H
N
O
Ph
OH
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
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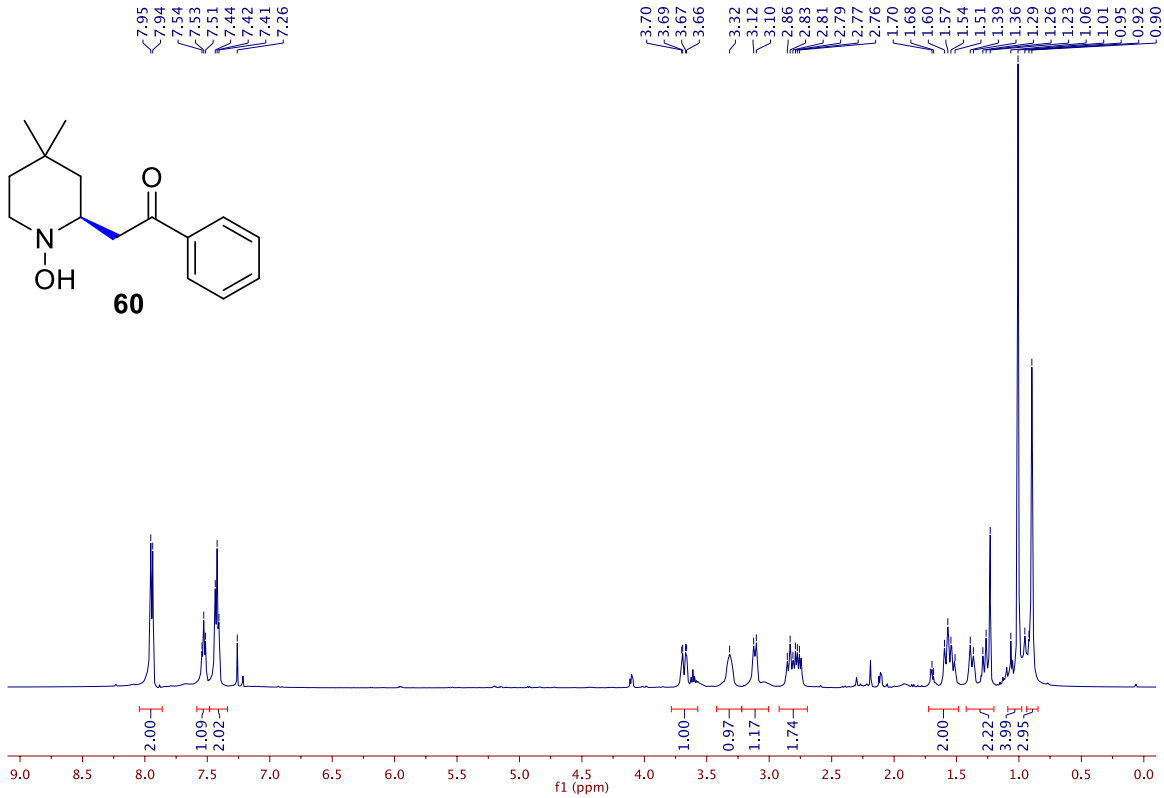
50
40
30
20
10
0
f1 (ppm)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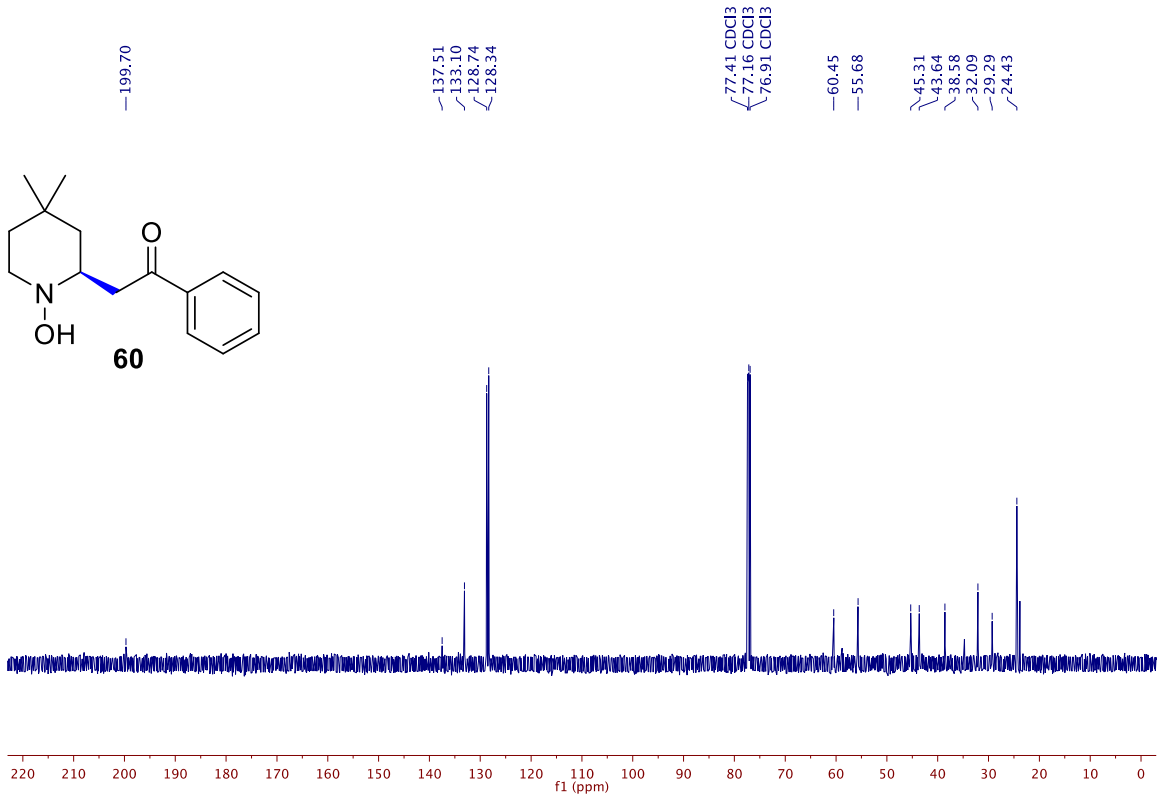
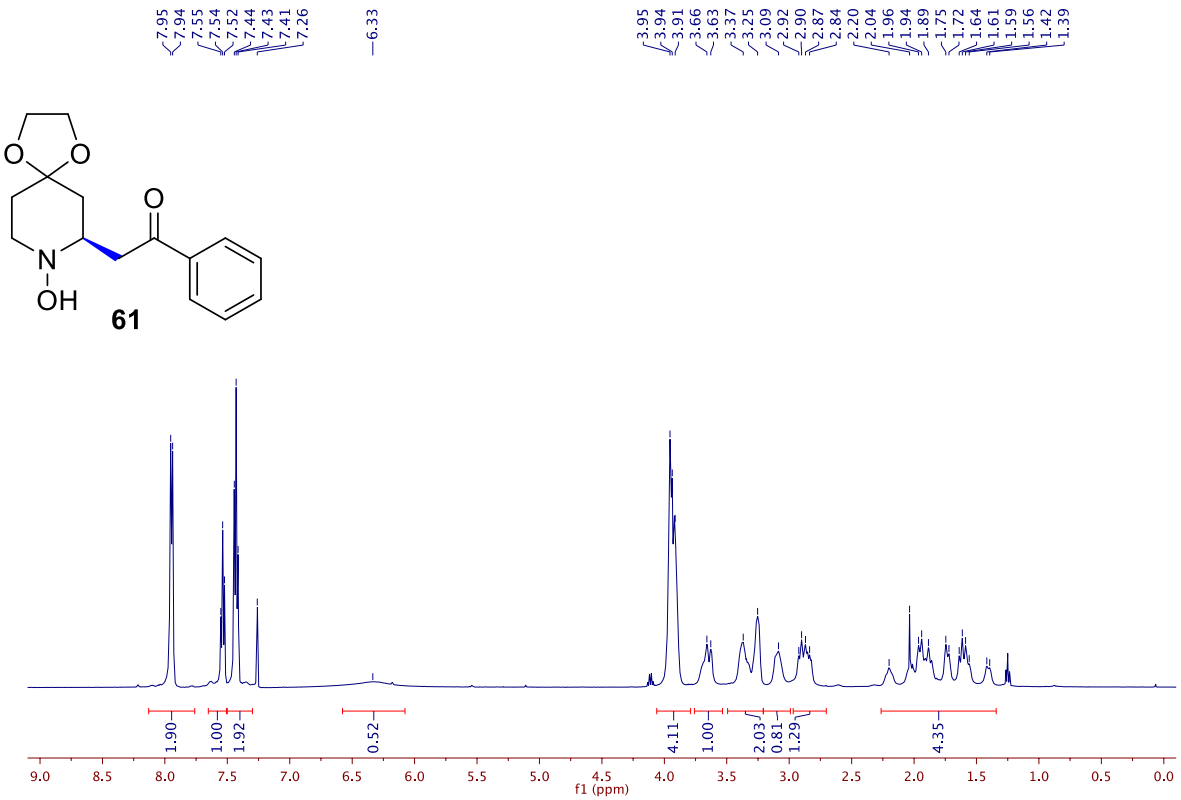
7.94
7.54
7.53
7.51
7.44
7.42
7.41
7.26
3.70
3.69
3.67
3.66
3.32
3.12
3.10
2.86
2.83
2.81
2.79
2.77
2.76
1.70
1.68
1.60
1.57
1.54
1.51
1.39
1.36
1.29
1.26
1.23
1.06
1.01
0.95
0.92
0.90
O
N
OH
60
2.00
1.09
2.02
1.00
0.97
1.17
1.74
2.00
2.22
3.99
2.95
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


199.70
137.51
133.10
128.74
128.34
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
60.45
55.68
45.31
43.64
38.58
32.09
29.29
24.43
O
N
OH
60
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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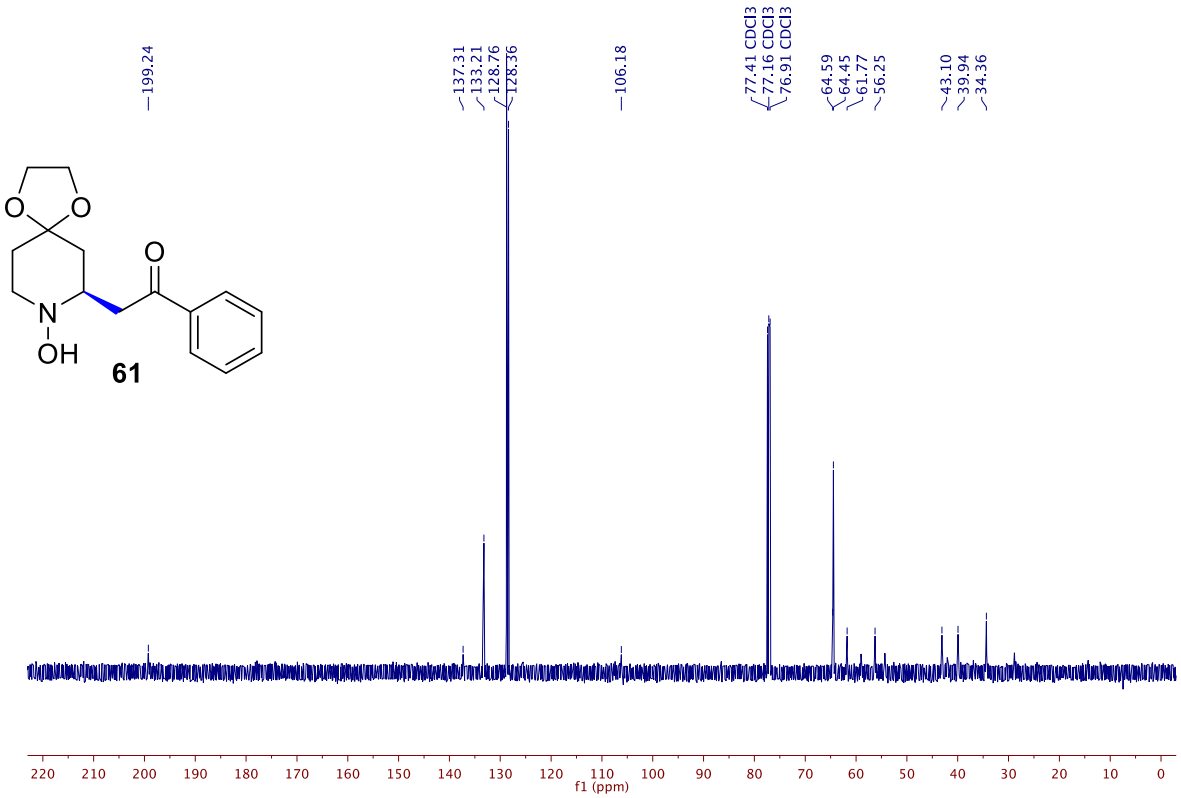
7.94
7.55
7.54
7.52
7.44
7.43
7.41
7.26
6.33
3.95
3.94
3.91
3.66
3.63
3.37
3.25
3.09
2.92
2.90
2.87
2.84
2.20
2.04
1.96
1.94
1.89
1.75
1.72
1.64
1.61
1.59
1.56
1.42
1.39
O
O
N
OH
O
61
1.90
1.00
1.92
0.52
4.11
1.00
2.03
0.81
1.29
4.35
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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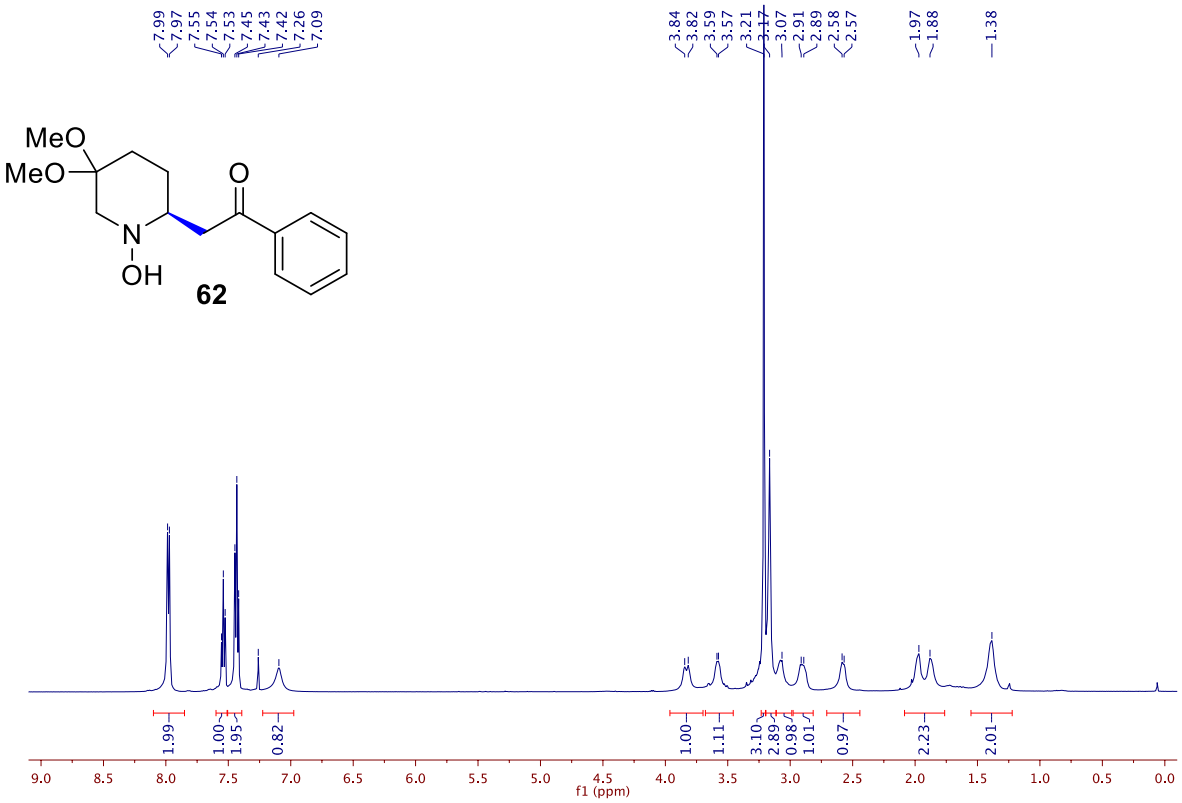
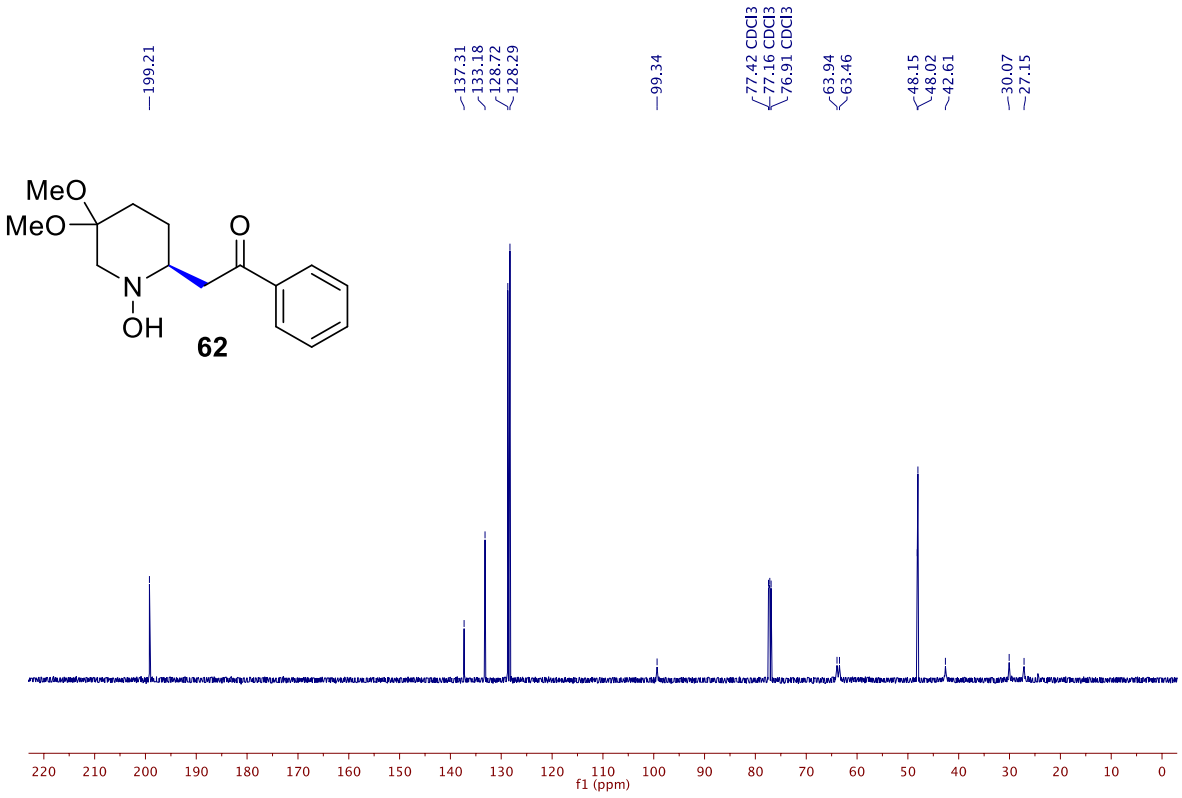
133.21
128.76
128.36
106.18
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
64.59
64.45
61.77
56.25
43.10
39.94
34.36
O
O
N
OH
O
61
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.99
7.97
7.55
7.54
7.53
7.45
7.43
7.42
7.26
7.09
3.84
3.82
3.59
3.57
3.21
3.17
3.07
2.91
2.89
2.58
2.57
1.97
1.88
1.38
MeO
MeO
O
N
OH
62
1.99
1.00
1.95
0.82
1.00
1.11
3.10
2.89
0.98
1.01
0.97
2.23
2.01
f1 (ppm)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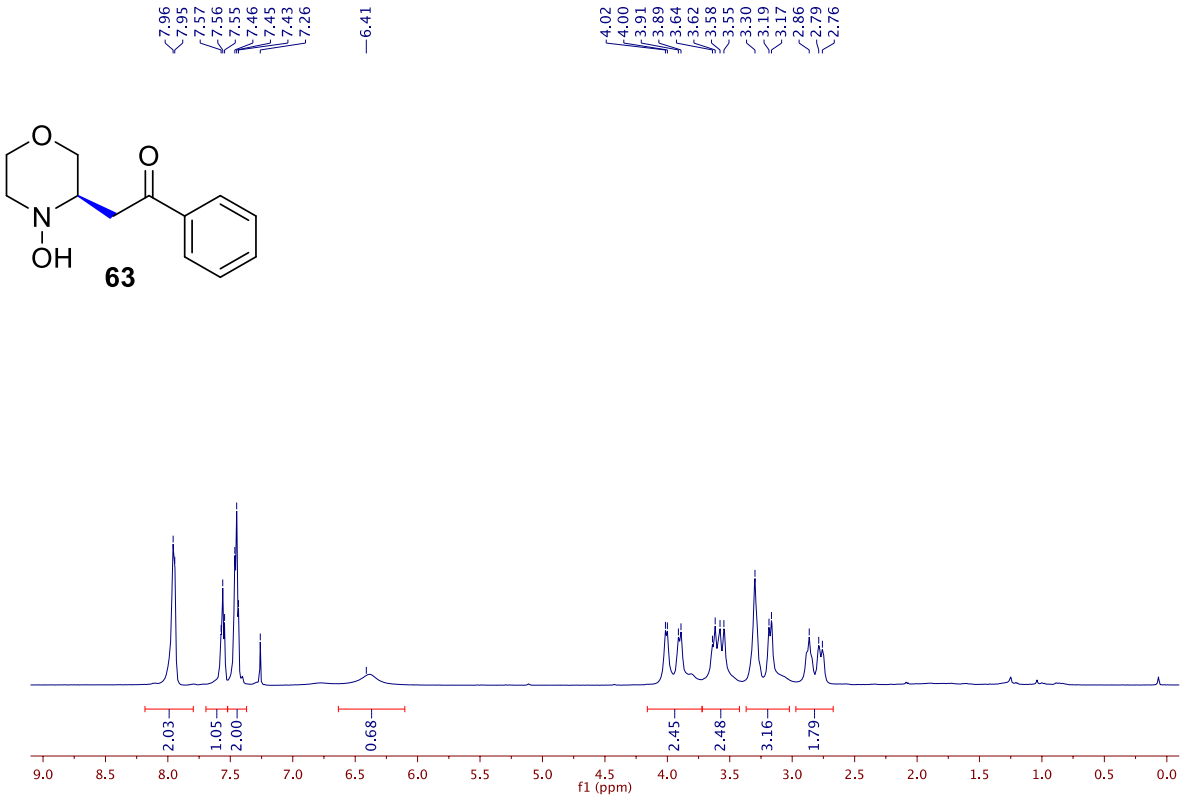
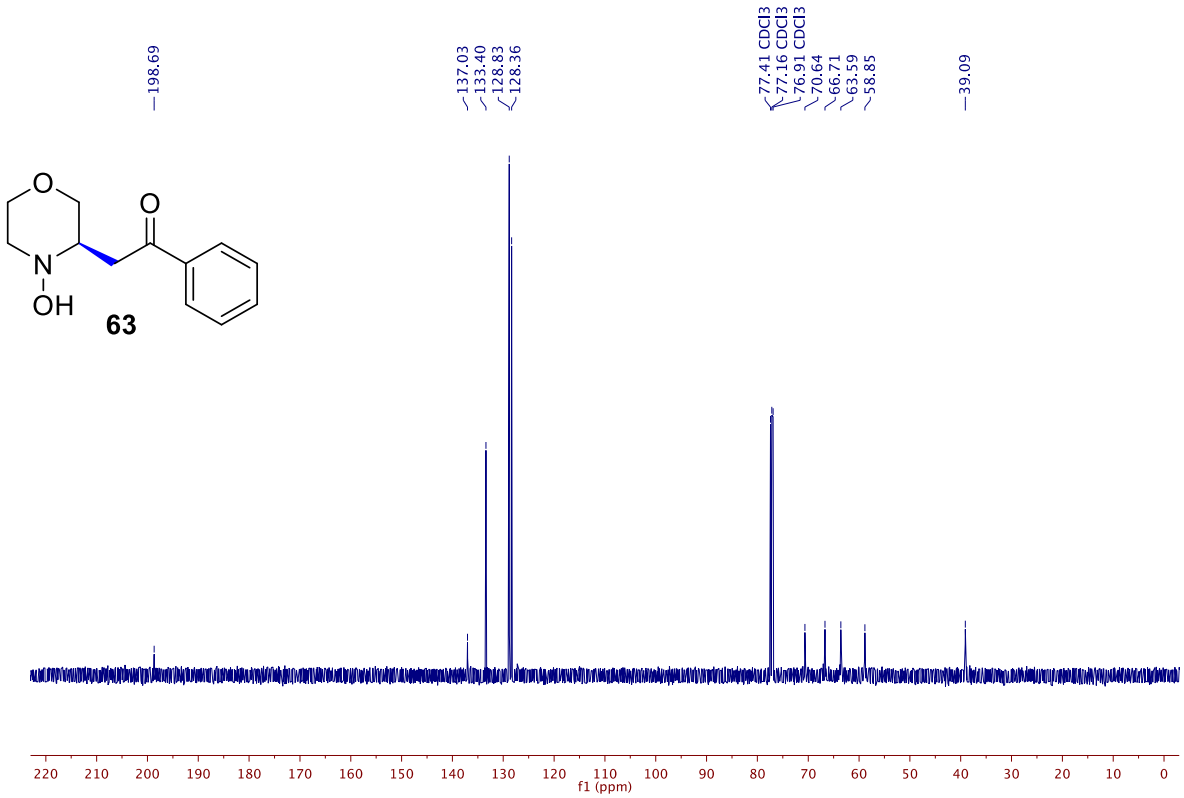
137.31
133.18
128.72
128.29
99.34
77.42 CDCl3
77.16 CDCl3
76.91 CDCl3
63.94
63.46
48.15
48.02
42.61
30.07
27.15
MeO
MeO
O
N
OH
62
f1 (ppm)


7.96
7.95
7.57
7.56
7.55
7.46
7.45
7.43
7.26
6.41
4.02
4.00
3.91
3.89
3.64
3.62
3.58
3.55
3.30
3.19
3.17
2.86
2.79
2.76
O
O
N
OH
63
2.03
1.05
2.00
0.68
2.45
2.48
3.16
1.79
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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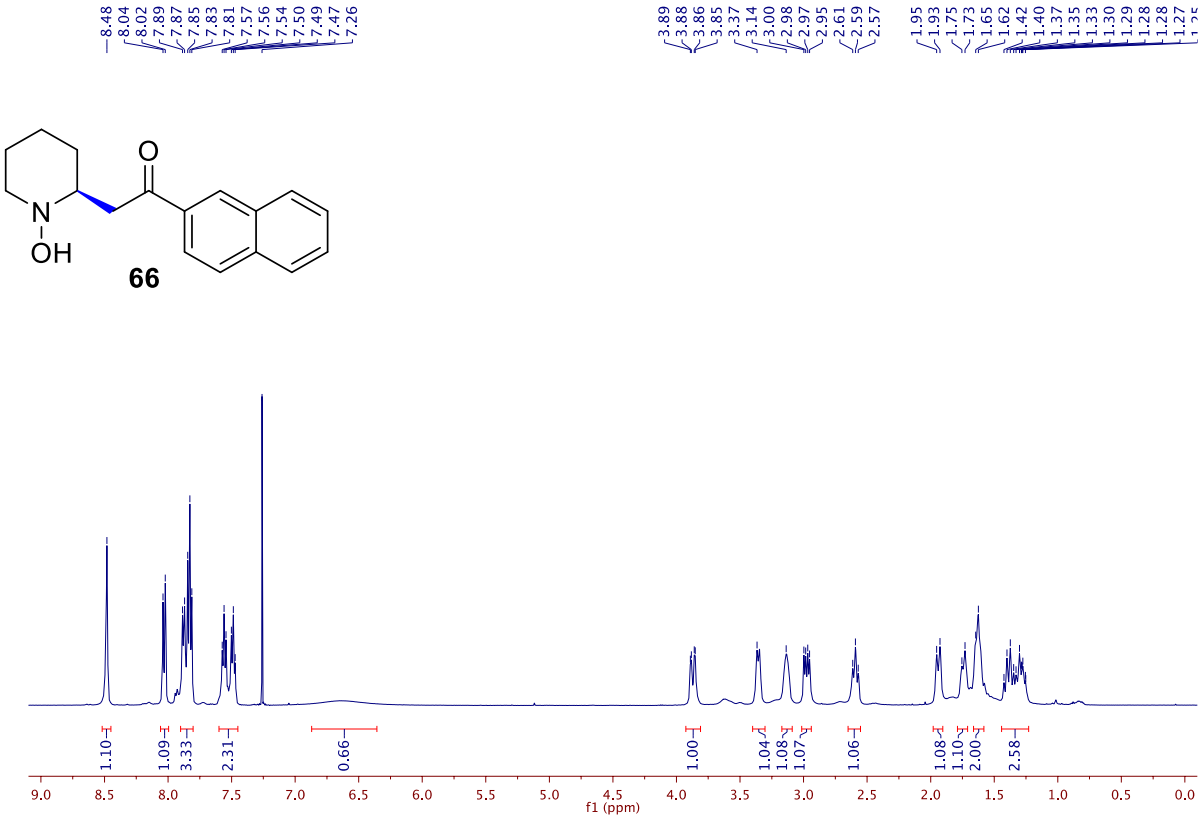
133.40
128.83
128.36
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
70.64
66.71
63.59
58.85
39.09
O
O
N
OH
63
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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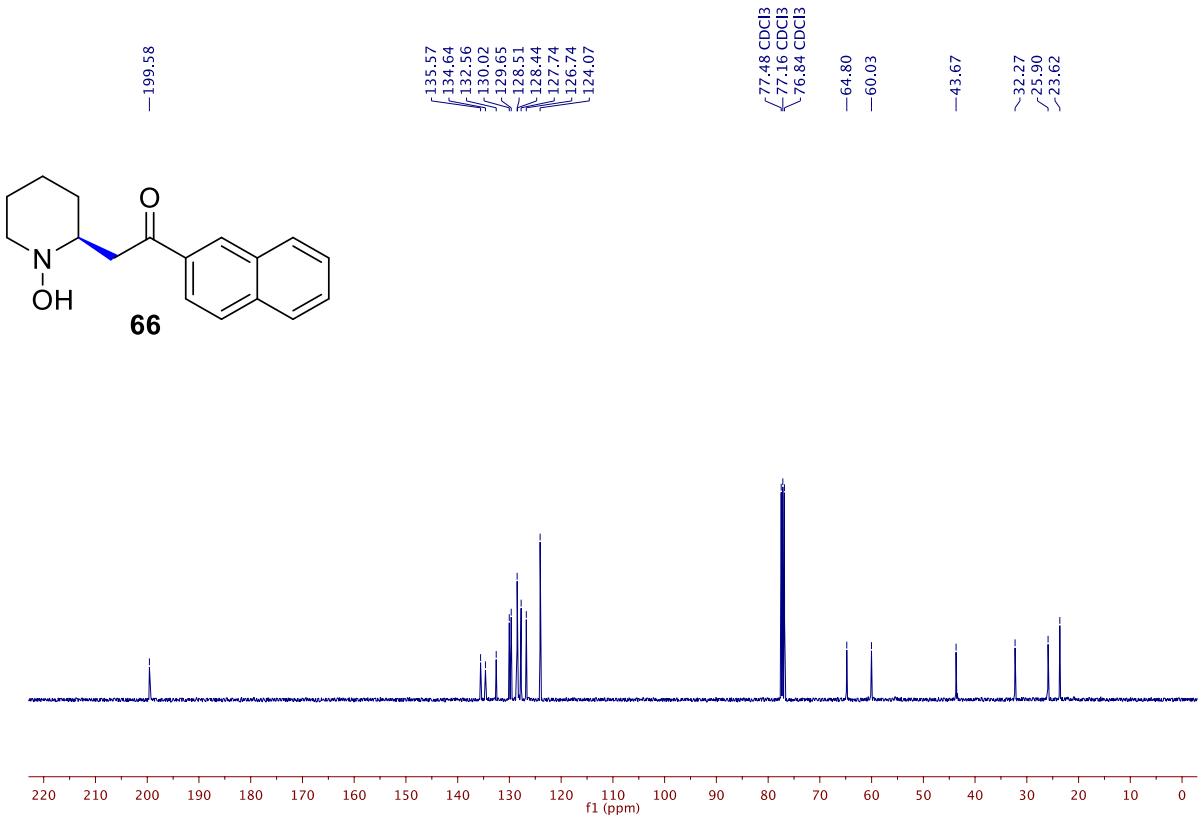
7.87
7.85
7.83
7.81
7.57
7.56
7.54
7.50
7.49
7.47
7.26
3.89
3.88
3.86
3.85
3.37
3.14
3.00
2.98
2.97
2.95
2.61
2.59
2.57
1.95
1.93
1.75
1.73
1.65
1.62
1.42
1.40
1.37
1.35
1.33
1.30
1.29
1.28
1.27
O
N
OH
66
1.10
1.09
3.33
2.31
0.66
1.00
1.04
1.08
1.07
1.06
1.08
1.10
2.00
2.58
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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129.65
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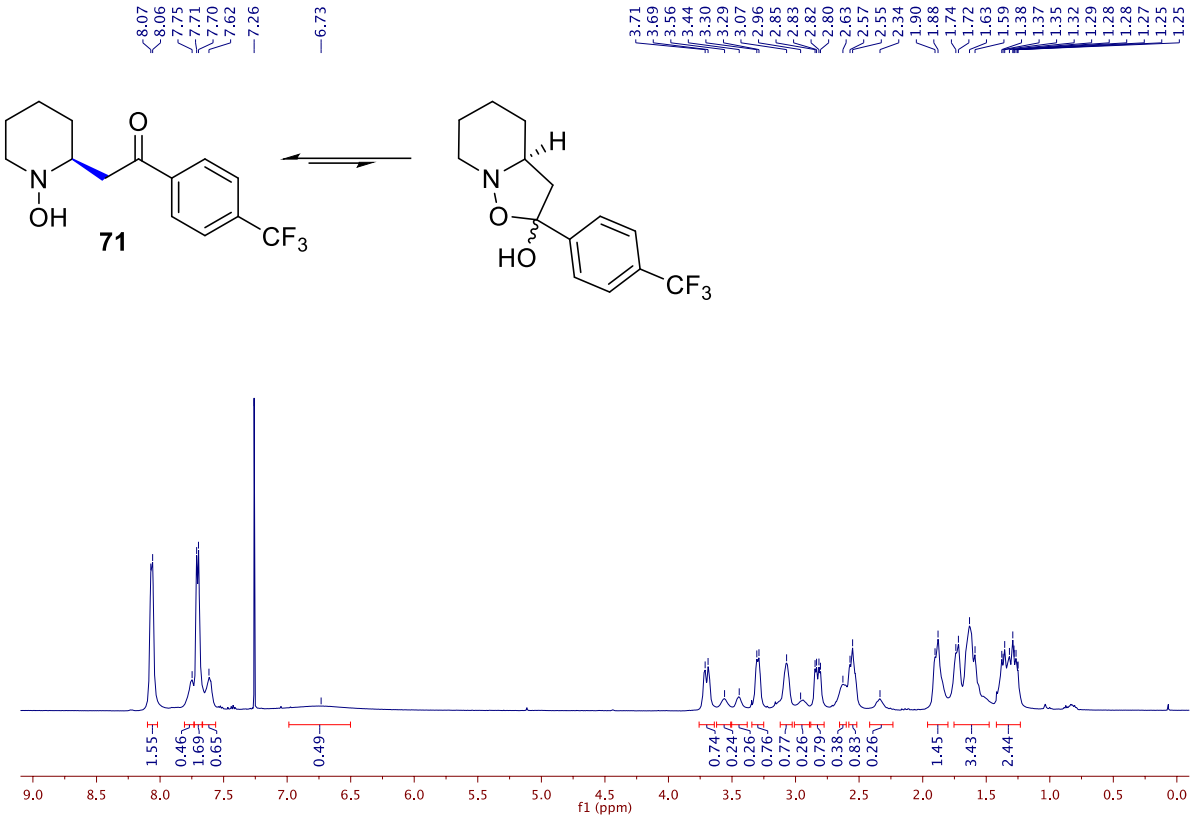
128.44
127.74
126.74
124.07
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
64.80
60.03
43.67
32.27
25.90
23.62
O
N
OH
66
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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8.06
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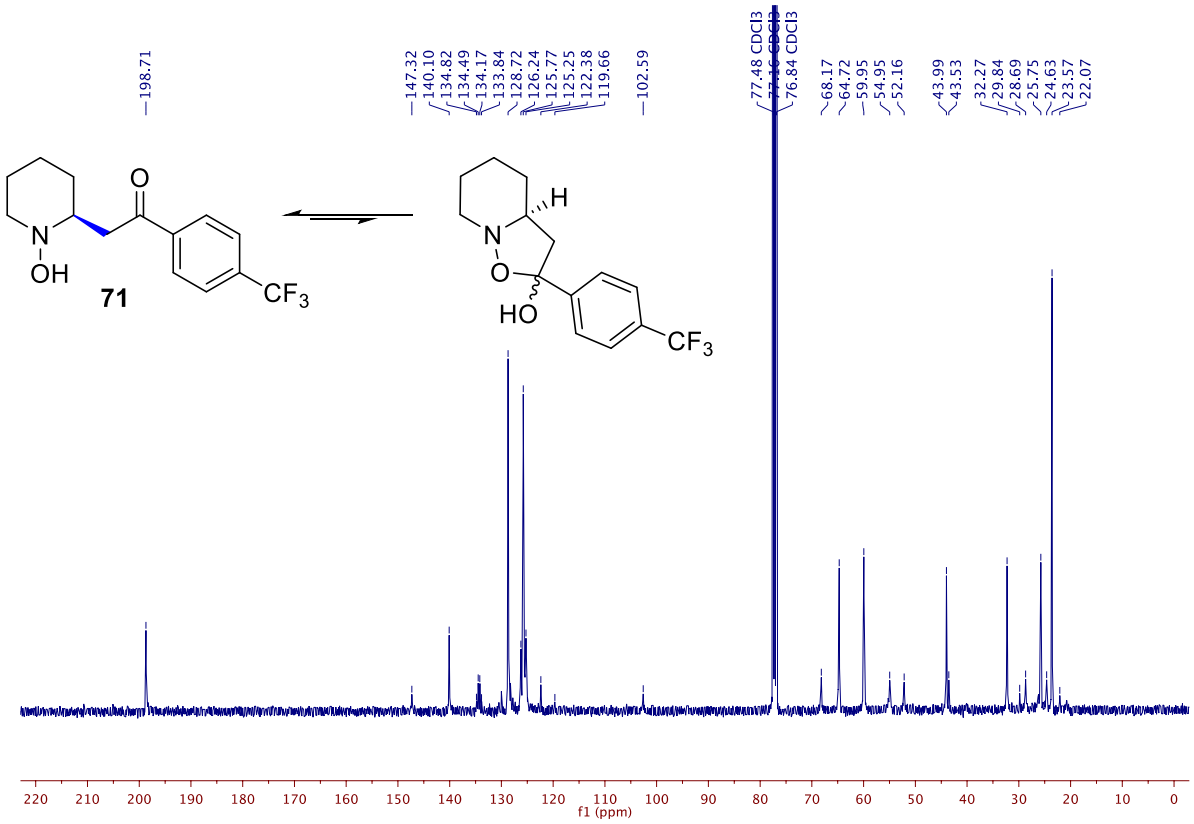
7.71
7.70
7.62
7.26
6.73
3.71
3.69
3.56
3.44
3.30
3.29
3.07
2.96
2.85
2.83
2.82
2.80
2.63
2.57
2.55
2.34
1.90
1.88
1.74
1.72
1.63
1.59
1.38
1.37
1.35
1.32
1.29
1.28
1.28
1.27
1.25
1.25
O
N
OH
71
CF3
H
N
O
HO
CF3
1.55
0.46
1.69
0.65
0.49
0.74
0.24
0.26
0.76
0.77
0.26
0.79
0.38
0.83
0.26
1.45
3.43
2.44
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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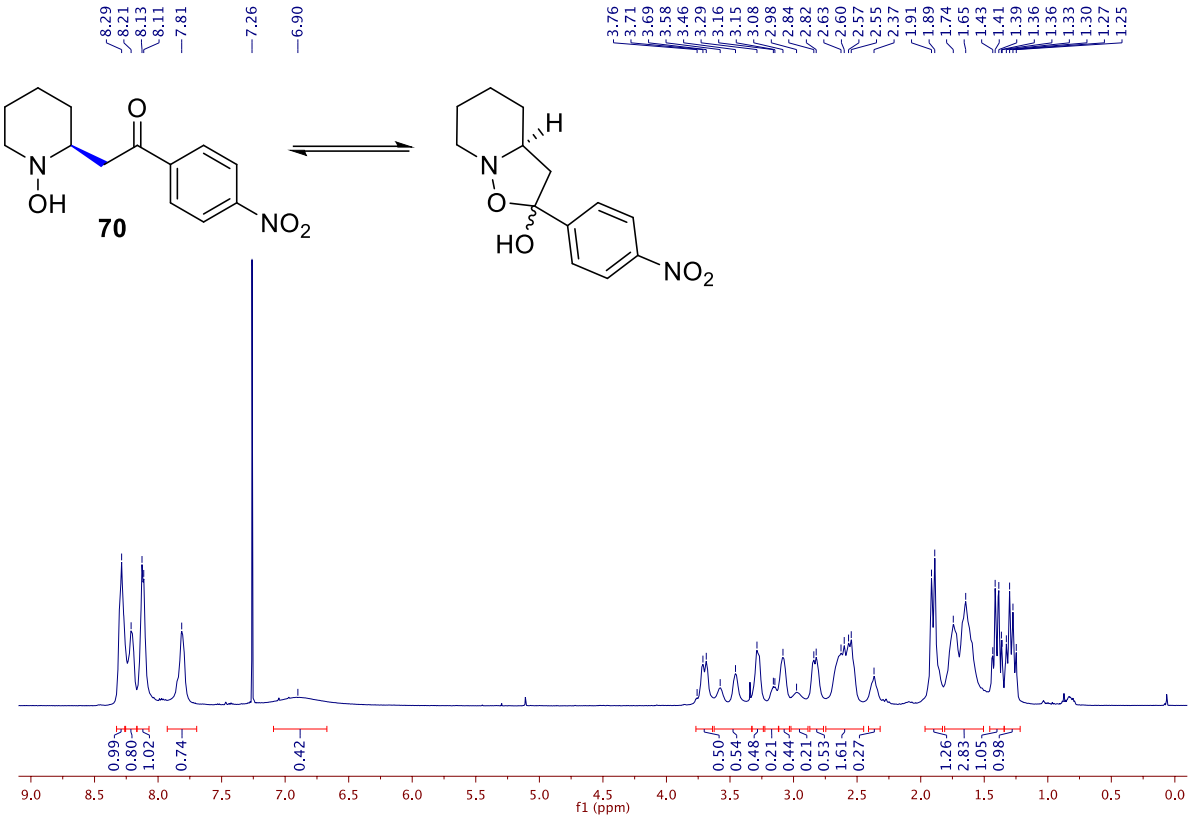
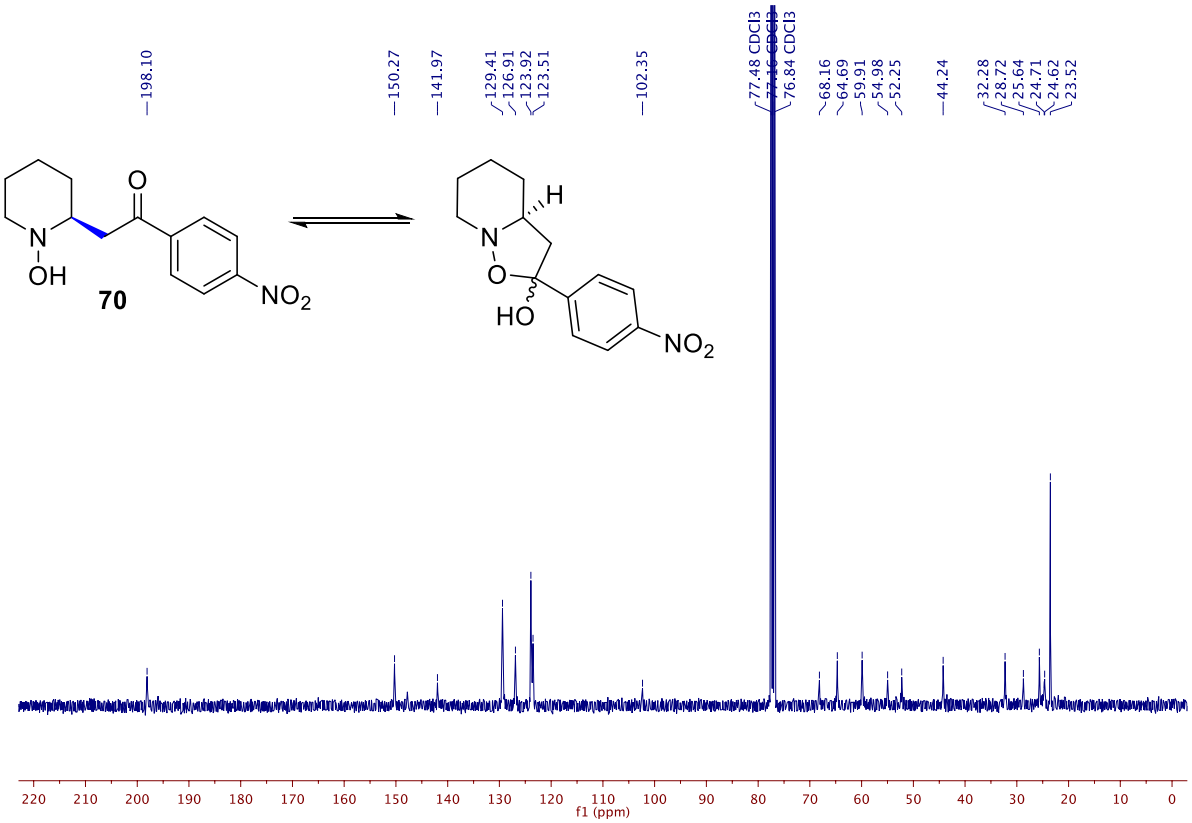
133.84
128.72
126.24
125.77
125.25
122.38
119.66
102.59
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
68.17
64.72
59.95
54.95
52.16
43.99
43.53
32.27
29.84
28.69
25.75
24.63
23.57
22.07
O
N
OH
71
CF3
H
N
O
HO
CF3
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.29
8.21
8.13
8.11
7.81
7.26
6.90
3.76
3.71
3.69
3.58
3.46
3.29
3.16
3.15
3.08
2.98
2.84
2.82
2.63
2.60
2.57
2.55
2.37
1.91
1.89
1.74
1.65
1.43
1.41
1.39
1.36
1.36
1.33
1.30
1.27
1.25
O
N
OH
70
NO2
H
N
O
HO
NO2
0.99
0.80
1.02
0.74
0.42
0.50
0.54
0.48
0.21
0.44
0.21
0.53
1.61
0.27
1.26
2.83
1.05
0.98
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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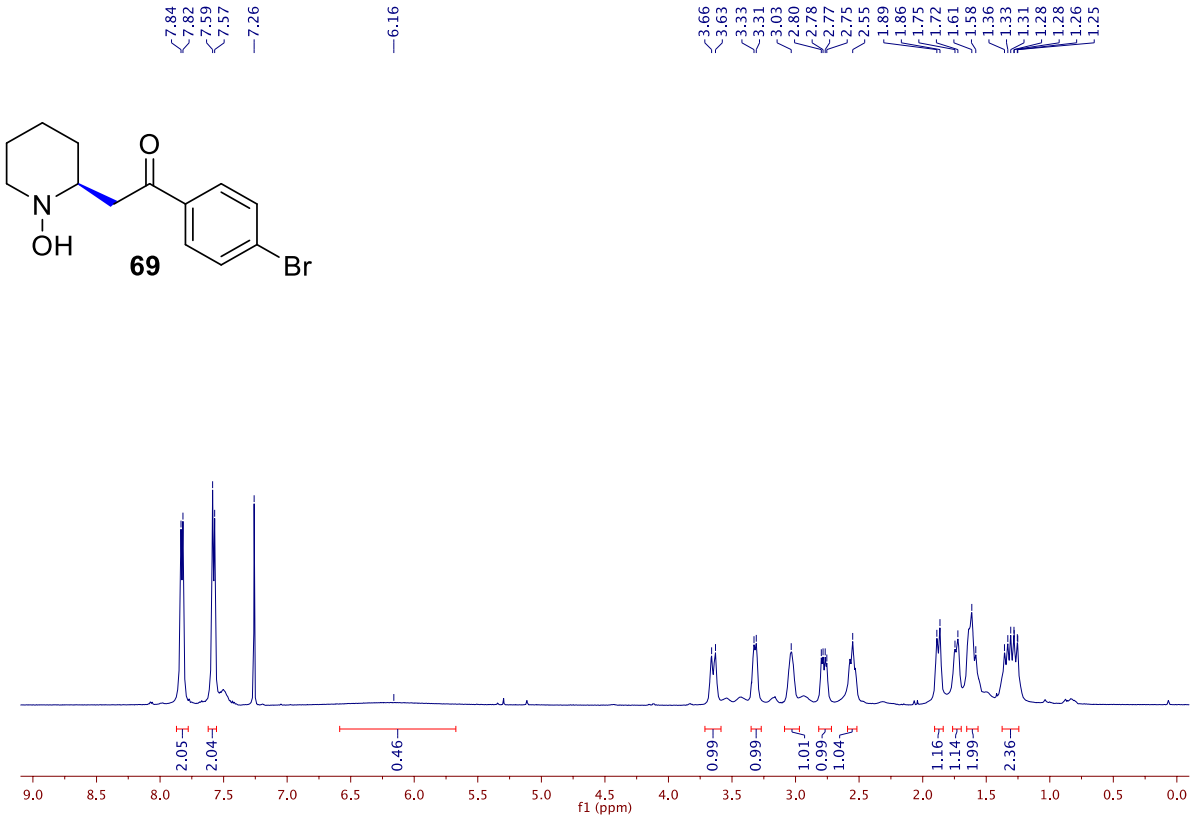
123.92
123.51
102.35
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
68.16
64.69
59.91
54.98
52.25
44.24
32.28
28.72
25.64
24.71
24.62
23.52
O
N
OH
70
NO2
H
N
O
HO
NO2
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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7.82
7.59
7.57
7.26
6.16
3.66
3.63
3.33
3.31
3.03
2.80
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2.77
2.75
2.55
1.89
1.86
1.75
1.72
1.61
1.58
1.36
1.33
1.31
1.28
1.28
1.26
1.25
O
N
OH
69
Br
2.05
2.04
0.46
0.99
0.99
1.01
0.99
1.04
1.16
1.14
1.99
2.36
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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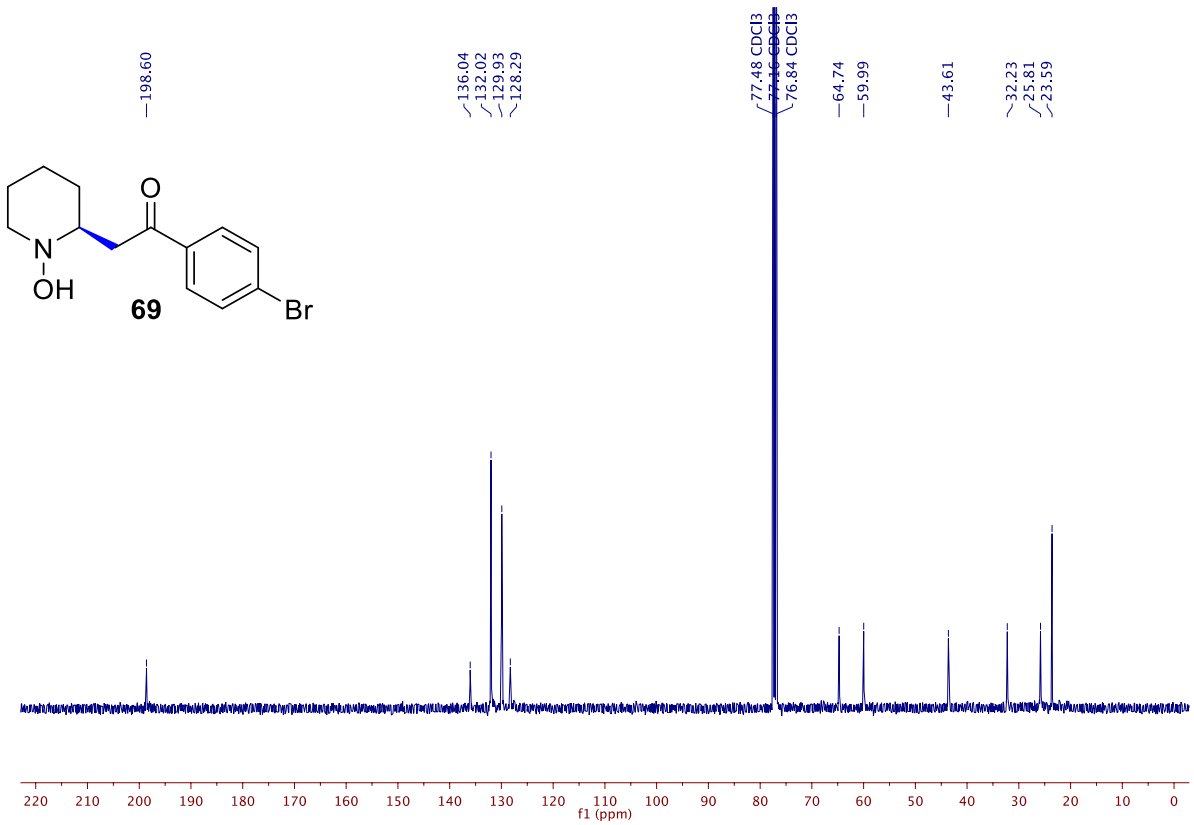
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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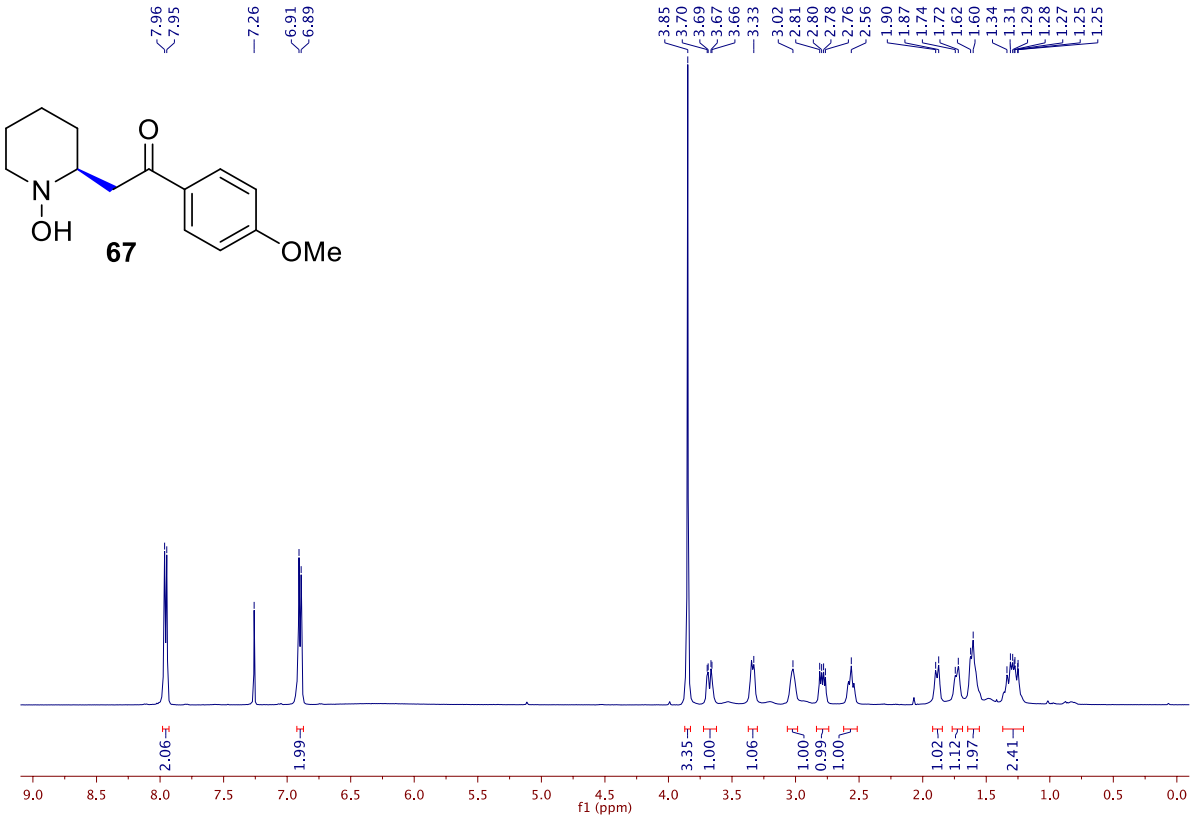
132.02
129.93
128.29
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
64.74
59.99
43.61
32.23
25.81
23.59
O
N
OH
69
Br
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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7.95
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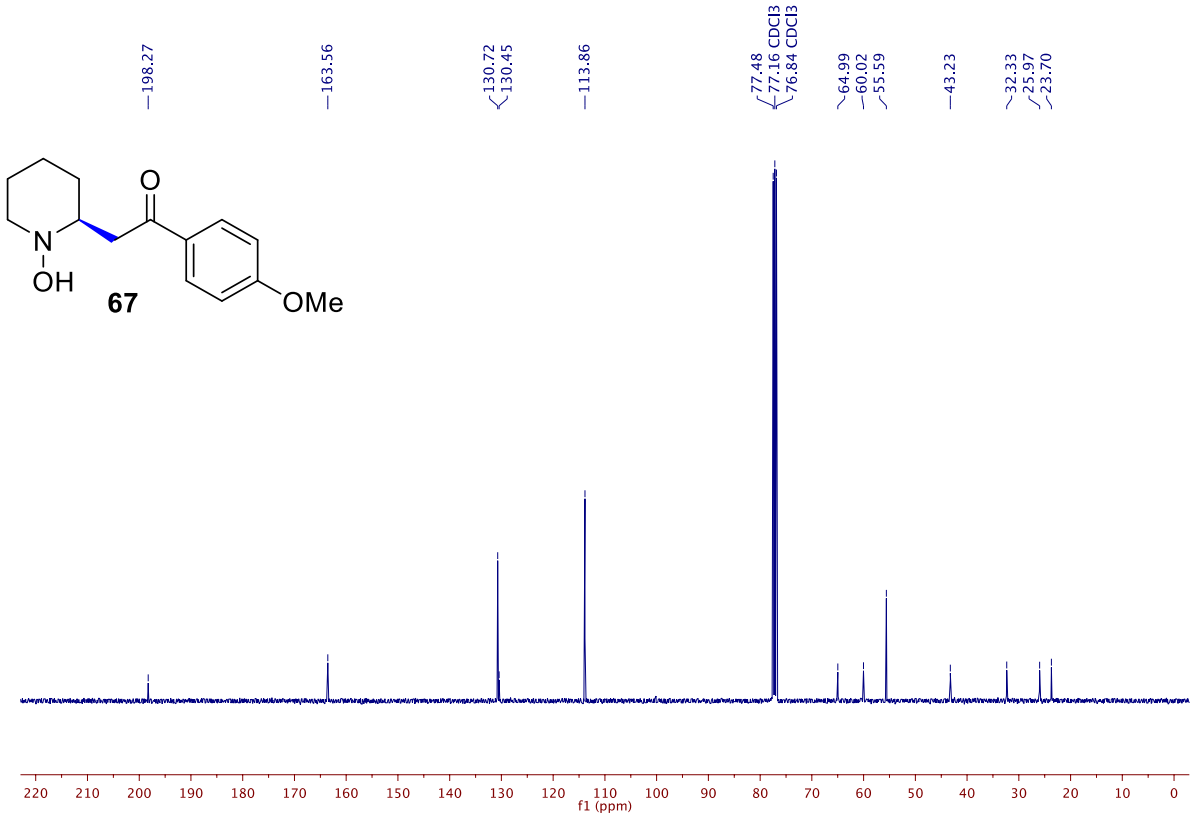
6.89
3.85
3.70
3.69
3.67
3.66
3.33
3.02
2.81
2.80
2.78
2.76
2.56
1.90
1.87
1.74
1.72
1.62
1.60
1.34
1.31
1.29
1.28
1.27
1.25
1.25
O
N
OH
67
OMe
2.06
1.99
3.35
1.00
1.06
1.00
0.99
1.00
1.02
1.12
1.97
2.41
f1 (ppm)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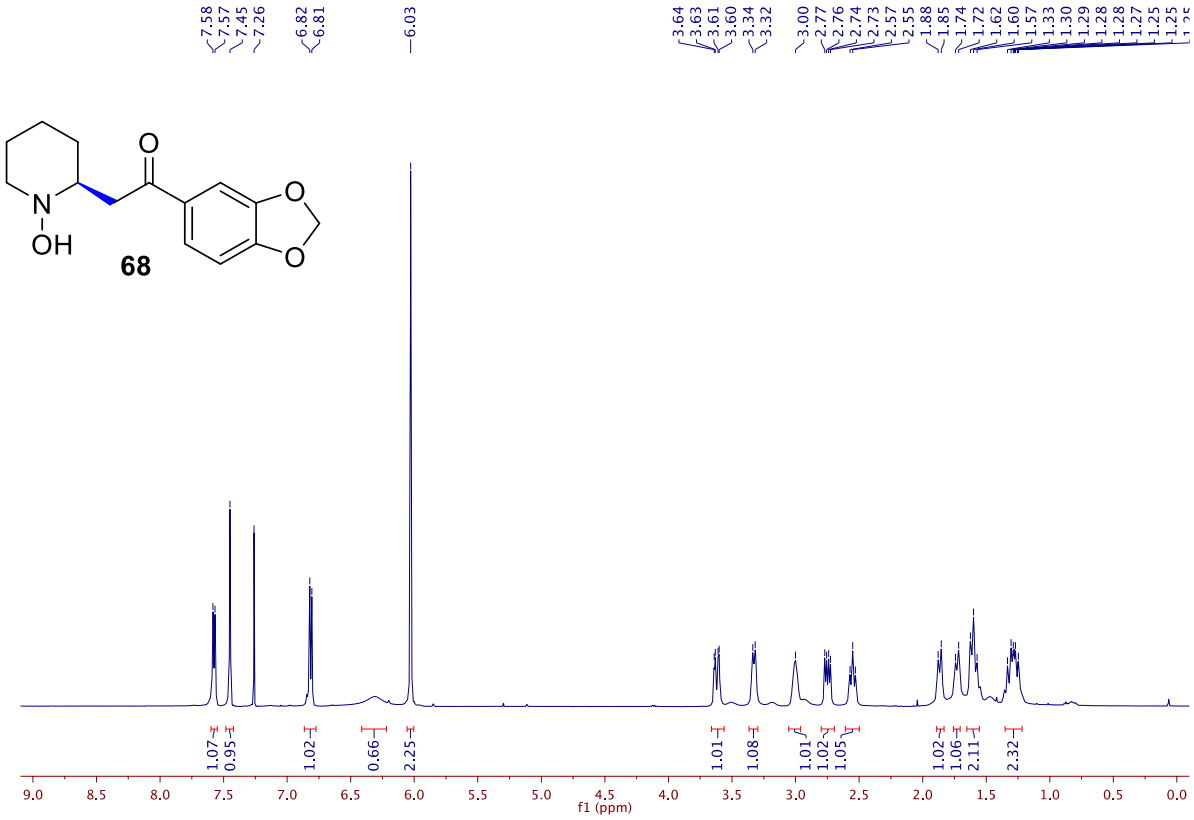
163.56
130.72
130.45
113.86
77.48
77.16 CDCl3
76.84 CDCl3
64.99
60.02
55.59
43.23
32.33
25.97
23.70
O
N
OH
67
OMe
f1 (ppm)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7.57
7.45
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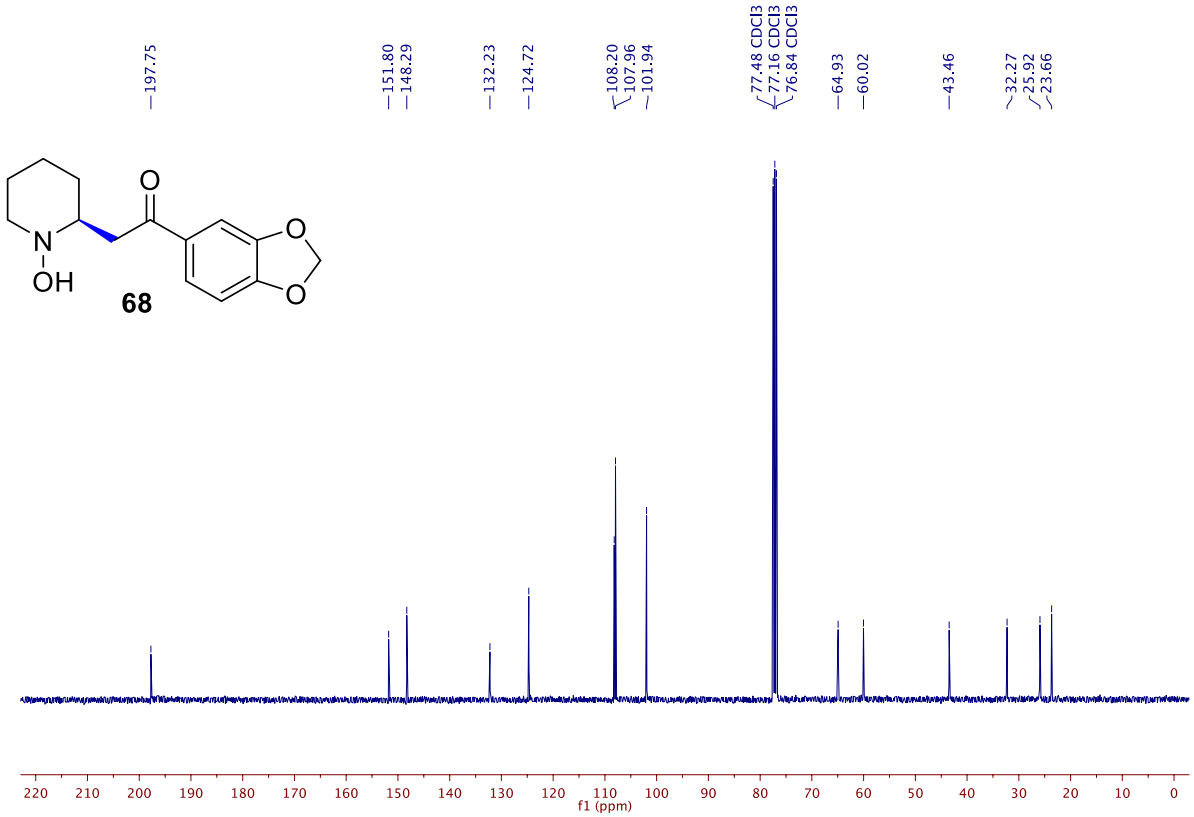
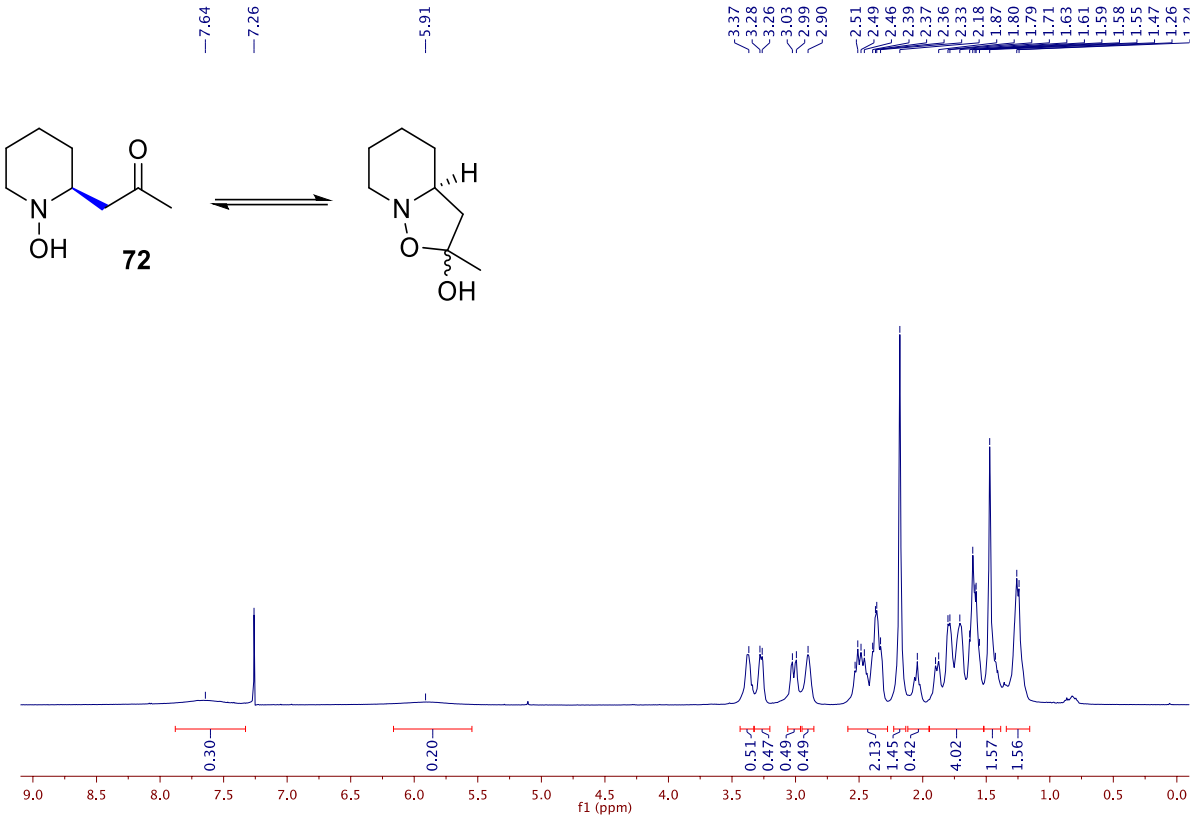
6.82
6.81
6.03
3.64
3.63
3.61
3.60
3.34
3.32
3.00
2.77
2.76
2.74
2.73
2.57
2.55
1.88
1.85
1.74
1.72
1.62
1.60
1.57
1.33
1.30
1.29
1.28
1.28
1.27
1.25
1.25
O
N
OH
O
O
68
1.07
0.95
1.02
0.66
2.25
1.01
1.08
1.01
1.02
1.05
1.02
1.06
2.11
2.32
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


197.75
151.80
148.29
132.23
124.72
108.20
107.96
101.94
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
64.93
60.02
43.46
32.27
25.92
23.66
O
N
OH
O
O
68
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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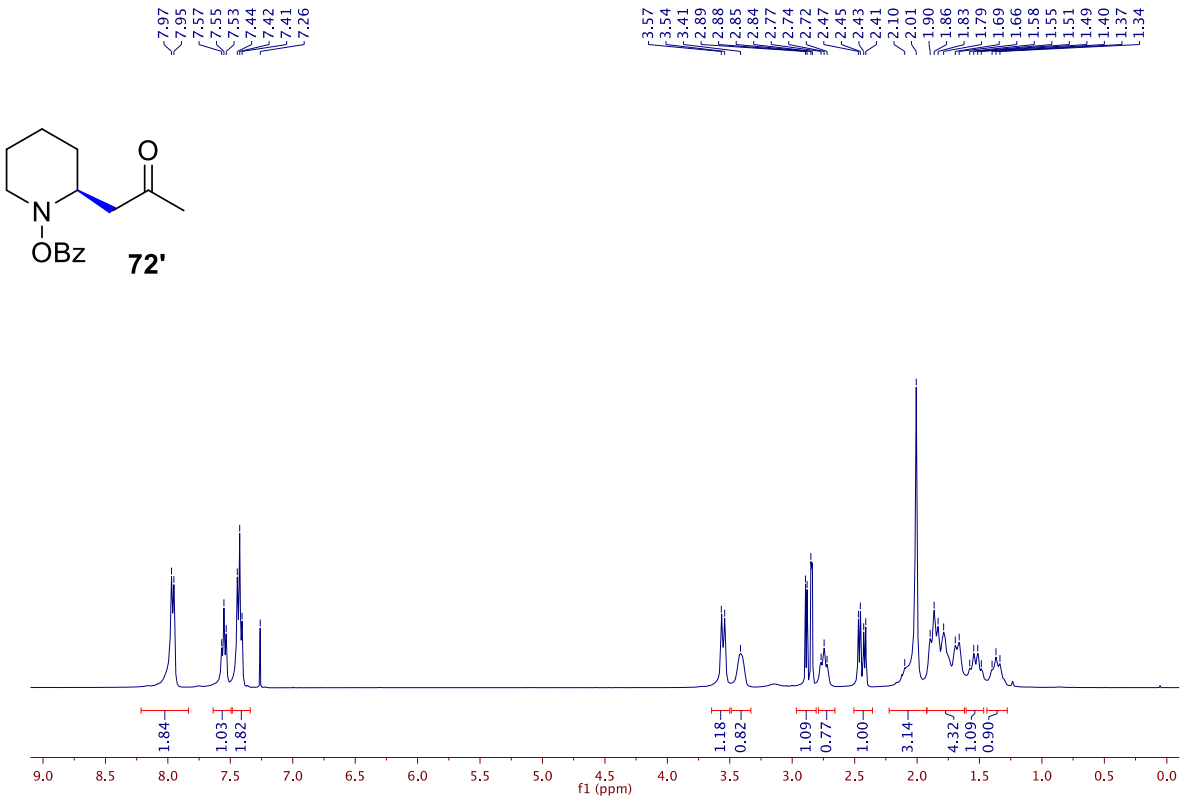
7.26
5.91
3.37
3.28
3.26
3.03
2.99
2.90
2.51
2.49
2.46
2.39
2.37
2.36
2.33
2.18
1.87
1.80
1.79
1.71
1.63
1.61
1.59
1.58
1.55
1.47
1.26
O
N
OH
72
H
N
O
OH
0.30
0.20
0.51
0.47
0.49
0.49
2.13
1.45
0.42
4.02
1.57
1.56
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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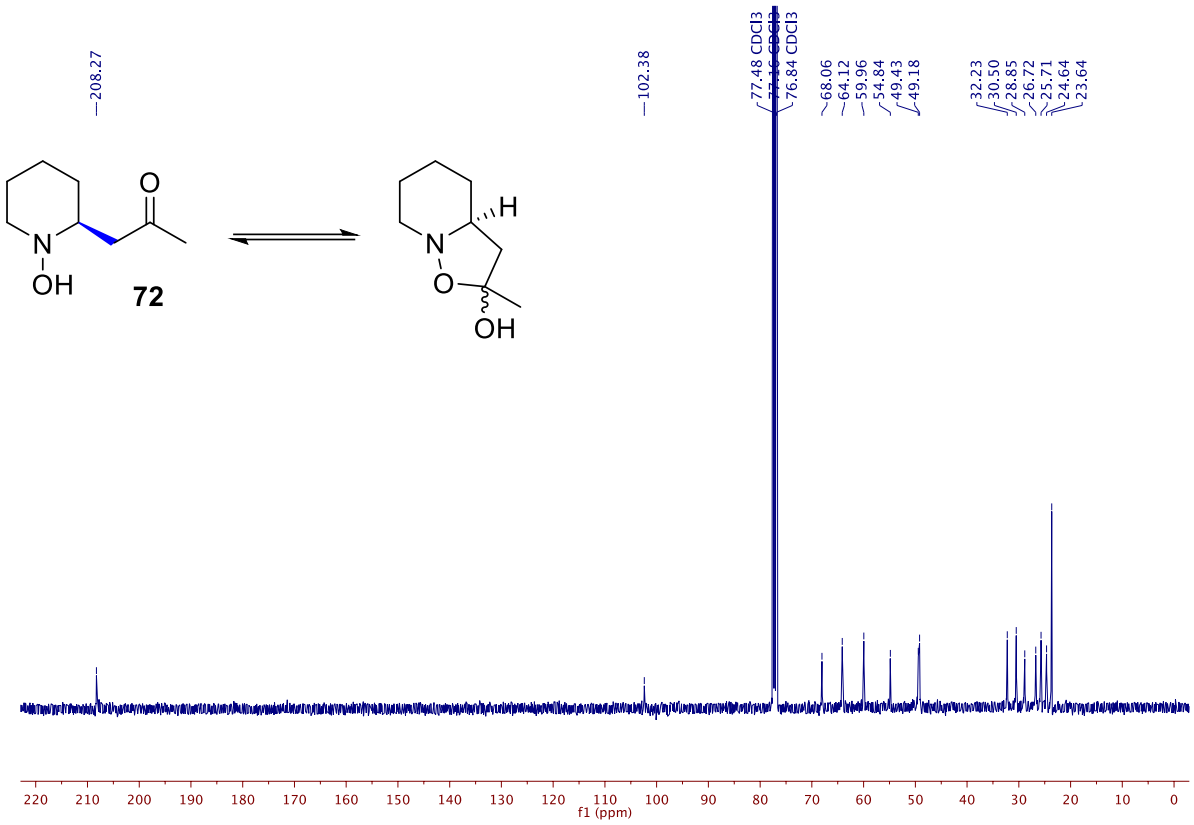
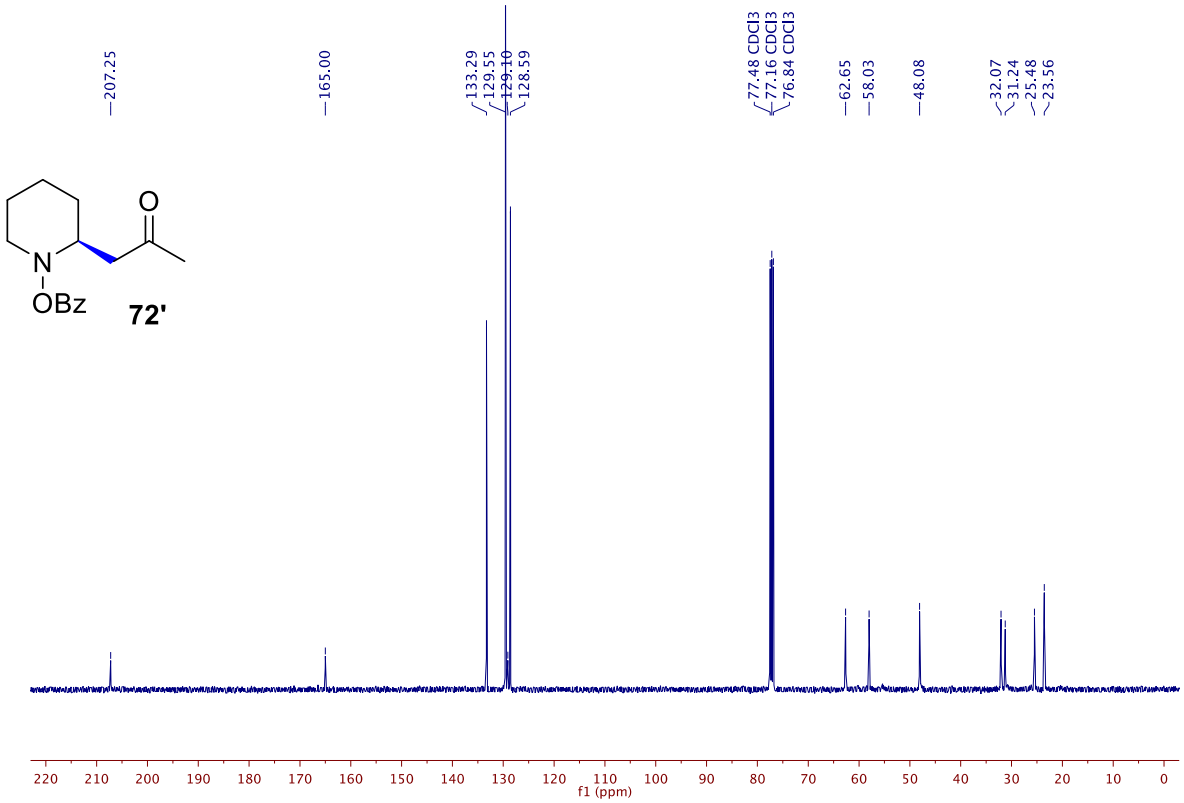
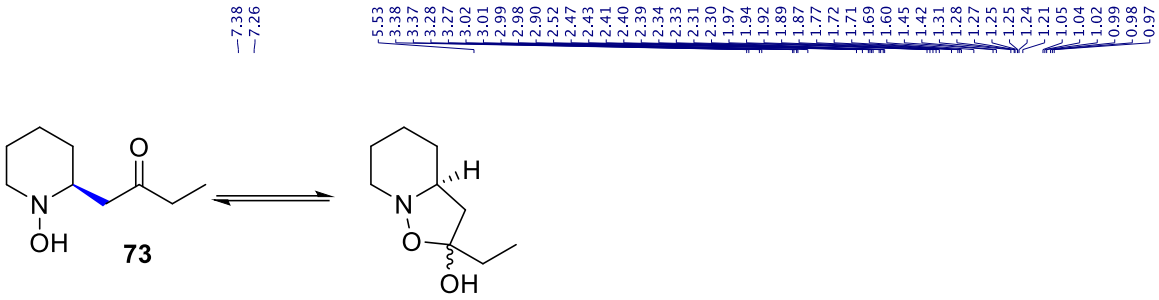
7.95
7.57
7.55
7.53
7.44
7.42
7.41
7.26
3.57
3.54
3.41
2.89
2.88
2.85
2.84
2.77
2.74
2.72
2.47
2.45
2.43
2.41
2.10
2.01
1.90
1.86
1.83
1.79
1.69
1.66
1.58
1.55
1.51
1.49
1.40
1.37
1.34
O
N
OBz
72'
1.84
1.03
1.82
1.18
0.82
1.09
0.77
1.00
3.14
4.32
1.09
0.90
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

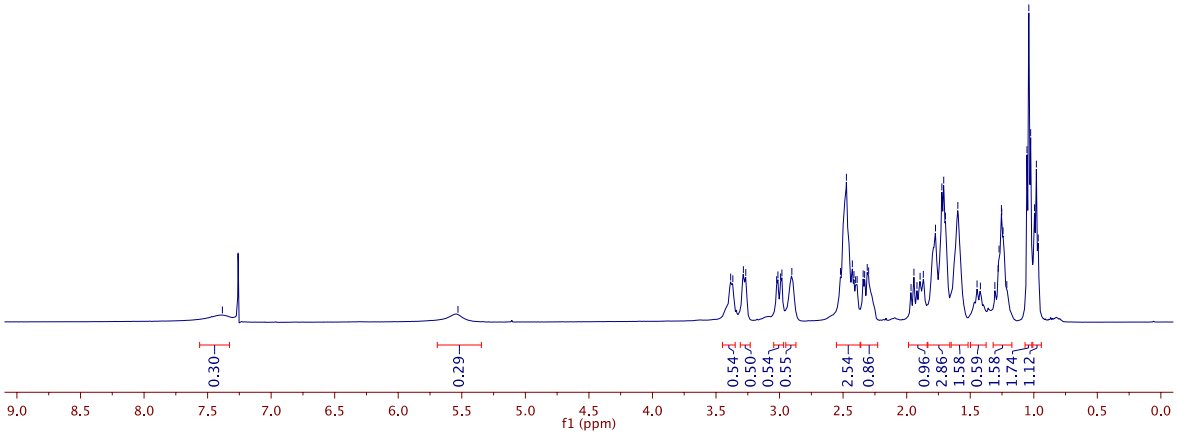

208.27
102.38
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
68.06
64.12
59.96
54.84
49.43
49.18
32.23
30.50
28.85
26.72
25.71
24.64
23.64
O
N
OH
72
H
N
O
OH
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


207.25
165.00
133.29
129.55
129.10
128.59
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
62.65
58.03
48.08
32.07
31.24
25.48
23.56
O
N
OBz
72'
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

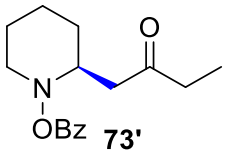

7.38
7.26
5.53
3.38
3.37
3.28
3.27
3.02
3.01
2.99
2.98
2.90
2.52
2.47
2.43
2.41
2.40
2.39
2.34
2.33
2.31
2.30
1.97
1.94
1.92
1.89
1.87
1.77
1.72
1.71
1.69
1.60
1.45
1.42
1.31
1.28
1.27
1.25
1.25
1.24
1.21
1.05
1.04
1.02
0.99
0.98
0.97

O
N
OH
H
N
O
OH

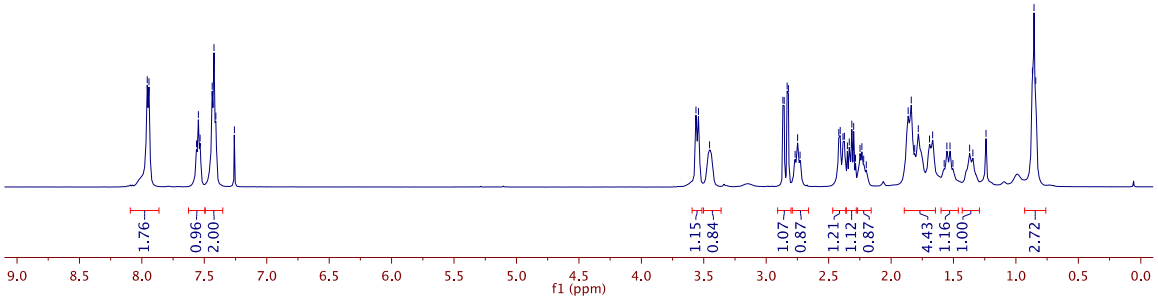
73

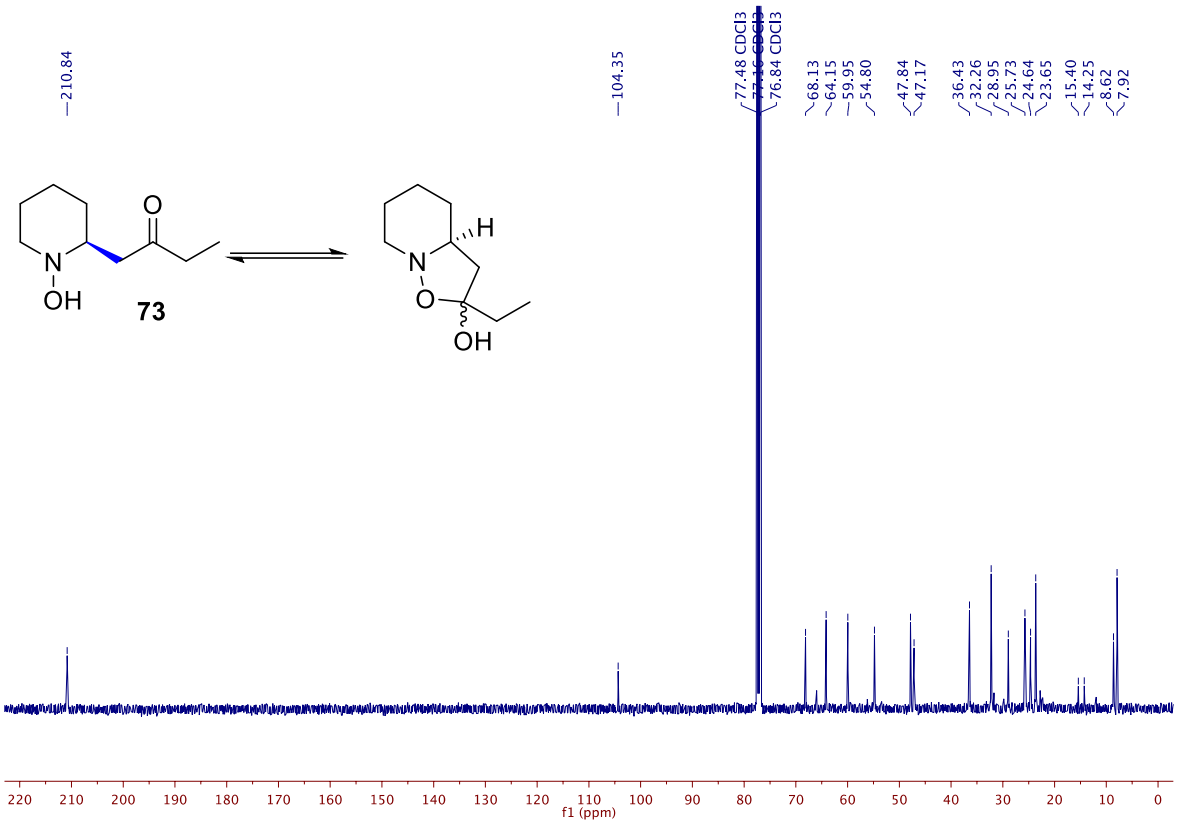

0.30
0.29
0.54
0.50
0.54
0.55
2.54
0.86
0.96
2.86
1.58
0.59
1.58
1.74
1.12
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


7.96
7.94
7.56
7.55
7.53
7.44
7.42
7.41
7.26
3.56
3.54
3.45
2.87
2.86
2.83
2.82
2.77
2.75
2.73
2.42
2.41
2.38
2.37
2.35
2.33
2.31
2.30
2.28
2.25
2.23
2.22
2.20
1.86
1.84
1.81
1.78
1.69
1.67
1.57
1.55
1.53
1.50
1.37
1.34
1.24
0.87
0.85
0.84


O
N
OBz

73'


1.76
0.96
2.00
1.15
0.84
1.07
0.87
1.21
1.12
0.87
4.43
1.16
1.00
2.72
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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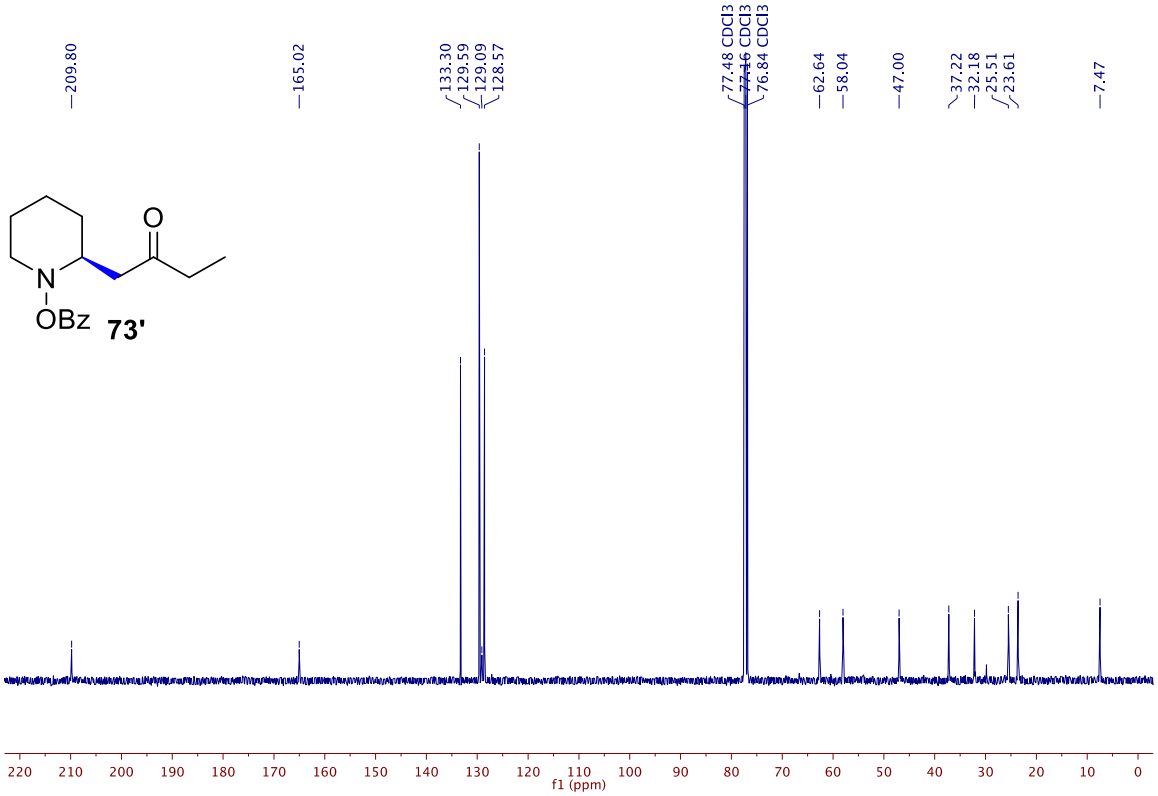
104.35
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
68.13
64.15
59.95
54.80
47.84
47.17
36.43
32.26
28.95
25.73
24.64
23.65
15.40
14.25
8.62
7.92
O
N
OH
73
H
N
O
OH
f1 (ppm)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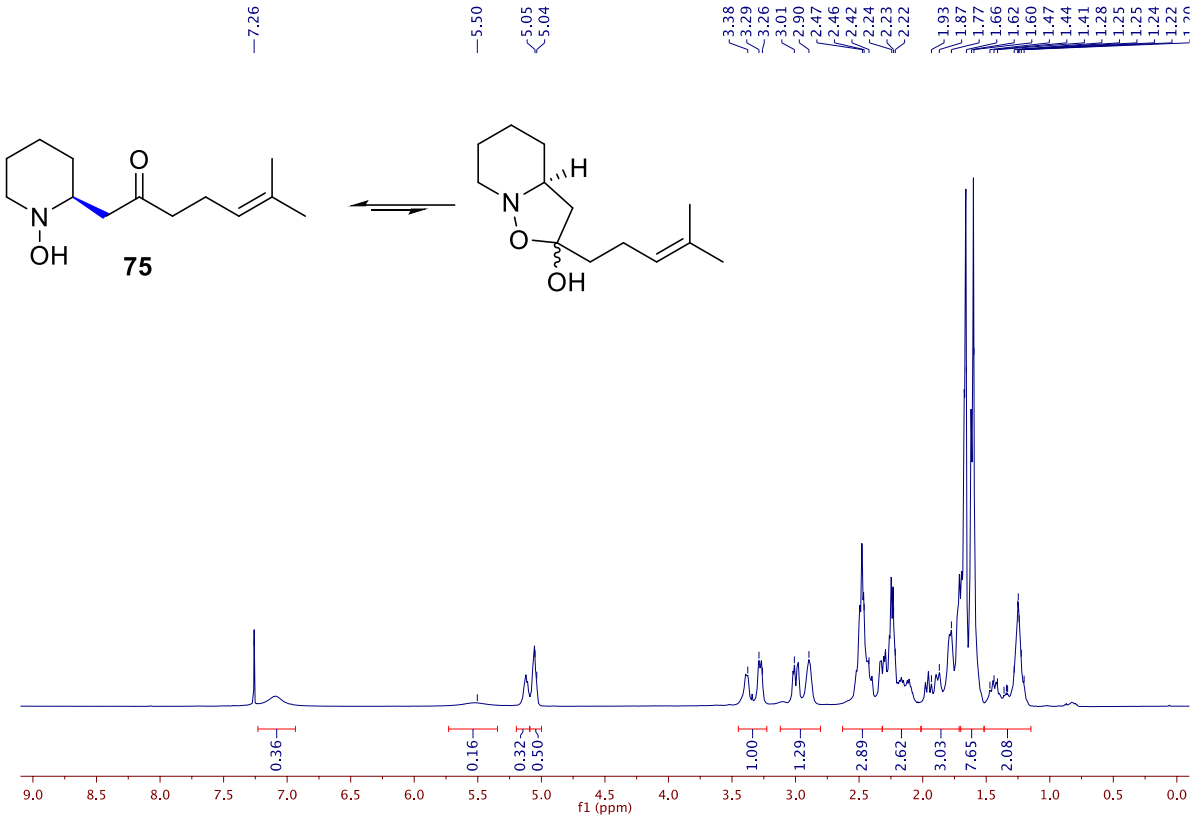
165.02
133.30
129.59
129.09
128.57
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
62.64
58.04
47.00
37.22
32.18
25.51
23.61
7.47
O
N
OBz
73'
f1 (ppm)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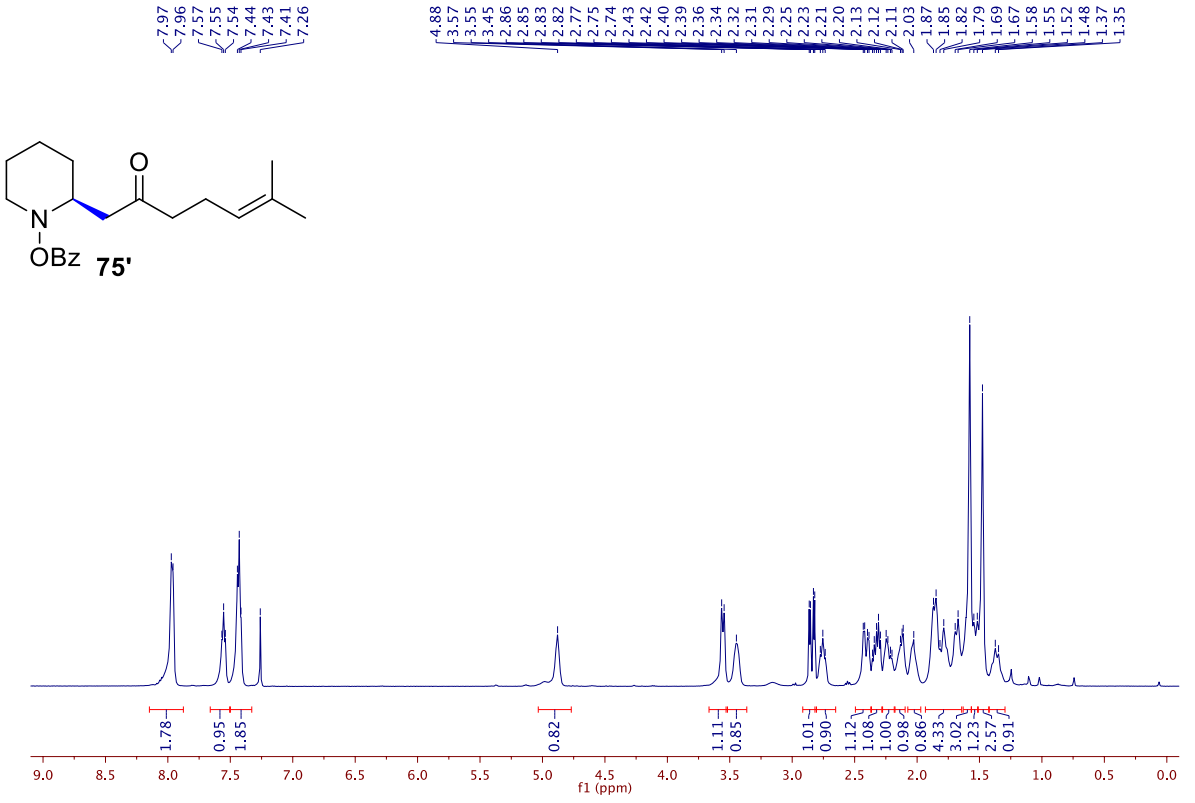
5.50
5.05
5.04
3.38
3.29
3.26
3.01
2.90
2.47
2.46
2.42
2.24
2.23
2.22
1.93
1.87
1.77
1.66
1.62
1.60
1.47
1.44
1.41
1.28
1.25
1.25
1.24
1.22
O
N
OH
75
H
N
O
OH
0.36
0.16
0.32
0.50
1.00
1.29
2.89
2.62
3.03
7.65
2.08
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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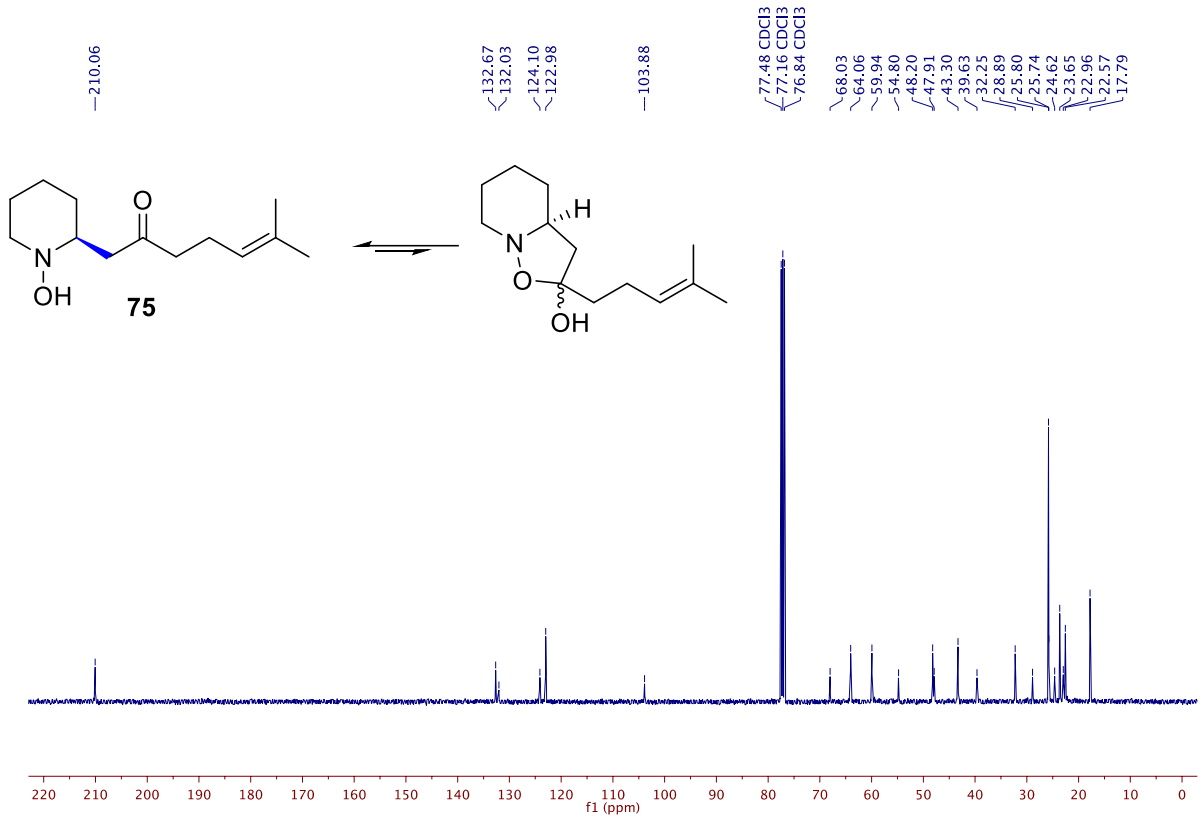
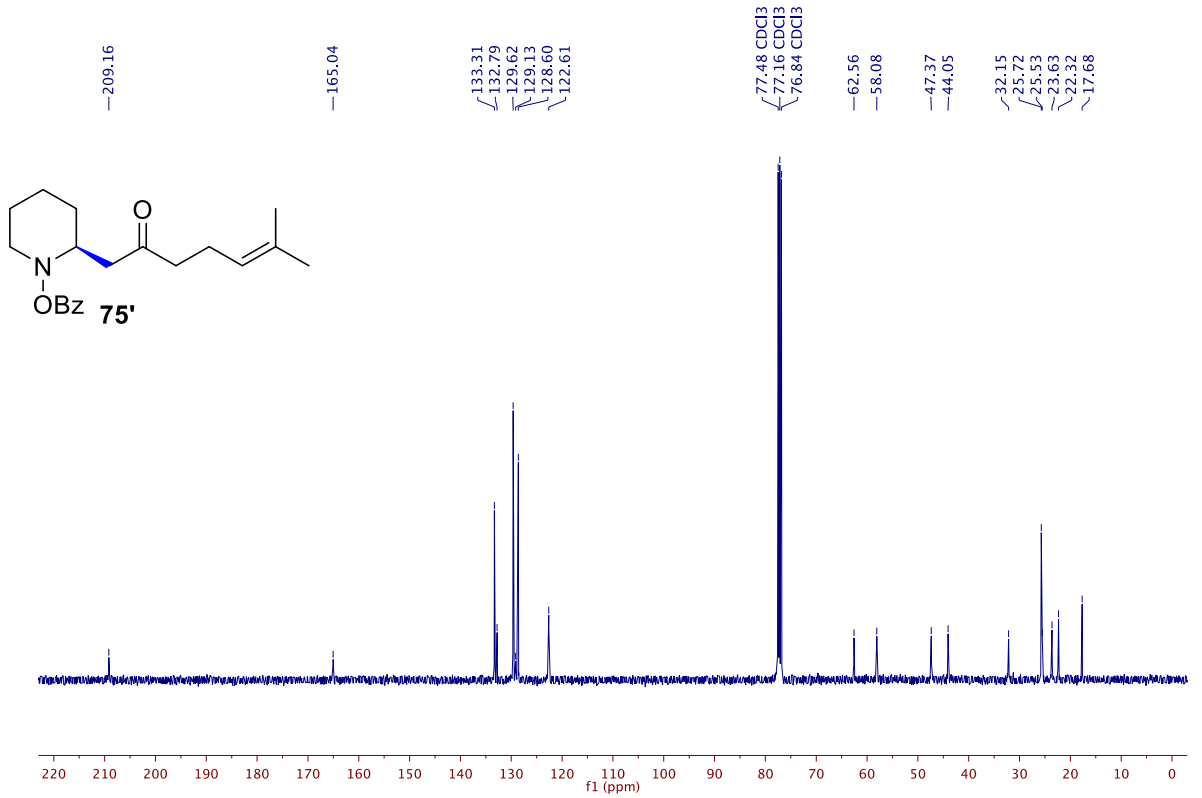
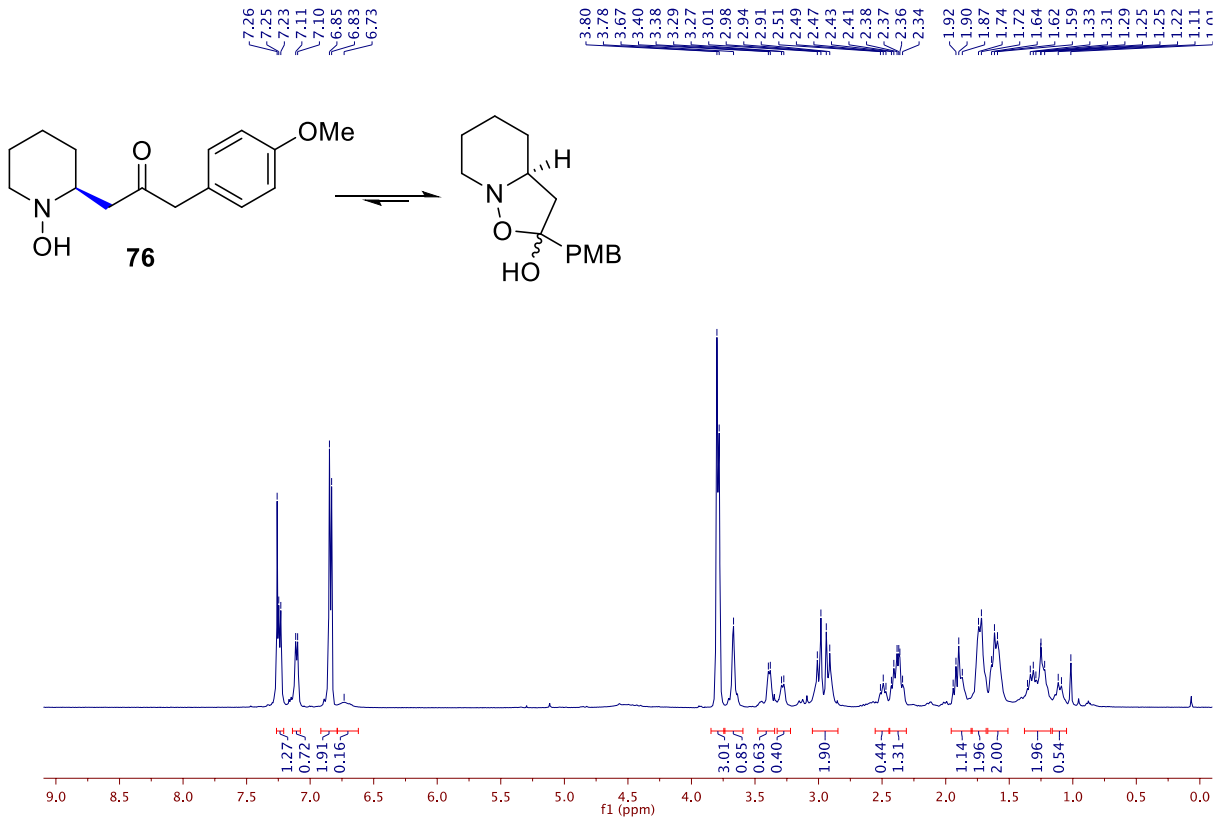
7.54
7.44
7.43
7.41
7.26
4.88
3.57
3.55
3.45
2.86
2.85
2.83
2.82
2.77
2.75
2.74
2.43
2.42
2.40
2.39
2.36
2.34
2.32
2.31
2.29
2.25
2.23
2.21
2.20
2.13
2.12
2.11
2.03
1.87
1.85
1.82
1.79
1.69
1.67
1.58
1.55
1.52
1.48
1.37
1.35
O
N
OBz
75'
1.78
0.95
1.85
0.82
1.11
0.85
1.01
0.90
1.12
1.08
1.00
0.98
0.86
4.33
3.02
1.23
2.57
0.91
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


210.06
132.67
132.03
124.10
122.98
103.88
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
68.03
64.06
59.94
54.80
48.20
47.91
43.30
39.63
32.25
28.89
25.80
25.74
24.62
23.65
22.96
22.57
17.79
O
N
OH
75
H
N
O
OH
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


209.16
165.04
133.31
132.79
129.62
129.13
128.60
122.61
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
62.56
58.08
47.37
44.05
32.15
25.72
25.53
23.63
22.32
17.68
O
N
OBz
75'
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.26
7.25
7.23
7.11
7.10
6.85
6.83
6.73
3.80
3.78
3.67
3.40
3.38
3.29
3.27
3.01
2.98
2.94
2.91
2.51
2.49
2.47
2.43
2.41
2.38
2.37
2.36
2.34
1.92
1.90
1.87
1.74
1.72
1.64
1.62
1.59
1.33
1.31
1.29
1.25
1.25
1.22
1.11
OMe
O
N
OH
76
H
N
O
HO
PMB
1.27
0.72
1.91
0.16
3.01
0.85
0.63
0.40
1.90
0.44
1.31
1.14
1.96
2.00
1.96
0.54
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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3.5
3.0
2.5
2.0
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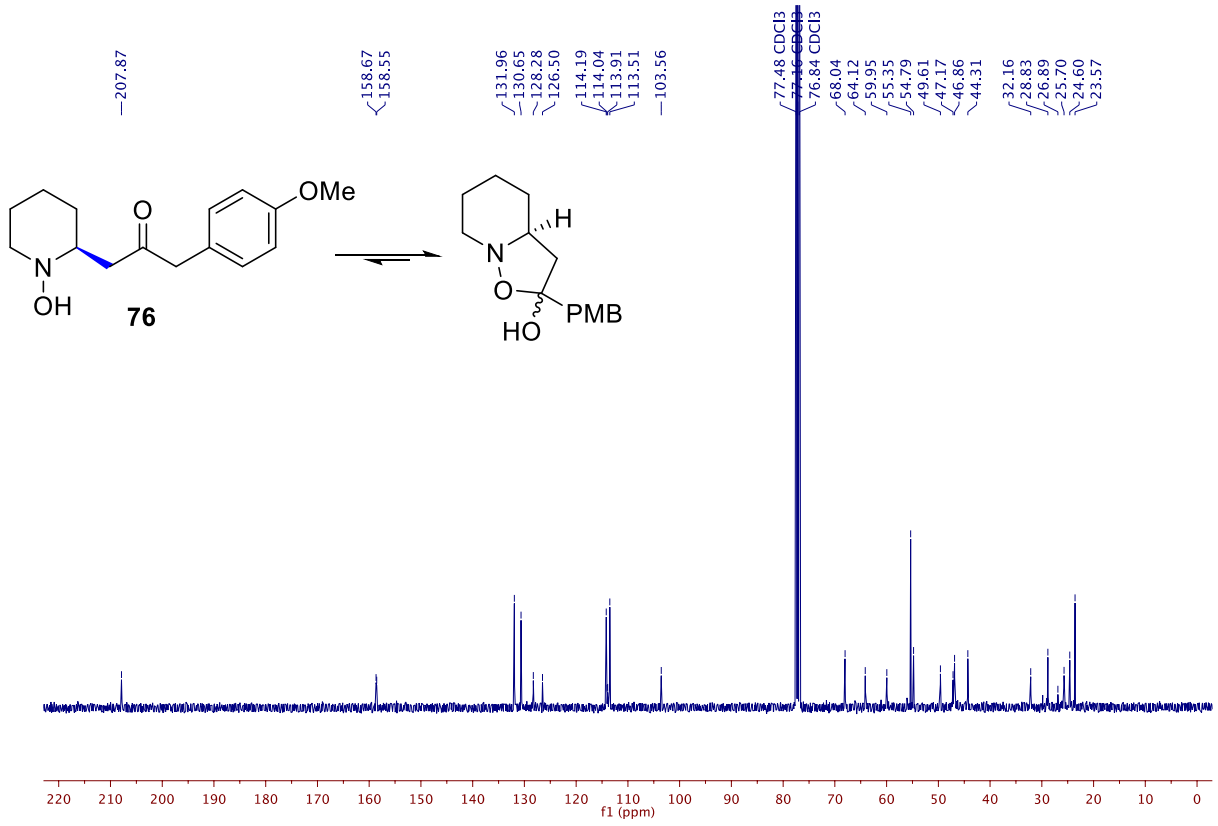
1.0
0.5
0.0
f1 (ppm)


207.87
158.67
158.55
131.96
130.65
128.28
126.50
114.19
114.04
113.91
113.51
103.56
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
68.04
64.12
59.95
55.35
54.79
49.61
47.17
46.86
44.31
32.16
28.83
26.89
25.70
24.60
23.57
OMe
O
N
OH
76
H
N
O
HO
PMB
220
210
200
190
180
170
160
150
140
130
120
110
100
90
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70
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50
40
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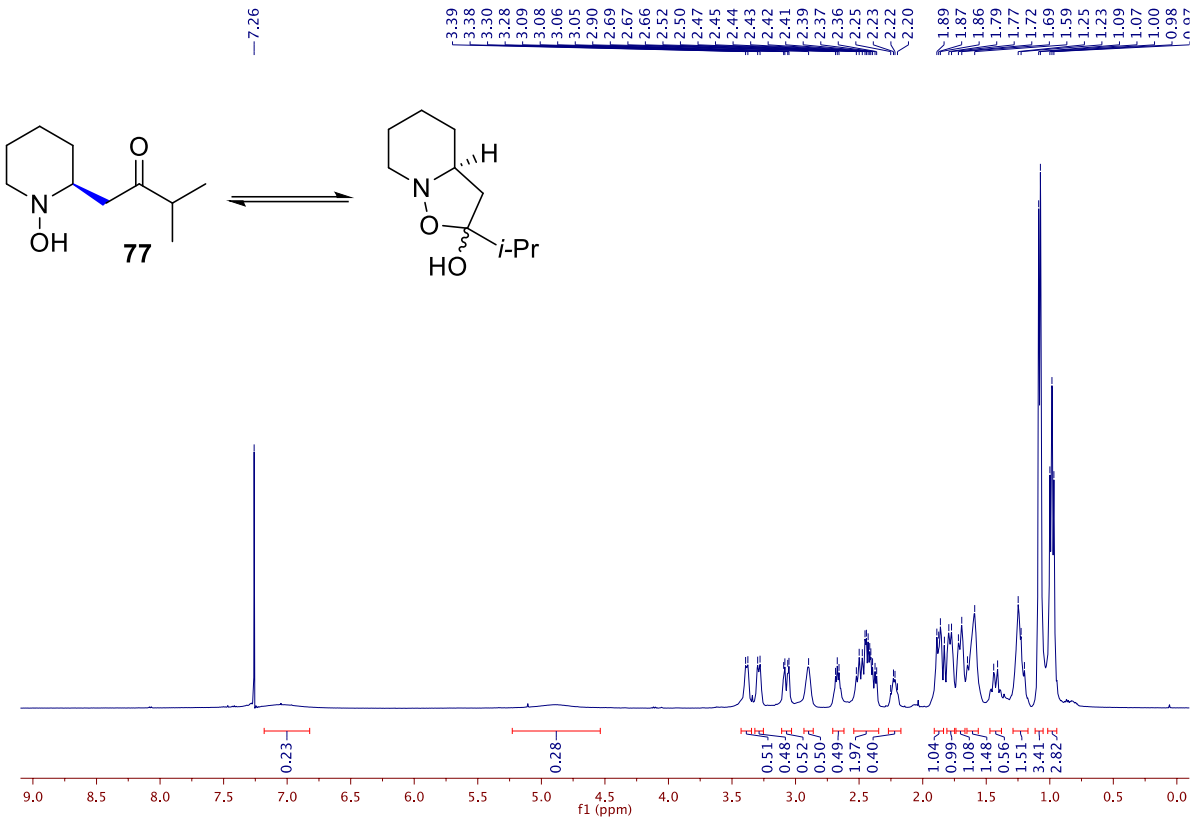
f1 (ppm)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3.39
3.38
3.30
3.28
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3.06
3.05
2.90
2.69
2.67
2.66
2.52
2.50
2.47
2.45
2.44
2.43
2.42
2.41
2.39
2.37
2.36
2.25
2.23
2.22
2.20
1.89
1.87
1.86
1.79
1.77
1.72
1.69
1.59
1.25
1.23
1.09
1.07
1.00
0.98
O
N
OH
77
H
N
O
HO
i-Pr
0.23
0.28
0.51
0.48
0.52
0.50
0.49
1.97
0.40
1.04
0.99
1.08
1.48
0.56
1.51
3.41
2.82
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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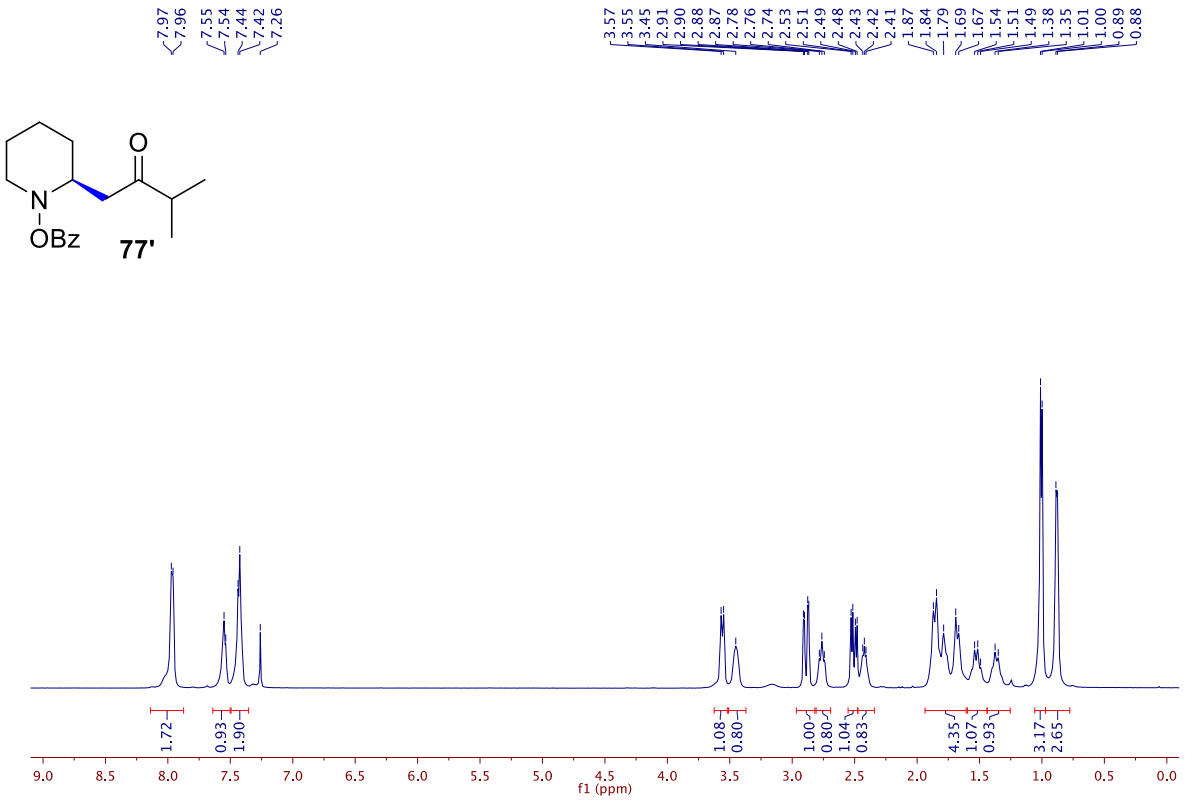
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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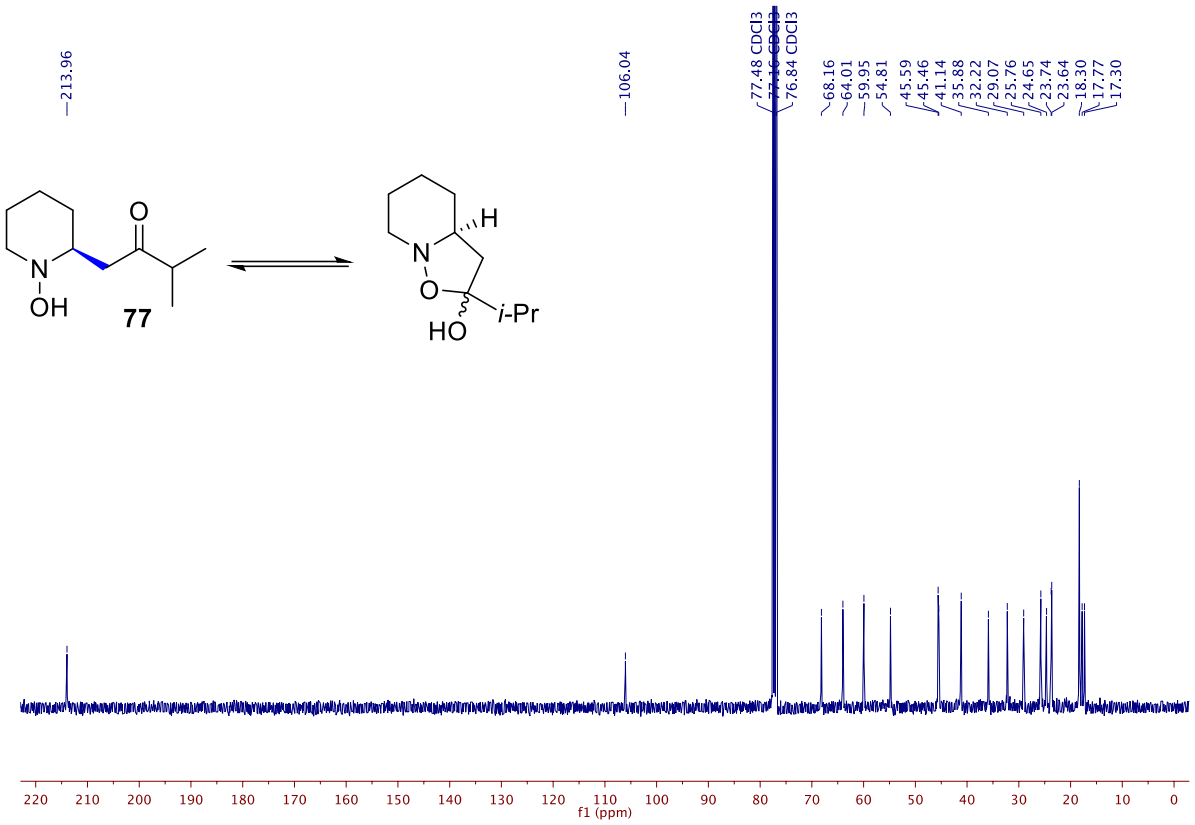
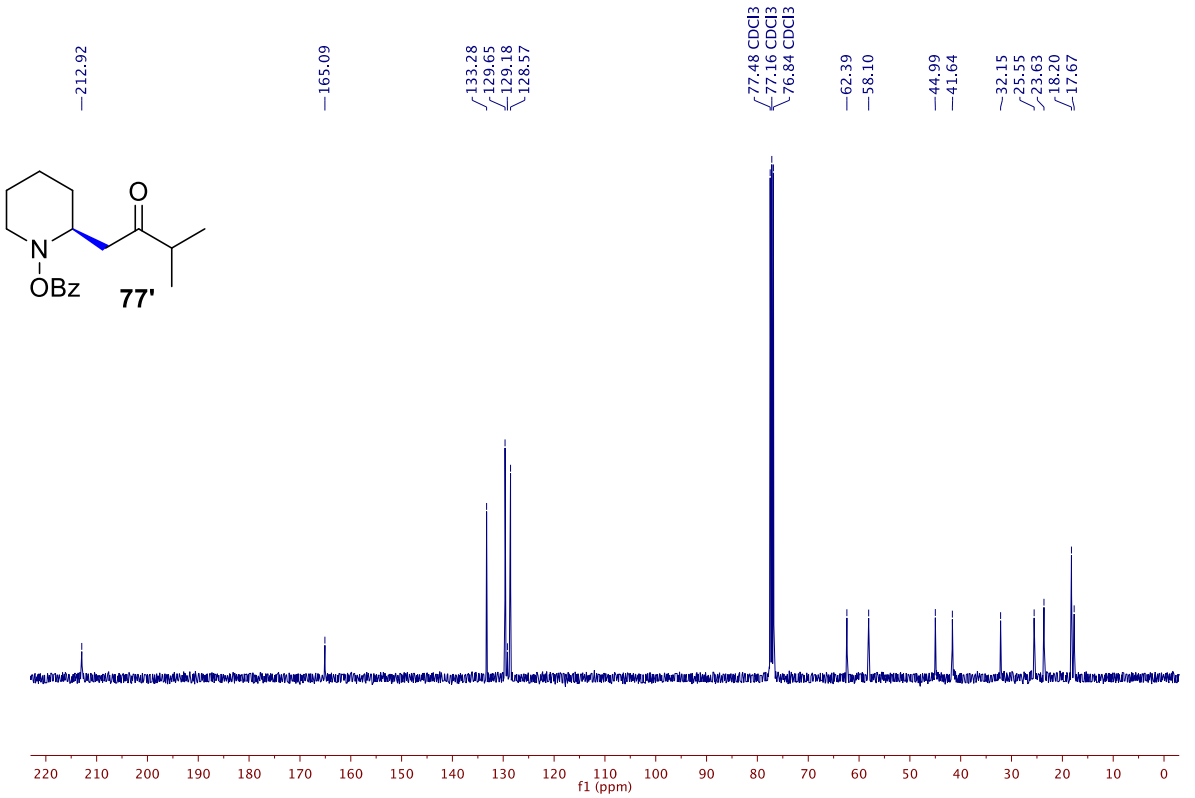
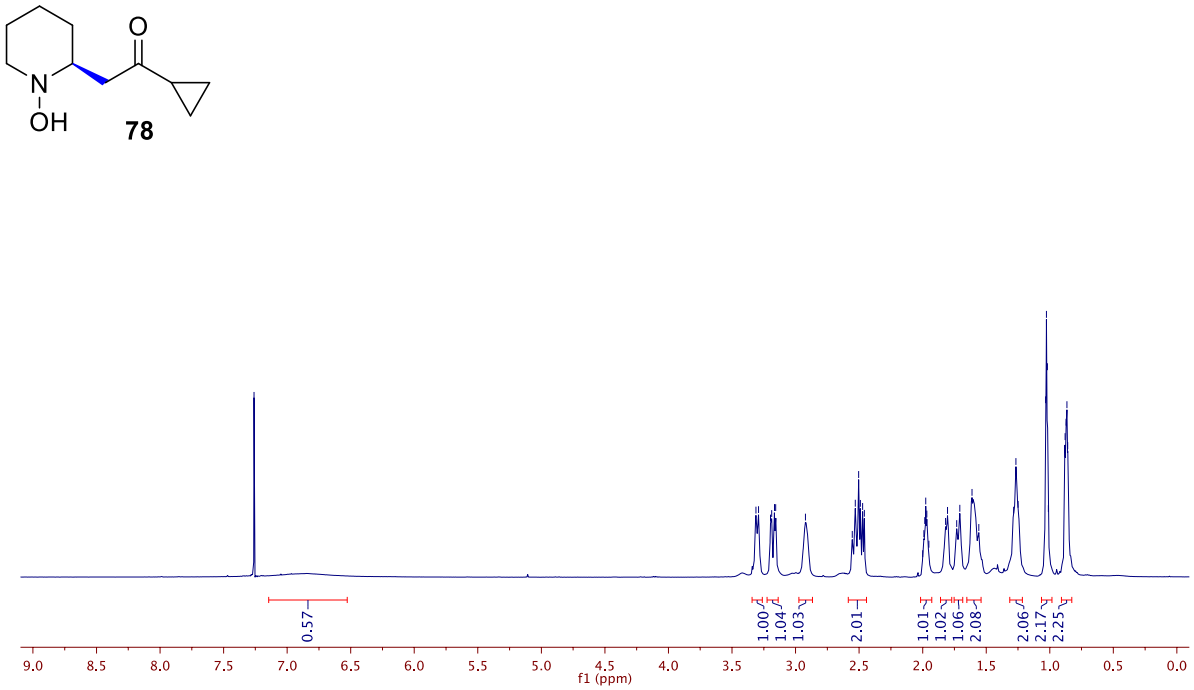
7.96
7.55
7.54
7.44
7.42
7.26
3.57
3.55
3.45
2.91
2.90
2.88
2.87
2.78
2.76
2.74
2.53
2.51
2.49
2.48
2.43
2.42
2.41
1.87
1.84
1.79
1.69
1.67
1.54
1.51
1.49
1.38
1.35
1.01
1.00
0.89
0.88
O
N
OBz
77'
1.72
0.93
1.90
1.08
0.80
1.00
0.80
1.04
0.83
4.35
1.07
0.93
3.17
2.65
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


213.96
106.04
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
68.16
64.01
59.95
54.81
45.59
45.46
41.14
35.88
32.22
29.07
25.76
24.65
23.74
23.64
18.30
17.77
17.30
N
OH
O
77
H
N
O
HO
i-Pr
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


212.92
165.09
133.28
129.65
129.18
128.57
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
62.39
58.10
44.99
41.64
32.15
25.55
23.63
18.20
17.67
N
OBz
O
77'
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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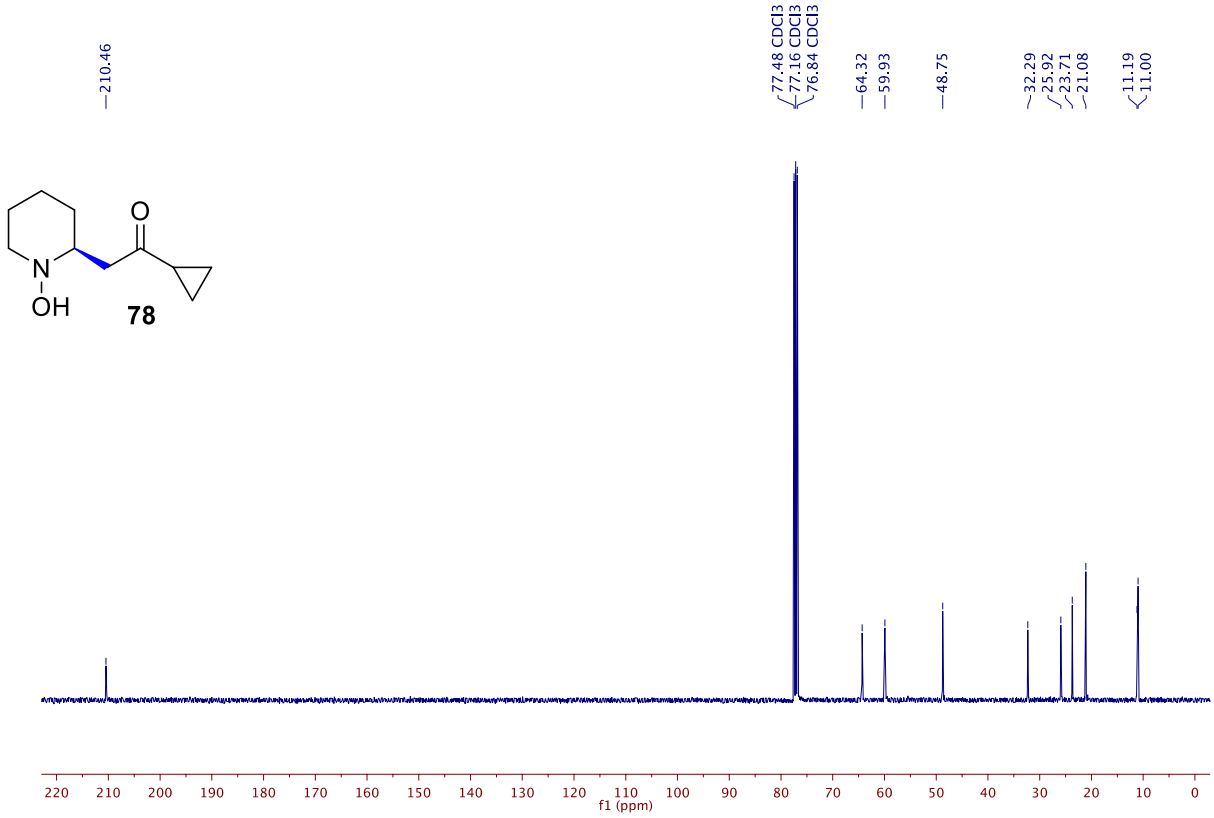
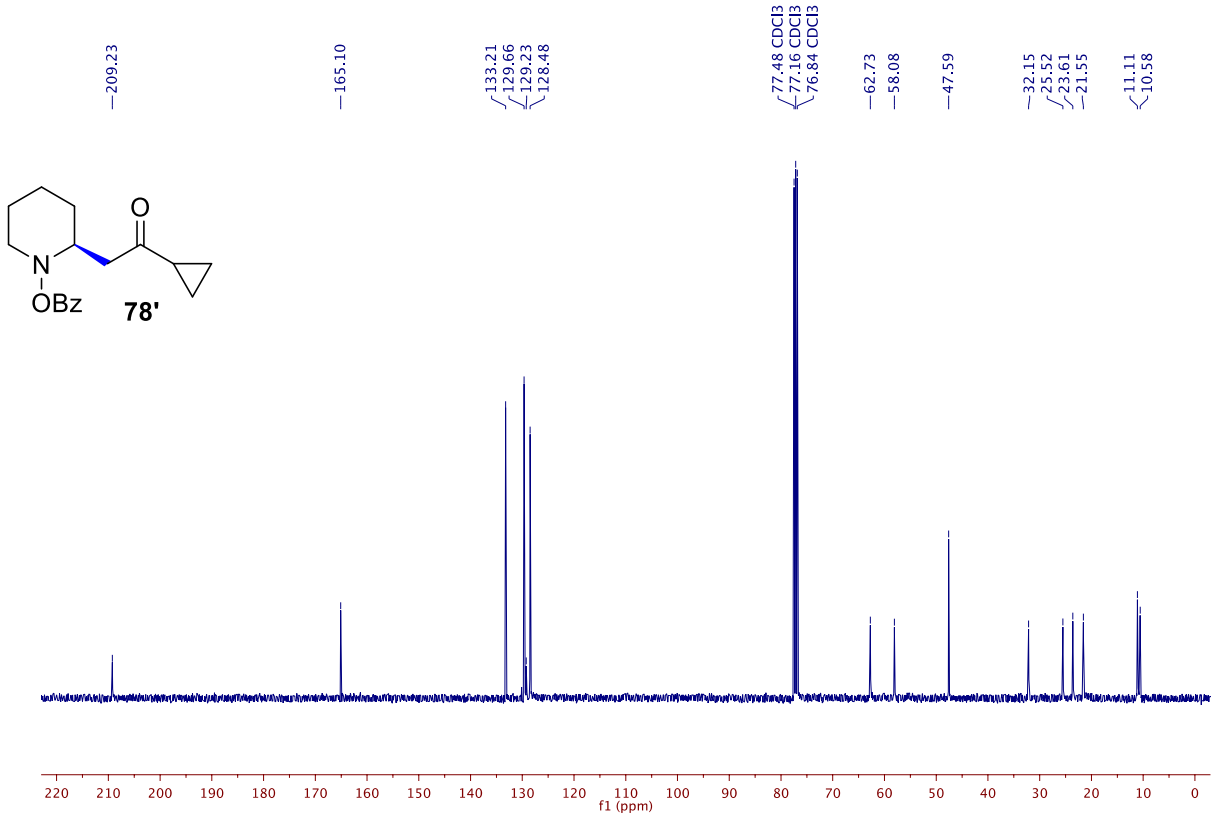
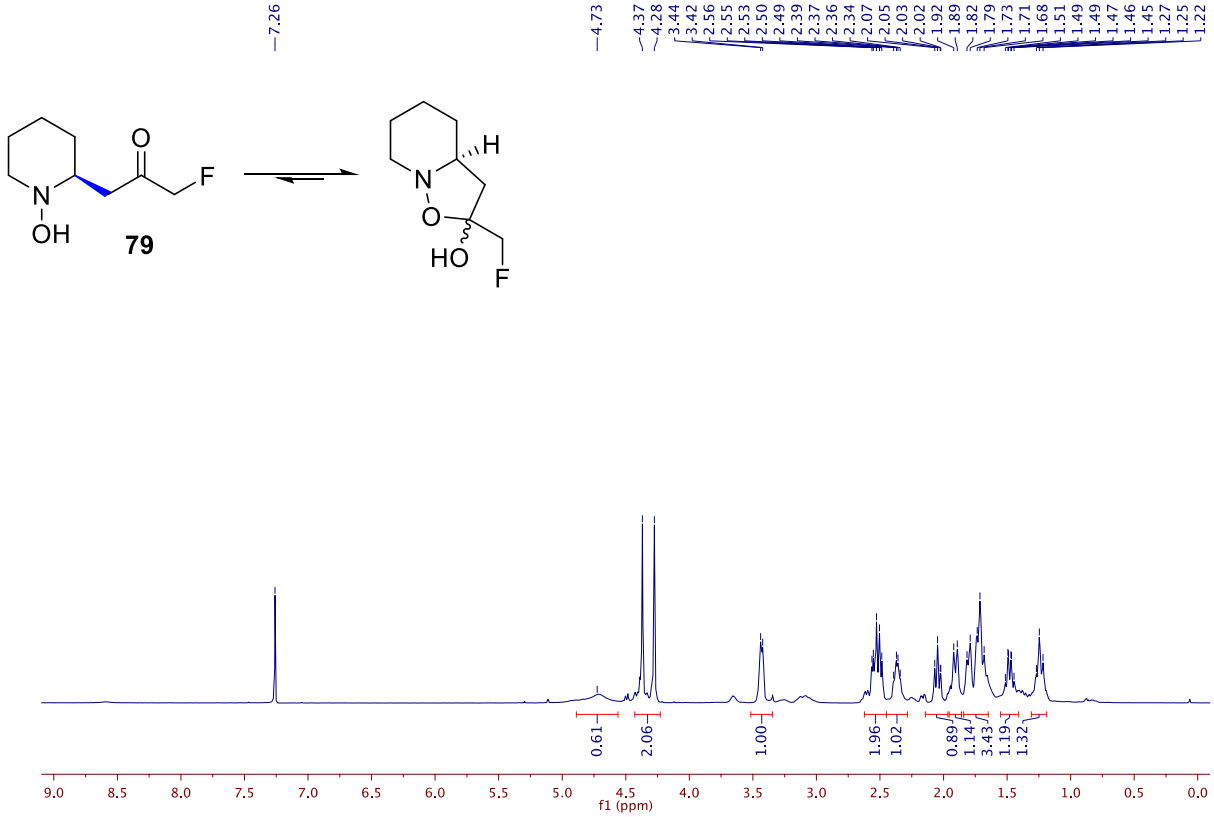
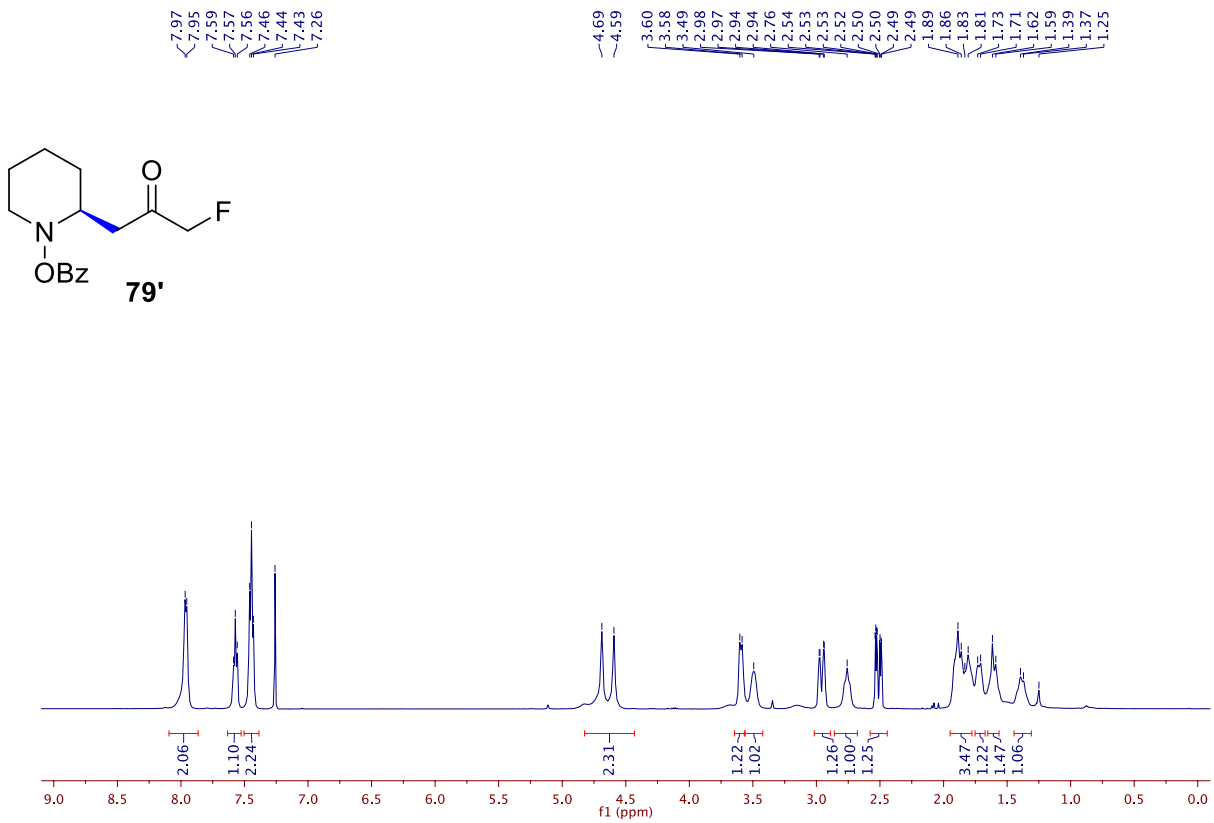
3.31
3.29
3.20
3.19
3.17
3.16
2.92
2.55
2.53
2.50
2.49
2.47
2.46
2.00
1.99
1.98
1.98
1.97
1.95
1.82
1.80
1.73
1.71
1.61
1.56
1.28
1.27
1.25
1.03
1.03
1.02
1.01
0.88
0.87
0.86
0.86
O
N
OH
78
0.57
1.00
1.04
1.03
2.01
1.01
1.02
1.06
2.08
2.06
2.17
2.25
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

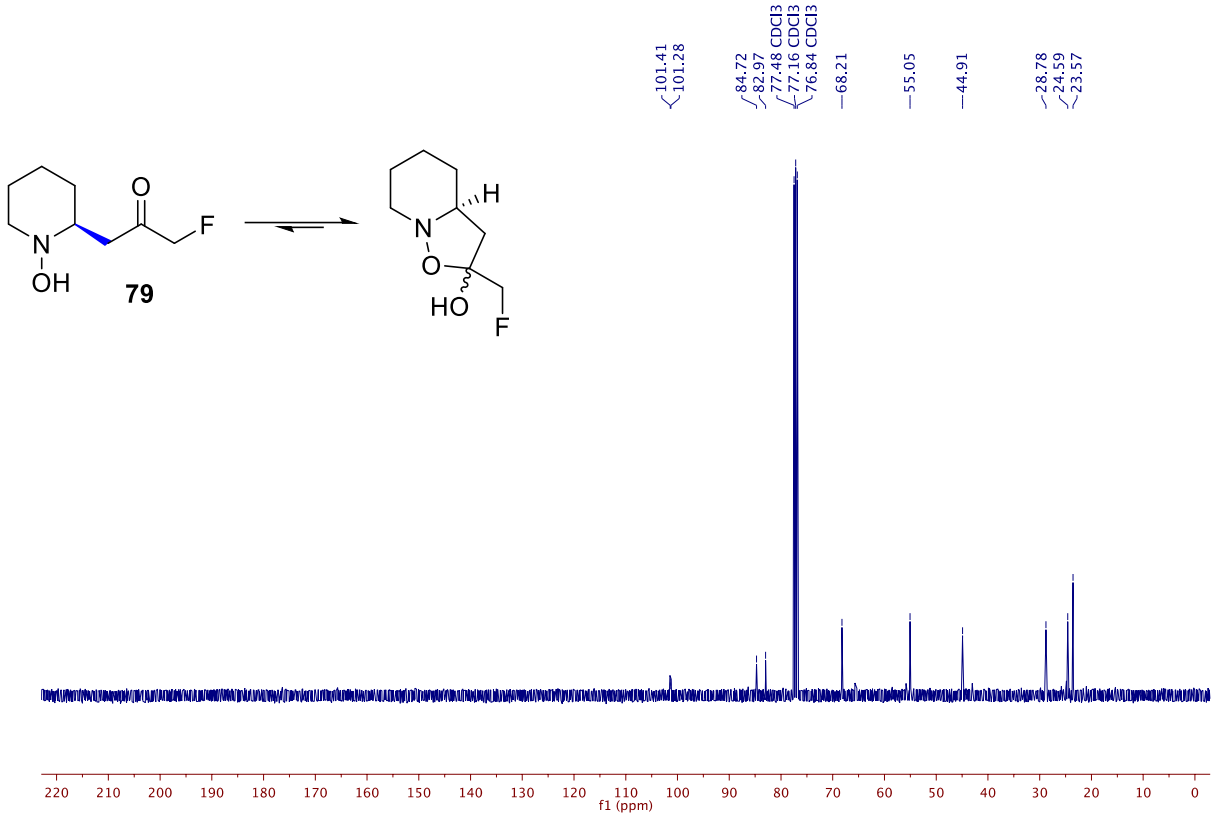

7.99
7.98
7.57
7.56
7.54
7.45
7.43
7.42
7.26
3.57
3.55
3.44
3.02
3.01
2.98
2.97
2.79
2.77
2.75
2.58
2.56
2.54
2.53
1.90
1.88
1.86
1.83
1.79
1.70
1.68
1.58
1.55
1.37
0.92
0.85
0.78
0.77
0.62
O
N
OBz
78'
1.79
0.96
1.92
1.18
0.86
1.08
0.93
1.00
5.16
1.14
1.03
3.18
0.91
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

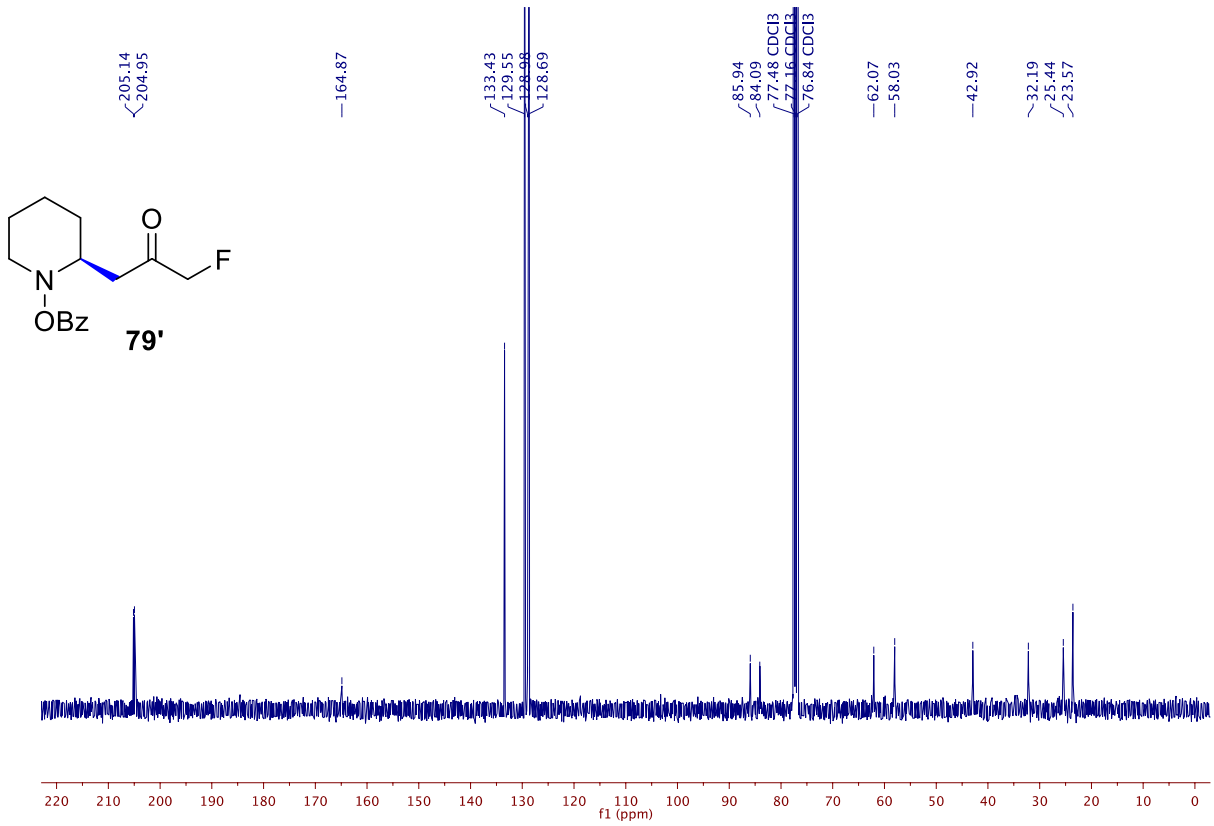

210.46
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
64.32
59.93
48.75
32.29
25.92
23.71
21.08
11.19
11.00
O
N
OH
78
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

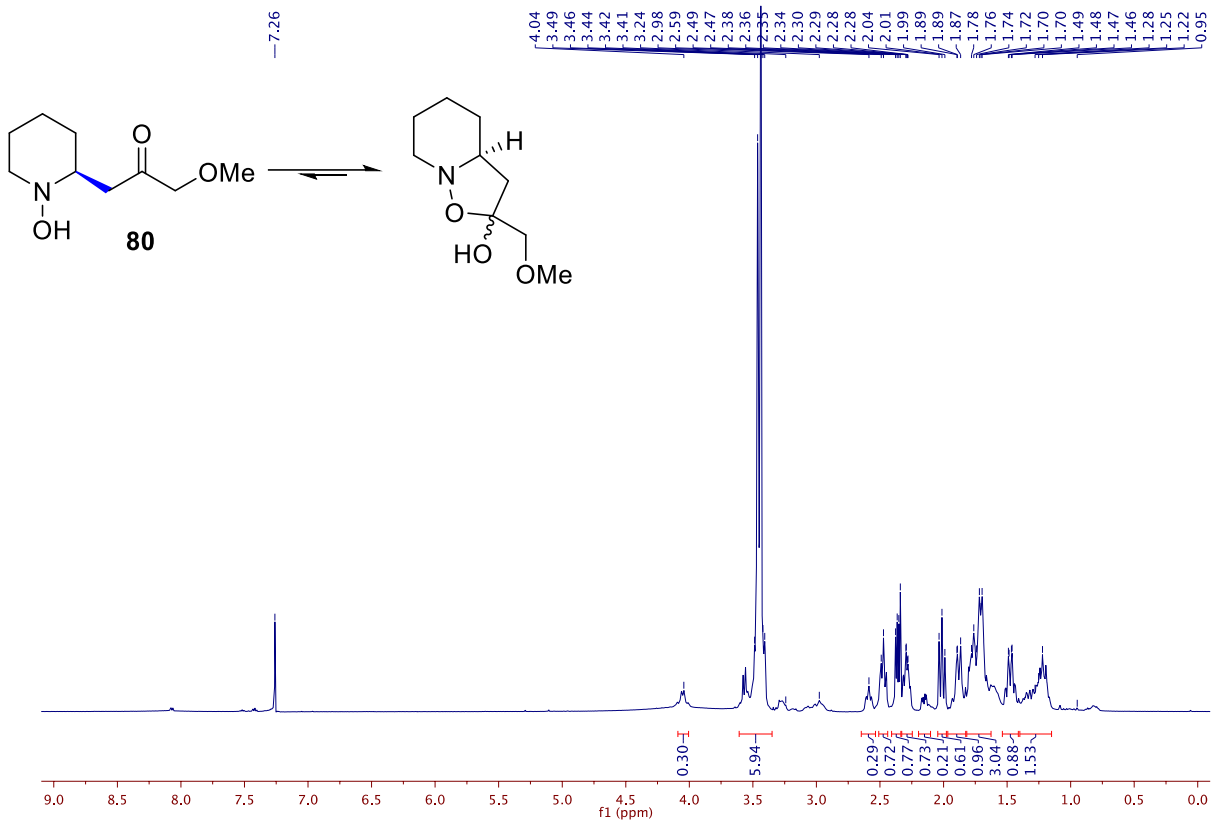

209.23
165.10
133.21
129.66
129.23
128.48
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
62.73
58.08
47.59
32.15
25.52
23.61
21.55
11.11
10.58
O
N
OBz
78'
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.26
4.73
4.37
4.28
3.44
3.42
2.56
2.55
2.53
2.50
2.49
2.39
2.37
2.36
2.34
2.07
2.05
2.03
2.02
1.92
1.89
1.82
1.79
1.73
1.71
1.68
1.51
1.49
1.49
1.47
1.46
1.45
1.27
1.25
1.22
O
F
N
OH
79
H
N
O
HO
F
0.61
2.06
1.00
1.96
1.02
0.89
1.14
3.43
1.19
1.32
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


7.97
7.95
7.59
7.57
7.56
7.46
7.44
7.43
7.26
4.69
4.59
3.60
3.58
3.49
2.98
2.97
2.94
2.94
2.76
2.54
2.53
2.53
2.52
2.50
2.50
2.49
2.49
1.89
1.86
1.83
1.81
1.73
1.71
1.62
1.59
1.39
1.37
1.25
O
F
N
OBz
79'
2.06
1.10
2.24
2.31
1.22
1.02
1.26
1.00
1.25
3.47
1.22
1.47
1.06
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


101.41
101.28
84.72
82.97
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
68.21
55.05
44.91
28.78
24.59
23.57
O
F
N
OH
79
H
N
O
HO
F
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


205.14
204.95
164.87
133.43
129.55
128.98
128.69
85.94
84.09
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
62.07
58.03
42.92
32.19
25.44
23.57
O
F
N
OBz
79'
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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4.04
3.49
3.46
3.44
3.42
3.41
3.24
2.98
2.59
2.49
2.47
2.38
2.36
2.35
2.34
2.30
2.29
2.28
2.04
2.01
1.99
1.89
1.89
1.87
1.78
1.76
1.74
1.72
1.70
1.70
1.49
1.48
1.47
1.46
1.28
1.25
1.22
0.95
O
OMe
N
OH
80
H
N
O
HO
OMe
0.30
5.94
0.29
0.72
0.77
0.73
0.21
0.61
0.96
3.04
0.88
1.53
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


7.98
7.96
7.58
7.56
7.55
7.45
7.44
7.43
7.26
3.88
3.84
3.81
3.78
3.59
3.57
3.49
3.33
3.17
2.91
2.89
2.87
2.86
2.77
2.75
2.73
2.42
2.41
2.39
2.38
1.87
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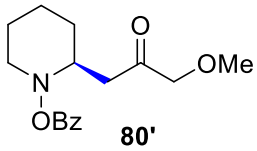
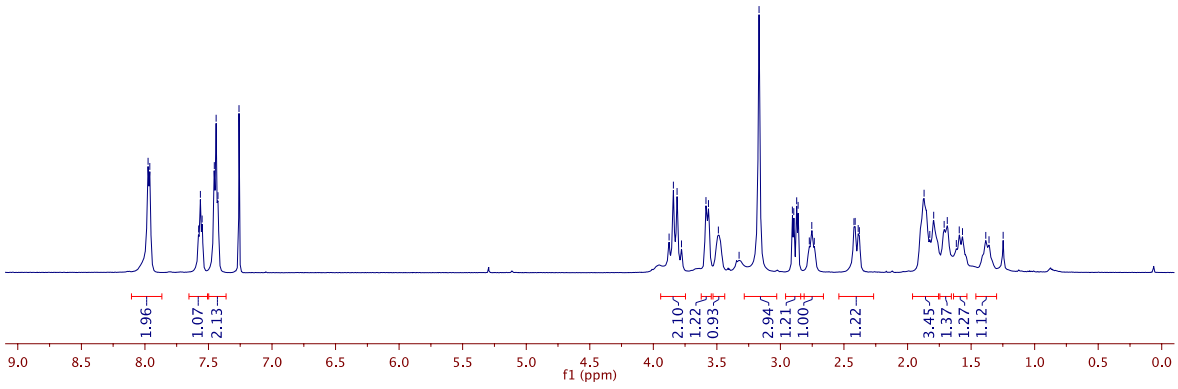
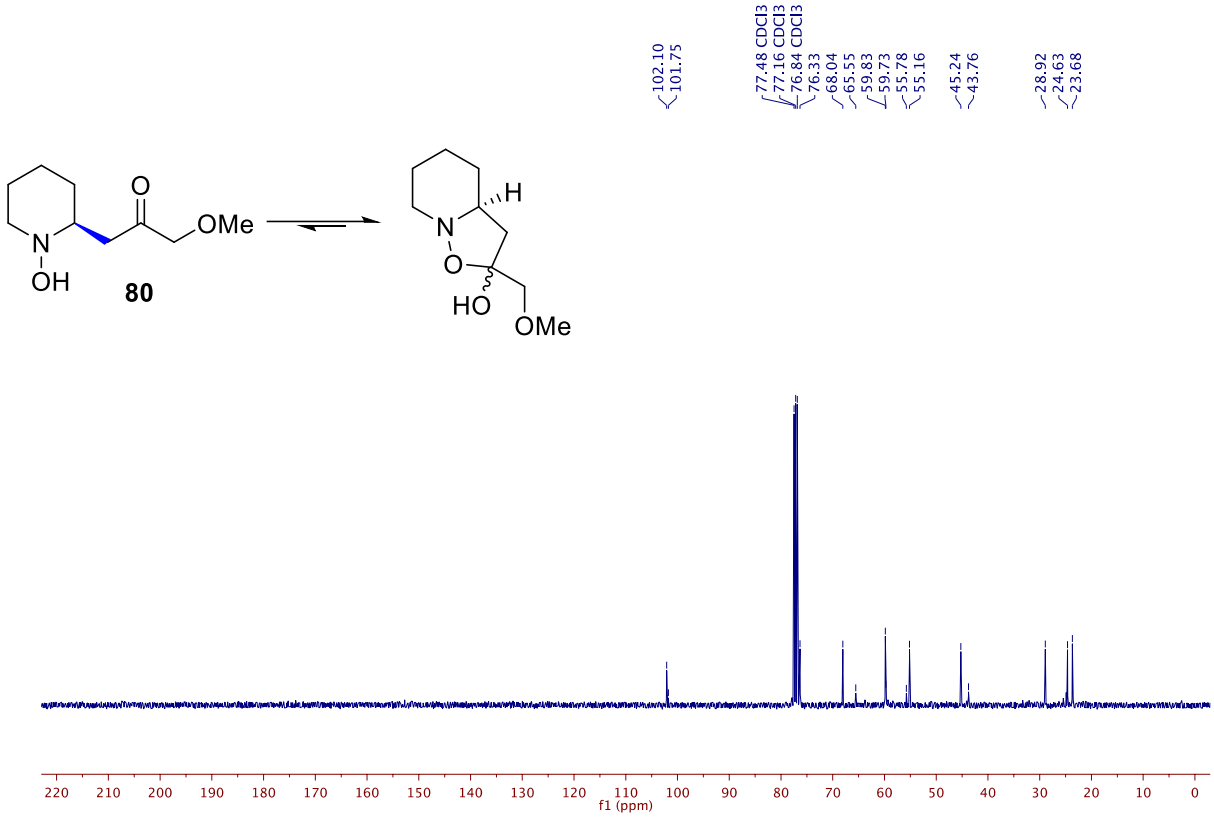
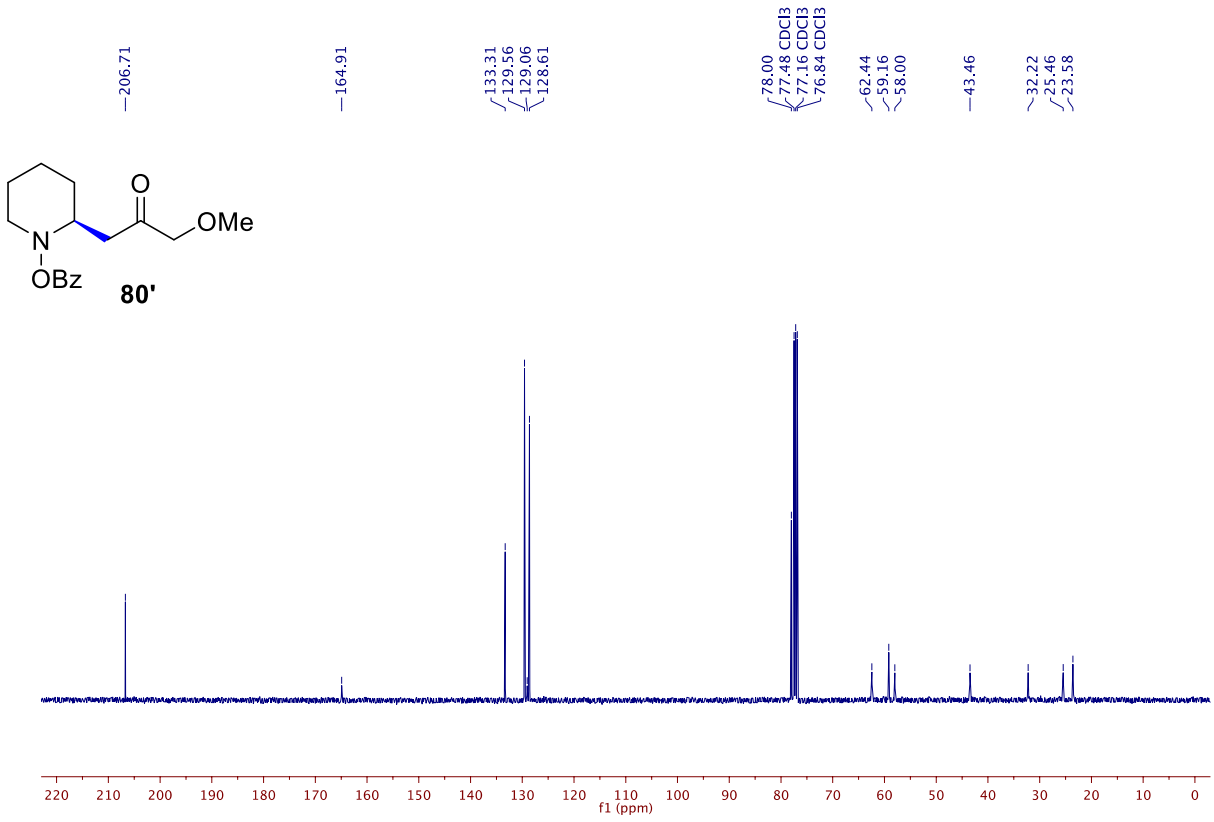
1.62
1.59
1.57
1.38
1.36
1.25


O
OMe
N
OBz
80'


1.96
1.07
2.13
2.10
1.22
0.93
2.94
1.21
1.00
1.22
3.45
1.37
1.27
1.12
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


102.10
101.75
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
76.33
68.04
65.55
59.83
59.73
55.78
55.16
45.24
43.76
28.92
24.63
23.68
O
OMe
N
OH
80
H
N
O
HO
OMe
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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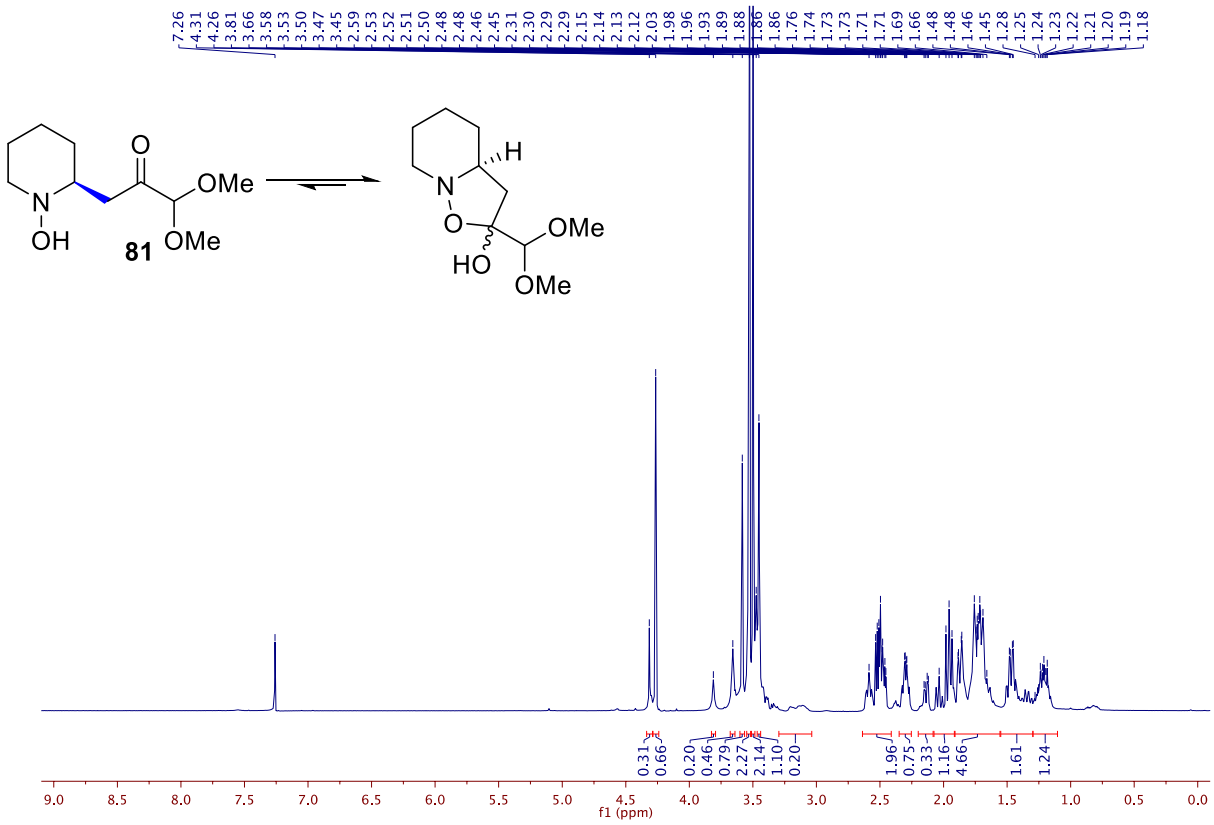
164.91
133.31
129.56
129.06
128.61
78.00
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
62.44
59.16
58.00
43.46
32.22
25.46
23.58
O
OMe
N
OBz
80'
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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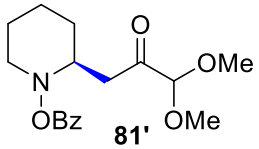
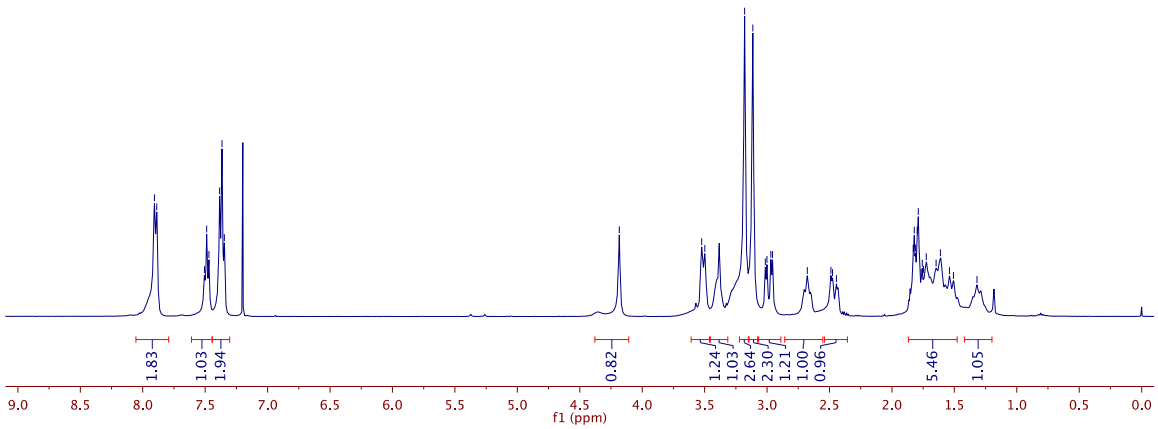
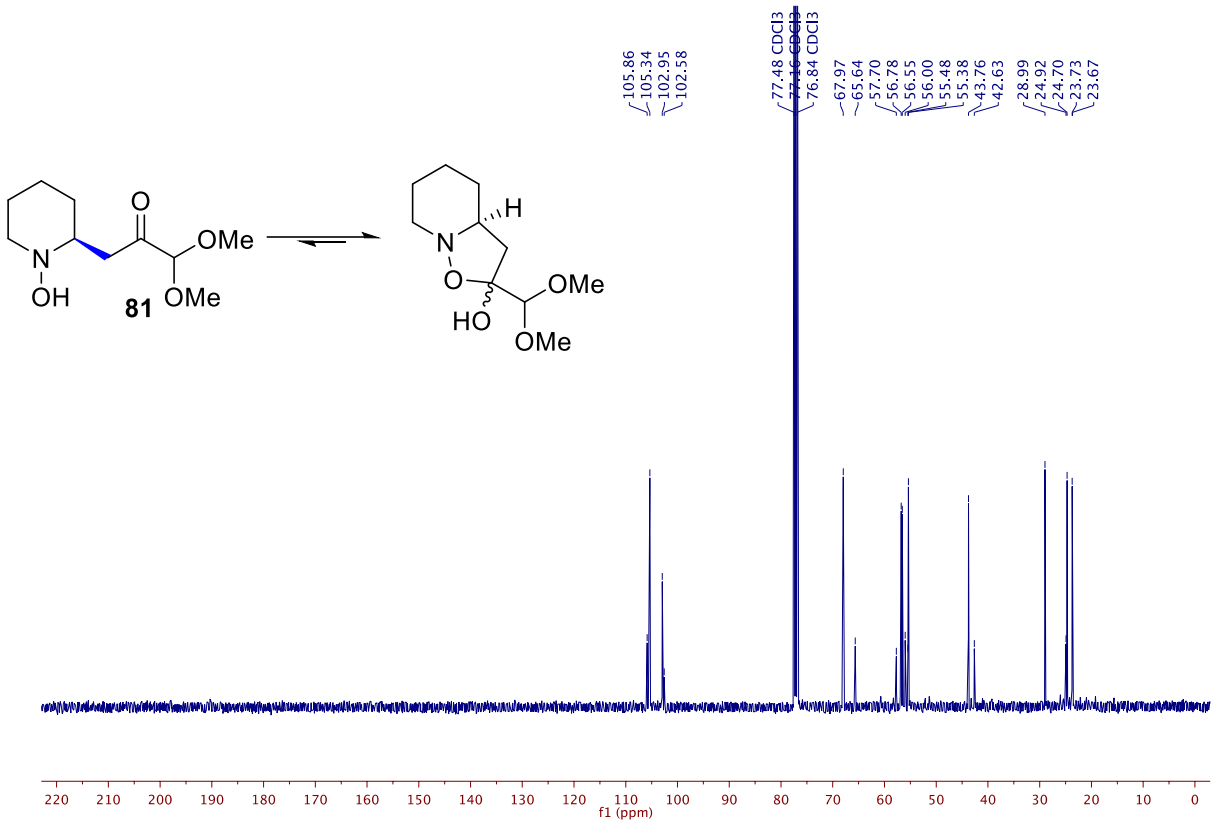
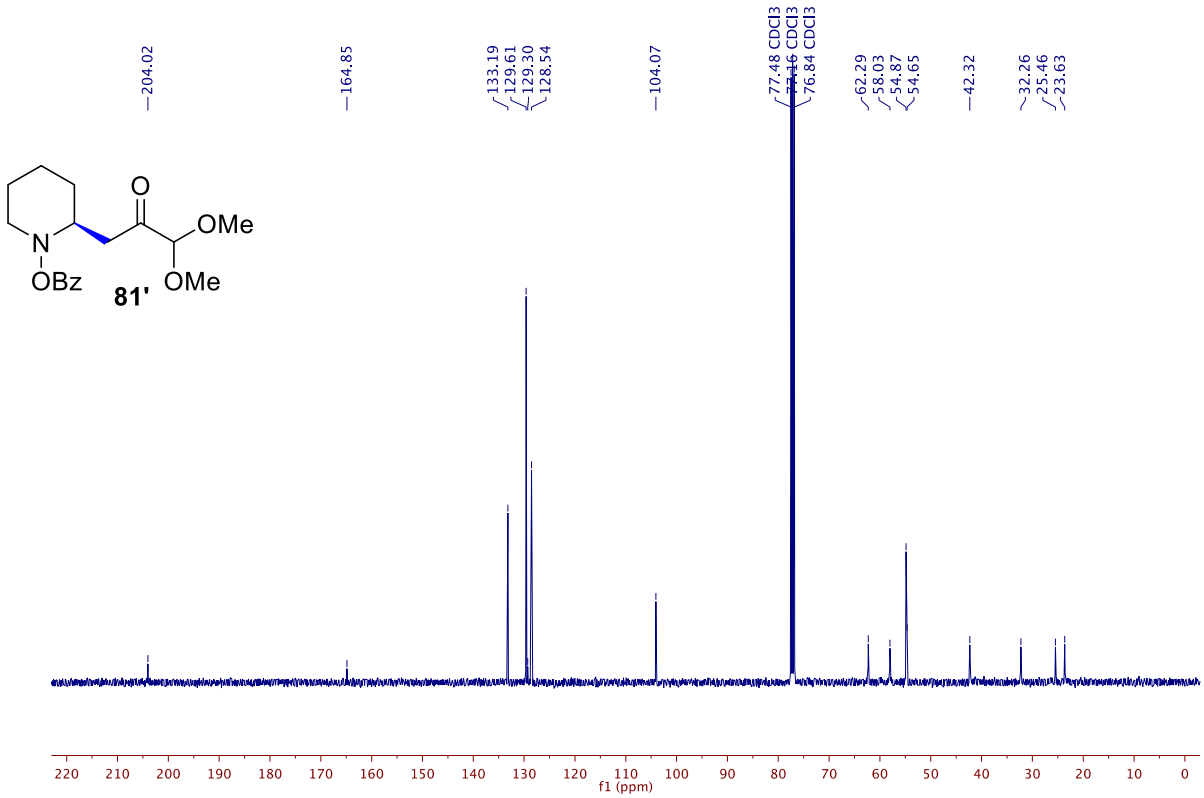
4.26
3.81
3.66
3.58
3.53
3.50
3.47
3.45
3.59
2.53
2.52
2.51
2.50
2.48
2.48
2.46
2.45
2.31
2.30
2.29
2.29
2.15
2.14
2.13
2.12
2.03
1.98
1.96
1.93
1.89
1.88
1.86
1.86
1.76
1.74
1.73
1.73
1.71
1.71
1.69
1.66
1.48
1.48
1.46
1.45
1.28
1.25
1.24
1.23
1.22
1.21
1.20
1.19
1.18
O
OMe
N
OH
OMe
81
H
N
O
HO
OMe
OMe
0.31
0.66
0.20
0.46
0.79
2.27
2.14
1.10
0.20
1.96
0.75
0.33
1.16
4.66
1.61
1.24
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

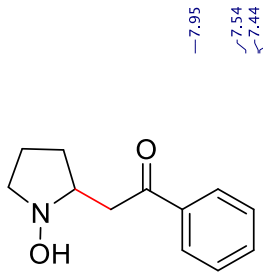

7.91
7.89
7.51
7.49
7.47
7.38
7.37
7.35
4.18
3.52
3.50
3.18
3.11
3.01
3.00
2.97
2.96
2.68
2.49
2.48
2.44
1.83
1.82
1.81
1.80
1.79
1.77
1.76
1.75
1.72
1.65
1.61
1.54
1.51
1.32


O
OMe
N
OBz
OMe
81'

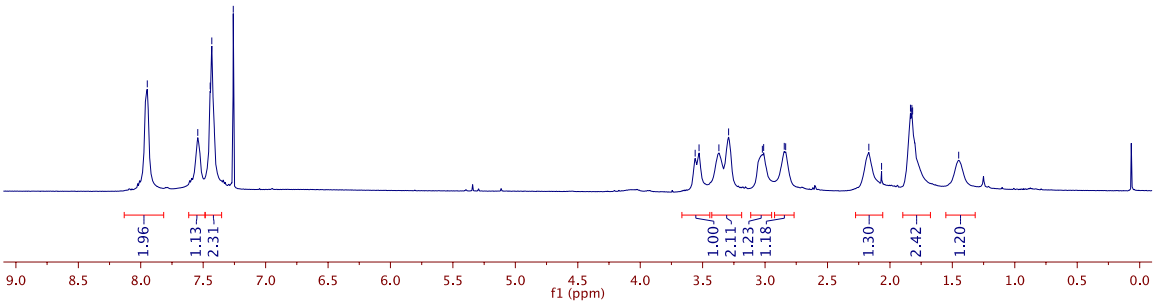

1.83
1.03
1.94
0.82
1.24
1.03
2.64
2.30
1.21
1.00
0.96
5.46
1.05
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

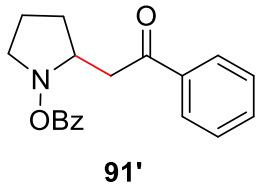

105.86
105.34
102.95
102.58
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
67.97
65.64
57.70
56.78
56.55
56.00
55.48
55.38
43.76
42.63
28.99
24.92
24.70
23.73
23.67
O
OMe
N
OH
OMe
81
H
N
O
HO
OMe
OMe
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


204.02
164.85
133.19
129.61
129.30
128.54
104.07
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
62.29
58.03
54.87
54.65
42.32
32.26
25.46
23.63
O
OMe
N
OBz
OMe
81'
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

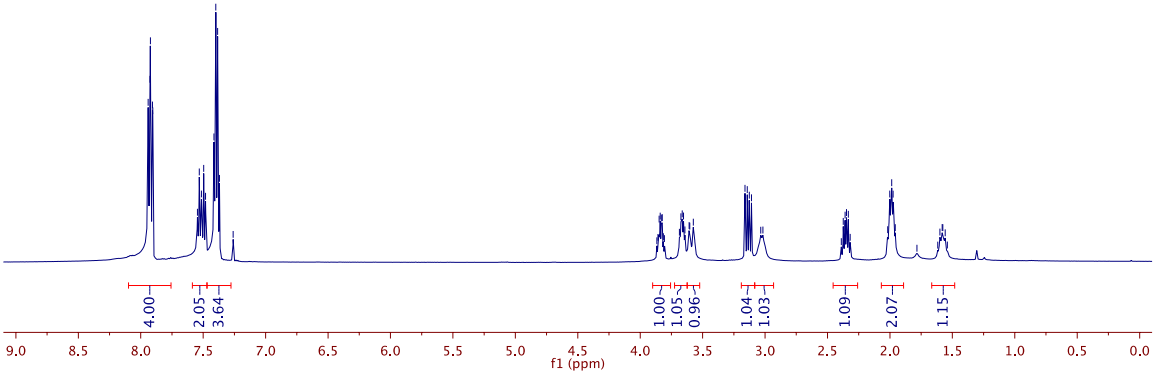


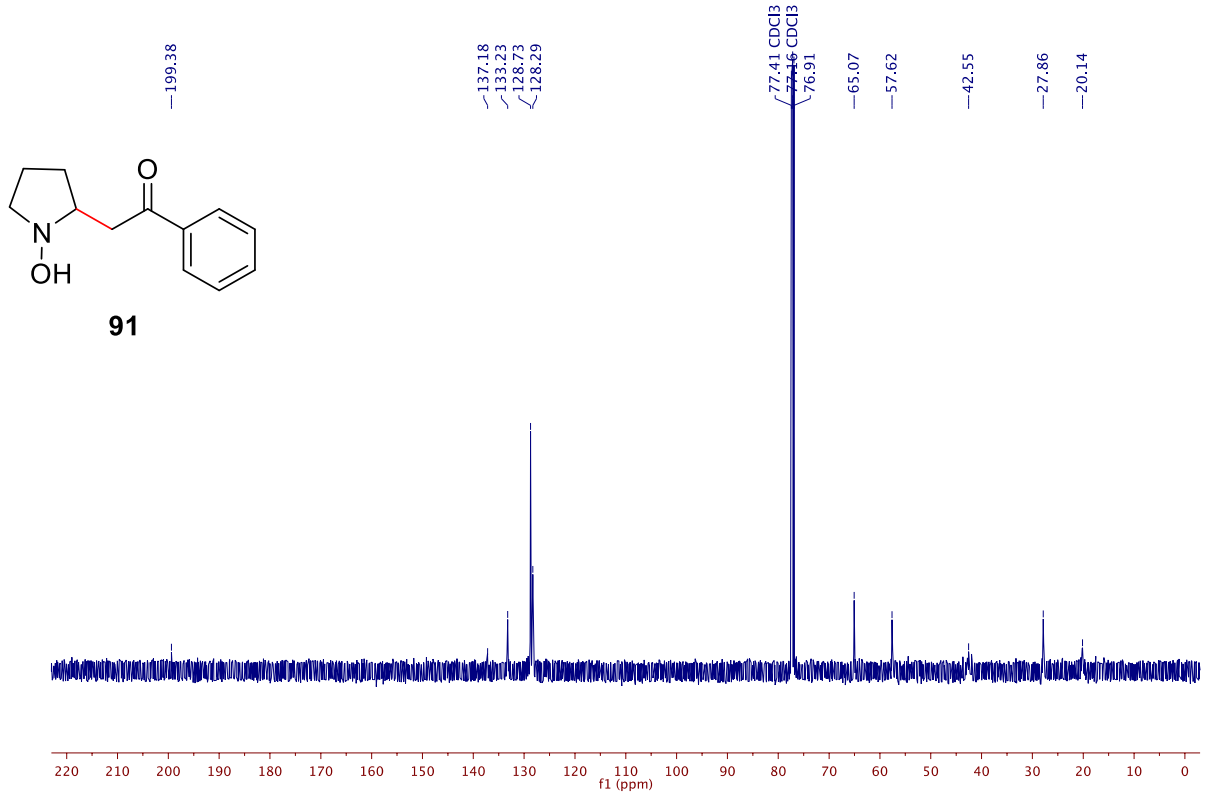
91

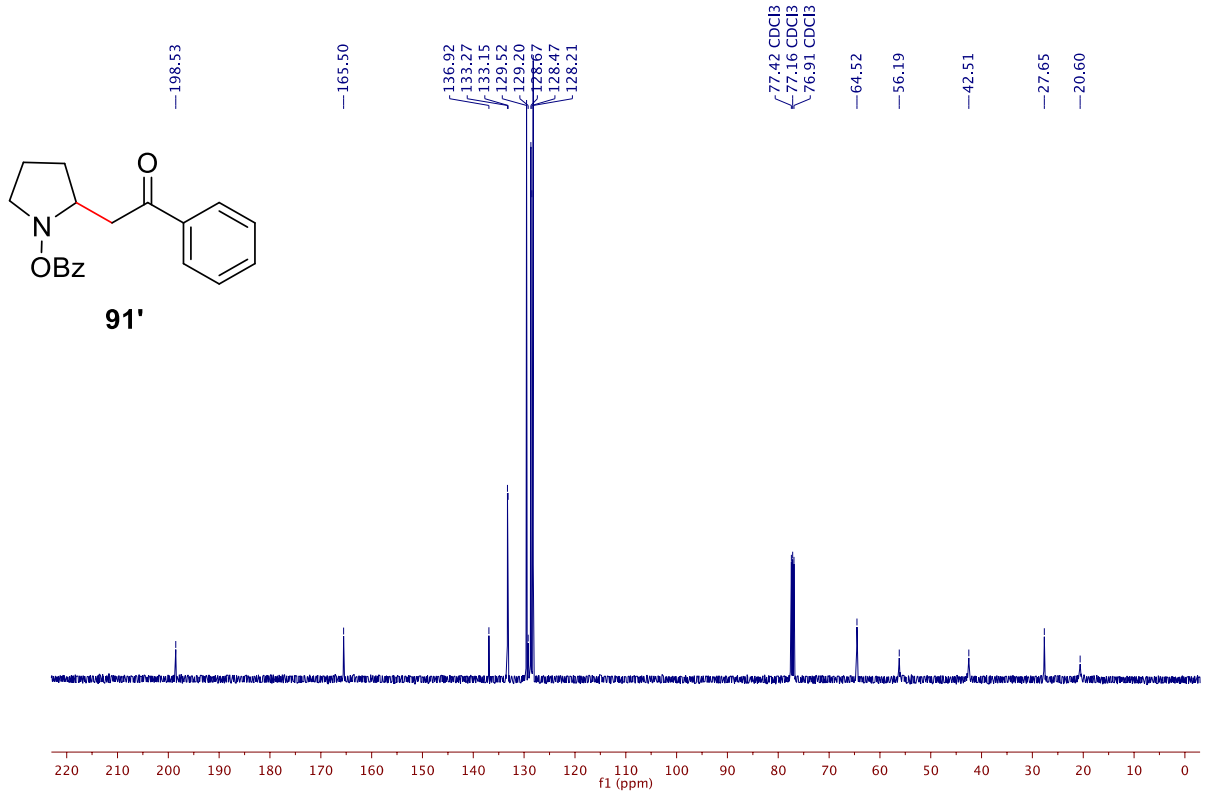


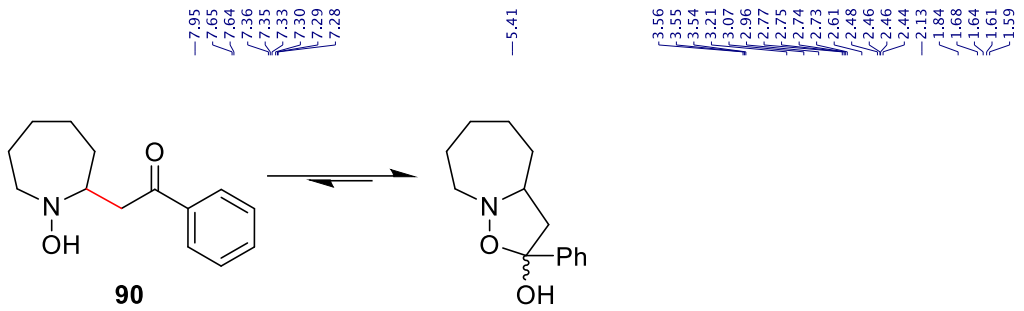


91'

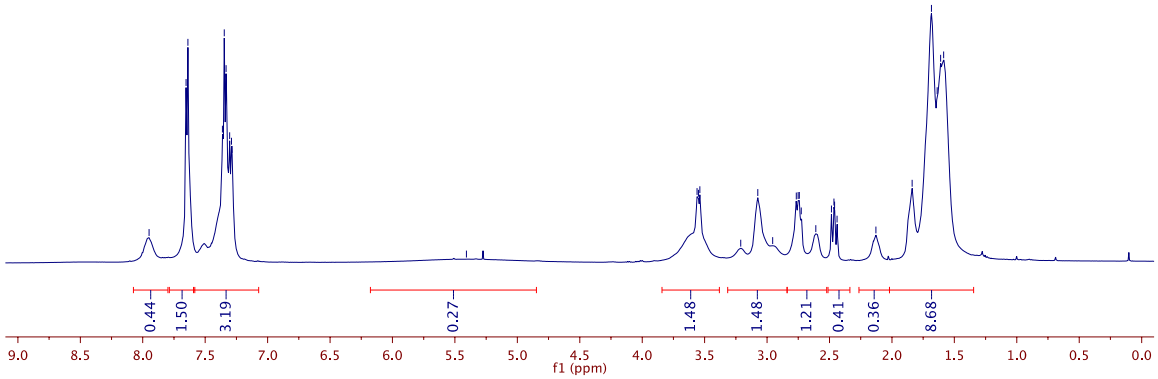



199.38
137.18
133.23
128.73
128.29
77.41 CDCl3
77.16 CDCl3
76.91
65.07
57.62
42.55
27.86
20.14
O
N
OH
91
f1 (ppm)

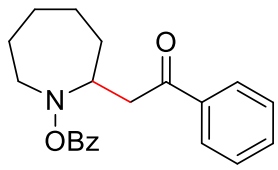

198.53
165.50
136.92
133.27
133.15
129.52
129.20
128.67
128.47
128.21
77.42 CDCl3
77.16 CDCl3
76.91 CDCl3
64.52
56.19
42.51
27.65
20.60
O
N
OBz
91'
f1 (ppm)


7.95
7.65
7.64
7.36
7.35
7.33
7.30
7.29
7.28
5.41
3.56
3.55
3.54
3.21
3.07
2.96
2.77
2.75
2.74
2.73
2.61
2.48
2.46
2.46
2.44
2.13
1.84
1.68
1.64
1.61
1.59
O
N
OH
N
O
Ph
OH

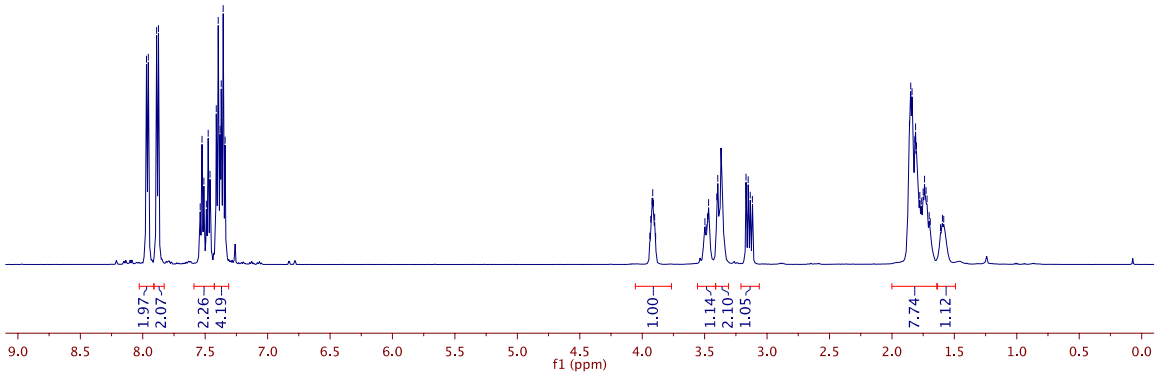
90

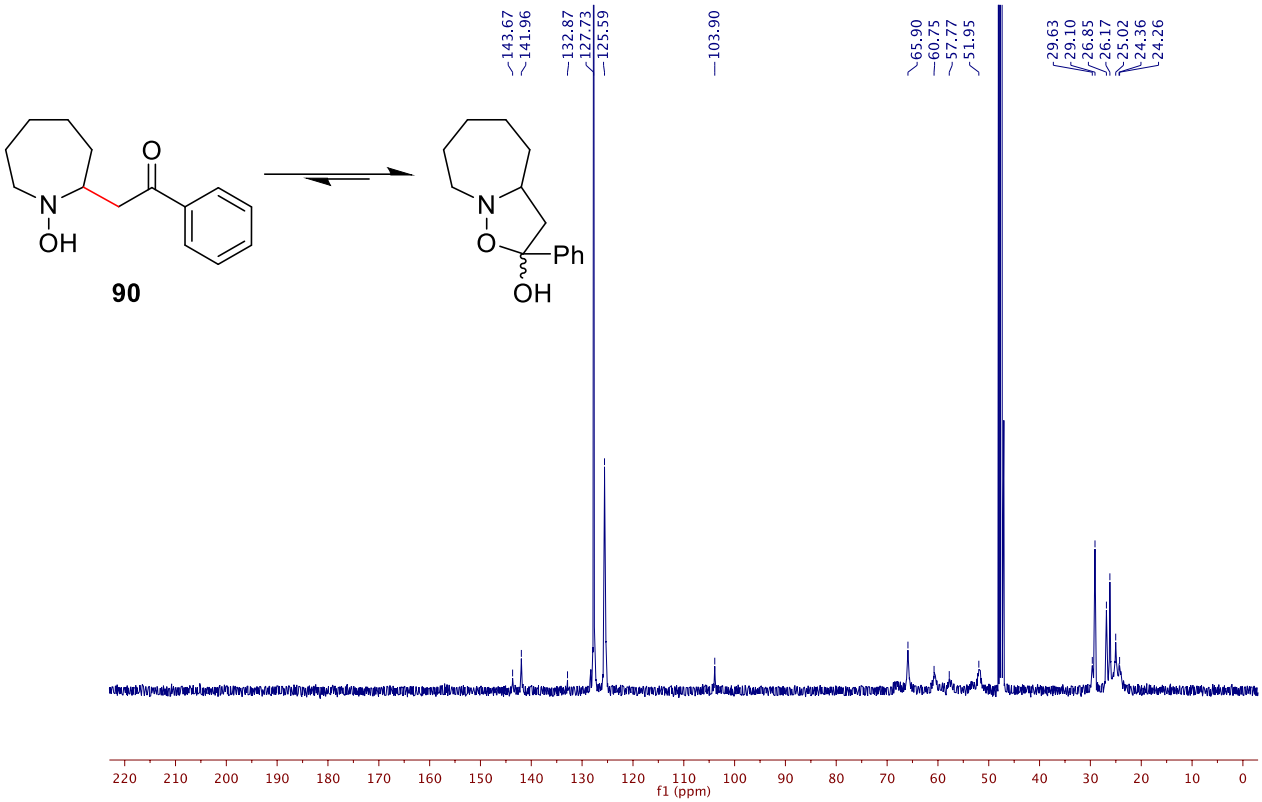

0.44
1.50
3.19
0.27
1.48
1.48
1.21
0.41
0.36
8.68
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


7.97
7.96
7.89
7.87
7.54
7.53
7.51
7.49
7.48
7.46
7.41
7.40
7.38
7.37
7.36
7.34
3.94
3.93
3.92
3.92
3.91
3.90
3.89
3.50
3.49
3.48
3.47
3.40
3.39
3.17
3.15
3.13
3.12
1.86
1.85
1.84
1.82
1.81
1.80
1.78
1.76
1.75
1.74
1.73
1.72
1.70
1.69
1.61
1.60
1.59

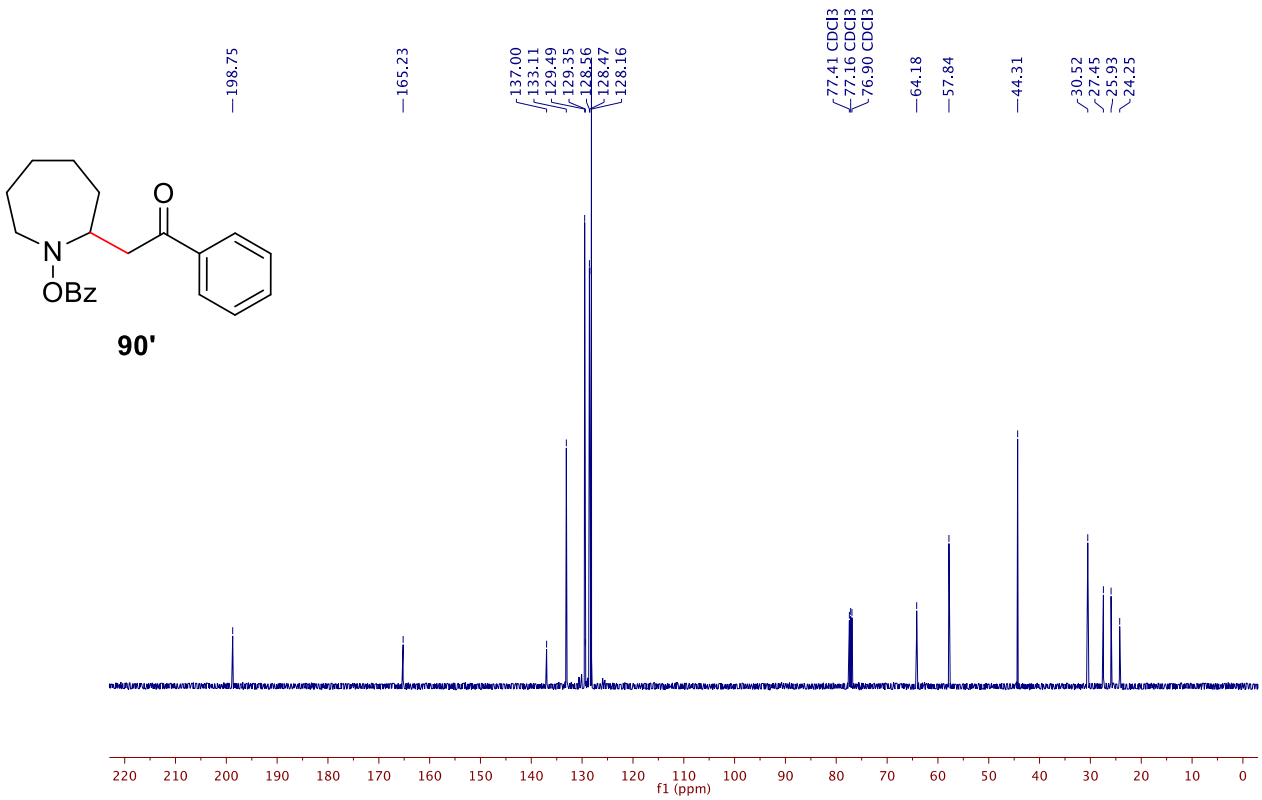

O
N
OBz

90'

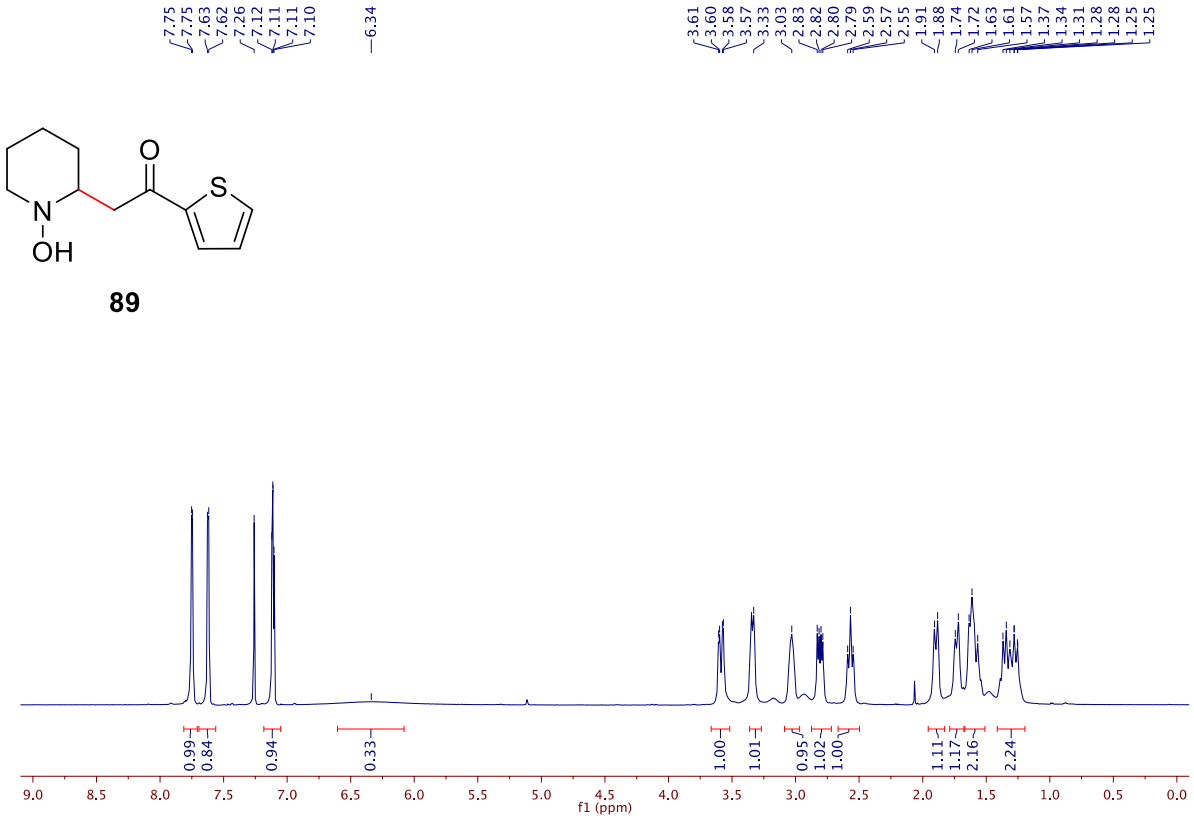

1.97
2.07
2.26
4.19
1.00
1.14
2.10
1.05
7.74
1.12
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

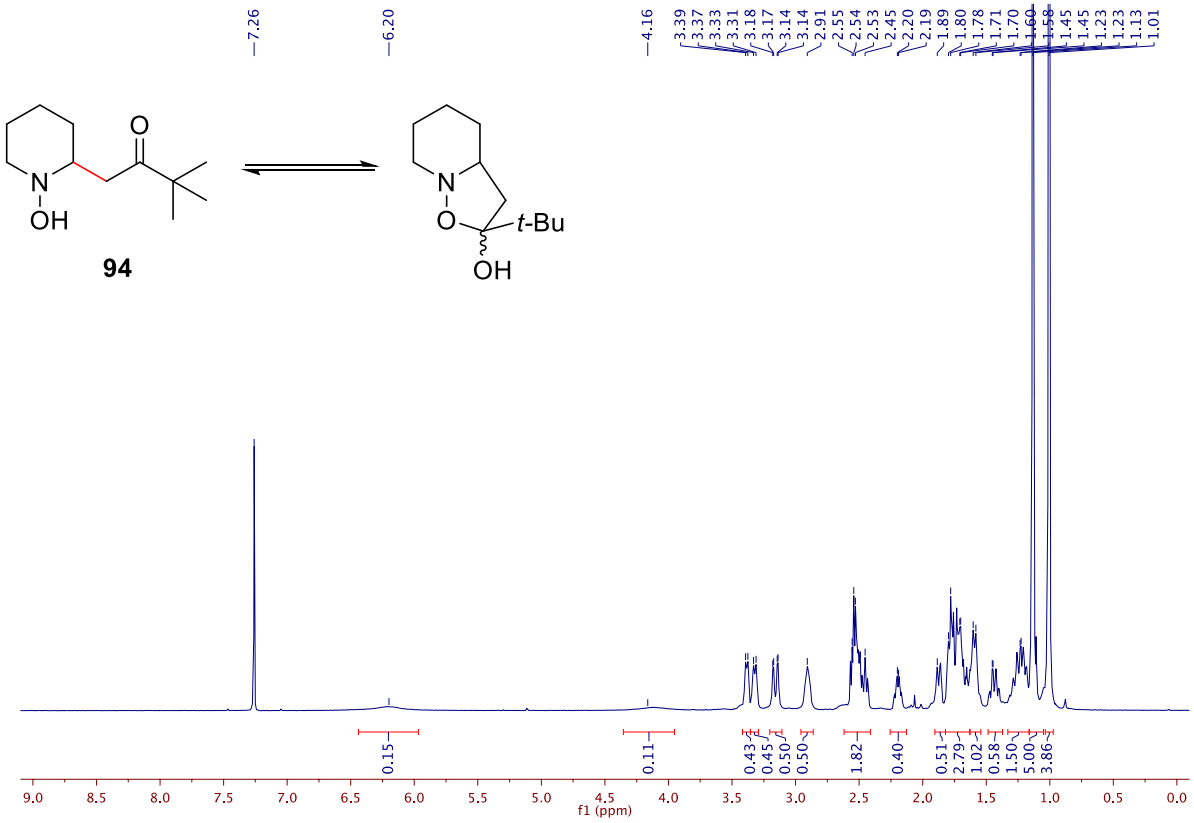

143.67
141.96
132.87
127.73
125.59
103.90
65.90
60.75
57.77
51.95
29.63
29.10
26.85
26.17
25.02
24.36
24.26
O
N
OH
O
N
O
Ph
OH
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

90

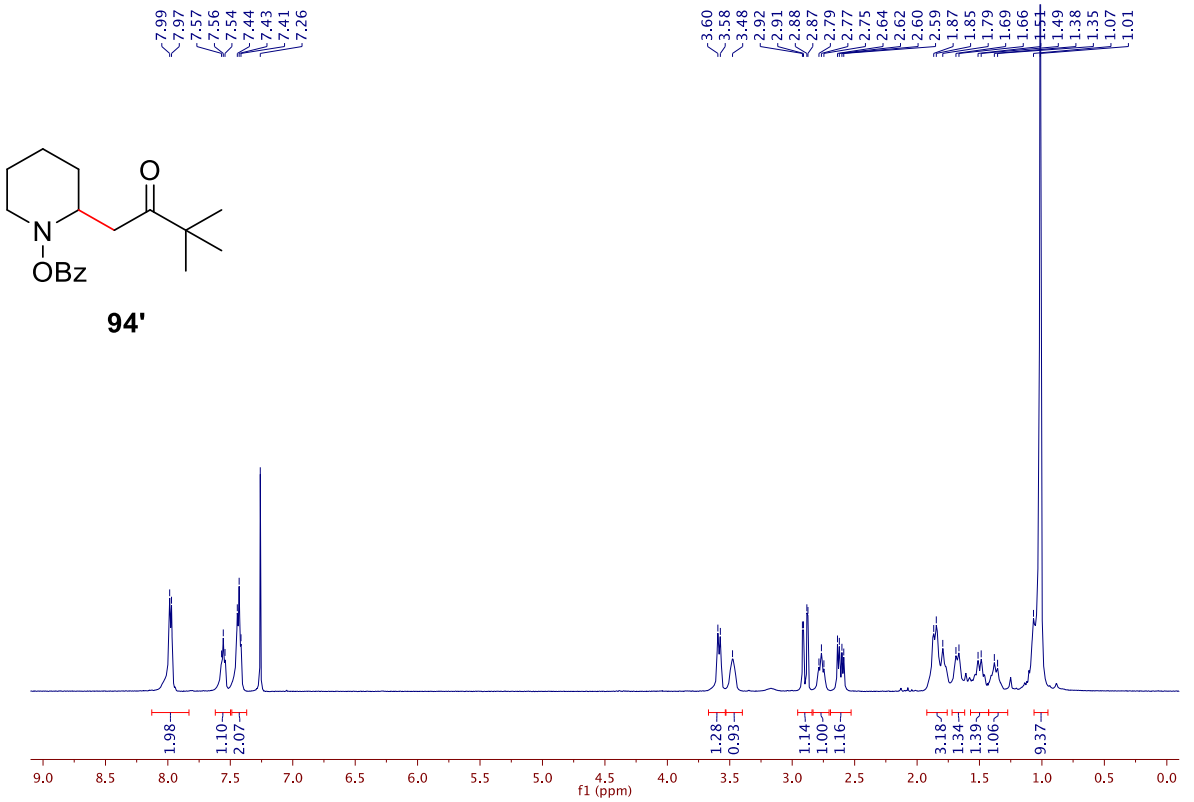

198.75
165.23
137.00
133.11
129.49
129.35
128.56
128.47
128.16
77.41 CDCl3
77.16 CDCl3
76.90 CDCl3
64.18
57.84
44.31
30.52
27.45
25.93
24.25
O
N
OBz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

90'

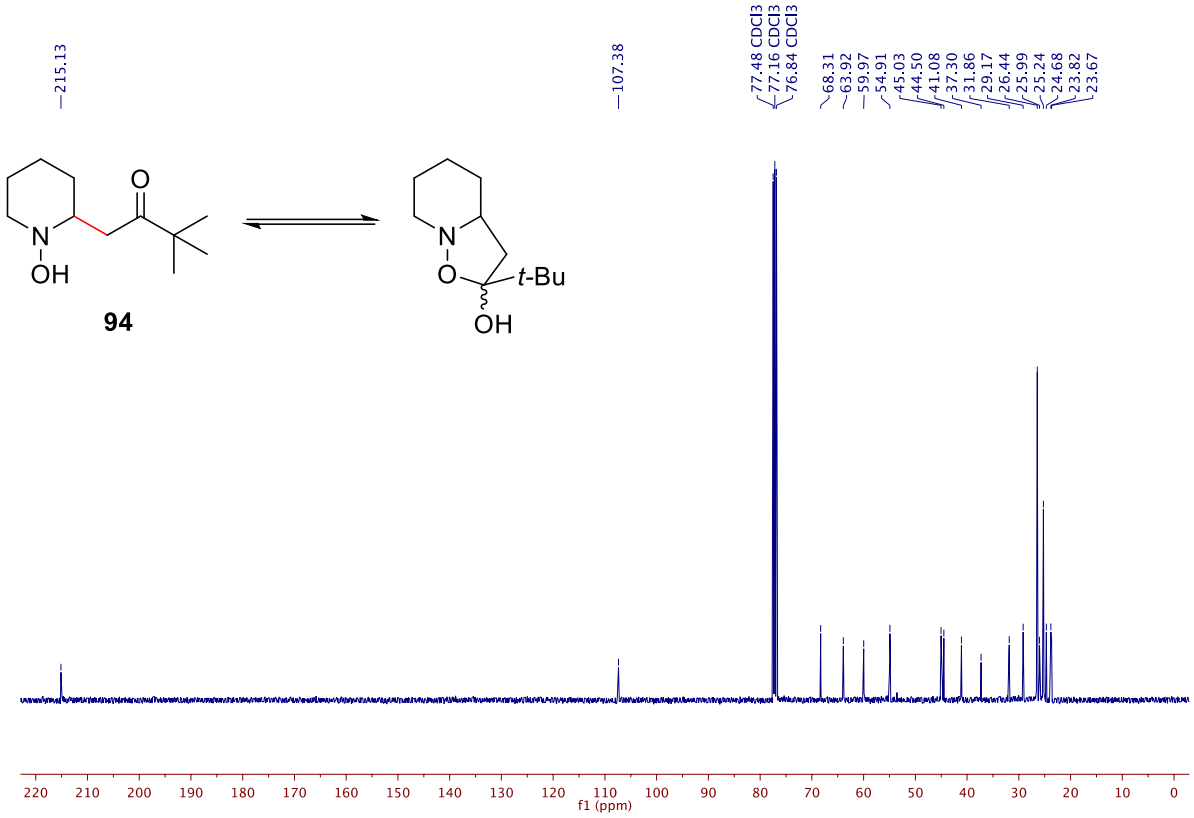

7.75
7.75
7.63
7.62
7.26
7.12
7.11
7.11
7.10
6.34
3.61
3.60
3.58
3.57
3.33
3.03
2.83
2.82
2.80
2.79
2.59
2.57
2.55
1.91
1.88
1.74
1.72
1.63
1.61
1.57
1.37
1.34
1.31
1.28
1.28
1.25
1.25
O
S
N
OH
89
0.99
0.84
0.94
0.33
1.00
1.01
0.95
1.02
1.00
1.11
1.17
2.16
2.24
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
192.29
144.86
133.82
132.32
128.23
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
64.92
59.94
44.32
32.20
25.89
23.59
O
S
N
OH
89
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

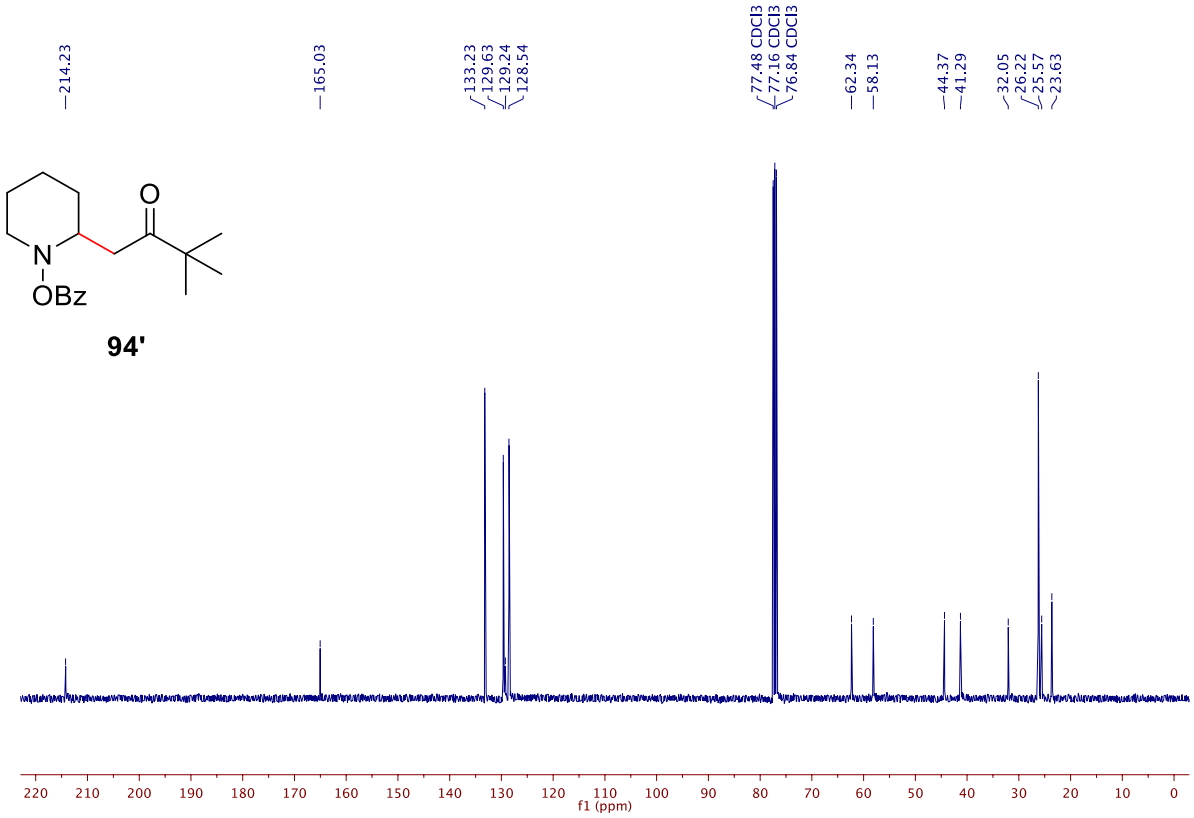

7.26
6.20
4.16
3.39
3.37
3.33
3.31
3.18
3.17
3.14
3.14
2.91
2.55
2.54
2.53
2.45
2.20
2.19
1.89
1.80
1.78
1.71
1.70
1.60
1.58
1.45
1.45
1.23
1.23
1.13
1.01
O
N
OH
O
N
O
t-Bu
OH
0.15
0.11
0.43
0.45
0.50
0.50
1.82
0.40
0.51
2.79
1.02
0.58
1.50
5.00
3.86
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

94

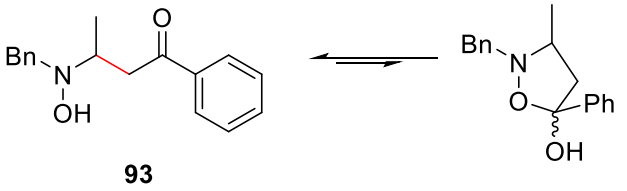

7.99
7.97
7.57
7.56
7.54
7.44
7.43
7.41
7.26
3.60
3.58
3.48
2.92
2.91
2.88
2.87
2.79
2.77
2.75
2.64
2.62
2.60
2.59
1.87
1.85
1.79
1.69
1.66
1.51
1.49
1.38
1.35
1.07
1.01
O
N
OBz
1.98
1.10
2.07
1.28
0.93
1.14
1.00
1.16
3.18
1.34
1.39
1.06
9.37
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

94'

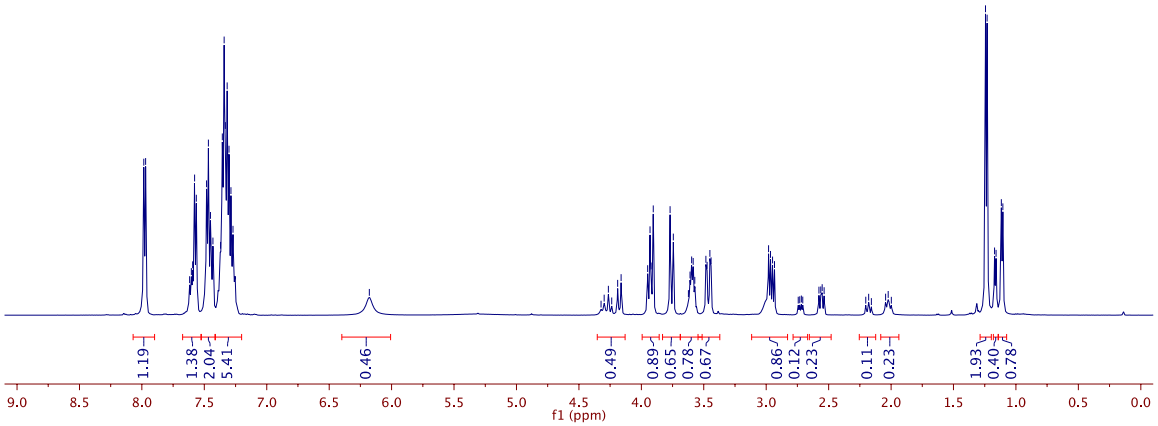

215.13
107.38
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
68.31
63.92
59.97
54.91
45.03
44.50
41.08
37.30
31.86
29.17
26.44
25.99
25.24
24.68
23.82
23.67
O
N
OH
94
N
O
t-Bu
OH
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

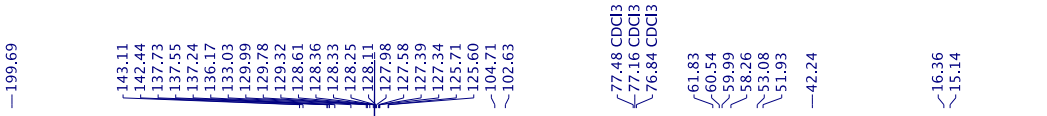

214.23
165.03
133.23
129.63
129.24
128.54
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
62.34
58.13
44.37
41.29
32.05
26.22
25.57
23.63
O
N
OBz
94'
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

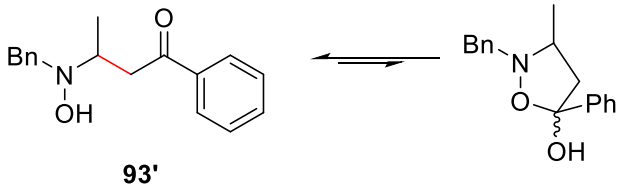

7.98
7.97
7.62
7.60
7.59
7.58
7.56
7.48
7.47
7.45
7.43
7.37
7.36
7.34
7.33
7.32
7.30
7.29
7.27
6.18
4.30
4.26
4.19
4.16
3.95
3.93
3.92
3.90
3.77
3.74
3.62
3.61
3.60
3.58
3.57
3.48
3.47
3.45
3.44
2.98
2.97
2.95
2.93
2.73
2.72
2.58
2.56
2.55
2.54
2.18
2.04
2.02
1.24
1.23
1.17
1.16
1.12
1.10


Bn
N
OH
O
Bn
N
O
Ph
OH

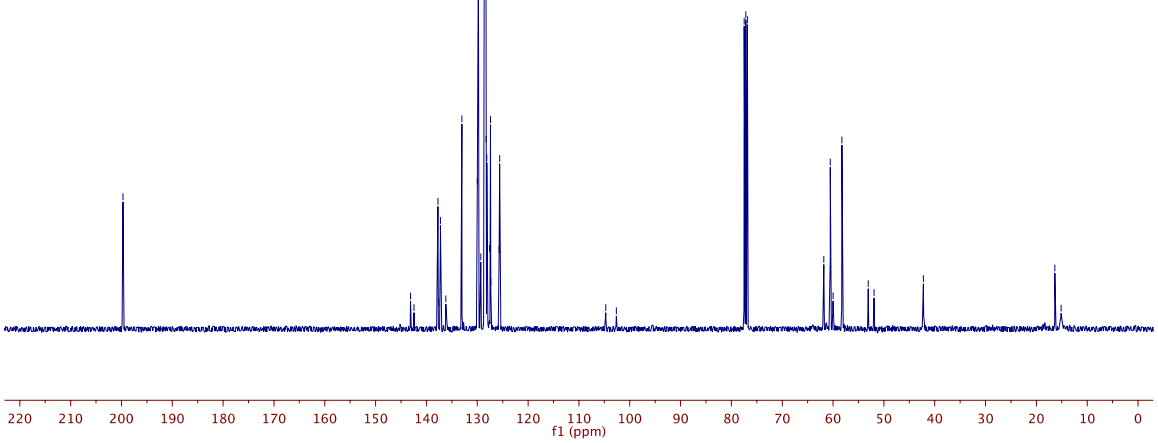
93

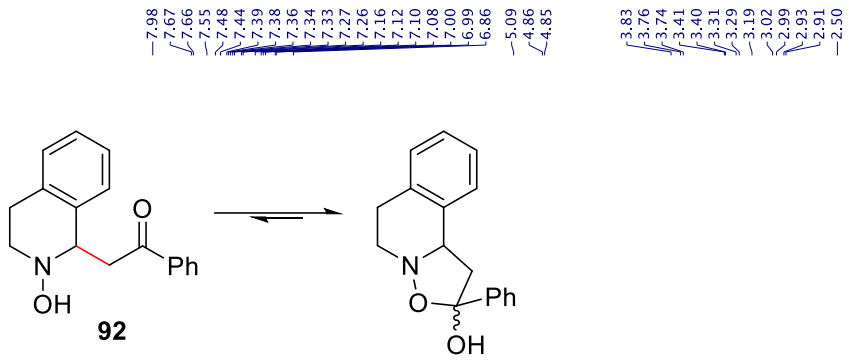

1.19
1.38
2.04
5.41
0.46
0.49
0.89
0.65
0.78
0.67
0.86
0.12
0.23
0.11
0.23
1.93
0.40
0.78
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

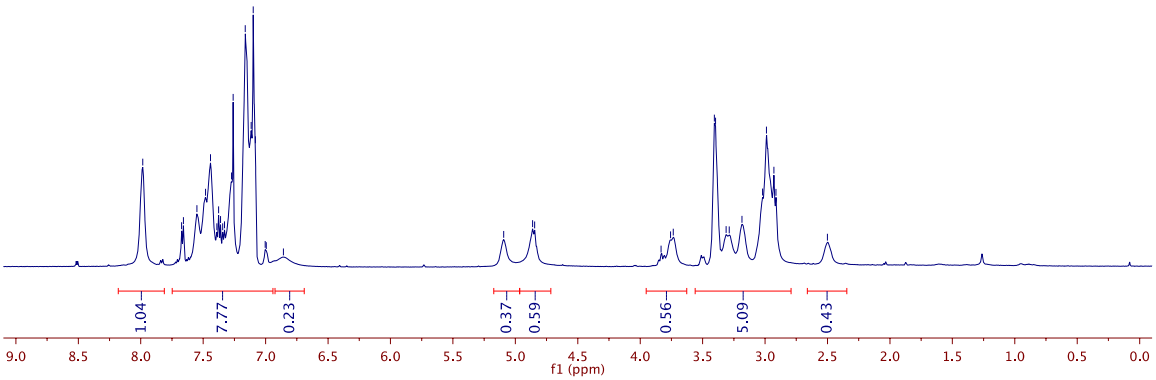

199.69
143.11
142.44
137.73
137.55
137.24
136.17
133.03
129.99
129.78
129.32
128.61
128.36
128.33
128.25
128.11
127.98
127.58
127.39
127.34
125.71
125.60
104.71
102.63
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
61.83
60.54
59.99
58.26
53.08
51.93
42.24
16.36
15.14


Bn
N
OH
O
Bn
N
O
Ph
OH

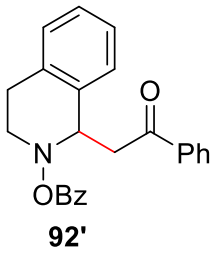
93'

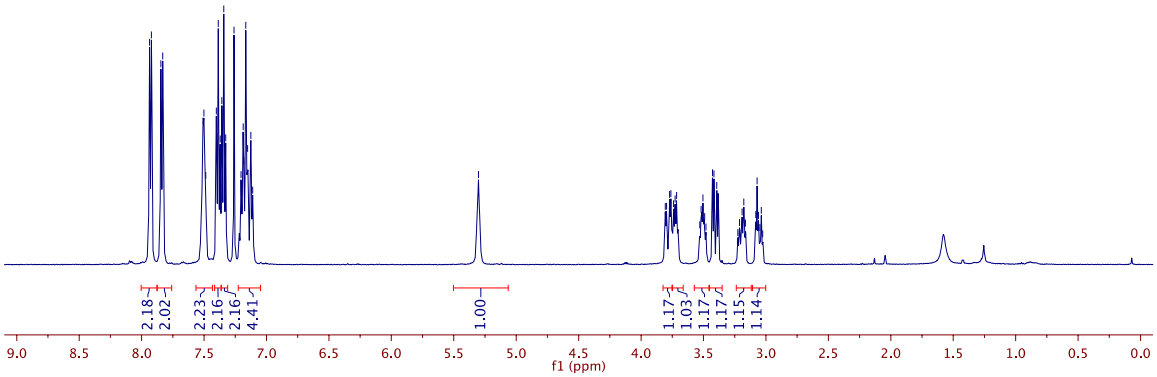

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

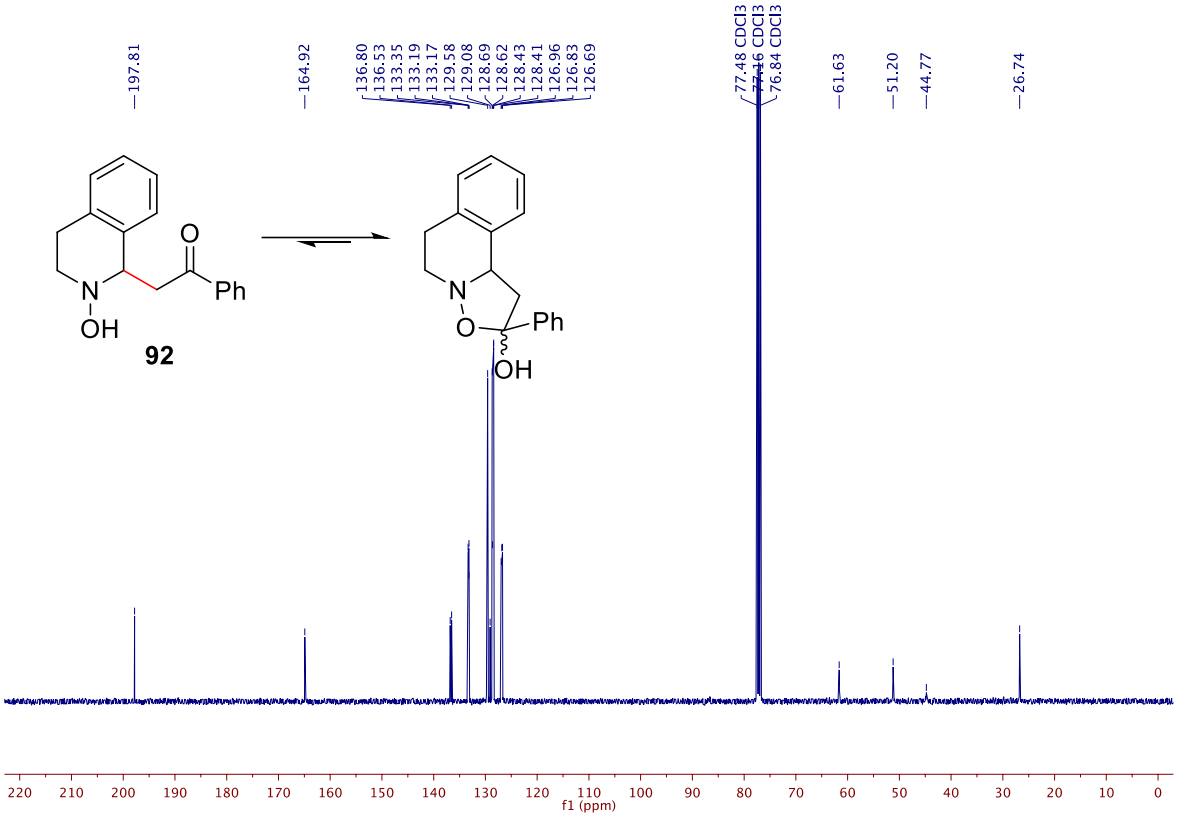

7.98
7.67
7.66
7.55
7.48
7.44
7.39
7.38
7.36
7.34
7.33
7.27
7.26
7.16
7.12
7.10
7.08
7.00
6.99
6.86
5.09
4.86
4.85
3.83
3.76
3.74
3.41
3.40
3.31
3.29
3.19
3.02
2.99
2.93
2.91
2.50
O
Ph
N
OH
92
N
O
Ph
OH


1.04
7.77
0.23
0.37
0.59
0.56
5.09
0.43
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


7.94
7.92
7.85
7.83
7.51
7.50
7.49
7.40
7.39
7.37
7.36
7.34
7.33
7.26
7.20
7.19
7.18
7.17
7.15
7.12
7.11
5.30
3.81
3.80
3.77
3.76
3.74
3.73
3.72
3.53
3.52
3.50
3.49
3.48
3.43
3.42
3.39
3.22
3.21
3.19
3.18
3.16
3.08
3.07
3.06
3.05
3.04
3.03


O
Ph
N
OBz
92'


2.18
2.02
2.23
2.16
2.16
4.41
1.00
1.17
1.03
1.17
1.17
1.15
1.14
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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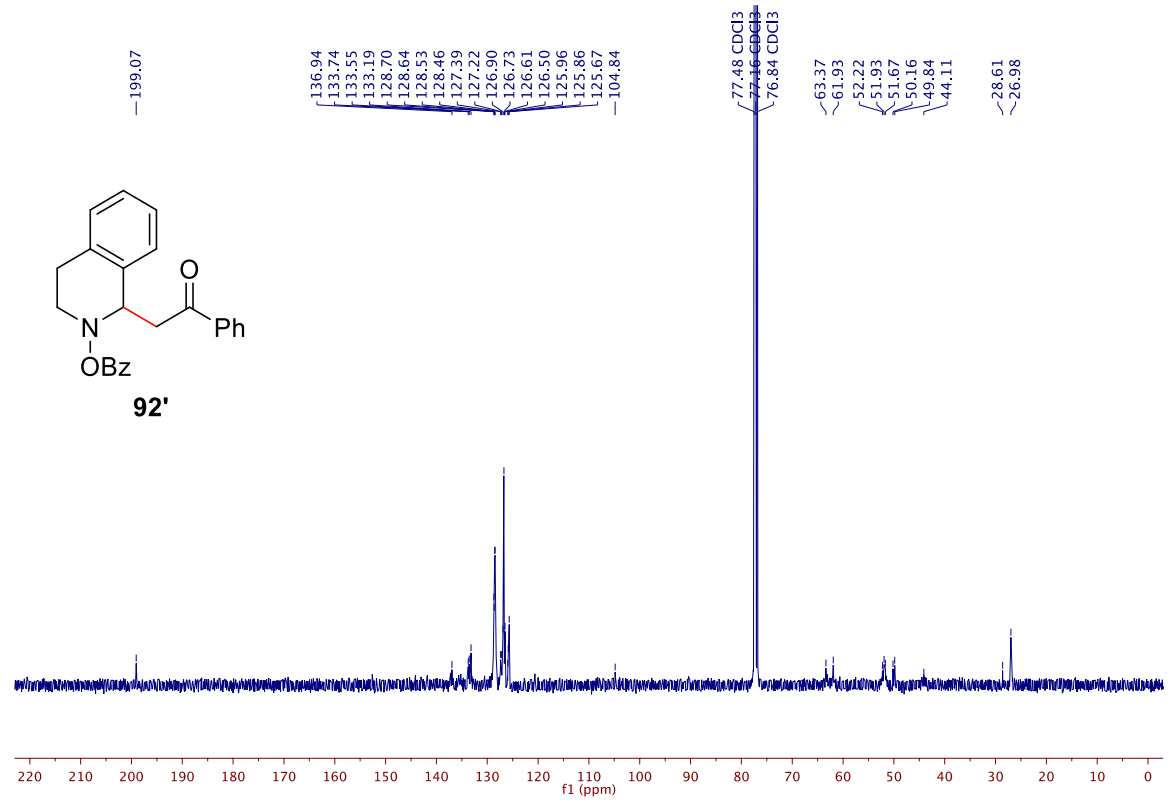
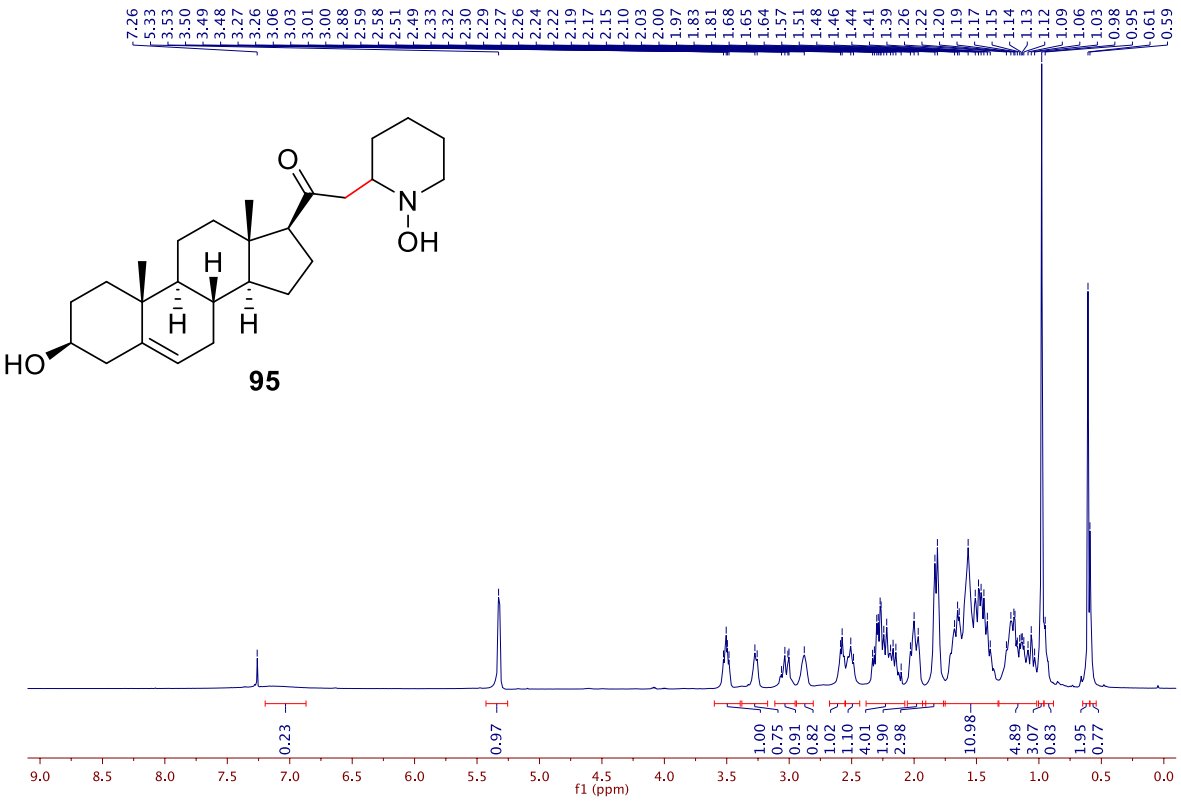
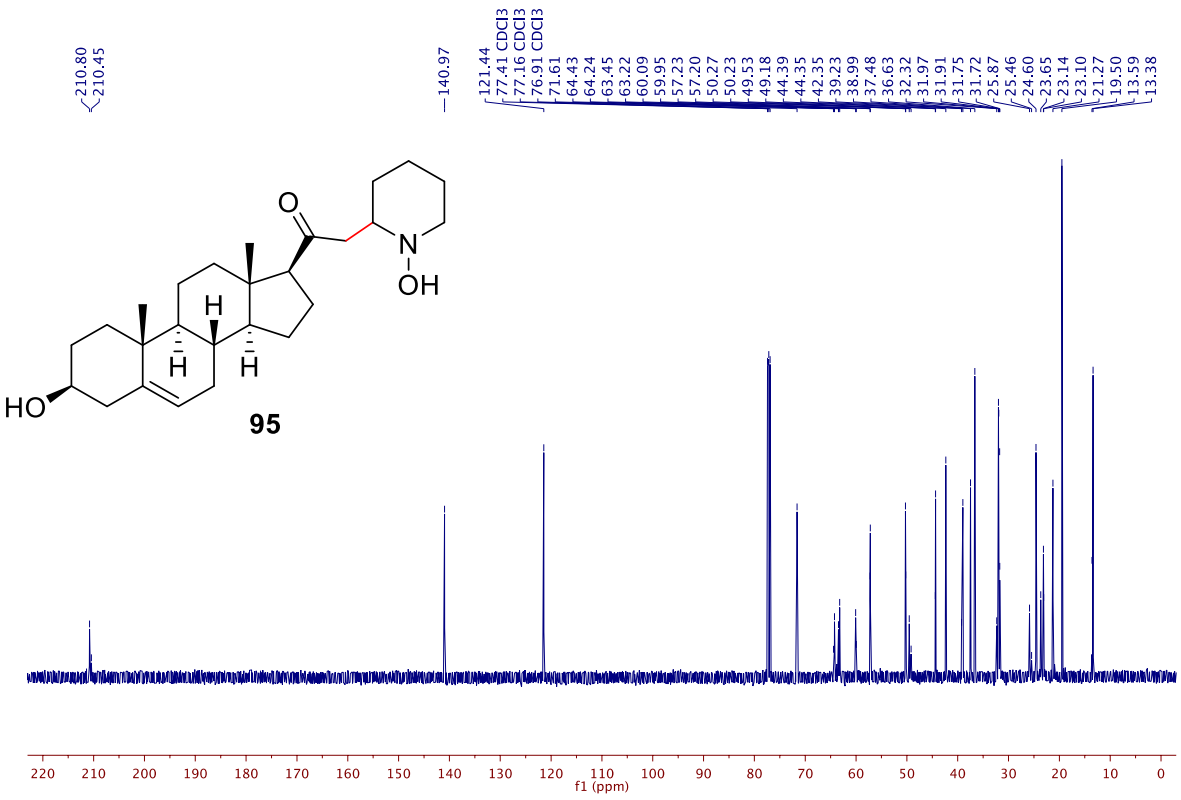
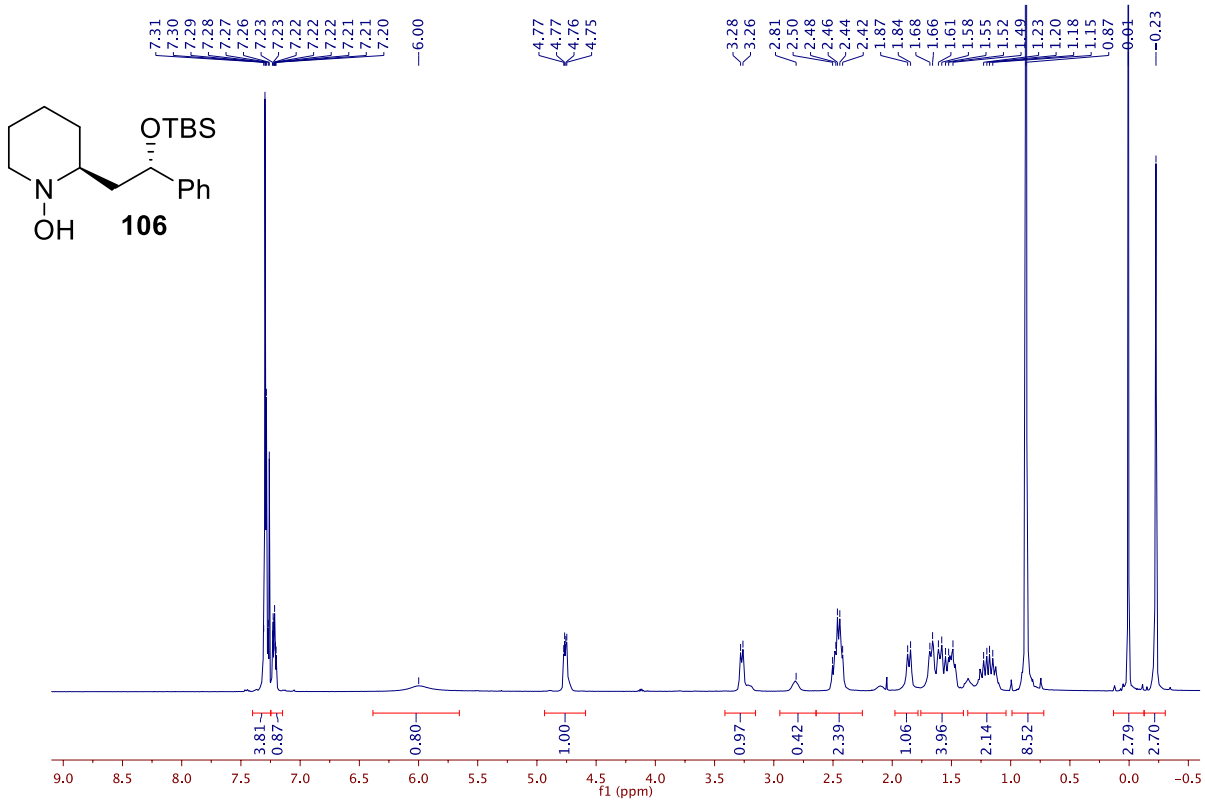
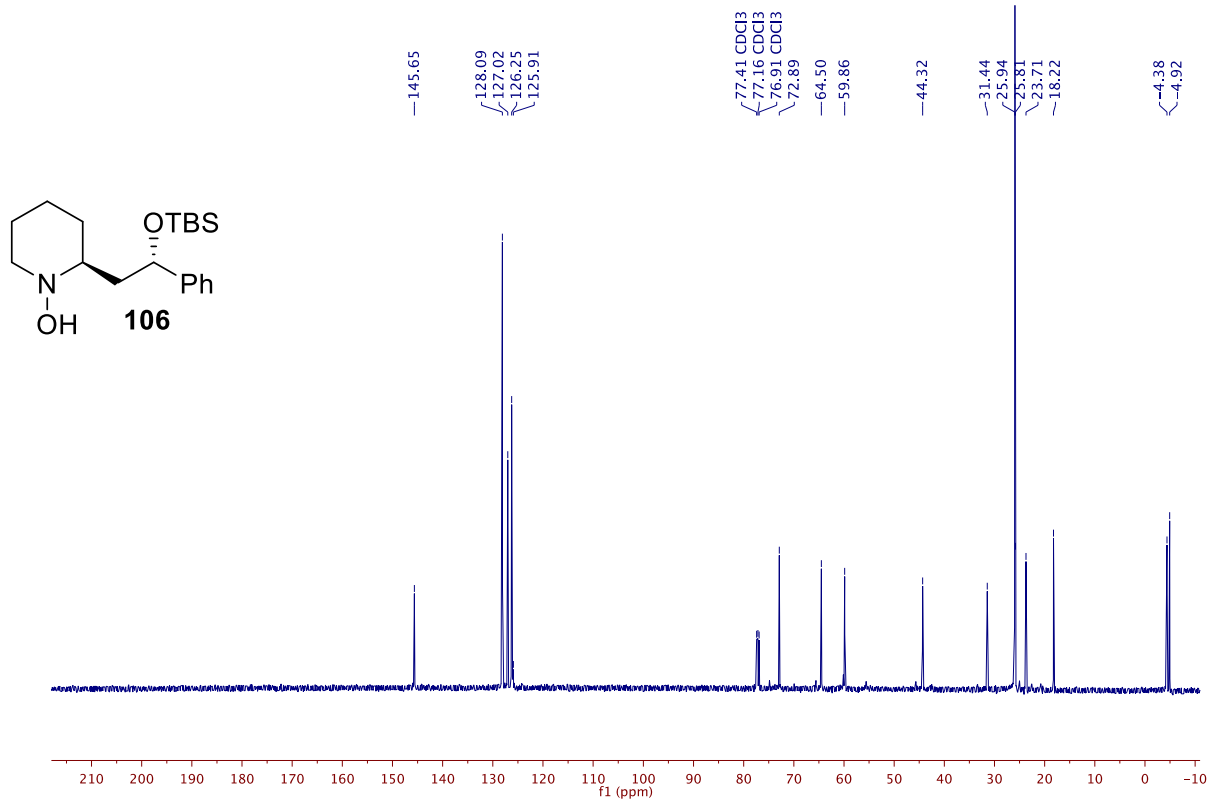
164.92
136.80
136.53
133.35
133.19
133.17
129.58
129.08
128.69
128.62
128.43
128.41
126.96
126.83
126.69
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
61.63
51.20
44.77
26.74
O
Ph
N
OH
92
N
O
Ph
OH
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

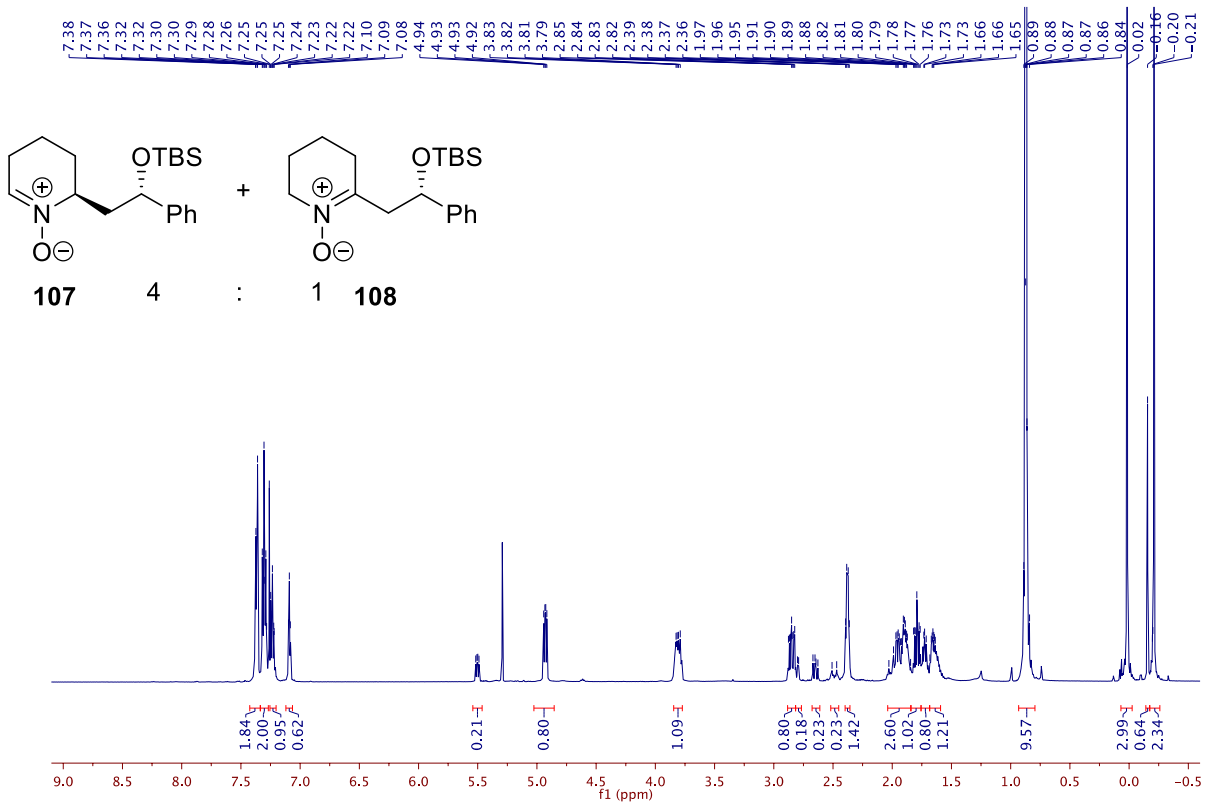

199.07
136.94
133.74
133.55
133.19
128.70
128.64
128.53
128.46
127.39
127.22
126.90
126.73
126.61
126.50
125.96
125.86
125.67
104.84
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
63.37
61.93
52.22
51.93
51.67
50.16
49.84
44.11
28.61
26.98
O
Ph
N
OBz
92'
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

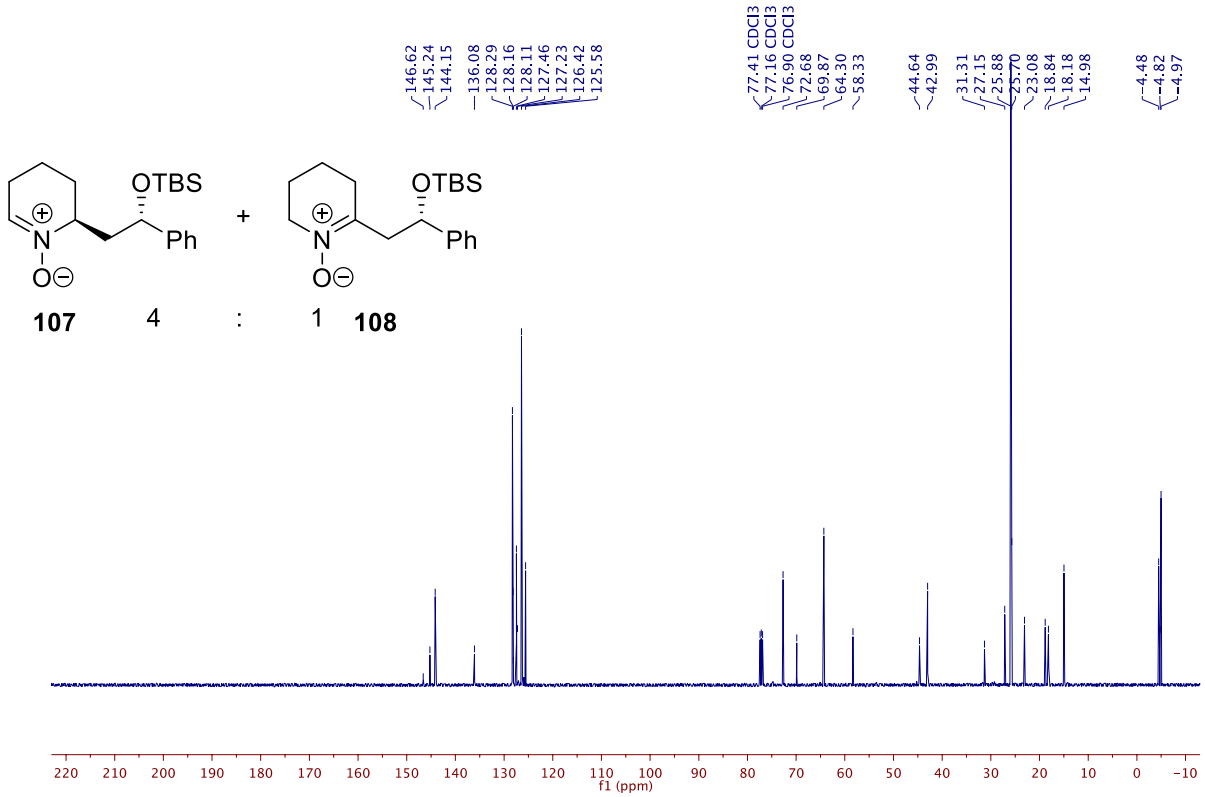

7.26
5.33
3.53
3.50
3.49
3.48
3.27
3.26
3.06
3.03
3.01
3.00
2.88
2.59
2.58
2.51
2.49
2.33
2.32
2.30
2.29
2.27
2.26
2.24
2.22
2.19
2.17
2.15
2.10
2.03
2.00
1.97
1.83
1.81
1.68
1.65
1.64
1.57
1.51
1.48
1.46
1.44
1.41
1.39
1.26
1.22
1.20
1.19
1.17
1.15
1.14
1.13
1.12
1.09
1.06
1.03
0.98
0.95
0.61
0.59
O
N
OH
H
H
H
HO
95
0.23
0.97
1.00
0.75
0.91
0.82
1.02
1.10
4.01
1.90
2.98
10.98
4.89
3.07
0.83
1.95
0.77
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

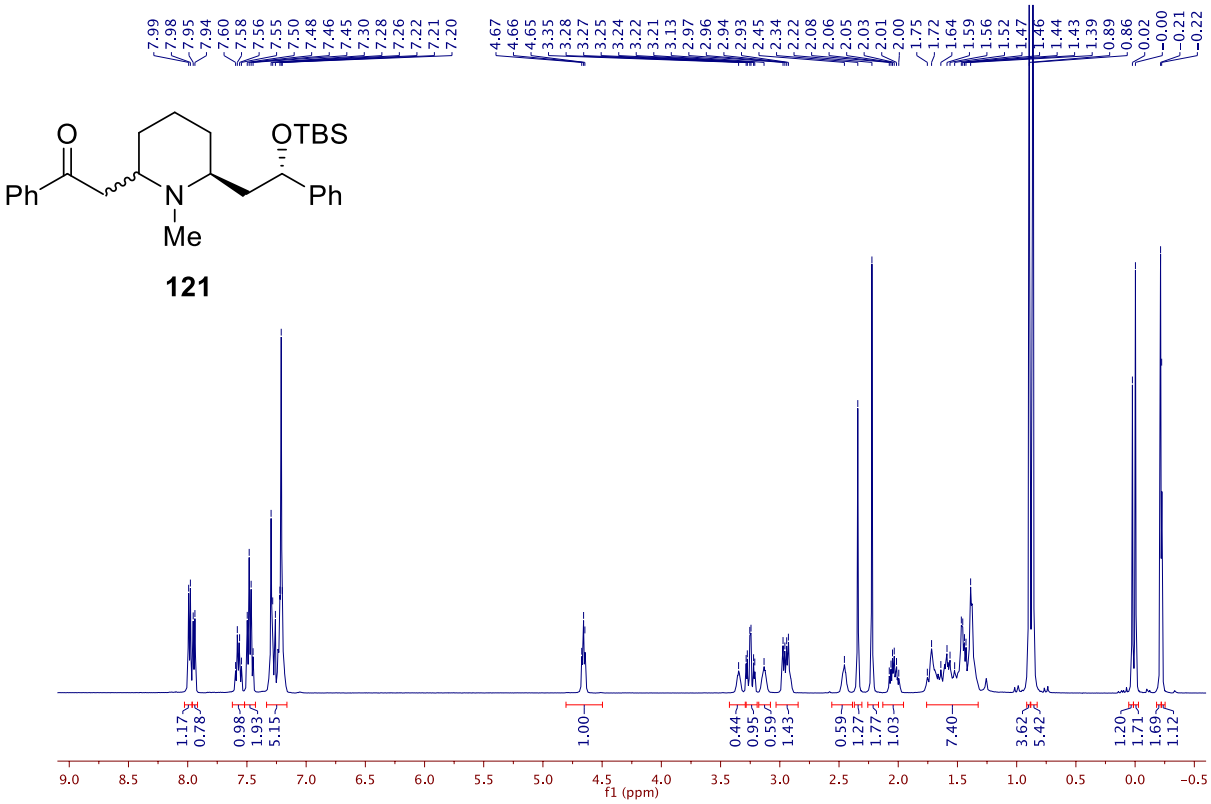

210.80
210.45
140.97
121.44
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
71.61
64.43
64.24
63.45
63.22
60.09
59.95
57.23
57.20
50.27
50.23
49.53
49.18
44.39
44.35
42.35
39.23
38.99
37.48
36.63
32.32
31.97
31.91
31.75
31.72
25.87
25.46
24.60
23.65
23.14
23.10
21.27
19.50
13.59
13.38
O
N
OH
H
H
H
HO
95
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

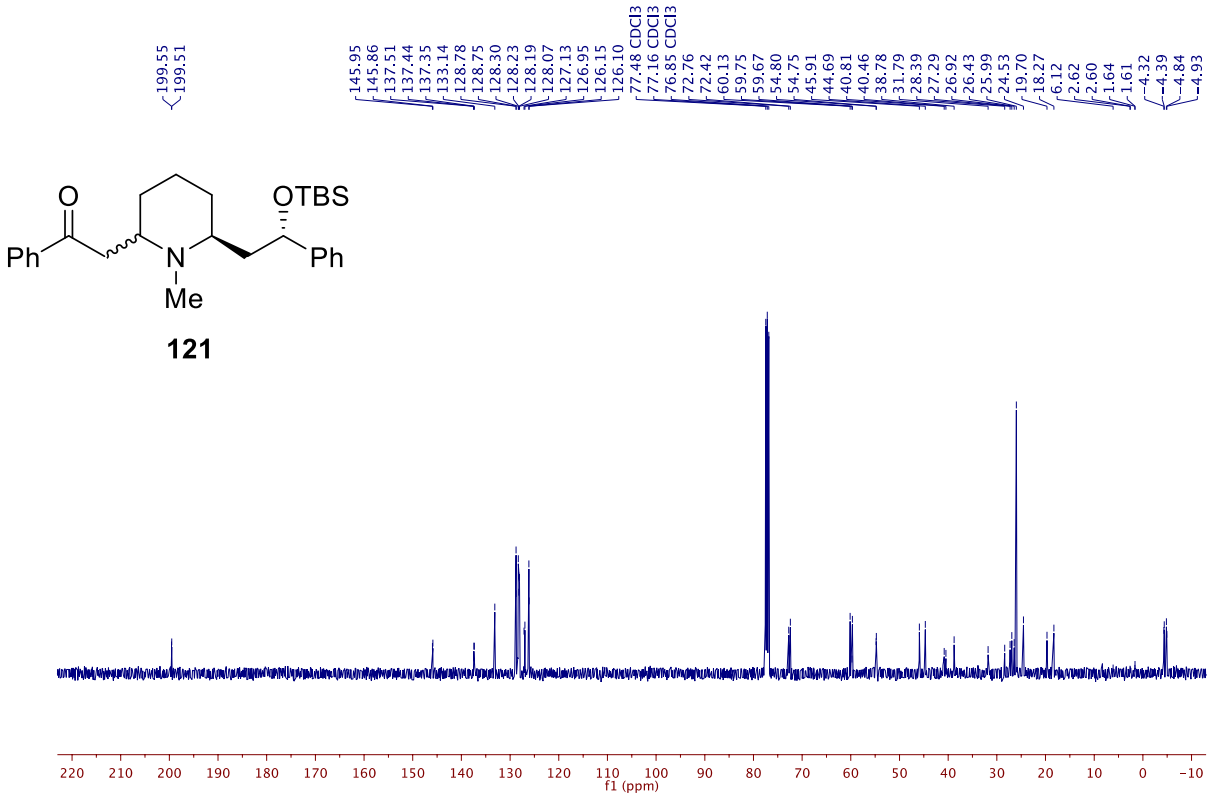

OTBS
Ph
N
OH
106
f1 (ppm)

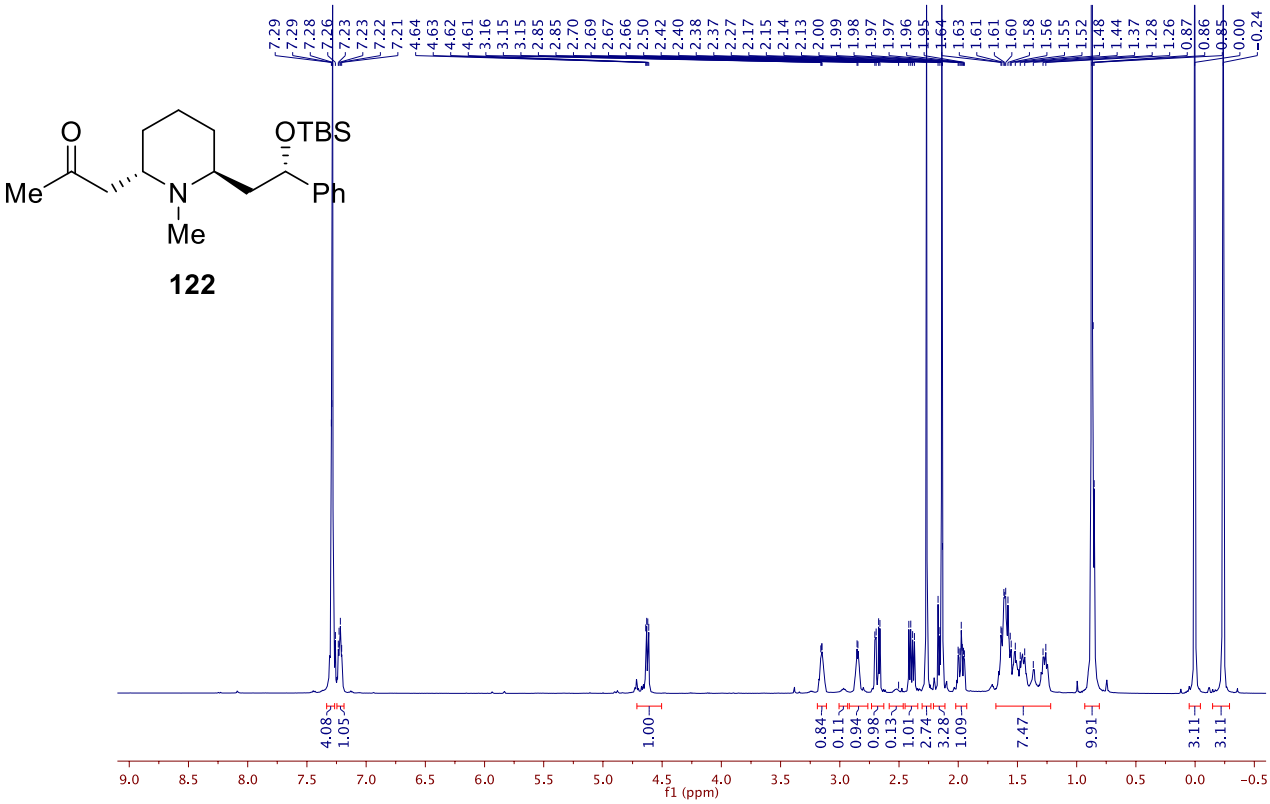

OTBS
Ph
N
OH
106
f1 (ppm)

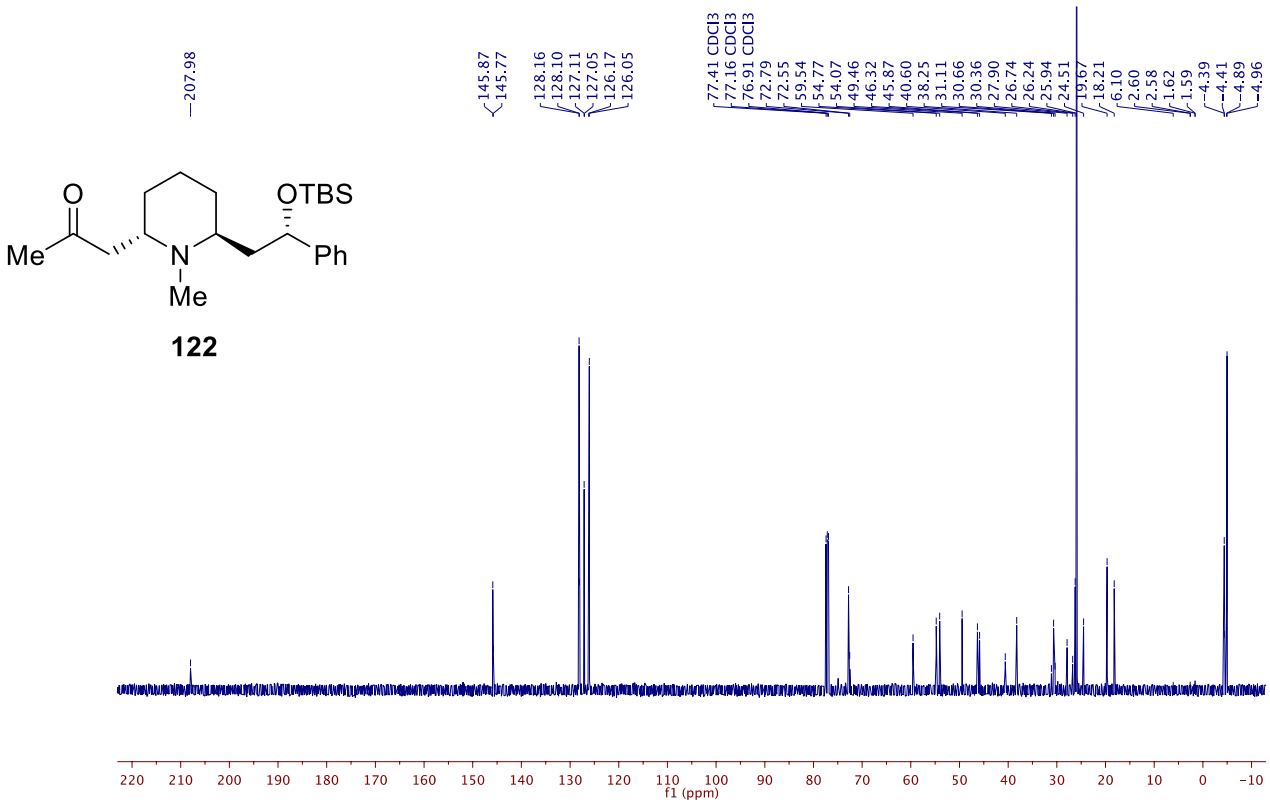

OTBS
Ph
OTBS
Ph
107 4 : 1 108

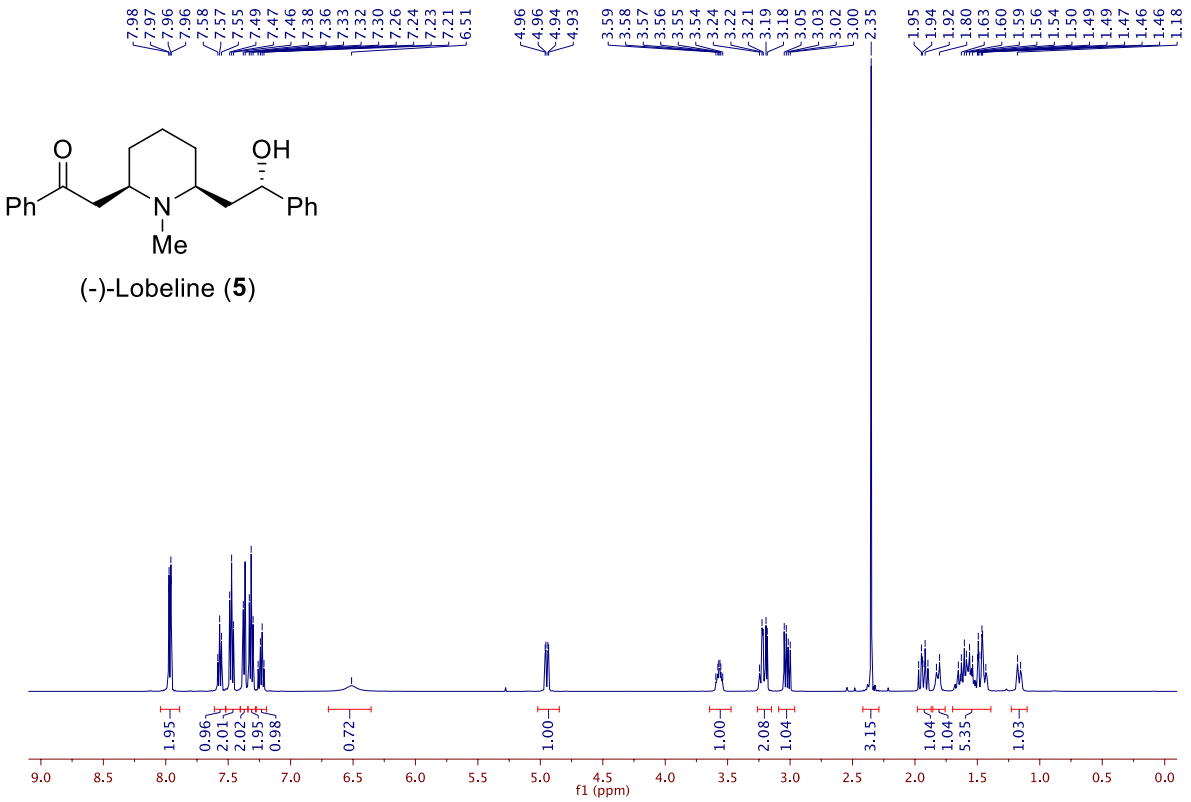

OTBS
Ph
OTBS
Ph
107 4 : 1 108


O
OTBS
Ph
N
Ph
Me
121
f1 (ppm)

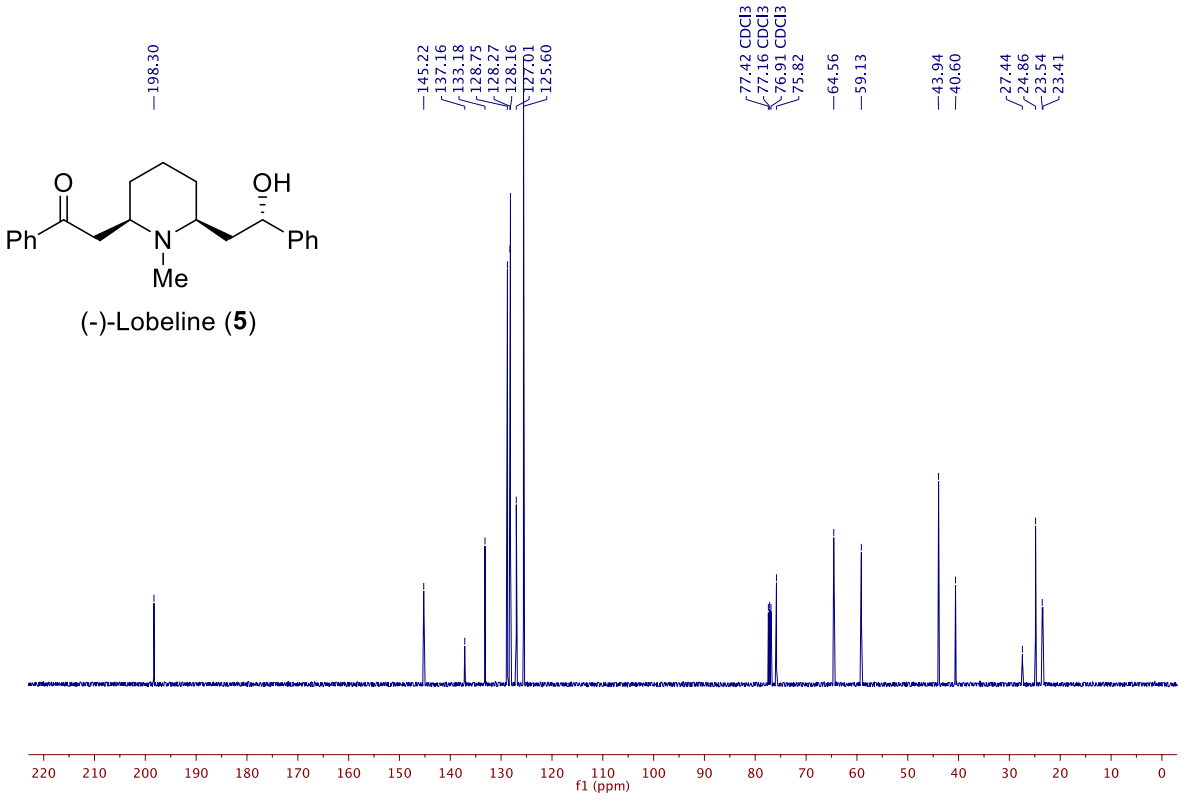

O
OTBS
Ph
N
Ph
Me
121
f1 (ppm)


O
OTBS
Me
N
Ph
Me
122
f1 (ppm)

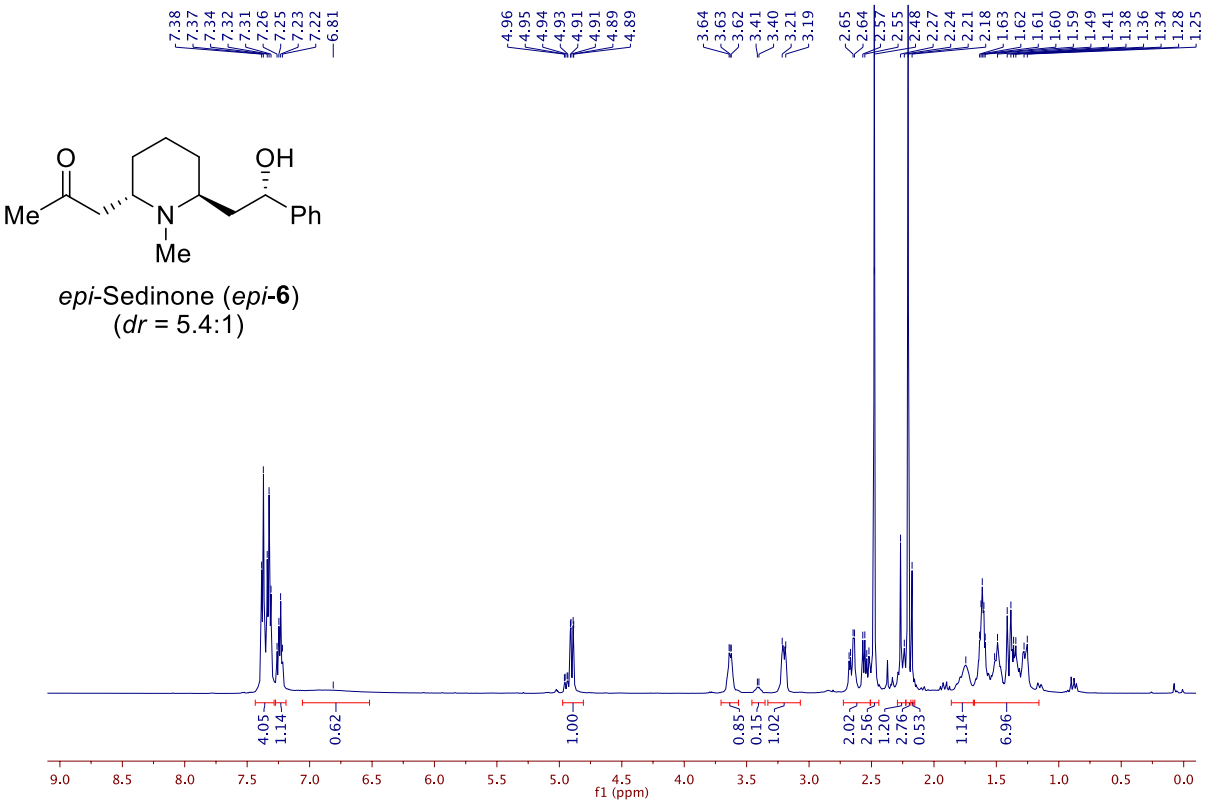

O
OTBS
Me
N
Ph
Me
122
f1 (ppm)



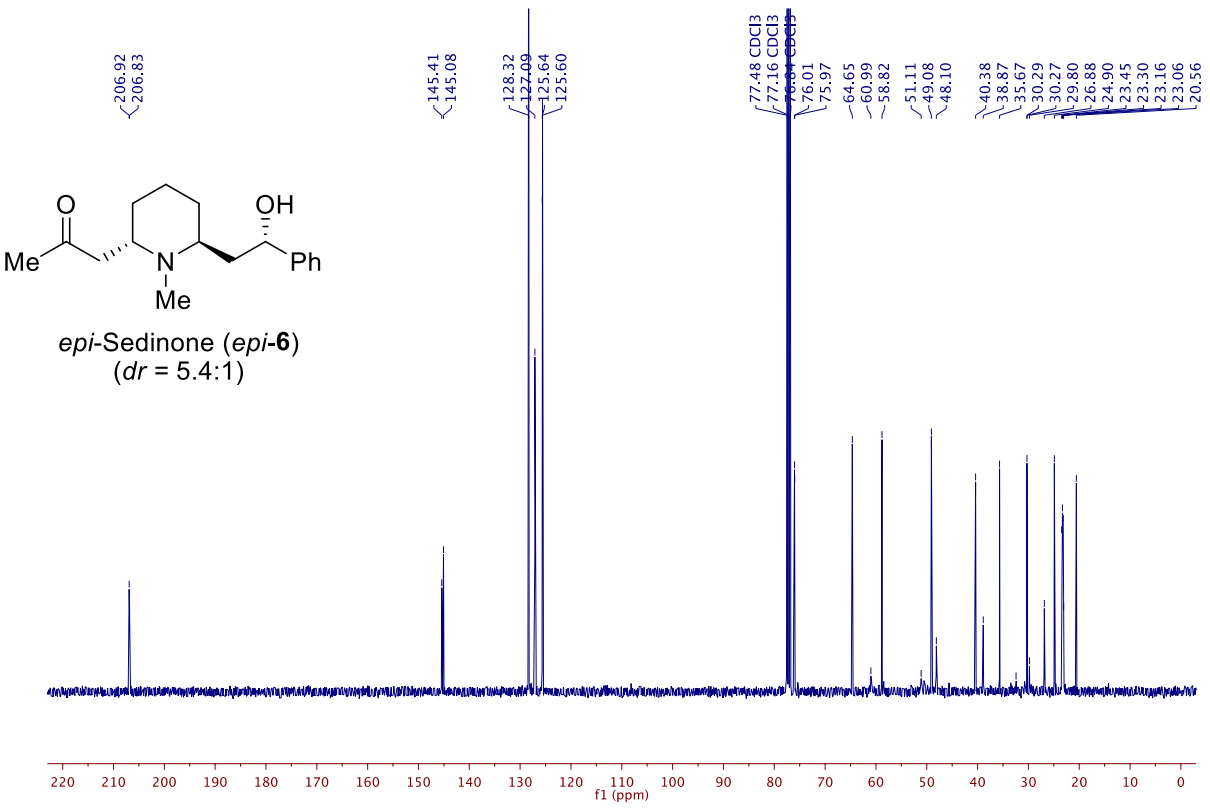
(-)-Lobeline (**5**)



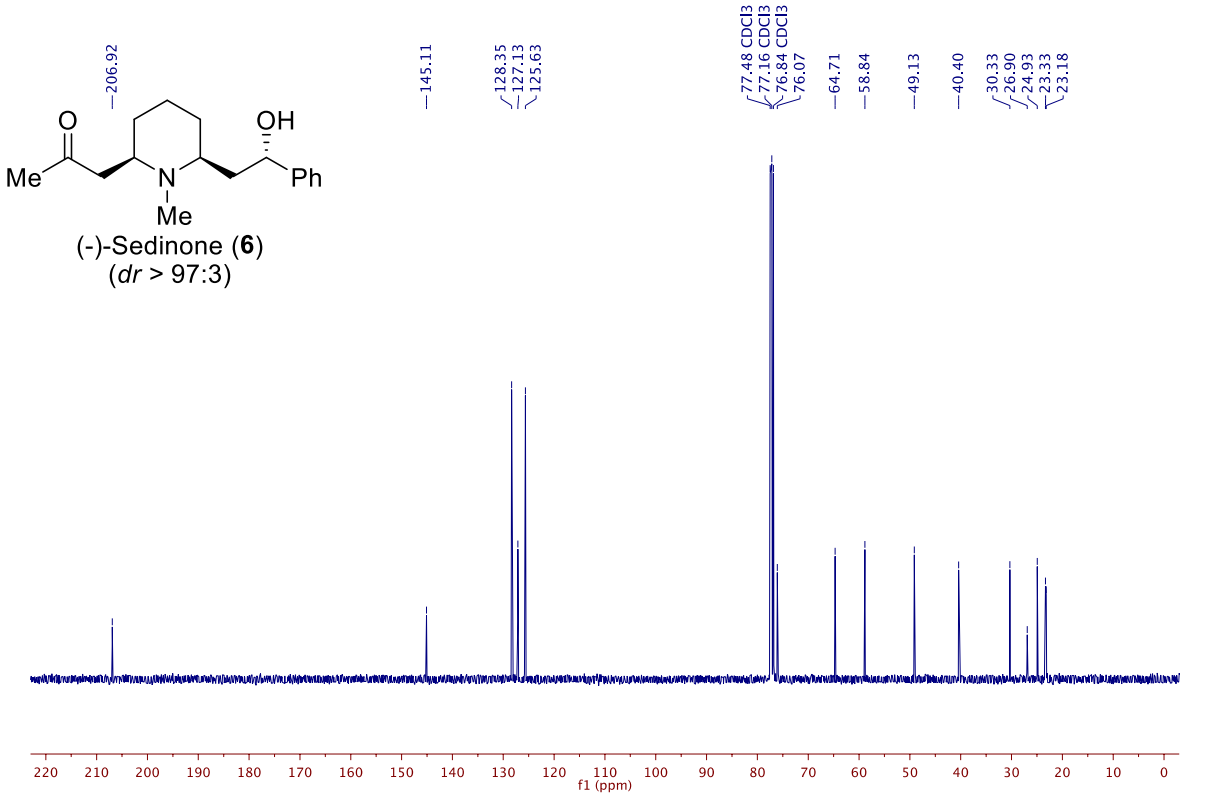
(-)-Lobeline (**5**)



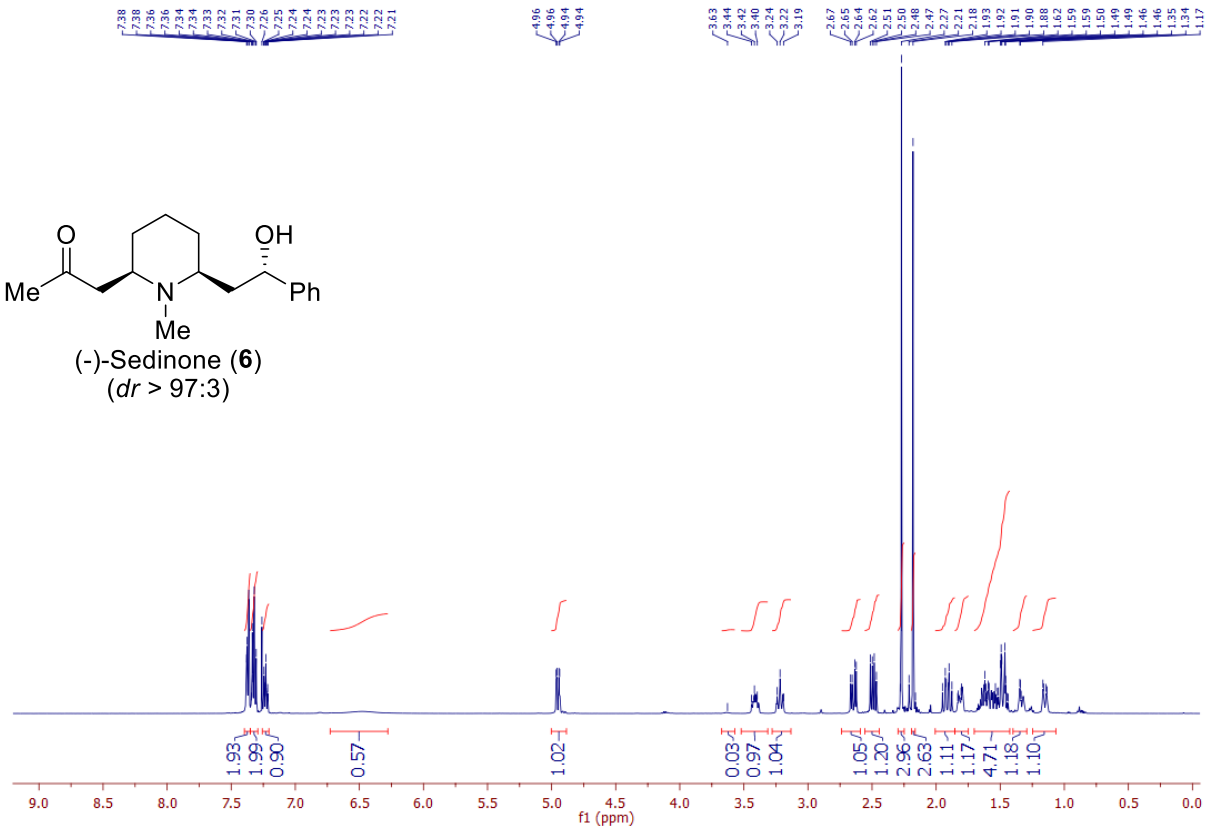
epi-Sedinone (*epi*-**6**)
(*dr* = 5.4:1)



epi-Sedinone (*epi*-**6**)
(*dr* = 5.4:1)

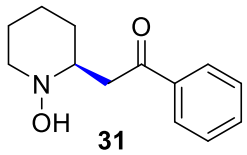


(-)-Sedinone (**6**)
(*dr* > 97:3)



(-)-Sedinone (**6**)
(*dr* > 97:3)

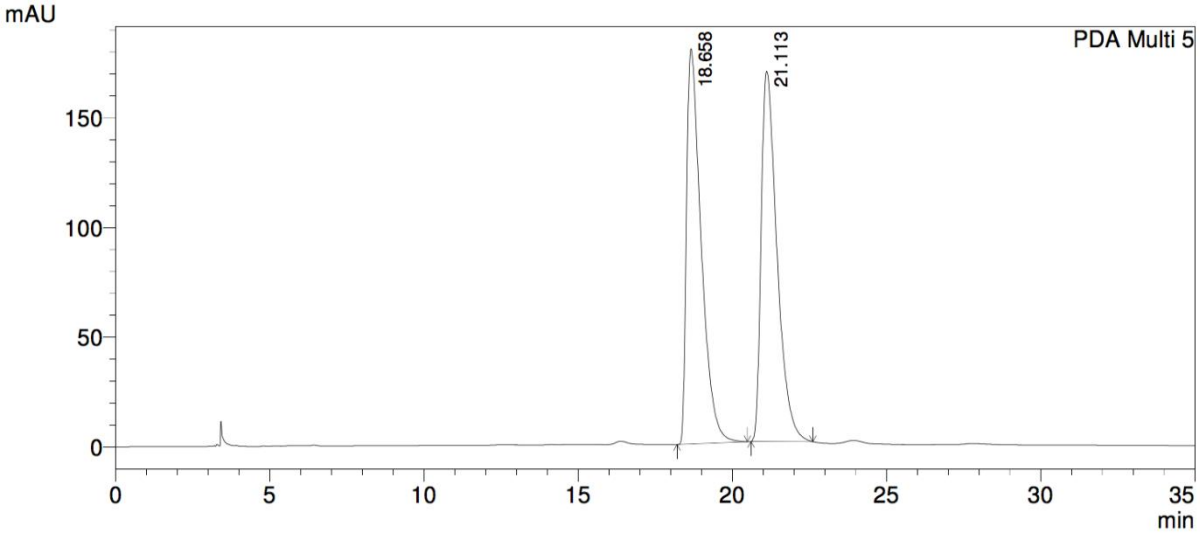
1.9. HPLC Traces.



31

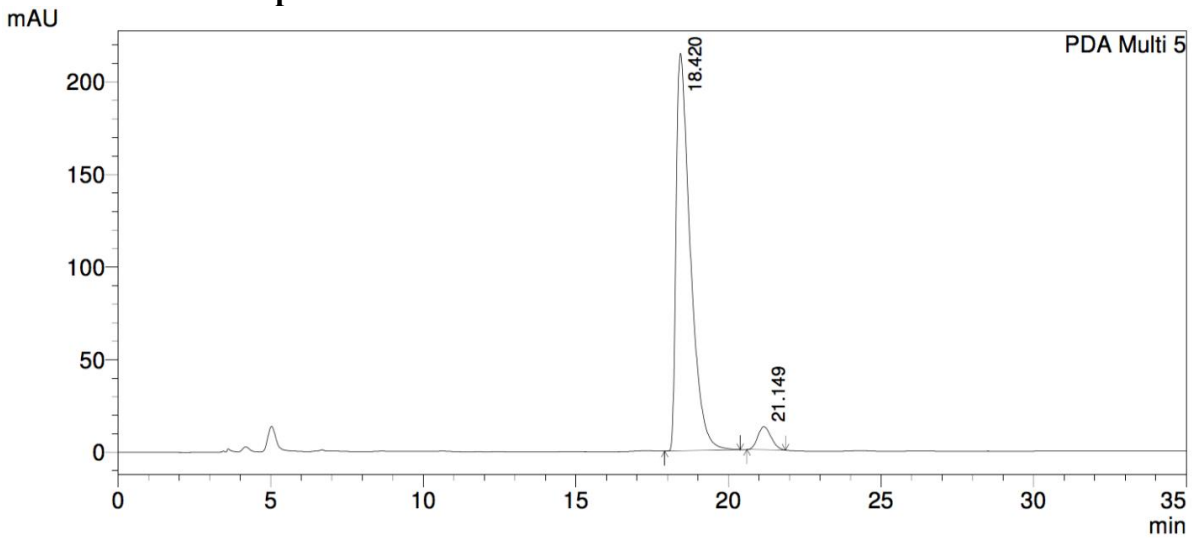
Conditions: HPLC (ChiralPak OD-H, 98:2 hexanes/*i*-PrOH, 1 mL/min, 254 nm)

Racemic Sample:

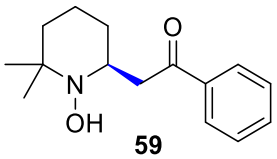


Peak#	Ret. Time	Area	Height	Area %	Height %
1	18.658	5952142	180281	49.728	51.632
2	21.113	6017315	168884	50.272	48.368
Total		11969457	349165	100.000	100.000

Enantioenriched Sample:



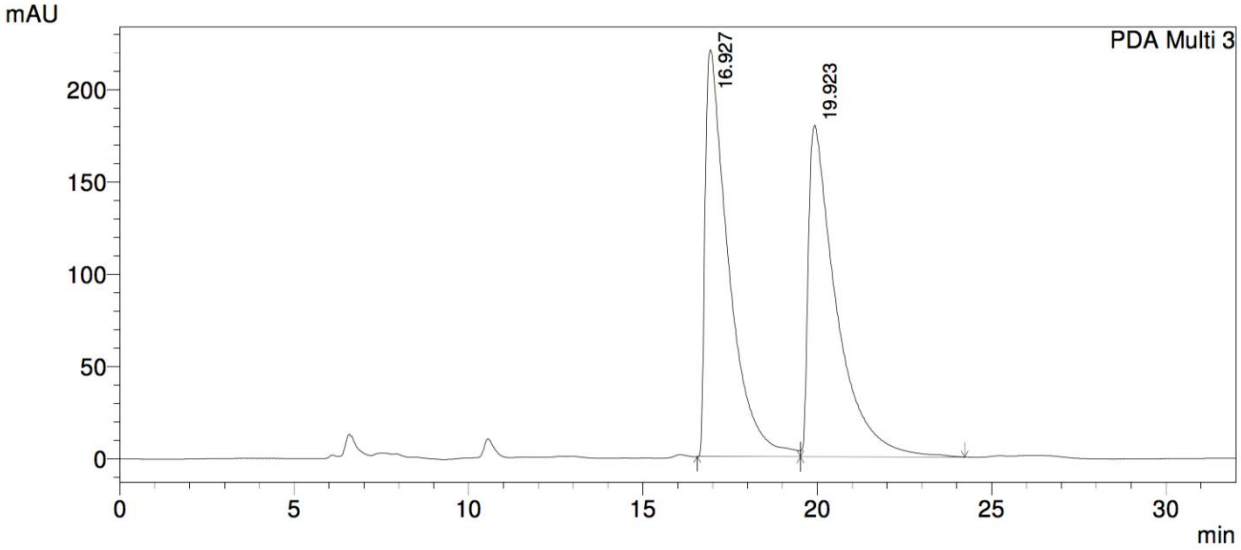
Peak#	Ret. Time	Area	Height	Area %	Height %
1	18.420	6924486	214602	94.789	94.506
2	21.149	380680	12476	5.211	5.494
Total		7305165	227077	100.000	100.000



59

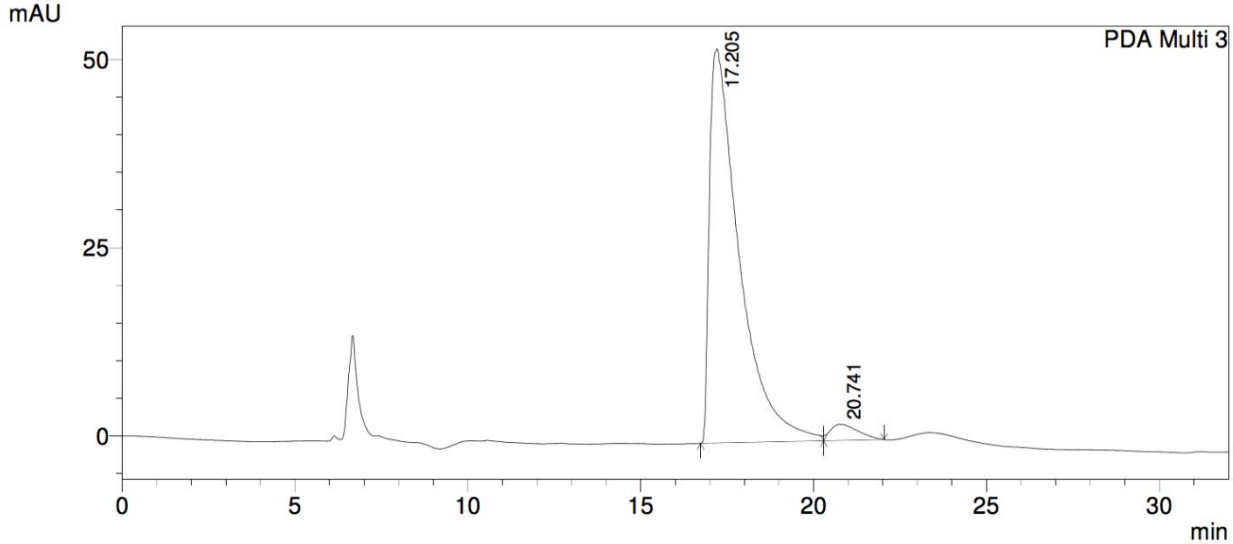
Conditions: HPLC (ChiralPak IA, 98:2 hexanes/*i*-PrOH, 1 mL/min, 220 nm)

Racemic Sample:

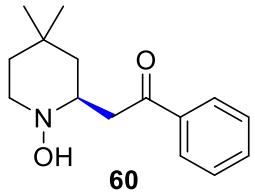


Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.927	10303750	220564	50.692	55.097
2	19.923	10022590	179757	49.308	44.903
Total		20326340	400321	100.000	100.000

Enantioenriched Sample:



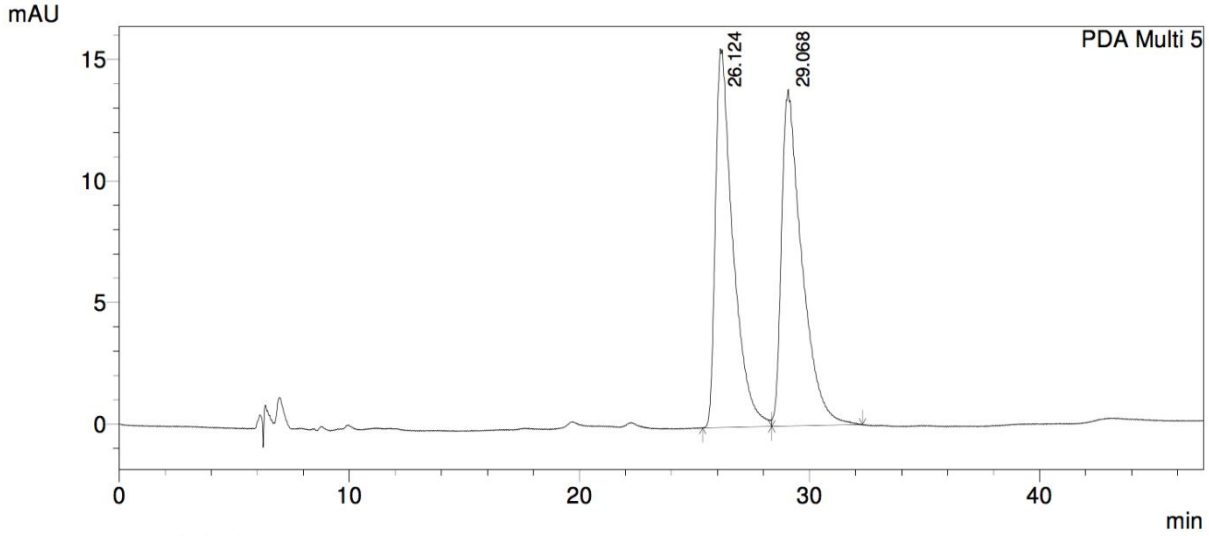
Peak#	Ret. Time	Area	Height	Area %	Height %
1	17.205	3139360	52311	96.361	96.055
2	20.741	118539	2149	3.639	3.945
Total		3257899	54460	100.000	100.000



60

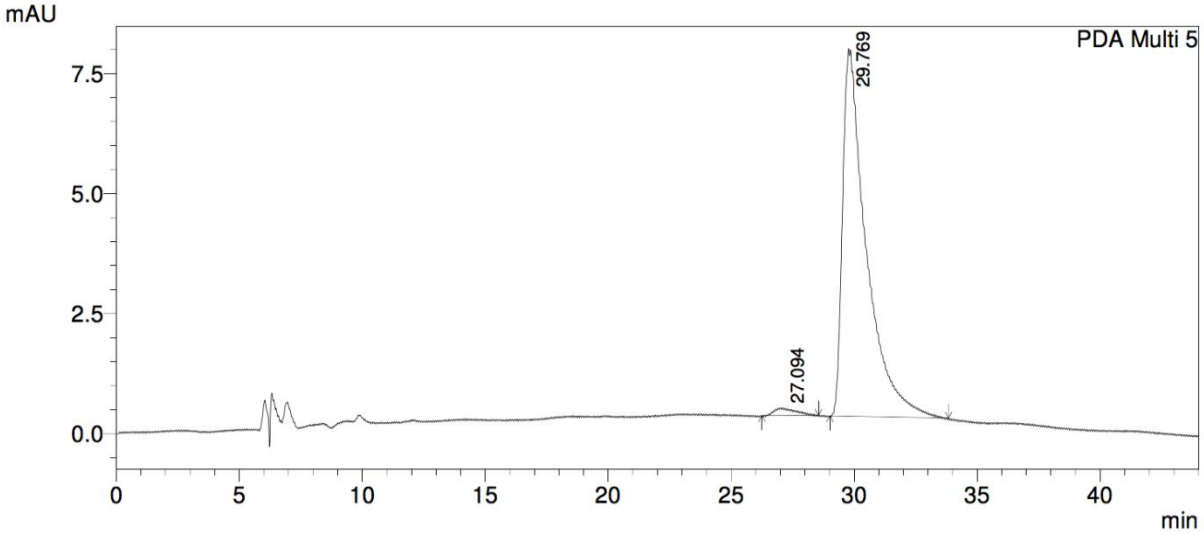
Conditions: HPLC (ChiralPak IA, 98:2 hexanes/*i*-PrOH, 1 mL/min, 254 nm)

Racemic sample:

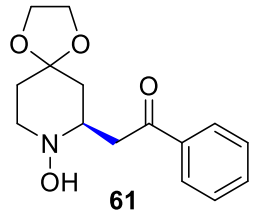


Peak#	Ret. Time	Area	Height	Area %	Height %
1	26.124	828397	15584	49.303	52.954
2	29.068	851823	13846	50.697	47.046
Total		1680220	29430	100.000	100.000

Enantioenriched Sample:



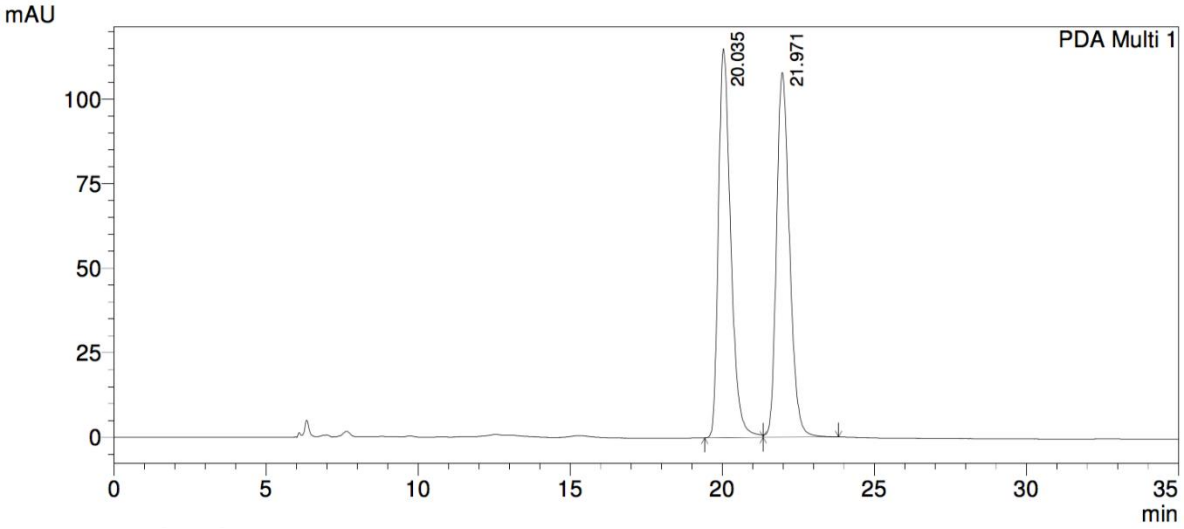
Peak#	Ret. Time	Area	Height	Area %	Height %
1	27.094	8901	160	1.714	2.050
2	29.769	510388	7649	98.286	97.950
Total		519289	7809	100.000	100.000



61

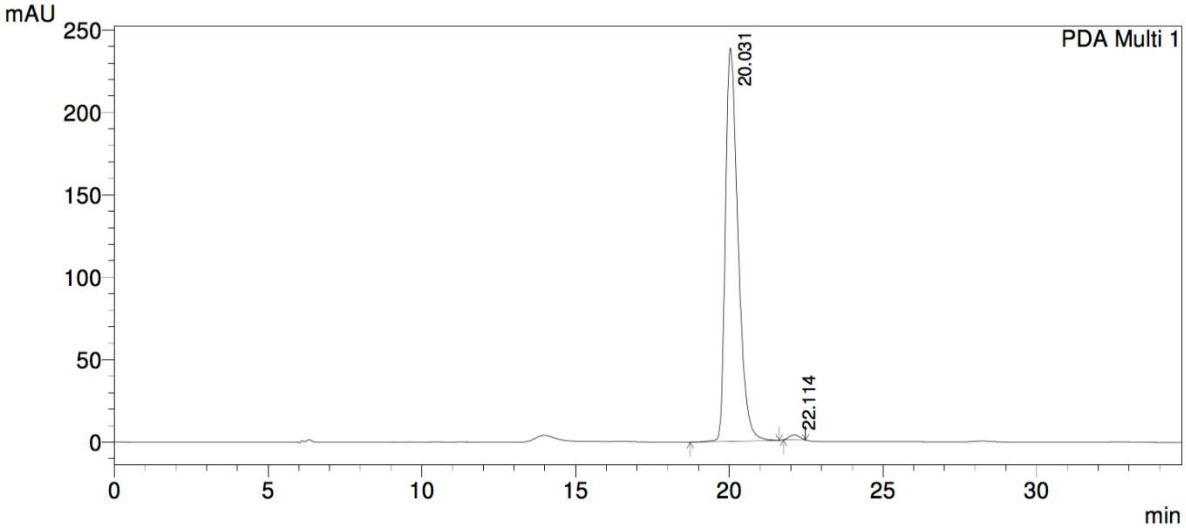
Conditions: HPLC (ChiralPak OD-H, 95:5 hexanes/*i*-PrOH, 1 mL/min, 254 nm)

Racemic Sample:

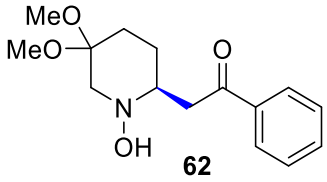


Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.035	3239277	114984	50.092	51.596
2	21.971	3227422	107872	49.908	48.404
Total		6466699	222856	100.000	100.000

Enantioenriched Sample:



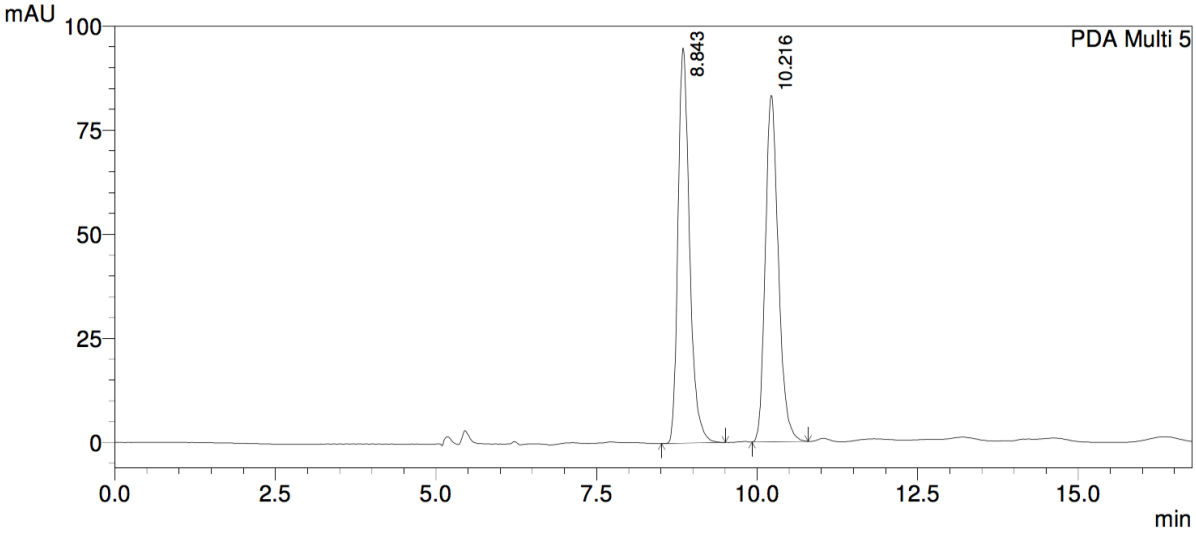
Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.031	6830704	238510	98.927	98.689
2	22.114	74057	3169	1.073	1.311
Total		6904761	241679	100.000	100.000



62

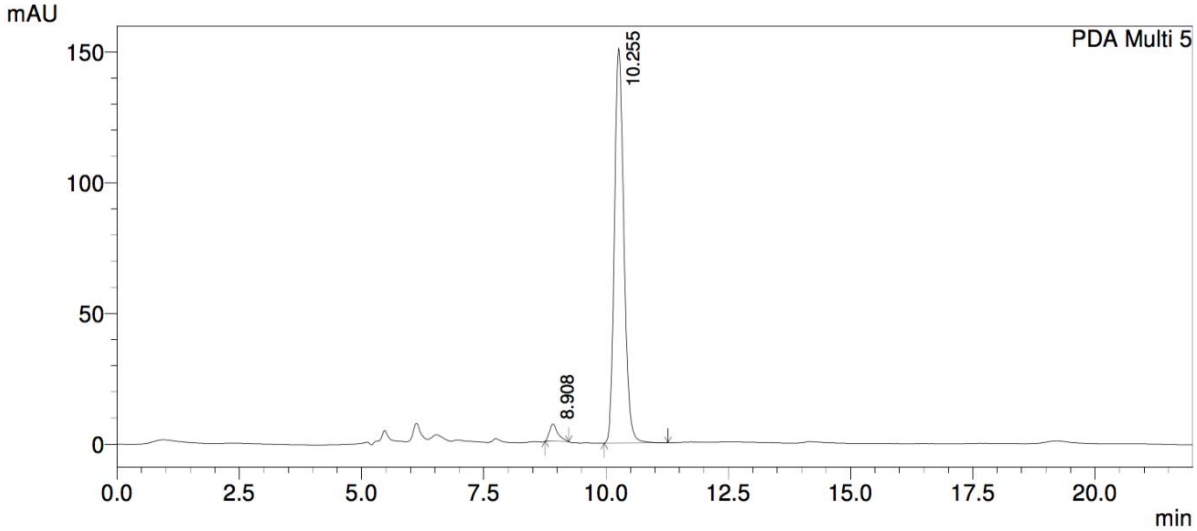
Conditions: HPLC (ChiralPak OD-H, 90:10 hexanes/*i*-PrOH, 1 mL/min, 254 nm)

Racemic Sample:

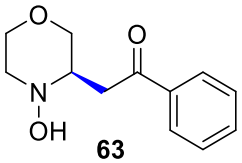


Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.843	1188162	94811	50.277	53.269
2	10.216	1175064	83176	49.723	46.731
Total		2363226	177987	100.000	100.000

Enantioenriched Sample:



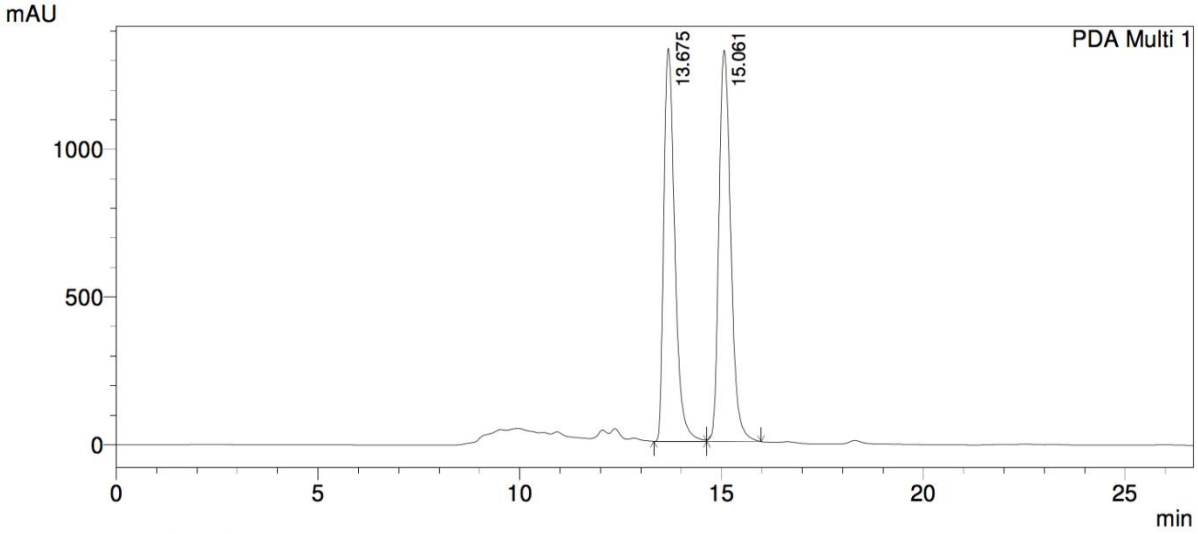
Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.908	79241	6632	3.748	4.209
2	10.255	2034966	150928	96.252	95.791
Total		2114207	157560	100.000	100.000



63

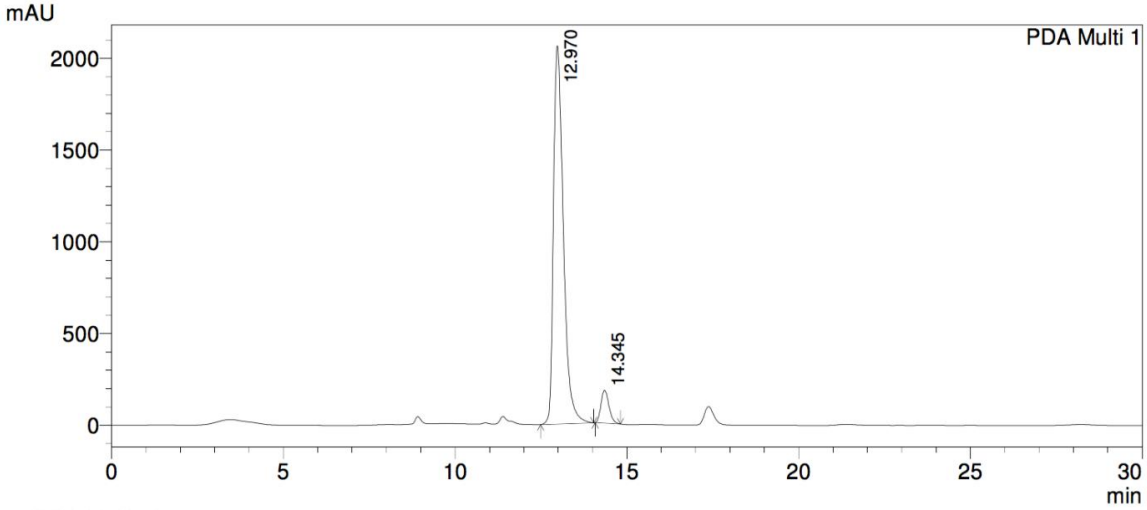
Conditions: HPLC (ChiralPak OD-H, 90:10 hexanes/*i*-PrOH, 1 mL/min, 254 nm)

Racemic Sample:

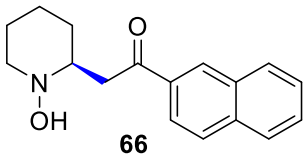


Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.675	25172210	1330370	48.214	50.106
2	15.061	27037356	1324764	51.786	49.894
Total		52209565	2655134	100.000	100.000

Enantioenriched Sample: HPLC (ChiralPak OD-H, 90:10 hexanes/*i*-PrOH, 1 mL/min, 254 nm), 88% *ee*



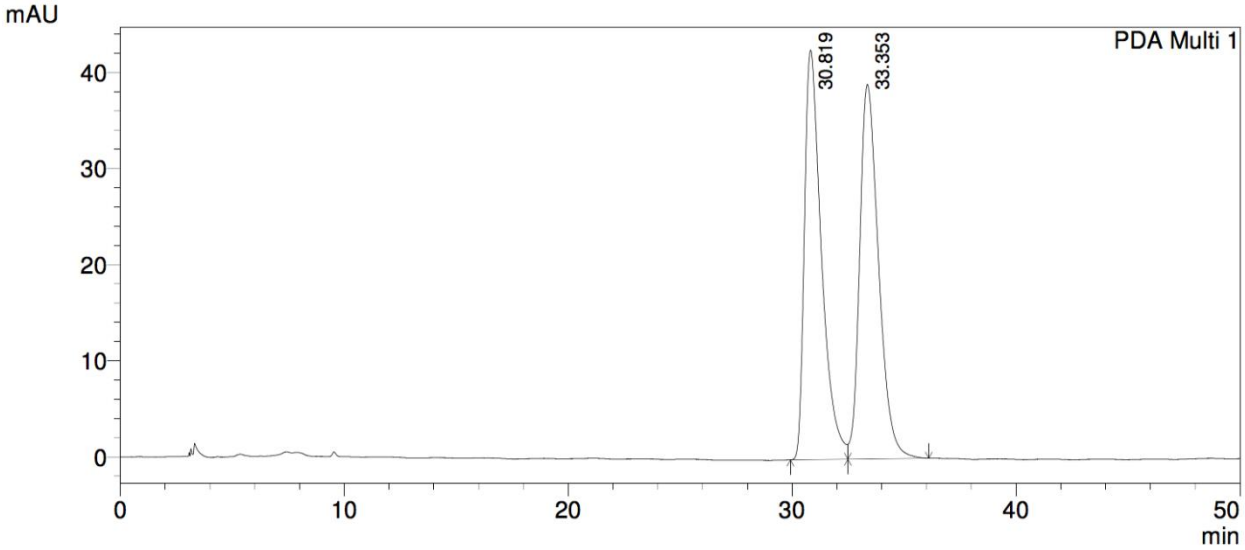
Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.970	41180227	2060380	93.945	92.272
2	14.345	2654071	172559	6.055	7.728
Total		43834298	2232939	100.000	100.000



66

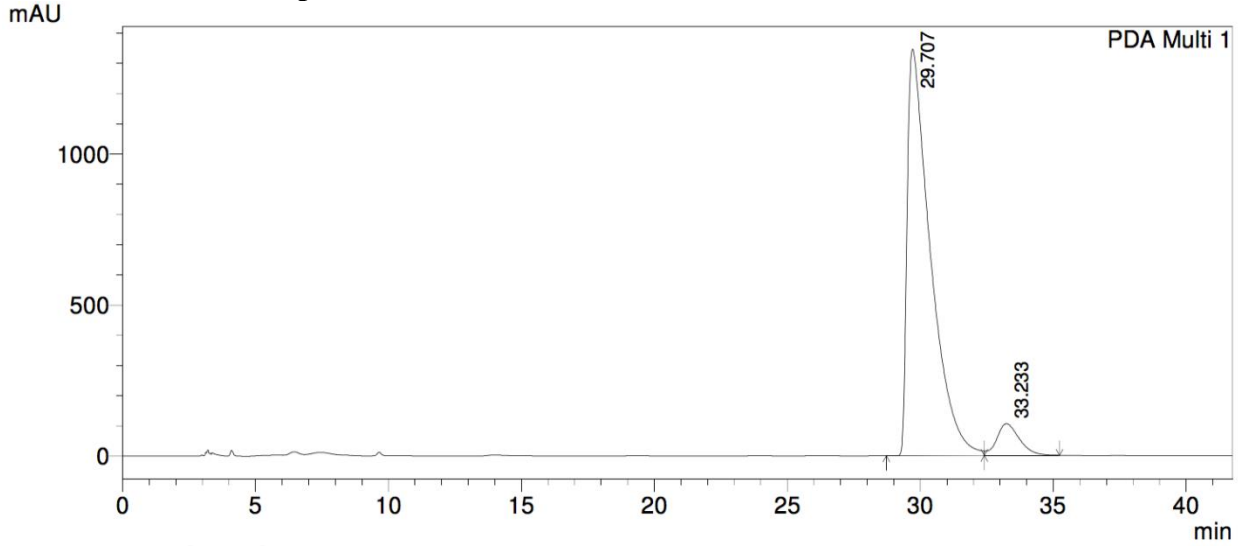
Conditions: HPLC (ChiralPak OD-H, 98:2 hexanes/*i*-PrOH, 1 mL/min, 215 nm)

Racemic Sample:

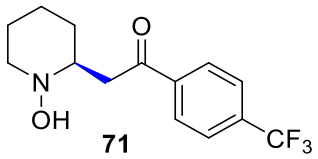


Peak#	Ret. Time	Area	Height	Area %	Height %
1	30.819	2250074	42598	49.531	52.235
2	33.353	2292709	38953	50.469	47.765
Total		4542784	81552	100.000	100.000

Enantioenriched Sample:



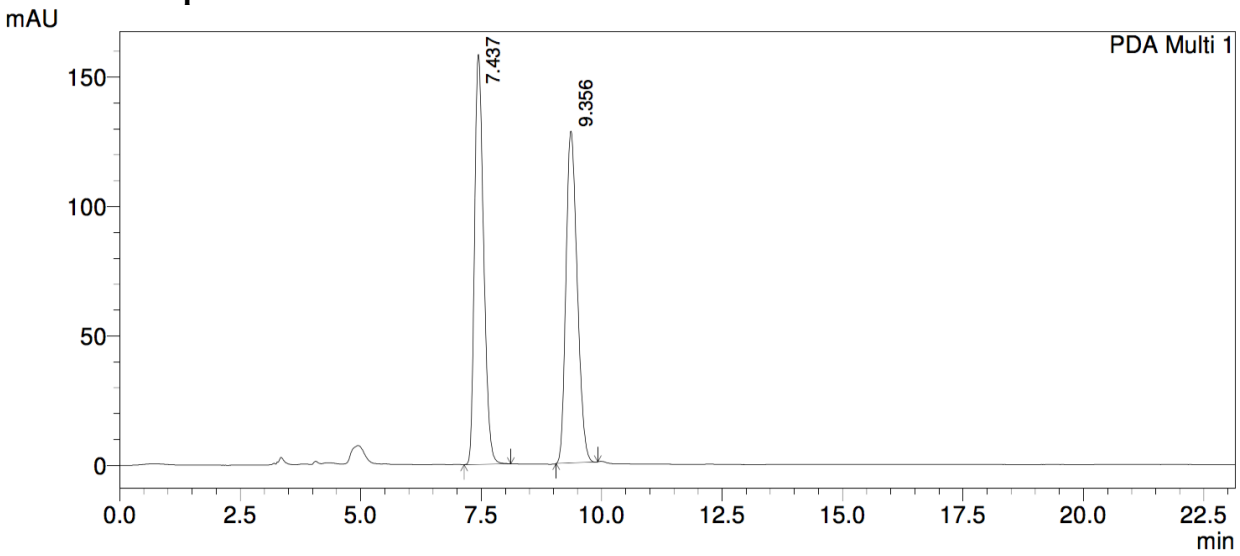
Peak#	Ret. Time	Area	Height	Area %	Height %
1	29.707	81738609	1345707	92.960	92.748
2	33.233	6190618	105226	7.040	7.252
Total		87929228	1450933	100.000	100.000



71

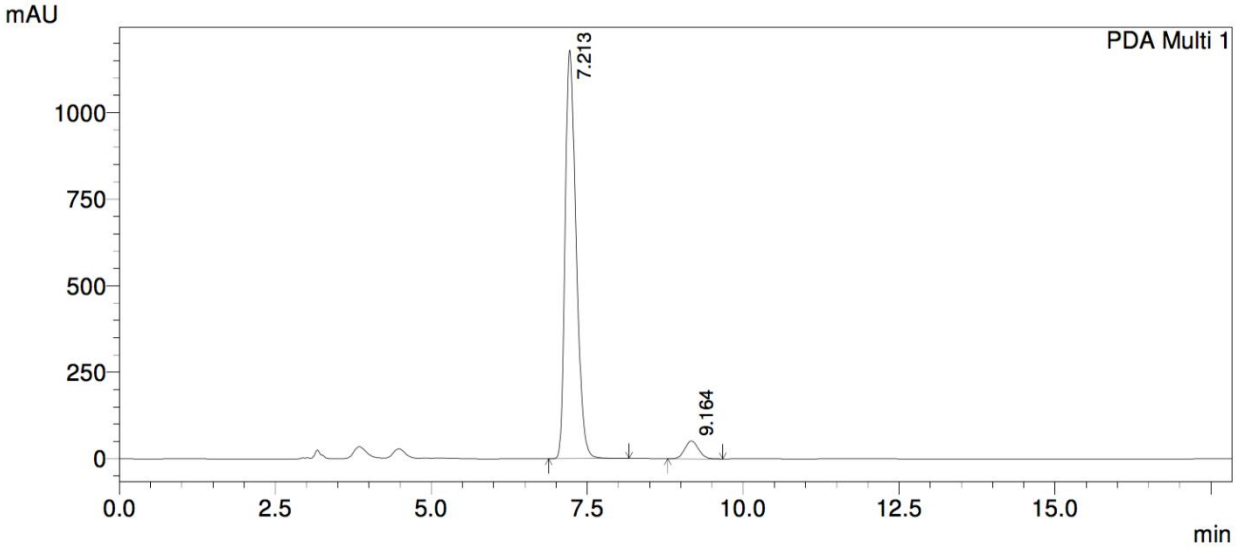
Conditions: HPLC (ChiralPak OD-H, 95:5 hexanes/*i*-PrOH, 1 mL/min, 215 nm)

Racemic Sample:

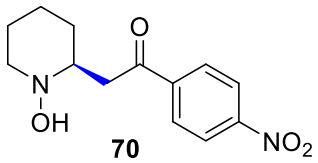


Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.437	2081735	158410	49.963	55.259
2	9.356	2084781	128259	50.037	44.741
Total		4166517	286669	100.000	100.000

Enantioenriched Sample:



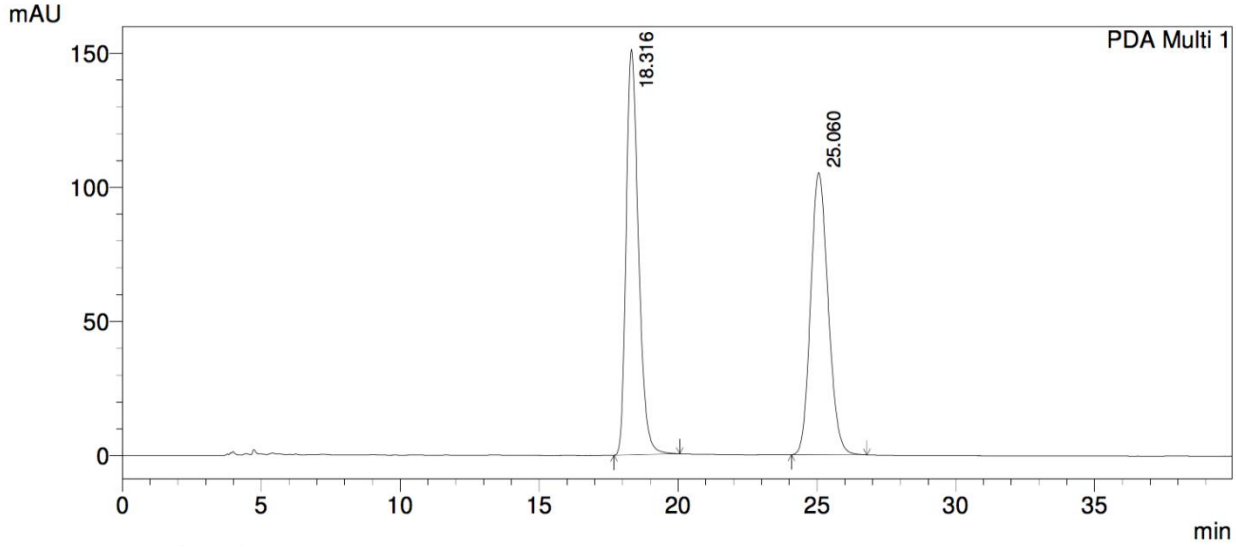
Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.213	14451879	1180494	94.854	95.840
2	9.164	784004	51241	5.146	4.160
Total		15235883	1231735	100.000	100.000



70

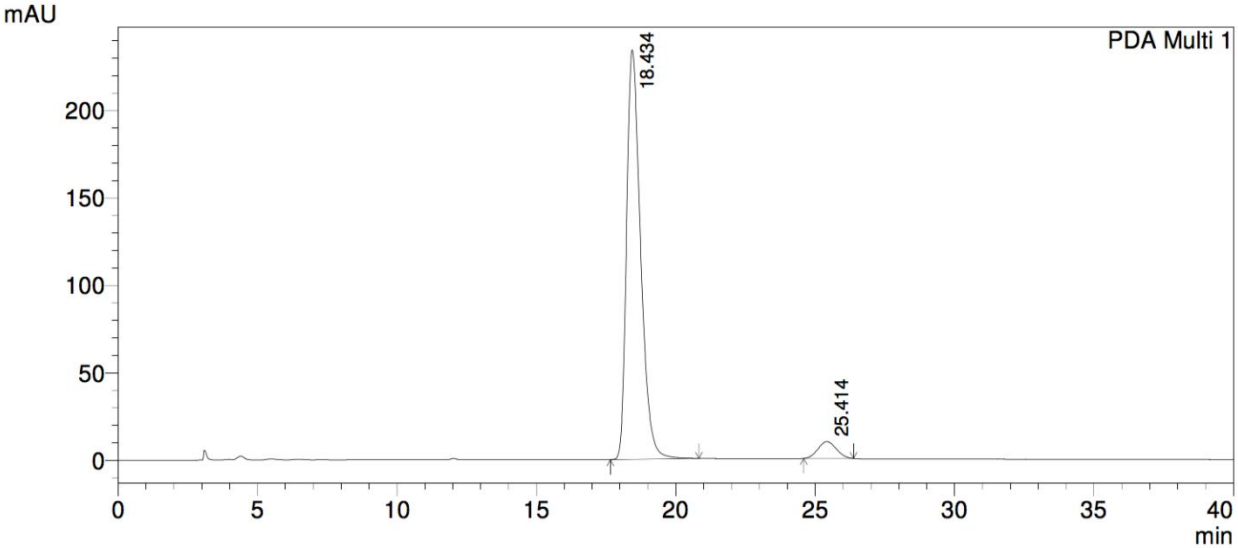
Conditions: HPLC (ChiralPak OD-H, 95:5 hexanes/*i*-PrOH, 1 mL/min, 254 nm)

Racemic Sample:

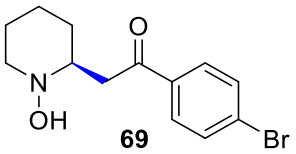


Peak#	Ret. Time	Area	Height	Area %	Height %
1	18.316	4652315	151199	50.280	58.973
2	25.060	4600463	105186	49.720	41.027
Total		9252777	256386	100.000	100.000

Enantioenriched Sample:



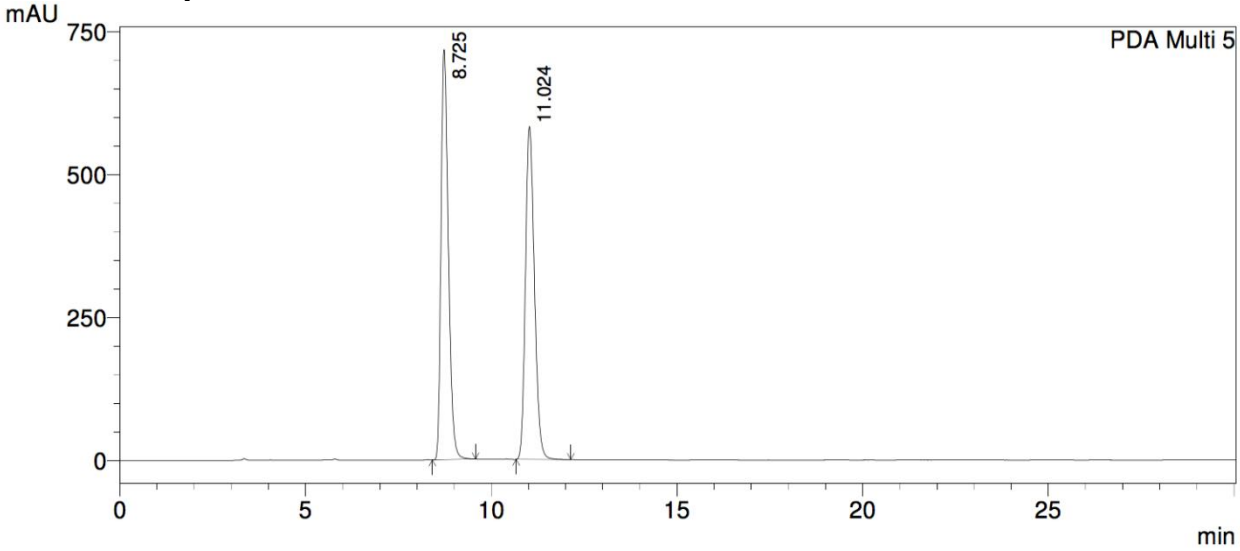
Peak#	Ret. Time	Area	Height	Area %	Height %
1	18.434	8178740	234085	94.878	96.042
2	25.414	441538	9647	5.122	3.958
Total		8620277	243731	100.000	100.000



69

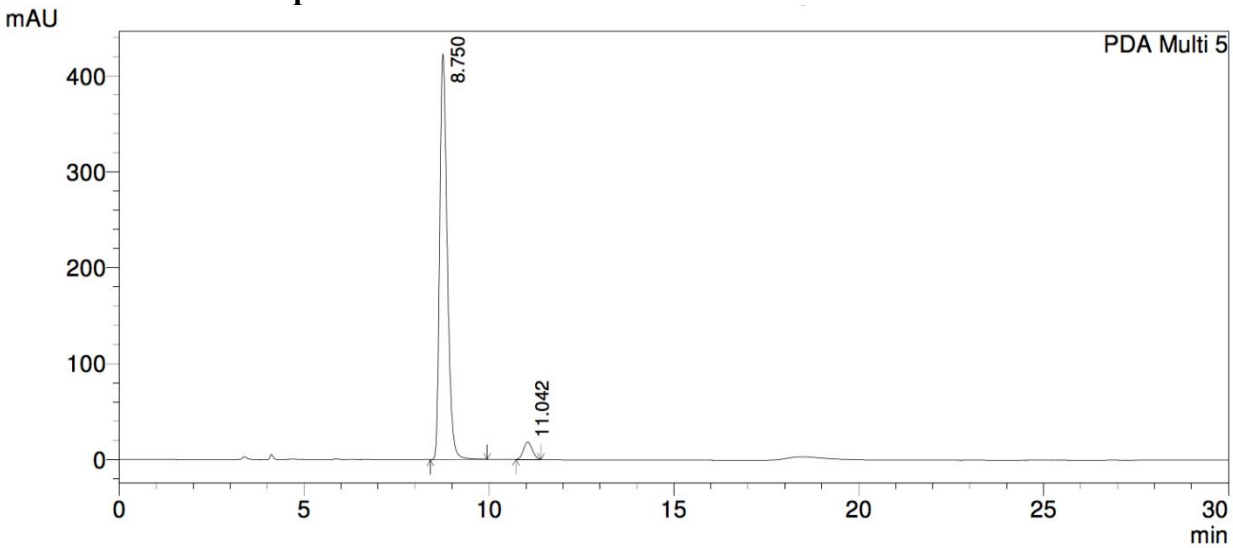
Conditions: HPLC (ChiralPak OD-H, 95:5 hexanes/*i*-PrOH, 1 mL/min, 254 nm)

Racemic Sample:

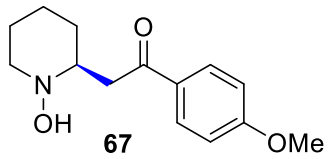


Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.725	9843686	717248	50.045	55.182
2	11.024	9825795	582539	49.955	44.818
Total		19669482	1299788	100.000	100.000

Enantioenriched Sample:



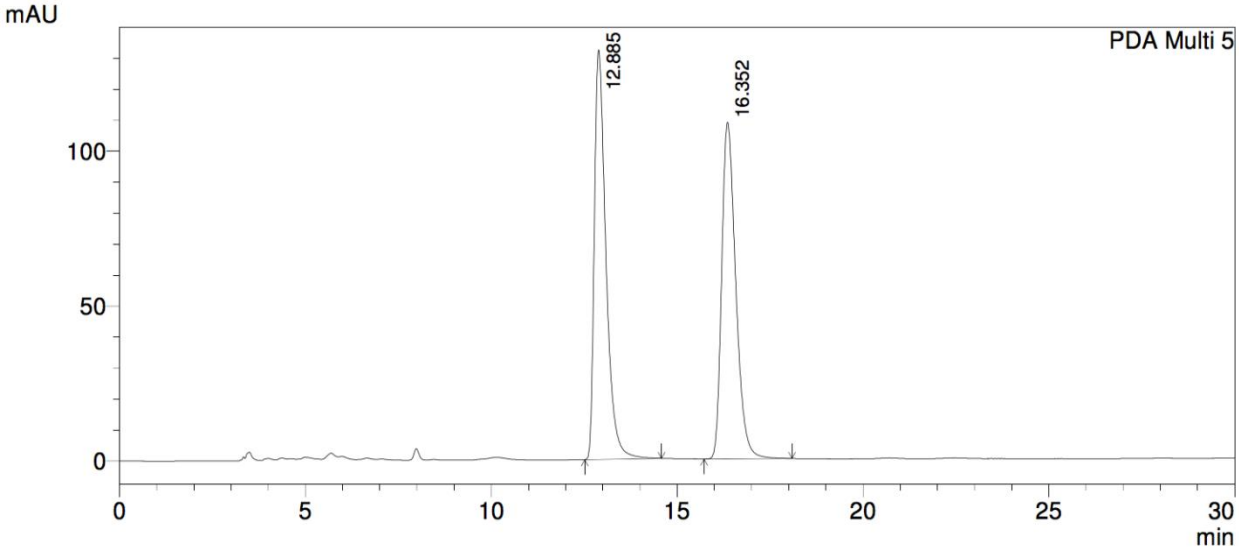
Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.750	6018177	422756	95.313	95.920
2	11.042	295931	17984	4.687	4.080
Total		6314108	440740	100.000	100.000



67

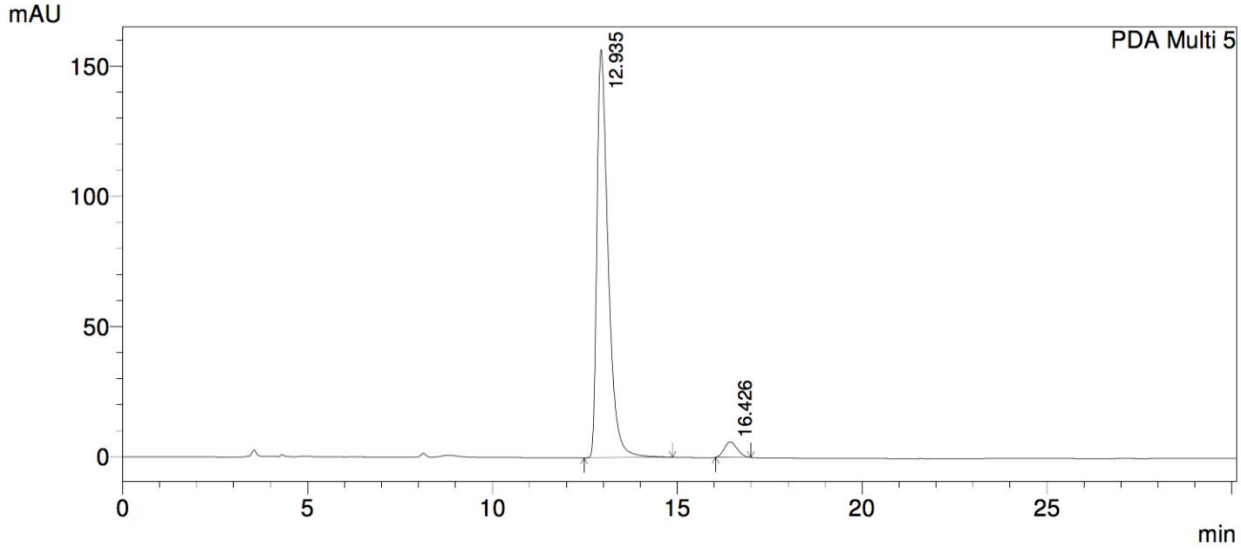
Conditions: HPLC (ChiralPak OD-H, 95:5 hexanes/*i*-PrOH, 1 mL/min, 254 nm)

Racemic Sample:

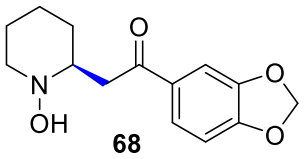


Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.885	2861416	132034	50.060	54.879
2	16.352	2854565	108558	49.940	45.121
Total		5715981	240592	100.000	100.000

Enantioenriched:



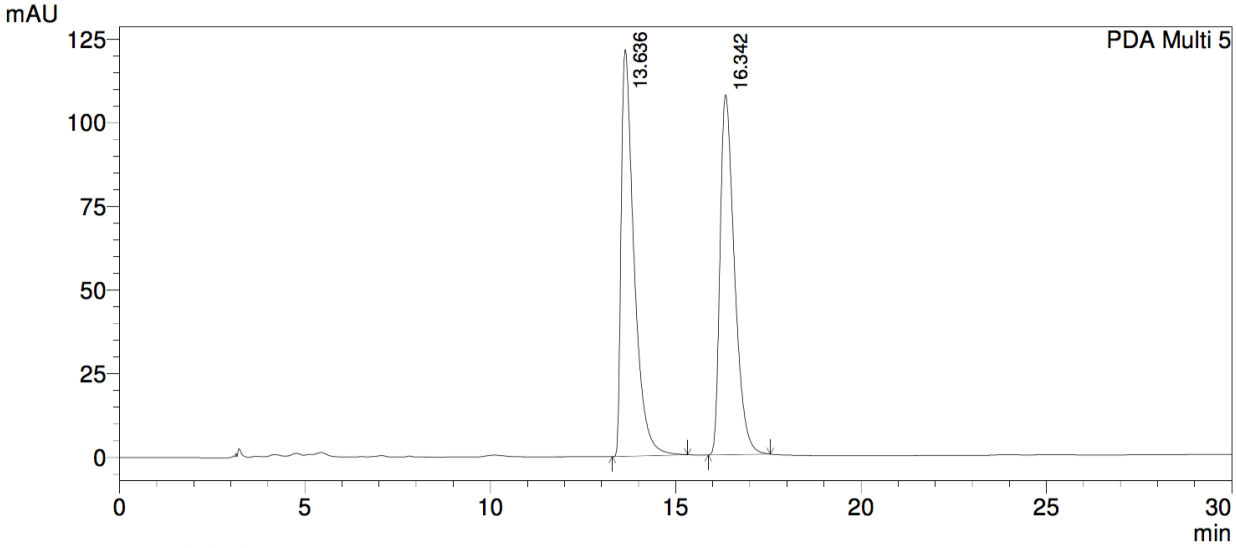
Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.935	3311341	156673	95.802	96.327
2	16.426	145112	5974	4.198	3.673
Total		3456452	162648	100.000	100.000



68

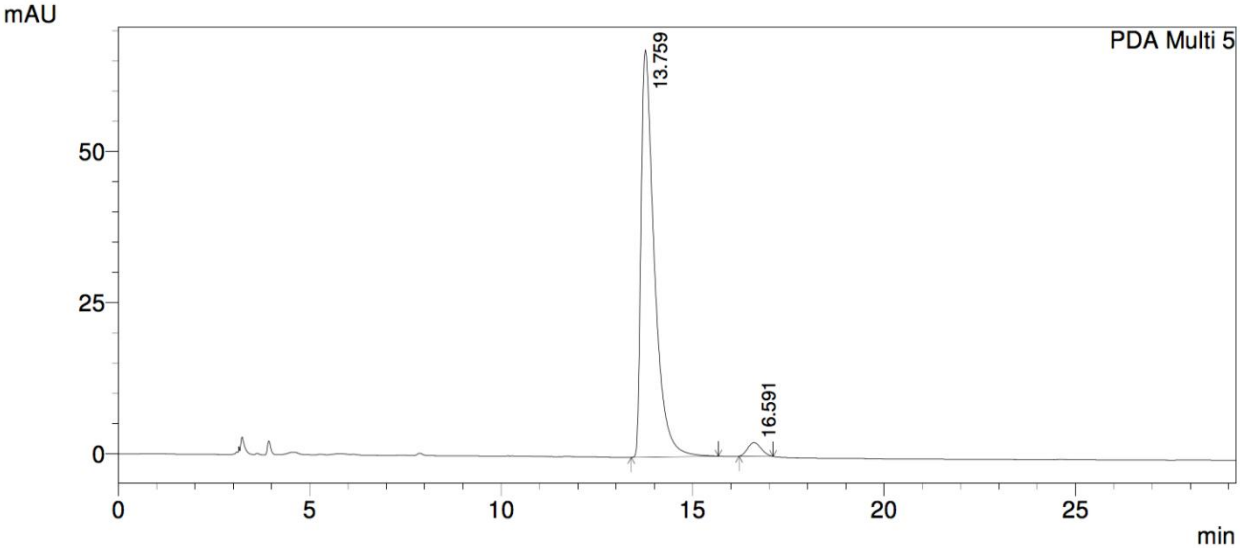
Conditions: HPLC (ChiralPak OD-H, 95:5 hexanes/*i*-PrOH, 1 mL/min, 254 nm)

Racemic Sample:

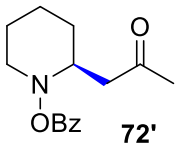


Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.636	2935315	121498	50.221	53.059
2	16.342	2909505	107488	49.779	46.941
Total		5844820	228986	100.000	100.000

Enantioenriched Sample:



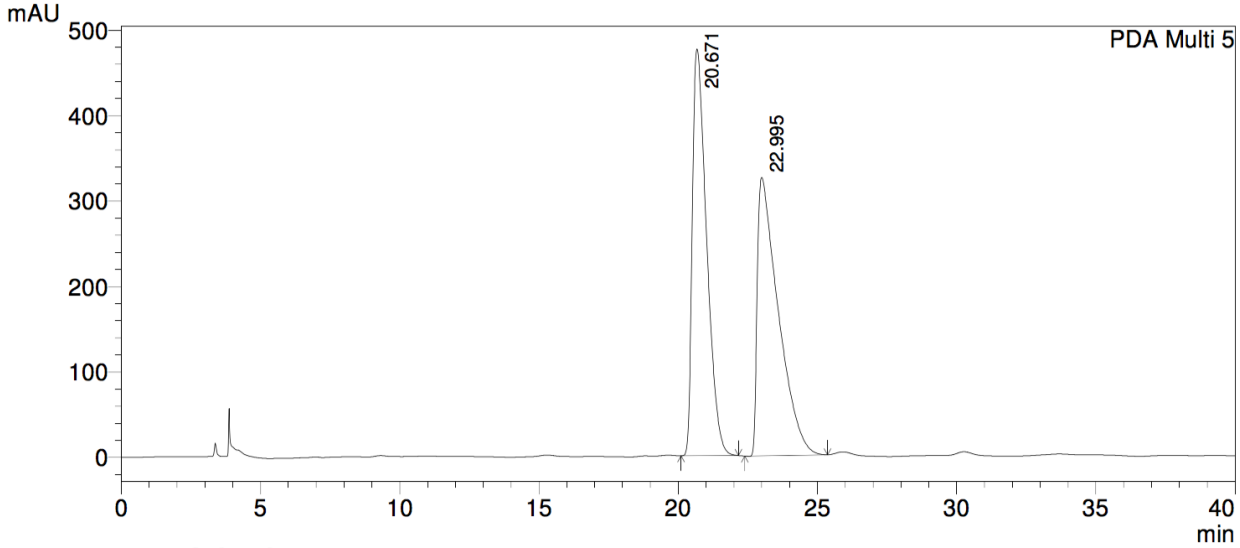
Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.759	1628948	67370	96.702	96.754
2	16.591	55553	2260	3.298	3.246
Total		1684501	69630	100.000	100.000



72'

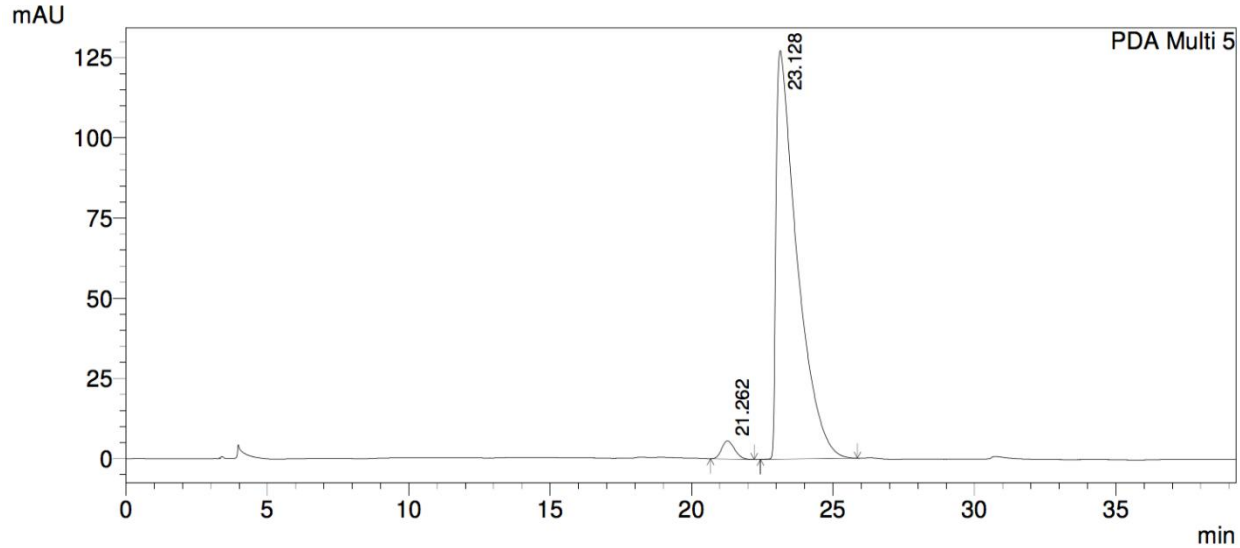
Conditions: HPLC (ChiralPak OD-H, 99:1 hexanes/*i*-PrOH, 1 mL/min, 254 nm)

Racemic Sample:

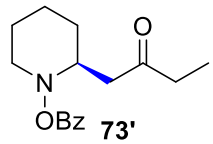


Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.671	17011683	475861	49.881	59.360
2	22.995	17093005	325796	50.119	40.640
Total		34104688	801658	100.000	100.000

Enantioenriched Sample:



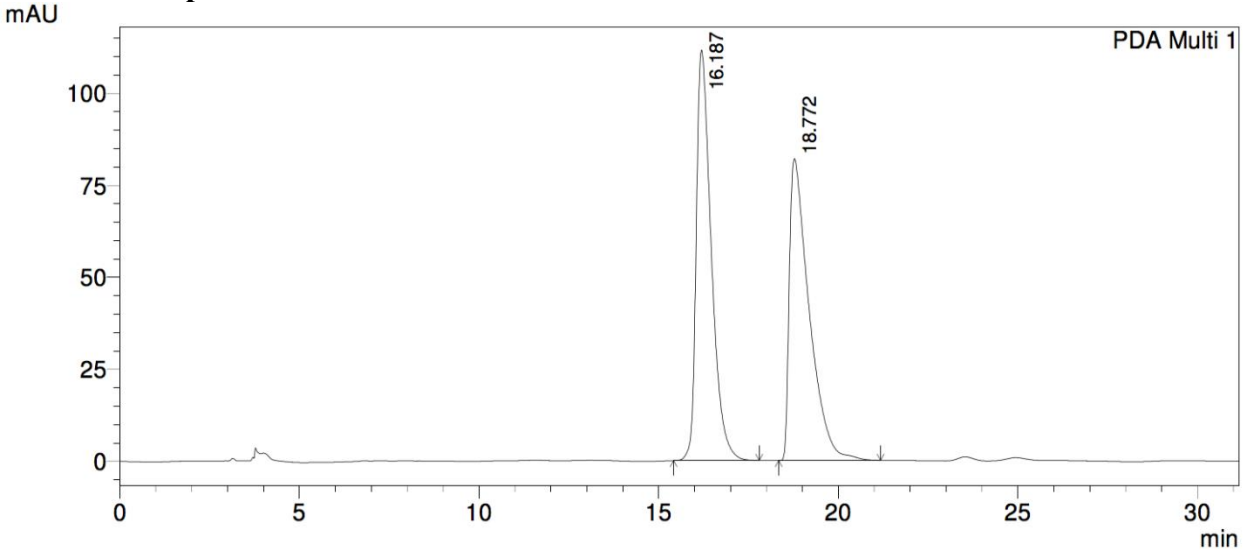
Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.262	179442	5651	2.660	4.248
2	23.128	6566841	127379	97.340	95.752
Total		6746282	133030	100.000	100.000



73'

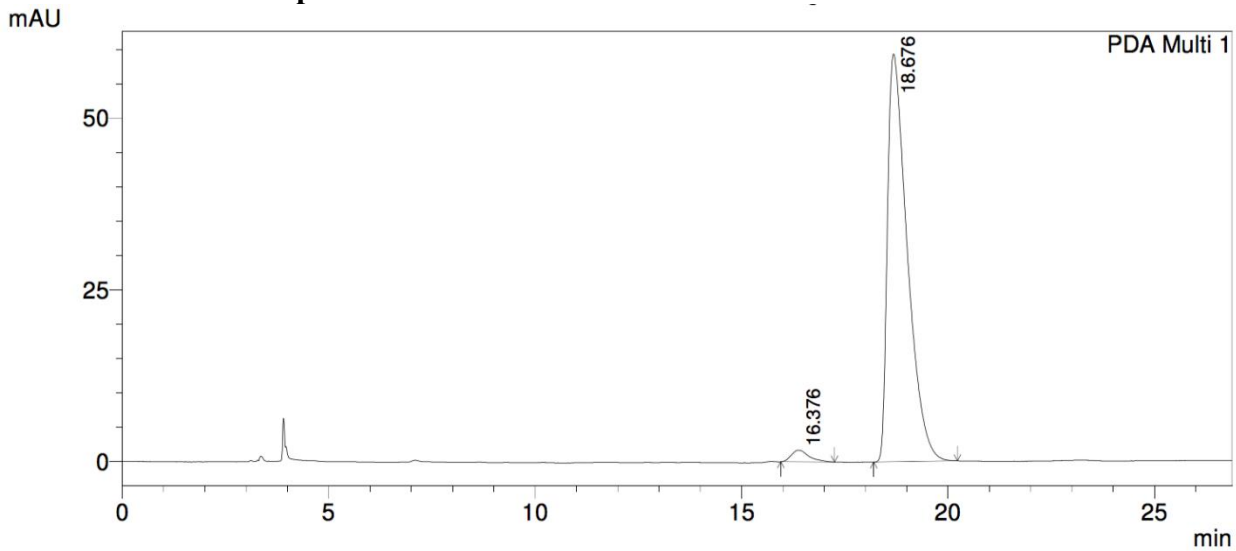
Conditions: HPLC (ChiralPak OD-H, 99:1 hexanes/*i*-PrOH, 1 mL/min, 254 nm)

Racemic Sample:

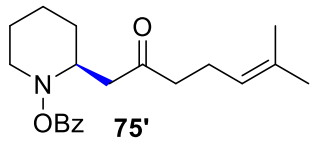


Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.187	3251227	111520	50.858	57.629
2	18.772	3141579	81994	49.142	42.371
Total		6392806	193514	100.000	100.000

Enantioenriched Sample:



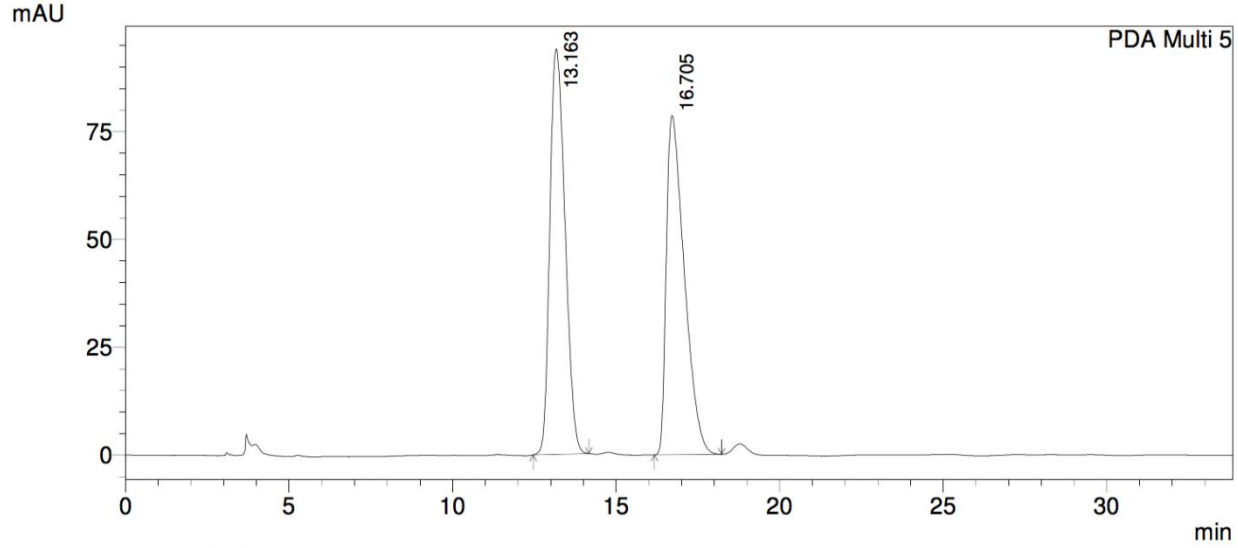
Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.376	50691	1710	2.496	2.798
2	18.676	1980395	59377	97.504	97.202
Total		2031086	61087	100.000	100.000



75'

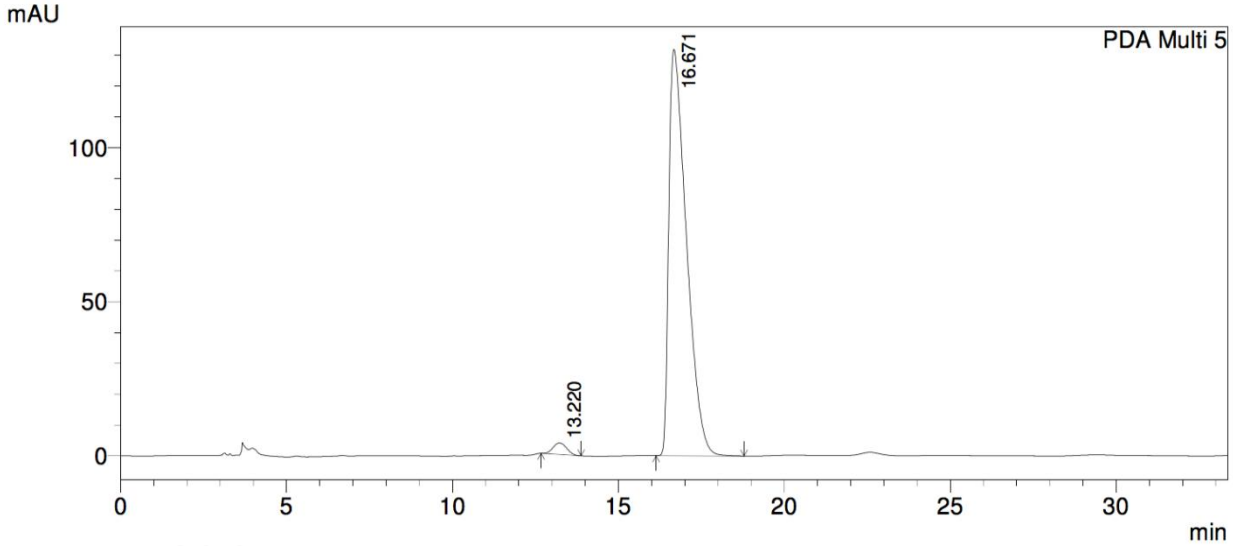
Conditions: HPLC (ChiralPak OD-H, 99:1 hexanes/*i*-PrOH, 1 mL/min, 254 nm)

Racemic Sample:

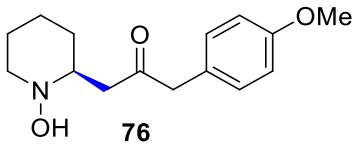


Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.163	3041718	94044	50.216	54.455
2	16.705	3015522	78655	49.784	45.545
Total		6057241	172699	100.000	100.000

Enantioenriched Sample:



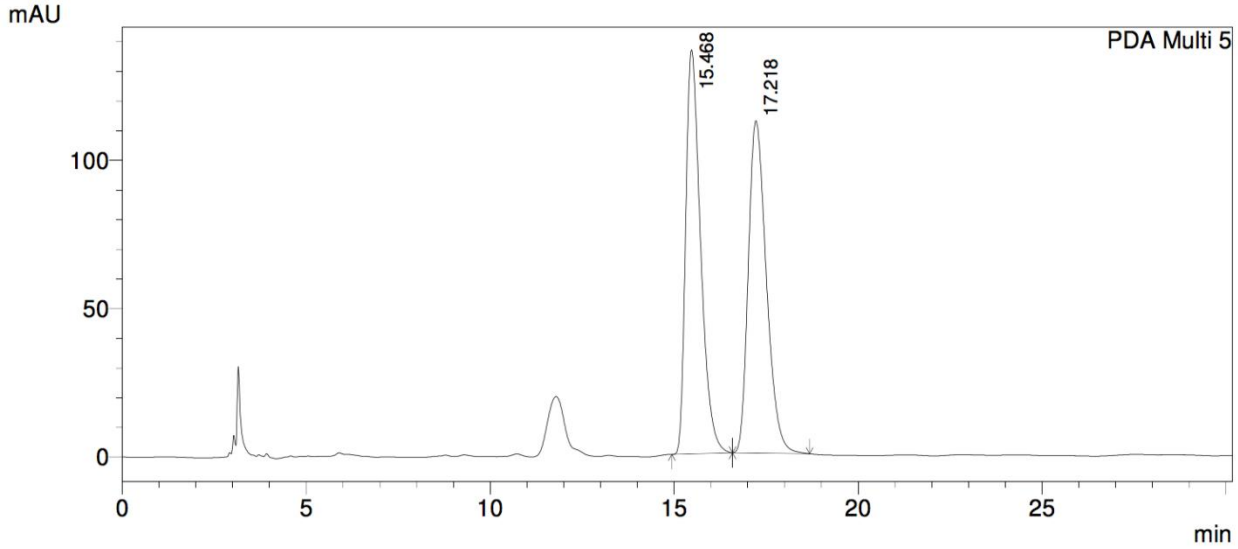
Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.220	105139	3709	2.116	2.737
2	16.671	4864102	131796	97.884	97.263
Total		4969241	135505	100.000	100.000



76

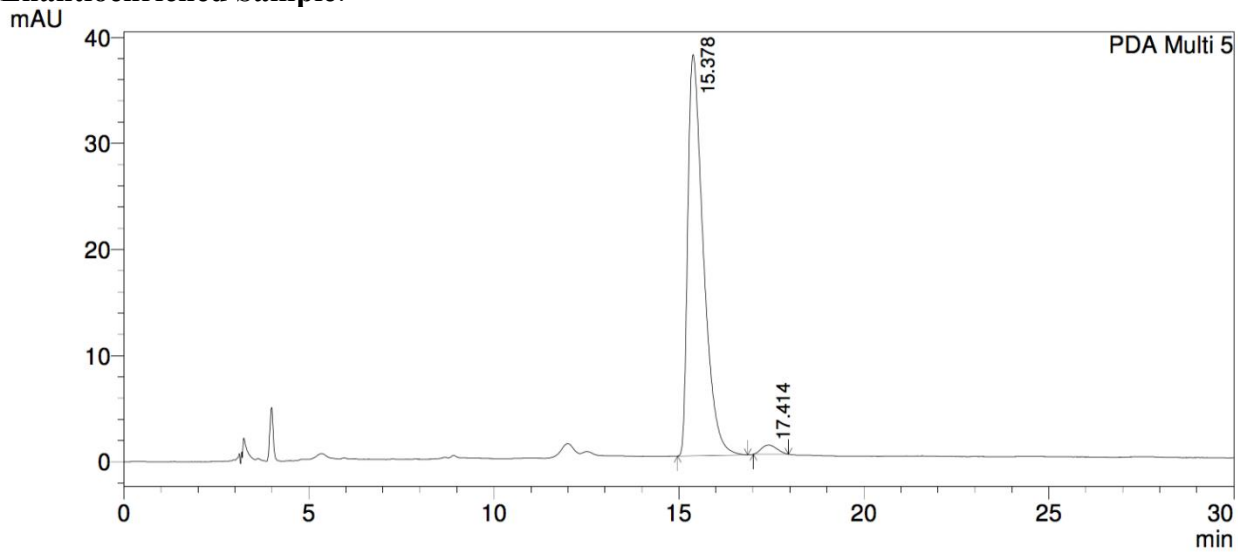
Conditions: HPLC (ChiralPak OD-H, 97:3 hexanes/*i*-PrOH, 1 mL/min, 254 nm)

Racemic Sample:

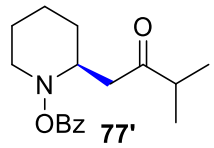


Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.468	3831520	136172	50.019	54.869
2	17.218	3828672	112004	49.981	45.131
Total		7660191	248176	100.000	100.000

Enantioenriched Sample:



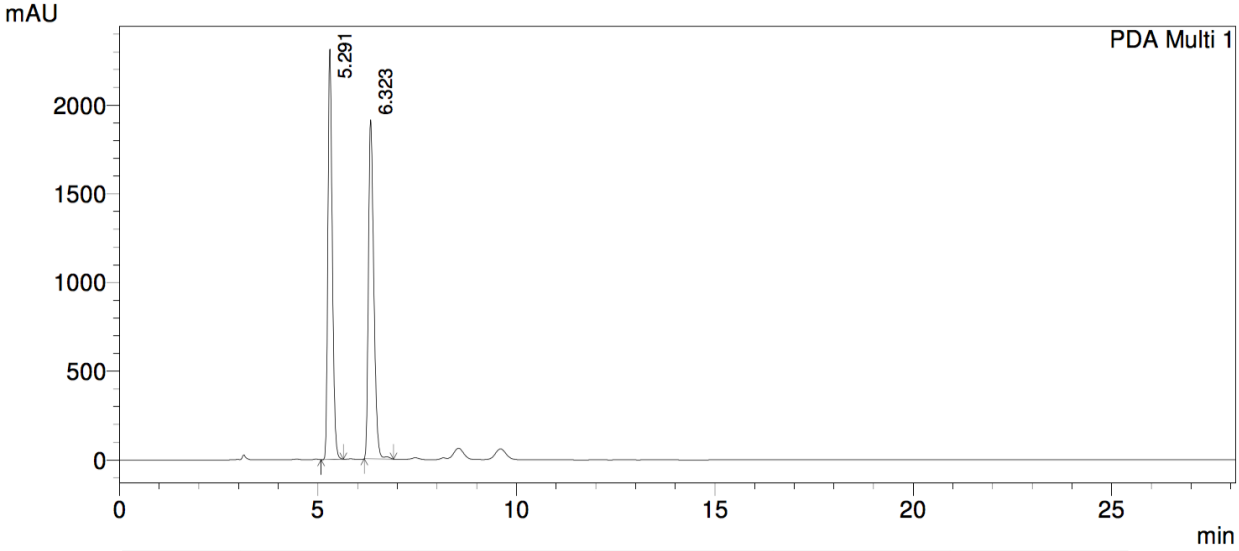
Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.378	1104567	37797	97.784	97.761
2	17.414	25031	866	2.216	2.239
Total		1129598	38663	100.000	100.000



77'

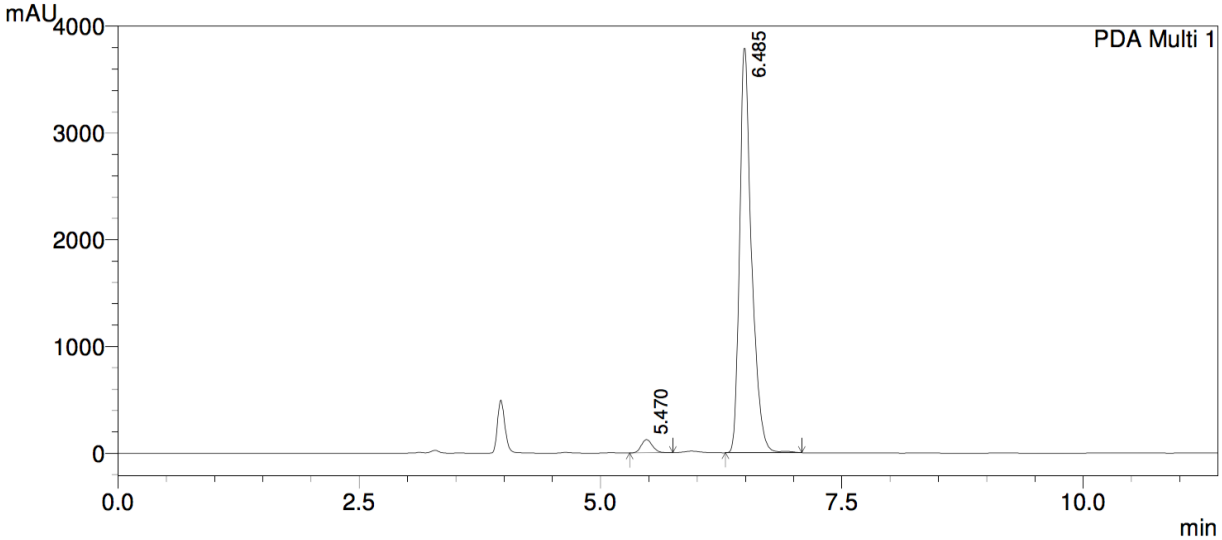
Conditions: HPLC (ChiralPak OD-H, 95:5 hexanes/*i*-PrOH, 1 mL/min, 215 nm)

Racemic Sample:

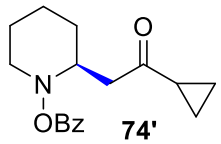


Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.291	17833478	2309022	49.887	54.735
2	6.323	17914616	1909519	50.113	45.265
Total		35748094	4218541	100.000	100.000

Enantioenriched Sample:



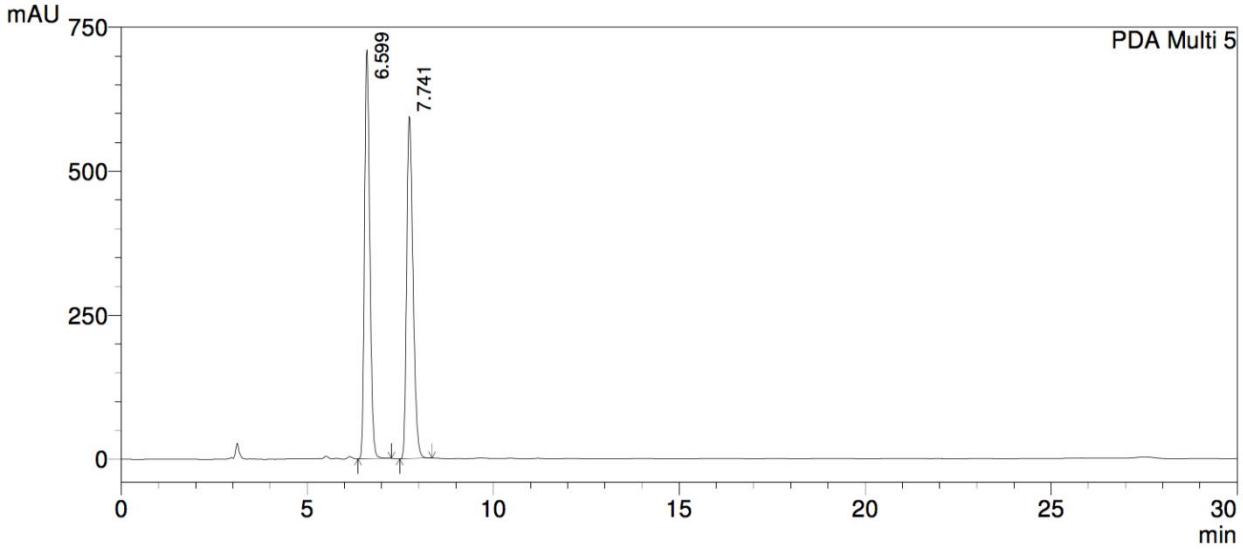
Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.470	992071	124271	2.939	3.176
2	6.485	32757928	3788035	97.061	96.824
Total		33749998	3912306	100.000	100.000



74'

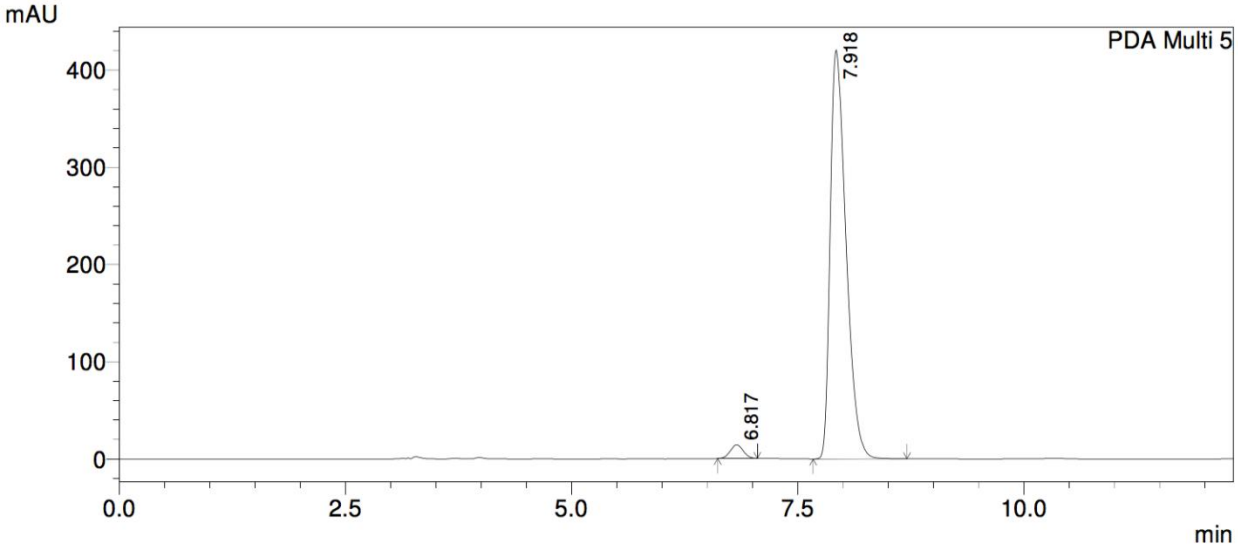
Conditions: HPLC (ChiralPak OD-H, 95:5 hexanes/*i*-PrOH, 1 mL/min, 254 nm)

Racemic Sample:

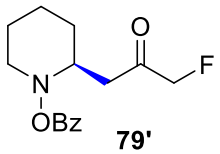


Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.599	6968760	709596	49.860	54.436
2	7.741	7007796	593945	50.140	45.564
Total		13976556	1303541	100.000	100.000

Enantioenriched Sample:



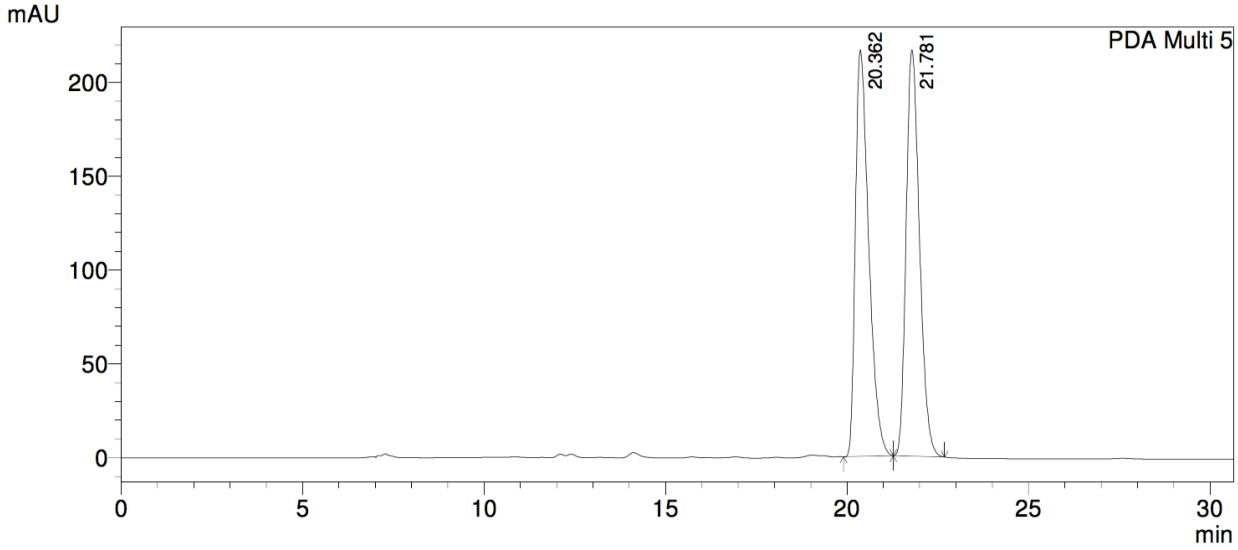
Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.817	142258	14233	2.708	3.272
2	7.918	5111098	420770	97.292	96.728
Total		5253356	435003	100.000	100.000



79'

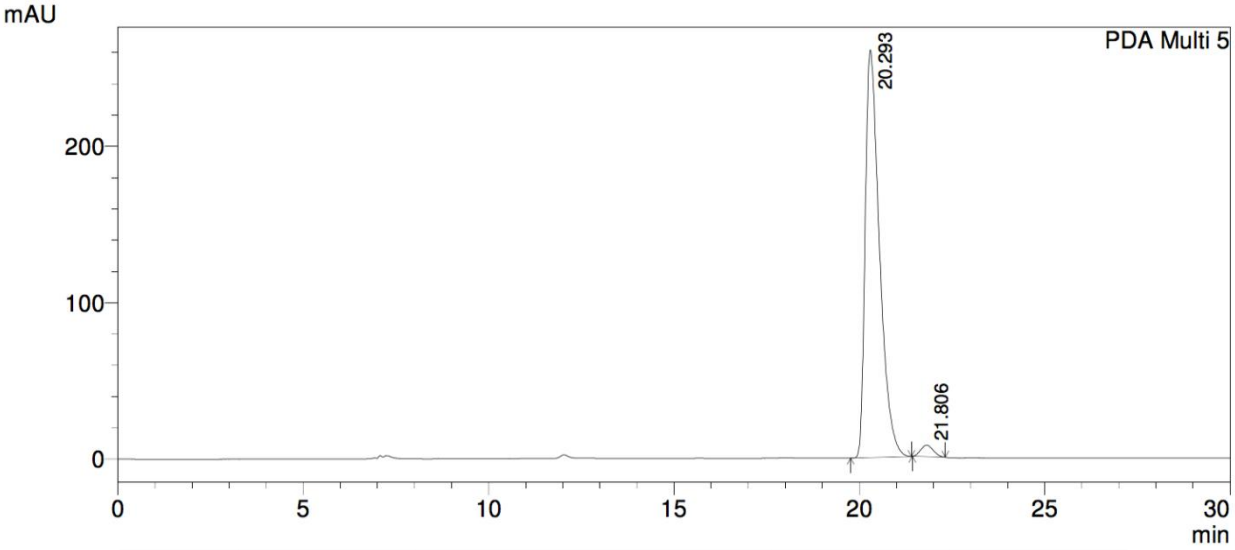
Conditions: HPLC (ChiralPak OD-H, 97:3 hexanes/*i*-PrOH, 1 mL/min, 254 nm)

Racemic Sample:

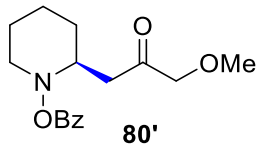


Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.362	5527800	216631	49.927	50.023
2	21.781	5543998	216433	50.073	49.977
Total		11071798	433064	100.000	100.000

Enantioenriched Sample:



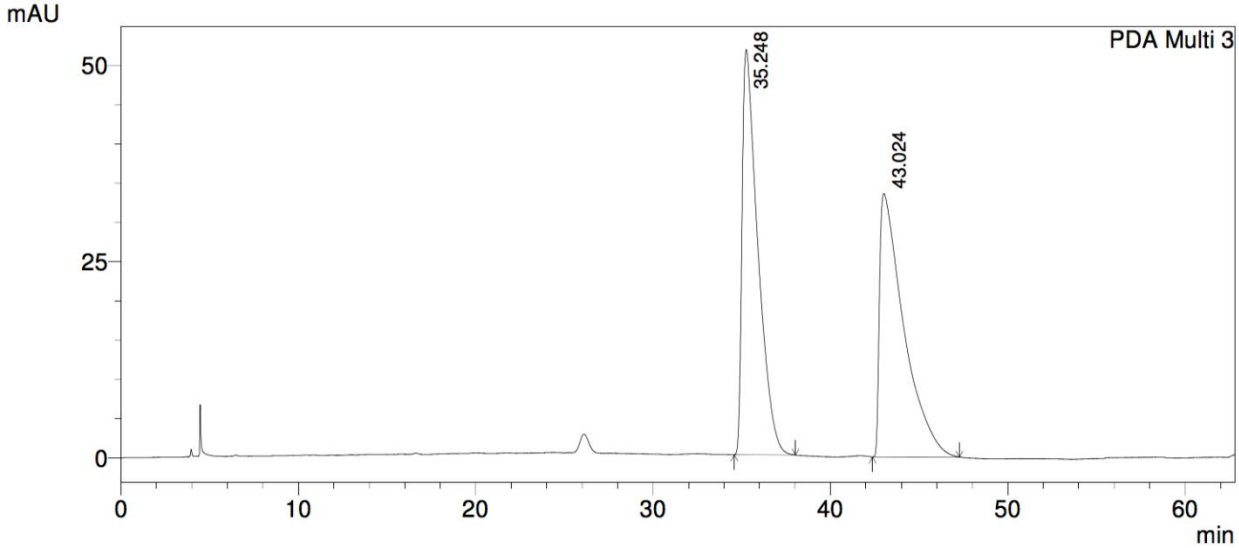
Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.293	6969940	260619	97.547	97.271
2	21.806	175260	7313	2.453	2.729
Total		7145200	267932	100.000	100.000



80'

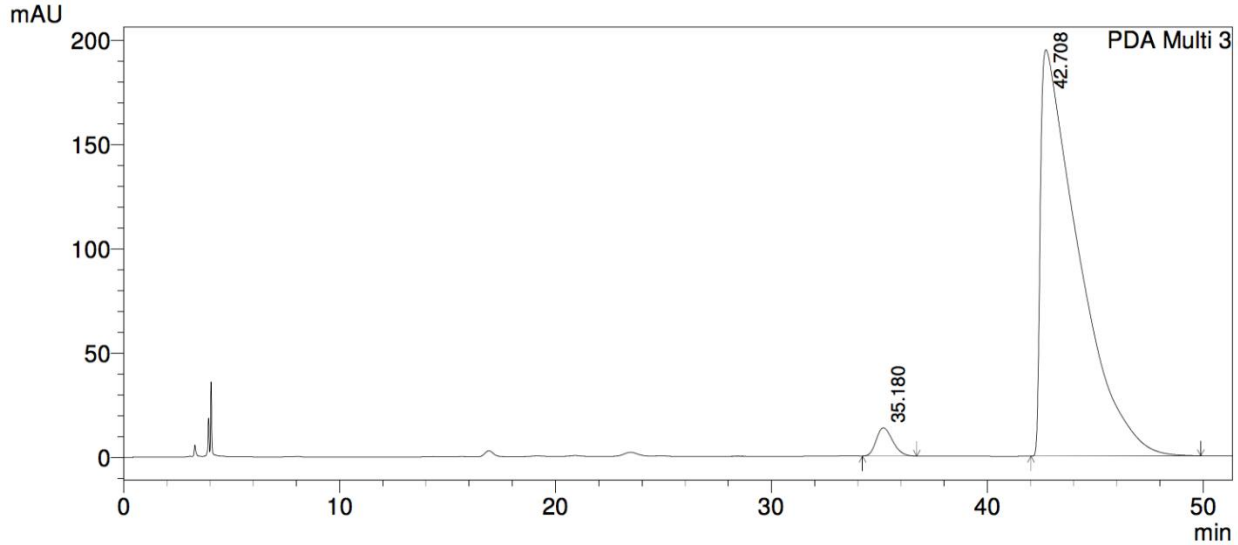
Conditions: HPLC (ChiralPak OD-H, 99:1 hexanes/*i*-PrOH, 1 mL/min, 230 nm)

Racemic Sample:

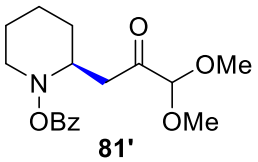


Peak#	Ret. Time	Area	Height	Area %	Height %
1	35.248	3198848	51696	50.115	60.631
2	43.024	3184114	33568	49.885	39.369
Total		6382962	85264	100.000	100.000

Enantioenriched Sample:



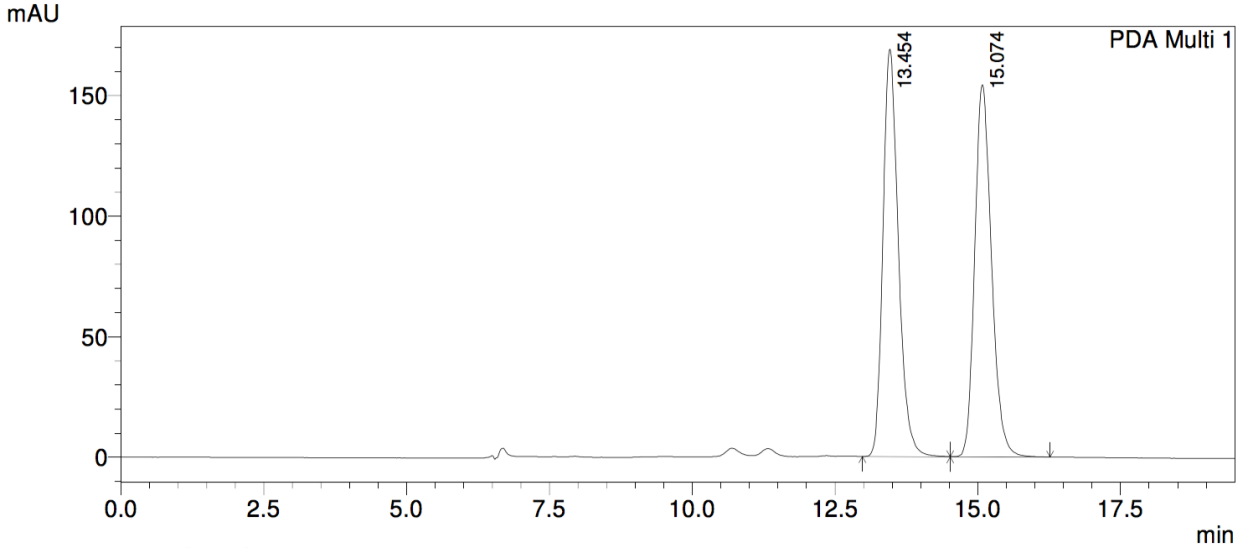
Peak#	Ret. Time	Area	Height	Area %	Height %
1	35.180	717200	13554	2.920	6.501
2	42.708	23844062	194925	97.080	93.499
Total		24561263	208479	100.000	100.000



81'

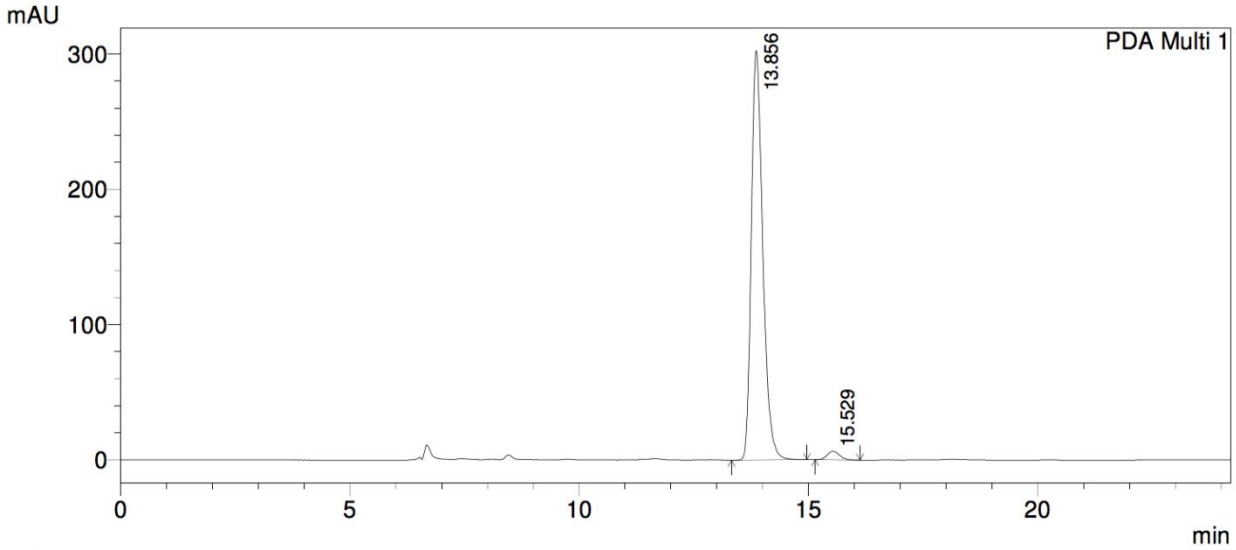
Conditions: HPLC (ChiralPak OJ-H, 95:5 hexanes/*i*-PrOH, 1 mL/min, 254 nm)

Racemic Sample:

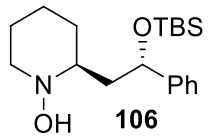


Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.454	3174035	168993	50.107	52.266
2	15.074	3160533	154337	49.893	47.734
Total		6334568	323331	100.000	100.000

Enantioenriched Sample:



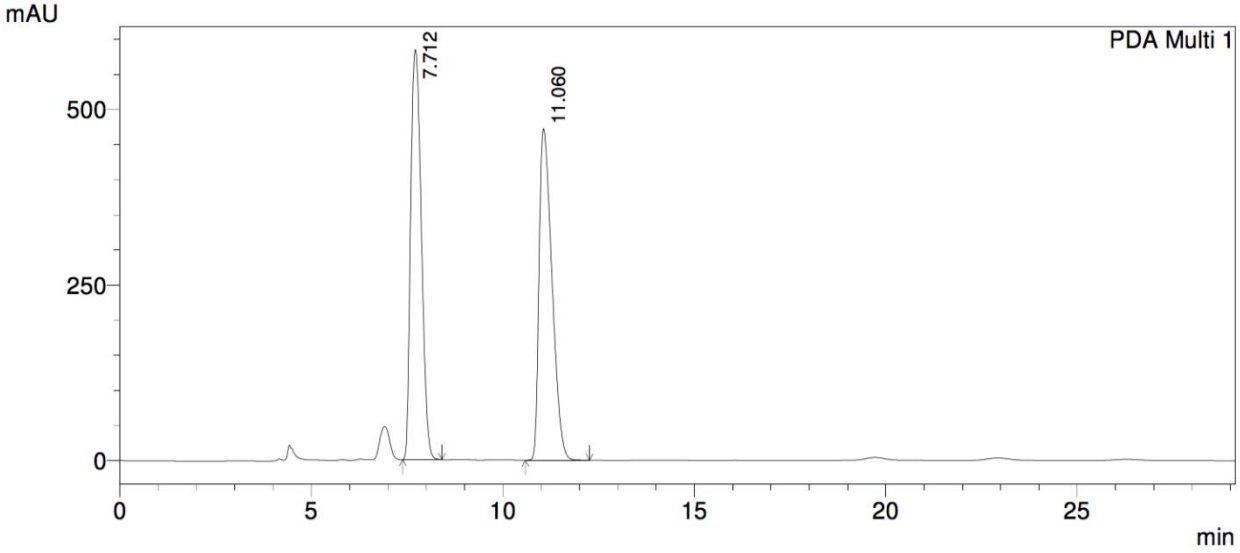
Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.856	5250265	302329	97.814	97.974
2	15.529	117347	6252	2.186	2.026
Total		5367612	308582	100.000	100.000



106

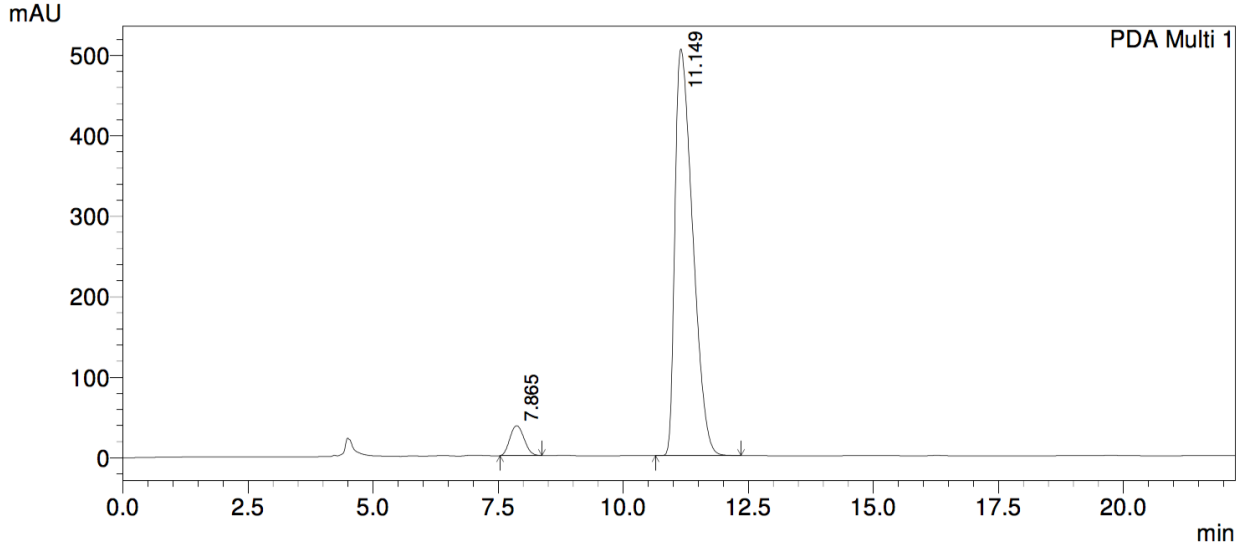
Conditions: HPLC (ChiralPak OD-H, 98:2 hexanes/*i*-PrOH, 1 mL/min, 215 nm)

Racemic Sample:



Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.712	11318560	583744	50.732	55.289
2	11.060	10991802	472069	49.268	44.711
Total		22310363	1055812	100.000	100.000

Enantioenriched Sample:



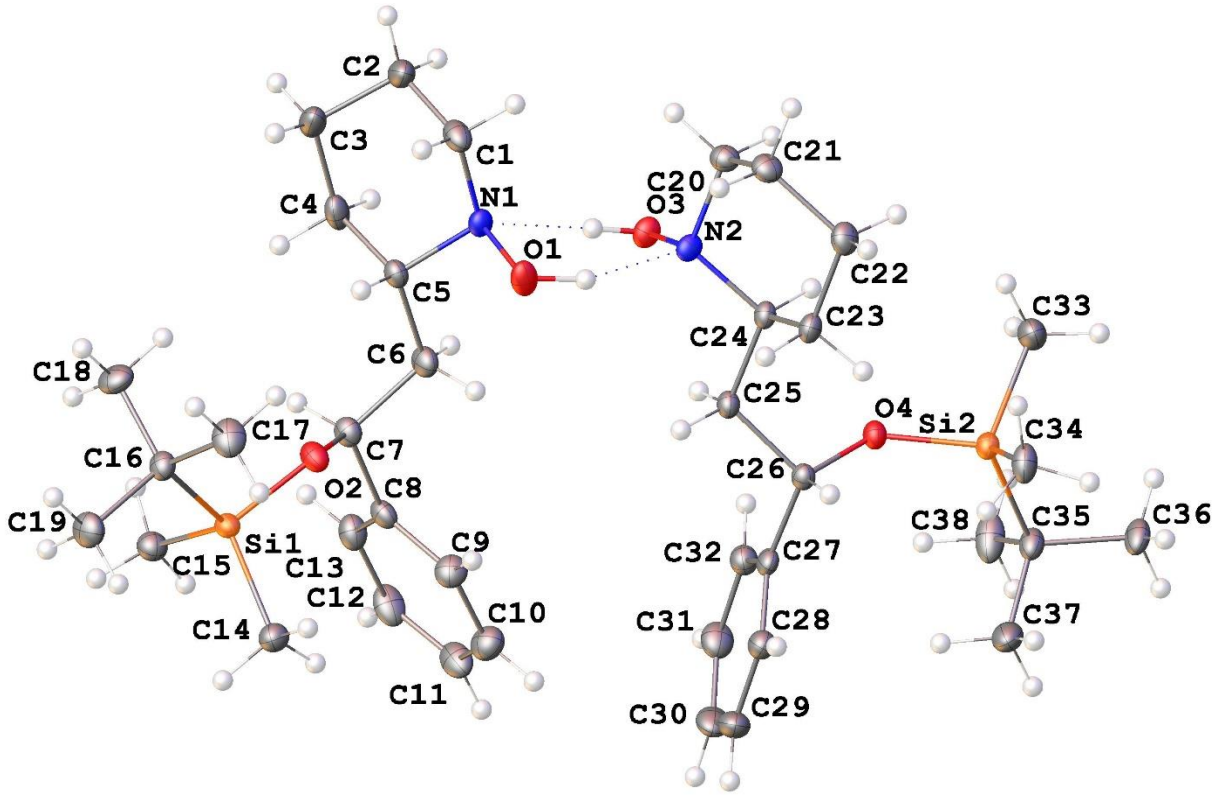
Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.865	732079	37076	5.538	6.835
2	11.149	12486313	505366	94.462	93.165
Total		13218392	542442	100.000	100.000

1.10. X-Ray Crystallography Data.

General information: The diffraction data were measured at 100 K on a Bruker D8 VENTURE diffractometer equipped with a microfocus Mo-target X-ray tube (λ = 0.71073 Å) and microfocus Cu-target X-ray tube (λ = 1.54178 Å) and PHOTON 100 CMOS detector. Data were collected using ϕ and ω scans to survey a hemisphere of reciprocal space. Data reduction and integration were performed with the Bruker APEX3 software package (Bruker AXS, version 2017.3-0, 2018). Data were scaled and corrected for absorption effects using the multi-scan procedure as implemented in SADABS (Bruker AXS, version 2014/5, Krause, Herbst-Irmer, Sheldrick & Stalke, *J. Appl. Cryst.* **2015**, *48*, 3-10). The structure was solved by SHELXT (Version 2018/2: Sheldrick, G. M. *Acta Crystallogr*. **2015**, ***A71***, 3-8) and refined by a full-matrix least-squares procedure using OLEX2 (O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann. J. Appl. Crystallogr. **2009**, *42*, 339-341) (XL refinement program version 2018/3, *Sheldrick, G. M. Acta Crystallogr*. **2015**, *C71*, 3-8). Crystallographic data and details of the data collection and structure refinement are listed in Table S2 for Mo radiation and Table S3 for Cu radiation.

Specific details for structure refinement: All atoms were refined with anisotropic thermal parameters. Hydrogen atoms were included in idealized positions for structure factor calculations except those bound to oxygen atoms O1 and O3. These hydrogen atoms were located in the difference Fourier map and allowed to be refined freely. All structures are drawn with thermal ellipsoids at 50% probability (Mo-radiation).

Figure 1.3. ORTEP representation of 106.



Crystal data and structure refinement for data collected with Mo X-ray tube (λ = 0.71073 Å).

Identification code	0584_lisnyak
Empirical formula	$C_{19}H_{33}NO_2Si$
Formula weight	335.55
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	17.1344(10)
b/Å	6.5231(4)
c/Å	18.2696(11)
α/°	90
β/°	100.047(2)
γ/°	90
Volume/Å^3	2010.7(2)
Z	4
ρ_{calc}g/cm^3	1.108
μ/mm^{-1}	0.126

F(000)	736.0
Crystal size/mm^3	0.36 × 0.32 × 0.24
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.528 to 55.996
Index ranges	-22 ≤ h ≤ 22, -7 ≤ k ≤ 8, -23 ≤ l ≤ 23
Reflections collected	62733
Independent reflections	8335 [R_{int} = 0.0487, R_{sigma} = 0.0486]
Data/restraints/parameters	8335/1/433
Goodness-of-fit on F^2	1.028
Final R indexes [I>=2σ (I)]	R_1 = 0.0368, wR_2 = 0.0686
Final R indexes [all data]	R_1 = 0.0585, wR_2 = 0.0742
Largest diff. peak/hole / e Å^{-3}	0.33/-0.21
Flack parameter	0.02(3)

Crystal data and structure refinement for data collected with Cu-target X-ray tube (λ = 1.54178 Å).

Identification code	0608_lisnyak
Empirical formula	$C_{19}H_{33}NO_2Si$
Formula weight	335.55
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	17.1453(12)
b/Å	6.5277(6)
c/Å	18.2721(14)
α/°	90
β/°	100.099(5)
γ/°	90
Volume/Å^3	2013.3(3)
Z	4
ρ_{calc}g/cm^3	1.107
μ/mm^{-1}	1.089
F(000)	736.0
Crystal size/mm^3	0.32 × 0.14 × 0.12
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	4.912 to 150.626
Index ranges	-21 ≤ h ≤ 21, -7 ≤ k ≤ 6, -22 ≤ l ≤ 22
Reflections collected	22270
Independent reflections	7436 [R_{int} = 0.1597, R_{sigma} = 0.1702]
Data/restraints/parameters	7436/1/427
Goodness-of-fit on F^2	0.986

Final R indexes [I>=2σ (I)]	R_1 = 0.0847, wR_2 = 0.1921
Final R indexes [all data]	R_1 = 0.1523, wR_2 = 0.2339
Largest diff. peak/hole / e Å^{-3}	0.75/-0.48
Flack parameter	0.05(5)

$$R_{int} = \Sigma \mid F_o^2 - \langle F_o^2 \rangle \mid / \Sigma \mid F_o^2 \mid$$

$$R1 = \Sigma \mid \mid F_o \mid - \mid F_c \mid \mid / \Sigma \mid F_o \mid$$

$$wR2 = [\Sigma [w (F_o^2 - F_c^2)^2] / \Sigma [w (F_o^2)^2]]^{1/2}$$

$$\text{Goodness-of-fit} = [\Sigma [w (F_o^2 - F_c^2)^2] / (n-p)]^{1/2}$$

n: number of independent reflections; p: number of refined parameters

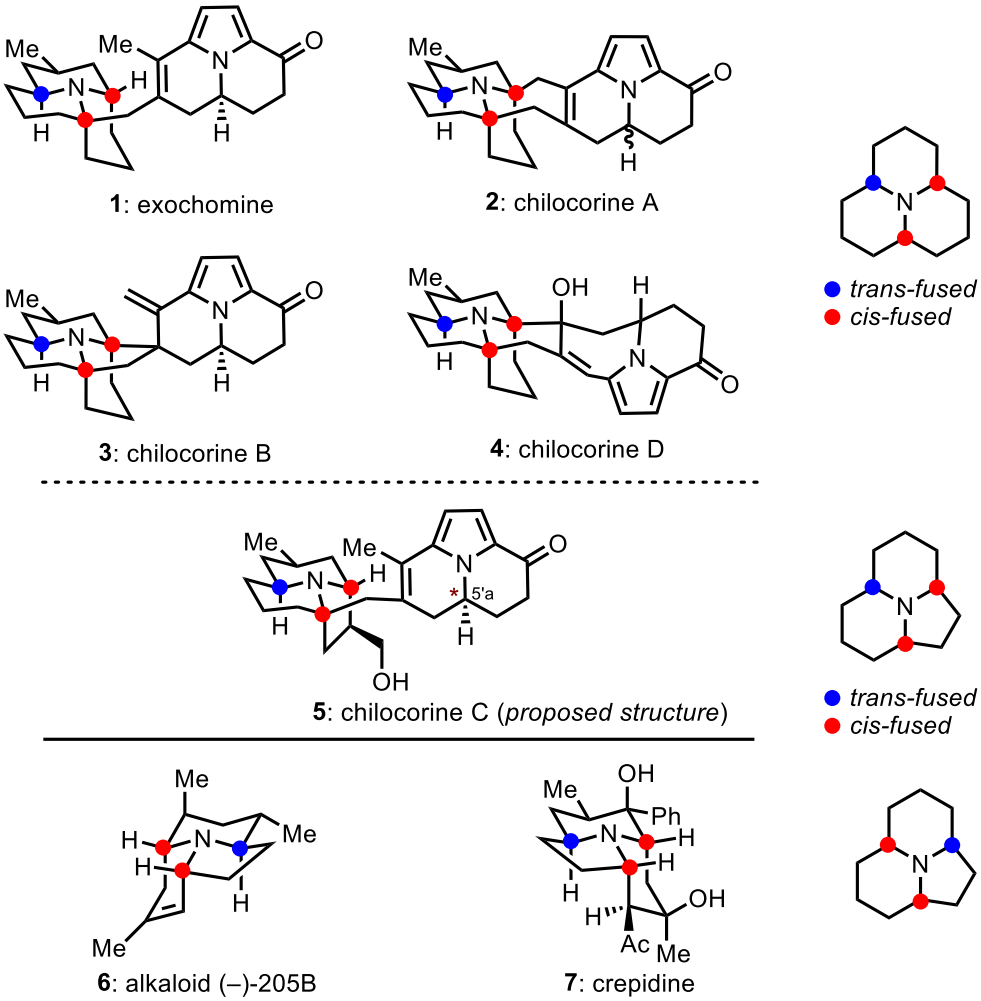
Chapter 2

Enantiospecific Total Synthesis of Chilocorine C

2.1. Isolation and Structural Features of Chilocorine C.

Chilocorine C (**5**) is a defensive hexacyclic alkaloid that was isolated from ladybug beetles (Coccinellidae) in 1998 by the Meinwald group.[1] It belongs to a class of "dimeric alkaloids" (selected examples are depicted on Figure 2.1)[2] and is present as a minor component in *Chilocorus cacti*. The term heterodimeric represents the fact that they are comprised of two similar fragments, only differing in their oxidation level: the saturated *aza*-tricycle and pyrrole containing heterocycle.[3] Meinwald and co-workers were able to isolate only 0.6 mg of **5** from 460 beetles, along with previously isolated chilocorine A (**2**)[2b] and chilocorine B (**3**)[2c] (Figure 2.1). The structure was primarily determined by NMR analysis (1D and 2D), with the 5'a stereocenter assigned by analogy with **1** and **3** for which X-Ray crystal structures were known. Unlike other members of the family (**1**-**4**), chilocorine C (**5**) exhibits an unusual structural variation in the saturated monomeric subunit that comprised of a 6/6/5 tricyclic (8b-azaacenonaphthylene) system, combining two indolizidine and one quinolizidine substructures. To date, there are only two other known alkaloids that exhibit the same saturated *aza*-tricyclic framework (**6**[4a] and **7**[4b]). One of them, namely alkaloid 205B (**6**), has established itself as a benchmark for testing newly developed methodologies, producing 5 total syntheses over the last two decades.[5] The structural analysis of these alkaloids revealed that both **6** and **7** are *cis*-fused quinolizidines with *trans*,*cis*-fusion of two indolizidine substructures, whereas chilocorine C contains a *tran*s-fused quinolizidine with *cis*,*cis*-fusion for both indolizidine substructures. Giving that even simple *cis*-fused indolizidines are extremely rare,[6] with only a few examples isolated from nature, the latter feature is very unique.

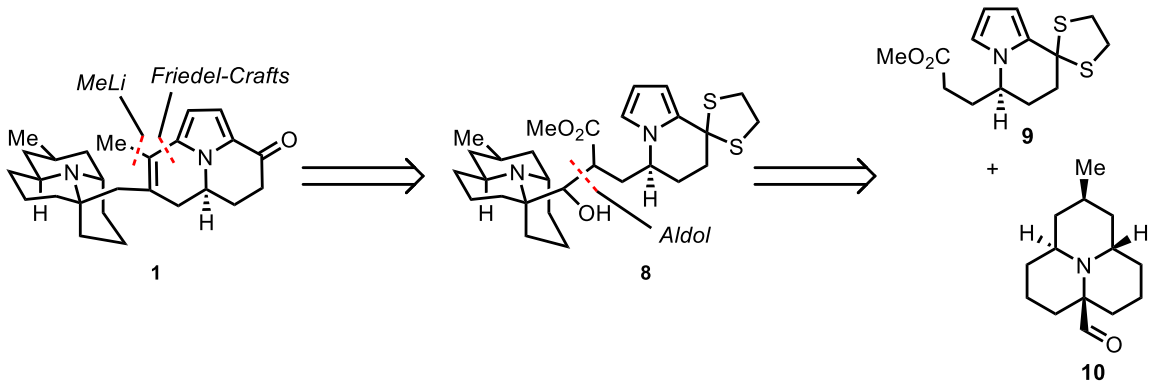
Figure 2.1. Structures of Selected Heterodimeric Ladybug Alkaloids and Other Alkaloids Containing 6/6/5 tricycle.



2.2. Total Synthesis of Exochomine.

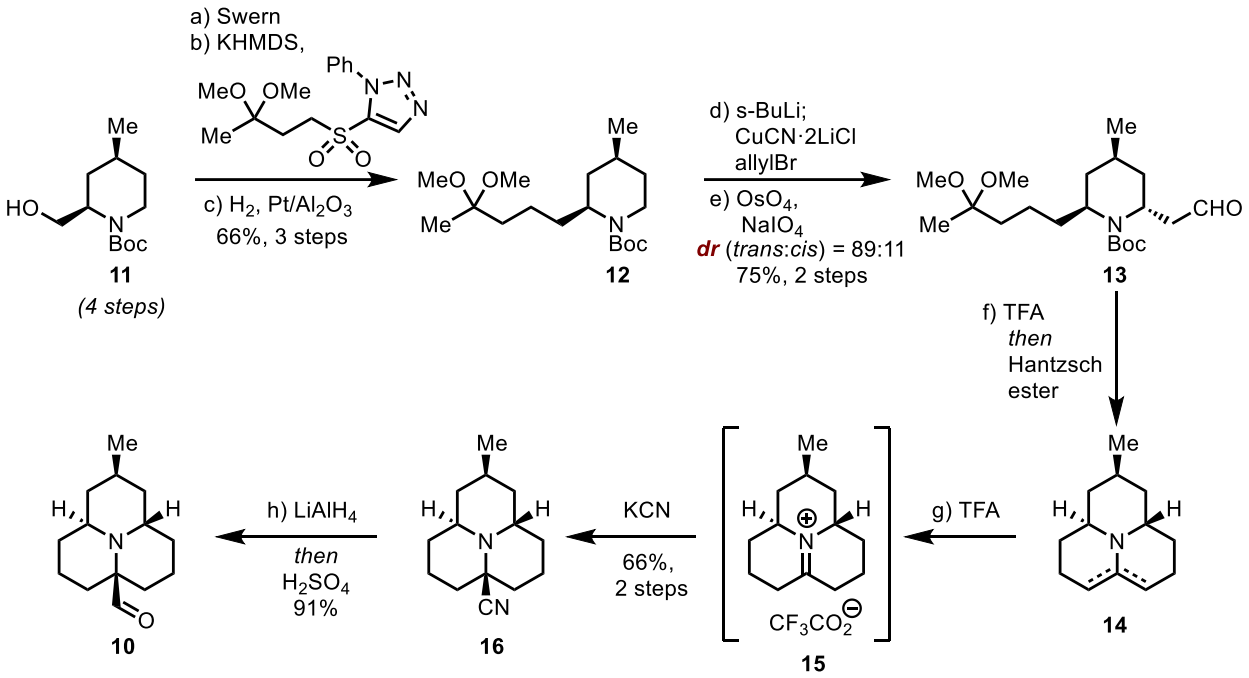
The major inspiration for this project came from a successful synthesis of exochomine (**1**) by our group,[7] due to structural similarities between **1** and **5** (Figure 2.1). In a retrosynthetic manner, exochomine was assembled by coupling two "monomeric" subunits **9** and **10** (Scheme 2.1).

Scheme 2.1. Retrosynthetic Analysis of Exochomine.



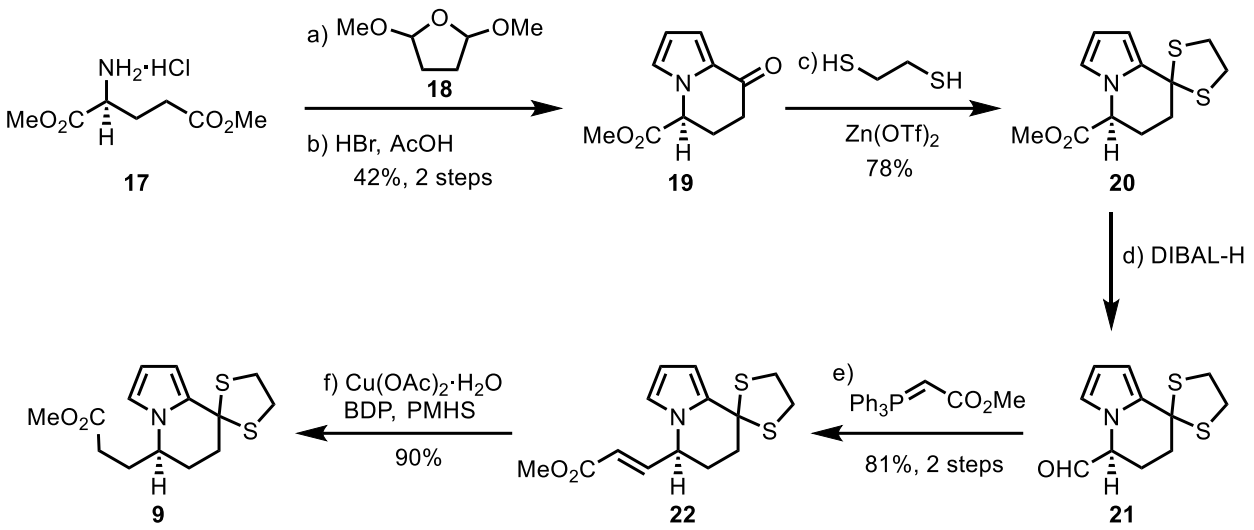
The synthesis of the *aza*-saturated tricycle **10** began from the conversion of *N*-Boc-protected aminoalcohol **11** (prepared in 4 steps from commercially available materials)[7] to **12** via a sequence of steps including a Swern oxidation, Julia–Kocienski olefination and hydrogenation (H_2, Pt/Al_2O_3) of the resulting double bond (66% over 3 steps) (Scheme 2.2). After α-deprotonation and Cu^I-promoted diastereoselective allylation (*dr* (*trans*:*cis*)= 89:11),[8] followed by subsequent oxidative cleavage with catalytic OsO_4 and $NaIO_4$, **12** was converted to the cyclization precursor **13** (75% over 2 steps). Exposure of **13** to TFA in 1,2-dichloroethane at 80 °C then promoted Boc-deprotection, imine and aldol condensations to provide the α,β-unsaturated tricycle that was reduced with Hantzsch ester to iminium salt **14** in a one-pot fashion. Further nucleophilic addition of KCN to the iminium salt produced α-aminonitrile **16** (66% over 2 steps). Lastly, the reduction of **16** with $LiAlH_4$ followed by acidic hydrolysis then delivered the desired aminoaldehyde coupling partner **10** (91%).

Scheme 2.2. Synthesis of the aminoaldehyde 10.



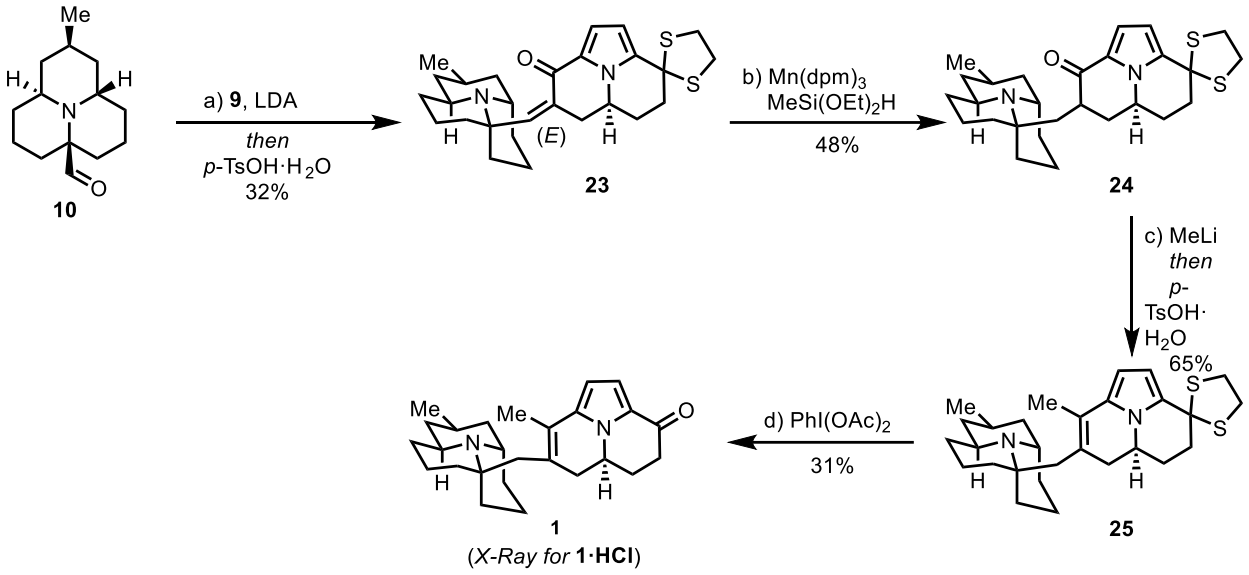
The synthesis of pyrrole "monomer" **9** started with readily available *L*-diethylglutamate salt **17** (Scheme 2.3), first undergoing condensation with **18** to form the pyrrole ring, followed by intramolecular Friedel-Crafts cyclization to deliver acyl pyrrole **19** (42% over 2 steps).[9] Further Lewis acid catalyzed protection of the ketone moiety with 1,2-ethanedithiol provided **20** (78%). The choice of the dithiane protecting group was essential, since the use of an acetal protecting group was not feasible, as it was easily removed even on SiO_2 during purification. Next, the ester group of **20** was converted to the respective aldehyde with DIBAL-H before being subjected to Wittig olefination, delivering **22** (81% over 2 steps). Final reduction of the α,β-unsaturated ester **22** to **9** was accomplished by following the protocol previously reported by Lipshutz (90%).[10]

Scheme 2.3. Synthesis of pyrrole coupling partner 9.



With both **9** and **10** in hand, the coupling was performed under aldol reaction conditions, generating the enolate from **9** with LDA (Scheme 2.4). The resulting aldol was then treated in the same pot with *p*-TsOH·H_2O to induce aldol dehydration and intramolecular Friedel-Crafts cyclization, giving **23** (32%). Several conditions were then tested for the 1,4-reduction of the enone **23**, with the only successful approach being an HAT-type reduction developed by Magnus[11a] and Shenvi[11b] (stoichiometric $Mn(dpm)_3$ and $MeSi(OEt)_2H$ as the hydride source here) giving **24** in 48% yield. The final methyl group was installed by treating acyl pyrrole **24** with MeLi, followed by quenching with *p*-TsOH·H_2O to induce dehydration of the resulting tertiary alcohol, giving **25** (65%). The thioacetal was then oxidatively removed by treatment with $PhI(OAc)_2$ to deliver exochomine (**1**) in 31% yield. Interestingly, the NMR of synthetic **1** didn't match the natural exochomine,[2a] however the single crystal X-Ray analysis confirmed its identity.

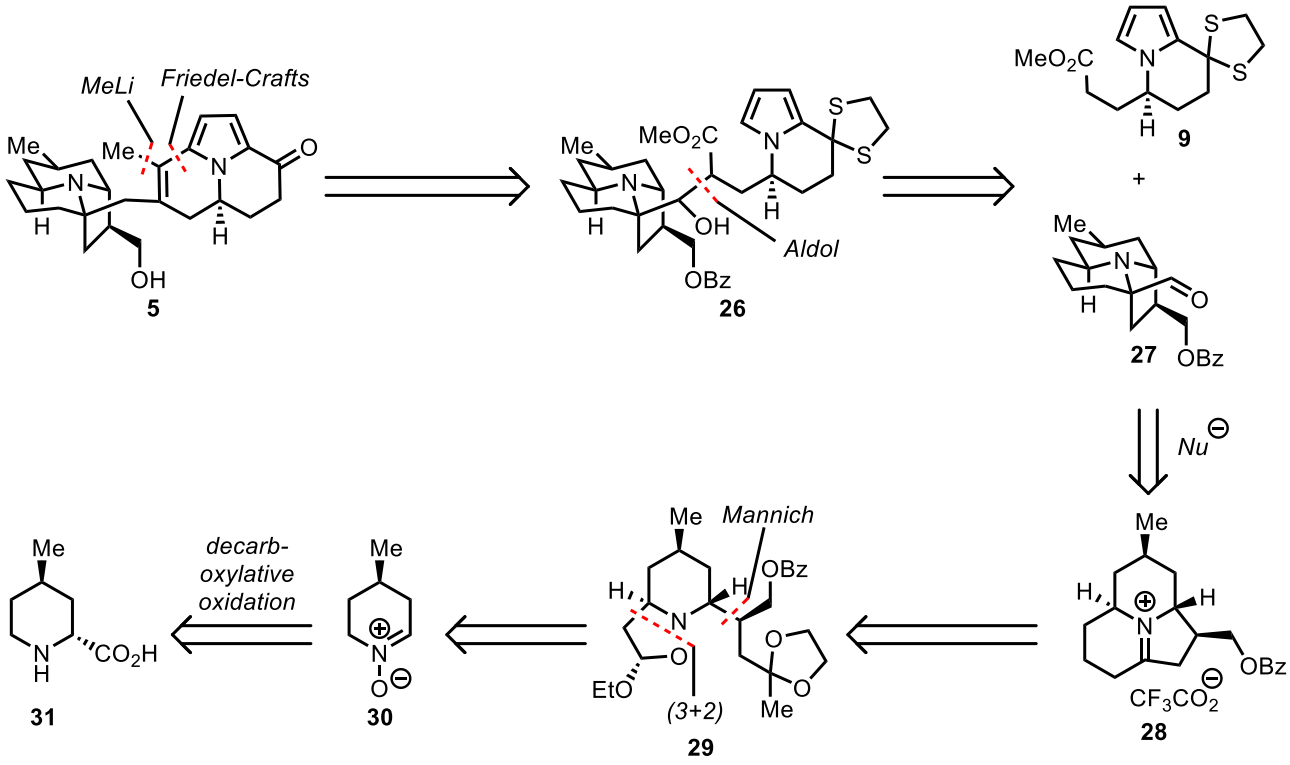
Scheme 2.4. Completion of the Total Synthesis of Exochomine.



2.3. Chilocorine C Retrosynthetic Analysis.

The first steps of the retrosynthetic analysis for the synthesis of chilocorine C (**5**) (Scheme 2.5) were inspired by the exochomine synthesis described above. Thus, we envisioned a similar aldol condensation of the two coupling partners **9** and **27** to take place. Since the synthesis of **9** was already established, the main focus was concentrated on the preparation of the structurally unique α-aminoaldehyde "monomer" **27**. Realizing that the aldehyde could be made from a similar nucleophilic addition to iminium, we then traced it back to **28**. This iminium salt was envisioned to be made by a series of condensations from isoxazolidine **29**, as it already has all of the necessary stereocenters in place. The installation of the required stereochemistry would then be possible by utilizing some elements of nitrone chemistry[12] such as (3+2)-cycloadditions and a Mukaiyama-Mannich reaction. These retrosynthetic transformations then led us to a chiral nitrone **30** that was envisioned to be prepared by utilizing the oxidative decarboxylation protocol described by Murahashi,[13] starting from commercially available **31**.

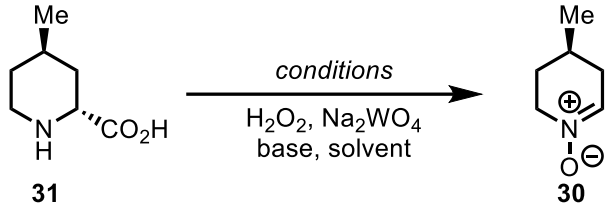
Scheme 2.5. Retrosynthetic Analysis of Chilocorine C.



2.4. Decarboxylative Oxidation and Synthesis of 31.

Following the exact conditions reported by Murahashi[13] the oxidation of our substrate **31** gave us a modest 25% yield of **30**, thus requiring a thorough study of the reaction parameters. As can be seen in Table 2.1., we screened several variables including: number of equivalents of H_2O_2, the nature of the base, presence of a phase-transfer catalyst, solvent, reaction concentration and time. It was found that several parameters were crucial. First, the base is essential for the reaction to proceed (entry 2) because of the zwitterionic nature of **31**. Second, the optimal solvent for the

Table 2.1. Screening of reaction conditions for the decarboxylative oxidation of 12.



31 **30**

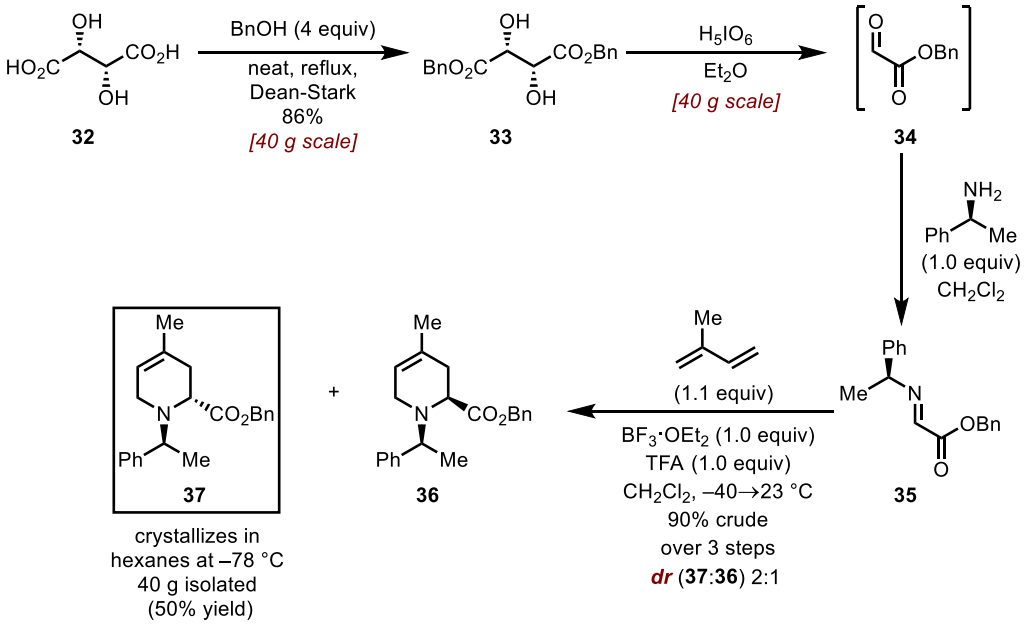
entry[a]	H_2O_2, equiv	Base, equiv	additive, equiv	solvent (M)	time, h	conversion,[b] %	**30**,[c] %
1[d]	3	K_2CO_3 (1.2)	Et_4NCl (0.1)	CH_2Cl_2/H_2O 4/1 (0.2 M)	12	95	25
2	3	–	Et_4NCl (0.1)	CH_2Cl_2/H_2O 4/1 (0.2 M)	24	<5	–
3	3	K_2CO_3 (1.2)	–	CH_2Cl_2/H_2O (0.2 M)	24	95	27
4	2	K_2CO_3 (1.1)	–	MeOH (0.2 M)	2	<5	–
5	2	K_2CO_3 (1.1)	–	D_2O (0.2 M)	2	50	37
6	4	K_2CO_3 (1.1)	–	D_2O (0.2 M)	6	91	27
7	2	K_2CO_3 (1.1)	–	D_2O (1.4 M)	6	85	39
8	3	K_2CO_3 (1.1)	–	D_2O (1.4 M)	7.5	full	38
10	3	K_3PO_4 (1.0)	–	D_2O (1.4 M)	4	92	52
13	3	K_3PO_4 (2.0)	–	D_2O (1.4 M)	3	full	trace
14	3	K_2HPO_4 (2.0)	–	D_2O (1.4 M)	12	40	14
15	3	K_3PO_4 (1.2)	–	CH_2Cl_2/H_2O 4/1 (0.2 M)	4	77	66
16	3	K_3PO_4 (1.2)	–	CH_2Cl_2/H_2O 12/1 (0.06 M)	4	76	90
17	3	K_3PO_4 (1.2)	Et_4NCl (0.1)	CH_2Cl_2/H_2O 12/1 (0.06 M)	3	76	95
18[e]	3	K_3PO_4 (1.2)	Et_4NCl (0.1)	CH_2Cl_2/H_2O 12/1 (0.06 M)	3	71	95

[a]Reactions were performed with **31** (20 mg, 0.14 mmol) and $Na_2WO_4 \cdot H_2O$ (4.6 mg, 0.014 mmol, 10 mol %) at 0 °C with subsequent warming to 23 °C; [b]Determined by crude NMR; [c]Based on reacted starting material. [d]Conditions from ref. 13; [e]Performed on 1 g (7 mmol) scale of **31**.

reaction is water or any biphasic media containing water. Third, the number of equivalents of H_2O_2 cannot exceed 3 (entry 6) due to the overoxidation of **30** to the corresponding hydroxamic acid. Fourth, a stronger base like K_3PO_4 provides a better yield. Fifth, increasing the ratio of CH_2Cl_2 to H_2O and diluting the reaction to 0.06 M significantly increases the isolated yield of **30**. Finally, the presence of a phase-transfer catalyst (Et_4NCl) also resulted in better scalability of the reaction. A gram scale oxidation can be performed with strong reproducibility under the established conditions (entry 18).

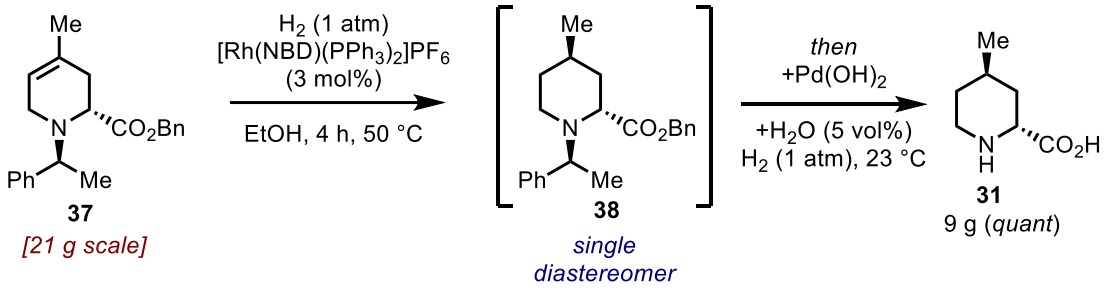
Although (*R*,*R*)-4-methylpipecolic acid (**31**) is a commercial reagent, the price of this valuable synthetic building block at the moment varied from $2000 to $90 per gram. There are few syntheses in academic and patent literature of this compound,[14] but most of them rely either on separation of diastereomeric salts and/or are too long in terms of the step count. As a result, we wanted to design our own potentially robust and scalable synthesis of this amino acid in the enantiopure form.

Scheme 2.6. Preparation of 37 via *Aza*-Diels-Alder Reaction.



The following synthesis has been developed (Scheme 2.6): first, we subjected tartaric acid (**32**) to esterification with benzyl alcohol (Dean-Stark trap) to afford **33** in 86% isolated yield.[15] This was followed by Malaprade oxidation with periodic acid to afford benzyl glyoxylate (**34**) in nearly quantitative yield.[16] This crude compound is carried forward and after condensation with (*S*)-α-phenylethylamine we isolated the imine intermediate **35**, which was further subjected to a dual Lewis/Bronsted acid promoted *aza*-Diels Alder reaction with isoprene, producing a mixture of diastereomers **36** and **37** (*dr* (**36**:**37**) = 1:2).[16] Although the diastereoselectivity of this reaction is rather poor, the mixture of two diastereomers could be separated by cooling the solution in hexanes to –78 °C, and then collecting the precipitated major diastereomer of the desired configuration (**37**).

Scheme 2.7. Completion of the Synthesis of 31.



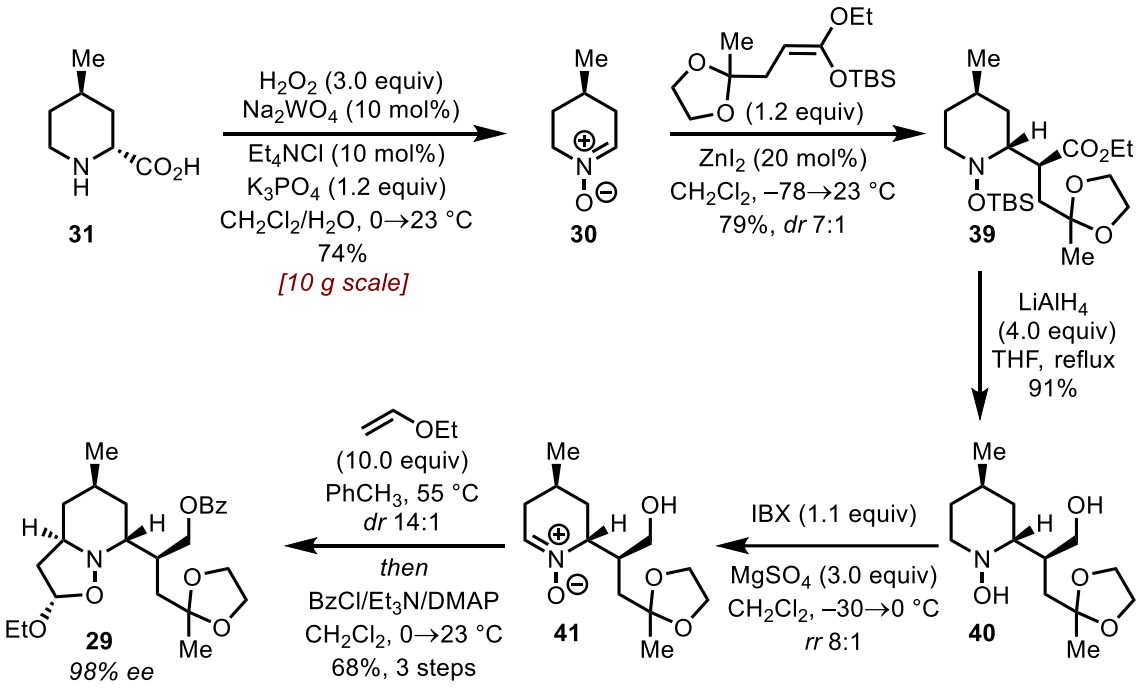
Hydrogenation of **37** under standard hydrogenation conditions (H_2, 1 atm) using a homogeneous [Rh(NBD)(PPh_3)$_2$]PF_6[17] catalyst delivers **38** as a single 2,4-*trans*-isomer (Scheme 2.7).[18] Once that reaction is completed, $Pd(OH)_2$ and water (to dissolve the end product (**31**)) were added and hydrogenation was renewed. After a few hours, the hydrogenolysis was completed and the desired amino acid **31** could be obtained in quantitative yield and analytically pure form after a single recrystallization from the MeOH/EtOH mixture. With the whole sequence being

performed on decagram scale with only one silica plug separation, the overall sequence comprises a very attractive method for a rapid preparation of this building block.

2.5. Gram Scale Synthesis of Isoxazolidine 29 using Nitrone Chemistry.

Once we established the necessary conditions for the decarboxylative oxidation protocol, the same reaction was gradually scaled up to 10 g, eventually producing **30** in 74% isolated yield (Scheme 2.8). With the chiral nitrone **30** in hand, we proceeded to install the right-hand sidechain. This transformation was achieved via a ZnI_2-catalyzed Mukaiyama-Mannich addition[19] to furnish **39** in 79% yield and 7:1 *dr* favoring the desired (8*S*, 2*R*)-isomer. The required ketene silyl acetal in this reaction is prepared in one step from a commercially available derivative of levulinic acid. The resulting ester **39** was then subjected to the reaction with $LiAlH_4$, reducing both the ester and cleaving the TBS group in a reductive fashion[20] to afford **40** (91% yield). In order to functionalize the other position of the piperidine ring we needed to selectively oxidize the obtained hydroxylamine to a less substituted aldonitrone **41**. Using the conditions developed in the previous chapter,[21b] the hydroxylamine **40** was subjected to a reaction with IBX (1.1 equiv)[21a] in the presence of anhydrous $MgSO_4$ providing the desired aldonitrone **41** with a high regioselective ratio (8:1) and quantitative yield. The use of $MgSO_4$ was required for better reproducibility, proving essential on a larger scale. Finally, the remaining two-carbon unit was installed via a (3+2)-cycloaddition reaction[22] with ethyl vinyl ether, producing the addition product with high 2,6-*trans* diastereoselectivity (*dr* 14:1), and was followed by a one-pot benzoyl protection of the primary alcohol to afford the Bz-protected isoxazolidine **29** with 68% yield. The enantiomeric excess of this material was measured to confirm that no racemization occurred in the first step.

Scheme 2.8. Streamlined Synthesis of the Isoxazolidine 29.

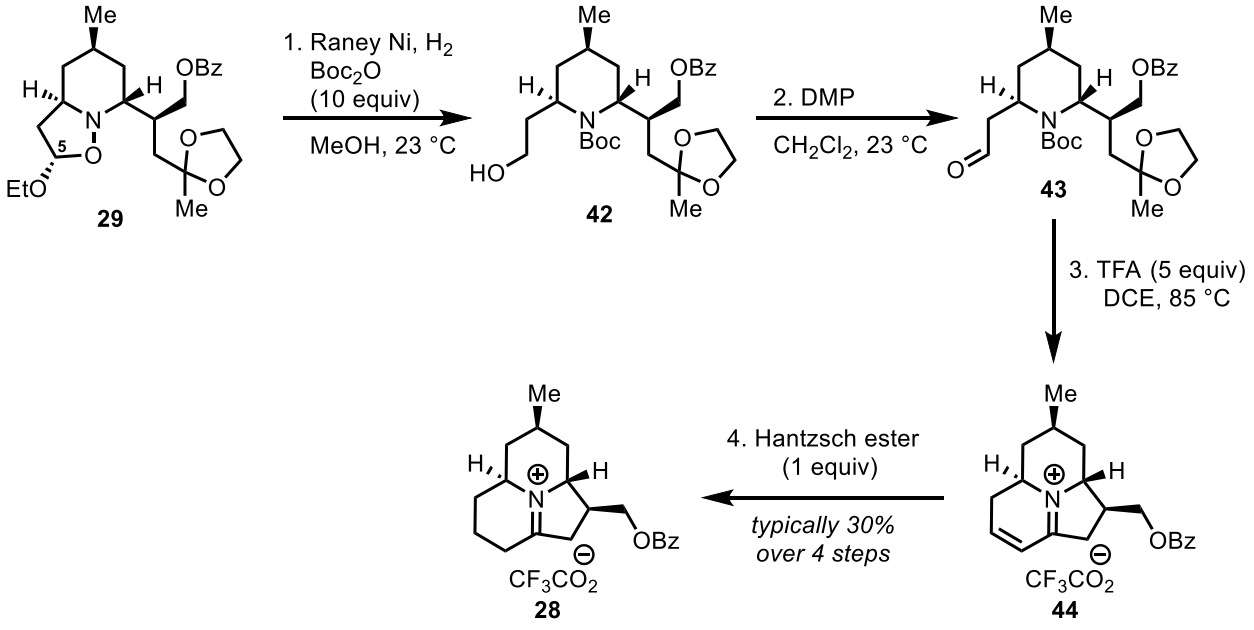


2.6. First Generation Approach to the Iminium Salt 28.

With **29** in hand, we started to screen different conditions for the N–O bond cleavage to access the β-aminoaldehyde required for the aldol condensation cascade. Indeed, several common systems based on transition metals (Zn^0, In^0, Fe^0, Pd^0, Sm^{II})[23] were screened without success, as they were either not able to cleave the N–O bond due to electronic and/or steric factors,[24] or produced multiple decomposition products. Further studies revealed that the β-aminoaldehyde resulting from N–O cleavage is not stable under the explored conditions – a common behavior that is reported in the literature.[25] The solution was eventually established, however, to prevent this decomposition. It required a fast carbamate protection of the free amine moiety once it is formed. Thus, hydrogenation of **29** with Raney Ni under H_2 atmosphere[23a] (Scheme 2.9) over 10 hours in the presence of a large excess of Boc_2O produced Boc-protected β-aminoalcohol **42**. If the reaction is interrupted before complete consumption of **29**, a small amount of **43** (<10% compared to **42**)

could also be isolated, suggesting the reduction of the aldehyde moiety happens after Boc-protection which is relatively fast for this amine. Nevertheless, since the full reduction to the primary alcohol **42** was unavoidable, the reaction time was always extended to ensure the full consumption of **29**. Further oxidation of **42** to **43** was achieved using Dess–Martin periodinane.[26] With *N*-Boc aminoaldehyde in hand, we then attempted the same TFA-promoted cascade sequence described for exochomine (**1**) (Scheme 2.2). Gratifyingly, the cyclization was successful, and **44** could be isolated as a sole product that was further reduced with Hantzsch ester to provide the iminium salt **28**. Despite being the first successful approach toward **28**, this method suffered from low yield (typically ~30% over 4 steps) due to the inefficient first step and further oxidation step manipulations. Since the oxidation state of the C5-position (highlighted in Scheme 2.9) of the

Scheme 2.9. First Generation Route Toward 28.



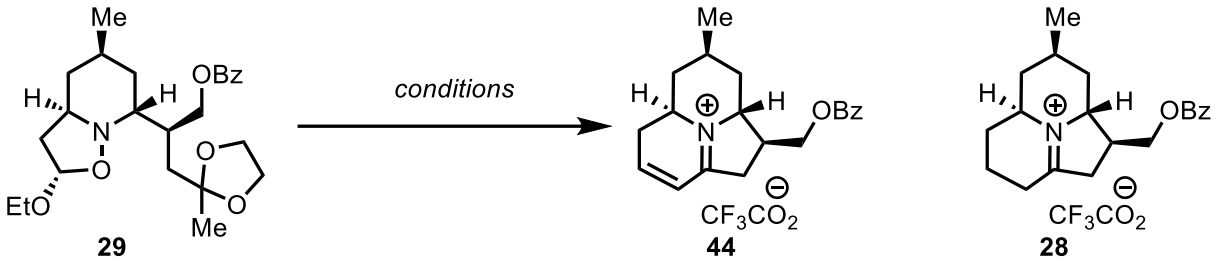
isoxazolidine **29** is exactly the one required for the aldol condensation to take place, we wondered whether a complimentary one step procedure, that could potentially combine the productive steps depicted in Scheme 2.9, could be developed.

2.7. Development of the Reductive Cyclization Cascade.

Two main criteria were established to develop a single pot reductive cascade that could afford **44** directly from **29**. First, the reductive system must be highly chemoselective for the N–O bond reduction and be unable to reduce the intermediate aldehyde and iminium functional groups (both of which are highly reducible). Second, this system must be able to operate under acidic conditions, since these are conditions required for the acetal cleavage and aldol condensation. Based on our previous experience (see section 2.6.), we were able to identify one such reductant – $Mo(CO)_6$.[27] To our delight, upon treating **29** with $Mo(CO)_6$ in hot TFA,[27b] and examining the crude NMR from this experiment, we observed a trace amount (<2%) of the desired α,β-unsaturated iminium salt **44**. Inspired by this result, we screened several reaction parameters: the amount of TFA, solvent mixture and the reaction time.

As can be seen from Table 2.2, several key parameters are crucial for the high yielding outcome of the desired product. First, without the addition of TFA, a low mass recovery was obtained alongside several decomposition products (entry 1). Second, the amount of water is critical for good mass recovery (entries 3 and 4), with the optimal CH_3CN/H_2O ratio being 4/1. Third, the amount of TFA is important for the reaction rate as well as for effective conversion of **29** to **44**, with the most effective amount of TFA being 2-3 equivalents (entries 6-9), but not lower (entry 10). To our surprise, the extension of the reaction time (entry 11) directly led to the full conversion to **28**, thus saving an additional step.

Table 2.2. Screening of Reaction Conditions for the Cascade Cyclization.

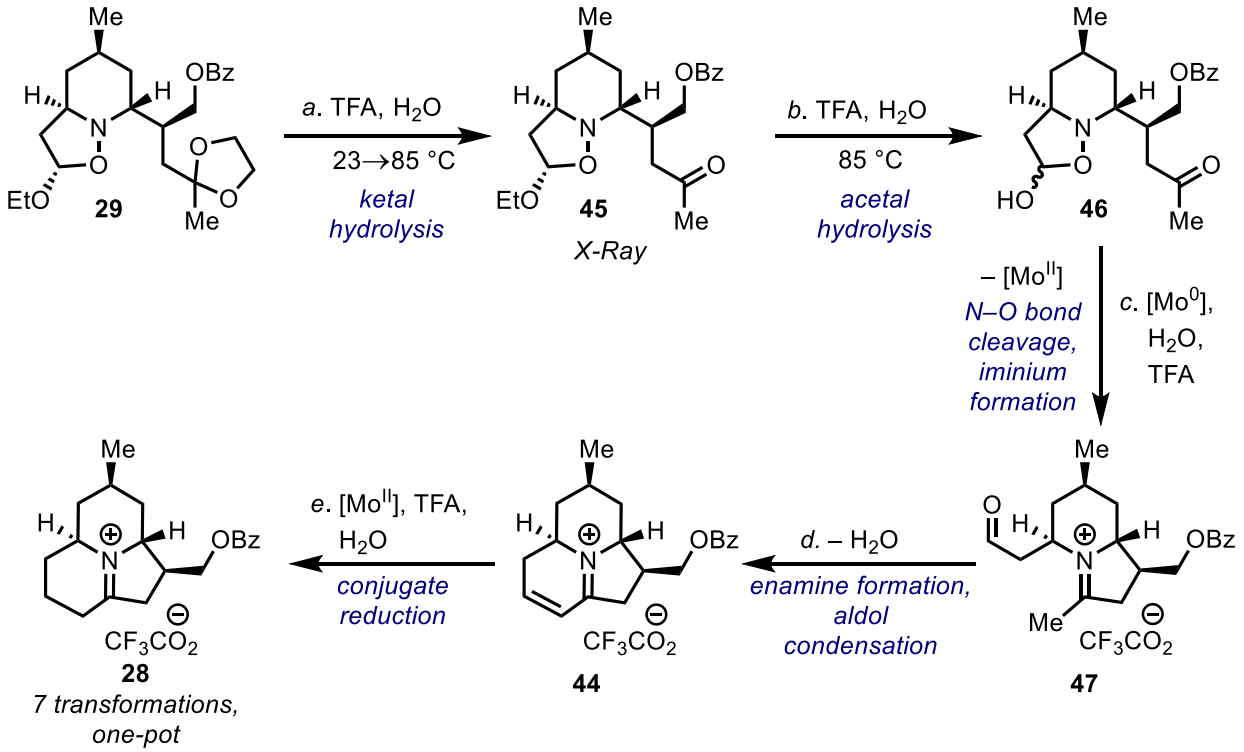


entry[a]	reductant	TFA, equiv[b]	solvent	time, h	mass recovery, %	result[c]
1	$Mo(CO)_6$	–	CH_3CN/H_2O 10/1	20	50%	decomp
2	$Mo(CO)_6$	10	CH_3CN	12	20%	**44**, 4%
3	$Mo(CO)_6$	10	CH_3CN/H_2O 10/1	12	35%	**44**, 20%
4	$Mo(CO)_6$	10	CH_3CN/H_2O 4/1	12	90%	**44**, 20%
5	$Mo(CH_3CN)_3(CO)_3$	10	CH_3CN/H_2O 4/1	12	50%	**44**, 18%
6	$Mo(CO)_6$	5	CH_3CN/H_2O 4/1	10	full	**44**, 80%
7	$Mo(CO)_6$	5	CH_3CN/H_2O 4/1	20	full	**44**, 52%
8	$Mo(CO)_6$	3	CH_3CN/H_2O 4/1	5	full	**44**, 90%
9	$Mo(CO)_6$	2	CH_3CN/H_2O 4/1	2	full	**44**, 90%
10	$Mo(CO)_6$	1	CH_3CN/H_2O 4/1	2	70%	decomp
11	$Mo(CO)_6$	2	CH_3CN/H_2O 4/1	**6**	full	**28**, 93%
12[d]	$Mo(CO)_6$	2	CH_3CN/H_2O 4/1	8	full	**28**, 70%[e]

[a]Reactions were performed with **29** (25 mg, 0.058 mmol, 1 equiv) and $Mo(CO)_6$ (18 mg, 0.069 mmol, 1.2 equiv) in the specified solvent mixture at reflux. [b]TFA was introduced to the reaction mixture at 0 °C before switching to reflux [c]Full conversion of **29** is observed in all cases. Yield of **44** or **28** is based on the crude NMR of the reaction mixture. [d]Reaction was performed on 3.0 g (6.92 mmol) scale (**29**); [e]Isolated yield.

The developed reductive cascade was then further studied in detail, revealing a clear stepwise process that was confirmed by isolation of the intermediates at each elementary step (Scheme 2.10). The first identified step is ketal hydrolysis, initiating at room temperature and yielding methyl ketone **45** (for which a single crystal suitable for X-Ray analysis was obtained to confirm the correct stereochemistry). Upon slow warming of the reaction mixture, the second step, acetal hydrolysis, takes place and by the time the mixture reaches the reflux (note that the temperature here stands for the oil bath temperature), the sole product in the solution is 5-hydroxy isoxazolidine **46**. Over prolonged refluxing of the reaction mixture, $Mo(CO)_6$ starts to dissolve by forming a soluble acetonitrile complex ($Mo(CH_3CN)_3(CO)_3$).[27] That is when N–O cleavage begins, followed by a ring closure to trap the unstable aminoaldehyde as iminium salt **47** (observed by NMR analysis), so that no further decomposition of β-aminoaldehyde mentioned above could take place. Once N–O cleavage is completed, the solution is diluted with benzene and a Dean-Stark apparatus is attached. As the reflux restarts the water is azeotropically removed from the reaction mixture, promoting enamine formation and aldol condensation to deliver **44**. Meanwhile, the Mo^{II} species that remains as the result of N–O cleavage, are still redox active (molybdenum can go up to +6 in terms of the oxidation state), and as a result this low valent molybdenum promotes further reduction of the dihydropyridinium salt **44** to the iminium salt **28**.[23b, 28] Overall, the whole process combines 7 chemical transformations in one pot, providing the desired product in high purity with a remarkable 70% isolated yield.

Scheme 2.10. Established Intermediate Steps of the Cascade.

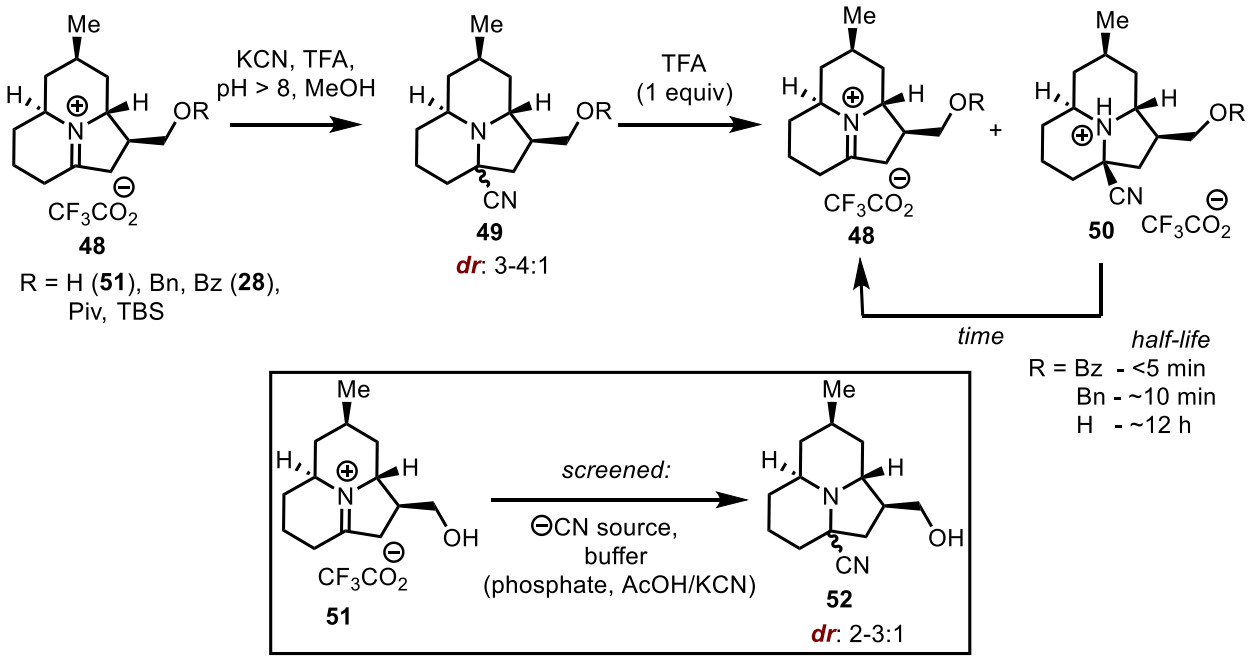


2.8. Studies on Nucleophilic Addition into Iminium 28.

With efficient access to **28**, we initiated a study of its reactivity. Since the most straightforward approach to aminoaldehyde **27** would be through a Strecker reaction (analogous to the exochomine approach),[7] that was the first reaction we tested. Upon exposure of **28** to KCN buffered with TFA in MeOH we obtained a 4:1 mixture of diastereomers of **49** (R = Bz) of initially unknown stereochemistry (Scheme 2.11). It became quickly evident, however, primarily from 2D-NMR experiments, that the undesired diastereomer was formed as the major product. Any attempt to switch the diastereoselectivity by changing the protecting group from Bz to Bn, Piv, TBS or having no protecting group (**51**), had little to no effect on *dr*. Interestingly, when the mixture of the two diastereomeric aminonitriles of **49** was exposed to just one equivalent of TFA in $CDCl_3$, the undesired aminonitrile underwent a rapid *retro*-Strecker reaction to **48**. The desired

diastereomeric aminonitrile salt **50**, however, had better stability in the presence of acid (especially when R = H), thus potentially suggesting the equilibrium of this reaction can be shifted. Encouraged by this observation, we screened different conditions for the Strecker reaction of **51** utilizing different nitrile sources (NaCN, $Zn(CN)_2$, $Ti(O\textit{i}\text{-}Pr)_4$/TMSCN, TMSCN/MeOH) and various buffer systems (phosphate, AcOH/KCN buffer with acidic/basic pH range). Unfortunately, none of these experiments produced a better *dr* (undesired:desired) than 2:1. Moreover, when we attempted to reduce a mixture of nitriles **52** with $LiAlH_4$ in order to obtain aminoaldehyde, a complete decyanation, followed by imine reduction was observed, thus precluding any further studies in this direction.

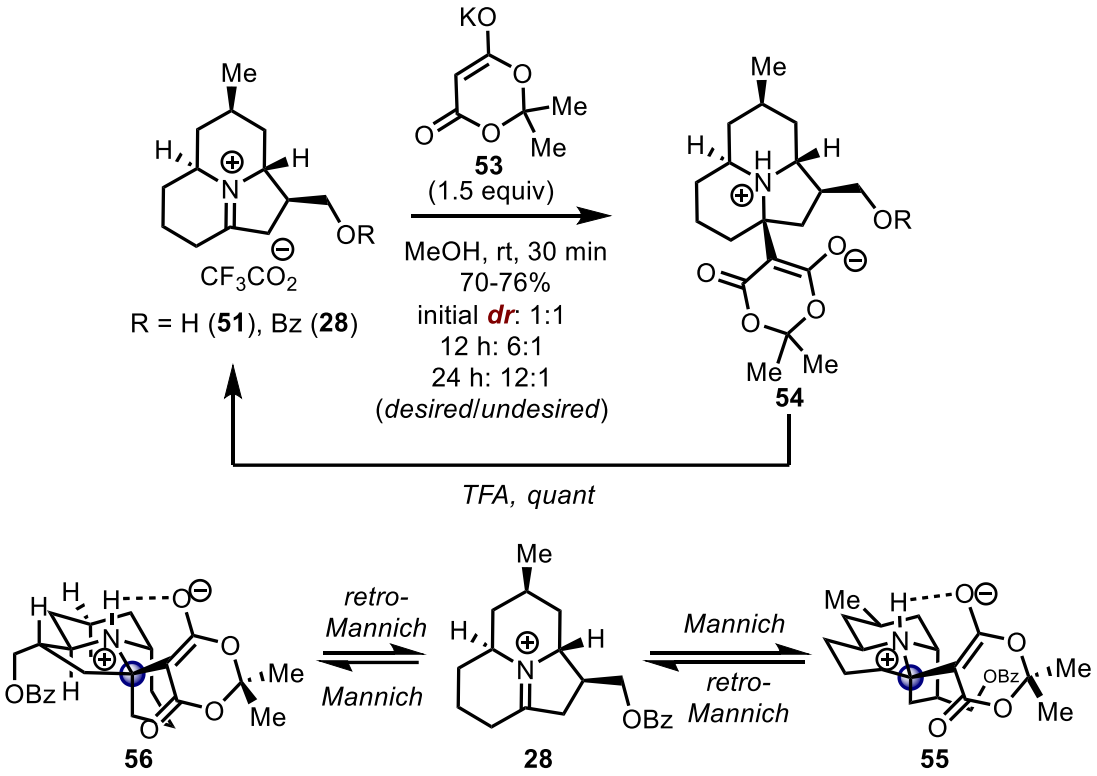
Scheme 2.11. Strecker Reaction Studies on Iminium Salt 28.



The first successful attempt in producing the desired diastereomer was observed when we treated **28** (or **51**) with a potassium salt of Meldrum's acid (**53**) in MeOH (Scheme 2.12).[29] Initially, this reaction produced a 1:1 mixture of diastereomers, which upon standing overnight in

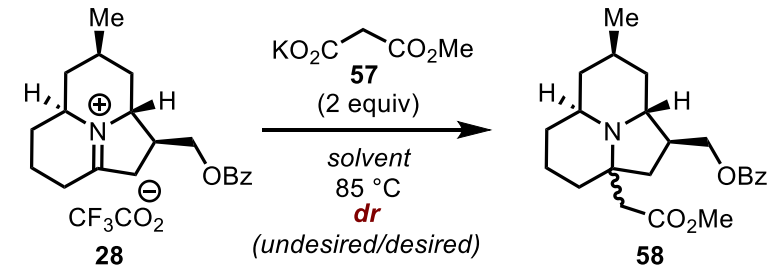
$CDCl_3$ equilibrated to 6:1 favoring the desired diastereomer **54** (the assignment of the desired diastereomer comes from the presence of the cross-peak in the COSY NMR between the NH^+ proton and the alpha CH to the imine in the quinolizidine substructure).[1] In 24 additional hours, the equilibrium shifted further to 12:1 favoring the desired diastereomer. As with the aminonitrile analogues of **49**, the exposure of **54** to TFA reproduced the iminium salt (**28** or **51**), suggesting a reversible character to this Mannich reaction (bottom part of the Scheme 2.12). Unfortunately, any attempt to convert **54** to **27** was unsuccessful because of the high stability of this zwitterionic material under basic/neutral conditions and a relative ease with which it undergoes a *retro*-Mannich reaction under acidic conditions.

Scheme 2.12. Addition of Meldrum's Acid Salt to 51 and 28.

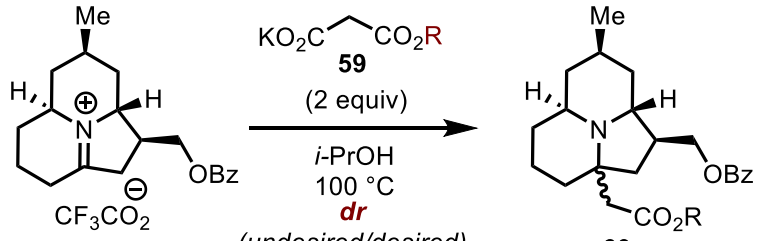


Nonetheless, we screened other 1,3-dicarbonyl nucleophiles and discovered that when **28** undergoes the decarboxylative Mannich reaction with *mono*-methylmalonate salt **57**, a β-aminoester **58** could be isolated as a 1.5:1 (undesired:desired) mixture of diastereomers when the reaction is conducted in 1,4-dioxane at 85 °C (Scheme 2.13).[30] Further screening of the reaction conditions revealed that the *dr* value is somewhat sensitive to the nature of the solvent, and in protic solvents like EtOH and 2-propanol shifts further to 1:1. Interestingly, changing the ester component to either a more bulky *t*-Bu or a less bulky H (**59**) didn't help in favoring the desired diastereomer.

Scheme 2.13. Addition of mono-Malonate Salts to 28.



1. 1,4-dioxane, full conversion after 5 h, ***dr*** 1.5/1
2. DMSO, full conversion after 1 h, ***dr*** 1.6/1
3. CH_3NO_2, 65% conversion after 14 h, ***dr*** 1.8/1
4. HFIP, no reaction, SM fully recovered
5. EtOH, ~30% conversion after 6 h, ~60% conversion after 22 h, ***dr*** 1/1
6. 2-propanol, 100 °C, full conversion, 20 h, ***dr*** 1/1

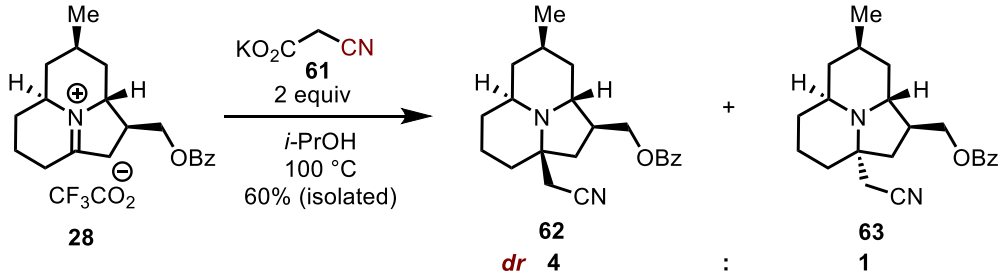


R = H, ***dr*** 1.5/1
t-Bu, ***dr*** 1/1

To our delight, however, we found that changing the ester group to a nitrile by using potassium cyanoacetate **61**,[31] drastically shifts the diastereomeric ratio favoring the desired

diastereomer **62** over **63** (*dr* 4:1) when the reaction is conducted in 2-propanol at 100 °C (Scheme 2.14). Of note, the same 1:1 ratio is observed as with *mono*-malonate salts when the reaction with **61** is conducted in 1,4-dioxane, highlighting the importance of the protic solvent for this reaction.

Scheme 2.14. Addition of Potassium Cyanoacetate 61 to 28.

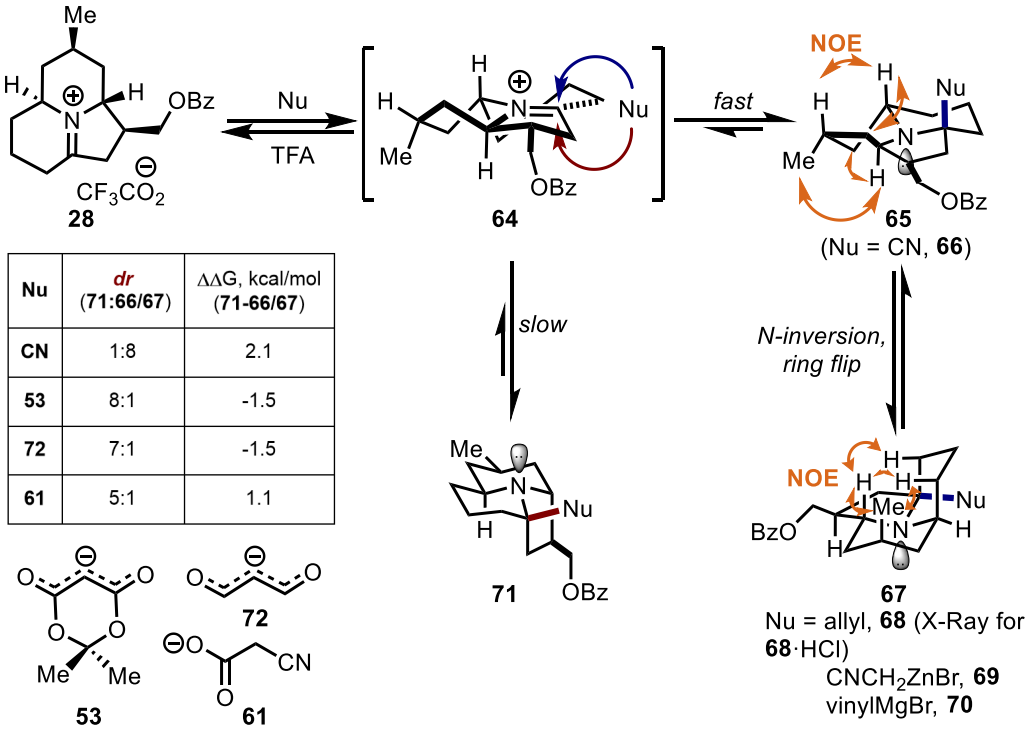


2.9. Computational Study of the Nucleophilic Addition to Iminium 28.

In order to explain the experimentally observed trends with the additions of nucleophiles **53**, **61**, **72** and CN to the iminium salt **28** we conducted a computational study, the first part of which is summarized in Scheme 2.15. First, we computed the free energy differences between each pair of isomers **71**/**66** (**67**) using DFT at the PW6B95-D3/def2-TZVPPD//PCM/B97-D2/6-31+G(d,p) level of theory. The thermodynamic parameters for the lowest energy conformation were computed with Arkane (RMG-Py software package).[32] The electronic energy (E_0) was obtained by a single point energy calculation (gas phase) at the PW6B95-D3/def2TZVPPD level of theory.[33] Thermal and entropy contribution to the free energy were estimated within a 1D-hindered rotor model[34] applied for the low frequency vibrations corresponding to the torsions about external (not belonging to a ring) C-C bonds. Vibrations that are not associated with hindered rotors were treated as harmonic. Moments of inertia of hindered rotors were obtained by computing the hindrance potentials associated with the corresponding torsion angle. The potentials were obtained by performing a series of relaxed scans over the corresponding C-C bonds with 30°

increments using the PCM/B3LYP/6-31G(d) level of theory, followed by fitting the data to a Fourier series or cosine function. Free energy of solvation (ΔG_{solv}) was obtained using the SMD method and M05-2X/6-31G(d) level of theory with the gas phase optimized (at B97-D/6-31+G(d,p) level) and PCM-optimized (B97-D/6-31+G(d,p)) geometries as an input.[35]

Scheme 2.15. Computational Studies of the Addition of Nucleophiles to 28.



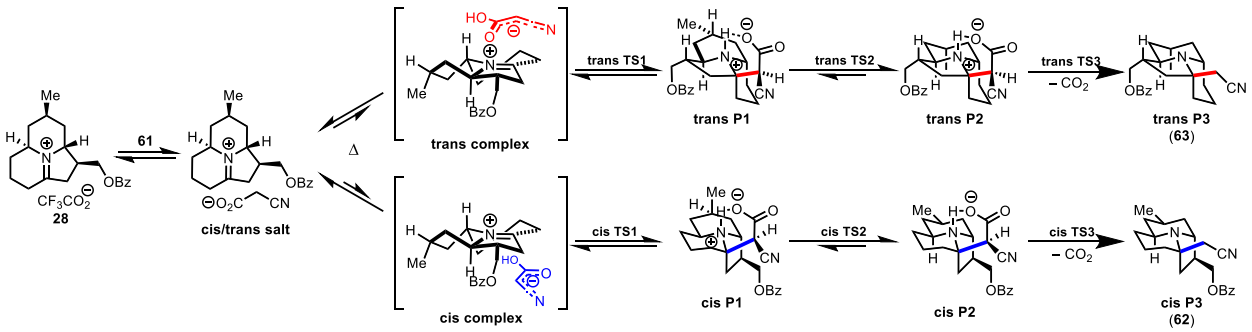
Nu	*dr* (71:66/67)	ΔΔG, kcal/mol (71-66/67)
CN	1:8	2.1
53	8:1	-1.5
72	7:1	-1.5
61	5:1	1.1

As can be seen from the inset table in Scheme 2.15, the trends for the preference in the major diastereomer for the addition of CN, **53** and **72** correlates well with the estimated ΔG^{0}_{298K} values. Another finding predicted the most stable conformation for the undesired aminonitrile **66** to have an antiperiplanar arrangement between the lone pair and CN group. That, in turn, explains the earlier observation of decyanation when **52** reacted with $LiAlH_4$, since the following feature is characteristic for strained antiperiplanar aminonitriles.[36] However, the difference in free energies computed for the two possible addition products of **61** (prior to decarboxylation), favors the

undesired isomer **67** (ΔG^0_{298K}(cis-trans)=1.1 kcal/mol). That suggested that the outcome of this reaction might be governed by kinetics.

In order to perform a computational study on kinetics of the reaction between **28** and **61**, we first assumed that the reaction has two distinct kinetic pathways (denoted *cis*- and *trans*- in Scheme 2.16), that are connected through the iminium salt **28**. Keto-enol tautomerization of cyanoacetate **61**[37] would then provide either *cis*- or *trans*- pre-reaction complexes for the Mannich reaction. The intermediacy of **cis/trans P2** was established by HRMS (ESI, positive mode, calcd. for $C_{23}H_{29}N_2O_4^+$ $[M+H]^+$ 397.2122, found 397.2122) on the crude reaction mixture at ~50% conversion. Anion metathesis was confirmed experimentally by heating **28** in *i*-PrOH with 2 equivalents of **61** at 60 °C for 3 h. The solution was then filtered and the filtrate was subsequently concentrated and dried. The presence of the cyanoacetate anion was confirmed by ^{13}C NMR and by the absence of ^{19}F chemical shifts. No methylene signals from cyanoacetate could be detected by ^{1}H NMR (d_4-MeOD) due to a rapid deuterium exchange with the solvent. The stoichiometric salt was then dissolved in *i*-PrOH and heated to 100 °C (oil bath) for 22 h. The solution was concentrated, and the residue was dried on high vacuum to afford the mixture of **62** and **63** (*dr* 4:1). The notion of the *cis*-/*trans*-pathway comes from the nature of the end product **62** (*cis*-fused indolizidine) or **63** (*trans*-fused indolizidine).

Scheme 2.16. Schematic representation of the reaction pathways in the Mannich reaction between 28 and 61.

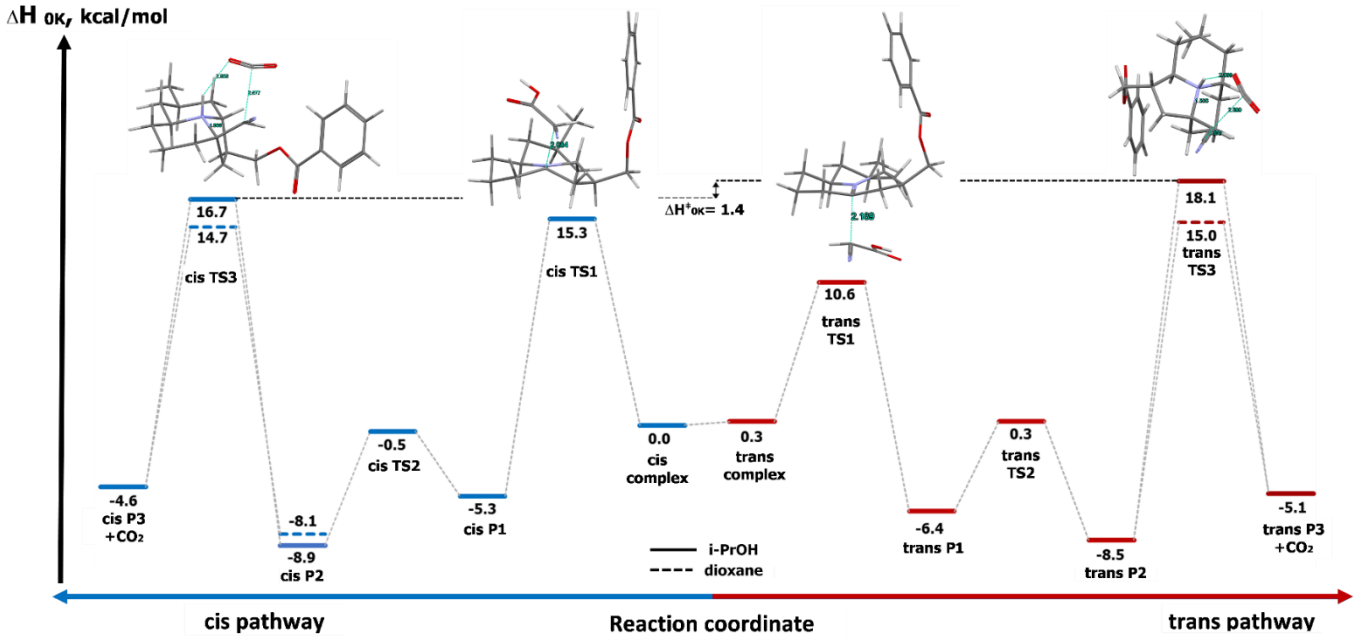


The conformational space for imine **28** and the salt (*cis*- and *trans*-) was investigated by the hierarchical approach. Due to considerable ring strain associated with the internal C=N(+) bond, the most stable conformations only differ in torsions about the external C-C bond connected to the benzoate. We used the previously calculated lowest energy conformation to locate the transition states. For modeling the enolate anion all tautomeric forms were evaluated by comparing their free energies calculated at the SMD(2-propanol)/PW6B95-D3/def2TZVPD level of theory, and the two lowest energy tautomers were considered.

To explore the PES of this reaction we used the hybrid functional PW6B95-D3(BJ) with the 6-31+G(d) basis set and PCM solvation model (default parameters, 2-propanol as solvent) for geometry optimizations. Besides providing accurate geometries in our benchmark study, this functional was recently highlighted for its general performance and, specifically, for giving accurate barrier heights.[38] Single point energies were calculated at the SMD(2-propanol)/PW6B95-D3/def2TZVPPD level of theory. For the barriers calculated in 1,4-dioxane, gas phase geometries (optimized with PW6B95-D3/6-31+G(d)) of transition states **TS1** and **TS3** and their corresponding starting materials were used for evaluation. Their single point energies were obtained with SMD(1,4-dioxane)/PW6B95-D3/def2TZVPPD.

For each pathway we evaluated 3 pairs of diastereomeric transition states. Once located, the transition states were verified by calculating the vibrational frequencies (only one imaginary frequency was present corresponding to the desired reaction coordinate). The transition states were then connected to the respective pre-reaction complexes and products, through intrinsic reaction coordinate (IRC) calculations. The ZPE-corrected potential energy surfaces calculated for two pathways with the lowest energy barriers are plotted on Figure 2.2.

Figure 2.2. Potential energy surface (ZPE-corrected) for cis and trans reaction pathways.



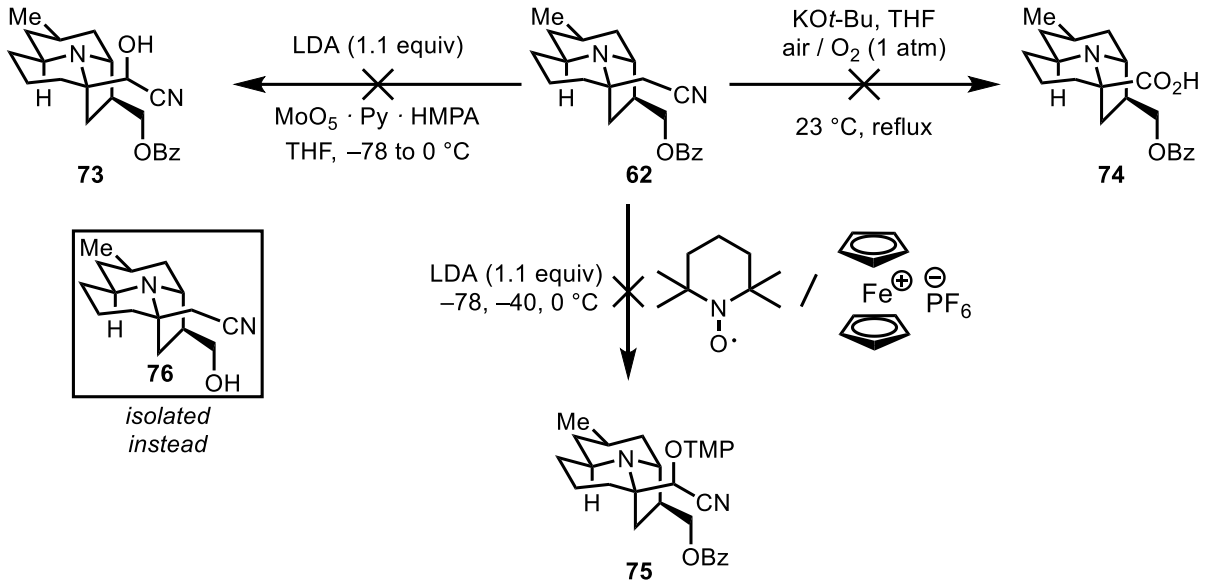
First, it was observed that for all the **cis/trans TS 1** found (8 overall) the addition of enolate is always followed by a barrierless nitrogen inversion. As a result, the corresponding products exhibit *syn* orientation between the *aza*-quaternary substituent and nitrogen lone pair. The higher barrier ($\Delta H^{\ddagger}$ (0 K) = 4.7 kcal/mol) for **cis TS1** is thus unsurprising, given that *anti* addition to the iminium (observed for **trans TS1**) is a highly stereoelectronically favored process. After the addition-*N*-inversion step, the Me-containing six-membered ring ends up in a metastable twist-

boat conformation, and both **cis/trans P1** further undergo a second, half-chair, transition state (denoted **cis TS2** and **trans TS2** on Scheme 2.16) affording **cis P2** and **trans P2**, respectively. Finally, irreversible decarboxylation of **cis**/**trans P2** occurs via **cis/trans TS3**, initially affording charge-separated complexes. In a protic environment, however, they are expected to rapidly convert to **cis/trans P3** through a proton transfer. Comparison of the activation energies for both diastereomers reveals that **cis P2** undergoes decarboxylation more readily than **trans P2**. Moreover, **trans TS3** was found to be the highest barrier for the entire process ($\Delta H^{\ddagger}$ (0 K) (**trans TS3**–**cis TS3**)=1.4 kcal/mol), potentially suggesting a Curtin-Hammett control with the *cis*-isomer being a major product.[39] When $\Delta H^{\ddagger}$ (0 K) (**trans TS3**–**cis TS3**) are compared in 1,4-dioxane,[40] a lower (0.3 kcal/mol) value is observed, suggesting a less selective reaction, in agreement with the experiment (see section 2.13).

2.10. Synthesis of the α-aminoaldehyde coupling partner.

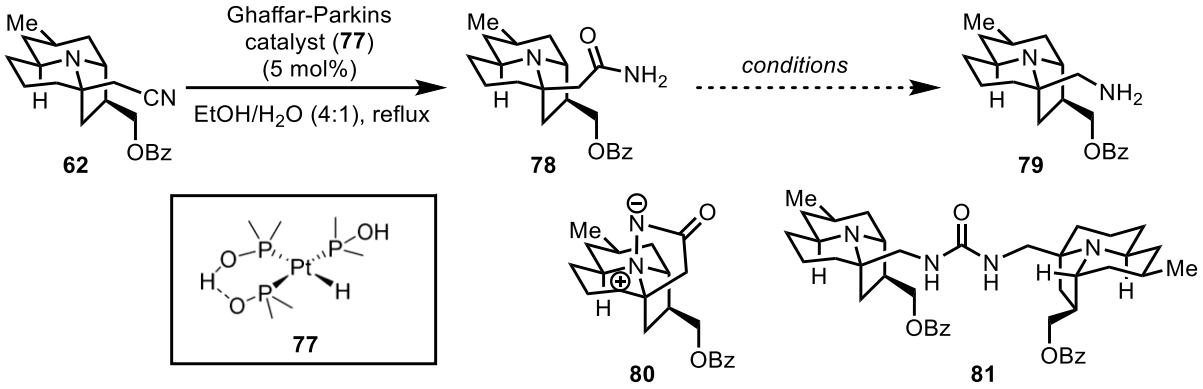
Having established a strategy to access the desired diastereomer **62**, we now needed to perform a dehomologation to access the desired α-aminoaldehyde **27**. The most straightforward method would be to perform an α-oxygenation to the cyanohydrin **73** (Scheme 2.17). We tested two existing protocols available for this transformation: 1) α-deprotonation of the nitrile followed by either quenching the resulting enolate with $MoO_5 \cdot Py \cdot HMPA$ complex[41a] to obtain **73** and 2) utilization of TEMPO/$Cp_2Fe^{+}PF_6^{-}$[41b] to obtain intermediate **75**. Unfortunately, neither method gave a satisfactory result and **76** was isolated instead. Direct oxygenation followed by degradation of the resulting peroxide to obtain **74** with KO*t*-Bu under an oxygen atmosphere also provided the same outcome (isolation of **76**).

Scheme 2.17. Attempt to Perform α-Oxygenation of the Nitrile.



With that result we then switched to a longer alternative. Thus, **62** was converted to carboxamide **78** using the Ghaffar-Parkins catalyst (5 mol%)[42] in wet ethanol (Table 2.3). Several conditions for the dehomologation of **78** via Hofmann rearrangement using hypervalent iodine reagents to obtain the primary amine **79** were then explored. Of note, it was found that the use of $PhI(OAc)_2$ in the mixture of $EtOAc/CH_3CN/H_2O$ (2/2/1),[43] as well as the use of PhINTs in CH_2Cl_2[44] leads to the formation of aminimide **80** as the sole product (Table 2.3, entry 1-2). Interestingly, such an "interrupted" Hofmann rearrangement leading to such aminimides had not been reported to the best of our knowledge.[45] When we tested $PhI(CF_3CO2)_2$ in aqueous acetonitrile[46] (entry 3), however, we noticed that although the reaction was very slow, a small amount (10%) of **79** could be isolated. While raising the temperature of the reaction resulted in higher conversion (entry 4, 61% brsm), a significant amount of **80** (10%) was produced. Furthermore, the formation of **80** could be completely suppressed by the addition of 1 equivalent of TFA (entry 5), since the tertiary amine now becomes protonated and non-nucleophilic. Unfortunately, these conditions were not as

Table 2.3. Screening of reaction conditions for the Hoffmann rearrangement of 78.



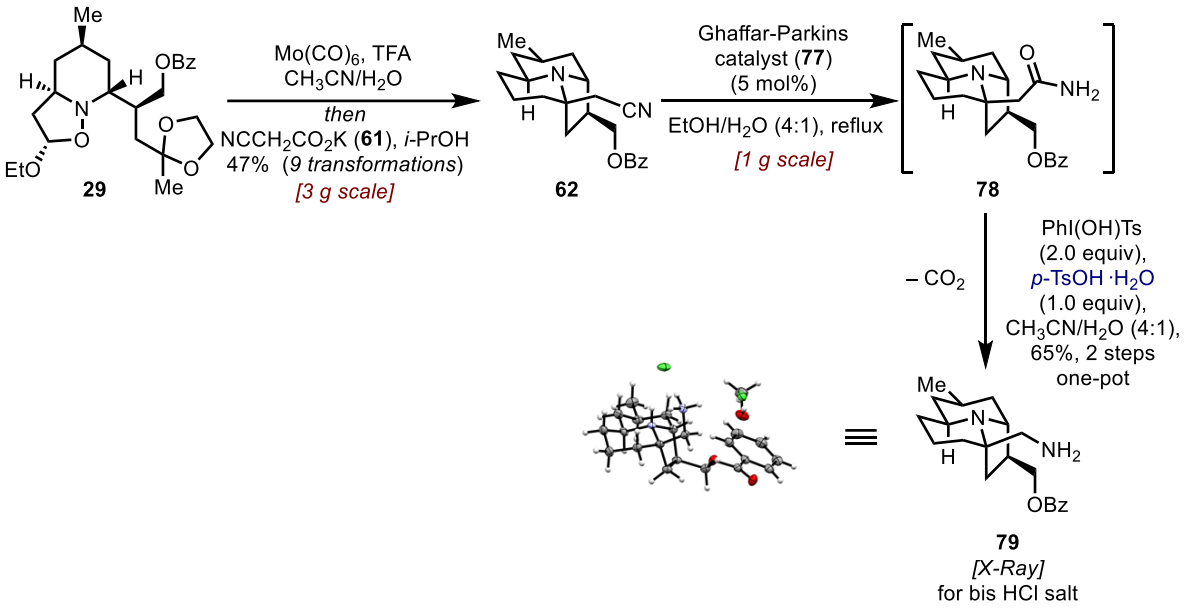
entry[a]	oxidant (equiv)	additive[b] (equiv)	solvent	time, h	temp, °C	result[c]
1	$PhI(OAc)_2$ (1.2)	–	$EtOAc/CH_3CN/H_2O$ = 2/2/1	10	0→23	**80** (80%)
2	PhINTs (1.1)	–	CH_2Cl_2	1	0→23	**80** (95%)
3	PhI (1.0) – *m*-CPBA (1.2)	HBF_4 (2.2)	CH_3CN/H_2O = 9/1	24	23→60	**79** (30%), **78** (45%)
3	$PhI(CF_3CO_2)_2$ (1.2)	–	CH_3CN/H_2O = 1/1	16	23	**79** (10%), **78** (85%)
4	$PhI(CF_3CO_2)_2$ (2.4)	–	CH_3CN/H_2O = 1/1	4	23→60	**79** (44%), **80** (10%), **78** (39%)
5	$PhI(CF_3CO_2)_2$ (2.0)	TFA (1)	CH_3CN/H_2O = 1/1	16	60	**79** (52%), **78** (30%)
6[d]	$PhI(CF_3CO_2)_2$ (2.0)	TFA (1)	CH_3CN/H_2O = 1/1	48	60	**79** (40%), **78** (15%)
7	PhI(OH)OTs (1.2)	*p*-TsOH•H_2O (1)	CH_3CN	2.5	82	**79** (66%), **81** (15%)
8[e]	PhI(OH)OTs (1.2)	*p*-TsOH•H_2O (1)	CH_3CN	4	82	**79** (40%), **81** (36%)
9	PhI(OH)OTs (2.0)	*p*-TsOH•H_2O (1)	CH_3CN/H_2O=4/1	4	82	**79** (74%), **78** (15%)
9[f]	PhI(OH)OTs (2.0)	*p*-TsOH•H_2O (1)	CH_3CN/H_2O=4/1	5	82	**79** (70%), **78** (10%)

[a]Reactions were performed with **78** (20 mg, 0.054 mmol, 1 equiv) [b]The additive was introduced to the reaction mixture prior to the addition of the oxidant [c]Isolated yield. [d]Reaction was performed on a 200 mg (0.54 mmol) scale (**78**). [e]Reaction was performed on a 300 mg (0.81 mmol) scale (**78**). [f]Reaction was performed on a 200 mg (0.54 mmol) scale (**78**).

successful on scale (entry 6), and we turned to Koser's reagent (PhI(OH)OTs),[47] this time using *p*-TsOH•H_2O as an additive. Although it did provide full conversion of **78** (entry 7), a new dimeric urea **81** was now forming as a by-product (15%). The formation of **81**, however, was found to be suppressed by performing the reaction in a CH_3CN/H_2O (4/1) solvent mixture at the expense of a lower conversion (90% brsm) giving **79** with a 70% isolated yield on a 200 mg scale (entry 9).

Additionally, the whole sequence leading to **79** could be streamlined starting from **29** (Scheme 2.18). First, the previously established decarboxylative Mannich step could now be

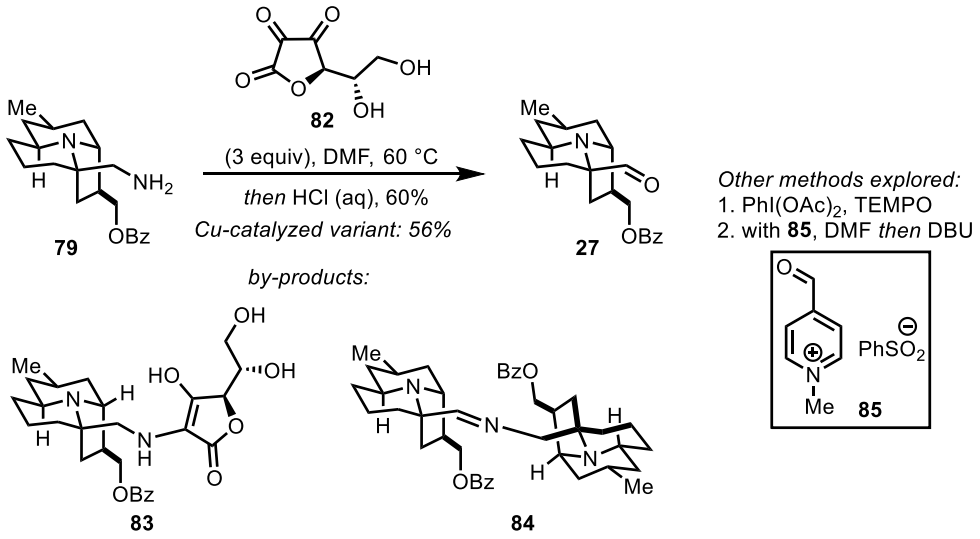
Scheme 2.18. Streamline Synthesis of 79.



incorporated into our reductive cascade without compromising the yield and diastereoselectivity.[48] Thus, **62** could be obtained directly from **29** in a one pot manner with 47% isolated yield, combining a total of 9 transformations. Furthermore, **79** could also be obtained in one pot from **62** by performing the **77**-catalyzed hydration along with the Hofmann rearrangement, providing **79** with a 65% isolated yield. The single crystal X-Ray analysis of **79** (as a bis hydrochloride salt) further confirmed the stereochemical outcome of the Mannich reaction.

For the final conversion of the primary amine functional group of **79** to the aldehyde, few protocols were tested (Scheme 2.19). The best yield of **27** was observed when dehydroascorbic acid (DHAA) **82** was used as an oxidant, with only one by-product isolated along the way (**83**, <10%). Additionally, the originally reported Cu^{I}-catalyzed variant of this protocol[49] with ascorbic acid under aerobic conditions provided **27** as well, but with a slightly lower yield (56% vs 60% with DHAA). The use of a transamination protocol by Rapoport that utilizes an **85**/DBU system gave a significantly lower yield and recovery of **27** (<10%).[50] The use of $PhI(OAc)_2$ and TEMPO[51] provided only trace **27**, but significant amounts of **84**.

Scheme 2.19. Oxidation of the Primary Amine to the Aldehyde.

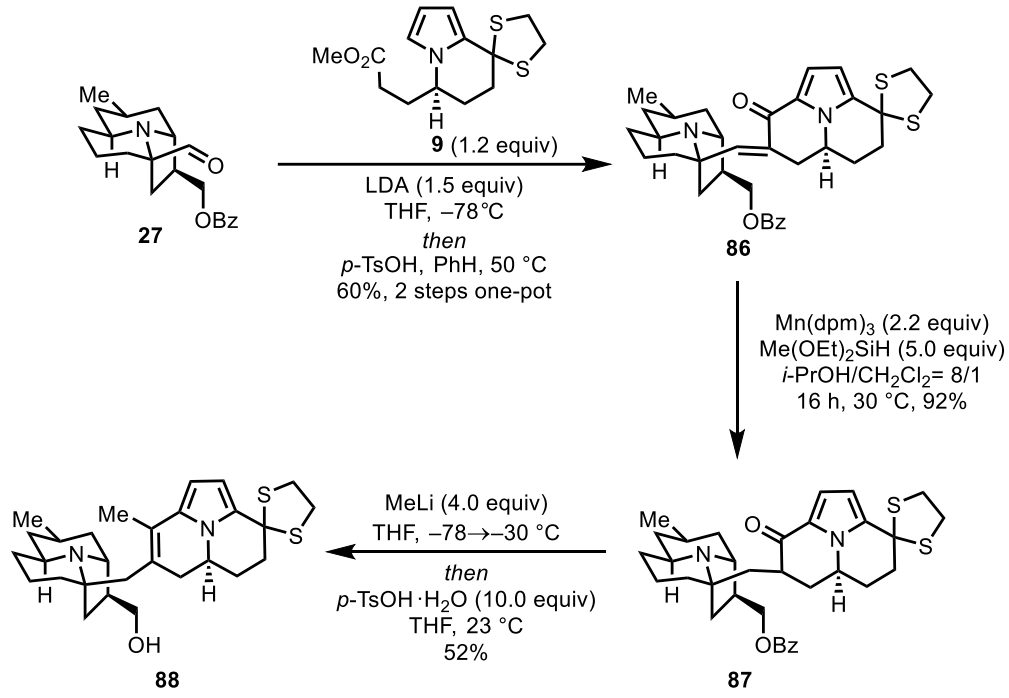


2.11. Completion of the Total Synthesis of Chilocorine C.

With the route to **27** now established, and with the synthesis of **9** already developed (Scheme 2.3), we then proceeded to couple the "monomeric" subunits (Scheme 2.20). Using a slightly modified condition developed for the exochomine synthesis (LDA, then *p*-TsOH) we were able to successfully isolate the enone **86** with 60% yield over 2 steps (one-pot). Notably, the use of anhydrous *p*-TsOH was found to have a significant impact on improving the isolated yield.

Further reduction of the enone under HAT conditions with $Mn(dpm)_3$ and $Me(OEt)_2SiH$ at 30 °C in *i*-PrOH/CH_2Cl_2 provided ketone **87** in a good yield (92%). Exposure of this ketone to excess MeLi (to additionally remove the Bz protecting group), followed by quenching the reaction mixture with *p*-TsOH·H_2O to promote dehydration of the resulting tertiary alcohol, provided aminoalcohol **88** (52% yield).

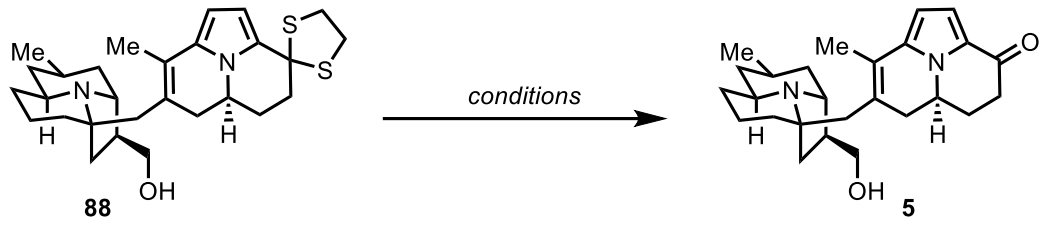
Scheme 2.20. Fragment Coupling.



For the final thioacetal deprotection of **88**, the original exochomine conditions[7,52] (Table 2.4, entry 1) provided a very low yield of **5** (13%). Thus, we further screened a range of commonly applied conditions for this deprotection (entries 2-5), but most of them led to the decomposition of the starting material (**88**). The latter comes from the very sensitive nature of **88** towards oxidation since it contains both tertiary amine and primary alcohol functional groups, as well as a nucleophilic double bond and a pyrrole ring. Pleasingly, however, when we tried the conditions reported by Scorrano,[53] using DMSO/HCl (aqueous) system for the oxidative removal of the

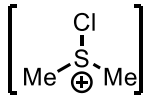
thiocetal, we found that **5** could be isolated in nearly quantitative yield (95%). The reaction relies on using the chlorosulfonium species **89** (that exists in an equilibrium between DMSO and hydrochloric acid) as an oxidant.

Table 2.4. Screening of Thioacetal Deprotection Conditions



88 **5**

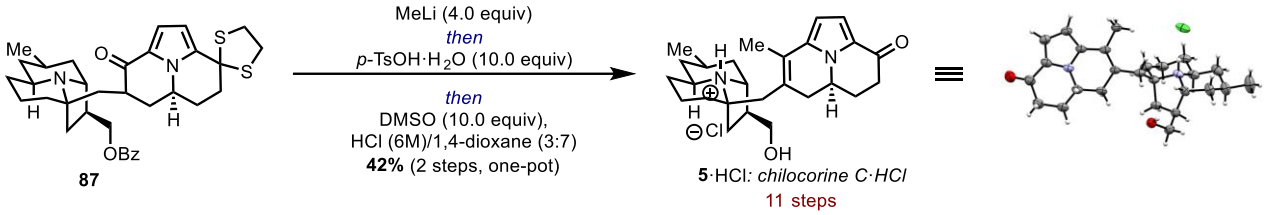
conditions:	*yield*
1. $PhI(OAc)_2$ (1.3 equiv), $CH_3CN/CH_2Cl_2/H_2O$	13%
2. O_2 (1 atm), *p*-TsOH·H_2O (5.0 equiv), THF/H_2O	NR
3. H_2O_2 (4 equiv), I_2 (5 mol%), SDS (20 mol%) THF/H_2O	decomp
4. I_2 (5 mol%), SDS (20 mol%), THF/H_2O	decomp
5. $TFA/CH_2Cl_2/H_2O$	decomp
6. DMSO (10 equiv), dioxane/HCl (6 M, aq), rt, 30 min	95%
7. 17 mg scale: DMSO (10 equiv), dioxane/HCl (6 M, aq), rt, 2 h	86%

via 

89

Finally, the last two steps were combined into a one-pot procedure to deliver **5**·HCl in 42% isolated yield, thus completing the total synthesis of chilocorine C (Scheme 2.21). Although, the NMR data was in full agreement with the natural sample obtained by Meinwald group[1] (although the chemical shifts showed a dependency on concentration),[54] we also obtained an X-Ray structure of **5**·HCl, revealing a unique hydrogen bonding network in the independent crystallographic unit cell.

Scheme 2.21. Completion of the Total Synthesis of Chilocorine C.



2.12. Conclusion.

In conclusion, we have successfully completed the first total synthesis of chilocorine C via a convergent strategy. Our approach features a series of consecutive transformations that enable a streamlined synthesis of the precursor **29** in a highly stereoselective manner. The key reductive cyclization cascade combined 9 separate transformations allowing for the access of **62** directly from **29** in a one-pot fashion. The final step of the cascade included the critical *aza*-quaternary stereocenter construction via a Mannich reaction/decarboxylation sequence with **61**. The success of this reaction and the inability of the initial approach to provide the desired selectivity, was justified computationally through DFT, providing some valuable mechanistic insights. A series of chemoselective reactions converted **62** to **27**, followed by the optimized final sequence to provide **5**·HCl. The synthetic brevity (11 steps overall) and scalability (7 steps were performed on a decagram/gram scale) of the developed approach provide further inspiration for the stereoselective synthesis of indolizidine, quinolizidine and pyrrole alkaloids of a similar type.

2.13. Experimental Details.

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), diethyl ether (Et_2O), and dichloromethane (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reaction temperatures correspond to the external temperature of the flask, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent, CAM (Cerium Ammonium Molybdate)/vanillin/ninhydrin or aqueous solution of potassium permanganate and sodium bicarbonate and heat as a developing agent. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Deactivated silica gel was prepared by stirring the commercial silica gel in 2% Et_3N solution in EtOAc for 2 h, followed by repetitive washings with EtOAc and then hexanes. Preparative thin-layer chromatography separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker 400 and 500 MHz instruments and calibrated using residual solvent as an internal reference [for $CDCl_3$: ^1H, δ 7.26 ppm and ^{13}C, δ 77.16 ppm; for D_2O ^1H, δ 4.79 ppm and ^{13}C, δ 49.50 ppm (MeOH as a standard)], unless otherwise noted. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet. IR spectra were recorded on a Nicolet iS5 FT-IR spectrometer using neat thin film technique. High-resolution mass spectra (HRMS) were recorded on Agilent 6244 Tof-MS using ESI (Electrospray Ionization) or CI (Chemical Ionization) at the University of Chicago Mass Spectroscopy Core

Facility. Chiral high-performance liquid chromatography (HPLC) analysis was performed using a Shimadzu Prominence analytical chromatograph with a commercial ChiralPak column (OD-H). X-ray diffraction data were measured on a Bruker D8 VENTURE diffractometer at the University of Chicago X-ray Laboratory and on a Bruker D8 diffractometer at the Advanced Photon Source (Argonne National Laboratory).

(*R*,*R*)-4-Methylpipecolic acid 31. To an oven-dried, 2 L round bottom flask equipped with a magnetic stir bar was added solid **33** (40.0 g, 0.12 mol, 1.0 equiv) followed by Et_2O (920 mL). The resulting mixture was stirred under a N_2 atmosphere at 23 °C for 15 min until a clear solution was obtained. Next, H_5IO_6 (27.6 g, 0.12 mol, 1.0 equiv) was quickly added and the resulting cloudy mixture was vigorously stirred at 23 °C for 2 h. Upon completion, the reaction contents were slowly filtered through a pad of Celite (washing with Et_2O, ~300 mL) and the filtrate was concentrated to near dryness. The resulting crude benzyl glyoxylate (**34**) was dissolved in CH_2Cl_2 (900 mL) and molecular sieves (100 g, 4Å, crushed, activated) were added. The resulting solution was cooled to 5 °C using an ice bath and (*S*)-α-phenylethylamine (30.6 mL, 29.1 g, 0.24 mol, 1.0 equiv) was added dropwise over 5 min. The ice bath was then removed, and the solution was stirred at 23 °C for 3 h. Upon completion, the mixture was filtered through a pad of Celite (washing with CH_2Cl_2, ~300 mL), concentrated, and dried under high vacuum for 2 h. The resulting crude material (**35**) was transferred to an oven-dried 2-neck 1 L round bottom flask equipped with a stir-bar and internal thermometer. The flask was back-filled with N_2 and then CH_2Cl_2 (500 mL) was introduced via addition funnel under a N_2 atmosphere. The resulting solution was cooled to –70 °C (internal temperature) using an acetone-dry ice bath. Then, TFA (16.8 mL, 25.1 g, 1.0 equiv) was slowly added over 10 min, followed by isoprene (24.3 mL, 16.5 g, 0.24 mol, 1.1 equiv) and BF_3•OEt_2 (27.2 mL, 31.2 g, 0.22 mol, 1.0 equiv) at a rate such that the temperature remained below

–70 °C over the course of the addition. The mixture was further stirred at –70 °C for 2 h after which time the bath was removed. When the internal temperature reached –20 °C, the septum was replaced with an addition funnel containing aqueous Na_2CO_3 (400 mL, prepared by diluting 200 mL of corresponding saturated solution with an equal volume of water) and the mixture was carefully neutralized with vigorous stirring over 30 min. The contents of the flask were then transferred to a separatory funnel. The resultant organic layer was separated, washed with saturated aqueous Na_2CO_3 (200 mL), water (400 mL), brine (200 mL), and dried (Na_2SO_4). The resulting solution was filtered through cotton and concentrated. Purification of the resultant residue via flash column chromatography [silica gel, short plug (60 g), hexanes/EtOAc, 9:1] afforded **37** (50.0 g, 68% yield) and its diastereomer **36** (2.3:1 *dr* favoring **37** as determined by ^{1}H NMR analysis) as a yellow oil. The mixture of diastereomers was dissolved in hexanes (100 mL) and placed in a freezer (–20 °C) for 24 h. The resulting white crystals were then filtered, washed with cold hexanes, and dried to afford pure **37** (21.6 g, 33% over 3 steps) as a white solid. **37**: R_f = 0.64 (silica gel, hexanes/EtOAc, 10/1, UV+$KMnO_4$); $[\alpha]_D^{25}$ = –18.6º (*c* = 1.00, $CHCl_3$); IR (film) ν_{max} 2930, 1733, 1452, 1180, 1154, 751, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.08 (m, 10 H), 5.19–5.15 (m, 1 H), 5.12–5.00 (m, 2 H), 4.02 (dd, *J* = 6.6, 2.1 Hz, 1 H), 3.85 (q, *J* = 6.7 Hz, 1 H), 3.06 (m, 1 H), 2.90–2.76 (m, 1 H), 2.55–2.41 (m, 1 H), 2.31–2.17 (m, 1 H), 1.56 (s, 3 H), 1.23 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 146.1, 136.3, 129.5, 128.7, 128.5, 128.3, 128.2, 127.3, 126.9, 120.1, 66.0, 62.0, 54.8, 47.4, 33.7, 23.1, 21.4; HRMS (ESI) calcd for $C_{22}H_{25}NO_2Na^+$ [M + Na^+] 358.1783, found 358.1782.

Next, an oven-dried, 1 L round bottom flask equipped with a magnetic stir bar at 23 °C was charged with **37** (21.5 g, 63.7 mmol, 1.0 equiv) and EtOH (150 mL) and then was transferred to an oil bath. $[Rh(NBD)(PPh_3)_2]PF_6$ (1.89 g, 2.19 mmol, 0.035 equiv) was added in one portion

with stirring. The reaction flask was then equipped with a flushing adapter with a balloon containing N_2 on top and the contents were evacuated and backfilled with N_2. The cycle was repeated 5 more times and the N_2 balloon was exchanged with a H_2 balloon. The contents were flushed 5 times with H_2 as above and the flask was then warmed to 50 °C and stirred at this temperature under a H_2 atmosphere for 4 h. Upon completion, the mixture was cooled to 23 °C and flushed with N_2. The reaction solution was then diluted with EtOH (280 mL), and both water (22 mL) and $Pd(OH)_2/C$ (20 wt %, 1.05 g, 1.49 mmol, 0.023 equiv) was quickly added in a single portion. The resultant mixture was flushed with N_2 (5 cycles) and H_2 (5 cycles) in the same manner as above under vigorous stirring and the mixture was left stirring under a H_2 atmosphere at 23 °C for 5 h. Upon completion, the solution was flushed with N_2, the contents were filtered directly through Celite (washing with MeOH), and the filtrate was concentrated to dryness. The resultant crude material (**31**) was suspended in boiling EtOH (200 mL), and MeOH (~150 mL) was added until a clear solution was obtained. The reaction contents were then cooled to 23 °C and placed in a freezer (–20 °C) for 20 h to promote crystallization. The resultant white precipitate was then filtered and washed with Et_2O (3 × 50 mL) to provide **31** (4.10 g). The filtrate was further diluted with Et_2O (100 mL) and placed in the freezer overnight again. Subsequent filtration and washing with cold Et_2O provided an additional portion of **31** (3.71 g, 7.81 g total, 86% yield). **31**: $[\alpha]_D^{25}$ = –18.4º (*c* = 0.50, 2 M HCl); literature $[\alpha]_D^{20}$ = –20º (*c* = 0.50, 2 M HCl)[14d]; ^{1}H NMR (500 MHz, D_2O) δ 3.89 (dd, *J* = 6.2, 4.7 Hz, 1 H), 3.27–3.18 (m, 2 H), 2.09 (dddd, *J* = 14.2, 6.3, 3.6, 1.4 Hz, 1 H), 1.90–1.70 (m, 1 H), 1.65 (ddd, *J* = 13.4, 8.3, 4.7 Hz, 1 H), 1.40 (dtd, J = 14.2, 8.3, 5.9 Hz, 1 H), 0.98 (d, *J* = 6.7 Hz, 3 H);^{13}C NMR (126 MHz, D_2O) δ 174.7, 56.0, 41.2, 33.1, 29.5, 25.8, 19.5; HRMS (CI) calcd for $C_7H_{14}NO_2^+$ [M + H^+] 144.1019, found 144.1019.

(*R*)-Nitrone 30. An oven-dried, N_2-flushed 2 L two-neck round bottom flask equipped with thermometer and a magnetic stir bar was charged with **31** (10.0 g, 70.0 mmol, 1.0 equiv) and CH_2Cl_2 (1.00 L). The resulting suspension was cooled to 5 °C (internal temperature) using an ice bath under a gentle stream of N_2. Next, a solution of Na_2WO_4•H_2O (2.30 g, 7.00 mmol, 0.1 equiv) and Et_4NCl (1.16 g, 7.00 mmol, 0.1 equiv) in H_2O (44 mL) was added dropwise via an addition funnel. Once the internal reaction temperature returned to 5 °C, aqueous H_2O_2 (35% w/w, 17.9 mL, 20.4 g, 210 mmol, 3.0 equiv) was added dropwise over the course of 5 min via an addition funnel. Next, a solution of K_3PO_4 (17.8 g, 84.0 mmol, 1.2 equiv) in H_2O (44 mL) was slowly added dropwise to the vigorously stirred biphasic mixture over 15 min, ensuring that the internal temperature was always below 10 °C. Once the addition was complete, the ice bath was removed and the resulting mixture warmed to 23 °C over the course of 1.5 h. Next, the reaction flask was placed in an ice bath and recooled to 10 °C. Solid Na_2SO_3 (10.0 g) was then carefully added portionwise with vigorous stirring to reduce any excess peroxides, and was followed by the addition of NaCl (17.0 g, 29.09 mmol). The mixture was then warmed to 23 °C and transferred to a 2 L separatory funnel. The aqueous layer was separated and extracted with CH_2Cl_2 (5 × 600 mL). The combined organic extracts were washed with brine (60 mL), dried (Na_2SO_4), filtered, and concentrated to afford **30** (5.82 g, 74% yield) as a yellow solid. **30**: R_f = 0.52 (silica gel, CH_2Cl_2/MeOH, 10:1, UV and $KMnO_4$); $[\alpha]_D^{25}$ = +147.0º (*c* = 0.5, $CHCl_3$); IR (film) ν_{max} 3385, 2955, 2928, 2872, 16312, 1454, 1444, 1190, 1167 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.15 (t, *J* = 3.2 Hz, 1 H) 1H), 3.81–3.72 (m, 2 H), 2.51 (m, 1 H), 2.25 (m, 1 H), 2.03 (m, 1 H), 1.97–1.91 (m, 1 H), 1.92–1.82 (m, 1 H), 1.70–1.60 (m, 1 H), 1.05 (d, *J* = 6.6, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.4, 77.4, 76.9, 57.5, 33.5, 30.6, 24.2, 20.5; HRMS (ESI) calcd for $C_6H_{12}NO^+$ [M + H^+] 114.0913, found 114.0915.

Ketene silyl acetal. A flame-dried, 500 mL Ar-flushed round bottom flask equipped with a magnetic stir bar was charged with solid LiHMDS (19.6 g, 117.1 mmol, 1.07 equiv) and placed in an acetone/dry ice bath under an Ar atmosphere. Next, THF (100 mL) was carefully introduced via cannula with stirring and the mixture was then warmed to 0 ºC and stirred at this temperature for 1 h. Upon completion, the resulting light yellow solution was cooled to –78 ºC and HMPA (68.7 mL, 394.9 mmol, 3.6 equiv) was added dropwise with vigorous stirring. Next, the solution of ethyl 3-(2-methyl-1,3-dioxolan-2-yl)propanoate (20.5 g, 108.9 mmol, 1.00 equiv) in THF (100 mL) was added via cannula over the course of 30 min. The resulting orange solution was stirred at –78 ºC for an additional 1 h and then a solution of TBSCl (16.42 g, 108.9 mmol, 1.00 equiv) in hexanes (40 mL) was added to the mixture via cannula over the course of 20 min. The resulting solution was stirred at –78 ºC for an additional 1 h and then slowly warmed to 23 ºC over the course of 2 h. Upon completion, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (130 mL) with active vigorous stirring. The resultant mixture was transferred to a separatory funnel containing pentane (900 mL). After discarding the aqueous layer, the organic layer was washed with H_2O (5 × 450 mL) and brine (450 mL), dried (Na_2SO_4), concentrated, and further dried under high vacuum overnight (with stirring) to afford crude ketene silyl acetal (32.0 g, 90% purity based on ^{1}H NMR analysis, 87% yield) as a yellow oil. IR (film) ν_{max} 2981, 2957, 2884, 2859, 1681, 1371 cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$) δ 3.94 (m, 4 H), 3.72 (q, *J* = 7.0 Hz, 2 H), 3.44 (t, *J* = 7.3 Hz, 1 H), 2.32 (d, *J* = 7.4 Hz, 3 H), 1.31 (s, 4 H), 1.27 (t, *J* = 7.0 Hz, 3 H), 0.93 (s, 9 H), 0.15 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.2, 111.0, 70.6, 64.7, 63.0, 34.8, 25.9, 23.3, 18.2, 14.6, –4.0; HRMS (ESI) calcd for $C_{15}H_{31}O_4Si^+$ [M + H$^+$] 303.1986, found 303.1991.

Hydroxylamine 40. A flame-dried, 250 mL round bottom flask equipped with a magnetic stir bar at 23 ºC was charged with **30** (4.53 g, 40.0 mmol, 1.0 equiv), molecular sieves (10.0 g, 4 Å, 325 mesh, powdered, activated), dry ZnI_2 (2.55 g, 8.0 mmol, 0.2 equiv), and CH_2Cl_2 (80 mL). The resulting suspension was then stirred for 20 min at 23 °C before being cooled to –78 ºC. Next, neat silyl ketene acetal (see above) (16.05 g, 47.7 mmol, 1.2 equiv, 90% purity) was added dropwise at –78 ºC, and the resulting mixture was allowed to slowly warm up to 23 °C with continued stirring for 9 h. Upon completion, the reaction contents were filtered through Celite (washing with CH_2Cl_2) and concentrated. The resultant crude material was purified by flash column chromatography (silica gel, hexanes/EtOAc, 20:1→10:1) to provide **39** (13.13 g, 79% yield) as a colorless oil. **39**: R_f = 0.45 (silica gel, hexanes/EtOAc, 10:1, CAM); $[\alpha]_D^{25}$ = –14.4º (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} 2954, 2930, 2886, 2857, 1736, 1461, 1373, 1253, 1178, 1046, 862, 836 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.19 (dq, *J* = 10.9, 7.1 Hz, 1 H), 4.08 (dq, *J* = 10.8, 7.1 Hz, 1 H), 3.96–3.77 (m, 4 H), 2.94 (dd, *J* = 11.7, 4.1 Hz, 1H), 2.85 (m, 2 H), 2.79–2.71 (m, 1 H), 2.42 (dd, *J* = 14.5, 1.9 Hz, 1 H), 2.11 (dd, *J* = 14.5, 11.3 Hz, 1 H), 1.82–1.68 (m, 2 H), 1.68–1.52 (m, 2 H), 1.32 (s, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 1.19 (m, 1 H), 1.00 (m, 1 H), 0.87 (s, 9 H), 0.84 (d, *J* = 5.6 Hz, 3 H), 0.08 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.2, 109.5, 64.8, 64.7, 63.3, 60.3, 50.2, 42.8, 38.3, 29.6, 27.7, 26.2, 25.0, 24.4, 22.8, 17.8, 14.4, –5.0, –5.2; HRMS (ESI) calcd for $C_{21}H_{41}NO_5SiNa^+$ [M + Na^+] 438.2646, found 438.2641.

Next, an oven-dried, N_2-flushed 1 L round bottom flask equipped with a magnetic stir bar at 23 °C was charged with $LiAlH_4$ (5.29 g, 139.5 mmol, 4.0 equiv) and placed in an ice bath. Then, THF (120 mL) was carefully added and the mixture was allowed to warm to 23 °C. A solution of **39** (14.51 g, 34.9 mmol, 1.0 equiv) in THF (150 mL) was added via addition funnel over course of 15 min. Once the addition was complete, the addition funnel was replaced by a condenser and

the reaction contents were brought to reflux under a gentle stream of N_2. Upon completion (typically 2-3 h of reaction time), the reaction solution was cooled to 0 ºC, neutralized with Na_2SO_4•$10H_2O$ (100.0 g), diluted with Et_2O (150 mL), and left to stir for 10 h. The resultant white precipitate was separated by filtration (washing with Et_2O) and the filtrate was concentrated. Purification of the resultant residue by flash column chromatography (silica gel, CH_2Cl_2/EtOAc, 1:1→0:1) afforded **40** (8.20 g, 72% over 2 steps) as a yellow oil. **40**: R_f = 0.15 (silica gel, EtOAc, $KMnO_4$); $[\alpha]_D^{25}$ = +25.7º (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} 3312, 2955, 2882, 2851, 1459, 1380, 1060, 1037 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.02–3.92 (m, 4 H), 3.77–3.73 (m, 1 H), 3.70–3.65 (m, 1 H), 3.10–3.08 (m, 1 H), 2.85–2.83 (m, 1 H), 2.76–2.72 (m, 2 H), 2.04–1.99 (m, 1 H), 1.87–1.82 (m, 1 H), 1.73–1.68 (m, 1 H), 1.53–1.41 (m, 4 H), 1.35 (s, 3 H), 1.02 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 110.2, 65.2, 65.1, 64.7, 64.7, 53.8, 38.0, 34.3, 31.0, 30.2, 24.9, 24.2, 17.2; HRMS (ESI) calcd for $C_{13}H_{25}NO_4Na^+$ [M + Na^+] 282.1676, found 282.1682. [Note: **40** exhibits severe oxygen-sensitivity undergoing a non-selective oxidation to the mixture of corresponding nitrones even at –20 ºC. Thus, the purified sample was subjected to the next step right away].

Aldonitrone 41. A flame-dried, 2-neck 1 L round bottom flask equipped with an internal thermometer and a magnetic stir bar at 23 ºC was charged with **40** (8.20 g, 31.6 mmol, 1.0 equiv) and CH_2Cl_2 (320 mL). Anhydrous $MgSO_4$ (11.4 g, 94.9 mmol, 3.0 equiv) was then added, and the resulting suspension was cooled to –20 ºC (internal temperature, MeOH/H_2O/dry ice bath). Next, freshly prepared, crystalline IBX[10] (9.74 g, 34.8 mmol, 1.1 equiv) was added in two portions with vigorous stirring. The resultant mixture was slowly warmed to 0 ºC over the course of 6 h and then was stirred at that temperature for an additional 9 h. Upon completion, the reaction mixture was warmed to 23 °C over 30 min, filtered (washing with CH_2Cl_2), and concentrated to provide a crude

mixture of **41** and corresponding isomeric ketonitrone (8.15 g, quant, *r.r.* = 8:1 favoring **41** as determined by ^{1}H NMR analysis) as a colorless oil that was used in the next step without any further purification. An analytical sample of **41** was purified by preparative TLC (CH_2Cl_2/MeOH, 20:1). **41**: R_f = 0.35 (silica gel, CH_2Cl_2/MeOH, 15/1, UV+$KMnO_4$); $[\alpha]_D^{25}$ = +5.2º (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} 3266, 2956, 2934, 2876, 1611, 1457, 1378, 1043 cm^{-1}; exists as 4:1 mixture with a cyclic isomer (drawn above) in $CDCl_3$. **41**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.20 (m, 1 H), 3.99–3.83 (m, 4 H), 3.77–3.60 (m, 2 H), 2.57 (m, 1 H), 2.42–2.31 (m, 1 H), 2.19–2.05 (m, 3 H), 2.06–1.94 (m, 1 H), 1.82–1.71 (m, 1 H), 1.65–1.51 (m, 1 H), 1.51–1.42 (m, 1 H), 1.32 (s, 3 H), 1.02 (d, *J* = 6.7 Hz, 3 H); cyclic isomer, key peaks: δ 4.55 (t, *J* = 2.9 Hz, 1 H), 3.17 (m, 1 H), 3.01 (m, 1 H), 1.28 (s, 1 H), 0.85 (d, J = 5.7 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.1, 109.8, 67.8, 64.8, 64.7, 64.6, 39.3, 34.6, 34.3, 33.3, 24.3, 21.8, 19.6; cyclic isomer, key peaks: δ 85.0, 64.5, 58.2, 40.0, 39.3, 35.3, 30.6, 25.8, 25.6, 24.3, 23.6; HRMS (ESI) calcd for $C_{13}H_{24}NO_4^+$ [M + H^+] 258.1700, found 258.1701.

Isoxazolidine 29. An oven dried 350 mL pressure vessel equipped with a magnetic stir bar at 23 ºC was charged with **41** (8.12 g, 8:1 *r.r.*, 31.6 mmol, 1.0 equiv) followed by toluene (240 mL) and ethyl vinyl ether (30.4 mL, 22.8 g, 316.0 mmol, 10.0 equiv). The reaction vessel was then sealed and placed in a water bath, preheated to 55 ºC. The mixture was stirred at this temperature for 17 h. Upon completion, the solution was cooled to 23 ºC and the contents were concentrated directly. The resulting oily residue was re-dissolved in CH_2Cl_2 (150 mL) and the solution was cooled to 0 ºC. Then, 4-DMAP (0.39 g, 3.16 mmol, 0.1 equiv) and Et_3N (13.1 mL, 9.59 g, 94.8 mmol, 3.0 equiv) were added sequentially followed by the dropwise addition of BzCl (3.68 mL, 4.45 g, 1.0 equiv). The resulting mixture was warmed to 23 ºC and stirred for an additional 2 h. Upon completion, the reaction solution was diluted with CH_2Cl_2 (150 mL) and saturated aqueous

$NaHCO_3$ (180 mL) was added. The resultant biphasic mixture was transferred to a separatory funnel, the layers were separated and the organic layer was washed with saturated aqueous $NaHCO_3$ (180 mL), saturated aqueous NH_4Cl (2 × 180 mL) and brine (180 mL). The organic phase was then dried ($MgSO_4$) and concentrated. The resultant crude product was then purified by flash column chromatography (silica gel, hexanes/EtOAc, 10:1→3:1) to afford **29** (8.10 g, 68% yield over 2 steps) as a yellow oil. **29**: R_f = 0.25 (silica gel, hexanes/EtOA, 4/1, UV+$KMnO_4$); $[\alpha]_D^{25}$ = +44.5º (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} 2977, 2950, 2929, 1719, 1276, 1114 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.10–7.95 (m, 2 H), 7.60–7.53 (m, 1 H), 7.48–7.37 (m, 2 H), 5.16–5.04 (m, 1 H), 4.54 (dd, *J* = 10.7, 4.2 Hz, 1 H), 4.40 (dd, *J* = 11.5, 3.7 Hz, 1 H), 4.01–3.89 (m, 4 H), 3.83–3.75 (m, 1 H), 3.52–3.40 (m, 2 H), 3.35–3.25 (m, 1 H), 2.36–2.28 (m, 1 H), 2.26–2.19 (m, 1 H), 2.18–2.06 (m, 2 H), 1.89–1.79 (m, 1 H), 1.77–1.66 (m, 1 H), 1.59–1.51 (m, 1 H), 1.51–1.44 (m, 1 H), 1.43–1.39 (m, 1 H), 1.38 (s, 3 H), 1.22 (t, *J* = 7.0 Hz, 3 H), 1.18–1.09 (m, 1 H), 0.90 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 132.9, 130.6, 129.7, 128.5, 110.4, 100.3, 65.9, 64.6, 64.4, 63.2, 58.3, 55.6, 43.1, 36.7, 35.6, 34.9, 29.3, 24.8, 24.3, 22.3, 15.4; HRMS (ESI) calcd for $C_{24}H_{36}NO_6^+$ [M + H^+] 434.2537, found 434.2537. Enantiopurity was determined by HPLC (ChiralPak OD-H, 95:5 hexanes/*i*-PrOH, 1 mL/min, 254 nm): t_{minor} = 6.8 min, t_{major} = 8.5 min (98% *ee*). The traces are shown in a separate section below.

Iminium salt 28. An oven dried 250 mL round bottom flask equipped with a magnetic stir bar at 23 °C was charged with **29** (3.00 g, 6.92 mmol, 1.0 equiv) followed by CH_3CN/H_2O (75 mL, 4/1, v/v). $Mo(CO)_6$ (2.19 g, 8.30 mmol, 1.2 equiv) was then added in a single portion and the resulting heterogeneous mixture was cooled to 0 ºC. Next, TFA (1.06 mL, 1.58 g, 13.8 mmol, 2.0 equiv) was added dropwise to the stirring solution. The ice bath was removed and the flask was equipped with condenser and placed in an oil bath. The mixture was then slowly brought to reflux

over a 30 min period. During this time, the color of the reaction solution changed from yellow (23 ºC) to green (around 70 ºC) and finally to a red-brown at reflux (with an oil bath temperature of 90 ºC) followed by the near complete dissolution of $Mo(CO)_6$. The resulting mixture was gently refluxed under a stream of N_2 for 2 h. The mixture was then allowed to cool to 23 °C and an aliquot was taken for the NMR analysis, revealing nearly full conversion of **29** to **44**. The mixture was then warmed to reflux with stirring for an additional 3 h. Upon completion, the contents were cooled to 23 ºC and TFA (2.65 mL, 34.6 mmol, 5.0 equiv) was added. The resulting solution was warmed to reflux for 35 minutes and then cooled back to 23 ºC. Finally, the mixture was diluted with benzene (80 mL) and the condenser was exchanged with a Dean–Stark trap. The mixture was warmed again to reflux (under N_2) with stirring and heating for 3 h until most of the H_2O was azeotropically distilled. The resulting dark-brown solution was then cooled to 23 ºC and concentrated directly. To the resultant brown viscous residue was added hexanes/Et_2O (250 mL, 1/1, v/v) and the resulting mixture was stirred vigorously for 1 h at 23 ºC. The solution was then carefully decanted from the residue and two more washes of that residue were repeated. The remaining residue was then dissolved in warm *i*-PrOH (50 mL, ~50 ºC), quickly filtered through a small pad of Celite (washing with warm *i*-PrOH), and concentrated to afford **28** (2.07 g, 70% yield) as a brown oil. **28**: $[\alpha]_D^{25}$ = +3.3º (*c* = 0.7, $CHCl_3$); IR (film) ν_{max} 2960, 2932, 1778, 1573, 1688, 1315, 1273, 1142 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02–7.99 (m, 2 H), 7.62–7.57 (m, 1 H), 7.46 (t, *J* = 7.8 Hz, 2 H), 4.56 (dd, *J* = 11.6, 5.3 Hz, 1 H), 4.45 (dd, *J* = 11.6, 6.8 Hz, 1 H), 4.32–4.23 (m, 1 H), 3.86–3.73 (m, 1 H), 3.33–3.22 (m, 1 H), 3.15–3.01 (m, 2 H), 2.87–2.72 (m, 2 H), 2.33–2.24 (m, 1 H), 2.16–2.07 (m, 1 H), 2.06–1.89 (m, 4 H), 1.79 (dd, *J* = 14.4, 3.2 Hz, 1 H), 1.66–1.56 (m, 1 H), 1.34 (td, *J* = 14.0, 10.9 Hz, 1 H), 1.06 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.4, 166.3, 160.9, 133.7, 129.8, 129.3, 128.8, 116.2, 66.4, 63.0, 56.5, 41.7, 40.4,

33.3, 32.0, 27.7, 26.6, 24.6, 21.9, 17.7; HRMS (ESI) calcd for $C_{20}H_{26}NO_2^+$ [M^+] 312.1964, found 312.1964. NMR data for **44** (after 3 washings with hexanes/Et_2O, 1/1): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03–7.95 (m, 2 H), 7.65–7.55 (m, 1 H), 7.52–7.42 (m, 2 H), 7.14–7.00 (m, 1 H), 6.50 (d, *J* = 9.2 Hz, 1H), 4.58 (dd, *J* = 11.5, 5.2 Hz, 1 H), 4.48 (dd, *J* = 11.5, 7.0 Hz, 1 H), 4.40–4.32 (m, 1 H), 4.12–4.01 (m, 1 H), 3.41–3.33 (m, 1 H), 3.23–3.11 (m, 1 H), 2.94–2.87 (m, 1 H), 2.84–2.70 (m, 1 H), 2.59–2.47 (m, 1 H), 2.28–2.22 (m, 1H), 2.11–1.99 (m, 2 H), 1.85 (dd, *J* = 14.3, 3.7 Hz, 1 H), 1.45–1.39 (m, 1 H), 1.09 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 166.3, 150.2, 133.7, 129.8, 129.3, 128.8, 118.7, 64.6, 63.3, 52.0, 42.7, 37.7, 33.2, 32.7, 29.1, 24.3, 22.4.

Intermediates 45 and 46. To a solution of **29** (0.200 g, 0.46 mmol, 1.0 equiv) in CH_3CN/H_2O (5 mL, 4/1, v/v) at 0 ºC was added TFA (70.4 μL, 0.92 mmol, 2.0 equiv) and the mixture was then warmed to 23 ºC. The resulting solution was slowly warmed to reflux over 10 min with final heating at reflux lasting for 2 min before being cooled back to 23 ºC. Upon completion, the reaction mixture was concentrated, re-dissolved in EtOAc (20 mL), transferred to a separatory funnel, and washed twice with saturated $NaHCO_3$ (2 × 5 mL). The organic layer was then dried (Na_2SO_4) and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 3:1→1:1→0:1) to afford **45** (34.4 mg, 19% yield) as a white solid and **46** (100.2 mg, 61% yield) as a colorless oil. **45** was recrystallized from CH_2Cl_2 to yield crystals of suitable quality for X-Ray crystallographic analysis. **45**: R_f = 0.54 (silica gel, hexanes/EtOAc, 3/1, UV+$KMnO_4$); IR (film) ν_{max} 2960, 2932, 1778, 1573, 1688, 1315, 1273, 1142 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04–7.99 (m, 2 H), 7.60–7.54 (m, 1 H), 7.48–7.42 (m, 2 H), 5.03 (dd, *J* = 6.2, 3.3 Hz, 1 H), 4.41–4.26 (m, 2 H), 3.82–3.73 (m, 1 H), 3.49–3.39 (m, 1 H), 3.32–3.27 (m, 1 H), 3.27–3.19 (m, 1 H), 2.89 (dd, *J* = 15.8, 8.0 Hz, 1 H), 2.72–2.64 (m, 1 H), 2.41 (dd,

J = 15.7, 4.0 Hz, 1 H), 2.25 (s, 3 H), 2.21–2.13 (m, 1 H), 2.08–2.01 (m, 1 H), 1.64–1.57 (m, 1 H), 1.55–1.49 (m, 1 H), 1.48–1.44 (m, 1 H), 1.46–1.38 (m, 1 H), 1.20 (t, *J* = 7.0 Hz, 3 H), 0.98 (q, *J* = 12.4 Hz, 1 H), 0.86 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.3, 166.7, 133.3, 130.1, 129.7, 128.6, 100.3, 77.5, 76.8, 66.3, 63.5, 59.4, 54.0, 45.3, 43.6, 36.1, 35.7, 31.4, 29.1, 24.6, 22.6, 15.4; HRMS (ESI) calcd for $C_{22}H_{32}NO_5^+$ [M + H^+] 390.2275, found 390.2276. **46**: R_f = 0.12 (silica gel, hexanes/EtOAc, 3/1, UV+$KMnO_4$); IR (film) ν_{max} 2950, 2924, 1718, 1274, 1114, 9912 cm^{-1}; major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10–7.89 (m, 2 H), 7.66–7.54 (m, 1 H), 7.51–7.37 (m, 2 H), 5.47–5.37 (m, 1 H), 4.40–4.26 (m, 2 H), 3.42–3.23 (m, 2 H), 2.95 (dd, *J* = 16.3, 7.4 Hz, 1 H), 2.93–2.86 (m, 1 H), 2.73–2.68 (m, 1 H), 2.49 (dd, *J* = 16.3, 4.7 Hz, 1 H), 2.24 (s, 3H), 2.18–2.15 (m, 2 H), 1.65–1.57 (m, 1 H), 1.55–1.43 (m, 2 H), 1.39–1.33 (m, 1 H), 1.04–0.96 (m, 1 H), 0.87 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.4, 166.6, 133.3, 130.1, 129.7, 128.6, 95.1, 66.0, 59.2, 54.5, 45.6, 45.3, 35.6, 35.5, 31.1, 29.0, 24.5, 22.5; HRMS (ESI) calcd for $C_{20}H_{28}NO_5^+$ [M + H^+] 362.1962, found 362.1963. [Note: Longer times for the reflux portion of the process resulted in the exclusive formation of **46**].

Mixture of aminonitriles 49 (R = Bz). To a stirring solution of **28** (0.200 g, 0.47 mmol, 1.0 equiv) in THF (2 mL) at 23 ºC was added KCN (0.184 g, 2.82 mmol, 6.0 equiv) and the resulting heterogeneous solution was stirred for 2 h at 23 ºC. Upon completion, the mixture was filtered, and the filtrate was concentrated directly. Purification of the resultant residue by flash column chromatography (Et_3N-deactivated silica gel, hexanes/EtOAc, 5:1→2:1) afforded a mixture of aminonitriles **49** (0.106 g, 5:1 ratio based on ^{1}H NMR analysis, 67% yield) as a colorless oil. **49**: R_f = 0.40 (Et_3N-deactivated silica gel plate, hexanes/EtOAc, 2/1, UV+$KMnO_4$); IR (film) ν_{max} 2927, 2863, 1773, 1457, 1272, 1114 cm^{-1}; **49**, major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06–8.03 (m, 2 H), 7.62–7.58 (m, 1 H), 7.49–7.45 (m, 2 H), 4.42 (dd, *J* = 10.9,

6.6 Hz, 1 H), 4.35 (dd, *J* = 10.9, 7.0 Hz, 1 H), 3.25 (ddd, *J* = 13.0, 7.7, 2.8 Hz, 1 H), 2.95–2.87 (m, 1 H), 2.58–2.51 (m, 1 H), 2.51–2.44 (m, 1 H), 2.17–2.08 (m, 1 H), 2.04–1.92 (m, 2 H), 1.88–1.81 (m, 2 H), 1.76–1.70 (m, 2 H), 1.60–1.55 (m, 1 H), 1.53–1.41 (m, 2 H), 1.23–1.12 (m, 1 H), 1.09–1.00 (m, 1 H), 0.97 (d, *J* = 7.0 Hz, 3 H); **49**, minor diastereomer, key peaks: δ 3.66–3.56 (m, 1 H), 2.81–2.74 (m, 1 H), 2.70–2.63 (m, 1 H), 2.32–2.22 (m, 1 H), 0.93 (d, *J* = 5.9 Hz, 3 H); **49**, major diastereomer: ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 133.3, 129.9, 129.7, 128.6, 121.5, 66.6, 63.3, 55.9, 53.0, 43.1, 40.9, 37.0, 34.8, 34.7, 31.4, 25.7, 22.6, 22.1; **49**, minor diastereomer, key peaks: δ 119.0, 66.8, 64.1, 62.3, 54.0, 51.6, 50.7, 38.2, 37.8, 33.9, 27.2. HRMS (ESI) calcd for $C_{21}H_{27}NO_2^+$ [M + H^+] 339.2067, found 339.2067. [Note: Upon storage, the *dr* ratio of **49** changes to 3:1].

Meldrum's Acid Adduct 54 (R = Bz). To a stirring solution of **28** (0.100 g, 0.236 mmol, 1.0 equiv) in MeOH (2 mL) at 23 ºC was added **53** (0.052 g, 0.283 mmol, 1.2 equiv). After stirring at 23 ºC for 1 h, another portion of the salt was added (43 mg, 1.0 equiv) and the mixture was stirred for an additional 2 h. Upon completion, the reaction solution was concentrated directly to dryness and the resultant residue was added to saturated aqueous $NaHCO_3$ (5 mL). The mixture was then further diluted with CH_2Cl_2 (10 mL) and transferred to a separatory funnel. After separating the layers, the aqueous layer was extracted further with CH_2Cl_2 (2 × 10 mL). The combined organic fractions were then dried (Na_2SO_4) and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 1:1→0:1) to afford **54** (0.058 g, *dr* = 8:1 based on ^{1}H NMR analysis, 54% yield) as a yellow oil. **54**: R_f = 0.30 (silica gel, EtOAc, UV); IR (film) ν_{max} 3422, 2926, 2871, 1719, 1734, 1685, 1583, 1270 cm^{-1}; **54**, major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.02 (br s, 1 H), 8.03–7.93 (m, 2 H), 7.62–7.54 (m, 1 H), 7.47–7.38 (m, 2 H), 4.43–4.30 (m, 2 H), 3.97–3.91 (m, 1 H), 3.37–3.23 (m, 1 H), 3.01–2.90

(m, 1 H), 2.84–2.75 (m, 1 H), 2.47–2.38 (m, 2 H), 2.10–2.01 (m, 2 H), 1.92–1.72 (m, 3 H), 1.77–1.72 (m, 1 H), 1.68–1.59 (m, 9 H), 1.35–1.21 (m, 2 H), 0.97 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 165.3, 163.2, 132.5, 128.7 (2 peaks), 127.7, 100.8, 75.3, 72.2, 65.8, 61.2, 54.4, 38.2, 35.6, 32.5, 31.7, 28.6, 26.4, 25.0, 23.5, 20.3, 18.4; HRMS (ESI) calcd for $C_{26}H_{34}NO_6^+$ [M + H^+] 456.2381, found 456.2379.

Malonaldehyde Adduct 71 (Nu = 72). To a solution of **28** (20.0 mg, 0.047 mmol, 1.0 equiv) in DMSO-d_6 (0.5 mL) at 23 ºC was added freshly prepared **72** (6.2 mg, 0.066 mmol, 1.4 equiv). The resultant clear, deep red colored solution was transferred to an NMR tube with reaction was monitored by ^{1}H NMR. After 20 h at 23 ºC, no further conversion was observed and the solution was diluted with H_2O (2 mL), transferred to a separatory funnel, and extracted with EtOAc (3 × 5 mL). The combined organic fractions were further washed with brine (3 × 5 mL), dried (Na_2SO_4) and concentrated. The resultant residue was re-dissolved in CH_2Cl_2 and passed through a short SiO_2 pad eluting with CH_2Cl_2/MeOH (20/1). The resulting solution was then concentrated and the crude residue was dried under high vacuum. Next, the crude mixture of diastereomers **71** (Nu = **72**) (~1:1 based on ^{1}H NMR analysis) was dissolved in $CDCl_3$ and the progress of isomerization was monitored by ^{1}H NMR, noting that the color of the solution changes from red to purple over time. After 2 d at 23 ºC, the solution was concentrated and the crude mixture was purified by preparative TLC (CH_2Cl_2/MeOH, 20:1) to afford **71** (Nu = **72**) (7.0 mg, 42% yield) as a pink oil. **71** (Nu = **72**): R_f = 0.44 (silica gel, CH_2Cl_2/MeOH = 20/1, UV+$KMnO_4$); IR (film) ν_{max} 3418, 2954, 2926, 1721, 1651, 1567, 1259 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 14.02 (br s, 1 H), 8.74 (br s, 1 H), 8.25 (br s, 1 H), 8.08–7.94 (m, 2 H), 7.67–7.51 (m, 1 H), 7.51–7.37 (m, 2 H), 4.39 (dd, J = 11.3, 5.8 Hz, 1 H), 4.28 (dd, J = 11.2, 6.4 Hz, 1 H), 3.89–3.70 (m, 1 H), 3.27–3.13 (m, 1 H), 2.95–2.82 (m, 1 H), 2.82–2.66 (m, 1 H), 2.37 (dd, J = 14.4, 10.6 Hz, 1 H), 2.26–2.11 (m, 1 H),

2.08–2.01 (m, 1 H), 1.99–1.92 (m, 1 H), 1.89–1.75 (m, 3 H), 1.77–1.64 (m, 3 H), 1.32–1.19 (m, 2 H), 0.96 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.9, 185.2, 166.3, 133.3, 129.7, 129.6, 128.5, 115.6, 73.7, 65.7, 61.5, 53.6, 39.3, 36.7, 36.6, 33.0, 32.8, 32.7, 29.7, 29.1, 25.8, 21.3, 18.5. ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.1, 185.3, 166.4, 133.4, 129.8, 129.8, 128.6, 115.8, 73.9, 65.8, 61.6, 53.7, 39.4, 36.8, 33.1, 32.9, 29.9, 29.4, 26.0, 21.4, 18.7; HRMS (ESI) calcd for $C_{23}H_{30}NO_4^+$ [M + H^+] 384.2169, found 353.2171.

Nitrile 62. An oven dried 350 mL pressure vessel equipped with adapter and magnetic stir bar was charged with **28** (3.00 g, 6.92 mmol, 1.0 equiv) followed by CH_3CN/H_2O (75 mL, 4/1 by volume). Then, $Mo(CO)_6$ (2.74 g, 10.38 mmol, 1.5 equiv) was added in one portion and the resulting heterogeneous mixture was cooled to 0 ºC. Next, TFA (1.30 mL, 1.98 g, 2.5 equiv) was added dropwise to the stirring solution. The ice bath was removed, and the vessel was equipped with condenser and placed on an oil bath. The mixture was then slowly brought to reflux over 1 h period. During this time the color of the solution changes from yellow (23 ºC), then green (around 70 ºC) to red-brown at reflux (oil bath temperature 90 ºC), followed by almost complete dissolution of $Mo(CO)_6$. The resulting mixture was gently refluxed under a stream of N_2 for 8 h. Upon completion, the flask was cooled to 23 ºC and additional TFA (1.30 mL, 1.98 g, 17.3 mmol, 2.5 equiv) was added. The resulting solution was brought back to reflux for 30 min and then cooled back to 23 ºC. The mixture was diluted with benzene (80 mL) and the condenser was replaced by a Dean-Stark trap. The mixture was brought back to reflux (under N_2), maintaining that reflux for the next 3 h until most of the H_2O was azeotropically distilled (14–15 mL). The resulting dark-brown solution was cooled to 23 ºC and concentrated on the rotary evaporator (bath temperature was set to 40 ºC). The resulting oil was dried under high vacuum for 2 h, back-filled with Ar, and dissolved in degassed *i*-PrOH (60 mL). Next, **61** (1.33 g, 10.8 mmol, 1.6 equiv) was quickly added

in one portion and the vessel was sealed. The resulting red-brown solution was then gradually warmed to 100 ºC (oil bath temperature) and stirred at this temperature for 15 h. The vessel was then cooled to 23 ºC and a new portion of **61** (2.00 g, 16.22 mmol, 2.4 equiv) was added. After flushing the contents with Ar, the vessel was sealed and the oil bath temperature was brought to 120 ºC. The solution was stirred at this temperature for 8 h. After cooling to 23 ºC the mixture was filtered through Celite (washing with MeOH) and concentrated. The resulting brown oil was diluted with EtOAc (100 mL), acidified to pH 3–4 with AcOH and transferred to a separatory funnel. The organic layer was washed with saturated aqueous $NaHCO_3/Na_2CO_3$ (100 mL, 1:1 by volume) and the aqueous layer was additionally extracted with EtOAc (3 × 100 mL). The combined organic fractions were washed with brine (100 mL), dried (Na_2SO_4) and concentrated. The crude product was purified by flash column chromatography (Et_3N-deactivated silica gel, hexanes/EtOAc, 4:1→2:1→1:1) to afford **63** (less polar fraction, 0.22 g, 9% yield) as a red oil and **62** (more polar fraction, 1.10 g, 47% yield) as a light-brown solid). **62**: R_f = 0.32 (silica gel, hexanes/EtOAc, 2:1, UV+$KMnO_4$); $[\alpha]_D^{25}$ = +8.6º (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} 2946, 2926, 2247, 1731, 1451, 1275, 1113 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05–7.97 (m, 2 H), 7.61–7.54 (m, 1 H), 7.50–7.43 (m, 2 H), 4.44–4.31 (m, 2H), 3.23 (ddd, *J* = 11.0, 5.7, 1.7 Hz, 1 H), 2.81–2.70 (m, 1 H), 2.66 (d, *J* = 16.6 Hz, 1 H), 2.52 (d, *J* = 16.6 Hz, 1 H), 2.37–2.31 (m, 1 H), 2.30–2.22 (m, 1 H), 2.00–1.94 (m, 1 H), 1.90–1.85 (m, 1 H), 1.83–1.76 (m, 1 H), 1.74–1.69 (m, 1 H), 1.69–1.63 (m, 2 H), 1.59–1.54 (m, 1 H), 1.54–1.47 (m, 3 H), 1.32–1.21 (m, 1 H), 1.03–0.94 (m, 1 H), 0.91 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 133.3, 130.1, 129.6, 128.7, 118.5, 66.4, 64.4, 60.8, 54.4, 41.4, 38.5, 35.3, 34.0, 33.3, 31.9, 31.3, 26.9, 22.0, 20.6; HRMS (ESI) calcd for $C_{22}H_{29}N_2O_2^+$ [M + H^+] 353.2218, found 353.2221. **63**: R_f = 0.60 (silica gel, hexanes/EtOAc, 2:1, UV+$KMnO_4$); $[\alpha]_D^{25}$ = +1.0º (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} 2924, 2860, 2247, 1719, 1492, 1272,

1114 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10–7.97 (m, 2 H), 7.62–7.54 (m, 1 H), 7.49–7.42 (m, 2 H), 4.38–4.25 (m, 2 H), 3.06–2.98 (m, 2 H), 2.66 (dd, *J* = 16.6 Hz, 2 H), 2.28–2.16 (m, 2 H), 2.04–1.98 (m, 1 H), 1.94–1.88 (m, 1 H), 1.76–1.56 (m, 7 H), 1.47–1.36 (m, 1 H), 1.32–1.19 (m, 2 H), 1.03 (d, *J* = 7.4 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 133.1, 130.3, 129.7, 128.6, 118.7, 66.7, 60.0, 52.9, 50.7, 42.8, 41.4, 37.7, 36.1, 30.7, 26.8, 25.9, 25.7, 22.5, 21.7; HRMS (ESI) calcd for $C_{22}H_{29}N_2O_2^+$ [M + H^+] 353.2218, found 353.2221.

Primary amine 79. An oven dried 100 mL round bottom flask equipped with magnetic stir bar at 23 ºC was charged with **62** (1.05 g, 2.98 mmol, 1.0 equiv) and EtOH/H_2O (60 mL, 4/1, v/v). Next, $(Me_2POH)_3Pt$ (**77**) (64.4 mg, 0.15 mmol, 5 mol %) was added and the resulting mixture was then heated reflux with stirring for 10 h. Upon completion, the reaction mixture was concentrated directly (rotovap bath set to 40 ºC) and dried under high vacuum to provide intermediate **78** as a yellow solid. Next, to the same flask was added CH_3CN/H_2O (10 mL, 4:1, v/v) followed by *p*-TsOH•H_2O (0.57 g, 2.98 mmol, 1.0 equiv). After the solution became clear, PhI(OH)(OTs) (1.40 g, 3.58 mmol, 1.2 equiv) was added in a single portion at 23 ºC. The color of the solution quickly changed from orange to dark-red followed by a rapid dissolution of PhI(OH)(OTs). The flask was then equipped with a condenser and the resulting solution was heated at reflux under a gentle stream of N_2. After 2.5 h of stirring at that temperature (during which time the reaction color gradually changed from red to yellow), the mixture was cooled to 23 ºC. Another portion of PhI(OH)(OTs) (0.93 g, 2.4 mmol, 0.8 equiv) was then added and the contents were then rewarmed to reflux and stirring was continued for an additional 2.5 h. Upon completion, the mixture was cooled to 23 ºC and concentrated directly. To the resultant residue was then added HCl (2 M in H_2O, 15 mL) and Et_2O (10 mL) and the resulting biphasic mixture was transferred to a separatory funnel. The aqueous layer was separated, washed with Et_2O

(2 × 10 mL) and neutralized to pH 9 by the addition of solid K_2CO_3 (~4.5 g). The crude product was extracted with EtOAc (6 × 100 mL) and the combined organic fractions were washed with saturated aqueous Na_2CO_3 (2 × 20 mL) and brine (20 mL), dried (Na_2SO_4), filtered (Celite), and concentrated to provide **79** (0.64 g, 65% yield) as a yellow oil that was used in the next step without any additional purification. The bis•HCl salt of **79** was prepared by dissolving the free base in dry Et_2O and adding an excess amount of HCl (~6.0 equiv, 1 M in Et_2O) to form a precipitate. The Et_2O was then carefully decanted the resulting solid was dried under high vacuum. A small amount of methanol was then added and the solution was left to crystallize for 3 d in a –20 ºC freezer to obtain crystals of sufficient quality for X-ray crystallographic analysis. **79**: R_f = 0.53 (Et_3N-deactivated silica gel, CH_2Cl_2/MeOH containing 10% v/v of aqueous NH_3•H_2O = 10/1, ninhydrin + UV); $[\alpha]_D^{25}$ = +8.5º (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} 2923, 2868, 2247, 1719, 1451, 1271, 1113 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08–7.88 (m, 2 H), 7.59–7.50 (m, 1 H), 7.43 (t, *J* = 7.8 Hz, 2 H), 4.35 (dd, *J* = 11.0, 6.0 Hz, 1 H), 4.28 (dd, *J* = 11.0, 7.0 Hz, 1 H), 3.17 (ddd, *J* = 10.8, 5.8, 1.8 Hz, 1 H), 2.82 (d, *J* = 13.1 Hz, 1 H), 2.77–2.65 (m, 1 H), 2.28 (d, *J* = 13.1 Hz, 1 H), 2.26–2.16 (m, 2 H), 1.87–1.74 (m, 2 H), 1.75–1.59 (m, 4 H), 1.55–1.37 (m, 5 H), 1.30 (dd, *J* = 13.5, 5.1 Hz, 1 H), 1.20–1.09 (m, 1 H), 0.97 (q, *J* = 11.8 Hz, 1 H), 0.88 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 133.1, 130.3, 129.6, 128.5, 68.1, 66.2, 60.6, 54.7, 50.0, 41.7, 38.1, 34.7, 34.5, 32.4, 30.3, 27.2, 22.2, 21.4; HRMS (ESI) calcd for $C_{21}H_{31}N_2O_2^+$ [M + H^+] 343.2380, found 353.2386.

Analytical data for 78, 80 and 81:

78: R_f = 0.85 (Et_3N-deactivated silica gel plate, CH_2Cl_2/MeOH containing 10% v/v of aqueous NH_3•H_2O = 10/1, UV); ^1H NMR (500 MHz, $CDCl_3$) δ 9.49 (br s, 1 H), 8.15–7.84 (m, 2 H), 7.61–7.55 (m, 1 H), 7.45 (t, *J* = 7.8 Hz, 2 H), 5.46 (br s, *J* = 5.4 Hz, 1 H), 4.39 (dd, *J* = 11.1,

5.8 Hz, 1 H), 4.33 (dd, *J* = 11.1, 6.5 Hz, 1 H), 3.51–3.37 (m, 1 H), 2.84 (d, *J* = 16.7 Hz, 1 H), 2.74 (qt, *J* = 11.2, 5.3 Hz, 1 H), 2.47–2.36 (m, 1 H), 2.30–2.22 (m, 1 H), 2.02 (d, *J* = 16.8 Hz, 1 H), 1.97–1.91 (m, 1 H), 1.90–1.80 (m, 1 H), 1.76–1.63 (m, 3 H), 1.56–1.44 (m, 4 H), 1.34 (dd, *J* = 13.7, 4.8 Hz, 1 H), 1.27–1.18 (m, 1 H), 1.01–0.94 (m, 1 H), 0.92 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 166.7, 133.3, 130.1, 129.6, 128.6, 67.3, 64.1, 60.1, 55.2, 46.4, 41.8, 37.5, 36.6, 34.6, 32.4, 32.1, 27.2, 22.1, 21.6; HRMS (ESI) calcd for $C_{22}H_{31}N_2O_3^+$ [M + H^+] 371.2324, found 371.2327.

80: IR (film) ν_{max} 3382, 2952, 2927, 1718, 1583, 1273 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03–7.90 (m, 2 H), 7.65–7.55 (m, 1 H), 7.46 (t, *J* = 7.6 Hz, 2 H), 4.41 (d, *J* = 4.8 Hz, 2 H), 3.62 (dd, *J* = 13.0, 5.7 Hz, 1 H), 3.26–3.20 (m, 1 H), 2.96 (d, *J* = 16.2 Hz, 1 H), 2.92–2.82 (m, 1 H), 2.64 (d, *J* = 16.1 Hz, 1 H), 2.38 (dd, *J* = 13.8, 9.1 Hz, 1 H), 2.25 (dd, *J* = 13.8, 8.8 Hz, 1 H), 2.14–2.00 (m, 3 H), 1.98–1.87 (m, 3 H), 1.83–1.70 (m, 2 H), 1.65–1.56 (m, 1 H), 1.55–1.44 (m, 2 H), 0.96 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.4, 166.3, 133.8, 129.6, 129.3, 128.9, 78.9, 76.5, 63.8, 61.1, 48.7, 37.4 (2 peaks), 36.1, 34.1, 29.9, 26.1, 23.5, 21.3, 16.6; HRMS (ESI) calcd for $C_{22}H_{29}N_2O_3^+$ [M + H^+] 369.2173, found 369.2172.

81: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.7 Hz, 4 H), 7.54 (t, *J* = 7.2 Hz, 2 H), 7.43 (t, *J* = 7.5 Hz, 4 H), 5.28 (br s, 2 H), 4.40–4.26 (m, 4 H), 3.31–3.19 (m, 2 H), 3.15–3.05 (m, 4 H), 2.84–2.67 (m, 2 H), 2.34–2.17 (m, 4 H), 1.91–1.77 (m, 4 H), 1.71–1.30 (m, 16 H), 1.22–0.94 (m, 4 H), 0.89 (d, *J* = 6.4 Hz, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6, 159.2, 133.1, 130.3, 129.6, 128.5, 68.0, 65.5, 60.6, 55.0, 47.7, 41.4, 38.0, 34.9, 34.4, 32.2, 30.8, 27.1, 22.1, 21.4; HRMS (ESI) calcd for $C_{43}H_{59}N_4O_5^+$ [M + H^+] 711.4480, found 711.4481.

Aldehyde 27. A flame-dried dried 50 mL round bottom flask equipped with magnetic stir bar at 23 ºC was charged with **79** (0.20 g, 0.59 mmol, 1.0 equiv) and DMF (2.5 mL, dried over 4

Å molecular sieves prior to use). Then, **82** (0.31 g, 1.76 mmol, 3.0 equiv) was added in a single portion and the reaction flask was placed in an oil bath that had been preheated to 60 ºC. The reaction contents were then stirred at that temperature for 11 h with stirring, during which time the color of the reaction mixture changed from red to purple (after ~2 h of heating). Upon completion, the reaction mixture was cooled to 0 ºC and then cold HCl (1 M in H_2O, 40 mL) was added. The resulting solution was warmed to 23 ºC and stirred for 2.5 h at this temperature. Once complete, the mixture was cooled to 0 ºC again and the pH was adjusted to 9 by the addition of NH_3 (28% aqueous solution, ~4 mL). The resulting solution was transferred to a separatory funnel and the product was extracted with EtOAc (3 × 50 mL). The organic fractions were washed with brine (2 × 35 mL), dried (Na_2SO_4), and concentrated. The crude product was passed through a short pad of SiO_2 (eluting with hexanes/EtOAc, 1/1), concentrated, and dried under high vacuum to provide **27** (0.120 g, 60% yield) as a yellow oil. **27**: R_f = 0.45 (silica gel, hexanes/EtOAc, 2/1, UV+DNP); $[\alpha]_D^{25}$ = +83.0º (*c* = 0.7, $CHCl_3$); IR (film) ν_{max} 2925, 2868, 1720, 1451, 1271, 1113 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.02 (d, *J* = 7.7 Hz, 2 H), 7.55 (t, *J* = 7.4 Hz, 1 H), 7.44 (t, *J* = 7.6 Hz, 2 H), 4.27–4.09 (m, 2 H), 2.76–2.65 (m, 1 H), 2.59–2.47 (m, 1 H), 2.26–2.21 (m, 1 H), 2.18–2.13 (m, 2 H), 1.86 (dd, *J* = 14.2, 4.3 Hz, 1H), 1.78–1.45 (m, 6 H), 1.44–1.37 (m, 1 H), 1.30–1.21 (m, 2 H), 1.13–1.01 (m, 1 H), 0.91 (d, *J* = 6.5 Hz, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.5, 166.7, 133.1, 130.3, 129.7, 128.5, 73.8, 67.1, 64.6, 54.0, 40.9, 37.7, 34.1, 31.7, 29.1, 27.4, 25.9, 22.2, 20.8; HRMS (ESI) calcd for $C_{21}H_{28}NO_3^+$ [M + H^+] 342.2064, found 342.2067.

Enone 86. An Ar-flushed, sealed, 5 mL flame-dried microwave vial equipped with magnetic stir bar at 23 ºC was charged with *i*-Pr_2NH (66 μL, 47.4 mg, 0.46 mmol, 1.6 equiv) and THF (1.65 mL). The resulting solution was cooled to 0 ºC and then *n*-BuLi (1.5 M in hexanes, 293 μL, 0.44 mmol, 1.5 equiv) was added dropwise slowly. The resulting light yellow solution was

stirred for 5 min at 0 ºC and then was cooled to –78 ºC. Next, a solution of **9**[7] (0.105 g, 0.35 mmol, 1.2 equiv) in THF (0.75 mL) was slowly introduced into the mixture via syringe. The resulting orange solution was stirred at –78 ºC for 40 min. A solution of **27** (0.100 g, 0.29 mmol, 1.0 equiv) in THF (0.75 mL) was added slowly via syringe over 5 min and the resulting mixture was stirred at –78 ºC for 4.5 h. Upon completion, the vial was taken out of the bath and immediately quenched by addition of anhydrous *p*-TsOH (0.66 M in benzene, 3.0 mL, 2.03 mmol, 7.0 equiv) under vigorous stirring. The contents were then warmed to 23 ºC and then carefully concentrated on the rotovap (without unsealing the vial). The resulting brownish gum was further dried under high vacuum for 30 min, back filled with Ar, and then re-dissolved in dry benzene (3 mL). The vial was wrapped with aluminum foil and placed in an oil bath that had already been pre-heated to 50 ºC and was then stirred at this temperature for 13 h. Upon completion, the resulting red-brown mixture was cooled to 23 ºC, the cap was removed, and saturated aqueous $NaHCO_3$ (20 mL) was added. The mixture was transferred to a separatory funnel containing EtOAc (40 mL) and the aqueous layer was separated and extracted additionally with EtOAc (2 × 40 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated. The resultant residue was purified by flash column chromatography (Et_3N-deactivated silica gel, hexanes/EtOAc, 2:1→1:1) to provide **86** (0.103 g, 60% yield) as a yellow solid. **86**: R_f = 0.44 (Et_3N-deactivated silica gel plate, hexanes/EtOAc, 1/1, UV + vanillin); $[\alpha]_D^{25}$ = –115.6º (*c* = 0.5, $CHCl_3$); IR (film) ν_{max} 2943, 2922, 1717, 1656, 1313, 1272 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.7 Hz, 2 H), 7.44 (t, *J* = 7.5 Hz, 1 H), 7.32 (t, *J* = 7.7 Hz, 2 H), 7.01 (d, *J* = 4.3 Hz, 1 H), 7.00 (m, 1 H), 6.47 (d, *J* = 4.3 Hz, 1 H), 4.41 (dd, *J* = 11.2, 5.0 Hz, 1 H), 4.18 (dd, *J* = 11.2, 5.8 Hz, 1 H), 3.92–3.83 (m, 1 H), 3.69 (d, *J* = 11.2 Hz, 1 H), 3.66–3.59 (m, 1 H), 3.56–3.44 (m, 2 H), 3.39–3.30 (m, 1 H), 3.21–3.10 (m, 1 H), 2.70 (dq, *J* = 10.7, 5.3 Hz, 1 H), 2.56–2.45 (m, 2 H), 2.39–2.21 (m, 3 H), 2.18–2.10 (m,

1 H), 2.02–1.96 (m, 1 H), 1.94–1.88 (m, 1 H), 1.86–1.77 (m, 2 H), 1.74–1.43 (m, 6 H), 1.31–1.20 (m, 2 H), 1.06–0.98 (m, 1 H), 0.91 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.6, 166.9, 150.2, 137.8, 133.1, 130.6, 130.1, 129.8, 129.6, 128.6, 115.6, 110.6, 67.6, 66.7, 62.3, 62.0, 54.3, 52.3, 41.8, 40.8, 40.7, 40.4, 37.7, 36.6, 34.3, 33.4, 33.2, 32.3, 30.0, 27.4, 22.2, 21.4; HRMS (CI) calcd for $C_{34}H_{41}N_2O_3S_2^+$ [M + H^+] 589.2553, found 589.2555.

Ketone 87. A 5 mL flame-dried microwave vial equipped with magnetic stir bar at 23 ºC was charged with **86** (64.0 mg, 0.11 mmol, 1.0 equiv) and $Mn(dpm)_3$ (144.6 mg, 0.24 mmol, 2.2 equiv) and then was sealed. The vial was evacuated under high vacuum through the needle and filled with Ar. This process was repeated 3 times. Then, *i*-PrOH (1.15 mL) and CH_2Cl_2 (0.15 mL) were added sequentially. The resulting olive black solution was stirred at 23 ºC for 10 min, at which time all the solids were dissolved. The mixture was further degassed by bubbling Ar through the solution. After 20 min, degassing was stopped, and to the stirring mixture was added $MeSi(OEt)_2H$ (87.1 μL, 73.2 mg, 0.55 mmol, 5.0 equiv) dropwise. After the addition was complete, the reaction mixture was warmed to 30 ºC (using a water bath) and stirred at this temperature for 16 h, during which time the color gradually changed to a light brown. Once complete, the reaction solution was concentrated directly on a rotary evaporator. The resultant residue was then dissolved in Et_2O (5 mL) and HCl (1 M in H_2O, 5 mL). After vigorously stirring the mixture for ~10 min, the organic layer was decanted with a pipette and a new portion of Et_2O (5 mL) was added. This washing and decanting was repeated two more times, and then the aqueous layer was neutralized to pH 8 by the addition of solid $NaHCO_3$ (0.240 g), diluted with CH_2Cl_2 (10 mL), and transferred to a separatory funnel. The aqueous layer was separated and extracted with CH_2Cl_2 (10 mL). The combined organic fractions were dried (Na_2SO_4), concentrated, and dried

under high vacuum for 2 h to provide **87** (59.2 mg, 92% yield, *dr* = 6:1 based on ^{1}H NMR analysis) as a light brown solid that was used in the next step without any additional purification.

Chilocorine C•HCl **(5**•HCl**)**. A 5 mL flame-dried microwave vial equipped with magnetic stir bar at 23 ºC was charged with **87** (50.5 mg, 0.09 mmol, 1.0 equiv), sealed, back-filled with Ar, and dissolved in THF (2 mL). The solution was then cooled to –78 ºC and then MeLi (1.6 M in Et_2O, 225 μL, 0.36 mmol, 4.0 equiv) was added slowly and dropwise. The mixture was then gradually warmed to –30 ºC with stirring over the course of 2 h. The resulting red solution was then cooled back to –78 ºC and quenched by a rapid addition of a solution of *p*-TsOH•H_2O (171 mg, 0.90 mmol, 10 equiv) in THF (1 mL). The vial was then warmed to 23 ºC, covered with aluminum foil, and stirred at 23 ºC for 8 h. Upon completion, the resulting black solution was concentrated to dryness (through the needle), dried under high vacuum, and back filled with Ar. To the resultant residue was added a mixture of aqueous HCl (6 M)/1,4-dioxane (2.5 mL, 3/7, v/v) and the resulting solution was cooled to 0 ºC. Next, DMSO (64.2 μL, 70.3 mg, 0.90 mmol, 10 equiv) was added via syringe and the resulting solution was warmed to 23 ºC and stirred at this temperature for additional 4 h. Upon completion, the vial was unsealed and the contents were diluted with EtOAc (2 mL) and then quickly poured into a cold (0 ºC) stirring solution of saturated aqueous Na_2CO_3 (5 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic fractions were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The resultant residue was then treated with Et_2O (5 mL), and the solids were removed by filtering through a 0.2 □m PTFE syringe filter. To the resulting clear yellow solution was added HCl (1 M in Et_2O, 200 μL) and the newly formed grey precipitate was filtered through the fine porosity glass frit and further re-dissolved by adding CH_2Cl_2 (2 mL). The collected filtrate was concentrated, and the crude salt was purified by preparative TLC (eluting with CH_2Cl_2/MeOH, 9/1) to yield **5**•HCl

(16.1 mg, 42% yield) as a cream colored crystalline solid. Crystals suitable for X-ray diffraction were obtained by vapor diffusion ($CHCl_3$/Et_2O). **5**•HCl: R_f = 0.33 (silica gel, CH_2Cl_2/MeOH, 9/1, UV, fluorescent under shortwave irradiation, highly intense under longwave radiation, stains red with vanillin); $[\alpha]_D^{25}$ = +36.3º (*c* = 0.1, $CHCl_3$); lit.: N/A.; IR (film) ν_{max} 3376, 2954, 2925, 2854, 1655, 1431 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.80 (br s, 1 H), 6.85 (d, *J* = 4.1 Hz, 1 H), 6.11 (d, *J* = 4.1 Hz, 1 H), 5.34 (br s, 1 H), 4.56 (m), 3.95 (dd, *J* = 12.1, 1.8 Hz, 1 H), 3.70 (dd, *J* = 12.1, 2.9 Hz, 1 H), 3.53 (d, *J* = 12.6 Hz, 1 H), 3.23 (d, *J* = 12.6 Hz, 1 H), 3.18 (m, 1 H), 2.86 (m, 1 H), 2.54 (dd, *J* = 15.9, 5.2 Hz, 1 H), 2.47 (m, 1 H), 2.43 (dd, *J* = 17.3, 4.3 Hz, 1 H), 2.23 (s, 3 H), 2.22 (m, 1 H), 2.17 (m, 1 H), 2.13 (m, 1 H), 2.13 (m, 1 H), 2.12 (m, 1 H), 2.10 (m, 1 H), 1.95–1.70 (m, 6 H), 1.68–1.66 (m, 2 H), 1.56 (m, 1 H), 1.51 (m, 1 H), 1.01 (d, *J* = 5.5 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.0, 135.1, 128.8, 125.2, 125.1, 113.6, 107.3, 70.6, 59.4, 58.4, 58.3, 49.1, 40.2, 39.4, 37.3, 36.7, 36.0, 32.0 (2 carbons), 30.7, 29.7, 28.6, 26.0, 21.1, 19.9, 15.5; HRMS (ESI) calcd for $C_{26}H_{37}N_2O_2^+$ [M + H^+] 409.2850, found 409.2852.

Table 2.5. ^{1}H NMR (500 MHz, $CDCl_3$) spectral data comparison of synthetic chilocorine C•HCl (5•HCl) and natural chilocorine C•HCl.

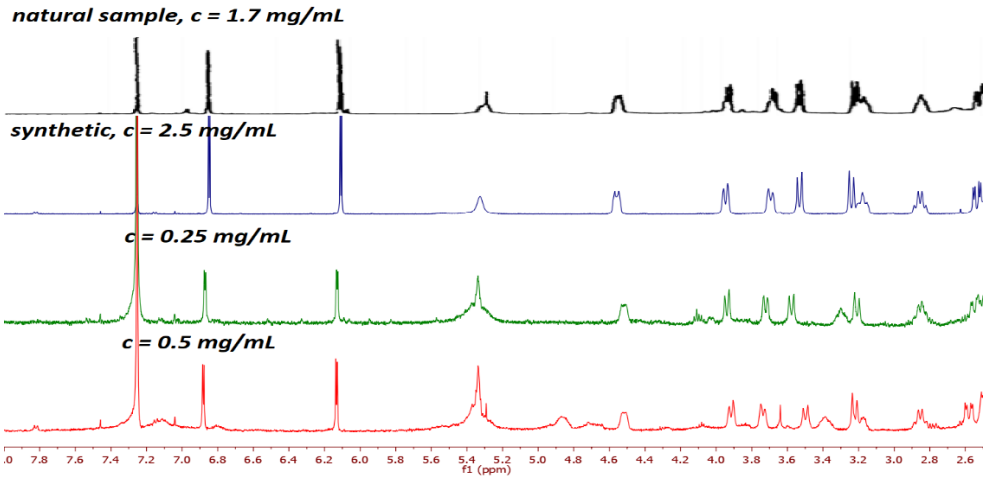
Synthetic 5•HCl *c* = 2.5 mg/mL	**Natural Chilocorine C**•HCl[1] *c* = 1.7 mg/mL	**Δ δ, ppm**
10.80 (br s, 1 H)	10.87 (br s, 1 H)	0.07
6.85 (d, *J* = 4.1 Hz, 1 H)	6.86 (d, *J* = 4.2 Hz, 1 H)	0.01
6.11 (d, *J* = 4.1 Hz, 1 H)	6.12 (d, *J* = 4.2 Hz, 1 H)	0.01
5.34 (br s, 1 H)	N/A[a]	-
4.56 (m)	4.55 (m, 1 H)	0.01
3.95 (dd, *J* = 12.1, 1.8 Hz, 1 H)	3.94 (dd, *J* = 12.2, 3.3 Hz, 1 H)	-0.01
3.70 (dd, *J* = 12.1, 2.9 Hz, 1 H)	3.69 (dd, *J* = 12.2, 4.0 Hz, 1 H)	-0.01
3.53 (d, *J* = 12.6 Hz, 1 H)	3.54 (d, *J* = 12.4, 1 H)	0.01
3.23 (d, *J* = 12.6 Hz, 1 H)	3.23 (d, *J* = 12.4, 1 H)	0.00
3.18 (m, 1 H)	3.18 (m, 1 H)	0.00
2.86 (m, 1 H)	2.85 (m, 1 H)	-0.01
2.54 (dd, *J* = 15.9, 5.2 Hz, 1 H)	2.53 (dd, *J* = 16.0, 5.8 Hz, 1 H)	-0.01
2.47 (m, 1 H)	2.48 (m, 1 H)	0.01
2.43 (dd, *J* = 17.3, 4.3 Hz, 1 H)	2.44 (dd, *J* = 17.5, 4.4 Hz, 1 H)	0.01
2.23 (s, 3 H)	2.24 (s, 3 H)	0.01
2.22 (m, 1 H)	2.23 (m, 1 H)	0.01
2.17 (m, 1 H)	2.17 (m, 1 H)	0.00
2.13 (m, 1 H)	2.13 (m, 1 H)	0.00
2.13 (m, 1 H)	2.13 (m, 1 H)	0.00
2.12 (m, 1 H)	2.12 (m, 1 H)	0.00
2.10 (m, 1 H)	2.10 (dd, *J* = 16.0, 10.6 Hz, 1 H)	0.00
1.95–1.70 (m, 6 H)	1.92 (m, 1 H)	
	1.86 (m, 1 H)	
	1.84 (m, 1 H)	
	1.83 (m, 1 H)	
	1.77 (m, 1 H)	
	1.74 (m, 1 H)	
1.68–1.66 (m, 2 H)	1.67 (m, 1 H)	
	1.66 (m, 1 H)	
1.56 (m, 1 H)	1.57 (m, 1 H)	0.01
1.51 (m, 1 H)	1.51 (m, 1 H)	0.00
1.01 (d, *J* = 5.5 Hz, 3 H)	1.00 (d, *J* = 5.7 Hz, 3 H)	-0.01
7.26 (s, $CDCl_3$)	7.26 (s, $CDCl_3$)	0.00

[a]Not present in the ^{1}H NMR characterization table[15], despite being present in the printed graphical copy.[55] We assigned this peak to the exchangeable proton of the hydroxy group (-CH_2O**H**).

Table 2.6.^{13}C NMR (500 MHz, $CDCl_3$) spectral data comparison of synthetic chilocorine C•HCl (5•HCl) and natural chilocorine C•HCl.

Synthetic 5•HCl *c* = 2.5 mg/mL	**Natural Chilocorine C**•HCl[15] *c* = 1.7 mg/mL	**Δ δ, ppm**
186.0	186.1	0.1
135.1	135.1	0
128.8	128.7	-0.1
125.2	125.2	0
125.1	125.1	0
113.6	113.7	0.1
107.3	107.3	0
70.6	70.5	-0.1
59.4	59.3	-0.1
58.4	58.3	-0.1
58.3	58.2	-0.1
49.1	49.1	0
40.2	40.2	0
39.4	39.3	-0.1
37.3	37.3	0
36.7	36.6	-0.1
36.0	35.9	-0.1
32.0 (2 carbons)	31.9 (2 carbons)	-0.1
30.7	30.6	-0.1
29.7	29.6	-0.1
28.6	28.6	0
26.0	26.0	0
21.1	21.1	0
19.9	19.9	0
15.5	15.5	0
77.0 (t, $CDCl_3$)	77.0 (t, $CDCl_3$)	0

Figure 2.3. Concentration dependent nature of chemical shifts of 5•HCl[55]



2.14. References.

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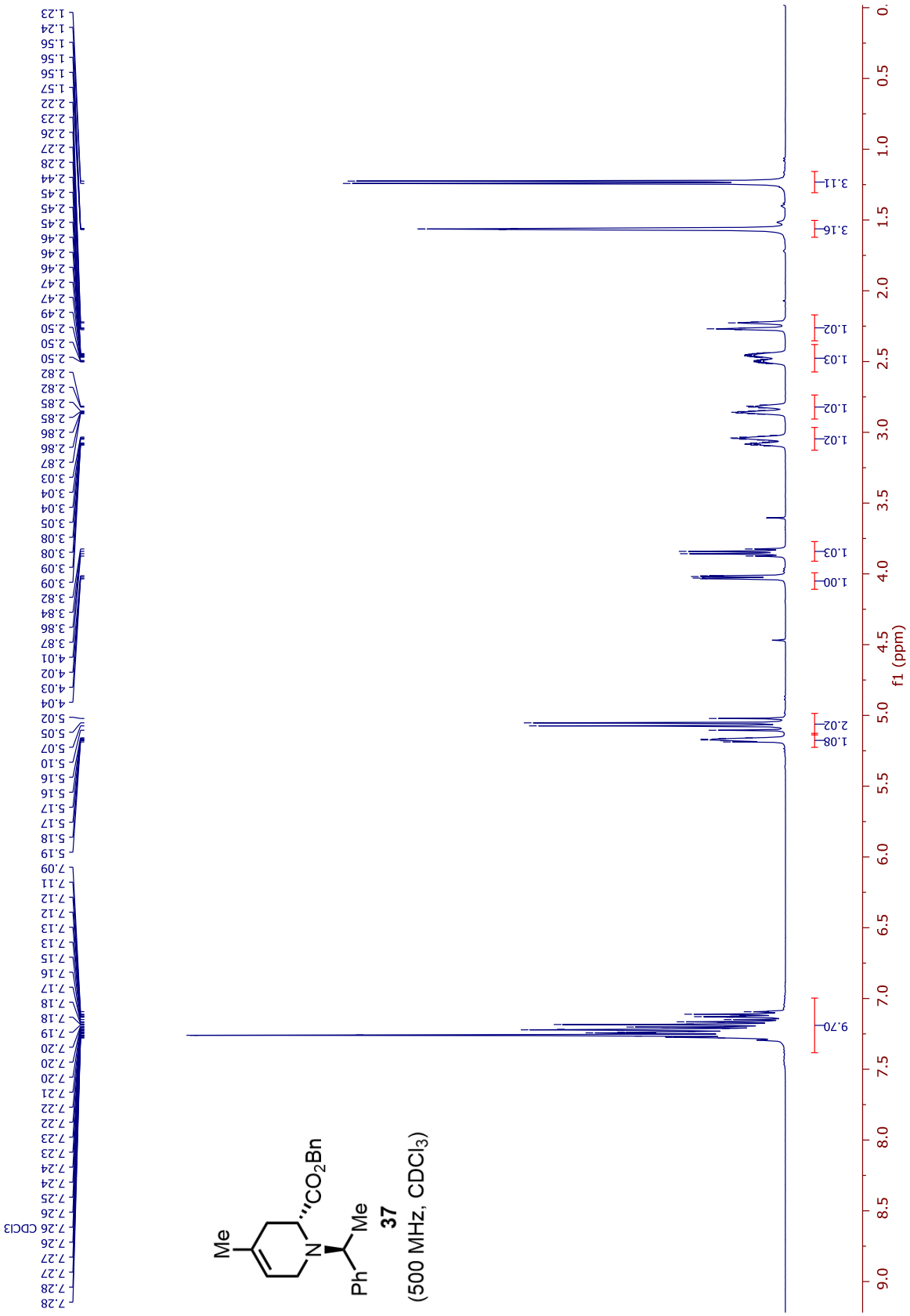
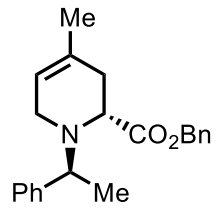
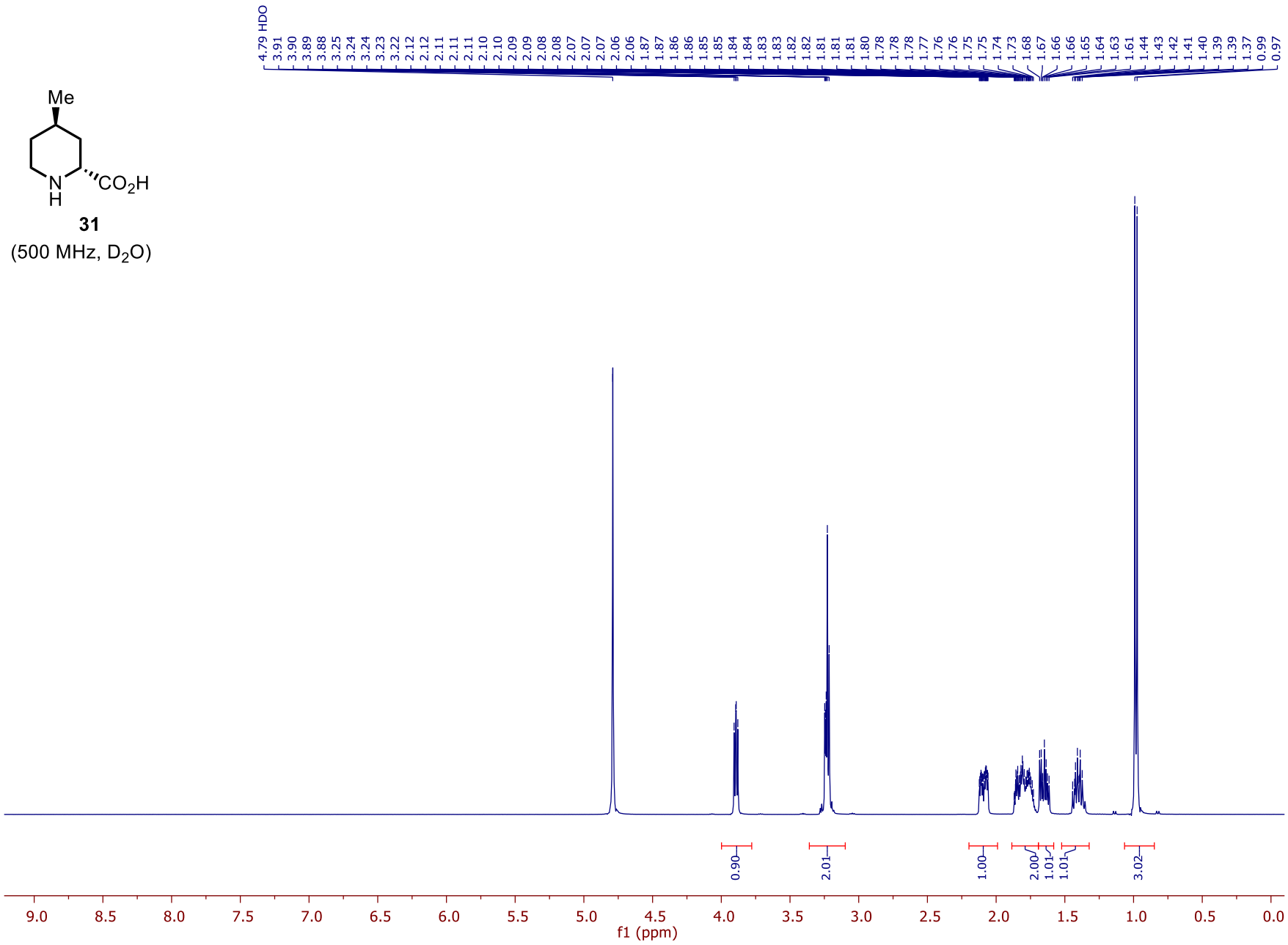
2.15. ^{1}H and ^{13}C NMR Data of Selected Intermediates.

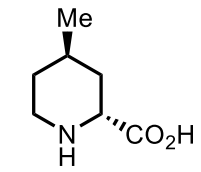




37

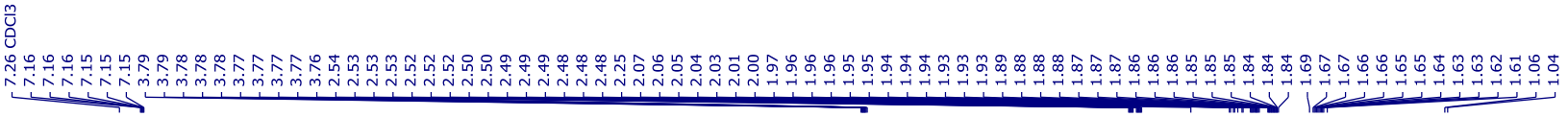
(126 MHz, $CDCl_3$)

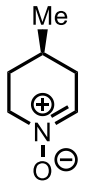

Me
N
H
CO2H
31
(500 MHz, D2O)
4.79 HDO
3.91
3.90
3.89
3.88
3.25
3.24
3.24
3.23
3.22
2.12
2.12
2.11
2.11
2.11
2.10
2.10
2.09
2.09
2.08
2.08
2.07
2.07
2.07
2.06
2.06
1.87
1.87
1.86
1.86
1.85
1.85
1.84
1.84
1.83
1.83
1.82
1.82
1.81
1.81
1.81
1.80
1.78
1.78
1.78
1.77
1.76
1.76
1.75
1.75
1.74
1.73
1.68
1.67
1.66
1.66
1.65
1.64
1.63
1.61
1.44
1.43
1.42
1.41
1.40
1.39
1.39
1.37
0.99
0.97
0.90
2.01
1.00
2.00
1.01
1.01
3.02
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



31

(126 MHz, D_2O)

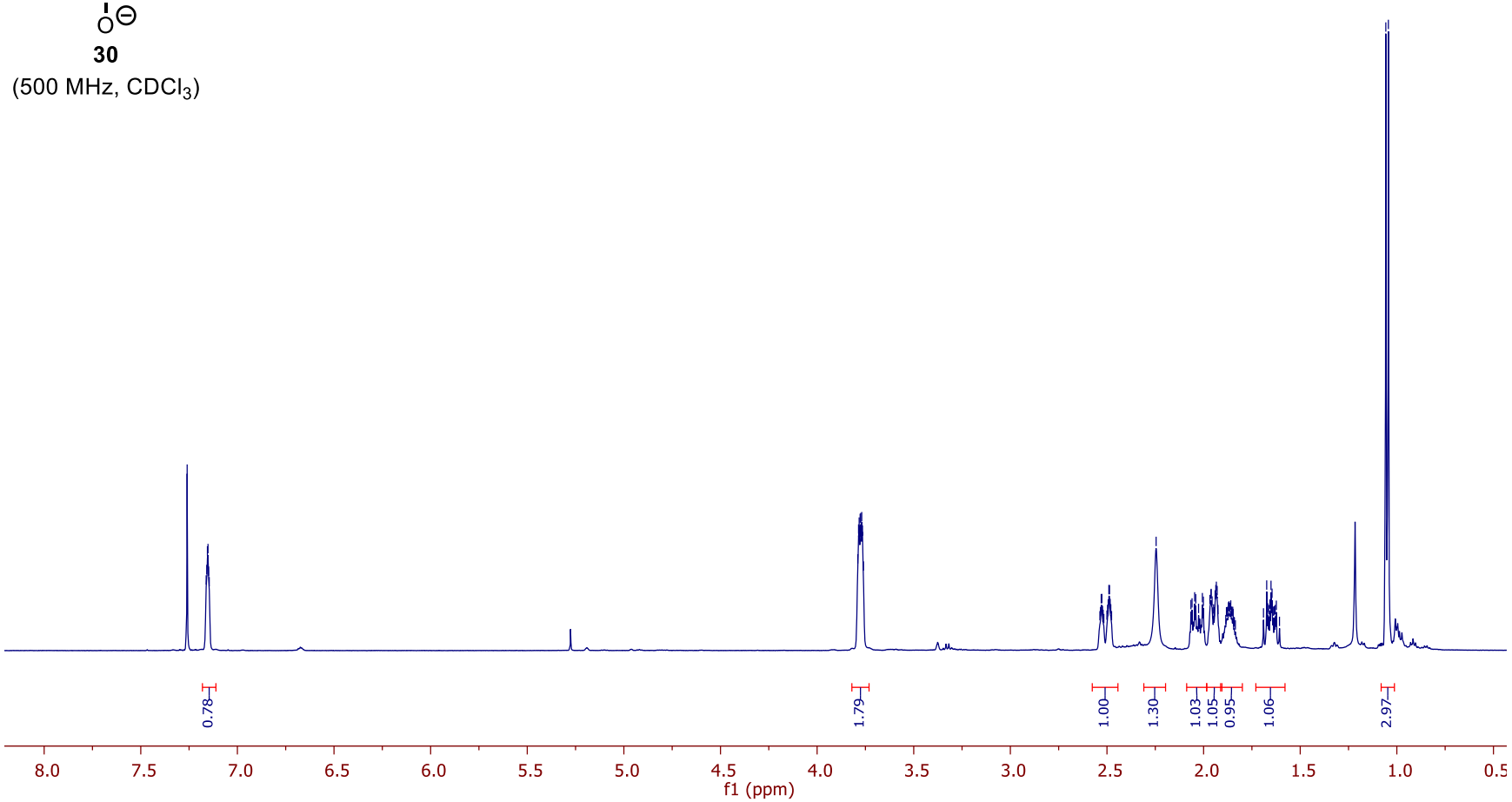


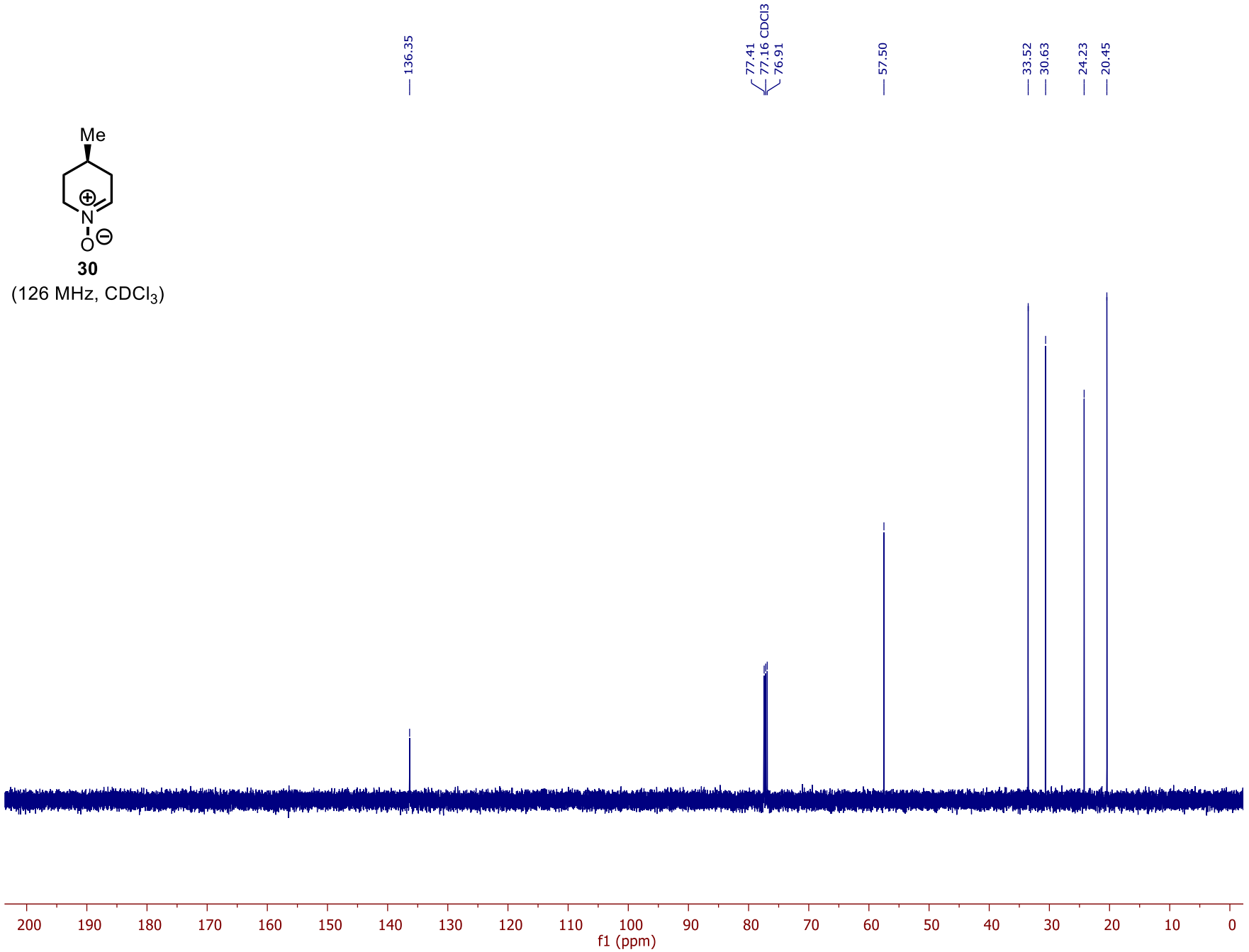


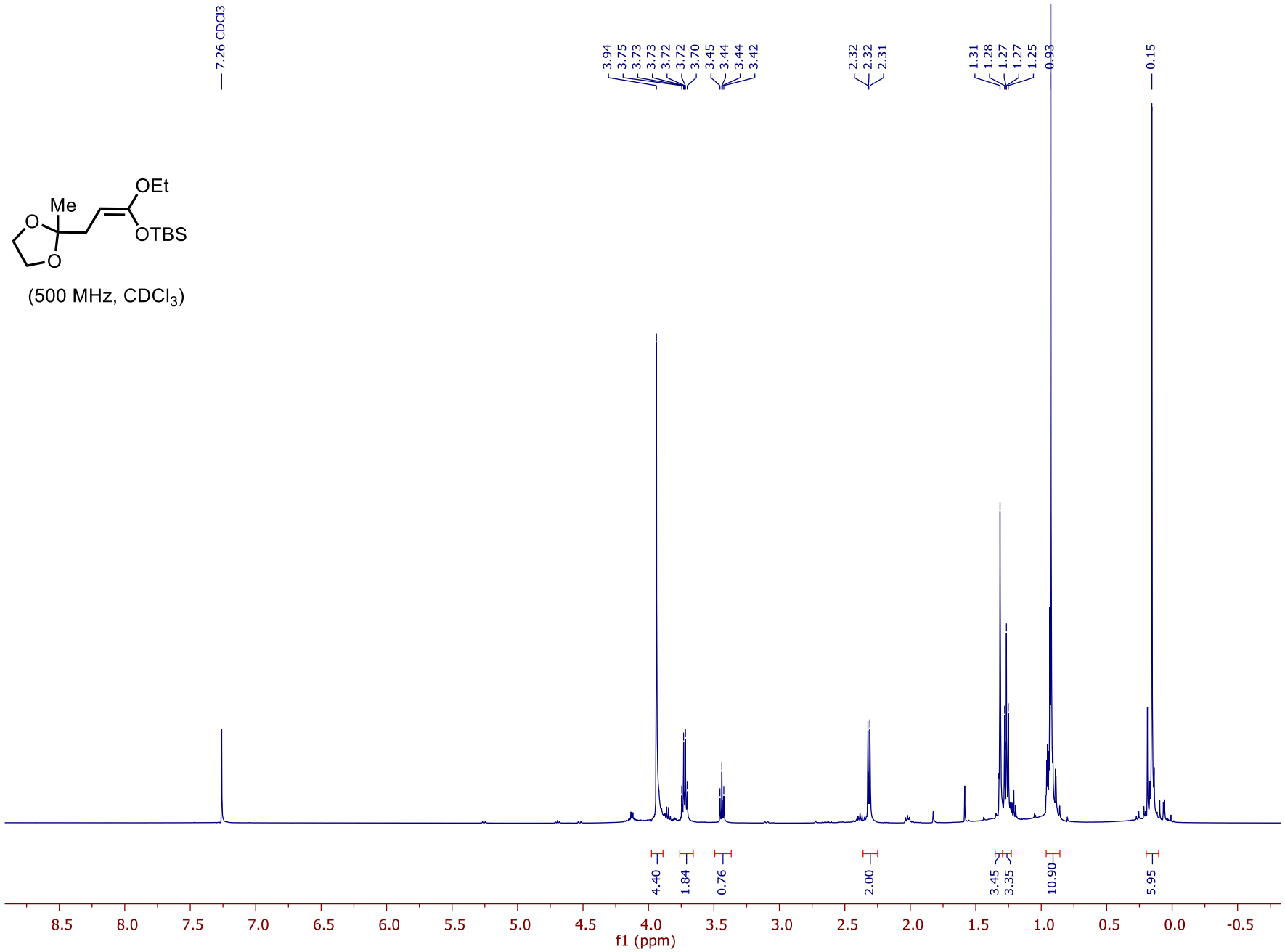
30

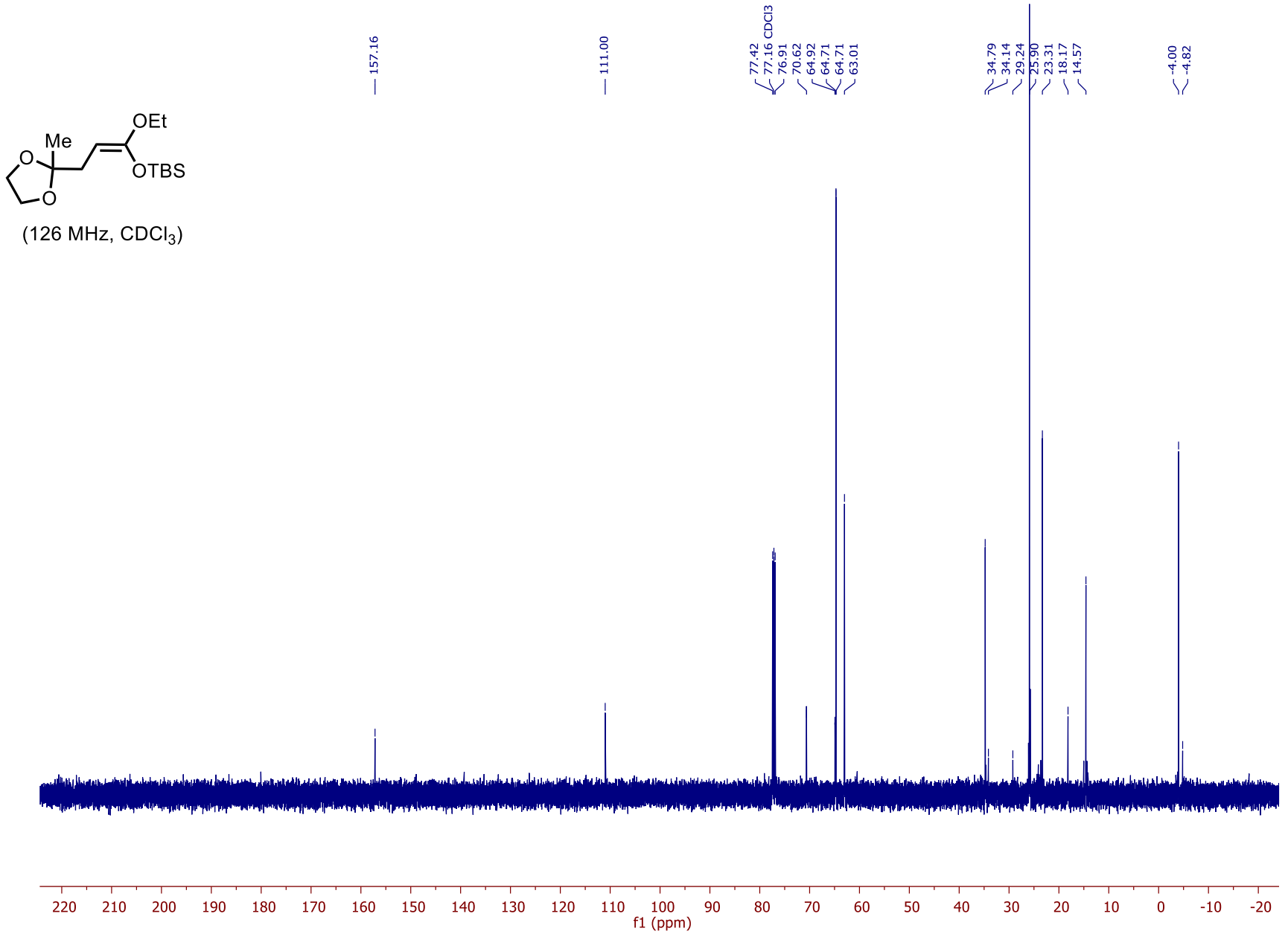
(500 MHz, $CDCl_3$)

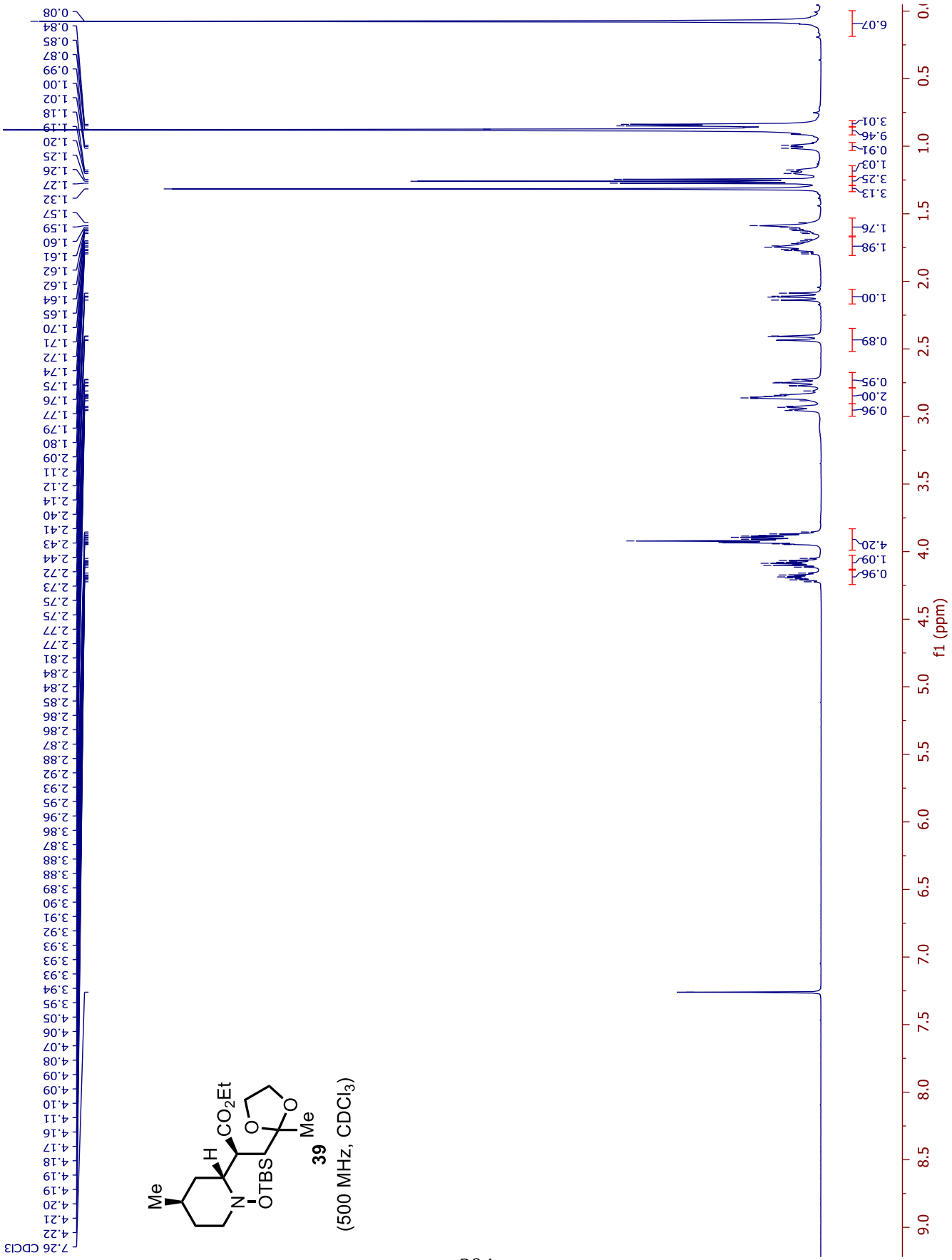
200

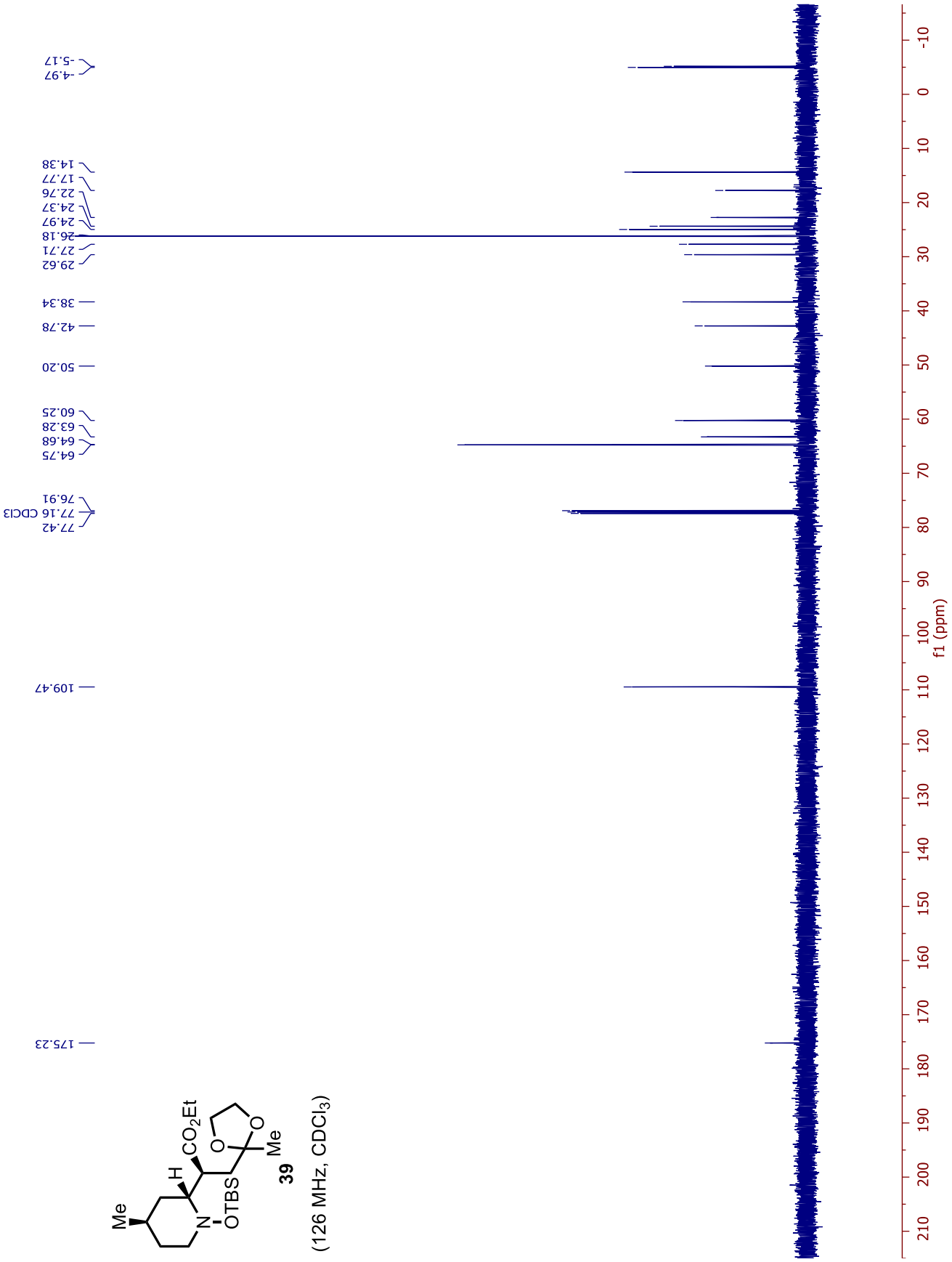


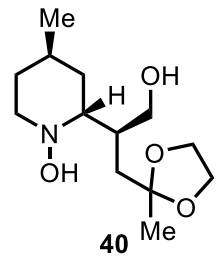

136.35
77.41
77.16 CDCl3
76.91
57.50
33.52
30.63
24.23
20.45
Me
N
O
30
(126 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.26 CDCl3
3.94
3.75
3.73
3.73
3.72
3.72
3.70
3.45
3.44
3.44
3.42
2.32
2.32
2.31
1.31
1.28
1.27
1.27
1.25
0.93
0.15
OEt
Me
OTBS
O
O
(500 MHz, CDCl3)
4.40
1.84
0.76
2.00
3.45
3.35
10.90
5.95
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


OEt
Me
OTBS
O
O
(126 MHz, CDCl3)
157.16
111.00
77.42
77.16 CDCl3
76.91
70.62
64.92
64.71
64.71
63.01
34.79
34.14
29.24
25.90
23.31
18.17
14.57
-4.00
-4.82
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

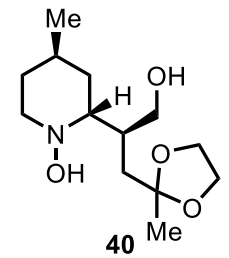

Me
H
CO2Et
N
OTBS
O
O
Me
39
(500 MHz, CDCl3)
f1 (ppm)


Me
H
CO2Et
N
OTBS
O
O
Me
39
(126 MHz, CDCl3)
175.23
109.47
77.42
77.16 CDCl3
76.91
64.75
64.68
63.28
60.25
50.20
42.78
38.34
29.62
27.71
26.18
24.97
24.37
22.76
17.77
14.38
-4.97
-5.17
f1 (ppm)



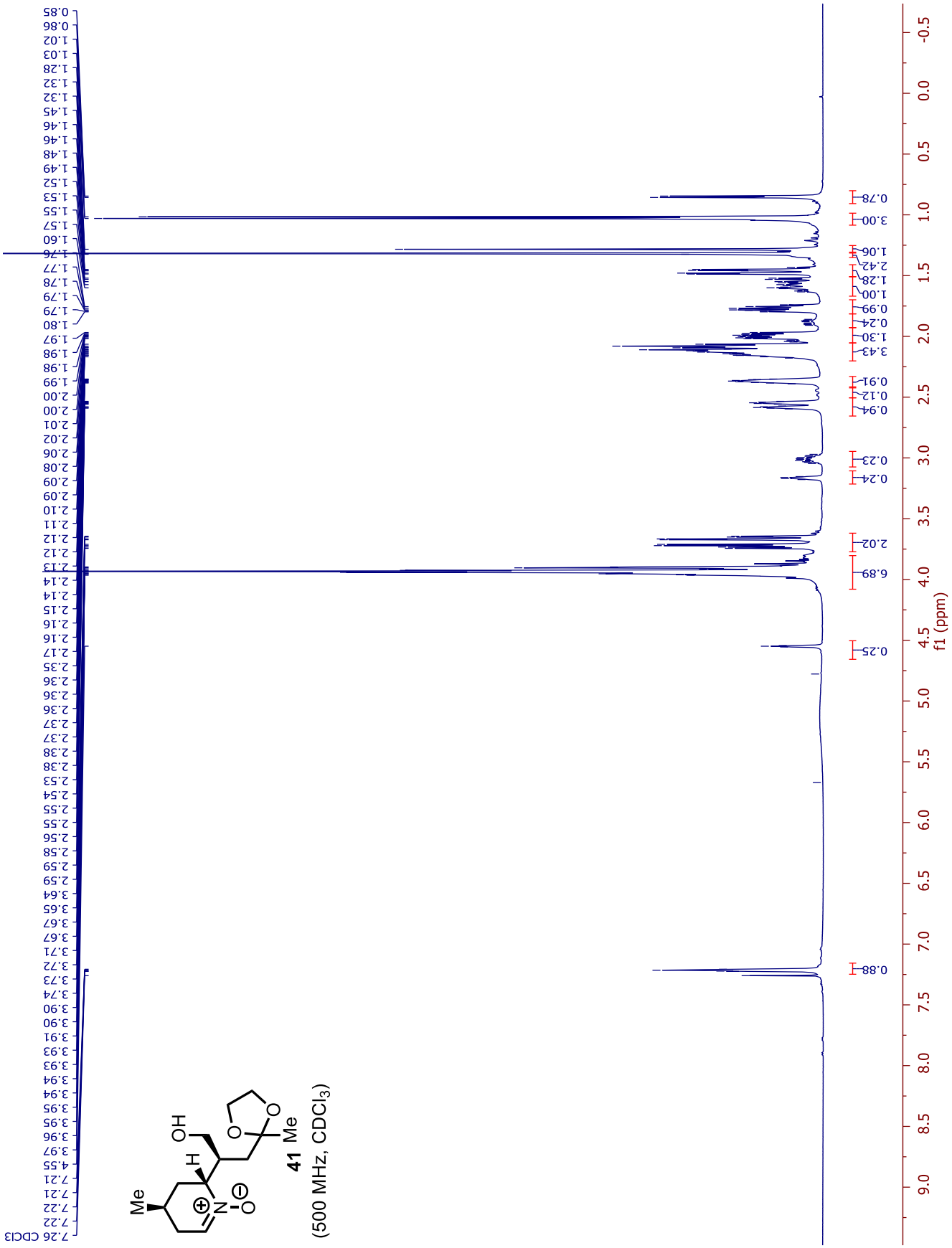
40

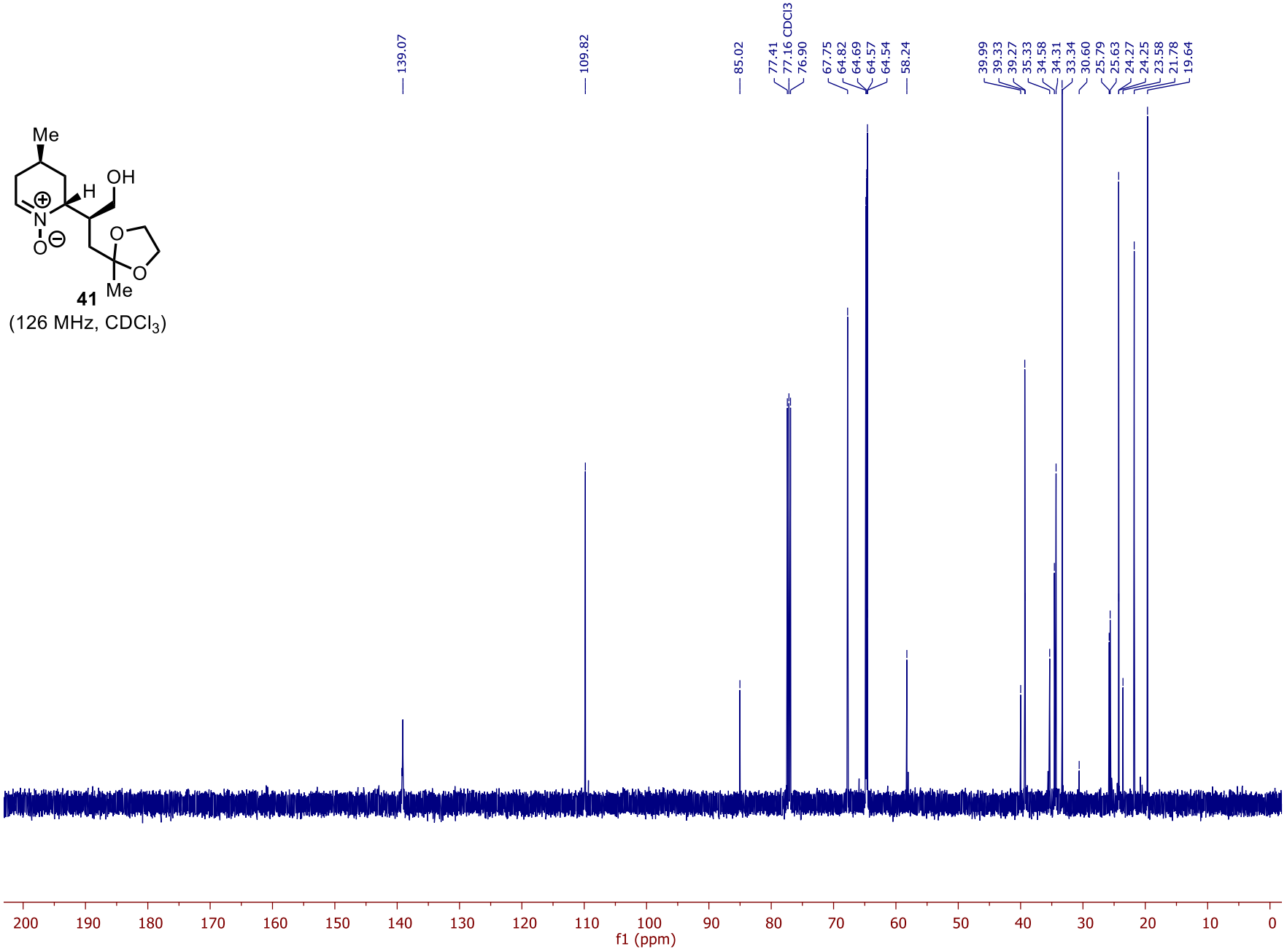
(500 MHz, $CDCl_3$)

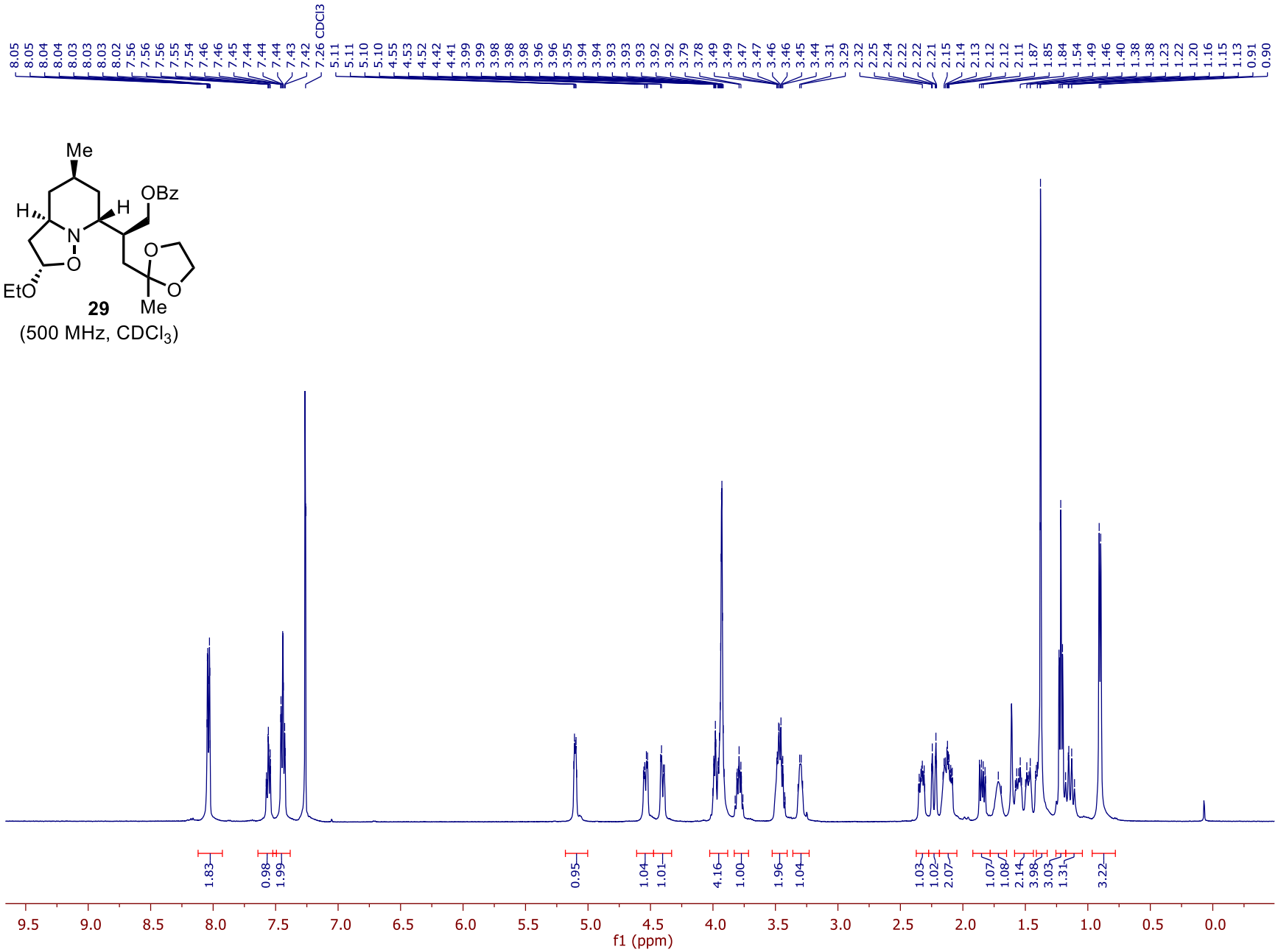


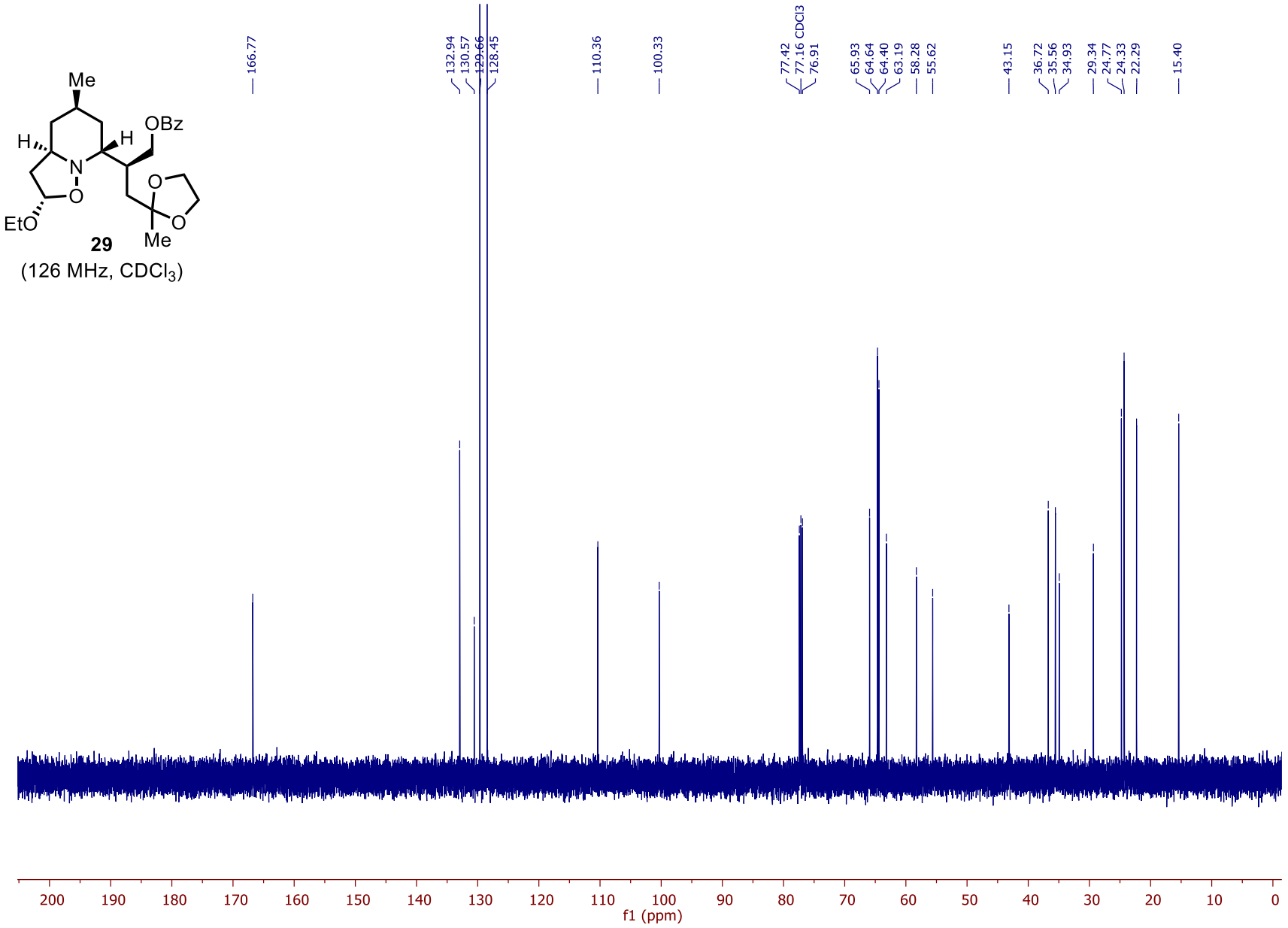
40

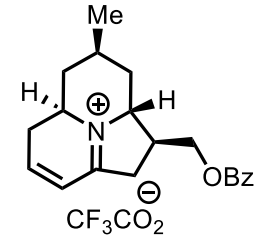
(126 MHz, $CDCl_3$)


Me
OH
H
O
O
O
N
41 Me
(500 MHz, CDCl3)
f1 (ppm)


139.07
109.82
85.02
77.41
77.16 CDCl3
76.90
67.75
64.82
64.69
64.57
64.54
58.24
39.99
39.33
39.27
35.33
34.58
34.31
33.34
30.60
25.79
25.63
24.27
24.25
23.58
21.78
19.64
Me
OH
H
N
O
O
O
Me
41
(126 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

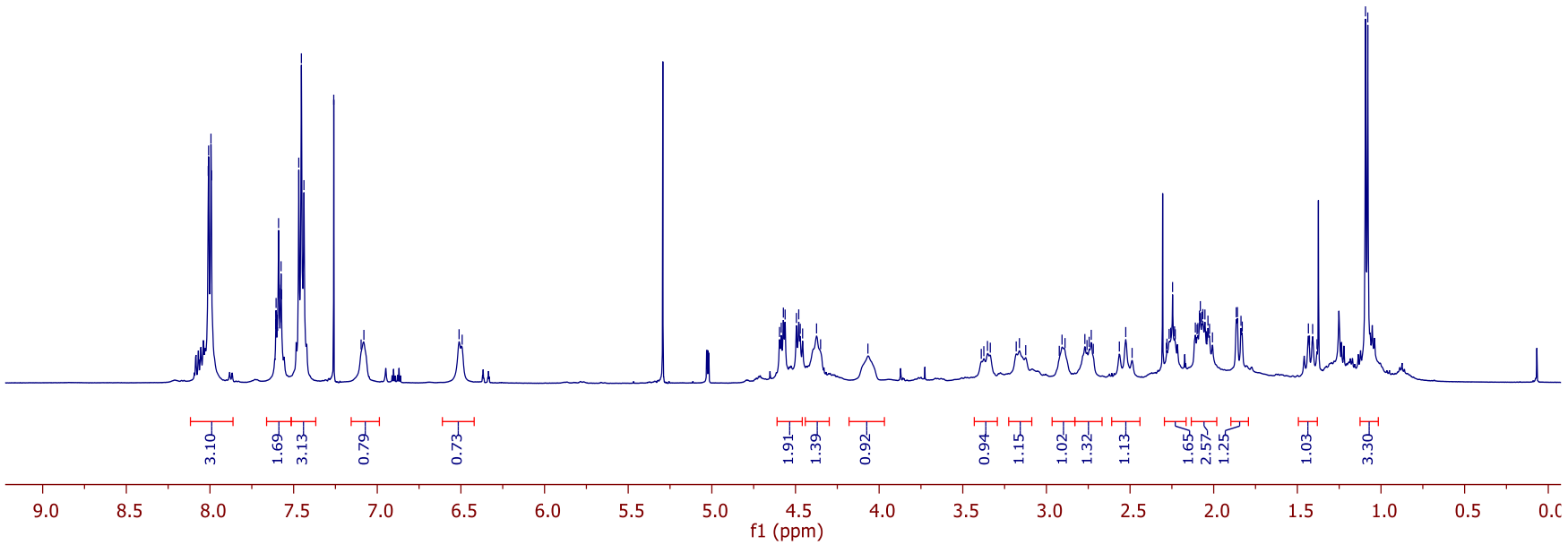

8.05 8.05 8.04 8.04 8.03 8.03 8.03 8.02 7.56 7.56 7.55 7.54 7.46 7.46 7.45 7.44 7.44 7.44 7.43 7.42 7.26 CDCl3
5.11 5.11 5.10 5.10 4.55 4.53 4.52 4.42 4.41 3.99 3.99 3.98 3.98 3.98 3.96 3.96 3.95 3.94 3.94 3.93 3.93 3.93 3.92 3.92 3.79 3.78 3.49 3.49 3.47 3.47 3.46 3.46 3.45 3.44 3.31 3.29
2.32 2.25 2.24 2.22 2.22 2.21 2.15 2.14 2.13 2.12 2.12 2.11 1.87 1.85 1.84 1.54 1.49 1.46 1.40 1.38 1.38 1.23 1.22 1.20 1.16 1.15 1.13 0.91 0.90
Me
OBz
H
H
N
O
O
O
O
EtO
Me
29
(500 MHz, CDCl3)
1.83 0.98 1.99 0.95 1.04 1.01 4.16 1.00 1.96 1.04 1.03 1.02 2.07 1.07 1.08 2.14 3.98 3.03 1.31 3.22
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

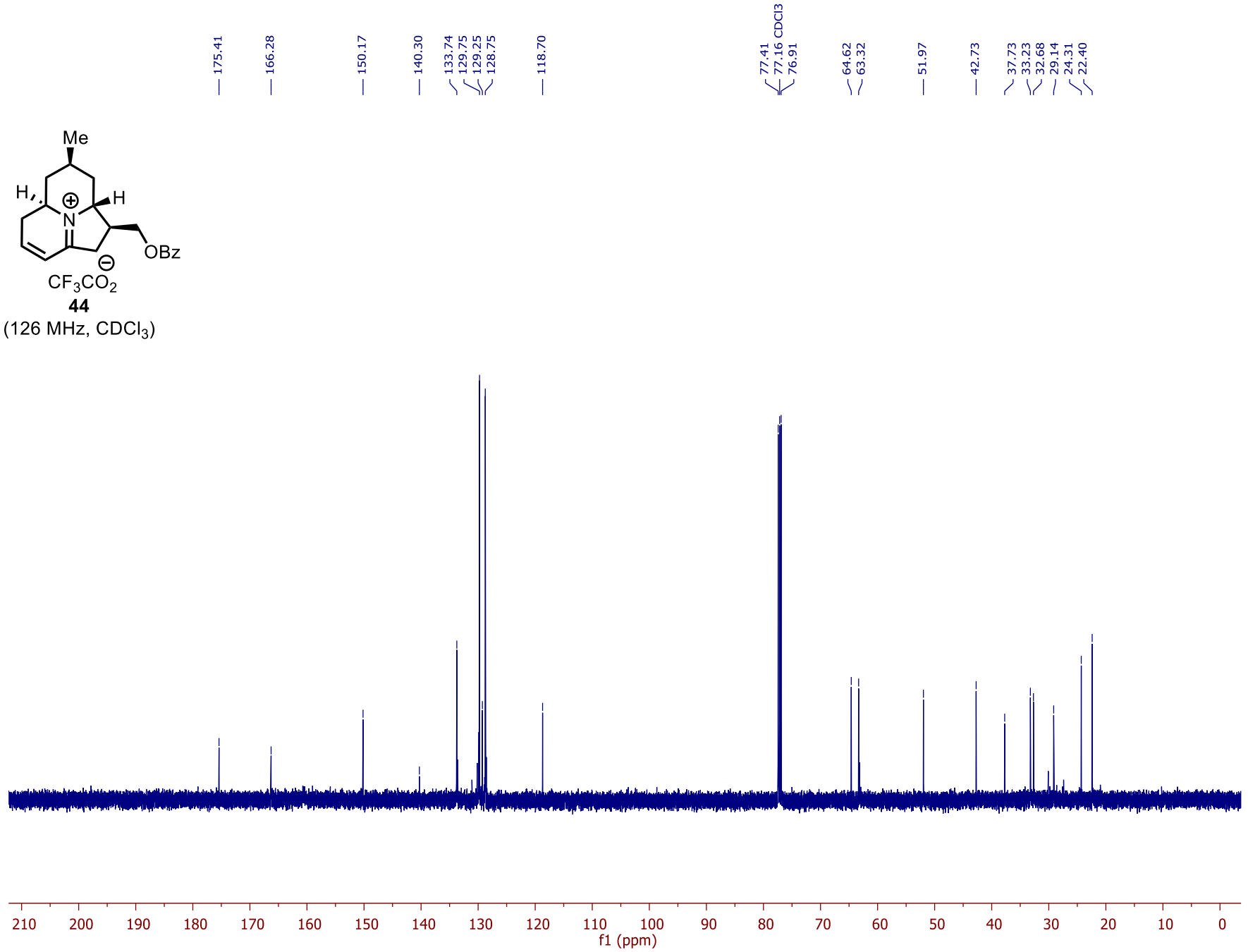

Me
H
H
OBz
N
O
O
O
EtO
Me
29
(126 MHz, CDCl3)
166.77
132.94
130.57
129.66
128.45
110.36
100.33
77.42
77.16 CDCl3
76.91
65.93
64.64
64.40
63.19
58.28
55.62
43.15
36.72
35.56
34.93
29.34
24.77
24.33
22.29
15.40
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

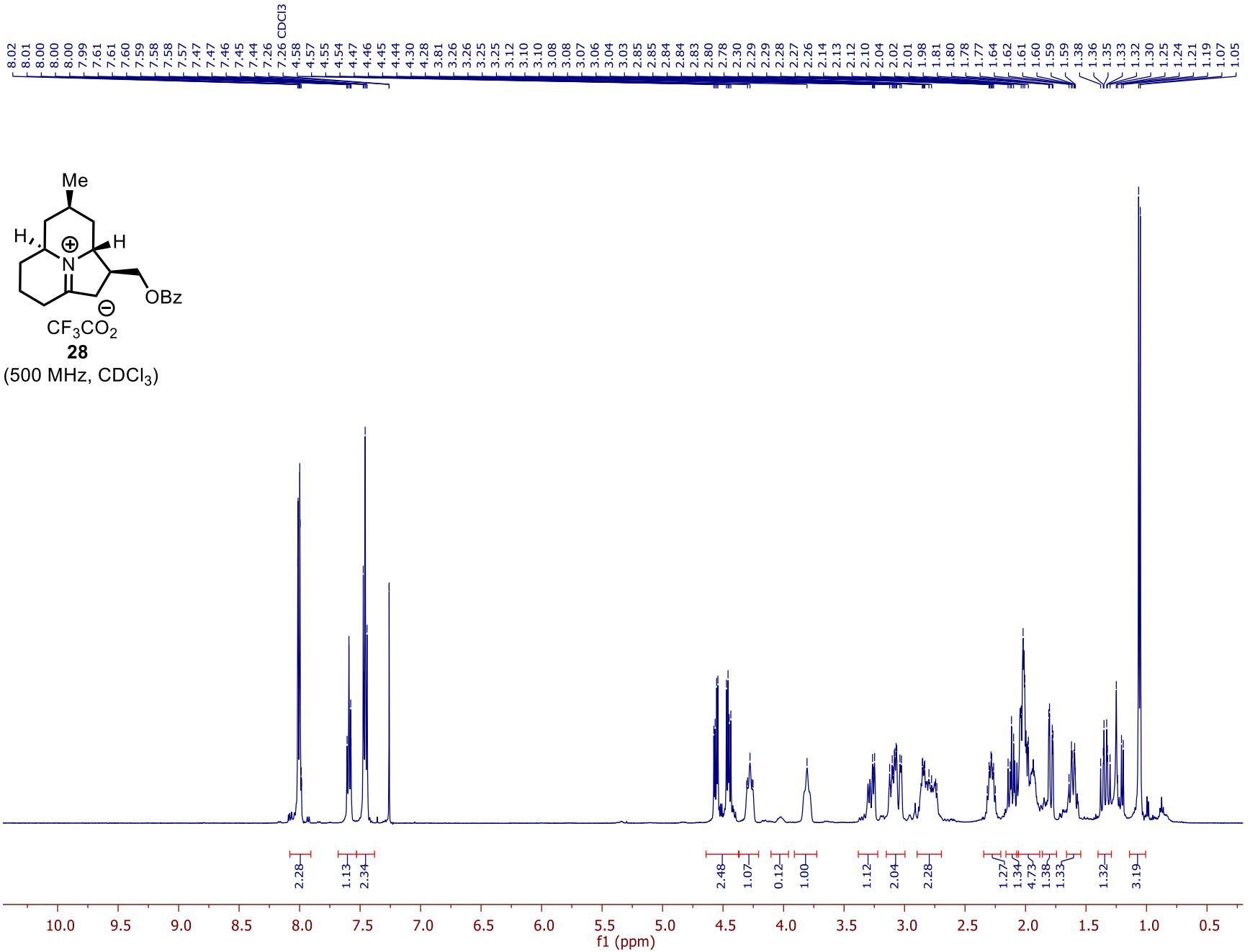


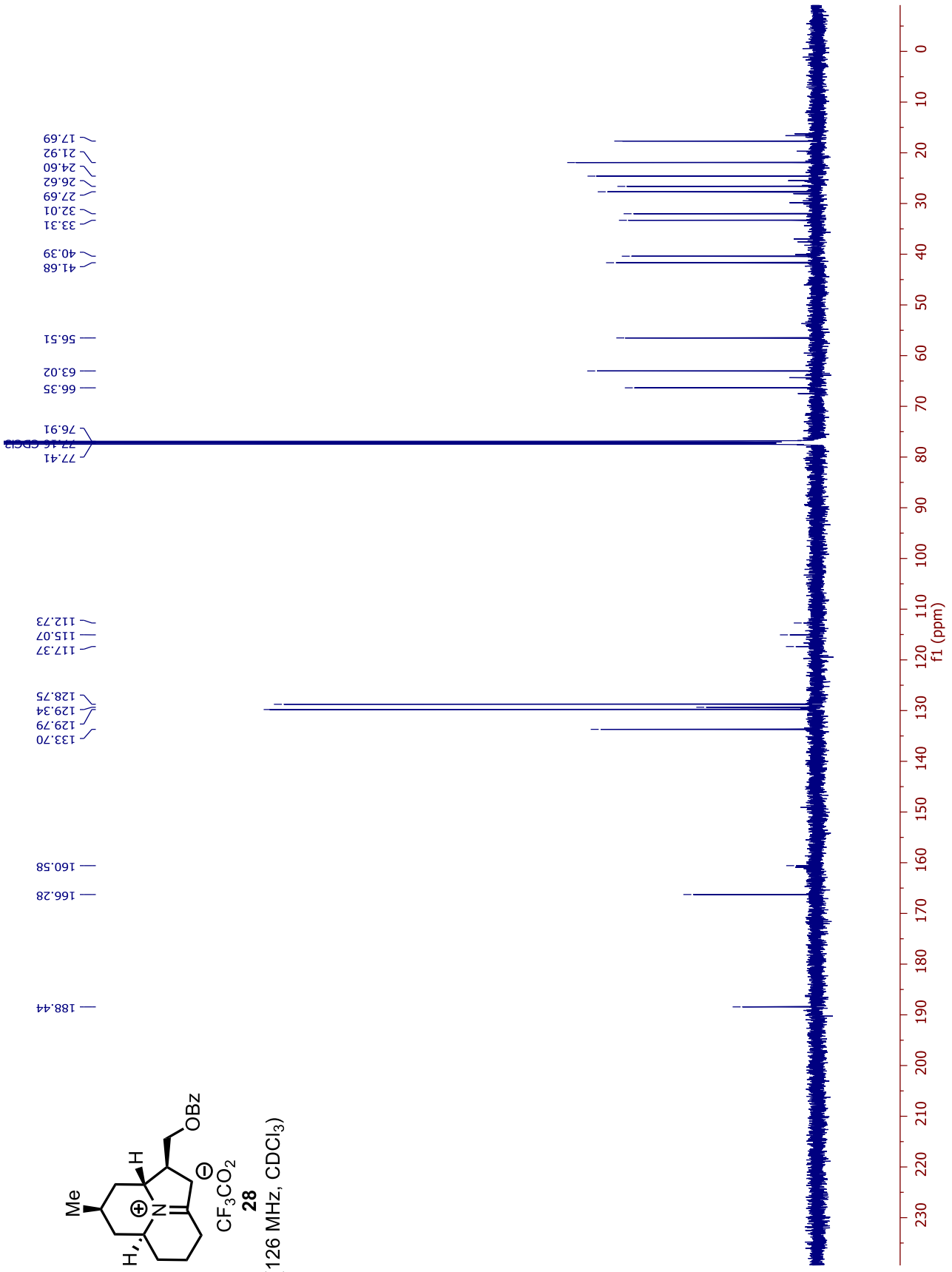
44

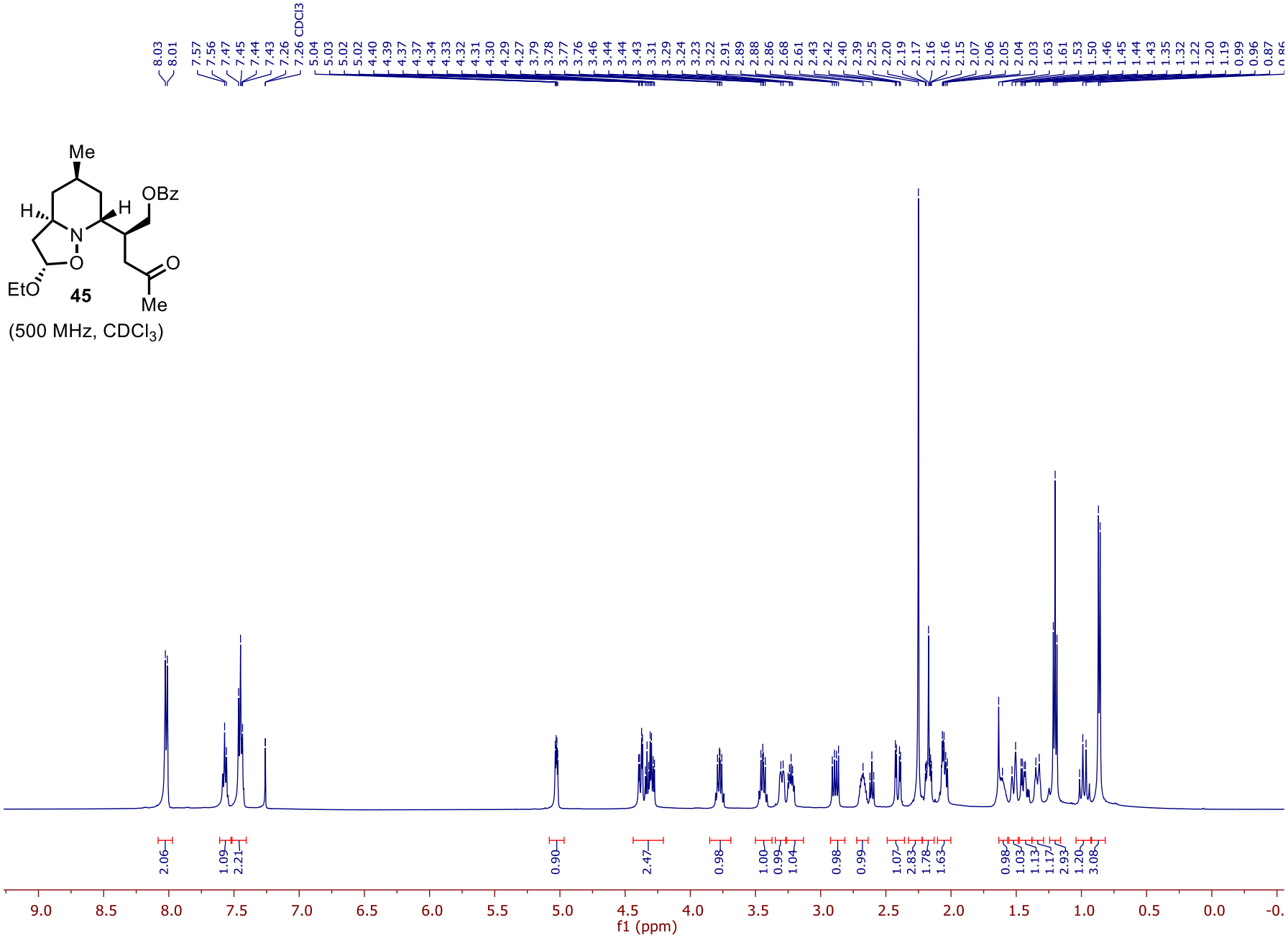
(500 MHz, $CDCl_3$)

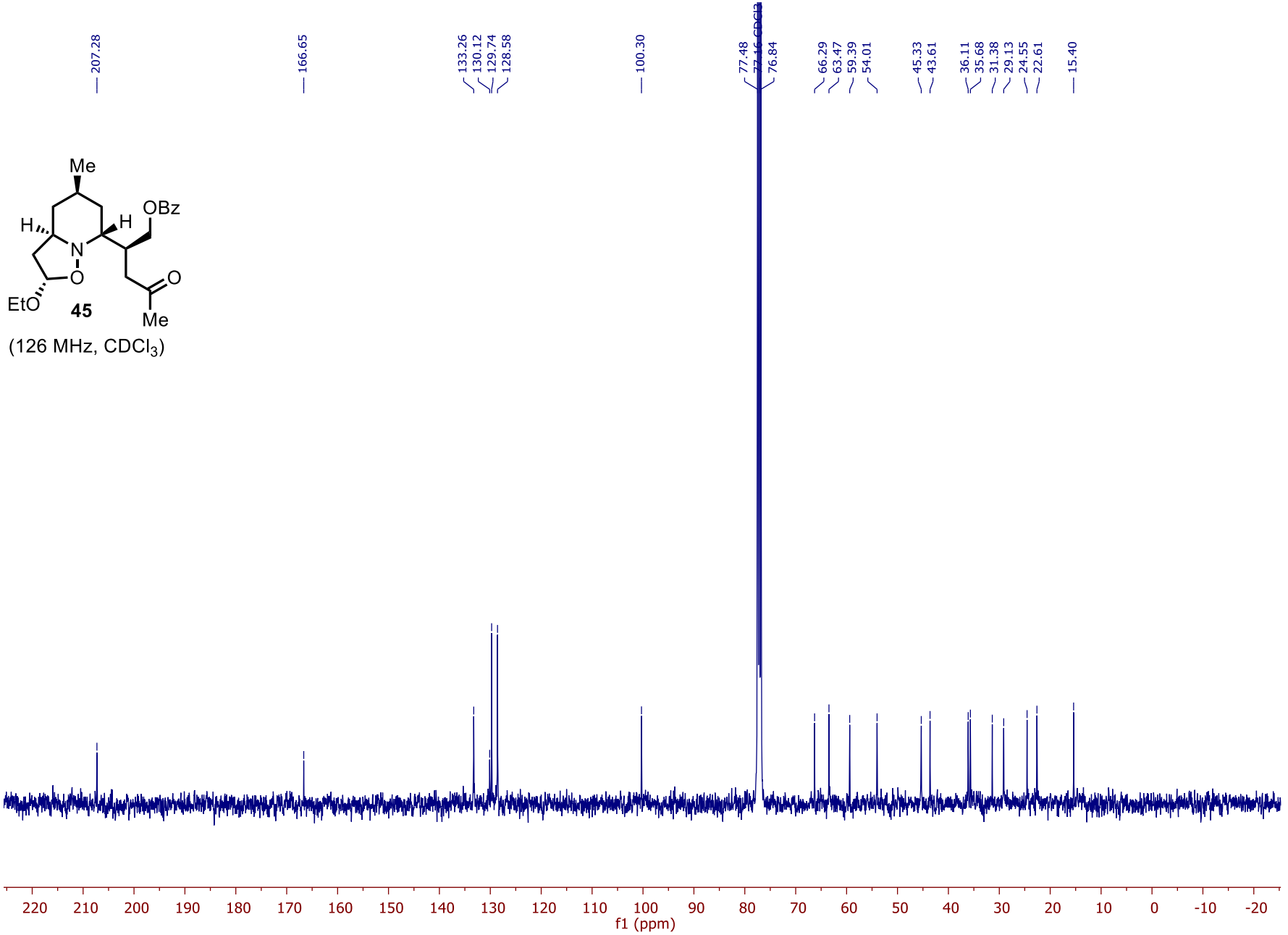


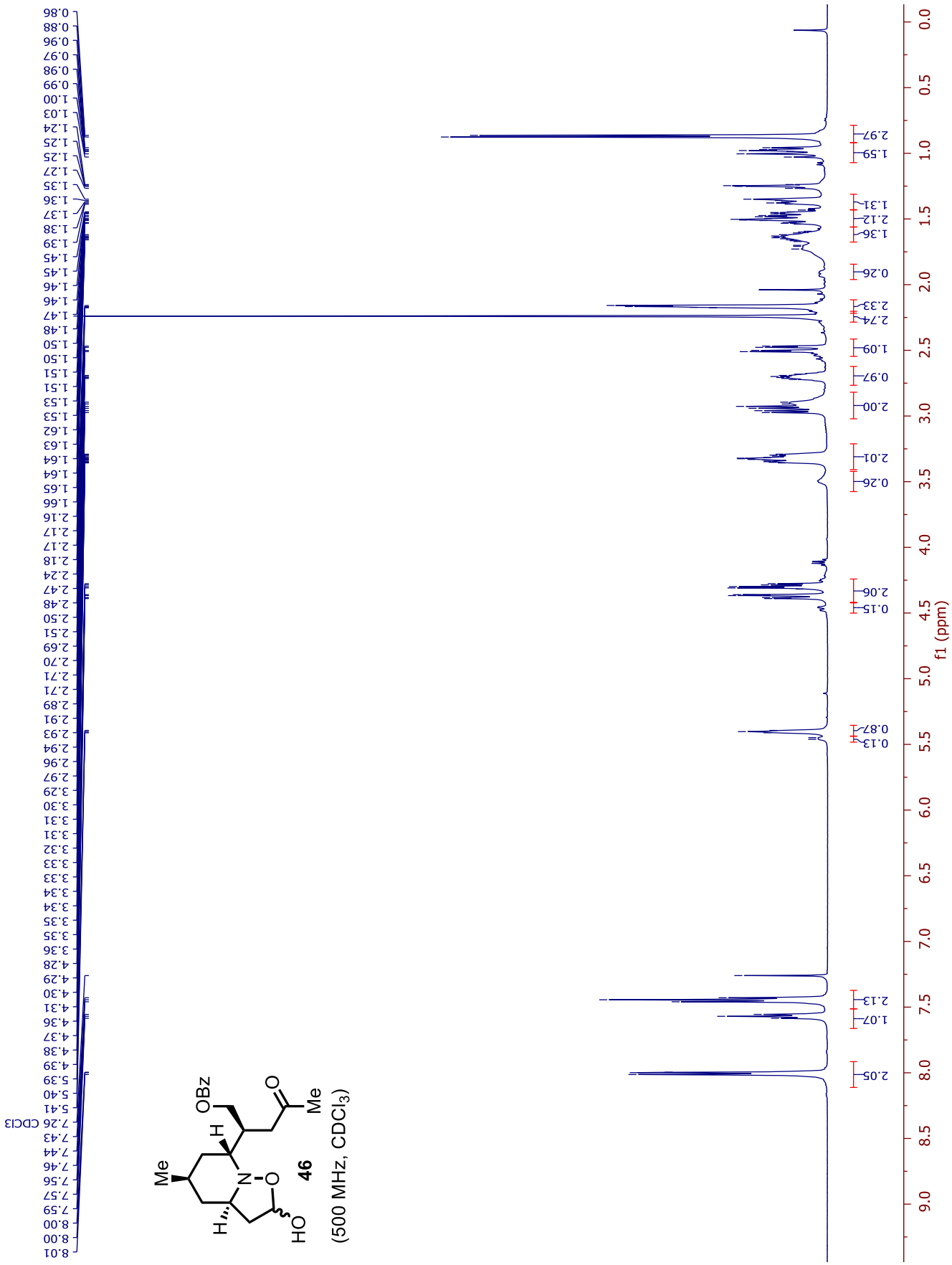

175.41
166.28
150.17
140.30
133.74
129.75
129.25
128.75
118.70
77.41
77.16 CDCl3
76.91
64.62
63.32
51.97
42.73
37.73
33.23
32.68
29.14
24.31
22.40
Me
H
H
N
OBz
CF3CO2
44
(126 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

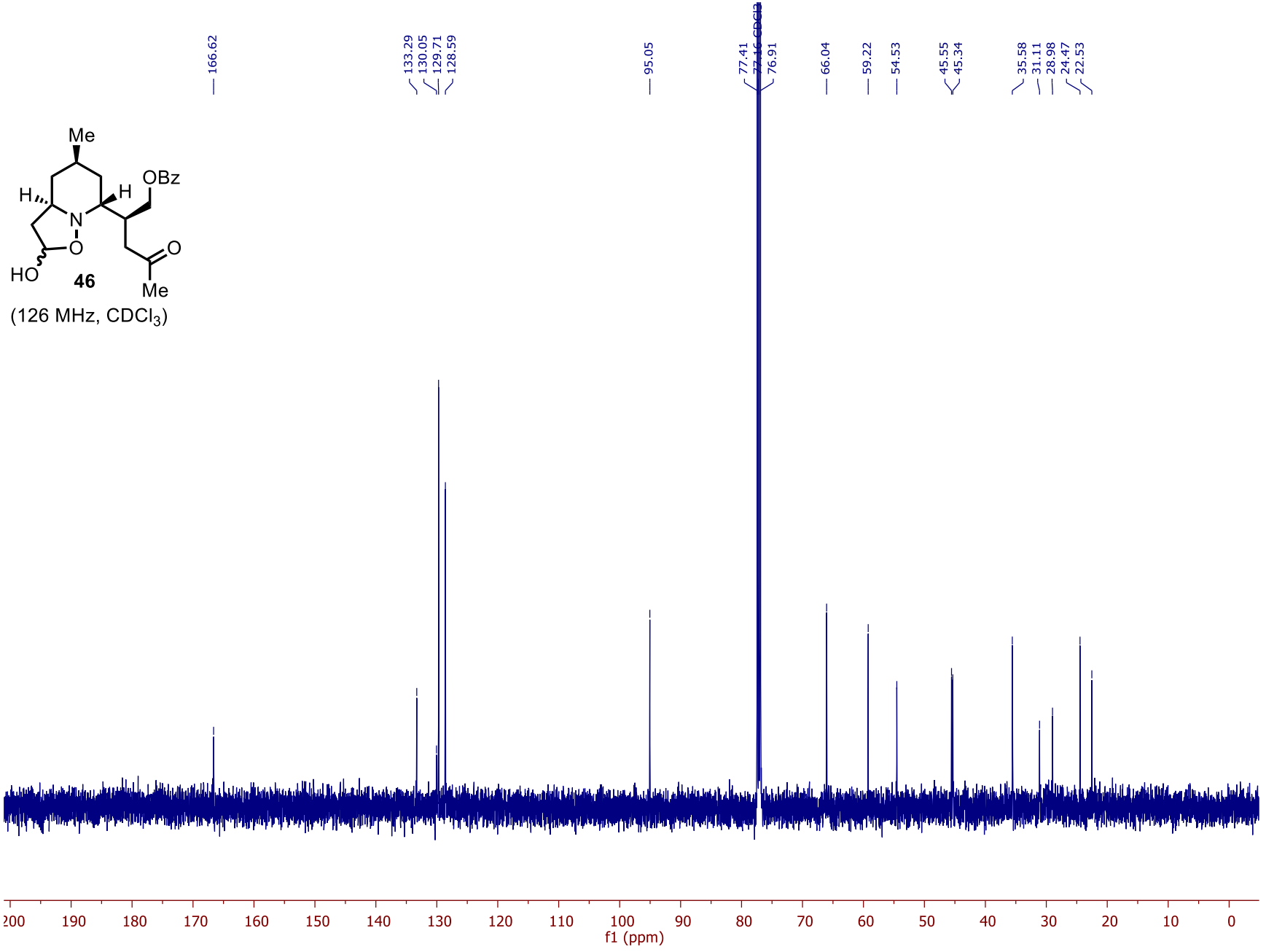

8.02 8.01 8.00 8.00 8.00 7.99 7.61 7.61 7.60 7.59 7.58 7.58 7.57 7.47 7.47 7.46 7.45 7.44 7.26 CDCl3 4.58 4.57 4.55 4.54 4.47 4.46 4.45 4.44 4.30 4.28 3.81 3.26 3.26 3.25 3.25 3.12 3.10 3.10 3.08 3.08 3.07 3.06 3.04 3.03 2.85 2.85 2.84 2.84 2.83 2.80 2.78 2.30 2.29 2.29 2.28 2.27 2.26 2.14 2.13 2.12 2.10 2.04 2.02 2.01 1.98 1.81 1.80 1.78 1.77 1.64 1.62 1.61 1.60 1.59 1.59 1.38 1.36 1.35 1.33 1.32 1.30 1.25 1.24 1.21 1.19 1.07 1.05
Me
H
H
N
OBz
CF3CO2
28
(500 MHz, CDCl3)
2.28 1.13 2.34 2.48 1.07 0.12 1.00 1.12 2.04 2.28 1.27 1.34 4.73 1.38 1.33 1.32 3.19
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

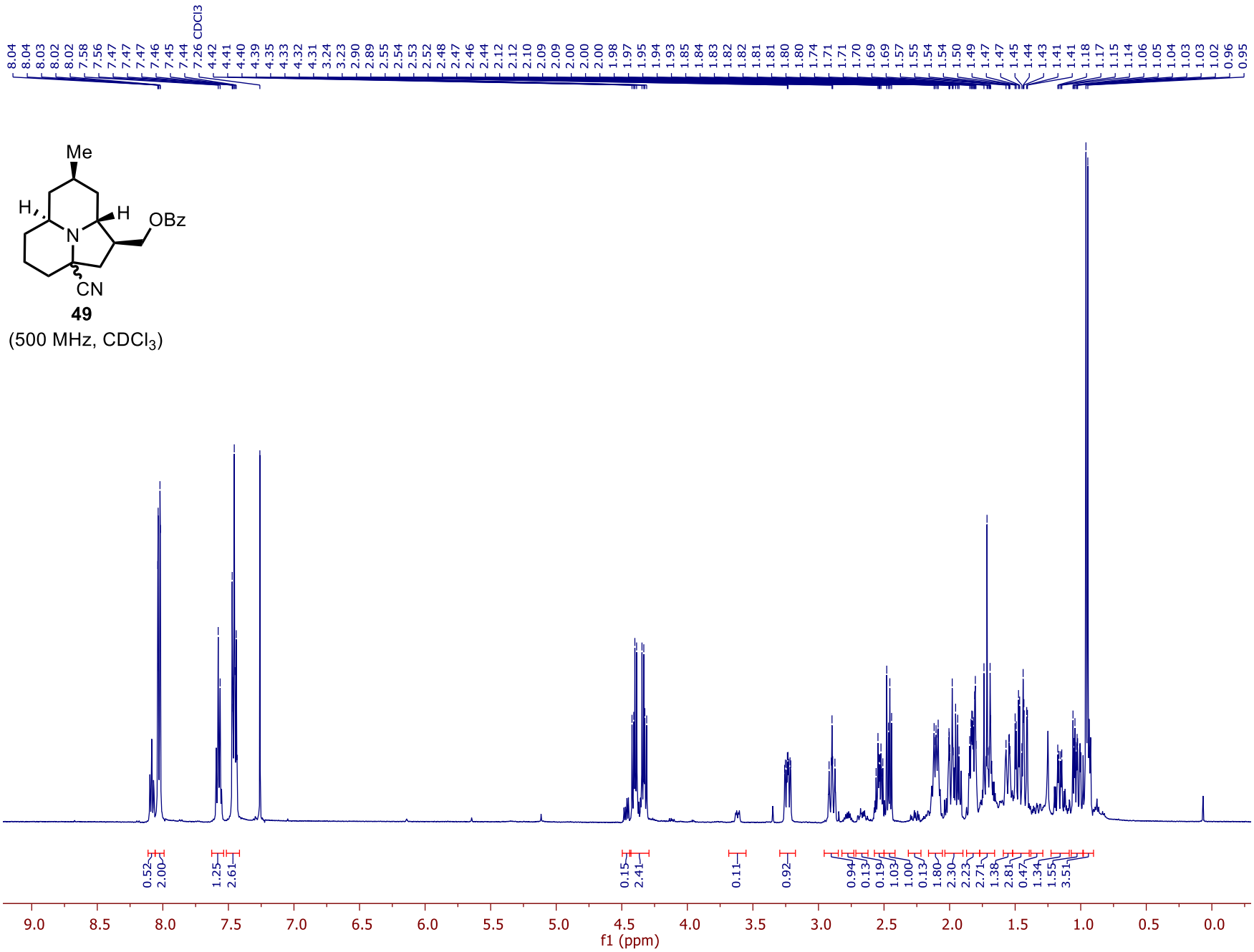

188.44
166.28
160.58
133.70
129.79
129.34
128.75
117.37
115.07
112.73
77.41
76.91
66.35
63.02
56.51
41.68
40.39
33.31
32.01
27.69
26.62
24.60
21.92
17.69
f1 (ppm)
OBz
Me
H
H
N
CF3CO2
28
(126 MHz, CDCl3)

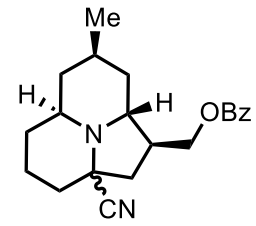

Me
H
H
OBz
N
O
EtO
45
O
Me
(500 MHz, CDCl3)
8.03
8.01
7.57
7.56
7.47
7.45
7.44
7.43
7.26
7.26 CDCl3
5.04
5.03
5.02
5.02
4.40
4.39
4.37
4.37
4.34
4.33
4.32
4.31
4.30
4.29
4.27
3.79
3.78
3.77
3.76
3.46
3.44
3.44
3.43
3.31
3.29
3.24
3.23
3.22
2.91
2.89
2.88
2.86
2.68
2.61
2.43
2.42
2.40
2.39
2.25
2.20
2.19
2.17
2.16
2.16
2.15
2.07
2.06
2.05
2.04
2.03
1.63
1.61
1.53
1.50
1.46
1.45
1.44
1.43
1.35
1.32
1.22
1.20
1.19
0.99
0.96
0.87
2.06
1.09
2.21
0.90
2.47
0.98
1.00
0.99
1.04
0.98
0.99
1.07
2.83
1.78
1.63
0.98
1.03
1.13
1.17
2.93
1.20
3.08
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.
f1 (ppm)


207.28
166.65
133.26
130.12
129.74
128.58
100.30
77.48
77.16 CDCl3
76.84
66.29
63.47
59.39
54.01
45.33
43.61
36.11
35.68
31.38
29.13
24.55
22.61
15.40
Me
OBz
H
H
N
O
O
EtO
45
Me
(126 MHz, CDCl3)
f1 (ppm)


OBz
H
O
Me
Me
N
O
H
HO
46
(500 MHz, CDCl3)
CDCl3
f1 (ppm)


166.62
133.29
130.05
129.71
128.59
95.05
77.41
76.91
66.04
59.22
54.53
45.55
45.34
35.58
31.11
28.98
24.47
22.53
Me
OBz
H
H
N
O
HO
O
Me
46
(126 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.04 8.04 8.03 8.02 8.02 7.58 7.56 7.47 7.47 7.47 7.46 7.45 7.44 7.26 CDCl3 4.42 4.41 4.40 4.39 4.35 4.33 4.32 4.31 3.24 3.23 2.90 2.89 2.55 2.54 2.53 2.52 2.48 2.47 2.46 2.44 2.12 2.12 2.10 2.09 2.09 2.00 2.00 2.00 1.98 1.97 1.95 1.94 1.93 1.85 1.84 1.83 1.82 1.82 1.81 1.81 1.80 1.80 1.74 1.71 1.71 1.70 1.69 1.69 1.57 1.55 1.54 1.54 1.50 1.49 1.47 1.47 1.45 1.44 1.43 1.41 1.41 1.18 1.17 1.15 1.14 1.06 1.05 1.04 1.03 1.03 1.02 0.96 0.95
Me
H
H
OBz
N
CN
49
(500 MHz, CDCl3)
220
0.52 2.00 1.25 2.61 0.15 2.41 0.11 0.92 0.94 0.13 0.19 1.03 1.00 0.13 1.80 2.30 2.23 2.71 1.38 2.81 0.47 1.34 1.55 3.51
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



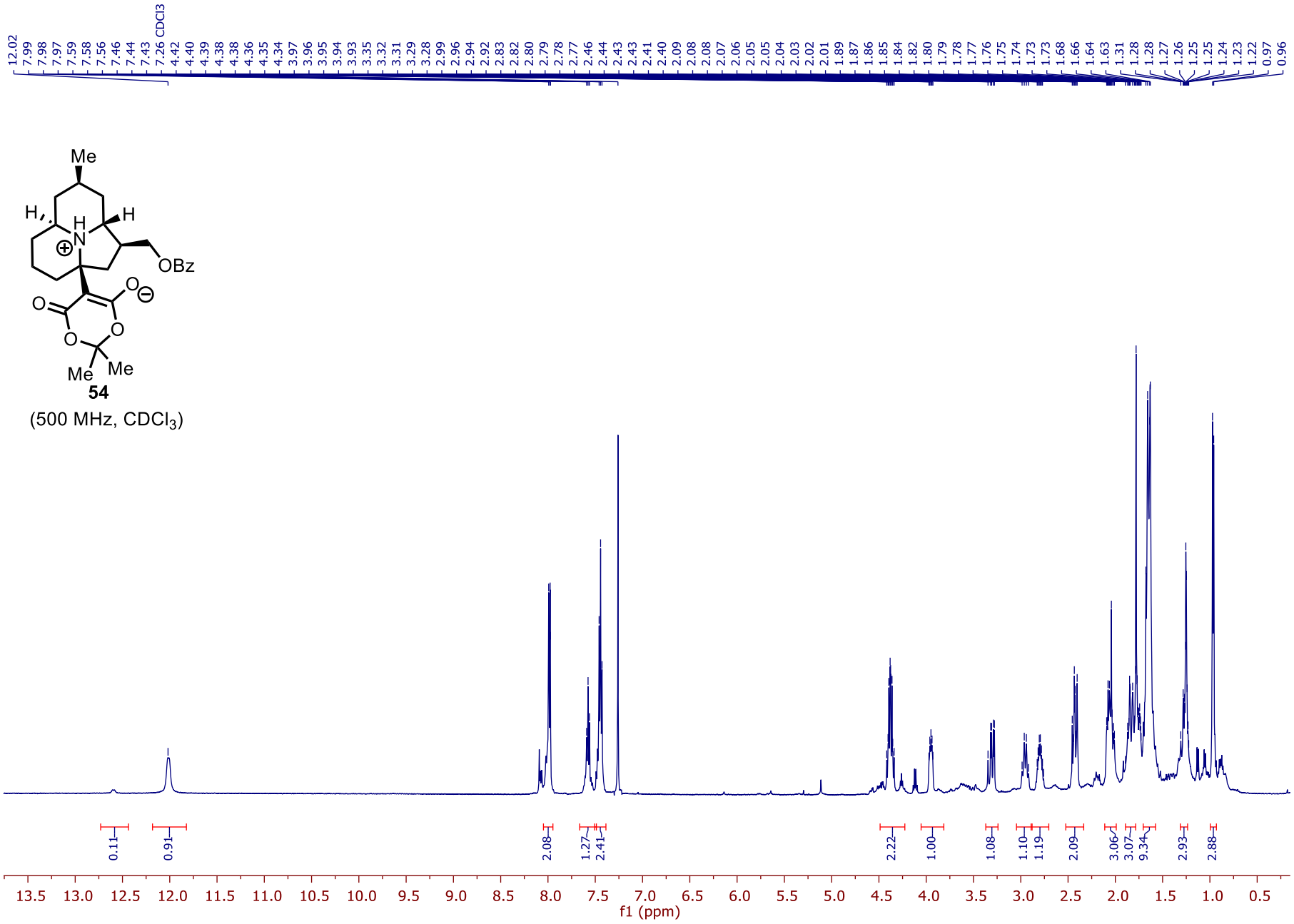
49

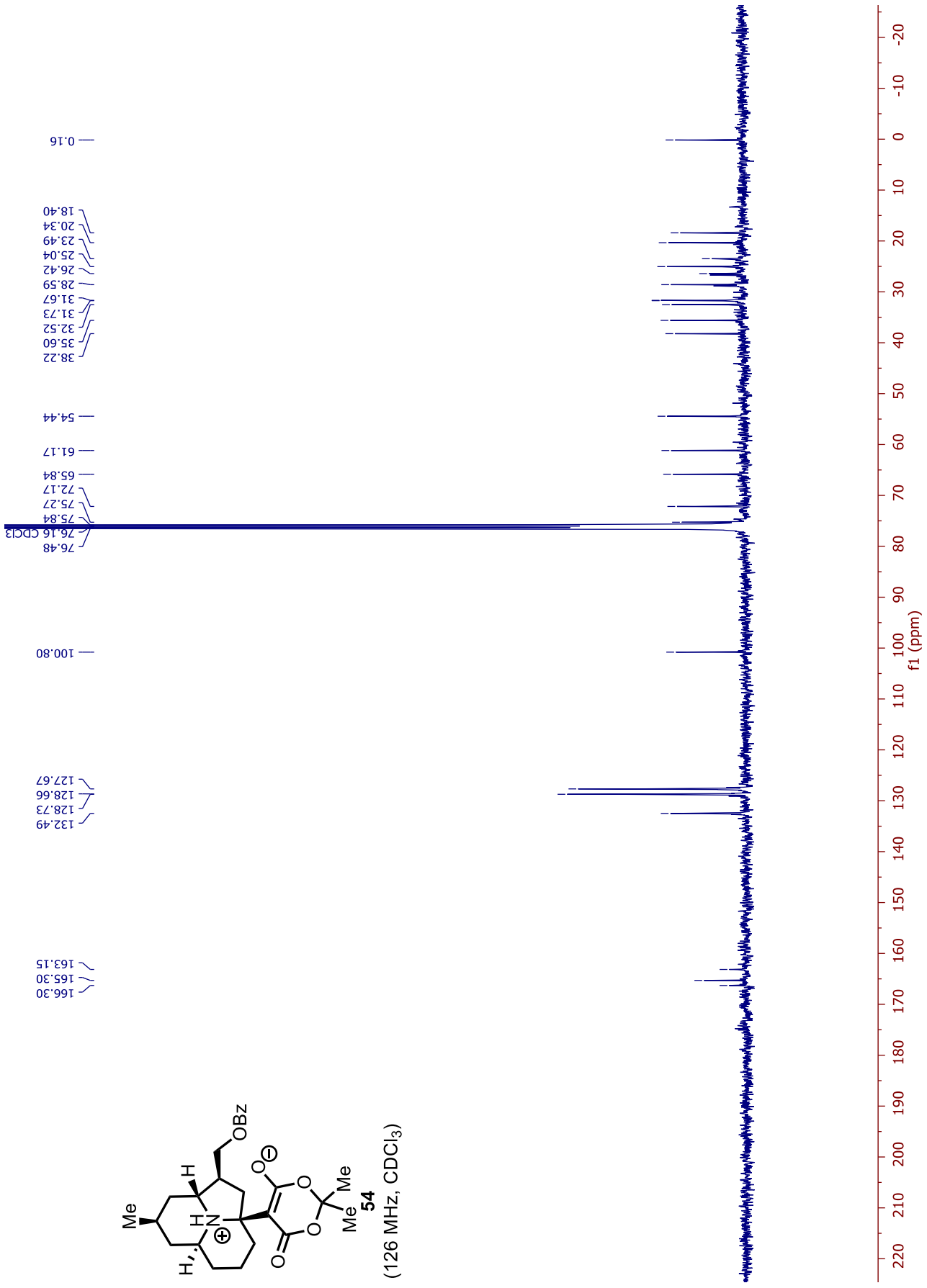
(126 MHz, $CDCl_3$)

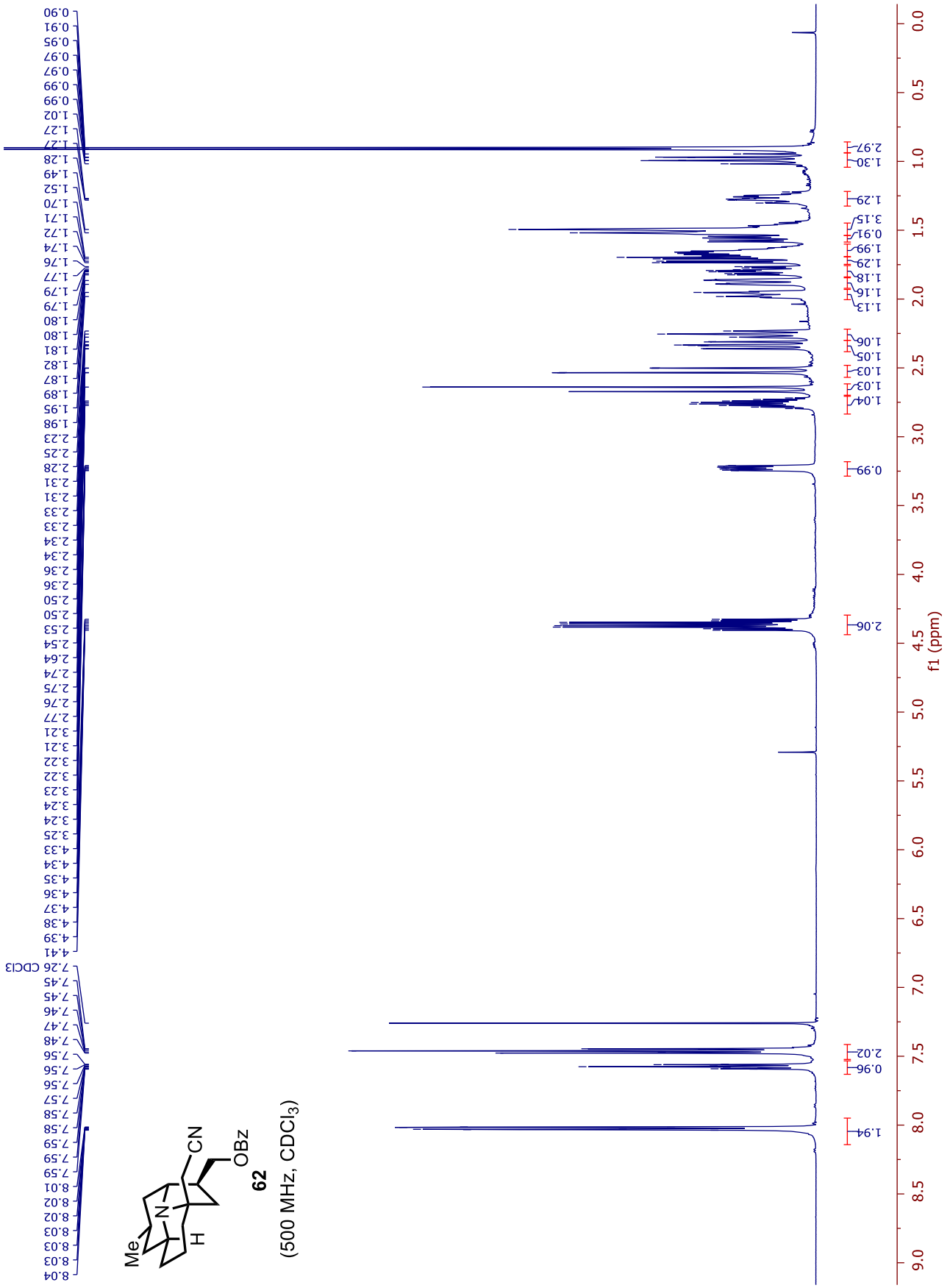
166.50
133.27
129.86
129.74
128.60
121.48
119.03
77.41
77.16 CDCl3
76.91
66.75
66.56
64.06
63.34
62.78
55.88
53.98
53.01
51.57
50.73
43.10
40.93
38.20
37.83
37.03
34.84
34.67
33.88
31.40
27.23
25.72
22.61
22.09

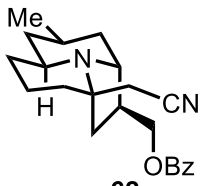
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

f1 (ppm)


12.02 7.99 7.98 7.97 7.59 7.58 7.56 7.46 7.44 7.43 7.26 CDCl3 4.42 4.40 4.39 4.38 4.38 4.36 4.35 4.34 3.97 3.96 3.95 3.94 3.93 3.35 3.32 3.31 3.29 3.28 2.99 2.96 2.94 2.92 2.83 2.82 2.80 2.79 2.78 2.77 2.46 2.44 2.43 2.43 2.41 2.40 2.09 2.08 2.08 2.07 2.06 2.05 2.05 2.04 2.03 2.02 2.01 1.89 1.87 1.86 1.85 1.84 1.82 1.80 1.79 1.78 1.77 1.76 1.75 1.74 1.73 1.73 1.68 1.66 1.64 1.63 1.31 1.28 1.28 1.27 1.26 1.25 1.25 1.24 1.23 1.22 0.97 0.96
Me
H
H
N
H
OBz
O
O
O
O
O
Me
Me
54
(500 MHz, CDCl3)
222
0.11 0.91 2.08 1.27 2.41 2.22 1.00 1.08 1.10 1.19 2.09 3.06 3.07 9.34 2.93 2.88
13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

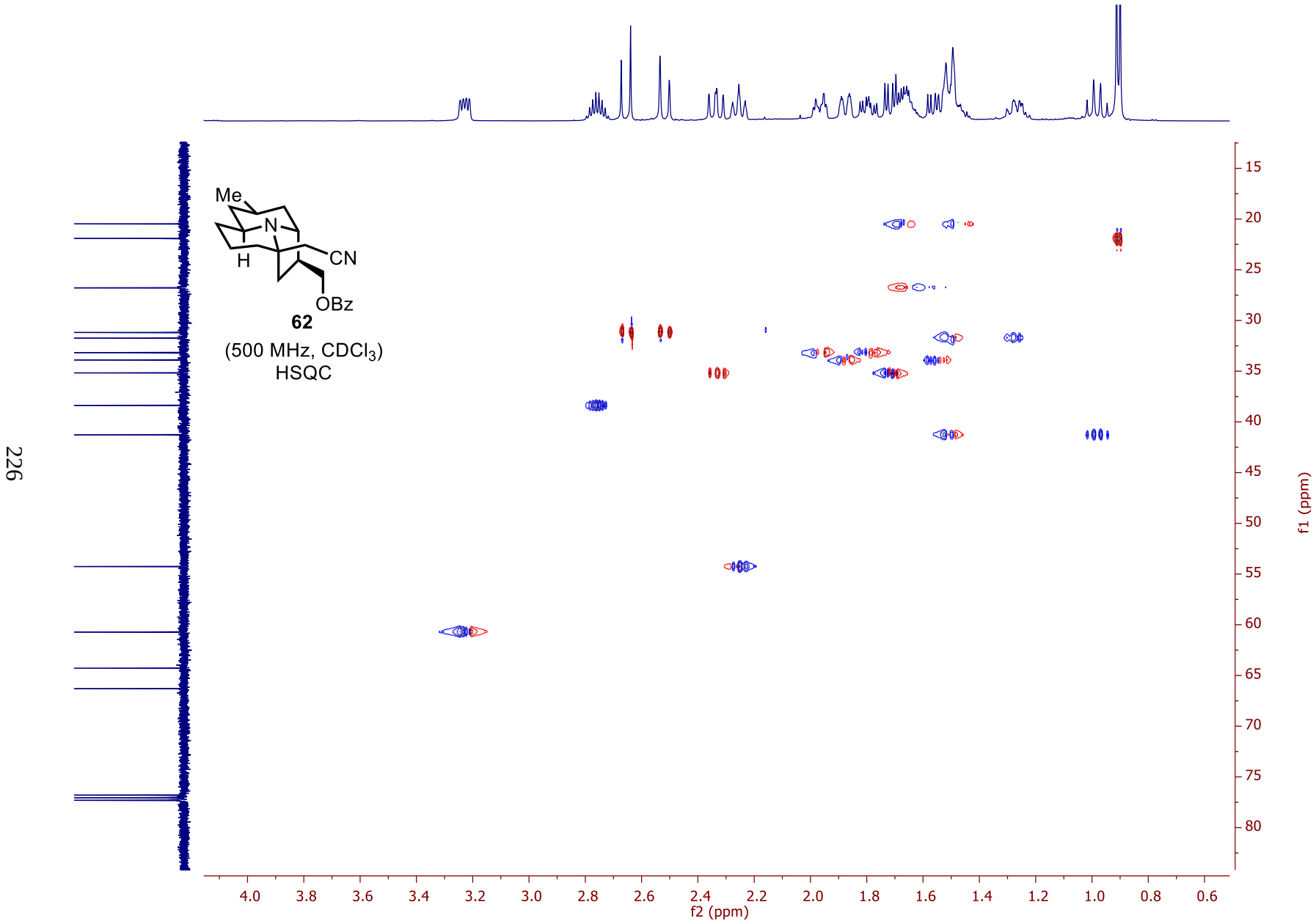

0.16
18.40
20.34
23.49
25.04
26.42
28.59
31.67
31.73
32.52
35.60
38.22
54.44
61.17
65.84
72.17
75.27
75.84
76.16 CDCl3
76.48
100.80
127.67
128.66
128.73
132.49
163.15
165.30
166.30
f1 (ppm)
Me
H
N
OBz
O
O
O
O
Me
Me
54
(126 MHz, CDCl3)

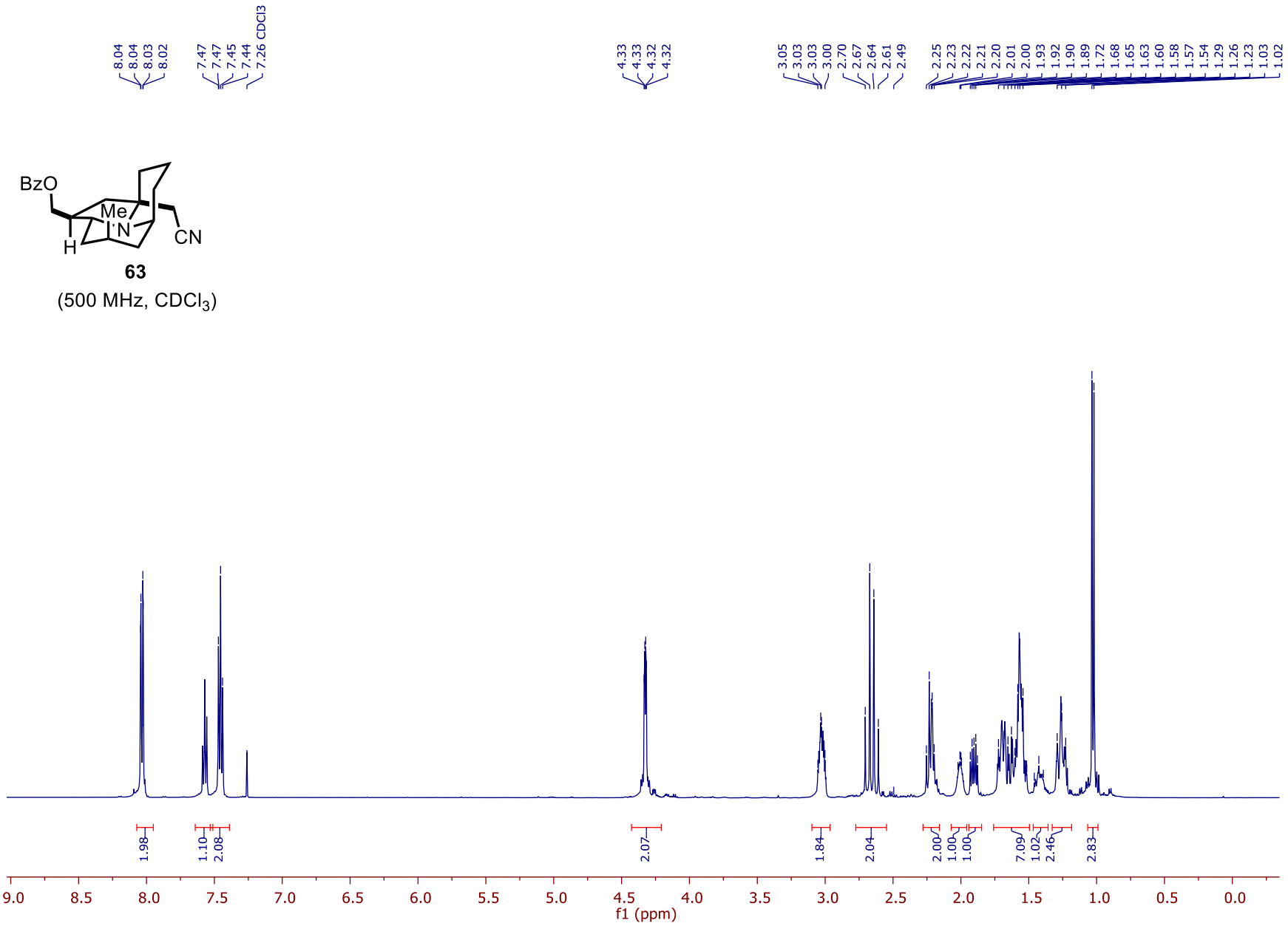

Me
N
H
CN
OBz
62
(500 MHz, CDCl3)
f1 (ppm)



62

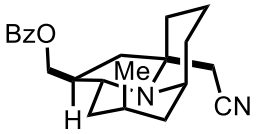
(126 MHz, $CDCl_3$)


Me
N
H
CN
OBz
62
(500 MHz, CDCl3)
HSQC
f2 (ppm)
f1 (ppm)



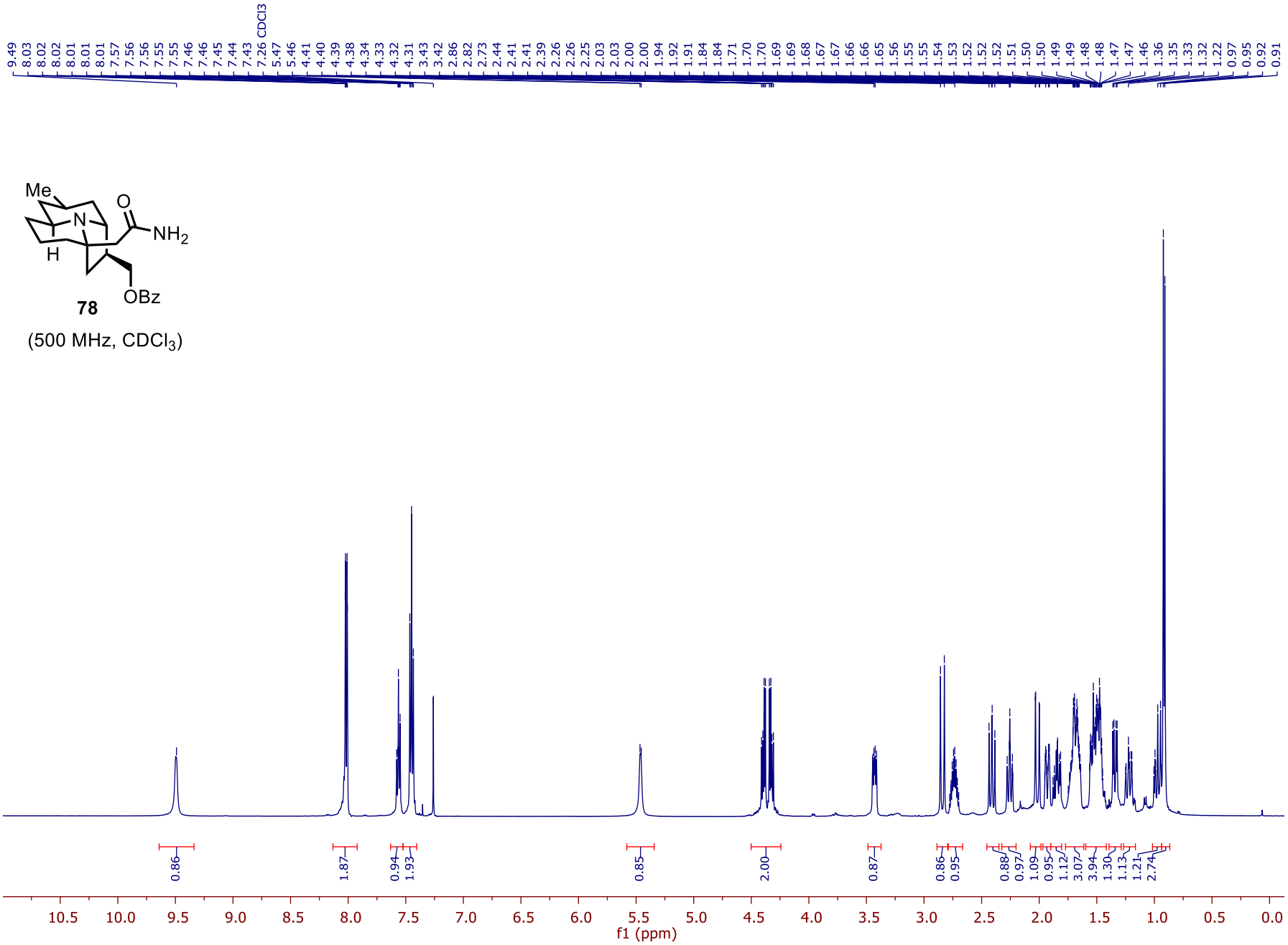
63

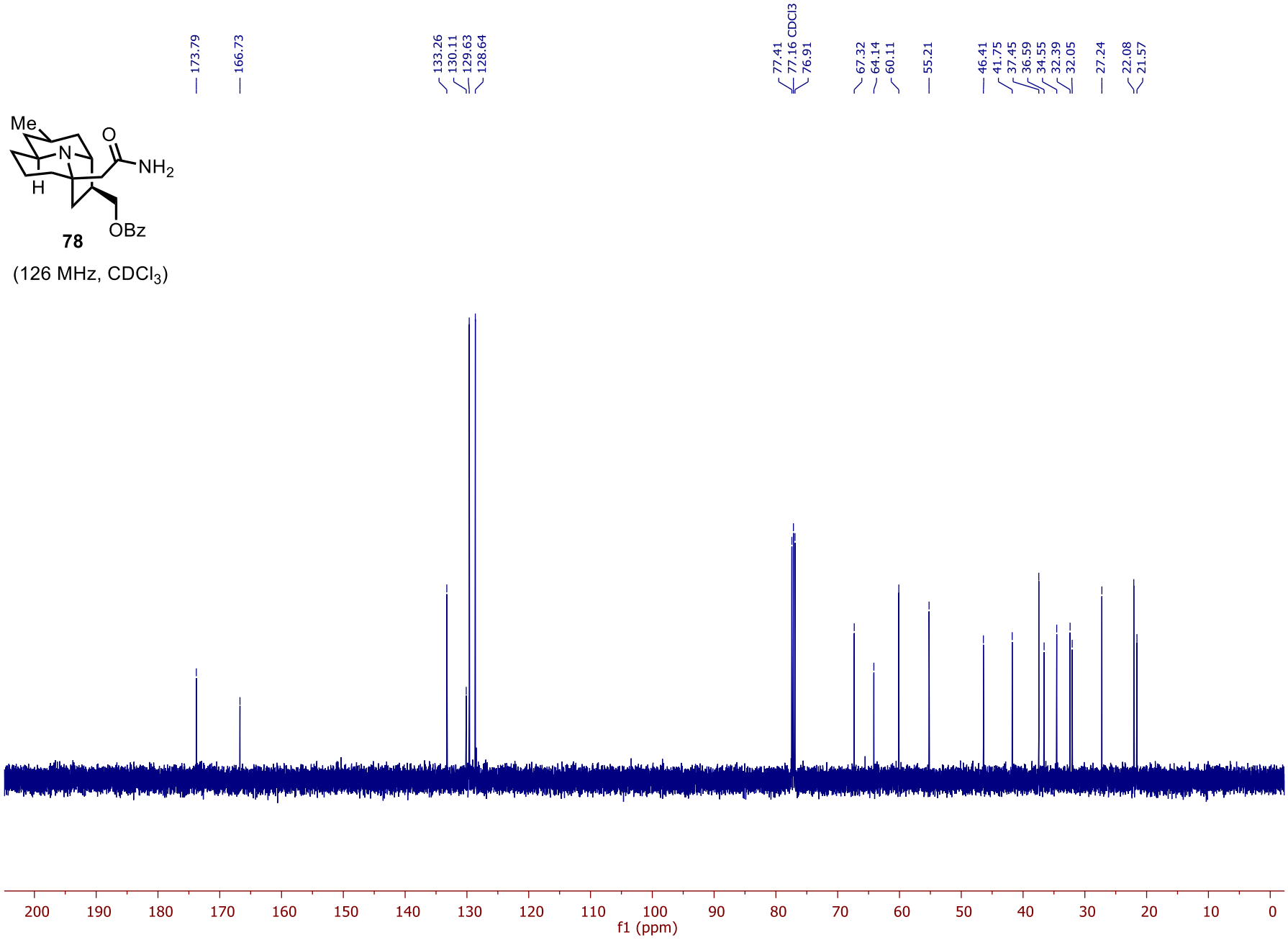
(500 MHz, $CDCl_3$)

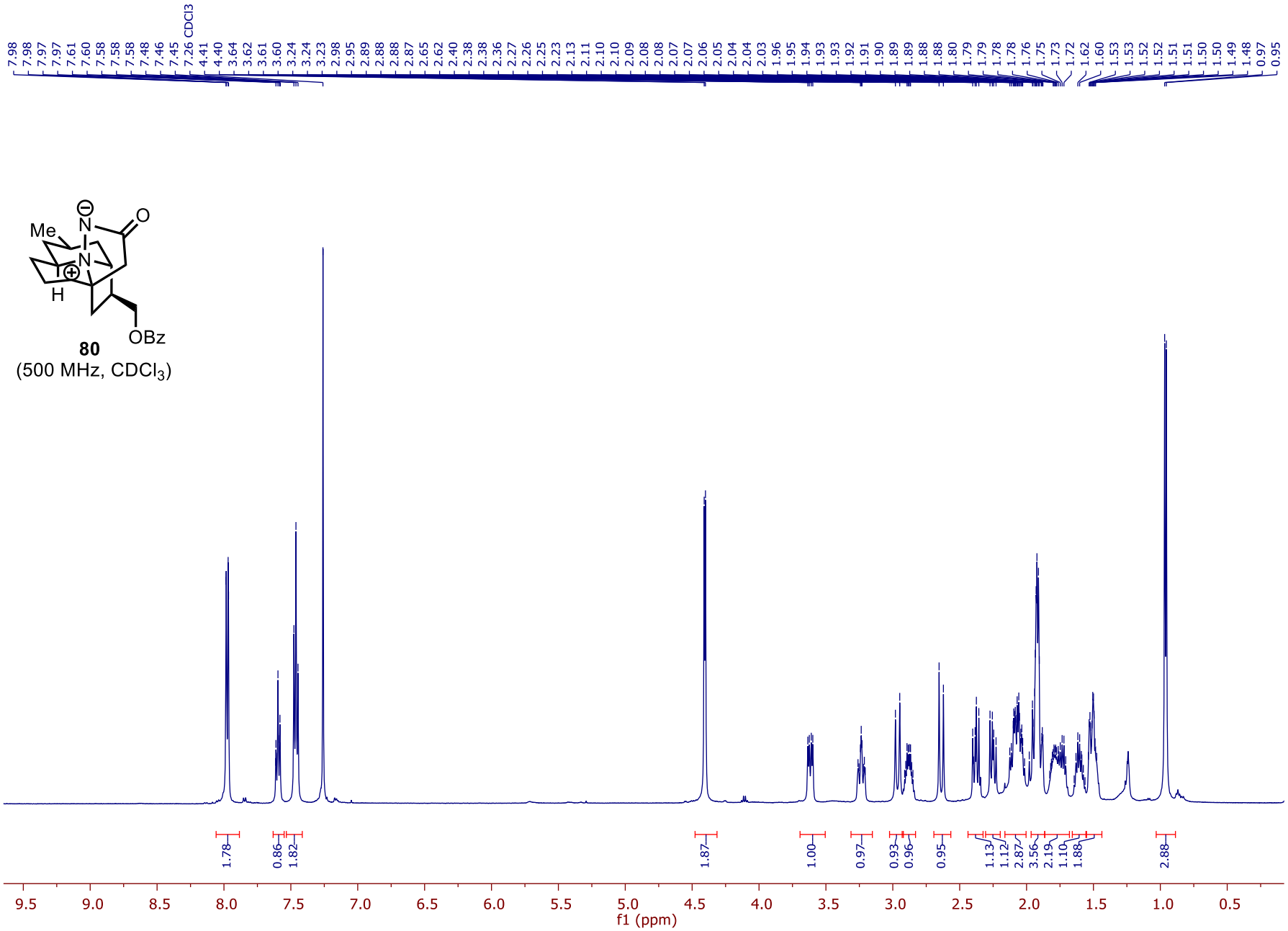


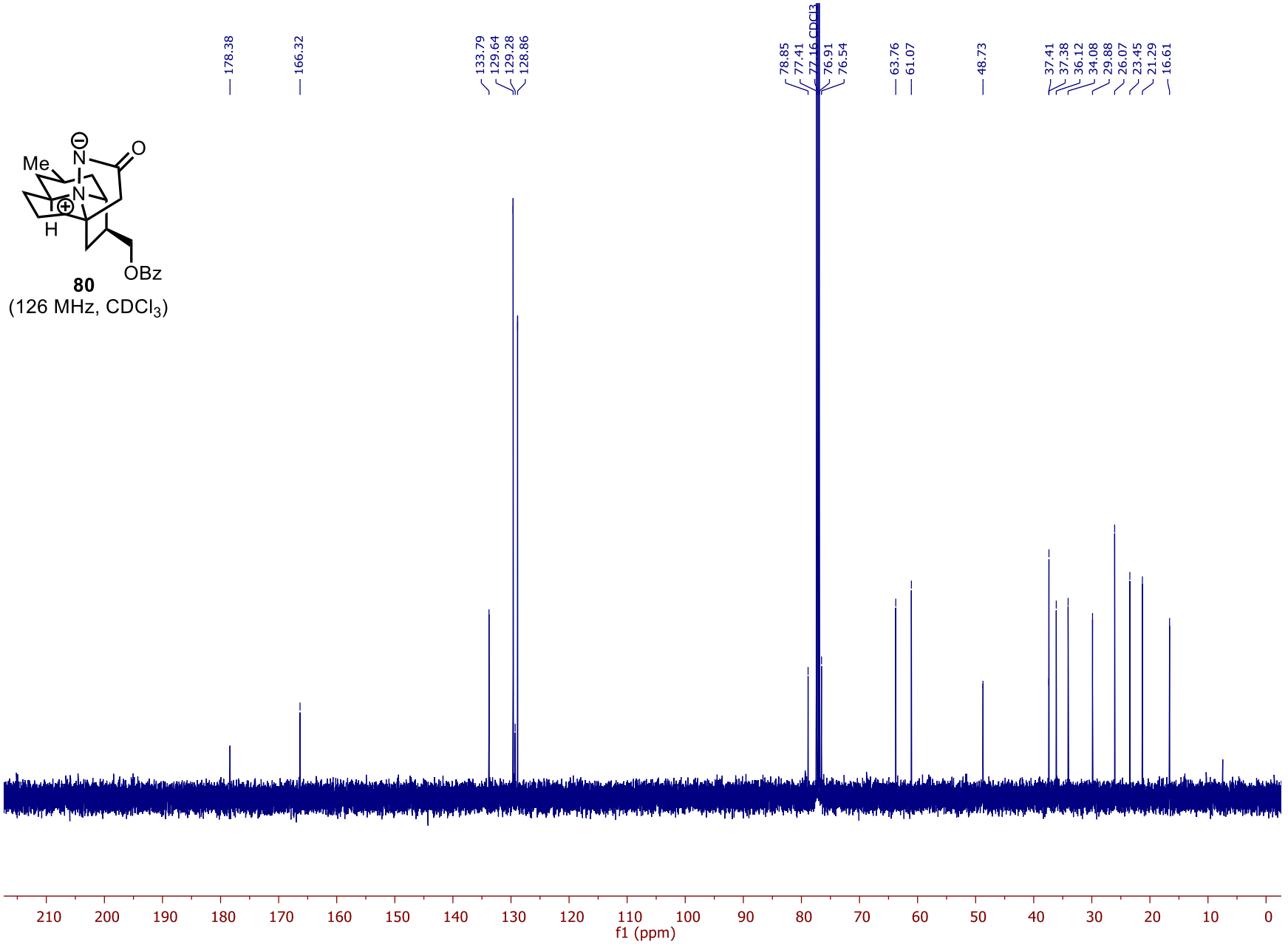
63

(126 MHz, $CDCl_3$)


9.49 8.03 8.02 8.02 8.01 8.01 8.01 7.57 7.56 7.56 7.55 7.55 7.46 7.45 7.44 7.43 7.26 CDCl3 5.47 5.46 4.41 4.40 4.39 4.38 4.34 4.33 4.32 4.31 3.43 3.42 2.86 2.82 2.73 2.44 2.41 2.41 2.39 2.26 2.25 2.03 2.03 2.00 2.00 1.94 1.92 1.91 1.84 1.84 1.71 1.70 1.70 1.69 1.69 1.68 1.67 1.67 1.66 1.66 1.65 1.56 1.55 1.55 1.54 1.53 1.52 1.52 1.52 1.51 1.50 1.50 1.49 1.49 1.48 1.48 1.47 1.47 1.46 1.36 1.35 1.33 1.32 1.22 0.97 0.95 0.92 0.91
Me
O
N
NH2
H
OBz
78
(500 MHz, CDCl3)
0.86 1.87 0.94 1.93 0.85 2.00 0.87 0.86 0.95 0.88 0.97 1.09 0.95 1.12 3.07 3.94 1.30 1.13 1.21 2.74
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

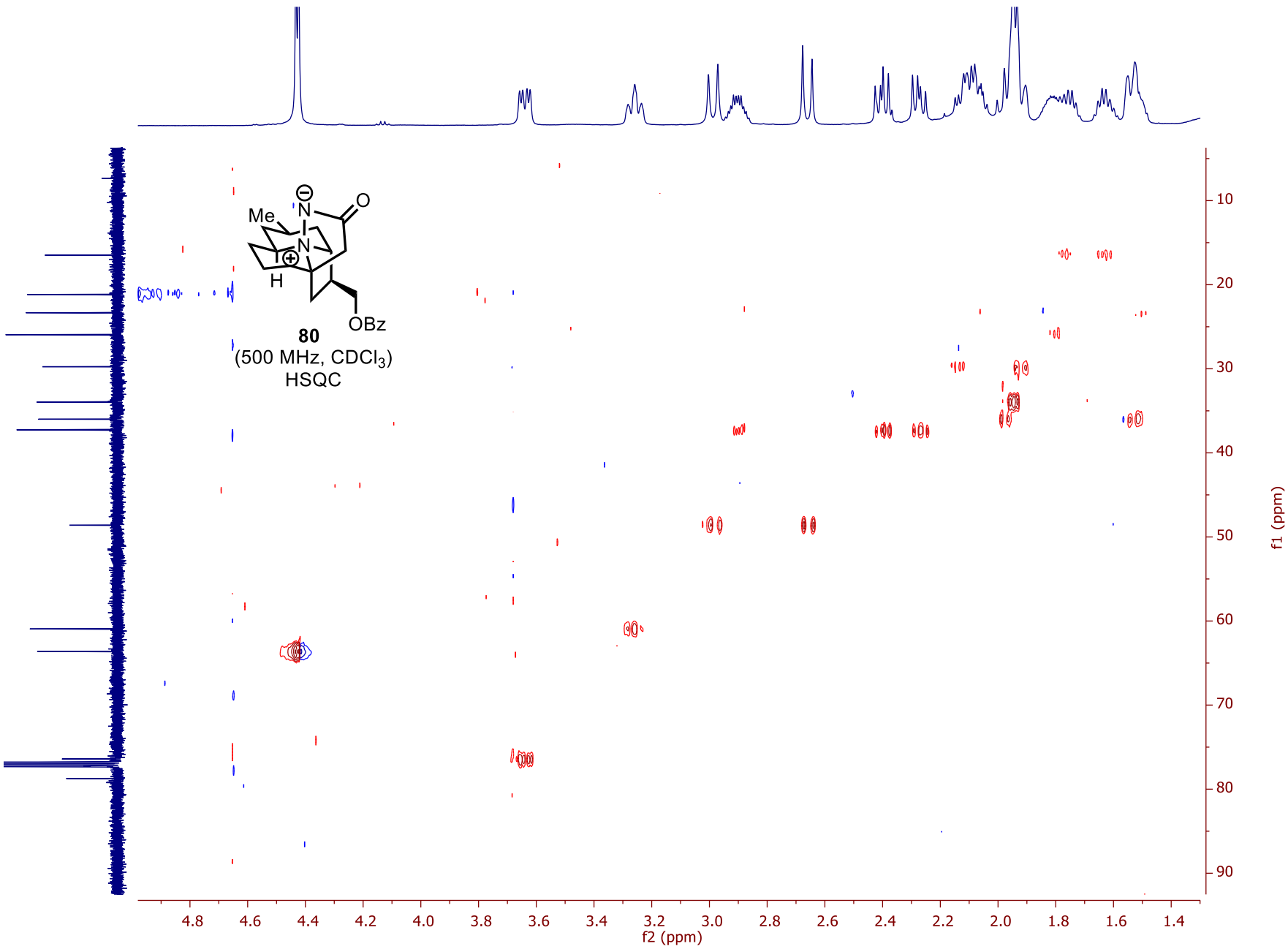

173.79
166.73
133.26
130.11
129.63
128.64
77.41
77.16 CDCl3
76.91
67.32
64.14
60.11
55.21
46.41
41.75
37.45
36.59
34.55
32.39
32.05
27.24
22.08
21.57
Me
O
N
NH2
H
OBz
78
(126 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

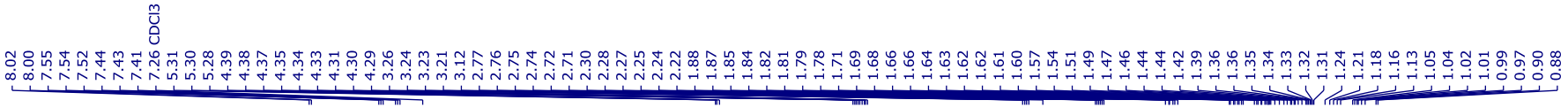

7.98 7.98 7.97 7.97 7.61 7.60 7.58 7.58 7.58 7.48 7.46 7.45 7.26 CDCl3 4.41 4.40 3.64 3.62 3.61 3.60 3.24 3.24 3.23 2.98 2.95 2.89 2.88 2.88 2.87 2.65 2.62 2.40 2.38 2.38 2.36 2.27 2.26 2.25 2.23 2.13 2.11 2.10 2.10 2.09 2.08 2.08 2.07 2.07 2.06 2.05 2.04 2.04 2.03 1.96 1.95 1.94 1.93 1.93 1.92 1.91 1.90 1.89 1.89 1.88 1.88 1.80 1.79 1.79 1.78 1.78 1.76 1.75 1.73 1.72 1.62 1.60 1.53 1.53 1.52 1.52 1.51 1.51 1.50 1.50 1.49 1.48 0.97 0.95
Me
N
O
H
OBz
80
(500 MHz, CDCl3)
1.78 0.86 1.82 1.87 1.00 0.97 0.93 0.96 0.95 1.13 1.12 2.87 3.56 2.19 1.10 1.88 2.88
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

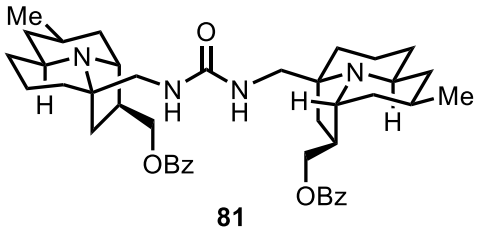


80

(126 MHz, $CDCl_3$)

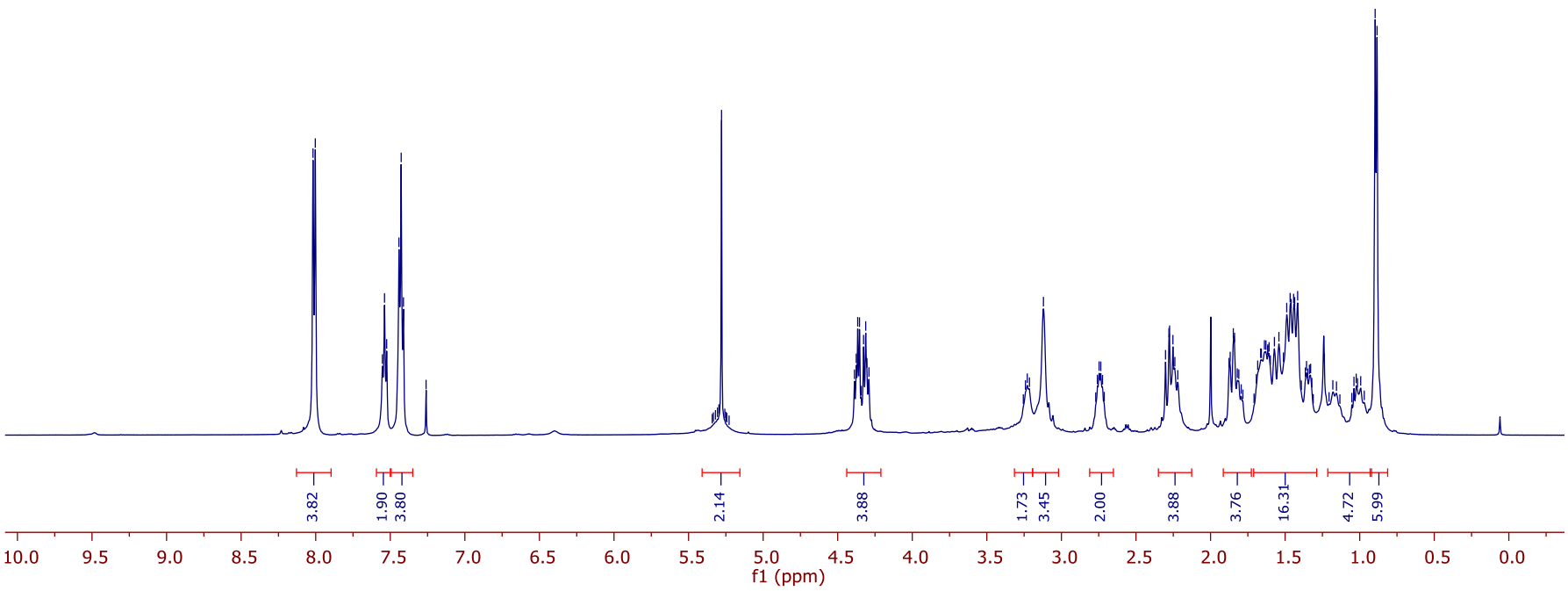

Me
N
O
N
H
OBz
80
(500 MHz, CDCl3)
HSQC
233
f2 (ppm)
f1 (ppm)
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
10
20
30
40
50
60
70
80
90

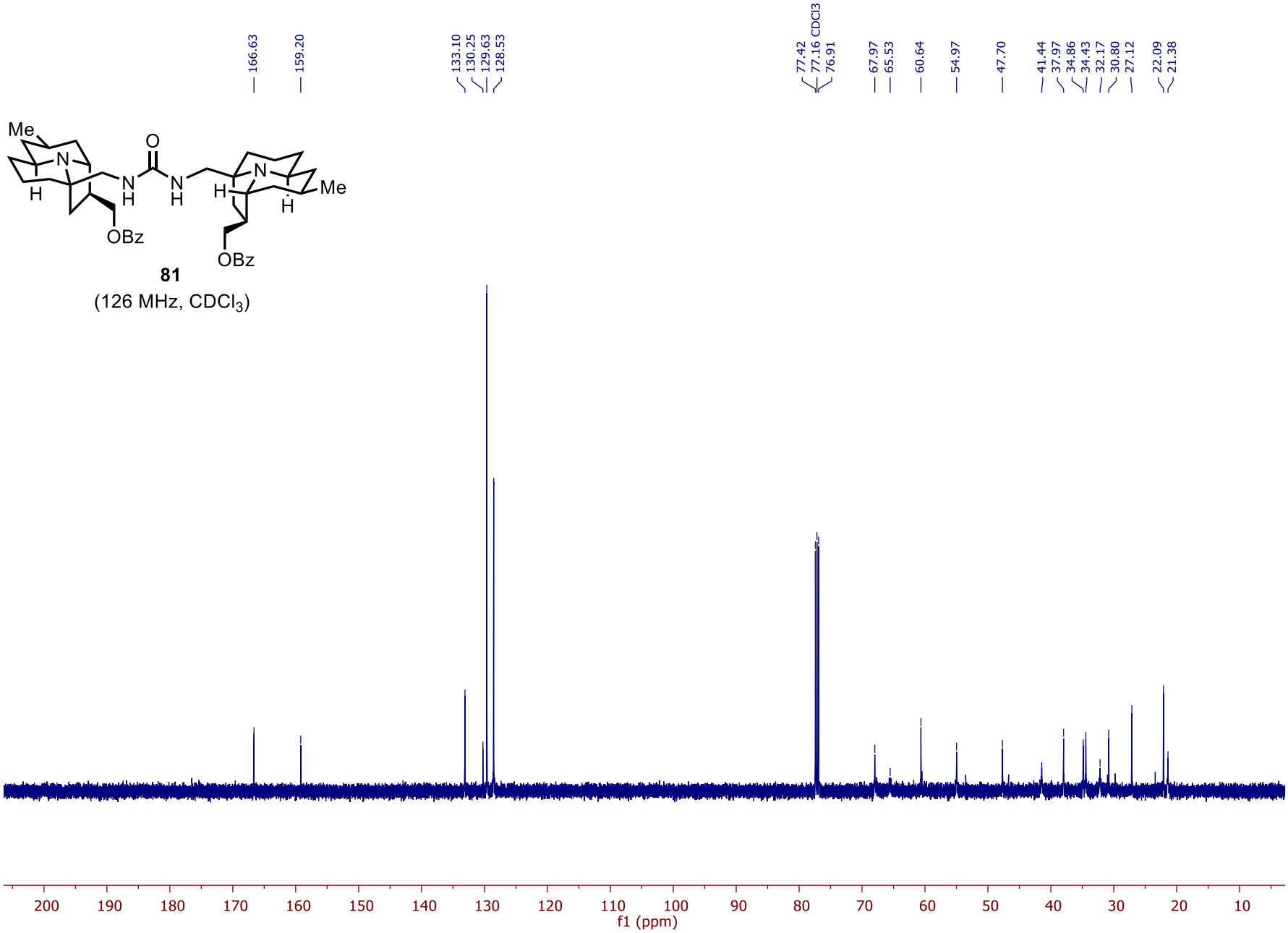


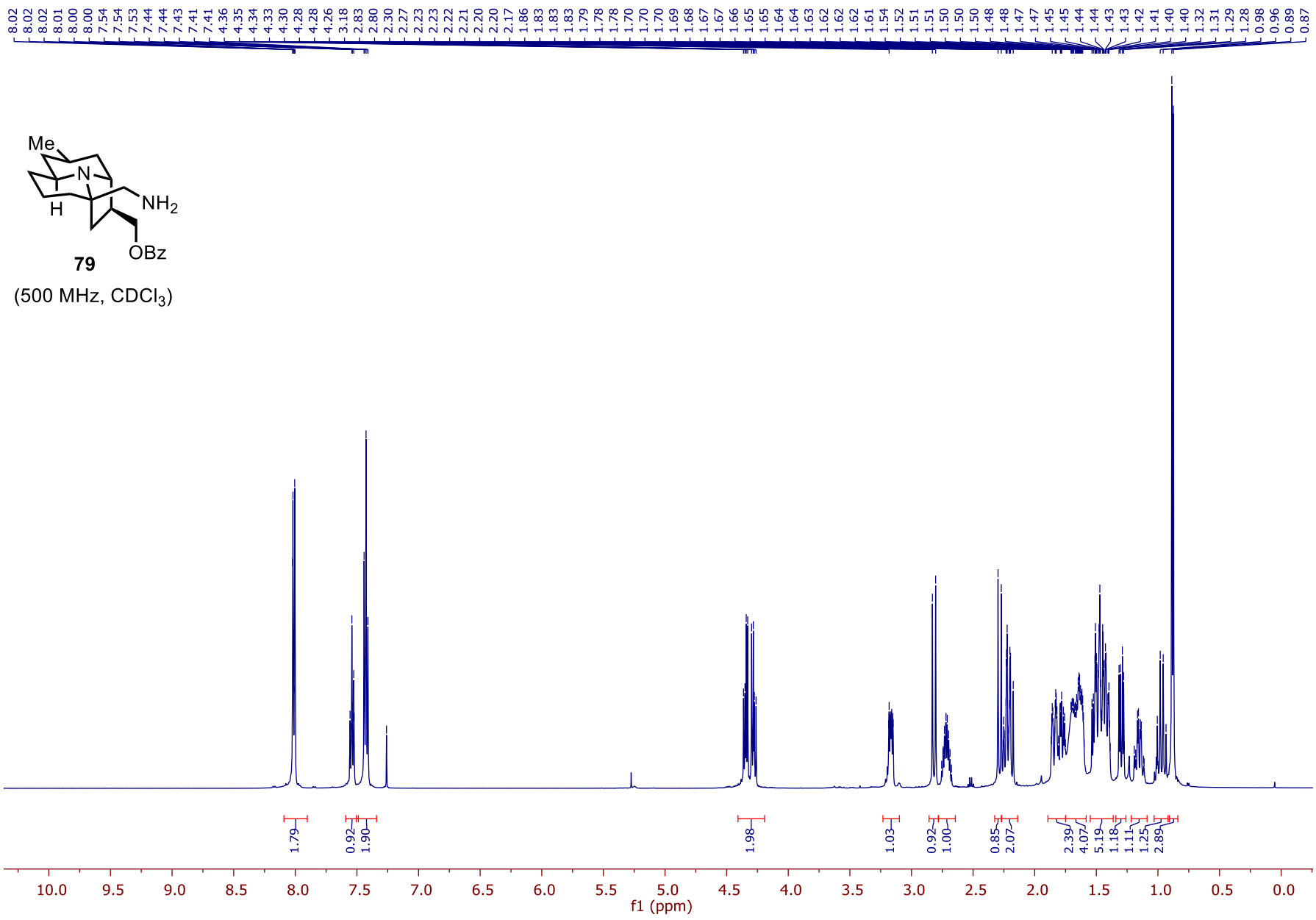


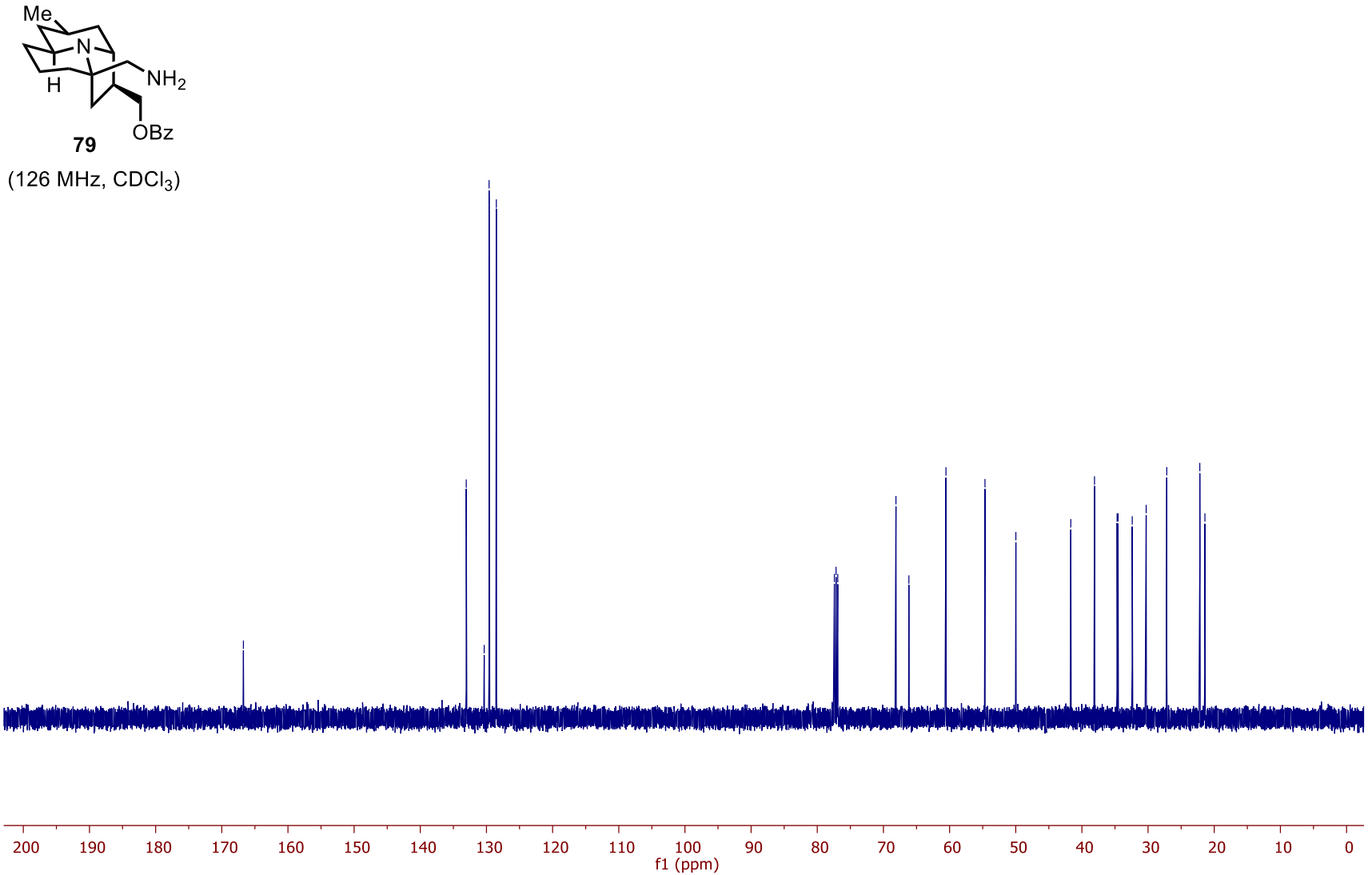
81

(500 MHz, $CDCl_3$)



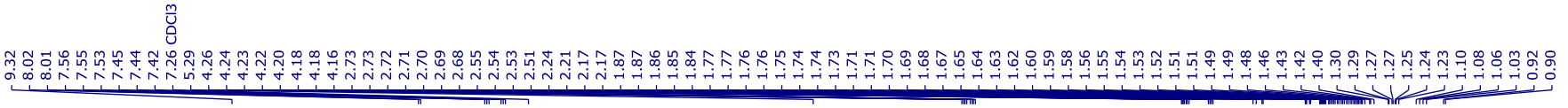

166.63
159.20
133.10
130.25
129.63
128.53
77.42
77.16 CDCl3
76.91
67.97
65.53
60.64
54.97
47.70
41.44
37.97
34.86
34.43
32.17
30.80
27.12
22.09
21.38
Me
N
H
O
N
H
N
H
N
H
Me
OBz
OBz
81
(126 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

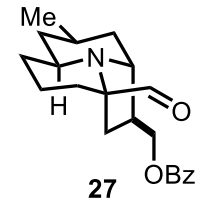

8.02 8.02 8.02 8.01 8.00 8.00 7.54 7.53 7.44 7.44 7.43 7.41 7.41 4.36 4.35 4.34 4.33 4.30 4.28 4.28 4.26 3.18 2.83 2.80 2.30 2.27 2.23 2.23 2.22 2.21 2.20 2.20 2.17 1.86 1.83 1.83 1.83 1.79 1.78 1.78 1.70 1.70 1.70 1.69 1.68 1.67 1.67 1.66 1.65 1.65 1.64 1.64 1.63 1.62 1.62 1.62 1.61 1.54 1.52 1.51 1.51 1.50 1.50 1.50 1.48 1.48 1.47 1.47 1.45 1.45 1.44 1.44 1.43 1.43 1.42 1.41 1.40 1.40 1.32 1.31 1.29 1.28 0.98 0.96 0.89 0.87
Me
N
H
NH2
OBz
79
(500 MHz, CDCl3)
1.79 0.92 1.90 1.98 1.03 0.92 1.00 0.85 2.07 2.39 4.07 5.19 1.18 1.11 1.25 2.89
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



79

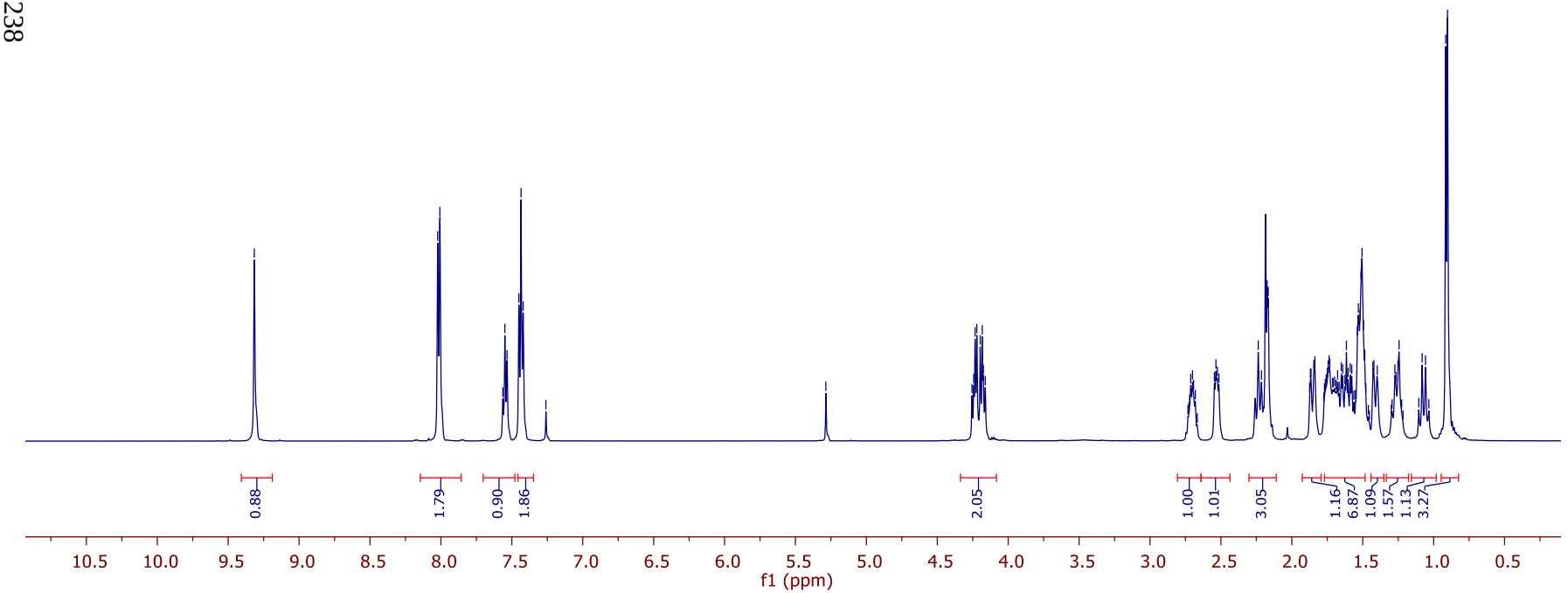
(126 MHz, $CDCl_3$)

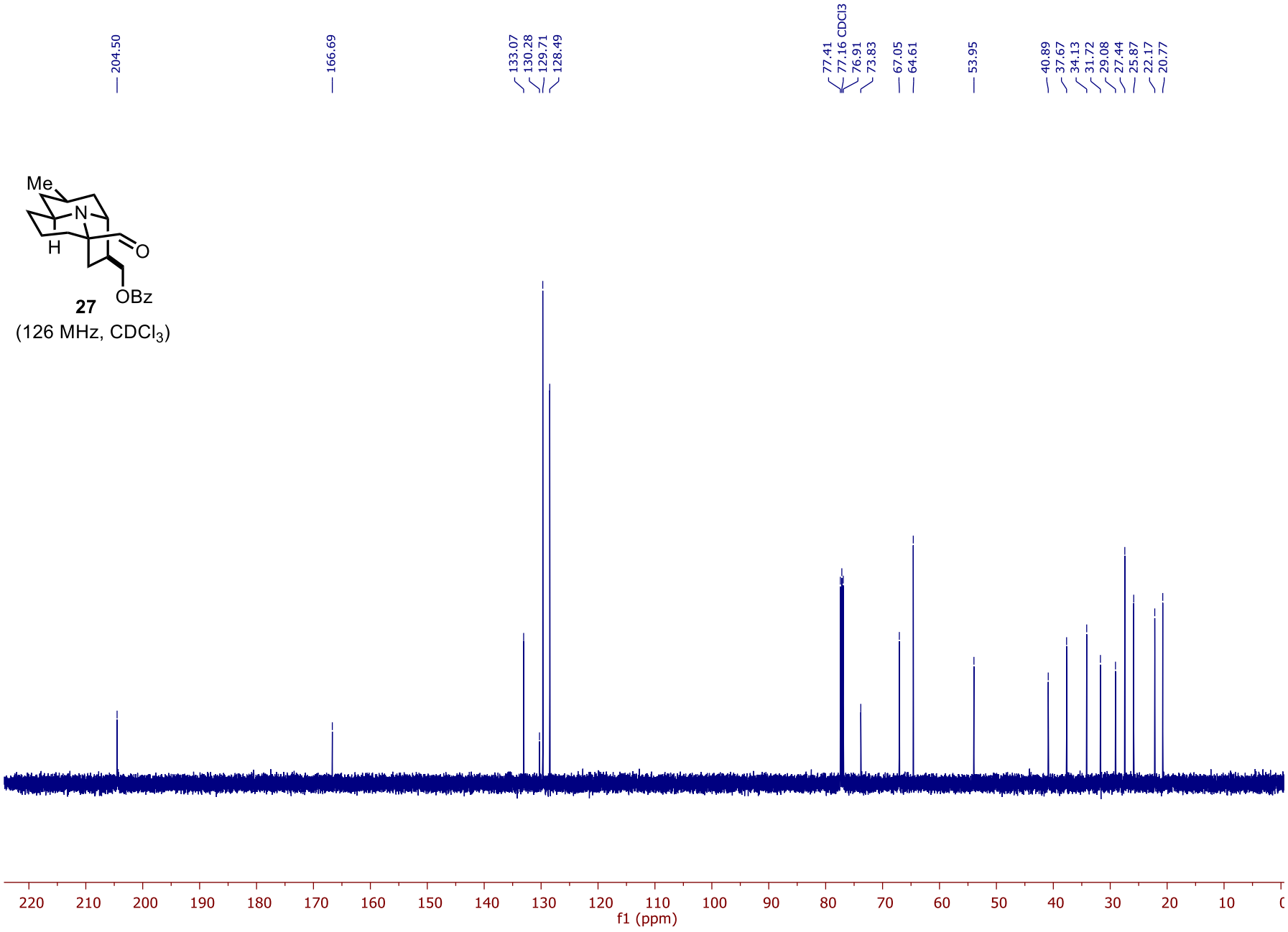


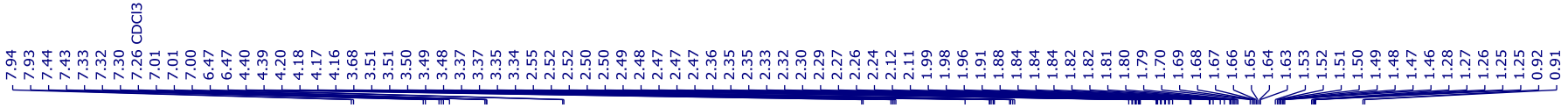


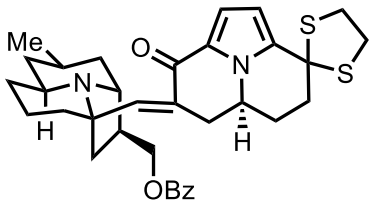
27

(500 MHz, $CDCl_3$)



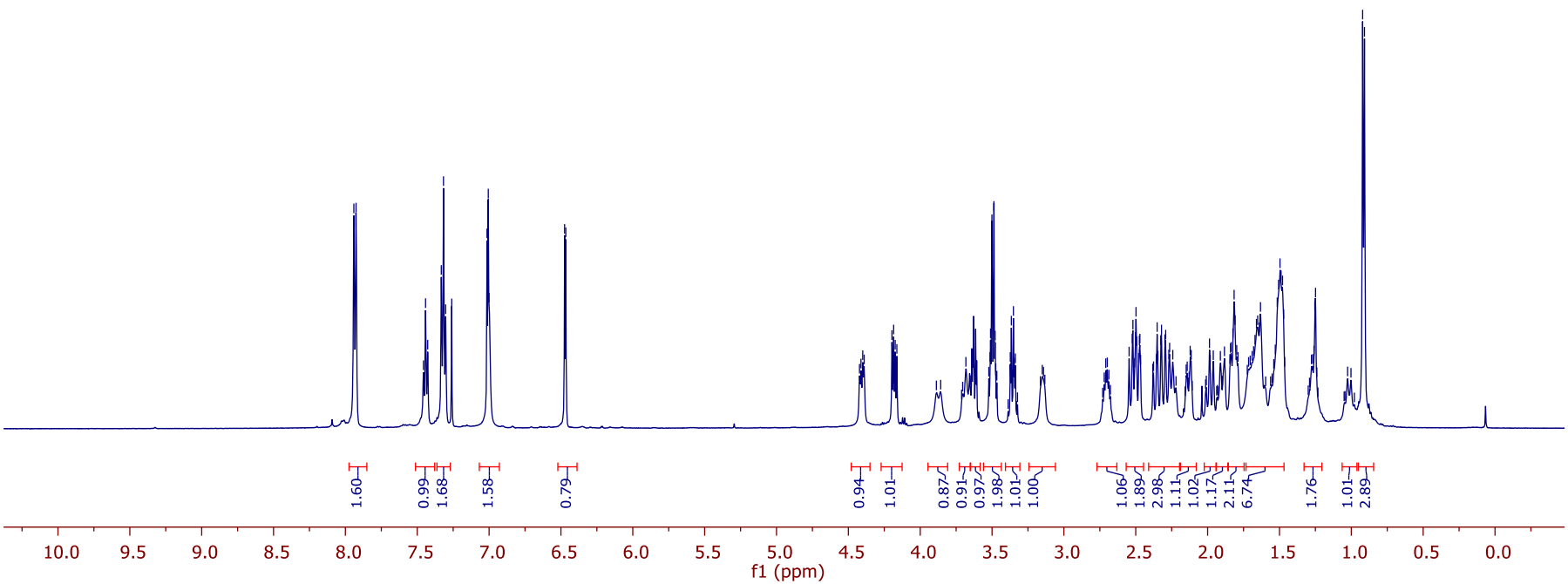

204.50
166.69
133.07
130.28
129.71
128.49
77.41
77.16 CDCl3
76.91
73.83
67.05
64.61
53.95
40.89
37.67
34.13
31.72
29.08
27.44
25.87
22.17
20.77
Me
N
H
O
OBz
27
(126 MHz, CDCl3)
f1 (ppm)

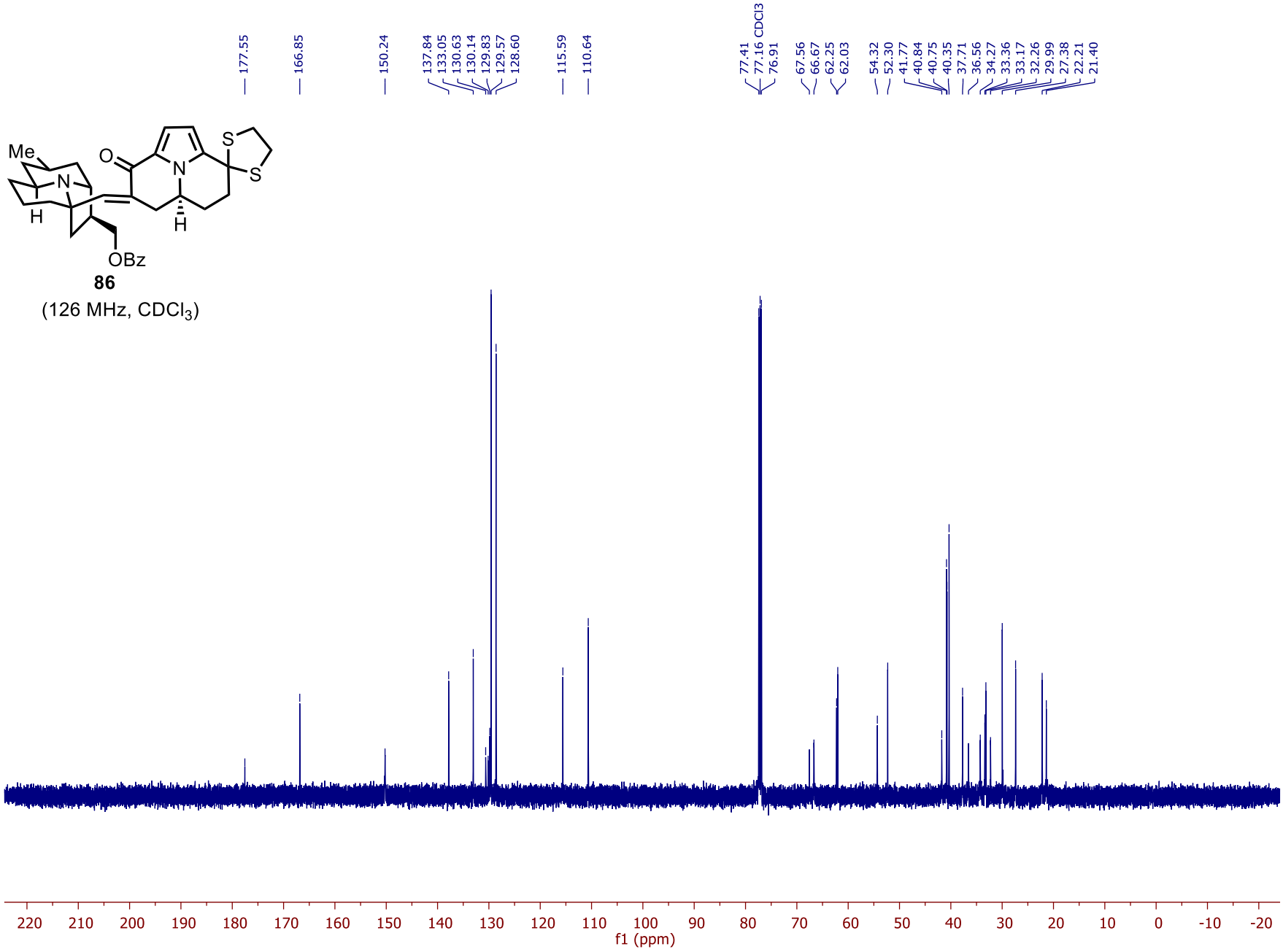




86

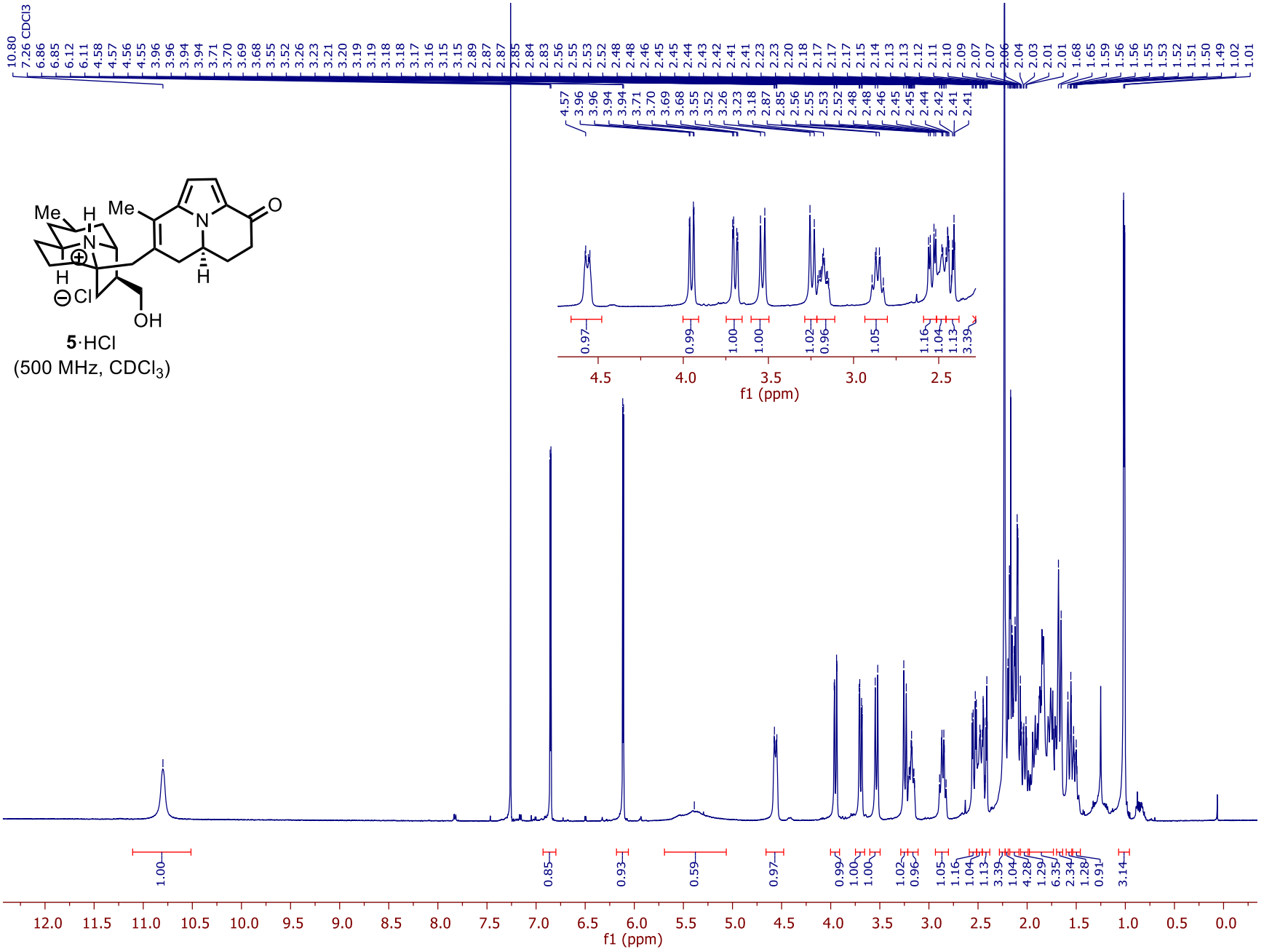
(500 MHz, $CDCl_3$)

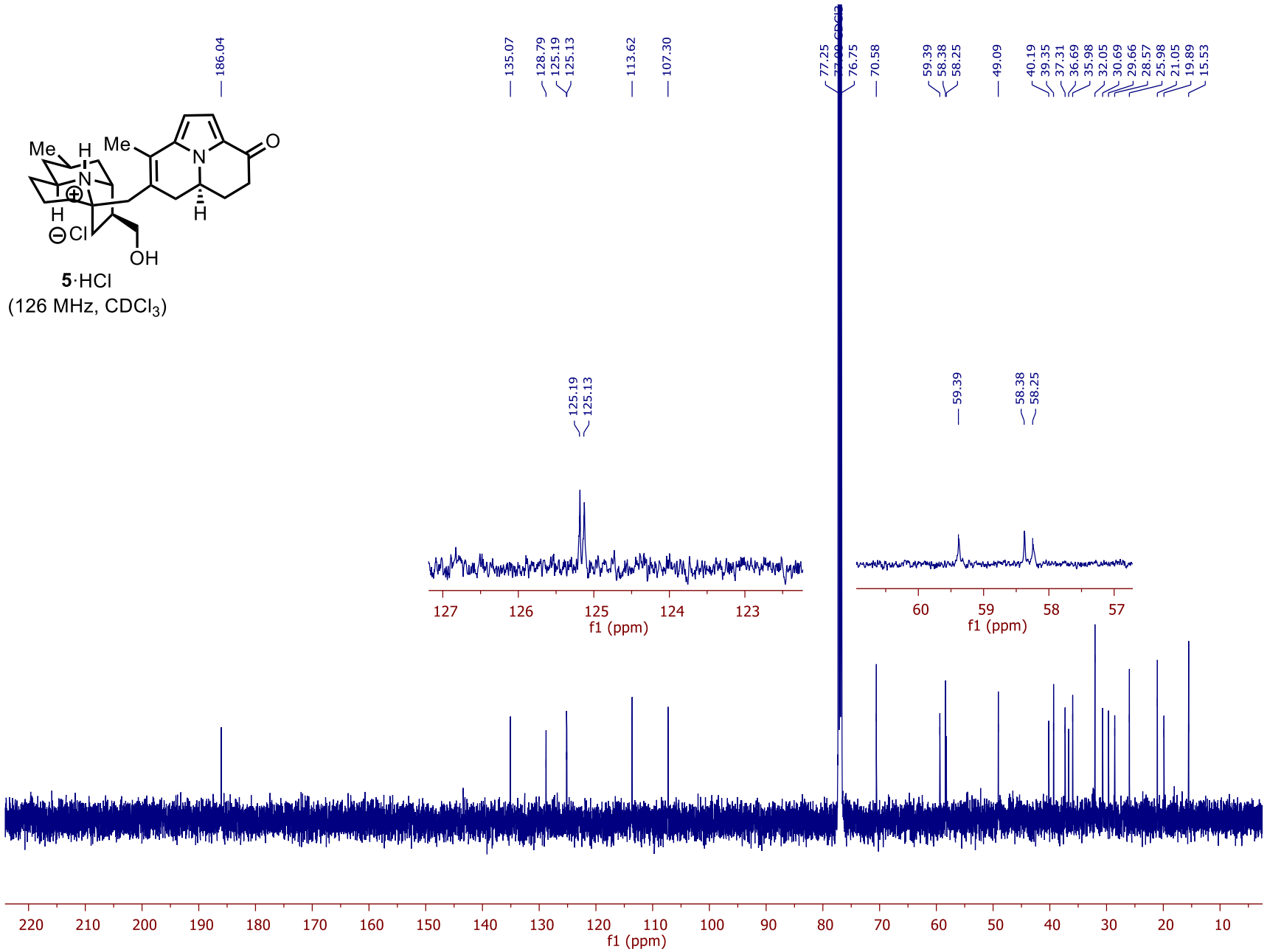


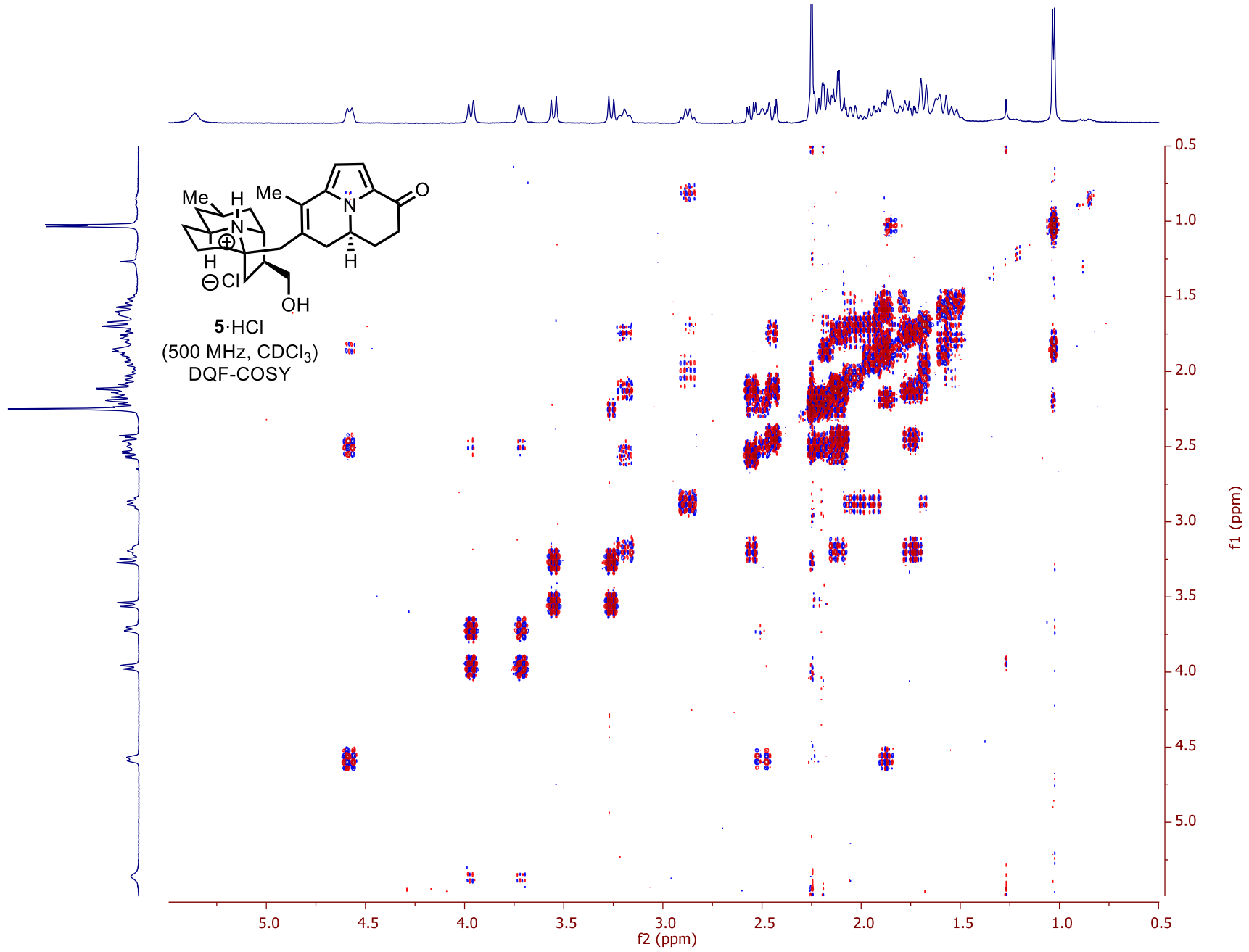


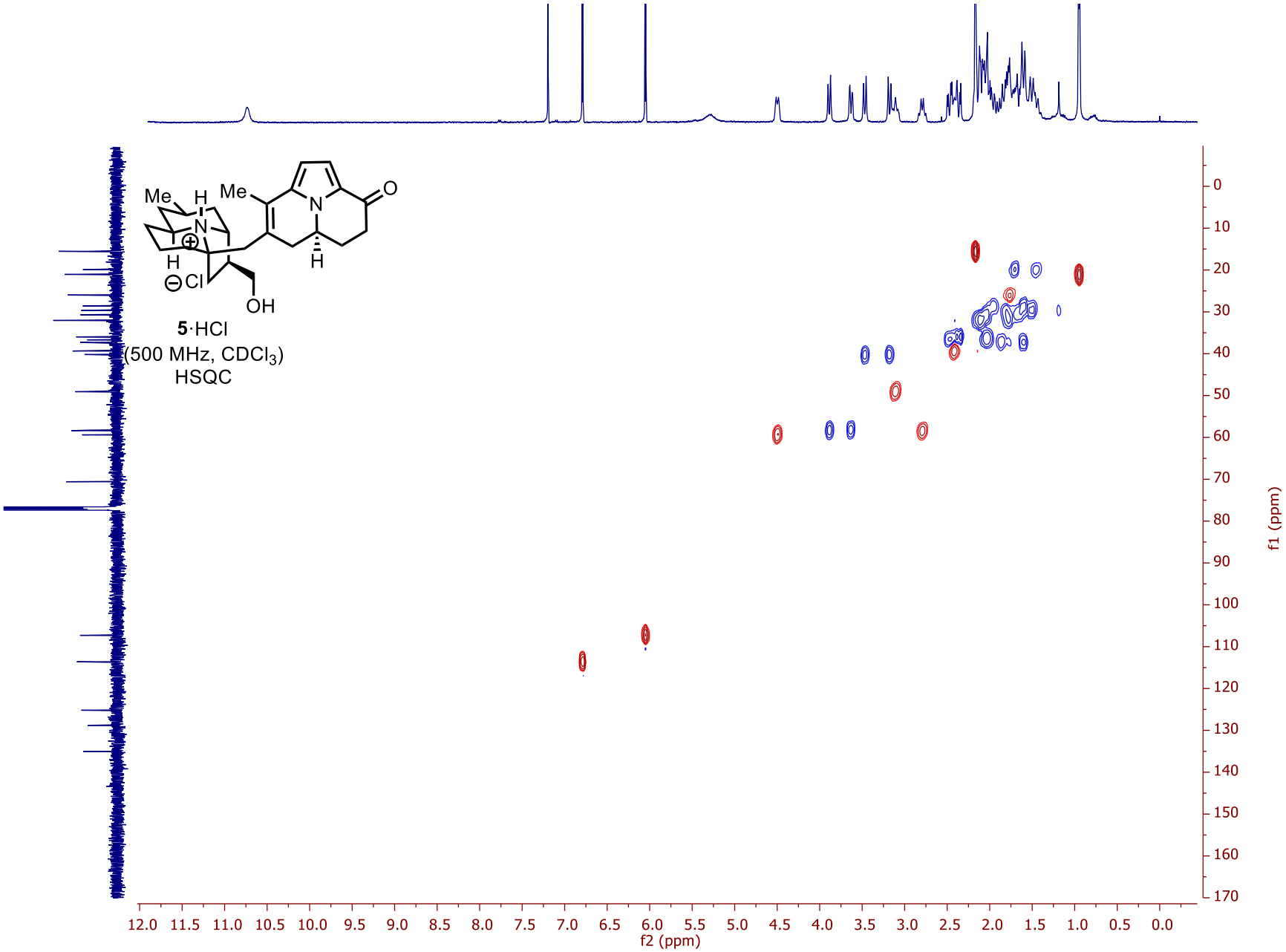
86

(126 MHz, $CDCl_3$)

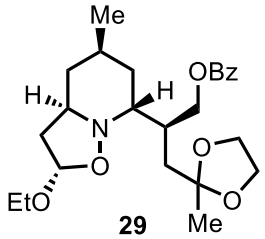

10.80
7.26 CDCl3
6.86
6.85
6.12
6.11
4.58
4.57
4.56
4.55
3.96
3.96
3.94
3.94
3.71
3.70
3.69
3.68
3.55
3.52
3.26
3.23
3.21
3.20
3.19
3.19
3.18
3.18
3.17
3.16
3.15
3.15
2.89
2.87
2.87
2.85
2.84
2.83
2.56
2.55
2.53
2.52
2.48
2.48
2.46
2.45
2.45
2.44
2.43
2.42
2.41
2.41
2.23
2.23
2.20
2.18
2.17
2.17
2.15
2.14
2.13
2.12
2.11
2.10
2.09
2.07
2.07
2.06
2.04
2.03
2.01
2.01
1.68
1.65
1.59
1.56
1.56
1.55
1.53
1.52
1.51
1.50
1.49
1.02
1.01
4.57
3.96
3.96
3.94
3.94
3.71
3.70
3.69
3.68
3.55
3.52
3.26
3.23
3.18
2.87
2.85
2.56
2.55
2.53
2.52
2.48
2.48
2.46
2.45
2.45
2.44
2.42
2.41
2.41
Me
H
Me
N
O
H
Cl
OH
5·HCl
(500 MHz, CDCl3)
0.97
0.99
1.00
1.00
1.02
0.96
1.05
1.16
1.04
1.13
3.39
4.5
4.0
3.5
3.0
2.5
f1 (ppm)
1.00
0.85
0.93
0.59
0.97
0.99
1.00
1.00
1.02
0.96
1.05
1.16
1.04
1.13
3.39
1.04
4.28
1.29
6.35
2.34
1.28
0.91
3.14
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


186.04
135.07
128.79
125.19
125.13
113.62
107.30
77.25
76.75
70.58
59.39
58.38
58.25
49.09
40.19
39.35
37.31
36.69
35.98
32.05
30.69
29.66
28.57
25.98
21.05
19.89
15.53
Me
H
Me
N
O
H
Cl
OH
5·HCl
(126 MHz, CDCl3)
f1 (ppm)


Me
H
Me
N
O
H
⊖Cl
OH
5·HCl
(500 MHz, CDCl3)
DQF-COSY
f2 (ppm)
f1 (ppm)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5


Me
H
Me
N
O
H
⊖Cl
OH
5·HCl
(500 MHz, CDCl3)
HSQC
f2 (ppm)
f1 (ppm)

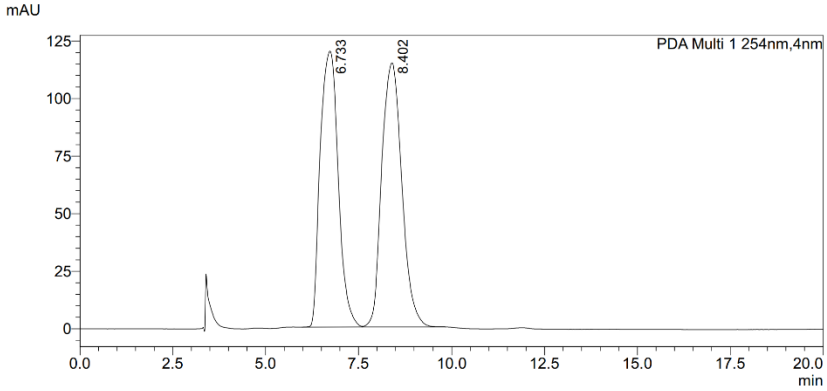
2.16. HPLC Traces.



29

Conditions: HPLC (ChiralPak OD-H, 95:5 hexanes/*i*-PrOH, 1 mL/min, 254 nm)

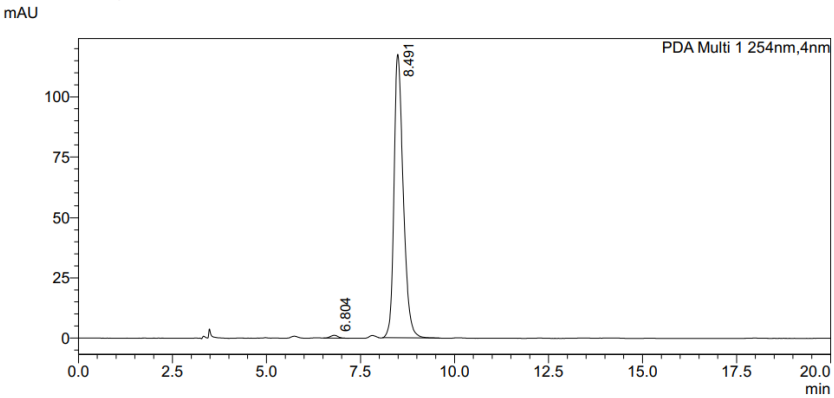
Racemic Sample:



PDA Ch1 254nm

Peak#	Ret. Time	Area	Area%
1	6.733	4045900	48.354
2	8.402	4321422	51.646
Total		8367323	100.000

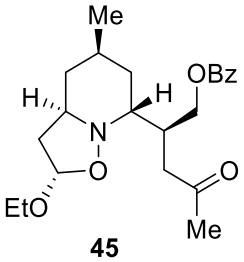
Enantioenriched Sample:



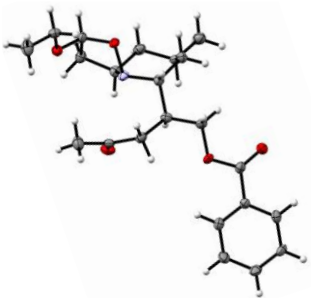
PDA Ch1 254nm

Peak#	Ret. Time	Area	Area%
1	6.804	16261	0.801
2	8.491	2014140	99.199
Total		2030400	100.000

2.17. X-Ray Crystallography Data.

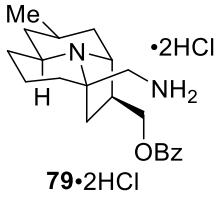


45

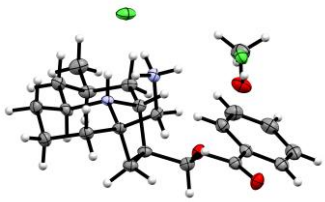


Identification code	tw4
Empirical formula	$C_{22}H_{31}NO_5$
Formula weight	389.48
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	15.3743(10)
b/Å	7.9428(5)
c/Å	17.4278(11)
α/°	90
β/°	104.217(2)
γ/°	90
Volume/Å^3	2063.0(2)
Z	4
ρ_{calc}g/cm^3	1.254
μ/mm^{-1}	0.088
F(000)	840.0
Crystal size/mm^3	0.389 × 0.227 × 0.135
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.822 to 50.142

Index ranges	$-18 \leq h \leq 17, 0 \leq k \leq 9, 0 \leq l \leq 20$
Reflections collected	3643
Independent reflections	3643 [R_{int} = 0.0405, R_{sigma} = 0.0588]
Data/restraints/parameters	3643/0/257
Goodness-of-fit on F^2	1.058
Final R indexes [I>=2σ (I)]	R_1 = 0.0617, wR_2 = 0.1070
Final R indexes [all data]	R_1 = 0.0941, wR_2 = 0.1175
Largest diff. peak/hole / e $Å^{-3}$	0.23/-0.21

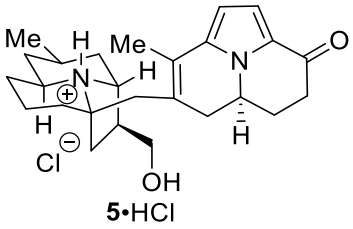


79•2HCl

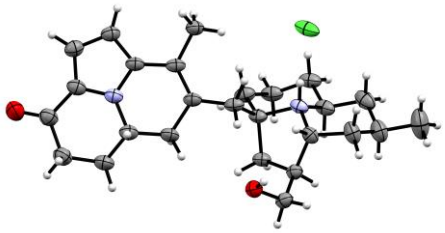


Identification code	0800_lisnyak
Empirical formula	$C_{22}H_{36}Cl_2N_2O_3$
Formula weight	447.43
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	8.0053(3)
b/Å	10.4289(3)
c/Å	14.1059(4)
α/°	90
β/°	97.603(2)
γ/°	90
Volume/$Å^3$	1167.30(6)
Z	2

ρ_{calc}g/cm^3	1.273
μ/mm^{-1}	2.697
F(000)	480.0
Crystal size/mm^3	0.32 × 0.12 × 0.08
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	6.322 to 149.148
Index ranges	-9 ≤ h ≤ 9, -12 ≤ k ≤ 11, -17 ≤ l ≤ 17
Reflections collected	19543
Independent reflections	4556 [R_{int} = 0.0566, R_{sigma} = 0.0525]
Data/restraints/parameters	4556/1/280
Goodness-of-fit on F^2	1.037
Final R indexes [I>=2σ (I)]	R_1 = 0.0374, wR_2 = 0.0815
Final R indexes [all data]	R_1 = 0.0493, wR_2 = 0.0866
Largest diff. peak/hole / e Å^{-3}	0.26/-0.22
Flack parameter	0.058(7)
Hooft Parameter	0.057(8)



5•HCl



Identification code	Vlad_xtal
Empirical formula	$C_{26}H_{37}ClN_2O_2$
Formula weight	445.02
Temperature/K	60.15
Crystal system	monoclinic

Space group	$P2_1$
a/Å	12.737(4)
b/Å	14.735(4)
c/Å	16.398(5)
α/°	90
β/°	107.353(5)
γ/°	90
Volume/Å^3	2937.6(14)
Z	4
ρ_{calc}g/cm^3	1.006
μ/mm^{-1}	0.045
F(000)	960.0
Crystal size/mm^3	0.03 × 0.03 × 0.01
Radiation	synchrotron (λ = 0.41328)
2Θ range for data collection/°	2.208 to 31.908
Index ranges	$-16 \leq h \leq 16$, $-19 \leq k \leq 19$, $-21 \leq l \leq 21$
Reflections collected	124799
Independent reflections	14406 [R_{int} = 0.0547, R_{sigma} = 0.0287]
Data/restraints/parameters	14406/3/575
Goodness-of-fit on F^2	1.079
Final R indexes [I>=2σ (I)]	R_1 = 0.0410, wR_2 = 0.1106
Final R indexes [all data]	R_1 = 0.0450, wR_2 = 0.1128
Largest diff. peak/hole / e Å^{-3}	0.40/-0.42
Flack parameter	0.05(4)

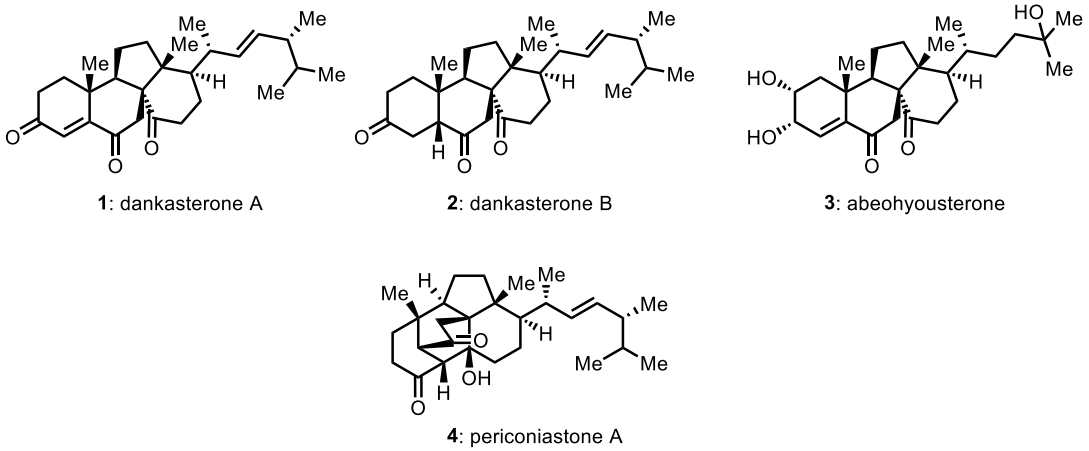
Chapter 3

Total Synthesis of Dankasterone B

3.1. Isolation, Structural Features and Biological Activity of Dankasterone B.

Dankasterone B (**2**) represents a unique cystostatic steroid that was isolated from *Halichondria* sponge-derived fungus *Gymnascella dankaliensis* in 2007 by Numata[1] among with previously known dankasterone A (**1**) (Figure 3.1).[2] Structurally, it contains a very rare 13(14→8)*abeo*-8-ergostane steroid core, that is believed to be a result of a 1,2-migration of the C13–C14 bond to the C8 position.[1,3] Several other 13(14→8)*abeo* steroids were later isolated that share the same core. Among them are abeohyousterone (**3**)[3] and periconiastone A (**4**).[4] All of these natural isolates exhibit biological activities. For example, **1** was found to exhibit significant cytotoxicity (ED_{50} 2.2 μg/mL) in the P-388 lymphocitic leukimia test system in cell culture, and both **1** and **2** showed activity against CT26 (IC_{50} 6.7 μM (**1**) and 8.4 μM (**2**)) and K562 (IC_{50} >20 μM (**1**) and 23.1 μM (**2**)) colorectal cancer cells.[5] Additionally, **3** was found to display bioactivity in HCT-116 cell line (IC_{50} 3.0 μM)[3] and **4** (that is derived directly from **2** by intramolecular aldol reaction) showed significant antibacterial properties against MRSA (4 μg/mL).[4] The structure of **2** was originally determined by NMR spectroscopy, and later confirmed by X-Ray crystallography of a synthetic material.[6]

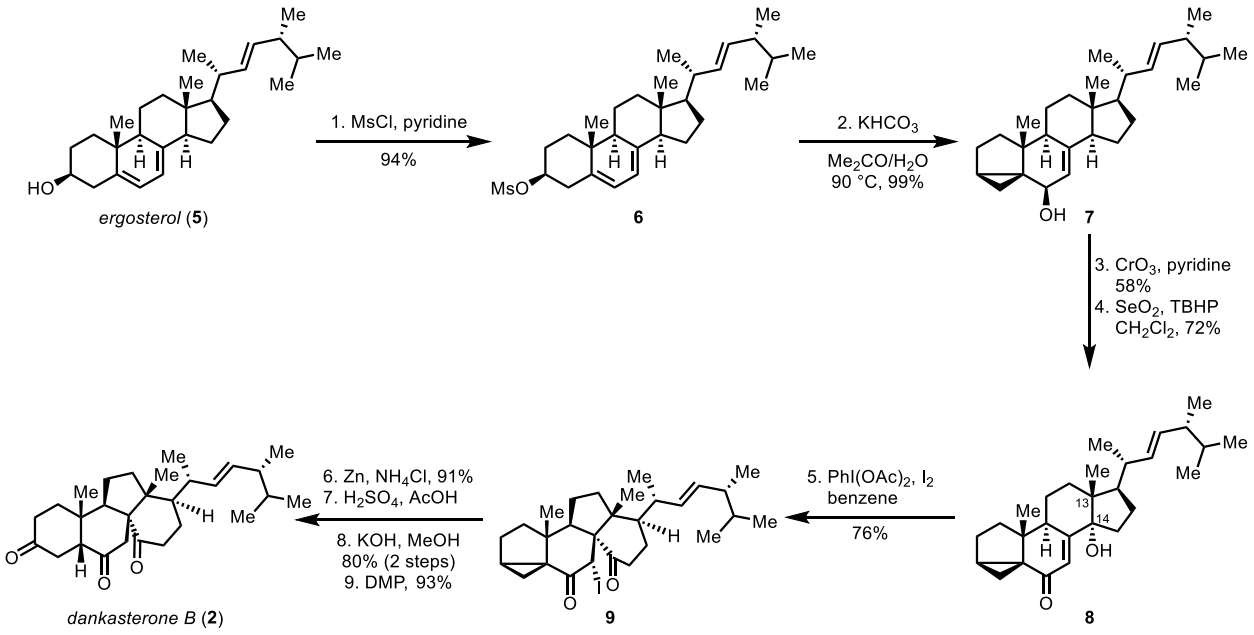
Figure 3.1. Naturally Occurring Compounds with a 13(14→8)*abeo* Steroid Skeleton.



3.2. Previous Syntheses of Dankasterone B.

During our work on total synthesis of dankasterone B (**2**) two outstanding total syntheses were published.[6,7] First synthesis came from Heretsch group,[6] and is by far the shortest total synthesis of this molecule. The synthesis starts from commercially available ergosterol (**5**), that is rapidly converted to **8** by previously established protocol[8] that involves mesylation of the secondary alcohol to afford **6**, aqueous basic treatment to trigger rearrangement to **7**, oxidation to the corresponding enone with CrO_3·pyridine complex, and allylic oxidation under SeO_2/TBHP conditions to afford **8** with 39% yield over 4 steps. Next, in order to initiate the radical cascade to form the required 13(14→8)*abeo* structure, several conditions were screened with $PhI(OAc)_2/I_2$ system being the most successful, affording **9** in a good 76% yield. In this reaction $PhI(OAc)_2$ generates 14-alkoxy radical, that undergoes β-scission of C13-C14 bond, followed by attack of the newly generated C13-centered radical on enone, giving the α-keto radical that is further quenched

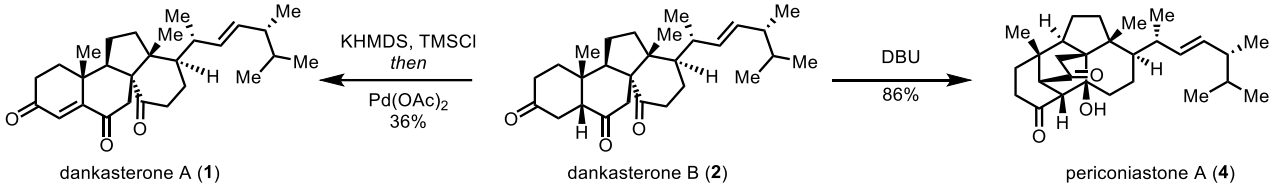
Scheme 3.1. Total Synthesis of Dankasterone B by Heretsch.



by I_2, giving **9**. The use of I_2 as a quencher is essential for this reaction, otherwise the cascade continues further via Dowd−Beckwith rearrangement.[9] Next, the α-iodo functionality is removed under Zn/NH_4Cl conditions (91% yield), followed by opening of the resultant *i*-steroid under strong acidic conditions (H_2SO_4 in AcOH), saponification (KOH) of the newly formed acylated alcohol (80% over 2 steps), and finally, oxidation of the recently installed 3-hydroxy group with Dess-Martin periodinane (93% yield) completes the synthesis of **2** in 9 steps.

Additionally, Heretsch and co-workers demonstrated that both dankasterone A (**1**) and periconiastone A (**4**) could be accessed from **2** in one step (Scheme 3.2).

Scheme 3.2. Syntheses of 1 and 4 from 2.

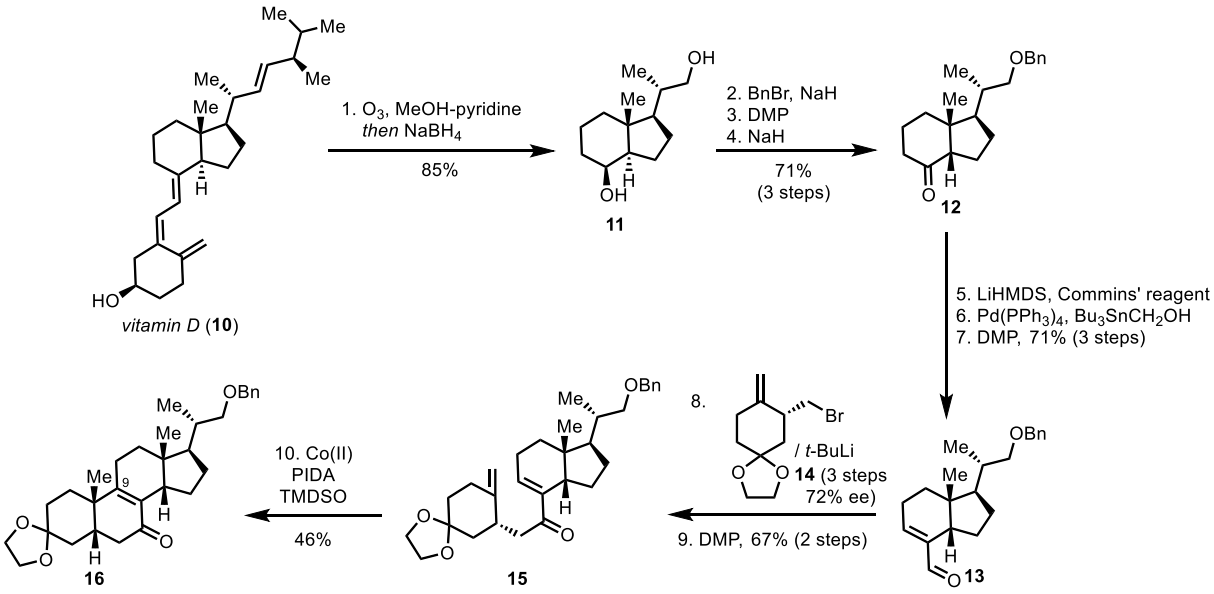


The second synthesis of dankasterone B was reported by the Ma group.[7] Similar to Heretsch, Ma starts his synthesis with another commercially available steroid – vitamin D (**10**) (Scheme 3.3). Following literature protocol,[10] **10** undergoes ozonolysis with a reductive ($NaBH_4$) workup to afford **11** (85% yield). Benzylation of the primary alcohol, followed by oxidation of the secondary alcohol with Dess-Martin periodinane to the corresponding ketone, and isomerization of this ketone to a *cis*-5/6-fused system with NaH, then delivers **12** (71% over 3 steps). The latter isomerization was found to be essential for the subsequent cycloisomerization step.

Ketone **12** was then converted into a vinyl triflate (LiHMDS/Commins' reagent), that was subjected to homologation *via* Stille coupling[11] with Bu_3SnCH_2OH, followed by oxidation of the

resulting primary alcohol with Dess-Martin periodinane, giving enal **13** in 71% yield over 3 steps. Lithiation of coupling partner **14**was followed by the addition of **13,** and a second DMP oxidation to give rise to **15** (67% over 2 steps). Bromide **14** in turn was prepared by L-threonine catalyzed asymmetric α-hydroxyformylation of 1,4-dioxaspiro[4.5]decan-8-one with aqueous formaldehyde[12] (34% yield, 72% *ee*), followed by both a Wittig olefination (with PPh_3CH_2Br) and Appel reaction (PPh_3, CBr_4). For the next step, in order to forge the key *cis*-decalin core, Ma and co-workers performed a Co(II)-catalyzed cycloisomerization[13] to form enone **16** in 46% yield. Of note, the use of MHAT conditions[14] for this reaction provided a mixture of saturated ketone isomers with the major diastereomer having the incorrect stereochemistry at C9 (Scheme 3.3). The use of a *trans*-5/6-fused analogue of **15** under MHAT conditions gave solely the reduction of both double bonds.

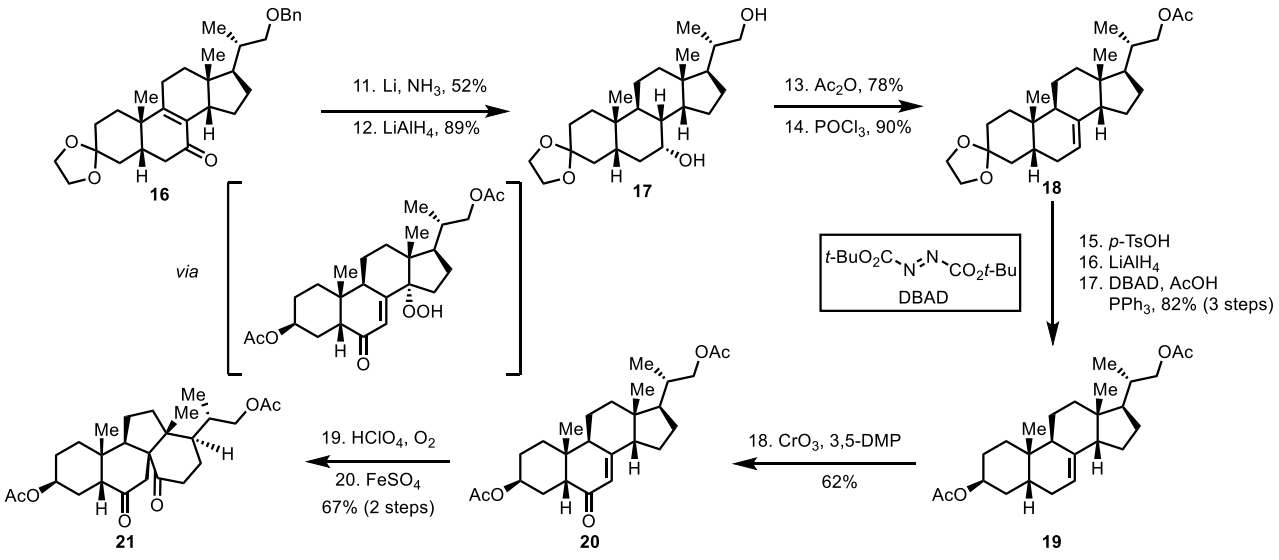
Scheme 3.3. Synthesis of *cis*-Decalin 16 by Ma group.



Next, enone **16** underwent Li/NH_3-promoted *anti*-reduction of the endocyclic double bond[15] and concomitant debenzylation, followed by $LiAlH_4$-mediated diastereoselective

reduction of the ketone moiety to afford the alcohol **17** (46% over 2 steps) (Scheme 3.4). Further, acetylation of the primary alcohol followed by $POCl_3$-promoted dehydration delivered **18** (70% over 2 steps). Deprotection of the ketal under acidic conditions (*p*-TsOH), diastereoselective reduction of the resulting ketone with $LiAlH_4$ and subsequent Mitsunobu reaction with AcOH, PPh_3 and di-tert-butyl azodicarboxylate produced acetate **19** (82% over 3 steps). The use of a Mitsunobu reaction for the acetylation was necessary in this instance since the isomeric acetate wasn't prone to saponification at a later stage. The allylic oxidation of **19** was then performed using CrO_3·3,5-DMP complex[16],affording enone **20** in a 62% yield. Next, C-H oxygenation of **20** at C14 was performed using conditions reported by Danieli group,[17] and the resulting hydroperoxide was subjected to an $FeSO_4$-promoted radical rearrangement similar to the one reported by Heretsch, to give the desired spirocycle **21** (67% over 2 steps).

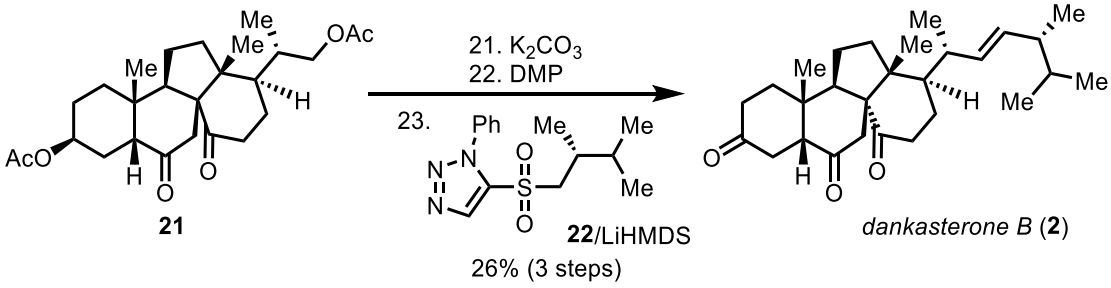
Scheme 3.4. Synthesis of Spirocycle 21 by Ma group.



Next, saponification of the acetate group of **21**, followed by a Dess-Martin periodinane promoted oxidation of the resulting alcohol to the aldehyde, and olefination under Julia-Kocienski

conditions with **22** (26% over 3 steps) finally delivered dankasterone B (**2**) in 23 steps total (Scheme 3.5).

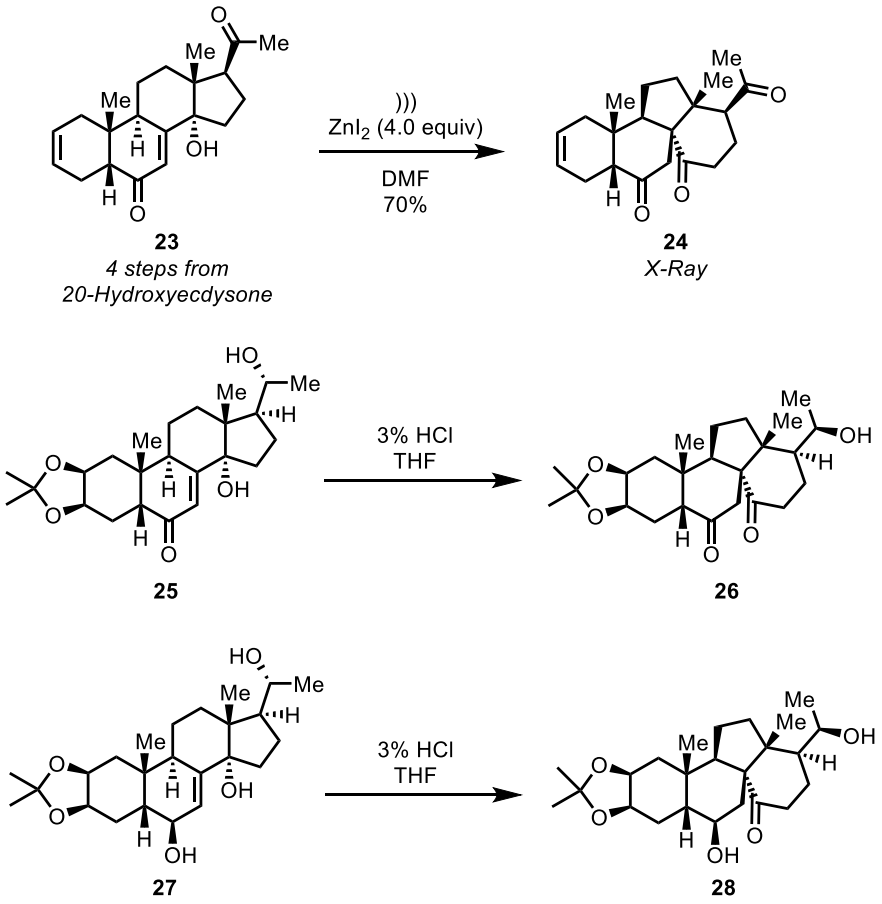
Scheme 3.5. Completion of the Total Synthesis of 2 by Ma group.



3.3. Other Approaches to Construction of 13(14→8)*abeo* Steroid Skeleton.

In addition to the radical rearrangement approach for the construction of the 13(14→8)*abeo* steroid skeleton outlined above, there are two other reports of construction of the same steroid core that do not rely on the intermediacy of the C14-alkoxy radical. Instead, Savchenko has reported the biomimetic rearrangement of compounds **23**, **25** and **27** to **24**, **26** and **28** respectively either via ZnI_2/sonication-promoted semipinacol rearrangement[18] or Bronsted acid promoted semipinacol rearrangement (Scheme 3.6).[19,20]

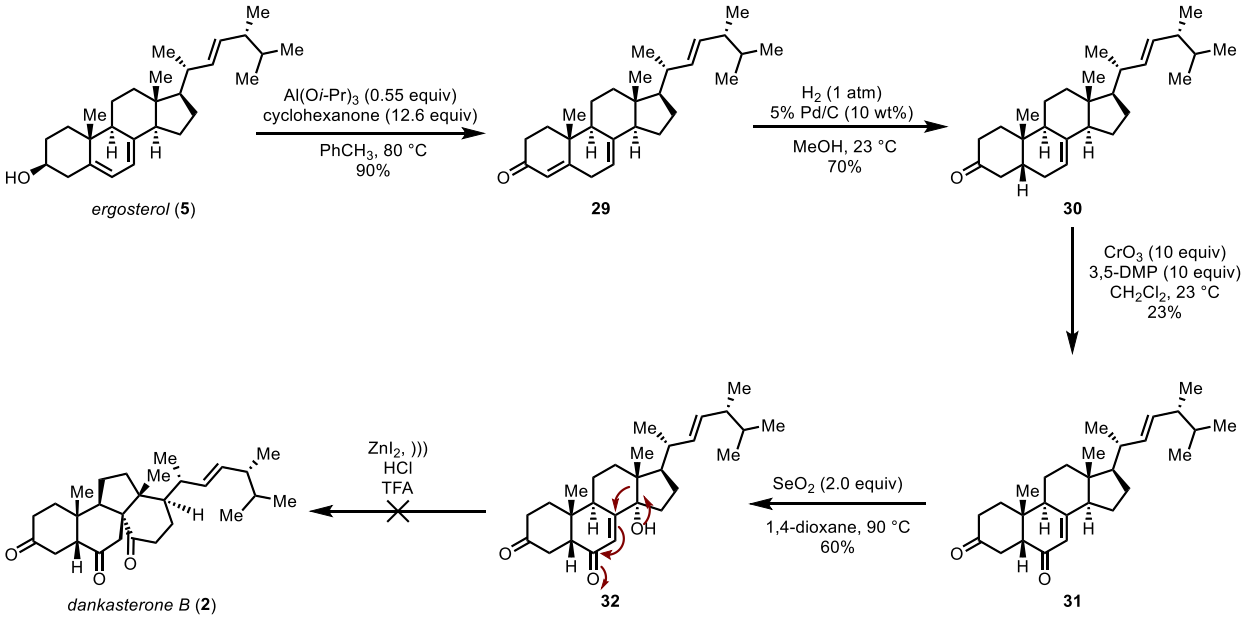
Scheme 3.6. Savchenko's Reported Semipinacol-type Rearrangement.



3.4. Attempted Semipinacol Rearrangement toward Synthesis of Dankasterone B.

In order to test whether the same biomimetic[1,3] rearrangement in the synthesis of dankasterone B might be accomplished using conditions reported by Savchenko, we rapidly prepared the intermediate **32** (Scheme 3.7). The synthesis began from ergosterol (**5**), that was first oxidized and rearranged to a more thermodynamically stable enone **29** (90% yield).[21] Further diastereoselective partial hydrogenation of **29** with Pd/C in MeOH delivered *cis*-fused ketone **30** (70% yield). Allylic oxidation of ketone **30** to enone **31** was then accomplished with CrO_3·3,5-DMP complex[16] in 23% yield (unoptimized). A subsequent allylic oxidation of the C14-position of **31** was accomplished with SeO_2 in 1,4-dioxane[22] giving allylic alcohol **32**. Unfortunately, all attempts to induce semipinacol rearrangement of **32** under the conditions reported by Savchenko (ZnI_2/sonication, 3% HCl in THF)[18,19] or others[23] either gave no reaction or led to gradual decomposition of starting material, thus the route was abandoned.

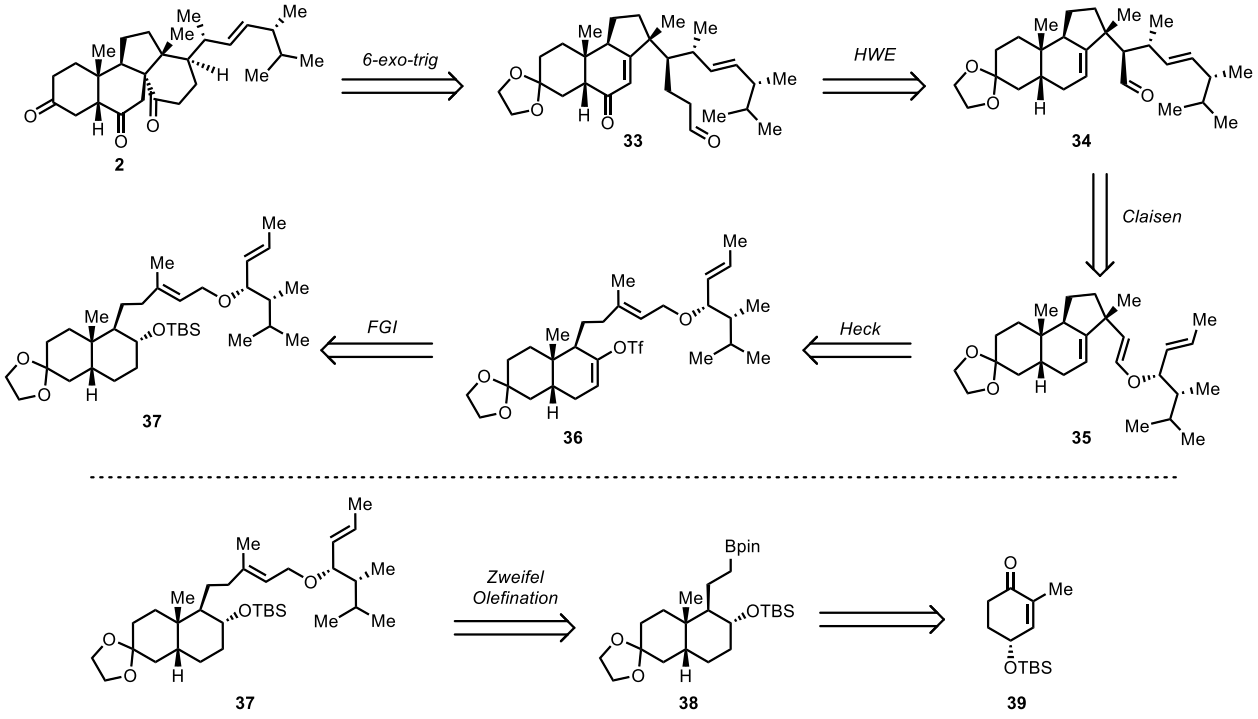
Scheme 3.7. Attempted Semipinacol Rearrangement of 32.



3.5. Retrosynthetic Analysis of Dankasterone B.

The initial retrosynthetic analysis towards this family of molecules was developed by my colleague, Dr. Boilevin, who also partially executed the route towards dankasterone A (**1**). For reasons that will be discussed later in this chapter, we ultimately switched targets to dankasterone B (**2**). The modified retrosynthesis for dankasterone B (**2**) is thus presented in Scheme 3.8 . First, we envisioned that C8-C14 could be disconnected by a 6-*exo*-*trig* cyclization affording intermediate aldehyde **33**. By homologation and allylic oxidation, this intermediate can be traced back to aldehyde **34**, which is in turn a product of a thermal Claisen rearrangement of enol ether **35**. That enol ether can be produced from a diastereoselective Heck reaction[24] of vinyl triflate **36**. After some trivial functional group interconversions **36** can be easily traced to allyl ether **37**.

Scheme 3.8. Retrosynthetic Analysis of Dankasterone B (2).

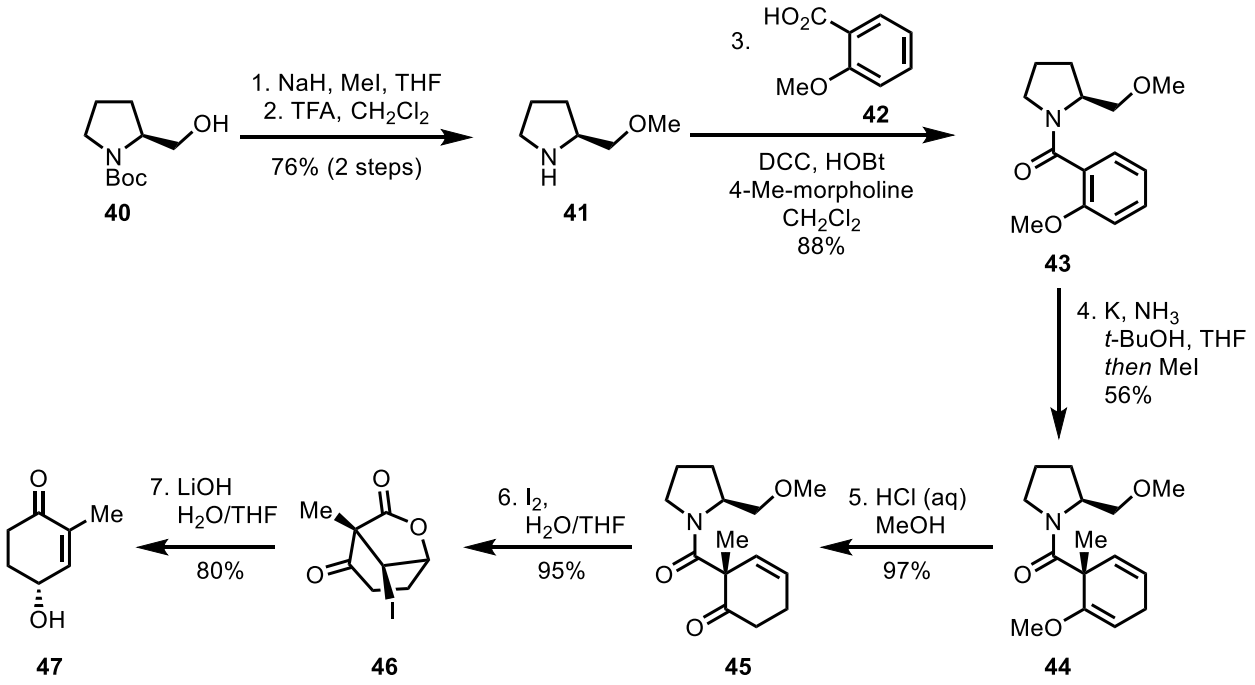


Finally, **37** can be obtained from borane **38** via Zweifel olefination,[25] and the decalin core of the latter can be constructed by analogy to literature procedure, tracing back to enone **39**.[26]

3.6. Synthesis of the Cyclic Enone Starting Material.

The preparation of the cyclic enone **47** has been reported in the literature (Scheme 3.9).[27] It starts with a commercially available *N*-Boc prolinol **40**, that is used as a chiral auxiliary for the subsequent methylation of the enolate. First, **40** undergoes methylation of the alcohol functional group, followed by Boc-deprotection to afford OMe-prolinol **41** (76% over 2 steps). After amide coupling with 2-methoxy benzoic acid **42**, the resulting benzamide **43** then subjected to a Birch reduction followed by methylation with MeI to afford methyl enol ether **44** in a 56% yield. After

Scheme 3.9. Reported Synthesis of 47.

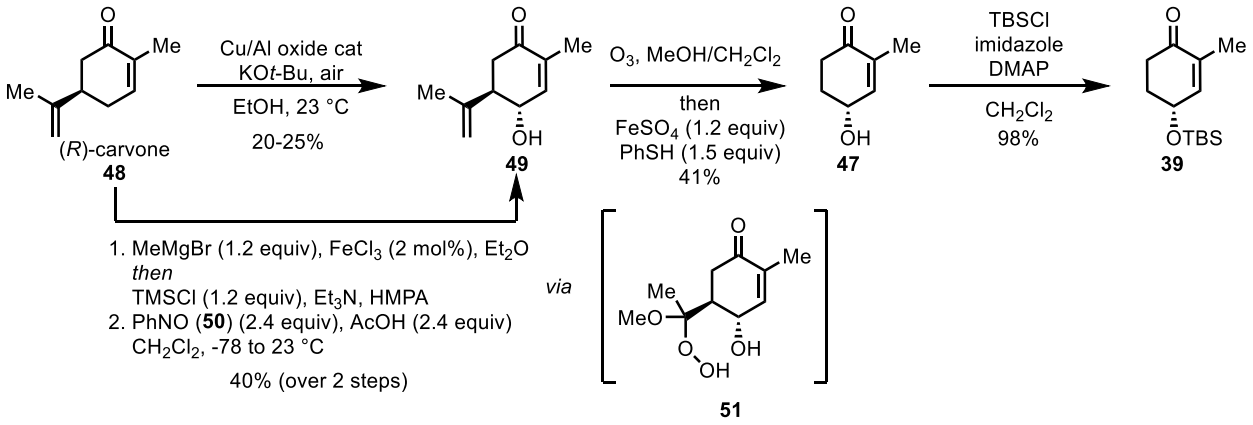


hydrolysis of the enol ether, ketone **45** could be isolated in almost quantitative yield. Subsequent iodolactonization results in the cleavage of the chiral auxiliary to afford iodolactone **46** (95%

yield). Fragmentation of **46** under basic conditions (LiOH in aqueous THF) then gives cyclic enone **47** (80% yield).

Despite the high overall yield of this route, we desired a more efficient synthesis of this valuable building block (**47**). Due to the structural resemblance between **47** and (*R*)-carvone (**48)**, we postulated that we could synthesize **47** directly from **48**. Following the literature procedure,[28] (*R*)-carvone **48** underwent a one step γ-hydroxylation to 4-hydroxy carvone **49** by using a Cu/Al oxide catalyst and air as an oxidant (Scheme 3.10). Despite the reported 42% yield[28,29], in our hands this reaction gave inconsistent 20-25% yield over several trials. A better yielding procedure involves a two step oxidation sequence, beginning with the generation of the thermodynamic enolate of **48** under reported conditions,[30] followed by vinylogous *O*-nitroso Mukaiyama aldol reaction with nitrosobenzene (**50**) (40% over 2 steps).[31] With **49** in hand, we then applied a reported 2 step one-pot protocol for the hydrodeisopropelynation.[32] Thus, after exposure of **49** to 1 equivalent of O_3 at –78 °C in $MeOH/CH_2Cl_2$ mixture, the resulting

Scheme 3.10. Developed Short Synthesis of 47.

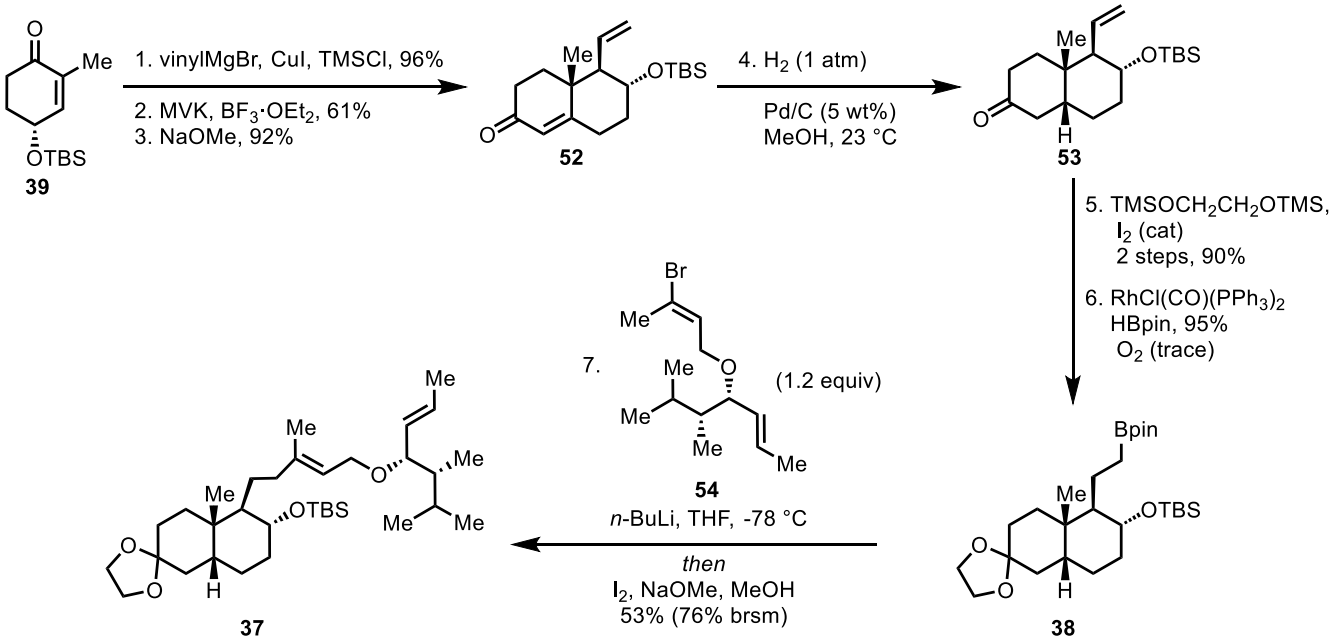


peroxyintermediate **51** then undergoes $FeSO_4$-promoted fragmentation, generating **47** after quenching the resulting secondary radical with PhSH. The relatively low yield (41%) in this reaction comes from the electron rich nature of the enone double bond of **49**, which also undergoes partial ozonolysis. Following TBS protection of **47** under TBSCl/imidazole/4-DMAP conditions, **39** can be isolated in a virtually quantitative yield.

3.7. Synthesis of 6-*exo-trig* Cyclization Precursor.

With sufficient access to **39** secured, we then proceeded to construct the decalin core.[26] First, **39** underwent Cu^I-promoted conjugate addition of vinyl magnesium bromideand the resulting enolate was trapped with TMSCl. A subsequent $BF_3{\cdot}OEt_2$ catalyzed Michael addition with methyl vinyl ketone andNaOMe-promoted annulation smoothly affords **52** (54% over 3 steps) (Scheme 3.11). Then, a diastereoselective partial hydrogenation with 5 wt% Pd/C in MeOH yielded *cis*-decalin **53**. After acetal protection of the ketone with $TMSOCH_2CH_2OTMS$

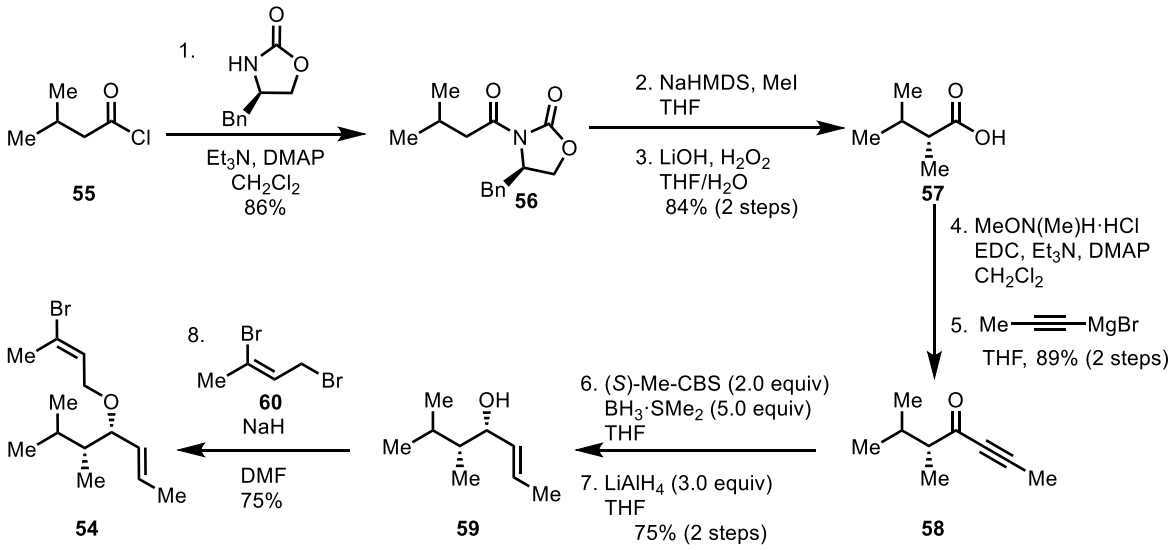
Scheme 3.11. Synthesis of Diallyl Ether 37.



and catalytic I_2,[32] followed by Rh(I)-catalyzed hydroboration with HBpin, the desired borane **38** could be isolated in 86% yield over 3 steps. Next, Zweifel olefination[25] was performed with vinyl lithium prepared *in situ* from **54** and *n*-BuLi to afford **37** (53% yield, 76% brsm).

The synthesis of vinyl bromide **54**was accomplished by Dr. Boilevin in 8 steps starting from isovaleryl chloride **55** (Scheme 3.12). First, **55** was coupled with Evans auxiliary ((*R*)-4-benzyloxazolidin-2-one) to produce **56**, followed by diastereoselective α-methylation with MeI of the enolate formed by treating **56** with NaHMDS. The resulting diastereomeric amide (*dr* > 98:2) was purified by column chromatography, and the chiral auxiliary was cleaved by treatment with $LiOH/H_2O_2$ to afford carboxylic acid **54** (84% over 2 steps). After forming the Weinreb amide and

Scheme 3.12. Synthesis of Vinyl Bromide 54.

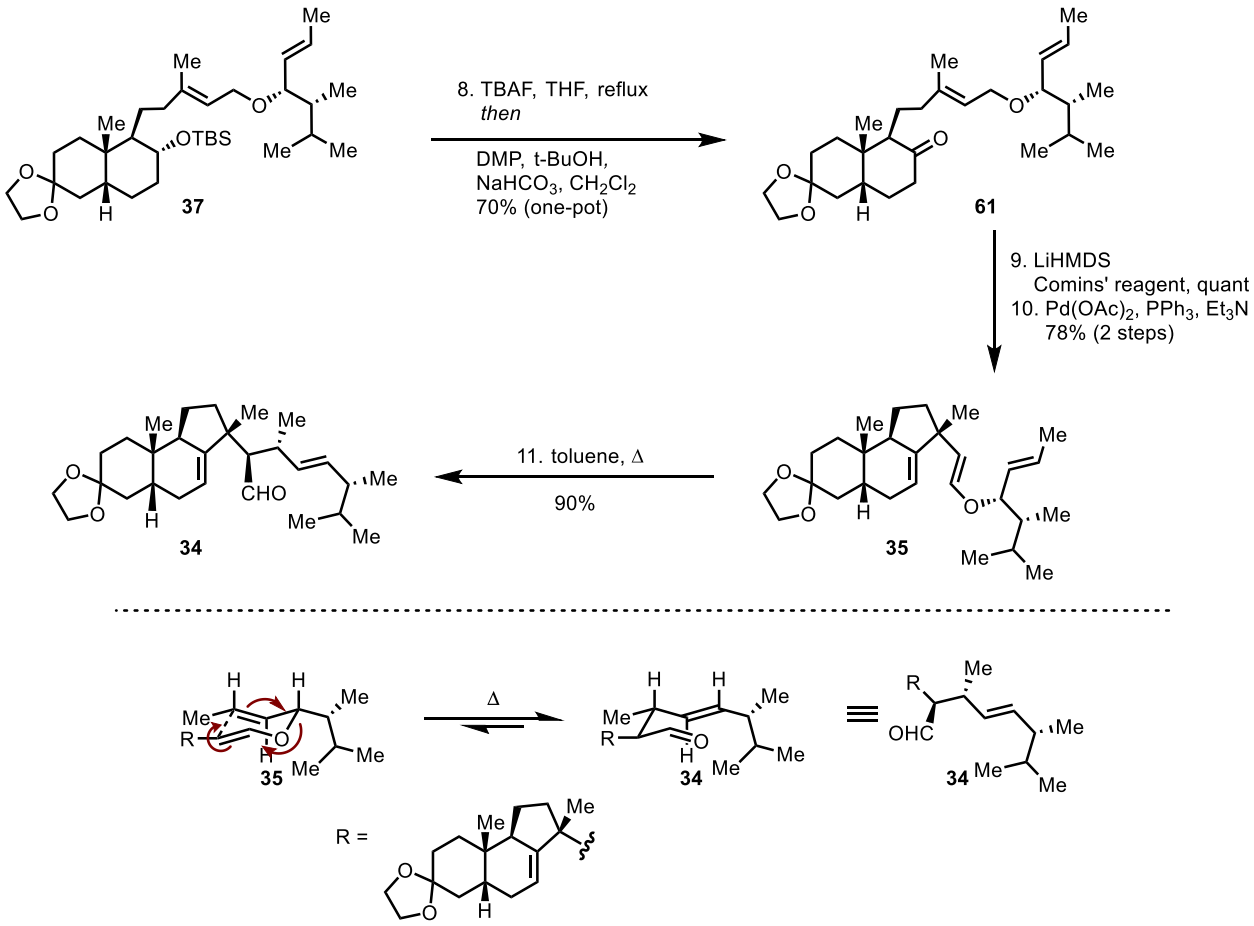


subsequent addition of 1-propynylmagnesium bromide,[33] ynone **58** was isolated in a good overall yield (89% over 2 steps). Next, (*S*)-Me-CBS promoted asymmetric reduction of the enone was performed,[34] and the resulting propargyl alcohol was reduced to *E*-allylic alcohol **59** with $LiAlH_4$

in 75% yield over 2 steps. Finally, after alkylation of **59** with **60**[35] the ether **54** could obtained in 75% isolated yield.

Next, the Zweifel olefination product **37** was converted to enol ether **35** in a 3 step sequence (Scheme 3.13). First, the TBS group was removed by treatment with TBAF in refluxing THF, thenaddition of Dess-Martin periodinane allowed for a one-pot deprotection/oxidation to afford **61** (70% yield). Then, the kinetic enolate formed by deprotonation with LiHMDS was trapped with Commins' reagent to gave the intermediate vinyl triflate. The subsequent Heck reaction[24] was performed with a $Pd(OAc)_2/PPh_3$ catalytic system to give enol ether **35** in 78% over 2 steps.

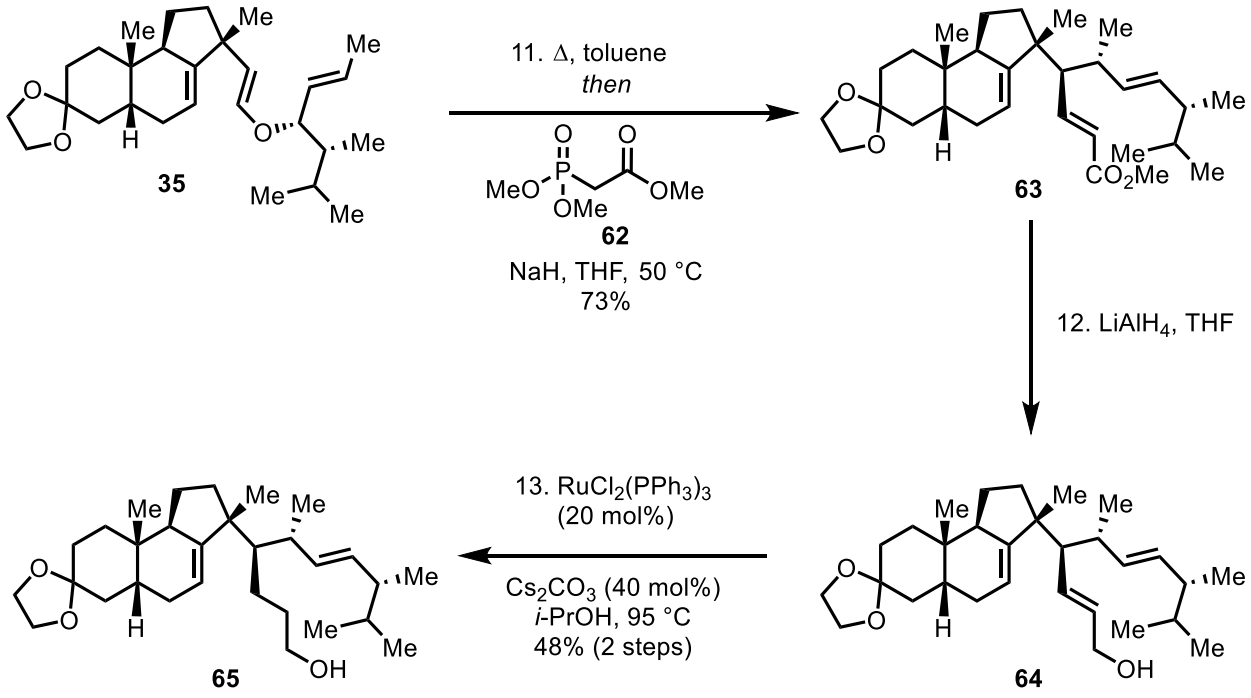
Scheme 3.13. Synthesis of the Aldehyde 34 and Transition State of the Claisen Rearrangement.



Heating **35** in toluene (130 °C) promoted the desired Claisen rearrangement and afforded the aldehyde **34** in 90% isolated yield. The desired stereochemical outcome of the thermal Claisen rearrangement could be explained by a chair-like transition state of the rearrangement (bottom of Scheme 3.13), and was later confirmed by completing the total synthesis of **2**.

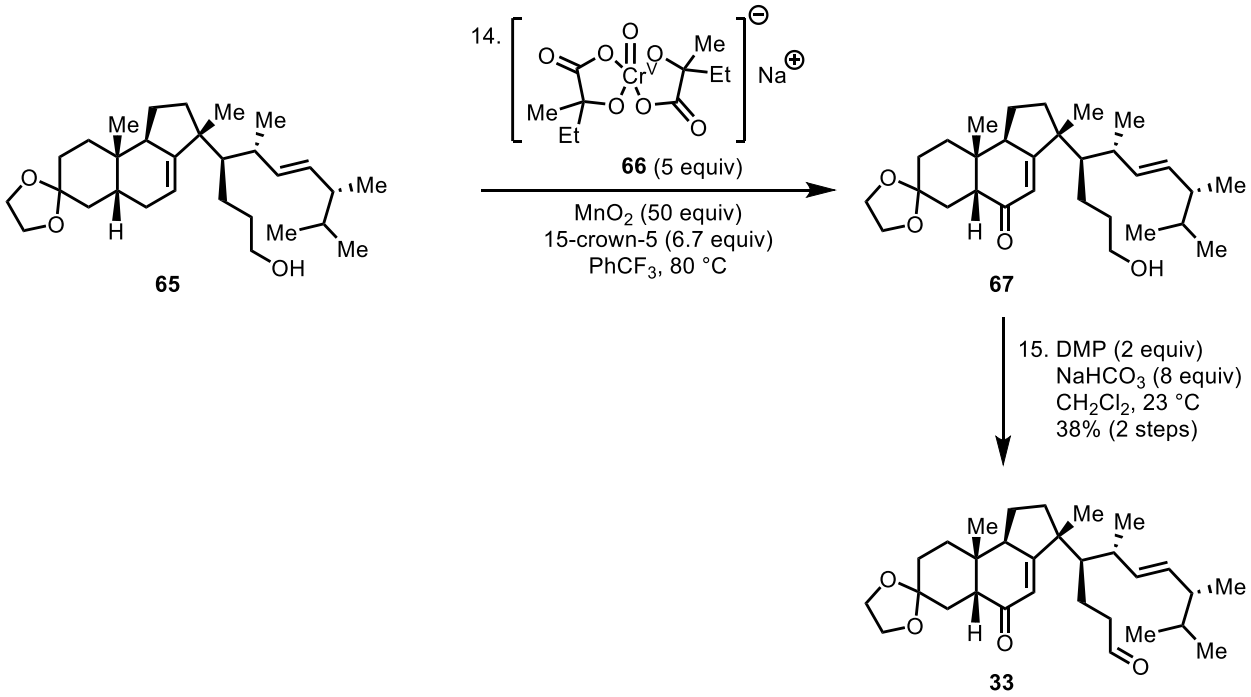
The subsequent homologation of the aldehyde **34** was accomplished by performing a HWE-reaction (that was combined in a one-pot procedure with the Claisen rearrangement) with **62** and NaH. Thus, **63** could be obtained from **35** directly in 73% yield (Scheme 3.14). Treatment of **63** with $LiAlH_4$ gives the1,2-reduction product **64**, that was further subjected to allylic reduction with a Ru(II) catalyst in *i*-PrOH to produce **65** (48% over 2 steps).[36]

Scheme 3.14. Synthesis of the Alcohol 65.



Finally, the allylic oxidation of the trisubstituted endocyclic alkene was accomplished with a Cr(V) (**66**)/MnO_2 system affording enone **67** (Scheme 3.15), which was further oxidized with Dess-Martin periodinane to cyclization precursor **33** (38% over 2 steps).

Scheme 3.15. Synthesis of the Cyclization Precursor 33.

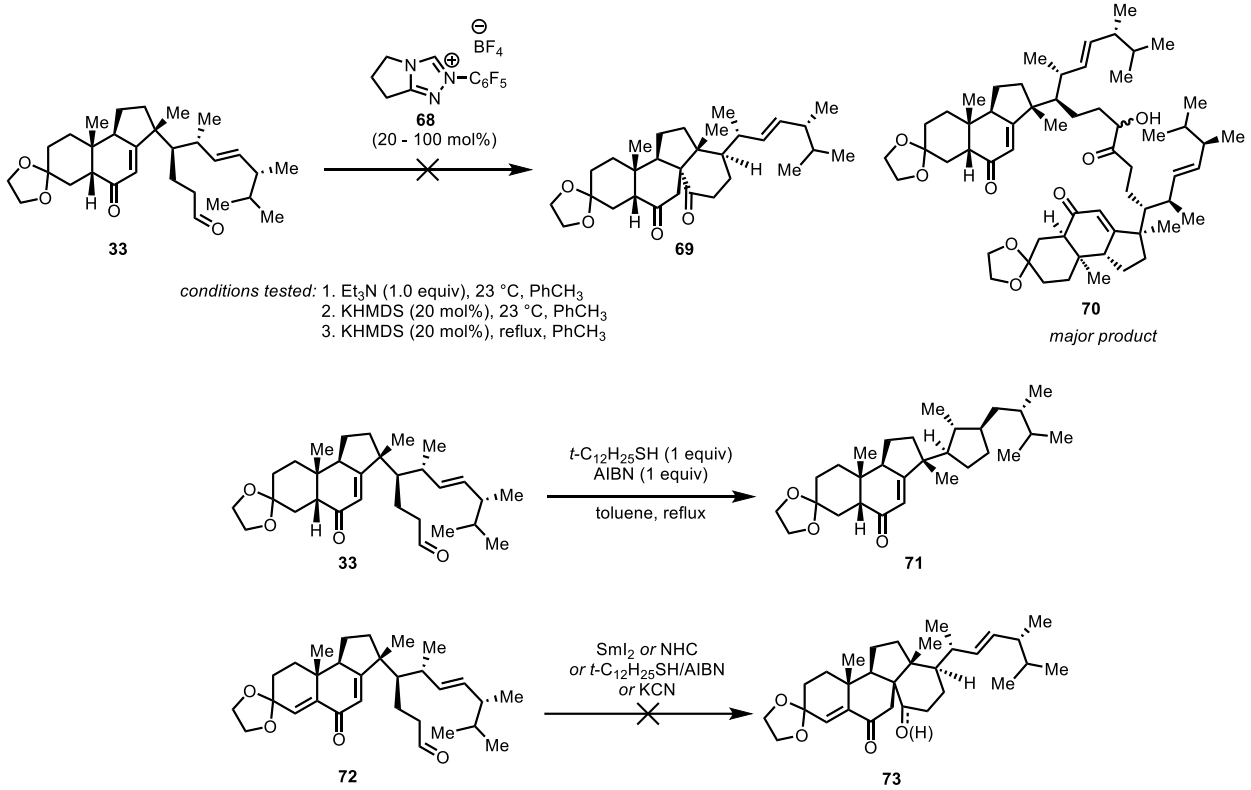


3.8. Studies of 6-*exo-trig* Cyclization.

With the cyclization precursor **33** one key step away from the construction of the desired 13(14→8)*abeo* skeleton, we tested several conditions to promote this reaction. Our first strategy to forge the C14-C8 bond and produce the 1,4-diketone was to attempt an NHC-promoted intramolecular Stetter reaction.[38] Several conditions were tested with one of the most efficient NHC-catalysts **68** (Scheme 3.16). Unfortunately, none of them promoted the desired 6-*exo-trig* cyclization: no reaction was observed with **68**/Et3N, and the dimeric hydroxyketone **70** was isolated with **68**/KHMDS. Alternatively, subjecting compound **33** to acyl radical cyclization conditions (t-$C_{12}H_{25}SH$, AIBN)[39] resulted in decarbonylation and subsequent 5-*exo-trig*

cyclization to form **71** as a single diastereomer.[8b] The Δ^4-analogue of **33** (**72**) that was first prepared by Dr. Boilevin, showed similar reactivity in the NHC/KCN-catalyzed Stetter reaction, but gave no reaction in a thiol promoted acyl radical cyclization. Moreover, any attempt to invoke **72** via SmI_2-mediated reductive cyclization also failed: either reduction of aldehyde/enone was observed or decomposition occurred (at higher temperatures) (Scheme 3.16).

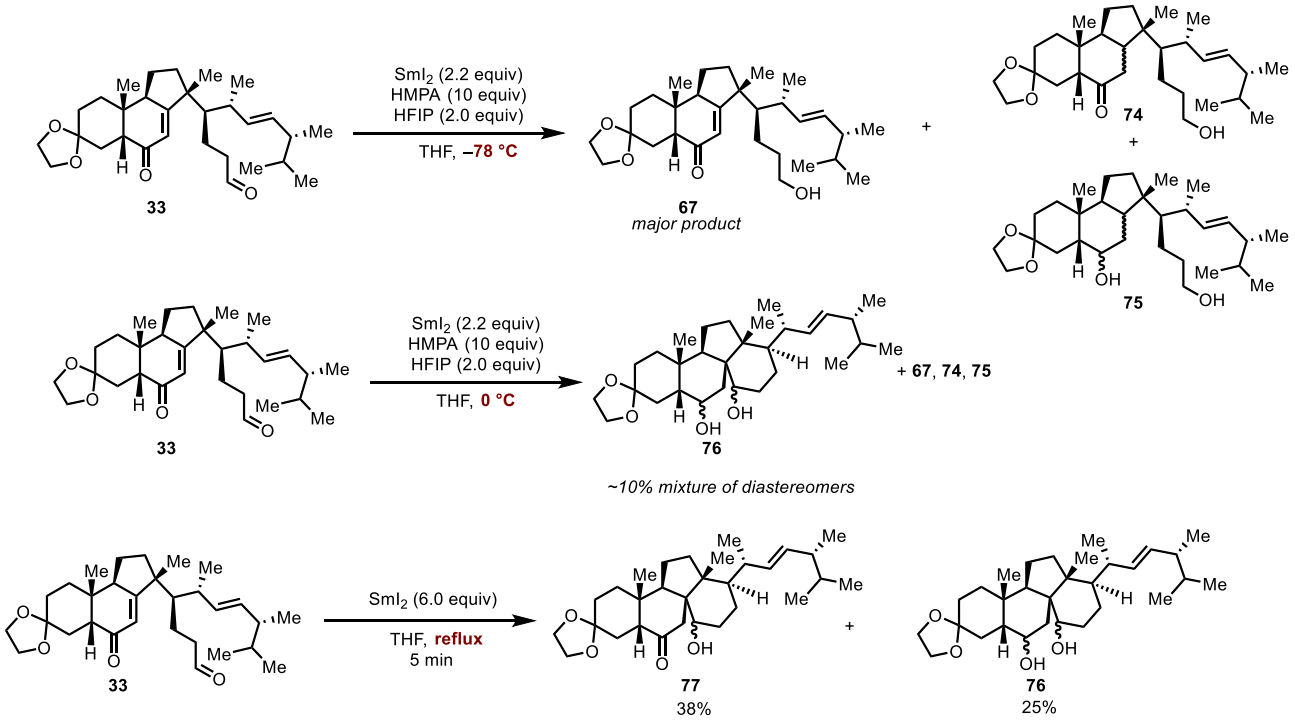
Scheme 3.16. Initial Exploration of 6-*exo-trig* Cyclization.



Remarkably, when the SmI_2-mediated reductive cyclization was attempted on **33** we did observe the formation of the desired 6-*exo-trig* cyclization product. When the reaction was conducted at –78 °C with HMPA/HFIP,[40] only reduction products (**67**, **74** and **75**) were isolated (Scheme 3.17). When we raised the temperature of the same reaction (without additives) to 0 °C, we observed <10% yield of what seemed to be the cyclization product **76,** alongside the previously

identified **67**, **74** and **75**. Encouraged by this result, we then performed the reaction at reflux,[41] affording cyclization products **77** (38%) and **76** (25%) as major products, with the remainder of the material isolated as the same reduction products outlined above.

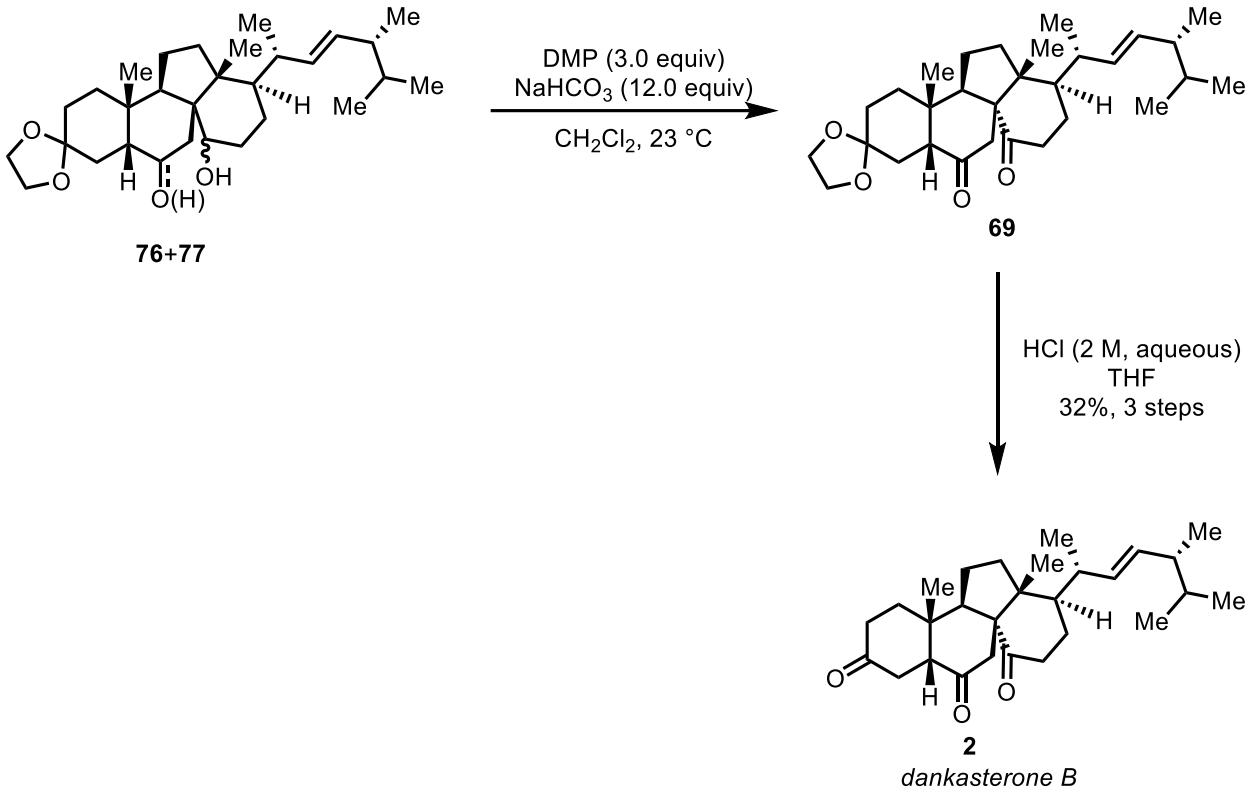
Scheme 3.17. SmI_2-mediated 6-*exo*-*trig* Cyclization.



3.9. Completion of the Total Synthesis of Dankasterone B.

With the route to **77**/**76** now established, the crude mixture of alcohols present after the SmI_2 cyclization reaction was then subjected to a Dess-Martin periodinane mediated oxidation to afford **69** (Scheme 3.18). Finally, acetal deprotection with aqueous HCl in THF afforded purification **2** in 32% yield over 3 steps (after PLC purification), thus completing the total synthesis of dankasterone B as well as a formal total syntheses of both dankasterone A (**1**) and periconiastone A (**4**).

Scheme 3.18. Completion of the Total Synthesis of Dankasterone B.



3.10. Conclusion.

Ultimately, we have successfully accomplished a 20 step total synthesis of a unique, biologically active, 13(14→8)*abeo* steroid dankasterone B as well as the formal total syntheses of dankasterone A and periconiastone A, starting from commercially available (*R*)-carvone using convergent strategy. Our synthesis combines several unique elements including the Zweifel olefination, diastereospecific intramolecular Heck reaction, diastereoselective Claisen rearrangement to install the ergosterol sidechain and a late-stage SmI_2-promoted 6-*exo*-*trig* cyclization. We hope that our synthesis will serve as an inspiration for future efforts towards the total synthesis of similar 13(14→8)*abeo* steroids.

3.11. Experimental Details.

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), diethyl ether (Et2O), and dichloromethane (CH2Cl2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reaction temperatures correspond to the external temperature of the flask, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent or aqueous solution of potassium permanganate and sodium bicarbonate and heat as a developing agent. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Deactivated silica gel was prepared by stirring the commercial silica gel in 2% Et3N solution in EtOAc for 2 h, followed by repetitive washings with EtOAc and then hexanes. Preparative thin-layer chromatography separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker 400 and 500 MHz instruments and calibrated using residual solvent as an internal reference [for $CDCl_3$: ^{1}H, δ 7.26 ppm and ^{13}C, δ 77.16 ppm], unless otherwise noted. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet. IR spectra were recorded on a Nicolet iS5 FT-IR spectrometer using neat thin film technique. High-resolution mass spectra (HRMS) were recorded on Agilent 6244 Tof-MS using ESI (Electrospray Ionization) at the University of Chicago Mass Spectroscopy Core Facility.

Enone 39. To an oven-dried, 1 L round bottom flask equipped with a magnetic stir bar was added **49**[28] (7.00 g, 42.1 mmol, 1.0 equiv) followed by a mixture of CH_2Cl_2 and MeOH (1:1 (v/v), 600 mL). The resulting solution was cooled to –78 °C using acetone-dry ice bath under N_2 atmosphere. Once cooled, O_3 (30%) was bubbled through the stirring solution carefully via the gas dispersion tube. The reaction was monitored by TLC (hexanes/EtOAc = 1:1) every 10 minutes to ensure that only 1 equiv of O_3 is consumed. Upon completion, N_2 was bubbled through the solution for 15 minutes, followed by a slow (~20 min) addition of PhSH (6.40 mL, 7.00 g, 63.2 mmol, 1.5 equiv) in MeOH (65 mL). To the mixture was then added $FeSO_4 \cdot 7H_2O$ (14.05 g, 50.5 mmol, 1.2 equiv) in one portion, and the resulting solution was left to slowly warm up to 23 °C over 10 h. Upon completion, the reaction was quenched by the addition of brine (300 mL). The resultant mixture was transferred to a separatory funnel containing CH_2Cl_2 (300 mL). The aqueous layer was separated and additionally extracted with CH_2Cl_2 (3 x 300 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4), filtered, and concentrated. The resultant crude product was then purified by flash column chromatography (silica gel, hexanes/EtOAc, 1:1→1:2) to afford **47** (2.21 g, 41%) as a yellow oil. All spectroscopic data matched that reported in Ref. 3.

Next, to a stirred solution of **47** (2.21 g, 17.4 mmol, 1.0 equiv) in CH_2Cl_2 (100 mL) were sequentially added *i*-Pr_2EtN (11.40 mL, 8.42 g, 65.3 mmol, 3.8 equiv), DMAP (0.64 g, 17.8 mmol, 0.30 equiv) and TBSCl (7.87 g, 52.2 mmol, 3.0 equiv) at 0 °C. The reaction mixture was then warmed to 23 °C and stirred at this temperature for 12 h. Upon reaction completion, H_2O (100 mL) was added and the reaction mixture was stirred vigorously for 15 minutes. The mixture was transferred to a separatory funnel, the layers were separated and the aqueous layer was additionally extracted with CH_2Cl_2 (100 mL). The combined organic layers were dried (Na_2SO_4), filtered and

concentrated. The residue was purified by flash column chromatography (silica gel, hexanes/EtOAc 95:5) to give **39** (4.13 g, 98%) as a colorless oil. **39**: R_f = 0.27 (hexanes/EtOAc 95:5, UV, $KMnO_4$); $[a]_D^{25}$= +65.76 ° (*c* = 1.00, $CHCl_3$); IR (film) n_{max} 2955, 2929, 2886, 2857, 1683, 1077, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.59 (s, 1 H), 4.56–4.40 (m, 1 H), 2.58 (dt, *J* = 16.7, 4.5 Hz, 1 H), 2.32 (ddd, *J* = 17.0, 13.0, 4.7 Hz, 1 H), 2.22–2.15 (m, 1 H), 2.00–1.91 (m, 1 H), 0.92 (s, 9 H), 0.16–0.10 (m, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.3, 149.1, 135.2, 67.5, 35.7, 33.5, 26.0, 18.3, 15.8, -4.4, -4.6; HRMS (ESI) calcd for $C_{13}H_{25}O_2Si^+$ [M + H^+] 241.1618, found 241.1618.

Bicyclic enone 52. To a flame-dried LiCl (174 mg, 4.10 mmol, 0.2 equiv) in a 250 mL round-bottom flask was added CuI (391 mg, 2.05 mmol, 0.1 equiv) and the flask was back-filled with Ar and sealed. Then, THF (129 mL) was added and the mixture was stirred at 23 °C until a clear light green solution is obtained (typically 15 min). The mixture was cooled to –40 °C and a solution of **39** (4.93 g, 20.51 mmol, 1.0 equiv) in THF (28 mL) was then added, followed by TMSCl (2.86 mL, 2.45 g, 22.56 mmol, 1.1 equiv). After stirring for 10 min, vinyl magnesium bromide (1 M in THF) (24.6 mL, 24.6 mmol, 1.2 equiv) was added dropwise to the reaction mixture which was further stirred at –40 °C for 30 min. The reaction mixture was then quenched by addition of saturated aqueous solution of NH_4Cl (70 mL), warmed to 23 °C and transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give the intermediate enol ether that was used in the following step without further purification. The previously prepared enol ether was dissolved in CH_2Cl_2 (103 mL), and the solution was cooled to –78 °C. To the resulting mixture were sequentially added $MeNO_2$ (3.30 mL, 3.78 g, 61.53 mmol, 3.0 equiv), *i*-PrOH (4.70 mL, 3.48 g, 61.53 mmol, 3.0 equiv) and freshly distilled MVK (8.55 mL, 7.20 g, 102.55 mmol, 5.0 equiv).

The solution was stirred for 5 min, before $BF_3 \cdot OEt_2$ (3.04 mL, 3.49 g, 24.61 mmol, 1.2 equiv) was added slowly dropwise. The resulted mixture was slowly warmed to –65 °C and stirred at this temperature for 12 h. Upon completion, the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ (100 mL), warmed to 23 °C and transferred to a separatory funnel. The phases were separated and the aqueous phase was extracted additionally with CH_2Cl_2 (100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography (silica gel, hexanes/Et_2O 6:1→3:1) to give the intermediate linear diketone (3.67 g, 53% over 2 steps) as a colorless oil. Next, to a stirred solution of the above intermediate (3.67 g, 10.84 mmol, 1.0 equiv) in MeOH (54 mL) was added a solution of NaOMe (0.5 M in MeOH) (32.50 mL, 16.25 mmol, 1.5 equiv) dropwise via an addition funnel at 23 °C. The resulting solution was stirred at 23 °C for 12 h. Upon completion, the reaction mixture was diluted with H_2O (180 mL), and transferred to a separatory funnel. The aqueous phase was extracted with EtOAc (2 x 180 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash chromatography (silica gel, hexanes/Et_2O 3:1) to give **52** (3.27 g, 94%) as a colorless oil. **52**: R_f = 0.27 (hexanes/Et_2O 3:1, UV, $KMnO_4$); $[a]_D^{25}$= +50.21 ° (*c* = 0.84, $CHCl_3$); IR (film) n_{max} 2950, 2857, 1680, 1096, 834, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.75 (s, 1 H), 5.60 (dt, *J* = 16.8, 10.0 Hz, 1 H), 5.19 (dd, *J* = 10.2, 2.1 Hz, 1 H), 5.07 (dd, *J* = 16.9, 2.1 Hz, 1 H), 3.82 (td, *J* = 10.4, 4.4 Hz, 1 H), 2.49–2.42 (m, 1 H), 2.38–2.23 (m, 3 H), 2.14–2.02 (m, 1 H), 1.93–1.86 (m, 2 H), 1.79–1.70 (m, 1 H), 1.53–1.41 (m, 1 H), 1.16 (s, 3 H), 0.85 (s, 9 H), 0.05 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.2, 168.1, 135.6, 124.3, 119.6, 69.5, 61.3, 38.8, 36.1, 35.4, 33.2, 31.1, 25.8, 18.6, 18.0, -4.1, -4.4; HRMS (ESI) calcd for $C_{19}H_{33}O_2Si^+$ [M + H^+] 321.2244, found 321.2246.

Ketal 53'. An oven-dried, 250 mL round-bottom flask equipped with a magnetic stir bar at 23 °C was charged with **52** (3.26 g, 10.17 mmol, 1.00 equiv) and MeOH (166 mL). The reaction flask was then equipped with a flushing adapter with a balloon containing N_2 on top and the contents were evacuated and backfilled with N_2. The cycle was repeated 5 more times and then 5 wt% Pd/C (0.33 g, 0.16 mmol, 0.02 equiv) was added. N_2 balloon was exchanged with a H_2 balloon. The contents were flushed 5 times with H_2 as above and the mixture was vigorously stirred at 23 °C for 4 h. Upon completion, the solution was flushed with N_2, the contents were filtered directly through Celite (washing with MeOH), and the filtrate was concentrated to dryness to provide **53** (3.27 g) as a clear oil that was used in the following step without further purification.

Next, to the solution of **53** (3.27 g, 10.17 mmol, 1.00 equiv) in CH_2Cl_2 (100 mL) was added I_2 (0.13 g, 0.51 mmol, 0.05 equiv), followed by 1,2-bis(trimethylsiloxy)ethane (5.00 mL, 4.21 g, 20.34 mmol, 2.00 equiv) at 23 °C. The resulting mixture was stirred at the same temperature for 18 h. Upon completion, the reaction was quenched by addition of aqueous solution of NaOH (1 M, 100 mL) and transferred to a separatory funnel. The aqueous phase was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash chromatography (silica gel, hexanes/EtOAc 8:1→6:1) to provide **53'** (3.07 g, 82% over 2 steps) as a white solid. **53'**: R_f = 0.44 (hexanes/EtOAc 6:1, $KMnO_4$); $[a]_D^{25}$= +24.40 ° (*c* = 1.45, $CHCl_3$); IR (film) n_{max} 2949, 2934, 2858, 1087, 833 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.52 (dt, *J* = 17.0, 10.0 Hz, 1 H), 5.09 (dd, *J* = 10.2, 2.3 Hz, 1 H), 5.01 (dd, *J* = 17.0, 2.3 Hz, 1 H), 3.96–3.90 (m, 4 H), 3.73–3.63 (m, 1 H), 2.32–2.26 (m, 1 H), 2.06–1.99 (m, 1 H), 1.90–1.81 (m, 1 H), 1.77–1.71 (m, 1 H), 1.69–1.57 (m, 3 H), 1.53–1.42 (m, 2 H), 1.37–1.19 (m, 3 H), 0.91 (s, 3 H), 0.84 (s, 9 H), 0.01 (s, 3 H), -0.01 (s, 3 H); ^{13}C NMR (126 MHz,

CDCl3) δ 137.9, 118.2, 110.0, 71.2, 64.4, 64.3, 49.6, 39.6, 36.2, 35.6, 35.1, 30.8, 30.2, 26.1, 25.7, 23.6, 18.3, -3.9, -4.2; HRMS (ESI) calcd for $C_{21}H_{39}O_3Si^+$ [M + H^+] 367.2663, found 367.2657.

Borane 38. A flame-dried 50 mL round-bottom flask equipped with a magnetic stir bar was charged with **53'** (3.06 g, 8.37 mmol, 1.0 equiv), back-filled with Ar and sealed. Then, THF (18 mL) was added, followed by addition of $RhCl(CO)(PPh_3)_2$ (0.58 g, 0.84 mmol, 0.1 equiv) at 23 °C. The resulting solution was stirred for 5 min, and then HBpin (2.43 mL, 2.14 g, 2.0 equiv) was added slowly dropwise at the same temperature. The septum was then removed for 30 seconds to expose the reaction mixture to air and then sealed back again. The resulting green solution was further stirred for 20 h at 23 °C. During this time the color of the solution changes from green to dark brown. Upon completion, the mixture was cooled to 0 °C and MeOH (4 mL) was added dropwise, followed by addition of H_2O (50 mL). The resulted biphasic solution was then transferred to a separatory funnel. The aqueous phase was extracted with Et_2O (3 x 70 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash chromatography (silica gel, hexanes/EtOAc 8:1) to provide **38** (3.11 g, 75%) as a yellow foam. **38**: R_f = 0.38 (hexanes/EtOAc 6:1, $KMnO_4$); $[a]_D^{25}$= –5.39 ° (*c* = 1.12, $CHCl_3$); IR (film) n_{max} 2976, 2934, 2884, 1405, 1079, 835, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.97–3.86 (m, 4 H), 3.56 (td, *J* = 10.6, 4.9 Hz, 1 H), 2.03 (t, *J* = 13.5 Hz, 1 H), 1.84–1.77 (m, 2 H), 1.74–1.62 (m, 2 H), 1.56–1.43 (m, 4 H), 1.43–1.23 (m, 5 H), 1.20 (s, 12 H), 1.09–1.00 (m, 1 H), 0.87 (s, 9 H), 0.85 (s, 3 H), 0.80–0.71 (m, 1 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 110.1, 82.8, 74.9, 64.3, 64.2, 45.4, 40.4, 37.3, 35.8, 34.7, 31.5, 30.9, 26.2, 25.8, 25.0, 25.0, 23.7, 22.6, 18.2, -3.7, -4.5; HRMS (ESI) calcd for $C_{27}H_{51}BO_5SiNa^+$ [M + Na^+] 517.3491, found 517.3490.

α,β-ynone 58. To a stirred solution of **57** (17.9 g, 154.0 mmol, 1.0 equiv) in CH_2Cl_2 (770 mL) were sequentially added MeO(Me)NH·HCl (19.5 g, 200.0 mmol, 1.3 equiv), Et_3N (36.4 mL, 261.0 mmol, 1.7 equiv), EDC (28.6 g, 184 mmol, 1.20 equiv) and DMAP (1.88 g, 15.4 mmol, 0.1 eq) at 0 °C. The reaction mixture was then stirred at 23 °C for 12 h and diluted with CH_2Cl_2 (800 mL). The organic phase was washed with 1% aqueous HCl (2 x 1.5 L) and then once with saturated aqueous $NaHCO_3$. The organic phase was dried (Na_2SO_4), filtered and carefully concentrated to give intermediate Weinreb amide (23.2 g, 145 mmol, 95%) as a yellowish liquid that was used in the next step without further purification.

To a stirred solution of the Weinreb amide described above (17.1 g, 107.0 mmol, 1.0 eq) in THF (535 mL) was added dropwise via canula propynyl magnesium bromide (0.5 M in THF) (428 mL, 214.0 mmol, 2.0 eq) at –78 °C. The resulting solution was then warmed to 23 °C and stirred at this temperature for 90 min. Upon completion, the reaction mixture quenched with saturated aqueous solution of NH_4Cl (300 mL). The reaction mixture was transferred to a separatory funnel, containing Et_2O (300 mL). The aqueous layer was additionally extracted with Et_2O (300 mL) and the organic phase was dried over Na_2SO_4, filtered and carefully concentrated (the product is volatile). The residue was purified by flash chromatography (silica gel, pentane/Et_2O 95:5) to give **58** (14.6 g, 105.0 mmol, 98%) as a yellowish liquid. **58**: R_f = 0.42 (hexanes/EtOAc 95:5, UV, $KMnO_4$); $[a]_D^{25}$= –16.98 ° (*c* = 1.25, $CHCl_3$); IR (film) n_{max} 2964, 2936, 2218, 1670, 1457, 1193 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.33 (p, *J* = 6.9 Hz, 1 H), 2.14 (dq, *J* = 13.6, 6.8 Hz, 1 H), 2.02 (s, 3 H), 1.08 (d, *J* = 6.9 Hz, 3 H), 0.95 (d, *J* = 6.8 Hz, 3 H), 0.87 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.5, 90.5, 79.8, 55.0, 30.1, 21.3, 18.6, 12.1, 4.2; HRMS (ESI) calcd for $C_9H_{15}O^+$ [M + H^+] 139.1117, found 139.1116.

Allyl alcohol 59. To a stirred solution of **58** (14.60 g, 105.0 mmol, 1.0 equiv) in THF (530 mL) were added sequentially dropwise via canula freshly prepared (*S*)-Me-CBS solution (1 M in toluene) (210 mL, 210.0 mmol, 2.0 equiv) and $BH_3 \cdot SMe_2$ (2 M in THF) (263 mL, 525.0 mmol, 5.0 equiv) at –50 °C. The reaction mixture was slowly warmed up to –30 °C, stirred for 1 h and then quenched by addition of EtOH (75 mL). Upon warming up to 23 °C, H_2O (500 mL) was added and the reaction mixture was transferred to a separatory funnel containing Et_2O (1 L). The phases were separated and the aqueous phase was additionally extracted with Et_2O (1 L). The combined organic layers were dried (Na_2SO_4), filtered and carefully concentrated (the product is volatile). The residue was purified by flash chromatography (silica gel, pentane/Et_2O 9:1→4:1) to give the intermediate propargyl alcohol (12.2 g, 83%) as a colorless liquid.

Next, to a stirred solution of the above intermediate (5.70 g, 40.6 mmol, 1.0 equiv) in THF (100 mL) was added dropwise solution of $LiAlH_4$ (2 M in THF) (100 mL, 203.0 mmol, 5.0 equiv) at 0 °C. The reaction mixture was then refluxed for 12 h. Upon completion, the reaction mixture was quenched by sequential dropwise addition of H_2O (8 mL), aqueous solution of NaOH (3 M, 8 mL) and finally H_2O (24 mL) at 0 °C. After stirring for 30 min at 23 °C, anhydrous $MgSO_4$ was added and the reaction mixture was filtered through Celite (washing with Et_2O). The solution was carefully concentrated (the product is volatile) and the residue was purified by flash chromatography (silica gel, pentane/Et_2O 9:1→7:3) to give **59** (5.20 g, 90%) as a colorless liquid. **59**: R_f = 0.44 (pentane/Et_2O 4:1, $KMnO_4$); $[a]_D^{25}$= +8.92 ° (*c* = 1.22, $CHCl_3$); IR (film) n_{max} 3367, 2960, 2935, 966 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.74–5.60 (m, 1 H), 5.53–5.44 (m, 1 H), 4.04–3.97 (m, 1 H), 1.73–1.69 (m, 3 H), 1.36–1.28 (m, 1 H), 1.26 (d, *J* = 3.9 Hz, 1 H), 0.93 (d, *J* = 6.9 Hz, 3 H), 0.88 (d, *J* = 6.9 Hz, 3 H), 0.80 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$)

δ 134.0, 127.0, 75.7, 44.7, 29.1, 21.7, 17.9, 17.8, 9.9; HRMS (ESI) calcd for $C_9H_{19}O^+$ [M + H^+] 143.1430, found 143.1426.

Vinyl bromide 54. To a stirred solution of **59** (10.0 g, 70.3 mmol, 1.0 equiv) in DMF (23.5 mL) was added NaH (purified from mineral oil) (2.02 g, 84.4 mmol, 1.20 equiv) at 0 °C. After stirring for 15 min at 23 °C, the solution was cooled back to 0 °C and a solution of **60**[35] (30.1 g, 140.6 mmol, 2.0 equiv) in DMF (23.5 mL) was then added dropwise. The resulting mixture was stirred at 23 °C for 12 h, then cooled to 0 °C and another portion of NaH (2.02 g, 84.4 mmol, 1.20 equiv) was added. After stirring for another 12 h at 23 °C, the reaction mixture was quenched by addition of saturated aqueous solution of NH_4Cl (50 mL), H_2O (50 mL) and then transferred to a separatory funnel containing EtOAc (100 mL). The phases were separated and the aqueous layer was additionally extracted with EtOAc (100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography (silica gel, pentane/Et_2O 97:3) to give **54** (14.5 g, 75%) as a yellowish liquid. **54**: R_f = 0.44 (pentane/Et_2O 98:2, $KMnO_4$); $[a]_D^{25}$= –29.16° (*c* = 1.55, $CHCl_3$); IR (film) n_{max} 2960, 2935, 2873, 1116, 1084, 1046, 971 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.04–5.95 (m, 1 H), 5.63 – 5.54 (m, 1 H), 5.34–5.25 (m, 1 H), 3.94–3.91 (m, 1 H), 3.76–3.72 (m, 1 H), 3.47–3.37 (m, 1 H), 2.25 (s, 3 H), 1.75–1.67 (m, 4 H), 1.39–1.33 (m, 1 H), 0.89 (d, *J* = 6.9 Hz, 3 H), 0.86 (d, *J* = 6.8 Hz, 3 H), 0.75 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 131.2, 129.7, 129.1, 123.6, 83.6, 64.5, 43.8, 28.5, 24.0, 21.8, 17.9, 17.1, 10.3; HRMS (ESI) calcd for $C_{13}H_{24}BrO^+$ [M + H^+] 275.1005, found 275.1010.

Diallyl ether 37. A flame-dried 100 mL round-bottom flask equipped with a magnetic stir bar was charged with **54** (1.08 g, 3.93 mmol, 1.2 equiv), back-filled with Ar and sealed. Then, THF (16.3 mL) was added and the mixture was cooled to –78 °C. Then, to the solution was added

freshly titrated solution of *n*-BuLi (2.39 M in hexanes) (3.30 mL, 7.89 mmol, 2.4 equiv) slowly down the wall of the reaction flask. The resulting solution was stirred for 20 min, followed by dropwise addition of the solution of **38** (1.62 g, 3.28 mmol, 1.0 equiv) in THF (16.3 mL). The resulting mixture was additionally stirred at –78 °C for 30 min and then slowly warmed to 0 °C over 1.5 h. Once the bath temperature reached 0 °C, a solution of I_2 (1.00 g, 3.93 mmol, 1.2 equiv) in MeOH (8 mL) was quickly added, followed by slow addition of freshly prepared solution of NaOMe (3 M in MeOH) (3.28 mL, 9.84 mmol, 3.0 equiv). The resulting mixture was additionally stirred at 0 °C for 30 min. Upon completion, the reaction mixture was quenched by dropwise addition of saturated aqueous solution of Na_2SO_3 until colorless, and then diluted with H_2O (20 mL). The resulted solution was then transferred to a separatory funnel, containing Et_2O (40 mL). The phases were separated and the aqueous phase was extracted additionally with Et_2O (2 x 70 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash chromatography (silica gel, hexanes/EtOAc 10:1) to provide **37** (0.97 g, 53%) as a yellow oil. **37**: R_f = 0.40 (hexanes/EtOAc 10:1, $KMnO_4$); $[a]_D^{25}$= –12.08 ° (*c* = 1.20, $CHCl_3$); IR (film) n_{max} 2955, 2935, 2874, 1463, 1375, 1254, 1083, 1062, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.61–5.47 (m, 1 H), 5.32–5.20 (m, 2 H), 4.00–3.96 (m, 1 H), 3.93– .91 (m, 4 H), 3.73–3.68 (m, 1 H), 3.54 (td, *J* = 10.6, 4.8 Hz, 1 H), 3.38 (t, *J* = 7.9 Hz, 1 H), 2.15–1.96 (m, 3 H), 1.80 (dtd, *J* = 15.7, 10.4, 5.6 Hz, 2 H), 1.74–1.63 (m, 10 H), 1.60–1.16 (m, 12 H), 0.88 (s, 9 H), 0.86 (d, *J* = 4.3 Hz, 3 H), 0.84 (d, *J* = 4.6 Hz, 3 H), 0.72 (d, *J* = 6.9 Hz, 3 H), 0.06–0.02 (m, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.8, 131.8, 128.2, 122.5, 109.9, 83.9, 74.6, 65.0, 64.4, 64.2, 43.7, 42.9, 40.2, 37.3, 35.8, 34.9, 34.6, 31.5, 30.9, 28.4, 27.4, 26.2, 25.8, 23.8, 23.4, 21.9, 18.2, 17.9, 16.9, 10.2, -3.8, -4.1; HRMS (ESI) calcd for $C_{34}H_{63}O_4Si^+$ [M + H^+] 563.4490, found 563.4491.

Ketone 61. A flame-dried 100 mL round-bottom flask equipped with a magnetic stir bar was charged with **37** (1.50 g, 2.66 mmol, 1.0 equiv), back-filled with Ar and sealed. Then, THF (16.3 mL) was added, followed by addition of TBAF (1 M in THF) (5.20 mL, 5.20 mmol, 1.95 equiv) at 23 °C. The reaction flask was equipped with condenser, transferred to an oil bath and refluxed under Ar atmosphere for 12 h. Upon completion, the solution was concentrated, the residual oil dried under high vacuum and the flask was back-filled with Ar. The crude alcohol was then dissolved in CH_2Cl_2 (30 mL) and cooled to 0 °C. To the resulting mixture was then sequentially added *t*-BuOH (0.76 mL, 0.59 g, 8.00 mmol, 3.0 equiv), $NaHCO_3$ (2.68 g, 32.00 mmol, 12.0 equiv) and DMP (3.38 g, 8.00 mmol, 3.0 equiv). The solution was then warmed to 23 °C and stirred at this temperature for 12 h. Upon completion, the reaction mixture was quenched by addition of saturated aqueous solution of $Na_2S_2O_3$ (30 mL) and stirred for 15 min. The resulted biphasic solution was then transferred to a separatory funnel, and the phases were separated. The aqueous phase was then extracted additionally with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash chromatography (silica gel, hexanes/EtOAc 4:1) to provide **61** (0.85 g, 70%) as a yellow oil. **61**: R_f = 0.55 (hexanes/EtOAc 4:1, $KMnO_4$); $[a]_D^{25}$= –18.96 ° (*c* = 0.50, $CHCl_3$); IR (film) n_{max} 2959, 2873, 1709, 1559, 1465, 1457, 1091 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.56 (dq, *J* = 15.4, 6.4 Hz, 1 H), 5.38–5.22 (m, 2 H), 4.01–3.96 (m, 4 H), 3.95–3.89 (m, 1 H), 3.68–3.64 (m, 1 H), 3.39–3.32 (m, 1 H), 2.57–2.52 (m, 1 H), 2.44–2.35 (m, 1 H), 2.26–2.10 (m, 3 H), 2.08–2.00 (m, 1 H), 1.94–1.88 (m, 1 H), 1.85–1.76 (m, 2 H), 1.76–1.68 (m, 8 H), 1.62 (ddt, *J* = 11.2, 9.4, 3.8 Hz, 4 H), 1.49–1.41 (m, 1 H), 1.40–1.33 (m, 1 H), 1.18–1.11 (m, 1 H), 0.88 (d, *J* = 6.9 Hz, 3 H), 0.85 (d, *J* = 6.8 Hz, 3 H), 0.77 (s, 3 H), 0.72 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.8, 139.3, 131.7, 128.5, 123.4, 109.2, 84.0, 64.6, 64.5, 64.4, 50.1, 43.7, 42.0, 40.2, 38.0, 36.2, 34.0,

31.6, 30.9, 28.6, 28.4, 23.6, 23.5, 21.9, 20.8, 17.9, 16.9, 10.3; HRMS (ESI) calcd for $C_{28}H_{47}O_4^+$ [M + H^+] 447.3469, found 447.3468.

Enol ether 35. A flame-dried 100 mL round-bottom flask equipped with a magnetic stir bar was charged with **61** (0.80 g, 1.79 mmol, 1.0 equiv), back-filled with Ar and sealed. Then, THF (9.1 mL) was added and the mixture was cooled to –78 °C. Then, to the solution was added solution of LiHMDS (1 M in THF) (4.50 mL, 2.50 mmol, 2.5 equiv) slowly dropwise. The resulting mixture was stirred for 5 min, followed by dropwise addition of the solution of Comins' reagent (2.11 g, 5.37 mmol, 3.0 equiv) in THF (3.5 mL). The resulting mixture was additionally stirred at –78 °C for 30 min and then slowly warmed to 23 °C over 2 h. Upon completion, the reaction mixture was quenched by addition of saturated aqueous solution of $NaHCO_3$ (15 mL) and stirred for 15 min. The resulted solution was then transferred to a separatory funnel containing 15 mL EtOAc, and the phases were separated. The aqueous phase was then extracted additionally with EtOAc (3 x 15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash chromatography (Et_3N-deactivated silica gel, hexanes/EtOAc 6:1) to provide intermediate vinyl triflate (0.95 g, 92%) as a yellow oil.

Next, a flame-dried 50 mL round-bottom flask equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (37 mg, 0.16 mmol, 0.1 equiv) and PPh_3 (172 mg, 0.66 mmol, 0.4 equiv), placed on high vacuum, flushed 3 times with Ar and sealed. Then, a solution of the vinyl triflate (0.95 g, 1.64 mmol, 1.0 equiv) in degassed $PhCH_3$ (16.4 mL) was added, followed by Et_3N (0.46 mL, 0.33 g, 3.30 mmol, 2.0 equiv). Ar was bubbled through the solution for 10 min and then the reaction mixture was transferred to an oil bath preheated to 70 °C. The reaction mixture was stirred at this temperature for 40 min (the color of the solution changes from yellow to dark red). Upon completion, the mixture was cooled to 23 °C, the product was purified by loading the contents of

the flask directly to a Et_3N-deactivated silica gel column and (eluting with 6:1, hexanes/EtOAc), to provide **35** (0.60 g, 78% over 2 steps) as a yellow oil. **35**: R_f = 0.62 (hexanes/EtOAc 6:1, $KMnO_4$); $[a]_D^{25}$= +80.92° (*c* = 0.50, $CHCl_3$); IR (film) n_{max} 2952, 2874, 1719, 1465, 1102 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.04 (d, *J* = 12.5 Hz, 1 H), 5.64–5.55 (m, 1 H), 5.38–5.32 (m, 1 H), 5.21–5.18 (m, 1 H), 4.95 (d, *J* = 12.5 Hz, 1 H), 3.98–3.90 (m, 4 H), 3.83–3.78 (m, 1 H), 2.70–2.60 (m, 1 H), 2.43–2.28 (m, 1 H), 1.78–1.67 (m, 6 H), 1.67–1.56 (m, 5 H), 1.50–1.25 (m, 6 H), 1.03 (s, 3 H), 0.91 (d, *J* = 6.8 Hz, 3 H), 0.88 (d, *J* = 6.9 Hz, 3 H), 0.78 (d, *J* = 6.8 Hz, 3 H), 0.74 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.9, 143.6, 131.0, 128.8, 116.2, 114.2, 109.7, 84.6, 64.3, 64.2, 44.4, 43.8, 40.7, 39.8, 38.7, 38.3, 34.7, 33.4, 31.0, 30.2, 28.7, 27.7, 23.1, 22.2, 21.8, 17.9, 17.7, 10.4; HRMS (ESI) calcd for $C_{28}H_{45}O_3^+$ [M + H^+] 429.3363, found 429.3351.

Methyl ester 63. An oven-dried 70 mL pressure vessel equipped with a magnetic stir bar was charged with **35** (0.58 g, 1.35 mmol, 1.0 equiv), toluene (34 mL), flushed with Ar and sealed. The vessel was then placed to a preheated to 130 °C oil bath, and the solution was stirred at this temperature for 17 h. Upon completion, the mixture was concentrated, and the residue was re-dissolved in THF (7.4 mL) and the resulted solution was cooled to 0 °C. In a separate flask, NaH (60% in mineral oil) (0.13 g, 3.27 mmol, 2.5 equiv) was dissolved in THF (8.0 mL). The resulting suspension was cooled to 0 °C and then trimethyl phosphonoacetate (0.63 mL, 0.71 g, 3.92 mmol, 3.0 equiv) was added slowly dropwise. The solution was then warmed to 23 °C and the resulted suspension was transferred to the pressure vessel via cannula. The resulted mixture was warmed to 23 °C and then placed to a preheated to 50 °C oil bath and stirred at this temperature for 13 h. Upon completion, the reaction mixture was quenched by addition of H_2O (12 mL), the contents were transferred to a separatory funnel, containing Et_2O (10 mL). The phases were separated and the aqueous phase was additionally extracted with Et_2O (2 x 12 mL). The combined organic layers

were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash chromatography (silica gel, hexanes/EtOAc 8:1) to provide **63** (0.48 g, *dr* (*E*:*Z*)=5:1, 73%) as a colorless oil. **63**: R_f = 0.50 (hexanes/EtOAc 8:1, UV, $KMnO_4$); $[a]_D^{25}$= +27.92° (*c* = 0.50, $CHCl_3$); IR (film) n_{max} 2956, 2873, 1726, 1295, 1188, 1101 cm^{-1}; major *E* isomer:^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (dd, *J* = 15.5, 11.2 Hz, 1 H), 5.80 (d, *J* = 15.5 Hz, 1 H), 5.27–5.12 (m, 3 H), 3.95–3.89 (m, 4 H), 3.72 (s, 3 H), 2.59–2.52 (m, 2 H), 2.38–2.29 (m, 1 H), 2.14–2.06 (m, 1 H), 2.04–2.00 (m, 1 H), 1.89–1.81 (m, 1 H), 1.78–1.52 (m, 7 H), 1.49–1.38 (m, 3 H), 1.29–1.17 (m, 2 H), 0.92 (d, *J* = 6.8 Hz, 3 H), 0.87 (s, 3 H), 0.85 (d, *J* = 7.0 Hz, 3 H), 0.81 (d, *J* = 6.8 Hz, 3 H), 0.79 (d, *J* = 6.8 Hz, 3 H), 0.72 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 149.4, 148.2, 135.1, 132.6, 123.6, 114.2, 109.5, 64.3, 64.2, 58.2, 51.5, 48.0, 43.6, 42.0, 38.9, 38.7, 38.5, 34.6, 33.4, 33.2, 33.1, 31.0, 30.12, 29.2, 23.6, 23.3, 22.4, 20.2, 19.8, 17.9; HRMS (ESI) calcd for $C_{31}H_{49}O_4^+$ [M + H^+] 485.3629, found 485.3625.

Alcohol 65. An oven-dried 50 mL round-bottom flask equipped with a magnetic stir bar was charged with $LiAlH_4$ (0.17 g, 4.48 mmol, 4.6 equiv) back-filled with Ar and sealed. THF (10 mL) was then added and the resulting suspension was cooled to 0 °C. Then, a solution of **63** (0.47 g, 0.97 mmol, 1.0 equiv) in THF (9 mL) was added slowly dropwise and the resulting mixture was brought to 23 °C. After stirring for 40 min at 23 °C, the mixture was cooled back to 0 °C and diluted with Et_2O (10 mL). H_2O (0.17 mL) was then added slowly dropwise, followed by aqueous solution of NaOH (4 M, 0.17 mL) and H_2O (0.51 mL). The resulting mixture was warmed to 23 °C. Then, anhydrous MgSO4 was added and solids were filtered through Celite (washing with Et_2O). The filtrate was concentrated in vacuum, to provide intermediate allylic alcohol **64**. Next, the crude allylic alcohol **64** was re-dissolved in *i*-PrOH in a microwave vial, and to the resulted solution was added $RuCl_2(PPh_3)_3$ (0.18 g, 0.19 mmol, 0.2 equiv) and Cs_2CO_3 (0.12 g, 0.37 mmol,

0.4 equiv). The contents were flushed with Ar, sealed, and placed on a preheated to 95 °C oil bath. The resulting solution was stirred at this temperature for 14 h. Upon completion, the vial was unsealed, the contents were diluted with EtOAc and filtered. The filtrate was concentrated and the residue was purified by flash chromatography (silica gel, hexanes/EtOAc 8:1→4:1) to provide **65** (0.21 g, 48% over 2 steps) as a colorless oil. **65**: R_f = 0.33 (hexanes/EtOAc 4:1, $KMnO_4$); $[a]_D^{25}$= +68.40° (*c* = 0.30, $CHCl_3$); IR (film) n_{max} 3421, 2955, 2871, 1576, 1472, 1101 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.45–5.39 (m, 1 H), 5.23–5.17 (m, 1 H), 5.16–5.13 (m, 1 H), 3.95–3.92 (m, 4 H), 3.61 (t, *J* = 6.8 Hz, 2 H), 2.60–2.53 (m, 1 H), 2.49–2.43 (m, 1 H), 2.39–2.32 (m, 1 H), 1.92–1.84 (m, 2 H), 1.79–1.33 (m, 15 H), 1.29–1.17 (m, 3 H), 0.97–0.96 (m, 6 H), 0.93 (d, *J* = 6.8 Hz, 3 H), 0.84–0.81 (m, 6 H), 0.74 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.4, 134.3, 133.6, 113.2, 109.7, 64.3, 64.3, 63.6, 52.2, 50.1, 43.7, 41.5, 38.8, 38.6, 38.5, 35.4, 34.7, 33.9, 33.2, 33.2, 31.0, 30.1, 27.9, 24.3, 23.4, 23.0, 22.5, 20.2, 19.9, 17.9; HRMS (ESI) calcd for $C_{30}H_{51}O_3^+$ [M + H^+] 459.3833, found 459.3836.

Aldehyde 33. An oven-dried 50 mL round-bottom flask equipped with a magnetic stir bar was charged with **66** (0.60 g, 1.87 mmol, 4.8 equiv) and activated MnO_2 (1.63 g, 18.74 mmol, 48.0 equiv), back-filled with Ar and sealed. A solution of **65** (0.18 g, 0.39 mmol, 1.0 equiv) in $PhCF_3$ (25 mL) was then added, followed by 15-crown-5 (0.50 mL, 0.55 g, 2.52 mmol, 6.5 equiv). The resulting suspension was then placed on a preheated to 95 °C oil bath and stirred at this temperature for 20 h. Upon completion, the contents were cooled to 23 °C and filtered through a silica gel (bottom)/celite (top) bed (washing with EtOAc). The filtrate was concentrated providing crude **67** that was used in the next step without further purification. Next, previously obtained **67** was re-dissolved in CH_2Cl_2 (5.4 mL), and the solution was cooled to 0 °C. To the resulted mixture was then added $NaHCO_3$ (0.18 g, 2.15 mmol, 5.5 equiv), followed by DMP (0.23 g, 0.54 mmol, 1.4

equiv). The solution was then brought to 23 °C, and stirred at this temperature for 20 h. Upon completion, the reaction mixture was quenched by addition of saturated aqueous solution of $Na_2S_2O_3$ (7 mL) and stirred for 15 min. The resulted biphasic solution was then transferred to a separatory funnel, and the phases were separated. The aqueous phase was then extracted additionally with CH_2Cl_2 (3 x 7 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash chromatography (silica gel, hexanes/EtOAc 2:1) to provide **33** (0.07 g, 38%) as a yellow oil. **33**: R_f = 0.40 (hexanes/EtOAc 2:1, $KMnO_4$); $[a]_D^{25}$= +77.72° (*c* = 0.71, $CHCl_3$); IR (film) n_{max} 2958, 2930, 2873, 1724, 1661, 1099 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.77 (s, 1 H), 5.75 (d, *J* = 2.9 Hz, 1 H), 5.41 (dd, *J* = 15.2, 8.7 Hz, 1 H), 5.19 (dd, *J* = 15.2, 8.4 Hz, 1 H), 3.96 (qt, *J* = 7.9, 4.0 Hz, 4 H), 3.07 (td, *J* = 8.1, 4.2 Hz, 1 H), 2.67–2.53 (m, 2 H), 2.33 (dt, *J* = 13.7, 6.4 Hz, 2H), 2.15–2.07 (m, 1 H), 1.94–1.87 (m, 1 H), 1.85–1.40 (m, 13 H), 1.07 (s, 3H), 1.00–0.92 (m, 6 H), 0.86 (s, 3 H), 0.85–0.80 (m, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.0, 179.7, 135.5, 132.1, 119.7, 107.8, 64.6, 64.5, 53.9, 52.3, 50.8, 46.0, 45.2, 43.7, 39.0, 37.2, 34.0, 33.9, 33.1, 33.0, 31.2, 27.0, 24.0, 22.5, 22.4, 22.4, 20.2, 19.9, 19.1, 18.0; HRMS (ESI) calcd for $C_{30}H_{47}O_4^+$ [M + H^+] 471.3464, found 471.3469.

Dankasterone B 2. An Ar-filled flame-dried 10 mL round-bottom flask equipped with a magnetic stir bar was charged with a freshly prepared solution of SmI_2 (0.1 M in THF) (3.62 mL, 0.362 mmol, 6.0 equiv) under Ar atmosphere. Degassed (freeze-pump-thaw) THF (3.62 mL) was then added and the resulting solution was brought to reflux under Ar atmosphere. Then, a solution of **33** (28.4 mg, 0.060 mmol, 1.0 equiv) in degassed THF (1.81 mL) was added slowly dropwise over 5 min to the refluxing solution of SmI_2. After stirring for 5 min at reflux, the mixture was brought to 23 °C and then quenched by addition of saturated aqueous solution of Rochelle salt (6 mL). The resulted mixture was transferred to a separatory funnel containing EtOAc (6 mL). The

phases were separated and the aqueous phase was additionally extracted with EtOAc (2 x 6 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude material was passed through a short silica gel plug eluting with EtOAc to afford the mixture of alcohols **77**+**76** that was used in the next step without further purification. Next, previously obtained **77**+**76** was dissolved in CH_2Cl_2 (1.6 mL) and cooled to 0 °C. To the resulted mixture was then added $NaHCO_3$ (60.5 mg, 0.72 mmol, 12.0 equiv), followed by DMP (76.4 mg, 0.18 mmol, 3.0 equiv). The solution was then brought to 23 °C, and stirred at this temperature for 20 h. Upon completion, the reaction mixture was quenched by addition of saturated aqueous solution of $Na_2S_2O_3$ (2 mL) and stirred for 15 min. The resulted biphasic solution was then transferred to a separatory funnel, and the phases were separated. The aqueous phase was then extracted additionally with CH_2Cl_2 (3 x 2 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash chromatography (silica gel, hexanes/EtOAc 2:1) to provide **69** (9.0 mg). Next, **69** was dissolved in THF (0.52 mL) and an aqueous solution of HCl (2M, 0.26 mL) was added. The mixture was stirred at 23 °C for 2 h. Upon completion, the reaction mixture was concentrated, dried on high vacuum and purified by using preparative thin-layer chromatography (hexanes/EtOAc 1:1) to provide **2** (8.0 mg, 32% over 3 steps) as a white solid. **2**: R_f = 0.28 (hexanes/EtOAc 1:1, UV, $KMnO_4$); $[a]_D^{25}$= +21.02° (*c* = 0.22, $CHCl_3$) (lit. $[a]_D^{25}$= +38.4° (c = 0.2, $CHCl_3$)[4]; $[a]_D^{25}$= +28.2° (c = 1.00, $CHCl_3$)[5]; $[a]_D^{25}$= +24.5° (c = 1.00, $CHCl_3$)[6]); IR (film) n_{max} 2957, 2926, 2872, 1720, 1467, 1383, 1161, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.28–5.19 (m, 2 H), 3.05 (t, *J* = 9.7 Hz, 1 H), 2.95 (dd, *J* = 13.3, 1.8 Hz, 1 H), 2.88 (d, *J* = 5.9 Hz, 1 H), 2.87–2.80 (m, 1 H), 2.82–2.74 (m, 1 H), 2.41 (p, *J* = 6.9 Hz, 1 H), 2.38–2.33 (m, 1 H), 2.33–2.25 (m, 2 H), 2.24–2.21 (m, 1 H), 2.20 (d, *J* = 6.2 Hz, 1 H), 2.18–2.15 (m, 1 H), 2.12–2.07 (m, 1 H), 2.03–1.92 (m, 3 H), 1.88–1.81 (m, 1 H), 1.69–1.60 (m, 2 H), 1.55–1.51 (m, 1 H), 1.48–1.41 (m, 1 H),

1.32–1.29 (m, 1 H), 1.27 (s, 3 H), 1.14 (d, *J* = 7.0 Hz, 3 H), 0.88 (d, *J* = 6.8 Hz, 3 H), 0.81 (d, *J* = 6.8 Hz, 3 H), 0.79 (d, *J* = 6.8 Hz, 3 H), 0.75 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.9, 208.6, 207.8, 135.4, 132.2, 65.8, 60.2, 53.4, 50.2, 45.6, 43.4, 40.7, 40.1, 38.7, 37.0, 36.9, 35.9, 34.2, 33.2, 32.8, 27.4, 25.7, 24.3, 23.5, 20.2, 19.8, 17.7, 15.3; HRMS (ESI) calcd for $C_{28}H_{43}O_3^+$ [M + H^+] 427.3205, found 427.3207.

Table 3.1. ^{1}H NMR spectral data comparison ($CDCl_3$) between our synthetic 2, natural 2 and synthetic 2 prepared by Heretsch group.

Synthetic 2	Natural 2[1]	Δ δ	Synthetic 2 by Heretsch[6]	Δ δ
5.28–5.19 (m, 2 H)	5.22 (dd, *J* = 15.3, 6.9 Hz, 1 H); 5.25 (dd, *J* = 15.3, 6.8 Hz, 1 H)	-	5.23 (m, 1 H); 5.23 (m, 1 H)	-
3.05 (t, *J* = 9.7 Hz, 1 H)	3.05 (td, *J* = 9.6, 1.8 Hz, 1 H)	0	3.05 t (t, *J* = 9.9 Hz, 1 H)	0
2.95 (dd, *J* = 13.3, 1.8 Hz, 1 H)	2.95 (dd, *J* = 13.2, 1.8 Hz, 1 H);	0	2.95 (dd, *J* = 13.2, 1.8 Hz, 1 H);	0
2.88 (d, *J* = 5.9 Hz, 1 H)	2.89 (m, 1 H)	0.01	2.89 (m, 1 H)	0.01
2.87–2.80 (m, 1 H)	2.83 (dt, *J* = 16.2, 1.6 Hz, 1 H);	-	2.84 (dt, *J* = 16.5, 2.0 Hz, 1 H)	-
2.82–2.74 (m, 1 H)	2.78 (ddd, *J* = 13.0, 12.8, 5.9 Hz, 1 H)	-	2.79 (ddd, *J* = 14.3, 12.8, 5.9 Hz, 1 H)	-
2.41 (p, *J* = 6.9 Hz, 1 H)	2.42 (m, 1 H)	0.01	2.42 (p, *J* = 6.9 Hz, 1 H)	0.01
2.38–2.33 (m, 1 H)	2.36 (ddd, *J* = 13.0, 4.3, 2.5 Hz, 1 H)	-	2.36 (ddd, *J* = 12.7, 4.2, 2.5 Hz, 1 H))	-
2.33–2.25 (m, 2 H)	2.29 (td, *J* = 13.0, 6.9 Hz, 1 H); 2.31 (m, 1 H)	-	2.29 (m, 1 H) 2.31 (m, 1 H)	-
2.24–2.21 (m, 1 H)	2.21 (ddt, *J* = 13.0, 5.7, 2.2 Hz, 1 H)	-	2.22 (dt, *J* = 5.7, 2.1, 1 H)	-
2.20 (d, *J* = 6.2 Hz, 1 H)	2.19 (dd, *J* = 16.2, 2.6, 1 H)	0.01	2.20 (d, *J* = 6.1 Hz, 1 H)	0
2.18–2.15 (m, 1 H)	2.14 (m, 1 H)	-	2.14 (m, 1 H)	-
2.12–2.07 (m, 1 H)	2.10 (m, 1 H)	-	2.10 (m, 1 H)	-
2.03–1.92 (m, 3 H)	1.95 (d, *J* = 13.2 Hz, 1 H); 1.99 (m, 1 H); 1.95 (m, 1 H)	-	1.95 d (d, *J* = 13.5 Hz, 1 H); 1.99 (m, 1 H); 1.95 (m, 1 H)	-
1.88–1.81 (m, 1 H)	1.84 (m, 1 H)	-	1.84 (m, 1 H)	-
1.69–1.60 (m, 2 H)	1.65 (m, 1 H); 1.63 (m, 1 H)	-	1.65 (m, 1 H); 1.64 (m, 1 H)	-
1.55–1.51 (m, 1 H)	1.54 (td, *J* = 13.2, 5.7 Hz, 1 H);	-	1.54 (td, *J* = 12.9, 5.7 Hz, 1 H);	-
1.48–1.41 (m, 1 H)	1.45 (m, 1 H)	-	1.45 (m, 1 H)	-
1.32–1.29 (m, 1 H)	1.31 ddt (13.2, 6.9, 2.5)	-	1.31 ddt (13.3, 6.8, 2.4)	-
1.27 (s, 3 H)	1.27 (s, 3 H)	0	1.27 (s, 3 H)	0
1.14 (d, *J* = 7.0 Hz, 3 H)	1.14 (d, *J* = 6.9 Hz, 3 H)	0	1.15 (d, *J* = 7.1 Hz, 3 H)	0.01
0.88 (d, *J* = 6.8 Hz, 3 H)	0.88 (d, *J* = 6.8 Hz, 3 H)	0	0.88 (d, *J* = 6.8 Hz, 3 H)	0
0.81 (d, *J* = 6.8 Hz, 3 H)	0.81 (d, *J* = 6.8 Hz, 3 H)	0	0.81 (d, *J* = 6.7 Hz, 3 H)	0
0.79 (d, *J* = 6.8 Hz, 3 H)	0.79 (d, *J* = 6.8 Hz, 3 H)	0	0.79 (d, *J* = 6.8 Hz, 3 H)	0
0.75 (s, 3 H)	0.75 (s, 3 H)	0	0.75 (s, 3 H)	0

Table 3.2. ^{13}C NMR spectral data comparison ($CDCl_3$) between our synthetic 2, natural 2 and synthetic 2 prepared by Heretsch group.

Synthetic 2	Natural 2[1]	Δ δ	Synthetic 2 by Heretsch[6]	Δ δ
214.9	214.7	0.2	214.7	0.2
208.6	208.5	0.1	208.5	0
207.8	207.6	0.2	207.6	0
135.4	135.2	0.2	135.2	0
132.2	132.0	0.2	132.0	0
65.8	65.6	0.2	65.6	0
60.2	60.1	0.1	60.0	0.1
53.4	53.2	0.2	53.2	0
50.2	50.0	0.2	50.0	0
45.6	45.4	0.2	45.4	0
43.4	43.2	0.2	43.2	0
40.7	40.5	0.2	40.5	0
40.1	40.0	0.1	40.0	0
38.7	38.5	0.2	38.5	0
37.0	36.9	0.1	36.9	0
36.9	36.8	0.1	36.8	0
35.9	35.8	0.1	35.8	0
34.2	34.1	0.1	34.1	0
33.2	33.0	0.2	33.0	0
32.8	32.7	0.1	32.7	0
27.4	27.2	0.2	27.2	0
25.7	25.5	0.2	25.5	0
24.3	24.1	0.2	24.1	0
23.5	23.4	0.1	23.4	0
20.2	20.0	0.2	20.0	0
19.8	19.7	0.1	19.7	0
17.7	17.5	0.2	17.5	0
15.3	15.2	0.1	15.1	0.1

3.12. References.

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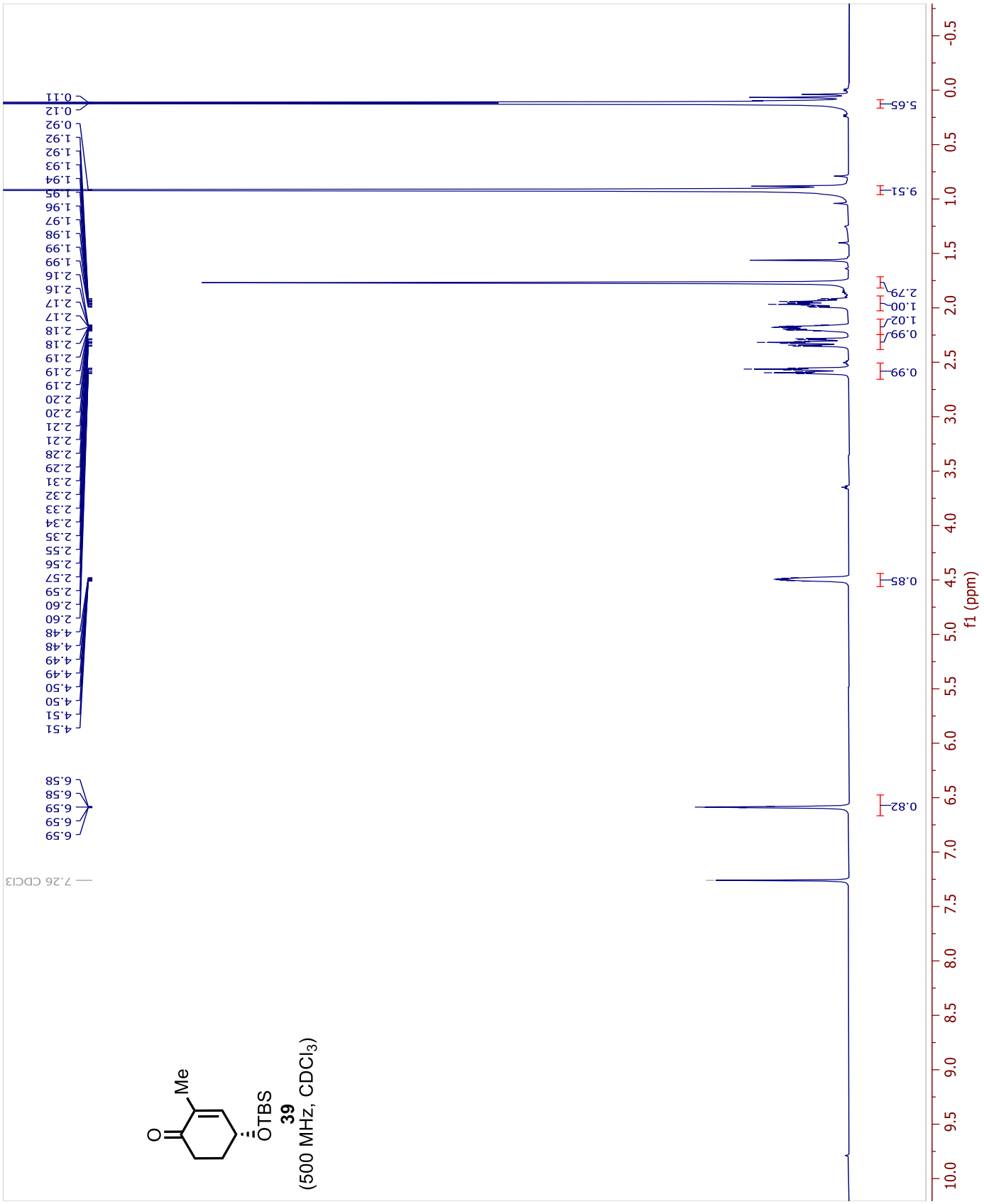
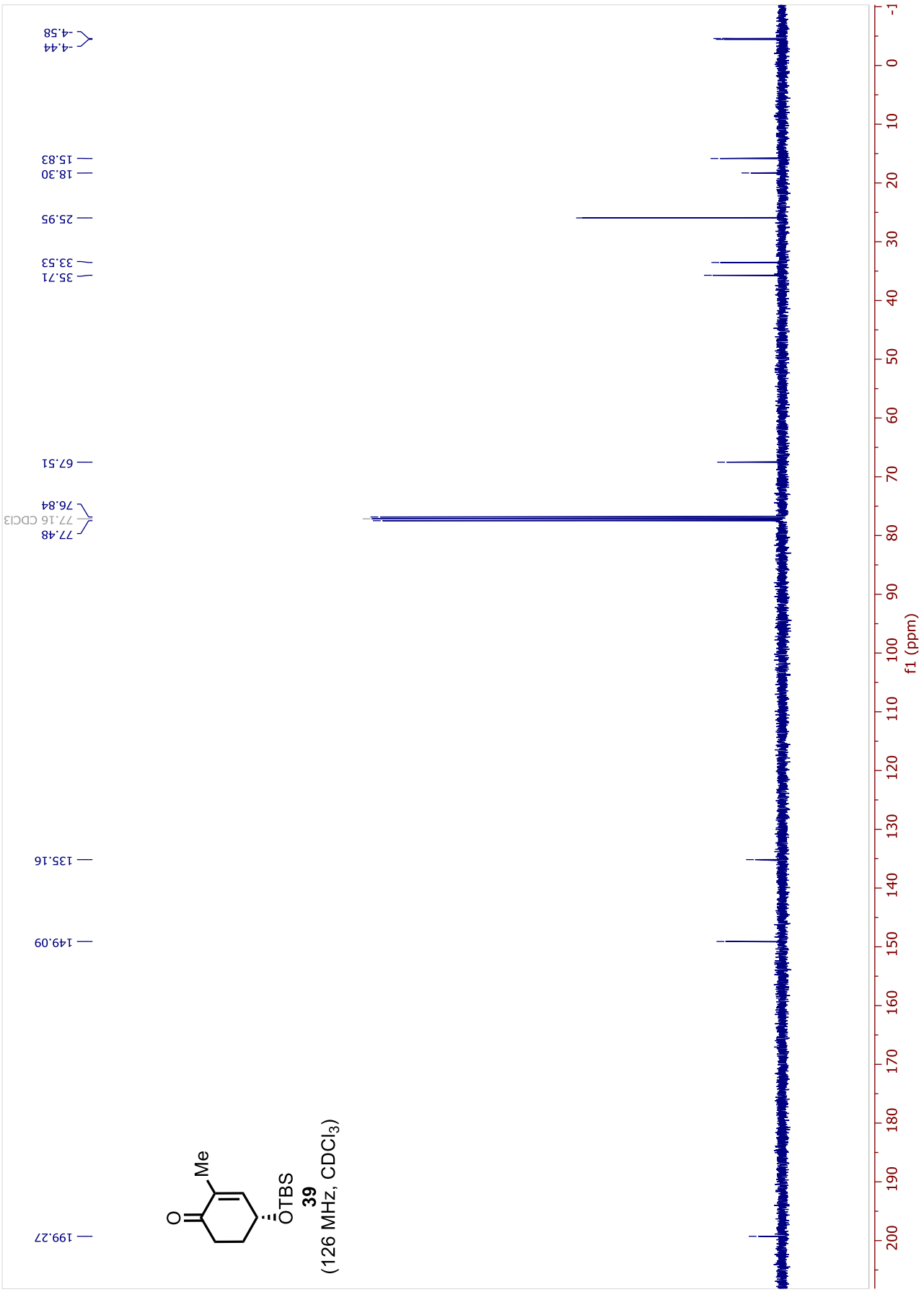
3.13. ^{1}H and ^{13}C NMR Data of Selected Intermediates.

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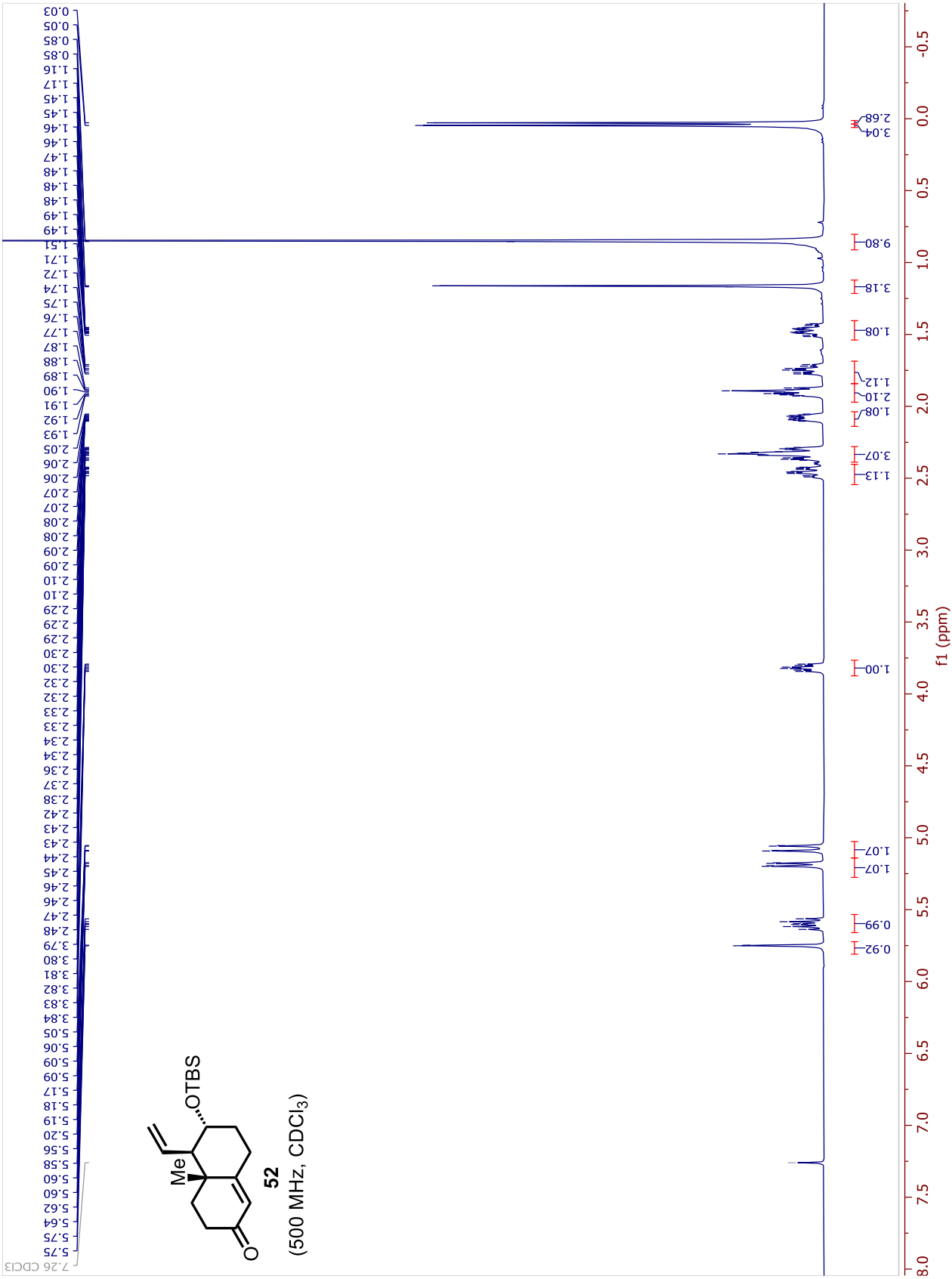
149.09
135.16
77.48
77.16 CDCl3
76.84
67.51
35.71
33.53
25.95
18.30
15.83
-4.44
-4.58
Me
OTBS
O
39
(126 MHz, CDCl3)
f1 (ppm)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O
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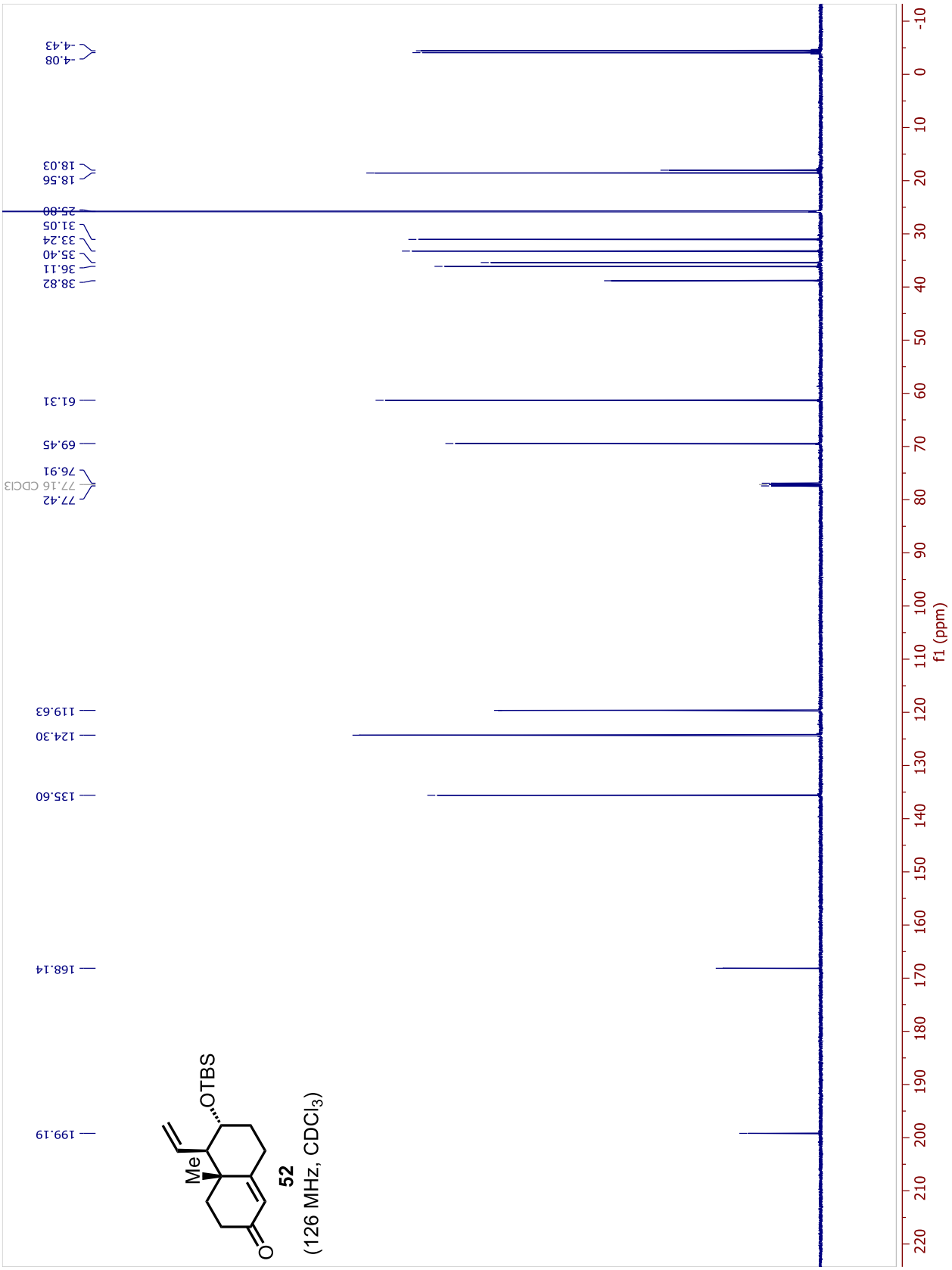
(500 MHz, CDCl3)
f1 (ppm)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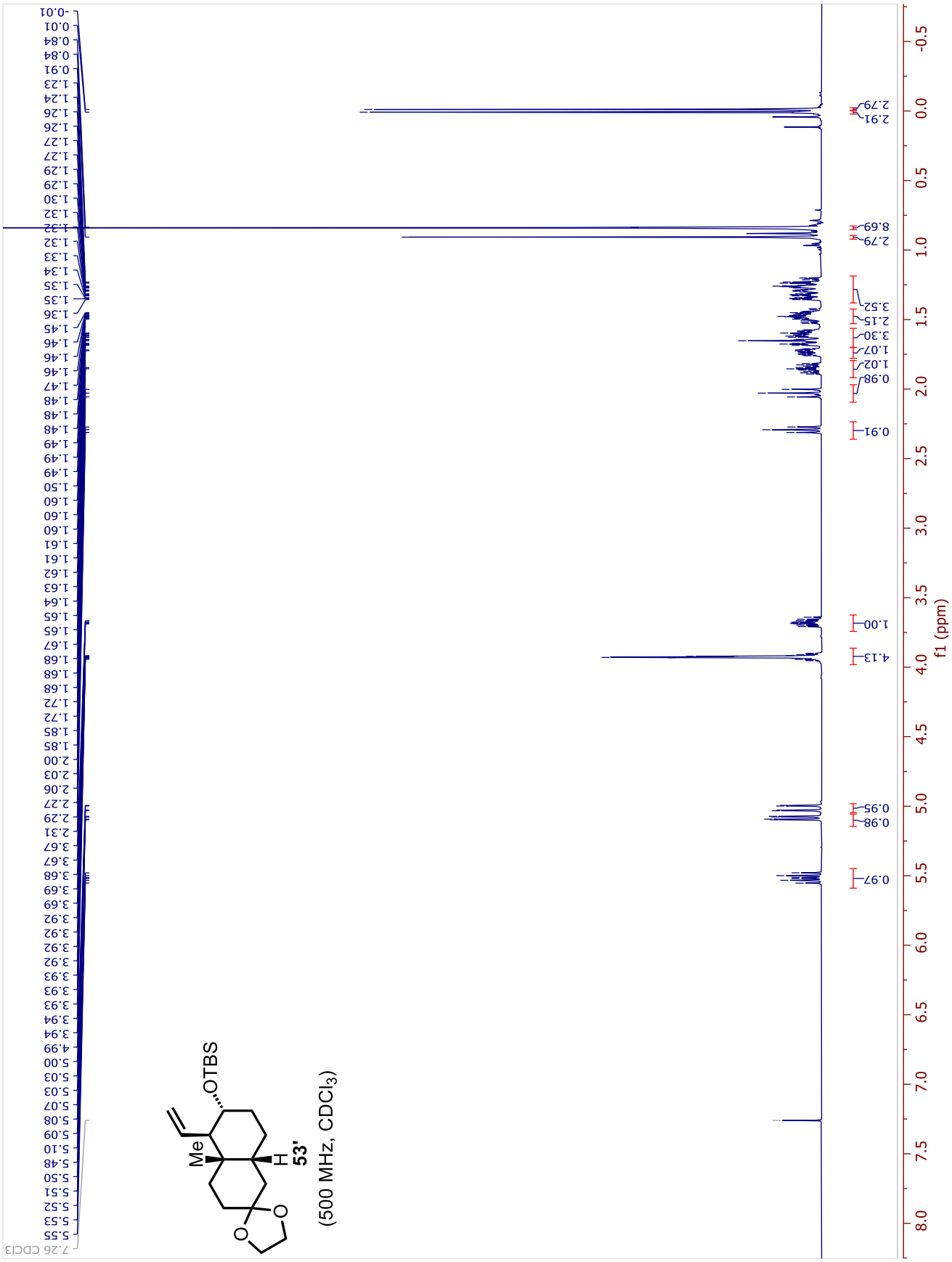
-4.08
18.03
18.56
25.80
31.05
33.24
35.40
36.11
38.82
61.31
69.45
76.91
77.16 CDCl3
77.42
119.63
124.30
135.60
168.14
199.19
OTBS
Me
O
52
(126 MHz, CDCl3)
f1 (ppm)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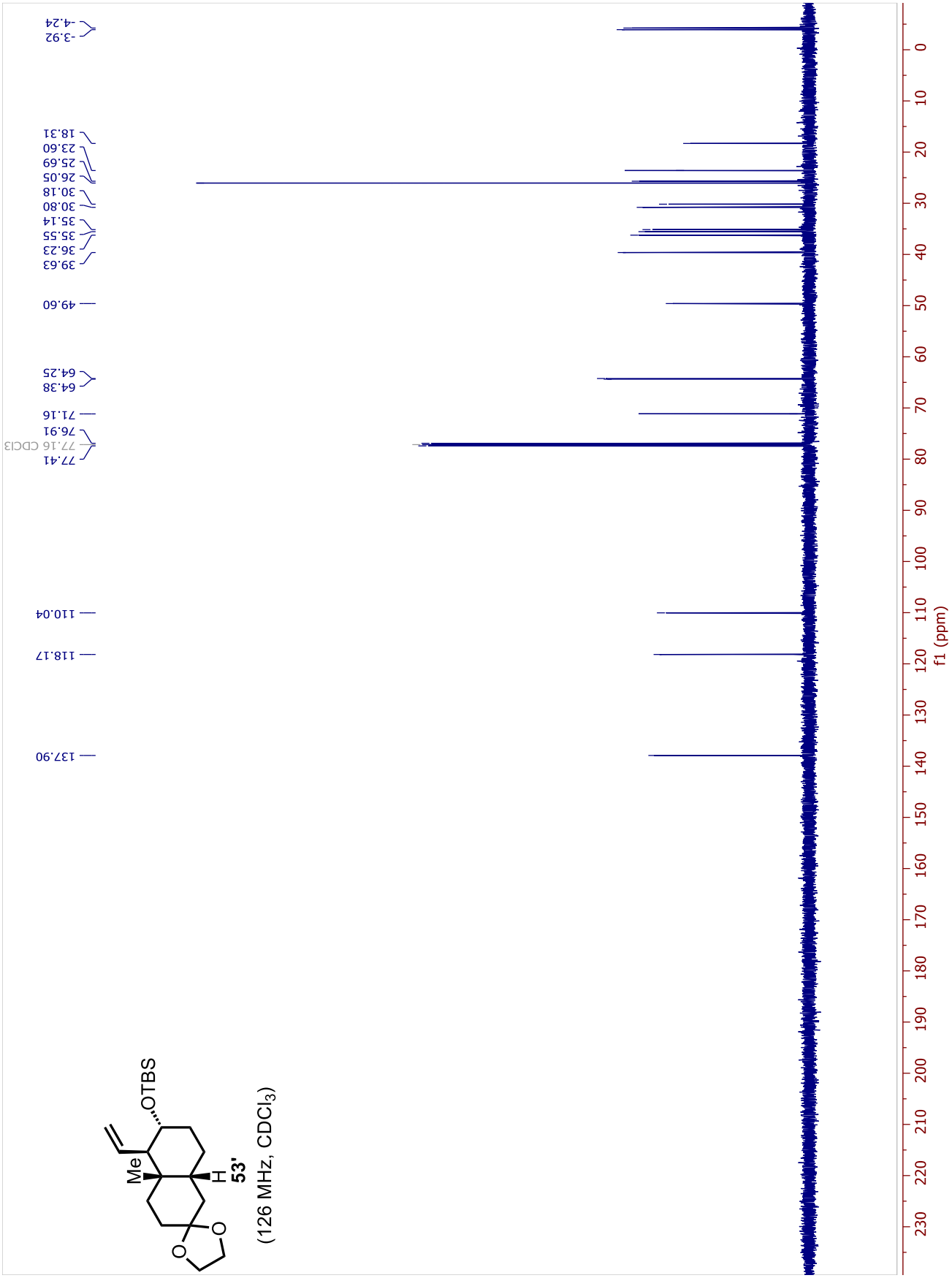
Me
H
O
O
53'
(500 MHz, CDCl3)
f1 (ppm)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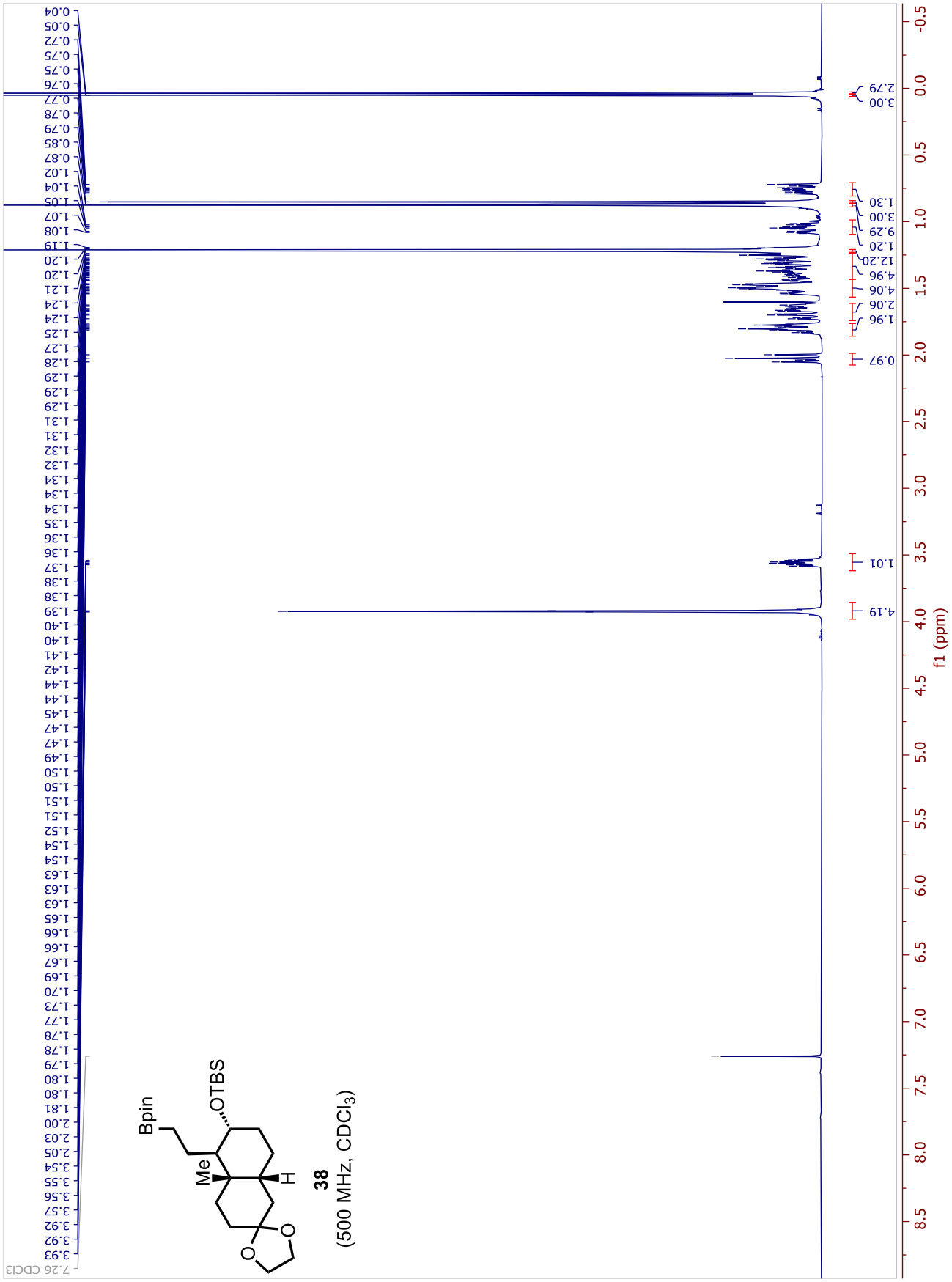
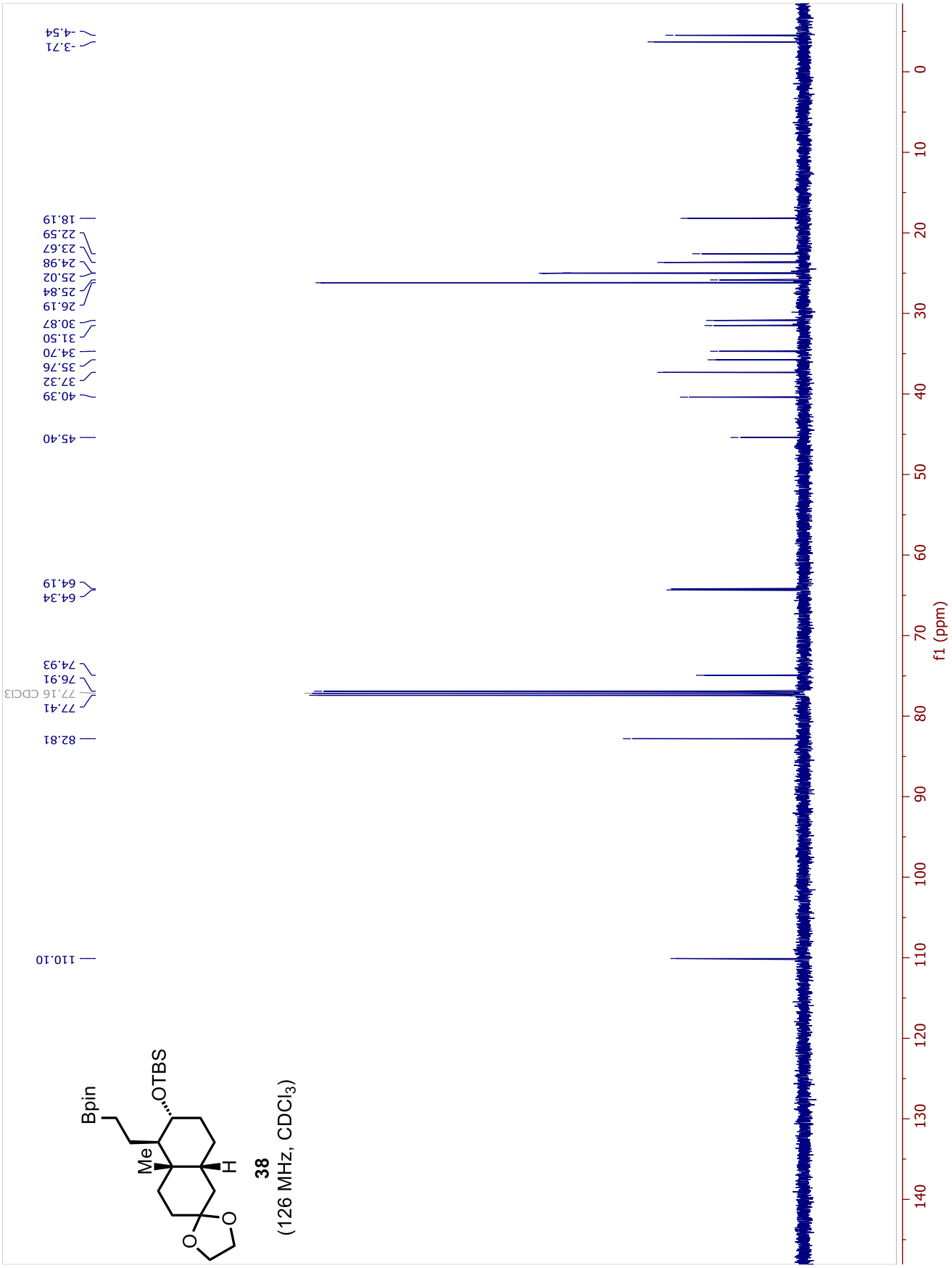
-4.24
18.31
23.60
25.69
26.05
30.18
30.80
35.14
35.55
36.23
39.63
49.60
64.25
64.38
71.16
76.91
77.16 CDCl3
77.41
110.04
118.17
137.90
f1 (ppm)
OTBS
Me
H
O
O
53'
(126 MHz, CDCl3)


Bpin
OTBS
Me
H
O
O
38
(500 MHz, CDCl3)
f1 (ppm)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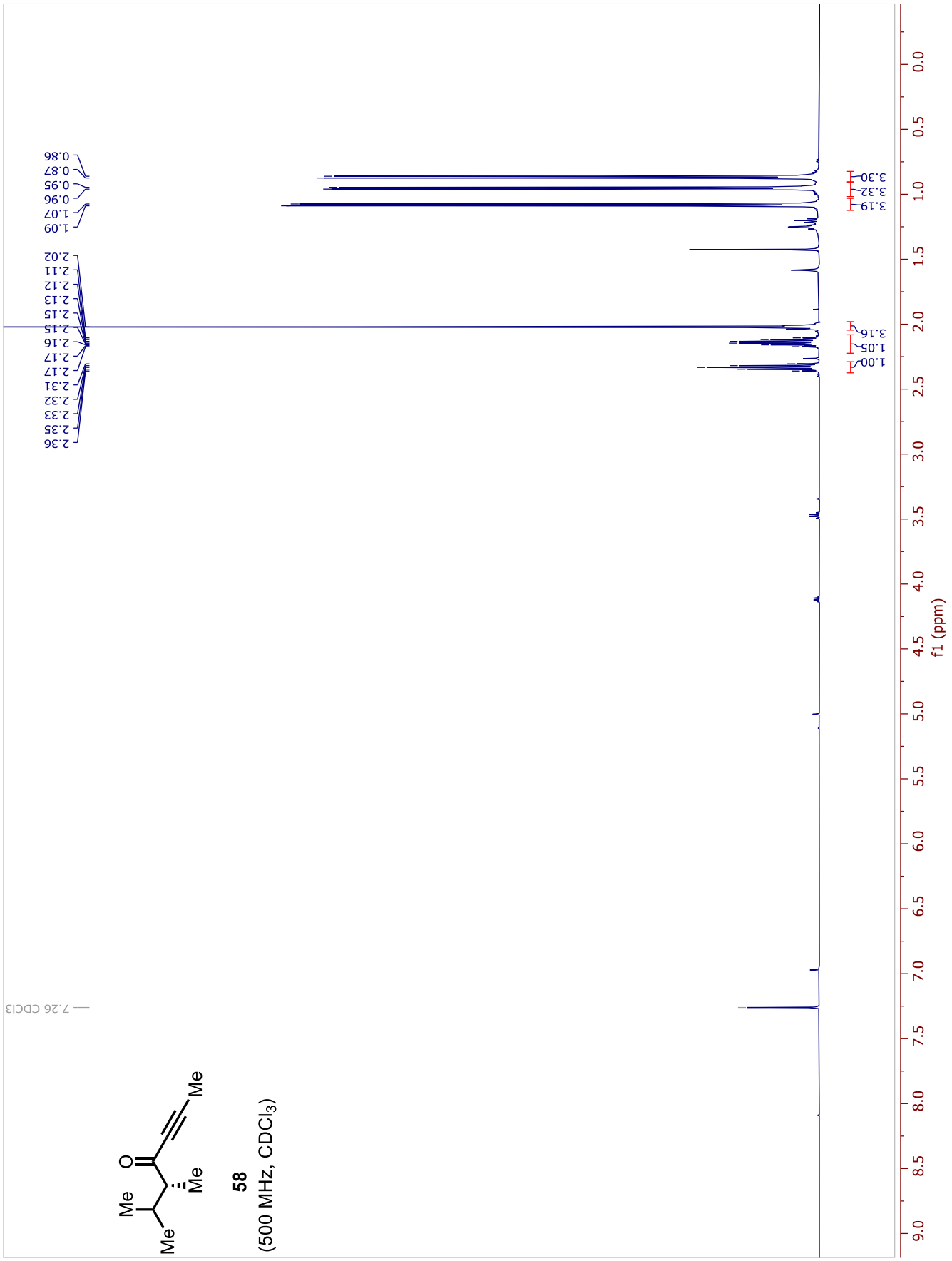
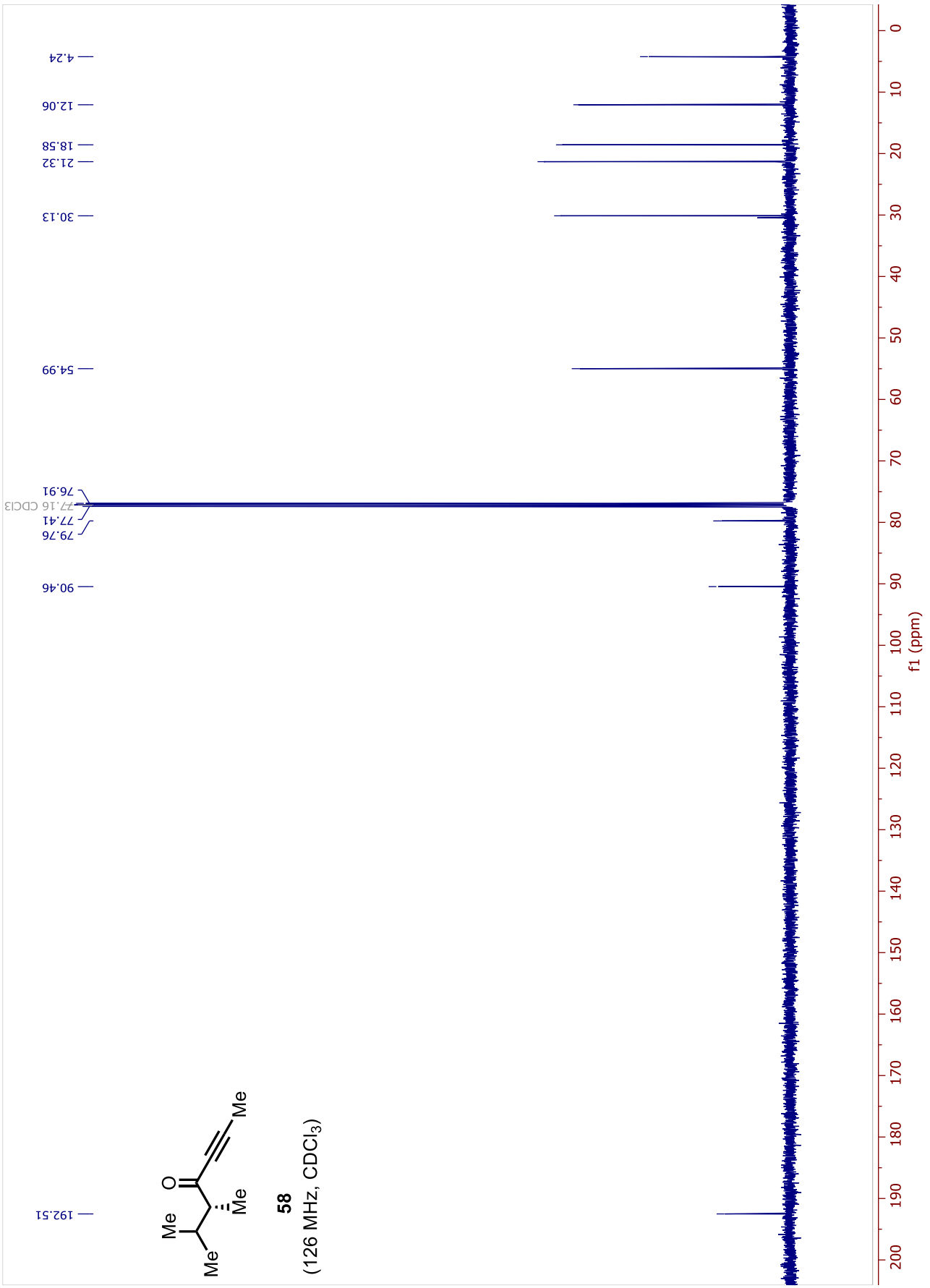
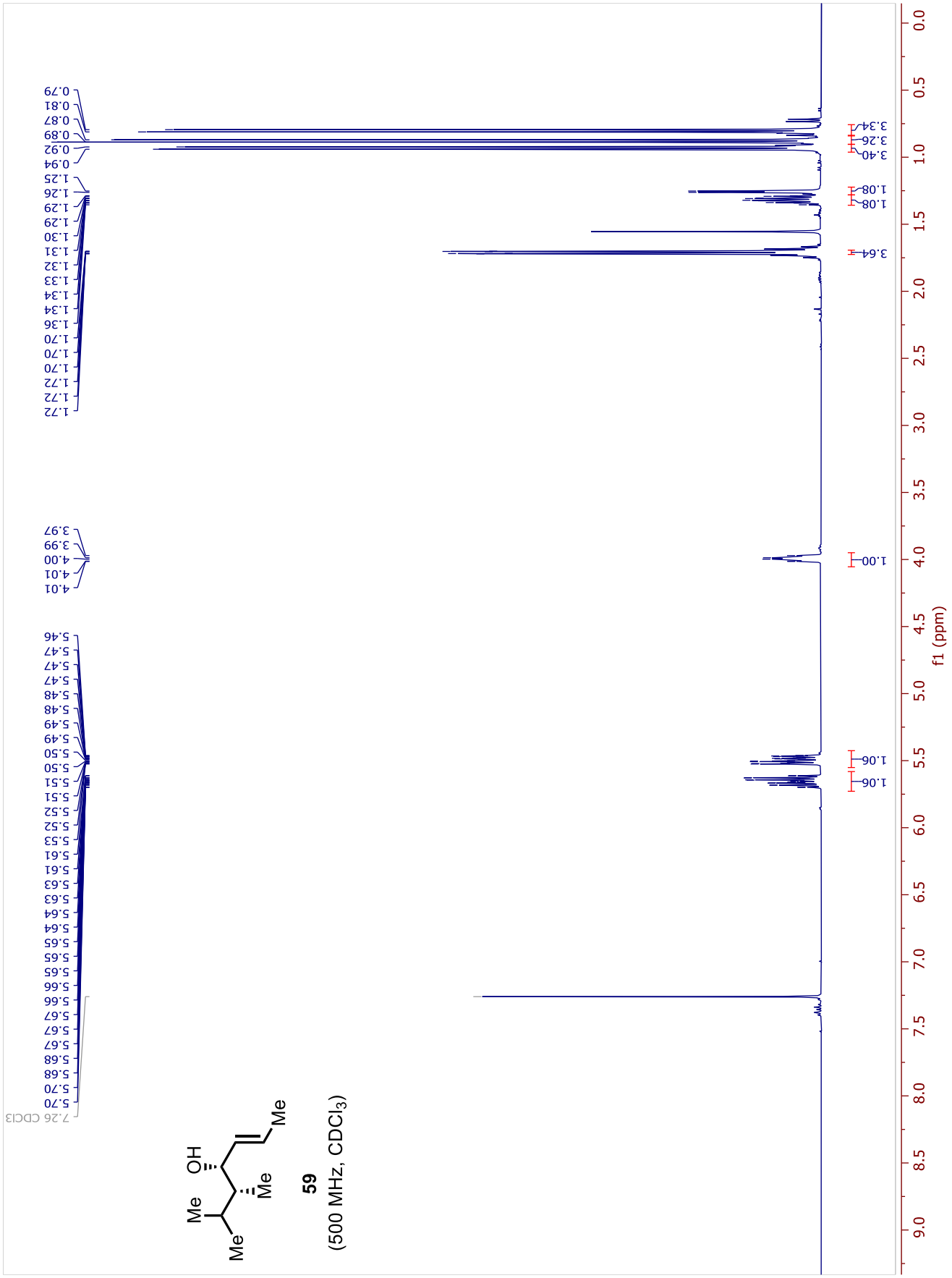
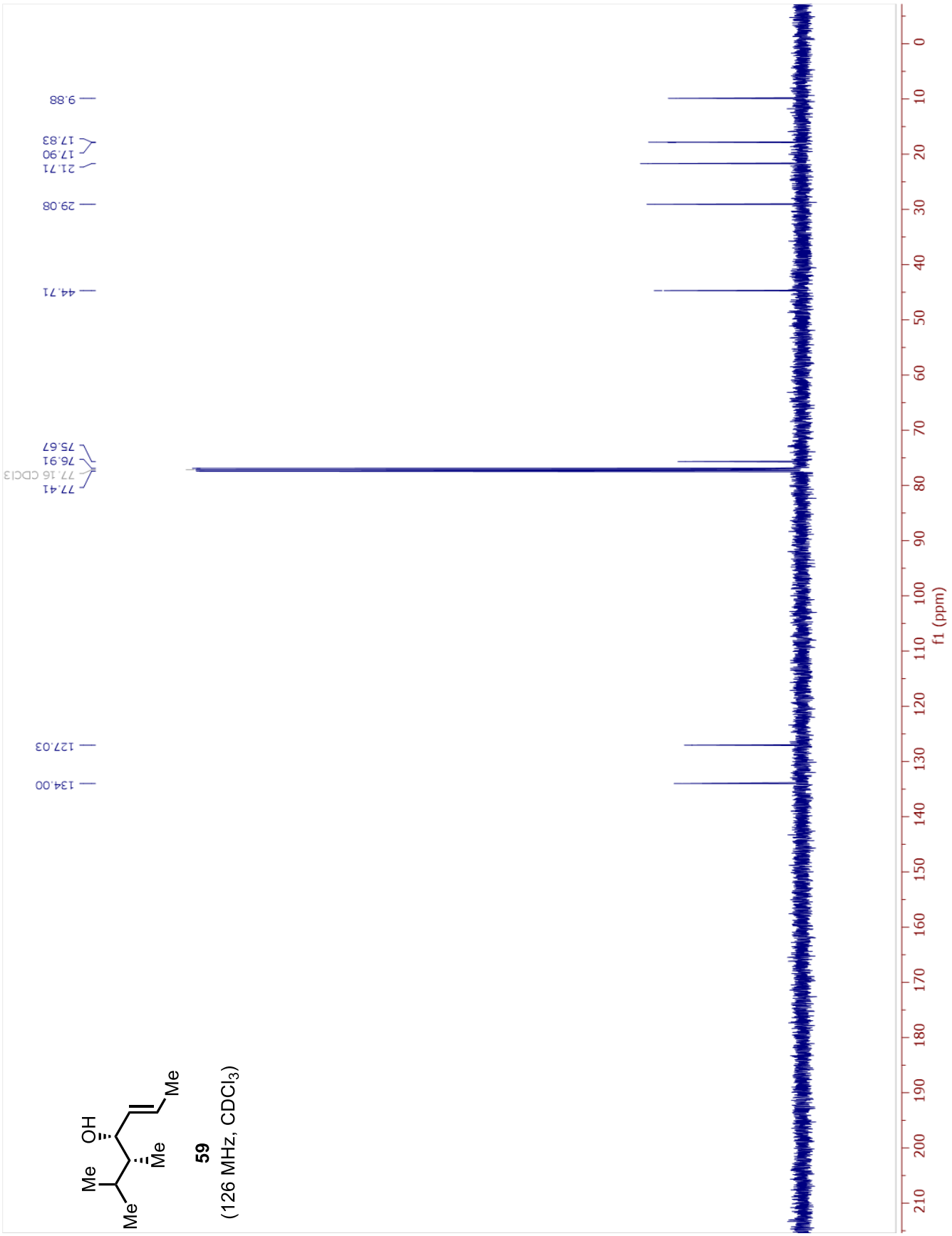
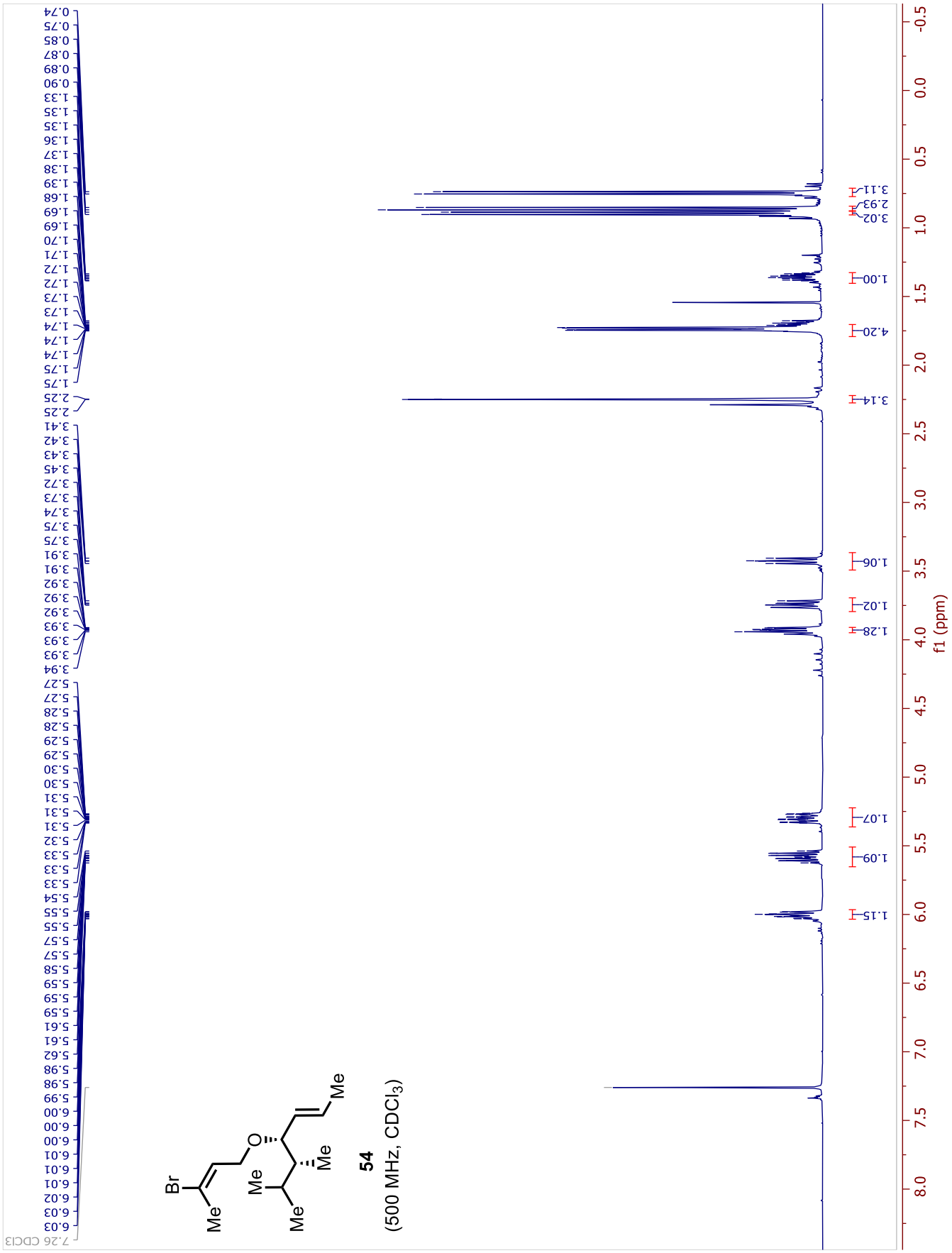
-3.71
18.19
22.59
23.67
24.98
25.02
25.84
26.19
30.87
31.50
34.70
35.76
37.32
40.39
45.40
64.19
64.34
74.93
76.91
77.16 CDCl3
77.41
82.81
110.10
f1 (ppm)
Bpin
OTBS
Me
H
O
O
38
(126 MHz, CDCl3)


Me
O
Me
Me
Me
58
(500 MHz, CDCl3)
7.26 CDCl3
2.36
2.35
2.33
2.32
2.31
2.17
2.17
2.16
2.15
2.15
2.13
2.12
2.11
2.02
1.09
1.07
0.96
0.95
0.87
0.86
3.30
3.32
3.19
3.16
1.05
1.00
f1 (ppm)


192.51
90.46
79.76
77.41
77.16 CDCl3
76.91
54.99
30.13
21.32
18.58
12.06
4.24
f1 (ppm)
Me
O
Me
Me
Me
58
(126 MHz, CDCl3)


Me
OH
Me
Me
Me
59
(500 MHz, CDCl3)
f1 (ppm)


Me
OH
Me
Me
Me
59
(126 MHz, CDCl3)
9.88
17.83
17.90
21.71
29.08
44.71
75.67
76.91
77.16 CDCl3
77.41
127.03
134.00
f1 (ppm)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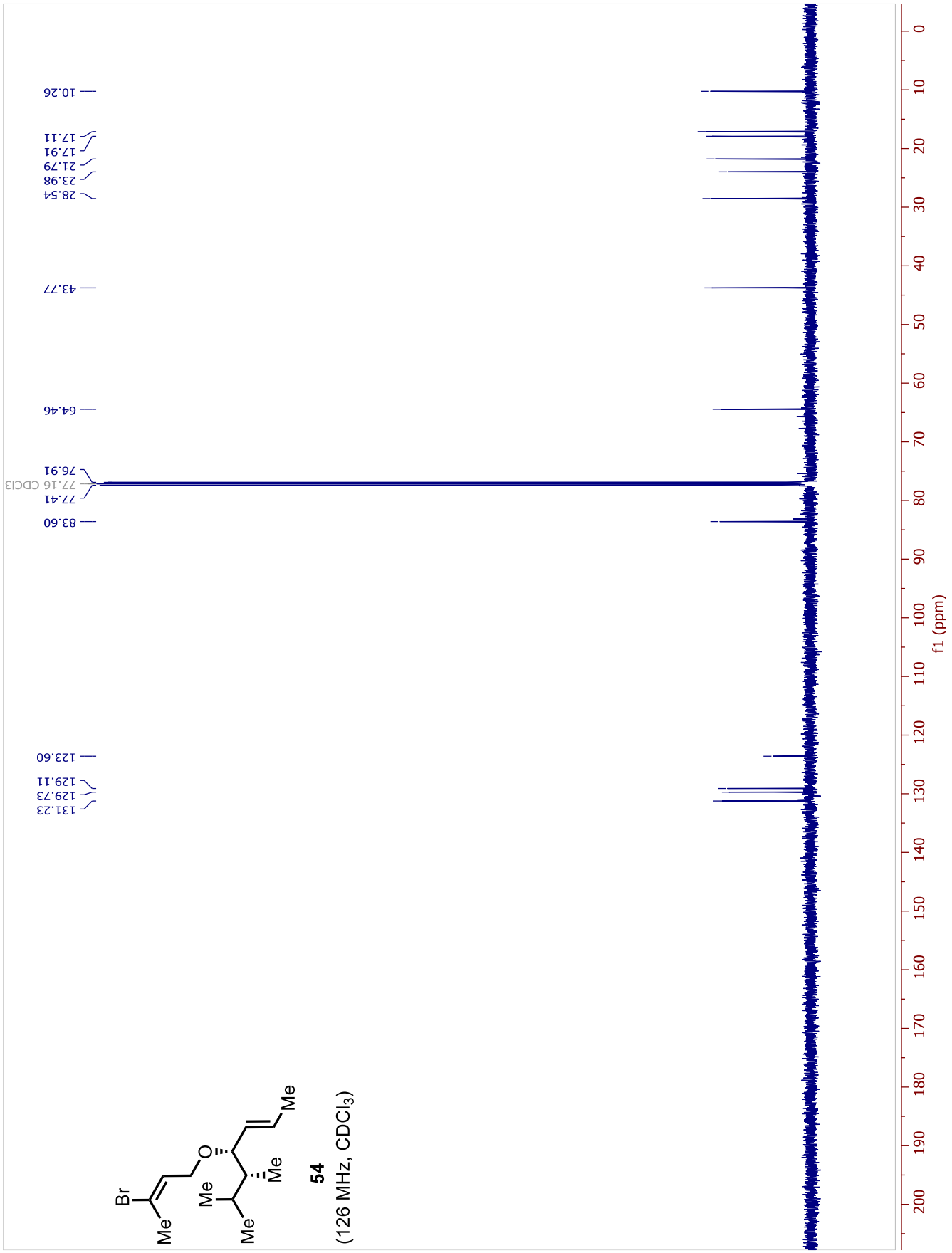
Me
Me
O
Me
Me
Me
54
(500 MHz, CDCl3)
f1 (ppm)


Br
Me
Me
O
Me
Me
Me
54
(126 MHz, CDCl3)
10.26
17.11
17.91
21.79
23.98
28.54
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77.16 CDCl3
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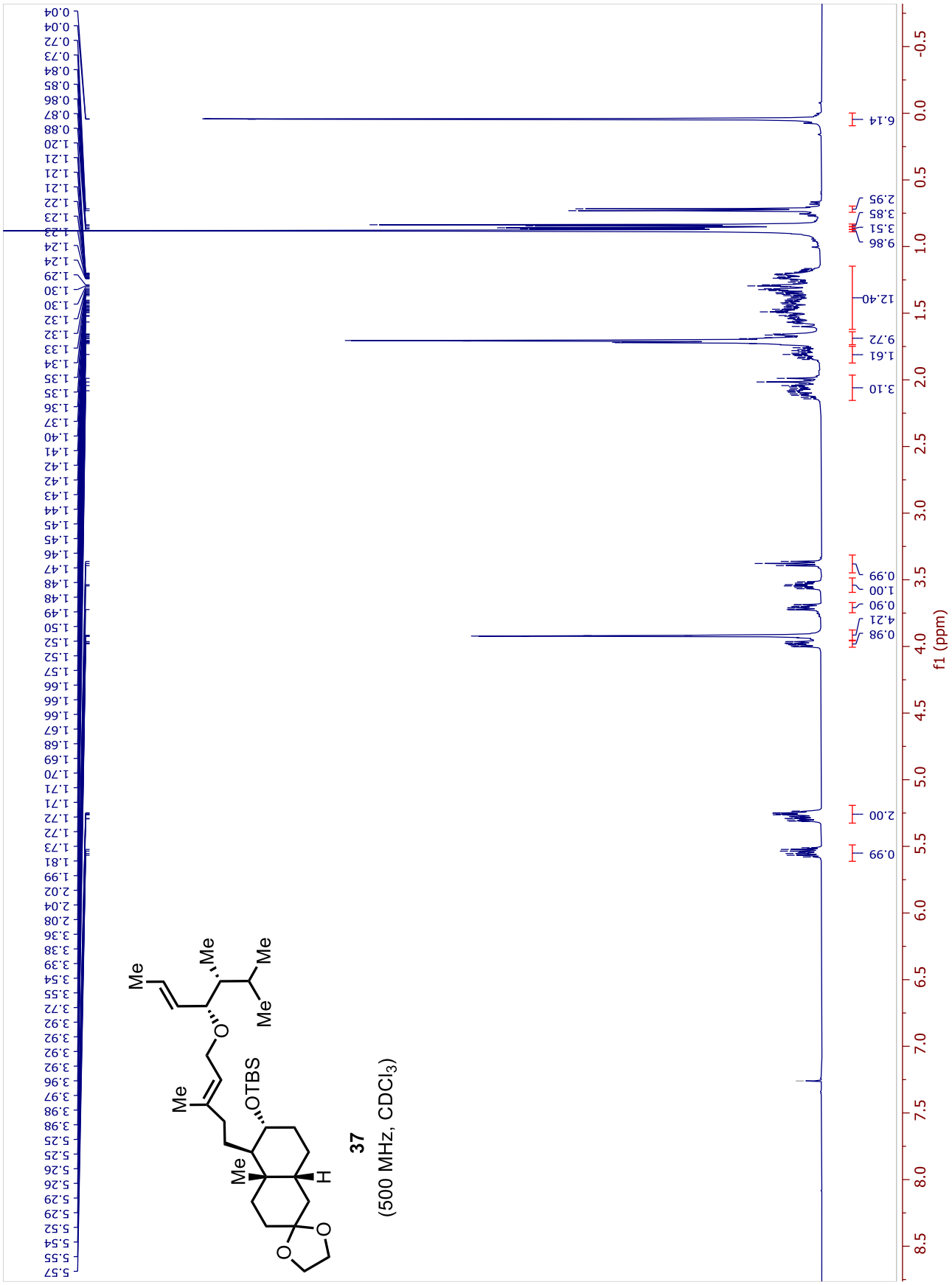
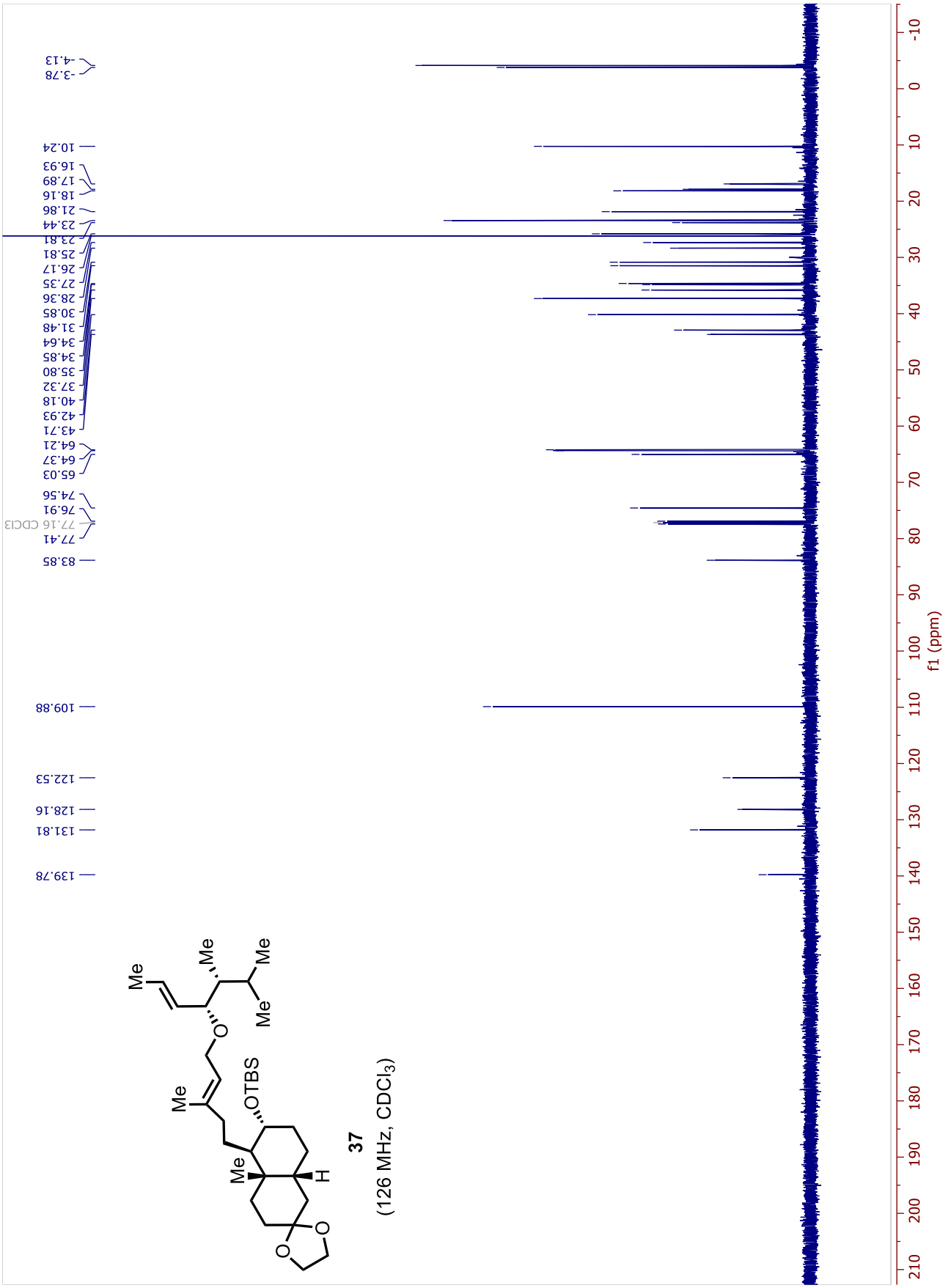
123.60
129.11
129.73
131.23
f1 (ppm)


Me
Me
Me
Me
Me
OTBS
Me
H
O
O
O
37
(500 MHz, CDCl3)
f1 (ppm)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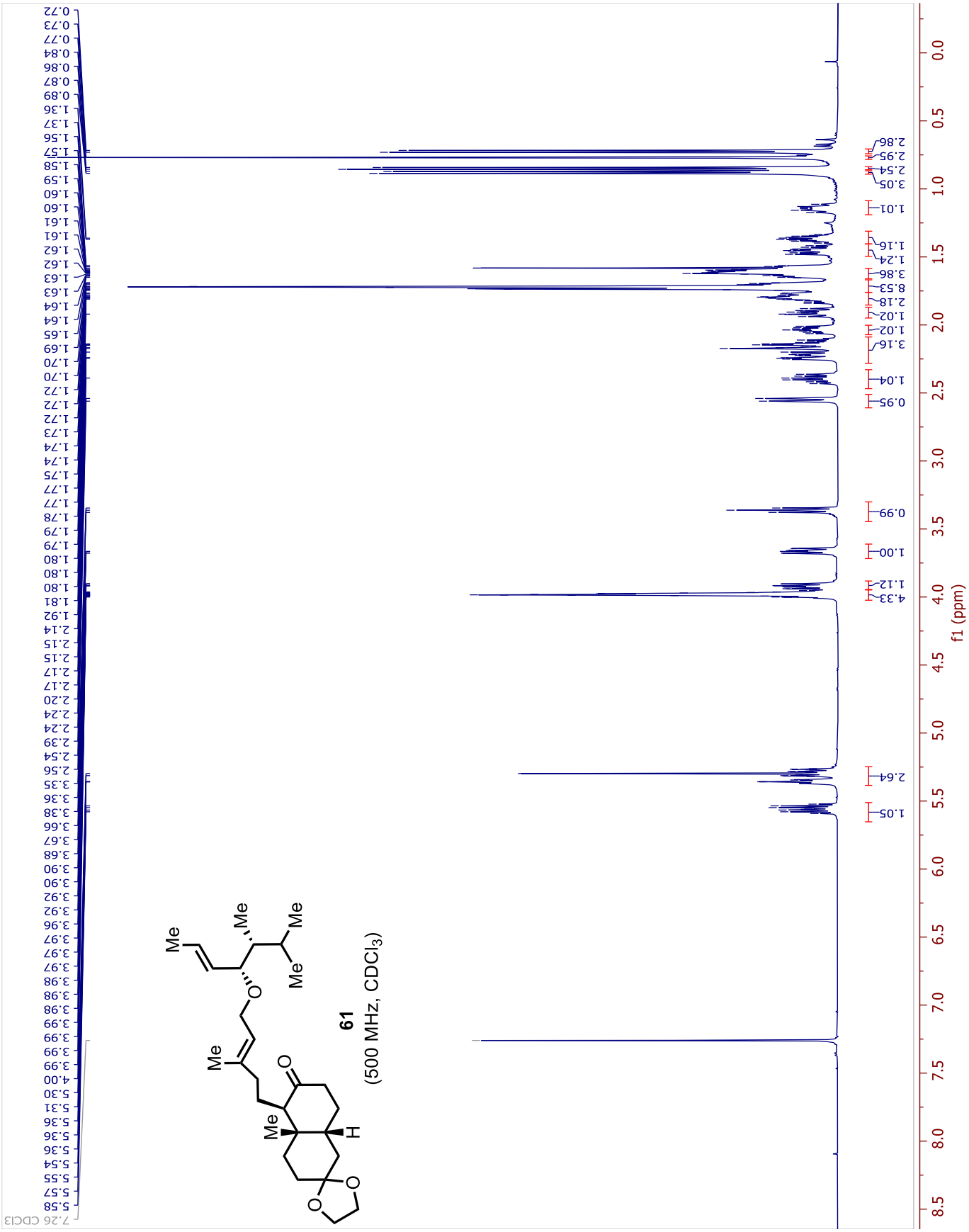
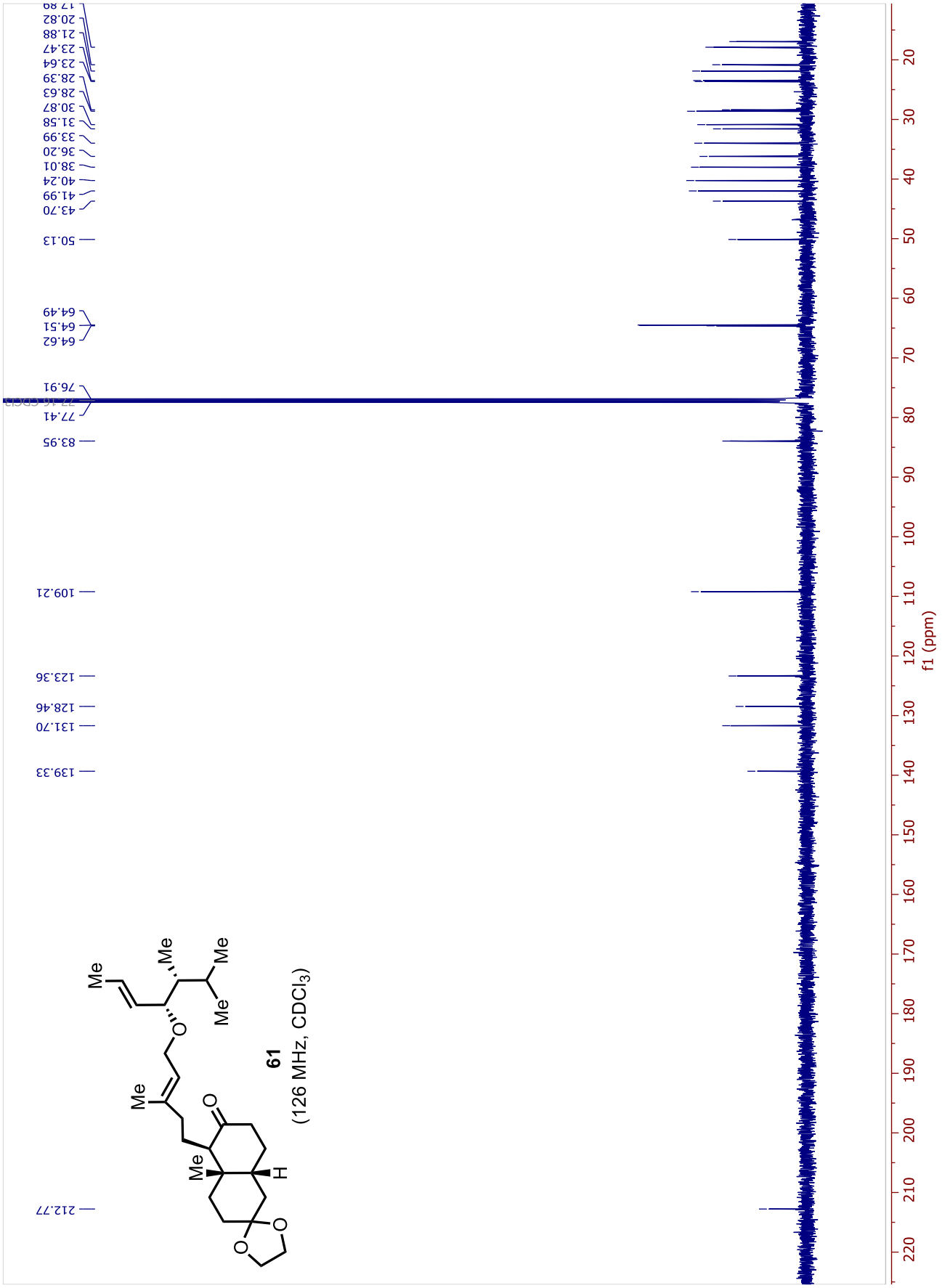
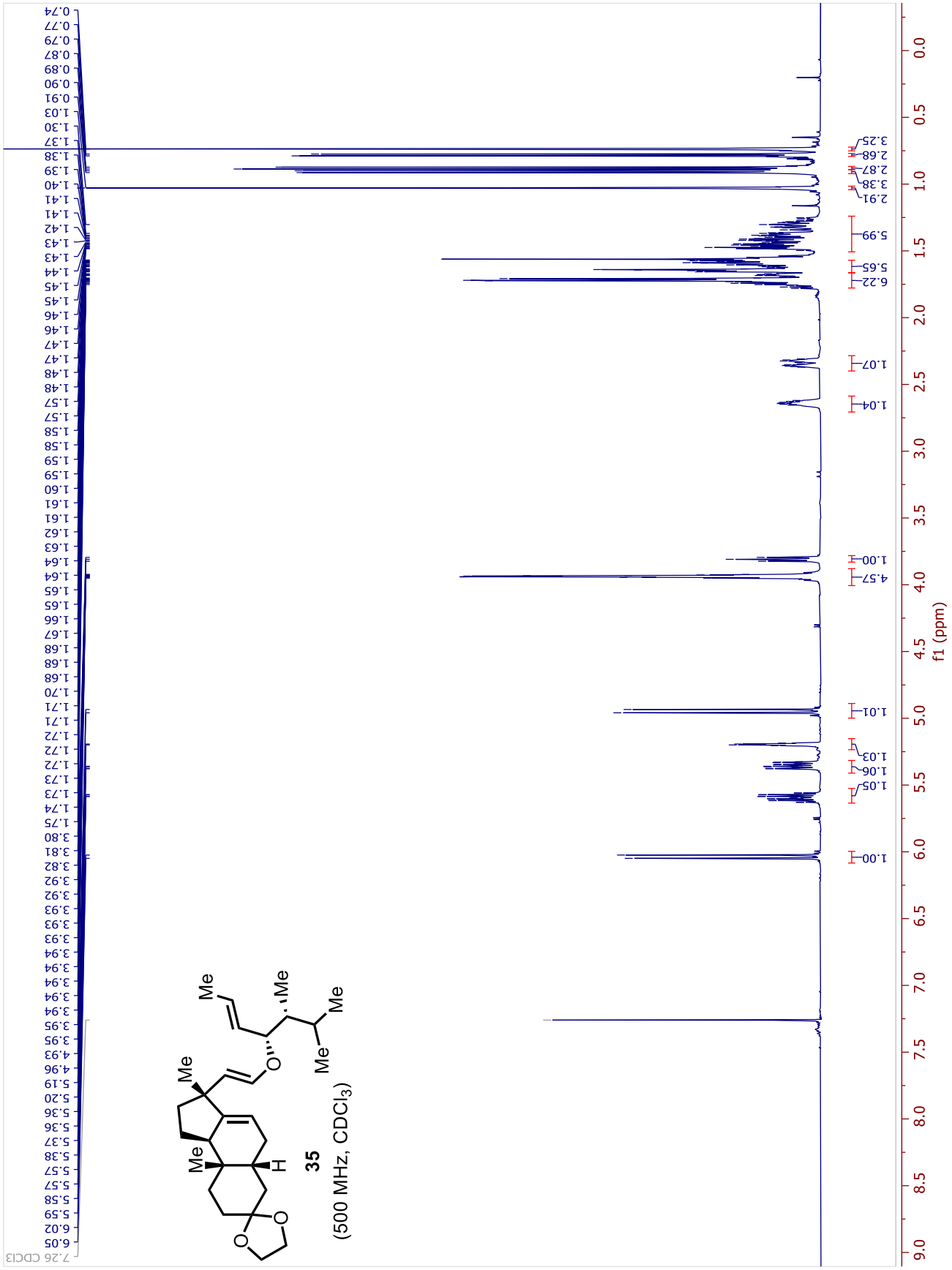
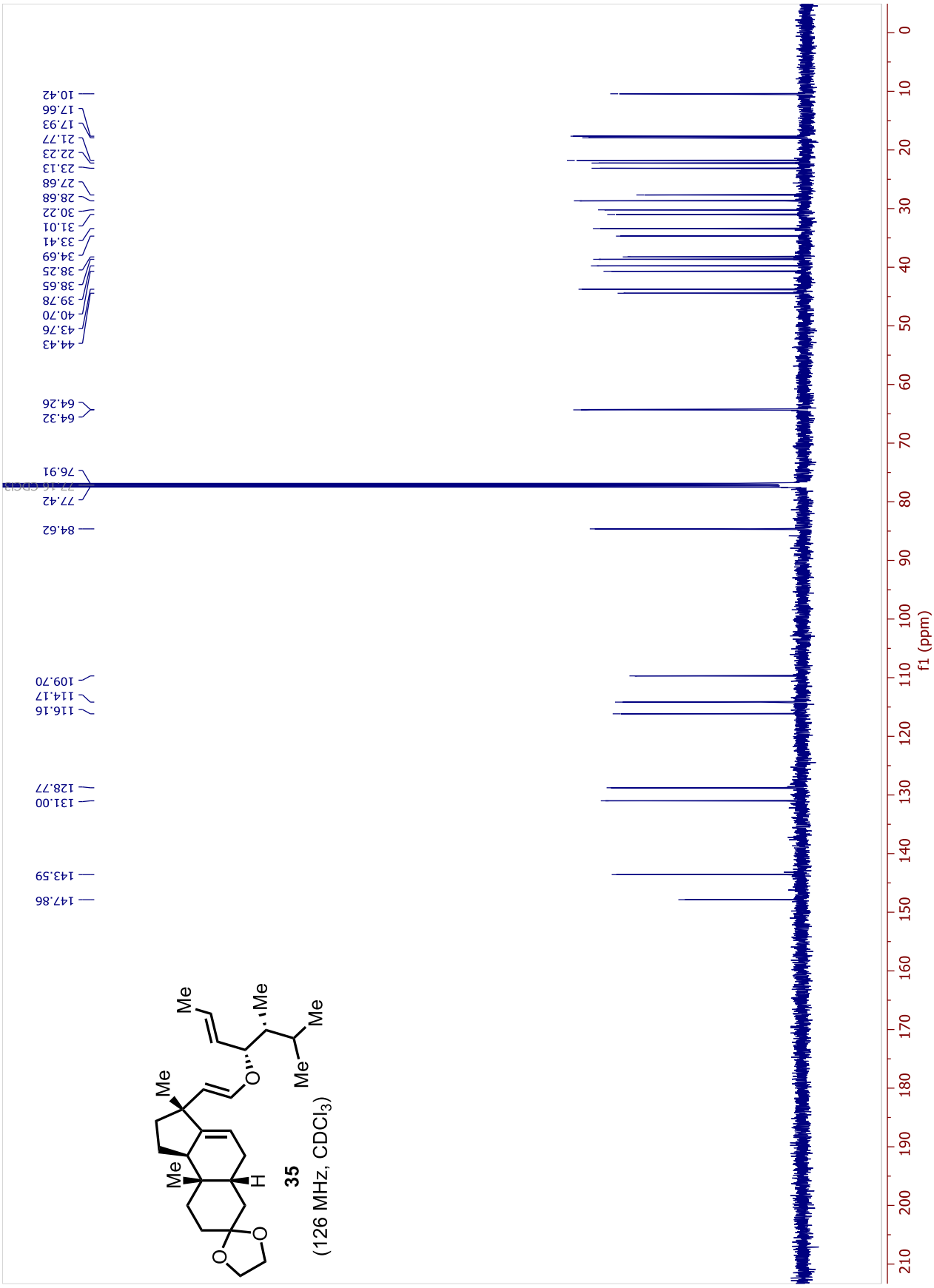
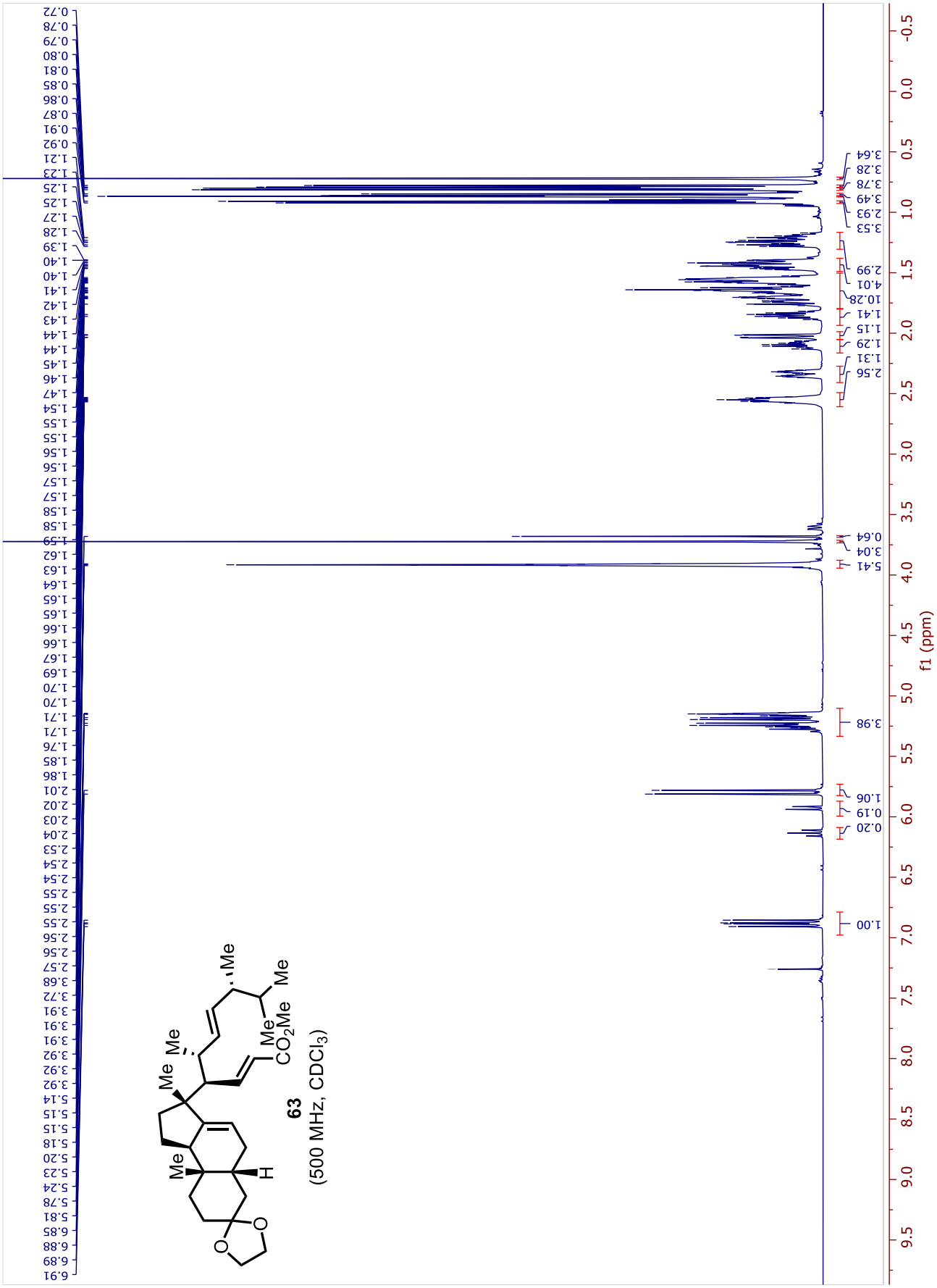
-3.78
10.24
16.93
17.89
18.16
21.86
23.44
23.81
25.81
26.17
27.35
28.36
30.85
31.48
34.64
34.85
35.80
37.32
40.18
42.93
43.71
64.21
64.37
65.03
74.56
76.91
77.16 CDCl3
77.41
83.85
109.88
122.53
128.16
131.81
139.78
Me
Me
Me
Me
O
OTBS
Me
H
O
O
37
(126 MHz, CDCl3)
f1 (ppm)

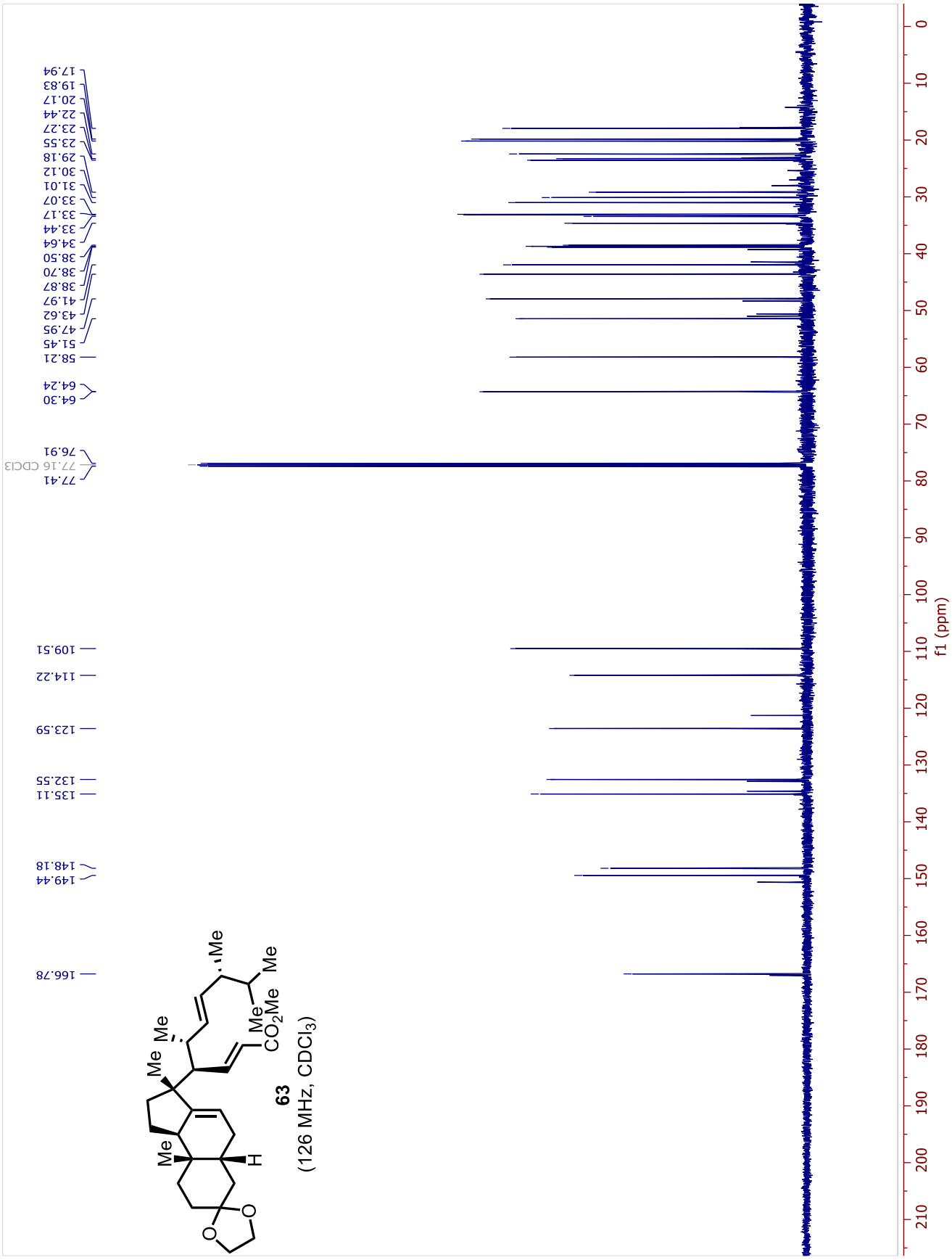

Me
Me
Me
Me
O
Me
O
Me
H
O
O
61
(500 MHz, CDCl3)
f1 (ppm)


17.89
20.82
21.88
23.47
23.64
28.39
28.63
30.87
31.58
33.99
36.20
38.01
40.24
41.99
43.70
50.13
64.49
64.51
64.62
76.91
77.41
83.95
109.21
123.36
128.46
131.70
139.33
212.77
Me
Me
Me
Me
O
Me
O
Me
H
O
O
61
(126 MHz, CDCl3)
f1 (ppm)


Me
Me
Me
Me
Me
H
O
O
O
35
(500 MHz, CDCl3)
f1 (ppm)


147.86
143.59
131.00
128.77
116.16
114.17
109.70
84.62
77.42
76.91
64.32
64.26
44.43
43.76
40.70
39.78
38.65
38.25
34.69
33.41
31.01
30.22
28.68
27.68
23.13
22.23
21.77
17.93
17.66
10.42
f1 (ppm)
Me
Me
Me
Me
Me
O
O
O
H
35
(126 MHz, CDCl3)


Me
Me
Me
Me
Me
CO_2Me
H
O
O
63
(500 MHz, $CDCl_3$)
f1 (ppm)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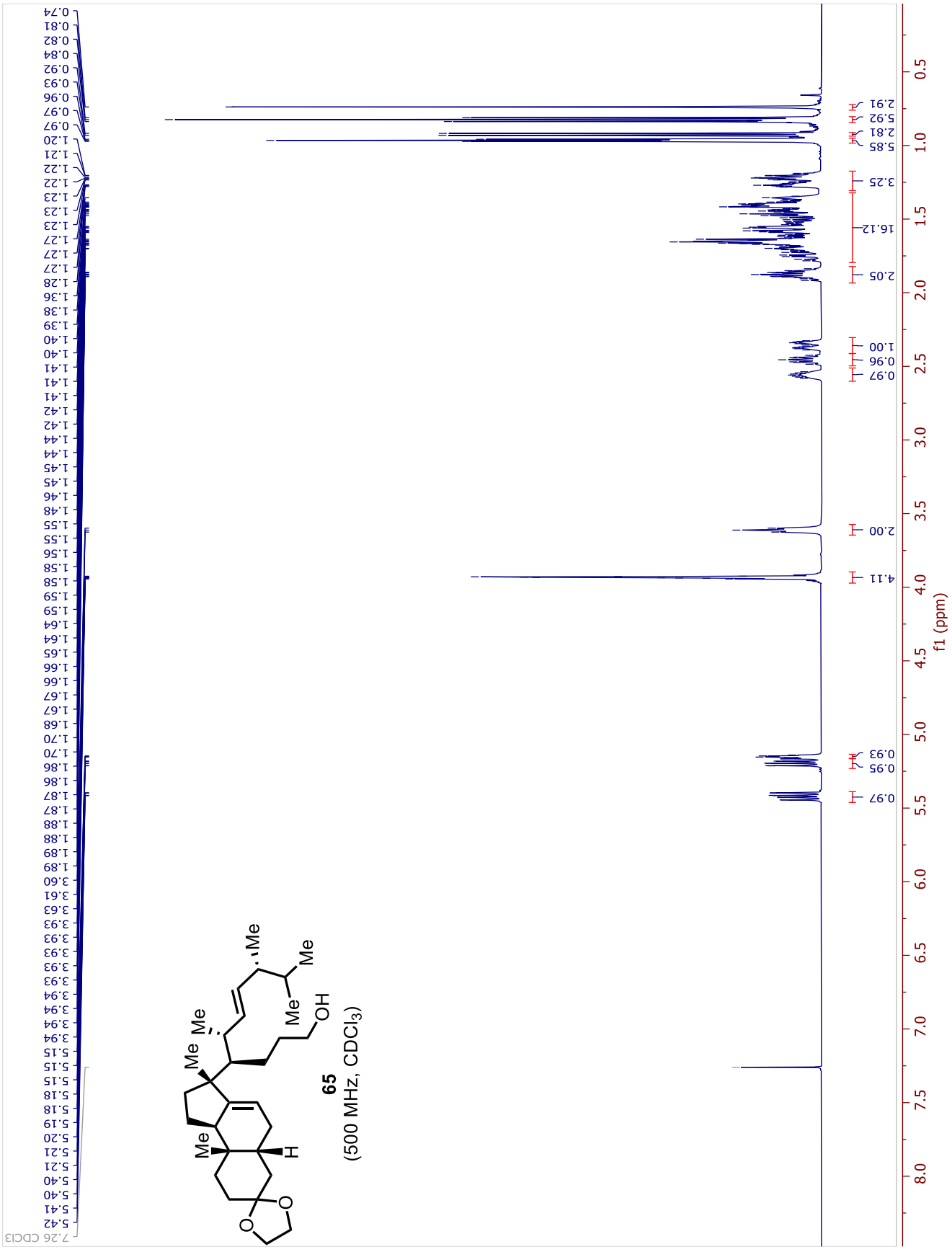
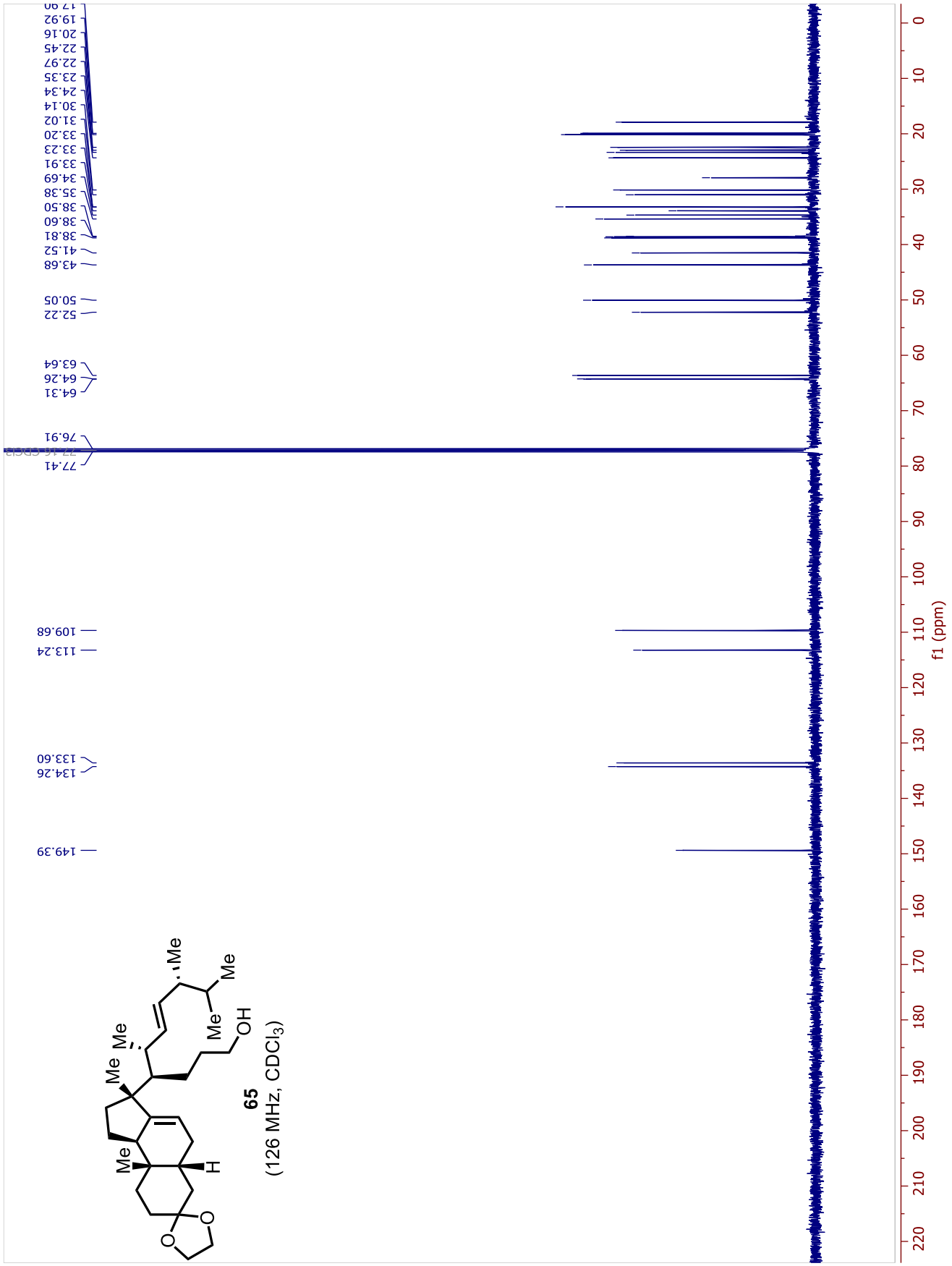
135.11
132.55
123.59
114.22
109.51
77.41
77.16 CDCl3
76.91
64.30
64.24
58.21
51.45
47.95
43.62
41.97
38.87
38.70
38.50
34.64
33.44
33.17
33.07
31.01
30.12
29.18
23.55
23.27
22.44
20.17
19.83
17.94
Me
Me
Me
Me
Me
CO2Me
H
O
O
63
(126 MHz, CDCl3)
f1 (ppm)


Me
Me
Me
Me
Me
OH
H
O
O
65
(500 MHz, CDCl3)
f1 (ppm)


17.90
19.92
20.16
22.45
22.97
23.35
24.34
30.14
31.02
33.20
33.23
33.91
34.69
35.38
38.50
38.60
38.81
41.52
43.68
50.05
52.22
63.64
64.26
64.31
76.91
77.41
109.68
113.24
133.60
134.26
149.39
Me
Me
Me
Me
Me
OH
H
O
O
65
(126 MHz, CDCl3)
0
10
20
30
40
50
60
70
80
90
100
110
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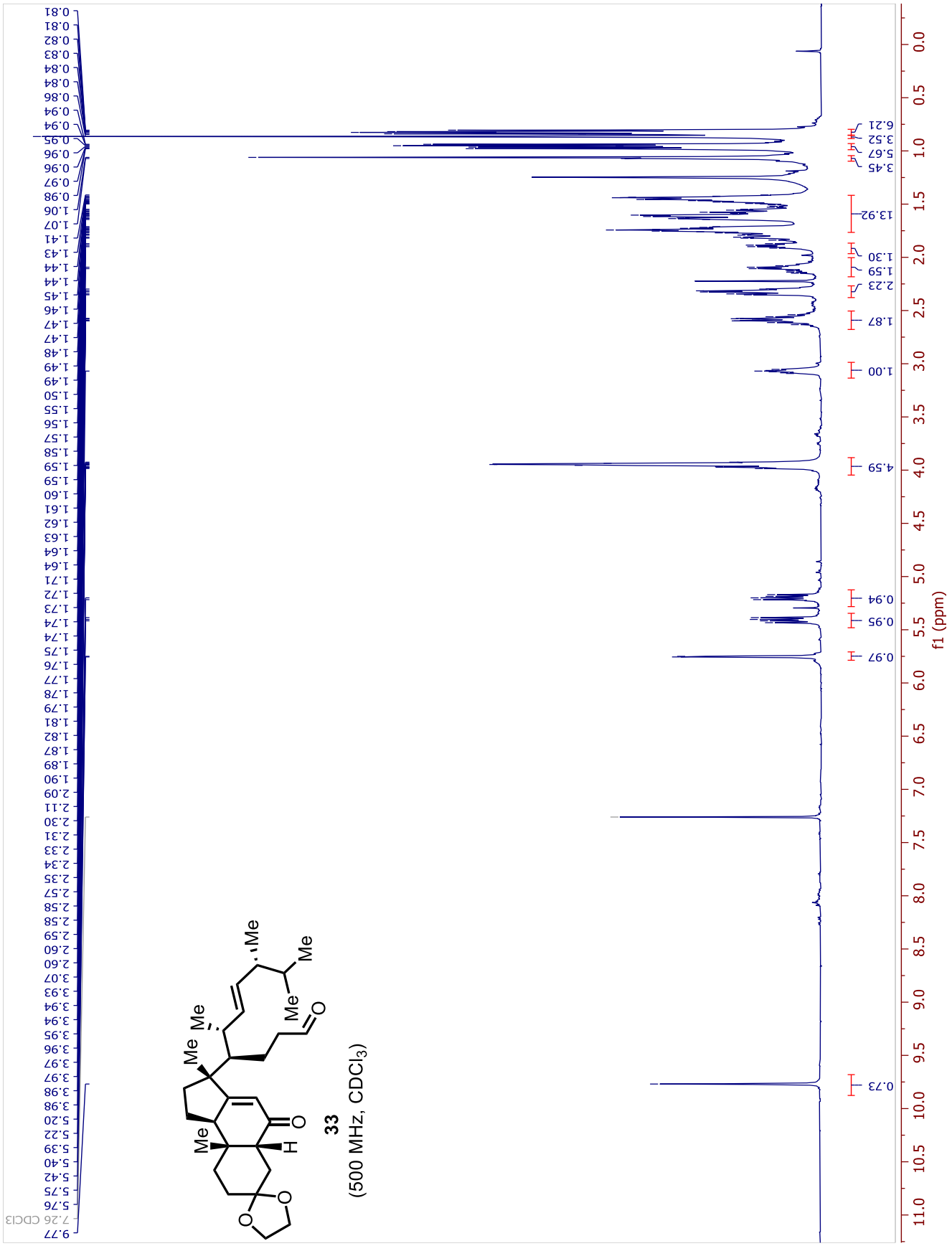
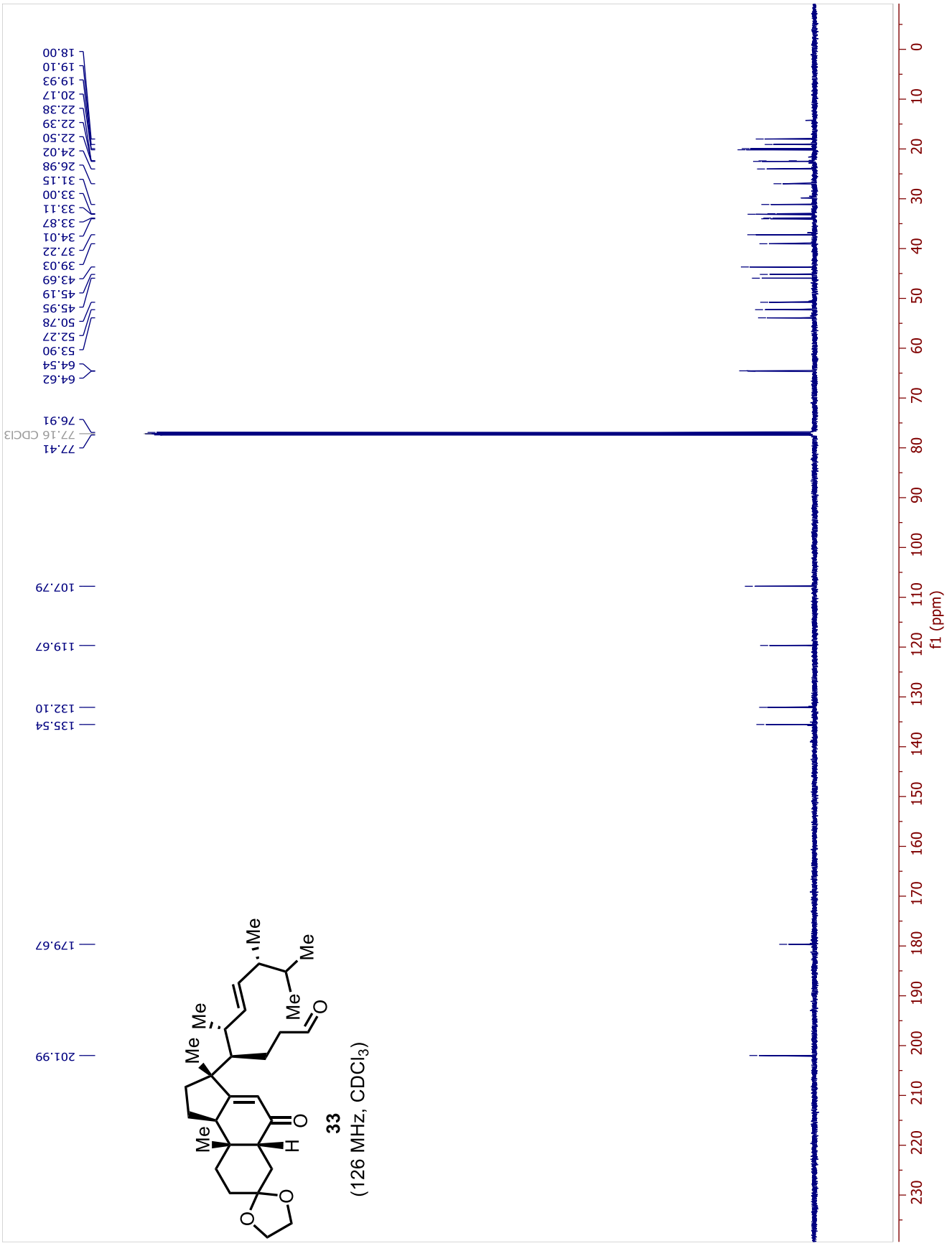
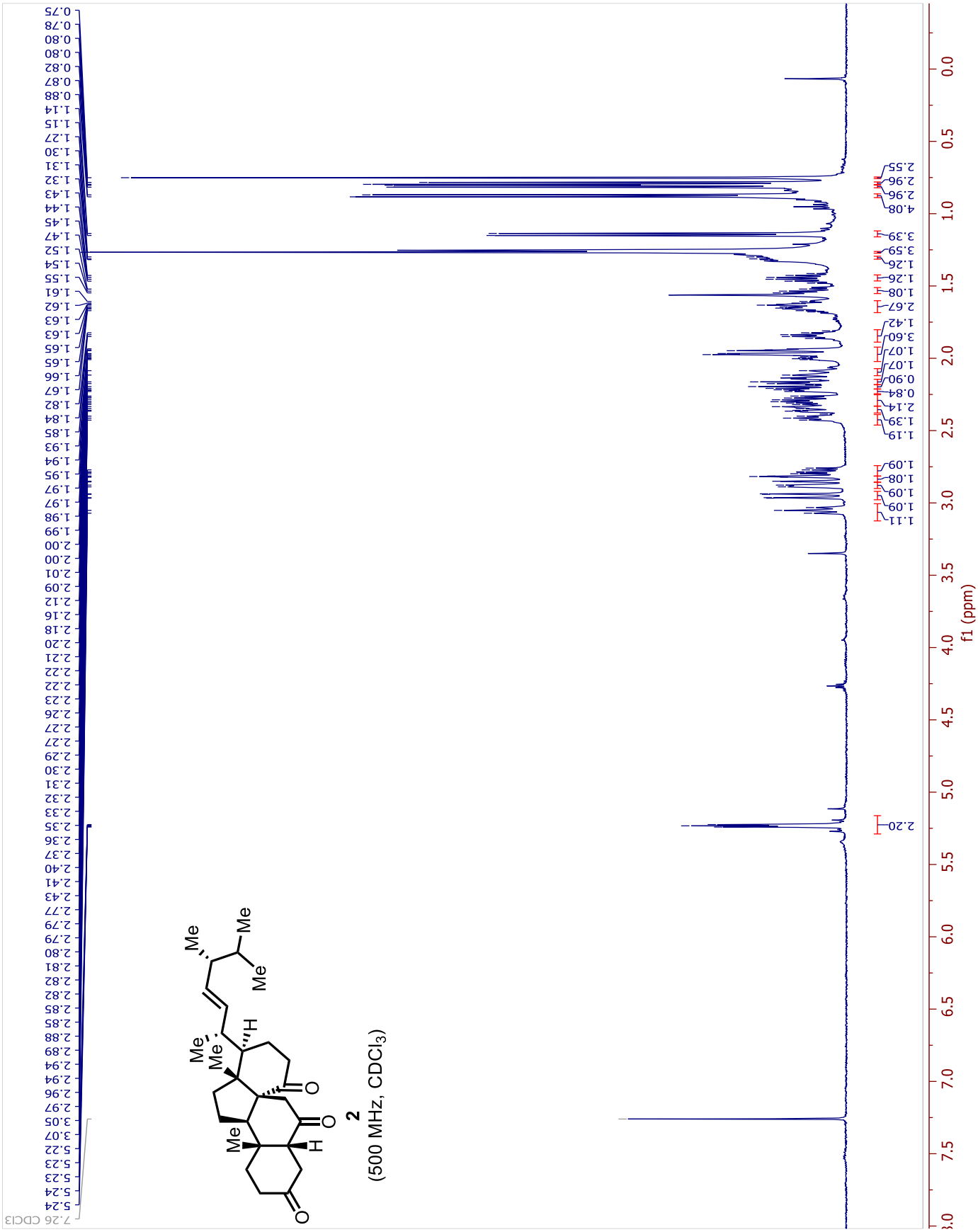
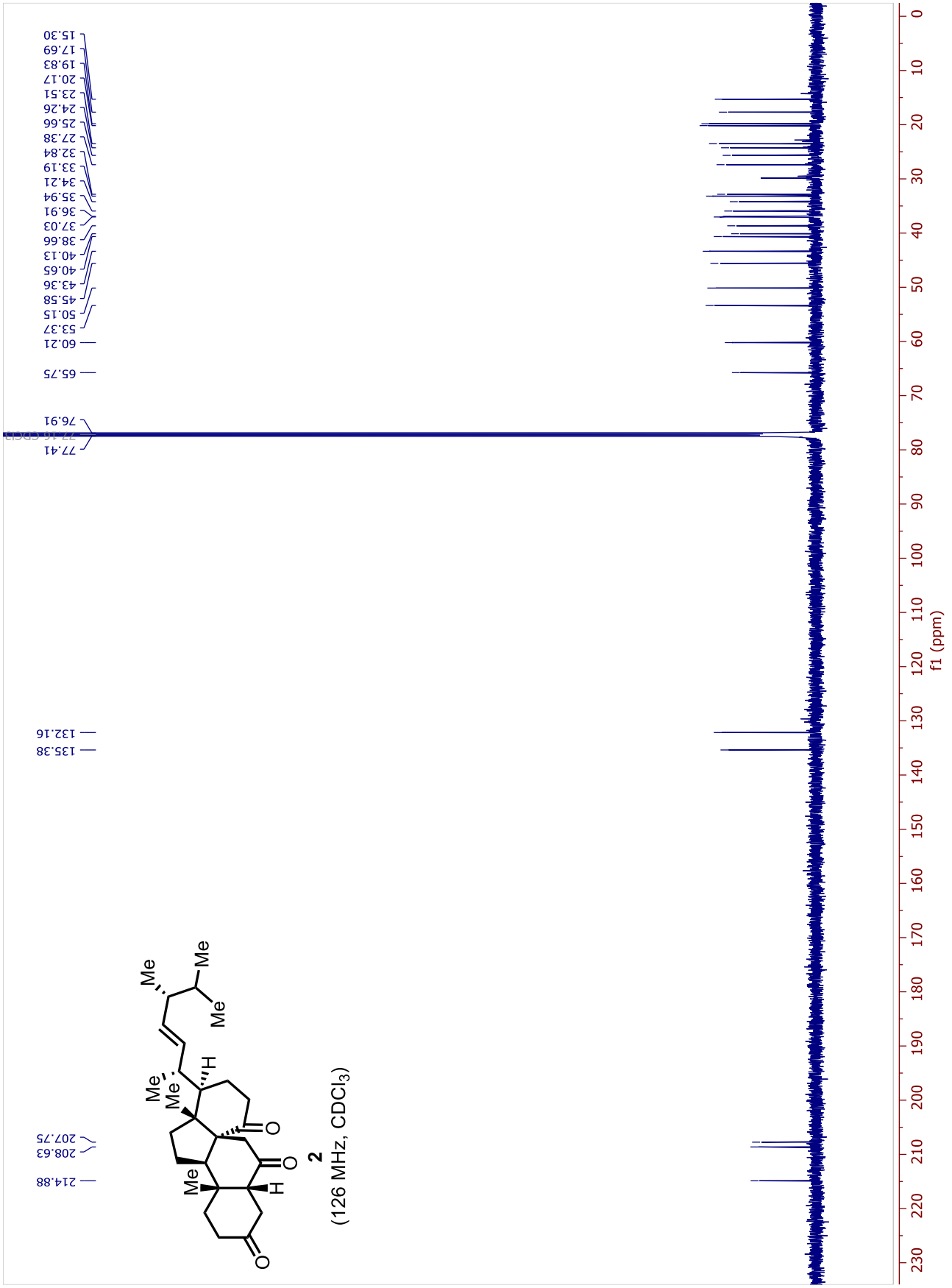
160
170
180
190
200
210
220
f1 (ppm)


Me
Me
Me
Me
Me
O
O
H
O
O
33
(500 MHz, CDCl3)
f1 (ppm)


18.00
19.10
19.93
20.17
22.38
22.39
22.50
24.02
26.98
31.15
33.00
33.11
33.87
34.01
37.22
39.03
43.69
45.19
45.95
50.78
52.27
53.90
64.54
64.62
76.91
77.16 CDCl3
77.41
107.79
119.67
132.10
135.54
179.67
201.99
Me
Me
Me
Me
Me
H
O
O
O
O
33
(126 MHz, CDCl3)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
f1 (ppm)


Me
Me
Me
Me
H
O
O
O
H
Me
2
(500 MHz, CDCl3)
f1 (ppm)


15.30
17.69
19.83
20.17
23.51
24.26
25.66
27.38
32.84
33.19
34.21
35.94
36.91
37.03
38.66
40.13
40.65
43.36
45.58
50.15
53.37
60.21
65.75
76.91
77.41
132.16
135.38
207.75
208.63
214.88
Me
Me
Me
Me
Me
H
H
O
O
O
2
(126 MHz, CDCl3)
f1 (ppm)