SYNTHESIS OF SIX MEMBERED NITROGEN HETEROCYCLES:

BORONATE MEDIATED FUNCTIONALIZATION OF PYRIDINE AND THE

SELECTIVE SYNTHESIS OF (+)-DYSOLINE

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by

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SYNTHESIS OF SIX MEMBERED NITROGEN HETEROCYCLES: BORONATE MEDIATED FUNCTIONALIZATION OF PYRIDINE AND THE SELECTIVE SYNTHESIS OF (+)-DYSOLINE

Publication_____

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Nitrogen containing heterocycles play a crucial role in the discovery and development of therapeutically important compounds. As of 2014 an analysis performed by Njarðarson *et al.* identified that 59 % (640 out of 1086) of all FDA approved drugs contain a nitrogen heterocycle.[1] Piperidine (19%, 72 FDA approved drugs) and pyridine (16.4%, 62 FDA approved drugs) represent the most abundant of these nitrogen heterocycles. Further inflating the role of *N*-heterocycles is their prevalence in Nature, in particular alkaloid natural products represent versatile structural motifs that have been of synthetic and therapeutic interest for decades. Discussed herein are two projects related to the preparation and study of *N*-heterocycles: A methodology involving

[1] Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014,** *57*, 10257-10274

boronate mediated functionalization of pyridines and the total synthesis of the chromone alkaloid (+)- dysoline.

Addition of a metalated nucleophile to pyridine boroinc ester with subsequent activation propagates a 1,2 boron to carbon migration. The resulting dihydropyridine intermediate can then be subjected to a variety of conditions allowing access to the desired pyridine, dihydropyridine, tetrahydropyridine or piperidine motif. This reaction was shown to work for a variety of nucleophiles, in addition substitution of the pyridine boronic ester was well tolerated. Expansion of this method into the quinoline and isoquinoline also gave positive results albeit with more moderate yields.

Dysoline, a novel chromone alkaloid isolated from *Dysoxylum binectariferun*, was reported to have selective cytotoxicity for HT1080 fibrosarcoma cells (IC_{50} of 0.21 μM). Given the scarcity of natural material a concise and selective synthesis of (+)-dysoline has been developed allowing for further biological evaluation. Construction of the C6 chromone core with complete regioselectivity was achieved with a Danheiser benzannulation. Additionally, an enantioselective nucleophile catalyzed aldol lactonization (NCAL) formed the piperidine ring with control of relative and absolute stereochemistry.

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Prior Publications

Coffin, A.; Ready, J. M. Selective Synthesis of (+)-Dysoline, *Org. Lett.* **2019**, 21, 648

Panda, S.; **Coffin, A**.; Nguyen, Q. N.; Tantillo, D. J.; Ready, J. M. Synthesis and Utility of Dihydropyridine Boronic Esters, *Angew. Chem. Int. Ed.* **2016**, *55*, 2205-2209

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List of Definitions

Å	angstrom
Ac	acetyl
AIBN	2,2'-azobis(2-methylpropionitrile)
Ar	aryl
aq	aqueous
BF_3•OEt_2	boron trifluoride etherate
BCl_3	boron trichloride
B_2H_6	diborane
Bn	benzyl
Boc	*tert*-butyl carbamate
Br_2	bromine
Bu	butyl
^{s}Bu	*sec*-butyl
^{t}Bu	*tert*-butyl
Bz	benzoyl
ºC	degrees celsius
CAN	cerium ammonium nitrate
cat	catalyst or catalytic amount
Cbz	carbobenzyloxy
CH_2Cl_2	dichloromethane
$CHCl_3$	chloroform

CoA	coenzyme A
cod	1,5 cyclooctadiene
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
Δ	heating or refluxing temperature
d	doublet
DABCO	1,4-diazobicyclo[2.2.2]octane
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMS	dimethyl sulfide
ee	enantiomeric excess
ESI+	electrospray ionization, positive mode
Et	ethyl
Et_2O	diethyl ether
g	grams
HCl	hydrochloric acid
^{c}Hex	cyclohexyl
HMBC	heteronuclear multi-bond correlation spectroscopy
HMPA	hexamethylphosphormide
HPLC	high performance liquid chromatography
HSQC	heteronuclear single quantum coherence spectroscopy

Hz	hertz
I_2	iodine
IBX	2-iodoxy benzoic acid
IC_{50}	half maximal inhibitory concentration
IL-6	Interleukin-6
IPA	Isopropyl alcohol
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
λ	wavelength
L	liter
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
$LiAlH_4$	lithium aluminum hydride
m	multiplit
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	methyl
MeOH	methanol
MHz	megahertz
MIDA	methyliminodiacetic acid
$[M+H]^+$	adduct ion
ms	mesyl
mmol	millimole
μM	micormolar

MOM	Methoxymethyl ether
M.S.	molecular sieves
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NHC	*N*-heterocyclic carbene
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
OAc	acetate
Ph	phenyl
PhCl	chlorobenzene
PhMe	toluene
pin	pinacol
PPh_3	triphenylphosphine
ppm	parts per million
^{i}Pr	isopropyl
$^{i}Pr_2NEt$	*N,N*-diisopropylethylamine (Hünigs base)
q	quartet
Rf	retention factor
rt	room temperature
s	singlet
sm	starting material
t	triplet
TFA	trifluoroacetic acid

TFAA	trifluoroacetic anhydride
Tf	trifluoromethanesulfonate (triflate)
THF	tetrahydrofuran
$TiCl_4$	titanium tetrachloride
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TNF-α	tumor necrosis factor
Troc	2,2,2-trichloroethyoxy carbonyl
Ts	toluenesulfonyl (tosyl)
*p*TSA	*p*-toluenesulfonic acid
UV	ultraviolet
xPhos	2-dicyclohexylphosphino-2',4',6'-triisoprpylbiphenyl

Chapter 1: Boronate Mediated Functionalization of Pyridine

1.1 Applicable Pyridine Synthesis

Considering the prominence that nitrogen heterocycles, in particular pyridine and piperidine, play in medicinal research, numerous strategies are available for their preparation and substitution.[1] For the purpose of brevity only select examples will be discussed, mainly those involving the substitution of already formed pyridine rings. These methods can be divided into those in which aromaticity is broken, invoking a Meisenheimer intermediate, and those that do not involve formation of a discrete dihydropyridine intermediate.

1.1.1 Pyridine Substitution Involving a Meisenheimer Intermediate

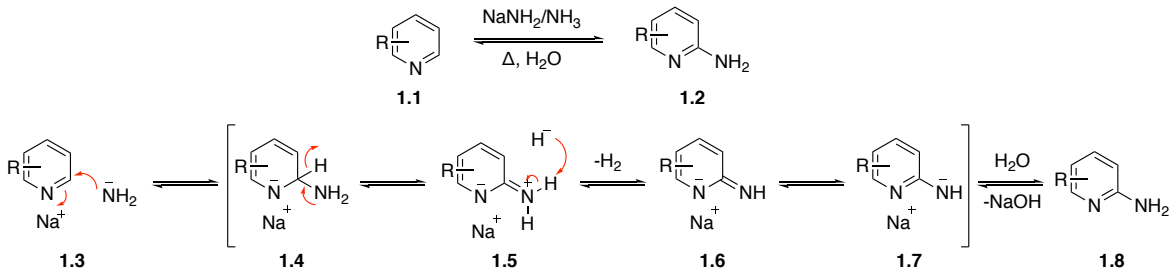
1.1.1.1 The Chichibabin Reaction

Addition of a nucleophile to *N*-activated pyridines, resulting in formation of a Meisenheimer intermediate, offer some of the oldest methods utilized for preparation of substituted pyridines. The earliest example of this type of reaction dates back to 1914 when Chichibabin reported the amination of pyridine with sodium amide (scheme 1.1).[2] The Chichibabin process has become a useful and common method for preparation of aminopyridine derivatives, more importantly this reaction showed that nitrogen activation leads to increased electrophilicity of the pyridine ring. Although the initial reaction required harsh conditions, advances over the years have allowed for moderate improvements in this transformation.

Mechanistically the Chichibabin reaction relies on activation of the pyridine nitrogen with sodium serving as a Lewis acid. Addition of ammonia to *N*-activated pyridine **1.3** generates a

Meisenheimer intermediate (**1.4**). Rearomatization of this intermediate, with formal loss of hydrogen, leads to the desired amino pyridine product **1.8.** This oxidation has also been proposed to occur through loss of sodium hydrides, with no clear evidence supporting either route.

Scheme 1.1 The Chichibabin Reaction

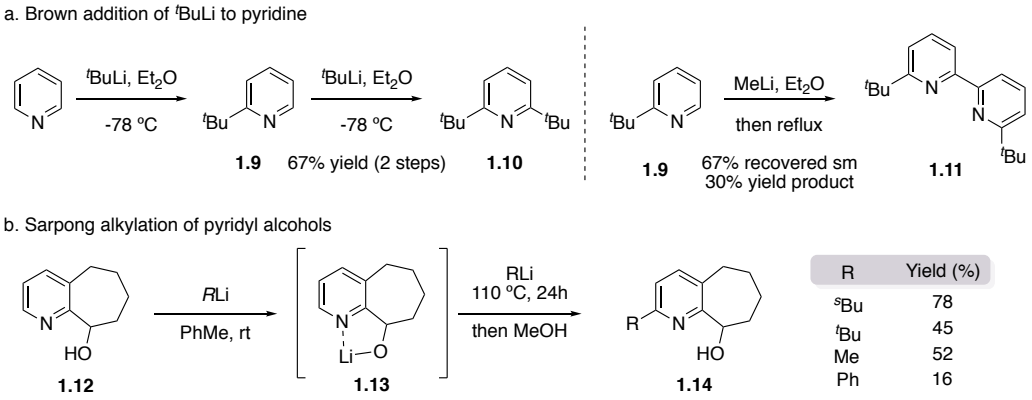


Building from the original Chichibabin reaction, Brown and coworkers demonstrated the application of this method for preparation of alkyl pyridine products (**1.10**, Scheme 1.2a).[3] This reaction exploits an analogous Chichibabin mechanism, in which lithium acts as a Lewis acid activating pyridine for attack from the alkyl nucleophile, *tert*-butyl lithium.[4] Interestingly, while *tert*-butyl lithium gives the desired 2-*tert*-butylpyridine (**1.9**) or 2,6-di-*tert*-butylpyridine (**1.10)**, methyl or ethyl lithium reagents instead lead to isolation of dimerized product **1.11**, in low yields, in addition to recovered starting material. This observation is attributed to competing metalation, giving the 2-lithio pyridine species which then acts as a nucleophile with a second equivalent of pyridine.

More recently Sarpong *et al.* expanded the scope of alkyl nucleophiles capable of addition under these conditions (Scheme 1.2b).[5] Formation of an adjacent lithium alkoxide **1.13** enhances the coordination of lithium, increasing the electrophilicity of pyridine resulting in a bias for nucleophilic addition as opposed to deprotonation. The authors also postulated that an increase in nucleophilicity of the alkyl lithium would result from an interaction of the alkoxide lone pair. While this methodology offers an expanded nucleophile substrate scope from that of Brown *et al.*,

only moderate yields were observed in addition to limiting the pyridine to those containing an α-hydroxyl functionality.

Scheme 1.2 Applications of the Chicibabin Reaction

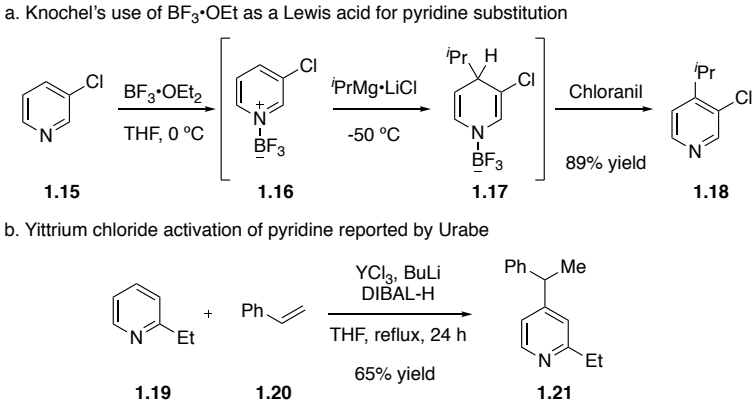


1.1.1.2 Lewis Acid Activation of Pyridine

Given the poor Lewis acidity of sodium and lithium, recent attention has focused on exploring alternate Lewis acids capable of activating pyridine. In particular Knochel *et. al.* reported the propensity of BF_3•OEt_2 to incite pyridines for attack from metalated nucleophiles (Scheme1.3a).[6] Improved reactivity of this systems allows for milder reaction conditions and an improved substrate scope, with various Grignard and alkylzinc nucleophiles showing good results. Interestingly, in contrast to previously reported methods, these conditions result in excellent regioselectivity for 4-substituted pyridine products **1.18**. Although this regioselectivity is not well understood it is postulated to derive from aggregation of the Grignard reagents, this aggregation is also proposed to be crucial in the increased reactivity of the nucleophile.

In a similar fashion Urabe reported the use of Yittrium chloride as a competent Lewis acid, leading to similar products (**1.21**, Scheme 1.3b).[7] As with BF_3•OEt_2 regioselectivity of this reaction is presumed the result of pyridine coordination to a metalated nucleophile complex. While good regioselectivity is observed in this reaction, only a limited substrate scope was reported.

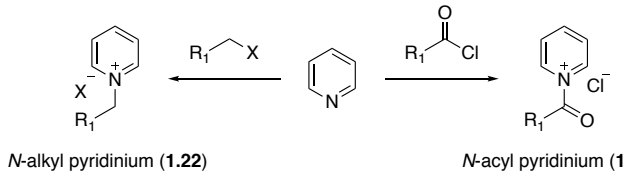
Scheme 1.3 Lewis Acid Activation of Pyridine



1.1.1.3 Activation by Pyridinium Formation

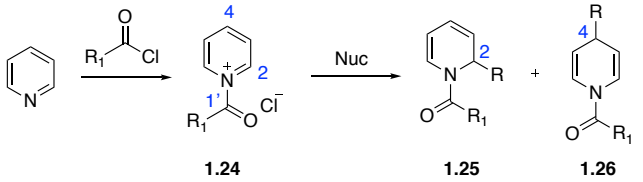
An alternative approach for nitrogen activation of pyridine involves formation of the *N*-acyl or *N*-alky pyridinium intermediates (**1.22** or **1.23**, Scheme 1.4). These intermediates provide an activated pyridine electrophile susceptible to nucleophilic addition by a variety of different reagents. Use of both *N*-acyl and *N*-alkyl pyridiniums have been reported with *N*-acyl pyridiniums generally showing enhanced reactivity, attributed to better activation of the pyridine π system. As with Lewis acid activation, formation of the *N*-acyl pyridinium can be done *in situ*, even in presence of metalated nucleophiles.

Scheme 1.4 N-Acyl and N-Alkyl Pyridinium Intermediates



In contrast to the high levels of regioselectivity observed for the Chichibain reaction, substitution of *N*-acyl pyridiniums often results in a mixture of products (Scheme 1.5).[8] In the absence of a directing group, selectivity is attributed to the hard/soft acid base model of substitution, analogous to enone addition.

Scheme 1.5 Substitution of N-Acyl Pyridinium

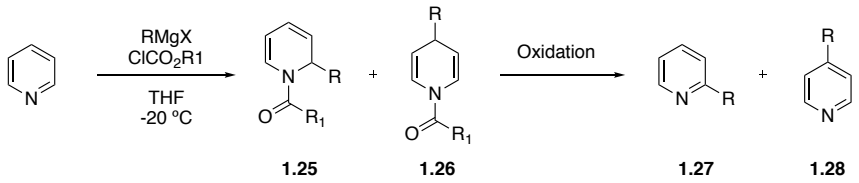


Nucleophile	Acyl chloride	yield (%)	C2/C4
EtMgBr	Me	76	70:30
EtMgBr	^{t}Bu	73	52:48
PhMgCl	Me	70	93:7
PhMgCl	^{t}Bu	66	52:48
BuMgBr	OMe	41	78/22
BuZnCl	OMe	99	19/81

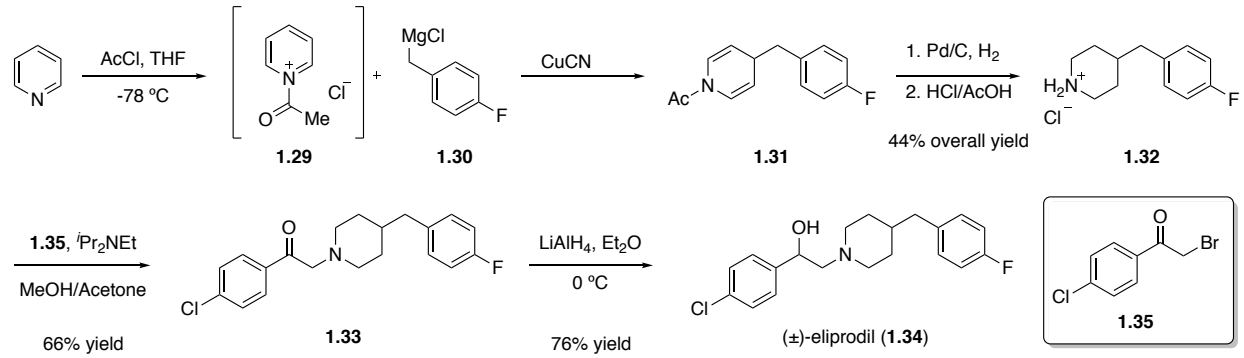
One of the greatest advantages inherent in using *N*-acylation for pyridine activation is formation of a discrete dihydropyridine intermediate (**1.25**, **1.26**).[9] This dihydropyridine can act as a pliable intermediate, allowing for access to a variety of different products. Simplest of these transformations is oxidation, often a very facile process and readily achieved under mild conditions, resulting in the substituted pyridine products (**1.27**, **1.28**, Scheme 1.6a).[10] Alternatively, reduction of this intermediate results in piperidine products (**1.31** to **1.32**, Scheme 1.6a), as demonstrated by Wanner and coworkers in their synthesis of eliprodil (**1.34,** Scheme 1.6b).[11] Key to this synthetic route is addition of a benzylic cuprate to *N*-acyl pyridinium **1.29** followed by reduction of dihydropyridine intermediate **1.31** to 4-substituted piperidine **1.32**.

Scheme 1.6 Utility of Dihydropyridine Intermediate

a. Oxidation of dihydropyridine intermediate



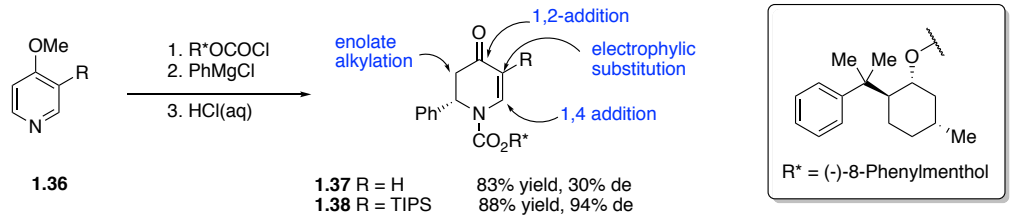
b. Synthesis of (±)-eliprodil (**1.34**)



1.1.1.4 Work by Dan Comins

At the forefront of *N*-acyl pyridinium research is Dan Comins, who demonstrated the utility of dihydropyridones (**1.37, 1.38**) as versatile intermediates for synthesis (Scheme 1.7). Formation of these intermediates is easily achieved by addition of Gringnard reagents to *N*-acylated-4-methoxy pyridine, followed by acid hydrolysis of the resulting dihydropyridine.[12] Formation of *N*-acyl-2,3-dihydro-4-pyridone (**1.37, 1.38**) not only provides a more stable intermediate than related dihydropyridines, it also contains several functional handles available for further derivatization. In particular this species is susceptible to enolate alkylation, 1,2 or 1,4 addition to the enone, or electrophilic substitution at the 5 position. Furthermore, Comins and coworkers demonstrated the use of chiral acylating agents resulting in optically active dihydropyridones with high levels of diastereoselectivity.[13] Several different chloroformates, derived from optically active alcohols, were shown proficient in this reaction providing various levels of diastereoselectivities. However, the most drastic improvement in selectivity was observed when a bulky TIPS group was substituted at the C3 position of the pyridine.

Scheme 1.7 Dihydropyridone as a Functional Handle



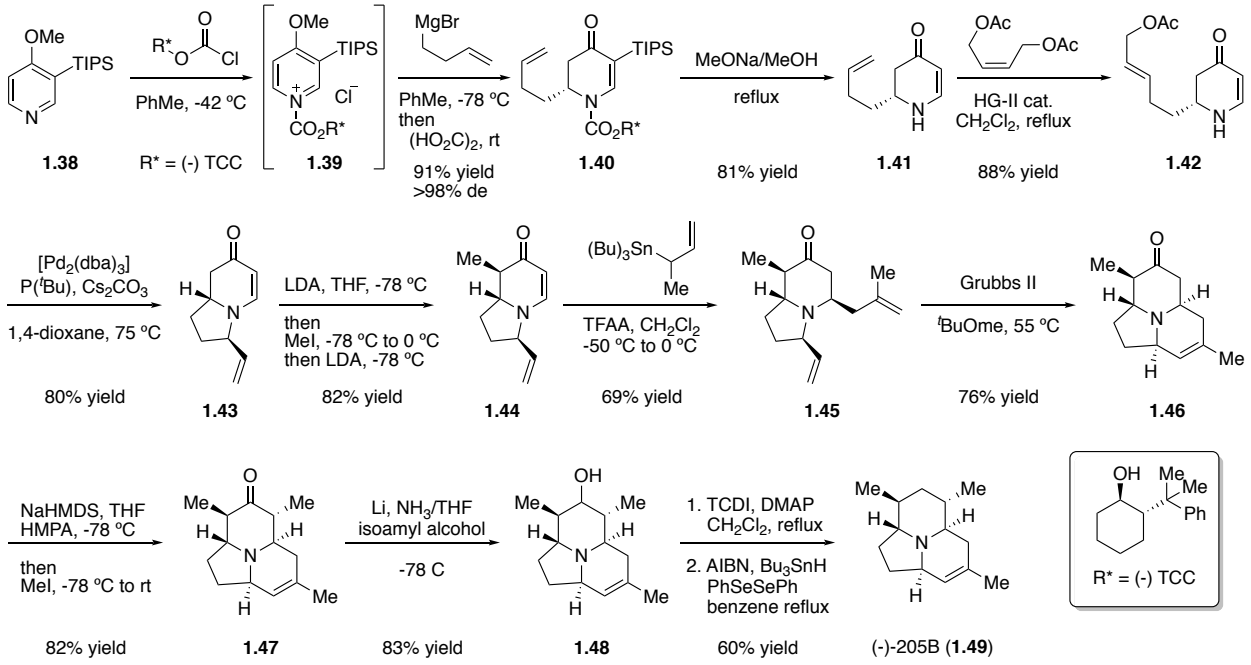
1.36

1.37 R = H 83% yield, 30% de
1.38 R = TIPS 88% yield, 94% de

This strategy provided a cornerstone for the synthesis of several alkaloid natural products reported by the Comins lab, as exemplified by the synthesis of (-)-205B (**1.49**, Scheme 1.8).[14] This synthesis commenced with preparation of dihydropyridinone **1.40**, resulting from addition of a homoallylic Grignard reagent to *N*-acyl pyridinium **1.39**, formed *in situ.* Using a chloroformate derived from (-) TCC for pyridine activation resulted in high levels of diastereoselctivity (>98%

de) for desired pyridinone **1.40**. Subsequent removal of the carbamate and silane can be achieved in one step, giving access to desired pyridinone **1.41** in high yield and optical purity. Sequential functionalization of this intermediate allowed for facile construction of the alkaloid core of (-)-205B (**1.49**). Particularly eloquent in this approach is the high level of stereocontrol imparted by the initially formed stereocenter in subsequent transformations.

Scheme 1.8 Synthesis of (-)-205B



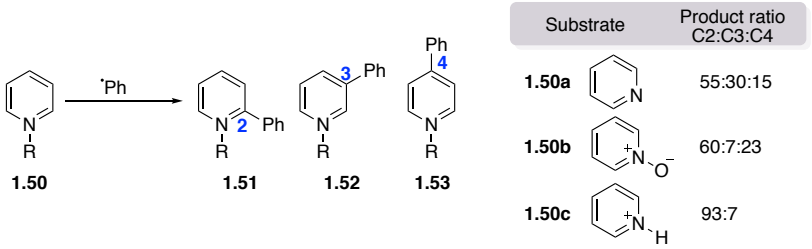
1.1.2 Alternative Methods for Pyridine Substitution

Apart from analogous Chicihiban reactions, involving a formal break in aromaticity, numerous methods have been reported for preparation of substituted pyridines. These methods include cross-coupling (Suzuki reaction), C-H activation, directed metalation or radical mediated processes.

1.1.2.1 The Minisci Reaction

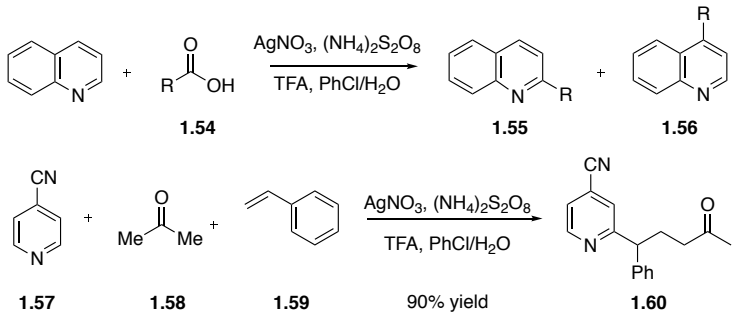
Originally based on the Gomberg-Bachman biaryl synthesis, addition of aryl radicals to heteroaromatic rings is a long-studied process, dating back to the 1920's.[15] Despite this, it was not until the 1960's that work by Minisci and others improved this reaction into a synthetically viable method.[16] Similar to additions to *N*-activated pyridines, early examples of radical additions to pyridine demonstrated poor regioselectivity for substitution. Initial improvement in regioselectivity was observed when pyridine *N*-oxides were utilized as the radical acceptor, albeit with only moderate success. A more dramatic improvement in selectivity was observed when this reaction was run under acidic conditions, presumably generating the protonated pyridine (**1.50c**) as the active species (Scheme 1.9).[17]

Scheme 1.9 Regioselectivity of the Minisci Reaction



Pivotal to enhancing the utility of this method, Minisci was prolific in reporting alternative methods for radical generation applicable to this process.[18] Developing systems that allowed for generation of alky radicals from carboxylic acids, alkyl iodides and alkenes, vastly expanded the substrate scope (Scheme 1.10).[19] Contrary to addition of aryl radicals, regioselecivity of alky radical addition was not improved using acidic conditions, furthermore, a mixture of mono- and dialkylation products often resulted. Subsequent studies revealed the ability to obtain high yields of monoalkylated products using a biphasic reaction system, although regiocontrol of addition still remains a challenge.

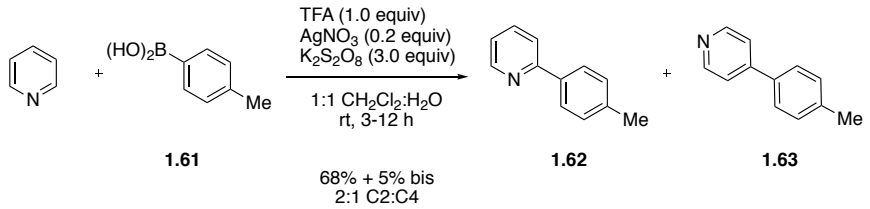
Scheme 1.10 Addition of Alky Radicals to Pyridine



R	Conversion (%)	C_2:C_4
^{n}Bu	31	43:57
^{i}Bu	100	34:66
^{t}Bu	88	100:0
^{c}Hex	100	32:68

Recently Baran *et al*. demonstrated use of aryl boronic acids as radical precursors for the Minisci reaction (Scheme 1.11). This reaction provides a method for the coupling of aryl groups with pyridine under mild conditions, albeit with only moderate regioselectivity.[20]

Scheme 1.11 Generation of Aryl Radicals from Boronic Acids

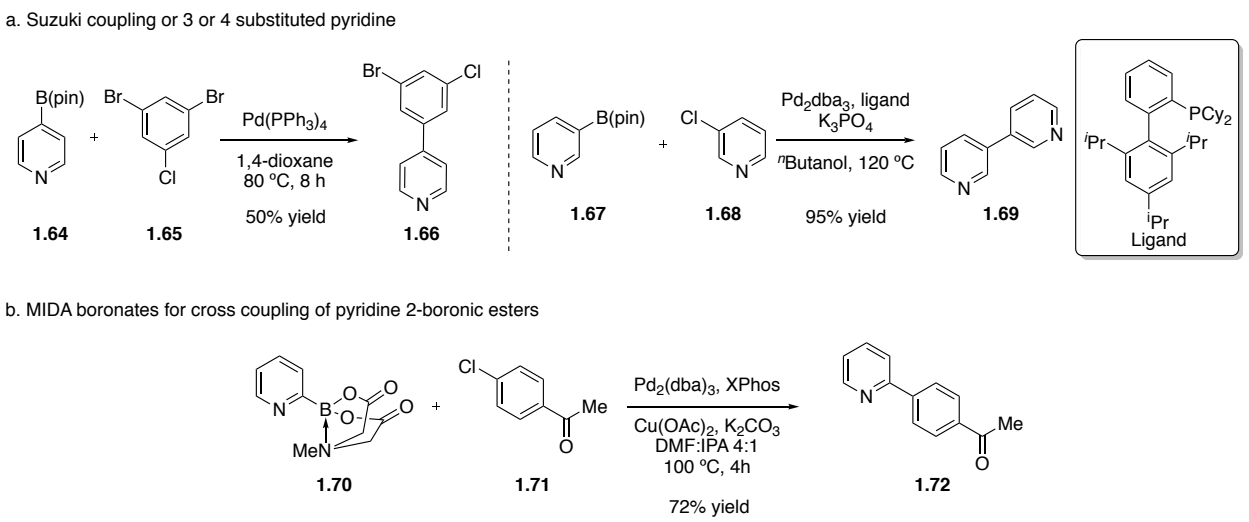


1.1.2.2 Transition Metal Couplings of Pyridine

Transition metal mediated cross coupling reactions represent one of the most useful methods for the preparation of substituted aromatic rings. Given the prevalence of such reactions, a number of examples have been reported involving pyridine substrates. Often good results are observed under standard Suzuki conditions, starting from the pyridine boronic ester or halogenated pyridine, for preparation of C4- or C3- substituted pyridines (**1.66**, **1.69**, Scheme 1.12a).[21] However, use of 2-pyridine boronic esters has traditionally presented a challenge. This result is primarily attributed to the inherent instability of 2-substituted heterocyclic boronic acids.[22] Addressing this issue, the Burke lab demonstrated that 2-pyridine boronic acid MIDA ester (**1.70**) presents a more stable

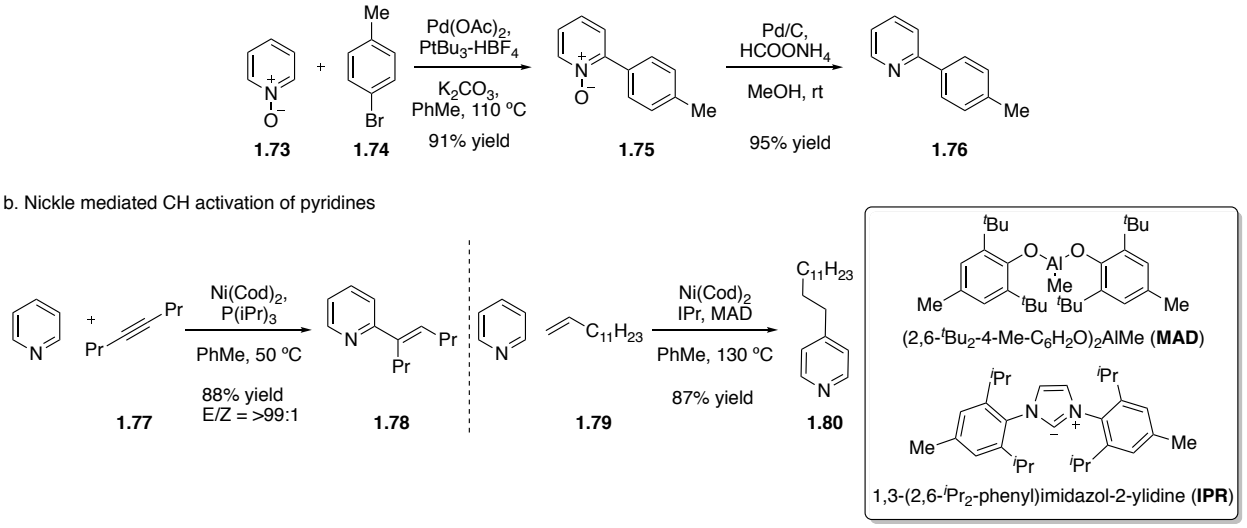
substrate, thus allowing for improved efficiency of coupling (Scheme 1.12b). This improvement is attributed to the slow release of boronic acid upon hydrolysis of the MIDA boronate with K_2CO_3, diminishing undesired decomposition pathways.

Scheme 1.12 Suzuki Couplings of Pyridine



Transition metal mediated couplings involving C-H activation offer a successful alternative to Suzuki reactions for C2- derivatization of pyridine. Notably Fagnou *et al.* demonstrated that *N*-oxides **1.73** can direct activation of Pyridine at C2 using palladium as the catalyst, forming 2 arylpyridine products (**1.75**, Scheme 1.13a).[23] Use of a nickel based catalyst system has been reported by the Hiyama lab in which the C2- or C4- substituted pyridine products can be obtained (**1.78**, **1.80**, Scheme 1.13b).[24] While the innate selectivity for these catalysts results in activation of pyridine at C2, this regioselectivity could be altered when a Lewis acid (MAD) was used in combination with a bulky NHC ligand (IPR) on nickel. Reversal of this innate selectivity is attribute to size of the Lewis acid in conjunction with the larger ligand on nickel, essentially blocking the 2 position of pyridine.

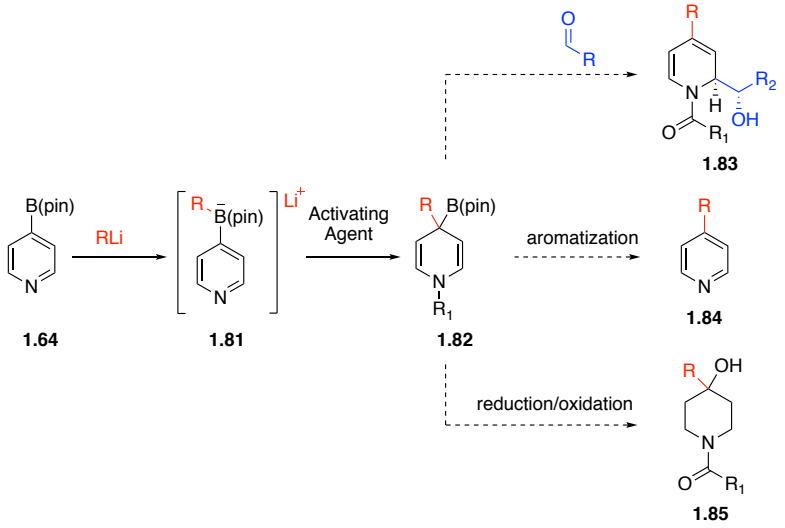
Scheme 1.13 CH Activation of Pyridine



1.2 Reaction Design

As highlighted, a number of methods are available for formation of substituted pyridines. While each offer a unique set of strengths and weaknesses the work of Dan Comins provides a particularly attractive model. Harnessing the power of dihydropyridines allows for a versatile strategy in the preparation of nitrogen heterocycles, not limited to substituted pyridines. Building from this concept, a complimentary approach would involve accessing dihydropyridine boronic ester **1.82** (Scheme 1.14a), for further functionalization. This desired intermediate could result from a 1,2-boron to carbon migration of boronate **1.81**, deriving from pyridine 4-boronic ester **1.64**. In addition to controlling the regioselectivity of addition, retention of the boronic ester provides an added handle for further functionalization. Generation of dihydropyridine boronic ester **1.82** could provide a suitable substrate for oxidation, reduction, or allyl borane chemistry, analogous to examples demonstrated by Hall *et al*.[25]

Scheme 1.14 Reaction Design



1.3 1,2 Boron to Carbon Migration

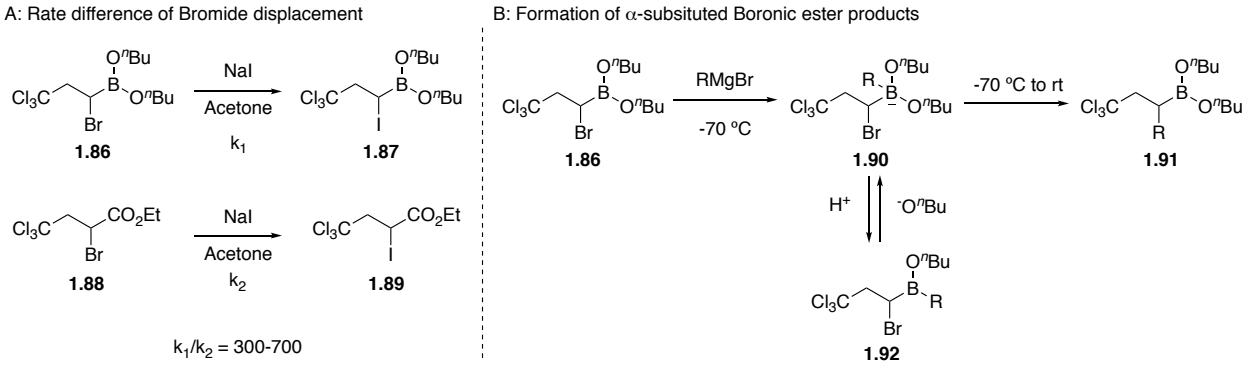
The utility of boron in facilitating carbon-carbon bond formation is well-established and dates back over 50 years. Brown, Matteson and Zweifel were early pioneers in this field establishing the propensity of nucleophiles to undergo a 1,2 boron to carbon migration by way of a boronate intermediate.[26] More recent work by Aggarwal, demonstrating and extending the utility of this transformation for the preparation of synthetically useful intermediates, has served to reinvigorate interest in this field.[27]

1.3.1 Matteson Homologation

One of the earliest examples of a 1,2 boron to carbon migration was observed by Matteson in the 1960's. Studies involving the rate of halogen displacement revealed a significantly higher rate constant for iodine addition to α-bromo boronic ester **1.86** compared to its ester analog **1.88** (Scheme 1.15a).[28] Additionally, treatment of boronic ester **1.86** with base did not result in elimination, as would be expected with a 1,1,1-trichloro 3-bromopropane derivative. Elaborating

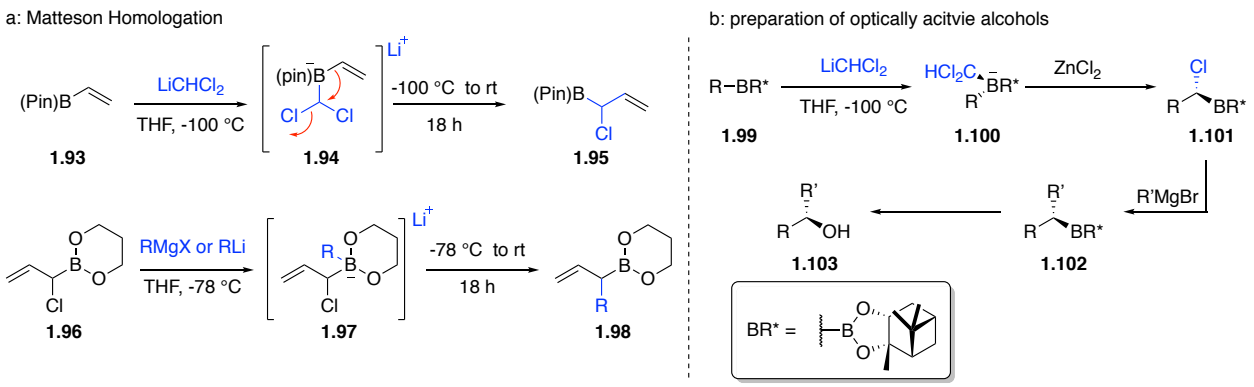
on this observation they reported that addition of a Grignard nucleophile to the same α-bromo boronic ester **1.86** leads to substituted α-boronic ester **1.91** (Scheme 1.15b). This reaction was presumed to occur by way of boronate intermediate **1.90**, as evidenced by formation of borinic ester **1.92** when the reaction was quenched with acid at -70 °C.

Scheme 1.15 Matteson's Observation of 1,2 Boron to Carbon Migration



Building from these initial results, Matteson demonstrated the use of α-chloro boronates **(1.94, 1.97)** as intermediates for carbon homologation, now known as the Matteson Homologation. These boronates could be accessed from α-chloro boronic esters (**1.96)** or by addition of (dichloromethyl) lithium to alkyl or vinyl boronic esters (**1.93**, Scheme 1.16a).[29] Additional work done by both Matteson and Brown demonstrated the versatility of this method, in particular showing that variation of the boronic ester is well tolerated.[30] This attribute led to the use of chiral boronic esters as auxiliaries, giving access to optically active alcohols, highlighted by Brown's use of α-pinine derived boronic esters (**1.99**, Scheme 1.16b).[31]

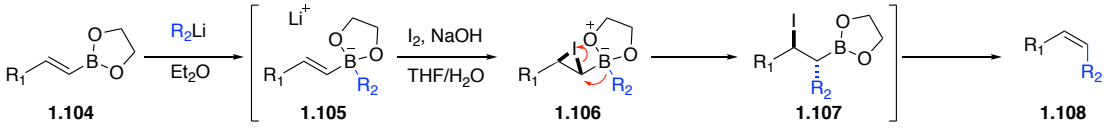
Scheme 1.16 The Matteson Homologation



1.3.2 Zweifel Olefination

Conceptually similar to the Matteson homologation, Zweifel demonstrated the use of this migration for preparation of Z olefins starting from vinyl boronic esters (Scheme 1.17).[32] This reaction involves addition of a lithium or Grignard nucleophile to a vinyl boronic ester **1.104** with subsequent boronate formation (**1.104** to **1.105**). Propagation of the requisite 1,2 boron to carbon migration is achieved by *in situ* iodonium formation/activation of the olefin. Treatment of the resulting β-iodo-α-substituted boronic ester **1.107** with base then leads to elimination of iodine and concurrent deborylation generating product alkene **1.108**.

Scheme 1.17 Zweifel Olefination



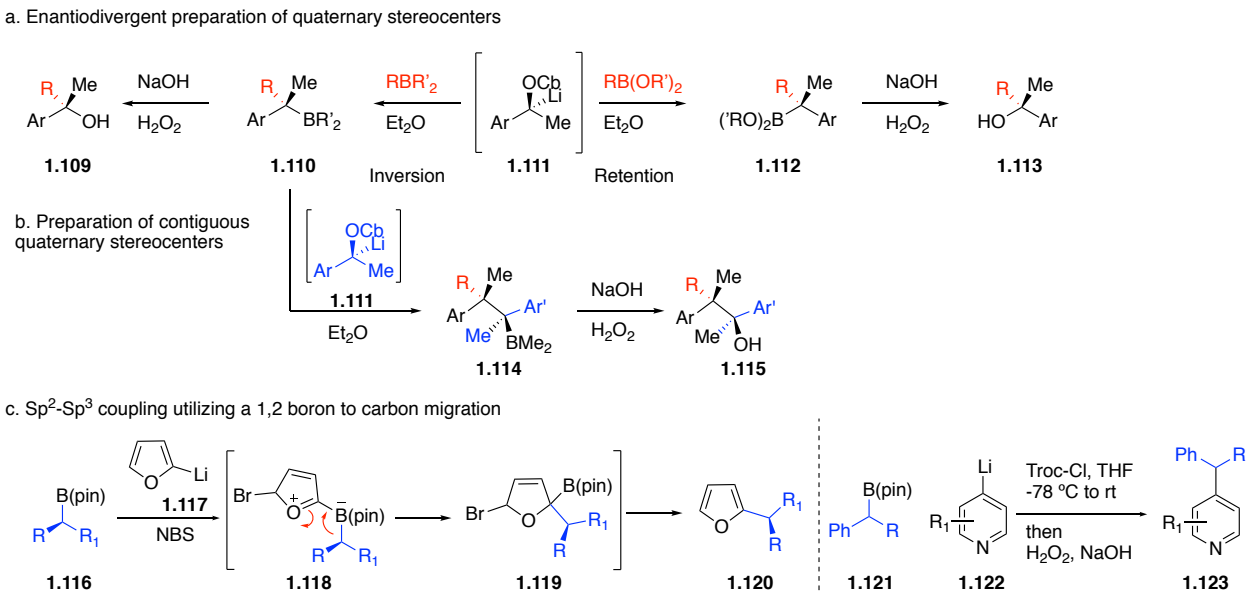
1.3.3 Work by Aggarwal

More recently the Aggarwal group has built upon this reaction paradigm, expanding its synthetic utility. In particular by exploiting the stereospecificity of 1,2 boron to carbon migrations they demonstrate the ability to access quaternary stereocenters with high levels of enantiocontrol,

starting from readily available optically active carbamates (**1.111** to **1.109** or **1.113**, Scheme 1.18a).[33] Interestingly it was observed that stereospecificity of this migration is dependent on the boron functionality. While migration involving boronic esters gave retention of the original carbamate stereocenter (**1.111** to **1.113**), use of boranes resulted in inversion of this center during migration (**1.111** to **1.109**). Additionally, this process can be done sequentially allowing for facile preparation of contiguous stereocenters with complete stereocontrol (**1.111** to **1.115**, Scheme 1.18b).[34]

In conjunction with this work Aggarwal demonstrated the utility of this boron to carbon migration for sp^2-sp^3 couplings of electron rich aromatic rings and substituted boronic esters (Scheme 1.18c).[35] Addition of lithiated furan **1.117** to boronic ester **1.116** forms furan boronate intermediate **1.118.** Subsequent activation with NBS initiates a boron to carbon migration, analogous to the Zweifel olefination. Concurrent with our research, and as an extension of this method, they have also reported the preparation of substituted pyridines (**1.123**) following an analogous strategy.[36]

Scheme 1.18 Aggarwals Extenstion of Boron Chemistry

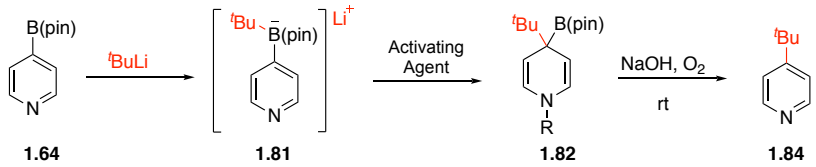


1.4 Results

1.4.1 Dihydropyridine Intermediate and Activation

Work on this project in the Ready lab was initiated by a postdoctoral associate, Santanu Panda. He demonstrated that addition of *tert*-BuLi to 4-pyridine boronic acid pinacol ester **1.64** resulted in formation of the anticipated dihydropyridine intermediate **1.82**, upon treatment with an acylating agent (Scheme 1.19).[37] Subsequent exposure of dihydropyridine **1.82** to oxygen and aqueous base led to formation of 4-*tert*-butylpyridine (**1.84**). While a variety of acylating agents showed proficiency in the reaction, initial screens of alkylating agents and Lewis acids resulted in greatly diminished reactivity.

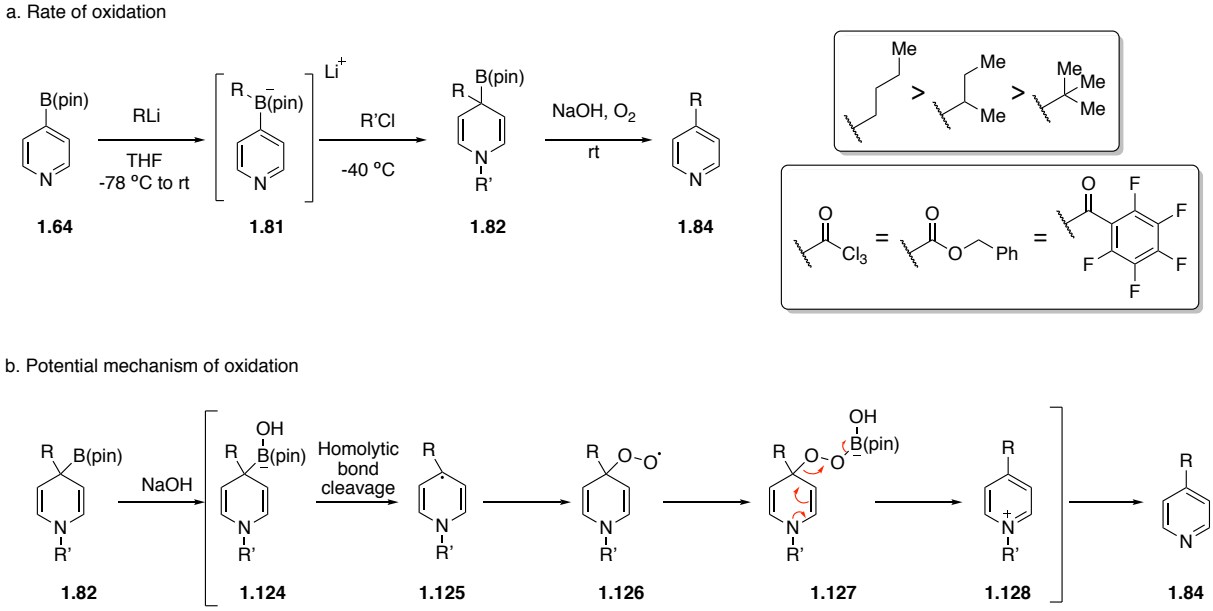
Scheme 1.19 Initial Results[†]



Unexpectedly oxidation of the dihydropyridine intermediate **1.82** was rapid and often hard to prevent. Subsequent studies showed that the oxidation rate followed the trend R = Ph > 1° alkyl > 3° alkyl, while modulation of the activating agent (both steric and electronic) showed no appreciable effect (Scheme 1.20a). Based on this data it was postulated that hydroxide mediated boronate formation could lead to homolytic cleavage of the boron carbon bond. Trapping of the carbon centered radical in conjunction with boron oxygen bond formation would furnish peroxide **1.127** (Scheme 1.20b). Elimination of oxygen and borate results in acyl pyridinium **1.128** which upon hydrolysis with surplus hydroxide would lead to the desired substituted pyridine **1.84**.

[†] Work done by Santanu Panda, Ph.D.

Scheme 1.20 Oxidation of Pinacol Boronic Ester[†]

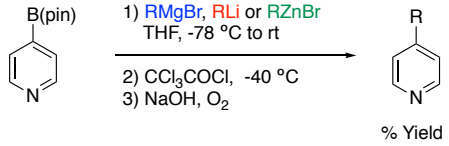


Given this facile oxidation of the dihydro pyridine intermediate, it was decided to explore the substrate scope of this reaction by directly oxidizing to the substituted pyridine products. In this way treatment with sodium hydroxide upon completion of migration under oxygen atmosphere ensured complete oxidation for all substrates.

1.4.2 Reaction Substrate Scope

Probing different nucleophiles capable of substitution in this reaction revealed a broad substrate scope (Scheme 1.21). Primary, secondary and tertiary alkyl lithium reagents were successfully employed, as were aryl and alkynyl lithium species. Similarly, alkyl, aryl and vinyl Grignard reagents provided the substituted pyridines in high yields. Aryl and alky zinc reagents also showed competent reactivity, allowing for the introduction of functionality not compatible with lithium and Grignard nucleophiles.

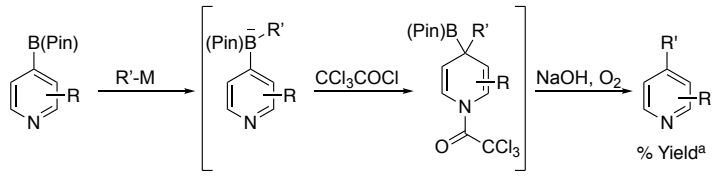
Scheme 1.21 Functionalization of Pyridine†



	1°	2°	3°	Vinyl	Aryl	Alkynyl
RLi	82-85	79	85		82-85	87
RMgBr	84-85	81		70	81	
RZnBr	83				83-89	

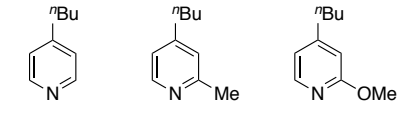
This coupling showed little influence from substitution on the pyridine ring itself (Scheme 1.22). Electron donating and withdrawing groups were well tolerated at the 2 and 3 positions. The observation that both 2- and 3-chloro-pyridines (**1.132, 1.133, 1.143-1.146**) were suitable substrates is particularly noteworthy given these reagents ability to participate in cross-coupling reactions. Compatibility of this functionality highlights the mildness of this method, in addition to providing a strategy for further functionalization of the substituted pyridine products.

Scheme 1.22 Pyridine Substrate Scope

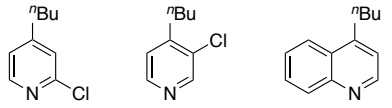


Typical conditions: Het-B(pin) (1 equiv.), R-M (1.1 equiv), -78 °C, CCl_3COCl (2 equiv), -78 °C to -40 °C, then 10 % NaOH aq, Rt.
[a]Isolated yield of product. Reaction run on 0.3 mmol scale

Lithium Reagents

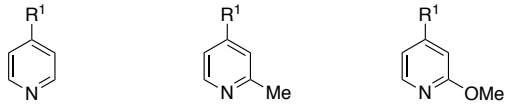


1.129*: 82% **1.130:** 93% **1.131:** 80%



1.132: 60% **1.133:** 50% **1.134:** 77%

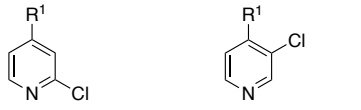
Grignard Reagents



1.135: R = ^{c}Hex 81%
1.136: R = ^{s}Bu 67%
1.137: R = Ph 81%

1.138: R = ^{c}Hex 80%
1.139: R = ^{s}Bu 60%
1.140: R = Ph 83%

1.141: R = ^{c}Hex 73%
1.142: R = Ph 77%



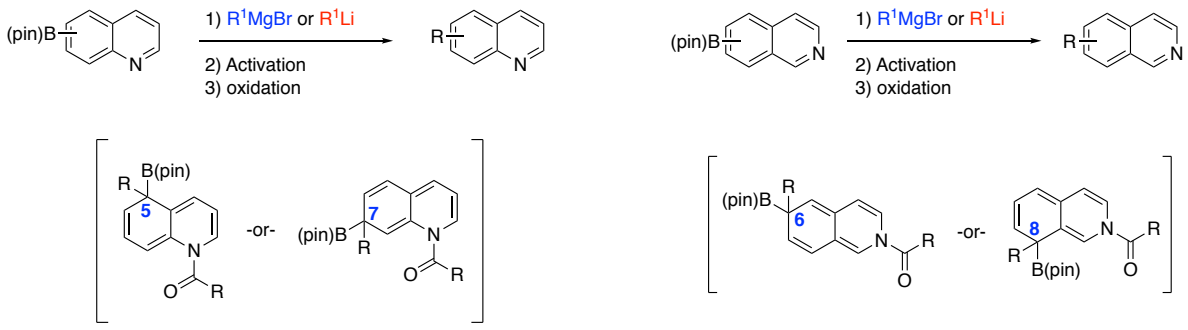
1.143: R = ^{s}Bu 57%
1.144: R = Ph 83%

1.145: R = ^{s}Bu 60%
1.146: R = Ph 80%

1.4.3 Expansion into Quinoline and Isoquinoline

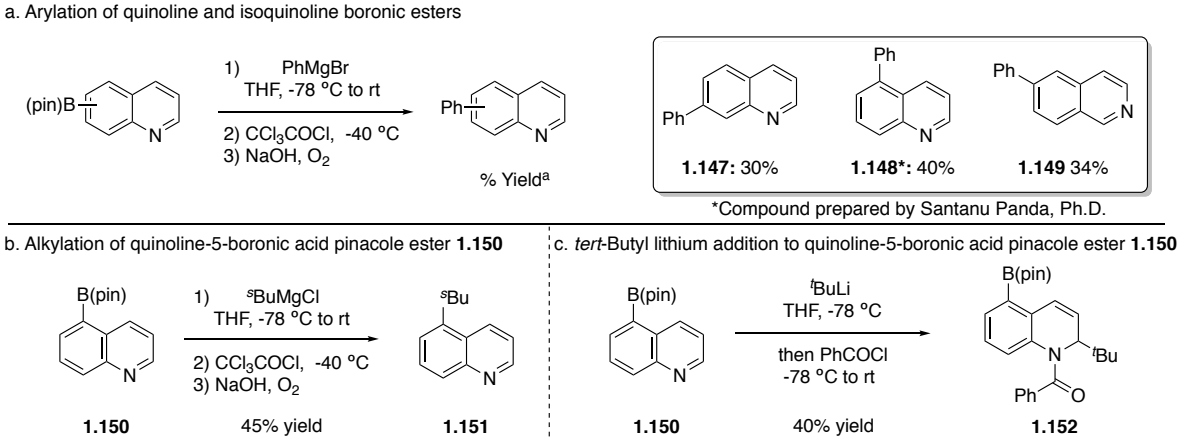
With the demonstrated success of pyridine substitution, we next explored the viability of quinoline and isoquinoline substrates in this reaction. While 4-quinoline boronic ester showed similar reactivity to that of pyridine (**1.134**, scheme 1.22), the more interesting question was the ability of nitrogen activation for promoting the 1,2 boron to carbon migration of a remote boronic ester. Given the requisite resonance necessary for invoking this migration it was predicted that 5 and 7 quinoline along with 6 and 8 isoquinoline boronic esters would be suitable substrates for this transformation (Scheme 1.23).

Scheme 1.23 Substitution of Quinoline and Isoquinoline Boronic Esters



Indeed treatment of 5 and 7 quinoline boronic acid pinacol esters, or 6 isoquinoline boronic acid pinacole ester, with phenyl Grignard resulted in the desired arylated products (**1.147-1.149**, Scheme 1.24a). Yields of quinoline and isoquinoline substituted products were more modest than those of pyridine and unfortunately attempts at optimizing the efficiency of this process, increasing temperature or changing oxidation reagents, showed little improvement. Similarly, substitution with an alkyl Grignard nucleophile, *sec*-butyl Grignard, demonstrated the same proficiency in this reaction (**1.151**, Scheme 1.24b). Interestingly, addition of *tert*-BuLi to quinoline boronic ester **1.150** results in almost exclusive addition to the C2 position of quinoline, resulting in isolation of the dihydro quinoline product **1.152** (Scheme 1.24c).

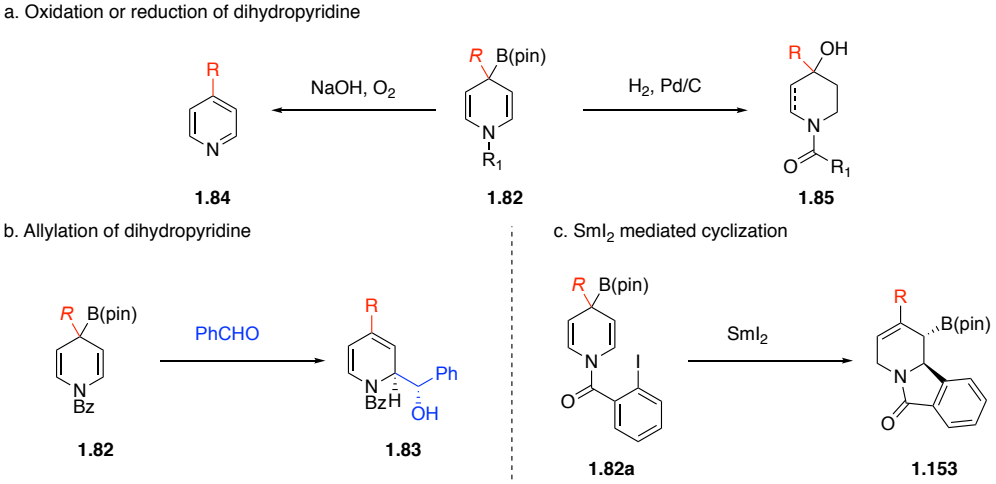
Scheme 1.24 Quinoline and Isoquinoline Substitution



1.4.4 Additional Derivatization of the Dihydropyridine Intermediate

With a substrate scope for this reaction established, additional work by Santanu Panda Ph.D. demonstrated the full utility of this method. While facile oxidation of dihydropyridine intermediate **1.82** resulted in substituted pyridines (**1.84**), reduction of this intermediate (fully or partially) gives *N*-acyl piperidine or tetrahydropyrine products (**1.85**, Scheme 1.25a). As initially expected, this intermediate provided a competent substrate for allylation reactions, resulting in homoallylic alcohols (**1.83**, scheme 1.25b). Additionally an unexpected, yet interesting, finding was a SmI_2 facilitated radical cyclization of aryl iodide **1.82a** (Scheme 1.25c).

Scheme 1.25 Additional Transformations of Dihydropyridine



In conclusion this methodology offers a unique mode for accessing substituted pyridine, piperidine and tetrahydropyridine substrates. A broad range of metalated nucleophiles was shown to be compatible for this reaction in addition, substitution on the pyridine is well tolerated. While only modest yields of quinoline and isoquinoline substrates are observed desired reactivity none the less occurred. Finally, the versatility of this reaction for preparation of analogous 6 membered nitrogen heterocycles further demonstrates the usefulness of this technique.

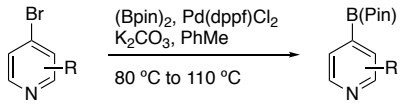
1.5 Experimental

1.5.1 General Information

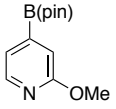
Unless otherwise stated, reactions were performed under nitrogen in flame dried or oven dried glassware. Solvents were dried using solvent purification columns purchased from Glass Contour, Laguna Beach, CA. Chemicals were purchased from Sigma-Aldrich, Fisher, or TCI and were used without purification. Cyclohexylmagnesium chloride**,** *sec*-butylmagnesium chloride lithium chloride complex and phenylmagnesium bromide were purchased from Aldrich and titrated prior to use with 2-hydroxybenzaldehyde phenylhydrazone. *n*-BuLi and *tert*-BuLi were purchased from Aldrich and titrated prior to use with diphenyl acetic acid. All reactions were monitored by thin-layer chromatography with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). Flash chromatography was performed with indicated solvents using silica gel (particle size 0.032-0.063m) purchased from Sorbent Technologies. ^{1}H NMR chemical shifts were measured at 400 MHz, referenced based on trace amounts of the deuterated solvent: chloroform ($CDCl_3$), $\delta = 7.26$, and reported in parts per million (ppm). coupling constants (*J*) are reported in Hertz (Hz) multiplicity reported as follows: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, p = pentet, dd = doublet of doublets, ddd = doublet of doublets of doublets, dt = doublet of triplets and m = multiplet. ^{13}C NMR chemical shifts were measured at 100 MHz, referenced based on trace amounts of the deuterated solvent: chloroform ($CDCl_3$), $\delta = 77.16$, and reported in parts per million (ppm). Mass spectra were acquired on an Agilent technologies 1200 series LC/MS using acetonitrile and water with 0.1% formic acid as the mobile phase passing through a c18 column and ionizing with an ESI probe.

1.5.2 Preparation of Boronic Esters

Boronic esters were purchased commercially and used after recrystallization from $CHCl_3$ and hexanes. Those not available were prepared from the corresponding bromide according to the following procedure:



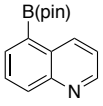
General method: Adapted the procedure reported by Ishiyama *et al.*[38] To a stirred solution of 7-bromo quinoline (1 equiv.) in toluene (0.2 mM) was added bis(pinacolato)diboron (1.5 equiv), KOAc (3 equiv.) and $Pd(dppf)Cl_2$ (10 mol %). The reaction mixture was degassed then heated to 80 ºC. After stirring for 1 h at 80 ºC the reaction temperature was increased to 110 ºC and the reaction stirred overnight (15 h). The reaction was then cooled to rt, diluted with EtOAc and washed with NaCl (sat.). The organic layer was collected, dried over Na_2SO_4 then filtered through a plug of celite and concentrated *in vacuo* giving a crude brown/black oil. This crude material was purified by silica gel chromatography. Recrystallization from a $CHCl_3$/Hexanes mixture could be used to further remove trace amounts of pinacol.



2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine[39] S-1.1: Prepared using general method, purified by silica gel chromatography (1:20 to 1:10 EtOAc/hexanes), yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.17 (dd, J = 4.85, J = 0.74 Hz, 1H), 7.17 (dd, J = 4.95, J = 0.53, 1H), 7.11 (s, 1H), 3.90 (s, 3H), 1.32 (s, 12H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 164.0, 146.4, 121.3, 116.7, 84.5, 83.6, 83.2, 25.0

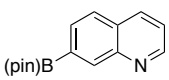


5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline 1.150: Prepared using general method, purified by flash column silica gel chromatography (1:3 EtOAc/Hexanes), white solid.

TLC: R_f = 0.27 (1:5 EtOAc/hexanes) visualized with UV

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.12-9.10 (m, 1H), 8.91 (dd, *J* = 4.19, *J* = 1.71 Hz, 1H), 8.19 (d, *J* = 8.45 Hz, 1H), 8.14 (dd, *J* = 6.83, *J* = 1.33 Hz, 1H), 7.71 (dd, *J* = 8.45, *J* = 6.86 Hz, 1H), 7.44 (dd, *J* = 8.47, *J* = 4.15 Hz, 1H), 1.42 (s, 12H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 173.8, 150.2, 148.2, 136.9, 136.3, 133.1, 132.2, 128.7, 121.5, 84.1, 25.1

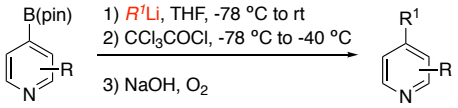


7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline S-1.2: Prepared using general method, purified by flash column silica gel chromatography (1:20 to 1:10 EtOAc/hexanes), white solid.

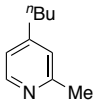
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.94 (dd, *J* = 4.23, *J* = 1.74 Hz, 1H), 8.60 (s, 1H), 8.14 (d, *J* = 8.15 Hz, 1H), 7.90 (dd, *J* = 8.09 Hz, *J* = 1.00 Hz, 1H), 7.8 (d, J = 8.09 Hz, 1H), 7.41, (dd, *J* = 8.28 Hz, *J* = 4.09 Hz, 1H), 1.39 (s, 12H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 150.6, 147.9, 137.5, 136.0, 131.2, 130.1, 127.0, 121.9, 84.3, 25.0

1.5.3 General Procedure A: Addition of Alkyl Lithium Reagents



To a -78 °C stirred solution of the desired 4-pyridine boronic acid pinacol ester (0.3 mmol) in THF (1.5 mL) was added *n*-BuLi (206 µL, 0.33 mmol) dropwise over 5 min. The reaction was stirred at -78 °C for 30 min then warmed to rt and stirred for an additional 15 min. The reaction was recooled to -78 °C and trichloroacetyl chloride (65 µL, 0.6 mmol) was added dropwise with constant stirring, after stirring at -78 °C for 30 min this mixture was warmed to -40 °C and stirred overnight (15h). 10% aqueous NaOH (10%, 1mL) solution was added and the reaction was warmed to rt. The reaction vessel was purged with oxygen and stirred under oxygen atmosphere (balloon) for 2h. Rochelles salt (sat. 1mL) was then added and the reaction continued to stir for 1 h. 10 mL of brine was added to the reaction mixture and the product was extracted with CH_2Cl_2 (3 × 10mL). The organic layer was collected, dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude product (care was taken during evaporation of the solvent due to potential product volatility). This crude material was purified by silica gel chromatography.

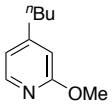


4-butyl-2-methylpyridine[40] **1.130:** Prepared using general procedure A, crude material was purified by silica gel chromatography (1:2 Et_2O/hexanes), yellow oil, 93% yield.

LRMS: (ESI+) Calcd. For $C_{10}H_{15}N$ $[M+H]^+$ 150.1, found 150.2

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.35 (d, *J* = 5.16 Hz, 1H), 6.96 (s, 1H), 6.90 (d, *J* = 5.16 Hz, 1H), 2.55 (t, J = 7.67 Hz, 2H), 2.51 (s, 3H), 1.62-1.54 (m, 2H), 1.39-1.29 (m, 2H), 0.92 (t, *J* = 7.37, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 158.2, 152.1, 149.0, 123.4, 121.1, 35.0, 32.6, 24.5, 22.4, 14.0

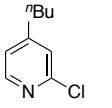


4-butyl-2-methoxypyridine 1.131: Prepared using general procedure A, purified by silica gel chromatography (1:2 Et_2O/hexanes), yellow oil, 80% yield.

LRMS: (ESI+) Calcd. For $C_{10}H_{15}NO$ $[M+H]^+$ 166.1, found 166.2

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.03 (d, J = 5.27 Hz, 1H), 6.70 (dd, J = 5.30, J = 1.30 Hz, 1H), 6.55 (s, 1H), 3.91 (s, 3H), 2.55 (t, J = 7.52 Hz, 2H), 1.62-1.54 (m, 2H), 1.38-1.29 (m, 2H), 0.92 (t, J = 7.47 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 164.6, 154.7, 146.5, 117.7, 110.4, 53.4, 35.0, 32.4, 22.4, 14.0

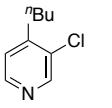


4-butyl-2-chloropyridine 1.132: Prepared using general procedure A, purified by silica gel chromatography (1:2 Et_2O/hexanes), yellow oil, 60% yield.

LRMS: (ESI+) Calcd. For $C_9H_{12}ClN$ $[M+H]^+$ 170.1, found 170.1

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.25 (d, J = 5.05 Hz, 1H), 7.14 (s, 1H), 7.02 (d, J = 5.05 Hz, 1H), 2.59 (t, J = 7.75 Hz, 2H), 1.63-1.56 (m, 2H), 1.39-1.30 (m, 2H), 0.93 (t, J = 7.35 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 155.2, 151.1, 149.3, 129.1, 122.8, 34.7, 32.2, 22.2, 13.8

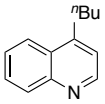


4-butyl-3-chloropyridine 1.133: Prepared using general procedure A, purified by silica gel chromatography (1:2 Et_2O/hexanes), yellow oil, 50% yield:

LRMS: (ESI+) Calcd. For $C_9H_{12}ClN$ $[M+H]^+$ 170.1, found 170.1

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.50 (s, 1H), 8.36 (d, J = 4.97 Hz, 1H), 7.14 (d, J = 4.97 Hz, 1H), 2.72 (t, J = 7.85 Hz, 2H), 1.65-1.57 (m, 2H), 1.44-1.35 (m, 2H), 0.95 (t, J = 7.34 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 149.4, 149.2, 147.7, 132.2, 124.9, 32.7, 31.0, 22.6, 14.0



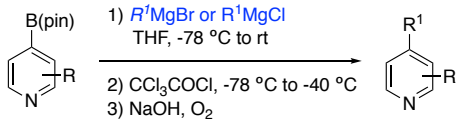
4-butylquinoline 1.134: Prepared using general procedure A, purified by silica gel chromatography (1% MeOH/CH_2Cl_2), yellow oil, 77% yield.

LRMS: (ESI+) Calcd. For $C_{13}H_{15}N$ $[M+H]^+$ 186.1, found 186.1

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.80 (d, *J* = 4.4 Hz, 1H), 8.11 (dd, *J* = 8.48, *J* = 0.70 Hz, 1H), 8.05 (dd, *J* = 8.48, *J* = 1.19 Hz, 1H), 7.70 (ddd, *J* = 8.3, *J* = 6.8, *J* = 1.4 Hz, 1H), 7.53 (ddd, *J* = 8.4, *J* = 6.8, *J* = 1.3 Hz, 1H), 7.23 (d, *J* = 4.28 Hz, 1H), 3.14 – 2.94 (m, 2H), 1.81 – 1.66 (m, 2H), 1.45 (h, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 7.3 Hz, 3H)

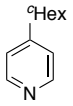
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 150.3, 148.9, 148.5, 130.4, 129.1, 127.6, 126.3, 123.7, 120.9, 32.3, 32.3, 22.9, 14.1

1.5.4 General Procedure B: Addition of Alkyl or Aryl Grignards



To a -78 °C stirred solution of the desired 4-pyridine boronic acid pinacol ester (0.3 mmol) in THF (1.5 mL) was added alkyl/aryl Gringard reagent (0.33 mmol) dropwise over 5 min. The reaction was stirred at -78 °C for 10 min then warmed to rt and stirred for 2 h. The reaction was recooled to -78 °C and trichloroacetyl chloride (65 µL, 0.6 mmol) was added dropwise with constant stirring. After stirring an additional 30 min at -78 °C this mixture was warmed to -40 °C and stirred overnight (18h). NaOH (10 %, 1 mL) was then added and the reaction was warmed to rt. The reaction vessel was purged with oxygen and stirred under oxygen atmosphere (balloon) for 2h at which Rochelles salt (sat., 1mL) was added. After stirring for 1 h NaCl (sat., 10mL) was added and the product was extracted with CH_2Cl_2. The organic layer was dried Na_2SO_4 then

concentrated *in vacuo* to afford the crude product (care was taken during evaporation of the solvent due to potential product volatility). This crude material was purified by silica gel chromatography.

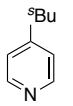


4-cyclohexylpyridine[41] **1.135:** Prepared using general procedure B, purified by silica gel chromatography (1:8 EtOAc/hexanes), yellow oil, 81% yield.

LRMS: (ESI+) Calcd. For $C_{11}H_{15}N$ $[M+H]^+$ 162.1, found 162.1

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.48 (d, *J* = 5.73 Hz, 2H), 7.1 (d, *J* = 5.90 Hz, 2H), 2.52-2.45 (m, 1H), 1.89-1.81 (m, 4H), 1.76-1.71 (m, 1H), 1.43-1.31 (m, 4H), 1.28-1.17 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 156.6, 149.8, 122.5, 44.0, 33.7, 26.7, 26.1

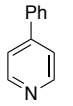


4-(*sec*-butyl)pyridine 1.136: Prepared using general procedure B, purified by silica gel chromatography, 67% yield.

LRMS: (ESI+) Calcd. For $C_9H_{13}N$ $[M+H]^+$ 136.1, found 136.1

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.49 (d, *J* = 5.68 Hz, 2H), 7.10 (d, *J* = 5.73 Hz, 2H), 2.63-2.54 (m, 1H), 1.64-1.57 (m, 2H), 1.24 (d, *J* = 7.01 Hz, 3H), 0.82 (t, *J* = 7.42 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 156.6, 149.9, 122.8, 41.3, 30.6, 21.1, 12.1

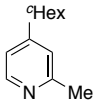


4-phenylpyridine (**1.137**)[42]: Prepared using general procedure B, purified by silica gel chromatography (1% MeOH/CH_2Cl_2), yellow solid, 84% yield,

LRMS: (ESI+) Calcd. For $C_{11}H_9N$ $[M+H]^+$ 156.1, found 156.1

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.66 (br S, 2H), 7.65 – 7.62 (m, 2H), 7.51 – 7.42 (m, 5H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 150.4, 148.4, 138.3, 129.3, 129.2, 127.1, 121.8

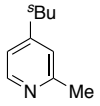


4-cyclohexyl-2-methylpyridine 1.138: Prepared using general procedure B, purified by silica gel chromatography (1:2 EtOAc/hexanes), yellow oil, 80% yield.

LRMS: (ESI+) Calcd. For $C_{12}H_{17}N$ $[M+H]^+$ 176.1, found 176.2

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.36 (d, *J* = 5.14 Hz, 1H), 6.98 (s, 1H), 6.92 (d, *J* = 5.14 Hz, 1H), 2.51 (s, 3H), 2.47-2.41 (m, 1H), 1.89-1.81 (m, 4H), 1.77-1.73 (m, 1H), 1.42-1.34 (m, 4H), 1.27-1.20 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 158.3, 157.0, 149.2, 122.0, 119.6, 44.0, 33.7, 26.7, 26.1, 24.6.

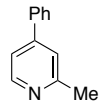


4-(*sec*-butyl)-2-methylpyridine 1.139: Prepared using general procedure B, purified by silica gel chromatography, 60% yield.

LRMS: data not obtained

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.37 (d, *J* = 5.18 Hz, 1H), 6.95 (s, 1H), 6.90 (d, *J* = 5.25 Hz, 1H), 2.58-2.49 (m, 1H), 2.52 (s, 3H), 1.62-1.55 (m, 2H), 1.21 (d, *J* = 6.90 Hz, 3H), 0.82 (t, *J* = 7.40 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 158.3, 156.9, 149.2, 122.2, 119.8, 41.2, 30.6, 24.6, 21.2, 12.2

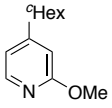


2-methyl-4-phenylpyridine[43] **1.140:** Prepared using general procedure B, purified by silica gel chromatography (1% MeOH/CH_2Cl_2), yellow oil, 83% yield.

LRMS: (ESI+) Calcd. For $C_{12}H_{11}N$ $[M+H]^+$ 170.1, found 170.1

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.54 (d, *J* = 5.18 Hz, 1H), 7.64 – 7.61 (m, 2H), 7.50-7.41 (m, 5H), 7.37 (brS, 1H), 7.31 (dd, *J* = 5.18 Hz, *J* = 1.37 Hz, 1H), 2.63 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 159.0, 149.8, 148.8, 138.6, 129.2, 129.0, 127.2, 121.4, 119.0, 24.8.

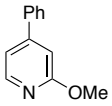


4-cyclohexyl-2-methoxypyridine 1.141: Prepared using general procedure B, purified by silica gel chromatography (1:2 Et_2O/hexanes), yellow oil, 73% yield.

LRMS: (ESI+) Calcd. For $C_{12}H_{17}NO$ $[M+H]^+$ 192.1, found 192.1

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.04 (d, *J* = 5.21 Hz, 1H), 6.73 (dd, *J* = 5.35, *J* = 1.24 Hz, 1H), 6.57 (s, 1H), 3.91 (s, 3H), 2.47-2.42 (m, 1H), 1.88-1.81 (m, 4H), 1.77-1.72 (m, 1H), 1.42-1.32 (m, 4H), 1.28-1.19 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 164.7, 159.7, 146.6, 116.3, 108.8, 53.4, 43.9, 33.6, 26.7, 26.1

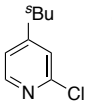


2-methoxy-4-phenylpyridine 1.142: Prepared using general procedure B, purified by silica gel chromatography (0.5% MeOH/CH_2Cl_2), yellow oil, 77% yield.

LRMS: (ESI+) Calcd. For $C_{12}H_{11}NO$ $[M+H]^+$ 186.1, found 186.1

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.21 (d, *J* = 5.37 Hz, 1H), 7.63 – 7.61 (m, 2H), 7.49-7.40 (m, 3H), 7.11 (dd, *J* = 5.37 Hz, J = 1.09 Hz, 1H) 3.99 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 165.0, 151.3, 147.4, 138.4, 129.1, 129.0, 127.1, 115.5, 108.6, 53.5.

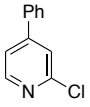


4-(*sec*-butyl)-2-chloropyridine 1.143: Prepared using general procedure B, purified by silica gel chromatography, 57% yield.

LRMS: data not obtained

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.27 (d, *J* = 5.20 Hz, 1H), 7.14 (d, *J* = 1.34 Hz, 1H), 7.03 (dd, *J* = 5.15, *J* = 1.37 Hz, 1H), 2.64-2.55 (m, 1H), 1.65-1.56 (m, 2H), 1.23 (d, *J* = 6.79 Hz, 3H), 0.83 (t, *J* = 7.40 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 160.2, 151.7, 150.0, 123.1, 121.6, 41.2, 30.5, 21.0, 12.1

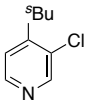


2-chloro-4-phenylpyridine[44] **1.144:** Prepared using general procedure B, purified by silica gel chromatography (1:10 EtOAc/hexanes), yellow solid, 83% yield.

LRMS: (ESI+) Calcd. For $C_{12}H_8ClN$ $[M+H]^+$ 190.0, found 190.0

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.43 (d, *J* = 5.21 Hz, 1H), 7.63 – 7.60 (m, 2H), 7.55 (d, *J* = 1.08 Hz, 1H) 7.53-7.47 (m, 3H), 7.43 (dd, *J* = 5.19 Hz, *J* = 1.51 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 152.4, 151.7, 150.1, 137.0, 129.8, 129.4, 127.2, 122.2, 120.6.

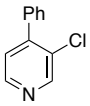


4-(*sec*-butyl)-3-chloropyridine 1.145: Prepared using general procedure B, purified by silica gel chromatography, 60% yield.

LRMS: data not obtained

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.52 (s, 1H), 8.41 (d, *J* = 5.04 Hz, 1H), 7.15 (d, *J* = 5.06 Hz, 1H), 3.21-3.12 (m, 1H), 1.70-1.54 (m, 2H), 1.23 (d, *J* = 6.94 Hz, 3H), 0.87 (t, *J* = 7.43 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 153.6, 149.5, 148.0, 122.1, 36.8, 29.4, 19.9, 11.9



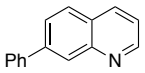
3-chloro-4-phenylpyridine[45] **1.146:** Prepared using general procedure B, purified by silica gel chromatography (0.5% MeOH/CH_2Cl_2), yellow oil, 80% yield.

LRMS: (ESI+) Calcd. For $C_{12}H_8ClN$ $[M+H]^+$ 190.0, found 190.0

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.68 (s, 1H), 8.53 (d, *J* = 4.96 Hz, 1H), 7.49 – 7.44 (m, 5H), 7.29 (d, *J* = 4.93 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 150.2, 147.9, 147.8, 136.6, 130.4, 129.1, 129.0, 128.6, 125.5.

1.5.5 Coupling with Quinoline and Isoquinoline

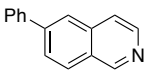


7-phenylquinoline[46] **1.147:** To a -78 °C stirred solution of 7-quinoline boronic acid pinacol ester (76 mg, 0.3 mmol) in THF (1.5 mL) was added phenyl magnesium bromide (351 µL, 0.33 mmol) (0.94 M in THF) dropwise over 5 min. The reaction was stirred at -78 °C and slowly allowed to warm to rt over 2 hours. After stirring at rt for an additional 20 min the reaction was cooled to -78 °C and trichloroacetyl chloride (65 µL, 0.6 mmol) was added dropwise. Upon complete addition of the acid chloride the reaction was warmed to 4 °C and stirred at temperature overnight (15h). NaOH (10%, 1 mL) was then added and the reaction was warmed to rt. The reaction vessel was purged with oxygen and the reaction was stirred under oxygen atmosphere (balloon) for 2 hours at which point Rochelle's salt (sat., 1 mL) was added. After stirring an additional 1 hour NaCl (sat., 10 mL) was added and the product was extracted with CH_2Cl_2 was then used to extract the product (3 x 10 mL). The organic layer was collected, dried over Na_2SO_4 and then concentrated *in vacuo* to give the crude product. The crude material was purified by silica gel chromatography (1:10 EtOAc/hexanes) to give a clear oil, 18 mg, 30% yield.

LRMS: (ESI+) Calcd. For $C_{15}H_{11}N$ $[M+H]^+$ 206.1, found 206.1

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.93 (dd, *J* = 4.30, *J* = 1.68 Hz, 1H), 8.32 (s, 1H), 8.17 (d, *J* = 8.40 Hz, 1H), 7.88 (d, J = 8.40, 1H), 7.82 (dd, *J* = 8.45, *J* = 1.85 Hz, 1H), 7.76-7.74 (m, 2H), 7.52-7.98 (m, 2H), 7.42-7.37 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 180.9, 148.6, 142.2, 140.2, 135.7, 129.0, 128.2, 127.9, 127.5, 127.1, 126.2, 121.0

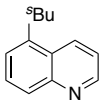


6-phenylisoquinoline[47] **1.149**: The title compound was prepared following the same procedure as for compound **1.147**. The crude material was purified by silica gel chromatography (1:10 EtOAc/hexanes), clear oil, 34% yield.

LRMS: (ESI+) Calcd. For $C_{15}H_{11}N$ $[M+H]^+$ 206.1, found 206.1

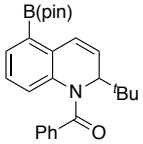
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.26 (s, 1H), 8.54 (d, *J* = 6.17 Hz, 1H), 8.09 (d, *J* = 7.71 Hz, 1H), 7.99 (s, 1H), 7.86 (dd, *J* = 8.62, *J* = 2.15 Hz, 1H), 7.72-7.68 (m, 3H), 7.52-7.48 (m, 2H), 7.44-7.40 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 179.1, 152.5, 143.6, 143.2, 140.4, 136.3, 129.2, 128.3, 127.9, 127.7, 127.3, 124.4, 120.8



5-(*sec*-butyl)quinoline 1.151: To a -78 °C stirred solution of 5-quinoline boronic acid pinacol ester (50 mg, 0.2 mmol) in THF (1.0 mL) was added *sec*-butylmagnesium chloride lithium chloride complex (184 µL, 0.22 mmol) (1.2 M in THF). The reaction was slowly allowed to warm to rt over 2 hours and then recooled to -78 °C and trichloroacetyl chloride (0.068 mL L, 0.6 mmol) was added dropwise. Upon complete addition of the acid chloride the reaction was warmed to -40 °C and stirred for 20h. 10% NaOH (1 mL) was then added and the reaction was warmed to rt. The reaction vessel was then purged with oxygen and the reaction was stirred under oxygen atmosphere for 2 hours. Rochelle's salt (sat. 1 mL) was then added and the reaction was stirred for an additional 1 hour. 20 mL of Brine was added and CH_2Cl_2 was then used to extract the product (3 x 10 mL). The organic layer was collected, dried over sodium sulfate and then concentrated *in vacuo* to give the crude product. The crude material was purified by silica gel chromatography (1:10 EtOAc/hexanes) to give a clear oil (16 mg, 0.09 mmol, 45% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.91 (d, *J* = 4.00 Hz, 1H), 8.47 (d, *J* = 8.70 Hz, 1H), 7.98 (d, *J* = 8.77 Hz, 1H), 7.69 (dd, *J* = 8.11, *J* = 7.56 Hz, 1H), 7.46-7.41 (m, 2H), 3.50-3.42 (m, 1H), 1.88-1.67 (m, 2H), 1.38 (d, *J* = 6.88 Hz, 3H), 0.91 (t, *J* = 7.50 Hz, 3H)



***N*-benzoyl-(2-(*tert*-butyl)-5-(boronic acid pinacol ester)quinoline 1.152**: To a -78 °C stirred solution of 5-quinoline boronic acid pinacol ester (50 mg, 0.2 mmol) in THF (1.0 mL) was added *tert*-Butyl Lithium (129 μL, 0.22 mmol) (1.7 M in THF). The reaction was stirred at -78 °C for 30 min at which point benzoyl chloride (0.046 mL, 0.4 mmol) was added dropwise. The reaction was then warmed to rt, diluted with CH_2Cl_2 and washed with brine. The organic layer was collected, dried over Na_2SO_4 then concentrated *in vacuo* giving a yellow oil. This material was purified by silica gel chromatography (1:10 to 1:5 EtOAc/hexanes) and the product was isolated as a yellow solid (34 mg, 0.08 mmol, 40% yield)

LRMS: data not obtained

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.51 (d, *J* = 10.01 Hz, 1H), 7.46 (dd, *J* = 7.42, *J* = 1.05 Hz, 1H), 7.19-7.13 (m, 4H), 6.74 (t, *J* = 7.73 Hz, 1H), 6.50 (d, *J* = 7.73, 1H), 6.24 (dd, *J* = 10.02, *J* = 5.90 Hz, 1H), 5.11 (d, *J* = 5.92 Hz, 1H), 1.39 (s, 12H), 0.87 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 170.8, 137.8, 136.5, 133.9, 132.8, 129.6, 129.1, 129.0, 127.9, 126.3, 125.7, 84.0, 59.9, 38.0, 26.5, 25.1, 25.0

1.6 References

[1] (a) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014,** *57*, 10257-10274. (b) Walsh, C. T. *Tetrahedron Lett.* **2015,** *56*, 3075-3081.

[2] McGill, C. K.; Rappa, A. Advances in the Chichibabin Reaction. In *Advances in Heterocyclic Chemistry*, Katriztzky, A. R. Ed. Academic Press, INC.: **1988**; Vol. 44, pp 2-73.

[3] Brown, H. C.; Kanner, B. *J. Am. Chem. Soc.* **1966,** *88*, 986-992.

[4] Francis, R. F.; Davis, W.; Wisener, J. T. *J. Org. Chem.* **1974,** *39*, 59-62.

[5] (a) Jeffrey, J. L.; Sarpong, R. *Org. Lett.* **2012,** *14*, 5400-5403. (b) Hardin Narayan, A. R.; Sarpong, R. *Org. Biomol. Chem.* **2012,** *10*, 70-78.

[6] Chen, Q.; du Jourdin, X. M.; Knochel, P. *J. Am. Chem. Soc.* **2013,** *135*, 4958-4961.

[7] Mizumori, T.; Hata, T.; Urabe, H. *Chem. Eur. J.* **2015,** *21*, 422-426.

[8] Comins, D. L.; O'Connor, S. Regioselective Substitution in Aromatic Six-Membered Nitrogen Heterocycles. In *Advances in Heterocyclic Chemistry*, Katritzky, A. R., Ed. Academic Press, Inc: **1988**; Vol. 44, pp 200-247.

[9] Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982,** *82*, 223-243.

[10] Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012,** *112*, 2642-2713.

[11] Pabel, J.; Höfner, G.; Wanner, K. T. *Bioorg. Med. Chem. Lett.* **2000,** *10*, 1377-1380.

[12] Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994,** *116*, 4719-4728.

[13] Comins, D. L.; Guerra-Weltzien, L., *Tetrahedron Lett.* **1996,** *37*, 3807-3810.

[14] (a) Tsukanov, S. V.; Comins, D. L. *Angew. Chem. Int. Ed.* **2011,** *50*, 8626-8628. (b) Comins, D. L.; Chen, X.; Morgan, L. A. *J. Org. Chem.* **1997,** *62*, 7435-7438.

[15] Gomberg, M.; Bachmann, W. E. *J. Am. Chem. Soc.* **1924,** *46*, 2339-2343

[16] (a) Minisci, F., *Synthesis* **1973**, 1-24. (b) Duncton, M. A. J. *Med. Chem. Commun.* **2011,** *2*, 1135-1161.

[17] (a) Dou, H. J. M.; Lynch, B. M., *Tetrahedron Lett.* **1965,** *6*, 897-901 (b) Minisci, F.; Vismara, E.; Fontana, F., *J. Org. Chem.* **1989,** *54*, 5224-5227.

[18] (a) Minisci, F., *Synthesis* **1973**, 1-24. (b) Minisci, F.; Fontana, F.; Pianese, G.; Yan, Y. M., *J. Org. Chem.* **1993,** *58*, 4207-4211. (c) Citterio, A.; Minisci, F.; Franchi, V., *J. Org. Chem.*

1980, *45*, 4752-4757. (d) Clerici, A.; Minisci, F.; Porta, O., *Tetrahedron* **1974,** *30*, 4201-4203.

[19] (a) Minisci, F.; Fontana, F.; Vismara, E. *J. Heterocycl. Chem.* **1990,** *27*, 79-96. (b) Fontana, F.; Minisci, F.; Nogueira Barbosa, M. C.; Vismara, E. *Tetrahedron* **1990,** *46*, 2525-2538. (c) Minisci, F.; Citterio, A.; Giordano, C. *Acc. Chem. Res.* **1983,** *16*, 27-32.

[20] Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2010,** *132*, 13194-13196.

[21] (a) Blass, B. E.; Iyer, P.; Abou-Gharbia, M.; Childers, W. E.; Gordon, J. C.; Ramanjulu, M.; Morton, G.; Arumugam, P.; Boruwa, J.; Ellingboe, J.; Mitra, S.; Reddy Nimmareddy, R.; Paliwal, S.; Rajasekhar, J.; Shivakumar, S.; Srivastava, P.; Tangirala, R. S.; Venkataramanaiah, K.; Bobbala, R.; Yanamandra, M.; Krishnakanth Reddy, L., *Bioorg. Med. Chem. Lett.* **2018,** *28*, 2270-2274. (b) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, 129, 3358 (c) Li, Z.; Gelbaum, C.; Fisk, J. S.; Holden, B.; Jaganathan, A.; Whiteker, G. T.; Pollet, P.; Liotta, C. L., *J. Org. Chem.* **2016,** *81*, 8520-8529.

[22] Knapp, D. M.; Gillis, E. P.; Burke, M. D., *J. Am. Chem. Soc.* **2009,** *131*, 6961-6963.

[23] Campeau, L.-C.; Rousseaux, S.; Fagnou, K., *J. Am. Chem. Soc*. **2005**, 127, 18020-18021.

[24] (a) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, 130, 2448-2449. (b) Nakao, Y.; Yamada, Y.; Kashihara, N.; Hiyama, T. *J. Am. Chem. Soc.* **2010**, 132, 13666-13668.

[25] (a) Lessard, S.; Peng, F.; Hall, D. G. *J. Am. Chem. Soc.* **2009,** *131*, 9612-9613. (b) Lachance, H.; Hall, D. G., Allylboration of Carbonyl Compounds. In *Organic Reactions*, al., S. E. D. e., Ed. John Wiley & Sons, Inc.: 2008; Vol. 73, pp 1-573.

[26] (a) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961,** *83*, 486-487. (b) Suzuki, A.; Nozawa, S.; Miyaura, N.; Itoh, M.; Brown, H. C. *Tetrahedron Lett.* **1969,** *10*, 2955-2958.

[27] Armstrong, R. J.; Aggarwal, V. K. *Synthesis* **2017,** *49*, 3323-3336.

[28] Matteson, D. S.; Mah, R. W. H. *J. Am. Chem. Soc.* **1963,** *85*, 2599-2603.

[29] (a) Matteson, D. S.; Majumdar, D. *Organometallics* **1983,** *2*, 1529-1535. (b) Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985,** *4*, 1687-1689.

[30] (a) Matteson, D. S. *J. Org. Chem.* **2013,** *78*, 10009-10023. (b) Matteson, D. S.; Ray, R. *J. Am. Chem. Soc.* **1980,** *102*, 7590-7591. (c) Matteson, D. S.; Sadhu, K. M. *J. Am. Chem. Soc.* **1983,** *105*, 2077-2078.

[31] (a) Brown, H. C.; Singaram, B. *Acc. Chem. Res.* **1988,** *21*, 287-293. (b) Matteson, D. S. *J. Org. Chem.* **2013,** *78*, 10009-10023.

[32] Armstrong, R. J.; Aggarwal, V. K. *Synthesis* **2017,** *49*, 3323-3336.

[33] (a) Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. *Nature* **2008,** *456*, 778-782. (b) Bagutski, V.; French, R. M.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2010,** *49*, 5142-5145. (c) Sonawane, R. P.; Jheengut, V.; Rabalakos, C.; Larouche-Gauthier, R.; Scott, H. K.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2011,** *50*, 3760-3763. (d) Leonori, D.; Aggarwal, V. K., *Angew. Chem. Int. Ed.* **2015,** *54*, 1082-1096.

[34] (a) Watson, C. G.; Balanta, A.; Elford, T. G.; Essafi, S.; Harvey, J. N.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2014,** *136*, 17370-17373. (b) Burns, M.; Essafi, S.; Bame, J. R.; Bull, S. P.; Webster, M. P.; Balieu, S.; Dale, J. W.; Butts, C. P.; Harvey, J. N.; Aggarwal, V. K. *Nature* **2014,** *513*, 183-188.

[35] Bonet, A.; Odachowski, M.; Leonori, D.; Essafi, S.; Aggarwal, V. K. *Nat Chem* **2014,** *6*, 584-589.

[36] Llaveria, J.; Leonori, D.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2015,** *137*, 10958-10961.

[37] Panda, S.; Coffin, A.; Nguyen, Q. N.; Tantillo, D. J.; Ready, J. M. *Angew. Chem. Int. Ed*. **2016,** 55, 2205-2209

[38] Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995,** *60*, 7508-7510.

[39] Wang, L.; Li, J.; Cui, X.; Wu, Y.; Zhu, Z.; Wu, Y. *Adv. Synth. Catal.* **2010,** *352*, 2002-2010.

[40] Kaiser, E. M.; Bartling, G. J.; Thomas, W. R.; Nichols, S. B.; Nash, D. R. *J. Org. Chem.* **1973,** *38*, 71-75.

[41] Branchaud, B. P.; Choi, Y. L. *J. Org. Chem.* **1988,** *53*, 4638-4641.

[42] Tanimoro, K.; Ueno, M.; Takeda, K.; Kirihata, M.; Tanimori, S. *J. Org. Chem.* **2012,** *77*, 7844-7849.

[43] Wei, Y.; Yoshikai, N. *J. Am. Chem. Soc.* **2013,** *135*, 3756-3759.

[44] Gurung, S. K.; Thapa, S.; Kafle, A.; Dickie, D. A.; Giri, R. *Org. Lett.* **2014,** *16*, 1264-1267.

[45] Guo, P.; Joo, J. M.; Rakshit, S.; Sames, D. *J. Am. Chem. Soc.* **2011,** *133*, 16338-16341.

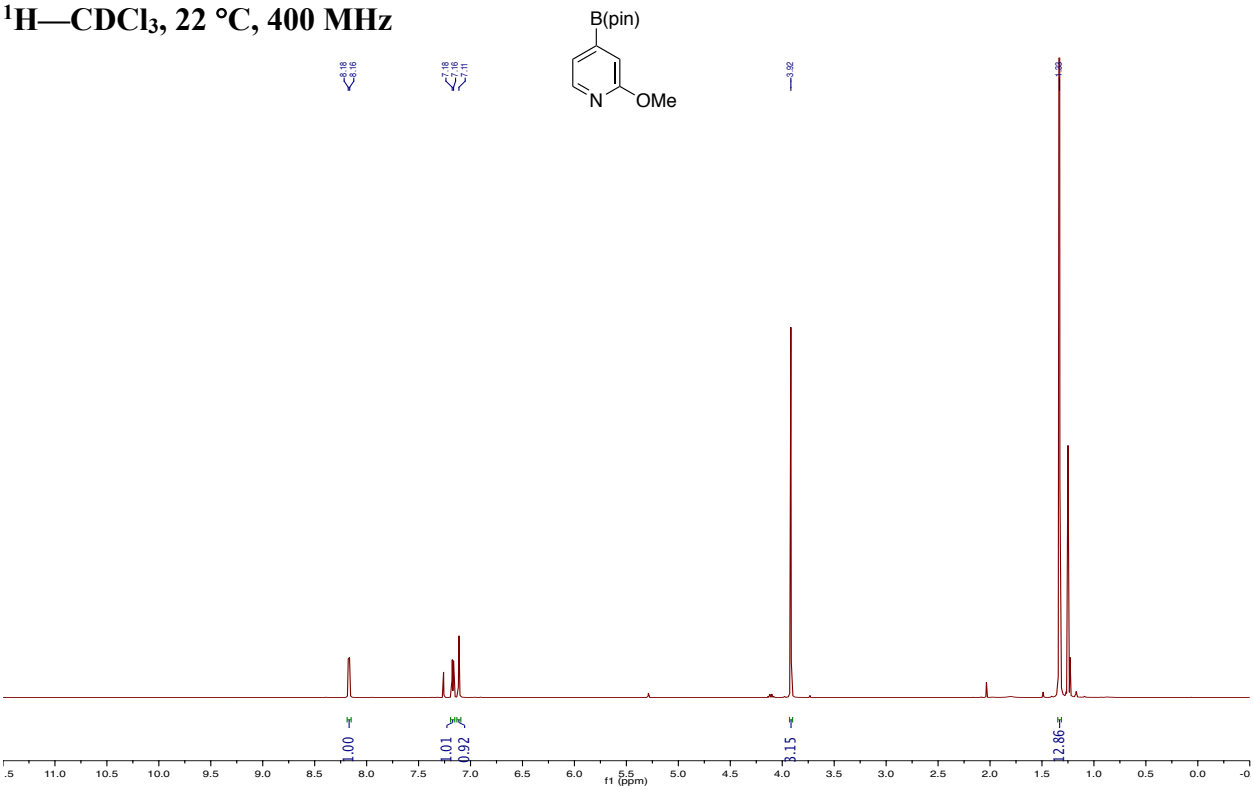
[46] Molander, G. A.; Canturk, B.; Kennedy, L. E. *J. Org. Chem.* **2009,** *74*, 973-980.

[47] Molander, G. A.; Iannazzo, L. *J. Org. Chem.* **2011,** *76*, 9182-9187.

Appendix 1: Chapter 1 NMR spectra

2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (S-1.1)

^{1}H—$CDCl_3$, 22 °C, 400 MHz



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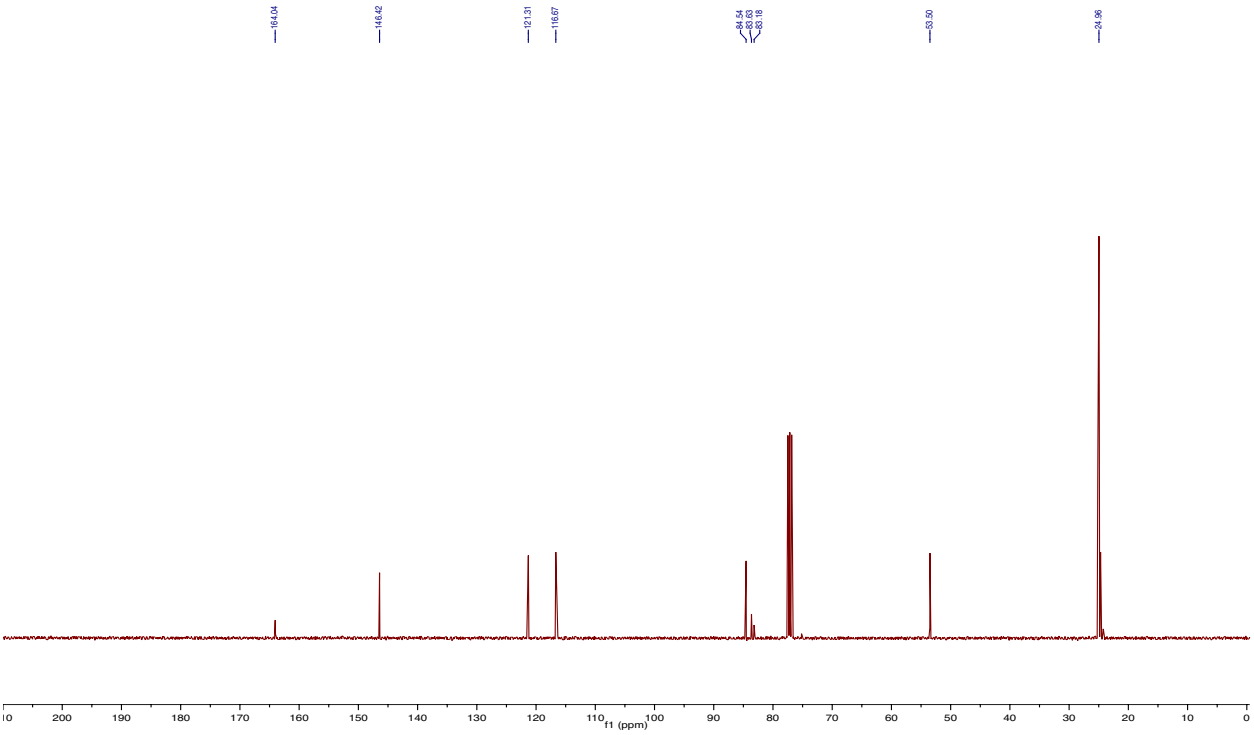

5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (1.150)

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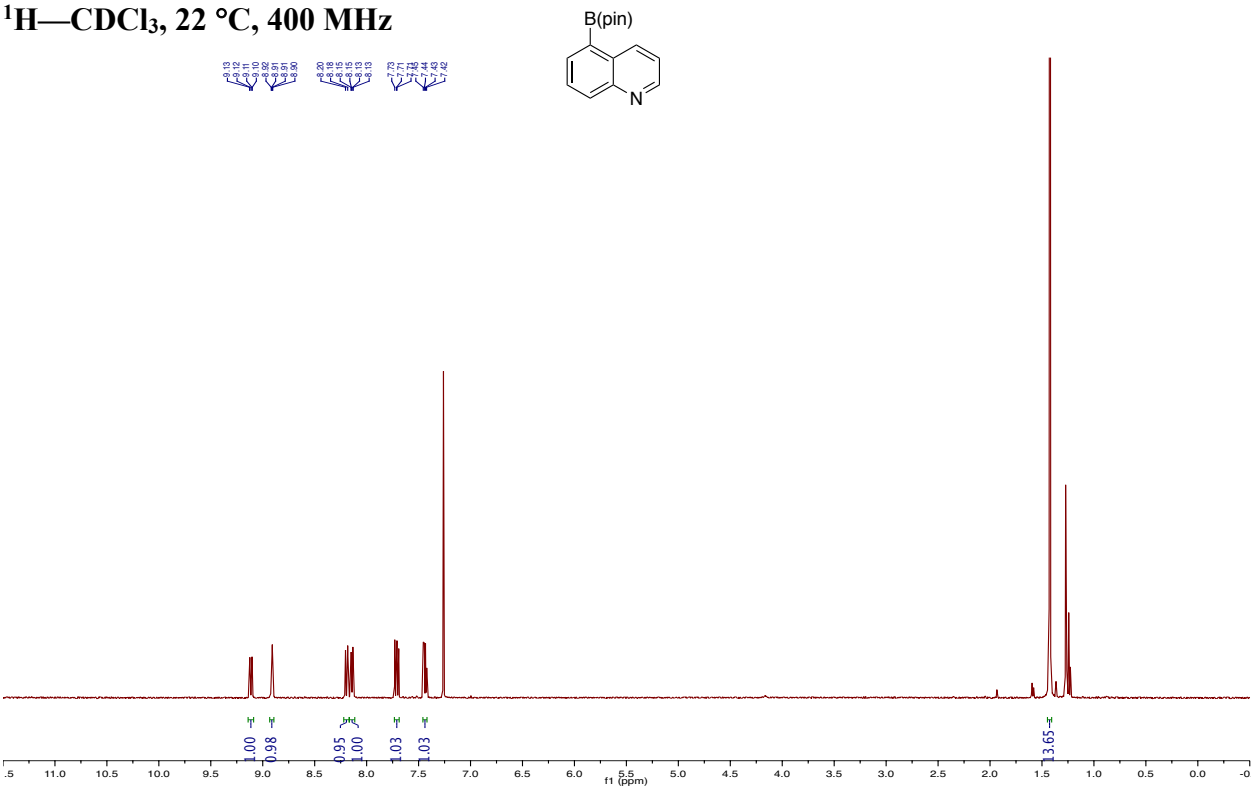

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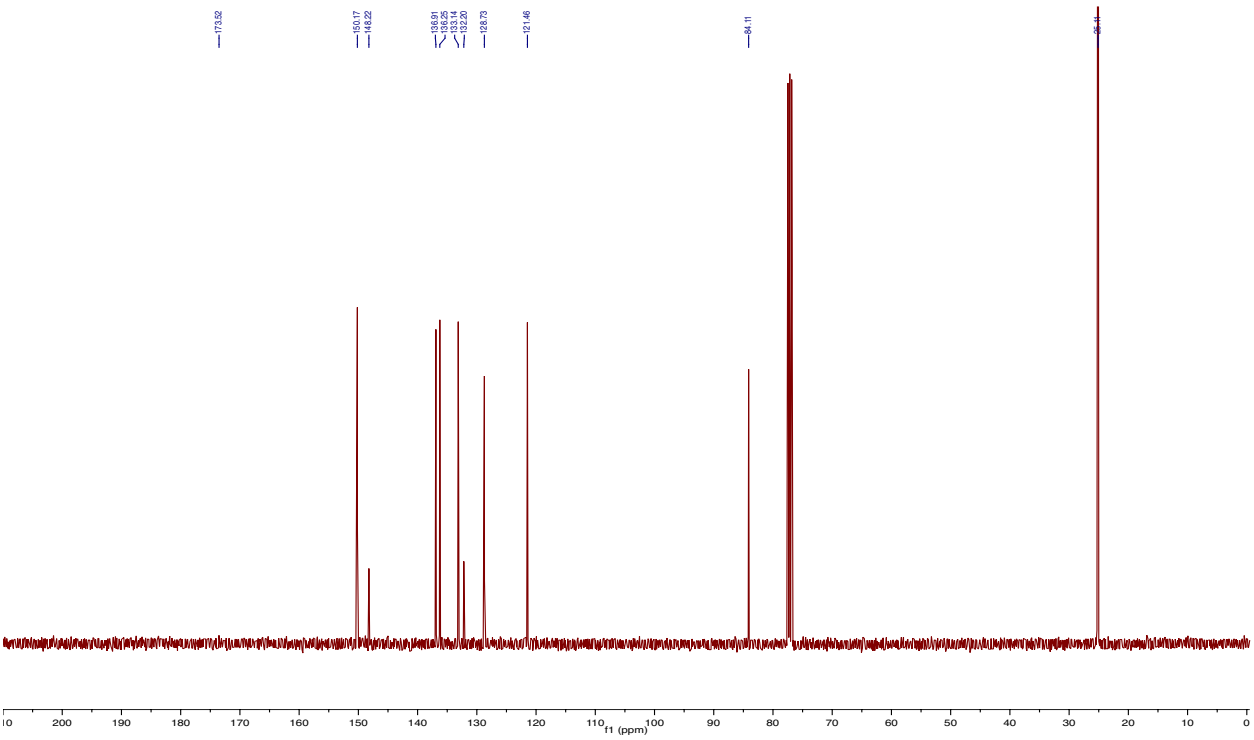

7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (S-1.2)

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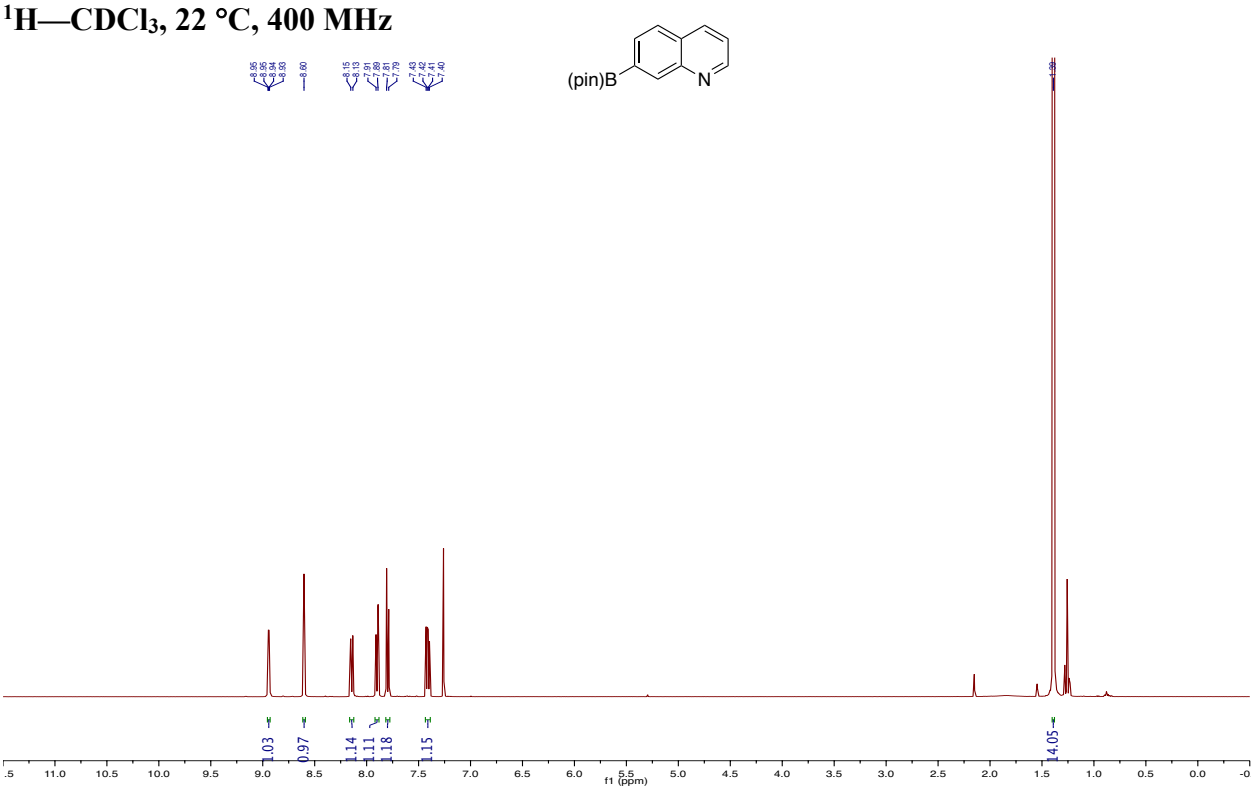

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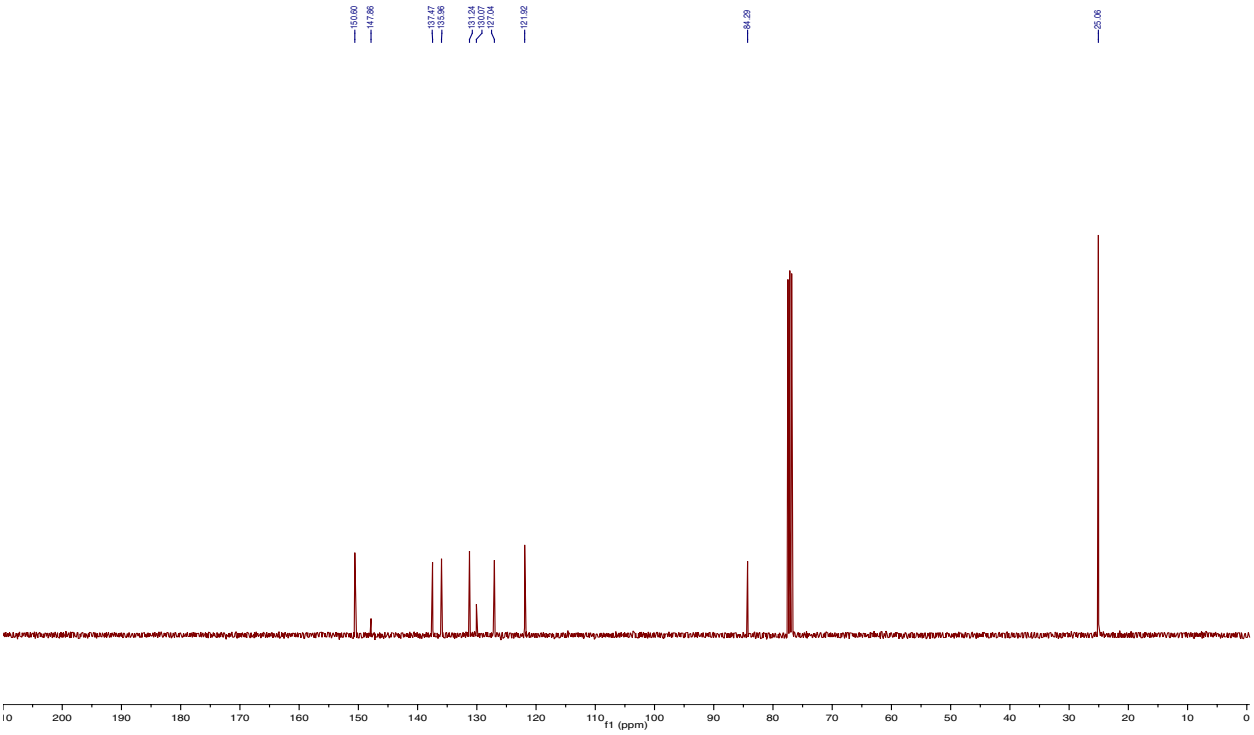
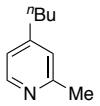


4-butyl-2-methylpyridine (1.130)



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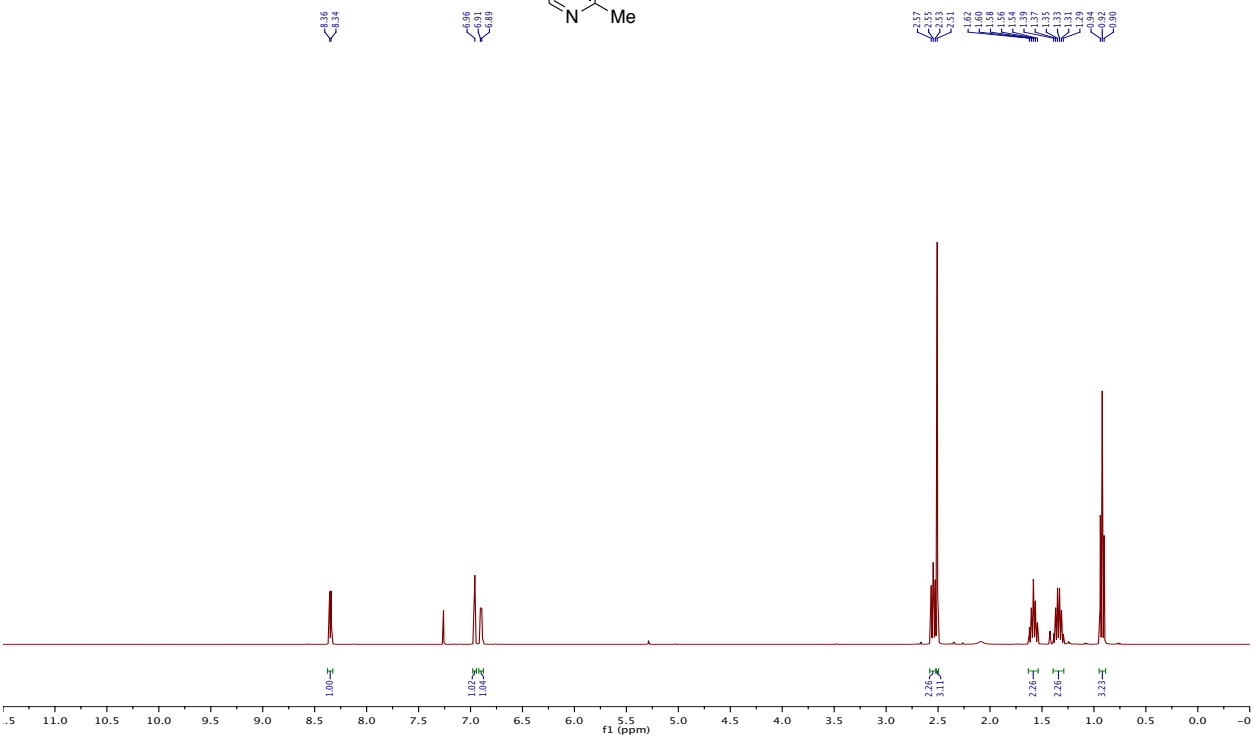

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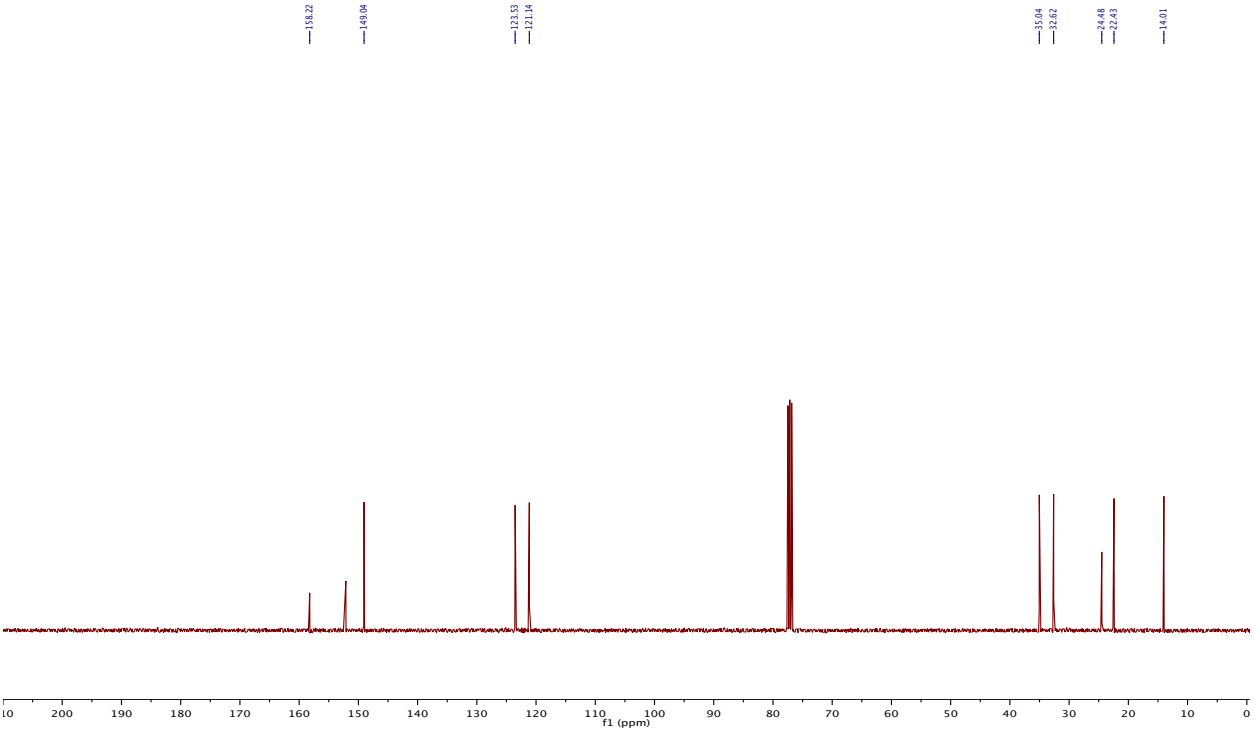

4-butyl-2-methoxypyridine (1.131)

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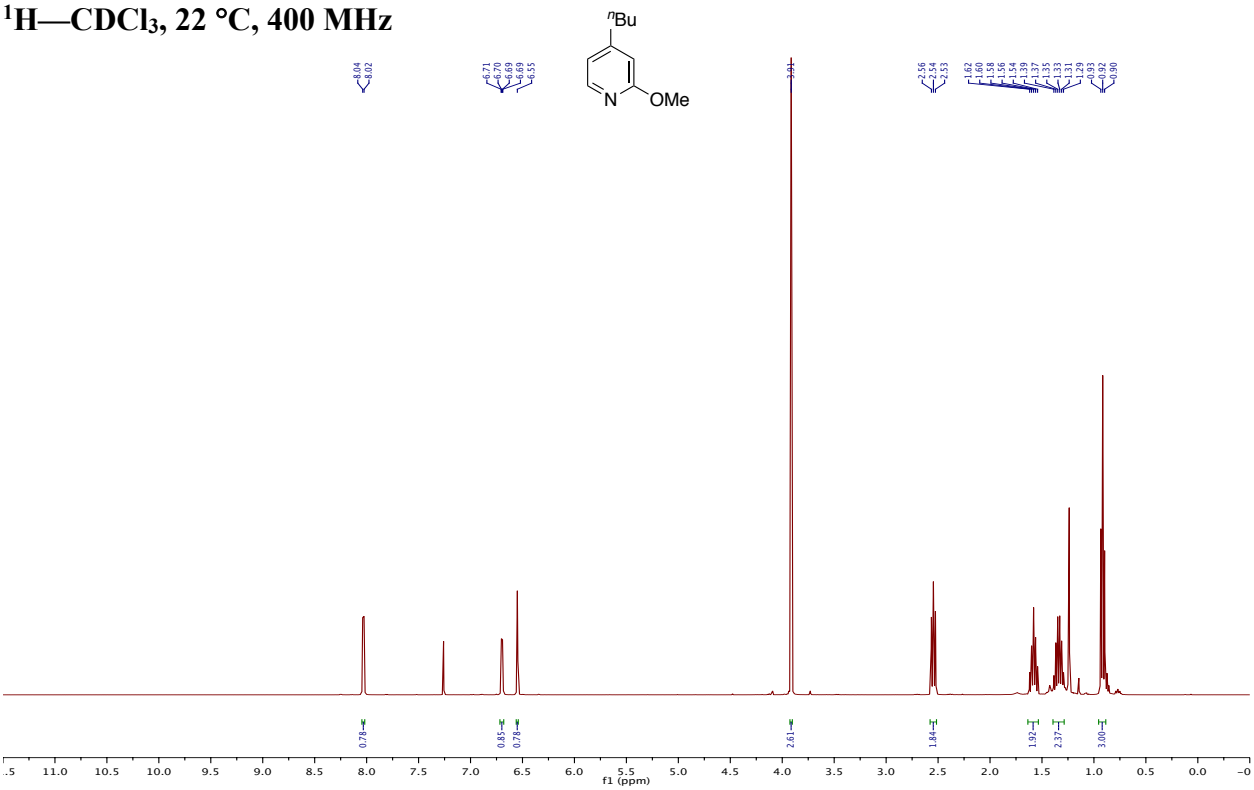

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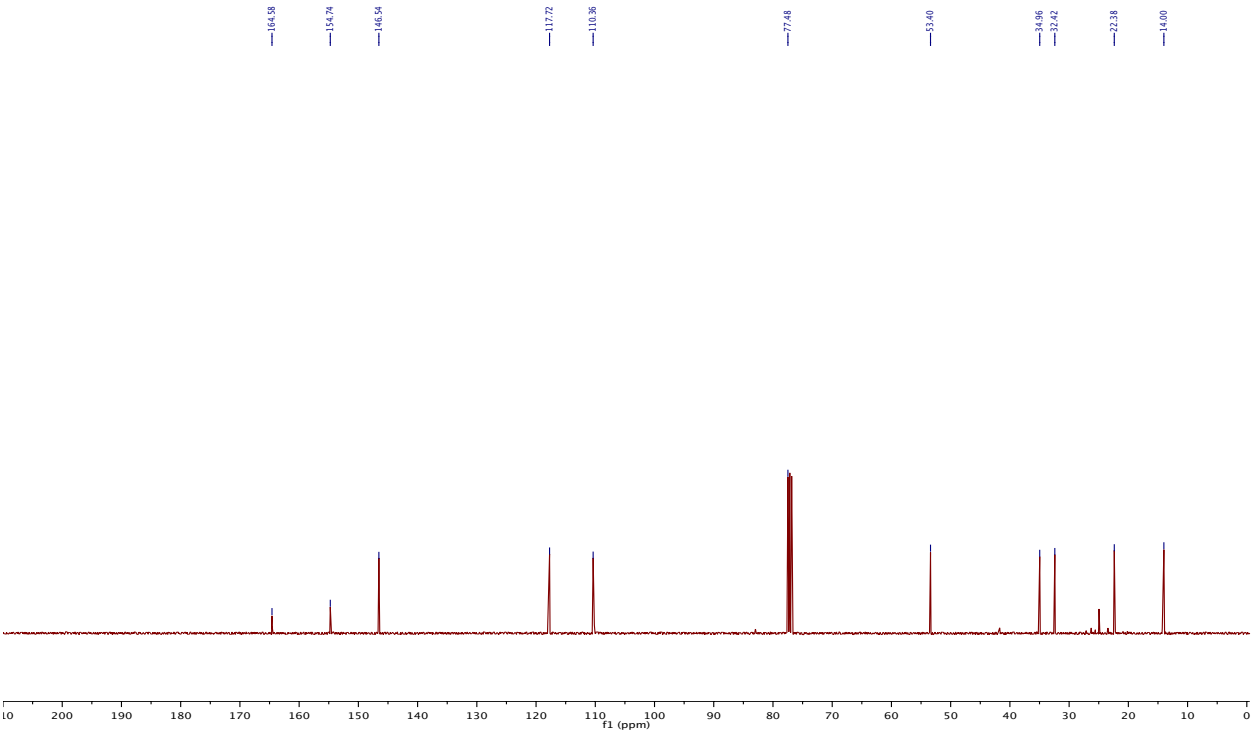

4-butyl-2-chloropyridine (1.132)

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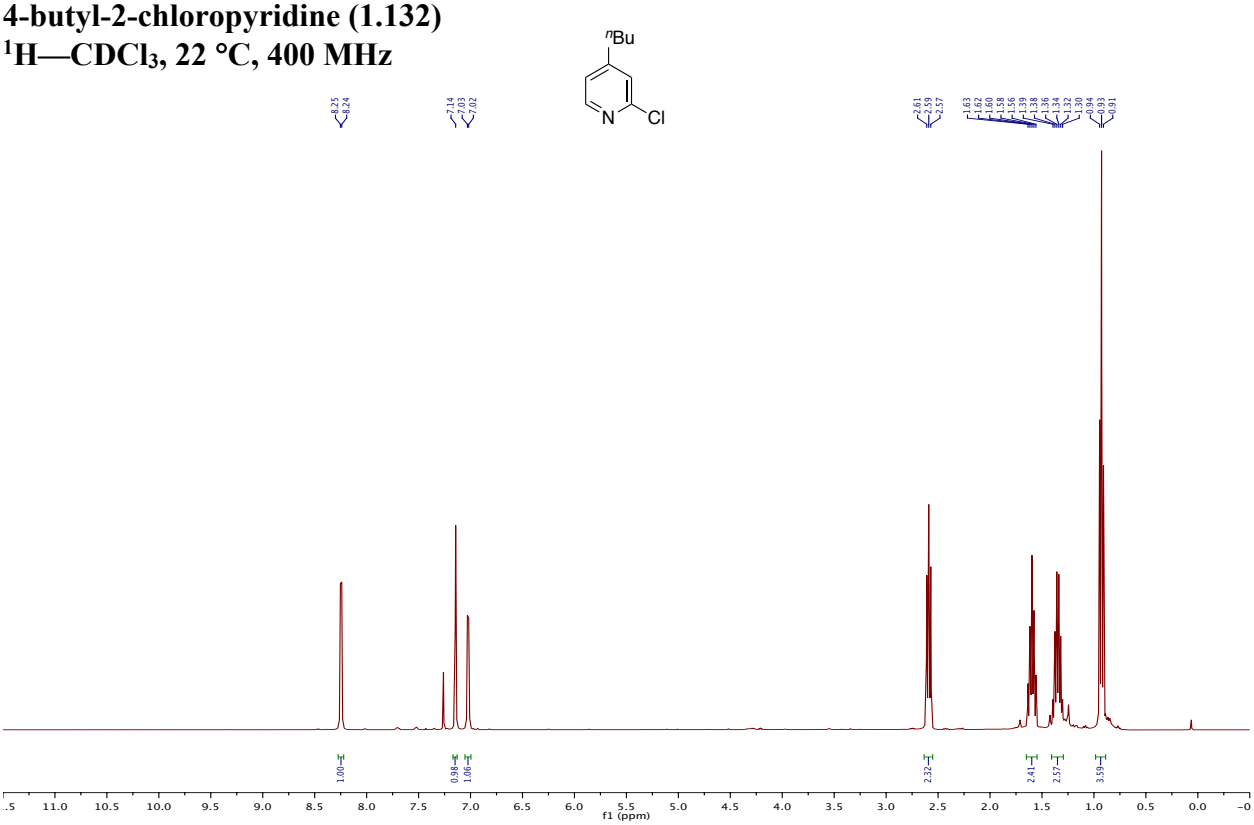

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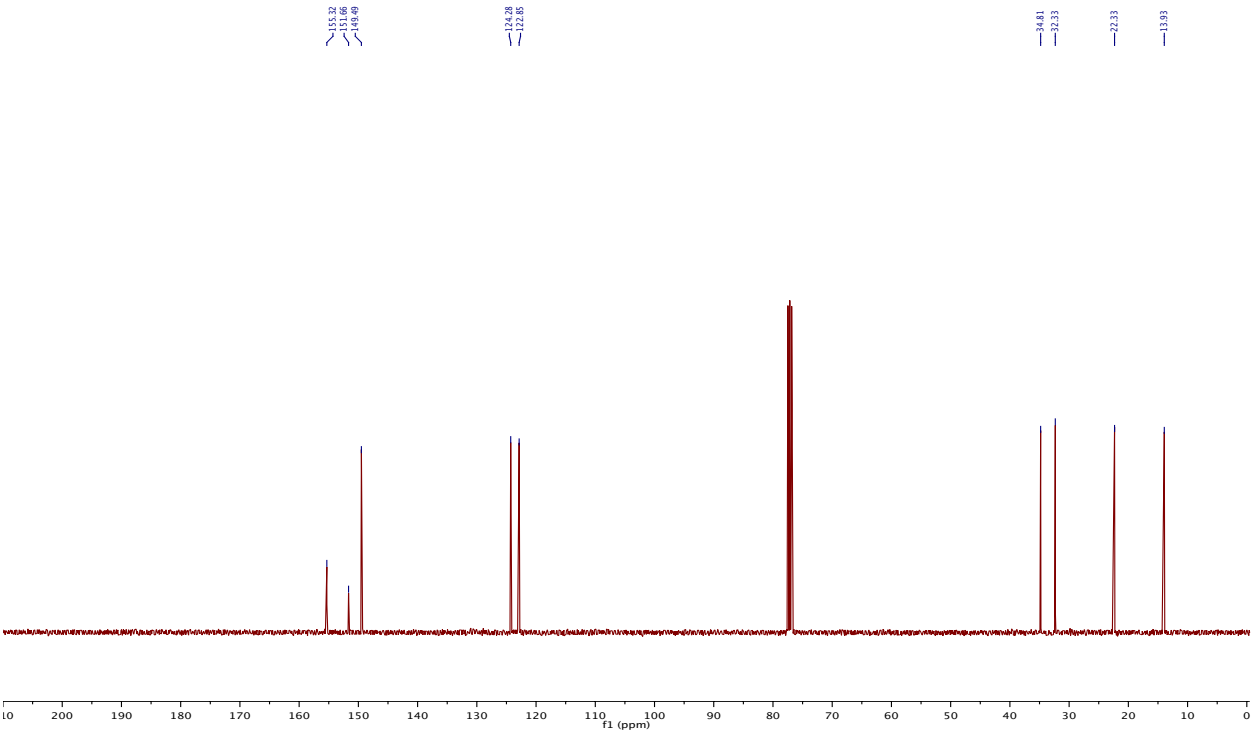

4-butyl-3-chloropyridine (1.133)

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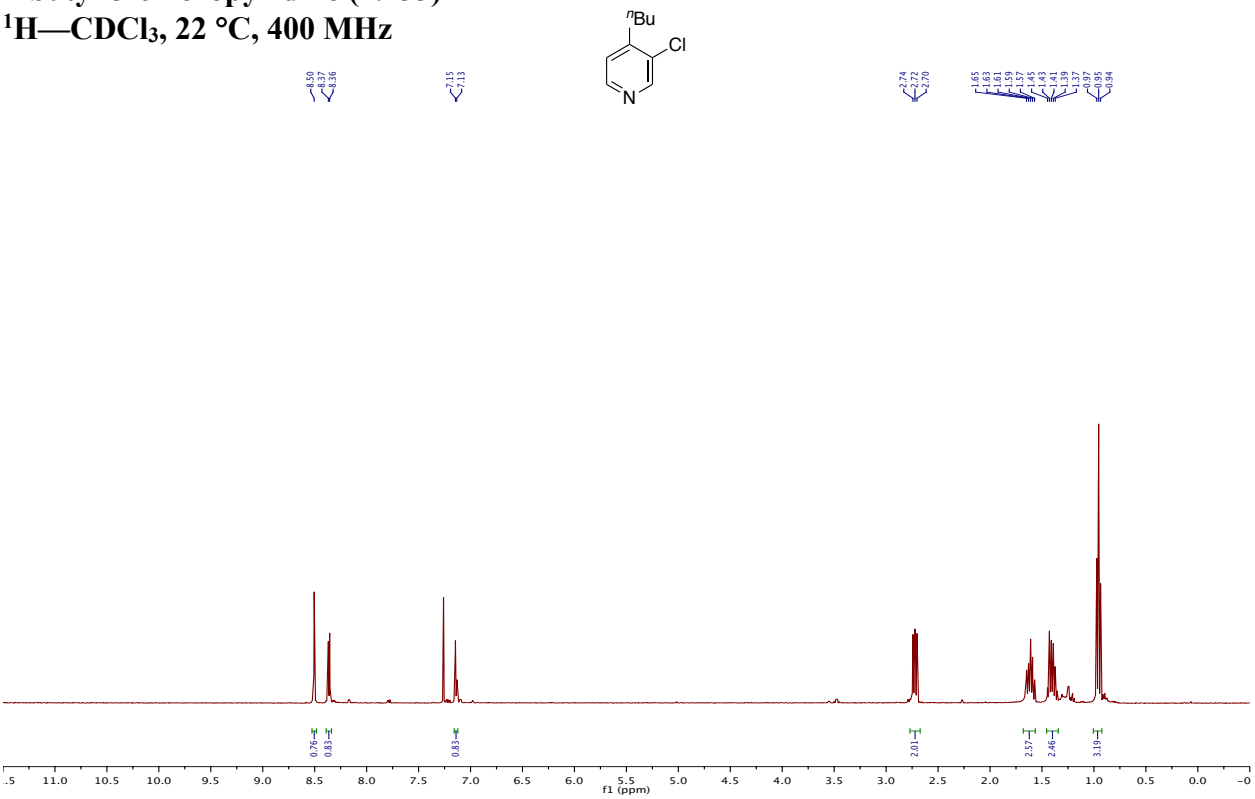

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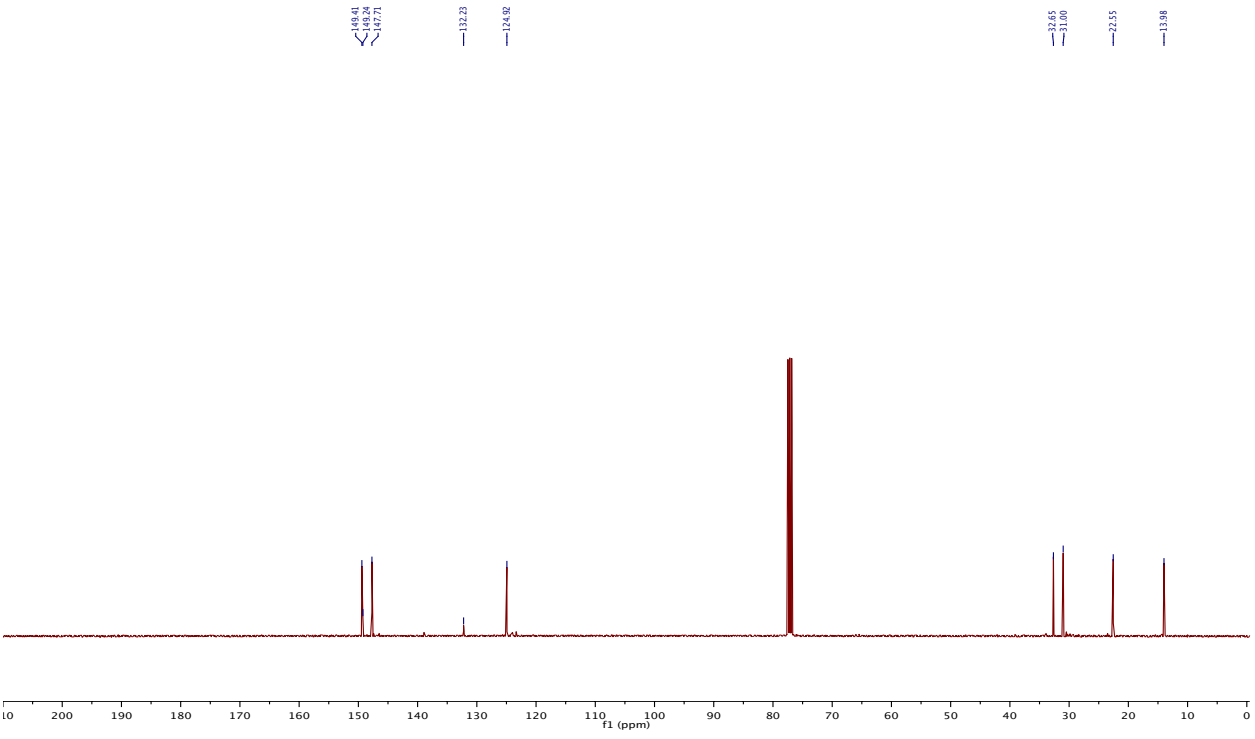

4-butylquinoline (1.134)

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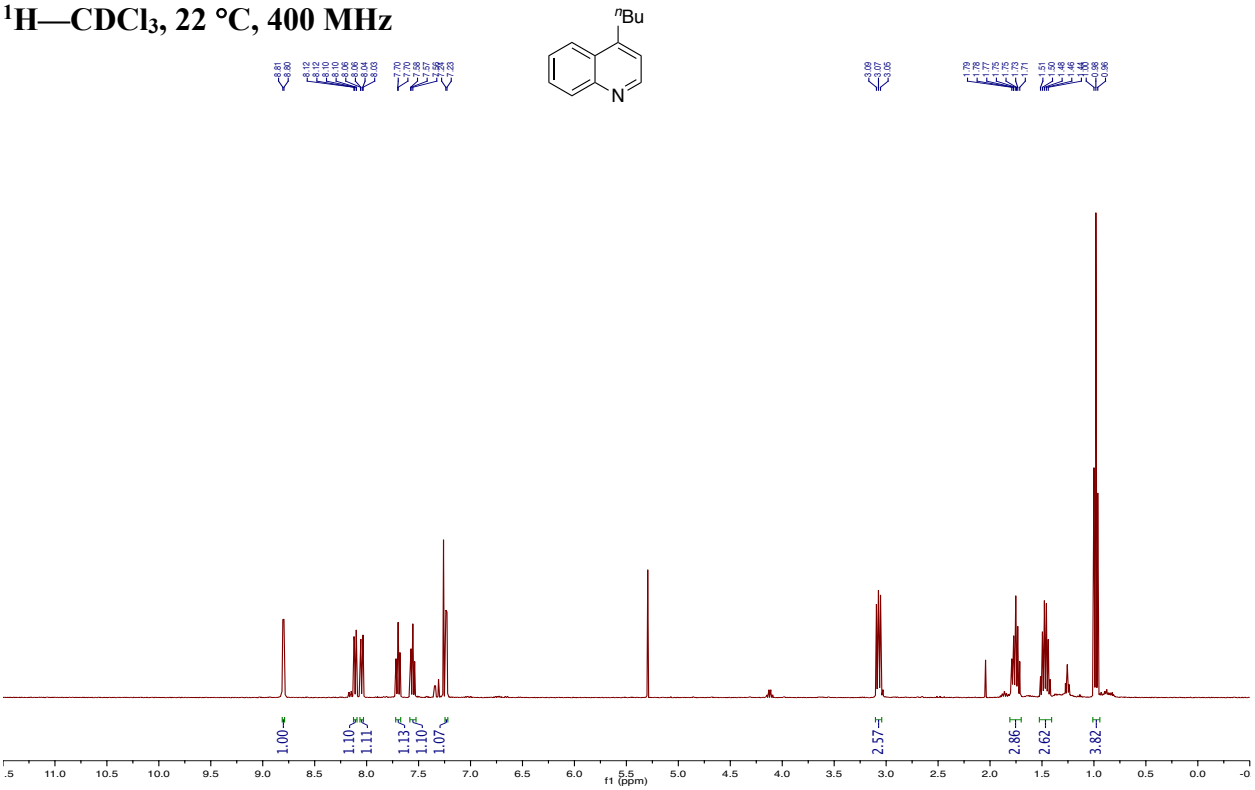

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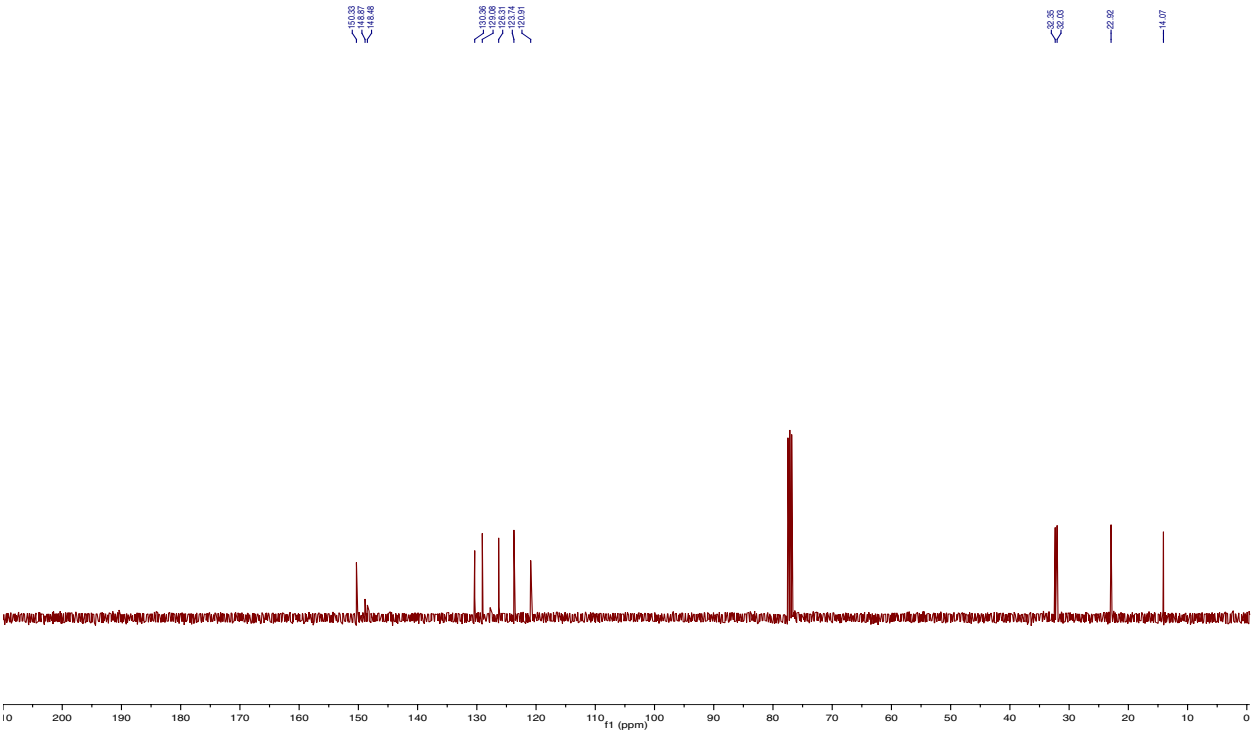

4-cyclohexylpyridine (1.135)

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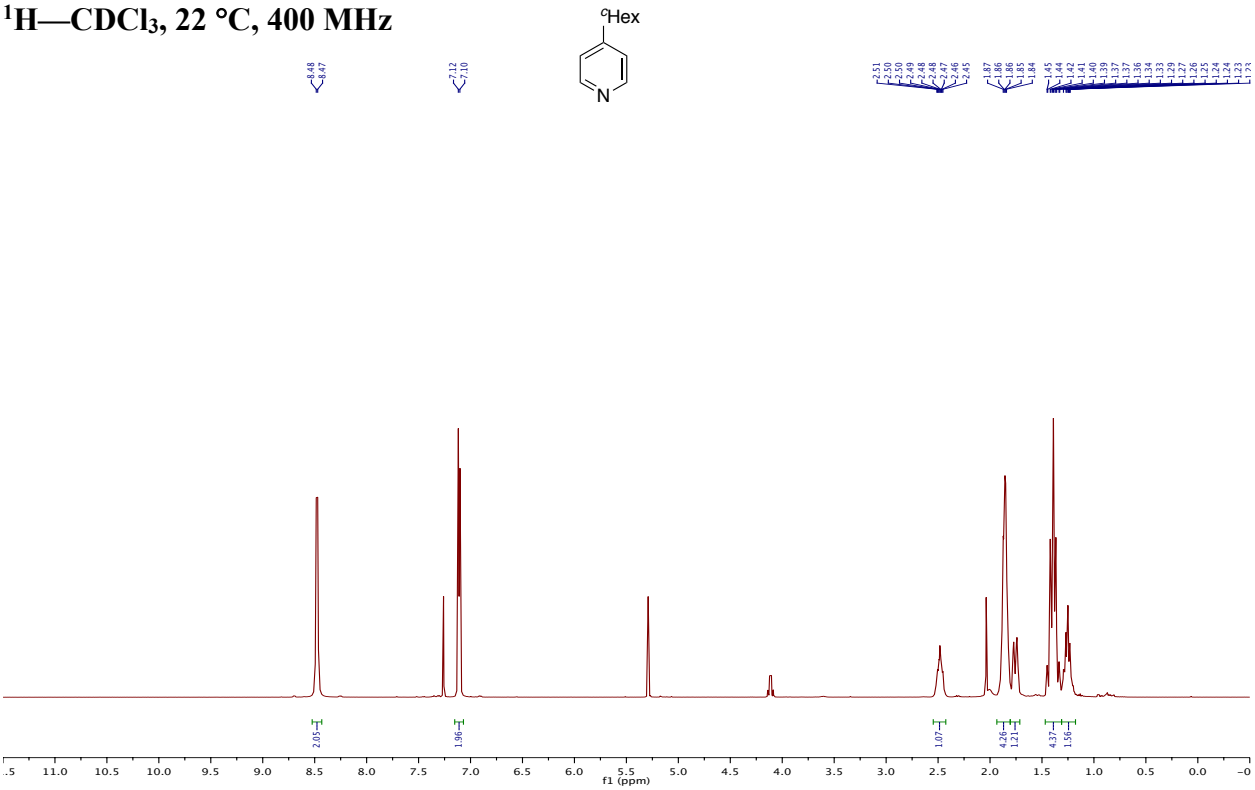

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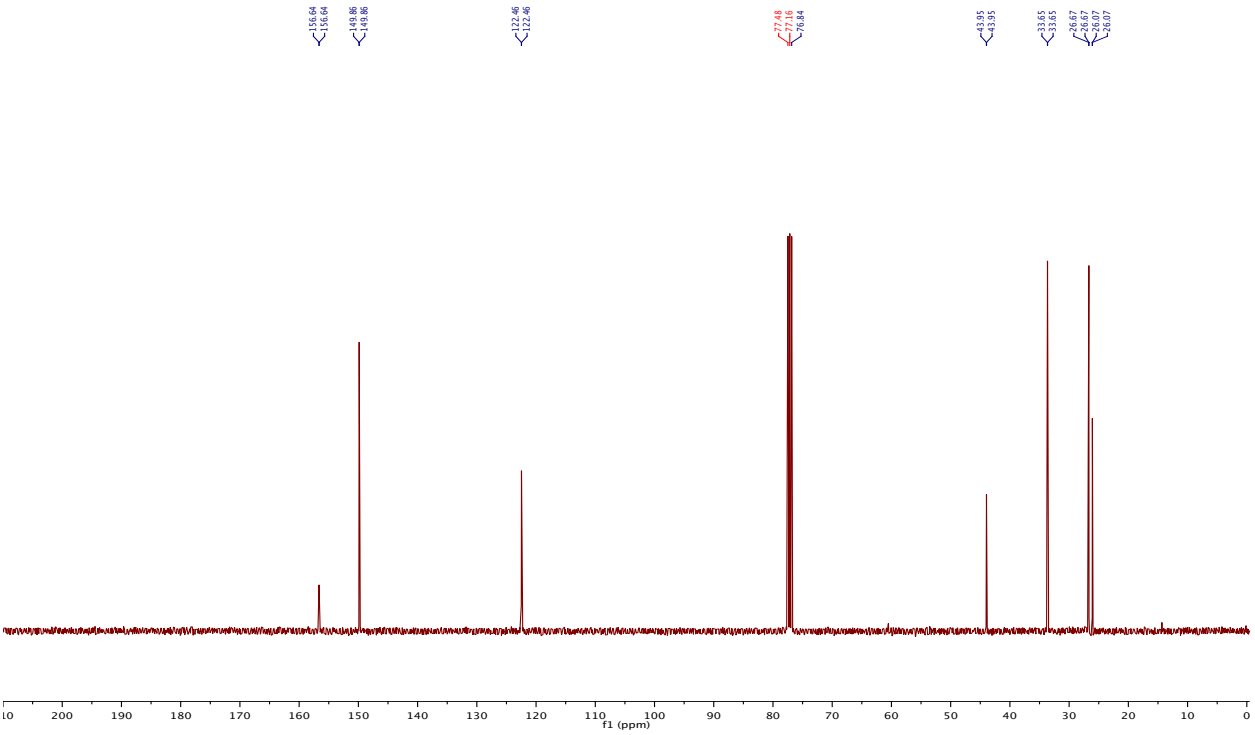

4-(*sec*-butyl)pyridine (1.136)

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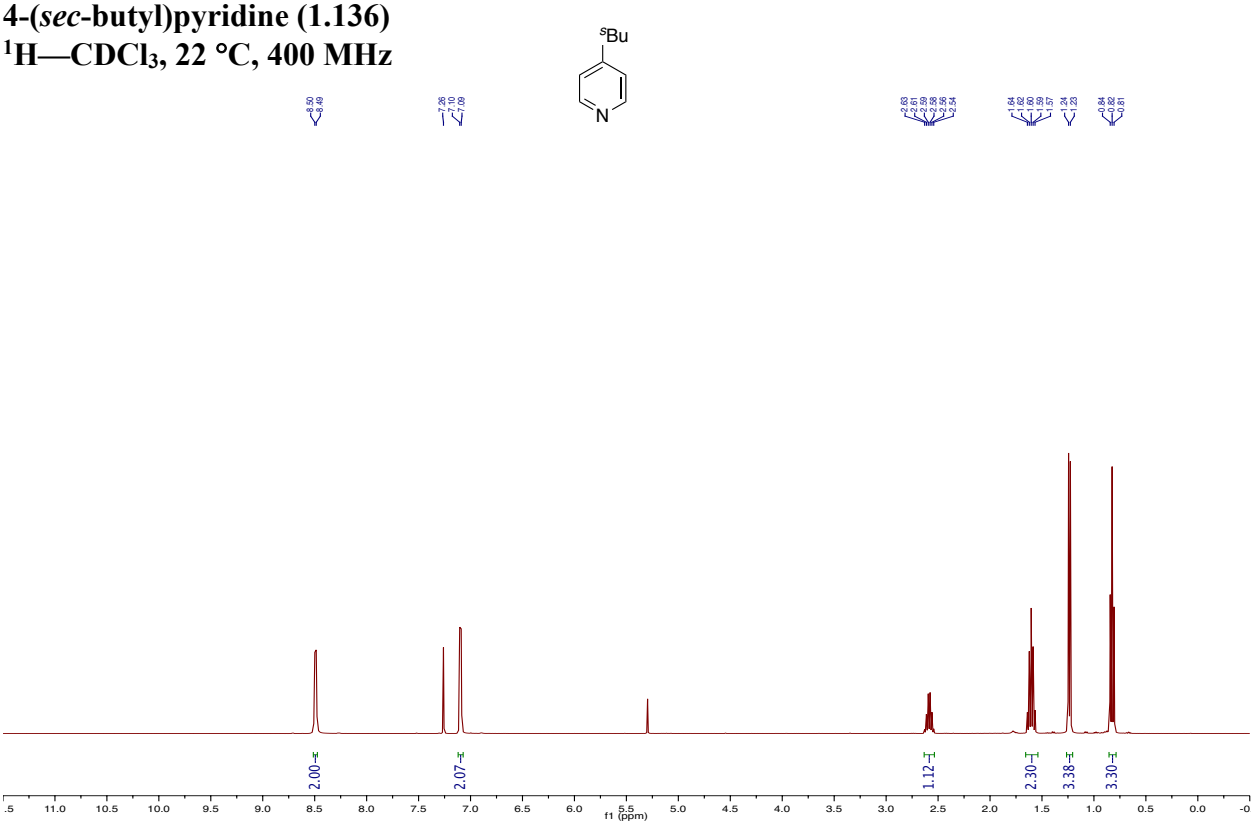
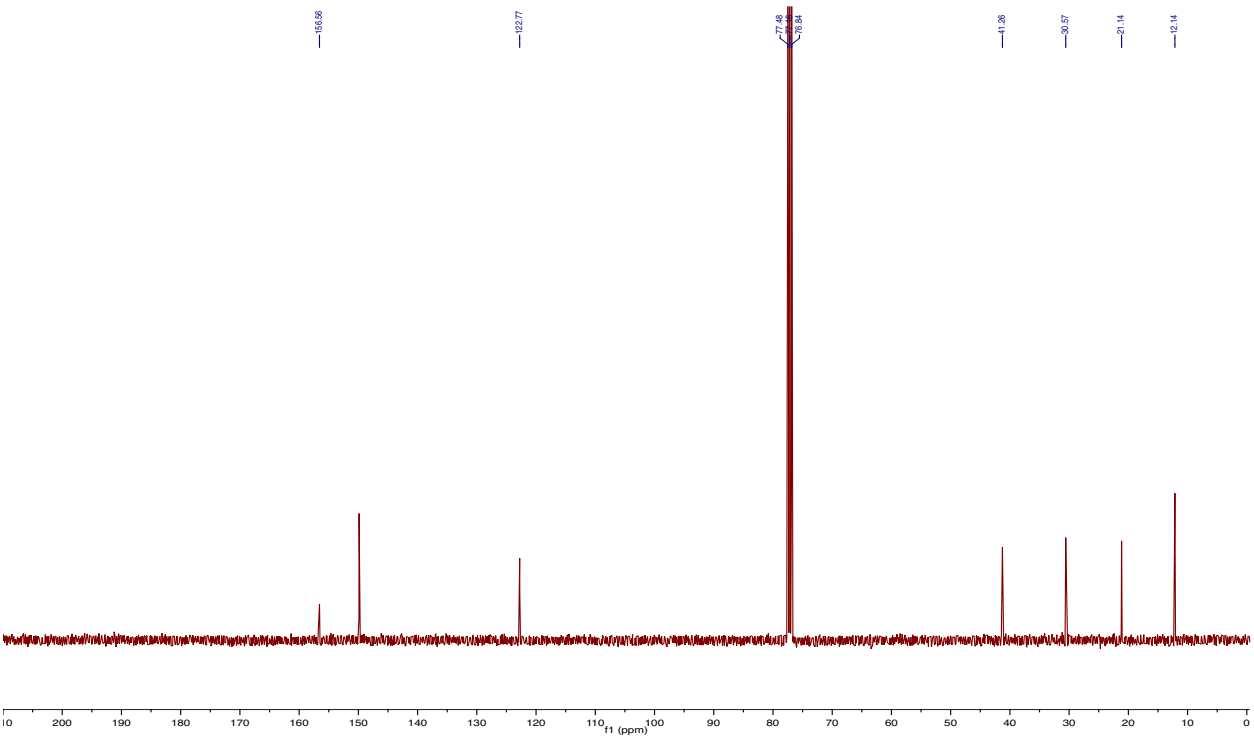
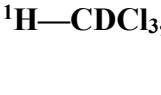


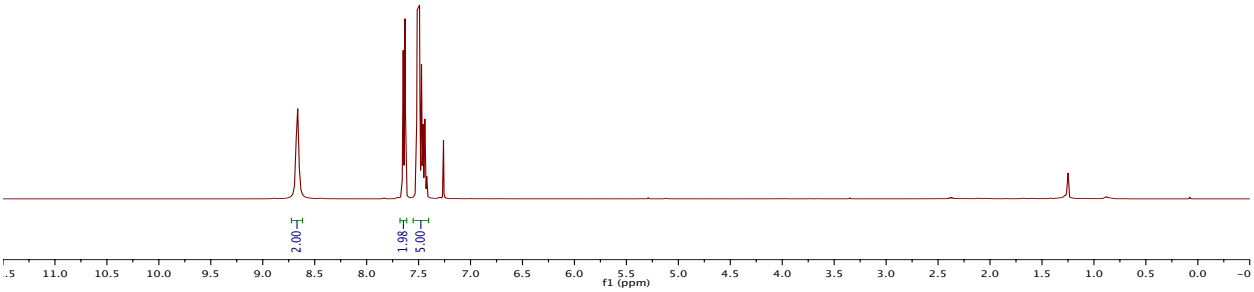
^{13}C—$CDCl_3$, 22 °C, 100 MHz



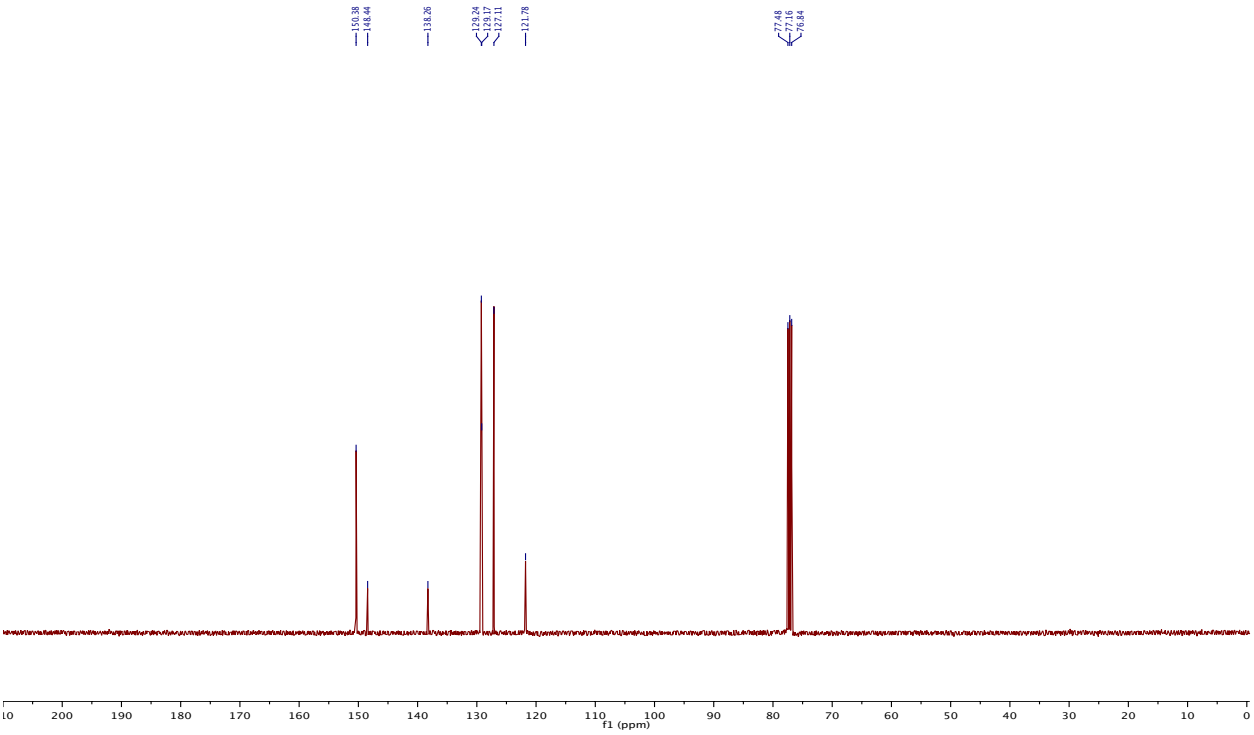
4-phenylpyridine (1.137)

^{1}H—$CDCl_3$, 22 °C, 400 MHz





^{13}C—$CDCl_3$, 22 °C, 100 MHz



4-cyclohexyl-2-methylpyridine (1.138)

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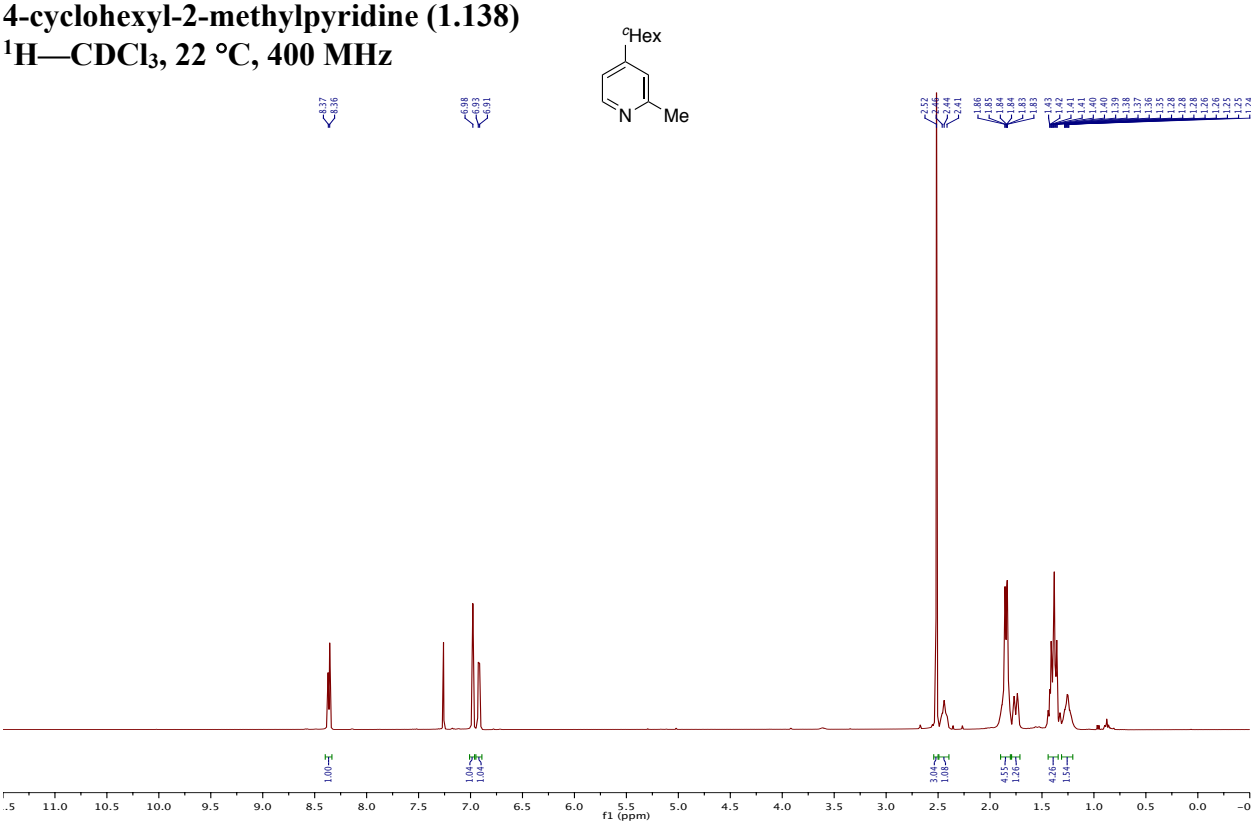

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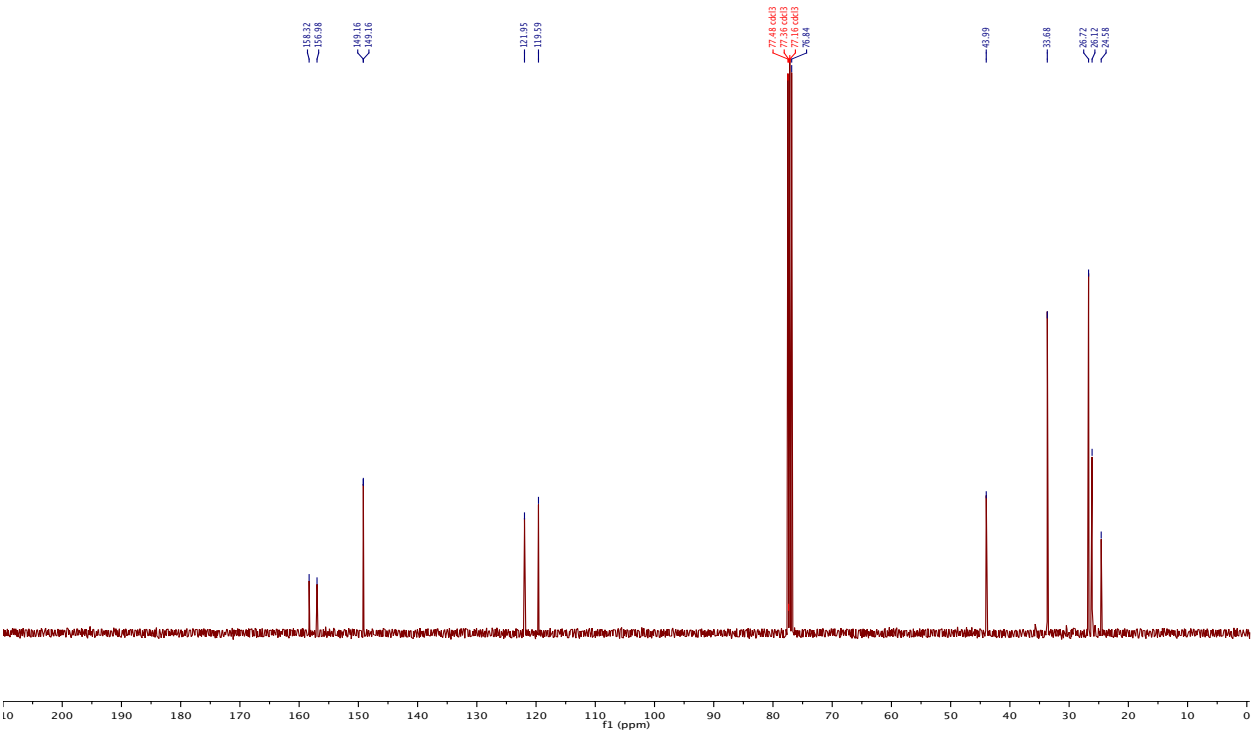

4-(*sec*-butyl)-2-methylpyridine (1.139)

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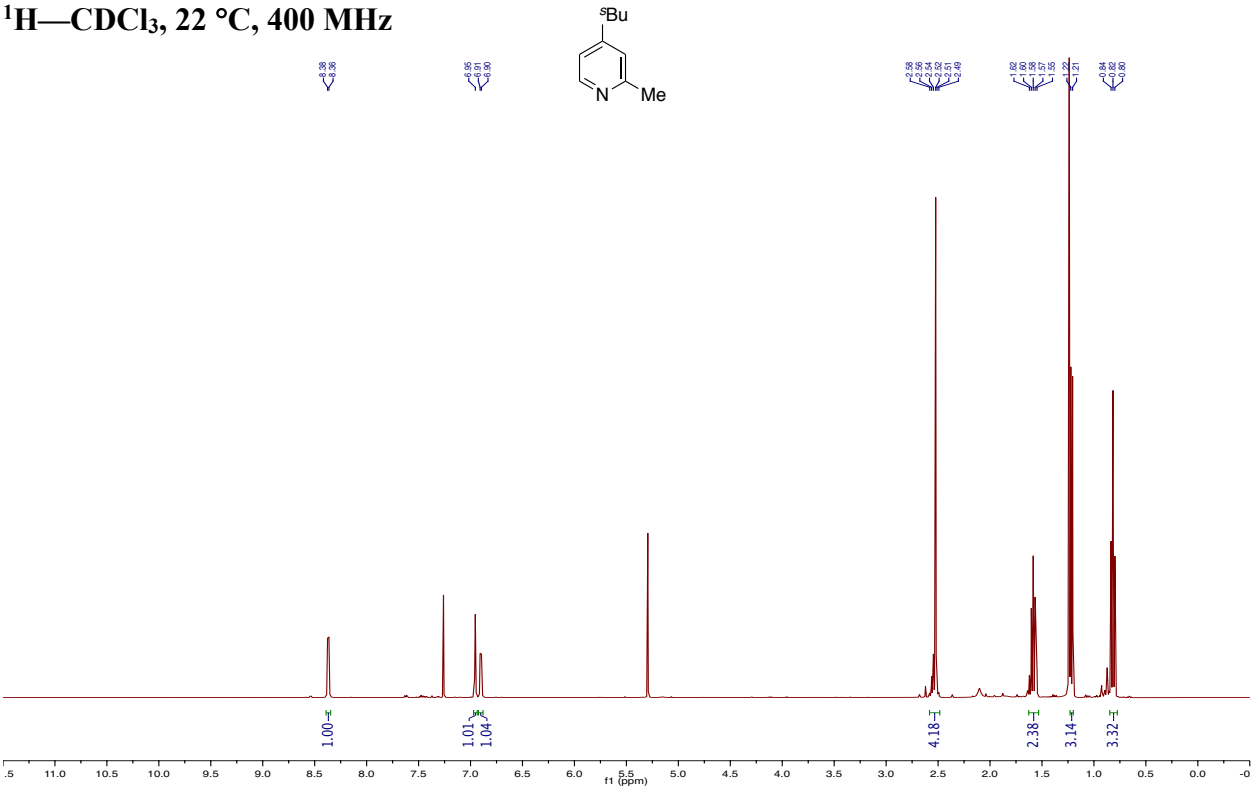

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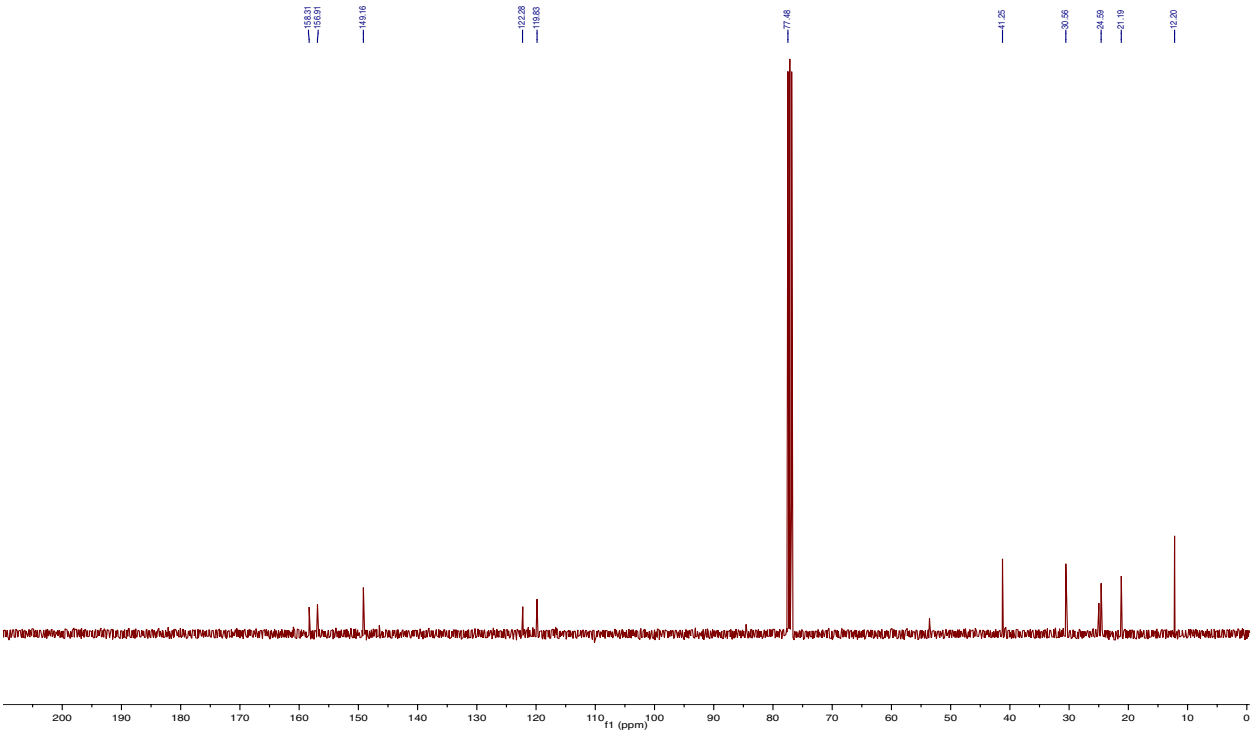
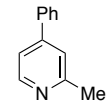


2-methyl-4-phenylpyridine (1.140)



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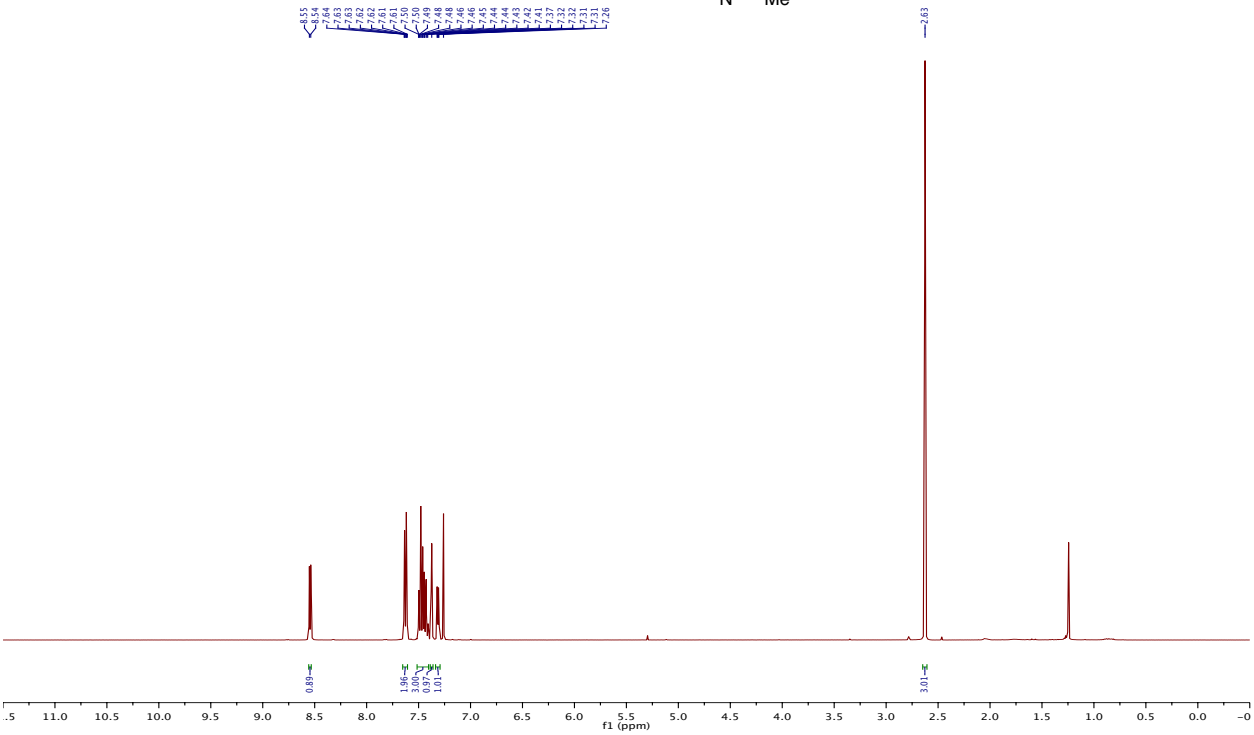

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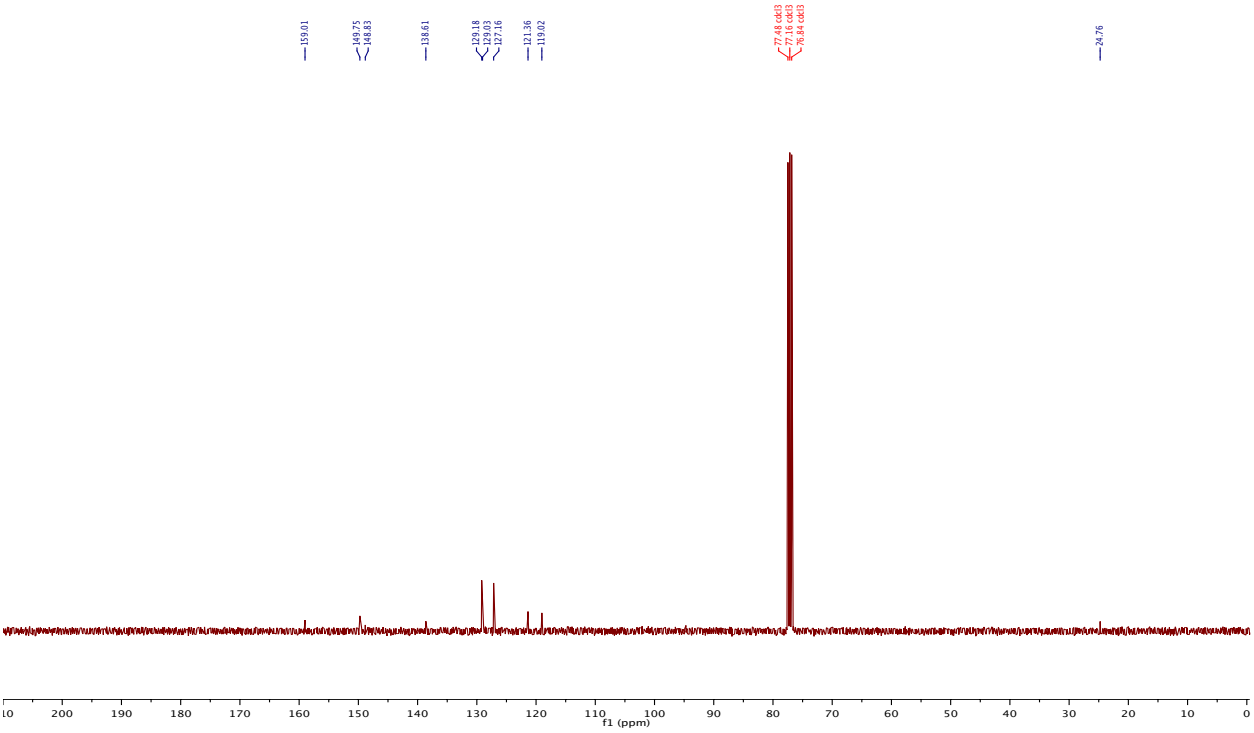

4-cyclohexyl-2-methoxypyridine (1.141)

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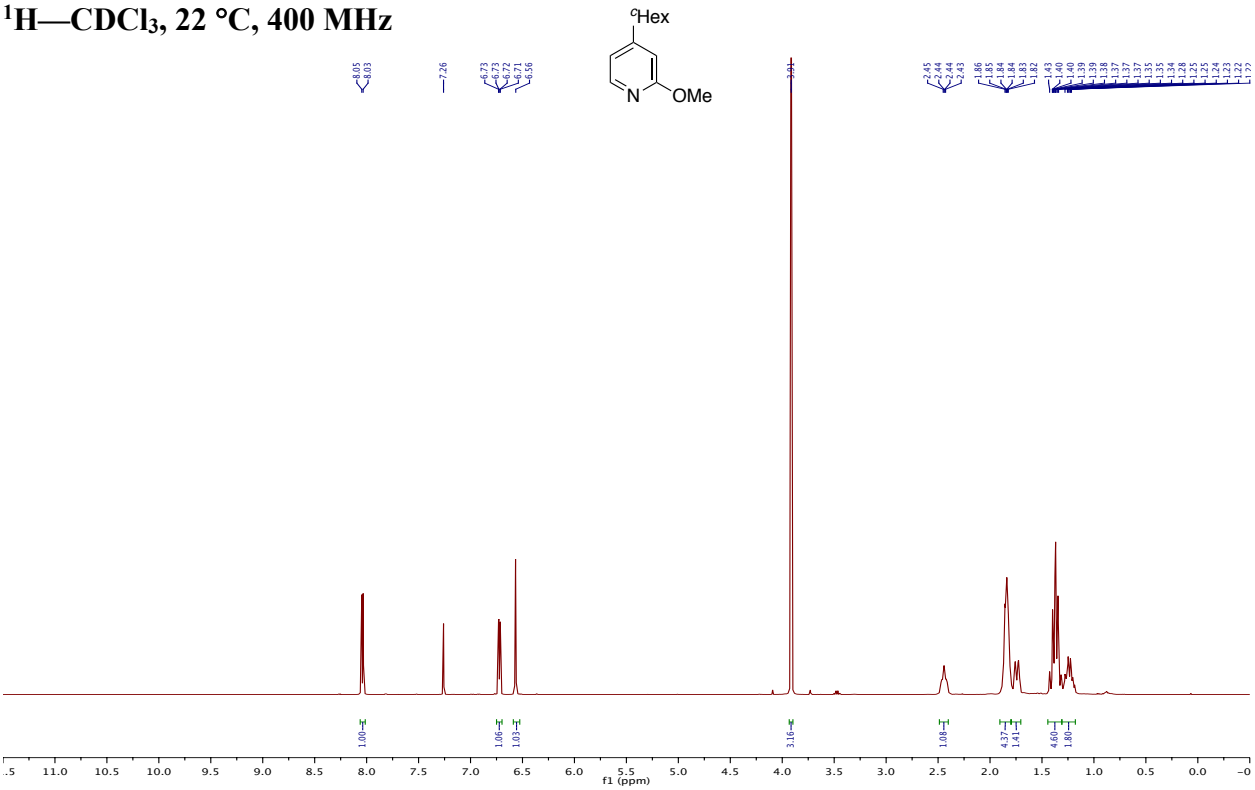

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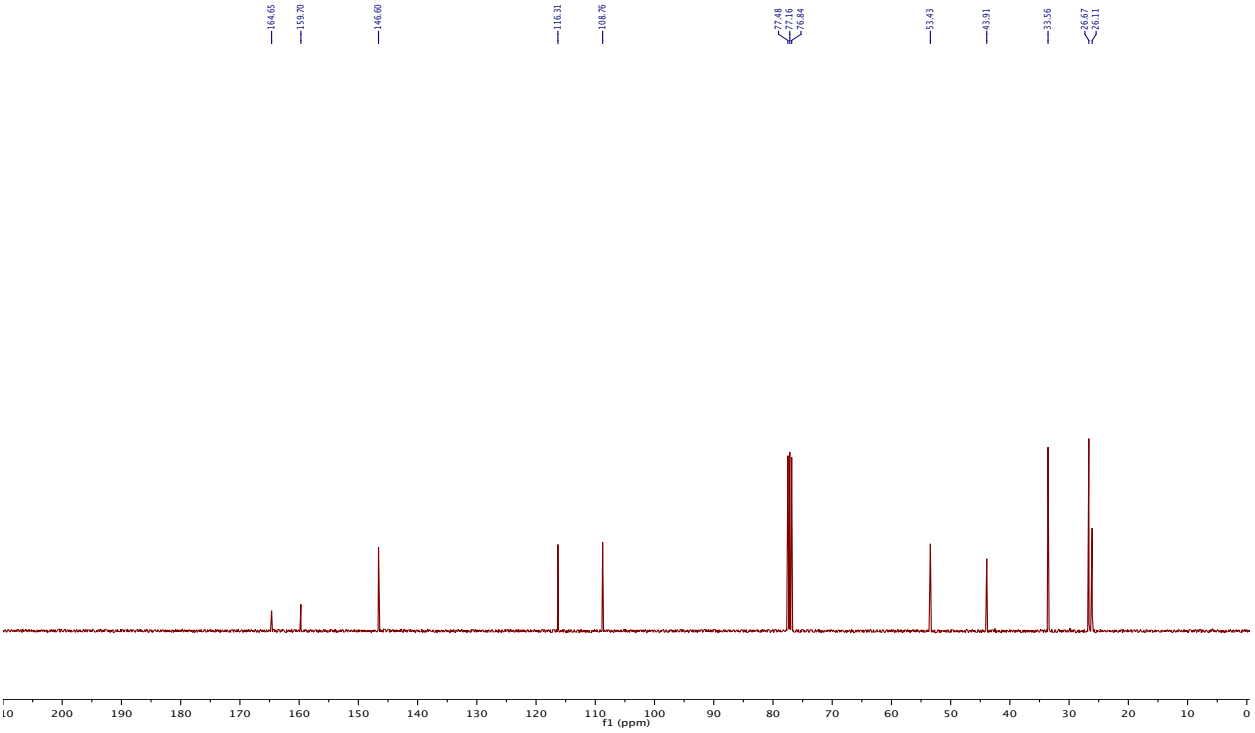

2-methoxy-4-phenylpyridine (1.142)

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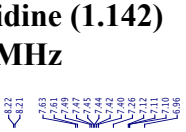

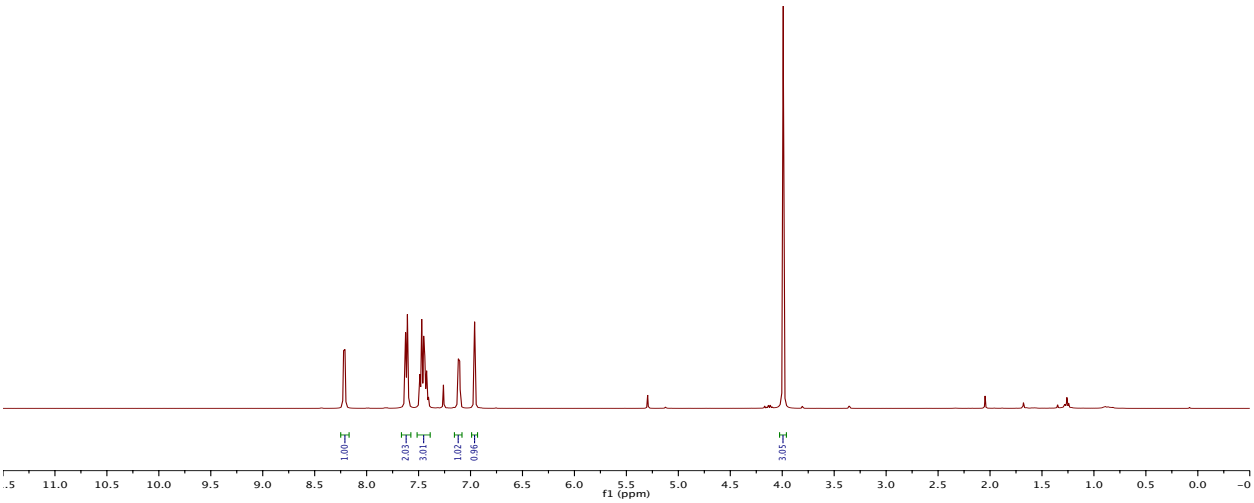

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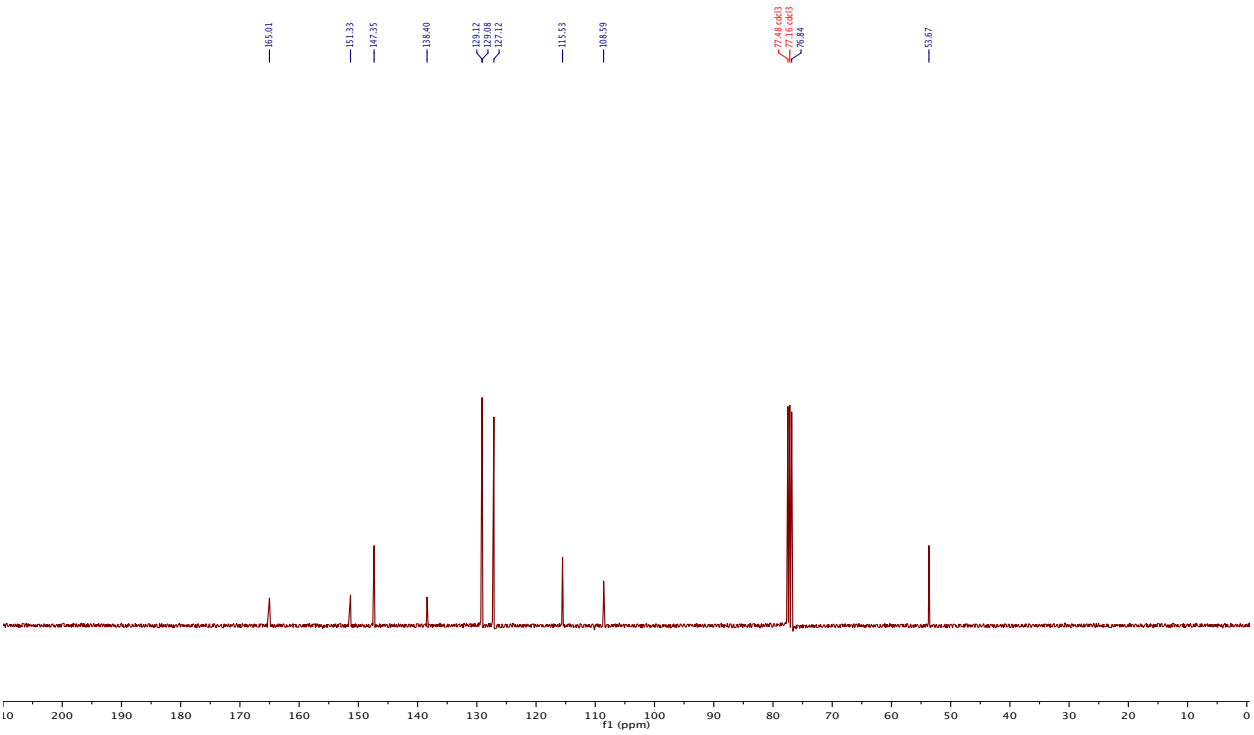

4-(*sec*-butyl)-2-chloropyridine (1.143)

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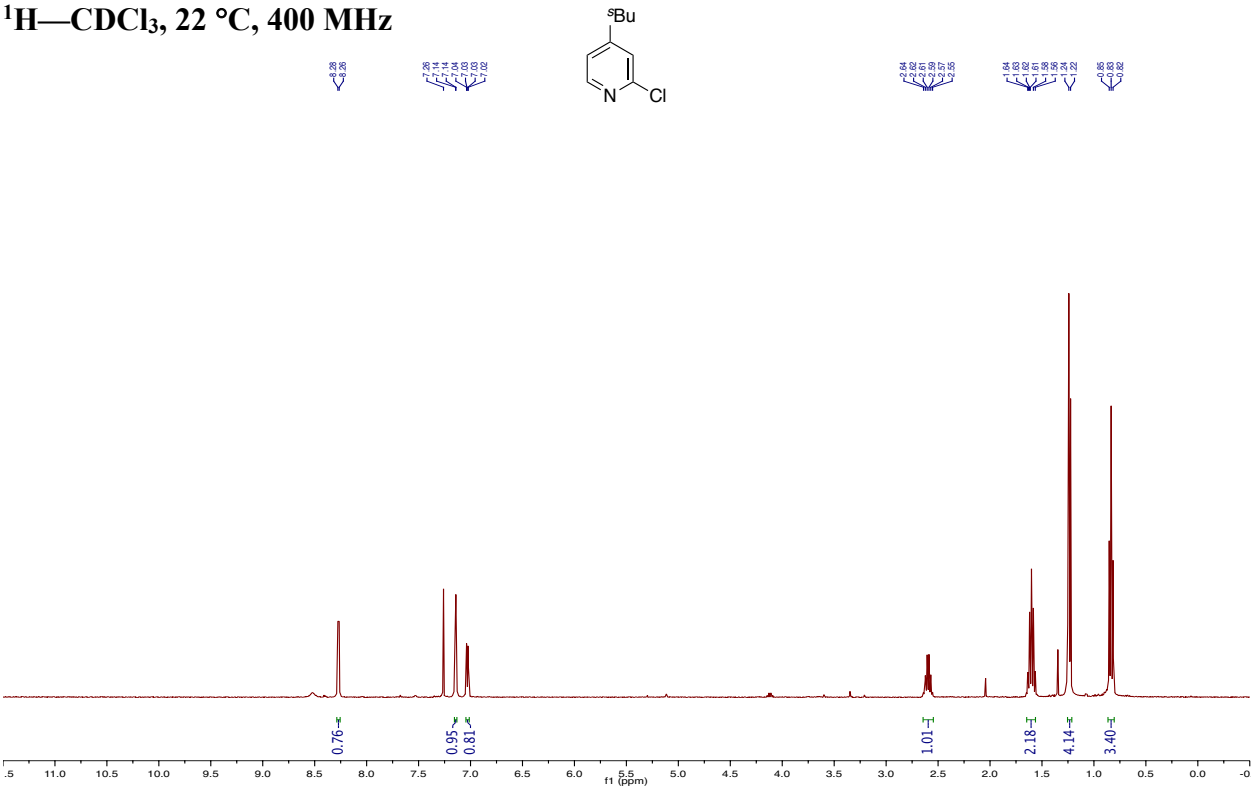
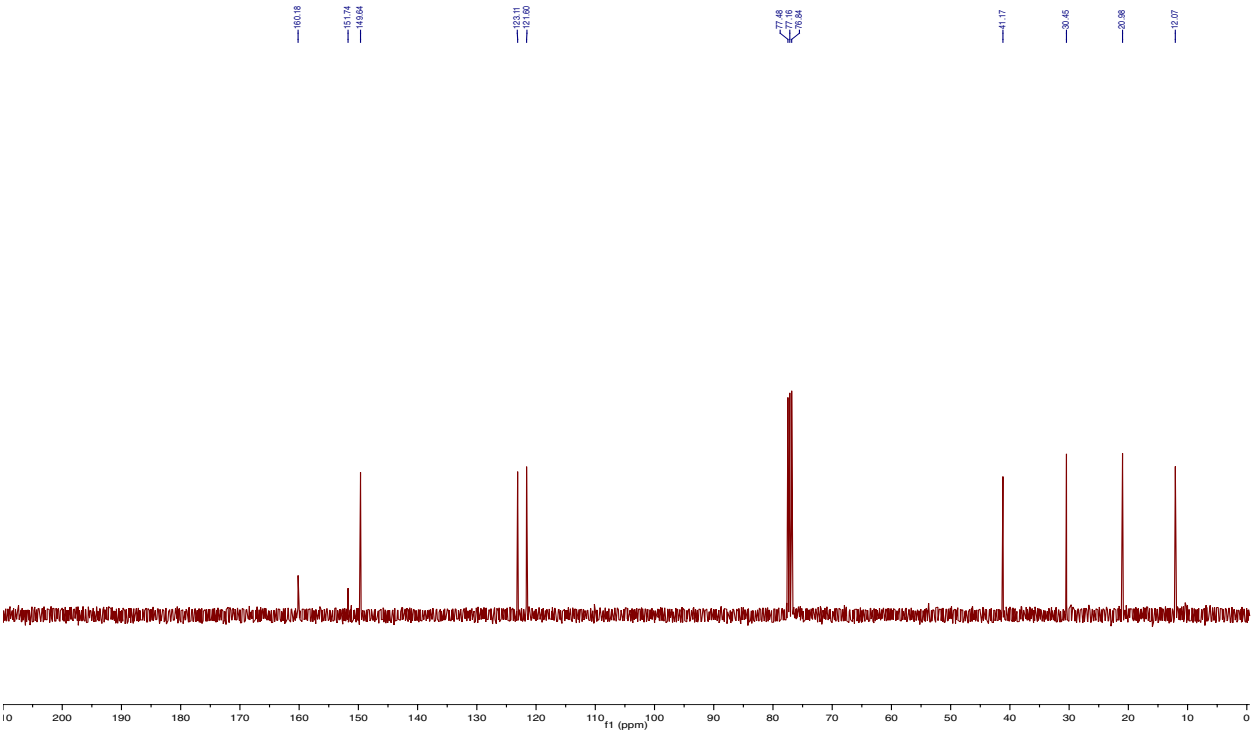
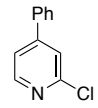


^{13}C—$CDCl_3$, 22 °C, 100 MHz



2-chloro-4-phenylpyridine (1.144)



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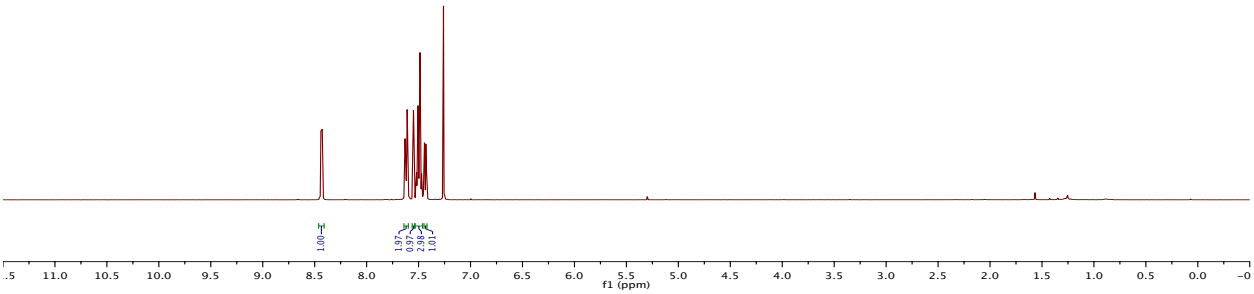
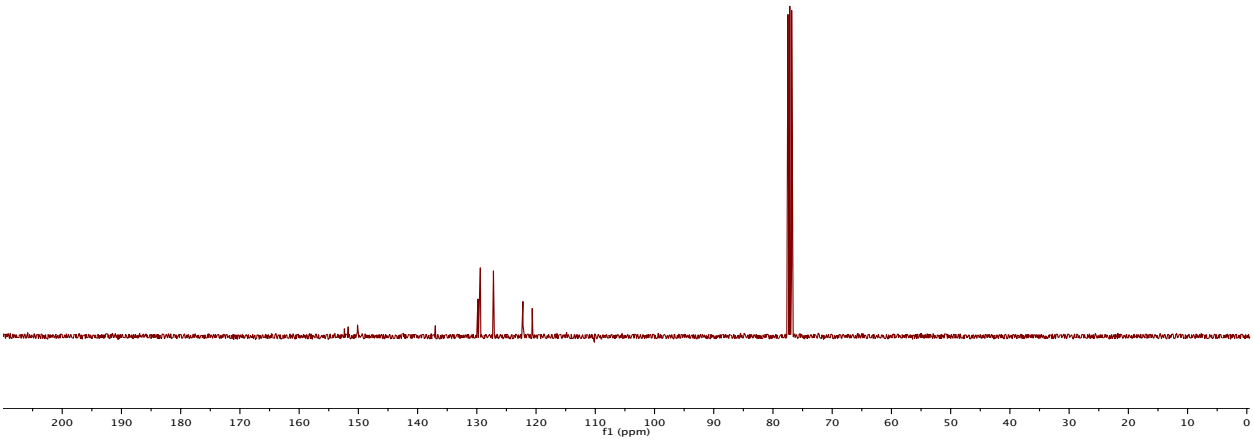


^{13}C—$CDCl_3$, 22 °C, 100 MHz



4-(*sec*-butyl)-3-chloropyridine (1.145)

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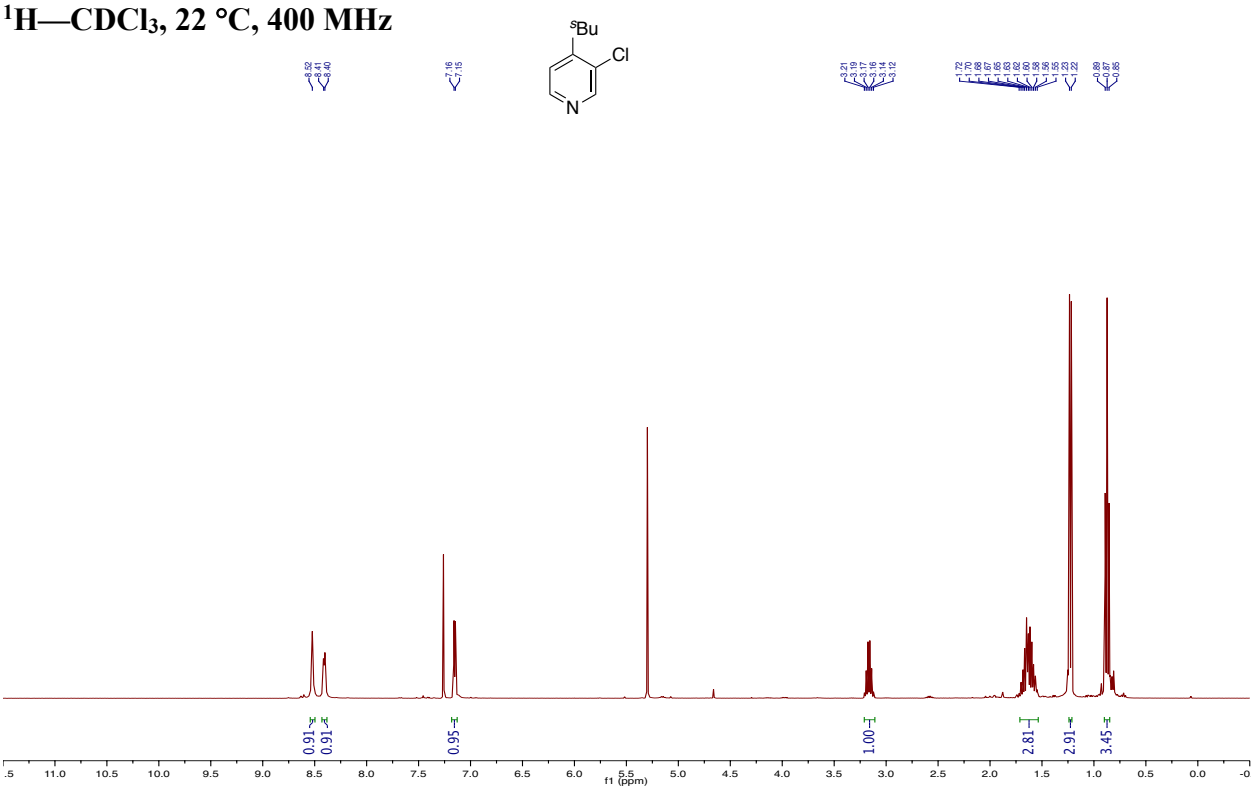
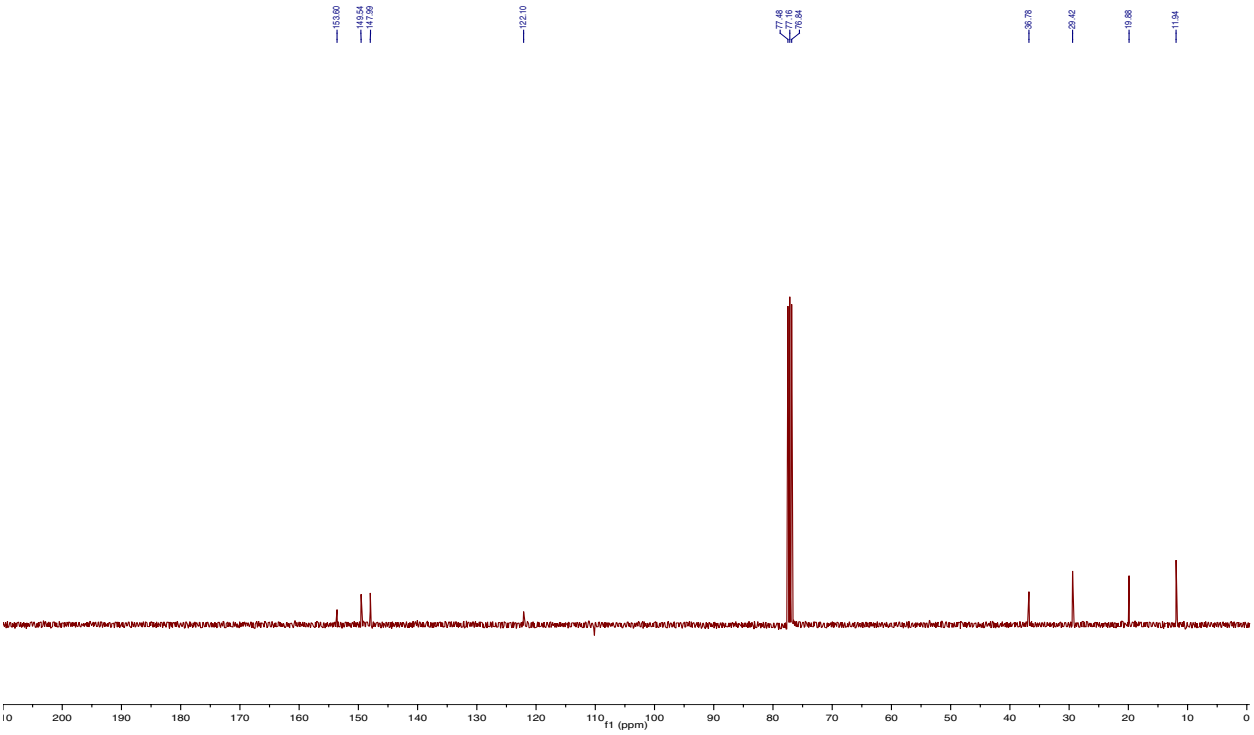
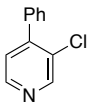


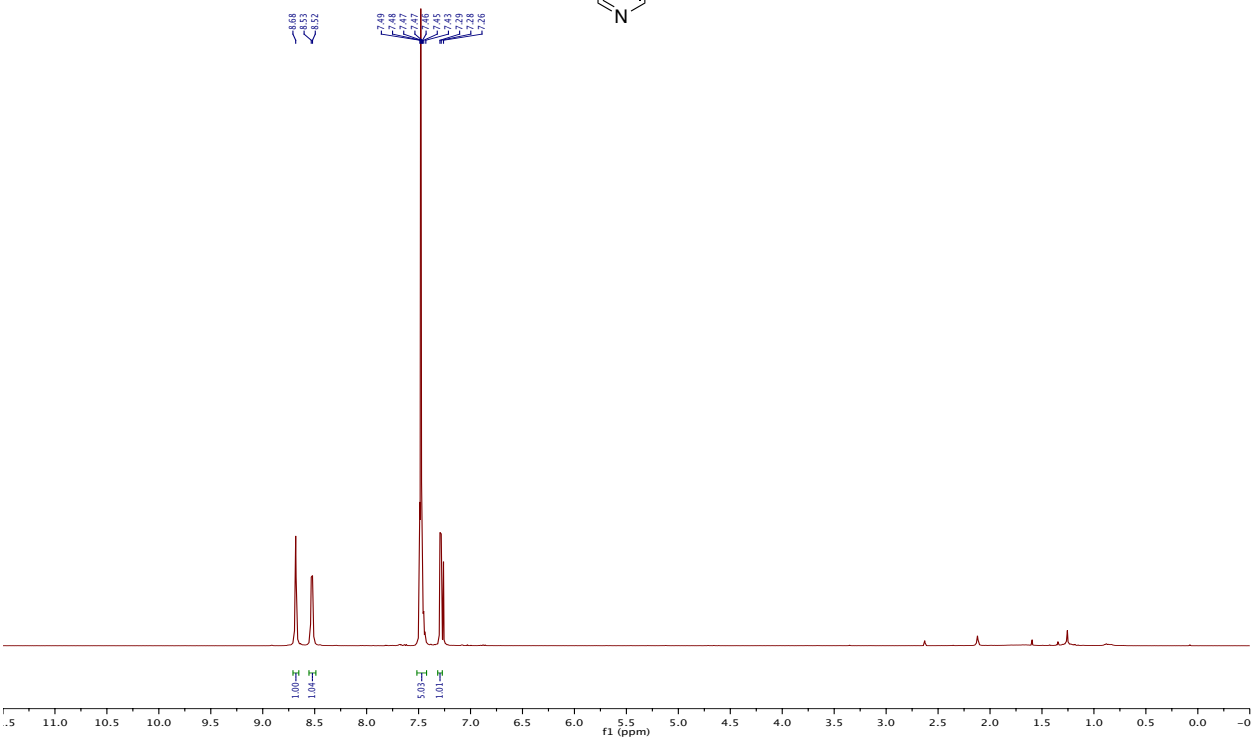
^{13}C—$CDCl_3$, 22 °C, 100 MHz



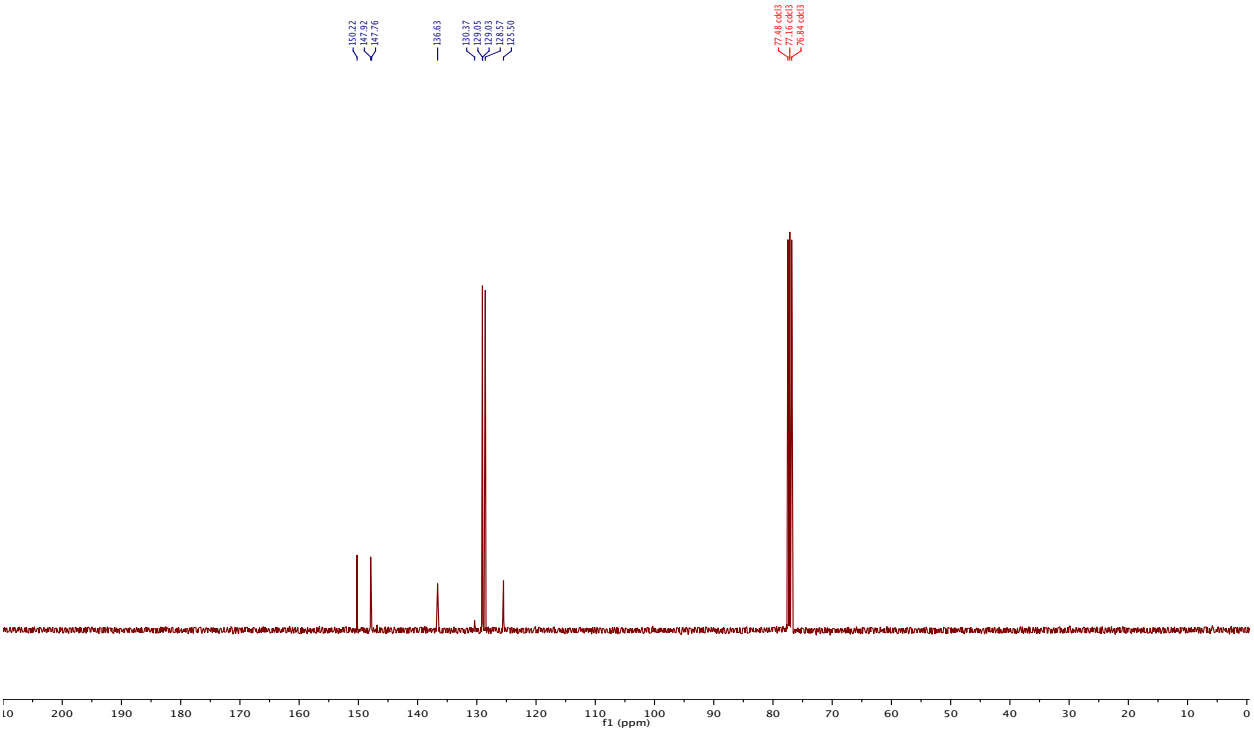
3-chloro-4-phenylpyridine (1.146)



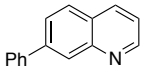
^{1}H—$CDCl_3$, 22 °C, 400 MHz



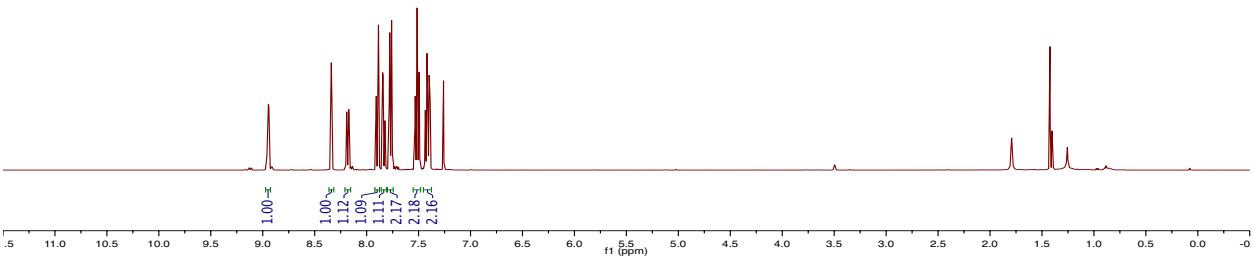
^{13}C—$CDCl_3$, 22 °C, 100 MHz



7-phenylquinoline (1.147)



^{1}H—$CDCl_3$, 22 °C, 400 MHz



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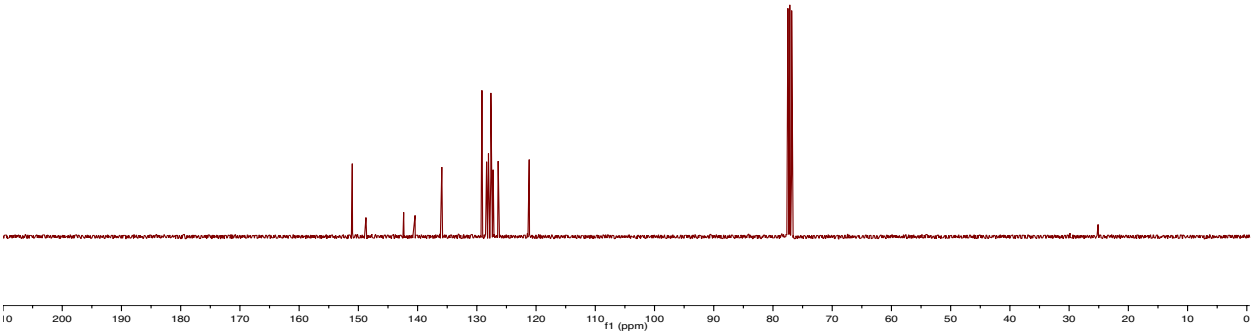

6-phenylisoquinoline (1.149)

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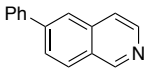

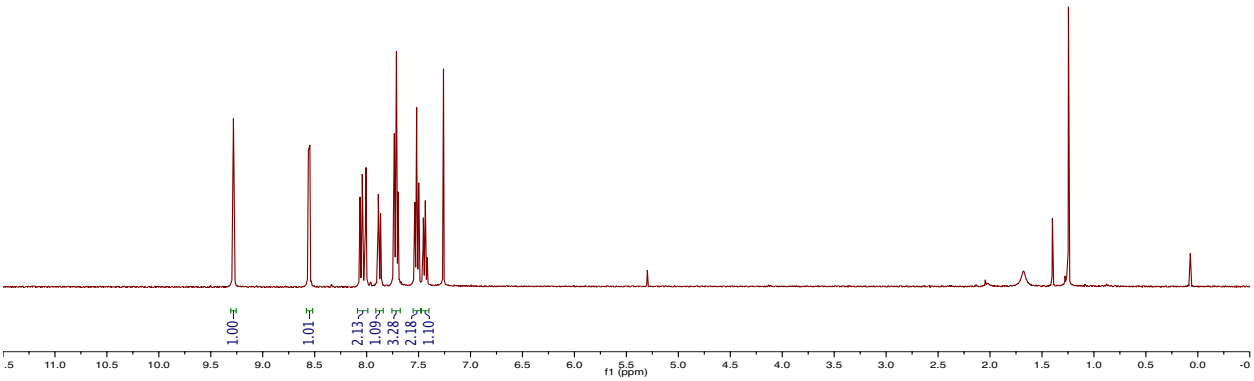

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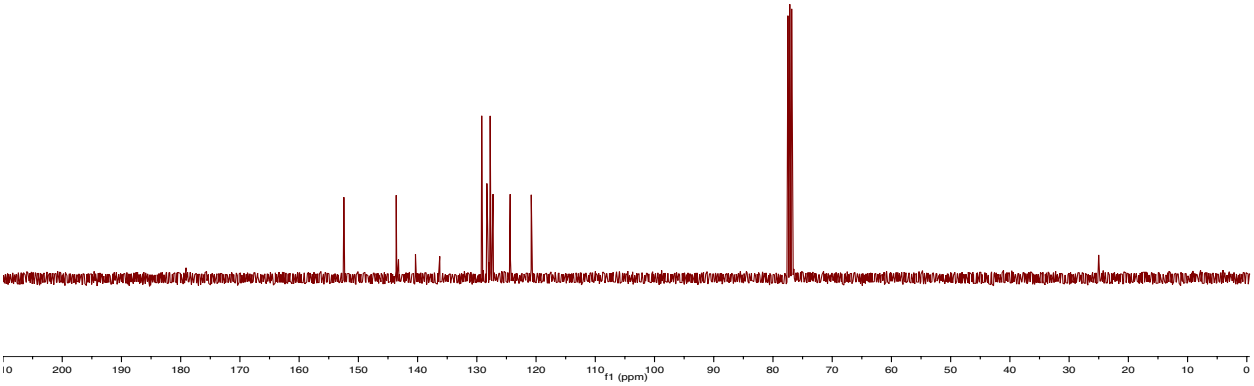
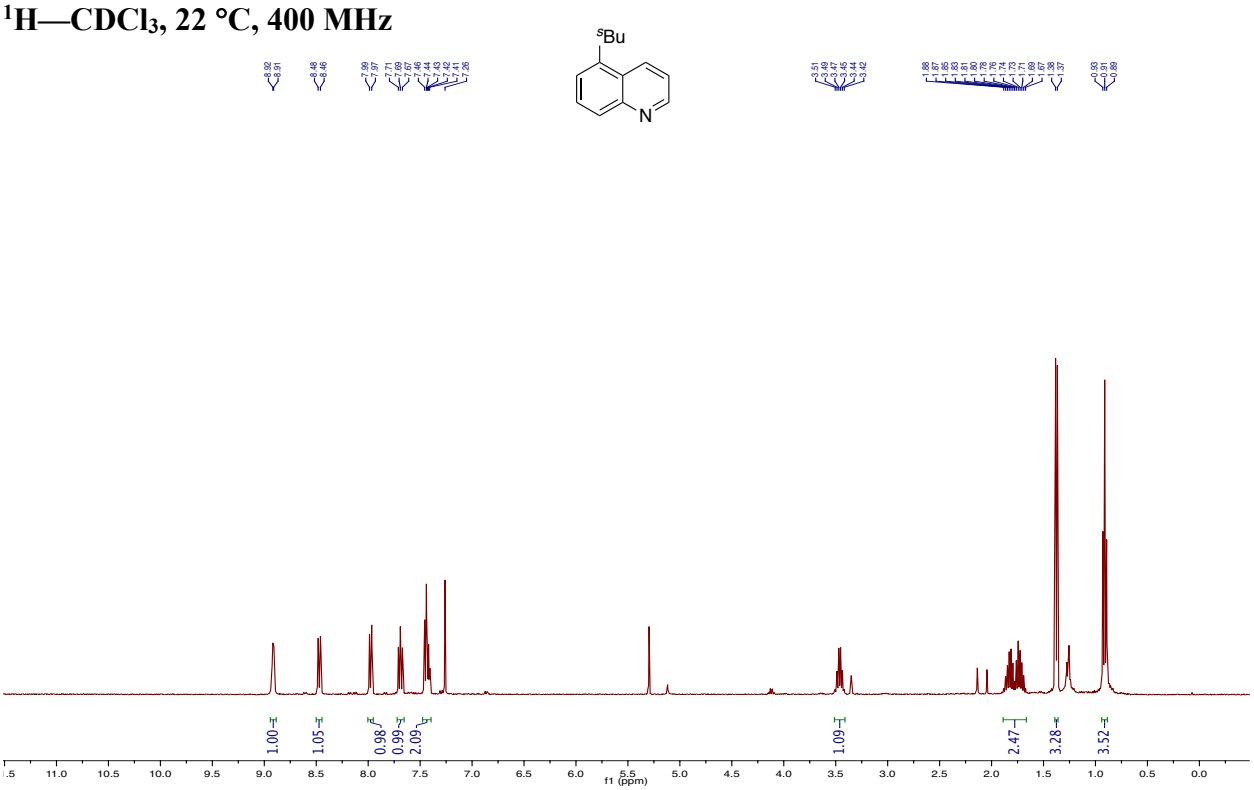
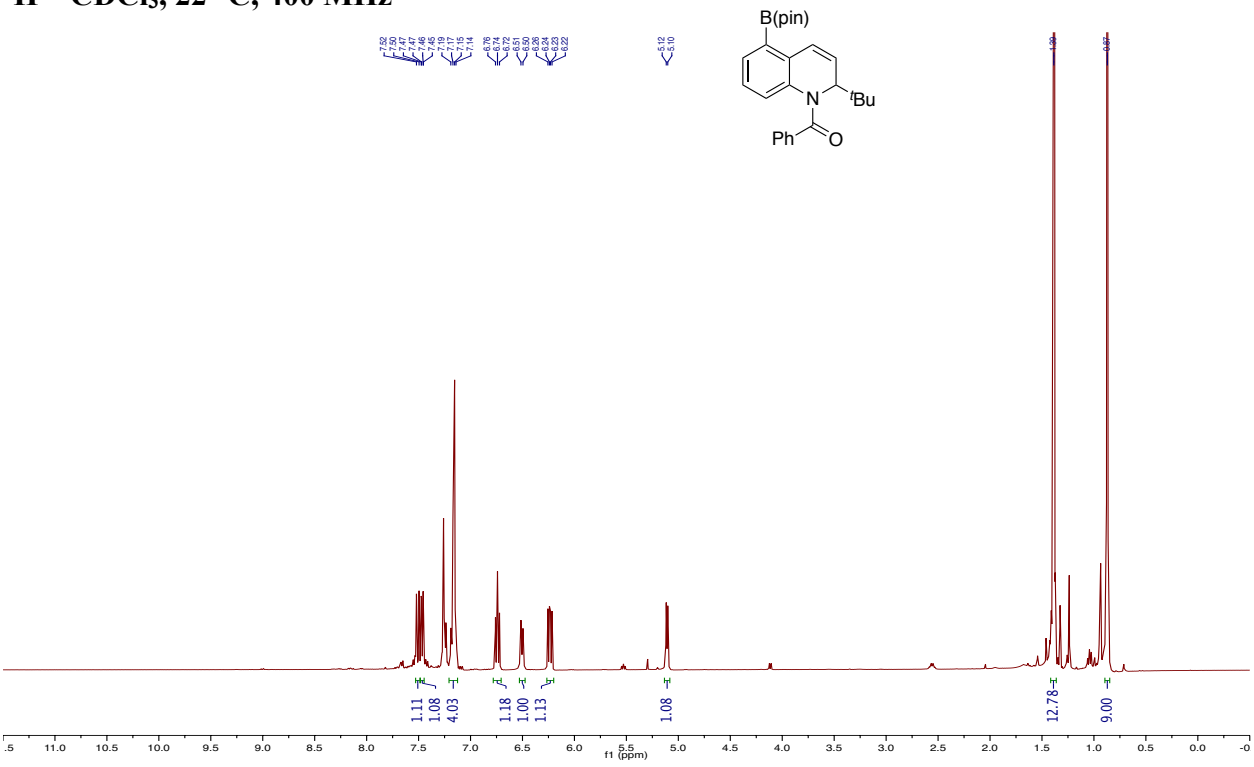


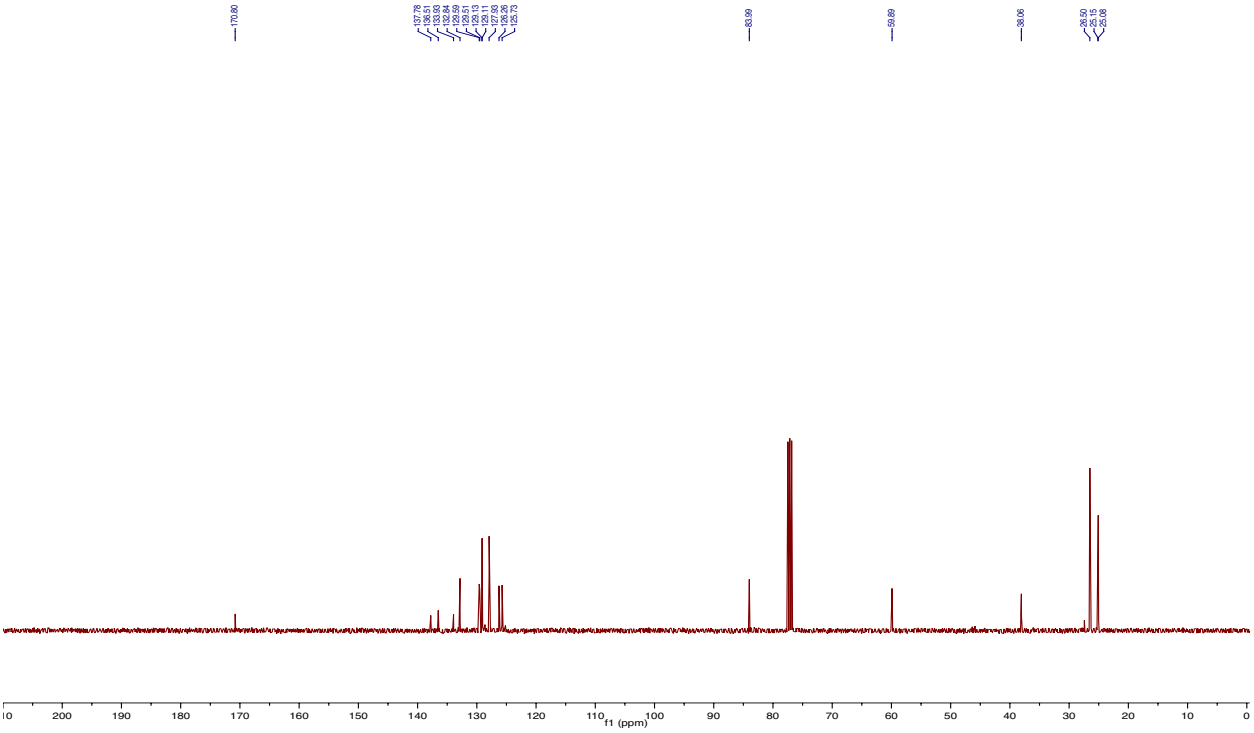
5-(*sec*-butyl)quinoline (1.151)
^{1}H—$CDCl_3$, 22 °C, 400 MHz



***N*-benzoyl-(2-(*tert*-butyl)-5-(boronic acid pinacole ester)quinoline (1.152)**
^{1}H—$CDCl_3$, 22 °C, 400 MHz



^{13}C—$CDCl_3$, 22 °C, 100 MHz

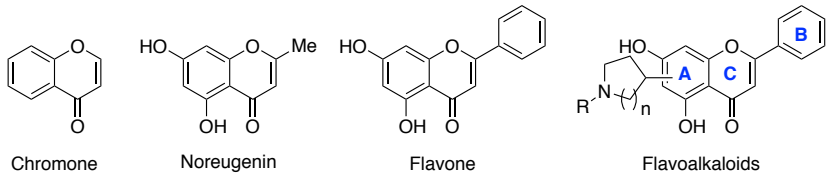


Chapter 2: Selective Synthesis of (+)-Dysoline

2.1 Chromone and Flavone Alkaloids

Chromones and flavonoids are phytochemicals of continued importance in medicinal chemistry. Secondary metabolites with these ring systems are found in a variety of plant species, many of which provide sources for traditional medicines and remedies.[1] Interest in chromones and flavonoids has led to the identification and development of several members of this family that demonstrate an array of medicinal properties including antioxidant, anticancer, antibacterial, antifungal, anti-HIV, anti-ulcer, and anti-inflammatory activities.[2]

Figure 2.1 Chromone and Flavone Core Motifs



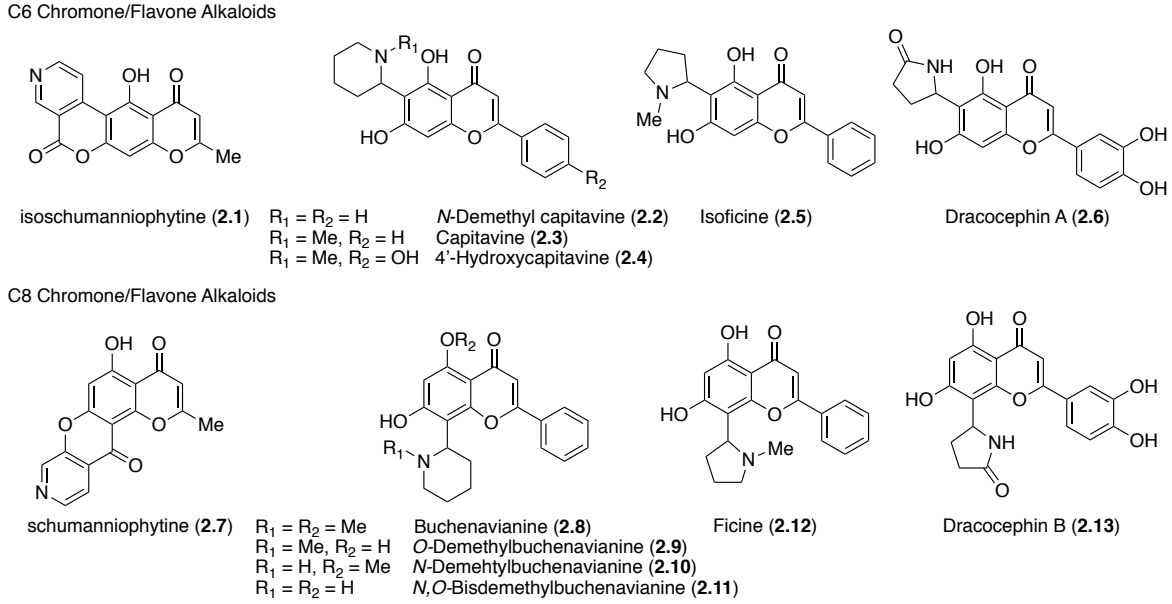
Specifically, chromone and flavone alkaloids have been identified and developed as valid medicinal chemistry scaffolds.[3] Of particular relevance is their amphoteric nature, containing both basic amine and acidic phenol moieties, intrinsic to these alkaloids. Unlike most alkaloid natural products, chromone and flavone alkaloids are classified based on the ring system to which the nitrogen heterocycle is attached. Accordingly, chromone alkaloids are those in which the nitrogen containing ring is attached to the A ring of the chromone core (Figure 2.1).

2.1.1 General Isolation/Biological Activity

While structural diversity of chromone and flavone alkaloids is not as extensive as other classes of alkaloid natural products, their ubiquity in nature has garnered a lot of attention. The isolation and identification of these alkaloids has been driven primarily due to their abundance in

plants with pronounced medicinal properties and traditional uses. Exemplifying this is the natural bioactivity of *D. heterophyllum*, from which dracocephins A (**2.6**) and B (**2.13**) are isolated (Figure 2.2). This herb is used in traditional Tibetan medicine for treatment of hypertension, lymphadenitis, hepatitis and bronchitis.[1,4] Schumanniophytine (**2.7**) and isoschumanniophytine (**2.1**) are both isolated from the bark of *S. problematicum*.[5] This bark has shown central and autonomic system depressant properties in addition to acting as a possible antiviral agent. In a similar fashion *S. magnificum* is an additional source for these compounds and has been used in Nigeria as a traditional remedy for snake bites.[6]

Figure 2.2 Select Chromone and Flavone Alkaloid Natural Products



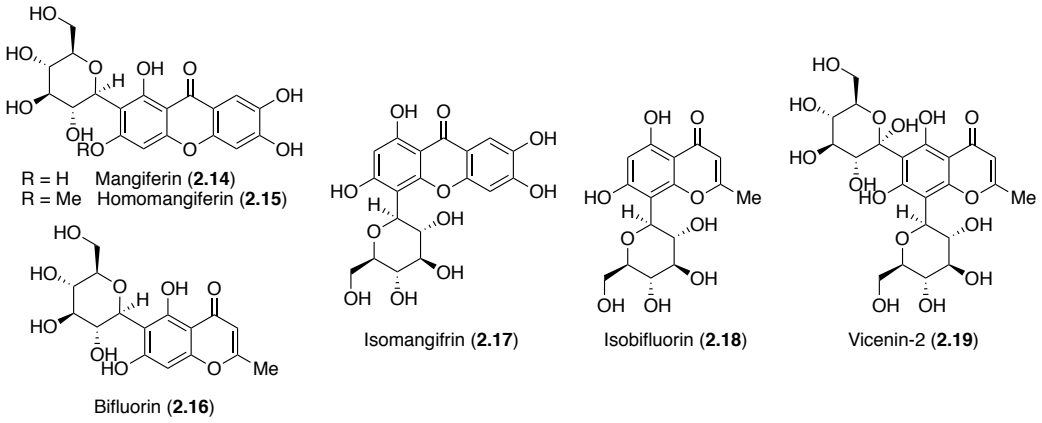
2.1.1.1 Chromone and Xanthone *C*-Glycoside Natural Products

Similar in structure to chromone and flavone alkaloids, chromone and xanthone *C*-glycoside natural products also present medicinally interesting structural motifs (Figure 2.3). Bifluorin (**2.16**)[7] and its C8 isomer isobifluorin (**2.18**)[8] have been isolated from several different sources, including the roots of *P. blflorum*, *E. caryophyllata* in addition to the flower buds of *S. aromaticum.*

Interest in bifluorin (**2.16**) derives from its reported ability to block activation of STAT1 and p38 MAPK leading to potent anti-inflammatory effects in mice. Contrasting the trend of chromone alkaloids, isobifluorin (**2.18**), the C8 isomer, showed drastically reduced biological activity for this indication. More recently vicenin-2 (**1.19**), isolated from *U. circulars,* has also garnered attention for its reported anti-inflammatory activity.[9]

Mangiferin (**2.14**), a xanthone *C*-glycoside isolated from different parts of the mango tree, has been studied for its antioxidant and anti-inflammatory ability.[10] While permeability and oral absorption provide significant liabilities for mangiferin (**2.14**) the potential of this scaffold for development of viable medicinal agents is an area of ongoing research.[11]

Figure 2.3 Chromone and Xanthone C-Glycoside Natural Products



2.1.1.2 CDK Activity of Chromone and Flavone Alkaloids

Interest in chromone and flavone alkaloids as therapeutic agents has been predominantly driven by their observed kinase inhibitory activity; in particular the potent cyclin-dependent kinase (CdK) activity demonstrated by several C8 chromone alkaloids (Table 2.1).[12] Given the importance in cell cycle progression, inhibitors of Cdk's are of interest as targets for several types of cancers.[13] Contrasting the pan Cdk activity reported for several C8 chromone and flavone

alkaloids, fewer examples describing biological activity of C6 chromone and flavone alkaloids have been described.

Table 2.1 CDK Activity of Select Chromone and Flavone Alkaloids

		Kinase activity (μM)			
Compound	Isolation source	Cdk1	Cdk5	GSK3	Clk1
Ficine (**2.12**)	*F. pantoniana*[14]	0.05[12]	0.09	1.3	1.6
Isoficine (**2.5**)	*F. pantoniana*[14]	>10[12]	>10	>10	>10
Capitavine (**2.3**)	*B. capitata*	>10[12]	>10	>10	>10
O-Debuchenavianine (**2.9**)	*B. macrophylla*	0.09[12]	1.7	5.1	8.5

2.1.1.3 Rohitukine (2.21) and Dysoline (2.20)

Rohitukine (**2.21**) represents arguably the most important chromone alkaloid isolated and studied to date. Originally reported in 1983 from the leaves of *Dysoxylum binectariferum*, initial interest in rohitukine (**2.21**) was driven by its anti-inflammatory and immunomodulation activity.[15] Subsequent studies demonstrated this chromone alkaloid's cytotoxicity towards HCT116 (colon cancer, IC_{50} = 7.5 μM) and HL60 (leukemia, IC_{50} = 8.8 μM) cell lines (Table 2.2).[16] Given this cyctotoxicity, rohitukine (**2.21**) served as a starting point for the development of flavopiridol (**2.22**) and riviciclib (**2.24**), both of which show improved activity (HCT116: IC_{50} = 0.046 μM, 0.31 μM; HL60: IC_{50} = 0.0018 μM, 0.75 μM, respectively) and are currently in clinic.[17] Moreover, flavopiridol (**2.22**) achieved orphan drug designation for treatment of myeloid leukemia in 2014.[18] Correlating with previously reported C8 chromone and flavone alkaloids rohitukine (**2.21**) and its analogs act as Cdk inhibitors, with subsequent studies demonstrating a mode of action based on inhibition of the Cdk9/T1 complex, in turn leading to cell cycle interruption and death.[13,19]

Importantly these compounds represent some of the first examples of synthetic Cdk inhibitors to enter clinical trials for oncology.

While flavopiridol (**2.22**) and riviciclib (**2.24**) demonstrate potent cytotoxicity and a safe PK profile, lack of oral bioavailability of these compounds requires IV administration for treatment. Further testimony to the continued interest in this series is the recent development of IllM-290 (**2.25**), demonstrating a similar biological activity profile with improved oral bioavailability.[20]

Figure 2.4 Dysoline (2.20) and Rohitukine (2.21)

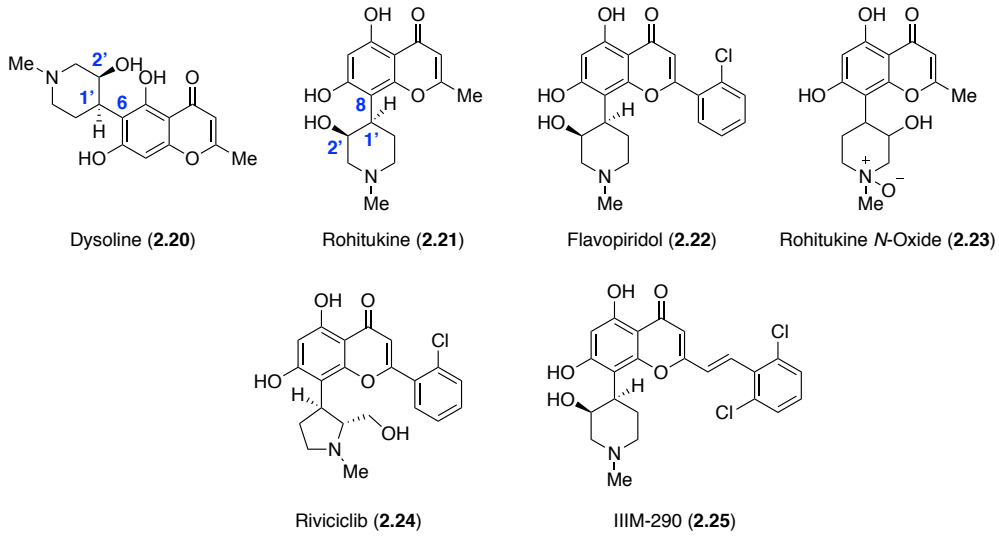


Table 2.2 Activity of Dysoline (2.20) and Rohitukine (2.21)

Compound	Kinase activity (μM)				Cell cytotoxicity (μM)		
	Cdk1	Cdk2	Cdk4/D1	Cdk9/T1	HT1080	HCT116	HL60
Dysoline (**2.20**)[16]		>10		>10	0.21	>10	>10
Rohitukine (**2.21**)[16]					>10	7.5	8.8
Flavopiridol (**2.22**)[19,20]	0.03	0.33	0.15	0.02		0.046	0.018
Riviciclib (**2.24**)[20]			0.063	0.02		0.31	0.75
IIIM-290 (**2.25**)[20]		0.016		0.0019		5	0.9

Dysoline (**2.20**), the C6-isomer of rohitukine (**2.21**), was first isolated in 2013 from *Dysoxylum binectariferum*.[21] Ethanolic extracts of bark from this tree resulted in isolation of a mixture of three compounds, rohitukine (**2.21**), rohitukine *N*-oxide (**2.23**), and dysoline (**2.20**), in varying quantities (1.13%, 0.001%, 0.0003% respectively, in relation to dry plant material). Interestingly biological screening of dysoline (**2.20**) revealed selective cytotoxicity towards HT1080 fibrosarcoma cells (IC_{50} = 0.21 μM, Table 2.2). Predictably little activity was observed in a screen against six other human cancer cell lines (IC_{50}'s > 10 μM), nor did this compound display substantial inhibition of CDK2, CDK9 or any of several other kinases tested. In addition, the isolation group reported dysoline (**2.20**) showed inhibition of TNF-α and IL-6 cytokine production (47% and 83% respectively, at 0.1 μM).

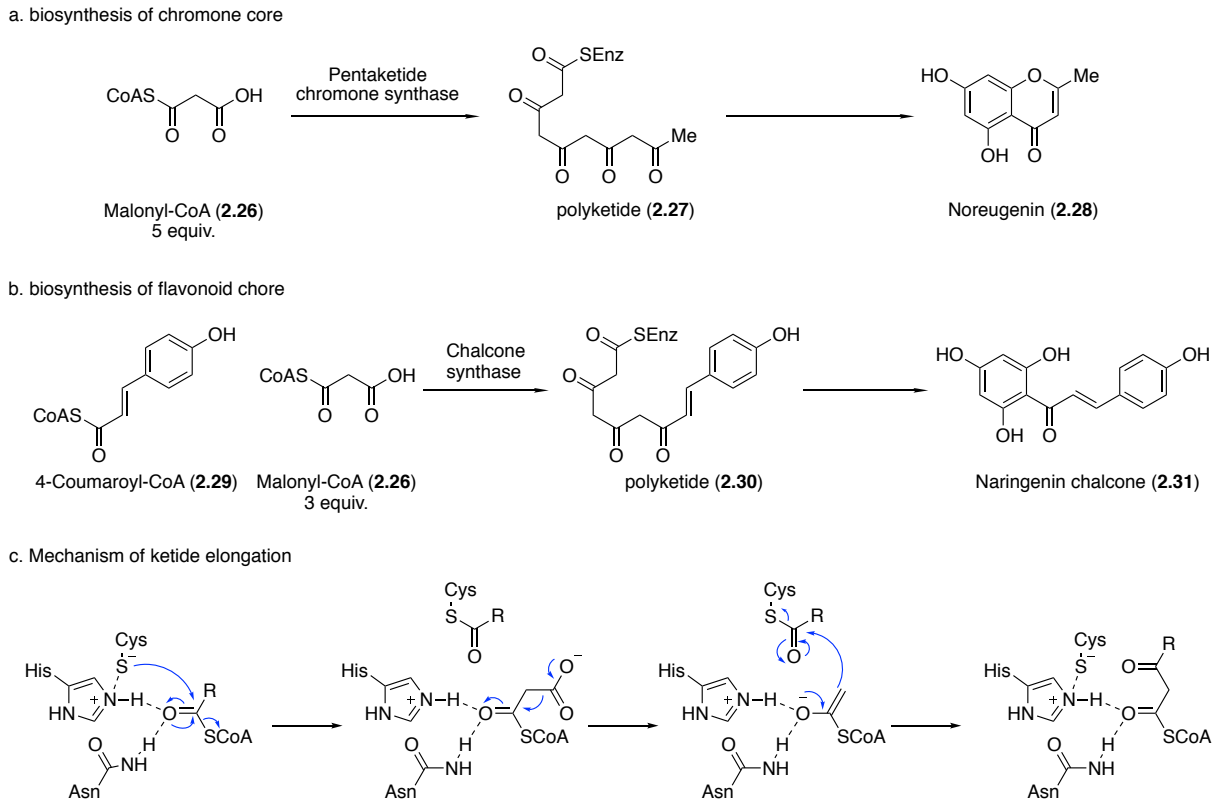
The unique biological activity reported for dysoline (**2.20**) in conjunction with the validity of the chromone-piperidine scaffold make this an attractive target for synthesis. An additional compelling reason for developing a synthetic route of dysoline (**2.20**) is the limited amount of material recovered during isolation. Furthermore, this product was only isolated from the bark of the tree, located in what is now a protected forest, rendering total synthesis the predominant method for obtaining additional material.

2.1.3 Proposed Biosynthetic Pathway for Chromone and Flavone Alkaloids

The biosynthetic pathway in which specific chromone and flavone alkaloids are prepared is not well described. However the chromone and flavone core biosynthesis has been elucidated and well-studied.[22] Specifically, chromones and flavones derive from a type III polyketide synthase in particular, *A. arborescens* has been shown to produce the chromone core. These polyketide synthases are part of the chalcone synthase superfamily and are unique in that the CoA thioesters

act without acyl carrier proteins. A sequence of decarboxylative condensations of malonyl-CoA (**2.26**) generates polyketide backbone **2.27** or **2.30** (Scheme 2.1) which can then undergo either a Claisen or aldol cyclization. In this way 5 molecules of malonyl-CoA (**2.26**) can be transformed to the polyketide **2.27,** leading to noreugenin (**2.28,** Scheme 2.1a). If 4-coumaroyl-CoA (**2.29**) is condensed with 3 equivalents of malonyl-CoA (**2.26**) terminal cyclization leads to naringenin chalcone (**2.31**) which can further cyclize giving the flavone core (Scheme 2.1b).[23]

Scheme 2.1 Biosynthesis of Chromone and Flavone



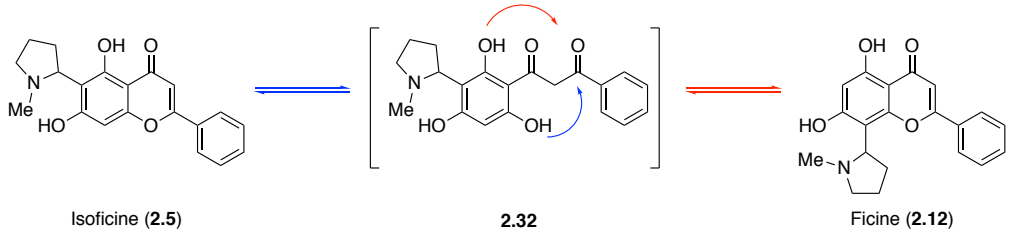
2.1.4 Previous Synthesis of Chromone and Flavone Alkaloids

Given the prevalent biological interest in compounds containing the chromone and flavone cores, several synthetic methods have been reported for their preparation. In line with the observed activity most of these methods focus on accessing the C8 substituted chromone or flavone

alkaloids, with fewer reports detailing preparation of the C6 regioisomer. Previous strategies invoked can be divided into two categories: chromone/flavone ring formation from a substituted *ortho*-hydroxy aryl ketone or direct substitution of the parent chromone ring.

Interconversion of C6 and C8 flavone isomers is known to occur via a Wessely-Moser rearrangement (Scheme 2.2). Under forcing conditions, such as refluxing HCl (aq. 70%), a mixture of products can be obtained as was reported in connection with the original isolation of ficine (**2.12**). While this rearrangement has been useful in the identification of novel chromone and flavone compounds it provides little synthetic utility, given the harsh conditions and resulting mixture of products.

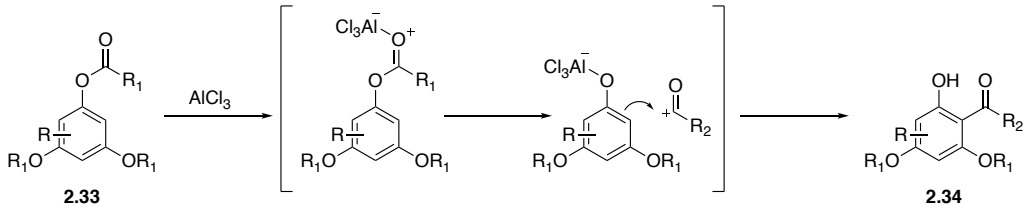
Scheme 2.2 Wessely-Moser Rearrangement



2.1.4.1 Synthesis of Chromone and Flavone Core from *ortho*-Hydroxyaryl Ketone

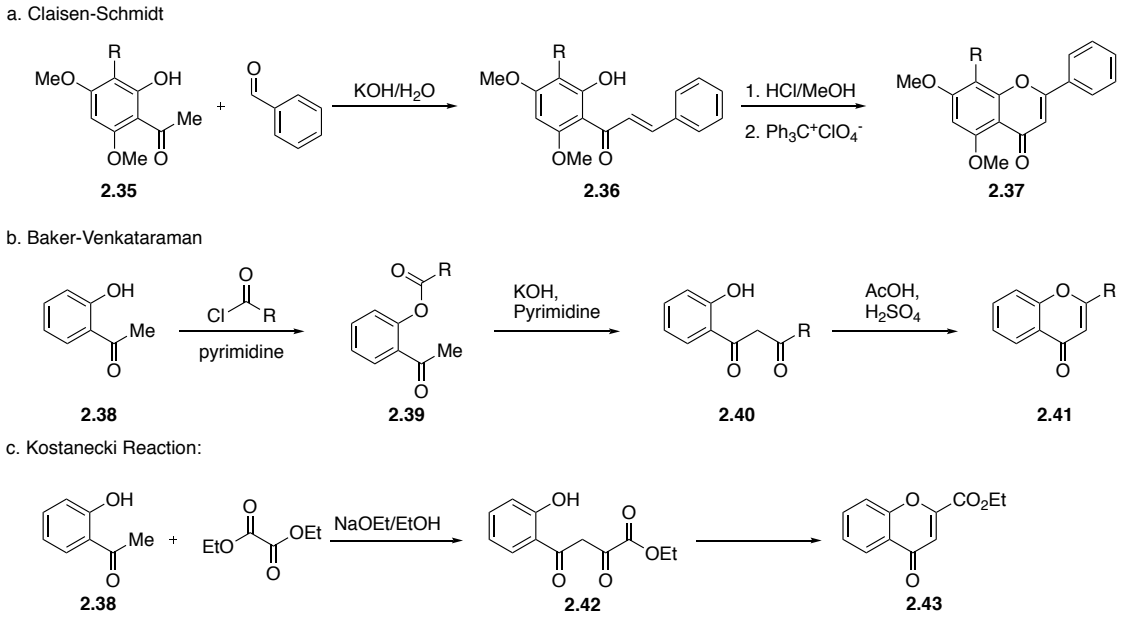
A common intermediate utilized in several synthesis of chromone and flavone alkaloids is a substituted *ortho*-hydroxyaryl ketone (**2.34**, Scheme 2.3). Access to this intermediate is generally achieved via a Fries rearrangement of the substituted acylated phenol precursor (**2.33**). This strategy allows for the installation of the requisite aryl ketone ortho to the free phenol, which can cyclize to form the pyrone functionality. Importantly, regioselectivity, C8 vs C6, in this synthetic approach is dictated by the substitution and protection pattern of the phlorogucinol core.

Scheme 2.3 Fries Rearrangement



Traditional carbonyl chemistry is often employed for further elaboration of the *ortho*-hydroxyaryl ketone intermediate (**2.34**, Scheme 2.3; **2.35**, **2.38**, Scheme 2.4**)** to the desired chromone or flavone. Techniques exploited for this transformation include, but are not limited to: Claisen-Schmidt, Baker-Venkatraramne rearrangement or Kostanecki reactions (Scheme 2.4).[24] If necessary, oxidation of the resulting cyclized compound is often rapid giving facile access to the desired chromone core.

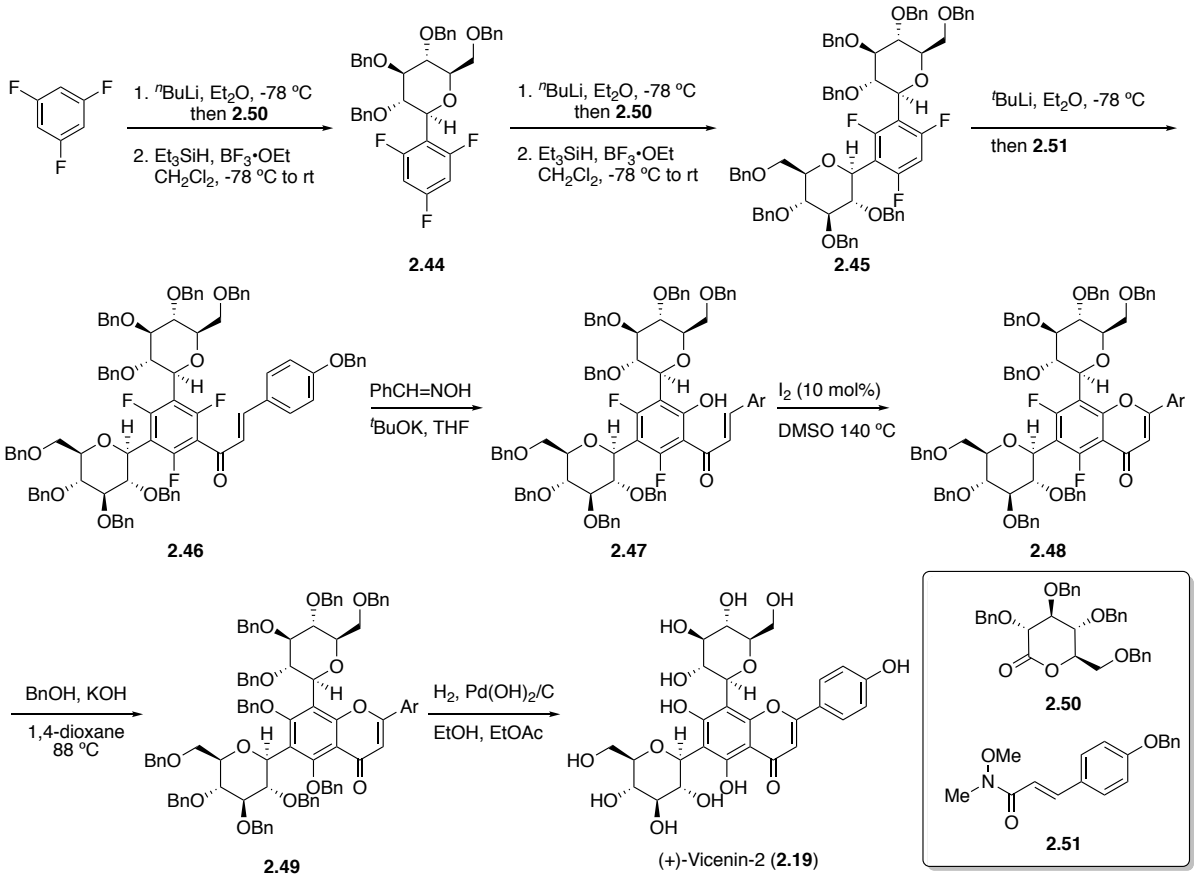
Scheme 2.4 Chromone and Flavonoid Formation Strategies



Recently the Suzuki lab reported a novel strategy for the synthesis of bis-*C*-glycosyl flavonoid (+)-vicenin-2 (**2.19**, Scheme 2.5).[25] Sequential *ortho*-lithiation of fluorobenzene was utilized for bis-glycosylation which upon a third lithiation and trapping with Weinreb amide **2.51**, gave the

substituted chalcone intermediate **2.46**. SnAr with benzaldoxime then furnished the requisite *ortho*-hydroxyaryl ketone **2.47**, which could be oxidatively cyclized with a catalytic amount of iodine, forming the flavone core. A final double SnAr with benzyl alcohol, followed by global deprotection furnishes the desired natural product, (+)-vicenin-2 (**2.19**). This synthesis provides a unique approach to building the flavone core substitution, however unlike other chromone and flavone natural products no regiochemical aspects needed consideration.

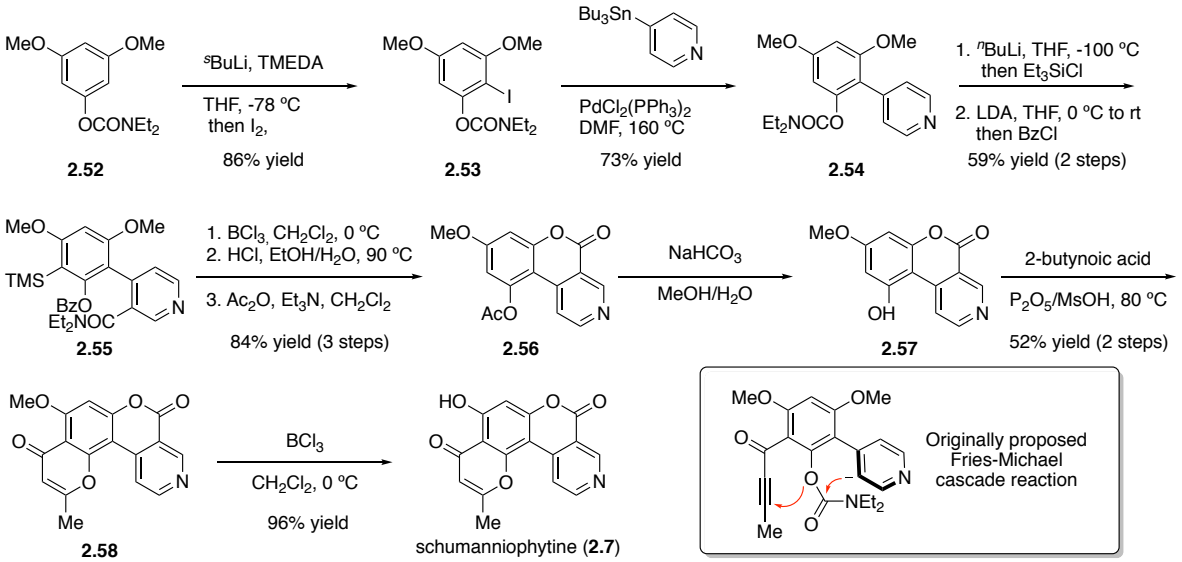
Scheme 2.5 Synthesis of (+)-Vicenin-2 (2.19)



Recently the Snieckus lab presented another novel approach for preparation of the chromone ring in their synthesis of schumanniophytine (**2.7**, Scheme 2.6).[26] Initially planned was a Fries-Michael cascade reaction sequence which would serve to form the chromone ring, in addition to acylating the adjacent pyridine. Unfortunately, attempts at this reaction sequence failed forcing

them to adhere to a more sequential approach. Ultimately Fries rearrangement of phenol **2.57** was accomplished using Eaton's reagent (P_2O_5/MsOH) with 2-butynoic acid, setting up a Michael addition for subsequent chromone formation. The authors reported that initial attempts at using the more traditional Baker-Venkataraman strategy resulted in only moderate yield and poor reproducibility for chromone formation.

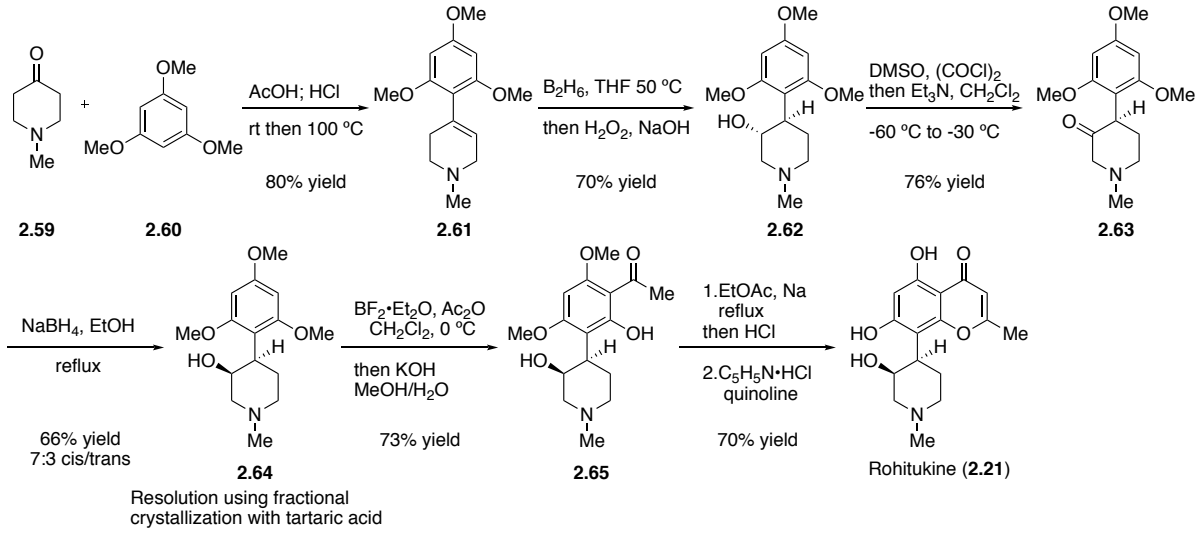
Scheme 2.6 Synthesis of Schumanniophytine (2.7)



The original synthesis of rohitukine (**2.21**) represents a more traditional approach commonly utilized for the preparation of chromone and flavone alkaloids (Scheme 2.7). Friedel Crafts alkylation of trimethoxy benzene (**2.60**) with *N*-methyl piperidinol (**2.59**) results in formation of *N*-methyl-4-aryltetrahydropyridine **2.61**. The key hydroxy functionality was installed by hydroboration which upon oxidation produced aryl piperidinol **2.62**, albeit with the undesired trans configuration. Oxidation followed by selective reduction with sodium borohydride was utilized to invert the alcohol stereocenter and obtain the desired *cis*-aryl piperidinol **2.64**. Selective demethylation, presumably driven by sterics, followed by acylation and Fries rearrangement gives *ortho*-hydroxyaryl ketone **2.65**. Claisen condensation with ethyl acetate and subsequent acid

promoted cyclization generates the desired chromone core, which upon deprotection furnishes rohitukine (**2.21**). In addition to issues of regioselectivity this synthetic route is racemic in nature, necessitating a resolution of aryl piperidinol intermediate **2.64**, by crystallization with tartaric acid, to obtain optically active product.

Scheme 2.7 Synthesis of Rohitukine (2.21)



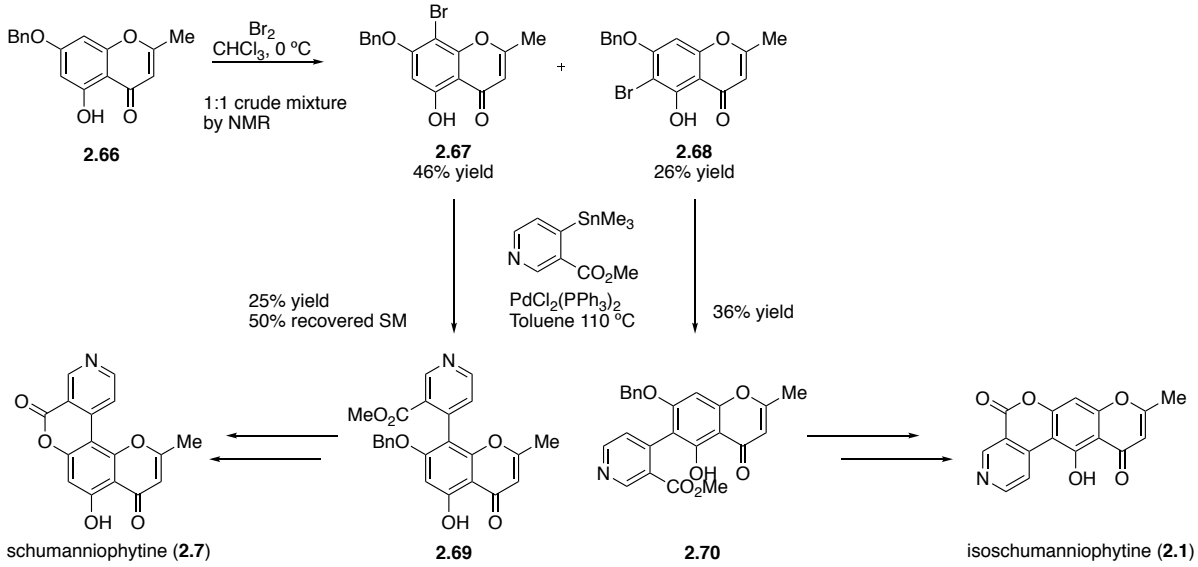
2.1.4.2 Direct Substitution of Chromone

Given their natural abundance, direct functionalization of the chromone or flavone core presents as a viable alternative synthetic strategy to access these types of natural products and their analogs. Selective halogenation, alkylation and glycosylations have all been reported with moderate levels of success and applicability.

The synthesis of schumanniophytine (**2.7**) and isoshumanniophytin (**2.1**) by the Kelly lab highlights the difficulty associated with substitution of the chromone core (Scheme 2.8).[27] In this synthesis direct bromination of chromone resulted in a 1:1 regioisomeric mixture. Additionally, while isolation of the C8 isomer was achieved in 46% yield, efficiency of C6 bromochromone isolation was drastically reduced due to the difficulty in separation of the 2 isomers. Also

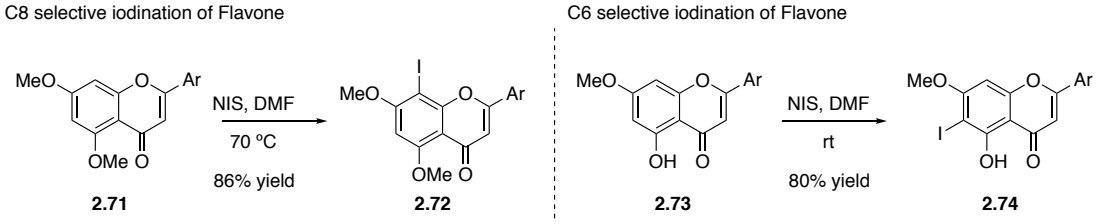
problematic in this strategy was difficulty encountered with the Stille coupling. Unfortunately only moderate yields were achieved despite the authors' attempts at optimization. Considering the authors' goal of preparing both regioisomers of the natural product, for structural confirmation, the lack of regioselectivity in bromination was not detrimental for their synthesis.

Scheme 2.8 Bromination and Cross Coupling of Chromone



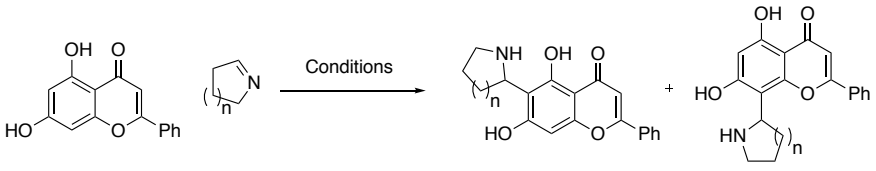
More recent work by Yu *et al.* demonstrated the ability to control regioselectivity of iodination, allowing access to both C8 and C6 iodochromone products (**2.72** and **2.74**, Scheme 2.9).[28] While initial use of iodine in this reaction resulted exclusively in di-iodinated products, switching to NIS allowed for diminished reactivity necessary to obtain mono iodination. Regioselectivity of iodination was reported to be dictated by the protection of the phenols, with di-methoxy chromone **2.71** giving C8 iodochromone **2.72.** Inversely, selective deprotection of the C5 methyl ether followed by treatment with NIS resulted in C6 iodochromone **2.74**.

Scheme 2.9 Regioselective Iodination of Flavone Core



In addition to halogenation, direct substation of the chromone core with carbon-based electrophiles has also been reported. In particular the Guéritte group demonstrated a regioselective Mannich addition of flavone to pyrrolidine and piperidine based reagents (**2.75**, Scheme 2.10).[29] Of particular interest and utility is the profound effect that solvent and reaction time have on regioselectivity, allowing access to both isomers based on choice of reaction conditions. While this method allows for regioselective access to flavone alkaloids the necessity of an α-nitrogen limits the synthetic utility of this approach.

Scheme 2.10 Regioselective Phenolic Mannich Reaction

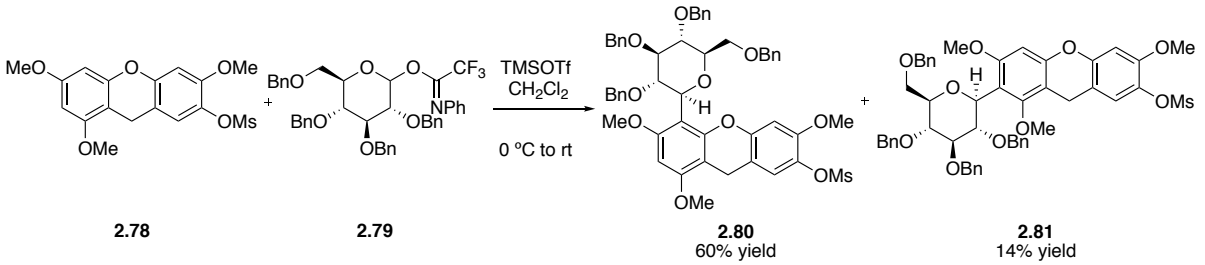


n	Conditions	Temp.	Time (h)	Conversion (%)	**2.76:2.77**
2	H_2O/THF	40 ºC	48h	>95	99:1
2	H_2O/THF	80 ºC	0.4	>95	12:1
2	H_2O/NaOH	40 ºC	168	90%	1:3
1	H_2O/NaOH	40 ºC	168	90%	5:95

Regioselective glycosylation of structurally similar xanthones has also been explored, with similar selectivity issues prevailing. In 2010 the Yu group reported the synthesis of mangiferin (**2.14**), isomangiferin (**2.17**) and homomangiferin (**2.15**), using a moderately selective Friedel-Crafts alkylation of reduced xanthone core **2.78**, resulting in a 5:1 mixture of products **2.80** and

2.81 (Scheme 2.11).[30] The authors postulated that fully oxidized xanthone would be too electron deficient for this reaction necessitating the use of the reduced form of the xanthone **(2.78)**.

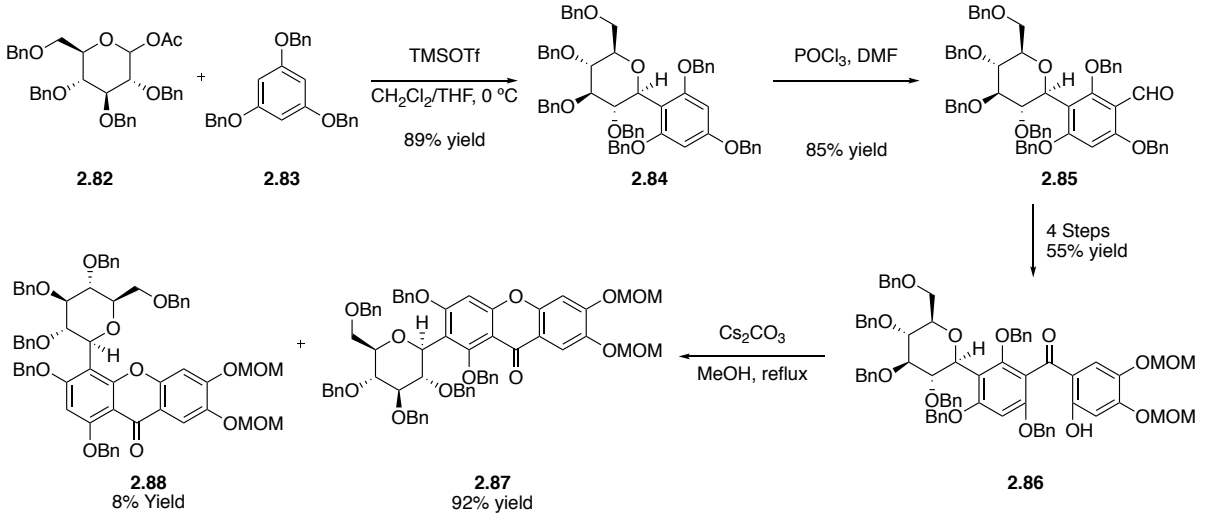
Scheme 2.11 Direct Glycosylation of Xanthone



2.78 **2.79** **2.80** 60% yield **2.81** 14% yield

In an effort to improve upon the poor regioselectivity and overall yield of the Yu synthesis the Li group reported an alternative method focused on preparation of mangiferin (**2.14**).[31] Following analogous strategies to those used for the preparation of chromone and flavone alkaloids, this synthesis started with the glycosylation of benzyl protected phloroglucinol **2.83** (Scheme 2.12). Formylation then set up for the preparation of benzophenone **2.85,** which upon cyclization generated the desired glycosylated xanthone products (**2.87** and **2.88**). In this synthesis regioselectivity was dictated by selective cyclization of benzophenenone intermediate **2.86,** resulting in the desired C6 glycosylated xanthone product **2.87** as the major product.

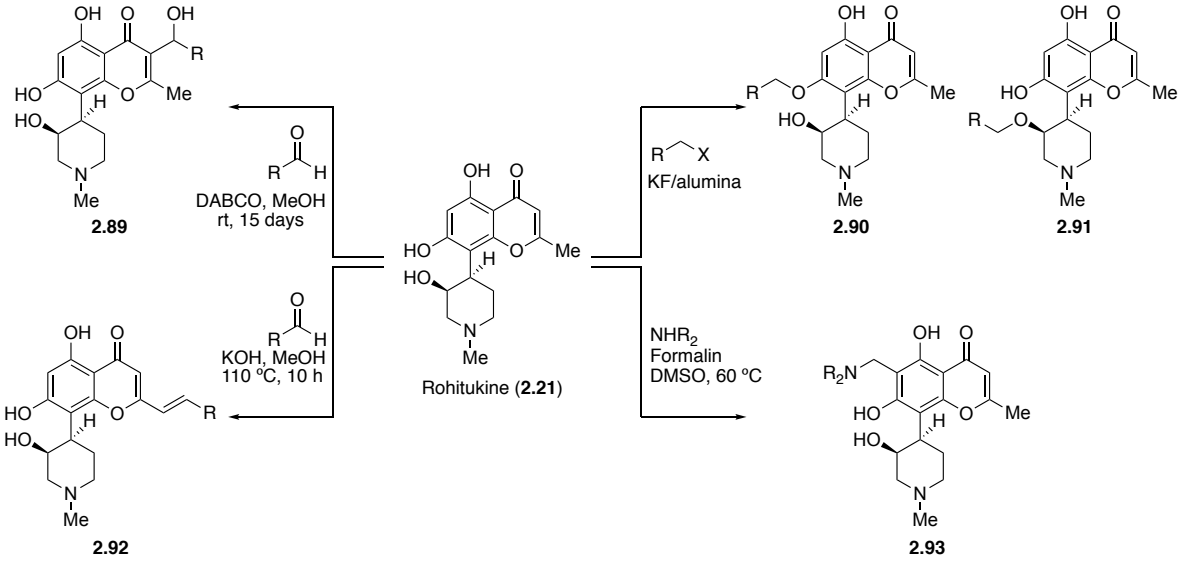
Scheme 2.12 Alternative Synthetic Strategy for Mangiferin



2.82 **2.83** **2.84** **2.85** **2.86** **2.87** 92% yield **2.88** 8% Yield

Semi-synthetic methods have particularly found use for the preparation of analogs related to rohitukine (**2.21**) and flovopyridol (**2.22**). This approach was highlighted in the development of IllM-290 (**2.25**).[20] Given the availability of rohitukine (**2.21**) various chemical transformations were utilized for probing the SAR of this scaffold in an attempt to improve the oral bioavailability of this series.

Scheme 2.13 Semisynthetic Examples of Chromone Alkaloids



2.2 Retrosynthetic Analysis of Dysoline

Paramount to the selective cytotoxicity reported for dysoline (**2.20**) is the C6 substitution of the chromone ring, in conjunction with the relative stereochemistry of the piperidine ring. While traditional methods for access to chromone alkaloids have demonstrated some regioselecitivity, this selectivity is predominantly for the C8 chromone alkaloids. Additionally, previous strategies fail to offer enantio- or diastereo- control, desired for an efficient synthesis. Given these difficulties an alternative synthetic strategy for preparation of the chromone core was explored. In particular

the use of a benzannulation presented a novel yet efficient and divergent strategy for accessing (+)-dysoline (**2.20**).

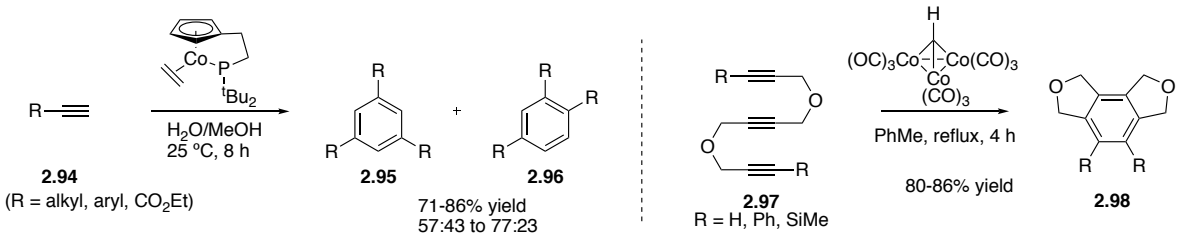
2.2.1 Benzannulation Reactions Overview

As an alternative to traditional approaches, benzannulation reactions can offer a more convergent and efficient transformation for the formation of highly substituted aromatic systems.[32] Taking the definition of annulation as 'a transformation involving fusion of a new ring to a molecule via two new bonds being formed' benzannulations are analogous to more traditional cycloaddition reactions although at a higher oxidation state, resulting in the formation of aromatic products. While a large number of benzannulation reactions exist only a few examples will be discussed. Further, these examples are classified based on the formal cyclization occurring: [2+2+2], [3+3], [4+2] or [5+1], with a particular emphasis on [4+2] benzannulation reactions.

2.2.1.1 [2+2+2] and [3+3] Benzannulation Reactions

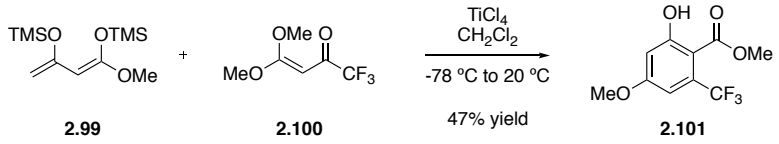
One of the earliest reported benzannulation reactions is the cobalt-mediated [2+2+2] cycloaddition of alkynes (Scheme 2.14). Although originally reported in 1948 this technique was brought to prominence in the 1970's and 80's by the work of Peter Volhardt.[33] This benzannulation strategy is particularly useful for the intramolecular trimerization of alkynes (**2.97** to **2.98**), however poor regioselectivity of the intermolecular variation inhibit its synthetic utility. Despite this limitation several examples of [2+2+2] reactions can be found in literature, with more recent attention focusing on alternative metal catalyst for this transformation.[34]

Scheme 2.14 Volhardt [2+2+2] Benzannulation



Less common than other benzannulation techniques is the use of a formal [3+3] annulation. One of the first reports of [3+3] annulations was in 1980 by Chan and coworker, in which β-keto acetals **2.100** cyclize with bis-silyl enolethers **2.99** in the presence of $TiCl_4$ (Scheme 2.15).[35] More recently Langer has worked on expanding the substrates amenable for this reaction, making it a more synthetically viable process.[36]

Scheme 2.15 [3+3] Benzannulation

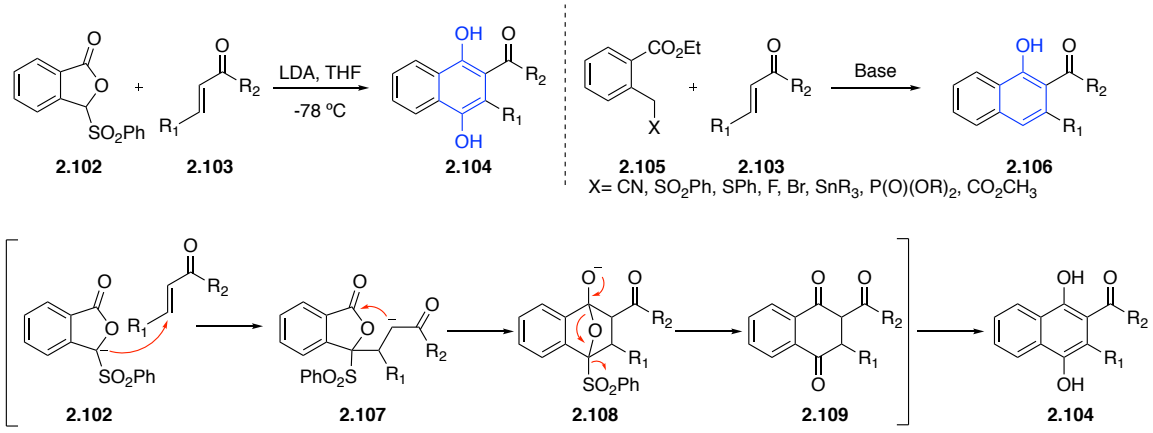


2.2.1.2 Hauser Annulation

One of the most commonly utilized benzannulation reactions in synthesis is the [4+2] cycloaddition of a 3-phenyl sulfonylphthalides (**2.102**) with a Michael acceptor (**2.103**), known as the Hauser annulation (Scheme 2.16).[37] First developed in the 1970's, this annulation provides efficient access to 1,4-dihydroxy-2,3-disubstituted napthalenes **2.104**, which are easily converted to the corresponding naphthoquinone or anthraquinone products. Mechanistically this reaction proceeds through an analogous Michael-Diekman cyclization sequence. Subsequent fragmentation of the resulting cyclic hemiketal (**2.108**) with elimination of the sulfonate anion gives diketone **2.109** which is readily tautomerized to the final 1,4-dihydroxynapthal product **2.104**. A further

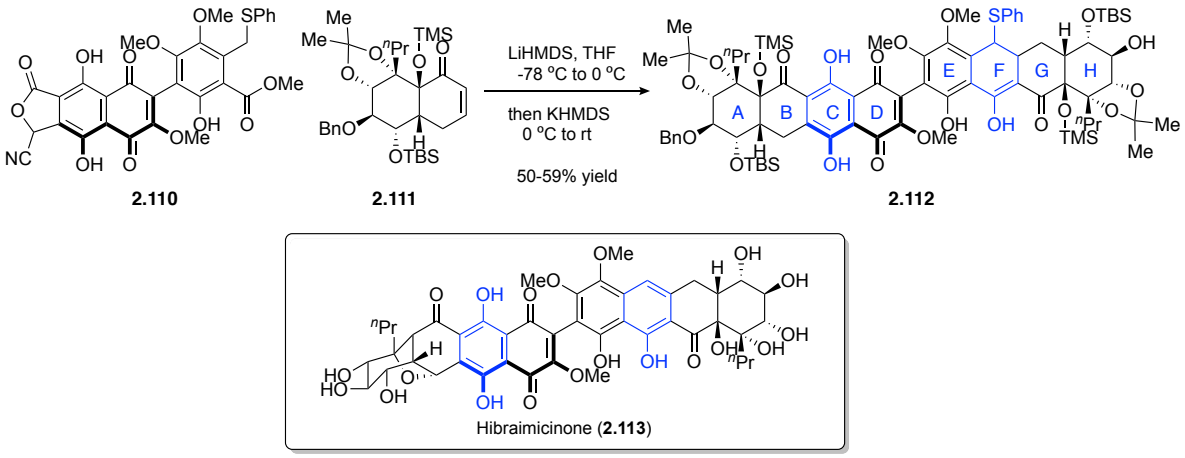
extension of the original reaction conditions, reported by Hauser and Rhee, demonstrated the use of alternative nucleophiles in this reaction, resulting in formation of 1-hydroxy-2,3-disubstituted naphthalene products **2.106**.[38]

Scheme 2.16 Hauser Annulation



The Hauser annulation has found widespread use for the synthesis of complex natural products. A particularly eloquent application was reported by the Shair lab in their synthesis of hibarimicinone (**2.113,** Scheme 2.17).[39] Using a Hauser annulation the authors were able to effect a two directional synthetic strategy building the C and F rings of the polycyclic skeleton of the natural product in one step.

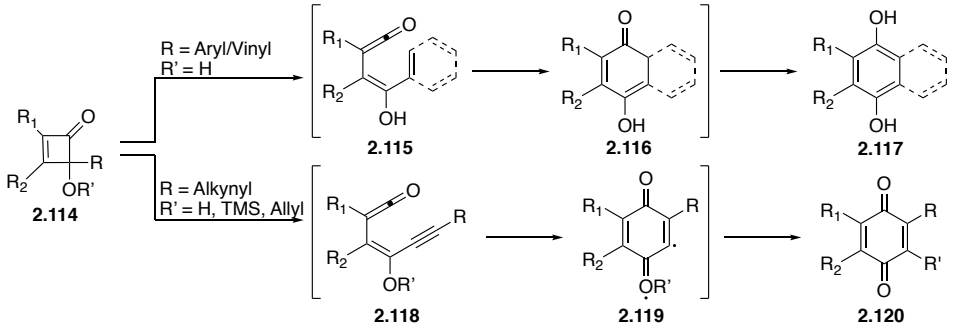
Scheme 2.17 Synthesis of Hibraimicinone



2.2.1.3 The Moore Expansion/Rearrangement

The propensity of cyclobutenones to undergo electrocyclic ring opening by either thermal or photolytic conditions is a well-established and studied transformation.[40] It was in the 1980's that the ability of α,β,γ,δ-unsaturated ketenes (**2.115, 2.118**, Scheme 2.18**)**, resulting from the ring opening of vinyl, alkynyl or aromatic cyclobutenones **2.114**, were reported to further undergo a 6π electrocyclization leading to 1,4-dihydro phenol (**2.117**) and quinonone (**2.120**) type products.[41] At the forefront of this research was Moore for which this ring expansion/rearrangement has been named. Moore reported that subjection of vinyl or aryl cyclobutanones (**2.114,** R = aryl or vinyl) results in formation of the desired 1,4-dihydro phenols or naphthols (**2.117**). Additionally, he reported that (2-alkynylethenyl)ketenes (**2.118**), generated from alkynylcyclobutenones (**2.114,** R = alkynyl), can undergo cyclization forming radical intermediate **2.119** which leads to substituted quinone products with migration of the R' substituent (**2.120**).

Scheme 2.18 The Moore Rearrangement

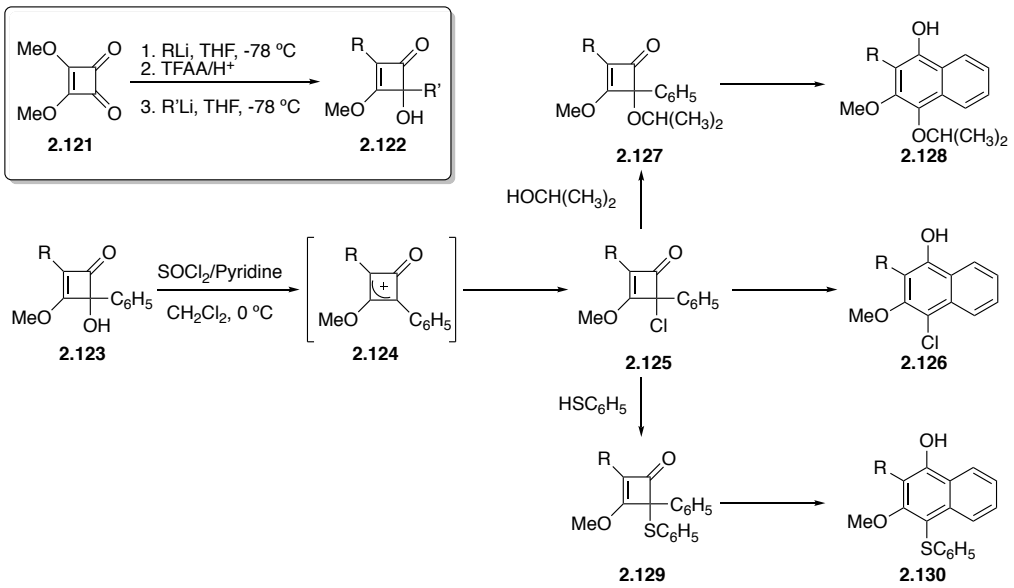


Increasing the utility of this methodology is the facile access of substituted cyclobutanones from dimethyl squarate (**2.121,** Scheme 2.19). Addition of aryl, vinyl or alkynyl lithium reagents, followed by acid promoted elimination and subsequent addition of a second lithium nucleophile leads to disubstituted hydroxyl cyclobutenones (**2.122,** Scheme 2.19). Regiochemistry of these products is based on order of nucleophile addition; however, upon chlorination both regioisomers

converge to give the same chlorinated cyclobutanone product (**2.125**). This later result is presumably due to generation of an allyl cation (**2.124**), leading to chlorination at the position adjacent to substitution offering the highest stabilization.[42]

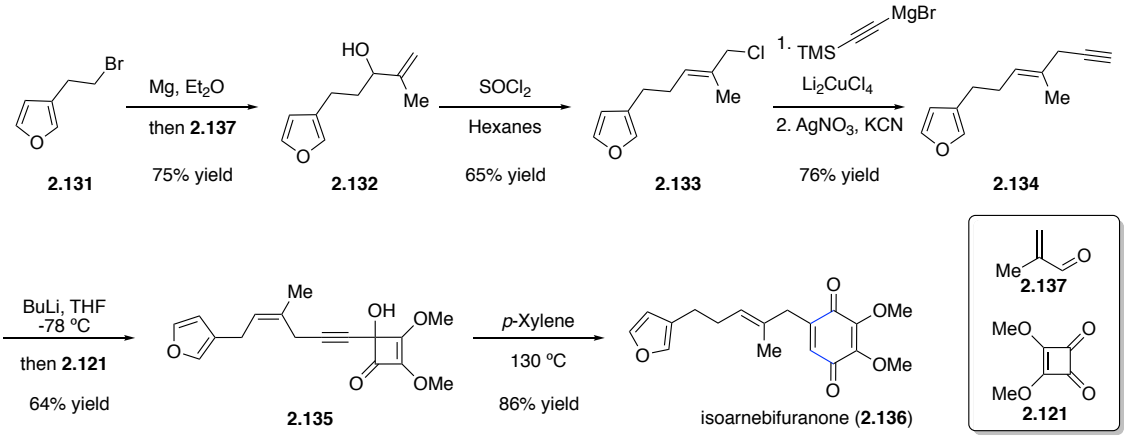
Subjecting these chloro cyclobutanones (**2.125**) to thermolysis leads to ring opening and subsequent 6π electrocyclizations and tautomerization giving access to substituted chlorophenols (**2.126**, Scheme 2.19). Further, substitution of these chloro cylclobutenones with sulfur or oxygen nucleophiles followed by rearrangement leads to bis hydroxyl- (**2.128**) or thio- phenol (**2.130**) products.

Scheme 2.19 Substitution of Dimethyl Squarate



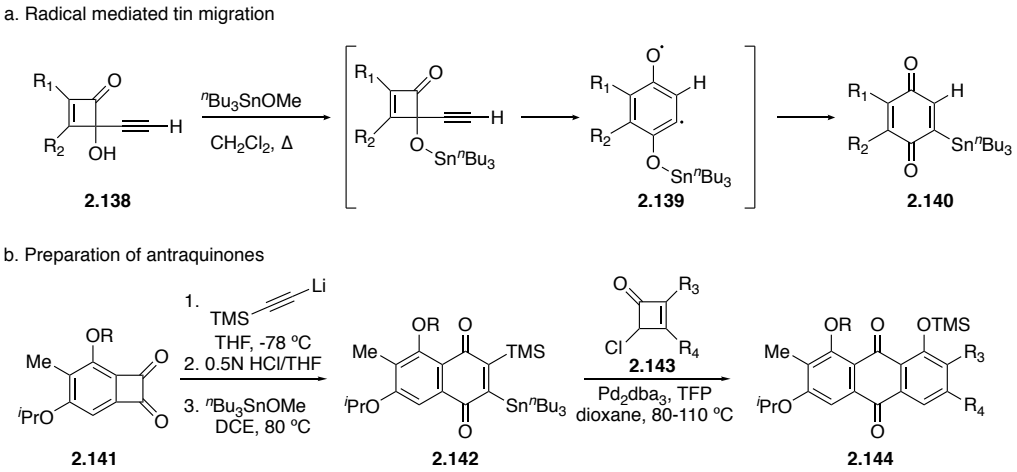
Demonstrating the usefulness of this method in synthetic applications Moore prepared several different quinone containing products, as highlighted with the synthesis of isoamebifuranone (**2.136,** Scheme 2.20).[43] Metalation of alkyne **2.134** followed by addition to dimethyl squarate (**2.121**) produces desired alkynyl cyclobutanone **2.135** for rearrangement. This strategy offered an efficient method for preparation of the highly substituted quinone of isoarnebifuranone (**2.136**).

Scheme 2.20 Synthesis of Isoarnebifuranone (2.136)



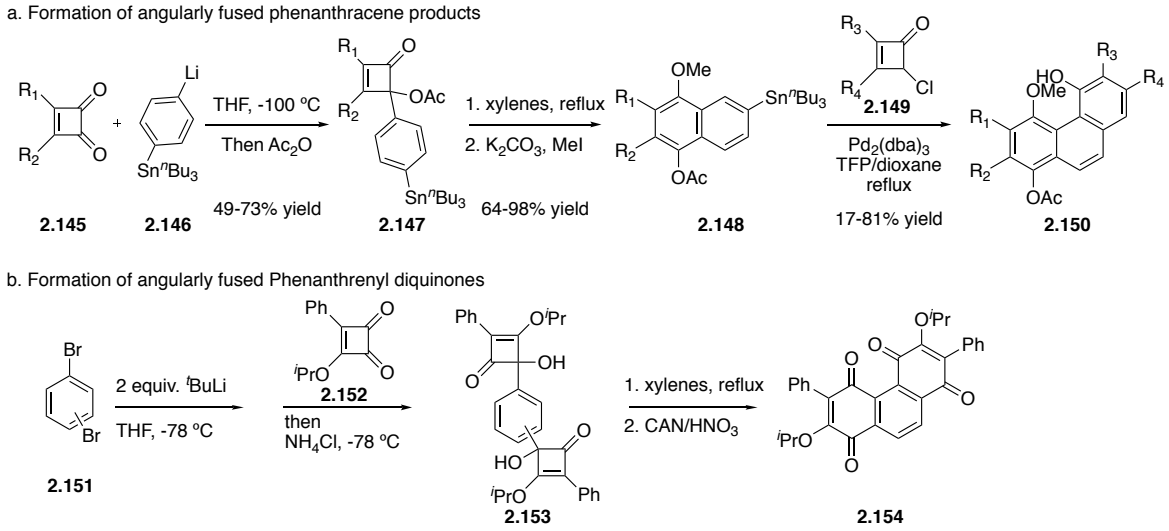
In a further extension of this method Liebeskind *et al*. reported that treatment of 4 ethynyl-4-hydroxy cyclobuten-1-one (**2.138**) with Bu_3SnOMe produced stannylquinones (**2.140,** Scheme 2.21a).[44] Mechanistically it is presumed that radical mediated migration of tin, after cyclization, enables the preparation of these products. While these stannyl quinones can be further functionalized after formation, Liebeskind demonstrated the ability for concurrent ring expansion and Stille coupling in one pot.[45] In addition he reported that sequential rearrangements enable facile generation of complex, highly oxygenated anthraquinone derivatives **2.144** (Scheme 2.21b).

Scheme 2.21 Liebeskind Synthesis of Naphthols and Anthraquinones



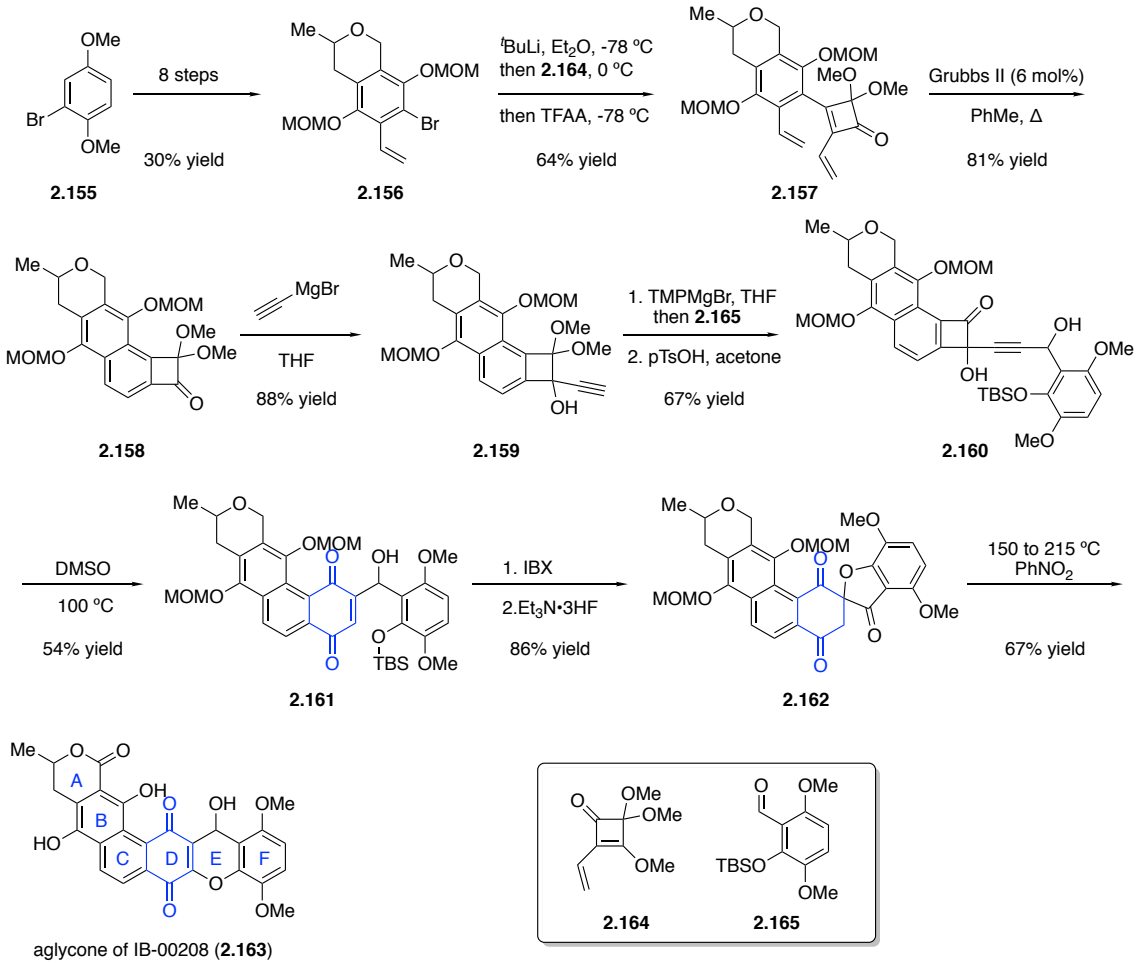
Expanding on this reaction, Liebeskind observed that oxidation state of the substituted cyclobutanone affected the regioselectivity of cyclization (Scheme 2.22a). If performed at the napthol oxidation state, (**2.148** to **2.150**) as opposed to the quinone (**2.142** to **2.144** scheme 2.21b), cyclization gives angularly fused phenanthracene products (**2.150**).[46] Access to angularly fused phenanthrenyl diquinone species (**2.154**) can be achieved from thermolysis of a 1,4 disubstituted benzene **2.153**, followed by oxidation (Scheme 2.22b).[47]

Scheme 2.22 Preparation Angularly Fused Systems



More recently this transformation was exploited by Martin *et al.* in their work towards the synthesis of xanthone natural products, as illustrated with the synthesis of the aglycone of IB-00208 (**2.163,** Scheme 2.23).[48] Key to their synthetic strategy is formation of the quinone D ring from a Moore rearrangement of alkynyl cyclobutanone **2.160**. Using what they term an acetylide stitching technique, addition of propargyl Grignard to the substituted naphthyl cyclobutanone **2.158** gave propargyl alcohol **2.159**. Double anion formation then allowed for aldehyde coupling giving the desired carbon-carbon bonds required for the product. Thermolysis of this alkynyl cyclobutanone **2.160** propagated the Moore rearrangement, forming the central quinone D ring of the aglycone of IB-00208 (**2.163**).

Scheme 2.23 Martin Synthesis of Xanthone Natural Products



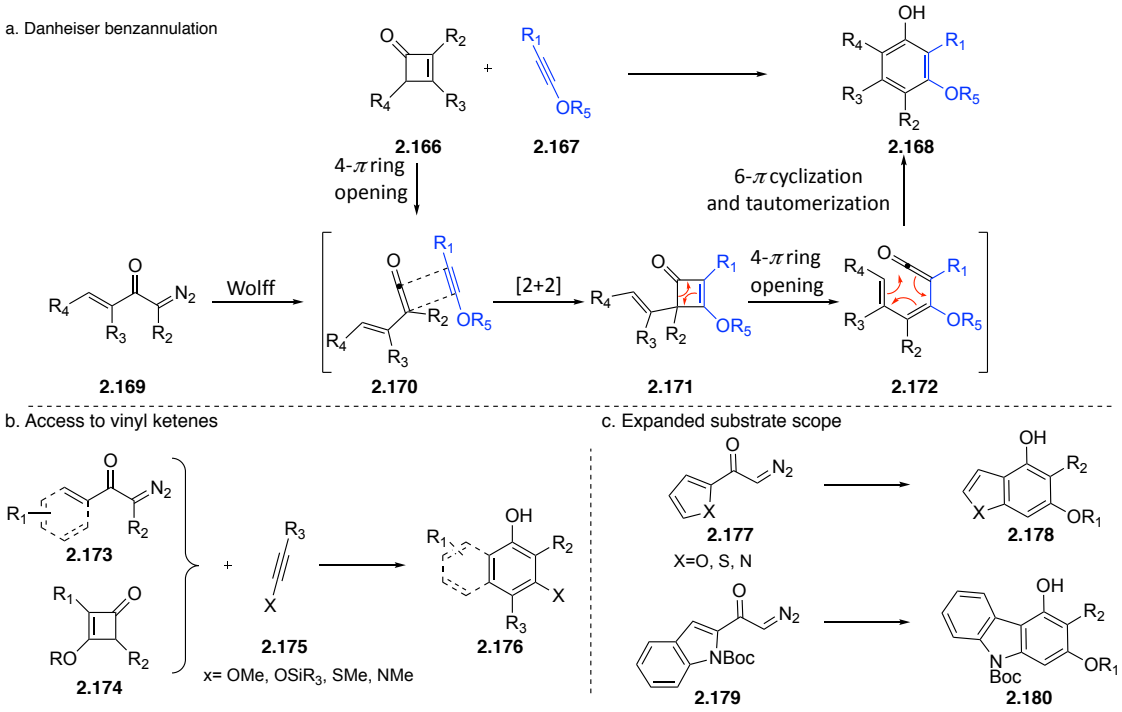
2.2.1.4 Danheiser Benzannulation

Concurrent with reports of Moore and Liebskend, Danheiser and coworkers demonstrated that access to the requisite vinyl cyclobutenones **2.171** can result from a [2+2] cycloaddition between a ketene **2.170** and ynol either **2.167** (Scheme 2.24). This newly formed vinyl cyclobutanone **2.171** can then undergo the same 4π-electorcyclic ring opening and 6π-electrocyclic ring closure followed by tautomerization resulting in resorcinol type products **2.168**.[49]

Ketene formation for these reactions can be achieved via thermal 4-π opening of a cyclobuteneone **2.166** or Wolf rearrangement of α-diazo ketone **2.169** (Scheme 2.24b).[50]

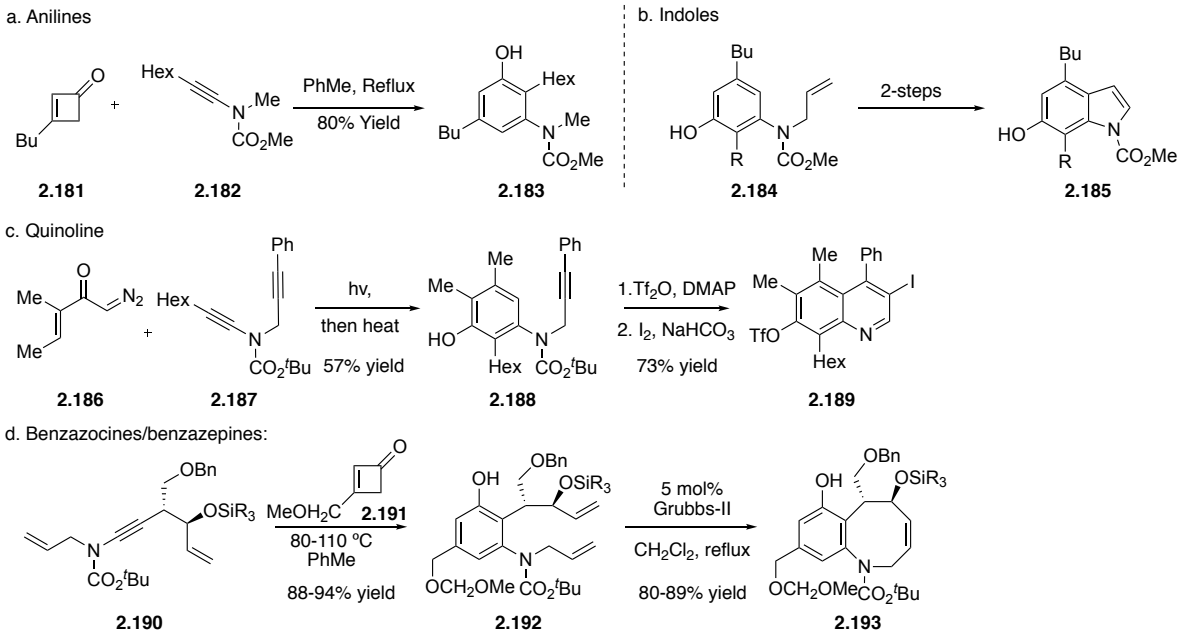
Importantly, the ability to use α-diazo ketones **2.169** as ketene precursors for this reaction allows for an expanded substrate scope, enabling access to a variety of different polycyclic aromatic and heteroaromatic systems, generally not accessible from cyclobutenones. In particular, if the requisite 2 substituted furan, thiophene, pyrrole **2.177** or indole **2.179** diazoketones are used this method allows access to benzofuran, benzothiophene, indole **2.178** or carbazole **2.180** products (Scheme 2.24c).

Scheme 2.24 Danheiser Benzannulation



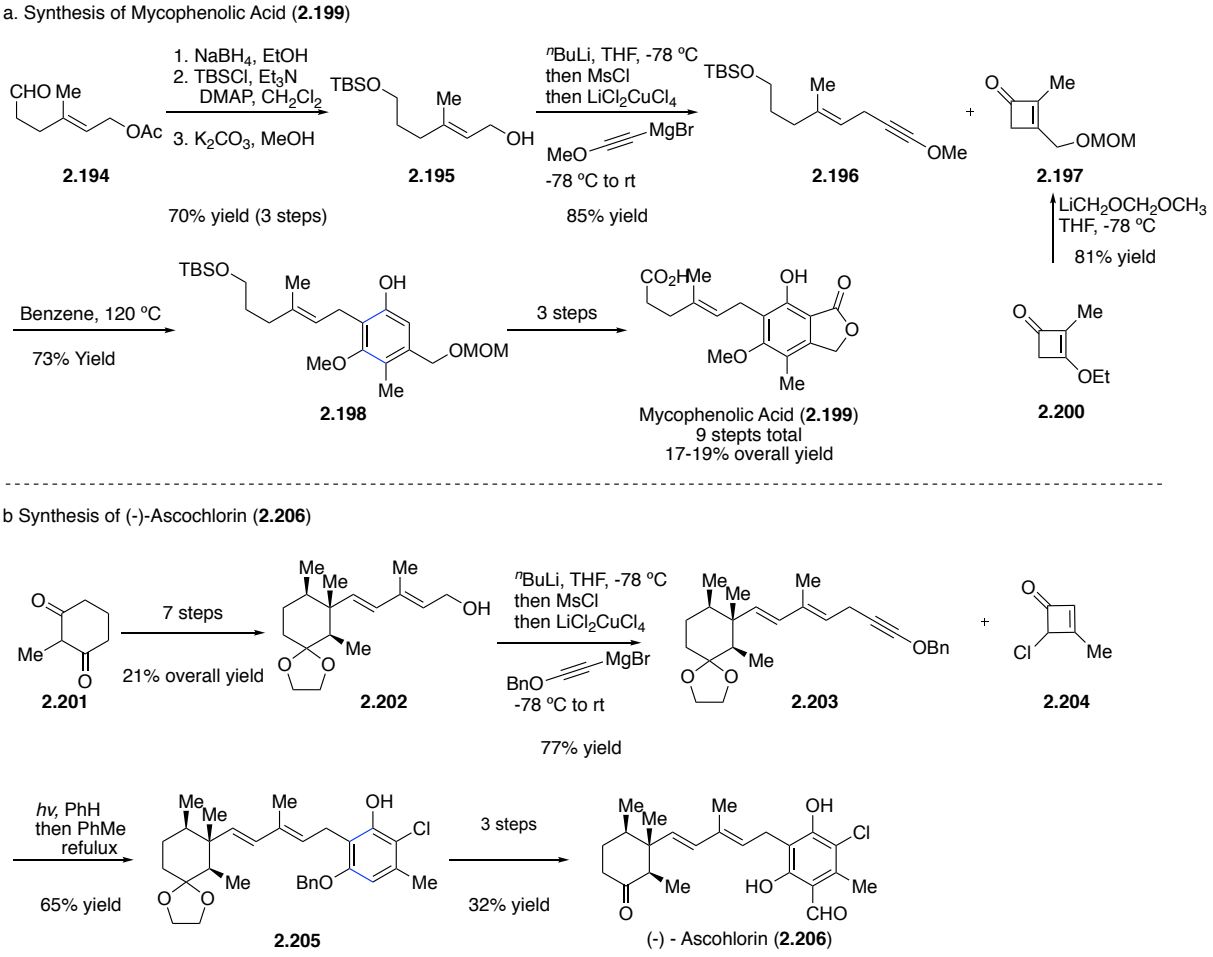
Initially reported ketenophiles suitable for [2+2] cycloadditions with the ketene partner were ynol ethers **2.167** and alkynes, although regioselectivity of the later was often poor. Further extending this methodology, the Danheiser lab has demonstrated the use of ynamides **(2.182, 2.187, 2.190)** as able keteneophiles.[51] Expansion to the ynamide functionality allows access to highly substituted aniline products (**2.183**, Scheme 2.25a), which can readily be converted to indoles (**2.185**, scheme 2.25b), quinolines (**2.189**, Scheme 2.25c) or benzazocines (**2.193**, Scheme 2.25d).

Scheme 2.25 Preparation of Heterocycles with the Danheiser Benzannulation



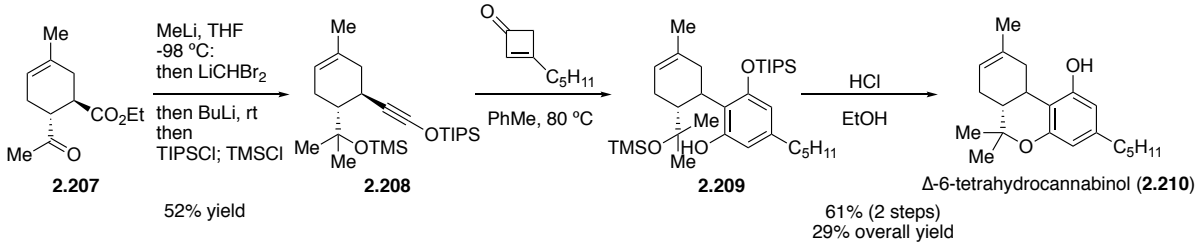
Demonstrating the utility of this method in synthesis Danhesier and coworkers have prepared several resorcinol containing natural products, as exemplified by the synthesis of the antibiotics mycophenolic acid **2.199** and (-)-Ascochlorin **2.206** (Scheme 2.26).[52] For the synthesis of mycophenolic acid (**2.199**, scheme 2.26a) desired ynol ether **2.196** was prepared in 4 steps from allylic acetate **2.194**. Late stage annulation was then used setting up the pentasubstituted resorcinol core. Overall, they were able to complete this synthesis in 9 steps with high yield. Following a similar synthetic strategy, (-)-ascohlorin (**2.206**) was also prepared in an efficient manner.

Scheme 2.26 Synthesis of Mycophenolic Acid 2.199 and (-)-Ascochlorin 2.206



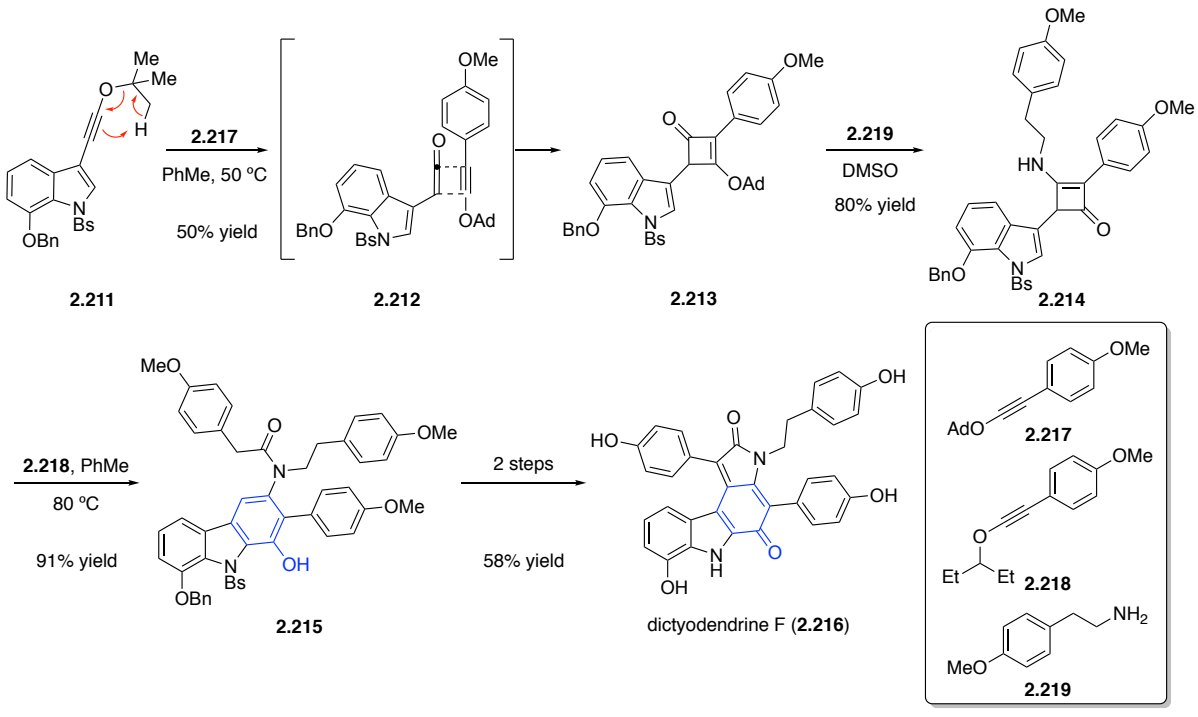
Kowalski and coworker used this benzannulation for their synthesis of Δ-6-tetrahydrocannabinol (**2.210**, Scheme 2.27).[53] In conjunction with a method they developed for ynol ether preparation, from the corresponding ethyl ester **2.207**, they were able to prepare the desired natural product, THC (**2.210**), in 4 steps with good overall yield.

Scheme 2.27 Kowalski Synthesis of Δ-6-tetrahydrocannobinol 2.210



The Ready lab's recent interest in using the Danheiser benzannulation as a synthetic strategy was initiated by a former graduate student, Wenhan Zhang Ph.D., in his synthesis of dictyodendrin F (**2.216**, Scheme 2.28).[54] Extending his previously developed methodology, using *tert*-butyl ynol ethers as ketene surrogates,[55] formation of the desired intermediary aryl cyclobutanone **2.213** was achieved readily from a [2+2] cycloaddition of indole *tert*-butyl ynol ether **2.211** and adamantane ynol ether **2.217**. Capitalizing on the ability to isolate cylcobuteneone **2.213**, given the mild conditions for ketene formation, allowed for further substitution with tyramine **2.219**, generating the requisite amino cyclobutanone intermediate **2.214**. This amino cyclobutanone **2.214** can subsequently participate in the desired ring expansion and concurrent acylation, furnishing the necessary amide functionality of the resulting carbazole **2.215,** thus providing an eloquent solution to a difficult acylation. With the fully substituted core in place oxidative cyclization and deprotection completed the synthesis providing a concise route to dictyodendrin F (**2.216**).

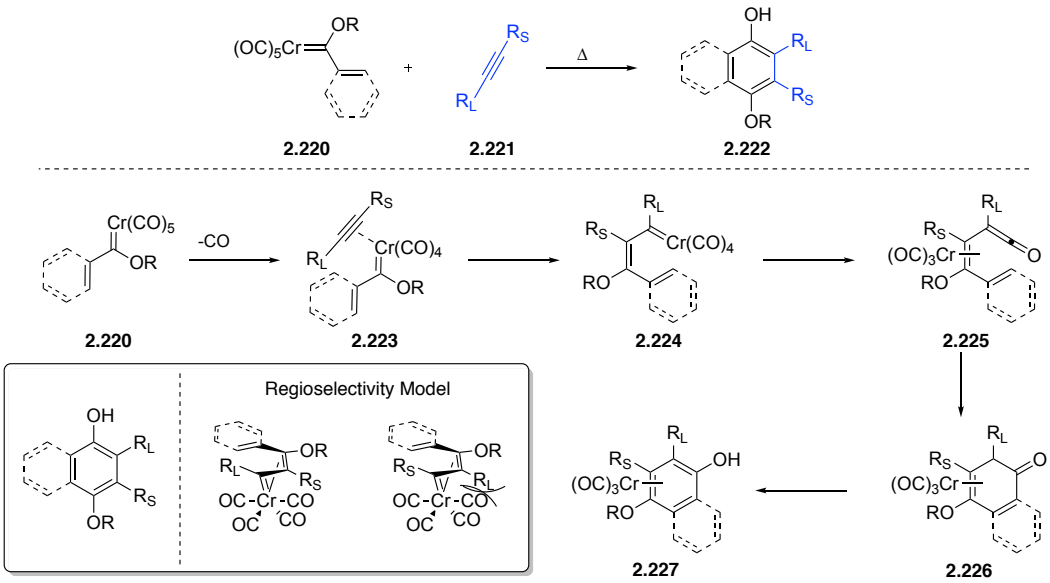
Scheme 2.28 Synthesis of Dictyodendrin F (2.216)



2.2.1.5 The Dötz Benzannulation

The reaction of a vinyl or phenyl alkoxy chromium carbene **2.220** with an alkyne **2.221**, resulting in formation of a new phenolic product was first reported by Dötz in 1975.[56] Alkyne insertion to the chromium carbene, with concurrent loss of CO, forms vinyl chromium carbene intermediate **2.224** (Scheme 2.29). Subsequent CO insertion generates unsaturated ketene **2.225**, analogous to intermediates in the Moore rearrangement and Danhieser annulation, which can undergo 6π-electrocyclization and tautomerization forming the desired 1,4-diphenol product **2.222**.[57] While chromium carbene complexes were first reported, and most commonly employed, for this reaction other metal carbene complexes have been shown effective, including manganese and dinuclear iron complexes.[58]

Scheme 2.29 Dötz Benzannulation

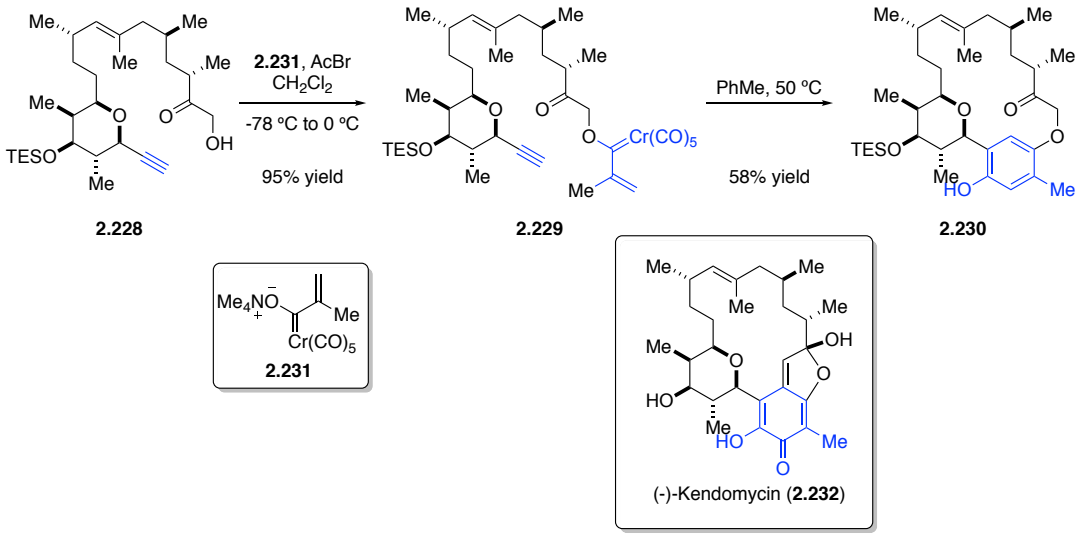


Analogous to the Hauser annulation, the Dötz benzannulation allows facile access to highly substituted 1,4 di-phenol products **2.222** with high levels of regioselectivity (Scheme 2.29). Given that alkyne insertion is the regio-defining step, selectivity is thus determined based on the sterics

of alkyne substitution, such that a ΔA value of >1.4 leads to complete regioselectivity, with electronic factors having little/no affect.[59]

The Dötz annulation has found utility in the synthesis of a number of different natural products, as demonstrated by the Nakata's lab synthesis of (-) – kendomycin (**2.232**, Scheme 2.30).[60] A late stage Dötz annulation was used for preparation of the highly functionalized 1,4-diphenol **2.230**, which was later converted into the *para*-quinone methide of the natural product.

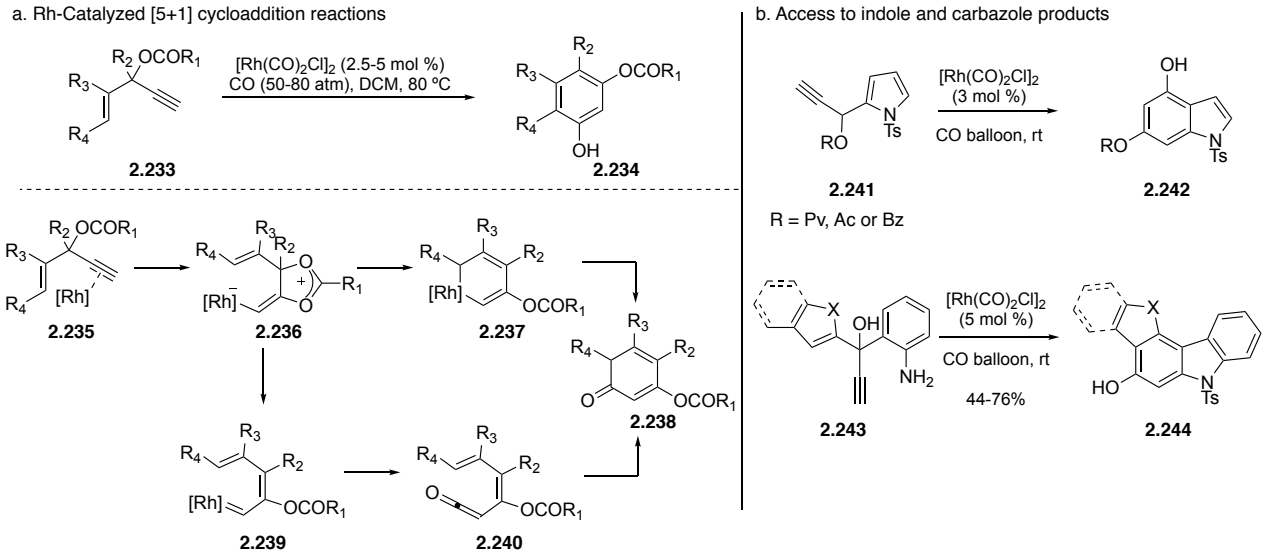
Scheme 2.30 Synthesis of (-)-Kendomycin (2.232)



More recent work involving analogous Dötz reactions have focused on eliminating the need for a stoichiometric amount of the chromium, or other metal, carbene complex. In particular work by the Tang group demonstrates the ability of rhodium to preform [5+1] carbonylative benzannulations (Scheme 2.31a).[61] Mechanistically there are two proposed pathways for this reaction, both initiating with the formation of a zwitterionic vinyl rhodium species **2.236**. This intermediate can then form either rhodium carbene **2.239**, which upon CO insertion mirrors the Dötz mechanism. Alternatively, a rhodacyclohexadiene intermediate **2.237** can undergo CO insertion followed by reductive elimination, leading to product **2.238**. Given the need for

participation of a neighboring carboxylate group substrate scope for these transformations can be limited, however following this strategy has allowed the Tang group to prepare several indole (**2.242**) and carbazole (**2.244**) derivatives (Scheme 2.31b).[62]

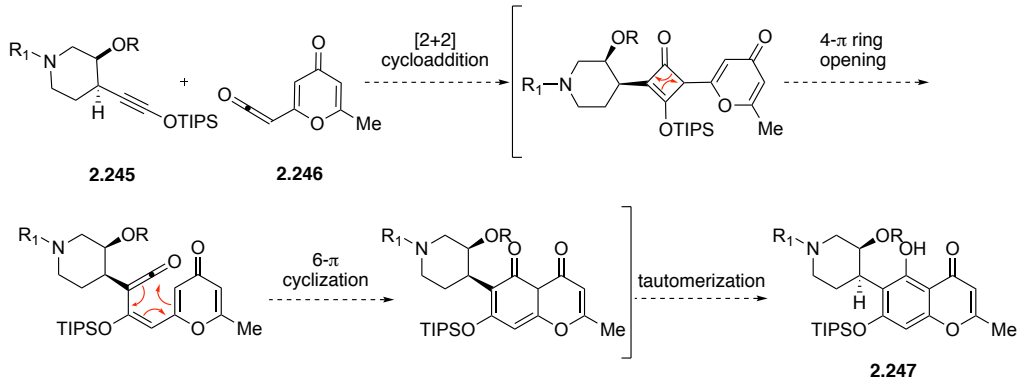
Scheme 2.31 Rhodium Catalyzed [5+1] Cycloadditions



2.2.2 Key Retrosynthetic Disconnect for Dysoline (2.20)

Examination of available methods revealed the potential for a Danheiser type benzannulation as a unique, yet effective strategy for the regioselective construction the chromone core of dysoline (**2.20**, Scheme 2.32). Following this logic, it was reasoned that subjection of piperidine ynol ether **2.245** and pyrone ketene **2.246** to annulation conditions would procure the desired connectivity for dysoline (**2.20)**. In addition to providing for regioselective formation of the chromone core, this late stage disconnection provides a divergent synthetic strategy allowing for the potential of facile analog generation.

Scheme 2.32 Danheiser Benzannulation for the Synthesis of (+)-Dysoline (2.20)



2.3 Preparation of Piperidine Ynol Ether 2.245

In accordance with this synthetic strategy an efficient synthesis of piperidine ynol ether **2.245** was pursued. Of primary focus in designing a route for the preparation of this fragment, was consideration of the stereochemical elements encompassed in addition to the ynol either functionality necessary for the desired benzannulation.

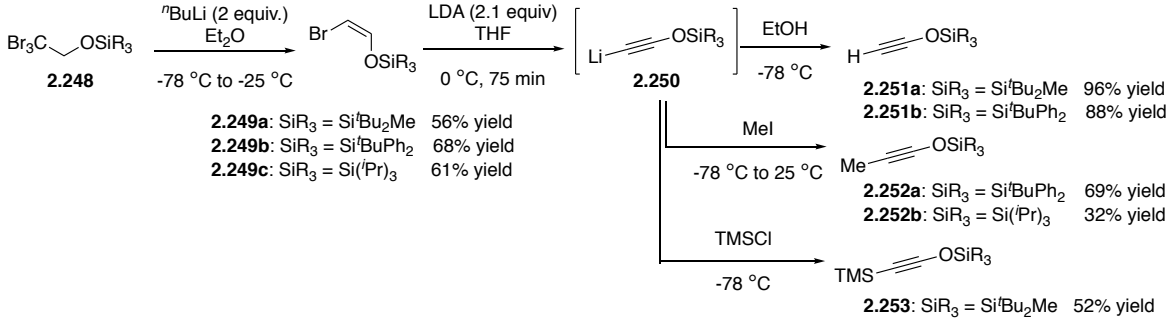
2.3.1 Methods for the Preparation of Silyl Ynol Eithers

The propensity for ynol ethers to act as both electrophiles and nucleophiles, due to the highly polarized nature of the alkyne, makes this functionality a valuable synthetic intermediate.[63,64] Accordingly, several methods for the synthesis of aryl, alkyl and silyl ynol ethers have been reported.[65] For the purpose of brevity only applicable strategies focused on the preparation of silyl ynol ethers will be discussed, mainly those involving: elimination, oxidation or rearrangement.

Initially reported by Pirrung and Hwu,[66] and later elaborated by Danheiser *et al.*,[67] access of terminal silyl ynol ethers by means of a dehydrohalogenation of (Z)-2-bromovinyl silyl ether (**2.249**, Scheme 2.33) provides an efficient means to access this functionality. The requisite (Z)-2-bromovinyl silyl ether (**2.249**) is easily prepared by treatment of silyl protected 2,2,2-tribromomethanol (**2.248**) with 2 equivalents of butyl lithium. Base promoted

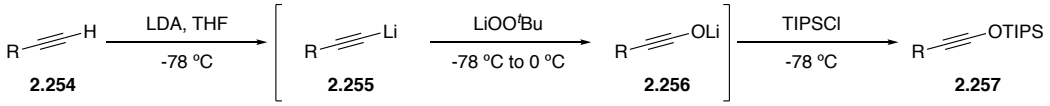
dehydrohalogenation then occurs upon treatment with LDA, generating the desired lithiated silyl ynol ether **2.250**. If ethanol is used to quench this reaction, terminal silyl ynol ether **2.251** can be isolated. Alternatively the lithium ynol ether **2.250** can be trapped with an electrophile, although this reaction was limited to MeI (**2.252**) and TMSCl (**2.253**). Of particular importance in the preparation and use of silyl ynol ethers is the size of the silyl group; with larger silyl protecting groups offering more stable ynol ether intermediates than those of smaller silyl groups.

Scheme 2.33 Preparation of Silyl Ynol Ethers by Elimination



Oxidation of terminal alkynes with LiOO^{t}Bu followed by silyl protection as reported by Julia *et al*. has offered an alternative method for accessing silyl ynol ethers (Scheme 2.34).[68] Particularly advantages about this approach is the relative abundance of the alkyne starting materials.

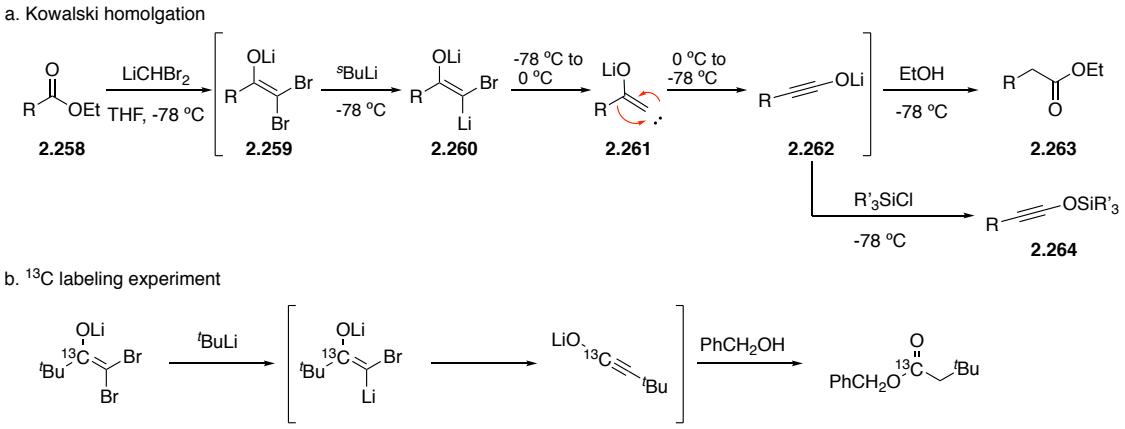
Scheme 2.34 Oxidation of Alkynes



In 1982 Kowalski and Fields reported a novel method for the homologation of ethyl esters **2.258**, originally termed a 'carbon analogue of the Hofmann rearrangement', this reaction is now known as the Kowalski homologation (Scheme 2.35a).[69] Treatment of the starting ester with lithiated dibromomethane forms α,α-dibromoketone lithium enolate **2.259**, which upon treatment with an alkyl lithium reagent undergoes metal halogen exchange followed by α-elimination

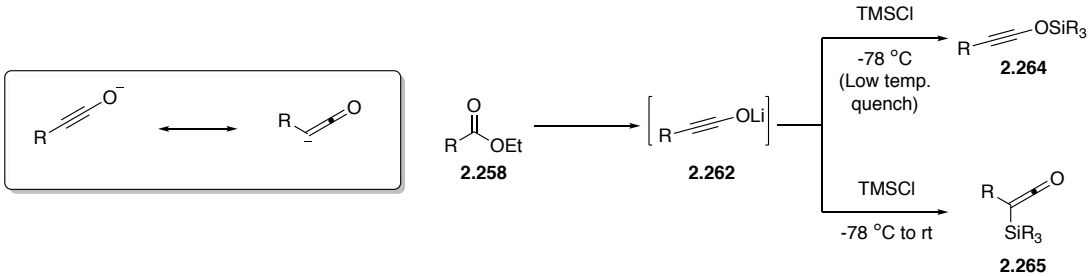
forming carbene **2.261**. Alkyl migration, as confirmed by ^{13}C labeling (Scheme 2.35b), of this carbene intermediate results in ynolate **2.262.** Trapping this ynolate with an alcohol gives the homologated ester product **2.263**, or instead if the ynolate is trapped with a silyl chloride ynol ether **2.264** can be obtained.

Scheme 2.35 Kowalski Homologation



Given that the ynolate has negative charge density at both the oxygen and carbon, regioselectivity of silylation, in both the Julia and Kowalski methods, needs to be considered.[70] As demonstrated by Kowalski, trapping of lithium ynolate **2.262** with sillyl chloride at -78 ºC, results in the desired silyl ynol ether **2.264**, however if the reaction is allowed to warm to room temperature before quenching, silylated ketene products **2.265** are observed instead.

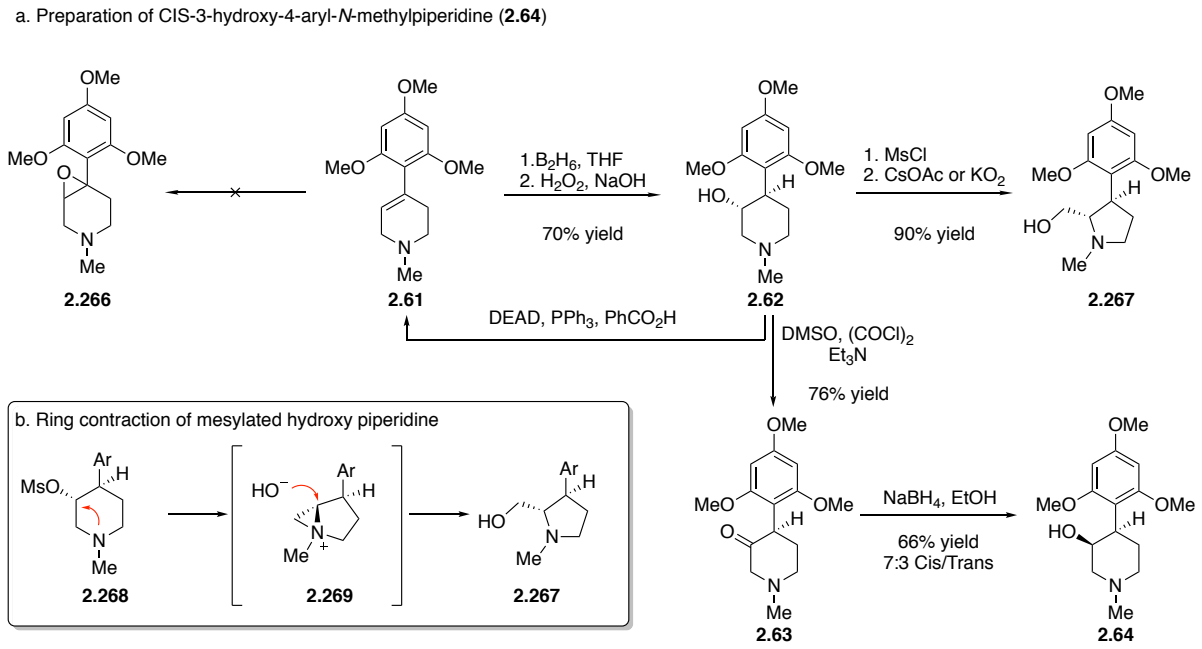
Scheme 2.36 Silyl Ynol Ether vs. Silyl Ketene



2.3.2 Synthesis of Piperidine Scaffold

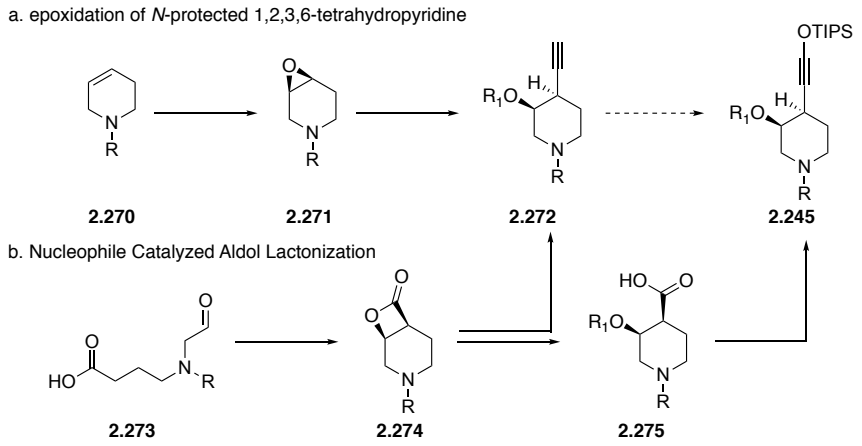
Of particular importance and challenge in the preparation of ynol either **2.245**, is the relative and absolute stereochemistry of the piperidine ring. As highlighted by the original synthesis of rohitukine (**2.21**), establishing the proper cis relationship between the piperidine alcohol and chromone ring proved difficult (Scheme 2.37a).[15] Initial attempts by Naik *et al.* to epoxidize the alkene intermediate **2.61,** failed to provide the desired product **2.266**. Hydroboration of alkene **2.61** produced the desired 3-hydroxy piperidine **2.62,** however with the undesired trans configuration. Subsequent attempts at inversion of the alcohol stereocenter using Mitsunobu conditions resulted in only elimination back to alkene **2.61**. Mesylation followed by Sn2 led to ring contraction of the piperidine, presumably through bicyclic aziridinium species **2.269,** generating pyrrolidine **2.267** (Scheme 2.37b).[71] Ultimately this functionality was installed with the proper configuration by oxidation of the trans isomer followed by sodium borohydride reduction, with only moderate selectivity achieved.

Scheme 2.37 Preparation of CIS 3-Hydroxy-4-aryl N-Me piperidine



In addition to the difficulty in preparing the proper relative stereochemistry of rohitukine (**2.21**), resolution of aryl piperidine derivative **2.64** by crystallization with tartaric acid was necessary to obtain enantiopure product. Cognizant that any synthesis of (+)-dysoline (**2.20**) needs to account for the enantio- and diastereoselectivity, in conjunction with the difficulties encountered in previous synthetic attempts, a variety of options for the preparation of piperidine ynol ether **2.245** were explored. Ultimately synthesis of this piperidine scaffold was focused on 2 different synthetic routes (Scheme 2.38). Route 1 involved the epoxidation of *N*-protected tetrahedropyridine **2.270,** followed by epoxide opening with potential oxidation of the resulting alkyne, by the method of Julia *et al*. (Scheme 2.38a). An alternative route using a nucleophile aldol lactonization (NCAL) reaction to furnish bicyclo β-lactone **2.274** was ultimately proven successful (Scheme 2.38b).

Scheme 2.38 Methods for the Preparation of Ynol Ether 2.245

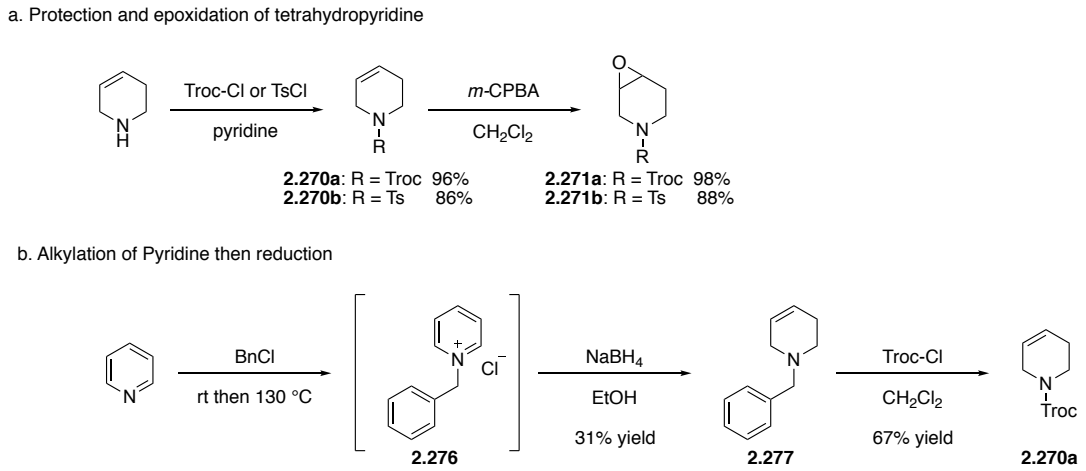


2.3.3 Preparation of CIS 3-Hydroxy-4-piperidine 2.245: Route 1

Attempts at preparing the requisite cis 3-hydroxy-4-piperidine ynol ether **2.245** following route 1 commenced with the protection of 1,2,3,6-tetrahydropyridine (Scheme 2.39a). Treatment with Troc-Cl or Tosyl-Cl gave the corresponding *N*-protected tetrahydropyridine products (**2.270**),

which upon treatment with *m*-CPBA furnished the 3,4-epoxy piperidines (**2.271**) in good yields. The expense and limited availability of 1,2,3,6-tetrahydropyridine, > $100 per gram, facilitated exploration of alternate paths for obtaining the desired carbamate protected piperidine **2.270a** (Scheme 2.39b). In this way alkylation of pyridine with benzyl chloride results in pyridinium chloride **2.276**, which upon treatment with $NaBH_4$ is reduced to *N*-benzyl 1,2,3,6-tetrahydropyridine (**2.277)**.[72] Subsequent treatment with 2 equivalents of chloroformate produces the desired carbamate **2.270a**, presumably through acylation of the tertiary amine followed by nucleophilic attack at the benzylic carbon with chloride.

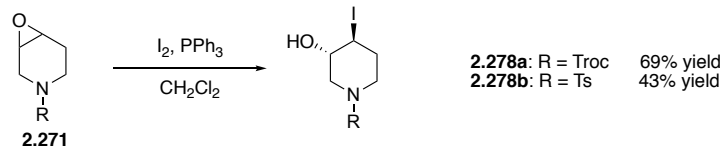
Scheme 2.39 Synthesis of 3,4-Epoxy Piperidine (2.271)



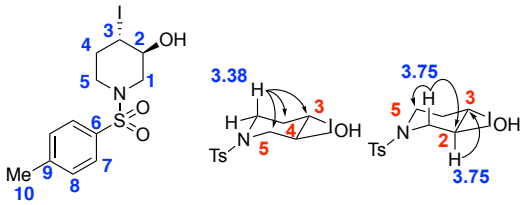
Epoxide opening with iodine furnishes the desired 3-hydroxy-4-iodo piperidine (**2.278**, Scheme 2.40a) with trans configuration. Regioselectivity of epoxide opening was determined using HMBC experiments, confirming the desired 4-iodo-3-hydroxy *N*-protected piperidine (**2.278**, Scheme 2.40b), in agreement with literature precedence.[73] This regioselectivity is proposed to result from steric interactions associated with attack of a soft nucleophile at C3, in addition to the proximity of the nitrogen lone pair.

Scheme 2.40 Epoxide Opening with Iodine

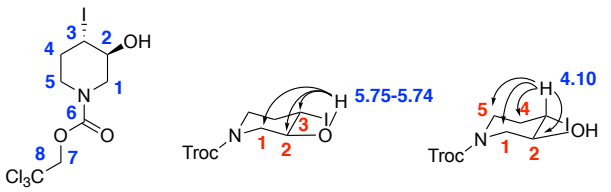
a. Epoxide opening with Iodine



b. HMBC confirmation of regioselecetivity



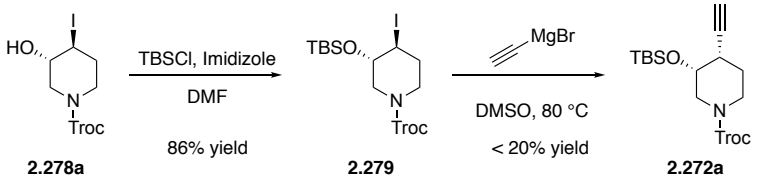
Carbon	^{13}C signals	^{1}H signals	HMBC coorilations
1	51.2	3.75, 2.36	46.9, 71.8
2	71.8	3.75	33.1
3	33.1	3.96	
4	36.0	2.21, 2.45	
5	46.9	3.38, 2.51	33.1, 36.0, 51.2
6	133.6		
7	127.6	6.68	
8	129.7	7.47	
9	143.7		
10	20.5	2.45	



Carbon	^{13}C signals	^{1}H signals	HMBC coorilations
1	50.0	4.03-9.92, 3.11-2.81	
2	71.5	3.53-3.43	
2-OH		5.75-5.74	35.8, 50.0, 71.5
3	35.8	4.10	36.5, 45.2, 50.0, 71.5
4	36.5	2.03-1.92, 2.39-2.31	
5	45.2	3.63, 3.11-2.81	
6	153.3		
7	74.5	4.86-4.78	
8	96.5		

Protection of trans iodo alcohol **2.278a** with TBS can be accomplished in good yield, setting up the desired substrate for installing the alkyne. In this fashion treatment of the iodo piperidine **2.279** with alkynyl Gringard resulted in only small amounts of desired product **2.272a**, as observed by NMR (Scheme 2.41).

Scheme 2.41 Alkyne Substitution



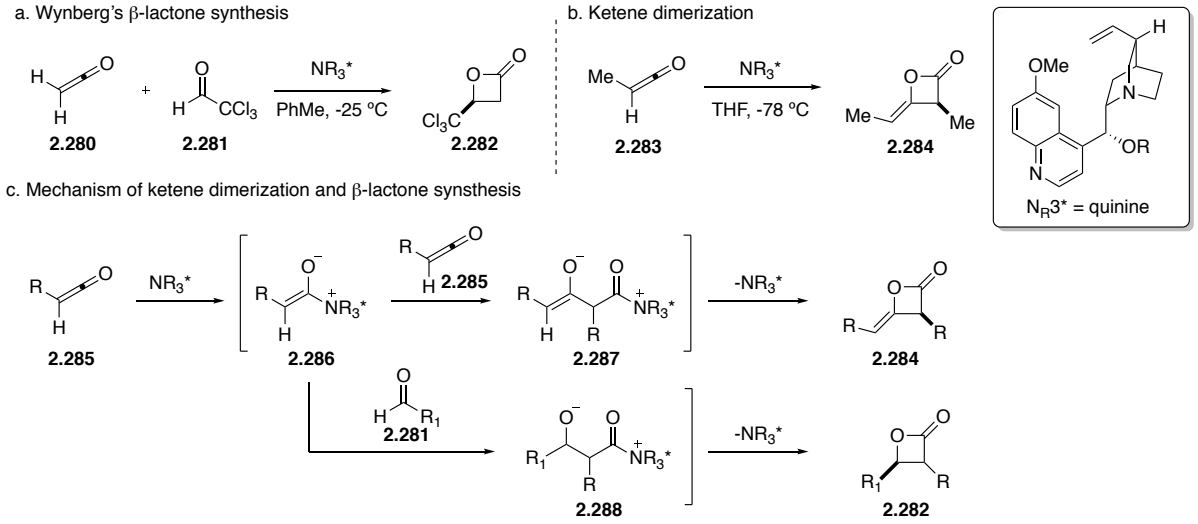
Given this low reactivity, in conjunction with the uncertainty of achieving enantioselective epoxidation, further efforts shifted to exploring an alternative route to the desired ynol ether **2.245**.[74] Specifically the use of a nucleophile catalyzed aldol lactonization (NCAL) was explored.

2.3.4 CIS 3-Hydroxy-4-piperidine 2.245: Route 2

2.3.4.1 Wynberg-Romo Nucleophile Catalyzed Aldol Lactonization Background

In 1982 Wynberg and Staring were the first to report formation of β-lactones (**2.282**) resulting from the cross reaction of ketenes (**2.280**) and aldehydes (**2.281**) in the presence of an amine catalyst, quinine (Scheme 2.42a).[75] Mechanistically this transformation involves formation of a zwitterionic C1 ammonium enolate (**2.286**), between ketene (**2.285**) and the amine catalyst.[76] Addition of this active enolate to the aldehyde followed by cyclization of resulting alkoxide **2.288** generates the desired β-lactone **2.282,** concurrent with expulsion of the amine catalyst. This method allowed for the first example of cross reactivity between a ketene and aldehyde in contrast to ketene dimerization (Scheme 2.42b).[77] Given the facile nature of this dimerization process it necessitates the use of electron deficient aldehydes, thus limiting the substrate scope available for β-lactone formation.

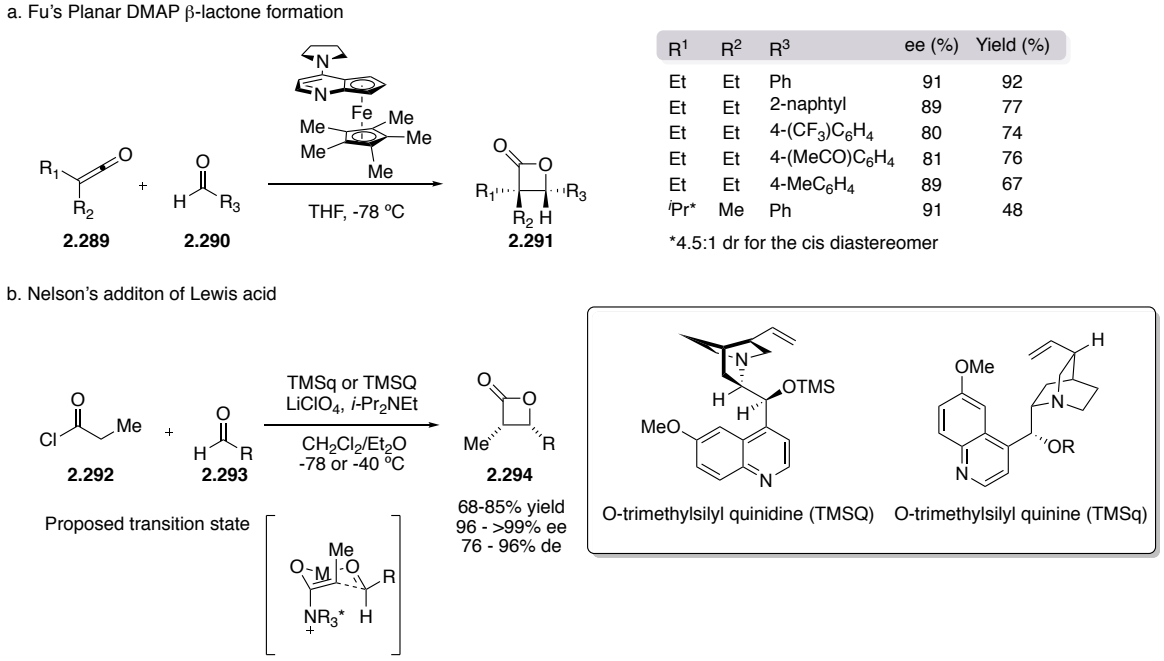
Scheme 2.42 Wynberg β-Lactone Synthesis



Subsequent reports by Fu and Wilson allowed for an expanded aldehyde substrate scope using a chiral DMAP catalyst, developed in the Fu lab (Scheme 2.43a).[78] Similarly Nelson and

coworkers reported that addition of a Lewis acid to the reaction mixture also allows for an expanded aldehyde substrate scope, presumably by mediating a closed transition state (Scheme 2.43b).[79] In addition both of these examples demonstrated that when disubstituted ketenes are used in this reaction high levels of diastereoselectivity for the Cis β-lactone products (**2.291** and **2.294**) are observed.

Scheme 2.43 Expansion of Wynberg β-Lactone Synthesis

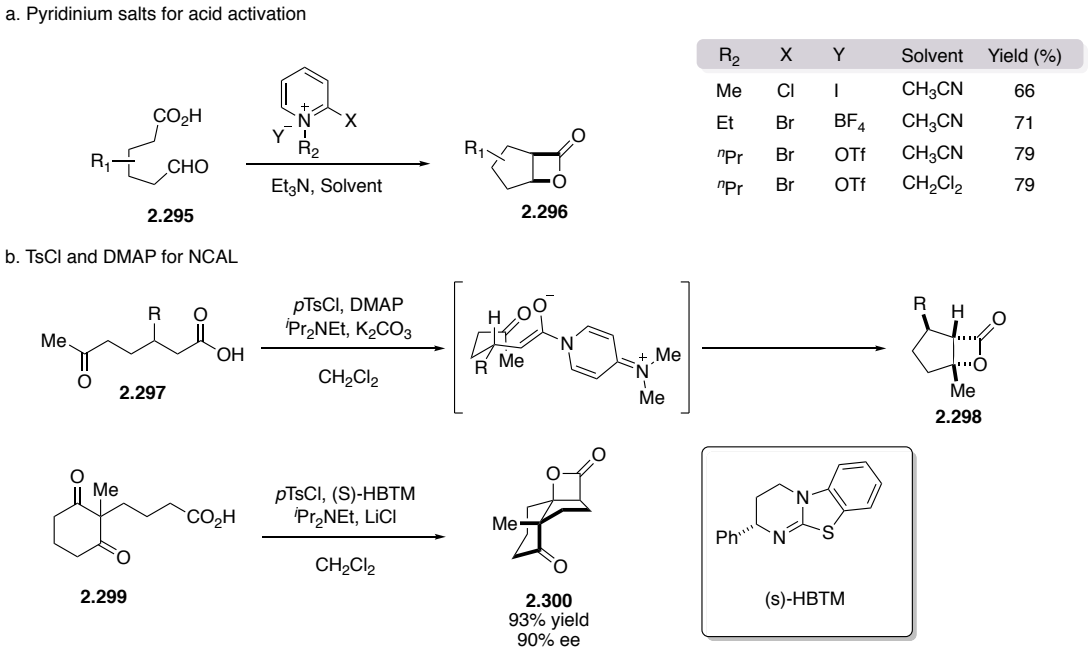


Concurrent with these reports, the Romo group demonstrated the utility of this approach for intramolecular cyclizations of acid aldehyde starting materials (**2.295**) leading to a variety of different bicyclic β-lactone products (**2.296**, Scheme 2.44a).[80] In their original work Romo *et al.* used Mukiyama's reagent for activation of the carboxylic acid, which subsequently reacts with the cinchona alkaloid catalyst either directly or via ketene formation.[81] Further investigation by the Romo group showed that modification of the activating agent increases conversion to the desired product. This improved conversion is due in part to the increased solubility of the pyridinium salt

in conjunction with preventing possible product decomposition, occurring through opening of the resulting β-lactone product **2.296** with iodine.[82]

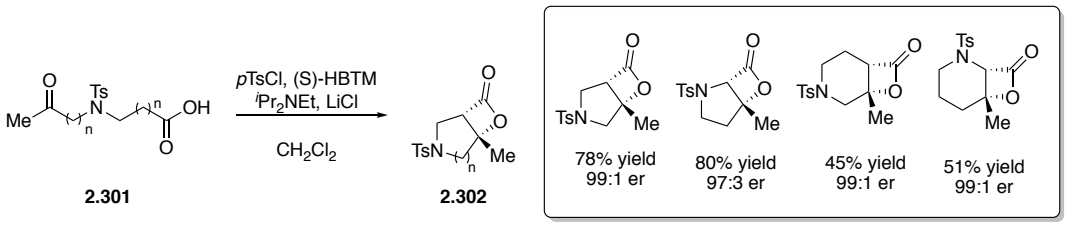
More recent work by Romo *et al.* has involved using tosyl chloride, to activate the carboxylic acid, for the NCAL reaction of various keto acid compounds (**2.297**).[83] Under these conditions DMAP is used as the nucleophilic catalyst, with optically active products formed using cyclic thiourea based catalyst HBTM (Scheme 2.44b). Further optimization of these conditions led to the use of LiCl in the reaction, based on the work of Nielson *et al.*, to achieve a catalytic system.

Scheme 2.44 Intramolecular Nucleophile Catalyzed Aldol Lactonization



Concurrent with our synthetic studies towards dysoline (**2.20**), use of this method for the preparation of nitrogen containing bicyclic β-lactones **2.302** was published by the Romo group (Scheme 2.45).[84] Building from previous work they found that a variety of optically active pyrrolidine and piperidine bicyclic β-lactones (**2.302**) could be obtained by treating precursor keto acids (**2.301**) with tosyl chloride and HBTM.

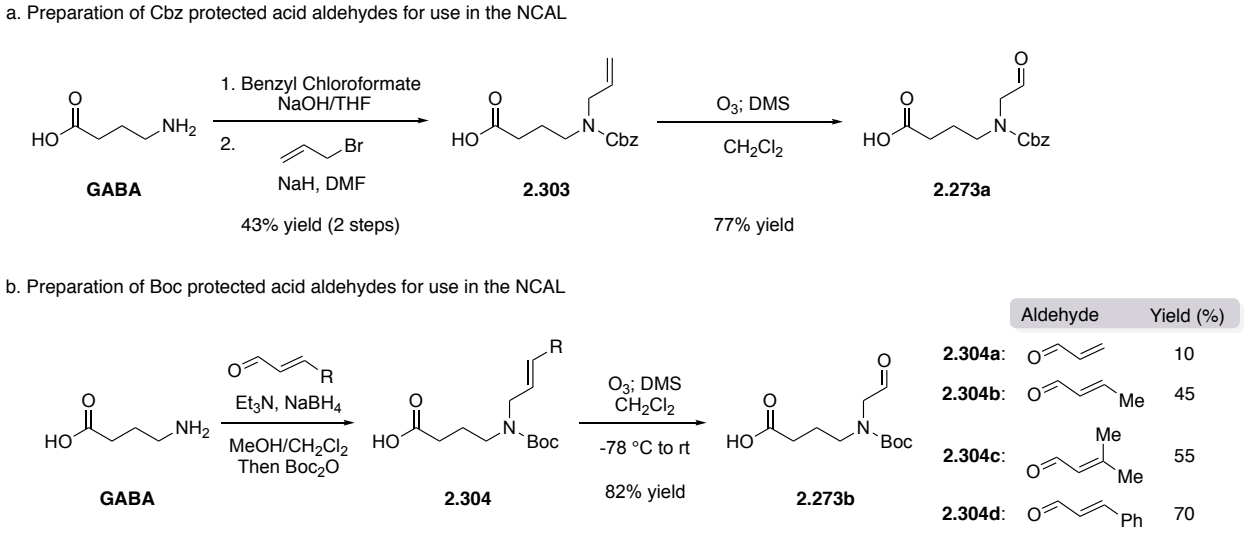
Scheme 2.45 Preparation of N-Hetereocyclic β-Lactones



2.3.4.2 Preparation of CIS 3-Hydroxy-4-piperidine ynol ether 2.245: Route 2

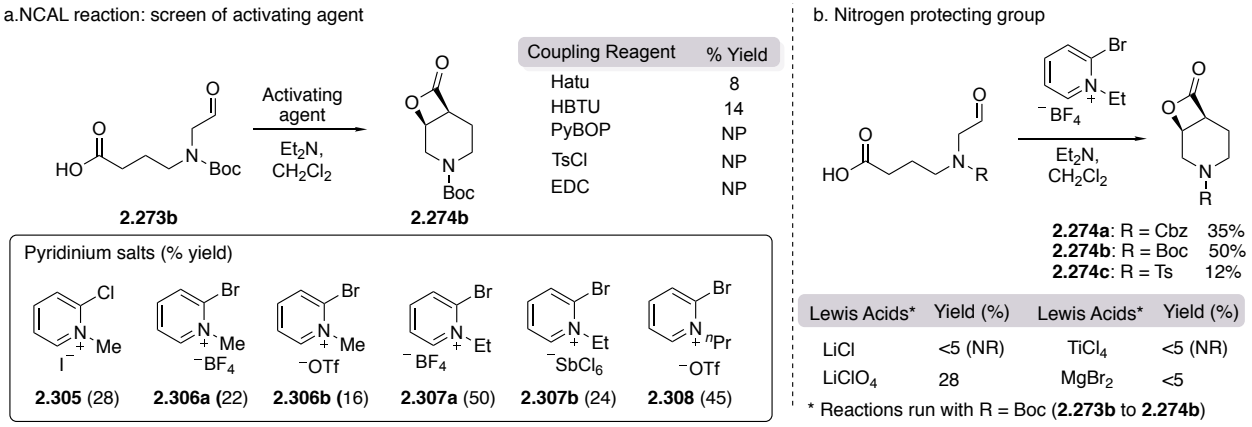
Given the complete enantio- and diastereo- control offered by a nucleophile aldol lactonization (NCAL) strategy, it was postulated to be an efficient method for the preparation of cis 3-hydroxy-4-piperidine ynol ether **2.245**. Access to the requisite *N*-protected carboxylic acid aldehyde **2.273** for use in the NCAL could be readily achieved starting from γ-amino butynoic acid (**GABA,** Scheme 2.46). Initial efforts focused on allylation of *N*-protected **GABA** showed moderate results when benzyl carbamate (**2.303**, Scheme 2.46a) was utilized as the nitrogen protecting group, however use of a *tert*-butyl carbamate resulted in poor and inconsistent yields of the desired product. Presumably competing *O*-allylation of the more sterically encumbered *tert*-butyl carbamate is responsible for this loss in reaction efficiency, consistent with literature reports.[85] Given this result, an alternative method involving reductive alkylation followed by *in situ* amine protection was developed (Scheme 2.46b).[86] A variety of aldehydes were screened for this reaction with *trans*-cinnamaldehdye giving the best results, most likely attributed to the formation of a more stable imine intermediate. Ozonolysis of the resulting allylic amines (**2.304**) proceeded cleanly affording the desired acid aldehyde **2.273b** in good yield.

Scheme 2.46 Acid Aldehyde Preparation



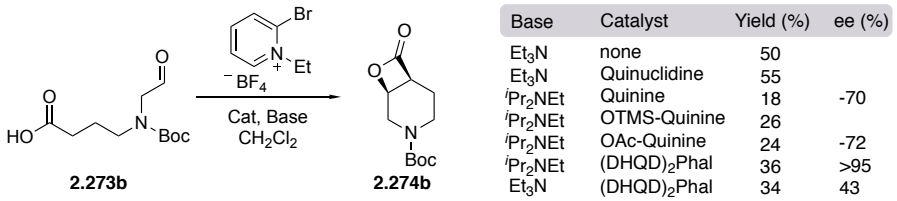
Subjection of acid aldehyde **2.273b** to the original conditions reported by Romo, [Mukiyama's reagent **2.305**, triethyl amine in acetonitrile] gratifyingly produced the desired bicyclic β-lactone **2.274b**, albeit in a moderate 28% yield (Scheme 2.47a). A screen of reagents for acid activation, including various pyridinium derivatives (**2.305-2.308**), revealed an improved yield when 2-bromo ethyl pyridinium tetrafluoroborate **2.307a** was used. Employing *N*-Cbz or *N*-Ts acid aldehydes also produced the desired β-lactones (**2.274a-c**, Scheme 2.47b) however in diminished yields. Additionally, no positive results were observed when a variety of different Lewis acids were added to the reaction. A slight increase in yield was however observed when a catalytic amount of quinuclidine was used (Scheme 2.48).

Scheme 2.47 NCAL Reaction



With optimized conditions for the racemic NCAL reaction, focus was next turned to establishing conditions to obtain enantioenriched product (Scheme 2.48). Different cinchona alkaloid catalysts were evaluated for this reaction, with the dimer $(DHQD)_2Phal$ providing the highest yield and enantioselectivity. Advantageously, both enantiomers of β-lactone **2.274b** are accessible depending on choice of the catalyst pseudo enantiomer enlisted (Scheme 2.48).

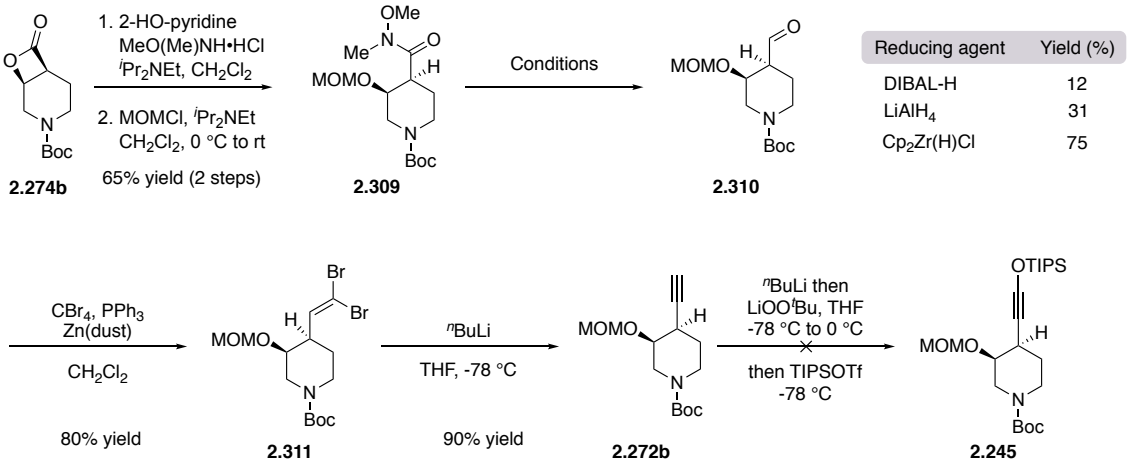
Scheme 2.48 Enantioselective NCAL



Initial attempts at conversion of β-lactone **2.274b** to the desired ynol ether **2.245**, for use in the benzannulation, focused on alkyne oxidation with LiOO*t*-Bu in accordance with the method of Julia *et al*. Opening of the lactone with Weinreb's amine followed by MOM protection of the resulting alcohol furnished the desired Weinreb amide **2.309,** with good efficiency (Scheme 2.49). Subsequent reduction using Schwartz reagent provided aldehyde **2.310** in preparation for a Corey-Fuchs homologation.[87] While DIBAL and LAH showed good conversion to the desired aldehyde, isolation of the product proved difficult under standard workup conditions, presumably due to

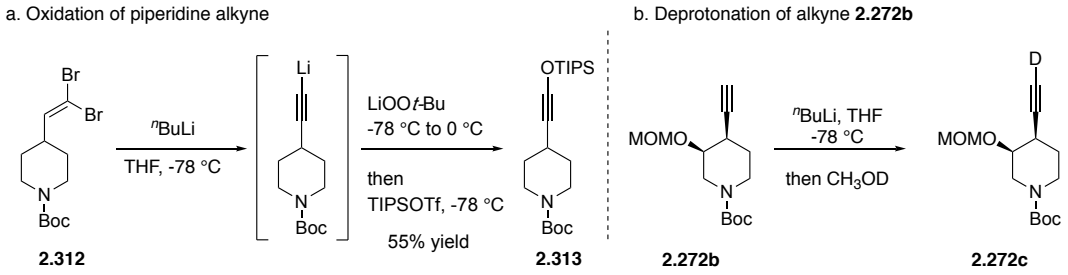
increased chelation of the MOM protecting group. Homologation of aldehyde **2.310** was then achieved, following the conditions of Corey and Fuchs, via vinyl dibromide **2.311**, which cleanly converted to terminal alkyne **2.272b** upon treatment with *n*-BuLi.[88]

Scheme 2.49 Lactone Opening and Corey-Fuchs Alkynlation



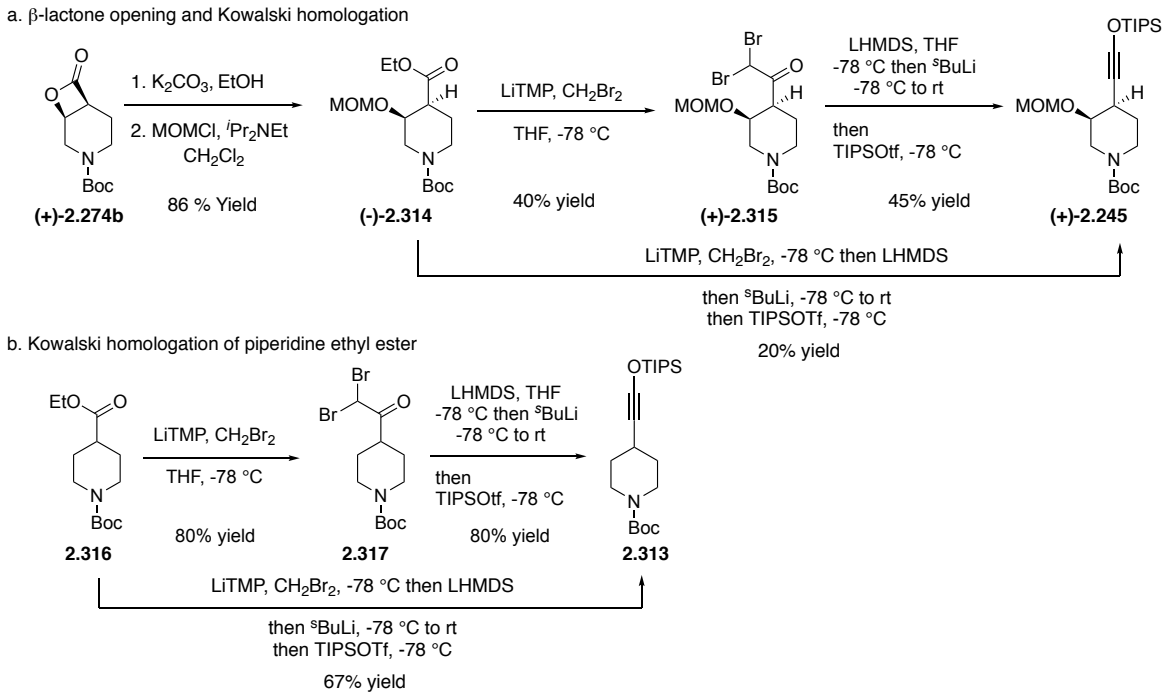
Unfortunately, all attempts at oxidation of this alkyne with LiOO*t*-Bu failed to yield the desired silyl ynol ether **2.245**. Rather, unreacted alkyne was recovered intact. While oxidation of the des-hydroxy piperidine **2.312** (Scheme 2.50a) proceeded smoothly from either alkyne or directly from the vinyl dibromide **2.312**, this reactivity could not be translated into our more elaborated substrate. Deprotonation of alkyne with *n*-BuLi followed by quenching with CH_3OD resulted in complete deuteration of the alkyne, confirming formation and stability of the lithium acetylide (Scheme 2.50b). Additionally use of an alternative oxidant (MeZnOO*t*-Bu) also failed to show desired reactivity. Potential interference from the MOM group led to the exploration of alternative protected alcohols with no avail.[89]

Scheme 2.50 Oxidation of Pieridine Alkyne



Unable to oxidize terminal alkyne **2.272b**, an alternative preparation of the desired ynol ether **2.245** was explored leveraging the chemistry of Kowalski. Synthesis of the required substituted piperidine ethyl ester **2.314** was easily achieved by ethanolysis of the β-lactone (**2.274b**) followed by MOM protection (Scheme 2.51a). Subjection of ethyl ester **2.314** to the lithium anion of dibromomethane resulted in the desired dibromo ketone **2.315**. Enolate formation followed by lithium halogen exchange and α-elimination, initiated the desired alkyl migration. Subsequent trapping of the ynolate intermediate with TIPSOTf furnished ynol ether **2.245** in moderate yield. Ynol ether formation could also be achieved in one pot directly from ethyl ester **2.314,** although a slight decrease in overall yield was observed. By contrast, the monosubstituted piperidine **2.316** underwent homologation in substantially higher yield, indicating that steric hindrance by the OMOM could be retarding the reaction (Scheme 2.51b). Nonetheless, the Kowalski homologation provided the desired ynol ether **2.245** with complete enantiospecificity, as indicated by complete retention of ee of dibromo ketone **2.315**.

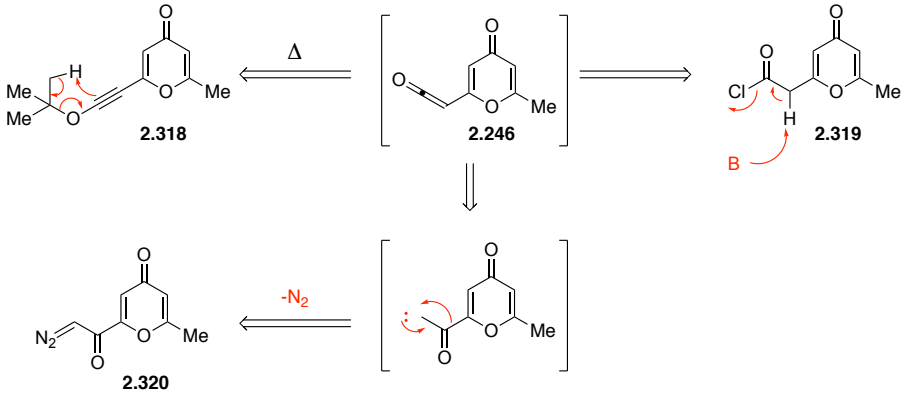
Scheme 2.51 Kowalski Homologation of Piperidine β-Lactone 2.274b



2.4 Preparation of Pyrone Ketene 2.246

With a suitable method for preparing ynol ether **2.245** in hand, attention was turned to accessing the requisite pyrone ketene **2.246** for the benzannulation reaction. Given the lability of the ketene functionality, usually attributed to facile dimerization, these intermediates are commonly generated *in situ*. Although there are numerous ways that have been utilized to generate ketenes[90] initial focus revolved around three methods: [1,5]-hydride shift of a *tert*-butyl ynol ether, elimination of HCl from an acid chloride or Wolf rearrangement of a diazoketone (Scheme 2.52).

Scheme 2.52 Methods for the Preparation of Ketenes



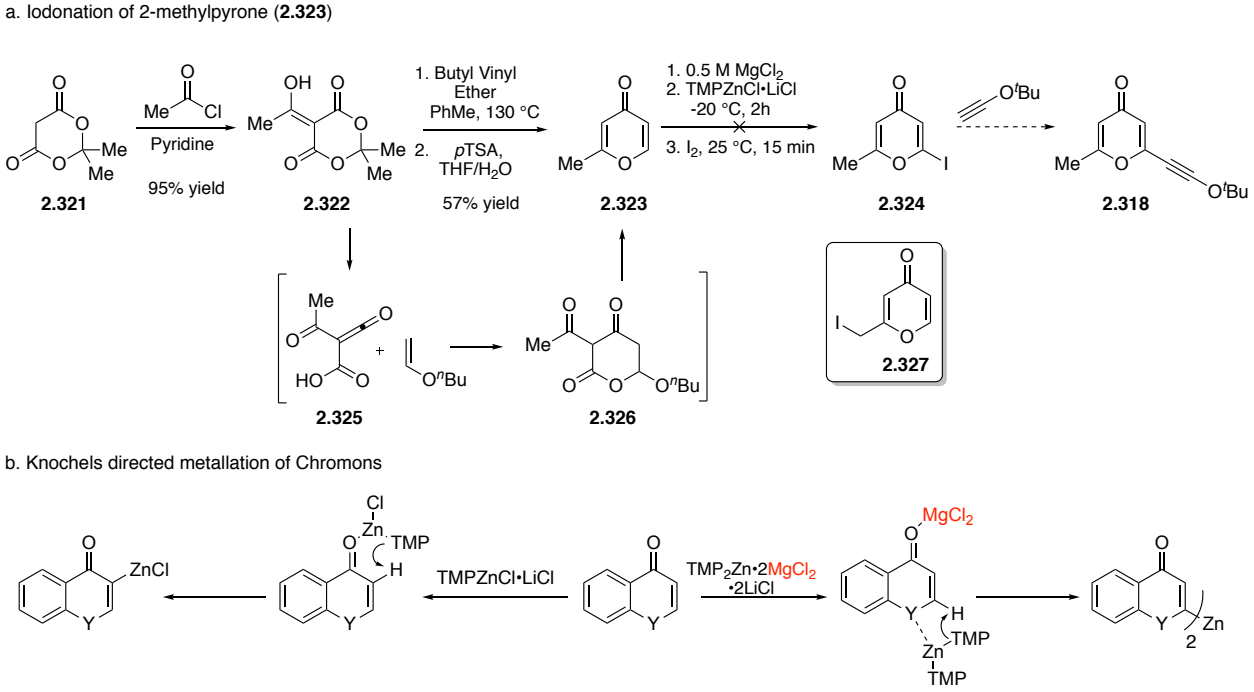
2.4.1 Pyrone Ketene Preparation from [1,5]-Hydride Shift

Leveraging previously explored chemistry by Wenhan Zhang, Ph.D., it was postulated that pyrone ketene **2.246** could arise from thermolysis of *tert*-butyl ynol ether **2.318** (Scheme 2.53a). In turn, access of the desired *tert*-butyl ynol ether **2.318** could result from Sonogashira coupling of 2-iodo-5 methyl pyrone (**2.324**) and *tert*-butyl ynol ether. Inspired by work of Knochel *et al.,* in their ability to modulate deprotonation and metalation of chromone rings based on a dual Lewis acid approach (Scheme 2.53b),[91] attempts at functionalization of 2-methyl pyrone **2.323** were undertaken.

Preparation of 2-methyl pyrone (**2.323**) is achieved in 3 steps starting with the acylation of Meldrum's acid (**2.321**). Heating of this product initiates a retro 6-π cyclization generating ketene **2.325** (Scheme 2.53a).[92] [4+2] cyclization of the ketene intermediate with butyl vinyl ether furnishes tetrahydro pyrone intermediate **2.326,** which upon heating undergoes a decarboxylation followed by dehydration to give the desired 2-methyl pyrone (**2.323)**. Unfortunately, all attempts at directed metalation and trapping with iodine failed to yield the desired 2-iodo-5-methyl

pyrone (**2.324**). Crude analysis points to formation of iodomethyl pyrone **2.327**, resulting from deprotonation of the 2-methyl as opposed to the cyclic proton.

Scheme 2.53 Selective Metalation of Methyl Pyrone (2.323)

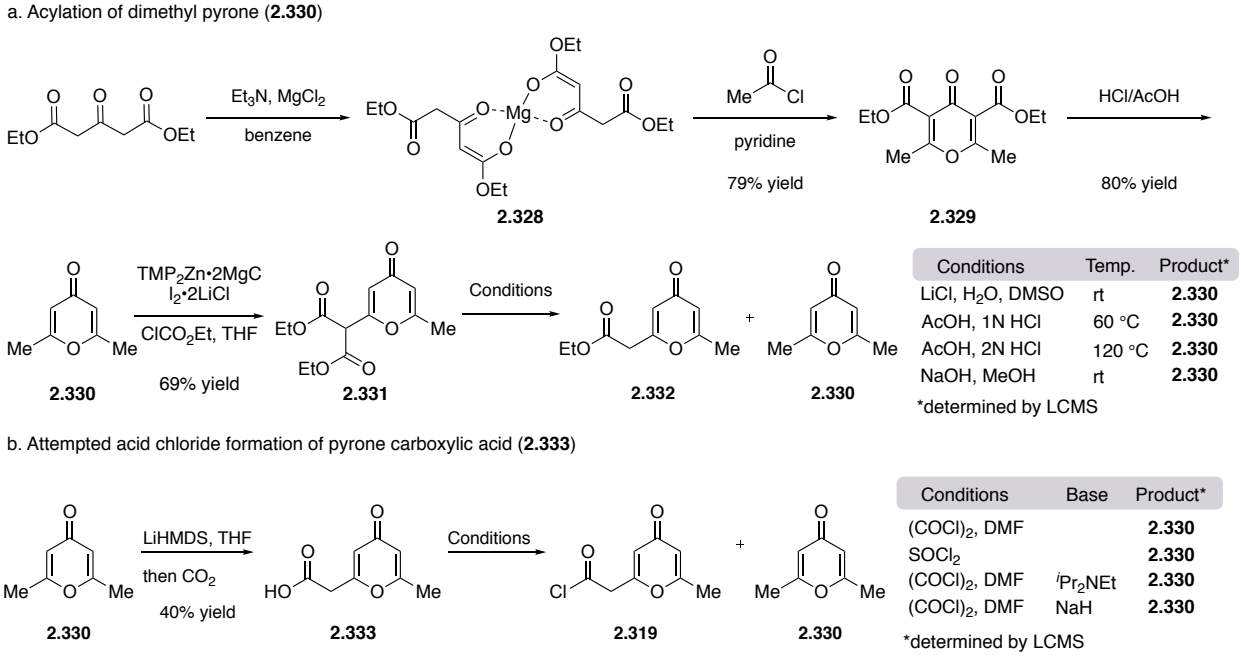


2.4.2 Pyrone Ketene 2.245 From Acid Chloride

Given the proclivity for deprotonation of the exocyclic methyl group, a second strategy for the preparation of the desired pyrone ketene **2.246** from the β-pyrone acid chloride **2.319** was studied (Scheme 2.54). In this way treatment of the dimethyl pyrone (**2.330**), prepared in 3 steps following a known procedure,[93] with base followed by trapping with ethyl chloroformate garnered diacylated pyrone **2.331** (Scheme 2.54a). Unexpectedly, attempts at obtaining the desired β-pyrone mono ethyl ester **2.332** by decarboxylation resulted in recovery of dimethyl pyrone **2.330** exclusively. To prevent di-addition from occurring during acylation, trapping of the intermediary lithiated pyrone with CO_2 was utilized to afford desired β-pyrone carboxylic acid **2.333** (Scheme

2.54b). Unfortunately, all attempts at conversion of this carboxylic acid to the desired acid chloride again resulted in exclusive isolation of dimethyl pyrone **2.330**.

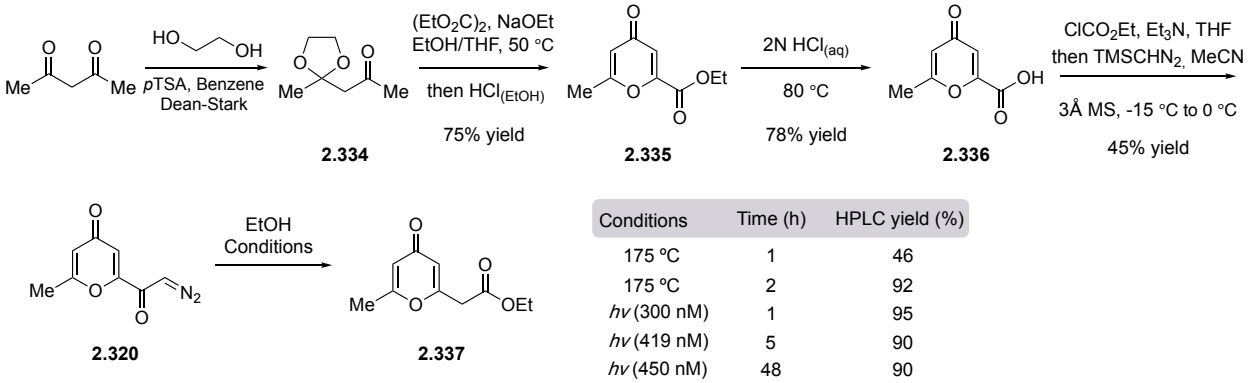
Scheme 2.54 Attempts at Preparation of Pyrone Acid Chloride 2.320



2.4.3 Pyrone Ketene Preparation From Diazo Ketone

With this observed inherent instability of a carbonyl group β to the pyrone, it was instead decided to pursue an Arndt-Eistart strategy, involving a Wolf rearrangement of pyrone diazoketone **2.320** (Scheme 2.55).[94] Preparation of the precursor pyrone ethyl ester **2.335** was achieved in 2 steps utilizing a Claisen condensation followed by acid-promoted cyclization. Hydrolysis then furnished the desired carboxylic acid **2.336**. Conversion of pyrone carboxylic acid **2.336** to diazoketone **2.320** was achieved using slightly modified conditions to those established by Arndt and Eistart.[95] While only a moderate yield was observed for this transformation, the major byproduct was identified as pyrone ethyl ester **2.335**, which could be recycled into the sequence.

Scheme 2.55 Pyrone Ketene Formation by Wolf Rearrangement



Conditions	Time (h)	HPLC yield (%)
175 ºC	1	46
175 ºC	2	92
hν (300 nM)	1	95
hν (419 nM)	5	90
hν (450 nM)	48	90

The propensity of pyrone diazo ketone **2.320** to undergo a Wolf rearrangement was explored by subjecting it to both thermal and photochemical conditions in the presence of ethanol. As expected, conversion of diazo ketone **2.320** to the homologated ethyl ester **2.337** proceeded cleanly under both conditions. It is particularly noteworthy that rate of ketene formation can be controlled through choice of light source. This element of control proved advantageous in the Danheiser benzannulation reaction as a means to modulate ketene concentration and minimize dimerization.

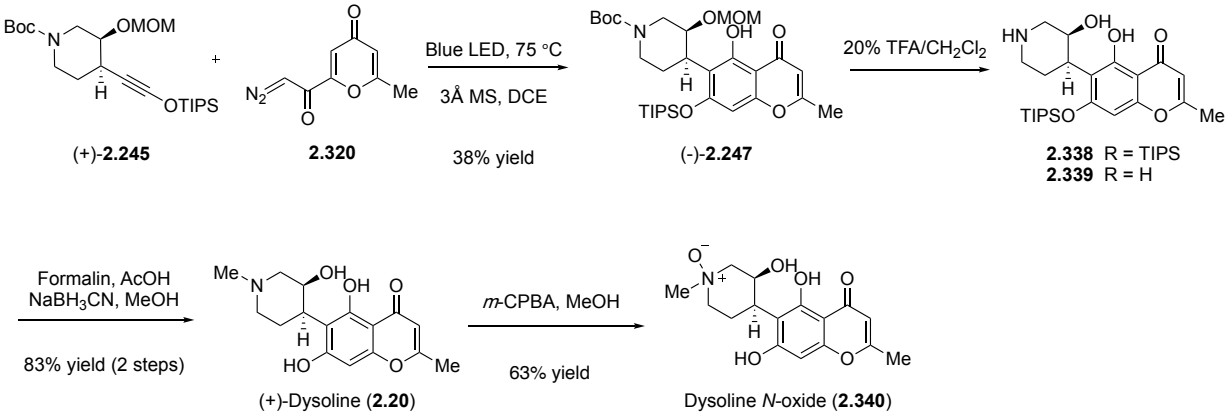
2.5 Danheiser Benzannulation and Completion of Dysoline (2.20)

With suitable methods for the preparation of the requisite ynol ether **2.245** and pyrone diazo ketone **2.320,** attention was turned to the key annulation step constructing the chromone ring of dysoline (**2.20**, Scheme 2.56). Thus, irradiation of a solution of the two fragments with blue LED light (450 nm) resulted in the desired benzannulation, furnishing the chromone core. Further optimization revealed that increasing the temperature in addition to the use of molecular sieves improved the yield for this transformation.

Success of the key annulation left deprotection and *N*-methylation as the remaining steps for completing the synthesis of dysoline (**2.20**). Interestingly, treatment of the fully protected

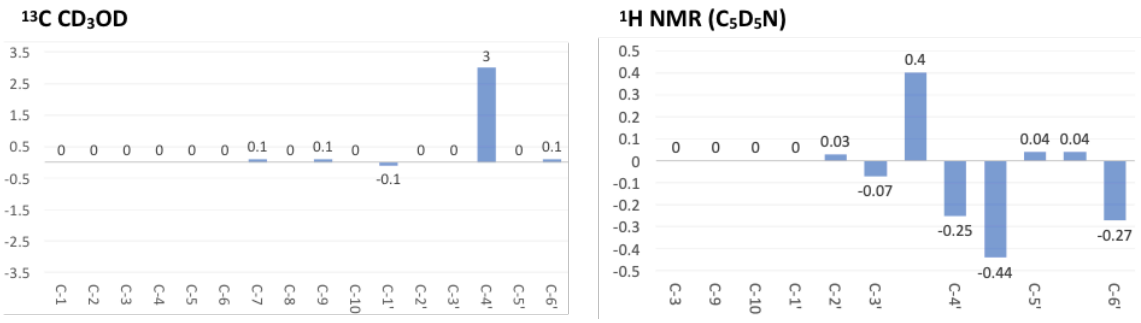
intermediate **2.247** with anhydrous acid (20% TFA in CH_2Cl_2) efficiently removed the Boc and MOM protecting groups with only partial (20%) removal of the TIPS. As expected, removal of this final protecting group was observed when the product was subjected to reductive amination conditions giving the desired natural product, dysoline (**2.20**).

Scheme 2.56 Benzannulation and Completion of Synthesis



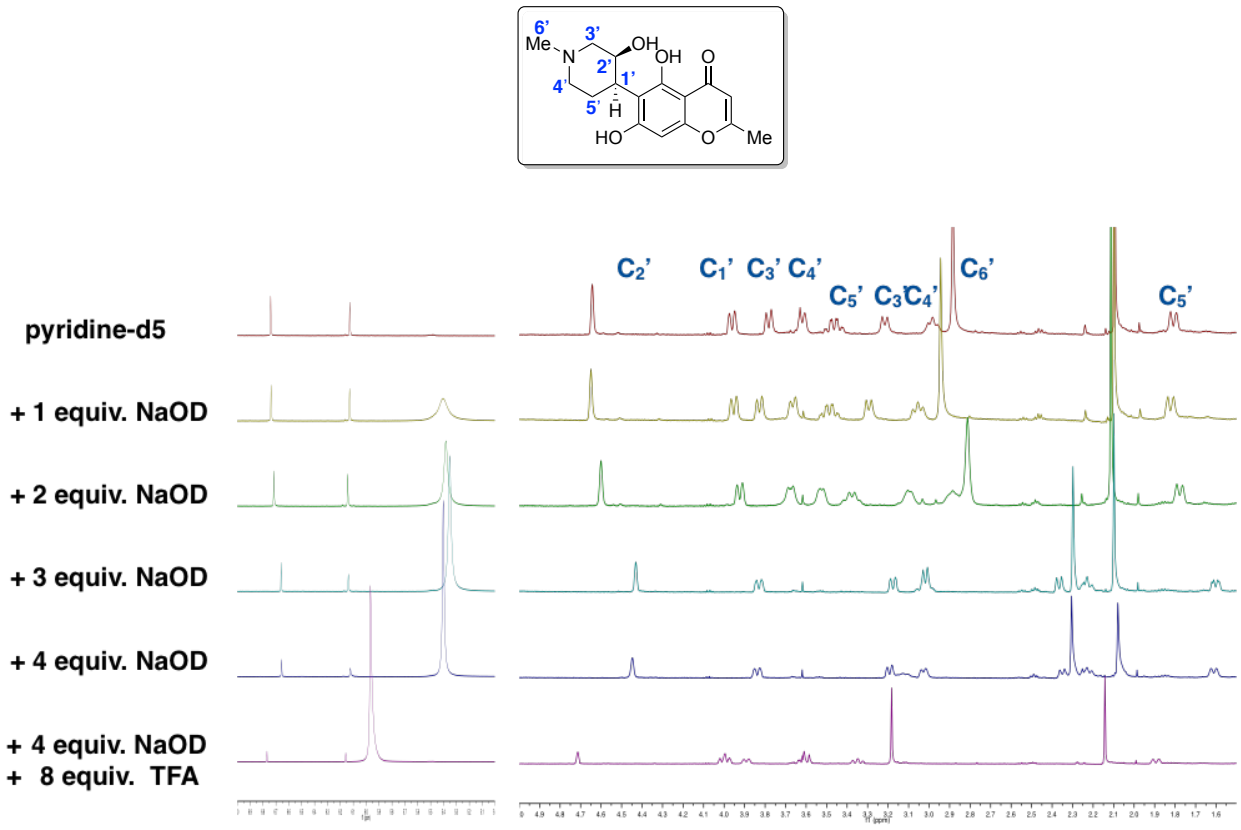
Comparison of the isolated and synthetic NMR spectra of dysoline (**2.20**) reveled matching ^{13}C NMR spectra, with one peak differing due to mis-annotation on the part of the isolation group. There was however, a discrepancy observed in the ^{1}H NMR spectra between the two samples. In particular signals corresponding to protons adjacent to the piperidine nitrogen showed a noticeable difference in chemical shift and splitting.

Figure 2.5 NMR Comparison of Isolated vs. Synthetic Dysoline



This discrepancy was initially attributed to the salt vs. free base form of the natural product, while the synthetic material was isolated as the TFA or formic acid salt the isolation group reported isolation of the free base of dysoline (**2.20**). NMR experiments to validate this hypothesis were undertaken, in particular titration of NaOD to a solution of the synthetic material in pyridine-d_5 was done in an effort to monitor signal shifts in relation to the protonation status of the amine (Figure 2.6). Interestingly, a drastic shift was observed upon formation of the free base form of the natural product, albeit the resulting spectra did not correlate with that reported by the isolation group.

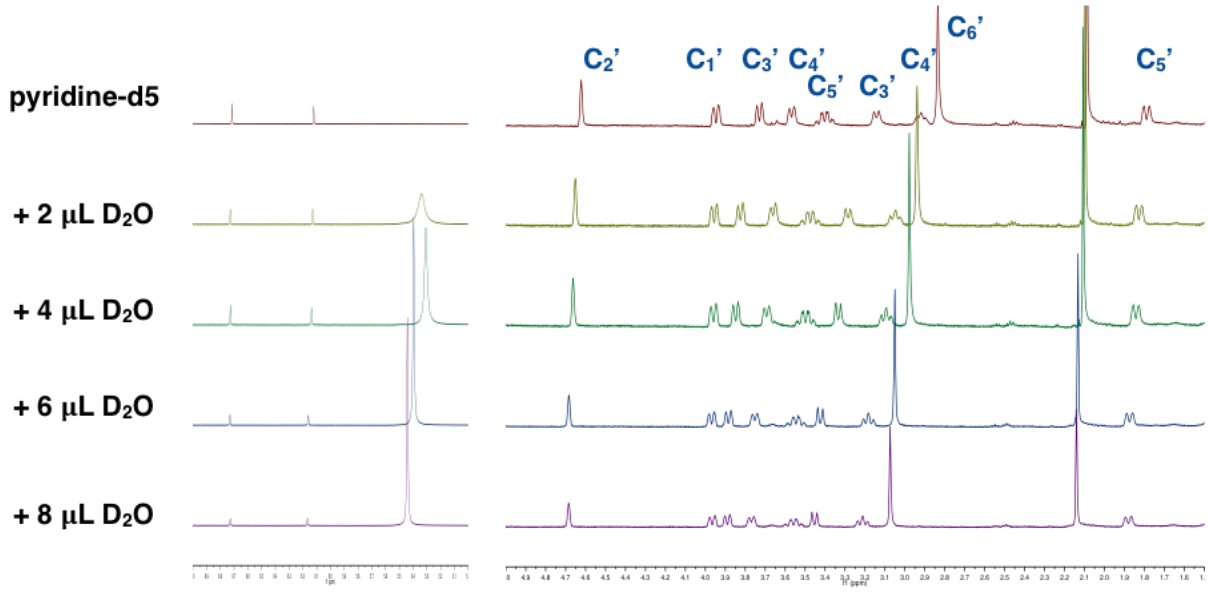
Figure 2.6 NMR Experiment: NaOD Titration of Dysoline (2.20)



In conjunction with the protonation status affecting the NMR spectra the amount of water in the NMR solvent was also observed to have an effect. This was determined by titration of D_2O

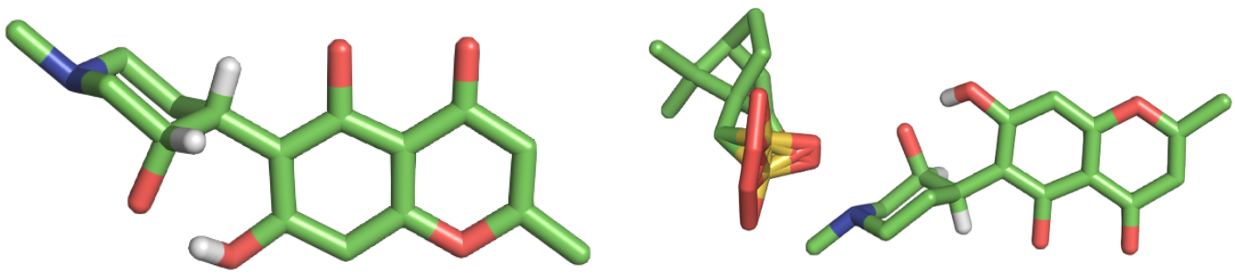
into a sample of the synthetic material, as the TFA salt, in pyridine-d5 (Figure 2.7). Consistent with the effect of D_2O on the ^1H NMR signals it is concluded that the isolation group instead isolated the HCl salt of the natural product and analysis was reported with wet pyridine-d_5.

Figure 2.7 NMR Experiment: D_2O Titration of Dysoline (2.20)



Further structural confirmation of the synthesized natural product was achieved by X-ray crystal structure (Figure 2.8). This material was crystalized with (-)-CSA allowing not only for determination of relative stereochemistry, but also assignment of absolute stereochemistry (1'R, 2'S). While the isolation group assigned the absolute stereochemistry based on that of rohitukine (**2.21**) no evidence was offered to support this assumption.

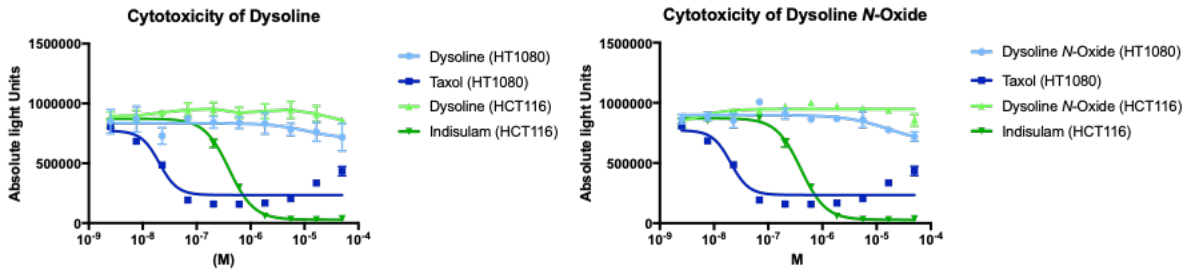
Figure 2.8 X ray Crystal Structure of (+) – Dysoline (2.20)



2.6 Biological Activity of Dysoline (2.20)

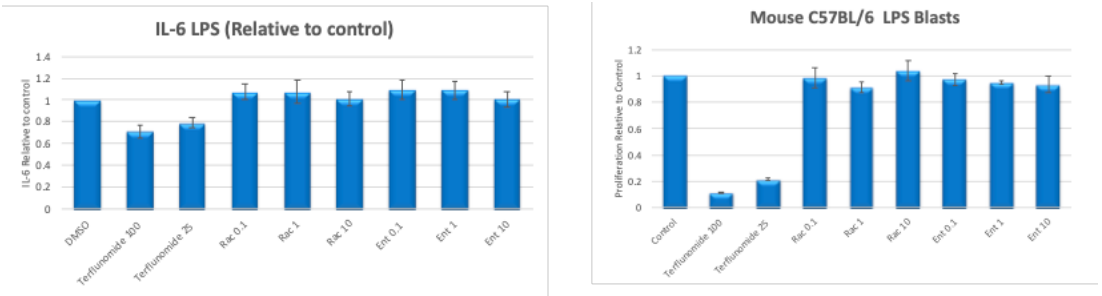
With the natural product in hand confirmation of the reported biological activity of dysoline (**2.20**) was attempted. Unfortunately, testing of both the optically active and racemic samples in cell cytotoxicity assays resulted in no activity for either the HT1080 or HCT116 cell lines (Figure 2.9). Additionally, dysoline-*N*-oxide (**2.340**) was tested with similar results observed.

Figure 2.9 Cytotoxicity Assay of Dysoline (2.20) and Dysoline-N-oxide (2.340)



Attempts to repeat the cytokine response activity reported by the isolation group also failed. Samples of the synthetic natural product were tested for the ability to modulate IL-6 cytokine response with no observed activity (Figure 2.10).

Figure 2.10 IL-6 Cytokine Response of Dysoline (2.20)



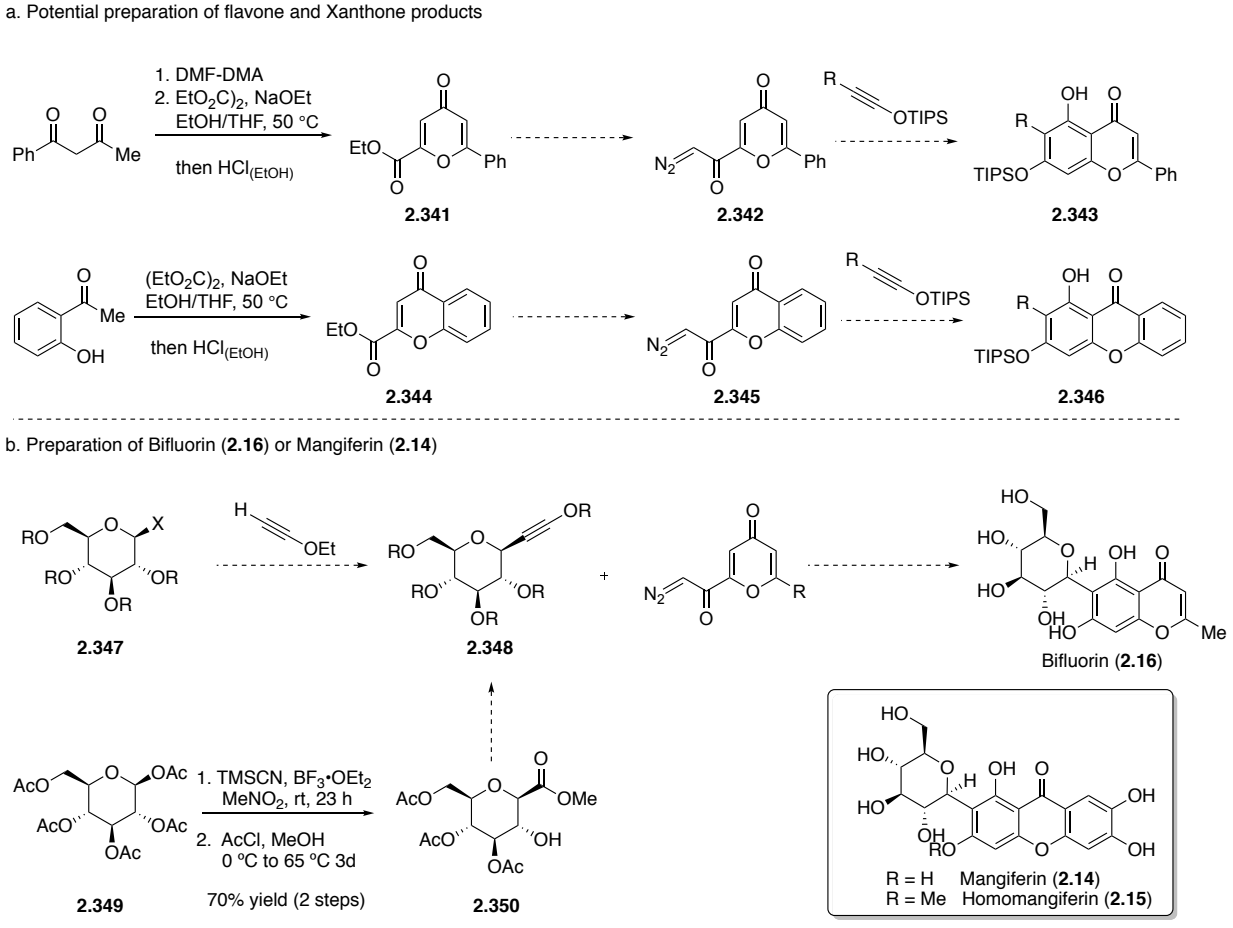
2.7 Conclusion and Future Direction

Despite the inability to reproduce the reported biological activity of dysoline (**2.20**) this natural product still holds potential. Given the validated scaffold of this natural product future screens against medicinally relevant targets might provide for potential use and development. To

this end the synthesized material will be submitted to the UT Southwestern compound collection for future use.

Moreover, this synthetic route to dysoline (**2.20**) offers a unique strategy for the preparation of C6 chromone alkaloids. An extension of this strategy would allow for the preparation of a variety of analogous scaffolds with similar substitution patterns, mainly flavone and xanthone containing products (Scheme 2.57a). This synthetic strategy also offers a potential route for the facile access of chromone, flavone and xanthone *C*-glycosides: such as bifluoroin (**2.16**) and mangiferin (**2.14**) (Scheme 2.57b)

Scheme 2.57 Future Potential for Synthetic Strategy



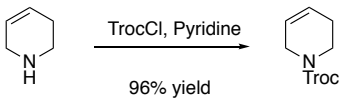
2.8 Experimental

2.8.1 General Information

Unless otherwise stated, reactions were performed under nitrogen in flame dried or oven dried glassware. Solvents were dried using solvent purification columns purchased from Glass Contour, Laguna Beach, CA. Chemicals were purchased from Sigma-Aldrich, Fisher, or TCI and were used without purification. 2,2,6,6-Tetramethyl piperidine (TMP) was distilled over calcium hydride prior to use, lithium bis(trimethylsilyl amide) (LHMDS) was purchased from Aldrich and titrated prior to use with 2-hydroxybenzaldehyde phenylhydrazone, *n*-BuLi and *sec*-BuLi were purchased from Aldrich and titrated prior to use with diphenyl acetic acid. All reactions were monitored by thin-layer chromatography with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). Flash chromatography was performed with indicated solvents using silica gel (particle size 0.032-0.063m) purchased from Sorbent Technologies. ^{1}H NMR chemical shifts were measured at 400 or 600 MHz, referenced based on trace amounts of the deuterated solvent: chloroform ($CDCl_3$), δ = 7.26, methanol (methanol-d_4), δ = 3.31, dimethylsulfoxide (DMSO-d_6), δ = 2.50, (Acetone-d_6), δ = 2.05, and reported in parts per million (ppm). coupling constants (*J*) are reported in Hertz (Hz) multiplicity reported as follows: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, p = pentet, dd = doublet of doublets, ddd = doublet of doublets of doublets, dt = doublet of triplets and m = multiplet. ^{13}C NMR chemical shifts were measured at 100 or 150 MHz, referenced based on trace amounts of the deuterated solvent: chloroform ($CDCl_3$), δ = 77.16, methanol (methanol-d_4), δ = 49.00, dimethylsulfoxide (DMSO-d_6), δ = 39.52, (Acetone-d_6), δ = 29.92, and reported in parts per million (ppm). Mass spectra were acquired on an Agilent technologies 1200 series LC/MS using acetonitrile and water with 0.1% formic acid as the mobile phase passing through a

c18 column and ionizing with an ESI probe. High resolution mass spectra were obtained by the UT Southwestern metabolomics core facility using a SCIEX TripleTOF® 6600 system. Optical rotation was measured on a Rudolph Research Analytical Autopol® IV Polarimeter at $\lambda = 589$ nm, unless otherwise noted. Enantiomeric excess was measured on a Shimadzu Prominence HPLC with an AD-H, OD-H, chiralpak 1A, or OJ- H column with IPA/hexanes, EtOH/MeOH, or MeOH as indicated.

2.8.2 Preparation of Ynol Ether 2.245 Route 1



2,2,2-trichloroethyl 3,6-dihydropyridine-1(2*H*)-carboxylate 2.270a: To a stirred solution of 1,2,3,6-tetrahydropyridine (0.454 ml, 5.0 mmol) in pyridine (20 mL) was added 2,2,2-trichloro ethyl chloroformate (0.808 mL, 6.0 mmol). This reaction was stirred at r.t. overnight at which point the pyridine was removed *in vacuo*. The resulting crude material was dissolved in EtOAc and water, then washed with NH_4Cl (sat.) followed by brine. The organic layer was collected and dried over Na_2SO_4 then concentrated *in vacuo* giving a crude red oil. This crude material was purified by running through a plug of silica gel and eluting with excess CH_2Cl_2. Removal of the solvent *in vacuo* gave the product as a clear oil (1.233g, 4.8 mmol, 96% yield).

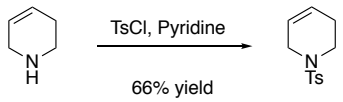
TLC: $R_f = 0.59$ (1:5 EtOAc/Hexanes) visualized with $KMnO_4$

LRMS: (ESI+) Calcd. For $C_8H_{10}Cl_3NO_2$ $[M+H]^+$ 258.0, found 258.0

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.89-5.83 (m, 1H), 5.71-5.68 (m, 1H), 4.76 (br s, 2H), 4.06-3.98 (m, 2H), 3.62 (dt, $J = 5.8$, $J = 20.5$ Hz, 2H), 2.19 (br s, 2H)

^{1}H NMR (400 MHz, DMSO-d_6, 70 °C) δ ppm 5.83 (m, 1H), 5.71 (m, 1H), 4.84 (s, 2H), 3.93 (d, $J = 32.1$ Hz, 2H), 3.52 (dt, $J = 34.1$, $J = 5.5$ Hz, 2H), 2.11 (s, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm (153.8, 153.5, rotamers), (125.5, 125.4, rotamers), (124.2, 123.7, rotamers), 95.8, (75.2, 75.1, rotamers), (44.0, 43.5, rotamers), (41.1, 40.8, rotamers), (25.3, 24.8, rotamers)

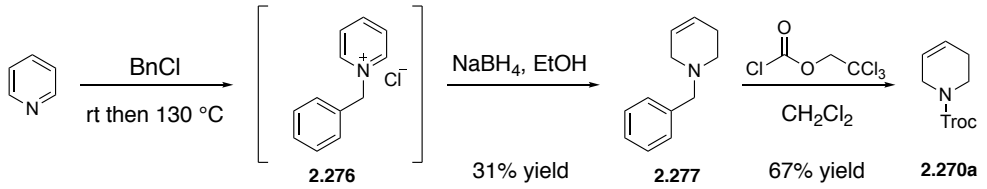


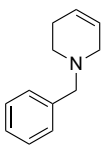
1-tosyl-1,2,3,6-tetrahydropyridine 2.270b: To a stirred solution of 1,2,3,6-tetrahydropyridine (0.454 ml, 5.0 mmol) in pyridine (20 mL) was added *p*-toluenesulfonyl chloride (1.049g, 5.5 mmol). This reaction was stirred at r.t. for 3 hours at which point they pyridine was removed *in vacuo*. The resulting crude material was dissolved in EtOAc and water then washed with HCl (1N), followed by brine. The organic layer was collected, dried over Na_2SO_4 then concentrated *in vacuo* giving a white solid. This solid could be recrystallized from MeOH to give pure product (0.793g, 3.3 mmol, 66% yield).

LRMS: data not obtained

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.67 (d, *J* = 8.26 Hz, 2H), 7.32 (d, *J* = 8.26 Hz, 2H), 5.78-5.72 (m, 1H), 5.63-5.58 (m, 1H), 3.58-3.56 (m, 2H), 3.17 (app t, *J* = 5.68 Hz, 2H), 2.43 (s, 3H), 2.24-2.18 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 143.6, 133.5, 129.7, 127.8, 125.2, 122.9, 44.9, 42.8, 25.4, 21.6





1-benzyl-1,2,3,6-tetrahydropyridine 2.277: Benzyl chloride (9.21 mL, 80 mmol) was added to pyridine (6.44 mL, 80 mmol) and the mixture was stirred neat for 12 hours at

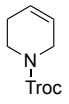
room temperature and then heated to 130 °C and stirred for 1 h. The reaction mixture was then cooled to rt forming a solid red product. The resulting material was dissolved in EtOH (60 mL), sonication was necessary to achieve complete dissolution, then cooled to 0 °C and solid $NaBH_4$ (3.93 g, 104 mmol) was added portion wise. The reaction was allowed to warm to rt and stirred for 6 hours at which point 15 mL of H_2O was added along with 1g of celite. After stirring for 10 hours (overnight) the reaction was filtered and the solvent was concentrated to 15 mL, removing EtOH. EtOAc was then added and the mixture was basified with 10% NaOH, the organic layer was collected and washed with brine then dried over Na_2SO_4 and concentrated *in vacuo* giving a crude red oil. This crude material was purified by vacuum distillation giving the product as a clear oil (4.2672g, 25 mmol, 31% yield).

TLC: R_f = 0.63 (streak, 1:1 EtOAc/Hexanes) visualized with UV and $KMnO_4$

LRMS: (ESI+) Calcd. For $C_{12}H_{15}N$ $[M+H]^+$ 174.1, found 174.1

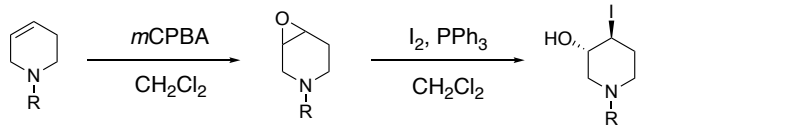
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.37-7.30 (m, 4H), 7.28-7.24 (m, 1H), 5.79-5.73 (m, 1H), 5.69-5.64 (m, 1H), 3.58 (s, 2H), 2.99-2.96 (m, 2H), 2.56 (t, *J* = 5.7 Hz, 2H), 2.20-2.14 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 138.4, 129.2, 128.2, 127.0, 125.4, 125.2, 63.0, 52.8, 49.6, 26.2



2,2,2-trichloroethyl 3,6-dihydropyridine-1(2*H*)-carboxylate 2.270a, Method 2: To a stirred solution of 1,2,3,6-tetrahydro pyridine (0.454 mL, 5 mmol) in pyridine (10 mL) was added 2,2,2-trichloro ethyl chloroformate (0.808 mL, 6 mmol). This reaction was stirred at rt overnight at which point the pyridine was removed *in vacuo*. The resulting crude material was then dissolved in ethyl acetate and washed with NH_4Cl (Sat.) followed by brine. The organic layer was collected, dried over Na_2SO_4 then concentrated in vacuo giving a red oil. This crude material

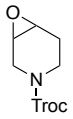
was purified by running through a short plug of silica eluting with excess CH_2Cl_2 giving the product as a clear oil (1.233g, 4.8 mmol, 96% yield)



2.271a: R = Troc 98% yield
2.271b: R = Ts 86% yield

2.278a: R = Troc 69% yield
2.278b: R = Ts 43% yield

General epoxidation procedure: To a stirred solution of the *N*-protected 3,6-dihydropyridine (4.8 mmol) in CH_2Cl_2 (25 mL) was added solid *m*-CPBA (1.398g, 6.24 mmol) portion wise. This reaction was then stirred at room temperature for 2 days at which point it was diluted with CH_2Cl_2. The organic layer was washed with $Na_2S_2O_3$ (sat.), NaOH (10%) 2x, the organic layer was collected washed with brine dried over Na_2SO_4 and concentrated *in vacuo* giving the desired product which required no further purification.



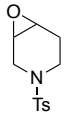
2,2,2-trichloroethyl 7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate 2.271a: prepared using general method, isolated as a clear oil (1.142g, 4.2 mmol, 88% yield)

TLC: R_f = 0.0.23 (streak, 1:5 EtOAc/Hexanes) visualized with $KMnO_4$

LRMS: (ESI+) Calcd. For $C_8H_{10}Cl_3NO_3$ $[M+H]^+$ 274.0, found 274.0

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.81-4.76 (m, 1H), 4.71-4.66 (m, 1H), 3.99 (dt, *J* = 4.2, *J* = 15.1 Hz, 1H), 3.90-3.78 (m, 1H), 3.59-3.54 (m, 1H), 3.33-3.30 (m, 1H), 3.29-3.22 (m, 2H), 2.17-2.09 (m, 1H), 2.02-1.94 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm (153.8, 153.7, rotamers), 95.7, (75.3, 75.2, rotamers), (50.7, 50.6, rotamers), (50.3, 50.0, rotamers), (43.0, 42.5, rotamers), 38.0, 37.8, rotamers), 24.6, 24.3, rotamers)



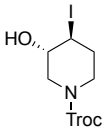
3-tosyl-7-oxa-3-azabicyclo[4.1.0]heptane 2.271b: prepared using general method, isolated as a white solid (0.724g, 2.9 mmol, 88% yield)

LRMS: data not obtained

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.63 (d, *J* = 8.41 Hz, 2H), 7.31 (d, *J* = 8.41 Hz, 2H), 3.85 (dd, *J* = 13.85, *J* = 3.91 Hz, 1H), 3.36 (dt, *J* = 12.01, *J* = 4.51 Hz, 1H), 3.29-3.25 (m, 2H), 3.08 (d, *J* = 13.24 Hz, 1H), 2.58-2.51 (m, 1H), 2.43 (s, 3H), 2.12-2.08 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 143.9, 133.3, 129.8, 127.7, 50.5, 49.9, 44.3, 39.3, 25.4, 21.7

General epoxide opening procedure: To a stirred solution of triphenyl phosphine (912mg, 3.48 mmol) in CH_2Cl_2 (5mL) was added Iodine (442mg, 3.48 mmol) followed by a solution of *N*-protected-3,4-epxoypiperdine, this reaction was stirred at rt for 24 hours at which point additional triphenyl phosphine (456mg, 1.7 mmol) and Iodine (221mg, 1.7 mmol) was added and the reaction stirred an additional 6 hours at rt. Upon completion the reaction was diluted with $CHCl_3$ and washed with $NaHCO_3$ (sat.) followed by $Na_2S_2O_3$ (sat.), water and brine. The organic layer was collected dried over Na_2SO_4 then concentrated *in vacuo* giving the crude product. The crude material was purified by silica gel chromatography.

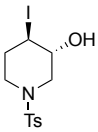


2,2,2-trichloroethyl-3-hydroxy-4-iodopiperidine-1-carboxylate 2.278a: prepared using general method, purified by silica gel chromatography (1:5 to1:4 EtOAc/Hexanes) product isolated as a white solid (1.174g, 2.9 mmol, 69% yield).

LRMS: data not obtained

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.75-5.74 (m, 1H), 4.86-4.76 (m, 2H), 4.10 (td, *J* = 4.6, *J* = 9.8 Hz, 1H), 4.03-3.92 (m, 1H), 3.63 (t, J = 15.1 Hz, 1H), 2.39-2.31 (m, 1H), 2.03-1.92 (m, 1H)

^{13}C NMR (100 MHz, DMSO-d_6, 80 °C) δ ppm 153.3, 96.5, 74.5, 71.5, 50.0, 45.2, 36.5, 35.8

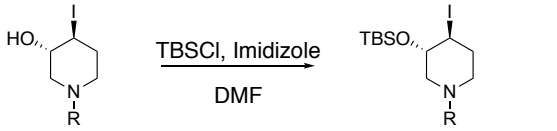


4-iodo-1-tosylpiperidin-3-ol 2.278b: prepared using general method, purified by silica gel chromatography (1:5 to 1:3 EtOAc/Hexanes) product isolated as a white solid (0.289g, 1.2 mmol, 41% yield).

LRMS: data not obtained

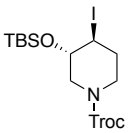
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.65 (d, J = 8.06 Hz, 2H), 7.34 (d, J = 7.97 Hz, 2H), 3.94-3.86 (m, 2H), 3.85-3.80 (m, 1H), 3.39-3.34 (m, 1H), 2.60 (t, J = 10.9 Hz, 1H), 2.54-2.50 (m, 2H), 2.45 (s, 3H), 2.42-2.37 (m, 1H), 2.30-2.20 (m, 1H)

^{13}C NMR (100 MHz, Acetone-d_6) δ ppm 144.7, 134.5, 130.7, 128.6, (72.8, 72.7, rotamers), 52.5, 47.8, 37.0, (34.1, 34.0, rotamers), 21.5



2.279a: R = Troc 86% yield
2.279b: R = Ts 50% yield

General TBS protection procedure: To a 0 °C stirred solution of imidazole (62 mg, 0.91 mmol) and *N*-protected-3-hydroxy-4-iodo piperdine (0.41 mmol) in CH_2Cl_2 (5 mL) was added TBSCl (68mg, 0.45 mmol) portion wise. The reaction was allowed to slowly warm to rt and stirred for 18 hours at which point complete consumption of starting material was observed by TLC. The reaction mixture was then diluted with CH_2Cl_2 and washed with water and brine, dried over Na_2SO_4 then concentrated *in vacuo* giving the crude product which was then purified by silica gel chromatography.

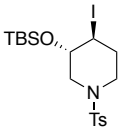


***N*-Troc-3-OTBS-4-iodopiperidine-1-carboxylate 2.279a**: prepared using general method, purified by silica gel chromatography (1:10 EtOAc/Hexanes) product isolated as a yellow oil (0.620g, 1.2 mmol, 86% yield).

LRMS: data not obtained

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.93-4.74 (m, 2H), 4.20-4.15 (m, 1H), 4.11-3.92 (m, 1H), 3.74-3.69 (m, 1H), 3.65-3.60 (m, 1H), 3.24-2.96 (m, 2H), 2.38-2.33 (m, 1H), 2.07-1.98 (m, 1H), 0.89 (s, 9H), 0.17-0.15 (m, 3H), 0.11 (s, 3H)

^{13}C NMR (100 MHz, DMSO-d_6) δ ppm (152.9, 152.5, rotamers), (95.9, 95.8, rotamers), (74.3, 74.2, rotamers), (72.7, 72.1, rotamers), (49.5, 49.3, rotamers), (44.6, 44.2, rotamers), (35.9, 35.5, rotamers), (34.6, 34.3, rotamers), (25.8, 25.7, rotamers), 17.7, (-4.9, -4.5, rotamers)



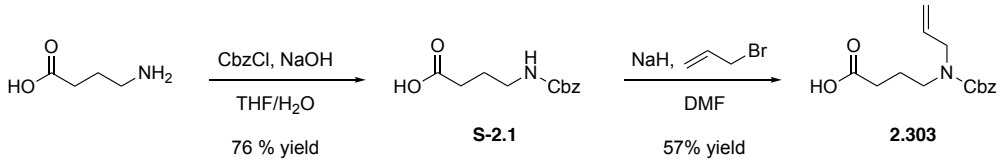
3-((*tert*-butyldimethylsilyl)oxy)-4-iodo-1-tosylpiperidine 2.279b: prepared using general method, purified by silica gel chromatography (1:10 to 1:5 EtOAc/Hexanes) product isolated as a yellow oil (0.125g, 0.25 mmol, 50% yield)

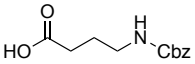
LRMS: data not obtained

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.63 (d, J = 8.09 Hz, 2H), 7.33 (d, J = 8.09 Hz, 2H), 3.85-3.75 (m, 2H), 3.74-3.69 (m, 1H), 3.41-3.35 (m, 1H), 2.50 (dt, J = 11.32, J = 2.89 Hz, 1H), 2.44 (s, 3H), 2.42-2.36 (m, 2H), 2.26-2.16 (m, 1H), 0.90 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 143.9, 133.7, 129.9, 127.6, 72.7, 51.6, 46.7, 35.5, 32.4, (26.0, 25.8, rotamers), 21.7, 18.2, (-4.1, -4.3, rotamers)

2.8.3 Preparation of Ynol Ether 2.245 Route 2





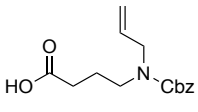
***N*-Cbz-4-aminobutanoic acid S-2.1:** To a 0 °C stirred solution of 4-amino butanoic acid (5.155 g, 50 mmol) in NaOH (3 M, 30 mL) was added a solution of benzyl

chloroformate (8.565 mL, 60 mmol) in THF (20 mL). This reaction was stirred at 0 °C for 30 min then warmed to rt and stirred for 3 hrs. The reaction mixture was washed with CH_2Cl_2 (100 mL) and the aqueous layer was collected cooled to 0 °C and acidified with concentrated HCl, causing formation of a white precipitate. This mixture was then extracted with EtOAc, the organic layer was collected washed with brine then dried over Na_2SO_4 and concentrated *in vacuo* giving a white solid (8.918 g, 30 mmol, 76% yield). Analytical data corresponds to literature reports.[96]

HRMS (ESI+) Calcd. For $C_{12}H_{15}NO_4$ $[M+H]^+$ 238.1079, found 238.1074

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.37-7.27 (m, 5H), 5.11 (s, 2H), 4.91 (br s, 11H), 3.29-3.22 (m, 2H), 2.39 (t, *J* = 7.15 Hz, 2H), 1.88-1.81 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 178.2, 156.7, 136.5, 128.7, 128.3, 128.2, 67.4, 40.4, 31.2, 25.1



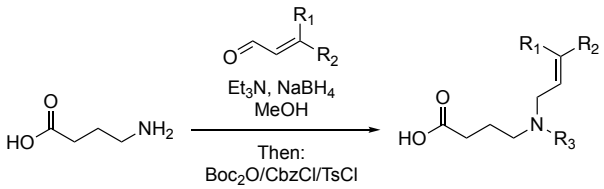
***N*-Allyl-*N*-Cbz-4-aminobutanoic acid 2.303:** To a 0 °C stirred suspension of sodium hydride (0.440 g, 11 mmol, 60% dispersion in mineral oil) in DMF (8 mL) was added a solution of 4-(((benzyloxy)carbonyl)amino)butanoic acid (723 mg, 3 mmol) in DMF (2 mL). This mixture was stirred at 0 °C until gas evolution ceased, about 10 min, at which point allyl bromide (0.312 mL, 3.6 mmol) was added. The reaction continued to stir at 0 °C for 1 hour until complete conversion to the desired product was observed by LCMS. The reaction was allowed to slowly warm to rt and stirred overnight at which point it was diluted with CH_2Cl_2 and brought to an acidic pH = 3 with 1 *N* HCl. The organic layer was collected, washed with brine then dried over Na_2SO_4 and concentrated giving a clear oil. This material was purified by silica gel chromatography (1:2 to 1:1 EtOAc/Hexanes). The product was obtained as a clear oil (0.479 g, 1.7 mmol, 57 % yield). Analytical data corresponds to literature reports.[97]

TLC: R_f = 0.37 (1:1 EtOAc/Hexanes) visualized by UV and $KMnO_4$

HRMS (ESI+) Calcd. For $C_{15}H_{19}NO_4$ $[M+H]^+$ 278.3280, found 278.1388

^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ ppm 7.37-7.28 (m, 5H), 5.84-5.74 (m, 1H), 5.17-5.10 (m, 2H), 5.15 (s, 2H), 3.90 (d, *J* = 5.63 Hz, 2H), 3.34 (t, *J* = 7.17 Hz, 2H), 2.35 (t, *J* = 7.08 Hz, 2H), 1.92-1.85 (m, 2H)

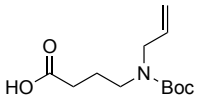
^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ ppm 177.4, 156.5, 137.0, 133.9, 128.6, 128.1, 128.0, 117.2, 67.5, 50.0, 31.2, 23.6



R_1	R_2	R_3	Compound	Yield (%)
H	H	Boc	**3.304a**	10
H	Me	Boc	**3.304b**	45
Me	Me	Boc	**3.304c**	55
H	Ph	Boc	**3.304d**	73
H	Ph	Ts	**S-2.2**	47
Me	Me	Cbz	**S-2.3**	34

General procedure for enamine formation: To a 0 °C stirred suspension of 4-amino butenoic acid (1 equiv) in CH_2Cl_2/MeOH (1:1, 0.5 M) was added Et_3N (3 equiv) followed by the desired aldehyde (2.2 equiv). This reaction was stirred at 0 °C for 30 min (imine formation time varied based on the aldehyde as specified for each substrate) at which point $NaBH_4$ (2.2 equiv) was added portion wise, with gas evolution. This mixture was stirred at 0 °C for 30 min then allowed to warm to rt and stirred for 2 hours. Boc_2O or TsCl (solid/liquid, 1.5 equiv) was then added, causing precipitate formation. The resulting heterogeneous solution was stirred overnight and was then diluted with CH_2Cl_2 and slowly brought to pH = 3 with 1 *N* HCl. The organic layer

was collected, and the aqueous layer was further extracted with CH_2Cl_2, the organic layers were combined washed with brine, dried over Na_2SO_4 then concentrated *in vacuo*. The resulting crude material was purified by silica gel chromatography.



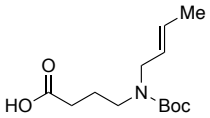
***N*-Boc-*N*-allyl-4-aminobutanoic acid 3.304a:** Reaction stirred at 0 °C for 30 min after addition of acrolein before $NaBH_4$ was added. Crude material was purified by silica gel chromatography (1:4 EtOAc/Hexanes) Isolated the product as a clear oil (0.243 g, 1 mmol, 10% yield)

TLC: R_f = 0.34 (streak, 1:1 EtOAc/Hexanes) visualized with $KMnO_4$

LRMS: (ESI+) Calcd. For $C_{12}H_{21}NO_4$ $[M+H]^+$ 244.1, found 244.1

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.81-5.71 (m, 1H), 5.13-5.08 (m, 2H), 3.82 (br s, 2H), 3.24 (br s, 2H), 2.35 (t, *J* = 7.12 Hz, 2H), 1.87-1.80 (m, 2H), 1.44 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 177.4, 155.9, 134.3, 116.6, 80.1, 49.9, 46.0, 31.4, 28.6, 23.8



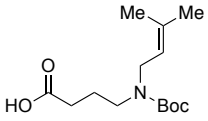
***N*-Boc-*N*-crotyl-4-aminobutanoic acid 3.304b:** Started with a mixture of Cis/Trans crotonaldehyde (1:20) as described by Aldrich. Reaction stirred at 0 °C for 30 min after addition of crotonaldehyde before $NaBH_4$ was added. Crude material was purified by silica gel chromatography (1:4 EtOAc/Hexanes) Isolated the product as a clear oil (1.165 g, 4.5 mmol, 45% yield)

TLC: R_f = 0.49 (streak, 1:1 EtOAc/Hexanes) visualized with $KMnO_4$

LRMS: (ESI+) Calcd. For $C_{13}H_{23}NO_4$ $[M+H]^+$ 258. 2, found 258.2

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.59-5.50 (m, 1H), 5.43-5.35 (m, 1H), 3.74-3.66 (m, 2H), 3.21 (br s, 2H), 2.34 (t, *J* = 7.25 Hz, 2H), 1.85-1.78 (m, 2H), 1.67 (dd, *J* = 1.13, *J* = 6.43 Hz, 3H), 1.44 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 178.6 (br), 155.9 (br), 128.3, 126.7, 79.9, (49.2, 48.5, rotamers), 45.3, 31.4 (br), 28.5, 23.4, 17.8



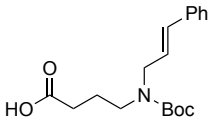
***N*-Boc-*N*-(3-methylbut-2-en-1-yl)-4-aminobutanoic acid 3.304c:** Reaction stirred at 0 °C for 30 min after addition of acrolein before $NaBH_4$ was added. Crude material was purified by silica gel chromatography (1:4 EtOAc/Hexanes) the product was isolated as a clear oil (2.989 g 11 mmol, 55% yield)

TLC: R_f = 0.51 (streak, 1:1 EtOAc/Hexanes) visualized with $KMnO_4$

HRMS (ESI+) Calcd. For $C_{14}H_{25}NO_4$ $[M+H]^+$ 272.1862, found 272.1858

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.14 (t, *J* = 6.75 Hz, 1H), 3.80 (Br S, 2H), 3.22 (Br S, 2H), 2.39 (t, *J* = 7.20 Hz, 2H), 1.84 (p, *J* = 7.16 Hz, 2H), 1.71 (s, 3H), 1.65 (s, 3H), 1.45 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 179.1 (br), 156.0 (br), 120.8, 79.9, 45.3, (44.7, 44.1, rotamers), 31.7, 28.6, 25.8, 23.4, 17.8



***N*-Boc-*N*-cinnamyl-4-aminobutanoic acid 3.304d:** Reaction stirred at 0 °C for 30 min then warmed to rt and stirred for 3 hours after addition of cinnamaldehyde before $NaBH_4$ was added. The crude reaction mixture was purified by silica gel chromatography (1:4 to 1:1 EtOAc/Hexanes +0.1 % AcOH) giving the desired product as a clear oil (8.496 g of a mixture of product and cinnamyl alcohol (2:1 respectively) 22 mmol of product,

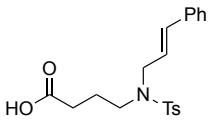
73% yield). Product to cinnamyl alcohol ratio was determined by NMR integration in this way 8.496 g of a mixture represented 7.021g, 22 mmol, of product and 1.475g, 11 mmol, of cinnamyl alcohol. This mixture could be taken directly to the next step with no consequences on that reaction, with subsequent purification allowing for removal of cinnamyl alcohol. Additionally this reaction could be further purified by PTLC in order to obtain pure product, however significant loss of material is observed.

TLC: R_f = 0.36 (streak, 1:1 EtOAC/Hexanes), visualized by UV

HRMS (ESI+) Calcd. For $C_{14}H_{17}NO_4$ (-*t*-Bu) $[M+H]^+$ 264.1236, found 264.1239

^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ ppm 7.37-7.28 (m, 4H), 7.25-7.21 (m, 1H), 6.47 (d, *J* = 15.97 Hz, 1H), 6.14 (dt, *J* = 6.21, *J* = 15.83 Hz, 1H), 3.98 (d, *J* = 6.07 Hz, 2H), 3.32 (t, *J* = 6.97 Hz, 2H), 2.38 (t, *J* = 7.20 Hz, 2H), 1.93-1.86 (m, 2H), 1.49 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ ppm 176.9 (br), 156.0 (br), 137.0, 132.4, 128.8, 127.7, 126.6, 125.7, 80.2, 49.4, 45.9 (br), 31.3, 28.7, 23.8



***N*-Cinnamyl-*N*-Ts-4-aminobutanoic acid S-2.2:** The crude reaction mixture was purified by silica gel chromatography (1:4 to 1:1 EtOAc/Hexanes +0.1 % AcOH) giving the desired product as white solid (1.7435 g, 4.7 mmol, 47% yield)

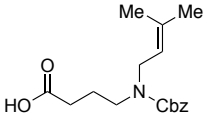
TLC: R_f = 0.18 (streak, 1:1 EtOAc/Hexanes) visualized by UV

HRMS (ESI+) Calcd. For $C_{20}H_{23}NO_4S$ $[M+H]^+$ 374.1426, found 374.1418

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.71 (d, *J* = 8.40 Hz, 2H), 7.30 (d, *J* = 8.40 Hz, 2H), 7.28-7.22 (m, 5H), 6.44 (d, *J* = 15.98 Hz, 1H), 5.92 (dt, *J* = 6.85, *J* = 15.80 Hz, 1H), 3.95 (d, *J* = 6.80

Hz, 2H), 3.22 (t, *J* = 7.06, 2H), 2.44-2.40 (m, 2H), 2.42 (s, 3H), 1.88 (appt. quintet, *J* = 7.06 Hz, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 177.6, 143.5, 137.0, 136.2, 134.3, 129.9, 128.7, 128.1, 127.4, 126.6, 123.9, 50.5, 46.5, 30.6, 23.4, 21.6

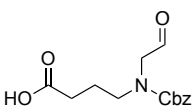


***N*-Cbz-*N*-cinnamyl-4-aminobutanoic acid S-2.3:** A slightly modified procedure was used: To a 0 °C stirred suspension of 4-amino butenoic acid (2.06 g, 20 mmol) in MeOH (30 mL) was added 3-methyl-2-butenol (3.74 mL, 20 mmol). This reaction was stirred at 0 °C for 30 min at which point $NaBH_4$ (1.663 g, 44 mmol) was added portion wise. This mixture was stirred at 0 °C for 30 min and then allowed to warm to rt and stirred for 2 hours. The solvent was then removed *in vacuo* giving a white solid. This solid was dissolved in a THF (30 mL)/NaOH (30 mL, 2 N) biphasic mixture at 0 °C and benzylchloroformate (6.281 mL, 44 mmol) was added dropwise. The reaction was allowed to slowly warm to rt and stirred overnight at which point it was diluted with CH_2Cl_2 and brought to pH = 3 with 1 *N* HCl. The organic layer was collected, and the aqueous layer was further extracted with CH_2Cl_2, the organic layers were combined washed with brine, dried over Na_2SO_4 then concentrated *in vacuo*. The resulting crude material was purified by silica gel chromatography (1:2 EtOAc/Hexanes) the product was isolated as a clear oil (2.0715 g, 6.8 mmol, 34% yield)

TLC: R_f = 0.62 (streak, 1:1 EtOAC/Hexanes) visualized by UV and $KMnO_4$

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.37-7.28 (m, 5H), 5.19-5.11 (m, 1H), 5.13 (s, 2H), 3.91-3.83 (m, 2H), 3.32-3.25 (m, 2H), 2.39-2.30 (m, 2H), 1.89-1.82 (m, 2H), [1.71, 1.59 (s, 6H, mixture of rotomers)]

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 178.8, 156.4, 136.8, (136.0, 135.6, rotamers), 128.6, (128.0, 127.9, rotamers), (120.3, 120.2, rotamers), 67.3, (46.1, 45.3, rotamers), 44.8, (31.4, 31.3, rotamers), 25.9, (23.4, 23.2, rotamers), 17.9



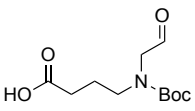
***N*-Cbz-*N*-(2-oxoethyl)-4-aminobutanoic acid 2.273a:** This material was purified by silica gel chromatography (1:1 to 4:1 EtOAc/Hexanes). Fractions containing product were combined and the solvent was removed giving the desired product as a clear oil (0.645 g, 2.3 mmol, 77% yield). Analytical data corresponds to literature reports.[97]

TLC: R_f = 0.29 (1:1 EtOAc/Hexanes) visualized by UV and $KMnO_4$

HRMS (ESI+) Calcd. For $C_{14}H_{17}NO_5$ $[M+H]^+$ 280.1185, found 280.1177

^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ ppm 9.58 (S, 1H), 7.37-7.27 (m, 5H), 5.15 (br s, 2H), 4.02 (s, 2H), 3.42 (t, *J* = 7.08 Hz, 2H), 2.39 (br s, 2H), 1.86 (quintet, *J* = 7.34 Hz, 2H)

^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ ppm 197.4, 176.8, 136.2, 128.5, 128.1, 127.9, 67.8, 57.5, 47.8, 30.6, 23.4, 14.1



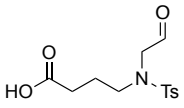
***N*-Boc-*N*-(2-oxoethyl)-4-aminobutanoic acid 2.273b:** This material was purified by silica gel chromatography (1:1 EtOAc/Hexanes). Fractions containing product were combined and the solvent was removed giving the desired product as a clear oil (3.3946 g, 14 mmol, 82% yield)

TLC: R_f = 0.25 (1:1 EtOAc/Hexane) visualized by UV and $KMnO_4$

HRMS (ESI+) Calcd. For $C_7H_{11}NO_5$ (-*t*-Bu) $[M+H]^+$ 190.0715, found 190.0708

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.57 (s, 1H), 3.97 (s, 1H), 3.88 (s, 1H) 3.38-3.29 (m, 2H), 2.41-2.32 (m, 2H), 1.85-1.78 (m, 2H) 1.48, 1.40 (s (rotamers), 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm all ^{13}C peaks are doubled due to rotamers (198.7, 198.6), (178.6, 178.5), (156.0, 155.4), (81.3, 81.1), (57.8, 57.4), (48.0, 47.8), (31.1, 30.9), (26.4, 26.3), (23.6,23.5)



***N*-Ts-*N*-(2-oxoethyl)-4-aminobutanoic acid 2.273c:** This material was purified by silica gel chromatography (1:1 to 3:1 EtOAc/Hexanes). Fractions containing product were combined and the solvent was removed giving the desired product as a clear oil which solidified to a white solid upon standing (0.880 g, 2.9 mmol, 73% yield)

HRMS (ESI+) Calcd. For $C_{13}H_{17}NO_5S$ $[M+H]^+$ 300.0906, found 300.0904

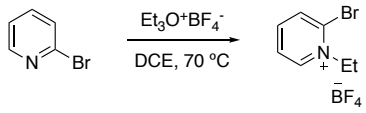
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.61 (t, J = 1.37 Hz, 1H), 7.68 (d, J = 8.25 Hz, 2H), 7.33 (d, J = 8.25 Hz, 2H), 3.84 (d, J = 1.31 Hz, 2H), 3.22 (t, J = 7.19 Hz, 2H), 2.47 (t, J = 7.07 Hz, 2H), 2.44 (s, 3H), 1.84 (appt. quintet, J = 7.08 Hz, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 198.0, 177.4, 144.3, 135.4, 130.1, 127.5, 57.3, 49.0, 30.4, 23.2, 21.7

2.8.3.1 Nucleophile Catalyzed Aldol Lactonization (NCAL)

OAc-Quinine and OTms-Quinine were prepared from commercially available Quinine following literature procedure.[98] The dimers $(DHQD)_2$Phal, $(DHQD)_2$Pyr and $(DHQD)_2$AQN were purchased commercially and used as is.

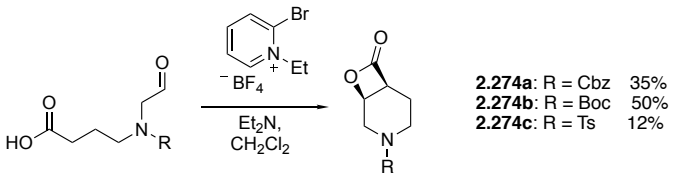
Mukaiyama's reagent (*N*-methyl-2-chloropyridinium iodide) was obtained commercially. *N*-ethyl/methyl-2-bromopyridinium salts (BF_4 or $SbCl_6$ were prepared following literature procedure (procedure detailed below).[99] *N*-Propyl-2-bromopyridinium triflate was prepared following the procedure of Romo et al.[82]



***N*-Ethyl-2-bromopyridinium tetrafluoroborate 2.307a**: To a stirred solution of triethyl oxonium tetrafluoroborate in 1,2-dichloro ethane was added 2-bromo pyridine. This mixture was heated to 70 °C and stirred at temperature for 15 hours, overnight. The reaction was then cooled to rt, transferred to an Erlenmeyer flask and 50 mL of Et_2O was added causing precipitate formation. The resulting mixture was cooled to -20 °C for a few hours then filtered to collect the product as a white solid. This product could be further purified by crystallization from acetone and Et_2O. Analytical data corresponds to literature reports.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (dd, J = 1.49, J = 6.11 Hz, 1H), 8.51 (dd, J = 1.29, J = 8.25 Hz, 1H), 8.44 (dt, J = 1.70, J = 7.85 Hz, 1H), 8.14 (dt, J = 1.53, J = 6.80 Hz, 1H), 4.75 (q, J = 7.3 Hz, 2H), 1.51 (t, J = 7.10 Hz, 3H)

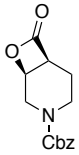
^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 147.7, 146.2, 138.0, 134.2, 127.2, 58.2, 14.8



General procedure for NCAL reaction: The procedure established by Romo *et al*. was followed with some slight modification.[80] To a stirred solution of pyridinium salt (1.5 equiv) in CH_2Cl_2 (0.13 M in relation to acid aldehyde) was added Et_3N (4 equiv) the desired amine catalyst (0.2

equiv) followed by the slow addition, via syringe pump over 12 hours, of the acid aldehyde (1 equiv) in CH_2Cl_2 (0.5 M, in relation to acid aldehyde). Upon complete addition of the acid aldehyde the reaction was stirred at rt for 24 hours. The reaction was then diluted with CH_2Cl_2 and washed with NH_4Cl (sat.) followed by brine. The organic layer was collected, dried over Na_2SO_4 then concentrated *in vacuo.* The resulting crude material was purified by silica gel chromatography. Dry loading of the crude material onto silica was found to be important to achieve good separation.

Et_3N was replaced with *i*-Pr_2NEt (4 equiv) for the enantioselective variant. Additionally, it was found that slightly better yields could be obtained when the total stir time post acid aldehyde addition was increase to 72 h.



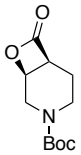
***N*-Cbz-8-oxa-3-azabicyclo[4.2.0]octan-7-one 2.274a** : [100] purified by silica gel chromatography (1:10 to 1:5 EtOAC/Hexanes). Fractions containing product were collected and the solvent was removed *in vacuo* giving a yellow oil (0.147 g, 0.48 mmol, 21% yield)

TLC: R_f = 0.27 (1:1) EtOAc/Hexanes) visualized with $KMnO_4$

HRMS (ESI+) Calcd. For $C_{14}H_{15}NO_4$ $[M+H]^+$ 262.1079, found 262.1084

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.38-7.29 (m, 5H), 5.21-5.09 (m, 2H), 4.82, 4.75 (d, *J* = 5.92 Hz, 1H, rotamers), 4.46, 4.35 (d, *J* = 15.60 Hz, 1H, rotamers), 3.87-3.84 (m, 1H), 3.74-3.65 (m, 1H), 3.52 (dt, *J* = 3.68, *J* = 13.11 Hz 1H), 3.42, 3.39 (d, *J* = 16.12, 1H, rotamers), 2.21-2.07 (m, 1H), 2.04-1.92 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm (169.7, 169.6) rotamers, (156.3, 155.8) rotamers, 136.4, 128.6, 128.2, (128.1, 128.0) rotamers, (69.2, 68.8) rotamers, 67.6, 47.6, (42.0, 41.6) rotamers, (40.0, 39.9) rotamers, 29.8, (19.8, 19.7) rotamers.



***N*-Boc-8-oxa-3-azabicyclo[4.2.0]octan-7-one 2.274b:**

Optimized raceimic conditions: To a stirred solution of pyridinium salt (6.110 g, 23 mmol) in CH_2Cl_2 (90 mL) was added quinuclidine (0.489 g, 4.5 mmol, 0.3 equiv) and Et_3N (8.42 mL, 60.4 mmol) followed by a solution of *N*-Boc-*N*-(2-oxoethyl)-4-aminobutanoic acid **9a** (3.696 g, 15.1 mmol) in CH_2Cl_2 (40 mL) dropwise via syringe pump over 12 hours. Upon complete addition of the acid aldehyde solution the reaction was stirred at rt for 24 hours at which point it was diluted with CH_2Cl_2 and washed with NH_4Cl (sat.) then brine, dried over Na_2SO_4 and concentrated *in vacuo* giving a crude red oil. This material was purified by silica gel chromatography (1:5 EtOAc/Hexanes). The product was isolated as a white solid (1.725 g, 7.6 mmol, 51% yield)

Optimized enantioselective conditions: To a stirred solution of *N*-Ethyl-2-bromopyridinium tetrafluoroborate **12** (3.276 g, 12 mmol) in CH_2Cl_2 (30 mL) was added solid $(DHQD)_2Phal$ (0.623 g, 0.8 mmol, 0.1 equiv) and *i*-Pr_2NEt (5.576 mL, 32 mmol) followed by a solution of *N*-Boc-*N*-(2-oxoethyl)-4-aminobutanoic acid **9a** (1.96 g, 8.0 mmol) in CH_2Cl_2 (10 mL) dropwise via syringe pump over 5 hours. Upon complete addition the reaction was stirred for 72 hours at which point it was diluted with CH_2Cl_2 and washed with NH_4Cl (sat.) then brine, dried over Na_2SO_4 and concentrated *in vacuo* giving a crude red oil. This material was purified by silica gel

chromatography (1:5 EtOAc/Hexanes). The product was isolated as a white solid (0.613 g, 2.7 mmol, 34% yield)

Optical purity was determined following opening of the lactone with benzylamine as described below.

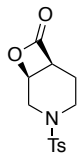
$[\alpha]_D^{23.1}$ 102.390 (*c* 1.0, CH_2Cl_2)

TLC: R_f = 0.44 (1:1) EtOAc/Hexanes) visualized with $KMnO_4$

HRMS (ESI+) Calcd. For $C_7H_9NO_4$ (-*t*-Bu) $[M+H]^+$ 172.0610, found 172.0607

^{1}H NMR (400 MHz, DMSO-d_6, 80 °C) δ ppm 4.85 (dt, *J* = 2.21, *J* = 6.28 Hz, 1H), 4.14 (dd, *J* = 2.35, *J* = 15.50 Hz, 1H), 3.96 (dd, *J* = 4.75, *J* = 10.46 Hz, 1H), 3.43-3.29 (m, 3H), 1.98-1.93 (m, 2H), 1.42 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$, rt) δ ppm (170.0, 169.8, rotamers), (1.55.6, 155.1, rotamers), 80.4, (69.4, 69.1, rotamers), 47.6, (42.4, 40.9, rotamers), (40.1, 39.2, rotamers), 28.4, 19.9 (Product decomposed when subjected to 80 °C in DMSO-d_6 overnight)



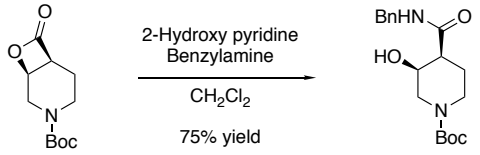
***N*-Ts-8-oxa-3-azabicyclo[4.2.0]octan-7-one 2.274c:** purified by silica gel chromatography (1:4 to 1:1 EtOAC/Hexanes). Fractions containing product were collected and the solvent was removed *in vacuo* giving a yellow oil (0.051 g, 0.18 mmol, 12% yield)

TLC: R_f = 0.30 (1:1) EtOAc/Hexanes) visualized with $KMnO_4$

HRMS (ESI+) Calcd. For $C_{13}H_{15}NO_4S$ $[M+H]^+$ 282.0800, found 282.0801

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.68 (d, J = 8.05 Hz, 2H), 7.33 (d, J = 8.05 Hz, 2H), 4.76-4.73 (m, 1H), 3.95 (dd, J = 2.54, J = 14.72 Hz, 1H), 3.81 (td, J = 3.00, J = 6.58 Hz, 1H), 3.46 (dd, J = 3.16, J = 14.48 Hz, 1H), 3.44-3.36 (m, 1H), 3.28-3.21 (m, 1H), 2.44 (s, 3H), 2.19-2.12 (m, 1H), 2.02-1.92 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 169.5, 144.1, 134.2, 130.0, 127.6, 68.2, 46.7, 45.1, 41.2, 21.8, 20.0



(-)-(3*S*, 4*S*)-*N*-Boc-4-(benzylcarbamoyl)-3-hydroxypiperidine S-2.4: To a stirred solution of the bicyclic β-lactam (0.023 g, 0.1 mmol) in CH_2Cl_2 (1 mL) was added 2-hydroxy pyridine (0.019 g, 0.2 mmol) followed by benzyl amine (0.022 mL, 0.2 mmol). The reaction was stirred at room temperature for 18 h, at which point complete consumption of the starting material was observed by TLC. The reaction was diluted with CH_2Cl_2 and washed with 1 *N* HCl, water then brine, dried over $MgSO_4$ and concentrated *in vacuo* giving a crude yellow oil. This crude material was purified by silica gel chromatography (1:5 to 1:1 EtOAc/Hexane). The product was isolated as a white solid (0.025 g, 0.075 mmol, 75% yield). The ee was determined by HPLC analysis using Daicel Chiralpak 1A column (25 cm 0.46 cm ID), conditions: 5% *i*-Propanol in *n*-hexane, 1.0 mL/min When $(DHQD)_2Phal$ is used as the catalyst: RT = 22.82 (major) and 28.98 (minor), >95% ee

$[\alpha]_D^{24.7}$ = -3.199 (*c* 0.5, CH_2Cl_2)

TLC: R_f = 0.21 (1:1) EtOAc/Hexanes) visualized with $KMnO_4$

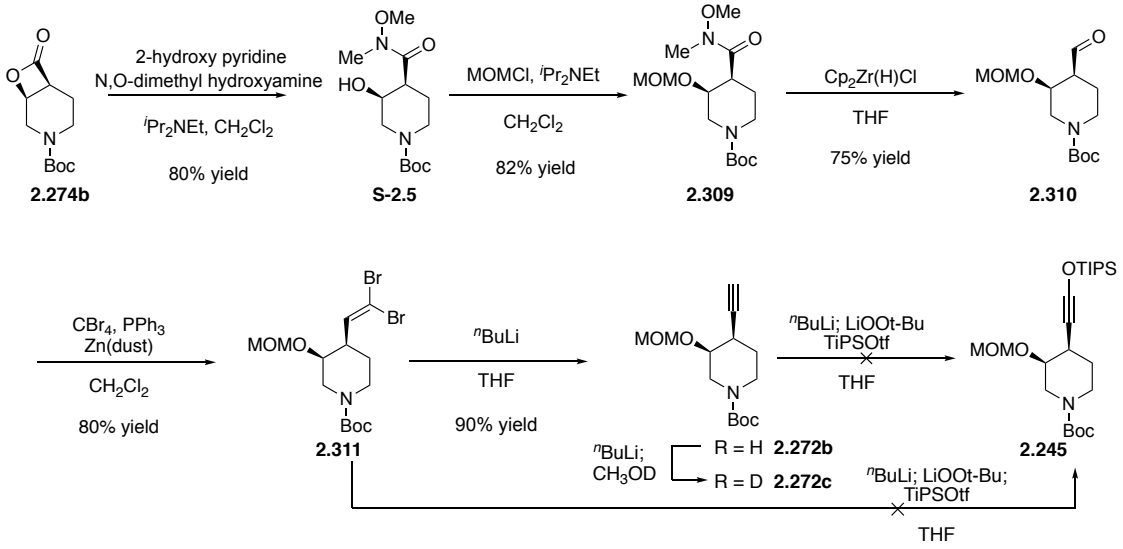
HRMS (ESI+) Calcd. For $C_{18}H_{26}N_2O_4$ $[M+H]^+$ 335.1975, found 335.1963

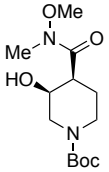
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.35-7.25 (m, 5H), 4.45 (d, *J* = 5.93 Hz, 2H), 4.18-4.10 (m, 3H), 2.88 (d, *J* = 12.73 Hz, 1H), 2.80 (t, J = 11.71 Hz, 1H), 2.39 (d, *J* = 11.93 Hz, 1H), 2.09 (appat. Dq, *J* = 4.06, *J* = 12.45 Hz, 1H), 1.71 (dd, *J* = 3.25, *J* = 13.28 Hz, 1H), 1.45 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 174.3, 155.9, 138.1, 128.8, 127.7, 127.6, 80.2, 65.4, 49.4, 46.6, 44.1, 43.4, 28.5, 24.2

2.8.3.2 Method 1: Corey-Fuchs Homologation and Oxidation

Corey-Fuchs sequence, preparation of vinyl dibromide and alkyne formation adapted from literature.[101]





***N*-Boc-3-hydroxy-4-(methoxy(methyl)carbamoyl)piperidine S-2.5:** To a 0 °C stirred solution of the *N*-Boc-8-oxa-3-azabicyclo[4.2.0]octan-7-one **2.274b** (0.100 g, 0.44 mmol) in CH_2Cl_2 (1 mL) was added 2-hydroxy pyridine (0.084 g, 0.88 mmol) followed by a 0 °C premixed solution of *N,O*-dimethyl hydroxyl amine hydrochloride (0.086 mg, 0.88 mmol) and *i*-Pr_2NEt (0.169 mL, 0.97 mmol) in CH_2Cl_2 (1 mL). The reaction was stirred at 0 °C for 10 min then warmed to rt and stirred overnight, 18 h, at which point complete consumption of the

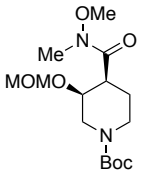
starting material was observed by TLC. The reaction was diluted with CH_2Cl_2 and washed with NH_4Cl (sat.) then brine, dried over $MgSO_4$ and concentrated *in vacuo* giving a clear oil. This crude material was purified by silica gel chromatography (1:1 to 2:1 EtOAc/Hexane) The product was isolated as a white solid (0.102 g, 0.35 mmol, 80% yield)

TLC: R_f = 0.17 (1:1 EtOAc/Hexanes) visualized with $KMnO_4$

HRMS (ESI+) Calcd. For $C_{13}H_{24}N_2O_5$ $[M+H]^+$ 289.1763, found 289.1765

^{1}H NMR (400 MHz, DMSO-d_6, 60 °C) δ ppm 4.62 (d, J = 3.65, 1H), 3.95-3.92 (m, 1H), 3.85-3.81 (m, 2H), 3.69 (s, 3H), 3.11 (s, 3H), 3.03 (d, J = 13.26 Hz, 1H), 2.95 (dt, J = 3.52, J = 10.43, 1H), 2.93-2.88 (m, 1H), 1.91-1.85 (m, 1H), 1.45-1.38 (m, 1H), 1.40 (s, 9H)

^{13}C NMR (150 MHz, DMSO-d_6, 60 °C) δ ppm 173.4, 154.3, 78.1, 64.3, 60.9, 48.5, 41.5, 40.6, 31.9, 27.9, 22.3



***N*-Boc-3-(methoxymethoxy)-4-(methoxy(methyl)carbamoyl)piperidine 2.309:** To a 0 °C stirred solution of *N*-Boc-3-hydroxy-4-(methoxy(methyl)carbamoyl)piperidine **S-2.5** (1.57 g, 5.5 mmol) in CH_2Cl_2 (30 mL) was added *i*-Pr_2NEt (3.92 mL, 22 mmol) followed by chloromethyl methyl ether (1.018 mL, 17 mmol). This reaction was allowed to warm to rt and stirred. After 12 hours incomplete conversion was observed by TLC. The reaction was cooled to 0 °C and additional chloromethyl methyl ether (3 equiv) was added. The reaction was again warmed to rt and stirred overnight at which point complete conversion was observed by TLC. Sometimes a 3rd addition of chloromethyl methyl ether (3 equiv) was required to push the reaction to conversion. Upon completion the reaction mixture was diluted with CH_2Cl_2 and washed with NH_4Cl (sat.) then brine, dried over Na_2SO_4 and

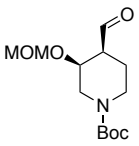
concentrated *in vacuo* giving a yellow oil. This crude material was purified by silica gel chromatography (1:1 to 2:1 EtOAc/Hexanes), and the product was isolated as a clear oil (1.494 g, 4.5 mmol, 82% yield)

TLC: R_f = 0.22 (1:1 EtOAc/Hexanes) visualized with $KMnO_4$

HRMS (ESI+) Calcd. For $C_{15}H_{28}N_2O_6$ $[M+H]^+$ 333.2026, found 333.2024

^{1}H NMR (600 MHz, DMSO-*d*$_6$, 60 °C) δ ppm 4.61 (d, *J* = 6.75, 1 H), 4.42 (d, *J* = 6.75 Hz, 1 H), 4.06-4.03 (m, 2 H), 3.91 (br S, 1 H), 3.70 (s, 3H), 3.20 (s, 3 H), 3.10 (s, 3H), 3.01-2.96 (m, 2 H), 1.95-1.88 (m, 1H), 1.42-1.38 (m, 1H), 1.39 (s, 9H)

^{13}C NMR (150 MHz, DMSO-*d*$_6$, 60 °C) δ ppm 171.8, 154.0, 93.5, 92.0, 78.2, 68.8, 60.8, 54.4, 45.2, 41.2, 31.9, 27.8, 22.1



***N*-Boc-3-(methoxymethoxy)-4-formylpiperidine 2.310:**

Method 1: Adapting the method reported by Georg,[102] a 25 mL flame dried round bottom flask was charged with solid Schwartz reagent (0.514 g, 2.0 mmol, weighed in the glovebox then sealed with a septum). The solid was suspended in THF (6 mL) at which point a solution of *N*-Boc-3-(methoxymethoxy)-4-(methoxy(methyl)carbamoyl) piperidine **2.309** (0.332 g, 1.0 mmol) in THF (2 mL) was added. The reaction was stirred at rt until complete conversion to the desired product was observed by TLC, 45 min. The reaction mixture was loaded directly onto a silica gel column and the product was eluted with EtOAc/Hexanes (1:1). Fractions containing product were collected and concentrated *in vacuo* giving the desired product as a clear oil. (0.208 g, 0.76 mmol, 76% yield)

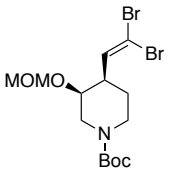
Method 2: In situ generation of Schwartz reagent could be used following the method developed by Snieckus. [103] To a stirred solution of *N*-Boc-3-(methoxymethoxy)-4-(methoxy(methyl)carbamoyl)piperidine **2.309** (0.332 g, 1 mmol) in THF (10 mL) was added solid Cp_2ZrCl_2 (0.438 g, 1.5 mmol, 1.5 equiv) followed by $LiAlH(Ot\text{-}Bu)_3$ (1.5 mL, 1 M solution in THF, 1.5 mmol) causing vigorous gas evolution. The reaction was stirred at rt becoming homogeneous after about 10 min. Complete conversion to the desired aldehyde was observed by TLC after 20 min. The reaction was then diluted with Et_2O and washed with HCl (0.5 N) followed by brine. The organic layer was collected, dried over Na_2SO_4 and concentrated *in vacuo* giving a yellow oil. This crude material was purified by silica gel chromatography (1:5 EtOAc/Hexanes) to provide the product as a yellow oil (0.193 g, 0.71 mmol, 71% yield)

TLC: R_f = 0.44 (1:1 EtOAc/Hexanes) visualized with $KMnO_4$

HRMS (ESI+) Calcd. For $C_9H_{15}NO_5$ (-*t*-Bu) $[M+H]^+$ 218.1028, found 218.1041

^{1}H NMR (600 MHz, DMSO-d_6, 60 °C) δ ppm 9.63 (s, 1H), 4.69 (d, J = 6.71 Hz, 1H), 4.52 (d, J = 6.75 Hz, 1H), 4.25-4.22 (m, 1H), 4.14 (d, J = 13.31 Hz, 1H), 3.97 (d, J = 10.13 Hz, 1H), 3.24 (s, 3H), 2.92 (d, J = 13.99 Hz, 1H), 2.68-2.64 (m, 1H), 1.71-1.61 (m, 2H), 1.34 (s, 9H)

^{13}C NMR (150 MHz, DMSO-d_6, 60 °C) δ ppm 202.4, 154.0, 93.8, 78.4, 68.1, 54.8, 50.5, 45.0, 41.7, 27.8, 19.7



***N*-Boc-3-(methoxymethyoxy)-4-(2,2-dibromovinyl)piperidine 2.311:** To a 0 °C stirred suspension of Zn dust (0.209 g, 3.2 mmol) and triphenyl phosphine (0.839 g, 3.2 mmol) in CH_2Cl_2 (5 mL) was added a solution of carbon tetrabromide (0.531g, 1.6 mmol) in CH_2Cl_2 (3 mL). This mixture was stirred at 0 °C for 30 min at which point a solution

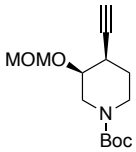
of *N*-Boc-3-(methoxymethoxy)-4-formylpiperidine **2.310** (0.218 g, 0.8 mmol) in CH_2Cl_2 (2 mL) was added dropwise. After stirring at 0 °C for 30 min the reaction was warmed to rt and stirred for 3 hours at which point it was diluted with CH_2Cl_2 and washed with water. The organic layer was collected, dried over Na_2SO_4 and concentrated *in vacuo* to give a white solid. This material was purified by silica gel chromatography (1:8 EtOAc/hexanes) to provide the product as a clear oil. (0.288 g, 0.67 mmol, 84% yield)

TLC: R_f = 0.29 (1:10 EtOAc/Hexanes) visualized with $KMnO_4$

HRMS (ESI+) Calcd. For $C_{14}H_{24}Br_2NO_4$ $[M+H]^+$ 428.0067, found 428.0061

^{1}H NMR (600 MHz, DMSO-d_6, 60 °C) δ ppm 6.60 (d, J = 8.81 Hz, 1H), 4.69 (d, J = 6.83 Hz, 1H), 4.53 (d, J = 6.53 Hz, 1H), 3.99 (ddd, J = 1.52, J = 4.06, J = 14.18 Hz, 1H), 3.83 (br s, 1H), 3.67 (br s, 1H), 3.30 (s, 3H), 2.97 (d, J = 14.26 Hz, 1H), 2.89 (br s, 1H), 2.64-2.60 (m, 1H), 1.65 (appart. dq, J = 4.38, J = 12.18 Hz, 1H), 1.50-1.45 (m, 1H), 1.40 (s, 9H)

^{13}C NMR (100 MHz, DMSO-d_6, 60 °C) δ ppm 154.0, 139.3, 93.9, 88.1, 78.4, 69.6, 54.8, 44.9, 43.4, 41.9, 27.8, 24.6



***N*-Boc-3-(methoxymethoxy)-4-ethynylpiperidine 2.272b:** To a -78 °C stirred solution of *N*-Boc-3-(methoxymethyoxy)-4-(2,2-dibromovinyl)piperidine **2.311** (0.064 g, 0.15 mmol) in THF (1.5 mL) was added *n*-BuLi (0.206 mL, 0.33 mmol) dropwise over 5 min. This reaction was stirred at -78 °C for 30 min at which point complete conversion to the desired alkyne was observed by TLC. MeOH (0.200 mL) was then added to quench the reaction, and the product was extracted with CH_2Cl_2. The organic layer was collected washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a clear oil (0.0381 g, 0.14

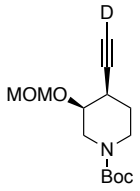
mmol, 93% yield). The crude reaction mixture was generally clean (>90%). However it could be further purified by silica gel chromatography (1:10 EtOAc/Hexanes)

TLC: R_f = 0.16 (1:10 EtOAc/Hexanes) visualized with $KMnO_4$

HRMS (ESI+) Calcd. For $C_{14}H_{23}NO_4$ $[M+H]^+$ 270.1705, found 270.1702

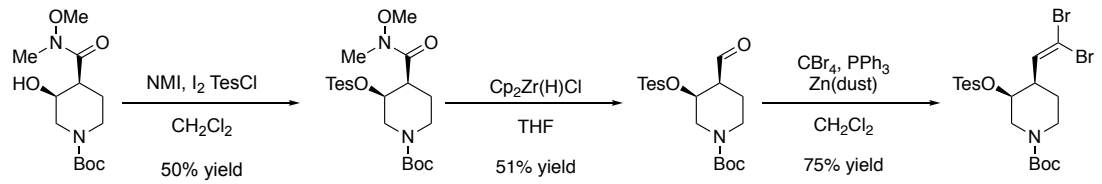
^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 4.76 (d, *J* = 6.86 Hz, 1H), 4.73 (d, *J* = 6.86 Hz, 1H), 3.69-3.58 (m, 2H), 3.51-3.44 (m, 3H), 3.42 (s, 3H), 2.97 (br s, 1H), 2.14 (d, *J* = 2.44 Hz, 1H), 1.91-1.86 (m, 1H), 1.70-1.65 (m, 1H), 1.46 (s, 9H)

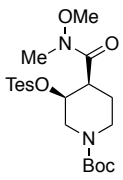
^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 154.9, 95.3, 93.2, 90.1, 83.2, 79.9, (71.8, 71.6, rotamers), 55.8, (45.4, 44.3, rotamers), (41.0, 40.5, rotamers), 32.5, 28.5



***N*-Boc-3-(methoxymethoxy)-4-ethynyl-*d*-piperidine 2.272c:** To a -78 °C stirred solution of *N*-Boc-3-(methoxymethoxy)-4-ethynylpiperidine **2.272b** (0.010g, 0.037 mmol) in THF (0.3 mL) was added *n*-BuLi (0.021 mL, 0.033 mmol) dropwise. This reaction was stirred at -78 °C for 20 min at which point methanol-d_4 (0.01 mL) was added and the solution was allowed to warm to rt then concentrated in vacuo. 77% *d* incorporation as determined by NMR

Attempted Corey-Fuchs homologation sequence with Tes protected alcohol: alkynylation and oxidation directly from the vinyl dibromide resulted in a messy reaction mixture with no discernable products. No attempt to prepare and isolate the parent alkyne in this sequence was made.





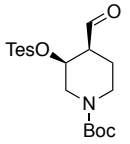
***N*-Boc-3-(triethylsilyl)oxy-4-(methoxy(methyl)carbamoyl)piperidine S-2.6:** Adapted the method reported by Stawinski.[104] To a stirred solution of *N*-Boc-3-hydroxy-4-(methoxy(methyl)carbamoyl)piperidine **S-2.5** (0.288 g, 1 mmol) in CH_2Cl_2 (10 mL) was added *N*-methyl Imidazole (0.239 mL, 3 mmol) followed by iodine (0.508 g, 2 mmol) and TesCl (0.185 mL, 1.1 mmol). This reaction was stirred at rt for 2 hours at which point it was diluted with EtOAc and washed with $Na_2S_2O_3$ (sat.). The organic layer was collected, dried over Na_2SO_4 and concentrated *in vacuo* giving a crude yellow oil. This crude material was purified by silica gel chromatography (1:4 then 1:1 EtOAc/hexanes) giving the product as a clear oil (0.203 g, 0.5 mmol, 50% yield.). Unreacted starting material was also isolated from the column (0.091 g, 0.32 mmol)

TLC: R_f = 0.48 (1:1 EtOAc/Hexanes) visualized with $KMnO_4$

HRMS (ESI+) Calcd. For $C_{19}H_{38}N_2O_5Si$ $[M+H]^+$ 403.2623, found 403.2608

^{1}H NMR (400 MHz, DMSO-d_6, 80 °C) δ ppm 4.19-4.17 (m, 1H), 3.87-3.81 (m, 2H), 3.69 (s, 3H), 3.09 (s, 3H), 3.02 (br s, 1H), 2.98-2.92 (m, 2H), 2.00-1.91 (m, 1H), 1.44-1.42 (m, 1H), 1.41 (s, 9H), 0.92 (t, J = 7.91 Hz, 9H), 0.55 (dq, J = 1.50, J = 7.98 Hz, 6H)

^{13}C NMR (100 MHz, DMSO-d_6, 80 °C) δ ppm 171.8, 153.8, 77.9, 65.8, 60.5, 48.5, 41.9, 41.2, 31.6, 27.7, 22.0, 5.9, 4.0



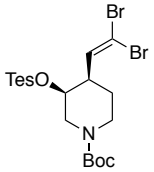
***N*-Boc-3-(triethylsilyl)oxy-4-formylpiperidine S-2.7:** To a stirred solution of *N*-Boc-3-(triethylsilyl)oxy-4-(methoxy(methyl)carbamoyl)piperidine **S-2.6** (0.189 g, 0.47 mmol) in THF (5 mL) was added solid Cp_2ZrCl_2 (0.205 g, 0.7 mmol, 1.5) followed by $LiAlH(Ot\text{-}Bu)_3$ (0.700 mL, 1 M solution in THF, 1.5 mmol) causing vigorous gas evolution. The reaction was stirred at rt becoming homogeneous after about 10 min. Complete conversion to the desired aldehyde was observed by TLC after 30 min, the reaction was then diluted with Et_2O and washed with HCl (0.5 N) followed by brine. The organic layer was collected, dried over Na_2SO_4 and concentrated *in vacuo* to give a yellow oil. This crude material was purified by silica gel chromatography (1:5 EtOAc/Hexane) to provide the product as a clear oil (0.081 g, 0.24 mmol, 51% yield)

TLC: R_f = 0.76 (1:1 EtOAc/Hexanes) visualized with $KMnO_4$

HRMS (ESI+) Calcd. For $C_{17}H_{33}NO_4Si$ $[M+H]^+$ 344.2252, found 344.2239

^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ ppm 9.81 (s, 1H), 4.28 (br s, 1H), 3.79 (dt, J = 5.24, J = 13.55 Hz, 1H), 3.71 (br s, 1H), 3.23 (d, J = 13.47 Hz, 1H), 3.06 (td, J = 3.78, J = 13.17 Hz, 1H), 2.43-2.39 (m, 1H), 2.15-2.05 (m, 1H), 1.66-1.60 (m, 1H), 1.47 (s, 9H), 0.97 (t, J = 7.55 Hz, 9H), 0.67-0.61 (m, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 203.8, 155.1, 79.9, 66.1, 52.8, (50.2, 49.2), (42.7, 41.5), 28.5, 21.1, 6.9, 4.9



***N*-Boc-3-(triethylsilyl)oxy-4-(2,2-dibromovinyl)piperidine S-2.8**: To a 0 °C stirred suspension of Zn dust (0.052 g, 0.8 mmol) and triphenyl phosphine (0.210 g, 0.8 mmol) in CH_2Cl_2 (0.5 mL) was added a solution of carbon tetrabromide (0.133g,

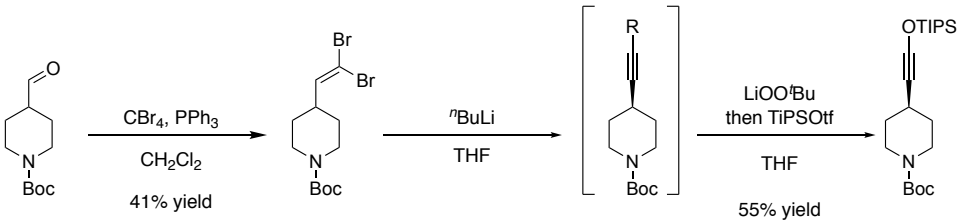
0.4 mmol) in CH_2Cl_2 (0.5 mL). This mixture was stirred at 0°C for 30 min at which point a solution of *N*-Boc-3-(triethylsilyl)oxy-4-formylpiperidine **S-2.7** (0.070 g, 0.2 mmol) in CH_2Cl_2 (1 mL) was added dropwise. After stirring at 0 °C for 30 min the reaction was warmed to rt and stirred for 3 hours at which point it was diluted with CH_2Cl_2 and washed with water. The organic layer was collected dried over Na_2SO_4 and concentrated *in vacuo* giving a crude white solid. This material was then purified by silica gel chromatography (1:8 EtOAc/hexanes) to provide the product as a clear oil. (0.076 g, 0.15 mmol, 75% yield)

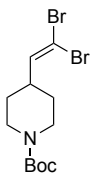
TLC: R_f = 0.63 (1:5 EtOAc/Hexanes) visualized with UV and $KMnO_4$

HRMS (ESI+) Calcd. For $C_{18}H_{33}Br_2NO_3Si$ $[M+H]^+$ 498.0669, found 498.0649

^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ ppm 6.45 (d, *J* = 8.88 Hz, 1H), 3.96-3.88 (m, 2H), 3.85 (br s, 1H), 2.98 (d, *J* = 13.25 Hz, 1H), 2.88 (dt, J = 3.05, J = 12.25 Hz, 1H), 2.53-2.46 (m, 1H), 1.92-1.82 (m, 1H), 1.46 (s, 10H) [1 ring proton under Boc peak- shows up with very broad baseline], 0.99 (t, *J* = 7.91 Hz, 9H), 0.64 (q, *J* = 7.91 Hz, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 155.3, 140.0, 88.7, 79.8, 66.8, (50.1, 49.1), 45.9, (43.4, 42.3), 28.6, 24.8, 7.0, 4.9





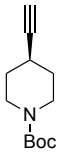
***N*-Boc-4-(2,2-dibromovinyl)piperidine 2.312:** To a 0 °C stirred solution of carbon tetrabromide (4.245 g, 12.8 mmol) in CH_2Cl_2 (20 mL) was added a solution of PPh_3 (6.713 g, 25.6 mmol) in CH_2Cl_2 (5 mL) dropwise. This mixture was stirred at 0 °C for 20 min at which point a solution of *N*-Boc-4-piperdine carboxaldehyde (1.36 g, 6.4 mmol) in CH_2Cl_2 (10

mL) was added dropwise over 10 min. This solution was allowed to gradually warm to rt and stir overnight, 18 h. The reaction mixture was then diluted with water and the product was extracted with CH_2Cl_2. The organic layer was collected, washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* giving an orange solid. This crude solid could then be triturated with Et_2O and filtered giving the product as a white solid. (0.959 g, 2.6 mmol, 41% yield) Analytical data corresponds to literature reports.[105]

HRMS (ESI+) Calcd. For $C_{18}H_{26}N_2O_4$ $[M+H]^+$ 335.1975, found 335.1963

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.23 (d, *J* = 8.92 Hz, 1H), 4.07 (br s, 2H), 2.77 (t, *J* = 12.62, 2 H), 2.49-2.39 (m, 1H), 1.70 (d, *J* = 13.16, 2H), 1.45 (s, 9H), 1.36-1.25 (m, 2H)

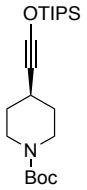
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 154.9, 141.7, 88.8, 79.7, 43.3, 40.8, 30.2, 28.6



***N*-Boc-4-ethynylpiperidine S-2.9**: To a -78 °C stirred solution of *N*-Boc-4-(2,2-dibromovinyl)piperidine **2.312** (0.200 g, 0.5 mmol) in THF (4 mL) was added *n*-BuLi (0.656 mL, 1.05 mmol) dropwise over 5 min. This reaction was stirred at -78 °C for 30 min at which point complete conversion to the desired alkyne was observed by TLC. MeOH (2 mL) was added to quench the reaction and the mixture was allowed to warm to rt. The mixture was diluted with CH_2Cl_2 and the organic layer was washed with brine then dried over Na_2SO_4 and concentrated *in vacuo* giving the product as a white solid (0.088 g, 0.42 mmol, 84% yield). Analytical data corresponds to literature reports.[106]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.72-3.66 (m, 2H), 3.21-3.14 (m, 2H), 2.61-2.54 (m, 1H), 2.10 (d, *J* = 2.44 Hz, 1H), 1.81-1.74 (m, 2H), 1.63-1.54 (m, 2H), 1.45 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 154.9, 86.6, 79.6, 69.6, 42.2, 31.3, 25.6, 26.9



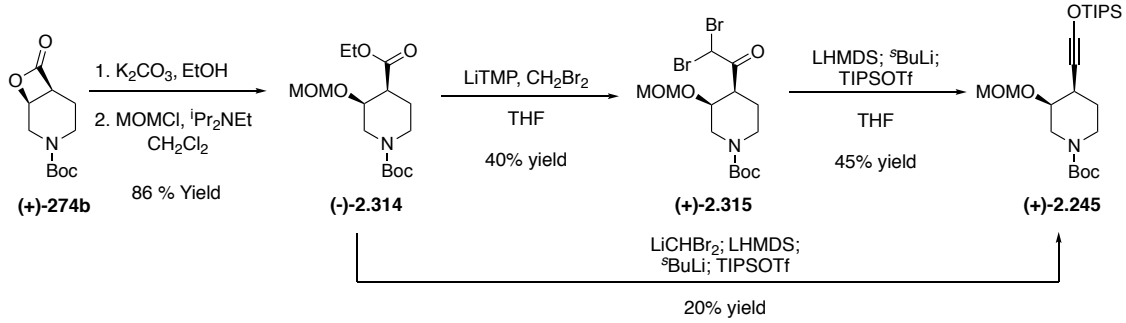
***N*-Boc-4-((triisopropylsilyl)oxy)ethynylpiperidine 2.313**: To a -78 °C stirred solution of *N*-Boc-4-(2,2-dibromovinyl)piperidine **2.312** (0.037 g, 0.1 mmol) in THF (0.5 mL) was added *n*-BuLi (0.188 mL, 0.3 mmol) dropwise. Upon complete addition the reaction was stirred at -78 °C for 45 min at which point a solution of LiO*t*-Bu was added via cannula. LiO*t*-Bu was prepared by the addition of LHMDS (0.300 mL, 0.3 mmol) to a -78 °C stirred solution of *t*-BuOOH (0.055 mL, 0.3 mmol, 5.5 M in nonane) in THF (0.5 mL). This mixture was stirred at -78 °C for 30 min before transfer. The resulting solution was stirred at -78 °C for 30 min then warmed to 0 °C and stirred for 3 hours. The reaction was then re-cooled to -78 °C and TIPSOTf (0.081 mL, 0.3 mmol) was added dropwise. Upon complete addition the reaction was stirred at -78 °C for 2 hours. The reaction was then diluted with Et_2O and quenched with $NaHCO_3$ (sat). The organic layer was collected washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* giving a crude orange oil. This crude material was purified by silica gel chromatography (1:20 to 1:10 EtOAc/Hexanes) Isolated the product as a clear oil (0.021 g, 0.055 mmol, 55% yield)

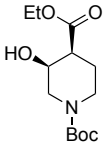
TLC: R_f = O.58 (1:10) EtOAc/Hexanes) visualized with $KMnO_4$, showed a weak UV signal

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.66-3.62 (m, 2H), 3.16 (ddd, *J* = 13.43 Hz, *J* = 8.32 Hz, *J* = 3.42 Hz, 2H), 2.49 (Sept (apparent), J = 3.97 Hz, 1H), 1.71-1.68 (m, 2H), 1.48-1.43 (m, 2H), 1.45 (s, 9H), 1.29-1.21 (m, 3H), 1.12 (d, *J* = 7.31 Hz, 18H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 155.0, 88.4, 79.4, 33.0, 32.8, 28.6, 26.0, 17.5, 12.4, 12.0

2.8.3.3 Method 2: Kowalski homologation





(-)-*(3S, 4S) N*-Boc-3-hydroxy-4-ethyl piperidinecarboxylate S-2.10: *N*-Boc-8-oxa-3-azabicyclo[4.2.0]octan-7-one **(+)-2.274b** (0.277 g, 1 mmol) was dissolved in EtOH (10 mL) and solid K_2CO_3 (0.414 g, 3 mmol) was added. This reaction was stirred at rt for 3 hours at which point complete conversion to the desired ethyl ester was observed by TLC. If the reaction was run for too long formation of a byproduct was observed by TLC. This product was never fully characterized; however an aldehyde peak was observed by ^{1}H NMR so it was assumed to be the result of a retroaldol. Upon completion the reaction mixture was then filtered through a plug of celite and eluted with EtOAc. This crude mixture could then be used in subsequent reactions with no further purification. For analytical purposes the material was purified by silica gel chromatography (1:10 to 1:6 EtOAC/Hexanes). Fractions containing product were collected and the solvent was removed *in vacuo* giving a yellow oil.

TLC: R_f= 0.56 (1:1 EtOAc/Hexanes) visualized with $KMnO_4$

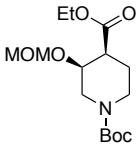
$[\alpha]_D^{23.5}$ = -19.710 (*c* 1.0, CH_2Cl_2)

HRMS (ESI+) Calcd. For $C_9H_{15}NO_5$ (-*t*-Bu) $[M+H]^+$ 218.1028, found 218.1027

^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ ppm 4.19 (q, *J* = 7.12 Hz, 2H), 4.16-3.98 (m, 3H), 3.01 (dd, *J* = 1.84, *J* = 13.75 Hz, 1H), 2.86 (ddd, *J* = 3.14, *J* = 10.96, *J* = 13.24 Hz, 1H), 2.71 (br s, 1H), 2.54

(ddd, J = 2.81, J = 4.31, J = 11.58 Hz, 1H), 2.12-2.01 (m, 1H), 1.76-1.70 (m, 1H), 1.46 (s, 9H), 1.28 (t, J = 7.39 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ ppm 173.8, 155.8, 80.1, 65.8, 61.0, 45.7, 43.1, 31.4, 28.6, 23.0, 14.3



(-)-*(3S, 4S) N*-Boc-3-(methoxymethoxy)-4-ethyl piperidinecarboxylate 2.314: To a 0 °C stirred solution of *N*-Boc-3-hydroxy-4-ethyl piperidinecarboxylate **(-)-S-2.10** (0.273 g, 1 mmol) in CH_2Cl_2 (10 mL) was added *i*-Pr_2NEt (0.712 mL, 4 mmol) followed by chloromethyl methyl ether (0.180 mL, 3 mmol). This reaction was allowed to warm to rt and was monitored by TLC. After 12 h incomplete conversion to the desired product was observed, the reaction was cooled to 0 °C and additional chloromethyl methyl ether (3 equiv) was added. The reaction was warmed to rt and stirred overnight at which point complete conversion was observed by TLC. Sometimes a 3rd addition of chloromethyl methyl ether (3 equiv) was required to push the reaction to conversion. The reaction mixture was diluted with CH_2Cl_2 and washed with NH_4Cl (sat.) followed by brine. The organic layer was collected, dried over Na_2SO_4 and concentrated *in vacuo* giving a yellow oil. This crude material was purified by silica gel chromatography (1:10 EtOAc/Hexanes), and the product was isolated as a clear oil (0.272 g, 0.86 mmol, 86% yield, 2 steps)

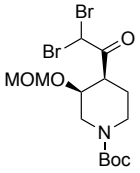
TLC: R_f=0.16 (1:5 EtOAc/Hexanes) visualized with $KMnO_4$

$[\alpha]_D^{23.5}$ = -58.191 (*c* 1.0, CH_2Cl_2)

HRMS (ESI+) Calcd. For $C_{11}H_{19}NO_6$ (-*t*-Bu) $[M+H]^+$ 262.1291, found 262.1287

^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ ppm 4.73 (d, *J* = 6.91 Hz, 1H), 4.58 (d, *J* = 6.91 Hz, 1H), 4.31 (d, *J* = 13.35 Hz, 1H), 4.21-4.10 (m, 4H), 3.34 (s, 3H), 2.89 (d, *J* = 14.23 Hz, 1H), 2.76 (t, *J* = 12.89 Hz, 1H), 2.53 (dt, *J* = 3.67, *J* = 11.93 Hz, 1H), 2.04 (dq, *J* = 4.30, *J* = 12.32 Hz, 1H), 1.76-1.70 (m, 1H), 1.45 (s, 9H), 1.27 (t, *J* = 7.20 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ ppm 172.2, 155.0, (95.0, 94.6), 79.6, (69.9, 69.8), 60.6, 55.6, (46.2, 45.4), 45.5, (43.2, 42.3), 28.4, (22.1, 21.9), 14.2



(+)-*(3S, 4S)* *N*-Boc-3-(methoxymethoxy)-4-(2,2-dibromoacetyl)piperidine carboxylate 2.315: To a 0 °C stirred solution of TMP (0.204 mL, 1.2 mmol) in THF (1.5 mL) was added *n*-BuLi (0.688 mL, 1.1 mmol) dropwise. This mixture was stirred at 0 °C for 30 min then cooled to -78 °C and added via cannula to a -78 °C stirred solution of *N*-Boc-3-(methoxymethoxy)-4-ethyl piperidinecarboxylate **(-)-2.314** (0.159 g, 0.5 mmol) and dibromomethane (0.084 mL, 1.2 mmol) in THF (1.5 mL). This reaction was stirred at -78 °C for 30 min. at which point it was transferred via cannula into a vigorously stirred 0 °C solution of 1 *N* HCl. The product was then extracted with Et_2O, and the organic layer was washed with $NaHCO_3$ (sat.) then brine, dried over $MgSO_4$ and concentrated *in vacuo* giving a crude red oil. This crude material was purified by silica gel chromatography (1:8 EtOAc/Hexanes). Fractions containing product were collected and the solvent was removed *in vacuo* giving the desired product as a clear oil (0.094 g, 0.2 mmol, 40% yield) The product was often isolated with a small amount of impurity (10%) which was very difficult to remove, although no detailed characterization was done the, m/z of this byproduct corresponds to the mono bromo ketone.

The ee was determined by HPLC analysis using Daicel Chiralpak 1A column (25 cm 0.46 cm ID), conditions: 1% *i*-Propanol in *n*-hexane, 1.0 mL/min, RT = 19.73 (major) and 23.32 (minor) >95 % ee

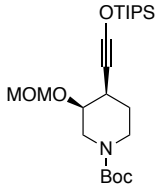
TLC: R_f= 0.18 (1:5 EtOAc/Hexanes) Visualized with $KMnO_4$

$[\alpha]_D^{23.4}$ = 7.599 (c 1.0, CH_2Cl_2)

HRMS (ESI+) Calcd. For $C_{14}H_{23}Br_2NO_5$ $[M+H]^+$ 444.0016, found 444.0015

^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ ppm 6.25 (s, 1H), 4.74 (d, *J* = 7.06 Hz, 1H), 4.54 (d, *J* = 7.06 Hz, 1H), 4.13-3.99 (m, 3H), 3.40-3.35 (m, 1H) 3.34 (s, 3H), 3.09 (dd, *J* = 3.8, *J* = 15.44 Hz, 1H), 3.00 (ddd, *J* = 2.44, *J* = 12.21, *J* = 14.22 Hz, 1H), 2.17-2.06 (m, 1H), 1.81-1.74 (m 1H), 1.45 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ ppm 194.8, 155.0, 95.2, 80.1, 70.9, 68.1, 56.5, 46.7, 42.7, 28.6, 25.8, 23.9



(+)-*(3S, 4R)* *N*-Boc-3-(methoxymethoxy)-4-((triisopropylsilyl)oxy) ethynyl piperidine 2.245: Used a modified procedure reported by Kowalski.108

Method 1 From dibromo ketone: To a -78 °C stirred solution of *(3S, 4S) N*-Boc-3-methoxymethoxy)-4-(2,2-dibromoacetyl)piperidinecarboxylate **(+)-2.315** (0.045 g, 0.1 mmol) in THF (1 mL) was added LHMDS (0.250 mL, 0.35 mmol). After stirring at -78 °C for 15 min, *s*–BuLi (0.250 mL, 0.35 mmol) was added dropwise. This reaction was stirred at -78 °C for 10 min then warmed to 0 °C and stirred for 6 hours at which point the reaction mixture was cooled to -78 °C and TIPSOTf (0.04 mL, 0.15 mmol) was added. After 10 min the reaction was warmed

to 0 °C and stirred at temperature overnight. The reaction mixture was then diluted with Et_2O and washed with $NaHCO_3$ followed by brine, dried over Na_2SO_4 and concentrated *in vacuo* giving a crude red oil. This crude material was then purified by silica gel chromatography (1:20 then 1:10 EtOAc/Hexanes) to provide the product as a clear oil (0.016 g, 0.04 mmol, 40% yield)

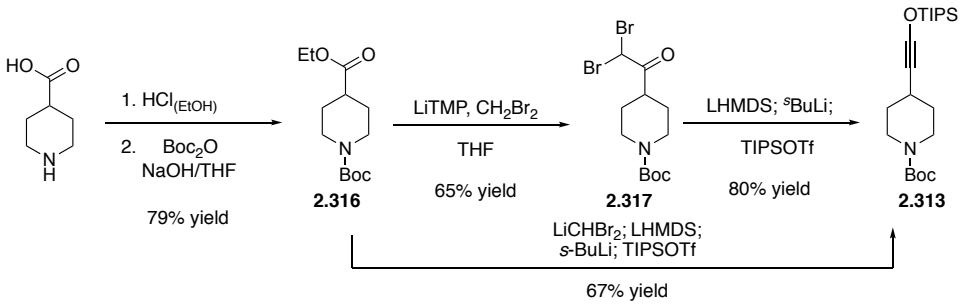
Method 2 From Ethyl ester: To a 0 °C stirred solution of TMP (0.187 mL, 1.10 mmol) in THF (0.5 mL) was added *n*-BuLi (0.625 mL, 1.0 mmol). This reaction was stirred at 0 °C for 20 min then cooled to -78 °C at which point the mixture was transferred via cannula into a -78 °C stirred solution of *(3S, 4S) N*-Boc-3-(methoxymethoxy)-4-ethyl piperidinecarboxylate **(-)-22** (0.159 g, 0.5 mmol) and dibromomethane (0.053 mL, 0.75 mmol) in THF (0.5 mL). Upon complete addition this reaction was stirred at -78 °C for 1.5 h and then LHMDS (0.650 mL, 0.065 mmol) was added dropwise. The reaction was stirred for 15 min at -78 °C at which point *s*-BuLi (1.964 mL, 2.75 mmol) was added dropwise. After stirring at -78 °C for an additional 10 min the reaction was warmed to 0 °C and stirred for 5 h. The reaction was then cooled to -78 °C and TIPSOTf (0.202 mL, 0.75 mmol) was added. The reaction was again warmed to 0 °C and stirred overnight at which point the mixture was diluted with Et_2O and washed with $NaHCO_3$ (sat.) followed by brine. The organic layer was collected, dried over Na_2SO_4 then concentrated *in vacuo* giving a crude yellow oil. This crude material was purified by silica gel chromatography (1:20 to 1:10 EtOAc/Hexanes). Fractions containing product were collected and the solvent was removed *in vacuo* giving a clear oil (0.044 g, 0.1 mmol 20% yield)

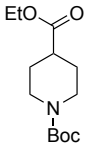
TLC: R_f= 0.28 (1:10 EtOAc/Hexanes) Visualized with $KMnO_4$

$[\alpha]_D^{23.5}$ = 35.195 (c 1.0, CH_2Cl_2)

^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 4.74 (d, *J* = 6.91 Hz, 1H), 4.68 (d, *J* = 6.91 Hz, 1 H), 3.55-3.50 (m, 2H), 3.41 (s, 3H), 3.39-3.22 (m, 3H), 2.93 (br s, 1H), 1.77-1.69 (m, 1H), 1.62-1.57 (m, 1H), 1.45 (s, 9H), 1.26 (quintet, *J* = 7.48 Hz, 3H), 1.12 (d, *J* = 7.46 Hz, 18H)

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 155.0, 95.1, 89.7, 79.7, 72.8, 55.7, (41.0, 40.5), 31.1, 29.8, 28.5, 17.8, 17.5, 12.4, 12.0





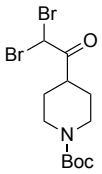
***N*-Boc-4-ethyl piperidinecarboxylate 2.316:** To a 0 °C stirred suspension of isonipecotic acid (1.9374 g, 15 mmol) in ethanol (25 mL) was added thionyl chloride (2 mL) dropwise. Upon complete addition of the thionyl chloride the reaction was heated to reflux and stirred at temperature overnight, 18h, becoming a homogeneous solution. The reaction was then concentrated *in vacuo* giving a white gum like solid. This solid was azeotroped with toluene until a white amorphous solid was obtained. The resulting solid was dissolved in THF (25 mL) and NaOH (30 ml, 2 N) at 0 °C, a solution of Boc_2O (4.9106g, 0.225 mmol) in THF (5 mL) was added. This reaction was stirred at 0 °C for 20 min then warmed to rt and stirred for 2 h at which point it was diluted with CH_2Cl_2 and washed with water than brine. The organic layer was collected, dried over Na_2SO_4 and concentrated *in vacuo* giving a clear oil. This oil was purified by silica gel chromatography (1:10 EtoAC/Hexanes) to provide the product as a clear oil. (3.0567 g, 11.9 mmol, 79% yield). Analytical data corresponds to literature reports.[107]

TLC: R_f = 0.40 (1:5) EtOAc/Hexanes) visualized with $KMnO_4$

HRMS (ESI+) Calcd. For $C_9H_{15}NO_4$ (-*t*-Bu) $[M+H]^+$ 202.1079, found 202.1077

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.13 (q, *J* = 7.10 Hz, 2H), 4.01 (br S, 2H), 2.82 (t, *J* = 11.50 Hz, 2H), 2.42 (tt, *J* = 11.05 Hz, *J* = 3.89 Hz, 1H), 1.88-1.85 (m, 2H), 1.65-1.55 (m, 2H), 1.44 (s, 9H), 1.25 (t, *J* = 7.22 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 174.7, 154.8, 79.7, 60.6, 43.3, 41.3, 28.6, 28.1, 14.3



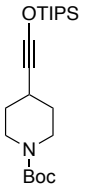
***N*-Boc-4-(2,2-dibromoacetyl)piperidinecarboxylate 2.317:** To a 0 °C stirred solution of TMP (0.748 mL, 4.4 mmol) in THF (5 mL) was added *n*-BuLi (2.5 mL, 4.0 mmol). This reaction was stirred at 0 °C for 20 min then cooled to -78 °C at which point the mixture was transferred via cannula into a -78 °C stirred solution of *N*-Boc-4-ethyl piperidinecarboxylate **2.316** (514 mg, 2 mmol) and dibromomethane (0.422 mL, 6 mmol) in THF (5 mL). Upon complete addition this reaction was stirred at -78 °C for 1.5 h at which point it was transferred via cannula into a vigorously stirred solution of 1 *N* HCl at 0 °C. The product was then extracted with Et_2O and the organic layer was washed with $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a yellow oil. This material was then purified by silica gel chromatography (1:8 EtOAc/Hexanes). Fractions containing product were collected and the solvent was removed *in vacuo* to give a white amorphous solid (0.478 g, 1.3 mmol, 65% yield)

TLC: R_f = 0.43 (1:5) EtOAc/Hexanes) visualized by UV and $KMnO_4$

HRMS (ESI+) Calcd. For $C_8H_{11}Br_2NO_3$ (-*t*-Bu) $[M+H]^+$ 327.9178, found 327.9181

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.83 (s, 1H), 4.15 (br s, 2H), 3.24 (tt, J = 11.45 Hz, J = 3.71 Hz, 1H), 2.82 (br s, 2H), 1.91-1.85 (m, 2H), 1.71 (qd, J = 12.23 Hz, J = 4.43 Hz, 2H), 1.96 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 197.9, 154.5, 79.8, 43.1, 42.8, 41.9, 29.7, 28.4



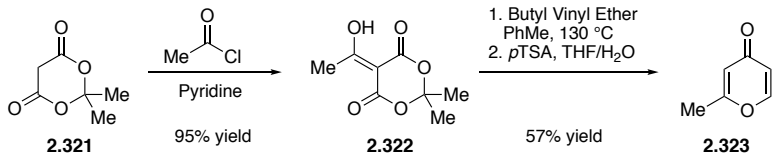
***N*-Boc-4-((triisopropylsilyl)oxy)ethynylpiperidine 2.313:** Used a modified procedure reported by Kowalski[108]

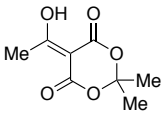
Method 1 From dibromo ketone: To a -78 °C stirred solution of *N*-Boc-4-(2,2-dibromoacetyl)piperidinecarboxylate **2.317** (0.096 g, 0.25 mmol) in THF (1.5 mL) was added LHMDS (0.350 mL, 0.35 mmol) dropwise. This reaction was stirred at -78 °C for 15 min at which point *s*-BuLi (0.629 mL, 0.88 mmol) was added dropwise. After stirring at -78 °C for an additional 10 min the reaction was warmed to 0 °C and stirred for 4.5 h. The mixture was then cooled to -78 °C and TIPSOTf (0.102 mL, 0.38 mmol) was added. The reaction was warmed to 0 °C and stirred overnight,18h. The mixture was then diluted with Et_2O and washed with $NaHCO_3$ (Sat.) followed by brine. The organic layer was collected, dried over Na_2SO_4 and concentrated *in vacuo* to give a crude yellow oil. This crude material was purified by silica gel chromatography (1% to 4% EtOAc/Hexanes). Fractions containing product were collected and the solvent was removed *in vacuo* giving a clear oil (0.076 g, 0.2 mmol 80% yield)

Method 2 From Ethyl ester: To a 0 °C stirred solution of TMP (0.172 mL, 1.01 mmol) in THF (0.5 mL) was added *n*-BuLi (0.575 mL, 0.92 mmol). This reaction was stirred at 0 °C for 20 min then cooled to -78 °C at which point the mixture was transferred via cannula into a -78 °C stirred solution of *N*-Boc-4-ethyl piperidinecarboxylate **2.316** (0.117 g, 0.46 mmol) and dibromomethane (0.049 mL, 0.69 mmol) in THF (0.5 mL). Upon complete addition this reaction was stirred at -78 °C for 1.5 h then LHMDS (0.600 mL, 0.06 mmol) was added dropwise. The reaction was stirred for 15 min at -78 °C, *s*-BuLi (1.807 mL, 2.53 mmol) was then added dropwise. After stirring at -78 °C for an additional 10 min the reaction was warmed to 0 °C and stirred for 5

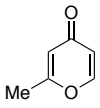
hours. The reaction was then cooled to -78 °C and TIPSOTf (0.185 mL, 0.69 mmol) was added. The reaction was warmed to 0 °C and stirred overnight, 18h, at which point the mixture was diluted with Et_2O and washed with $NaHCO_3$ (Sat.) followed by brine. The organic layer was collected, dried over Na_2SO_4 then concentrated *in vacuo* giving a crude yellow oil. This crude material was purified by silica gel chromatography (1% to 4% EtOAc/Hexanes). Fractions containing product were collected and the solvent was removed *in vacuo* giving a clear oil (0.114 g, 0.3 mmol 67% yield)

2.8.4 Preparation of Pyrone Ketene 2.246





5-(1-hydroxyethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione 2.322: To a stirred solution of Meldrums acid (3.169g, 22 mmol) in CH_2Cl_2 (10 mL) was added pyridine (3.544 mL, 44 mmol). This reaction mixture was then cooled to -30 °C and a solution of freshly distilled acetyl chloride (1.848 mL, 26 mmol) in CH_2Cl_2 (10mL) was added dropwise via addition funnel over 30 min. The reaction was stirred at -30 °C for 1 hour then slowly allowed to warm to 0 °C over 3 hours. 5 mL of methanol was then added and the reaction stirred for 15 min at r.t. CH_2Cl_2 (50 mL) was added and the mixture was transferred to a sepratory funnel and washed with NH_4Cl (sat. 3x 30 mL) then water. The aq layer was combined and extracted with additional CH_2Cl_2 (3x 50 mL) then the combined organic layers where washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* giving an orange solid. (3.8292g, 21 mmol, 95% yield)



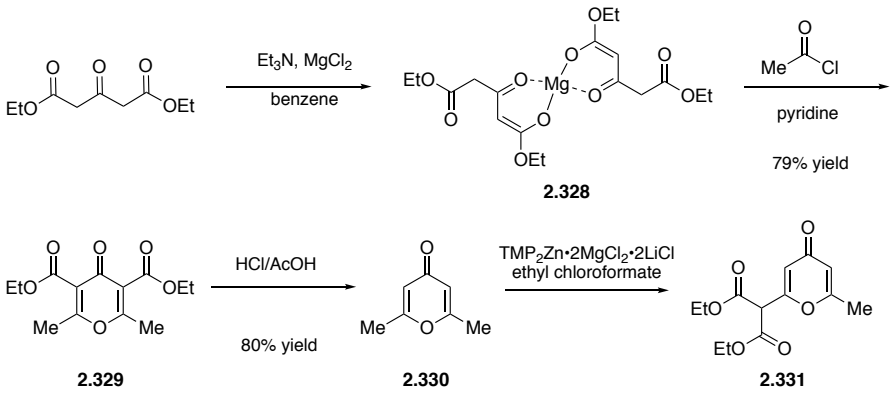
2-methyl-4*H*-pyran-4-one 2.323: Acylated Meldrums acid **2.322** (3.829g, 21 mmol) was dissolved in toluene 30 mL and to this was added butyl vinyl either (10.653 mL, 82 mmol). The reaction was heated to 80 °C and stirred at temperature for 6 hours at which point it was cooled to r.t. and concentrated *in vacuo*. The crude mixture was then redissolved in THF (50 mL) and water (15 mL). Solid *p*-toluene sulfonic acid (361 mg, 2.1 mmol) was then added and the reaction was heated to reflux for 18 hours, overnight. The reaction was then cooled to r.t. and 1g of solid $NaHCO_3$ was added, the reaction stirred an additional 15 min at r.t. and was then filtered through cintered glass. The supernatant was then concentrated *in vacuo* removing the THF and the resulting brown oil/water mixture was extracted with CH_2Cl_2 (3x) the combined organic layer was then washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* giving a brown oil. This crude material was then purified by silica gel chromatography (2 to 3% MeOH in CH_2Cl_2) fractions containing product were collected and the solvent was removed *in vacuo* giving the product as a red oil (1.31g, 12 mmol, 57% yield)

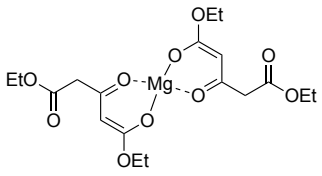
TLC: R_f = 0.17 (1:1 EtOAc/Hexanes) visualized with UV

LRMS: (ESI+) Calcd. For $C_6H_6O_2$ $[M+H]^+$ 111.1, found 111.1

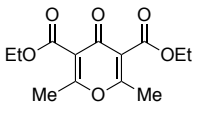
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.67 (d, *J* = 5.82 Hz, 1H), 6.2 (dd, *J* = 2.49, *J* = 5.88 Hz, 1H), 6.14 (br d, *J* = 2.18 Hz, 1H), 2.26 (br s, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 179.3, 166.3, 155.1, 116.7, 115.6, 19.9





diethyl acetone-1,3-dicarboxylate Magnesium complex[109] **2.328:** To a suspension of $MgCl_2$ (anhydrous 10 mesh beads, 2.38g, 25 mmol) in Benzene (40 mL) was added diethyl acetone-1,3-dicarboxylate (9.08 mL, 50 mmol) followed by triethyl amine (6.97 mL, 50 mmol). This reaction mixture was then heated to reflux and stirred at temperature for 2 hours. The reaction was then cooled to r.t. and the benzene was removed *in vacuo*. The resulting crude material was then washed with 30 mL of anhydrous Et_2O causing formation of a white precipitate. This precipitate was filtered and washed with an additional 10 mL of anhydrous Et_2O, the organic layer was then collected and concentrated *in vacuo* giving a yellow oil as the product (10.466g, 24 mmol, 96 % yield)

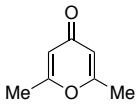


diethyl 2,6-dimethyl-4-oxo-4*H*-pyran-3,5-dicarboxylate 2.329: To a 0 °C Stirred solution of diethyl acetone-1,3-dicarboxylate Magnesium complex (10.466g, 24 mmol) in pyridine (30 mL) was added freshly distilled Acetyl Chloride (7.5 mL, 106 mmol) dropwise over 10 min. This reaction mixture was slowly allowed to warm to r.t. and stirred at r.t. for 18 hours (overnight). The reaction was then poured into 20 mL of 2N HCl and ICE and the resulting mixture was extracted with CH_2Cl_2. The organic layer was collected and washed

with brine then dried of Na_2SO_4 and concentrated *in vacuo* giving a red oil. This crude oil was purified by silica gel chromatography (1:10-1:2 EtOAc/Hexanes) fractions containing product were collected and the solvent was removed *in vacuo* giving a yellow crystalline solid (5.067g, 19 mmol, 79% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.34 (q, *J* = 7.1 Hz, 4H), 2.34 (s, 6H), 1.34 (t, *J* = 7.15 Hz, 6H)

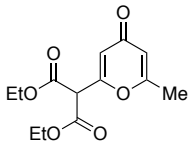
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 171.8, 165.3, 164.1, 121.6, 61.9, 18.6, 14.2



2,6-dimethyl-4*H*-pyran-4-one [110] 2.330: A stirred solution of pyrrole-3,5-diethylester (5.07g, 19 mmol) in Acetic acid (15 mL) and HCl (2N, 30 mL) was heated to reflux and stirred at temperature for 4 hours at which point complete decarboxylation was observed by LCMS. This reaction was then slowly poured into a saturated solution of $NaHCO_3$ and the product was extracted with DCM. The organic layer was collected washed with Brine then dried over Na_2SO_4 and concentrated *in vacuo* giving the desired product as a light yellow crystalline solid. No further purification was required. (1.881g, 15.2 mmol, 80% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.04 (s, 2H), 2.23 (s, 6H)

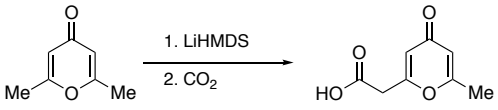
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 180.2, 165.5, 113.7, 19.8



diethyl 2-(6-methyl-4-oxo-4*H*-pyran-2-yl)malonate 2.331: To a -78 °C stirred solution of dimethyl pyrone **2.330** (50 mg, 0.4 mmol) in THF (2 mL) was added TMP_2Zn•2MgCl•LiCl (1.13mL, 0.52 mmol). This reaction was stirred at -78 °C for 30 min at which point ethyl chloroformate (0.114 mL, 1.2 mmol) was added and the reaction was allowed to warm to rt over 1 hour. The reaction was stirred an additional 30 min at rt then quenched by

the addition of NH_4Cl (aq. Sat.) and the product was extracted with EtOAc. The organic layer was collected and washed with brine then dried over $MgSO_4$ and concentrated giving a yellow oil. This crude mixture was purified by silica gel chromatography (1:4 to 1:1 EtOAc/Hexanes), isolated the product as a yellow oil (17.3 mg, 0.06 mmol, 15% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.32 (d, *J* = 2.24 Hz, 1H), 6.12 (dd, *J* = 2.24, *J* = 0.76 Hz, 1H), 4.48 (s, 1H), 4.27 (qd, J = 7.16, *J* = 0.81 Hz, 4H), 2.26 (d, *J* = 0.67 Hz, 3H), 1.29 (t, *J* = 7.15 Hz, 6H)



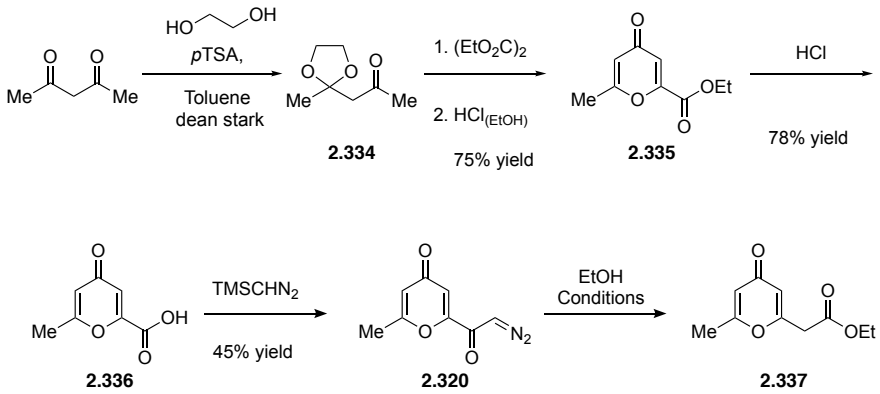
2.330 40% yield **2.333**

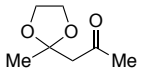
2-(6-methyl-4-oxo-4*H*-pyran-2-yl)acetic acid 2.333: To a stirred solution of 2,6-dimethyl-4*H*-pyran-4-one (50 mg, 0.4 mmol) in THF (2 mL) was added HPMA (0.077mL, 0.44 mmol) and TMSCl (0.066 mL, 0.52 mmol). This reaction was stirred at r.t. for 10 min then cooled to -40 °C and a solution of LHMDS in THF (0.600 mL, 0.6 mmol, 1M) was then added dropwise. The reaction continued to stir at -40 °C for 30 min ate which point CO_2 (CO_2 was generated by trapping from dry ICE in a balloon with drying tube attached) was bubbled through the reaction mixture for 15 min. The reaction was then slowly allowed to warm to r.t. and stirred under a balloon of CO_2 overnight. 0.5 mL of TFA was then added followed by 0.5 mL of H_2O. The water layer was collected, and the product was purified by C18 column chromatography (0-4 % MeCN in Water with 0.1% TFA buffer). Fractions containing product were collected and the solvent removed *in vacuo* giving a white solid (25 mg, 0.15 mmol, 40% yield)

^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.30 (d, *J* = 2.10 Hz, 1H), 6.20 (m, 1H), 3.67 (s, 2H), 2.32 (s, 3H)

^{13}C NMR (100 MHz, CD_3OD) δ ppm 181.4, 169.6, 168.2, 163.8, 114.4, 112.7, 38.4, 18.3

2.8.4.1 Preparation of Diazo Ketone B

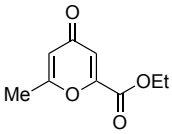




1-(2-Methyl-1,3-dioxolan-2-yl)propan-2-one 2.334: Acetyl acetone (12.67 mL, 100 mmol) was dissolved in benzene (150 mL). To this solution was added ethylene glycol (5.59 mL, 100 mmol) followed by *p*-TSA (0.120 g, 1 mmol). The reaction vessel was fitted with a Dean-Stark and reflux condenser and the reaction was heated to reflux and stirred at that temperature with the removal of water for 5 h. The reaction was then cooled to rt and dry solid K_2CO_3 (4g) was added. After stirring at rt for 10 min the suspension was filtered through a plug of celite and the product was eluted with excess CH_2Cl_2. Removal of this solvent *in vacuo* gave the product as a light brown oil. This product could then be purified by distillation, 60 °C 0.1 mmHg (8.519 g, 59 mmol, 59% yield). Data corresponds to literature reports.[111]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.97-3.93 (m, 4H), 2.75 (s, 2H), 2.20 (s, 3H), 1.39 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 206.1, 107.9, 64.7, 52.6, 31.7, 24.5



Ethyl 6-methyl-4-oxo-4H-pyran-2-carboxylate 2.335: Sodium metal (1.84 g, 80.0 mmol) was added to ethanol (50 mL). Upon complete dissolution of the sodium, THF (70 mL) was added and the mixture was cooled to 0 °C at which point 1-(2-methyl-1,3-dioxolan-2-yl)propan-2-one **2.334** (2.889 g, 20 mmol) was added slowly followed by diethyl

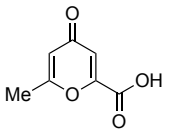
oxylate (2.870 mL, 20 mmol). This reaction was stirred at 0 °C for 30 min and then warmed to 50 °C and stirred at that temperature for 18 h. The reaction was then cooled to rt and concentrated *in vacuo* to about 30 mL (removal of THF). The resulting reaction mixture was then added to a stirred solution HCl (formed by adding acetyl chloride (10 mL) to ethanol (50 mL) and stirring for 20 min at 0 °C). Upon complete addition this mixture was heated to 50 °C and stirred at that temperature for 8 h, at which point it was cooled to r.t. and diluted with CH_2Cl_2 and washed with $NaHCO_3$ (sat.). The aqueous layer was further extracted with CH_2Cl_2 and the organic layers were then combined, washed with brine dried over Na_2SO_4 and concentrated *in vacuo* giving a crude red oil. This crude material was purified by silica gel chromatography (1:3 to 1:1 EtOAc/Hexanes). Fractions containing product were collected and the solvent was removed *in vacuo* giving the product as a red oil. (2.8392 g, 15.6 mmol, 78% yield)

TLC: R_f = 0.23 (1:1 EtOAc/Hexanes) visualized with UV

HRMS (ESI+) Calcd. For $C_9H_{10}O_4$ $[M+H]^+$ 183.0652, found 183.0650

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.00 (d, *J* = 2.30 Hz, 1H), 6.21 (d, *J* = 2.30 Hz, 1H), 4.39 (q, *J* = 7.18, 2H), 2.35 (s, 3H), 1.38 (t, *J* = 7.18 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 179.6, 166.6, 160.1, 152.8, 118.9, 116.1, 63.0, 20.1, 14.2



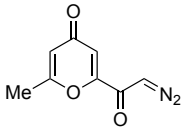
6-Methyl-4-oxo-4H-pyran-2-carboxylic acid 2.336: Ethyl 6-methyl-4-oxo-4H-pyran-2-carboxylate **2.335** (1.0293 g, 5.7 mmol) was dissolved in 2N HCl (10 mL). This reaction was then heated to 80 °C and stirred at temperature for 5 h. Upon complete hydrolysis as observed by LCMS the reaction was then cooled to rt and the solvent was removed *in vacuo* giving the product as a brown solid (0.836 g, 4.4 mmol, 77% yield, isolated the product

as the HCl salt). Pyrone formation and hydrolysis of ethyl ester could be done in 1 step with treatment of subsequent Claisen product with aqueous HCl however the poor solubility and high polarity of carboxylic acid **2.336** compromised purification.

HRMS (ESI+) Calcd. For $C_7H_6O_4$ $[M+H]^+$ 155.0344, found 155.0345

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.75 (d, J = 2.49 Hz, 1H), 6.29 (br S, 1H), 2.29 (s, 3H)

^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 178.7, 167.0, 161.1, 153.6, 117.5, 115.2, 19.4



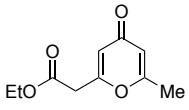
2-(2-Diazoacetyl)-6-methyl-4H-pyran-4-one 2.320: To a -15 °C suspension of 6-methyl-pyrone-2-carboxylic acid **2.336** (0.154 g, 1.0 mmol) in THF (5 mL) was added Et_3N (0.167 mL, 1.2 mmol) followed by ethyl chloroformate (0.128 mL, 1.2 mmol). This mixture was stirred at -15 °C for 1 h at which point it was filtered through a syringe containing a plug of celite, trying to keep the solution at -15 °C. MeCN (3 mL) was then added to the solution followed by a solution of $TMSCHN_2$ (0.500 mL, 1.0 mmol, 2N). This reaction was then warmed to 0 °C and stirred at temperature for 3 hours. The reaction was then concentrated *in vacuo* and the crude material was purified by silica gel chromatography (1:1 to 4:1 EtOAc/Hexanes) Fractions containing product were collected and the solvent was removed *in vacuo* giving the product as a red solid (0.080 g, 0.45 mmol, 45% yield) Note: care was taken when working up and purifying reaction material to exclude light as some light sensitivity of the product is expected. Efficiency of the Wolf rearrangement on this product decreased after prolonged storage. This was often accompanied by the product turning from a white solid to more orange in color. Separation of the product completely from the methyl and ethyl ester often proved difficult however a small amount (10-20%) of carry over did not have any adverse effect on subsequent reactions.

TLC: R_f = 0.07 (1:1 EtOAc/Hexane) Visualized with UV

HRMS (ESI+) Calcd. For $C_8H_6N_2O_3$ $[M+H]^+$ 179.0457, found 179.0459

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.92 (d, *J* = 2.38 Hz, 1H), 6.21 (m, 1H), 6.04 (s, 1H), 2.34 (d, *J* = 0.69 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 179.3, 178.1, 165.1, 157.5, 116.2, 114.3, 56.0, 20.0



Ethyl 2-(6-methyl-4-oxo-4*H*-pyran-2-yl)acetate 2.337:

Thermal conditions: An oven dried sealed tube was charged with 2-(2-Diazoacetyl)-6-methyl-4H-pyran-4-one **2.320** (0.09 g 0.05 mmol), toluene (0.5 mL) and ethanol (0.0088 mL, 0.15 mmol) the tube was then sealed and placed in a preheated oil bath at 175 °C and stirred at temperature for the allotted time. The reaction was then allowed to cool to rt and analyzed by LCMS.

Photolytic conditions: For reactions carried out at 300 nm or 419 nm a Rayonet *hv* reactor was used with the proper bulb providing the desired wavelength. For reactions carried out at 450 nm light a blue LED spotlight (10 watt, 120 V) was used. Reactions were generally run in 10 x 75 mm test tube sealed with a septum.

representative procedure: An oven dried 10 x 75 mm teste tube was charged with pyrone diazoketone **8** (0.040 g 0.22 mmol), 1,2-dichloroethane (1 mL, degassed by freeze pump thaw 3x) and ethanol (0.051 mL, 0.88 mmol). The test tube was then sealed with a septum and the reaction mixture was irradiated with *hv* light, (419 nm) for 10 hours. The resulting mixture was then concentrated *in vacuo* and the crude material was purified by silica gel chromatography (2% MeOH in CH_2Cl_2). The desired product was isolated as a red oil with 10% of pyrone ethyl ester

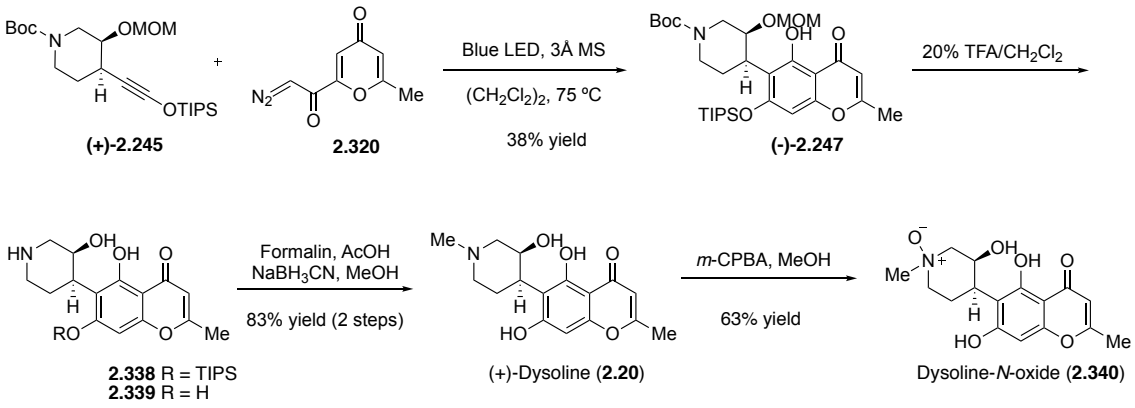
25, as determined by NMR. This material was most likely carried through from the previous step and not as a result of the rearrangement and ketene trapping.

HRMS (ESI+) Calcd. For $C_{10}H_{12}O_4$ $[M+H]^+$ 197.0814, found 197.0812

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.18 (d, *J* = 2.13 Hz, 1H), 6.09 (d, *J* = 1.94 Hz, 1H), 4.21 (q, *J* = 7.16 Hz, 2H), 3.50 (s, 2H), 2.25 (s, 3H), 1.28 (t, *J* = 7.07 Hz, 3H)

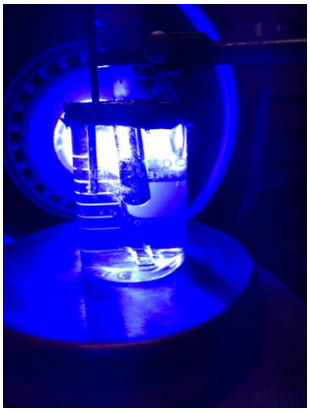
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 179.9, 167.0, 161.0, 115.8, 114.3, 61.9, 39.6, 19.9, 14.2

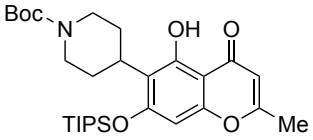
2.8.5 Benzannulation and Completion of Dysoline (2.20) Synthesis



General reaction set up for benzannulation reaction: Best results this reaction were found when a 10 x 75 mm oven dried test tube were used. The test tube was immersed in a water bath at 75 ºC in a 5 x 8.5 cm 150 mL beaker, covered with aluminum foil. Larger diameter beaker let to slower conversion rates of the diazoketone. A blue LED spotlight (10 watt, 120 V) was then used to expose the reaction mixture to 450 nm light. the mixture (see pictures below for reaction set up).





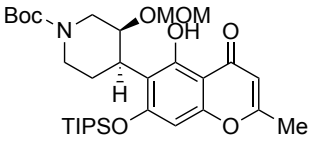


***N*-Boc-1'-(5-hydroxy-2-methyl-4-oxo-7-((triisopropylsilyl)oxy)-4*H*-chromen-6-yl)piperidine S-2.11**: To a solution of *N*-Boc-4-((triisopropylsilyl)oxy)ethynylpiperidine **2.313** (0.071 g, 0.18 mmol) in 1,2-dichloroethane (1 mL, degassed by freeze pump thaw 3x) was added 2-(2-diazoacetyl)-6-methyl-4H-pyran-4-one **2.320** (0.037 g, 0.18 mmol). The reaction mixture was transferred into a 10 x 75mm test tube containing 100 mg of 3Ä M.S. and the test tube was sealed with a septum. The reaction mixture was then placed in a beaker containing water at 75 ºC and the setup was irradiated with blue LED light. This reaction was stirred at this temperature exposed to light for 48 hours at which point it was concentrated in vacuo giving a crude red oil. This crude material was purified by silica gel chromatography (10% to 20% EtOAc/Hexanes) fractions containing product were collected and the solvent was removed *in vacuo* giving a light yellow oil which turned to a solid as the desired product. (0.039 g, 0.07 mmol, 39% yield)

TLC: 0.72 (1:1 EtOAc/Hexane) Visualized with UV

^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 13.05 (s, 1H), 6.26 (s, 1H), 5.99 (s, 1H), 4.23 (br s, 2H), 3.35 (tt, *J* = 3.58, *J* = 12.35 Hz, 1H), 2.72 (br. s, 2H), 2.43-2.34 (m, 2H), 2.32 (s, 3H), 1.50 (br s, 2H), 1.47 (s, 9H), 1.40-1.32 (m, 3H), 1.14 (d, *J* = 7.64 Hz, 18H)

^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 182.8, 166.4, 160.7, 160.0, 156.0, 118.0, 108.8, 105.5, 96.5, 79.2, 33.5, 26.7, 28.6, 20.6, 18.2, 13.2



(-)-(2'*S*, 1'*R*) *N*-Boc-2'-(methoxymethoxy)-1'-(5-hydroxy-2-methyl-4-oxo-7-((triisopropylsilyl)oxy)-4*H*-chromen-6-yl)piperidine 2.247: To a solution of (+)-*(3S, 4R) N*-Boc-3-(methoxymethoxy)-4-((triisopropylsilyl)oxy)ethynylpiperidine **2.245** (0.036g, 0.08 mmol) in 1,2-dichloroethane (1 mL, dried over 3A M.S. then degassed by freeze pump thaw 3x) was added 2-(2-Diazoacetyl)-6-methyl-4H-pyran-4-one **2.320** (0.014g, 0.08 mmol). The reaction mixture was transferred into a 10X75mm test tube containing 100 mg of 3A M.S. and the test tube was sealed with septum. The reaction mixture was then placed in a beaker containing water at 75 ºC and blue LED light was shown on the reaction. This reaction was stirred at temperature with light for 48 hours at which point it was concentrated *in vacuo* giving a crude red oil. This crude material was purified by silica gel chromatography (10% to 20% EtOAc/Hexanes) fractions containing product were collected and the solvent was removed *in vacuo* giving a light yellow oil which turned to a solid as the desired product. (0.017 g, 0.03 mmol, 38% yield)

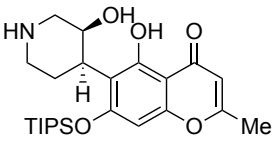
TLC: R_f = 0.65 (1:1 EtOAc/Hexane) visualized by UV and $KMnO_4$

$[\alpha]_D^{23.8}$ = -36.194 (c 1, CH_2Cl_2)

HRMS (ESI+) Calcd. For $C_{31}H_{49}NO_8Si$ $[M+H]^+$ 592.3300, found 592.3310

^{1}H NMR (600 MHz, $CDCl_3$, 50 °C) δ ppm 13.19 (s, 1H), 6.27 (s, 1H), 5.99 (s, 1H), 4.64 (d, *J* = 6.43, 1H), 4.35 (d, *J* = 6.43 Hz, 1H), 3.86 (br s, 1H), 3.42-3.36 (m, 1H), 3.21-3.14 (m, 1H), 3.00 (s, 3H), 2.89 (br s, 1H), 2.72 (br s, 1H), 2.32 (s, 3H), 1.59 (dd, *J* = 2.52, *J* = 14.26 Hz, 1H), 1.47 (s, 9H), 1.41-1.35 (m, 3H), 1.27 (s, 2H), 1.17,1.15 (d, *J* = 7.40 Hz, 18H)

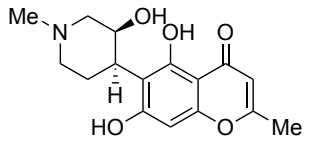
^{13}C NMR (150 MHz, $CDCl_3$, 50 °C) δ ppm 182.7, 166.3, 162.0, 160.9, 156.4, 115.1, 109.0, 105.4, 96.4, 94.8, 79.3, 72.6, 54.9, 39.6, 29.9, 28.7, 24.8, 20.4, 18.2, 17.9, 13.5, 12.6



5-Hydroxy-2-methyl-6-(piperidin-4-yl)-7-((triisopropylsilyl)oxy)-4*H*-chromen-4-one 2.338 and 2.339: (2'*S*, 1'*R*) *N*-Boc-2'-(methoxymethoxy)-1'-(5-hydroxy-2-methyl-4-oxo-7-((triisopropylsilyl)oxy)-4*H*-chromen-6-yl)piperidine **2.247** (0.022 g, 0.037 mmol) was dissolved in 20% TFA in CH_2Cl_2 (0.5 mL). This reaction was stirred at rt for 6 hours at which point complete conversion was observed by LCMS. Upon completion the reaction was concentrated *in vacuo* giving the product as a clear oil. This crude material could be used in the next step with no further purification. 1H NMR showed complete deprotection of the Boc and MOM group with a mixture of +/– the TIPS protecting group (80:20)

^{1}H NMR (400 MHz, Methanol-d_4) δ ppm 6.44 (s, 1H), 6.13 (s, 1H), 3.56-3.48 (m, 3H), 2.97 (dt, *J* = 2.28, *J* = 13.26 Hz, 2H), 2.81-271 (m, 2H), 2.34 (s, 3H), 1.78 (d, *J* = 13.31 Hz, 2H), 1.49-1.39 (m, 3H), 1.18 (d, *J* = 7.68 Hz, 18H)

^{13}C NMR (100 MHz, Methanol-d_4) δ ppm 184.3, 169.8, 161.8, 160.8, 157.8, 117.0, 109.3, 106.3, 98.0, 46.3, 32.9, 26.7, 20.3, 18.5, 14.2 (*unable to get good enough signal for 2 13C NMR peaks designated as C-1' and C-2')



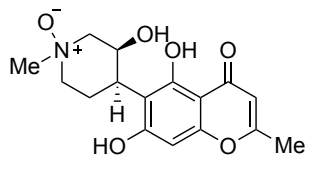
(+)-Dysoline (2.20): To a solution of 5-hydroxy-6-((3*S*,4*R*)-3-hydroxypiperidin-4-yl)-2-methyl-7-((triisopropylsilyl)oxy)-4*H*-chromen-4-one **2.338** (0.010g, 0.018 mmol) in MeOH was added formalin (0.0054 mL, 0.065 mmol, 37% solution in H_2O) followed by acetic acid (0.0051 mL, 0.072 mmol) then solid $NaBH_3CN$ (0.0017 g, 0.027 mmol) This reaction was stirred at rt for 2 hours at which point complete conversion to the desired product was observed by LCMS. The crude reaction mixture was then concentrated *in vacuo* giving a crude red oil. This material was purified by Semi-Prep HPLC, C18 (Luna 5 □, 250x 20 mm) column, 2.5 mL/min flow rate 25% to 28% MeCN/H_2O (+0.1 %TFA) over 10 min, RT = 7.5 min observed at 220 nm wavelength. Isolated the product as a clear oil (0.0063 g, 0.015 mmol, 83% yield) Isolated as the TFA salt

$[\alpha]_D^{22.8}$ = 9.999 (c 0.42, MeOH)

HRMS (ESI+) Calcd. For $C_{16}H_{19}NO_5$ $[M+H]^+$ 306.1341, found 306.1350

^{1}H NMR (600 MHz, Methanol-*d*$_4$) δ ppm 6.42 (s, 1H), 6.10 (s, 1H), 4.26 (br, s 1H)), 3.74-3.71 (m, 1H), 3.57-3.54 (m, 1H), 3.47 (dt, *J* = 2.56, *J* = 12.52 Hz, 1H), 3.37 (d, *J* = 12.52 Hz, 1H) 3.20 (td, *J* = 2.93, *J* = 12.78 Hz, 1H), 3.16-3.06 (m, 1H) 2.89 (s, 3H) 2.37 (s, 3H) 1.77 (dd, *J* = 2.35, *J* = 14.26 Hz, 1H)

^{13}C NMR (150 MHz, Methanol-*d*$_4$) δ ppm 184.1, 169.5, 164.2, 161.2, 158.5, 111.5, 109.0, 105.0, 95.7, 68.3, 61.6, 56.7, 44.1, 36.2, 22.9, 20.3



Dysoline-*N*-Oxide 2.340: To a stirred solution of dysoline (**2.20**) (0.0073g, 0.024 mmol) in MeOH was added *m*-CPBA (0.016 g, 0.072 mmol) solid . The reaction was stirred at rt and monitored by LCMS.

After 2 hours only partial completion was observed so an additional *m*-CPBA (3 equiv) was added. The reaction was then stirred overnight. Upon complete conversion the reaction mixture was purified directly by Semi-Prep HPLC, C18 (Luna 5 υ, 250x 20 mm) column, 2.5 mL/min flow rate 0% to 28% MeCN/H_2O (+0.1 %TFA) over 10 min, RT = 4.3 min observed at 220 nm wavelength. Isolated the product as a white solid (0.0064 g, 0.015 mmol, 63% yield) Isolated as the TFA salt

HRMS (ESI+) Calcd. For $C_{16}H_{19}NO_6$ $[M+H]^+$ 322.1291, found 322.1291

^{1}H NMR (600 MHz, Methanol-*d*$_4$) δ ppm 6.34 (s, 1H), 6.06 (S, 1H), 4.32 (br s, 1H), 3.81 (d, *J* = 13.12 Hz, 1H), 3.77-3.63 (m, 4H), 3.51 (br s, 1H), 3.26 (br s, 3H), 2.36 (s, 3H), 1.71 (d, *J* = 13.74 Hz, 1H)

^{13}C NMR (150 MHz, Methanol-*d*$_4$) δ ppm 184.0, 169.3, 166.9, 165.4, 161.0, 158.5, 112.1, 108.7, 104.5, 96.2, 70.9, 67.9, 60.1, 37.2, 21.4, 20.3

2.8.6 Biological Testing

Cell Culture and toxicity testing. All cell lines were screened for mycoplasma by PCR and authenticated by short tandem repeat (STR) analysis through the McDermott Core at UT Southwestern. Cell lines were cultured in RPMI 1640 (Sigma) supplemented with 5% FBS (Sigma) and 2 mM L-glutamine (Sigma). For dose-response analyses, cells were plated in 96-well plates at 15% confluence in 100 µl of the above medium and were allowed to adhere overnight. On the next day, this medium was removed and new medium containing one of 10 concentrations of the compound was added, starting from 50 µM and decreasing in threefold serial dilutions in DMSO. The final concentration of DMSO in each well was 0.5%. Each dose of compound was tested in duplicate, and the values displayed represent the averages of these duplicates. Viability was determined using CellTiter Glo according to the manufacturer's procedures.

Positive controls included in the assay: Taxol (HT1080) and Indisulam (HCT116)

Cytokine response assay: Following manufacturer instructions, freshly harvested mouse spleenocyte cells were utilized, the cells were treated with ConA and LPS to promote T and B cell activity respectively. The cells were then incubated with dysoline for 72 h at 37 ºC with 5% CO_2, terflunomide was used as a positive control. Cells were tested in the Celltiter-Glo assay to measure viability in addition to testing for IL-6 cytokine response using a Quantikine ELISA assay. no IL-6 inhibition was observed

2.8.7 Table of NMR Peaks for Isolated vs. Synthetic Dysoline (2.20)

	^{1}H NMR (C_5D_5N)			^{1}H Methanol-d_4	^{13}C Methanol-d_4		
Carbon	Reported	Observed	Δ	Observed	Reported	Observed	Δ
C-1					164.2	164.2	0
C-2					169.5	169.5	0
C-3	6.13	6.14	0	6.10	109.0	109.0	0
C-4					184.1	184.1	0
C-5					105.0	105.0	0
C-6					161.2	161.2	0
C-7					111.6	111.5	0.1
C-8					158.5	158.5	0
C-9	6.74	6.74	0	6.42	95.8	95.7	0.1
C-10	2.11	2.11	0	2.37	20.3	20.3	0
C-1’	3.98-3.95	3.98-3.95	0	3.74-3.71	36.2	36.2	0
C-2’	4.68	4.65	0.03	4.26	68.3	68.3	0
C-3’	3.72-3.58	3.79-3.76	0.07	3.47	61.6	61.6	0
		3.21-3.18		3.37			
C-4’	3.89-3.86	3.64-3.60	0.25	3.57-3.54	59.7*	56.7	3
	3.43-3.40	2.99-2.95	0.44	3.20			
C-5’	3.17-3.13	3.21-3.18	0.04	3.16-3.06	22.9	22.9	0
	1.87-1.85	1.83-1.80	0.04	1.77			
C-6’	3.15	2.88	0.27	2.89	44.2	44.1	0.1

* This difference is attributed to miss-annotation in the isolation paper-the spectra overlay without discrepancy
**Difference in proton NMR peaks attributed to differences in protonation status of our synthetic material compared to the natural sample

2.9 References

[1] (a) Ilkei, V.; Hazai, L.; Antus, S.; Bölcskei, H. in *Studies in Natural Products Chemistry, Vol. 56* (Ed.: R. Atta ur), Elsevier, **2018**, pp. 247; (b) Houghton, P. J. in *The Alkaloids: Chemistry and Pharmacology, Vol. 31* (Ed.: A. Brossi), Academic Press, **1987**, pp. 67.

[2] (a) Keri, R. S.; Budagumpi, S.; Pai, R. K.; Balakrishna, R. G. *Eur. J. Med. Chem.* **2014**, *78*, 340-374. (b) Singh, M.; Kaur, M.; Silakari, O. *Eur. J. Med. Chem.* **2014**, *84*, 206-239.

[3] Khadem, S.; Marles, R. J., *Molecules* **2012,** *17*, 191-206.

[4] Wang, L.; Wang, S.; Yang, S.; Guo, X.; Lou, H.; Ren, D. *Phytochemistry* **2012,** *82*, 166-171.

[5] Schlittler, E.; Spitaler, U. *Tetrahedron Lett.* **1978,** *19*, 2911-2914.

[6] Houghton, P. J.; Hairong, Y. *Planta Med.* **1985,** *51*, 23-27.

[7] Lee, H.-H.; Shin, J.-S.; Lee, W.-S.; Ryu, B.; Jang, D. S.; Lee, K.-T. *J. Nat. Prod.* **2016**, *79*, 711-720.

[8] (a) Ghosal, S.; Kumar, Y.; Singh, S.; Ahad, K. *Phytochemistry* **1983,** *22*, 2591-2593. (b) Yongwen, Z.; Yuwu, C. *Phytochemistry* **1997,** *45*, 401-403.

[9] Marrassini, C.; Davicino, R.; Acevedo, C.; Anesini, C.; Gorzalczany, S.; Ferraro, G. *J. Nat. Prod.* **2011,** *74*, 1503-1507.

[10] Dhulap, S.; Mandhare, A.; Hirwani, R. *Expert Opin. Ther. Pat.* **2013,** *23*, 1561-1580.

[11] Ma, H.; Chen, H.; Sun, L.; Tong, L.; Zhang, T. *Fitoterapia* **2014,** *93*, 54-61.

[12] Nguyen, T. B.; Lozach, O.; Surpateanu, G.; Wang, Q.; Retailleau, P.; Iorga, B. I.; Meijer, L.; Guéritte, F. *J. Med. Chem.* **2012**, *55*, 2811-2819.

[13] (a) Abou Zahr, A.; Borthakur, G. *Expert Opin. Emerg. Drugs* **2017,** *22*, 137-148. (b) Ingham, M.; Schwartz, G. K. *J. Clin. Oncol.* **2017,** *35*, 2949-2959.

[14] Johns, S. R.; Russel, J. H.; Heffernan, M. L., *Tetrahedron Lett.* **1965,** *6*, 1987-1991.

[15] Naik, R. G.; Kattige, S. L.; Bhat, S. V.; Alreja, B.; de Souza, N. J.; Rupp, R. H. *Tetrahedron* **1988,** *44*, 2081-2086.

[16] Ismail, I. S.; Nagakura, Y.; Hirasawa, Y.; Hosoya, T.; Lazim, M. I. M.; Lajis, N. H.; Shiro, M.; Morita, H. *J. Nat. Prod.* **2009**, *72*, 1879-1883.

[17] K. Jain, S.; B. Bharate, S.; Vishwakarma, A. R. *Mini-Rev. Med. Chem.* **2012,** *12*, 632-649.

[18] FDA grants orphan drug status to Alvocidib for AML (2014), (**available at** https://www.healio.com/hematology-oncology/leukemia/news/online/%7b74c6a69e-4529-400d-98e9-d5ee6c602122%7d/fda-grants-orphan-drug-status-to-alvocidib-for-aml).

[19] Kim, K. S.; Kimball, S. D.; Misra, R. N.; Rawlins, D. B.; Hunt, J. T.; Xiao, H.-Y.; Lu, S.; Qian, L.; Han, W.-C.; Shan, W.; Mitt, T.; Cai, Z.-W.; Poss, M. A.; Zhu, H.; Sack, J. S.; Tokarski, J. S.; Chang, C. Y.; Pavletich, N.; Kamath, A.; Humphreys, W. G.; Marathe, P.; Bursuker, I.; Kellar, K. A.; Roongta, U.; Batorsky, R.; Mulheron, J. G.; Bol, D.; Fairchild, C. R.; Lee, F. Y.; Webster, K. R. *J. Med. Chem.* **2002,** *45*, 3905-3927.

[20] Bharate, S. B.; Kumar, V.; Jain, S. K.; Mintoo, M. J.; Guru, S. K.; Nuthakki, V. K.; Sharma, M.; Bharate, S. S.; Gandhi, S. G.; Mondhe, D. M.; Bhushan, S.; Vishwakarma, R. A. *J. Med. Chem.* **2018,** *61*, 1664-1687.

[21] Jain, S. K.; Meena, S.; Qazi, A. K.; Hussain, A.; Bhola, S. K.; Kshirsagar, R.; Pari, K.; Khajuria, A.; Hamid, A.; Shaanker, R. U.; Bharate, S. B.; Vishwakarma, R. A. *Tetrahedron Lett.* **2013**, *54*, 7140.

[22] (a) Abe, I.; Utsumi, Y.; Oguro, S.; Morita, H.; Sano, Y.; Noguchi, H. *J. Am. Chem. Soc.* **2005**, *127*, 1362-1363. (b) Abe, I.; Morita, H. *Nat. Prod. Rep.* **2010**, *27*, 809-838.

[23] (a) Winkel-Shirley, B. *Curr. Opin. Plant Biol.* **2002,** *5*, 218-223 (b) Hahlbrock, K.; Grisebach, H. *Ann. Rev. Plant Physiol.* **1979,** *30*, 105-130

[24] (a) Gaspar, A.; Matos, M. J.; Garrido, J.; Uriarte, E.; Borges, F. *Chem. Rev.* **2014**, *114*, 4960-4992. (b) K. K. Murthi, M. Dubay, C. McClure, L. Brizuela, M. D. Boisclair, P. J. Worland, M. M. Mansuri, K. Pal, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1037-1041.

[25] Ho, T. C.; Kamimura, H.; Ohmori, K.; Suzuki, K. *Org. Lett.* **2016,** *18*, 4488-4490.

[26] Macklin, T. K.; Reed, M. A.; Snieckus, V. *Eur. J. Org. Chem.* **2008,** 1507-1509.

[27] Kelly, T. R.; Kim, M. H. *J. Org. Chem.* **1992,** *57*, 1593-1597.

[28] Lu, K.; Chu, J.; Wang, H.; Fu, X.; Quan, D.; Ding, H.; Yao, Q.; Yu, P. *Tetrahedron Lett.* **2013,** *54*, 6345-6348.

[29] (a) Nguyen, T. B.; Wang, Q.; Guéritte, F. *Eur. J. Org. Chem.* **2011,** 7076-7079. (b) also see reference 10 (c) Ilkei, V.; Spaits, A.; Prechl, A.; Müller, J.; Könczöl, Á.; Lévai, S.; Riethmüller, E.; Szigetvári, Á.; Béni, Z.; Dékány, M.; Martins, A.; Hunyadi, A.; Antus, S.;

Szántay, C.; Balogh, G. T.; Kalaus, G.; Bölcskei, H.; Hazai, L. *Tetrahedron* **2017,** *73*, 1503-1510.

[30] Wu, Z.; Wei, G.; Lian, G.; Yu, B. *J. Org. Chem.* **2010,** *75*, 5725-5728.

[31] Wei, X.; Liang, D.; Wang, Q.; Meng, X.; Li, Z. *Org. Biomol. Chem.* **2016,** *14*, 8821-8831.

[32] (a) Crampton, M. R. Nucleophilic Aromatic Substitution. In *Arene Chemistry*, John Wiley & Sons, Inc: **2015**; pp 131-173. (b) Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951,** *49*, 273-412.

[33] (a) Gandon, V. Cobalt-Mediated [2+2+2] Cycladdition. In *Transition-Metal-Mediated Ring Construction*, Tanaka, K., Ed. John Wiley & Sons, Inc: **2013**. (b) Yamamoto, Y. Ruthenium-Mediated [2+2+2] Cycloaddition. In *Transition-Metal-Mediated Aromatic Ring Construction*, Tanaka, K., Ed. John Wiley&Sons, Inc.: **2013**; pp 71-125. (C) Vollhardt, K. P. C. *Angew. Chem. Int. Ed* **1984,** *23*, 539-556.

[34] For recent examples see: (a) Chaubet, G.; Goh, S. S.; Mohammad, M.; Gockel, B.; Cordonnier, M.-C. A.; Baars, H.; Phillips, A. W.; Anderson, E. A. *Chem. Eur. J.* **2017,** *23*, 14080-14089. (b) Brenna, D.; Villa, M.; Gieshoff, T. N.; Fischer, F.; Hapke, M.; Jacobi von Wangelin, A., *Angew. Chem. Int. Ed* **2017,** *56*, 8451-8454. (c) Ruhl, K. E.; Rovis, T. *J. Am. Chem. Soc.* **2016,** *138*, 15527-15530. (d) More, A. A.; Ramana, C. V. *J. Org. Chem.* **2016,** *81*, 3400-3406. (e) Jungk, P.; Fischer, F.; Thiel, I.; Hapke, M. *J. Org. Chem.* **2015,** *80*, 9781-9793. (f) Röse, P.; Garcia, C. C. M.; Pünner, F.; Harms, K.; Hilt, G. *J. Org. Chem.* **2015,** *80*, 7311-7316.

[35] (a) Chan, T.-H.; Brownbridge, P. *J. Am. Chem. Soc.* **1980,** *102*, 3534-3538. (b) Chan, T.-H.; Brownbridge, P. *J. Chem. Soc. Chem. Commun.* **1979**, 578-579

[36] Selected examples: (a) Sher, M.; Tam Dang, T. H.; Ahmed, Z.; Rashid, M. A.; Fischer, C.; Langer, P. *J. Org. Chem.* **2007,** *72*, 6284-6286. (b) Langer, P.; Bose, G. *Angew. Chem. Int. Ed* **2003,** *42*, 4033-4036.

[37] (a) Mal, D.; Pahari, P. *Chem. Rev.* **2007,** *107*, 1892-1918. (b) Nicolaou, K. C.; Lu, M.; Chen, P.; Shah, A. A. *Angew. Chem. Int. Ed.* **2015,** *54*, 12687-12691.

[38] Hauser, F. M.; Rhee, R. P., *J. Org. Chem.* **1978,** *43*, 178-180.

[39] Liau, B. B.; Milgram, B. C.; Shair, M. D. *J. Am. Chem. Soc.* **2012,** *134*, 16765-16772.

[40] Baldwin, J. E.; McDaniel, M. C. *J. Am. Chem. Soc.* **1968,** *90*, 6118-6124.

[41] (a) Karlsson, J. O.; Nghi, V. N.; Foland, L. D.; Moore, H. W. *J. Am. Chem. Soc.* **1985,** *107*, 3392-3393. (b) Foland, L. D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W. *J. Am. Chem. Soc.* **1989,** *111*, 975-989. (c) Perri, S. T.; Moore, H. W. *J. Am. Chem. Soc.* **1990,** *112*, 1897-1905. (d) Liebeskind, L. S.; Iyer, S.; Jewell, C. F. *J. Org. Chem.* **1986,** *51*, 3065-3067. (e) Perri, S. T.; Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1986,** *51*, 3067-3068.

[42] (a) Xu, S. L.; Moore, H. W. *J. Org. Chem.* **1989,** *54*, 4024-4026. (b) Xu, S. L.; Moore, H. W. *J. Org. Chem.* **1992,** *57*, 326-338.

[43] (a) Moore, H. W.; Perri, S. T. *J. Org. Chem.* **1988,** *53*, 996-1003. (b) Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Am. Chem. Soc.* **1989,** *111*, 989-995. (c) Perri, S. T.; Dyke, H. J.; Moore, H. W. *J. Org. Chem.* **1989,** *54*, 2032-2034. (d) Enhsen, A.; Karabelas, K.; Heerding, J. M.; Moore, H. W. *J. Org. Chem.* **1990,** *55*, 1177-1185.

[44] (a) Liebeskind, L. S.; Foster, B. S. *J. Am. Chem. Soc.* **1990,** *112*, 8612-8613. (b) Krysan, D. J.; Gurski, A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1992,** *114*, 1412-1418. (c) Gurski, A.; Liebskind, L. S. *J. Am. Chem. Soc.* **1993,** *115*, 6101-6108. (d) Liebeskind, L. S.; Iyer, S.; Jewell, C. F. *J. Org. Chem.* **1986,** *51*, 3065-3067.

[45] (a) Liebeskind, L. S.; Riesinger, S. W. *J. Org. Chem.* **1993,** *58*, 408-413. (b) Koo, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1995,** *117*, 3389-3404.

[46] Edwards, J. P.; Krysan, D. J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1993,** *115*, 9868-9869.

[47] Liebeskind, L. S.; Wang, J. *J. Org. Chem.* **1993,** *58*, 3550-3556.

[48] (a) Nichols, A. L.; Zhang, P.; Martin, S. F. *Org. Lett.* **2011,** *13*, 4696-4699. (b) Yang, J.; Knueppel, D.; Cheng, B.; Mans, D.; Martin, S. F. *Org. Lett.* **2015,** *17*, 114-117. (c) Blumberg, S.; Martin, S. F. *Org. Lett.* **2017,** *19*, 790-793.

[49] (a) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984,** *49*, 1672-1674. (b) Lawlor, M. D.; Lee, T. W.; Danheiser, R. L. *J. Org. Chem.* **2000,** *65*, 4375-4384. (c) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990,** *55*, 1959-1964.

[50] Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990,** *112*, 3093-3100

[51] (a) Willumstad, T. P.; Boudreau, P. D.; Danheiser, R. L. *J. Org. Chem.* **2015,** *80*, 11794-11805; (b) Mak, X. Y.; Crombie, A. L.; Danheiser, R. L. *J. Org. Chem.* **2011,** *76*, 1852-1873.

[52] (a) Danheiser, R. L.; Gee, S. K.; Perez, J. J. *J. Am. Chem. Soc.* **1986,** *108*, 806-810; (b) Dudley, G. B.; Takaki, K. S.; Cha, D. D.; Danheiser, R. L. *Org. Lett.* **2000,** *2*, 3407-3410.

[53] Kowalski, C. J.; Lal, G. S., *J. Am. Chem. Soc.* **1988,** *110*, 3693-3695.

[54] Zhang, W.; Ready, J. M., *J. Am. Chem. Soc.* **2016,** *138*, 10684-10692.

[55] Zhang, W.; Ready, J. M., *Angew. Chem. Int. Ed.* **2014,** *53*, 8980-8984.

[56] Dötz, K. H., *Angew. Chem. Int. Ed* **1975,** *14*, 644-645.

[57] (a)Wang, Z., Dötz Benzannulation. In *Comprehensive Organic Name Reactions and Reagents*, John Wiley & Sons, Inc.: 2010. (b) Hofmann, P.; Hämmerle, M. *Angew. Chem. Int. Ed* **1989,** *28*, 908-910. (c) Harrity, J. P. A.; Kerr, W. J.; Middlemiss, D. *Tetrahedron* **1993,** *49*, 5565-5576.

[58] (a) Chen, J. T.; Huang, T. M.; Cheng, M. C.; Lin, Y. C.; Wang, Y. *Organometallics* **1992,** *11*, 1761-1763. (b) Busetto, L.; Marchetti, F.; Mazzoni, R.; Salmi, M.; Zacchini, S.; Zanotti, V. *Chem. Commun.* **2010,** *46*, 3327-3329.

[59] (a) Bos, M. E.; Wulff, W. D.; Miller, R. A.; Chamberlin, S.; Brandvold, T. A., *J. Am. Chem. Soc.* **1991,** *113*, 9293-9319. (b) Yamashita, A.; Toy, A., *Tetrahedron Lett.* **1986,** *27*, 3471-3474. (c) Wu, C.; Berbasov, D. O.; Wulff, W. D., *J. Org. Chem.* **2010,** *75*, 4441-4452. (d) Wulff, W. D.; Tang, P. C.; McCallum, J. S., *J. Am. Chem. Soc.* **1981,** *103*, 7677-7678.

[60] (a) Tanaka, K.; Watanabe, M.; Ishibashi, K.; Matsuyama, H.; Saikawa, Y.; Nakata, M., *Org. Lett.* **2010,** *12*, 1700-1703. (b)Tanaka, K.; Matsuyama, H.; Watanabe, M.; Fujimori, Y.; Ishibashi, K.; Ozawa, T.; Sato, T.; Saikawa, Y.; Nakata, M., *J. Org. Chem.* **2014,** *79*, 9922-9947

[61] Song, W.; Blaszczyk, S. A.; Liu, J.; Wang, S.; Tang, W., *Org. Biomol. Chem.* **2017,** *15*, 7490-7504.

[62] (a) Song, W.; Li, X.; Yang, K.; Zhao, X.-l.; Glazier, D. A.; Xi, B.-m.; Tang, W., *J. Org. Chem.* **2016,** *81*, 2930-2942. (b) Li, X.; Xie, H.; Fu, X.; Liu, J.-t.; Wang, H.-y.; Xi, B.-m.; Liu, P.; Xu, X.; Tang, W., *Chem. Eur. J.* **2016,** *22*, 10410-10414.

[63] Shindo, M., *Synthesis* **2003**, 2275-2288.

[64] For examples of reactions with Ynol ether see: (a) Gray, V. J.; Wilden, J. D., *Org. Biomol. Chem.* **2016,** *14*, 9695-9711. (b) Minehan, T. G., *Acc. Chem. Res.* **2016,** *49*, 1168-1181. (c) Qi, X.; Ready, J. M., *Angew. Chem. Int. Ed.* **2008,** *47*, 7068-7070. (d) also see ref. 55 (e) Winterton, S. E.; Ready, J. M., *Org. Lett.* **2016,** *18*, 2608-2611.

[65] For a more detailed discussion on the preparation of ynol ethers see: Zhang, W. Synthesis of Aryl Ynol Ethers and Their Synthetic Applications. Ph.D. Dissertation, The University of Texas Southwestern Medical Center, Dallas, TX, 2016.

[66] Pirrung, M. C.; Hwu, J. R. *Tetrahedron Lett.* **1983,** *24*, 565-568.

[67] Danheiser, R. L.; Nishida, A.; Savariar, S.; Trova, M. P. *Tetrahedron Lett.* **1988,** *29*, 4917-4920.

[68] Julia, M.; Saint-Jalmes, V. P.; Verpeaux, J.-N. *Synlett* **1993,** 233-234.

[69] (a) Kowalski, C. J.; Fields, K. W., *J. Am. Chem. Soc.* **1982,** *104*, 321-323. (b) Kowalski, C. J.; Reddy, R. E., *J. Org. Chem.* **1992,** *57*, 7194-7208. (c) Reddy, R. E.; Kowalski, C. J., *Org. Synth.* **1993,** *71*, 146-152. (d) Kowalski, C. J.; Haque, M. S.; Fields, K. W. *J. Am. Chem. Soc.* **1985,** *107*, 1429-1430.

[70] Kowalski, C. J.; Lal, G. S.; Haque, M. S., *J. Am. Chem. Soc.* **1986,** *108*, 7127-7128.

[71] Lam, Y.-h.; Houk, K. N.; Cossy, J.; Gomez Pardo, D.; Cochi, A., *Helvetica Chimica Acta* **2012,** *95*, 2265-2277.

[72] (a) Takemura, S.; Miki, Y.; Uono, M.; Yoshimura, K.; Kuroda, M.; Suzuki, A., *Chem. Pharm. Bull.* **1981,** *29*, 3026-3032. (b) Olofson, R. A.; Schnur, R. C.; Bunes, L.; Pepe, J. P., *Tetrahedron Lett.* **1977,** *18*, 1567-1570.

[73] (a) Sukeda, M.; Ichikawa, S.; Matsuda, A.; Shuto, S., *J. Org. Chem.* **2003,** *68* (9), 3465-3475. (b) Scheunemann, M.; Hennig, L.; Funke, U.; Steinbach, J. *Tetrahedron* **2011,** *67*, 3448-3456. (c) Gil, L.; Compère, D.; Guilloteau-Bertin, B.; Chiaroni, A.; Marazano, C., *Synthesis* **2000**, 2117-2126.

[74] Chang, D.; Heringa, M. F.; Witholt, B.; Li, Z., *J. Org. Chem.* **2003,** *68*, 8599-8606.

[75] Wynberg, H.; Staring, E. G. J., *J. Am. Chem. Soc.* **1982,** *104*, 166-168.

[76] Gaunt, M. J.; Johansson, C. C. C., *Chem. Rev.* **2007,** *107*, 5596-5605.

[77] (a) Sauer, J. C., *J. Am. Chem. Soc.* **1947,** *69*, 2444-2448 (b) Calter, M. A., *J. Org. Chem.* **1996,** *61*, 8006-8007.

[78] Wilson, J. E.; Fu, G. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 6358-6360

[79] Zhu, C.; Shen, X.; Nelson, S. G. *J. Am. Chem. Soc.* **2004**, *126*, 5352-5353.

[80] Cortez, G. S.; Tennyson, R. L.; Romo, D. *J. Am. Chem. Soc.* **2001**, *123*, 7945-7946.

[81] (a) Funk, R. L.; Abelman, M. M.; Jellison, K. M. *Synlett* **1989**, 36-37. (b) Brady, W. T.; Marchand, A. P.; Giang, Y. F.; Wu, A.-H., *Synthesis* **1987**, 395-396.

[82] Oh, S. H.; Cortez, G. S.; Romo, D. *J. Org. Chem.* **2005**, *70*, 2835-2838.

[83] G. Liu, M. E. Shirley, D. Romo, *J. Org. Chem.* **2012**, *77*, 2496-2500.

[84] Kong, W.; Romo, D. *J. Org. Chem.* **2017**, *82*, 13161-13170.

[85] Thodi, K.; Barbayianni, E.; Fotakopoulou, I.; Bornscheuer, U. T.; Constantinou-Kokotou, V.; Moutevelis-Minakakis, P.; Kokotos, G., *J. Mol. Catal. B-Enzym.* **2009,** *61*, 241-246.

[86] Mouna, A. M.; Nguyen, C.; Rage, I.; Xie, J.; Née, G.; Mazaleyrat, J. P.; Wakselman, M., *Synth. Commun.* **1994,** *24*, 2429-2435

[87] (a) White, J. M.; Tunoori, A. R.; Georg, G. I. *J. Am. Chem. Soc.* **2000**, *122*, 11995-11996. (b) Zhao, Y.; Snieckus, V. *Org. Lett.* **2014**, *16*, 390-393.

[88] Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.

[89] The corresponding $Si(Et_3)$ protected alcohol was attempted in the path with no success. See experimental for more detail.

[90] Allen, A. D.; Tidwell, T. T. *Chem. Rev.* **2013,** *113*, 7287-7342.

[91] Klier, L.; Bresser, T.; Nigst, T. A.; Karaghiosoff, K.; Knochel, P. *J. Am. Chem. Soc.* **2012,** *134*, 13584-13587.

[92] Crimmins, M. T.; Washburn, D. G.; Zawacki, F. J., *Org. Synth.* **2000,** *77*, 114-117.

[93] Mihovilovic, M. D.; Spreitzer, H. *Monatshefte fur Chemie* **2005**, 136, 1197-1203.

[94] (a) Arndt, F.; Eistert, B.; Partale, W. *Ber. Dtch. Chem. Ges.* **1927**, 60, 1364–1370. (b) Kirmse, W., *Eur. J. Org. Chem.* **2002,** *2002*, 2193-2256. (d) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994,** *94*, 1091-1160.

[95] (a) Cesar, J.; Sollner Dolenc, M. *Tetrahedron Lett.* **2001**, *42*, 7099. (b) Podlech, J.; Seebach, D., *Angew. Chem. Int. Ed.* **1995,** *34*, 471-472. (c) Müller, A.; Vogt, C.; Sewald, N. *Synthesis* **1998**, 837-841

[96] Gutiérrez-Abad, R.; Illa, O.; Ortuño, R. M. *Org. Lett.* **2010**, *12*, 3148

[97] Sikriwal, D.; Dikshit, D. K. *Tetrahedron* **2011**, *67*, 210

[98] (a) OAc-Quinine: Molnár, I. G.; Gilmour, R. *J. Am. Chem. Soc.* **2016**, *138*, 5004. (b) OTMS-quinine: Mir, R.; Dudding, T. *J. Org. Chem.* **2017**, *82*, 709

[99] Li, P.; Xu, J.-C. *Tetrahedron* **2000**, *56*, 8119

[100] The compound was also reported by Sikriwal and Dikshit (ref 97) however attempts at repeating their conditions resulted in lower yields than reported.

[101] Mori, M.; Tonogaki, K.; Kinoshita, A. *Org. Synth.* **2005**, *81*, 1

[102] White, J. M.; Tunoori, A. R.; Georg, G. I. *J. Am. Chem. Soc.* **2000**, *122*, 11995

[103] Zhao, Y.; Snieckus, V. *Org. Lett.* **2014**, *16*, 390

[104] Bartoszewicz, A.; Kalek, M.; Nilsson, J.; Hiresova, R.; Stawinski, J. *Synlett* **2008**, *2008*, 37-40.

[105] Liu, P.; Hu, Z.; DuBois, B. G.; Moyes, C. R.; Hunter, D. N.; Zhu, C.; Kar, N. F.; Zhu, Y.; Garfunkle, J.; Kang, L.; Chicchi, G.; Ehrhardt, A.; Woods, A.; Seo, T.; Woods, M.; van Heek, M.; Dingley, K. H.; Pang, J.; Salituro, G. M.; Powell, J.; Terebetski, J. L.; Hornak, V.; Campeau, L.-C.; Lamberson, J.; Ujjainwalla, F.; Miller, M.; Stamford, A.; Wood, H. B.; Kowalski, T.; Nargund, R. P.; Edmondson, S. D. *ACS Med. Chem. Lett.* **2015**, *6*, 936

[106] Raimundo, B. C.; Oslob, J. D.; Braisted, A. C.; Hyde, J.; McDowell, R. S.; Randal, M.; Waal, N. D.; Wilkinson, J.; Yu, C. H.; Arkin, M. R. *J. Med. Chem.* **2004**, *47*, 3111-3130.

[107] Wei, Z.-Y.; Brown, W.; Takasaki, B.; Plobeck, N.; Delorme, D.; Zhou, F.; Yang, H.; Jones, P.; Gawell, L.; Gagnon, H.; Schmidt, R.; Yue, S.-Y.; Walpole, C.; Payza, K.; St-Onge, S.; Labarre, M.; Godbout, C.; Jakob, A.; Butterworth, J.; Kamassah, A.; Morin, P.-E.; Projean, D.; Ducharme, J.; Roberts, E. *J. Med. Chem.* **2000**, *43*, 3895

[108] Reddy, R. E.; Kowalski, C. J. *Org. Synth.* **1998**, *9*, 426

[109] Mbofana, C. T.; Miller, S. J. *J. Am. Chem. Soc.* **2014**, 136, 3285-3293

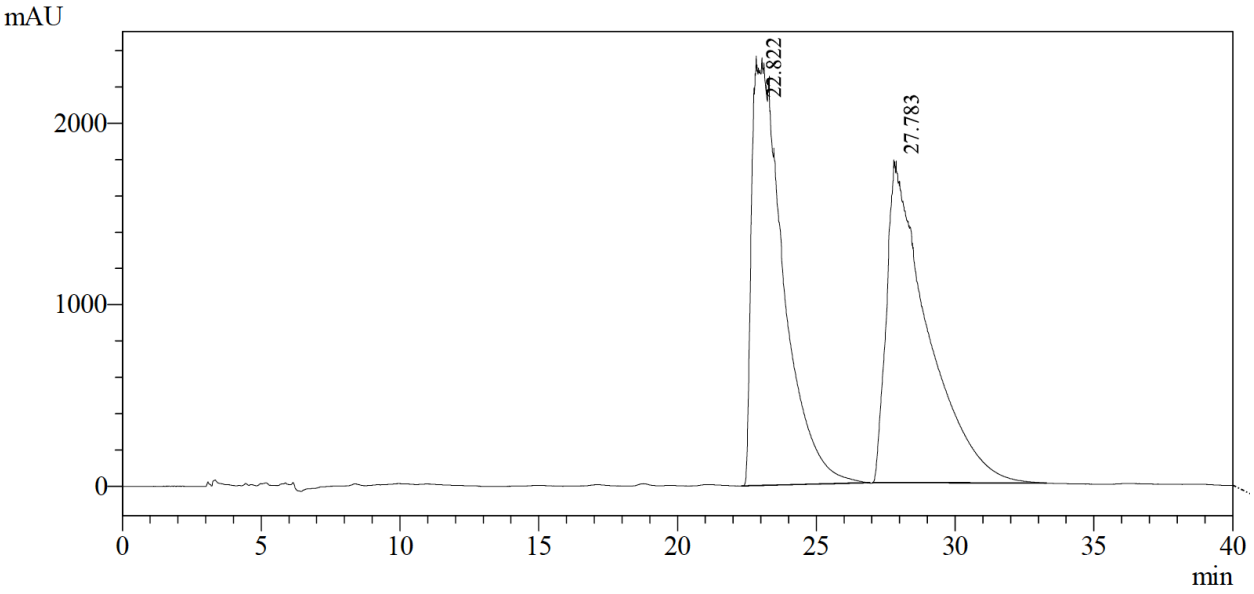
[110] Mihovilovic, M. D.; Spreitzer, H. *Monatshefte fur Chemie* **2005**, 136, 1197-1203

[111] Nawrat, C. C.; Lewis, W.; Moody, C. J. *J. Org. Chem.* **2011**, *76*, 7872

Appendix 2: Chiral HPLC traces

(rac) *N*-Boc-4-(benzylcarbamoyl)-3-hydroxypiperidine S-2.4

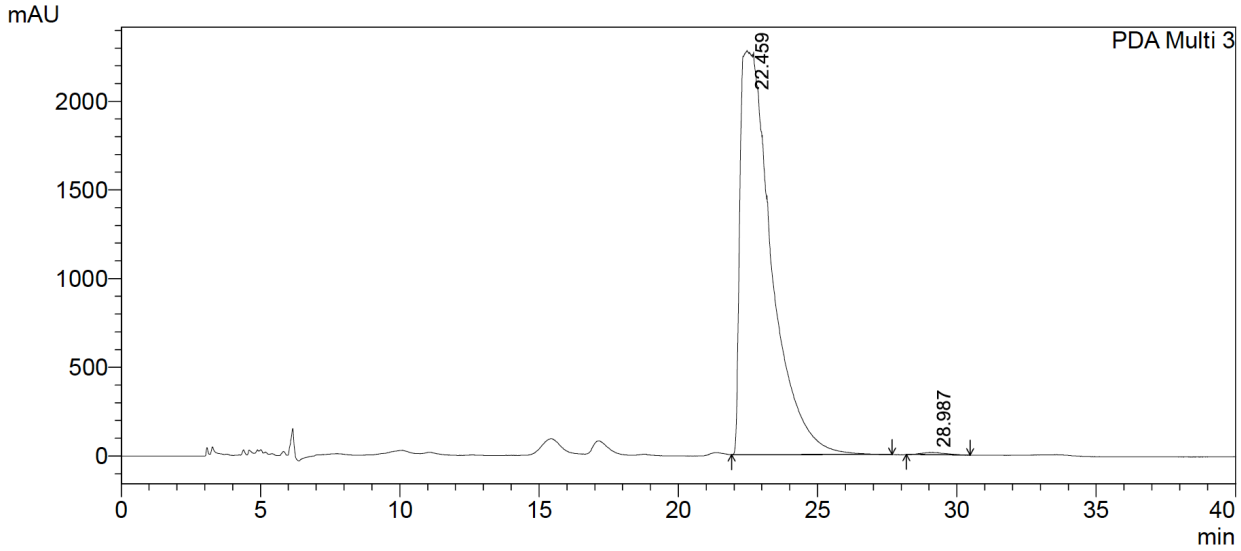
Conditions: 5% IPA/hexanes, 1 mL/min chiralpak 1A column



PDA Ch2 190nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	22.822	186966647	2367013	50.571	57.082
2	27.783	182744154	1779691	49.429	42.918
Total		369710801	4146704	100.000	100.000

(-)-(3*S*, 4*S*) *N*-Boc-4-(benzylcarbamoyl)-3-hydroxypiperidine S-2.4: Enantiopure sample using $(DHQD)_2Phal$

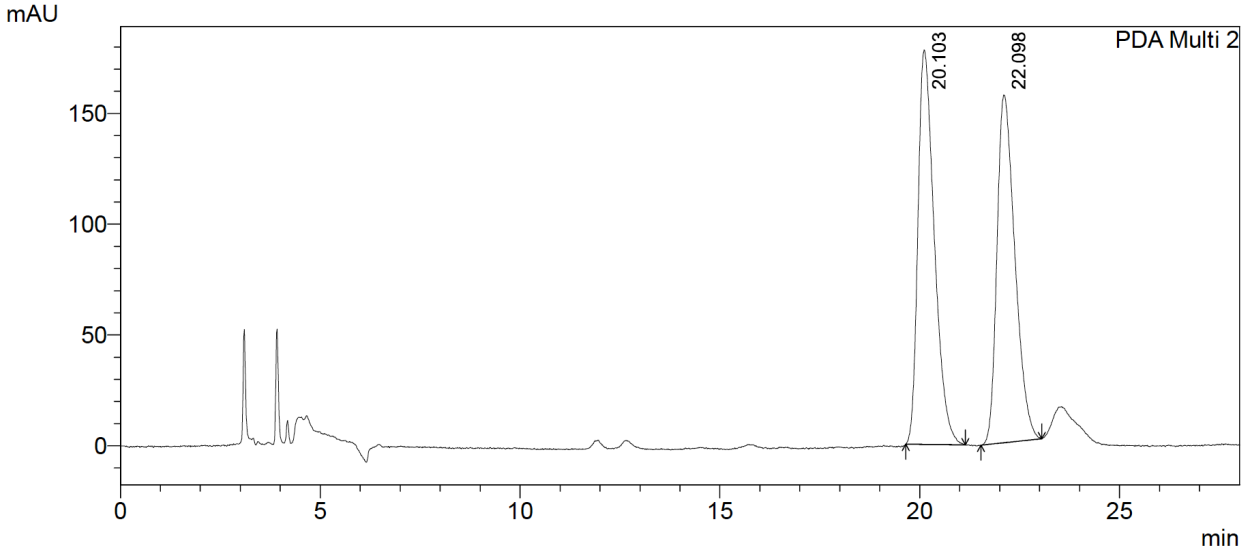


PDA Ch3 190nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	22.459	178429124	2280502	99.549	99.420
2	28.987	809189	13293	0.451	0.580
Total		179238313	2293795	100.000	100.000

***(rac) N*-Boc-3-(methoxymethoxy)-4-(2,2-dibromoacetyl)piperidinecarboxylate 2.315**

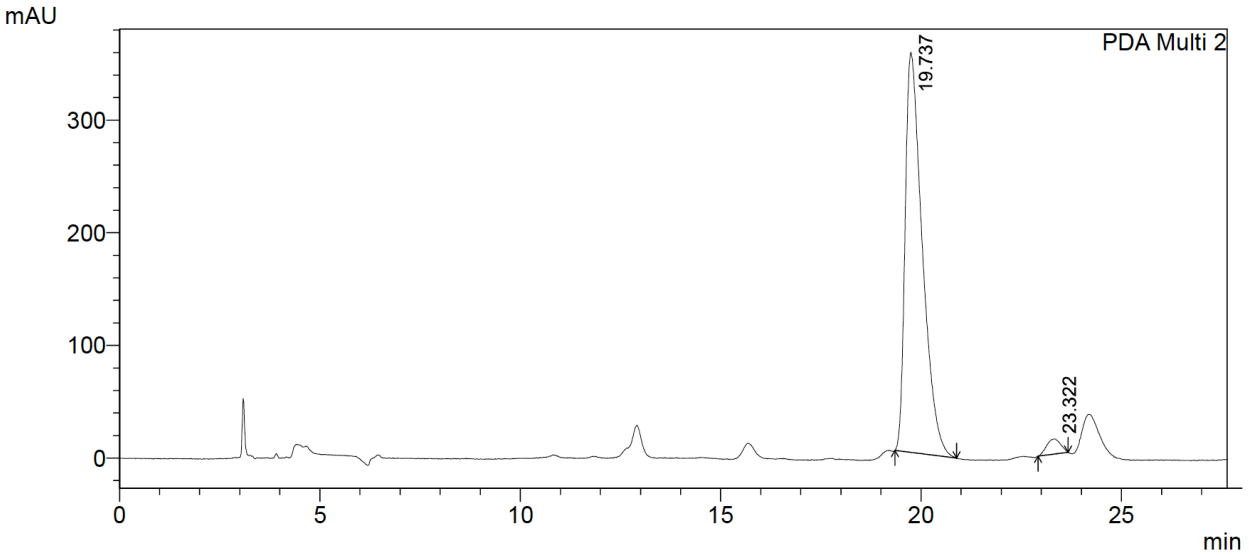
Conditions: 1% IPA/hexanes, 1 mL/min chiralpak 1A column



PDA Ch2 190nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.103	5078694	178193	50.920	53.161
2	22.098	4895176	157003	49.080	46.839
Total		9973870	335196	100.000	100.000

(+)-*(3S, 4S) N*-Boc-3-(methoxymethoxy)-4-(2,2-dibromoacetyl)piperidinecarboxylate 2.315



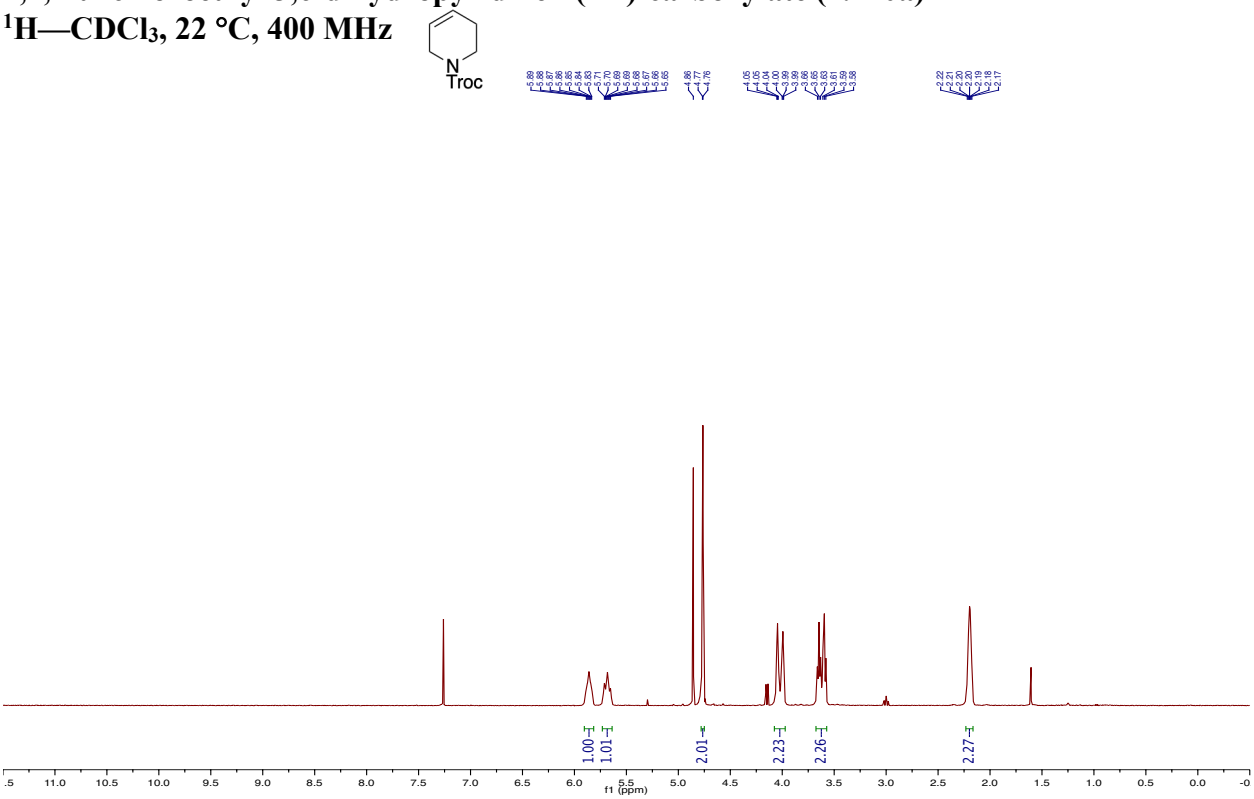
PDA Ch2 190nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.737	10569630	355234	96.931	96.320
2	23.322	334696	13572	3.069	3.680
Total		10904326	368806	100.000	100.000

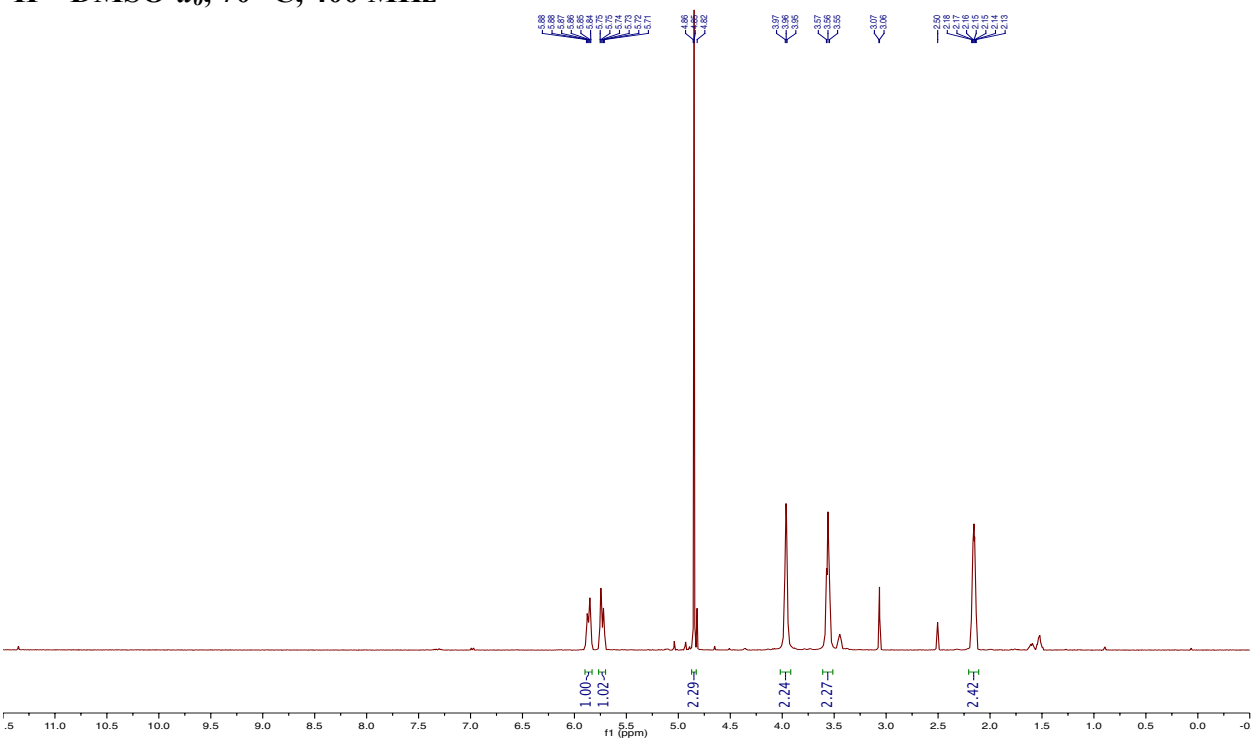
Appendix 3: Chapter 2 NMR spectra

2,2,2-trichloroethyl 3,6-dihydropyridine-1(2*H*)-carboxylate (2.270a)

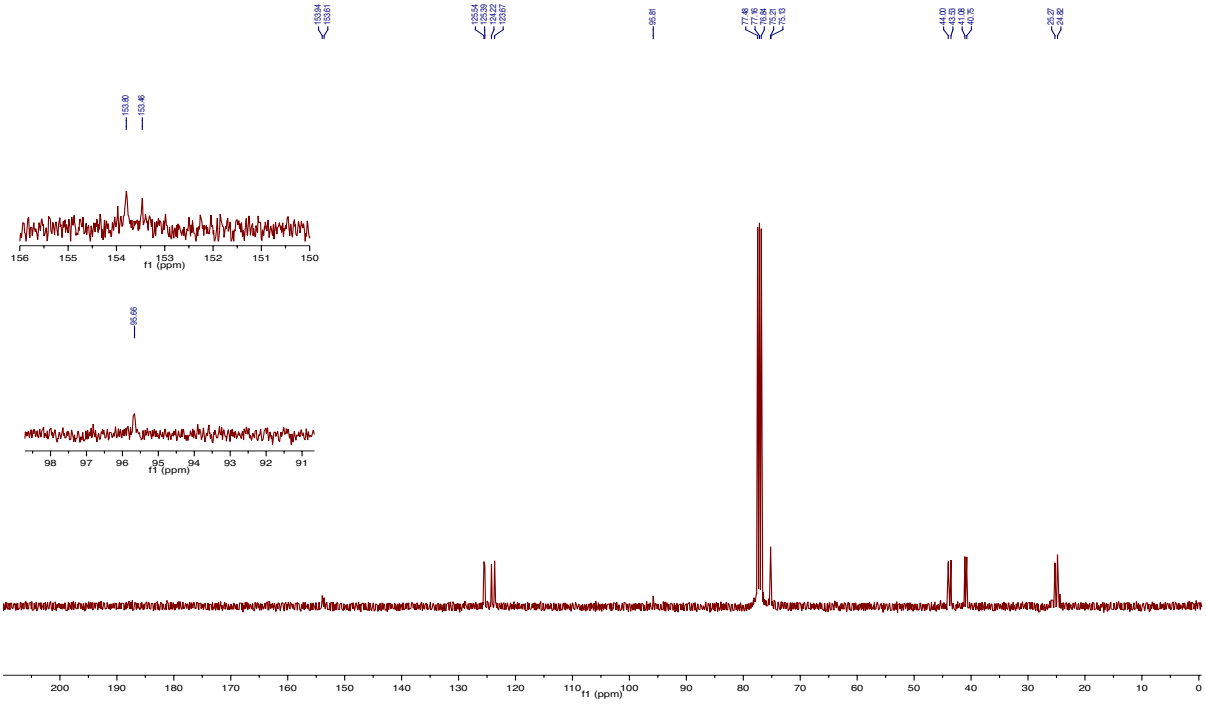
^{1}H—$CDCl_3$, 22 °C, 400 MHz



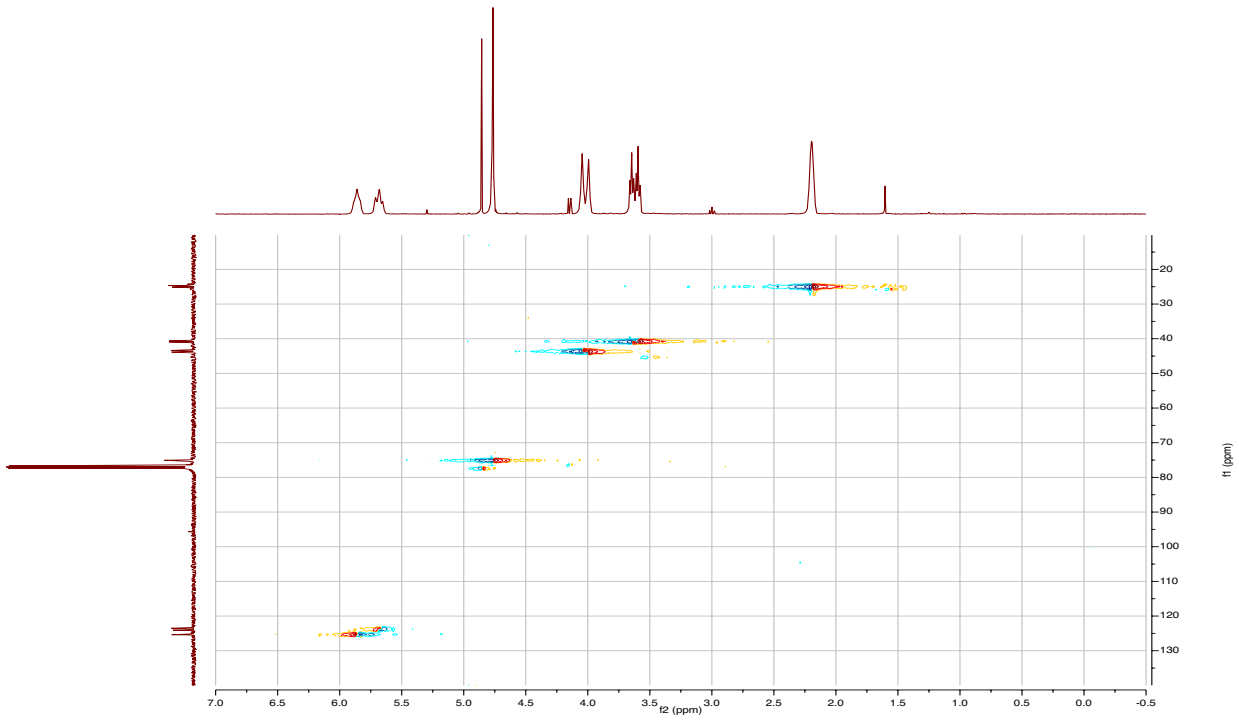
^{1}H—DMSO-d_6, 70 °C, 400 MHz



^{13}C—$CDCl_3$, 22 °C, 100 MHz

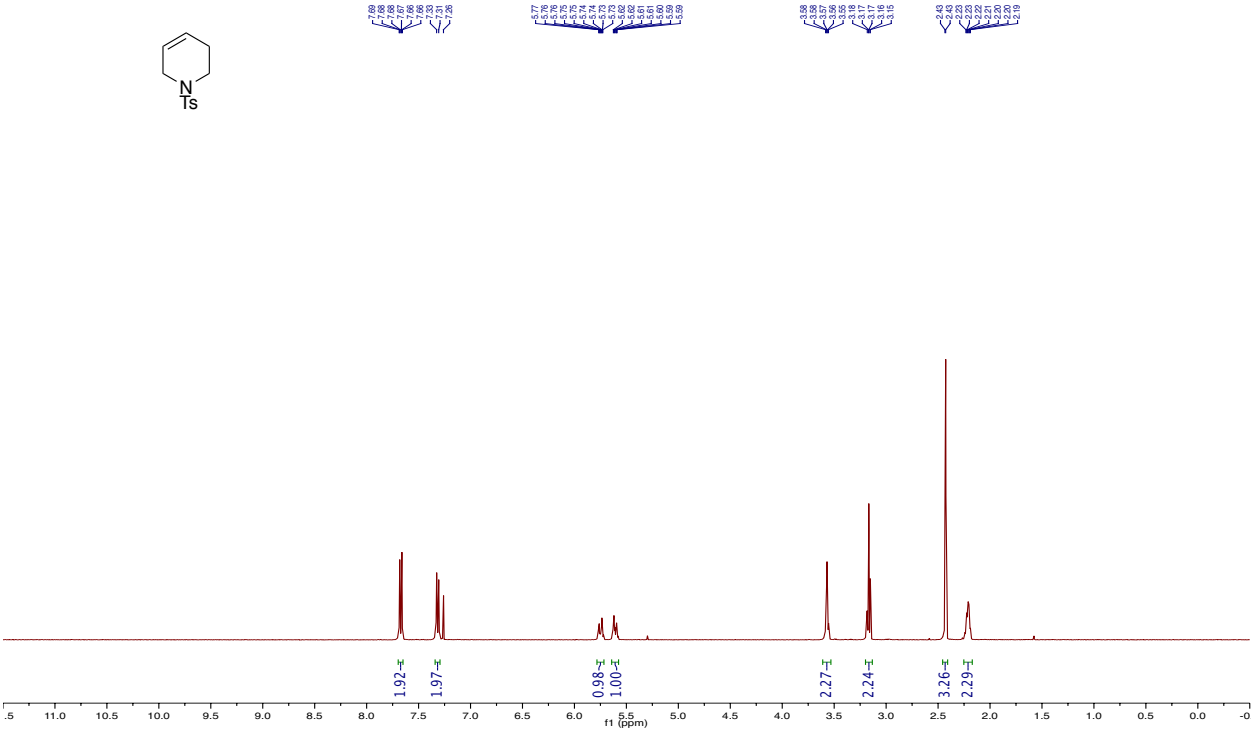


HSQC, 22 °C, 100 MHz

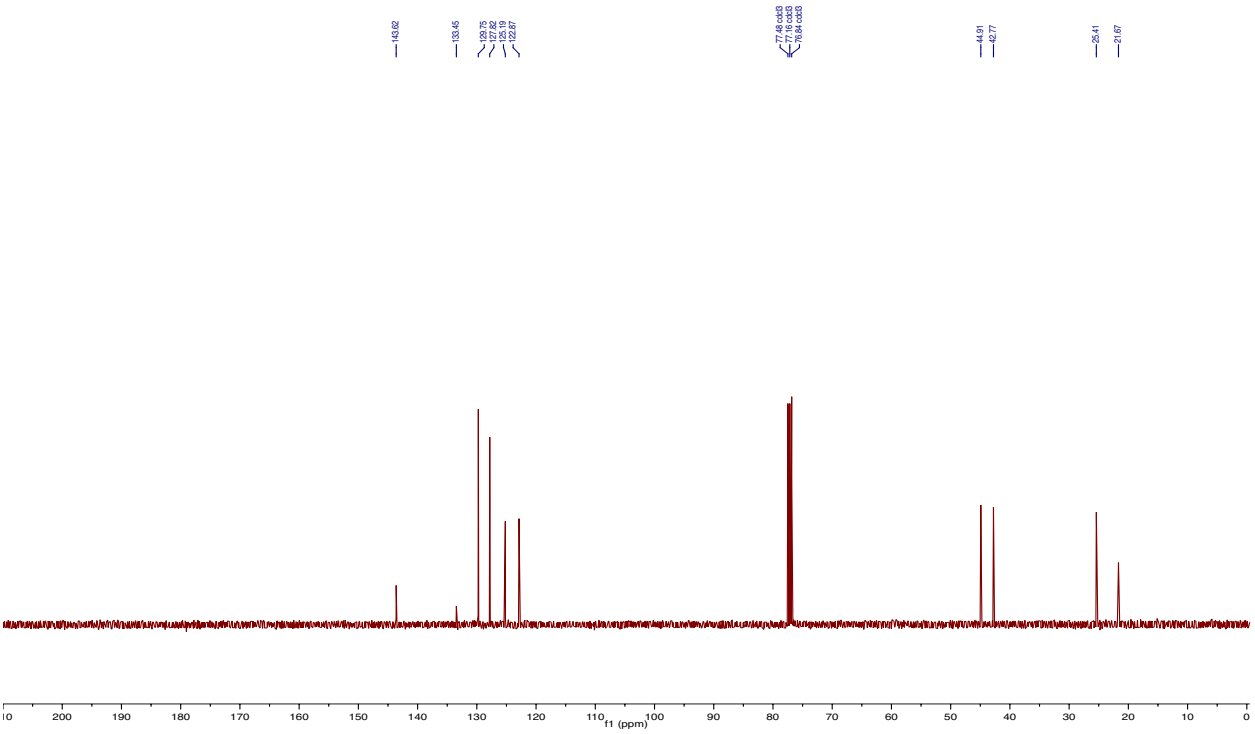


tosyl-1,2,3,6-tetrahydropyridine (2.270b)

^{1}H—$CDCl_3$, 22 °C, 400 MHz

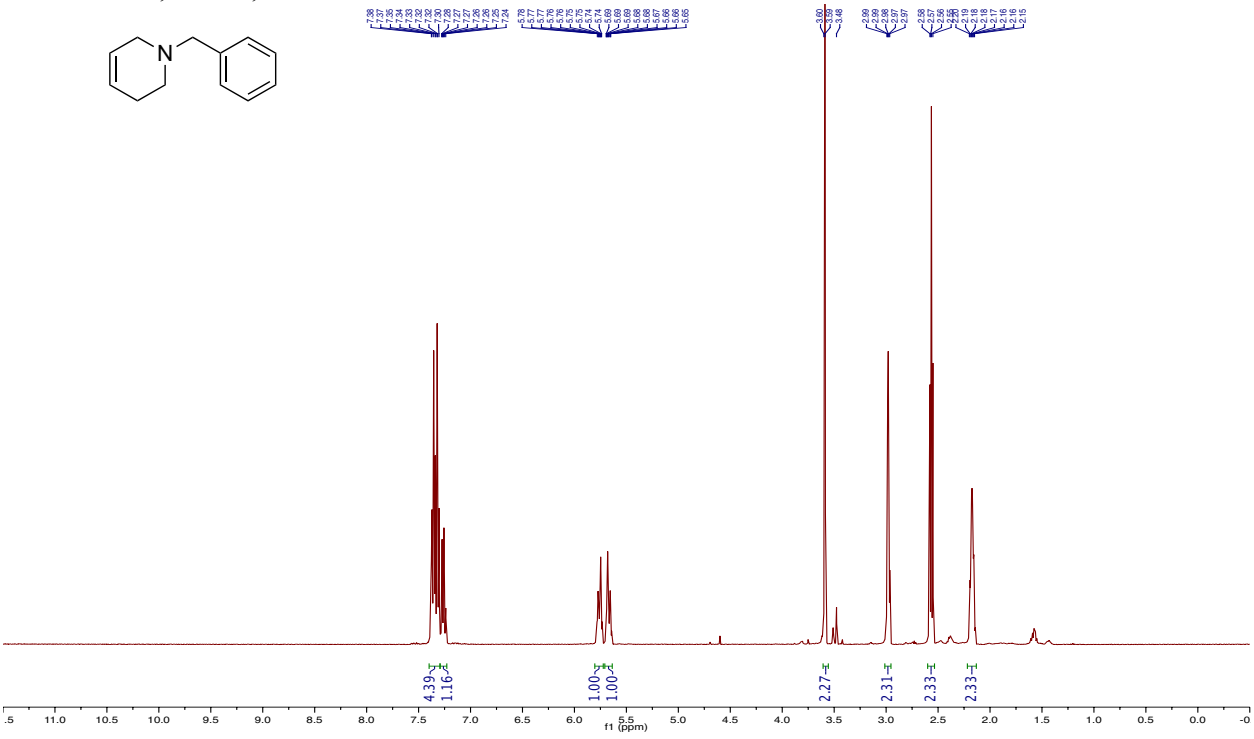


^{13}C—$CDCl_3$, 22 °C, 100 MHz

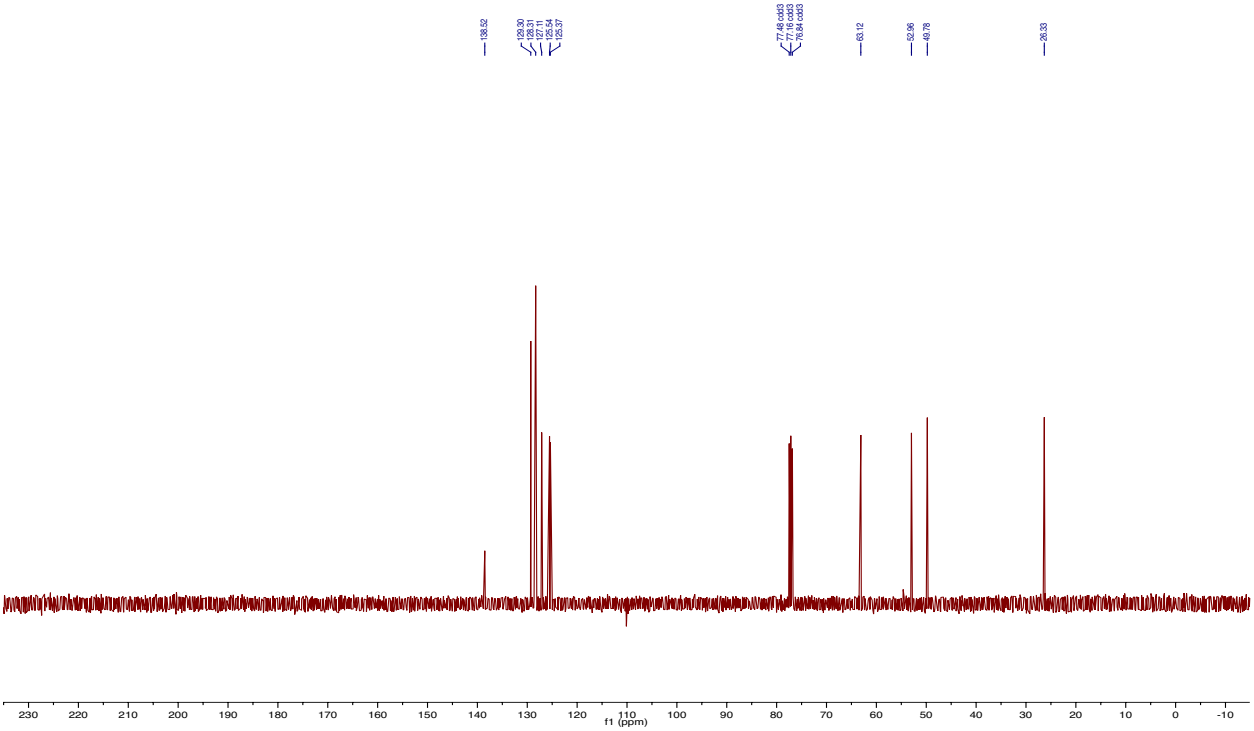


1-benzyl-1,2,3,6-tetrahydropyridine (2.277)

^{1}H—$CDCl_3$, 22 °C, 400 MHz

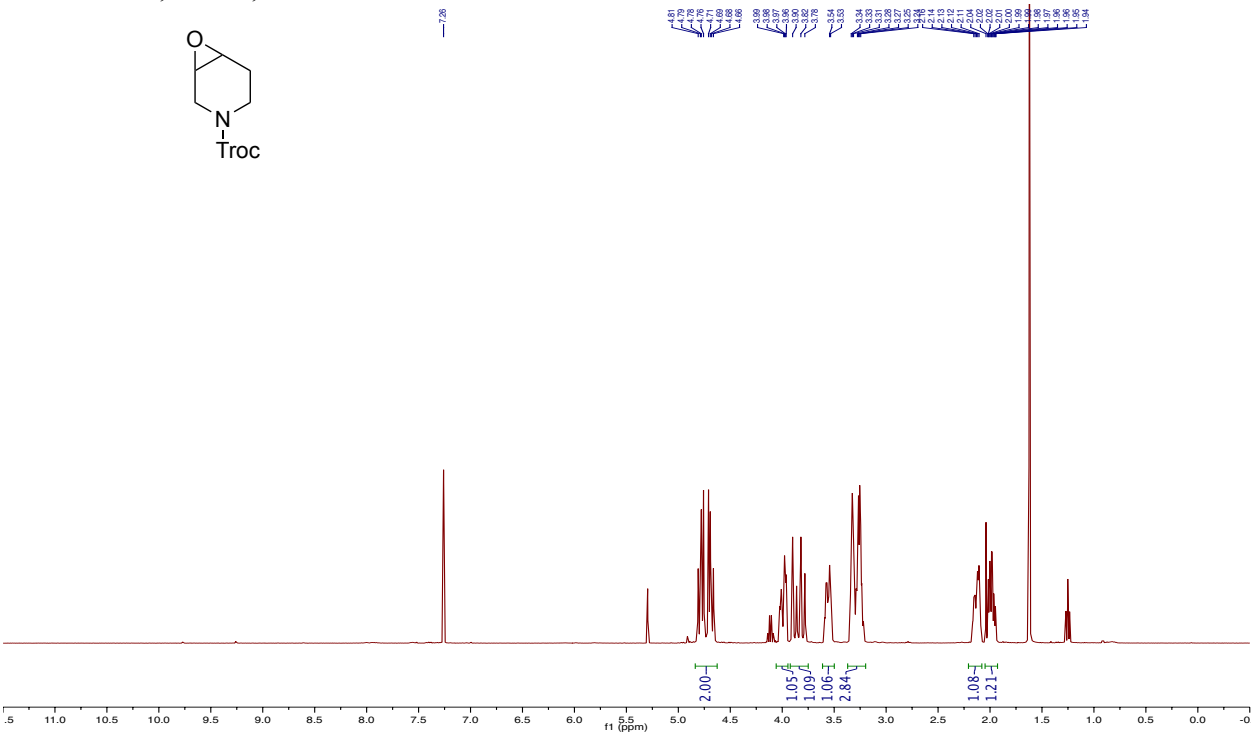


^{13}C—$CDCl_3$, 22 °C, 100 MHz

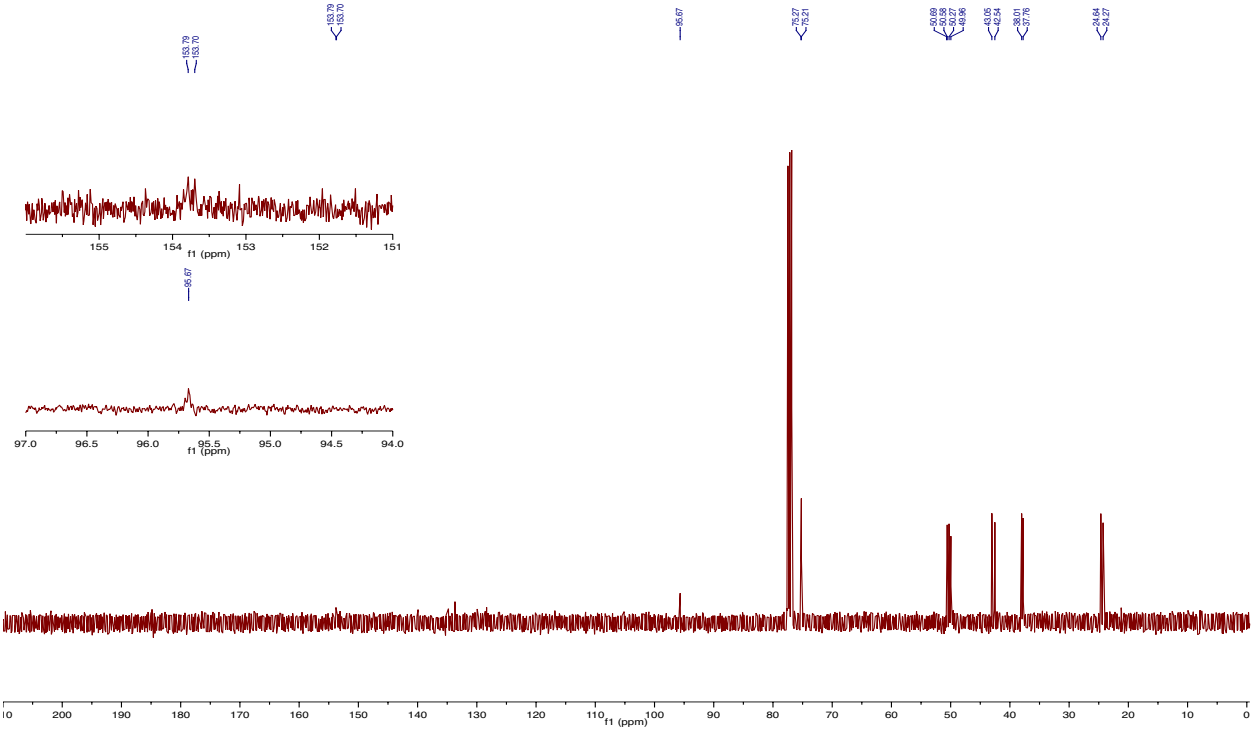


2,2,2-trichloroethyl 7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (2.271a)

^{1}H—$CDCl_3$, 22 °C, 400 MHz

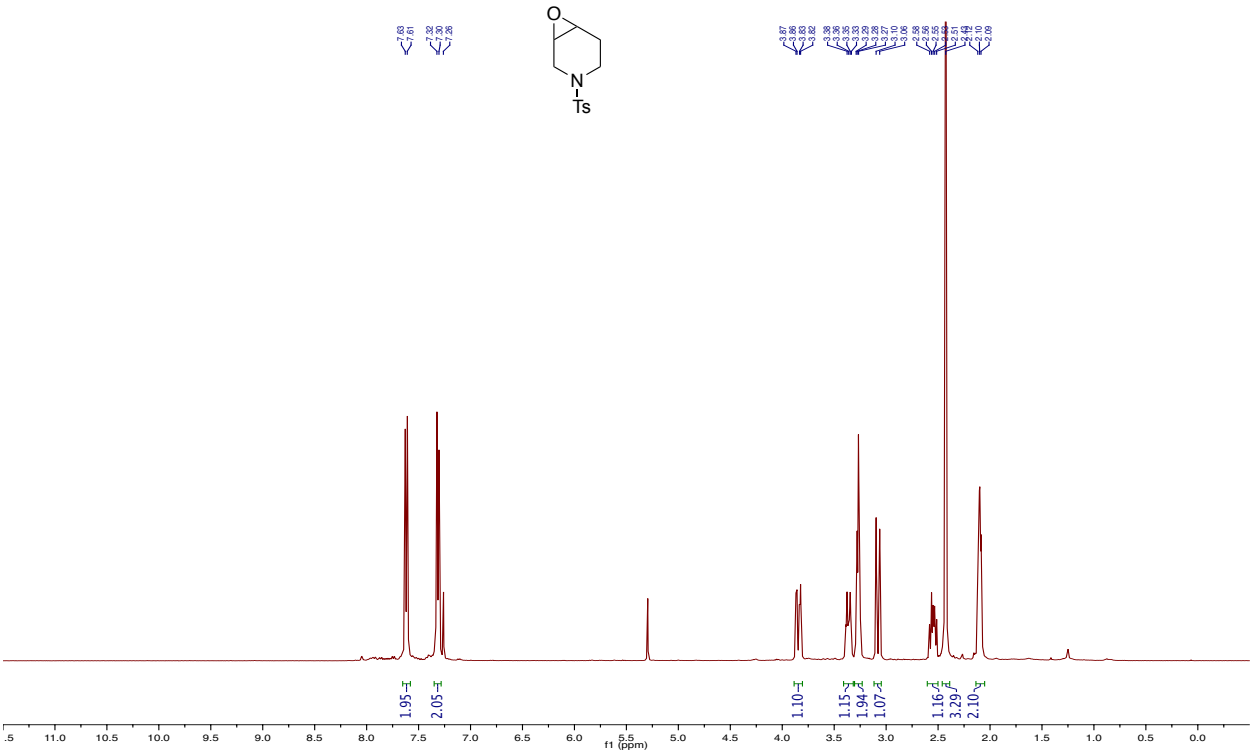


^{13}C—$CDCl_3$, 22 °C, 100 MHz

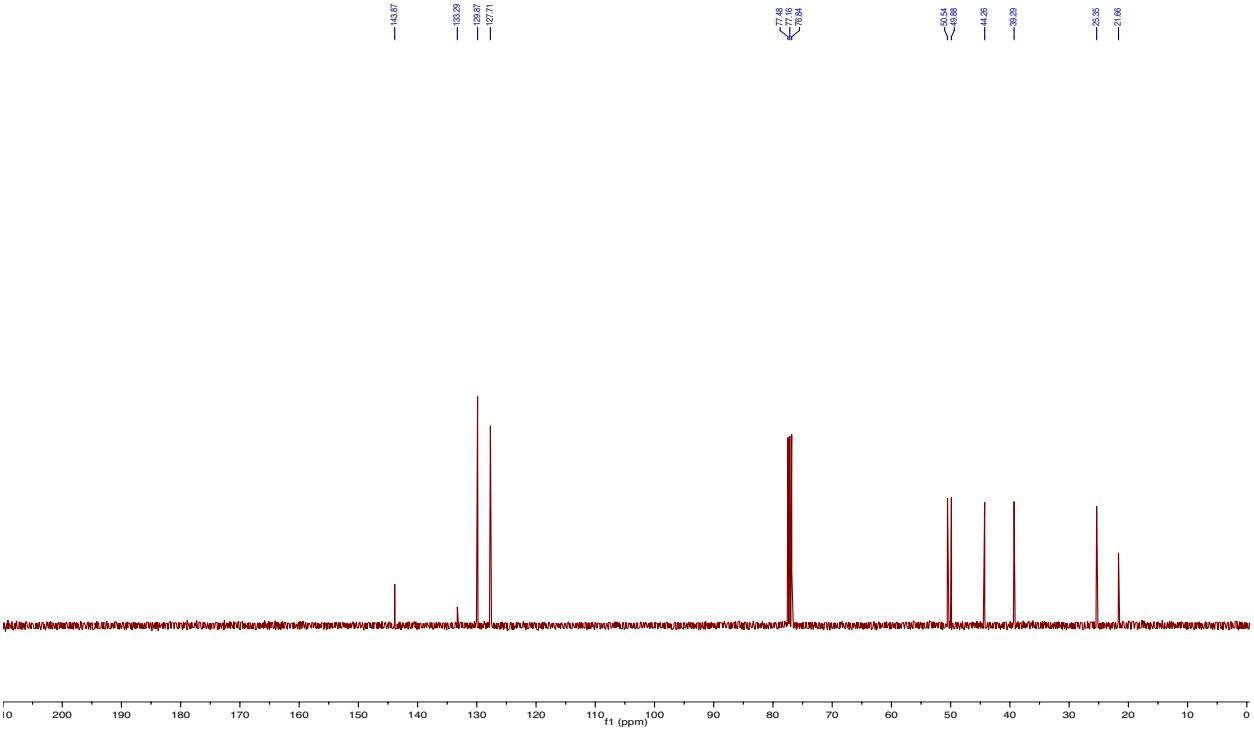


3-tosyl-7-oxa-3-azabicyclo[4.1.0]heptane (2.271b)

^{1}H—$CDCl_3$, 22 °C, 400 MHz

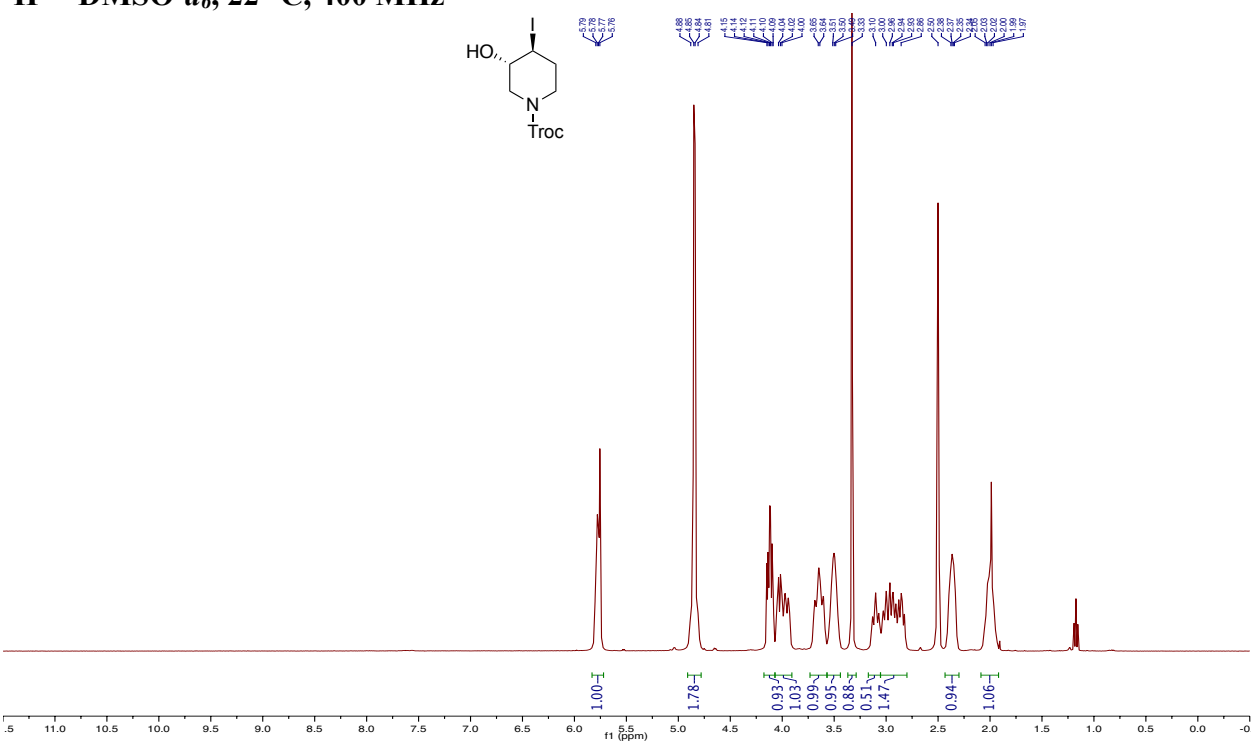


^{13}C—$CDCl_3$, 22 °C, 100 MHz

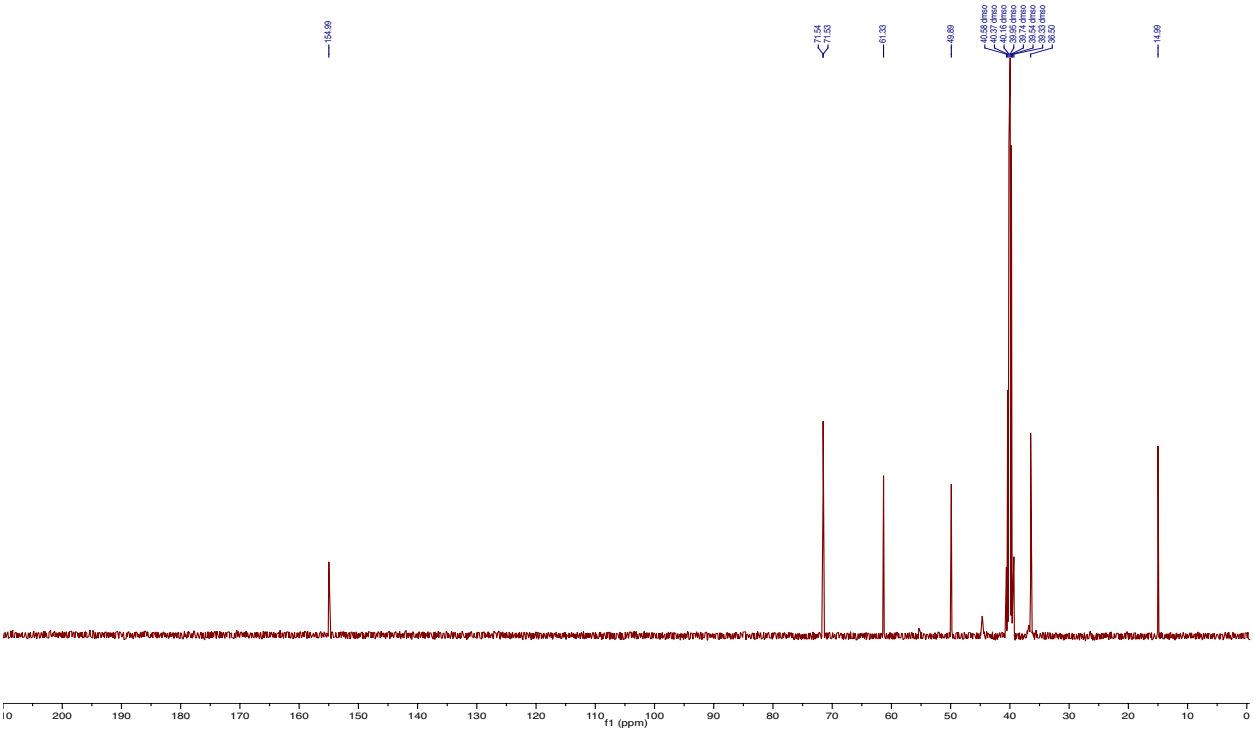


2,2,2-trichloroethyl-3-hydroxy-4-iodopiperidine-1-carboxylate (2.278a)

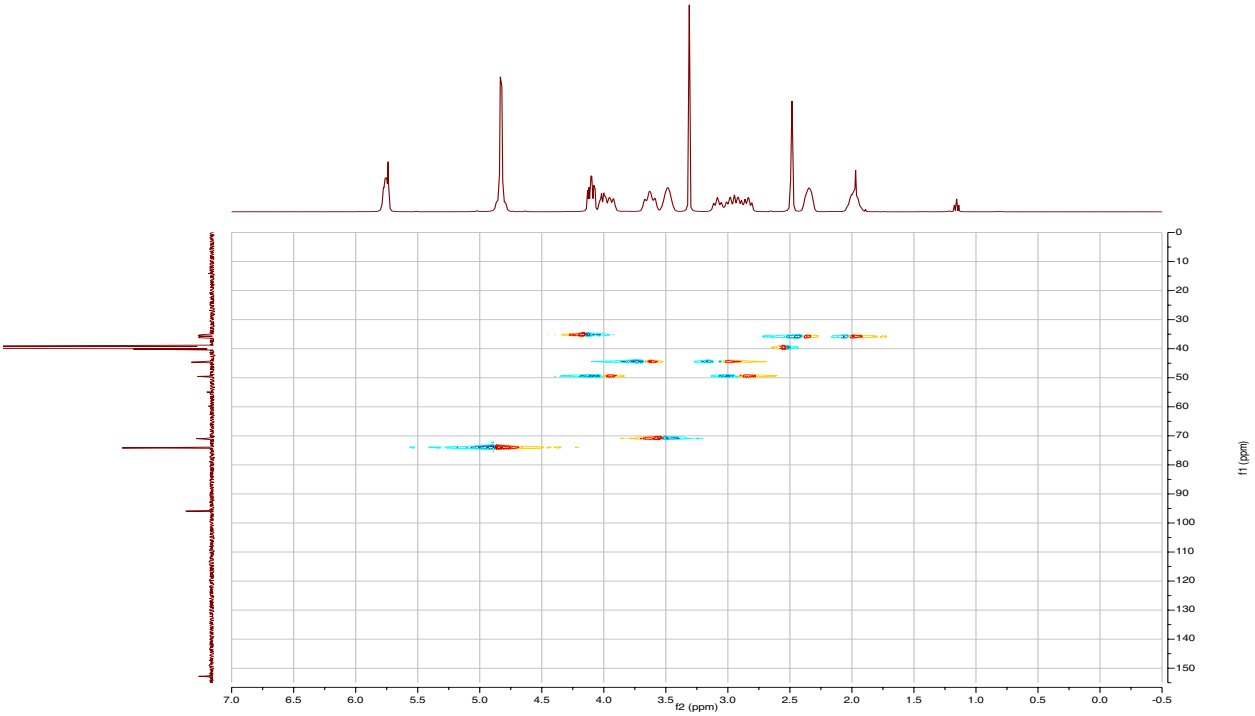
^{1}H— DMSO-*d*$_6$, 22 °C, 400 MHz



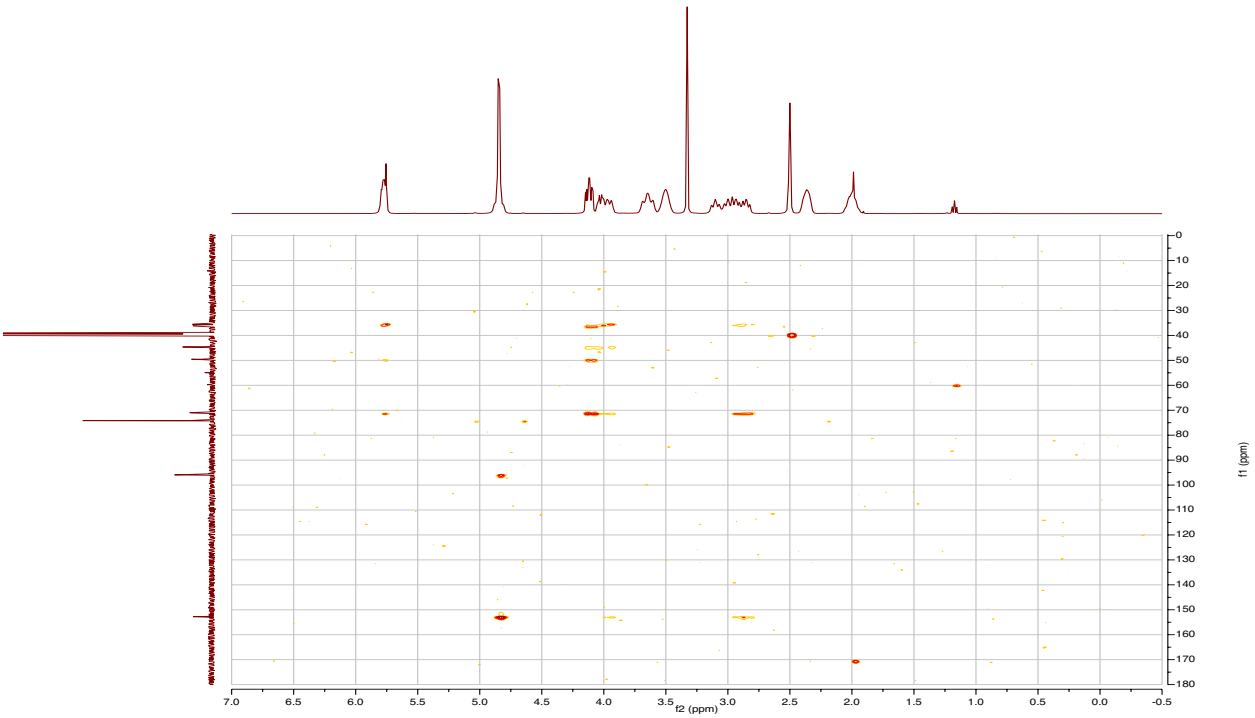
^{13}C— DMSO-*d*$_6$, 80 °C, 100 MHz



HSQC-DMSO-*d*$_6$, 22 °C, 400 MHz

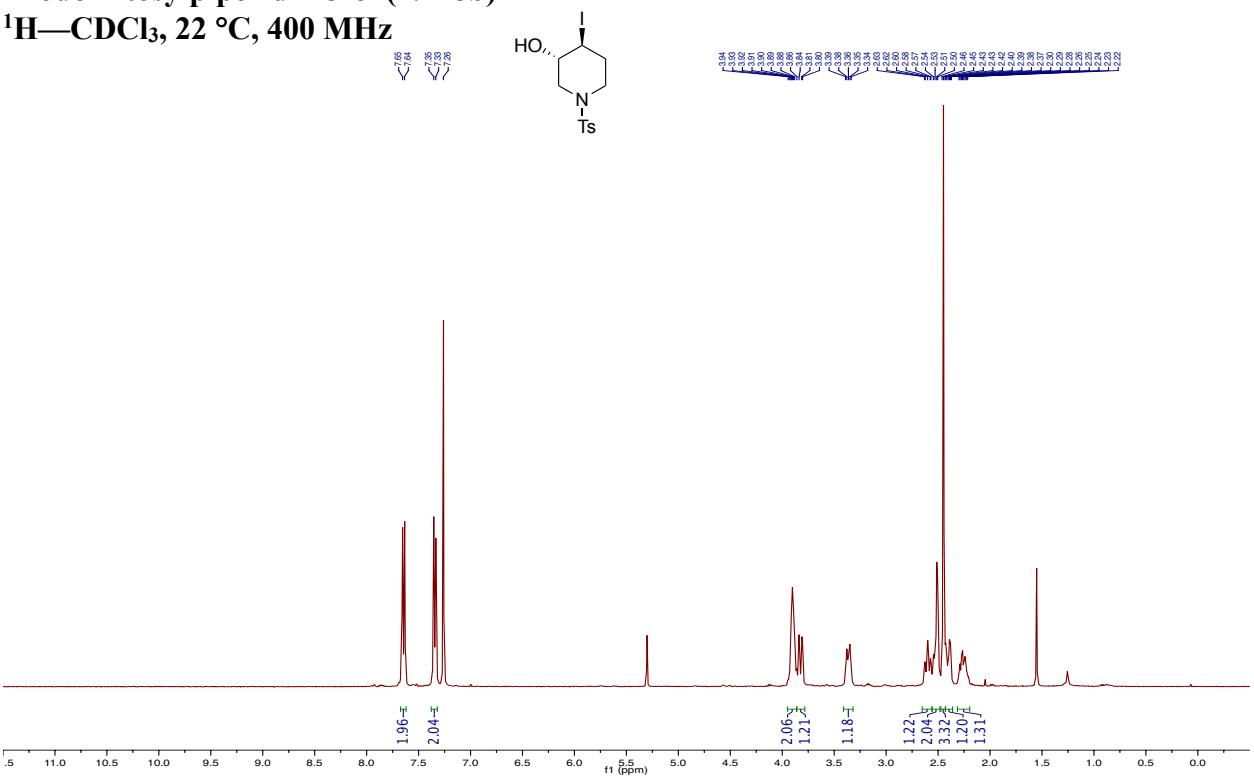


HMBC-DMSO-*d*$_6$, 22 °C, 400 MHz

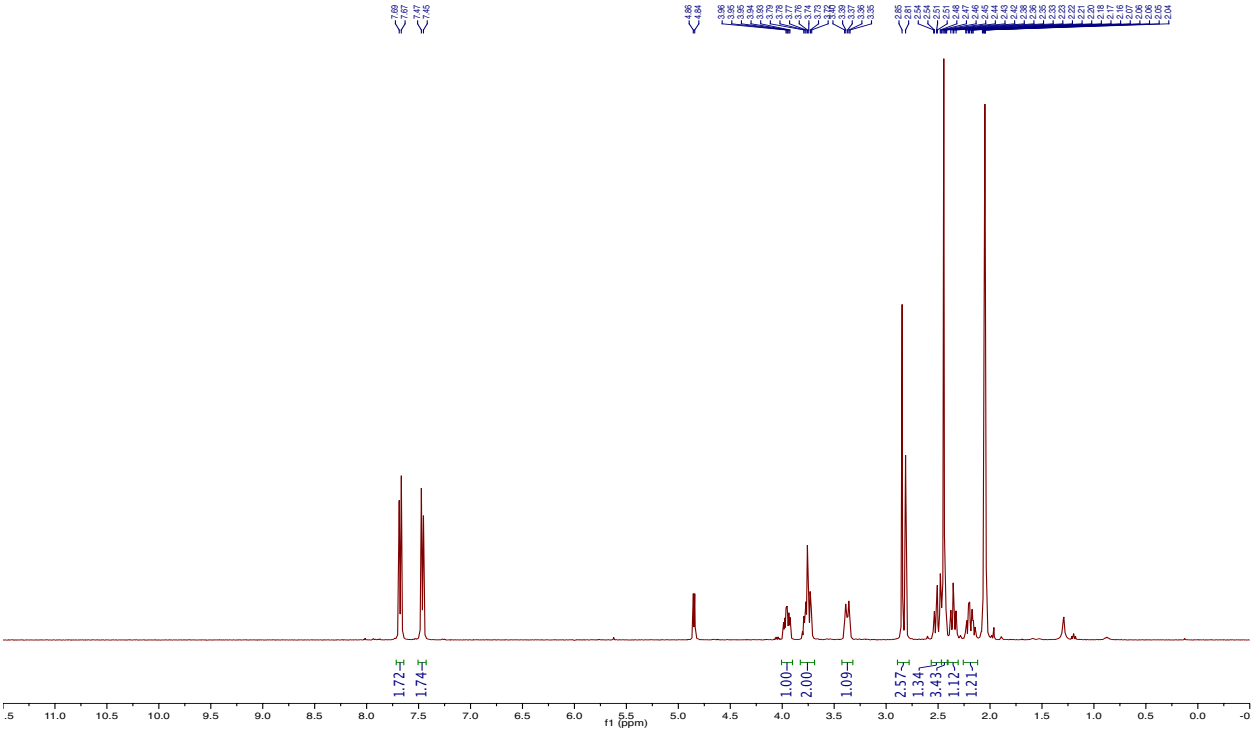


4-iodo-1-tosylpiperidin-3-ol (2.278b)

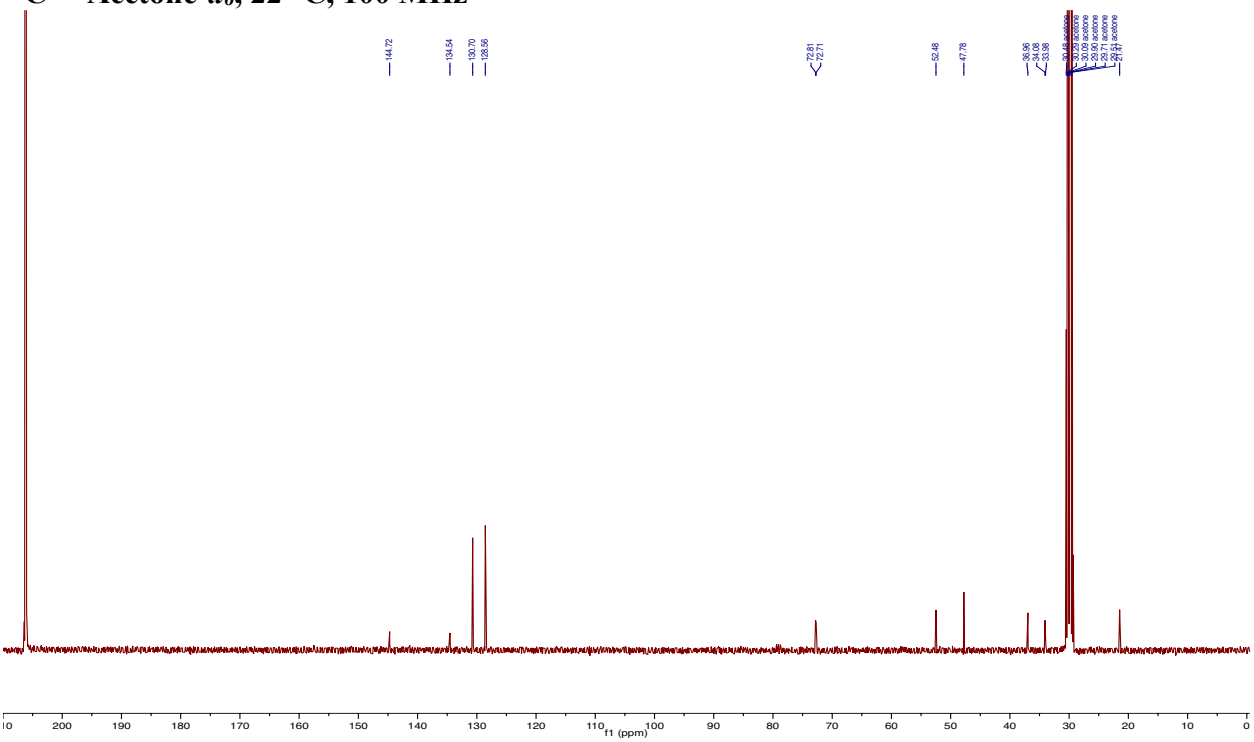
^{1}H—$CDCl_3$, 22 °C, 400 MHz



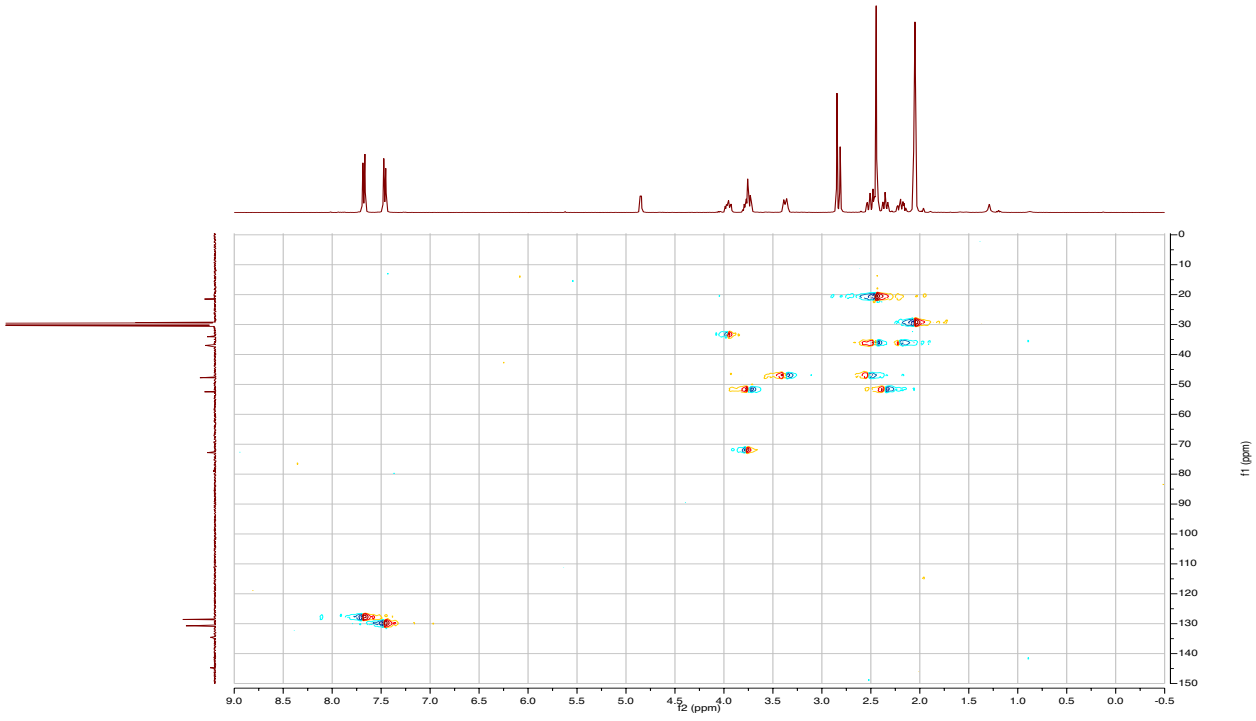
^{1}H—Acetone-d_6, 22 °C, 400 MHz



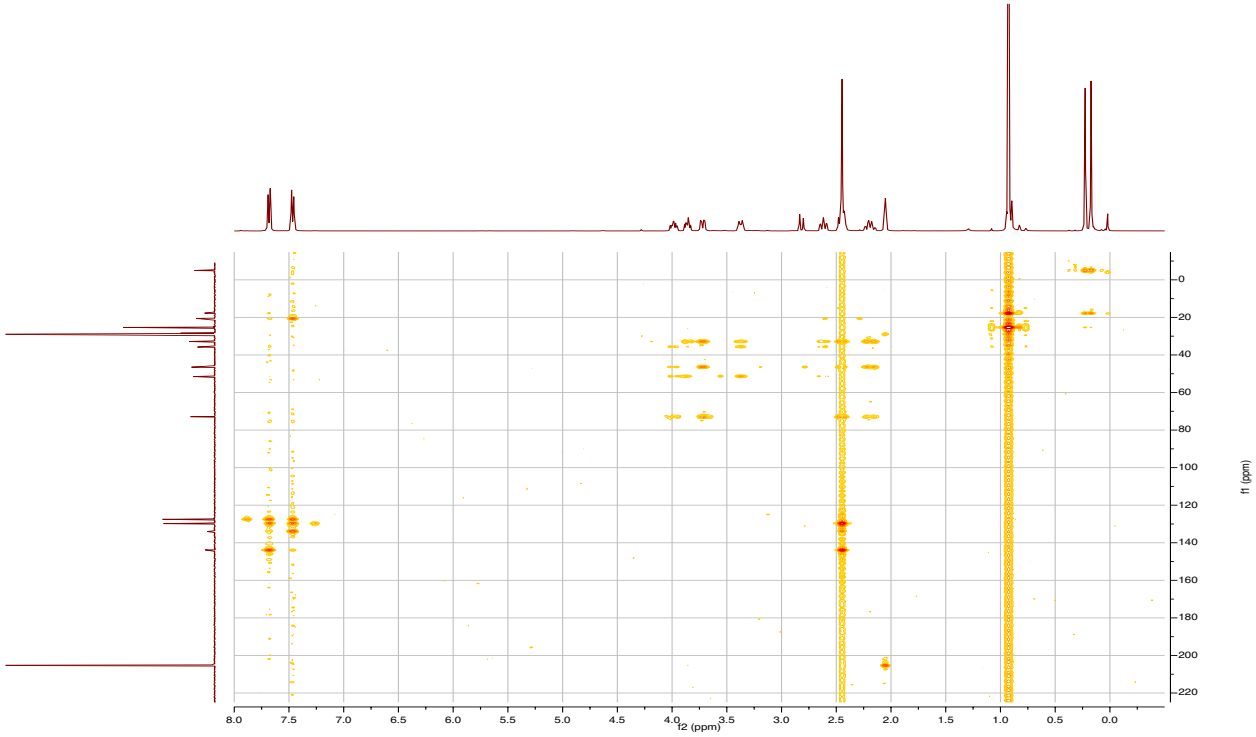
^{13}C— Acetone-d_6, 22 °C, 100 MHz



HSQC-Acetone-d_6, 22 °C, 400 MHz

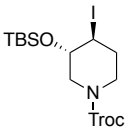


HMBC-Acetone-d_6, 22 °C, 400 MHz

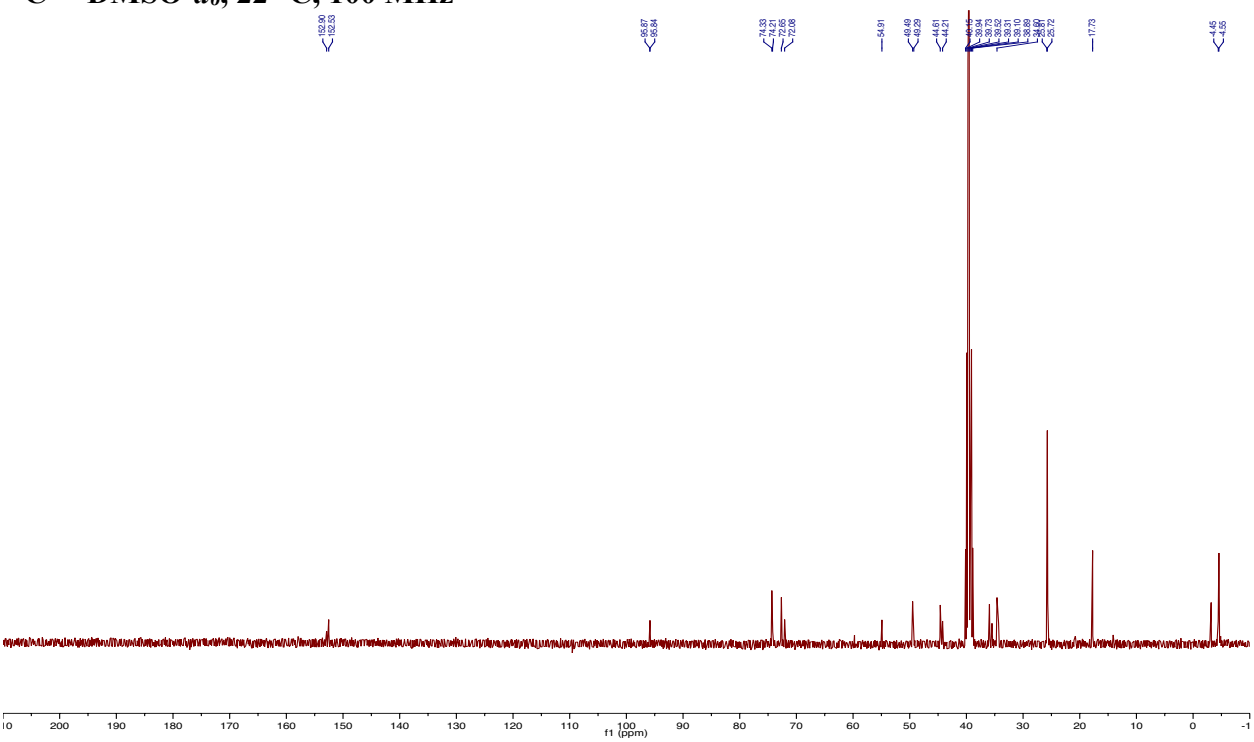


***N*-Troc-3-OTBS-4-iodopiperidine-1-carboxylate (2.279a)**

^{1}H— DMSO-d_6, 22 °C, 400 MHz

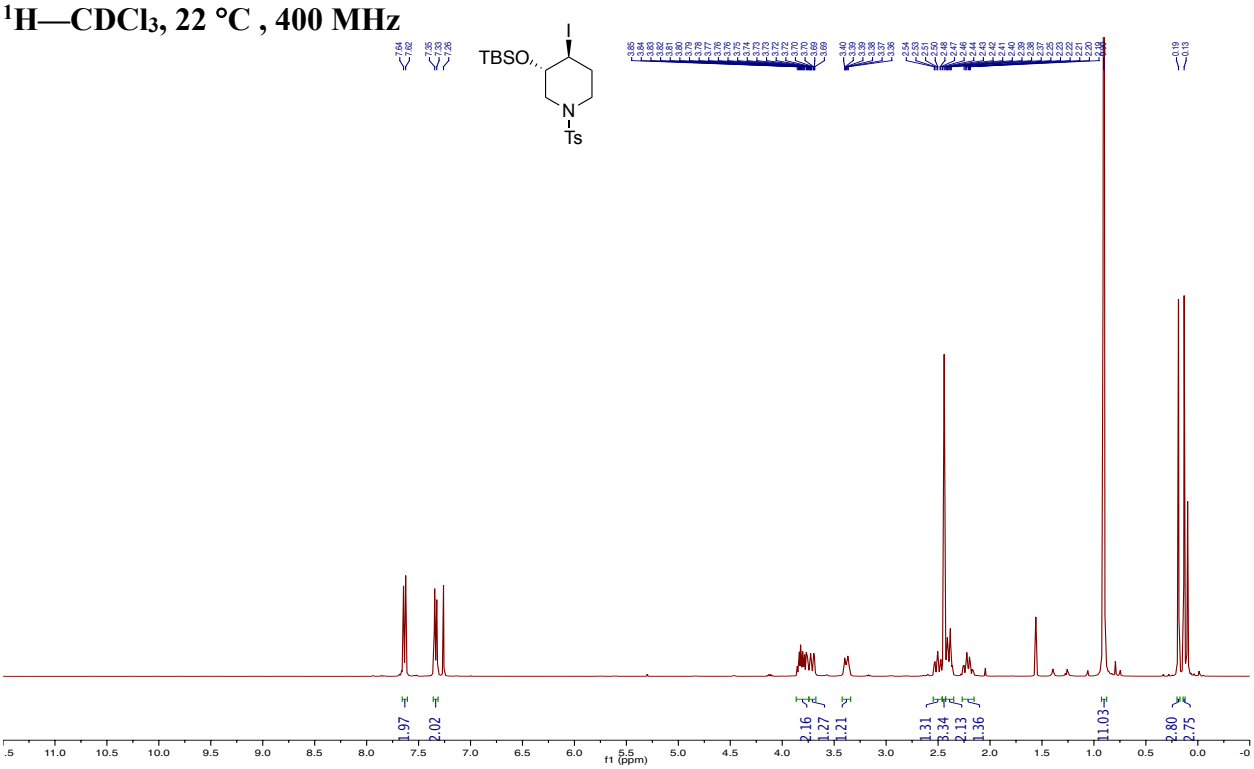


^{13}C— DMSO-*d*$_6$, 22 °C, 100 MHz

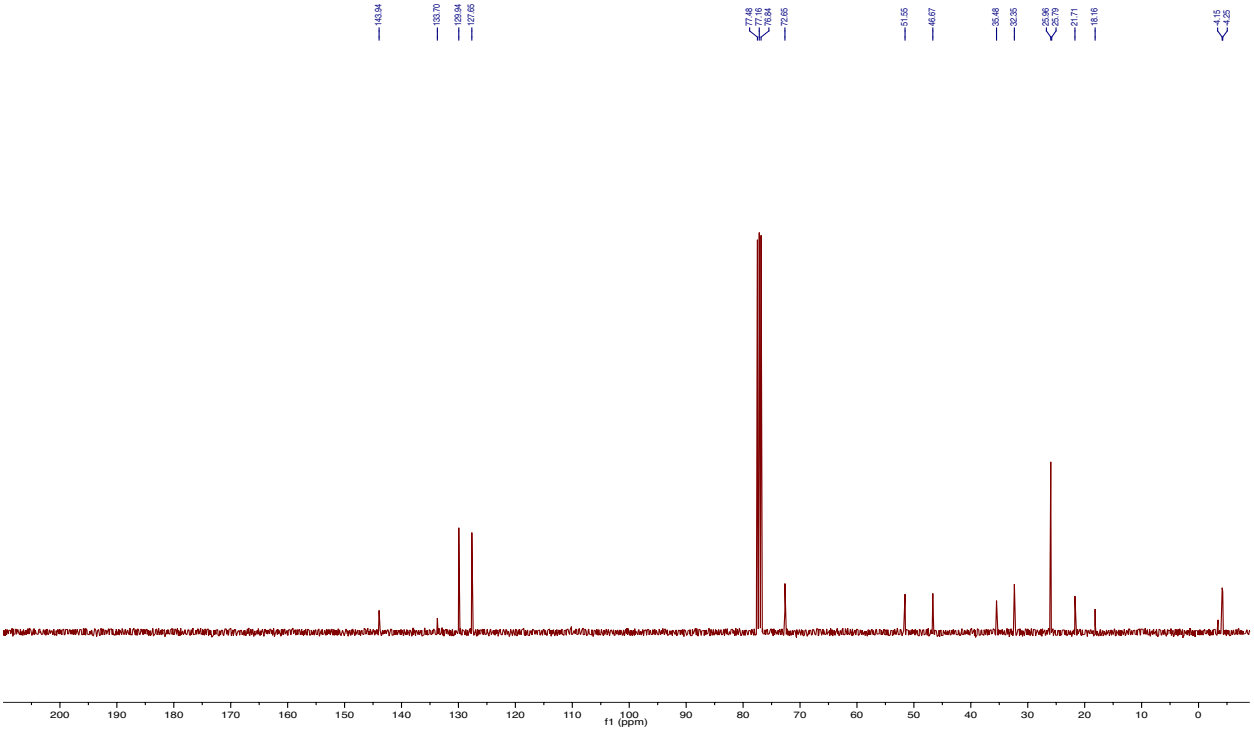


3-((*tert*-butyldimethylsilyl)oxy)-4-iodo-1-tosylpiperidine (2.279b)

^{1}H—$CDCl_3$, 22 °C , 400 MHz

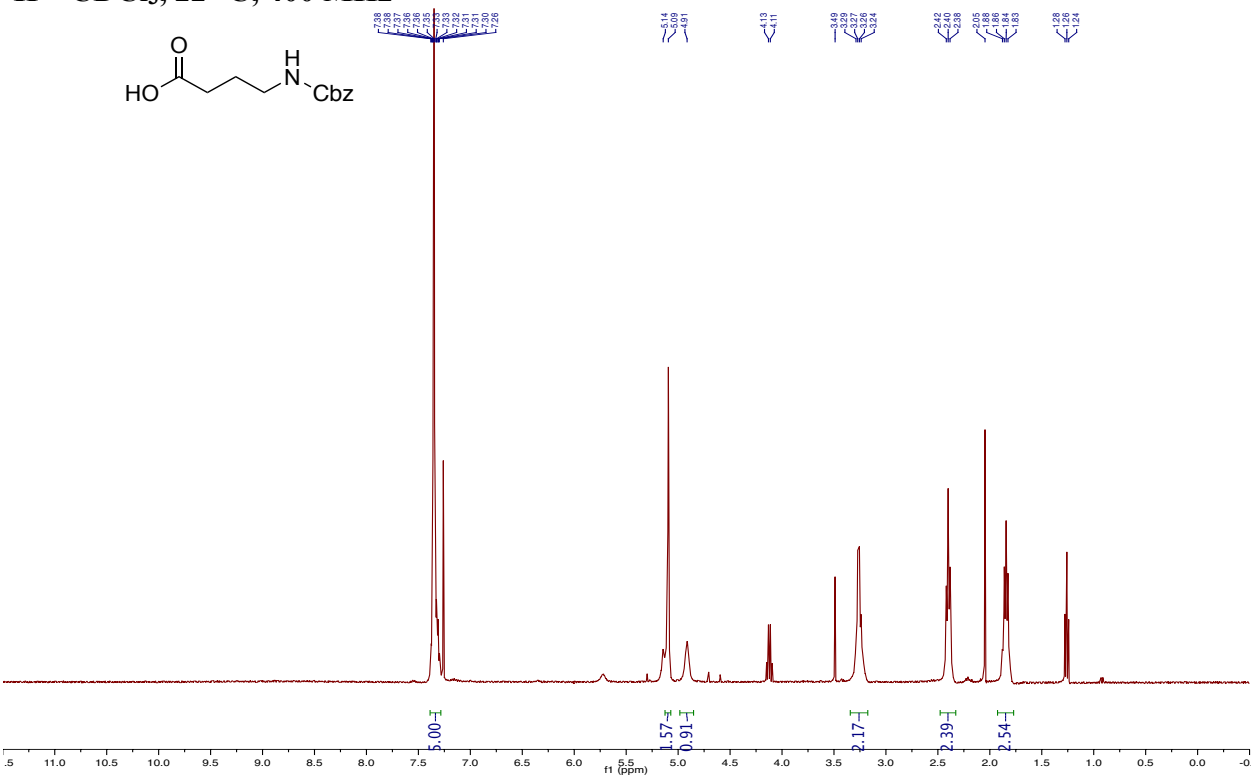


^{13}C—$CDCl_3$, 22 °C, 100 MHz

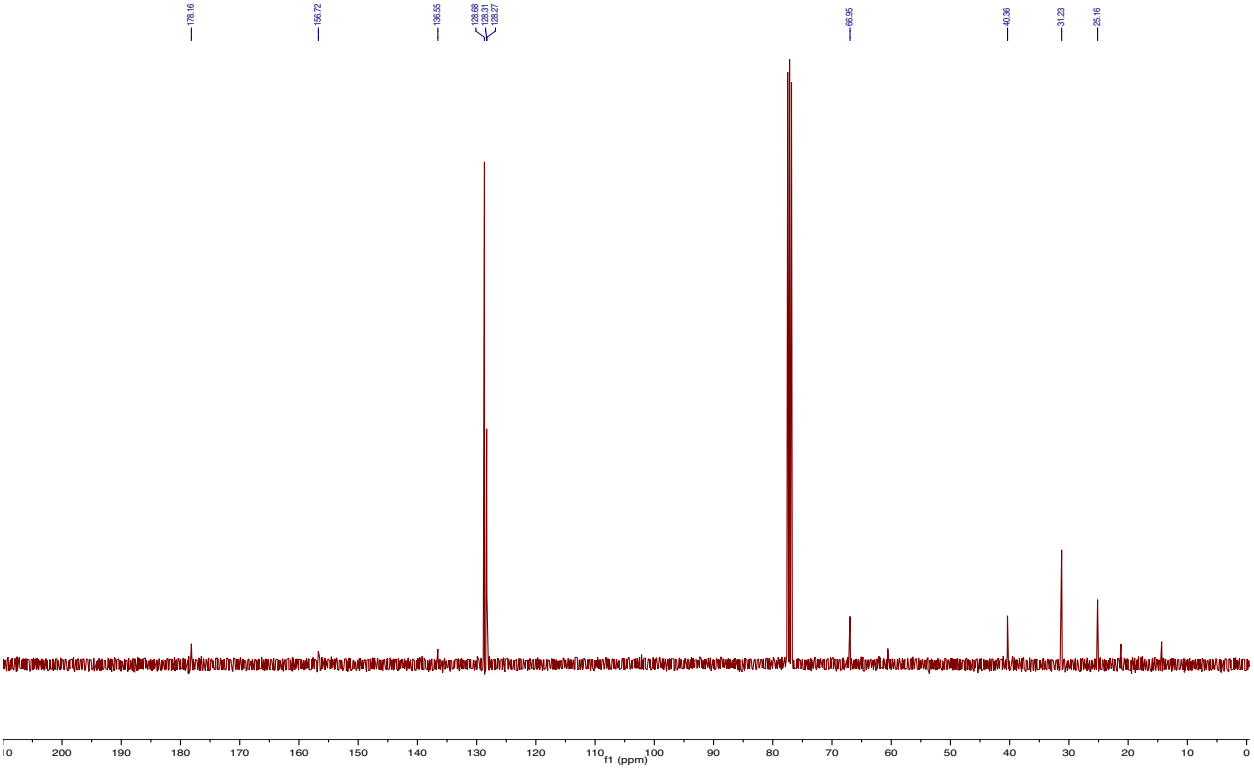


***N*-Cbz-4-aminobutanoic acid (S-2.1)**

^{1}H – $CDCl_3$, 22 °C, 400 MHz

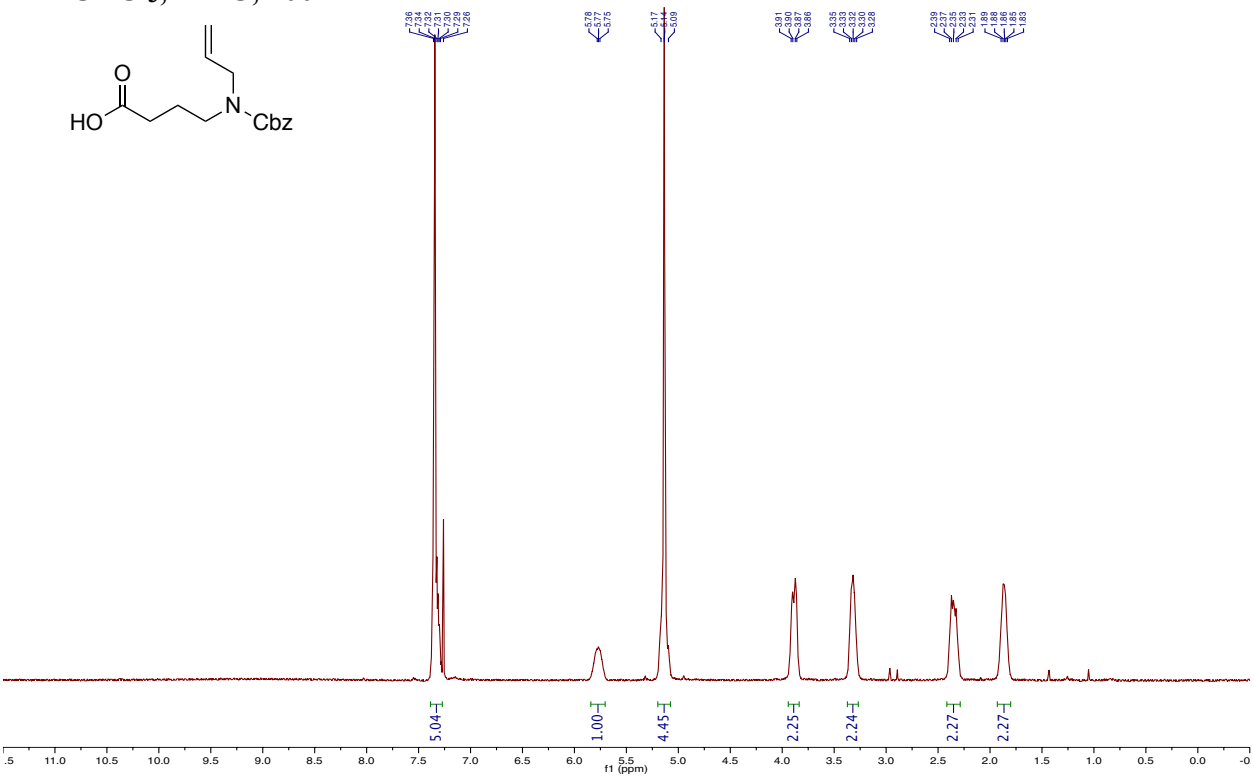


^{13}C – $CDCl_3$, 22 °C, 100 MHz

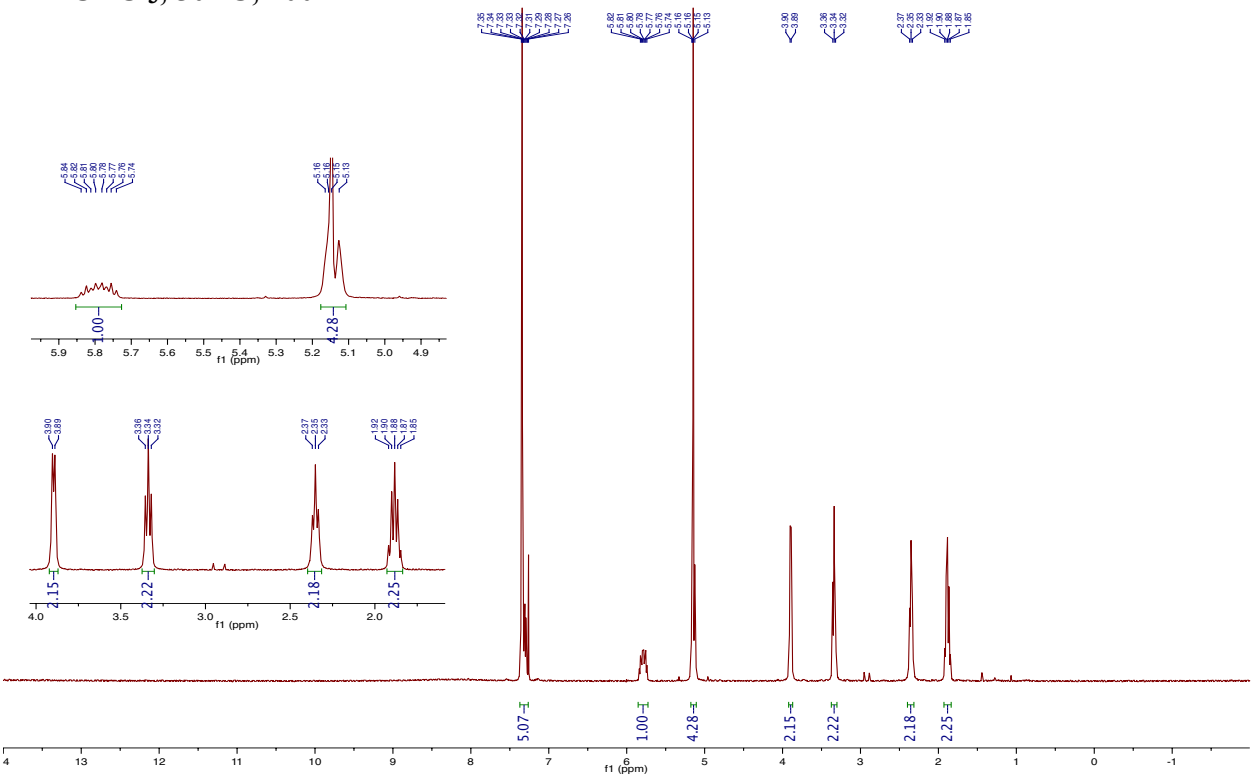


***N*-allyl-*N*-Cbz-4-aminobutanoic acid (2.303)**

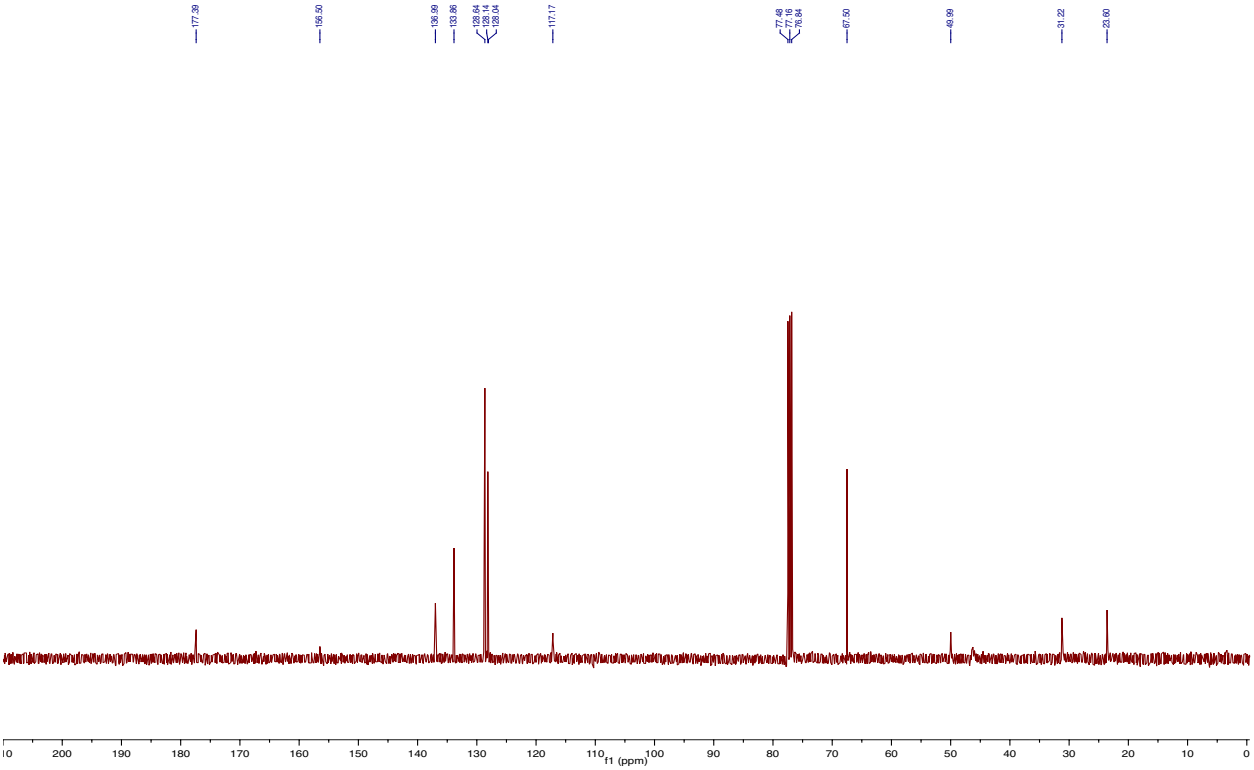
^{1}H – $CDCl_3$, 22 °C, 400 MHz



^{1}H – $CDCl_3$, 50 °C, 400 MHz

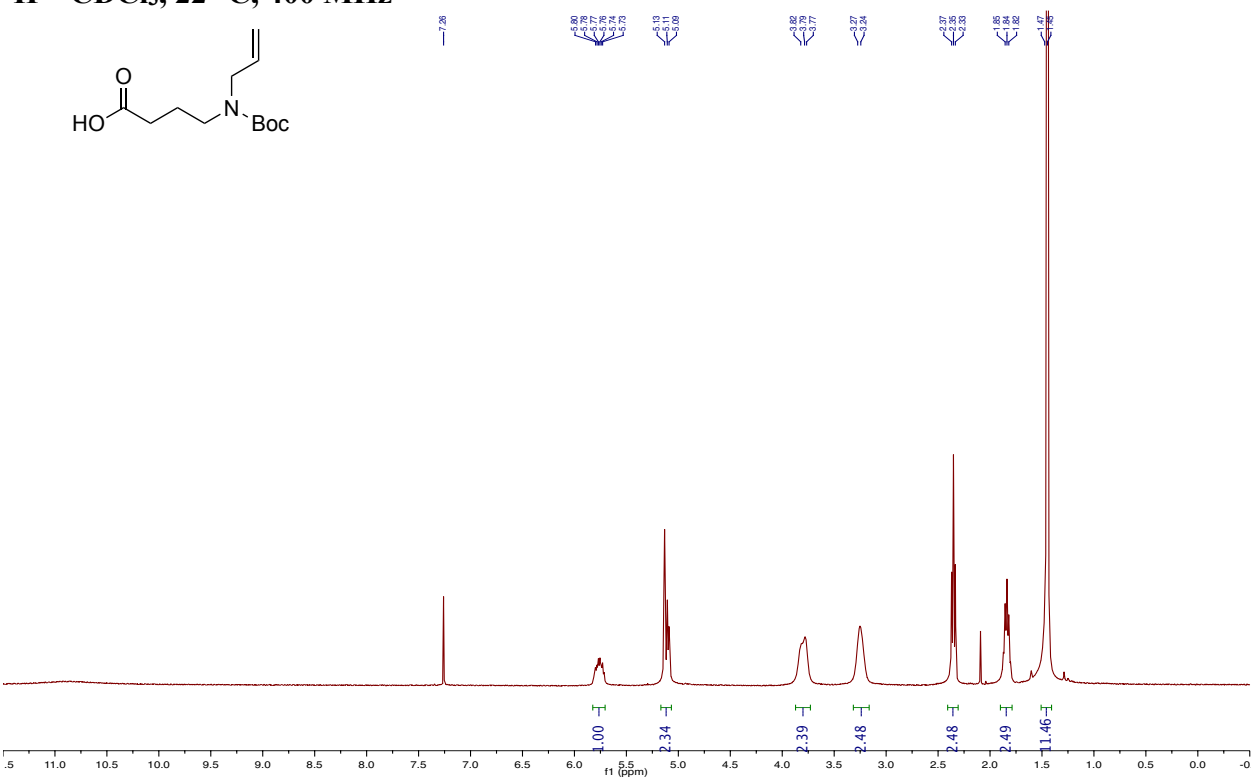


^{13}C – $CDCl_3$, 50 °C, 100 MHz

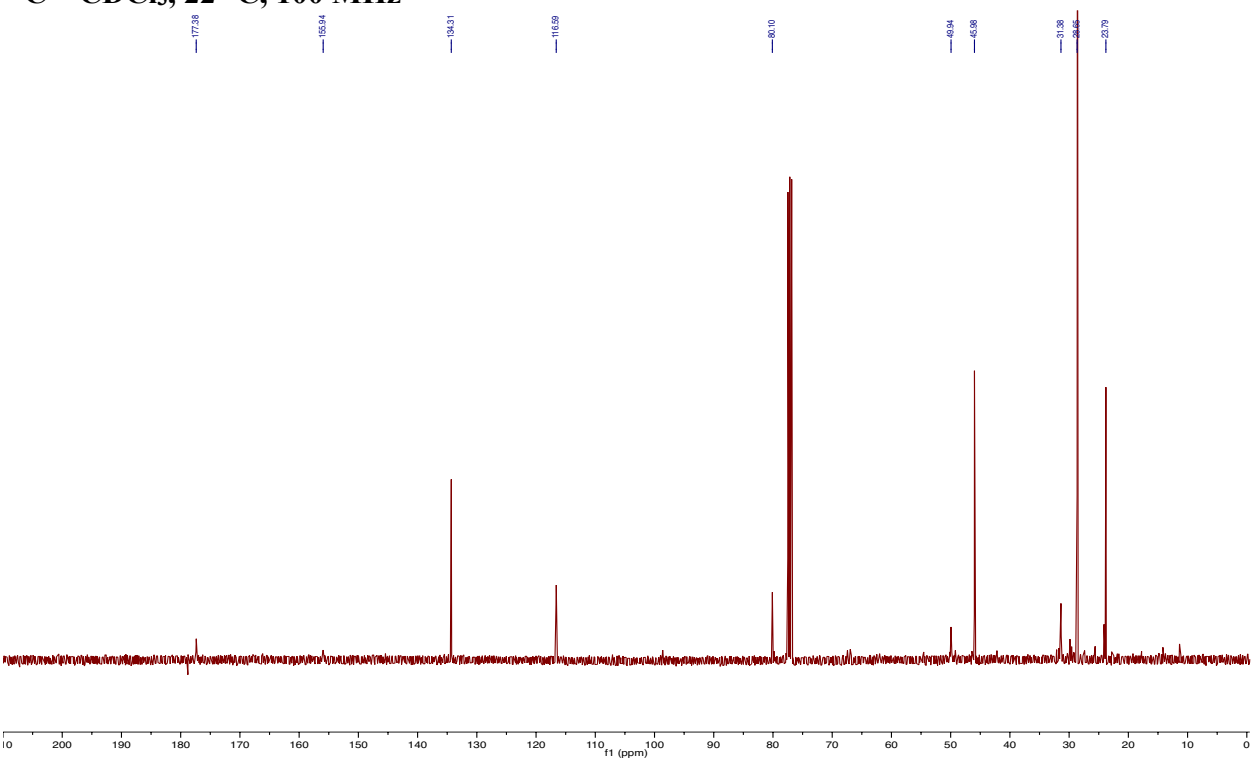


***N*-Boc-*N*-allyl-aminobutanoic acid (2.304a)**

^{1}H – $CDCl_3$, 22 °C, 400 MHz

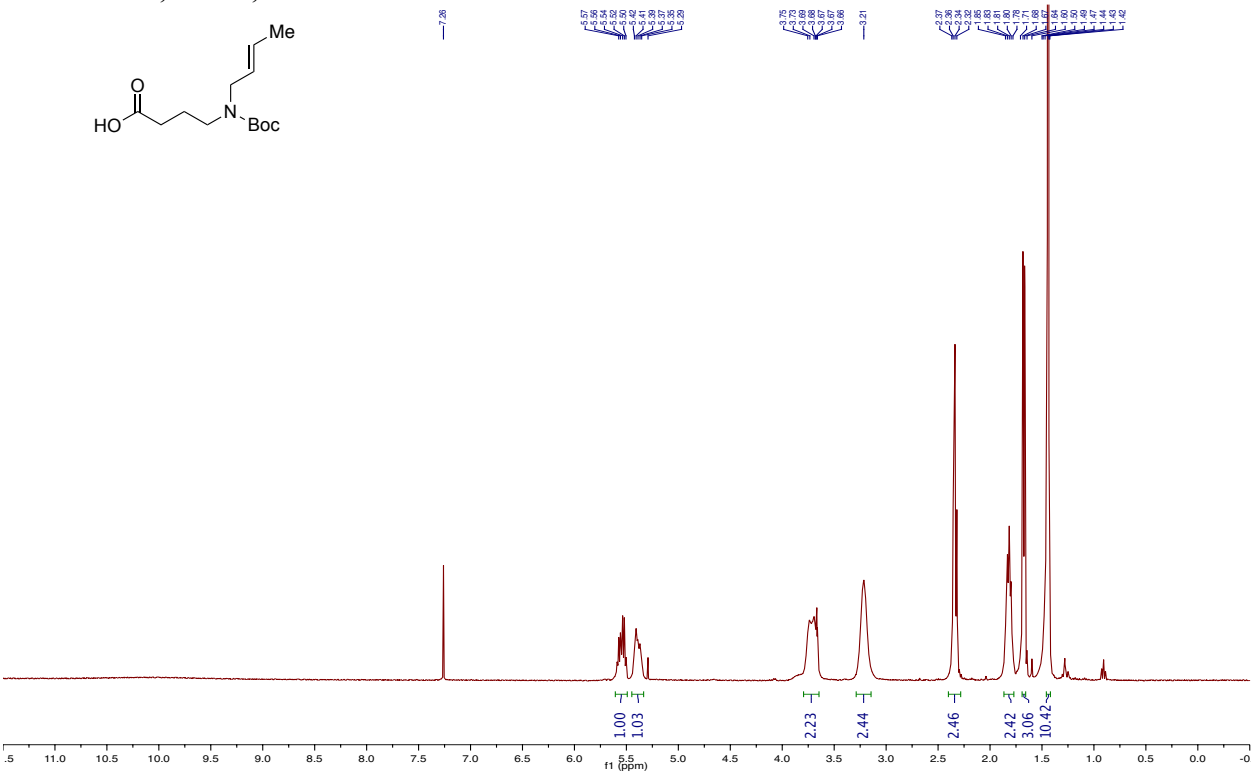


^{13}C – $CDCl_3$, 22 °C, 100 MHz

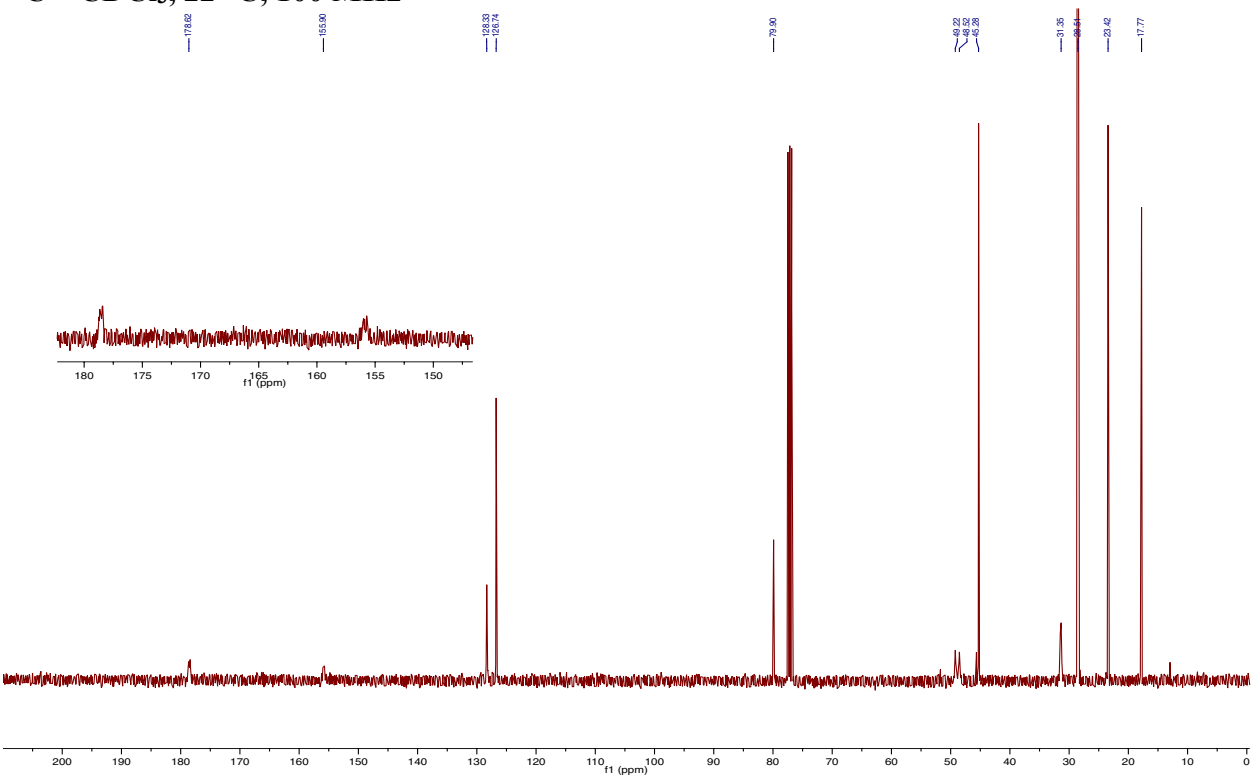


***N*-Boc-*N*-crotyl aminobutanoic acid (2.304b)**

^{1}H – $CDCl_3$, 22 °C, 400 MHz

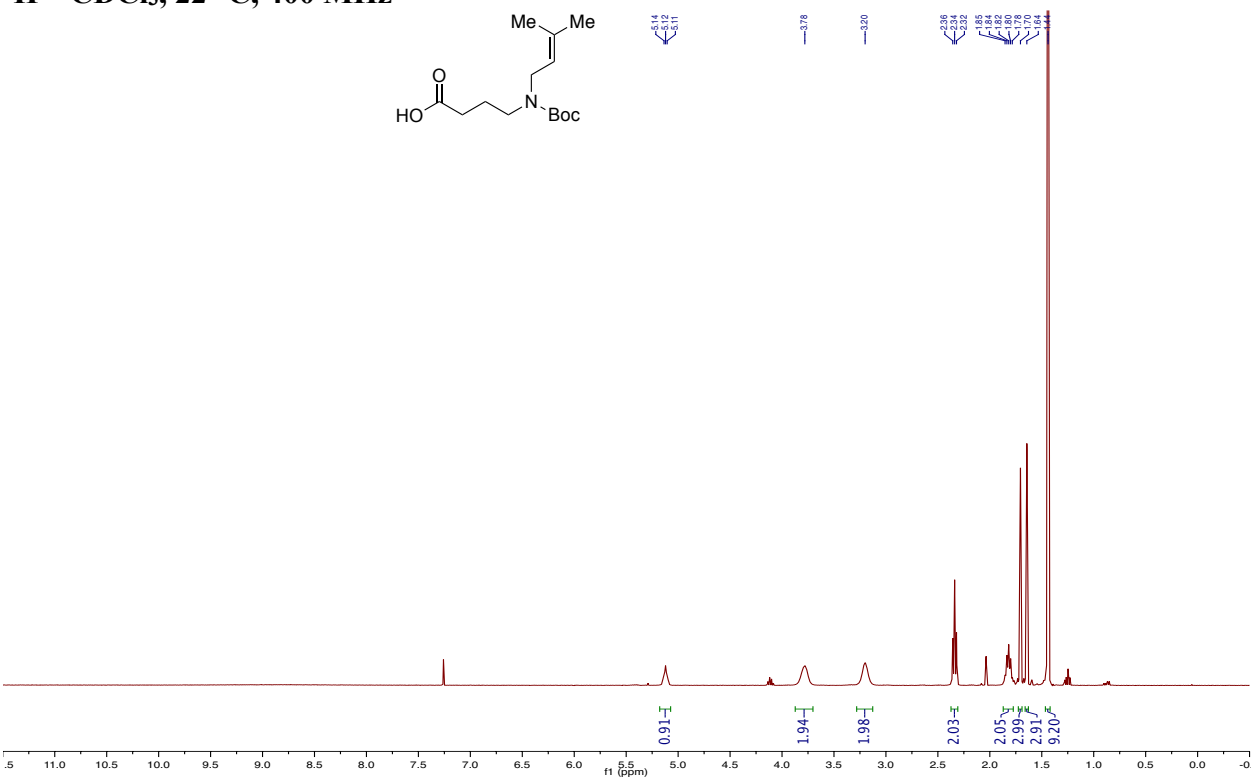


^{13}C – $CDCl_3$, 22 °C, 100 MHz

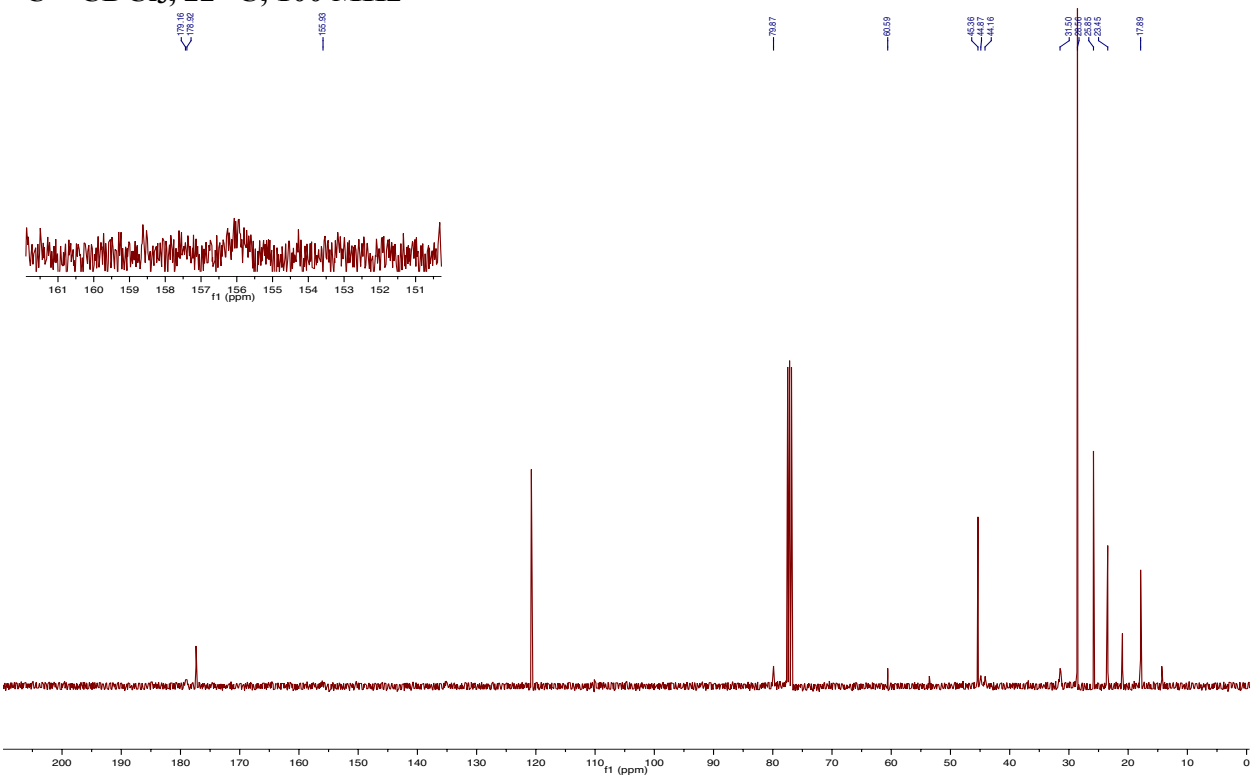


_N_-Boc-_N_-(3-methylbut-2-en-1-yl)aminobutanoic acid (2.304c)

^{1}H – $CDCl_3$, 22 °C, 400 MHz

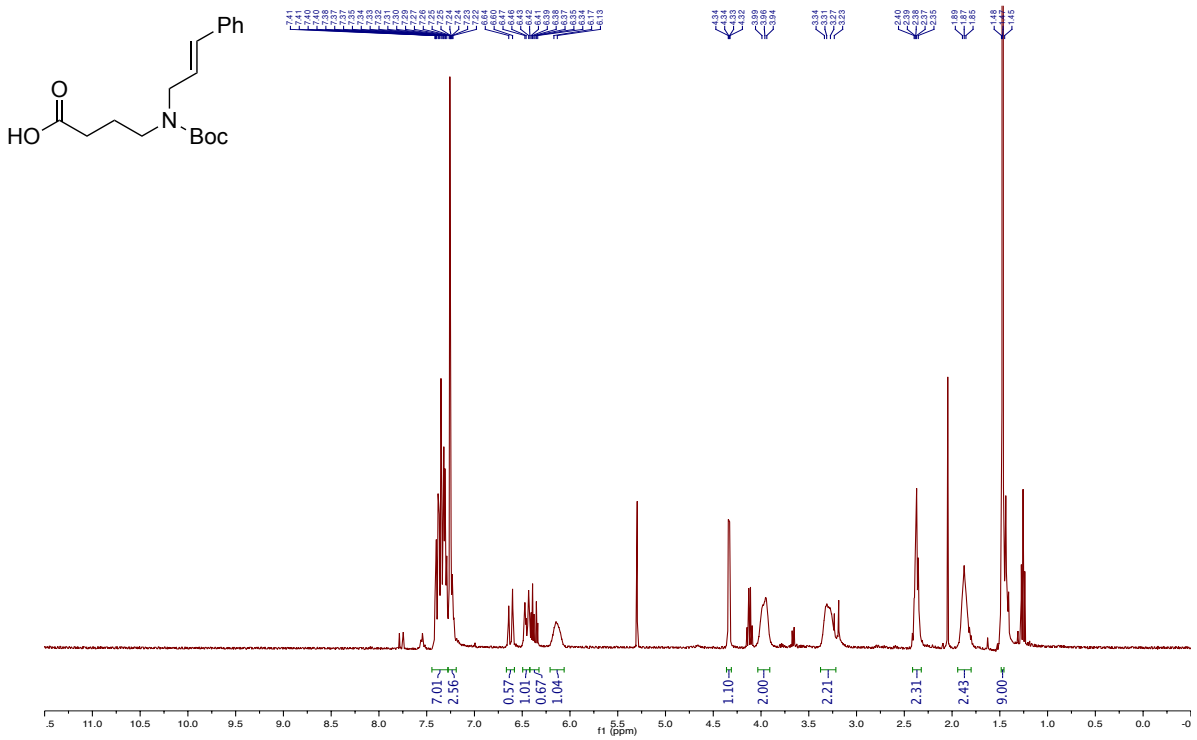


^{13}C – $CDCl_3$, 22 °C, 100 MHz

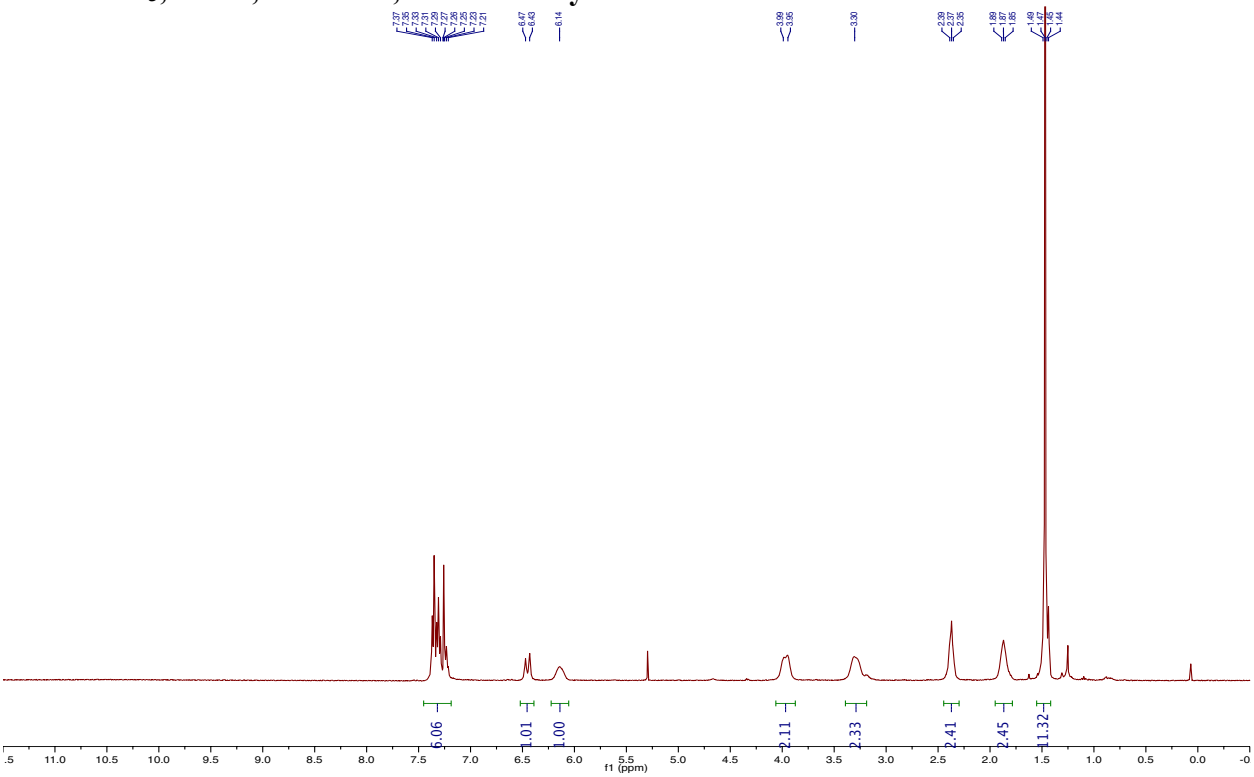


***N*-Boc-*N*-cinnamyl-4-aminobutanoic acid (2.304d)**

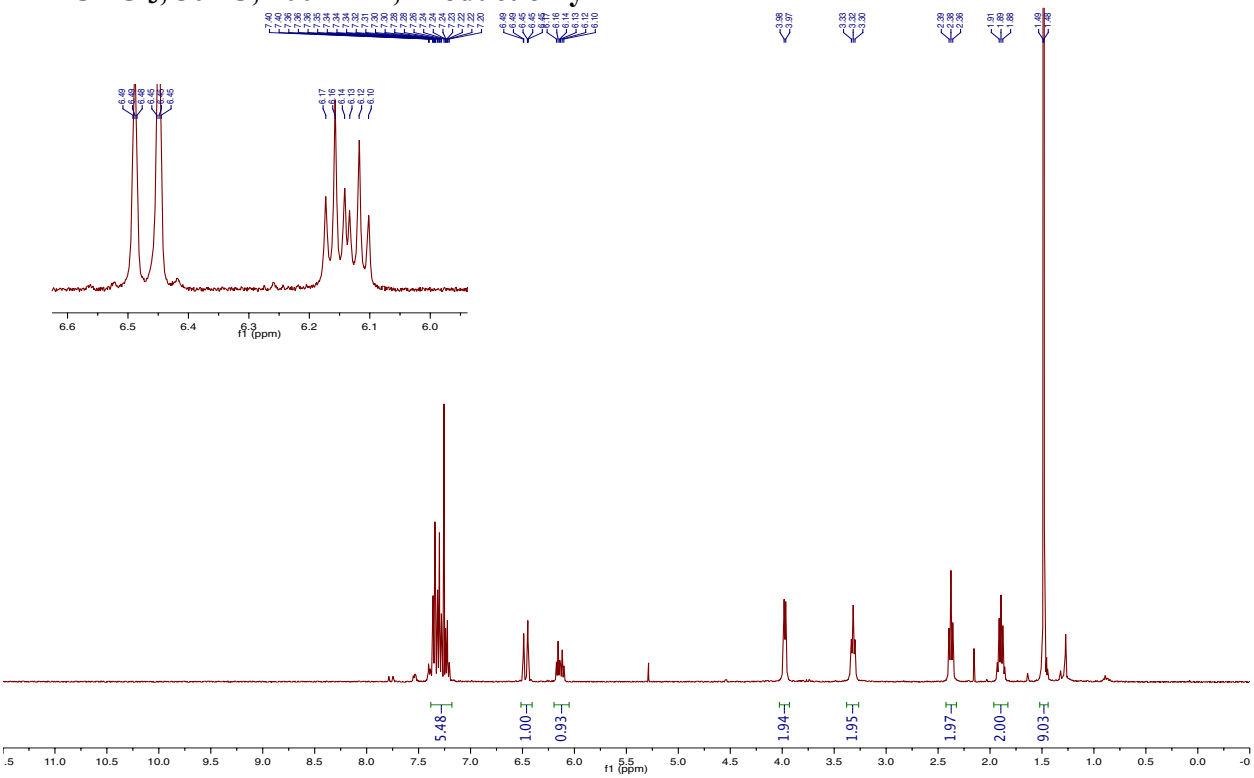
^{1}H – $CDCl_3$, 22 °C, 400 MHz, Product+cinnamyl alcohol (2:1)



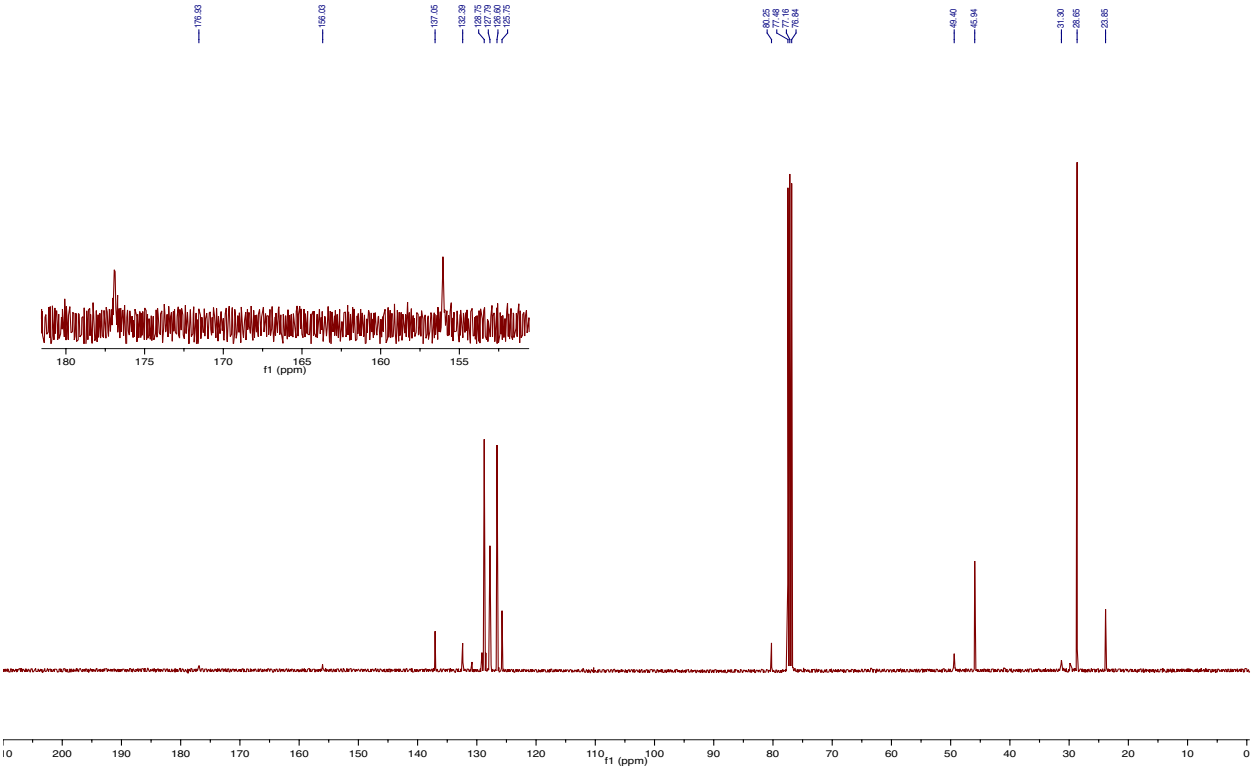
^{1}H – $CDCl_3$, 22 °C, 400 MHz, Product only



^{1}H – $CDCl_3$, 50 °C, 400 MHz, Product only

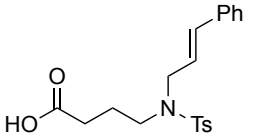


^{13}C – $CDCl_3$, 50 °C, 100 MHz, Product only

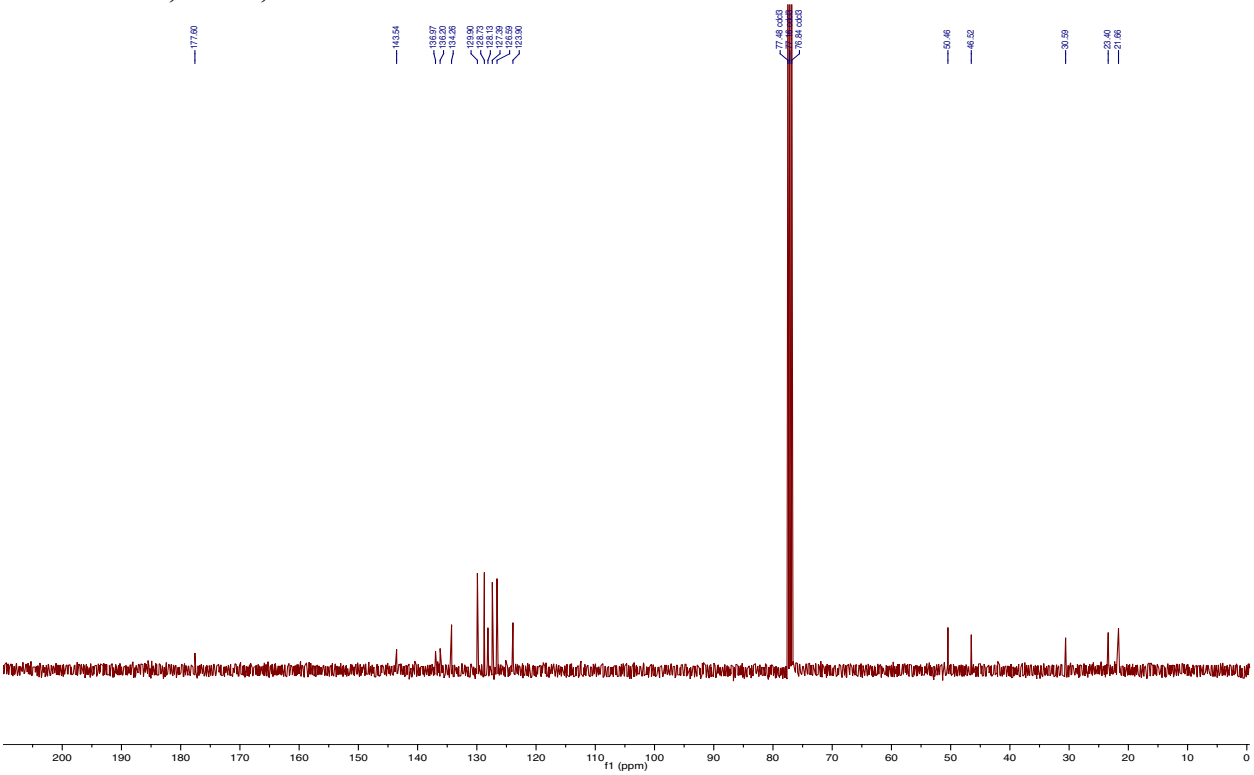


Cinnamyl-*N*-Ts-4-aminobutanoic acid (S-2.2)

^{1}H – $CDCl_3$, 22 °C, 400 MHz

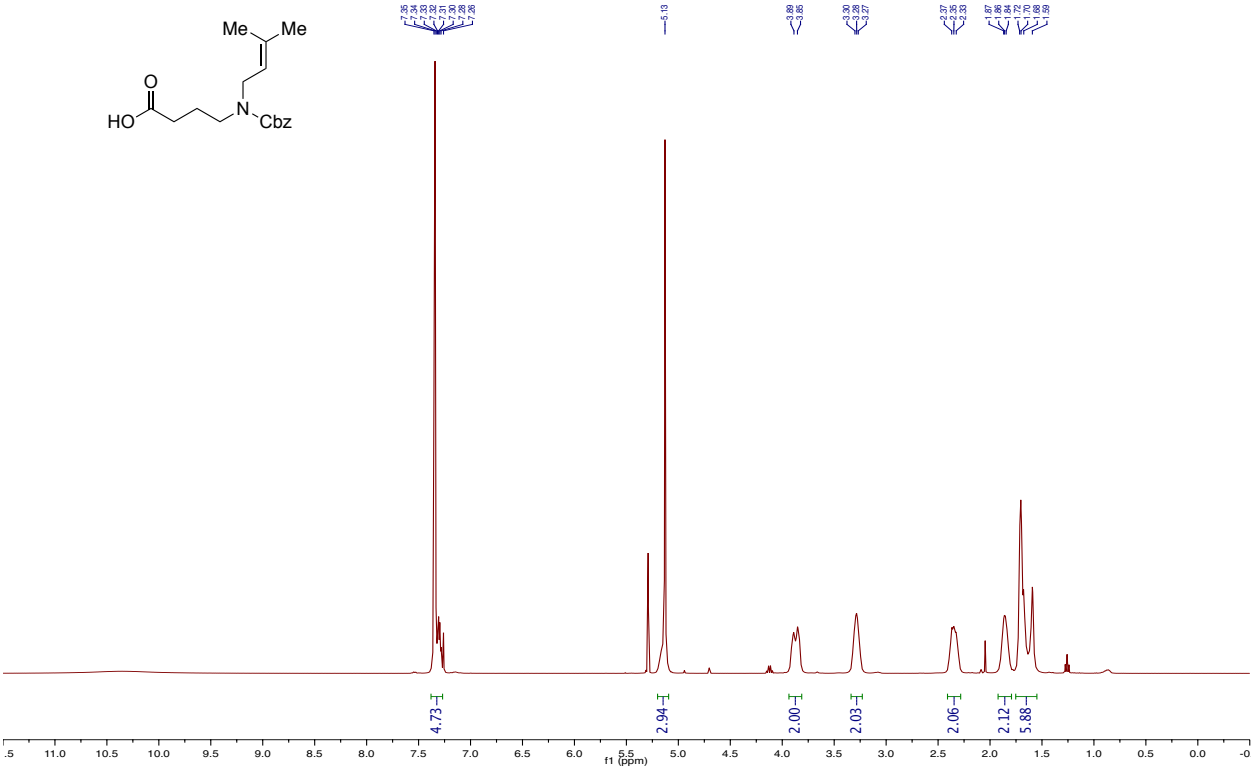


^{13}C – $CDCl_3$, 22 °C, 100 MHz

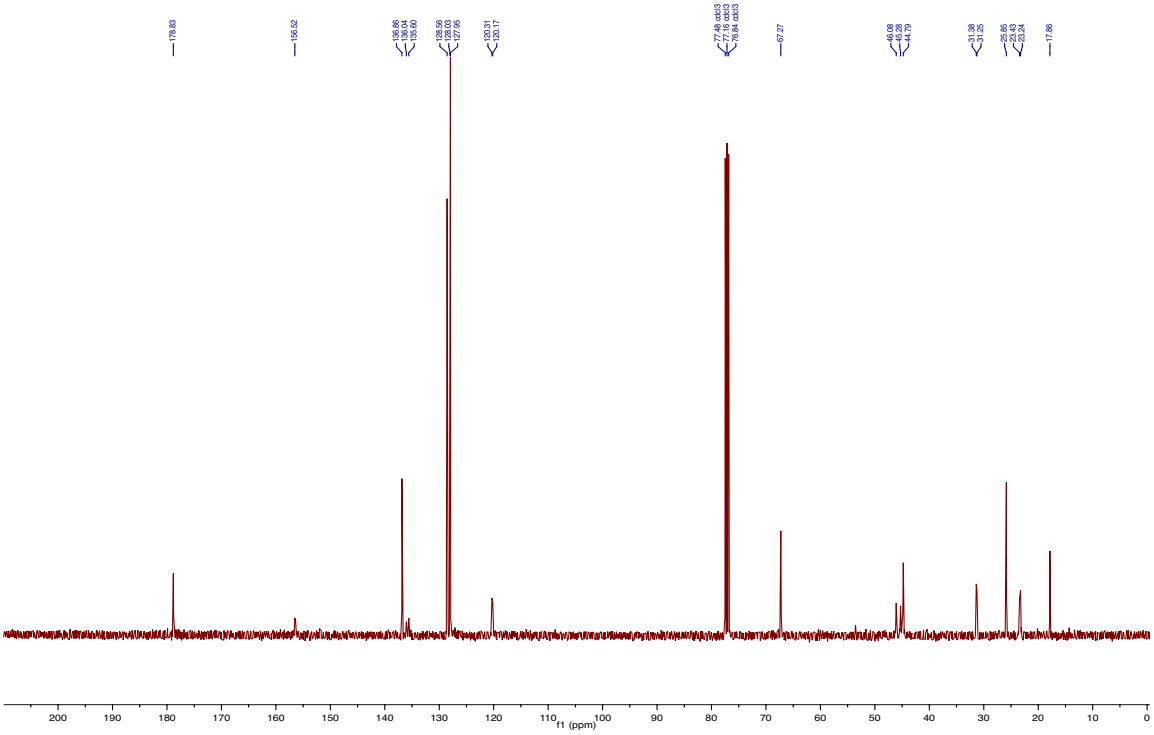


***N*-Cbz-*N*-cinnamyl-4-aminobutanoic acid (S-2.3)**

^{1}H – $CDCl_3$, 22 °C, 400 MHz

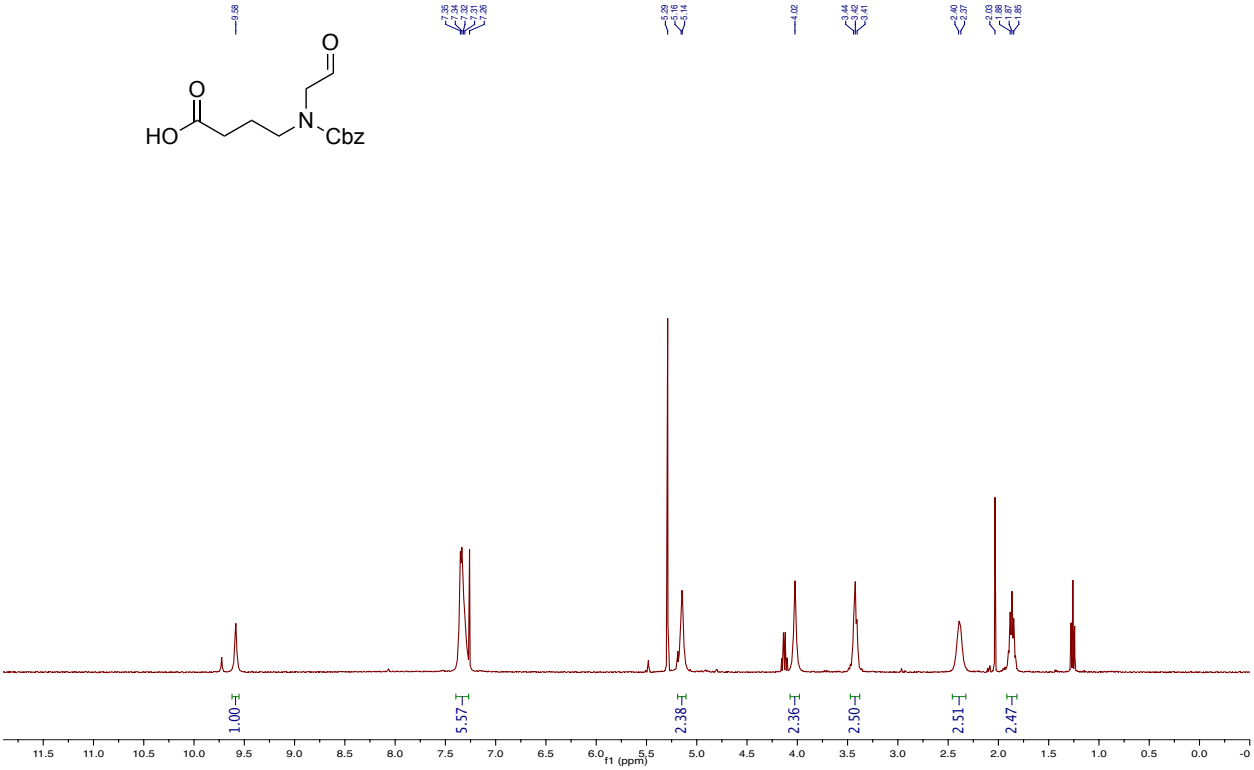


^{13}C – $CDCl_3$, 22 °C, 100 MHz

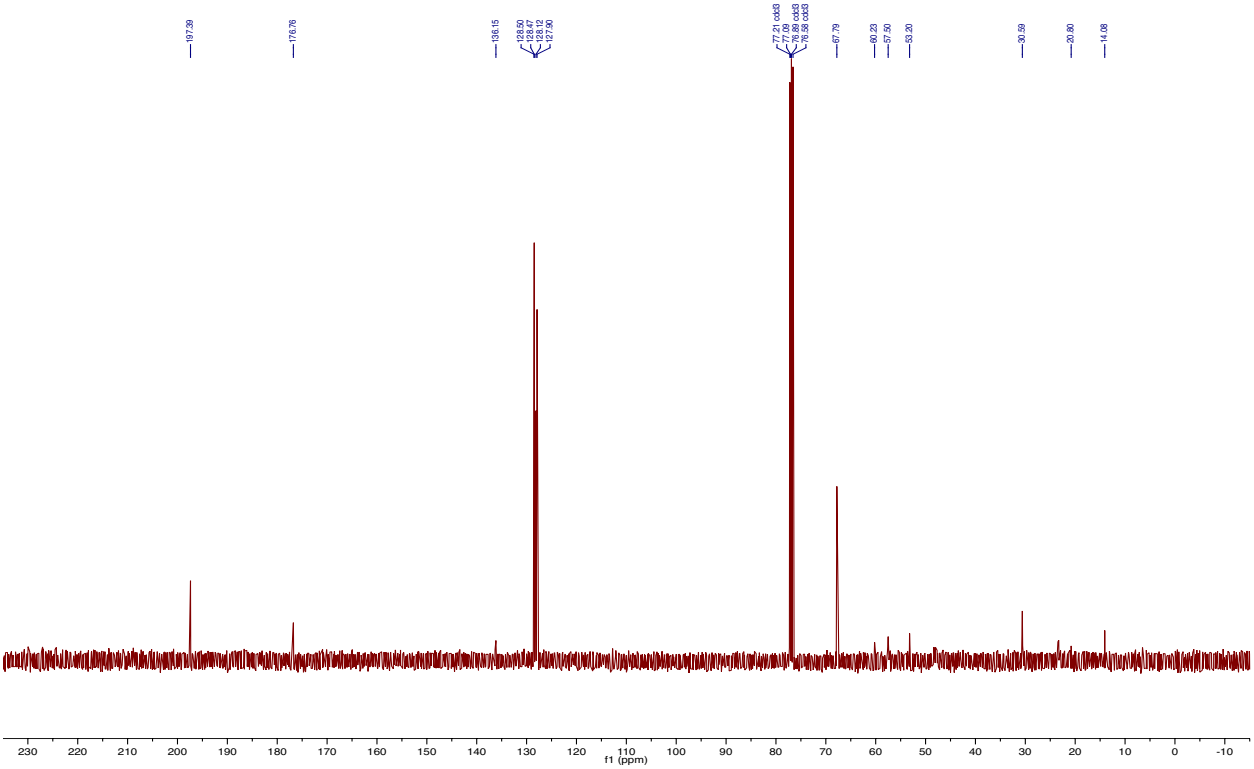


***N*-Cbz-*N*-(2-oxoethyl)-4-aminobutanoic acid (2.273a)**

^{1}H – $CDCl_3$, 50 °C, 400 MHz

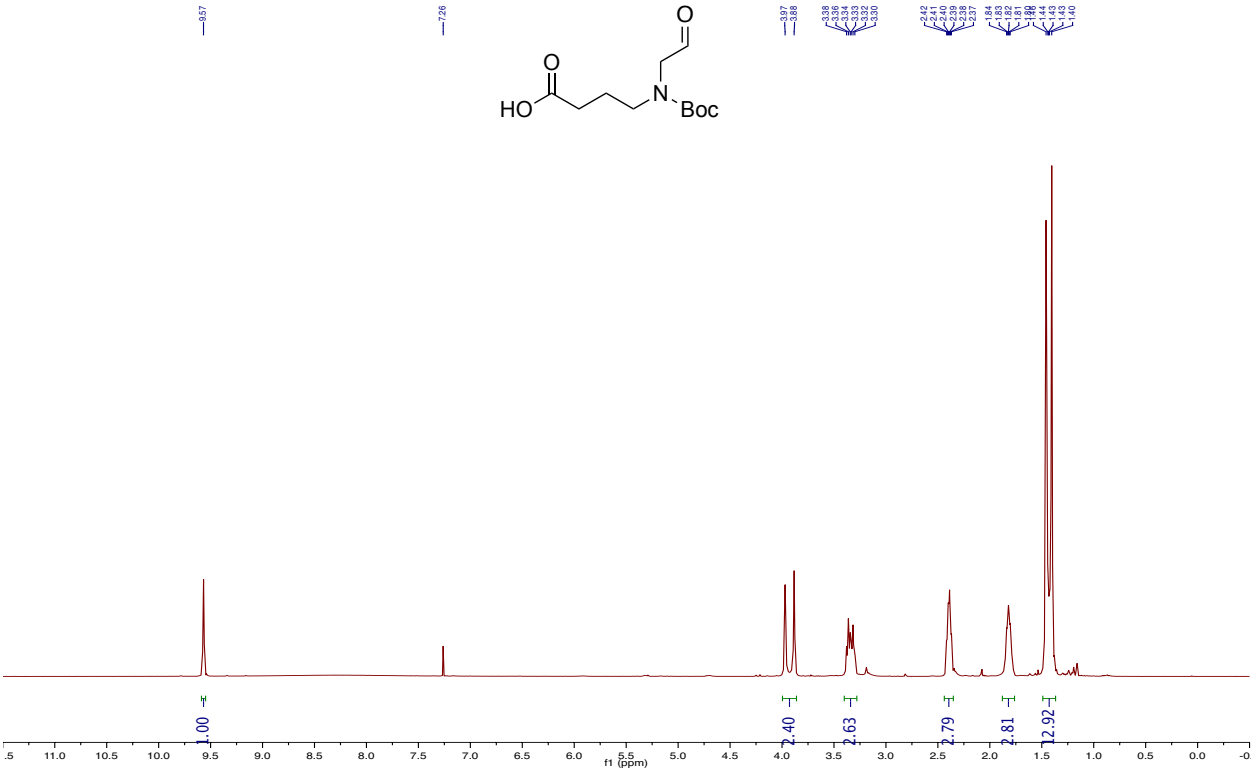


^{13}C – $CDCl_3$, 50 °C, 100 MHz

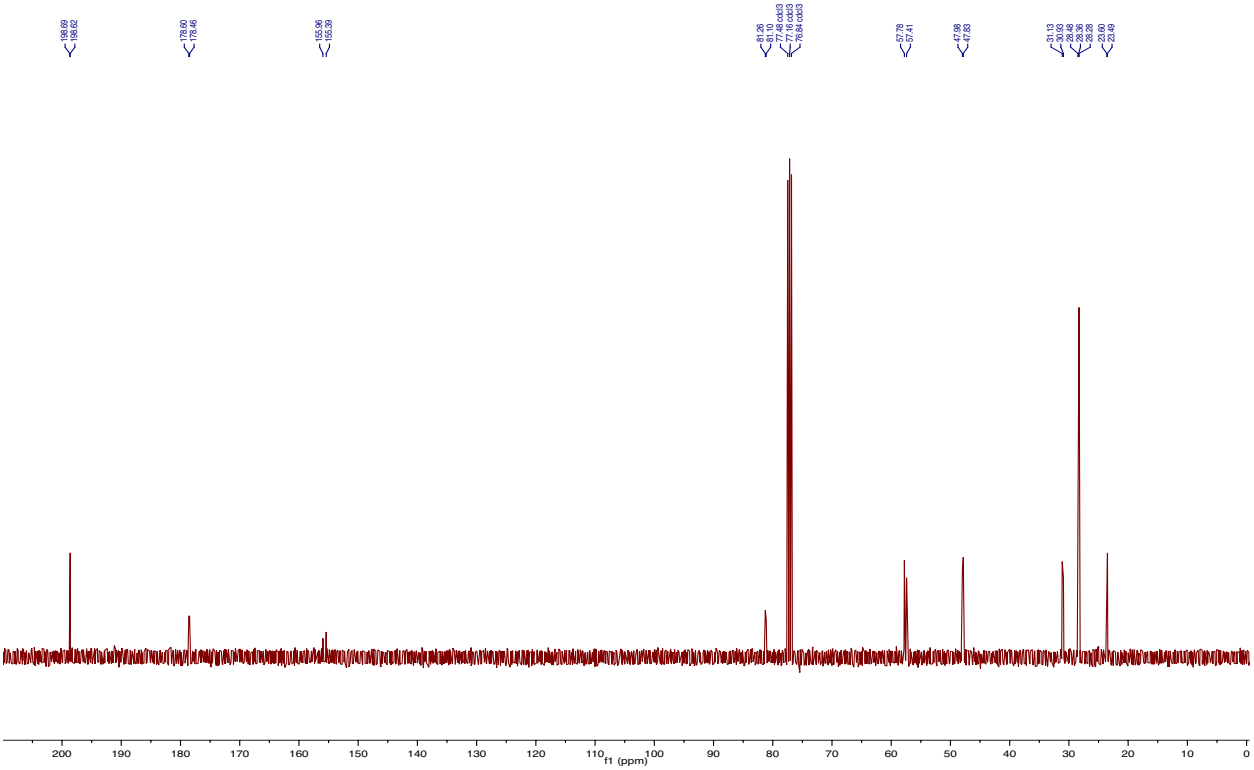


_N_-Boc-_N_-(2-oxoethyl)-4-aminobutanoic acid (2.273b)

^{1}H – $CDCl_3$, 22 °C, 400 MHz

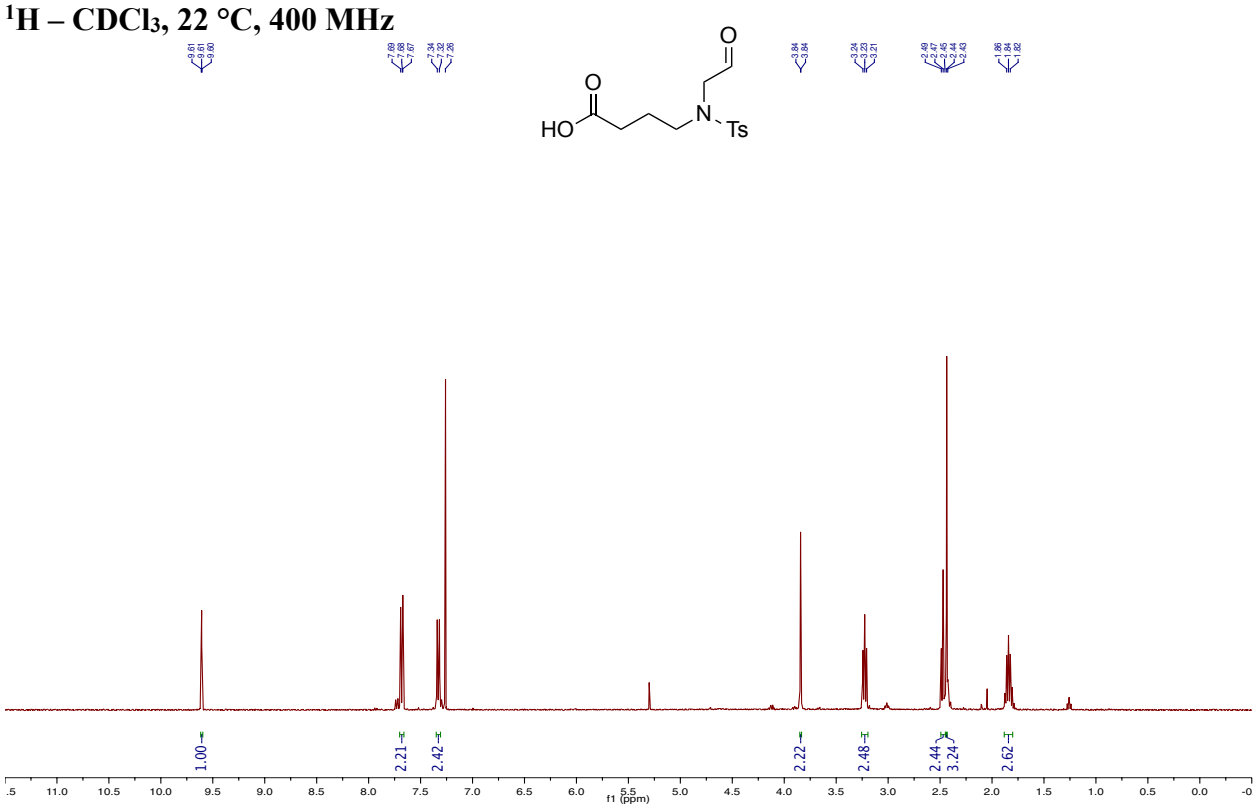


^{13}C – $CDCl_3$, 22 °C, 100 MHz

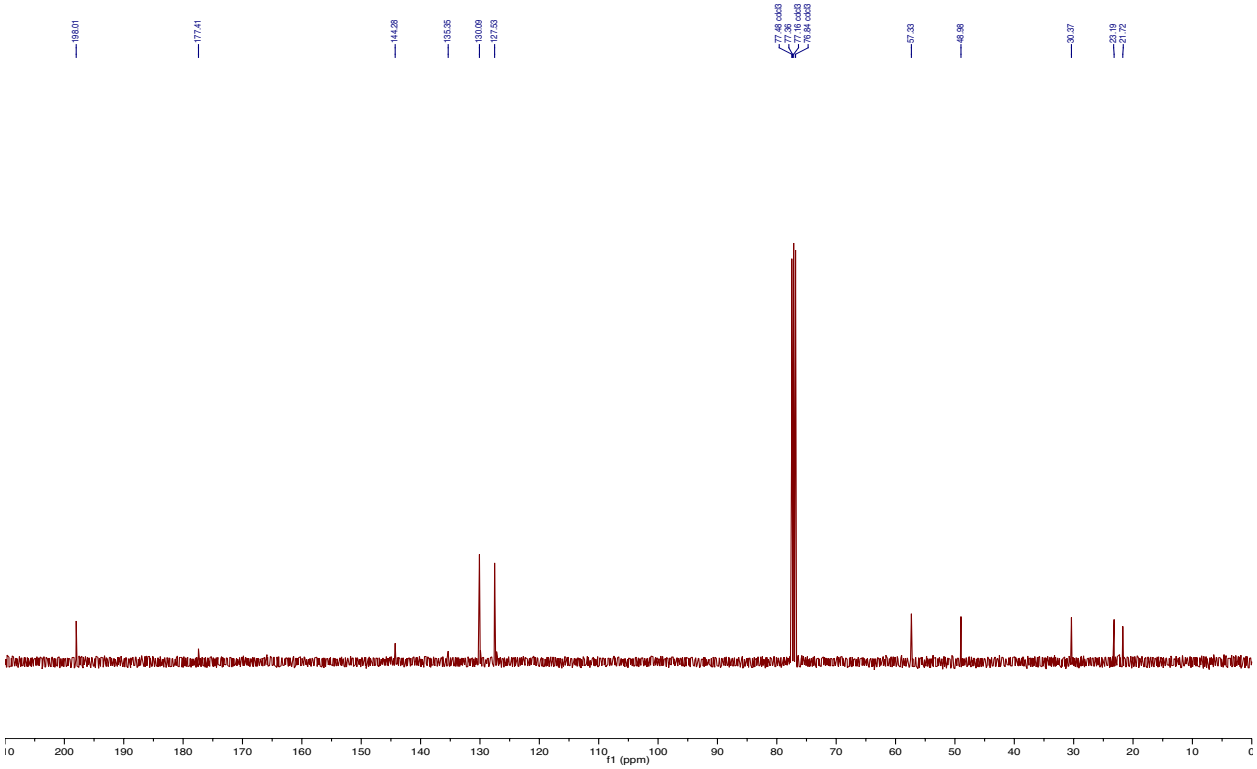


_N_-Ts-_N_-(2-oxoethyl)-4-aminobutanoic acid (2.273c)

^{1}H – $CDCl_3$, 22 °C, 400 MHz

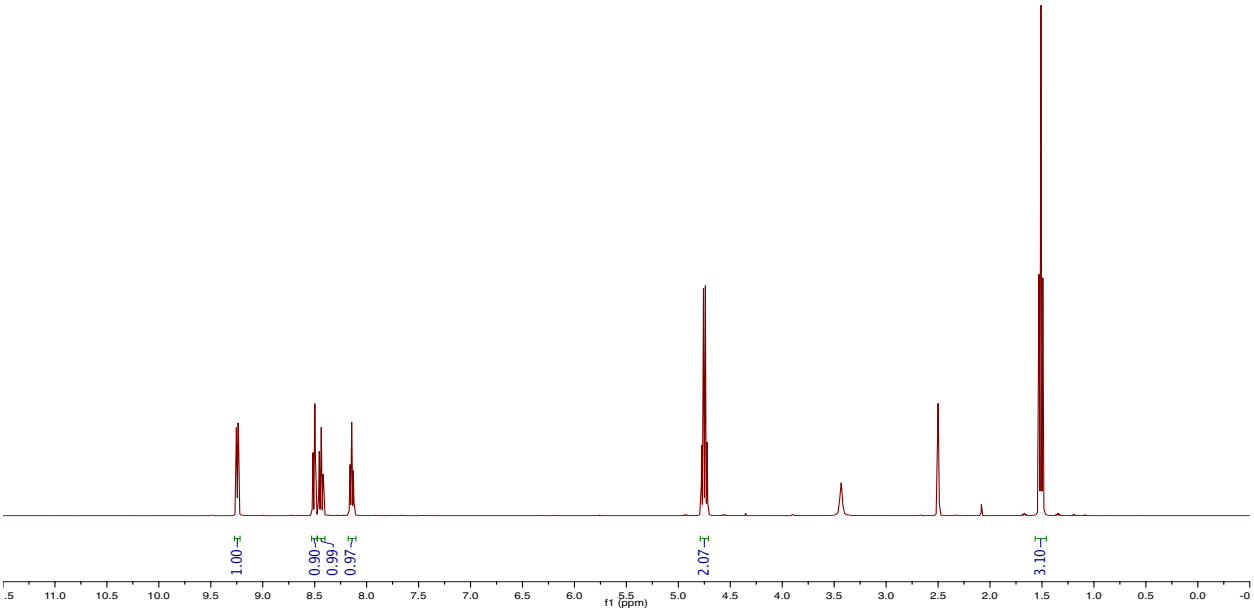


^{13}C – $CDCl_3$, 22 °C, 100 MHz

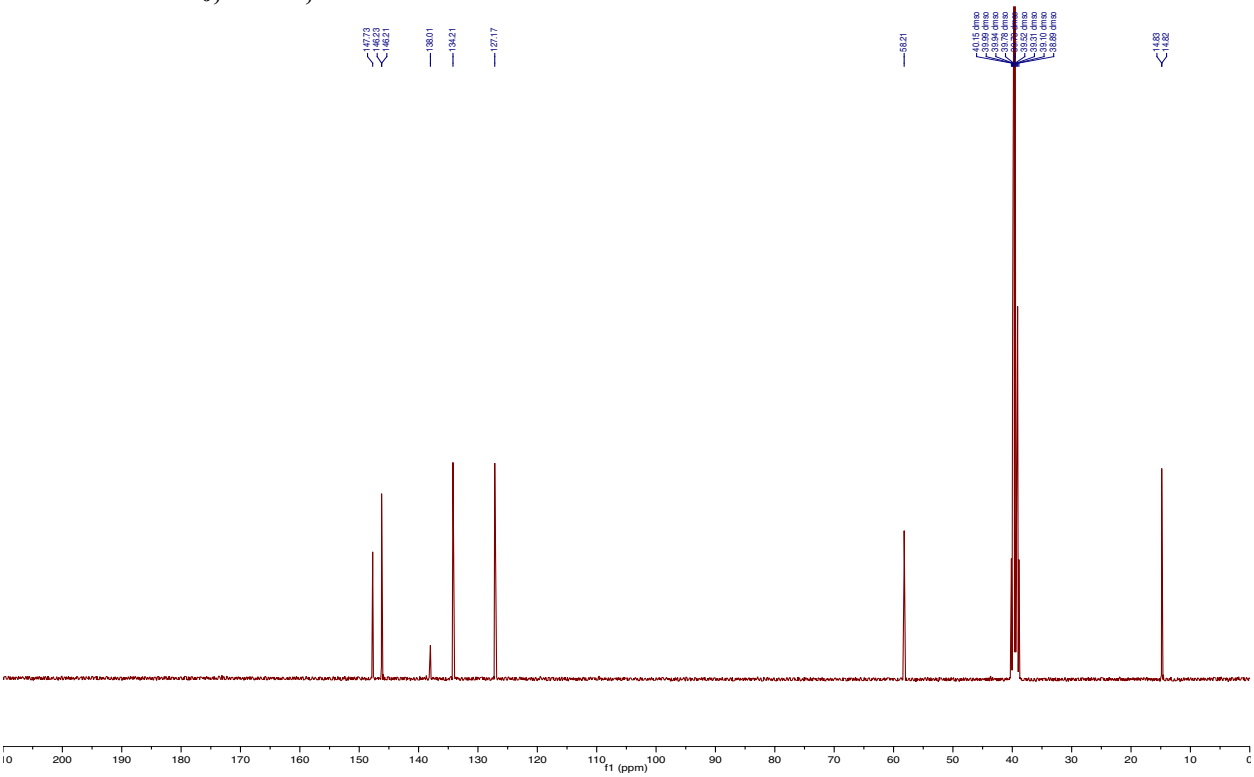


_N_-Ethyl-2-bromopyridinium tetrafluoroborate (3.307a)

^{1}H – DMSO-d_6, 22 °C, 400 MHz

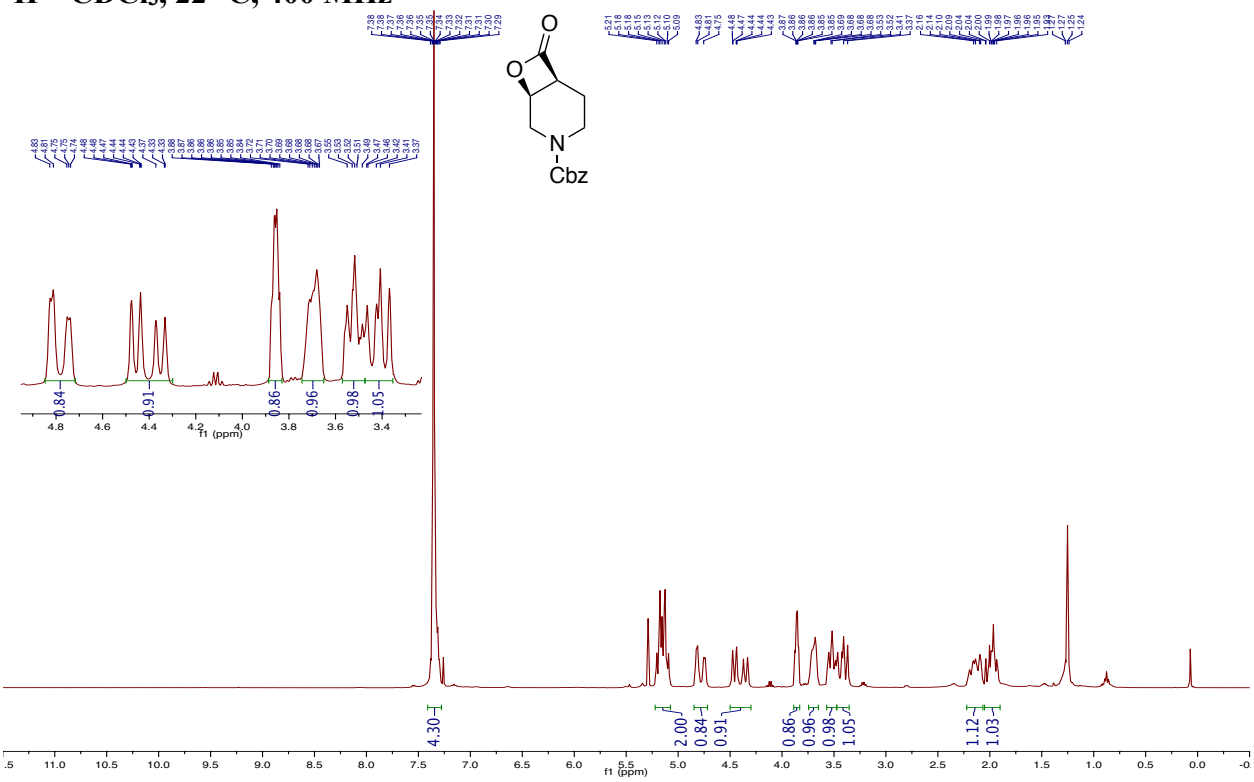


^{13}C – DMSO-d_6, 22 °C, 100 MHz

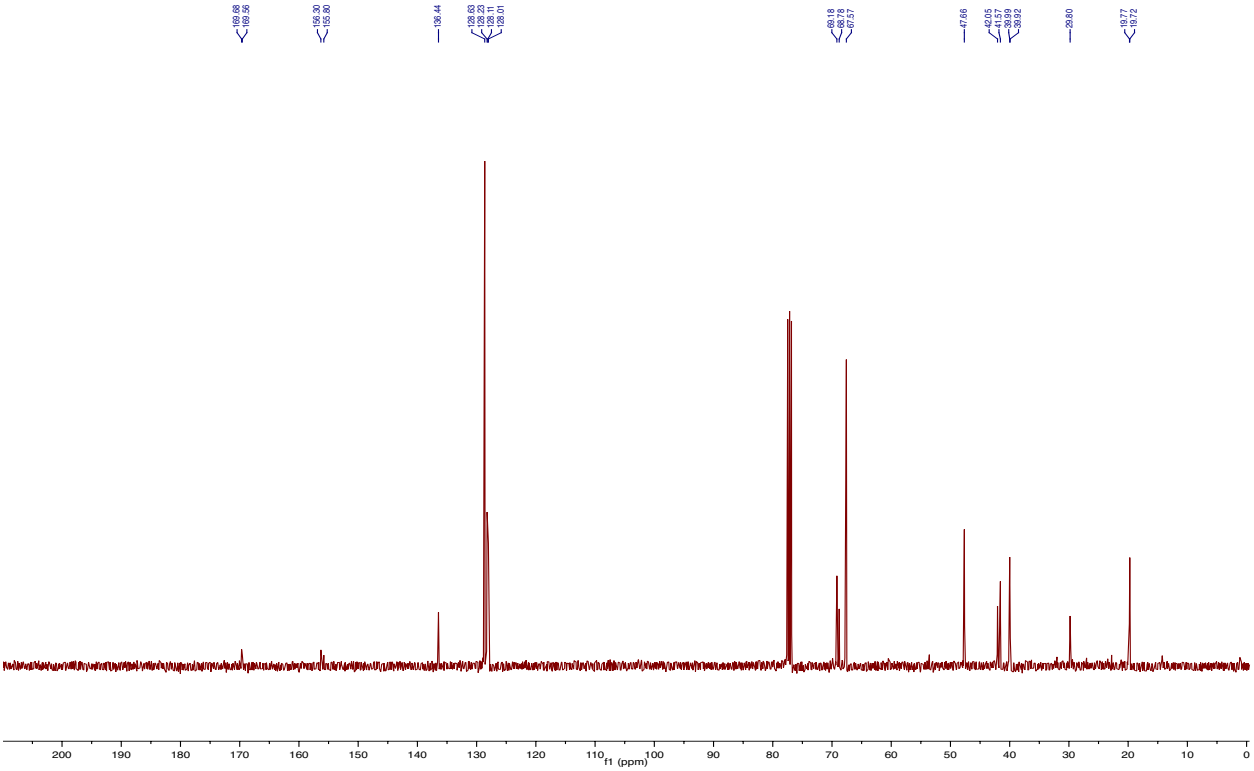


N-Cbz-8-oxa-3-azabicyclo[4.2.0]octan-7-one (2.274a)

^{1}H – $CDCl_3$, 22 °C, 400 MHz

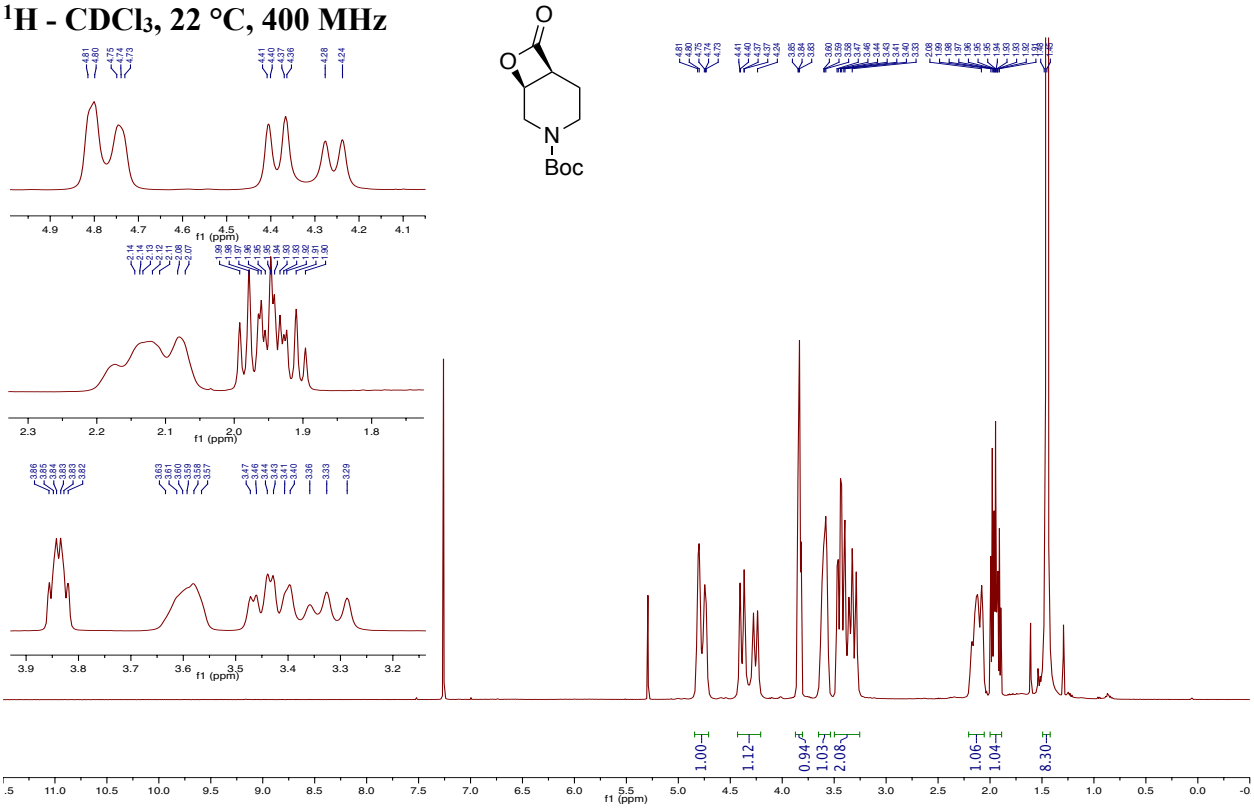


^{13}C – $CDCl_3$ 22 °C, 100 MHz

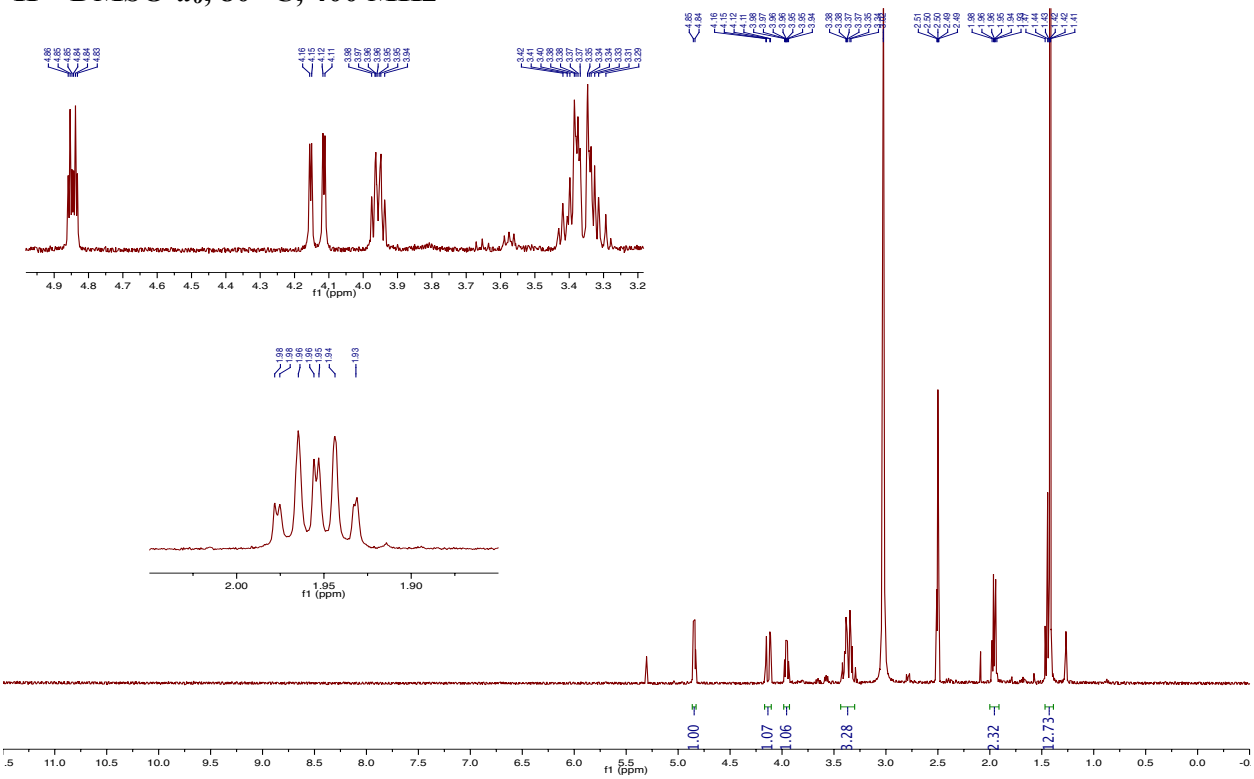


_N_-Boc-8-oxa-3-azabicyclo[4.2.0]octan-7-one 2.274b

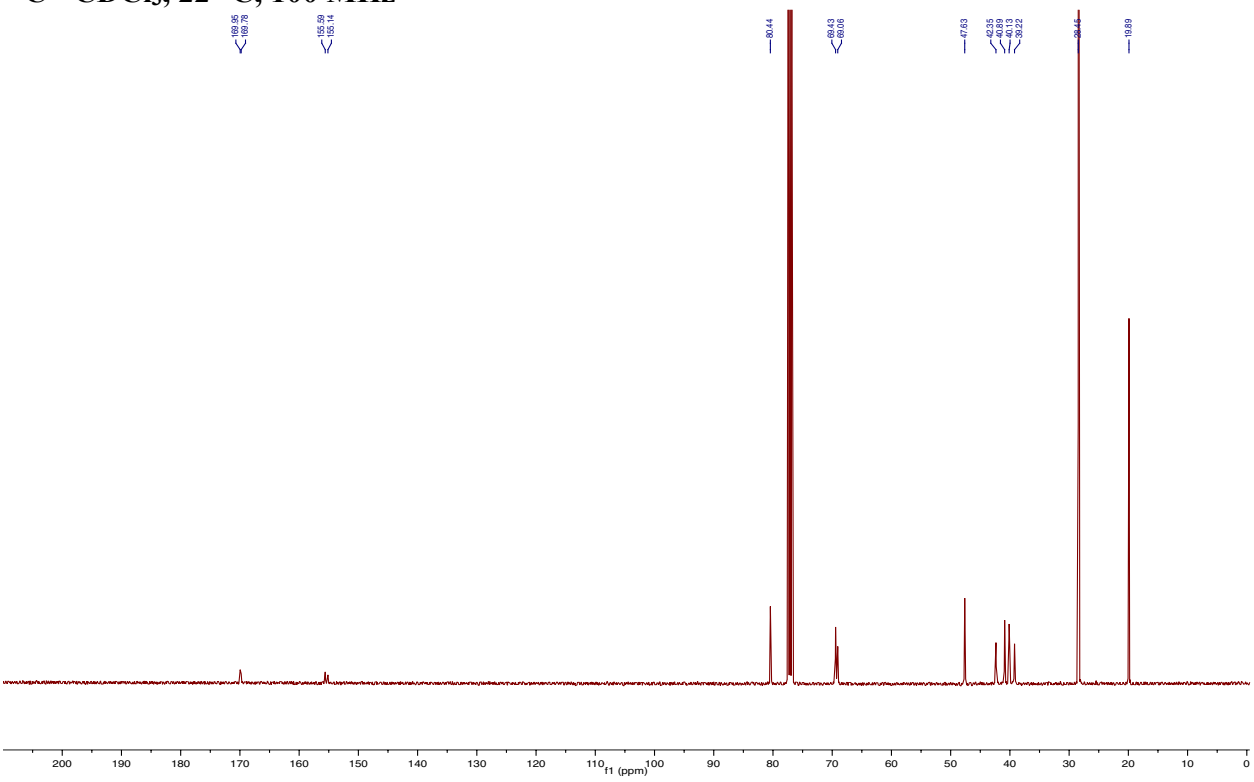
^{1}H - $CDCl_3$, 22 °C, 400 MHz



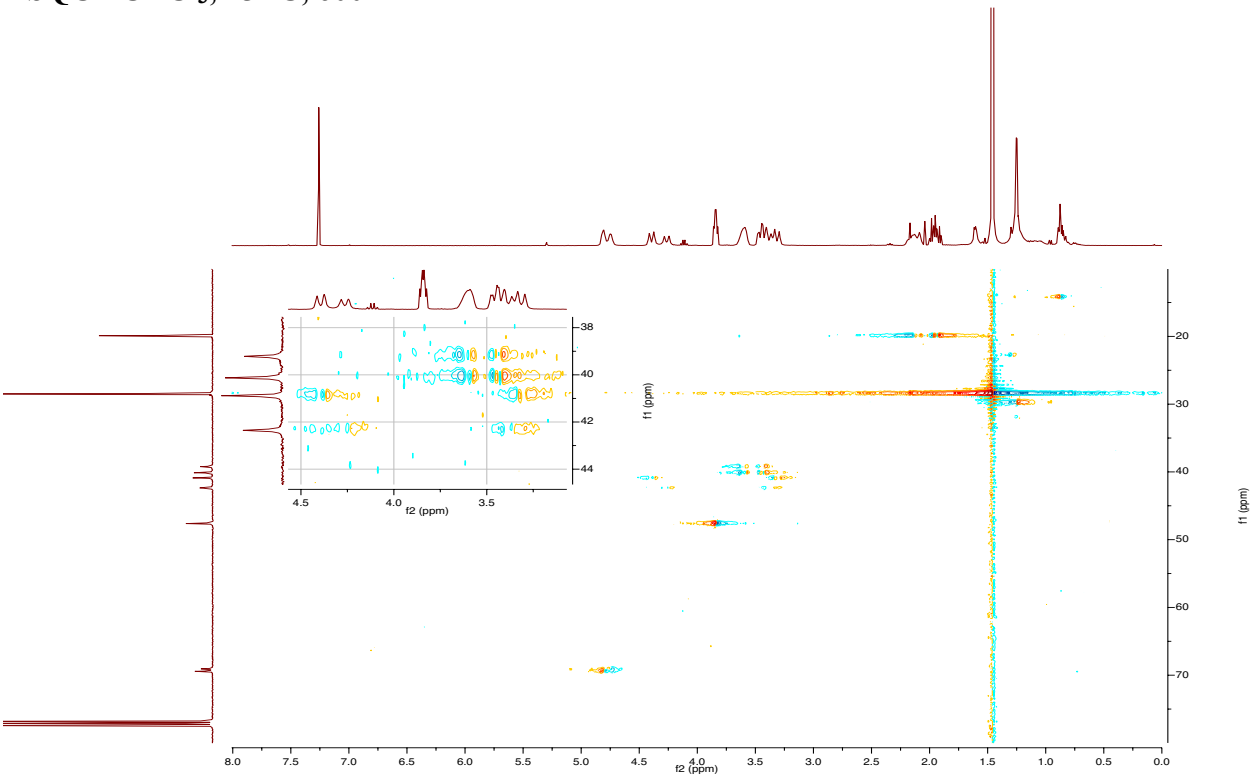
^{1}H – DMSO-d_6, 80 °C, 400 MHz



^{13}C - $CDCl_3$, 22 °C, 100 MHz

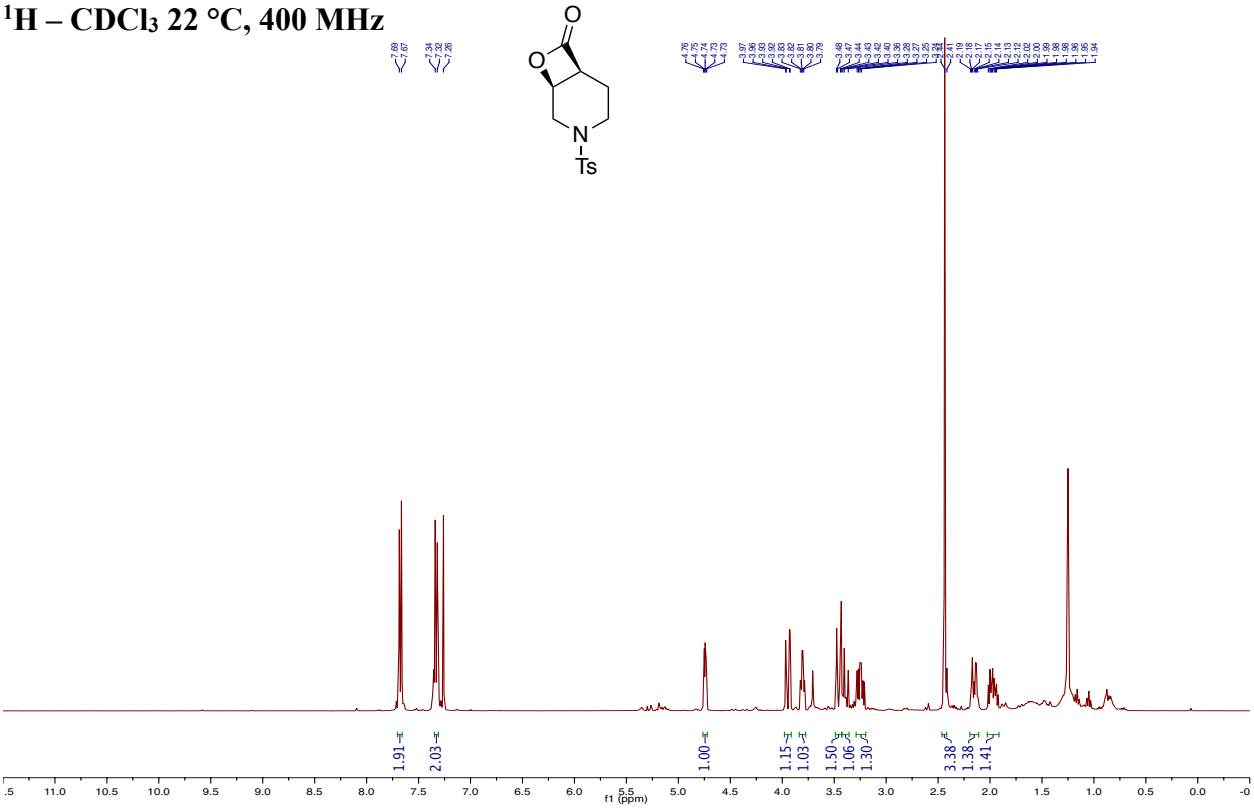


HSQC - $CDCl_3$, 25 °C, 600 MHz

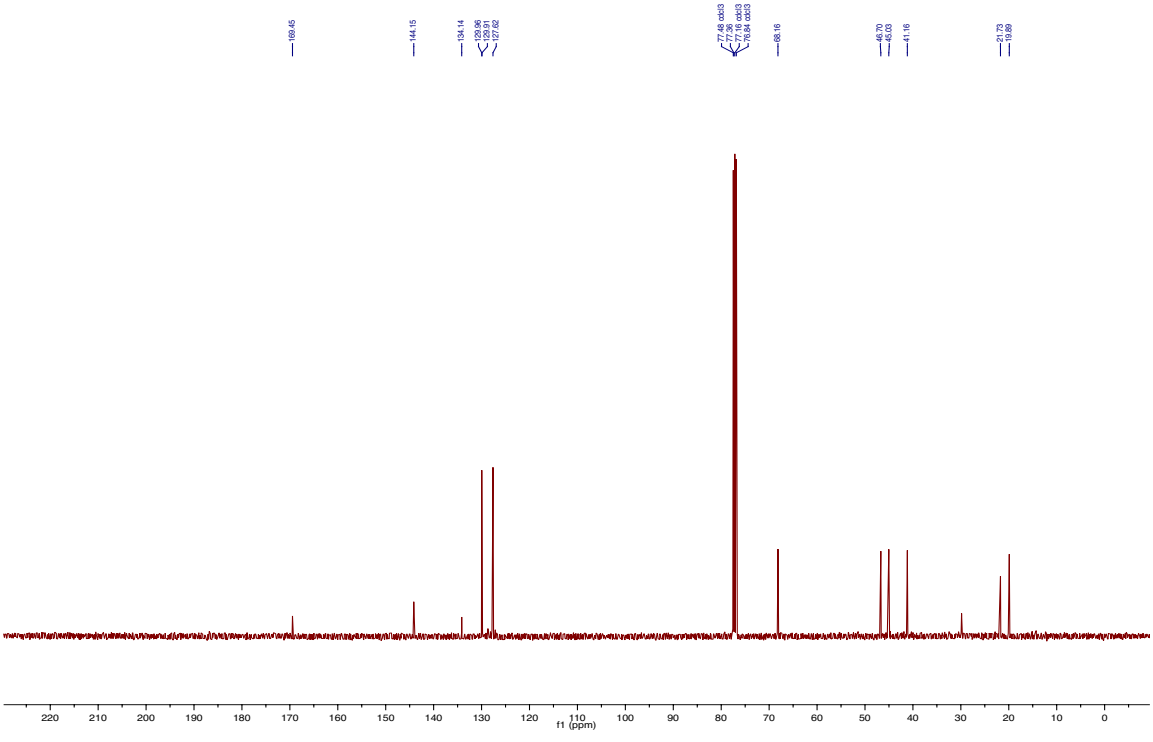


_N_-Ts-8-oxa-3-azabicyclo[4.2.0]octan-7-one (2.274c)

^{1}H – $CDCl_3$ 22 °C, 400 MHz

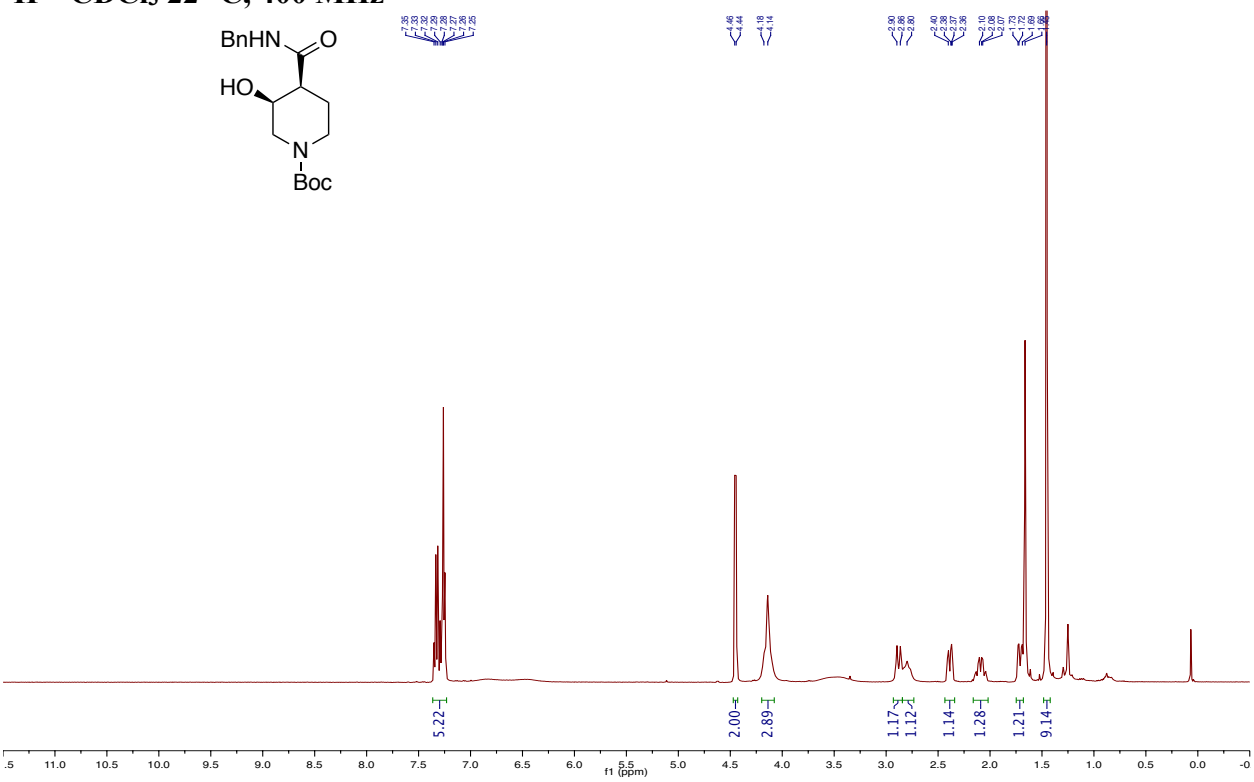


^{13}C – $CDCl_3$, 22 °C, 100 MHz

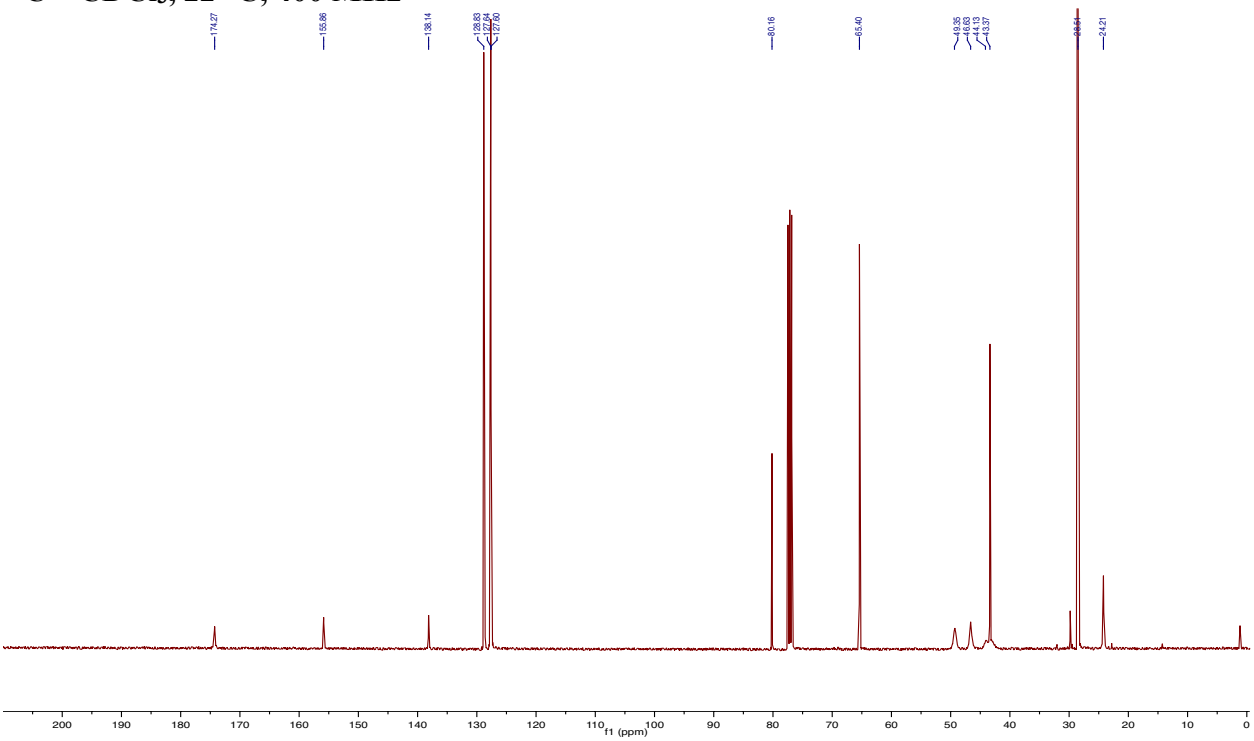


(-)-(3*S*, 4*S*)-*N*-Boc-4-(benzylcarbamoyl)-3-hydroxypiperidine (S-2.4)

^{1}H – $CDCl_3$ 22 °C, 400 MHz

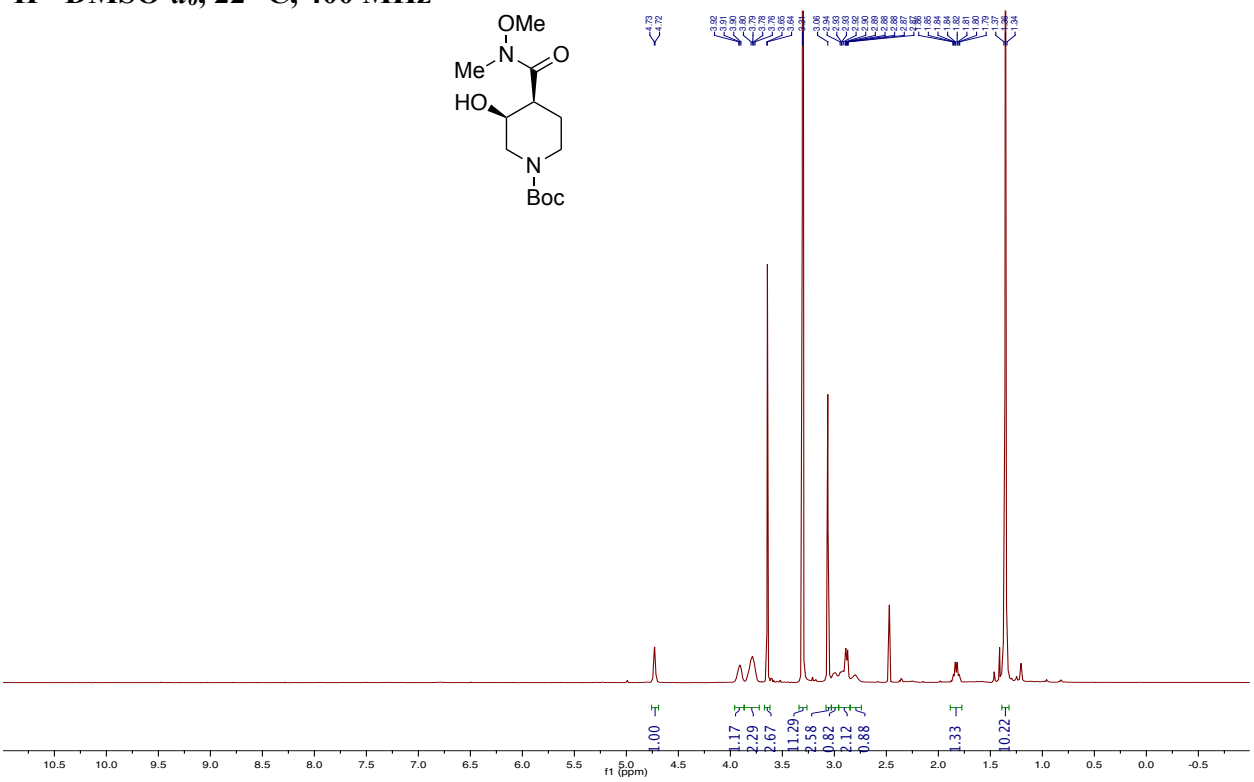


^{13}C – $CDCl_3$, 22 °C, 400 MHz

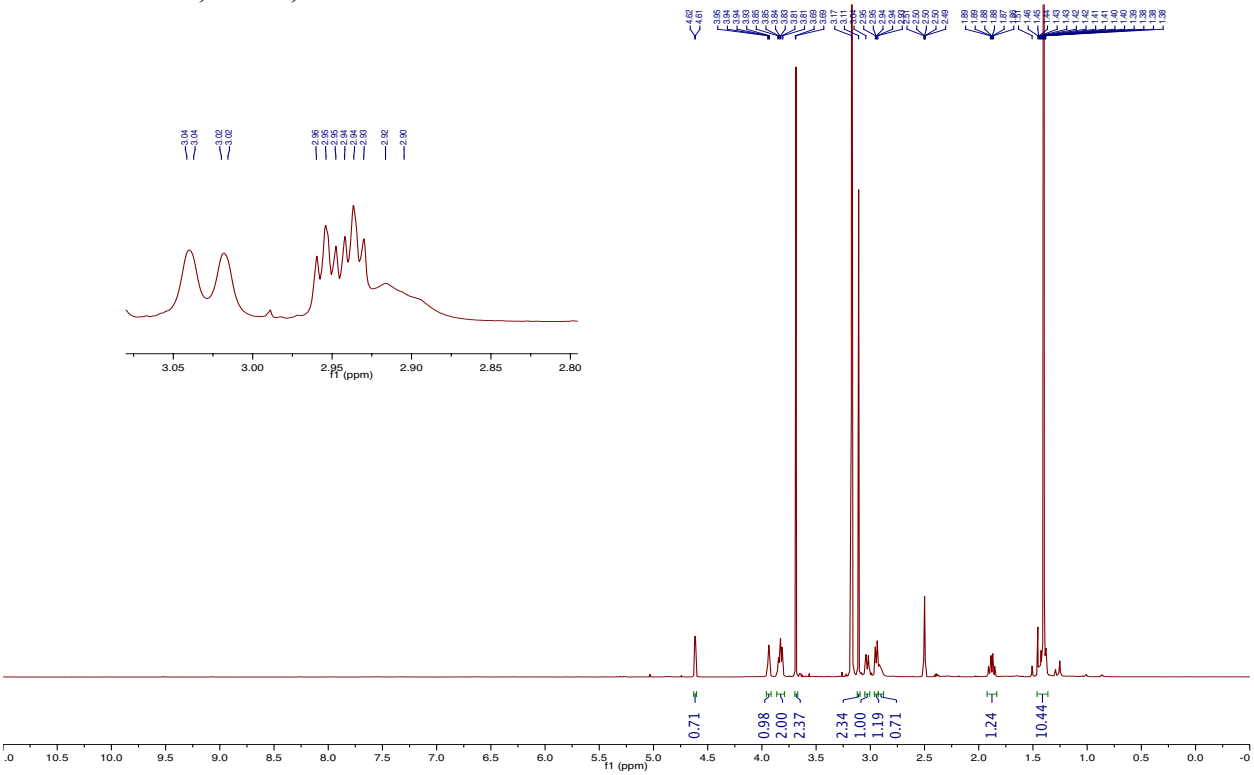


_N_-Boc-3-hydroxy-4-(methoxy(methyl)carbamoyl)piperidine (S-2.5)

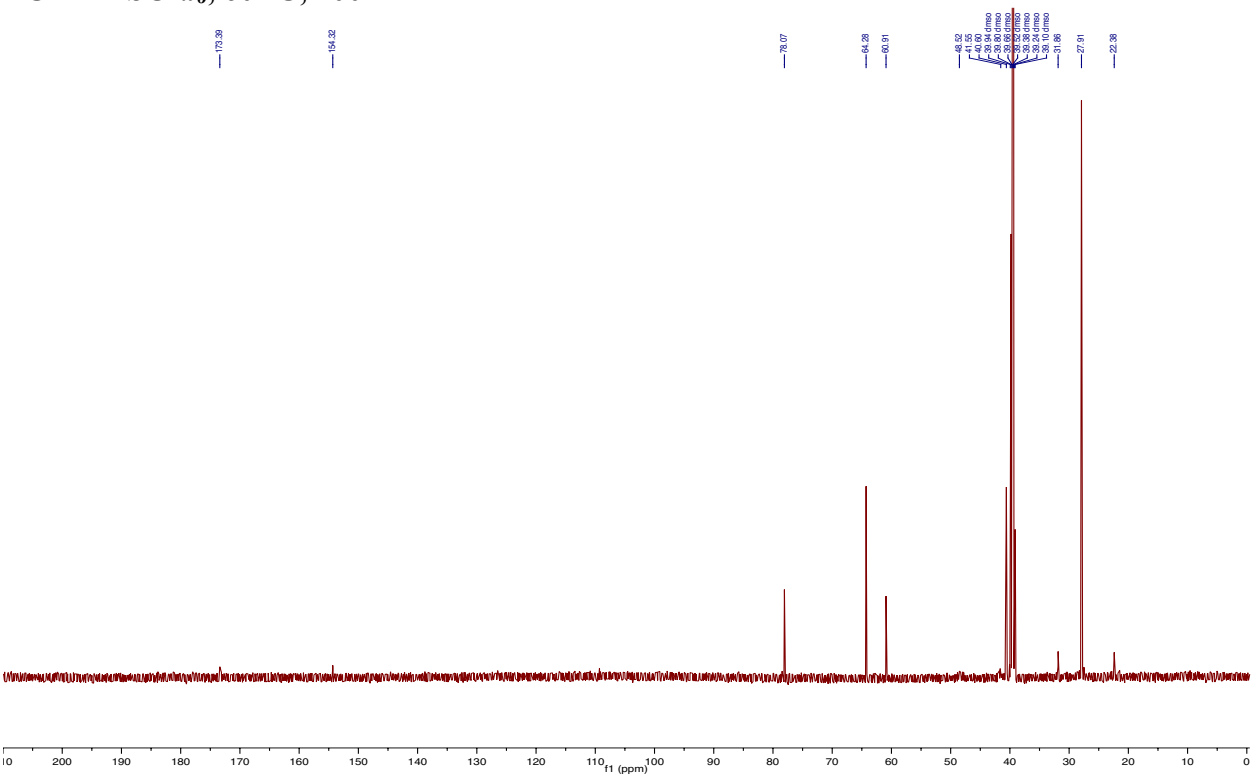
^{1}H - DMSO-_d_$_6$, 22 °C, 400 MHz



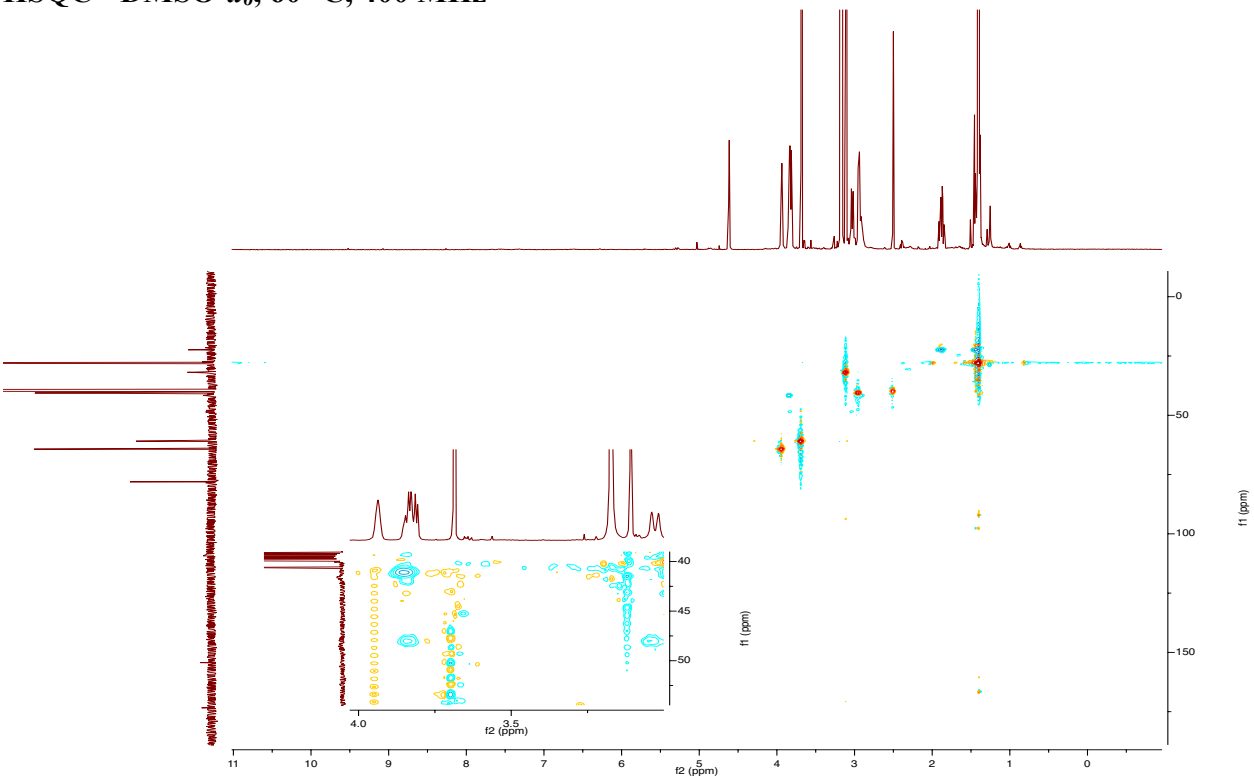
^{1}H - DMSO-_d_$_6$, 60 °C, 400 MHz



^{13}C - DMSO-*d*$_6$, 60 °C, 100 MHz

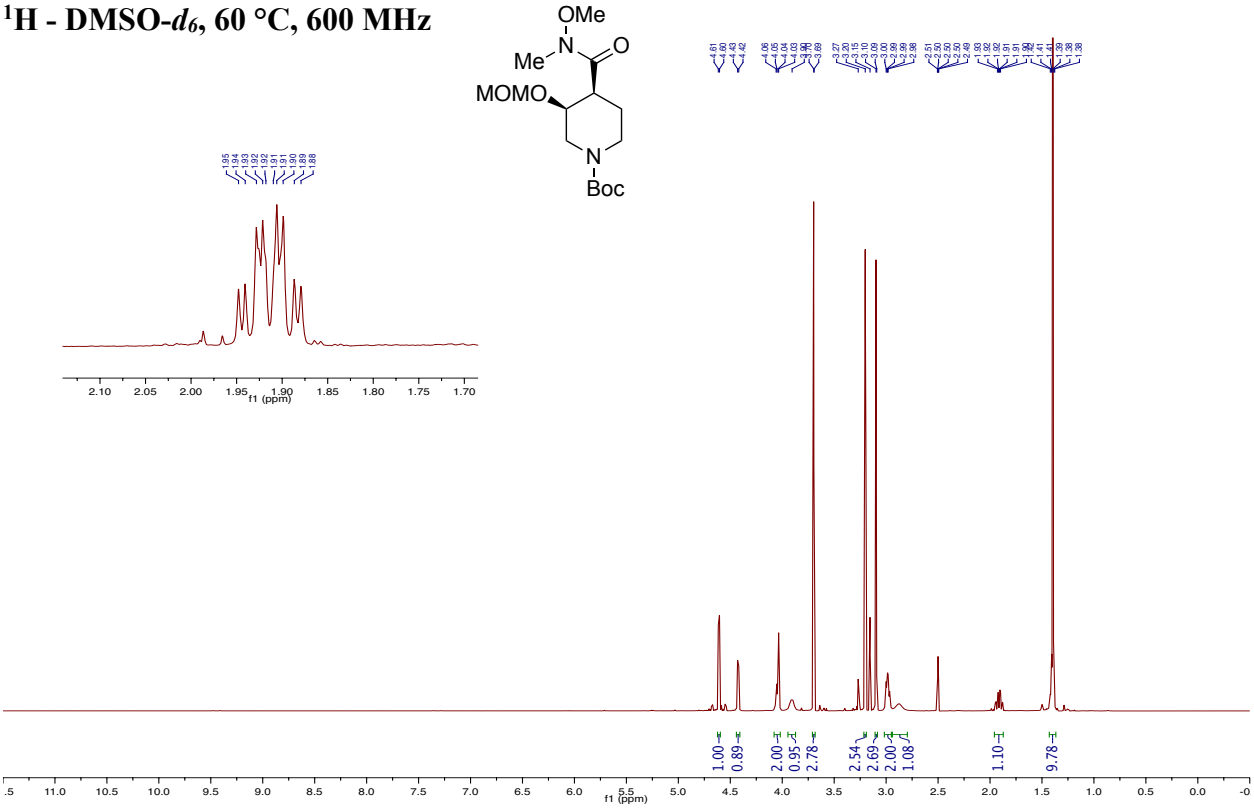


HSQC - DMSO-*d*$_6$, 60 °C, 400 MHz

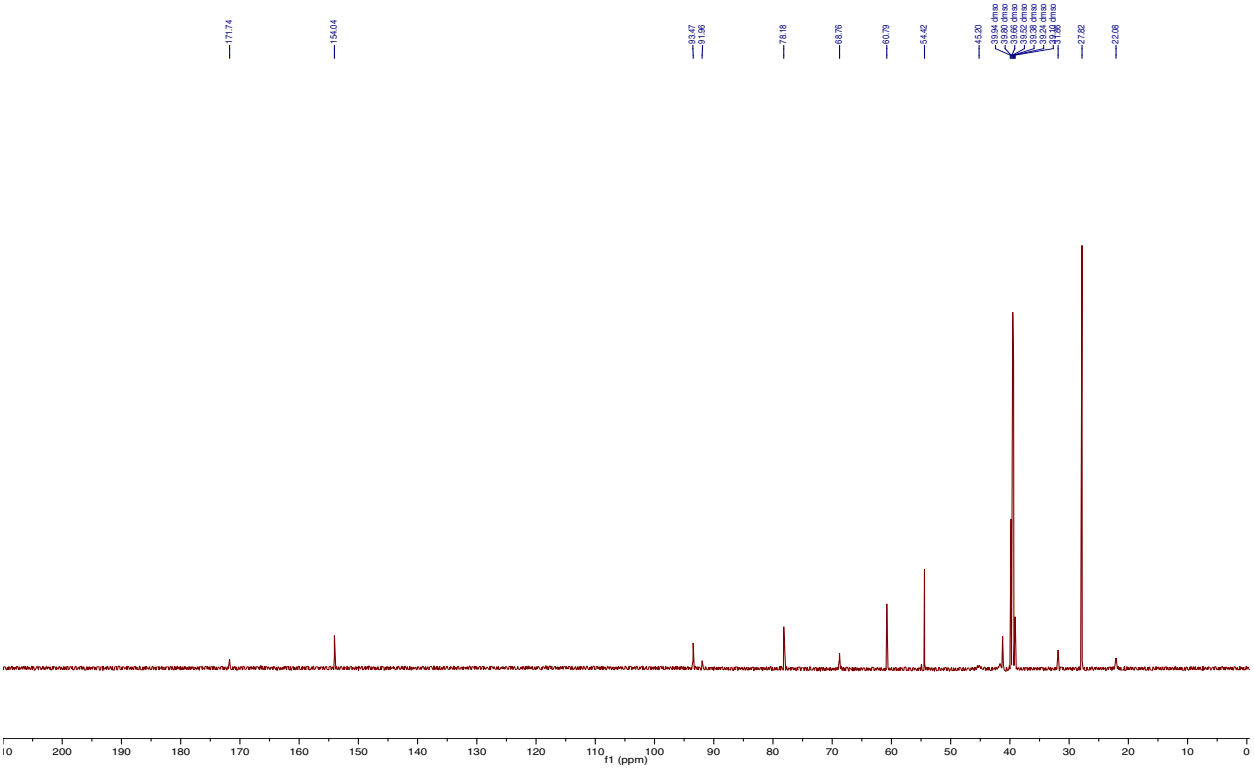


_N_-Boc-3-(methoxymethoxy)-4-(methoxy(methyl)carbamoyl)piperidine (2.309)

^{1}H - DMSO-d_6, 60 °C, 600 MHz

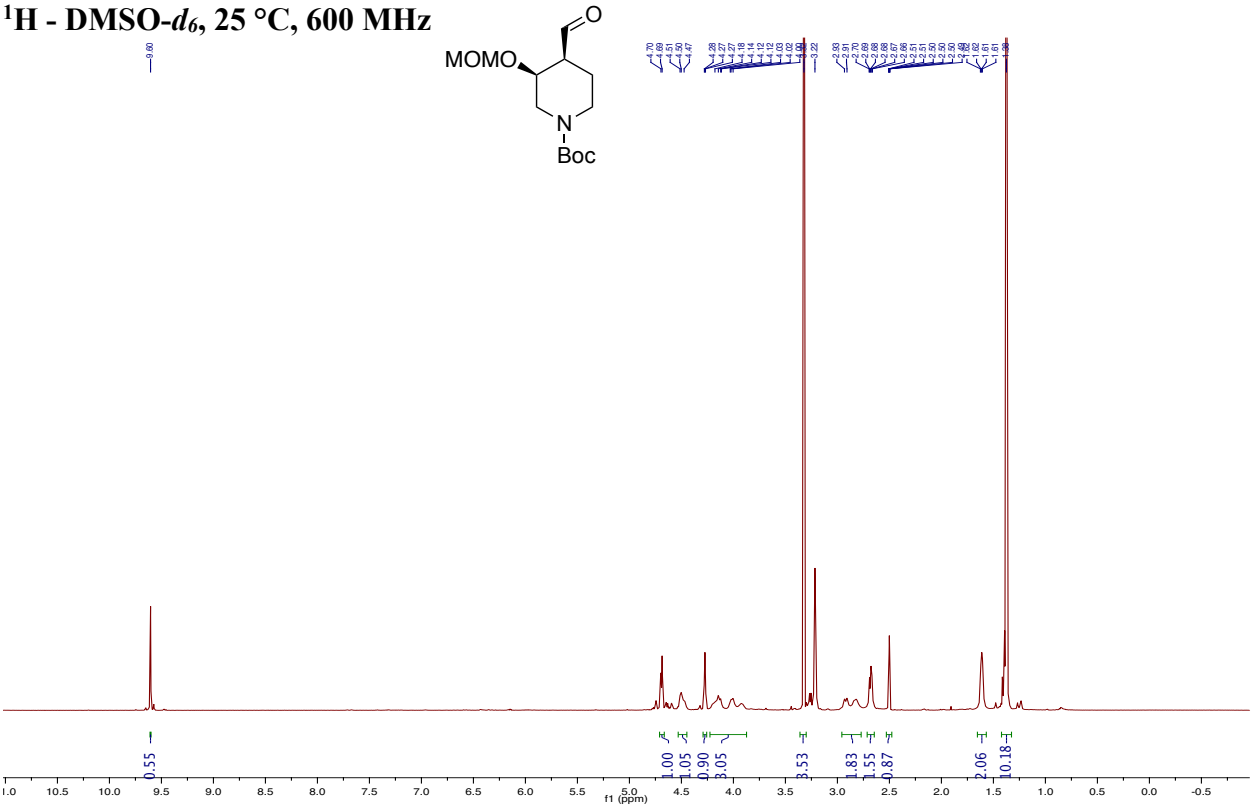


^{13}C - DMSO-d_6, 60 °C, 150 MHz

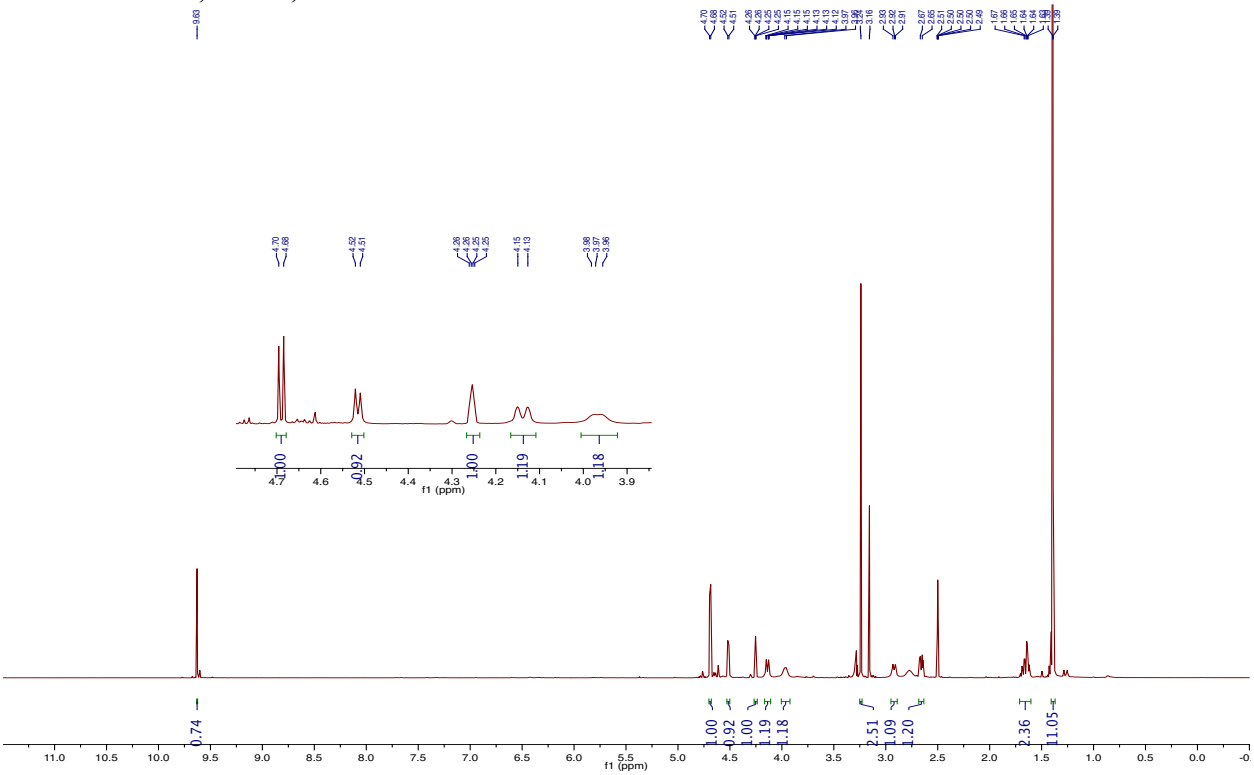


_N_-Boc-3-(methoxymethoxy)-4-formylpiperidine (2.310)

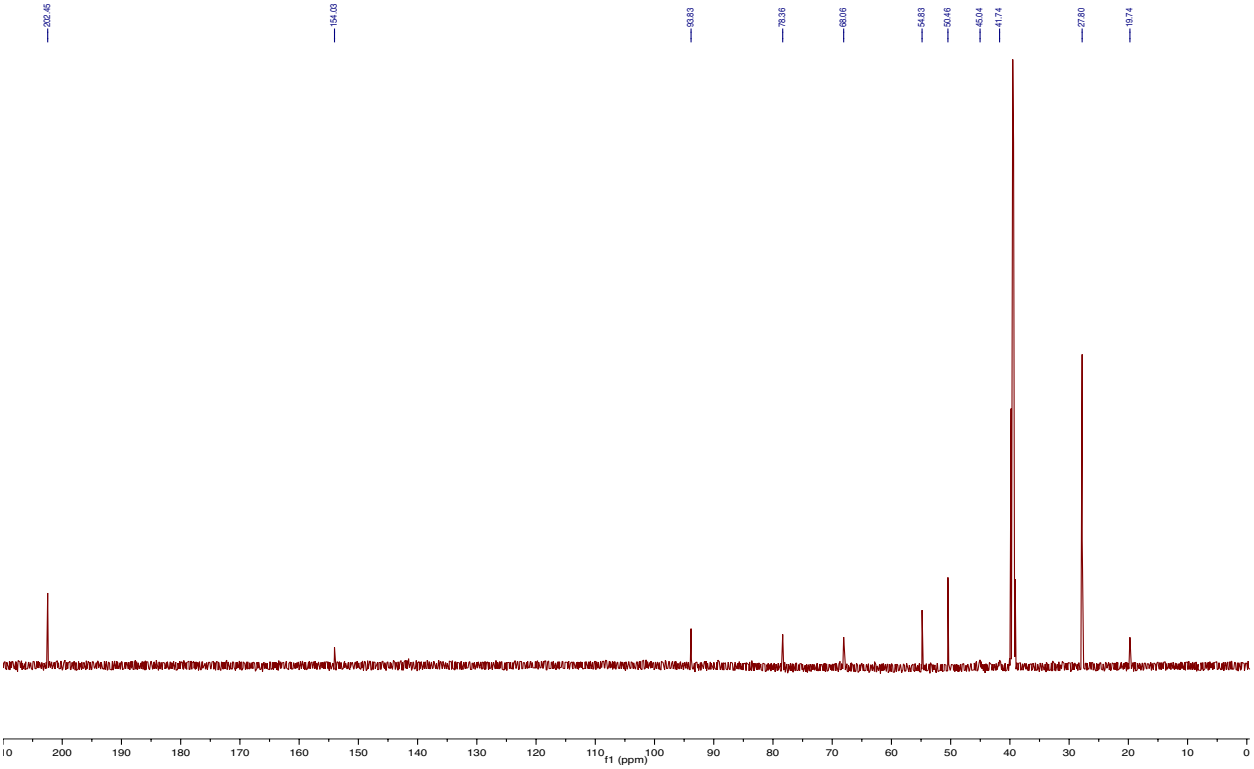
^{1}H - DMSO-_d_$_6$, 25 °C, 600 MHz



^{1}H - DMSO-_d_$_6$, 60 °C, 600 MHz

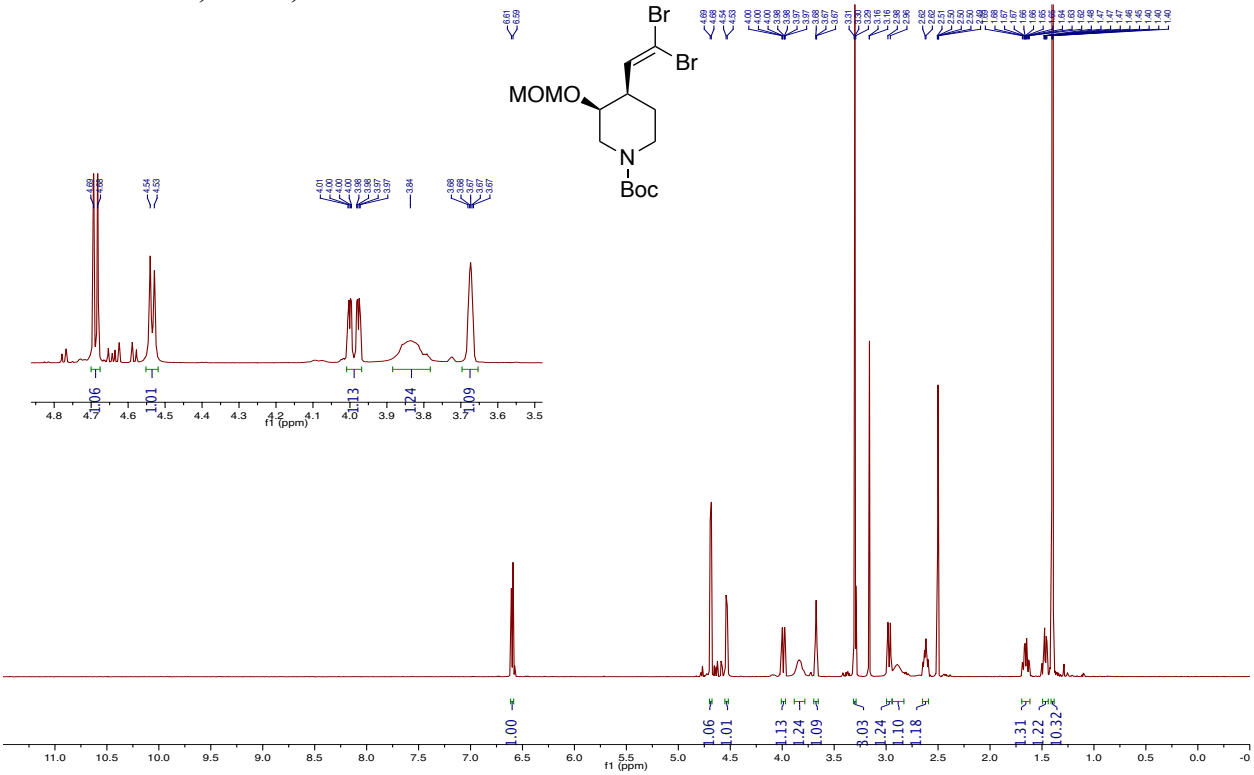


^{13}C - DMSO-*d*$_6$, 60 °C, 150 MHz

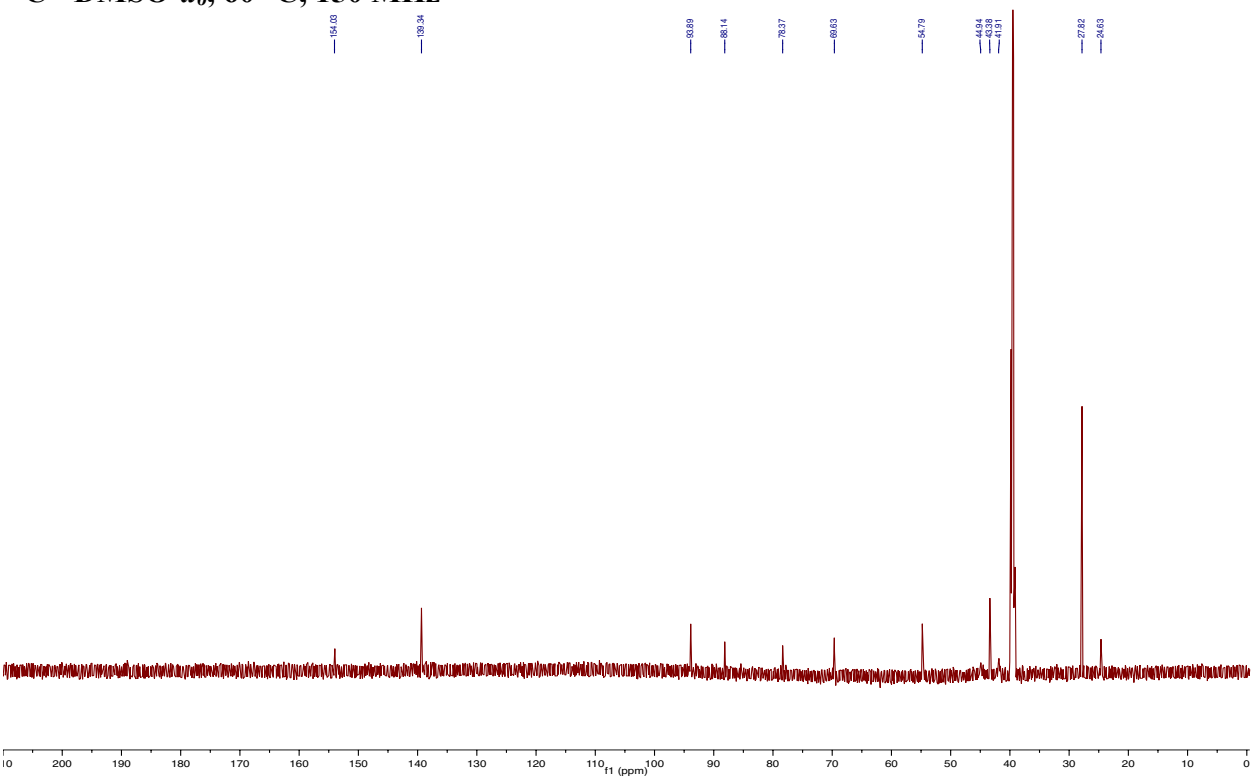


***N*-Boc-3-(methoxymethyoxy)-4-(2,2-dibromovinyl)piperidine (2.311)**

^{1}H - DMSO-*d*$_6$, 60 °C, 600 MHz

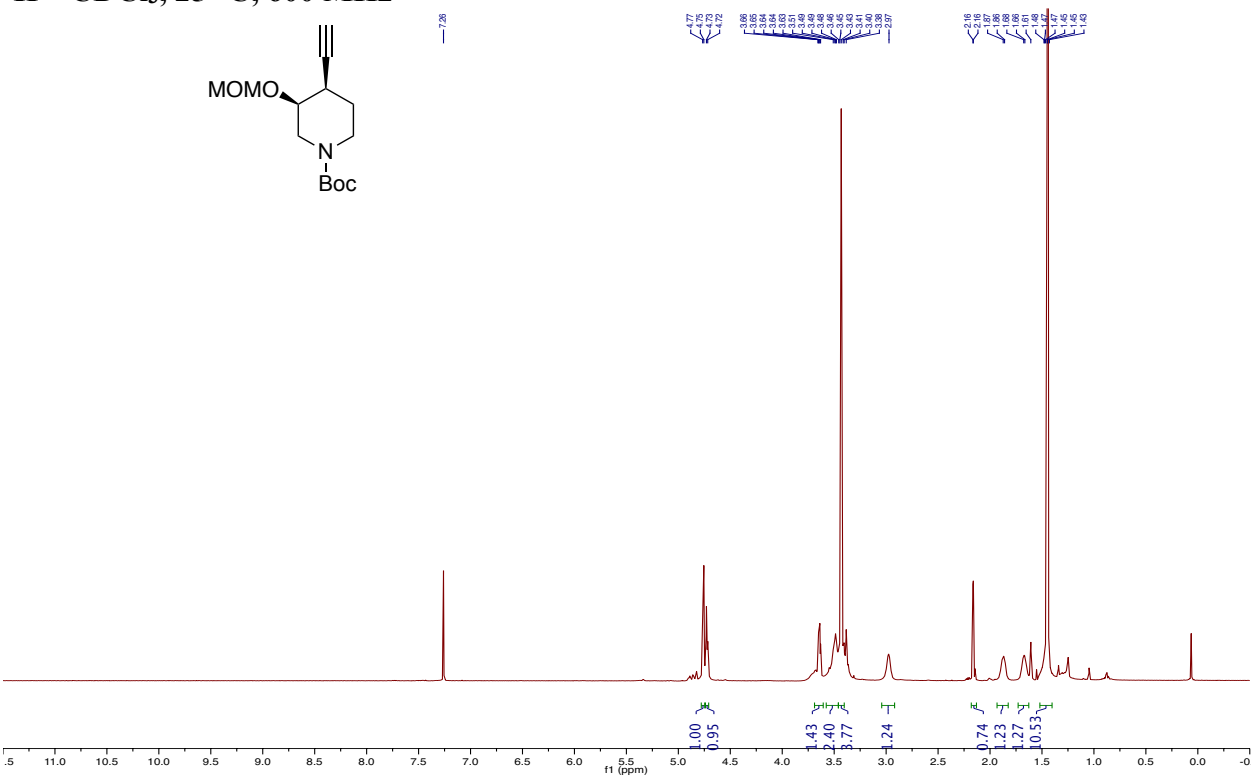


^{13}C - DMSO-d_6, 60 °C, 150 MHz

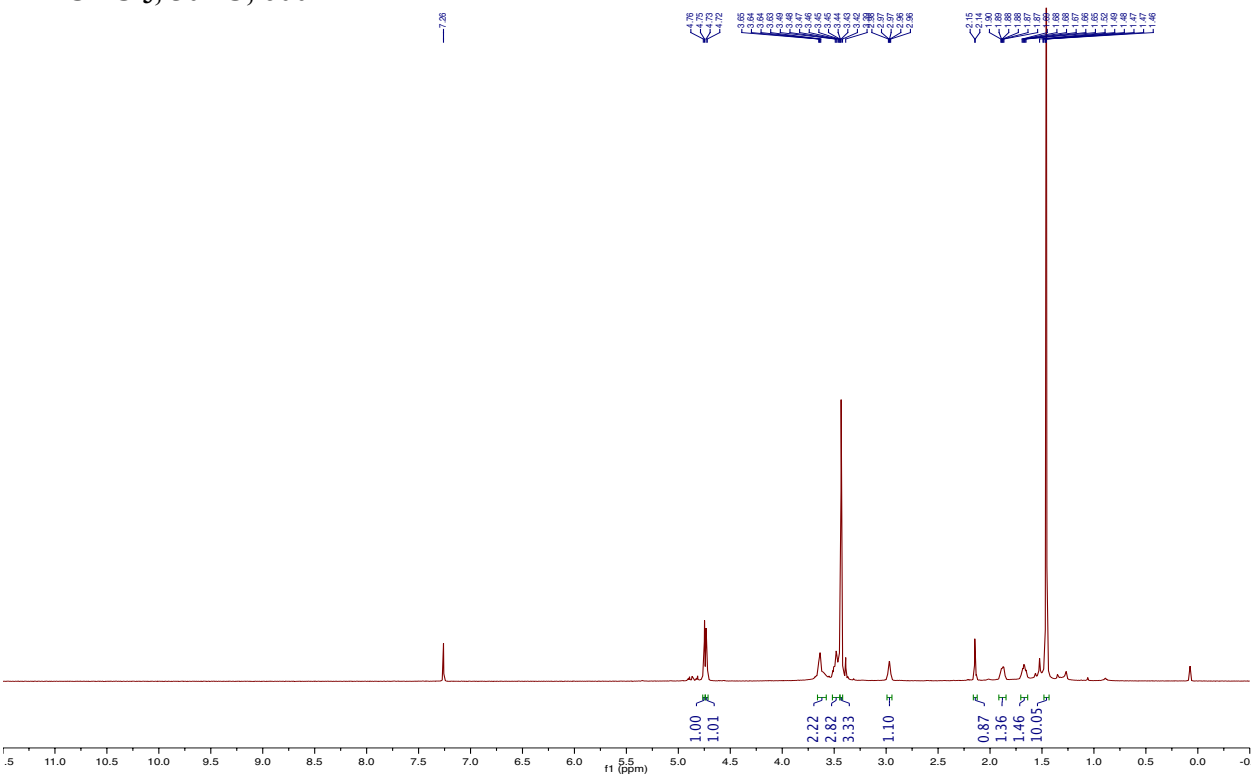


***N*-Boc-3-(methoxymethoxy)-4-ethynylpiperidine 2.272b**

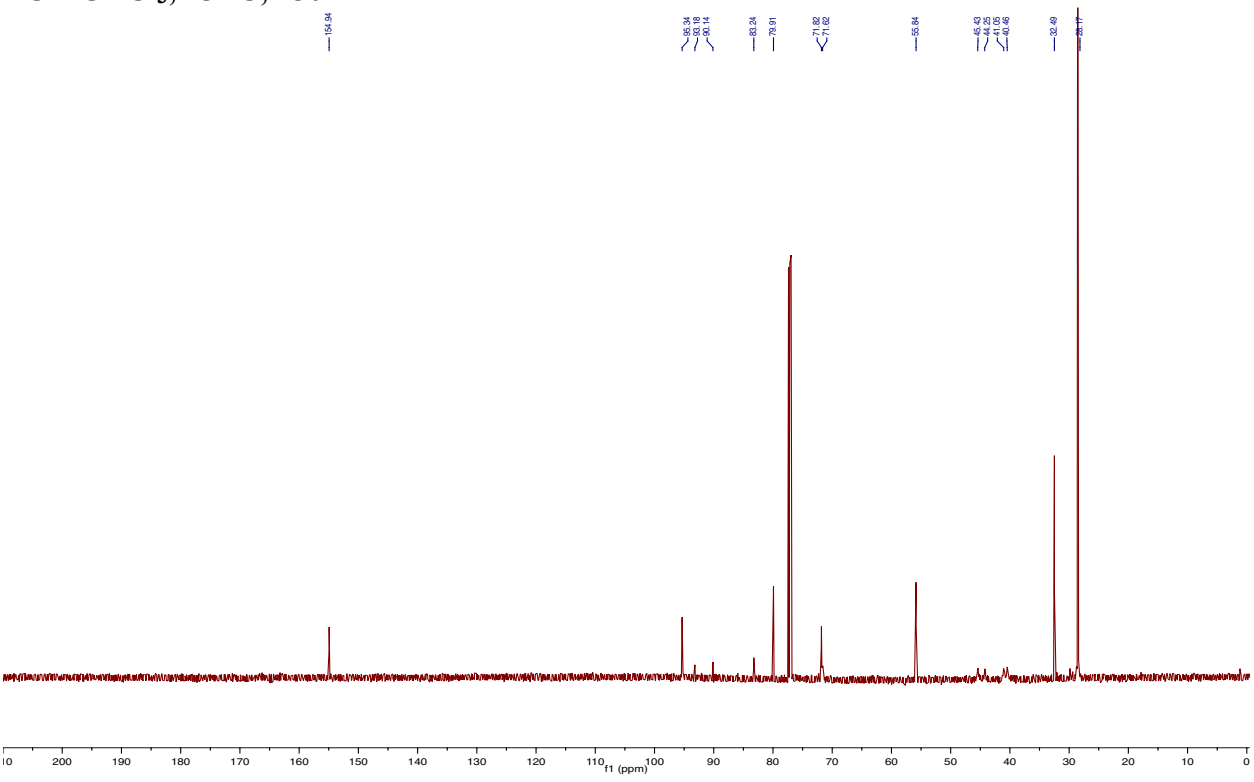
^{1}H – $CDCl_3$, 25 °C, 600 MHz



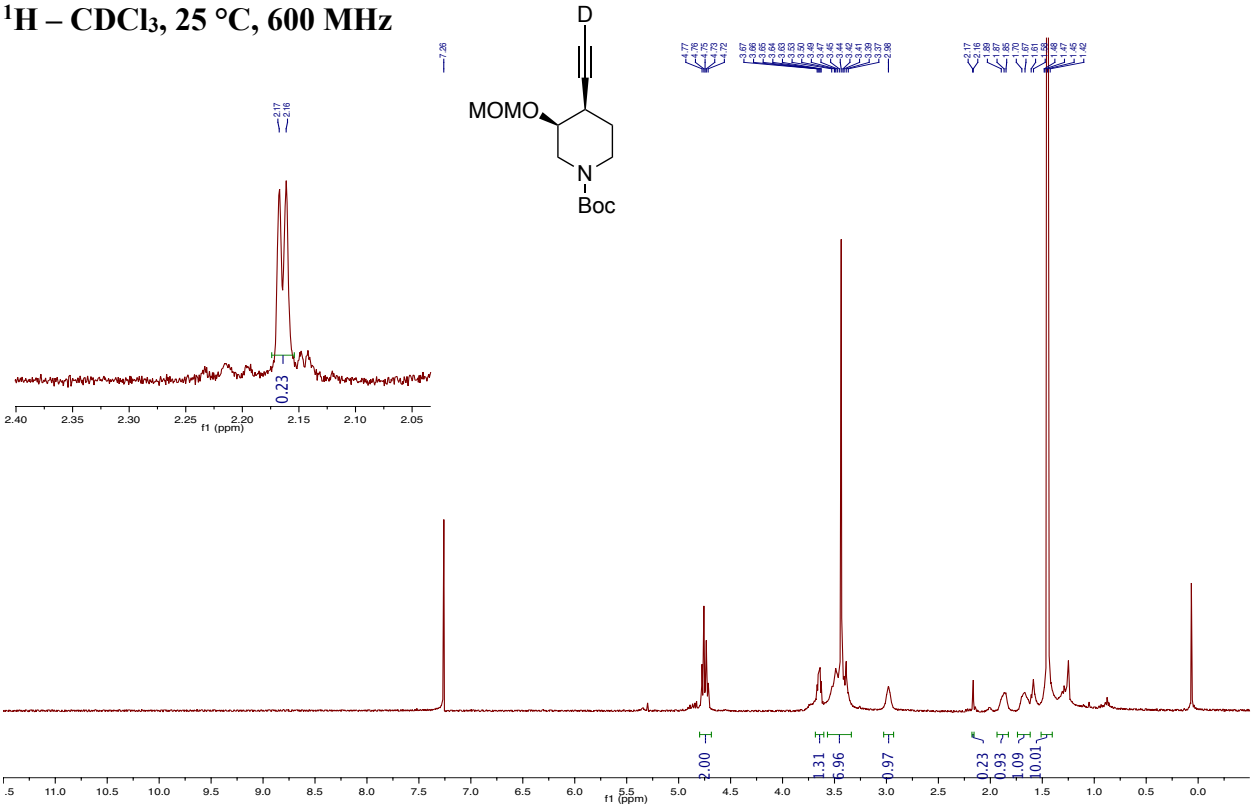
^{1}H - $CDCl_3$, 50 °C, 600 MHz



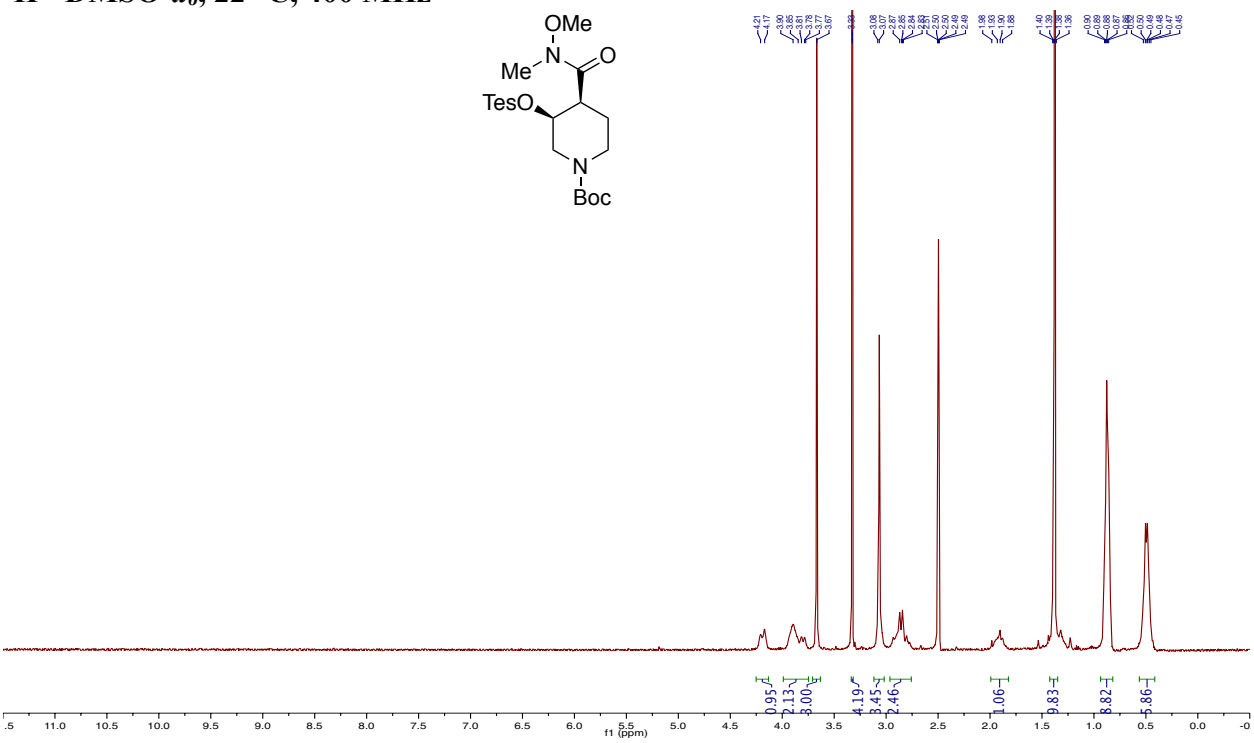
^{13}C – $CDCl_3$, 25 °C, 150 MHz



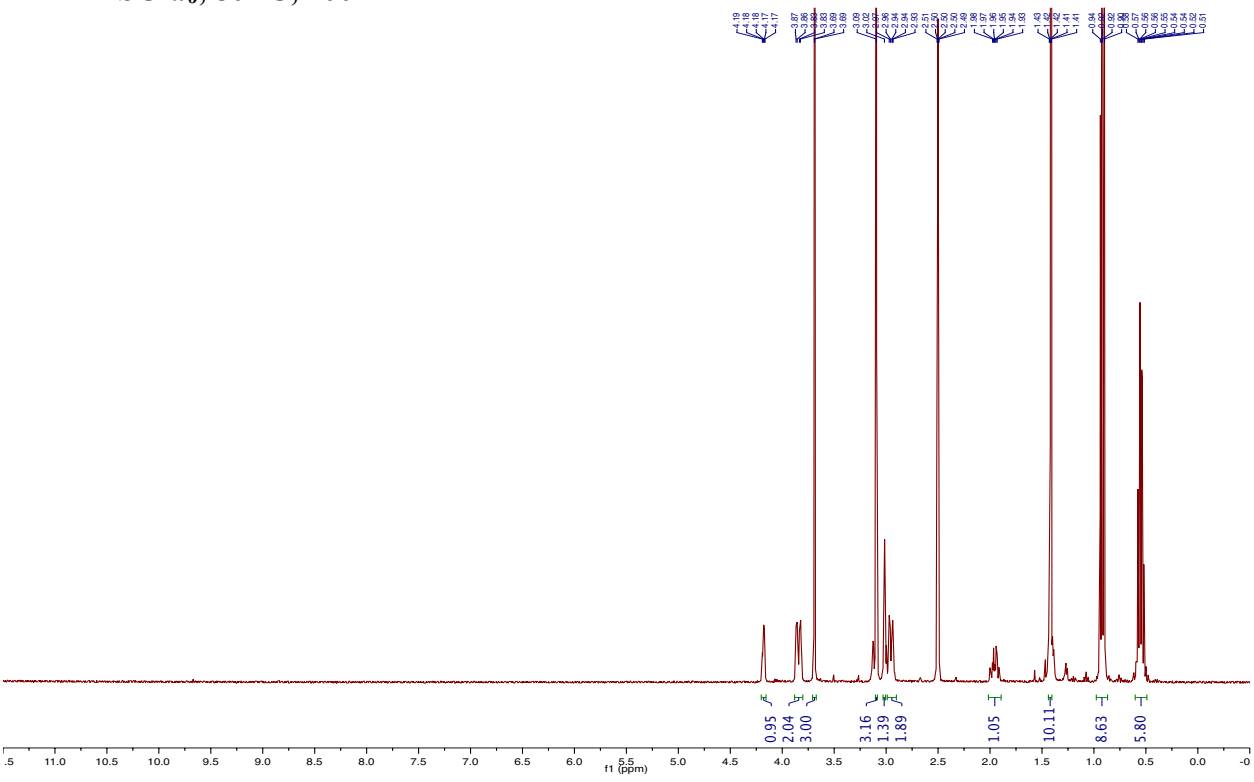
_N_-Boc-3-(methoxymethoxy)-4-ethynyl-_d_-piperidine 2.272c
^{1}H – $CDCl_3$, 25 °C, 600 MHz



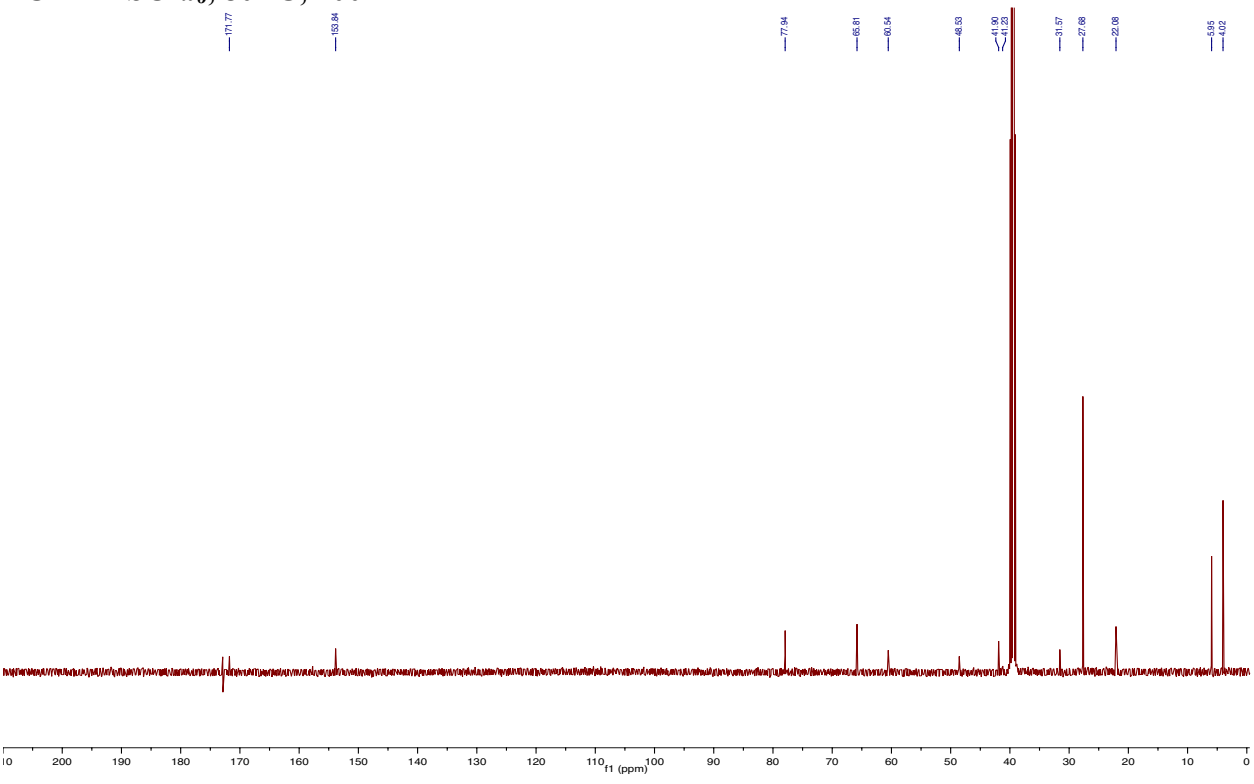
_N_-Boc-3-(triethylsilyl)oxy-4-(methoxy(methyl)carbamoyl)piperidine (S-2.6)
^{1}H - DMSO-d_6, 22 °C, 400 MHz



^{1}H - DMSO-d_6, 80 °C, 400 MHz

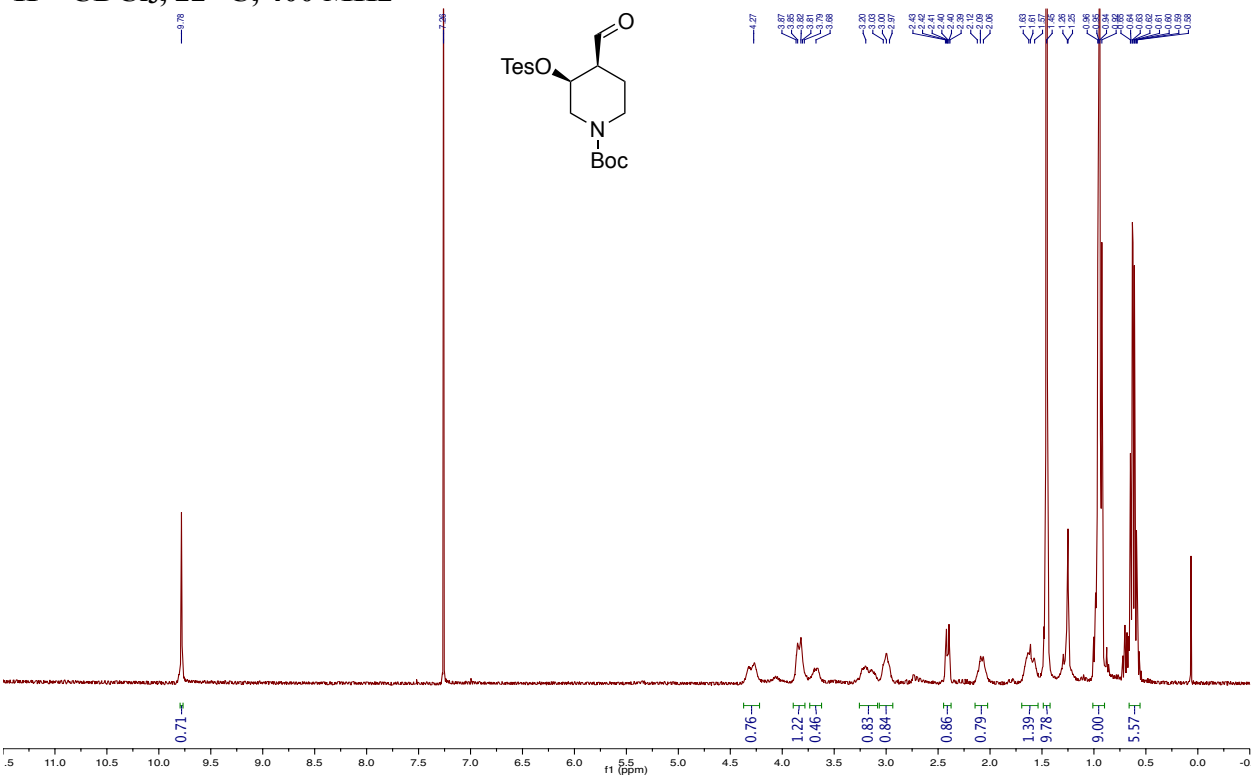


^{13}C - DMSO-d_6, 80 °C, 100 MHz

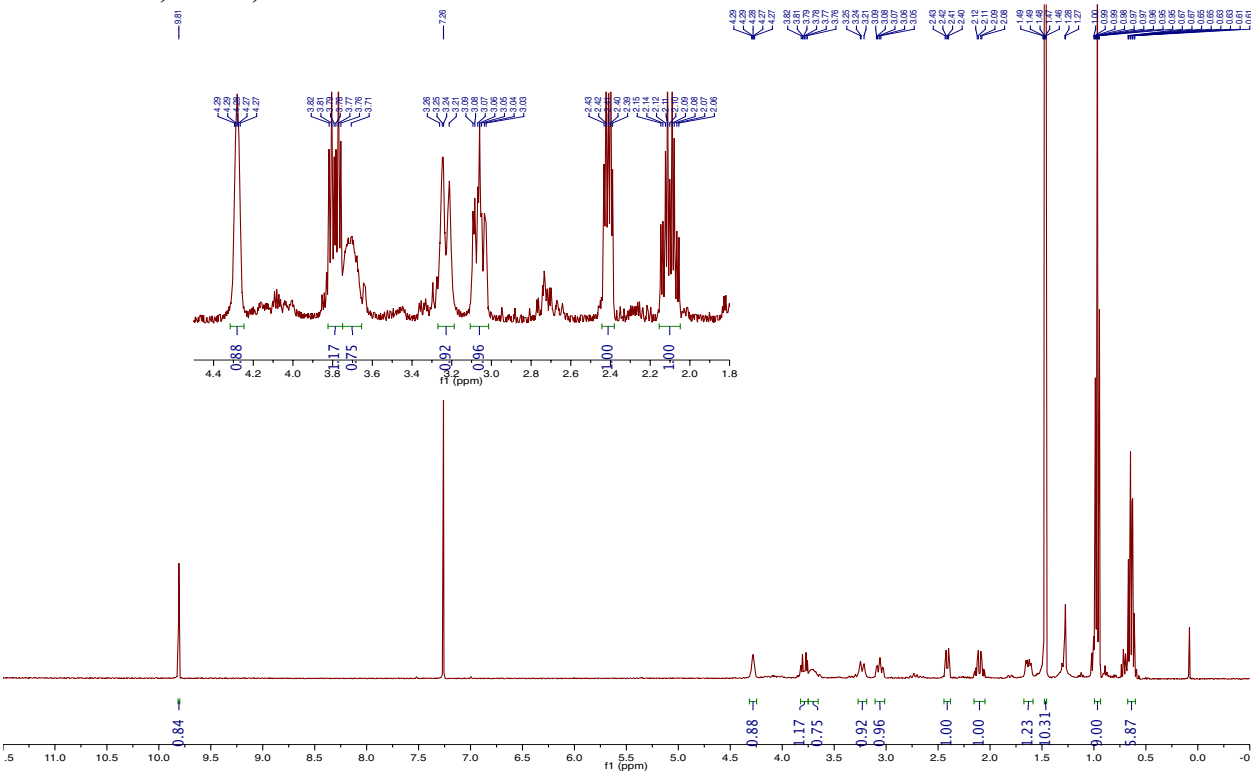


***N*-Boc-3-(triethylsilyl)oxy-4-formylpiperidine (S-2.7)**

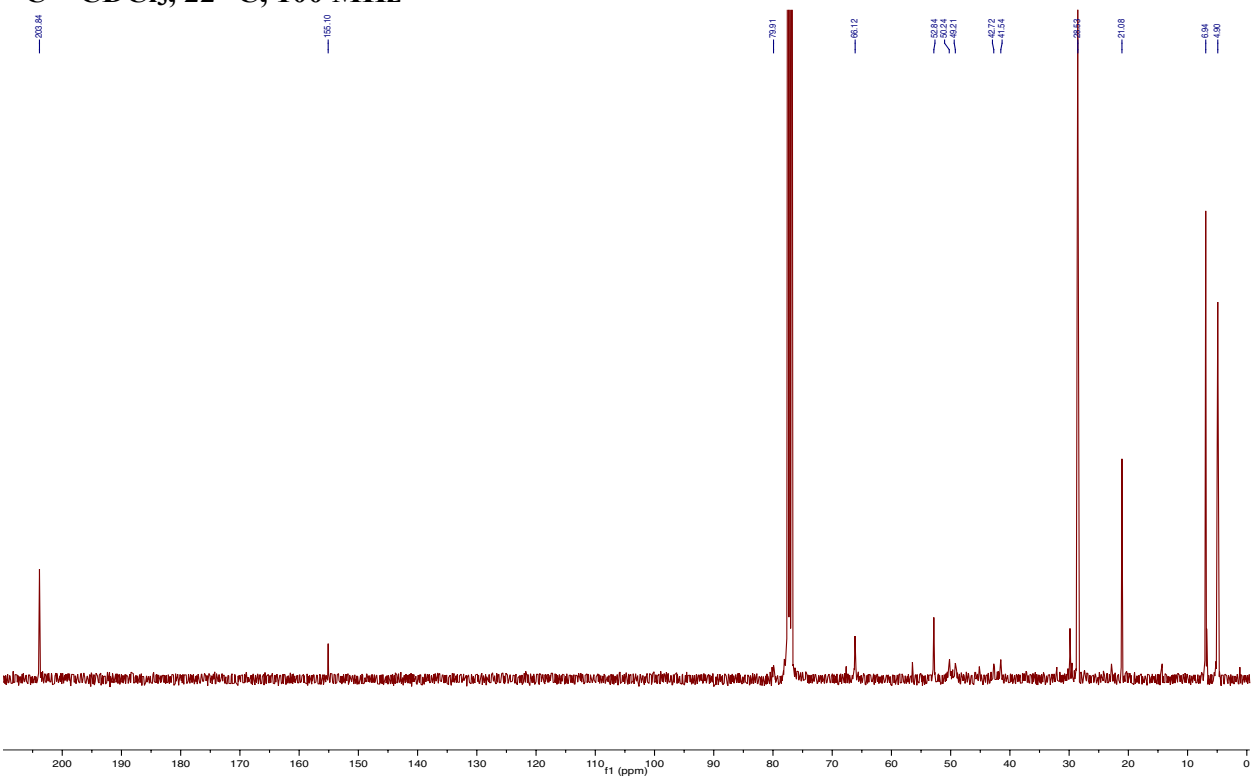
^{1}H – $CDCl_3$, 22 °C, 400 MHz



^{1}H – $CDCl_3$, 50 °C, 400 MHz

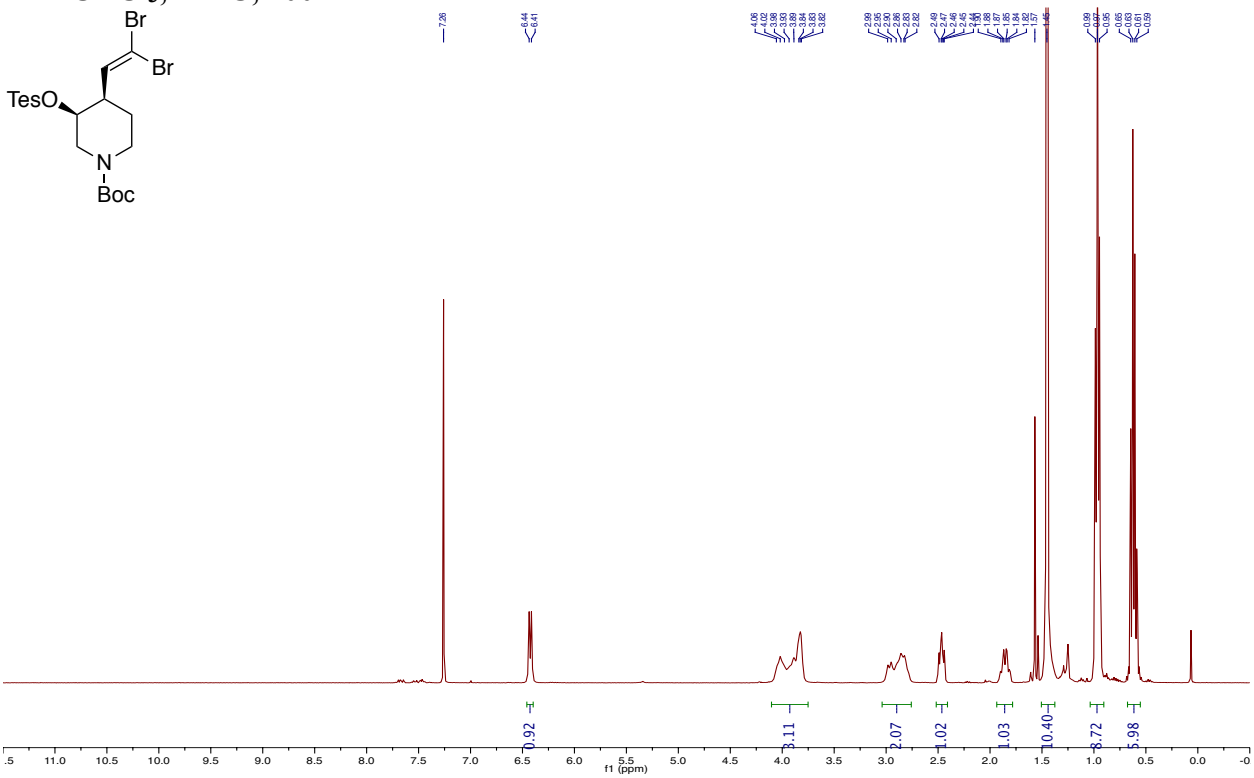


^{13}C – $CDCl_3$, 22 °C, 100 MHz

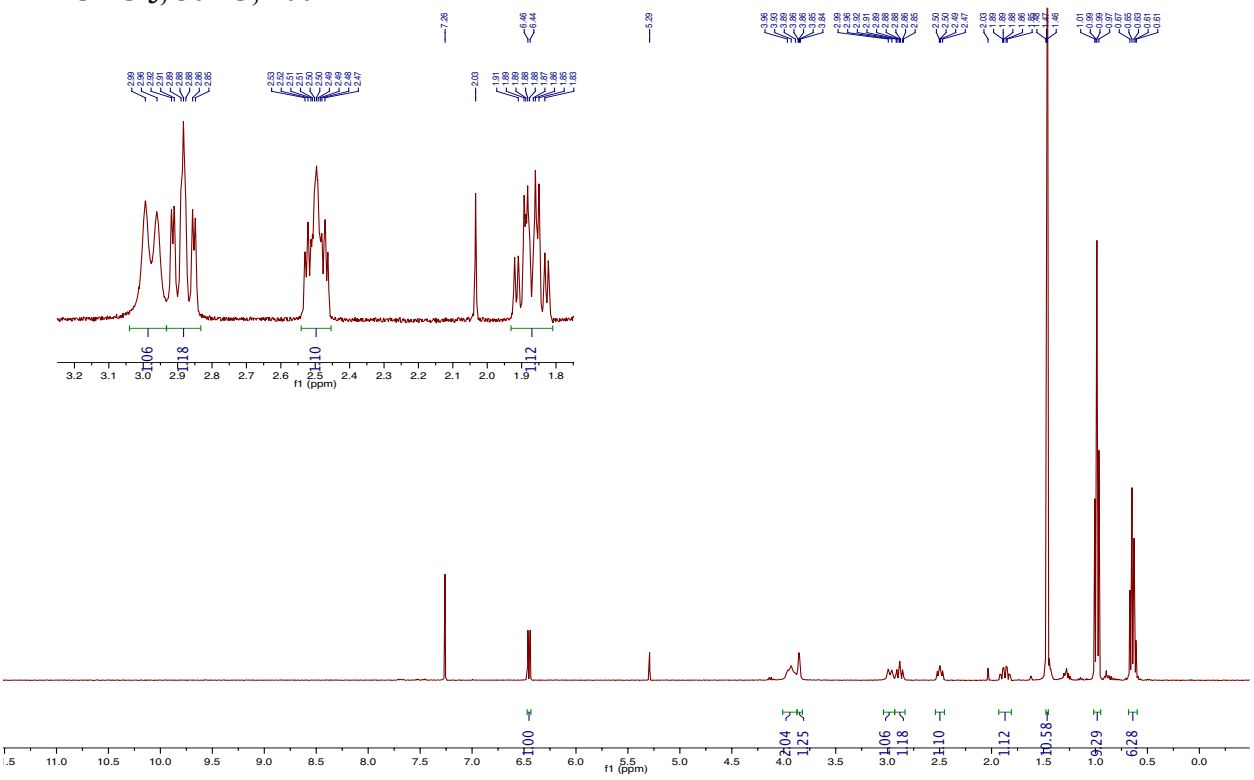


***N*-Boc-3-(triethylsilyl)oxy-4-(2,2-dibromovinyl)piperidine (S-2.8)**

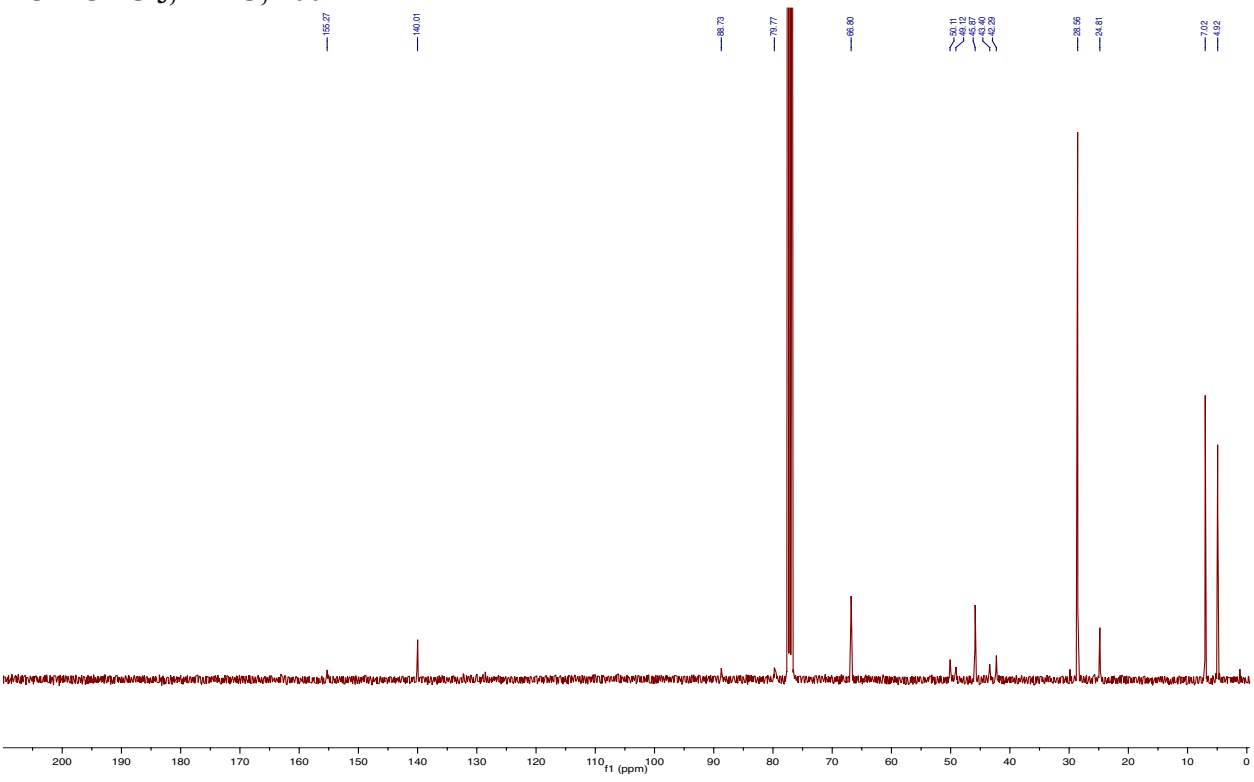
^{1}H – $CDCl_3$, 22 °C, 400 MHz



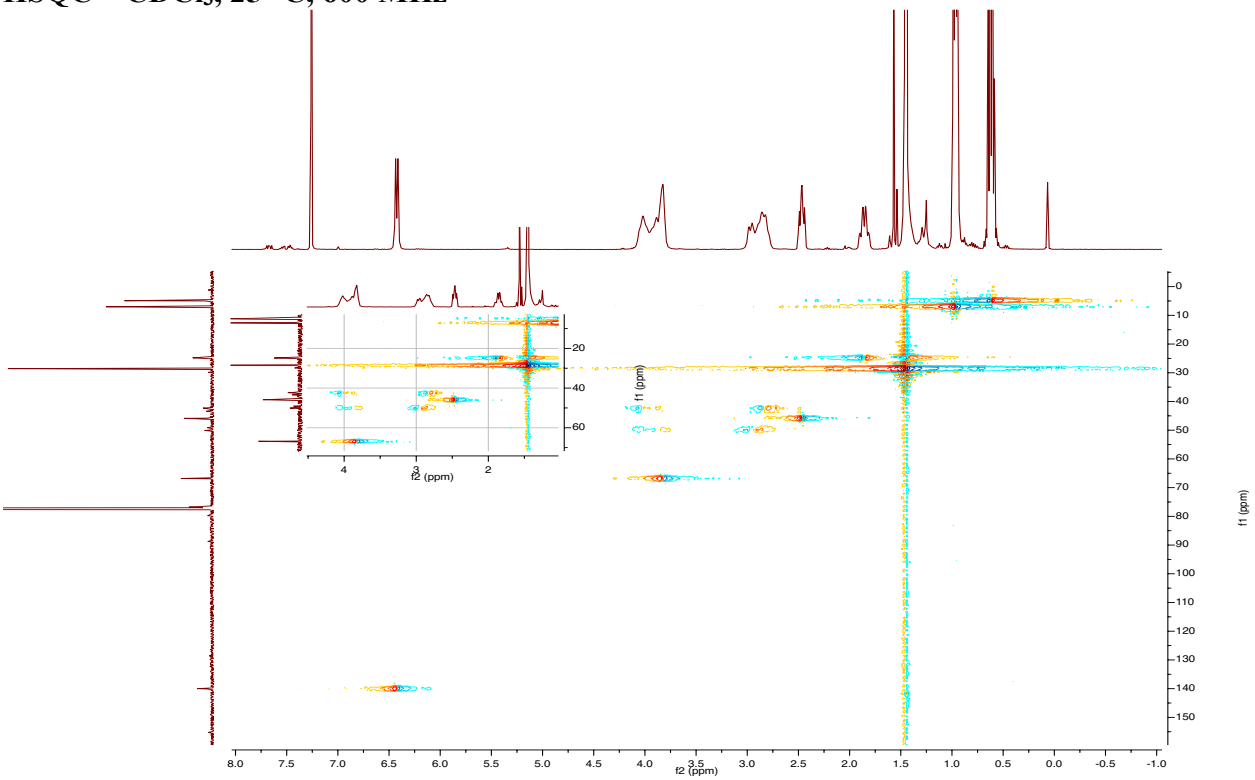
^{1}H – $CDCl_3$, 50 °C, 400 MHz



^{13}C – $CDCl_3$, 22 °C, 100 MHz

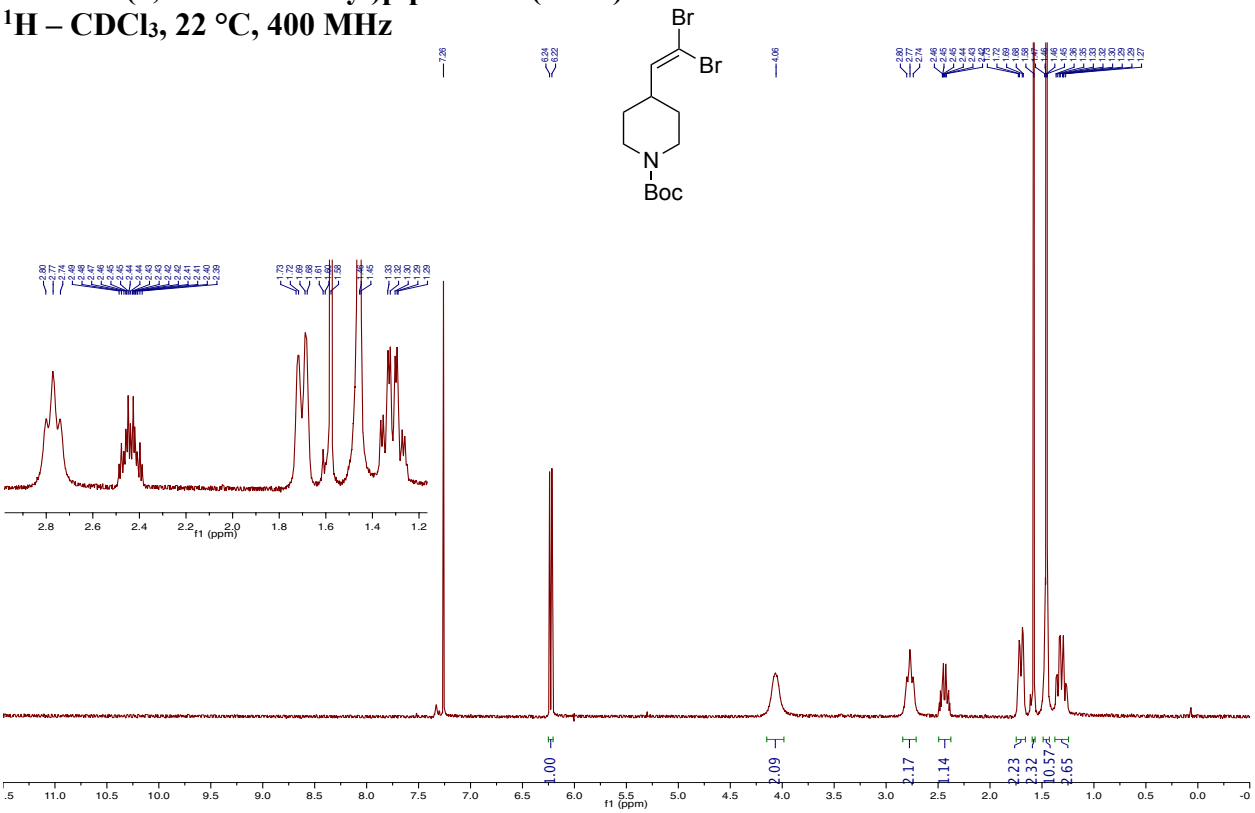


HSQC – $CDCl_3$, 25 °C, 600 MHz

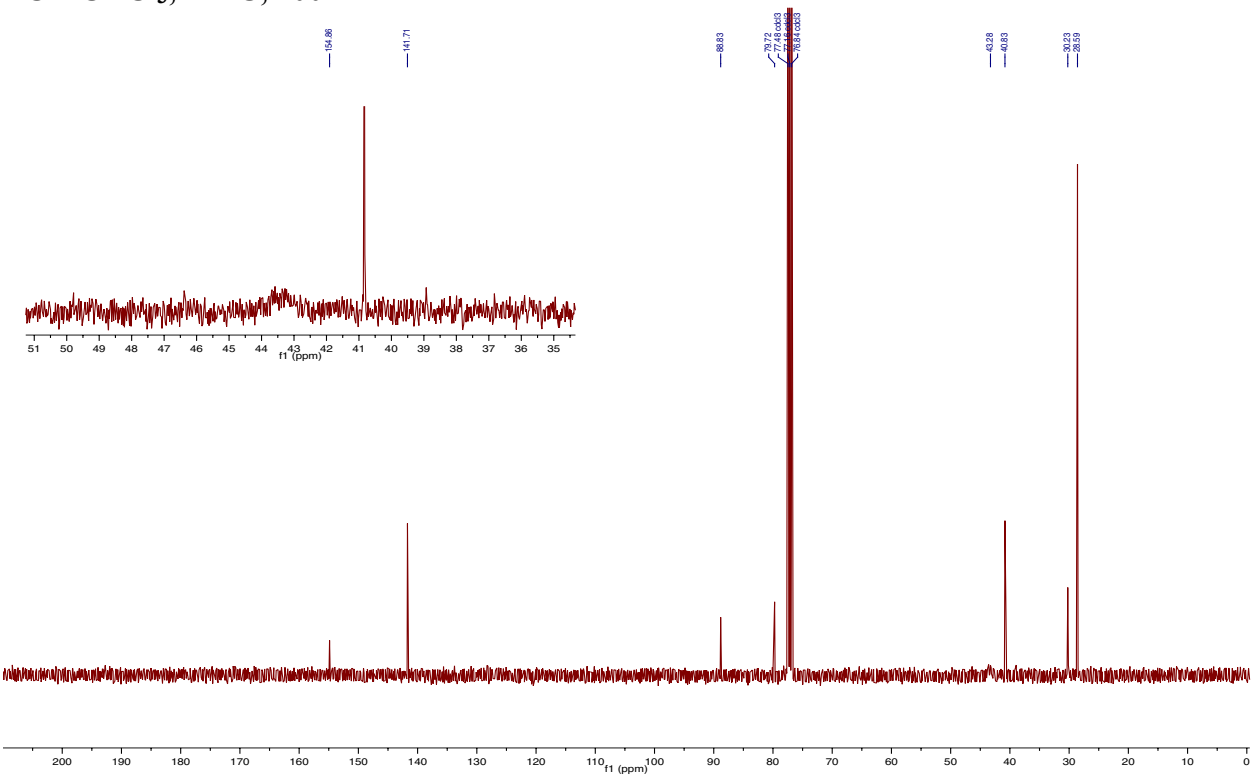


***N*-Boc-4-(2,2-dibromovinyl)piperidine (2.312)**

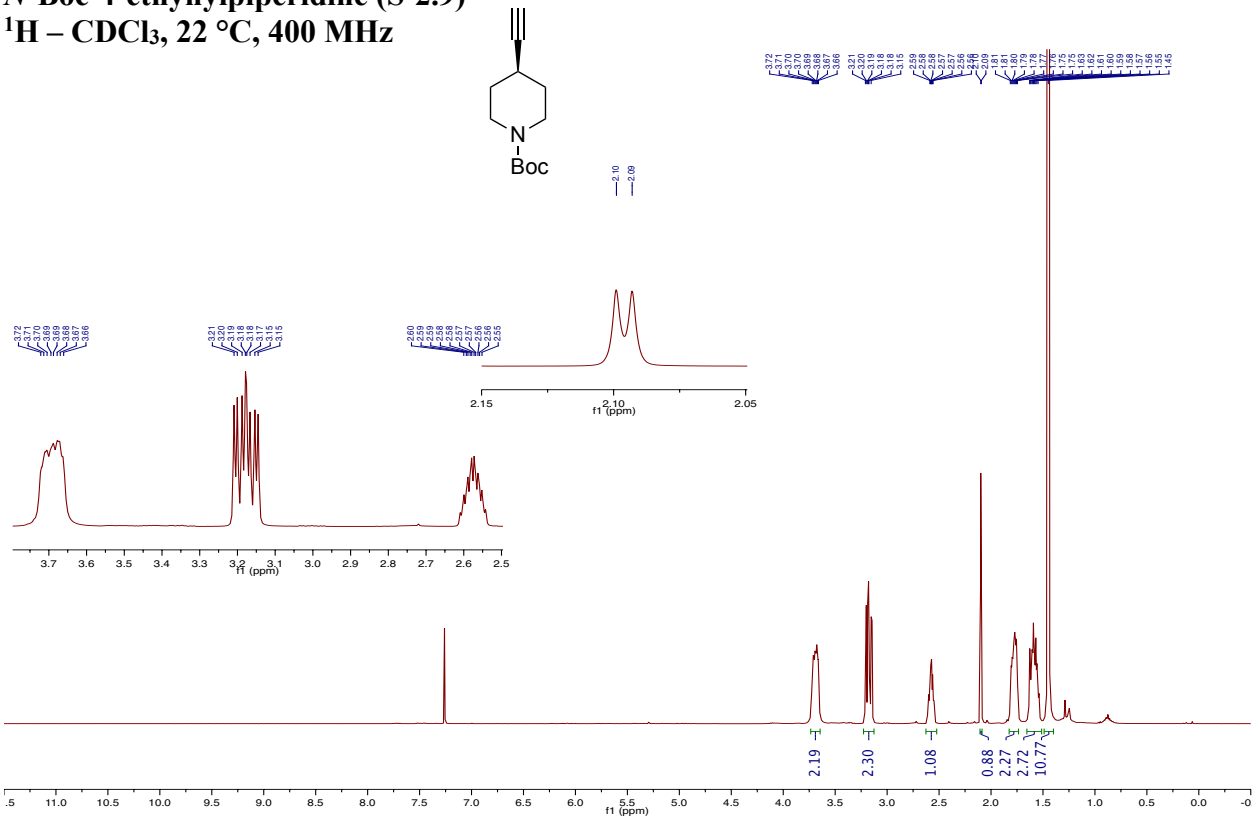
^1H – $CDCl_3$, 22 °C, 400 MHz



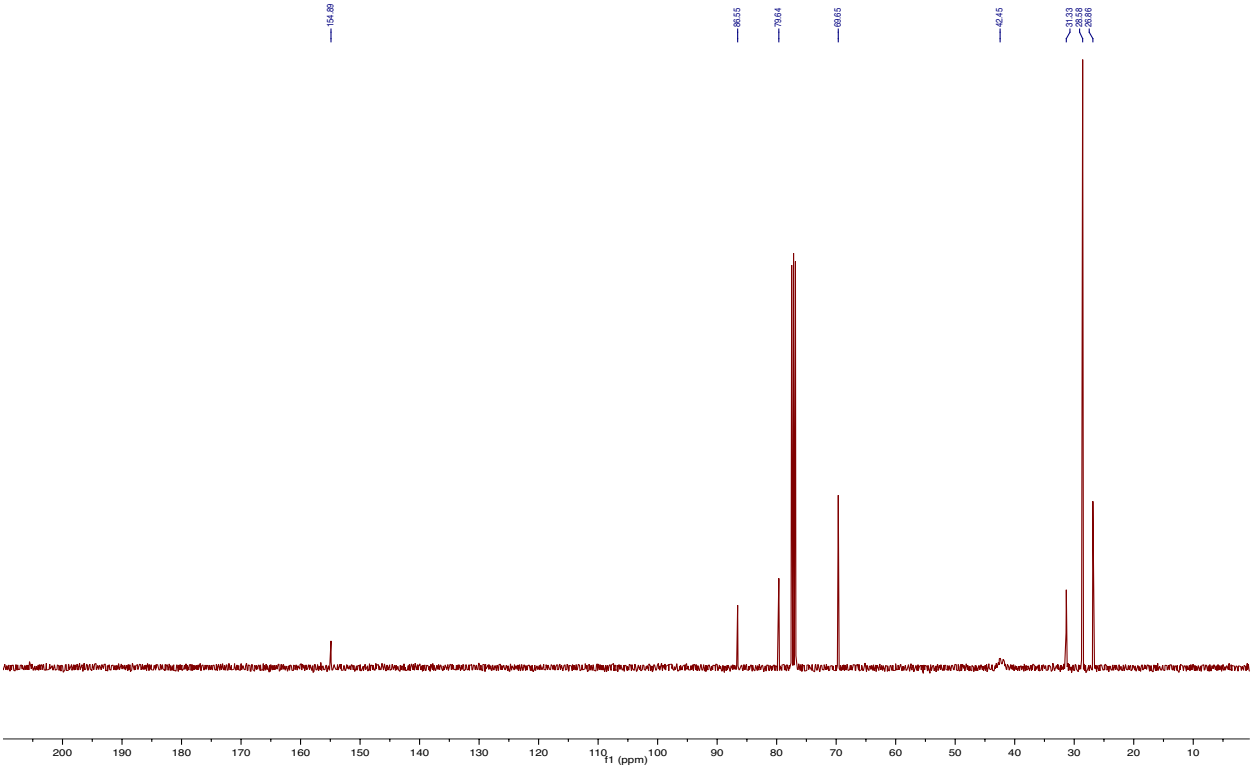
^{13}C – $CDCl_3$, 22 °C, 100 MHz



***N*-Boc-4-ethynylpiperidine (S-2.9)**
^{1}H – $CDCl_3$, 22 °C, 400 MHz

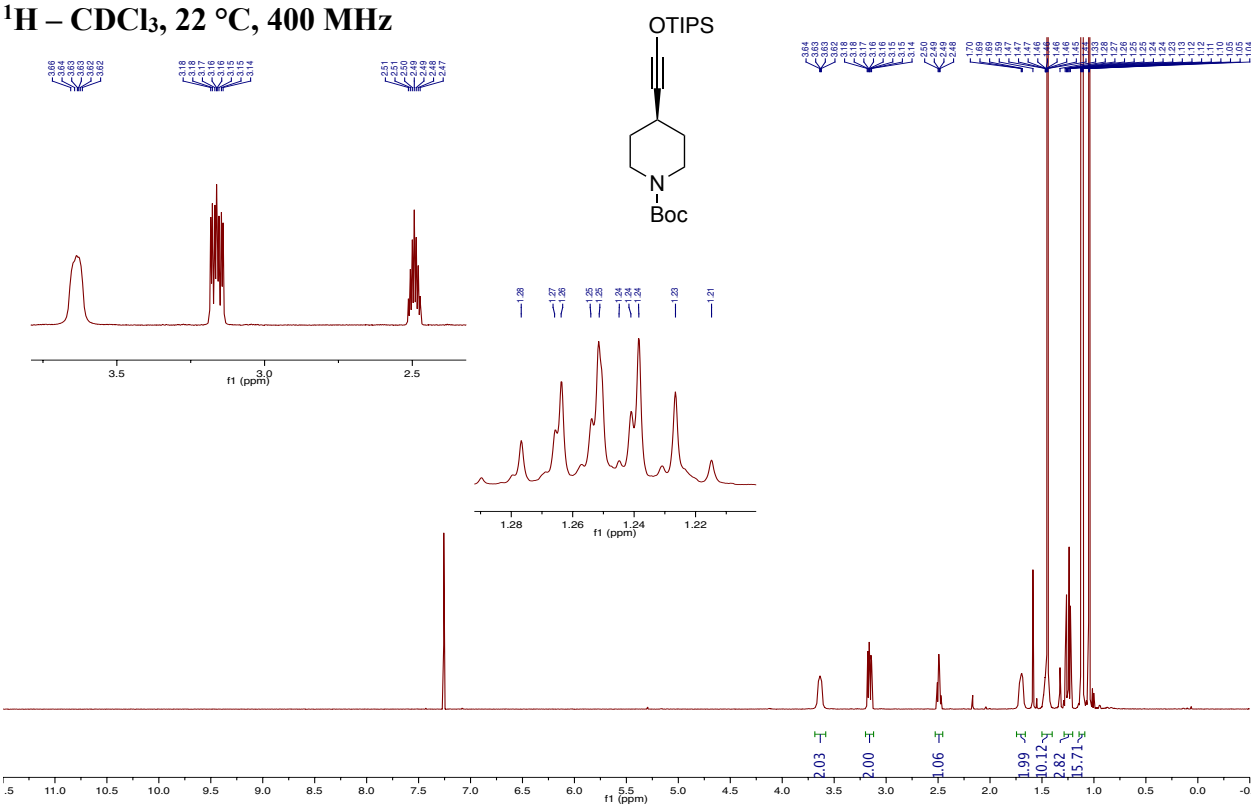


^{13}C – $CDCl_3$, 22 °C, 100 MHz

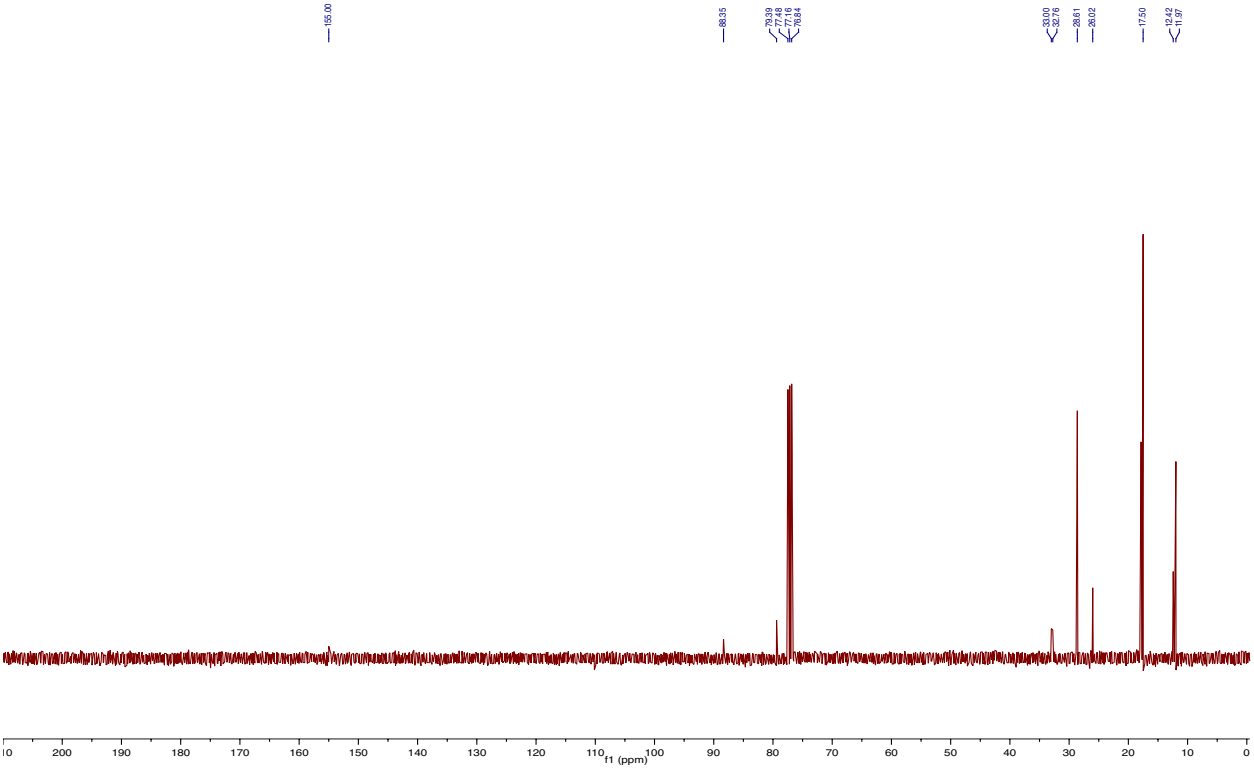


***N*-Boc-4-((triisopropylsilyl)oxy)ethynylpiperidine (2.313)**

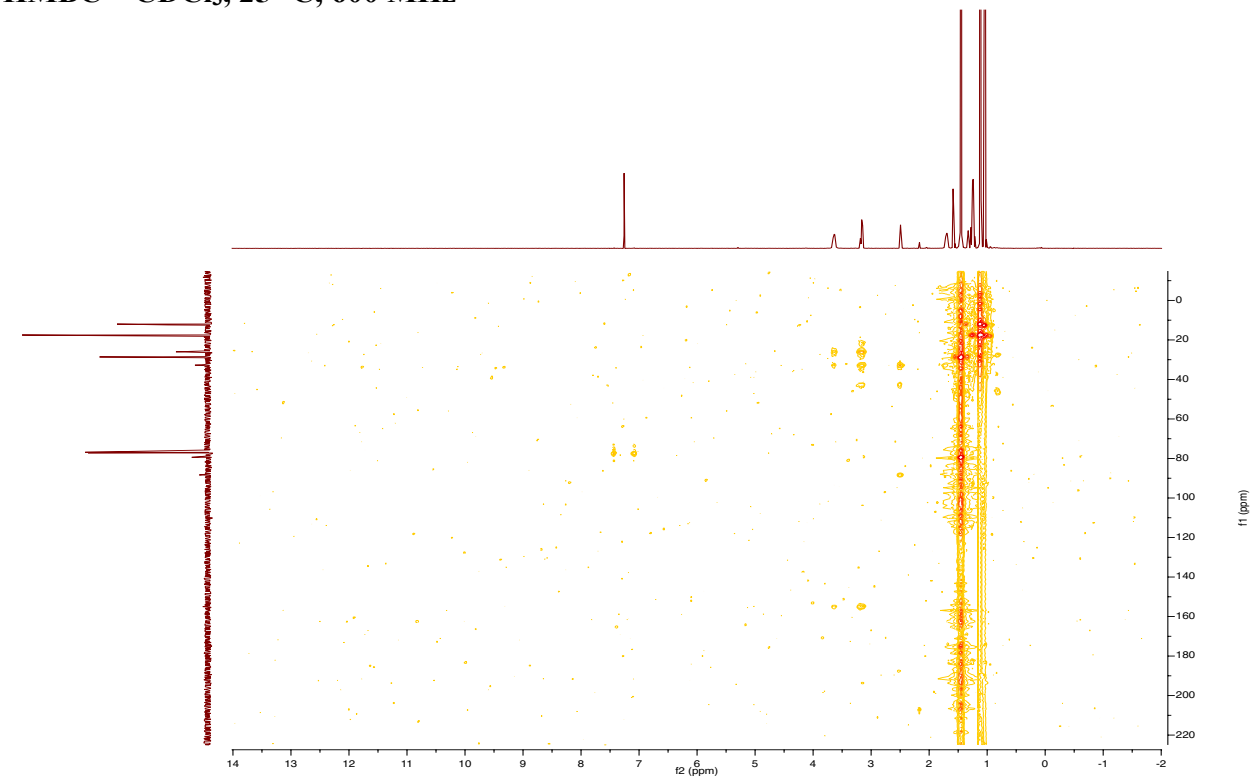
^{1}H – $CDCl_3$, 22 °C, 400 MHz



^{13}C – $CDCl_3$, 22 °C, 100 MHz

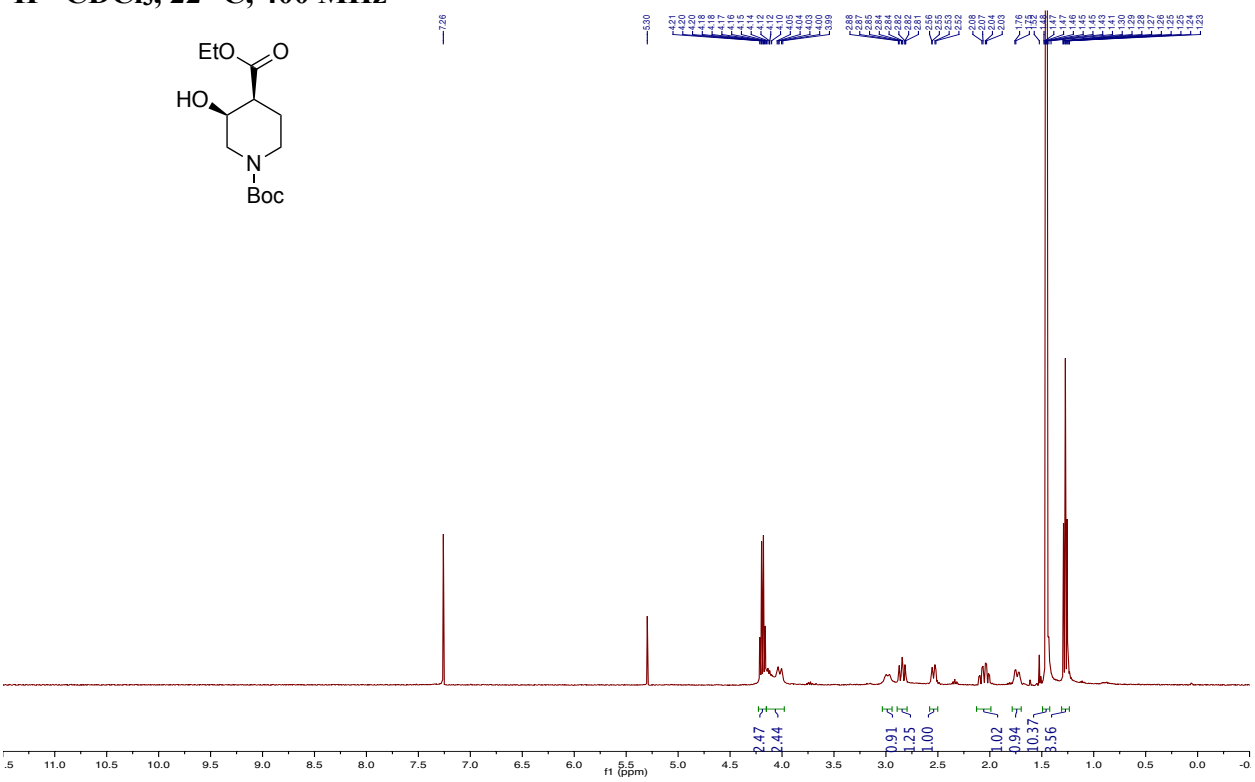


HMBC – $CDCl_3$, 25 °C, 600 MHz

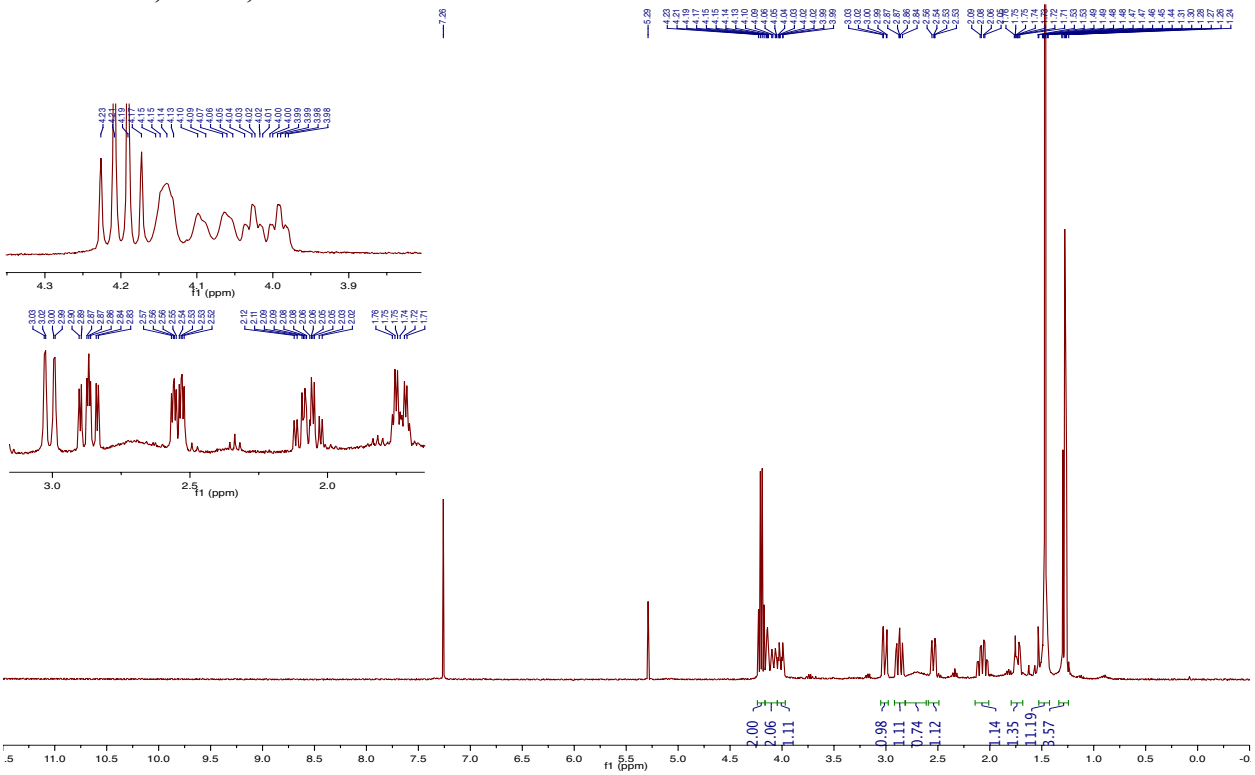


_N_-Boc-3-hydroxy-4-ethyl piperidinecarboxylate ((-)-S-2.10)

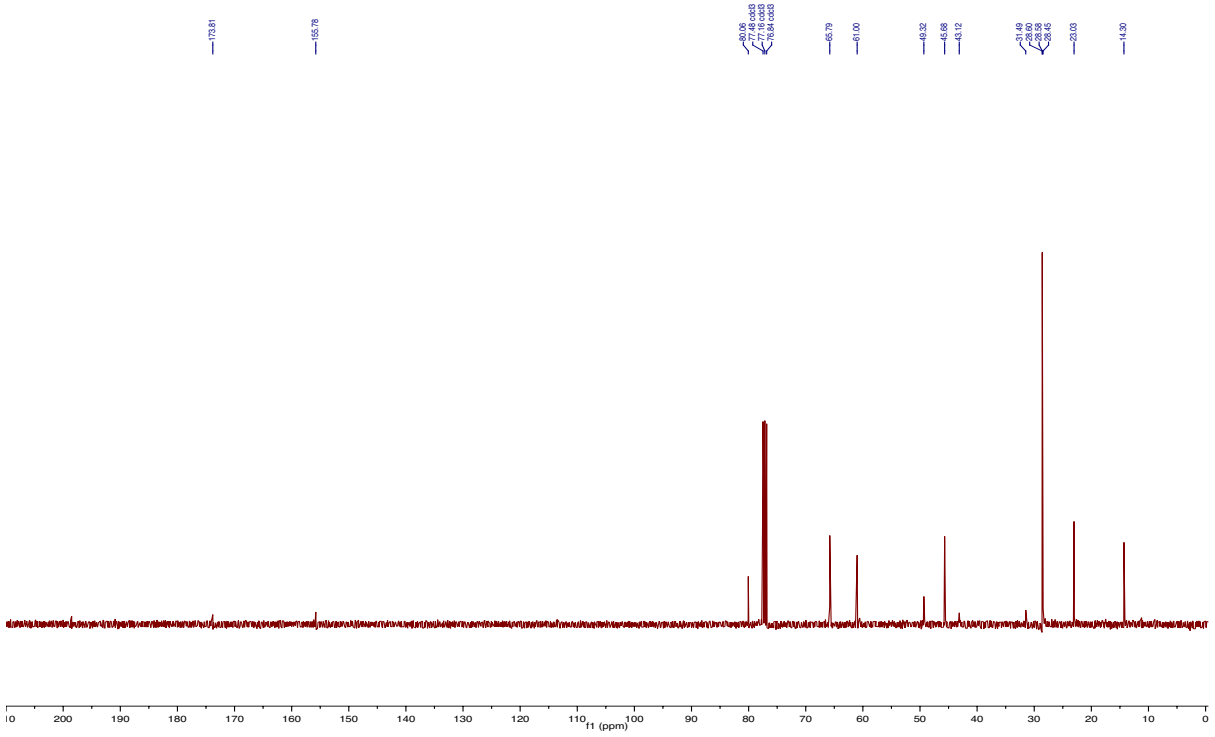
^{1}H - $CDCl_3$, 22 °C, 400 MHz



^{1}H - $CDCl_3$, 50 °C, 400 MHz

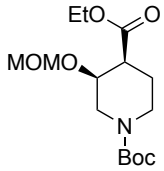


^{13}C - $CDCl_3$, 50 °C, 100 MHz

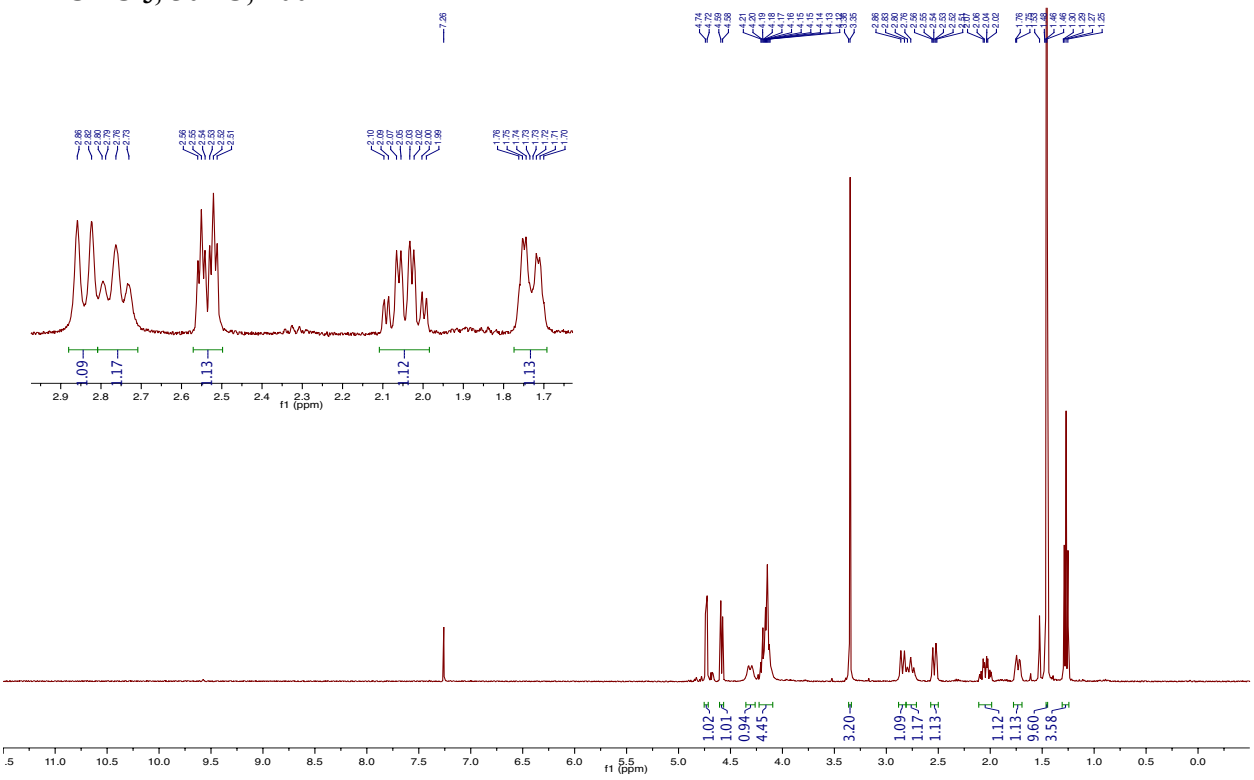


***N*-Boc-3-(methoxymethoxy)-4-ethyl piperidinecarboxylate ((-)-2.314)**

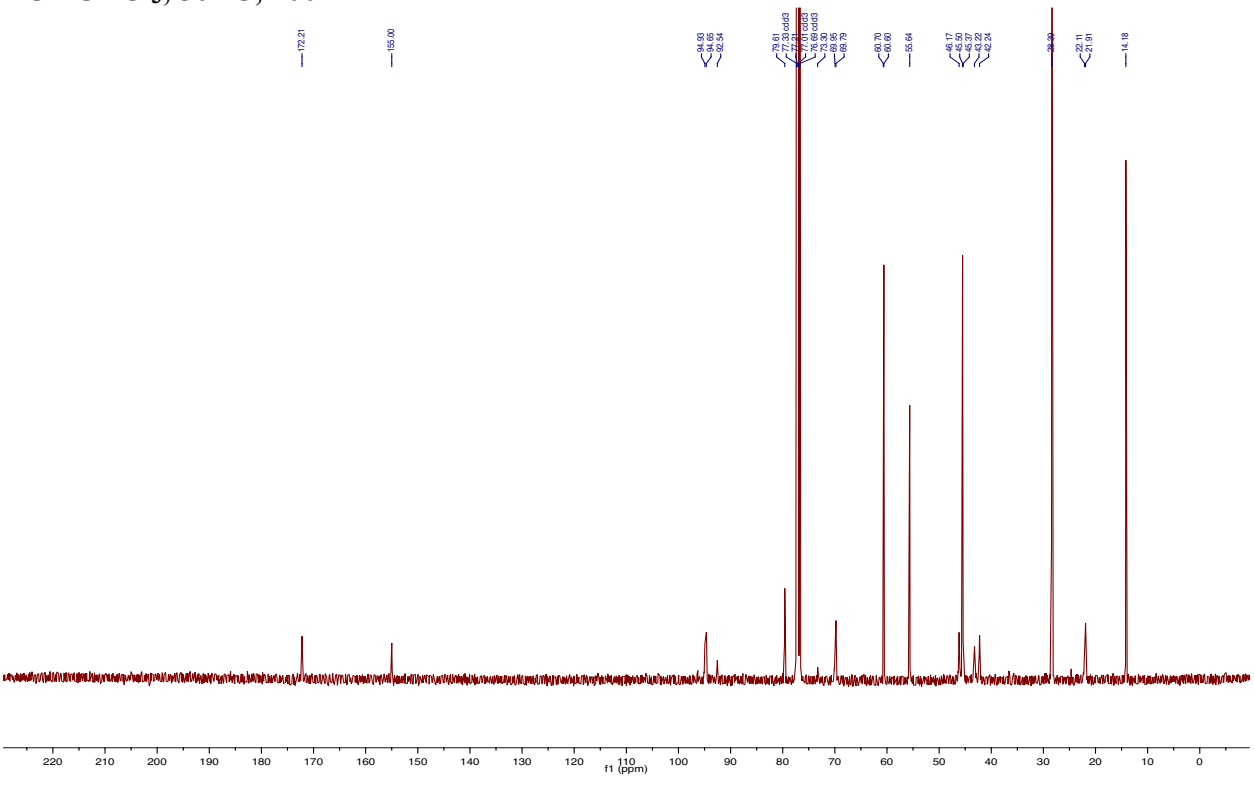
^{1}H - $CDCl_3$, 22 °C, 400 MHz



^{1}H - $CDCl_3$, 50 °C, 400 MHz

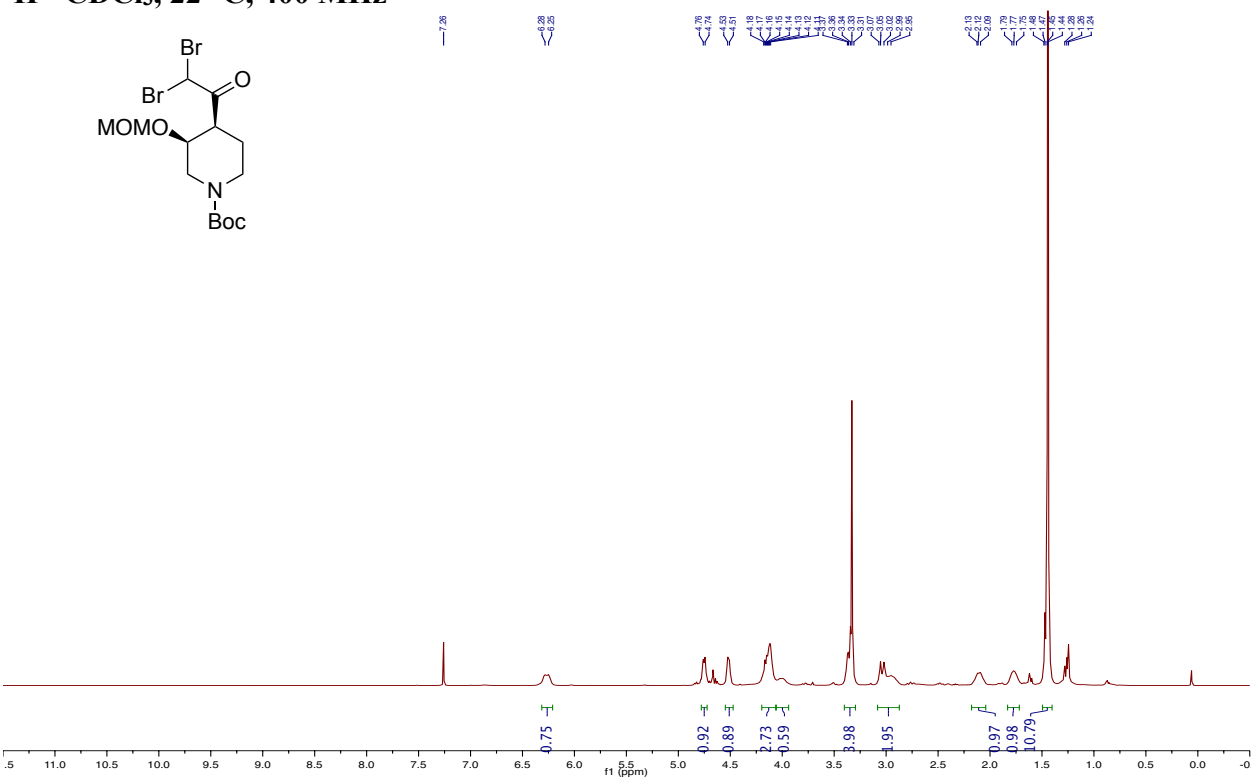


^{13}C - $CDCl_3$, 50 °C, 100 MHz

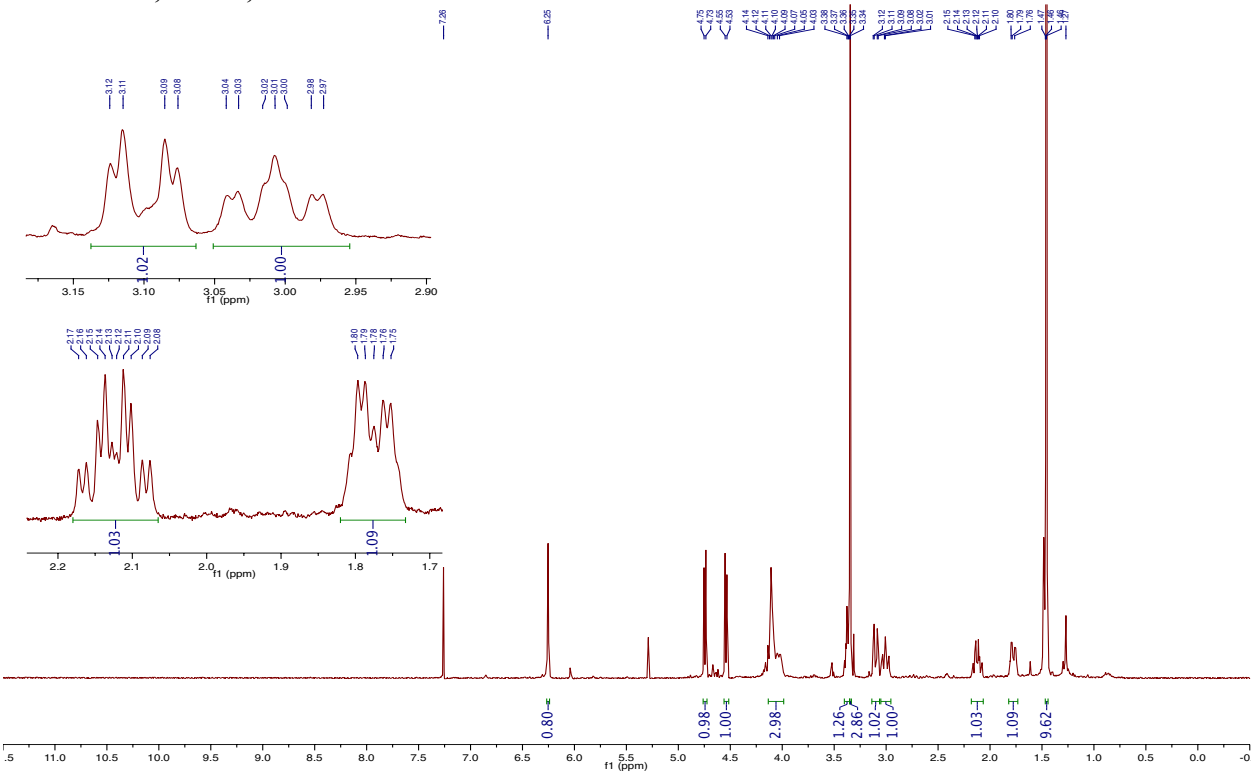


***(3S, 4S) N*-Boc-3-(methoxymethoxy)-4-(2,2-dibromoacetyl)piperidinecarboxylate ((+)-2.315)**

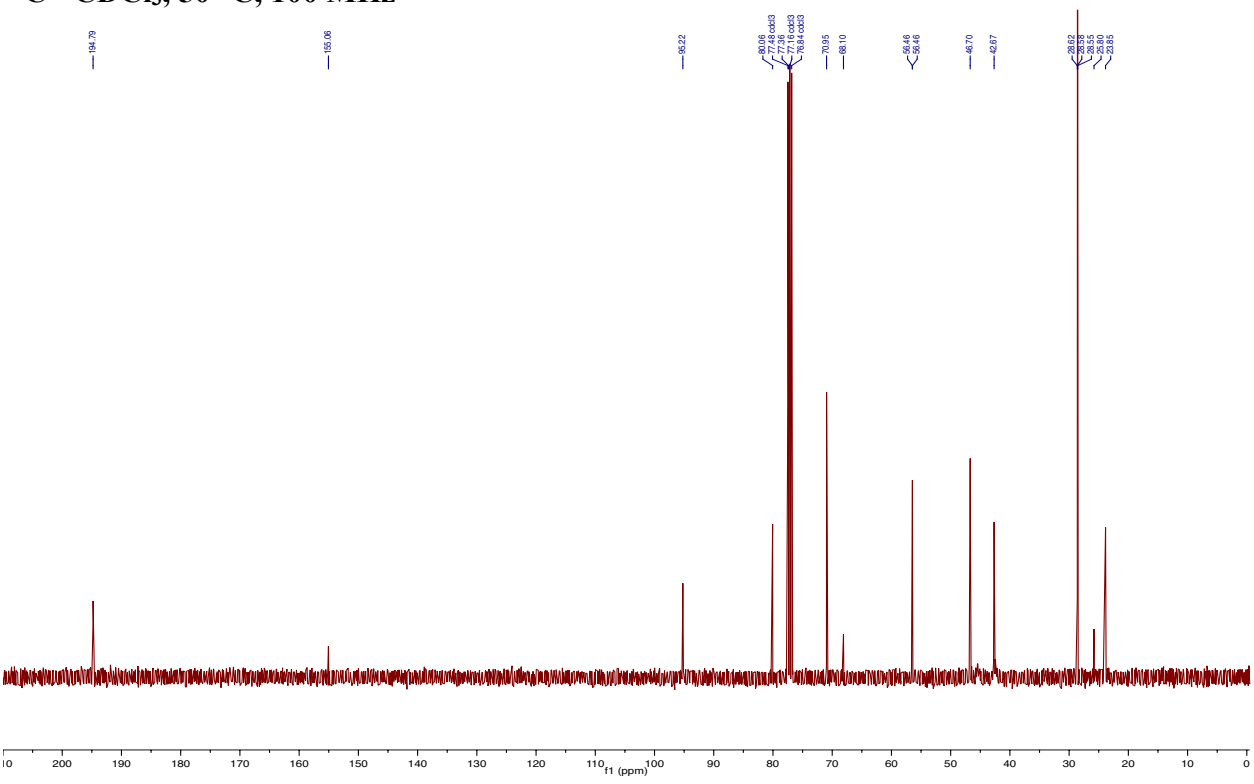
^{1}H - $CDCl_3$, 22 °C, 400 MHz



^{1}H - $CDCl_3$, 50 °C, 400 MHz

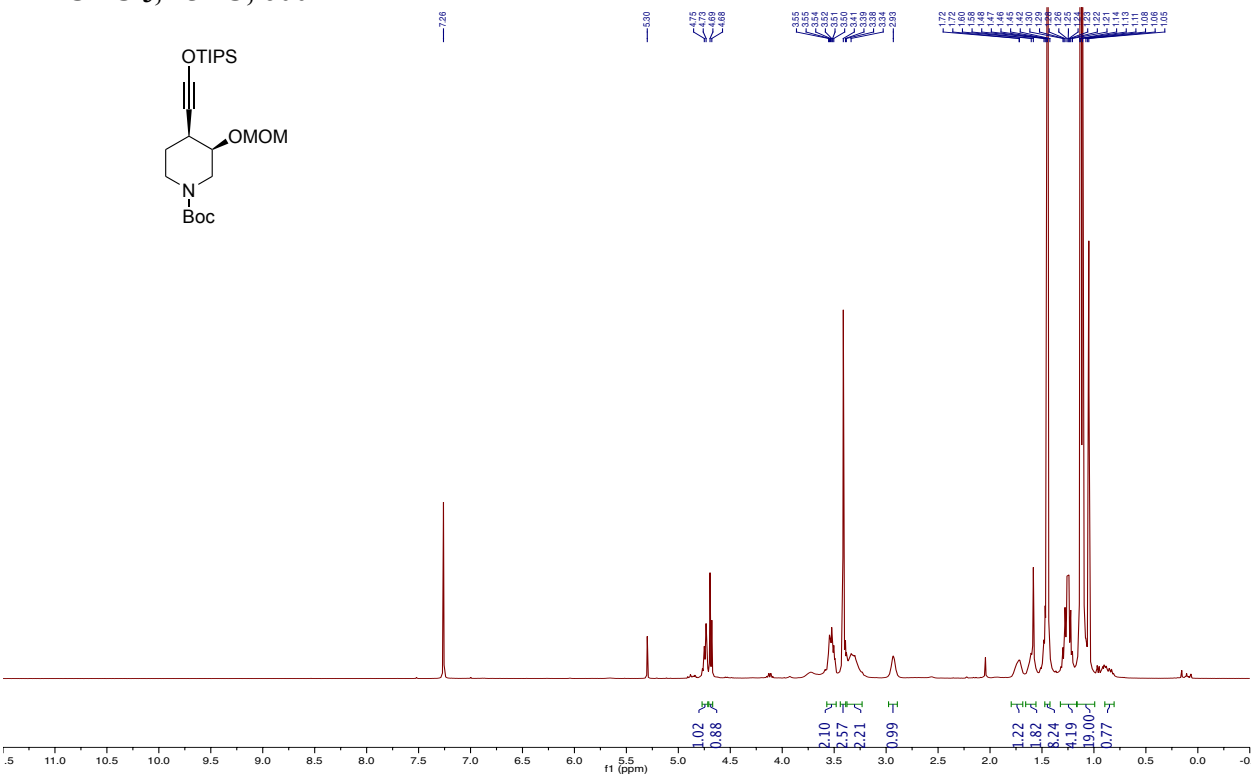


^{13}C - $CDCl_3$, 50 °C, 100 MHz

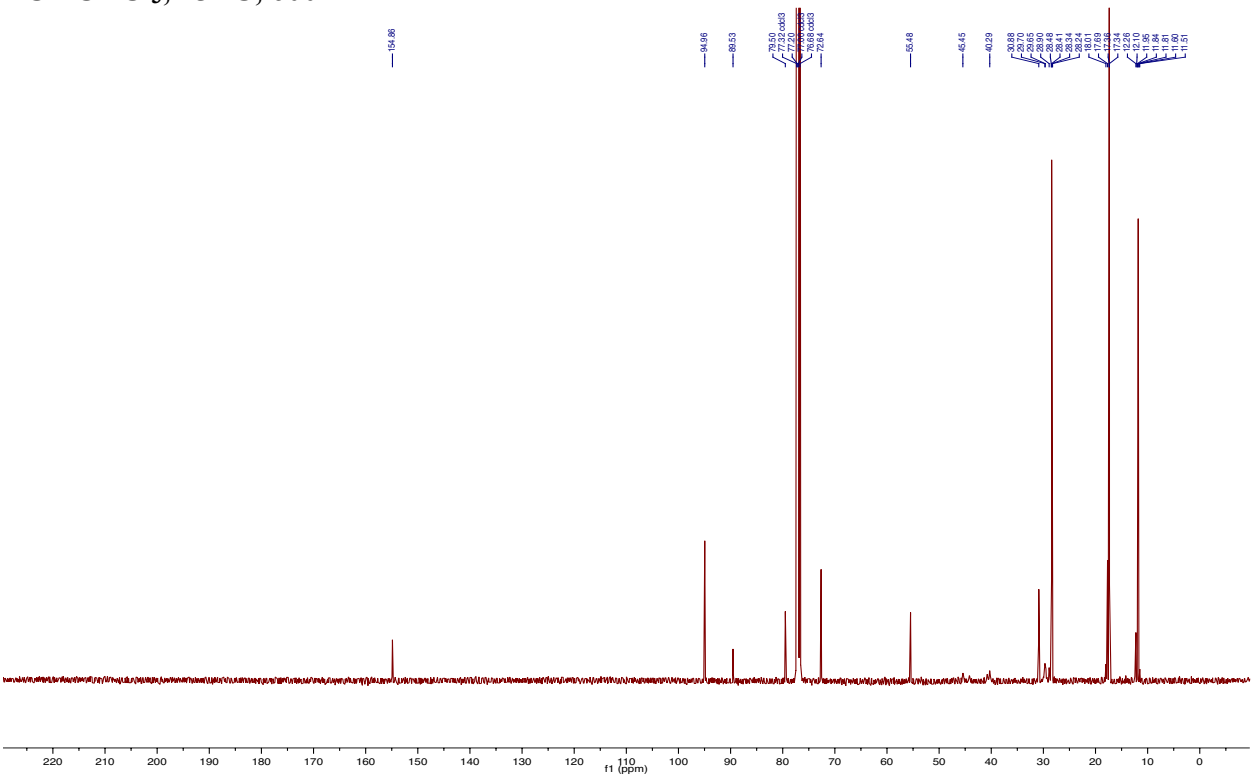


***(3S, 4R) N*-Boc-3-(methoxymethoxy)-4-((triisopropylsilyl)oxy)ethynylpiperidine ((+)-2.245)**

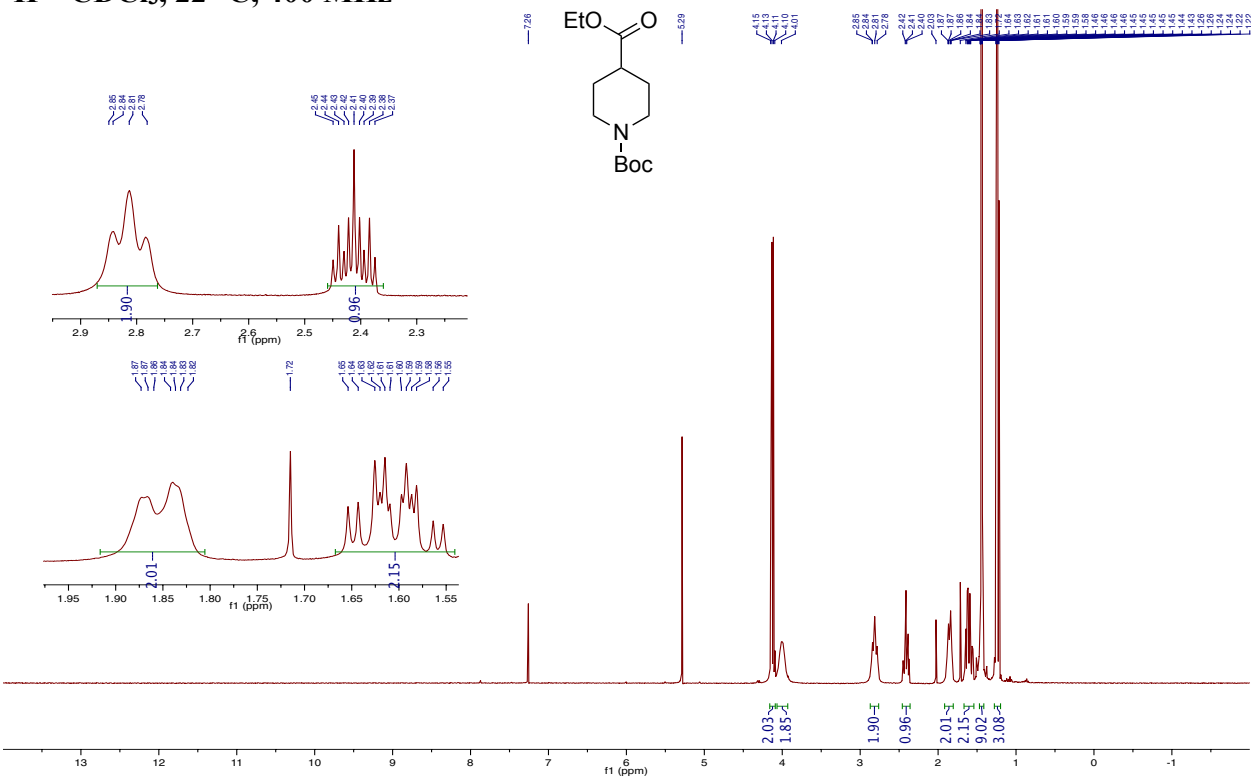
^{1}H - $CDCl_3$, 25 °C, 600 MHz



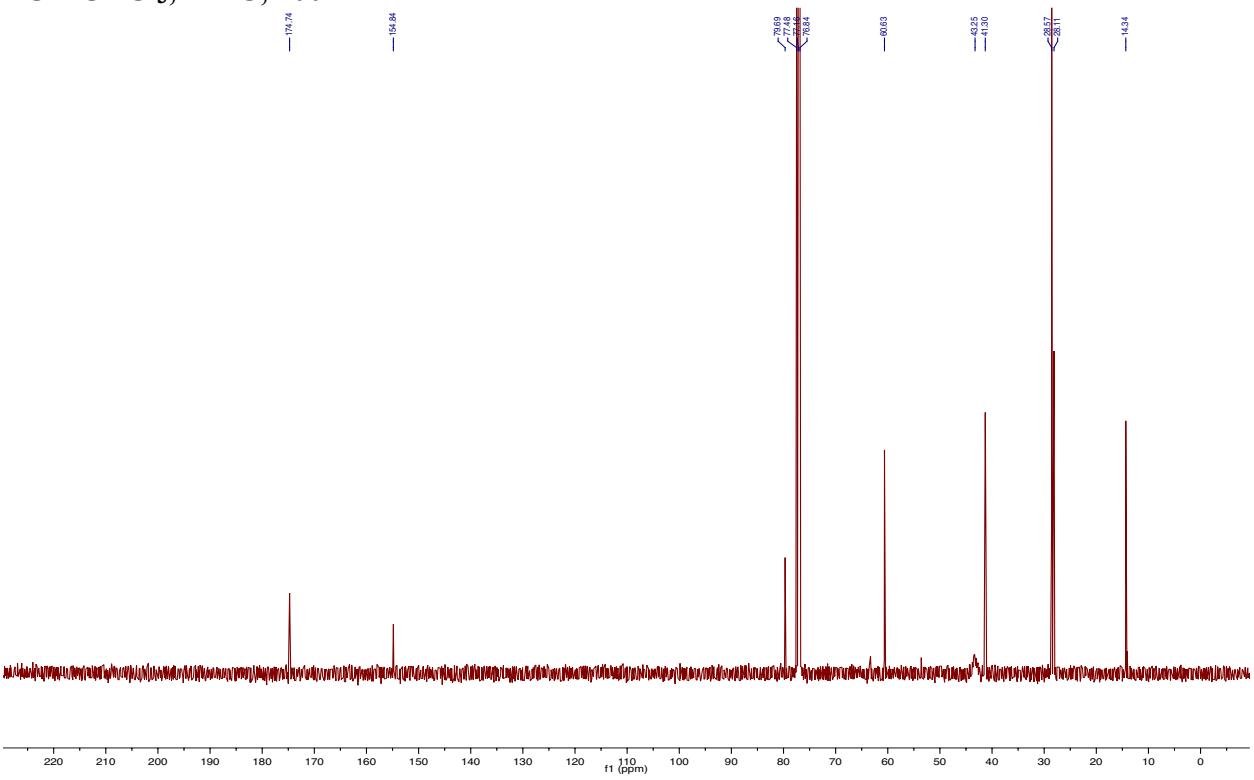
^{13}C - $CDCl_3$, 25 °C, 600 MHz



***N*-Boc-4-ethyl piperidinecarboxylate (2.316)**
^{1}H – $CDCl_3$, 22 °C, 400 MHz

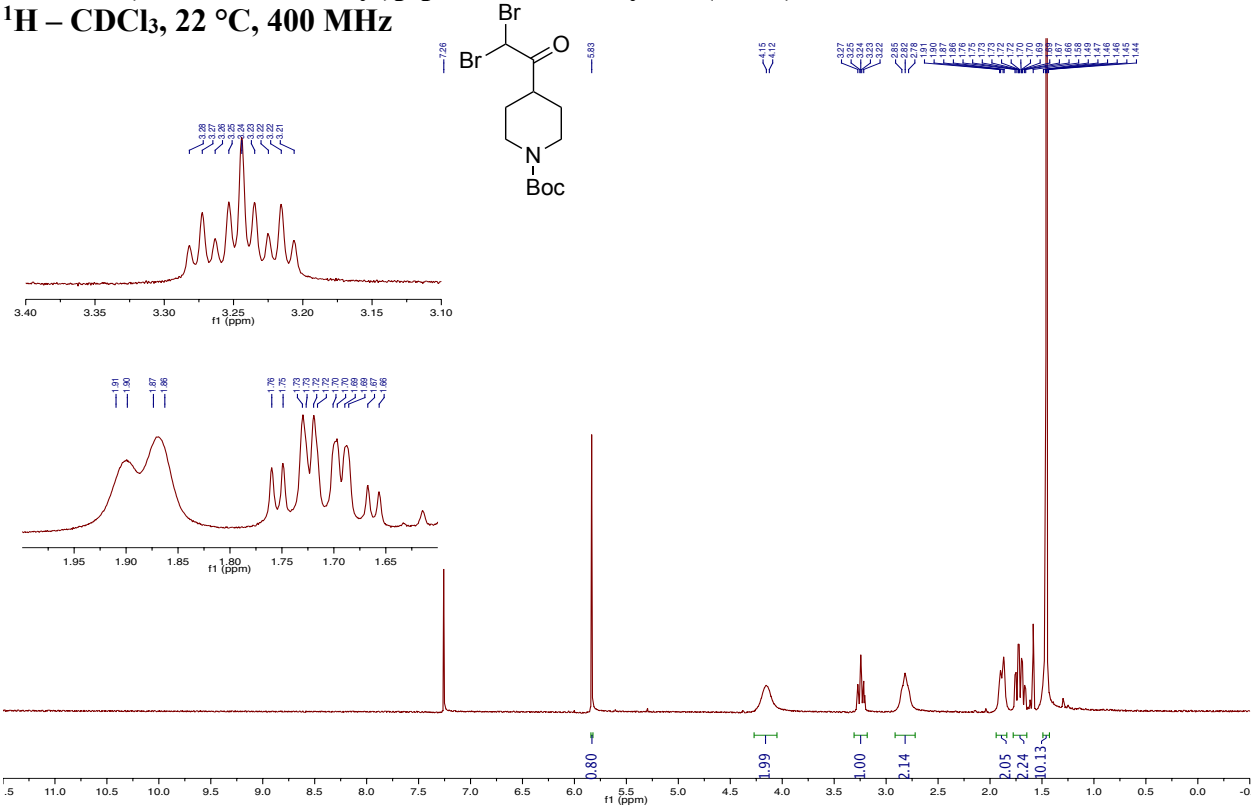


^{13}C – $CDCl_3$, 22 °C, 100 MHz

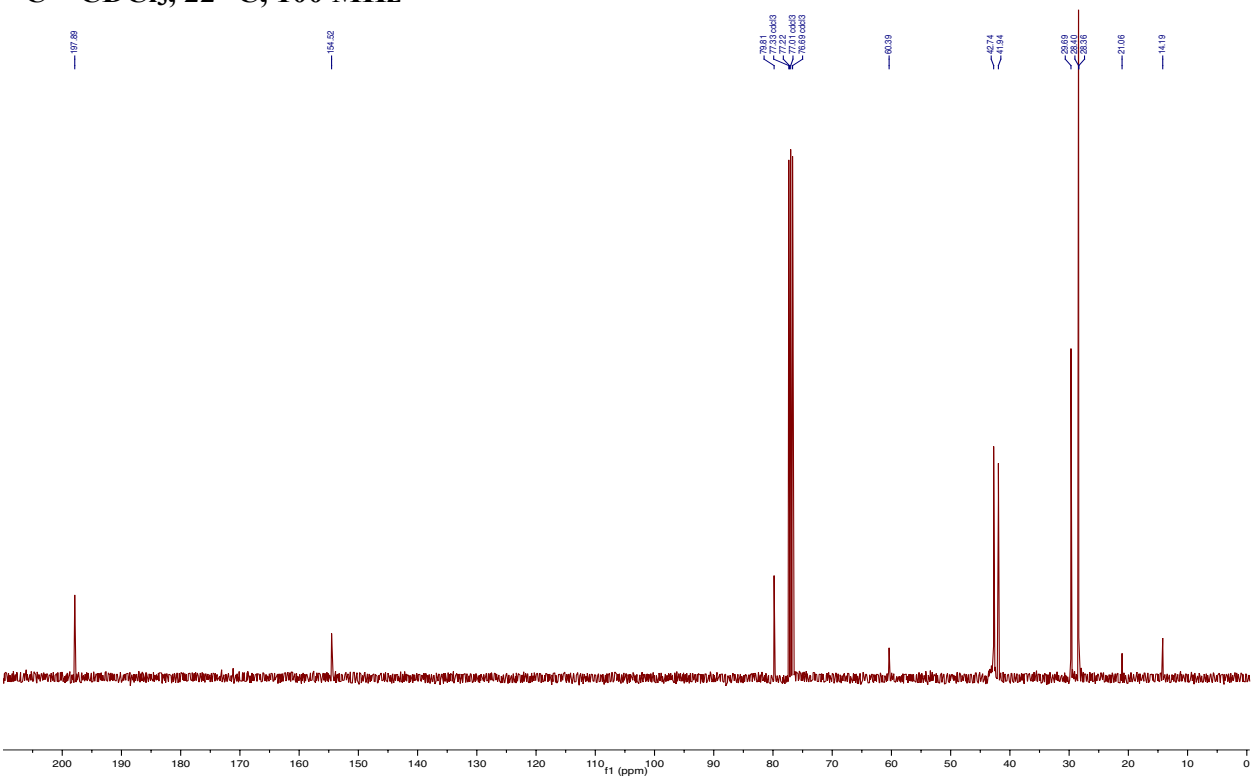


***N*-Boc-4-(2,2-dibromoacetyl)piperidinecarboxylate (2.317)**

^{1}H – $CDCl_3$, 22 °C, 400 MHz

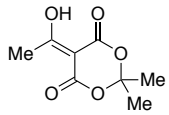


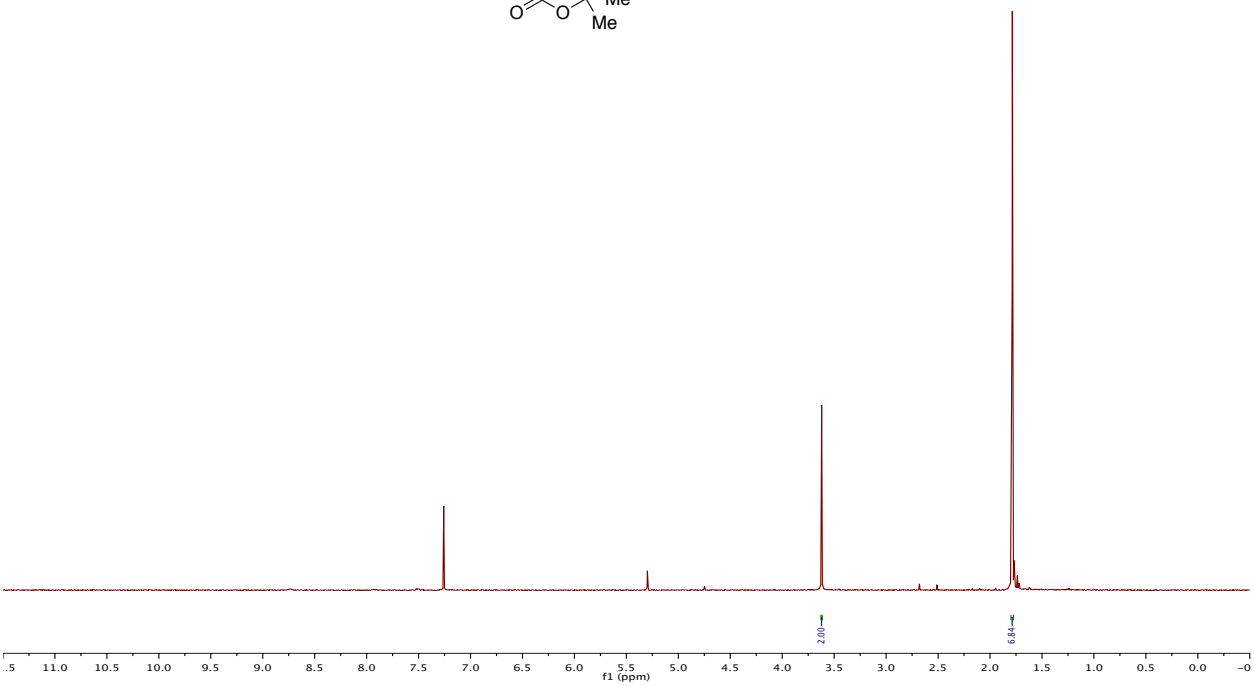
^{13}C – $CDCl_3$, 22 °C, 100 MHz



5-(1-hydroxyethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.322)

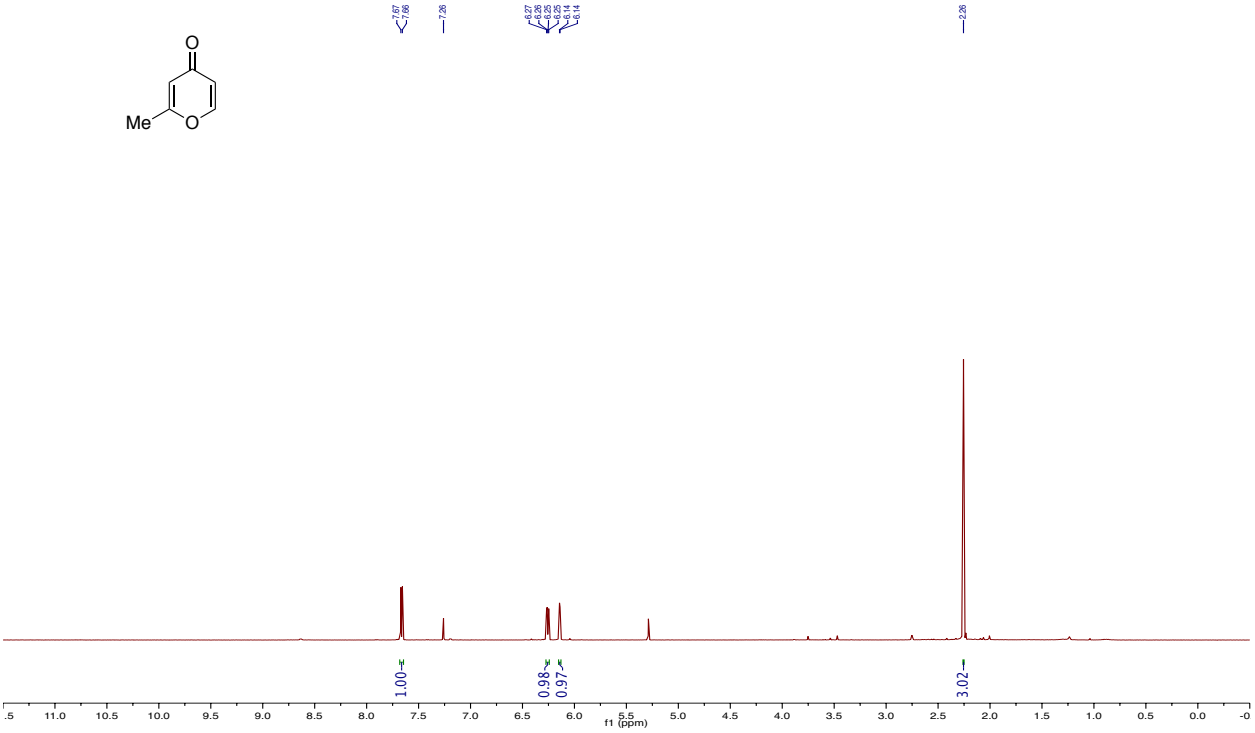
^{1}H—$CDCl_3$, 22 °C , 400 MHz



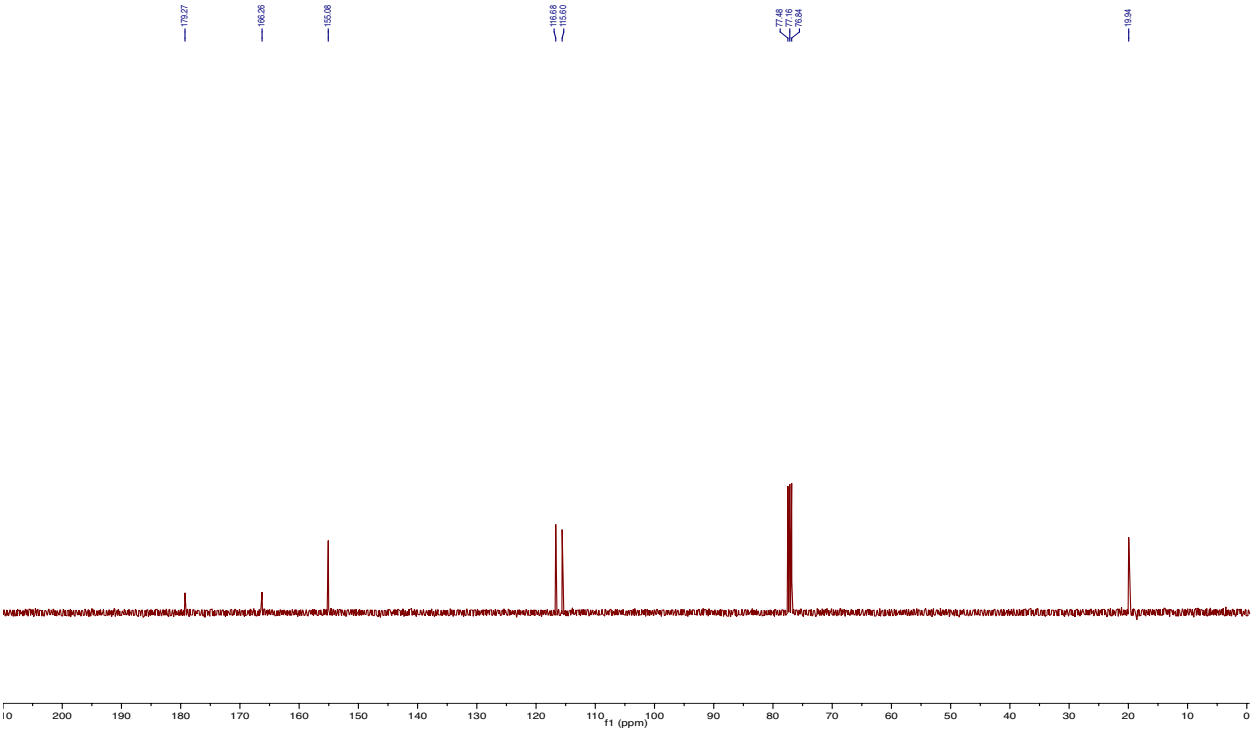


2-methyl-4*H*-pyran-4-one (2.323)

^{1}H—$CDCl_3$, 22 °C , 400 MHz

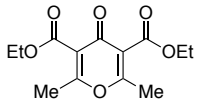


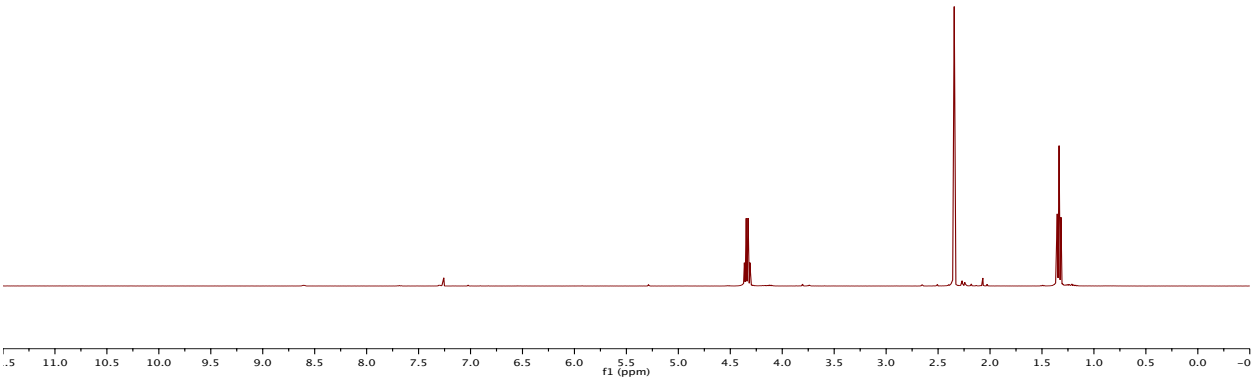
^{13}C—$CDCl_3$, 22 °C, 100 MHz



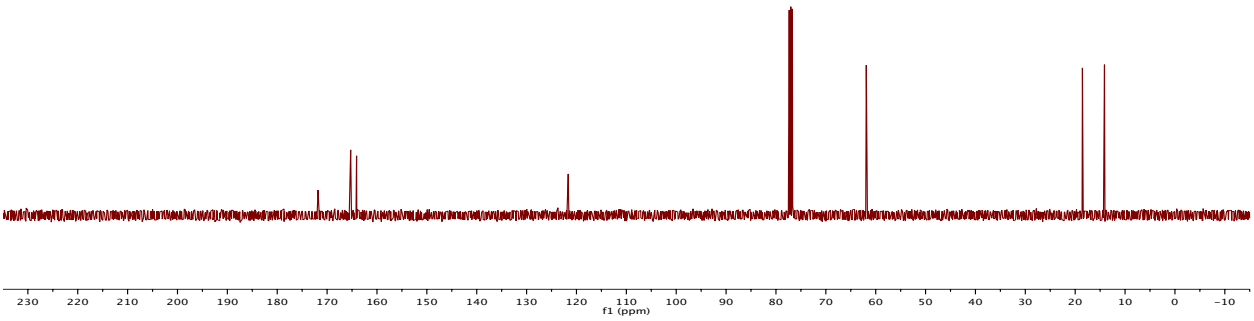
diethyl 2,6-dimethyl-4-oxo-4*H*-pyran-3,5-dicarboxylate (2.329)

^{1}H—$CDCl_3$, 22 °C , 400 MHz



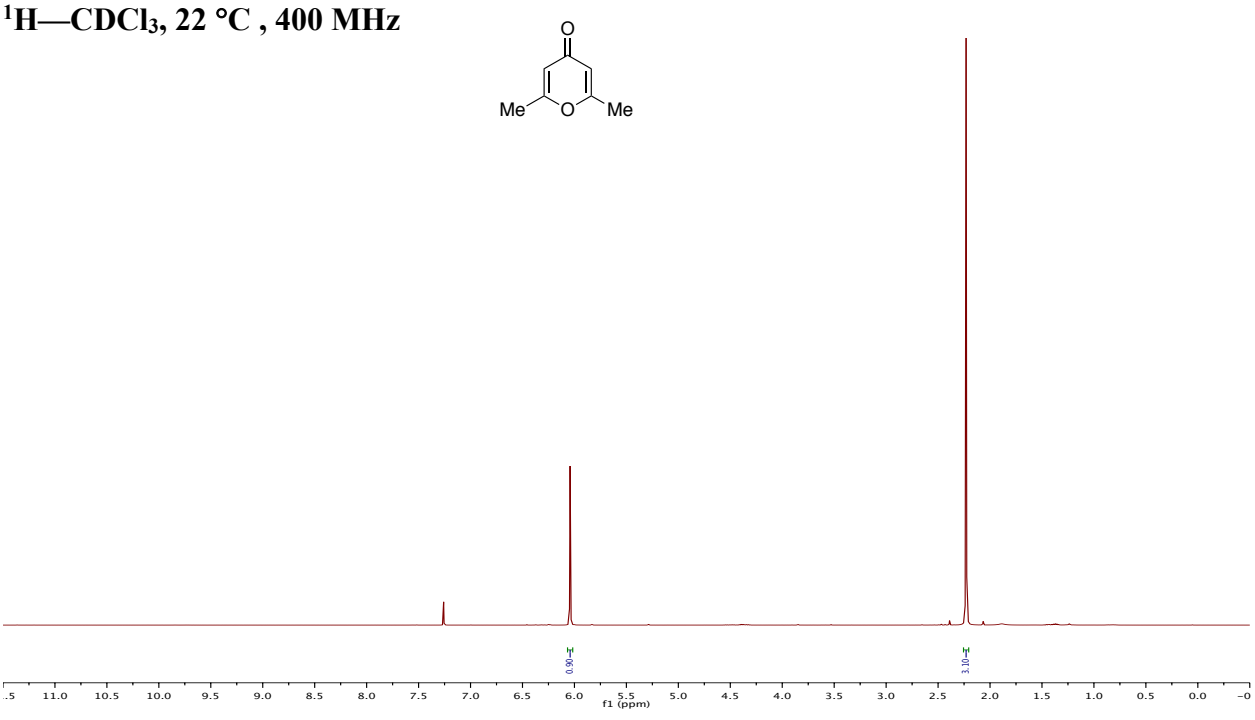


^{13}C—$CDCl_3$, 22 °C, 100 MHz

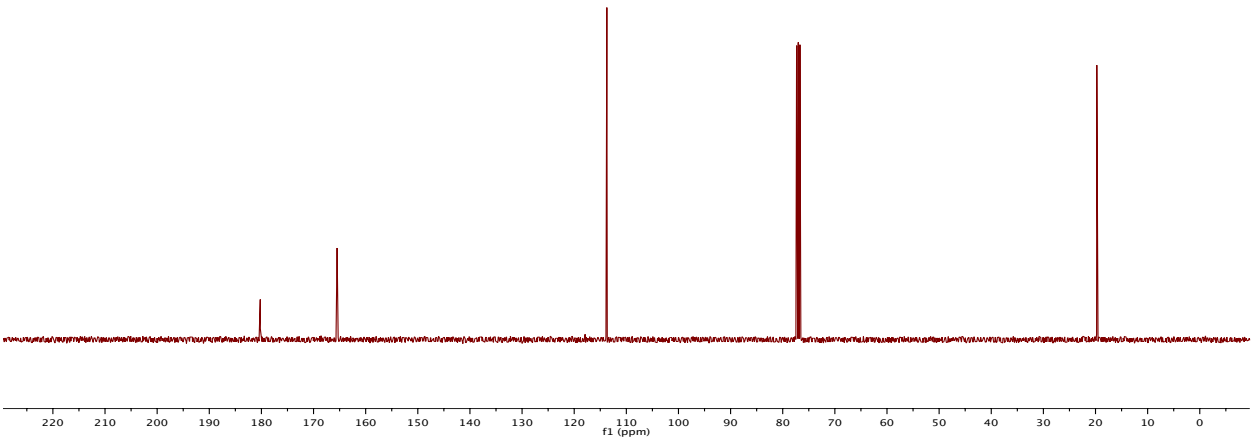


2,6-dimethyl-4*H*-pyran-4-one (2.330)

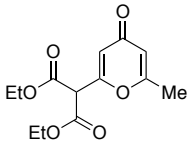
^{1}H—$CDCl_3$, 22 °C , 400 MHz

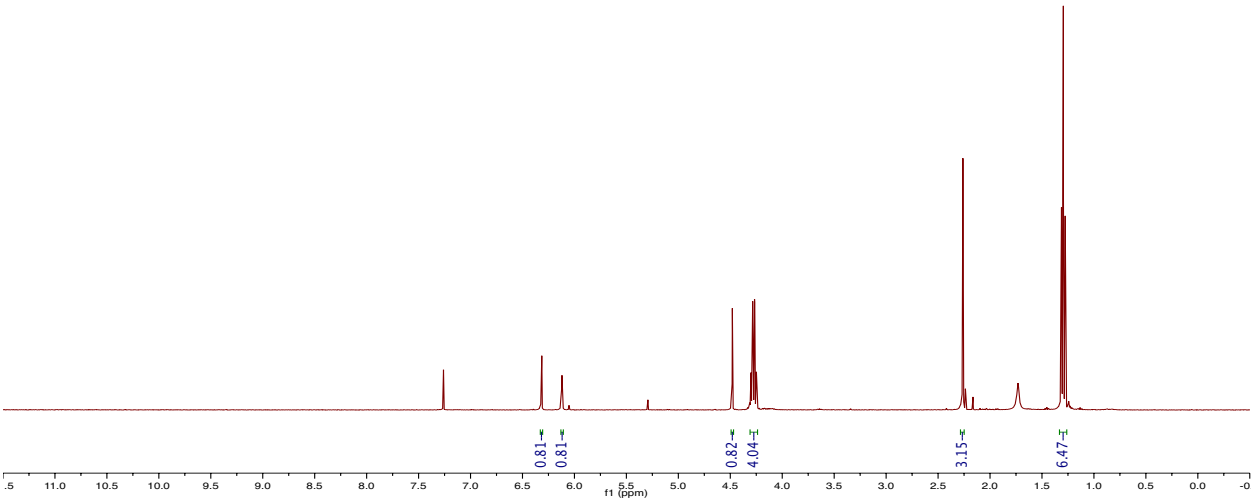


^{13}C—$CDCl_3$, 22 °C, 100 MHz

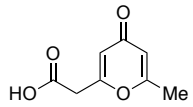


diethyl 2-(6-methyl-4-oxo-4H-pyran-2-yl)malonate (2.331)
^{1}H—$CDCl_3$, 22 °C , 400 MHz

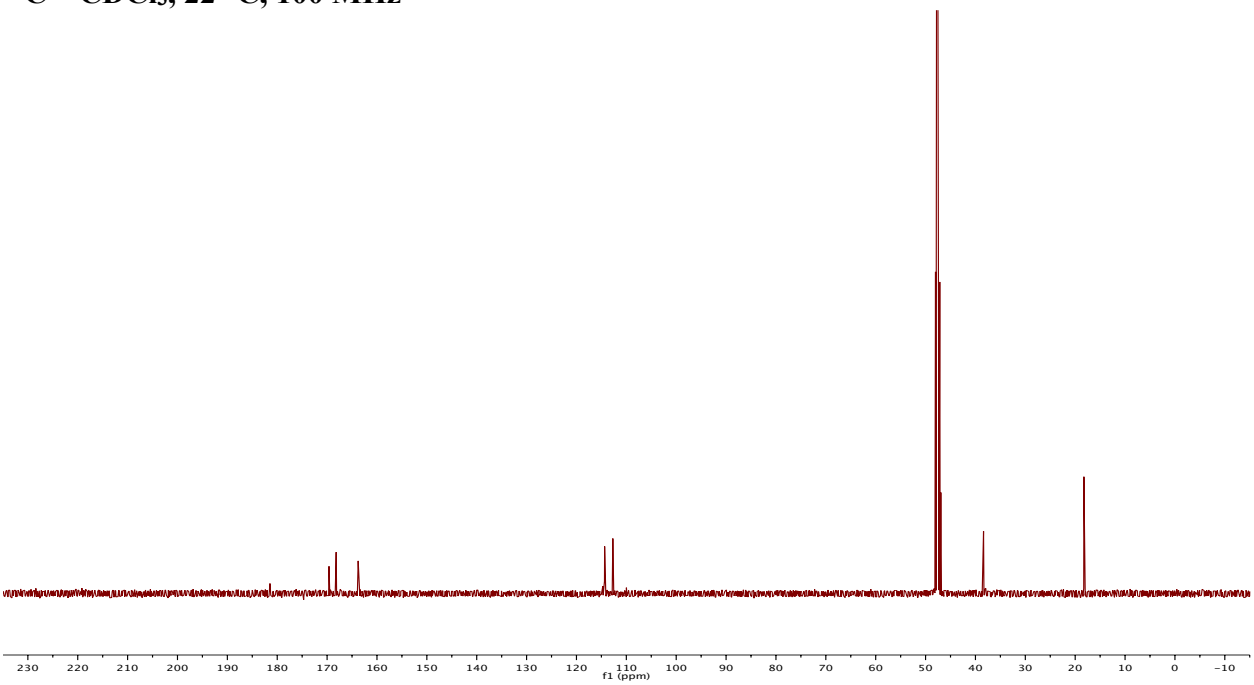




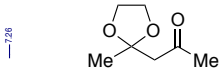
2-(6-methyl-4-oxo-4*H*-pyran-2-yl)acetic acid (2.333)
^{1}H—$CDCl_3$, 22 °C , 400 MHz

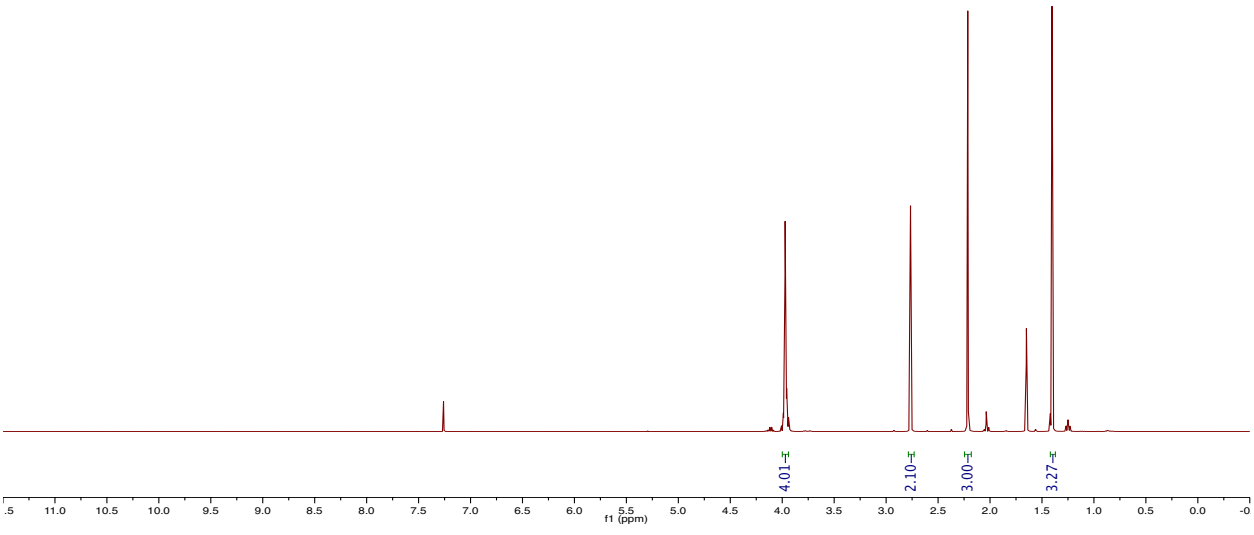


^{13}C—$CDCl_3$, 22 °C, 100 MHz

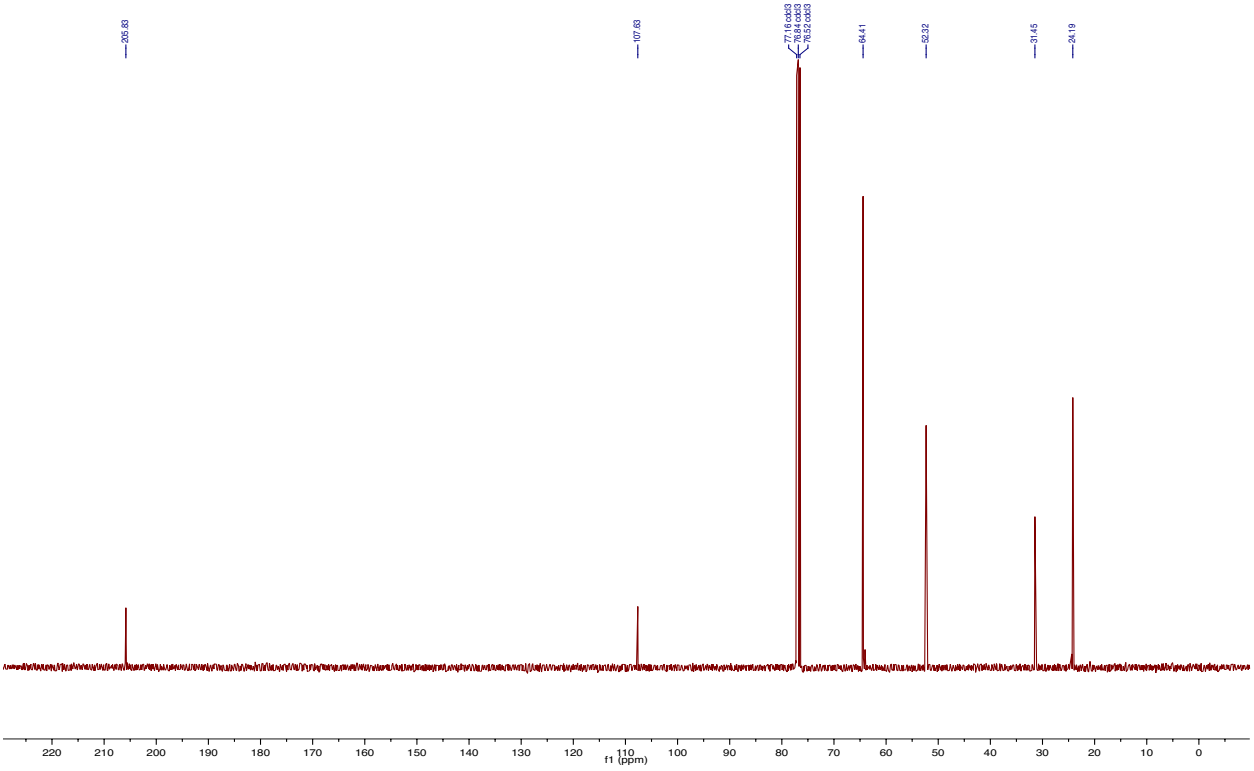


1-(2-methyl-1,3-dioxolan-2-yl)propan-2-one (2.334)
^{1}H - $CDCl_3$, 22 °C, 400 MHz



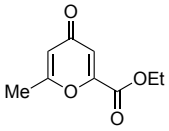


^{13}C - $CDCl_3$, 22 °C, 100 MHz

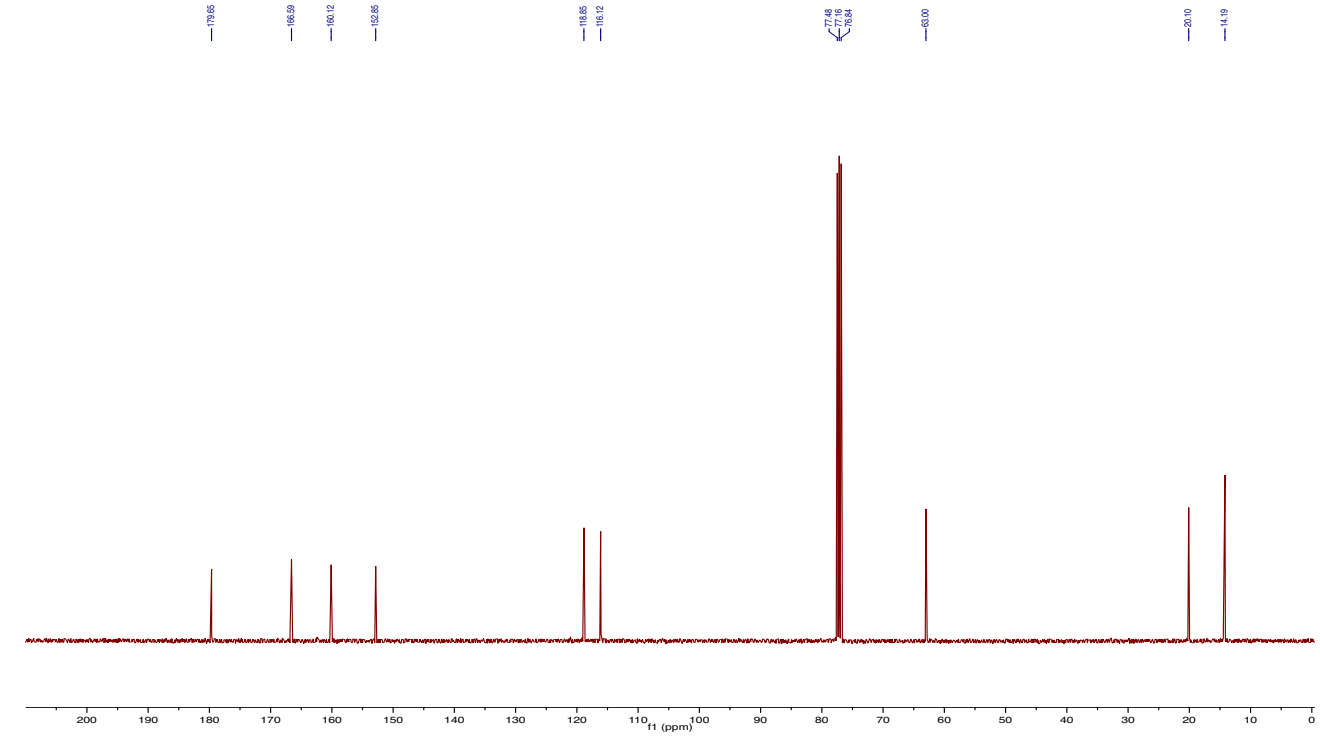


ethyl 6-methyl-4-oxo-4H-pyran-2-carboxylate (2.335)

^{1}H - $CDCl_3$, 22 °C, 400 MHz

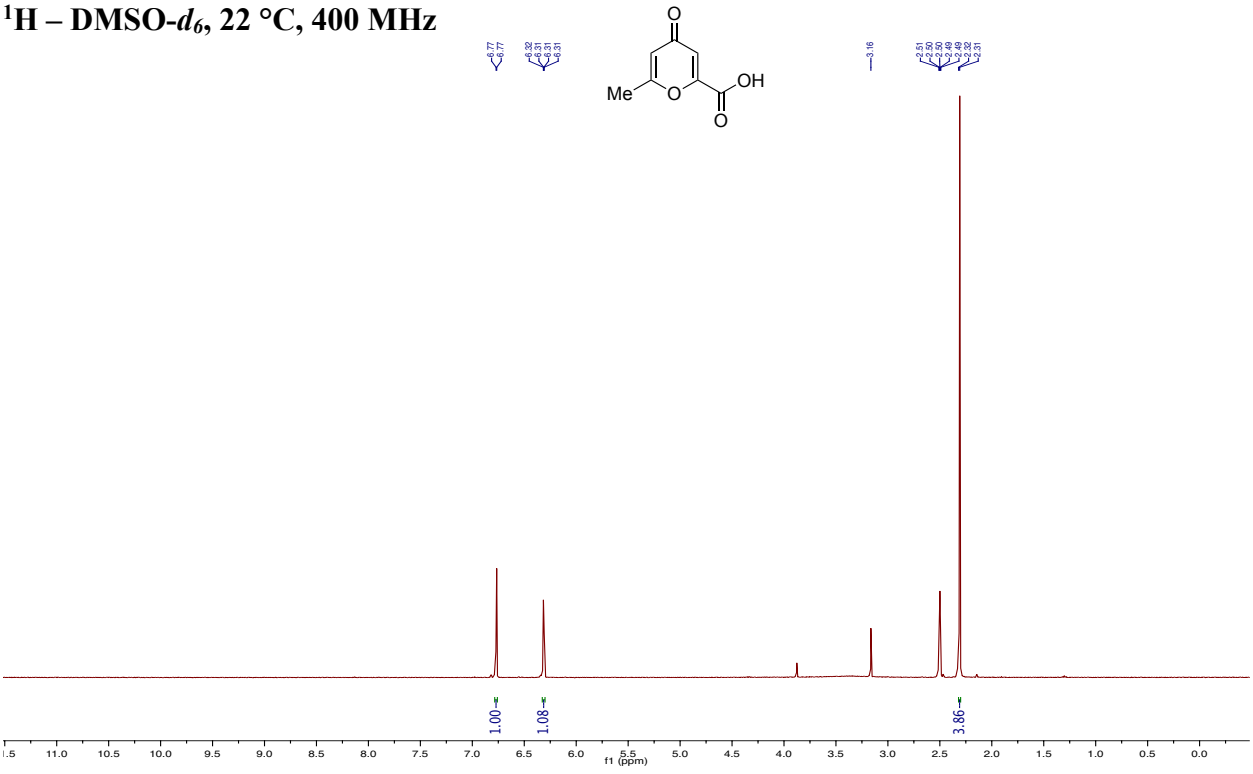


^{13}C - $CDCl_3$, 22 °C, 400 MHz

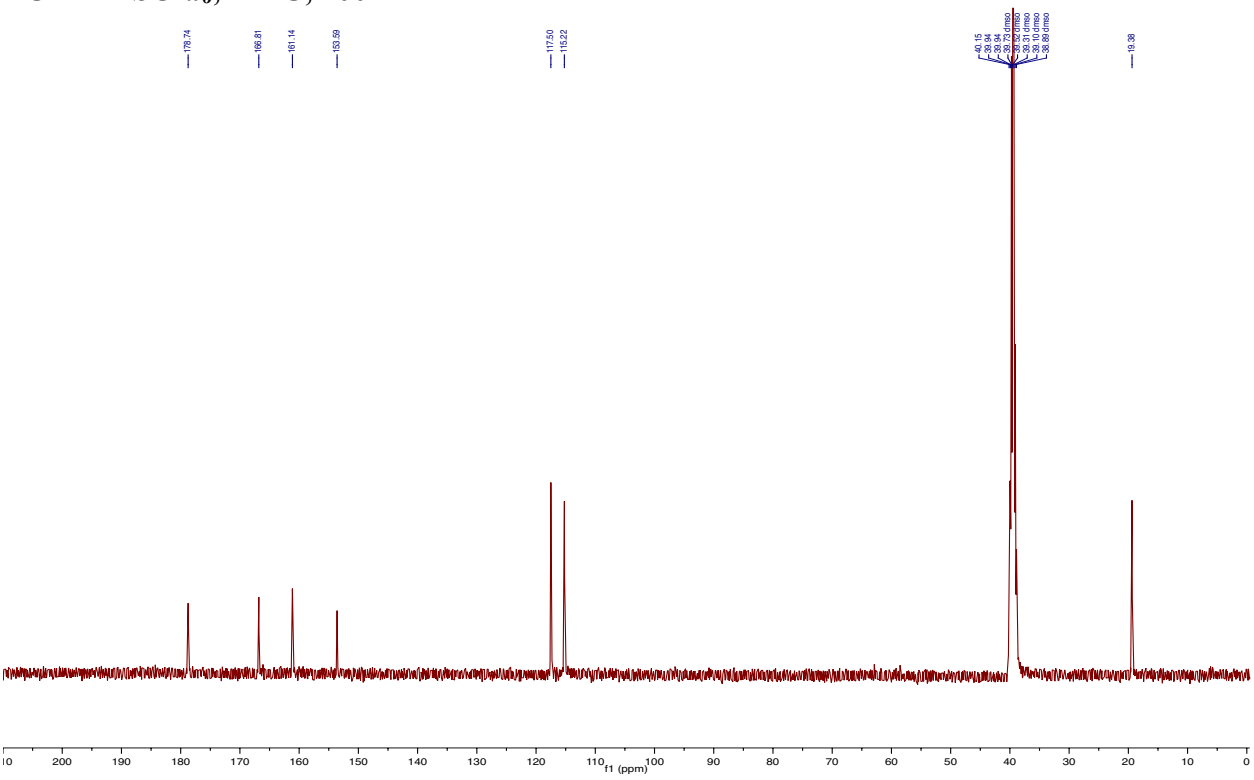


6-methyl-4-oxo-4H-pyran-2-carboxylic acid (2.336)

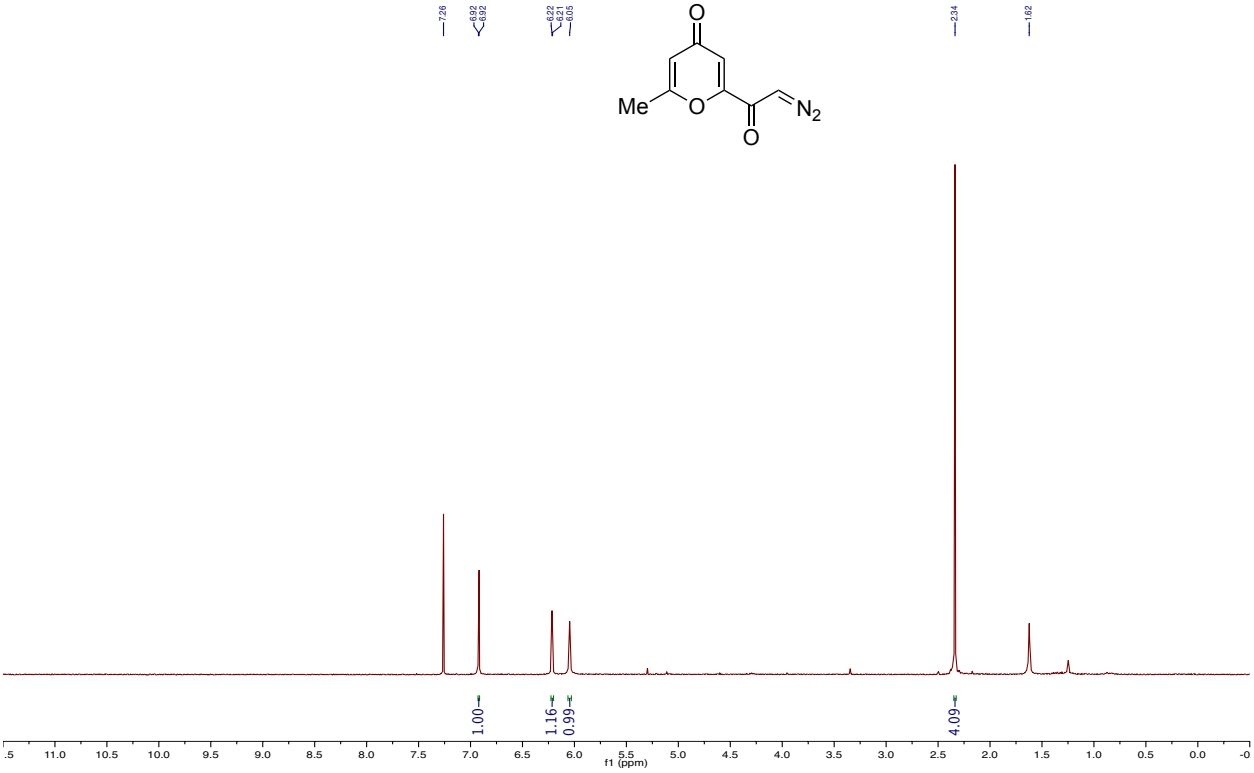
^{1}H – DMSO-d_6, 22 °C, 400 MHz



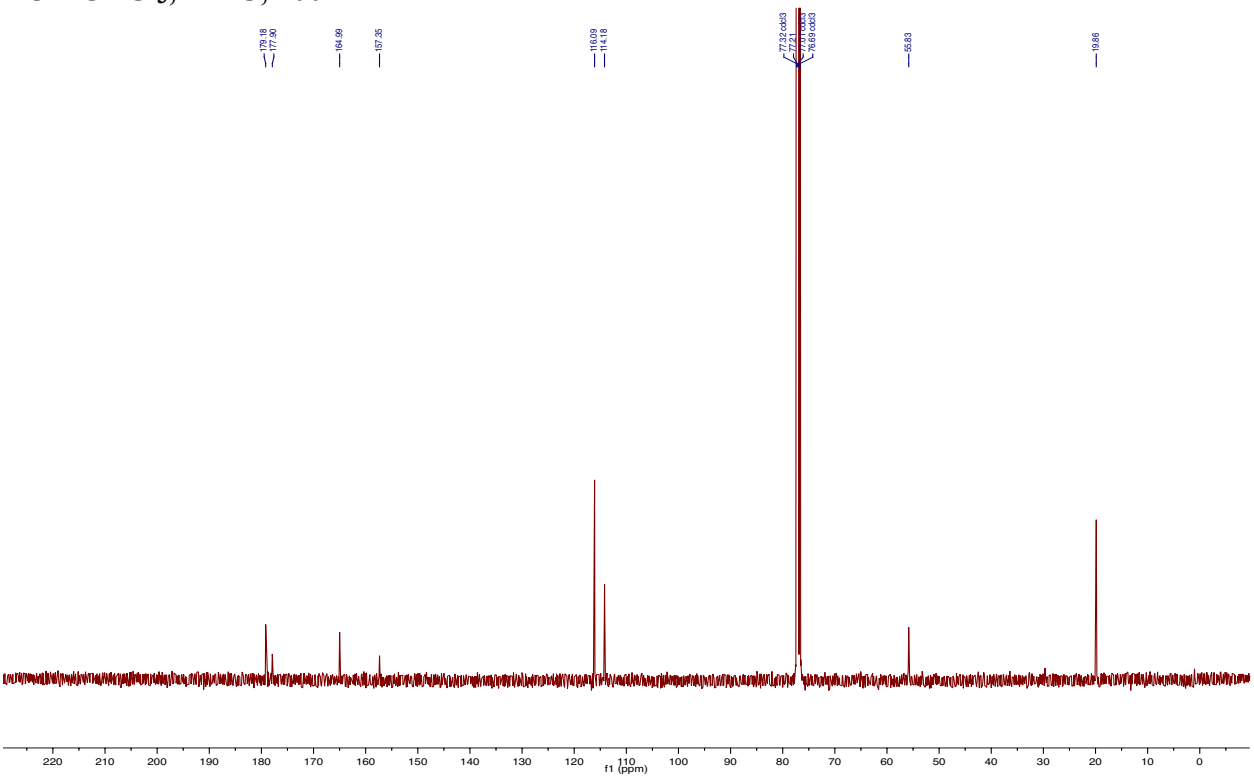
^{13}C – DMSO-d_6, 22 °C, 100 MHz



2-(2-diazoacetyl)-6-methyl-4H-pyran-4-one (2.320)
^{1}H - $CDCl_3$, 22 °C, 400 MHz

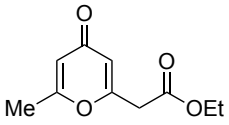


^{13}C – $CDCl_3$, 22 °C, 100 MHz

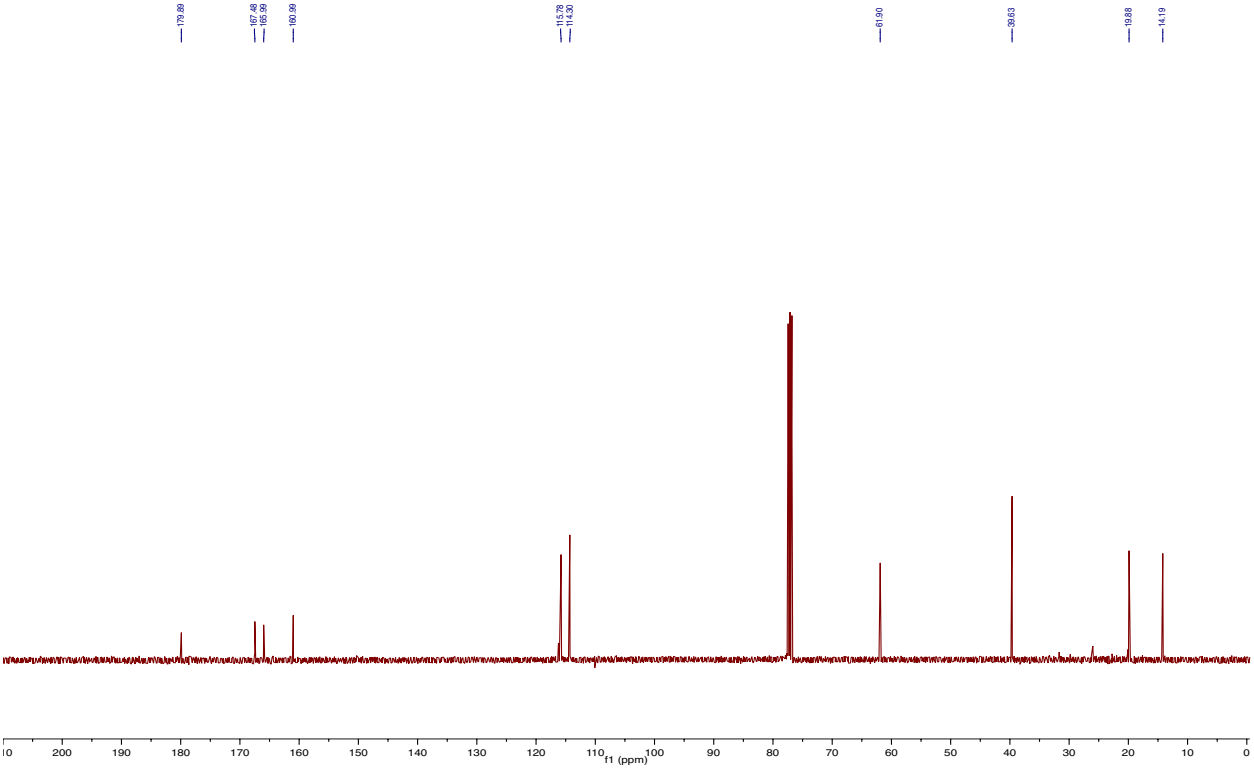


ethyl 2-(6-methyl-4-oxo-4*H*-pyran-2-yl)acetate (2.337)

^{1}H - $CDCl_3$, 22 °C, 400 MHz

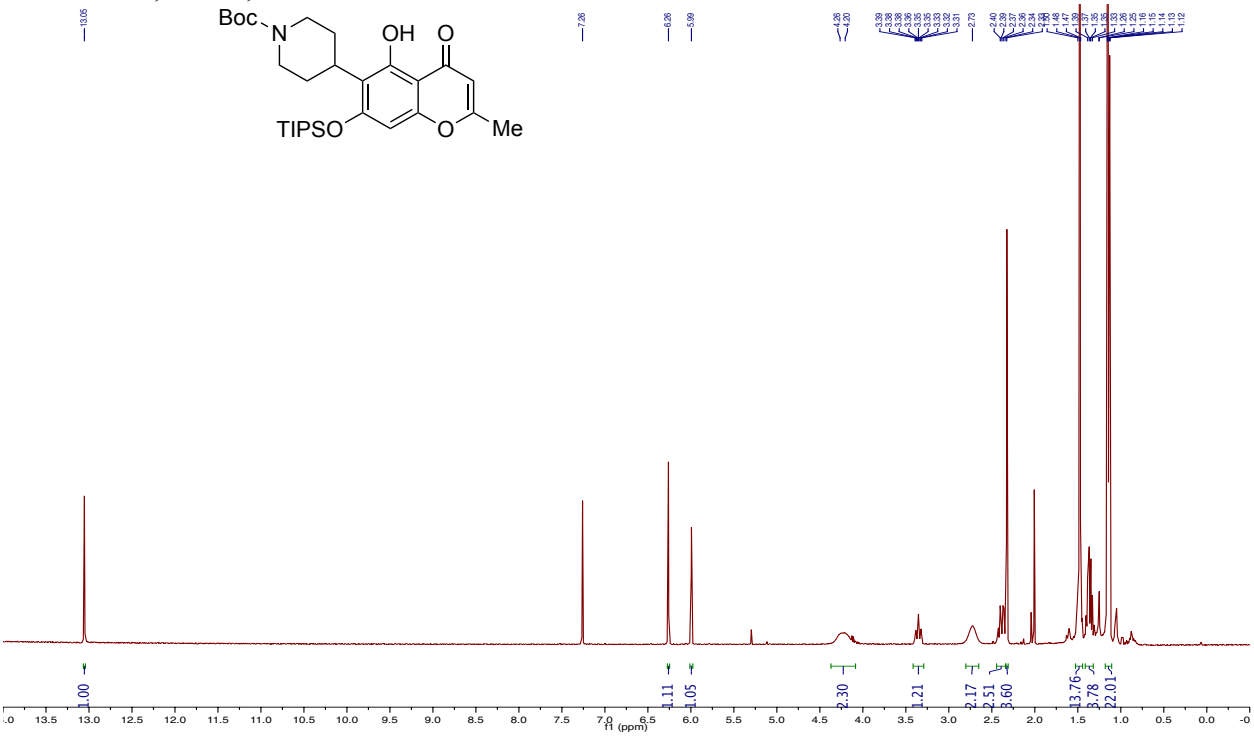


^{13}C - $CDCl_3$, 22 °C, 100 MHz

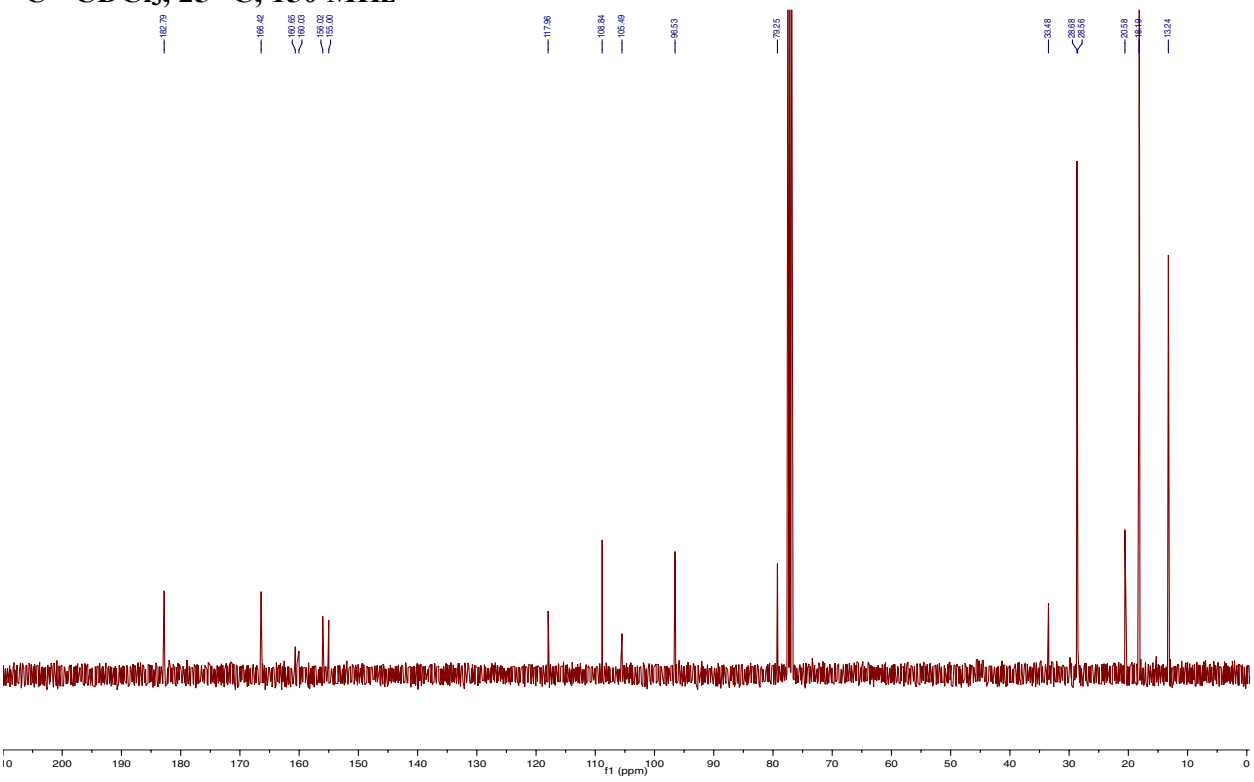


***N*-Boc-1'-(5-hydroxy-2-methyl-4-oxo-7-((triisopropylsilyl)oxy)-4H-chromen-6-yl)piperidine (S-2.11)**

^{1}H - $CDCl_3$, 25 °C, 600 MHz

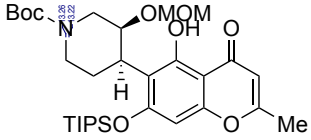


^{13}C - $CDCl_3$, 25 °C, 150 MHz

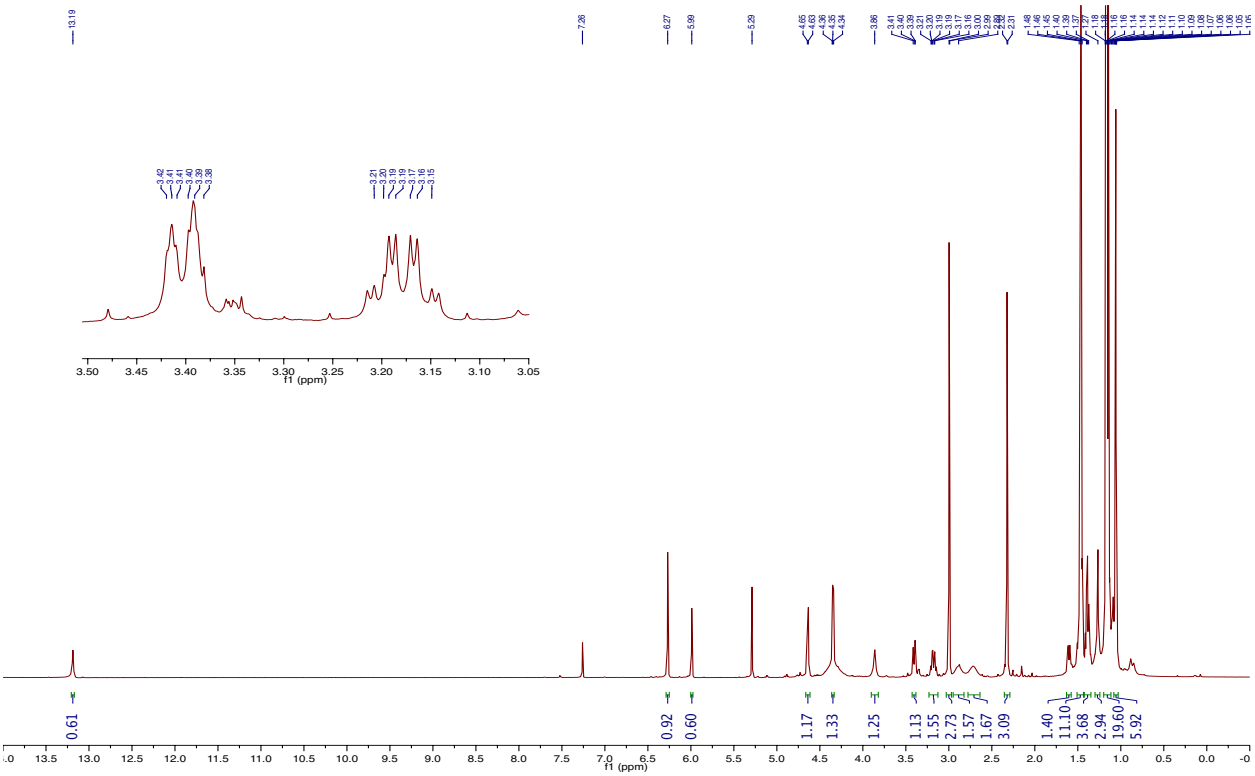


(2'S, 1'R) N-Boc-2'-(methoxymethoxy)-1'-(5-hydroxy-2-methyl-4-oxo-7-((triisopropylsilyl)oxy)-4H-chromen-6-yl)piperidine (-)-2.247

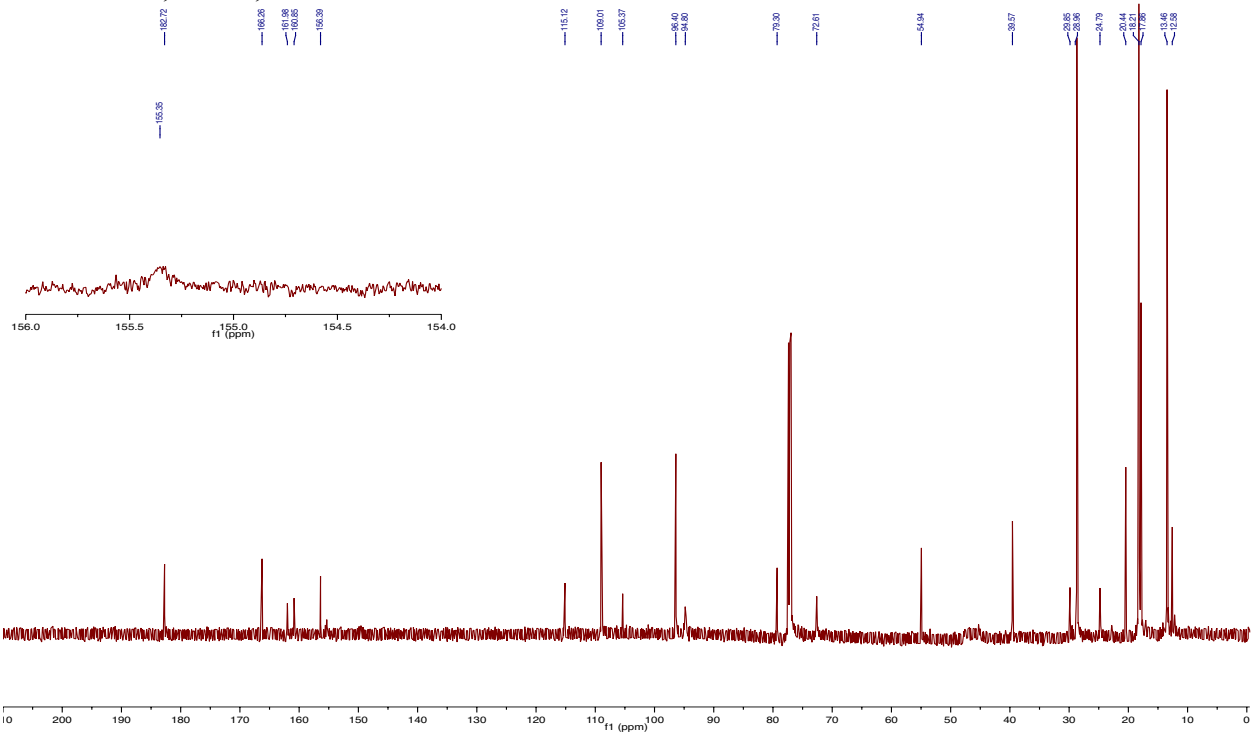
^{1}H - $CDCl_3$, 25 °C, 600 MHz



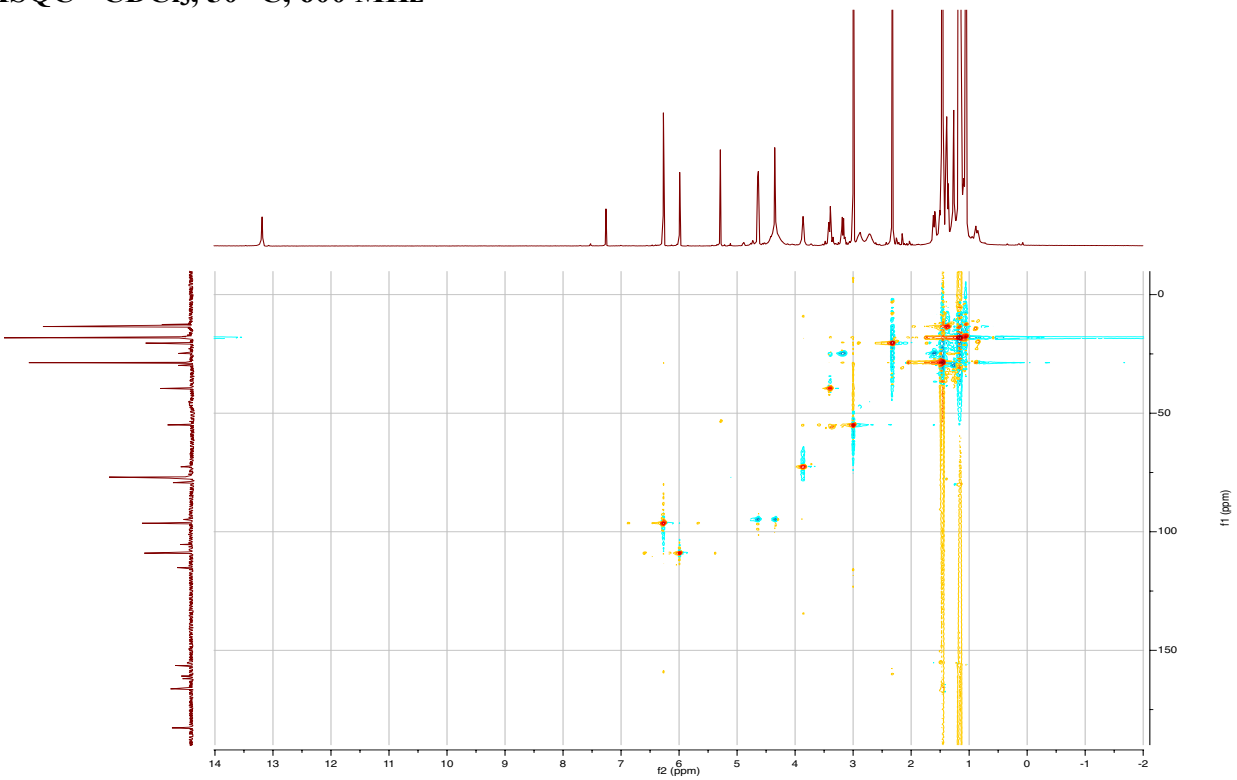
^{1}H - $CDCl_3$, 50 °C, 600 MHz



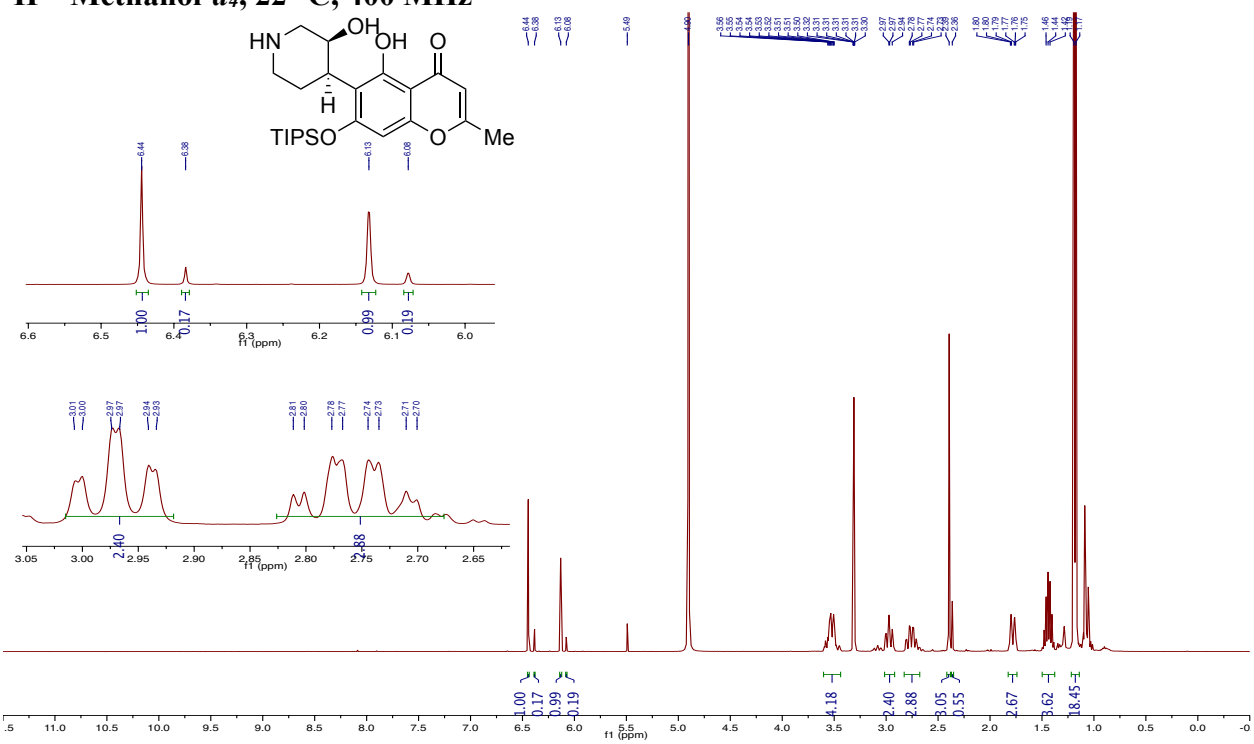
^{13}C - $CDCl_3$, 50 °C, 150 MHz



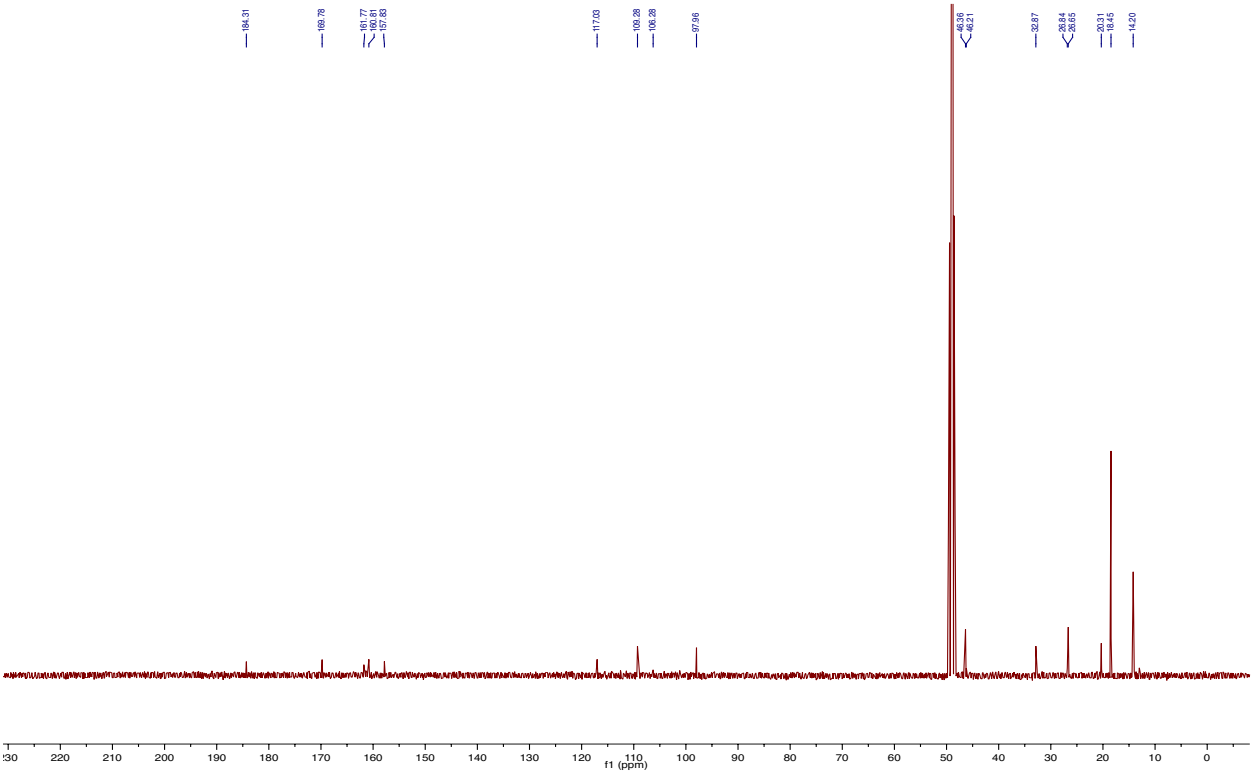
HSQC - $CDCl_3$, 50 °C, 600 MHz



5-hydroxy-2-methyl-6-(piperidin-4-yl)-7-((triisopropylsilyl)oxy)-4H-chromen-4-one (2.338)
^{1}H – Methanol-d_4, 22 °C, 400 MHz

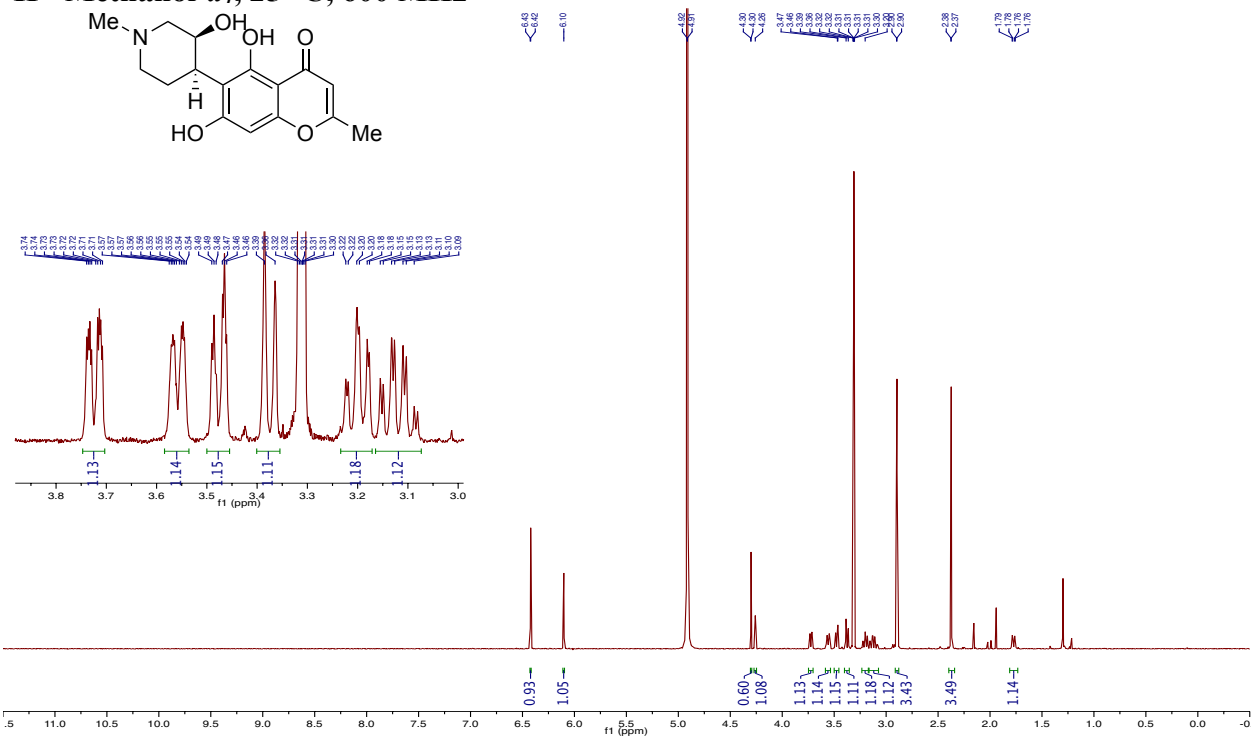


^{13}C - Methanol-*d*$_4$, 22 °C, 100 MHz

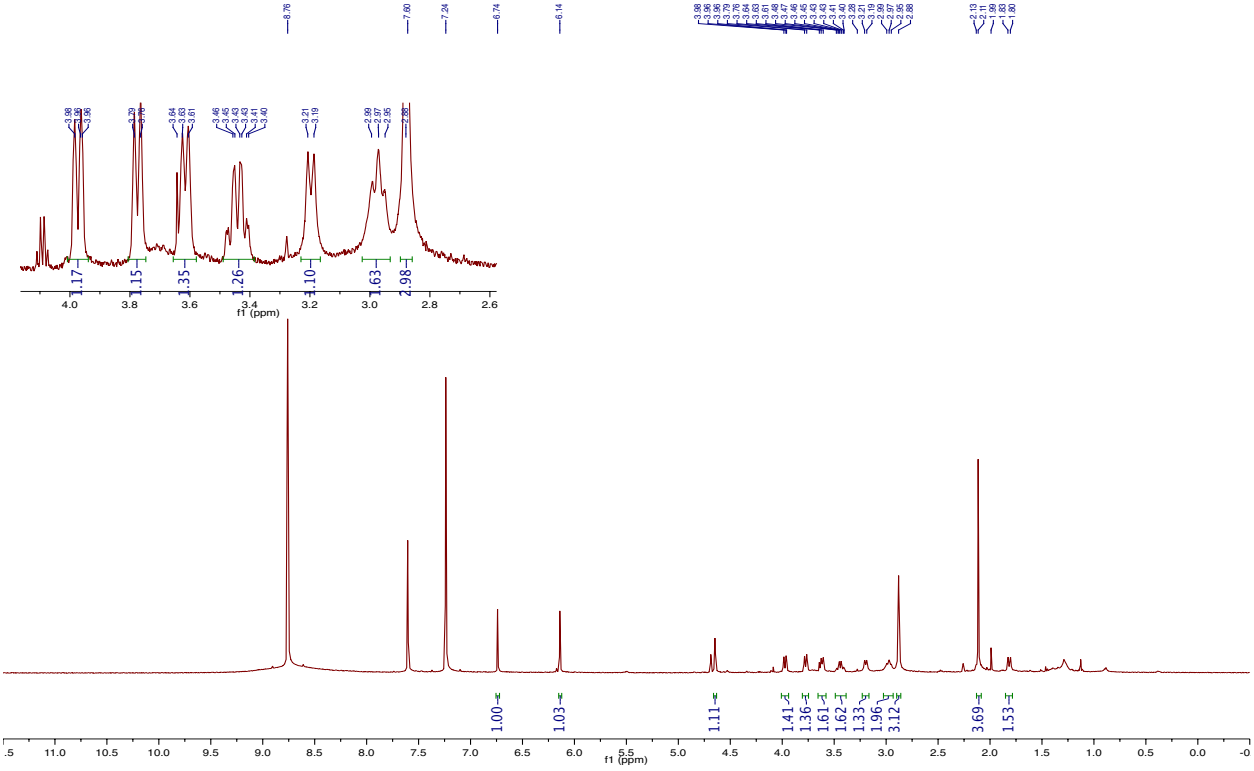


(+)-Dysoline (2.20)

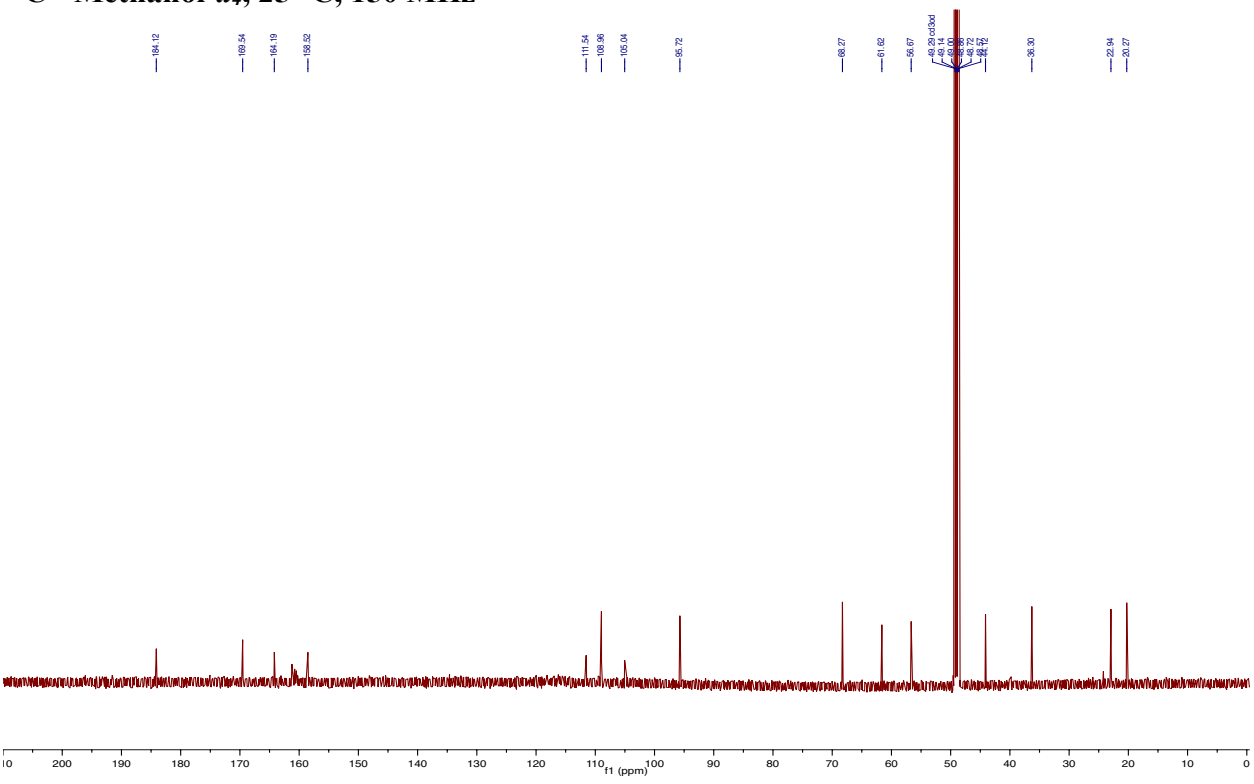
^{1}H - Methanol-*d*$_4$, 25 °C, 600 MHz



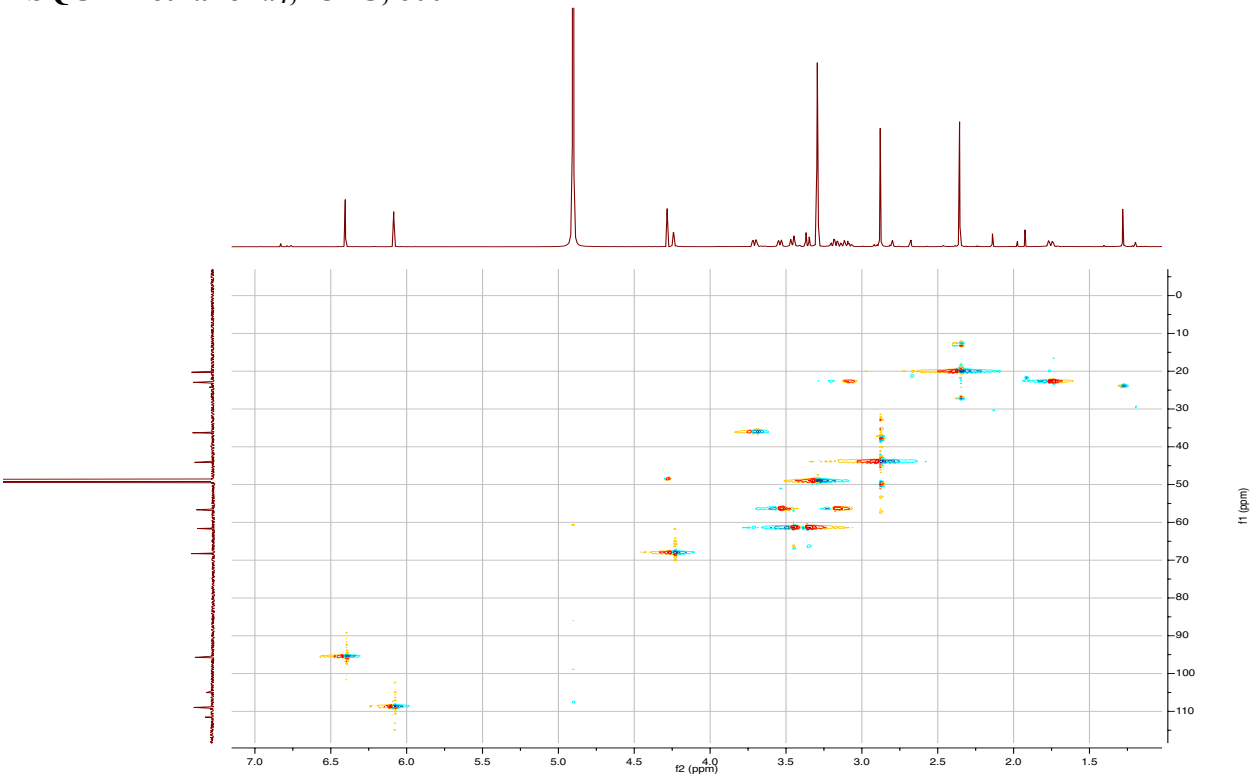
^{1}H - Pyridine - d_5, 25 °C, 600 MHz



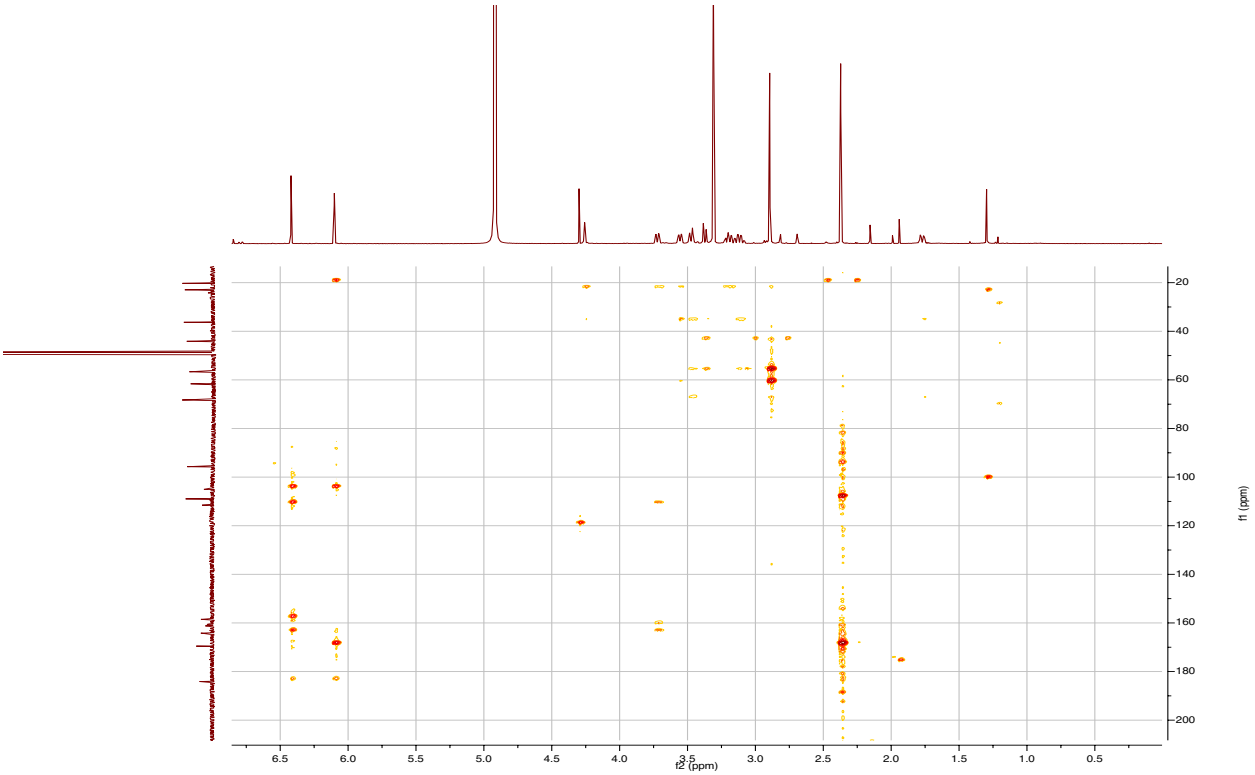
^{13}C - Methanol-d_4, 25 °C, 150 MHz



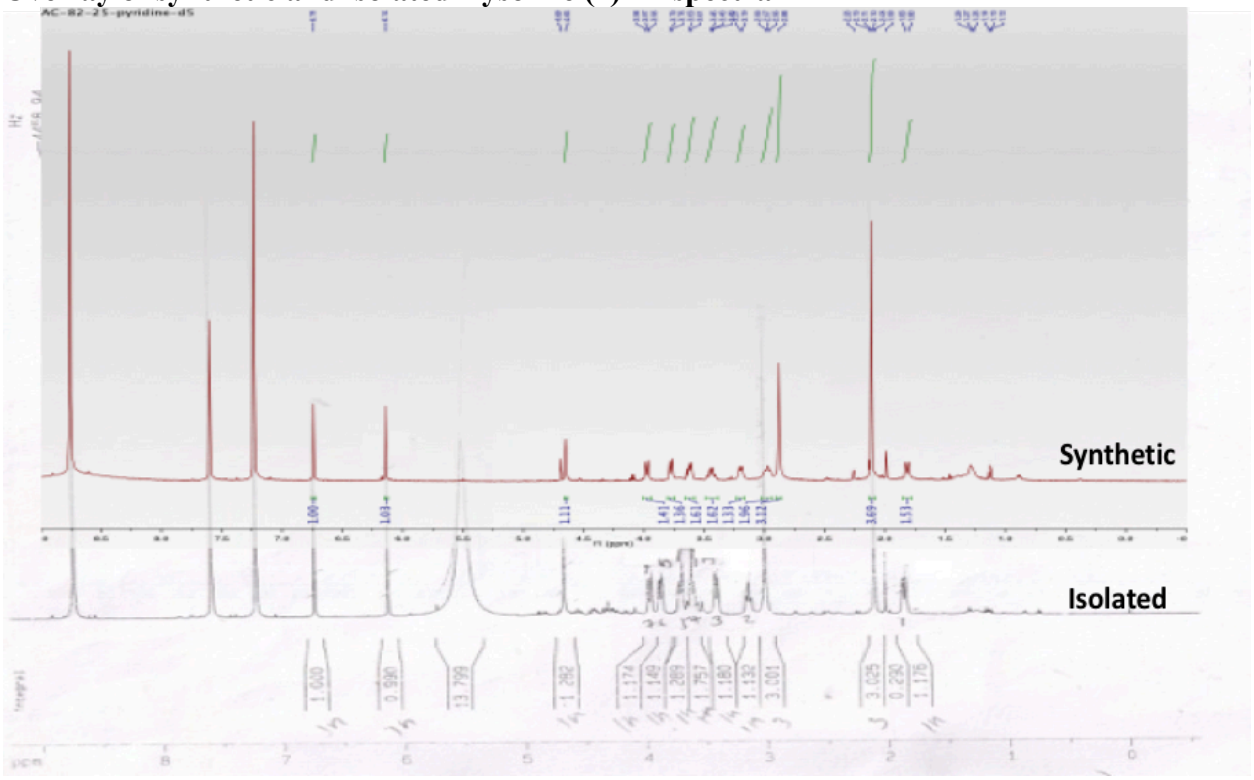
HSQC - Methanol-d_4, 25 °C, 600 MHz



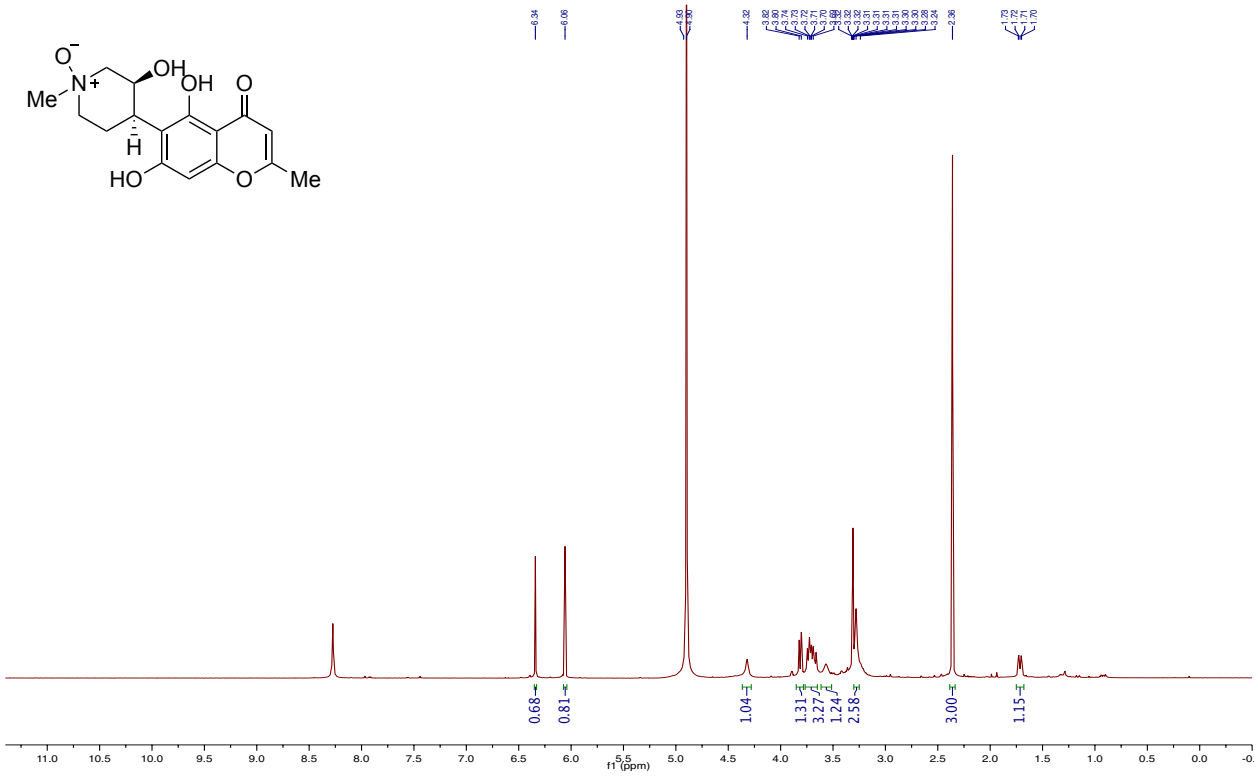
HMBC - Methanol-d_4, 25 °C, 600 MHz



Overlay of synthetic and isolated Dysoline (1) ^{1}H spectra



Dysoline-*N*-Oxide (2.340)
^{1}H - Methanol-*d*$_4$, 25 °C, 600 MHz



^{13}C - Methanol-*d*$_4$, 25 °C, 150 MHz