UNIVERSITY OF CALIFORNIA, SAN DIEGO

Synthesis of Natural and Designed Antitumor Agents: Epothilones and Thailanstatin A

A dissertation submitted in partial satisfaction of the

requirements for the degree

Doctor of Philosophy

in

Chemistry

by

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2016

The dissertation of Derek James Rhoades is approved, and it is acceptable for quality and form for publication on microfilm and electronically:

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DEDICATION

This work is dedicated to my beautiful wife, Amanda, and to our future together.

EPIGRAPH

You aren't going to have good ideas, unless you have lots of ideas, and some sort of principle of selection.

–Linus Pauling

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LIST OF ABBREVIATIONS

18-Cr-6	18-crown-6
Ac	acetyl
Acac	acetylacetonyl
AcOH	acetic acid
ACP	acyl carrier protein
ADC	antibody drug conjugate
AIBN	2,2'-azo *bis*isobutyronitrile
AIOM	asymmetric intramolecular oxa-Michael
aka	also known as
aq.	aqueous
Ar	aryl (substituted aromatic ring)
atm	1 atmosphere = 10^5 Pa (pressure)
Boc	*tert*-butoxycarbonyl
bp	boiling point
Bu	butyl
n-BuLi	*n*-butyl lithium
t-BuLi	*tert*-butyl lithium
°C	degrees Celsius
ca.	circa (approximately)
calcd	calculated
cat.	catalytic
$CDCl_3$	deuterated chloroform

$CHCl_3$	chloroform
CH_2Cl_2	methylene chloride
CH_3OH	methanol
CI	chemical ionization
CM	cross metathesis
conc.	concentrated
Cp	cyclopentadienyl
CSA	(±)-camphor-10-sulfonic acid
Cy	cyclohexyl
d	doublet
dba	dibenzylideneacetone
DBU	1,4-diazabicyclo[5.4.0]undec-7-ene
DCE	1,1-dichloroethane
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
dddd	doublet of doublet of doublet of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
ddt	doublet of doublet of triplets
dr	diastereomeric ratio
dt	doublet of triplets
DET	diethyl tartrate
DHP	3,4-dihydro-2*H*-pyran

DIBAL	diisobutylaluminum hydride
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	dimethylformamide
DMP	Dess–Martin periodinane
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
dppf	diphenylphosphinoferrocene
dr	diastereomeric ratio
EC_{50}	half maximal effective concentration
ee	enantiomeric excess
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
EDG	electron donating group
equiv	equivalents
ESI	electrospray ionization
Et	ethyl
EtOH	ethanol
Et_3N	triethylamine
EtOAc	ethyl acetate
EWG	electron withdrawing group
FDA	Food & Drug Administration (U.S. government)
FT	fourier transform

g	gram(s)
GI_{50}	50% growth inhibition
GPCR	G-protein coupled receptor
GTP	guanosine triphosphate
h	hours (length of reaction time)
H-bond	hydrogen bond
HCl	hydrochloric acid
Het	heterocycle
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol (hexafluoroisopropanol)
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HWE	Horner–Wadsworth–Emmons
i	iso
IC_{50}	50% inhibitory concentration
Ipc	isopinocampheyl
IR	infrared
KHMDS	potassium *bis*(trimethylsilyl)amide
L	liter
LAH	lithium aluminum hydride
LDA	lithium diisopropylamine
LiHMDS	lithium *bis*(trimethylsilyl)amide
m	meta

m	multiplet
M	molar
*m*CPBA	3-chloroperoxybenzoic acid
MDR1	multidrug resistance protein 1 (also known as P-gp)
Me	methyl
MeOH	methanol
MHz	megahertz
mmol	millimole
mL	milliliter
mp	melting point
MsCl	mesyl chloride
MTBE	methyl *t*-butyl ether
n	normal (*e.g*. unbranched alkyl chain)
NaHMDS	sodium *bis*(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NCI	National Cancer Institute (U.S. government)
NIH	National Institutes of Health (U.S. government)
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine-*N*-oxide
NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NRPS	non-ribosomal polypeptide synthetase

o	ortho
p	para
PCP	peptidyl carrier protein
P-gp	P-glycoprotein (also known as MDR1)
Ph	phenyl
Phth	pthalimide
PKS	polyketide synthase
PMB	*p*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
i-Pr	isopropyl
PTLC	preparative thin layer chromatography
Py	pyridine
quant.	quantitative
R_f	retention factor (in chromatography)
s	singlet
SAR(s)	structure-activity relationship(s)
SEM	2-(trimethylsilyl)ethoxymethyl
SMC	small molecule conjugate
t	tertiary
t	triplet
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate

TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBHP	*tert*-butyl hydroperoxide
TBS	*t*-butyldimethylsilyl
Teoc	2-(trimethylsilyl)ethoxycarbonyl
TES	triethylsilyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
THP	2-tetrahydropyranyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Tr	trityl (triphenylmethyl)
Ts	*p*-toluenesulfonyl
UV	ultraviolet

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just to name a few. A special shout out to “The Chinese Mafia” is also warranted, as their ever-existing presence in the lab was a major reason why I chose not to leave this group. We humans thrive on inspiration, and thus I am thankful I could glean some from my colleagues during the tumultuous times when I lost mine.

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Chapter 1 is a partial reprint of the material as it appears in “Synthesis and Biological Evaluation of Novel Epothilone B Side Chain Analogues, K.C. Nicolaou, D. Rhoades, Y. Wang, S. Totokotsopoulos, R. Bai, E. Hamel, *ChemMedChem* **2015**, *10*, 1974–1979 (D. Rhoades did all of the synthetic chemistry).” Chapter 1 is also a partial reprint of material that has yet to be published, with K.C. Nicolaou, Y. Wang, R. Bai, and E. Hamel as co-authors (D. Rhoades and Y. Wang equally contributed to all of the synthetic chemistry). Chapter 2 is a partial reprint as it appears in “Total Synthesis of Thailanstatin A, K.C. Nicolaou, D. Rhoades, M. Lamani, M.R. Pattanayak, S.M. Kumar, *J. Am. Chem. Soc.* **2016**, *138*, 7532–7535 (D. Rhoades did all of the synthetic chemistry).”

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Publications

6. Nicolaou, K. C., Wang, Y.,* **Rhoades**, **D**.* Synthesis and biological evaluation of aziridinyl epothilone B analogues. *Manuscript in preparation*, (*co-first author).

5. Nicolaou, K. C., **Rhoades**, **D**., Lamani, M., Pattanayak, M., Kumar, S. M. Total synthesis of thailanstain A. *J. Am. Chem. Soc.* **2016**, *138*, 7532–7535.

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2. Kinder, D. H., **Rhoades**, **D**. **J**., Mahfouz, T. M. Modeling of σ_2 selective agonists for the development of new anticancer agents that utilize the celecoxib scaffold. In: Proceedings of the 101st Annual Meeting of the American Association for Cancer Research (AACR); 2010 Apr 17–21; Washington, D. C.: AACR; Cancer Res **2010**, *70*, Abstract 737.

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ABSTRACT OF THE DISSERTATION

Synthesis of Natural and Designed Antitumor Agents:
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Doctor of Philosophy in Chemistry

University of California, San Diego, 2016

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The epothilones are an intriguing class of natural products and a classic in total synthesis. Their remarkable biological properties have been under investigation for the last two decades and endeavors into their synthesis reached levels of global intensity. Clinical trials of natural and designed epothilones are currently ongoing, and one derivative is approved by the U.S. Food and Drug Administration (FDA). In spite of the massive attention that the epothilones, in particular epothilone B, have enjoyed over the years, the excitement has waned since its initial burst in the mid 1990's. This was mostly due to their generally narrow therapeutic window. However, the continuing maturation of various selective drug delivery systems, such as antibody drug conjugates (ADCs), has provoked

a renaissance for designed analogues of the epothilones and other natural products that were originally pursued but ultimately abandoned because of undesired side effects stemming from their potency and their specific formulation. Thus, Chapter 1 of this dissertation describes the molecular design and synthesis of epothilone B analogues that possess attachment sites suitable for conjugation to ADCs or related systems. These analogues were synthesized utilizing a Stille coupling protocol with the historically successful macrocyclic vinyl iodide **1.33** and novel *N*-arylpyrazolyl stannanes as the coupling partners. As a further development, the use of an aziridine functional group as an isosteric replacement for the epoxide moiety of epothilone B was investigated. These efforts culminated in the discovery of a convenient, commercially viable route for accessing a plethora of novel aziridinyl epothilone B analogues in seven steps from natural epothilone B. Highlights of this synthesis include the recently developed Ess–Kürti–Falck aziridination, and an in-depth survey of the Horner–Wadsworth–Emmons reaction and its related Still–Gennari modification as it relates to *β*-heteroaryl phosphonates, an understudied yet highly valuable class of compounds for the synthesis of complex heterocycles.

Thailanstatin A is a recently isolated natural product with impressive therapeutic potential. Its unique mechanism of action as a potent inhibitor of the spliceosome, as well as its structural features which are naturally tailored to accommodate ADCs or related technologies, prompted its total synthesis. Chapter 2 of this dissertation describes the total synthesis of thailanstatin A, which was accomplished in a longest linear sequence of 9 steps from readily available starting materials. The tetrahydropyran components of this molecule conveniently derive from cheap chiral pool materials, L-threonine and D-glucal, and a final

stage Suzuki coupling between advanced vinyl iodide and vinyl boronate pinacol ester intermediates was employed to deliver the target molecule in a reliable manner. A key methodological development realized en route to the target was the oxa-Michael/hydrogenation sequence of an $\alpha,\beta,\gamma,\delta$-unsaturated aldehyde to enable diastereodivergent access to highly substituted tetrahydropyrans. The high utility of this approach is currently guiding the exploration of designed analogues of this natural product, the results of which will provide potential lead compounds for therapeutic candidates and add new insights into the SARs of this intriguing class of bioactive compounds.

Chapter 1: Synthesis and Biological Evaluation of Novel Epothilone B Analogues

A. Introduction

1. Isolation

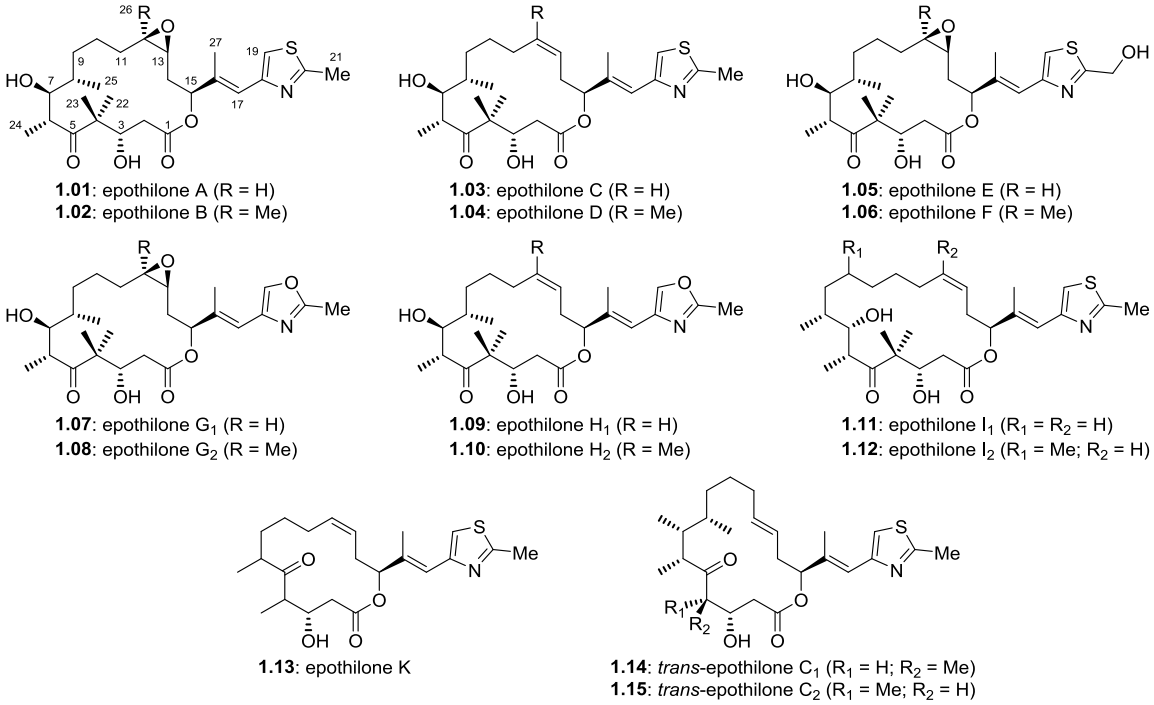


Figure **1.01**: Molecular structures of epothilones **1.01**–**1.15**.

The epothilone family (Figure **1.01**) of natural products represents, arguably, the world's largest endeavor in synthetic organic chemistry.[1] This was due to an avalanche of excitement that was triggered in the wake of one of the most clinically successful chemotherapeutics to date: the taxanes.[2] However, the realization of their vast biomedical potential was far from immediate, and, in a similar fashion to the taxanes, nearly a decade would pass before industry and academia alike caught on to their clinical promise.

In 1985, Reichenbach isolated the myxobacterium strain *Sorangium cellulosum* (strain So ce90) from a soil specimen taken from the coasts of the Zambesi River in Mozambique in 1980, from which the epothilone family was originally discovered.[3] Presently, approximately 40 different natural epothilones have been isolated from various

strains of *Sorangium cellulosum*, the major isolates being epothilones A, B, C, and D (**1.01**–**1.04**, Figure **1.01**).[4] These natural products have not been observed in any other living organism, and occur in *ca.* 2% of known *Sorangium* species. It is noteworthy that myxobacteria, gram negative members of the δ-subgroup of proteobacteria, are a valuable source of bioactive secondary metabolites, and *Sorangium cellulosum* in particular is responsible for producing approximately 50% of all known myxobacterial secondary

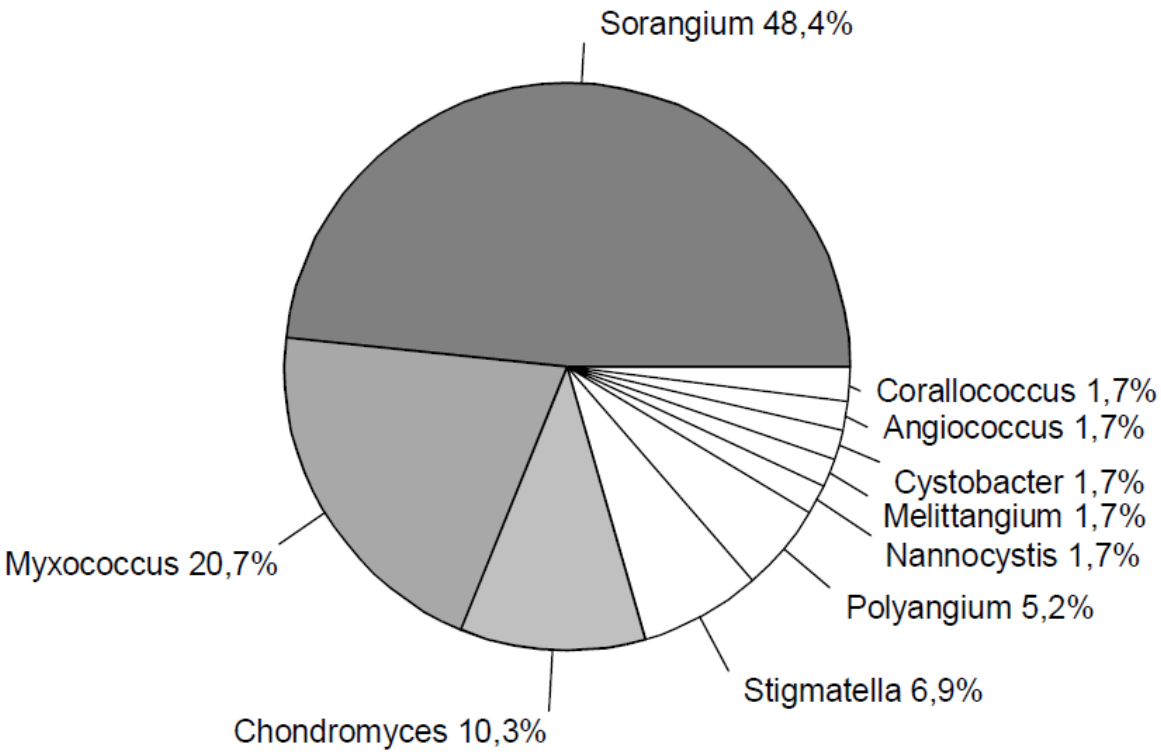


Figure **1.02**: Distribution of secondary metabolites isolated from myxobacteria by genus.

metabolites (Figure **1.02**).[5] Figure **1.03** depicts common visual characteristics of *Sorangium cellulosum* colonies (Figure **1.03**a), which possess swarming growth patterns (Figure **1.03**b and **1.03**c), fruiting bodies (**Figure 1.03**d), adherence to/growth on cellulose (Figure **1.03**e and **1.03**f), the propensity to form biofilms, and the displaying of 'wolfpack' behavior.[6]

Seven years after the soil sample collection, epothilones A and B (**1.01** and **1.02**, Figure **1.01**) were identified and originally noted for their antifungal activity; this was not surprising, and rather expected, given that unlike bacteriostatic organisms, myxobacteria are cellulolytic organisms that compete in their natural habitat with biodegrading fungi for their common energy source, cellulose (Figure **1.03**e).[6] The absolute configurations of **1.01**

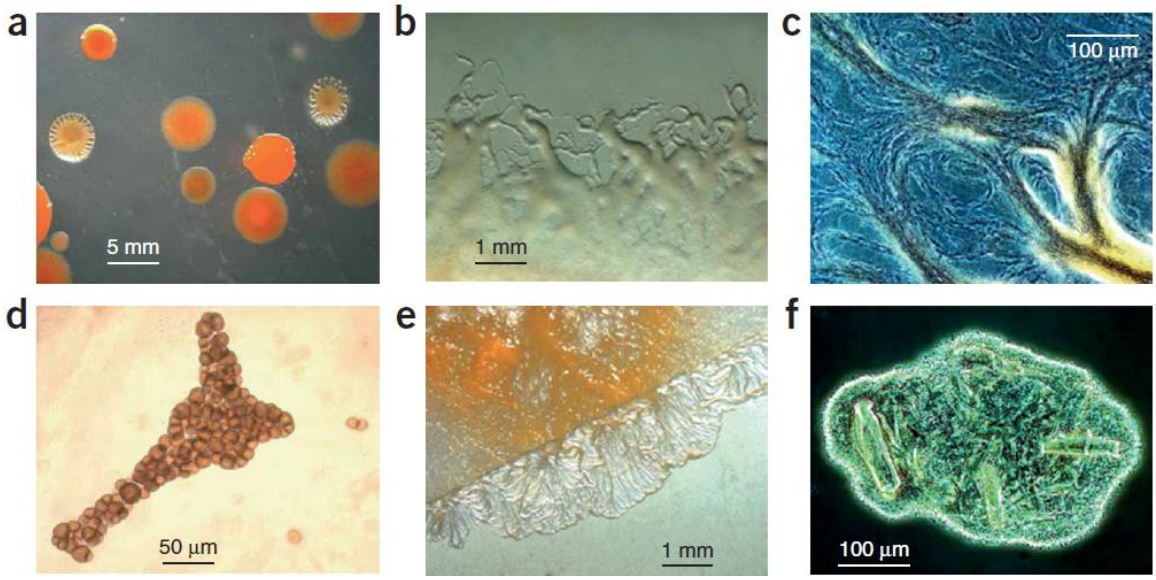


Figure **1.03**: *S. Cellulosum* colonies (a), swarming growth patterns (b and c), fruiting bodies (d), and growth (e) and adherence (f) to cellulose.

and **1.02** were revealed by X-ray crystallography in 1987, but not reported in the literature until 1996 by Höfle.[7] Since cytotoxic properties were noted alongside their fungicidal activities, the epothilones were abandoned as potential antifungals for agricultural purposes and shelved for several years. Then in 1995 they were rediscovered by Merck and reported as compounds with a taxane-like mechanism of action, which immediately garnered strong attention and pursuit from the drug development community.[8]

The term epothilone was eventually coined as a portmanteau of three of its prominent structural features: its epoxide, its thiazole ring, and its ketone functionality. Its prototypical scaffold consists of a 16-membered macrolactone ring with a *β*-hydroxy ketone moiety, a 2-methylthiazole side chain with a trisubstituted diene spacer, and a di- or trisubstituted epoxide (*e.g.* **1.01** and **1.02**, Figure **1.01**) or (*Z*)-olefin (*e.g.* **1.03** and **1.04** Figure **1.01**) functionality, respectively. However, as previously mentioned,[4] other minor epothilones with variated structures do exist, such as 2-hydroxymethylthiazolyl containing epothilones E and F (**1.05** and **1.06**, **Figure 1.01**), oxazole containing epothilones G and H (**1.07**–**1.10**, Figure **1.01**), 18-membered epothilones I (**1.11** and **1.12**, Figure **1.01**), 14-membered epothilone K (**1.13**, Figure **1.01**), and 12,13-(*E*) olefinic isomer *trans*-epothilone C (**1.14** and **1.15**, Figure **1.01**).[4] The variety of structures displayed from the minor epothilones suggests multiple points of promiscuity (*i.e.* relaxed substrate specificity) in its myxobacterial biosynthetic machinery.

2. Biosynthesis and Fermentation

Biosynthetic pathways for myxobacterial polyketides generally fall into 3 main categories: polyketide synthases (PKS, usually type I), non-ribosomal polypeptide synthetase (NRPS), or a hybrid of the two.[9] Epothilones fall into the latter category– the macrocyclic core derives from PKS origin, while the thiazole side chain derives from NRPS origin; these multienzyme, assembly-line type complexes are responsible for generating the remarkable chemical diversity, oftentimes with desirable pharmacological properties, that has popularized the secondary metabolite profile of *Sorangium cellulosum*.[10] Interestingly, the epoxide is introduced at a late stage on the corresponding 12,13-olefinic precursors *via* a molecular oxygen dependent cytochrome P450 oxidase

enzyme (termed EpoK), and thus these natural products are further tailored by a wholly separate enzyme superfamily.[11]

The biosynthesis of the epothilones has been investigated in rigorous detail. Early biosynthetic studies established that acetate (from malonyl-CoA), propionate (from methylmalonyl CoA), the methyl group of *S*-adenosyl-methionine (SAM), and cysteine are the building blocks for the carbon skeleton.[12] Figure **1.04** depicts the proposed biosynthesis, which starts (module 0) as a prototypical PKS-derived acyl carrier protein (ACP) tethered thioester, passes off an acetate starter unit to the NRPS-derived peptidyl carrier protein (PCP) in module 1, where the thiazole is formed, and is then transferred back to the PKS system where further chain elongations and oxidations occur prior to macrocyclization (lactone formation) and final epoxidation.[13] The successful sequencing,

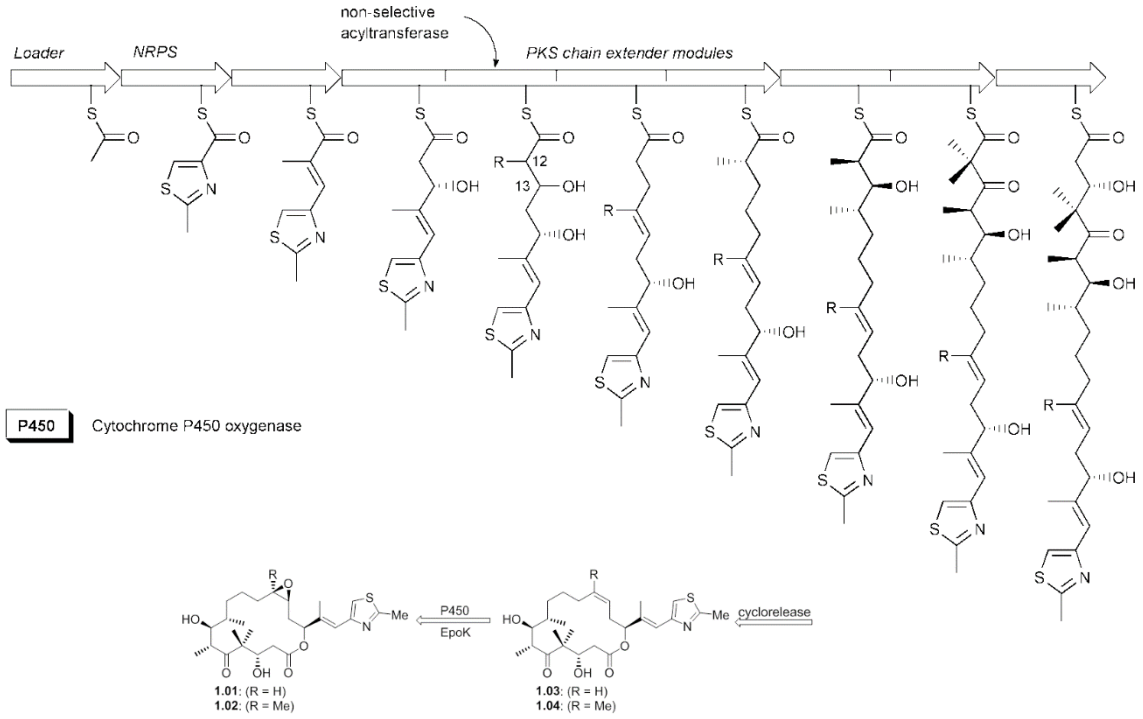


Figure **1.04**: Proposed biosynthesis **1.01** and **1.02** through a hybrid PKS/NRPS system with a late stage, cytochrome P450-mediated epoxidation of **1.03** and **1.04**.

cloning, and heterologous expression of the epothilone gene cluster into *Escherichia coli* and other more rapidly reproducing microogranisms (the doubling time of *Sorangium cellulsoum* strains can be as long as three days) quickly led to improved fermentation routes optimized for the production of the major epothilones (**1.01**–**1.04** Figure **1.01**), where multigram quantities could be recrystallized from massive broths (upwards of 700 L).[14] Because of the cost effectiveness of this approach *vis-à-vis* total synthesis [one exception is sagopilone (**1.20**, Figure **1.07**), which is currently in clinical trials and is a totally synthetic epothilone analogue (44 steps)],[15] the majority of pharmaceutical companies have pinned their interest on molecular scaffolds which can be synthesized from the natural product itself, and these will be presented in due course. However, it is crucial to mention that the ability to glean **1.02** directly *via* fermentation inspired a creative, commercially viable approach to a new generation of novel epothilone B analogues synthesized and biologically evaluated in this dissertation.

3. Mechanism of Action, Clinical Candidates, Potent Analogues, and Structure-Activity Relationships

The epothilones, like the taxanes, are members of a privileged class of pharmacologic agents known as microtubule stabilizers.[16] Generally speaking, they are also known colloquially as "spindle poisons" (Figure **1.05**), referring to the tubulin protein that they bind to *in vitro* and *in vivo*, which is the fundamental unit comprising microtubules that are essential for normal cell functioning and undergo a rapid guanosine triphosphate (GTP)-mediated polymerization/depolymerization process during mitosis; microtubules are heterodimeric proteins, in which α and β tubulin subunits dimerize in a head-to-tail fashion to form hollow tubes with an outer diameter of *ca*. 25 nM; they play a prolific role

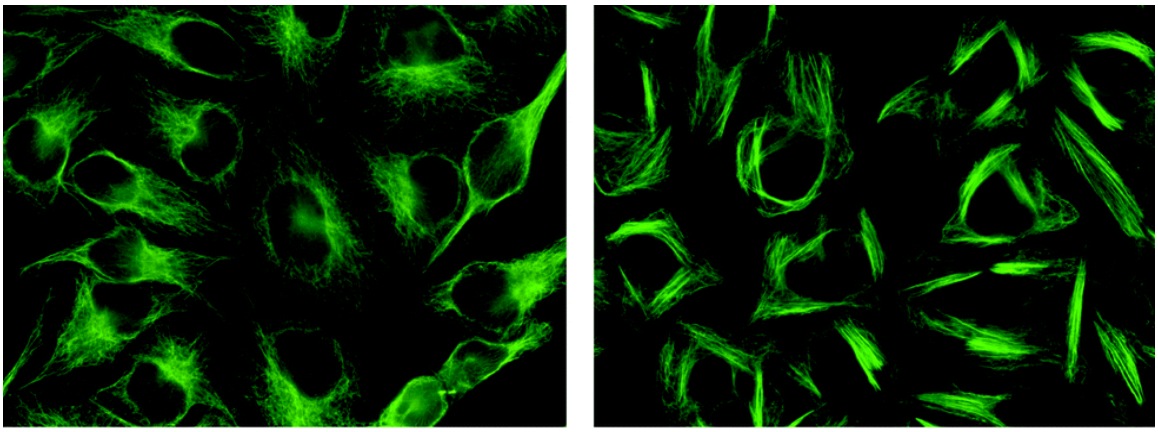


Figure **1.05**: Effects of microtubule stabilizing agents on HeLa cells.

in cell division, and their disruption causes cell cycle arrest ($G_2 \rightarrow M$ transition) and subsequent apoptosis (Figure **1.06**, top).[17] All drugs known to bind tubulin in humans bind to the β subunit; furthermore, a plethora of tubulin binding agents have been reported and characterized, and many of them are shown in Figure **1.06** (bottom), which displays both tubulin stabilizing and destabilizing agents, as well as their proposed, oftentimes distinct binding site to the tubulin protein, relative to one another.[18]

Although paclitaxel has enjoyed success in the realm of chemotherapeutics, there is clearly more work to be done not only in terms of developing safer and more effective drugs, but also the basic science underpinnings of how tubulin works. Indeed, the complex intracellular signaling that pervades the tubulin polymerization/depolymerization process is daunting, and at least four (likely more) isoforms of β tubulin are thought to exist.[19] Furthering the understanding of this clinically successful drug target will undoubtedly assist the next generation of anti-mitotic therapeutics, both in terms of selectivity and potency, as well as how to avoid or overcome resistance that may develop due to tubulin mutations.[20] Even though a multitude of binding and docking studies have been carried out

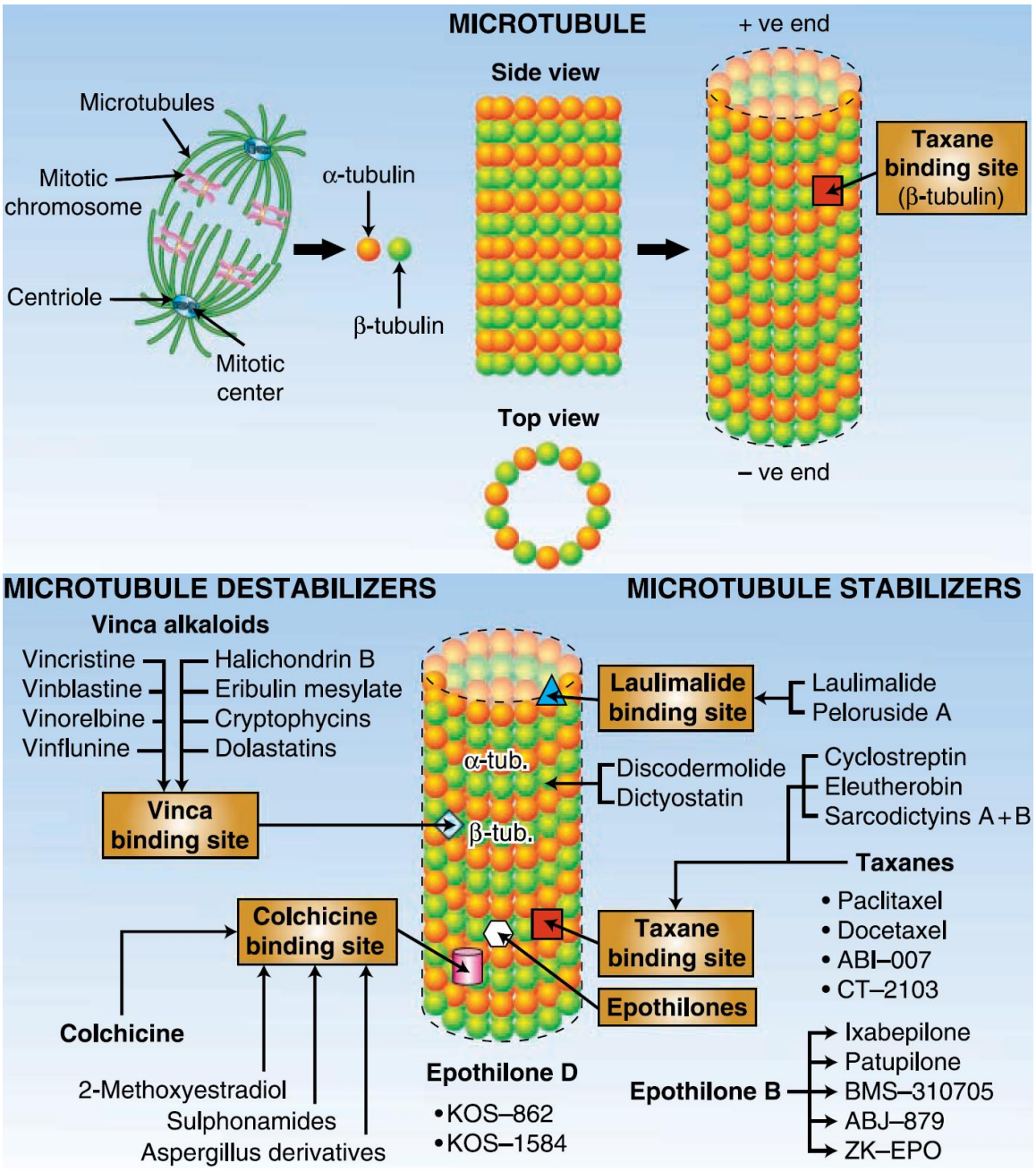


Figure **1.06**: (Top) Summary graphic of tubulin. (Bottom) Summary graphic of many (not comprehensive) tubulin stabilizing and destabilizing agents.

with epothilones **1.01**–**1.04** (Figure 1.01) over the years, including, computational, crystallographic, and NMR solution experiments, it is generally unclear how effectively these results, obtained in artificial, *ex vivo* systems, actually translate into a reliable

structure-based drug design platform.[21] This is also because tubulin (as can be seen by its multiple putative binding sites in Figure **1.06**) is not the prototypical drug target, from a pharmacological perspective. In my opinion, I believe it is quite unique because it is a large polymeric drug target, constantly being rebuilt and deconstructed; thus, several possible binding modes exist in this dynamic setting, and the propensity for allostery with such a large complex is all but guaranteed, but not clearly elucidated. Therefore, tubulin as a pharmacological target clearly differentiaties itself from drugs that target, for example, G-

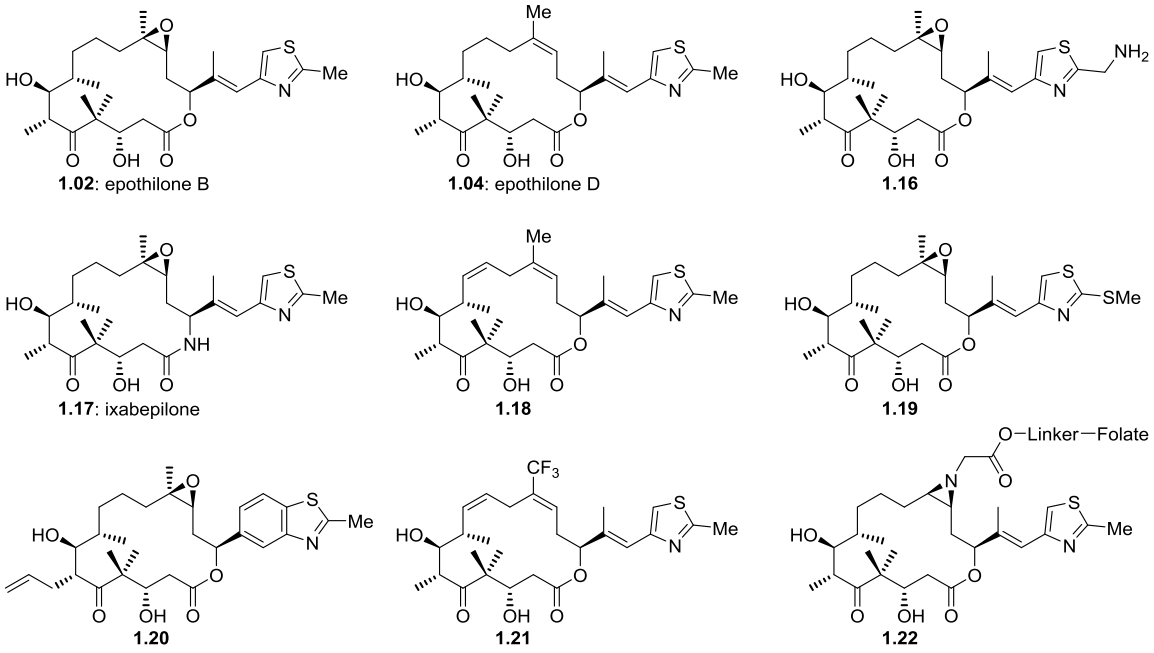


Figure **1.07**: Molecular structures of current and previous clinical candidates, natural products **1.02** and **1.04**, and designed analogues **1.16**–**1.22**.

protein coupled receptors (GPCRs), enzyme active sites, or even various areas of the DNA backbone, which possess a much smaller and specific area for drug binding.[22]

The epothilones are unique in that a few of the natural products (*i.e.* **1.02** and **1.04**, Figure **1.07**) themselves were introduced into clinical trials, similar to the classical antibiotics penicillin and tetracycline. Figure **1.07** shows a selection of clinical candidates

and potent epothilone analogues, most of which possess the epothilone B scaffold. As of the time of this writing, a Phase II clinical trial for **1.02** (EPO906/patupilone) has been published, and Kosan is still continuing with its development of **1.04** (KOS-1584), with Phase II trials in progress and a phase I study published, however its partner Roche has recently withdrawn its initial support, and Kosan has since been acquired by Bristol-Myers Squibb (BMS).[23] BMS is currently the only pharmaceutical company with a clinically approved epothilone, ixabepilone (**1.17**, Figure **1.07**).[24] Other clinically developed candidates by BMS include 21-methylamino thiazole derivative **1.16** (BMS-310705) and 12,13-aziridinyl folate conjugate **1.22** (BMS-753493), both of which possess published clinical trial data, but have since been discontinued.[25, 26] It is noteworthy that **1.22** is the only clinical candidate known to possess the less potent epothilone A (26-desmethyl) scaffold, due to the inherent limitations of its synthetic preparation. 20-desmethyl-20-methylsulfanyl-epothilone B **1.19** (ABJ879) was made in this lab during a previous collaboration with Novartis, and is among the most potent epothilones synthesized in the Nicolaou laboratory; however, clinical pursuit of this promising candidate was also

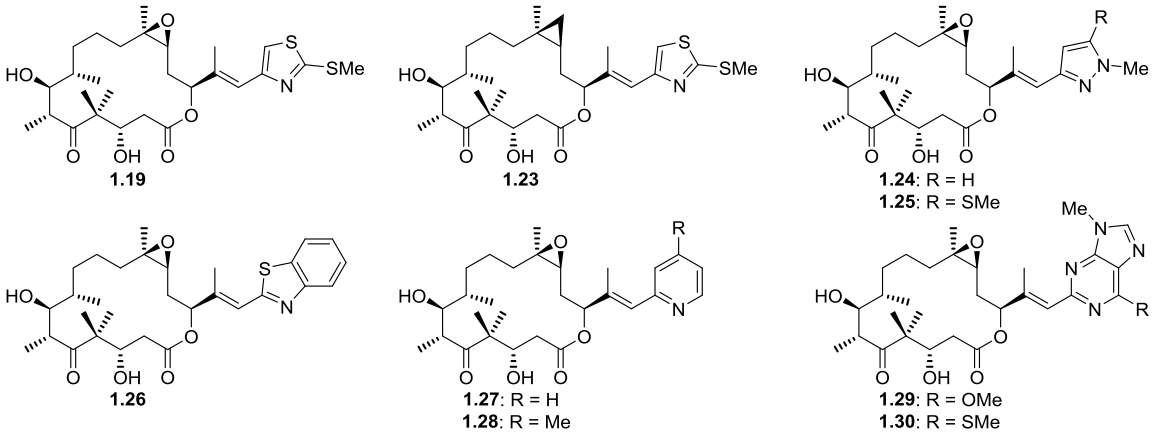


Figure **1.08**: Molecular structures of potent epothilone B analogues **1.19** and **1.23**–**1.30** synthesized in the Nicolaou laboratory.

discontinued in early human studies.[27] The 9,10-olefinic analogues **1.18** and **1.21** are potent compounds with increased structural rigidity owing to the extra degree of unsaturation within the macrocycle and are still alive in the clinical pipeline.[28] Lastly, the fully synthetic analogue **1.20** is being pursued by Bayer-Schering, and is also still in development.[15, 29]

Figure **1.08** shows the most potent epothilone B analogues synthesized in the Nicolaou laboratory, with former clinical candidate **1.19** and methylthio pyrazole derivative **1.25** being the most potent. 12,13-cyclopropyl epothilone B **1.23** is an active epoxide isostere, and other heteroaromatic side chains including benzothiazole (**1.26**), pyridine (**1.27** and **1.28**), pyrazoles (**1.24** and **1.25**), and purines (**1.29** and **1.30**) are as potent are more potent than natural **1.02**. Thus, the most apparent structure-activity relationships (SARs) for side chain analogues is the requirement for a nitrogen-containing heterocycle, with considerable tolerance for sterics. In addition, electron rich heterocycles tend to increase potency, which adds to the belief that the N atom participates as a crucial

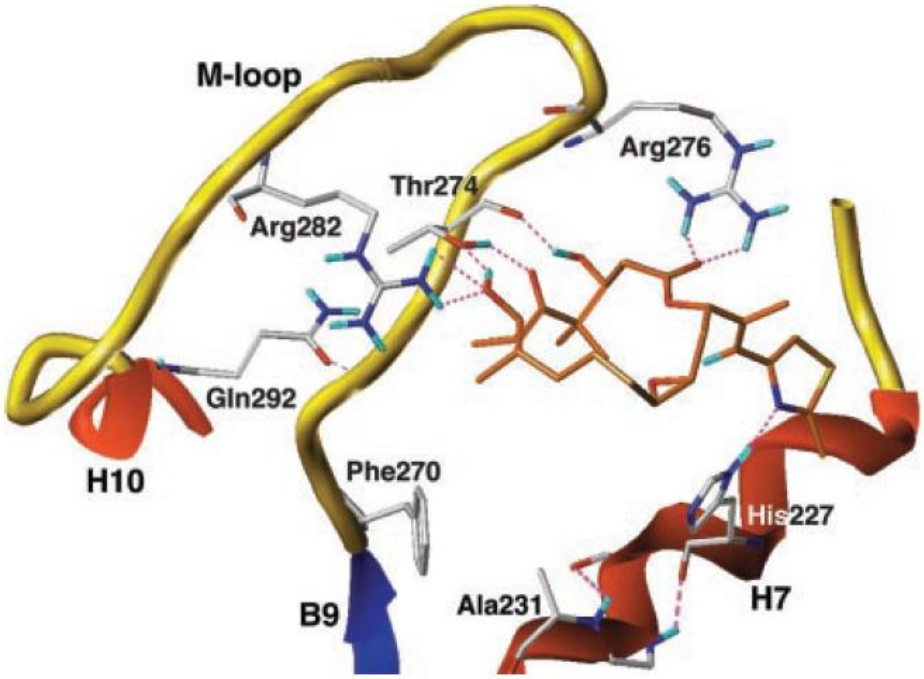
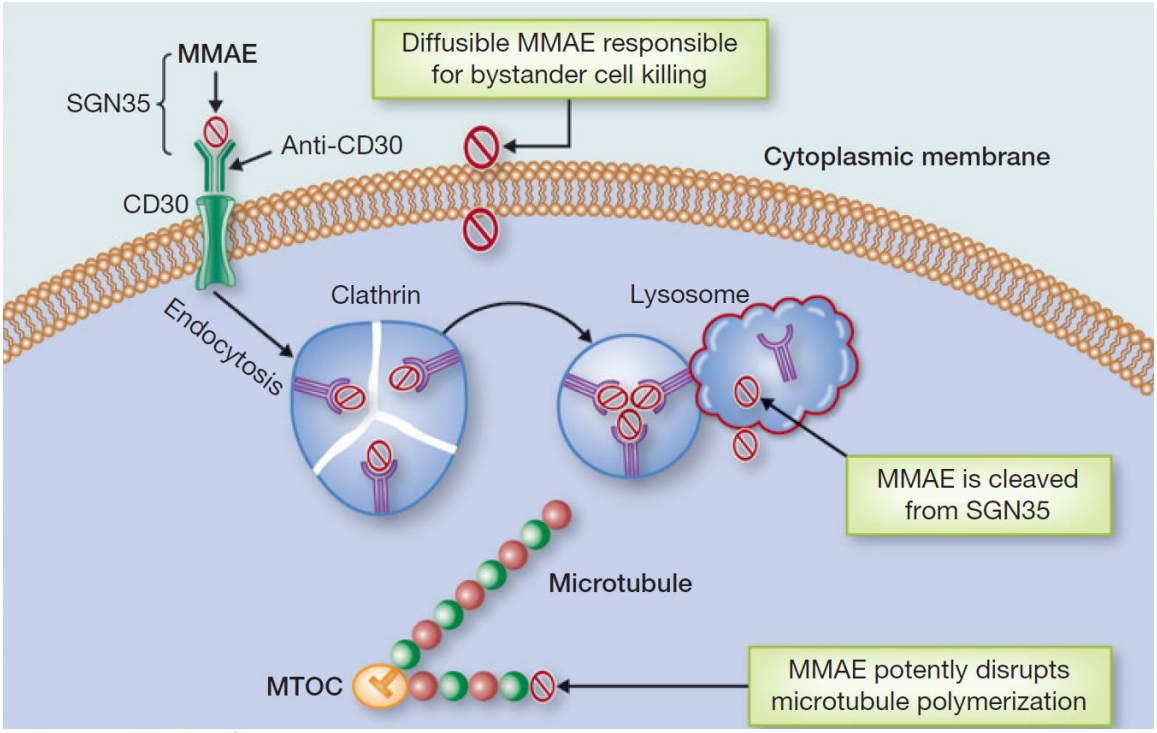
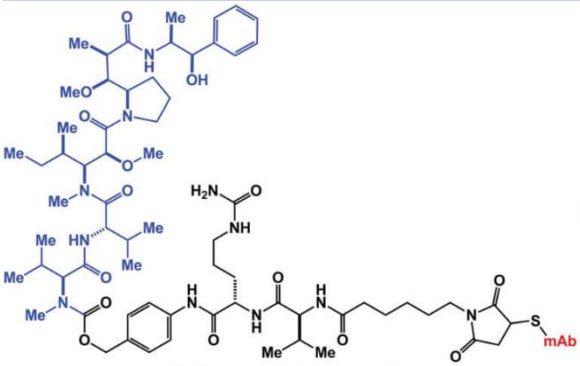
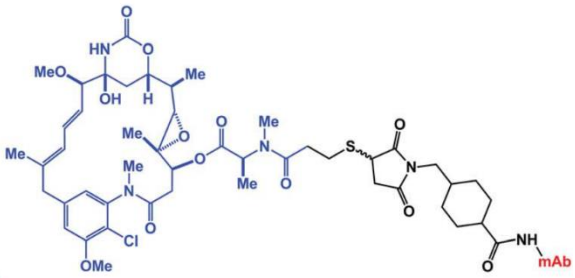


Figure **1.09**: X-ray crystal structure of **1.01** bound to β tubulin





1.31: brentuximab vedotin



1.32: trastuzumab emtansine

Figure **1.10**: (Top) General mechanism of action of **1.31** *via* a CD30-dependent, monoclonal antibody (mAb) directed targeting to lymphoma cells, internalization into degradative lysosomes, and finally release of the cytotoxic payload for disruption of the microtubule organizing center (MTOC) and subsequent cell death. (Bottom) Molecular structures of brentuximab vedotin (**1.31**) and trastuzumab emtansine [(**1.32**); the natural product structures are shown in blue, the linker in black, and the mAb in red.]

hydrogen bond (H-Bond) acceptor with a histidine residue of β tubulin (Figure **1.09**).[21d]

Taking this into account, as well as the remarkable number of side chain replacements that have been performed since the beginning of epothilone analogue studies, we were able to deduce a starting point for the design of a new generation of lead compounds based on previously gained SARs.[30] However, it is worthy to note that before

embarking on this project, we considered the prospect of selective drug delivery systems, such as antibody drug conjugates (ADCs), small molecule conjugates (SMCs), and similar technologies as a desirable option for any analogues that possess desirable potencies and drug-like properties.[31] Considering the only two currently FDA approved ADCs, brentuximab vedotin (Adecetris®, **1.31**, Figure **1.10**) and ado-trastuzumab emtansine (Kadcyla®, **1.32**, Figure **1.10**) both employ tubuling binding agents with potencies comparable to the epothilones as their cytotoxic payloads, we deemed it reasonable toapproach the design of novel epothilone B analogues in the context of this rapidly maturing field.[32]

Due to the copious amounts of synthetic studies of epothilones and the presence of excellent reviews of the subject,[1, 33] this section of the dissertation serves only as a brief overview with focus on the results of studies that have aided the design and synthesis of the new molecular structures presented in this dissertation and described in more detail moving forward.

B. Synthesis of Epothilone B Side Chain Analogues

1. Molecular Design

In a similar fashion to previous studies, we opted to pursue a library of novel side chains *via* the reliance on the Stille coupling as the key step, which has a track record of historical success in this laboratory.[34] Figure **1.11** depicts the general strategy for accessing designed analogues **1.34**–**1.43**. As a divergence from previously developed epothilone B pyrazole analogues (*e.g.* **1.24** and **1.25**, Figure **1.08**), we sought to endow this generation of analogues with an amino (NH_2) containing functionality for the purposes of conjugation

to various drug delivery systems, as described in the previous section. This required new syntheses of pyrazole stannanes (**B**, Figure **1.11**) as well as scaling up the known vinyl iodide **1.33**.

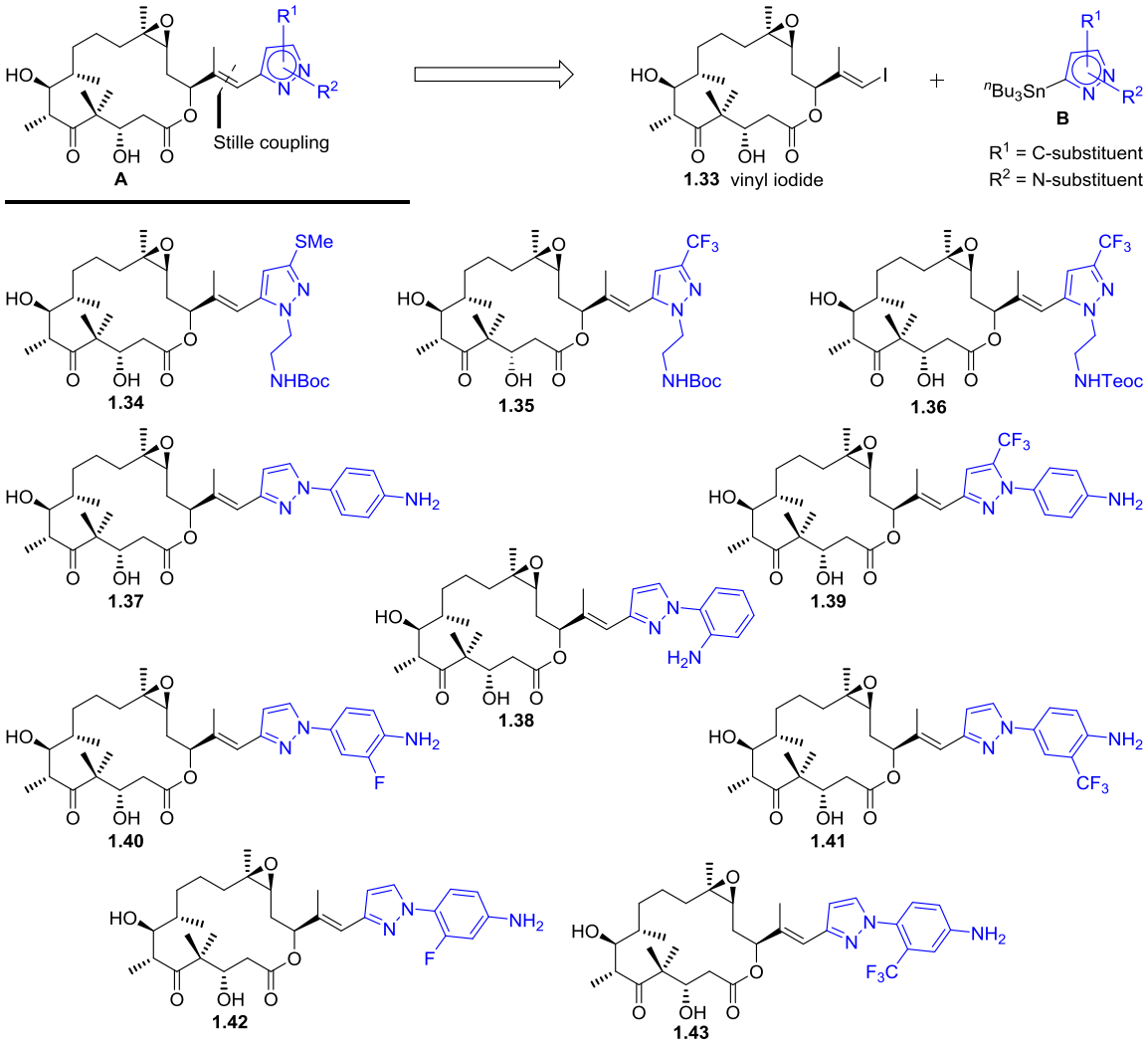
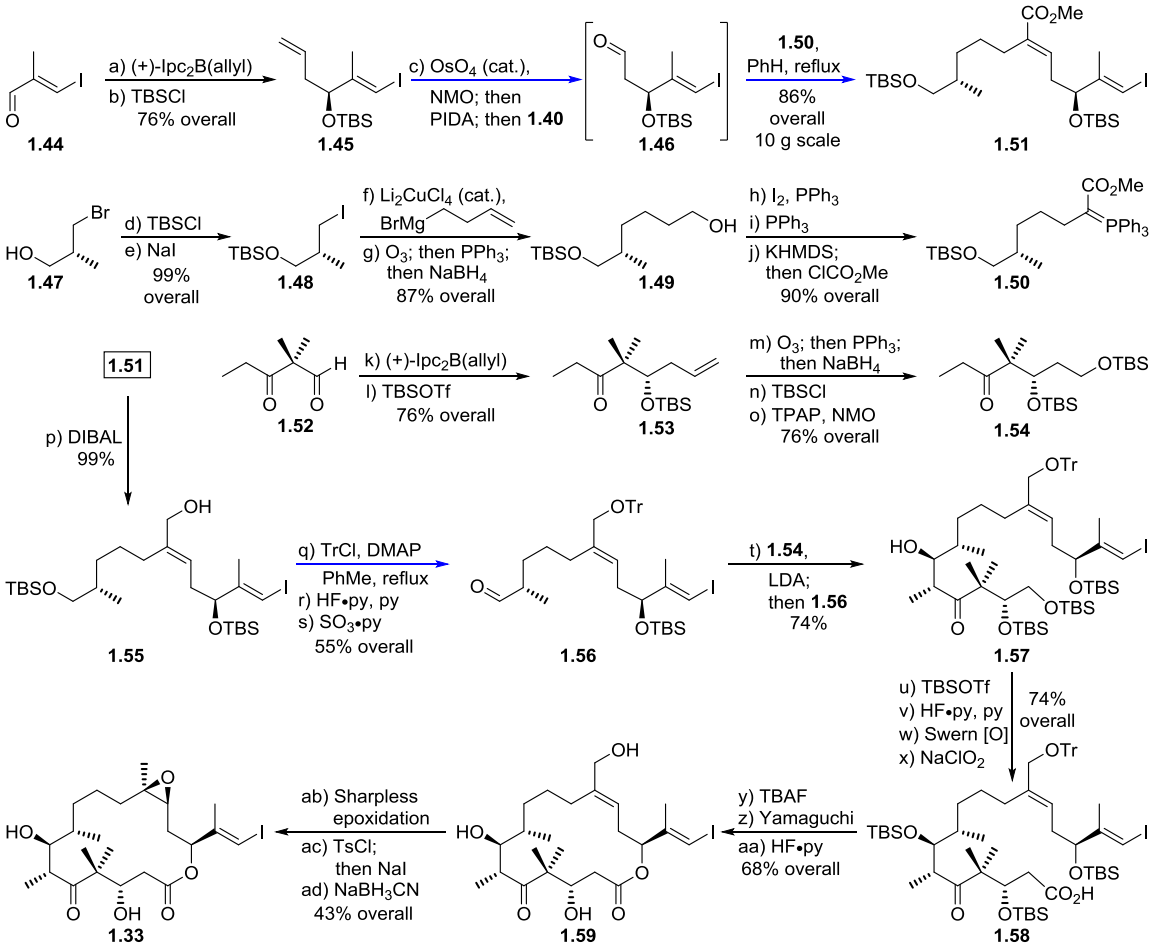


Figure **1.11**: A: General strategy for the synthesis of epothilone B side chain analogues (**A**) from vinyl iodide **1.33** and pyrazole stannanes (**B**), and synthesized epothilone B side chain analogues **1.34**–**1.43**.

2. Synthesis of Vinyl Iodide **1.33**

To facilitate the synthesis of several analogues, vinyl iodide **1.33** was prepared on large scale following a route that has been continuously improved over time,[34] with a few new optimizations incorporated herein. This route is summarized in Scheme **1.01**. The blue arrows represent points of optimization. Specifically, a convenient one pot procedure for the Wittig reaction between stabilized ylide **1.50** and aldehyde **1.46** (generated *in situ* from olefin **1.45** *via* a modified Upjohn's dihydroxylation protocol)[35] delivered northern fragment **1.51** in 86% on a decagram scale. Overall, this modification removed three steps and three purifications from the previous route. Another important modification was during



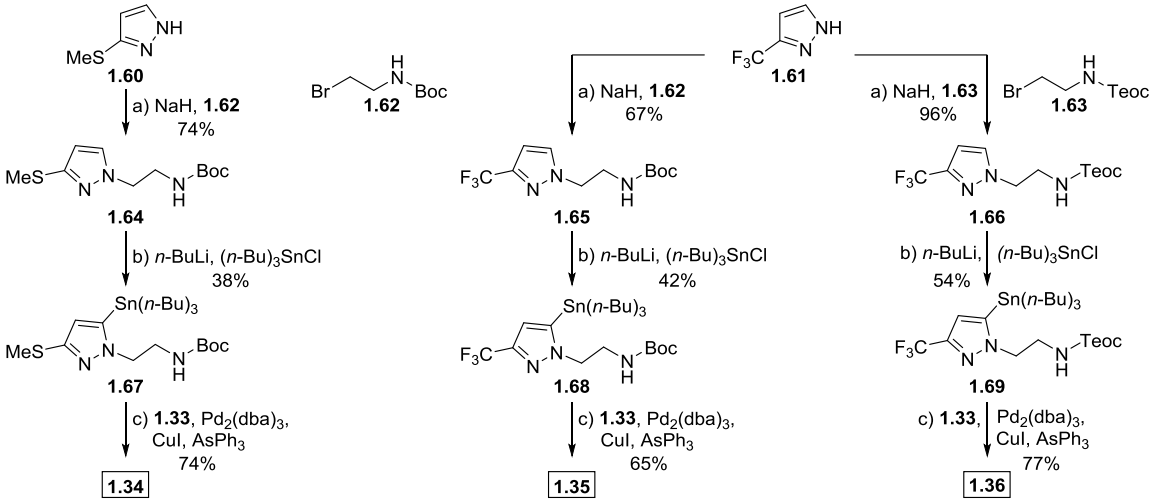
Scheme 1.01: Synthesis of vinyl iodide **1.33** [blue arrows are optimized steps (29 total steps)].

the triphenylmethyl protection step (step q, Scheme **1.01**). When this reaction is performed in DMF, scalability and reproducibility was a serious problem. Investigating early studies revealed that TrCl/DMAP salts are isolable complexes, and their reactivity is inversely proportional to the dielectric constant (*i.e.* polarity) of the reaction solvent, but also cannot be too nonpolar due to solubility issues with the substrate and precipitation of the DMAP-triphenylmethyl complex; ergo, a switch to PhMe as solvent remedied the situation and provided the protected allylic alcohol in 83% yield.[36] All of the other transformations shown in Scheme **1.01** were generally non-capricious in nature. A notable outlier is the two Brown's allylation reactions (steps a and k, Scheme **1.01**), where the magnesium salts following reagent preparation require careful filtration in order to produce optimal levels of *ee*.[37] Overall, this route is very dependable, and should further improvements ever be needed, protecting group/oxidation state manipulations (the two culprits for the high step counts of polyketide natural product total syntheses in general) would be an ideal place to begin.

3. Synthesis of Pyrazolyl Stannanes and Epothilone B Side Chain Analogues **1.34**–**1.43** *via* Stille Coupling

Scheme **1.02** summarizes the synthesis of Teoc-protected and Boc-protected aminoethyl pyrazole analogues **1.34**–**1.36** from the readily available building blocks 3-(methylthio)-1*H*-pyrazole (**1.60**)[38] and commercially available 3-(trifluoromethyl)-1*H*-pyrazole (**1.61**). Thus, alkylation of **1.60** with *N*-boc bromide **1.62** (prepared from the corresponding commercially available bromoamine by the standard method)[39] under basic conditions (NaH) led to pyrazole derivative **1.64** (74% yield) which was regioselectively stannylated through lithiation (*n*-BuLi), followed by addition of *n*-BuSnCl (38% yield).

Palladium-catalyzed coupling of the latter with vinyl iodide **1.33** ($Pd_2(dba)_3$, $AsPh_3$, CuI) furnished epothilone analogue **1.34** in 74% yield. Similar processing of trifluoromethyl



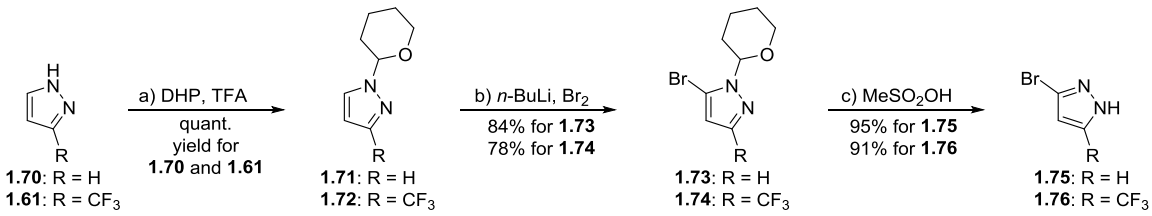
Scheme **1.02**: Synthesis of pyrazolyl stannanes **1.67**–**1.69** and analogues **1.34**–**1.36** *via* Stille coupling with vinyl iodide **1.33**.

pyrazole **1.61** employing *N*-boc protected bromide **1.62** and vinyl iodide **1.33** afforded epothilone analogue **1.35** [65% yield for the last step (**1.68** + **1.33** → **1.35**)] *via* intermediates **1.65** (67% yield) and **1.68** (42% yield). Analogue **1.36** was prepared from trifluoromethyl pyrazole **1.61** and *N*-Teoc protected bromide **1.63**[40] in a similar manner [42% yield for the last step (**1.69** + **1.33** → **1.36**)] *via* intermediates **1.66** (96% yield) and **1.69** (54% yield). It is noteworthy that **1.64**–**1.66**, **1.67**–**1.69**, and especially **1.34**–**1.36** exhibit signal splitting in their ^1H and ^{13}C NMR spectra, apparently due to hindered rotation (*i.e.* rotamers) around their bulky protecting groups (Boc and Teoc, respectively).

Several attempts to remove the Boc (Brønsted and Lewis acids) or Teoc (fluoride) groups from analogues **1.34**–**1.36** under various conditions in order to obtain the free amino epothilones were met with failure. TLC and LCMS analysis of reaction mixtures demonstrated liberation of the free amine, which decomposed rapidly. Concluding that the

strongly basic and nucleophilic nature of the so placed primary amino group was responsible for the lability of these transiently detected compounds, we proceeded with the design and synthesis of aniline-type analogues (*i.e.* **1.37**–**1.43**, Figure **1.11**). We reasoned that the less basic character of this moiety would abrogate its destructive effect on the molecule (which may be exerted intramolecularly or intermolecularly), and yet be reactive enough to form amide bonds for conjugation purposes. In addition, anilines are quite tolerant to the intended Stille coupling conditions such that a final deprotection step would not be necessary.[41]

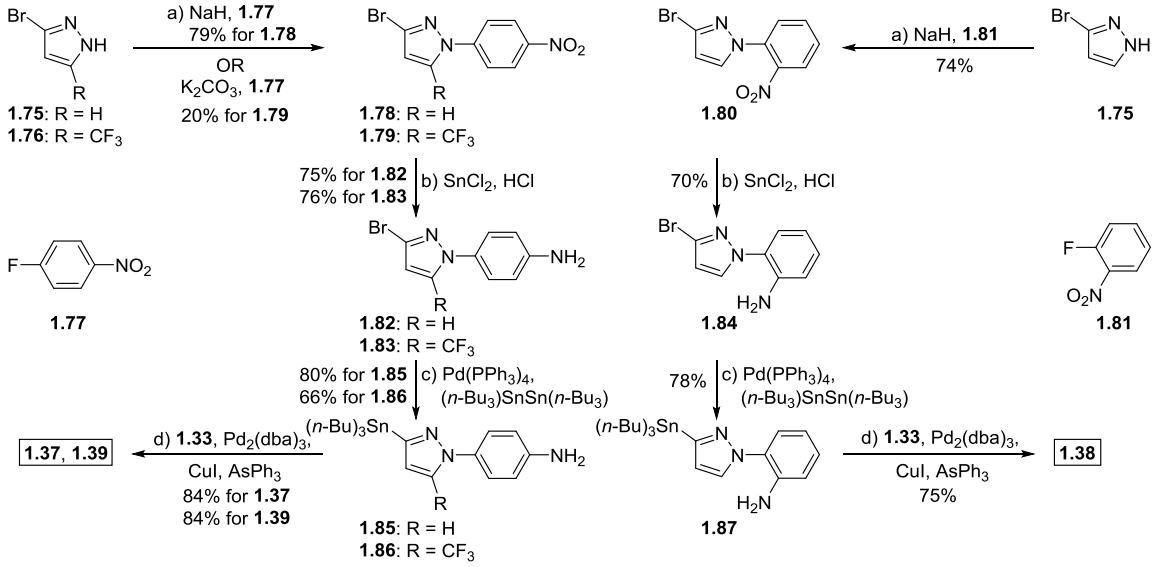
Scheme **1.03** depicts the synthesis of bromopyrazoles **1.75** and **1.76** from commercially available pyrazoles **1.61** and **1.70**, respectively. Thus, protection of **1.61** or **1.70** with 3,4-dihydro-*2H*-pyran (DHP) in the presence of TFA led to tetrahydropyran derivatives **1.71** or **1.72** in quantitative yield. These intermediates were regioselectively brominated *via* their lithioderivatives (*n*-BuLi; Br_2) to afford bromopyrazoles **1.73** (84% yield) and **1.74** (78% yield). Acid ($MeSO_2OH$)-mediated deprotection of the latter led



Scheme **1.03**: Synthesis of bromopyrazoles **1.75** and **1.76** from commercially available pyrazoles **1.61** and **1.70**.

smoothly to the desired pyrazole building blocks **1.75** (95% yield) and **1.76** (91% yield), respectively.

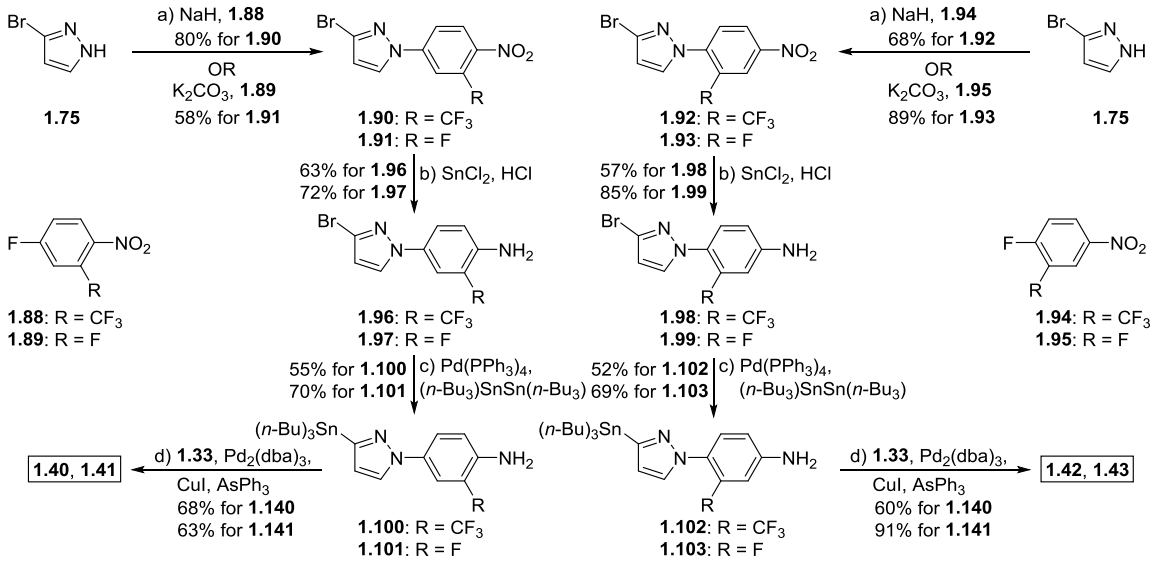
Scheme 3 summarizes the synthesis of epothilone analogues **1.37**–**1.39** from bromopyrazoles **1.75** and **1.76**. Reaction of **1.75** or **1.76** with commercially available 1-fluoro-4-nitrobenzene (**1.77**) in the presence of NaH resulted in the formation of *N*-aryl bromopyrazole derivatives **1.78** (79% yield) or **1.79** (20% yield, 60% yield of *N*-aryl regioisomer) through nucleophilic aromatic substitution. Reduction of the nitro group within **23a** and **23b** to the corresponding anilines was best realized with $SnCl_2$ in the presence of HCl (**1.82**, 75% yield; **1.83**, 76% yield).[42] Subsequent palladium-catalyzed



Scheme **1.04**: Synthesis of pyrazolyl stannanes **1.85**–**1.87** and epothilone B side chain analogues **1.37**–**1.39**.

[$Pd(PPh_3)_4$] stannylation of the latter using (*n*-Bu_3)Sn(*n*-Bu_3) furnished stannanes **1.85** (80% yield) and **1.86** (66% yield), respectively. A similar sequence of reactions starting from bromopyrazole **1.75** and commercially available 1-fluoro-2-nitrobenzene (**1.81**) led to the required amino stannane **1.87** as shown in Scheme 3. Palladium-catalyzed couplings [$Pd_2(dba)_3$, $AsPh_3$, CuI] of stannanes **1.85**, **1.86**, and **1.87** with vinyl iodide **1.33** provided

targeted epothilone analogues **1.37** (84% yield), **1.38** (75% yield), and **1.39** (84% yield), respectively, as shown in Scheme **1.04**.



Scheme **1.05**: Synthesis of pyrazolyl stannanes **1.100**–**1.103** and epothilone B side chain analogues **1.40**–**1.43**.

Epothilone analogues **1.40**–**1.43** were synthesized from vinyl iodide **1.33** and pyrazole stannanes **1.100**–**1.103**, respectively, employing analogous reactions to those described above for epothilones **1.37**–**1.39** (Scheme **1.04**) and in similar yields, as shown in Scheme **1.05**. It is worthy to note that, depending on the specific substrate, homodimerized heterocycles can be formed under the reaction conditions; when this occurs, purification of the final product is complicated, besides the fact that removing tin byproducts from the Stille coupling is already a tedious chore.[43] Various mixtures of Et_2O/Hex. or EtOAc/Hex. as the mobile phase were generally best for the separation of any dimerized pyrazoles as a result of stannane homodimerization. The final coupling step was generally done on a scale suitable to provide *ca*. 510 mg of final compound.

C. Biological Evaluation of Analogues **1.34**–**1.43**

1. NCI-60 Cytotoxicity Results

Table 1.01: Selected NCI-60 data [(GI_{50}, nM)[a]][b] for **1.37**–**1.42**.

Cell Line	**1.37**	**1.38**	**1.39**	**1.40**	**1.41**	**1.42**
CCRF-CEM	34.1	22.6	47.6	6.09	12.3	13.6
HL-60(TB)	15.8	17.2	7.88	< 5.00[c]	7.36	14.1
K-562	24.7	24.4	15.7	< 5.00	10.2	20.7
MOLT-4	38.9	27.6	48.1	< 5.00	14.2	28.3
RPMI-8226	21.3	17.8	11.1	< 5.00	9.98	19.6
SR	30.3	27.4	NA[d]	< 5.00	7.29	29.2
A549/ATCC	36.9	34.5	48.8	6.05	13.4	37.6
HOP-92	146	80.7	–	< 5.00	16.1	–[e]
NCI-H23	25.2	35.8	88.5	5.72	18.3	24.2
NCI-H460	20.5	20.3	6.45	< 5.00	8.73	20.8
COLO 205	18.6	20.4	14.7	< 5.00	8.48	18.2
HCT-116	18.7	18.3	5.31	< 5.00	4.82	17.1
HCT-15	26.7	32.5	22.0	< 5.00	11.0	22.6
HT29	19.6	18.8	5.29	< 5.00	5.74	18.4
KM12	19.2	20.6	5.25	< 5.00	9.16	17.7
SW-620	25.0	24.5	5.40	< 5.00	6.23	23.6
SF-539	19.0	15.8	24.8	9.41	9.55	26.2
SNB-75	11.4	16.4	NA	< 5.00	5.75	11.7
U251	35.6	30.8	38.1	< 5.00	14.6	36.2
LOX IMVI	23.6	31.3	25.0	< 5.00	10.3	23.1
M14	19.2	18.0	13.7	< 5.00	4.88	18.7
MDA-MB-435	8.09	9.56	2.08	< 5.00	< 3.25	8.35
SK-MEL-5	20.0	21.9	22.1	< 5.00	10.1	18.0
OVCAR-3	18.1	18.8	15.8	< 5.00	10.2	17.6
A498	102	18.8	66.0	< 5.00	11.3	80.2
RXF 393	38.4	39.6	40.7	9.39	14.0	30.6
PC-3	30.4	34.3	32.2	9.75	12.7	25.8
MCF7	15.2	17.7	3.65	< 5.00	< 3.25	14.0
HS 578T	44.0	31.6	36.4	5.51	7.10	37.2
MDA-MB-468	39.2	23.4	23.1	7.22	10.6	20.9

[a] $^{a}GI_{50}$ = the concentration that inhibits growth by 50%.
[b] See section H for complete NCI-60 results.
[c] A *less than* symbol (<) indicates the actual GI_{50} is below the sensitivity threshold of the screen.
[d] NA = Results not available.
[e] A "–" indicates a GI_{50} > 100 nM

The synthesized epothilone analogues were submitted to the NCI for testing against the NCI-60 human cancer cell line panel.[44] The *N*-Boc (**1.34** and **1.35**) and *N*-Teoc (**1.36**) protected analogues did not exhibit significant activity beyond the initial one-dose test (10 μM threshold) and, therefore, were not screened further. Compounds **1.37**–**1.43**, however, having passed the initial one-dose test, were subjected to duplicate five-dose screens (see section H for more details) that revealed potent activities against a number of tumor cell lines. Table **1.01** displays cytotoxicity data for analogues **1.37**–**1.42**. Based on this data, analogues **1.40** and **1.41** exhibited the strongest activities in this study.

2. Further Cytotoxicity Studies & Tubulin Assembly Induction Assay

In order to obtain further insights regarding the biological properties of the synthesized epothilone analogues **1.34**–**1.43**, we investigated their ability to induce tubulin polymerization and growth inhibition against human breast (MCF-7) and ovarian (OVCAR-8) cancer cells. This data was obtained from a collaboration with E.H. Hamel, utilizing his developed assay, which measures the induction of tubulin assembly; like cytotoxicity data, a lower value (in this case EC_{50}, measured in μM) is indicative of a potent tubulin binding agent, while a large value is indicative of loss of tubulin binding affinity.[45] Epothilones **1.01**–**1.04**, ixabepilone (**1.17**), and paclitaxel (PTX) were tested in parallel for comparison purposes. As shown in Table **1.02**, analogues **1.34**–**1.36** did not show significant activities in all three assays, whereas all other synthesized compounds (**1.37**–**1.43**) exhibited comparable or higher potencies to the naturally occurring **1.01**–**1.04**, **1.17**, and PTX. Analogues **1.40** and **1.41**, were proven in this study to be highly potent, exhibiting stronger potencies than all the standard epothilones tested (**1.01**–**1.04**, **1.17**) and PTX (Table **1.02**).

Table **1.02**: Tubulin assembly induction and cytotoxicity assays for analogues **1.34**–**1.43**.

	Tubulin Induction[a] (EC_{50}, μM, ± SD)	Cytotoxicity (GI_{50}, nM, ± SD)[b] MCF-7[c]	OVCAR-8[d]
PTX	–	8.5 ± 0.7	6.5 ± 2
1.01	16 ± 2	10 ± 2	11 ± 2
1.02	3.5 ± 0.7	5.5 ± 0.7	3.5 ± 0.7
1.03	18 ± 0.7	70 ± 10	110 ± 7
1.04	18 ± 0^3	14 ± 1	13 ± 4
1.17	4.5 ± 0.7	7.0 ± 1	35 ± 10
1.34	> 40	1,600 ± 500	900 ± 0^3
1.35	> 40	4,400 ± 900	1,200 ± 40
1.36	> 40	1,800 ± 700	1,300 ± 100
1.37	15 ± 4	10 ± 0^3	38 ± 10
1.38	8.0 ± 1	5.5 ± 0.7	23 ± 10
1.39	> 40	900 ± 100	300 ± 0^3
1.40	7.8 ± 1	2.5 ± 0.7	1.8 ± 0.4
1.41	2.5 ± 0.5	3.0 ± 1	2.5 ± 0.4
1.42	19 ± 1	14 ± 2	38 ± 10
1.43	> 40	9.0 ± 1	35 ± 5

[a] In these experiments each 100 μL reaction mixture contained 1.0 mg/mL (10 μM) tubulin, 0.4 M monosodium glutamate (taken from 2.0 M stock solution adjusted to pH 6.6 with HCl, 0.5 mM $MgCl_2$, 2% (*v*/*v*) dimethyl sulfoxide, and varying compound concentrations. Incubation was for 30 min at room temperature (about 22 °C). Reaction mixtures were centrifuged for 10 min in an Eppendorf centrifuge at room temperature at 14,000 rpm. Protein was determined in 50 μL of the supernatant, using the Lowry assay, see ref. [45]; EC_{50} = drug concentration yielding an unbound protein supernatant 50% that of controls.

[b] Cell growth was evaluated using the standard NCI assay, the parameter measured with sulforhodamine B; GI_{50} = compound concentration that reduces cell growth by 50% after 96 h at 37 °C; SD = standard deviation, a SD of 0 indicates that the same value was obtained in all three assays.

[c] Human breast cancer cell line.

[d] Human ovarian cancer cell line.

D. Structure-Activity Relationships and Conclusions

1. Structure-Activity Relationships

The results of the biological evaluation of the synthesized analogues (**1.34**–**1.43**, Figure **1.11**) are consistent and provide further support to previously established structure-activity relationships within the epothilone class. The critical nature of a basic *N*-atom at a specific location of the side chain serving as a H-bond acceptor through H-bonding (potentially with the protonated form of a histidine residue in *β*-tubulin)[21] and the steric tolerance of the side chain binding pocket are evident in the present series of compounds.

Thus, loss of activity occurred with the three analogues equipped with bulky protecting groups on the side chain attached to the essential *N*-atom of their pyrazole moiety (*i.e.* **1.34**–**1.36**, Figure **1.11**). All other analogues (*i.e.* **1.37**–**1.43**, Figure **1.11**) exhibited strong activities except for **1.43**, which demonstrated lower potencies against certain cell lines (*e.g.* MCF-7 and OVCAR-8, Table **1.02**, as well as the NCI-60 human tumor cell line panel, see section H for details). The significant loss of potency of compound **1.39** versus **1.37** (see Table **1.02**) may be attributed to the electron withdrawing effect of the CF_3 group that weakens the H-bond accepting ability of the pyrazole *N*-atom involved in the docking of these molecules to their tubulin binding site. Compounds **1.40** and **1.41** proved to be the most potent as seen in Tables **1.01** and **1.02**. Containing F residues at the *ortho* position of the aniline moiety, these analogues enjoy the well-known benefits of fluorine as an enhancing element for bioactivity,[46] while also allowing for the H-bond between the crucial *N*-atom and the β-tubulin histidine residue, as opposed to the considerably less potent analogue **1.43**, which may be suffering from steric interactions arising from the adjacent CF_3 group, which interrupt this critical binding mode.

2. Conclusion

A number of novel epothilone B side chain analogues (**1.34**–**1.43**, Figure **1.11**) were designed, synthesized, and evaluated with regard to their tubulin binding affinities and cancer cell growth inhibitory properties. Importantly, we were able to confirm a proof-of-concept *N*-arylpyrazole moiety as a heterocycle that improves activity and provides a crucial handle for ADC or SMC compatibility. The observed biological activities of these new analogues fall within existing structure-activity relationships for the epothilone family

and provide further guidance for future designs directed toward higher potencies and possible conjugation to cancer cell-specific antibodies and other delivery systems for targeted cancer chemotherapy.

E. Synthesis of Novel Aziridinyl Epothilone Analogues

1. Background and Initial Explorations

Moving forward with our studies, we realized that another opportunity for novel analogue development involved the validated, yet little explored, 12,13-aziridine isostere. As mentioned previously in Figure **1.07**, epothilone A analogue **1.22** was until recently being pursued by BMS as a novel SMC consisting of **1.22** conjugated to folate through a peptide linker.[26] In 2001, one year after their report for the preparation of **1.17** from **1.02** (Figure **1.12**A**)**,[24] a synthetic route for accessing the 12,13-aziridinyl motif was published by BMS, in which they produce 12,13-aziridinyl epothilone A (**1.104**) in 8 steps from epothilone A (**1.01**, Figure **1.12**A); in subsequent patent literature over the next several years, BMS slightly optimized the route of preparation.[47] However its yield and efficiency was poor, and their synthetic approach left the entire rest of the molecule unamenable to any further practical changes.

In spite of these impressive advances, further exploration surrounding the aziridine motif remained limited, and attempts to install the aziridine directly from an olefinic precursor was unsuccessful. Furthermore, while it is well known that the trisubstituted epoxide present in epothilone B (**1.02**) confers additional stability as well as potency [*ca*. 10-fold increase relative to epothilone A(**1.01**)],[1] accessing the analogous trisubstituted aziridinyl epothilone B motif proved to be elusive, despite efforts utilizing classical Evans-type aziridination conditions, which may in fact produce a trisubstituted aziridine, but with

low, irreproducible yields and the little product that is isolated is not stable towards *N*-deprotection.[48]

Another potentially powerful synthetic strategy involves replacement of the heterocyclic side chain in a reliable and concise manner, especially if this could be done from the natural product (*i.e.* **1.02**) itself. Although the Stille coupling strategy we employed for epothilone B side chain analogues **1.34**–**1.43** has proven itself presently and historically reliable, an alternative, commercially viable, and green chemistry approach would be an asset worthy of investigation.

With these goals in mind, a new synthetic route for accessing a broad range of aziridinyl epothilone B analogues (**I**, Figure **1.12**B) has been developed *via* a strategy that, in comparison to previous synthetic endeavors (Figure **1.12**A), combines high efficiency with remarkable chemical diversity. Thus, the synthesis of novel aziridinyl epothilone B analogues **I** was accomplished by utilizing an optimized Horner–Wadsworth–Emmons (HWE) reaction[49] with heterocyclic phosphonates **II** and aziridinyl methyl ketone **III**, the recently developed Ess–Kürti–Falck aziridination[50] to afford **III** from olefin methyl ketone **IV**, epoxide deoxygenation to produce **IV** from epoxy ketone **V**,[51] whose generation can be realized *via* ozonolysis of epothilone B (**1.02**) itself,[52] followed by protection of its secondary alcohol functionalities.

Previous reports from our group have shown that the epoxidation of epothilone D (**1.04**) with electrophilic reagents delivered epothilone B (**1.02**) with a modest level of diastereoselectivity (dr *ca*. 5:1),[33b] as such a direct approach for accessing aziridinyl epothilone B **1.105** from **1.04** seemed reasonable (Figure **1.13**). In addition, the recently described Ess–Kürti–Falck aziridination offered additional encouragement for this

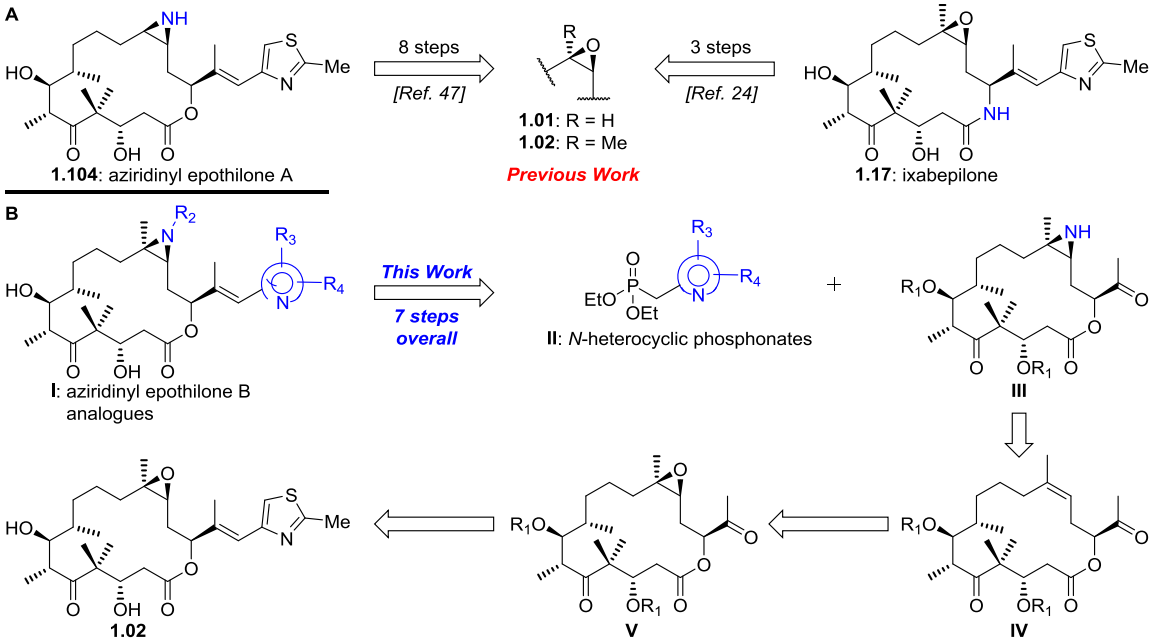


Figure **1.12**: A: Previous syntheses of aziridinyl epothilone A (**1.104**) from epothilone A (**1.01**) and ixabepilone (**1.17**) from epothilone B (**1.02**). B: General synthetic strategy for accessing aziridinyl epothilone B analogues **I** from *N*-heterocyclic phosphonates **II** and aziridinyl methyl ketone **III**, which derives from olefin methyl ketone **IV**, epoxy ketone **V**, and ultimately **1.02**.

strategy, since this method offers direct access to free secondary aziridines, in contrast to classical methods.

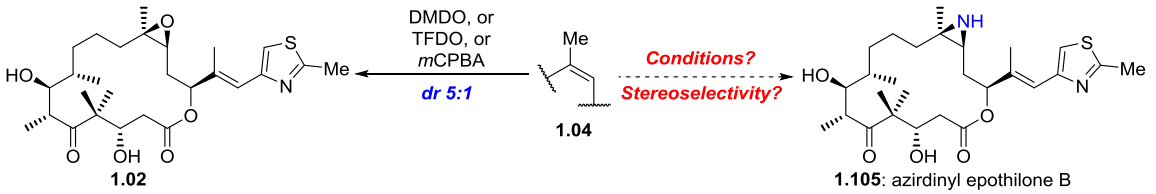
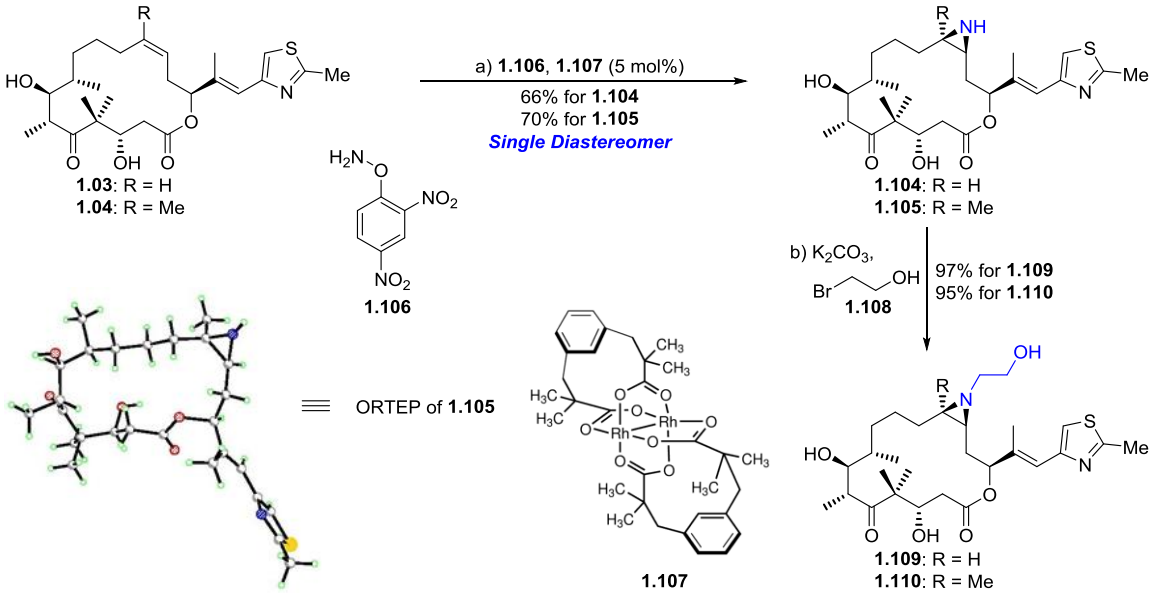


Figure **1.13**: The stereoselective formation of epothilone B (**1.02**) from epothilone D (**1.04**) (left) portends a stereoselective, direct aziridination strategy for accessing aziridinyl epothilone B (**1.105**) (right).

Preliminary studies to investigate the feasibility of this approach were carried out on the corresponding natural products, epothilones C and D (**1.03** and **1.04**, Scheme **1.06**). Exposure of **1.03** or **1.04** to aminating reagent (DPH, **1.106**) and $Rh_2(esp)_2$ cat. **1.107** in TFE under the reported conditions delivered 12,13-aziridinyl epothilones A (**1.104**) and B (**1.105**) in 70% and 66% yield as single diastereomers, respectively. ^{13}C NMR spectra of

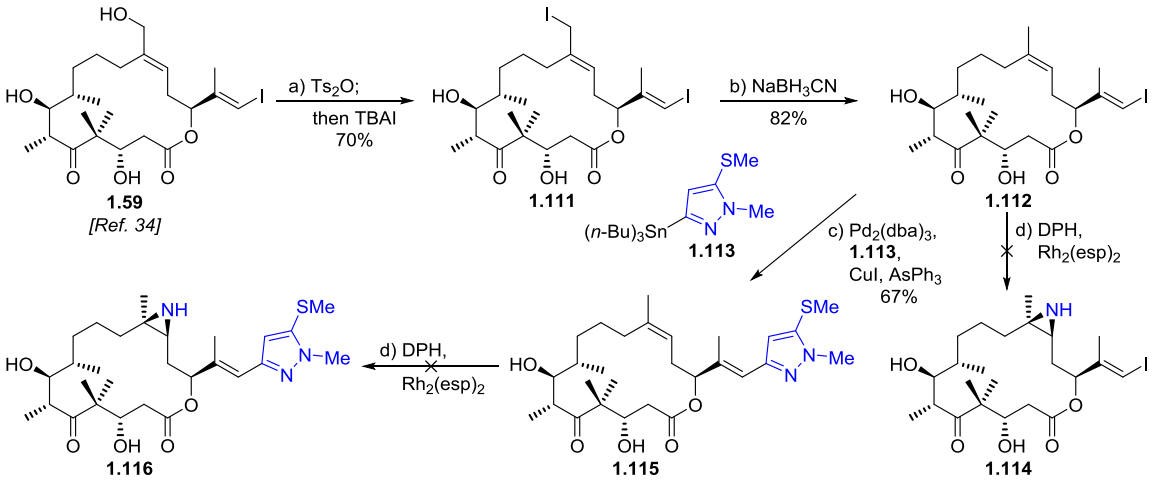
1.104 was consistent with those reported by BMS,[47b] and the excellent observed diastereoselectivity was further verified unambiguously by X-ray crystallography of **1.105** (see ORTEP in Scheme **1.06**). Subsequent *N*-alkylation of aziridines **1.104** and **1.105** with commercially available 2-bromoethanol (**1.108**) and K_2CO_3 in warm DMF provided tertiary aziridinyl epothilones A (**1.109**) and B (**1.110**) in excellent yields (97% and 95%, respectively). The newly formed tertiary aziridines possess a valuable primary hydroxyl linker attachment site, useful for various drug delivery systems, as demonstrated by the clinical studies of **1.22**.[26] Having successfully installed the key trisubstituted aziridine



Scheme **1.06**: Aziridination of epothilones C (**1.03**) and D (**1.04**) and synthesis of tertiary aziridines **1.109** and **1.110** via *N*-alkylation of **1.104** and **1.105**.

functionality, it became apparent that the possibility of incorporating designed heterocyclic side chains into the newly synthesized motif in a concise, selective manner would create immense opportunity for achieving broad chemical diversity with unprecedented molecular architectures and novel SARs.

2. Attempted Stille Coupling Approach



Scheme **1.07**: Synthesis of epothilone D analogue **1.115** from vinyl iodide **1.59**, and attempted synthesis of aziridines **1.116** and **1.114**.

To this end, the synthesis of vinyl iodide **1.112** was prepared from vinyl iodide **1.59** (Scheme **1.07**) in an effort to adapt the historically productive Stille coupling strategy of epothilone B (**1.02**) side chain analogues into a convenient route toward new aziridinyl epothilone B analogues containing designed, potency-enhancing heterocycles, such as **1.116** (Scheme **1.07**). Conversion of the primary allylic alcohol of **1.59**[34] to the corresponding tosylate (Ts_2O), followed by treatment with TBAI furnished primary alkyl iodide **1.111** (70% yield). Reduction of the alkyl iodide with excess $NaBH_3CN$ in DMPU provided vinyl iodide **1.112** (82% yield). Unfortunately, attempted aziridination of **1.112** utilizing the same conditions for the preparation of **1.104** and **1.105** was not a fruitful endeavor, and the highly anticipated aziridinyl vinyl iodide **1.114** was unable to be produced in significant quantities. Therefore, the heterocyclic side chain was introduced first *via* Stille coupling of **1.112** with readily available pyrazolyl stannane **1.113**[34c] to afford epothilone D side chain analogue **1.115** in 67% yield. Disappointingly, exposure of **1.115** to the same aziridination conditions led to complex reaction mixtures, presumably due to

oxidative side reactions involving the electron rich heterocycle and the thiomethyl functional group.[53]

3. Historical Inspirations and New Synthetic Route Development

To address this dilemma, we sought to further build upon early pioneering synthetic studies involving **1.01** and **1.02**, namely the epoxide deoxygenation of the natural product, and the potential for utilization of a methyl ketone instead of a vinyl iodide to reliably install the heterocyclic side chain (Figure **1.14**). In 2000, BMS reported the Mg/Cp_2TiCl_2 or WCl_6/*n*-BuLi mediated epoxide deoxygenation of **1.01** or **1.02** to afford **1.03** or **1.04**, en route to cyclopropyl analogues **1.117** and **1.118**, respectively (Figure **1.14**A).[54] In

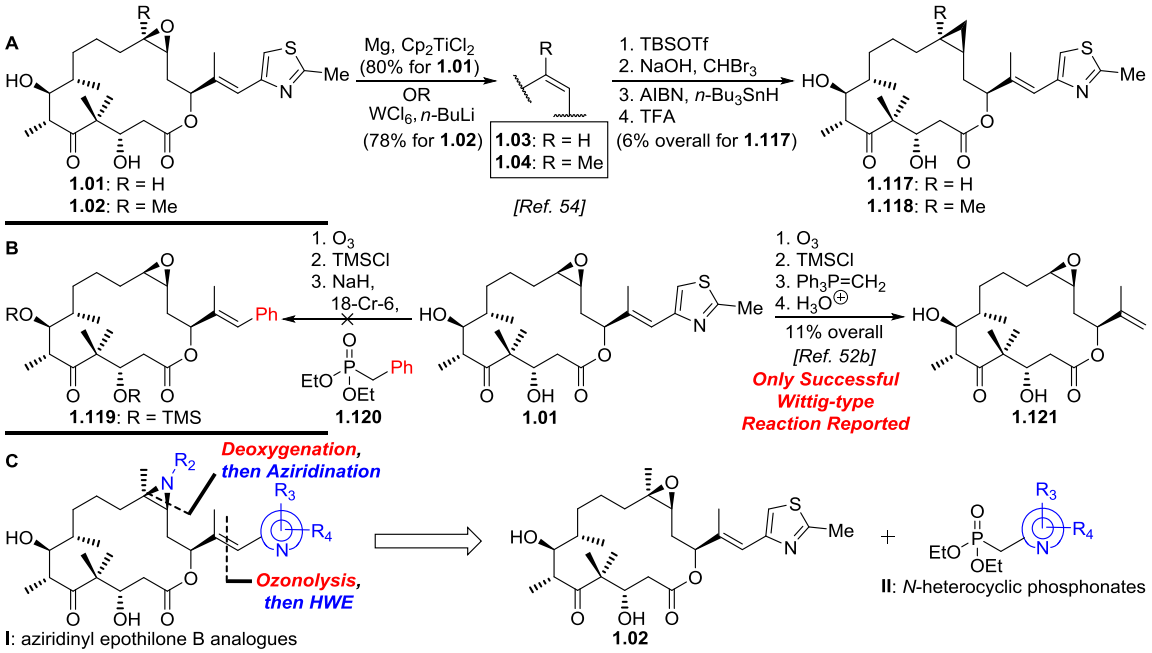


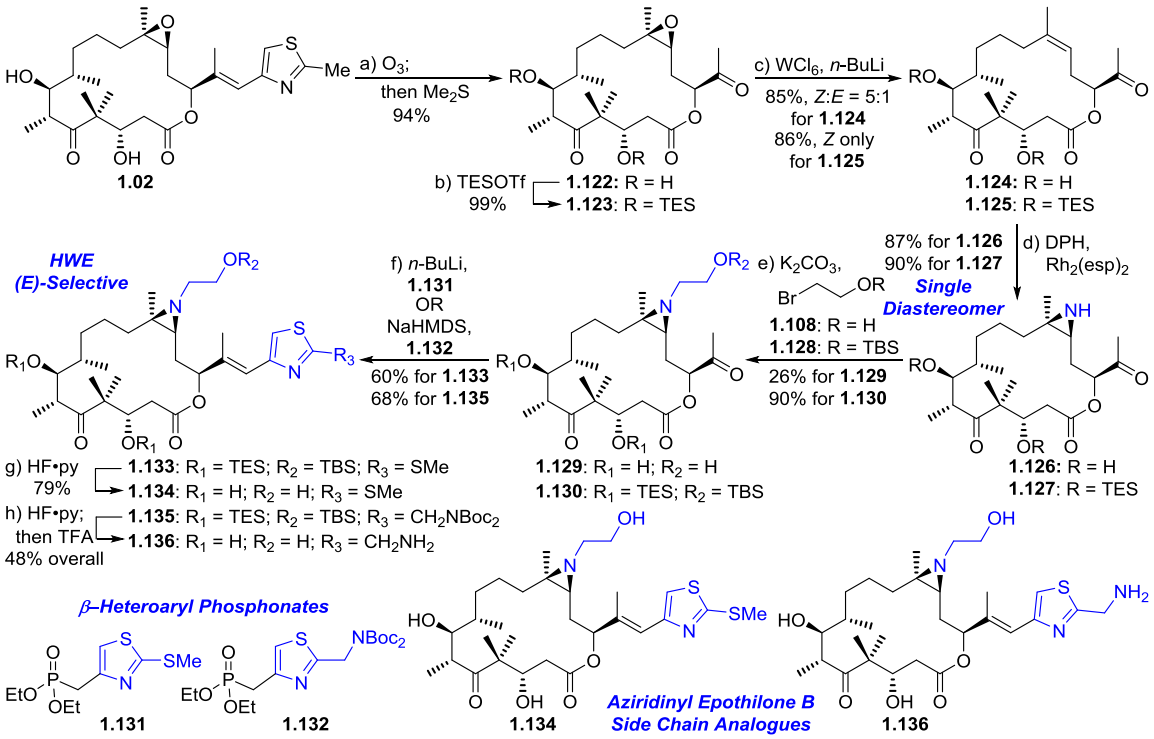
Figure **1.14**: A: Epothilones C or D (**1.03** or **1.04**) were generated *via* deoxygenation of epothilones A or B (**1.01** or **1.02**) during the pursuit of 12,13-cyclopropyl analogues **1.117** and **1.118**, respectively. B: Ozonolysis and olefination studies on epothilone A (**1.01**). C: Retrosynthetic plan for achieving desired aziridinyl epothilone B analogues **I** from epothilone B (**1.02**) and N-heterocyclic phosphonates **II**.

addition, earlier work by Höfle revealed that terminal olefin **1.121** is obtainable from a four step sequence beginning with ozonolytic cleavage of **1.01** (Figure **1.14**B).[52b] However,

only the methyl ketone product from **1.01** (*not* **1.02**) was explored to any significant degree. Höfle reported one approach from **1.01** that diverged to either a Suzuki or Stille coupling strategy, but the examples were extremely limited and narrow in substrate scope.[55] In terms of an economical, concise, Wittig-type strategy, only the simplest methylenation product **1.121** was successfully (Figure **1.14**B, right), and attempted HWE reaction with *β*-phenyl phosphonate **1.120** under 18-Cr-6 conditions were met with failure (Figure **1.14**B, left).[52b] In light of these observations and the results of preliminary investigations, it was deemed a worthwhile challenge to build upon this previous work and devise a new route to introduce both the aziridine and the heterocyclic side chain moieties starting from **1.02** (Figure **1.14**C), which is readily available *via* fermentation and thus represents a commercially viable route for the modular production of a wide array of analogues.

Thus, starting from **1.02**, careful treatment with freshly generated O_3 at low temperature (78 C produced methyl ketone **1.122** (94% yield), and protection of the two hydroxyl groups (TESOTf) furnished protected methyl ketone **1.123** (99% yield). Deoxygenation of the epoxide moiety proceeded stereoselectively with **1.122** or **1.123** to afford (*Z*)-trisubstituted olefin **1.124** (85%, *Z*:*E* = 5:1) or **1.125** (86%, *Z* only).[51, 54] Pleasingly, Ess–Kürti–Falck aziridination provided aziridinyl methyl ketones **1.126** (87% yield) and **1.127** (90% yield), both of which were isolated as single diastereomers.[50] *N*-alkylation of aziridine **1.126** or **1.127** with 2-bromoethanol (**1.108**) or TBS-protected derivative **1.128** in the presence of K_2CO_3 afforded tertiary aziridines **1.129** (26% yield) and **1.130** (90% yield). HWE coupling of *β*-heteroaryl phosphonates **1.131** and **1.132** (see Scheme **1.09** for their preparation) using *n*-BuLi or NaHMDS as base produced protected aziridinyl analogues **1.133** (60% yield) and **1.135** (68% yield). Finally, global deprotection

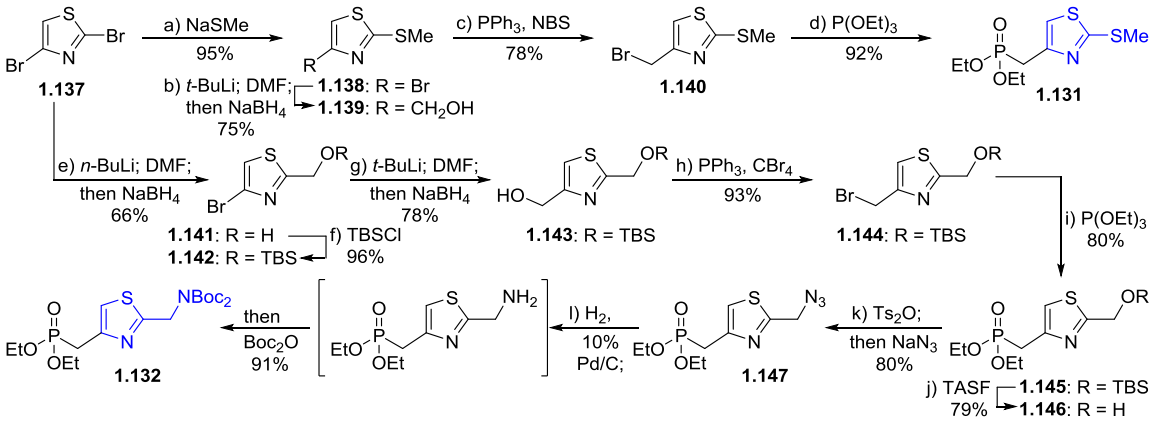
(HF•py or HF•py then TFA) led to epothilone B aziridinyl analogues **1.134** (79% yield) and **1.136** (48% overall yield), respectively. It is notable that this new HWE route creates the opportunity a wide array of potential heterocycles to be introduced in a practical manner. In addition, the methyl ketone starting material (*e.g.* **1.130**, Scheme **1.08**) is readily accessible in four steps from **1.02**, and the phospohonate coupling partners (e.g. **1.131** and **1.132**) manifest a green chemistry approach, which is a welcomed departure from the Stille protocol previously championed by myself and others in the Nicolaou laboratory. Indeed, the use of organotin species for the late stage functionalization of biologically important compounds is a major issue for the development of active pharmaceutical ingredients.[43b]



Scheme **1.08**: Synthesis of aziridinyl epothilone B side chain analogues **1.134** and **1.136** from **1.02** and *N*-heterocyclic phosphonates **1.131** and **1.132**.

The synthesis of heteroaryl phosphonates **1.131** and **1.132** is described in Scheme **1.09**, and their preparation begins from commercially available 2,5-dibromothiazole **1.137**.

Thus thiomethylion of 1.137 (NaSMe, 95% yield),[56] followed by a lithium-halogen metal exchange/DMF quench/$NaBH_4$ reduction sequence to achieve formal hydroxymethylation led to thiazole **1.139** in 75% yield through the intermediacy of (5-bromo-2-thiomethyl)-



Scheme **1.09**: Synthesis of phosphonates **1.131** and **1.132** from 2,5-dibromothiazole (**1.137**).

thiazole **1.138**. Subsequent bromination (NBS, PPh_3, 78% yield) and Michaelis–Arbuzov reaction[57] [$P(OEt)_3$, 92% yield] furnished phosphonate **1.131**. Alternatively, regioselective hydroxymethylation at the 2 position of **1.137** (*n*-BuLi, DMF; then $NaBH_4$, 66% yield) produced alcohol **1.141**, which was then protected as its TBS ether to generate **1.142** (TBSCl, 96% yield).[56] Another iteration of the established hydroxymethylation sequence (*t*-BuLi, DMF; then $NaBH_4$, 78% yield) afforded known (5-hydroxymethyl)thiazole **1.143**.[58] Bromination (PPh_3, CBr_4, 93% yield)[59] and Arbuzov reaction [$P(OEt)_3$, 80% yield] proceeded smoothly to deliver TBS protected phosphonate **1.145**. Mild deprotection (TBAF produced a strange mixture of phosphonate salts) with TASF to unmask the alcohol functionality of **1.146** (79% yield), followed by tosylation (Ts_2O) and *in situ* treatment with NaN_3 afforded phosphonate azide **1.147** (80% yield). Finally, hydrogenation of the azide

moiety (10% Pd/C, 1 atm H_2) and trapping of the nascent free amine with Boc_2O produced phosphonate **1.132** (91% yield).

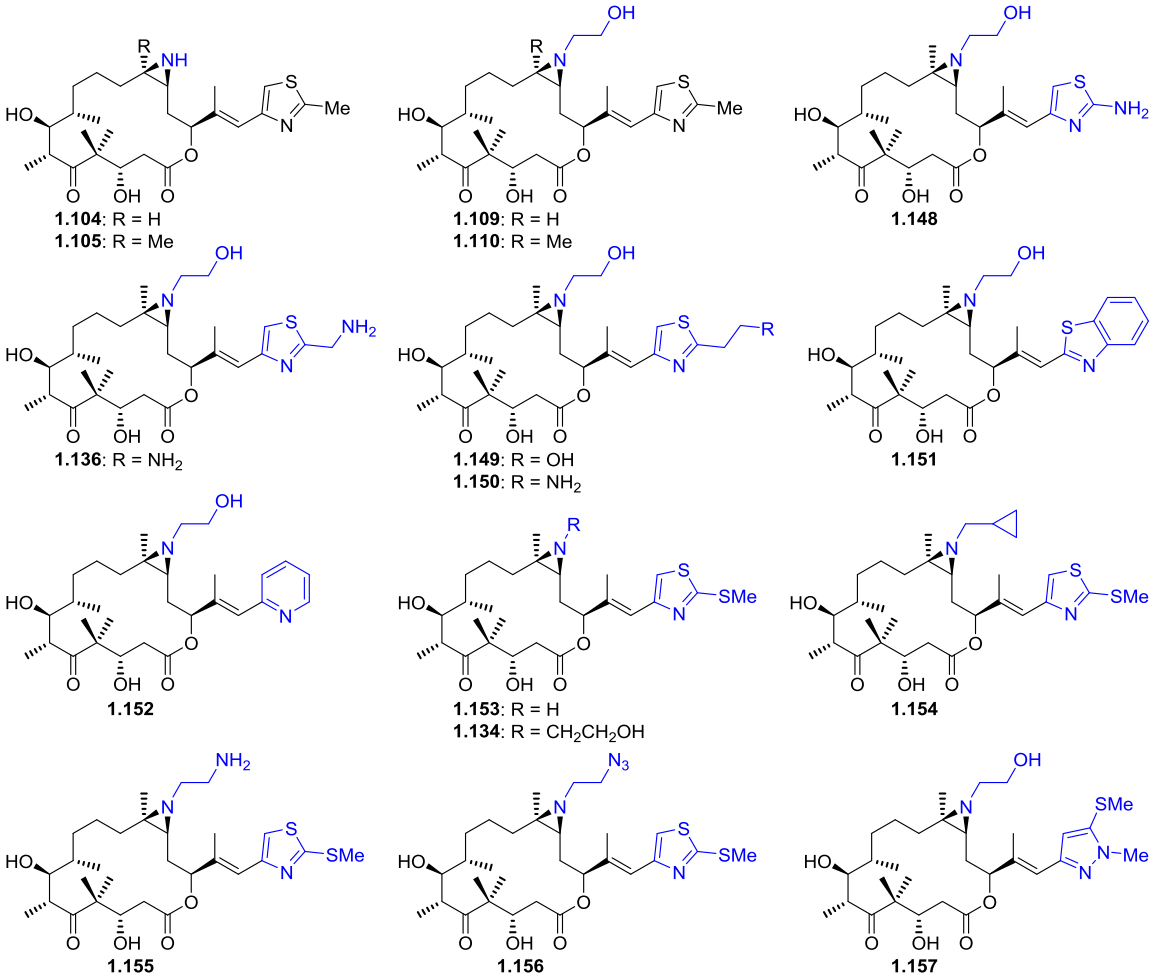


Figure **1.15**: Aziridinyl epothilone analogues synthesized and evaluated in this study.

4. Synthesis of Analogue Library

Our newfound success at developing this novel sequence prompted the design and synthesis of a new library of unprecedented epothilone B analogues possessing the 12,13-aziridinyl isostere as well as designed *N*-heterocyclic side chains. Figure **1.15** depicts all of the aziridine containing analogues synthesized in this dissertation, including aziridinyl epothilone A analogues **1.104** and **1.105** and aziridinyl epothilone B analogues **1.105** and

1.110, all of which possess the natural methylthiazole side chain, as well as aziridinyl analogues **1.134**, **1.136**, and **1.148**–**1.157** that contain designed *N*-heterocyclic side chains.

Ostensibly, the synthesis of these side chain analogues required the preparation of the corresponding *N*-heterocyclic phosphonates, which are shown in Figure **1.16**. Gratifyingly, the HWE coupling conditions employed for the synthesis of analogues **1.134** and **1.136** (Scheme **1.08**) were, for the most part, broad in substrate scope with respect to the nature of the *N*-heterocyclic phosphonate. Scheme **1.10** concisely summarizes the

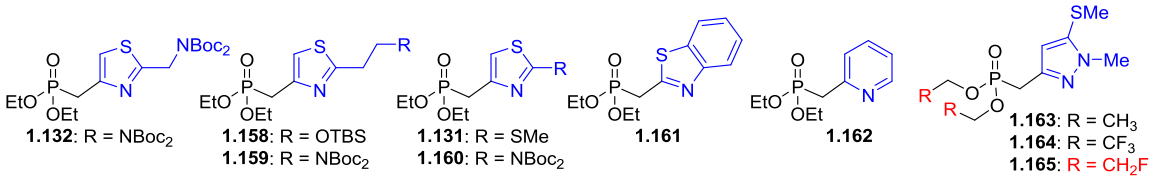
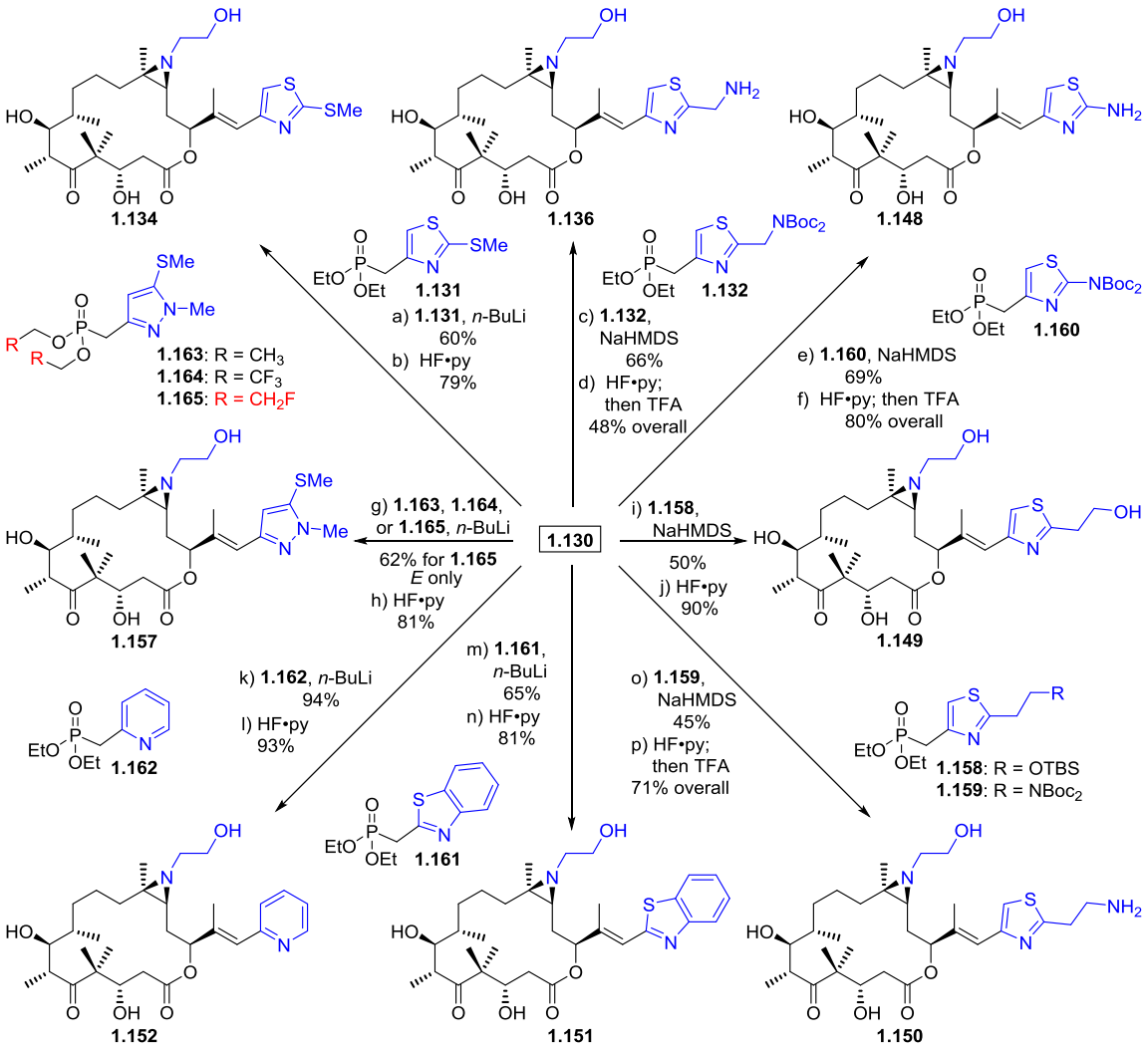


Figure **1.16**: *N*-heterocyclic phosphonates synthesized in this study.

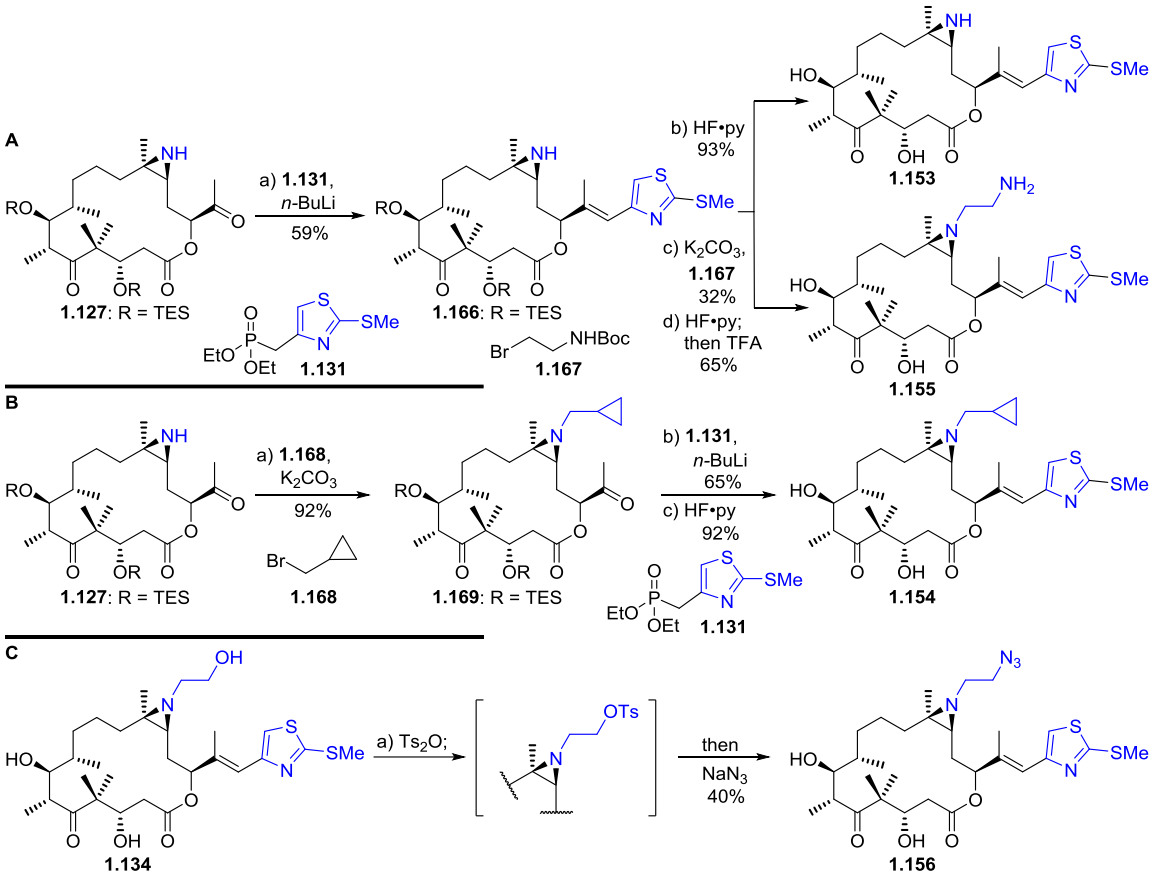
synthesis of analogues **1.134**, **1.136**, and **1.148**–**1.152** from methyl ketone **1.130** utilizing the described strategy. With some exceptions, *n*-BuLi was the base of choice for phosphonate substrates that did not possess Boc protected amino functionalities. Conversely, NaHMDS gave superior results as the base when amino groups (*i.e.* -N-Boc$_2$) were embedded into the phosphonate substrate. For successful small scale reactions, the phosphonate carbanion was generated in excess at low temperature, and then transferred into a separate flask containing of the methyl ketone (*e.g.* **1.127**), also at low temperature, and then the temperature was adjusted accordingly, depending on the specific reaction and substrate under investigation.



Scheme **1.10**: Synthesis of aziridinyl epothilone B side chain analogues **1.134**, **1.136**, and **1.148**–**1.152** from methyl ketone **1.130**.

The synthesis of aziridinyl epothilone B analogues **1.153**–**1.156** is summarized in Scheme **1.11**. Beginning in Scheme **1.11**A, protected analogue **1.166**, generated from methyl ketone **1.127** *via* HWE reaction with phosphonate **1.131** (59% yield), was either deprotected with HF•py complex to afford secondary aziridine analogue **1.153** (93% yield), or the secondary aziridine of **1.166** was alkylated with 2-bromo-*N*-Boc-ethylamine **1.167**

(32% yield, along with 35% recovered starting material) and then subjected to global deprotection (HF•py; then TFA, 65% yield) to afford analogue **1.155**. The same methyl



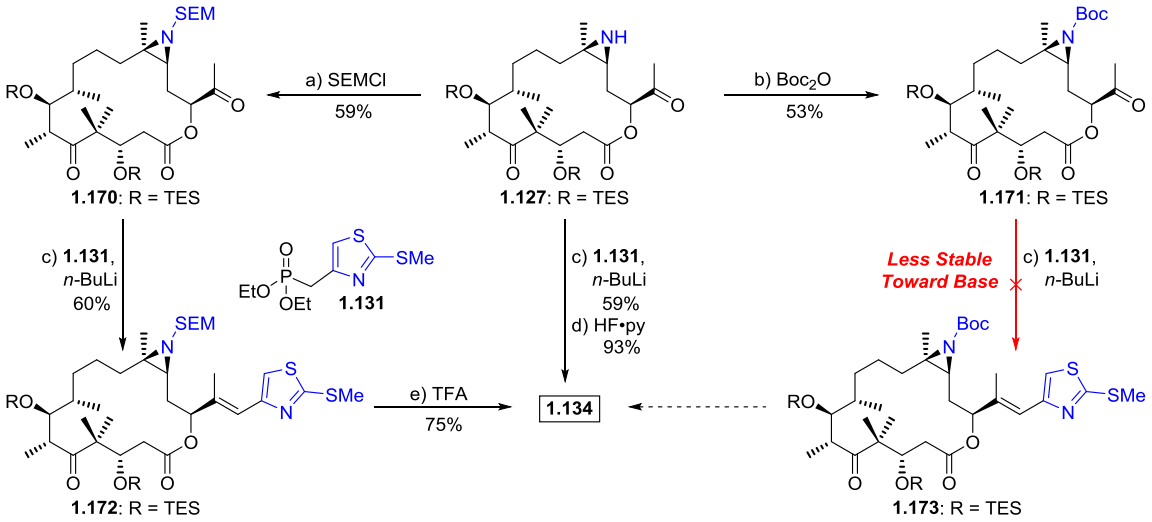
Scheme **1.11**: Synthesis of aziridinyl epothilone B side chain analogues **1.153**–**1.156**. A: Synthesis analogues **1.153** and **1.155** from methyl ketone **1.127**. B: Synthesis of analogue **1.154** from methyl ketone **1.169**, obtained *via* *N*-alkylation of methyl ketone **1.127**. C: Synthesis of analogue **1.156** from analogue **1.134**.

ketone **1.127** also served as a precursor to analogue **1.154** (Scheme **1.11**B). Thus, *N*-alkylation of the secondary aziridine of **1.127** with cyclopropylmethyl bromide **1.168** provided methyl ketone **1.169** (92% yield). HWE coupling (n-BuLi, 65% yield) and deprotection (HF•py, 92% yield) furnished analogue **1.154** which, as a departure from the polar group on the *N*-ethylamino spacer, possesses a nonpolar cyclopropyl group in the same region. Another interesting change made to this region is shown in Scheme **1.11**C.

Here, azide containing analogue **1.156** was synthesized from analogue **1.134** *via* a one pot tosylation/azidation sequaentce (40% yield). The synthesis of analogues 1.153-1.156 allows us to further probe the functional group tolerability of this potential region, which is potentially suited for ADC, SMC, or other bioconjugation technologies.

5. Extension of Synthetic Route to Secondary (Free –NH) Aziridine Motif

After establishing a streamlined process for the synthesis of tertiary aziridinyl epothilone B analogues, a similar route for obtaining the corresponding free (–NH) amine (secondary aziridine) analogues was investigated (Scheme **1.12**). Intriguingly, it was found that aziridinyl methyl ketone **1.127** was able to be successfully coupled with heteroaryl



Scheme **1.12**: Protecting group manipulations and realization of SEM-protected methyl ketone **1.170** as a key intermediate for the synthesis of free –NH (*i.e.* secondary aziridinyl) epothilone B side chain analogues.

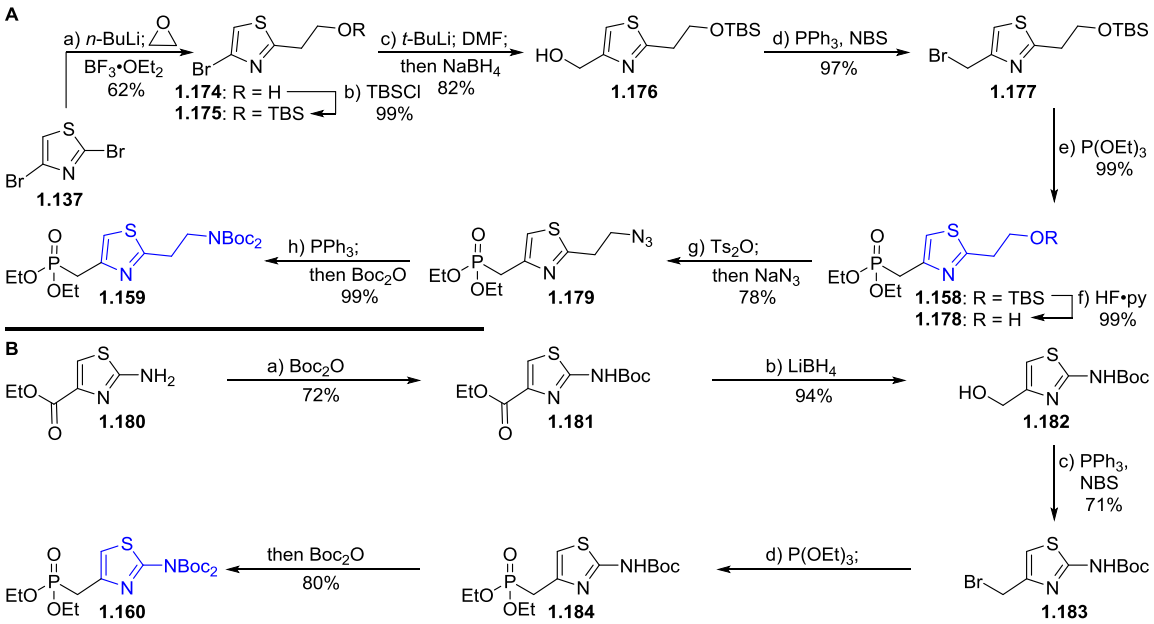
phosphonate **1.131** directly to afford analogue **1.134** (55% overall yield) after global deprotection, without protecting the aziridine functionality. While it is remarkable that the free –NH aziridine moiety managed to survived the strongly basic reaction conditions, this phenomenon was found to be dependent on the given phosphonate substrate in question;

thus, we naturally began considering a more robust HWE aziridinyl methyl ketone substrate to provide a facile route for accessing a wide variety secondary aziridinyl epothilone B side chain analogues, similar to **1.134**. This led to the synthesis of SEM protected methyl ketone **1.170** (SEMCl, 59% yield) and Boc protected methyl ketone **1.171** (Boc_2O, 53% yield), which were both subsequently subjected to HWE coupling reactions. Exposure of **1.171** to *n*-BuLi and phosphonate **1.131** was able to generate the desired product **1.173**, however it was contaminated with impurities that were difficult to remove, and the material was not able to be cleanly converted to analogue **1.134**. We reasoned that the electron withdrawing nature of the Boc protecting group rendered the aziridine functionality more susceptible toward base induced elimination. Fortunately, methyl ketone **1.170** served as a viable coupling partner with phosphonate **1.131**, affording protected analogue **1.172** in an acceptable 60% yield. Deprotection (TFA, 75% yield) provided analogue **1.131**. It is anticipated that **1.170** will serve as a key intermediate for the synthesis of other secondary aziridinyl epothilone B side chain analogues as these studies continue to evolve.

6. Synthesis of *N*-Heterocyclic Phosphonates

Schemes **1.13** and **1.14** summarize the preparation of *N*-heterocyclic phosphonates **1.158**–**1.165**. The synthesis of phosphonates **1.158**–**1.160**, which contain the thiazole motif, is summarized in Scheme **1.13**. The synthesis of phosphonates **1.158** and **1.159** (Scheme **1.13**A) began from commercially available 2,5-dibromothiazole (**1.137**). Lithium-halogen metal exchange at the 2 position, followed by treatment with ethylene oxide and BF_3•Et_2O provided thiazole **1.174** (62% yield). TBS protection (TBSCl, 99% yield) of **1.174** afforded thiazole **1.175**, which was subjected to the formal

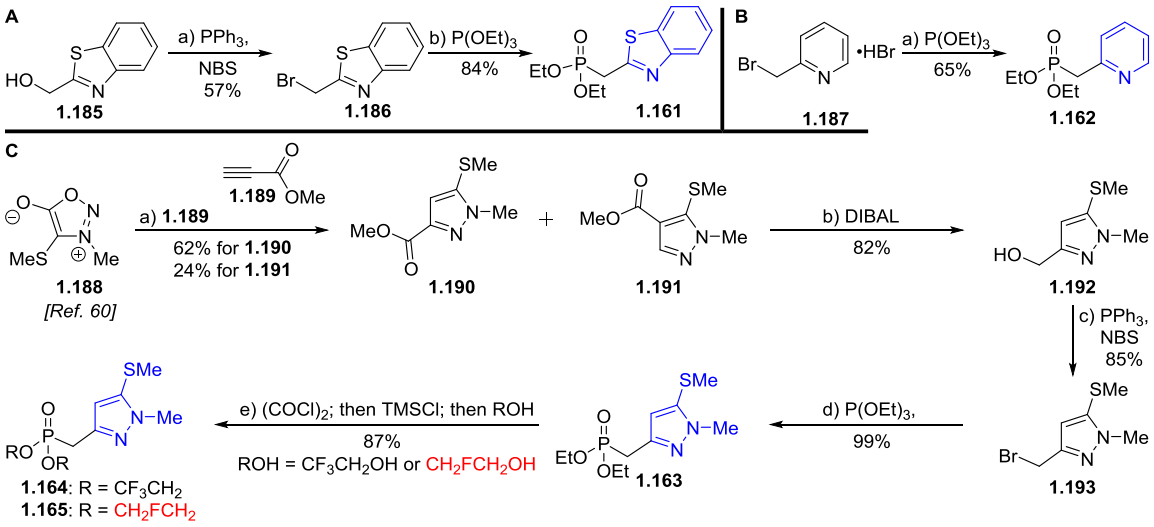
hydroxymethylation sequence we previously reported for the preparation of phosphonates **1.131** and **1.132** in Scheme **1.09**. Thus, lithium-halogen metal exchange at the 5 position, followed by DMF quench and a one pot $NaBH_4$ reduction produced hydroxymethyl thiazole **1.176** in 82% yield. Bromination (PPh_3/NBS, 97% yield) of **1.176** produced



Scheme **1.13**: Synthesis of *N*-heterocyclic phosphonates **1.158**–**1.160**. A: Synthesis of phosphonates **1.158** and **1.159**. B: Synthesis of phosphonate **1.160**.

bromomethyl thiazole **1.177**, which was then heated with $P(OEt)_3$ (Michaelis–Arbuzov reaction, 99% yield) to generate phosphonate **1.158**, possessing a 2-ethoxy substituent on the thiazole ring (see analogue **1.149** in Figure **1.14**). Further elaboration, including deprotection (HF•py, 99% yield) to provide primary alcohol **1.178**, tosylation/azidation (Ts_2O, NaN_3, 78% yield) to furnish primary azide **1.179**, and finally Staudinger reduction (PPh_3) and subsequent treatment with Boc_2O afforded bis-protected 2-ethylaminothiazolyl phosphonate **1.159** in 99% yield. The synthesis of thiazolyl phosphonate **1.160** is delineated in Scheme **1.13**B, and begins with commercially available ethyl 2-

aminothiazole-4-carboxylate **1.180**, whose *N*-Boc protection (Boc_2O, 72% yield) proceeded smoothly to provide carbamate **1.181**. Reduction of **1.181** ($LiBH_4$, 94% yield) to afford alcohol **1.182**, followed by bromination (PPh_3/NBS, 71% yield) to bromide **1.183**, and final Arbuzov reaction/bis-Boc protection [$P(OEt)_3$; then Boc_2O, 80% yield], provided



Scheme **1.14**: Synthesis of *N*-heterocyclic phosphonates **1.161**–**1.165**. A: Synthesis of phosphonate **1.161**. B: Synthesis of phosphonate **1.162**. C: Synthesis of phosphonate **1.163**–**1.165**.

2-aminothiazolyl phosphonate **1.160**. Likewise, Scheme **1.14** describes the synthesis of *N*-heterocyclic phosphonates **1.161–1.165**. The synthesis of benzothiazolyl phosphonate **1.161** is shown in Scheme **1.14**A, and is conveniently prepared from commercially available 2-(hydroxymethyl)benzothiazole **1.185** by bromination (PPh_3/NBS, 57% yield) followed by Arbuzov reaction [$P(OEt)_3$, 84% yield]. Conveniently, pyridinyl phosphonate **1.162** (Scheme **1.14**B) was easily produced in one step from the commercially available hydrobromide salt **1.187** *via* Arbuzov reaction [$P(OEt)_3$, 65% yield]. The preparation of pyrazolyl phosphonates **1.163–1.165** is summarized in Scheme **1.14**C, and starts from readily available sydnone **1.188**.[60] Refluxing **1.188** in neat methyl propiolate (**1.189**)

produced the desired product **1.190** (62% yield) along with regioisomer **1.191** (24% yield) *via* a cycloaddition/retrocycloaddition cascade.[Ref] Methyl ester **1.190** was then transformed by reduction (DIBAL, 82% yield) to afford alcohol **1.192**, bromination (PPh_3/NBS, 85% yield) to afford bromomethyl thiazole **1.193**, and finally Arbuzov reaction [$P(OEt)_3$, 99% yield] to provide phosphonate **1.163**. Subsequent conversion of **1.163** to the corresponding alkoxy phosphonate congeners **1.164** and **1.165** was accomplished by treatment with $(COCl)_2$ to generate the phosphoryl dichloride, followed by a reaction quench with TMSCl, and in situ exposure of the so formed *bis*-TMS phosphonate with the appropriate alcohol [2,2,2,-trifluoroethanol (TFE) or 2-fluoroethanol, 87% yield].

F. Biological Evaluation of Aziridinyl Epothilone Analogues

1. Cytotoxicity Studies & Tubulin Assembly Induction Assay

In continuation of our collaboration with the group of Hamel at the NCI branch of the NIH, we were able to obtain data for all of the synthesized analogues listed in Table **1.03**. Activities for paclitaxel (PTX), and natural epothilones **1.101**–**1.104** are also provided and were produced contemporaneously with aziridinyl epothilone A analogues **1.104** and **1.109**, epothilone D analogue **1.116**, and aziridinyl epothilone B analogues **1.105** and **1.110**, and aziridinyl epothilone B side chain analogues **1.134**, **1.136**, and **1.148**–**1.153**. To further expand the cytotoxicity profile of this generation of analogues, additional cell lines were included in this biological evaluation: SNB-75 [human glioblastoma (a very aggressive brain tumor cell line)], MDA-MB-435 (human melanoma cell line), and NCI/ADR-RES, which is a type of OVCAR-8 (human ovarian cancer cell line) that overexpresses P-gp, and thus represents a difficult to treat, highly resistant *in vitro* cancer

cell line model that has proven useful for assessing whether or not highly active compounds are viable substrates for P-gp, and/or if their activity is maintained upon their exposure.

Table **1.03**: Tubulin assembly induction and cytotoxicity assays for aziridinyl epothilone B analogues.

	Tubulin Induction[a]	Cytotoxicity (GI_{50}, nM, ± SD)[b]				
	(EC_{50}, µM, ± SD)	MCF-7[c]	OVCAR-8[d]	NCI/ ADR-RES[e]	MDA-MB-435[f]	SNB-75[g]
PTX	5.0 ± 1	7.8 ± 2	10 ± 2	4,200 ± 1,000	4.0 ± 1	15 ± 0[3]
1.01	14 ± 3	14 ± 4	20 ± 5	35 ± 5	15 ± 2	14 ± 3
1.02	3.8 ± 0.4	9.2 ± 2	11 ± 3	19 ± 4	5.3 ± 0.7	6.5 ± 2
1.03	18 ± 0.7	70 ± 10	110 ± 7	110 ± 40	–	–
1.04	18 ± 0[3]	14 ± 1	13 ± 4	17 ± 4	–	–
1.104	> 40	2.5 ± 0.7	5.5 ± 0.7	38 ± 4	–	–
1.105	19 ± 0.7	2.0 ± 0[3]	1.5 ± 0.7	35 ± 7	–	–
1.109	1.9 ± 0.4	2.0 ± 0[3]	3.0 ± 0[3]	8.3 ± 3	–	–
1.110	18 ± 2	3.0 ± 1	4.5 ± 0.7	55 ± 20	–	–
1.115	9.3 ± 1	5.0 ± 1	22 ± 5	52 ± 10		
1.134	14 ± 3	28 ± 6	75 ± 10	55 ± 7	42 ± 5	60 ± 10
1.136	> 60	65 ± 7	93 ± 20	2,800 ± 400	20 ± 3	130 ± 20
1.148	13 ± 0.4	330 ± 40	290 ± 10	3,800 ± 300	220 ± 30	280 ± 30
1.149	> 60	38 ± 2	93 ± 20	3,800 ± 400	12 ± 2	38 ± 5
1.150	9.1 ± 1	15 ± 3	8.6 ± 1	45 ± 6	3.8 ± 0.7	50 ± 10
1.151	7.9 ± 1	11 ± 1	23 ± 7	630 ± 80	3.5 ± 0.3	12 ± 3
1.152	> 60	250 ± 40	170 ± 20	4,000 ± 1,000	30 ± 4	98 ± 10
1.153	5.0 ± 1	4.0 ± 1	16 ± 4	8.8 ± 1	4.5 ± 0.5	11 ± 3
1.154	5.1 ± 0.4	18 ± 3	15 ± 2	18 ± 4	9.5 ± 2	16 ± 3
1.155	6.1 ± 0.1	14 ± 2	63 ± 3	70 ± 10	15 ± 4	23 ± 6
1.156	5.4 ± 0.6	13 ± 3	15 ± 0[3]	3.2 ± 0.8	7.3 ± 2	22 ± 3
1.157	4.6 ± 0.9	78 ± 4	10 ± 1	7.5 ± 2	12 ± 2	10 ± 2

[a] In these experiments each 100 µL reaction mixture contained 1.0 mg/mL (10 µM) tubulin, 0.4 M monosodium glutamate (taken from 2.0 M stock solution adjusted to pH 6.6 with HCl, 0.5 mM $MgCl_2$, 2% (*v*/*v*) dimethyl sulfoxide, and varying compound concentrations. Incubation was for 30 min at room temperature (about 22 °C). Reaction mixtures were centrifuged for 10 min in an Eppendorf centrifuge at room temperature at 14,000 rpm. Protein was determined in 50 µL of the supernatant, using the Lowry assay, see ref. [45]; EC_{50} = drug concentration yielding an unbound protein supernatant 50% that of controls.

[b] Cell growth was evaluated using the standard NCI assay, the parameter measured with sulforhodamine B; GI_{50} = compound concentration that reduces cell growth by 50% after 96 h at 37 °C; SD = standard deviation, a SD of 0 indicates that the same value was obtained in all three assays.

[c] Human breast cancer cell line.

[d] Human ovarian cancer cell line.

[e] The NCI/ADR-RES cell line is an isogenic clone of OVCAR-8 that overexpresses P-glycoprotein, resulting in multidrug resistance.

[f] Human melanoma cancer cell line.

[g] Human glioblastoma (brain cancer) cell line.

G. Structure-Activity Relationships & Conclusions

1. Structure-Activity Relationships

From the biological data summarized in Table **1.03**, several general observations can be made. For example, analogues **1.104**, **1.105**, **1.109**, and **1.110**, which possess the free secondary aziridine or *N*-ethoxy tertiary aziridine moiety and the natural 2-methylthiazole functional group, displayed high potencies in general, of of them surpassing the activities of the natural epothilones and paclitaxel (PTX, Table **1.03**). Intriguingly, the epothilone A or B aziridines (**1.104** and **1.105**) displayed relatively weak EC_{50} values (>40 and 19 μM, respectively) for the induction of tubulin assembly assay, yet maintain high cytotoxicity. Indeed, epothilone B aziridine analogue **1.105** is *ca*. ten times more potent than epothilone B (**1.02**) in MCF-7 human breast cancer cells (1.5 vs. 11 nM, Table **1.03**). During our attempted Stille coupling approach, we synthesized novel epothilone D analogue **1.115** (Scheme **1.07**), and its biological evaluation showed it to be a potent derivative vs. **1.04** by *ca*. threefold vs. MCF-7 breast cancer cells. Thiomethyl thiazole aziridinyl analogues **1.134**, **1.153**, and **1.156** maintained high potencies, and showed that the functional group tolerability of the *N*-ethyl linker region is fairly broad, with a primary alcohol, amine, or azide acceptable, and even the aliphatic cyclopropyl analogue **1.154** displays potency essentially equal to epothilone A (**1.01**) and surpasses epothilone B (**1.02**) in the NCI/ADR-RES cell line. Analogues **1.149** and **1.150**, which possess an unprecedented 2-hydroxyethyl or 2-aminoethyl thiazole side chains, respectively, were also potent compounds (**1.150** $-NH_2$ > **1.149** –OH), especially the amino group containing **1.150**; this is a valuable insight because this functional group is a highly useful for bioconjugation strategies (*i.e*. amide bond formation). Conversely, an amino group directly

attached to the thiazole ring (i.e. **1.148**) or with a one carbon spacer (i.e. **1.136**) were far less potent than the ethylamino thiazolyl analogue 1.150; perhaps an amino group too close to the thiazole N-atom interrupts the crucial H-bonding with tubulin necessary for high potencies. In accordance with previous communications from the Nicolaou lab regarding potent side chains, benzothiazole analogue **1.151** and pyrazole analogue **1.157** were also potent compounds, however pyridinyl analogue **1.152** did not perform as well as its previously synthesized, epoxide-containing congener. Probably the most important information gleaned from this biological data is the very promising activities displayed by analogues **1.109**, **1.153**, **1.156**, and **1.157** in the NCI/ADR-RES cell line. Particularly striking is the activities of analogues **1.156** and **1.157**, which are actually the highest in the NCI-ADR-Res cell line, displaying potencies roughly three to six times greater than **1.02** (Table **1.03**). Lastly, it is noteworthy to mention that, while tubulin binding and cytotoxicity have been shown to correlate with several of the synthesized analogues, other factors such as cellular uptake and distribution, solubility, and ionization states vary greatly depending on the chemical nature present on these designed epothilones. Therefore, these assays are just a few of several that are used to investigate the observed differences in biological activity.[61] In any event, the obtained SAR data from this study is guiding the future directions of this project, which are currently underway in the Nicolaou laboratory, and will be reported in due course.

2. Conclusions

In summary, the strategic application of ozonolysis, epoxide deoxygenation, the recently described Ess–Kürti–Falck aziridination, and the HWE reaction have established a robust, economically feasible entry into aziridinyl epothilone B analogues possessing

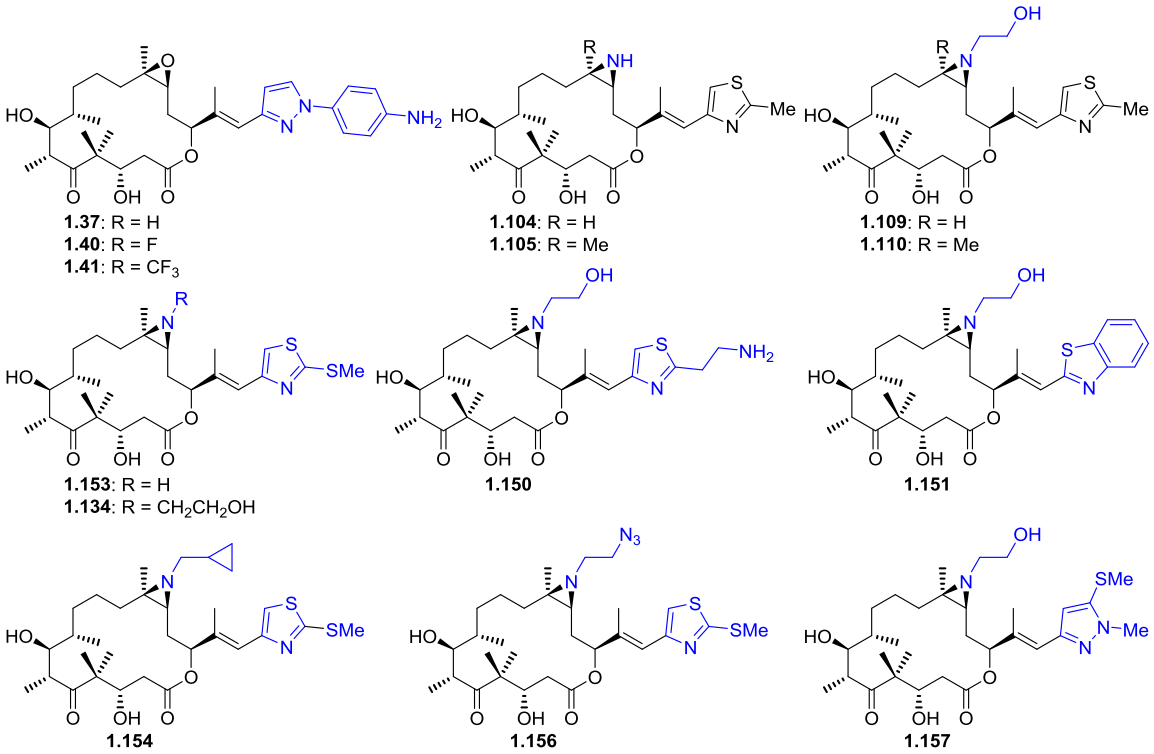


Figure **1.17**: Most potent new epothilone analogues synthesized and evaluated in this dissertation.

chemical features which were previously inaccessible. The broad synthetic power of this route is demonstrated by accomplishing a formally stereoretentive aziridine-for-epoxide bioisosteric switch and replacement of the heterocyclic side chain in only seven total steps from natural epothilone B (**1.02**). Figure **1.17** shows the most potent new epothilone analogues synthesized in this dissertation. Enhancing potency while simultaneously installing functional groups conducive to selective drug delivery was the primary goal and key accomplishment of this project. In our opinion, we feel that epothilones are excellent candidates as ADC payloads, and our results reflect this potential. Further investigations are ongoing to provide a new library of biologically interesting epothilone analogues with improved SAR and features specifically tailored for ADC development and other types of personalized cancer therapies.

H. Experimental Section

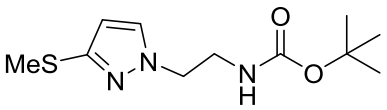
1. General Procedures

All reactions were carried out under an argon atmosphere with dry solvent under anhydrous conditions, unless otherwise noted. Dry acetonitrile (MeCN), dimethylformamide (DMF), dichloromethane, tetrahydrofuran, diethyl ether and toluene were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogenous material, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) carried out on S-2 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of *p*-anisaldehyde, an aqueous solution of cerium sulfate or a basic aqueous solution of potassium permanganate as developing agents. E. Merck silica gel (60, partical size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on a Bruker DRX-600 instrument and calibrated using residual undeuterated solvent ($CDCl_3$, δ_H = 7.26 ppm, δ_C = 77.16 ppm; C_6D_6, δ_H = 7.16 ppm, δ_C = 128.06 ppm; CD_2Cl_2, δ_H = 5.32 ppm, δ_C = 53.84 ppm) as an internal reference. The following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, qd = quartet of doublets, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dq = doublet of quartets, br = broad. Infrared (IR) spectra were recorded on a Perkin−Elmer 100 FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on an Agilent ESI-TOF (time of flight) mass spectrometer using MALDI (matrix-assisted laser desorption ionization) or ESI (electrospray ionization).

Optical rotations were recorded on a POLARTRONIC M100 polarimeter at 589 nm, and are reported in units of 10^{-1} (deg cm^2 g^{-1}).

2. Preparation of Compounds

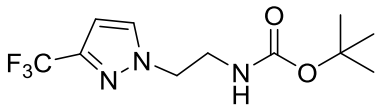
General method for the synthesis of 1.64–1.66.



1.64

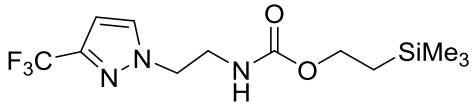
***tert*-Butyl (2-(3-(methylthio)-1*H*-pyrazol-1-yl)ethyl)carbamate 1.64**: To a stirred solution of 3-(methylthio)-1*H*-pyrazole 16a (1.0 g, 8.8 mmol, 1.2 equiv) in THF (88 mL) at 0 °C was added NaH (60% in mineral oil, 352 mg, 8.8 mmol, 1.2 equiv) in small portions. After 15 min, a solution of *tert*-butyl (2-bromoethyl)carbamate **1.60** (1.64 g, 7.3 mmol, 1.0 equiv) in THF (14.6 mL) was added dropwise, and after the reaction mixture warmed to room temperature, it was set to reflux for 12 h. Upon cooling back down to 25 °C, the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (25 mL), and the phases were separated. The aqueous layer was extracted with methylene chloride (3 x 15 mL), and the combined organic layers were dried with anhydrous magnesium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 30% ethyl acetate in methylene chloride) to afford pure **1.64** (1.39 g, 5.4 mmol, 74%) as a white amorphous solid. **1.64**: R_f = 0.62 (silica gel, 50% ethyl acetate in methylene chloride); FT-IR (neat) ν_{max} 3347, 3114, 2977, 2928, 1694, 1501, 1452, 1391, 1365, 1270, 1248, 1164, 1083, 1048, 984, 964, 923, 857, 750, 667 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.32 (d, *J* = 2.1 Hz, 1 H), 6.16 (d, *J* = 2.1 Hz, 1 H), 4.92 (br s, 1 H), 4.16 (m, 2 H), 3.52 (m, 2 H), 2.47 (s, 3 H), 1.41 (s, 9 H) ppm; ^{13}C NMR (151 MHz,

$CDCl_3$) δ = 155.8, 147.4, 131.4, 105.8, 79.6, 51.6, 40.7, 28.3, 16.4 ppm; HRMS (ESI) calcd for $C_{11}H_{19}N_3O_2S$ $[M+H]^+$ 258.1271, found 258.1272.



1.65

***tert*-Butyl (2-(3-(trifluoromethyl)-1*H*-pyrazol-1-yl)ethyl)carbamate 1.65**: Prepared from *tert*-butyl (2-bromoethyl)carbamate **1.62** (695 mg, 3.1 mmol, 1.0 equiv) and 3-(trifluoromethyl)-1*H*-pyrazole **1.61** (500 mg, 3.7 mmol, 1.2 equiv) according to the general procedure described above for the preparation of **1.64** to give **1.65** (1.39 g, 5.4 mmol, 67%) as a white amorphous solid. **1.65**: R_f = 0.47 (silica gel, 50% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3344, 2981, 2933, 1693, 1512, 1493, 1455, 1385, 1367, 1341, 1321, 1240, 1163, 1124, 1053, 1008, 988, 967, 930, 911, 856, 768, 738, 703 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.43 (br s, 1 H), 6.49 (br s, 1 H), 4.91 (br s, 1 H), 4.28 (m, 2 H), 3.55 (m, 2 H), 1.40 (s, 9 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 155.9, 142.4 (q, J = 38.2 Hz), 138.8, 118.5 (q, J = 268.5 Hz), 104.3, 79.8, 52.1, 40.5, 28.2 ppm; HRMS (ESI) calcd for $C_{11}H_{16}F_3N_3O_2$ $[M+H]^+$ 280.1267, found 280.1267.

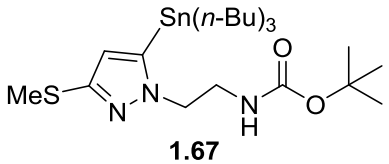


1.66

2-(Trimethylsilyl)ethyl (2-(3-(trifluoromethyl)-1*H*-pyrazol-1-yl)ethyl)carbamate 1.66: Prepared from 2-(trimethylsilyl)ethyl (2-(3-(trifluoromethyl)-1*H*-pyrazol-1-yl)ethyl)carbamate **1.63** (335 mg, 1.3 mmol, 1.0 equiv) and 3-(trifluoromethyl)-1*H*-pyrazole **1.61** (200 mg, 1.5 mmol, 1.2 equiv) according to the general procedure described above for the preparation of **1.64** to yield **1.66** (402 mg, 1.44 mmol, 96%) as a colorless

oil. **1.66**: R_f = 0.30 (silica gel, 40% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3337, 2978, 2939, 1687, 1501, 1474, 1457, 1388, 1358, 1333, 1311, 1262, 1180, 1120, 1045, 1013, 988, 964, 960, 940, 915, 874, 772, 710 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.53 (br s, 1 H), 6.62 (br s, 1 H), 5.10 (br s, 1 H), 4.34 (m, 2 H), 4.13 (m, 2 H), 3.69 (m, 2 H), 0.95 (m, 2 H), 0.02 (s, 9 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 156.8, 139.1, 132.1 (q, J = 39.0 Hz), 117.5 (q, J = 269.2 Hz), 107.8, 63.4, 50.6, 40.6, 17.8, -1.4 ppm; HRMS (ESI) calcd for $C_{12}H_{20}F_3N_3O_2Si$ $[M+H]^+$ 324.1350, found 324.1355.

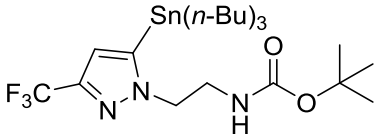
General method for the synthesis of 19a–19c.



1.67

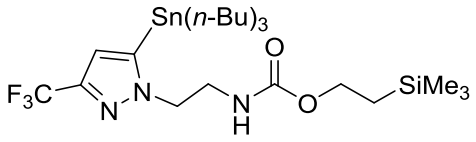
***tert*-Butyl (2-(3-(methylthio)-5-(tributylstannyl)-1*H*-pyrazol-1-yl)ethyl)carbamate 1.67**: *n*-Butyllithium (2.5 M hexanes, 6.1 mL, 15.3 mmol, 3.0 equiv) was added dropwise to a stirred solution of **1.64** (1.31 g, 5.1 mmol, 1.0 equiv) in THF (51 mL) at –78 °C. After stirring for 10 min, tributyltin chloride (1.5 mL, 5.6 mmol, 1.1 equiv) was added dropwise, and stirring was continued at –78 °C for an additional 30 min. The reaction mixture was then quenched with a saturated aqueous solution of ammonium chloride (20 mL) and allowed to warm to 25 °C. The two phases were separated, the aqueous layer was extracted with ethyl acetate (3 x 15 mL), and the combined organic layers were dried with anhydrous magnesium sulfate and concentrated *in vacuo*. The oily residue was purified by flash column chromatography (silica gel, 40% ethyl acetate in hexanes) to provide **1.67** (1.06 g, 1.9 mmol, 38%) as a colorless oil. **1.67**: R_f = 0.37 (silica gel, 40% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3361, 2956, 2925, 2871, 2853, 1713, 1503, 1456, 1391, 1376, 1364,

1300, 1265, 1247, 1168, 1118, 1071, 1047, 1026, 983, 960, 864, 775, 758, 670 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.16 (s, 1 H), 5.17 (br s, 1 H), 4.07 (m, 2 H), 3.60 (m, 2 H), 2.49 (s, 3 H), 1.56 – 1.46 (m, 6 H), 1.42 (s, 9 H), 1.35 – 1.29 (m, 6 H), 1.16 – 1.05 (m, 6 H), 0.87 (t, *J* = 7.4 Hz, 9 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 155.8, 147.0, 144.9, 114.3, 79.3, 53.4, 40.9, 28.9, 28.4, 27.1, 16.4, 13.6, 10.4 ppm; HRMS (ESI) calcd for $C_{23}H_{45}N_3O_2SSn$ $[M+H]^+$ 548.2327, found 548.2331.



1.68

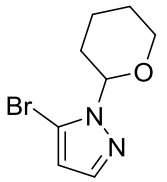
***tert*-Butyl (2-(5-(tributylstannyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)ethyl)carbamate 1.68**: Prepared from carbamate **1.65** (1.67 g, 6.0 mmol, 1.0 equiv) according to the general procedure described above for the preparation of **1.67** to provide **1.68** (1.43 g, 2.5 mmol, 42%) as a colorless oil. **1.68**: R_f = 0.42 (silica gel, 20% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3354, 2958, 2928, 2873, 2855, 1714, 1504, 1456, 1392, 1365, 1356, 1268, 1249, 1210, 1160, 1125, 1073, 1040, 999, 974, 962, 865, 804, 779, 758, 746, 736, 722, 692, 669 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.49 (s, 1 H), 4.97 (br s, 1 H), 4.16 (m, 2 H), 3.65 (m, 2 H), 1.57 – 1.46 (m, 6 H), 1.43 (s, 9 H), 1.36 – 1.30 (m, 6 H), 1.21 – 1.10 (m, 6 H), 0.88 (t, *J* = 7.3 Hz, 9 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 155.7, 145.5, 142.5 (q, *J* = 37.2 Hz), 119.1 (q, *J* = 268.9 Hz), 112.8, 79.6, 53.9, 40.6, 28.8, 28.3, 27.1, 13.6, 10.5 ppm; HRMS (ESI) calcd for $C_{23}H_{42}F_3N_3O_2Sn$ $[M+H]^+$ 570.2324, found 570.2324.



1.69

2-(Trimethylsilyl)ethyl(2-(5-(tributylstannyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)ethyl)carbamate 1.69: Prepared from carbamate **1.66** (110 mg, 0.31 mmol, 1.0 equiv) according to the general procedure described above for the preparation of **1.67** to provide **1.69** (102 mg, 0.17 mmol, 54%) as a colorless oil. **1.69**: R_f = 0.62 (silica gel, 20% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3330, 2956, 2928, 2873, 2855, 1720, 1516, 1464, 1416, 1377, 1356, 1250, 1211, 1162, 1128, 1063, 1042, 975, 946, 860, 838, 805, 774, 748, 694, 665 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.49 (s, 1 H), 5.11 (br s, 1 H), 4.16 – 4.11 (m, 2 H), 3.73 – 3.69 (m, 2 H), 1.54 – 1.48 (m, 6 H), 1.38 – 1.29 (m, 6 H), 1.22 – 1.06 (m, 6 H), 0.99 – 0.94 (m, 2 H), 0.88 (t, *J* = 7.3 Hz, 9 H), 0.03 (s, 9 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 156.7, 145.6, 122.7 (q, *J* = 39.0 Hz), 112.8 (q, *J* = 269.2 Hz), 99.6, 63.3, 53.7, 40.8, 28.9, 27.2, 17.7, 13.6, 10.5, -1.5 ppm; HRMS (ESI) calcd for $C_{24}H_{46}F_3N_3O_2SiSn$ $[M+H]^+$ 614.2406, found 614.2401.

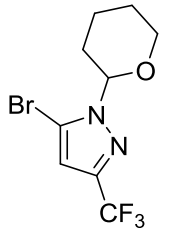
General method for the synthesis of 1.73 and 1.74.



1.73

5-Bromo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole 1.73: *n*-Butyllithium (2.5 M hexanes, 32.1 mL, 80.3 mmol, 1.3 equiv) was added dropwise to a stirred solution of **1.71** (9.4 g, 61.8 mmol, 1.0 equiv) in THF (172 mL) at –78 °C. After stirring for 15 min, bromine

(4.1 mL, 80.3 mmol. 1.3 equiv) was carefully added dropwise to the reaction mixture. The rate of addition was slow enough so as to allow complete decolorization of bromine prior to the next drop. After being allowed to warm to –30 °C over 1.5 h, the reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate (50 mL), and allowed to warm to 25 °C. The two phases were separated, the aqueous layer was extracted with ethyl acetate (3 x 25 mL), and the combined organic layers were dried with anhydrous magnesium sulfate and concentrated *in vacuo*. Purification of the crude material by flash column chromatography (silica gel, 10% ethyl acetate in hexanes) afforded **1.73** (12.0 g, 51.9 mmol, 84%) as a white amorphous solid. **1.73**: R_f = 0.29 (silica gel, 10% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3120, 2944, 2857, 1499, 1440, 1391, 1342, 1310, 1245, 1204, 1180, 1085, 1041, 977, 953, 911, 877, 822, 755 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.57 (d, *J* = 1.8 Hz, 1 H), 6.33 (d, *J* = 1.8 Hz, 1 H), 5.45 (dd, *J* = 10.0, 2.6 Hz, 1 H), 4.09 – 4.04 (m, 1 H), 3.72 –3.66 (m, 1 H), 2.50 – 2.41 (m, 1 H), 2.15 – 2.10 (m, 1 H), 1.96 –1.90 (m, 1 H), 1.76 – 1.67 (m, 2 H), 1.63 – 1.57 (m, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 141.0, 113.5, 109.3, 84.7, 68.1, 29.5, 25.0, 22.8 ppm; HRMS (ESI) calcd for $C_8H_{11}BrN_2O$ $[M+H]^+$ 231.0127, found 231.0129.

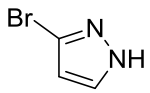


1.74

5-Bromo-1-(tetrahydro-2*H*-pyran-2-yl)-3-(trifluoromethyl)-1*H*-pyrazole 1.74: Prepared from pyrazole **1.72** (2.50g, 11.4 mmol, 1.0 equiv) according to the general

procedure described above for the preparation of **1.73** to yield brominated pyrazole **1.74** (2.66 g, 8.9 mmol, 78%) as a white amorphous solid. **1.74**: R_f = 0.67 (silica gel, 20% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3151, 2968, 2949, 2926, 2869, 1468, 1447, 1421, 1386, 1353, 1319, 1287, 1223, 1204, 1171, 1120, 1080, 1060, 1043, 997, 969, 940, 911, 880, 847, 823, 794, 742, 719, 649 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.61 (s, 1 H), 5.51 (dd, *J* = 9.6, 2.8 Hz, 1 H), 4.08 – 4.03 (m, 1 H), 3.73 – 3.66 (m, 1 H), 2.50 – 2.40 (m, 1 H), 2.18 – 2.11 (m, 1 H), 1.98 – 1.91 (m, 1 H), 1.77 – 1.59 (m, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 143.1 (q, *J* = 39.1 Hz), 117.5 (q, *J* = 270.0 Hz), 114.8, 107.7 (q, *J* = 2.1 Hz), 85.4, 68.0, 29.1, 24.8, 22.3 ppm; HRMS (ESI) calcd for $C_9H_{10}BrF_3N_2O$ $[M+Na]^+$ 320.9821, found 320.9817.

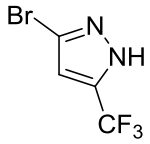
General method for the synthesis of 1.75 and 1.76.



1.75

5-Bromo-1*H*-pyrazole 1.76: To a stirred solution of **1.73** (6.24 g, 27.0 mmol, 1.0 equiv) in methanol (450 mL) was added methanesulfonic acid (8.8 mL, 135 mmol, 5.0 equiv) at 25 °C and the reaction mixture was stirred for 1 h. Then the resulting reaction mixture was neutralized by the addition of solid sodium bicarbonate (22 g, 0.262 mol, 20 equiv), filtered, and concentrated *in vacuo*. Purification of the residue by flash column chromatography (silica gel, 20% ethyl acetate in hexanes) provided **1.75** (3.77 g, 25.7 mmol, 95%) as a white solid. **1.75**: R_f = 0.20 (silica gel, 20% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3143, 3034, 2966, 2904, 2858, 2774, 2628, 1544, 1475, 1388, 1342, 1241, 1182, 1082, 1047, 996, 957, 919, 870, 815, 755, 655, 607 cm^{-1}; ^1H NMR (600 MHz,

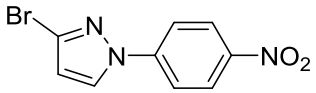
$CDCl_3$) δ = 12.20 (br s, 1 H), 7.59 (d, *J* = 2.4 Hz, 1 H), 6.37 (d, *J* = 2.4 Hz, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 131.1, 125.7, 108.0 ppm; HRMS (ESI) calcd for $C_3H_3BrN_2$ $[M+H]^+$ 146.9552 found 146.9556.



1.76

5-Bromo-3-(trifluoromethyl)-1*H*-pyrazole 1.76: Prepared from pyrazole **1.74** (2.22 g, 3.34 mmol, 1.0 equiv) according to the general procedure described above for the preparation of **1.75** to yield deprotected pyrazole **1.76** (1.46 g, 3.0 mmol, 91%) as a white amorphous solid. **1.76**: R_f = 0.63 (silica gel, 20% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3119, 3016, 2970, 2934, 2898, 2818, 2771, 1542, 1494, 1456, 1377, 1362, 1319, 1301, 1283, 1232, 1175, 1137, 1071, 1032, 990, 982, 844, 803, 746, 723, 621 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 12.12 (br s, 1 H), 6.63 (s, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 141.97 (q, *J* = 37.6 Hz), 117.2, 116.9 (q, *J* = 269.0 Hz), 107.3 (q, *J* = 2.3 Hz) ppm; HRMS (ESI) calcd for $C_4H_2BrF_3N_2$ $[M-H]^-$ 212.9281 found 212.9289.

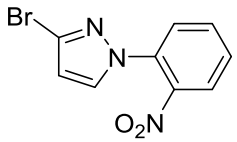
General method for the synthesis of 1.78, **1.80**, **1.90**, **1.92**.



1.78

3-Bromo-1-(4-nitrophenyl)-1*H*-pyrazole 1.78: Sodium hydride (60% *w*/*w* in mineral oil, 41 mg, 1.02 mmol, 1.5 equiv) was carefully added in portions to a stirred solution of **1.75** (100 mg, 0.68 mmol, 1.0 equiv) in THF (6.8 mL) at 0 °C. After 20 min, 1-fluoro-4-nitrobenzene **1.77** (0.08 mL, 0.75 mmol, 1.1 equiv) was added dropwise, and the reaction

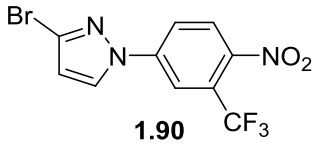
mixture was heated to 60 °C. Upon consumption of the starting material as indicated by TLC, the reaction mixture was cooled to 25 °C, quenched with a saturated aqueous solution of ammonium chloride (1.2 mL), and the two phases were separated. The aqueous layer was extracted with ethyl acetate (3 x 5 mL), and the combined organic layers were dried with anhydrous magnesium sulfate and concentrated *in vacuo*. The obtained crude residue was purified by flash column chromatography (silica gel, 20% ethyl acetate in hexanes) to afford *N*-arylpyrazole **1.78** (144 mg, 0.54 mmol, 79%) as a white solid. **1.78**: R_f = 0.30 (silica gel, 20% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3144, 1595, 1516, 1407, 1359, 1335, 1200, 1176, 1112, 1042, 955, 937, 852, 749, 732, 684 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 8.33 (d, *J* = 9.2 Hz, 2 H), 7.93 (d, *J* = 2.6 Hz, 1 H), 7.84 (d, *J* = 9.2 Hz, 2 H), 6.58 (d, *J* = 2.6 Hz, 1H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 145.9, 143.7, 130.7, 129.0, 125.6, 118.6, 112.6 ppm; HRMS (ESI) calcd for $C_9H_6BrN_3O_2$ $[M+H]^+$ 267.9716 found 267.9711.



1.80

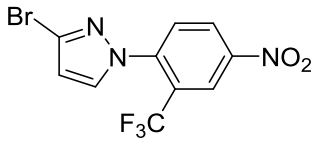
3-Bromo-1-(2-nitrophenyl)-1*H*-pyrazole 1.80: Prepared from pyrazole **1.75** (100 mg, 0.68 mmol, 1.0 equiv) and 1-fluoro-2-nitrobenzene **1.81** according to the general procedure described above for the preparation of **1.78** to yield *N*-arylpyrazole **1.80** (134 mg, 0.50 mmol, 74%) as a white amorphous solid. **1.80**: R_f = 0.15 (silica gel, 20% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3216, 2877, 1682, 1608, 1532, 1513, 1466, 1416, 1364, 1303, 1185, 1104, 1045, 955, 941, 852, 777, 746, 705 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.92

(dd, *J* = 8.1 1.4 Hz, 1 H), 7.69 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1 H), 7.59 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.59 (d, *J* = 2.5 Hz, 1 H), 7.55 (ddd, *J* = 8.1, 7.5, 1.4 Hz, 1 H), 6.51 (d, *J* = 2.5 Hz, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 133.5, 133.1, 132.4, 129.5, 129.3, 127.1, 125.4, 111.4 ppm; HRMS (ESI) calcd for $C_9H_6BrN_3O_2$ $[M+H]^+$ 267.9716 found 267.9704.



1.90

3-Bromo-1-(4-nitro-3-(trifluoromethyl)phenyl)-1*H*-pyrazole 1.90: Prepared from pyrazole **1.75** (300 mg, 2.04 mmol, 1.0 equiv) and **1.88** according to the general procedure described above for the preparation of **1.78** to yield *N*-arylpyrazole **1.90** (548 mg, 1.63 mmol, 80%) as a white amorphous solid. **1.90**: R_f = 0.41 (silica gel, 25% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3135, 3094, 2925, 2869, 1596, 1538, 1514, 1458, 1433, 1397, 1345, 1296, 1274, 1238, 1176, 1143, 1072, 1042, 952, 904, 885, 859, 841, 756, 723, 660, 613 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.17 (d, *J* = 2.2 Hz, 1 H), 8.07 (d, *J* = 8.9 Hz, 1 H), 7.98 (dd, *J* = 8.9, 2.2 Hz, 1 H), 7.94 (d, *J* = 2.6 Hz, 1 H), 6.61 (d, *J* = 2.6 Hz, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 145.5, 142.0, 131.4, 129.0, 127.5, 125.8 (q, *J* = 34.7 Hz), 121.3, 118.9 (q, *J* = 274.0 Hz), 117.7 (q, *J* = 5.8 Hz), 113.2 ppm; HRMS (ESI) calcd for $C_{10}H_5BrF_3N_3O_2$ $[M+H]^+$ 335.9590 found 335.9581.

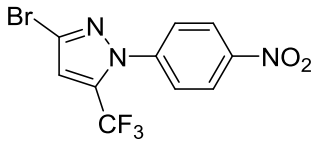


1.92

3-Bromo-1-(4-nitro-2-(trifluoromethyl)phenyl)-1*H*-pyrazole 1.92: Prepared from pyrazole **1.75** (450 mg, 3.06 mmol, 1.0 equiv) and **1.94** according to the general procedure

described above for the preparation of **1.78** to yield *N*-arylpyrazole **1.92** (699 mg, 2.08 mmol, 68%) as a white amorphous solid. **1.92**: R_f = 0.53 (silica gel, 25% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3129, 3094, 2924, 2855, 1624, 1594, 1536, 1511, 1442, 1407, 1346, 1313, 1287, 1173, 1139, 1116, 1075, 1048, 1031, 954, 942, 916, 886, 848, 790, 752, 735, 720, 668, 653, 625 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 8.69 (d, *J* = 2.4 Hz, 1 H), 8.51 (dd, *J* = 8.8, 2.4 Hz, 1 H), 7.87 (d, *J* = 8.8 Hz, 1 H), 7.71 (d, *J* = 2.3 Hz, 1 H), 6.57 (d, *J* = 2.6 Hz, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 146.9, 142.6, 133.9 (q, *J* = 3.3 Hz), 130.5, 130.1, 127.9, 125.4 (q, *J* = 33.4 Hz), 123.5 (q, *J* = 5.5 Hz), 119.2 (q, *J* = 274.3 Hz), 111.9 ppm; HRMS (ESI) calcd for $C_{10}H_5BrF_3N_3O_2$ $[M+H]^+$ 335.9590 found 335.9583.

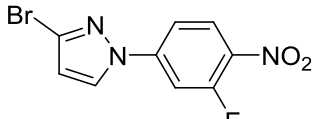
General method for the synthesis of 1.79, **1.91**, **1.93**.



1.79

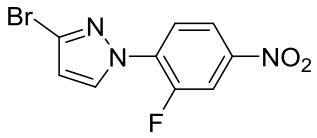
3-Bromo-1-(4-nitrophenyl)-5-(trifluoromethyl)-1*H*-pyrazole 1.79: To a stirred suspension of **1.76** (5.0 g, 23.3 mmol, 1.0 equiv) and anhydrous potassium carbonate (3.9 g, 27.9 mmol, 1.2 equiv) in DMF (116 mL), 1-fluoro-4-nitrobenzene **1.77** (2.5 mL, 23.5 mmol, 1.01 equiv) was added at 25 °C, and the reaction mixture was heated to 80 °C. After 12 h, the reaction mixture was allowed to cool to 25 °C, and was then quenched with a saturated aqueous solution of ammonium chloride (20 mL), and the two phases were separated. The aqueous layer was extracted with ethyl acetate (3 x 15 mL), and the combined organic layers were washed with water (2 x 15 mL) and brine (15 mL), dried with anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash column chromatography (silica gel, 8% → 20% ethyl acetate in hexanes) with a slow gradient to

separate the undesired regioisomer afforded **1.79** (1.57 g, 4.66 mmol, 20%) as a white amorphous solid. **1.79**: R_f = 0.61 (silica gel, 20% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3149, 2923, 2853, 1598, 1527, 1502, 1454, 1347, 1288, 1216, 1180, 1141, 1112, 1076, 986, 963, 854, 812, 757, 689 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 8.37 (d, *J* = 9.0 Hz, 2 H), 7.71 (d, *J* = 9.0 Hz, 2 H), 6.93 (s, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 148.1, 143.1, 134.3 (q, *J* = 40.4 Hz), 128.6, 125.9, 124.9, 116.1 (q, *J* = 270.0 Hz), 113.3 (q, *J* = 2.6 Hz) ppm; HRMS (ESI) calcd for $C_{10}H_5BrF_3N_3O_2$ $[M+H]^+$ 335.9590 found 335.9588.



1.91

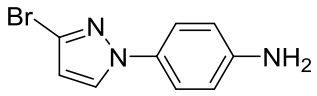
3-Bromo-1-(3-fluoro-4-nitrophenyl)-1*H*-pyrazole 1.91: Prepared from pyrazole **1.75** (120 mg, 0.82 mmol, 1.0 equiv) and **1.89** according to the general procedure described above for the preparation of **1.79** to yield *N*-arylpyrazole **1.91** (141 mg, 0.49 mmol, 58%) as a white amorphous solid. **1.91**: R_f = 0.29 (silica gel, 20% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3124, 3087, 2923, 2873, 1618, 1597, 1532, 1512, 1489, 1443, 1410, 1350, 1308, 1279, 1255, 1218, 1173, 1110, 1055, 1041, 969, 954, 881, 831, 751, 700, 656, 629 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.98 (dd, *J* = 9.0, 5.3 Hz, 1 Hz), 7.57 (d, *J* = 2.3 Hz, 1 H), 7.35 (dd, *J* = 8.4, 2.4 Hz, 1 H), 7.22 (dt, *J* = 6.7, 2.5 Hz, 1 H), 6.53 (d, *J* = 2.3 Hz, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 163.5 (d, *J* = 258.9 Hz), 140.4 (d, *J* = 2.9 Hz), 135.1 (d, *J* = 11.1 Hz), 132.5, 130.2, 127.9 (d, *J* = 9.9 Hz), 116.0 (d, *J* = 23.1 Hz), 114.6 (d, *J* = 25.9 Hz), 111.9 ppm; HRMS (ESI) calcd for $C_9H_5BrFN_3O_2$ $[M+H]^+$ 285.9622 found 285.9627.



1.93

3-Bromo-1-(2-fluoro-4-nitrophenyl)-1*H*-pyrazole 1.93: Prepared from pyrazole **1.75** (120 mg, 0.82 mmol, 1.0 equiv) and **1.95** according to the general procedure described above for the preparation of **1.79** to yield *N*-arylpyrazole **1.93** (215 mg, 0.75 mmol, 89%) as a white amorphous solid. **1.93**: R_f = 0.63 (silica gel, 20 % ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3175, 3136, 3090, 2945, 1609, 1512, 1406, 1340, 1228, 1133, 1030, 953, 915, 893, 836, 810, 768, 739 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 8.28 – 8.25 (m, 1 H), 8.20 – 8.17 (m, 2 H), 8.10 (t, *J* = 2.6 Hz, 1 H), 6.61 (d, *J* = 2.6 Hz, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 150.7 (d, *J* = 252.9 Hz), 145.8 (d, *J* = 7.7 Hz), 133.3 (14.6 Hz), 132.5 (d, *J* = 8.5 Hz), 130.8 (d, *J* = 1.3 Hz), 123.8, 120.8 (d, *J* = 3.3 Hz), 113.4 (d, *J* = 26.1 Hz), 112.5 (d, *J* = 2.5 Hz) ppm; HRMS (ESI) calcd for $C_9H_5BrFN_3O_2$ $[M+H]^+$ 285.9622 found 285.9636.

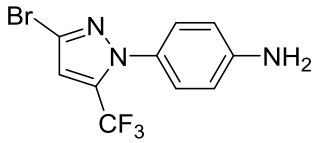
General method for the synthesis of 1.82–1.84 and 1.96–1.99.



1.82

4-(3-Bromo-1*H*-pyrazol-1-yl)aniline 1.82: A solution of concentrated hydrochloric acid in isopropanol (15% *v*/*v* HCl in *i*-PrOH, 0.74 mL) was carefully added to a flask containing tin dichloride (364 mg, 1.9 mmol, 3.0 equiv) and **1.78** (171 mg, 0.64 mmol, 1.0 equiv) at 0 °C with stirring. The reaction mixture was then heated to 70 °C until the starting material was consumed as judged by TLC. Following neutralization with a saturated aqueous

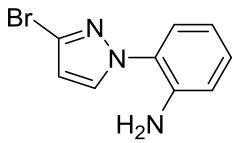
solution of sodium bicarbonate (15 mL), the two phases were separated, the aqueous layer was extracted with ethyl acetate (3 x 4 mL), and the combined organic layers were dried with anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, 40% ethyl acetate in hexanes) afforded **1.82** (114 mg, 0.48 mmol, 75%) as a pale yellow amorphous solid. **1.82**: R_f = 0.47 (silica gel, 50% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3420, 3353, 3223, 3143, 2923, 1624, 1521, 1416, 1366, 1286, 1176, 1127, 1044, 957, 942, 827, 751 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.65 (d, *J* = 2.4 Hz, 1 H), 7.38 (d, *J* = 8.9 Hz, 2 H), 6.71 (d, *J* = 8.9 Hz, 2 H), 6.41 (d, *J* = 2.4 Hz, 1 H), 3.76 (br s, 2 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 145.8, 131.9, 128.8, 127.1, 121.2, 115.5, 109.9 ppm; HRMS (ESI) calcd for $C_9H_8BrN_3$ $[M+H]^+$ 237.9974 found 237.9983.



1.83

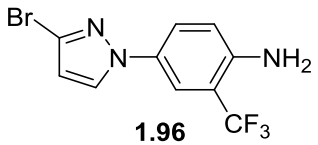
4-(3-Bromo-4-(trifluoromethyl)-1*H*-pyrazol-1-yl)aniline 1.83: Prepared from pyrazole **1.79** (342 mg, 1.02 mmol, 1.0 equiv) according to the general procedure described above for the preparation of **1.82** to yield *N*-arylpyrazole **1.83** (238 mg, 0.78 mmol, 76%) as a pale yellow amorphous solid. **1.83**: R_f = 0.61 (silica gel, 20% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3149, 2923, 2853, 1598, 1527, 1502, 1454, 1347, 1288, 1216, 1180, 1141, 1112, 1076, 986, 963, 854, 812, 757, 689 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 8.37 (d, *J* = 9.0 Hz, 2 H), 7.71 (d, *J* = 9.0 Hz, 2 H), 6.93 (s, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 148.1, 143.1, 134.3 (q, *J* = 40.4 Hz), 128.6, 125.9, 124.9, 116.1 (q, *J* = 270.0 Hz), 113.3

(q, J = 2.6 Hz) ppm; HRMS (ESI) calcd for $C_{10}H_5BrF_3N_3O_2$ $[M+H]^+$ 335.9590 found 335.9588.



1.84

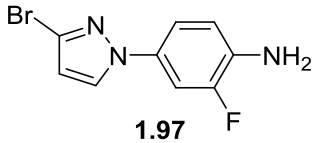
2-(3-Bromo-1*H*-pyrazol-1-yl)aniline 1.84: Prepared from pyrazole **1.80** (121 mg, 0.45 mmol, 1.0 equiv) according to the general procedure described above for the preparation of **1.82** to yield *N*-arylpyrazole **1.84** (75 mg, 0.32 mmol, 70%) as an orange amorphous solid. **1.84**: R_f = 0.51 (silica gel, 20% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3452, 3359, 3143, 1619, 1511, 1462, 1420, 1363, 1339, 1282, 1180, 1159, 1044, 957, 942, 749, 673 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.59 (d, J = 2.4 Hz, 1 H), 7.19 – 7.12 (m, 2 H), 6.84 – 6.76 (m, 2 H), 6.46 (d, J = 2.4 Hz, 1 H), 4.55 (br s, 2 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 141.2, 132.1, 129.2, 127.3, 126.2,124.3, 118.3, 117.5, 109.7 ppm; HRMS (ESI) calcd for $C_9H_8BrN_3$ $[M+H]^+$ 237.9974 found 237.9963.



1.96

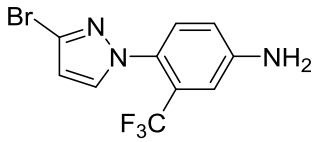
4-(3-Bromo-1*H*-pyrazol-1-yl)-2-(trifluoromethyl)aniline 1.96: Prepared from pyrazole **1.90** (227 mg, 0.68 mmol, 1.0 equiv) according to the general procedure described above for the preparation of **1.82** to yield *N*-arylpyrazole **1.96** (132 mg, 0.43 mmol, 63%) as a pale yellow amorphous solid. **1.96**: R_f = 0.36 (silica gel, 25% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3504, 3408, 3245, 3148, 2924, 1637, 1590, 1516, 1465, 1454, 1414, 1370, 1347, 1313, 1297, 1263, 1232, 1172, 1142, 1107, 1075, 1043, 961, 951, 898, 859, 822,

750, 686, 646, 614 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.67 (m, 2 H), 7.55 (dd, *J* = 8.7, 2.1 Hz, 1 H), 6.79 (d, *J* = 8.7 Hz, 1 H), 6.45 (d, *J* = 2.3 Hz, 1 H), 4.27 (br s, 2 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 143.6, 130.9, 128.8, 127.8, 124.6, 121.7 (q, *J* = 272.6 Hz), 118.3 (q, *J* = 5.5 Hz), 118.1, 113.8 (q, *J* = 31.0 Hz), 110.4 ppm; HRMS (ESI) calcd for $C_{10}H_7BrF_3N_3$ $[M+H]^+$ 305.9848 found 305.9850.



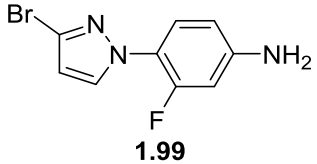
1.97

4-(3-Bromo-1*H*-pyrazol-1-yl)-2-fluoroaniline 1.97: Prepared from pyrazole **1.91** (380 mg, 1.3 mmol, 1.0 equiv) according to the general procedure described above for the preparation of **1.82** to yield *N*-arylpyrazole **1.97** (240 mg, 0.94 mmol, 72%) as a light brown oil. **1.97**: R_f = 0.29 (silica gel, 20% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3451, 3357, 3219, 3144, 2923, 2852, 1601, 1515, 1499, 1441, 1421, 1364, 1344, 1294, 1274, 1205, 1165, 1141, 1040, 971, 954, 875, 860, 812, 784, 756, 681, 625 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.60 (d, *J* = 2.5 Hz, 1 H), 6.94 – 6.91 (m, 2 H), 6.83 – 6.80 (m, 1 H), 6.48 (d, *J* = 2.5 Hz, 1 H), 4.21 (br s, 2 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 154.6 (d, *J* = 237.7 Hz), 137.3 (d, *J* = 2.4 Hz), 132.0, 127.8, 125.9 (d, *J* = 9.1 Hz), 118.2 (d, *J* = 8.0 Hz), 115.9 (d, *J* = 22.0 Hz), 111.0 (d, *J* = 25.3 Hz), 110.1 ppm; HRMS (ESI) calcd for $C_9H_7BrFN_3$ $[M+H]^+$ 255.9880 found 255.9870.



1.98

4-(3-Bromo-1*H*-pyrazol-1-yl)-3-(trifluoromethyl)aniline 1.98: Prepared from pyrazole **1.92** (340 mg, 1.0 mmol, 1.0 equiv) according to the general procedure described above for the preparation of **1.82** to yield *N*-arylpyrazole **1.98** (179 mg, 0.59 mmol, 57%) as a pale orange amorphous solid. **1.98**: R_f = 0.19 (silica gel, 25% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3478, 3349, 3230, 3147, 3030, 1632, 1527, 1457, 1424, 1367, 1336, 1269, 1169, 1128, 1078, 1046, 1032, 958, 944, 905, 872, 830, 758, 681, 647 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.45 (d, *J* = 1.6 Hz, 1 H), 7.24 (s, 1 H), 6.97 (d, *J* = 2.5 Hz, 1 H), 6.82 (dd, *J* = 8.5, 2.5 Hz, 1 H), 6.41 (d, *J* = 2.4 Hz, 1 H), 4.06 (br s, 2 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 147.5, 134.3 (q, *J* = 1.8 Hz), 130.8, 128.4, 127.4, 127.2 (q, *J* = 31.3 Hz), 120.2 (q, *J* = 273.6 Hz), 117.6, 112.2 (q, *J* = 5.2 Hz), 109.4 ppm; HRMS (ESI) calcd for $C_{10}H_7BrF_3N_3$ $[M+H]^+$ 305.9848 found 305.9854.

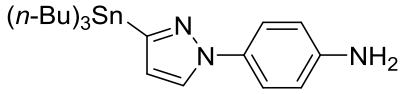


1.99

4-(3-Bromo-1*H*-pyrazol-1-yl)-3-fluoroaniline 1.99: Prepared from pyrazole **1.93** (420 mg, 1.47 mmol, 1.0 equiv) according to the general procedure described above for the preparation of **1.82** to yield *N*-arylpyrazole **1.99** (320 mg, 1.25 mmol, 85%) as a white amorphous solid. **1.99**: R_f = 0.24 (silica gel, 33% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3468, 3354, 3227, 3146, 2924, 1633, 1590, 1527, 1461, 1423, 1370, 1327, 1256, 1171, 1134, 1038, 955, 937, 840, 813, 754 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.67 (t, *J* = 2.4

Hz, 1 H), 7.50 – 7.47 (m, 1 H), 6.46 (m, 2 H), 6.43 (d, J = 2.4 Hz, 1 H), 3.90 (br s, 2 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 154.0 (d, J = 247.6 Hz), 147.4 (d, J = 10.8 Hz), 132.9 (d, J = 7.3 Hz), 127.3, 126.2 (d, J = 1.8 Hz), 119.2 (d, J = 11.0 Hz), 111.1 (d, J = 2.8 Hz), 109.8, 102.4 (d, J = 23.5 Hz) ppm; HRMS (ESI) calcd for $C_9H_7BrFN_3$ $[M+H]^+$ 255.9980 found 255.9980.

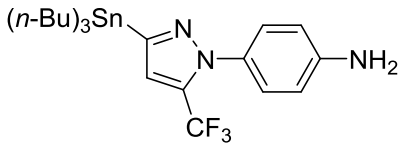
General method for the synthesis of 25a–25g.



1.85

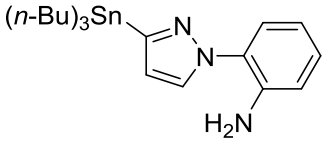
4-(3-(Tributylstannyl)-1*H*-pyrazol-1-yl)aniline 1.85: To a sealed tube containing **1.82** (120 mg, 0.50 mmol, 1.0 equiv) and tetrakis(triphenylphosphine)palladium (58 mg, 0.05 mmol, 0.1 equiv) in carefully degassed (freeze-pump-thaw technique) toluene (5 mL) was added hexabutylditin (0.76 mL, 1.5 mmol, 3.0 equiv) with stirring. The reaction mixture was heated to 110 °C and stirred for 12 h. The reaction mixture was allowed to cool to 25 °C, then filtered through celite and concentrated *in vacuo*. Flash column chromatography (silica gel, 5% → 25% ethyl acetate in hexanes) provided stannane **1.85** (180 mg, 0.40 mmol, 80%) as a light brown oil. **1.85**: R_f = 0.24 (silica gel, 25% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3463, 3343, 2955, 2923, 2870, 2852, 1625, 1520, 1479, 1463, 1417, 1376, 1342, 1283, 1216, 1170, 1125, 1072, 1030, 956, 874, 865, 827, 751, 692, 669, 625 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.83 (d, J = 1.9 Hz, 1 H), 7.46 (d, J = 8.6 Hz, 2 H), 6.72 (d, J = 8.6 Hz, 2 H), 6.46 (d, J = 1.9 Hz, 1 H), 1.62 – 1.55 (m, 6 H), 1.38 – 1.32 (m, 6 H), 1.17 – 1.05 (m, 6 H), 0.89 (t, J = 7.4 Hz, 9H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ =

153.4, 144.9, 133.0, 126.6, 121.3, 115.6, 115.2, 29.3, 27.4, 13.9, 10.1 ppm; HRMS (ESI) calcd for $C_{21}H_{35}N_3Sn$ $[M+H]^+$ 450.1929 found 450.1926.



1.86

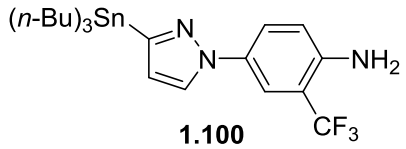
4-(3-(Tributylstannyl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)aniline 1.86: Prepared from pyrazole **1.83** (177 mg, 0.58 mmol, 1.0 equiv) according to the general procedure described above for the preparation of **1.85** to yield stannane **1.86** (192 mg, 0.36 mmol, 66%) as a light brown oil. **1.86**: R_f = 0.29 (silica gel, 20% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3474, 3379, 3219, 2957, 2924, 2872, 2853, 1627, 1519, 1463, 1417, 1376, 1350, 1278, 1195, 1164, 1130, 1097, 1066, 1016, 986, 960, 875, 830, 746, 696, 668, 645 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.23 (d, *J* = 8.4 Hz, 2 H), 6.75 (m, 3 H), 1.60 – 1.55 (m, 6 H), 1.39 –1.30 (m, 6 H), 1.18 – 1.06 (m, 6 H), 0.88 (t, *J* = 7.4 Hz, 9 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 152.8, 132.4 (q, *J* = 38.4 Hz), 131.1, 127.1, 125.3, 118.3 (q, *J* = 269.0 Hz), 116.4, 115.3, 29.2, 27.4, 13.8, 10.2 ppm; HRMS (ESI) calcd for $C_{22}H_{34}F_3N_3Sn$ $[M+H]^+$ 518.1803 found 518.1815.



1.87

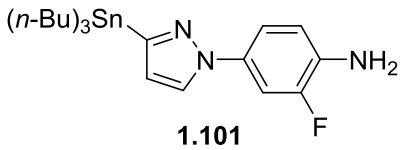
2-(3-(Tributylstannyl)-1*H*-pyrazol-1-yl)aniline 1.87: Prepared from pyrazole **1.84** (182 mg, 0.76 mmol, 1.0 equiv) according to the general procedure described above for the preparation of **1.85** to yield stannane **1.87** (276 mg, 0.60 mmol, 78%) as a pale orange oil.

1.87: R_f = 0.36 (silica gel, 10% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3463, 3337, 2956, 2925, 2870, 2852, 1617, 1589, 1509, 1462, 1376, 1340, 1293, 1159, 1072, 1019, 959, 875, 744, 695, 671 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ = 7.42 (d, *J* = 2.3 Hz, 1 H), 6.95 – 6.91 (m, 2 H), 6.54 (ddd, *J* = 7.9, 7.3, 1,4 Hz, 1 H), 6.48 (d, *J* = 2.3 Hz, 1 H), 6.40 (ddd, *J* = 7.9, 1.4, 0.3 Hz, 1 H), 4.75 (br s, 2 H), 1.74 – 1.68 (m, 6 H), 1.44 – 1.37 (m, 6 H), 1.22 – 1.19 (m, 6 H), 0.91 (t, *J* = 7.3 Hz, 9 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 132.8, 131.2, 128.9, 128.5, 128.4, 126.0, 123.4, 119.5, 104.3, 29.9, 27.0, 14.3, 13.8 ppm; HRMS (ESI) calcd for $C_{21}H_{35}N_3Sn$ $[M+H]^+$ 450.1929 found 450.1926.



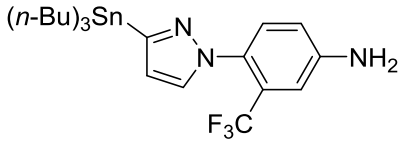
1.100

4-(3-(Tributylstannyl)-1*H*-pyrazol-1-yl)-2-(trifluoromethyl)aniline 1.100: Prepared from pyrazole **1.96** (450 mg, 1.47 mmol, 1.0 equiv) according to the general procedure described above for the preparation of **1.85** to yield stannane **1.100** (415 mg, 0.80 mmol, 55%) as a light brown oil. **1.100**: R_f = 0.36 (silica gel, 25% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3509, 3402, 2957, 2925, 2872, 2853, 1638, 1517, 1464, 1418, 1356, 1299, 1260, 1212, 1142, 1113, 1032, 962, 901, 877, 825, 751, 686 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.85 (d, *J* = 2.3 Hz, 1 H), 7.75 (d, *J* = 2.6 Hz, 1 H), 7.61 (dd, *J* = 8.7, 2.6 Hz, 1 H), 6.80 (d, *J* = 8.7 Hz, 1 H), 6.48 (d, *J* = 2.3 Hz, 1 H), 4.19 (br s, 2 H), 1.65 – 1.56 (m, 6 H), 1.39 – 1.31 (m, 6 H), 1.13 – 1.09 (m, 6 H), 0.88 (t, *J* = 7.3 Hz, 9 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 154.3, 142.8 (q, *J* = 1.7 Hz), 132.1, 126.5, 124.7, 121.9 (q, *J* = 270.9 Hz), 118.3 (q, *J* = 5.5 Hz), 118.0, 115.7, 113.9 (q, *J* = 30.9 Hz), 29.2, 27.4, 13.9, 10.1 ppm; HRMS (ESI) calcd for $C_{22}H_{34}F_3N_3Sn$ $[M+H]^+$ 518.1803 found 518.1781.



1.101

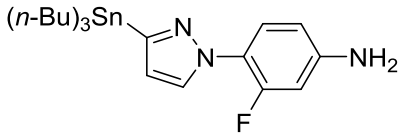
2-Fluoro-4-(3-(tributylstannyl)-1*H*-pyrazol-1-yl)aniline 1.101: Prepared from pyrazole **1.97** (1.13 g, 4.4 mmol, 1.0 equiv) according to the general procedure described above for the preparation of **1.85** to yield stannane **1.101** (1.44 g, 3.10 mmol, 70%) as a light brown oil. **1.101**: R_f = 0.32 (silica gel, 10% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3453, 3334, 2956, 2926, 2852, 1600, 1518, 1486, 1463, 1376, 1346, 1293, 1271, 1197, 1139, 1073, 1030, 971, 875, 808, 756, 693 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ = 7.22 (d, *J* = 2.3 Hz, 1 H), 6.67 (dd, *J* = 9.2, 2.9 Hz, 1 H), 6.60 (ddd, *J* = 8.8, 2.9, 0.9 Hz, 1 H), 6.41 (d, *J* = 2.3 Hz, 1 H), 6.11 (dd, *J* = 8.8, 5.2 Hz, 1 H), 4.64 (br s, 2 H), 1.72 – 1.66 (m, 6 H), 1.44 – 1.36 (m, 6 H), 1.21 – 1.17 (m, 6 H), 0.91 (t, *J* = 7.4 Hz, 9 H) ppm; ^{13}C NMR (151 MHz, C_6D_6) δ = 154.5 (d, *J* = 235.4 Hz), 153.7, 137.6 (d, *J* = 2.3 Hz), 134.1 (d, *J* = 19.7 Hz), 129.5, 117.9 (d, *J* = 8.1 Hz), 114.8, 114.2 (d, *J* = 21.9 Hz), 110.2 (d, *J* = 25.3 Hz), 29.6, 27.7, 14.0, 10.4 ppm; HRMS (ESI) calcd for $C_{21}H_{34}FN_3Sn$ $[M+H]^+$ 468.1835 found 468.1816.



1.102

4-(3-(Tributylstannyl)-1*H*-pyrazol-1-yl)-3-(trifluoromethyl)aniline 1.102: Prepared from pyrazole **1.98** (600 mg, 1.96 mmol, 1.0 equiv) according to the general procedure described above for the preparation of **1.85** to yield stannane **1.102** (520 mg, 1.0 mmol,

52%) as a light brown oil. **1.102**: R_f = 0.29 (silica gel, 25% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3322, 3208, 2957, 2924, 2872, 2853, 1633, 1523, 1457, 1376, 1349, 1334, 1267, 1219, 1173, 1131, 1073, 1046, 1019, 958, 905, 873, 829, 758, 647 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.62 (dm, *J* = 2.3 Hz, 1 H), 7.23 (d, *J* = 8.5 Hz, 1 H), 6.96 (d, *J* = 2.7 Hz, 1 H), 6.81 (dd, *J* = 8.5, 2.7 Hz, 1 H), 6.45 (d, *J* = 2.3 Hz, 1 H), 4.01 (br s, 2 H), 1.59 – 1.53 (m, 6 H), 1.36 – 1.29 (m, 6 H), 1.11 – 1.08 (m, 6 H), 0.86 (t, *J* = 7.3 Hz, 9 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 153.2, 146.9, 131.8, 130.6, 127.1 (q, *J* = 31.0 Hz), 120.4 (q, *J* = 274.0 Hz), 117.7, 114.4, 112.4 (q, *J* = 5.2 Hz), 29.2, 27.4, 13.8, 10.1 ppm; HRMS (ESI) calcd for $C_{22}H_{34}F_3N_3Sn$ $[M+H]^+$ 518.1803 found 518.1801.

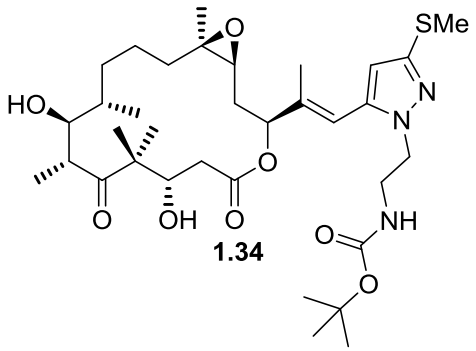


1.103

3-Fluoro-4-(3-(tributylstannyl)-1*H*-pyrazol-1-yl)aniline 1.103: Prepared from pyrazole **1.99** (591 mg, 2.3 mmol, 1.0 equiv) according to the general procedure described above for the preparation of **1.85** to yield stannane **1.103** (735 mg, 1.59 mmol, 69%) as a pale orange oil. **1.103**: R_f = 0.19 (silica gel, 20% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3362, 3210, 2956, 2925, 2853, 1635, 1589, 1525, 1462, 1325, 1295, 1247, 1170, 1130, 1073, 1020, 964, 838, 811, 755, 693, 666, 624 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ = 7.90 (dd, *J* = 5.3, 2.3 Hz, 1 H), 7.79 (t, *J* = 8.6 Hz, 1 H), 6.58 (d, *J* = 2.3 Hz, 1 H), 5.91 – 5.86 (m, 2 H), 2.57 (br s, 2 H), 1.77 – 1.71 (m, 6 H), 1.46 – 1.39 (m, 6 H), 1.26 – 1.23 (m, 6 H), 0.92 (t, *J* = 7.4 Hz, 9 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 154.0 (d, *J* = 246.8 Hz), 153.1, 146.5 (d, *J* = 9.2 Hz), 130.3 (d, *J* = 6.0 Hz), 126.2 (d, *J* = 1.6 Hz), 114.9, 111.2 (d,

J = 2.8 Hz), 102.6 (d, *J* = 23.7 Hz), 29.2, 27.4, 13.9, 10.1 ppm; HRMS (ESI) calcd for $C_{21}H_{34}FN_3Sn$ $[M+H]^+$ 468.1835 found 468.1815.

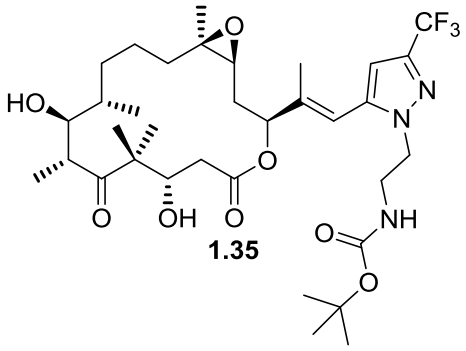
General method for the synthesis of epothilones 5–14.



1.34

Epothilone 1.34: A solution of vinyl iodide **1.33** (20 mg, 0.037 mmol, 1.0 equiv) and stannane **1.67** (49 mg, 0.09 mmol, 2.5 equiv) in degassed DMF (0.42 mL) was added to a stirring suspension of tris(dibenzylideneacetone)bispalladium (3.6 mg, 0.004 mmol, 0.1 equiv), copper iodide (3.0 mg, 0.016 mmol, 0.4 equiv), and triphenylarsine (2.4 mg, 0.008 mmol, 0.2 equiv) in degassed DMF (0.12 mL) at 25 °C. Following consumption of the starting material as indicated by TLC (15 to 30 min), the reaction mixture was diluted with ethyl acetate (1 mL) and filtered through celite. The filtrate was then washed with H_2O (2 x 2 mL) and brine (3 mL). Then the organic layer was dried with anhydrous magnesium sulfate and concentrated *in vacuo* to afford an oily residue which was purified by flash column chromatography (silica gel, 5% $\rightarrow$ 50% ethyl acetate in hexanes) and subsequent preparative TLC (silica gel, 50% ethyl acetate in hexanes) to provide **1.34** (19 mg, 0.029 mmol, 77%) as a white amorphous solid. **1.34**: R_f = 0.44 (silica gel, 70% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = +21.1 (*c* = 1.0, $CHCl_3$); FT-IR (neat) ν_{max} 3394, 2974, 2932, 1686, 1519, 1452, 1367, 1250, 1167, 1056, 1007, 973, 910, 857, 777, 730, 669 cm^{-1}; ^1H NMR (600

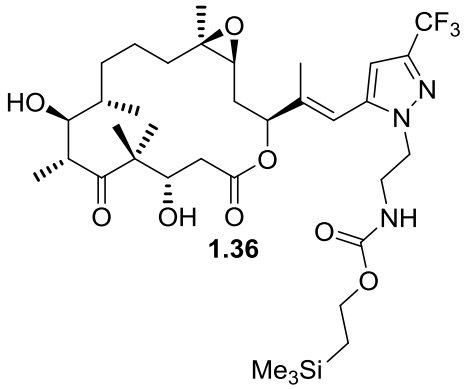
MHz, $CDCl_3$, rotamer peaks found in square brackets) δ = [6.39, 6.33] (br s, 1 H), 6.10 (br s, 1 H), 5.43 (d, *J* = 8.5 Hz, 1 H), [4.86, 4.71] (m, 1 H), 4.23 (dd, *J* = 10.1, 2.3 Hz, 1 H), 4.21 – 4.13 (m, 2 H), 4.10 – 3.98 (m, 1 H), 3.84 – 3.64 (m, 2 H), 3.57 – 3.43 (m, 2 H), 3.26 – 3.17 (m, 2 H), 2.79 – 2.77 (m, 1 H), 2.56 – 2.51 (m, 1 H), 2.49 (s, 3 H), 2.29 – 1.88 (m, 4 H), 1.83 (s, 3 H), 1.77 – 1.70 (m, 2 H), 1.59 – 1.45 (m, 2 H), 1.39 (s, 3 H), 1.35 (s, 3 H), 1.31 – 1.28 (m, 5 H), 1.24 (s, 3 H), 1.15 (d, *J* = 6.9 Hz, 3 H), 1.05 – 0.97 (m, 6 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$, rotamer peaks found in square brackets) δ = 220.4, 170.2, 156.4, [146.6, 146.3], [140.6, 140.4], 117.0, 113.9, [106.5, 105.9], [80.5, 79.9], 78.5, 76.6, [71.8, 71.2], [62.1, 61.7], [54.6, 54.0], [49.2, 48.2], [42.3, 42.0], [39.8, 39.6], 36.2, [33.3, 32.7], 32.0, [31.1, 30.7], 29.7, [28.3, 28.0], [22.8, 22.7], [22.5, 22.4], [22.0, 21.8], 19.5, 17.5, [16.7, 16.5], 16.0, 15.1, 14.1, [13.2, 13.0] ppm; HRMS (ESI) calcd for $C_{34}H_{55}N_3O_8S$ $[M+H]^+$ 666.3782 found 666.3787.



1.35

Epothilone 1.35: Prepared from vinyl iodide **1.33** (20 mg, 0.037 mmol, 1.0 equiv) and stannane **1.68** (51 mg, 0.09 mmol, 2.5 equiv) according to the general procedure described above for the preparation of **1.34** to yield **1.35** (16.5 mg, 0.024 mmol, 65%) as a white amorphous solid. **1.35**: R_f = 0.30 (silica gel, 50% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = +11.0 (*c* = 1.0, $CHCl_3$); FT-IR (neat) ν_{max} 3384, 2967, 2932, 1684, 1482, 1392, 1367, 1251, 1232,

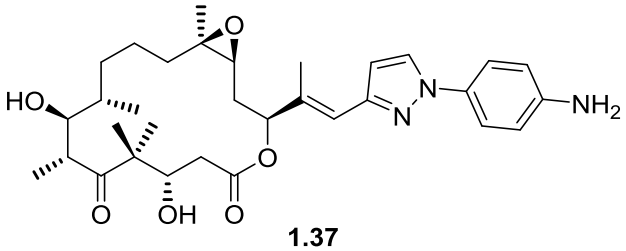
1167, 1129, 1059, 1007, 975, 942, 916, 857, 759, 735 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, rotamer peaks found in square brackets) δ = [6.44, 6.38] (br s, 1 H), 6.43 (s, 1 H), 5.44 (dd, *J* = 9.4, 1.8 Hz, 1 H), 4.84 – 4.77 (m, 1 H), [4.53, 4.31 –4.08] (m, 4 H), 3.26 – 3.20 (m, 1 H), 2.80 – 2.77 (m, 1 H), 2.57 – 2.50 (m, 1 H), 2.30 – 2.01 (m, 3 H), 1.96 – 1.89 (m , 1 H), [1.85, 1.83] (s, 3 H), 1.80 – 1.70 (m, 3 H), 1.67 – 1.42 (br m, 6 H), 1.39 (s, 3 H), 1.36 – 1.32 (m, 5 H), 1.29 (s, 3 H), 1.25 (s, 3 H), 1.16 (d, *J* = 6.8 Hz, 3 H), 1.06 – 0.98 (m, 6 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$, rotamer peaks found in square brackets) δ = 220.3, 170.2, 156.4, [142.1, 141.9], 140.4 (q, *J* = 29.5 Hz), 118.2 (q, *J* = 268.5 Hz), 116.2, [104.5, 104.2], [80.8, 80.2], 78.3, 76.4, 73.5, [71.8, 71.1], [62.1, 61.8], [54.5, 54.1], [49.9, 49.0], [42.1, 42.0], [39.6, 39.5], 36.3, 33.3, 32.7, [32.0, 31.9], 31.1, 30.7, 29.7, [28.3, 27.9], [22.8, 22.7], [22.4, 22.0], [17.3, 16.7], 16.1, 15.1, [13.2, 13.1] ppm; HRMS (ESI) calcd for $C_{34}H_{52}F_3N_3O_8$ $[M+H]^+$ 688.3779 found 666.3782.



1.36

Epothilone 1.36: Prepared from vinyl iodide **1.33** (20 mg, 0.037 mmol, 1.0 equiv) and stannane **1.69** (55 mg, 0.09 mmol, 2.5 equiv) according to the general procedure described above for the preparation of **1.34** to yield **1.36** (20 mg, 0.027 mmol, 74%) as a colorless oil. **1.36**: R_f = 0.35 (silica gel, 50% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = +26.3 (*c* = 1.0, $CHCl_3$); FT-IR (neat) ν_{max} 3381, 2967, 2930, 1680, 1475, 1422, 1367, 1243, 1232, 1169,

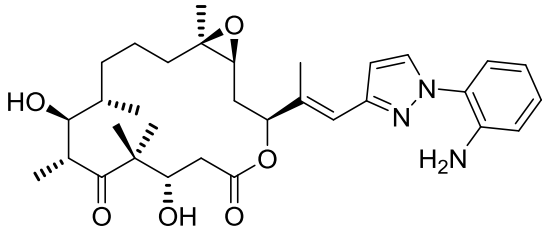
1135, 1050, 1015, 987, 942, 912, 857, 760, 730 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, rotamer peaks found in square brackets) δ = [6.47, 6.41] (br s, 1 H), [6.44, 6.38] (br s, 1 H), 5.43 (d, *J* = 7.1 Hz, 1 H), [4.99, 4.91] (br s, 1 H), 4.28 – 4.15 (m, 4 H), 4.12 – 3.78 (m, 2 H), 3.70 – 3.52 (m, 2 H), 3.35 – 3.19 (m, 1 H), 2.78 (m, 1 H), 2.70 – 2.41 (m, 2 H), 2.34 – 1.91 (m 4 H), [1.88, 1.84] (s, 3 H), 1.80 – 1.63 (m, 4 H), 1.61 – 1.39 (m, 6 H), 1.37 (s, 3 H), 1.35 – 1.32 (m, 2 H), 1.30 (s, 3 H), 1.25 – 1.06 (m, 3 H), 1.01 – 0.91 (m, 6 H), [0.02, 0.00] (s, 9 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$, rotamer peaks found in square brackets) δ = 220.3, 170.1, 157.3, [142.1, 141.9], 140.4 (q, *J* = 29.1 Hz), 118.6 (q, *J* = 269.2 Hz), 116.2, 112.7, [104.5, 104.1], 78.4, 76.3, [73.9, 73.1], [71.9, 71.3], [64.1, 63.7], [62.3, 62.2], [61.9, 61.6], [53.8, 54.5], [49.8, 49.0], [42.3, 41.8], [40.2, 39.5], [36.5. 36.1], [32.5, 31.9], [31.0, 30.8], 29.7, 27.8, 26.9, [22.5, 22.4], 22.1, [17.8, 17.6], 17.5, [16.8, 16.7], 15.4, [13.6, 13.2], [-1.5, -1.7] ppm; HRMS (ESI) calcd for $C_{34}H_{52}F_3N_3O_8$ $[M+H]^+$ 732.3867 found 732.3838.



1.37

Epothilone 1.37: Prepared from vinyl iodide **1.33** (10 mg, 0.019 mmol, 1.0 equiv) and stannane **1.85** (22 mg, 0.048 mmol, 2.5 equiv) according to the general procedure described above for the preparation of **1.34** to yield **1.37** (9 mg, 0.016 mmol, 84%) as a white foam. **1.37**: R_f = 0.29 (silica gel, 70% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = +17.0 (*c* = 0.2, $CHCl_3$); FT-IR (neat) ν_{max} 3361, 2925, 2853, 1733, 1687, 1523, 1464, 1378, 1262, 1146, 1060, 978, 881, 834, 758 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.74 (d, *J* = 2.4 Hz, 1 H), 7.43 (d, *J* = 8.8 Hz, 2 H), 6.73 (d, *J* = 8.8 Hz, 2 H), 6.60, (s, 1 H), 6.46 (d, *J* = 2.4 Hz, 1 H), 5.46 (dd,

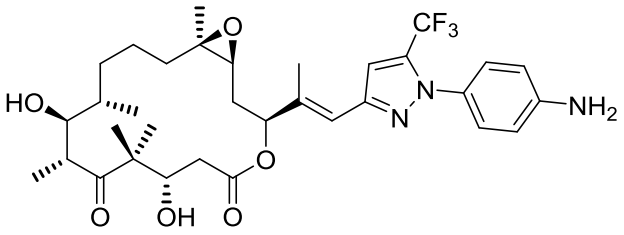
J = 7.3, 2.9 Hz, 1 H), 4.20 (dd, *J* = 10.2, 3.1 Hz, 1 H), 3.79 (t, *J* = 4.3 Hz, 1 H), 3.33 – 3.28 (m, 1 H), 2.82 (dd, *J* = 7.3, 4.9 Hz, 1 H), 2.54 (dd, *J* = 14.2, 10.2 Hz, 1 H), 2.38 (dd, *J* = 14.2, 3.1 Hz, 1 H), 2.11 (d, *J* = 1.0 Hz, 3 H), 2.09 – 2.06 (m, 1 H), 1.98 – 1.91 (m, 1 H), 1.74 – 1.66 (m, 2 H), 1.64 – 1.36 (m, 6 H), 1.35 (s, 3 H), 1.28 (s, 3 H), 1.15 (d, *J* = 6.8 Hz, 3 H), 1.07 (s, 3 H), 0.99 (d, *J* = 7.0 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 220.8, 170.6, 149.5, 145.3, 136.4, 132.1, 127.4, 120.9, 118.3, 115.4, 107.4, 74.2, 73.2, 61.6, 61.3, 52.8, 43.0, 39.1, 36.5, 32.1, 31.9, 29.7, 23.0, 22.9, 22.7, 21.4, 17.3, 16.0, 14.3, 13.9 ppm; HRMS (ESI) calcd for $C_{32}H_{45}N_3O_6$ [*M*+H]$^+$ 568.3381 found 568.3368.



1.38

Epothilone 1.38: Prepared from vinyl iodide **1.33** (15 mg, 0.028 mmol, 1.0 equiv) and stannane **1.87** (36 mg, 0.07 mmol, 2.5 equiv) according to the general procedure described above for the preparation of **1.34** to yield **1.38** (12 mg, 0.021 mmol, 75%) as a white foam. **1.38**: R_f = 0.32 (silica gel, 50 % ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –43.3 (*c* = 0.2, $CHCl_3$); FT-IR (neat) ν_{max} 3456, 3351, 2958, 2926, 2856, 1732, 1687, 1619, 1514, 1462, 1380, 1288, 1251, 1147, 1053, 1009, 978, 953, 911, 886, 751, 673 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.69 (d, *J* = 2.4 Hz, 1 H), 7.18 – 7.14 (m, 2 H), 6.83 (dd, *J* = 8.0, 1.2 Hz, 1 H), 6.77 (dt, *J* = 7.6, 1.2 Hz, 1 H), 6.59 (s, 1 H), 6.49 (d, 2.4 Hz, 1 H), 5.48 (dd, *J* = 6.8, 3.6 Hz, 1 H), 4.11 (dd, *J* = 10.0, 3.5 Hz, 1 H), 3.85 (br s, 1 H), 3.79 (t, *J* = 4.3 Hz, 1 H), 3.29 (qd, *J* = 6.9, 6.9 Hz, 1 H), 2.82 (dd, *J* = 6.8, 5.6 Hz, 1 H), 2.55 (dd, *J* = 14.4, 9.9 Hz, 1 H), 2.42 (dd, *J* = 14.4, 3.3 Hz, 1 H), 2.10 (d, *J* = 1.1 Hz, 3 H), 1.99 – 1.94 (m, 1 H), 1.71 – 1.58

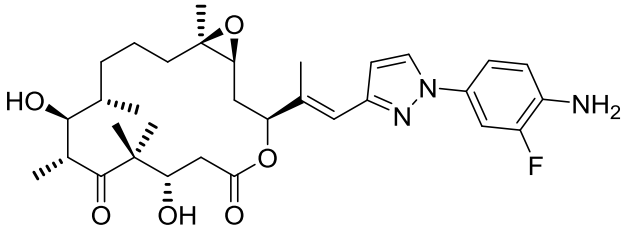
(m, 6 H), 1.47 – 1.38 (m, 5 H), 1.34 (s, 3 H), 1.28 (s, 3 H), 1.16 (d, *J* = 6.9 Hz, 3 H), 1.08 (s, 3 H), 1.00 (d, *J* = 7.0 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 220.9, 170.8, 149.9, 136.3, 130.7, 128.7, 126.4, 124.1, 118.7, 118.4, 117.5, 107.3, 74.8, 73.8, 61.4, 61.3, 52.6, 43.7, 39.1, 36.7, 32.0, 31.9, 30.9, 29.9, 28.0, 27.0, 21.2, 21.0, 17.4, 15.9, 14.3, 13.8 ppm; HRMS (ESI) calcd for $C_{32}H_{45}N_3O_6$ [*M*+H]$^+$ 568.3381 found 568.3369.



1.39

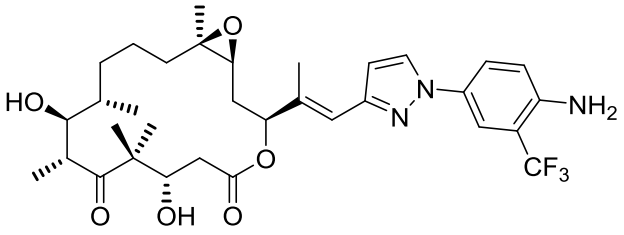
Epothilone 1.39: Prepared from vinyl iodide **1.33** (10 mg, 0.019 mmol, 1.0 equiv) and stannane **1.86** (22 mg, 0.048 mmol, 2.5 equiv) according to the general procedure described above for the preparation of **1.34** to yield **1.39** (9 mg, 0.016 mmol, 84%) as a white foam. **1.39**: R_f = 0.34 (silica gel, 70% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = +22.4 (*c* = 1.0, $CHCl_3$); FT-IR (neat) ν_{max} 3340, 2925, 2843, 1732, 1690, 1527, 1445, 1378, 1250, 1137, 1040, 962, 880, 825, 758 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.21 (d, *J* = 8.5 Hz, 2 H), 6.78 (s, 1 H), 6.71 (d, *J* = 8.5 Hz, 2 H), 6.55 (s, 1 H), 5.46 (dd, *J* = 6.5, 3.4 Hz, 1 H), 4.14 (dd, *J* = 9.7, 3.2 Hz, 1 H), 3.88 (br s, 2 H), 3.79 (m, 2 H), 3.28 (qd, *J* = 6.8, 6.8 Hz, 1 H), 2.81 (t, *J* = 6.2 Hz, 1 H), 2.54 (dd, *J* = 14.3, 10.2 Hz, 1 H), 2.49 (br s, 1 H), 2.41 (dd, *J* = 14.3, 3.2 Hz, 1 H), 2.08 (s, 3 H), 2.07 – 2.04 (m, 2 H), 1.98 – 1.93 (m, 1 H), 1.71 – 1.67 (m, 2 H), 1.53 – 1.37 (m, 6 H), 1.33 (s, 3 H), 1.28 (s, 3 H), 1.16 (d, *J* = 6.9 Hz, 3 H), 1.08 (s, 3 H), 0.99 (d, *J* = 6.9 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 220.6, 170.5, 148.2, 147.4, 137.8, 132.8 (q, *J* = 38.9 Hz), 129.8, 126.9, 117.4, 117.0 (q, *J* = 269.3 Hz), 114.7, 108.3, 76.5, 74.6, 73.5, 61.2, 61.1, 52.6, 43.4, 38.9, 36.5, 31.9, 31.7, 30.7, 22.9, 22.8, 20.9, 20.8,

17.2, 15.7, 14.1 ppm; HRMS (ESI) calcd for $C_{39}H_{58}F_3N_3O_6$ $[M+H]^+$ 636.3255 found 636.3164.



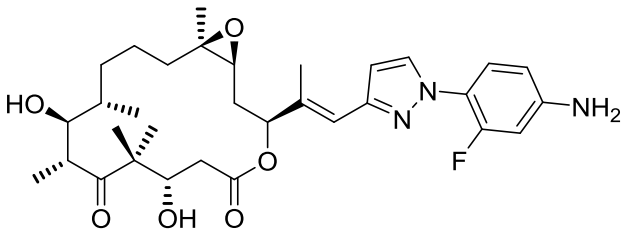
1.40

Epothilone 1.40: Prepared from vinyl iodide **1.33** (18 mg, 0.034 mmol, 1.0 equiv) and stannane **1.101** (39 mg, 0.085 mmol, 2.5 equiv) according to the general procedure described above for the preparation of **1.34** to yield **1.40** (12 mg, 0.020 mmol, 63%) as a white foam. **1.40**: R_f = 0.55 (silica gel, 70% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –10.0 (*c* = 0.2, $CHCl_3$); FT-IR (neat) ν_{max} 3456, 3374, 2924, 2853, 1733, 1685, 1632, 1518, 1464, 1380, 1258, 1188, 1145, 1044, 977, 879, 814, 769, 652 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.70 (s, 1 H), 6.95 (dd, *J* = 8.8, 2.5 Hz, 1 H), 6.92 – 6.82 (m, 2 H), 6.58 (s, 1 H), 6.50 (s, 1 H), 5.47 (dd, *J* = 6.5, 3.5 Hz, 1 H), 4.12 (dd, *J* = 9.7, 3.2 Hz, 1 H), 3.78 (t. *J* = 4.2 Hz, 1 H), 3.29 (qd, *J* = 6.9, 6.9 Hz, 1 H), 2.82 (t, *J* = 6.2 Hz, 1 H), 2.55 (dd, *J* = 14.4, 9.9 Hz, 1 H), 2.41 (dd, *J* = 14.4, 3.3 Hz, 1 H), 2.09 (s, 3 H), 2.08 – 2.04 (m, 2 H), 2.00 – 1.94 (m, 1 H), 1.73 – 1.67 (m, 2 H), 1.54 – 1.37 (m, 6 H), 1.35 (s, 3 H), 1.28 (s, 3 H), 1.16 (d, *J* = 6.9 Hz, 3 H), 1.07 (s, 3 H), 0.99 (d, *J* = 7.0 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 220.8, 170.4, 154.5 (d, *J* = 237.9 Hz), 150.2, 136.9, 136.7, 130.5, 126.3, 118.5, 118.3 (d, *J* = 8.7 Hz), 115.2 (d, *J* = 22.3 Hz), 110.7 (d, *J* = 25.4 Hz), 107.7, 74.8, 73.8, 61.4, 61.3, 52.6, 43.7, 39.1, 36.7, 32.0, 31.8, 30.8, 29.8, 23.1, 23.0, 21.3, 21.0, 17.4, 15.9, 14.3 ppm; HRMS (ESI) calcd for $C_{32}H_{44}FN_3O_6$ $[M+H]^+$ 586.3314 found 586.3313.



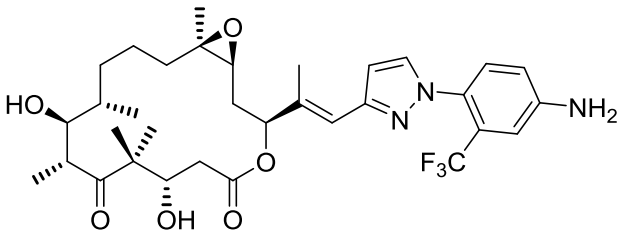
1.41

Epothilone 1.41: Prepared from vinyl iodide **1.33** (20 mg, 0.037 mmol, 1.0 equiv) and stannane **1.100** (48 mg, 0.09 mmol, 2.5 equiv) according to the general procedure described above for the preparation of **1.34** to yield **1.41** (16 mg, 0.025 mmol, 68%) as a white foam. **1.41**: R_f = 0.49 (silica gel, 70% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –43.3 (*c* = 3.0, $CHCl_3$); FT-IR (neat) ν_{max} 3491, 3389, 3259, 2963, 2929, 2878, 1731, 1688, 1641, 1587, 1521, 1453, 1381, 1333, 1315, 1300, 1263, 1143, 1111, 1062, 1049, 1008, 977, 911, 859, 825, 757, 734, 686 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.77 (d, *J* = 2.5 Hz, 1 H), 7.71 (d, *J* = 2.5 Hz, 1 H), 7.56 (dd, *J* = 8.8, 2.5 Hz, 1 H), 6.81 (d, *J* = 8.8 Hz, 1 H), 6.59 (s, 1 H), 6.48 (d, *J* = 2.5 Hz, 1 H), 5.45 (dd, *J* = 7.4, 3.1 Hz, 1 H), 4.19 (dd, *J* = 10.2, 3.2 Hz, 1 H), 3.78 (t, *J* = 4.3 Hz, 1 H), 3.34 – 3.29 (m, 1 H), 2.82 (dd, *J* = 7.3, 5.0 Hz, 1 H), 2.54 (dd, *J* = 14.2, 10.2 Hz, 1 H), 2.38 (dd, *J* = 14.2, 3.3 Hz, 1 H), 2.10 (d, *J* = 1.1 Hz, 3 H), 2.09 – 2.06 (m, 1 H), 1.97 – 1.91 (m, 1 H), 1.74 – 1.69 (m, 2 H), 1.51 – 1.37 (m, 5 H), 1.36 (s, 3 H), 1.34 – 1.32 (m, 1 H), 1.28 (s, 3 H), 1.16 (d, *J* = 6.9 Hz, 3 H), 1.08 (s, 3 H), 1.00 (d, *J* = 7.0 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 220.9, 170.7, 150.1, 143.3, 137.2, 131.2, 127.5, 124.4, 121.2 (q, *J* = 272.6 Hz), 118.1, 118.08 (q, *J* = 5.5 Hz), 113.8 (q, *J* = 30.9 Hz), 108.0, 74.4, 73.4, 61.7, 60.6, 52.9, 43.3, 39.2, 36.6, 32.2, 32.1, 30.9, 23.0, 22.8, 21.3, 20.4, 17.3, 16.0, 14.3, 14.0 ppm; HRMS (ESI) calcd for $C_{33}H_{44}F_3N_3O_6$ $[M+H]^+$ 636.3255 found 636.3242.



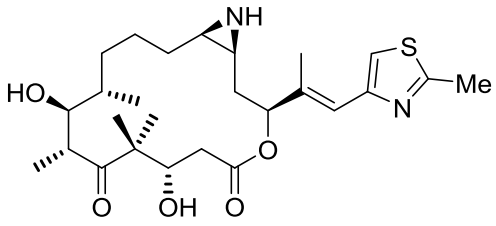
1.42

Epothilone 1.42: Prepared from vinyl iodide **1.33** (15 mg, 0.028 mmol, 1.0 equiv) and stannane **1.103** (33 mg, 0.07 mmol, 2.5 equiv) according to the general procedure described above for the preparation of **1.34** to yield **1.42** (15 mg, 0.026 mmol, 91%) as a white foam. **1.42**: R_f = 0.44 (silica gel, 70% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –65.0 (*c* = 0.2, $CHCl_3$); FT-IR (neat) ν_{max} 3443, 3362, 3237, 2958, 2925, 1730, 1688, 1635, 1590, 1528, 1460, 1382, 1327, 1258, 1171, 1046, 965, 915, 887, 841, 815, 762, 734 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.78 (t, *J* = 2.3 Hz, 1 H), 7.53 – 7.50 (m, 1 H), 6.60 (s, 1 H), 6.52 – 6.47 (m, 3 H), 5.46 (dd, *J* = 7.2, 3.1 Hz, 1 H), 4.17 (d, *J* = 9.4 Hz, 1 H), 3.88 (br s, 2 H), 3.79 (t, *J* = 4.2 Hz, 1 H), 3.29 (qd, *J* = 6.8, 6.8 Hz, 1 H), 2.82 (dd, *J* = 7.0, 5.4 Hz, 1 H), 2.58 – 2.55 (br s, 1 H), 2.54 (dd, *J* = 14.1, 10.1 Hz, 1 H), 2.39 (dd, *J* = 14.2, 3.2 Hz, 1 H), 2.10 (s, 3 H), 2.09 – 2.07 (m, 1 H), 1.97 – 1.92 (m, 1 H), 1.74 – 1.65 (m, 3 H), 1.53 – 1.49 (m, 1 H), 1.46 – 1.38 (m, 4 H), 1.35 (s, 3 H), 1.28 (s, 3 H), 1.16 (d, *J* = 6.9 Hz, 3 H), 1.08 (s, 3 H), 1.00 (d, *J* = 7.0 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 220.8, 170.7, 154.3 (d, *J* = 247.6 Hz), 149.5, 147.0 (d, *J* = 10.5 Hz), 136.8, 131.4 (d, *J* = 7.7 Hz), 125.9 (d, *J* = 1.4 Hz), 119.7 (d, *J* = 10.4 Hz), 118.5, 111.1 (d, *J* = 2.2 Hz), 107.3, 102.6 (d, *J* = 23.2 Hz), 74.5, 73.5, 61.6, 61.3, 52.9, 43.4, 39.2, 36.7, 32.2, 32.1, 30.9, 23.0, 22.8, 21.3, 20.6, 17.3, 15.9, 14.0 ppm; HRMS (ESI) calcd for $C_{32}H_{44}FN_3O_6$ [M+H]+ 586.3287, found 586.3289.



1.43

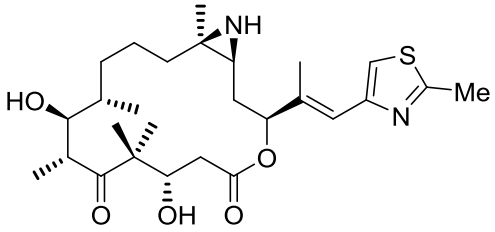
Epothilone 1.43: Prepared from vinyl iodide **1.33** (26 mg, 0.048 mmol, 1.0 equiv) and stannane **1.102** (63 mg, 0.12 mmol, 2.5 equiv) according to the general procedure described above for the preparation of **1.34** to yield **1.43** (18 mg, 0.028 mmol, 60%) as a white foam. **1.43**: R_f = 0.41 (silica gel, 70% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –54.2 (*c* = 1.0, $CHCl_3$); FT-IR (neat) ν_{max} 3496, 3384, 3265, 2963, 2928, 2882, 1740, 1685, 1642, 1590, 1521, 1438, 1365, 1354, 1322, 1292, 1263, 1136, 1110, 1076, 1048, 1010, 972, 905, 868, 832, 755, 734, 690 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.54 (m, 1 H), 7.25 (m, 1 H), 6.99 (d, *J* = 2.6 Hz, 1 H), 6.84 (dd, *J* = 8.5, 2.3 Hz, 1 H), 6.58 (s, 1 H), 6.44 (d, *J* = 2.6 Hz, 1 H), 5.46 (dd, *J* = 7.1, 3.0 Hz, 1 H), 4.15 (m, 1 H), 4.03 (br s, 2 H), 3.86 (br s, 1 H), 3.78 (dd, *J* = 7.4, 3.8 Hz, 1 H), 3.27 (qd, *J* = 6.5, 6.5 Hz, 1 H), 2.83 (dd, *J* = 6.9, 5.3 Hz, 1 H), 2.53 (dd, *J* = 14.2, 10.0 Hz, 1 H), 2.52 (br s, 1 H), 2.38 (dd, *J* = 14.2, 3.2 Hz, 1 H), 2.14 – 2.10 (m, 1 H), 2.08 (s, 3 H), 1.97 – 1.92 (m, 1 H), 1.74 – 1.68 (m, 2 H), 1.51 – 1.38 (m, 6 H), 1.31 (s, 3 H), 1.28 (s, 3 H), 1.15 (d, *J* = 6.9 Hz, 3 H), 1.07 (s, 3 H), 1.00 (d, *J* = 6.9 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 220.7, 170.6, 149.7, 147.0, 136.7, 132.7, 130.4, 128.9, 126.8 (q, *J* = 30.4 Hz), 120.2 (q, *J* = 272.9 Hz), 118.4, 117.6, 112.3 (q, *J* = 30.9 Hz), 106.6, 77.5, 74.3, 73.3, 61.5, 61.2, 52.7, 43.2, 39.0, 36.6, 32.1, 32.0, 22.9, 22.7, 21.0, 20.5, 17.1, 15.7, 13.9 ppm; HRMS (ESI) calcd for $C_{33}H_{44}F_3N_3O_6$ $[M+H]^+$ 636.3255 found 636.3268.



1.104

Epothilone 1.104: To a stirred solution of epothilone C **1.03** (50 mg, 0.11 mmol, 1.0 equiv) in 2,2,2-trifluoroethanol (1.1 mL) at 25 °C, *O*-(2,4-dinitrophenyl)hydroxylamine **1.106** (23 mg, 0.12 mmol, 1.1 equiv) and $Rh_2(esp)_2$ **1.107** (4 mg, 0.005 mmol, 0.05 equiv) were added sequentially. After 4 h, the reaction mixture was diluted with ethyl acetate (5 mL) and washed with a saturated aqueous solution of sodium bicarbonate (10 mL). The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 3 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. Flash column chromatography (silica gel, 4 → 11% methanol in dichloromethane) afforded pure epothilone **1.105** as a white solid (34 mg, 0.067 mmol, 66% yield). **1.105**: R_f = 0.22 (silica gel, 7% MeOH in DCM); $[\alpha]_D^{25}$ = –45.7 (*c* = 1.4, $CHCl_3$); FT-IR (neat) ν_{max} 3437, 3312, 2929, 2874, 1731, 1688, 1507, 1466, 1453, 1368, 1344, 1296, 1254, 1176, 1144, 1085, 1040, 1009, 978, 934, 911, 883, 855, 833, 731, 674, 647, 608 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.97 (s, 1 H), 6.66 (s,1 H), 5.59 (m, 1 H), 4.18 (dd, *J* = 10.7, 3.9 Hz, 1 H), 3.82 (dd, *J* = 6.7, 3.6 Hz, 1 H), 3.30 (qd, *J* = 6.9, 6.9 Hz, 1 H), 2.71 (s, 3 H), 2.53 (dd, *J* = 12.8, 10.8 Hz, 1 H), 2.44 (dd, *J* = 12.8, 3.9 Hz, 1 H), 2.06 (s, 3 H), 2.06 – 2.04 (m, 1 H), 1.94 – 1.90 (m, 2 H), 1.85 – 1.73 (m, 2 H), 1.61 – 1.54 (m, 2 H), 1.52 –1.46 (m, 2 H), 1.40 (s, 3 H), 1.33 – 1.22 (m, 3 H), 1.13 (d, *J* = 6.9 Hz, 3 H), 1.04 (s, 3 H), 0.94 (d, *J* = 7.0 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 220.1, 171.0, 164.9, 152.2, 136.5, 119.0, 115.7, 76.3, 75.8, 75.3, 52.3, 44.7, 37.9, 34.5, 34.0, 29.9, 29.7, 27.8, 25.8, 24.6, 22.7, 19.1,

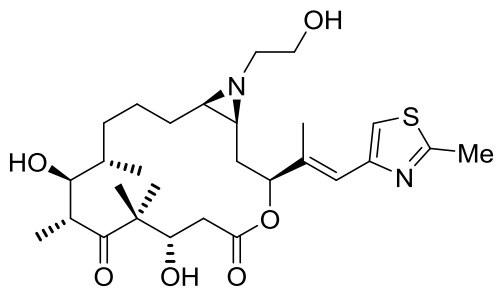
18.9, 17.3, 16.2, 15.0 ppm; HRMS (ESI) calcd for $C_{26}H_{40}N_2O_5S$ $[M+H]^+$ 493.2731, found 493.2723.



1.105

Epothilone 1.105: To a stirred solution of epothilone D **1.04** (50 mg, 0.10 mmol, 1.0 equiv) in 2,2,2-trifluoroethanol (1.1 mL) at 25 °C, *O*-(2,4-dinitrophenyl)hydroxylamine **1.106** (23 mg, 0.12 mmol, 1.1 equiv) and $Rh_2(esp)_2$ **1.107** (4 mg, 0.005 mmol, 0.05 equiv) were added sequentially. After 4 h, the reaction mixture was diluted with ethyl acetate (5 mL) and washed with a saturated aqueous solution of sodium bicarbonate (10 mL). The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 3 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. Flash column chromatography (silica gel, 4 → 11% methanol in dichloromethane) afforded pure epothilone **1.105** as a white solid (36 mg, 0.071 mmol, 70% yield). **1.105**: R_f = 0.24 (silica gel, 7% methanol in dichloromethane); $[\alpha]_D^{25}$ = –35.5 (*c* = 0.6, $CHCl_3$); FT-IR (neat) ν_{max} 3294, 2958, 2930, 2876, 1730, 1687, 1598, 1557, 1503, 1452, 1383, 1292, 1256, 1179, 1148, 1042, 1009, 980, 915, 882, 834, 731, 669, 648 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.98 (s, 1 H), 6.63 (s,1 H), 5.54 (dd, *J* = 3.9, 3.9 Hz, 1 H), 4.15 (ddd, *J* = 10.5, 3.5, 3.5 Hz, 1 H), 3.80 (dd, *J* = 5.3, 4.2 Hz, 1 H), 3.35 (dq, *J* = 6.5, 6.5 Hz, 1 H), 2.71 (s, 3 H), 2.52 (dd, *J* = 12.8, 10.6 Hz, 1 H), 2.42 (dd, *J* = 12.9, 3.5 Hz, 1 H), 2.07 (s, 3 H), 2.06 (s, 1 H), 1.96–1.76 (m, 4 H), 1.52–1.42 (m, 5 H), 1.39 (s, 3 H), 1.29–1.25 (m, 3 H), 1.24

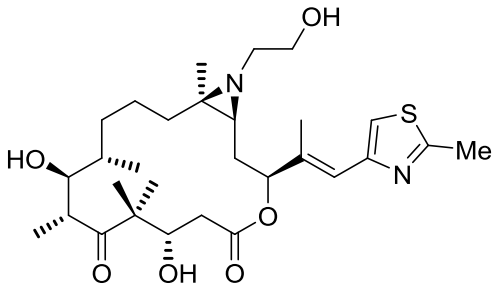
(s, 3 H), 1.13 (d, *J* = 6.9 Hz, 3 H), 1.04 (s, 3 H), 0.97 (d, *J* = 6.9 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 220.8, 171.1, 165.1, 152.3, 136.7, 119.2, 116.0, 76.4, 75.8, 74.9, 52.6, 44.5, 39.1, 38.5, 35.4, 31.4, 30.4, 29.9, 29.4, 25.5, 22.3, 22.2, 19.5, 19.3, 17.6, 16.3, 14.7 ppm; HRMS (ESI) calcd for $C_{27}H_{42}N_2O_5S$ $[M+H]^+$ 507.2887, found 507.2903.



1.109

Epothilone 1.109: To a stirred suspension of epothilone **1.104** (12 mg, 0.024 mmol, 1.0 equiv) in dimethylformamide (0.2 mL) at 25 °C was added K_2CO_3 (7.0 mg, 0.052 mmol, 2.0 equiv) and 2-bromoethanol **1.108** (10 µL, 0.156 mmol, 6.0 equiv). The reaction mixture was heated to 70 °C for 15 h, and then allowed to cool to 25 °C. Then the reaction mixture was diluted with ethyl acetate (2.5 mL) and washed with water (2.5 mL). The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 1 mL). The combined organic layers were backwashed with brine (2 mL), dried with anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash column chromatography (silica gel, 12% methanol in dichloromethane) afforded pure epothilone **1.109** as a white solid (12.5 mg, 0.023 mmol, 97% yield). **1.109**: R_f = 0.18 (silica gel, 7% methanol in dichloromethane); $[\alpha]_D^{25}$ = –54.7 (*c* = 1.0, $CHCl_3$); FT-IR (neat) ν_{max} 3380, 2934, 2876, 1731, 1688, 1507, 1465, 1371, 1292, 1256, 1189, 1151, 1055, 1007, 980, 912, 731, 645 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.97 (s, 1 H), 6.60 (s,1 H), 5.54 (m, 1 H), 4.00 (dd, *J* = 10.3, 1.4 Hz, 1 H), 3.81 (dd, *J* = 7.4, 2.8 Hz, 1 H), 3.78 – 3.70 (m, 2 H), 3.28 (qd, *J* =

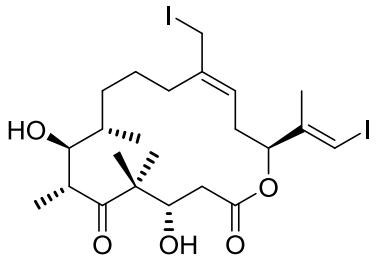
7.1, 7.1 Hz, 1 H), 2.81 – 2.79 (m, 1 H), 2.71 (s, 3 H), 2.52 (dd, *J* = 13.4, 10.4 Hz, 1 H), 2.43 (dd, *J* = 13.3, 1.8 Hz, 1 H), 2.21 – 2.18 (m, 1 H), 2.11 (s, 3 H), 2.09 – 2.00 (m, 2 H), 1.75 – 1.67 (m, 2 H), 1.57 – 1.50 (m, 5 H), 1.36 – 1.34 (m, 2 H), 1.29 –1.22 (m, 2 H), 1.15 (d, *J* = 6.9 Hz, 3 H), 1.06 (s, 3 H), 0.97 (d, *J* = 7.0 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 220.1, 171.2, 165.0, 152.2, 135.9, 119.0, 116.2, 76.4, 75.7, 63.4, 61.6, 52.1, 45.4, 44.9, 39.3, 38.7, 34.1, 30.3, 29.7, 27.5, 25.4, 24.7, 22.2, 19.2, 18.8, 17.6, 16.0, 15.1 ppm; HRMS (ESI) calcd for $C_{28}H_{44}N_2O_6S$ $[M+Na]^+$ 559.2812, found 559.2916.



1.110

Epothilone 1.110: To a stirred suspension of epothilone **1.105** (15 mg, 0.030 mmol, 1.0 equiv) in dimethylformamide (0.8 mL) at 25 °C was added K_2CO_3 (21 mg, 0.156 mmol, 6.0 equiv) and 2-bromoethanol **1.108** (10 µL, 0.156 mmol, 6.0 equiv). The reaction mixture was heated to 70 °C for 15 h, and then allowed to cool to 25 °C. Then the reaction mixture was diluted with ethyl acetate (2.5 mL) and washed with water (2.5 mL). The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 1 mL). The combined organic layers were backwashed with brine (2 mL), dried with anhydrous magnesium sulfate, and concentrated *in vacuo*. Flash column chromatography (silica gel, 12% methanol in dichloromethane) afforded pure epothilone **1.110** as a white solid (15.2 mg, 0.029 mmol, 95% yield). **1.110**: R_f = 0.19 (silica gel, 7% methanol in dichloromethane); $[\alpha]_D^{25}$ = –42.3 (*c* = 1.0, $CHCl_3$); FT-IR (neat) ν_{max} 3369, 2929, 1730,

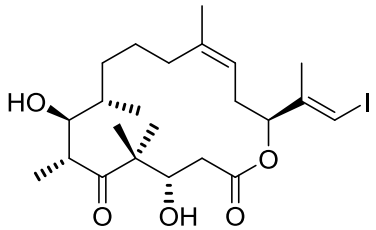
1685, 1465, 1374, 1263, 1152, 1053, 1009, 980, 882 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.97 (s, 1 H), 6.60 (s,1 H), 5.54 (dd, *J* = 3.9, 3.9 Hz, 1 H), 4.00 (dd, *J* = 10.5, 3.5 Hz, 1 H), 3.81 (dd, *J* = 5.3, 4.2 Hz, 1 H), 3.78–3.70 (m, 2 H), 3.28 (dq, *J* = 6.5, 6.5 Hz, 1 H), 2.81–2.79 (m, 1 H), 2.71 (s, 3 H), 2.52 (dd, *J* = 12.8, 10.6 Hz, 1 H), 2.43 (dd, *J* = 12.9, 3.5 Hz, 1 H), 2.21–2.18 (m, 1 H), 2.11 (s, 3 H), 2.09–2.00 (m, 2 H), 1.75–1.67 (m, 2 H), 1.57–1.50 (m, 5 H), 1.36 (s, 3 H), 1.34–1.25 (m, 3 H), 1.24 (s, 3 H), 1.15 (d, *J* = 6.9 Hz, 3 H), 1.06 (s, 3 H), 0.97 (d, *J* = 6.9 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 220.2, 171.4, 165.1, 152.4, 136.0, 119.1, 116.4, 76.6, 75.9, 63.5, 61.8, 52.2, 45.6, 45.1, 39.4, 38.9, 34.3, 30.4, 29.9, 27.7, 25.5, 24.8, 22.4, 19.4, 18.9, 17.8, 16.1, 15.2 ppm; HRMS (ESI) calcd for $C_{29}H_{46}N_2O_6S$ $[M+Na]^+$ 573.2974, found 573.2982.



1.111

Allylic iodide 1.111: To a stirred solution of **1.59** (9.6 mg, 0.018 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) at 0 °C was added triethylamine (0.013 mL, 0.090 mmol, 5.0 equiv), followed by *p*-toluenesulfonic anhydride (18 mg, 0.054 mmol, 3.0 equiv) and 4-dimethylaminopyridine (2.2 mg, 18 mmol, 1.0 equiv). After the starting material was converted into the tosylate intermediate (as judged by TLC), the mixture was diluted with dry acetone (3 mL), and concentrated *in vacuo* until around 1.5 mL of solution was left. Sodium iodide (14 mg, 0.090 mmol, 5.0 equiv) was then added to the reaction mixture with stirring. After 20 min, the reaction mixture was quenched with water (10 mL), and

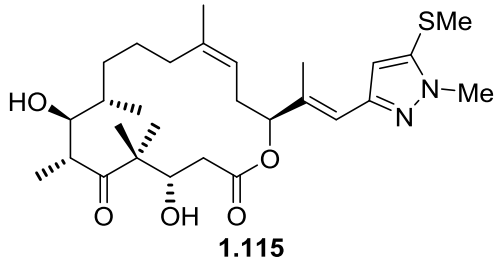
extracted with ethyl acetate (3 × 15 mL), and the combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified *via* flash column chromatography (silica gel, 10 → 30% ethyl acetate in hexanes) to afford pure **1.111** (10 mg, 0.015 mmol, 88%) as a colorless liquid. **1.111**: R_f = 0.24 (silica gel, 25% EtOAc in Hexanes); $[\alpha]_D^{22}$ –28.2 (c = 0.39, CH_2Cl_2); FT-IR (neat) ν_{max} 3488, 2924, 2854, 1735, 1686, 1464, 1378, 1259, 1147, 1046, 1007, 977, 884, 792, 737, 688, 668 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ = 6.44 (s, 1 H), 5.17 (dd, *J* = 9.6, 5.4 Hz, 1 H), 5.12 (dd, *J* = 9.6, 2.4 Hz, 1 H), 3.85 (ddd, *J* = 10.8, 7.8, 3.0 Hz, 1 H), 3.63 (d, *J* = 9.0 Hz, 1 H), 3.57 (q, *J* = 3.6 Hz, 1 H), 3.54 (d, *J* = 9.0 Hz, 1 H), 2.76 (qd, *J* = 6.0, 3.0 Hz, 1 H), 2.68 (br s, 1 H), 2.22 (ddd, *J* = 13.2, 6.6, 6.6 Hz, 1 H), 2.18–2.11 (m, 2 H), 2.07 (ddd, *J* = 13.2, 6.6, 6.6 Hz, 1 H), 1.95 (dd, *J* = 14.4, 3.0 Hz, 1 H), 1.69 (s, 3 H), 1.60 (d, *J* = 7.2 Hz, 1 H), 1.52 (dd, *J* = 14.4, 4.8 Hz, 1 H), 1.44–1.28 (m, 2 H), 1.02 (d, *J* = 6.6 Hz, 3 H), 1.01–0.84 (m, 2 H), 0.91 (d, *J* = 6.6 Hz, 3 H), 0.80 (s, 3 H), 0.78 (s, 3 H) ppm; ^{13}C NMR (150 MHz, C_6D_6) δ = 219.1, 169.2, 145.6, 140.2, 125.0, 80.4, 76.7, 74.3, 72.8, 53.1, 42.1, 39.5, 38.5, 32.4, 31.6, 28.6, 25.5, 22.3, 21.0, 18.5, 15.9, 13.9, 12.2 ppm; HRMS (ESI) calcd for $C_{23}H_{36}I_2O_5Na$ $[M+Na]^+$ 669.0544, found 669.0570.



1.112

Vinyl iodide 1.112: To a stirred solution of allyl iodide **1.111** (10.0 mg, 0.0155 mmol, 1.0 equiv.) in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (0.5 mL) at room temperature was added sodium cyanoborohydride (12.4 mg, 0.186 mmol, 12.0 equiv.). The

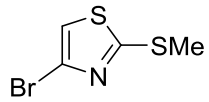
resulting reaction mixture was stirred at the same temperature for 40 min, then quenched by adding water (5 mL). After dilution with EtOAc (50 mL), the organic layer was washed with brine (3 × 10 mL), dried with anhydrous sodium sulfate, and concentrated *in vacuo*. The obtained residue was purified *via* flash column chromatography (silica gel, 10 → 30% ethyl acetate in hexanes) to afford pure **1.112** (6.5 mg, 0.012 mmol, 80%) as a colorless liquid. **1.112**: R_f = 0.36 (silica gel, 30% EtOAc in Hexanes); $[\alpha]_D^{22}$ –27.6 (c = 0.38, CH_2Cl_2); FT-IR (neat) ν_{max} 3478, 2924, 2853, 1732, 1686, 1463, 1377, 1261, 1146, 1007, 976, 741, 614 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ = 6.46 (s, 1 H), 5.26 (dd, *J* = 9.6, 2.4 Hz, 1 H), 4.99 (dd, *J* = 9.0, 5.4 Hz, 1 H), 3.91 (ddd, *J* = 10.8, 7.8, 3.0 Hz, 1 H), 3.63 (q, *J* = 3.0 Hz, 1 H), 2.82 (qd, *J* = 6.6, 3.0 Hz, 1 H), 3.71 (br s, 1 H), 2.40 (ddd, *J* = 15.6, 10.2, 10.2 Hz, 1 H), 2.20 (dd, *J* = 15.6, 10.8 Hz, 1 H), 2.18–2.12 (m, 1 H), 1.99 (dd, *J* = 15.6, 3.0 Hz, 1 H), 1.82 (dd, *J* = 15.6, 4.2 Hz, 1 H), 1.76 (s, 3 H), 1.74–1.69 (m, 1 H), 1.65 (d, *J* = 7.8 Hz, 1 H), 1.56 (s, 3 H), 1.44–1.28 (m, 2 H), 1.14–0.80 (m, 2 H), 1.05 (d, *J* = 6.6 Hz, 3 H), 0.98 (d, *J* = 6.6 Hz, 3 H), 0.81 (s, 3 H). 0.80 (s, 3 H) ppm; ^{13}C NMR (150 MHz, C_6D_6) δ = 219.1, 169.4, 146.2, 138.7, 120.6, 80.1, 77.6, 74.5, 72.8, 53.1, 42.2, 39.6, 38.8, 32.1, 31.8, 31.7, 25.9, 23.0, 22.3, 21.0, 18.5, 16.0, 14.0 ppm; HRMS (ESI) calcd for $C_{23}H_{37}IO_5Na$ $[M+Na]^+$ 543.1578, found 543.1562.



1.115

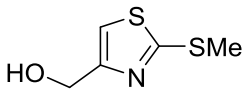
Epothilone 1.115: Prepared from vinyl iodide **1.112** (43 mg, 0.083 mmol, 1.0 equiv) and stannane **1.113** (88 mg, 0.21 mmol, 2.5 equiv) according to the general procedure described

above for the preparation of **1.34** to yield **1.115** (29 mg, 0.056 mmol, 67%) as a white foam. **1.115**: R_f = 0.38 (silica gel, 50% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –75.7 (*c* = 0.7, CH_2Cl_2); FT-IR (neat) ν_{max} 3415, 2973, 2932, 1731, 1692, 1491, 1467, 1455, 1382, 1329, 1284, 1251, 1174, 1150, 1119, 1048, 1011, 977, 959, 879, 859, 843, 812, 794, 722, 695 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ = 6.82 (s, 1 H), 6.27 (s, 1 H), 5.44 (dd, *J* = 10.1, 1.2 Hz, 1 H), 5.17 (dd, *J* = 9.8, 5.2 Hz, 1 H), 4.24 (dd, *J* = 11.0, 2.8 Hz, 1 H), 3.74 (dd, *J* = 3.5, 3.5 Hz, 1 H), 3.39 (s, 3 H), 3.09 (br s, 1 H), 2.98 (qd, *J* = 6.8, 2.8 Hz, 1 H), 2.63 (dt, *J* = 15.1, 9.8 Hz, 1 H), 2.41 (dd, *J* = 14.9, 11.1 Hz, 1 H), 2.29 – 2.24 (m, 1 H), 2.10 (dd, *J* = 14.8, 2.8 Hz, 1 H), 2.07 (d, *J* = 1.3 Hz, 3 H), 1.86 – 1.78 (m, 2 H), 1.76 (s, 3 H), 1.62 (br s, 3 H), 1.61 – 1.56 (m, 1 H), 1.25 – 1.17 (m, 3 H), 1.12 (d, *J* = 6.8 Hz, 3 H), 1.04 (d, *J* = 6.9 Hz, 3 H), 1.03 (s, 3 H), 1.01 (s, 3 H) ppm; ^{13}C NMR (151 MHz, C_6D_6) δ = 219.7, 170.1, 148.9, 138.3, 137.8, 136.4, 121.6, 118.4, 109.8, 79.2, 74.6, 72.7, 53.6, 53.4, 42.2, 40.0, 38.7, 36.1, 32.8, 32.0, 31.7, 25.9, 23.1, 22.8, 18.5, 16.1, 15.9, 13.9 ppm; HRMS (ESI) calcd for $C_{28}H_{44}N_2O_5S$ $[M+H]^+$ 521.3044 found 521.3034.



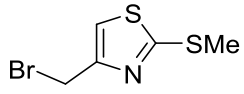
1.138

Thiomethyl thiazole 1.138: Methylthio thiazole **1.138** was prepared from commercially available 2,4-dibromothiazole **1.137** as previously described.[56] The physical and spectral data are consistent with those reported.[56]



1.139

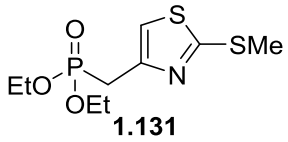
Hydroxymethyl thiazole 1.139: To a stirred solution of thiomethyl thiazole **1.138** (1.48 g, 7.04 mmol, 1.0 equiv.) in diethyl ether (20 mL) at –78 °C was carefully added *tert*-butyllithium (1.4 M pentanes, 6.0 mL, 8.40 mmol, 1.2 equiv.). After 5 min, DMF (1.03 mL, 14.1 mmol, 2.0 equiv.) was added and stirring was continued for an additional 20 min. Then the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (10 mL), and allowed to warm to 25 °C. The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 20 → 50% ethyl acetate in hexanes) to afford pure hydroxymethyl thiazole **1.139** (0.850 g, 5.27 mmol, 75%) as a colorless oil. **1.139**: R_f = 0.26 (silica gel, 50% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3334, 3118, 2924, 2860, 1529, 1407, 1314, 1261, 1213, 1135, 1037, 966, 944, 849, 752, 725 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.05 (s, 1 H), 4.71 (s, 2 H), 2.69 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.5, 156.5, 114.0, 61.2, 17.0 ppm; HRMS (ESI) calcd for $C_5H_8NOS_2$ $[M+H]^+$ 162.0042, found 162.0048.



1.140

Bromomethyl thiazole 1.140: To a stirred solution of hydroxymethyl thiazole **1.139** (642 mg, 3.98 mmol, 1.0 equiv.) in dichloromethane (6 mL) at –78 °C was added triphenylphosphine (1.10 g, 4.18 mmol, 1.05 equiv.), followed by *N*-bromosuccinimide

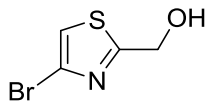
(708 mg, 3.98 mmol, 1.0 equiv.). After 5 min, the reaction mixture was quenched with water (5 mL) and allowed to warm to 25 °C. The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 1 → 5% ethyl acetate in hexanes) to afford pure bromomethyl thiazole **1.140** (0.696 g, 3.10 mmol, 78%) as a colorless oil. **1.140**: R_f = 0.27 (silica gel, 10% diethyl ether in hexanes); FT-IR (neat) ν_{max} 3103, 2924, 2850, 1511, 1411, 1314, 1214, 1147, 1108, 1055, 1037, 966, 882, 746, 701, 672 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.16 (s, 1 H), 4.51 (s, 2 H), 2.69 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.7, 152.3, 117.0, 27.1, 16.9 ppm; HRMS (ESI) calcd for $C_5H_7NS_2Br$ $[M+H]^+$ 223.9198, found 223.9201.



1.131

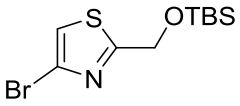
Phosphonate 1.131: Triethyl phosphite (5 mL, 29.2 mmol, 6.4 equiv.) was added to a flask containing bromomethyl thiazole **1.140** (1.02 g, 4.55 mmol, 1.0 equiv.) at 25 °C. The reaction mixture was heated to 160 °C for 2 h with stirring, and then the excess triethyl phosphite was removed under a steady flow of N_2(g). The residue was allowed to cool to 25 °C and then purified by flash column chromatography (silica gel, 70 → 100% ethyl acetate in hexanes) to afford pure phosphonate **1.131** (1.18 g, 4.19 mmol, 92%) as a colorless oil. **1.131**: R_f = 0.20 (silica gel, ethyl acetate); FT-IR (neat) ν_{max} 3463, 3108, 2982, 2929, 1646, 1515 1478, 1411, 1393, 1368, 1314, 1248, 1163, 1097, 1023, 966, 947, 867, 842, 808, 781, 716, 660 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.08 (d, J = 3.6 Hz, 1 H),

4.08 (dq, *J* = 8.4, 7.2 Hz, 4 H), 3.32 (d, *J* = 21.0 Hz, 2 H), 2.65 (s, 3 H), 1.28 (t, *J* = 7.2 Hz, 6 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.1, 146.8 (d, *J* = 8.1 Hz), 115.6 (d, *J* = 8.0 Hz), 62.4 (d, *J* = 6.5 Hz), 29.5 (d, *J* = 140 Hz), 16.9, 16.5 (d, *J* = 6.0 Hz) ppm; HRMS (ESI) calcd for $C_9H_{17}NO_3PS_2$ $[M+H]^+$ 282.0382, found 282.0378.



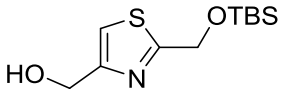
1.141

Hydroxymethyl thiazole 1.141: Hydroxymethyl thiazole **1.141** was prepared from commercially available 2,4-dibromothiazole **1.137** as previously described.[4] The physical and spectral data are consistent with those reported.[4]



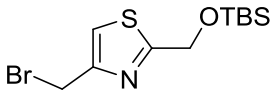
1.142

Silyl ether thiazole 1.142: Silyl ether thiazole **1.142** was prepared from hydroxymethyl thiazole **1.141** as previously described.[56] The physical and spectral data are consistent with those reported.[56]



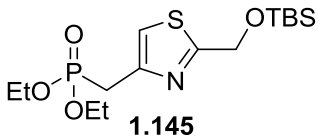
1.143

Hydroxymethyl thiazole 1.143: Prepared from silyl ether thiazole **1.142** (2.42 g, 7.85 mmol, 1.0 equiv.) according to the procedure described above for the preparation of **1.139** to afford hydroxymethyl thiazole **1.143** (1.59 g, 6.13 mmol, 78%) as a colorless oil. The physical and spectral data are consistent with those reported.[58]



1.144

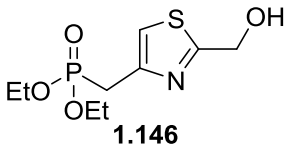
Bromomethyl thiazole 1.144: To a stirred solution of hydroxymethyl thiazole **1.143** (1.41 g, 5.43 mmol, 1.0 equiv.) in acetonitrile (45 mL) at 25 °C was added triphenylphosphine (2.42 g, 9.23 mmol, 1.7 equiv.), 2,6-lutidine (0.25 mL, 2.17 mmol, 0.4 equiv.), and carbon tetrabromide (3.06 g, 9.23 mmol, 1.7 equiv.) sequentially. The reaction mixture was stirred for 2 h, then quenched with a saturated aqueous solution of sodium bicarbonate (20 mL), and extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 5 → 10% ethyl acetate in hexanes) to afford pure bromomethyl thiazole **1.144** (1.60 g, 4.96 mmol, 91%) as a colorless oil. **1.144**: R_f = 0.31 (silica gel, 10% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3106, 2954, 2929, 2885, 2857, 1519, 1492, 1471, 1463, 1426, 1390, 1355, 1255, 1197, 1145, 1111, 1006, 964, 939, 836, 778, 706, 684, 662 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.23 (s, 1 H), 4.95 (s, 2 H), 4.55 (s, 2 H), 0.95 (s, 9 H) 0.13 (s, 6 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 174.6, 151.9, 117.4, 63.3, 27.4, 25.9, 18.4, -5.3 ppm; HRMS (ESI) calcd for $C_{11}H_{20}BrNOSSi$ $[M+H]^+$ 322.0291, found 322.0285.



1.145

Phosphonate 1.145: Triethyl phosphite (2.2 mL, 12.8 mmol, 20 equiv.) was added to a flask containing bromomethyl thiazole **1.144** (202 mg, 0.63 mmol, 1.0 equiv.) at 25 °C. The reaction mixture was heated to 160 °C for 3 h with stirring, and then the excess triethyl

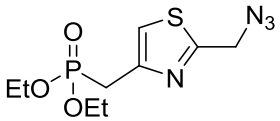
phosphite was removed under a steady flow of N_2(g). The residue was allowed to cool to 25 °C and purified by flash column chromatography (silica gel, 50 → 100% ethyl acetate in hexanes) to afford pure phosphonate **1.145** (192 mg, 0.51 mmol, 80%) as a colorless oil. **1.145**: R_f = 0.28 (silica gel, ethyl acetate); FT-IR (neat) ν_{max} 3476, 3107, 2955, 2930, 2903, 2858, 1519, 1472, 1463, 1444, 1392, 1361, 1321, 1253, 1198, 1164, 1099, 1055, 1027, 959, 837, 779, 722, 708, 674, 658 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.17 (d, *J* = 3.5 Hz, 1 H), 4.94 (s, 2 H), 4.11 – 4.06 (m, 4 H), 3.34 (d, *J* = 21.0 Hz, 2 H), 1.27 (t, *J* = 7.1 Hz, 6 H), 0.95 (s, 9 H) 0.12 (s, 6 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 173.2, 146.1 (d, *J* = 8.3 Hz) 116.1 (d, *J* = 6.4 Hz), 63.2, 62.4 (d, *J* = 6.6 Hz), 29.0 (d, *J* = 141.0 Hz), 25.9, 18.4, 16.5 (d, *J* = 6.0 Hz), -5.3 ppm; HRMS (ESI) calcd for $C_{15}H_{30}NO_4PSSi$ $[M+H]^+$ 380.1475, found 380.1475.



1.146

Phosphonate 1.146: To a stirred solution of phosphonate **1.145** (56 mg, 0.15 mmol, 1.0 equiv.) in DMF (1 mL) at 0 °C was added tris(dimethylamino)sulfonium difluorotrimethylsilicate (204 mg, 0.75 mmol, 5.0 equiv.) followed by water (0.03 mL, 1.5 mmol, 10 equiv). The reaction mixture was allowed to slowly warm to 25 °C, and stirring was continued for 10 h. Water (3 mL) and ethyl acetate (3 mL) were added, and the two phases were separated. The aqueous layer was extracted with ethyl acetate (3 x 2 mL), and the combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (5% methanol in dichloromethane) to afford pure phosphonate **1.146** (31 mg, 0.12 mmol, 79%)

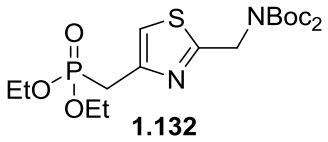
as a colorless oil. **1.146**: R_f = 0.33 (silica gel, 5% methanol in dichloromethane); FT-IR (neat) ν_{max} 3319, 2983, 2909, 1520, 1477, 1443, 1393, 1346, 1325, 1231, 1163, 1139, 1097, 1050, 1022, 957, 874, 845, 809, 784, 723, 670 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.14 (d, *J* = 3.2 Hz, 1 H), 4.81 (s, 2 H), 4.08 – 4.04 (m, 4 H), 3.32 (d, *J* = 21.0 Hz, 2 H), 1.25 (t, *J* = 7.1 Hz, 6 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 172.5, 146.0 (d, *J* = 8.2 Hz) 116.4 (d, *J* = 6.8 Hz), 62.5 (d, *J* = 6.6 Hz), 61.9, 28.9 (d, *J* = 141.5 Hz), 16.5 (d, *J* = 6.0 Hz) ppm; HRMS (ESI) calcd for $C_9H_{16}NO_4PS$ $[M+H]^+$ 266.0610, found 266.0601.



1.147

Azide 1.147: To a stirred solution of phosphonate **1.146** (687 mg, 2.59 mmol, 1.0 equiv.) in dichloromethane (10.4 mL) at 25 °C was added triethylamine (0.72 mL, 5.18 mmol, 2.0 equiv.) and 4-(dimethylamino)pyridine (32 mg, 0.26 mmol, 0.1 equiv.). After cooling to –20 °C, *p*-tolunesulfonic anhydride (1.27 g, 3.89 mmol, 1.5 equiv.) was added in one portion. Stirring was continued for 30 min, and then the reaction mixture was quenched with water (5 mL) and allowed to warm to 25 °C. The two phases were separated, and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The crude residue was then resuspended in dimethylformamide (5 mL), and cooled to –20 °C with stirring. Sodium azide (505 mg, 7.77 mmol, 3.0 equiv.) was added, and stirring was continued for an additional 15 min. The reaction mixture was then quenched with water (5 mL), allowed to warm to 25 °C, and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*.

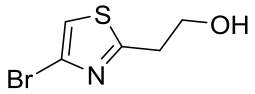
Purification by flash column chromatography (5% methanol in dichloromethane) afforded pure azide **1.147** (643 mg, 2.22 mmol, 86%) as a colorless oil. **1.147**: R_f = 0.44 (silica gel, 5% methanol in dichloromethane); FT-IR (neat) ν_{max} 3470, 3111, 2983, 2930, 2100, 1517, 1443, 1393, 1327, 1250, 1162, 1098, 1053, 1026, 965, 874, 810, 783, 724 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.25 (d, *J* = 3.5 Hz, 1 H), 4.63 (s, 2 H), 4.12 – 4.07 (m, 4 H), 3.37 (d, *J* = 21.0 Hz, 2 H), 1.27 (t, *J* = 7.1 Hz, 6 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 164.3, 147.4 (d, *J* = 8.1 Hz) 117.6 (d, *J* = 7.5 Hz), 62.4 (d, *J* = 6.6 Hz), 51.4, 29.1 (d, *J* = 141.1 Hz), 16.5 (d, *J* = 6.0 Hz) ppm; HRMS (ESI) calcd for $C_9H_{15}N_4O_3PS$ $[M+H]^+$ 291.0675, found 291.0675.



1.132

Phosphonate 1.132: To a stirred solution of azide **1.147** (200 mg, 0.69 mmol, 1.0 equiv.) in ethyl acetate (4 mL) at 25 °C was added 5% palladium on carbon (50 mg, 25% *w*/*w*) and the flask was capped with a hydrogen balloon. Stirring was continued for 12 h. Then the hydrogen balloon was removed, and the reaction mixture was filtered through a pad of celite and concentrated *in vacuo*. The crude residue was then resuspended in tetrahydrofuran (5 mL) at 25 °C, and triethylamine (0.26 mL, 1.80 mmol, 2.6 equiv.), 4-(dimethylamino)pyridine (9 mg, 0.07 mmol, 0.1 equiv.), and di-*tert*-butyl dicarbonate (332 mg, 1.52 mmol, 2.2 equiv.) were added sequentially with stirring. The reaction mixture was heated to 60 °C for 2.5 h, allowed to cool to 25 °C, and then quenched with a saturated aqueous solution of ammonium chloride (3 mL). The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic layers

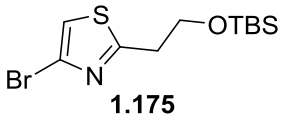
were dried with anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (50 → 100% ethyl acetate) afforded pure phosphonate **1.132** (293 mg, 0.63 mmol, 91%) as a colorless oil. **1.132**: R_f = 0.27 (silica gel, ethyl acetate); FT-IR (neat) ν_{max} 3459, 3109, 2980, 2934, 1793, 1753, 1699, 1519, 1479, 1458, 1422, 1393, 1367, 1341, 1254, 1228, 1129, 1054, 1026, 965, 890, 853, 783 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.15 (d, *J* = 3.5 Hz, 1 H), 5.04 (s, 2 H), 4.10 – 4.05 (m, 4 H), 3.34 (d, *J* = 21.0 Hz, 2 H), 1.48 (s, 18 H) 1.26 (t, *J* = 7.1 Hz, 6 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.8, 151.9, 146.2 (d, *J* = 7.7 Hz), 116.3 (d, *J* = 7.2 Hz), 83.4, 62.3 (d, *J* = 6.6 Hz), 47.8, 29.0 (d, *J* = 140.9 Hz), 28.1, 16.5 (d, *J* = 6.1 Hz) ppm; HRMS (ESI) calcd for $C_{19}H_{33}N_2O_7PS$ $[M+Na]^+$ 487.1638, found 487.1620.



1.174

Hydroxyethyl thiazole 1.174: To a stirred solution of 2,4-dibromothiazole **1.137** (10.2 g, 42.0 mmol, 1.0 equiv.) in diethyl ether (250 mL) at –78 °C was carefully added *n*-butyllithium (2.5 M hexanes, 16.8 mL, 42.0 mmol, 1.0 equiv.). The reaction mixture was stirred for 20 min and then a solution of oxirane (2.5 M tetrahydrofuran, 16.8 mL, 42.0 mmol, 1.0 equiv.) was added, followed by dropwise addition of a solution of boron trifluoride diethyl etherate (5.18 mL, 42.0 mmol, 1.0 equiv.) in diethyl ether (30 mL). After 20 min, the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (50 mL) and allowed to warm to 25 °C. The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 80 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue

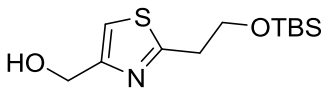
was purified by flash column chromatography (silica gel, 30 → 60% ethyl acetate in hexanes) to afford pure thiazole **1.174** (5.42 g, 26.0 mmol, 62%) as a colorless oil. **1.174**: R_f = 0.24 (silica gel, 50% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3350, 3122, 2881, 1480, 1421, 1330, 1257, 1210, 1135, 1085, 1052, 938, 887, 857, 832, 733 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.12 (s, 1 H), 4.02 (td, *J* = 6.0, 6.0 Hz, 2 H), 3.22 (t, *J* = 6.0 Hz, 2 H), 2.67 (t, *J* = 6.0 Hz, 1 H) ppm;^{13}C NMR (151 MHz, $CDCl_3$) δ = 169.7, 124.6, 116.5, 61.3, 36.2 ppm; HRMS (ESI) calcd for C_5H_7NOSBr $[M+H]^+$ 207.9426, found 207.9421.



1.175

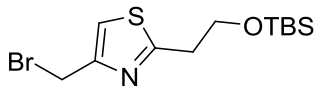
Silyl ether 1.175: To a stirred solution of hydroxyethyl thiazole **1.174** (5.38 g, 25.9 mmol, 1.0 equiv.) in dimethylformamide (25 mL) at 25 °C was added *tert*-butyldimethylsilyl chloride (4.68 g, 31.0 mmol, 1.2 equiv.) followed by imidazole (2.64 g, 38.9 mmol, 1.5 equiv.). After 1 h, the reaction mixture was diluted with ethyl acetate (100 mL), then washed with water (20 mL) and brine (20 mL). The two phases were separated, and the organic layer was dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 2 → 8% ethyl acetate in hexanes) to afford pure silyl ether **1.175** (8.25 g, 25.6 mmol, 99%) as a colorless oil. **1.175**: R_f = 0.24 (silica gel, 5% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3125, 2954, 2928, 2856, 1481, 1471, 1437, 1388, 1361, 1331, 1254, 1147, 1099, 1050, 1006, 939, 914, 884, 831, 810, 776, 728 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.09 (s, 1 H), 3.93 (t, *J* = 6.0 Hz, 2 H), 3.19 (t, *J* = 6.0 Hz, 2 H), 0.87 (s, 9 H), 0.02 (s, 6 H) ppm; ^{13}C NMR (151

MHz, $CDCl_3$) δ = 169.6, 124.1, 116.7, 61.9, 37.2, 26.0, 18.4, -5.3 ppm; HRMS (ESI) calcd for $C_{11}H_{21}NOSiSBr$ $[M+H]^+$ 322.0291, found 322.0281.



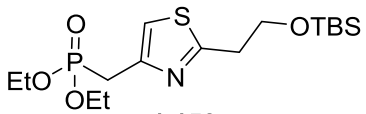
1.176

Hydroxymethyl thiazole 1.176: To a stirred solution of silyl ether **1.175** (2.45 g, 7.60 mmol, 1.0 equiv.) in diethyl ether (75 mL) at –78 °C was carefully added *t*-butyllithium (1.7 M pentanes, 5.40 mL, 9.12 mmol, 1.2 equiv.). After 1 min, dimethylformamide (1.17 mL, 15.2 mmol, 2.0 equiv.) was added dropwise. After 5 min, the reaction mixture was quenched with methanol (30 mL). Then sodium borohydride (1.44 g, 38.0 mmol, 5.0 equiv.) was added and the reaction mixture was allowed to warm to 0 °C. After 5 min, the reaction mixture was quenched with water (60 mL) and allowed to warm to 25 °C. The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 40 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 30 → 60% ethyl acetate in hexanes) to afford pure thiazole **1.176** (1.70 g, 6.23 mmol, 82%) as a colorless oil. **1.176**: R_f = 0.32 (silica gel, 60% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3301, 2954, 2928, 2857, 1530, 1471, 1387, 1361, 1254, 1156, 1096, 969, 937, 913, 834, 810, 774, 660 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.05 (s, 1 H), 4.73 (d, *J* = 6.0 Hz, 2 H), 3.94 (t, *J* = 6.0 Hz, 2 H), 3.18 (t, *J* = 6.6 Hz, 2 H), 3.09 (t, *J* = 6.0 Hz, 1 H), 0.87 (s, 9 H), 0.02 (s, 6 H) ppm;^{13}C NMR (151 MHz, $CDCl_3$) δ = 169.0, 155.6, 114.7, 62.2, 60.9, 37.0, 26.0, 18.4, -5.3 ppm; HRMS (ESI) calcd for $C_{12}H_{24}NO_2SiS$ $[M+H]^+$ 296.1111, found 296.1102.



1.177

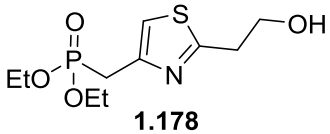
Bromomethyl thiazole 1.177: To a stirred solution of hydroxymethyl thiazole **1.176** (2.45 g, 8.96 mmol, 1.0 equiv.) in dichloromethane (30 mL) at –78 °C was added triphenylphosphine (2.47 g, 9.41 mmol, 1.05 equiv.), followed by *N*-bromosuccinimide (1.59 g, 8.96 mmol, 1.0 equiv.). After 5 min, the reaction mixture was quenched with water (50 mL) and allowed to warm to 25 °C. The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 2 → 8% ethyl acetate in hexanes) to afford pure bromomethyl thiazole **1.177** (2.93 g, 8.71 mmol, 97%) as a colorless oil. **1.177**: R_f = 0.19 (silica gel, 5% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 2954, 2928, 2883, 2856, 1517, 1471, 1424, 1387, 1361, 1333, 1254, 1214, 1161, 1095, 1053, 1006, 977, 937, 915, 834, 810, 775, 731, 679, 659 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.16 (s, 1 H), 4.55 (s, 2 H), 3.95 (t, *J* = 6.0 Hz, 2 H), 3.19 (t, *J* = 6.0 Hz, 2 H), 0.87 (s, 9 H), 0.02 (s, 6 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 169.2, 151.4, 117.8, 77.4, 62.1, 37.1, 27.4, 26.0, 18.4, -5.3 ppm; HRMS (ESI) calcd for $C_{12}H_{23}NOSiSBr$ $[M+H]^+$ 336.0448, found 336.0441.



1.158

Phosphonate 1.158: Triethyl phosphite (5.0 mL, 29.2 mmol, 3.5 equiv.) was added to a flask containing bromomethyl thiazole **1.177** (2.83 g, 8.41 mmol, 1.0 equiv.) at 25 °C. The

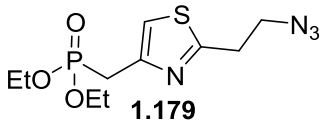
reaction mixture was heated to 160 °C for 2 h with stirring, and then the excess triethyl phosphite was removed under a steady flow of N_2(g). The residue was allowed to cool to 25 °C and purified by flash column chromatography (silica gel, 50 → 100% ethyl acetate in hexanes) to afford pure phosphonate **1.158** (3.29 g, 8.36 mmol, 99%) as a colorless oil. **1.158**: R_f = 0.35 (silica gel, ethyl acetate); FT-IR (neat) ν_{max} 3468, 2955, 2929, 2857, 1652, 1519, 1472, 1444, 1391, 1361, 1323, 1252, 1162, 1097, 1054, 1026, 964, 917, 836, 811, 777, 723, 662 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.09 (d, *J* = 3.6 Hz, 1 H), 4.08 (dq, *J* = 8.4, 7.2 Hz, 4 H), 3.93 (t, *J* = 6.0 Hz, 2 H), 3.36 (d, *J* = 21.0 Hz, 2 H), 3.17 (t, *J* = 6.0 Hz, 2 H), 1.28 (t, *J* = 7.2 Hz, 6 H), 0.88 (s, 9 H), 0.02 (s, 6 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.6, 145.7 (d, *J* = 8.0 Hz), 116.2 (d, *J* = 7.1 Hz), 62.4 (d, *J* = 6.5 Hz), 62.3, 37.1, 29.5 (d, *J* = 140.1 Hz), 26.0, 18.4, 16.6 (d, *J* = 6.0 Hz), -5.3 ppm; HRMS (ESI) calcd for $C_{16}H_{32}NO_4SiPSNa$ $[M+Na]^+$ 416.1451, found 416.1441.



1.178

Phosphonate 1.178: To a stirred solution of phosphonate **1.158** (2.75 g, 6.99 mmol, 1.0 equiv.) in tetrahydrofuran (20 mL) at 0 °C was added hydrogen fluoride-pyridine complex (70% HF, 0.90 mL, 34.9 mmol). After 1 h, the reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate (50 mL) and allowed to warm to 25 °C. The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 0 → 10% methanol in dichloromethane) to afford pure alcohol **1.178** (1.94 g,

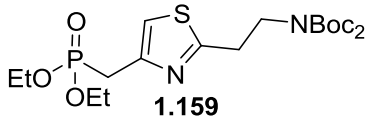
6.95 mmol, 99%) as a colorless oil. **1.178**: R_f = 0.20 (silica gel, 5% methanol in dichloromethane); FT-IR (neat) ν_{max} 3389, 2982, 2909, 1653, 1519, 1477, 1443, 1393, 1368, 1324, 1226, 1162, 1126, 1098, 1048, 1017, 963, 874, 842, 808, 784, 722, 668 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.07 (d, *J* = 3.6 Hz, 1 H), 4.07 (dq, *J* = 7.8, 6.6 Hz, 4 H), 3.96 (td, *J* = 6.0, 6.0 Hz, 2 H), 3.66 (t, *J* = 6.0 Hz, 1 H), 3.33 (d, *J* = 21.0 Hz, 2 H), 3.16 (t, *J* = 6.0 Hz, 2 H), 1.27 (t, *J* = 7.2 Hz, 6 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 168.3, 146.1 (d, *J* = 8.6 Hz), 115.8 (d, *J* = 8.0 Hz), 62.4 (d, *J* = 6.6 Hz), 61.3, 35.7, 29.5 (d, *J* = 140.4 Hz), 16.5 (d, *J* = 6.0 Hz) ppm; HRMS (ESI) calcd for $C_{10}H_{18}NO_4PSNa$ $[M+Na]^+$ 302.0586, found 302.0577.



1.179

Azide 1.179: To a stirred solution of phosphonate **1.178** (1.37 g, 4.91 mmol, 1.0 equiv.) in dichloromethane (10 mL) at 25 °C was added triethylamine (2.05 mL, 14.7 mmol, 3.0 equiv.) and 4-(dimethylamino)pyridine (60 mg, 0.49 mmol, 0.1 equiv.). After cooling to –20 °C, *p*-tolunesulfonic anhydride (3.20 g, 9.81 mmol, 2.0 equiv.) was added in one portion. After 30 min, the reaction mixture was quenched with water (10 mL) and allowed to warmed to 25 °C. The two phases were separated, and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The crude residue was then resuspended in dimethylformamide (5 mL) at 25 °C, and sodium azide (957 mg, 14.7 mmol, 3.0 equiv.) was added with stirring. The reaction mixture was heated to 65 °C for 2 h, and then allowed to cool to 25 °C. The reaction mixture was then quenched with water

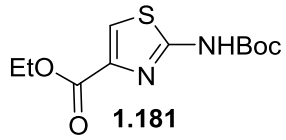
(20 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, 0 → 4% methanol in dichloromethane) afforded pure azide **1.179** (1.16 g, 3.81 mmol, 78%) as a colorless oil. **1.179**: R_f = 0.38 (silica gel, 5% methanol in dichloromethane); FT-IR (neat) ν_{max} 3464, 3111, 2983, 2931, 2098, 1647, 1519, 1477, 1445, 1394, 1323, 1250, 1163, 1124, 1098, 1053, 1025, 965, 873, 846, 828, 783, 725, 663 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.14 (d, *J* = 3.6 Hz, 1 H), 4.09 (dq, *J* = 7.8, 7.2 Hz, 4 H), 3.71 (t, *J* = 6.6 Hz, 2 H), 3.37 (d, *J* = 21.0 Hz, 2 H), 3.23 (t, *J* = 6.6 Hz, 2 H), 1.29 (t, *J* = 7.2 Hz, 6 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 165.9, 146.7 (d, *J* = 8.1 Hz), 116.5 (d, *J* = 7.2 Hz), 62.4 (d, *J* = 6.0 Hz), 50.7, 33.1, 29.6 (d, *J* = 140.3 Hz), 16.6 (d, *J* = 6.0 Hz) ppm; HRMS (ESI) calcd for $C_{10}H_{17}N_4O_3PSNa$ $[M+Na]^+$ 327.0651, found 327.0661.



1.159

Phosphonate 1.159: To a stirred solution of azide **1.179** (1.06 g, 3.48 mmol, 1.0 equiv.) in tetrahydrofuran/water (9:1, 15 mL) at 25 °C was added triphenylphosphine (2.74 g, 10.5 mmol, 3.0 equiv.). The reaction mixture was heated to 65 °C for 1.5 h, and then allowed to cool to 25 °C. Then water (6 mL), sodium bicarbonate (0.882 g, 10.5 mmol, 3.0 equiv.), and di-*tert*-butyl dicarbonate (1.52 g, 6.96 mmol, 2.0 equiv.) were added sequentially, and stirring was continued for 2.5 h. The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by

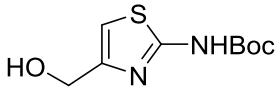
flash column chromatography (silica gel, 0 → 7.5% methanol in dichloromethane) to afford phosphonate **1.159** (1.65 g, 3.44 mmol, 99%) as a colorless oil. **1.159**: R_f = 0.37 (silica gel, 5% methanol in dichloromethane); FT-IR (neat) ν_{max} 3471, 2980, 2933, 1791, 1748, 1697, 1519, 1478, 1444, 1393, 1367, 1353, 1254, 1220, 1166, 1126, 1054, 1026, 962, 892, 854, 806, 779, 722 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.10 (d, *J* = 3.6 Hz, 1 H), 4.08 (dq, *J* = 7.8, 7.2 Hz, 4 H), 3.96–3.94 (m, 2 H), 3.35 (d, *J* = 21.0 Hz, 2 H), 3.25–3.23 (m, 2 H), 1.49 (s, 18 H), 1.28 (t, *J* = 7.2 Hz, 6 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.7, 152.3, 146.5 (d, *J* = 7.8 Hz), 116.1 (d, *J* = 7.2 Hz), 82.8, 62.4 (d, *J* = 6.0 Hz), 46.1, 32.9, 29.5 (d, *J* = 140.0 Hz), 28.2, 16.6 (d, *J* = 6.0 Hz) ppm; HRMS (ESI) calcd for $C_{20}H_{35}N_2O_7PSNa$ $[M+Na]^+$ 501.1795, found 501.1803.



1.181

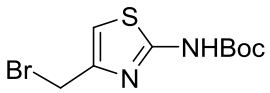
Thiazole carbamate 1.181: To a stirred solution of commercially available aminothiazole ester **1.180** (500 mg, 2.90 mmol, 1.0 equiv.) in tetrahydrofuran (9.7 mL) at 25 °C was added triethylamine (0.53 mL, 3.77 mmol, 1.3 equiv.), 4-(dimethylamino)pyridine (35 mg, 0.29 mmol, 0.1 equiv.), and di-*tert*-butyl-dicarbonate (696 mg, 3.19 mmol, 1.1 equiv.) sequentially. The reaction mixture was heated to 60 °C for 1 h, allowed to cool to 25 °C, and then quenched with a saturated aqueous solution of ammonium chloride (5 mL). The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (25% ethyl acetate in hexanes) afforded pure thiazole carbamate **1.181** (569 mg, 2.10 mmol, 72%) as a white

solid. **1.181**: R_f = 0.24 (silica gel, 25% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3168, 3068, 2980, 2935, 1713, 1553, 1478, 1455, 1393, 1368, 1331, 1294, 1235, 1207, 1154, 1098, 1071, 1021, 957, 915, 875, 802, 734, 682 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 8.67 (br s, 1 H), 7.77 (s, 1 H), 4.35 (q, *J* = 7.2 Hz, 2 H), 1.52 (s, 9 H), 1.36 (t, *J* = 7.2 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 161.5, 159.8, 152.3, 142.1, 121.7, 83.3, 61.4, 28.3, 14.5 ppm; HRMS (ESI) calcd for $C_{11}H_{16}N_2O_4S$ $[M+Na]^+$ 295.0723, found 295.0712.



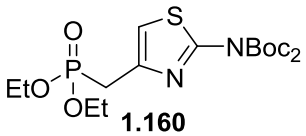
1.182

Hydroxymethyl thiazole 1.182: To a stirred solution of thiazole carbamate **1.181** (1.14 g, 4.19 mmol, 1.0 equiv.) in diethyl ether (14 mL) at 25 °C was added lithium borohydride (2.0 M tetrahydrofuran, 10.5 mL, 21.0 mmol, 5.0 equiv.). After 1 h, the reaction mixture was slowly quenched with a saturated aqueous solution of ammonium chloride (10 mL). The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 x 8 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (70% ethyl acetate in hexanes) afforded pure alcohol **1.182** (907 mg, 3.94 mmol, 94%) as a colorless oil. **1.182**: R_f = 0.57 (silica gel, 70% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3320, 3185, 3064, 2979, 2934, 1718, 1557, 1478, 1455, 1394, 1369, 1330, 1294, 1245, 1157, 1076, 1033, 965, 915, 868, 792, 732, 685 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.74 (s, 1 H), 4.57 (s, 2 H), 1.57 (s, 9 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 161.6, 152.6, 151.0, 109.2, 83.1, 60.1, 28.3 ppm; HRMS (ESI) calcd for $C_9H_{14}N_2O_3S$ $[M+Na]^+$ 253.0617, found 253.0616.



1.183

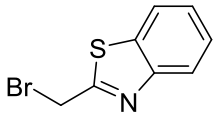
Bromomethyl thiazole 1.183: To a stirred solution of hydroxymethyl thiazole **1.182** (115 mg, 0.50 mmol, 1.0 equiv.) in dichloromethane (5 mL) at –78 °C was added triphenylphosphine (135 mg, 0.51 mmol, 1.05 equiv.), followed by *N*-bromosuccinimide (89 mg, 0.50 mmol, 1.0 equiv.). After 15 min, the reaction mixture was quenched with water (2.5 mL) and allowed to warm to 25 °C. The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 20% ethyl acetate in hexanes) to afford pure bromomethyl thiazole **1.183** (104 mg, 0.35 mmol, 71%) as a colorless oil. **1.183**: R_f = 0.31 (silica gel, 20% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3164, 3056, 2978, 2933, 2803, 1713, 1553, 1478, 1454, 1432, 1393, 1368, 1332, 1289, 1243, 1215, 1151, 1068, 1033, 977, 910, 865, 791, 763, 701, 655 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 10.08 (br s, 1 H), 6.88 (s, 1 H), 4.54 (s, 2 H), 1.56 (s, 9 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 161.4, 152.6, 146.8, 111.6, 83.2, 28.4, 27.8 ppm; HRMS (ESI) calcd for $C_9H_{13}BrN_2O_2S$ $[M+H]^+$ 292.9954, found 292.9950.



1.160

Phosphonate 1.160: Triethyl phosphite (2.4 mL, 14.2 mmol, 20 equiv.) was added to a flask containing bromomethyl thiazole **1.183** (208 mg, 0.71 mmol, 1.0 equiv.) at 25 °C. The stirred reaction mixture was heated to 160 °C for 3 h, and then the excess triethyl

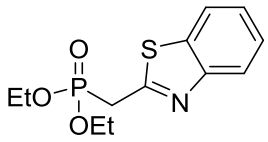
phosphite was removed under a steady flow of N_2(g). The residue was allowed to cool to 25 °C and resuspended in tetrahydrofuran (2.4 mL). To the stirred solution was added triethylamine (0.26 mL, 1.85 mmol, 2.6 equiv.), 4-(dimethylamino)pyridine (9 mg, 0.07 mmol, 0.1 equiv.), and di-*tert*-butyl-dicarbonate (340 mg, 1.56 mmol, 2.2 equiv.) sequentially. The reaction mixture was heated to 60 °C for 3.5 h, allowed to cool to 25 °C, and quenched with a saturated aqueous solution of ammonium chloride (10 mL). The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (65% ethyl acetate in hexanes) afforded pure phosphonate **1.160** (256 mg, 0.57 mmol, 80%) as a colorless oil. **1.160**: R_f = 0.28 (silica gel, 65% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3475, 3109, 2981, 2934, 1776, 1725, 1526, 1490, 1458, 1395, 1370, 1345, 1326, 1248, 1156, 1120, 1054, 1027, 966, 948, 846, 802, 777 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.03 (d, *J* = 3.6 Hz, 1 H), 4.10 – 4.05 (m, 4 H), 3.28 (d, *J* = 21.0 Hz, 2 H), 1.52 (s, 18 H), 1.27 (t, *J* = 7.1 Hz, 6 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 158.0, 149.8, 142.8 (d, *J* = 8.3 Hz), 114.5 (d, *J* = 7.7 Hz), 84.7, 62.4 (d, *J* = 6.2 Hz), 29.3 (d, *J* = 140.7 Hz), 27.9, 16.5 (d, *J* = 6.0 Hz) ppm; HRMS (ESI) calcd for $C_{18}H_{31}N_2O_7PS$ $[M+Na]^+$ 473.1482, found 473.1471.



1.186

Bromomethyl benzothiazole 1.186: To a stirred solution of commercially available hydroxymethyl benzothiazole **1.185** (1.00 g, 6.05 mmol, 1.0 equiv.) in dichloromethane/tetrahydrofuran (1:1, 40 mL) at –78 °C was added triphenylphosphine

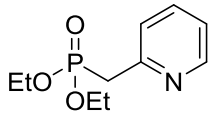
(1.59 g, 6.05 mmol, 1.0 equiv.), followed by *N*-bromosuccinimide (1.08 g, 6.05 mmol, 1.0 equiv.). After 5 min, the reaction mixture was quenched with water (20 mL) and allowed to warm to 25 °C. The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 2 → 8% ethyl acetate in hexanes) to afford pure bromomethyl benzothiazole **1.186** (0.780 g, 3.42 mmol, 57%) as a white crystalline solid. **1.186**: R_f = 0.48 (silica gel, 10% ethyl acetate in hexanes); m.p. 45–46 °C; FT-IR (neat) ν_{max} 3059, 3028, 1594, 1557, 1505, 1456, 1430, 1313, 1278, 1242, 1190, 1157, 1125, 1090, 1061, 1013, 938, 901, 851, 756, 727, 706 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 8.03 (d, *J* = 8.4 Hz, 1 H), 7.88 (d, *J* = 7.8 Hz, 1 H), 7.51 (ddd, *J* = 7.8, 7.8, 1.2 Hz, 1 H), 7.43 (ddd, *J* = 7.8, 7.8, 1.2 Hz, 1 H), 4.82 (s, 2 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.2, 152.8, 136.2, 126.5, 125.9, 123.5, 121.8, 27.1 ppm; HRMS (ESI) calcd for $C_8H_7NS_2Br$ $[M+H]^+$ 227.9477, found 227.9466.



1.161

Phosphonate 1.161: Triethyl phosphite (2.0 mL, 11.7 mmol, 3.4 equiv.) was added to a flask containing bromomethyl benzothiazole **1.186** (775 mg, 3.40 mmol, 1.0 equiv.) at 25 °C. The stirred reaction mixture was heated to 160 °C for 2 h, and then the excess triethyl phosphite was removed under a steady flow of N_2(g). The residue was allowed to cool to 25 °C and purified by flash column chromatography (silica gel, 60 → 90% ethyl acetate in hexanes) to afford pure phosphonate **1.161** (820 mg, 2.87 mmol, 84%) as a colorless oil.

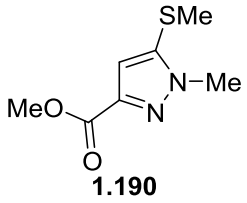
1.161: R_f = 0.32 (silica gel, ethyl acetate); FT-IR (neat) ν_{max} 3470, 3060, 2982, 2907, 1639, 1593, 1539, 1511, 1475, 1456, 1436, 1392, 1368, 1313, 1244, 1195, 1162, 1093, 1045, 1015, 963, 891, 842, 761, 731, 708, 677 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.80 (d, *J* = 7.8 Hz, 1 H), 7.86 (d, *J* = 7.8 Hz, 1 H), 7.47 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1 H), 7.38 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1 H), 4.19–4.13 (m, 4 H), 3.73 (d, *J* = 21.6 Hz, 2 H), 1.32 (t, *J* = 7.2 Hz, 6 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 161.2 (d, *J* = 9.3 Hz), 153.1 (d, *J* = 2.4 Hz), 136.1, 126.3, 125.3, 123.1, 121.7, 63.0 (d, *J* = 6.6 Hz), 33.3 (d, *J* = 139 Hz), 16.5 (d, *J* = 6.0 Hz) ppm; HRMS (ESI) calcd for $C_{12}H_{16}NO_3PSNa$ $[M+Na]^+$ 308.0481, found 308.0482.



1.162

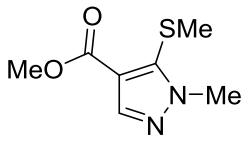
Phosphonate 1.162: Triethyl phosphite (1.5 mL, 8.75 mmol, 3.7 equiv.) was added to a flask containing commercially available bromomethyl pyridine hydrobromide salt **1.187** (410 mg, 2.38 mmol, 1.0 equiv.) at 25 °C. The stirred reaction mixture was heated to 160 °C for 2.5 h, and then the triethyl phosphite was removed under a steady flow of N_2(g). The residue was cooled to 25 °C and purified by flash column chromatography (silica gel, 50 → 80% ethyl acetate in hexanes) to afford pure phosphonate **1.162** (355 mg, 2.87 mmol, 65%) as a colorless oil. **1.162**: R_f = 0.33 (silica gel, ethyl acetate); FT-IR (neat) ν_{max} 3467, 2983, 2931, 2908, 1588, 1570, 1474, 1435, 1392, 1368, 1238, 1199, 1162, 1097, 1048, 1018, 957, 839, 809, 748, 704 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 8.54 (dd, *J* = 4.8, 1.8 Hz, 1 H), 7.64 (ddd, *J* = 7.8, 7.8, 1.8 Hz, 1 H), 7.39 (ddd, *J* = 7.8, 2.4, 1.2 Hz, 1 H), 7.19–7.16 (m, 1 H), 4.08 (dq, *J* = 7.8, 7.2 Hz, 4 H), 3.42 (d, *J* = 22.2 Hz, 2 H), 1.27 (t, *J* = 7.2 Hz, 6 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 152.9 (d, *J* = 8.3 Hz), 149.7 (d, *J* = 2.5

Hz), 136.7 (d, *J* = 2.6 Hz), 124.5 (d, *J* = 5.0 Hz), 122.0 (d, *J* = 3.3 Hz), 62.4 (d, *J* = 6.5 Hz), 36.9 (d, *J* = 134.6 Hz), 16.5 (d, *J* = 6.0 Hz) ppm; HRMS (ESI) calcd for $C_{10}H_{17}NO_3P$ $[M+H]^+$ 230.0941, found 230.0948.



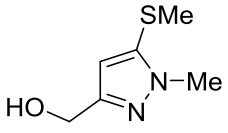
1.190

Pyrazole ester 1.190: To a stirred suspension of sydnone **1.188**[60] (3.09 g, 21.1 mmol, 1.0 equiv.) in xylenes (10 mL) at 25 °C was added methyl propiolate (3.55 g, 42.3 mmol, 2.0 equiv.). The reaction mixture was heated to 130 °C for 12 h, then allowed to cool to 25 °C and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 5 → 30% ethyl acetate in hexanes) to afford pure pyrazole ester **1.190** (2.44 g, 13.1 mmol, 62%) as a colorless oil and its regioisomer **1.191** (0.943 g, 5.06 mmol, 24%) as a colorless oil. **1.190**: R_f = 0.26 (silica gel, 40% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3137, 2996, 2951, 1718, 1503, 1458, 1441, 1397, 1366, 1320, 1290, 1217, 1126, 1076, 1044, 1010, 977, 946, 808, 776, 721 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.77 (s, 1 H), 3.92 (s, 3 H), 3.90 (s, 3 H), 2.43 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.6, 142.7, 138.8, 111.2, 52.2, 37.5, 18.6 ppm; HRMS (ESI) calcd for $C_7H_{11}N_2O_2S$ $[M+H]^+$ 187.0536, found 187.0531.



1.191

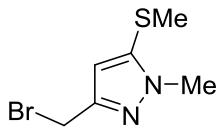
1.191: R_f = 0.37 (silica gel, 40% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 2996, 2949, 1713, 1519, 1435, 1405, 1389, 1365, 1314, 1275, 1221, 1169, 1108, 1045, 983, 945, 871, 805, 777, 728 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.93 (s, 1 H), 3.97 (s, 3 H), 3.85 (s, 3 H), 2.48 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 163.0, 141.9, 139.8, 116.4, 51.5, 37.4, 18.8 ppm; HRMS (ESI) calcd for $C_7H_{11}N_2O_2S$ $[M+H]^+$ 187.0536, found 187.0529.



1.192

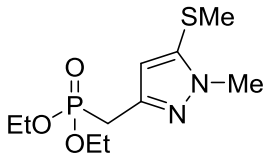
Hydroxymethyl pyrazole 1.192 To a stirred solution of pyrazole ester **1.190** (2.44 g, 13.1 mmol, 1.0 equiv.) in dichloromethane (36 mL) at –78 °C was added diisobutylaluminum hydride (1.0 M dichloromethane, 40.0 mL, 40.0 mmol, 3.0 equiv.) dropwise. After 10 min, the reaction mixture was quenched with an aqueous solution of HCl (2.0 M, 30 mL), allowed to warm to 25 °C, and stirred for an additional 2 h. The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 50 → 100% ethyl acetate in hexanes) to afford pure pyrazole **1.192** (1.70 g, 10.7 mmol, 82%) as a colorless oil. **1.192**: R_f = 0.22 (silica gel, ethyl acetate); FT-IR (neat) ν_{max} 3327, 2925, 2869, 1508, 1423, 1318, 1379, 1279, 1216, 1147, 1057, 1020, 1001, 976, 771 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.25 (s, 1 H), 4.62 (d, *J* = 6.0 Hz, 2 H), 3.83 (s, 3 H), 2.40 (s, 3 H), 2.27 (t, *J* =

6.0 Hz, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 151.7, 137.5, 107.1, 59.2, 36.5, 18.8 ppm; HRMS (ESI) calcd for $C_6H_{11}N_2OS$ $[M+H]^+$ 159.0587, found 159.0581.



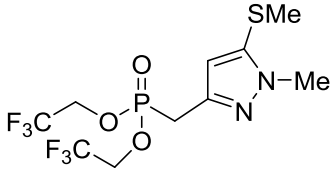
1.193

Bromomethyl pyrazole 1.193: To a stirred solution of hydroxymethyl pyrazole **1.192** (1.70 g, 10.7 mmol, 1.0 equiv.) in dichloromethane (20 mL) at –78 °C was added triphenylphosphine (2.96 g, 11.3 mmol, 1.05 equiv.), followed by *N*-bromosuccinimide (1.90 g, 10.7 mmol, 1.0 equiv.). After 5 min, the reaction mixture was quenched with water (20 mL) and allowed to warm to 25 °C. The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 5 → 20% ethyl acetate in hexanes) to afford pure bromomethyl pyrazole **1.193** (2.03 g, 9.06 mmol, 85%) as a colorless oil. **1.193**: R_f = 0.30 (silica gel, 20% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 3122, 2924, 1503, 1425, 1317, 1285, 1213, 1159, 1111, 1082, 1043, 1007, 974, 801, 767, 711 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.30 (s, 1 H), 4.43 (s, 2 H), 3.84 (s, 3 H), 2.41 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 148.4, 138.1, 108.4, 36.7, 25.3, 18.7 ppm; HRMS (ESI) calcd for $C_6H_{10}N_2SBr$ $[M+H]^+$ 220.9743, found 220.9749.



1.163

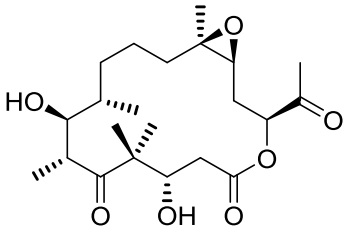
Phosphonate 1.163: Triethyl phosphite (4 mL, 23.3 mmol, 2.6 equiv.) was added to a flask containing bromomethyl pyrazole **1.193** (2.03 g, 9.06 mmol, 1.0 equiv.) at 25 °C. The stirred reaction mixture was then heated to 160 °C for 2 h, and then the excess triethyl phosphite was removed under a steady flow of N_2(g). The residue was allowed to cool to 25 °C and purified by flash column chromatography (silica gel, 50 → 90% acetone in hexanes) to afford pure phosphonate **1.163** (2.49 g, 8.97 mmol, 99%) as a colorless oil. **1.163**: R_f = 0.43 (silica gel, acetone); FT-IR (neat) ν_{max} 3471, 2982, 2927, 1505, 1441, 1425, 1392, 1368, 1253, 1163, 1097, 1054, 1025, 963, 848, 815, 757, 727, 696 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.27 (d, *J* = 1.8 Hz, 1 H), 4.08 (dq, *J* = 7.2, 7.2 Hz, 4 H), 3.81 (s, 3 H), 3.15 (d, *J* = 20.4 Hz, 2 H), 2.39 (s, 3 H), 1.28 (t, *J* = 7.2 Hz, 6 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 142.6 (d, *J* = 7.1 Hz), 137.4 (d, *J* = 2.3 Hz), 108.7 (d, *J* = 3.3 Hz), 62.3 (d, *J* = 6.3 Hz), 36.5, 26.9 (d, *J* = 141.0 Hz), 18.7, 16.6 (d, *J* = 6.0 Hz) ppm; HRMS (ESI) calcd for $C_{10}H_{20}N_2O_3PS$ $[M+H]^+$ 279.0927, found 279.0930.



1.164

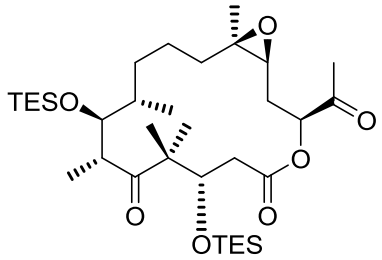
Trifluoroethyl phosphonate 1.164: To a flask containing phosphonate **1.163** (2.49 g, 8.97 mmol, 1.0 equiv.) was added trimethylsilyl chloride (5.75 mL, 45.3 mmol, 5.1 equiv.), and the reaction mixture was stirred at 80 °C for 72 h. The reaction mixture was then allowed

to cool to 25 °C, and the trimethylsilyl chloride was removed *in vacuo*. The residue was resuspended in dichloromethane (30 mL), and the solution was cooled to 0 °C with stirring. Then a solution of oxalyl chloride (3.05 g, 24.0 mmol, 2.5 equiv.) in dichloromethane (5 mL) was added dropwise. The reaction mixture was allowed to warm to 25 °C and stirred for 4 h. Then the solvent was removed *in vacuo*, and the residue was resuspended in dichloromethane (30 mL). The solution was cooled to 0 °C with stirring, and triethyl amine (7.58 mL, 54.4 mmol, 6.0 equiv.), 2,2,2-trifluoroethanol (2.72 mL, 36.2 mmol, 4.0 equiv.) and 4-(dimethylamino)pyridine (22.1 mg, 0.181 mmol, 0.02 equiv.) were added sequentially. The reaction mixture was allowed to slowly warm to 25 °C and stirred for 12 h. Then the reaction mixture was diluted with ethyl acetate (100 mL), and washed with water (20 mL) and brine (20 mL). The two phases were separated, and the organic layer was dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 20 → 60% ethyl acetate in hexanes) to afford pure trifluoroethyl phosphonate **1.164** (3.00 g, 7.77 mmol, 87%) as a colorless oil. **1.164**: R_f = 0.17 (silica gel, 50% ethyl acetate in hexanes); FT-IR (neat) ν_{max} 2971, 1504, 1422, 1291, 1260, 1168, 1103, 1070, 1007, 963, 879, 845, 780, 704 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.21 (d, *J* = 1.8 Hz, 1 H), 4.42–4.31 (m, 4 H), 3.81 (d, *J* = 1.2 Hz, 3 H), 3.33 (d, *J* = 21.0 Hz, 2 H), 2.39 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 140.3 (d, *J* = 8.1 Hz), 138.2 (d, *J* = 2.1 Hz), 122.7 (qd, *J* = 275.9, 8.0 Hz), 108.6 (d, *J* = 5.3 Hz), 62.5 (qd, *J* = 37.7, 6.0 Hz), 36.6, 26.8 (d, *J* = 143.3 Hz), 18.6 ppm; HRMS (ESI) calcd for $C_{10}H_{14}N_2O_3PS$ $[M+H]^+$ 387.0361, found 387.0346.



1.122

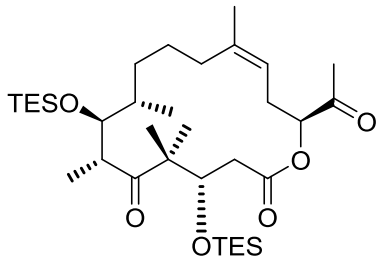
Epoxy methyl ketone 1.122: To a stirred solution of epothilone B (**1.02**) (122 mg, 0.240 mmol, 1.0 equiv.) in dichloromethane (5 mL) at –78 °C was bubbled freshly generated ozone. After the color of the solution changed to light blue, the reaction mixture was quenched with dimethyl sulfide (0.18 mL, 2.45 mmol, 10 equiv.), allowed to warm to 25 °C, and stirred for 1 h. The solvent was removed *in vacuo*, and the obtained residue was purified by flash column chromatography (silica gel, 40 → 70% ethyl acetate in hexanes) to afford pure epoxy methyl ketone **1.122** (93.0 mg, 0.225 mmol, 94%) as an amorphous solid. **1.122**: R_f = 0.26 (silica gel, 60% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = +12.7 (c = 0.60, CH_2Cl_2); FT-IR (neat) ν_{max} 3473, 2960, 2937, 2879, 1746, 1723, 1689, 1465, 1423, 1368, 1284, 1250, 1180, 1145, 1076, 1010, 980, 957, 916, 733, 672 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 5.31 (dd, *J* = 10.2, 1.8 Hz, 1 H), 4.31 (ddd, *J* = 10.8, 4.8, 3.0 Hz, 1 H), 4.10 (d, *J* = 4.8 Hz, 1 H), 3.70 (ddd, *J* = 3.6, 3.6, 3.6 Hz, 1 H), 3.25 (qd, *J* = 6.6, 5.4 Hz, 1 H), 2.82 (dd, *J* = 9.0, 3.0 Hz, 1 H), 2.57 (br s, 1 H), 2.54 (dd, *J* = 14.4, 10.8 Hz, 1 H), 2.34 (ddd, *J* = 15.0, 3.0, 1.8 Hz, 1 H), 2.28 (s, 3 H), 2.27 (dd, *J* = 15.0, 3.0 Hz, 1 H), 1.79–1.72 (m, 2 H), 1.69–1.63 (m, 1 H), 1.49–1.43 (m, 1 H), 1.44–1.37 (m, 1 H), 1.42 (s, 3 H), 1.36–1.25 (m, 2 H), 1.29 (s, 3 H), 1.20 (d, *J* = 6.6 Hz, 3 H), 1.09 (s, 3 H), 0.99 (d, *J* = 7.2 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 220.6, 205.0, 170.7, 76.8, 74.5, 71.7, 62.5, 62.2, 53.4, 42.7, 40.0, 37.4, 32.9, 31.3, 29.0, 26.4, 23.3, 22.6, 22.5, 18.0, 17.3, 14.4 ppm; HRMS (ESI) calcd for $C_{22}H_{36}O_7Na$ $[M+Na]^+$ 435.2353, found 435.2351.



1.123

Silyl ether 1.123: To a stirred solution of epoxide **1.122** (150 mg, 0.364 mmol, 1.0 equiv) in dichloromethane (5 mL) at –78 °C was added 2,6-lutidine (0.126 mL, 1.09 mmol, 3.0 equiv) followed by triethylsilyl trifluoromethanesulfonate (0.197 mL, 0.873 mmol, 2.4 equiv). After 5 min, the reaction mixture was quenched with water (10 mL), and allowed to warm to 25 °C. The two phases were separated, and the aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 5 → 15% ethyl acetate in hexanes) to afford pure silyl ether **1.123** (231 mg, 0.360 mmol, 99%) as an amorphous solid. **1.123**: R_f = 0.37 (silica gel, 20% ethyl acetate in hexanes); $[\alpha]_D^{25}$ –14.0 (c = 1.0, CH_2Cl_2); FT-IR (neat) ν_{max} 2955, 2913, 2877, 1749, 1734, 1696, 1459, 1414, 1381, 1308, 1240, 1196, 1157, 1106, 1080, 1064, 1040, 1010, 985, 916, 859, 836, 783, 737, 676 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 5.01 (dd, *J* = 10.2, 1.8 Hz, 1 H), 4.04 (dd, *J* = 10.2, 2.4 Hz, 1 H), 3.91 (d, *J* = 9.0 Hz, 1 H), 3.04 (dq, *J* = 9.6, 6.6 Hz, 1 H), 2.94 (dd, *J* = 16.2, 2.4 Hz, 1 H), 2.86 (dd, *J* = 10.2, 4.2 Hz, 1 H), 2.77 (dd, *J* = 16.2, 4.2 Hz, 1 H), 2.37 (dd, *J* = 16.2, 2.4 Hz, 1 H), 2.24 (s, 3 H), 1.76–1.68 (m, 2 H), 1.63–1.58 (m, 1 H), 1.55–1.45 (m, 2 H), 1.42–1.38 (m, 1 H), 1.30 (s, 3 H), 1.27–1.23 (m, 1 H), 1.25 (s, 3 H), 1.17 (s, 3 H), 1.10 (d, *J* = 6.6 Hz, 3 H), 1.07–1.04 (m, 1 H), 1.00 (t, *J* = 7.8 Hz, 9 H), 0.99 (d, *J* = 7.2 Hz, 3 H), 0.98–0.95 (m, 1 H), 0.93 (t, *J*

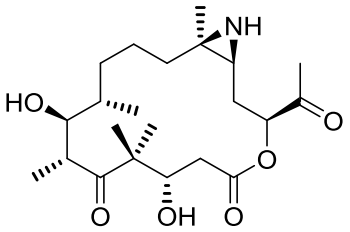
= 7.8 Hz, 9 H), 0.67 (q, *J* = 7.8 Hz, 6 H), 0.61 (q, *J* = 7.8 Hz, 6 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 215.2, 203.4, 171.8, 80.3, 76.5, 76.3, 62.5, 62.2, 53.5, 48.6, 39.4. 36.8, 32.1, 31.1, 30.3, 26.0, 24.9, 24.7, 23.7, 22.6, 19.7, 17.8, 7.3, 7.1, 5.7, 5.4 ppm; HRMS (ESI) calcd for $C_{34}H_{64}O_7Si_2Na$ $[M+Na]^+$ 663.4083, found 663.4057.



1.125

Olefin methyl ketone 1.125: To a stirred suspension of tungsten hexachloride (496 mg, 1.25 mmol, 2.0 equiv) in tetrahydrofuran (7 mL) at –78 °C was carefully added *n*-butyllithium (1.6 M hexanes, 1.56 mL, 2.50 mmol, 4.0 equiv). The reaction mixture was allowed to warm to 25 °C, stirred for 40 min, and then cooled to –20 °C. A solution of silyl ether **1.123** (401 mg, 0.626 mmol, 1.0 equiv) in tetrahydrofuran (4 mL) was then added dropwise, and the reaction mixture was allowed to slowly warm to 0 °C over 2 h. Then the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (10 mL), and allowed to warm to 25 °C. The two phases were separated, the aqueous layer was extracted with ethyl acetate (3 × 5 mL), and the combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 2.5 → 30% ethyl acetate in hexanes) to afford pure olefin **1.125** (335 mg, 0.536 mmol, 86%) as a colorless oil. **1.125**: R_f = 0.21 (silica gel, 10% diethyl ether in hexanes); $[\alpha]_D^{25}$ = –18.2 (c = 1.0, CH_2Cl_2); FT-IR (neat) ν_{max} 2953, 2912, 2877, 1747, 1731 ,1696, 1459, 1414, 1381, 1365, 1307, 1275, 1263, 1240,

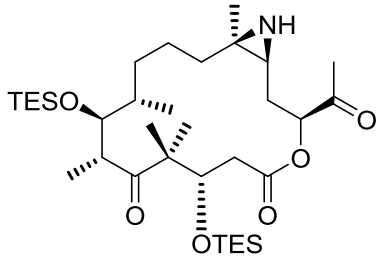
1198, 1159, 1110, 1062, 1042, 1018, 984, 859, 835, 783, 744, 674 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 5.16 (dd, *J* = 7.8, 7.8 Hz, 1 H), 4.84 (dd, *J* = 10.2, 1.8 Hz, 1 H), 4.04 (dd, *J* = 10.2, 1.8 Hz, 1 H), 3.91 (dd, *J* = 9.0 Hz, 1 H), 3.01 (dq, *J* = 9.6, 6.6 Hz, 1 H), 2.91 (dd, *J* = 16.2, 1.8 Hz, 1 H), 2.76 (dd, *J* = 16.2, 10.8 Hz, 1 H), 2.53 (ddd, *J* = 15.0, 10.2, 10.2 Hz, 1 H), 2.41 (dd, *J* = 14.4, 10.8 Hz, 1 H), 2.24 (dd, *J* = 14.4, 7.2 Hz, 1 H), 2.19 (s, 3 H), 1.76–1.66 (m, 2 H), 1.69 (s, 3 H), 1.57–1.49 (m, 2 H), 1.22 (s, 3 H), 1.14 (s, 3 H), 1.10–1.00 (m, 2 H), 1.09 (d, *J* = 6.6 Hz, 3 H), 0.98 (t, *J* = 7.8 Hz, 9 H), 0.97 (d, *J* = 6.6 Hz, 3 H), 0.88 (t, *J* = 7.8 Hz, 9 H), 0.65 (q, *J* = 7.8 Hz, 6 H), 0.55 (q, *J* = 7.8 Hz, 6 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 215.2, 204.4, 171.9, 142.4, 117.7, 80.1, 79.8, 76.6, 53.6, 48.2, 39.3, 37.6, 32.3, 31.4, 28.6, 27.5, 26.3, 25.1, 23.7, 23.2, 19.2, 17.7, 7.4, 7.0, 5.8, 5.4 ppm; HRMS (ESI) calcd for $C_{34}H_{64}O_6Si_2Na$ $[M+Na]^+$ 647.4134, found 647.4134.



1.126

Aziridine methyl ketone 1.126: To a stirred solution of olefin methyl ketone **1.124** (47.0 mg, 0.119 mmol, 1.0 equiv) in 2,2,2-trifluoroethanol (0.5 mL) at 25 °C was added *O*-(2,4-dinitrophenyl)hydroxylamine **1.106** (35.5 mg, 0.180 mmol, 1.5 equiv), followed by bis[rhodium(α,α,α',α',-tetramethyl-1,3-benzenedipropionic acid)] **1.107** (4.5 mg, 5.9 μmol, 0.05 equiv). The resulting mixture was stirred at the same temperature for 30 min, and then diluted with dichloromethane (30 mL). The solution was washed with a saturated aqueous solution of sodium bicarbonate (3 × 10 mL), followed by brine (10 mL). The organic layer was dried with anhydrous sodium sulfate and concentrated *in vacuo*. The

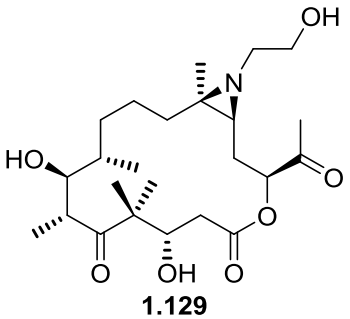
obtained residue was purified by flash column chromatography (silica gel, 5 → 30% methanol in ethyl acetate) to afford pure aziridine **1.126** (42.5 mg, 0.103 mmol, 87%) as a white solid. **1.126**: R_f = 0.22 (silica gel, 20% methanol in ethyl acetate); m.p 175–176 °C; $[\alpha]_D^{25}$ = –2.1 (c = 0.33, CH_2Cl_2); FT-IR (neat) ν_{max} 3460, 3298, 2957, 2927, 1741, 1722, 1687, 1464, 1421, 1367, 1283, 1258, 1173, 1147, 1075, 1056, 1008, 980, 939, 858, 735 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ = 5.10 (dd, *J* = 6.6, 3.0 Hz, 1 H), 4.36 (dd, *J* = 10.8, 3.6 Hz, 1 H), 3.80 (dd, *J* = 6.0, 3.6 Hz, 1 H), 3.22 (dq, *J* = 6.6, 6.6 Hz, 1 H), 2.48 (dd, *J* = 13.8, 10.8 Hz, 1 H), 2.24 (dd, *J* = 13.8, 3.6 Hz, 1 H), 1.81–1.76 (m, 1 H), 1.65 (s, 3 H), 1.58–1.54 (m, 1 H), 1.53–1.48 (m, 1 H), 1.42–1.26 (m, 7 H), 1.25 (s, 3 H), 1.10 (d, *J* = 7.2 Hz, 3 H), 1.03 (s, 3 H), 0.99 (d, *J* = 7.2 Hz. 3 H), 0.78 (s. 3 H) ppm; ^{13}C NMR (150 MHz, C_6D_6) δ = 219.2, 204.8, 170.6, 77.7, 76.2, 73.2, 52.8, 44.3, 39.9, 39.0, 38.0, 36.1, 32.4, 29.7, 28.8, 25.9, 25.9, 23.0, 20.6, 20.3, 17.7, 15.3 ppm; HRMS (ESI) calcd for $C_{22}H_{37}NO_6Na$ $[M+Na]^+$ 434.2513, found 434.2512.



1.127

Aziridine methyl ketone 1.127: To a stirred solution of olefin **1.125** (320 mg, 0.512 mmol, 1.0 equiv) in 2,2,2-trifluoroethanol (3 mL) at 25 °C was added *O*-(2,4-dinitrophenyl)hydroxylamine **1.106** (153 mg, 0.768 mmol, 1.5 equiv) followed by bis[rhodium(α,α,α′,α′,-tetramethyl-1,3-benzenedipropionic acid)] **1.107** (7.8 mg, 0.0102 mmol, 0.02 equiv). The reaction mixture was stirred for 30 min, diluted with

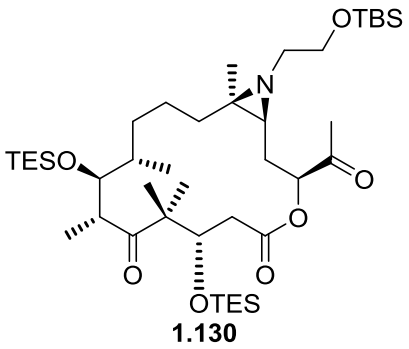
dichloromethane (40 mL), and washed with a saturated aqueous solution of sodium bicarbonate (3 × 15 mL), followed by brine (20 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 2.5 → 5% methanol in dichloromethane) to afford pure aziridine methyl ketone **1.127** (290 mg, 0.462 mmol, 90%) as a pale yellow oil. **1.127**: R_f = 0.29 (silica gel, 5% methanol in ethyl acetate); $[\alpha]_D^{25}$ = –14.5 (c = 0.64, CH_2Cl_2); FT-IR (neat) ν_{max} 2953, 2918, 2877, 1747, 1732, 1696, 1460, 1414, 1382, 1307, 1240, 1199, 1157, 1107, 1067, 1043, 1018, 985, 858, 835, 783, 736, 675 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ = 4.90 (dd, *J* = 9.0, 1.8 Hz, 1 H), 4.18 (d, *J* = 9.6 Hz, 1 H), 4.07 (dd, *J* = 9.0, 3.0 Hz, 1 H), 2.88 (dq, *J* = 10.2, 6.6 Hz, 1 H), 2.76–2.68 (m, 2 H), 1.94 (d, *J* = 16.2 Hz, 1 H), 1.83–1.78 (m, 1 H), 1.76–1.65 (m, 2 H), 1.72 (s, 3 H), 1.60–1.53 (m, 1 H), 1.51–1.45 (m, 1 H), 1.41–1.35 (m, 3 H), 1.26–1.19 (m, 1 H), 1.19 (d, *J* = 6.6 Hz, 3 H), 1.15 (s, 3 H), 1.09–1.04 (m, 24 H), 0.79–0.71 (m, 12 H), 0.67 (s, 3 H) ppm; ^{13}C NMR (151 MHz, C_6D_6) δ = 213.9, 202.3, 171.7, 80.8, 78.2, 76.7, 53.1, 48.3, 42.4, 39.4, 39.3, 36.9, 33.7, 31.43, 31.37, 25.7, 25.4, 25.2, 25.0, 22.8, 20.0, 17.7, 7.5, 7.3, 6.0, 5.8 ppm; HRMS (ESI) calcd for $C_{34}H_{66}NO_6Si_2$ $[M+H]^+$ 640.4423, found 640.4442.



1.129

Tertiary aziridine 1.129: To a stirred solution of aziridine **1.126** (39.2 mg, 95.3 µmol, 1.0 equiv) in dimethylformamide (0.8 mL) at room temperature was added 2-bromoethanol

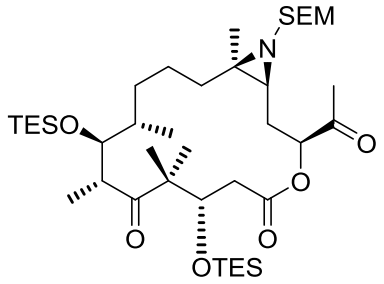
1.108 (119 mg, 0.953 mmol, 10 equiv.), followed by triethylamine (0.11 mg, 0.76 mmol, 8.0 equiv). The resulting mixture was heated to 70 °C, and stirred at the same temperature for 12 h. The reaction was cooled to room temperature, and quenched by adding water. The mixture was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were dried with anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (silica gel, 5 → 10% methanol in dichloromethane) to afford pure alkylated aziridine **1.129** (11.4 mg, 25.0 µmol, 26%) as a pale yellow oil. **1.129**: R_f = 0.38 (silica gel, 10% methanol in dichloromethane); $[\alpha]_D^{25}$ = –14.3 (c = 0.14, CH_2Cl_2); FT-IR (neat) ν_{max} 3406, 2934, 2878, 1742, 1720, 1688, 1466, 1421, 1368, 1255, 1179, 1148, 1068, 1008, 981, 956, 751, 711 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2) δ = 5.25 (dd, *J* = 9.6, 1.8 Hz, 1 H), 4.25 (dd, *J* = 10.8, 3.0 Hz, 1 H), 3.70 (dd, *J* = 6.0, 3.6 Hz, 1 H), 3.65 (dd, *J* = 6.0, 3.6 Hz, 1 H), 3.63 (dd, *J* = 6.0, 3.6, Hz, 1 H), 3.25 (dq, *J* = 6.6, 6.6 Hz, 1 H), 2.72 (ddd, *J* = 12.6, 6.6, 4.2 Hz, 1 H), 2.50 (ddd, *J* = 12.6, 6.0, 4.2 Hz, 1 H), 2.48 (dd, *J* = 14.4, 10.8 Hz, 1 H), 2.32 (dd, *J* = 14.4, 2.4 Hz, 1 H), 2.45 (s, 3 H), 2.21 (ddd, *J* = 15.6, 4.2, 2.4 Hz, 1 H), 1.60–1.58 (m, 4 H), 1.48–1.43 (m, 2 H), 1.40 (s, 3 H), 1.35–1.32 (m, 3 H), 1.16 (d, *J* = 7.2 Hz, 3 H), 1.15 (s, 3 H), 1.03 (s, 3 H), 0.96 (d, *J* = 7.2 Hz, 3 H) ppm; ^{13}C NMR (150 MHz, CD_2Cl_2) δ = 220.3, 205.8, 171.1, 78.4, 75.4, 72.1, 62.4, 54.7, 53.2, 49.6, 44.0, 43.7, 39.9, 36.7, 35.8, 30.5, 29.8, 26.5, 22.6, 21.9, 18.6, 17.5, 16.1, 14.6 ppm; HRMS (ESI) calcd for $C_{24}H_{42}NO_7$ $[M+H]^+$ 456.2956, found 456.2967.



1.130

Tertiary aziridine 1.130: To a stirred solution of aziridine **1.127** (105 mg, 0.164 mmol, 1.0 equiv.) in dimethylformamide (0.8 mL) at 25 °C was added (2-bromoethoxy)-*tert*-butyldimethylsilane **1.128** (196 mg, 0.820 mmol, 5.0 equiv.), followed by potassium carbonate (91 mg, 0.656 mmol, 4.0 equiv.). The reaction mixture was heated to 75 °C, stirred for 12 h, and then allowed to cool to 25 °C. Water (1.5 mL) was added, and the quenched reaction mixture was extracted with ethyl acetate (3 × 3 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 10 → 40% ethyl acetate in hexanes) to afford pure *N*-alkylated aziridine **1.130** (118 mg, 0.148 mmol, 90%) as a pale yellow oil. **1.130**: R_f = 0.31 (silica gel, 30% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –6.9 (c = 0.26, CH_2Cl_2); FT-IR (neat) ν_{max} 2953, 2931, 2877, 1748, 1734, 1697, 1462, 1414, 1382, 1361, 1307, 1250, 1196, 1158, 1109, 1079, 1042, 1008, 985, 835, 780, 737, 667 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ = 4.94 (dd, *J* = 9.0, 1.8 Hz, 1 H), 4.19 (d, *J* = 9.6 Hz, 1 H), 4.05 (dd, *J* = 7.8, 4.8 Hz, 1 H), 3.84 (ddd, *J* = 9.6, 6.6, 6.6 Hz, 1 H), 3.77 (ddd, *J* = 10.2, 5.4, 5.4 Hz, 1 H), 2.85 (dq, *J* = 9.6, 6.6 Hz, 1 H), 2.75–2.71 (m, 2 H), 2.42 (ddd, *J* = 12.6, 6.6, 6.6 Hz, 1 H), 2.19 (d, *J* = 16.2 Hz, 1 H), 1.86–1.76 (m, 2 H), 1.83 (s, 3 H), 1.72–1.59 (m, 3 H), 1.48–1.36 (m, 2 H), 1.25–1.10 (m, 3 H), 1.21 (d, *J* = 7.2 Hz, 3 H), 1.16 (s, 3 H),

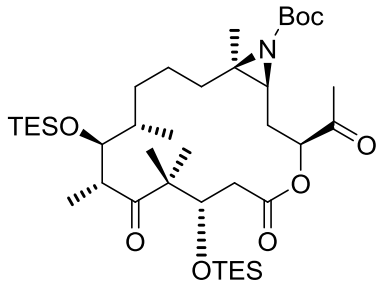
1.11–1.06 (m, 18 H), 1.04 (m, *J* = 6.6 Hz, 3 H), 1.00 (s, 9 H), 0.83–0.77 (m, 6 H), 0.72 (q, *J* = 7.8 Hz, 6 H), 0.68 (s, 3 H), 0.10 (s, 6 H) ppm; ^{13}C NMR (151 MHz, C_6D_6) δ = 213.9, 202.5, 171.9, 80.8, 78.1, 76.8, 64.3, 54.6, 53.1, 50.7, 48.3, 42.8, 39.4, 36.9, 35.9, 31.7, 31.6, 26.2 (3 C), 25.5, 25.1, 25.0, 23.0, 20.0, 18.5, 17.8, 15.5, 7.4, 7.3, 6.0, 5.8, -5.12, -5.13 ppm; HRMS (ESI) calcd for $C_{42}H_{84}NO_7Si_3$ $[M+H]^+$ 798.5550, found 798.5541.



1.170

Protected aziridine 1.170: To a stirred solution of **1.127** (65.0 mg, 0.102 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) at 0 °C was added *N*,*N*-diisopropylethylamine (26.3 mg, 0.203 mmol, 2.0 equiv), followed by 2-(trimethylsilyl)ethoxymethyl chloride (25.5 mg, 0.153 mmol, 1.5 equiv). The resulting reaction mixture was stirred at the same temperature for 2 h. The reaction mixture was quenched by adding H_2O (5 mL), extracted with ethyl acetate (2 × 10 mL), and the combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 5 → 20% ethyl acetate in hexanes) to afford pure protected aziridine **1.170** (46.0 mg, 59.7 µmol, 59%) as a colorless oil. **1.170**: R_f = 0.23 (silica gel, 20% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –3.1 (c = 0.16, CH_2Cl_2); FT-IR (neat) ν_{max} 2953, 2877, 1748, 1734, 1697, 1460, 1414, 1382, 1368, 1307, 1286, 1247, 1197, 1158, 1105, 1043, 1018, 1009, 985, 940, 860, 836, 783, 736 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ = 4.93 (dd, *J* = 9.0, 3.0 Hz, 1 H), 4.18 (d, *J* = 9.6 Hz, 1 H), 4.15 (d, *J* = 8.4 Hz, 1 H), 4.07 (d, *J* = 8.4 Hz, 1 H), 4.06

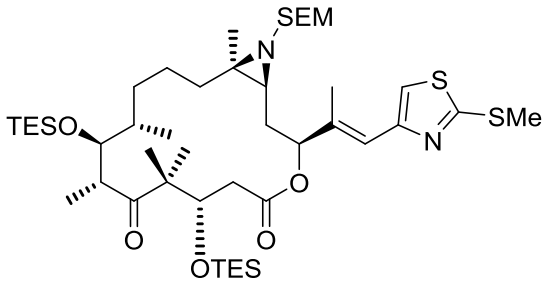
(dd, *J* = 9.0, 3.6 Hz, 1 H), 3.87–3.80 (m, 2 H), 2.85 (dq, *J* = 9.0, 6.6 Hz, 1 H), 2.76–2.68 (m, 2 H), 2.11–2.08 (m, 1 H), 1.85–1.79 (m, 2 H), 1.75 (s, 3 H), 1.74–1.68 (m, 1 H), 1.67–1.56 (m, 2 H), 1.52–1.48 (m, 1 H), 1.42–1.34 (m, 1 H), 1.29–1.25 (m, 1 H), 1.24–1.21 (m, 1 H), 1.19 (d, *J* = 7.2 Hz, 3 H), 1.15 (s, 3 H), 1.11 (s, 3 H), 1.10–1.06 (m, 18 H), 1.08–1.02 (m, 2 H), 1.04 (d, *J* = 6.6 Hz, 3 H), 0.80–0.76 (m, 6 H), 0.74–0.70 (m, 6 H), 0.68 (s, 3 H), 0.06 (s, 9 H) ppm; ^{13}C NMR (150 MHz, C_6D_6) δ = 213.9, 202.4, 171.7, 84.0, 80.8, 78.0, 76.7, 65.9, 53.1, 48.3, 47.7, 43.8, 39.5, 36.9, 35.5, 31.6, 31.1, 25.3, 25.0, 24.9, 22.9, 20.0, 18.4, 17.8, 15.8, 7.5 (3 C), 7.3 (3 C), 6.0 (3 C), 5.8 (3 C), –1.2 (3 C) ppm; HRMS (ESI) calcd for $C_{40}H_{80}NO_7Si_3^+$ $[M+H]^+$ 770.5237, found 770.5249.



1.171

Protected aziridine 1.171: To a stirred solution of **1.127** (28 mg, 39 µmol, 1.0 equiv) in MeCN (1 mL) at 0 °C was added triethylamine (16 mg, 0.12 mmol, 3.0 equiv), followed by Boc_2O (26 mg, 0.12 mmol, 3 equiv) and catalytic DMAP (1.0 mg). The resulting mixture was stirred at 25 °C for 5 min. Then the solvent was removed *in vacuo*, and the obtained residue was purified by flash column chromatography (silica gel, 5 → 15% ethyl acetate in hexanes) to afford pure methyl ketone **1.171** (23 mg, 31 µmol, 78%) as a colorless oil. **1.171**: R_f = 0.36 (silica gel, 20% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –14.1 (c = 0.64, CH_2Cl_2); FT-IR (neat) ν_{max} 2954, 2813, 2877, 1749, 1733, 1713, 1698, 1457, 1415, 1384, 1367, 1348, 1297, 1269, 1248, 1157, 1109, 1071, 1053, 1044, 1019, 1009, 984, 941,

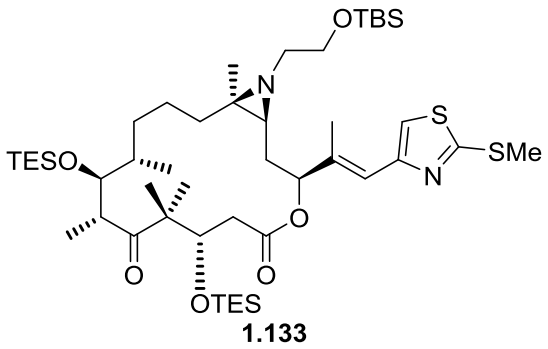
914, 864, 836, 811, 783, 736 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ = 4.98 (dd, *J* = 9.6, 2.4 Hz, 1 H), 4.01 (dd, *J* = 10.2, 2.4 Hz, 1 H), 3.91 (d, *J* = 9.0 Hz, 1 H), 3.00 (dq, *J* = 9.6, 7.2 Hz, 1 H), 2.91 (dd, *J* = 16.2, 1.2 Hz, 1 H), 2.74 (dd, *J* = 16.2, 10.2 Hz, 1 H), 2.39 (ddd, *J* = 15.6, 3.0, 3.0 Hz, 1 H), 2.33 (dd, *J* = 10.8, 3.6 Hz, 1 H), 2.22 (s, 3 H), 1.78 (ddd, *J* = 13.2, 13.2, 4.8 Hz, 1 H), 1.62–1.57 (m, 2 H), 1.50–1.40 (m, 2 H), 1.46 (s, 9 H), 1.36–1.32 (m, 1 H), 1.25–1.18 (m, 1 H), 1.22 (s, 3 H), 1.21 (s, 3 H), 1.15 (s, 3 H), 1.07 (d, *J* = 6.6 Hz, 3 H), 1.03–0.99 (m, 1 H), 0.98 (d, *J* = 6.6 Hz, 3 H), 0.97 (t, *J* = 7.8 Hz, 9 H), 0.91 (t, *J* = 7.8 Hz, 9 H), 0.64 (q, *J* = 7.8 Hz, 6 H), 0.59 (t, *J* = 7.8 Hz, 6 H) ppm; ^{13}C NMR (150 MHz, C_6D_6) δ = 215.3, 203.5, 171.9, 161.4, 81.4, 80.5, 76.6, 53.4, 48.7, 48.3, 46.5, 39.5, 36.6, 33.1, 31.1, 30.0, 28.3 (3 C), 26.1, 24.7, 24.6, 23.8, 20.3, 19.9, 17.9, 7.3 (3 C), 7.1 (3 C), 5.8 (3 C), 5.4 (3 C) ppm; HRMS (ESI) calcd for $C_{39}H_{73}NO_8Si_2Na^+$ $[M+Na]^+$ 762.4767, found 762.4799.



1.172

Protected epothilone 1.172: To a stirred solution of phosphonate **1.131** (120 mg, 0.427 mmol, 23 equiv) in tetrahydrofuran (1.0 mL) at –78 °C was added a solution of *n*-butyllithium (2.5 M, 0.14 mL, 0.34 mmol, 19 equiv) in hexanes. The resulting reaction mixture was stirred at the same temperature for 10 min, and then added to a stirred solution of methyl ketone **1.170** (14.0 mg, 18.2 μmol, 1.0 equiv) in tetrahydrofuran (0.5 mL). The resulting reaction mixture was allowed to slowly warm to 25 °C over 2.5 h. The reaction

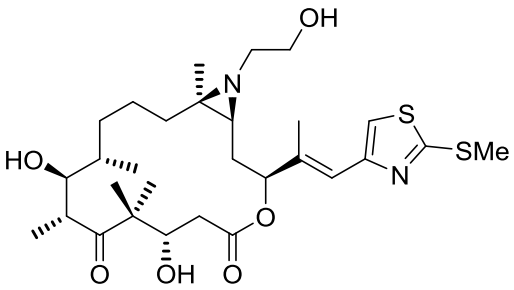
mixture was then quenched with a saturated aqueous solution of ammonium chloride (5 mL), the organic layer was extracted with ethyl acetate (3 × 15 mL), and the combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 5 → 15% ethyl acetate in hexanes) to afford protected epothilone **1.172** (9.8 mg, 11 μmol, 60%) as a colorless oil. **1.172**: R_f = 0.23 (silica gel, 15% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –5.5 (c = 0.40, CH_2Cl_2); FT-IR (neat) ν_{max} 2952, 2912, 2876, 1742, 1696, 1459, 1417, 1380, 1345, 1303, 1281, 1247, 1197, 1181, 1157, 1095, 1069, 1036, 1018, 985, 940, 860, 836, 782, 738 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ = 6.64 (s, 1 H), 6.44 (s, 1 H), 5.46 (dd, *J* = 7.8, 4.2 Hz, 1 H), 4.29 (dd, *J* = 8.4, 4.2 Hz, 1 H), 4.13 (d, *J* = 8.4 Hz, 1 H), 4.12 (d, *J* = 8.4 Hz, 1 H), 4.08 (d, *J* = 8.4 Hz, 1 H), 3.90 (ddd, *J* = 9.0, 7.8, 7.8 Hz, 1 H), 3.78 (ddd, *J* = 9.0, 7.8, 7.8 Hz, 1 H), 3.03 (dq, *J* = 8.4, 6.6 Hz, 1 H), 2.69 (dd, *J* = 16.2, 8.4 Hz, 1 H), 2.60 (dd, *J* = 16.2, 4.2 Hz, 1 H), 2.28 (s, 3 H), 2.22 (ddd, *J* = 13.8, 4.2, 4.2 Hz, 1 H), 2.20 (s, 3 H), 2.10 (ddd, *J* = 15.0, 9.0, 9.0 Hz, 1 H), 1.91–1.84 (m, 2 H), 1.72–1.67 (m, 1 H), 1.66–1.58 (m, 1 H), 1.54–1.48 (m, 2 H), 1.40 (dd, *J* = 9.0, 2.4 Hz, 1 H), 1.18 (s, 3 H), 1.17 (s, 3 H), 1.16 (d, *J* = 7.2 Hz, 3 H), 1.13 (d, *J* = 7.2 Hz, 3 H), 1.09–1.03 (m, 18 H), 0.91 (s, 3 H), 0.82–0.75 (m, 6 H), 0.73–0.69 (m, 6 H), 0.05 (s, 9 H) ppm; ^{13}C NMR (150 MHz, C_6D_6) δ = 214.6, 170.6, 165.3, 153.6, 138.6, 120.7, 116.5, 84.2, 80.0, 79.5, 75.6, 65.8, 53.5, 47.8, 46.8, 44.2, 40.5, 37.5, 36.3, 34.7, 32.4, 25.4, 23.5, 22.5, 20.1, 18.4, 17.5, 15.9, 15.8, 14.6, 7.4 (3 C), 7.3 (3 C), 5.9 (3 C), 5.8 (3 C), –1.1 (3 C) ppm.



1.133

Protected epothilone 1.133: To a stirred solution of phosphonate **1.131** (115 mg, 0.409 mmol, 15 equiv.) in tetrahydrofuran (0.5 mL) at –78 °C was carefully added *n*-butyllithium (1.6 M hexanes, 0.20 mL, 0.327 mmol, 12 equiv.). After stirring for 45 min at the same temperature, a solution of tertiary aziridine **1.130** (21.6 mg, 0.027 mmol, 1.0 equiv.) in tetrahydrofuran (0.5 mL) was added. The reaction mixture was allowed to slowly warm to 0 °C and stirred for an additional 2 h. Then the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (10 mL) and allowed to warm to 25 °C. The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 5 → 15% ethyl acetate in hexanes) to afford pure protected epothilone **1.133** (15.0 mg, 0.016 mmol, 60%) as a colorless oil. **1.133**: R_f = 0.30 (silica gel, 15% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –3.0 (c = 1.15, CH_2Cl_2); FT-IR (neat) ν_{max} 2953, 2931, 2877, 1741, 1697, 1463, 1421, 1381, 1304, 1249, 1198, 1157, 1110, 1076, 1037, 1019, 985, 836, 779, 738, 674, 663 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ = 6.7 (s, 1 H), 6.4 (s, 1 H), 5.45 (dd, *J* = 8.4, 3.6 Hz, 1 H), 4.24 (dd, *J* = 8.4, 3.6 Hz, 1 H), 4.17 (d, *J* = 9.0 Hz, 1 H), 3.87–3.79 (m, 2 H), 3.03 (dq, *J* = 9.0, 7.2 Hz, 1 H), 2.75 (ddd, *J* = 12.0, 6.0, 6.0 Hz, 1 H), 2.72 (dd, *J*

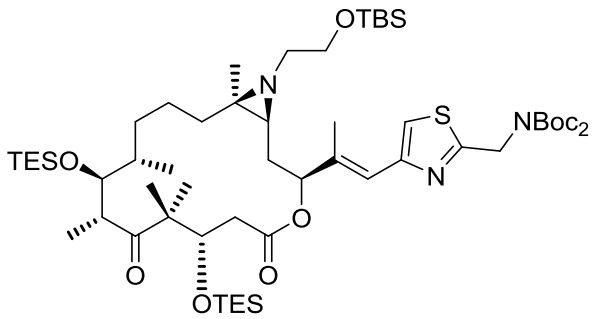
= 15.6, 8.4 Hz, 1 H), 2.59 (dd, *J* = 16.2, 3.0 Hz, 1 H), 2.46 (ddd, *J* = 12.0, 6.0, 6.0 Hz, 1 H), 2.30 (s, 3 H), 2.28–2.27 (m, 1 H), 2.20 (s, 3 H), 2.09–2.03 (m, 1 H), 1.90–1.81 (m, 2 H), 1.75–1.70 (m, 1 H), 1.66–1.59 (m, 1 H), 1.53–1.46 (m, 2 H), 1.27 (dd, *J* = 9.6, 3.0 Hz, 1 H), 1.24–1.20 (m, 1 H), 1.19 (d, *J* = 6.6 Hz, 3 H), 1.18 (s, 3 H), 1.16 (s, 3 H), 1.13 (d, *J* = 7.0 Hz, 3 H), 1.10–1.05 (m, 18 H), 0.99 (s, 9 H), 0.87 (s, 3 H), 0.84–0.77 (m, 6 H), 0.73–0.69 (m, 6 H), 0.094 (s, 3 H), 0.091 (s, 3 H) ppm; ^{13}C NMR (150 MHz, C_6D_6) δ = 214.5, 170.7, 165.3, 153.7, 138.9, 120.5, 116.5, 80.1, 79.6, 75.9, 64.3, 54.9, 53.4, 50.1, 48.1, 43.3, 40.2, 37.4, 36.4, 35.4, 32.4, 26.2, 25.5, 23.6, 23.1, 20.1, 18.5, 17.6, 15.9, 15.6, 14.7, 7.42, 7.36, 5.95, 5.80, -5.12 ppm; HRMS (ESI) calcd for $C_{47}H_{89}N_2O_6Si_3S_2$ $[M+H]^+$ 925.5464, found 925.5454.



1.134

Epothilone 1.134: To a stirred solution of protected epothilone **1.133** (30.0 mg, 0.032 mmol, 1.0 equiv.) in tetrahydrofuran (1.0 mL) at 0 °C was added hydrogen fluoride-pyridine complex (70% HF, 0.10 mL, 3.85 mmol, 120 equiv.). The reaction mixture was allowed to warm to 25 °C and stirred for 1 h. Then the reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate (5 mL), and the two phases were separated. The aqueous layer was extracted with ethyl acetate (3 × 5 mL), and the combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 5 → 20%

methanol in ethyl acetate) to afford pure epothilone **1.134** (15.0 mg, 0.026 mmol, 79%) as a colorless oil. **1.134**: R_f = 0.41 (silica gel, 20% methanol in ethyl acetate); $[\alpha]_D^{25}$ = –16.3 (c = 0.64, CH_2Cl_2); FT-IR (neat) ν_{max} 3373, 2927, 1729, 1685, 1654, 1559, 1460, 1452, 1424, 1259, 1149, 1037, 981, 881, 802, 735, 700 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ = 6.71 (s, 1 H), 6.47 (s, 1 H), 5.55 (dd, *J* = 4.2 Hz, 1 H), 4.12 (dd, *J* = 9.0, 3.0 Hz, 1 H), 3.92–3.89 (m, 1 H), 3.68–3.62 (m, 2 H), 3.34 (ddd, *J* = 13.8, 6.6, 6.6 Hz, 1 H), 2.56–2.52 (m, 1 H), 2.37–2.31 (m, 2 H), 2.43–2.20 (m, 1 H), 2.18 (s, 3 H), 2.05 (s, 3 H), 1.86–1.83 (m, 1 H), 1.66 (ddd, *J* = 15.6, 4.8, 4.8 Hz, 1 H), 1.63–1.59 (m, 1 H), 1.52–1.43 (m, 2 H), 1.41–1.34 (m, 2 H), 1.22 (ddd, *J* = 13.8, 6.6, 6.6 Hz, 1 H), 1.17 (s, 3 H), 1.10 (d, *J* = 7.0 Hz, 3 H), 1.09–1.06 (m, 1 H), 1.04 (d, *J* = 7.0 Hz, 3 H), 1.00–0.98 (m, 1 H), 0.94 (s, 3 H), 0.76 (s, 3 H) ppm; ^{13}C NMR (151 MHz, C_6D_6) δ = 219.5, 170.9, 165.7, 153.6, 136.5, 118.6, 116.3, 76.8, 75.7, 63.8, 62.4, 55.7, 52.1, 47.0, 45.7, 42.3, 39.0, 35.2, 34.0, 30.8, 28.7, 25.4, 22.4, 21.8, 18.6, 16.2, 15.99, 15.98, 15.3 ppm; HRMS (ESI) calcd for $C_{29}H_{47}N_2O_6S_2$ $[M+H]^+$ 583.2870, found 583.2861.

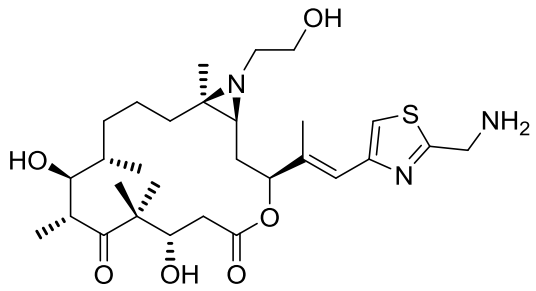


1.135

Protected epothilone 1.135: To a stirred solution of phosphonate **1.132** (97 mg, 0.209 mmol, 8.3 equiv.) in tetrahydrofuran (0.5 mL) at –78 °C was carefully added sodium bis(trimethylsilyl)amide (1.0 M tetrahydrofuran, 0.17 mL, 0.17 mmol, 6.8 equiv.). After

stirring for 35 min at the same temperature, a solution of tertiary aziridine **1.130** (20 mg, 0.025 mmol, 1.0 equiv.) in tetrahydrofuran (0.4 mL) was added. The reaction mixture was stirred for an additional 2 h at the same temperature, quenched with a saturated aqueous solution of ammonium chloride (10 mL), and allowed to warm to 25 °C. The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 5 → 20% ethyl acetate in hexanes) to afford pure protected epothilone **1.135** (18.8 mg, 0.017 mmol, 68%) as a colorless oil. **1.135**: R_f = 0.24 (silica gel, 15% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –4.4 (c = 0.84, CH_2Cl_2); FT-IR (neat) ν_{max} 2954, 2933, 2877, 1796, 1742, 1697, 1460, 1418, 1380, 1367, 1343, 1303, 1251, 1230, 1124, 1008, 985, 836 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ = 6.68 (s, 1 H), 6.54 (s, 1 H), 5.44 (dd, *J* = 9.0, 3.0 Hz, 1 H), 5.08 (s, 2 H), 4.23 (dd, *J* = 9.0, 3.0 Hz, 1 H), 4.19 (d, *J* = 8.4 Hz, 1 H), 3.87–3.79 (m, 2 H), 3.04 (dq, *J* = 8.4, 6.6 Hz, 1 H), 2.78–2.70 (m, 2 H), 2.59 (dd, *J* = 16.2, 3.0 Hz, 1 H), 2.47 (ddd, *J* = 12.6, 6.6, 6.6 Hz, 1 H), 2.33 (s, 3 H), 2.27 (ddd, *J* = 14.4, 3.0, 3.0 Hz, 1 H), 2.04 (ddd, *J* = 15.0, 9.0, 9.0 Hz, 1 H), 1.90–1.80 (m, 2 H), 1.76–1.71 (m, 1 H), 1.66–1.59 (m, 1 H), 1.52–1.48 (m, 2 H), 1.37 (s, 18 H), 1.26 (dd, *J* = 15.6, 9.0 Hz, 1 H), 1.22–1.17 (m, 1 H), 1.20 (d, *J* = 7.2 Hz, 3 H), 1.19 (s, 3 H), 1.16 (s, 3 H), 1.14 (d, *J* = 6.6 Hz, 3 H), 1.09 (t, *J* = 7.8 Hz, 9 H), 1.06 (t, *J* = 7.8 Hz, 9 H), 1.00 (s, 9 H), 0.85–0.78 (m, 6 H), 0.74–0.70 (m, 6 H), 0.101 (s, 3 H), 0.097 (s, 3 H) ppm; ^{13}C NMR (151 MHz, C_6D_6) δ = 214.4, 170.7, 167.1, 153.4, 152.4, 138.7, 120.7, 117.4, 82.4, 80.2, 79.6, 75.9, 64.3, 54.9, 53.4, 50.2, 48.1, 47.8, 43.3, 40.1, 37.4, 36.4, 35.4, 32.3, 27.9, 26.2, 25.5, 23.6, 23.3, 20.2, 18.5, 17.6, 15.6, 14.7, 7.43,

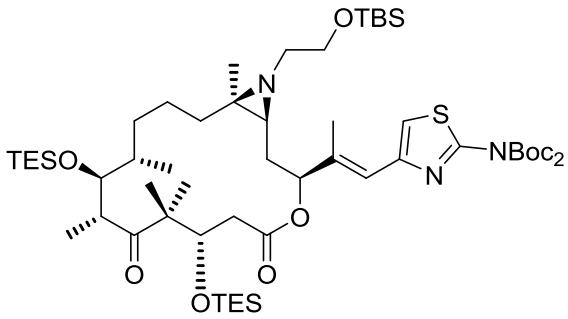
7.37, 6.0, 5.8, -5.1 ppm; HRMS (ESI) calcd for $C_{57}H_{106}N_3O_{10}Si_3S$ $[M+H]^+$ 1108.6901, found 1108.6892.



1.136

Epothilone 1.136: To a stirred solution of protected epothilone **1.135** (32 mg, 0.029 mmol, 1.0 equiv.) in tetrahydrofuran (2.0 mL) at 0 °C was added hydrogen fluoride-pyridine complex (70% HF, 0.20 mL, 7.70 mmol, 265 equiv.). The reaction mixture was allowed to warm to 25 °C and stirred for an additional 5 h. Then the reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate (10 mL), and the two phases were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The crude material was resuspended in dichloromethane (2.0 mL) and cooled to 0 °C. Trifluoroacetic acid (0.50 mL, 6.50 mmol, 224 equiv.) was added, the reaction mixture was stirred for 2.5 h, and then allowed to warm to 25 °C. The solvent was removed *in vacuo*, and the resulting residue was redissolved in ethyl acetate (15 mL). A saturated aqueous solution of sodium bicarbonate (5 mL) was added with stirring. After 10 min, the two phases were separated, and the organic layer was dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 0 → 20% methanol in acetone) to afford pure epothilone **1.136** (10.6 mg, 0.014 mmol, 48%) as a colorless oil. **1.136**: R_f = 0.18 (silica gel, 10% methanol

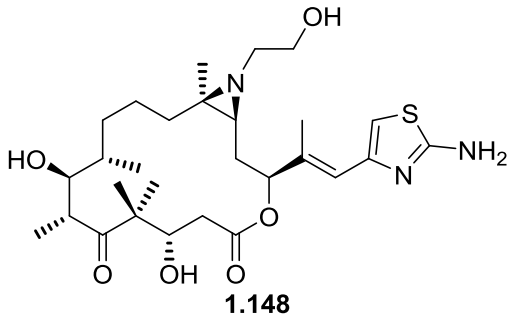
in acetone); $[\alpha]_D^{25}$ = –0.9 (c = 0.47, CH_2Cl_2); FT-IR (neat) ν_{max} 3386, 2922, 2851, 1676, 1557, 1463, 1396, 1261, 1201, 1180, 1132, 1033, 832, 800, 721, 672 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2) δ = 7.09 (s, 1 H), 6.55 (s, 1 H), 5.42 (dd, *J* = 5.4 Hz, 1 H), 4.10–4.08 (m, 1 H), 3.73 (dd, *J* = 4.8, 4.8 Hz, 1 H), 3.68–3.60 (m, 2 H), 3.30–3.26 (m, 1 H), 2.61 (t, *J* = 4.8 Hz, 1 H), 2.50 (dd, *J* = 13.8, 10.2 Hz, 1 H), 2.38 (dd, *J* = 13.8, 2.4 Hz, 1 H), 2.09 (s, 3 H), 1.96–1.87 (m, 2 H), 1.70–1.65 (m, 1 H), 1.56–1.49 (m, 1 H), 1.46–1.26 (m, 6 H), 1.35 (m, 3 H), 1.15 (s, 3 H), 1.12 (d, *J* = 7.2 Hz, 3 H), 1.03 (s, 3 H), 0.96 (d, *J* = 7.2 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, CD_2Cl_2) δ = 220.7, 174.2, 171.3, 152.8, 137.5, 119.4, 116.6, 77.9, 75.4, 74.4, 62.4, 55.2, 53.8, 53.0, 48.4, 44.3, 43.6, 39.6, 35.5, 35.0, 32.1, 29.8, 21.7, 20.7, 20.3, 17.5, 16.4, 15.9, 14.1 ppm; HRMS (ESI) calcd for $C_{29}H_{47}N_3O_6SNa$ $[M+Na]^+$ 588.3078, found 588.3087.



1.148a

Epothilone 1.148a: To a stirred solution of phosphonate **1.160** (118 mg, 0.263 mmol, 14 equiv.) in tetrahydrofuran (1.0 mL) at –78 °C was carefully added sodium *bis*(trimethylsilyl)amide (1.0 M tetrahydrofuran, 0.26 mL, 0.263 mmol, 14 equiv.). After stirring for 30 min at the same temperature, a solution of methyl ketone **1.130** (15.0 mg, 0.019 mmol, 1.0 equiv.) in tetrahydrofuran (1.0 mL) was added. The reaction mixture was allowed to slowly warm to 0 °C, stirred for an additional 3.5 h, and quenched with a

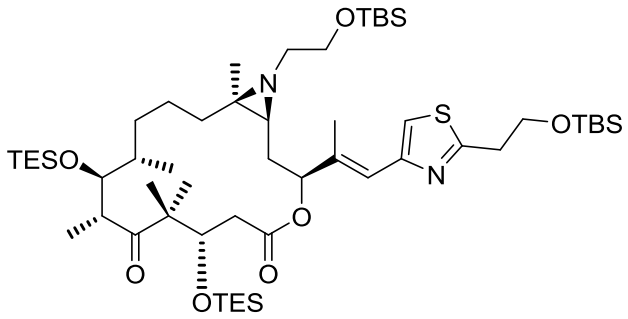
saturated aqueous solution of ammonium chloride (10 mL). The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 5 → 20% ethyl acetate in hexanes) to afford protected epothilone **1.148a** (14.2 mg, 0.013 mmol, 69%) as a colorless oil. **1.148a**: R_f = 0.20 (silica gel, 10% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –7.5 (c = 1.0, CH_2Cl_2); FT-IR (neat) ν_{max} 2954, 2933, 2877, 2858, 1780, 1728, 1696, 1505, 1460, 1413, 1370, 1334, 1283, 1249, 1158, 1120, 1041, 1007, 984, 836, 806, 779, 738 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ = 6.57 (s, 1 H), 6.33 (s, 1 H), 5.43 (dd, *J* = 8.6, 2.8 Hz, 1 H), 4.22 (dd, *J* = 9.2, 2.6 Hz, 1 H), 4.18 (d, *J* = 9.0 Hz, 1 H), 3.87–3.79 (m, 2 H), 3.01 (dq, *J* = 7.2, 7.2 Hz, 1 H), 2.73 (ddd, *J* = 12.0, 5.9, 5.9 Hz, 1 H), 2.68 (dd, *J* = 16.1, 9.3 Hz, 1 H), 2.56 (dd, *J* = 16.1, 2.9 Hz, 1 H), 2.44 (ddd, *J* = 12.0, 6.0, 6.0 Hz, 1 H), 2.34 (s, 3 H), 2.26–2.24 (m, 1 H), 2.08–2.02 (m, 1 H), 1.87–1.80 (m, 2 H), 1.75–1.69 (m, 1 H), 1.64–1.57 (m, 1 H), 1.51–1.48 (m, 1 H), 1.37 (s, 18 H), 1.34–1.21 (m, 3 H), 1.19 (d, *J* = 6.9 Hz, 3 H), 1.18 (s, 3 H), 1.15 (s, 3 H), 1.13 (d, *J* = 6.9 Hz, 3 H), 1.10–1.05 (m, 18 H), 0.99 (s, 9 H), 0.85 (s, 3 H), 0.83–0.77 (m, 6 H), 0.74–0.70 (m, 6 H), 0.100 (s, 3 H), 0.097 (s, 3 H) ppm; ^{13}C NMR (151 MHz, C_6D_6) δ = 214.6, 170.7, 157.8, 150.0, 149.2, 138.3, 121.0, 114.4, 84.2, 80.2, 79.7, 75.9, 64.3, 55.0, 53.5, 50.3, 48.2, 43.4, 40.2, 37.5, 36.4, 35.4, 32.4, 27.7, 26.2, 25.5, 23.7, 23.3, 20.2, 18.6, 17.7, 15.7, 14.6, 7.5, 7.4, 6.0, 5.9, -5.1, ppm; HRMS (ESI) calcd for $C_{56}H_{103}N_3O_{10}Si_3S$ $[M+H]^+$ 1094.6745, found 1094.6742.



1.148

Epothilone 1.148: To a stirred solution of protected epothilone **1.148a** (10.0 mg, 0.009 mmol, 1.0 equiv.) in tetrahydrofuran (2.0 mL) at 0 °C was added hydrogen fluoride-pyridine complex (70% HF, 0.05 mL, 1.94 mmol, 215 equiv.). The reaction mixture was allowed to warm to 25 °C and stirred for an additional 5 h. Then the reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate (10 mL), and the two phases were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The crude material was resuspended in dichloromethane (1.0 mL) and cooled to 0 °C. Trifluoroacetic acid (0.10 mL, 1.30 mmol, 144 equiv.) was added, the reaction mixture was stirred for 6 h, and then allowed to warm to 25 °C. The solvent was removed *in vacuo*, and the resulting residue was redissolved in ethyl acetate (15 mL). A saturated aqueous solution of sodium bicarbonate (5 mL) was then added with stirring. After 10 min, the two phases were separated, and the organic layer was dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 10% methanol in dichloromethane) to afford pure epothilone **1.148** (4.0 mg, 0.007 mmol, 80%) as a colorless oil. **1.148**: R_f = 0.13 (silica gel, 10% methanol in dichloromethane); $[\alpha]_D^{25}$ = –16.7 (c = 0.15, CH_2Cl_2); FT-IR (neat) ν_{max}

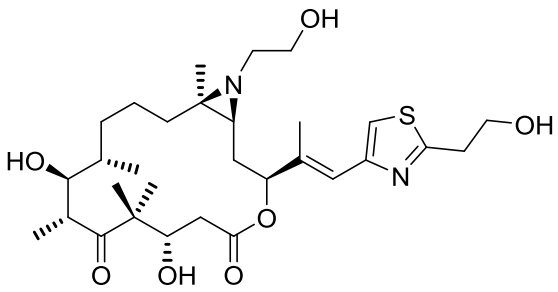
3332, 2926, 2856, 1727, 1686, 1529, 1464, 1378, 1346, 1262, 1148, 1054, 1009, 982, 885, 875, 799, 735, 689 cm^{-1}; ^{1}H NMR (600 MHz, CD_2Cl_2) δ = 6.40 (s, 1 H), 6.32 (s, 1 H), 5.37 (dd, *J* = 5.2, 5.2 Hz, 1 H), 5.12 (br s, 2 H), 4.07 (dd, *J* = 10.1, 2.0 Hz, 1 H), 3.73–3.70 (m, 4 H), 3.26 (dq, *J* = 7.2, 7.2 Hz, 1 H), 2.74–2.64 (m, 2 H), 2.47 (dd, *J* = 13.9, 10.2 Hz, 1 H), 2.35 (dd, *J* = 13.9, 2.3 Hz, 1 H), 2.06 (s, 3 H), 2.03–1.98 (m, 3 H), 1.72–1.66 (m, 1 H), 1.55–1.41 (m, 5 H), 1.34 (s, 3 H), 1.32–1.27 (m, 3 H), 1.21 (s, 3 H), 1.11 (d, *J* = 6.9 Hz, 3 H), 1.03 (s, 3 H), 0.96 (d, *J* = 6.9 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, CD_2Cl_2) δ = 220.7, 171.3, 167.0, 148.8, 136.6, 119.7, 107.6, 78.0, 75.3, 74.4, 61.7, 54.8, 53.1, 44.3, 39.6, 35.6, 34.2, 32.3, 31.5, 30.1, 27.6, 23.1, 21.7, 20.6, 17.5, 16.7, 15.7, 14.3 ppm; HRMS (ESI) calcd for $C_{28}H_{45}N_3O_6S$ $[M+Na]^+$ 574.2921, found 574.2899.



1.149a

Protected epothilone 1.149a: To a stirred solution of phosphonate **1.158** (200 mg, 0.508 mmol, 12 equiv.) in tetrahydrofuran (0.8 mL) at –78 °C was carefully added sodium bis(trimethylsilyl)amide (1.0 M tetrahydrofuran, 0.41 mL, 0.41 mmol, 9.7 equiv.). After stirring for 25 min at the same temperature, a solution of tertiary aziridine **1.130** (33.6 mg, 0.042 mmol, 1.0 equiv.) in tetrahydrofuran (0.5 mL) was added. The reaction mixture was allowed to slowly warm to 0 °C, stirred for an additional 2 h, and then quenched with a saturated aqueous solution of ammonium chloride (10 mL). The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined

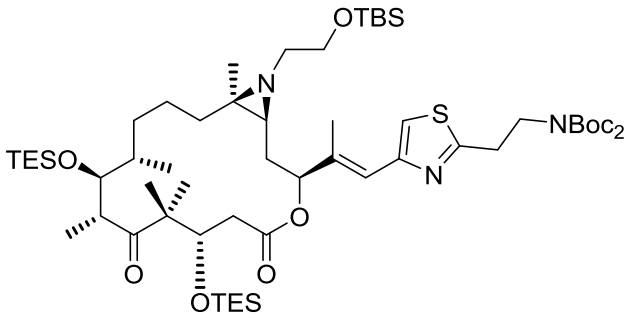
organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 5 → 15% ethyl acetate in hexanes) to afford pure protected epothilone **1.149a** (21.8 mg, 0.021 mmol, 50%) as a colorless oil. **1.149a**: R_f = 0.36 (silica gel, 15% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –2.9 (c = 0.63, CH_2Cl_2); FT-IR (neat) ν_{max} 2954, 2931, 2877, 2858, 1743, 1697, 1502, 1462, 1414, 1381, 1361, 1304, 1252, 1198, 1158, 1103, 1007, 984, 940, 916, 836, 812, 778, 735, 678, 662 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.78 (s, 1 H), 6.60 (s, 1 H), 5.48 (dd, *J* = 8.4, 3.0 Hz, 1 H), 4.23 (dd, *J* = 8.4, 2.4 Hz, 1 H), 4.18 (d, *J* = 9.0 Hz, 1 H), 3.86–3.78 (m, 2 H), 3.77 (t, *J* = 6.0 Hz, 2 H), 3.06–2.99 (m, 1 H), 3.02 (t, *J* = 6.0 Hz, 2 H), 2.77–2.70 (m, 2 H), 2.60 (dd, *J* = 16.2, 3.0 Hz, 1 H), 2.45 (ddd, *J* = 12.0, 6.0, 6.0 Hz, 1 H), 2.36 (s, 3 H), 2.30 (ddd, *J* = 15.0 Hz, 1 H), 2.06 (ddd, *J* = 15.6, 9.0, 9.0 Hz, 1 H), 1.90–1.81 (m, 2 H), 1.76–1.71 (m, 1 H), 1.66–1.58 (m, 1 H), 1.52–1.48 (m, 2 H), 1.28 (dd, *J* = 9.6, 3.0 Hz, 1 H), 1.24–1.20 (m, 1 H), 1.20 (d, *J* = 6.6 Hz, 3 H), 1.18 (s, 3 H), 1.16 (s, 3 H), 1.13 (d, *J* = 7.2 Hz, 3 H), 1.09 (t, *J* = 7.8 Hz, 9 H), 1.06 (t, *J* = 7.8 Hz, 9 H), 1.00 (s, 9 H), 0.94 (s, 9 H), 0.86 (s, 3 H), 0.85–0.77 (m, 6 H), 0.74–0.70 (m, 6 H), 0.096 (s, 3 H), 0.094 (s, 3 H), 0.02 (s, 6 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 214.5, 170.7, 166.6, 153.3, 138.3, 121.1, 117.1, 80.1, 79.7, 75.9, 64.3, 62.3, 54.9, 53.4, 50.2, 48.1, 43.3, 40.2, 37.4, 37.2, 36.4, 35.4, 32.4, 26.2, 26.0, 25.5, 23.6, 23.2, 20.2, 18.5, 18.4, 17.6, 15.6, 14.8, 7.43, 7.37, 6.0, 5.8, -5.1, -5.4 ppm; HRMS (ESI) calcd for $C_{54}H_{105}N_2O_7Si_4S$ $[M+H]^+$ 1037.6714, found 1037.6720.



1.149

Epothilone 1.149: To a stirred solution of protected epothilone **1.149a** (6.9 mg, 0.007 mmol, 1.0 equiv.) in tetrahydrofuran (1.5 mL) at 0 °C was added hydrogen fluoride-pyridine complex (70% HF, 0.03 mL, 1.16 mmol, 165 equiv.). The reaction mixture was allowed to warm to 25 °C and stirred for an additional 4 h. Then the reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate (10 mL), and the two phases were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 0 → 30% methanol in ethyl acetate) to afford pure epothilone **1.149** (3.5 mg, 0.006 mmol, 90%) as a colorless oil. **1.149**: R_f = 0.35 (silica gel, 30% methanol in ethyl acetate); $[\alpha]_D^{25}$ = –20.0 (c = 0.35, 10:1 CH_2Cl_2/methanol); FT-IR (neat) ν_{max} 3362, 2931, 2877, 1726, 1687, 1561, 1505, 1466, 1425, 1383, 1334, 1266, 1148, 1054, 1008, 981, 938, 883, 735, 675 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.08 (s, 1 H), 6.56 (s, 1 H), 5.41 (dd, *J* = 6.0, 3.6 Hz, 1 H), 4.09 (dd, *J* = 10.2, 2.4 Hz, 1 H), 3.97 (t, *J* = 6.0 Hz, 2 H), 3.71 (dd, *J* = 4.8, 4.8 Hz, 1 H), 3.69–3.62 (m, 2 H), 3.29–3.25 (m, 1 H), 3.20–3.18 (t, *J* = 6.0 Hz, 2 H), 2.66 (ddd, *J* = 12.0, 4.8, 4.8 Hz, 1 H), 2.59 (ddd, *J* = 12.0, 4.8, 4.8 Hz, 1 H), 2.49 (dd, *J* = 13.8, 10.2 Hz, 1 H), 2.37 (dd, *J* = 13.8, 2.4 Hz, 1 H), 2.08 (s, 3 H), 2.00–1.94 (m, 1 H), 1.91 (ddd, *J* = 7.2, 7.2, 7.2 Hz, 1 H), 1.68–1.64 (m, 1 H), 1.67–1.35 (m, 6 H), 1.35 (s, 3 H),

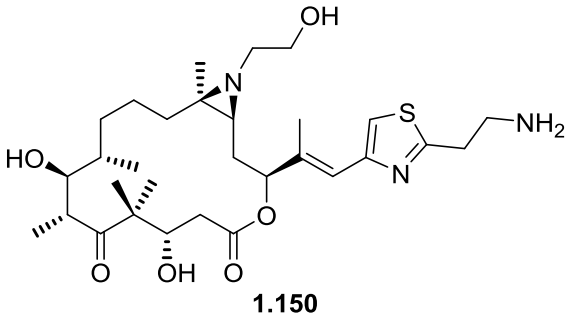
1.30–1.22 (m, 1 H), 1.26 (s, 3 H), 1.17 (s, 3 H), 1.13 (d, *J* = 6.6 Hz, 3 H), 1.03 (s, 3 H), 0.96 (d, *J* = 6.6 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 220.6, 171.4, 168.1, 152.7, 137.2, 119.2, 116.6, 77.9, 75.9, 75.0, 62.4, 61.5, 55.3, 52.7, 48.1, 44.8, 43.4, 39.5, 36.0, 35.5, 34.7, 31.8, 29.5, 21.8, 21.4, 19.9, 17.6, 16.5, 15.9, 14.5 ppm; HRMS (ESI) calcd for $C_{30}H_{48}N_2O_7SNa$ $[M+H]^+$ 603.3074, found 603.3081.



1.150a

Protected epothilone 1.150a: To a stirred solution of phosphonate **1.159** (330 mg, 0.690 mmol, 12 equiv.) in tetrahydrofuran (1.0 mL) at –78 °C was carefully added sodium *bis*(trimethylsilyl)amide (1.0 M tetrahydrofuran, 0.41 mL, 0.41 mmol, 9.7 equiv.). After stirring for 25 min at the same temperature, a solution of tertiary aziridine **1.130** (45.0 mg, 0.056 mmol, 1.0 equiv.) in tetrahydrofuran (0.5 mL) was added. The reaction mixture was allowed to slowly warm to 0 °C, stirred for an additional 2 h, and then quenched with a saturated aqueous solution of ammonium chloride (10 mL). The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 5 → 20% ethyl acetate in hexanes) to afford pure protected epothilone **1.150a** (28.2 mg, 0.025 mmol, 45%) as a colorless oil. **1.150a**: R_f = 0.30 (silica gel, 20% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –4.0

(c = 1.0, CH_2Cl_2); FT-IR (neat) ν_{max} 2954, 2935, 2877, 1794, 1744, 1697, 1500, 1459, 1390, 1367, 1353, 1306, 1278, 1251, 1220, 1158, 1118, 1040, 1008, 984, 858, 835, 779, 738, 668 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.71 (s, 1 H), 6.53 (s, 1 H), 5.43 (dd, *J* = 8.4, 3.0 Hz, 1 H), 4.20 (dd, *J* = 9.0, 3.0 Hz, 1 H), 4.18 (d, *J* = 8.4 Hz, 1 H), 4.08 (t, *J* = 7.2 Hz, 2 H), 3.86–3.79 (m, 2 H), 3.28–3.20 (m, 2 H), 3.03 (dq, *J* = 9.0, 7.2 Hz, 1 H), 2.78–2.70 (m, 2 H), 2.61 (dd, *J* = 16.2, 3.0 Hz, 1 H), 2.46 (ddd, *J* = 13.2, 6.6, 6.6 Hz, 1 H), 2.34 (s, 3 H), 2.29 (ddd, *J* = 15.0, 3.0, 3.0 Hz, 1 H), 2.04 (ddd, *J* = 15.6, 9.0, 9.0 Hz, 1 H), 1.91–1.81 (m, 2 H), 1.75–1.71 (m, 1 H), 1.67–1.59 (m, 1 H), 1.52–1.48 (m, 2 H), 1.39 (s, 18 H), 1.26 (dd, *J* = 10.2, 3.6 Hz, 1 H), 1.22–1.8 (m, 1 H), 1.20 (d, *J* = 7.2 Hz, 3 H), 1.19 (s, 3 H), 1.16 (s, 3 H), 1.13 (d, *J* = 6.6 Hz, 3 H), 1.09 (t, *J* = 7.8 Hz, 9 H), 1.06 (t, *J* = 7.8 Hz, 9 H), 0.99 (s, 9 H), 0.87 (s, 3 H), 0.85–0.77 (m, 6 H), 0.74–0.70 (m, 6 H), 0.097 (s, 3 H), 0.093 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 214.4, 170.7, 165.9, 153.8, 152.6, 138.6, 120.8, 117.0, 81.8, 80.2, 79.6, 75.9, 64.3, 54.9, 53.4, 50.2, 48.1, 46.1, 43.3, 40.1, 37.3, 36.4, 35.4, 32.9, 32.3, 28.0, 26.2, 25.5, 23.6, 23.3, 20.1, 15.5, 17.6, 15.6, 14.8, 7.43, 7.37, 6.0, 5.8, -5.1 ppm; HRMS (ESI) calcd for $C_{58}H_{108}N_3O_{10}Si_3S$ $[M+H]^+$ 1122.7058, found 1122.7033.

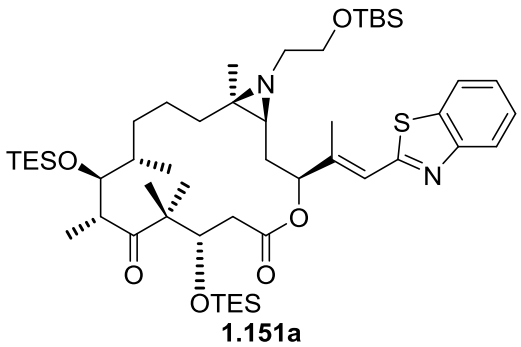


1.150

Epothilone 1.150: To a stirred solution of protected epothilone **1.150a** (14.9 mg, 0.013 mmol, 1.0 equiv.) in tetrahydrofuran (2.0 mL) at 0 °C was added hydrogen fluoride-

pyridine complex (70% HF, 0.06 mL, 2.31 mmol, 178 equiv.). The reaction mixture was allowed to warm to 25 °C and stirred for an additional 5 h. Then the reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate (10 mL), and the two phases were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The crude material was resuspended in dichloromethane (1.0 mL) and cooled to 0 °C. Trifluoroacetic acid (0.10 mL, 1.30 mmol, 100 equiv.) was added, the reaction mixture was stirred for 3 h, and then allowed to warm to 25 °C. The solvent was removed *in vacuo*, and the resulting residue was redissolved in ethyl acetate (15 mL). A saturated aqueous solution of sodium bicarbonate (5 mL) was added with stirring. After 10 min, the two phases were separated, and the organic layer was dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 40% methanol in acetone) to afford pure epothilone **1.150** (5.5 mg, 0.010 mmol, 71%) as a colorless oil. **1.150**: R_f = 0.39 (silica gel, 40% methanol in acetone); $[\alpha]_D^{25}$ = –27.2 (c = 0.50, 10:1 CH_2Cl_2/MeOH); FT-IR (neat) ν_{max} 3360, 2925, 2855, 1727, 1686, 1559, 1505, 1464, 1425, 1382, 1336, 1265, 1147, 1053, 1008, 980, 937, 883, 826, 733, 701, 669 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.05 (s, 1 H), 6.56 (s, 1 H), 5.43 (dd, *J* = 4.8, 4.8 Hz, 1 H), 4.09 (dd, *J* = 10.2, 2.4 Hz, 1 H), 3.73 (t, *J* = 4.8 Hz, 1 H), 3.68–3.60 (m, 2 H), 3.28 (dq, *J* = 6.6, 6.6 Hz, 1 H), 3.09 (s, 4 H), 2.61 (t, *J* = 5.4 Hz, 2 H), 2.50 (dd, *J* = 13.8, 10.2 Hz, 1 H), 2.38 (dd, *J* = 13.8, 2.4 Hz, 1 H), 2.10 (s, 3 H), 1.96–1.86 (m, 2 H), 1.70–1.65 (m, 1 H), 1.54–1.24 (m, 9 H), 1.35 (s, 3 H), 1.26 (s, 2 H), 1.15 (s, 3 H), 1.12 (d, *J* = 6.6 Hz, 3 H), 1.03 (s, 3 H), 0.96 (d, *J* = 6.6 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 220.7, 171.3, 168.4, 152.7, 137.5, 119.3, 116.5, 78.0, 75.4, 74.4, 62.4,

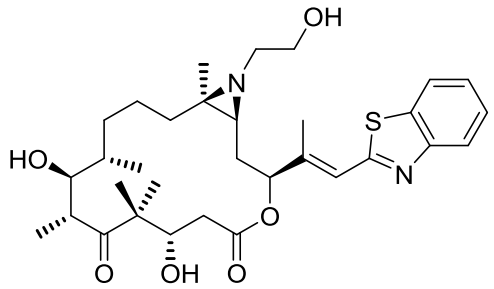
55.3, 53.0, 48.3, 44.3, 43.5, 42.0, 39.6, 37.5, 35.5, 35.1, 32.1, 29.8, 21.7, 20.7, 20.3, 17.5, 16.4, 15.9, 14.1 ppm; HRMS (ESI) calcd for $C_{30}H_{49}N_3O_6SNa$ $[M+Na]^+$ 602.3234, found 602.3217.



1.151a

Protected epothilone 1.151a: To a stirred solution of phosphonate **1.161** (150 mg, 0.533 mmol, 13 equiv.) in tetrahydrofuran (0.5 mL) at –78 °C was carefully added *n*-butyllithium (2.5 M hexanes, 0.17 mL, 0.425 mmol, 10 equiv.). After stirring for 20 min at the same temperature, a solution of tertiary aziridine **1.130** (28.7 mg, 0.041 mmol, 1.0 equiv.) in tetrahydrofuran (0.5 mL) was added. The reaction mixture was allowed to slowly warm to 10 °C, stirred for an additional 1 h, and then quenched with a saturated aqueous solution of ammonium chloride (10 mL). The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 5 → 30% ethyl acetate in hexanes) to afford pure protected epothilone **1.151a** (22 mg, 0.027 mmol, 65%) as a colorless oil. **1.151a**: R_f = 0.30 (silica gel, 15% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –4.8 (c = 1.00, CH_2Cl_2); FT-IR (neat) ν_{max} 2952, 2876, 1745, 1696, 1643, 1460, 1434, 1414, 1381, 1306, 1283, 1248, 1198, 1157, 1107, 1008, 985, 835 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2) δ = 7.99 (dd, *J* = 8.4, 1.2 Hz, 1

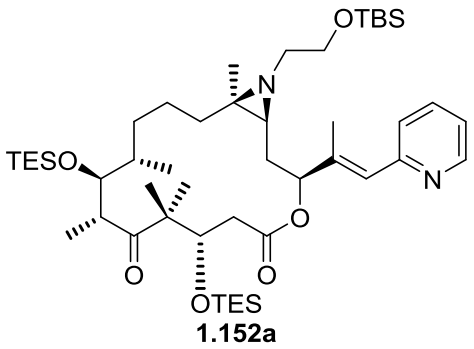
H), 7.91 (dd, *J* = 8.4, 1.2 Hz, 1 H), 7.48 (ddd, *J* = 7.8, 6.6, 1.2 Hz, 1 H), 7.38 (ddd, *J* = 7.8, 6.6, 1.2 Hz, 1 H), 6.80 (s, 1 H), 5.22 (dd, *J* = 7.8, 3.6 Hz, 1 H), 4.15 (dd, *J* = 7.8, 3.6 Hz, 1 H), 3.88 (d, *J* = 8.4 Hz, 1 H), 3.71–3.65 (m, 2 H), 3.05 (dq, *J* = 8.4, 6.6 Hz, 1 H), 2.72–2.62 (m, 3 H), 2.39 (ddd, *J* = 13.2, 6.6, 6.6 Hz, 1 H), 2.29 (s, 3 H), 2.16 (ddd, *J* = 15.0, 3.0, 3.0 Hz, 1 H), 1.78 (ddd, *J* = 15.0, 9.0, 9.0 Hz, 1 H), 1.66–1.58 (m, 4 H), 1.48–1.43 (m, 2 H), 1.31 (dd, *J* = 10.2, 3.0 Hz, 1 H), 1.28–1.24 (m, 1 H), 1.19 (s, 3 H), 1.16 (s, 3 H), 1.12 (s, 3 H), 1.09 (d, *J* = 7.2 Hz, 3 H), 0.99 (t, *J* = 8.4 Hz, 9 H), 0.98 (d, *J* = 6.6 Hz, 3 H), 0.94 (t, *J* = 7.8 Hz, 9 H), 0.86 (s, 9 H), 0.69–0.62 (m, 12 H), 0.03 (s, 3 H), 0.02 (s, 3 H) ppm; ^{13}C NMR (150 MHz, CD_2Cl_2) δ = 215.8, 171.2, 164.7, 153.9, 146.9, 135.4, 126.5, 125.3, 123.3, 121.7, 120.5, 80.1, 79.0, 75.8, 64.1, 54.8, 49.9, 48.2, 43.7, 40.6, 37.1, 36.1, 34.9, 32.2, 26.1, 25.3, 24.1, 22.6, 20.0, 18.6, 17.7, 15.52, 15.50, 7.3, 7.1, 5.8, 5.6, -5.23, -5.25 ppm; HRMS (ESI) calcd for $C_{50}H_{89}N_2O_6Si_3S$ $[M+H]^+$ 929.5744, found 929.5768.



1.151

Epothilone 1.151: To a stirred solution of protected epothilone **1.151a** (22.0 mg, 0.024 mmol, 1.0 equiv.) in tetrahydrofuran (2.0 mL) at 0 °C was added hydrogen fluoride-pyridine complex (70% HF, 0.10 mL, 3.85 mmol, 150 equiv.). The reaction mixture was allowed to warm to 25 °C and stirred for an additional 9 h. Then the reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate (10 mL), and the two phases were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL),

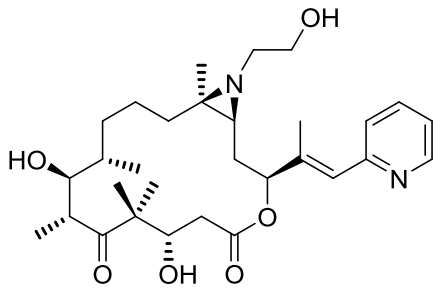
and the combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 5 → 20% methanol in ethyl acetate) to afford pure epothilone **1.151** (11.3 mg, 0.019 mmol, 81%) as a colorless oil. **1.151**: R_f = 0.39 (silica gel, 20% methanol in ethyl acetate); $[\alpha]_D^{25}$ = –15.7 (c = 1.13, CH_2Cl_2); FT-IR (neat) ν_{max} 3366, 2927, 2855, 1735, 1688, 1647, 1467, 1434, 1380, 1261, 1148, 1052, 1010, 980, 937, 876, 761, 730, 709 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2) δ = 7.99 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.91 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.49 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1 H), 7.39 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1 H), 6.88 (s, 1 H), 5.56 (dd, *J* = 3.6, 3.6 Hz, 1 H), 4.05 (dd, *J* = 10.2, 2.4 Hz, 1 H), 3.75 (dd, *J* = 6.0, 3.6 Hz, 1 H), 3.71–3.61 (m, 2 H), 3.31 (dq, *J* = 7.2, 7.2 Hz, 1 H), 2.70 (ddd, *J* = 13.2, 7.2, 4.2 Hz, 1 H), 2.58–2.53 (m, 2 H), 2.45 (dd, *J* = 13.8, 1.8 Hz, 1 H), 2.32 (s, 3 H), 2.06 (ddd, *J* = 15.0, 6.0, 6.0 Hz, 1 H), 1.86 (ddd, *J* = 15.6, 7.8, 3.6 Hz, 1 H), 1.70–1.64 (m, 1 H), 1.60–1.48 (m, 2 H), 1.47–1.38 (m, 2 H), 1.37 (s, 3 H), 1.38–1.28 (m, 2 H), 1.27–1.25 (m, 1 H), 1.15 (s, 3 H), 1.13 (d, *J* = 7.2 Hz, 3 H), 1.04 (s, 3 H), 0.97 (d, *J* = 7.2 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, CD_2Cl_2) δ = 220.5, 171.4, 164.8, 153.8, 144.8, 153.3, 126.6, 125.4, 123.2, 121.8, 119.2, 77.1, 76.4, 75.4, 62.5, 55.5, 52.6, 47.7, 45.2, 43.2, 39.4, 35.3, 34.3, 31.5, 30.1, 29.1, 21.8, 19.5, 17.7, 16.9, 16.5, 14.8 ppm; HRMS (ESI) calcd for $C_{32}H_{47}N_2O_6S$ $[M+H]^+$ 587.3149, found 587.3153.



1.152a

Protected epothilone 1.152a: To a stirred solution of phosphonate **1.162** (317 mg, 1.38 mmol, 28 equiv.) in tetrahydrofuran (1 mL) at –78 °C was carefully added *n*-butyllithium (2.5 M hexanes, 0.44 mL, 1.11 mmol, 22 equiv.). After stirring for 30 min at the same temperature, a solution of tertiary aziridine **1.130** (40.0 mg, 0.050 mmol, 1.0 equiv.) in tetrahydrofuran (0.5 mL) was added. The reaction mixture was allowed to slowly warm to 25 °C, stirred for an additional 1.5 h, and then quenched with a saturated aqueous solution of ammonium chloride (10 mL). The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 10 → 40% ethyl acetate in hexanes) to afford pure protected epothilone **1.152a** (41 mg, 0.047 mmol, 94%) as a colorless oil. **1.152a**: R_f = 0.23 (silica gel, 30% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –4.5 (c = 1.0, CH_2Cl_2); FT-IR (neat) ν_{max} 2953, 2935, 2877, 1743, 1696, 1655, 1586, 1561, 1464, 1430, 1381, 1304, 1250, 1198, 1158, 1108, 1069, 1018, 1007, 985, 835, 777, 739, 676 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ = 8.51 (d, *J* = 5.0 Hz, 1 H), 7.02 (ddd, *J* = 7.2, 7.2, 1.8 Hz, 1 H), 6.89 (d, *J* = 7.8 Hz, 1 H), 6.75 (s, 1 H), 6.53 (dd, *J* = 7.2, 5.4 Hz, 1 H), 5.48 (dd, *J* = 8.4, 3.0 Hz, 1 H), 4.22 (dd, *J* = 9.0, 3.0 Hz, 1 H), 4.18 (d, *J* = 9.0 Hz, 1 H), 3.86–3.78 (m, 2 H), 3.04 (dq, *J* = 9.0,

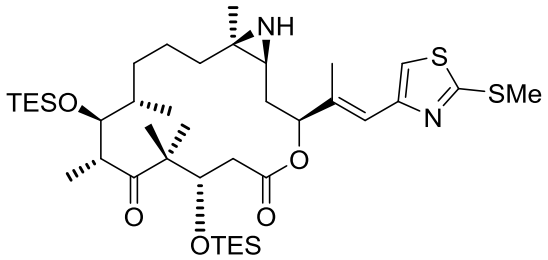
6.6 Hz, 1 H), 2.77–2.71 (m, 2 H), 2.59 (dd, *J* = 16.2, 3.0 Hz, 1 H), 2.48–2.43 (m, 1 H), 2.45 (s, 3 H), 2.31 (ddd, *J* = 15.0, 3.0, 3.0 Hz, 1 H), 2.07 (ddd, *J* = 15.0, 9.0, 9.0 Hz, 1 H), 1.90–1.81 (m, 2 H), 1.76–1.71 (m, 1 H), 1.66–1.59 (m, 1 H), 1.52–1.48 (m, 2 H), 1.29 (dd, *J* = 9.6, 3.6 Hz, 1 H), 1.25–1.21 (m, 1 H), 1.20 (d, *J* = 7.2 Hz, 3 H), 1.18 (s, 3 H), 1.16 (s, 3 H), 1.13 (d, *J* = 6.6 Hz, 3 H), 1.09 (t, *J* = 7.8 Hz, 9 H), 1.06 (t, *J* = 7.8 Hz, 9 H), 0.99 (s, 9 H), 0.84 (s, 3 H), 0.83–0.78 (m, 6 H), 0.73–0.69 (m, 6 H), 0.09 (s, 3 H), 0.08 (s, 3 H) ppm; ^{13}C NMR (151 MHz, C_6D_6) δ = 214.5, 170.7, 157.0, 149.4, 142.5, 135.6, 126.6, 124.7, 121.0, 80.2, 79.8, 75.9, 64.3, 54.9, 53.4, 50.3, 48.1, 43.3, 40.2, 37.4, 36.4, 35.4, 32.3, 26.2 (3C), 25.4, 23.6, 23.2, 20.2, 18.5, 17.6, 15.6, 14.7, 7.43, 7.37, 6.0, 5.8, -5.1 ppm; HRMS (ESI) calcd for $C_{48}H_{89}N_2O_6Si_3$ $[M+H]^+$ 873.6023, found 873.6044.



1.152

Epothilone 1.152: To a stirred solution of protected epothilone **1.152a** (39.0 mg, 0.045 mmol, 1.0 equiv.) in tetrahydrofuran (2.0 mL) at 0 °C was added hydrogen fluoride-pyridine complex (70% HF, 0.20 mL, 7.70 mmol, 170 equiv.). The reaction mixture was allowed to warm to 25 °C and stirred for an additional 5 h. Then the reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate (10 mL), and the two phases were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography

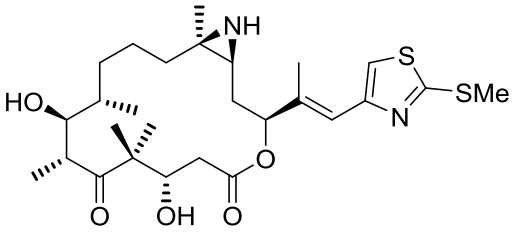
(silica gel, 5 → 40% methanol in ethyl acetate) to afford pure epothilone **1.152** (22 mg, 0.042 mmol, 93%) as a colorless oil. **1.152**: R_f = 0.40 (silica gel, 30% methanol in ethyl acetate); $[\alpha]_D^{25}$ = –34.4 (c = 1.0, CH_2Cl_2); FT-IR (neat) ν_{max} 3340, 2959, 2927, 2875, 1731, 1686, 1589, 1562, 1469, 1434, 1383, 1334, 1261, 1150, 1049, 1010, 982, 885, 800, 771, 745, 704 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2) δ = 8.54 (d, *J* = 4.8 Hz, 1 H), 7.70 (ddd, *J* = 7.8, 7.8, 1.8 Hz, 1 H), 7.28 (d, *J* = 7.8 Hz, 1 H), 7.15 (ddd, *J* = 7.8, 4.8, 1.2 Hz, 1 H), 6.60 (s, 1 H), 5.40 (dd, *J* =7.2, 3.0 Hz, 1 H), 4.22 (dd, *J* = 11.2, 2.4 Hz, 1 H), 3.65 (t, *J* = 4.8 Hz, 1 H), 3.62–3.55 (m, 2 H), 3.21 (qd, *J* = 6.6, 5.2 Hz, 1 H), 2.70–2.66 (m, 1 H), 2.62–2.59 (m, 1 H), 2.48 (dd, *J* = 13.2, 10.2 Hz, 1 H), 2.34 (dd, *J* = 13.8, 2.4 Hz, 1 H), 2.08 (s, 3 H), 2.01–1.96 (m, 1 H), 1.95–1.90 (m, 1 H), 1.73–1.67 (m, 1 H), 1.54–1.43 (m, 4 H), 1.41–1.34 (m, 3 H), 1.37 (s, 3 H), 1.17 (s, 3 H), 1.11 (d, *J* = 6.6 Hz, 3 H), 1.03 (s, 3 H), 0.95 (d, *J* = 7.2 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, CD_2Cl_2) δ = 220.8, 171.3, 156.2, 149.4, 141.4, 136.8, 125.0, 124.4, 121.8, 77.7, 74.8, 73.6, 62.2, 60.6, 55.0, 48.9, 44.2, 43.7, 39.8, 35.6, 35.2, 32.2, 30.1, 21.4, 20.8, 19.6, 17.3, 16.5, 15.8, 13.6 ppm; HRMS (ESI) calcd for $C_{30}H_{46}N_2O_6Na$ $[M+Na]^+$ 553.3248, found 553.3255.



1.166

Protected epothilone 1.166: To a stirred solution of phosphonate **1.131** (190 mg, 0.675 mmol, 9.6 equiv.) in tetrahydrofuran (1.0 mL) at –78 °C was carefully added *n*-butyllithium (2.5 M hexanes, 0.22 mL, 0.550 mmol, 7.7 equiv.). After stirring for 30 min at the same

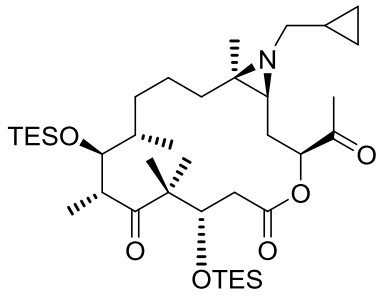
temperature, a solution of aziridine methyl ketone **1.127** (45 mg, 0.070 mmol, 1.0 equiv.) in tetrahydrofuran (0.5 mL) was added. The reaction mixture was allowed to slowly warm to 25 °C, stirred for an additional 1 h, and then quenched with a saturated aqueous solution of ammonium chloride (10 mL). The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 30 → 100% ethyl acetate in hexanes) to afford pure protected epothilone **1.166** (32 mg, 0.042 mmol, 59%) as a colorless oil. **1.166**: R_f = 0.34 (silica gel, 70% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –13.3 (c = 0.36, CH_2Cl_2); FT-IR (neat) ν_{max} 2953, 2928, 2876, 1742, 1696, 1459, 1416, 1345, 1304, 1240, 1197, 1157, 1068, 1035, 1019, 985, 915, 862, 838, 783, 737, 676 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ = 6.63 (s, 1 H), 6.43 (s, 1 H), 5.39 (dd, *J* = 8.4, 3.0 Hz, 1 H), 4.26 (dd, *J* = 9.0, 3.6 Hz, 1 H), 4.15 (d, *J* = 8.4 Hz, 1 H), 3.06 (dq, *J* = 8.4, 7.2 Hz, 1 H), 2.72 (dd, *J* = 16.2, 8.4 Hz, 1 H), 2.60 (dd, *J* = 16.2, 3.6 Hz, 1 H), 2.22 (s, 3 H), 2.20 (s, 3 H), 2.11–2.06 (m, 1 H), 1.89–1.84 (m, 2 H), 1.79–1.70 (m, 2 H), 1.61–1.55 (m, 2 H), 1.49–1.36 (m, 2 H), 1.24–1.18 (m, 1 H), 1.18 (d, *J* = 7.2 Hz, 3 H), 1.17 (s, 3 H), 1.13 (d, *J* = 7.2 Hz, 3 H), 1.08 (t, *J* = 7.8 Hz, 9 H), 1.07 (t, *J* = 7.8 Hz, 9 H), 1.05 (s, 3 H), 0.85 (s, 3 H), 0.81–0.77 (m, 6 H), 0.75–0.71 (m, 6 H) ppm; ^{13}C NMR (151 MHz, C_6D_6) δ = 214.4, 170.7, 165.3, 153.6, 138.8, 120.1, 116.4, 80.2, 79.3, 75.9, 53.5, 47.9, 41.7, 40.0, 39.4, 37.2, 35.2, 34.0, 31.9, 25.8, 25.1, 23.3, 23.1, 20.0, 17.5, 15.9, 14.9, 7.4, 7.3, 6.0, 5.8 ppm; HRMS (ESI) calcd for $C_{39}H_{71}N_2O_5Si_2S_2$ $[M+H]^+$ 767.4337, found 767.4358.



1.153

Epothilone 1.153: To a stirred solution of protected epothilone **1.166** (13.0 mg, 0.017 mmol, 1.0 equiv.) in tetrahydrofuran (1.0 mL) at 0 °C was added hydrogen fluoride-pyridine complex (70% HF, 0.10 mL, 3.85 mmol, 220 equiv.). The reaction mixture was allowed to warm to 25 °C and stirred for 1 h. Then the reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate (10 mL), and the two phases were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 5 → 15% methanol in ethyl acetate) to afford pure epothilone **1.153** (8.5 mg, 0.016 mmol, 93%) as a colorless oil. **1.153**: R_f = 0.29 (silica gel, 15% methanol in ethyl acetate); $[\alpha]_D^{25}$ = –28.8 (c = 0.85, CH_2Cl_2); FT-IR (neat) ν_{max} 3292, 2956, 2930, 2875, 1730, 1687, 1456, 1422, 1384, 1334, 1293, 1263, 1174, 1145, 1037, 1009, 980, 881, 735, 668 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2) δ = 7.04 (s, 1 H), 6.54 (s, 1 H), 5.55 (dd, *J* = 4.2, 4.2 Hz, 1 H), 4.08 (ddd, *J* = 14.4, 3.6, 3.6 Hz, 1 H), 3.78 (dd, *J* = 6.6, 3.6 Hz, 1 H), 3.33 (dq, *J* = 6.6, 6.6 Hz, 1 H), 2.71 (s, 3 H), 2.54 (dd, *J* = 12.6, 10.8 Hz, 1 H), 2.43 (dd, *J* = 12.6, 4.2 Hz, 1 H), 2.14 (s, 3 H), 2.00 (s, 1 H), 1.96 (ddd, *J* = 15.0, 4.2, 4.2 Hz, 1 H), 1.85 (dd, *J* = 9.0, 4.8 Hz, 1 H), 1.78–1.71 (m, 2 H), 1.58–1.49 (m, 2 H), 1.45–1.34 (m, 3 H), 1.40 (s, 3 H), 1.24–1.20 (m, 1 H), 1.22 (s, 3 H), 1.10 (d, *J* = 7.2 Hz, 3 H), 1.01 (s, 3 H), 0.95 (d, *J* = 6.6 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, CD_2Cl_2) δ = 220.6, 171.2, 165.7, 153.5, 137.2, 118.3, 116.3,

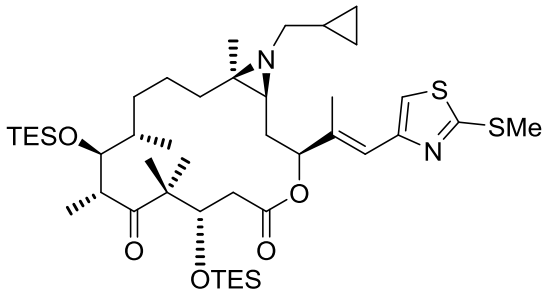
76.3, 76.2, 75.6, 60.6, 52.6, 44.9, 38.7, 38.4, 35.2, 31.1, 30.3, 28.8, 25.7, 22.6, 22.4, 18.9, 17.6, 16.9, 16.3, 14.9 ppm; HRMS (ESI) calcd for $C_{27}H_{42}N_2O_5S_2Na$ $[M+Na]^+$ 561.2427, found 561.2409.



1.169

Cyclopropylmethyl aziridine 1.169: To a stirred solution of aziridine methyl ketone **1.127** (40.0 mg, 0.063 mmol, 1.0 equiv.) in dimethylformamide (0.4 mL) at 25 °C was added bromomethylcyclopropane **1.168** (50.6 mg, 0.375 mmol, 6.0 equiv.), followed by potassium carbonate (43.0 mg, 0.312 mmol, 5.0 equiv.). The reaction mixture was heated to 75 °C and stirred for 16 h. Then the reaction mixture was allowed to cool to 25 °C and quenched with water (10 mL). The mixture was extracted with ethyl acetate (3 × 5 mL), and the combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 10 → 40% ethyl acetate in hexanes) to afford pure cyclopropylmethyl aziridine **1.169** (40.0 mg, 0.058 mmol, 92%) as a pale yellow oil. **1.169**: R_f = 0.23 (silica gel, 30% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –6.5 (c = 1.0, CH_2Cl_2); FT-IR (neat) ν_{max} 2952, 2918, 2877, 1747, 1732, 1696, 1460, 1414, 1381, 1308, 1284, 1239, 1197, 1158, 1109, 1070, 1042, 1010, 984, 941, 862, 835, 783, 725, 676 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ = 4.93 (dd, *J* = 9.0, 3.6 Hz, 1 H), 4.19 (d, *J* = 9.6 Hz, 1 H), 4.06 (dd, *J* = 7.8, 4.8 Hz, 1 H), 2.85 (dq, *J* = 9.6, 6.6 Hz, 1 H), 2.72–2.71 (m, 2 H), 2.60 (dd, *J* = 12.0, 5.4 Hz, 1 H), 2.11 (ddd,

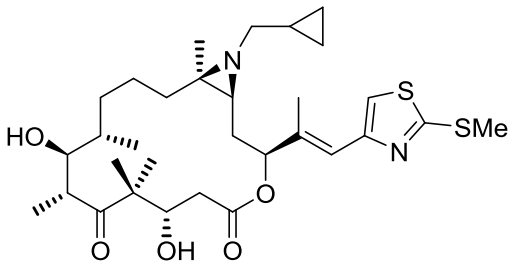
J = 15.6, 3.0, 3.0 Hz, 1 H), 1.98 (dd, *J* = 12.0, 7.2 Hz, 1 H), 1.85–1.76 (m, 2 H), 1.77 (s, 3 H), 1.73–1.56 (m, 3 H), 1.48–1.35 (m, 2 H), 1.26–1.22 (m, 1 H), 1.21 (d, *J* = 6.6 Hz, 3 H), 1.16 (s, 3 H), 1.10 (t, *J* = 7.8 Hz, 9 H), 1.08 (t, *J* = 7.8 Hz, 9 H), 1.04 (d, *J* = 6.6 Hz, 3 H), 1.03 (s, 3 H), 0.99–0.92 (m, 2 H), 0.86–0.77 (m, 6 H), 0.74–0.70 (m, 6 H), 0.68 (s, 3 H), 0.45–0.42 (m, 2 H), 0.22–0.16 (m, 2 H) ppm; ^{13}C NMR (151 MHz, C_6D_6) δ = 213.9, 202.5, 171.8, 80.8, 78.2, 76.7, 56.7, 53.1, 50.1, 48.3, 43.2, 39.4, 36.9, 36.0, 31.6, 25.3, 25.1, 24.9, 23.0, 20.1, 17.8, 15.3, 12.0, 7.5, 7.3, 6.0, 5.8, 3.6, 3.4 ppm; HRMS (ESI) calcd for $C_{38}H_{72}NO_6Si_2$ $[M+H]^+$ 694.4893, found 694.4895.



1.154a

Protected epothilone 1.154a: To a stirred solution of phosphonate **1.131** (150 mg, 0.533 mmol, 13 equiv.) in tetrahydrofuran (0.5 mL) at –78 °C was carefully added *n*-butyllithium (2.5 M hexanes, 0.17 mL, 0.425 mmol, 10 equiv.). After stirring for 20 min at the same temperature, a solution of cyclopropylmethyl aziridine **1.169** (28.7 mg, 0.041 mmol, 1.0 equiv.) in tetrahydrofuran (0.5 mL) was added. The reaction mixture was allowed to slowly warm to 10 °C, stirred for an additional 1 h, and quenched with a saturated aqueous solution of ammonium chloride (10 mL). The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 5 → 30% ethyl acetate in hexanes) to afford pure

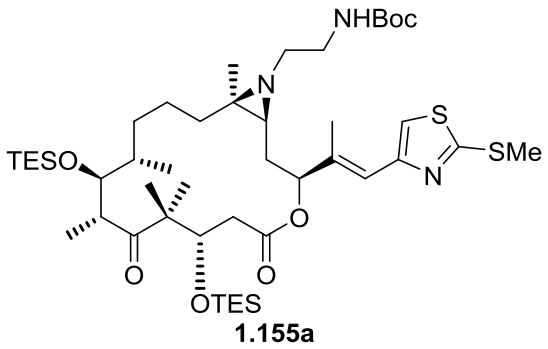
protected epothilone **1.154a** (22.1 mg, 0.027 mmol, 65%) as a colorless oil. **1.154a**: R_f = 0.22 (silica gel, 20% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = +4.2 (c = 1.0, CH_2Cl_2); FT-IR (neat) ν_{max} 2953, 2926, 2876, 1741, 1696, 1461, 1423, 1380, 1240, 1180, 1158, 1110, 1069, 1036, 1017, 985, 915, 863, 836, 782, 738, 674 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ = 6.66 (s, 1 H), 6.42 (s, 1 H), 5.47 (dd, *J* = 7.8, 3.6 Hz, 1 H), 4.28 (dd, *J* = 8.4, 3.6 Hz, 1 H), 4.16 (d, *J* = 9.0 Hz, 1 H), 3.03 (dq, *J* = 8.4, 6.6 Hz, 1 H), 2.71 (dd, *J* = 16.2, 8.4 Hz, 1 H), 2.62–2.58 (m, 2 H), 2.31–2.27 (m, 1 H), 2.30 (s, 3 H), 2.20 (s, 3 H), 2.10 (ddd, *J* = 15.0, 9.0, 9.0 Hz, 1 H), 1.99 (dd, *J* = 12.0, 7.2 Hz, 1 H), 1.90–1.82 (m, 2 H), 1.74–1.68 (m, 1 H), 1.66–1.59 (m, 1 H), 1.54–1.47 (m, 2 H), 1.24–1.18 (m, 1 H), 1.19 (d, *J* = 6.6 Hz, 3 H), 1.18 (s, 3 H), 1.16–1.13 (m, 1 H), 1.14 (d, *J* = 6.6 Hz, 3 H), 1.10 (s, 3 H), 1.08 (t, *J* = 7.8 Hz, 9 H), 1.06 (t, *J* = 7.8 Hz, 9 H), 1.00–0.96 (m, 1 H), 0.90 (s, 3 H), 0.83–0.76 (m, 6 H), 0.73–0.69 (m, 6 H), 0.45–0.38 (m, 2 H), 0.23–0.15 (m, 2 H) ppm; ^{13}C NMR (151 MHz, C_6D_6) δ = 214.6, 170.7, 165.2, 153.7, 138.8, 120.6, 116.5, 79.7, 75.7, 56.9, 53.5, 49.5, 47.9, 43.5, 40.4, 37.5, 36.6, 35.2, 32.4, 30.2, 25.5, 23.6, 22.7, 20.1, 17.6, 15.9, 15.4, 14.6, 12.0, 7.43, 7.36, 5.9, 5.8, 3.6, 3.4 ppm; HRMS (ESI) calcd for $C_{43}H_{77}N_2O_5Si_2S_2$ $[M+H]^+$ 821.4807, found 821.4789.



1.154

Epothilone 1.154: To a stirred solution of protected epothilone **1.154a** (18.0 mg, 0.022 mmol, 1.0 equiv.) in tetrahydrofuran (2.0 mL) at 0 °C was added hydrogen fluoride-

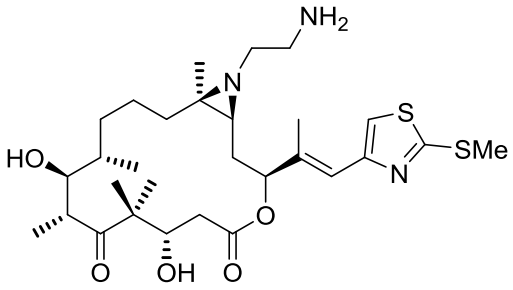
pyridine complex (70% HF, 0.20 mL, 3.85 mmol, 175 equiv.). The reaction mixture was allowed to warm to 25 °C, stirred for 3.5 h, and then quenched with a saturated aqueous solution of sodium bicarbonate (10 mL). The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 1 → 5% methanol in ethyl acetate) to afford pure epothilone **1.154** (12.0 mg, 0.020 mmol, 92%) as a colorless oil. **1.154**: R_f = 0.39 (silica gel, 5% methanol in ethyl acetate); $[\alpha]_D^{25}$ = –31.2 (c = 1.0, CH_2Cl_2); FT-IR (neat) ν_{max} 3375, 2957, 2924, 2853, 1729, 1687, 1555, 1464, 1424, 1378, 1251, 1148, 1036, 1009, 981, 939, 882, 832, 734 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2) δ = 7.01 (s, 1 H), 6.48 (s, 1 H), 5.44 (dd, *J* = 4.8, 4.8 Hz, 1 H), 4.09 (dd, *J* = 10.2, 3.0 Hz, 1 H), 3.73 (dd, *J* = 4.8, 4.8 Hz, 1 H), 3.32 (dq, *J* = 6.6, 6.6 Hz, 1 H), 2.70 (s, 3 H), 2.48 (dd, *J* = 13.8, 4.2 Hz, 1 H), 2.41–2.37 (m, 1 H), 2.40 (dd, *J* = 13.8, 3.0 Hz, 1 H), 2.30–2.26 (m, 1 H), 2.12 (s, 3 H), 1.92–1.90 (m, 2 H), 1.76–1.66 (m, 2 H), 1.56–1.38 (m, 4 H), 1.37 (s, 3 H), 1.33–1.27 (m, 2 H), 1.24–1.22 (m, 1 H), 1.13 (s, 3 H), 1.11 (d, *J* = 7.2 Hz, 3 H), 1.04 (s, 3 H), 0.96 (d, *J* = 7.2 Hz, 3 H) 0.53–0.45 (m, 2 H), 0.20–0.16 (m, 1 H), 0.11–0.08 (m, 1 H) ppm; ^{13}C NMR (151 MHz, CD_2Cl_2) δ = 220.8, 171.6, 165.8, 153.3, 137.9, 118.9, 116.3, 78.1, 75.5, 57.9, 52.9, 48.2, 44.5, 43.2, 39.6, 35.5, 35.2, 32.0, 30.3, 23.0, 22.0, 21.3, 20.4, 17.7, 16.9, 16.3, 15.7, 14.1, 11.5, 4.2, 4.0 ppm; HRMS (ESI) calcd for $C_{31}H_{49}N_2O_5S_2$ $[M+H]^+$ 593.3077, found 593.3063.



1.155a

Protected epothilone 1.155a: To a stirred solution of protected epothilone **1.166** (20.0 mg, 0.026 mmol, 1.0 equiv.) in dimethylformamide (0.3 mL) at 25 °C was added *tert*-butyl *N*-(2-bromoethyl) carbamate **1.167** (35.0 mg, 0.157 mmol, 6.0 equiv.), followed by potassium carbonate (18.0 mg, 0.130 mmol, 5.0 equiv.). The reaction mixture was heated to 75 °C and stirred for 12 h. The reaction mixture was then allowed to cool to 25 °C, quenched with water (5 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 10 → 40% methanol in ethyl acetate) to afford pure protected epothilone **1.155a** (7.5 mg, 0.008 mmol, 32%) as a colorless oil, along with recovered **1.166** (7.0 mg, 0.009 mmol, 35%). **1.155a**: R_f = 0.34 (silica gel, 40% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –5.1 (c = 0.75, CH_2Cl_2); FT-IR (neat) ν_{max} 3373, 2955, 2934, 2876, 1741, 1697, 1500, 1458, 1424, 1383, 1365, 1248, 1159, 1111, 1069, 1036, 1019, 985, 863, 837, 782, 739, 677 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ = 6.64 (s, 1 H), 6.47 (s, 1 H), 5.37 (dd, *J* = 8.4, 3.6 Hz, 1 H), 5.02 (br s, 1 H), 4.24 (dd, *J* = 9.0, 3.6 Hz, 1 H), 4.15 (d, *J* = 9.0 Hz, 1 H), 3.31 (dddd, *J* = 12.6, 6.6, 6.6, 6.6 Hz, 1 H), 3.21 (dddd, *J* = 12.6, 6.0, 6.0, 6.0, Hz, 1 H), 3.00 (ddd, *J* = 14.4, 6.6, 6.6 Hz, 1 H), 2.68 (dd, *J* = 16.2, 8.4 Hz, 1 H), 2.57 (dd, *J* = 16.2, 3.6 Hz, 1 H), 2.44–2.40 (m, 1 H), 2.27 (s, 3 H), 2.21

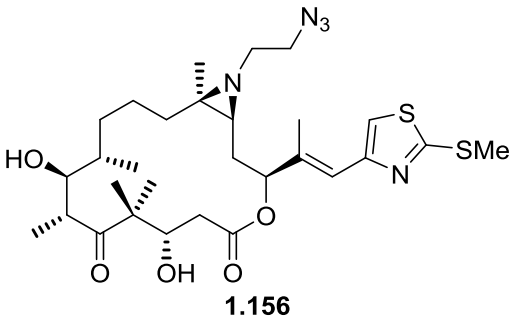
(s, 3 H). 2.11–2.07 (m, 2 H), 1.97–1.92 (m, 1 H), 1.87–1.83 (m, 1 H), 1.70–1.63 (m, 2 H), 1.57–1.51 (m, 1 H), 1.47 (s, 9 H), 1.44–1.38 (m, 1 H), 1.36–1.29 (m, 1 H), 1.18 (d, *J* = 6.6 Hz, 3 H), 1.17 (s, 3 H), 1.17–1.15 (m, 1 H), 1.12 (d, *J* = 6.6 Hz, 3 H), 1.073 (t, *J* = 8.4 Hz, 9 H), 1.070 (t, *J* = 8.4 Hz, 9 H), 1.03–1.00 (m, 1 H), 0.97 (s, 3 H), 0.87 (s, 3 H), 6.54 (m, 6 H), 0.74–0.70 (m, 6 H) ppm; ^{13}C NMR (151 MHz, C_6D_6) δ = 214.5, 170.6, 165.4, 155.9, 153.6, 138.7, 120.7, 116.6, 80.1, 79.4, 78.5, 75.8, 53.4, 51.7, 49.6, 48.0, 44.0, 41.5, 40.3, 37.3, 36.1, 34.9, 32.3, 28.5, 25.4, 23.6, 22.9, 20.2, 17.6, 15.9, 15.4, 14.7, 7.4, 7.3, 6.0, 5.8 ppm; HRMS (ESI) calcd for $C_{46}H_{84}N_3O_7S_2Si_2$ $[M+H]^+$ 910.5284, found 910.5293.



1.155

Epothilone 1.155: To a stirred solution of protected epothilone **1.155a** (6.0 mg, 0.007 mmol, 1.0 equiv.) in tetrahydrofuran (1.0 mL) at 0 °C was added hydrogen fluoride-pyridine complex (70% HF, 0.10 mL, 3.85 mmol, 500 equiv.). After 2 h, the reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate (5 mL) and allowed to warm to 25 °C. The two phases were separated, the aqueous layer was extracted with ethyl acetate (3 × 5 mL), and the combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The crude material was resuspended in dichloromethane (1.0 mL) and cooled to 0 °C. Trifluoroacetic acid (0.05 mL, 0.65 mmol, 90 equiv.) was added, the reaction mixture was stirred for 1 h, and then allowed to warm to 25 °C. The solvent was removed *in vacuo*, and the resulting residue was redissolved in

ethyl acetate (15 mL). A saturated aqueous solution of sodium bicarbonate (5 mL) was added with stirring. After 10 min, the two phases were separated, and the organic layer was dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 10 → 30% methanol in acetone) to afford pure epothilone **1.155** (2.5 mg, 0.004 mmol, 65%) as a colorless oil. **1.155**: R_f = 0.30 (silica gel, 30% methanol in acetone); $[\alpha]_D^{25}$ = –10.8 (c = 0.25, CH_2Cl_2); FT-IR (neat) ν_{max} 3366, 2929, 1729, 1686, 1565, 1421, 1370, 1338, 1252, 1149, 1037, 1008, 981, 881, 715 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2) δ = 7.02 (s, 1 H), 6.49 (s, 1 H), 5.41 (dd, *J* = 5.4, 5.4 Hz, 1 H), 4.09 (dd, *J* = 9.6, 3.0 Hz, 1 H), 3.74 (dd, *J* = 4.8, 4.8 Hz, 1 H), 3.41 (s, 1 H), 3.27 (ddd, *J* = 12.0, 6.6, 6.6 Hz, 1 H), 2.84–2.75 (m, 2 H), 2.70 (s, 3 H), 2.54–2.38 (m, 5 H), 2.11 (s, 3 H), 1.95–1.93 (m, 1 H), 1.90–1.85 (m, 2 H), 1.83–1.82 (m, 1 H), 1.71–1.65 (m, 1 H), 1.60–1.36 (m, 4 H), 1.35 (s, 3 H), 1.30–1.22 (m, 2 H), 1.28 (s, 3 H), 1.11 (d, *J* = 6.6 Hz, 3 H), 1.05 (s, 3 H), 0.96 (d, *J* = 6.6 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, CD_2Cl_2) δ = 206.7, 171.4, 165.9, 153.3, 138.0, 119.0, 116.4, 78.6, 75.4, 74.6, 70.4, 53.0, 50.8, 48.4, 44.3, 43.1, 39.6, 35.6, 32.3, 30.2, 28.2, 21.9, 20.9, 20.6, 17.6, 16.9, 16.1, 15.6, 14.0 ppm; HRMS (ESI) calcd for $C_{29}H_{48}N_3O_5S_2$ $[M+H]^+$ 604.2849, found 604.2854.

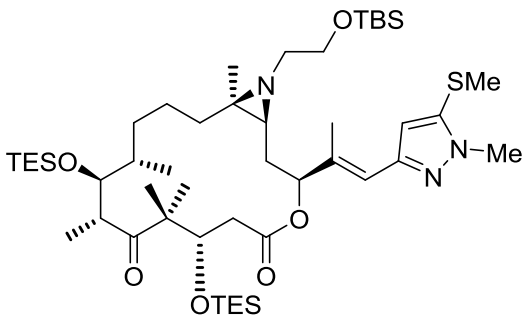


1.156

Epothilone 1.156: To a stirred solution of epothilone **1.134** (12.8 mg, 0.022 mmol, 1.0 equiv.) in dichloromethane (1 mL) at 0 °C was added *p*-toluenesulfonic anhydride (35.8

mg, 0.11 mmol, 5.0 equiv.), followed by triethylamine (12.3 µL, 0.088 mmol, 4.0 equiv.) and 4-(dimethylamino)pyridine (2 mg, 0.016 mmol, 0.7 equiv.). After 30 min the reaction mixture was allowed to warm to 25 °C, and stirred for an additional 15 min. The reaction mixture was quenched with methanol (0.5 mL) and water (10 mL). The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was filtered through silica gel, and washed with ethyl acetate. The filtrate was concentrated *in vacuo*. The crude tosylate was resuspended in dimethylformamide (0.5 mL) at 25 °C, sodium azide (5.7 mg, 0.088 mmol, 4.0 equiv.) was added, and the reaction mixture was stirred for 17 h. Then the reaction mixture was quenched with water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 50 → 90% methanol in ethyl acetate) to afford pure epothilone **1.156** (5.3 mg, 0.009 mmol, 40%) as an amorphous solid. **1.156**: R_f = 0.35 (silica gel, ethyl acetate); $[\alpha]_D^{25}$ = –34.2 (c = 0.55, CH_2Cl_2); FT-IR (neat) ν_{max} 3432, 2929, 2101, 1731, 1687, 1554, 1423, 1384, 1263, 1148, 1036, 1009, 979, 881, 735 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2) δ = 7.03 (s, 1 H), 6.48 (s, 1 H), 5.38 (dd, *J* = 7.8, 3.6 Hz, 1 H), 4.12–4.09 (m, 1 H), 3.95 (br s, 1 H), 3.74 (ddd, *J* = 4.8, 4.8, 4.8 Hz, 1 H), 3.44–3.37 (m, 2 H), 3.26 (qd, *J* = 6.6, 4.8 Hz, 1 H), 2.70 (s, 3 H), 2.67 (ddd, *J* = 12.6, 6.0, 6.0 Hz, 1 H), 2.59 (ddd, *J* = 12.6, 6.6, 6.6 Hz, 1 H), 2.49–2.45 (m, 2 H), 2.39 (dd, *J* = 15.0, 3.0 Hz, 1 H), 2.13 (s, 3 H), 2.01 (ddd, *J* = 15.0, 4.2, 4.2 Hz, 1 H), 1.82 (ddd, *J* = 16.2, 7.8, 7.8 Hz, 1 H), 1.71–1.65 (m, 1 H), 1.51–1.41 (m, 4 H), 1.35 (s, 3 H), 1.30–1.28 (m, 1 H), 1.26–1.22 (m, 1 H), 1.16 (s, 3 H), 1.12 (d, *J* = 7.2 Hz, 3 H), 1.05 (s, 3 H), 0.97 (d, *J* = 6.6 Hz, 3 H) ppm; ^{13}C

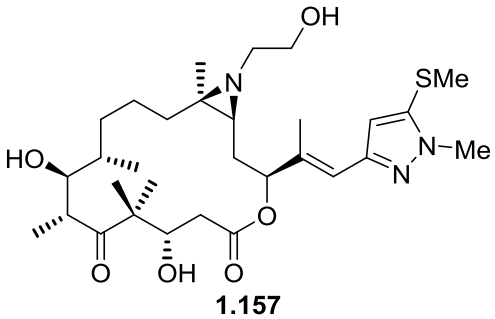
NMR (151 MHz, CD_2Cl_2) δ = 220.7, 171.2, 166.0, 153.1, 138.3, 119.3, 116.5, 78.8, 74.5, 74.2, 53.1, 52.3, 51.9, 49.0, 43.9, 43.8, 39.7, 35.9, 35.8, 32.7, 30.7, 22.0, 21.3, 20.3, 17.5, 16.9, 16.1, 15.4, 13.6 ppm; HRMS (ESI) calcd for $C_{29}H_{46}N_5O_5S_2$ $[M+H]^+$ 608.2935, found 608.2933.



1.157a

Protected epothilone 1.157a: To a stirred solution of phosphonate **1.164** (350 mg, 0.906 mmol, 16 equiv.) in tetrahydrofuran (1.0 mL) at –78 °C was carefully added *n*-butyllithium (2.5 M hexanes, 0.29 mL, 0.725 mmol, 13 equiv.). After stirring for 45 min at the same temperature, a solution of methyl ketone **1.130** (45.0 mg, 0.056 mmol, 1.0 equiv.) in tetrahydrofuran (0.6 mL) was added. The reaction mixture was allowed to slowly warm to 25 °C, stirred for an additional 2 h, and quenched with a saturated aqueous solution of ammonium chloride (10 mL). The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 10 → 60% ethyl acetate in hexanes) to afford protected epothilone **1.157a** (36.5 mg, 0.040 mmol, 70%, *E*:*Z* = 1:1) as a colorless oil. **1.157a**: R_f = 0.32 (silica gel, 30% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –5.3 (c = 1.0, CH_2Cl_2); FT-IR (neat) ν_{max} 2952, 2929, 2876, 2857, 1740, 1696, 1461, 1415, 1380, 1280, 1251,

1200, 1181, 1158, 1102, 1040, 1018, 1006, 984, 940, 916, 834, 812, 778, 733, 677 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ = 6.80 (s, 1 H), 6.78 (d, *J* = 5.4 Hz, 1 H), 6.37 (s, 1 H), 6.30 (s, 1 H), 6.28 (s, 1 H), 5.49 (dd, *J* = 8.4, 2.4 Hz, 1 H), 4.24 (ddd, *J* = 16.8, 8.4, 1.8 Hz, 2 H), 4.18 (dd, *J* = 8.4, 3.0 Hz, 2 H), 3.90–3.78 (m, 4 H), 3.46 (s, 3 H), 3.42 (s, 3 H), 3.10–3.02 (m, 2 H), 2.85–2.81 (m, 1 H), 2.76–2.68 (m, 3 H), 2.62–2.55 (m, 3 H), 2.47–2.43 (m, 2 H), 3.29 (ddd, *J* = 15.0, 4.2, 4.2 Hz, 1 H), 2.26 (s, 3 H), 2.20–2.15 (m, 1 H), 2.10–2.03 (m, 1 H), 1.90–1.85 (m, 4 H), 1.89 (s, 3 H), 1.82 (s, 3 H), 1.78–1.71 (m, 3 H), 1.76 (s, 3 H), 1.66–1.47 (m, 7 H), 1.21–1.13 (m, 28 H), 1.10–1.03 (m, 36 H), 0.99 (s, 9 H), 0.98 (s, 9 H), 0.93 (s, 3 H), 0.85 (s, 3 H), 0.83–0.78 (m, 6 H), 0.77–0.70 (m, 18 H), 0.090 (s, 3 H), 0.088 (s, 3 H), 0.082 (s, 3 H), 0.074 (s, 3 H) ppm; ^{13}C NMR (151 MHz, C_6D_6) δ = 214.5, 170.7,148.8, 148.4, 138.5, 137.3, 136.0, 135.9, 119.7, 119.0, 110.2, 110.1, 80.4, 80.1, 79.5, 76.0, 75.8, 74.0, 64.4, 64.3, 55.3, 54.9, 53.5, 53.4, 50.6, 50.2, 48.2, 48.1, 43.4, 43.2, 40.2, 40.1, 37.4, 37.3, 36.6, 36.4, 36.2, 36.1, 35.6, 35.4, 32.3, 26.2, 25.5, 25.4, 23.8, 23.5, 23.2, 23.1, 20.3, 20.1, 19.1, 18.5, 18.4, 17.7, 17.6, 15.7, 15.6, 14.9, 7.4, 7.3, 7.2, 6.0, 5.9, 5.8, –5.1 ppm (^{1}H and ^{13}C NMR were recorded as mixture); HRMS (ESI) calcd for $C_{48}H_{92}N_3O_6Si_3S$ $[M+H]^+$ 922.6009, found 922.6010.

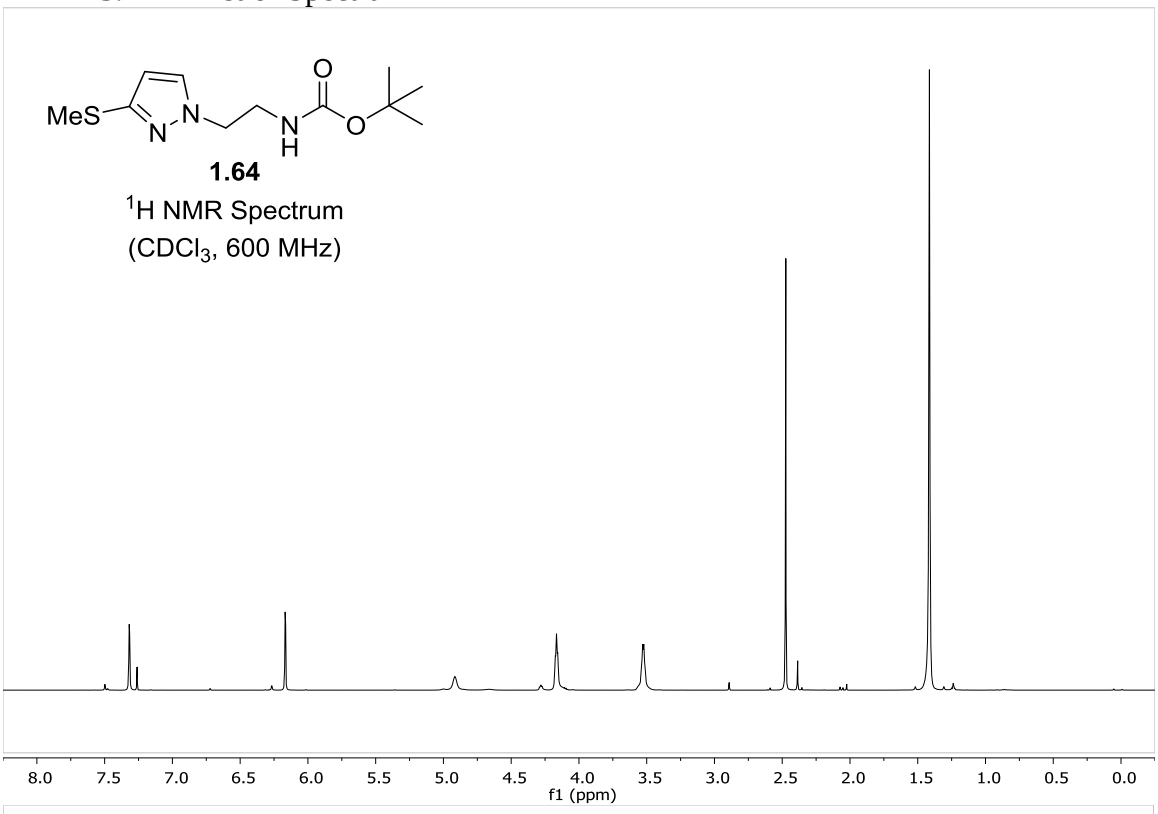


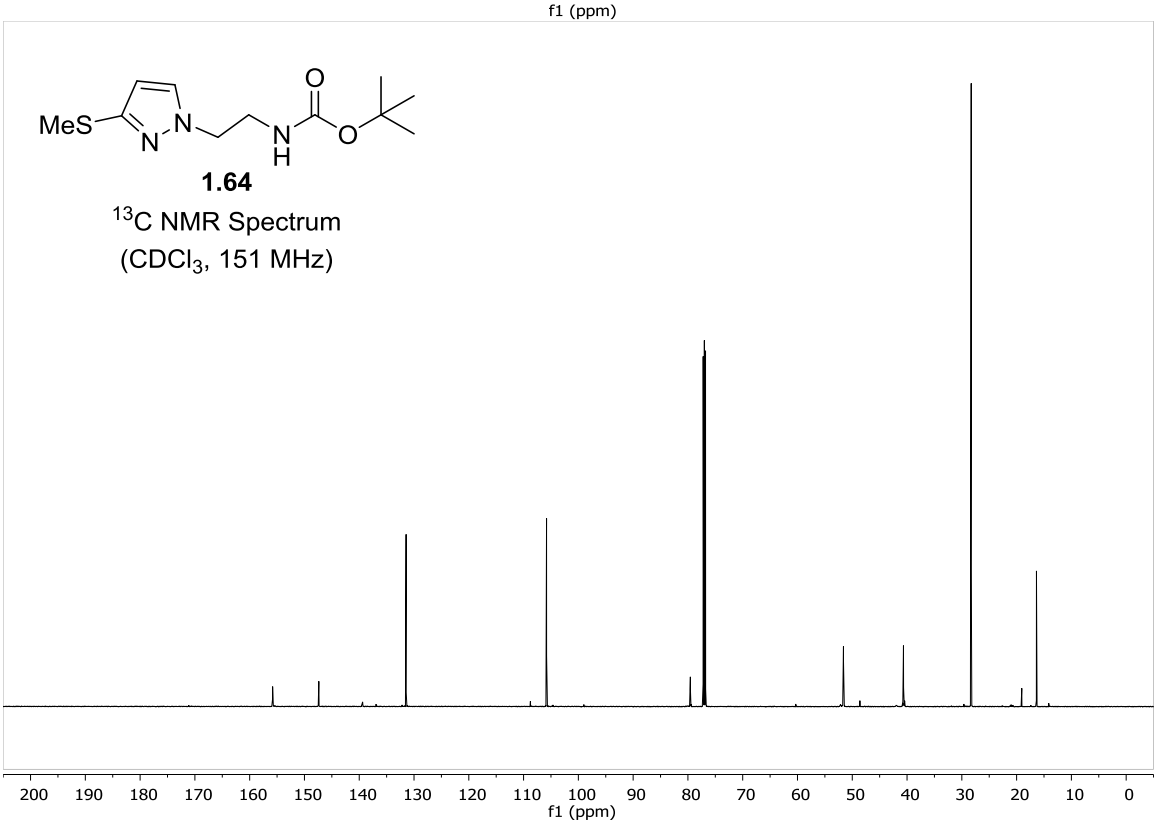
1.157

Epothilone 1.157: To a stirred solution of protected epothilone **1.157a** (8.0 mg, 0.009 mmol, 1.0 equiv.) in tetrahydrofuran (1.0 mL) at 0 °C was added hydrogen fluoride-

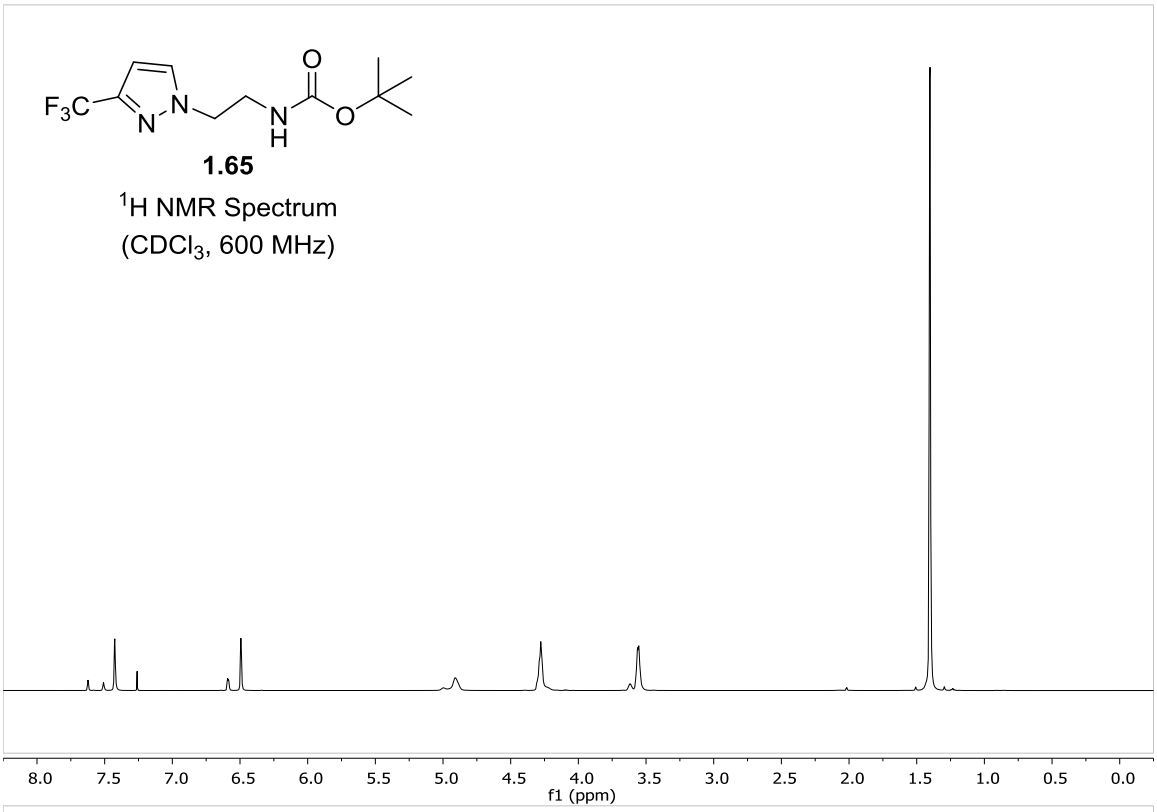
pyridine complex (70% HF, 0.10 mL, 3.85 mmol, 428 equiv.). The reaction mixture was allowed to warm to 25 °C, stirred for 5 h, and then quenched with a saturated aqueous solution of sodium bicarbonate (10 mL). The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 5 → 20% methanol in ethyl acetate) to afford pure epothilone **1.157** (4.1 mg, 0.007 mmol, 81%) as a colorless oil. **1.157**: R_f = 0.28 (silica gel, 20% methanol in ethyl acetate); $[\alpha]_D^{25}$ = –20.0 (c = 0.10, CH_2Cl_2); FT-IR (neat) ν_{max} 3367, 2922, 2852, 1727, 1687, 1555, 1462, 1378, 1334, 1274, 1261, 1148, 1057, 980, 885, 802, 764, 749, 671 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2) δ = 6.40 (s, 1 H), 6.33 (s, 1 H), 6.31 (dd, *J* = 8.4, 4.2 Hz, 1 H), 6.21 (s, 1 H), 6.15 (s, 1 H), 5.43 (dd, *J* = 4.8, 4.8 Hz, 1 H), 4.05–4.02 (m, 2 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.77–3.73 (m, 2 H), 3.68–3.60 (m, 4 H), 3.31–3.26 (m, 1 H), 3.24–3.20 (m, 1 H), 2.76–2.73 (m, 1 H), 2.65–2.61 (m, 1 H), 2.59–2.55 (m, 1 H), 2.53–2.46 (m, 3 H), 2.44–2.37 (m, 3 H), 2.41 (s, 6 H), 2.06–2.02 (m, 1 H), 1.94–1.92 (m, 1 H), 1.90–1.82 (m, 2 H), 1.87 (s, 3 H), 1.70–1.64 (m, 2 H), 1.56–1.42 (m, 8 H), 1.37–1.30 (m, 5 H), 1.34 (s, 3 H), 1.33 (s, 3 H), 1.14 (s, 6 H), 1.20 (d, *J* = 7.2 Hz, 6 H), 1.07 (s, 3 H), 1.03 (s, 3 H), 0.97 (d, *J* = 7.2 Hz, 3 H), 0.96 (d, *J* = 7.2 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, CD_2Cl_2) δ = 220.7, 171.3, 148.4, 147.9, 137.8, 137.0, 135.8, 119.0, 118.1, 109.6, 109.3, 77.8, 75.9, 75.0, 74.8, 73.9, 73.8, 62.4, 62.2, 60.6, 55.3, 54.7, 52.8, 52.7, 49.4, 48.2, 44.8, 44.6, 43.4, 39.7, 39.5, 36.9, 36.8, 36.0, 35.8, 35.5, 34.7, 32.9, 31.8, 31.1, 29.5, 21.9, 21.8, 21.4, 20.2, 19.9, 19.4, 19.1, 19.0, 17.6, 17.3, 16.5, 16.3, 15.7, 14.5, 13.2 ppm (^1H and ^{13}C NMR were recorded as mixture); HRMS (ESI) calcd for $C_{30}H_{49}N_3O_6SNa$ $[M+Na]^+$ 602.3234, found 602.3235.

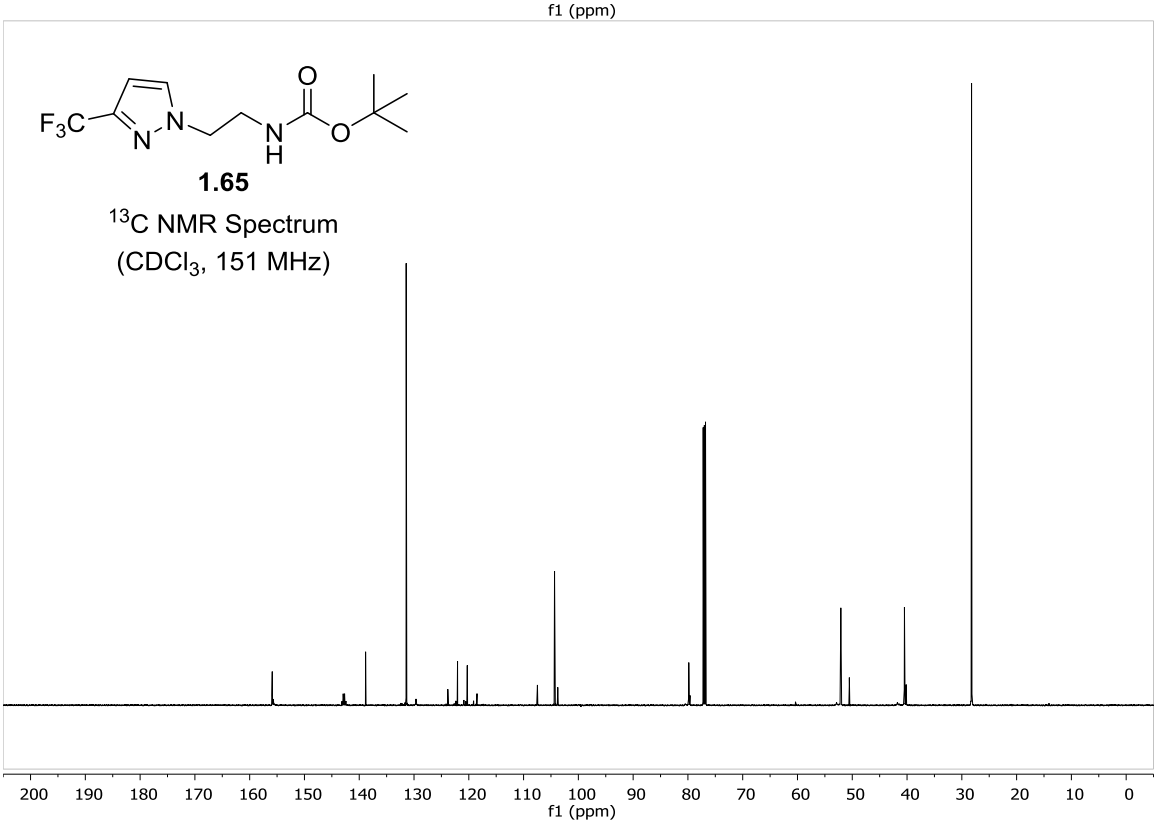
3. List of Spectra



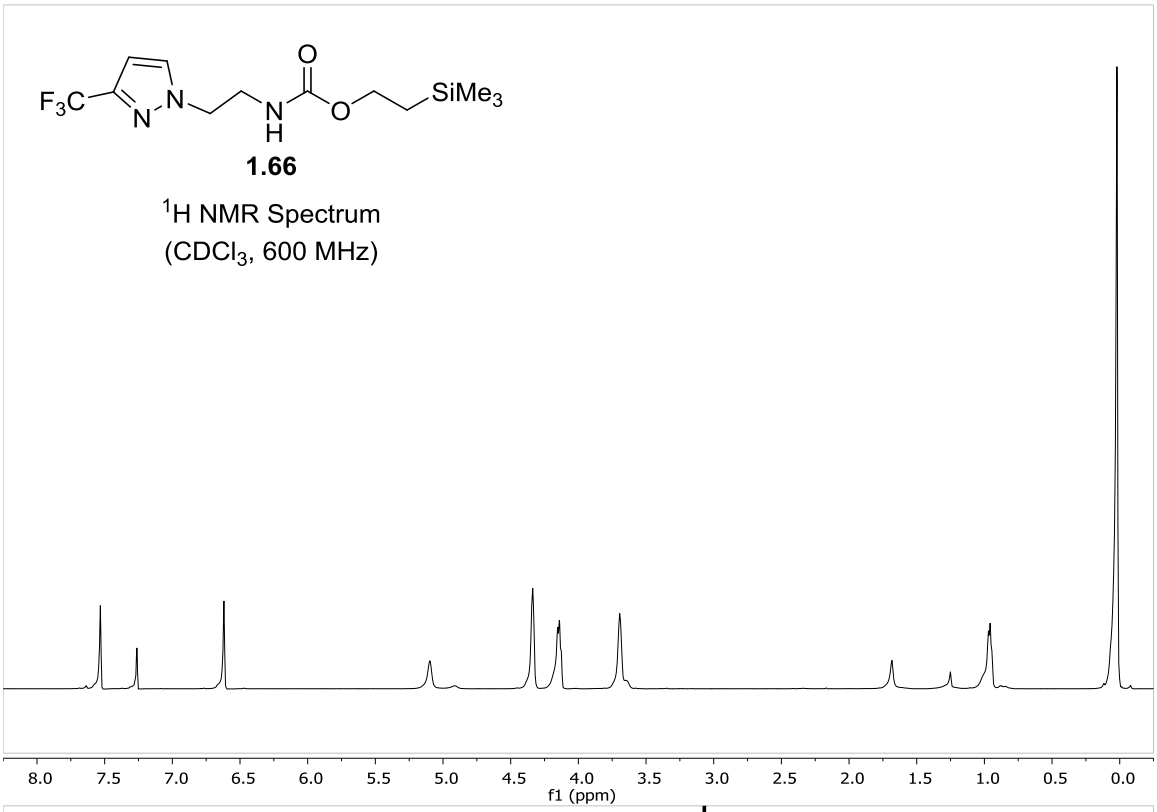


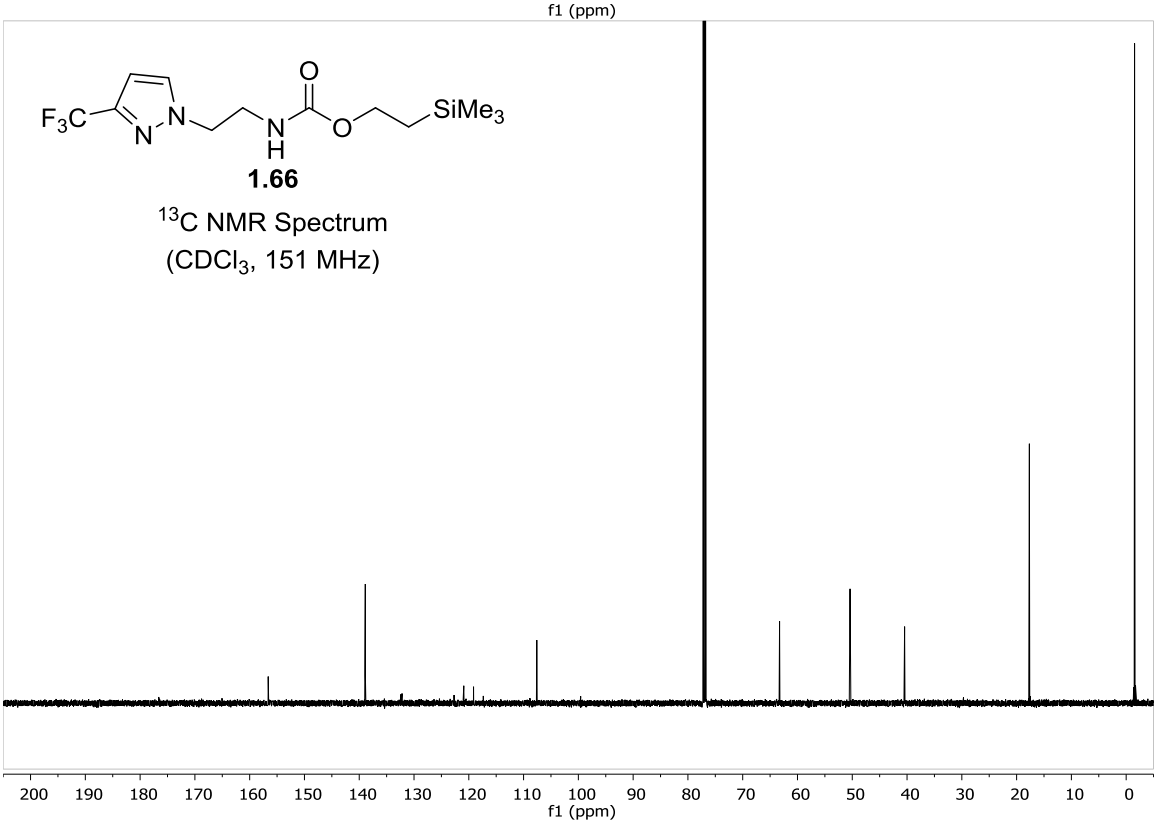
Spectra **1.01**: Compound **1.64**: ^{1}H and ^{13}C NMR



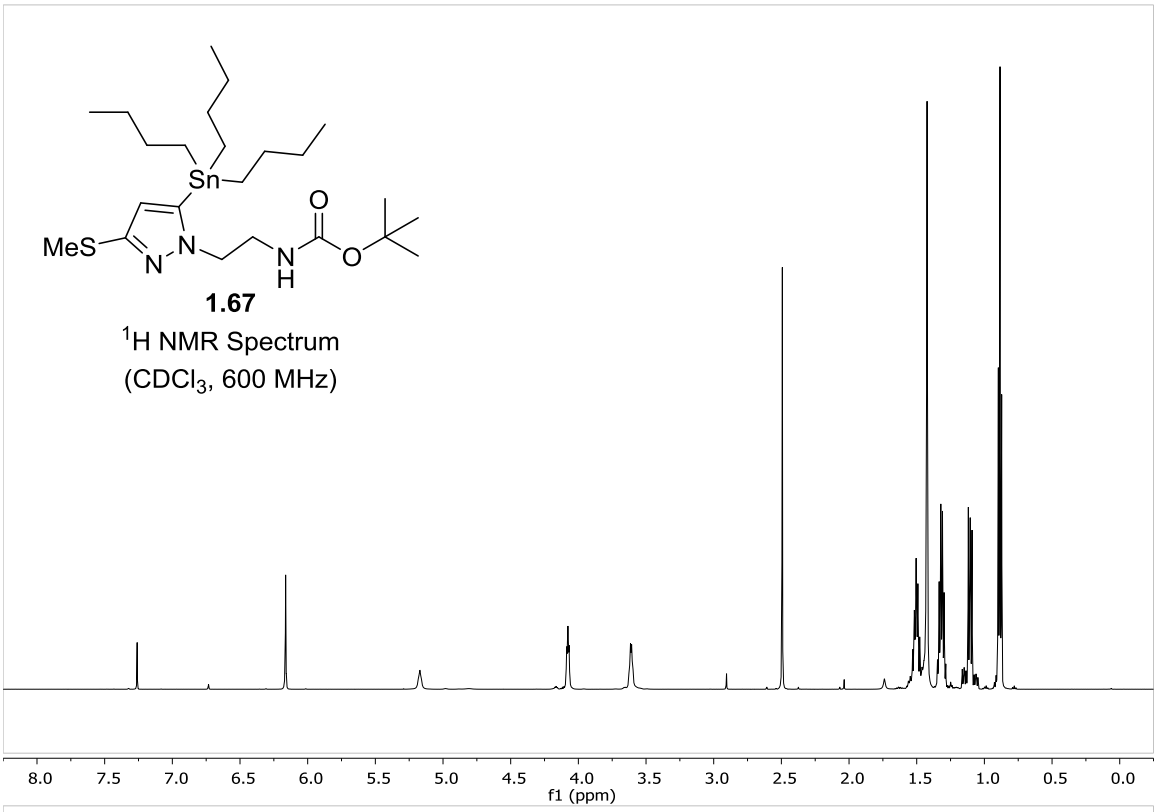


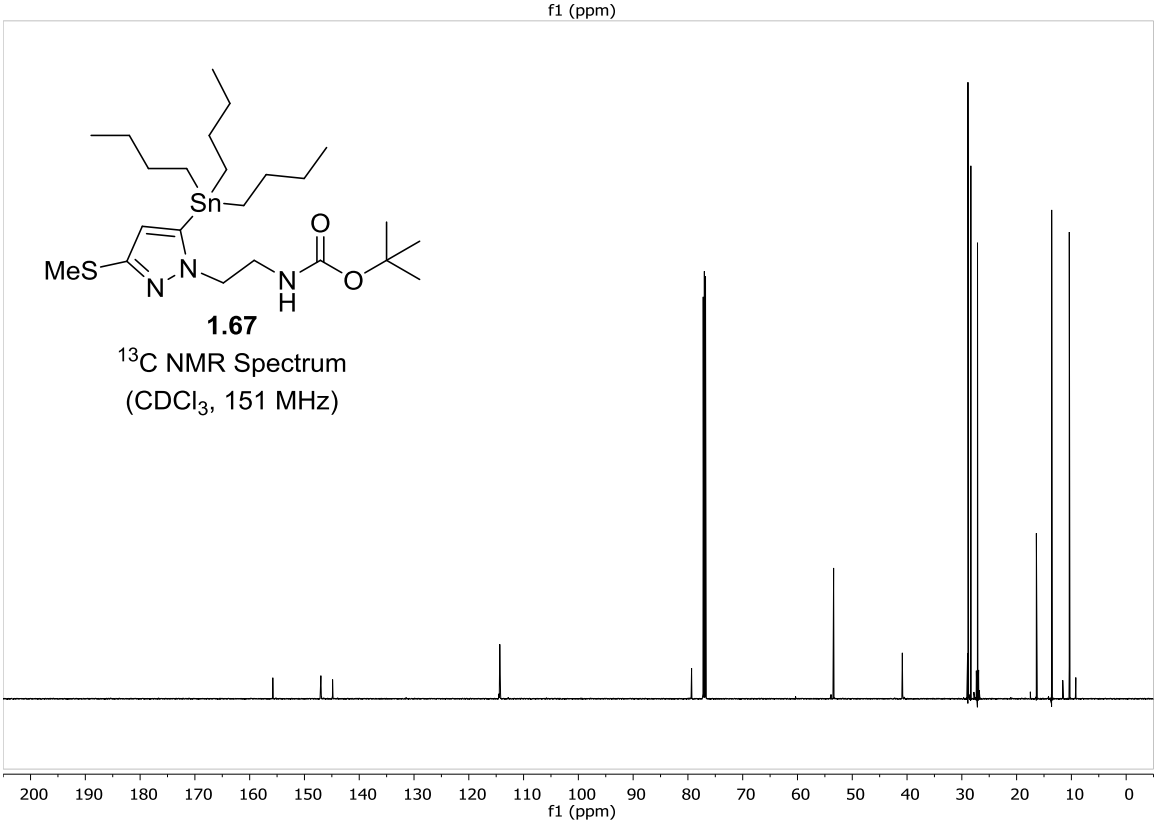
Spectra **1.02**: Compound **1.65**: ^{1}H and ^{13}C NMR



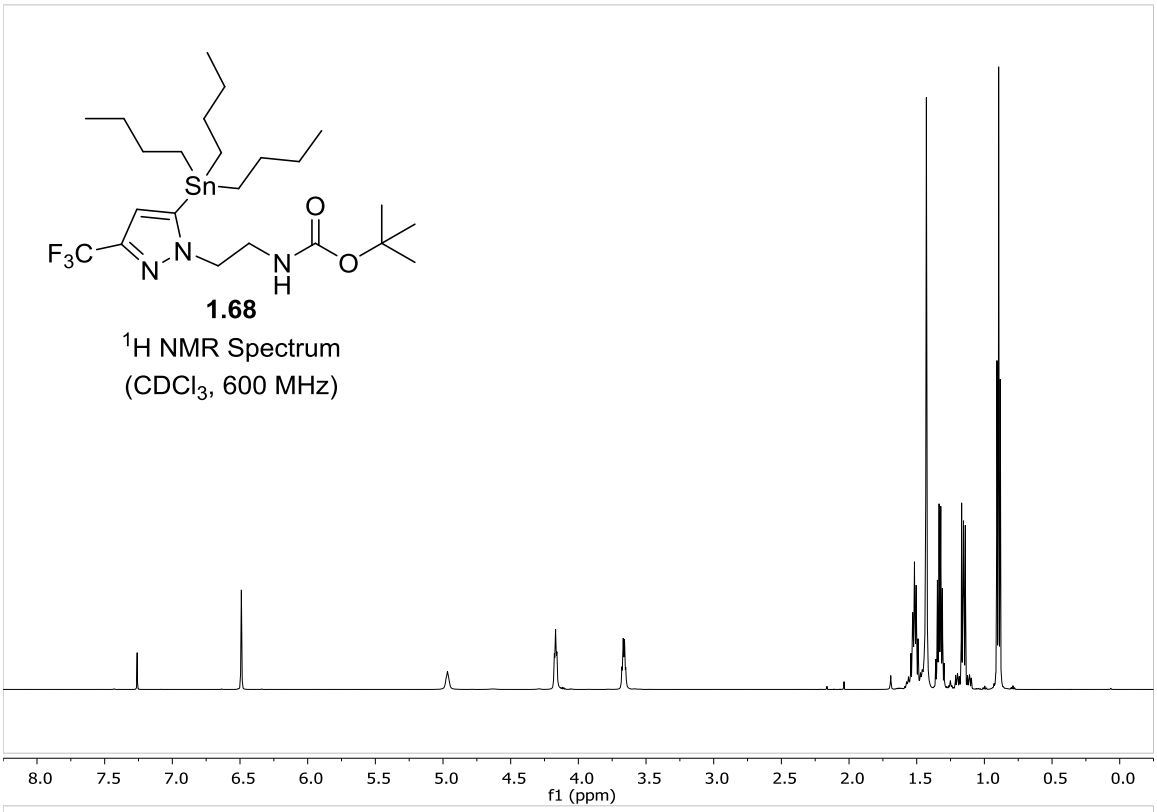


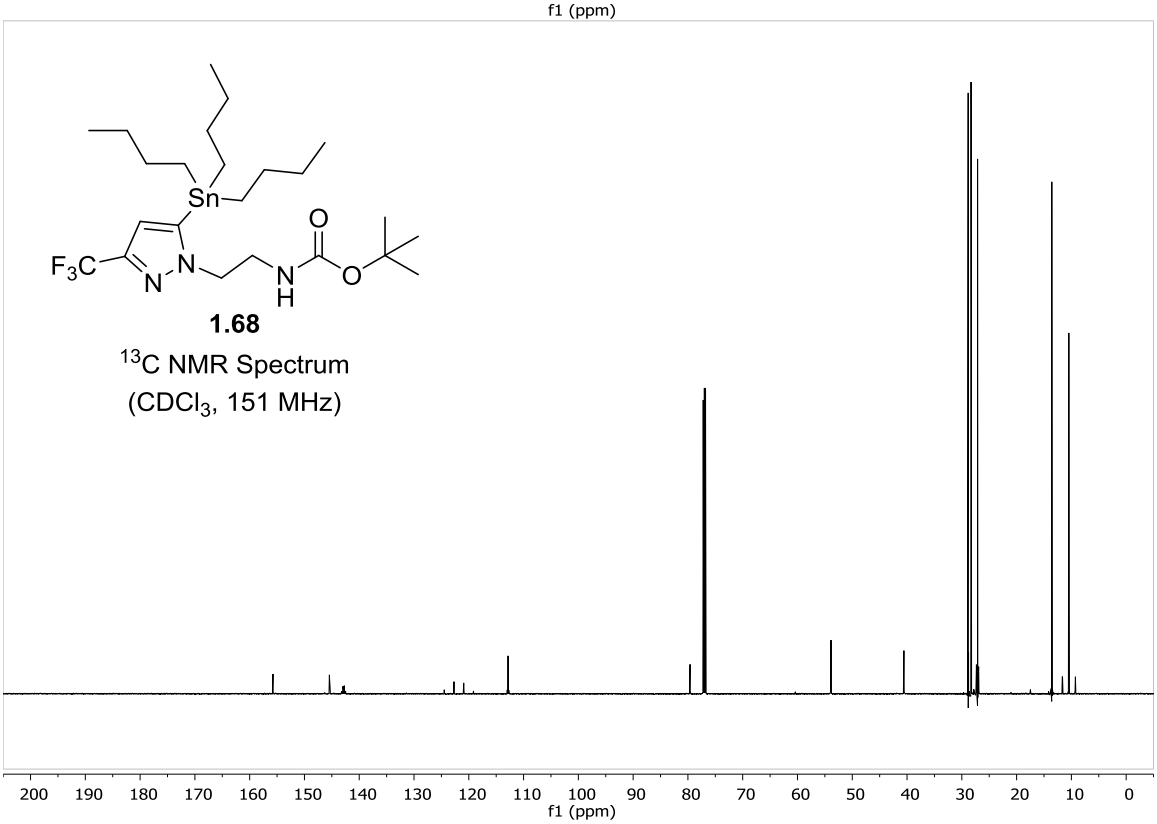
Spectra **1.03**: Compound **1.66**: ^{1}H and ^{13}C NMR



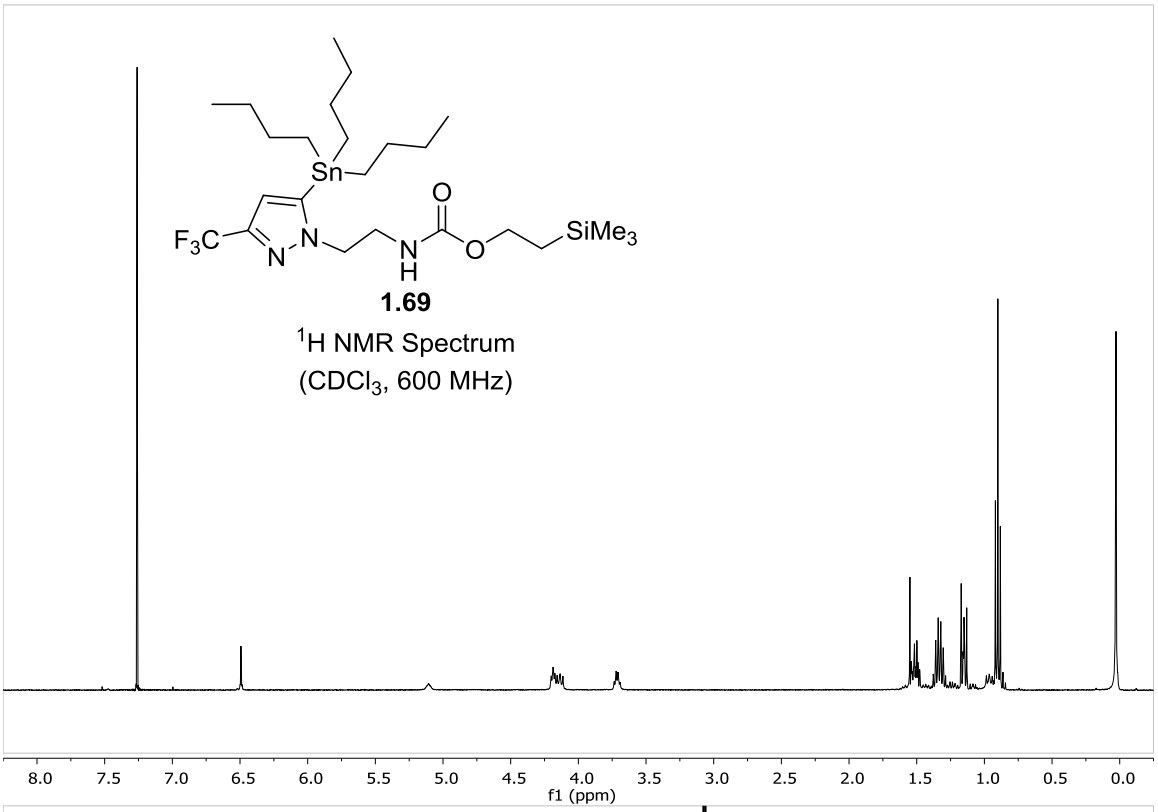


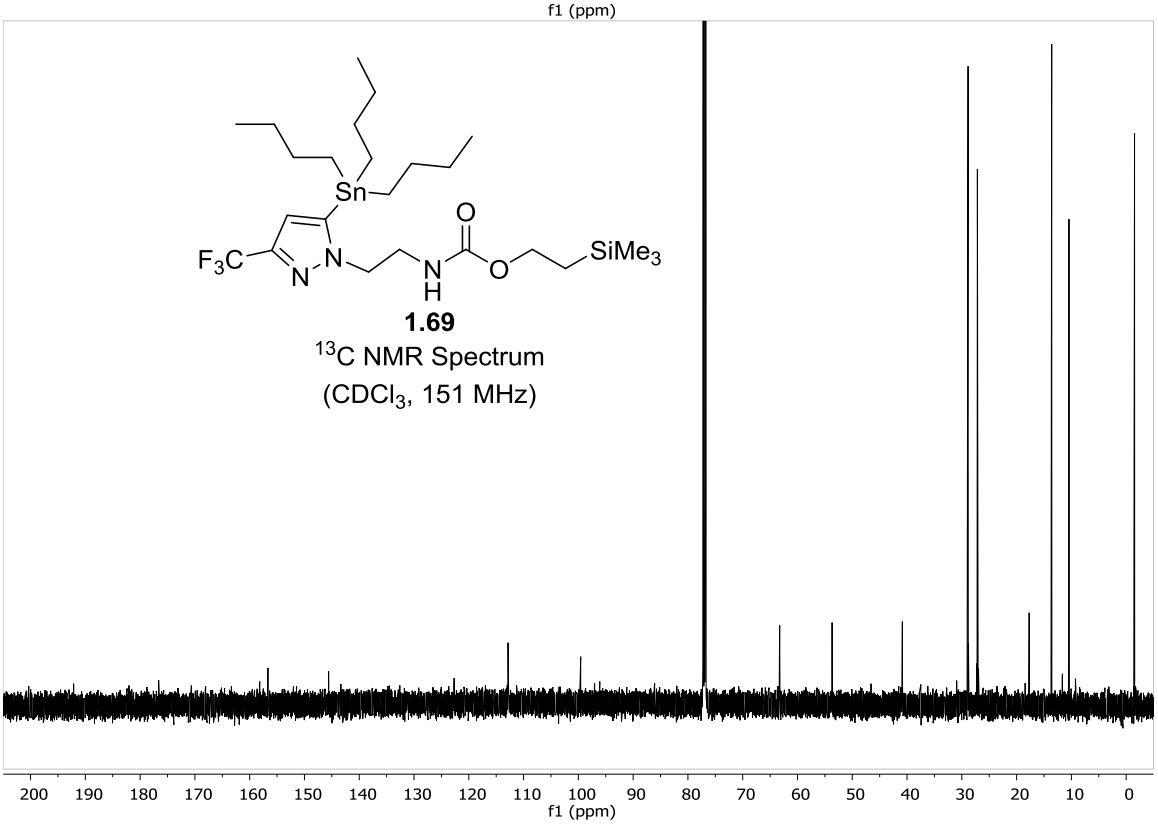
Spectra **1.04**: Compound **1.67**: ^{1}H and ^{13}C NMR



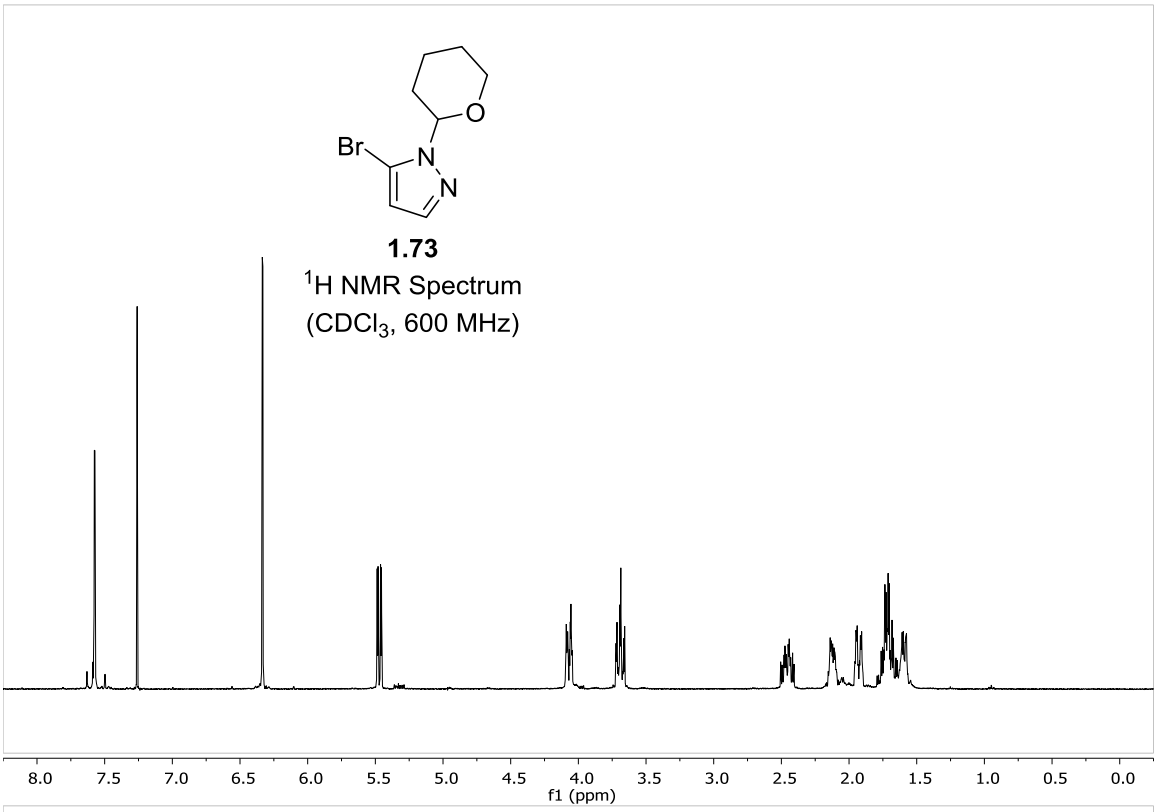


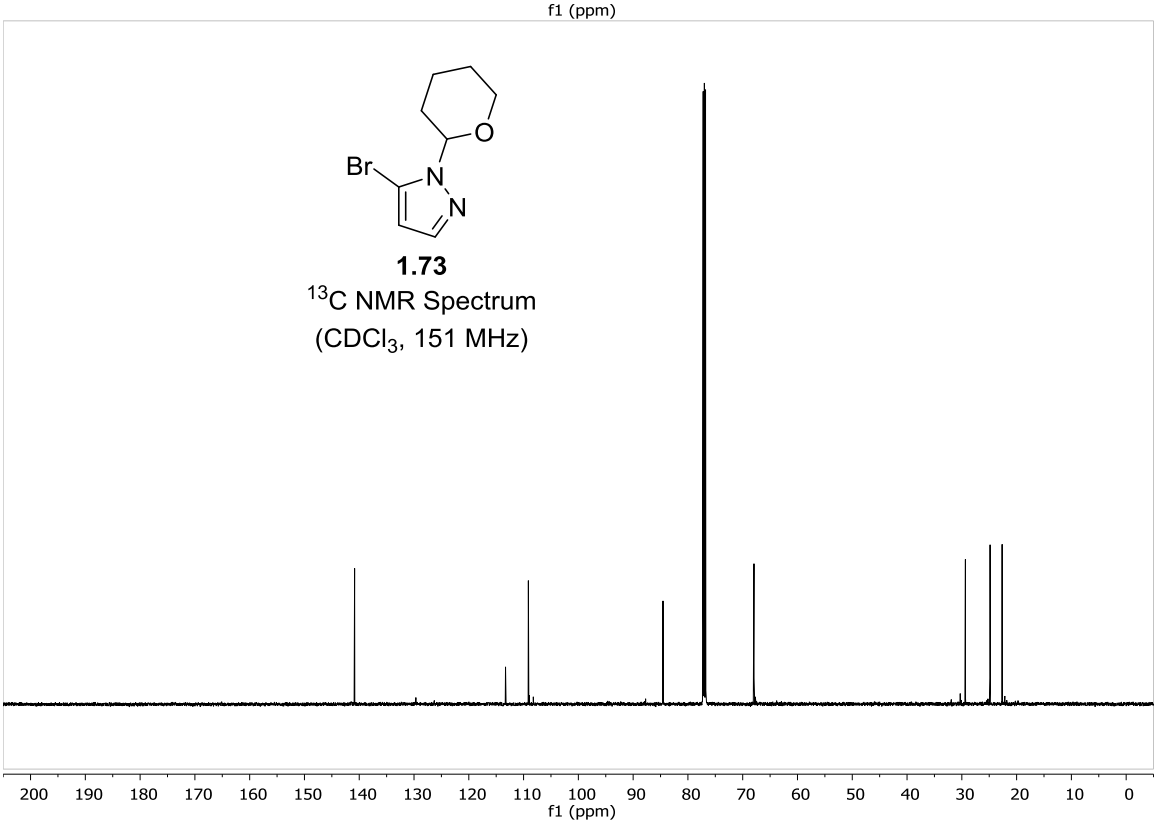
Spectra **1.05**: Compound **1.68**: ^{1}H and ^{13}C NMR



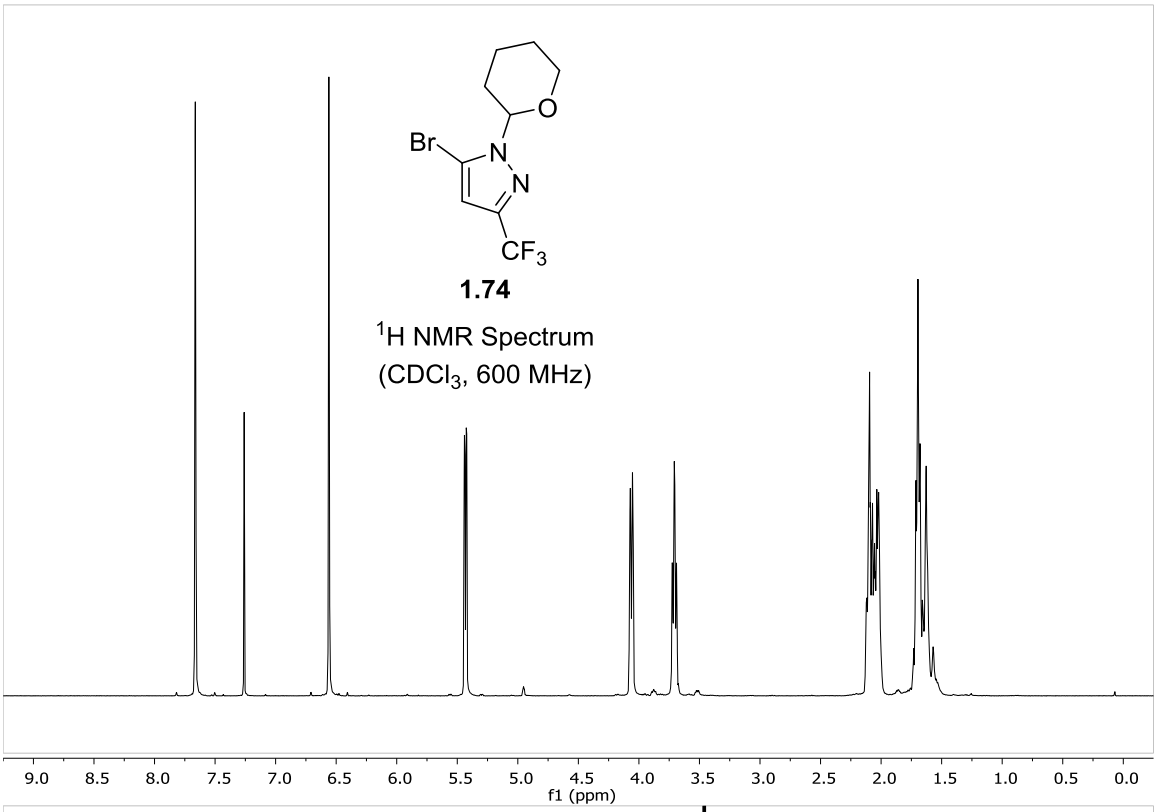


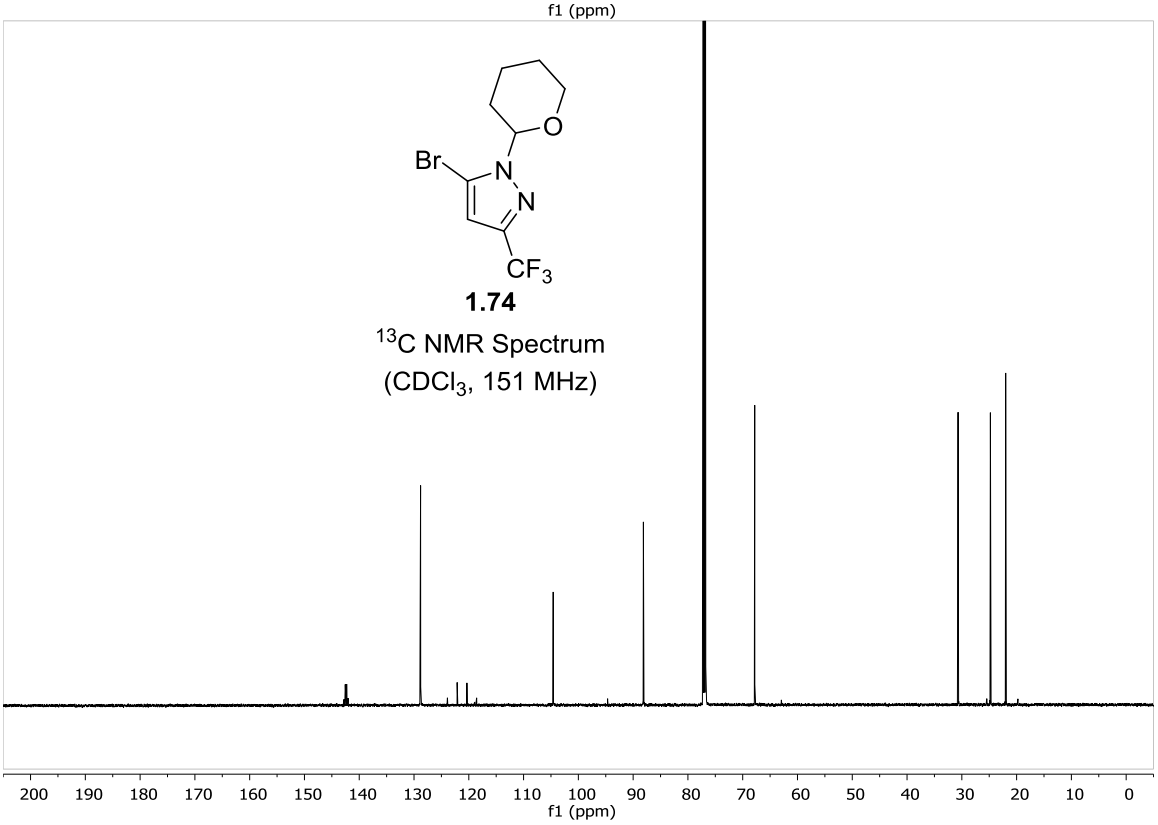
Spectra **1.06**: Compound **1.69**: ^{1}H and ^{13}C NMR



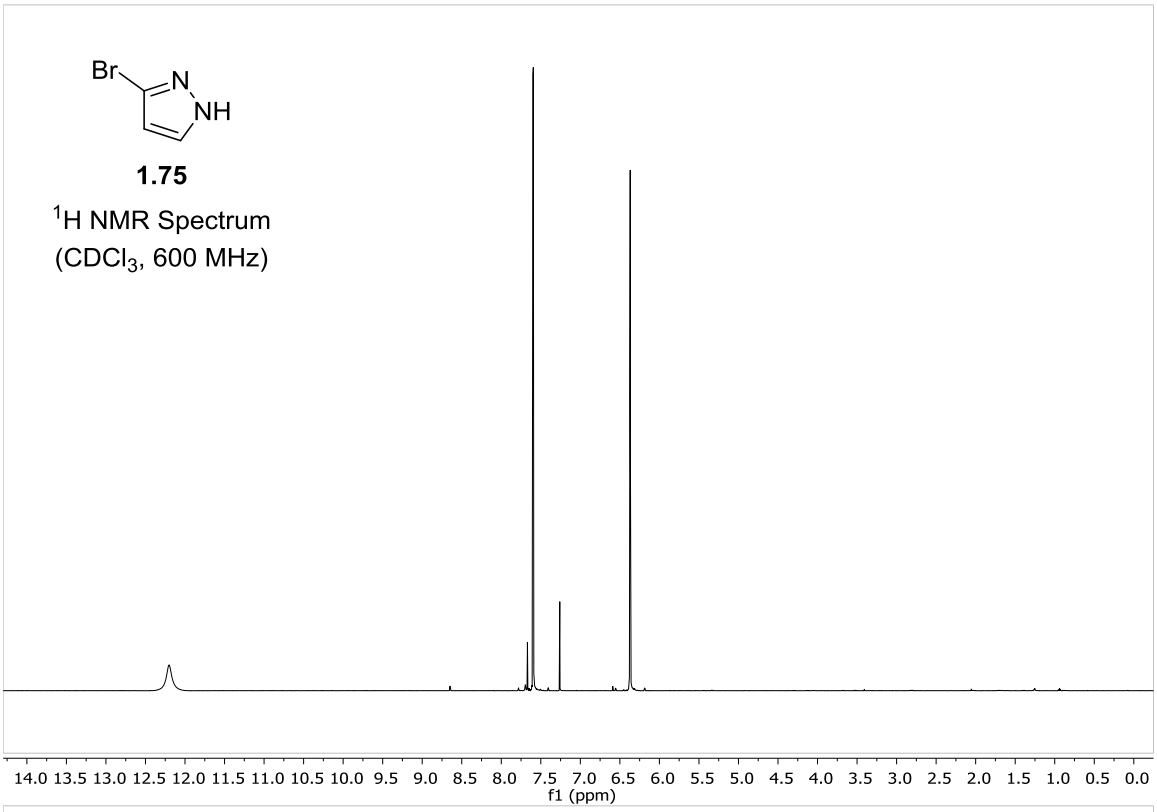


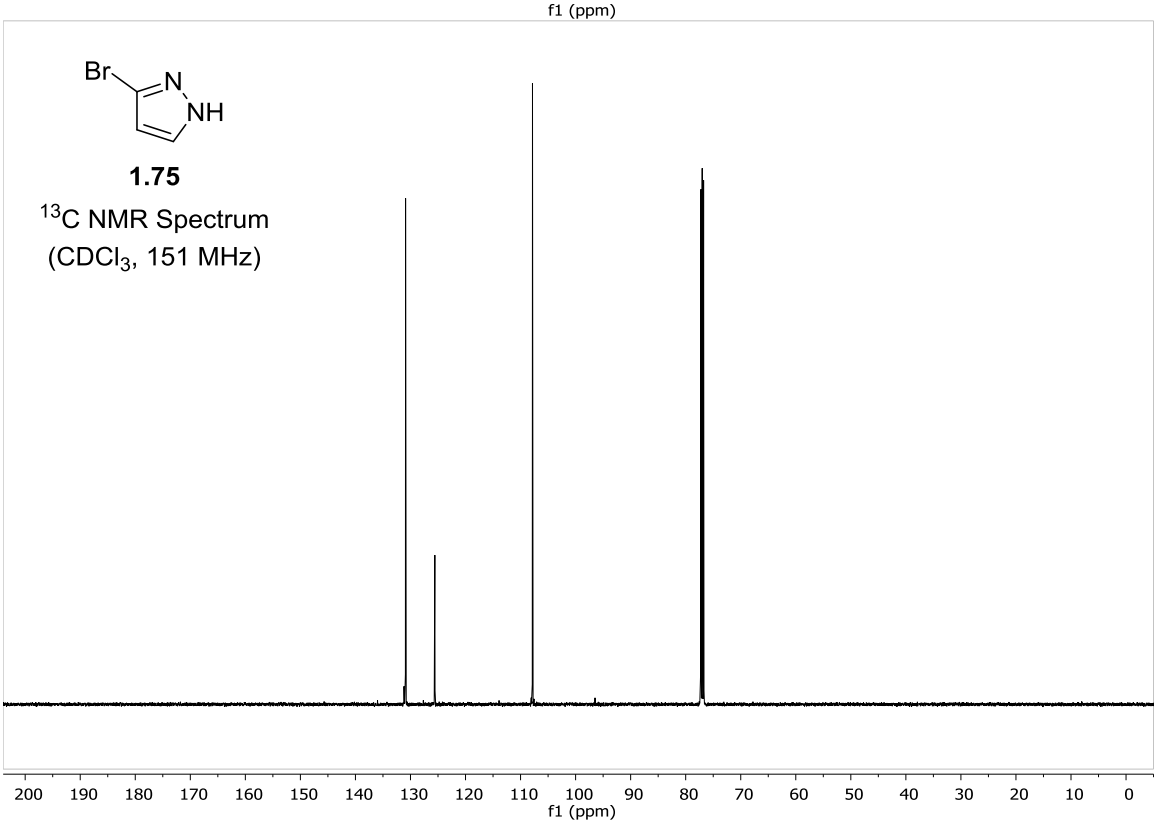
Spectra **1.07**: Compound **1.73**: ^{1}H and ^{13}C NMR



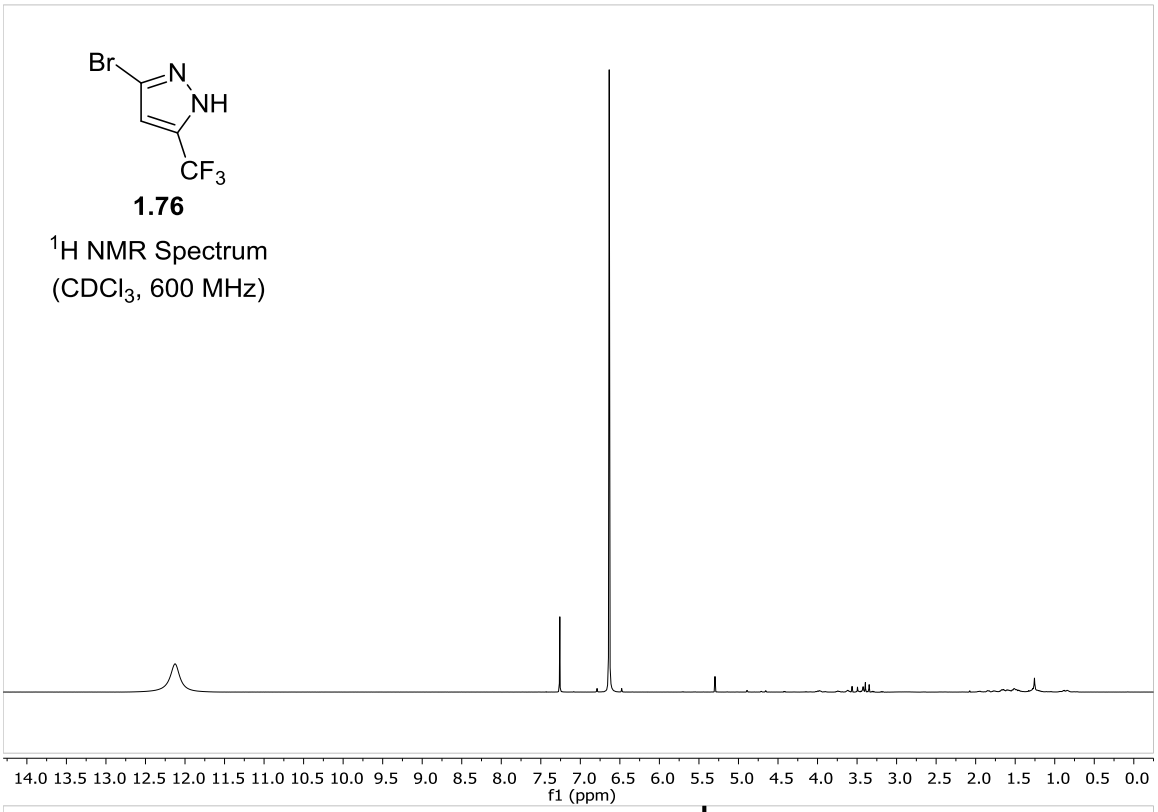


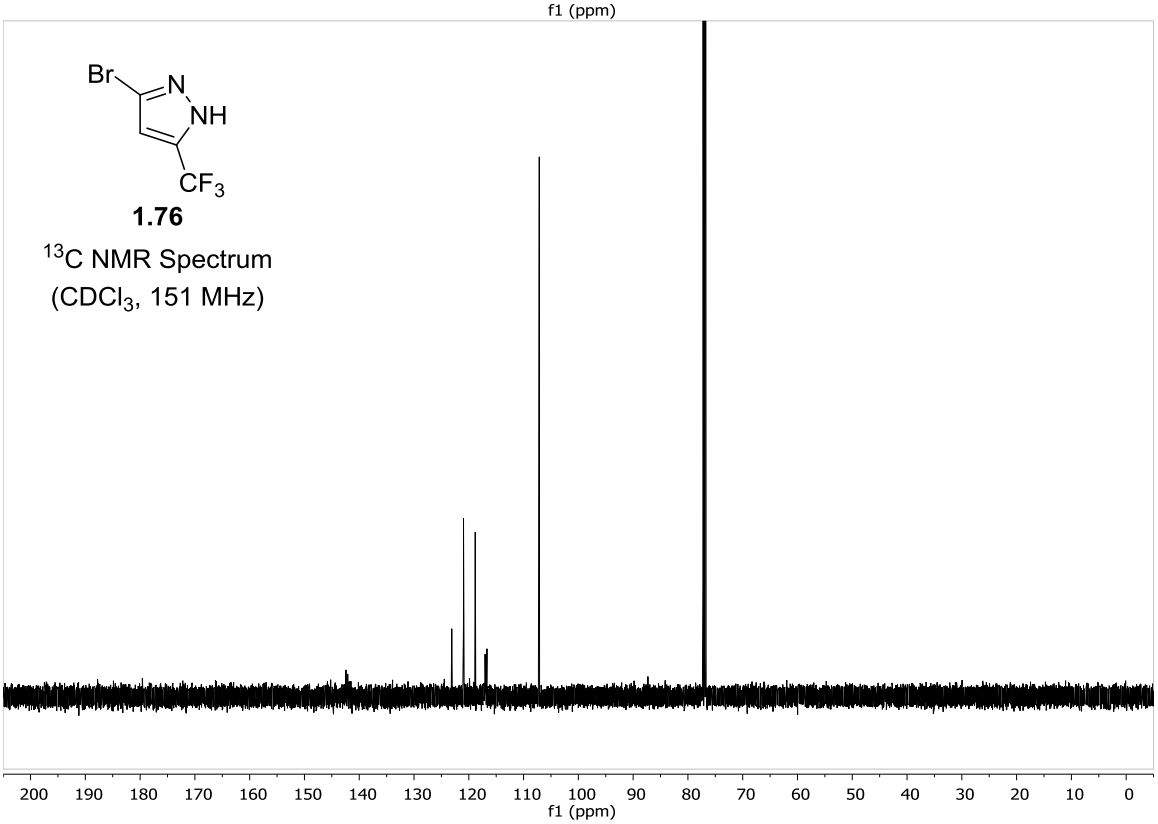
Spectra **1.08**: Compound **1.74**: ^{1}H and ^{13}C NMR



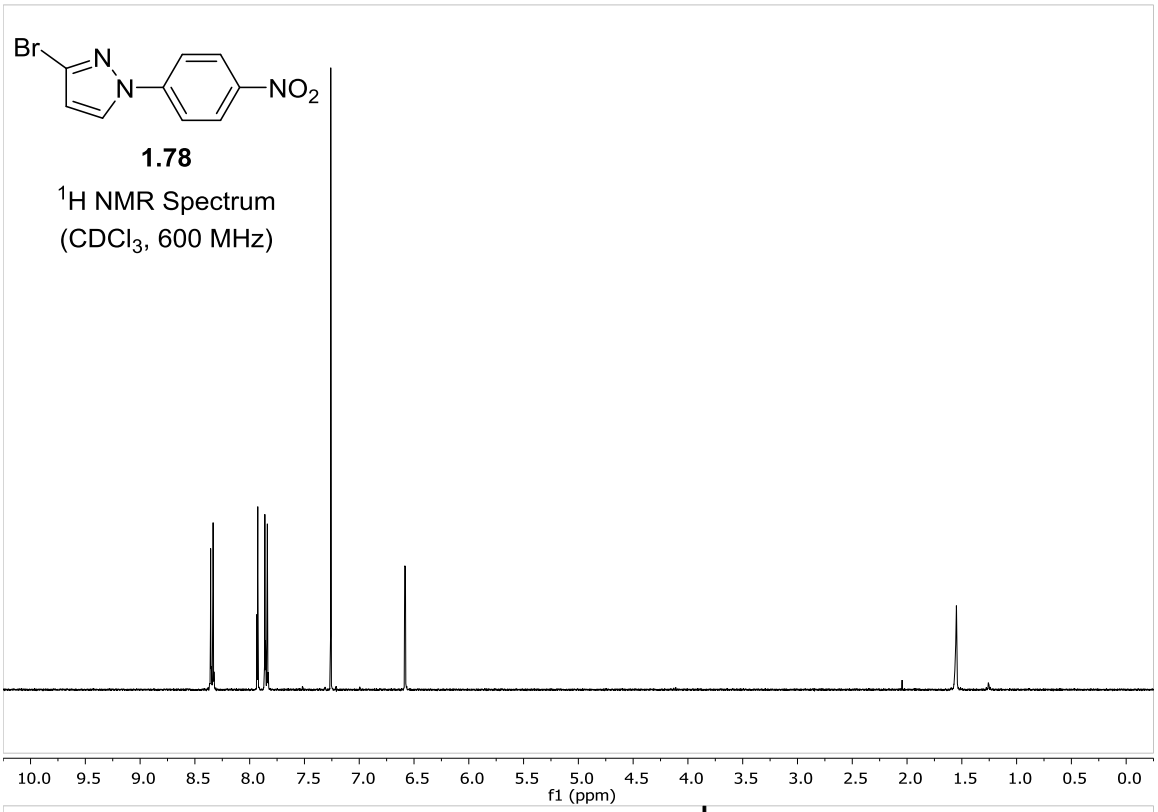


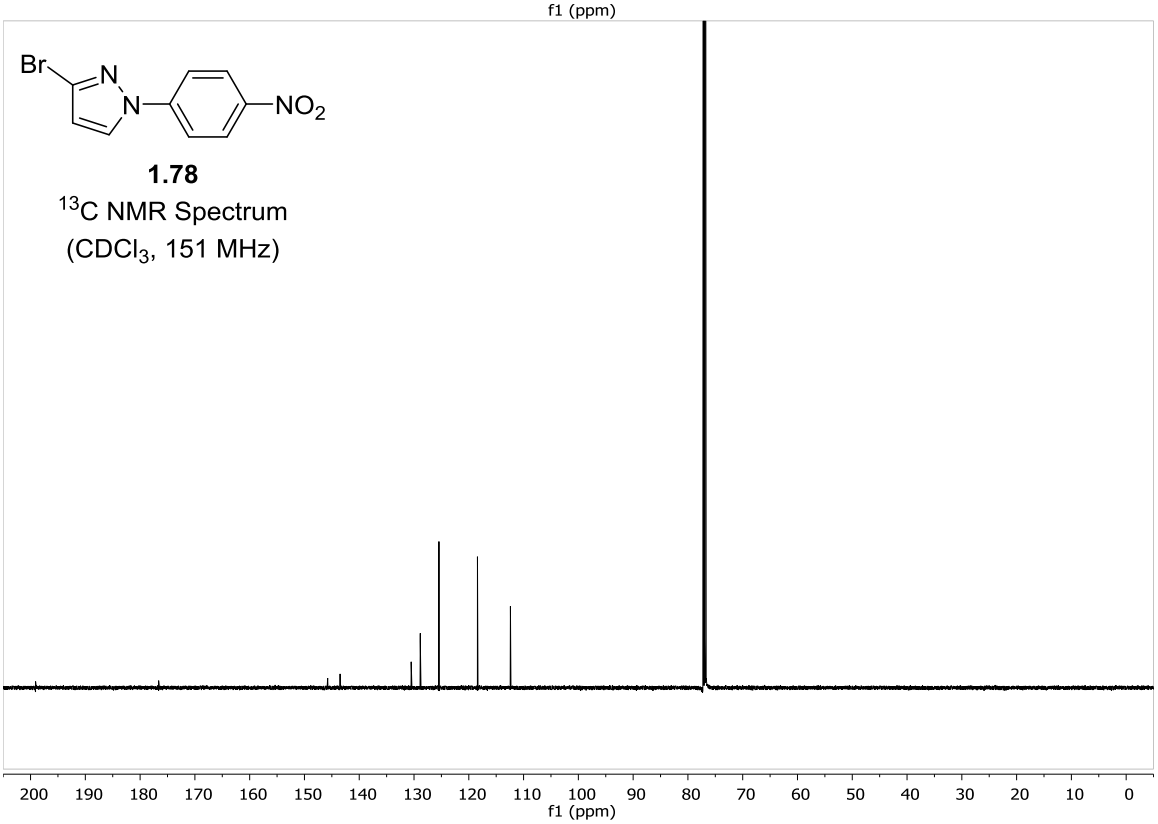
Spectra **1.09**: Compound **1.75**: ^{1}H and ^{13}C NMR



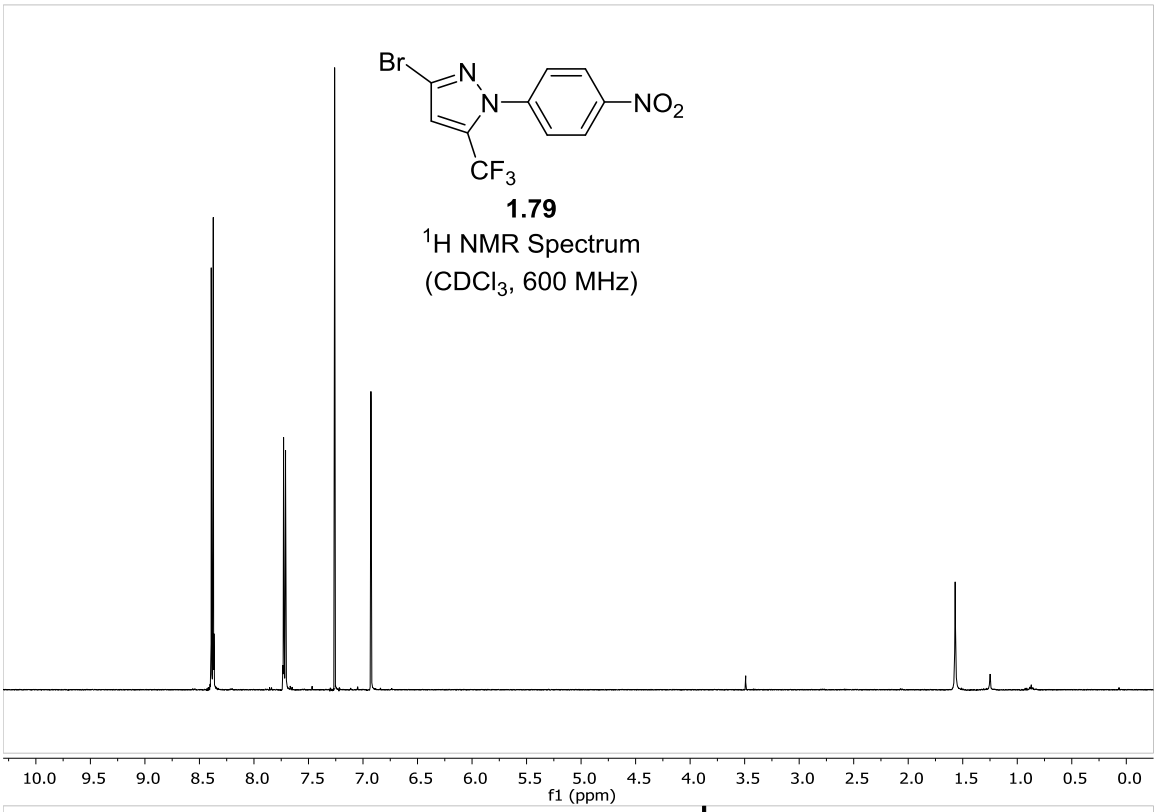


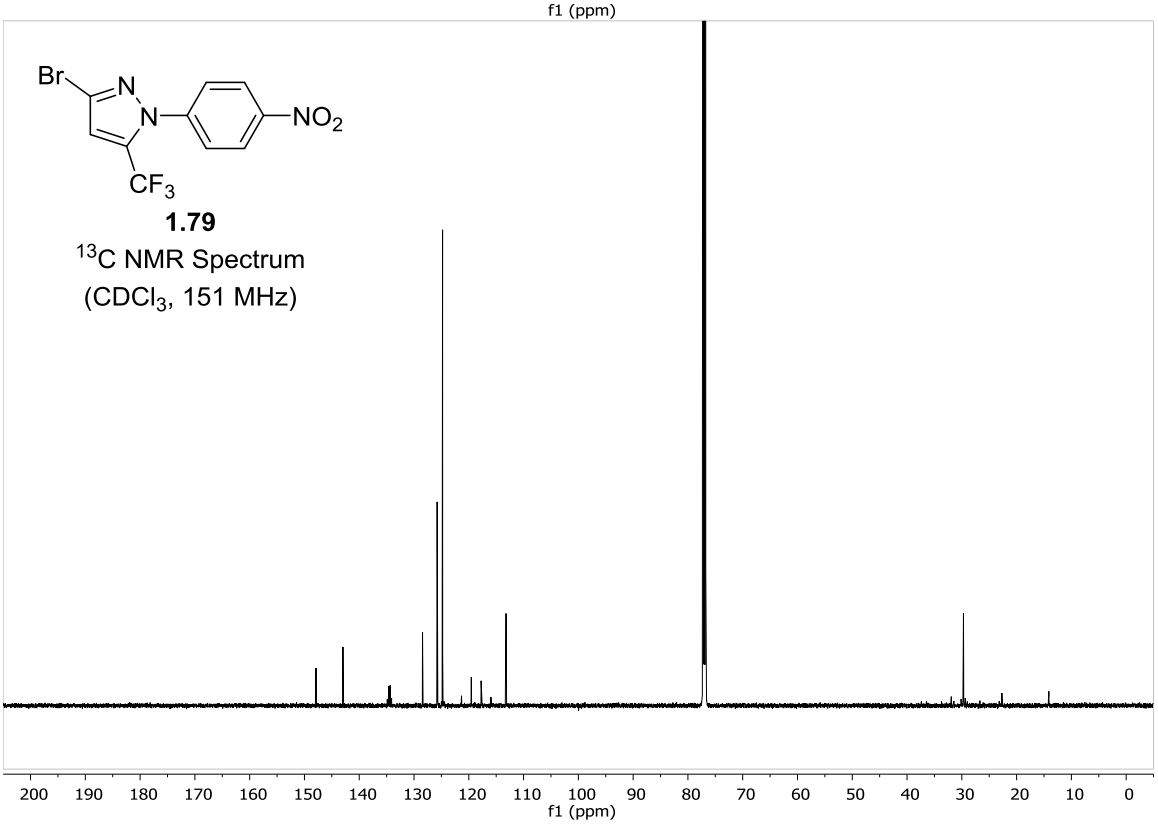
Spectra **1.10**: Compound **1.76**: ^{1}H and ^{13}C NMR



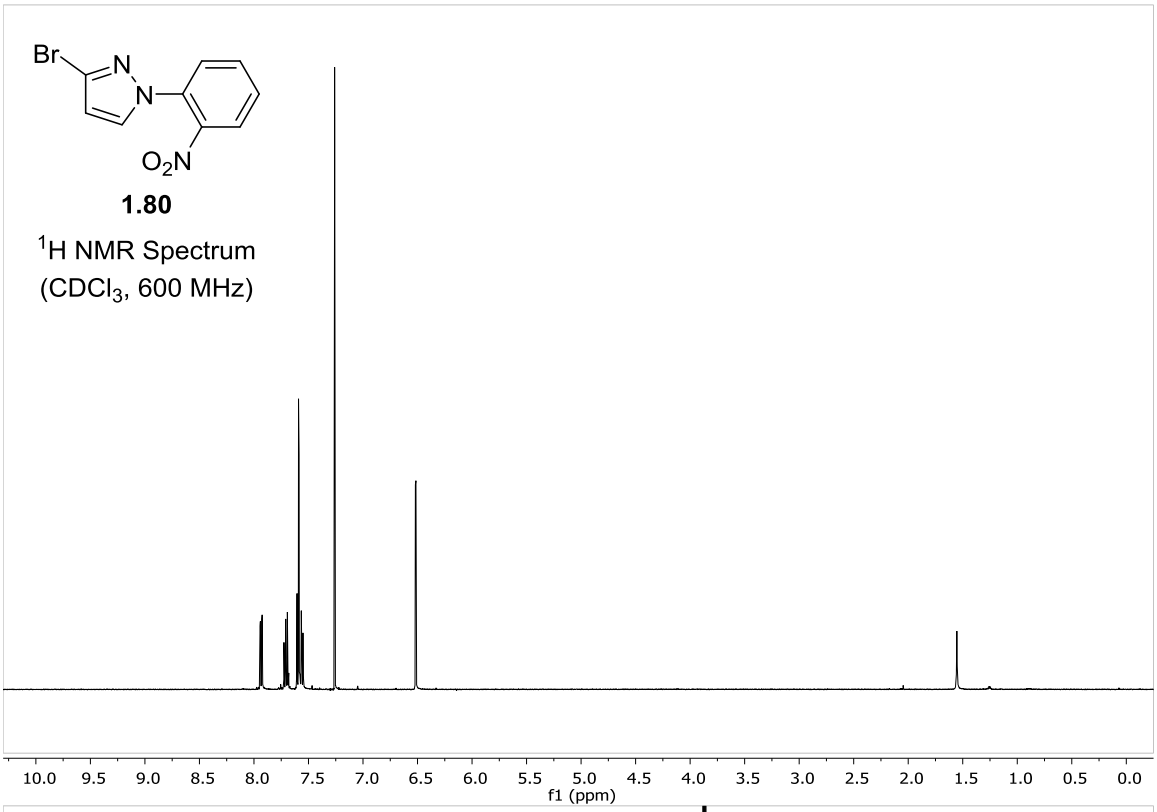


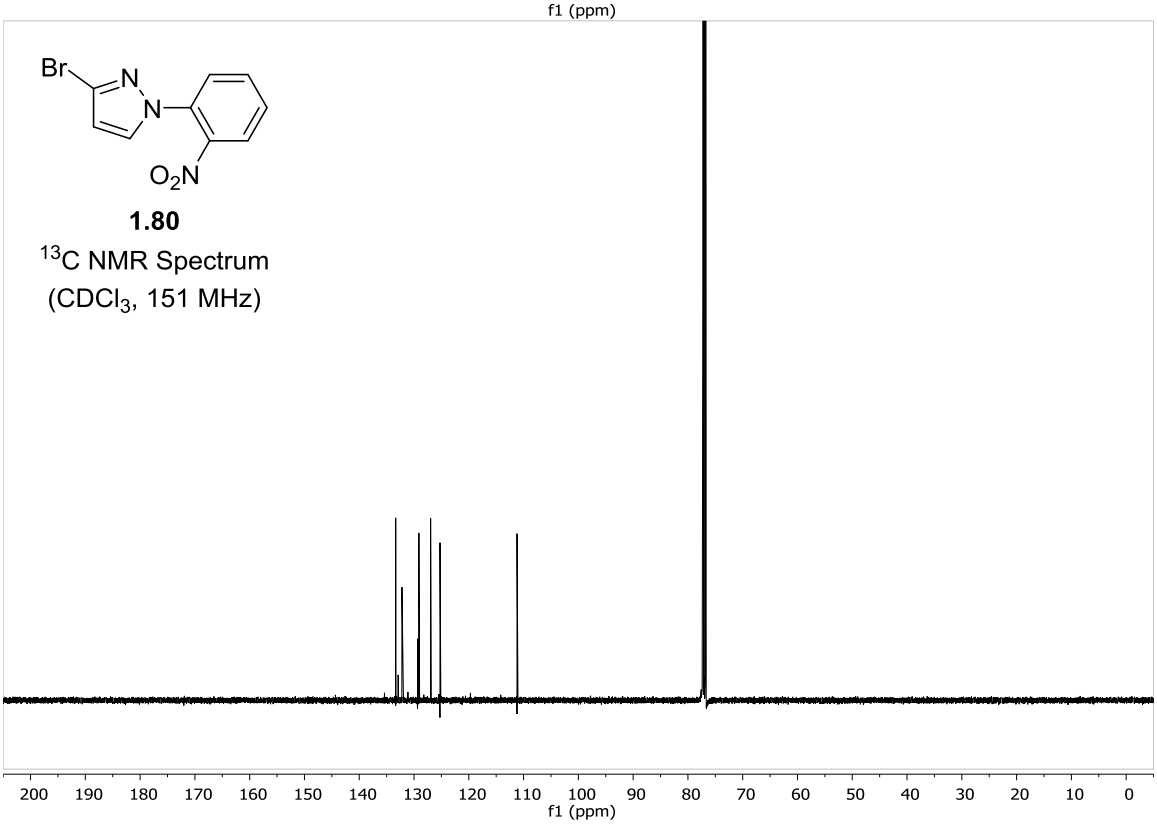
Spectra **1.11**: Compound **1.78**: ^{1}H and ^{13}C NMR



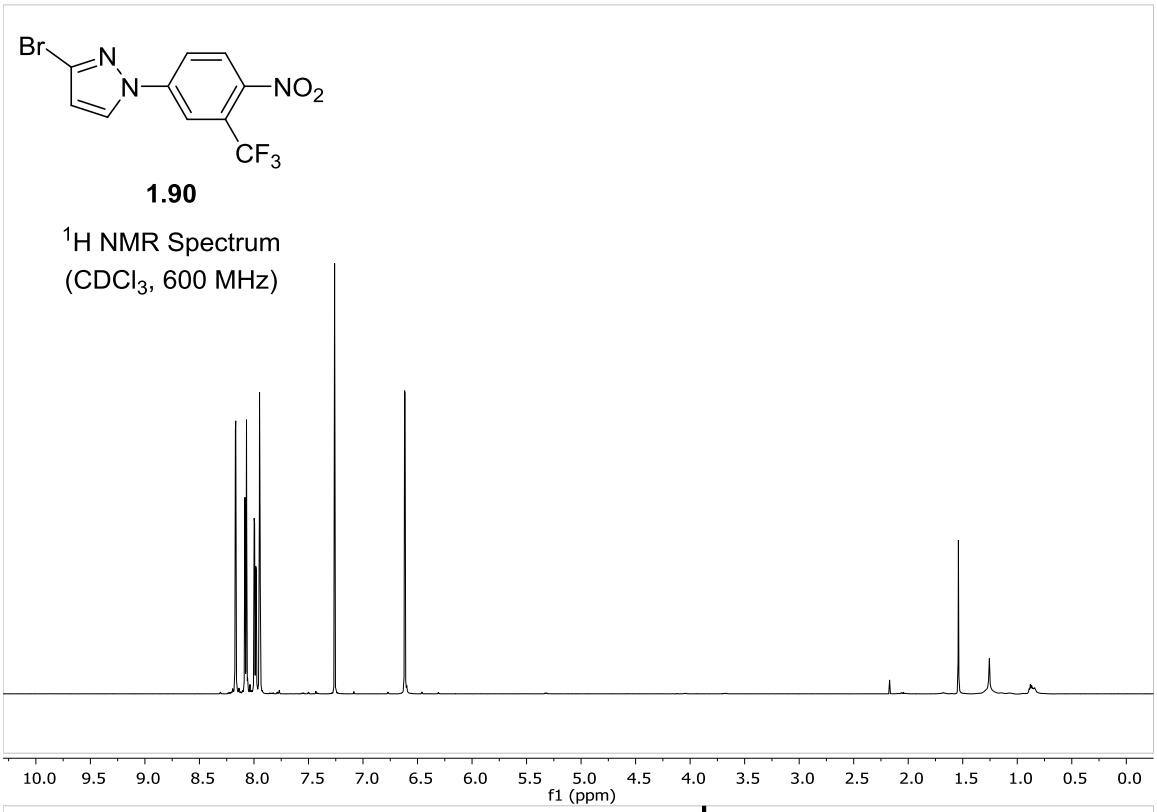


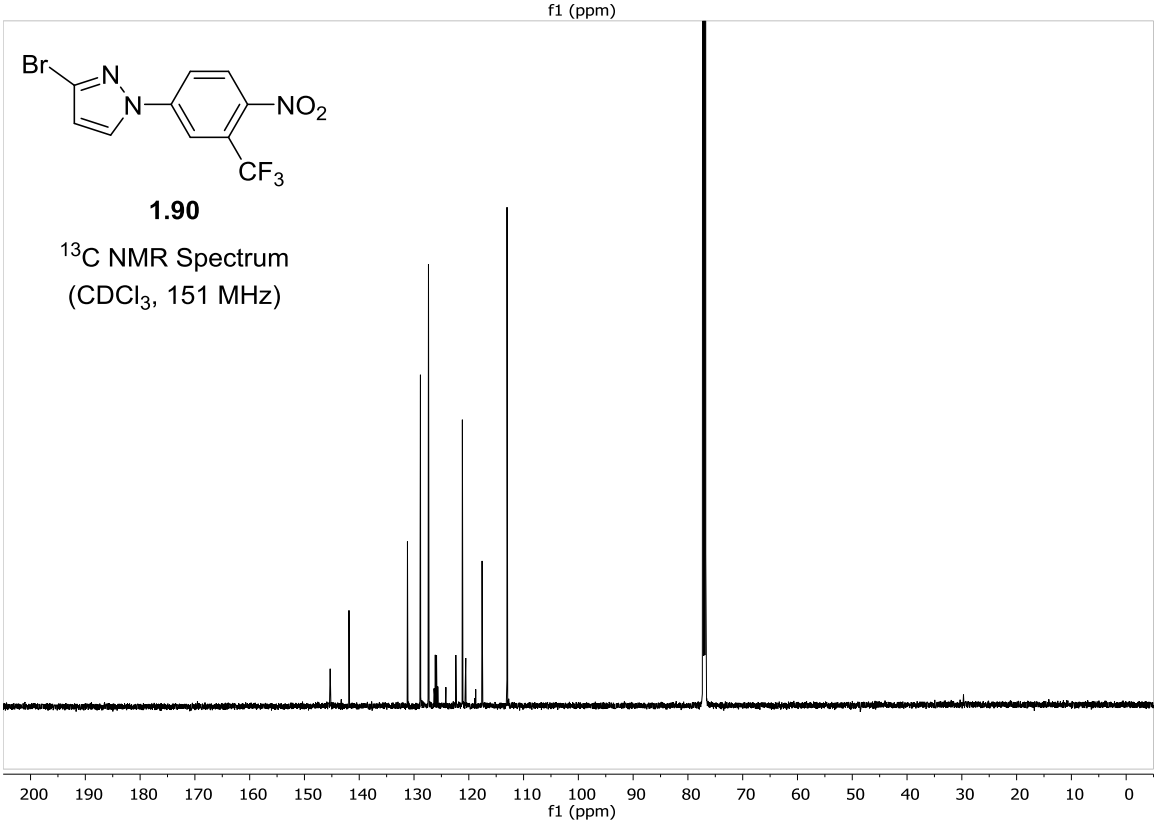
Spectra **1.12**: Compound **1.79**: ^{1}H and ^{13}C NMR



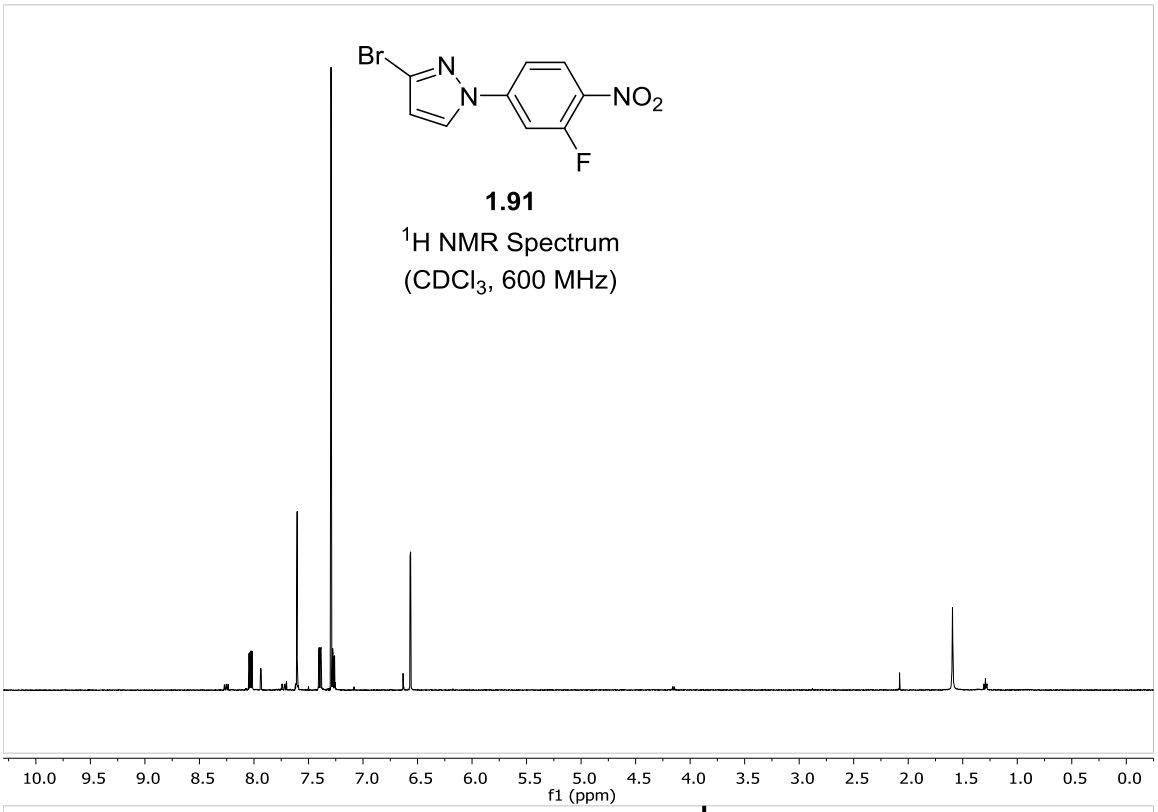


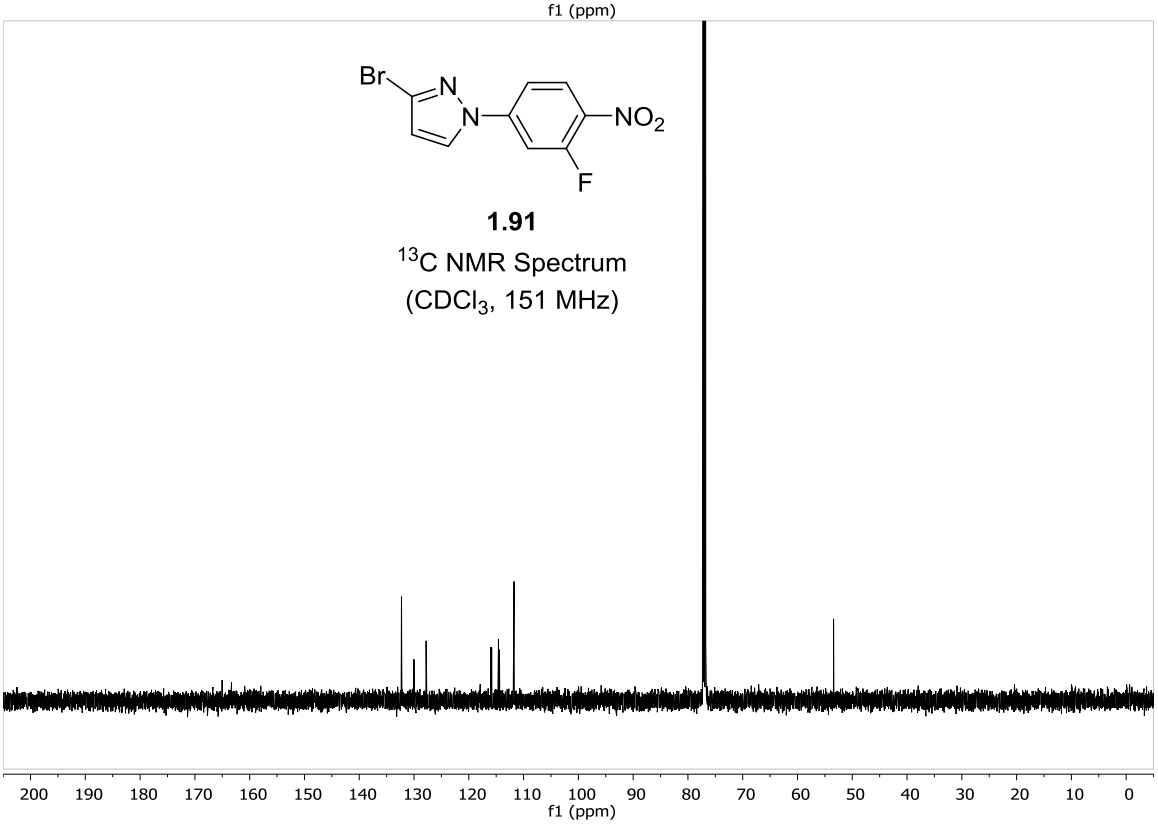
Spectra **1.13**: Compound **1.80**: ^{1}H and ^{13}C NMR



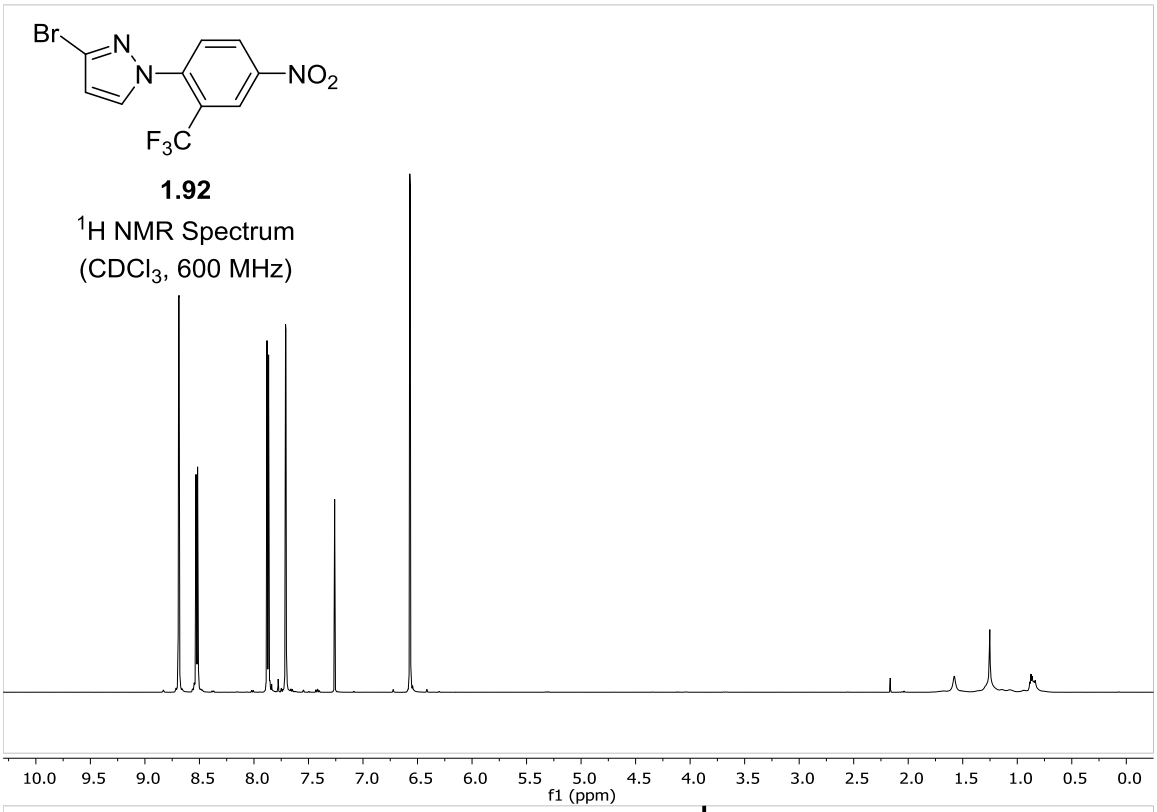


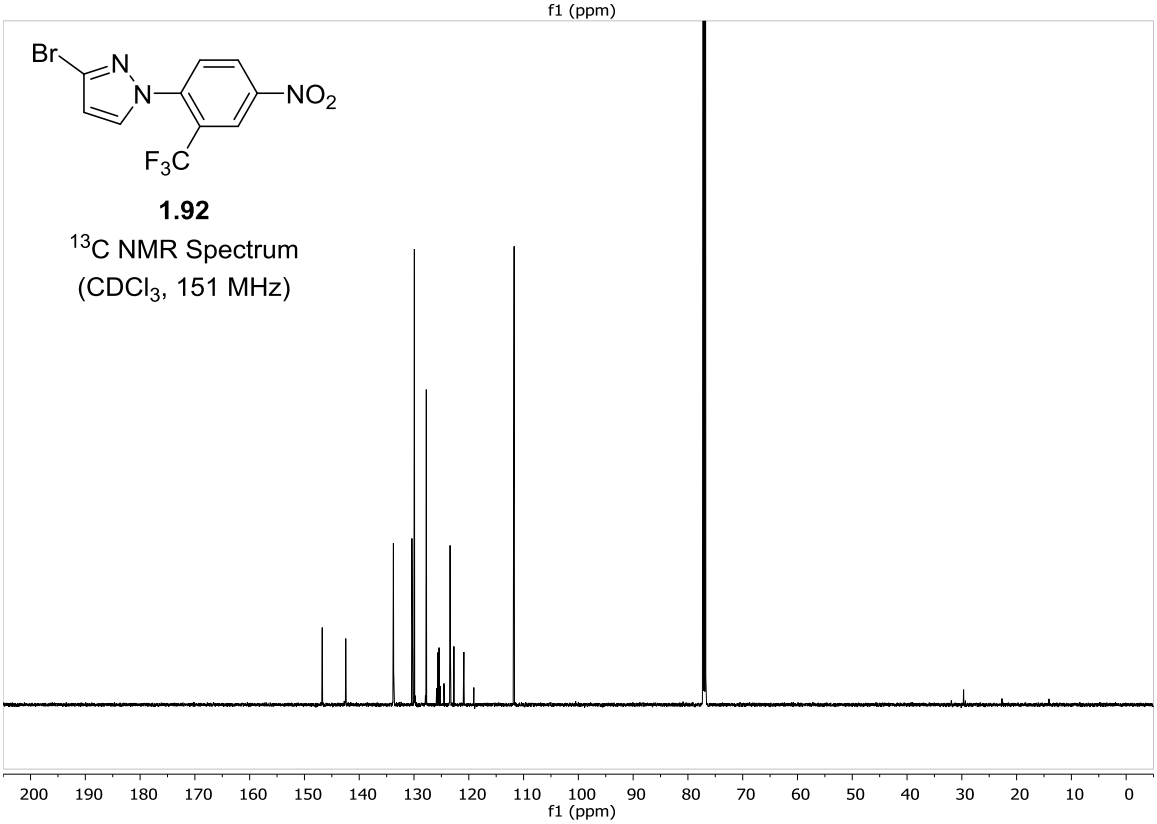
Spectra **1.14**: Compound **1.90**: ^{1}H and ^{13}C NMR



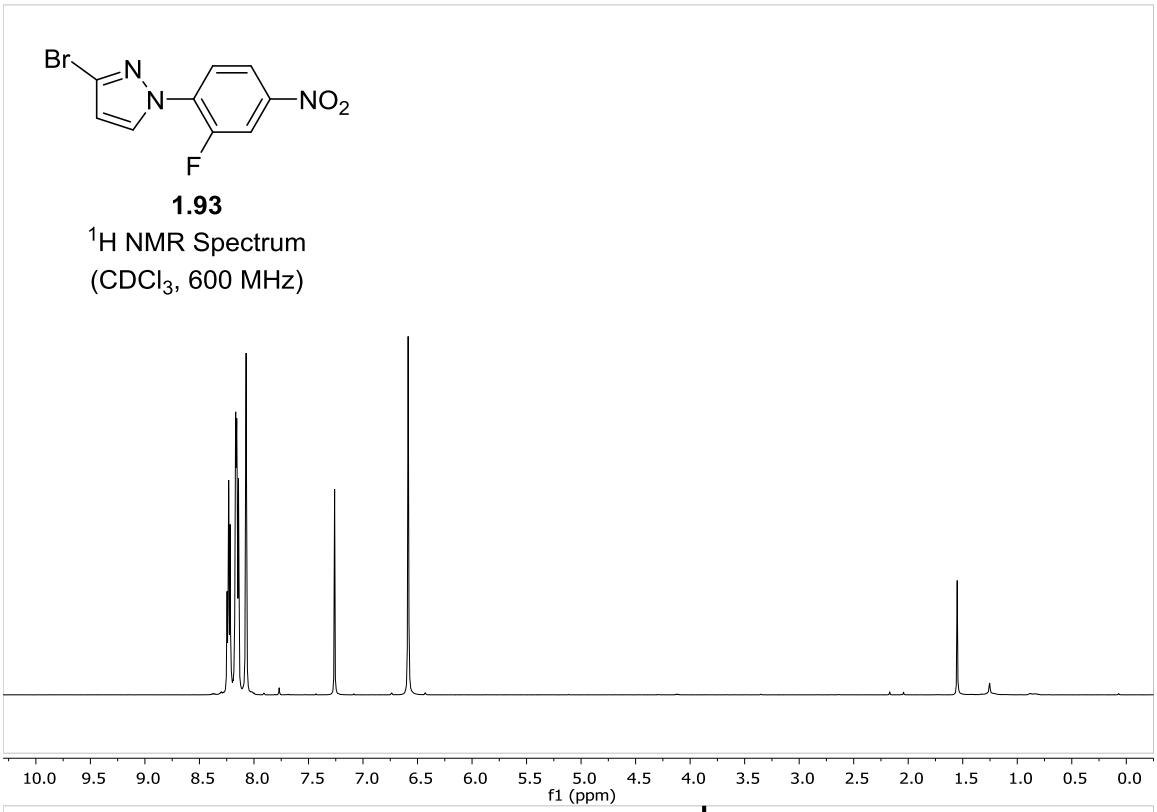


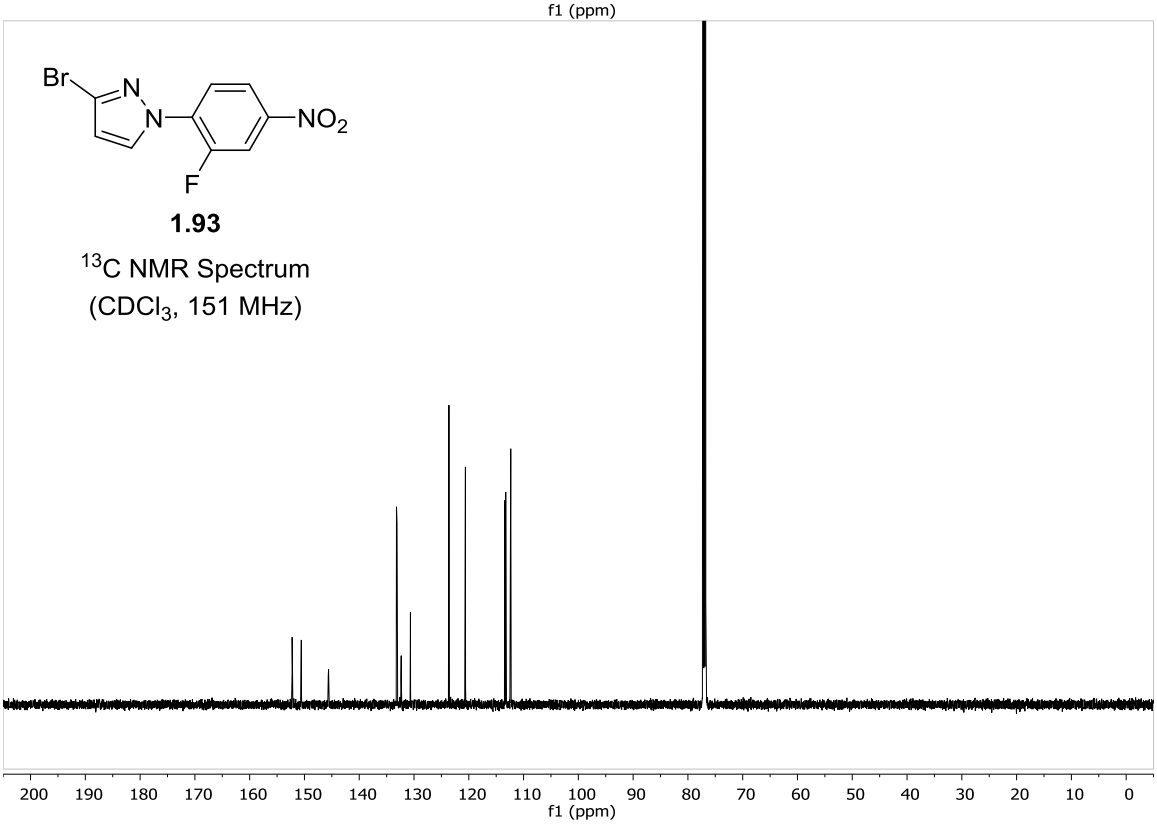
Spectra **1.15**: Compound **1.91**: ^{1}H and ^{13}C NMR



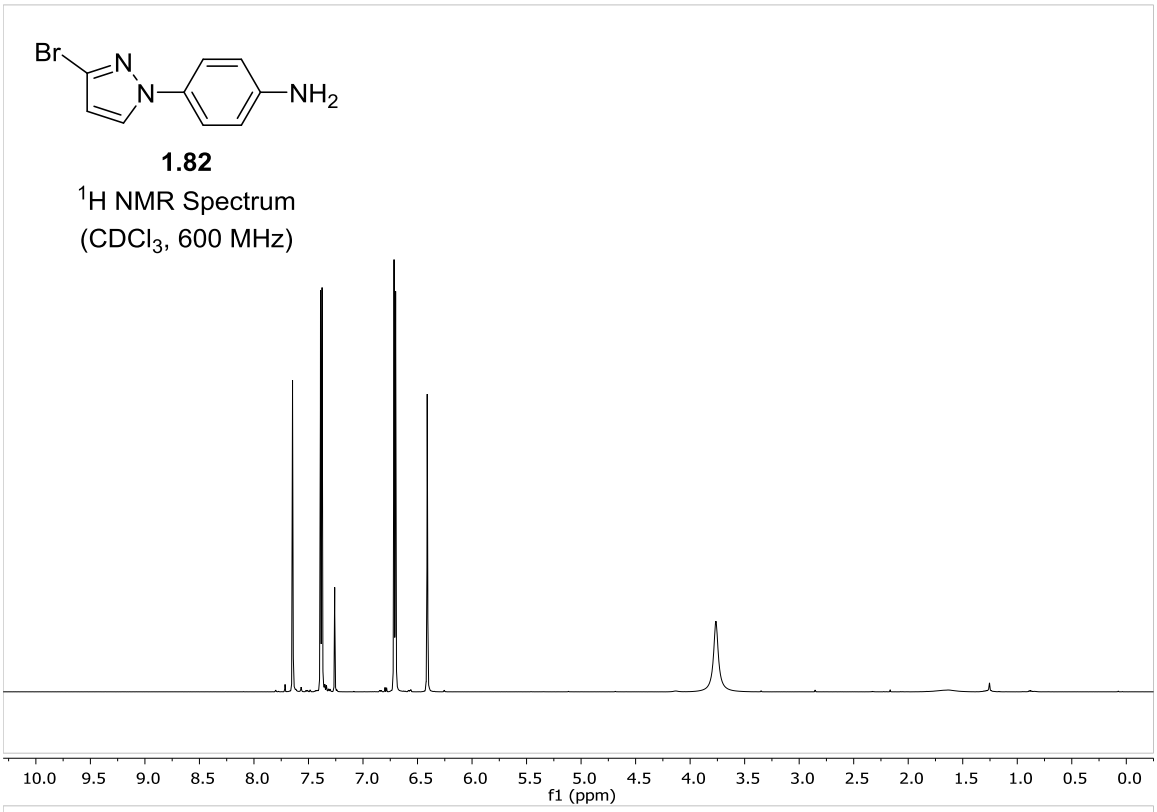


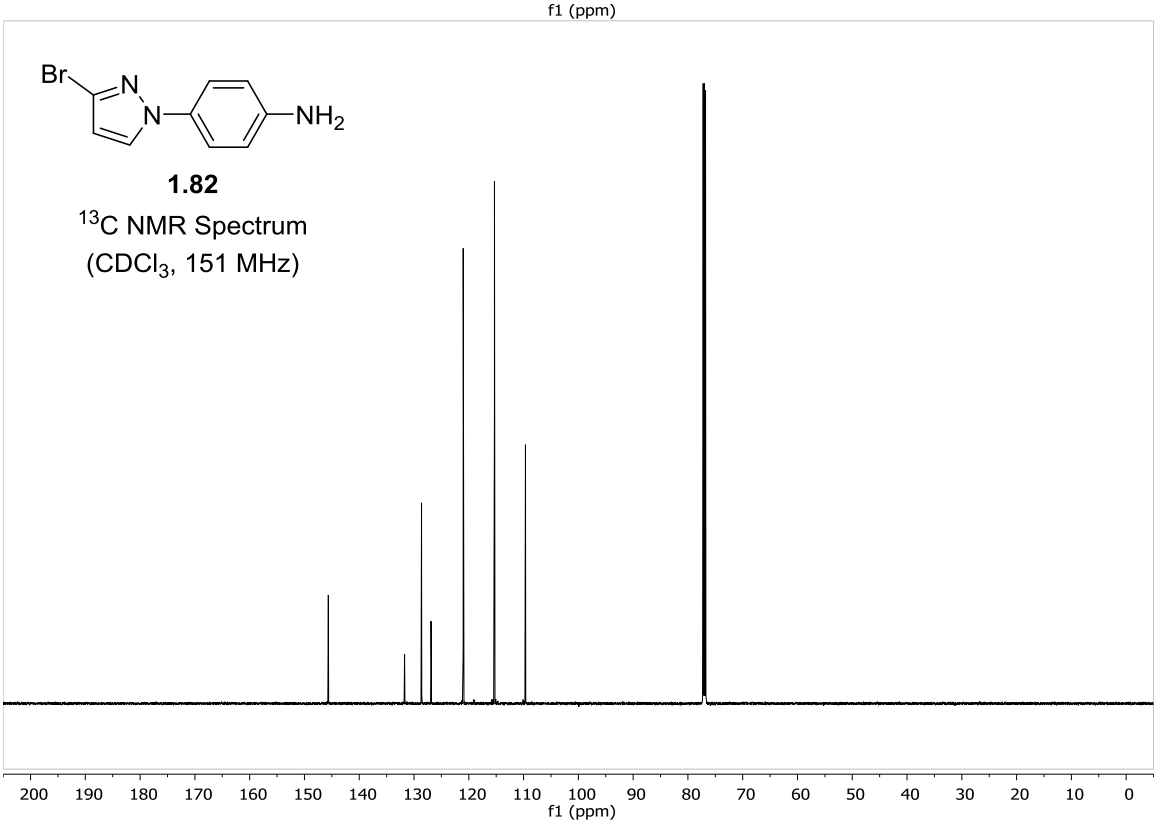
Spectra **1.16**: Compound **1.92**: ^{1}H and ^{13}C NMR



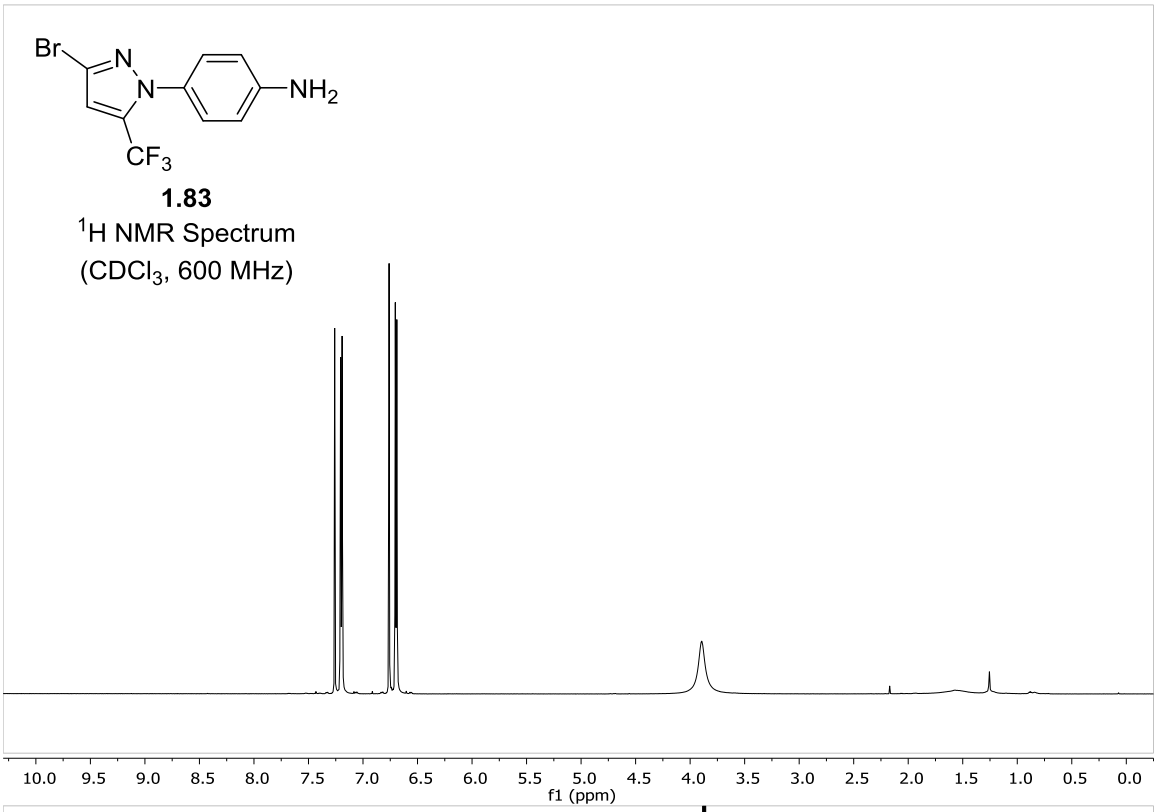


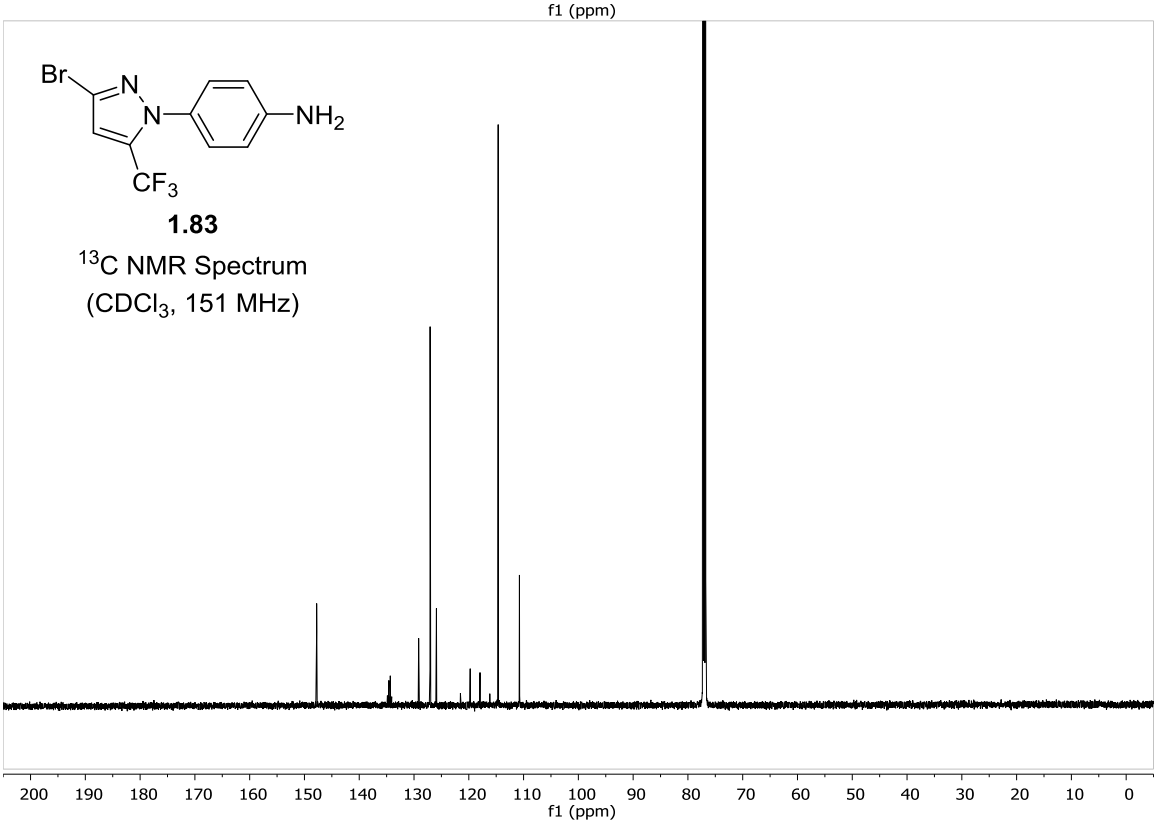
Spectra **1.17**: Compound **1.93**: ^{1}H and ^{13}C NMR



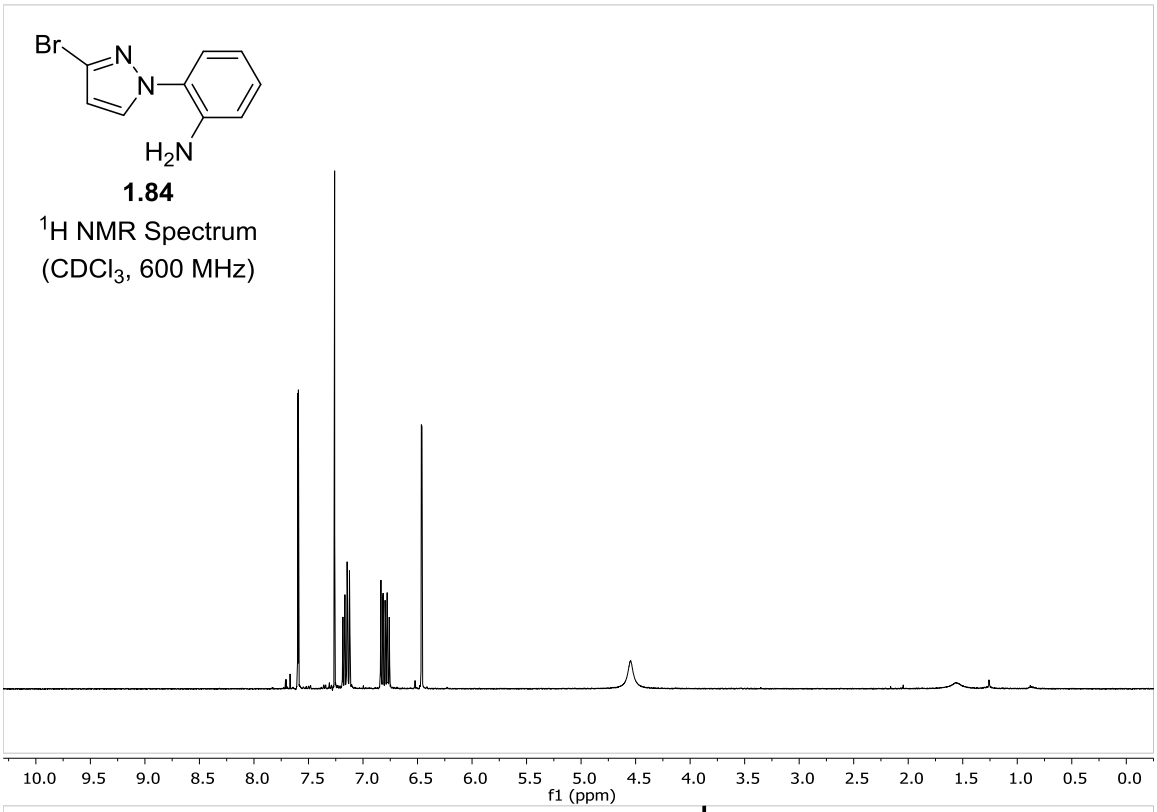


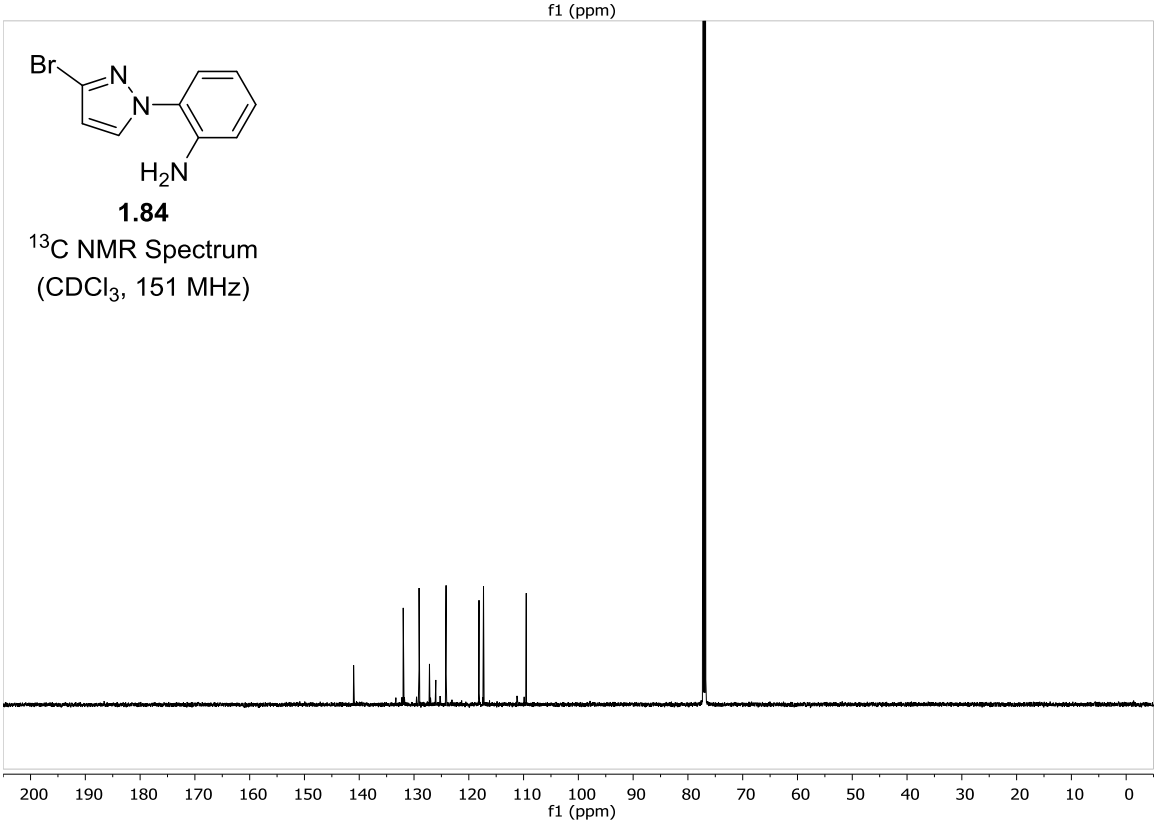
Spectra **1.18**: Compound **1.82**: ^{1}H and ^{13}C NMR



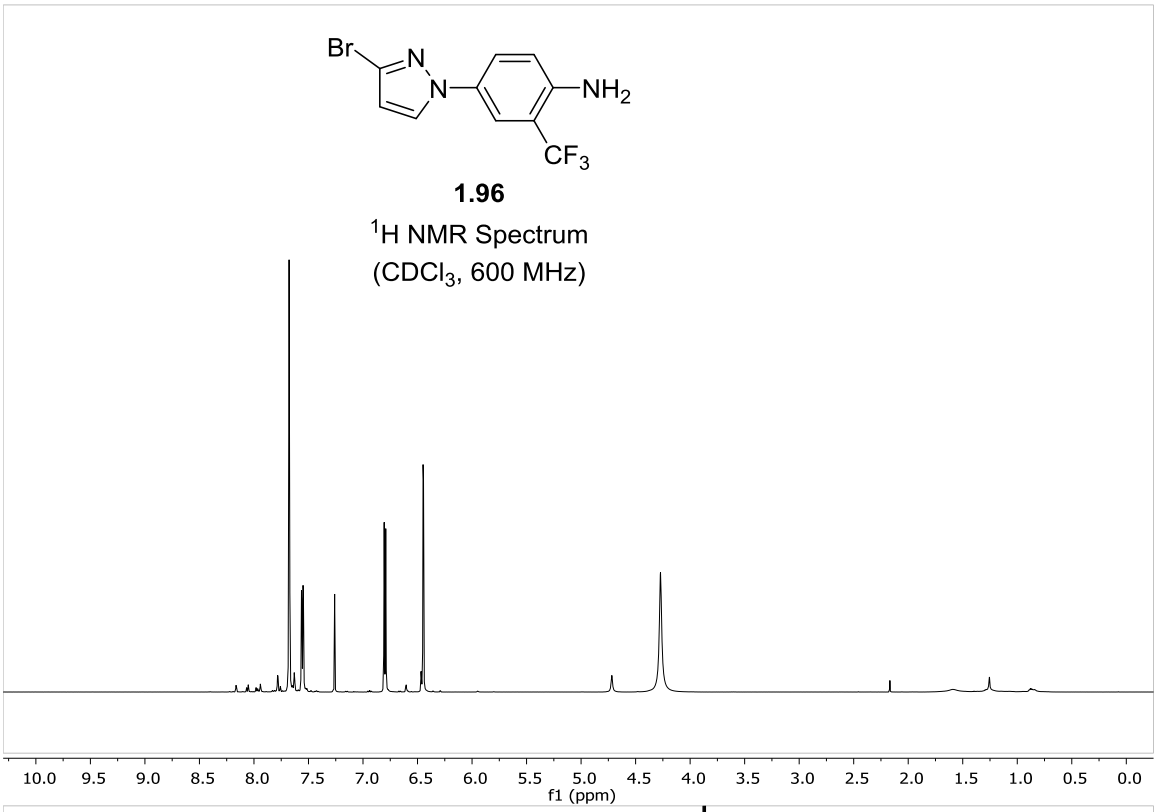


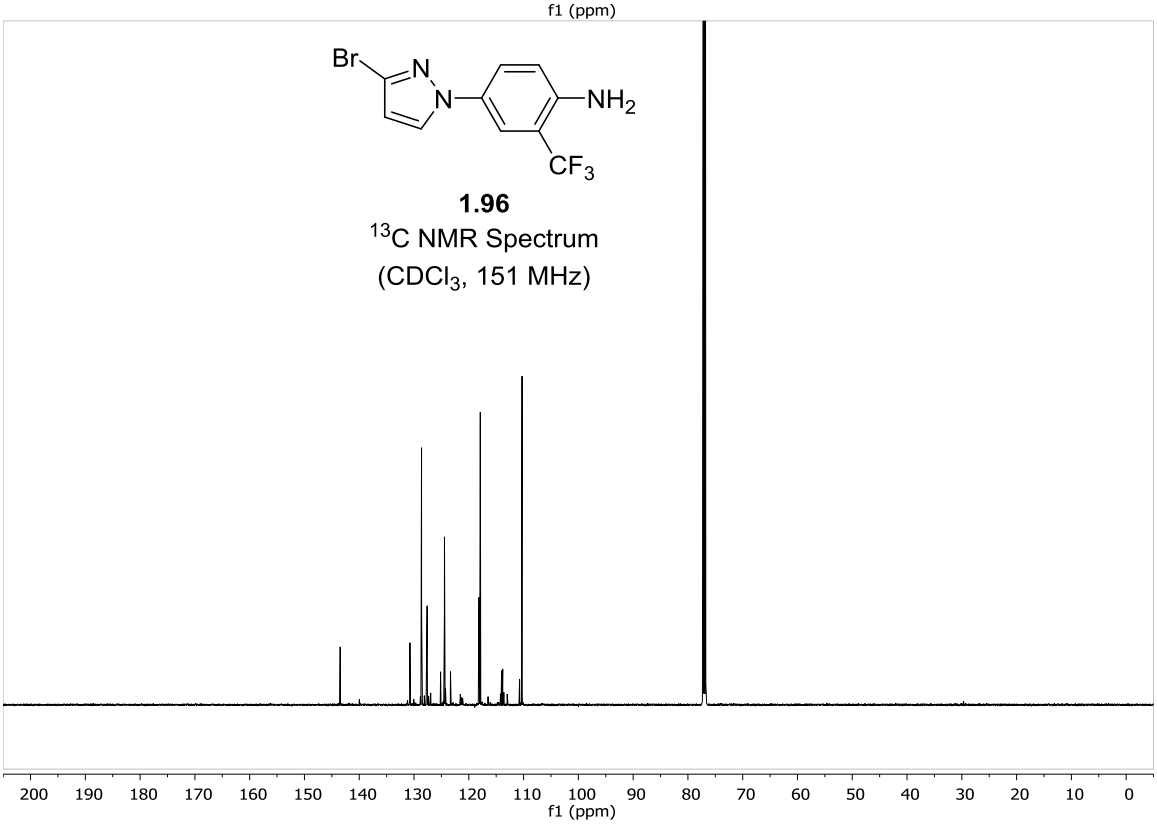
Spectra **1.19**: Compound **1.83**: ^{1}H and ^{13}C NMR



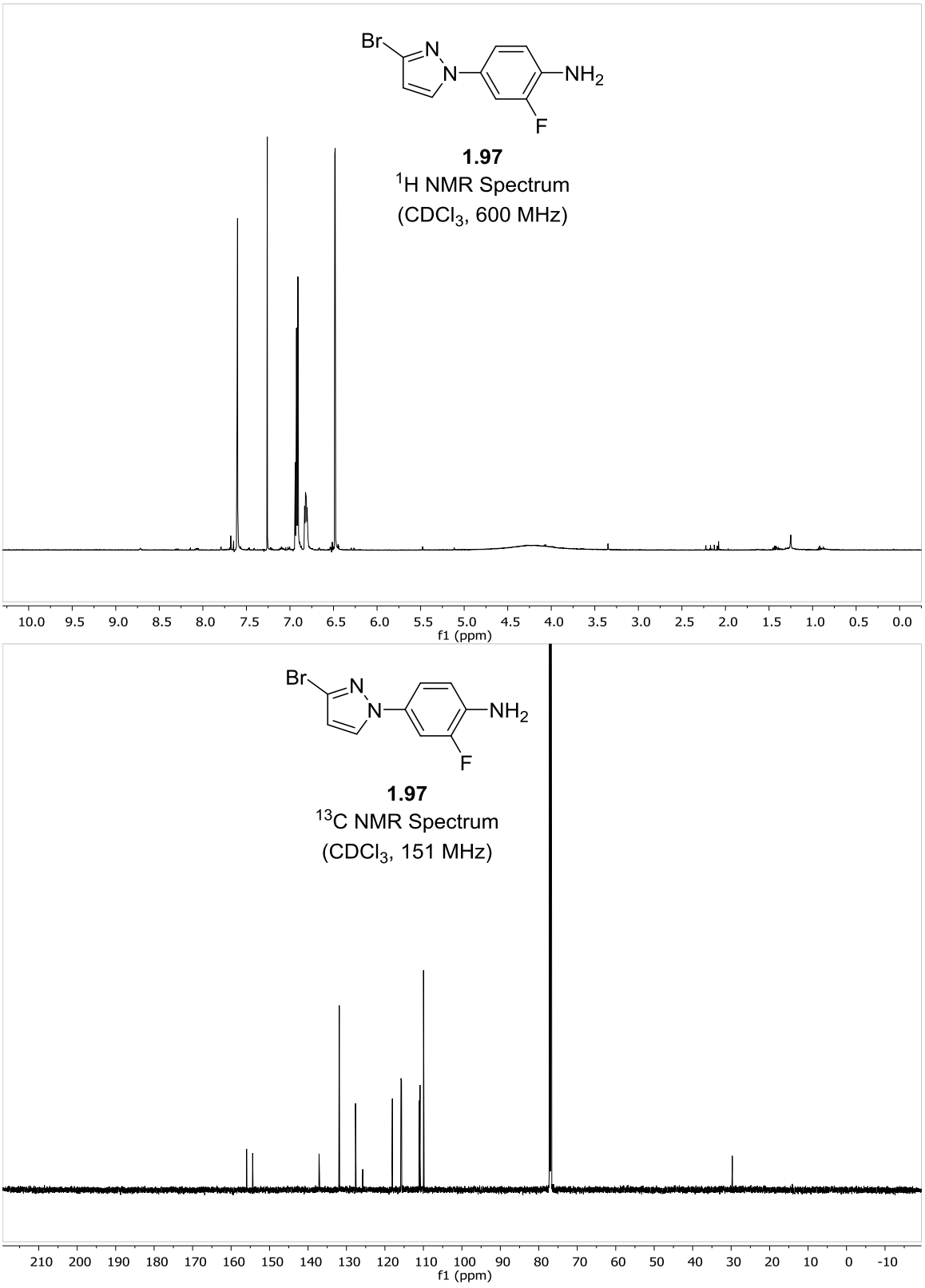


Spectra **1.20**: Compound **1.84**: ^{1}H and ^{13}C NMR

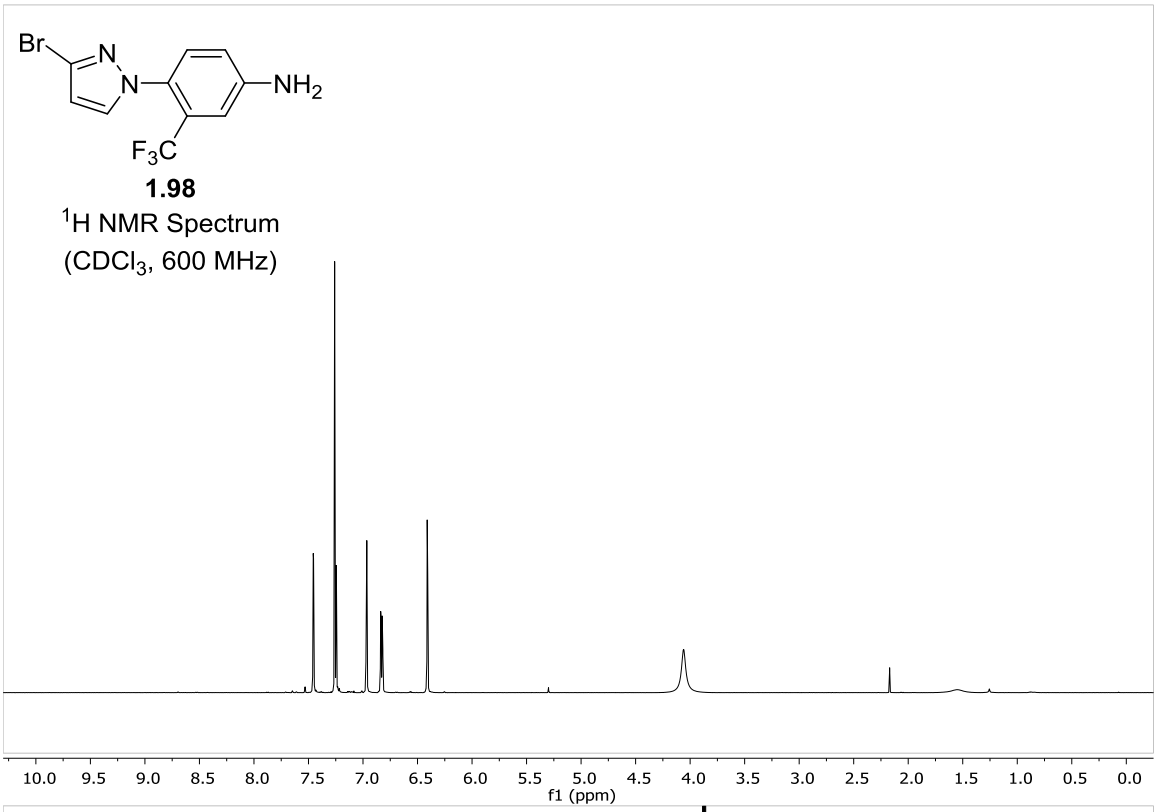


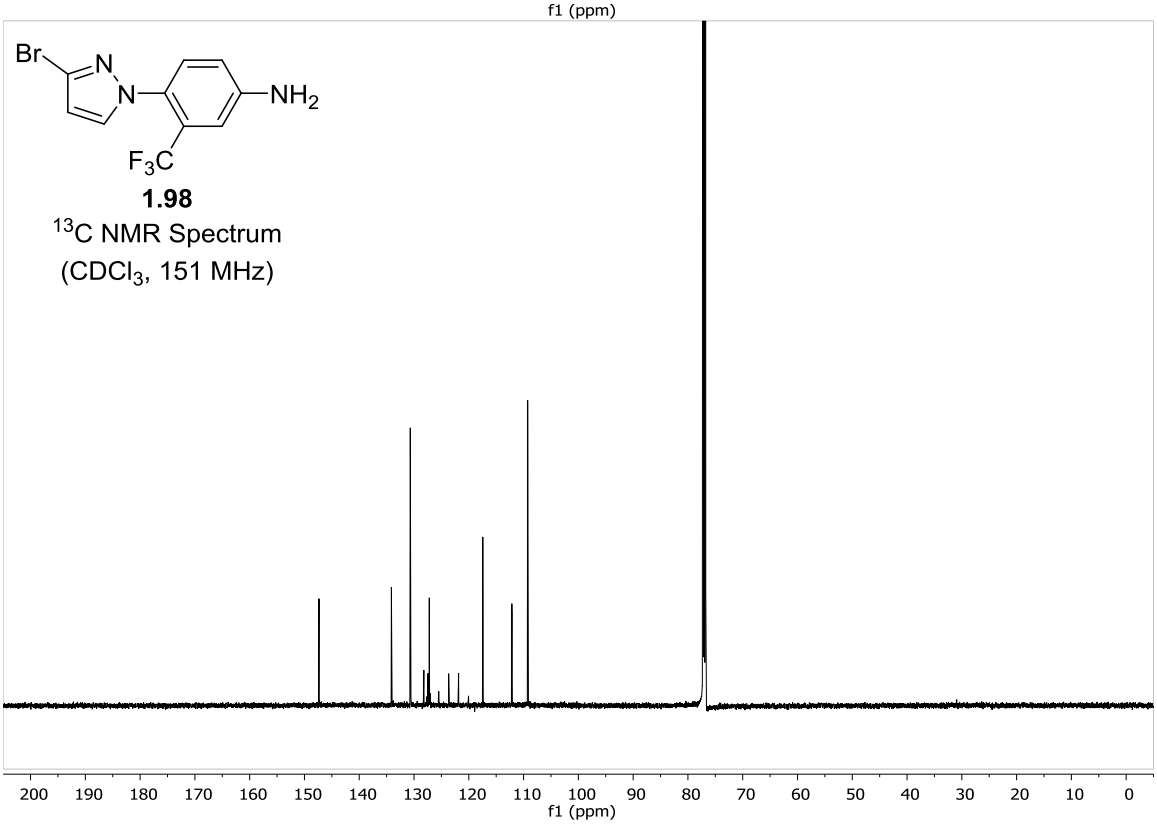


Spectra **1.21**: Compound **1.96**: ^{1}H and ^{13}C NMR

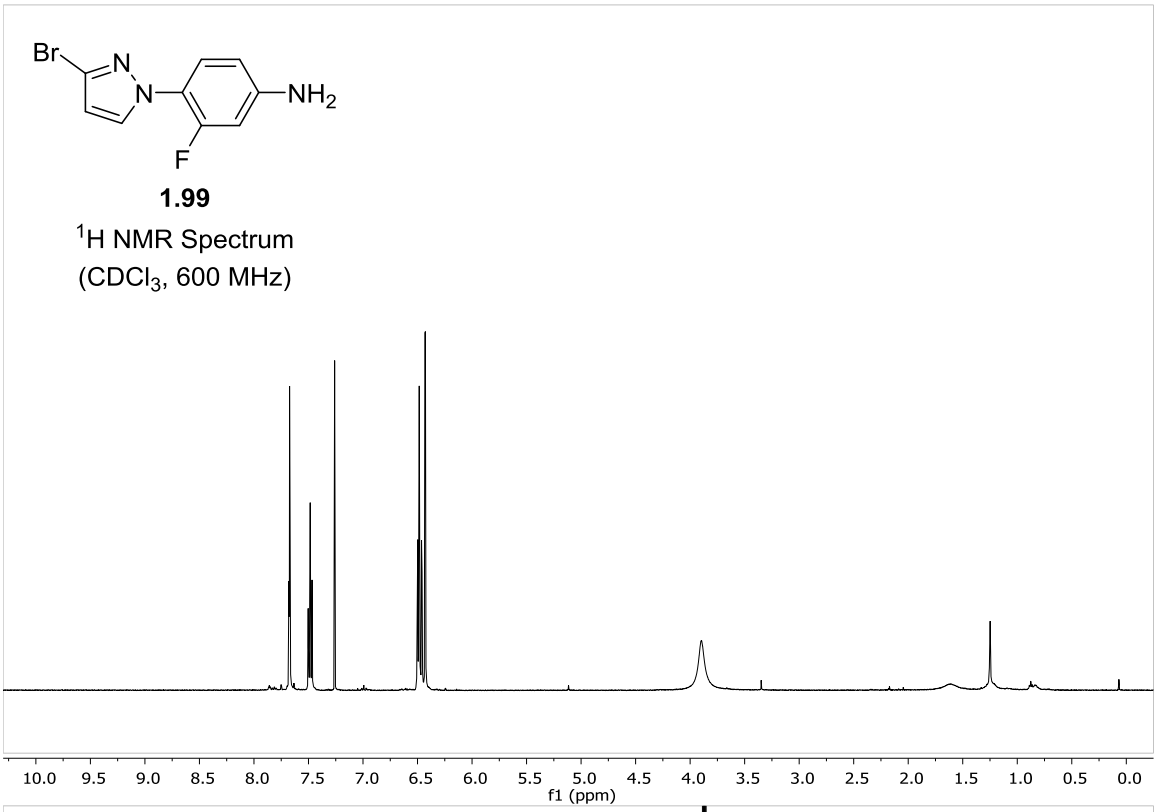


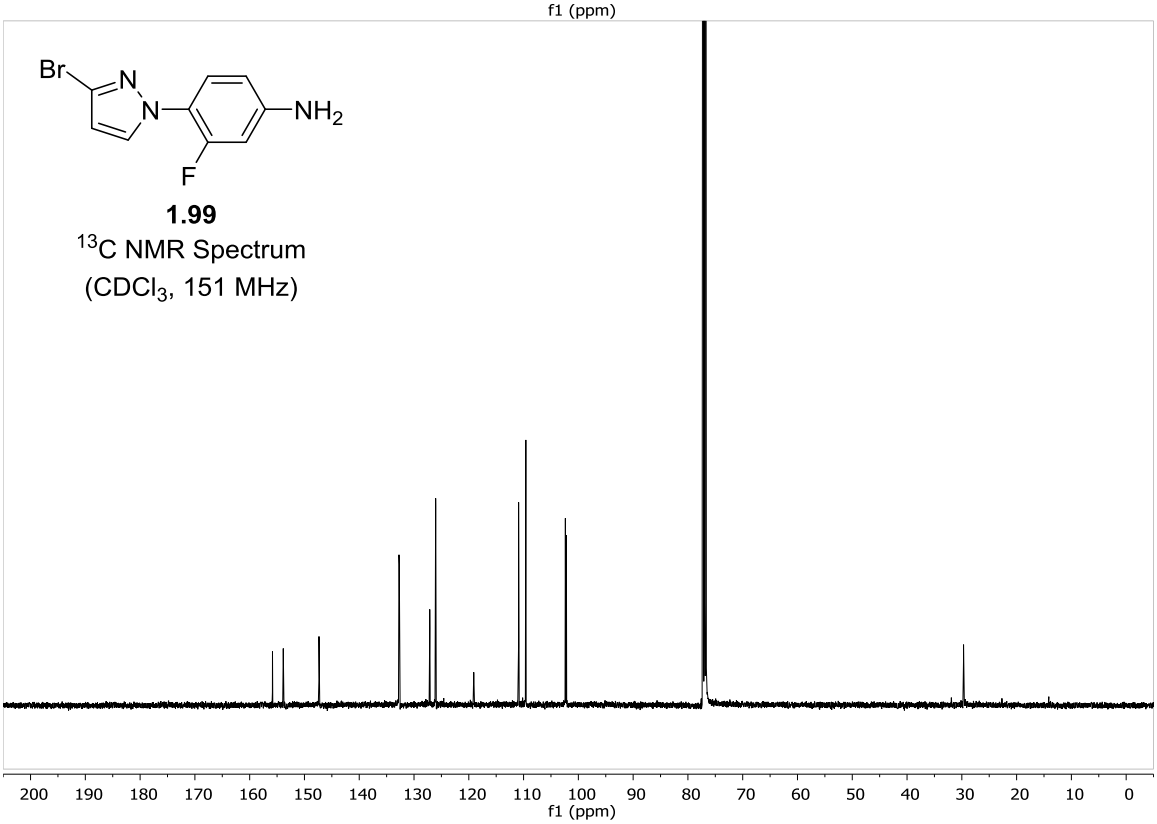
Spectra **1.22**: Compound **1.97**: ^{1}H and ^{13}C NMR



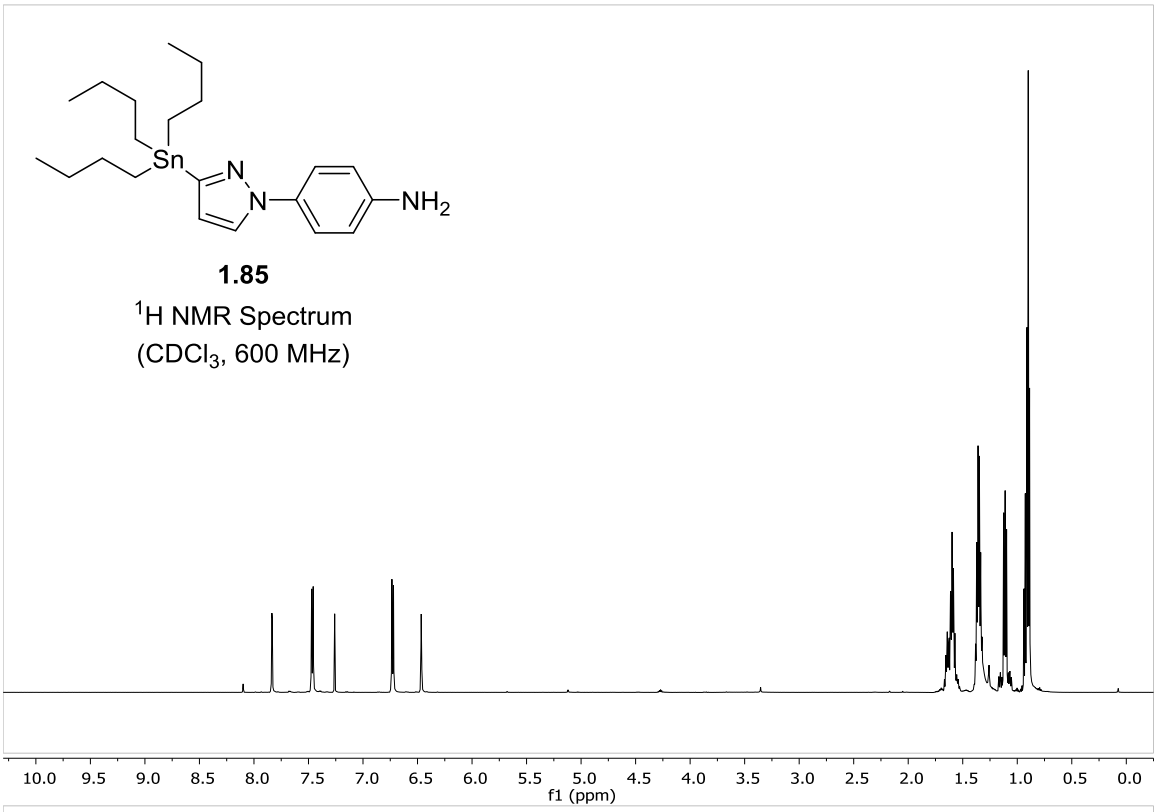


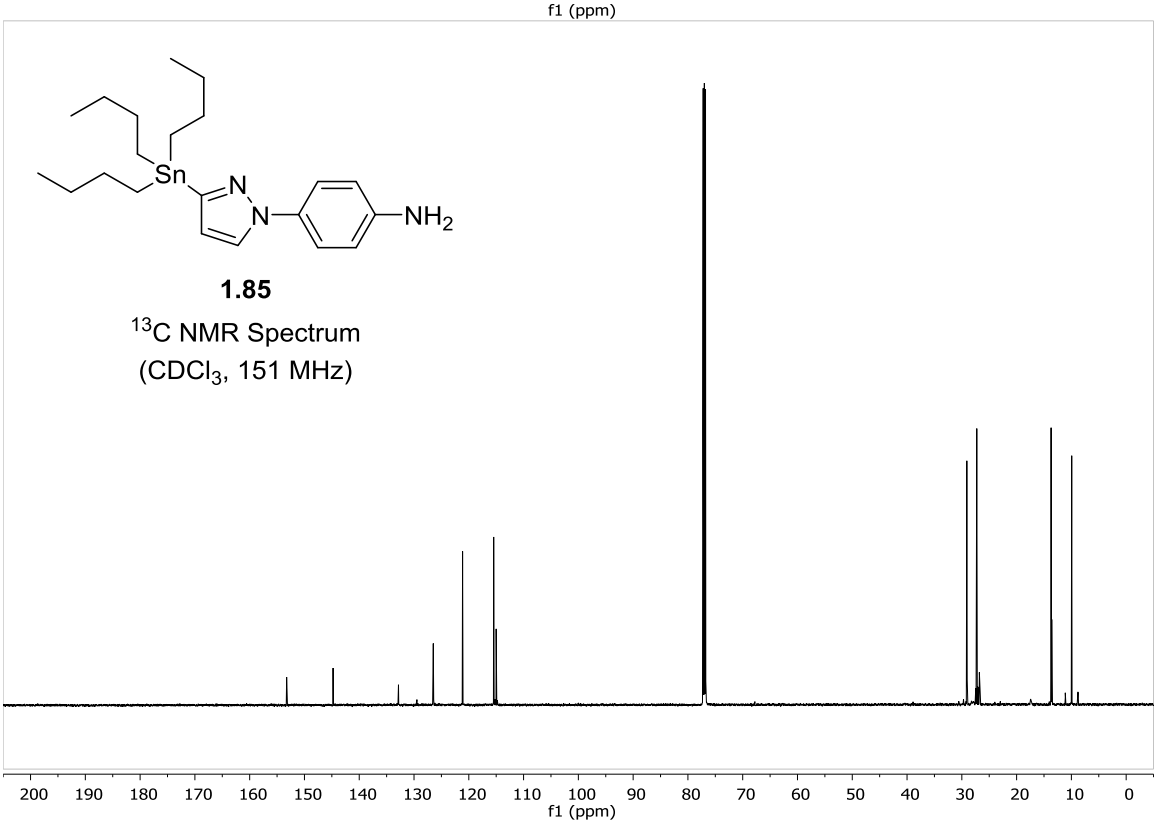
Spectra **1.23**: Compound **1.98**: ^{1}H and ^{13}C NMR



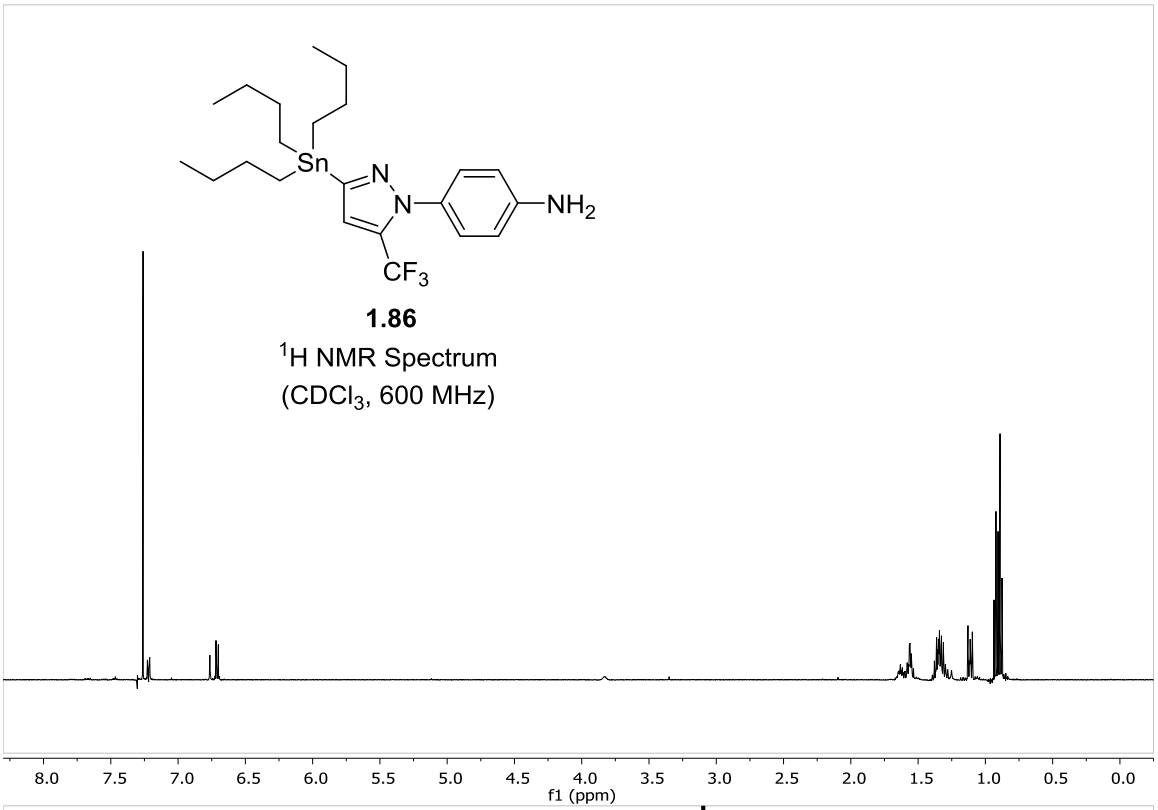


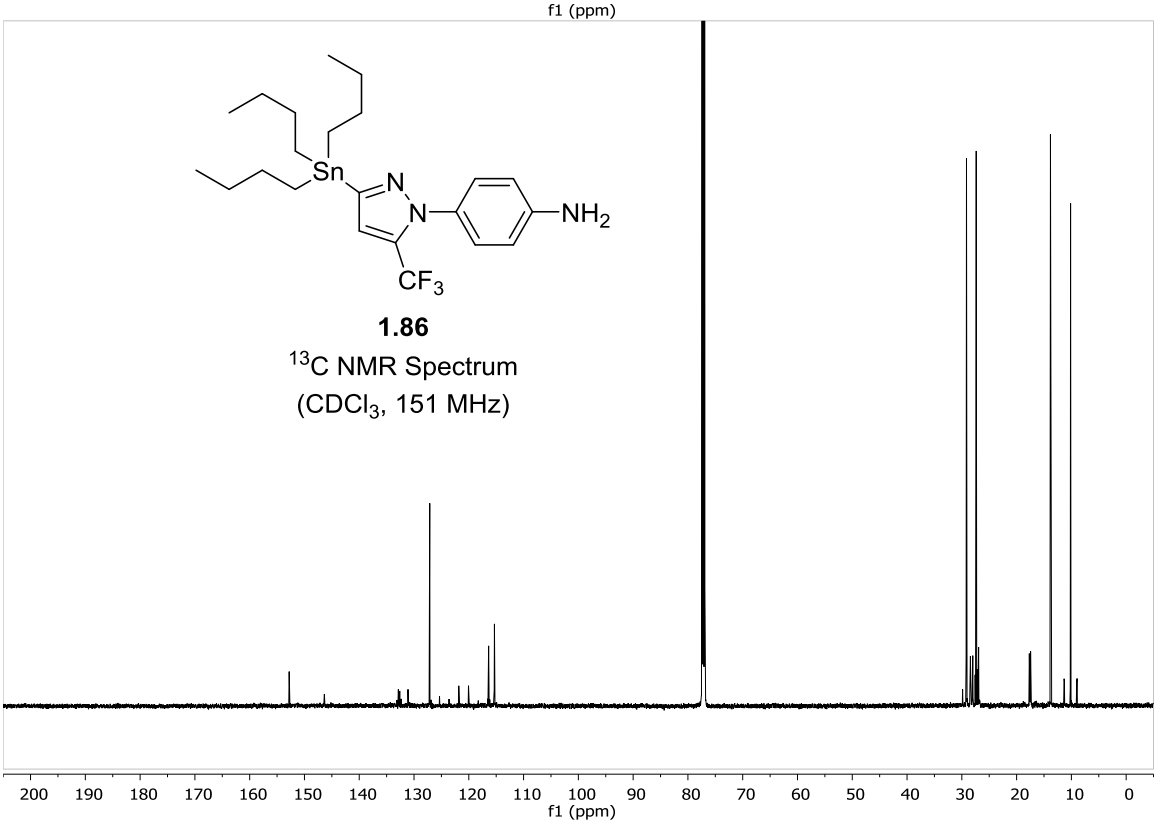
Spectra **1.24**: Compound **1.99**: ^{1}H and ^{13}C NMR



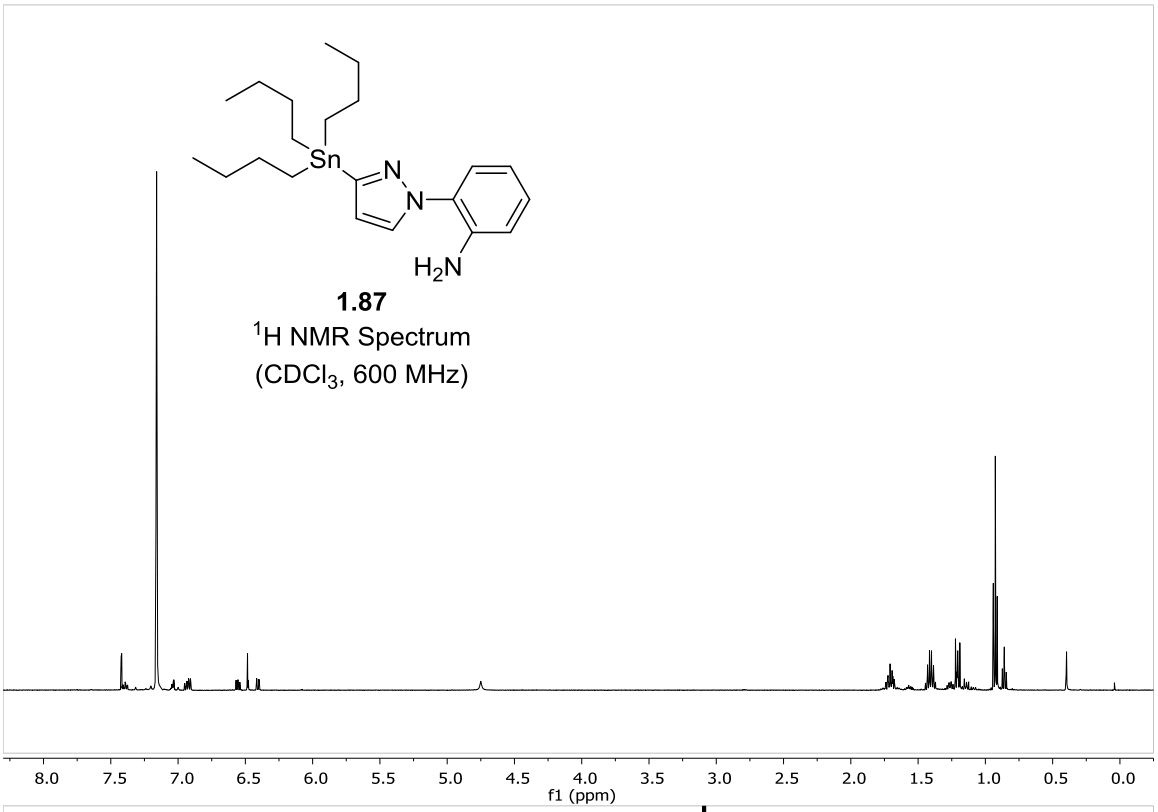


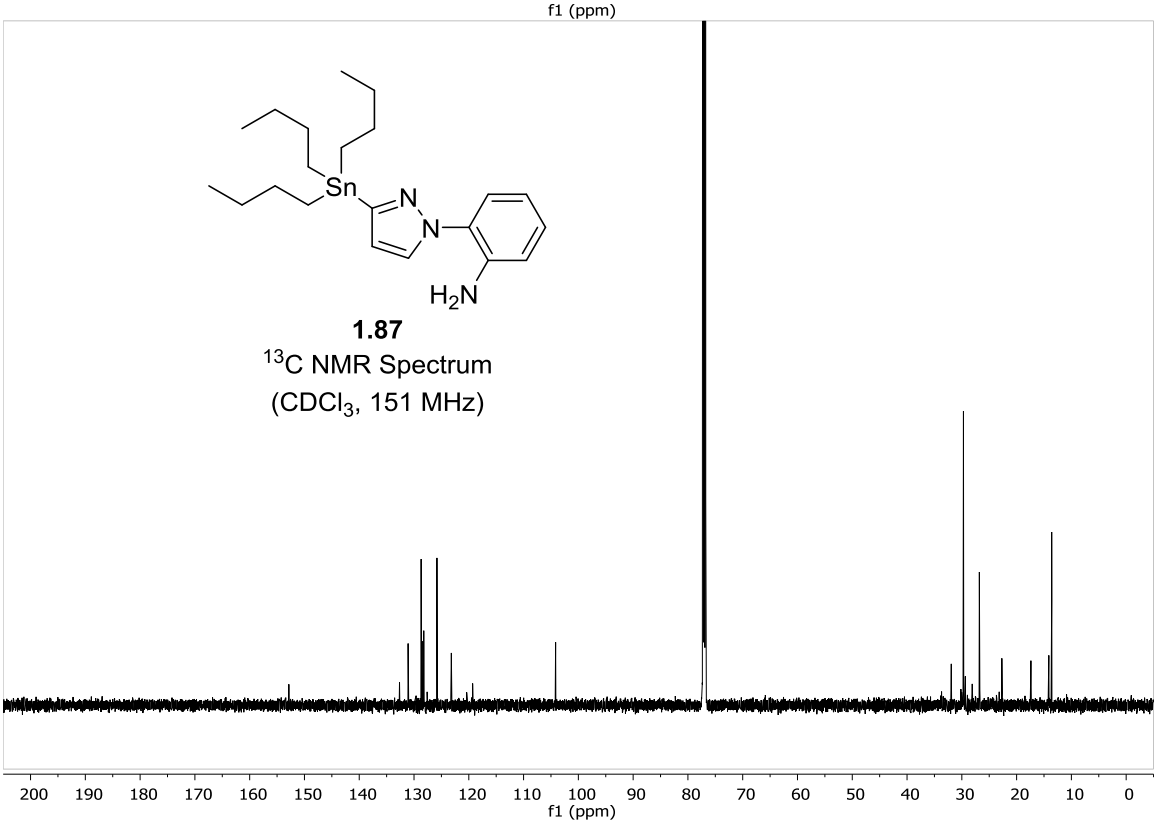
Spectra **1.25**: Compound **1.85**: ^{1}H and ^{13}C NMR



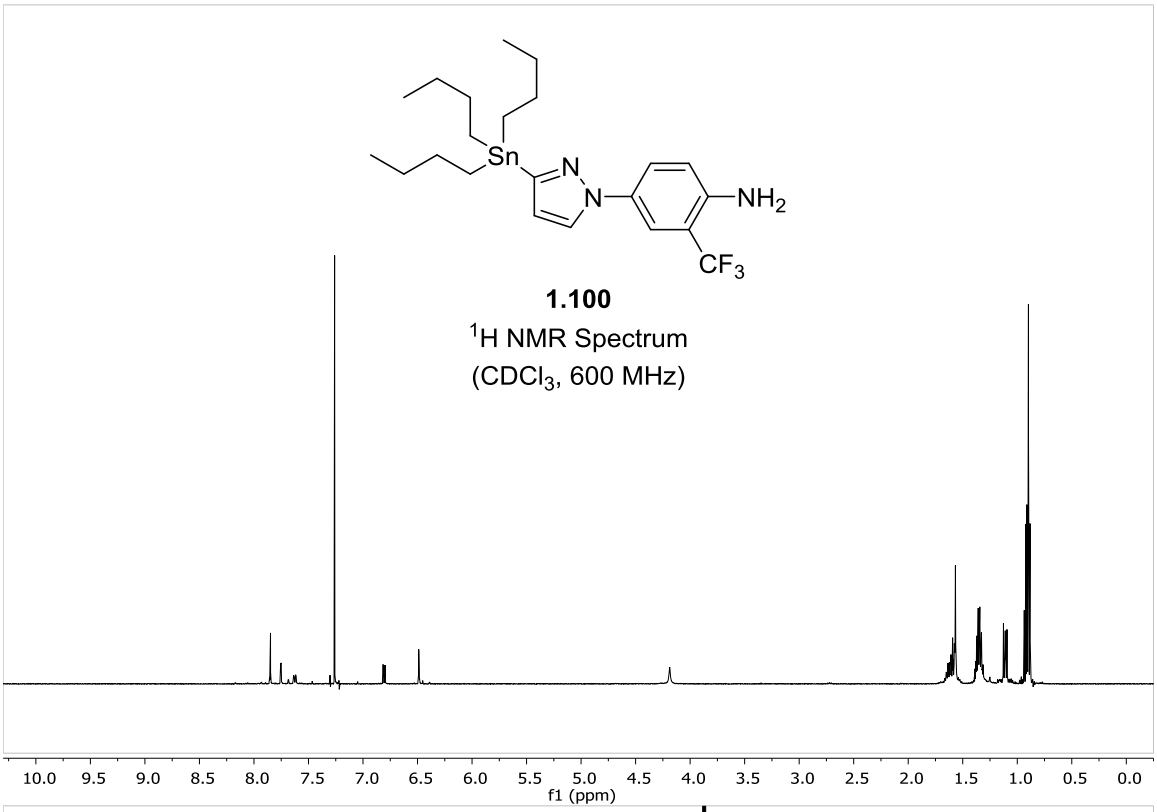


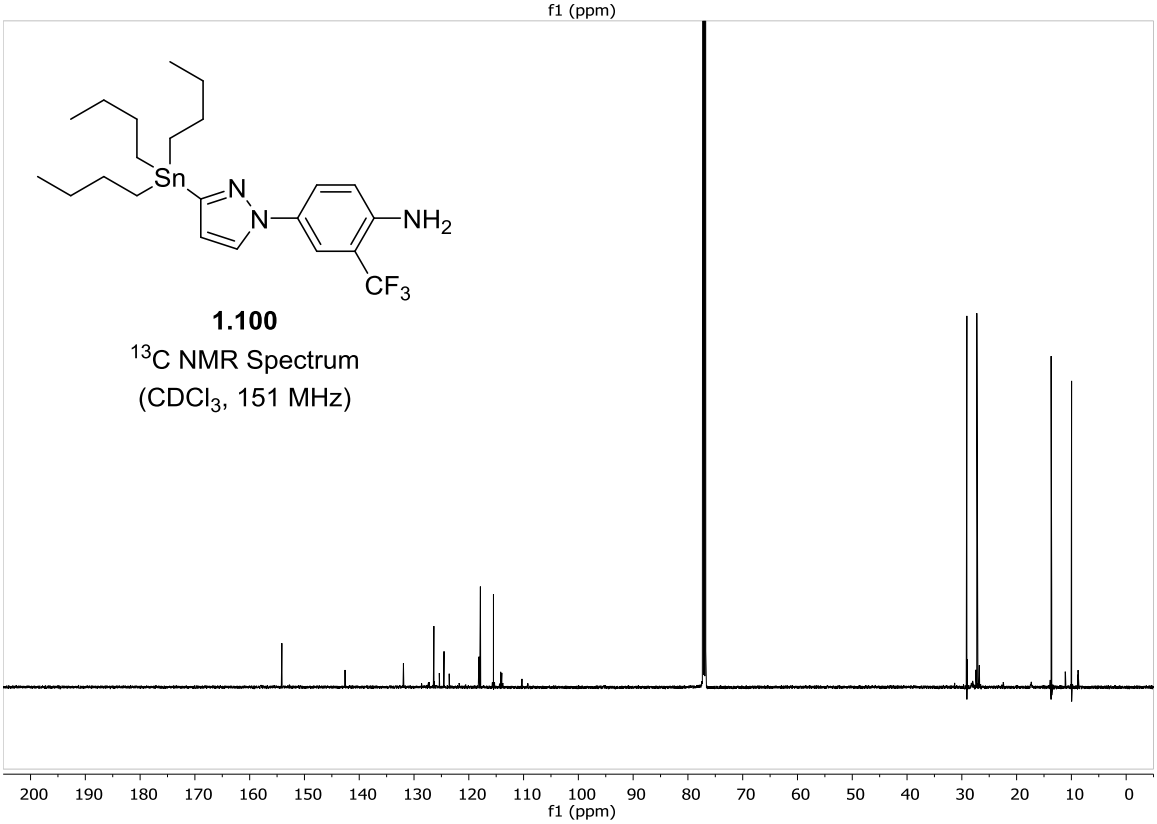
Spectra **1.26**: Compound **1.86**: ^{1}H and ^{13}C NMR



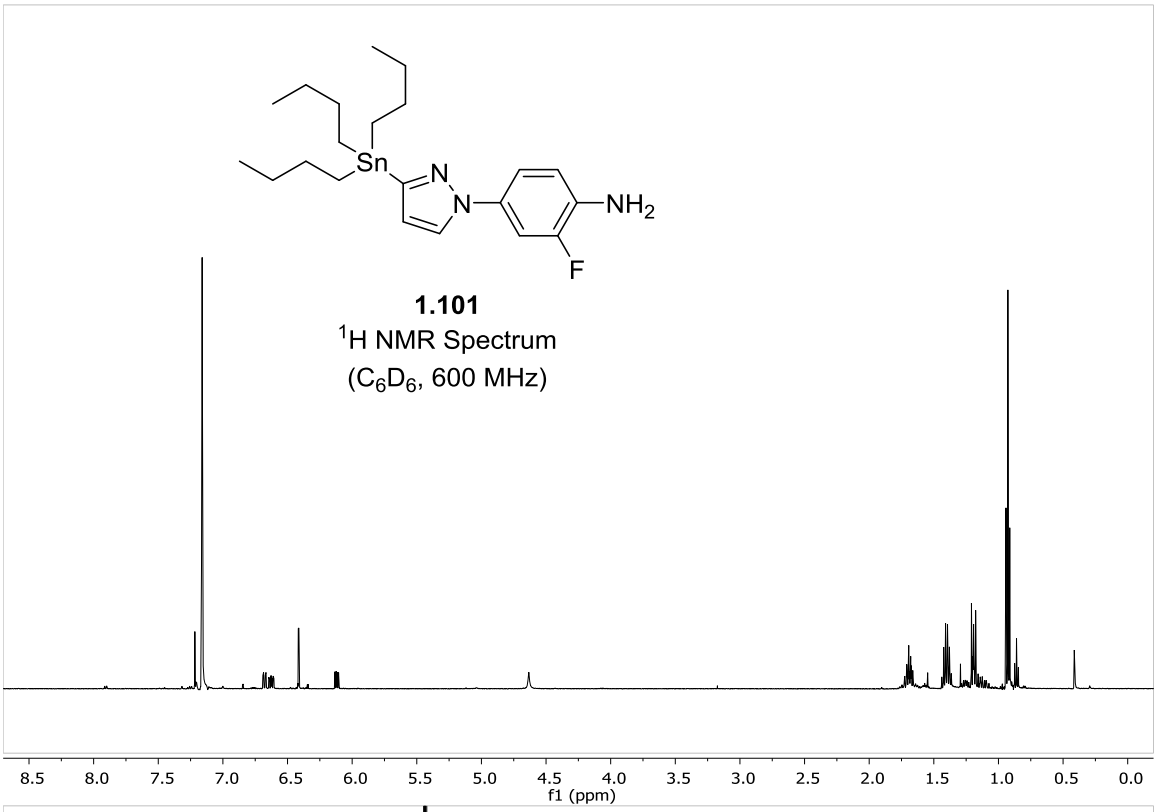


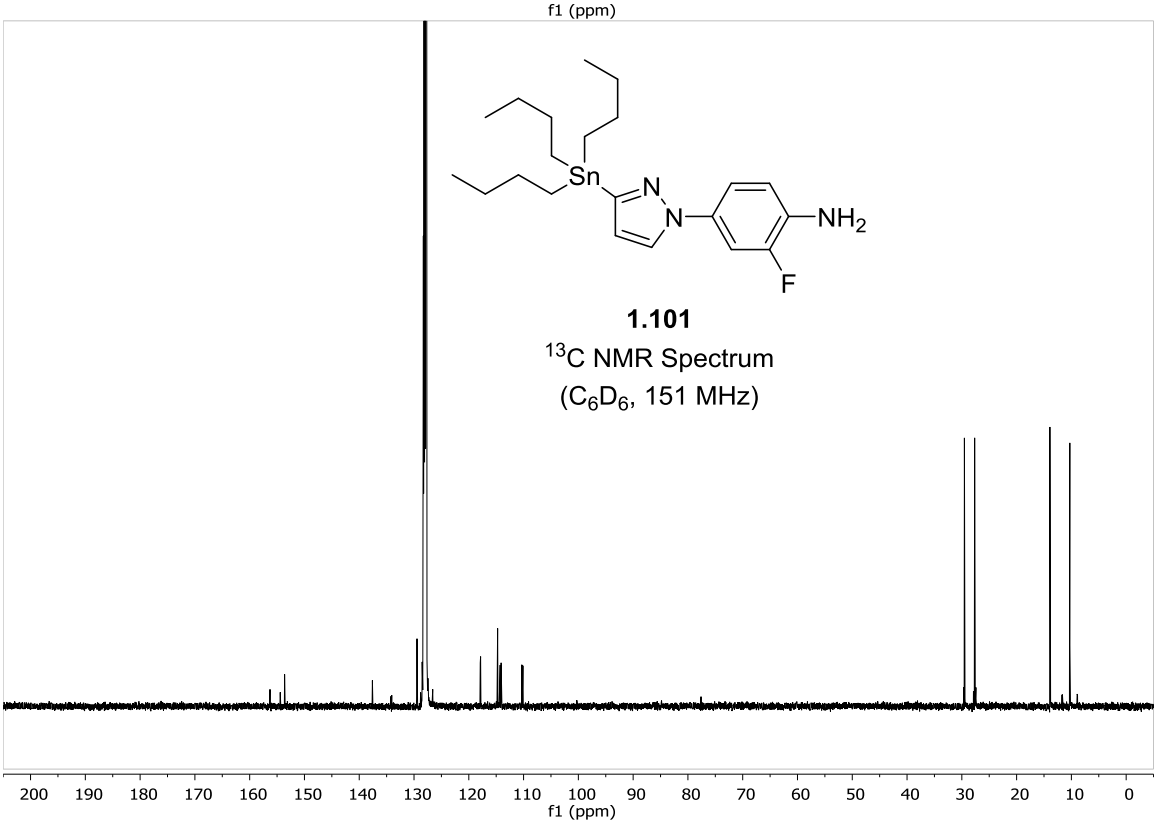
Spectra **1.27**: Compound **1.87**: ^{1}H and ^{13}C NMR



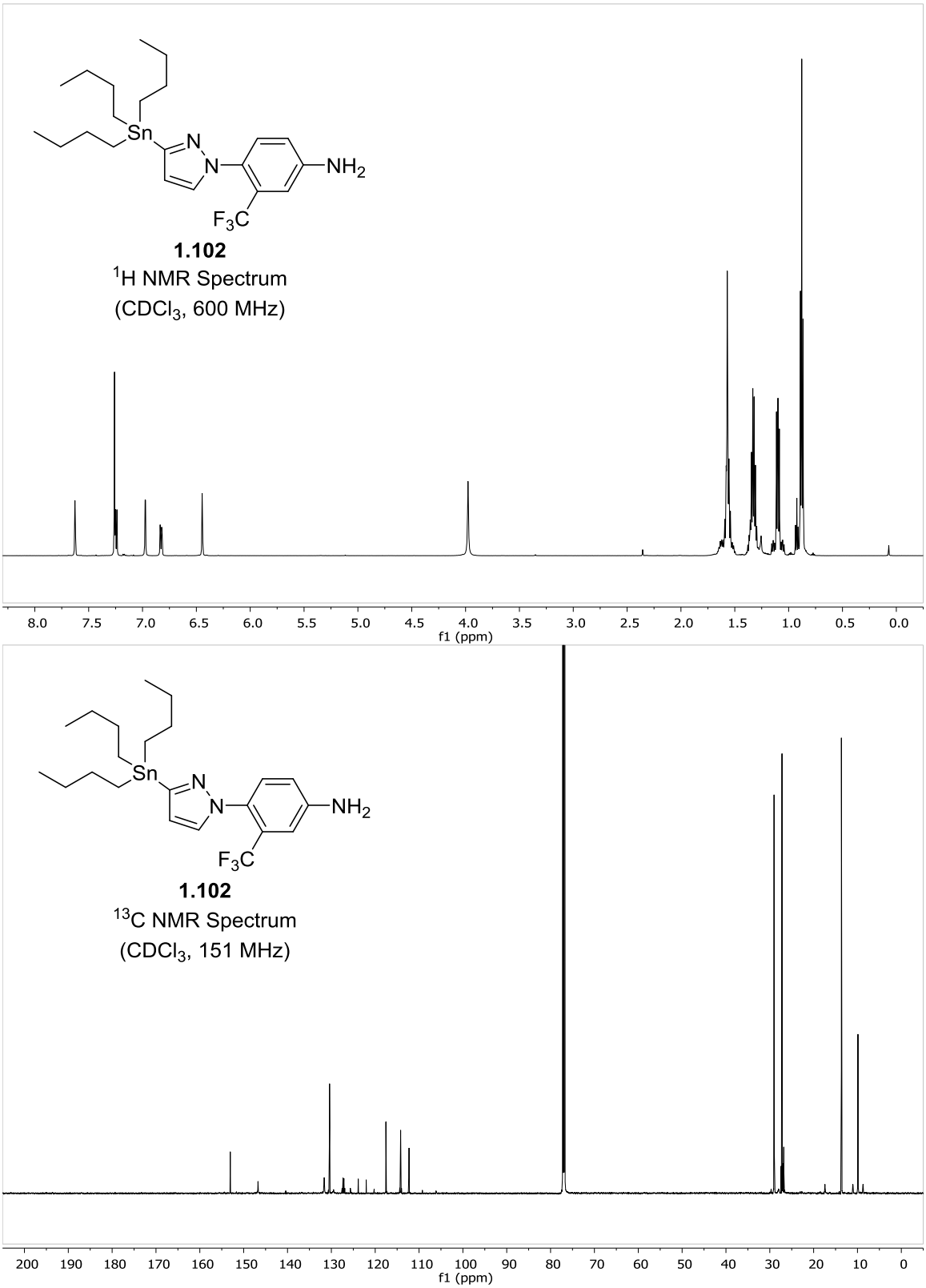


Spectra **1.28**: Compound **1.100**: ^{1}H and ^{13}C NMR

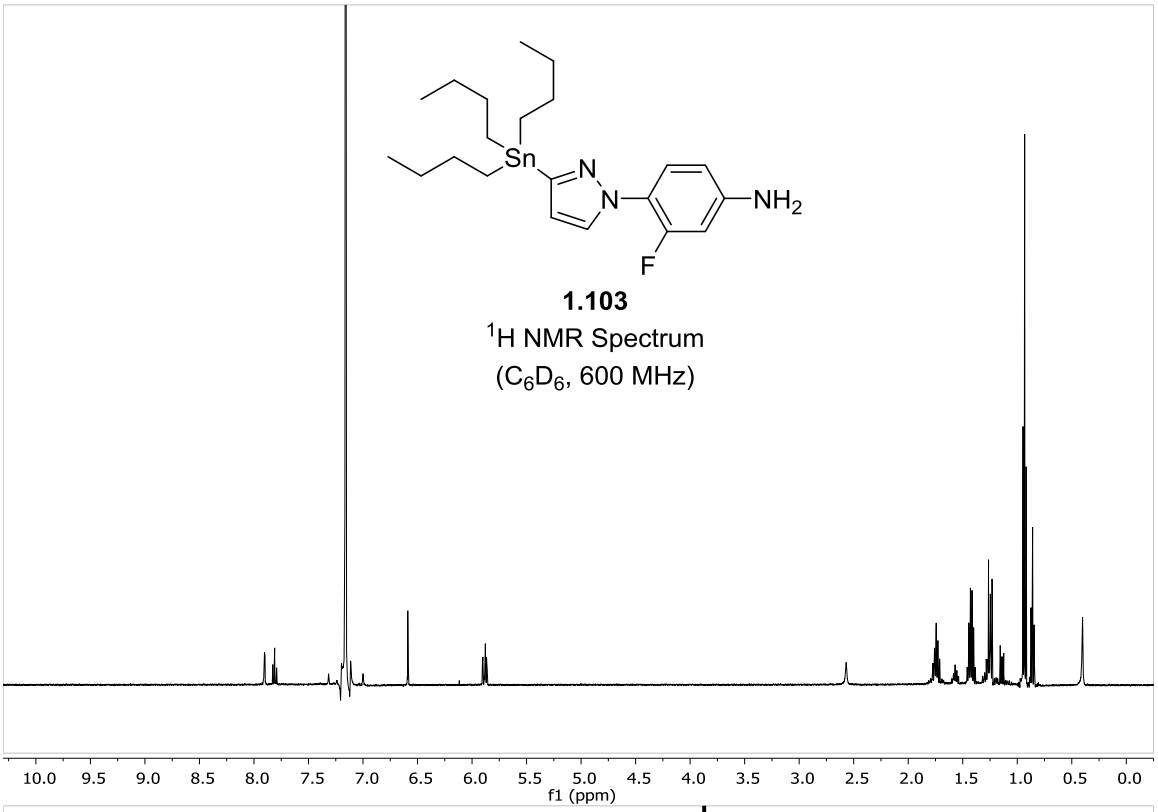


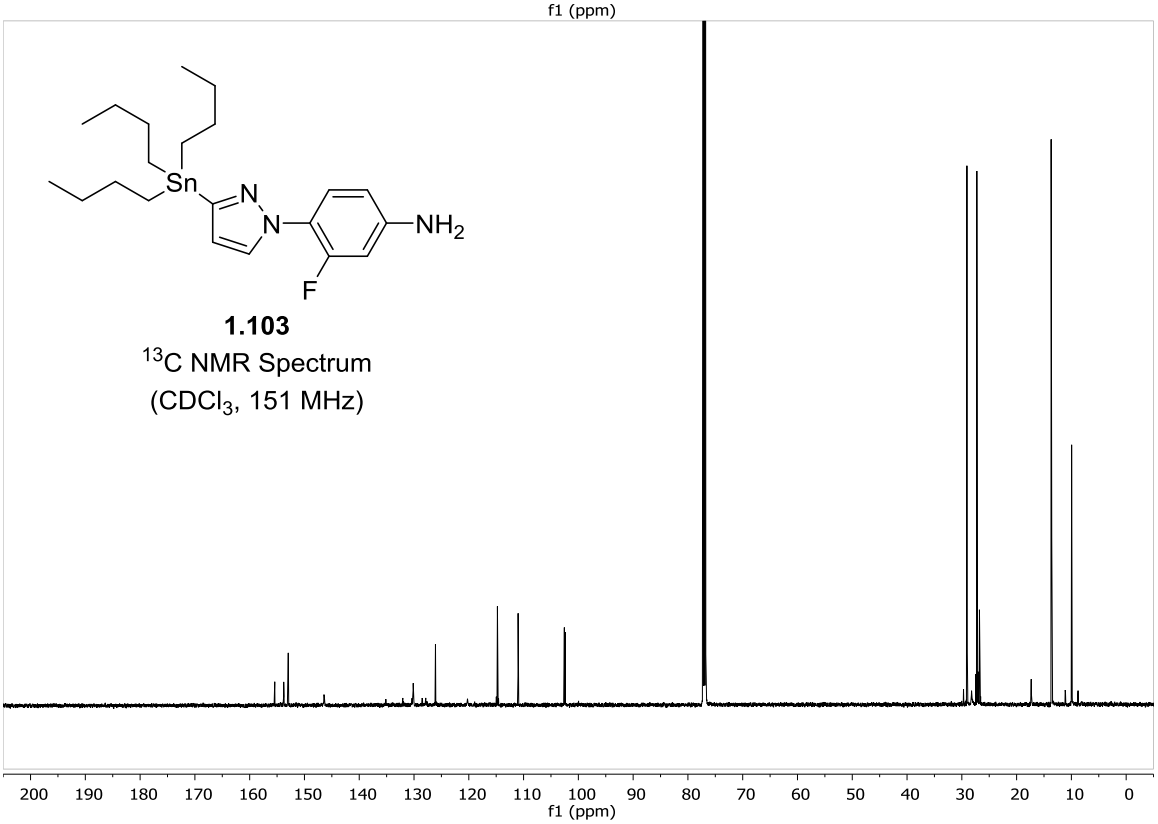


Spectra **1.29**: Compound **1.101**: ^{1}H and ^{13}C NMR

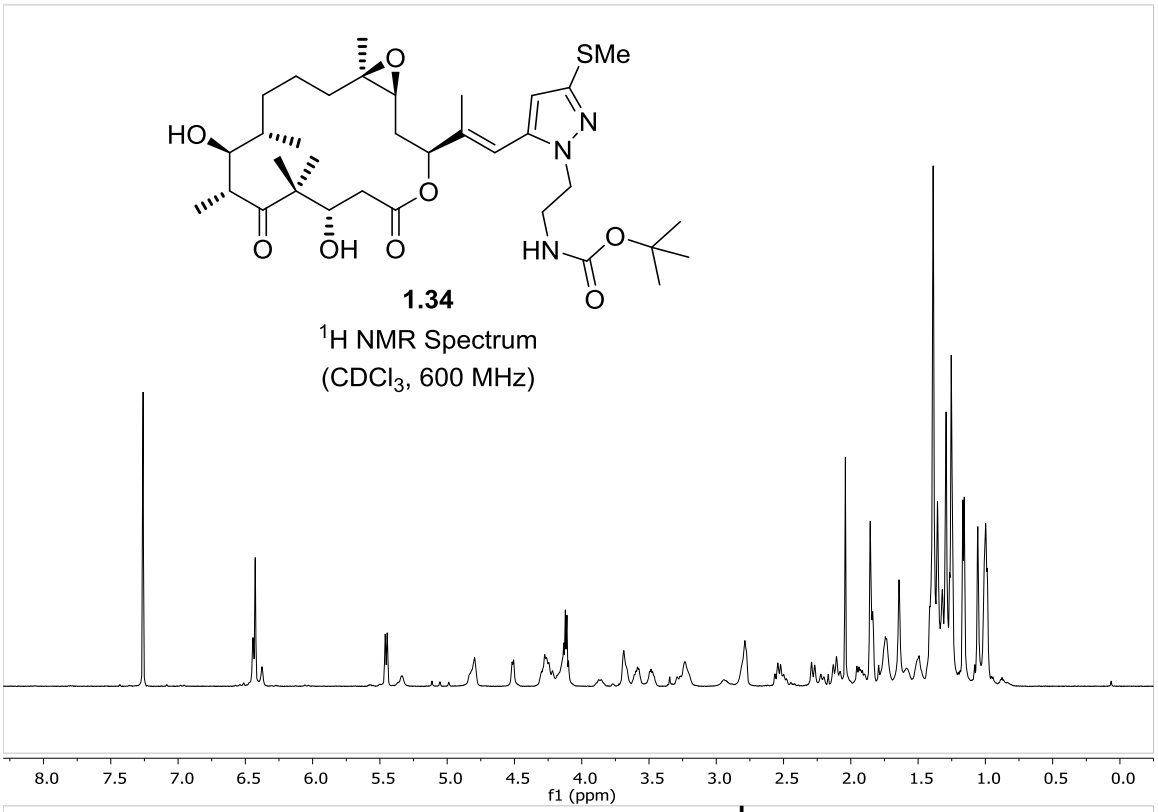


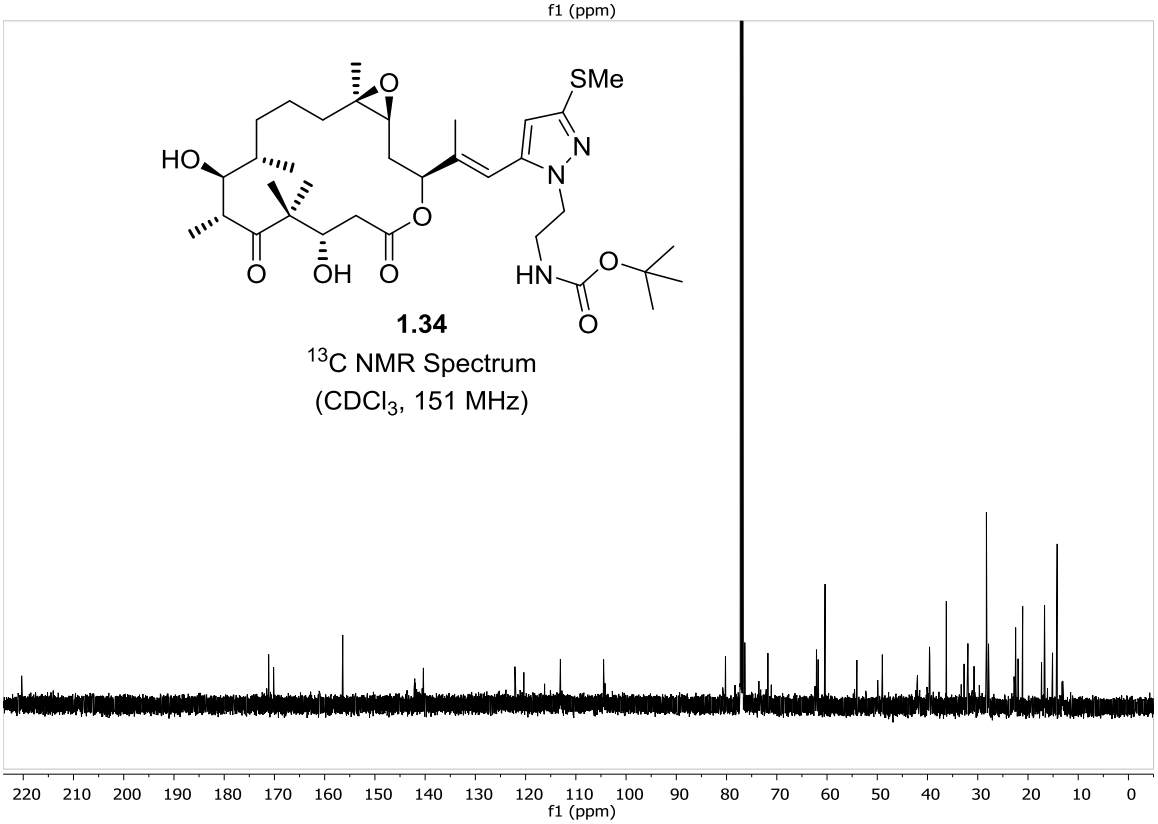
Spectra **1.30**: Compound **1.102**: ^{1}H and ^{13}C NMR



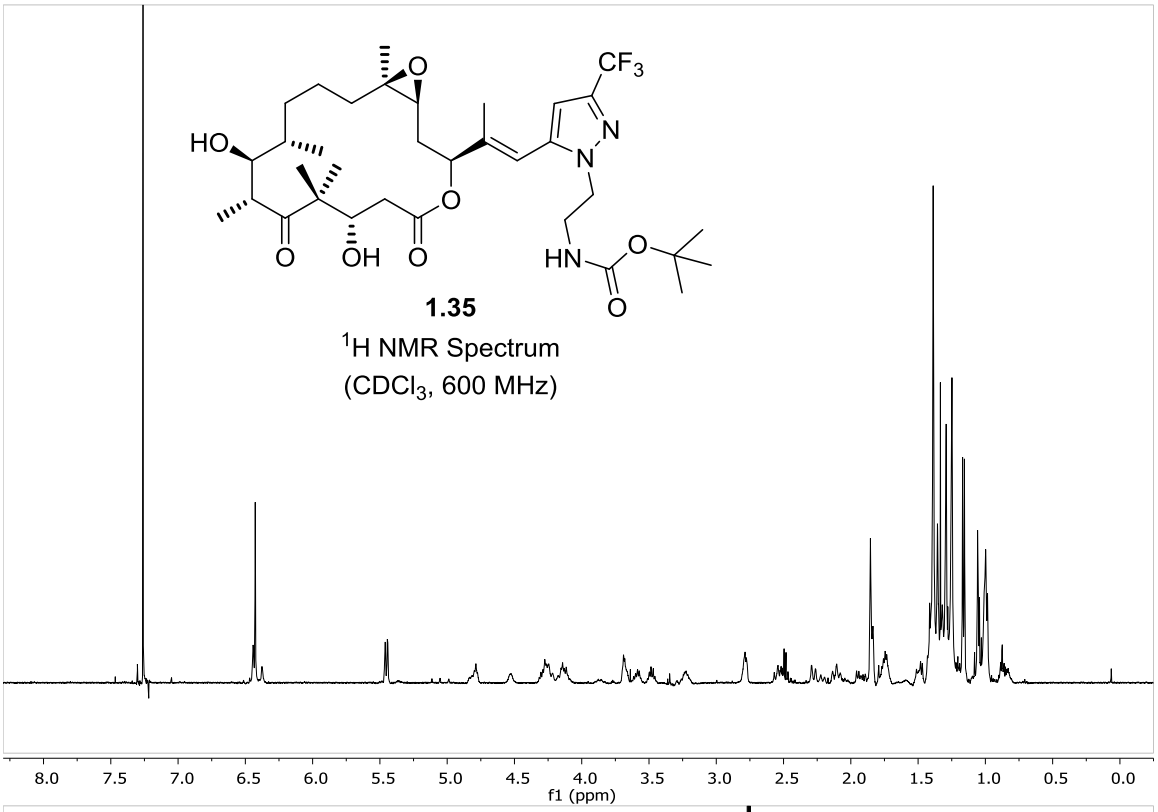


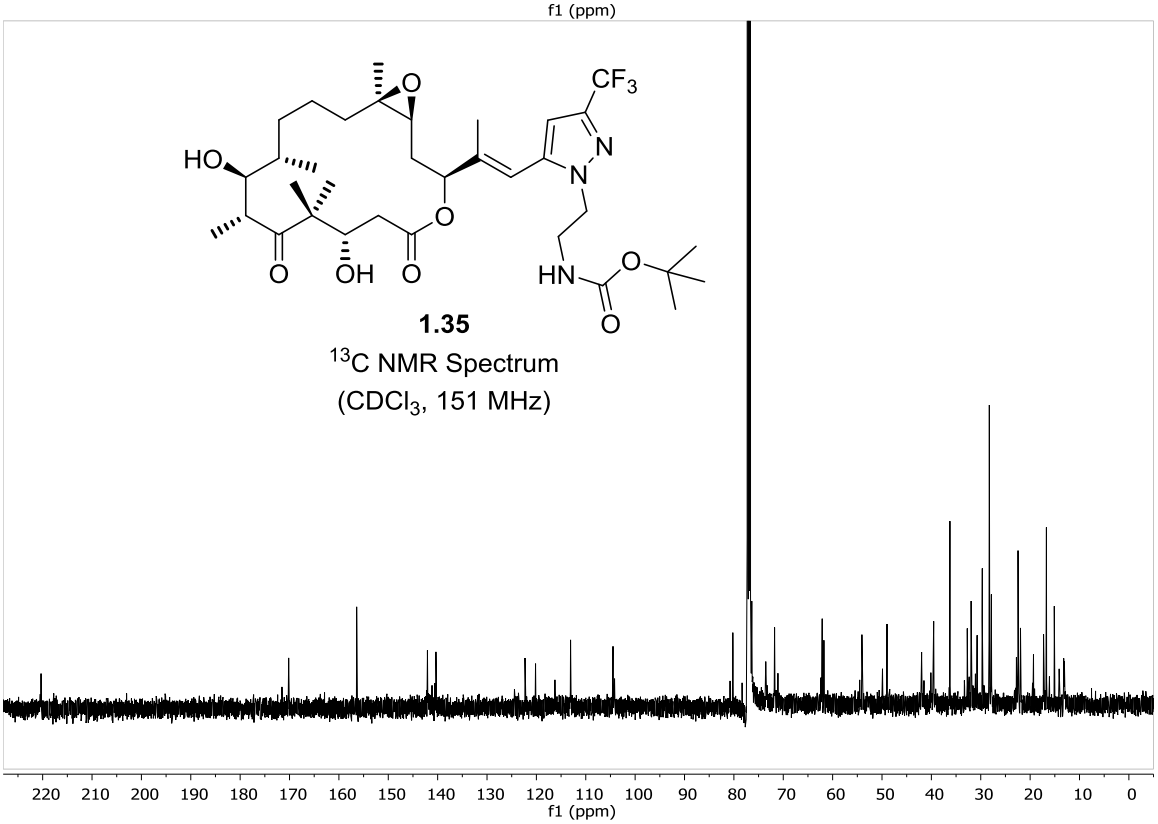
Spectra **1.31**: Compound **1.103**: ^{1}H and ^{13}C NMR



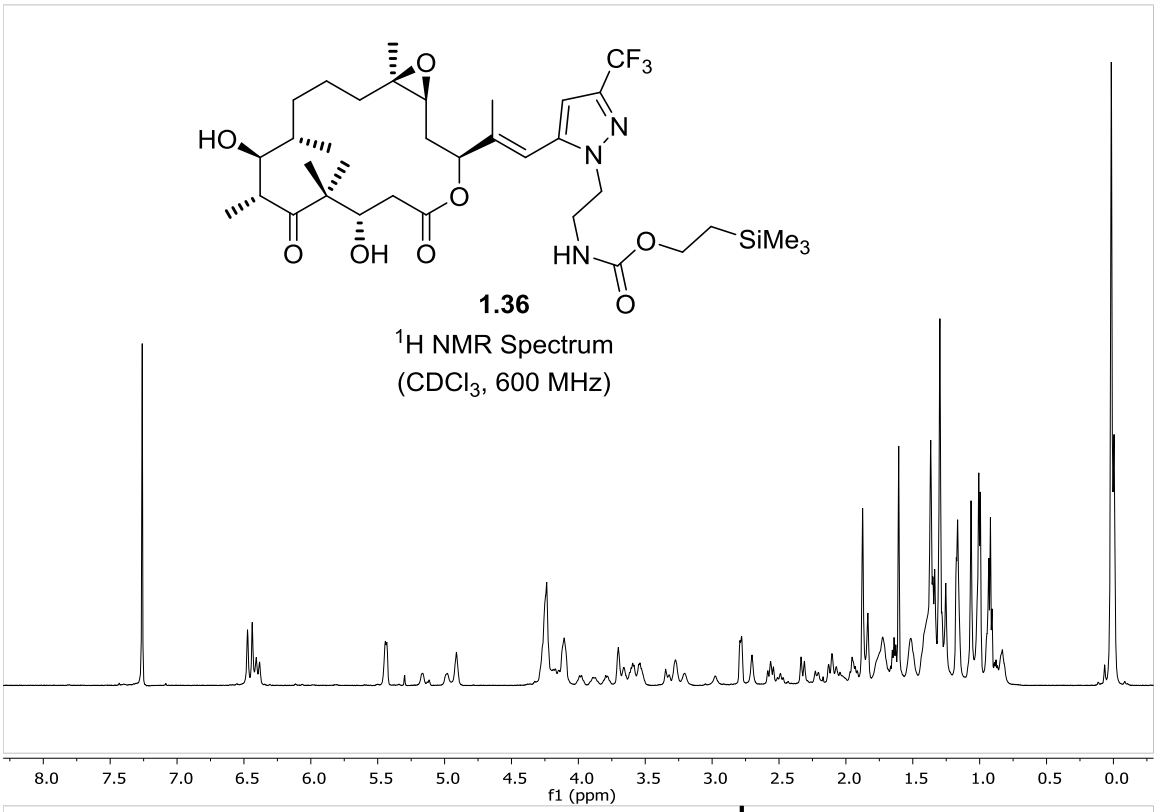


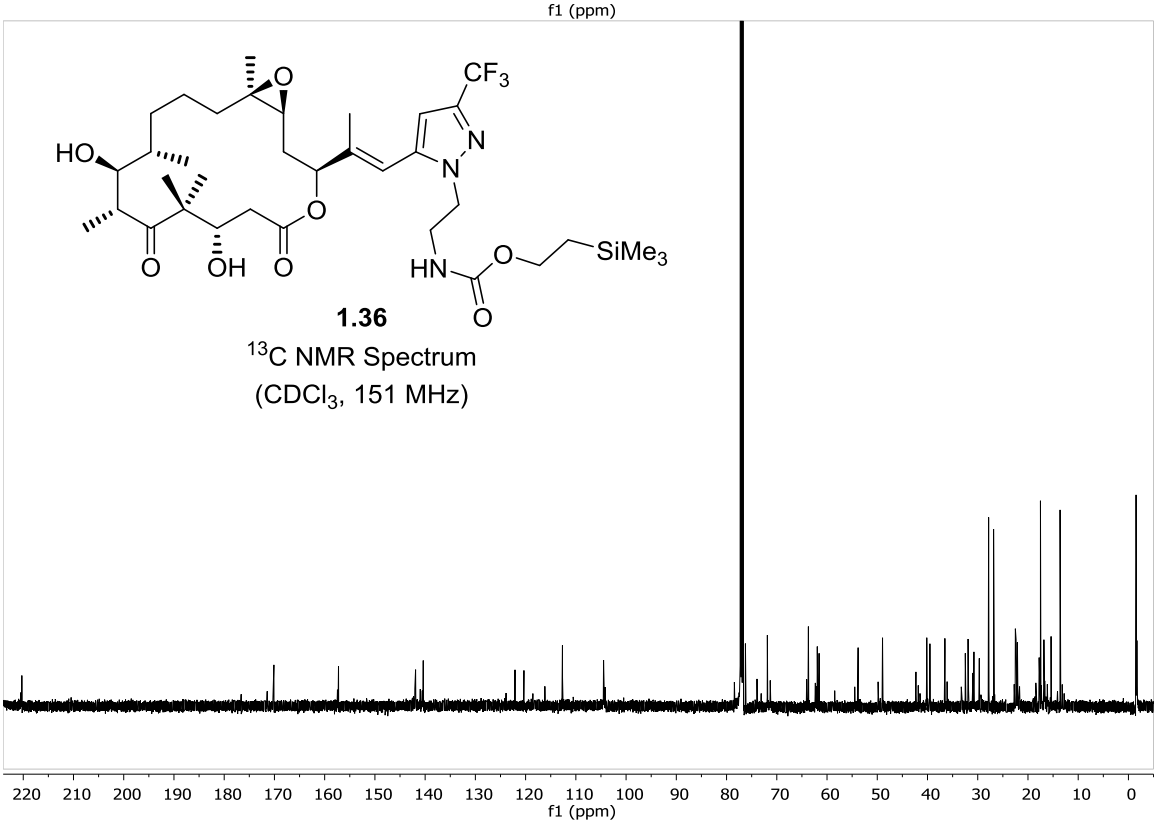
Spectra **1.32**: Compound **1.34**: ^{1}H and ^{13}C NMR



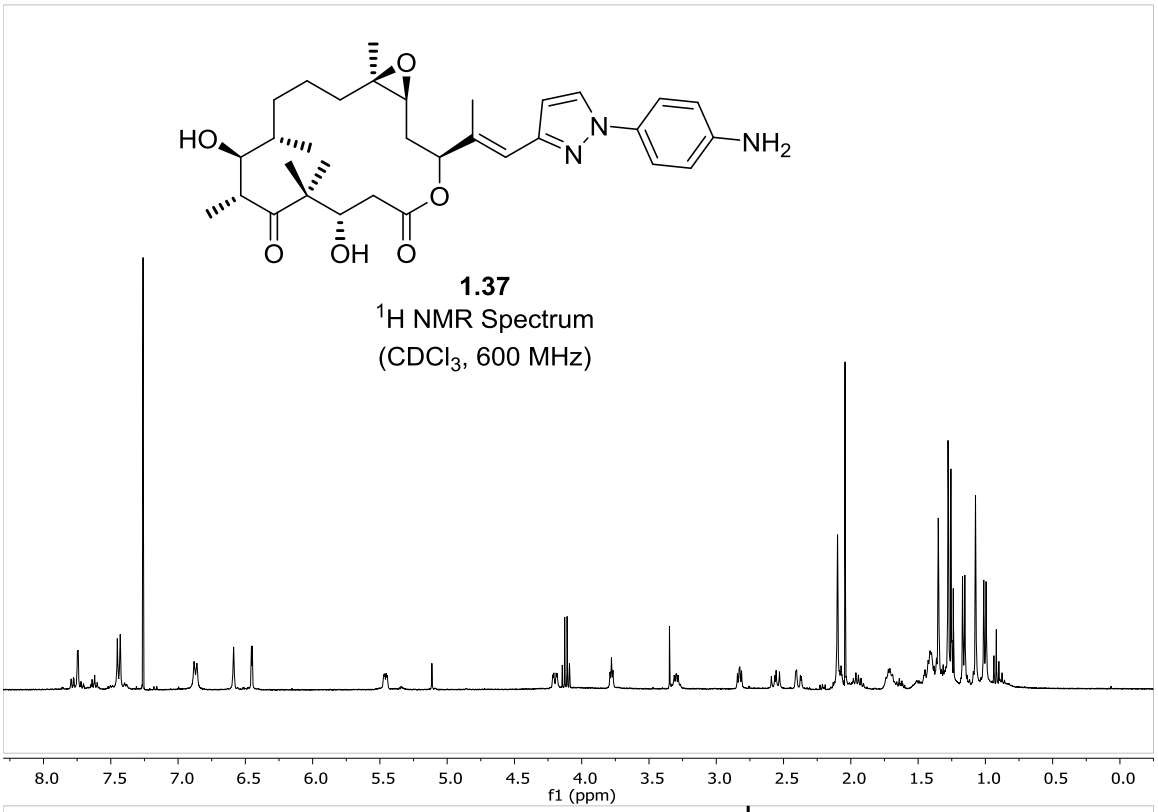


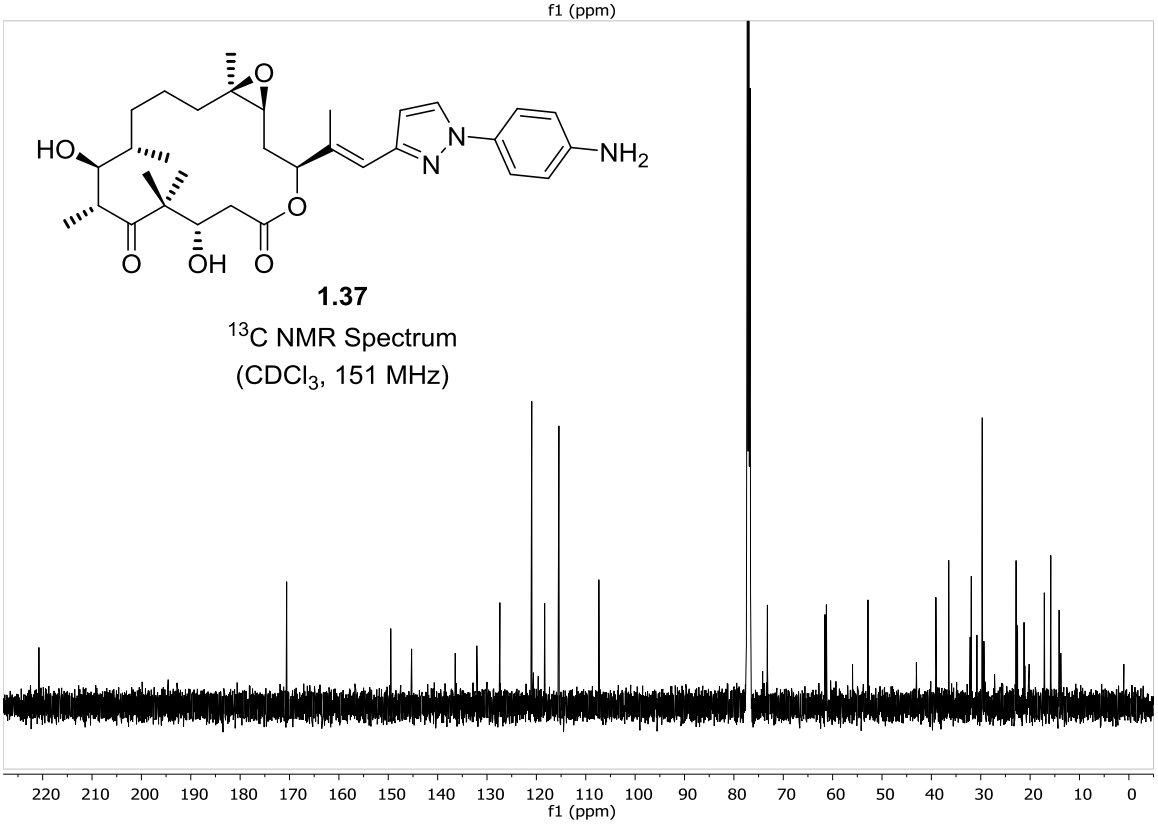
Spectra **1.33**: Compound **1.35**: ^{1}H and ^{13}C NMR



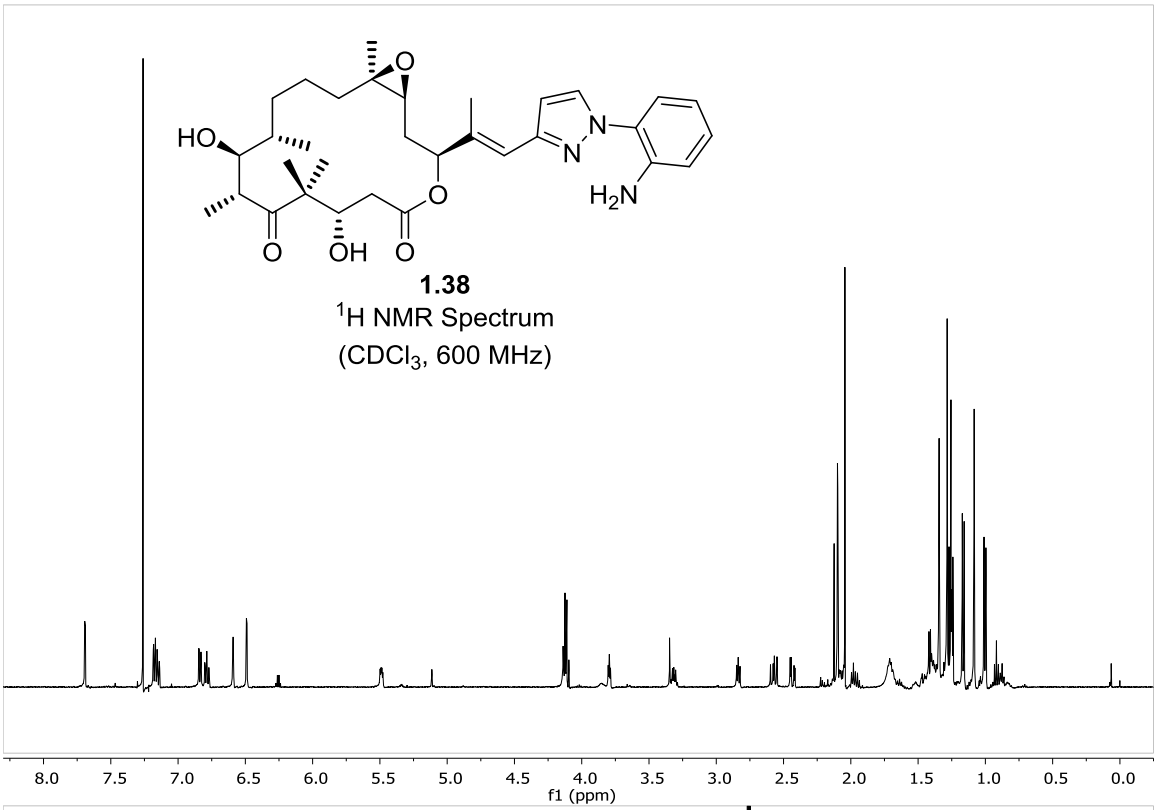


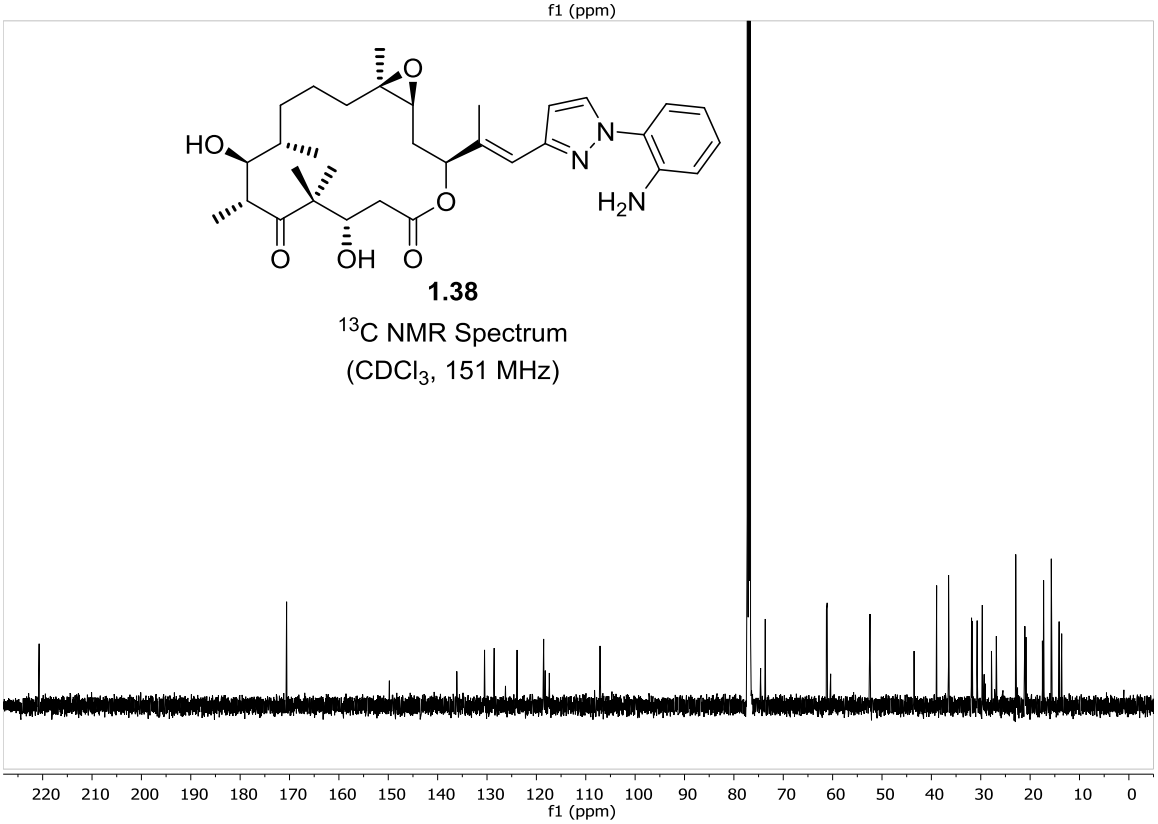
Spectra **1.34**: Compound **1.36**: ^{1}H and ^{13}C NMR



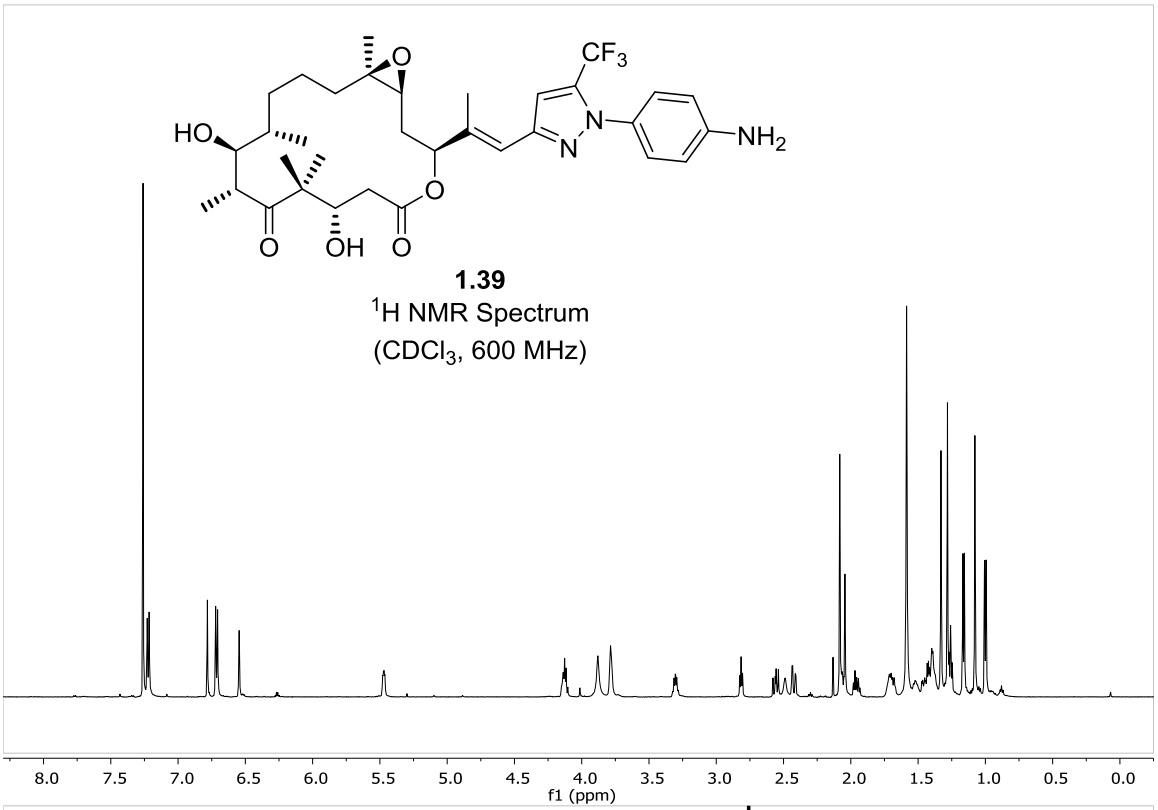


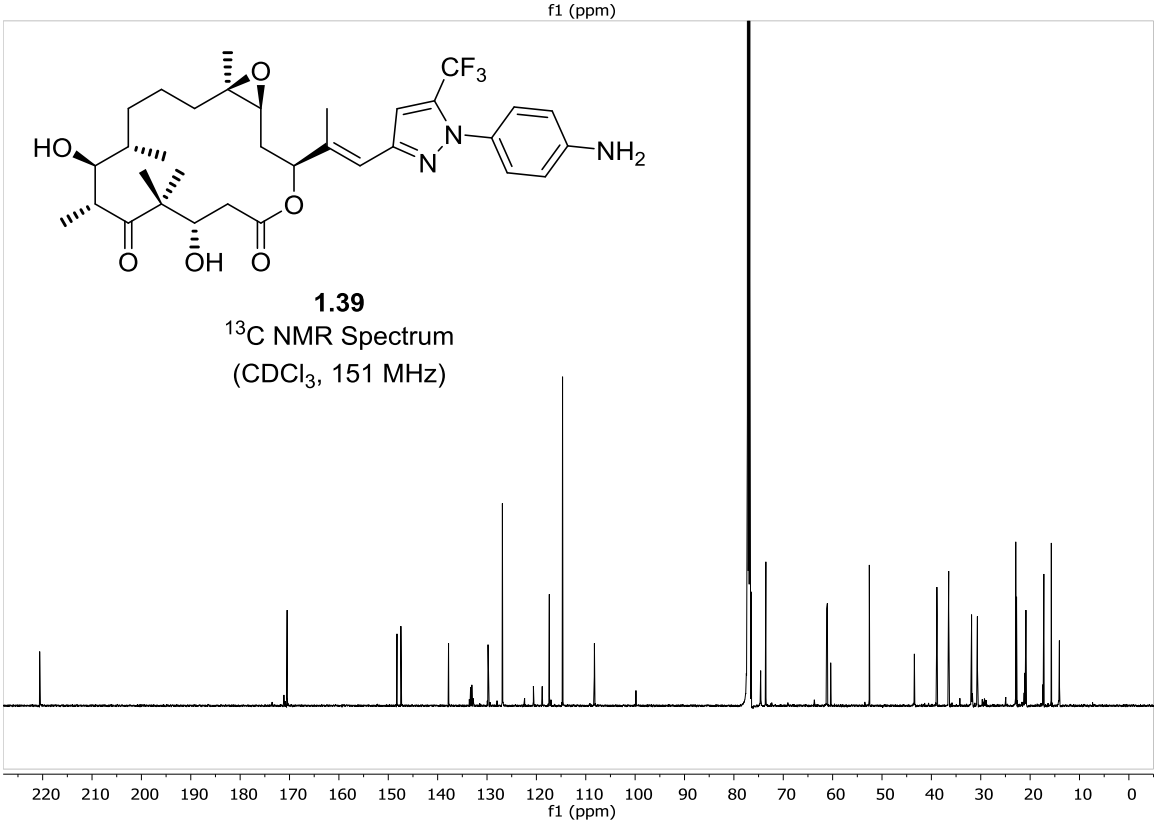
Spectra **1.35**: Compound **1.37**: ^{1}H and ^{13}C NMR



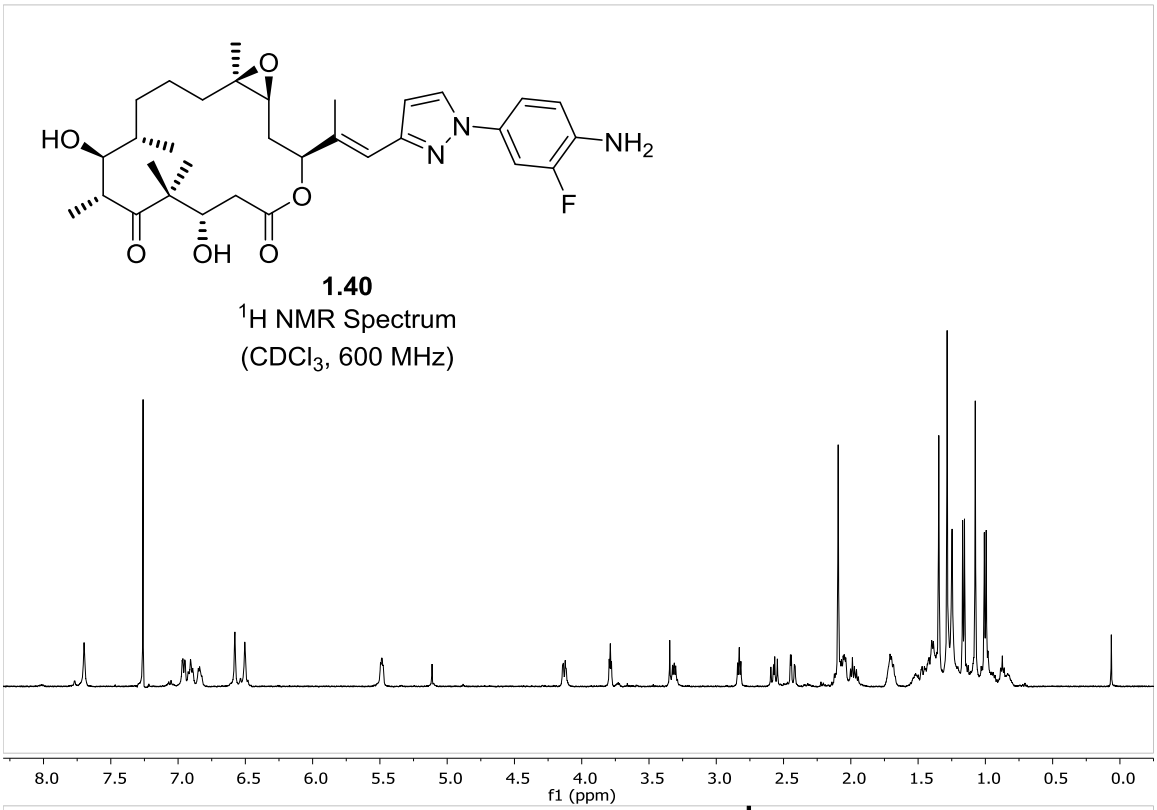


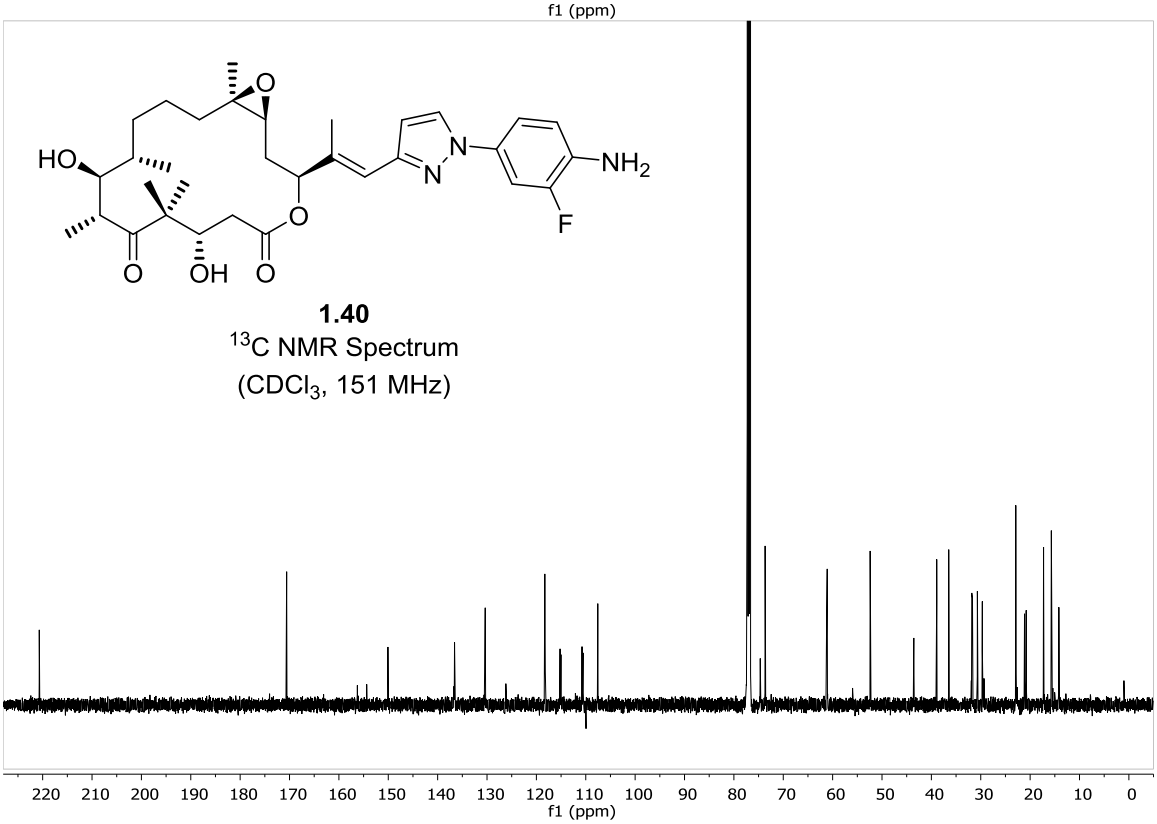
Spectra **1.36**: Compound **1.38**: ^{1}H and ^{13}C NMR



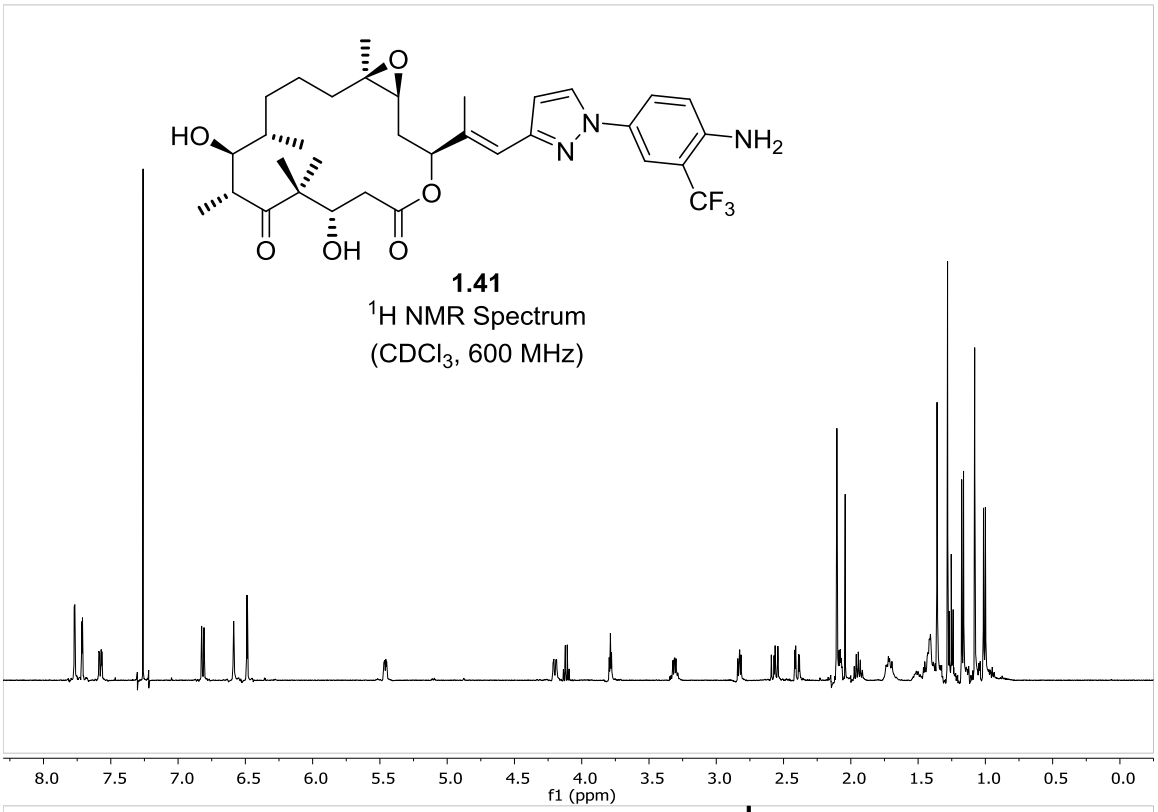


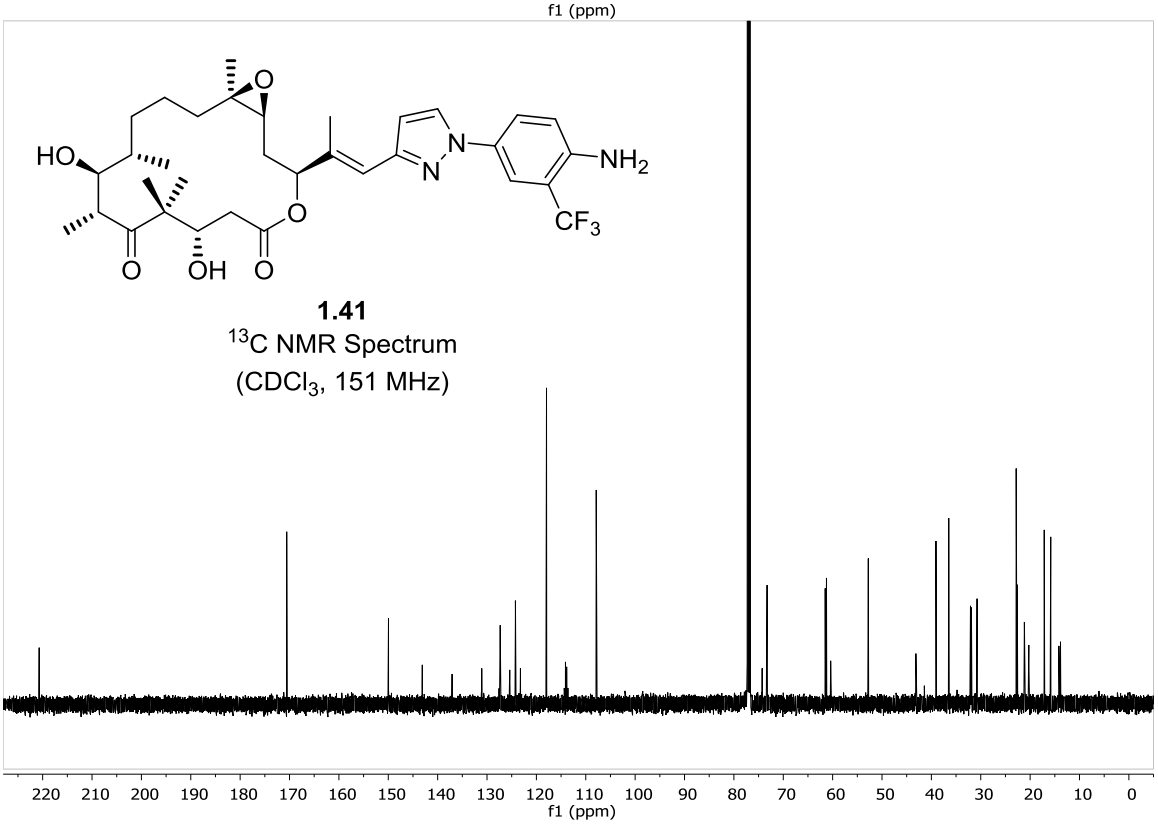
Spectra **1.37**: Compound **1.39**: ^{1}H and ^{13}C NMR



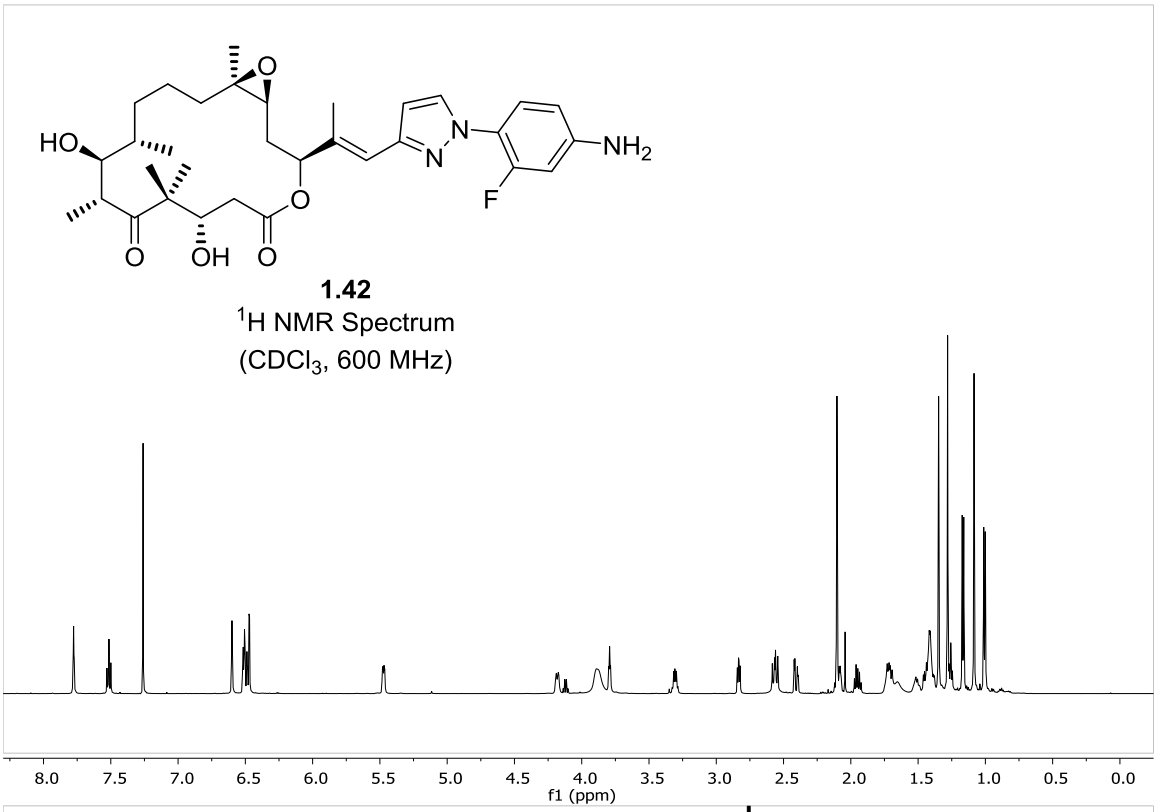


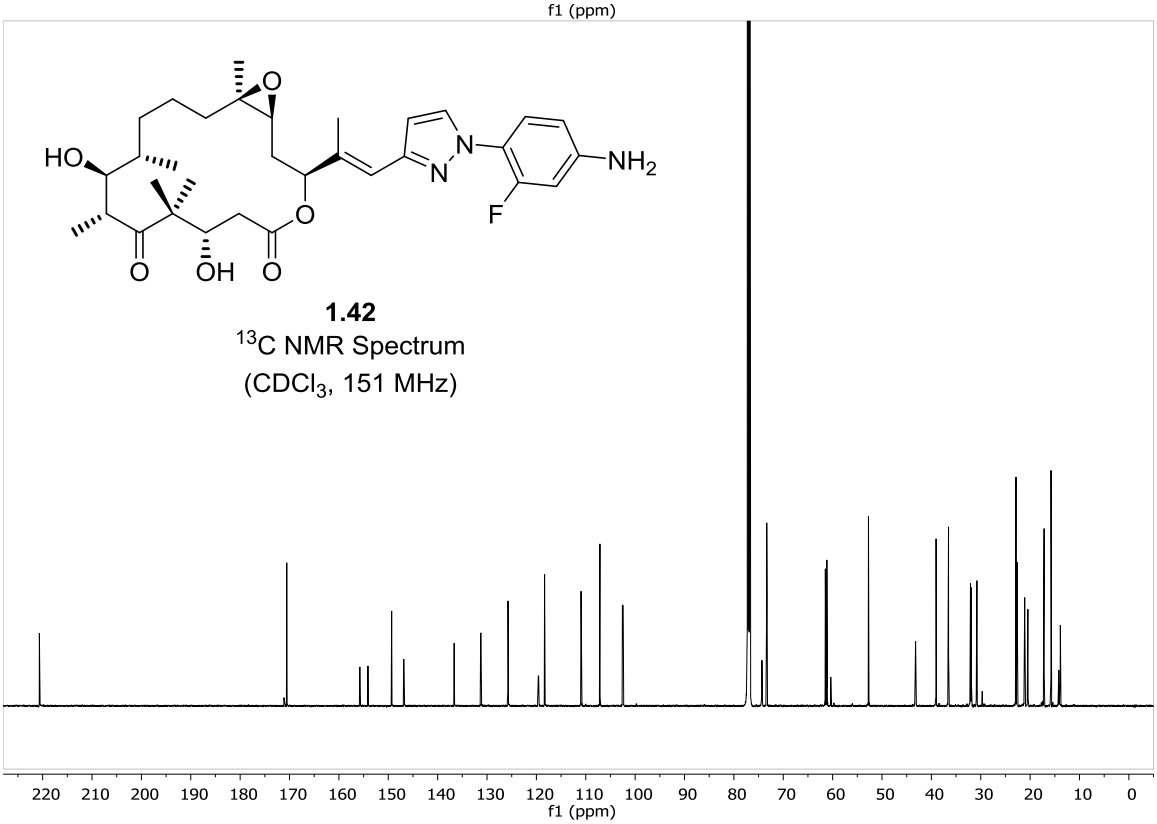
Spectra **1.38**: Compound **1.40**: ^{1}H and ^{13}C NMR



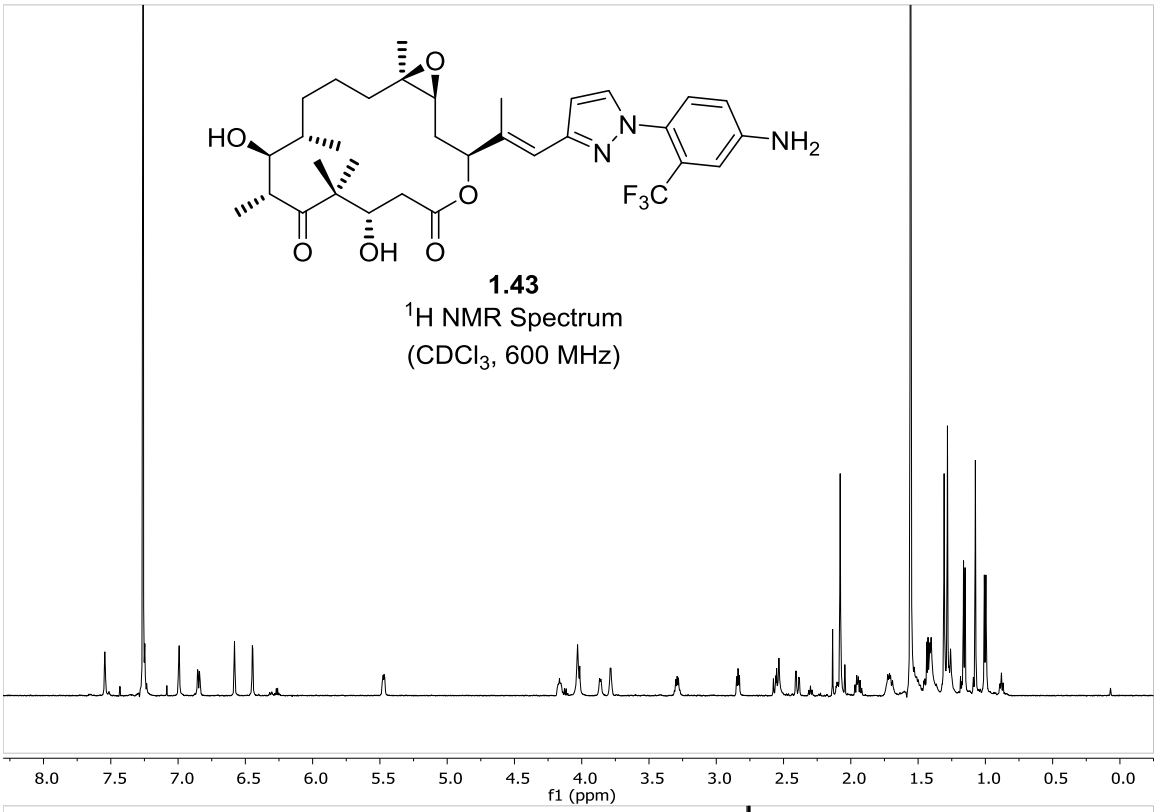


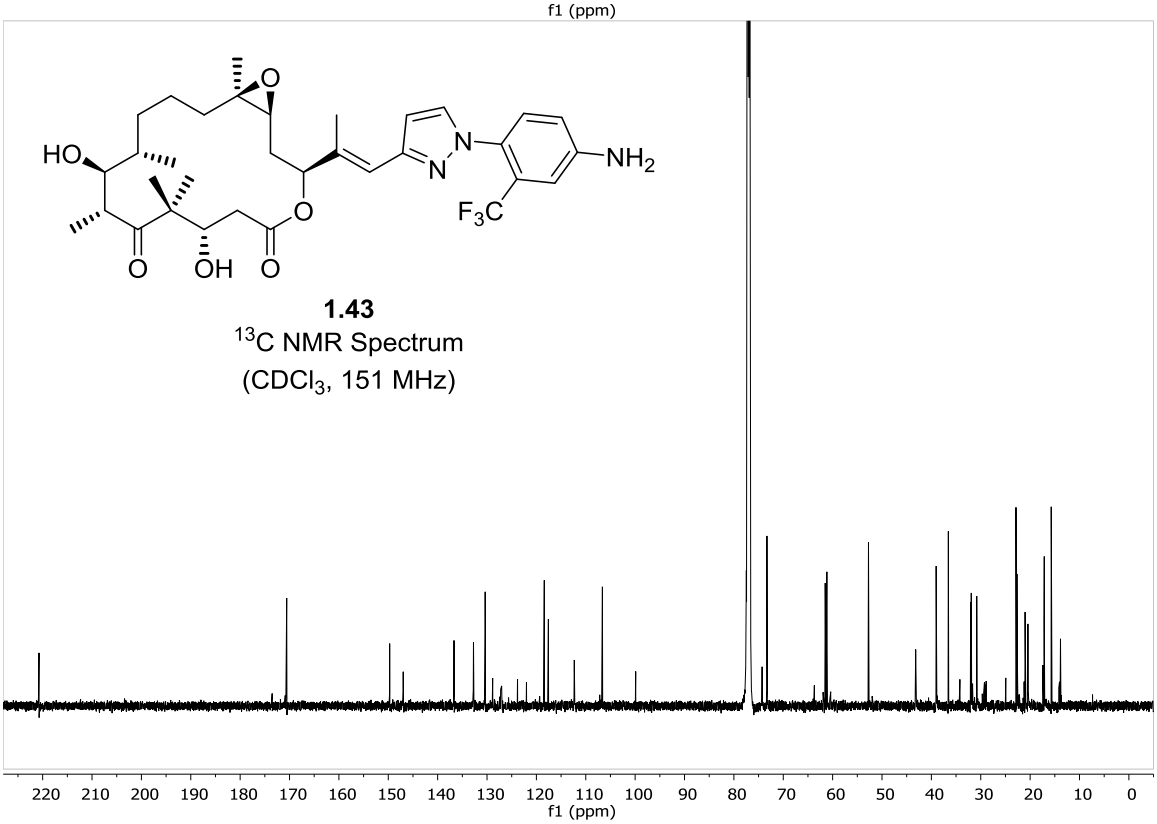
Spectra **1.39**: Compound **1.41**: ^{1}H and ^{13}C NMR



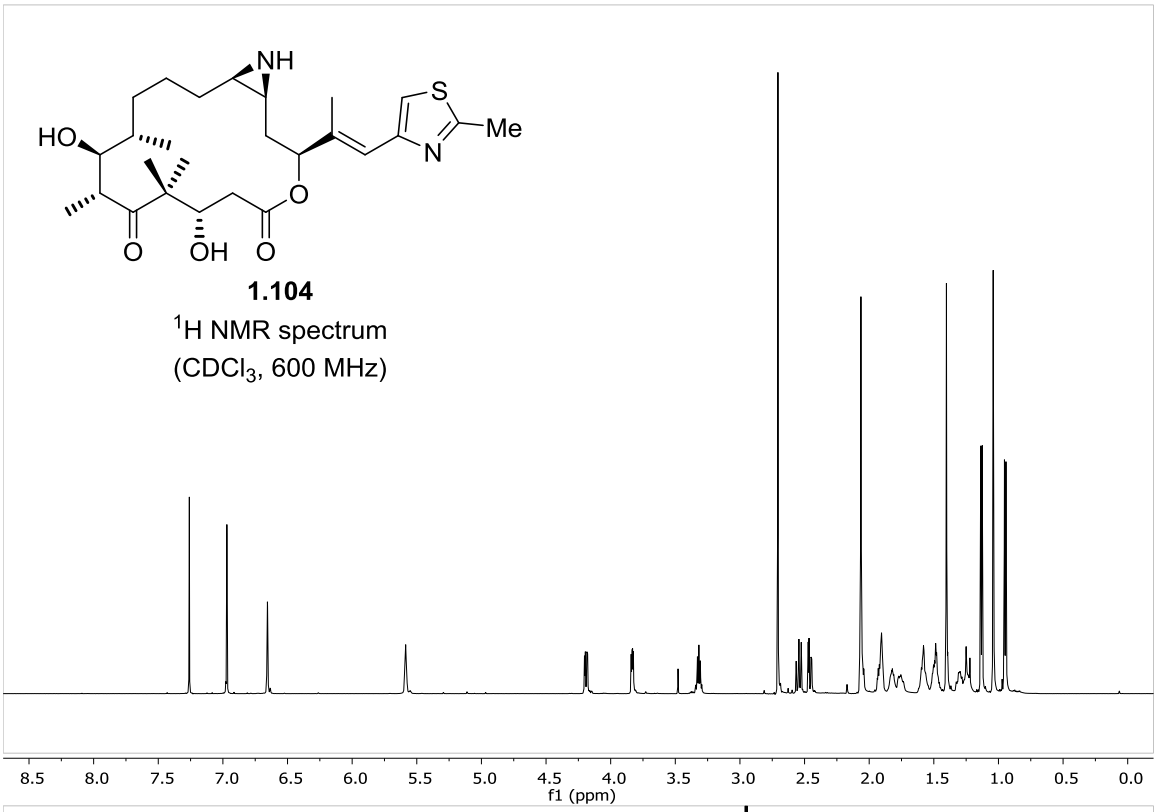


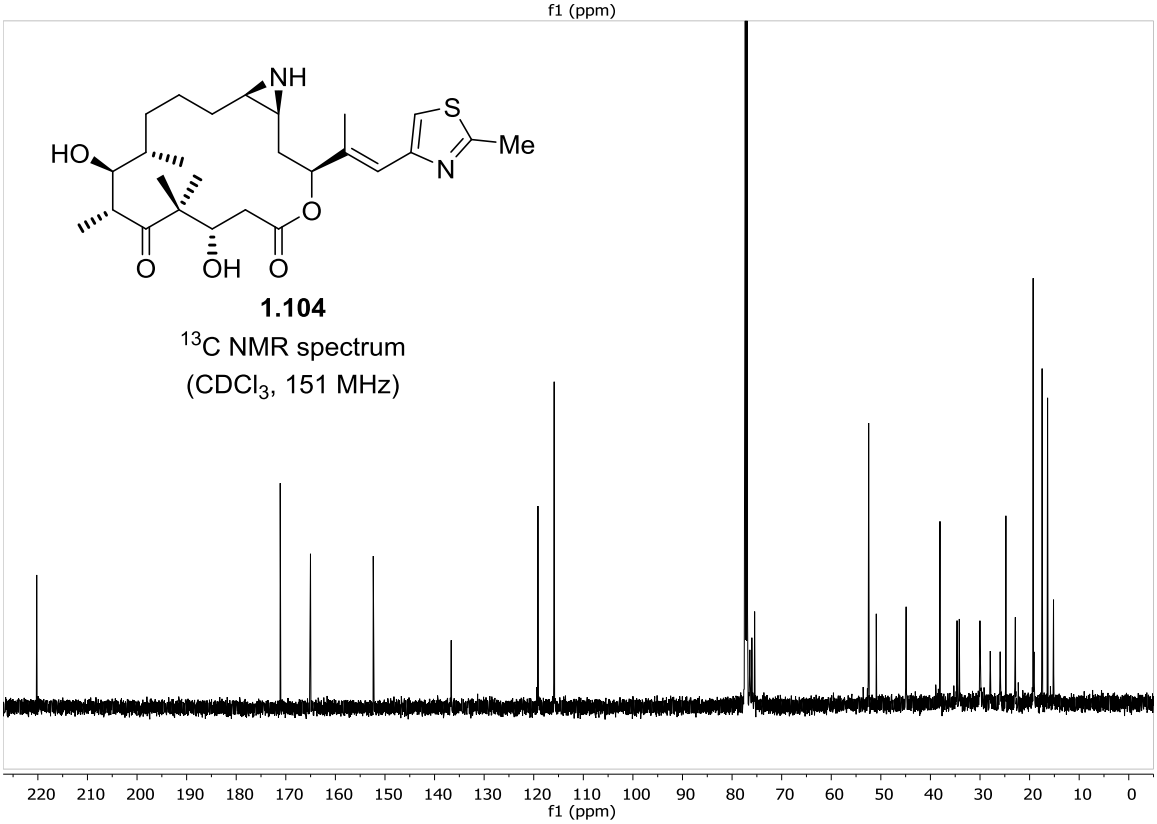
Spectra **1.40**: Compound **1.42**: ^{1}H and ^{13}C NMR



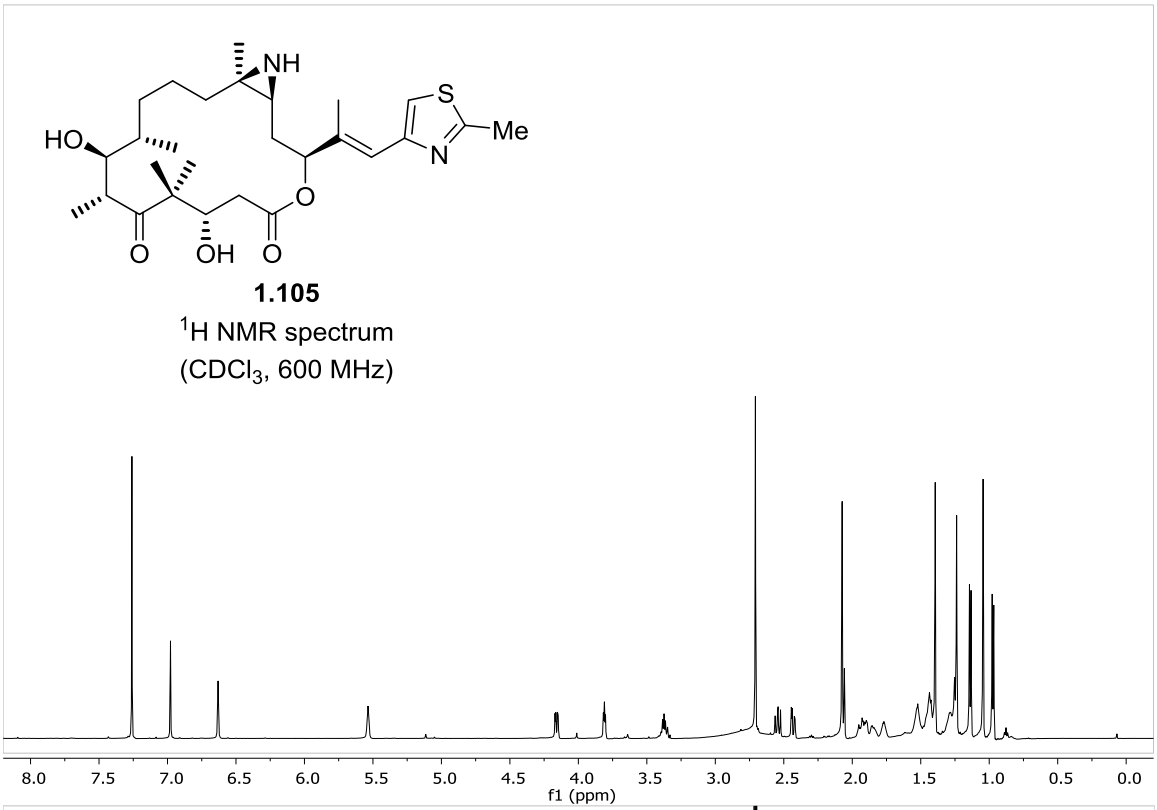


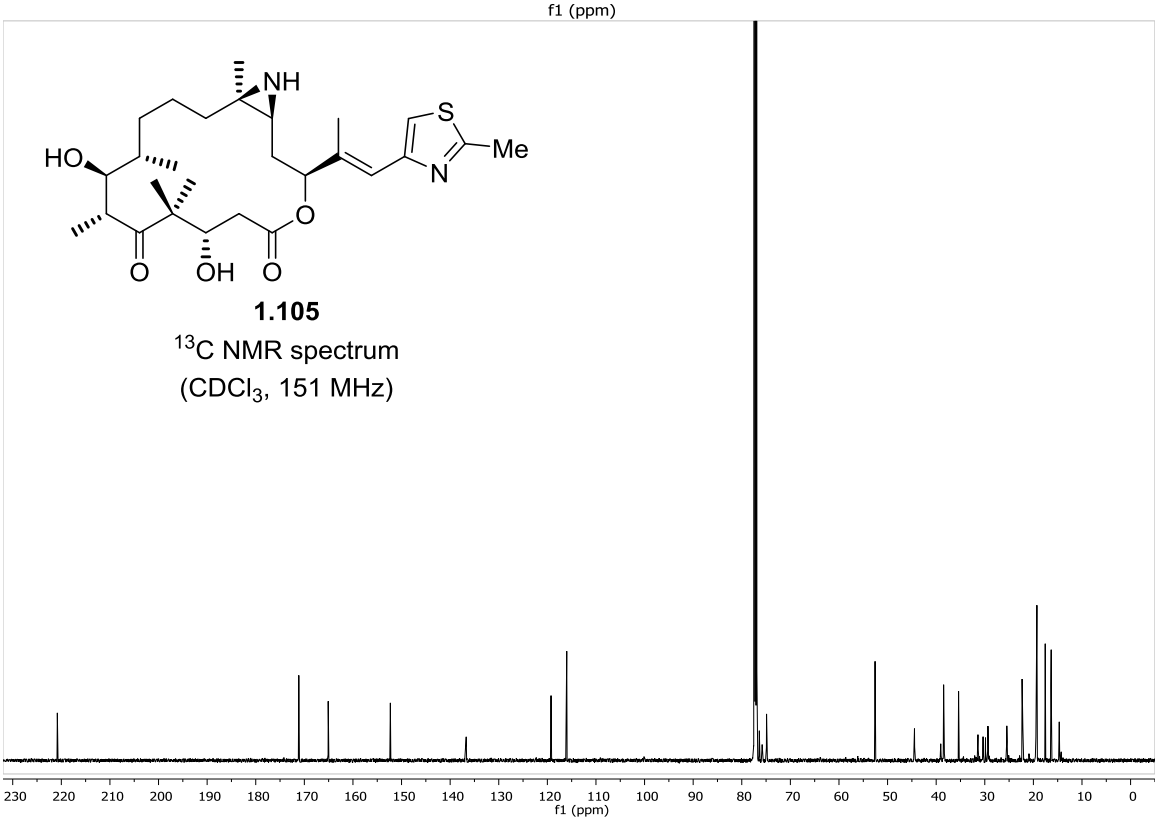
Spectra **1.41**: Compound **1.43**: ^{1}H and ^{13}C NMR



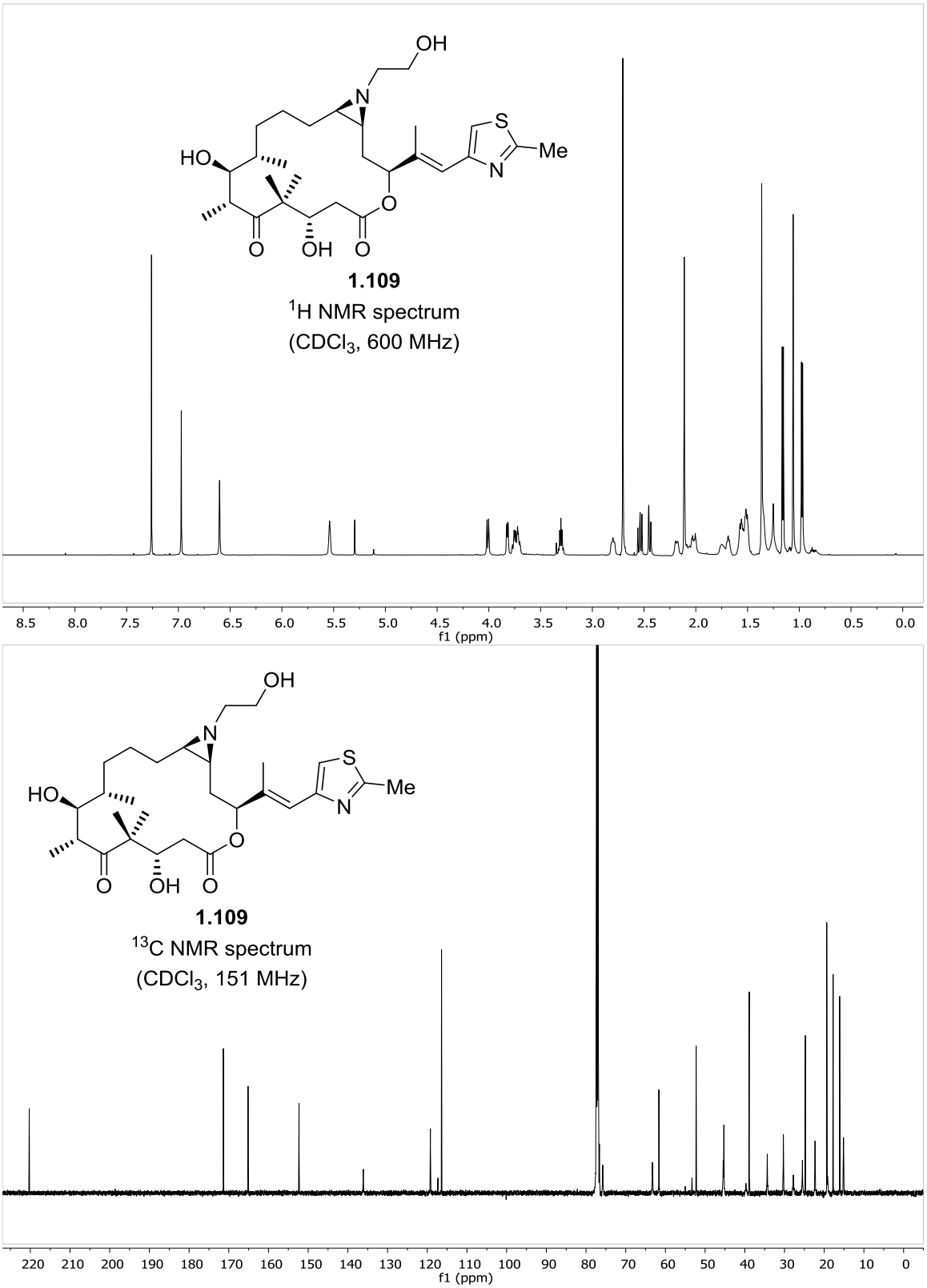


Spectra **1.42**: Compound **1.104**: ^{1}H and ^{13}C NMR

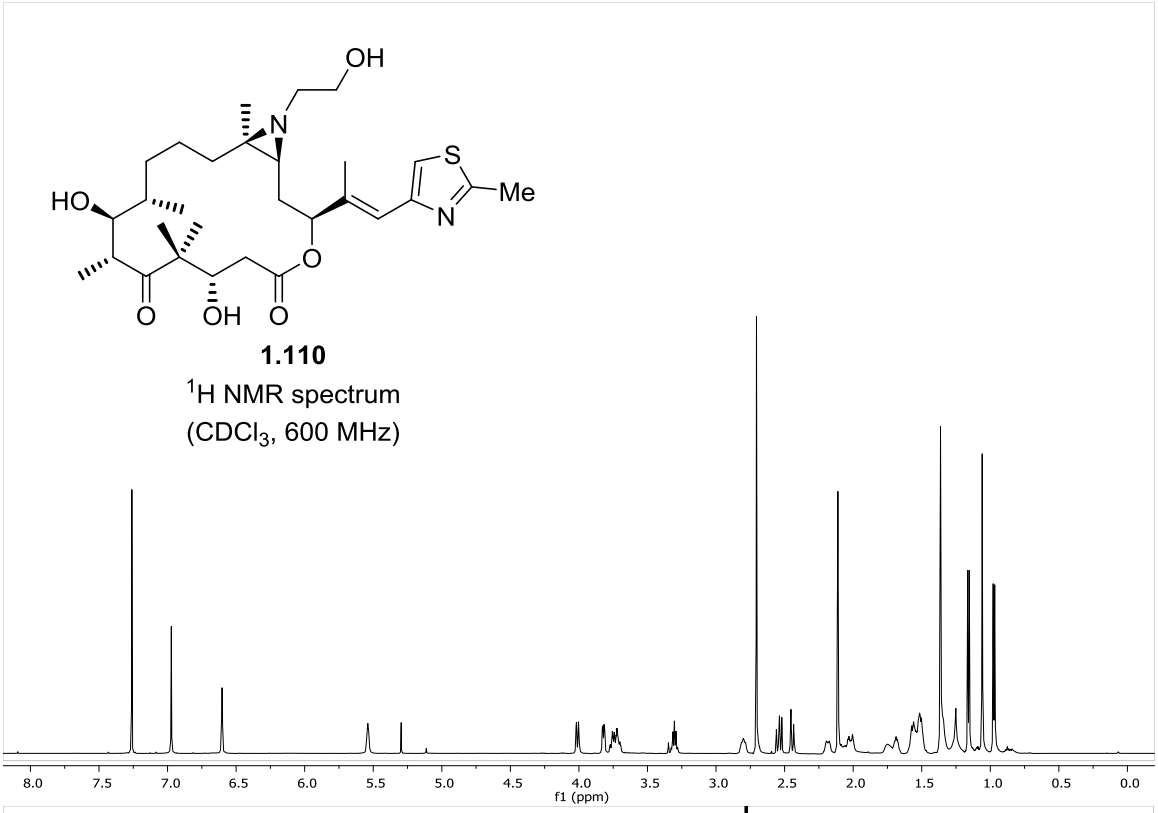


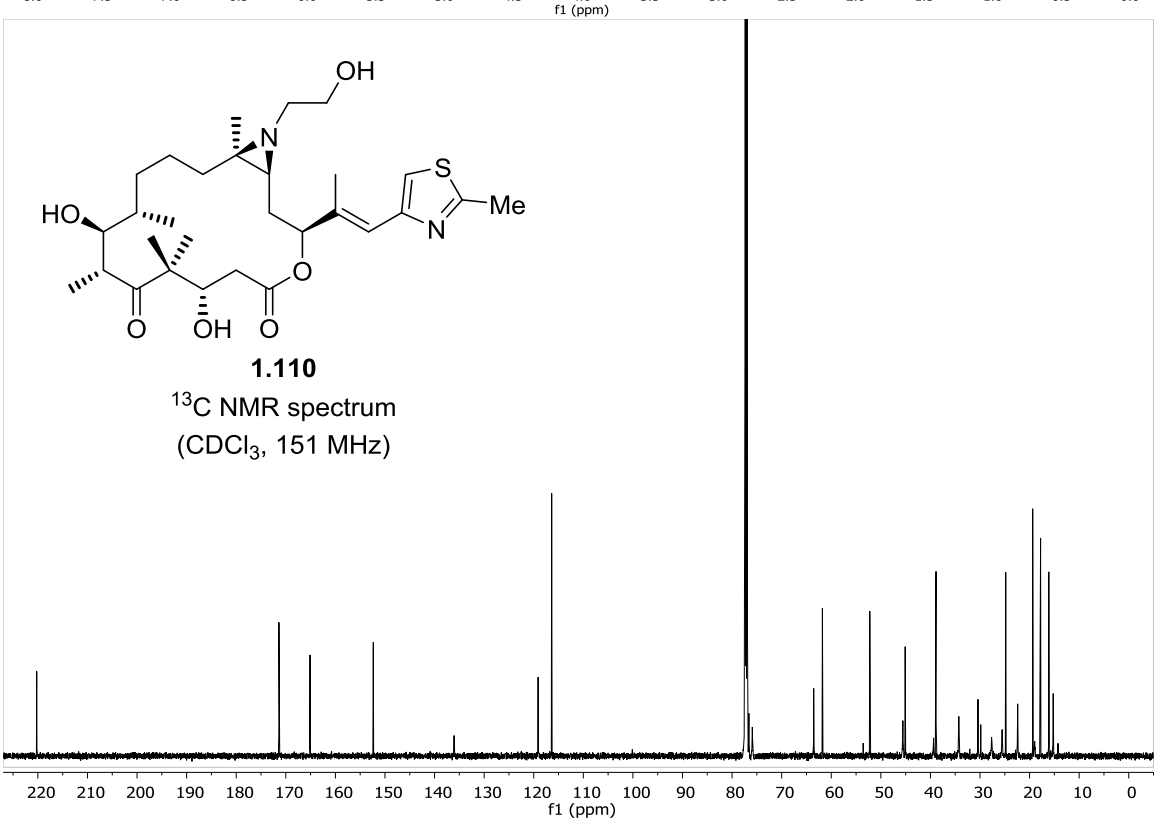


Spectra **1.43**: Compound **1.105**: ^{1}H and ^{13}C NMR

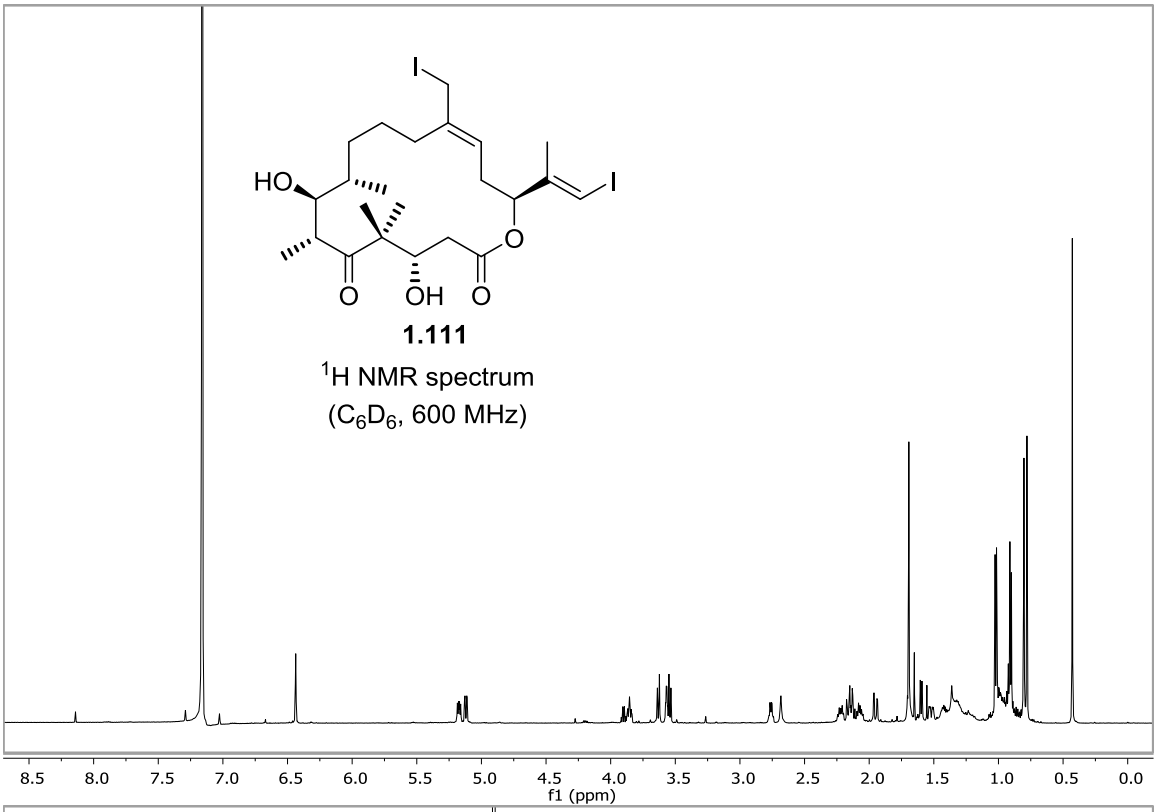


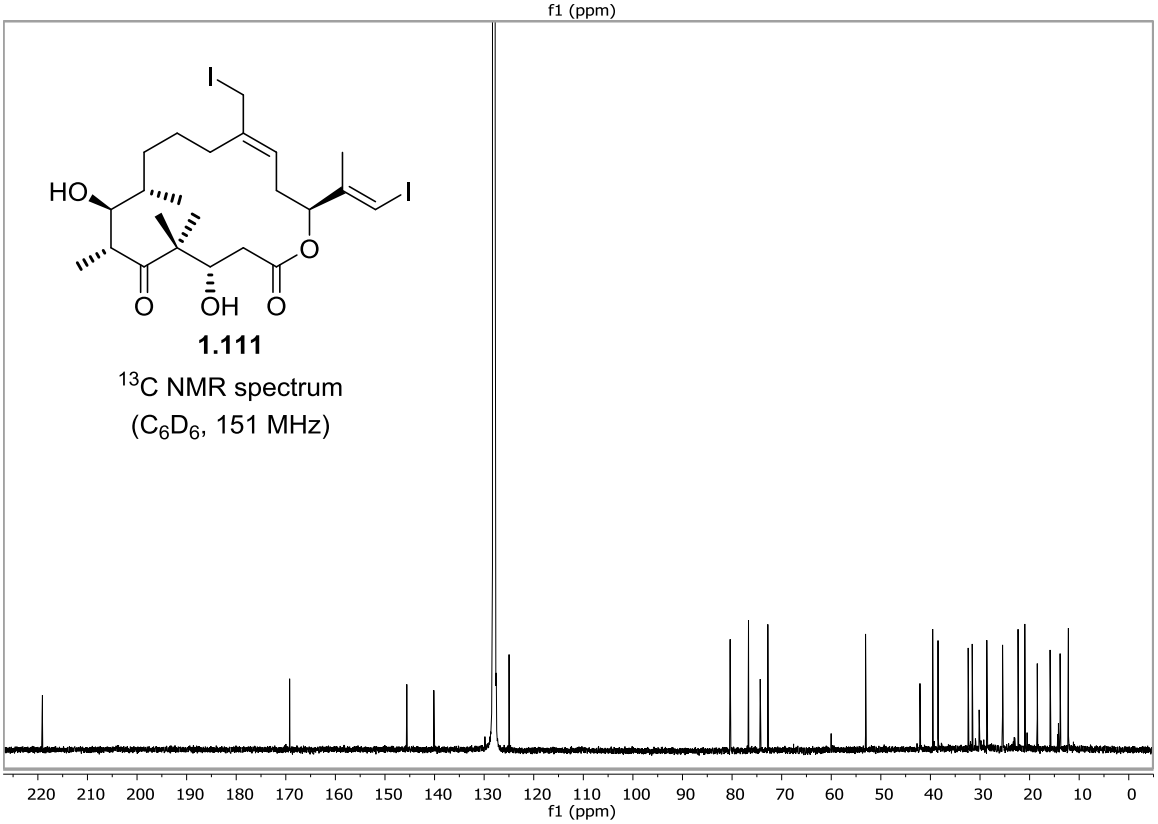
Spectra **1.44**: Compound **1.109**: ^{1}H and ^{13}C NMR



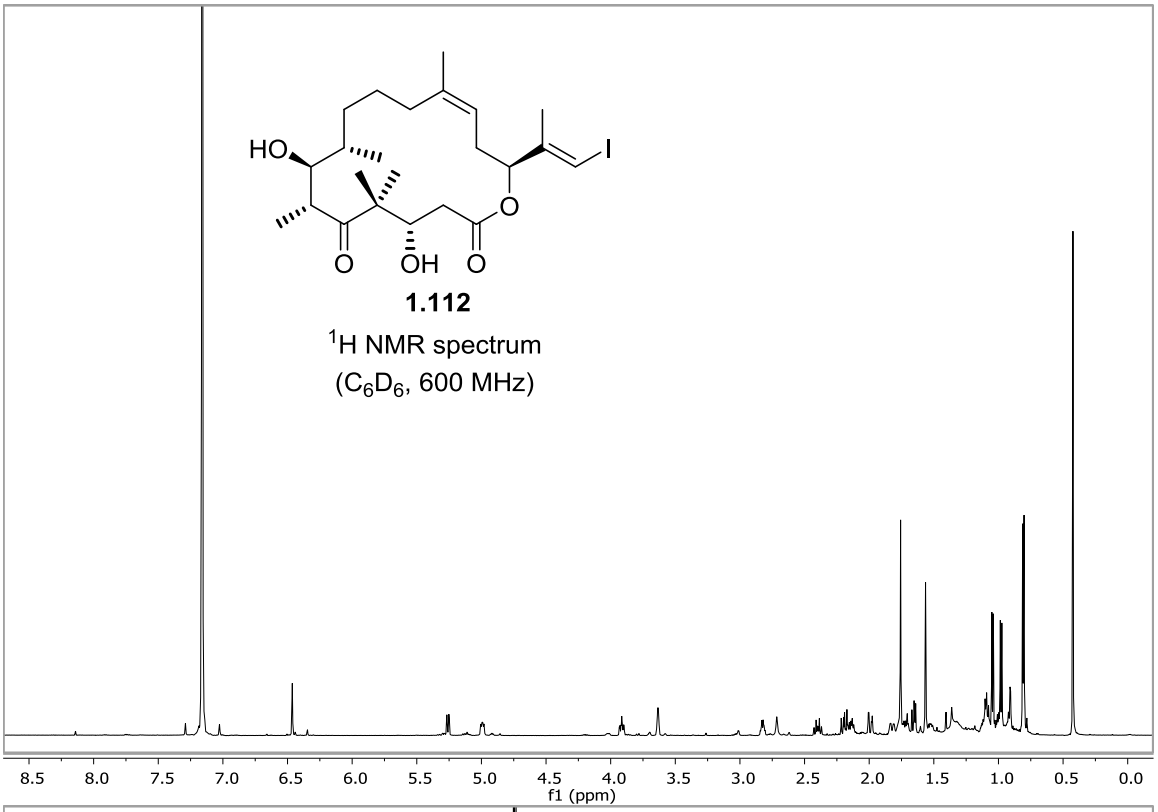


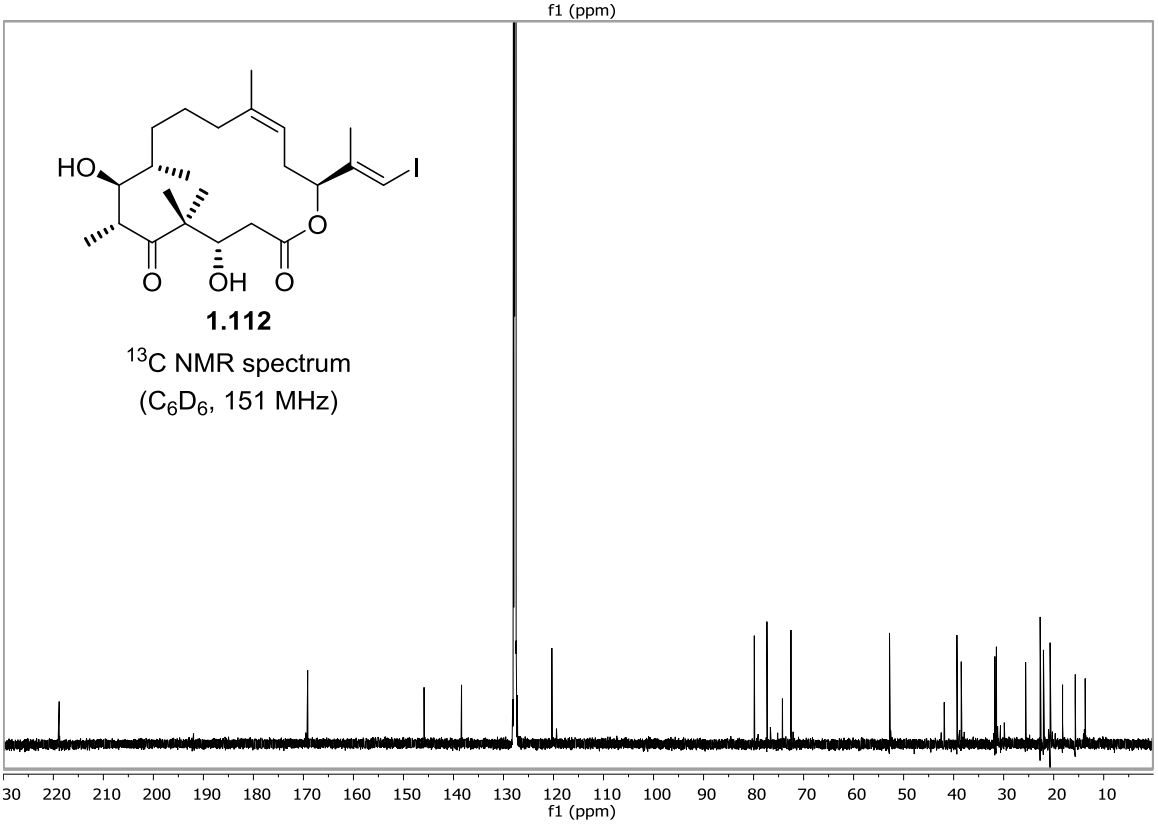
Spectra **1.45**: Compound **1.110**: ^{1}H and ^{13}C NMR



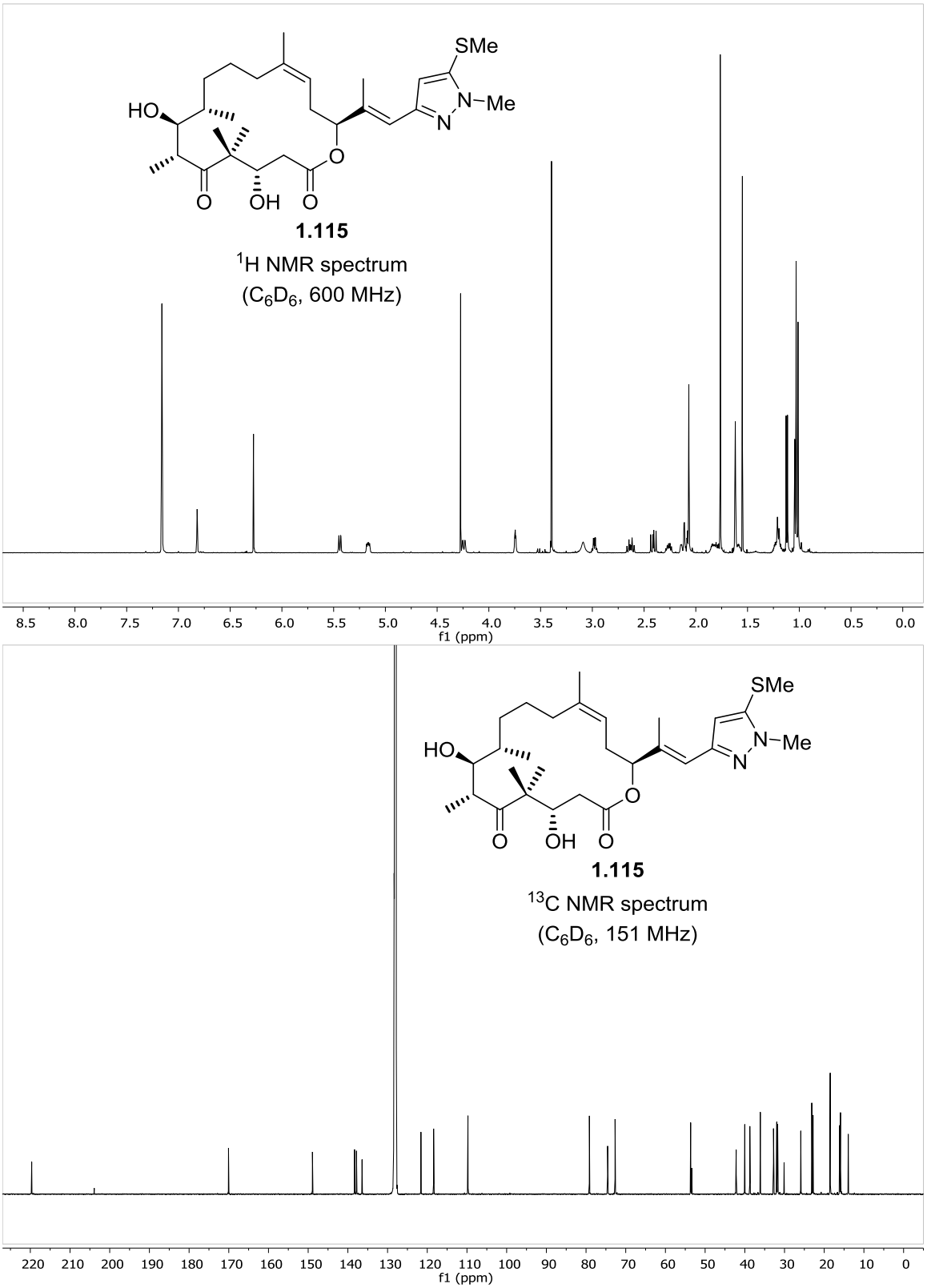


Spectra **1.46**: Compound **1.111**: ^{1}H and ^{13}C NMR

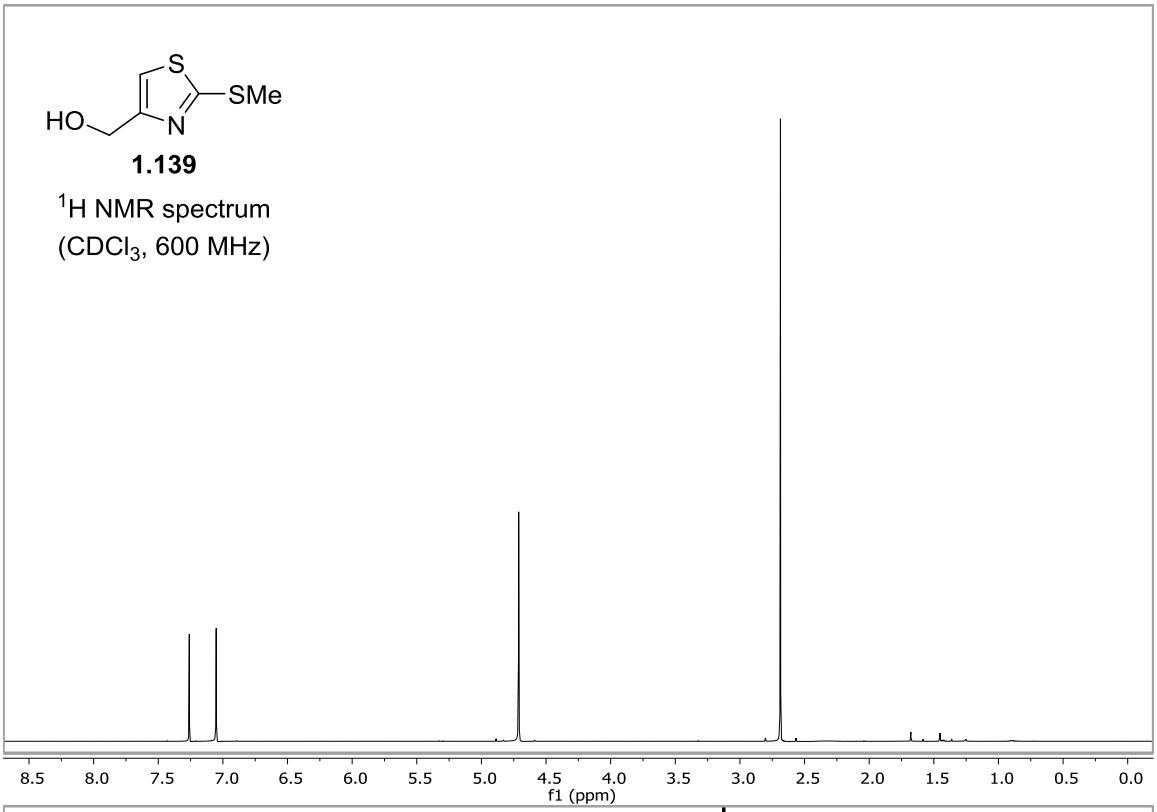


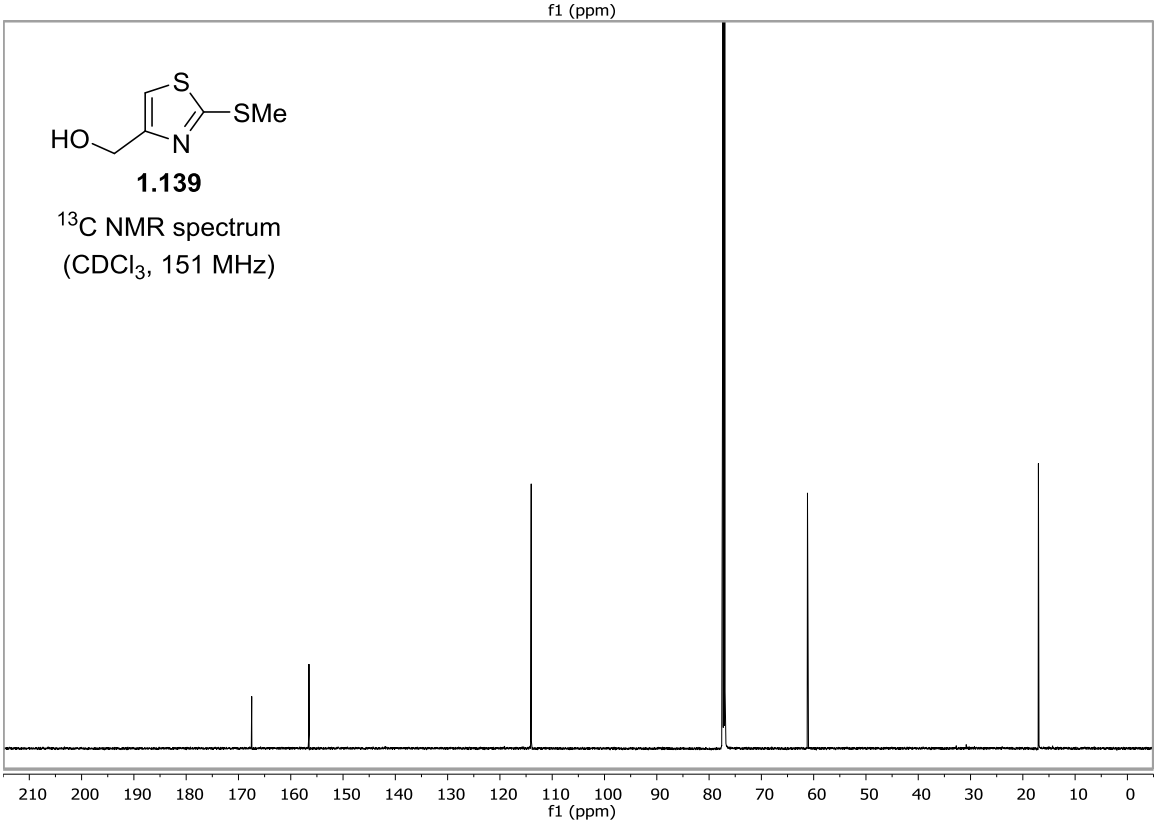


Spectra **1.47**: Compound **1.112**: ^{1}H and ^{13}C NMR

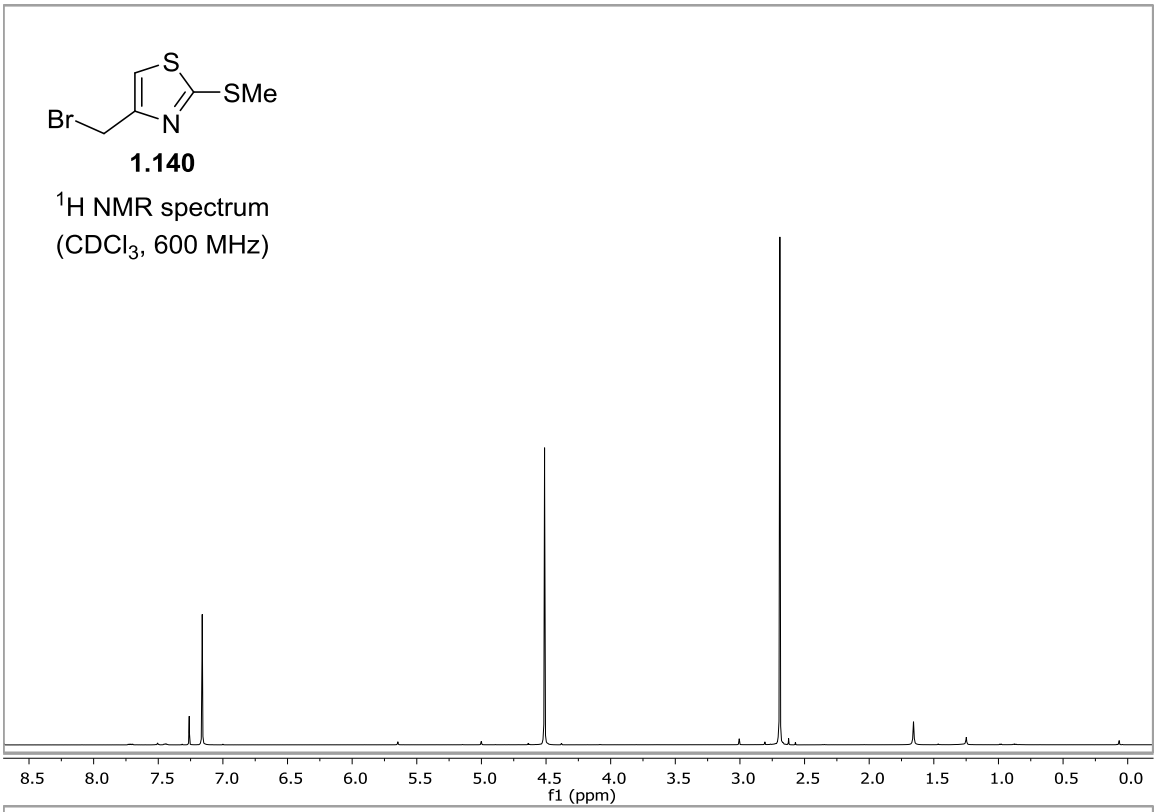


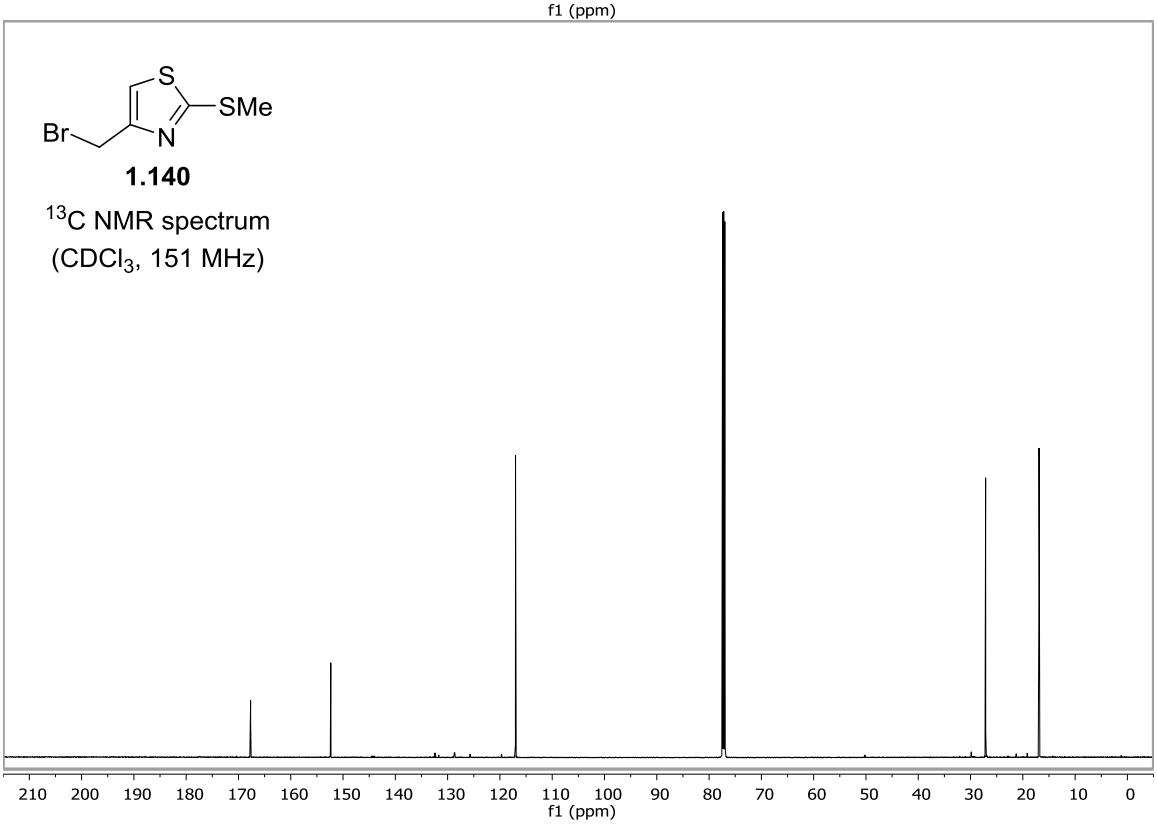
Spectra **1.48**: Compound **1.115**: ^{1}H and ^{13}C NMR



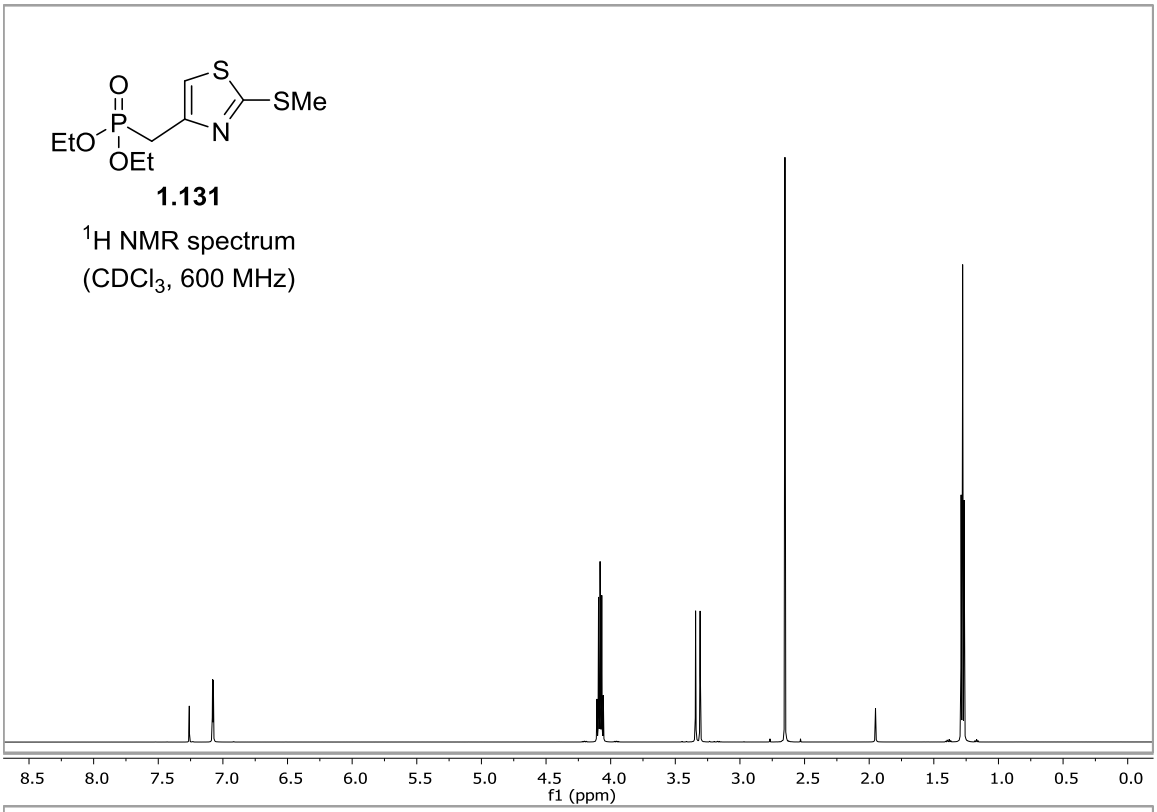


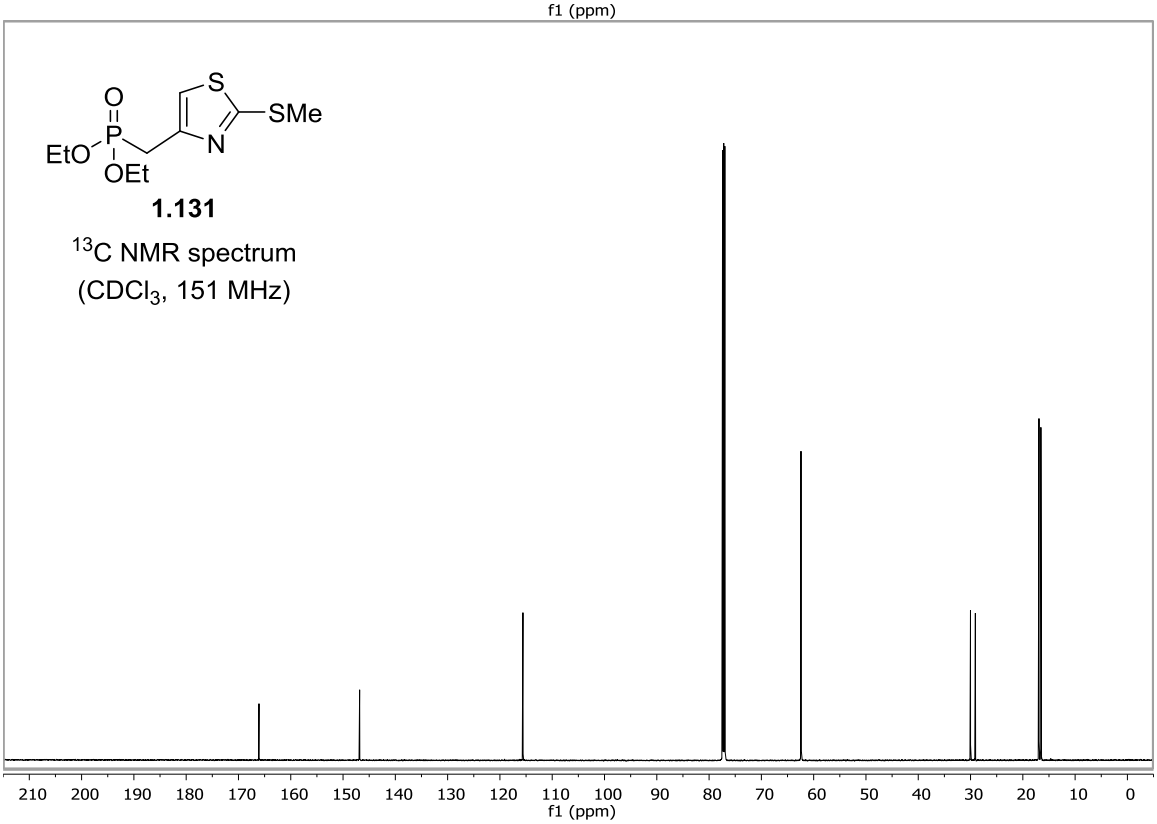
Spectra **1.49**: Compound **1.139**: ^{1}H and ^{13}C NMR



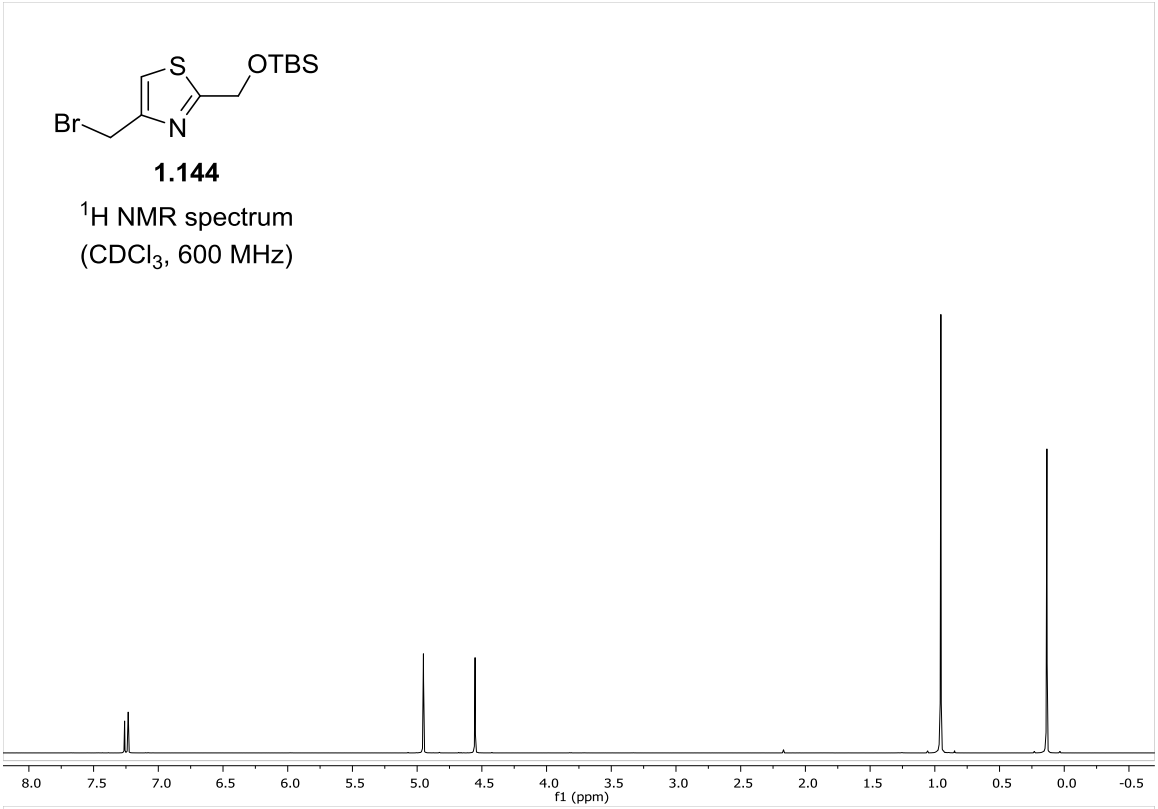


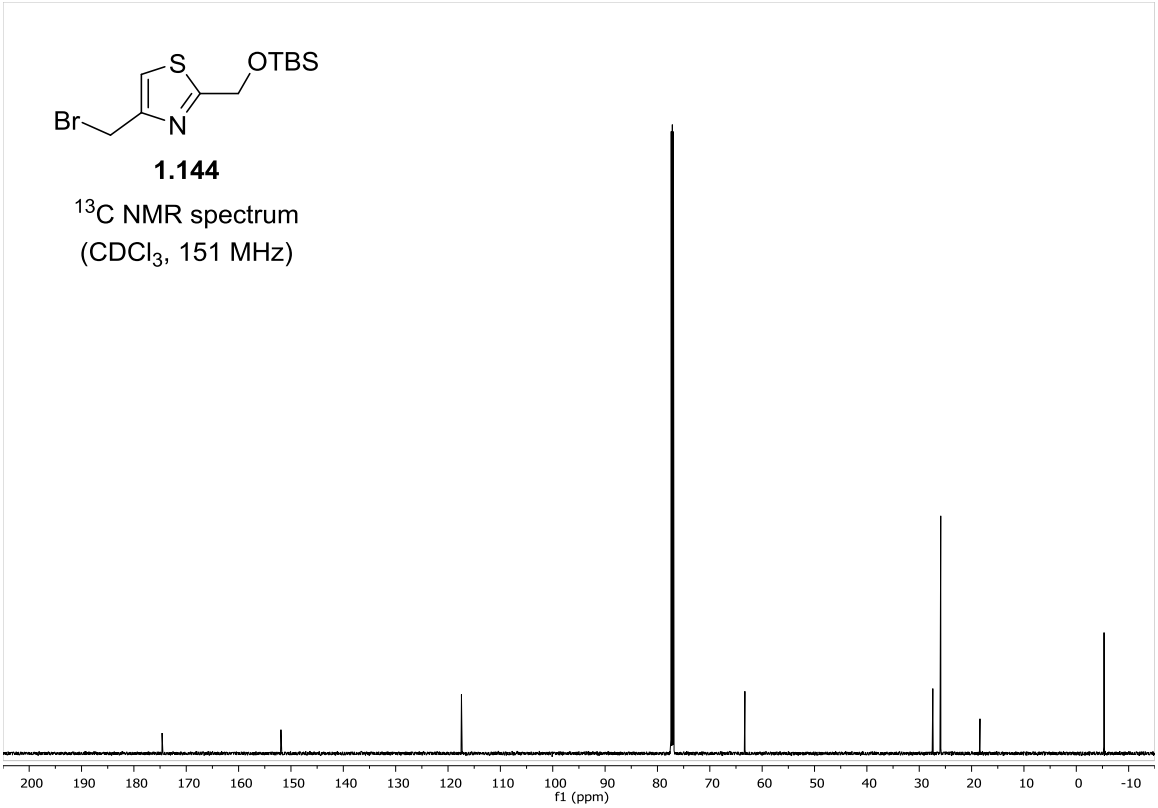
Spectra **1.50**: Compound **1.140**: ^{1}H and ^{13}C NMR



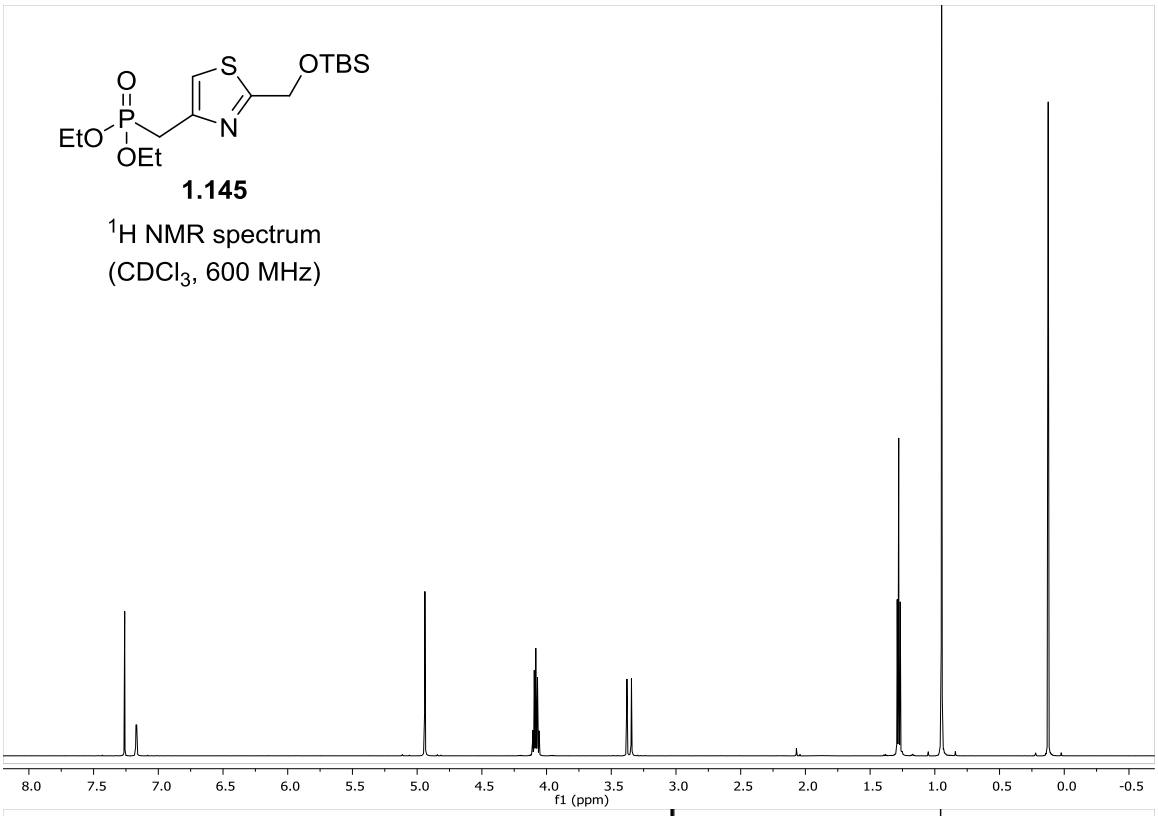


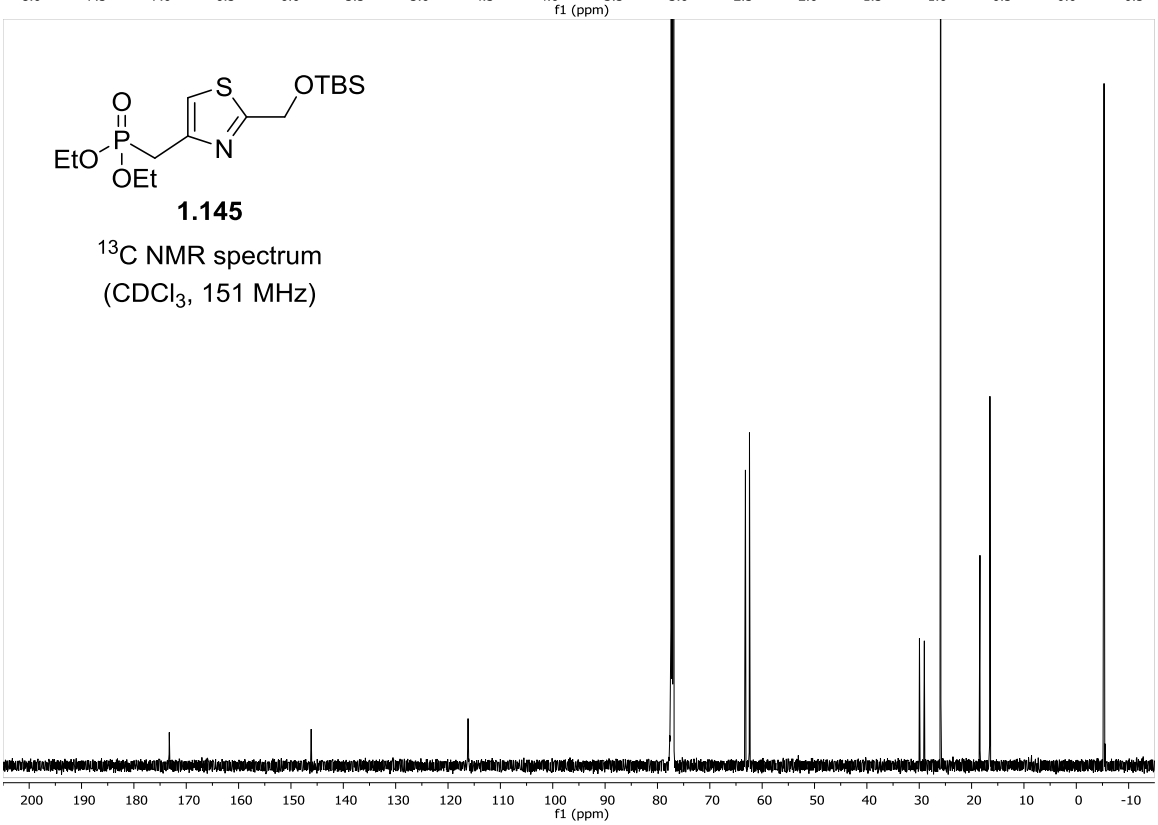
Spectra **1.51**: Compound **1.131**: ^{1}H and ^{13}C NMR



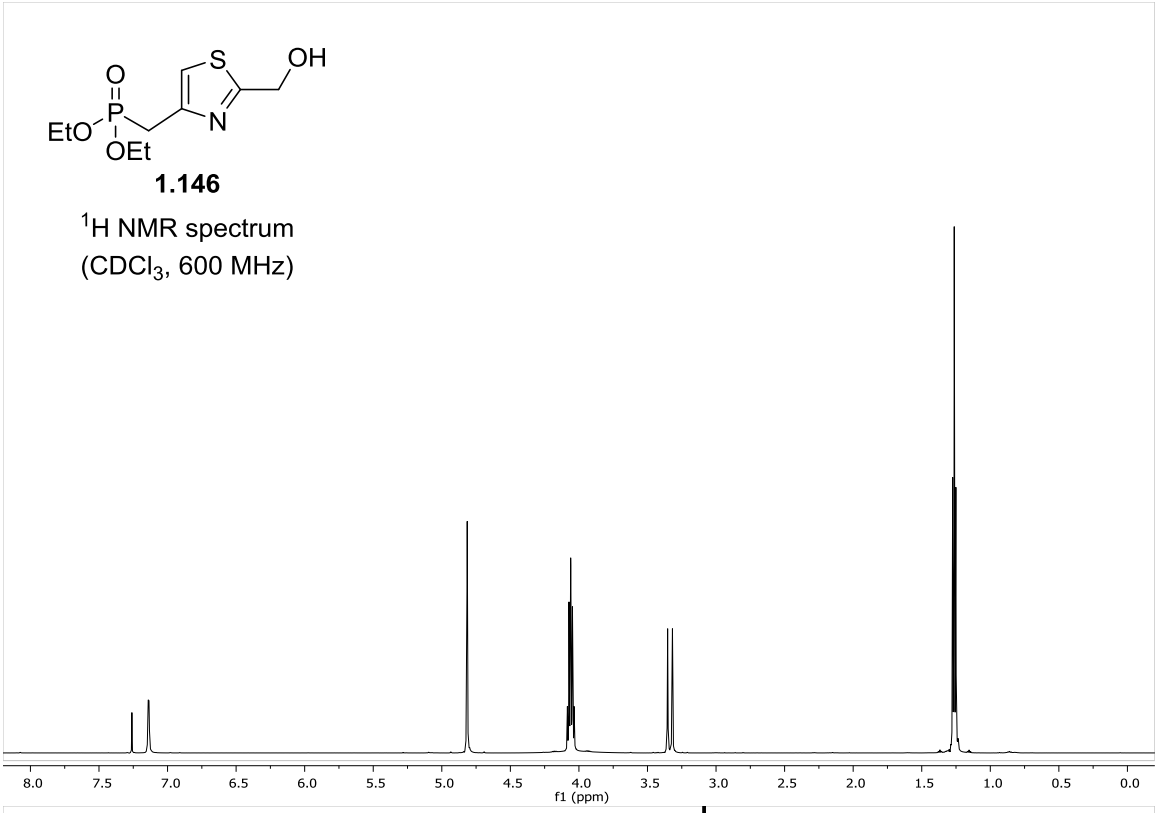


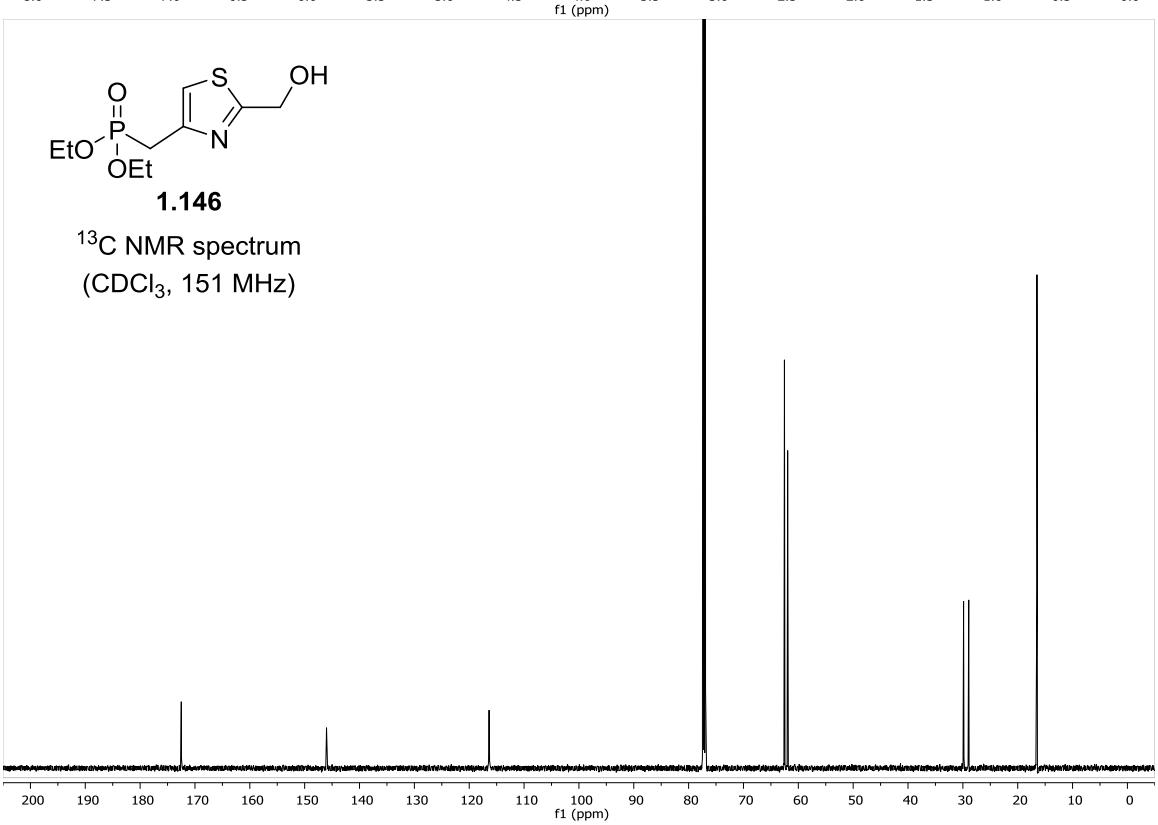
Spectra **1.52**: Compound **1.144**: ^{1}H and ^{13}C NMR



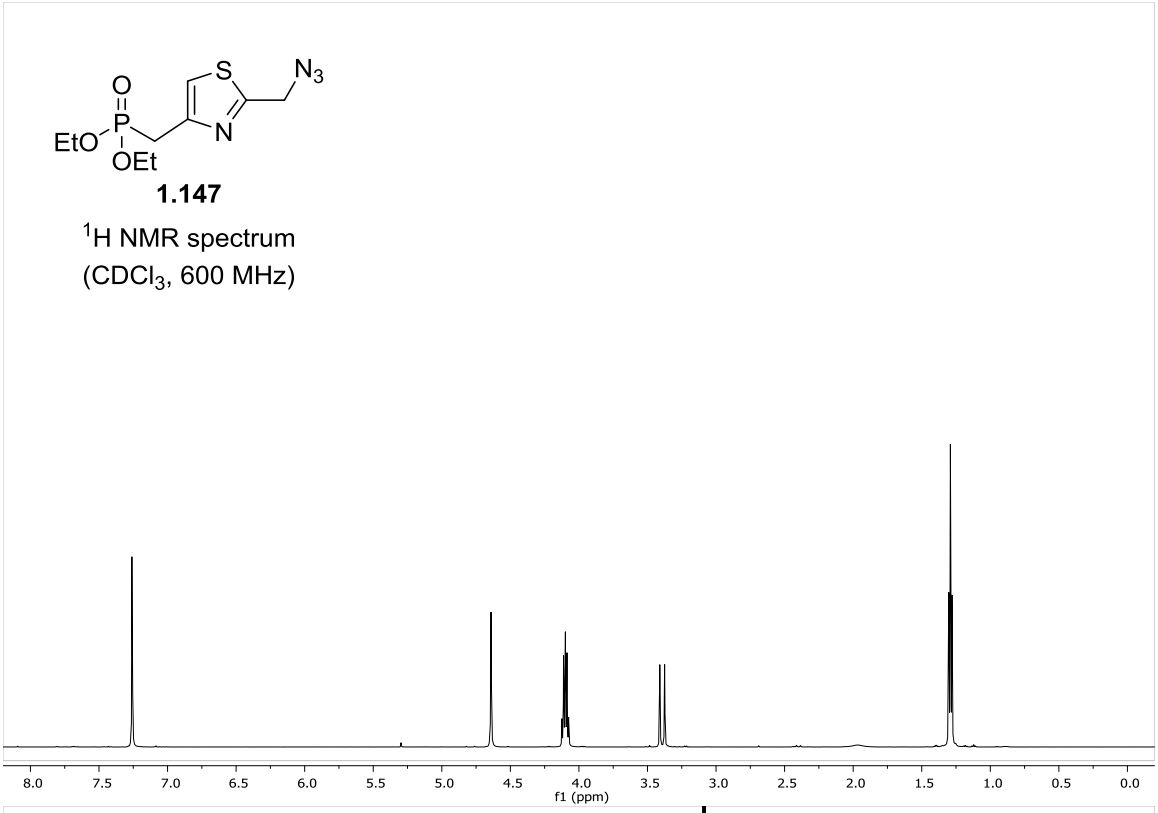


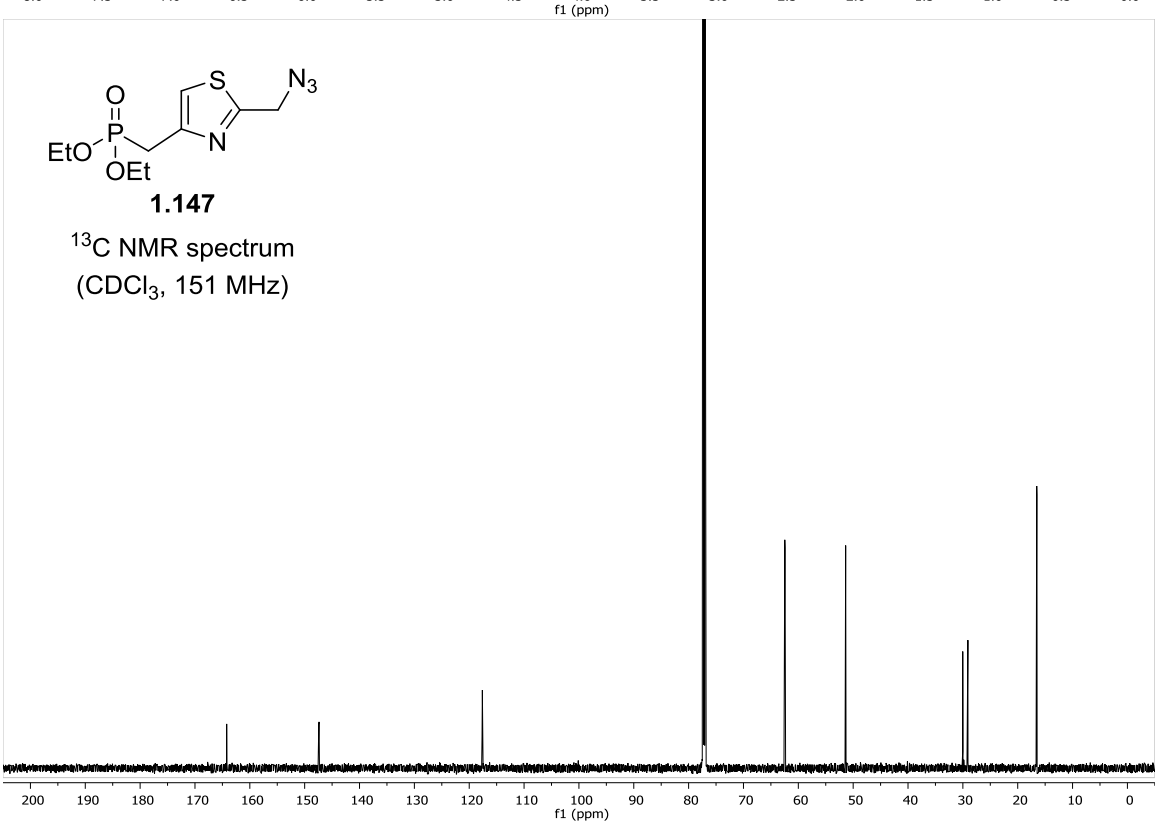
Spectra **1.53**: Compound **1.145**: ^{1}H and ^{13}C NMR



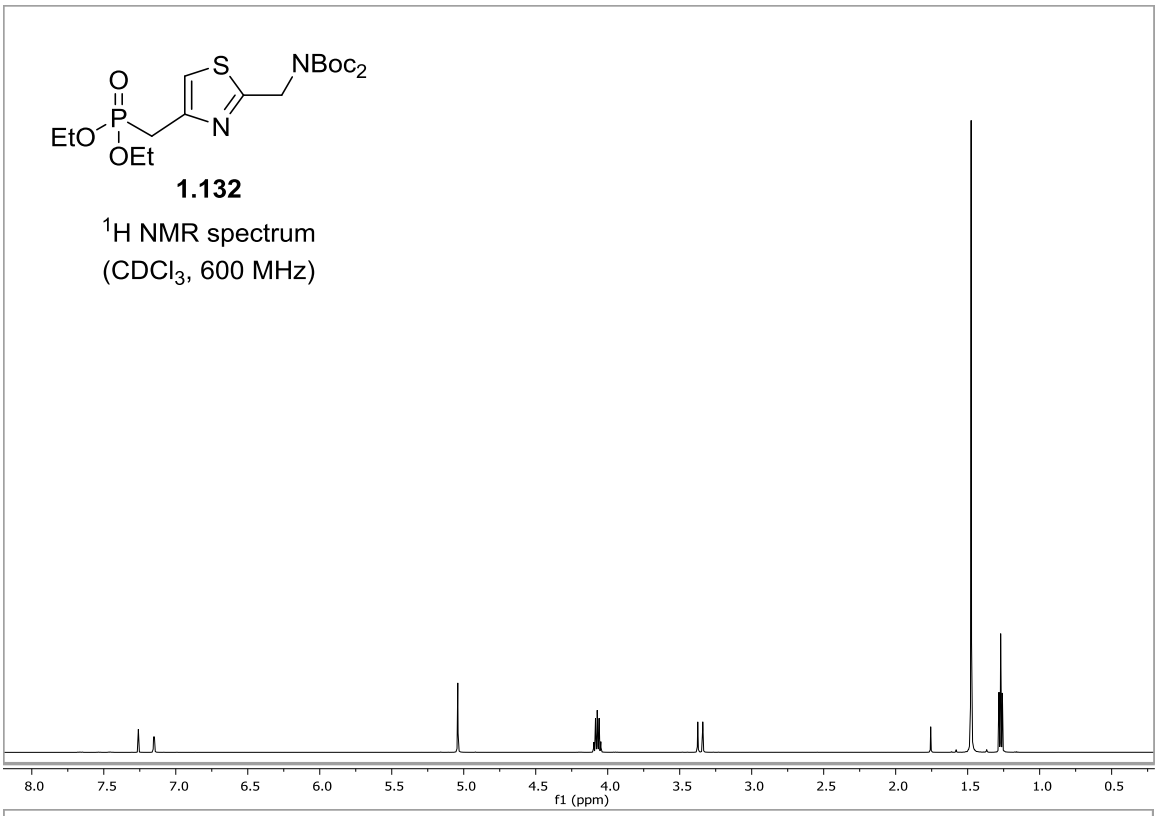


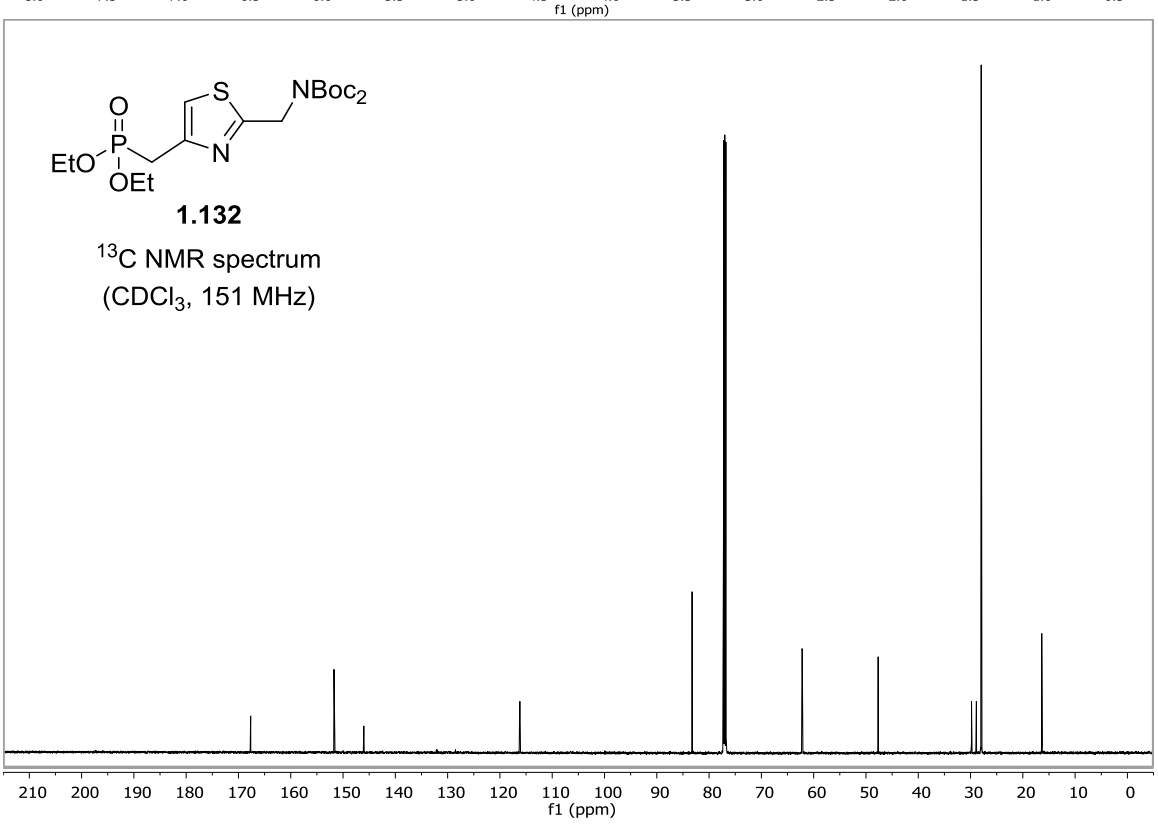
Spectra **1.54**: Compound **1.146**: ^{1}H and ^{13}C NMR



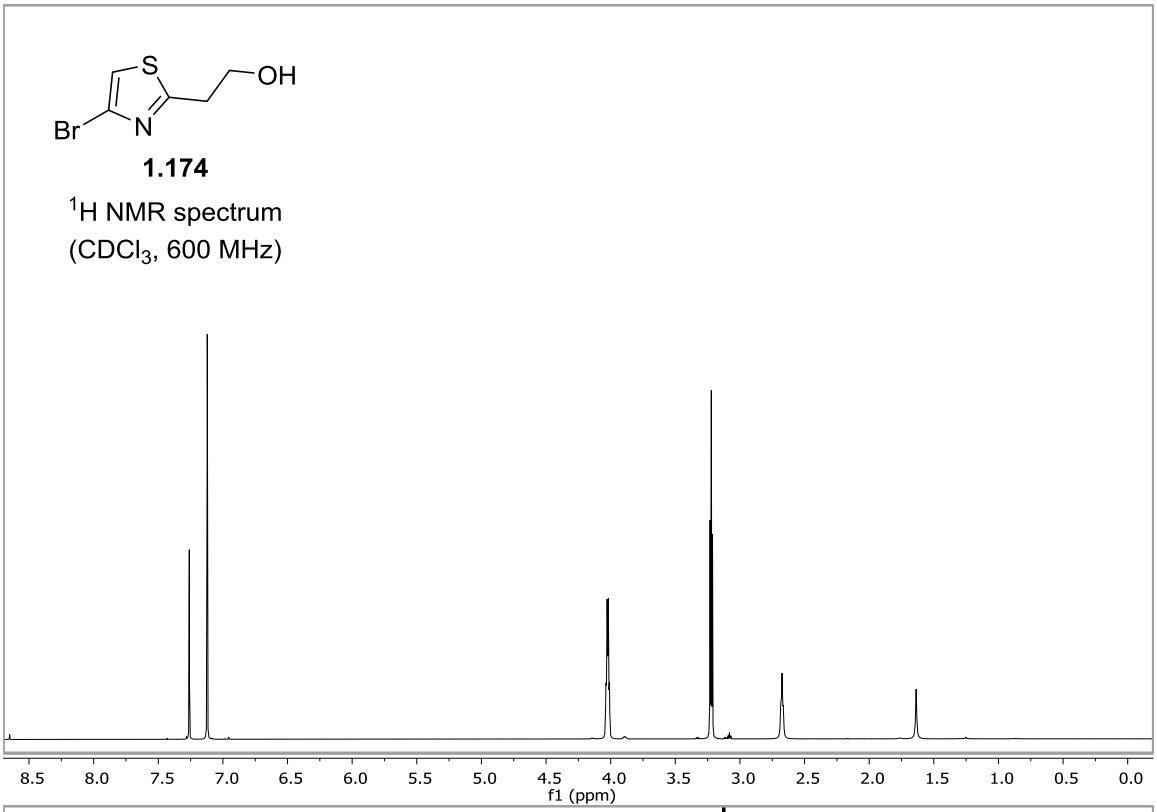


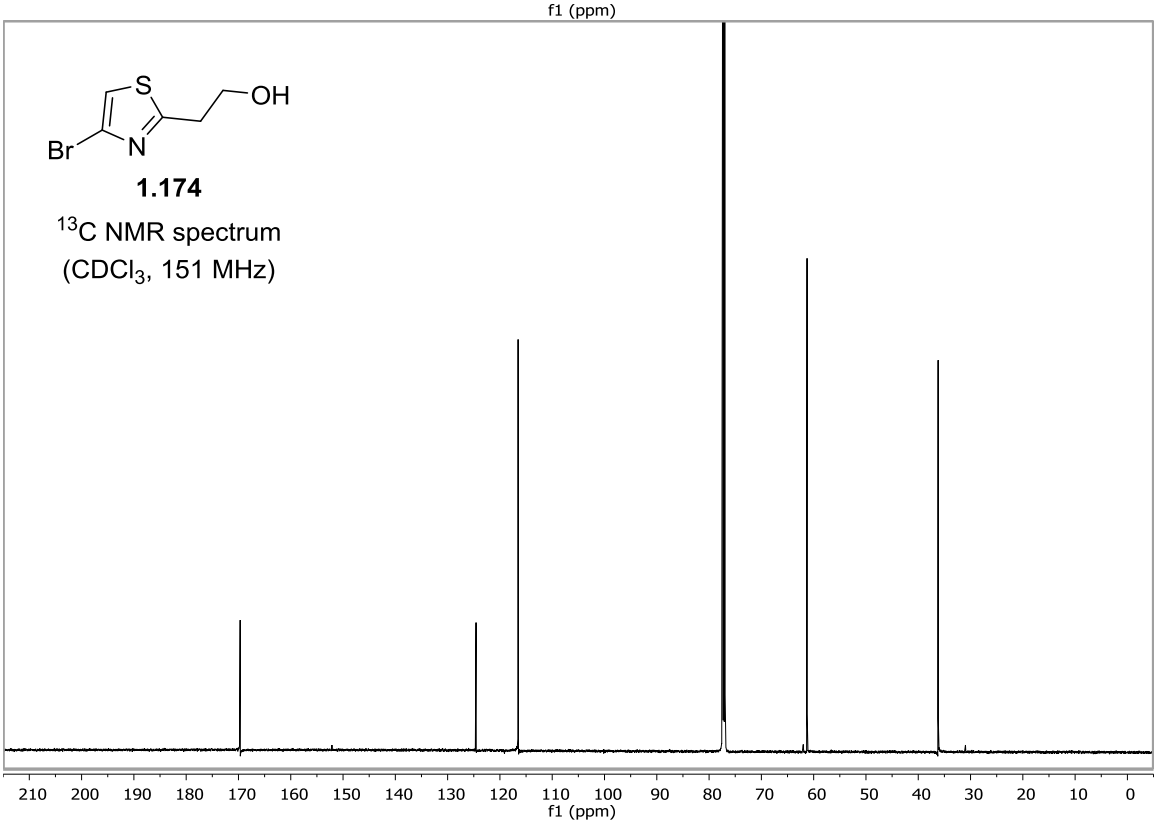
Spectra **1.55**: Compound **1.147**: ^{1}H and ^{13}C NMR



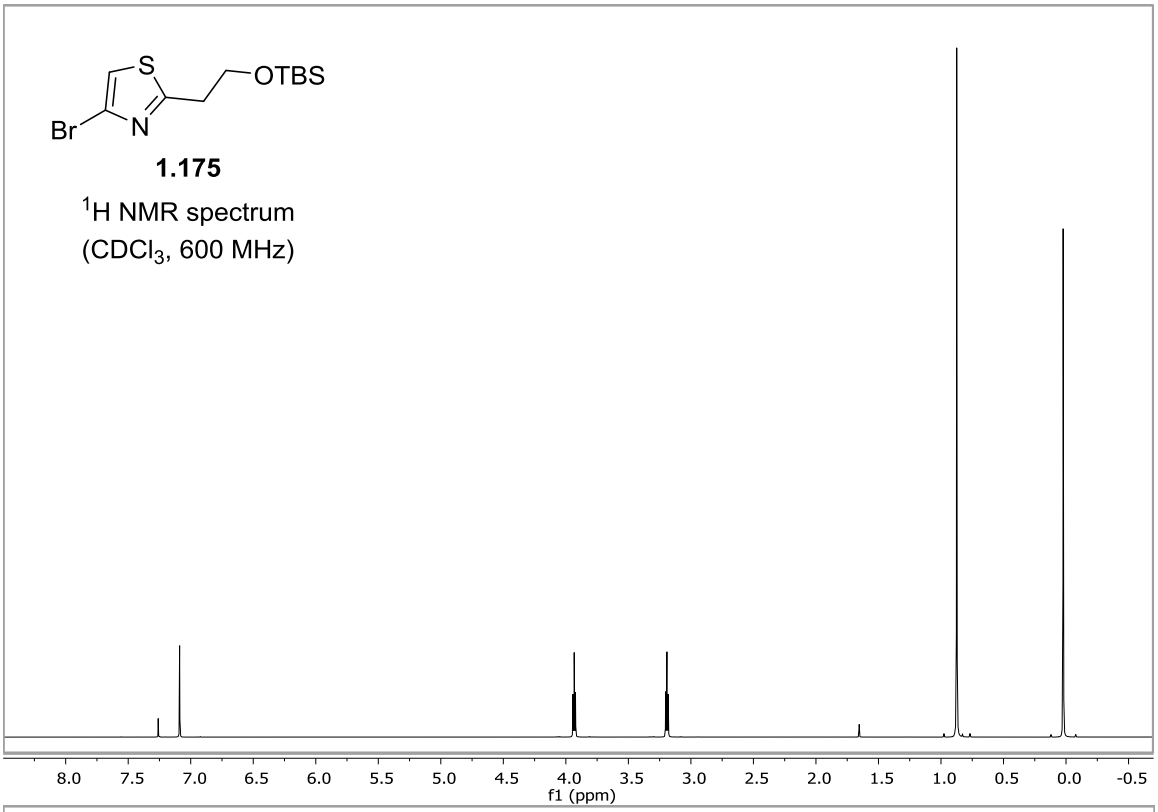


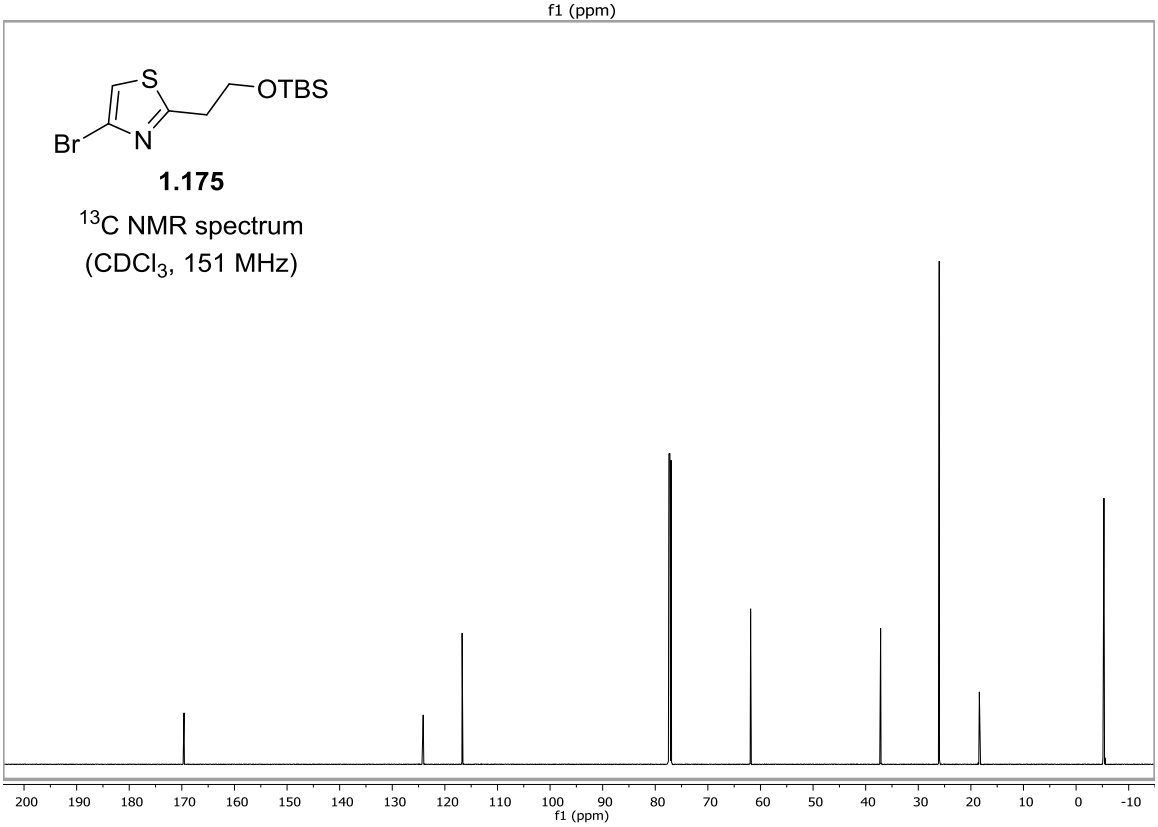
Spectra **1.56**: Compound **1.132**: ^{1}H and ^{13}C NMR



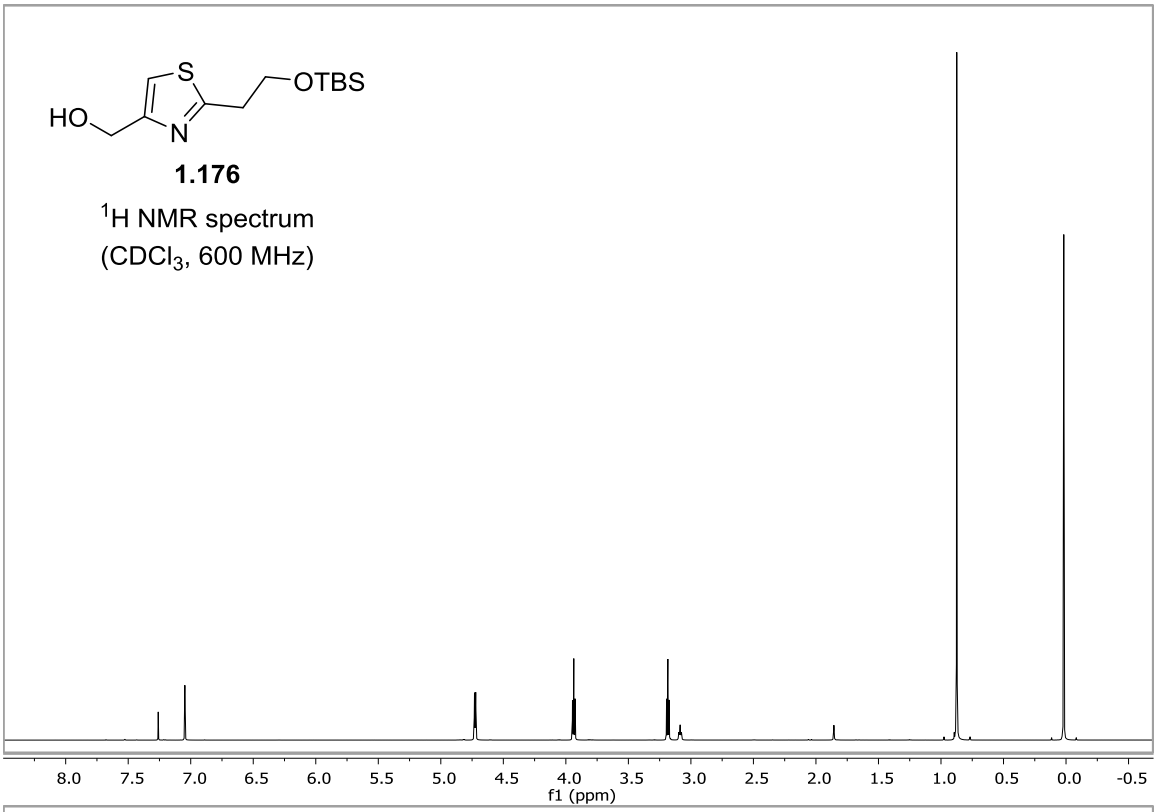


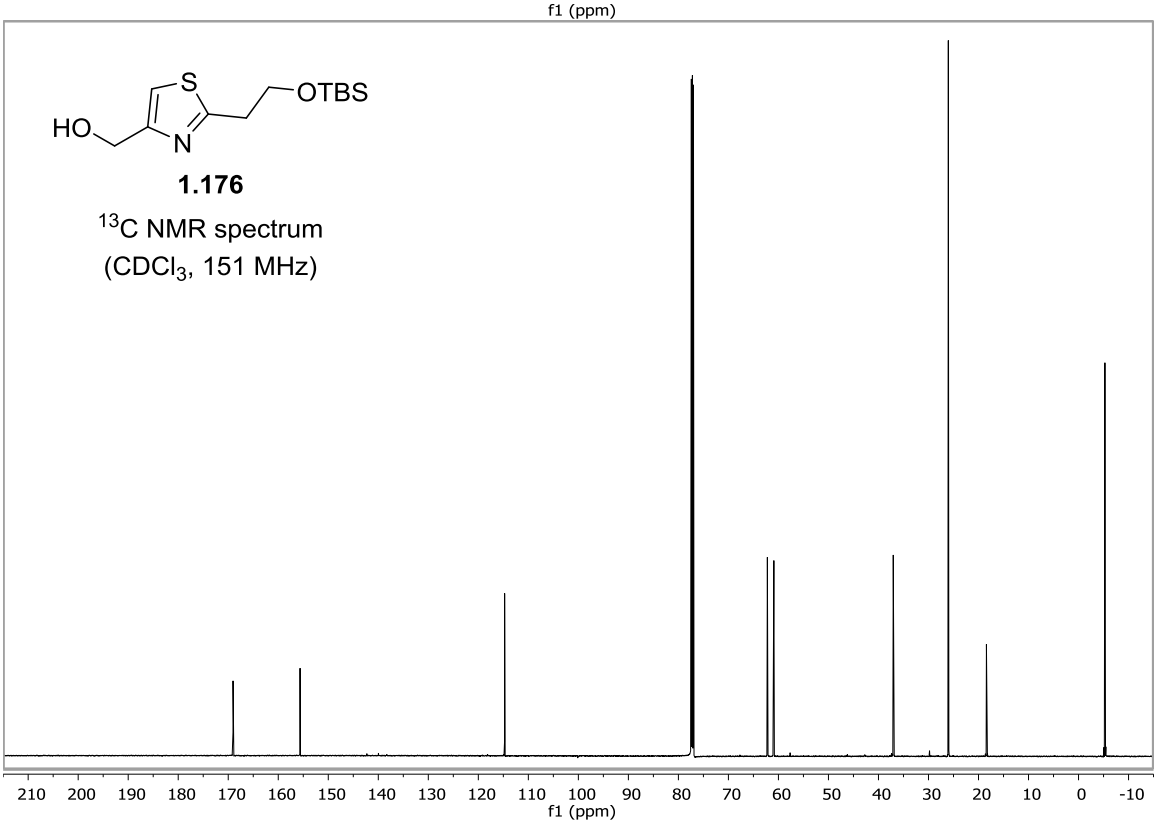
Spectra **1.57**: Compound **1.174**: ^{1}H and ^{13}C NMR



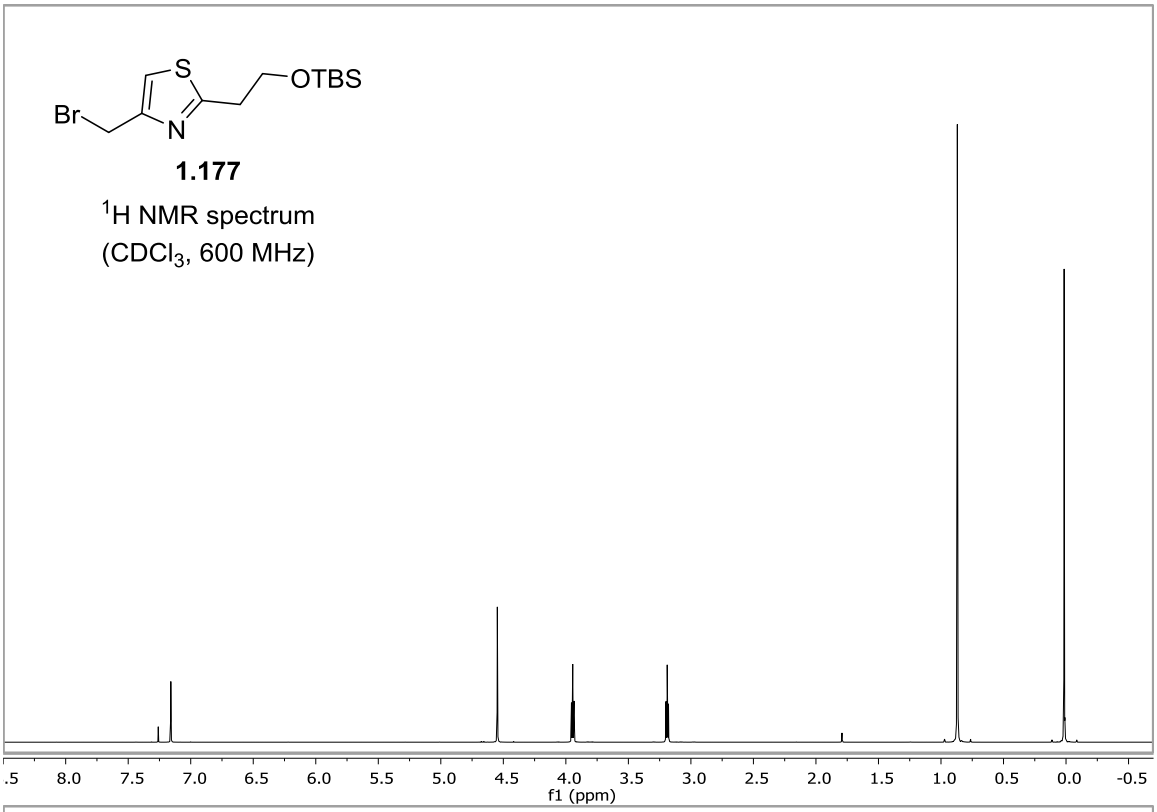


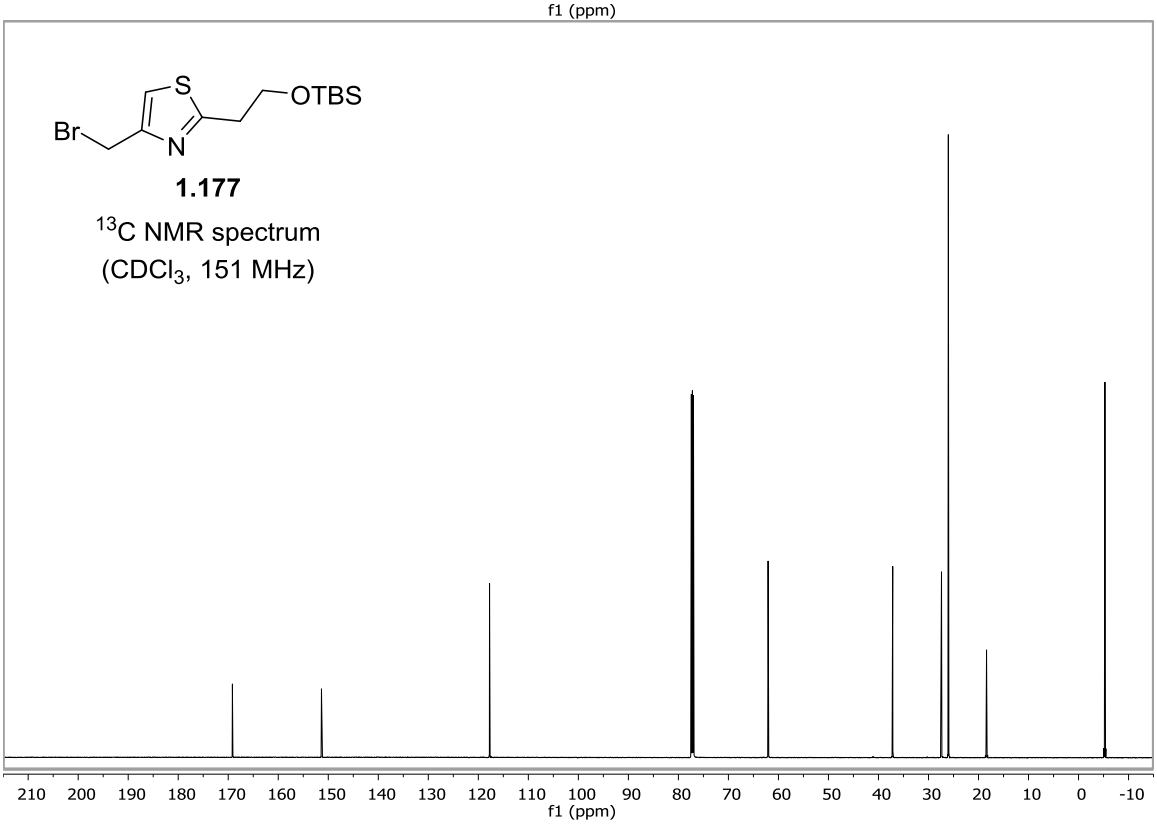
Spectra **1.58**: Compound **1.175**: ^{1}H and ^{13}C NMR



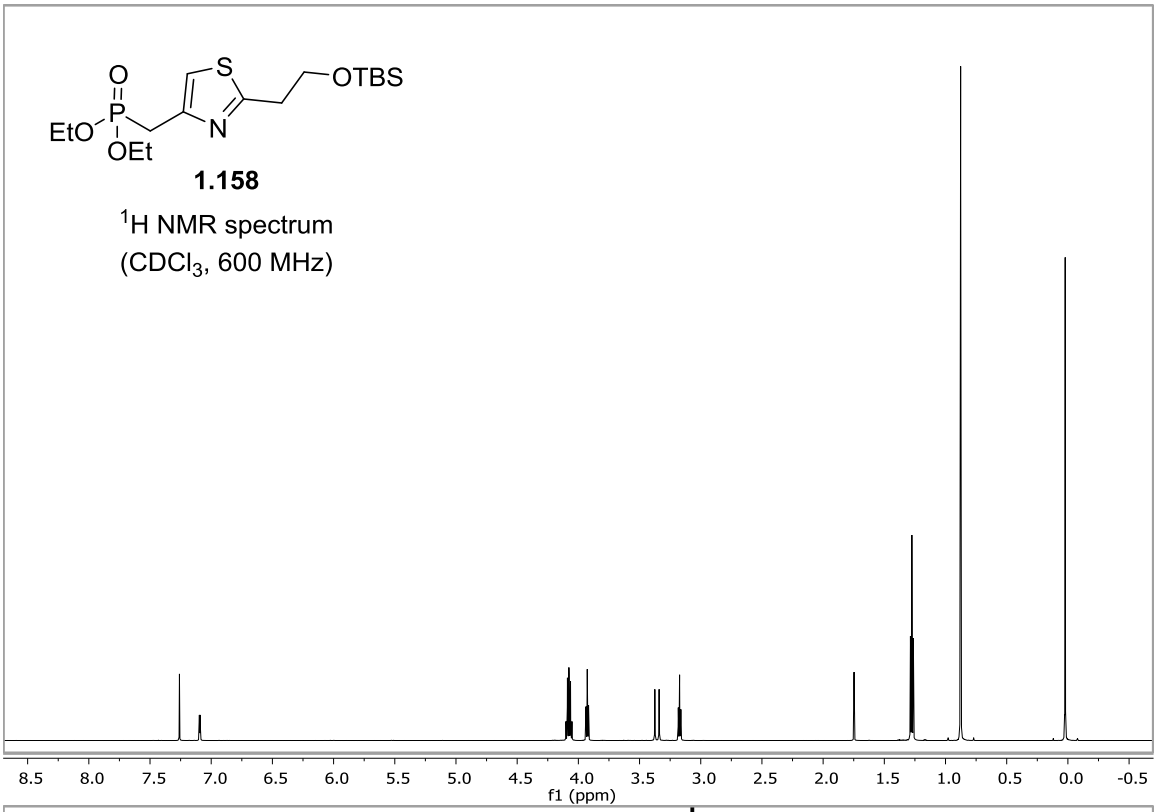


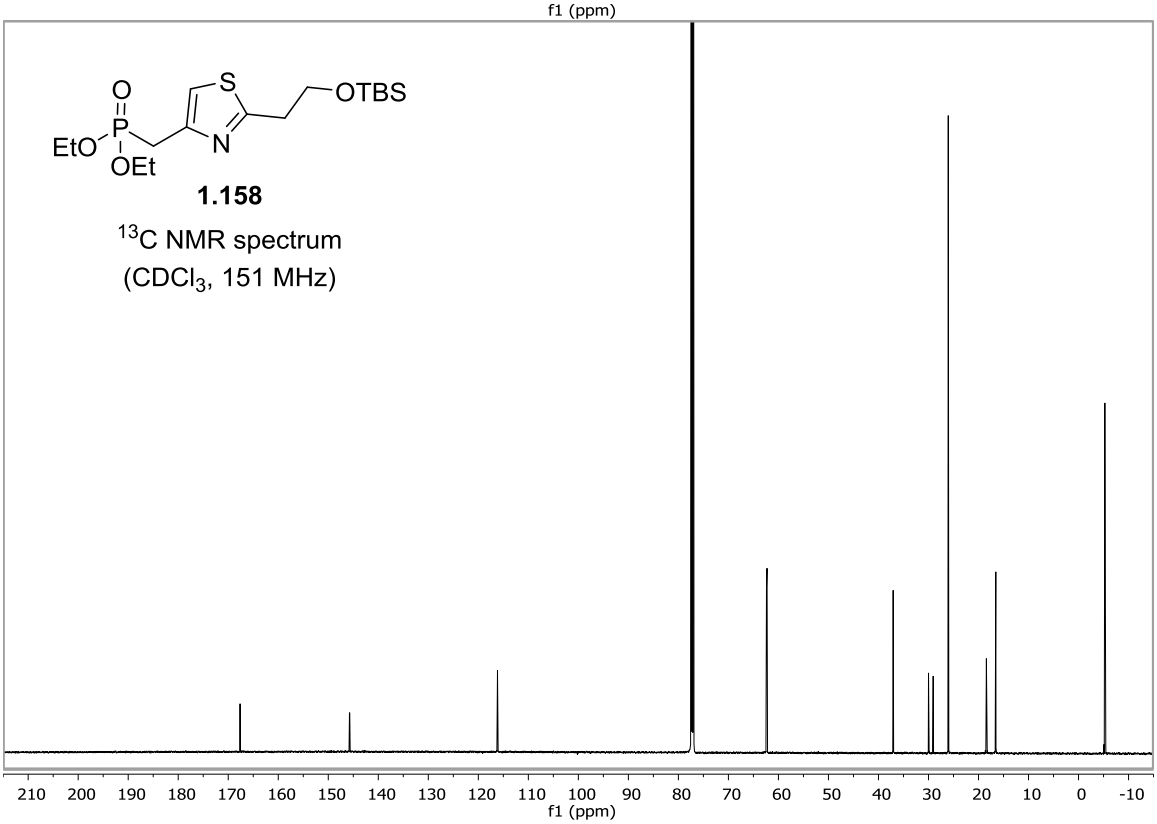
Spectra **1.59**: Compound **1.176**: ^{1}H and ^{13}C NMR



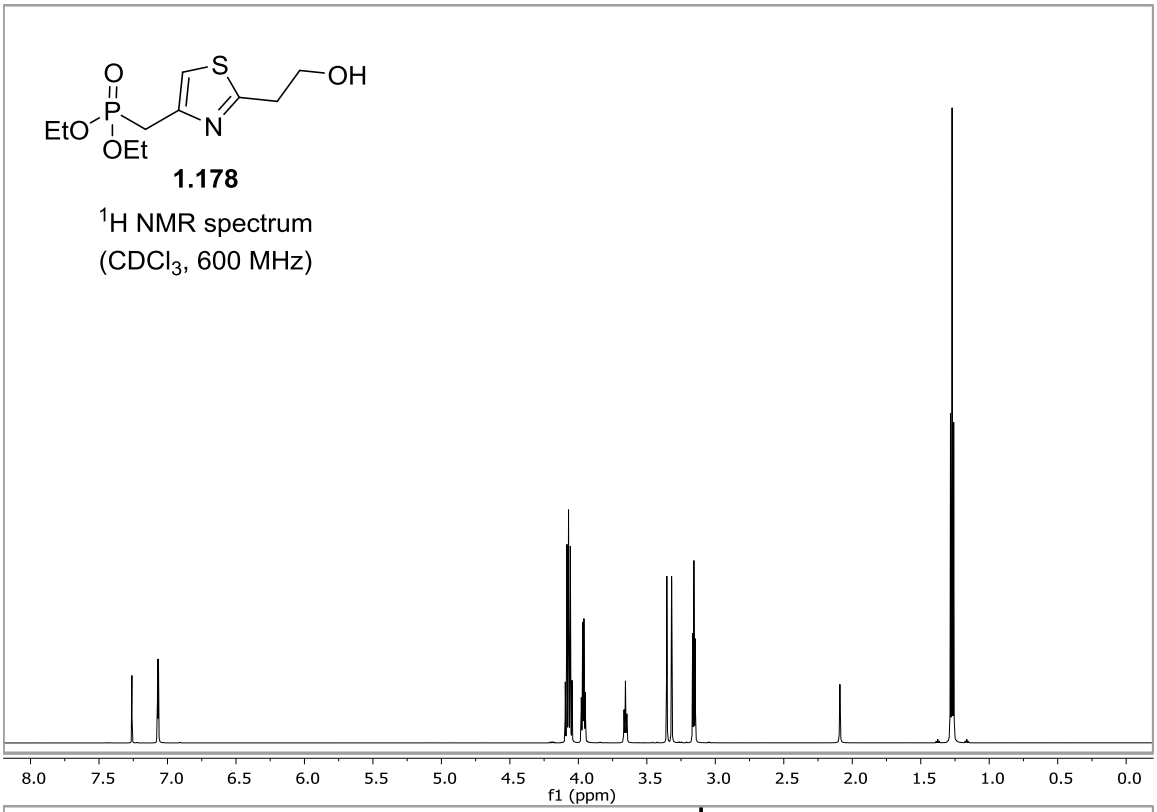


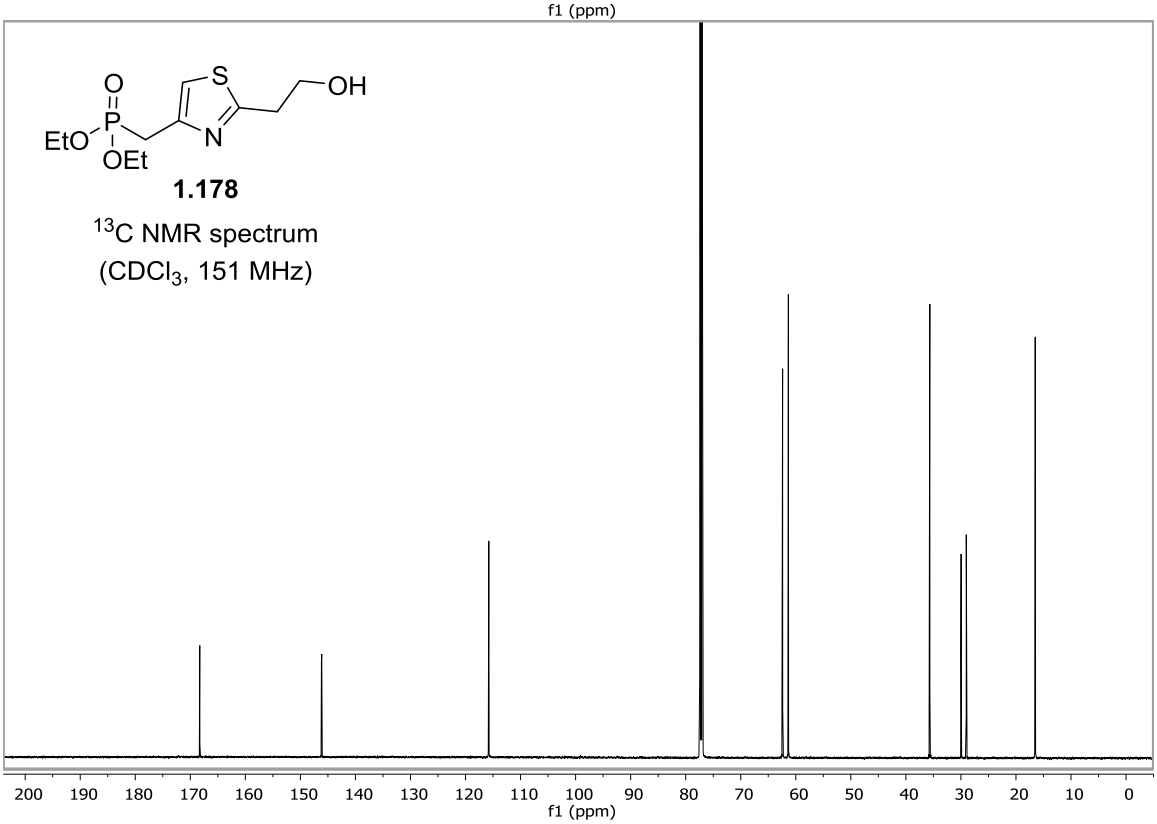
Spectra **1.60**: Compound **1.177**: ^{1}H and ^{13}C NMR



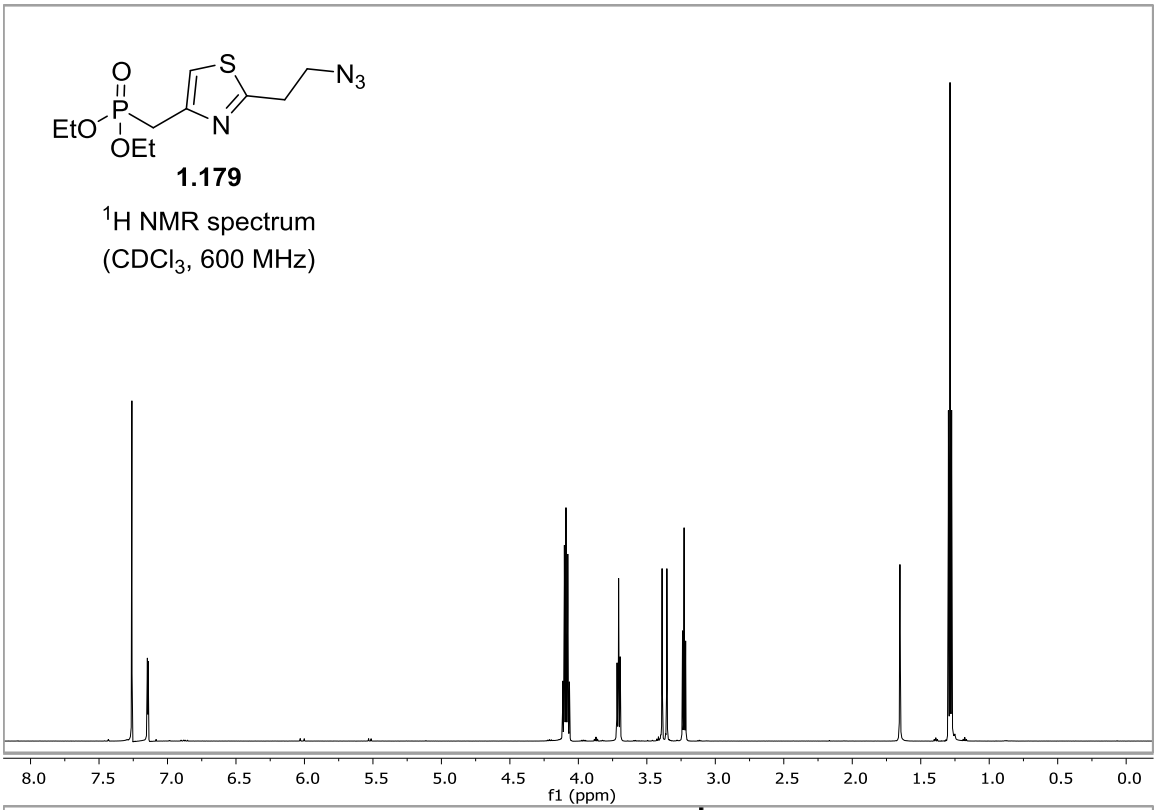


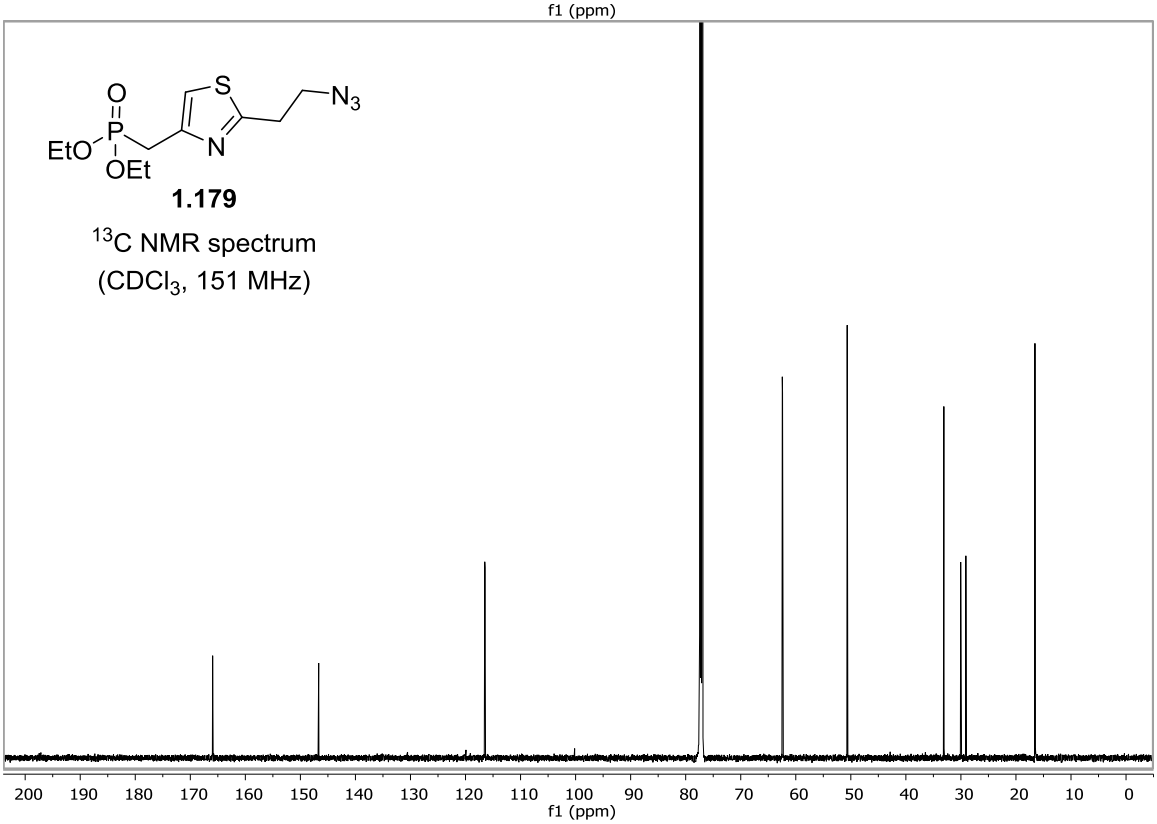
Spectra **1.61**: Compound **1.158**: ^{1}H and ^{13}C NMR



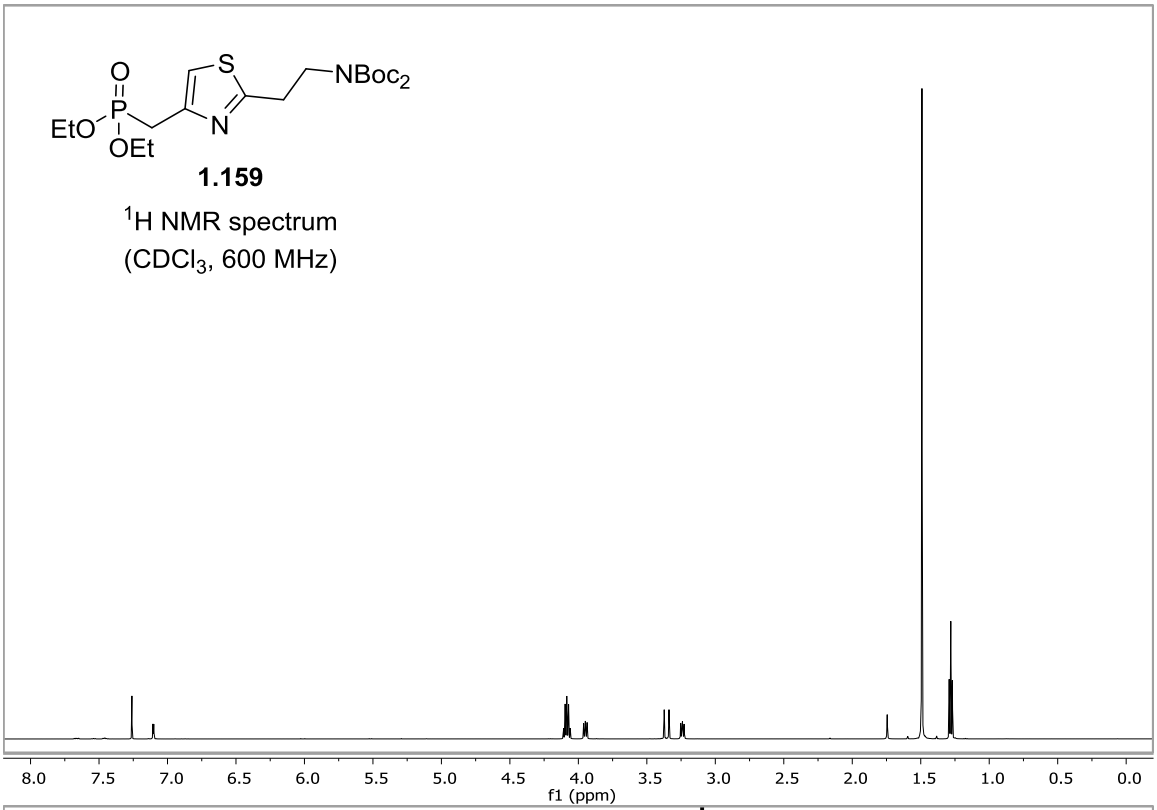


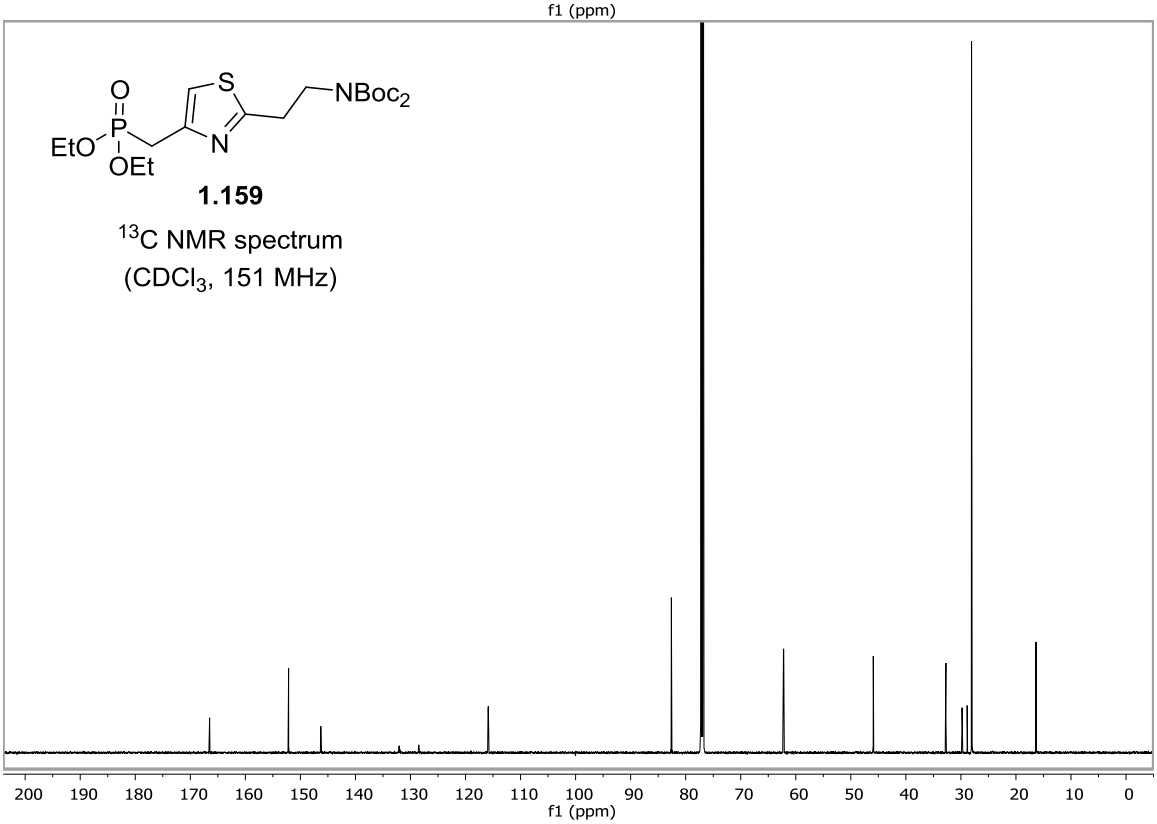
Spectra **1.62**: Compound **1.178**: ^{1}H and ^{13}C NMR



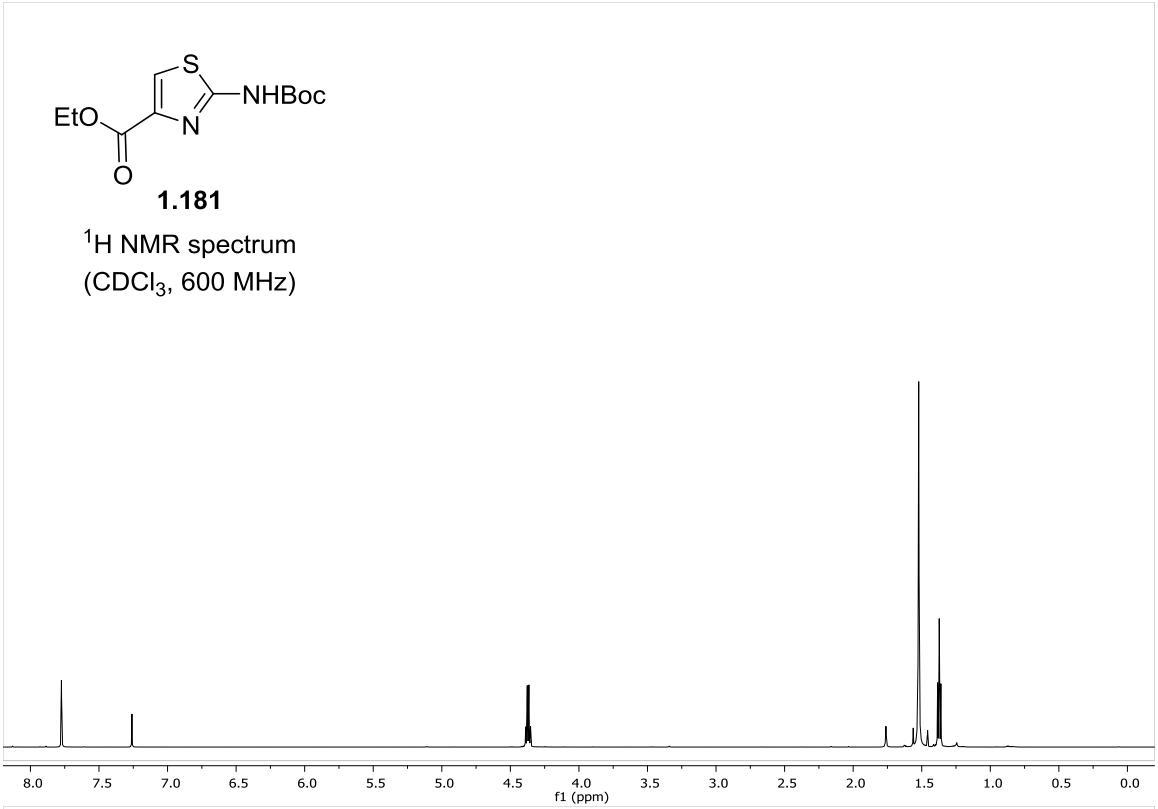


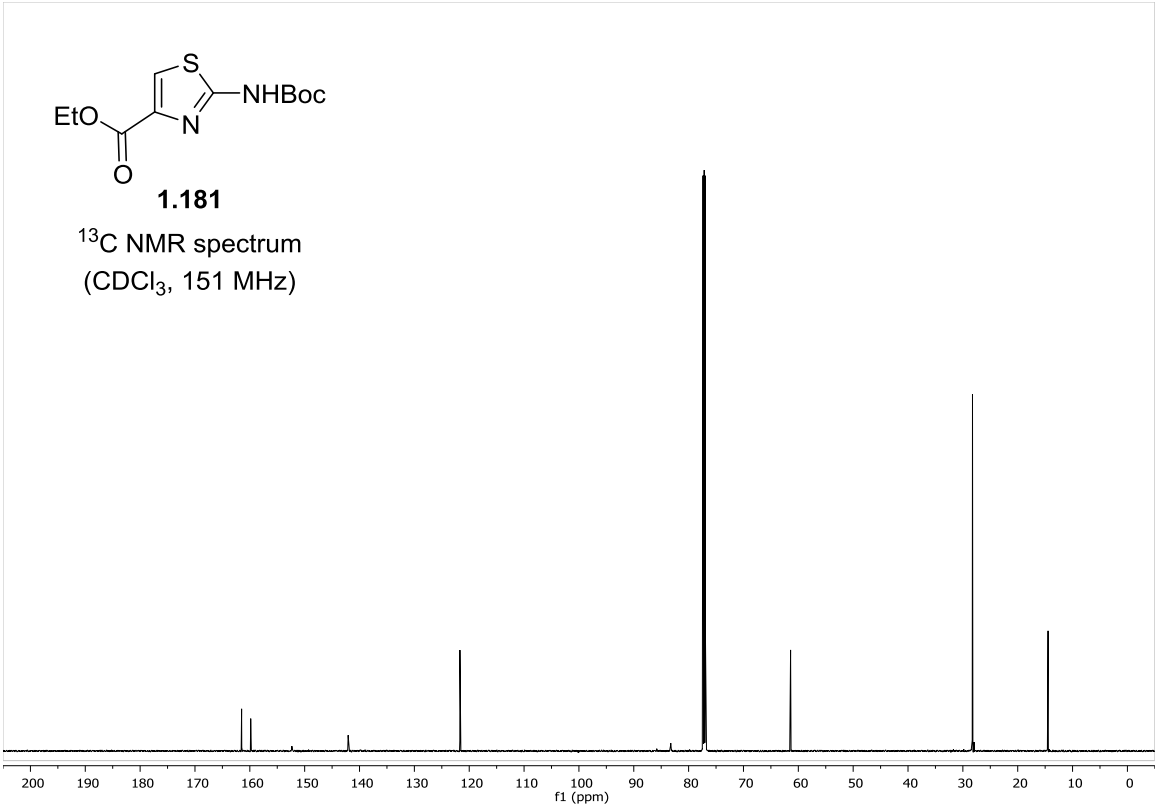
Spectra **1.63**: Compound **1.179**: ^{1}H and ^{13}C NMR



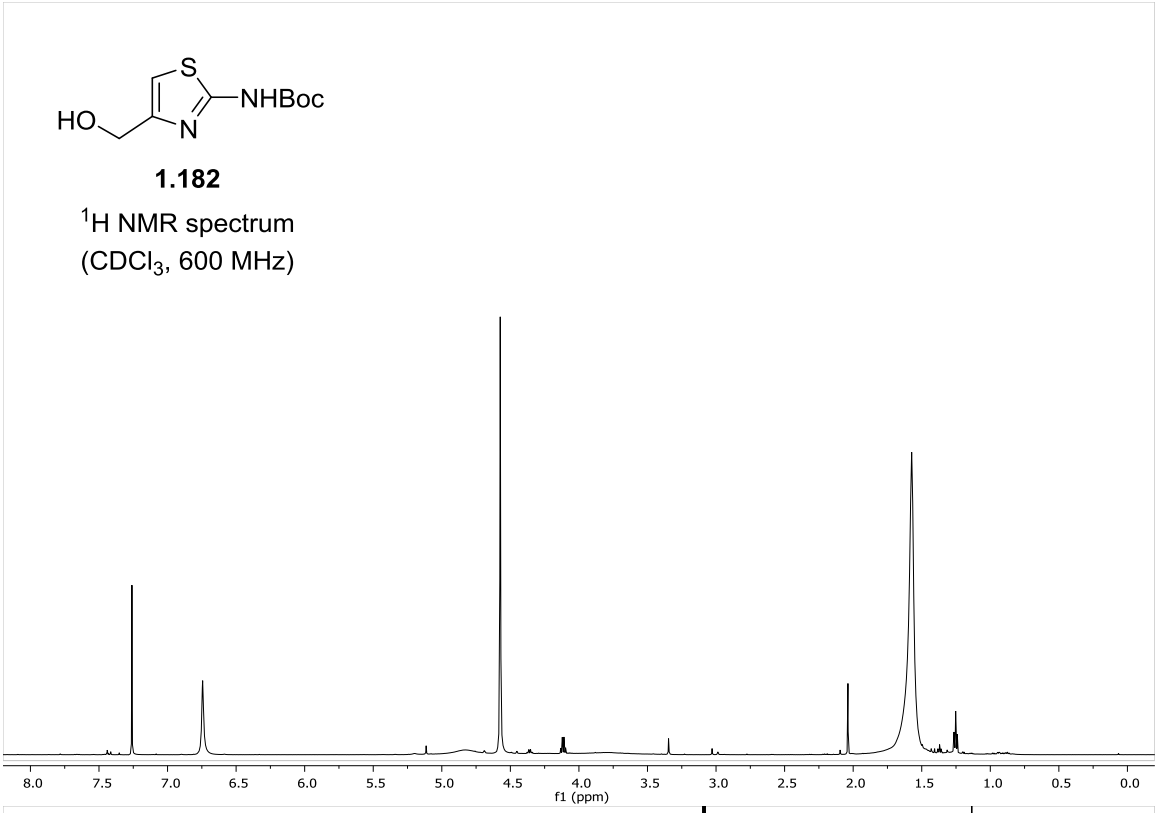


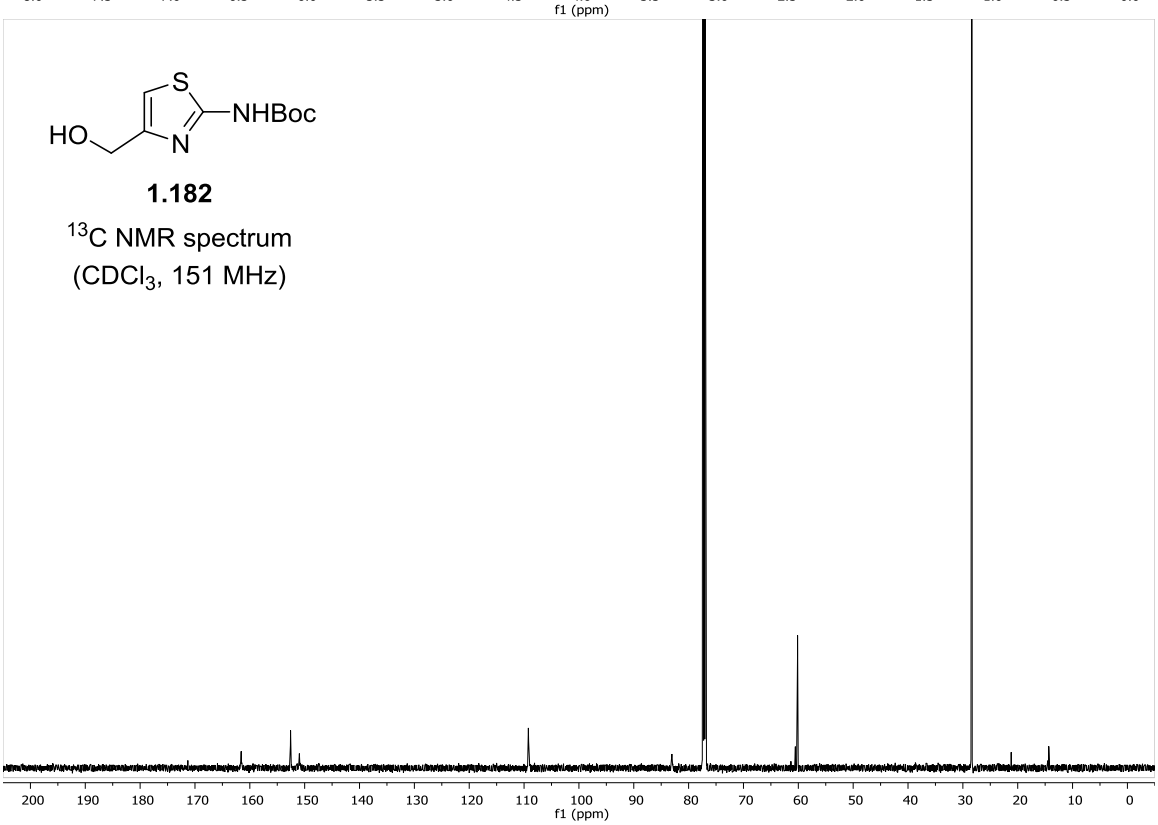
Spectra **1.64**: Compound **1.159**: ^{1}H and ^{13}C NMR



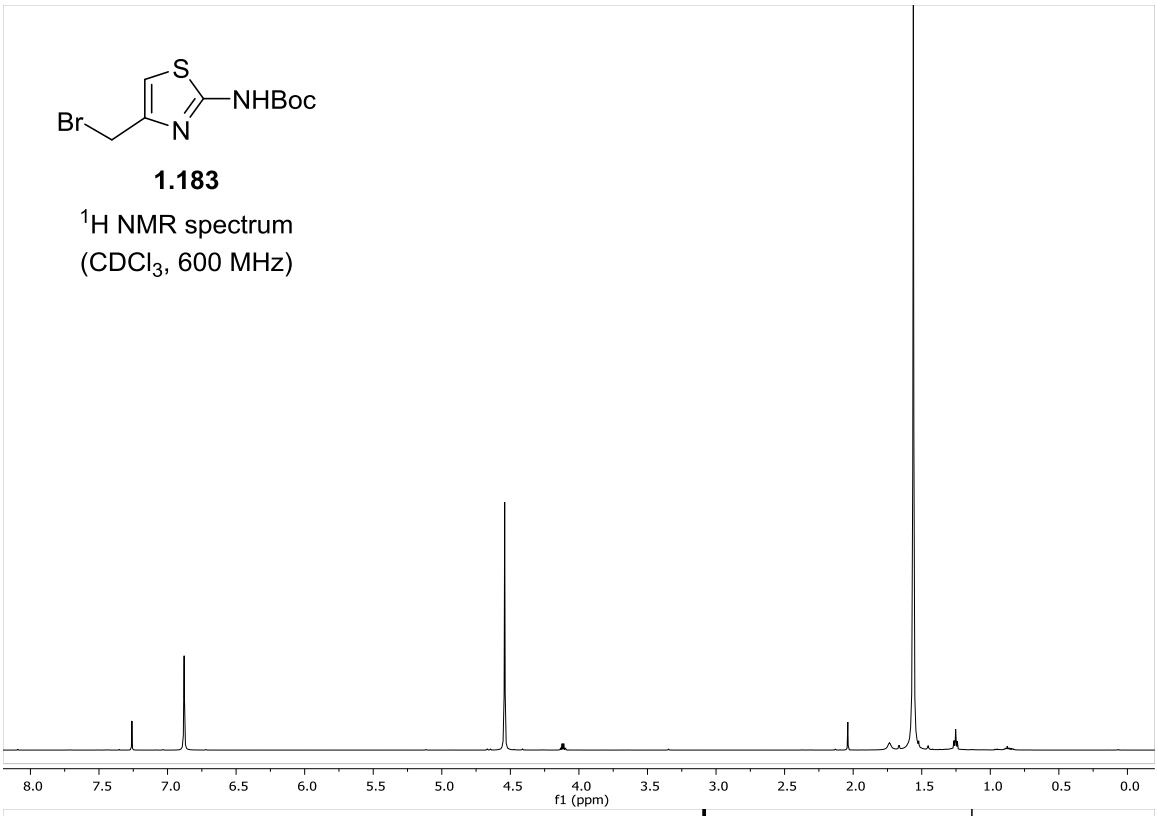


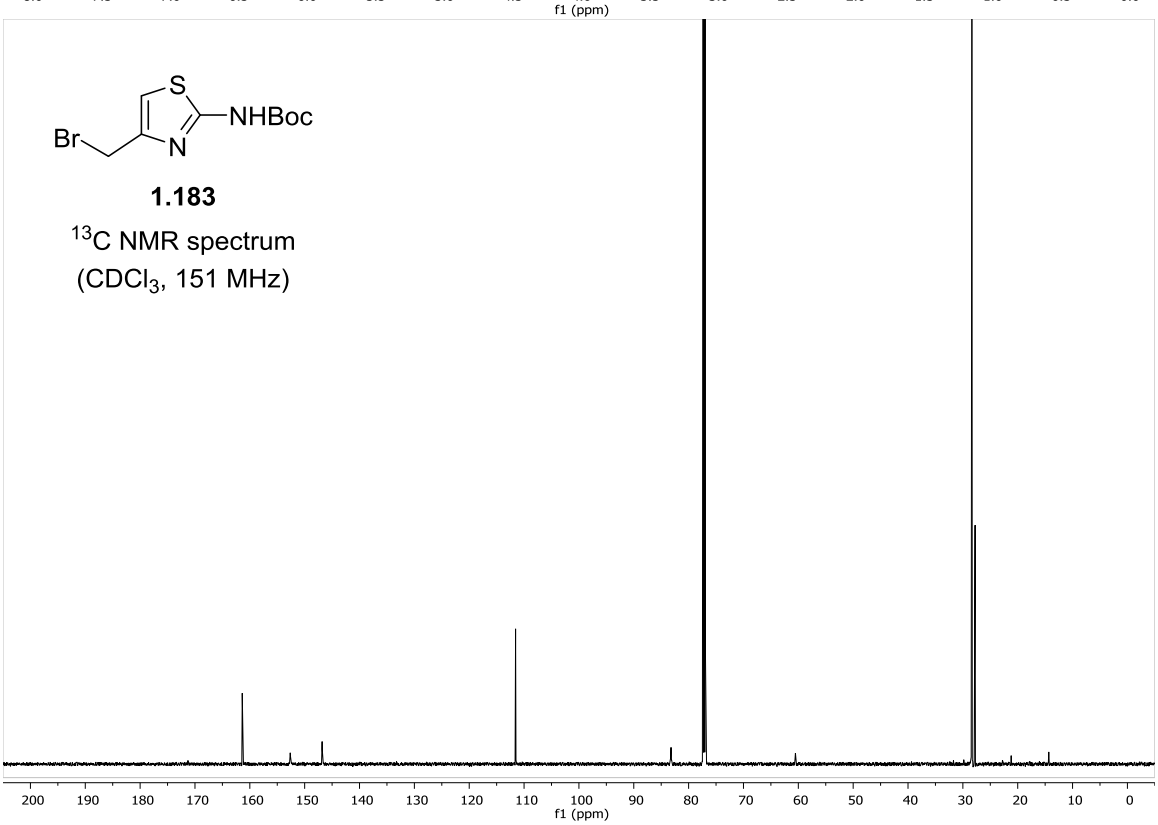
Spectra **1.65**: Compound **1.181**: ^{1}H and ^{13}C NMR



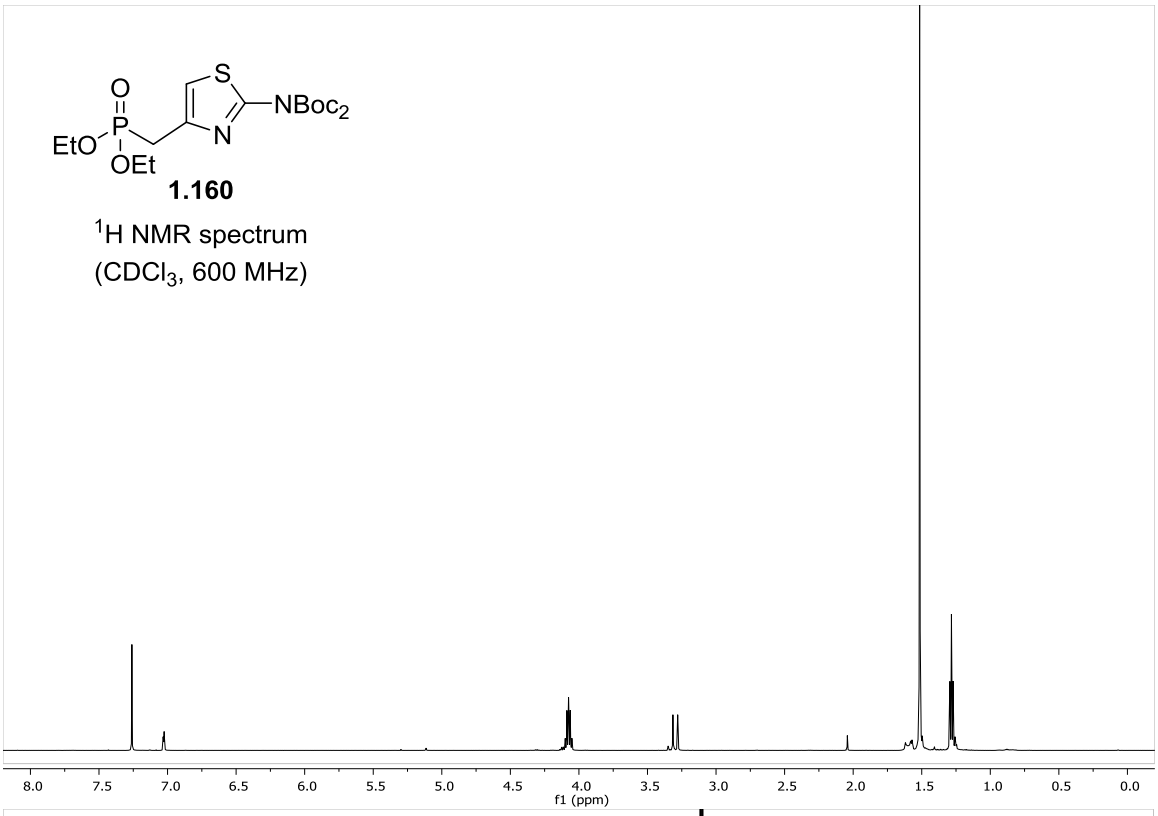


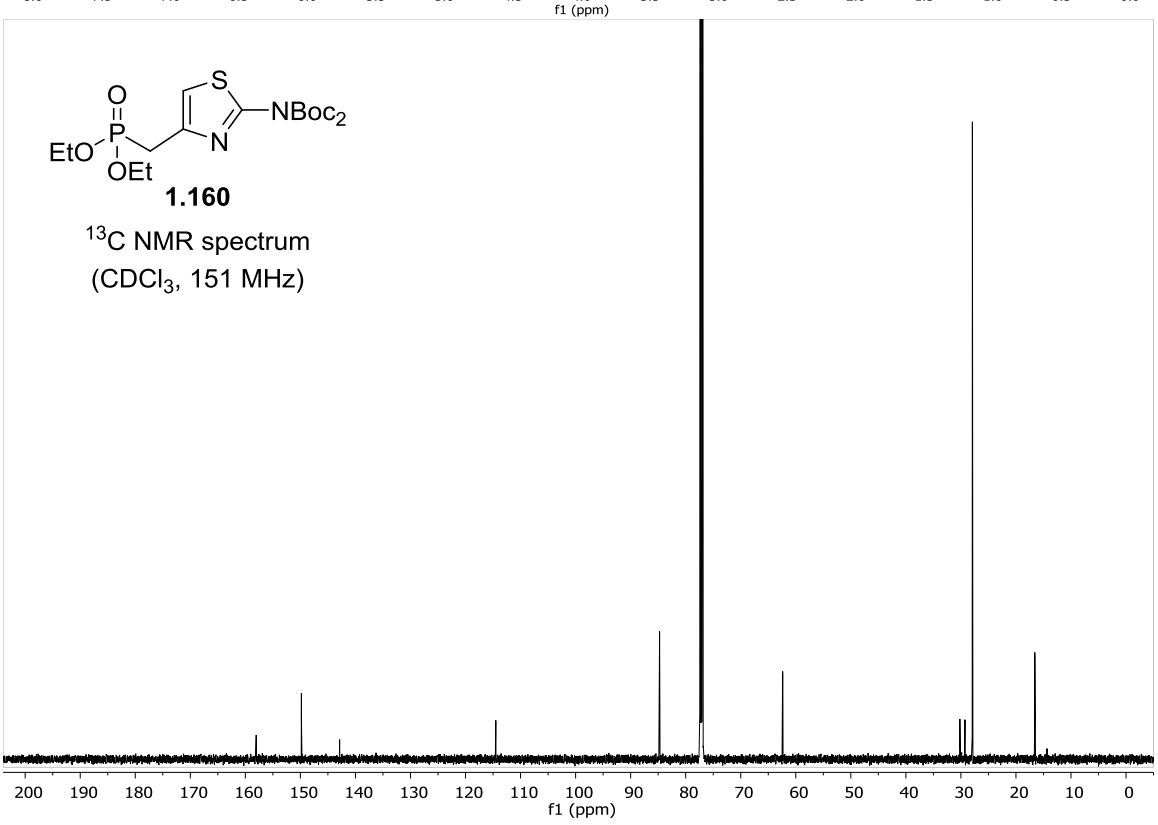
Spectra **1.66**: Compound **1.182**: ^{1}H and ^{13}C NMR



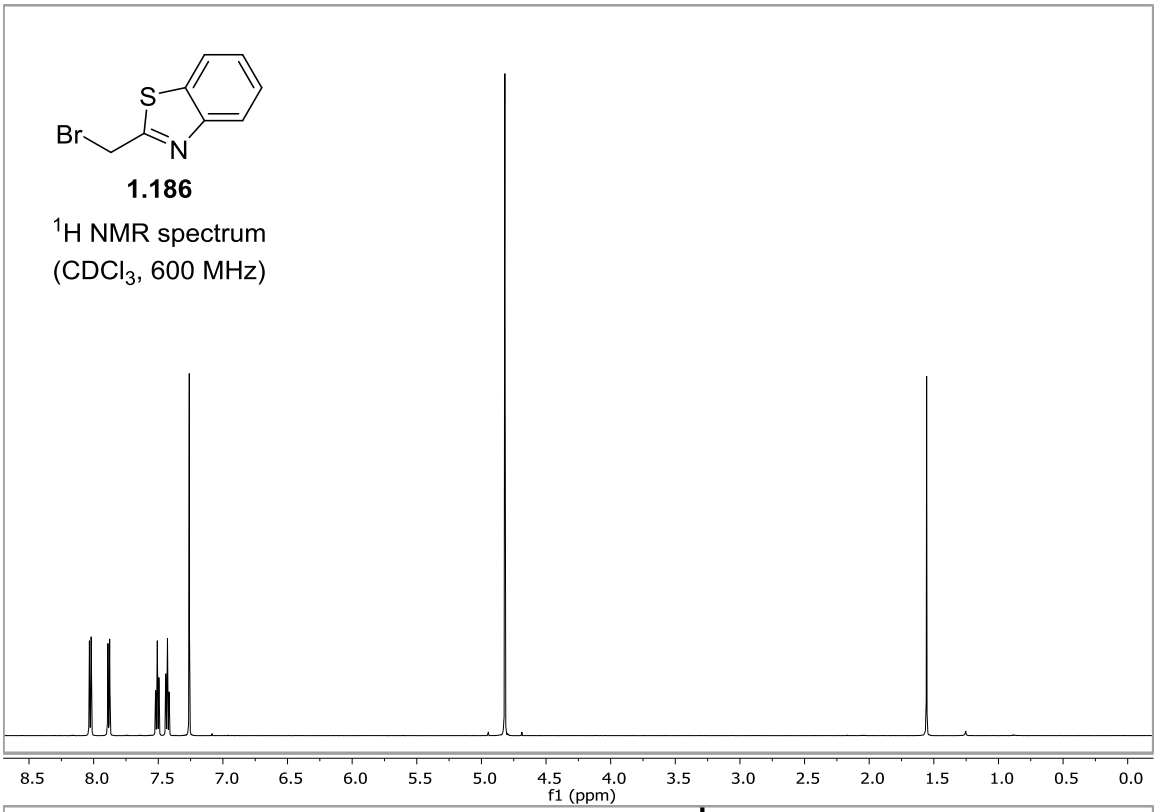


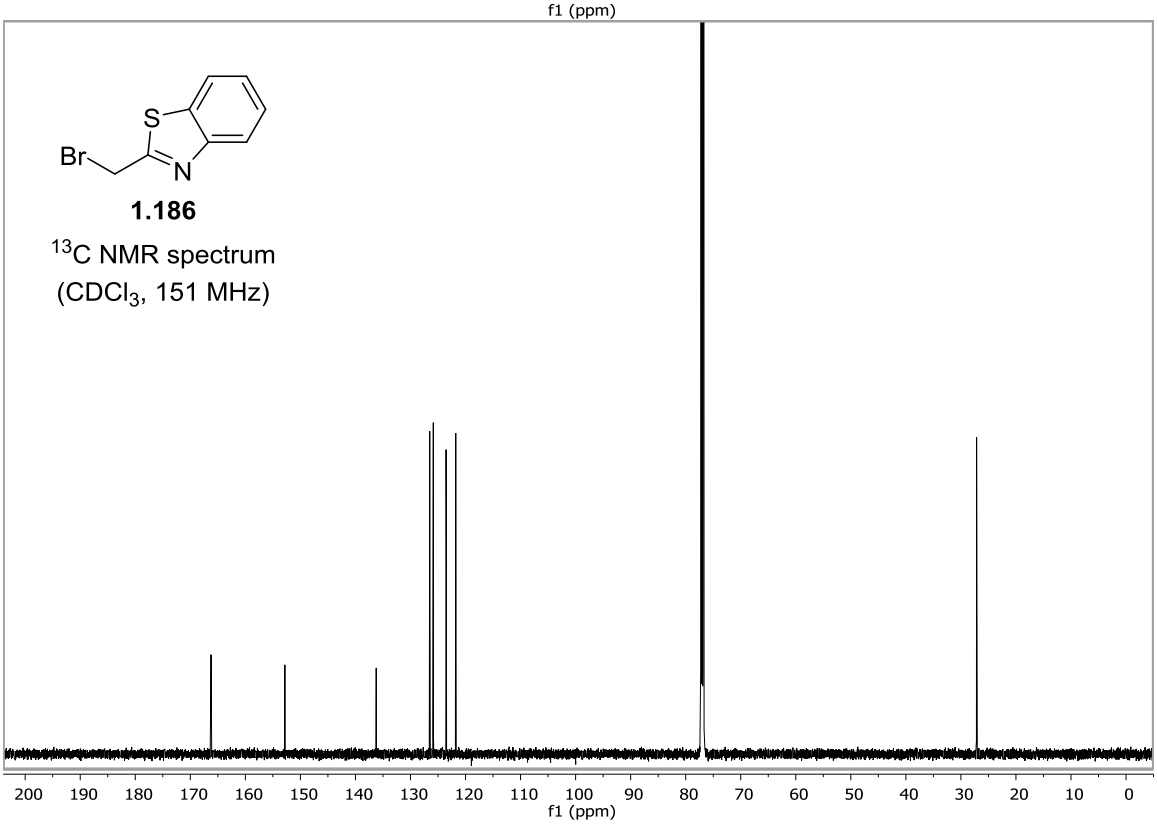
Spectra **1.67**: Compound **1.183**: ^{1}H and ^{13}C NMR



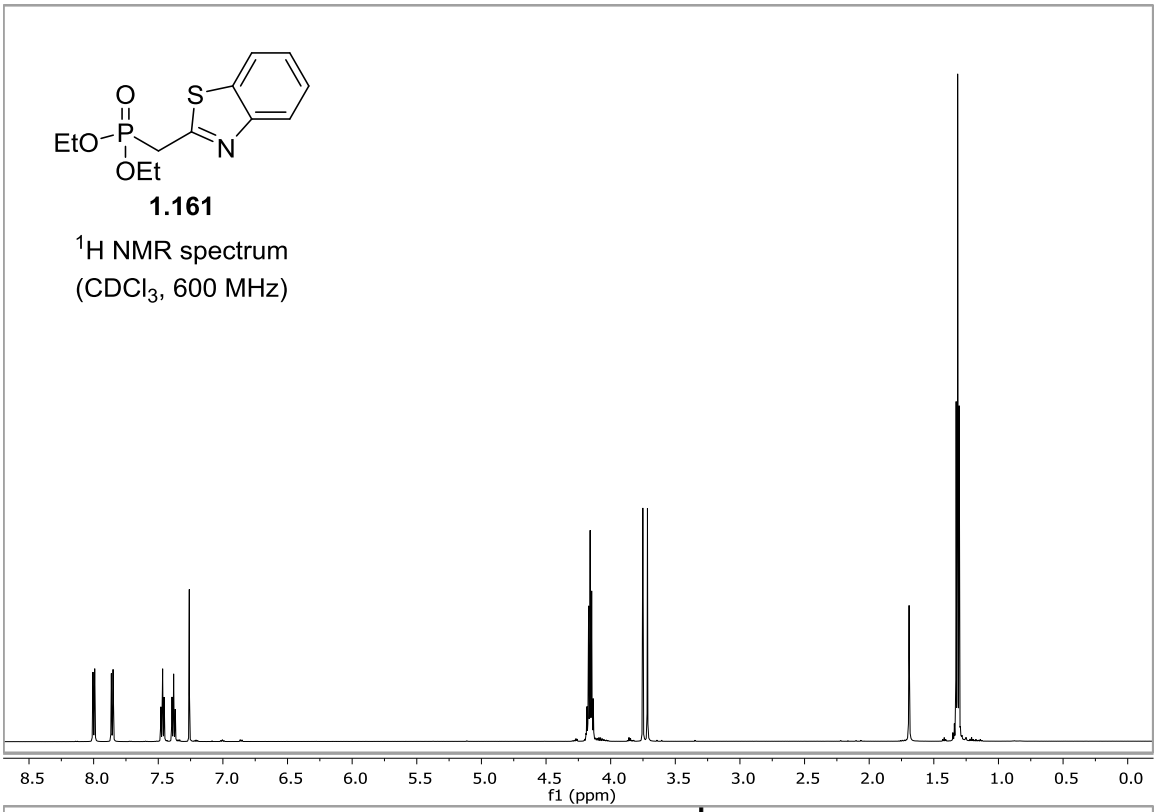


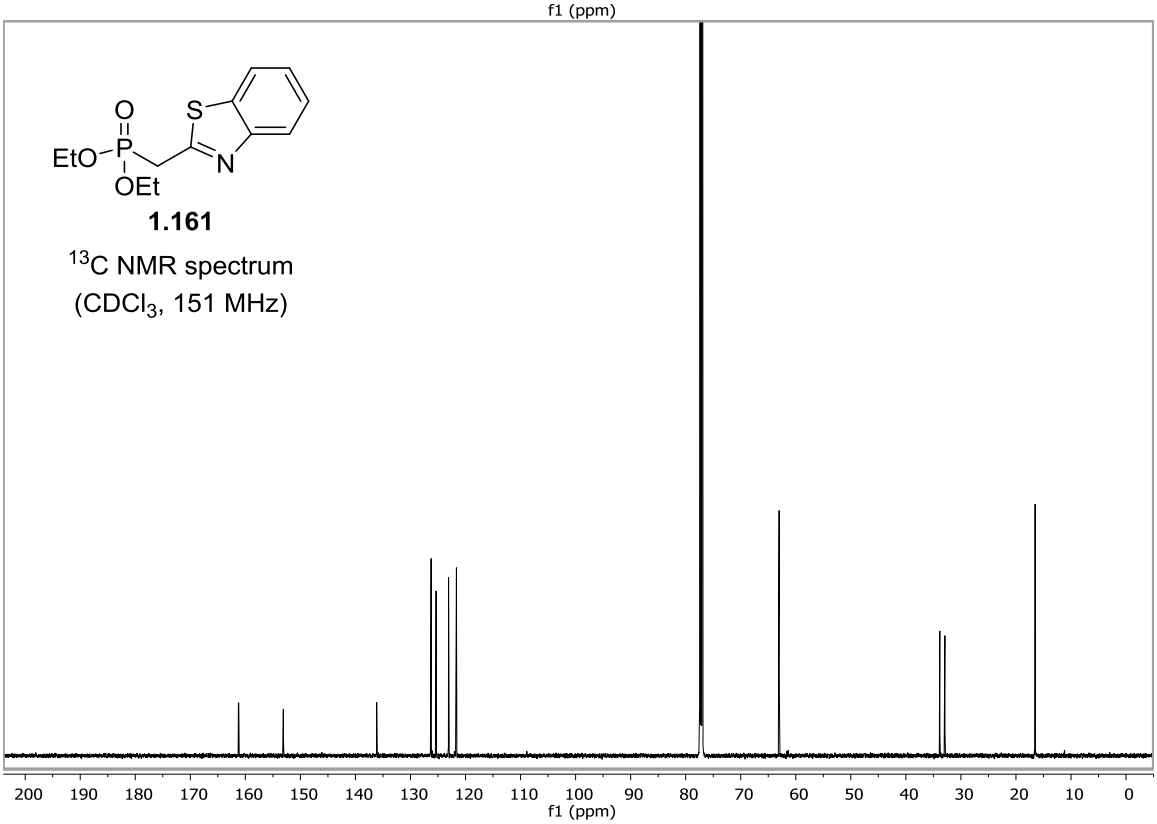
Spectra **1.68**: Compound **1.160**: ^{1}H and ^{13}C NMR



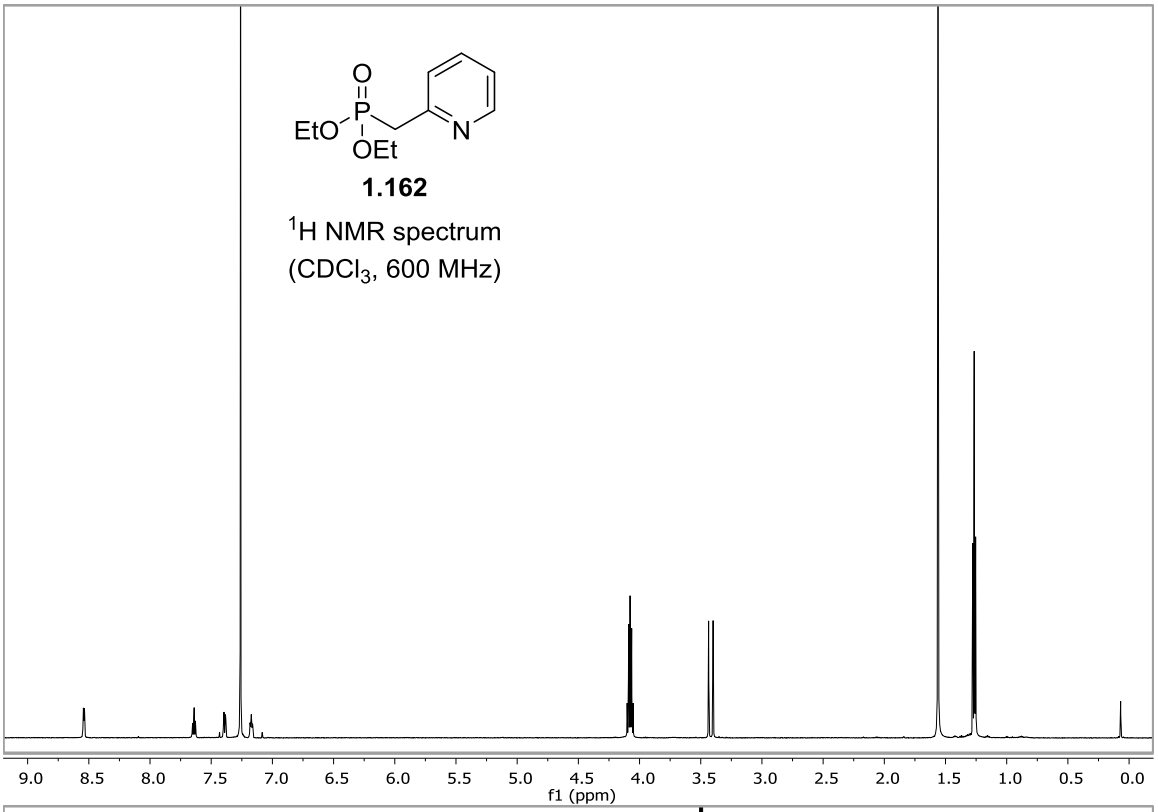


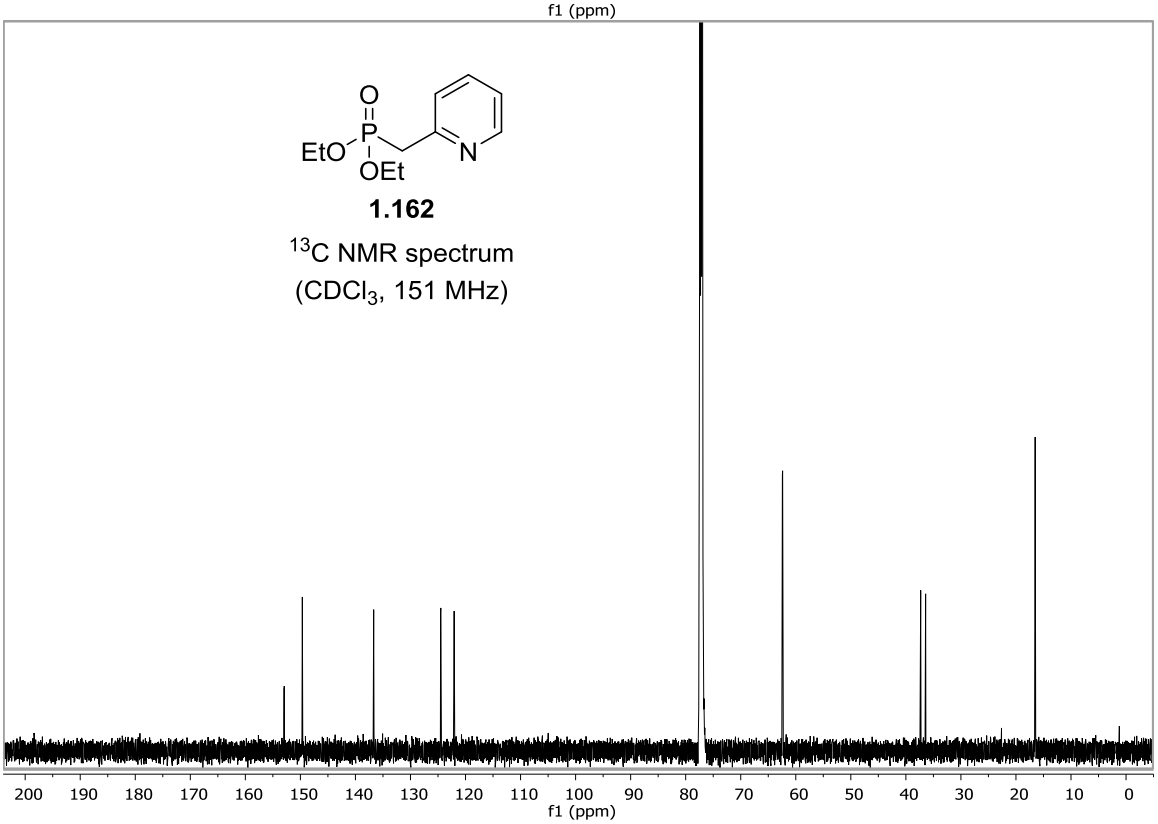
Spectra **1.69**: Compound **1.186**: ^{1}H and ^{13}C NMR



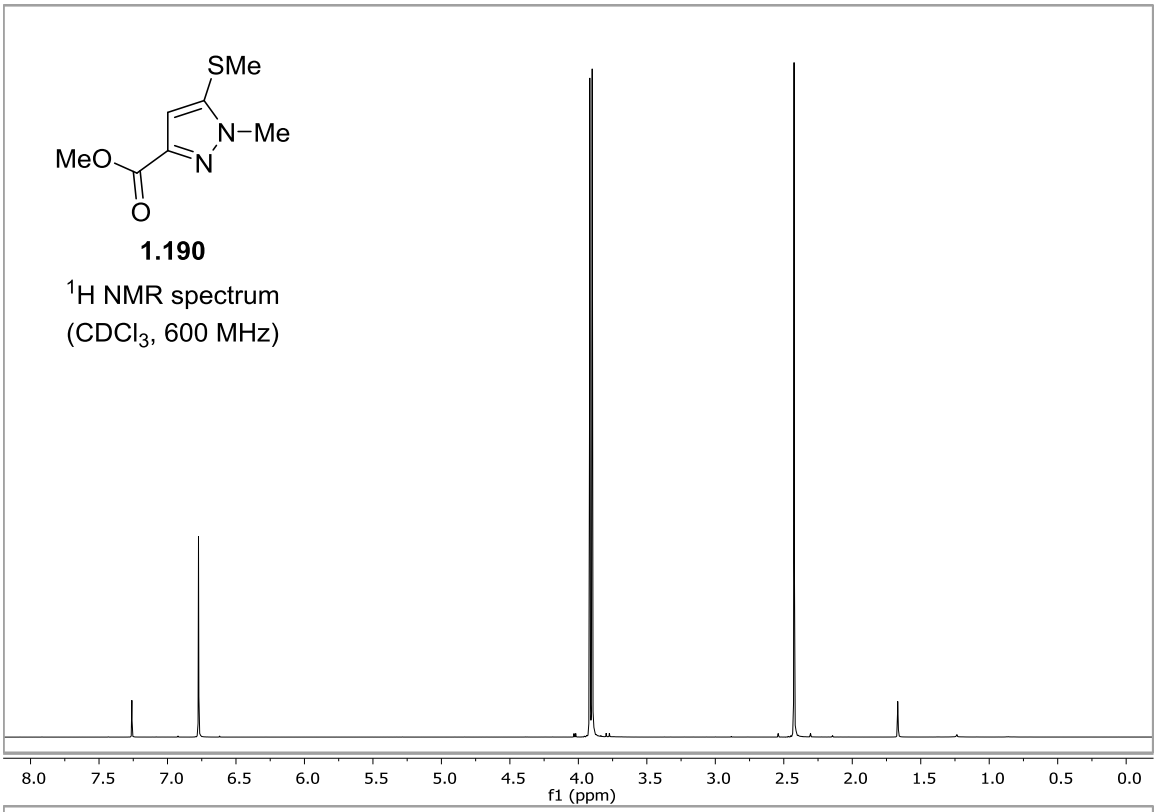


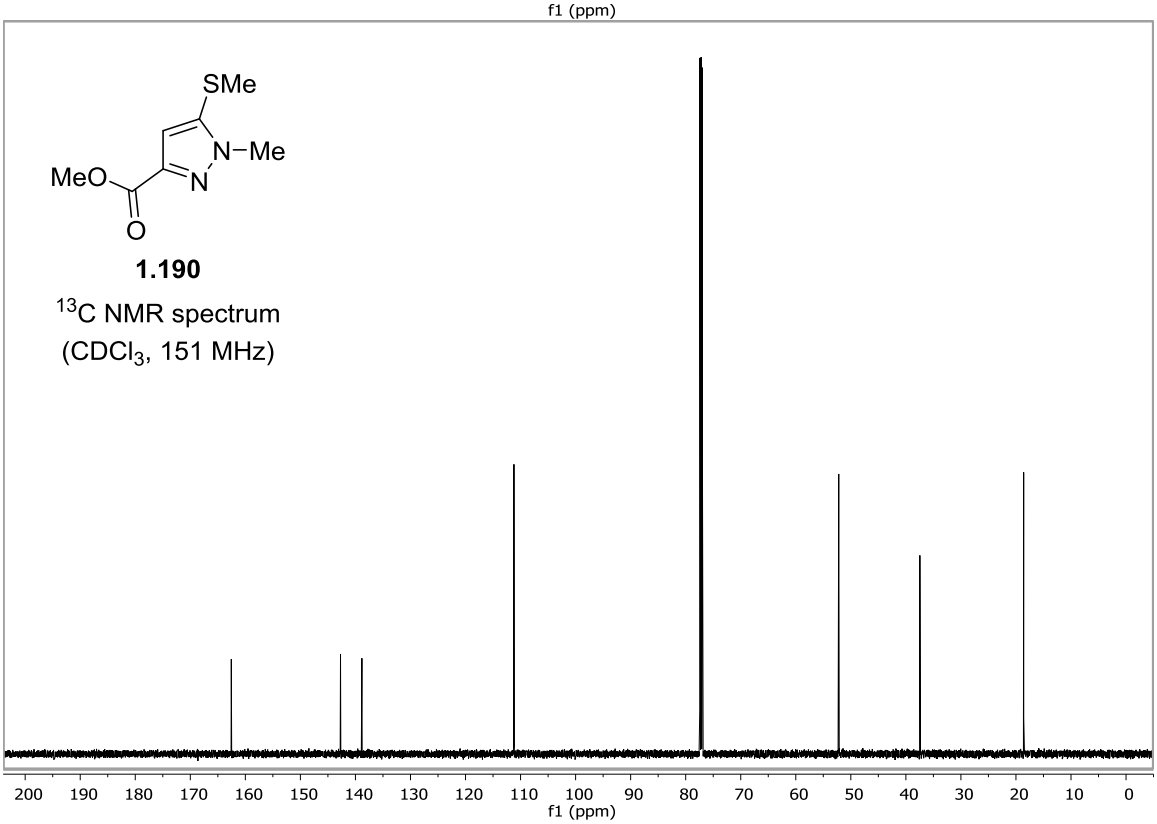
Spectra **1.70**: Compound **1.161**: ^{1}H and ^{13}C NMR



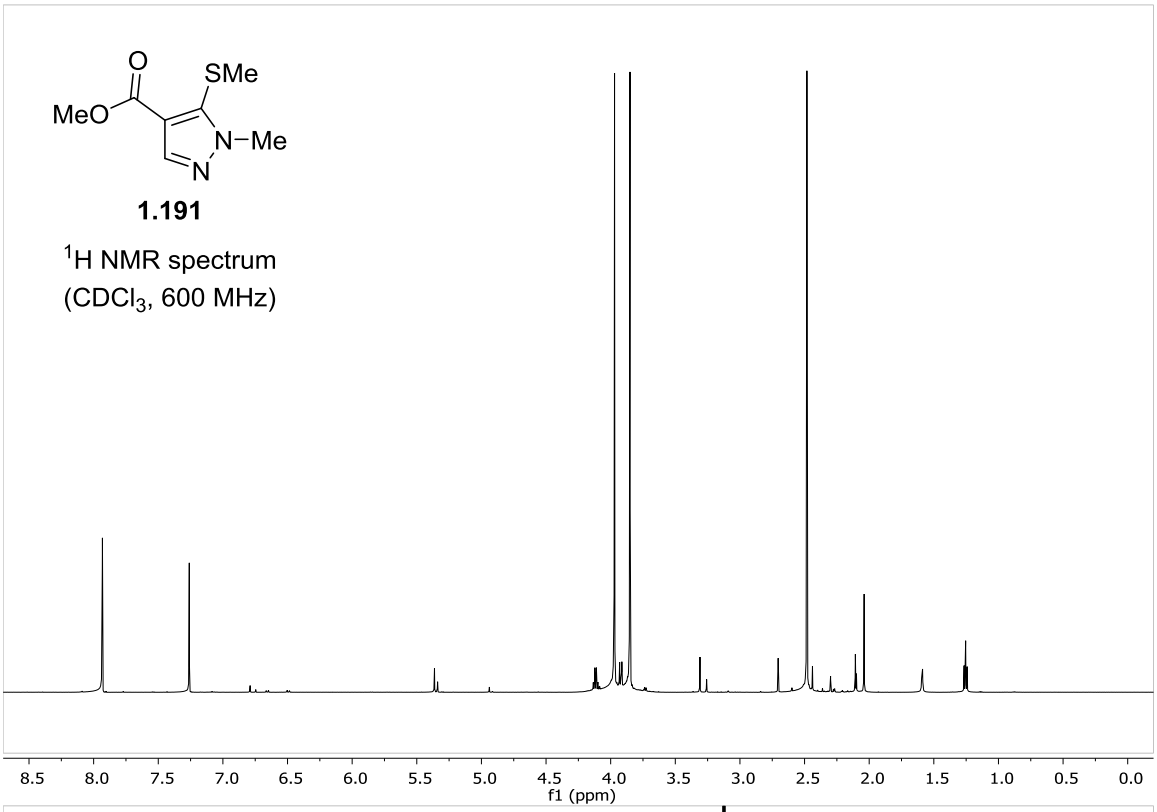


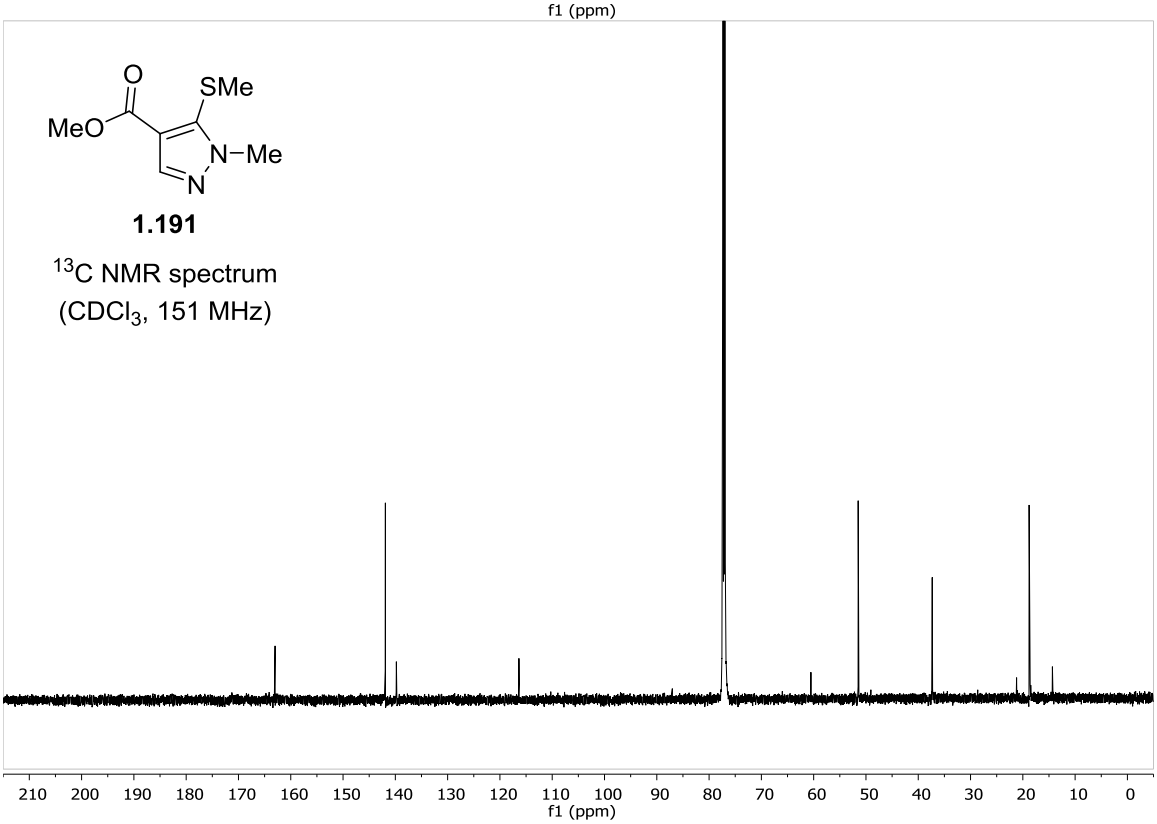
Spectra **1.71**: Compound **1.162**: ^{1}H and ^{13}C NMR



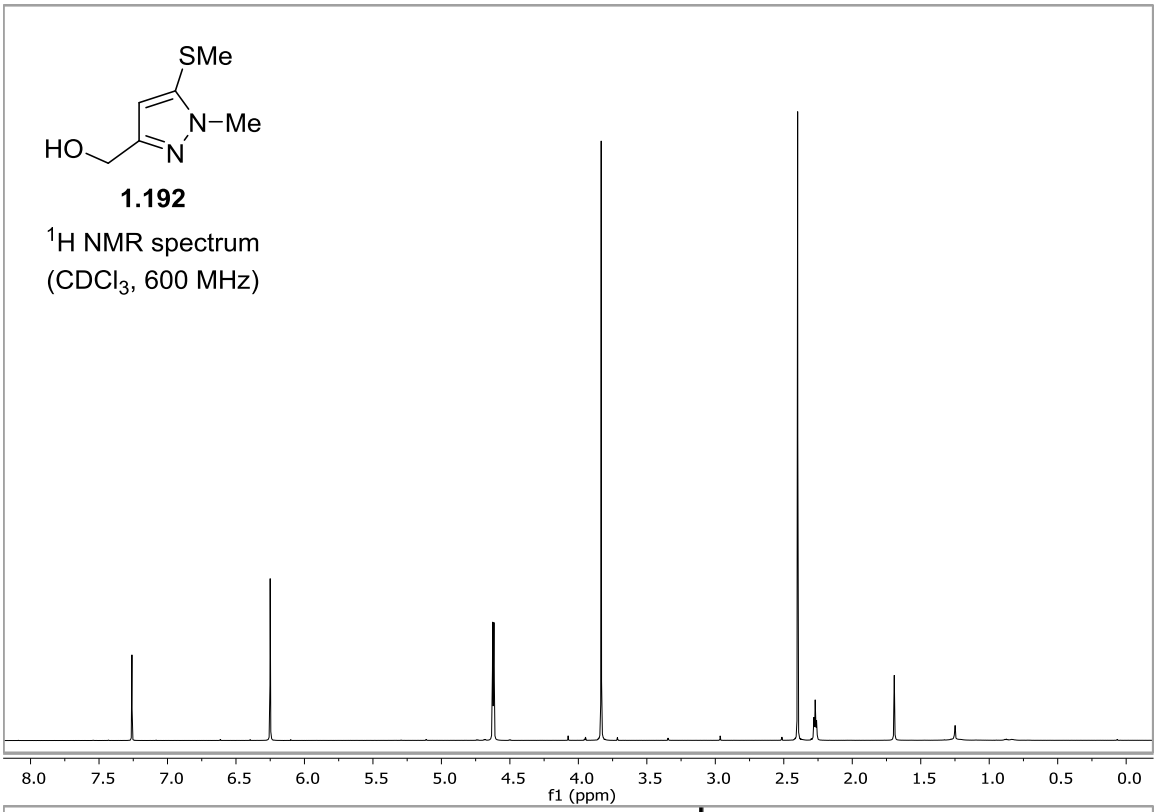


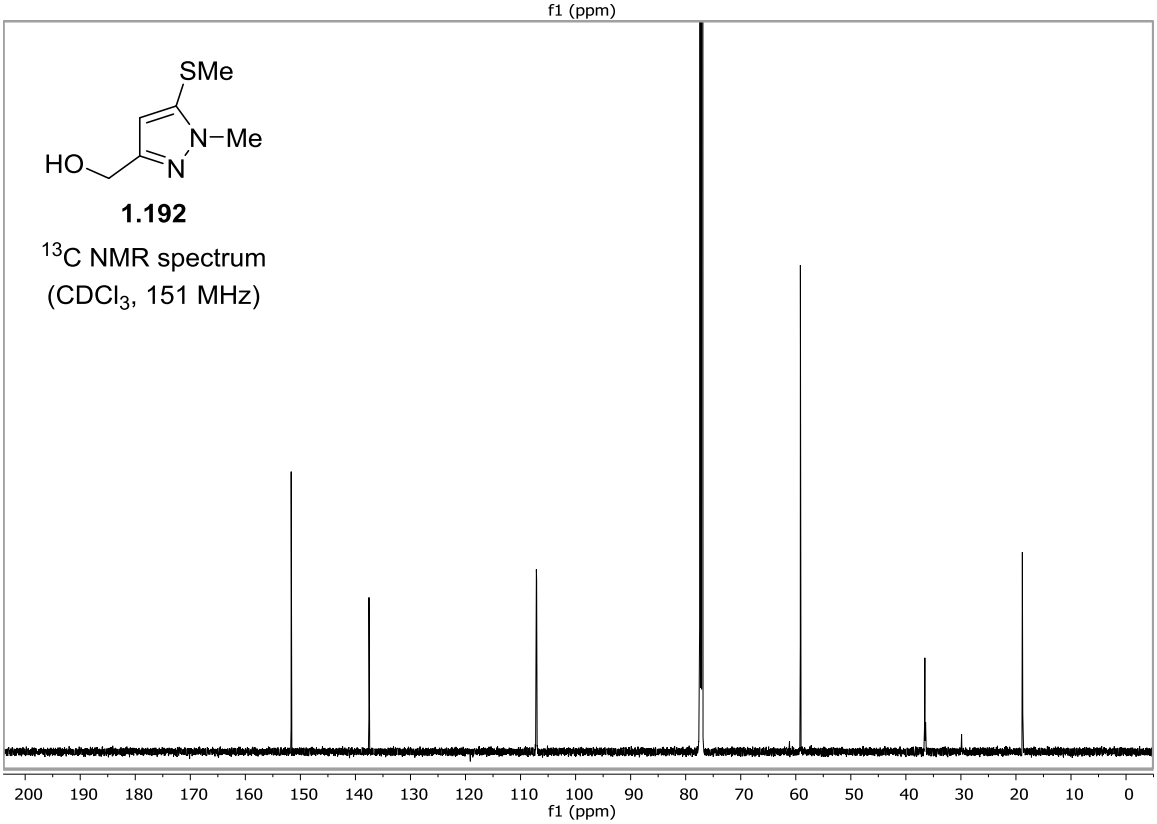
Spectra **1.72**: Compound **1.190**: ^{1}H and ^{13}C NMR



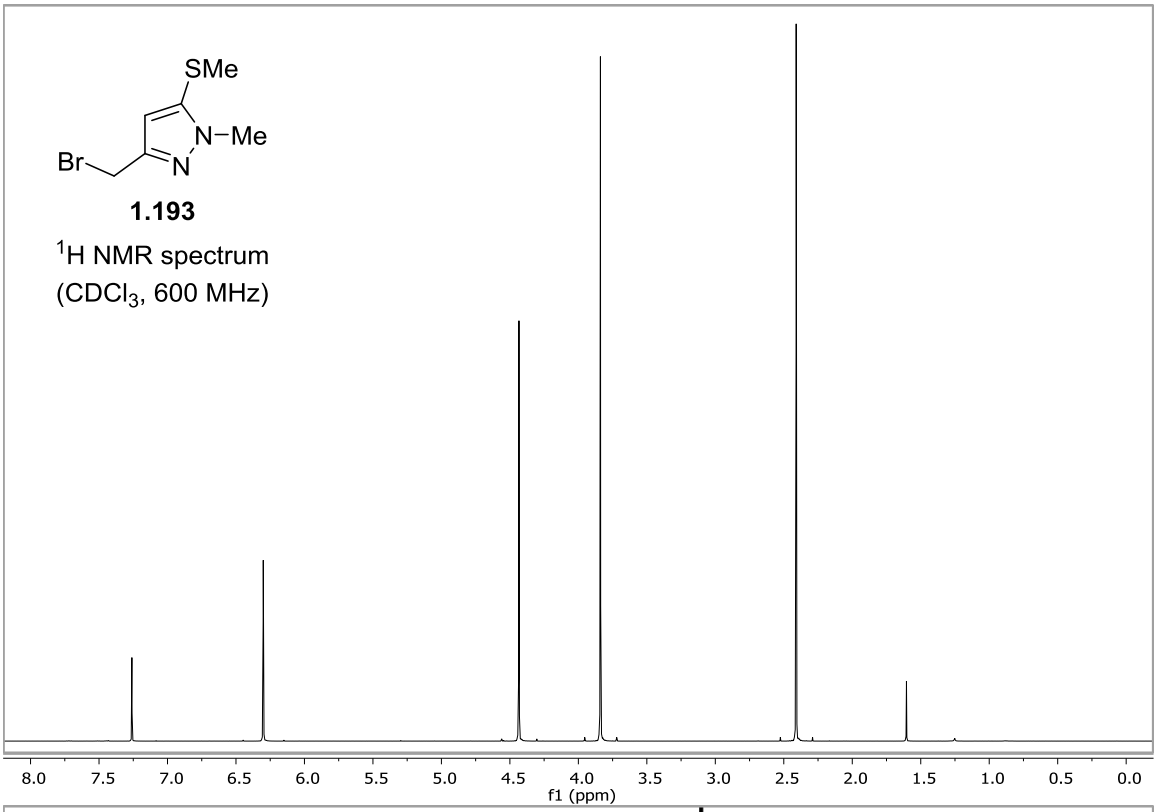


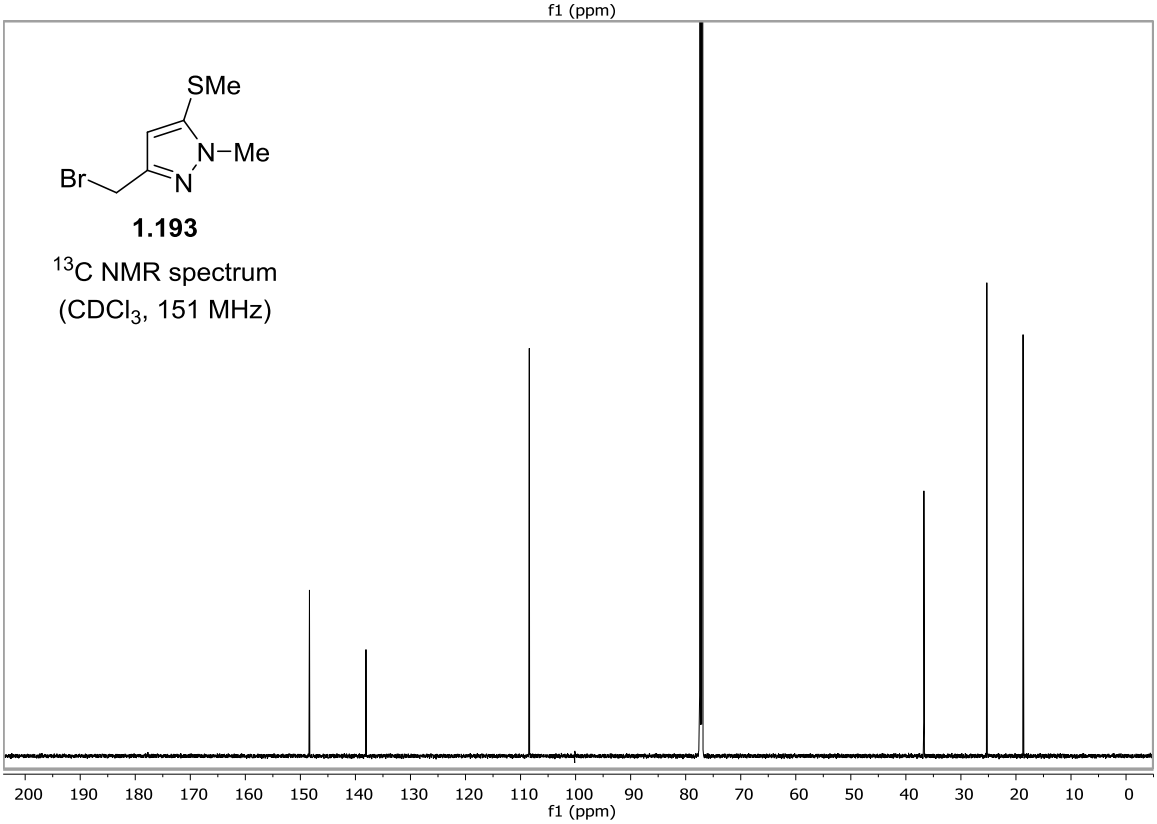
Spectra **1.73**: Compound **1.191**: ^{1}H and ^{13}C NMR



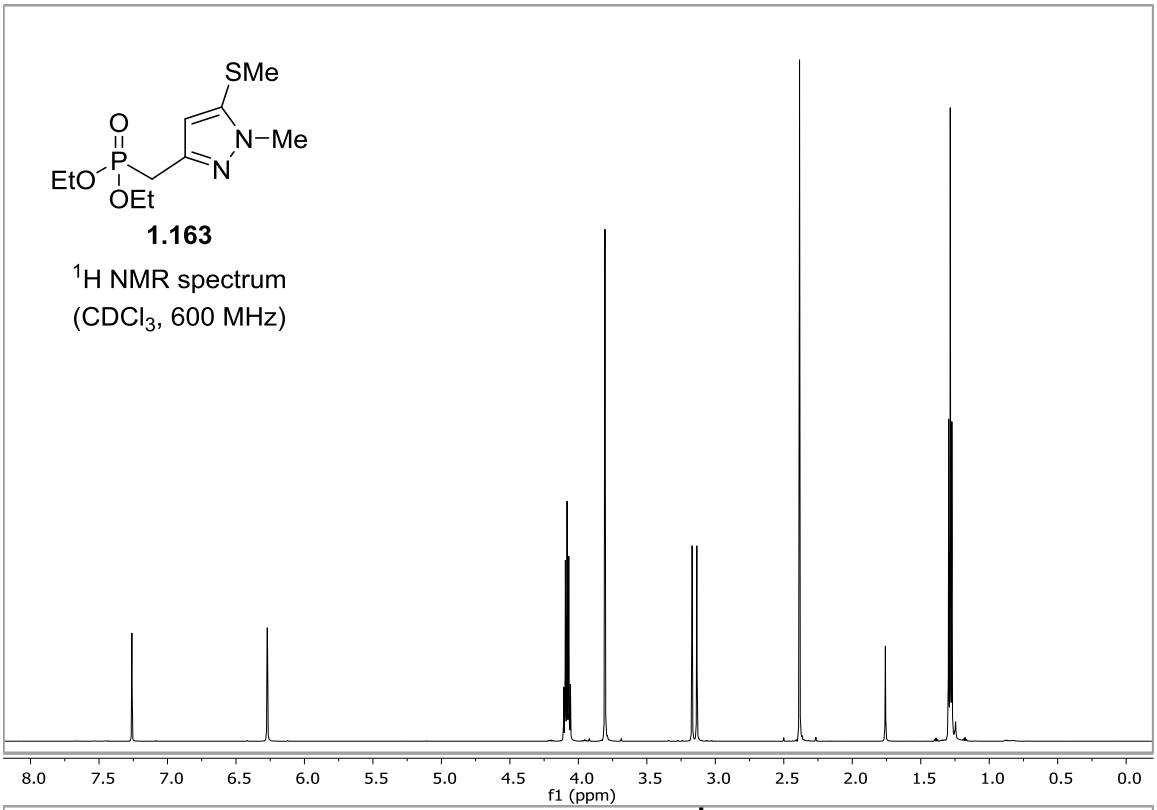


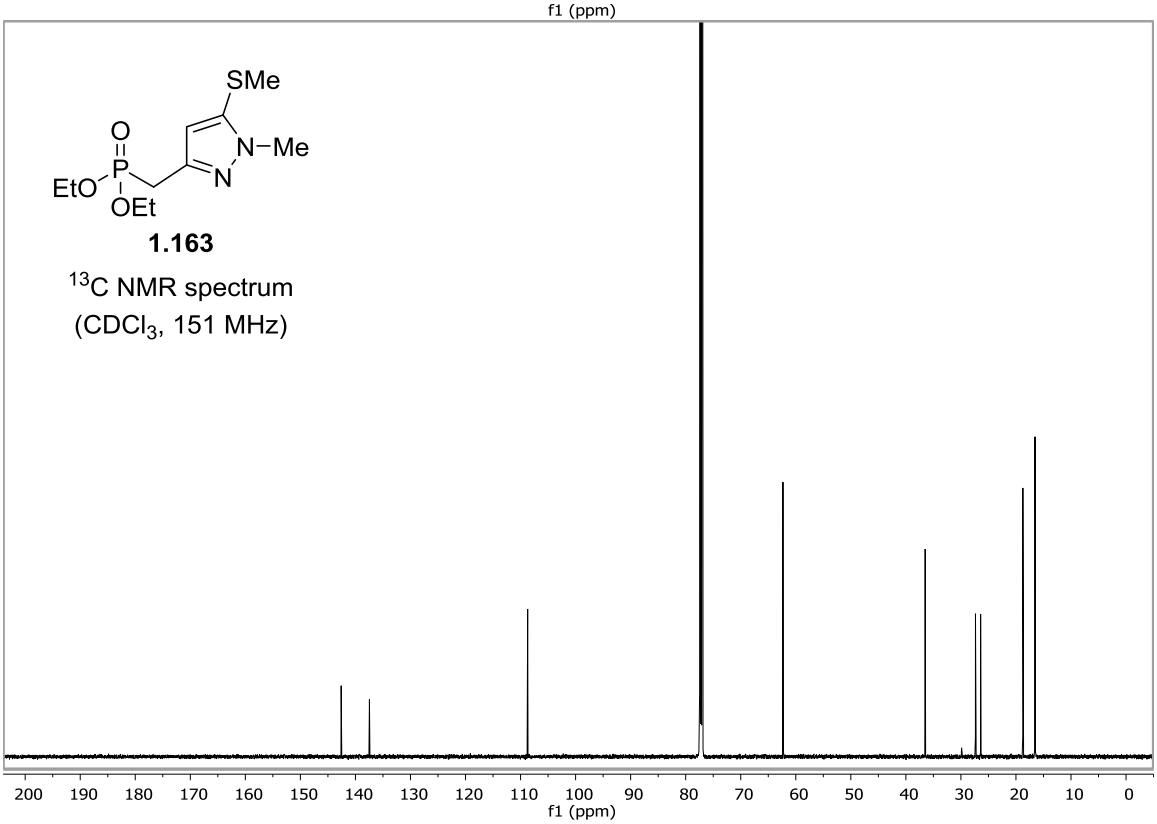
Spectra **1.74**: Compound **1.192**: ^{1}H and ^{13}C NMR



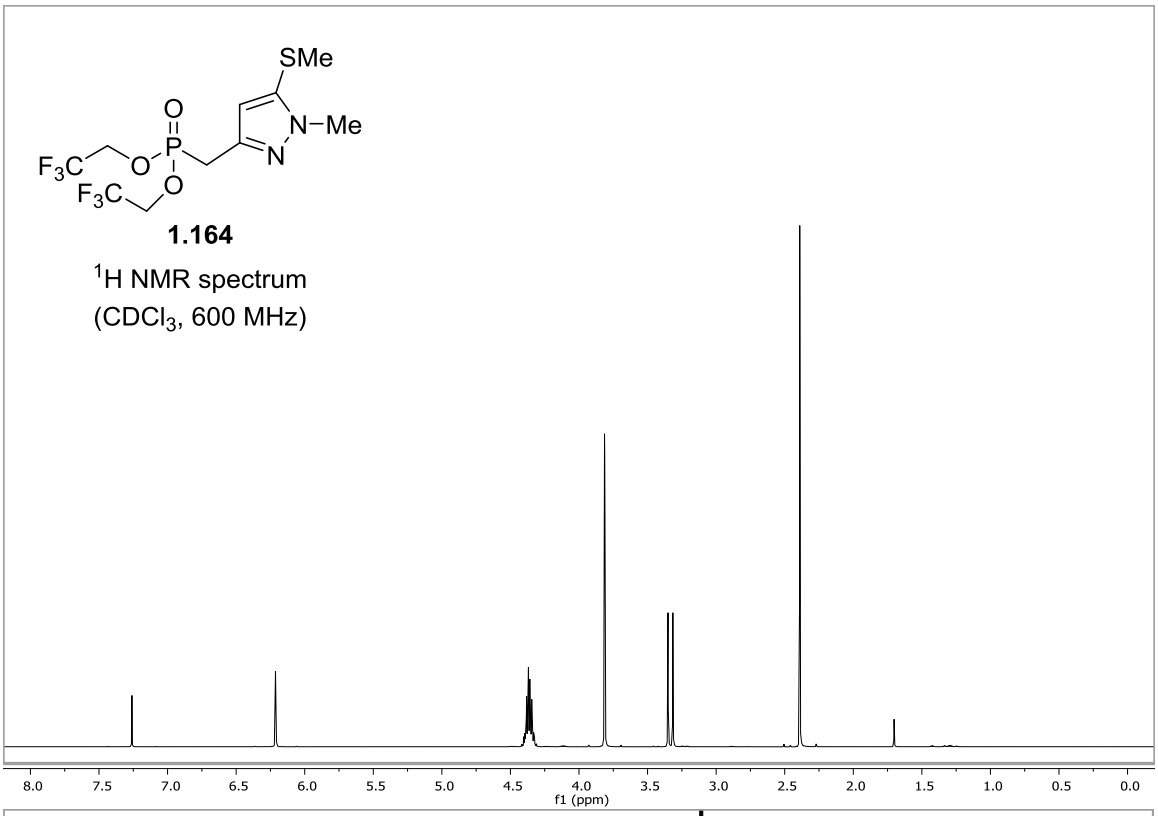


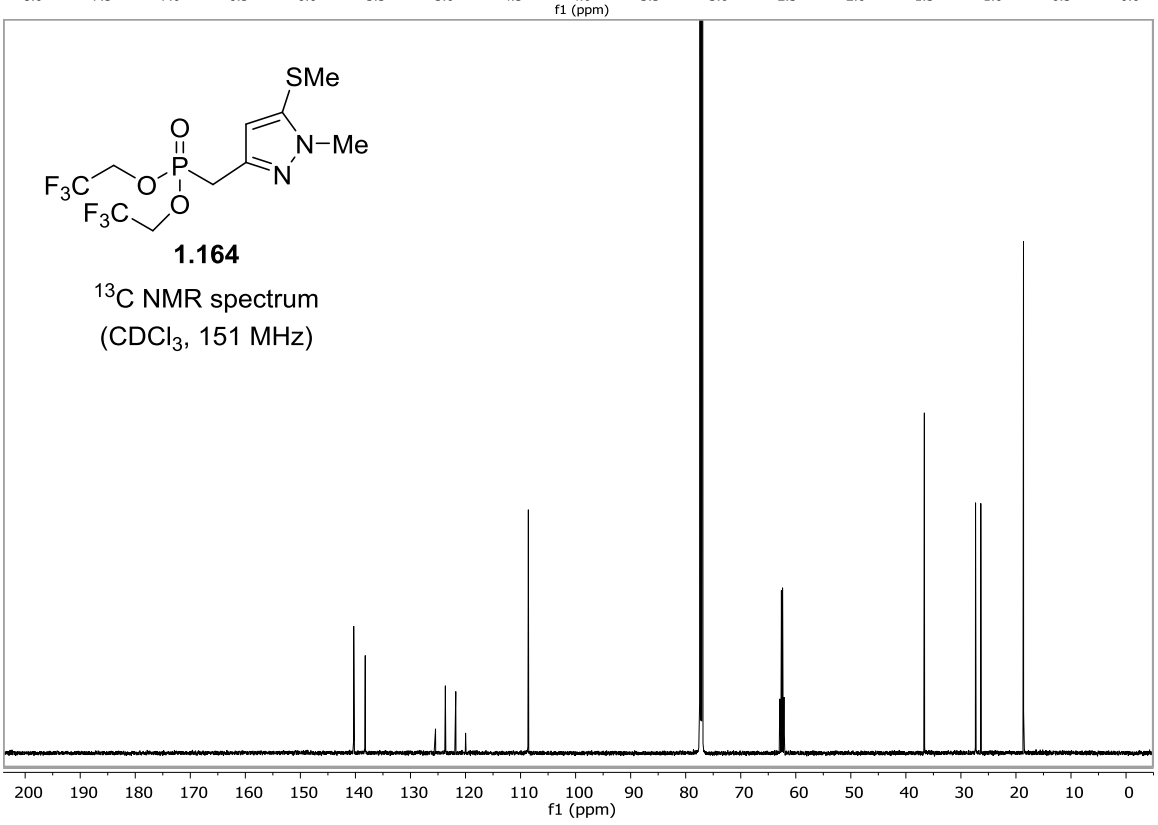
Spectra **1.75**: Compound **1.193**: ^{1}H and ^{13}C NMR



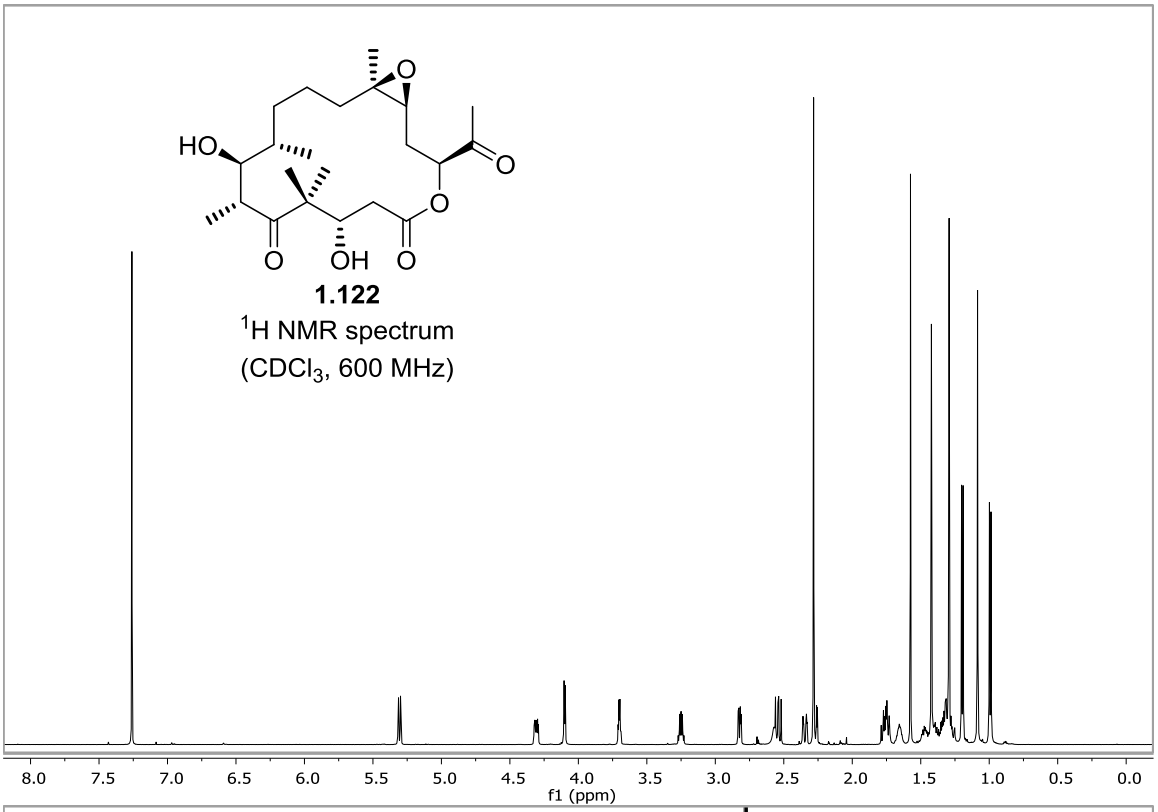


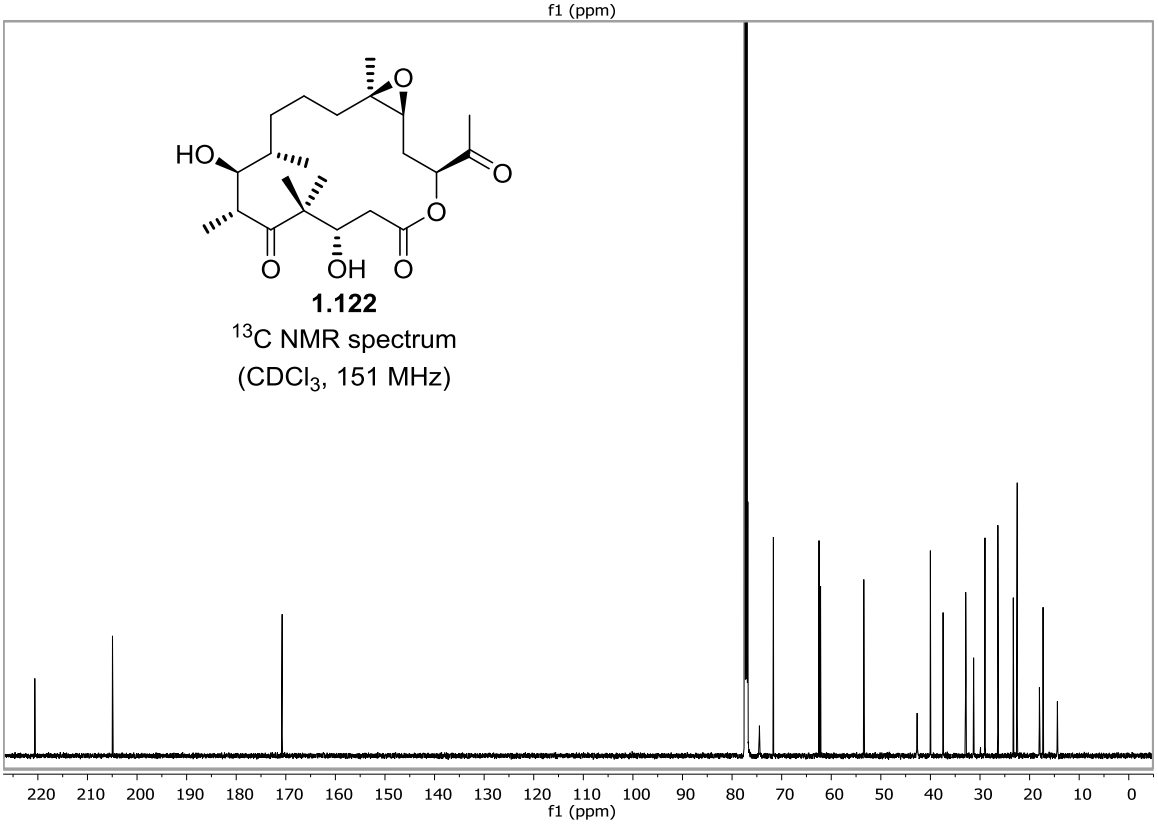
Spectra **1.76**: Compound **1.163**: ^{1}H and ^{13}C NMR



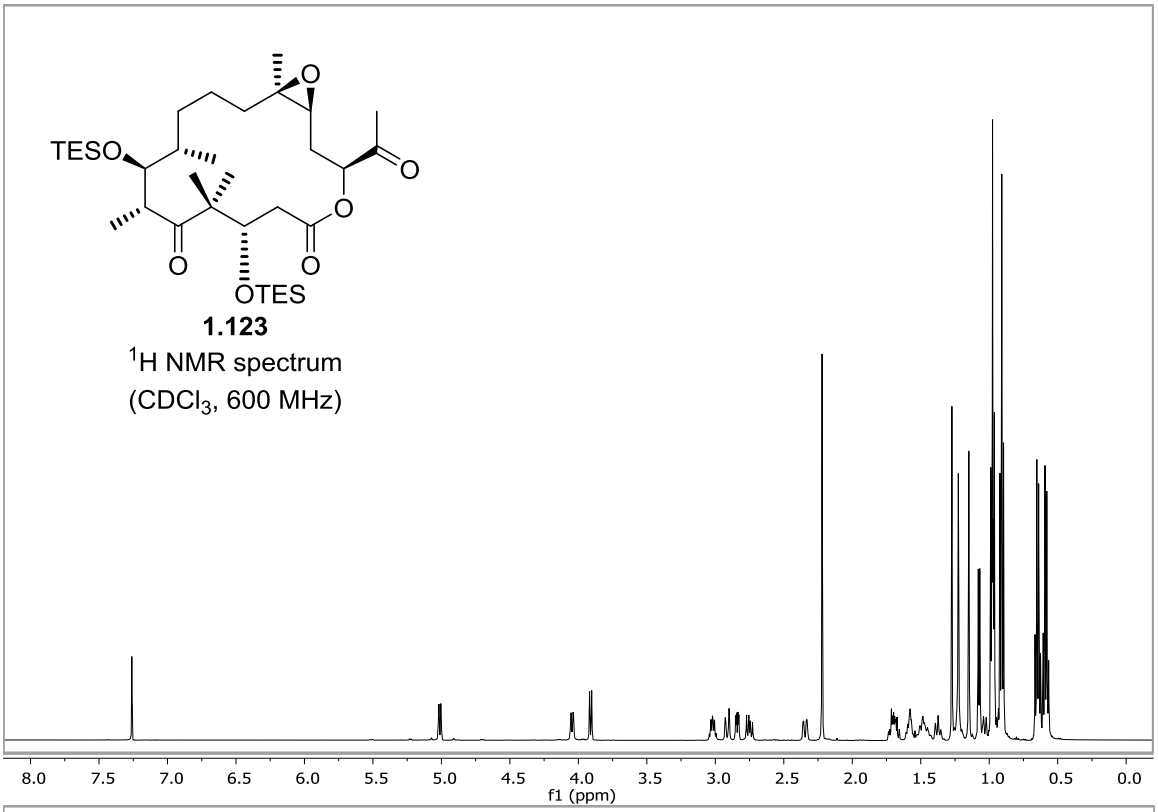


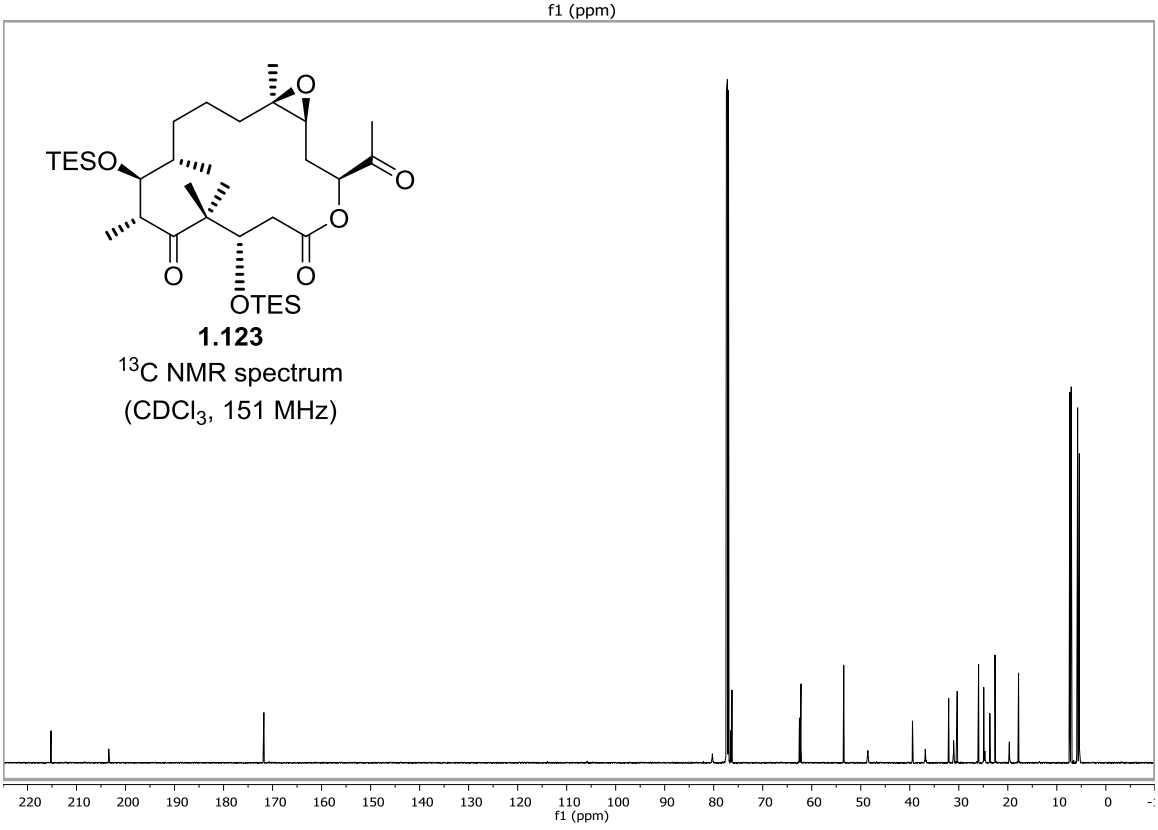
Spectra **1.77**: Compound **1.164**: ^{1}H and ^{13}C NMR



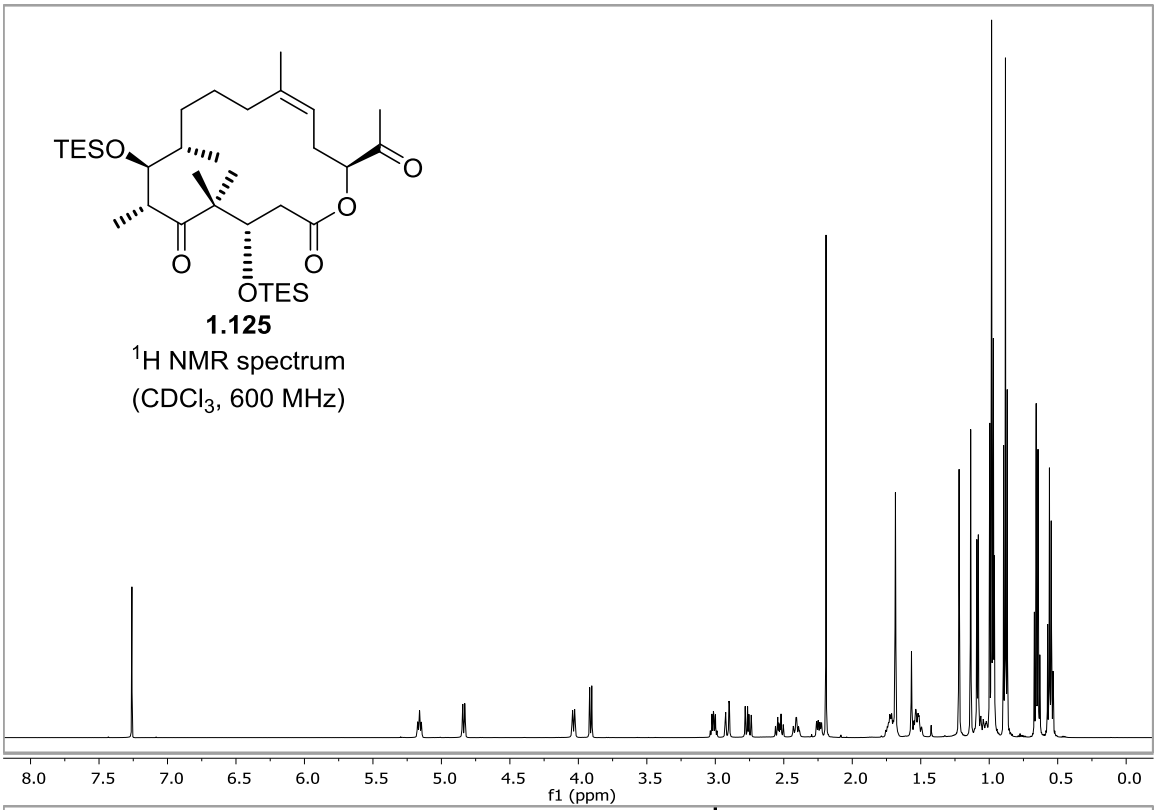


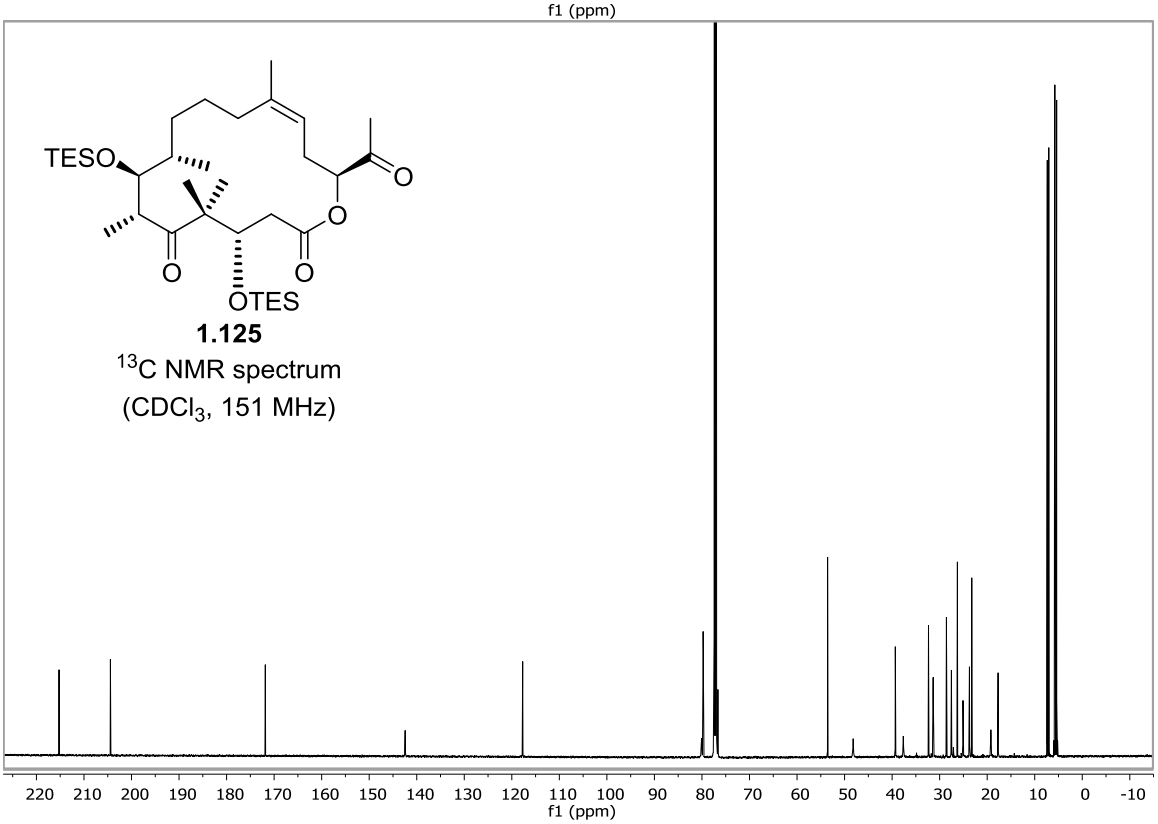
Spectra **1.78**: Compound **1.122**: ^{1}H and ^{13}C NMR



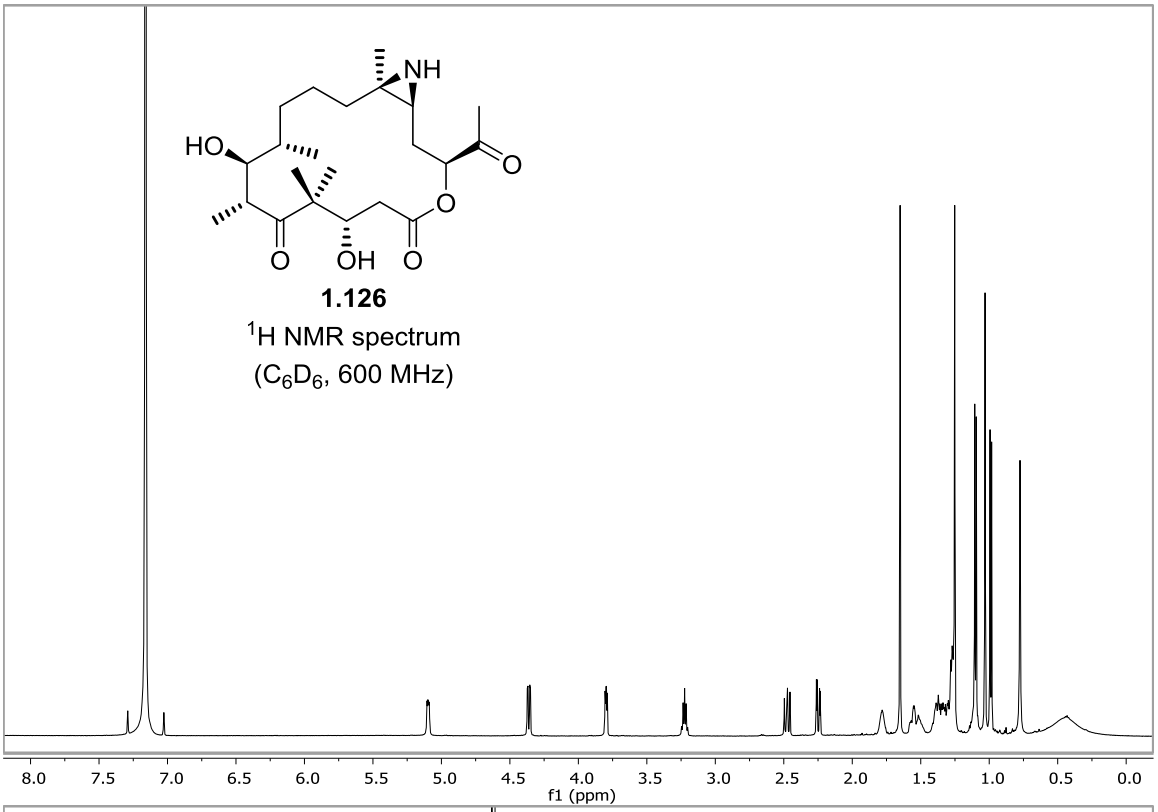


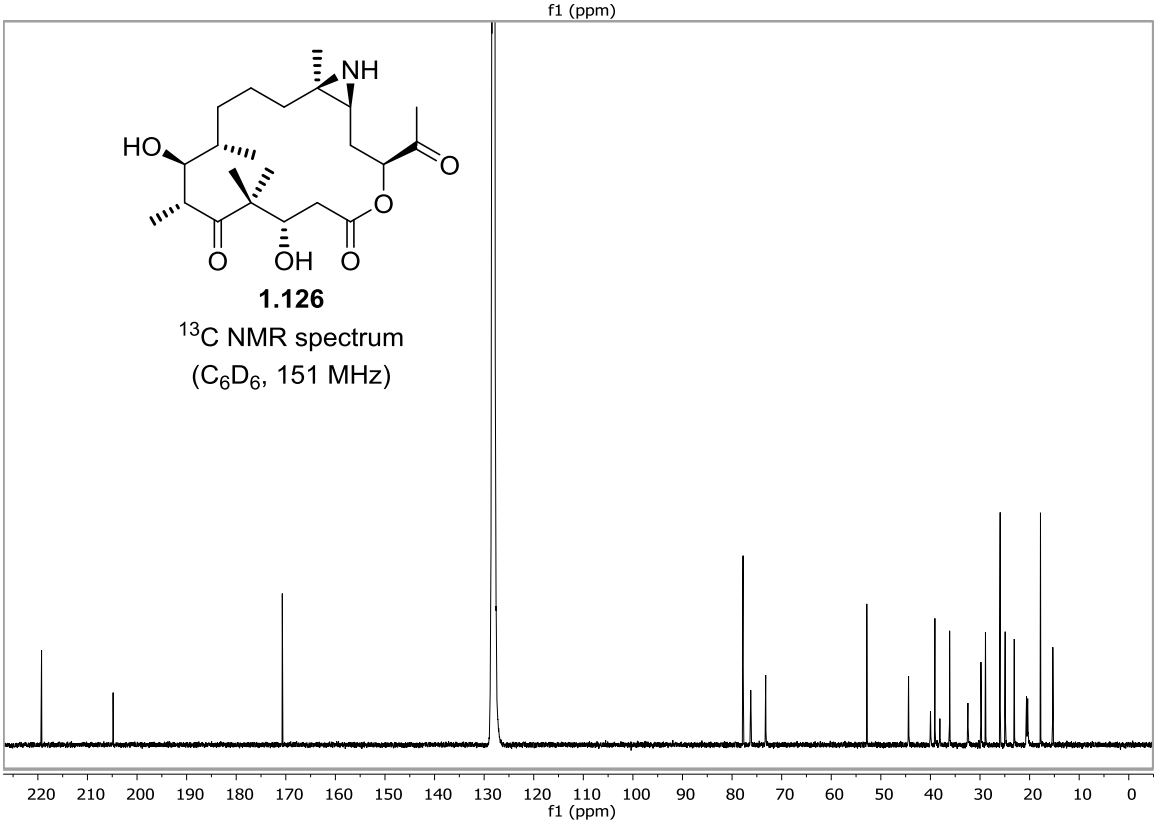
Spectra **1.79**: Compound **1.123**: ^{1}H and ^{13}C NMR



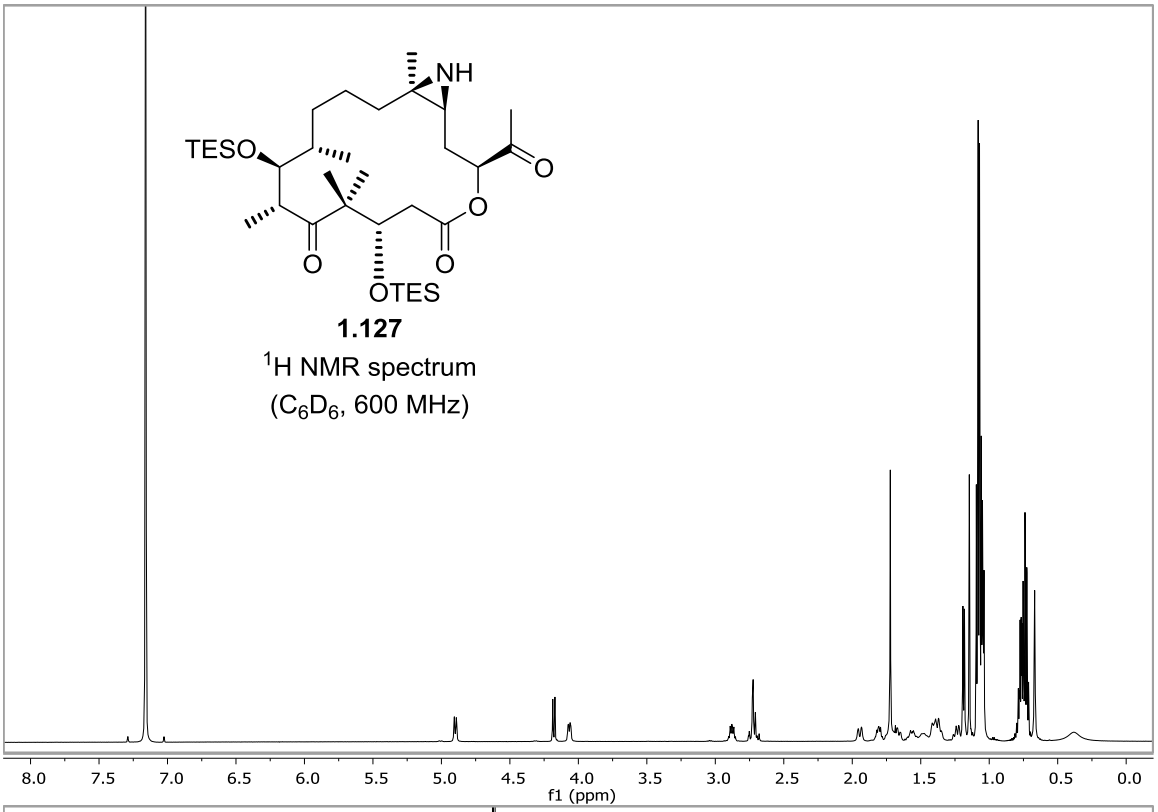


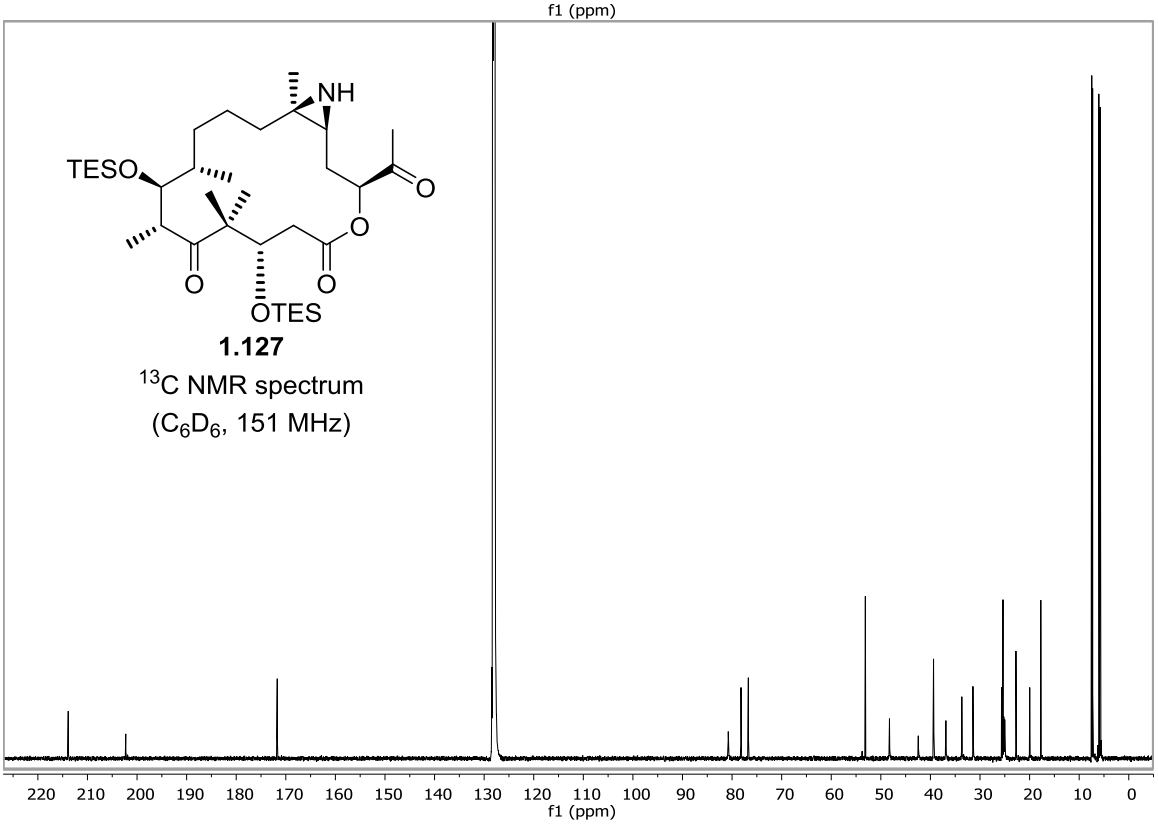
Spectra **1.80**: Compound **1.125**: ^{1}H and ^{13}C NMR



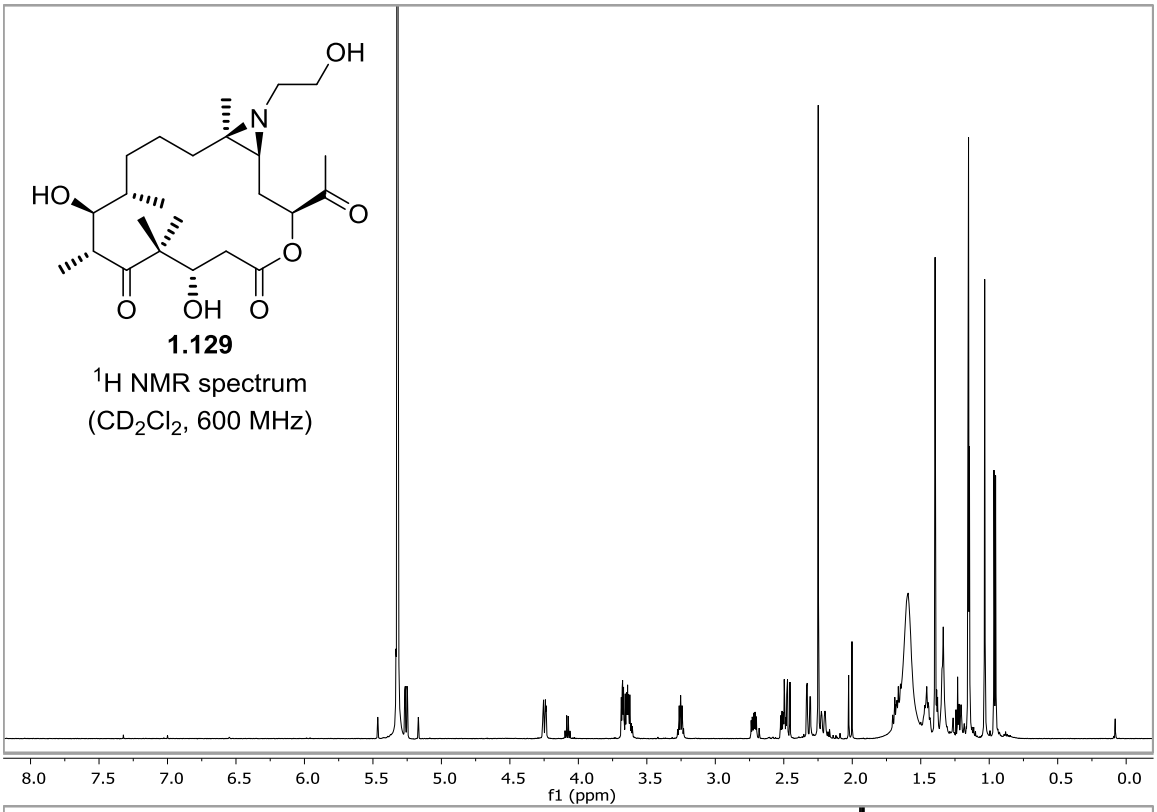


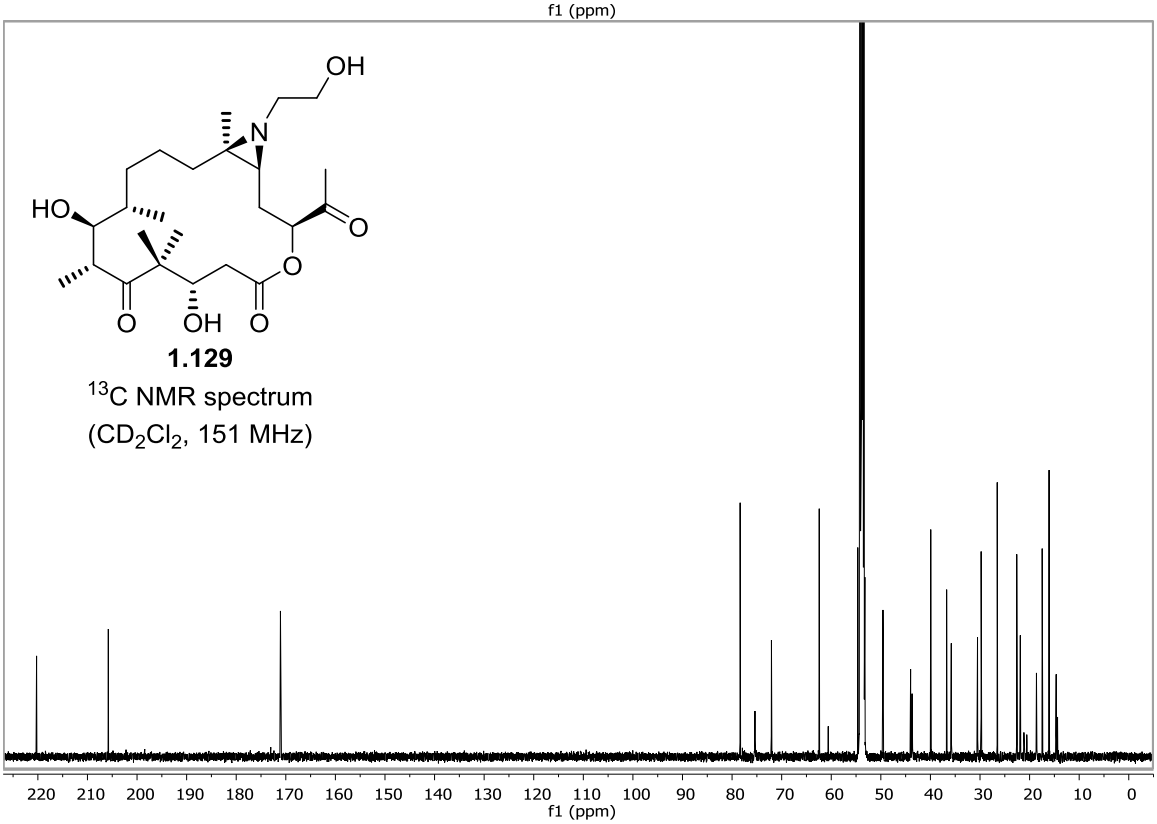
Spectra **1.81**: Compound **1.126**: ^{1}H and ^{13}C NMR



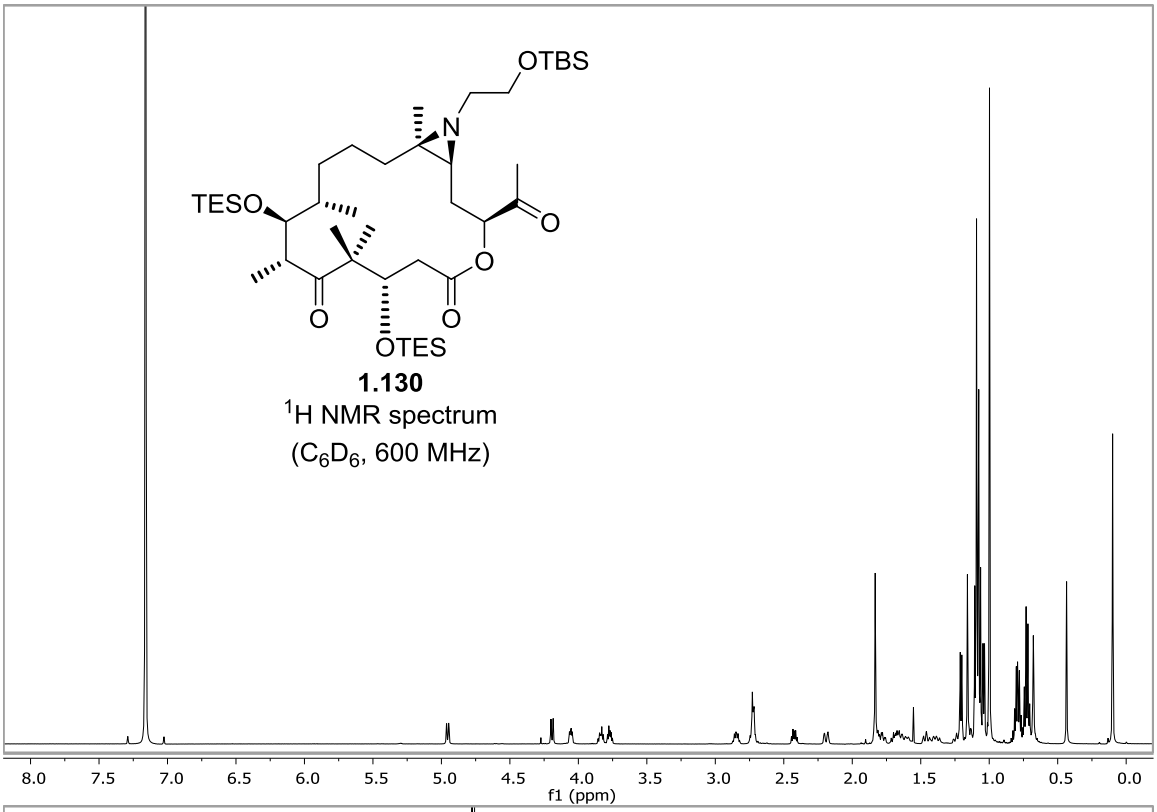


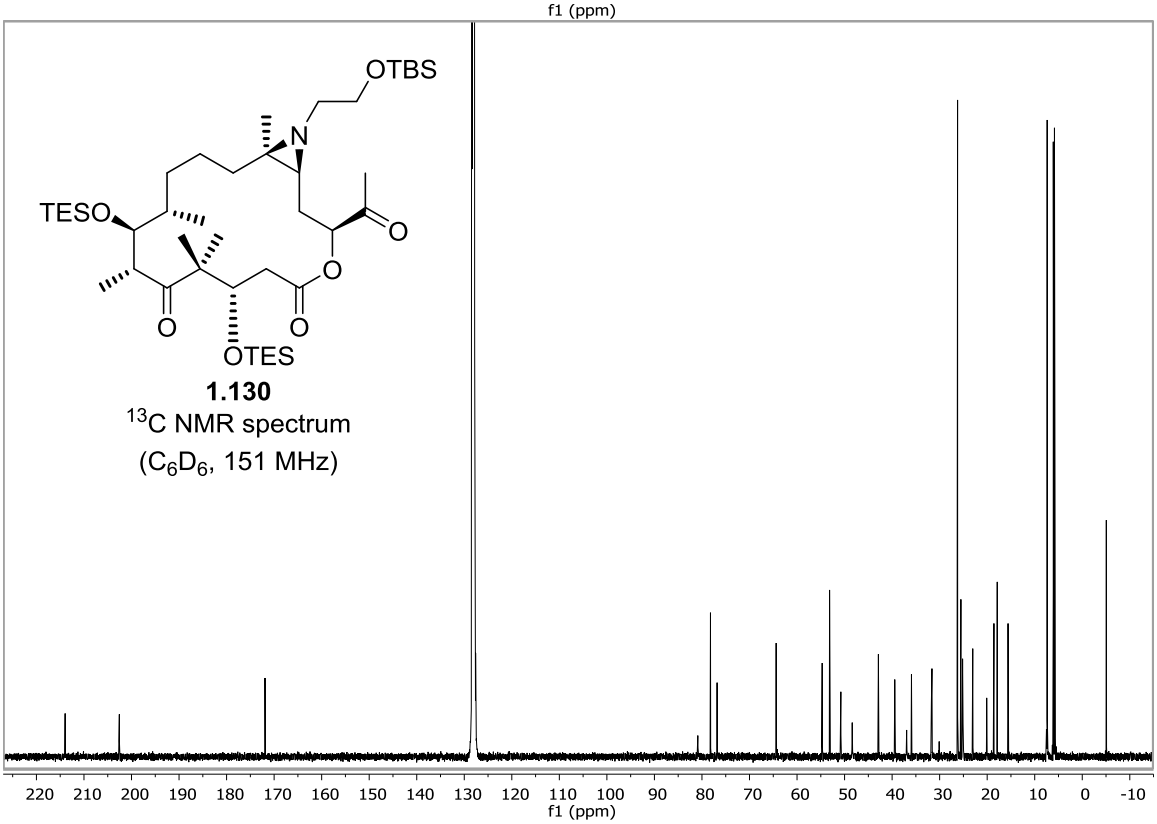
Spectra **1.82**: Compound **1.127**: ^{1}H and ^{13}C NMR



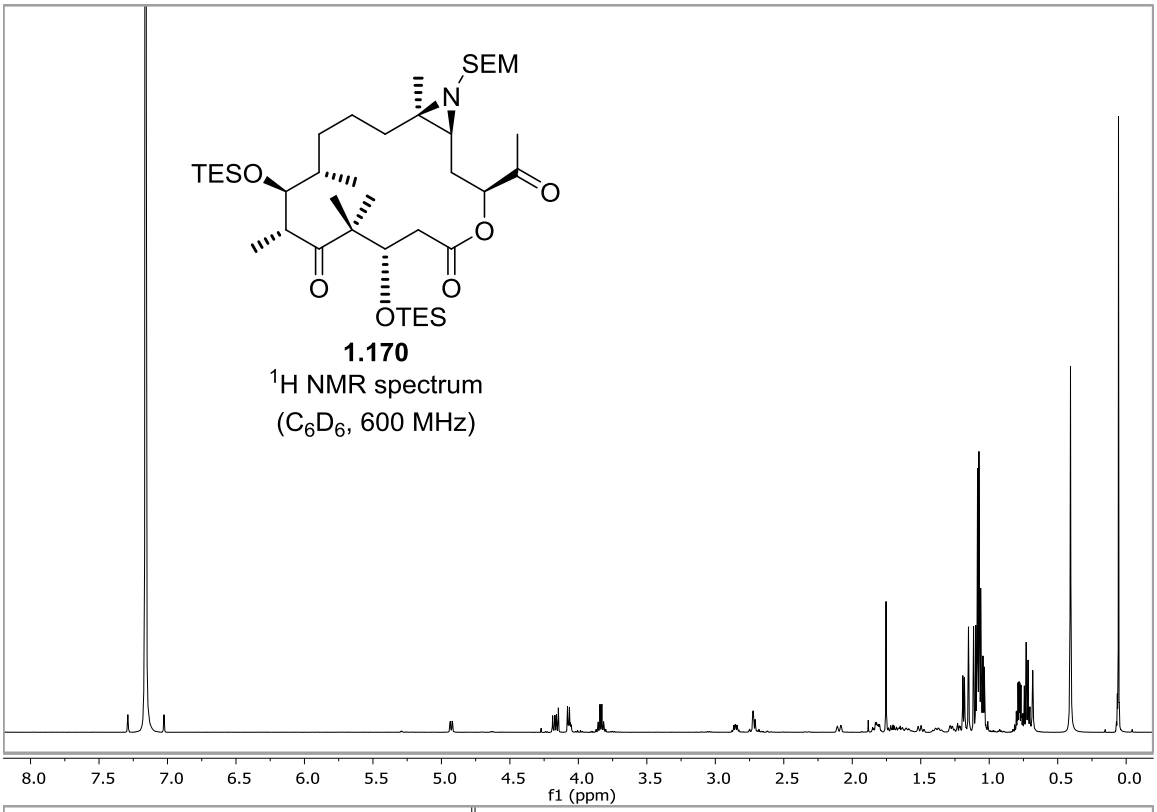


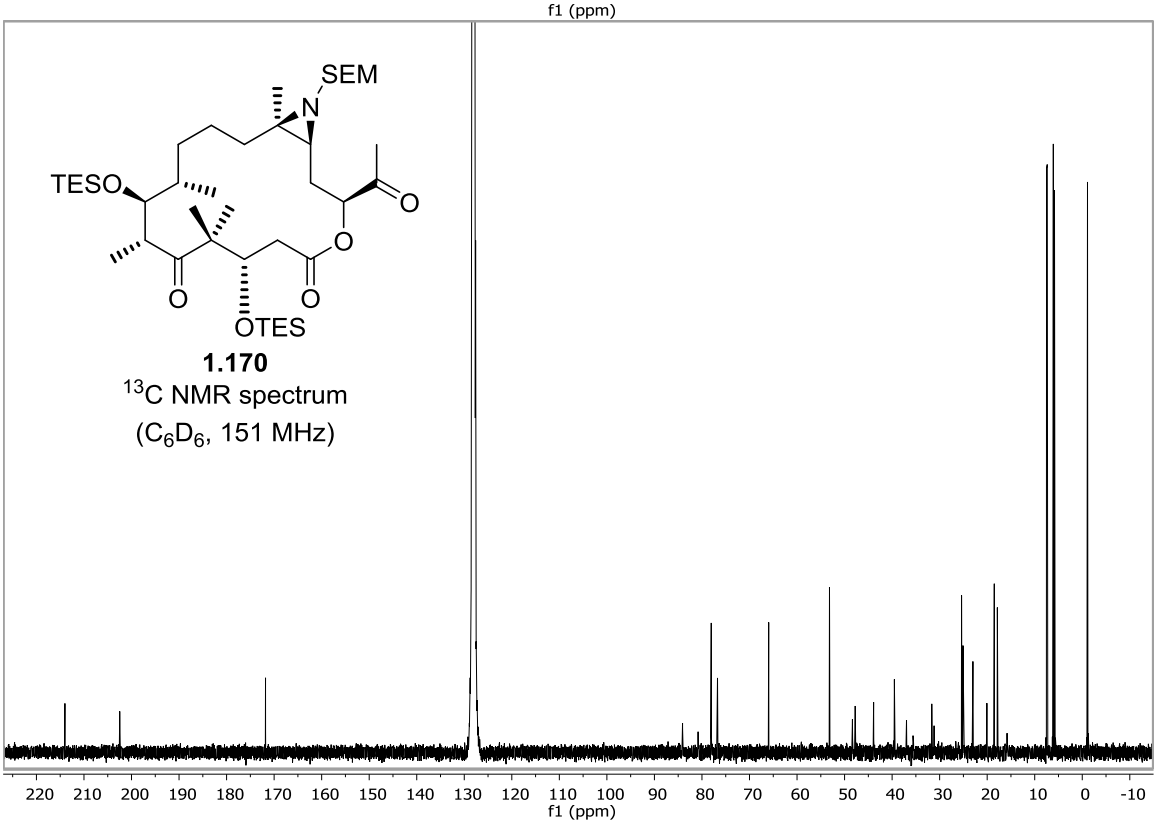
Spectra **1.83**: Compound **1.129**: ^{1}H and ^{13}C NMR



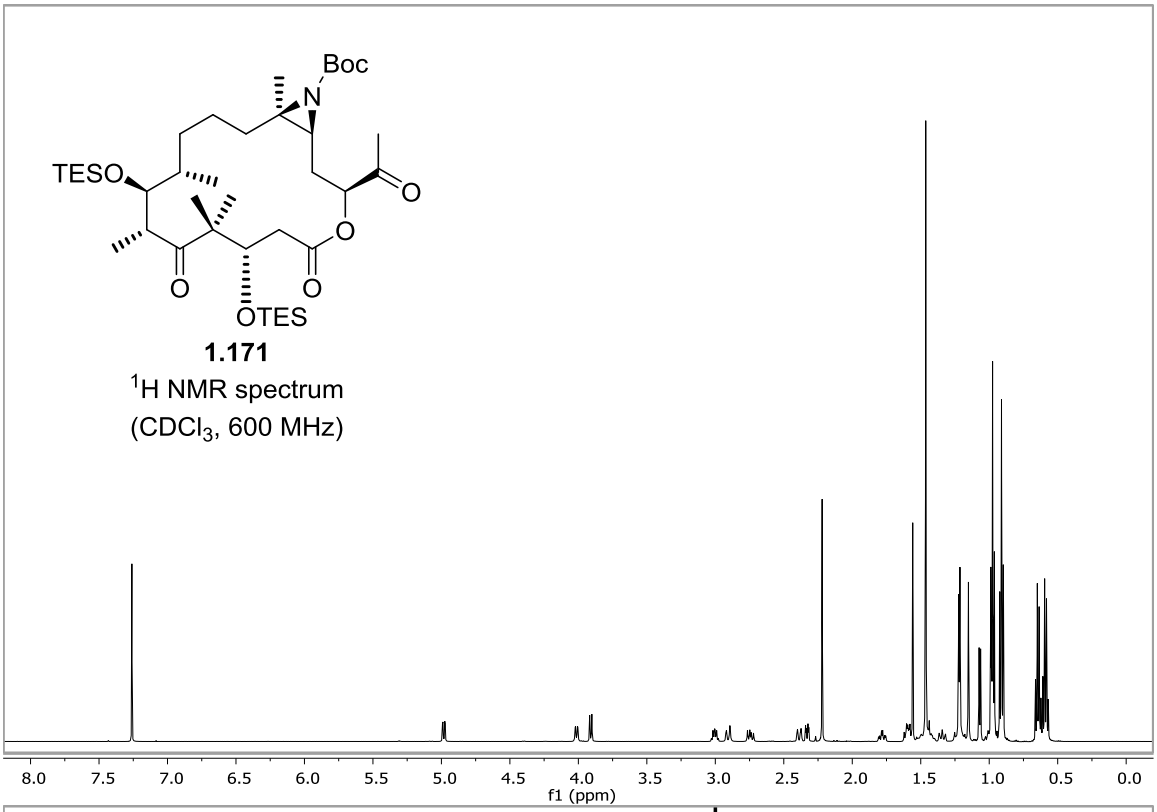


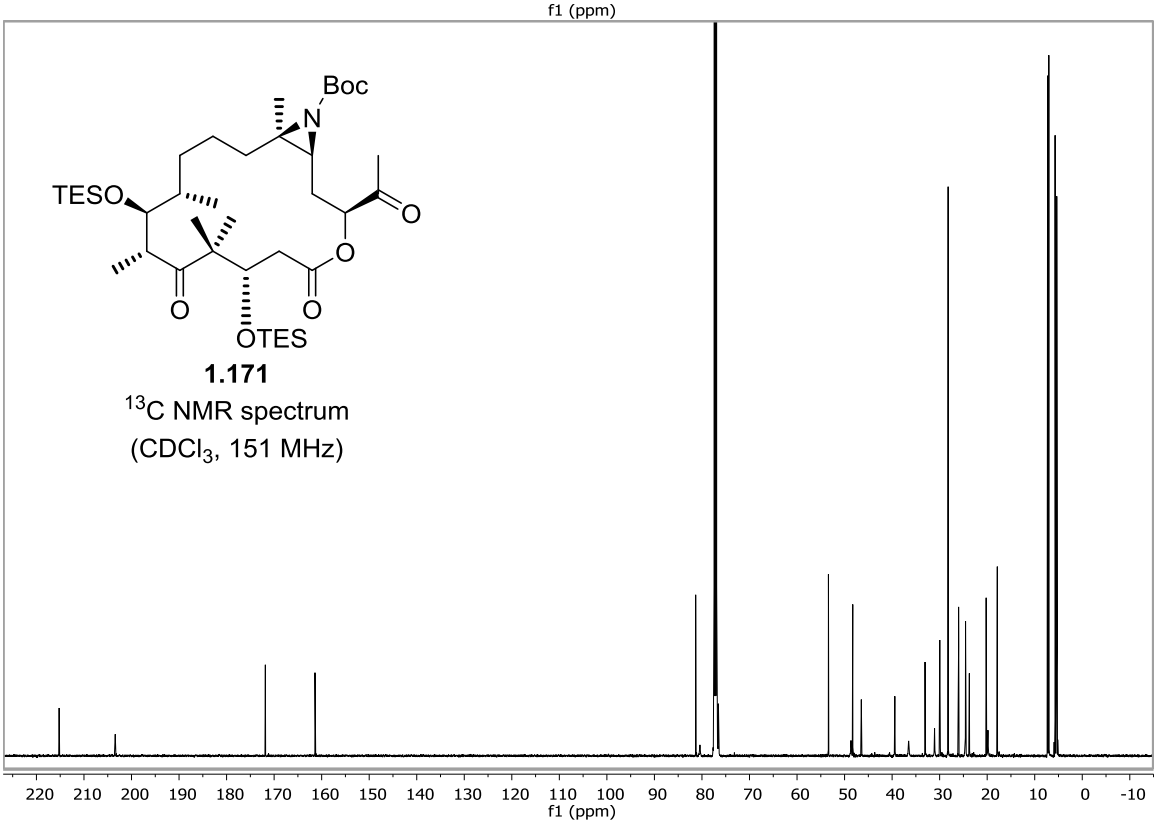
Spectra **1.84**: Compound **1.130**: ^{1}H and ^{13}C NMR



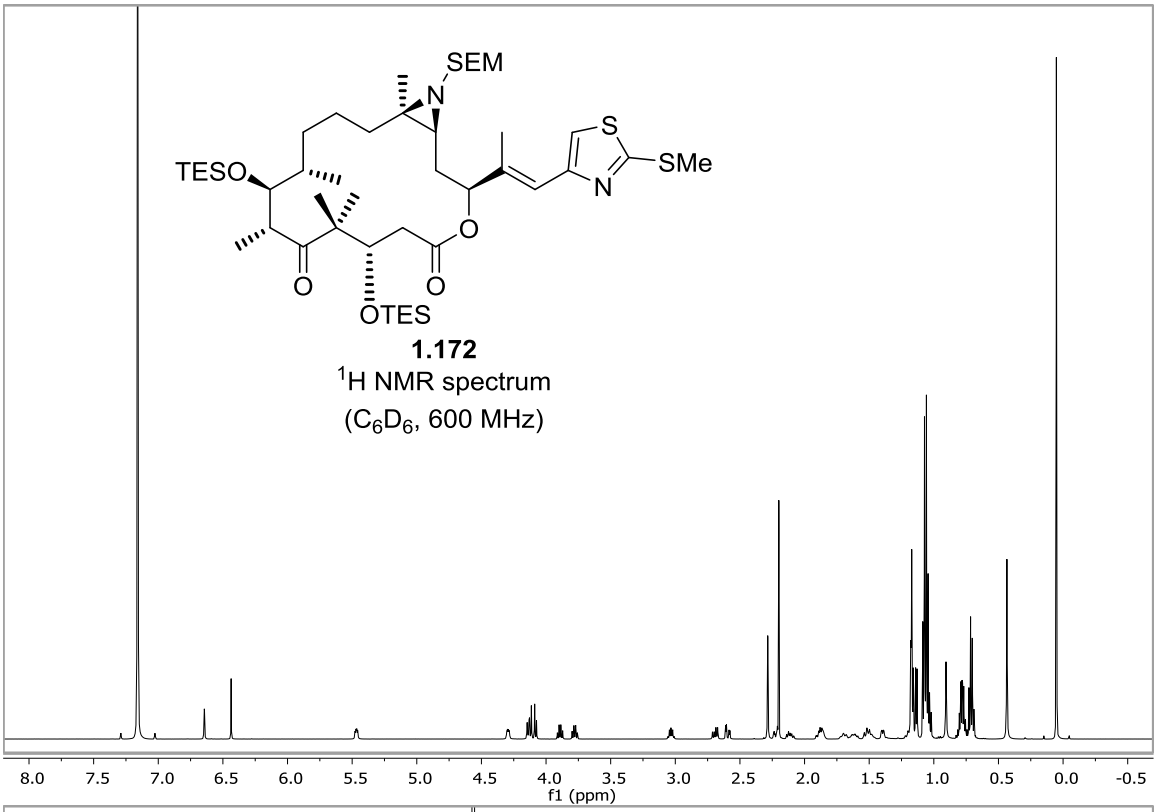


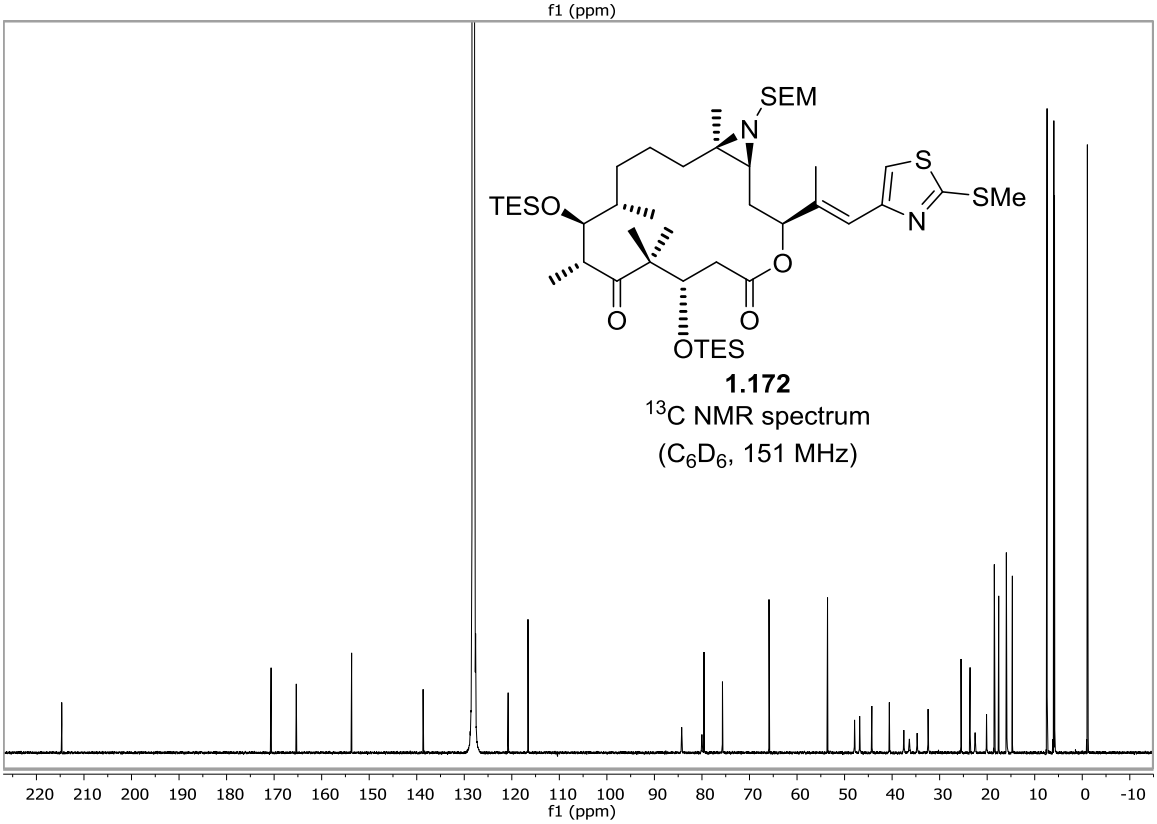
Spectra **1.85**: Compound **1.170**: ^{1}H and ^{13}C NMR



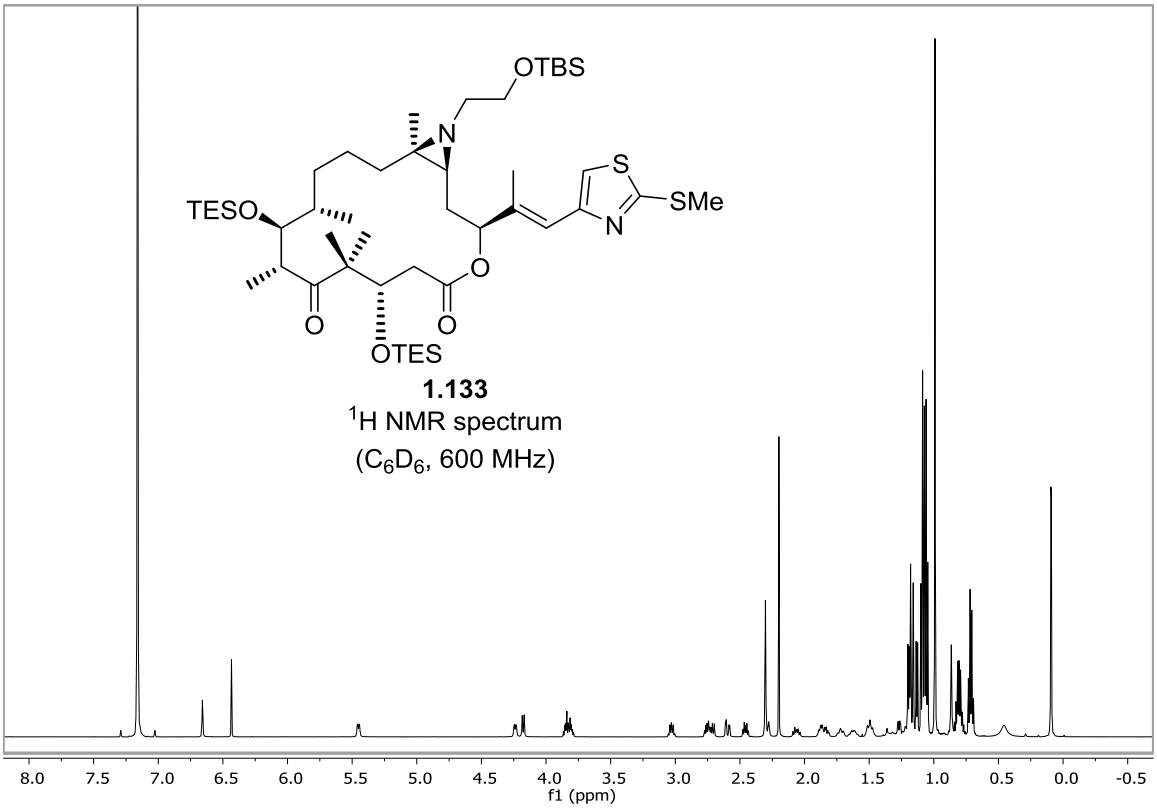


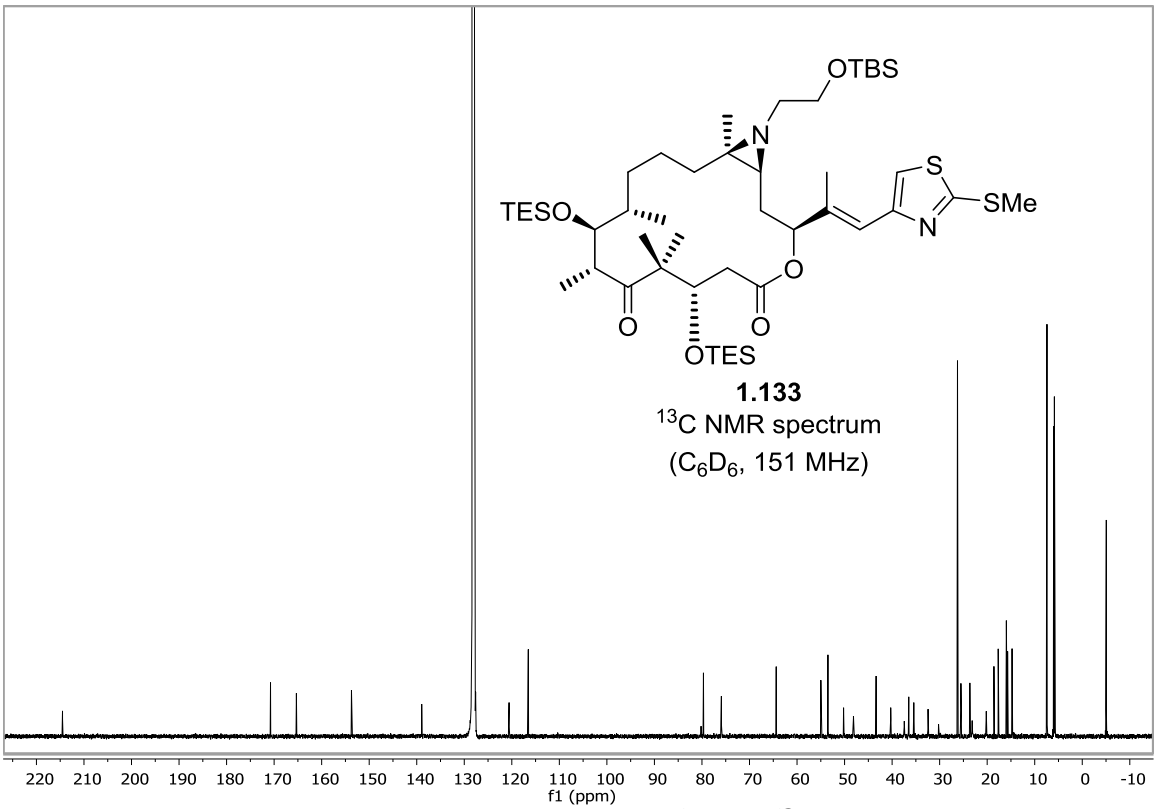
Spectra **1.86**: Compound **1.171**: ^{1}H and ^{13}C NMR



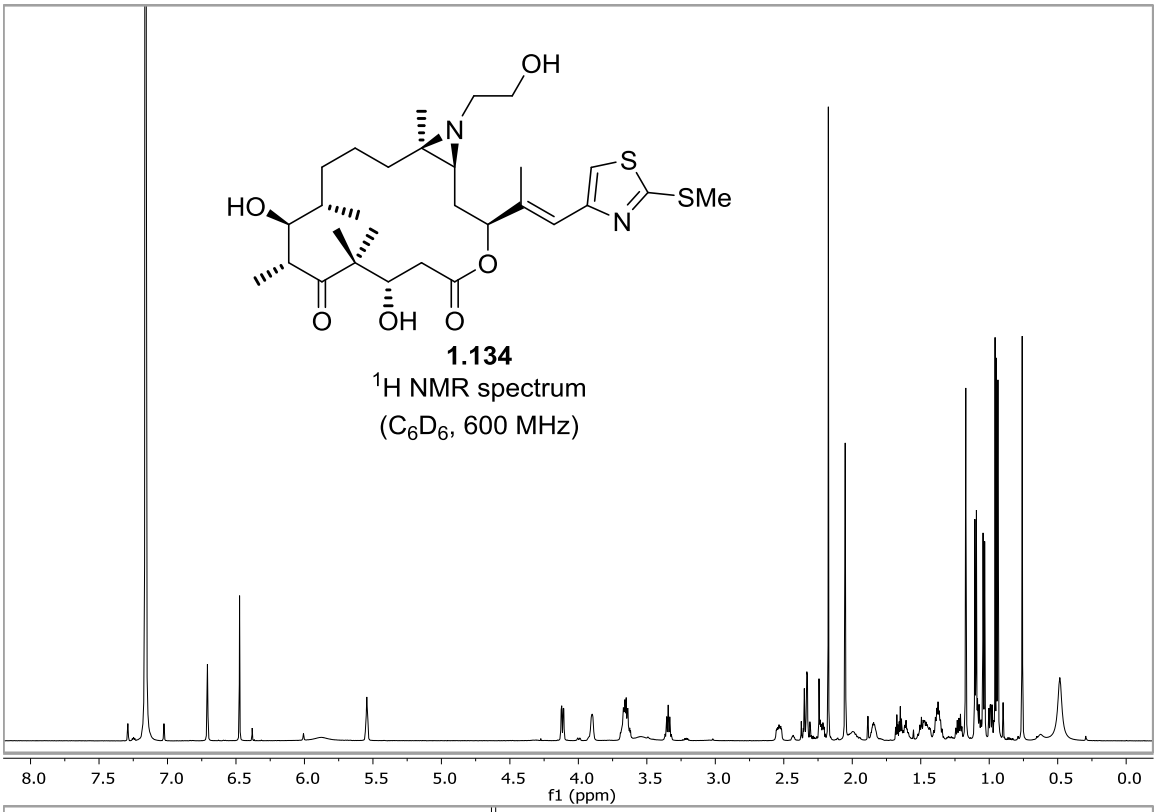


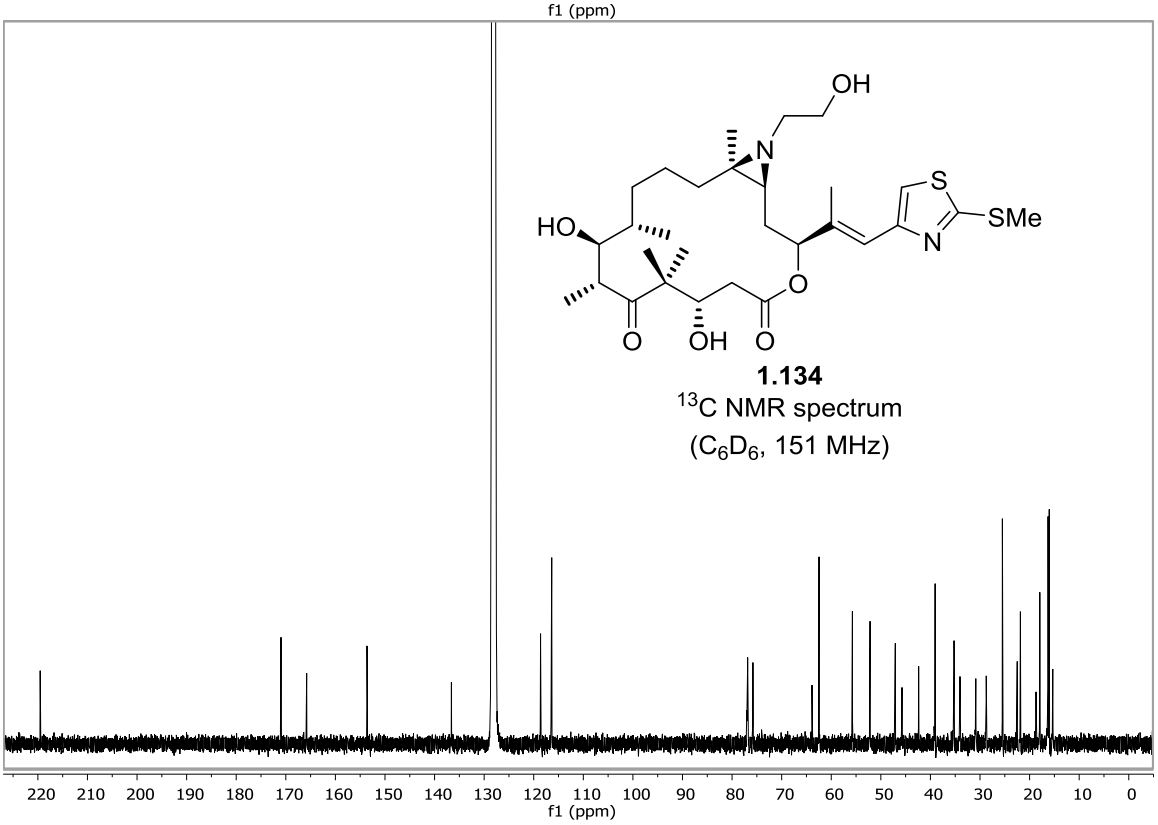
Spectra **1.87**: Compound **1.172**: ^{1}H and ^{13}C NMR



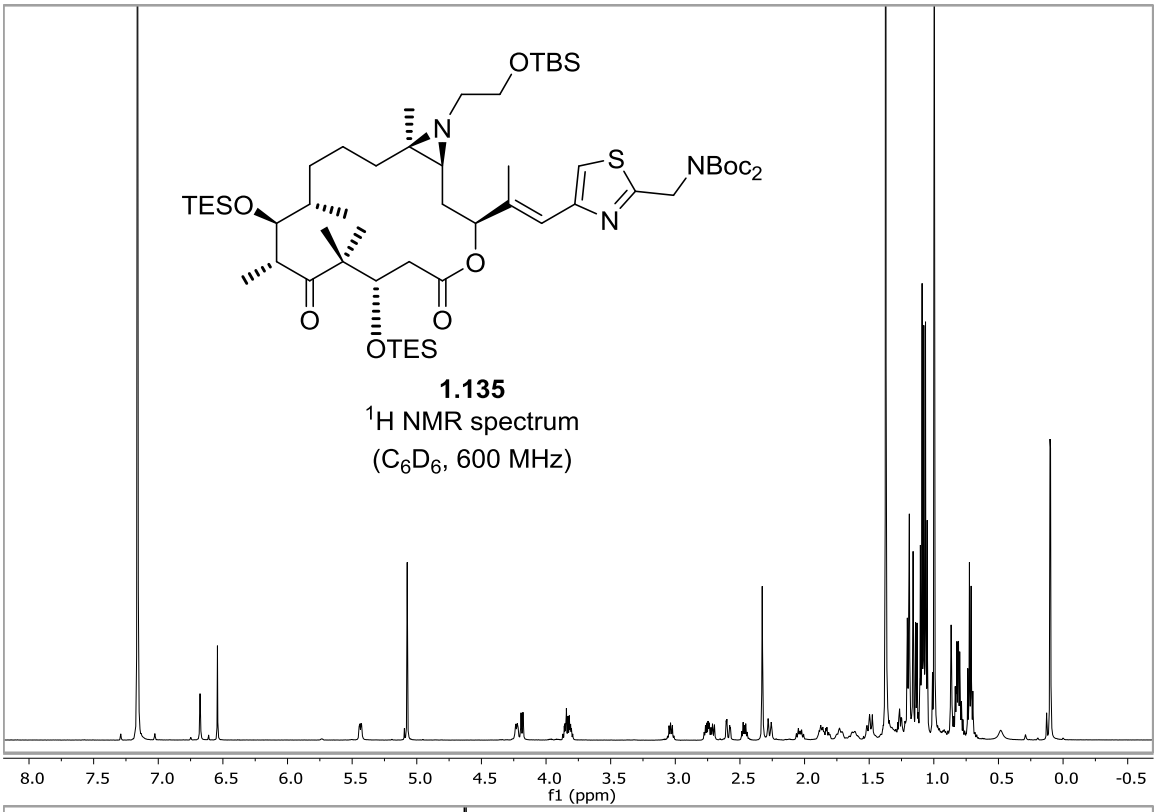


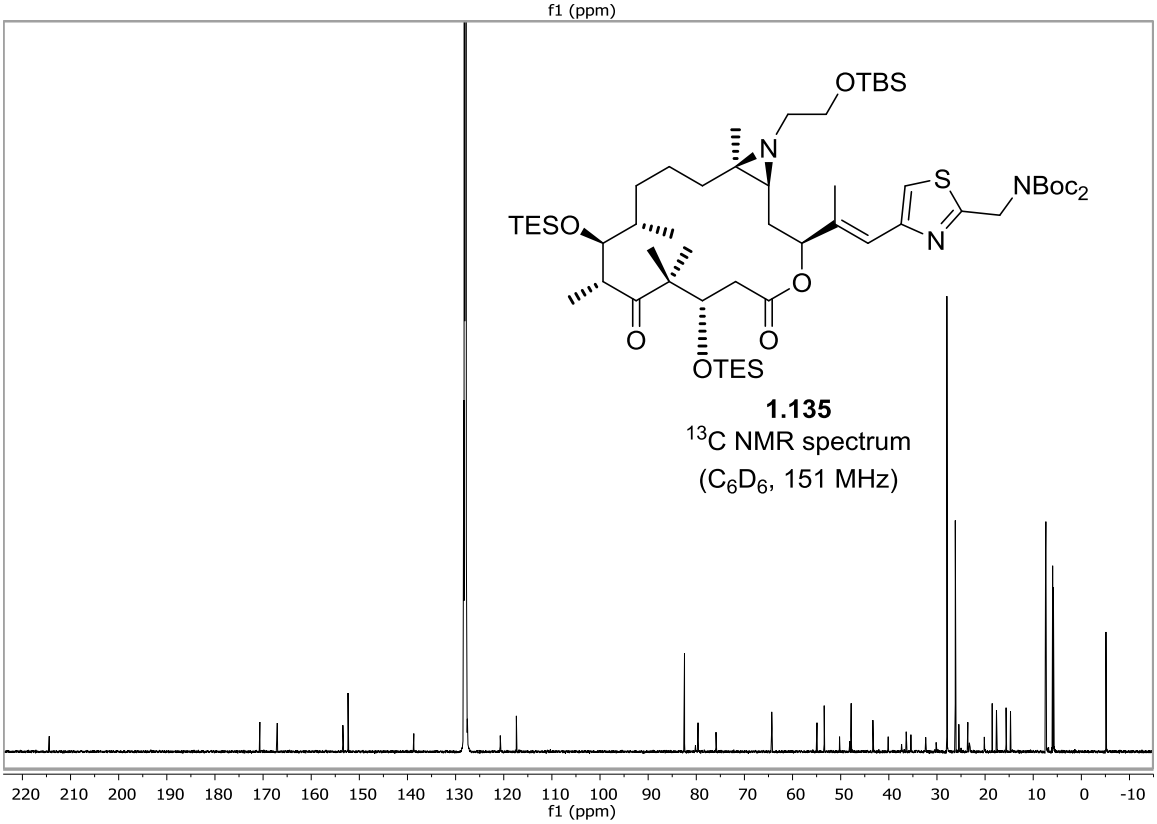
Spectra **1.88**: Compound **1.133**: ^{1}H and ^{13}C NMR



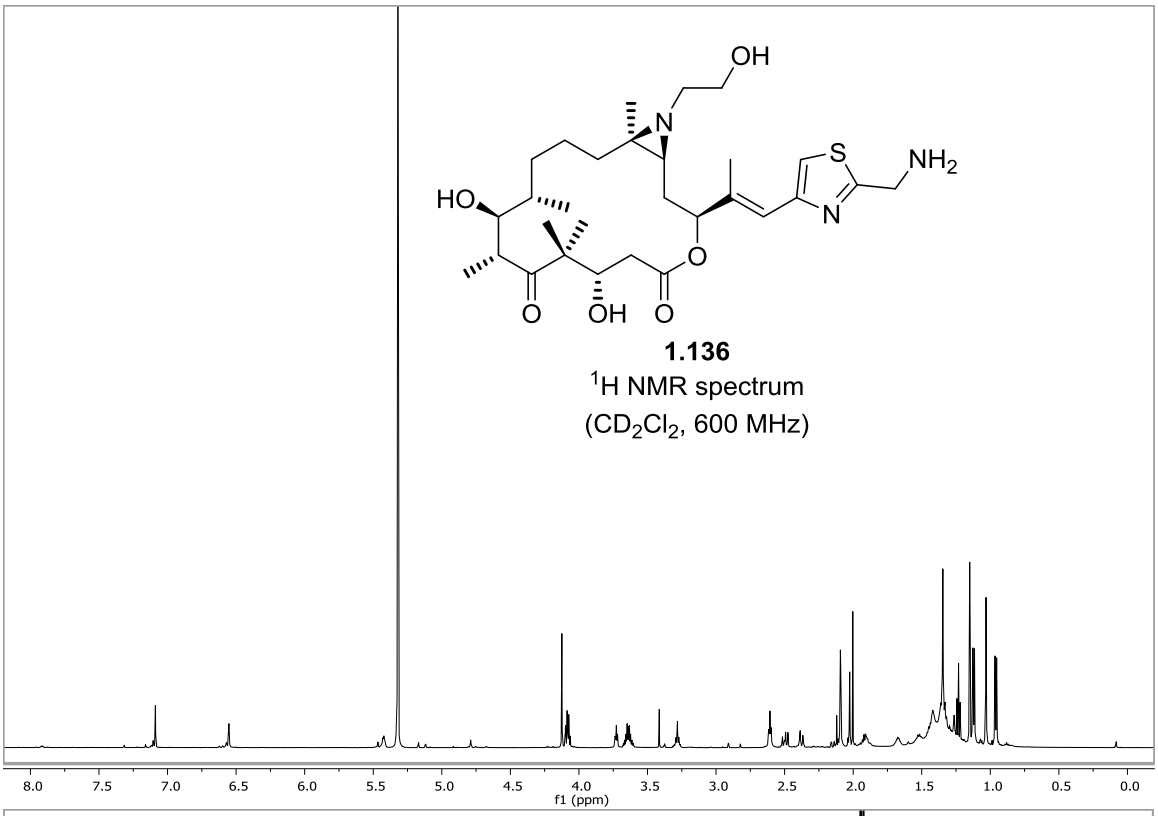


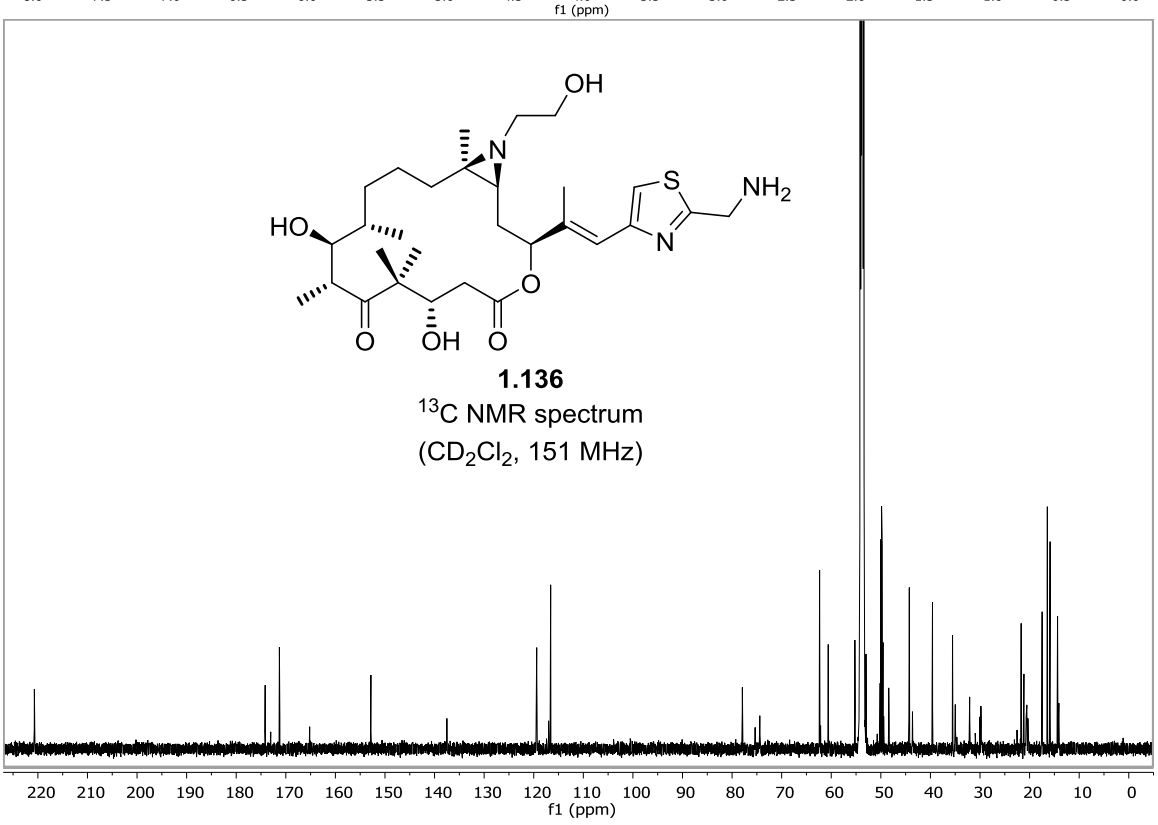
Spectra **1.89**: Compound **1.134**: ^{1}H and ^{13}C NMR



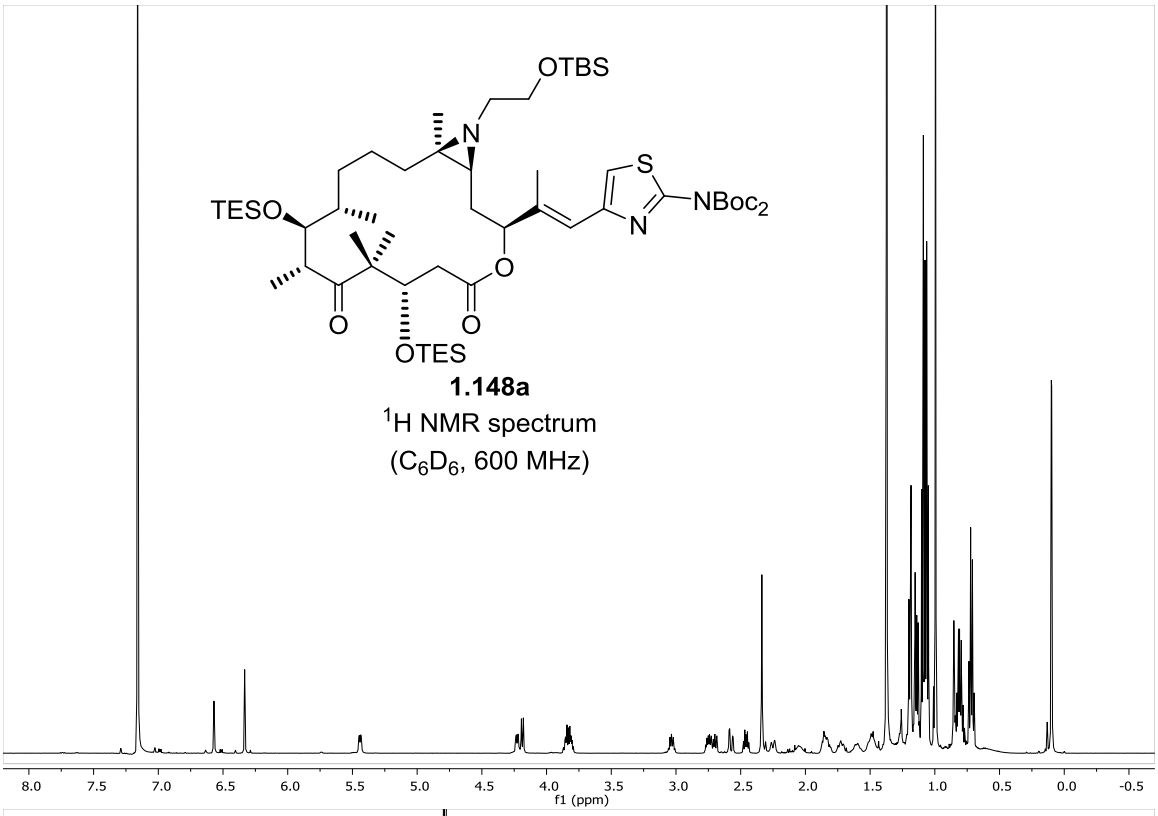


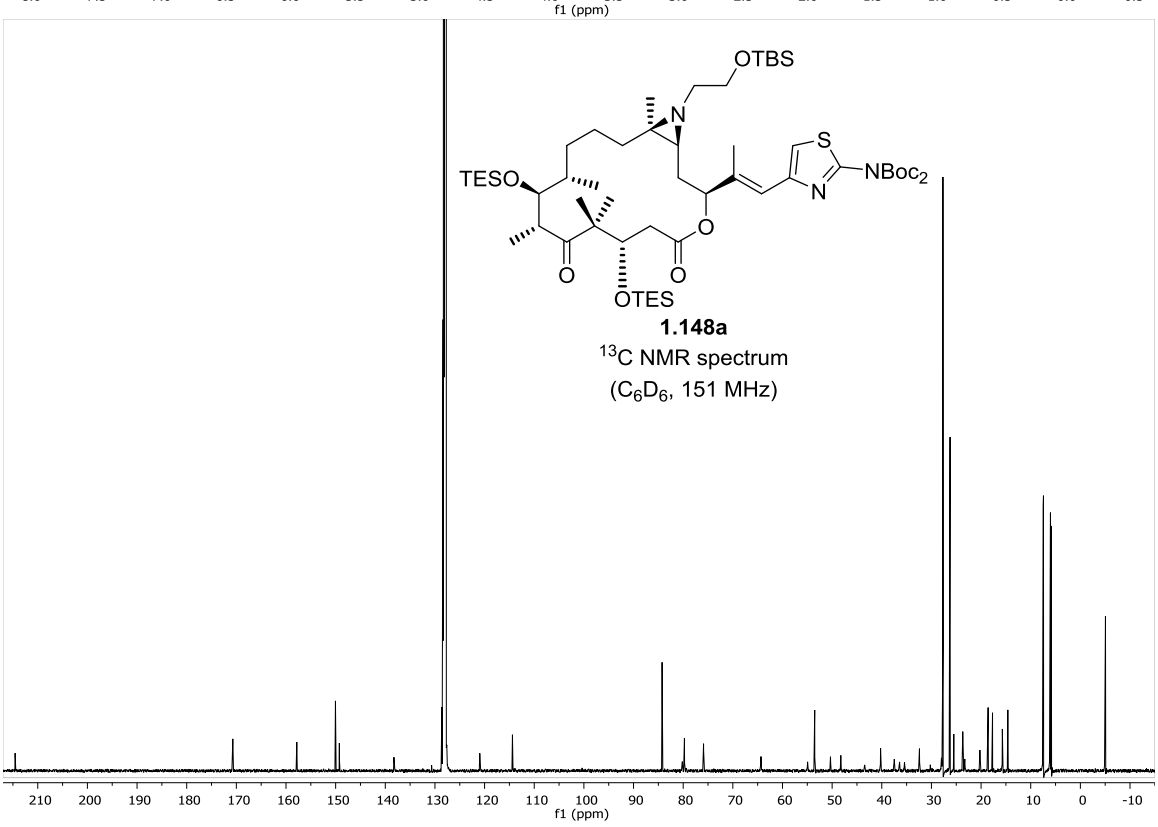
Spectra **1.90**: Compound **1.135**: ^{1}H and ^{13}C NMR



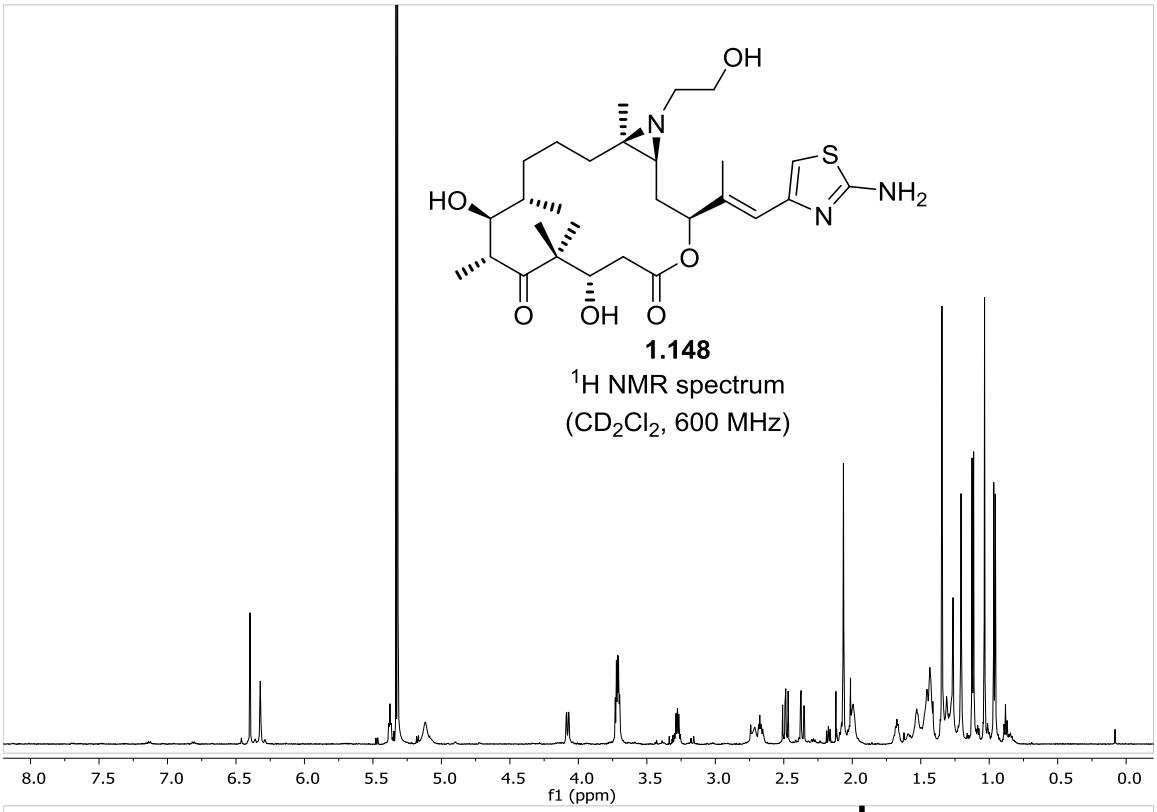


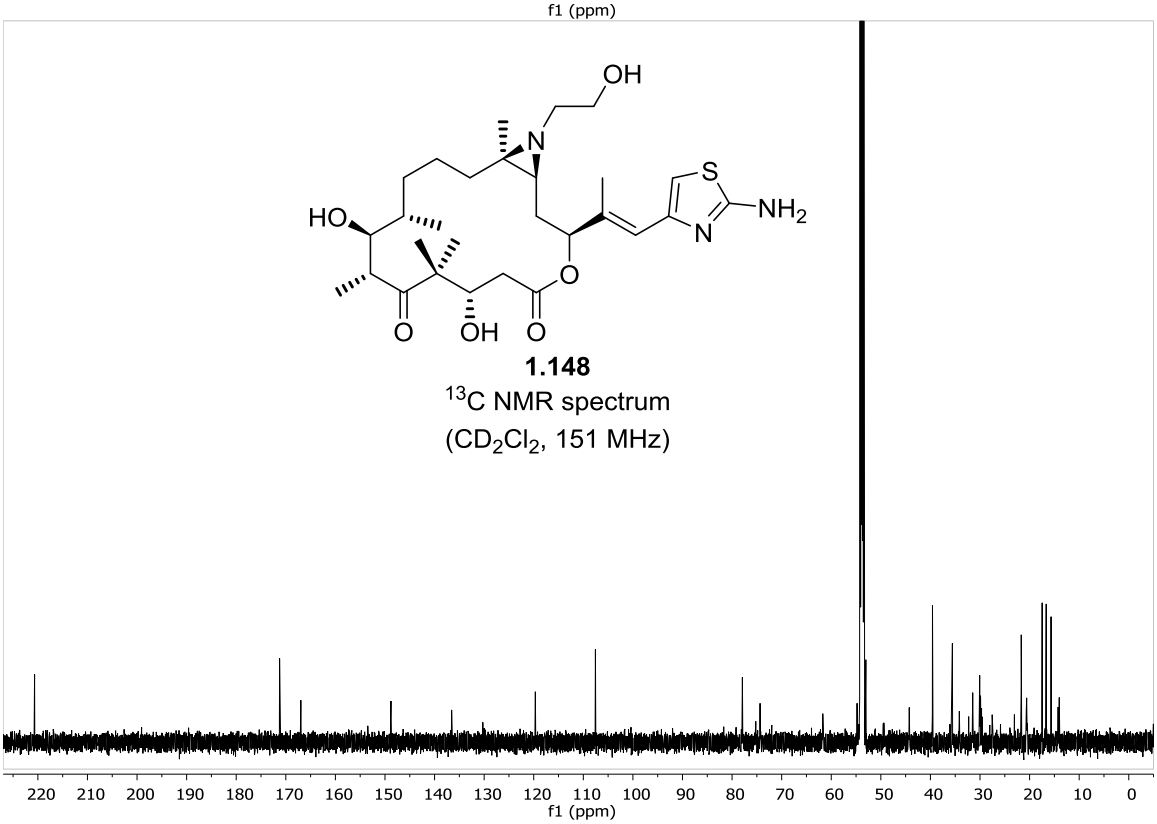
Spectra **1.91**: Compound **1.136**: ^{1}H and ^{13}C NMR



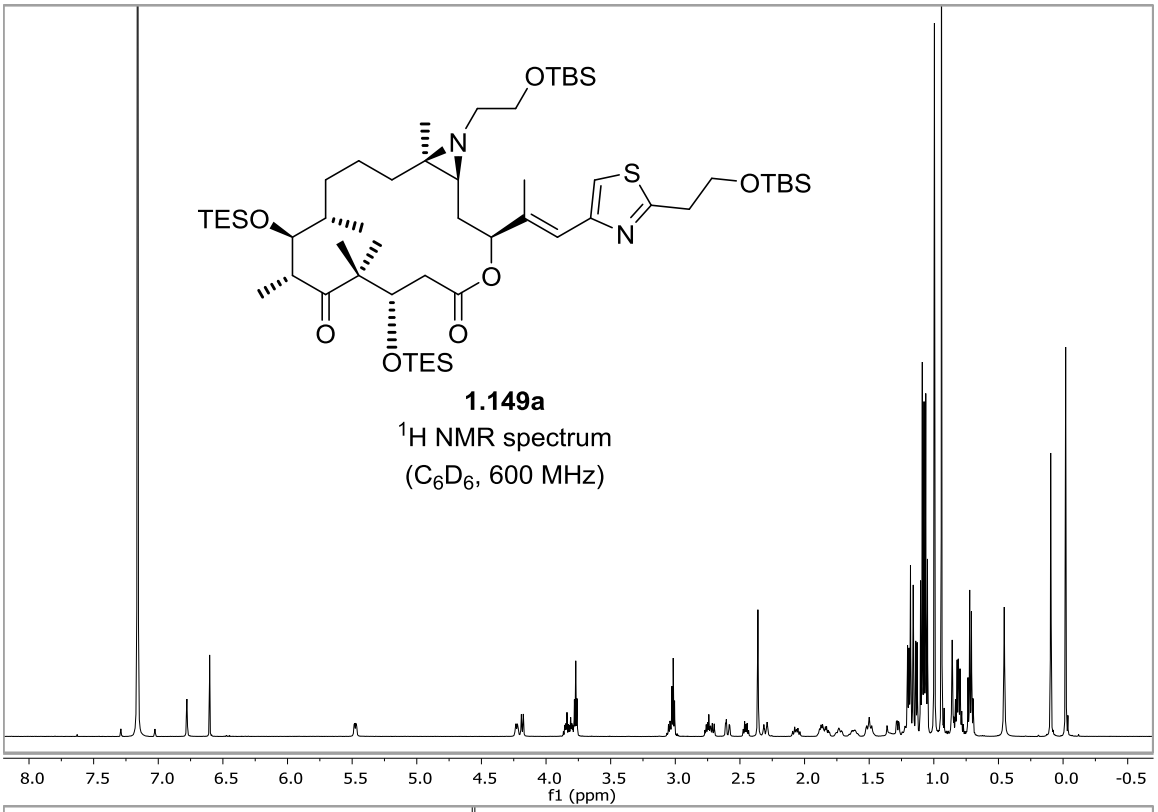


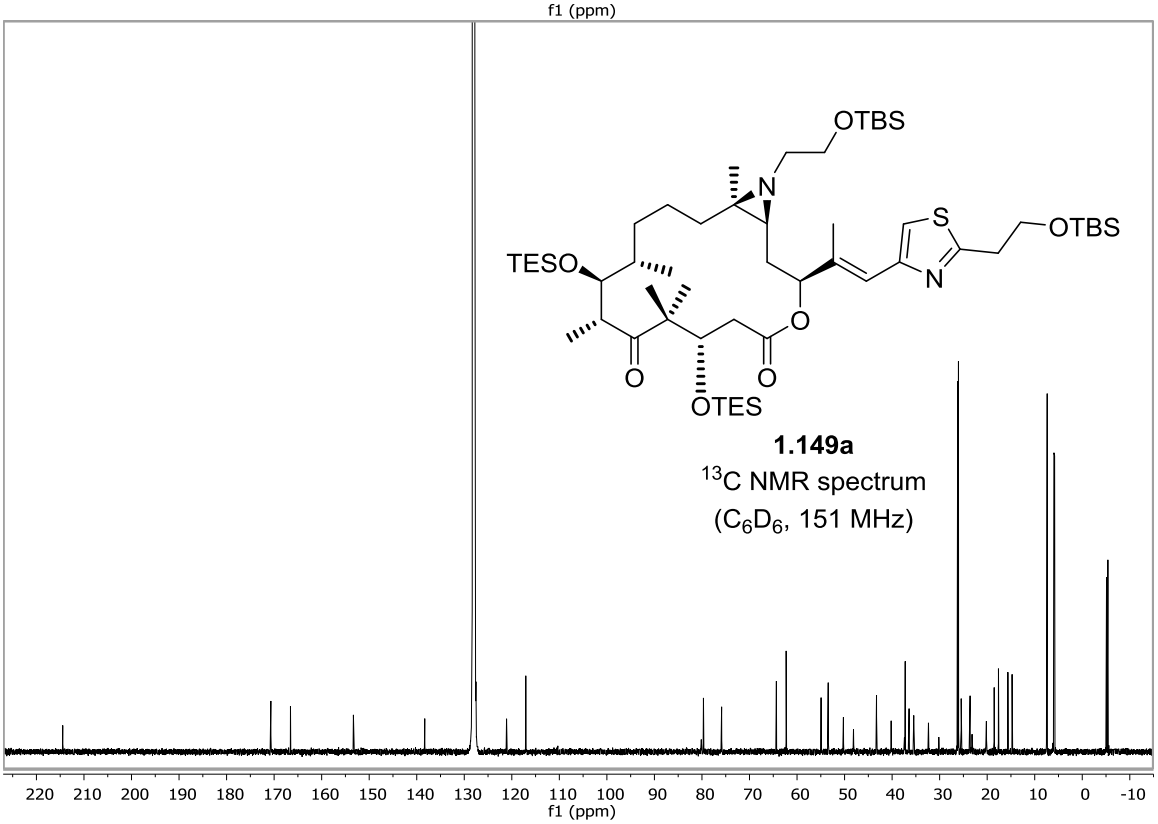
Spectra **1.92**: Compound **1.148a**: ^{1}H and ^{13}C NMR



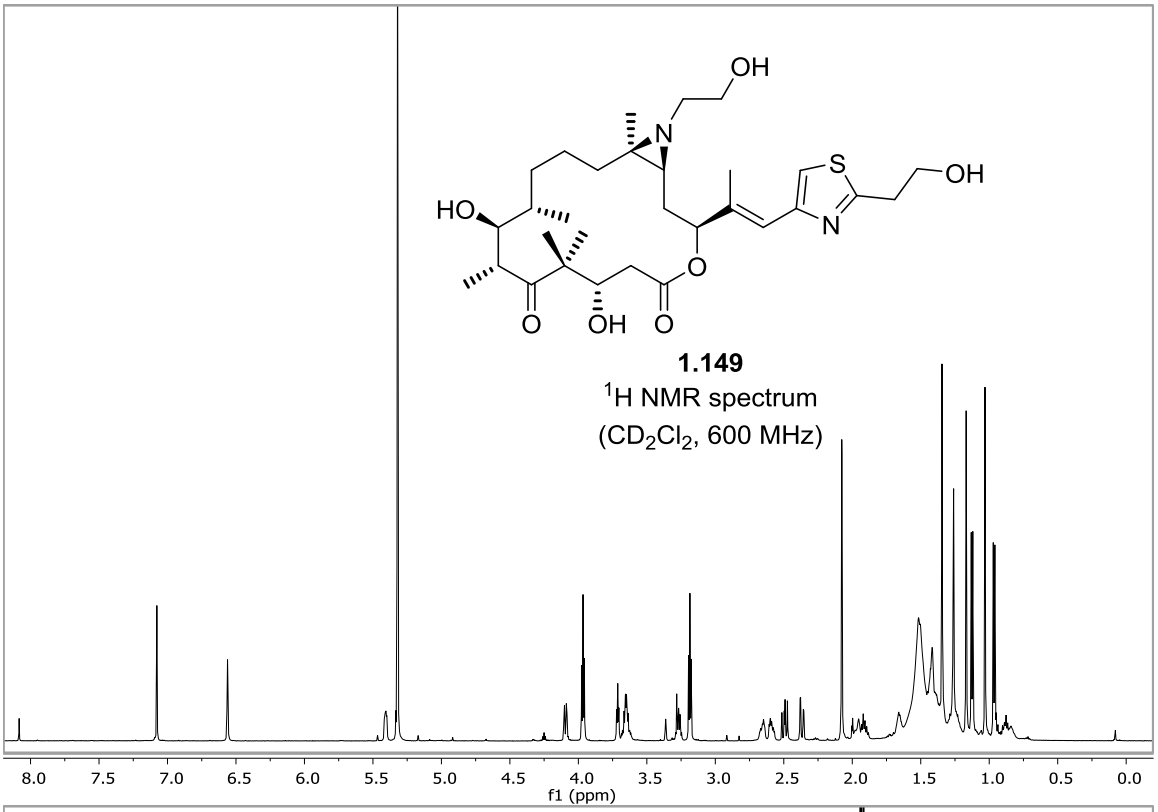


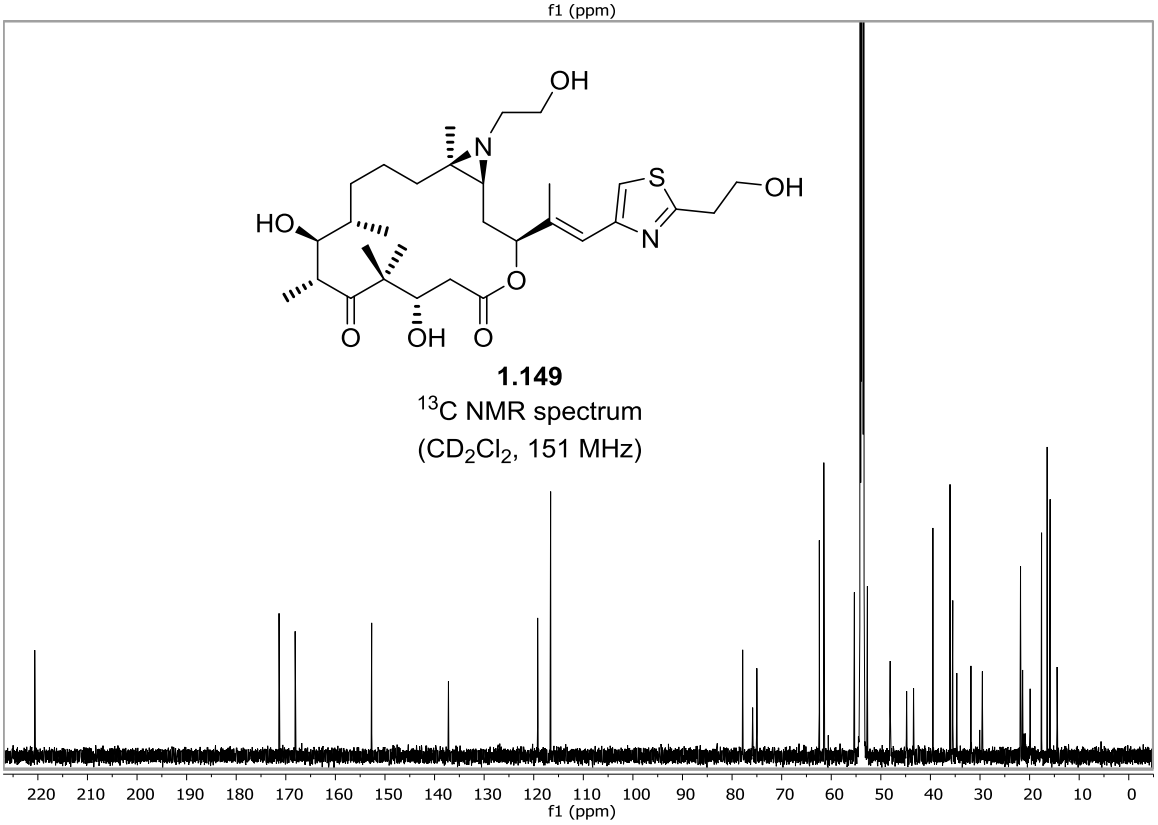
Spectra **1.93**: Compound **1.148**: ^{1}H and ^{13}C NMR



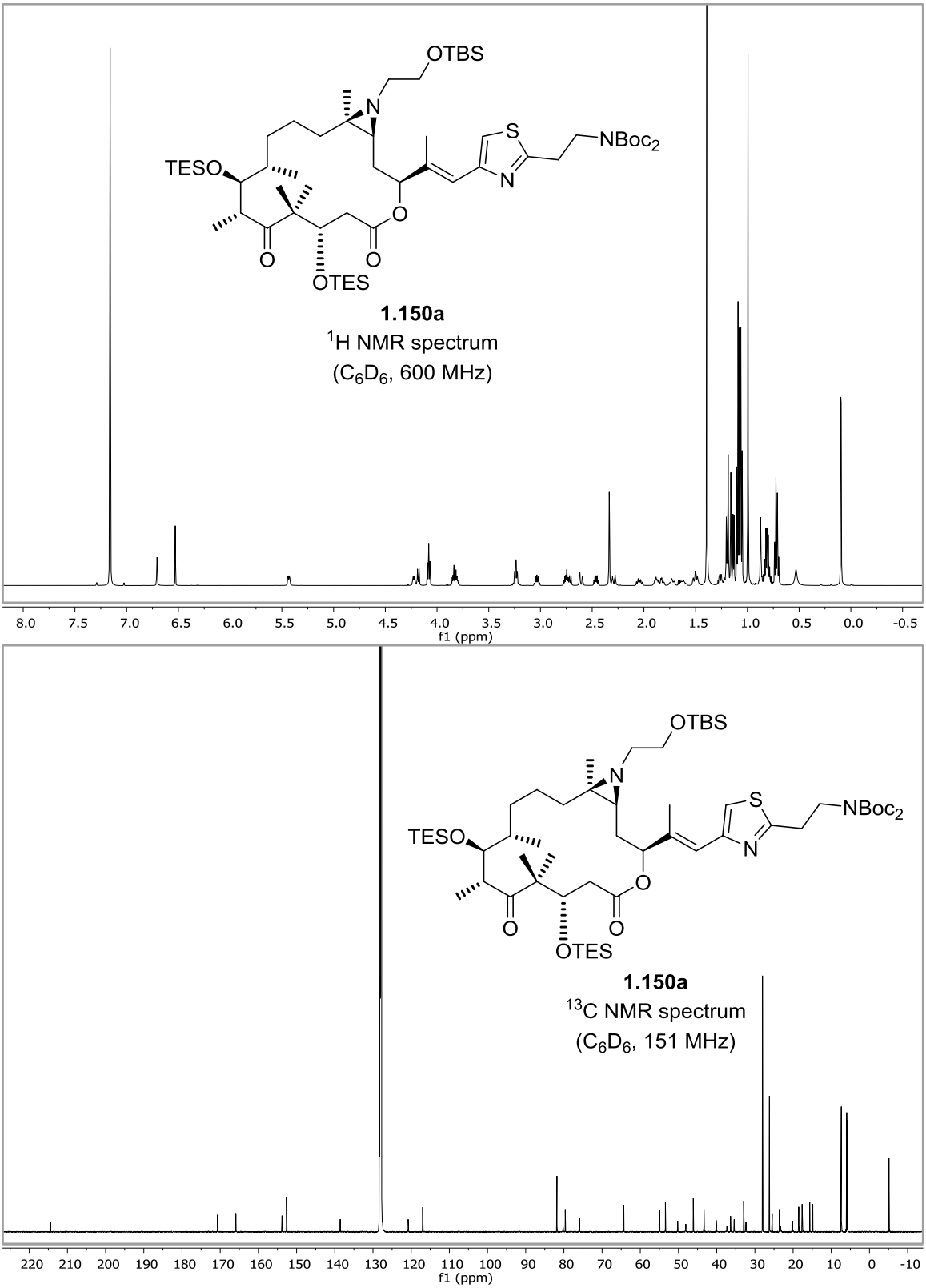


Spectra **1.94**: Compound **1.149a**: ^{1}H and ^{13}C NMR

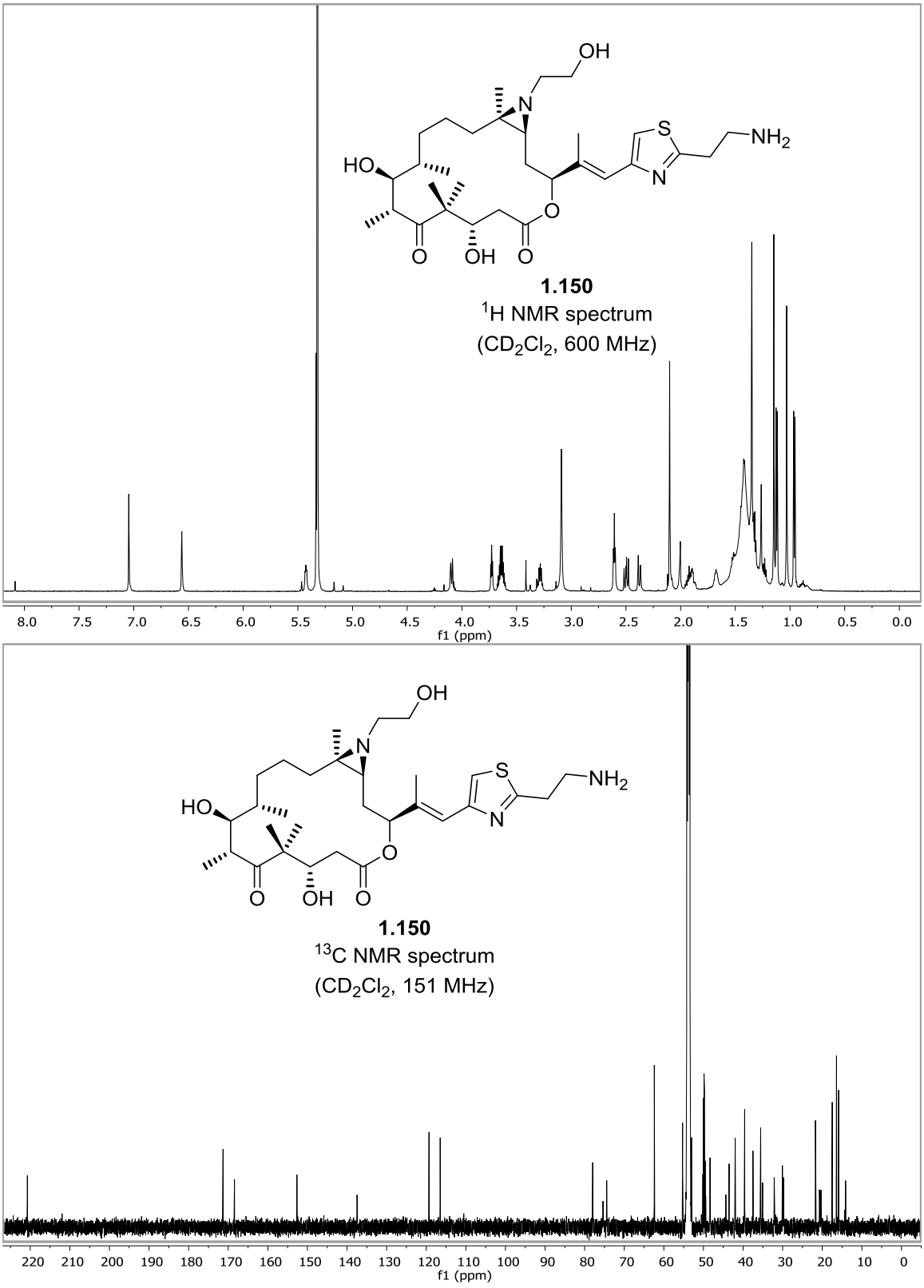




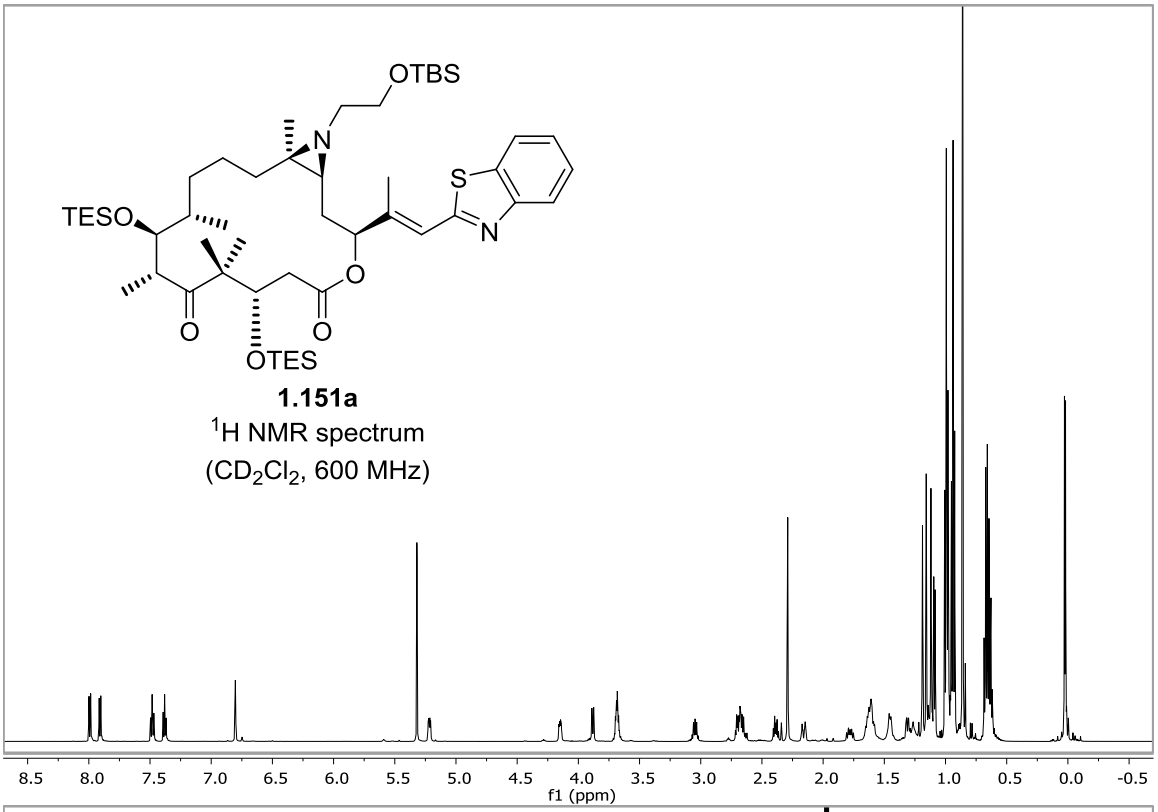
Spectra **1.95**: Compound **1.149**: ^{1}H and ^{13}C NMR

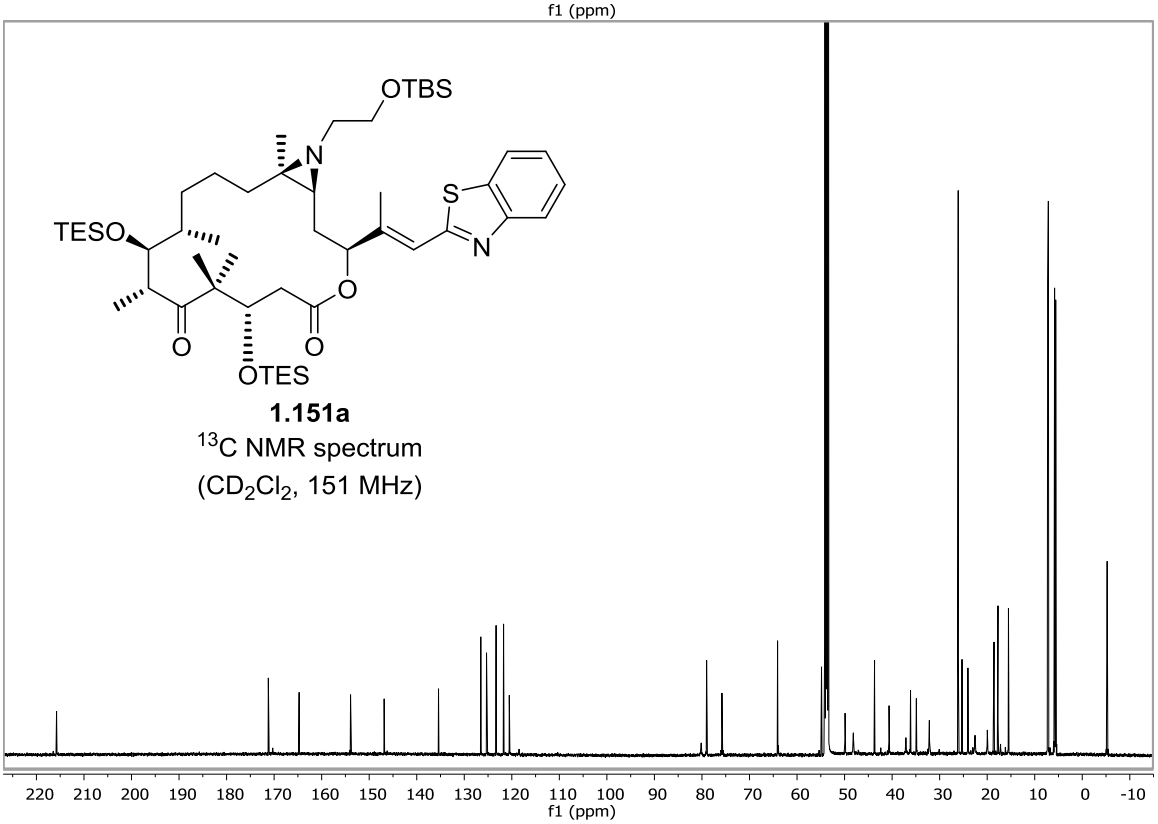


Spectra **1.96**: Compound **1.150a**: ^{1}H and ^{13}C NMR

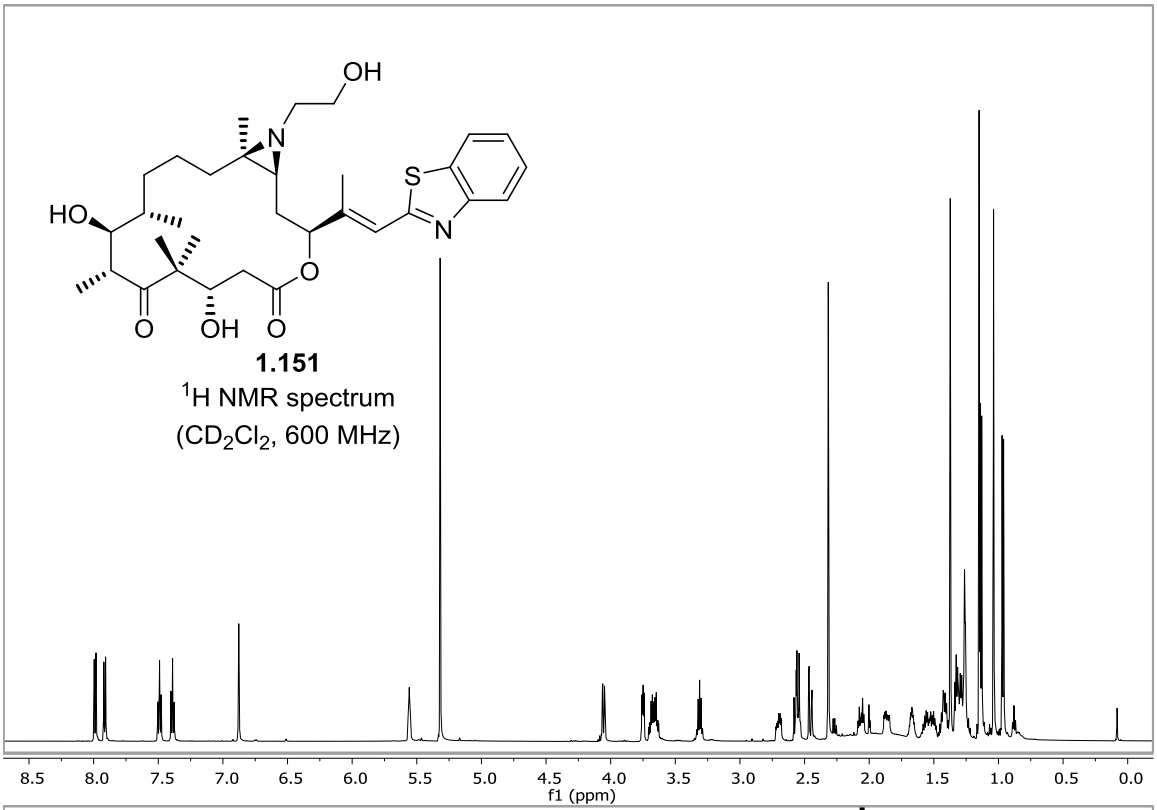


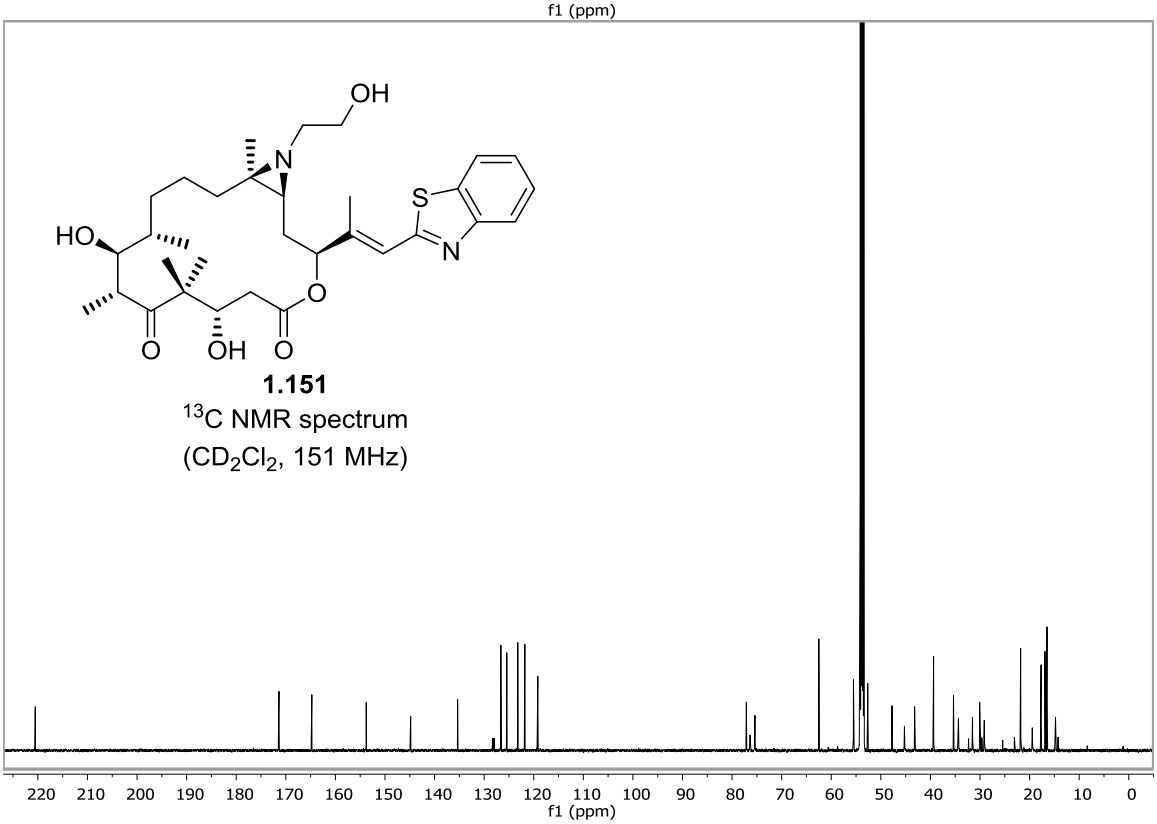
Spectra **1.97**: Compound **1.150**: ^{1}H and ^{13}C NMR



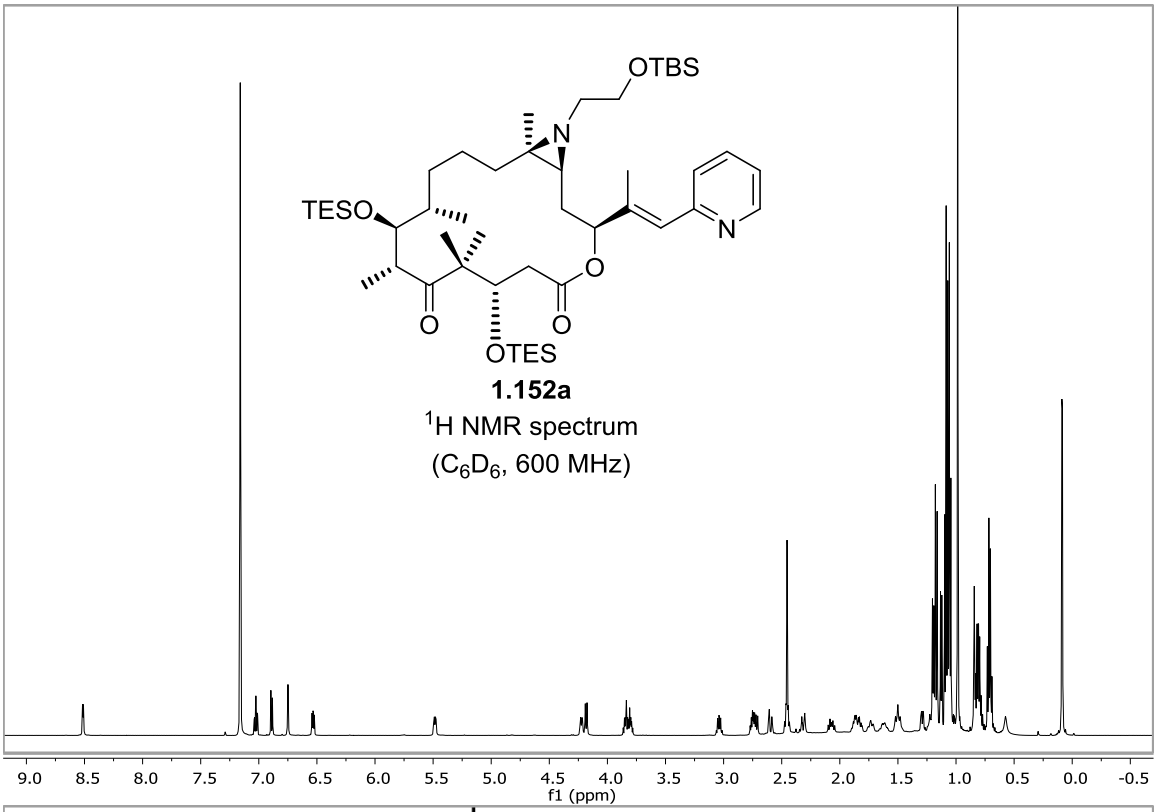


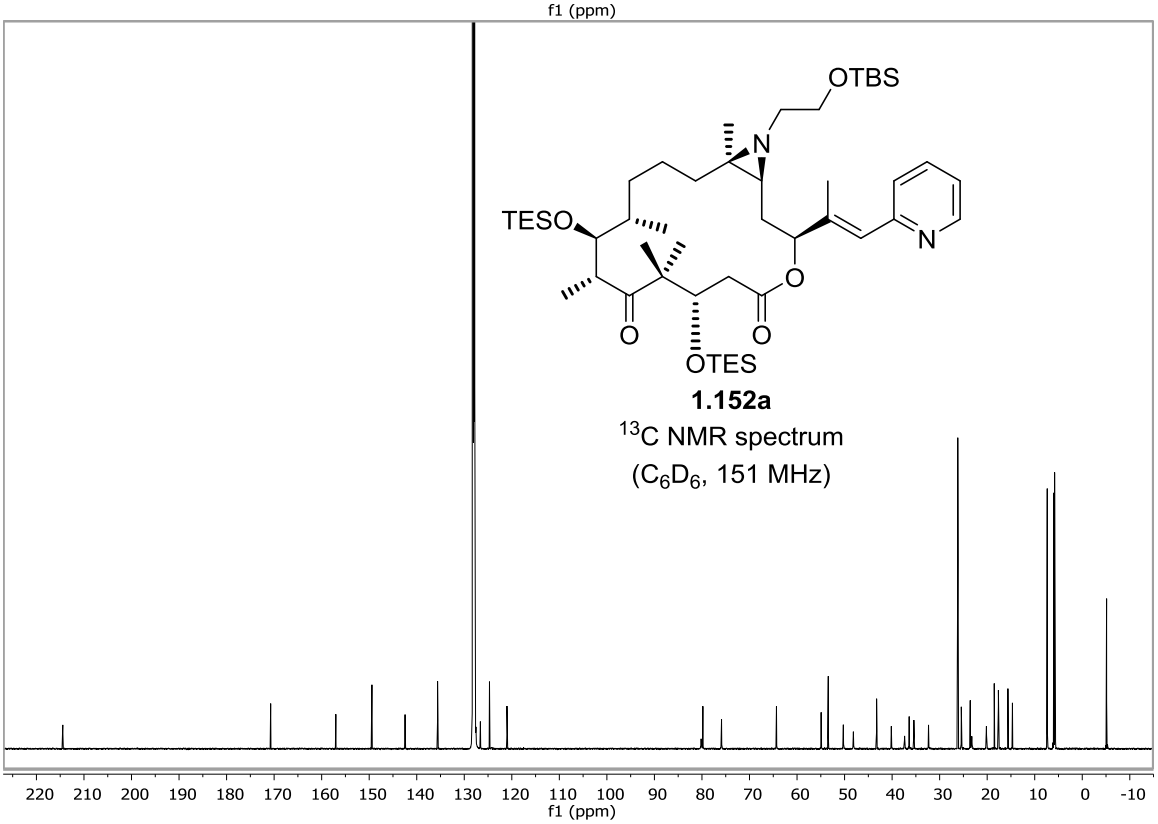
Spectra **1.98**: Compound **1.151a**: ^{1}H and ^{13}C NMR



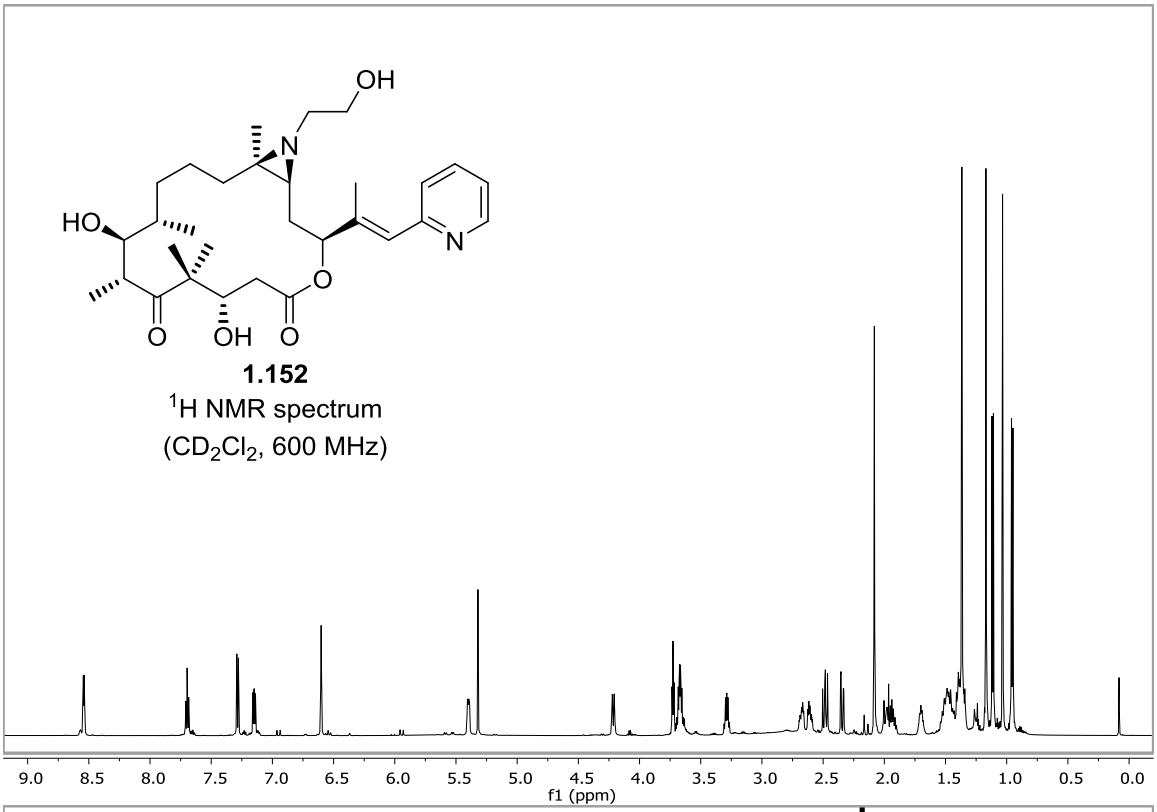


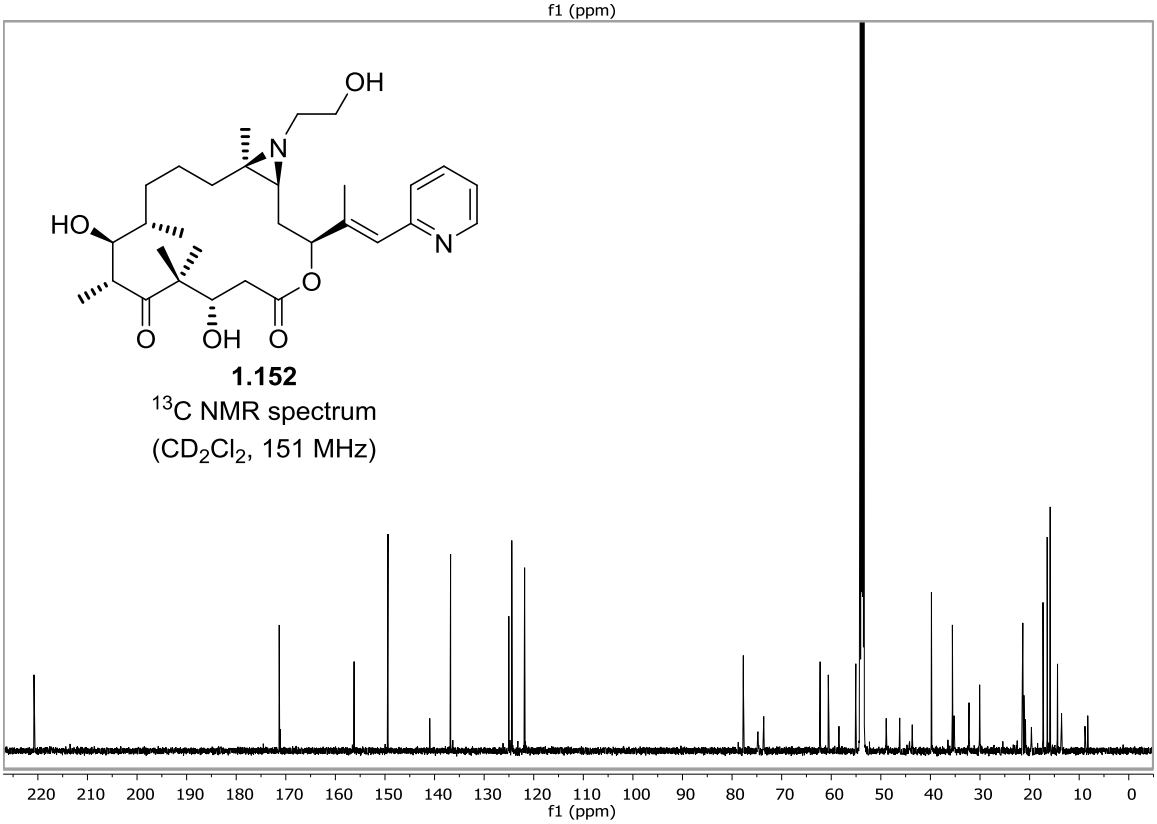
Spectra **1.99**: Compound **1.151**: ^{1}H and ^{13}C NMR



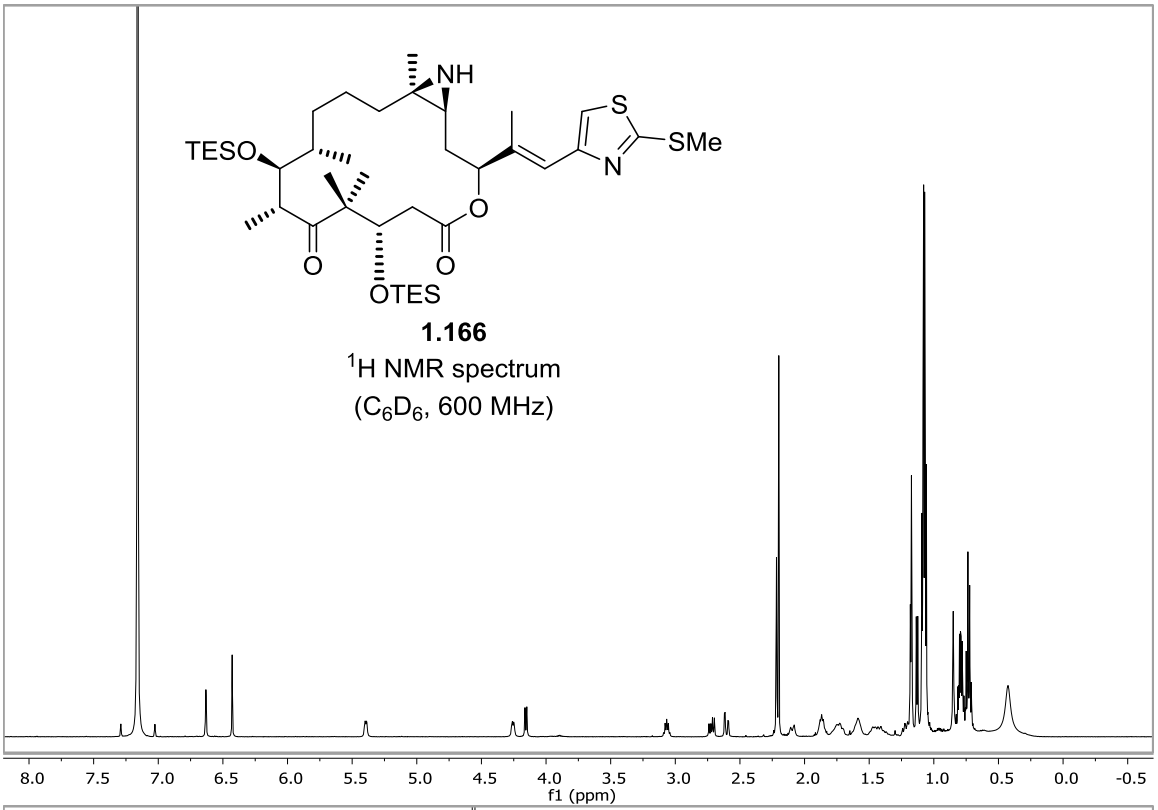


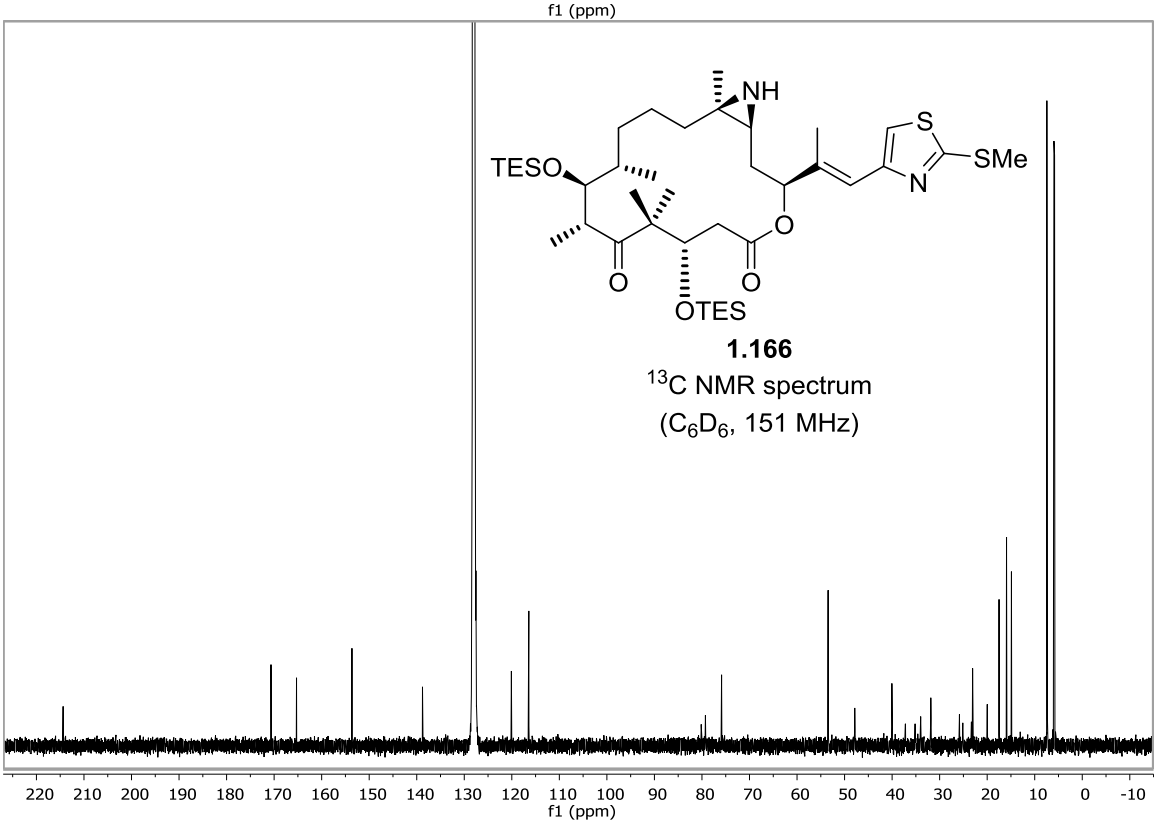
Spectra **1.100**: Compound **1.152a**: ^{1}H and ^{13}C NMR



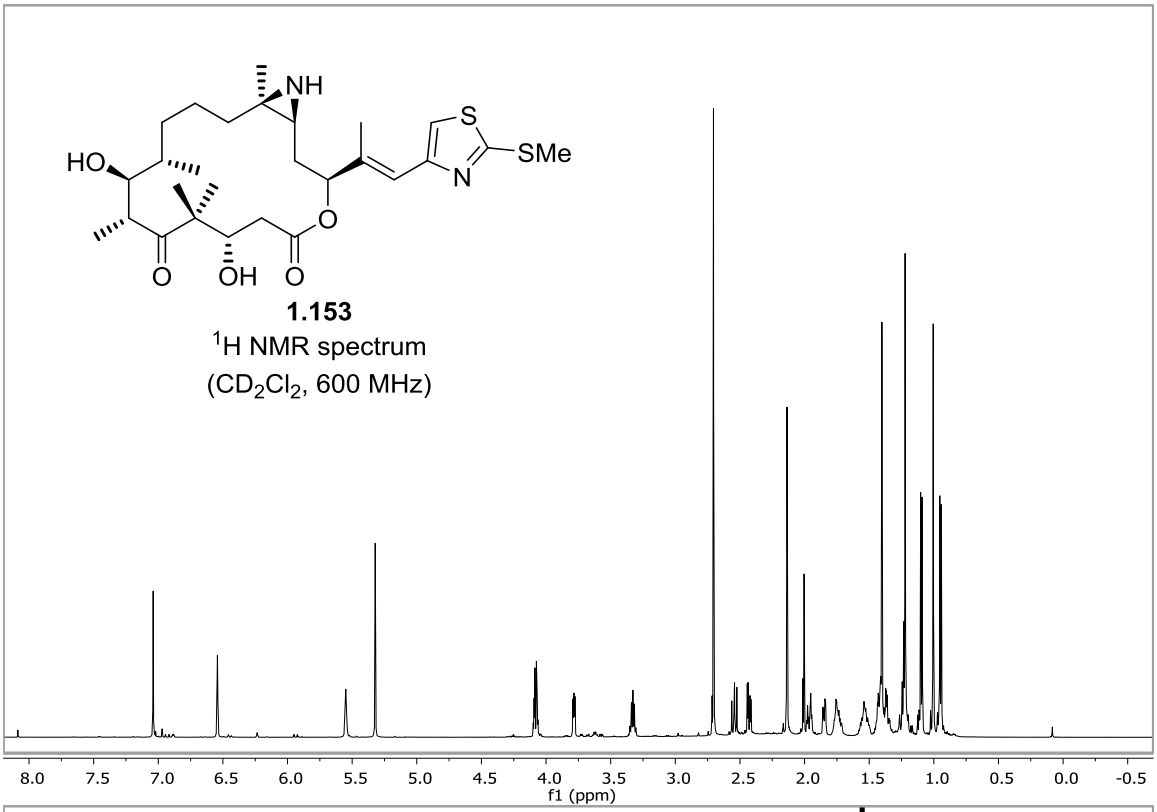


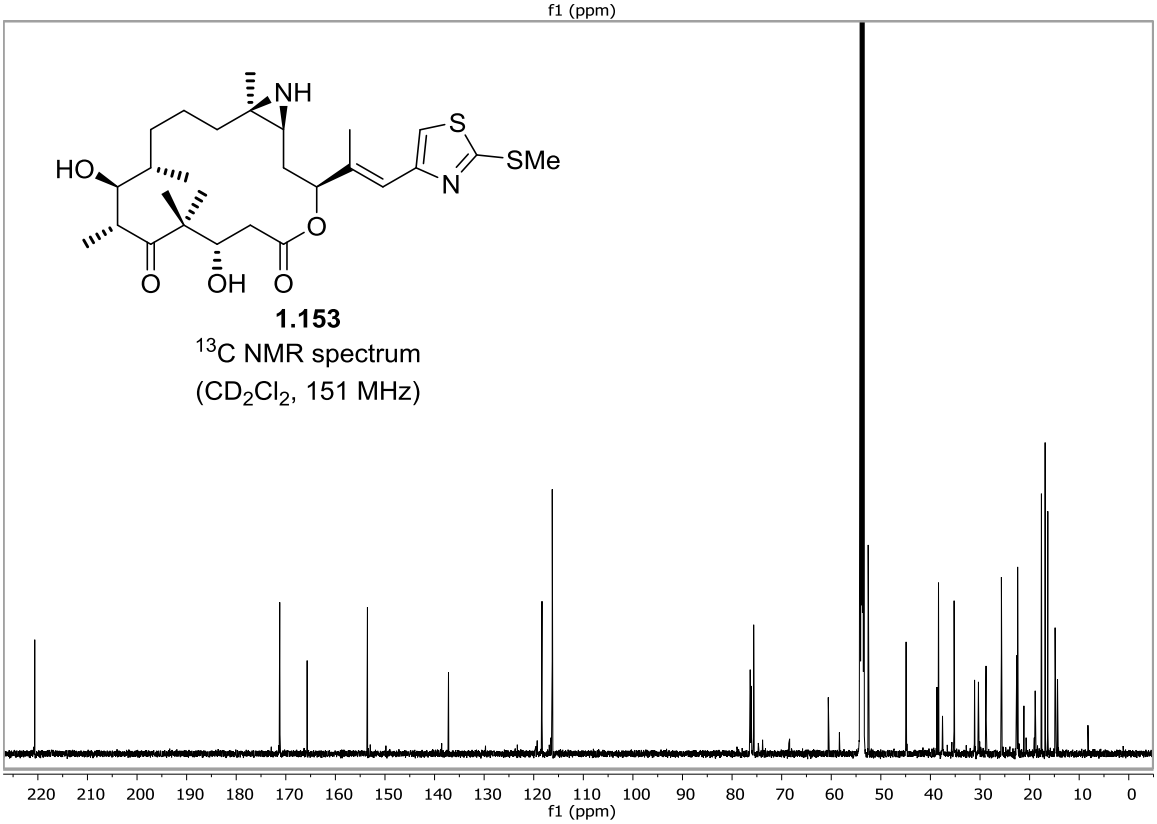
Spectra **1.101**: Compound **1.152**: ^{1}H and ^{13}C NMR



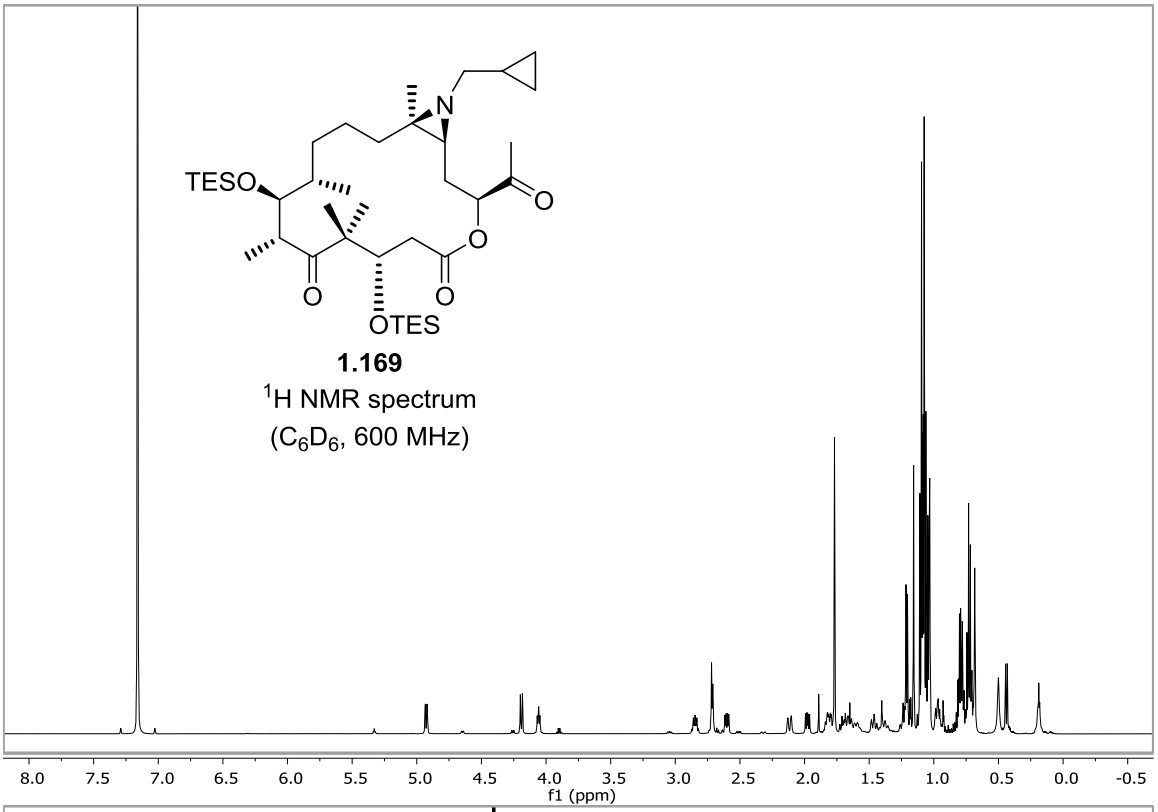


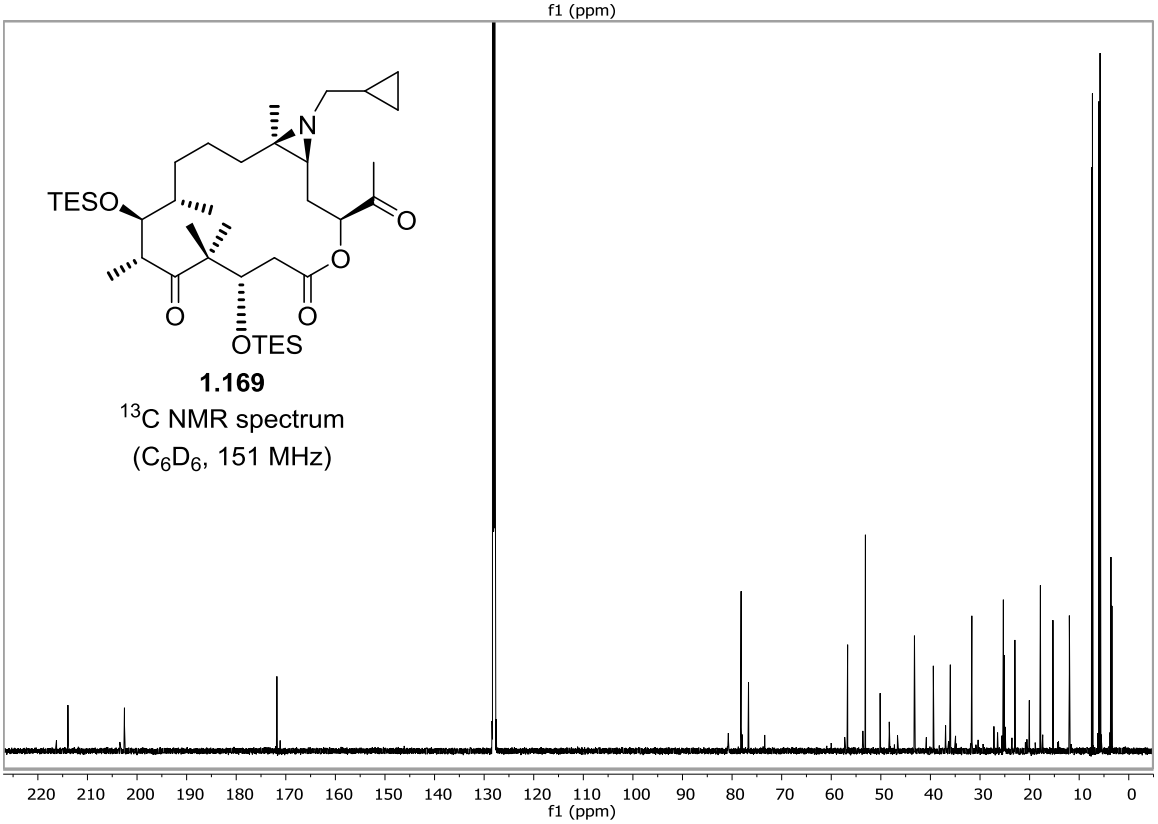
Spectra **1.102**: Compound **1.166**: ^{1}H and ^{13}C NMR



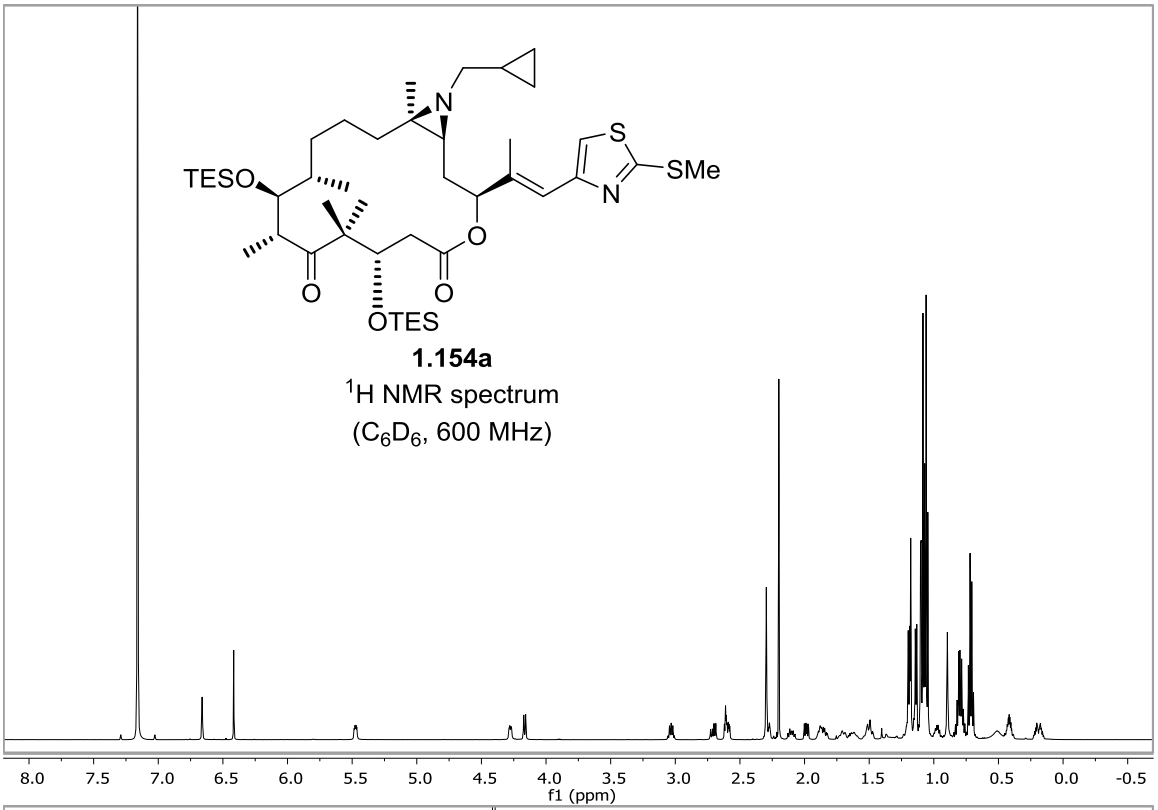


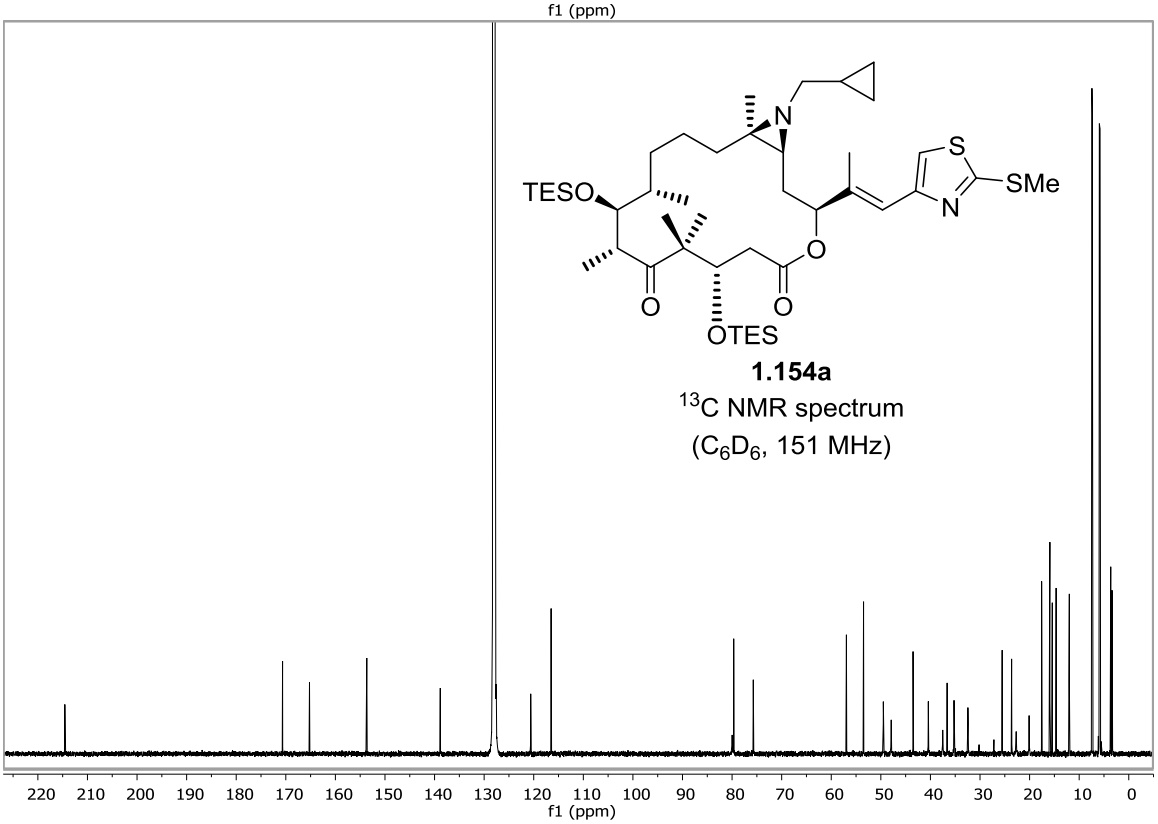
Spectra **1.103**: Compound **1.153**: ^{1}H and ^{13}C NMR



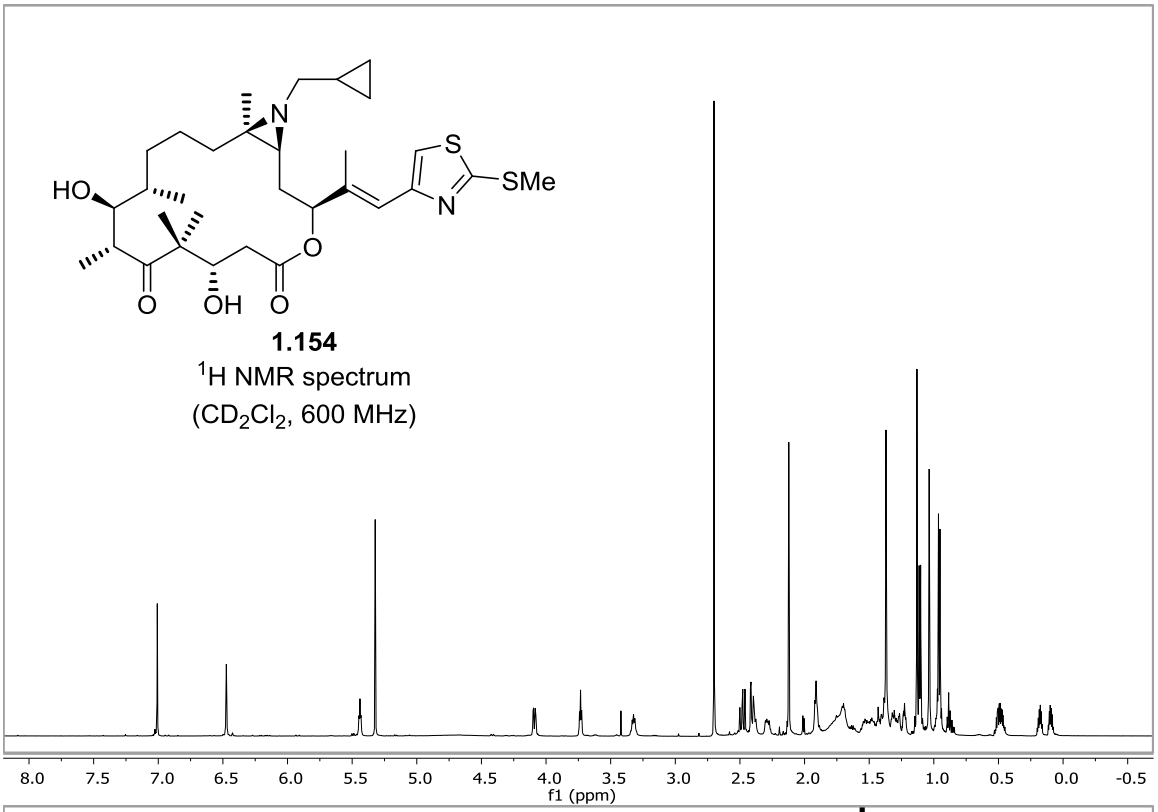


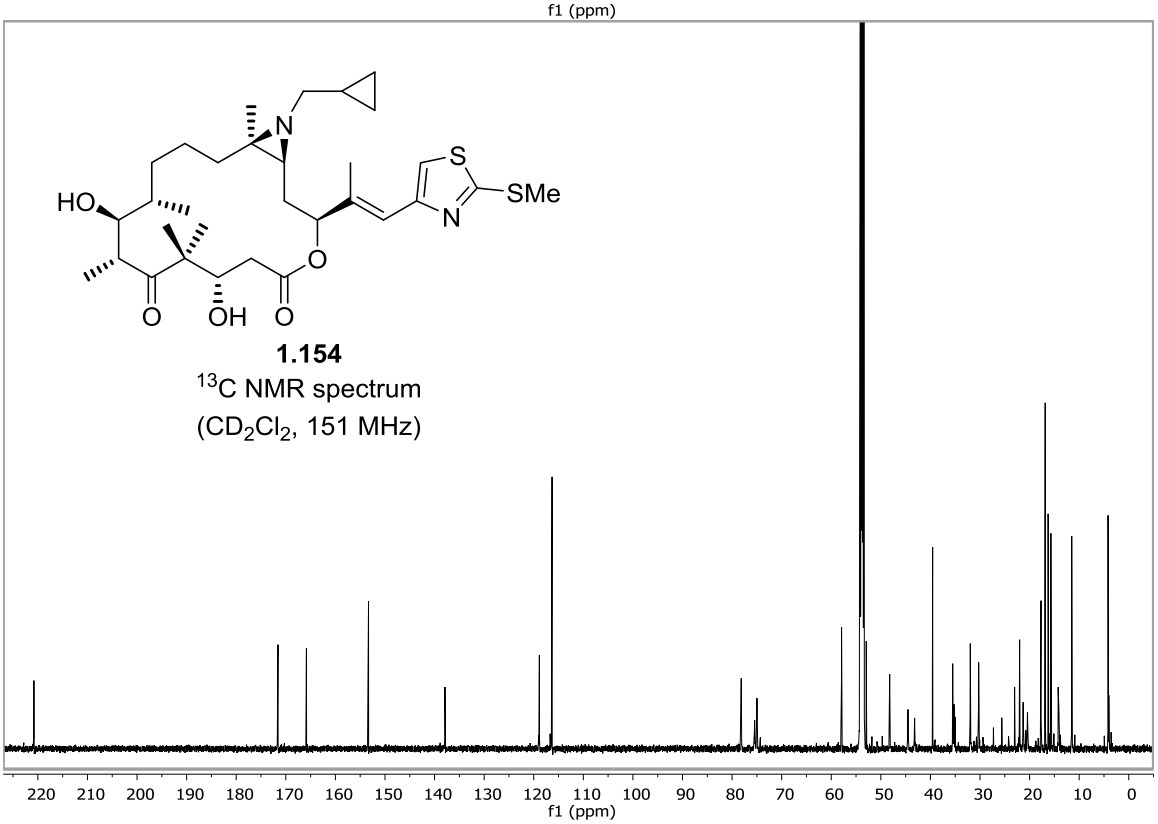
Spectra **1.104**: Compound **1.169**: ^{1}H and ^{13}C NMR



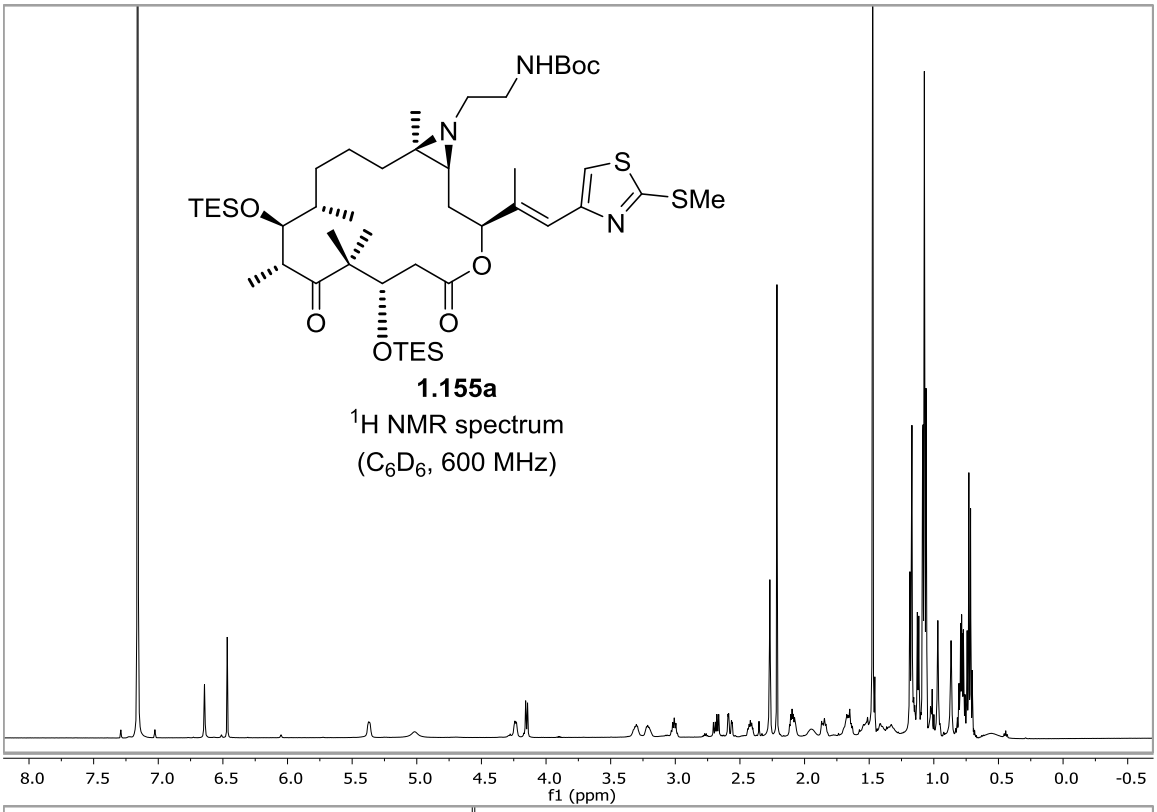


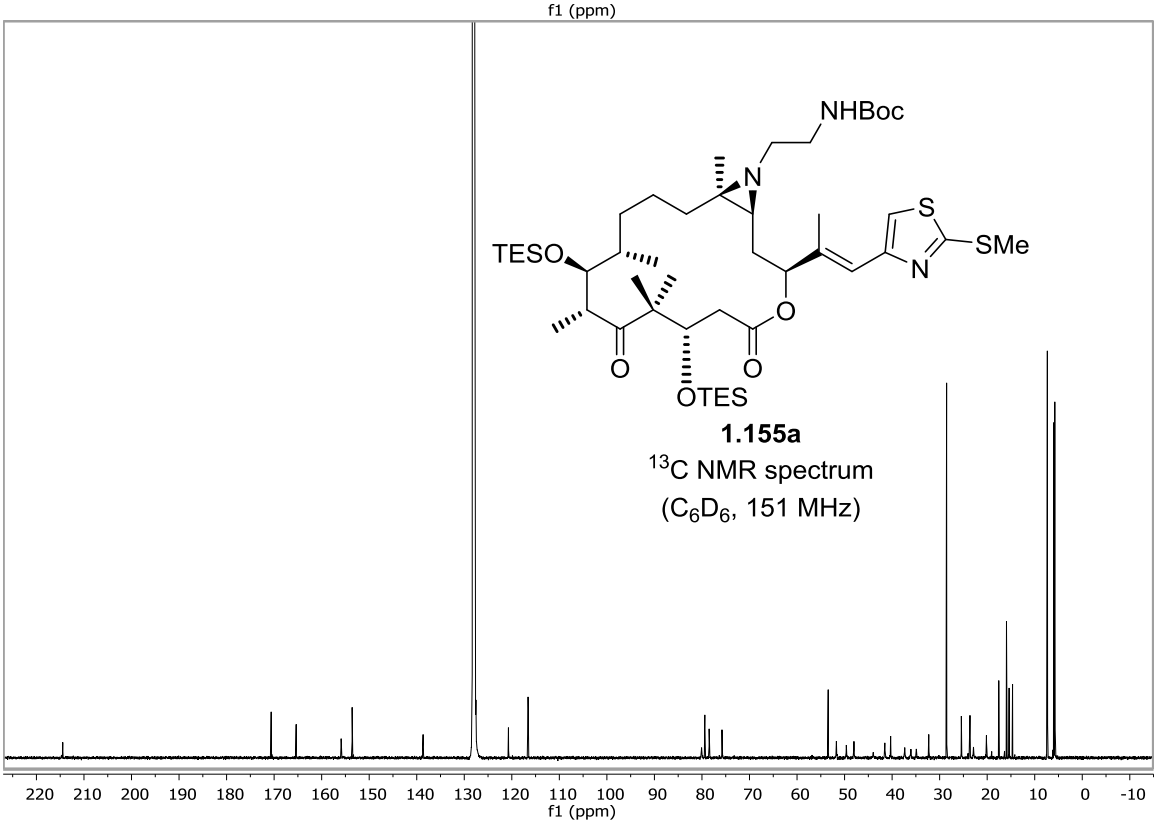
Spectra **1.105**: Compound **1.154a**: ^{1}H and ^{13}C NMR



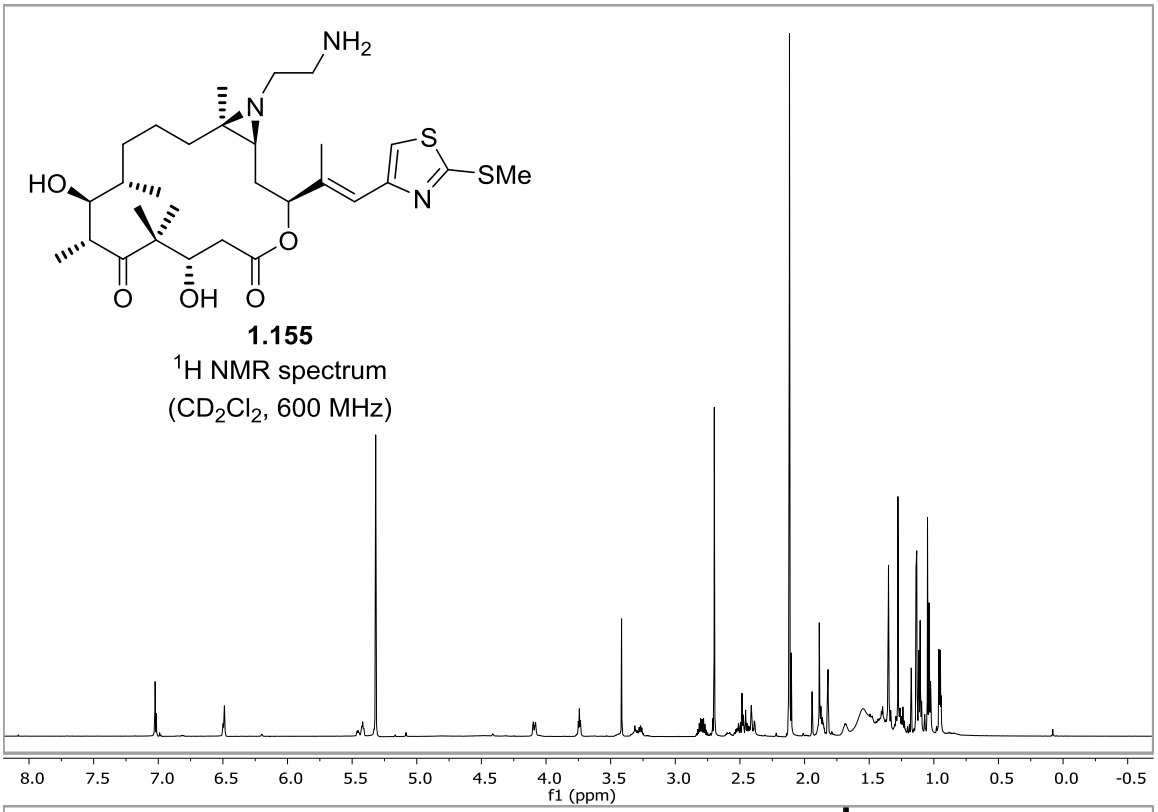


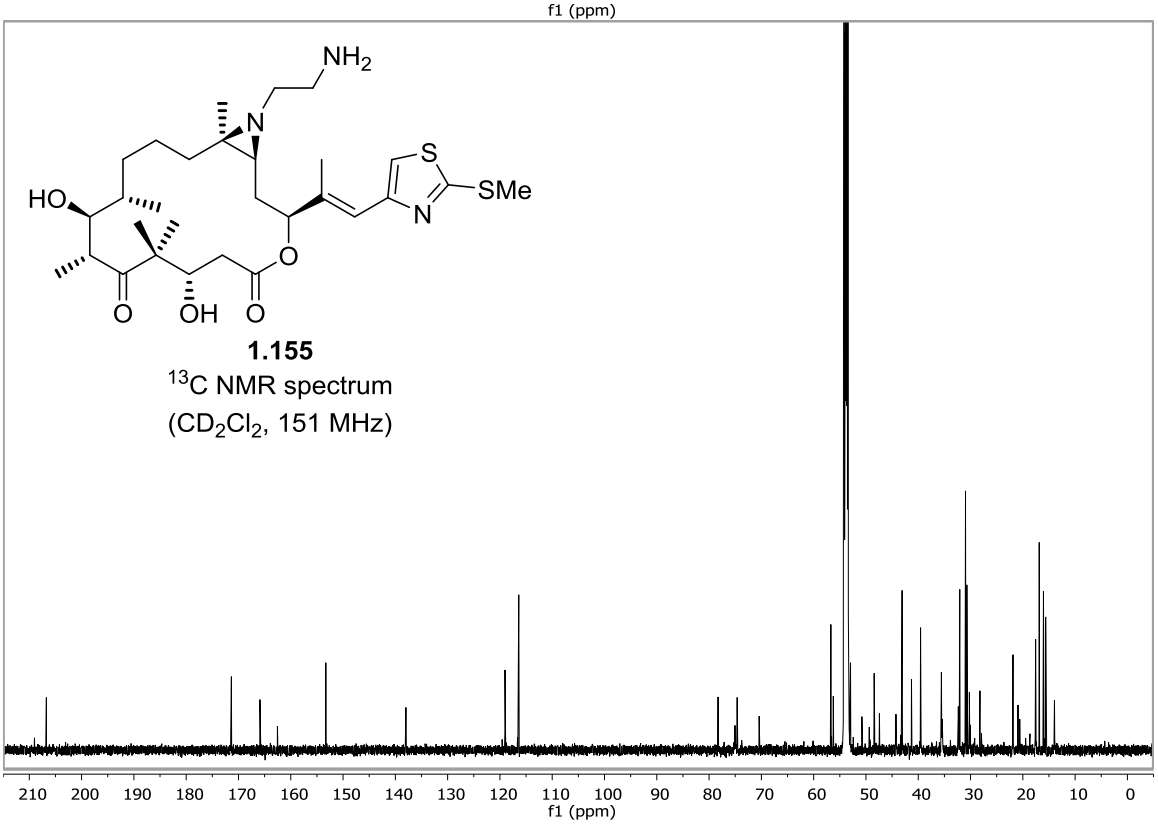
Spectra **1.106**: Compound **1.154**: ^{1}H and ^{13}C NMR



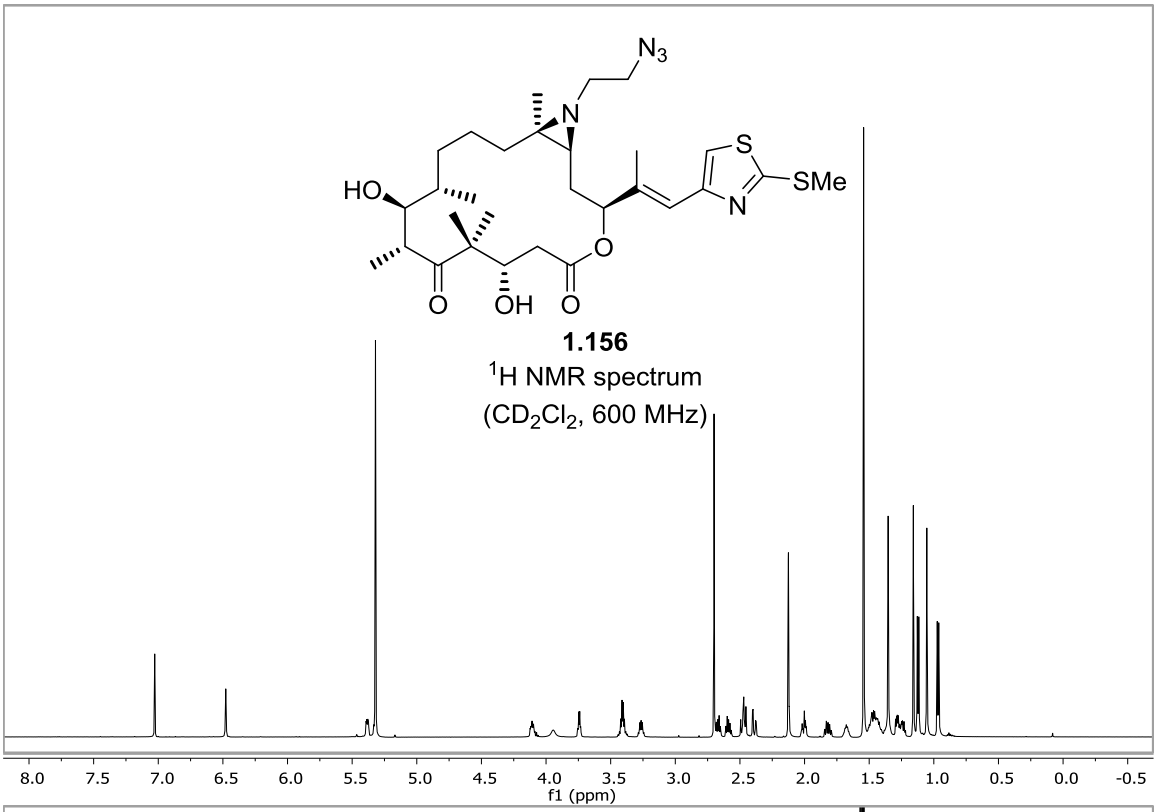


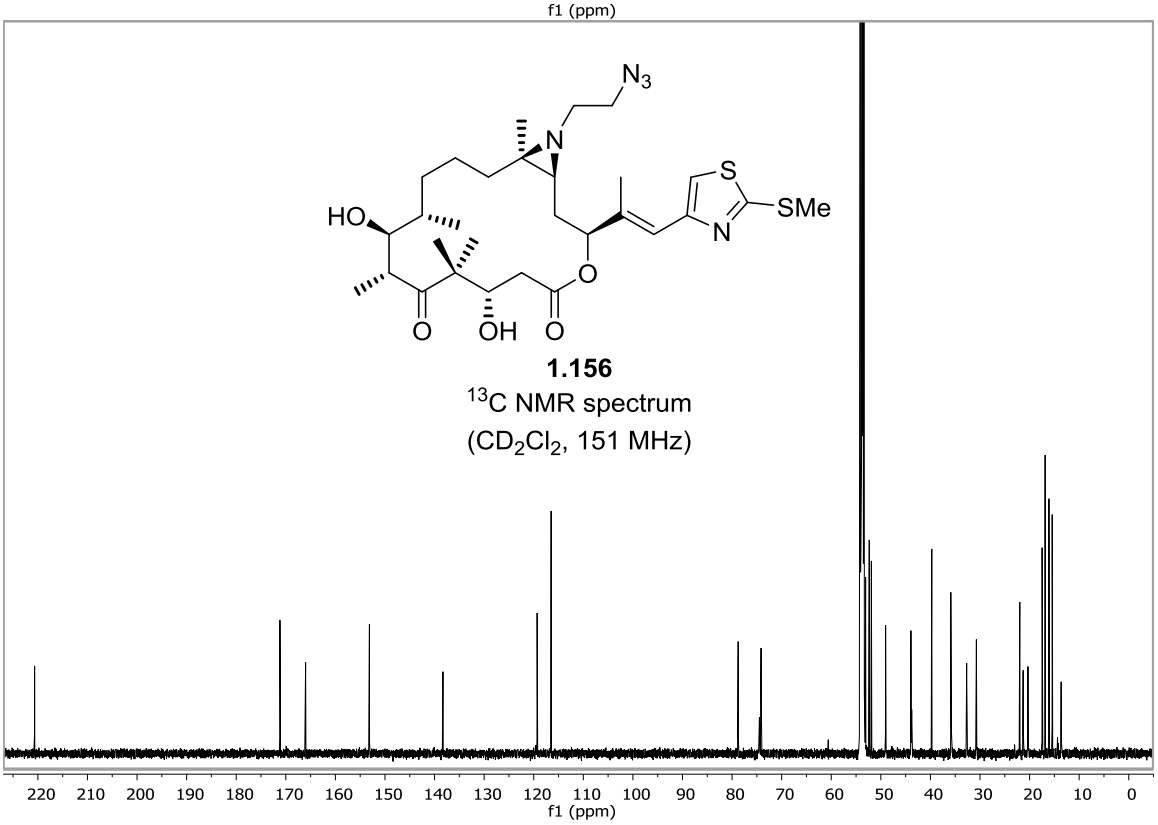
Spectra **1.107**: Compound **1.155a**: ^{1}H and ^{13}C NMR



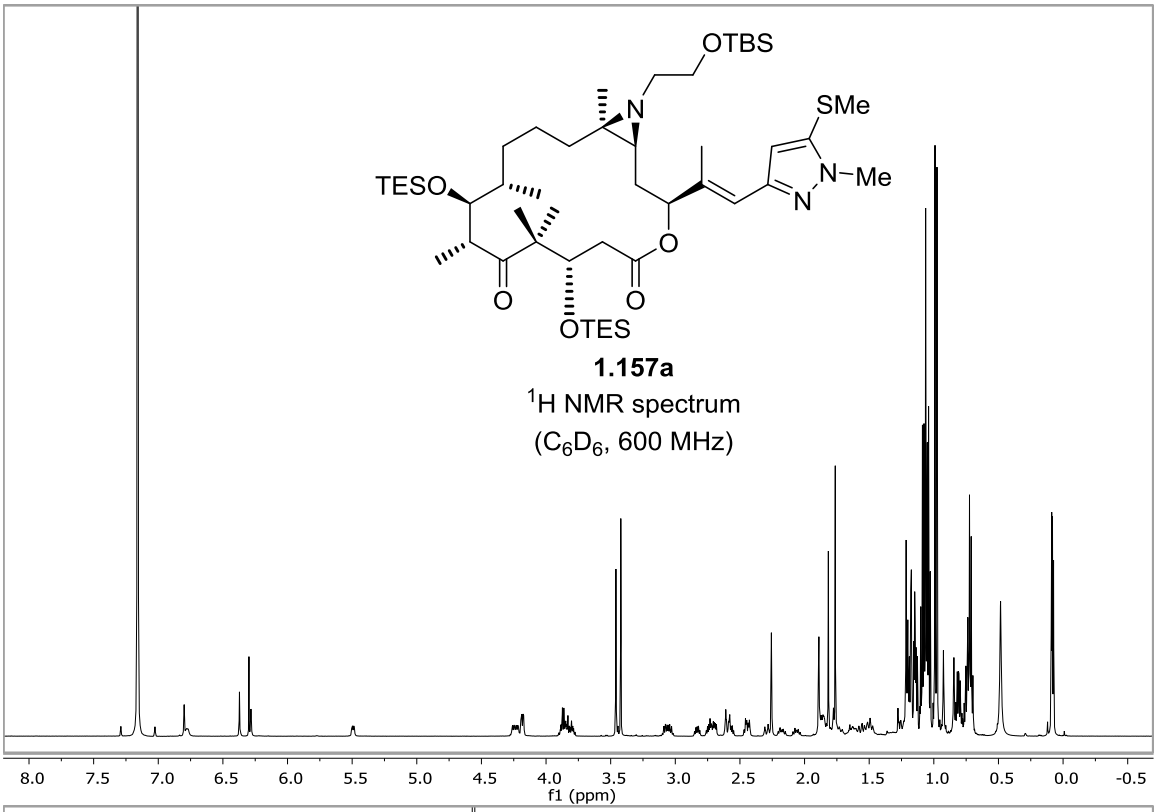


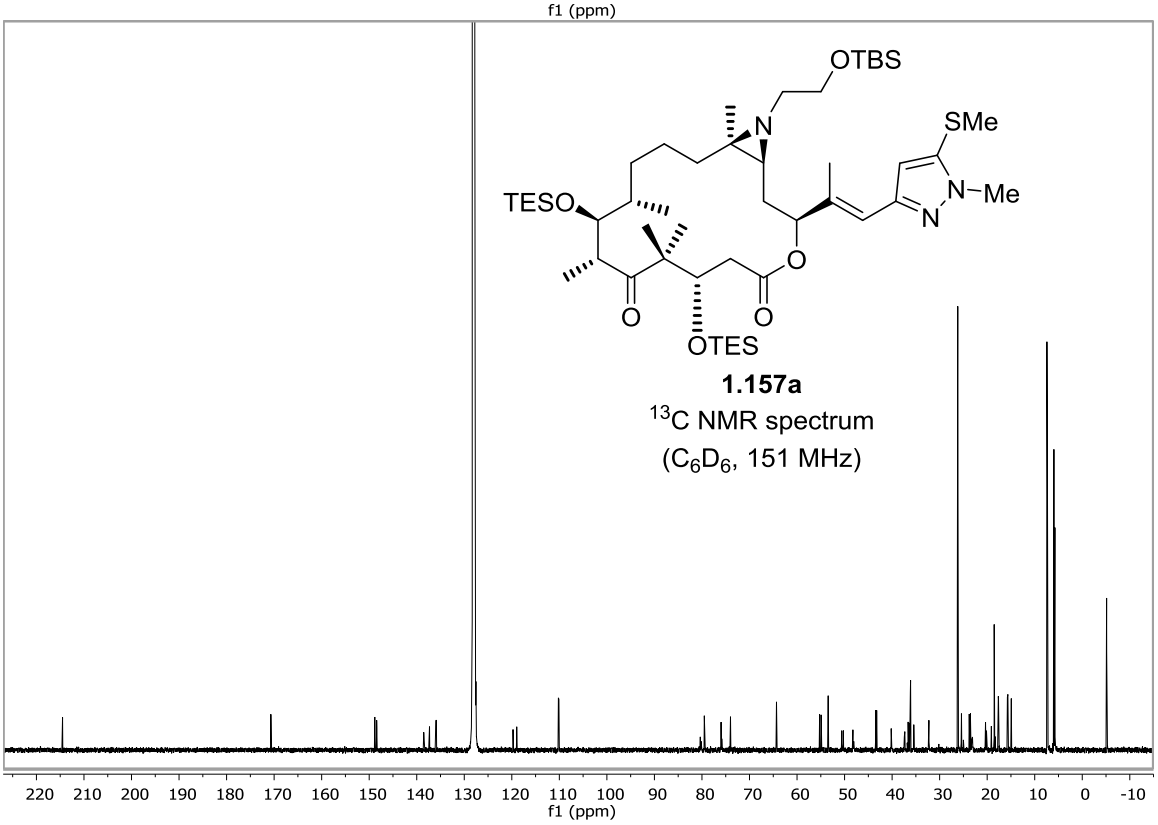
Spectra **1.108**: Compound **1.155**: ^{1}H and ^{13}C NMR



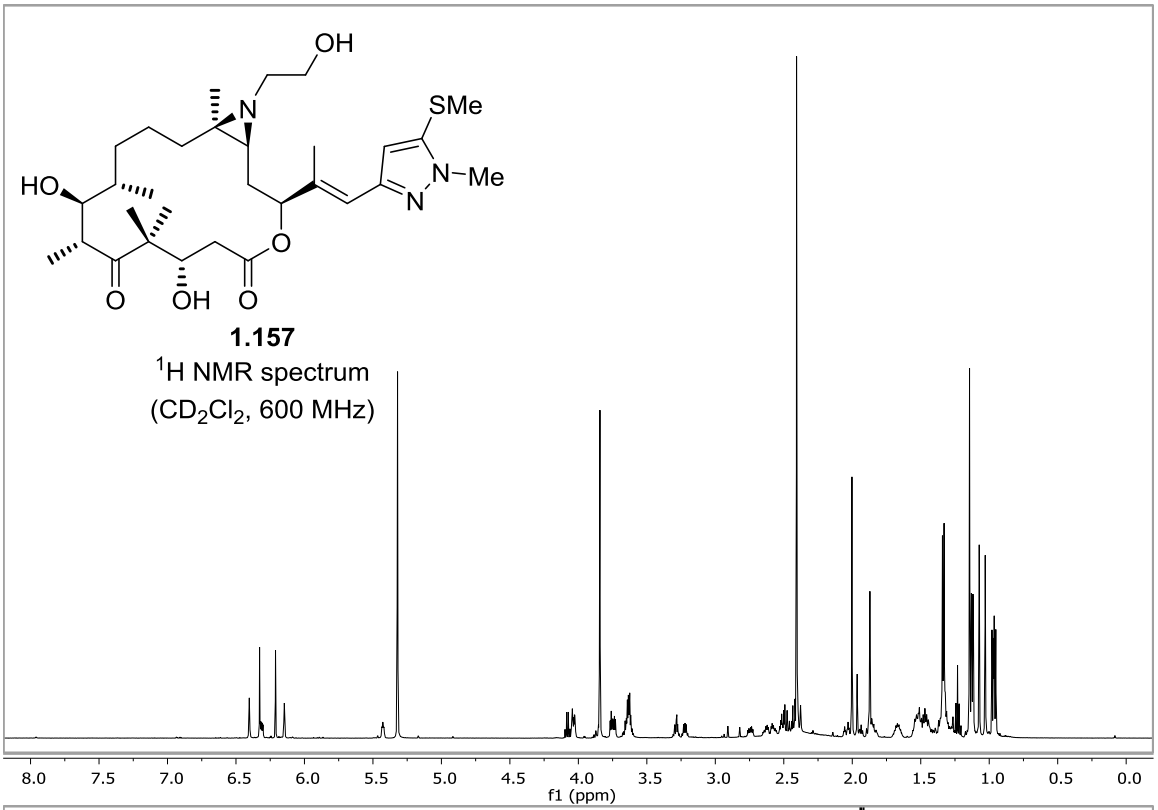


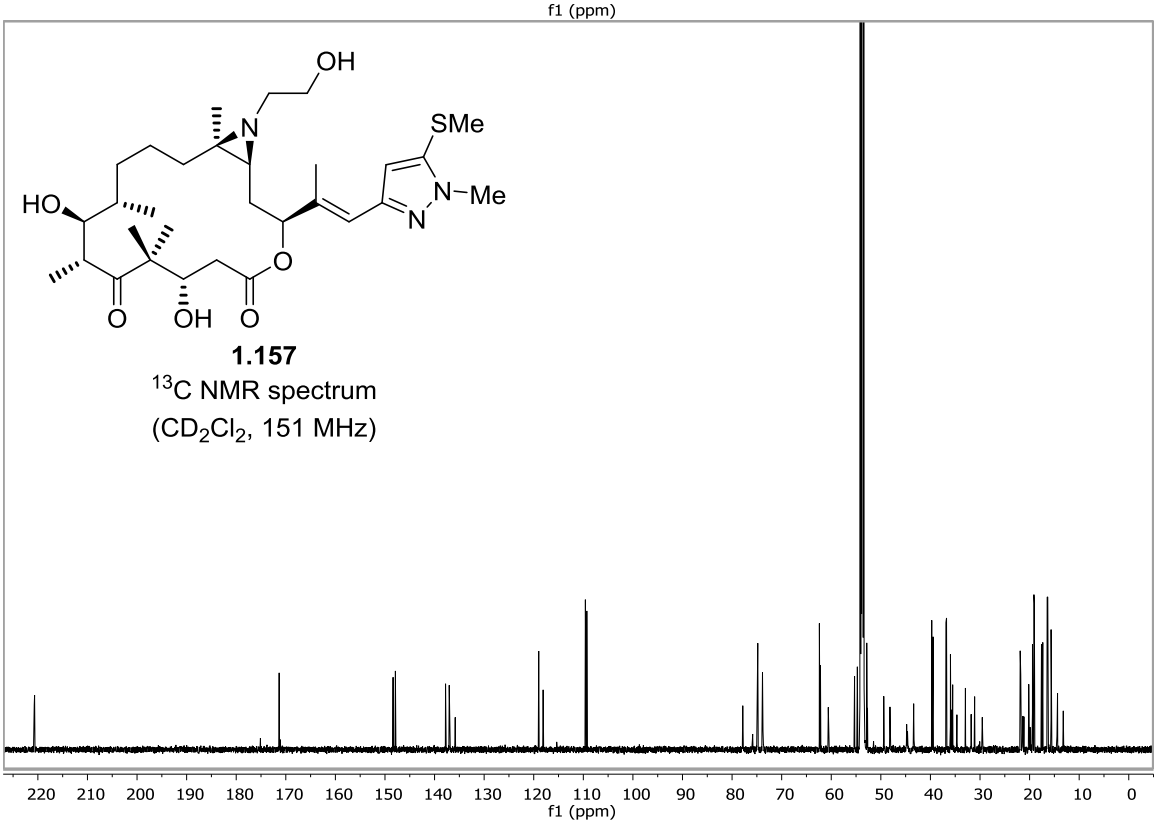
Spectra **1.109**: Compound **1.156**: ^{1}H and ^{13}C NMR





Spectra **1.110**: Compound **1.157a**: ^{1}H and ^{13}C NMR





Spectra **1.111**: Compound **1.157**: ^{1}H and ^{13}C NMR

4. NCI-60 One Dose Screening Results for Analogues **1.34** and **1.35**

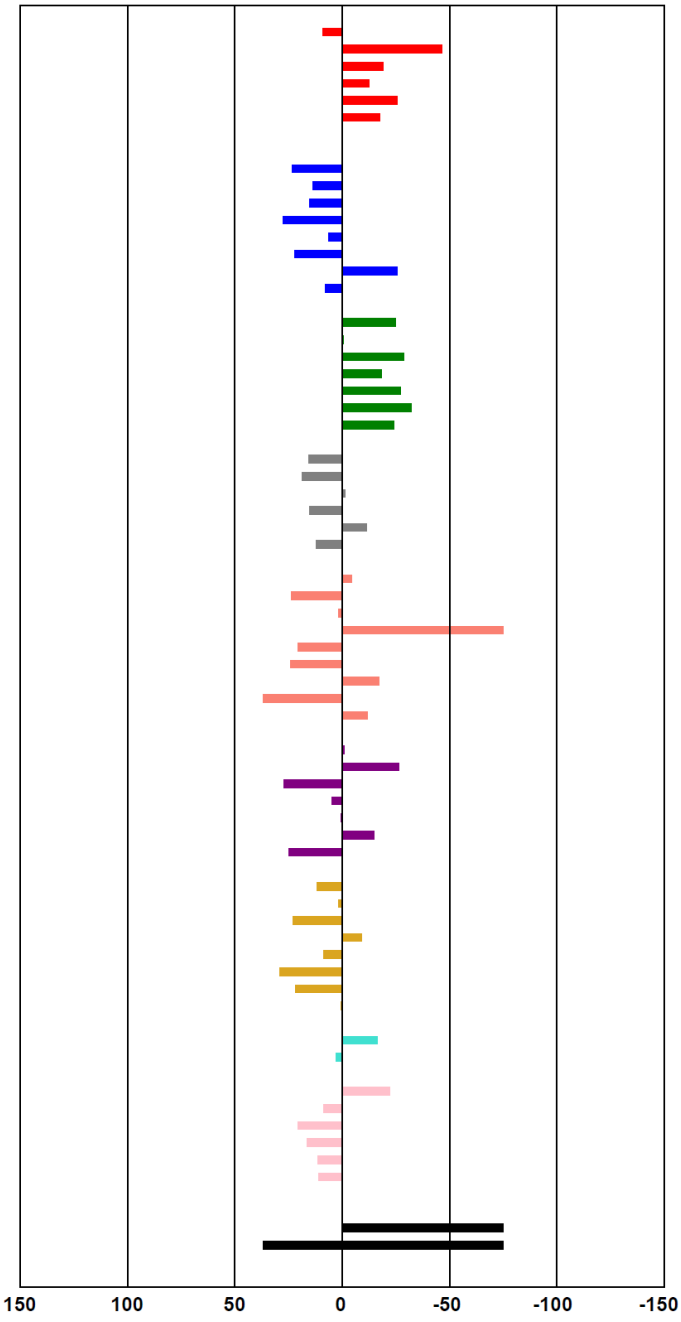
Developmental Therapeutics Program

One Dose Mean Graph

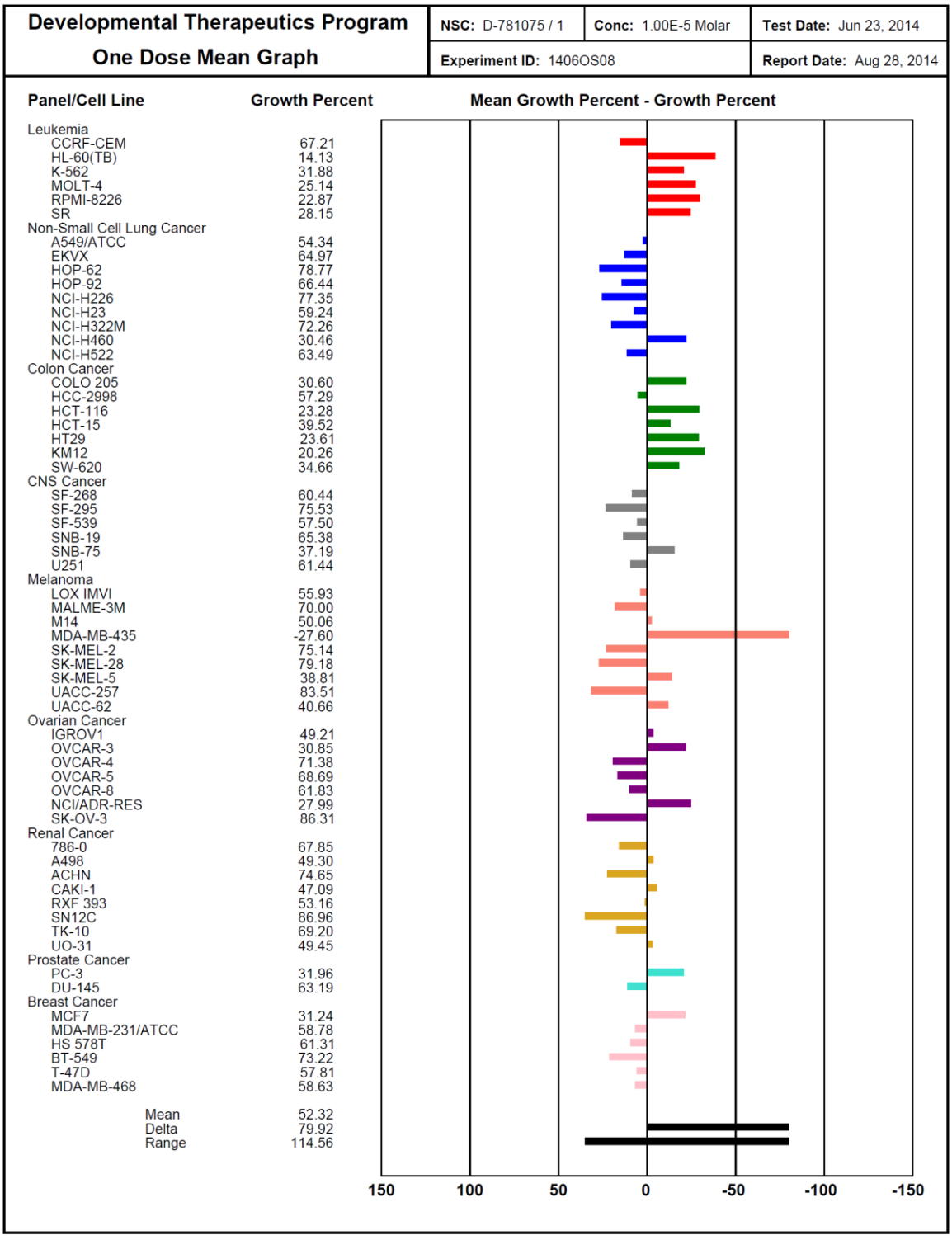
NSC: D-781081 / 1 | **Conc:** 1.00E-5 Molar | **Test Date:** Jun 23, 2014

Experiment ID: 1406OS08 | **Report Date:** Aug 28, 2014

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	63.94
HL-60(TB)	8.76
K-562	36.43
MOLT-4	42.73
RPMI-8226	29.73
SR	37.70
Non-Small Cell Lung Cancer	
A549/ATCC	55.22
EKVX	78.29
HOP-62	68.71
HOP-92	70.31
NCI-H226	82.67
NCI-H23	61.36
NCI-H322M	77.23
NCI-H460	29.59
NCI-H522	63.07
Colon Cancer	
COLO 205	30.53
HCC-2998	54.70
HCT-116	26.73
HCT-15	37.10
HT29	28.15
KM12	23.11
SW-620	31.26
CNS Cancer	
SF-268	70.58
SF-295	73.53
SF-539	54.01
SNB-19	70.36
SNB-75	43.92
U251	67.20
Melanoma	
LOX IMVI	51.08
MALME-3M	78.67
M14	56.67
MDA-MB-435	-19.77
SK-MEL-2	75.59
SK-MEL-28	79.05
SK-MEL-5	38.41
UACC-257	91.93
UACC-62	43.78
Ovarian Cancer	
IGROV1	54.42
OVCAR-3	28.84
OVCAR-4	82.37
OVCAR-5	59.81
OVCAR-8	55.49
NCI/ADR-RES	40.44
SK-OV-3	79.93
Renal Cancer	
786-0	66.59
A498	56.60
ACHN	77.85
CAKI-1	46.37
RXF 393	63.59
SN12C	83.99
TK-10	76.77
UO-31	55.50
Prostate Cancer	
PC-3	39.04
DU-145	57.97
Breast Cancer	
MCF7	33.26
MDA-MB-231/ATCC	63.80
HS 578T	75.48
BT-549	71.38
T-47D	66.19
MDA-MB-468	65.98
Mean	55.23
Delta	75.00
Range	111.70



NCI-60 One Dose Screening Results **1.01**: Compound **1.34**



NCI-60 One Dose Screening Results **1.02**: Compound **1.35**

5. NCI-60 Five Dose Screening Results for Analogues **1.37**–**1.43**

National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

NSC : D - 781077 / 1	Experiment ID : 1408NS31	Test Type : 08	Units : Molar
Report Date : August 28, 2014	Test Date : August 11, 2014	QNS :	MC :
COMI : KCDR_5A	Stain Reagent : SRB Dual-Pass Related	SSPL : 0ZAS	

			Log10 Concentration											
	Time		Mean Optical Densities					Percent Growth						
Panel/Cell Line	Zero	Ctrl	-8.3	-7.3	-6.3	-5.3	-4.3	-8.3	-7.3	-6.3	-5.3	-4.3	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.532	2.315	2.326	1.243	0.889	0.876	0.731	101	40	20	19	11	3.41E-8	> 5.00E-5	> 5.00E-5
HL-60(TB)	0.953	2.815	2.712	1.059	0.891	0.974	1.070	94	6	-7	1	6	1.58E-8	.	> 5.00E-5
K-562	0.270	1.982	1.960	0.758	0.518	0.477	0.503	99	28	14	12	14	2.47E-8	> 5.00E-5	> 5.00E-5
MOLT-4	0.789	2.789	2.761	1.671	1.360	1.354	1.392	99	44	29	28	30	3.89E-8	> 5.00E-5	> 5.00E-5
RPMI-8226	0.955	2.649	2.739	1.250	1.258	1.220	1.144	105	17	18	16	11	2.13E-8	> 5.00E-5	> 5.00E-5
SR	0.632	2.556	2.411	1.366	1.283	1.401	1.211	92	38	34	40	30	3.03E-8	> 5.00E-5	> 5.00E-5
Non-Small Cell Lung Cancer															
A549/ATCC	0.482	2.243	2.182	1.239	1.002	0.919	1.016	97	43	30	25	30	3.69E-8	> 5.00E-5	> 5.00E-5
EKVX	0.786	1.659	1.526	1.427	1.268	1.170	1.230	85	73	55	44	51	.	> 5.00E-5	> 5.00E-5
HOP-62	0.578	1.970	1.907	1.346	1.141	1.081	1.063	95	55	40	36	35	1.12E-7	> 5.00E-5	> 5.00E-5
HOP-92	1.431	1.845	1.821	1.703	1.564	1.578	1.522	94	66	32	35	22	1.46E-7	> 5.00E-5	> 5.00E-5
NCI-H226	0.545	1.731	1.775	1.504	1.285	1.206	1.149	104	81	62	56	51	> 5.00E-5	> 5.00E-5	> 5.00E-5
NCI-H23	0.675	2.424	2.332	1.219	0.995	0.884	1.009	95	31	18	12	19	2.52E-8	> 5.00E-5	> 5.00E-5
NCI-H322M	1.153	2.671	2.541	1.728	1.425	1.431	1.572	91	38	18	18	28	2.97E-8	> 5.00E-5	> 5.00E-5
NCI-H460	0.417	3.173	3.205	0.908	0.764	0.758	0.751	101	18	13	12	12	2.05E-8	> 5.00E-5	> 5.00E-5
NCI-H522	1.063	2.678	2.568	1.916	1.052	0.902	0.989	93	53	-1	-15	-7	5.64E-8	4.78E-7	> 5.00E-5
Colon Cancer															
COLO 205	0.434	1.892	1.776	0.702	0.490	0.403	0.359	92	18	4	-7	-17	1.86E-8	1.11E-6	> 5.00E-5
HCC-2998	0.694	2.079	2.015	1.282	0.902	0.750	0.847	95	42	15	4	11	3.60E-8	> 5.00E-5	> 5.00E-5
HCT-116	0.311	2.423	2.372	0.616	0.487	0.456	0.502	98	14	8	7	9	1.87E-8	> 5.00E-5	> 5.00E-5
HCT-15	0.378	2.639	2.389	1.179	0.861	0.622	0.777	89	35	21	11	18	2.67E-8	> 5.00E-5	> 5.00E-5
HT29	0.303	1.645	1.617	0.533	0.440	0.405	0.436	98	17	10	8	10	1.96E-8	> 5.00E-5	> 5.00E-5
KM12	0.609	2.902	2.787	1.025	0.857	0.904	1.001	95	18	11	13	17	1.92E-8	> 5.00E-5	> 5.00E-5
SW-620	0.358	2.278	2.215	0.931	0.891	0.992	1.092	97	30	28	33	38	2.50E-8	> 5.00E-5	> 5.00E-5
CNS Cancer															
SF-268	0.741	2.078	1.923	1.493	1.237	1.144	1.120	88	56	37	30	28	1.06E-7	> 5.00E-5	> 5.00E-5
SF-295	0.977	3.016	2.762	2.177	1.272	1.135	1.241	88	59	14	8	13	7.91E-8	> 5.00E-5	> 5.00E-5
SF-539	0.914	2.414	2.189	1.285	0.533	0.370	0.472	85	25	-42	-60	-48	1.90E-8	1.18E-7	.
SNB-19	0.847	2.415	2.349	1.897	1.556	1.448	1.495	96	67	45	38	41	3.01E-7	> 5.00E-5	> 5.00E-5
SNB-75	0.784	1.486	1.224	0.976	0.727	0.607	0.627	63	27	-7	-23	-20	1.14E-8	3.08E-7	> 5.00E-5
U251	0.492	2.402	2.358	1.289	0.810	0.753	0.813	98	42	17	14	17	3.56E-8	> 5.00E-5	> 5.00E-5
Melanoma															
LOX IMVI	0.406	2.360	2.219	0.978	0.817	0.675	0.830	93	29	21	14	22	2.36E-8	> 5.00E-5	> 5.00E-5
MALME-3M	0.674	1.174	1.114	0.985	0.832	0.834	0.919	88	62	32	32	49	1.26E-7	> 5.00E-5	> 5.00E-5
M14	0.396	1.598	1.578	0.586	0.291	0.347	0.745	98	16	-27	-12	29	1.92E-8	.	> 5.00E-5
MDA-MB-435	0.594	2.550	2.179	0.193	0.210	0.168	0.478	81	-68	-65	-72	-20	8.09E-9	1.75E-8	.
SK-MEL-2	0.944	1.859	1.861	1.469	1.091	1.074	1.144	100	57	16	14	22	7.55E-8	> 5.00E-5	> 5.00E-5
SK-MEL-28	0.736	2.192	2.066	1.631	1.455	1.407	1.635	91	61	49	46	62	.	> 5.00E-5	> 5.00E-5
SK-MEL-5	0.728	2.822	2.700	1.164	0.779	0.676	0.888	94	21	2	-7	8	2.00E-8	.	> 5.00E-5
UACC-257	1.091	2.302	2.327	1.946	1.748	1.671	1.888	102	71	54	48	66	.	> 5.00E-5	> 5.00E-5
UACC-62	1.034	2.855	2.913	2.163	1.975	1.746	1.899	103	62	52	39	48	6.76E-7	> 5.00E-5	> 5.00E-5
Ovarian Cancer															
IGROV1	0.630	2.300	2.198	1.520	1.567	1.322	1.334	94	53	56	41	42	1.30E-6	> 5.00E-5	> 5.00E-5
OVCAR-3	0.486	1.558	1.566	0.594	0.521	0.482	0.448	101	10	3	-1	-8	1.81E-8	3.01E-6	> 5.00E-5
OVCAR-4	0.688	1.433	1.352	1.176	1.048	0.969	0.969	89	65	48	38	38	3.97E-7	> 5.00E-5	> 5.00E-5
OVCAR-5	0.693	1.659	1.415	1.180	1.004	0.938	0.805	75	50	32	25	12	5.25E-8	> 5.00E-5	> 5.00E-5
OVCAR-8	0.588	2.355	2.436	1.456	1.194	1.029	1.128	105	49	34	25	31	4.82E-8	> 5.00E-5	> 5.00E-5
NCI/ADR-RES	0.663	2.285	2.249	1.593	0.632	0.463	0.503	98	57	-5	-30	-24	6.56E-8	4.19E-7	> 5.00E-5
SK-OV-3	0.635	1.617	1.605	1.387	1.053	0.962	1.007	99	77	43	33	38	3.01E-7	> 5.00E-5	> 5.00E-5
Renal Cancer															
786-0	0.700	2.326	2.208	1.878	1.234	0.991	0.973	93	72	33	18	17	1.84E-7	> 5.00E-5	> 5.00E-5
A498	1.366	1.982	1.897	1.743	1.521	1.312	1.347	86	61	25	-4	-1	1.02E-7	3.66E-6	> 5.00E-5
ACHN	0.508	2.220	2.005	1.455	1.239	1.084	1.281	87	55	43	34	45	1.32E-7	> 5.00E-5	> 5.00E-5
CAKI-1	1.025	3.146	2.854	2.414	1.947	1.706	1.817	86	65	43	32	37	2.52E-7	> 5.00E-5	> 5.00E-5
RXF 393	0.755	1.409	1.395	1.042	0.847	0.720	0.792	98	44	14	-5	6	3.84E-8	.	> 5.00E-5
SN12C	0.743	2.790	2.780	1.869	1.640	1.499	1.491	100	55	44	37	37	1.40E-7	> 5.00E-5	> 5.00E-5
TK-10	1.103	1.909	1.859	1.652	1.431	1.415	1.490	94	68	41	39	48	2.28E-7	> 5.00E-5	> 5.00E-5
UO-31	0.963	2.517	2.282	1.998	1.627	1.651	1.596	85	67	43	44	41	2.48E-7	> 5.00E-5	> 5.00E-5
Prostate Cancer															
PC-3	0.765	2.474	2.327	1.425	1.175	1.207	1.259	91	39	24	26	29	3.04E-8	> 5.00E-5	> 5.00E-5
DU-145	0.398	1.571	1.550	0.833	0.426	0.350	0.335	98	37	2	-12	-16	3.07E-8	7.32E-7	> 5.00E-5
Breast Cancer															
MCF7	0.371	2.071	1.751	0.652	0.588	0.528	0.596	81	17	13	9	13	1.52E-8	> 5.00E-5	> 5.00E-5
MDA-MB-231/ATCC	0.689	1.622	1.643	1.306	1.117	1.062	0.883	102	66	46	40	21	3.12E-7	> 5.00E-5	> 5.00E-5
HS 578T	1.018	2.004	1.833	1.492	1.140	1.045	0.945	83	48	12	3	-7	4.40E-8	9.37E-6	> 5.00E-5
BT-549	1.310	2.572	2.477	2.135	1.750	1.759	1.682	92	65	35	36	29	1.60E-7	> 5.00E-5	> 5.00E-5
T-47D	0.669	1.421	1.367	1.081	1.002	1.054	1.086	93	55	44	51	55	.	> 5.00E-5	> 5.00E-5
MDA-MB-468	0.923	2.040	1.977	1.423	0.998	0.908	0.891	94	45	7	-2	-3	3.92E-8	3.15E-6	> 5.00E-5

NCI-60 Five Dose Results **1.01**: Compound **1.37**

National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

NSC : D - 781076 / 1	Experiment ID : 1408NS31	Test Type : 08	Units : Molar
Report Date : September 22, 2014	Test Date : August 11, 2014	QNS :	MC :
COMI : KCDR_4A	Stain Reagent : SRB Dual-Pass Related	SSPL : 0ZAS	

Log10 Concentration

	Time	Mean Optical Densities						Percent Growth							
Panel/Cell Line	Zero	Ctrl	-8.3	-7.3	-6.3	-5.3	-4.3	-8.3	-7.3	-6.3	-5.3	-4.3	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.532	2.409	2.325	1.020	0.805	0.762	0.704	96	26	15	12	9	2.26E-8	> 5.00E-5	> 5.00E-5
HL-60(TB)	0.953	2.812	2.839	1.059	0.873	0.834	0.807	101	6	-8	-12	-15	1.72E-8	1.27E-7	> 5.00E-5
K-562	0.270	2.092	1.987	0.817	0.486	0.425	0.394	94	30	12	8	7	2.44E-8	> 5.00E-5	> 5.00E-5
MOLT-4	0.789	2.754	2.705	1.447	1.248	0.927	0.846	97	33	23	7	3	2.76E-8	> 5.00E-5	> 5.00E-5
RPMI-8226	0.955	2.691	2.578	1.212	1.291	1.170	0.962	93	15	19	12	.	1.78E-8	> 5.00E-5	> 5.00E-5
SR	0.632	2.651	2.421	1.367	1.178	1.044	0.783	89	36	27	20	7	2.74E-8	> 5.00E-5	> 5.00E-5
Non-Small Cell Lung Cancer															
A549/ATCC	0.482	2.215	2.168	1.191	0.876	0.843	0.795	97	41	23	21	18	3.45E-8	> 5.00E-5	> 5.00E-5
EKVX	0.786	1.623	1.567	1.397	1.280	1.129	1.072	93	73	59	41	34	1.57E-6	> 5.00E-5	> 5.00E-5
HOP-62	0.578	1.912	1.905	1.348	1.116	0.944	0.929	99	58	40	27	26	1.38E-7	> 5.00E-5	> 5.00E-5
HOP-92	1.431	1.934	1.816	1.699	1.622	1.522	1.436	76	53	38	18	1	8.07E-8	> 5.00E-5	> 5.00E-5
NCI-H226	0.545	1.787	1.735	1.485	1.319	1.206	0.948	96	76	62	53	32	7.14E-6	> 5.00E-5	> 5.00E-5
NCI-H23	0.675	2.510	2.465	1.444	1.117	0.994	0.963	98	42	24	17	16	3.58E-8	> 5.00E-5	> 5.00E-5
NCI-H322M	1.153	2.661	2.600	1.820	1.540	1.393	1.508	96	44	26	16	24	3.86E-8	> 5.00E-5	> 5.00E-5
NCI-H460	0.417	3.141	3.164	0.885	0.711	0.674	0.576	101	17	11	9	6	2.03E-8	> 5.00E-5	> 5.00E-5
NCI-H522	1.063	2.615	2.523	1.838	0.985	0.932	0.790	94	50	-7	-12	-26	4.98E-8	3.72E-7	> 5.00E-5
Colon Cancer															
COLO 205	0.434	1.798	1.758	0.708	0.458	0.334	0.229	97	20	2	-23	-47	2.04E-8	5.86E-7	> 5.00E-5
HCC-2998	0.694	2.121	2.033	1.416	0.881	0.792	0.846	94	51	13	7	11	5.18E-8	> 5.00E-5	> 5.00E-5
HCT-116	0.311	2.264	2.247	0.547	0.502	0.449	0.415	99	12	10	7	5	1.83E-8	> 5.00E-5	> 5.00E-5
HCT-15	0.378	2.609	2.647	1.229	0.756	0.636	0.623	102	38	17	12	11	3.25E-8	> 5.00E-5	> 5.00E-5
HT29	0.303	1.713	1.637	0.545	0.408	0.411	0.355	95	17	7	8	4	1.88E-8	> 5.00E-5	> 5.00E-5
KM12	0.609	2.905	2.889	1.046	0.856	0.871	0.974	99	19	11	11	16	2.06E-8	> 5.00E-5	> 5.00E-5
SW-620	0.358	2.283	2.238	0.909	0.884	0.932	1.042	98	29	27	30	36	2.45E-8	> 5.00E-5	> 5.00E-5
CNS Cancer															
SF-268	0.741	2.185	2.077	1.629	1.176	1.086	0.979	93	61	30	24	16	1.16E-7	> 5.00E-5	> 5.00E-5
SF-295	0.977	3.058	3.021	2.166	1.285	1.012	1.098	98	57	15	2	6	7.37E-8	> 5.00E-5	> 5.00E-5
SF-539	0.914	2.509	2.332	1.091	0.822	0.698	0.626	89	11	-10	-24	-32	1.58E-8	1.67E-7	> 5.00E-5
SNB-19	0.847	2.369	2.286	1.744	1.432	1.348	1.299	95	59	38	33	30	1.37E-7	> 5.00E-5	> 5.00E-5
SNB-75	0.784	1.503	1.313	0.985	0.700	0.563	0.517	74	28	-11	-28	-34	1.64E-8	2.63E-7	> 5.00E-5
U251	0.492	2.333	2.260	1.187	0.736	0.686	0.628	96	38	13	11	7	3.08E-8	> 5.00E-5	> 5.00E-5
Melanoma															
LOX IMVI	0.406	2.345	2.303	1.140	0.957	0.783	0.618	98	38	28	19	11	3.13E-8	> 5.00E-5	> 5.00E-5
MALME-3M	0.674	1.168	1.166	0.989	0.877	0.855	0.919	100	64	41	37	50	2.01E-7	> 5.00E-5	> 5.00E-5
M14	0.396	1.530	1.531	0.509	0.278	0.410	0.645	100	10	-30	1	22	1.80E-8	.	> 5.00E-5
MDA-MB-435	0.594	2.587	2.518	0.186	0.153	0.166	0.383	97	-69	-74	-72	-36	9.56E-9	1.92E-8	.
SK-MEL-2	0.944	1.807	1.845	1.394	1.072	1.016	1.086	104	52	15	8	16	5.69E-8	> 5.00E-5	> 5.00E-5
SK-MEL-28	0.736	2.244	2.139	1.595	1.518	1.487	1.321	93	57	52	50	39	3.86E-6	> 5.00E-5	> 5.00E-5
SK-MEL-5	0.728	2.857	2.771	1.246	0.858	0.795	0.827	96	24	6	3	5	2.19E-8	> 5.00E-5	> 5.00E-5
UACC-257	1.091	2.300	2.206	1.749	1.644	1.625	1.603	92	54	46	44	42	1.61E-7	> 5.00E-5	> 5.00E-5
UACC-62	1.034	2.866	2.815	2.102	1.921	1.790	1.570	97	58	48	41	29	3.45E-7	> 5.00E-5	> 5.00E-5
Ovarian Cancer															
IGROV1	0.630	2.241	2.223	1.531	1.449	1.199	1.216	99	56	51	35	36	5.65E-7	> 5.00E-5	> 5.00E-5
OVCAR-3	0.486	1.642	1.657	0.628	0.509	0.482	0.450	101	12	2	-1	-8	1.88E-8	2.55E-6	> 5.00E-5
OVCAR-4	0.688	1.444	1.440	1.145	1.074	0.906	0.818	100	60	51	29	17	5.59E-7	> 5.00E-5	> 5.00E-5
OVCAR-5	0.693	1.651	1.502	1.211	1.029	0.898	0.662	84	54	35	21	-5	8.19E-8	3.34E-5	> 5.00E-5
OVCAR-8	0.588	2.280	2.221	1.333	1.114	0.908	0.891	96	44	31	19	18	3.85E-8	> 5.00E-5	> 5.00E-5
NCI/ADR-RES	0.663	2.442	2.429	2.016	0.935	0.671	0.630	99	76	15	.	-5	1.34E-7	6.04E-6	> 5.00E-5
SK-OV-3	0.635	1.660	1.655	1.149	0.955	0.879	0.893	99	50	31	24	25	5.08E-8	> 5.00E-5	> 5.00E-5
Renal Cancer															
786-0	0.700	2.340	2.121	1.656	0.849	0.824	0.692	87	58	9	8	-1	7.36E-8	3.63E-5	> 5.00E-5
A498	1.366	1.960	1.800	1.562	1.342	1.254	1.290	73	33	-2	-8	-6	1.88E-8	4.45E-7	> 5.00E-5
ACHN	0.508	2.281	2.312	1.513	1.332	1.202	1.125	102	57	46	39	35	2.26E-7	> 5.00E-5	> 5.00E-5
CAKI-1	1.025	3.134	3.013	2.352	2.020	1.536	1.558	94	63	47	24	25	3.30E-7	> 5.00E-5	> 5.00E-5
RXF 393	0.755	1.438	1.367	1.066	0.788	0.670	0.608	90	46	5	-11	-19	3.96E-8	9.88E-7	> 5.00E-5
SN12C	0.743	2.789	2.622	1.824	1.504	1.315	1.212	92	53	37	28	23	7.56E-8	> 5.00E-5	> 5.00E-5
TK-10	1.103	1.898	1.829	1.623	1.425	1.356	1.319	91	65	40	32	27	2.07E-7	> 5.00E-5	> 5.00E-5
UO-31	0.963	2.488	2.406	2.018	1.648	1.543	1.441	95	69	45	38	31	3.09E-7	> 5.00E-5	> 5.00E-5
Prostate Cancer															
PC-3	0.765	2.441	2.370	1.453	1.089	1.143	1.088	96	41	19	23	19	3.43E-8	> 5.00E-5	> 5.00E-5
DU-145	0.398	1.604	1.664	0.947	0.385	0.337	0.329	105	46	-3	-15	-17	4.20E-8	4.29E-7	> 5.00E-5
Breast Cancer															
MCF7	0.371	2.116	1.969	0.649	0.659	0.573	0.463	92	16	17	12	5	1.77E-8	> 5.00E-5	> 5.00E-5
MDA-MB-231/ATCC	0.689	1.553	1.595	1.286	1.079	0.848	0.746	105	69	45	18	7	3.12E-7	> 5.00E-5	> 5.00E-5
HS 578T	1.018	2.019	1.853	1.435	1.121	0.976	0.887	83	42	10	-4	-13	3.16E-8	2.57E-6	> 5.00E-5
BT-549	1.310	2.492	2.352	2.023	1.751	1.604	1.445	88	60	37	25	11	1.40E-7	> 5.00E-5	> 5.00E-5
T-47D	0.669	1.396	1.366	1.068	0.960	0.949	0.842	96	55	40	39	24	1.06E-7	> 5.00E-5	> 5.00E-5
MDA-MB-468	0.923	2.021	1.908	1.258	0.965	0.858	0.778	90	30	4	-7	-16	2.34E-8	1.12E-6	> 5.00E-5

NCI-60 Five Dose Results **1.02**: Compound **1.38**

National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

NSC : D - 781491 / 1	Experiment ID : 1409NS43	Test Type : 08	Units : Molar
Report Date : September 17, 2014	Test Date : September 02, 2014	QNS :	MC :
COMI : KCDR_2A	Stain Reagent : SRB Dual-Pass Related	SSPL : 0ZAS	

Log10 Concentration

	Time	Mean Optical Densities						Percent Growth						
Panel/Cell Line	Zero	Ctrl	-9.0	-8.0	-7.0	-6.0	-5.0	-9.0	-8.0	-7.0	-6.0	-5.0	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.640	2.965	3.040	2.683	1.291	1.065	0.856	103	88	28	18	9	4.76E-8	> 1.11E-5	> 1.11E-5
HL-60(TB)	0.615	2.785	2.639	1.536	0.702	0.674	0.605	93	42	4	3	-2	7.88E-9	4.55E-6	> 1.11E-5
K-562	0.230	2.136	2.177	1.288	0.585	0.467	0.405	102	56	19	12	9	1.57E-8	> 1.11E-5	> 1.11E-5
MOLT-4	0.782	3.174	3.195	2.690	1.572	1.323	1.030	101	80	33	23	10	4.81E-8	> 1.11E-5	> 1.11E-5
RPMI-8226	0.766	2.393	2.457	1.580	1.043	1.000	0.831	104	50	17	14	4	1.11E-8	> 1.11E-5	> 1.11E-5
Non-Small Cell Lung Cancer															
A549/ATCC	0.502	2.169	2.211	1.650	1.161	0.907	0.681	103	69	40	24	11	4.88E-8	> 1.11E-5	> 1.11E-5
EKVX	0.676	1.960	1.757	1.823	1.327	1.140	0.956	84	89	51	36	22	1.23E-7	> 1.11E-5	> 1.11E-5
HOP-62	0.715	1.482	1.292	1.259	1.084	0.937	0.871	75	71	48	29	20	9.15E-8	> 1.11E-5	> 1.11E-5
HOP-92	1.280	1.615	1.604	1.594	1.459	1.408	1.308	97	94	53	38	8	1.83E-7	> 1.11E-5	> 1.11E-5
NCI-H226	0.773	2.093	2.131	2.065	1.892	1.661	1.295	103	98	85	67	40	4.64E-6	> 1.11E-5	> 1.11E-5
NCI-H23	0.450	1.445	1.434	1.254	0.914	0.805	0.711	99	81	47	36	26	8.85E-8	> 1.11E-5	> 1.11E-5
NCI-H322M	0.752	1.781	1.760	1.499	1.126	1.025	1.017	98	73	36	27	26	4.65E-8	> 1.11E-5	> 1.11E-5
NCI-H460	0.308	2.884	2.975	1.170	0.605	0.580	0.357	104	33	12	11	2	6.45E-9	> 1.11E-5	> 1.11E-5
NCI-H522	0.828	2.206	2.136	1.829	0.496	0.341	0.282	95	73	-40	-59	-66	1.76E-8	4.89E-8	3.74E-7
Colon Cancer															
COLO 205	0.454	1.910	1.780	1.265	0.584	0.466	0.282	91	56	9	1	-38	1.47E-8	1.17E-6	> 1.11E-5
HCC-2998	0.488	1.608	1.605	1.142	0.660	0.527	0.367	100	58	15	3	-25	1.74E-8	1.47E-6	> 1.11E-5
HCT-116	0.271	2.206	2.101	0.833	0.510	0.395	0.327	95	29	12	6	3	5.31E-9	> 1.11E-5	> 1.11E-5
HCT-15	0.236	1.609	1.450	1.136	0.418	0.295	0.259	88	66	13	4	2	2.20E-8	> 1.11E-5	> 1.11E-5
HT29	0.256	1.442	1.378	0.598	0.235	0.199	0.100	95	29	-8	-22	-61	5.29E-9	6.60E-8	5.72E-6
KM12	0.400	2.316	2.221	0.942	0.655	0.605	0.448	95	28	13	11	3	5.25E-9	> 1.11E-5	> 1.11E-5
SW-620	0.273	2.028	2.017	0.756	0.772	0.780	0.671	99	28	28	29	23	5.40E-9	> 1.11E-5	> 1.11E-5
CNS Cancer															
SF-268	0.614	2.056	1.963	1.671	1.147	0.902	0.691	94	73	37	20	5	4.85E-8	> 1.11E-5	> 1.11E-5
SF-295	0.541	2.447	2.202	1.961	0.785	0.546	0.528	87	74	13	.	-2	2.77E-8	1.39E-6	> 1.11E-5
SF-539	0.972	2.706	2.462	2.139	1.281	0.796	0.645	86	67	18	-18	-34	2.48E-8	3.47E-7	> 1.11E-5
SNB-19	0.559	1.879	1.909	1.761	1.117	0.976	0.817	102	91	42	32	20	7.71E-8	> 1.11E-5	> 1.11E-5
U251	0.518	2.416	2.472	1.902	1.089	0.780	0.669	103	73	30	14	8	3.81E-8	> 1.11E-5	> 1.11E-5
Melanoma															
LOX IMVI	0.333	2.199	2.165	1.498	0.840	0.780	0.507	98	62	27	24	9	2.50E-8	> 1.11E-5	> 1.11E-5
MALME-3M	0.795	1.355	1.299	1.177	1.061	1.058	1.031	90	68	47	47	42	8.34E-8	> 1.11E-5	> 1.11E-5
M14	0.356	1.569	1.469	1.023	0.367	0.276	0.331	92	55	1	-22	-7	1.37E-8	1.21E-7	> 1.11E-5
MDA-MB-435	0.293	1.616	1.438	0.154	0.123	0.075	0.129	87	-48	-58	-74	-56	2.08E-9	4.90E-9	1.87E-8
SK-MEL-2	1.169	2.243	2.285	1.958	1.063	1.004	0.777	104	73	-9	-14	-34	2.13E-8	8.61E-8	> 1.11E-5
SK-MEL-28	0.607	2.024	1.914	1.734	1.342	1.260	1.043	92	80	52	46	31	2.35E-7	> 1.11E-5	> 1.11E-5
SK-MEL-5	0.788	3.186	3.179	2.378	1.069	0.909	0.832	100	66	12	5	2	2.21E-8	> 1.11E-5	> 1.11E-5
UACC-257	0.952	2.062	2.020	1.909	1.552	1.456	1.388	96	86	54	45	39	3.22E-7	> 1.11E-5	> 1.11E-5
UACC-62	0.890	2.804	2.795	2.157	1.484	1.309	1.124	100	66	31	22	12	3.20E-8	> 1.11E-5	> 1.11E-5
Ovarian Cancer															
IGROV1	0.594	2.312	2.363	1.654	1.348	1.266	1.052	103	62	44	39	27	5.01E-8	> 1.11E-5	> 1.11E-5
OVCAR-3	0.470	1.634	1.666	1.151	0.509	0.532	0.431	103	58	3	5	-8	1.58E-8	2.73E-6	> 1.11E-5
OVCAR-4	1.146	2.180	2.039	2.016	1.849	1.843	1.632	86	84	68	67	47	7.89E-6	> 1.11E-5	> 1.11E-5
OVCAR-5	0.709	1.835	1.827	1.470	1.138	0.903	0.767	99	68	38	17	5	4.36E-8	> 1.11E-5	> 1.11E-5
OVCAR-8	0.480	1.998	2.109	1.847	0.951	0.718	0.613	107	90	31	16	9	5.29E-8	> 1.11E-5	> 1.11E-5
NCI/ADR-RES	0.474	1.574	1.597	1.498	1.185	0.720	0.612	102	93	65	22	13	2.46E-7	> 1.11E-5	> 1.11E-5
SK-OV-3	0.782	1.996	1.900	1.744	1.193	1.130	1.067	92	79	34	29	23	4.90E-8	> 1.11E-5	> 1.11E-5
Renal Cancer															
786-0	0.577	2.088	1.876	1.826	1.221	0.824	0.672	86	83	43	16	6	7.25E-8	> 1.11E-5	> 1.11E-5
A498	1.270	2.132	2.086	2.035	1.604	1.288	1.362	95	89	39	2	11	6.60E-8	> 1.11E-5	> 1.11E-5
ACHN	0.440	1.819	1.701	1.535	1.000	0.864	0.750	91	79	41	31	22	6.35E-8	> 1.11E-5	> 1.11E-5
CAKI-1	1.251	3.349	3.182	3.025	2.442	2.280	1.929	92	85	57	49	32	8.38E-7	> 1.11E-5	> 1.11E-5
RXF 393	0.622	1.263	1.280	1.181	0.759	0.620	0.476	103	87	21	.	-23	4.07E-8	1.06E-6	> 1.11E-5
SN12C	1.165	3.295	3.288	3.260	2.482	2.414	1.908	100	98	62	59	35	2.56E-6	> 1.11E-5	> 1.11E-5
TK-10	0.796	1.743	1.701	1.558	1.148	0.966	0.778	96	80	37	18	-2	5.59E-8	8.53E-6	> 1.11E-5
UO-31	0.709	2.405	2.210	2.049	1.468	1.371	1.148	88	79	45	39	26	7.81E-8	> 1.11E-5	> 1.11E-5
Prostate Cancer															
PC-3	0.611	2.401	2.389	1.931	1.012	1.004	0.808	99	74	22	22	11	3.22E-8	> 1.11E-5	> 1.11E-5
DU-145	0.339	1.559	1.550	1.416	0.540	0.307	0.193	99	88	16	-10	-43	3.79E-8	4.76E-7	> 1.11E-5
Breast Cancer															
MCF7	0.232	1.400	1.168	0.487	0.386	0.330	0.259	80	22	13	8	2	3.65E-9	> 1.11E-5	> 1.11E-5
MDA-MB-231/ATCC	0.732	1.750	1.795	1.564	1.276	1.118	0.743	104	82	53	38	1	1.84E-7	> 1.11E-5	> 1.11E-5
HS 578T	1.208	2.375	2.317	2.048	1.550	1.229	0.980	95	72	29	2	-19	3.64E-8	1.35E-6	> 1.11E-5
BT-549	0.991	2.218	2.015	1.930	1.474	1.151	0.914	83	76	39	13	-8	5.73E-8	4.70E-6	> 1.11E-5
T-47D	0.773	1.630	1.467	1.353	1.125	1.099	0.991	81	68	41	38	25	5.10E-8	> 1.11E-5	> 1.11E-5
MDA-MB-468	0.780	1.382	1.418	1.234	0.746	0.604	0.490	106	75	-4	-23	-37	2.31E-8	9.79E-8	> 1.11E-5

NCI-60 Five Dose Results **1.03**: Compound **1.39**

National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

NSC : D - 781080 / 1	Experiment ID : 1408NS31	Test Type : 08	Units : Molar
Report Date : September 22, 2014	Test Date : August 11, 2014	QNS :	MC :
COMI : KCDR_9A	Stain Reagent : SRB Dual-Pass Related	SSPL : 0ZAS	

			Log10 Concentration											
	Time		Mean Optical Densities					Percent Growth						
Panel/Cell Line	Zero	Ctrl	-8.3	-7.3	-6.3	-5.3	-4.3	-8.3	-7.3	-6.3	-5.3	-4.3	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.532	2.238	1.431	0.891	0.795	0.744	0.791	53	21	15	12	15	6.09E-9	> 5.00E-5	> 5.00E-5
HL-60(TB)	0.953	2.880	1.364	0.741	0.711	0.753	0.761	21	-22	-25	-21	-20	< 5.00E-9	1.54E-8	> 5.00E-5
K-562	0.270	1.856	0.777	0.527	0.392	0.355	0.352	32	16	8	5	5	< 5.00E-9	> 5.00E-5	> 5.00E-5
MOLT-4	0.789	2.736	1.704	1.308	1.028	0.886	0.985	47	27	12	5	10	< 5.00E-9	> 5.00E-5	> 5.00E-5
RPMI-8226	0.955	2.628	1.238	1.162	1.203	1.137	1.045	17	12	15	11	5	< 5.00E-9	> 5.00E-5	> 5.00E-5
SR	0.632	2.491	1.382	1.166	1.103	1.021	0.829	40	29	25	21	11	< 5.00E-9	> 5.00E-5	> 5.00E-5
Non-Small Cell Lung Cancer															
A549/ATCC	0.482	2.269	1.406	1.038	0.875	0.829	0.922	52	31	22	19	25	6.05E-9	> 5.00E-5	> 5.00E-5
EKVX	0.786	1.673	1.504	1.348	1.222	1.202	1.116	81	63	49	47	37	4.32E-7	> 5.00E-5	> 5.00E-5
HOP-62	0.578	1.994	1.602	1.215	0.953	0.911	0.972	72	45	26	24	28	3.27E-8	> 5.00E-5	> 5.00E-5
HOP-92	1.431	1.827	1.591	1.557	1.484	1.506	1.400	40	32	13	19	-2	< 5.00E-9	3.94E-5	> 5.00E-5
NCI-H226	0.545	1.702	1.541	1.270	1.235	1.170	0.943	86	63	60	54	34	7.99E-6	> 5.00E-5	> 5.00E-5
NCI-H23	0.675	2.436	1.578	1.190	0.977	1.009	1.125	51	29	17	19	26	5.72E-9	> 5.00E-5	> 5.00E-5
NCI-H322M	1.153	2.685	2.106	1.687	1.445	1.477	1.674	62	35	19	21	34	1.39E-8	> 5.00E-5	> 5.00E-5
NCI-H460	0.417	3.113	0.872	0.756	0.686	0.681	0.644	17	13	10	10	8	< 5.00E-9	> 5.00E-5	> 5.00E-5
NCI-H522	1.063	2.694	2.234	1.645	0.915	1.005	1.164	72	36	-14	-5	6	2.01E-8	.	> 5.00E-5
Colon Cancer															
COLO 205	0.434	1.751	0.906	0.562	0.366	0.342	0.270	36	10	-16	-21	-38	< 5.00E-9	1.20E-7	> 5.00E-5
HCC-2998	0.694	2.331	1.750	1.452	0.993	1.078	1.228	64	46	18	23	33	3.12E-8	> 5.00E-5	> 5.00E-5
HCT-116	0.311	2.126	0.624	0.381	0.403	0.322	0.514	17	4	5	1	11	< 5.00E-9	> 5.00E-5	> 5.00E-5
HCT-15	0.378	2.584	1.356	0.978	0.686	0.612	0.706	44	27	14	11	15	< 5.00E-9	> 5.00E-5	> 5.00E-5
HT29	0.303	1.718	0.616	0.455	0.414	0.406	0.360	22	11	8	7	4	< 5.00E-9	> 5.00E-5	> 5.00E-5
KM12	0.609	2.849	1.301	0.908	0.815	0.877	1.117	31	13	9	12	23	< 5.00E-9	> 5.00E-5	> 5.00E-5
SW-620	0.358	2.186	0.823	0.820	0.838	0.966	1.122	25	25	26	33	42	< 5.00E-9	> 5.00E-5	> 5.00E-5
CNS Cancer															
SF-268	0.741	2.162	1.715	1.457	1.107	1.044	1.030	69	50	26	21	20	5.17E-8	> 5.00E-5	> 5.00E-5
SF-295	0.977	3.016	2.484	1.639	1.021	1.080	1.287	74	32	2	5	15	1.89E-8	> 5.00E-5	> 5.00E-5
SF-539	0.914	2.394	1.867	1.092	0.753	0.722	0.779	64	12	-18	-21	-15	9.41E-9	1.27E-7	> 5.00E-5
SNB-19	0.847	2.396	1.982	1.590	1.501	1.338	1.319	73	48	42	32	30	4.15E-8	> 5.00E-5	> 5.00E-5
SNB-75	0.784	1.555	1.115	0.853	0.638	0.555	0.598	43	9	-19	-29	-24	< 5.00E-9	1.05E-7	> 5.00E-5
U251	0.492	2.478	1.452	1.065	0.717	0.739	0.733	48	29	11	12	12	< 5.00E-9	> 5.00E-5	> 5.00E-5
Melanoma															
LOX IMVI	0.406	2.288	1.174	0.987	0.816	0.835	0.704	41	31	22	23	16	< 5.00E-9	> 5.00E-5	> 5.00E-5
MALME-3M	0.674	1.166	0.998	0.910	0.853	0.867	0.937	66	48	36	39	53	.	> 5.00E-5	> 5.00E-5
M14	0.396	1.494	0.602	0.294	0.260	0.549	0.599	19	-26	-34	14	18	< 5.00E-9	.	> 5.00E-5
MDA-MB-435	0.594	2.616	0.224	0.158	0.219	0.247	0.465	-62	-73	-63	-58	-22	< 5.00E-9	< 5.00E-9	.
SK-MEL-2	0.944	1.968	1.757	1.384	1.217	1.100	1.247	79	43	27	15	30	3.21E-8	> 5.00E-5	> 5.00E-5
SK-MEL-28	0.736	2.234	1.873	1.525	1.499	1.611	1.400	76	53	51	58	44	1.98E-5	> 5.00E-5	> 5.00E-5
SK-MEL-5	0.728	2.873	1.457	0.970	0.875	0.755	0.653	34	11	7	1	-10	< 5.00E-9	6.40E-6	> 5.00E-5
UACC-257	1.091	2.418	2.043	1.743	1.732	1.742	1.690	72	49	48	49	45	4.58E-8	> 5.00E-5	> 5.00E-5
UACC-62	1.034	2.869	2.303	2.016	1.823	1.833	1.674	69	54	43	44	35	1.08E-7	> 5.00E-5	> 5.00E-5
Ovarian Cancer															
IGROV1	0.630	2.316	1.613	1.506	1.407	1.218	1.123	58	52	46	35	29	1.06E-7	> 5.00E-5	> 5.00E-5
OVCAR-3	0.486	1.602	0.731	0.547	0.451	0.417	0.426	22	5	-7	-14	-12	< 5.00E-9	1.35E-7	> 5.00E-5
OVCAR-4	0.688	1.412	1.209	1.062	0.985	0.898	0.827	72	52	41	29	19	7.17E-8	> 5.00E-5	> 5.00E-5
OVCAR-5	0.693	1.694	1.574	1.214	1.026	0.965	0.867	88	52	33	27	17	6.38E-8	> 5.00E-5	> 5.00E-5
OVCAR-8	0.588	2.431	1.803	1.337	1.104	1.027	1.240	66	41	28	24	35	2.13E-8	> 5.00E-5	> 5.00E-5
NCI/ADR-RES	0.663	2.267	1.938	1.618	0.795	0.740	0.699	79	60	8	5	2	7.67E-8	> 5.00E-5	> 5.00E-5
SK-OV-3	0.635	1.656	1.346	1.061	0.864	0.832	0.911	70	42	22	19	27	2.52E-8	> 5.00E-5	> 5.00E-5
Renal Cancer															
786-0	0.700	2.255	1.823	1.289	0.789	0.873	1.213	72	38	6	11	33	2.22E-8	> 5.00E-5	> 5.00E-5
A498	1.366	2.008	1.637	1.506	1.255	1.324	1.320	42	22	-8	-3	-3	< 5.00E-9	2.67E-7	> 5.00E-5
ACHN	0.508	2.226	1.833	1.472	1.386	1.185	1.149	77	56	51	39	37	6.18E-7	> 5.00E-5	> 5.00E-5
CAKI-1	1.025	3.171	2.570	2.179	1.980	1.668	1.699	72	54	45	30	31	1.28E-7	> 5.00E-5	> 5.00E-5
RXF 393	0.755	1.316	1.098	0.870	0.694	0.689	0.724	61	20	-8	-9	-4	9.39E-9	2.61E-7	> 5.00E-5
SN12C	0.743	2.700	2.216	1.646	1.399	1.346	1.353	75	46	33	31	31	3.68E-8	> 5.00E-5	> 5.00E-5
TK-10	1.103	1.920	1.815	1.626	1.416	1.351	1.336	87	64	38	30	28	1.75E-7	> 5.00E-5	> 5.00E-5
UO-31	0.963	2.560	2.122	1.907	1.685	1.555	1.318	73	59	45	37	22	2.26E-7	> 5.00E-5	> 5.00E-5
Prostate Cancer															
PC-3	0.765	2.297	1.692	1.137	1.080	1.087	1.120	61	24	21	21	23	9.75E-9	> 5.00E-5	> 5.00E-5
DU-145	0.398	1.595	1.303	0.608	0.335	0.294	0.362	76	18	-16	-26	-9	1.38E-8	1.68E-7	> 5.00E-5
Breast Cancer															
MCF7	0.371	2.050	0.611	0.563	0.564	0.483	0.414	14	11	11	7	3	< 5.00E-9	> 5.00E-5	> 5.00E-5
MDA-MB-231/ATCC	0.689	1.630	1.376	1.255	0.999	0.893	0.888	73	60	33	22	21	1.17E-7	> 5.00E-5	> 5.00E-5
HS 578T	1.018	2.021	1.531	1.264	0.997	0.904	0.874	51	24	-2	-11	-14	5.51E-9	4.18E-7	> 5.00E-5
BT-549	1.310	2.436	2.071	1.903	1.538	1.482	1.237	68	53	20	15	-6	6.03E-8	2.70E-5	> 5.00E-5
T-47D	0.669	1.364	1.132	0.995	0.913	0.897	0.834	67	47	35	33	24	3.49E-8	> 5.00E-5	> 5.00E-5
MDA-MB-468	0.923	1.983	1.491	1.254	1.086	1.033	0.997	54	31	15	10	7	7.22E-9	> 5.00E-5	> 5.00E-5

NCI-60 Five Dose Results **1.04**: Compound **1.40**

National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

NSC : D - 781079 / 1	Experiment ID : 1408NS31	Test Type : 08	Units : Molar
Report Date : September 22, 2014	Test Date : August 11, 2014	QNS :	MC :
COMI : KCDR_8A	Stain Reagent : SRB Dual-Pass Related	SSPL : 0ZAS	

Log10 Concentration

Panel/Cell Line	Time Zero	Mean Optical Densities Ctrl	-8.5	-7.5	-6.5	-5.5	-4.5	Percent Growth -8.5	-7.5	-6.5	-5.5	-4.5	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.532	2.325	2.237	0.836	0.854	0.778	0.635	95	17	18	14	6	1.23E-8	> 3.25E-5	> 3.25E-5
HL-60(TB)	0.953	2.660	2.497	0.729	0.726	0.812	0.677	90	-24	-24	-15	-29	7.36E-9	2.02E-8	> 3.25E-5
K-562	0.270	1.681	1.386	0.561	0.401	0.390	0.322	79	21	9	9	4	1.02E-8	> 3.25E-5	> 3.25E-5
MOLT-4	0.789	2.569	2.330	1.312	1.078	1.079	0.758	87	29	16	16	-4	1.42E-8	2.06E-5	> 3.25E-5
RPMI-8226	0.955	2.580	2.329	1.177	1.271	1.245	0.839	85	14	19	18	-12	9.98E-9	1.28E-5	> 3.25E-5
SR	0.632	2.320	1.697	1.069	1.143	1.003	0.551	63	26	30	22	-13	7.29E-9	1.39E-5	> 3.25E-5
Non-Small Cell Lung Cancer															
A549/ATCC	0.482	2.234	1.883	1.029	0.942	0.940	0.606	80	31	26	26	7	1.34E-8	> 3.25E-5	> 3.25E-5
EKVX	0.786	1.674	1.622	1.359	1.311	1.254	0.904	94	64	59	53	13	3.80E-6	> 3.25E-5	> 3.25E-5
HOP-62	0.578	1.917	1.821	1.223	1.083	0.955	0.796	93	48	38	28	16	2.95E-8	> 3.25E-5	> 3.25E-5
HOP-92	1.431	1.827	1.746	1.578	1.622	1.619	1.327	80	37	48	48	-7	1.61E-8	2.39E-5	> 3.25E-5
NCI-H226	0.545	1.732	1.608	1.260	1.247	1.205	0.579	89	60	59	56	3	4.14E-6	> 3.25E-5	> 3.25E-5
NCI-H23	0.675	2.369	2.280	1.269	1.155	1.192	0.872	95	35	28	30	12	1.83E-8	> 3.25E-5	> 3.25E-5
NCI-H322M	1.153	2.710	2.564	1.723	1.537	1.530	1.558	91	37	25	24	26	1.84E-8	> 3.25E-5	> 3.25E-5
NCI-H460	0.417	3.117	2.535	0.746	0.726	0.714	0.300	78	12	11	11	-28	8.73E-9	6.20E-6	> 3.25E-5
NCI-H522	1.063	2.660	2.480	1.450	0.983	0.986	1.000	89	24	-8	-7	-6	1.29E-8	1.88E-7	> 3.25E-5
Colon Cancer															
COLO 205	0.434	1.822	1.579	0.497	0.443	0.377	0.155	82	5	1	-13	-64	8.48E-9	3.60E-7	1.70E-5
HCC-2998	0.694	2.426	2.260	1.669	1.209	1.344	0.807	90	56	30	38	6	5.60E-8	> 3.25E-5	> 3.25E-5
HCT-116	0.311	2.169	1.397	0.480	0.453	0.463	0.311	58	9	8	8	.	4.82E-9	> 3.25E-5	> 3.25E-5
HCT-15	0.378	2.649	2.099	0.994	0.846	0.759	0.443	76	27	21	17	3	1.10E-8	> 3.25E-5	> 3.25E-5
HT29	0.303	1.713	1.184	0.470	0.433	0.416	0.281	62	12	9	8	-7	5.74E-9	1.07E-5	> 3.25E-5
KM12	0.609	2.831	2.327	0.978	0.919	0.958	0.722	77	17	14	16	5	9.16E-9	> 3.25E-5	> 3.25E-5
SW-620	0.358	2.229	1.463	0.864	0.952	1.058	0.624	59	27	32	37	14	6.23E-9	> 3.25E-5	> 3.25E-5
CNS Cancer															
SF-268	0.741	2.096	1.917	1.454	1.242	1.151	0.888	87	53	37	30	11	4.75E-8	> 3.25E-5	> 3.25E-5
SF-295	0.977	3.039	2.761	1.739	1.242	1.168	0.878	87	37	13	9	-10	1.77E-8	9.72E-6	> 3.25E-5
SF-539	0.914	2.486	2.317	0.999	0.883	0.906	0.595	89	5	-3	-1	-35	9.55E-9	1.33E-7	> 3.25E-5
SNB-19	0.847	2.472	2.235	1.690	1.482	1.412	1.071	85	52	39	35	14	4.55E-8	> 3.25E-5	> 3.25E-5
SNB-75	0.784	1.550	1.242	0.883	0.751	0.746	0.598	60	13	-4	-5	-24	5.25E-9	1.84E-7	> 3.25E-5
U251	0.492	2.409	2.169	1.068	0.773	0.829	0.450	87	30	15	18	-9	1.46E-8	1.52E-5	> 3.25E-5
Melanoma															
LOX IMVI	0.406	2.300	1.724	0.983	0.870	0.784	0.355	70	30	24	20	-13	1.03E-8	1.33E-5	> 3.25E-5
MALME-3M	0.674	1.198	1.187	0.900	0.872	0.942	0.824	98	43	38	51	29	.	> 3.25E-5	> 3.25E-5
M14	0.396	1.498	1.103	0.333	0.310	0.581	0.369	64	-16	-22	17	-7	4.88E-9	.	> 3.25E-5
MDA-MB-435	0.594	2.595	0.995	0.172	0.276	0.296	0.489	20	-71	-54	-50	-18	< 3.25E-9	5.39E-9	.
SK-MEL-2	0.944	1.907	1.918	1.352	1.071	1.158	0.740	101	42	13	22	-22	2.41E-8	1.04E-5	> 3.25E-5
SK-MEL-28	0.736	2.242	2.229	1.508	1.516	1.554	0.811	99	51	52	54	5	3.98E-6	> 3.25E-5	> 3.25E-5
SK-MEL-5	0.728	2.717	2.474	0.949	0.813	0.771	0.091	88	11	4	2	-88	1.01E-8	3.43E-6	1.24E-5
UACC-257	1.091	2.352	2.201	1.754	1.758	1.787	1.234	88	53	53	55	11	4.27E-6	> 3.25E-5	> 3.25E-5
UACC-62	1.034	2.904	2.707	2.024	1.970	1.721	1.042	89	53	50	37	.	3.28E-7	> 3.25E-5	> 3.25E-5
Ovarian Cancer															
IGROV1	0.630	2.311	1.972	1.588	1.461	1.360	1.024	80	57	49	43	23	2.75E-7	> 3.25E-5	> 3.25E-5
OVCAR-3	0.486	1.621	1.509	0.594	0.540	0.502	0.375	90	9	5	1	-23	1.02E-8	3.72E-6	> 3.25E-5
OVCAR-4	0.688	1.400	1.319	1.065	1.042	0.961	0.704	89	53	50	38	2	2.66E-7	> 3.25E-5	> 3.25E-5
OVCAR-5	0.693	1.668	1.647	1.100	1.150	0.935	0.653	98	42	47	25	-6	2.31E-8	2.09E-5	> 3.25E-5
OVCAR-8	0.588	2.411	2.279	1.311	1.142	1.131	0.706	93	40	30	30	6	2.07E-8	> 3.25E-5	> 3.25E-5
NCI/ADR-RES	0.663	2.212	2.195	1.624	0.857	0.751	0.635	99	62	13	6	-4	5.69E-8	1.20E-5	> 3.25E-5
SK-OV-3	0.635	1.632	1.621	1.325	0.975	0.907	0.713	99	69	34	27	8	1.15E-7	> 3.25E-5	> 3.25E-5
Renal Cancer															
786-0	0.700	2.273	2.040	1.311	1.071	1.016	0.637	85	39	24	20	-9	1.86E-8	1.59E-5	> 3.25E-5
A498	1.366	1.984	1.775	1.590	1.261	1.271	1.160	66	36	-8	-7	-15	1.13E-8	2.17E-7	> 3.25E-5
ACHN	0.508	2.268	2.083	1.380	1.309	1.237	0.521	90	50	46	41	1	3.17E-8	> 3.25E-5	> 3.25E-5
CAKI-1	1.025	3.167	2.894	2.179	1.990	1.787	1.219	87	54	45	36	9	8.92E-8	> 3.25E-5	> 3.25E-5
RXF 393	0.755	1.400	1.318	0.939	0.806	0.773	0.573	87	29	8	3	-24	1.40E-8	4.12E-6	> 3.25E-5
SN12C	0.743	2.727	2.629	1.704	1.537	1.550	1.109	95	48	40	41	18	3.01E-8	> 3.25E-5	> 3.25E-5
TK-10	1.103	1.906	1.843	1.656	1.466	1.410	1.057	92	69	45	38	-4	2.03E-7	2.59E-5	> 3.25E-5
UO-31	0.963	2.580	2.400	1.935	1.695	1.556	1.002	89	60	45	37	2	1.56E-7	> 3.25E-5	> 3.25E-5
Prostate Cancer															
PC-3	0.765	2.305	2.101	1.148	1.127	1.103	0.796	87	25	24	22	2	1.27E-8	> 3.25E-5	> 3.25E-5
DU-145	0.398	1.531	1.492	0.562	0.365	0.329	0.348	97	14	-8	-17	-13	1.20E-8	1.41E-7	> 3.25E-5
Breast Cancer															
MCF7	0.371	2.100	1.123	0.610	0.582	0.573	0.390	43	14	12	12	1	< 3.25E-9	> 3.25E-5	> 3.25E-5
MDA-MB-231/ATCC	0.689	1.619	1.621	1.320	1.218	1.016	0.704	100	68	57	35	2	6.72E-7	> 3.25E-5	> 3.25E-5
HS 578T	1.018	2.075	1.678	1.292	1.138	1.093	0.843	62	26	11	7	-17	7.10E-9	6.35E-6	> 3.25E-5
BT-549	1.310	2.462	2.233	1.863	1.648	1.713	1.301	80	48	29	35	-1	2.81E-8	3.10E-5	> 3.25E-5
T-47D	0.669	1.404	1.257	0.982	0.991	1.031	0.649	80	43	44	49	-3	2.06E-8	2.85E-5	> 3.25E-5
MDA-MB-468	0.923	1.962	1.718	1.184	1.026	1.047	0.861	77	25	10	12	-7	1.06E-8	1.42E-5	> 3.25E-5

NCI-60 Five Dose Results **1.05**: Compound **1.41**

National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

NSC : D - 781078 / 1	Experiment ID : 1408NS31	Test Type : 08	Units : Molar
Report Date : September 22, 2014	Test Date : August 11, 2014	QNS :	MC :
COMI : KCDR_7A	Stain Reagent : SRB Dual-Pass Related	SSPL : 0ZAS	

		Log10 Concentration												
	Time	Mean Optical Densities						Percent Growth						
Panel/Cell Line	Zero	Ctrl	-8.3	-7.3	-6.3	-5.3	-4.3	-8.3	-7.3	-6.3	-5.3	-4.3	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.532	2.189	1.544	1.123	0.794	0.783	0.737	61	36	16	15	12	1.36E-8	> 5.00E-5	> 5.00E-5
HL-60(TB)	0.953	2.628	2.428	1.011	0.830	0.912	0.925	88	3	-13	-4	-3	1.41E-8	8.14E-8	> 5.00E-5
K-562	0.270	1.894	1.769	0.654	0.480	0.474	0.409	92	24	13	13	9	2.07E-8	> 5.00E-5	> 5.00E-5
MOLT-4	0.789	2.720	2.598	1.479	1.252	1.175	1.101	94	36	24	20	16	2.83E-8	> 5.00E-5	> 5.00E-5
RPMI-8226	0.955	2.571	2.599	1.190	1.134	1.142	1.020	102	15	11	12	4	1.96E-8	> 5.00E-5	> 5.00E-5
SR	0.632	2.508	2.435	1.305	1.193	1.262	0.735	96	36	30	34	5	2.92E-8	> 5.00E-5	> 5.00E-5
Non-Small Cell Lung Cancer															
A549/ATCC	0.482	2.197	2.217	1.216	0.974	0.917	0.997	101	43	29	25	30	3.76E-8	> 5.00E-5	> 5.00E-5
EKVX	0.786	1.601	1.481	1.347	1.202	1.145	1.065	85	69	51	44	34	7.05E-7	> 5.00E-5	> 5.00E-5
HOP-62	0.578	1.925	1.878	1.232	1.060	0.937	1.037	96	49	36	27	34	4.67E-8	> 5.00E-5	> 5.00E-5
HOP-92	1.431	1.821	1.767	1.637	1.659	1.644	1.560	86	53	58	55	33	8.19E-6	> 5.00E-5	> 5.00E-5
NCI-H226	0.545	1.678	1.651	1.386	1.221	1.154	0.940	98	74	60	54	35	7.87E-6	> 5.00E-5	> 5.00E-5
NCI-H23	0.675	2.303	2.242	1.144	0.945	0.852	1.033	96	29	17	11	22	2.42E-8	> 5.00E-5	> 5.00E-5
NCI-H322M	1.153	2.676	2.556	1.704	1.429	1.426	1.593	92	36	18	18	29	2.83E-8	> 5.00E-5	> 5.00E-5
NCI-H460	0.417	3.089	3.142	0.900	0.699	0.725	0.682	102	18	11	12	10	2.08E-8	> 5.00E-5	> 5.00E-5
NCI-H522	1.063	2.563	2.496	1.628	0.968	0.817	1.155	96	38	-9	-23	6	3.06E-8	.	> 5.00E-5
Colon Cancer															
COLO 205	0.434	1.806	1.725	0.646	0.441	0.386	0.323	94	15	1	-11	-26	1.82E-8	5.53E-7	> 5.00E-5
HCC-2998	0.694	1.999	1.885	1.213	0.759	0.676	0.689	91	40	5	-3	-1	3.17E-8	2.23E-6	> 5.00E-5
HCT-116	0.311	2.077	1.967	0.519	0.407	0.409	0.483	94	12	5	6	10	1.71E-8	> 5.00E-5	> 5.00E-5
HCT-15	0.378	2.447	2.243	0.975	0.723	0.545	0.599	90	29	17	8	11	2.26E-8	> 5.00E-5	> 5.00E-5
HT29	0.303	1.557	1.534	0.466	0.398	0.393	0.346	98	13	8	7	3	1.84E-8	> 5.00E-5	> 5.00E-5
KM12	0.609	2.834	2.634	0.971	0.806	0.906	1.019	91	16	9	13	18	1.77E-8	> 5.00E-5	> 5.00E-5
SW-620	0.358	2.295	2.239	0.883	0.938	1.040	1.101	97	27	30	35	38	2.36E-8	> 5.00E-5	> 5.00E-5
CNS Cancer															
SF-268	0.741	2.128	2.007	1.506	1.262	1.113	1.054	91	55	38	27	23	9.79E-8	> 5.00E-5	> 5.00E-5
SF-295	0.977	2.913	2.647	1.989	1.074	0.988	1.133	86	52	5	1	8	5.58E-8	> 5.00E-5	> 5.00E-5
SF-539	0.914	2.554	2.209	1.550	0.808	0.684	0.680	79	39	-12	-25	-26	2.62E-8	2.94E-7	> 5.00E-5
SNB-19	0.847	2.392	2.345	1.866	1.546	1.375	1.428	97	66	45	34	38	2.94E-7	> 5.00E-5	> 5.00E-5
SNB-75	0.784	1.472	1.222	0.969	0.674	0.615	0.611	64	27	-14	-22	-22	1.17E-8	2.26E-7	> 5.00E-5
U251	0.492	2.324	2.312	1.261	0.812	0.738	0.784	99	42	17	13	16	3.62E-8	> 5.00E-5	> 5.00E-5
Melanoma															
LOX IMVI	0.406	2.331	2.184	0.958	0.778	0.695	0.724	92	29	19	15	16	2.31E-8	> 5.00E-5	> 5.00E-5
MALME-3M	0.674	1.162	1.099	0.941	0.810	0.879	0.957	87	55	28	42	58	.	> 5.00E-5	> 5.00E-5
M14	0.396	1.480	1.471	0.540	0.263	0.379	0.628	99	13	-34	-4	21	1.87E-8	.	> 5.00E-5
MDA-MB-435	0.594	2.513	2.200	0.193	0.088	0.188	0.466	84	-68	-85	-68	-22	8.35E-9	1.79E-8	.
SK-MEL-2	0.944	1.789	1.802	1.331	1.084	1.104	1.252	102	46	17	19	36	4.19E-8	> 5.00E-5	> 5.00E-5
SK-MEL-28	0.736	2.201	2.108	1.726	1.469	1.457	1.287	94	68	50	49	38	5.36E-7	> 5.00E-5	> 5.00E-5
SK-MEL-5	0.728	2.759	2.735	0.949	0.616	0.639	0.706	99	11	-15	-12	-3	1.80E-8	1.29E-7	> 5.00E-5
UACC-257	1.091	2.320	2.341	1.896	1.723	1.765	1.947	102	65	51	55	70	> 5.00E-5	> 5.00E-5	> 5.00E-5
UACC-62	1.034	2.909	2.915	2.125	1.939	1.754	1.762	100	58	48	38	39	3.33E-7	> 5.00E-5	> 5.00E-5
Ovarian Cancer															
IGROV1	0.630	2.283	2.111	1.433	1.370	1.253	1.227	90	49	45	38	36	4.61E-8	> 5.00E-5	> 5.00E-5
OVCAR-3	0.486	1.583	1.587	0.577	0.472	0.475	0.418	100	8	-3	-2	-14	1.76E-8	2.76E-7	> 5.00E-5
OVCAR-4	0.688	1.397	1.299	1.117	1.053	0.962	0.890	86	60	51	39	28	6.44E-7	> 5.00E-5	> 5.00E-5
OVCAR-5	0.693	1.694	1.469	1.228	1.009	0.899	0.802	77	53	32	21	11	7.18E-8	> 5.00E-5	> 5.00E-5
OVCAR-8	0.588	2.348	2.419	1.383	1.059	0.979	1.126	104	45	27	22	31	4.14E-8	> 5.00E-5	> 5.00E-5
NCI/ADR-RES	0.663	2.187	2.213	1.529	0.557	0.429	0.472	102	57	-16	-35	-29	6.20E-8	3.01E-7	> 5.00E-5
SK-OV-3	0.635	1.630	1.627	1.368	0.974	0.955	0.971	100	74	34	32	34	1.98E-7	> 5.00E-5	> 5.00E-5
Renal Cancer															
786-0	0.700	2.228	2.113	1.631	1.138	0.951	1.122	92	61	29	16	28	1.09E-7	> 5.00E-5	> 5.00E-5
A498	1.366	2.025	1.853	1.741	1.520	1.344	1.449	74	57	23	-2	13	8.02E-8	.	> 5.00E-5
ACHN	0.508	2.097	2.042	1.486	1.183	1.075	1.075	97	62	42	36	36	2.01E-7	> 5.00E-5	> 5.00E-5
CAKI-1	1.025	3.114	2.820	2.242	1.790	1.678	1.757	86	58	37	31	35	1.20E-7	> 5.00E-5	> 5.00E-5
RXF 393	0.755	1.370	1.360	0.982	0.742	0.679	0.697	98	37	-2	-10	-8	3.06E-8	4.51E-7	> 5.00E-5
SN12C	0.743	2.714	2.712	1.763	1.495	1.441	1.429	100	52	38	35	35	6.74E-8	> 5.00E-5	> 5.00E-5
TK-10	1.103	1.888	1.846	1.626	1.441	1.364	1.331	95	67	43	33	29	2.53E-7	> 5.00E-5	> 5.00E-5
UO-31	0.963	2.490	2.260	1.894	1.600	1.527	1.269	85	61	42	37	20	1.85E-7	> 5.00E-5	> 5.00E-5
Prostate Cancer															
PC-3	0.765	2.327	2.157	1.301	1.166	1.221	1.185	89	34	26	29	27	2.58E-8	> 5.00E-5	> 5.00E-5
DU-145	0.398	1.573	1.554	0.742	0.365	0.319	0.272	98	29	-8	-20	-32	2.51E-8	3.01E-7	> 5.00E-5
Breast Cancer															
MCF7	0.371	1.989	1.640	0.608	0.558	0.501	0.509	78	15	12	8	9	1.40E-8	> 5.00E-5	> 5.00E-5
MDA-MB-231/ATCC	0.689	1.609	1.661	1.315	1.059	0.976	0.767	106	68	40	31	8	2.22E-7	> 5.00E-5	> 5.00E-5
HS 578T	1.018	2.052	1.851	1.488	1.211	1.021	0.951	81	45	19	.	-7	3.72E-8	5.51E-6	> 5.00E-5
BT-549	1.310	2.471	2.388	2.064	1.666	1.675	1.586	93	65	31	31	24	1.36E-7	> 5.00E-5	> 5.00E-5
T-47D	0.669	1.395	1.336	1.061	0.987	1.010	0.943	92	54	44	47	38	1.23E-7	> 5.00E-5	> 5.00E-5
MDA-MB-468	0.923	1.892	1.842	1.143	0.781	0.773	0.848	95	23	-15	-16	-8	2.09E-8	1.97E-7	> 5.00E-5

NCI-60 Five Dose Results **1.06**: Compound **1.42**

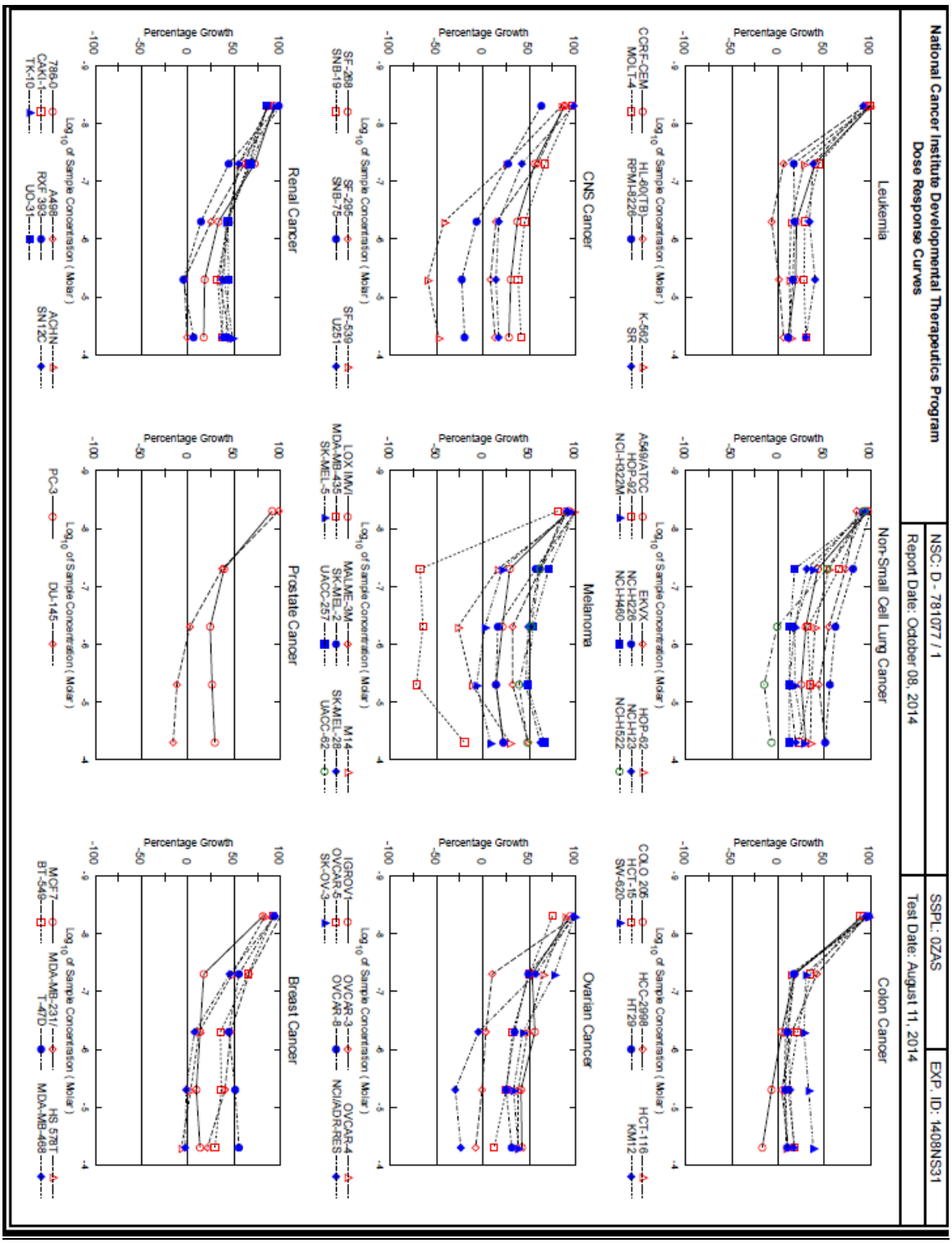
National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

NSC : D - 781492 / 1	Experiment ID : 1409NS43	Test Type : 08	Units : Molar
Report Date : September 17, 2014	Test Date : September 02, 2014	QNS :	MC :
COMI : KCDR_6A	Stain Reagent : SRB Dual-Pass Related	SSPL : 0ZAS	

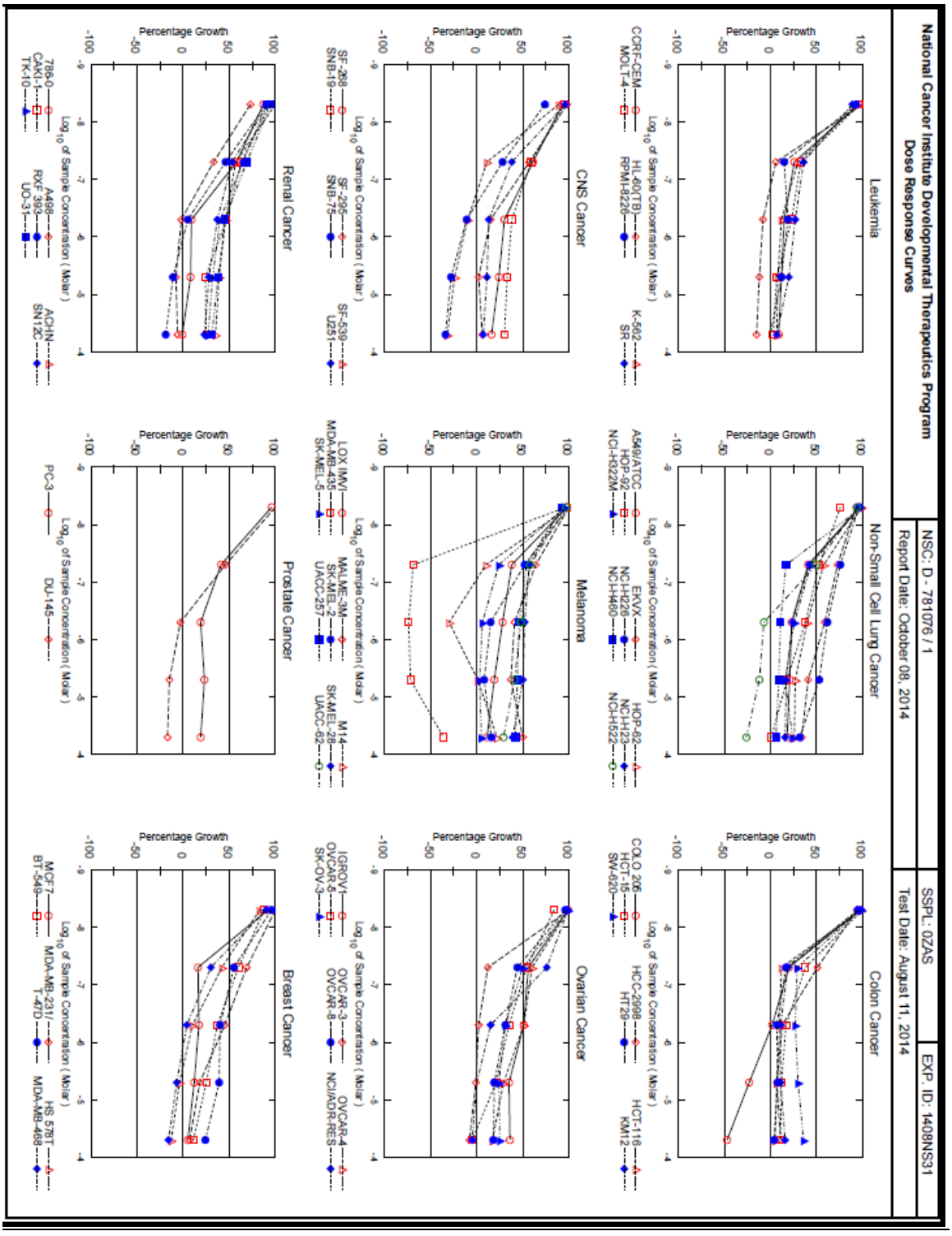
		Log10 Concentration													
	Time	Mean Optical Densities						Percent Growth							
Panel/Cell Line	Zero	Ctrl	-9.0	-8.0	-7.0	-6.0	-5.0	-9.0	-8.0	-7.0	-6.0	-5.0	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.640	2.915	2.866	2.874	2.857	0.966	0.912	98	98	97	14	12	4.13E-7	> 1.11E-5	> 1.11E-5
HL-60(TB)	0.615	2.778	2.708	2.643	2.518	0.607	0.596	97	94	88	-1	-3	2.96E-7	1.07E-6	> 1.11E-5
K-562	0.230	2.107	2.085	2.012	1.916	0.439	0.375	99	95	90	11	8	3.56E-7	> 1.11E-5	> 1.11E-5
MOLT-4	0.782	3.159	3.154	3.175	3.123	1.432	1.144	100	101	98	27	15	5.33E-7	> 1.11E-5	> 1.11E-5
RPMI-8226	0.766	2.422	2.333	2.320	2.299	0.962	0.939	95	94	93	12	10	3.74E-7	> 1.11E-5	> 1.11E-5
Non-Small Cell Lung Cancer															
A549/ATCC	0.502	2.294	2.267	2.174	2.132	1.020	0.811	99	93	91	29	17	5.08E-7	> 1.11E-5	> 1.11E-5
EKVX	0.676	1.923	1.840	1.775	1.864	1.182	0.972	93	88	95	41	24	7.47E-7	> 1.11E-5	> 1.11E-5
HOP-62	0.715	1.405	1.359	1.262	1.234	0.965	0.703	93	79	75	36	-2	4.90E-7	9.98E-6	> 1.11E-5
HOP-92	1.280	1.660	1.561	1.566	1.638	1.478	1.337	74	75	94	52	15	1.27E-6	> 1.11E-5	> 1.11E-5
NCI-H226	0.773	2.046	1.964	1.947	2.035	1.463	1.393	94	92	99	54	49	6.35E-6	> 1.11E-5	> 1.11E-5
NCI-H23	0.450	1.385	1.392	1.456	1.323	0.738	0.680	101	108	93	31	25	5.48E-7	> 1.11E-5	> 1.11E-5
NCI-H322M	0.752	1.790	1.746	1.759	1.706	1.154	1.053	96	97	92	39	29	6.81E-7	> 1.11E-5	> 1.11E-5
NCI-H460	0.308	2.895	2.898	2.888	2.394	0.571	0.429	100	100	81	10	5	3.02E-7	> 1.11E-5	> 1.11E-5
NCI-H522	0.828	2.258	2.128	2.157	1.925	0.380	0.289	91	93	77	-54	-65	1.78E-7	4.28E-7	1.03E-6
Colon Cancer															
COLO 205	0.454	1.772	1.758	1.630	1.585	0.382	0.240	99	89	86	-16	-47	2.50E-7	7.73E-7	> 1.11E-5
HCC-2998	0.488	1.665	1.577	1.569	1.426	0.632	0.468	93	92	80	12	-4	3.06E-7	6.23E-6	> 1.11E-5
HCT-116	0.271	2.093	2.103	1.971	1.437	0.447	0.375	101	93	64	10	6	2.01E-7	> 1.11E-5	> 1.11E-5
HCT-15	0.236	1.495	1.525	1.416	1.374	0.508	0.252	102	94	90	22	1	4.29E-7	> 1.11E-5	> 1.11E-5
HT29	0.256	1.454	1.465	1.388	0.870	0.250	0.183	101	95	51	-3	-29	1.17E-7	9.96E-7	> 1.11E-5
KM12	0.400	2.110	2.161	2.109	1.648	0.552	0.498	103	100	73	9	6	2.54E-7	> 1.11E-5	> 1.11E-5
SW-620	0.273	2.038	2.019	1.973	1.439	0.784	0.680	99	96	66	29	23	3.01E-7	> 1.11E-5	> 1.11E-5
CNS Cancer															
SF-268	0.614	2.076	1.984	1.908	1.828	1.070	0.802	94	88	83	31	13	4.81E-7	> 1.11E-5	> 1.11E-5
SF-295	0.541	2.383	2.306	2.164	2.144	0.633	0.477	96	88	87	5	-12	3.14E-7	2.19E-6	> 1.11E-5
SF-539	0.972	2.628	2.618	2.424	2.406	1.025	0.866	99	88	87	3	-11	3.05E-7	1.86E-6	> 1.11E-5
SNB-19	0.559	1.913	1.865	1.903	1.818	0.984	0.839	96	99	93	31	21	5.53E-7	> 1.11E-5	> 1.11E-5
U251	0.518	2.421	2.350	2.313	2.182	0.865	0.678	96	94	87	18	8	3.86E-7	> 1.11E-5	> 1.11E-5
Melanoma															
LOX IMVI	0.333	2.159	2.094	2.099	1.911	0.859	0.769	96	97	86	29	24	4.76E-7	> 1.11E-5	> 1.11E-5
MALME-3M	0.795	1.359	1.357	1.321	1.310	1.027	0.978	100	93	91	41	32	7.36E-7	> 1.11E-5	> 1.11E-5
M14	0.356	1.656	1.611	1.495	1.325	0.384	0.313	97	88	75	2	-12	2.42E-7	1.56E-6	> 1.11E-5
MDA-MB-435	0.293	1.624	1.552	1.386	0.802	0.132	0.086	95	82	38	-55	-71	5.99E-8	2.86E-7	9.82E-7
SK-MEL-2	1.169	2.257	2.297	2.269	2.216	1.058	0.885	104	101	96	-10	-24	3.03E-7	9.02E-7	> 1.11E-5
SK-MEL-28	0.607	1.973	1.950	1.864	1.827	1.280	1.125	98	92	89	49	38	1.06E-6	> 1.11E-5	> 1.11E-5
SK-MEL-5	0.788	3.030	2.845	2.973	2.955	0.888	0.806	92	97	97	4	1	3.56E-7	> 1.11E-5	> 1.11E-5
UACC-257	0.952	2.119	2.077	1.946	2.101	1.516	1.425	96	85	98	48	41	1.03E-6	> 1.11E-5	> 1.11E-5
UACC-62	0.890	2.749	2.684	2.610	2.568	1.404	1.267	97	93	90	28	20	4.88E-7	> 1.11E-5	> 1.11E-5
Ovarian Cancer															
IGROV1	0.594	2.382	2.345	2.319	2.137	1.370	1.127	98	97	86	43	30	7.78E-7	> 1.11E-5	> 1.11E-5
OVCAR-3	0.470	1.644	1.646	1.633	1.545	0.552	0.417	100	99	92	7	-11	3.44E-7	2.66E-6	> 1.11E-5
OVCAR-4	1.146	2.244	2.153	2.091	2.136	1.821	1.748	92	86	90	61	55	> 1.11E-5	> 1.11E-5	> 1.11E-5
OVCAR-5	0.709	1.847	1.823	1.775	1.735	1.054	0.875	98	94	90	30	15	5.19E-7	> 1.11E-5	> 1.11E-5
OVCAR-8	0.480	1.941	1.984	1.915	2.072	0.764	0.532	103	98	109	19	4	5.06E-7	> 1.11E-5	> 1.11E-5
NCI/ADR-RES	0.474	1.561	1.553	1.572	1.567	1.374	0.776	99	101	101	83	28	4.38E-6	> 1.11E-5	> 1.11E-5
SK-OV-3	0.782	1.835	1.828	1.729	1.694	1.027	0.930	99	90	87	23	14	4.20E-7	> 1.11E-5	> 1.11E-5
Renal Cancer															
786-0	0.577	2.089	1.983	1.838	1.889	1.106	0.779	93	83	87	35	13	5.69E-7	> 1.11E-5	> 1.11E-5
A498	1.270	2.114	1.920	1.954	1.985	1.314	1.125	77	81	85	5	-11	3.03E-7	2.27E-6	> 1.11E-5
ACHN	0.440	1.871	1.820	1.734	1.635	0.913	0.795	96	90	83	33	25	5.12E-7	> 1.11E-5	> 1.11E-5
CAKI-1	1.251	3.364	3.328	3.220	3.184	2.661	2.244	98	93	91	67	47	7.81E-6	> 1.11E-5	> 1.11E-5
RXF 393	0.622	1.316	1.271	1.356	1.255	0.736	0.548	94	106	91	16	-12	3.95E-7	4.21E-6	> 1.11E-5
SN12C	1.165	3.211	3.177	3.185	3.281	2.231	1.948	98	99	103	52	38	1.57E-6	> 1.11E-5	> 1.11E-5
TK-10	0.796	1.784	1.694	1.673	1.694	1.150	0.930	91	89	91	36	14	6.12E-7	> 1.11E-5	> 1.11E-5
UO-31	0.709	2.397	2.256	2.256	2.173	1.509	1.372	92	92	87	47	39	9.54E-7	> 1.11E-5	> 1.11E-5
Prostate Cancer															
PC-3	0.611	2.453	2.291	2.285	2.242	0.982	0.917	91	91	89	20	17	4.06E-7	> 1.11E-5	> 1.11E-5
DU-145	0.339	1.506	1.583	1.586	1.565	0.414	0.308	107	107	105	6	-9	4.01E-7	2.87E-6	> 1.11E-5
Breast Cancer															
MCF7	0.232	1.327	1.260	1.181	0.729	0.340	0.315	94	87	45	10	8	8.59E-8	> 1.11E-5	> 1.11E-5
MDA-MB-231/ATCC	0.732	1.671	1.687	1.704	1.704	1.248	0.901	102	104	104	55	18	1.51E-6	> 1.11E-5	> 1.11E-5
HS 578T	1.208	2.361	2.268	2.208	2.201	1.451	1.030	92	87	86	21	-15	3.99E-7	4.30E-6	> 1.11E-5
BT-549	0.991	2.175	2.124	1.966	1.963	1.419	1.081	96	82	82	36	8	5.53E-7	> 1.11E-5	> 1.11E-5
T-47D	0.773	1.431	1.421	1.368	1.391	1.017	0.982	98	90	94	37	32	6.58E-7	> 1.11E-5	> 1.11E-5
MDA-MB-468	0.780	1.360	1.346	1.360	1.321	0.696	0.644	98	100	93	-11	-18	2.89E-7	8.73E-7	> 1.11E-5

NCI-60 Five Dose Results **1.07**: Compound **1.43**

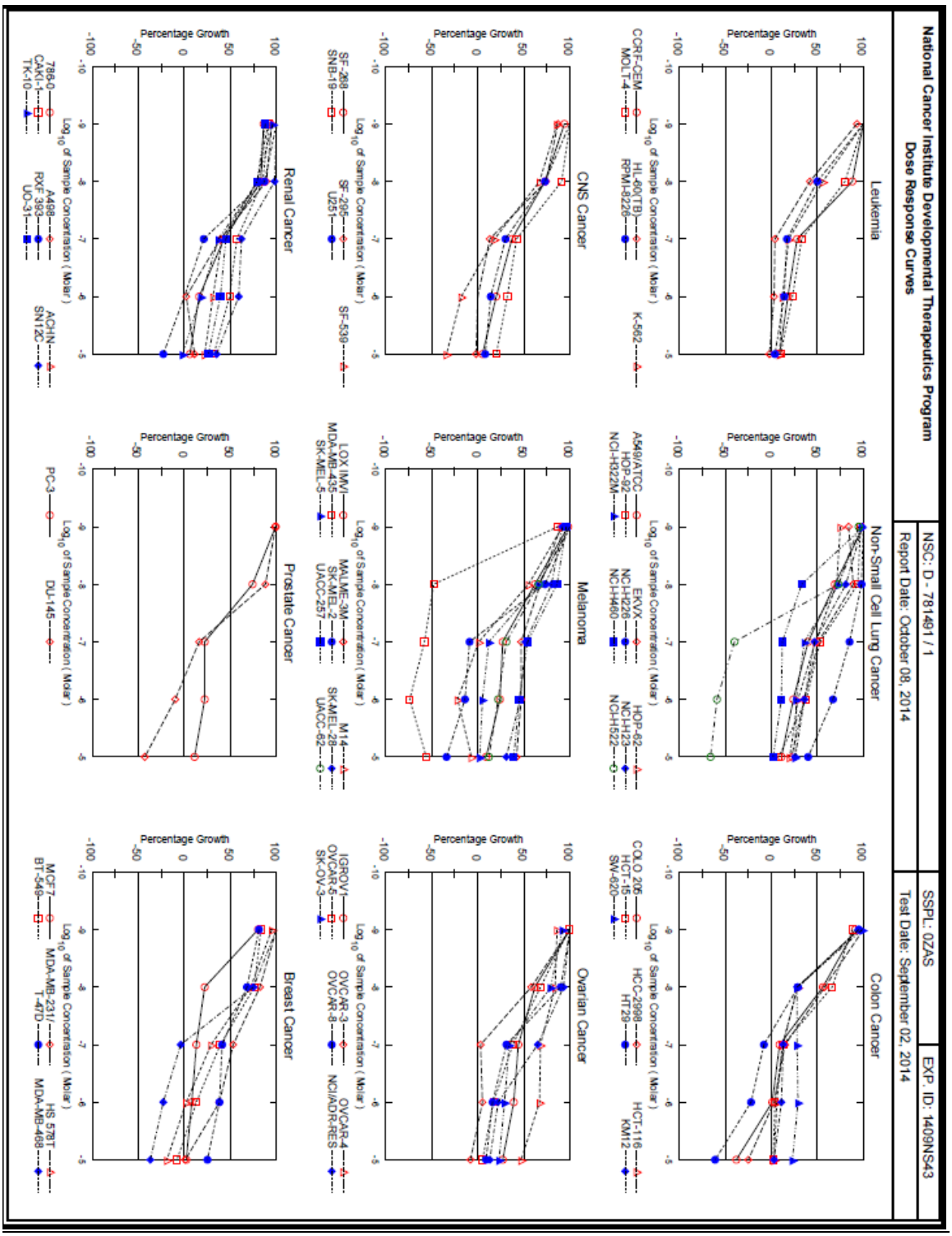
6. NCI-60 Dose-Response Curves for **1.37**–**1.43**



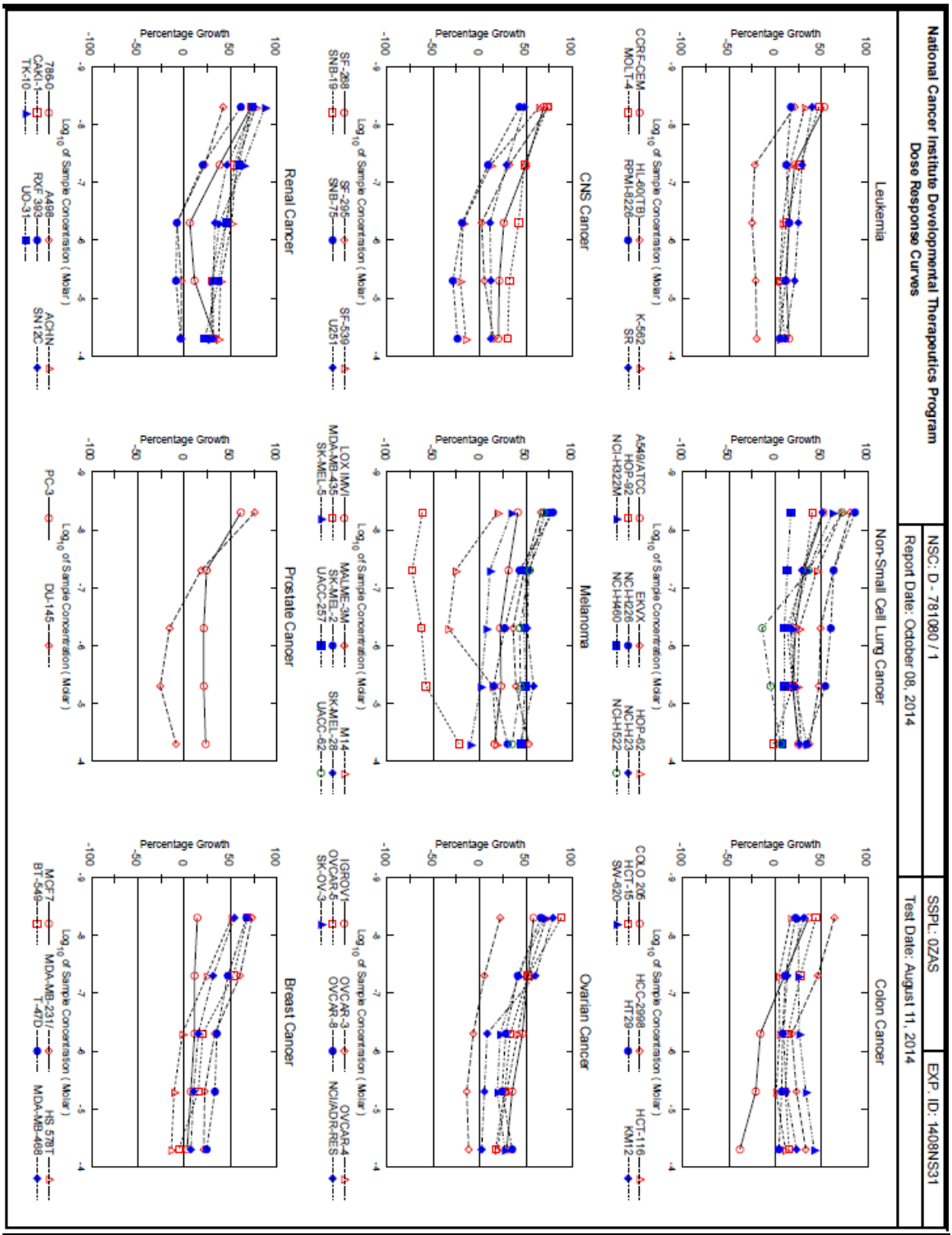
NCI-60 Dose Response Curve **1.01**: Compound **1.37**



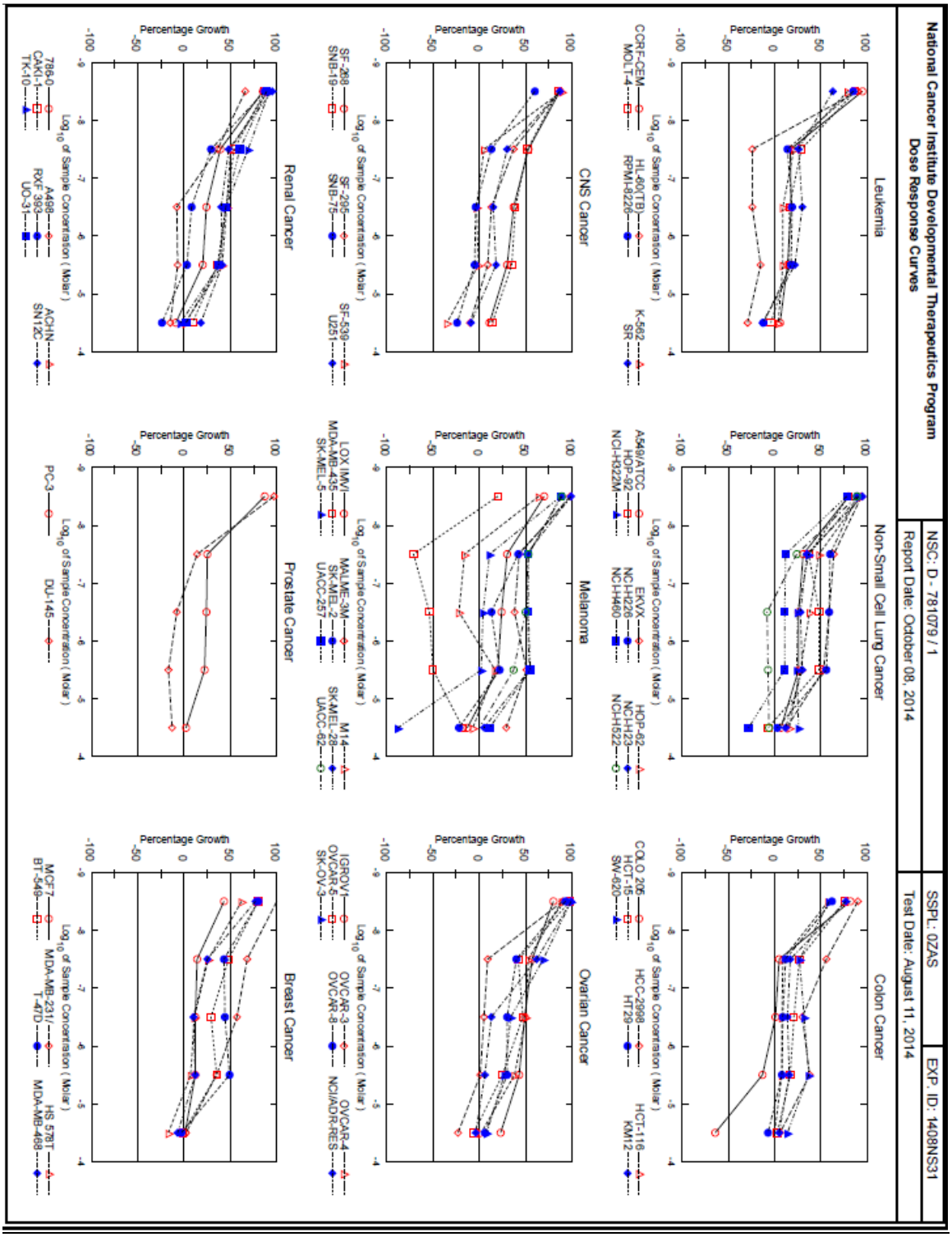
NCI-60 Dose Response Curve **1.02**: Compound **1.38**



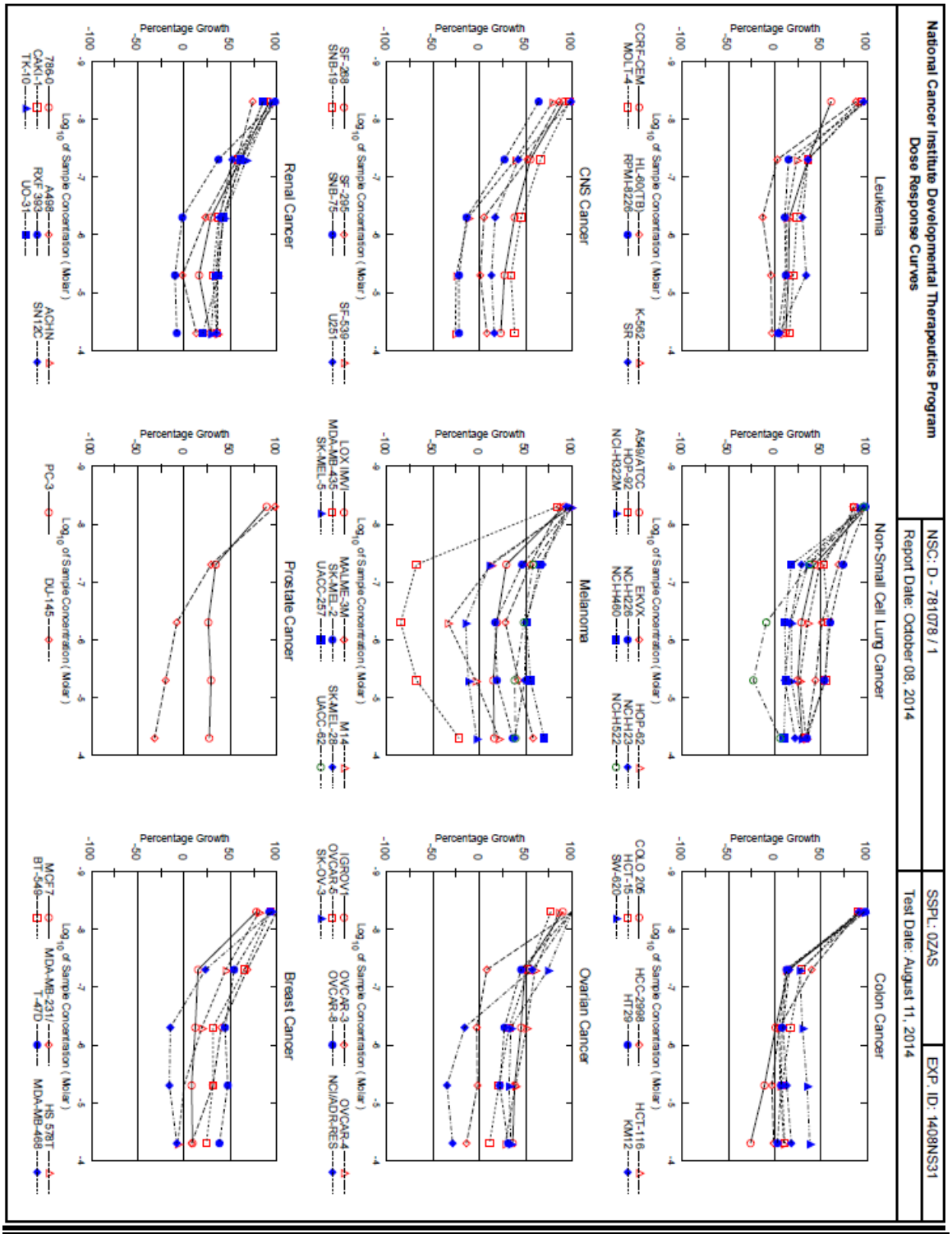
NCI-60 Dose Response Curve **1.03**: Compound **1.39**



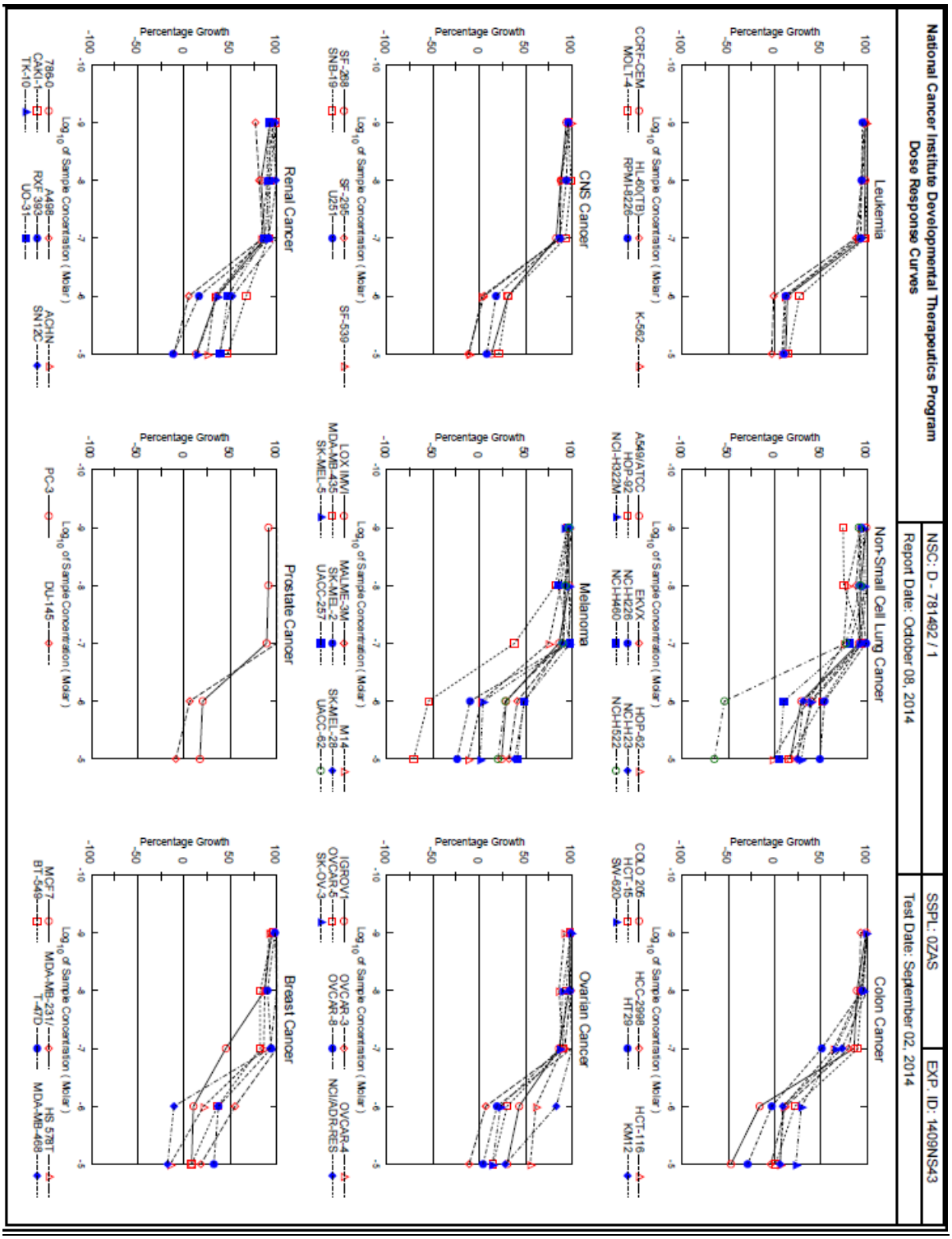
NCI-60 Dose Response Curve **1.04**: Compound **1.40**



NCI-60 Dose Response Curve **1.05**: Compound **1.41**



NCI-60 Dose Response Curve **1.06**: Compound **1.42**



NCI-60 Dose Response Curve **1.07**: Compound **1.43**

Chapter 1 is a partial reprint of the material as it appears in "Synthesis and Biological Evaluation of Novel Epothilone B Side Chain Analogues, K.C. Nicolaou, D. Rhoades, Y. Wang, S. Totokotsopoulos, R. Bai, E. Hamel, *ChemMedChem* **2015**, *10*, 1974–1979 (D. Rhoades did all of the synthetic chemistry)." Chapter 1 is also a partial reprint of material that has yet to be published, with K.C. Nicolaou, Y. Wang, R. Bai, and E. Hamel as co-authors (D. Rhoades and Y. Wang equally contributed to all of the synthetic chemistry).

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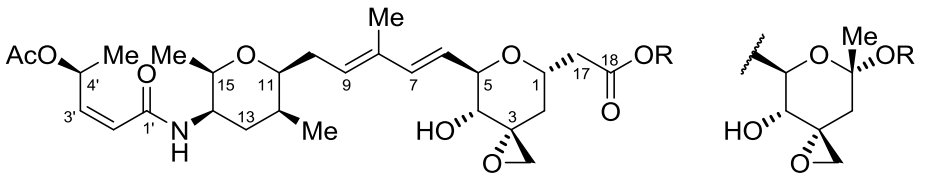
Chapter 2: Total Synthesis of Thailanstatin A

A. Introduction

1. Isolation



2.01: thailanstatin A (R = H)
2.02: thailanstatin A methyl ester (R = Me)
2.03: FR901464 (R = H)
2.04: spliceostatin A (R = Me)

Figure **2.01**: Molecular structures of thailanstatin A (**2.01**), its methyl ester (**2.02**), and structurally related eastern fragment congeners FR901464 (**2.03**) and spliceostatin A (**2.04**).

Thailanstatin A (**2.01**, Figure **2.01**) is a recently described polyketide natural product with fascinating biological properties and exceptional clinical potential as an anticancer agent. Isolated in 2013 by Cheng and co-workers as a result of elegant genome mining and cultivation studies of *Burkholderia thailandensis* MSMB43,[1] its identification was greatly assisted by biosynthetic and genomics studies of **2.03** and its congeners, which allowed for the identification of the gene cluster that produces **2.01** *via* transcriptional analysis. Shortly thereafter, a collaboration between Pfizer, Novartis, and the NCI branch of the NIH identified a bacterial strain that produces larger quantities of **2.01**; they also embarked on semisynthetic studies and reported other related compounds, referred to collectively as spliceostatins (due to their mechanism of action, *vide infra*), some of which are depicted in Figure **2.02**; interestingly, it was found that carboxylic acid derivatives such as an amide or methyl ester (**2.02**, Figure **2.01**) improve the potency of the compound by enhancing its cellular membrane permeability.[2] The improved stability of **2.01** versus **2.03** and **2.04** (which possess hemiacetal and acetal moieties, respectively) has made it an

attractive target for drug discovery. Indeed, the fervently expanding research endeavors involving **2.01**, from both academic institutions and major players in the pharmaceutical

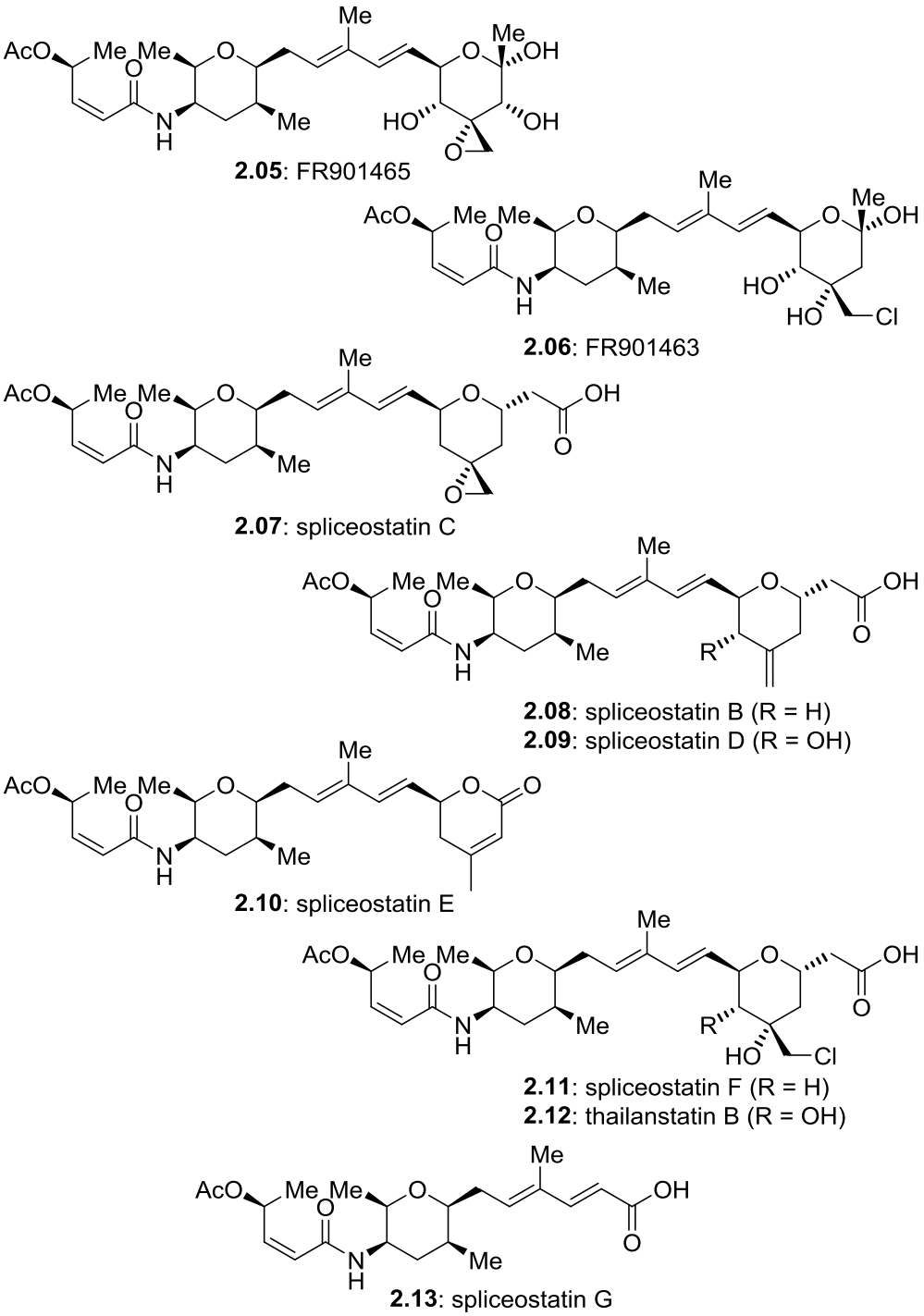


Figure **2.02**: Molecular structures of **2.05**–**2.13**, generally referred to as spliceostatins.

industry, is testament to the vast promise that this molecule (or designed analogues thereof) holds as a novel antiproliferative treatment. Shortly after the initial isolation report, we decided to pursue the total synthesis of **2.01**, with the goals of providing substantial amounts of material from cheap, commercially available resources. Furthermore, we envisioned that a modular synthetic route capable of producing a wide array of designed analogues would be critical for fueling an effective medicinal chemistry effort that can serve as a complementary approach *vis-à-vis* semisynthesis. Thus, we began to investigate a convergent total synthesis of **2.01**, starting with a review of the biosynthetic pathway of the natural product to obtain inspiration for possible key transformations.

2. Biosynthesis and Fermentation

As aforementioned, previous biosynthetic investigations of the bioactive congener FR910464 (**2.03**, Figure **2.01**) provided the biological tools necessary for the successful isolation and cultivation of thailanstatin A (**2.01**, Figure **2.01**). The amagalmation of these

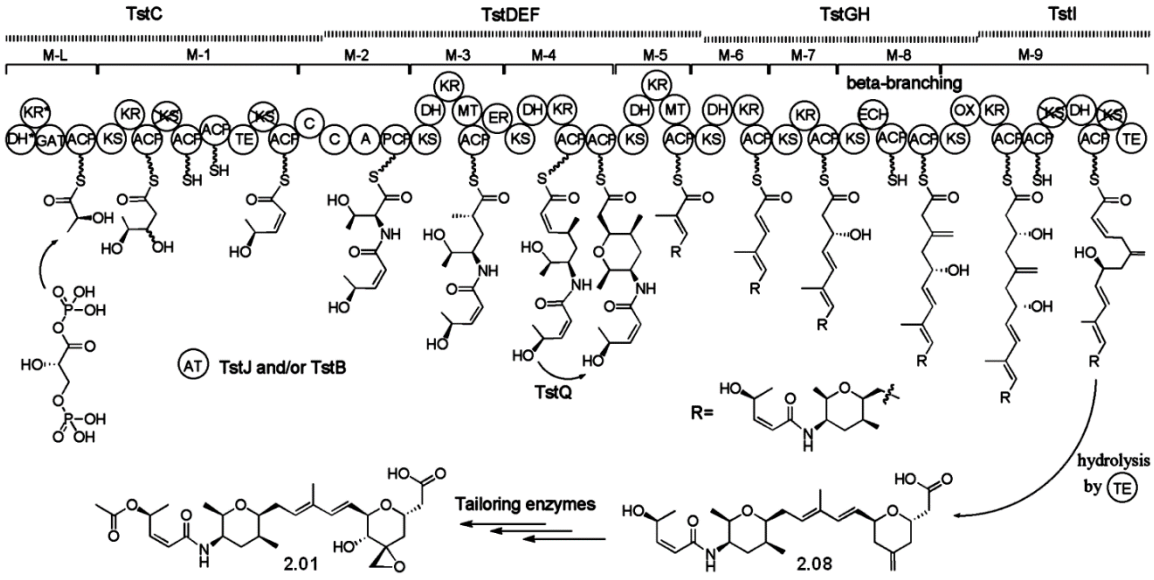


Figure **2.03**: Proposed biosynthesis of **2.01** *via* a hybrid PKS/NRPS superenzyme family. Hydroxylation and epoxidation of the eastern tetrahydropyran moiety, as well as acetate placement on the (*Z*) allylic alcohol side chain, is proposed to occur at a later stage from spliceostatin B (**2.08**).

various biosynthetic and genetic analyses have culminated in a fairly comprehensive proposed biosynthesis for **2.01** (Figure **2.03**),[3] which largely involves the well known PKS superenzyme family; however, like the epothilones, it also possesses a NPRS component and is thus a hybrid.[4] Further analysis and refinement of this biosynthetic pathway by Pfizer led to a highly optimized fermentation route capable of producing **2.01** in an impressive 2.5g/L batch quantity.[5] Based on their heavy investment utilizing this fermentation-based strategy, it is likely that Pfizer has at least one (if not several) compounds currently in pre-clinical stages.

3. Mechanism of Action and Clinical Relevance

The primary driving force behind the current zeal engulfing this family of natural products lies with their unique mechanism of action as a highly potent inhibitor of the splicesome (hence the name spliceostatin). The splicesome is a highly complex molecular machine that is responsible for the processing of pre-messenger RNA (pre-mRNA) prior to its translation into target proteins. Specifically, the spliceosome binds to and site-specifically excises introns that separate exons, removes the intron as a lariat (*i.e.* a

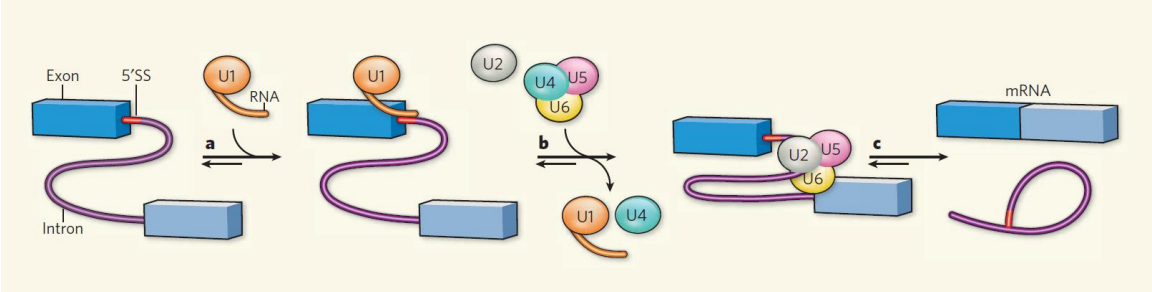


Figure **2.04**: General description of pre-mRNA splicing. A: The U1 snRNA binds to the 5′ splice site (5′SS), forming a U1-intron complex. B: The remaining spliceosome components (U2, U4–U6) assemble around the U1-intron complex, U1 and U4 are displaced, forming the catalytically active spliceosome complex. C: The splicesome removes the intron as a lariat, and splices combines the two previously distant exons to produce mRNA that is ready for translation.

discarded byproduct of RNA splicing), and religates the exons together to form a functional mRNA prior to translation.[6] This process is fundamentally explained in Figure **2.04**.[7] When the human genome project was first completed, even the world's leading geneticists were surprised by the relatively small number of human genes that exist, given the very large number of proteins that are produced by humans. In other words, the size of the human genome is substantially smaller than the size of the human proteome; this was a resounding moment in molecular biology in the sense that the spliceosome was found to play a massive role in effectively expanding the human genome, to a significantly higher degree than previously thought.[8] Since cancer cells tend to elicit higher mutation rates in their respective spliceosomes versus healthy cells, a potent spliceosome inhibitor could represent a first-in-class mechanism of action as a novel chemotherapeutic.[9] Since the spliceosome is complicit in a wide variety of cellular processes, small molecule inhibitors also have clinical potential beyond the realm of antineoplastic agents. For example, **2.01** has elicited beneficial effects in a glucocorticoid-induced model of glaucoma and thus **2.01** or related compounds may provide therapeutic benefit for this debilitating ophthalmogic disease, which is a prominent cause of blindness in the world.[10]

A very recent example of **2.01** in ADC development, which caught our attention immediately since our group is interested in the synthesis of potential payloads for ADCs,

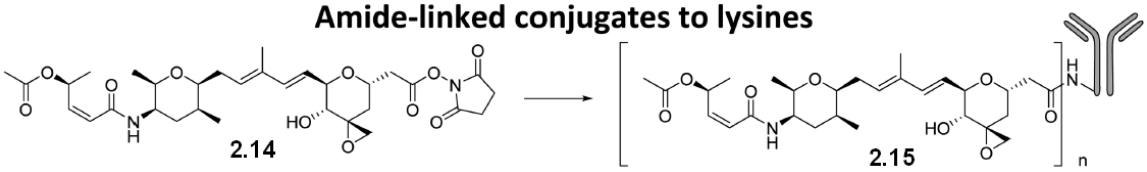


Figure **2.05**: Bioconjugation of a succinimide-activated thailanstatin A (**2.14**) to generate a trastuzumab conjugate *via* amide bond formation with lysine residue(s) of the antibody itself.

was reported *ca.* six weeks after our publication of the total synthesis of **2.01**; Pfizer unsurprisingly (due to their previously mentioned thorough investigations of the biosynthesis of **2.01**, *vide infra*) published an ADC with natural **2.01** as the cytoxic payload (Figure **2.05**).[11] Perhaps the most intriguing aspect of this study was the demonstration that the carboxylic acid functionality, activated as an *O*-succinimide (**2.14**, Figure **2.05**) could be directly attached to lysine residues of the antibody itself (**2.15**, Figure **2.05**), thereby forgoing any type of linker whatsoever.

Although **2.01** already enjoys major attention from pharma, the vast majority of studies aimed toward pushing it into the clinical setting relies soley on the aforementioned fermentation-based approach. While this can certainly provide enough material for pre-clinical investigations and human clinical trials, the molecular scaffold of **2.01** is quite limited from a semisynthetic standpoint. For example, the *exo*-methylene epoxide is a sensitive functional group, rendering many traditional synthetic manipulations incompatible. In addition, the secondary (*Z*)-allylic acetate is susceptible to hydrolysis under basic conditions. Lastly, the presence of its nine stereocenters, which are virtually impossible to invert or otherwise change, represent a very specific component of chemical space, and semisynthesis does not offer reasonable solutions for expanding or further exploring the chemical space that is privileged for splicesome inhibition. Taken together, we considered the development of a concise total synthesis of **2.01** programmed with convenient points of divergence in order to provide designed compounds with improved drug-like properties for the identification of potential lead compounds for drug development purposes, especially ones suited for ADC production or related selective drug delivery apparatuses.

B. Total Synthesis of Thailanstatin A

1. Retrosynthetic Analysis

Figure **2.06** shows the retrosynthetic analysis planned for the total synthesis of **2.01**. An obvious initial disconnection to obtain optimal synthetic convergence is the diene linker between the two, highly functionalized tetrahydropyran moieties. We chose to employ the

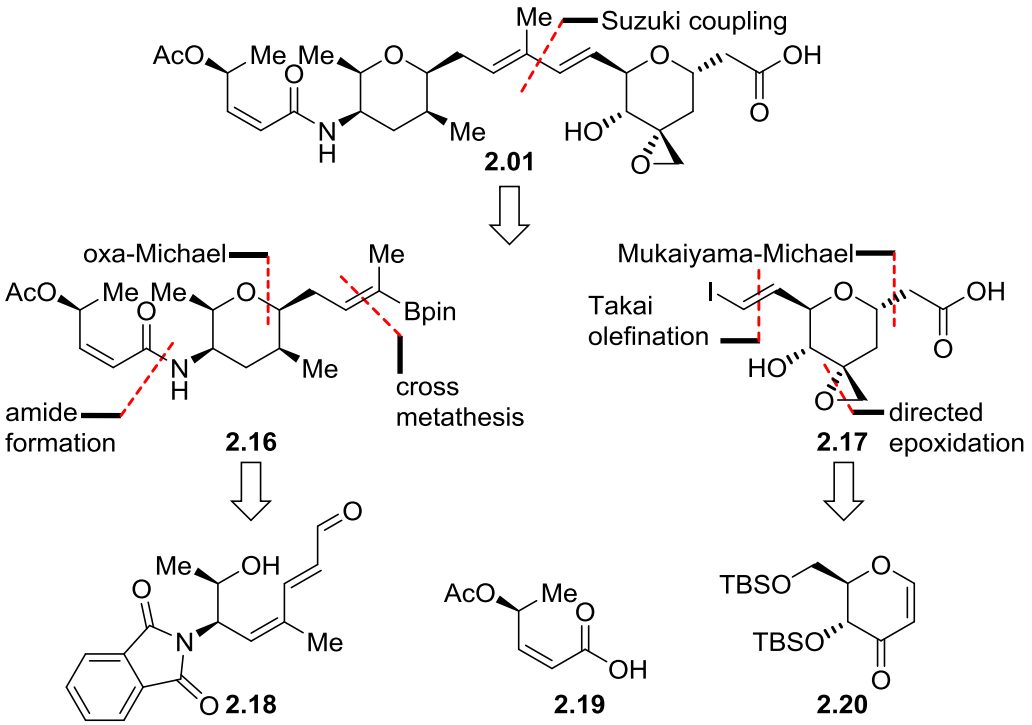


Figure **2.06**: Retrosynthetic analysis of **2.01** through advanced tetrahydropyrans **2.16** and **2.17**, and key building blocks **2.18**–**2.20**, respectively.

Suzuki coupling for this transformation due to its historical reliability, proven track record for preserving the olefin geometry of the coupling product (*i.e.* not causing olefin isomerization), and the relatively benign nature of the chemical components. Although the related Stille coupling is valuable, it is not preferable for the last step of the synthesis of natural products and/or analogues that are to be subsequently evaluated biologically.[12]

Importantly, the previously reported syntheses of thailanstatin A congeners **2.03**, **2.04**, and **2.10** utilized either: a highly moisture and functional group sensitive hydrozirconation/Negishi coupling, a poor yielding (and isomerization-prone) cross metathesis, or a Julia olefination under strongly basic conditions.[13, 14] In contrast, our choice of the Suzuki coupling allows it to be the final step, with no deprotections or additional manipulations necessary. Since we intended to design a route conducive to analogue development, we surmised that the Suzuki coupling is the ideal reaction to depend on when repeating a final coupling steps several times with structurally different starting materials.

Further disconnection of **2.16** at the amide linkage (amide bond formation), the vinyl boronate olefinic bond (cross metathesis), and the tetrahydropyran system (oxa-Michael reaction) as indicated in Figure **2.06** revealed doubly conjugated hydroxy aldehyde **2.18** and acetoxy carboxylic acid **2.19** as potential key building blocks. Disassembly of **2.17** at the vinyl iodide (Takai olefination), epoxide (directed epoxidation) and tetrahydropyran (Mukaiyama–Michael reaction) sites traced this advanced intermediate back to the known and readily available pyranone **2.20** as a starting material.

2. Biosynthetic Inspiration

For the synthesis of the 2,3,5,6-tetrasubstituted tetrahydropyran ring embedded within intermediate **2.16**, we were inspired by the proposed biosynthesis of **2.01** (Figure **2.07**), which involves an intramolecular oxa-Michael reaction of an ACP-bound *α*,*β*-unsaturated thioester of a PKS complex.[1,4] However, in an effort to preserve atom and step economy,[15] and in order to establish a foundation for a diastereodivergent approach to highly functionalized tetrahydropyrans, we sought to explore the asymmetric

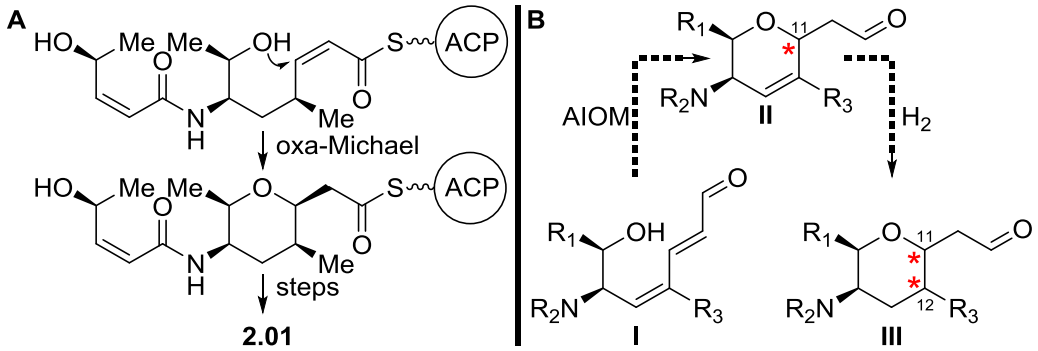
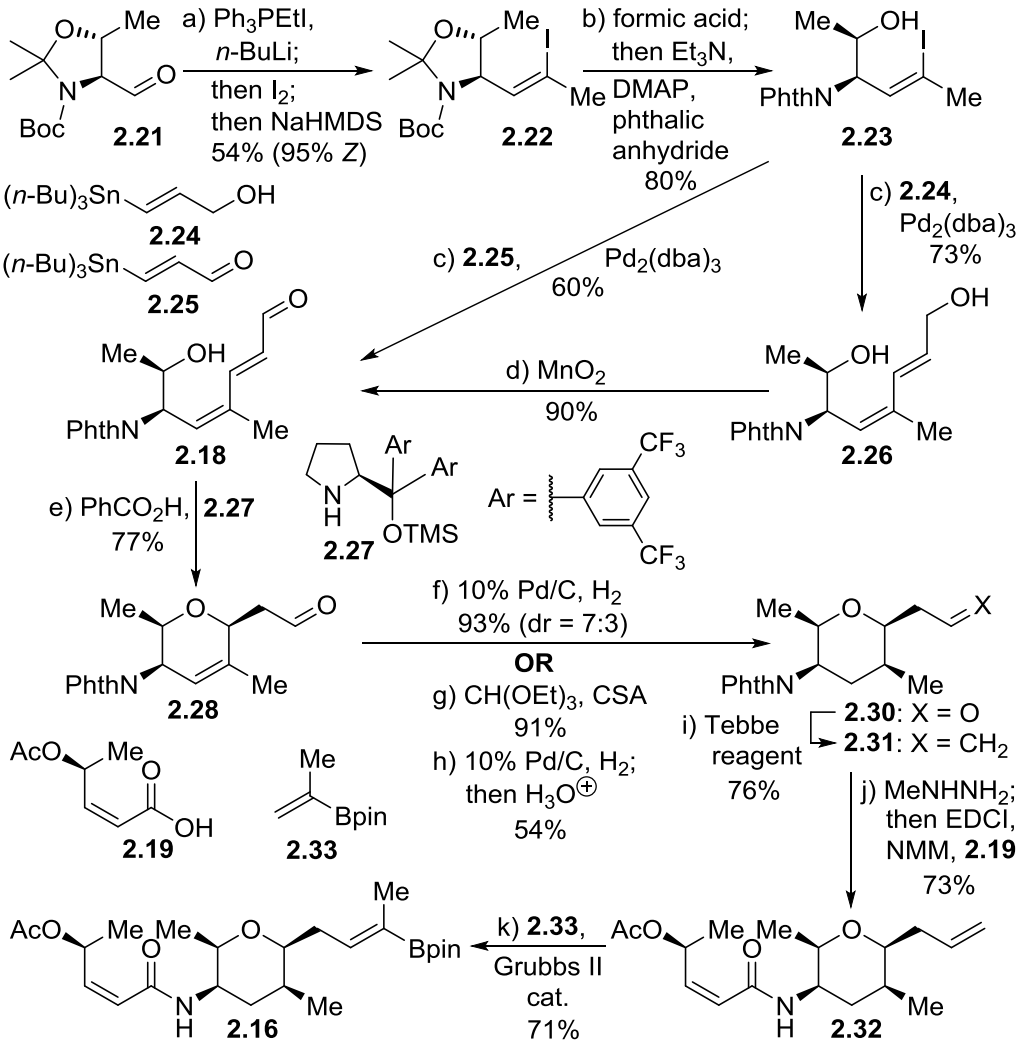


Figure **2.07**: A: Proposed biosynthetic formation of the tetrasubstituted tetrahydropyran system of thailanstatin A (**2.01**) through an oxa-Michael reaction. B: Proposed diastereodivergent approach to tetrasubstituted dihydropyrans **II** from *α*,*β*,*γ*,*δ*-unsaturated aldehyde **I** through asymmetric intramolecular oxa-Michael (AIOM) reaction and tetrasubstituted tetrahydropyrans **III** from **II** *via* hydrogenation.

intramolecular oxa-Michael (AIOM) reaction[16] with an unprecedented substrate possessing an additional degree of unsaturation, *i.e.* an *α*,*β*,*γ*,*δ*-unsaturated aldehyde (**I**, Figure **2.07**). If successful, this scenario would constitute an entry to 2,6-*syn* or 2,6-*anti* tetrasubstituted dihydropyrans **II** (Figure **2.07**) in a diastereoselective manner *via* catalyst control. Furthermore, subsequent substrate-controlled hydrogenation could allow access to tetrasubstituted tetrahydropyrans **III** (Figure **2.07**) with defined stereochemistry at C11 and C12, respectively.

3. Synthesis of Western Fragment

The synthesis of vinyl boronate **2.16** from Garner aldehyde **2.21**[17] is summarized in Scheme **2.01**. Thus, *α*-methyliodomethylenation of **2.21** under Stork–Zhao conditions[18] furnished olefinic iodo-Boc derivative **2.22** (54% yield, *Z*:*E ca*. 95:5, chromatographically separated) from which the desired iodo-Phth derivative **2.23** was generated by protecting group exchange (formic acid; then phthalic anhydride, Et_3N, DMAP cat.) in 80% overall yield. Interestingly, the use of $CHCl_3$ as the solvent proved crucial for preventing the undesired E2-type elimination of the iodine atom to form a methyl alkyne. Stille coupling

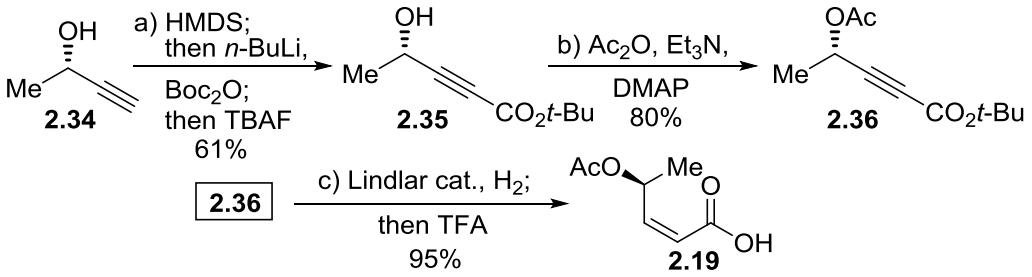


Scheme **2.01**: Synthesis of vinyl boronate **2.16**.

of **2.23** with hydroxy stannane **2.24**[19] [$Pd_2(dba)_3$, 73% yield] led to dienol **2.26**, whose MnO_2 oxidation afforded the desired (*E*,*Z*)-*α*,*β*,*γ*,*δ*-unsaturated aldehyde **2.18** in 90% yield.The same aldehyde (**2.18**) could also be obtained in one step directly from vinyl iodide **2.23** and aldehyde stannane **2.25**[20] through Stille coupling [$Pd_2(dba)_3$, 60% yield]. Exposure of **2.18** to diaryl prolinol catalyst **2.27**[21] (0.2 equiv) in the presence of benzoic acid (0.2 equiv) in CH_2Cl_2 induced the desired asymmetric intramolecular oxa-Michael reaction, providing 2,6-*syn* dihydropyran **2.28** in 77% yield (dr > 20:1). Aldehyde **2.28**

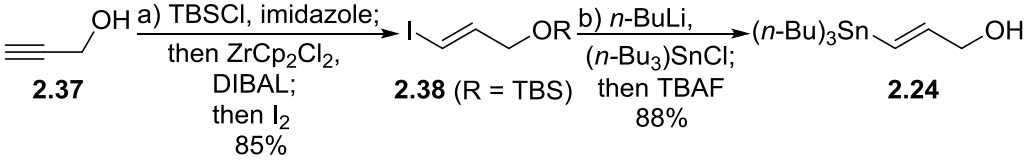
proved to be a challenging substrate for the subsequent hydrogenation reaction, in terms of both chemoselectivity as well as diastereoselectivity. Optimal results were achieved by masking the aldehyde moiety as a diethoxy acetal [**2.29**, $CH(OEt)_3$, CSA, 91% yield]. It was found that stereoselective hydrogenation from the *α* face of the ring system could be achieved with 10% Pd/C in ethanol under a H_2 atmosphere at high pressure (80 bar) to afford 2,3,5,6-*syn* tetrahydropyran **2.30** (54% yield) after mild aqueous acidic workup. Remarkably, however, and after extensive experimentation, it was discovered that aldehyde **2.28** could be efficiently hydrogenated directly (H_2, 80 bar) in excellent yield with 10% Pd/C in hexafluoroisopropanol (HFIP) solvent, albeit with modest diastereoselectivity (93%, 7:3 dr, 65% yield for **2.30**). Methylenation (Tebbe reagent) of saturated aldehyde **2.30** provided olefin **2.31** in 76% yield. Rupture of the phthalimide moiety within the latter with methylhydrazine, followed by direct amide coupling with carboxylic acid **2.19**[13a] (EDCI, NMM) led to amide **2.32** (73% yield), an advanced intermediate reported in the synthesis of FR901464.[13d] Cross metathesis of **2.32** with commercially available isopropenylboronic acid pinacol ester **2.33** (Grubbs II cat., $ClCH_2CH_2Cl$) afforded vinyl boronate **2.16** in 71% yield.

During the course of the synthesis of vinyl boronate **2.16**, we were able to develop new routes for building blocks **2.19** and **2.24**. Scheme **2.02** shows the new route for carboxylic acid **2.19**; this was designed to facilitate a simpler workup and purification protocol than the original method reported by Jacobsen *et al.*[13a] Therefore, commercially available (*S*)-3-butyn-2-ol **2.34** was protected *in situ* as the corresponding TMS ether, followed by lithiation, homologation (Boc_2O), and deprotection (TBAF) to afford *t*-butyl ester **2.35** in 61% yield. Acetylation (Ac_2O, Et_3N, DMAP, 80% yield) provided *bis* ester



Scheme **2.02**: Preparation of carboxylic acid **2.19** from commercially available (*S*)-3-butyn-2-ol (**2.34**).

2.36, an intermediate that is easy to handle and purify, in contrast to previously reported methods. Lindlar reduction proceeded smoothly to deliver the (Z) olefin, and final treatment with TFA furnished acid **2.19** (95% yield). Scheme **2.03** describes a new, convenient route to the very common allylic alcohol stannane **2.24** from commercially available propargyl alcohol (**2.37**). Although this compound can be synthesized in one step



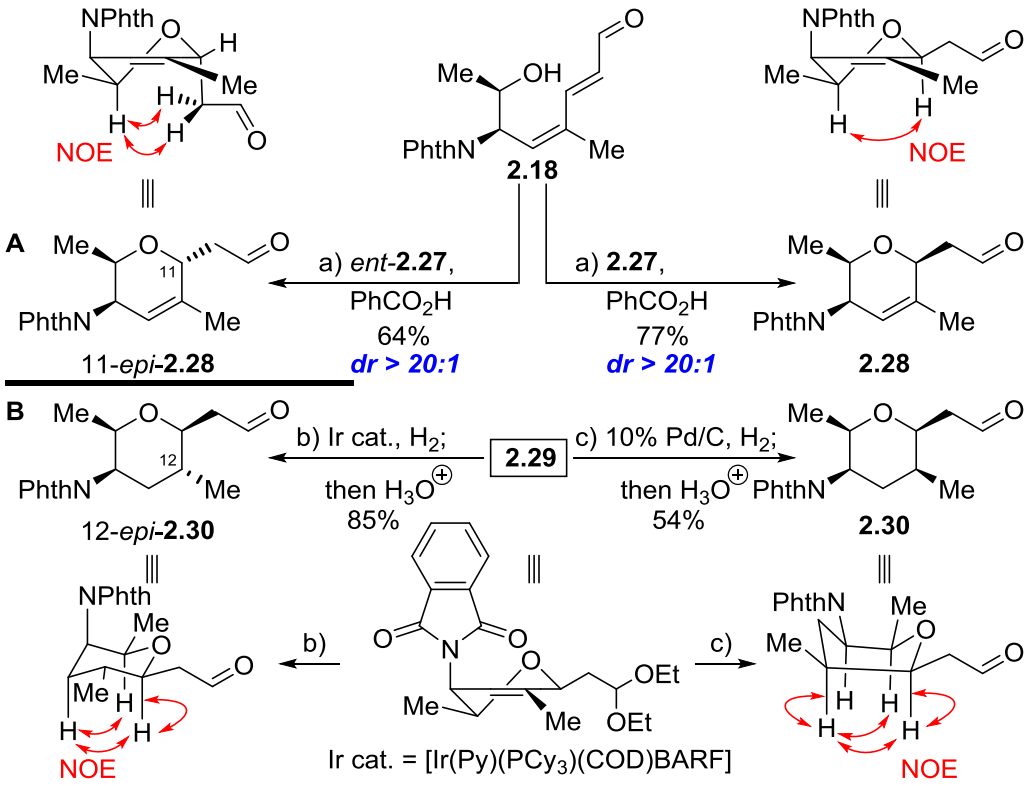
Scheme **2.03**: Convenient new synthesis of allylic alcohol stannane **2.24** from propargyl alcohol (**2.37**).

from **2.37** using either AIBN or Pd(0) and (n-Bu)$_3$SnH,[19, 22] these reactions suffer from incomplete regioselectivity, as well as mixtures of olefin isomers. This often requires tedious, and many times multiple, chromatographic purifications, a highly undesirable event, especially when handling multigram quantities of trialkyl tin reagents. As a practical solution, we opted to protect **2.37** as the silyl ether (TBSCl, imidazole, quant.) and, after a quick filtration through a silica plug, protected **2.37** was subjected to a hydrozirconation/iodination sequence utilizing the *in situ* generated Schwartz reagent ($ZrCp_2Cl_2$, DIBAL)[23] to afford vinyl iodide **2.38** in a regiospecific (*i.e. E* selective) manner.

Lastly, lithium-halogen metal exchange, (n-Bu)$_3$SnCl quench, and treatment of the crude material with TBAF provided **2.24** in a very clean fashion. Our group has used this route for this project (and others now) to reliably produce **2.24** in quantities of 20–30 grams with the critical benefit of a facile purification and no detectable undesired byproducts.

4. Discovery of a Diastereodivergent Route for Accessing Highly Functionalized Tetrahydropyrans *via* a Novel Oxa–Michael/Hydrogenation Sequence

Amidst our exploration of the oxa-Michael reaction of aldehyde **2.18**, it was discovered that the reaction displays an unusually high degree of catalyst control, especially as compared with typical AIOM reactions, in which α,β-unsaturated aldehydes, esters, and amides generally favor the 2,6-*syn* tetrahydropyran product.[16] Elegant studies by Hong have also shown that olefin geometry (*i.e.* *E* or *Z* α,β-unsaturated aldehydes) can render AIOM reactions stereoselective as a consequence of substrate control, while catalyst control alone is rarely useful for high levels of 2,6-*anti* stereoselectivity.[24] As depicted in Scheme **2.04**A, we found that 2,6-*syn* dihydropyrans **2.28** or 2,6-*anti* dihydropyran 11-*epi*-**2.28** (half-chair structures confirmed by NOESY, see Section D details) could be accessed in comparable yields with virtually complete stereoselectivity, based solely on catalyst control. In addition, complementary stereoselectivity for the hydrogenation of acetal substrate **2.29** could be achieved under specific reaction conditions. Thus, as shown in Scheme **2.04**B, treatment of **2.29** with [Ir(Py)(PCy$_3$)(COD)BARF] catalyst,[25] a counteranion analogue of Crabtree's catalyst, in CH_2Cl_2 under 1 atm of H_2 cleanly provided 12-*epi*-**2.30** after workup with dilute acid. Delivery of hydrogen to the β face of **2.29** was likely facilitated by the O atom(s) of the acetal and/or the imide carbonyl O atom(s). In

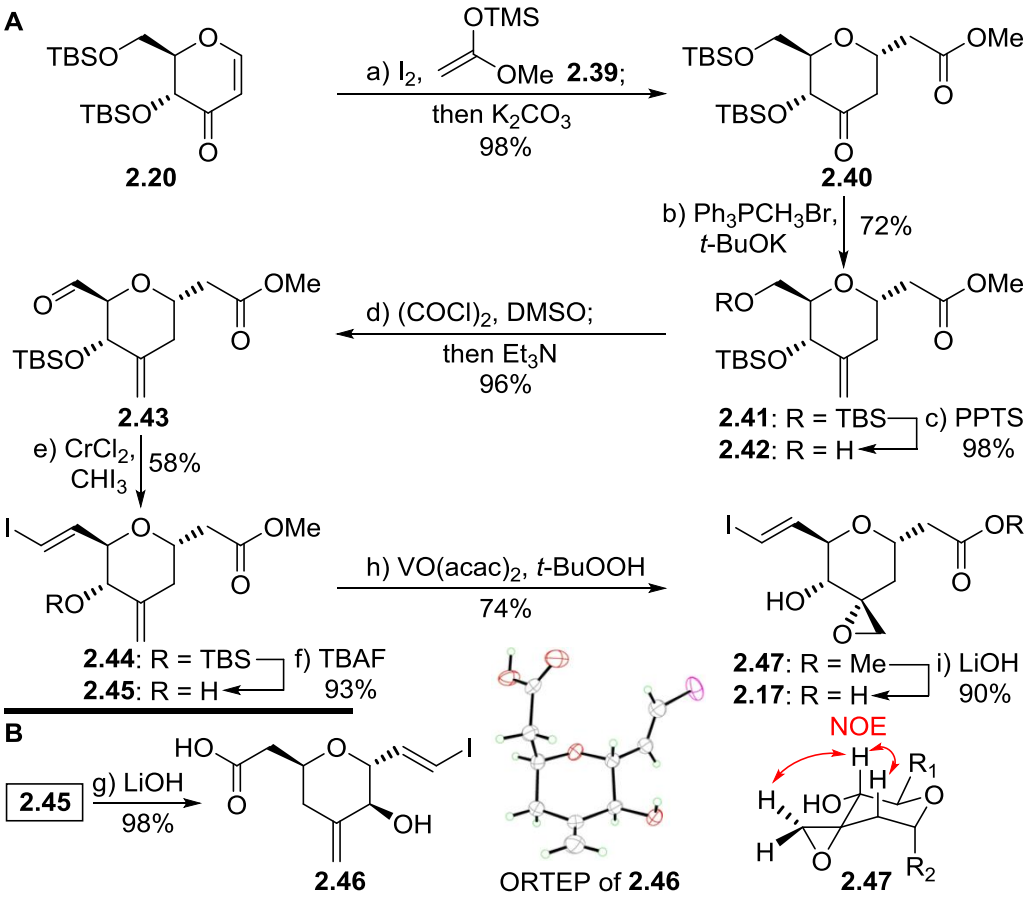


Scheme **2.04**: Diastereodivergent synthesis of 2,3,5,6-tetrasubstituted tetrahydropyrans.

contrast, use of heterogeneous conditions led to **2.30**, the product of H_2 delivery to the α face of **2.29**, as dictated by the hindered nature of its β face. The relative configurations of **2.30** and 12-*epi*-**2.30** were confirmed by NOESY studies, which also revealed a chair conformation for 12-*epi*-**2.30** and a boat conformation for **2.30** (due to the large 1,3 diaxial interaction between the bulky *N*-phthaloyl moiety and the adjacent axial methyl group, see section D for details). This AIOM/hydrogenation approach may prove useful as a general method for the synthesis of highly substituted tetrahydropyrans.

5. Synthesis of Eastern Fragment

The syntheses of key vinyl iodide building blocks **2.17** and **2.47** are summarized in Scheme **2.05**A. Thus, pyranone derivative **2.20**[26] was reacted with ketene silyl acetal **2.39**



Scheme **2.05**: Synthesis of vinyl iodides **2.17** and **2.47**.

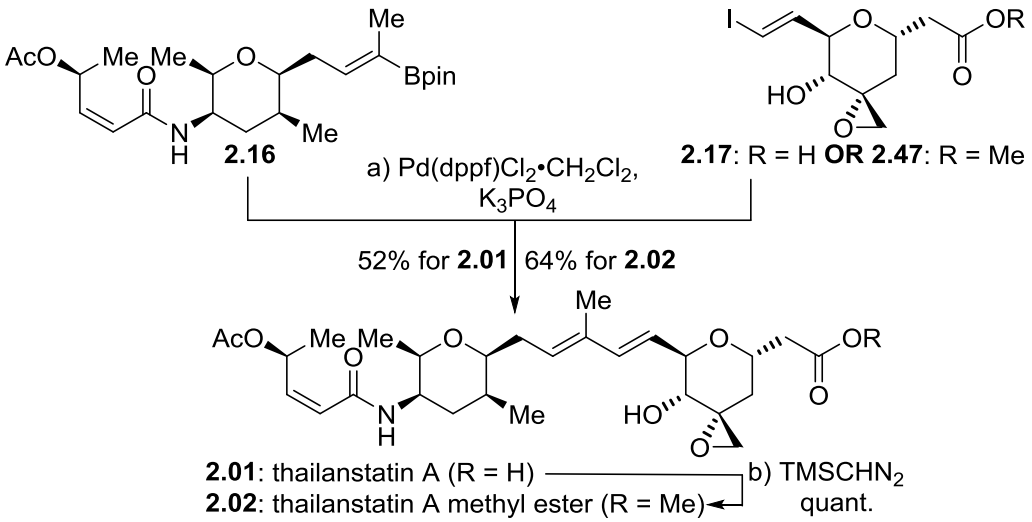
in the presence of iodine to afford stereoselectively, after treatment with methanolic K_2CO_3, ketone methyl ester **2.40** in 98% yield on a 10 gram scale.[27] Wittig reaction of the latter with the ylide derived from the phosphonium salt of MeBr and *t*-BuOK yielded terminal olefin **2.41** (72% yield), whose conversion to aldehyde **2.43** was achieved by selective monodesilylation (PPTS, 98% yield) followed by Swern oxidation [$(COCl)_2$, DMSO; Et_3N, 96% yield] of the resulting primary alcohol (*i.e.* **2.42**).[12] Takai olefination ($CrCl_2$, CHI_3)[28] of aldehyde **2.43** then led to the desired (*E*)-vinyl iodide **2.44** in 58% yield. Desilylation of the latter (TBAF, 93% yield) furnished allylic alcohol **2.45**. Saponification of **2.45** (LiOH) provided acid **2.46** as a crystalline solid (m.p. = 128–136 °C, EtOAc). X-

Ray crystallographic analysis (see ORTEP in Scheme **2.05**B and section D for details) unambiguously confirmed the 2,6-*anti* configuration of the tetrahydropyran ring system. Directed epoxidation of **2.45** with *t*-BuOOH and $VO(acac)_2$ cat. delivered the targeted epoxy methyl ester **2.47** (74% yield), whose NOESY analysis confirmed its relative stereochemistry (Scheme **2.05**B, see section D for details).[29] Subsequent conversion of methyl ester **2.47** to carboxylic acid **2.17** was accomplished through the action of LiOH (90% yield).

6. Completion of the Total Synthesis of Thailanstatin A

Scheme **2.06** depicts the final coupling of vinyl iodides **2.17** and **2.47** with vinyl boronate **2.16** to afford the desired targets **2.01** and **2.02**, respectively. At first, methyl ester **2.02** was obtained through Suzuki coupling utilizing $Pd(PPh_3)_4$ cat. and Tl(OEt) as the base.[30] While the reaction was completed quickly (< 15 min, 25 °C), the basic thallium(I) salts caused significant decomposition, presumably due to epoxide and acetate ruptures. To circumvent this problem, the more stable $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ complex was used with K_3PO_4 as the base in a biphasic system to deliver thailanstatin A (**2.01**) and its methyl ester **2.02** (64% yield), respectively. Despite our efforts to purify **2.01** by standard chromatographic techniques, we were relegated to employing semipreparative HPLC for its purification (see section D for details). The yield was approximated by treatment of crude **2.01** with $TMSCHN_2$ to generate chromatographically stable methyl ester **2.02** (52% overall yield).

The high convergency of the developed synthetic strategy amounts to a rapid and efficient synthesis of thailanstatin A (**2.01**) and its congeners, while the stereochemical divergency of the method to produce tetrasubstituted tetrahydropyrans bodes well for its



Scheme **2.06**: Completion of the total synthesis of thailanstatin A (**2.01**) and its methyl ester (**2.02**).

application to the construction of a variety of designed analogues within this family of bioactive molecules for biological evaluation. Such studies may lead to the identification of useful biological tools and potential drug candidates to be developed as anticancer drugs or employed as payloads for ADCs or other cancer cell selective delivery systems for the purposes of targeted and personalized cancer therapies.

C. Future Directions & Conclusions

1. Future Directions

Further development of this synthetic route to achieve a library of novel analogues with desirable drug-like properties is ongoing. New collaborations with groups in industry and academia are currently being formed, and it is anticipated that potential lead compounds can be generated in sufficient quantities to explore the utility of this natural product family to its fullest potential. If an exceptional lead compound can be identified, our collaborators can develop novel ADCs or other selective drug delivery systems for the purpose of ushering in a new era of potent, effective, and safe chemotherapeutics.

2. Conclusions

The total synthesis of the spliceosome inhibitor thailanstatin A (**2.01**) has been achieved in a longest linear sequence of nine steps from readily available starting materials. A key feature of the developed synthetic strategy is the implementation of a unique, biomimetic asymmetric intramolecular oxa–Michael reaction/hydrogenation sequence that allows diastereodivergent access to highly functionalized tetrahydropyrans, which can be used for the synthesis of designed analogues of this bioactive molecule. From a broader perspective, this methodological realization can also be applied for the general synthesis of dihydropyrans and tetrahydropyrans, both of which are very common and useful heterocycles found in nature.

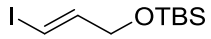
D. Experimental Section

1. General Procedures

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry acetonitrile (MeCN), diethyl ether (Et_2O), dimethylformamide (DMF), methylene chloride (CH_2Cl_2), tetrahydrofuran (THF), triethylamine (Et_3N), and toluene were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on S-2 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an acidic aqueous solution of *p*-anisaldehyde, an aqueous solution of cerium sulfate, or a basic aqueous solution of potassium permanganate and heat as developing agents. E. Merck silica gel (60, particle size 0.040 – 0.063 mm) was used for flash column chromatography. NMR spectra were recorded on a Bruker DRX-600 instrument and calibrated using residual undeuterated solvent (CD_2Cl_2: δ_H = 5.32 ppm, δ_C = 53.84 ppm; $CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm; C_6D_6: δ_H = 7.16 ppm, δ_C = 128.06 ppm) as an internal reference. The following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, qd = quartet of doublets, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddq = doublet of doublet of quartets, br = broad. Infrared (IR) spectra were recorded on a Perkin–Elmer 100 FT-IR spectrometer. High-resolution

mass spectra (HRMS) were recorded on an Agilent ESI-TOF (time of flight) mass spectrometer using MALDI (matrix-assisted laser desorption ionization) or ESI (electrospray ionization). Optical rotations were recorded on a POLARTRONIC M100 polarimeter at 589 nm, and are reported in units of 10^{-1} (deg cm^2g^{-1}).

2. Preparation of Compounds

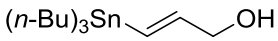


2.38

Vinyl iodide 2.38: To a stirred solution of propargyl alcohol (1.95 g, 34.7 mmol, 1.0 equiv) in CH_2Cl_2 (116 mL) was added imidazole (4.72 g, 69.4 mmol, 2.0 equiv) followed by TBSCl (7.85 g, 52.1 mmol, 1.5 equiv) at 25 °C. After 45 min, the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (75 mL), and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (25 mL), and the combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was filtered through a short silica plug, thoroughly eluted with 2% Et_2O in hexanes (350 mL), and concentrated *in vacuo*. The obtained colorless oil (5.9 g, 34.7 mmol, quant.) was used directly in the following step.

To a stirred suspension of $ZrCp_2Cl_2$ (17.2 g, 59 mmol, 1.7 equiv) in THF (30 mL) was added DIBAL (59 mL, 1.0 M THF, 59 mmol, 1.7 equiv) dropwise at 0 °C. After 30 min, a solution of TBS propargyl alcohol (5.9 g, 34.7 mmol, 1.0 equiv) in THF (35 mL) was added dropwise *via* cannula, the original flask was rinsed with additional THF (3 x 2 mL), and the reaction mixture was allowed to warm to 25 °C. After stirring for an additional 1 h, the reaction mixture was cooled to –78 °C, and iodine (16.7 g, 65.9 mmol, 1.9 equiv) was added in one portion. After 30 min, the reaction mixture was quenched with an aqueous

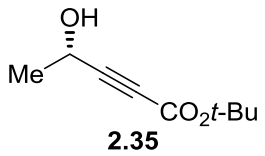
solution of hydrochloric acid (1.0 M, 100 mL), and allowed to warm to 25 °C. The phases were separated, the aqueous layer was extracted with Et_2O (75 mL), and the combined organic layers were washed with a saturated aqueous solution of sodium thiosulfate (100 mL), a saturated aqueous solution of sodium bicarbonate (100 mL), and brine (100 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, hexanes $\rightarrow$ 3% Et_2O in hexanes) to afford vinyl iodide **2.38** (8.8 g, 29.5 mmol, 85% yield) as a colorless oil. The physical and spectral data were consistent with those reported.[23]



2.24

Stannane 2.24: To a stirred solution of vinyl iodide **2.38** (8.8 g, 29.5 mmol, 1.0 equiv) in Et_2O (148 mL) was added *n*-butyllithium (17.7 mL, 2.5 M hexanes, 44.3 mmol, 1.5 equiv) dropwise at –78 °C. After 20 min, *n*-tributyltin chloride (12 mL, 44.3 mmol, 1.5 equiv) was added dropwise, and the reaction mixture was stirred for an additional 20 min. Then the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (50 mL), and allowed to warm to 25 °C. The phases were separated, and the organic layer was dried with anhydrous sodium sulfate and concentrated *in vacuo*. The crude material was redissolved in a solution of *n*-tetrabutylammonium fluoride (148 mL, 1.0 M THF, 148 mmol, 5.0 equiv) with vigorous stirring at 25 °C. After 1 h, the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (70 mL), and the phases were separated. The organic layer was dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 10% ethyl acetate in hexanes) to obtain stannane **2.24** (9.0 g,

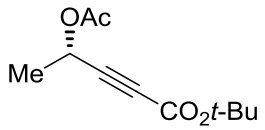
25.9 mmol, 88%) as a slightly yellow oil. The physical and spectral data were consistent with those reported.[19]



2.35

***tert*-Butyl ester 2.35**: To a stirred solution of (*S*)-(–)-2-butynol **2.34** (1.23 g, 17.5 mmol, 1.0 equiv) in THF (8.8 mL) was added HMDS (2.0 mL, 9.6 mmol, 0.55 equiv) followed by a drop (*ca*. 10 µL, 0.18 mmol, 0.01 equiv) of concentrated sulfuric acid, and the reaction mixture was heated to 70 °C. After 3 h, the reaction mixture was cooled to –78 °C, and *n*-butyllithium (8.4 mL, 2.5 M hexanes, 21 mmol, 1.2 equiv) was added dropwise over 15 min. After stirring for 30 min at the same temperature, a solution of di-*tert*-butyl dicarbonate (5.0 g, 22.8 mmol, 1.3 equiv) in THF (5 mL) was added dropwise over 10 min *via* cannula, the original flask was rinsed with additional THF (3 x 0.5 mL), and the reaction mixture was allowed to warm to 0 °C. After 20 min, the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (20 mL), and allowed to warm to 25 °C. The phases were separated, the aqueous layer was extracted with Et_2O (15 mL), and the combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The crude material was redissolved in THF (70 mL) with stirring, and *n*-tetrabutylammonium fluoride (35 mL, 1.0 M THF, 35 mmol, 2.0 equiv) was added dropwise at 25 °C. After 20 min, the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (50 mL), the phases were separated, and the aqueous layer was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue

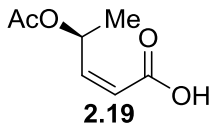
was purified by flash column chromatography (silica gel, 5 → 15% ethyl acetate in hexanes) to provide *tert*-butyl ester **2.35** (1.82 g, 10.7 mmol, 61 %) as a colorless oil. **2.35**: R_f = 0.26 (silica gel, 20% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –31.8 (*c* = 1.0, CH_2Cl_2); FT-IR (neat) ν_{max} 3407, 2982, 2936, 2876, 2231, 1841, 1705, 1478, 1457, 1394, 1369, 1255, 1154, 1126, 1063, 1037, 985, 895, 842, 808, 790, 754 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.62 (qd, *J* = 6.6, 0.7 Hz, 1 H), 1.91 (d, *J* = 4.3 Hz, 1 H), 1.51 (d, *J* = 6.8 Hz, 1 H), 1.50 (s, 9 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.5, 86.0, 83.9, 77.3, 58.3, 28.1, 23.50 ppm; HRMS (ESI-TOF) calcd for $C_9H_{14}O_3Na^+$ $[M+Na]^+$ 193.0835, found 193.0833.



2.36

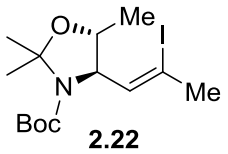
Acetate 2.36: To a stirred solution of **2.35** (680 mg, 4.0 mmol, 1.0 equiv) in CH_2Cl_2 (80 mL) was added triethylamine (2.8 mL, 20.0 mmol, 5.0 equiv), followed by acetic anhydride (1.13 mL, 12.0 mmol, 3.0 equiv) and DMAP (98 mg, 0.8 mmol, 0.2 equiv) at 25 °C. After 12 h, the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (50 mL), and the phases were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL), and the combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 5% ethyl acetate in hexanes) to provide acetate **2.36** (679 mg, 3.2 mmol, 80%) as a colorless oil. **2.36**: R_f = 0.34 (silica gel, 10% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –117 (*c* = 1.0, CH_2Cl_2); FT-IR (neat) ν_{max} 2983, 2939, 2875, 2237, 1748, 1708, 1479, 1457, 1370, 1337, 1277, 1260, 1226, 1157, 1137, 1101, 1051, 1013, 983, 938, 843, 753 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.51 (q, *J* = 6.8 Hz, 1 H), 2.08 (s,

3 H), 1.53 (d, *J* = 6.8 Hz, 3 H), 1.49 (s, 9 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.8, 152.2, 84.0, 82.5, 77.6, 59.6, 28.1, 21.0, 20.6 ppm; HRMS (ESI-TOF) calcd for $C_{11}H_{16}O_4Na^+$ $[M+Na]^+$ 235.0941, found 235.0938.



2.19

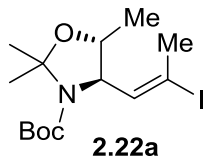
Acid 2.19: To a stirred solution of acetate **2.36** (512 mg, 2.41 mmol, 1.0 equiv) in EtOH (16 mL) was added quinoline (0.06 mL, 0.48 mmol, 0.2 equiv) and Lindlar's catalyst (102 mg, 5% $Pd/CaCO_3$ poisoned with lead, 20% *w*/*w*) at 25 °C. After 10 min, the reaction mixture was placed under an atmosphere of H_2 (1 atm), and stirring was continued for 4 h. Then the H_2 atmosphere was removed, and the reaction mixture was filtered through celite and concentrated *in vacuo*. The crude material was redissolved in a solution of trifluoroacetic acid (4.5 mL, 10% *v*/*v* in CH_2Cl_2) with stirring at 25 °C. After 1 h, the reaction mixture was concentrated *in vacuo*, and the remaining trifluoroacetic acid was azeotropically removed *in vacuo* with ethyl acetate (3 x 5 mL). The obtained residue was purified by flash column chromatography (silica gel, 20 → 80% ethyl acetate in hexanes) to afford pure acid **2.19** (362 mg, 2.29 mmol, 95%) as a pale yellow oil. **2.19**: R_f = 0.56 (silica gel, ethyl acetate); $[\alpha]_D^{25}$ = +18.1 (*c* = 1.0, CH_2Cl_2); FT-IR (neat) ν_{max} 3571, 3185, 3114, 3052, 2985, 2938, 2877, 2735, 2684, 2585, 1738, 1724, 1699, 1650, 1431, 1371, 1240, 1195, 1119, 1048, 1019, 956, 925, 866, 826, 741, 698 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.31 – 6.15 (m, 2 H), 5.82 (d, *J* = 10.7 Hz, 1 H), 2.06 (s, 3 H), 1.38 (d, *J* = 6.3 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.6, 170.4, 150.8, 119.3, 68.9, 21.3, 19.7 ppm; HRMS (ESI-TOF) calcd for $C_7H_9O_4Na^+$ $[M+Na]^+$ 203.0291, found 203.0284.



2.22

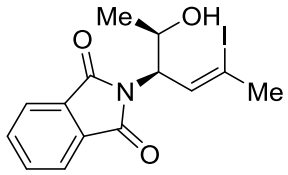
Vinyl Iodide 2.22: To a stirred suspension of triethylphosphonium iodide (27.9 g, 66.6 mmol, 2.0 equiv) in THF (333 mL) at 25 °C was added *n*-butyllithium (26.6 mL, 2.5 M hexanes, 66.6 mmol, 2.0 equiv) dropwise. After stirring for 15 min, the resulting red orange solution was transferred to a stirred solution of iodine (16.1 g, 63.3 mmol, 1.9 equiv) in THF (450 mL) at –78 °C dropwise *via* cannula. The resulting thick yellow paste was warmed to –20 °C, and NaHMDS (63.3 mL, 1.0 M THF, 63.3 mmol, 1.9 equiv) was added dropwise, and stirring was continued for 10 min. The resulting deep red homogenous solution was cooled back down to –78 °C, and a solution of aldehyde **2.21** (8.1 g, 33.3 mmol, 1.0 equiv) in THF (100 mL) was added dropwise *via* cannula, and the original flask was rinsed with additional THF (3 x 2 mL). After stirring for an additional 30 min, the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (300 mL) and allowed to warm to 25 °C. The phases were separated, the aqueous layer was extracted with ethyl acetate (3 x 75 mL), and the combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 2 $\rightarrow$ 8% ethyl acetate in hexanes) to afford pure (*Z*)-vinyl iodide **2.22** (6.86 g, 18.0 mmol, 54 %) as a white amorphous solid and a small amount of (*E*) isomer **2.22a** (0.36 g, 0.94 mmol, 5 %) as a colorless oil. **2.22**: R_f = 0.22 (silica gel, 5% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = +98.0 (*c* = 1.0, CH_2Cl_2); FT-IR (neat) ν_{max} 2977, 2933, 2871, 1698, 1654, 1475, 1454, 1428, 1376, 1365, 1338, 1274, 1253, 1213, 1177, 1163, 1127, 1083, 1063, 991, 979, 934, 860, 775 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$)

δ 5.36 – 5.34 (m, 1 H), 4.06 – 3.97 (m, 1 H), 3.85 (qd, *J* = 6.1, 6.1 Hz, 1 H), 2.54 (s, 3 H), 1.61 (br s, 3 H), 1.51 (br s, 3 H), 1.43 (br s, 9 H), 1.38 (d, *J* = 6.0 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.1, 134.7, 101.0, 94.4, 79.8, 75.2, 69.6, 34.0, 28.7, 26.6, 25.4, 18.2 ppm; HRMS (ESI-TOF) calcd for $C_{14}H_{24}INO_3Na^+$ $[M+Na]^+$ 404.0693, found 404.0706.



2.22a

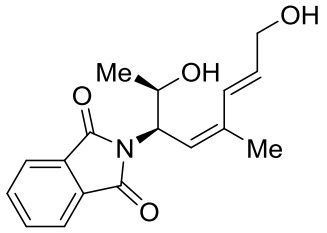
Data for **2.22a**: R_f = 0.24 (silica gel, 5% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –20.0 (*c* = 1.0, CH_2Cl_2); FT-IR (neat) ν_{max} 2977, 2932, 2872, 1699, 1641, 1552, 1476, 1455, 1387, 1376, 1365, 1348, 1289, 1256, 1213, 1176, 1137, 1121, 1081, 1062, 981, 935, 859, 778, cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.98 – 5.94 (m, 1 H), 4.04 – 3.95 (m, 1 H), 3.82 (qd, *J* = 6.0, 6.0 Hz, 1 H), 2.44 (br s, 3 H), 1.59 (br s, 3 H), 1.50 (br s, 3 H), 1.44 (br s, 9 H), 1.28 (d, *J* = 6.0 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.0, 140.5, 95.8, 94.4, 80.0, 74.4, 63.2, 28.5, 28.1, 26.5, 25.4, 17.5 ppm; HRMS (ESI-TOF) calcd for $C_{14}H_{24}INO_3Na^+$ $[M+Na]^+$ 404.0693, found 404.0706.



2.23

Alcohol 2.23: Vinyl iodide **2.22** (487 mg, 1.28 mmol, 1.0 equiv) was dissolved in formic acid (13 mL) with stirring at 25 °C. After 20 min, the reaction mixture was concentrated *in vacuo*, and the remaining formic acid was azeotropically removed *in vacuo* with toluene (3 x 5 mL). The crude material was redissolved in $CHCl_3$ (13 mL), and triethylamine (3.6 mL, 25.6 mmol, 20 equiv), DMAP (16 mg, 0.13 mmol, 0.1 equiv), and phthalic anhydride (209

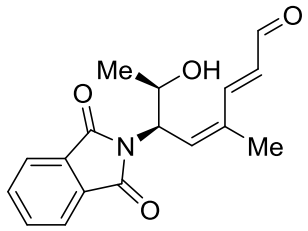
mg, 1.41 mmol, 1.1 equiv) were added with stirring, and the reaction mixture was heated to 70 °C. After 48 h at the same temperature, the reaction mixture was allowed to cool to 25 °C, and then concentrated *in vacuo*. The obtained residue was purified directly by flash column chromatography (silica gel, 10 → 30% ethyl acetate in hexanes) to afford alcohol **2.23** (386 mg, 1.04 mmol, 81%) as a white amorphous solid. **2.23**: R_f = 0.22 (silica gel, 30% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = +111 (*c* = 0.2, CH_2Cl_2); FT-IR (neat) ν_{max} 3466, 2970, 2917, 1773, 1704, 1646, 1612, 1467, 1427, 1386, 1359, 1334, 1221, 1188, 1174, 1150, 1127, 1085, 1050, 1034, 1012, 985, 917, 886, 865, 832, 794, 718, 700 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.89 – 7.82 (m, 2 H), 7.78 – 7.71 (m, 2 H), 6.15 (dq, *J* = 8.8, 1.5 Hz, 1 H), 4.87 (dd, *J* = 8.8, 7.2 Hz, 1 H), 4.32 (qd, *J* = 6.6, 6.6 Hz, 1 H), 2.56 (d, *J* = 1.5 Hz, 3 H), 2.41 (d, *J* = 8.4 Hz, 1 H), 1.27 (d, *J* = 6.4 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.7, 134.3, 131.9, 130.5, 123.7, 106.0, 68.3, 63.6, 34.2, 21.1 ppm; HRMS (ESI-TOF) calcd for $C_{14}H_{14}INO_3H^+$ $[M+H]^+$ 372.0091, found 372.0084.



2.26

Dienol 2.26: To a stirred solution of alcohol **2.23** (2.0 g, 5.4 mmol, 1.0 equiv) and stannane **2.24** (2.3 g, 6.5 mmol, 1.2 equiv) in NMP (90 mL) at 25 °C was added tris(dibenzylideneacetone)dipalladium (494 mg, 0.54 mmol, 0.1 equiv). After 18 h, the reaction mixture was filtered through a short silica plug, and rinsed thoroughly with ethyl acetate (300 mL). The resulting organic phase was washed with an aqueous solution of lithium chloride (1.0 M, 4 x 100 mL), dried with anhydrous sodium sulfate, and

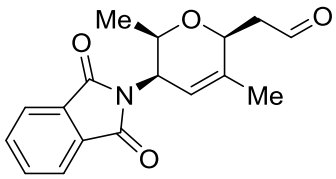
concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 10 → 20 → 40 → 50 → 80% ethyl acetate in hexanes) to afford diene **2.26** (1.19 g, 3.9 mmol, 73% yield) as a white foam. **2.26**: R_f = 0.38 (silica gel, 70% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = +51.7 (*c* = 0.3, CH_2Cl_2); FT-IR (neat) ν_{max} 3440, 2973, 2922, 2857, 1769, 1702, 1614, 1467, 1453, 1387, 1332, 1260, 1187, 1172, 1141, 1112, 1089, 1073, 1014, 1000, 967, 912, 889, 868, 793, 720 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.83 – 7.78 (m, 2 H), 7.73 – 7.65 (m, 2 H), 6.80 (d, *J* = 15.6 Hz, 1 H), 5.94 (dt, *J* = 15.6, 5.6 Hz, 1 H), 5.86 (d, *J* = 9.8 Hz, 1 H), 5.09 (dd, *J* = 9.8, 8.2 Hz, 1 H), 4.34 (qd, *J* = 6.6, 6.6 Hz, 1 H), 4.27 (d, *J* = 5.6 Hz, 1 H), 2.49 (br s, 1 H) 1.87 (s, 3 H), 1.22 (d, *J* = 6.3 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.9, 136.6, 134.2, 132.1, 131.8, 127.2, 124.0, 123.5, 68.3, 63.9, 54.8, 21.4, 20.7 ppm; HRMS (ESI-TOF) calcd for $C_{17}H_{19}NO_4Na^+$ $[M+Na]^+$ 324.1206, found 324.1194.



2.18

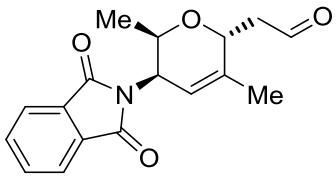
Aldehyde 2.18: Procedure A, MnO_2 oxidation: To a stirred solution of dienol **2.26** (1.0 g, 3.32 mmol, 1.0 equiv) in CH_2Cl_2 (66 mL) was added MnO_2 (3.36 g, 33.4 mmol, 10 equiv) at 25 °C. After 15 min, additional MnO_2 (3.36 g, 33.4 mmol, 10 equiv) was added, and stirring was continued for 30 min. The reaction mixture was then filtered through celite, rinsed thoroughly with ethyl acetate (150 mL), and concentrated *in vacuo*. The obtained white foam (894 mg, 2.99 mmol, 90%) was sufficiently pure for use in the following step.

Procedure B, Stille coupling: To a stirred solution of alcohol **2.23** (100 mg, 0.27 mmol, 1.0 equiv) and stannane **2.25** (140 mg, 0.41 mmol, 1.5 equiv) in NMP (4.5 mL) at 25 °C was added tris(dibenzylideneacetone)dipalladium (25 mg, 0.027 mmol, 0.1 equiv). After 18 h, the reaction mixture was filtered through a short silica plug, and rinsed thoroughly with ethyl acetate (30 mL). The resulting organic phase was washed with an aqueous solution of lithium chloride (1.0 M, 4 x 10 mL), dried with anhydrous sodium sulfate, and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 10 → 50% ethyl acetate in hexanes) to afford aldehyde **2.18** (48 mg, 0.16 mmol, 73% yield) as a white foam. **2.18**: R_f = 0.30 (silica gel, 50% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = +257 (*c* = 0.7, CH_2Cl_2); FT-IR (neat) ν_{max} 3463, 3060, 2970, 2925, 2854, 2729, 1769, 1705, 1632, 1613, 1597, 1467, 1453, 1385, 1333, 1262, 1188, 1172, 1135, 1111, 1080, 1059, 1019, 972, 919, 889, 863, 797, 719 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.70 (d, *J* = 7.8 Hz, 1 H), 7.86 – 7.84 (m, 2 H), 7.75 – 7.73 (m, 2 H), 7.72 (d, *J* = 15.6 Hz, 1 H), 6.30 (d, *J* = 10.0 Hz, 1 H), 6.23 (dd, *J* = 15.6, 7.8 Hz, 1 H), 5.16 (dd, *J* = 10.0, 7.8 Hz, 1 H), 4.42 (qd, *J* = 6.5, 6.5 Hz, 1 H), 2.46 (d, *J* = 7.8 Hz, 1 H), 1.26 (d, *J* = 6.3 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 193.4, 168.7, 147.1, 135.8, 134.5, 132.9, 131.8, 131.4, 123.7, 67.9, 54.5, 21.4, 20.3 ppm; HRMS (ESI-TOF) calcd for $C_{17}H_{17}NO_4Na^+$ $[M+Na]^+$ 322.1050, found 322.1058.



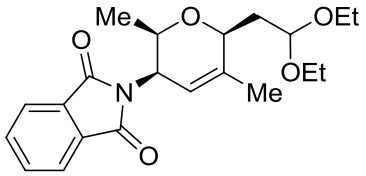
2.28

Dihydropyran 2.28: To a stirred solution of aldehyde **7** (860 mg, 2.77 mmol, 1.0 equiv) in CH_2Cl_2 (55 mL) at 0 °C was added benzoic acid (68 mg, 0.55 mmol, 0.20 equiv) followed by diphenyl prolinol catalyst **2.27** (339 mg, 0.55 mmol, 0.20 equiv). After 6.5 h, the reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate (40 mL), and allowed to warm to 25 °C. The phases were separated, the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL), and the combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 20 → 30 → 50% ethyl acetate in hexanes) to afford pure dihydropyan **2.28** (640 mg, 2.13 mmol, 77%) as a white foam along with recovered **7** (149 mg, 0.50 mmol, 18%). **2.28**: R_f = 0.33 (silica gel, 25% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –266 (*c* = 1.0, CH_2Cl_2); FT-IR (neat) ν_{max} 2977, 2920, 2855, 2730, 1770, 1712, 1611, 1556, 1467, 1443, 1386, 1363, 1351, 1327, 1291, 1193, 1165, 1125, 1088, 1072, 1041, 900, 871, 836, 795, 720, 689 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.98 (dd, *J* = 2.2, 2.2 Hz, 1 H), 7.83 – 7.80 (m, 2 H), 7.72 – 7.69 (m, 2 H), 5.59 (dt, *J* = 5.8, 1.6 Hz, 1 H), 4.66 – 4.61 (m, 1 H), 4.60 – 4.55 (m, 1 H), 3.94 (qd, *J* = 6.4, 3.4 Hz, 1 H), 2.98 (ddd, *J* = 16.1, 8.2, 2.6 Hz, 1 H), 2.75 (ddd, *J* = 16.1, 3.6, 1.9 Hz, 1 H), 1.74 (d, *J* = 1.1 Hz, 3 H), 1.08 (d, *J* = 6.4 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 202.7, 168.5, 137.2, 131.9, 123.3, 74.0, 48.3, 45.9, 19.1, 17.1 ppm; HRMS (ESI-TOF) calcd for $C_{17}H_{17}NO_4Na^+$ $[M+Na]^+$ 322.1050, found 322.1048.



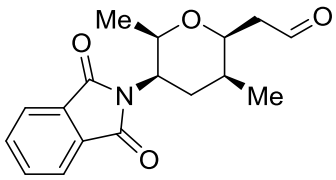
11-*epi*-**2.28**

Dihydropyran 11-*epi*-2.28: To a stirred solution was aldehyde **7** (100 mg, 0.33 mmol, 1.0 equiv) in CH_2Cl_2 (6.6 mL) at 0 °C was added benzoic acid (8.5 mg, 0.07 mmol, 0.20 equiv) followed by diphenyl prolinol catalyst *ent*-**2.27** (42 mg, 0.07 mmol, 0.20 equiv). After 6.5 h, the reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate (5 mL) and allowed to warm to 25 °C. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 20 → 30 → 50% ethyl acetate in hexanes) to afford pure dihydropyan 11-*epi*-**2.28** (640 g, 2.13 mmol, 64%) as a white foam along with recovered **7** (149 mg, 0.50 mmol, 28%). 11-*epi*-**2.28**: R_f = 0.16 (silica gel, 25% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –331 (*c* = 1.0, CH_2Cl_2); FT-IR (neat) ν_{max} 2976, 2922, 2859, 2732, 1771, 1711, 1612, 1467, 1444, 1385, 1355, 1331, 1282, 1172, 1125, 1107, 1088, 1072, 1034, 898, 839, 795, 765, 720, 689 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.86 (dd, *J* = 4.0, 1.4 Hz, 1 H), 7.89 – 7.77 (m, 2 H), 7.75 – 7.68 (m, 2 H), 5.58 (dt, *J* = 5.4, 1.6 Hz, 1 H), 4.88 (dd, *J* = 10.1, 10.1 Hz, 1 H), 4.63 – 4.61 (m, 1 H), 4.07 (qd, *J* = 6.4, 3.6 Hz, 1 H), 2.78 (ddd, *J* = 15.8, 10.4, 4.0 Hz, 1 H), 2.67 (ddd, *J* = 15.8, 3.4, 1.4 Hz, 1 H), 1.79 (s, 3 H), 1.07 (d, *J* = 6.4 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 201.2, 168.5, 139.4, 134.2, 131.9, 123.4, 117.6, 71.9, 66.4, 48.1, 45.1, 19.5, 16.8 ppm; HRMS (ESI-TOF) calcd for $C_{17}H_{17}NO_4Na^+$ $[M+Na]^+$ 322.1050, found 322.1041.



2.29

Acetal 2.29: To a stirred solution of dihydropyran **2.28** (511 mg, 1.71 mmol, 1.0 equiv) in EtOH (17.1 mL) at 25 °C was added triethylorthoformate (2.85 mL, 17.1 mmol, 10 equiv) followed by camphorsulfonic acid (40 mg, 0.17 mmol, 0.1 equiv). After 2 h, the reaction mixture was concentrated *in vacuo*, and the obtained residue was purified by flash column chromatography (silica gel, 10 → 15% ethyl acetate in hexanes) to provide acetal **2.29** (583 mg, 1.56 mmol, 91%) as a colorless oil. **2.29**: R_f = 0.32 (silica gel, 20% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –366 (*c* = 1.0, CH_2Cl_2); FT-IR (neat) ν_{max} 2974, 2932, 2874, 1771, 1713, 1612, 1467, 1443, 1385, 1342, 1327, 1291, 1162, 1124, 1089, 1059, 1043, 1020, 950, 923, 899, 871, 834, 795, 749, 720, 704, 688 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.82 – 7.80 (m, 2 H), 7.71 – 7.68 (m, 2 H), 5.49 (dt, *J* = 5.9, 1.8 Hz, 1 H), 4.89 (dd, *J* = 8.5, 3.3 Hz, 1 H), 4.54 (ddq, *J* = 6.2, 3.4, 1.6 Hz, 1 H), 4.22 (dd, *J* = 10.0, 10.0 Hz, 1 H), 3.88 (qd, *J* = 6.4, 3.3 Hz, 1 H), 3.76 – 3.69 (m, 2 H), 3.61 (dq, *J* = 9.6, 7.0 Hz, 1 H), 3.54 (dq, *J* = 9.2, 7.0 Hz, 1 H), 2.17 – 2.04 (m, 2 H), 1.74 (d, *J* = 0.9 Hz, 3 H), 1.24 (t, *J* = 7.0 Hz, 3 H), 1.22 (t, *J* = 7.0 Hz, 3 H), 1.08 (d, *J* = 6.4 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 141.9, 133.8, 131.9, 123.1, 116.5, 100.9, 74.8, 71.5, 62.2, 62.0, 48.6, 36.4, 19.0, 17.1, 15.47, 15.46 ppm; HRMS (ESI-TOF) calcd for $C_{21}H_{27}NO_5Na^+$ $[M+Na]^+$ 396.1781, found 396.1783.



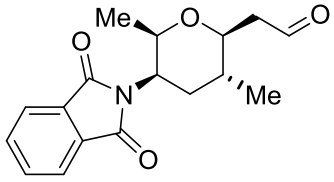
2.30

Tetrahydropyran 2.30: To a stirred solution of acetal **2.29** (50 mg, 0.13 mmol, 1.0 equiv) in EtOH (4.3 mL) at 25 °C was added 10% Pd/C (17.5 mg, 35% *w*/*w*). The reaction mixture was placed in a bomb reactor, evacuated three times with H_2, and placed under a pressurized H_2 atmosphere (80 bar). After 24 h, the H_2 atmosphere was removed, the reaction mixture was filtered through a celite pad, rinsed thoroughly with ethyl acetate (30 mL), and concentrated *in vacuo*. The crude residue was redissolved in acetone (1.3 mL) with stirring, and an aqueous solution of hydrochloric acid (0.1 M, 3.9 mL, 0.39 mmol, 3.0 equiv) was added at 25 °C. After 15 min, the reaction mixture was neutralized with solid sodium bicarbonate (200 mg) and diluted with ethyl acetate (5 mL) and water (5 mL). The phases were separated, the aqueous layer was extracted with ethyl acetate (3 x 3 mL), and the combined organic layers were concentrated *in vacuo*. The obtained residue was purified by flash chromatography (silica gel, 30% ethyl acetate in hexanes) to provide tetrahydropyran **2.30** (21 mg, 0.07 mmol, 54%) as a colorless oil. **2.30**: R_f = 0.29 (silica gel, 30% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –4.2 (*c* = 1.0, CH_2Cl_2); FT-IR (neat) ν_{max} 2972, 2936, 2879, 2728, 1772, 1709, 1612, 1467, 1396, 1371, 1330, 1291, 1194, 1173, 1105, 1079, 1056, 980, 934, 881, 794, 719, 659 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.92 (dd, *J* = 2.2, 2.3 Hz, 1 H), 7.87 – 7.79 (m, 2 H), 7.76 – 7.66 (m, 2 H), 4.52 (ddd, *J* = 10.2, 7.1, 6.0 Hz, 1 H), 4.43 (ddd, *J* = 9.2, 6.5, 4.3 Hz, 1 H), 4.11 (qd, *J* = 6.5, 6.5 Hz, 1 H), 2.86 (ddd, *J* = 15.9, 9.2, 2.6 Hz, 1 H), 2.52 – 2.43 (m, 3 H), 2.24 – 2.15 (m, 1 H), 1.77 (ddd, *J* = 13.1,

7.0, 4.0 Hz, 1 H), 1.07 (d, *J* = 6.6 Hz, 3 H), 0.93 (d, *J* = 7.0 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 202.7, 168.7, 134.2, 131.8, 123.4, 73.2, 70.6, 50.9, 45.0, 30.3, 28.1, 16.8, 16.3 ppm; HRMS (ESI-TOF) calcd for $C_{17}H_{19}NO_4Na^+$ $[M+Na]^+$ 324.1206, found 324.1211.

Procedure for the direct hydrogenation of **2.28**:

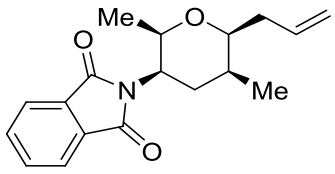
To a stirred solution of dihydropyran **2.28** (100 mg, 0.33 mmol, 1.0 equiv) in hexafluoroisopropanol (7.3 mL) at 25 °C was added 10% Pd/C (50 mg, 50% *w*/*w*). The reaction mixture was placed in a bomb reactor, evacuated three times with H_2, and placed under a pressurized H_2 atmosphere (80 bar). After 24 h, the H_2 atmosphere was removed, the reaction mixture was filtered through a celite pad, rinsed thoroughly with ethyl acetate (30 mL), and concentrated *in vacuo*. The obtained residue was purified by flash chromatography (silica gel, 35% *t*-butyl methyl ether in hexanes) to provide tetrahydropyran **2.30** (63 mg, 0.21 mmol, 65%) and tetrahydropyran 12-*epi*-**2.30** (27 mg, 0.09 mmol, 28%) as colorless oils.



12-*epi*-**2.30**

Tetrahydropyran 12-*epi*-2.30: To a stirred solution of acetal **2.29** (120 mg, 0.32 mmol, 1.0 equiv) in CH_2Cl_2 (3.2 mL) was added [Ir(Py)(PCy_3)(COD)BARF] (24 mg, 0.016 mmol, 0.05 equiv) at 25 °C. The reaction mixture was placed under an atmosphere of H_2 (1 atm), stirred for 10 h, and then concentrated *in vacuo*. The crude residue was redissolved in acetone (3.2 mL) with stirring, and an aqueous solution of hydrochloric acid (0.1 M, 9.6

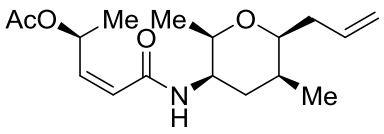
mL, 0.96 mmol, 3.0 equiv) was added at 25 °C. After 15 min, the reaction mixture was neutralized with solid sodium bicarbonate (600 mg) and diluted with ethyl acetate (12 mL) and water (12 mL). The phases were separated, the aqueous layer was extracted with ethyl acetate (3 x 5 mL), and the combined organic layers were concentrated *in vacuo*. The obtained residue was purified by flash chromatography (silica gel, 30% ethyl acetate in hexanes) to afford pure tetrahydropyran 12-*epi*-**2.30** (69 mg, 0.23 mmol, 85%) as a colorless oil. 12-*epi*-**2.30**: R_f = 0.34 (silica gel, 30% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = +47.8 (*c* = 0.6, CH_2Cl_2); FT-IR (neat) ν_{max} 2973, 2936, 2872, 2848, 2732, 1771, 1709, 1611, 1467, 1437, 1404, 1371, 1356, 1328, 1285, 1241, 1207, 1184, 1170, 1142, 1094, 1067, 1044, 1030, 990, 958, 927, 897, 851, 795, 764, 721, 694 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.95 (dd, *J* = 2.8, 2.0 Hz, 1 H), 7.87 – 7.80 (m, 2 H), 7.76 – 7.69 (m, 2 H), 4.43 (ddd, *J* = 6.1, 3.2, 1.5 Hz, 1 H), 3.83 (qd, *J* = 6.4, 3.4 Hz, 1 H), 3.62 (ddd, *J* = 10.0, 8.1, 3.4 Hz, 1 H), 2.76 (ddd, *J* = 16.1, 8.1, 2.8 Hz, 1 H), 2.68 (ddd, *J* = 16.1, 3.3, 2.0 Hz, 1 H), 2.61 – 2.49 (m, 2 H), 2.00 (ddd, *J* = 15.0, 4.8, 1.7 Hz, 1 H), 1.78 (ddd, *J* = 15.0, 12.3, 6.5 Hz, 1 H), 1.04 (d, *J* = 6.4 Hz, 3 H), 0.84 (d, *J* = 6.5 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 202.9, 169.0, 134.2, 131.8, 123.4, 79.7, 74.1, 49.4, 47.3, 36.7, 30.2, 17.9, 17.7 ppm; HRMS (ESI-TOF) calcd for $C_{17}H_{19}NO_4Na^+$ $[M+Na]^+$ 324.1206, found 324.1216.



2.31

Olefin 2.31: To a stirred solution of tetrahydropyran **2.30** (86 mg, 0.29 mmol, 1.0 equiv) in THF (5.1 mL) at –20 °C was added Tebbe reagent (0.58 mL, 0.5 M toluene, 0.29 mmol, 1.0 equiv) dropwise. The reaction mixture was allowed to slowly warm to 0 °C over 1 h,

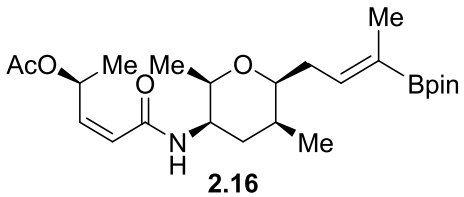
and was then quenched with a saturated aqueous solution of sodium bicarbonate (10 mL). The phases were separated, the aqueous layer was extracted with ethyl acetate (3 x 5 mL), and the combined organic layers were concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 5 → 10% ethyl acetate in hexanes) to provide **2.31** (66 mg, 0.22 mmol, 76%) as a colorless oil. **2.31**: R_f = 0.24 (silica gel, 10% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –14.4 (*c* = 0.5, CH_2Cl_2); FT-IR (neat) ν_{max} 3072, 2974, 2936, 2878, 1773, 1713, 1640, 1612, 1467, 1429, 1396, 1372, 1356, 1329, 1291, 1193, 1159, 1110, 1088, 1069, 1057, 1033, 994, 911, 874, 795, 718, 667 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.84 – 7.81 (m, 2 H), 7.73 – 7.70 (m, 2 H), 6.00 (dddd, *J* = 17.1, 10.2, 6.8, 6.8 Hz, 1 H), 5.15 – 5.11 (m, 1 H), 5.07 – 5.05 (m, 1 H), 4.49 (ddd, *J* = 10.1, 6.0, 6.0 Hz, 1 H), 4.09 (qd, *J* = 6.5, 6.5 Hz, 1 H), 3.82 (ddd, *J* = 8.6, 5.4, 5.4 Hz, 1 H), 2.50 – 2.43 (m, 2 H), 2.29 – 2.24 (m, 1 H), 2.09 – 2.03 (m, 1 H), 1.79 (ddd, *J* = 13.2, 6.0, 4.8 Hz, 1 H), 1.14 (d, *J* = 6.7 Hz, 3 H), 0.98 (d, *J* = 7.0 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.8, 136.4, 134.1, 132.0, 123.3, 116.4, 71.3, 51.1, 35.8, 31.2, 29.3, 17.1, 15.9 ppm; HRMS (ESI-TOF) calcd for $C_{18}H_{21}NO_3Na^+$ $[M+Na]^+$ 322.1414, found 322.1414.



2.32

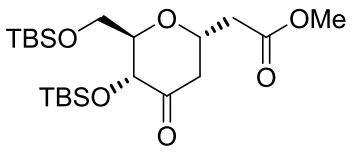
Amide 2.32: To a stirred solution of olefin **2.31** (52 mg, 0.17 mmol, 1.0 equiv) in benzene (8.5 mL) was added methylhydrazine (0.09 mL, 1.7 mmol, 10 equiv) at 25 °C. After 2 h, the reaction mixture was washed with an aqueous solution of sodium hydroxide (0.1 M, 10 mL), and the phases were separated. The aqueous layer was extracted with ethyl acetate (3 x 4 mL), and the combined organic layers were dried with anhydrous sodium sulfate and

concentrated *in vacuo*. The crude amine was redissolved in CH_2Cl_2 (2.4 mL) with stirring, and NMM (0.06 mL, 0.51 mmol, 3.0 equiv), EDCI (98 mg, 0.51 mmol, 3.0 equiv), and a solution of acid **2.19** (54 mg, 0.34 mmol, 2.0 equiv) in CH_2Cl_2 (0.3 mL) were added sequentially at 25 °C. After 2 h, the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (2.5 mL), and the phases were separated. The aqueous layer was extracted with ethyl acetate (3 x 2 mL), and the combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 10 $\rightarrow$ 30% ethyl acetate in hexanes) to provide amide **2.32** (37 mg, 0.12 mmol, 73%) as a colorless oil. **2.32**: R_f = 0.31 (silica gel, 30% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = –87.5 (*c* = 0.2, CH_2Cl_2); FT-IR (neat) ν_{max} 3445, 3357, 3076, 2976, 2935, 2882, 2857, 1738, 1668, 1639, 1519, 1468, 1445, 1369, 1335, 1317, 1242, 1176, 1158, 1123, 1079, 1049, 1010, 972, 953, 914, 884, 859, 844, 813, 785, 742, 711 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.29 – 6.24 (m, 1 H), 5.97 (d, *J* = 9.1 Hz, 1 H), 5.89 (dd, *J* = 11.6, 7.9 Hz, 1 H), 5.79 (dddd, *J* = 17.2, 10.2, 7.7, 6.1 Hz, 1 H), 5.70 (dd, *J* = 11.6, 1.3 Hz, 1 H), 5.13 – 5.09 (m, 1 H), 5.06 – 5.04 (m, 1 H), 3.94 (ddd, *J* = 11.7, 4.6, 2.5 Hz, 1 H), 3.66 (qd, *J* = 6.5, 2.3 Hz, 1 H), 3.54 (ddd, *J* = 7.2, 2.8, 2.8 Hz, 1 H), 2.36 – 2.31 (m, 1 H), 2.16 – 2.09 (m, 1 H), 2.04 (s, 3 H), 2.00 – 1.87 (m, 2 H), 1.80 – 1.75 (m, 1 H), 1.39 (d, *J* = 6.5 Hz, 3 H), 1.15 (d, *J* = 6.5 Hz, 3 H), 1.02 (d, *J* = 7.4 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.5, 165.0, 143.9, 134.9, 122.6, 116.9, 80.9, 76.1, 69.1, 47.3, 37.5, 36.1, 29.0, 21.4, 20.1, 18.0, 15.1 ppm; HRMS (ESI-TOF) calcd for $C_{17}H_{27}NO_4Na^+$ $[M+Na]^+$ 332.1832, found 332.1831.



2.16

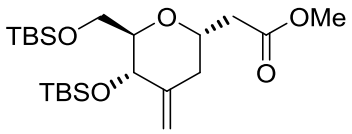
Boronate 2.16: To a stirred solution of amide **2.32** (90 mg, 0.29 mmol, 1.0 equiv) in $ClCH_2CH_2Cl$ (3 mL) was added vinyl boronate **2.33** (243 mg, 1.45 mmol, 5.0 equiv) followed by Grubbs 2nd generation catalyst (25 mg, 0.03 mmol, 0.1 equiv). The reaction mixture was heated to 80 °C, stirred for 1 h, and allowed to cool to 25 °C. The solvent was removed *in vacuo*, and the obtained residue was purified by flash column chromatography (silica gel, 15 $\rightarrow$ 20% ethyl acetate in hexanes) to provide boronate **2.16** (95 mg, 0.21 mmol, 71%) as a white amorphous solid. **2.16**: R_f = 0.30 (silica gel, 30% ethyl acetate in hexanes); $[\alpha]_D^{25} = -137$ (*c* = 1.0, $CHCl_3$); FT-IR (neat) ν_{max} 3349, 2977, 2928, 1739, 1669, 1633, 1521, 1457, 1411, 1370, 1305, 1242, 1146, 1052, 859 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.28 – 6.23 (m, 2 H), 5.99 (d, *J* = 9.1 Hz, 1 H), 5.88 (dd, *J* = 11.6, 7.9 Hz, 1 H), 5.70 (dd, *J* = 11.6, 1.3 Hz, 1 H), 3.93 (ddd, *J* = 11.7, 4.6, 2.5 Hz, 1 H), 3.67 (qd, *J* = 6.5, 2.3 Hz, 1 H), 3.60 (ddd, *J* = 7.4, 2.8, 2.8 Hz, 1 H), 2.38 – 2.34 (m, 1 H), 2.29 – 2.24 (m, 1 H), 2.03 (s, 3 H), 1.99 – 1.89 (m, 2 H), 1.83 – 1.78 (m, 1 H), 1.69 (br s, 3 H), 1.38 (d, *J* = 6.5 Hz, 3 H), 1.25 (br s, 12 H), 1.15 (d, *J* = 6.4 Hz, 3 H), 1.01 (d, *J* = 7.4 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.5, 165.0, 143.7, 141.1, 122.7, 83.4, 80.5, 76.1, 69.0, 47.3, 36.0, 32.5, 28.9, 25.0, 24.9, 21.4, 20.1, 18.0, 15.2, 14.4 ppm; HRMS (ESI TOF) calcd for $C_{24}H_{40}BNO_6Na^+$ $[M+Na]^+$ 472.2846, found 472.2845.



2.40

Ketone 2.40: To a stirred solution of enone **2.20** (10.0 g, 26.8 mmol, 1.0 equiv) in MeCN (150 mL) at –20 °C was added a solution of silyl enol ether **2.39** (7.84 g, 53.6 mmol, 2.0 equiv) in MeCN (50 mL) followed by iodine (68 mg, 0.1 mmol, 0.1 equiv). After 30 min, the reaction mixture was quenched with a saturated aqueous solution of sodium thiosulfate (50 mL), followed by a saturated aqueous solution of sodium bicarbonate (50 mL), and allowed to warm to 25 °C. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The crude material was redissolved in methanol (100 mL) with stirring, and potassium carbonate (100 mg, 0.7 mmol, 0.03 equiv) was added with stirring at 25 °C. After 10 min, the reaction mixture was concentrated *in vacuo*, and the obtained residue was purified by flash column chromatography (silica gel, 3 $\rightarrow$ 5% ethyl acetate in hexanes) to provide ketone **2.40** (11.8 g, 26.3 mmol, 98%) as a colorless oil. **2.40**: R_f = 0.42 (silica gel, 15% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = +51.3 (*c* = 1.0, $CHCl_3$); FT-IR (neat) ν_{max} 2954, 2930, 2886, 2857, 1736, 1472, 1463, 1254, 1133, 1087, 1043, 1006, 865, 779 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.80 – 4.76 (m, 1 H), 4.33 (d, *J* = 8.4 Hz, 1 H), 3.86 (dd, J = 11.3, 3.4 Hz, 1 H), 3.82 (dd, *J* = 11.3, 2.3 Hz, 1 H), 3.71 – 3.67 (m, 1 H), 3.68 (s, 3 H), 2.75 (ddd, *J* = 14.4, 6.3, 1.1 Hz, 1 H), 2.66 (dd, *J* = 15.2, 7.7 Hz, 1 H), 2.48 – 2.43 (m, 2 H), 0.91 (s, 9 H), 0.90 (s, 9 H), 0.14 (s, 3 H), 0.08 (s, 3 H), 0.06 (s, 3 H), 0.03 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 206.2, 170.7, 78.7, 74.3, 71.2,

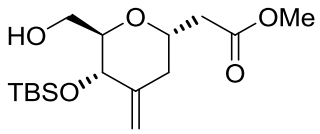
63.1, 52.0, 45.0, 38.2, 26.0, 25.9, 18.55, 18.54, –4.2, –5.0, –5.2, –5.4 ppm; HRMS (ESI-TOF) calcd for $C_{21}H_{42}O_6Si_2Na^+$[M+Na]$^+$ 469.2418, found 469.2413.



2.41

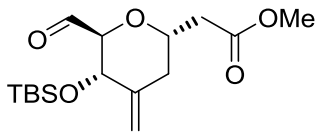
Olefin 2.41: To a stirred suspension of methyltriphenylphosphonium bromide (2.87 g, 8.0 mmol, 2.0 equiv) in THF (10 mL) at 0 °C was added *t*-BuOK (673 mg, 6.0 mmol, 1.5 equiv). After 30 min, the suspension was transferred *via* cannula to a stirred solution of ketone **2.40** (1.79 g, 4.0 mmol, 1.0 equiv) in THF (60 mL) at 0 °C. The reaction mixture was allowed to slowly warm to 25 °C over 1 h. Then the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (25 mL). The phases were separated, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 3 → 5% ethyl acetate in hexanes) to provide olefin **2.41** (1.28 g, 2.88 mmol, 72%) as a colorless oil. **2.41**: R_f = 0.28 (silica gel, 5% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = +51.5 (*c* = 1.0, $CHCl_3$); FT-IR (neat) ν_{max} 2953, 2930, 2886, 2858, 1744, 1658, 1473, 1463, 1361, 1254, 1104, 1055, 1006, 864, 777 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.07 (s, 1 H) 4.87 (s, 1 H), 4.28 – 4.24 (m, 1 H), 4.02 (d, *J* = 6.6 Hz, 1 H), 3.73 (dd, *J* = 10.7, 4.7 Hz, 1 H), 3.68 (dd, *J* = 9.9, 4.7 Hz, 1 H), 3.67 (s, 3 H), 3.48 – 3.46 (m, 1 H), 2.65 (dd, *J* = 15.0, 7.3 Hz, 1 H), 2.48 (dd, *J* = 15.0, 6.7 Hz, 1 H), 2.39 (dd, *J* = 13.1, 4.8 Hz, 1 H), 2.31 (dd, *J* = 13.1, 4.8 Hz, 1 H), 0.92 (s, 9 H), 0.88 (s, 9 H), 0.08 (s, 3 H), 0.045 (s, 3 H), 0.038 (s, 6 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.8, 143.9, 110.3, 79.0, 70.6, 70.3, 62.6, 51.8, 37.8, 37.5, 26.1,

26.0, 18.5, 18.4, –4.4, –4.87, –4.94, –5.2 ppm; HRMS (ESI-TOF) calcd for $C_{22}H_{44}NO_5Si_2Na^+$ $[M+Na]^+$ 467.2625, found 467.2618.



2.42

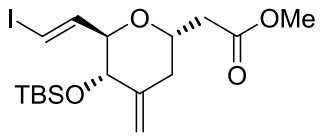
Alcohol 2.42: To a stirred solution of olefin **2.41** (1.0 g, 2.32 mmol, 1.0 equiv) in methanol (15 mL) was added pyridium *p*-toluenesulfonate (583 mg, 2.32 mmol, 1.0 equiv) at 25 °C. After 12 h, the reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate (15 mL). The phases were separated, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 25 → 30% ethyl acetate in hexanes) to provide alcohol **2.42** (730 mg, 2.27 mmol, 98%) as a colorless oil. **2.42**: R_f = 0.30 (silica gel, 25% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = +76.5. (*c* = 1.0, $CHCl_3$); FT-IR (neat) ν_{max} 2953, 2930, 2887, 2858, 1739, 1658, 1473, 1463, 1437, 1389, 1253, 1166, 1098, 1047, 862, 837, 777 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.11 (s, 1 H), 4.88 (s, 1 H), 4.40–4.36 (m, 1 H), 3.93 (d, *J* = 7.4, 1 H), 3.71–3.64 (m, 2 H), 3.69 (s, 3 H), 3.53 (ddd, *J* = 7.4, 6.2, 3.4 Hz, 1 H), 2.73 (dd, *J* = 15.4, 8.8 Hz, 1 H), 2.49–2.44 (m, 2 H), 2.32 (dd, *J* = 13.4, 3.7 Hz, 1 H), 2.15 (t, *J* = 6.8 Hz, 1 H), 0.92 (s, 9 H), 0.09 (s, 3 H), 0.04 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.9, 143.6, 110.4, 77.7, 70.6, 69.9, 61.7, 51.9, 37.8, 36.8, 26.0, 18.3, –4.34, –5.0 ppm; HRMS (ESI-TOF) calcd for $C_{16}H_{30}O_5SiNa^+$ $[M+Na]^+$ 353.1760, found 353.1747.



2.43

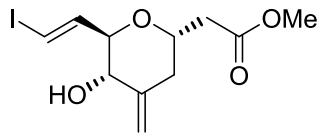
Aldehyde 2.43: To a stirred solution of oxalyl chloride (1.2 mL, 13.4 mmol, 1.5 equiv) in CH_2Cl_2 (21 mL) at –78 °C was slowly added dimethyl sulfoxide (1.9 mL, 26.8 mmol, 3.0 equiv) over 5 min, and the reaction mixture was allowed to slowly warm to –60 °C over an additional 20 min. Then a solution of alcohol **2.42** (2.95 g, 8.93 mmol, 1.0 equiv) in CH_2Cl_2 (41 mL) was added dropwise *via* cannula over 45 min, and the original flask was rinsed with additional CH_2Cl_2 (3 x 3 mL). The reaction mixture was allowed to slowly warm to –45 °C over 30 min, at which point triethylamine (7.2 mL, 51.6 mmol, 5.8 equiv) was added dropwise over 5 min, and the reaction mixture was warmed to 0 °C over 10 min. Then the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (75 mL), and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL), and the combined organic layers were washed with brine (25 mL), dried with anhydrous sodium sulfate, and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 10 → 30% ethyl acetate in hexanes) to provide aldehyde **2.43** (2.80 g, 8.5 mmol, 96%) as a colorless oil. **2.43**: R_f = 0.35 (silica gel, 30% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = +68.2 (*c* = 1.0, $CHCl_3$); FT-IR (neat) ν_{max} 2954, 2930, 2904, 2858, 1739, 1736, 1473, 1463, 1437, 1389, 1360, 1323, 1255, 1210, 1158, 1123, 1092, 1006, 907, 837, 777 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.74 (s, 1 H), 5.02 (s, 1 H), 4.89 (s, 1 H), 4.36 (d, *J* = 4.2 Hz, 1 H), 4.26 – 4.22 (m, 1 H), 4.10 (d, *J* = 4.2 Hz, 1 H), 3.71 (s, 3 H), 2.72 (dd, *J* = 15.4, 7.8 Hz, 1 H), 2.53 (dd, *J* = 15.4, 5.4 Hz, 1 H), 2.44 (dd, *J* = 13.0, 8.4 Hz, 1 H), 2.25 (dd, *J* = 13.0, 3.5 Hz, 1 H), 0.89 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3

H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 201.6, 171.2, 142.5, 112.1, 84.6, 72.6, 70.5, 52.0, 39.3, 36.0, 25.9, 18.3, -4.5, -4.9 ppm; HRMS (ESI-TOF) calcd for $C_{16}H_{28}NO_5SiNa^+$ $[M+Na]^+$ 351.1604, found 351.1581.



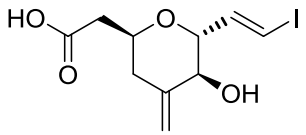
2.44

Vinyl iodide 2.44: To a stirred solution of anhydrous $CrCl_2$ (597 mg, 4.86 mmol, 6.0 equiv) and CHI_3 (957 mg, 2.43 mmol, 3.0 equiv) in THF (16 mL) at 25 °C was added a solution of aldehyde **2.43** (266 mg, 0.81 mmol, 1.0 equiv) in THF (8 mL) *via* cannula, and the original flask was rinsed with additional THF (3 x 1 mL). After 12 h, the reaction mixture was quenched with water (15 mL). The phases were separated, and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 10% Et_2O in hexanes) to provide vinyl iodide **2.44** (213 mg, 0.47 mmol, 58%) as a colorless oil. **2.44**: R_f = 0.29 (silica gel, 10% Et_2O in hexanes); $[\alpha]_D^{25}$ = +93.3 (*c* = 1.0, CH_2Cl_2); FT-IR (neat) ν_{max} 2952, 2857, 1740, 1656, 1613, 1472, 1436, 1318, 1253, 1165, 1117, 1006, 859, 837, 777 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.55 (dd, *J* = 14.5, 6.2 Hz, 1 H), 6.41 (dd, *J* = 14.5, 1.1 Hz, 1 H), 5.13 (s, 1 H), 4.90 (s, 1 H), 4.41 – 4.38 (m, 1 H), 3.88 – 3.86 (m, 1 H), 3.80 – 3.78 (m, 1 H), 3.68 (s, 3 H), 2.68 (dd, *J* = 15.0, 7.7 Hz, 1 H), 2.52 – 2.46 (m, 2 H), 2.31 (dd, *J* = 13.4, 3.6 Hz, 1 H), 0.92 (s, 9 H), 0.07 (s, 3 H), 0.03 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.5, 143.8, 142.8, 110.6, 80.5, 80.1, 73.8, 70.4, 51.9, 37.7, 37.1, 25.9, 18.3, -4.5, -4.6 ppm; HRMS (ESI-TOF) calcd for $C_{17}H_{29}O_4INa^+$ $[M+Na]^+$ 475.0777, found 475.0772.



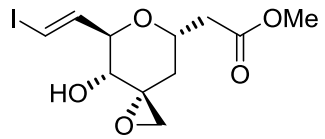
2.45

Alcohol 2.45: To a stirred solution of vinyl iodide **2.44** (200 mg, 0.44 mmol, 1.0 equiv) in THF (4.4. mL) at 0 °C was added tetra-*n*-butylammonium fluoride (1.0 M THF, 0.52 mL, 0.52 mmol, 1.2 equiv) dropwise, and the reaction mixture was allowed to slowly warm to 25 °C. After 3 h, the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (10 mL), and the two phases were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL), and the combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (20 → 25% ethyl acetate in hexanes) to afford pure alcohol **2.45** (138 mg, 0.41 mmol, 93%) as a colorless oil. **2.45**: R_f = 0.33 (silica gel, 30% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = +66.7 (*c* = 1.0, CH_2Cl_2); FT-IR (neat) ν_{max} 3451, 3073, 2990, 2949, 2904, 1735, 1655, 1609, 1472, 1437, 1382, 1321, 1272, 1203, 1165, 1089, 1045, 1002, 950, 908 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.62 (dd, *J* = 14.7, 5.7 Hz, 1 H), 6.53 (dd, *J* = 14.7, 1.3 Hz, 1 H), 5.13 (s, 1 H), 4.98 (s, 1 H), 4.33 – 4.29 (m, 1 H), 4.11 – 4.09 (m, 1 H), 3.92 (d, *J* = 5.4 Hz, 1 H), 3.69 (s, 3 H), 2.66 (dd, *J* = 15.3, 7.9 Hz, 1 H), 2.48 (dd, *J* = 15.3, 5.9 Hz, 1 H), 2.43 – 2.36 (m, 2 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.3, 142.4, 141.9, 111.9, 81.4, 79.9, 72.6, 69.4, 52.0, 38.5, 36.6 ppm; HRMS (ESI-TOF) calcd for $C_{11}H_{15}O_4INa_+$ $[M+Na]^+$ 360.9913, found 360.9909.



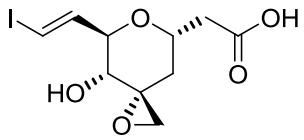
2.46

Acid 2.46: To a stirred solution of alcohol **2.45** (107 mg, 0.32 mmol, 1.0 equiv) in 1:1 THF/H_2O (2.8 mL) at 0 °C was added LiOH (62 mg, 2.6 mmol, 8.0 equiv), and the reaction mixture was allowed to slowly warm to 25 °C. After 12 h, the reaction mixture was neutralized with phosphate buffer (NaH_2PO_4, 1.0 M, 10 mL) and the phases were separated. The aqueous layer was extracted with ethyl acetate (3 x 7 mL), and the combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The resulting acid **2.46** (101 mg, 0.34 mmol, 98%) was sufficiently pure for characterization and X-ray crystallographic purposes. **2.46**: R_f = 0.30 (silica gel, 10% methanol in CH_2Cl_2); m.p. = 128 – 136 °C (ethyl acetate); $[\alpha]_D^{25}$ = +61.0 (*c* = 1.0, MeOH); FT-IR (neat) ν_{max} 3385, 3074, 2923, 1711, 1608, 1407, 1265, 1169, 1085, 1043, 1018, 951, 912, 838, 812 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.63 (dd, *J* = 14.7, 5.8 Hz, 1 H), 6.56 (dd, *J* = 14.7, 1.2 Hz, 1 H), 5.15 (s, 1 H), 5.01 (s, 1 H), 4.34 – 4.30 (m, 1 H), 4.17 – 4.08 (m, 1 H), 3.95 (d, *J* = 5.2 Hz, 1 H), 2.71 (dd, *J* = 15.6, 7.9 Hz, 1 H), 2.55 (dd, *J* = 15.6, 5.6 Hz, 1 H), 2.49 – 2.38 (m, 2 H) 1.25 (br s, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.4, 142.1, 141.5, 112.3, 81.9, 80.0, 72.5, 69.2, 38.1, 36.4 ppm; HRMS (ESI-TOF) calcd for $C_{10}H_{12}IO_4^-$ $[M\text{-}H^+]^-$ 322.9786, found 322.9786.



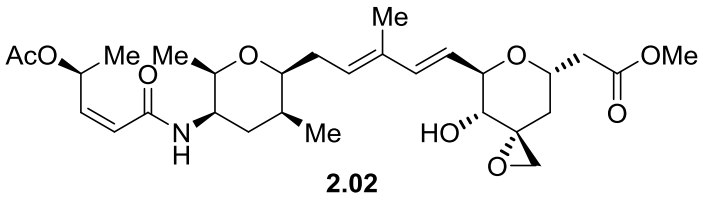
2.47

Epoxide 2.47: To a stirred solution of alcohol **2.45** (120 mg, 0.35 mmol, 1.0 equiv) in CH_2Cl_2 (8 mL) at 0 °C was added vanadyl acetoacetonate (4.0 mg, 0.035 mmol, 0.1 equiv) followed by a solution of *tert*-butylhydroperoxide (5.5 M decanes, 0.13 mL, 0.70 mmol, 2.0 equiv), and the reaction mixture was allowed to slowly warm to 25 °C. After 3 h, the reaction mixture was filtered through a short silica plug, rinsed thoroughly with ethyl acetate (30 mL), and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 15 $\rightarrow$ 35%) to provide epoxide **2.47** (92 mg, 0.26 mmol, 74%) as a colorless oil. **2.47**: R_f = 0.30 (silica gel, 40% ethyl acetate in hexanes); $[\alpha]_D^{25}$ = +61.7 (*c* = 1.0, CH_2Cl_2); FT-IR (neat) ν_{max} 3385, 2923, 1730, 1608, 1407, 1260, 1169, 1083, 1043, 1018, 953, 908 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.70 (dd, *J* = 14.6, 5.0 Hz, 1 H), 6.53 (dd, *J* = 14.6, 1.6 Hz, 1 H), 4.54 – 4.46 (m, 1 H), 4.14 – 4.08 (m, 1 H), 3.70 (s, 3 H), 3.50 (dd, *J* = 9.2, 7.5 Hz, 1 H), 2.98 (d, *J* = 4.4 Hz, 1 H), 2.91 (dd, *J* = 15.5, 8.3 Hz, 1 H), 2.68 – 2.61 (m, 2 H), 2.17 (dd, *J* = 14.3, 5.3 Hz, 1 H), 1.85 (d, *J* = 9.2 Hz, 1 H), 1.72 (dd, *J* = 14.3, 4.0 Hz, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.4, 142.3, 80.2, 76.8, 69.1, 69.0, 57.1, 52.0, 49.5, 37.9, 34.4 ppm; HRMS (ESI-TOF) calcd for $C_{11}H_{15}IO_5Na^+$ $[M+Na]^+$ 376.9862, found 376.9859.



2.17

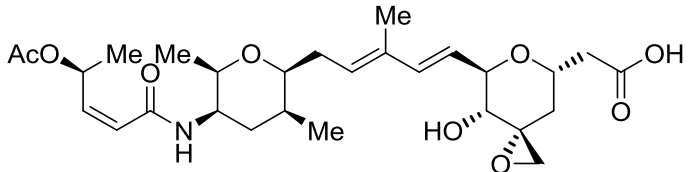
Acid 2.17: To a stirred solution of epoxide **2.47** (20 mg, 0.06 mmol, 1.0 equiv) in 10:1 THF/H_2O THF (1.2 mL) at 0 °C was added LiOH (2.2 mg, 0.09 mmol, 1.5 equiv), and the reaction mixture was allowed to slowly warm to 25 °C. After 6 h, the reaction mixture was neutralized with phosphate buffer (NaH_2PO_4, 1.0 M, 3 mL) and the phases were separated. The aqueous layer was extracted with ethyl acetate (3 x 2 mL), and the combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The resulting acid **2.17** (18 mg, 0.054 mmol, 90%) was sufficiently pure for direct use in the next step. **2.17**: R_f = 0.32 (silica gel, 1% acetic acid in 95:5 CH_2Cl_2/MeOH); $[\alpha]_D^{25}$ = +61.7 (*c* = 0.3, CH_2Cl_2); FT-IR (neat) ν_{max} 3419, 3063, 2926, 1714, 1610, 1408, 1263, 1237, 1171, 1086, 1066, 1033, 944, 922, 856, 812, 742, 709 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.70 (dd, *J* = 14.6, 5.1 Hz, 1 H), 6.55 (dd, *J* = 14.6, 1.5 Hz, 1 H), 4.56 – 4.46 (m, 1 H), 4.14 – 4.07 (m, 1 H), 3.52 (d, *J* = 7.7 Hz, 1 H), 3.01 (d, *J* = 4.4 Hz, 1 H), 2.96 (dd, *J* = 15.7, 8.4 Hz, 1 H), 2.71 (dd, *J* = 15.7, 6.1 Hz, 1 H), 2.66 (d, *J* = 4.4 Hz, 1 H), 2.20 (dd, *J* = 14.3, 5.3 Hz, 1 H), 1.74 (dd, *J* = 14.3, 3.9 Hz, 1 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.8, 142.2, 80.5, 76.8, 69.0, 68.9, 57.1, 49.5, 37.6, 34.4 ppm; HRMS (ESI-TOF) calcd for $C_{11}H_{12}IO_5^-$ [M-H^+]$^-$ 338.9735, found 338.9740.



2.02

Thailanstatin A methyl ester (**2.02**): To a stirred solution of epoxide **2.47** (7 mg, 0.02 mmol, 1.0 equiv) and boronate **2.16** (27 mg, 0.06 mmol, 3.0 equiv) in rigorously degassed (freeze-pump-thaw technique x 3) 3:1:1 1,4-dioxane/MeCN/H_2O (0.22 mL) at 25 °C was added tripotassium phosphate monohydrate (4.6 mg, 0.02 mmol, 1.0 equiv) followed by Pd(dppf)Cl_2•CH_2Cl_2 (0.32 mg, 0.04 μmol, 0.02 equiv). After 10 min, the reaction mixture was filtered through a layer of celite, and rinsed thoroughly with ethyl acetate (25 mL). The organic layer was washed with brine (5 mL), dried with anhydrous sodium sulfate, and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, 45 → 20% hexanes in ethyl acetate) to provide methyl ester **2.02** (7.0 mg, 0.013 mmol, 64%) as a colorless oil. **2.02**: R_f = 0.18 (silica gel, 20% hexanes in ethyl acetate); $[\alpha]_D^{25}$ = +3.0 (*c* = 0.1, CH_2Cl_2); FT-IR (neat) ν_{max} 3378, 2974, 2934, 1736, 1667, 1638, 1520, 1439, 1370, 1332, 1317, 1244, 1169, 1116, 1057, 1009, 972, 933, 898, 856, 814, 785, 720 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.37 (d, *J* = 15.8 Hz, 1 H), 6.28 – 6.23 (m, 1 H), 5.98 (d, *J* = 9.0 Hz, 1 H), 5.89 (dd, *J* = 11.6, 7.9 Hz, 1 H), 5.70 (dd, *J* = 11.6, 1.3 Hz, 1 H), 5.62 (dd, *J* = 15.8, 6.2 Hz, 1 H), 5.51 (dd, *J* = 7.1, 7.1 Hz, 1 H), 4.52 – 4.48 (m, 1 H), 4.21 (dd, *J* = 6.5, 6.5 Hz, 1 H), 3.96 – 3.93 (m, 1 H), 3.70 (s, 3 H), 3.66 (qd, *J* = 6.3, 2.1 Hz, 1 H), 3.54 – 3.51 (m, 2 H), 2.99 (d, *J* = 4.6 Hz, 1 H), 2.93 (dd, *J* = 15.4, 7.8 Hz, 1 H), 2.69 (dd, *J* = 15.4, 6.6 Hz, 1 H), 2.64 (d, *J* = 4.6 Hz, 1 H), 2.41 – 2.36 (m, 1 H), 2.26 – 2.21 (m, 1 H), 2.14 (dd, *J* = 14.2, 5.2 Hz, 1 H), 2.04 (s, 3 H), 1.99 – 1.91 (m, 2 H), 1.82 – 1.74

(m, 2 H), 1.76 (s, 3 H), 1.39 (d, *J* = 6.5 Hz, 3 H), 1.15 (d, *J* = 6.4 Hz, 3 H), 1.02 (d, *J* = 7.4 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.6, 170.5, 165.0, 143.8, 138.6, 134.7, 129.6, 123.1, 122.7, 80.9, 76.1, 75.8, 69.9, 69.1, 68.9, 57.3, 52.0, 49.8, 47.3, 38.2, 36.0, 34.7, 32.2, 29.1, 21.4, 20.1, 18.0, 15.3, 12.8 ppm; HRMS (ESI-TOF) calcd for $C_{29}H_{43}NO_9Na^+$ $[M+Na]^+$ 572.2830, found 572.2823.



2.01

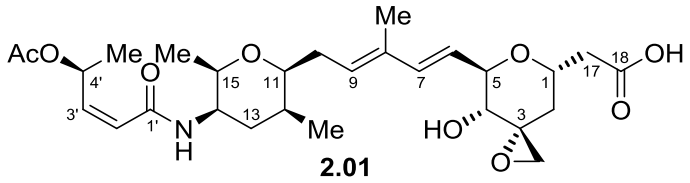
Thailanstatin A (2.01): To a stirred solution of epoxide **2.17** (4.0 mg, 0.012 mmol, 1.0 equiv) and boronate **2.16** (5.8 mg, 0.013 mmol, 1.1 equiv) in rigorously degassed (freeze-pump-thaw technique x 3) 3:1:1 1,4-dioxane/MeCN/H_2O (0.64 mL,) at 25 °C was added tripotassium phosphate monohydrate (2.8 mg, 0.012 mmol, 1.0 equiv) followed by $Pd(dppf)Cl_2•CH_2Cl_2$ (0.1 mg, 0.125 μmol, 0.025 equiv). After 10 min, the reaction mixture was neutralized with phosphate buffer (NaH_2PO_4, 1.0 M, 2.5 mL), filtered through a layer of celite, and rinsed thoroughly with ethyl acetate (20 mL). Then the organic layer was dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified by reversed-phase HPLC (C18, φ19 × 150 mm, Atlantis, 40 → 50% aqueous MeCN containing 0.03% TFA) to afford thailanstatin A (**2.01**) (*ca*. 3.0 mg, 0.006 mmol, 52%) as a white foam. **2.01**: R_f = 0.35 (silica gel, 1% acetic acid in ethyl acetate); $[\alpha]_D^{25}$ = +3.0 (*c* = 0.1, CH_2Cl_2); FT-IR (neat) ν_{max} 3347, 3036, 2976, 2933, 1731, 1667, 1634, 1523, 1442, 1370, 1333, 1317, 1244, 1116, 1051, 1008, 970, 957, 928, 894, 859, 812, 783, 710 cm^{-1}; ^{1}H NMR (600 MHz, CD_2Cl_2) δ 6.36 (d, *J* = 15.8 Hz, 1 H), 6.30 – 6.25 (m, 1 H), 6.24

(d, *J* = 9.0 Hz, 1 H), 5.90 (dd, *J* = 11.6, 7.8 Hz, 1 H), 5.75 (dd, *J* = 11.6, 1.2 Hz, 1 H), 5.62 (dd, *J* = 15.8, 6.2 Hz, 1 H), 5.51 (dd, *J* = 7.0, 7.0 Hz, 1 H), 4.48 – 4.44 (m, 1 H), 4.25 (dd, *J* = 6.4, 6.4 Hz, 1 H), 3.92 – 3.89 (m, 1 H), 3.68 (qd, *J* = 6.5, 2.2 Hz, 1 H), 3.55 (ddd, *J* = 7.2, 7.2, 2.7 Hz, 1 H), 3.48 (d, *J* = 6.7 Hz, 1 H), 2.95 (dd, *J* = 15.6, 9.0 Hz, 1 H), 2.95 (d, J = 4.6 Hz, 1 H), 2.65 (d, *J* = 4.6 Hz, 1 H), 2.62 (dd, *J* = 15.6, 5.2 Hz, 1 H), 2.39 – 2.34 (m, 1 H), 2.24 – 2.19 (m, 1 H), 2.05 (dd, *J* = 14.0, 5.0 Hz, 1 H), 2.01 (s, 3 H), 1.94 – 1.93 (m, 2 H), 1.79 (dd, *J* = 14.0, 5.1 Hz, 1 H), 1.78 –1.76 (m, 1 H), 1.76 (s, 3 H), 1.34 (d, *J* = 6.5 Hz, 3 H), 1.12 (d, *J* = 6.5 Hz, 3 H), 1.00 (d, *J* = 7.4 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, CD_2Cl_2) δ 173.3, 170.7, 165.1, 144.0, 138.6, 134.9, 130.1, 123.2, 122.8, 81.4, 76.6, 76.5, 70.5, 68.96, 68.95, 57.5, 50.4, 47.4, 38.3, 36.2, 34.8, 32.3, 29.5, 21.4, 20.2, 17.9, 15.2, 12.7 ppm; HRMS (ESI-TOF) calcd for $C_{28}H_{41}NO_9Na^+$ $[M+Na]^+$ 558.2674, found 558.2671.

To approximate the yield of this step, the crude material from the aforementioned procedure was redissolved in 3:2 toluene/MeOH (0.5 mL) with stirring, and a solution of $TMSCHN_2$ (2.0 M Et_2O, 18 µL, 0.036 mmol, 3.0 equiv) was added dropwise at 25 °C. After 1 h, the reaction mixture was concentrated *in vacuo* and then purified directly by flash column chromatography (silica gel, 45 → 20% hexanes in ethyl acetate) to provide methyl ester **2.02** (3.3 mg, 0.006 mmol, 52%) as a colorless oil.

3. Comparison of Spectral Data of Natural and Synthetic Thailanstatin A

Table **2.01**: Comparison of ^{1}H NMR spectroscopic data of natural and synthetic thailanstatin A (**2.01**).



2.01

position	**reported natural[1]** δ ^{1}H [ppm; mult; *J* (Hz)] 600 MHz	**synthetic** δ ^{1}H [ppm; mult; *J* (Hz)] 600 MHz	**deviation** (natural–synthetic) Δδ (ppm)[a]
1	4.51; m	4.46, m	0.05
2[b]	2.12; d; (not reported)	2.05; dd; 14.0, 5.0	0.07
	1.80; m	1.79; dd; 14.0, 5.1	0.01
4	3.51; d; 7.3	3.48; d; 6.7	0.03
5	4.27; t; 6.3	4.25; dd; 6.4, 6.4	0.02
6	5.66; dd; 16.0, 6.0	5.62; dd; 15.8, 6.2	0.04
7	6.37; d; 16.0	6.36; d; 15.8	0.01
9	5.48; t; 7.0	5.51; dd; 7.0, 7.0	–0.03
10	2.38; m	2.36; m	0.02
	2.24; m	2.22; m	0.02
11	3.59; td; 7.4, 2.5	3.55; ddd; 7.2, 7.2, 2.7	0.04
12	1.78 (overlap)	1.77; m (overlap)	0.01
13	1.95; m	1.93; m	0.02
14	3.92; m	3.90; m	0.02
15	3.74; qd; 6.5, 2.0	3.68; qd; 6.5, 2.2	0.06
16	1.16; d; 6.5	1.12; d; 6.5	0.04
17[b]	3.02; dd; 15.0, 9.0	2.95; dd; 15.6, 9.0	0.07
	2.60; dd; 15.0, 5.0	2.62; dd; 15.6, 5.2	0.02
19	2.99; d; 4.6	2.95; d; 4.6	0.04

Table **2.01**: Comparison of ^{1}H NMR spectroscopic data of natural and synthetic thailanstatin A (**2.01**), continued.

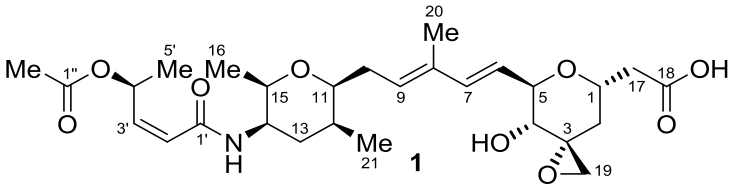
	2.67; d; 4.5	2.65; d; 4.6	0.02
20	1.77; s	1.76; s	0.01
21	1.01; d; 7.3	1.00; d; 7.4	0.01
2'	5.84; dd; 11.6, 1.0	5.75; dd; 11.6, 1.2	0.09
3'	5.95; dd; 11.6, 8.0	5.90; dd; 11.6, 7.8	0.05
4'	6.33; m	6.27, m	0.06
5'	1.36; d; 6.5	1.34; d; 6.5	0.02
2"	2.06; s	2.01; s	0.05
NH[c]	6.69; d; 8.7	6.24; d; 9.0	0.45

[a]These deviations may be partly due to the fact that the chemical shifts of the reported ^{1}H NMR signals were based on a slightly different calibration (δ_H = 5.36 for $CHDCl_2$, see Ref. 1) than the one used in this work (δ_H = 5.32 for $CHDCl_2$, see Ref. 31).

[b]The chemical shifts (δ) for the ^{13}C NMR signals at these positions appear to have been inadvertently interchanged in the original report.[1]

[c]Two hydroxy groups were not oberservable in the ^{1}H NMR spectrum.

Table **2.02**: Comparison of ^{13}C NMR spectroscopic data of natural and synthetic thailanstatin A (**2.01**).



position	reported natural[1]	Synthetic	deviation
	δ ^{13}C [ppm]	δ ^{13}C [ppm]	(natural–synthetic)
	151 MHz	151 MHz	Δδ (ppm)[a]
1	68.6	69.0	–0.4
2[b]	34.4	34.8	–0.4
3	57.1	57.5	–0.4
4	70.1	70.5	–0.4
5	75.9	76.5	–0.6
6	123.0	123.2	–0.2
7	138.0	138.6	–0.6
8	134.5	134.9	–0.4
9	129.4	130.1	–0.7
10	31.8	32.3	–0.5
11	81.1	81.4	–0.3
12	29.1	29.5	–0.4
13	35.7	36.2	–0.5
14	47.0	47.4	–0.4
15	76.2	76.6	–0.4
16	17.4	17.9	–0.5
17[b]	38.1	38.3	–0.2
18	173.8	173.3	0.5

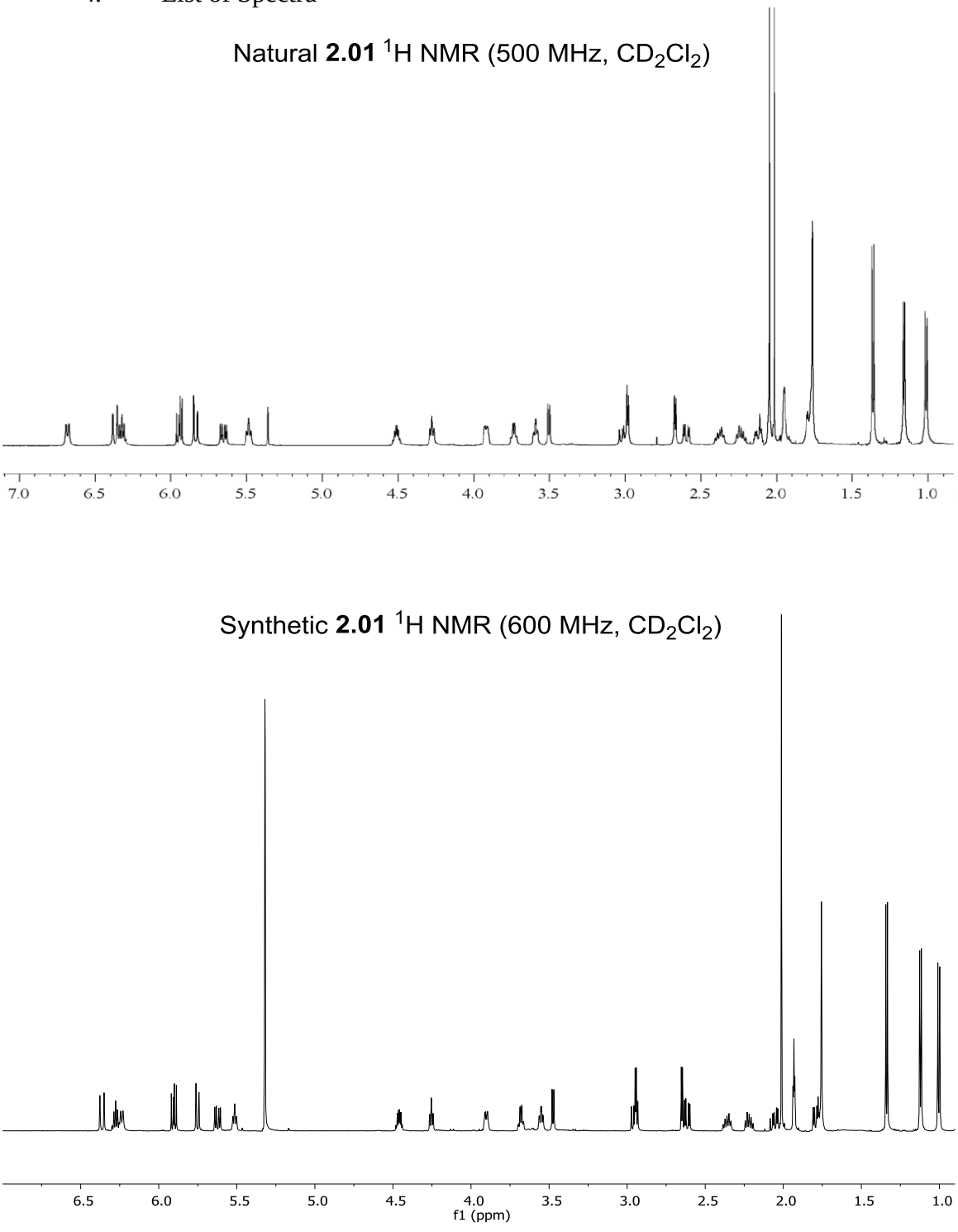
Table **2.02**: Comparison of ^{13}C NMR spectroscopic data of natural and synthetic thailanstatin A (**2.01**), continued.

19	49.9	50.4	–0.5
20	12.3	12.7	–0.4
21	14.7	15.2	–0.5
1'	164.9	165.1	–0.2
2'	122.4	122.8	–0.4
3'	143.6	144.0	–0.4
4'	68.6	69.0	–0.4
5'	19.8	20.2	–0.4
1"	170.3	170.7	–0.4
2"	21.0	21.4	–0.4

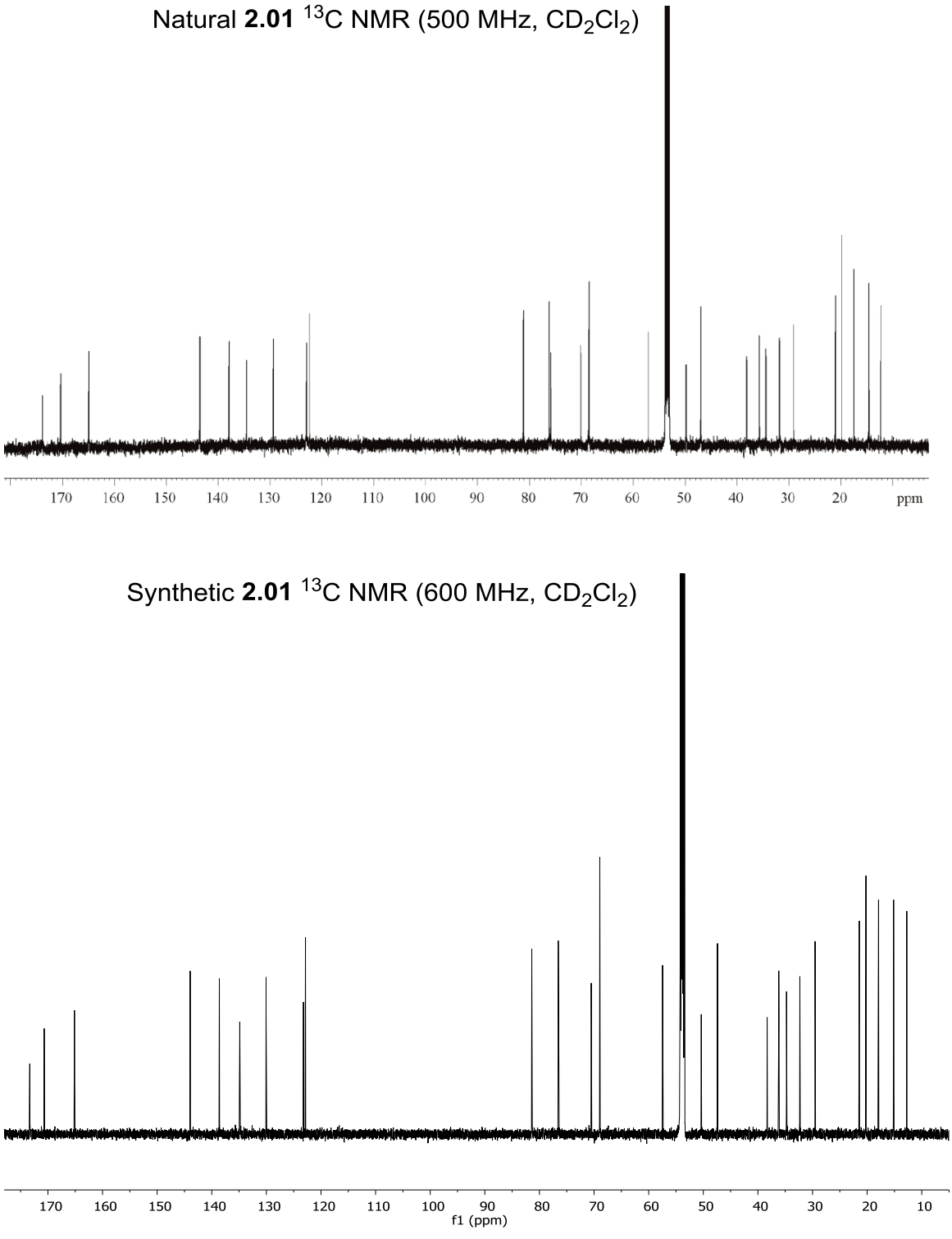
[a]These deviations may be partly due to the fact that the chemical shifts of the reported ^{1}H NMR signals were based on a slightly different calibration (δ_C = 53.44 for $CHDCl_2$, see Ref. 1) than the one used in this work (δ_C = 53.84) for $CHDCl_2$, see Ref. 31).

[b]The chemical shifts (δ) for the ^{13}C NMR signals at these positions appear to have been inadvertently interchanged in the original report.[1]

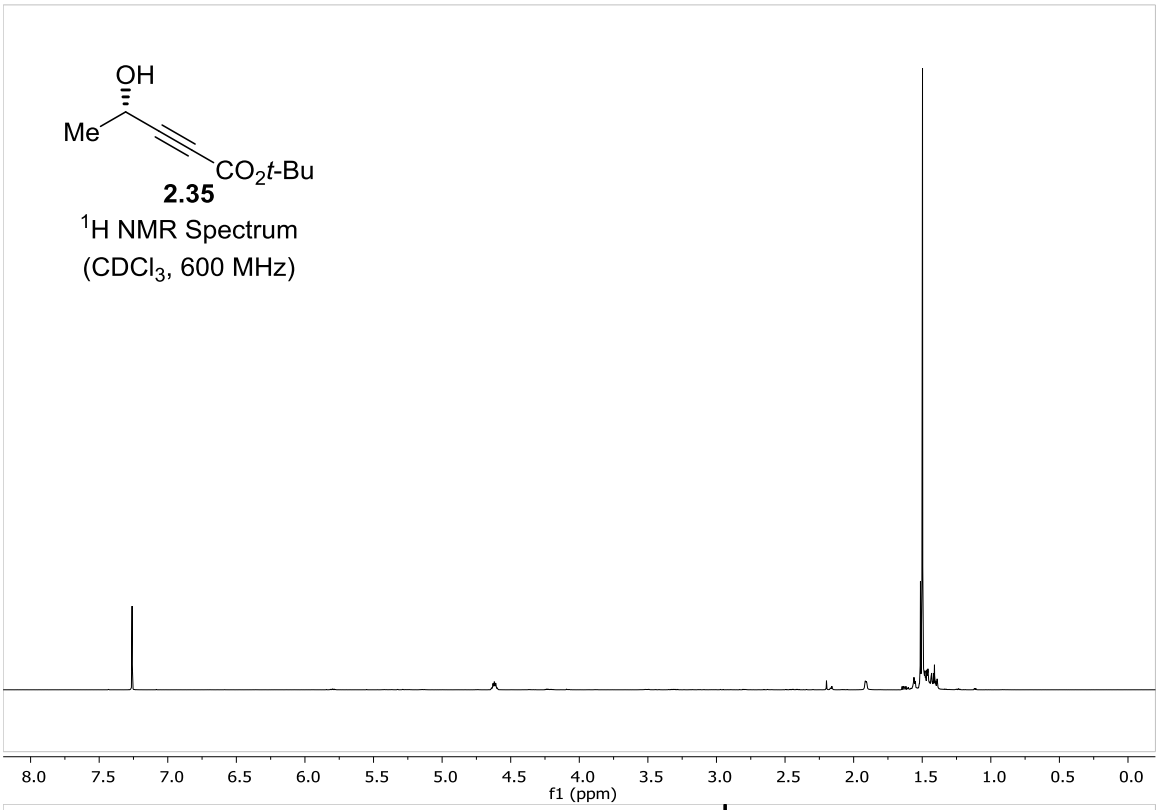
4. List of Spectra

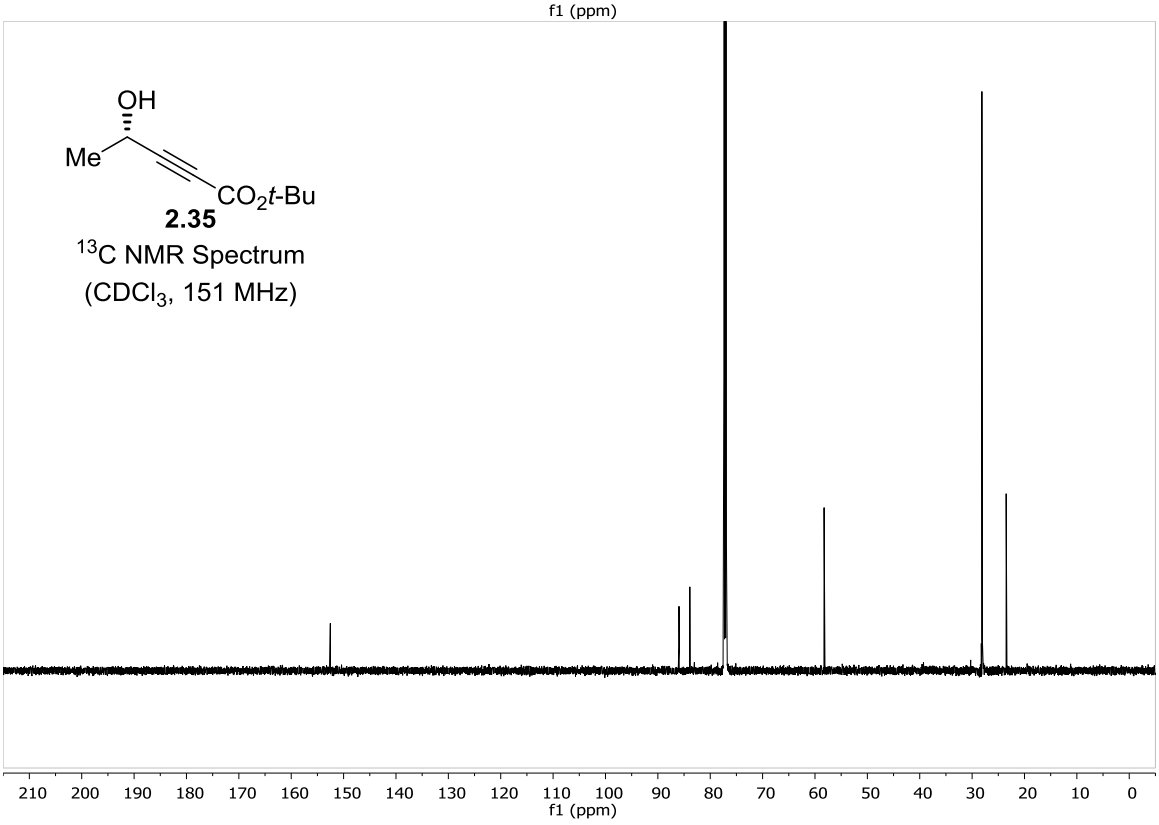


Spectra **2.01**: Compound **2.01**: Comparison of Natural and Synthetic ^{1}H NMR

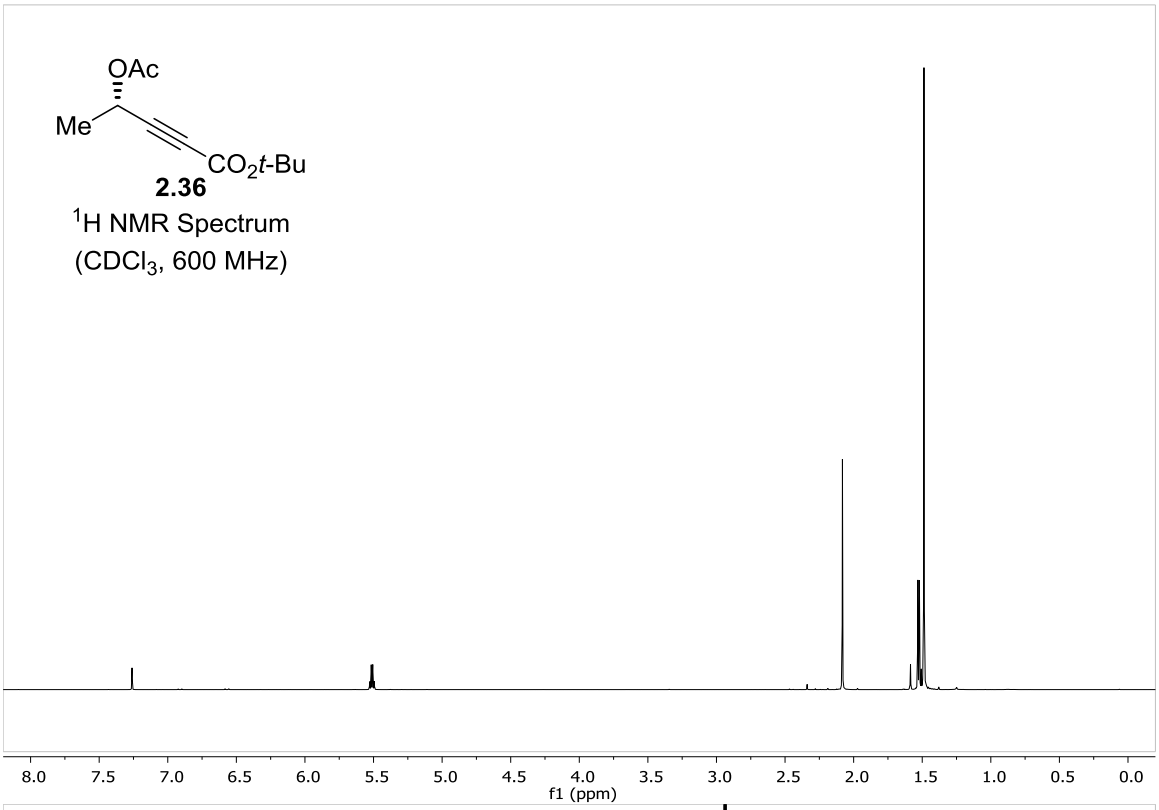


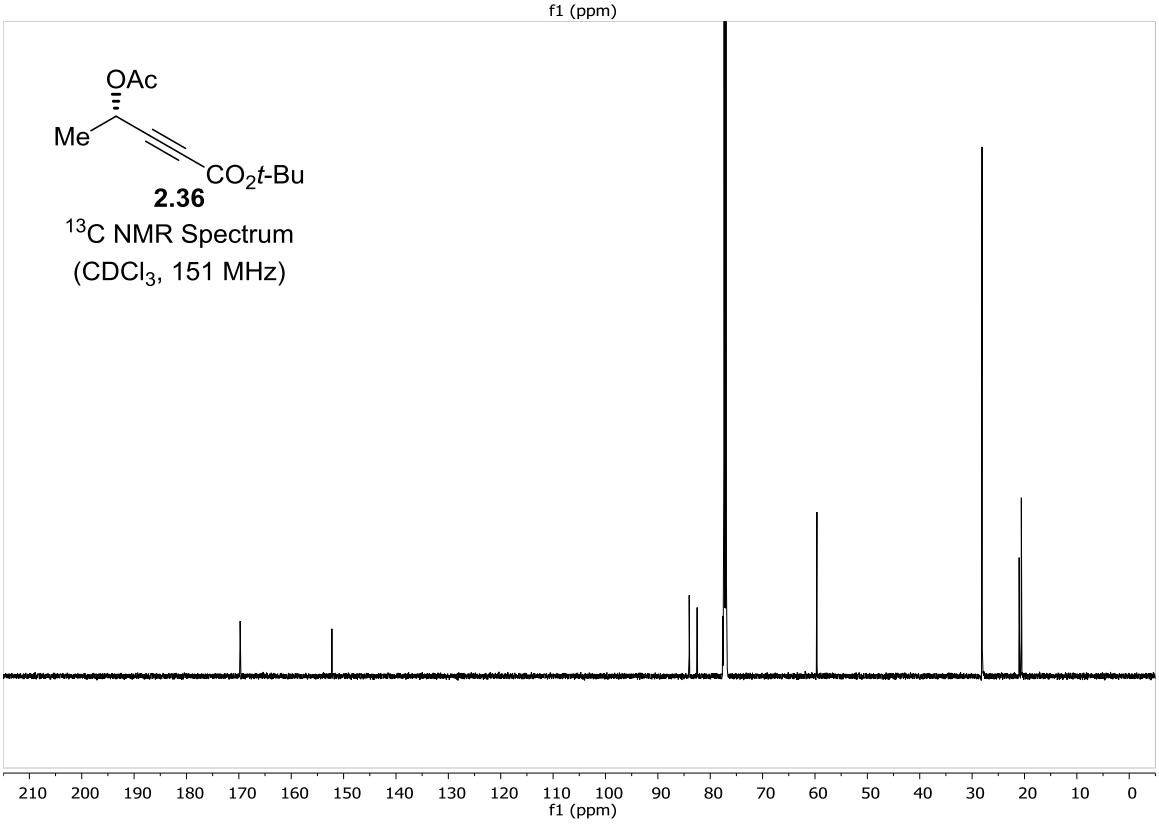
Spectra **2.02**: Compound **2.01**: Comparison of Natural and Synthetic ^{13}C NMR



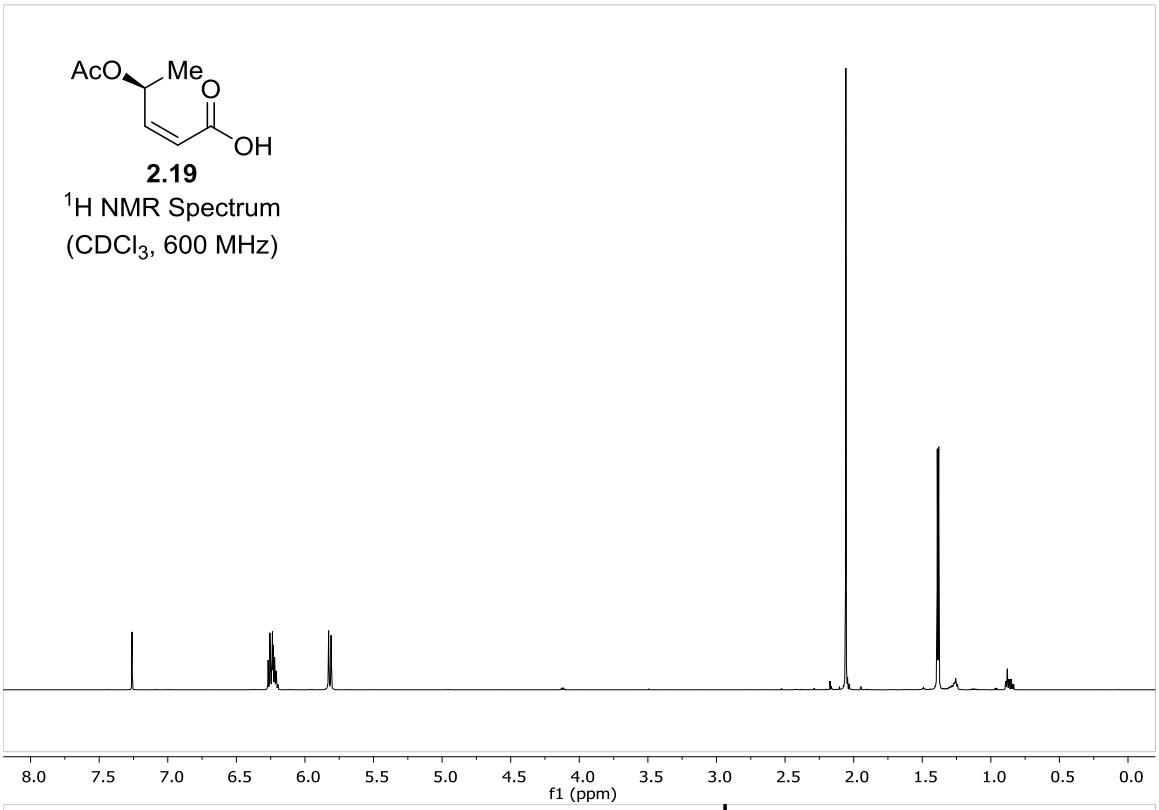


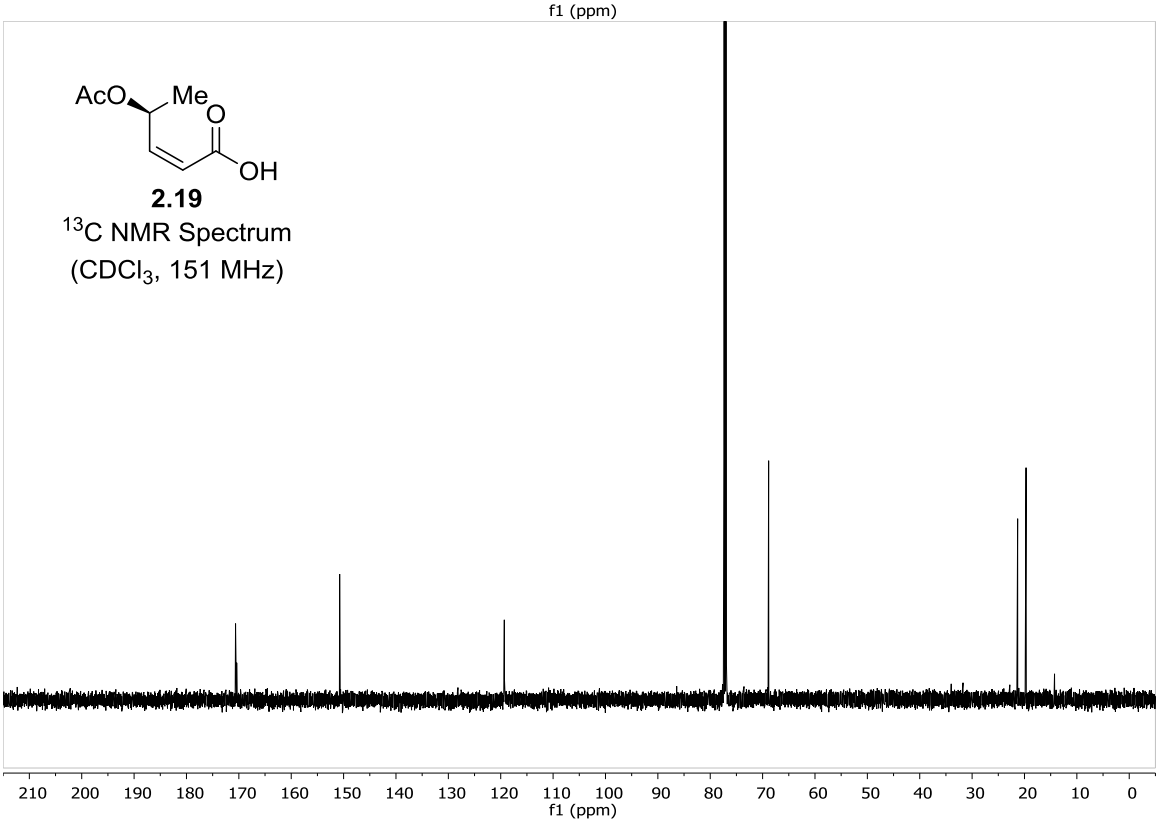
Spectra **2.03**: Compound **2.35**: ^{1}H and ^{13}C NMR



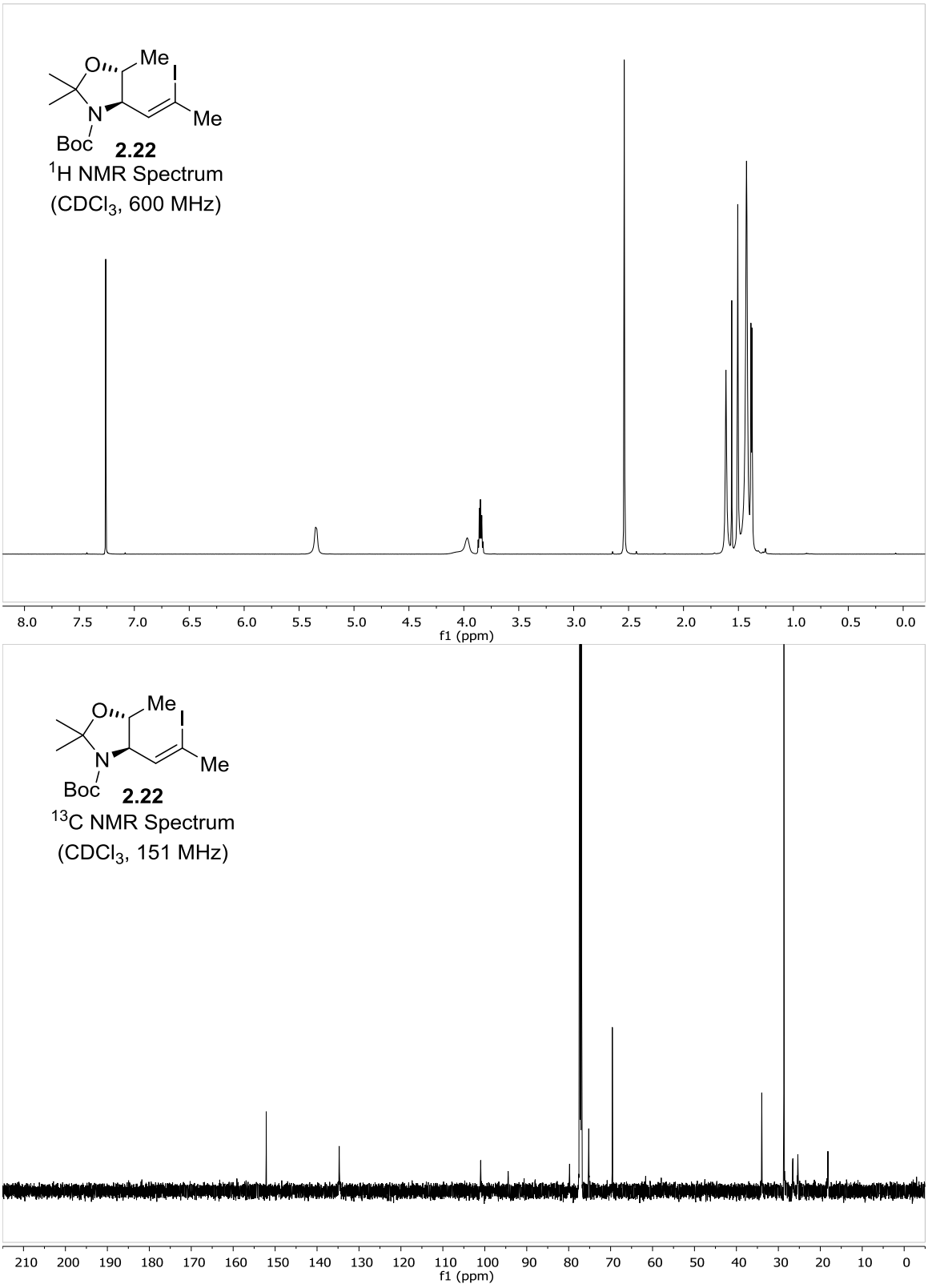


Spectra **2.04**: Compound **2.36**: ^{1}H and ^{13}C NMR

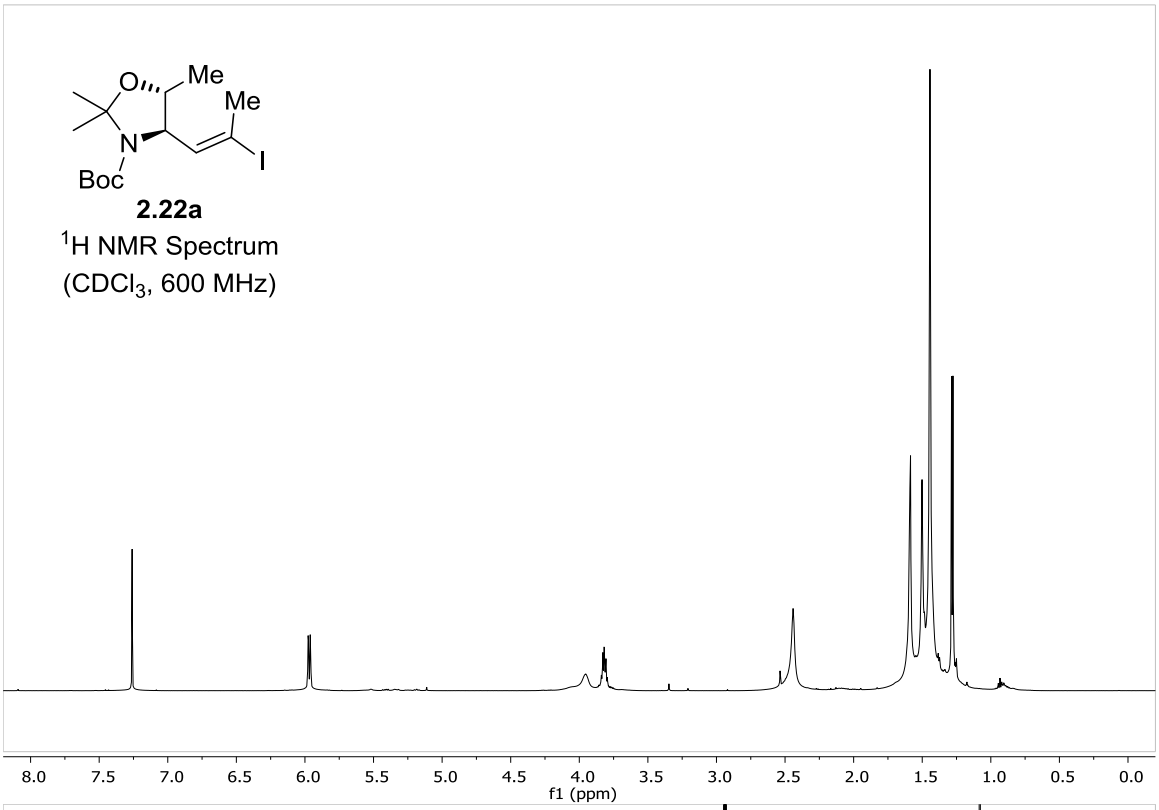


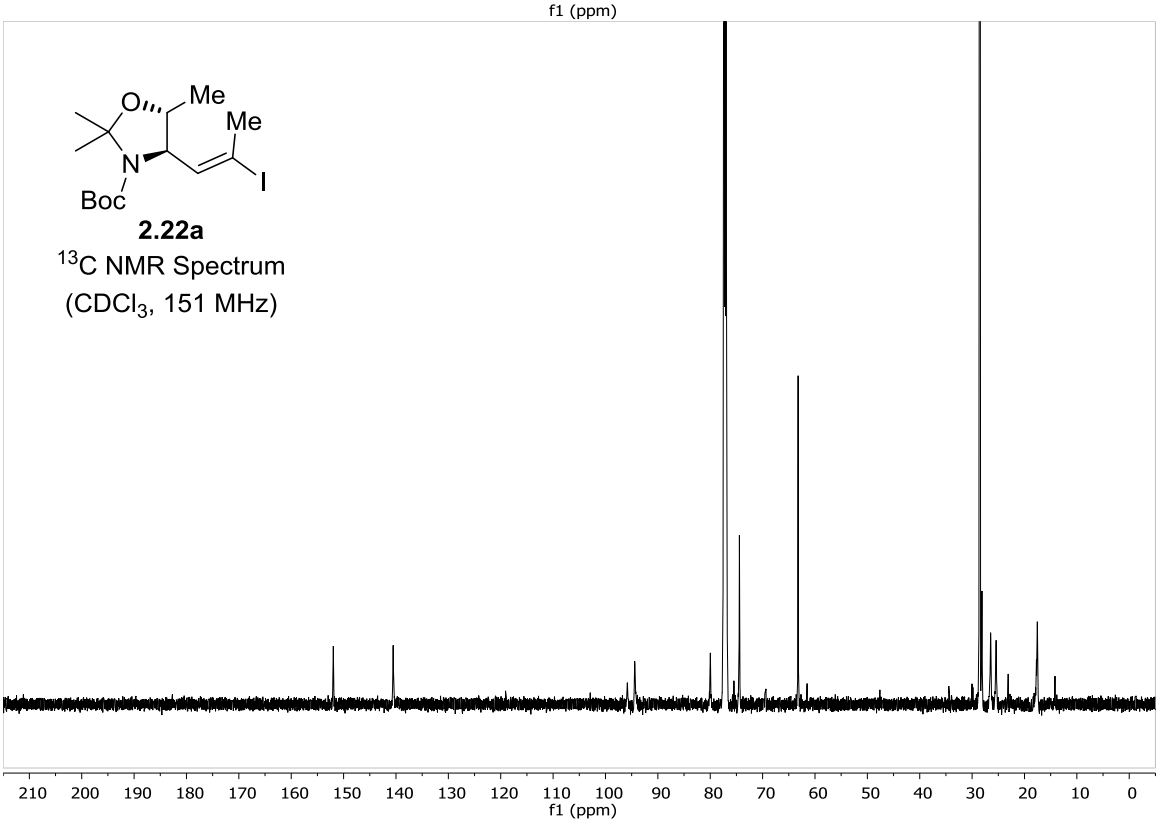


Spectra **2.05**: Compound **2.19**: ^{1}H and ^{13}C NMR

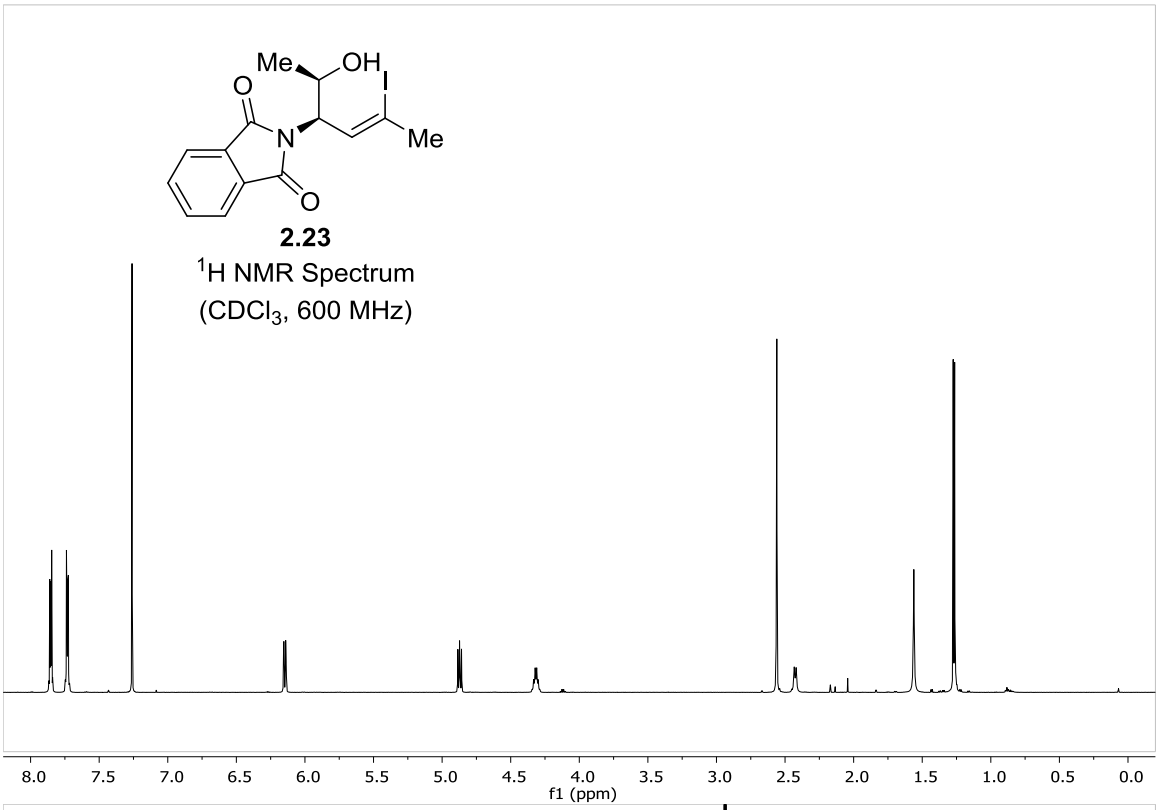


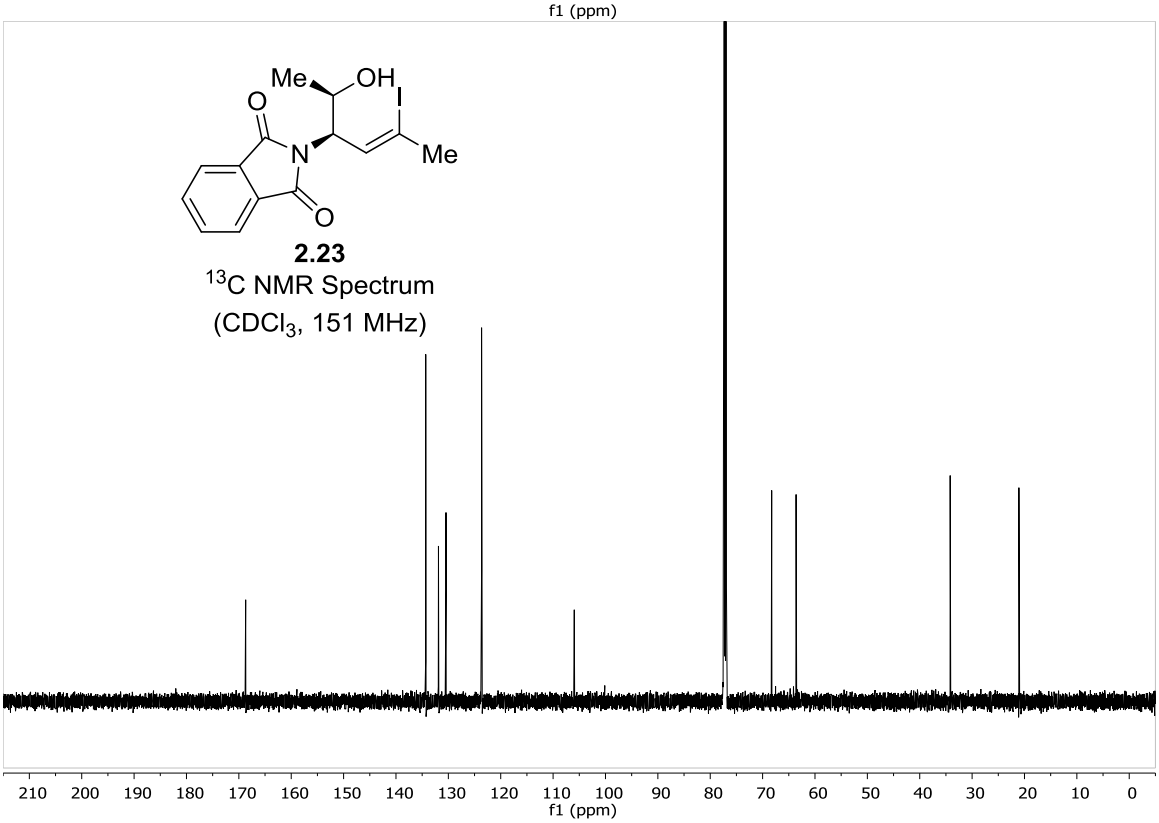
Spectra **2.06**: Compound **2.22**: ^{1}H and ^{13}C NMR



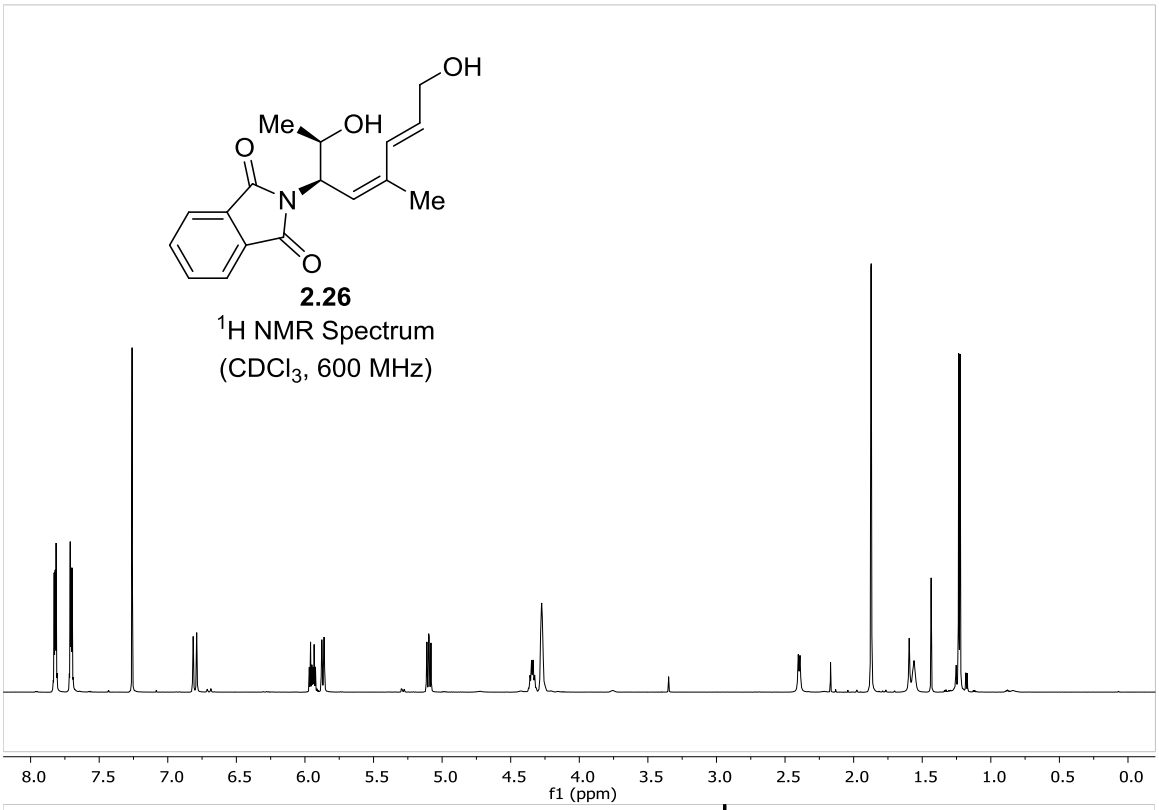


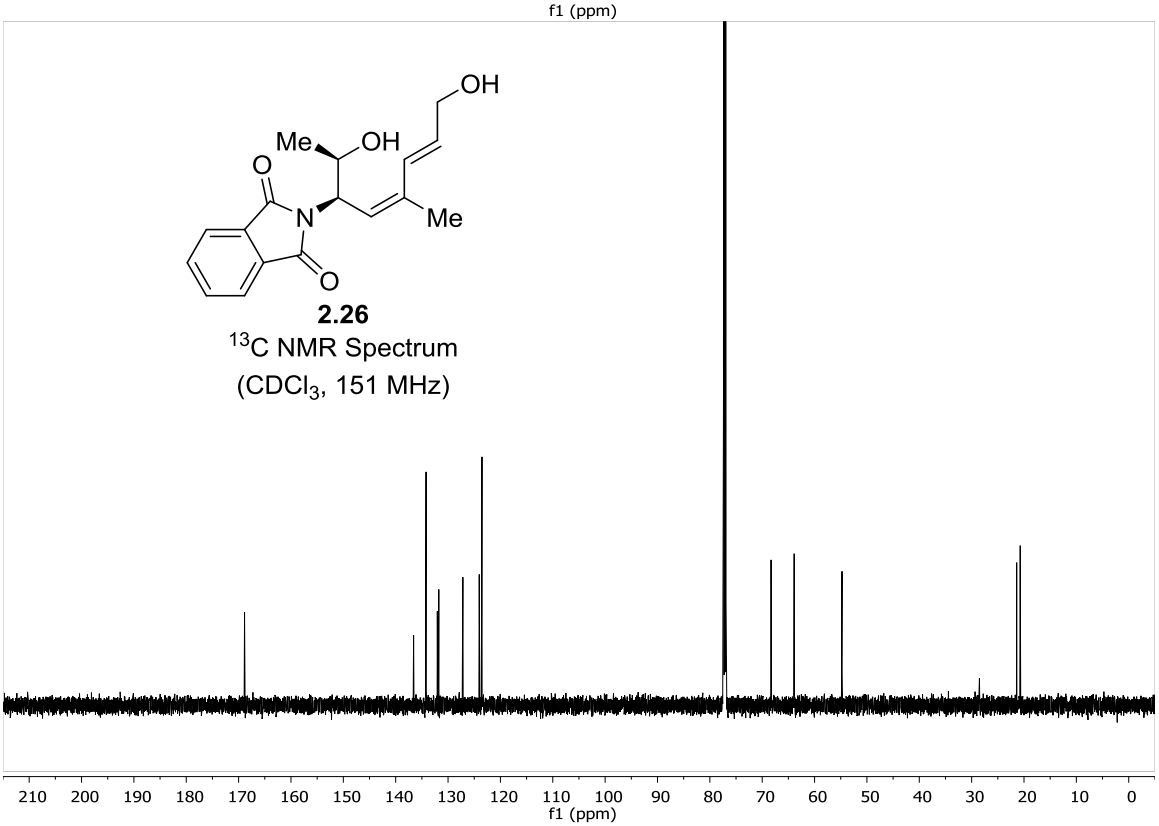
Spectra **2.07**: Compound **2.22a**: ^{1}H and ^{13}C NMR



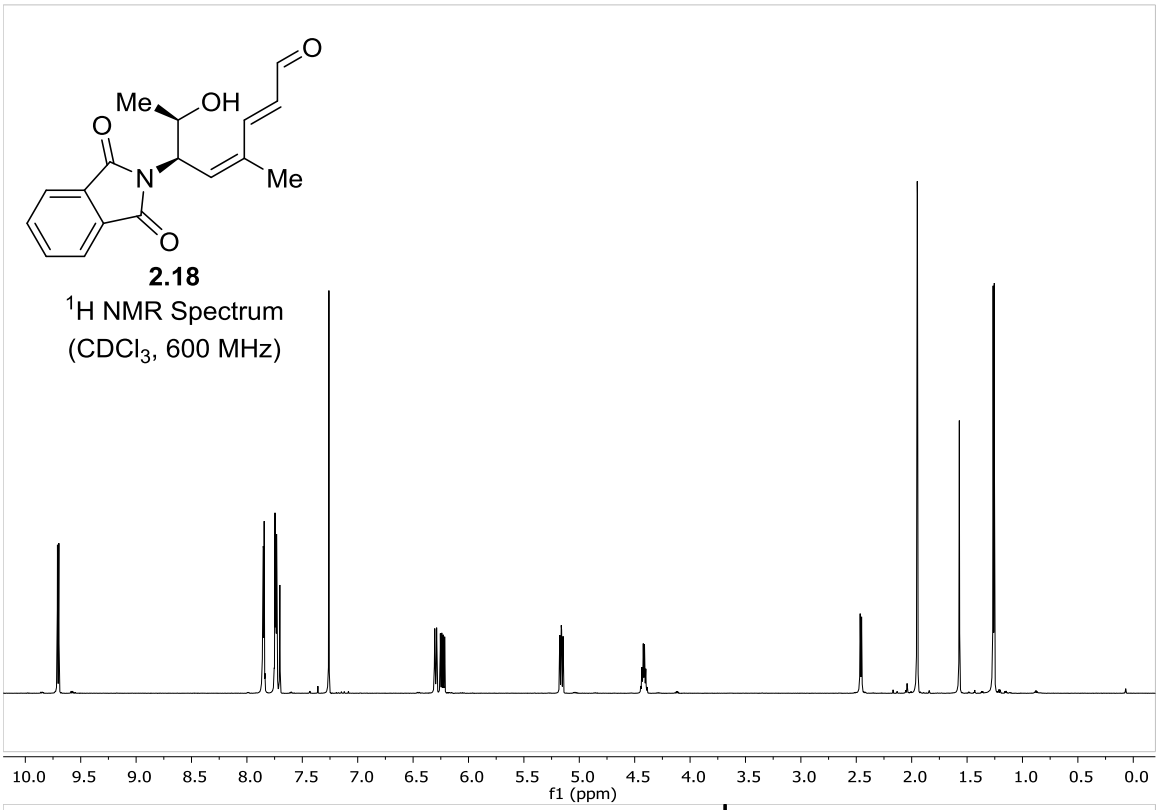


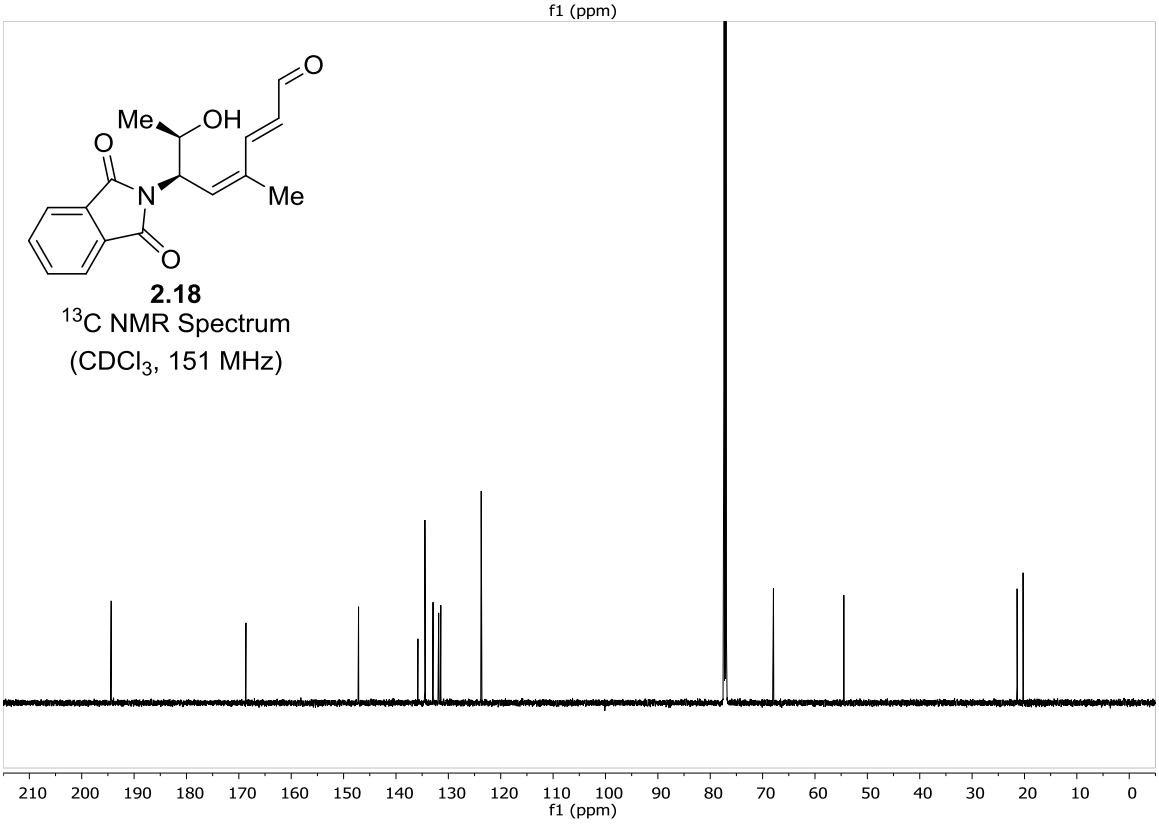
Spectra **2.08**: Compound **2.23**: ^{1}H and ^{13}C NMR



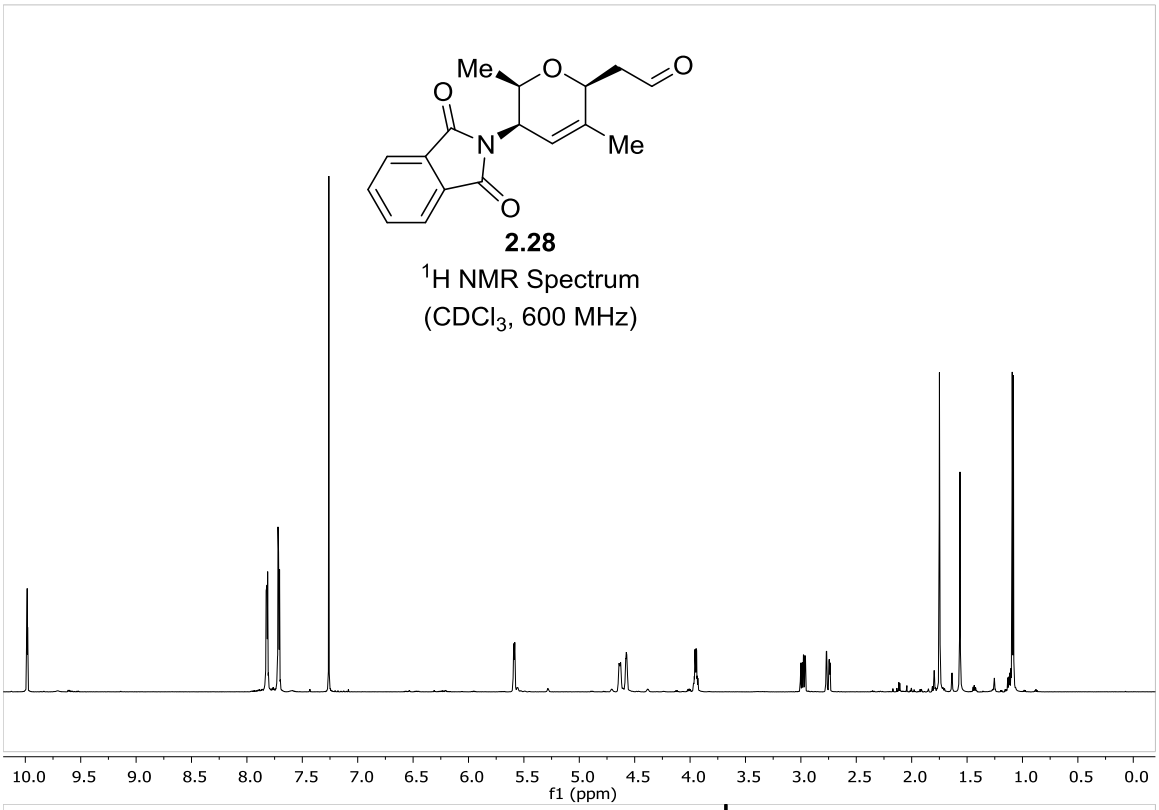


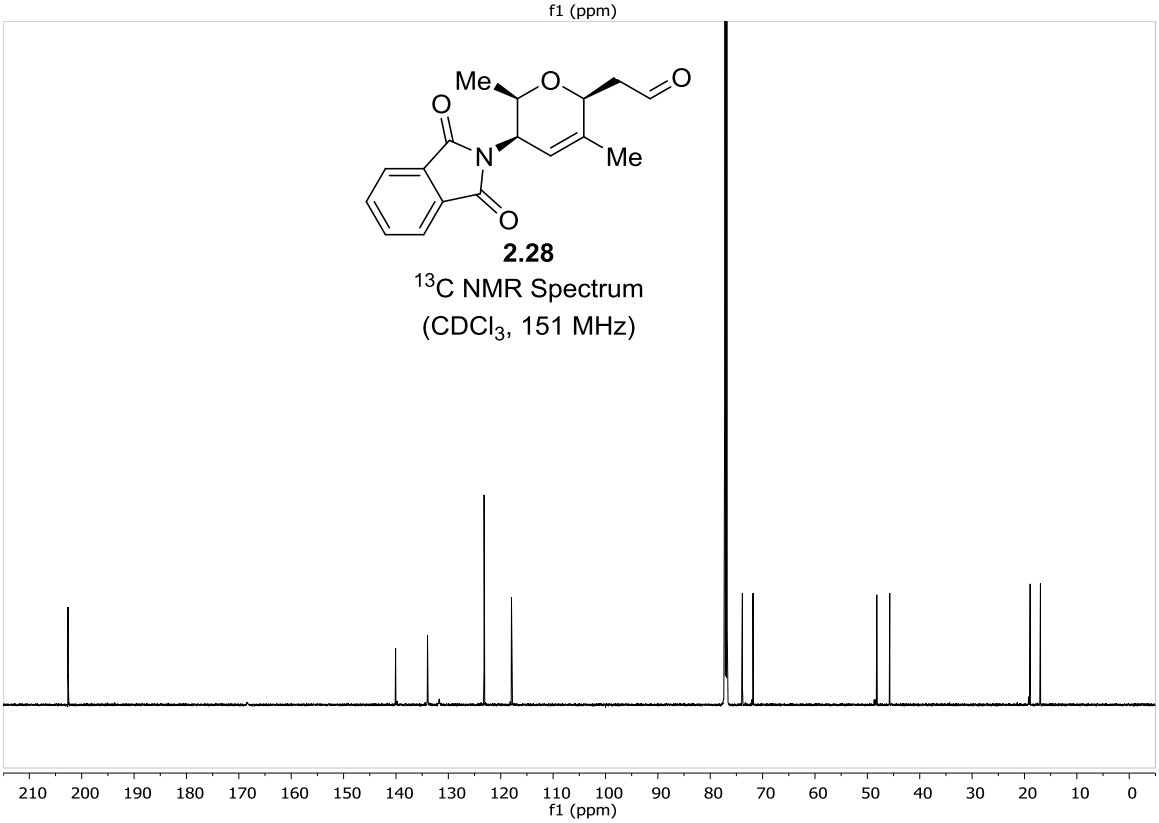
Spectra **2.09**: Compound **2.26**: ^{1}H and ^{13}C NMR



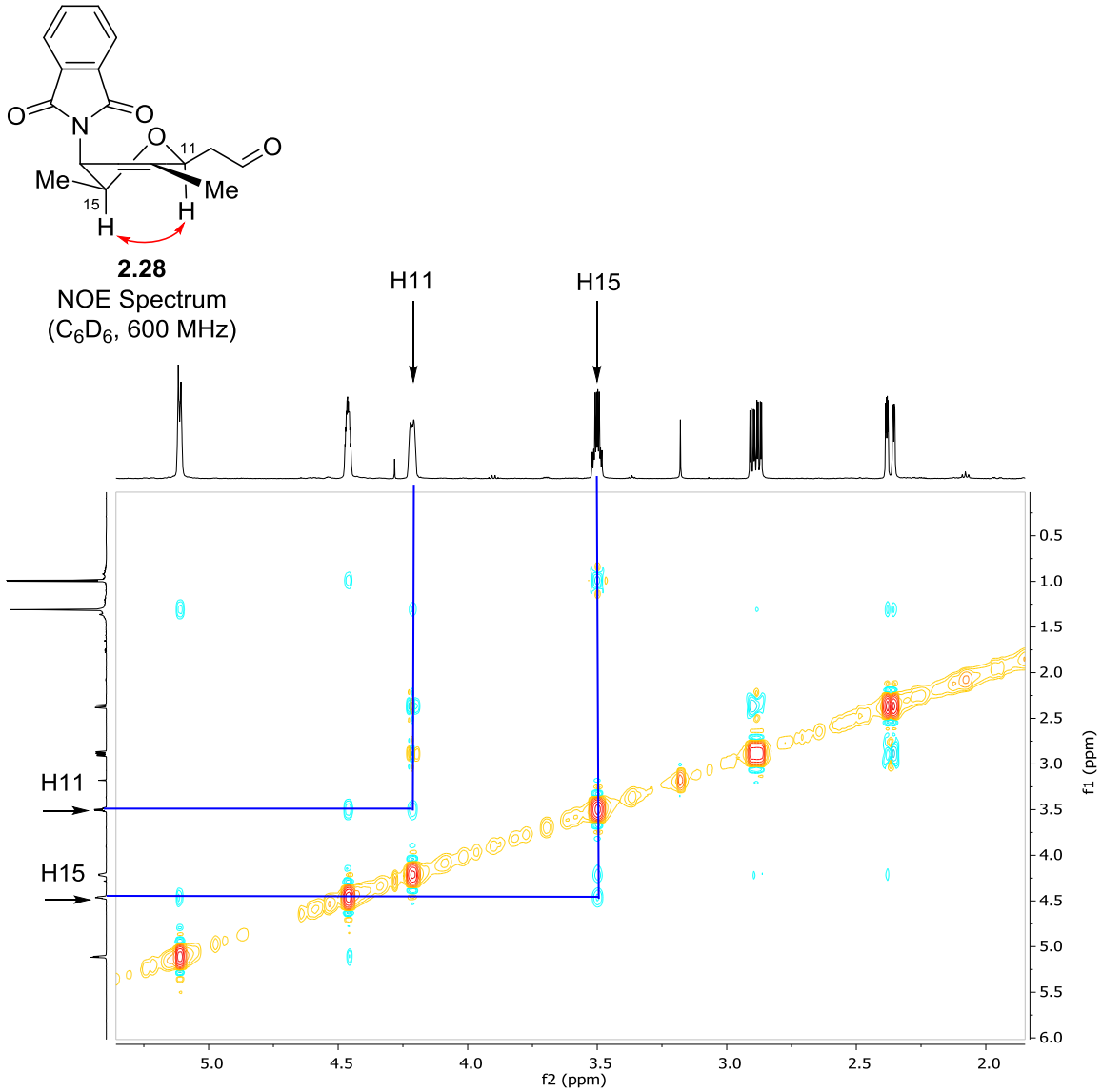


Spectra **2.10**: Compound **2.18**: ^{1}H and ^{13}C NMR

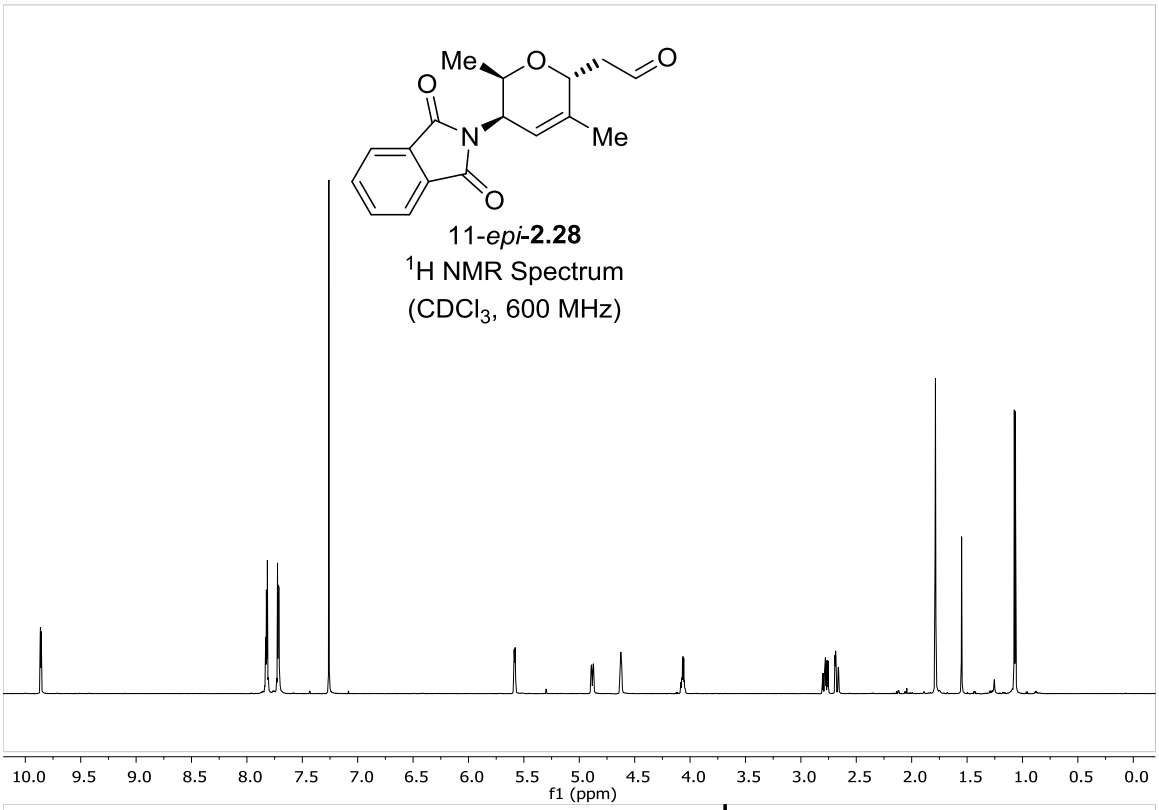


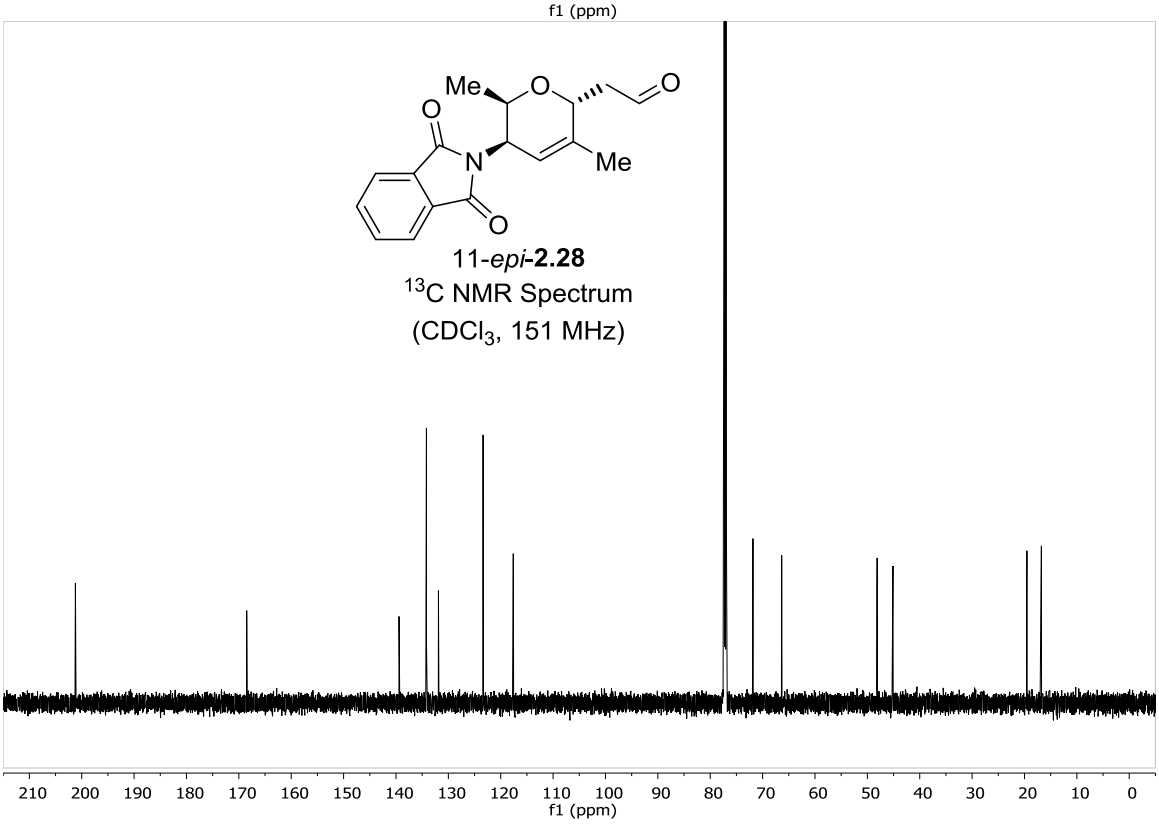


Spectra **2.11**: Compound **2.28**: ^{1}H and ^{13}C NMR

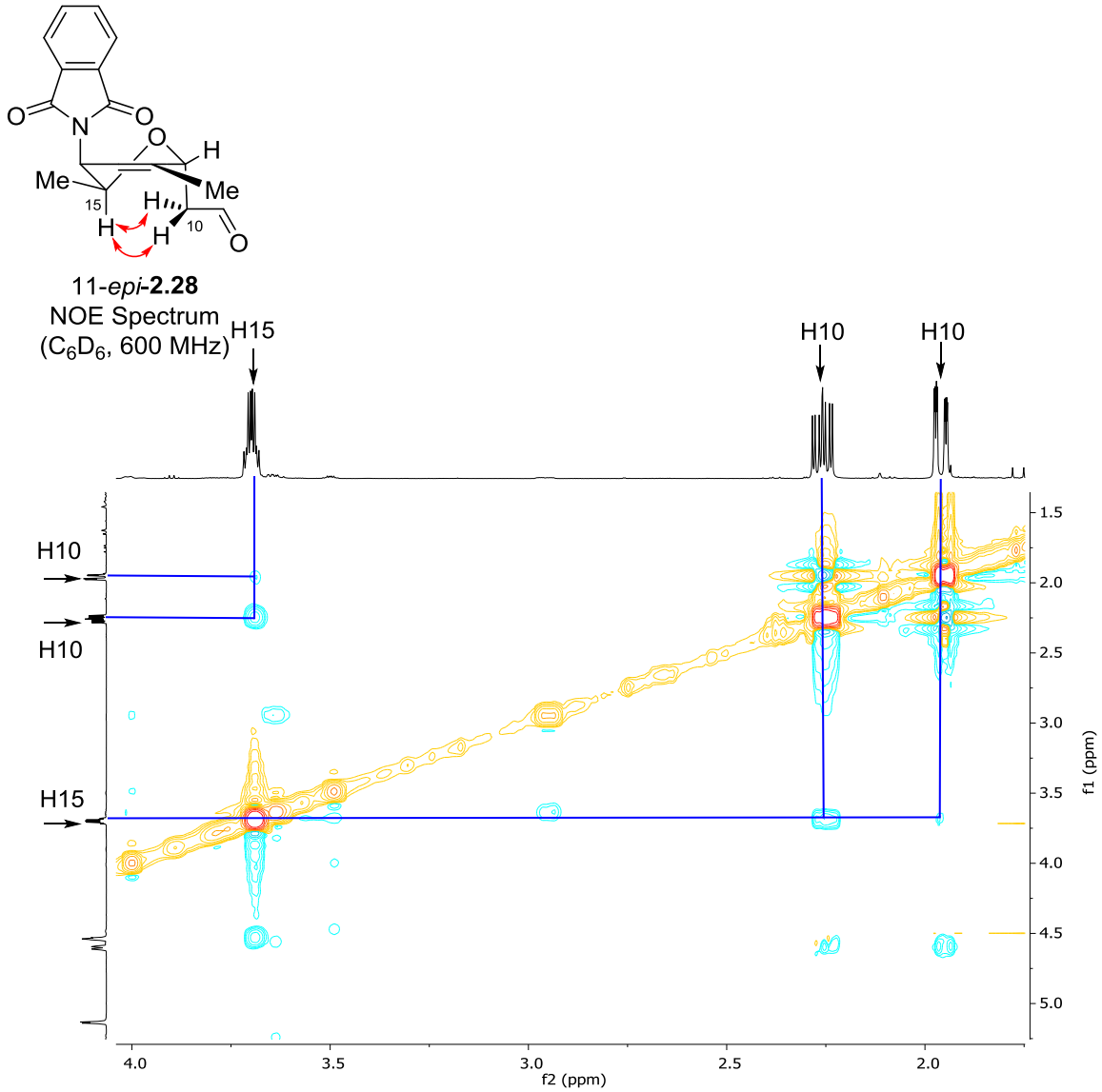


Spectrum **2.12**: Compound **2.28**: ^{1}H NOESY NMR

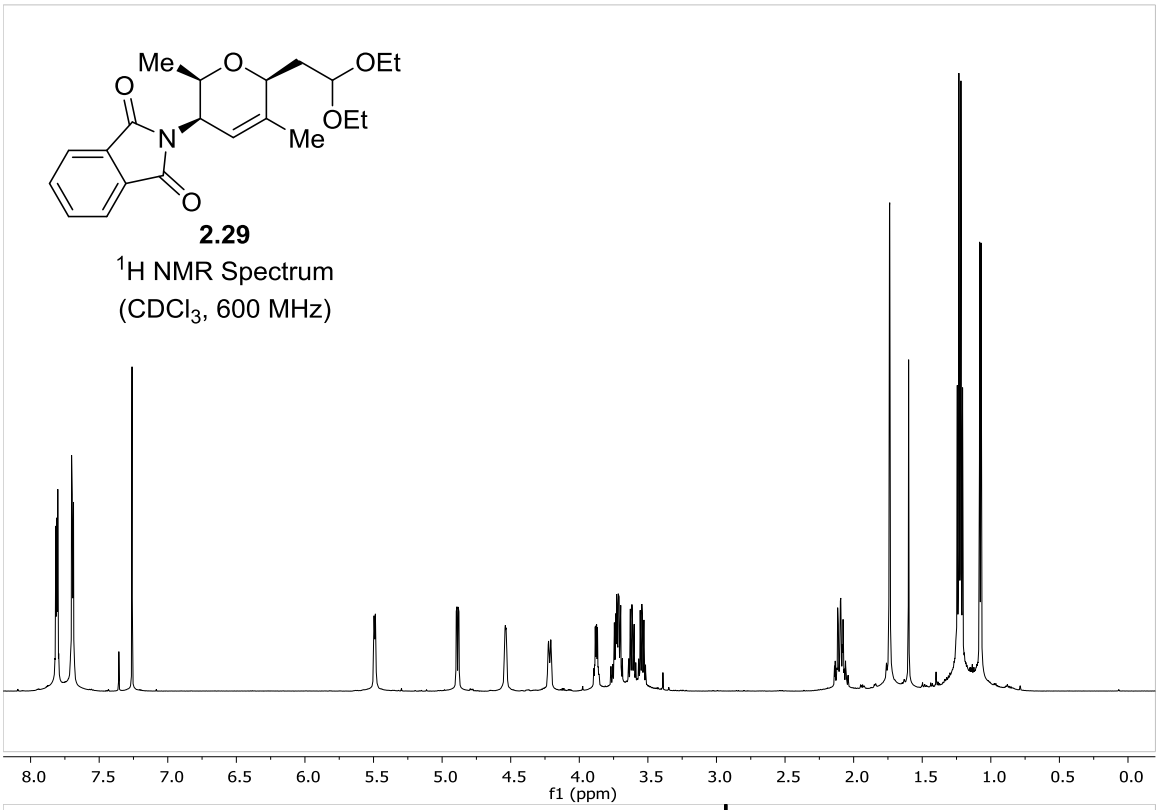


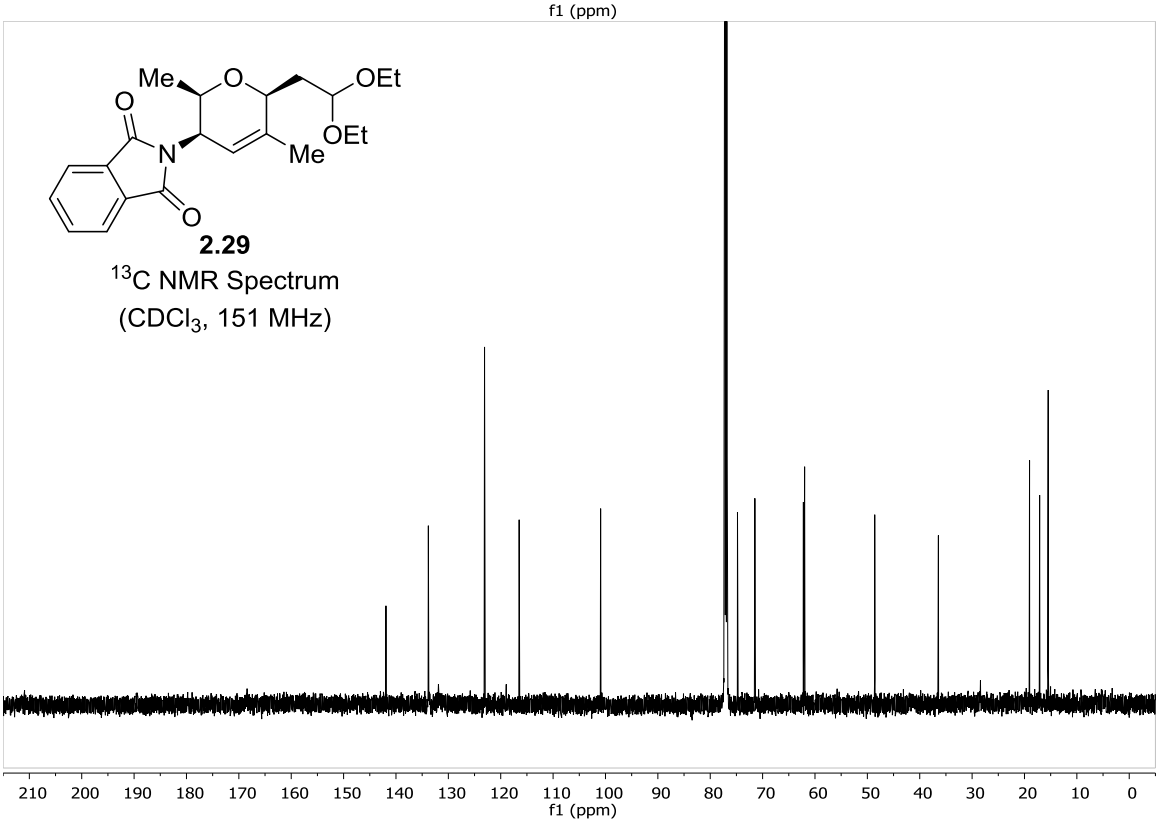


Spectra **2.13**: Compound 11-*epi*-**2.28**: ^{1}H and ^{13}C NMR

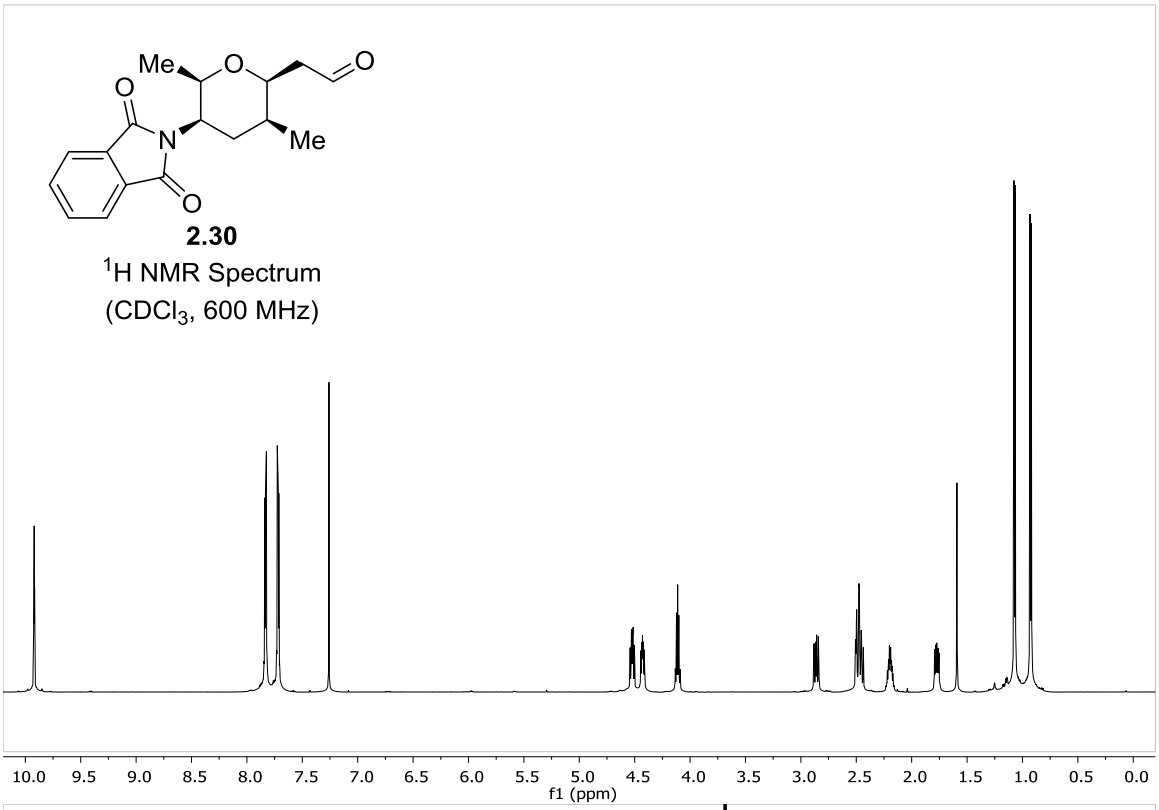


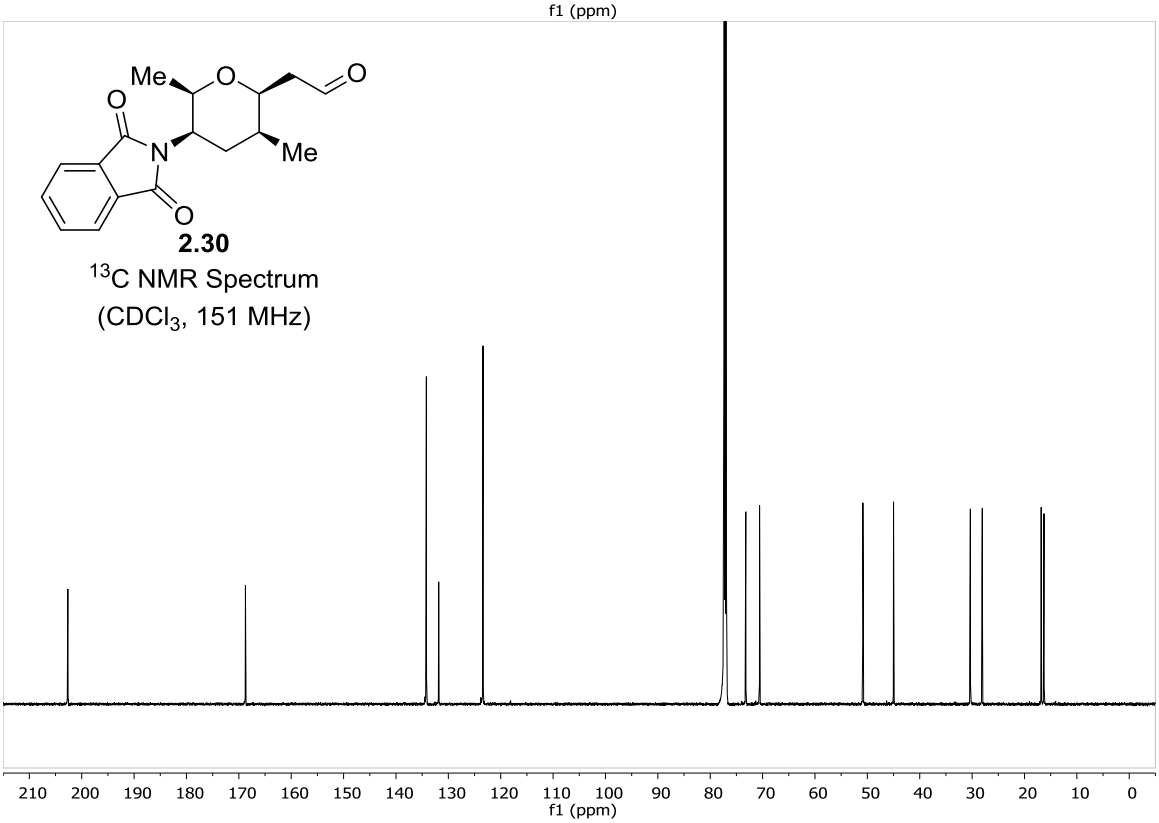
Spectrum **2.14**: Compound 11-*epi*-**2.28**: ^{1}H NOESY NMR



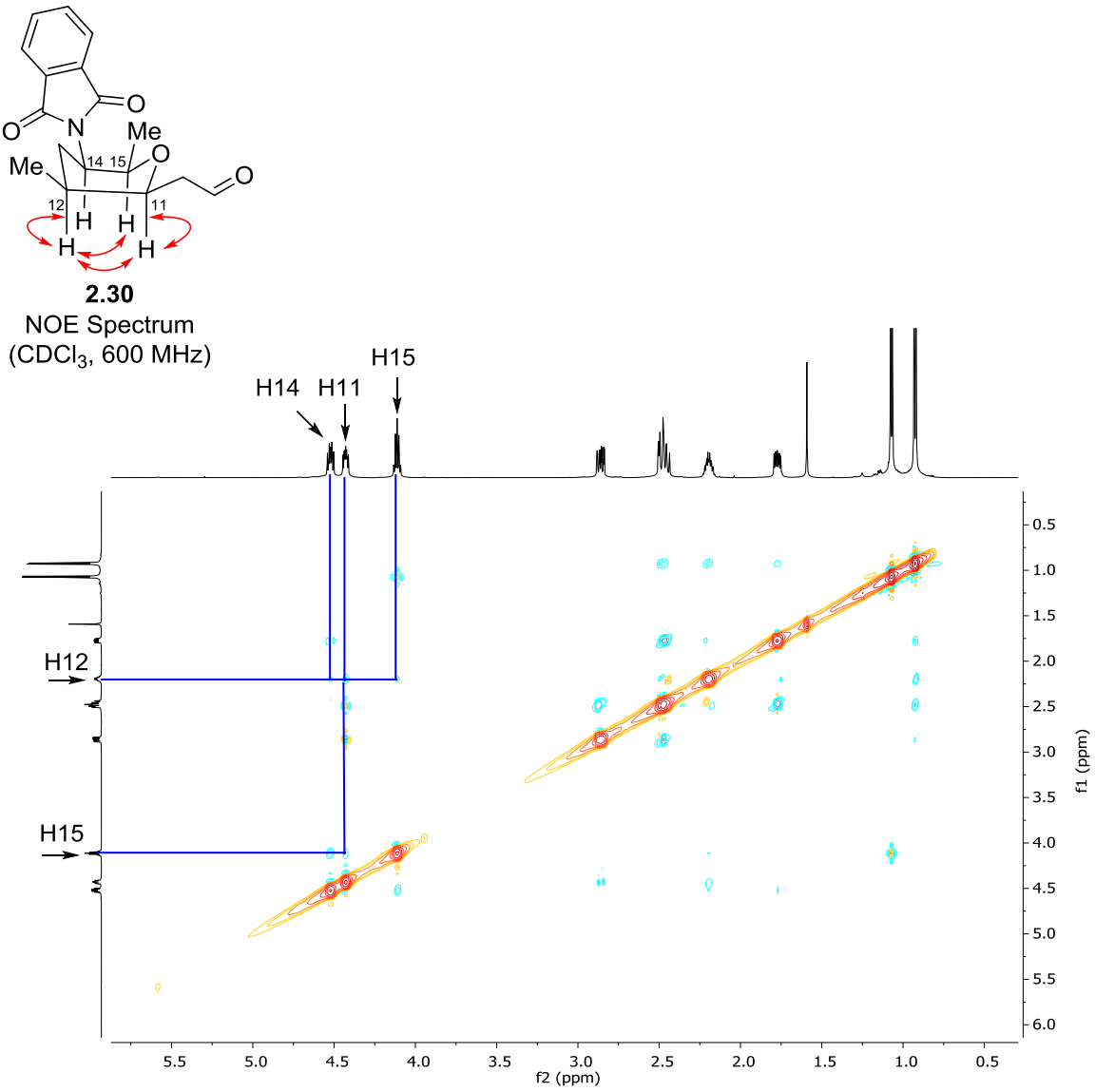


Spectra **2.15**: Compound **2.29**: ^{1}H and ^{13}C NMR

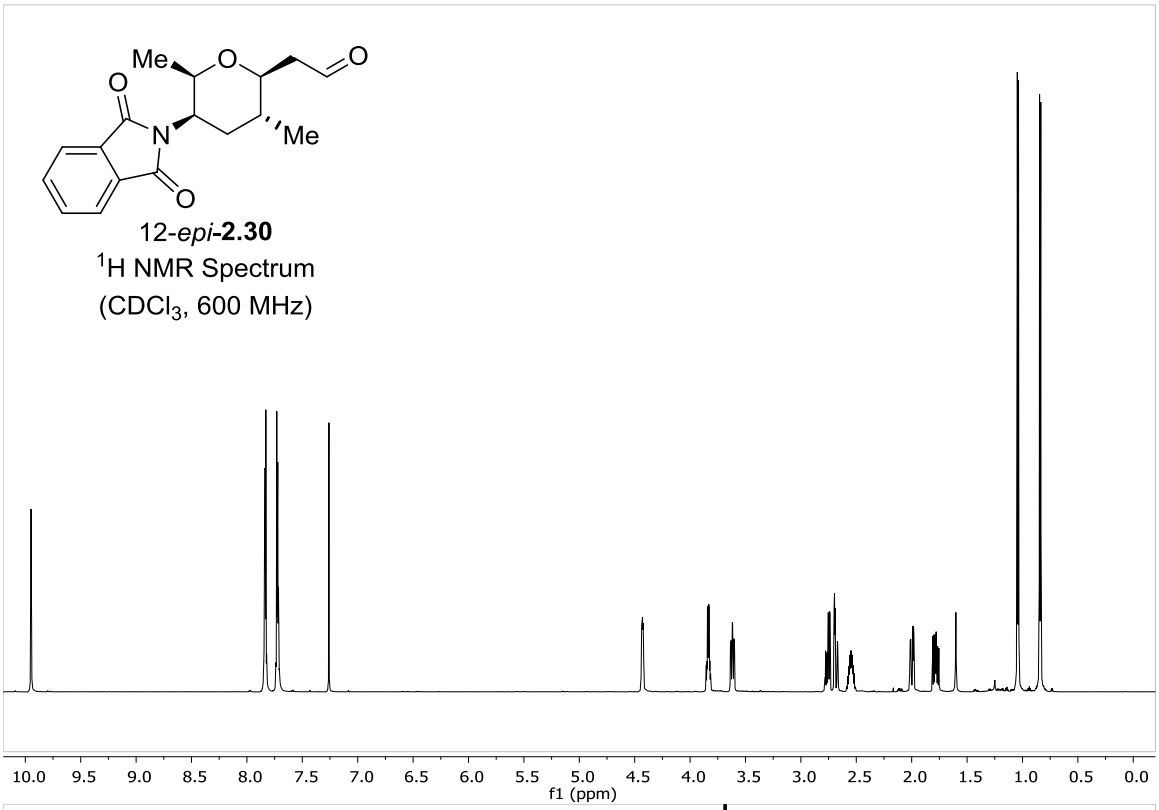


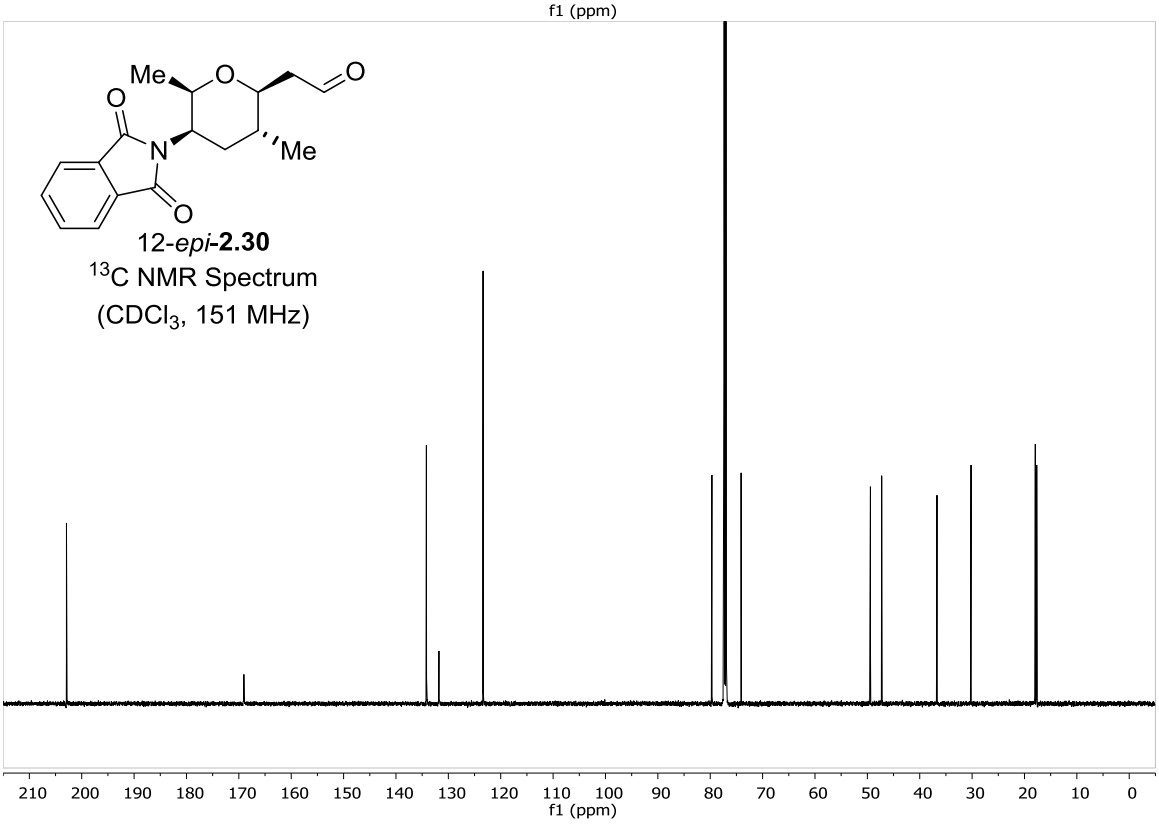


Spectra **2.16**: Compound **2.30**: ^{1}H and ^{13}C NMR

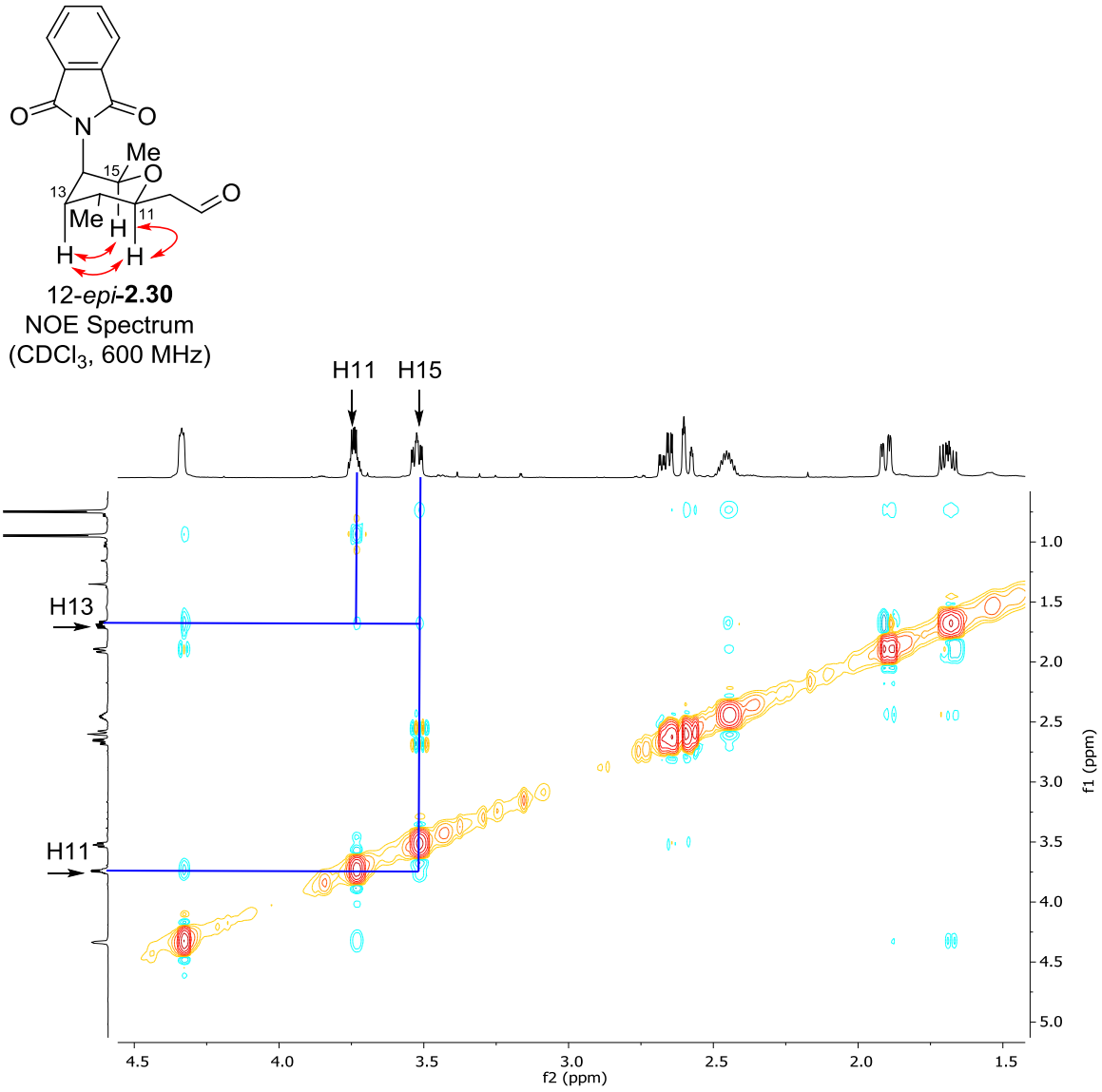


Spectrum **2.17**: Compound **2.30**: ^{1}H NOESY NMR

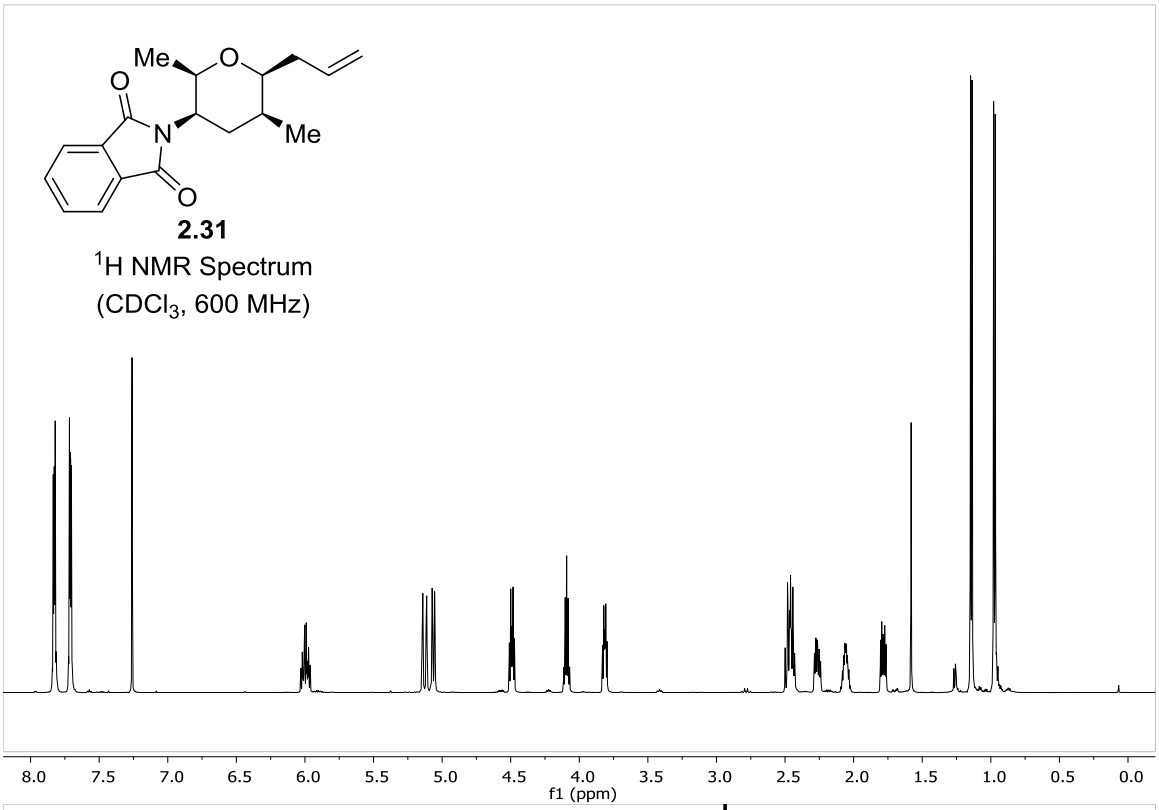


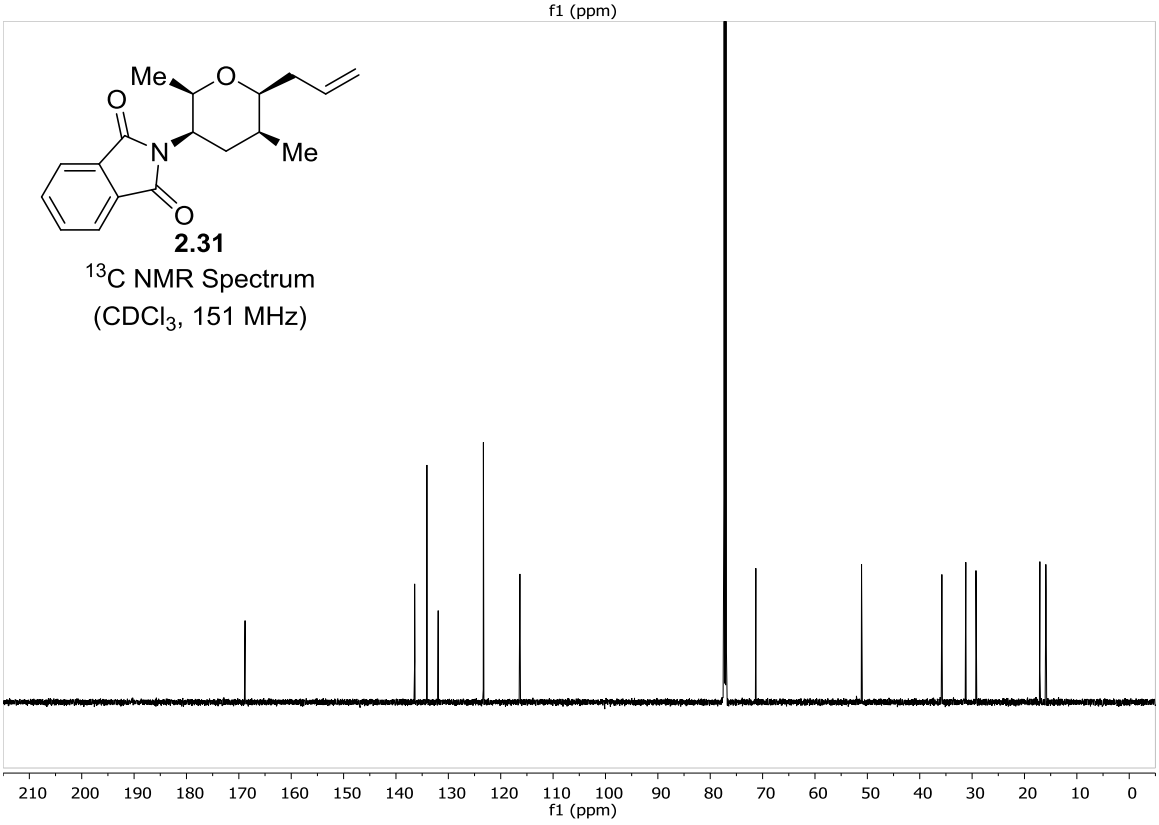


Spectra **2.18**: Compound 12-*epi*-**2.30**: ^{1}H and ^{13}C NMR

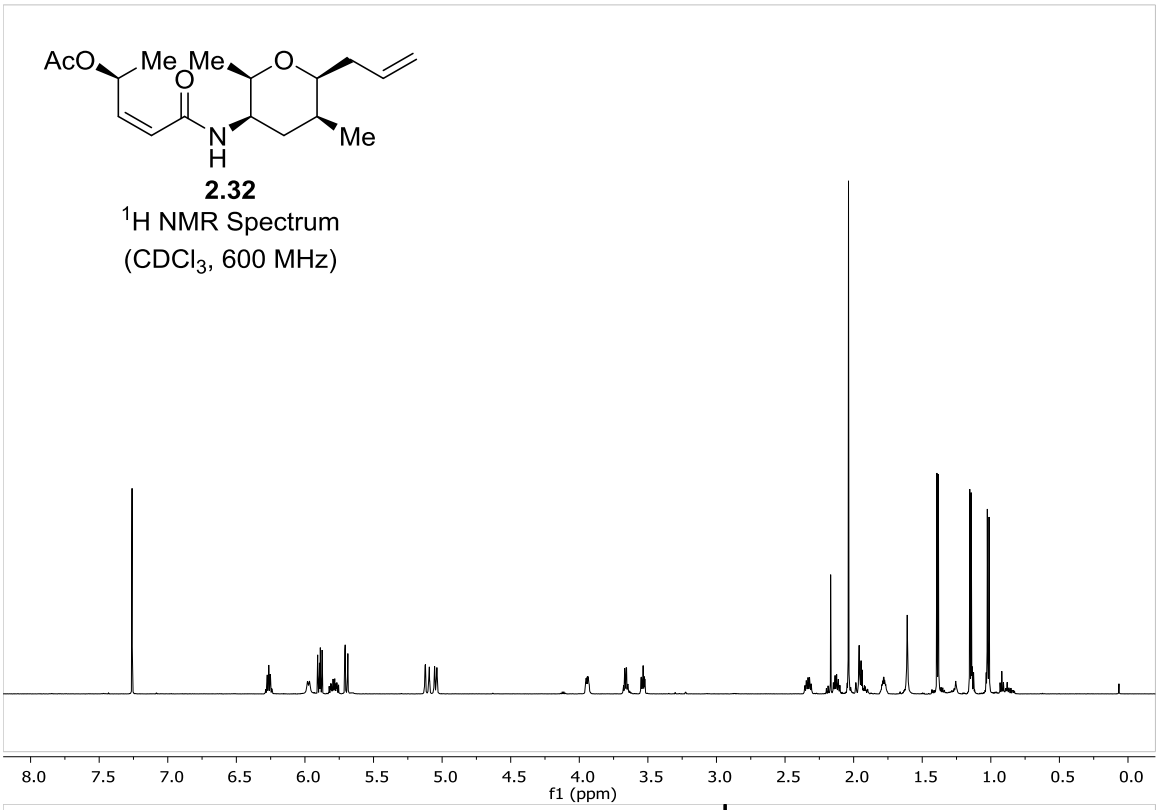


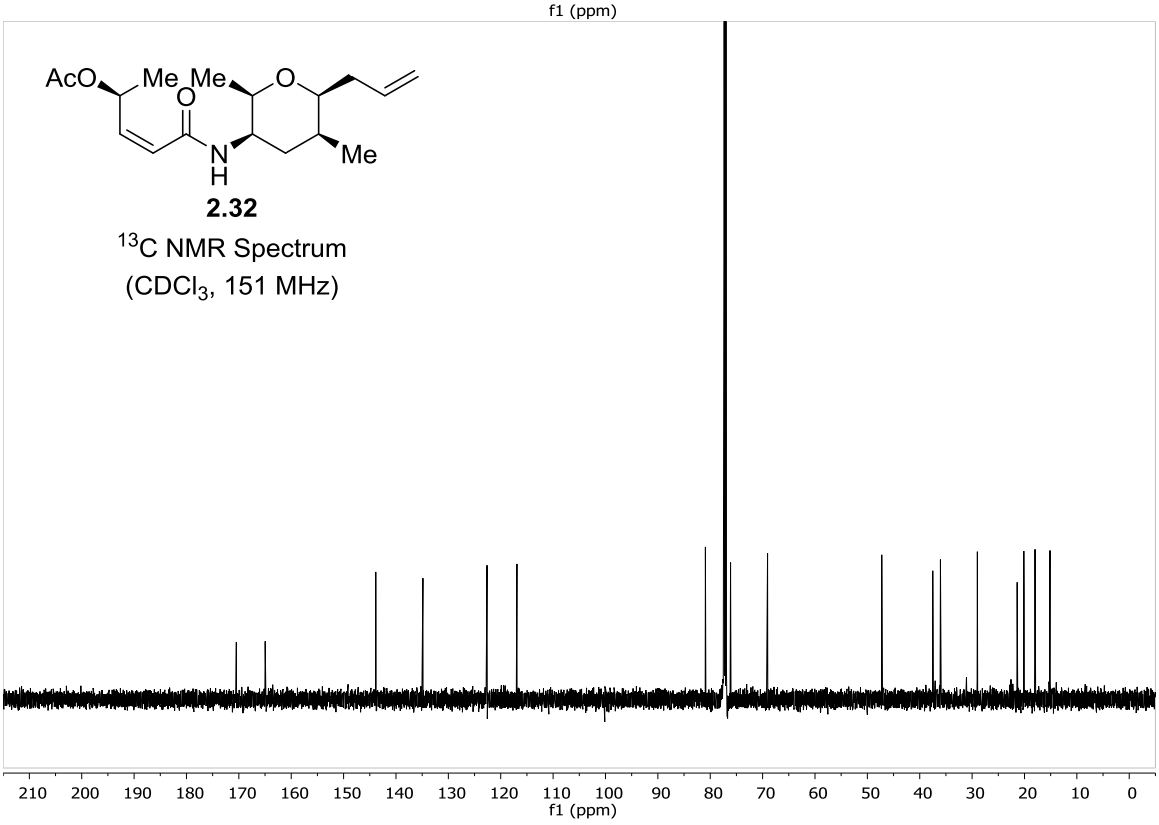
Spectrum **2.19**: Compound 12-*epi*-**2.30**: ^{1}H NOESY NMR



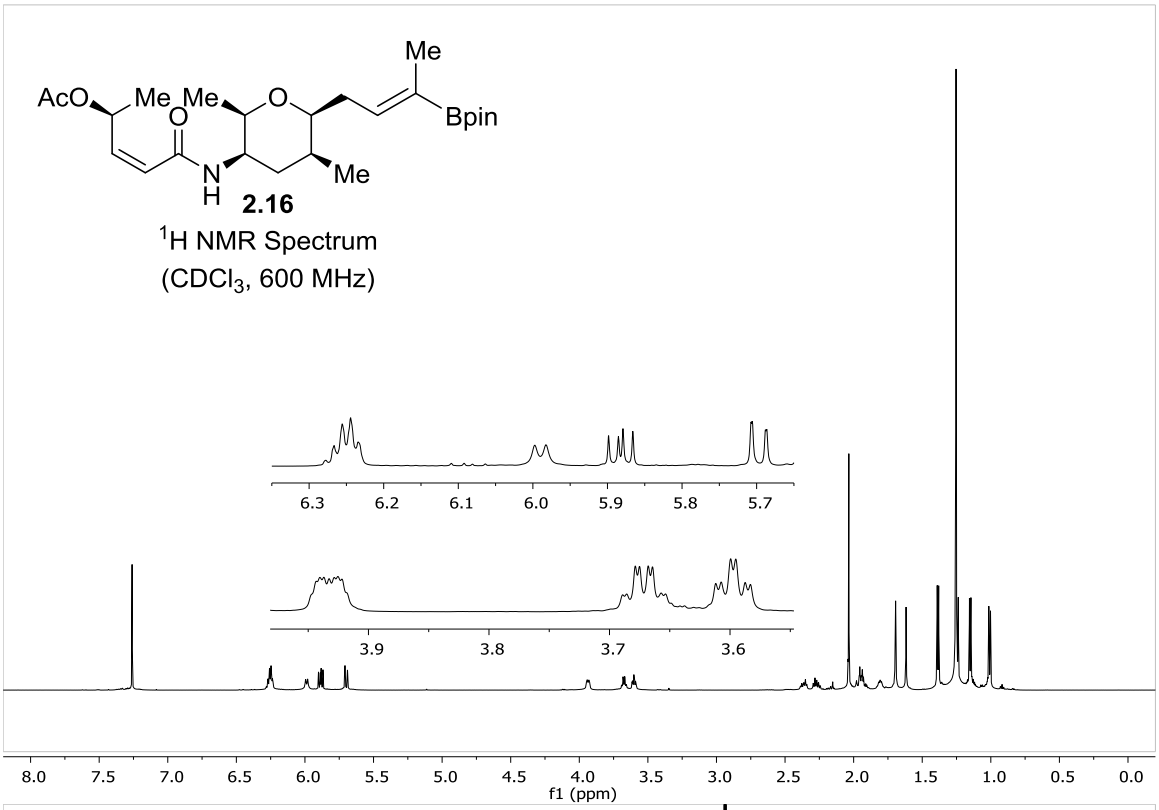


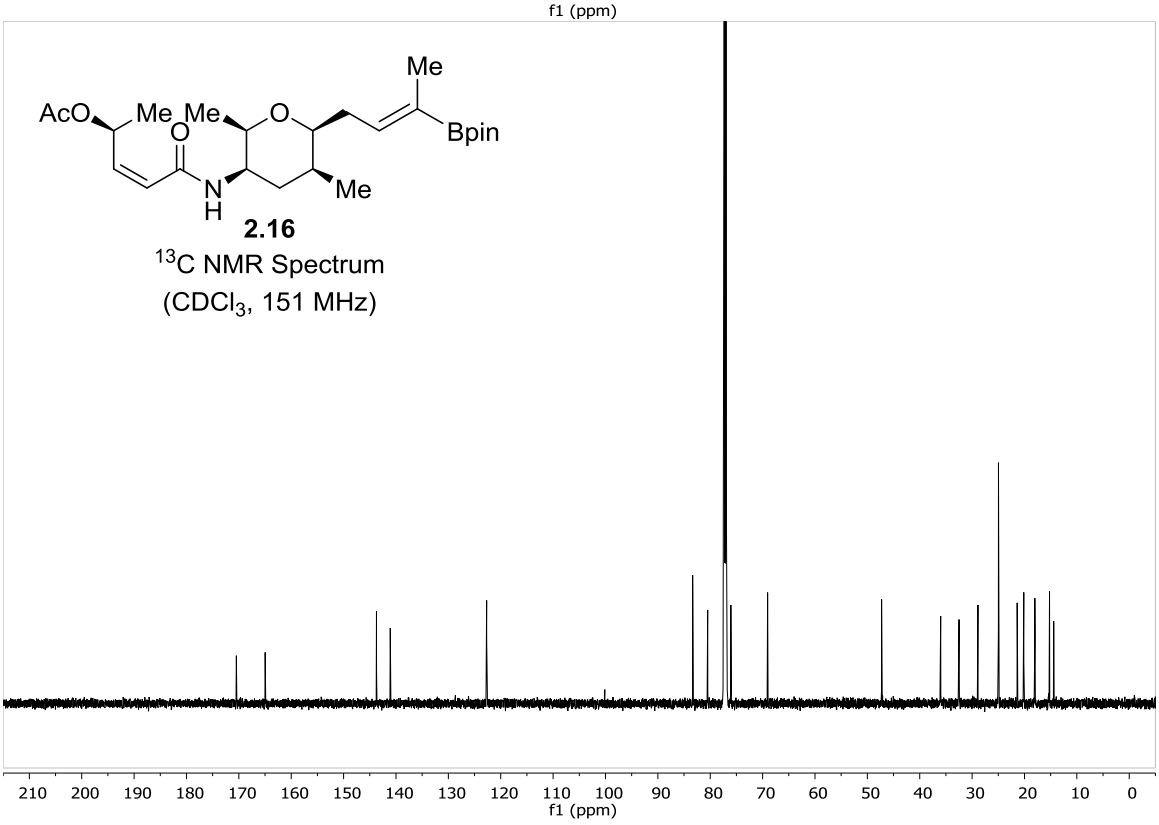
Spectra **2.20**: Compound **2.31**: ^{1}H and ^{13}C NMR



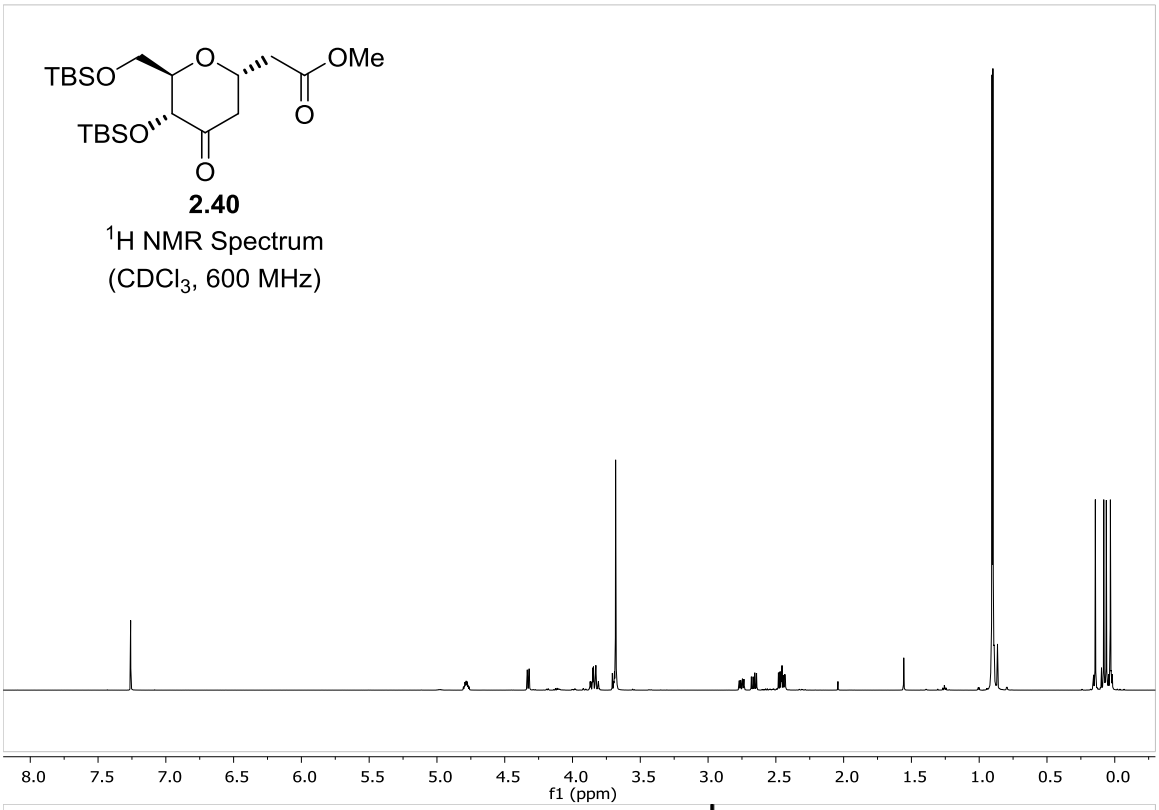


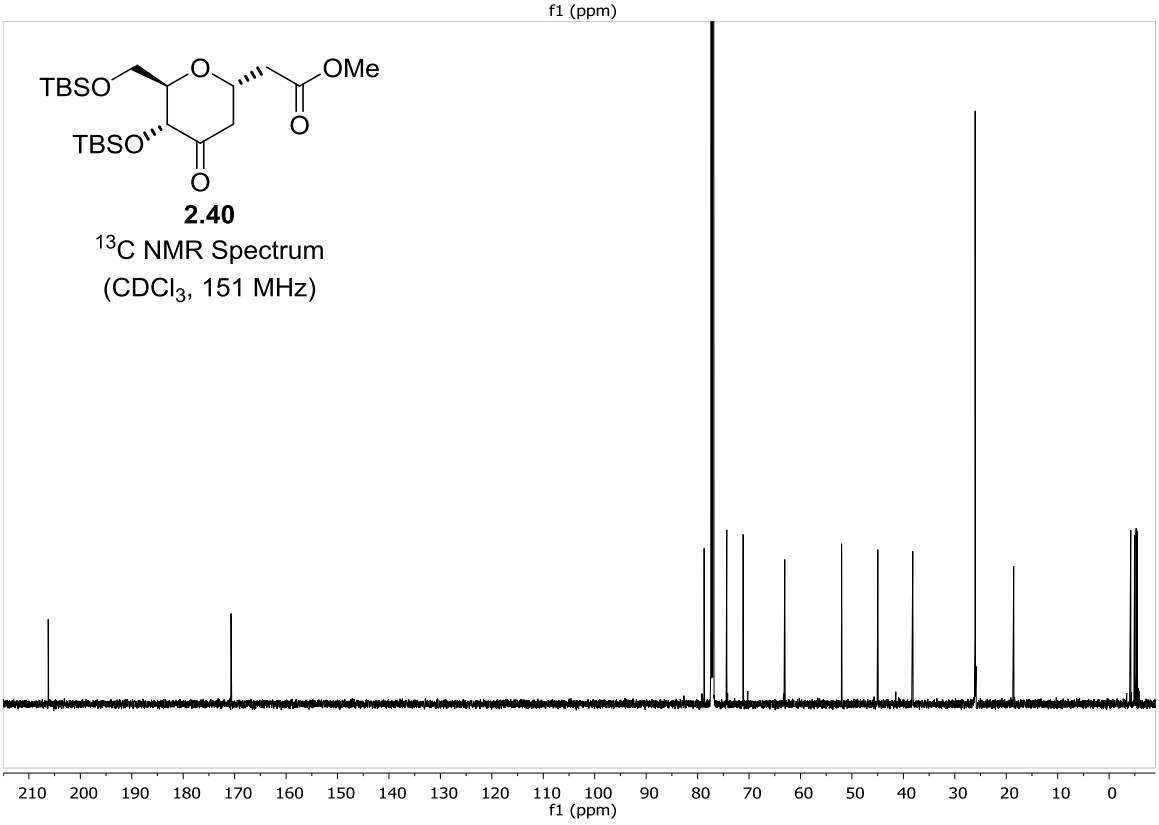
Spectra **2.21**: Compound **2.32**: ^{1}H and ^{13}C NMR



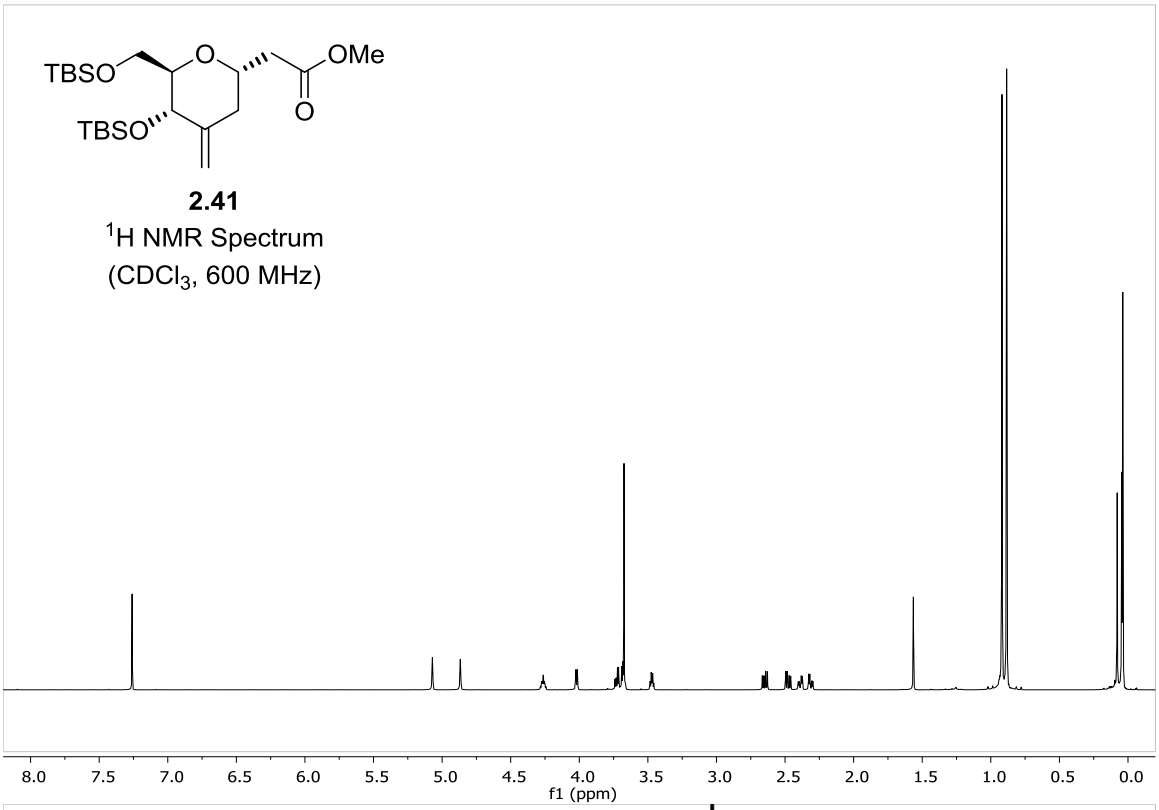


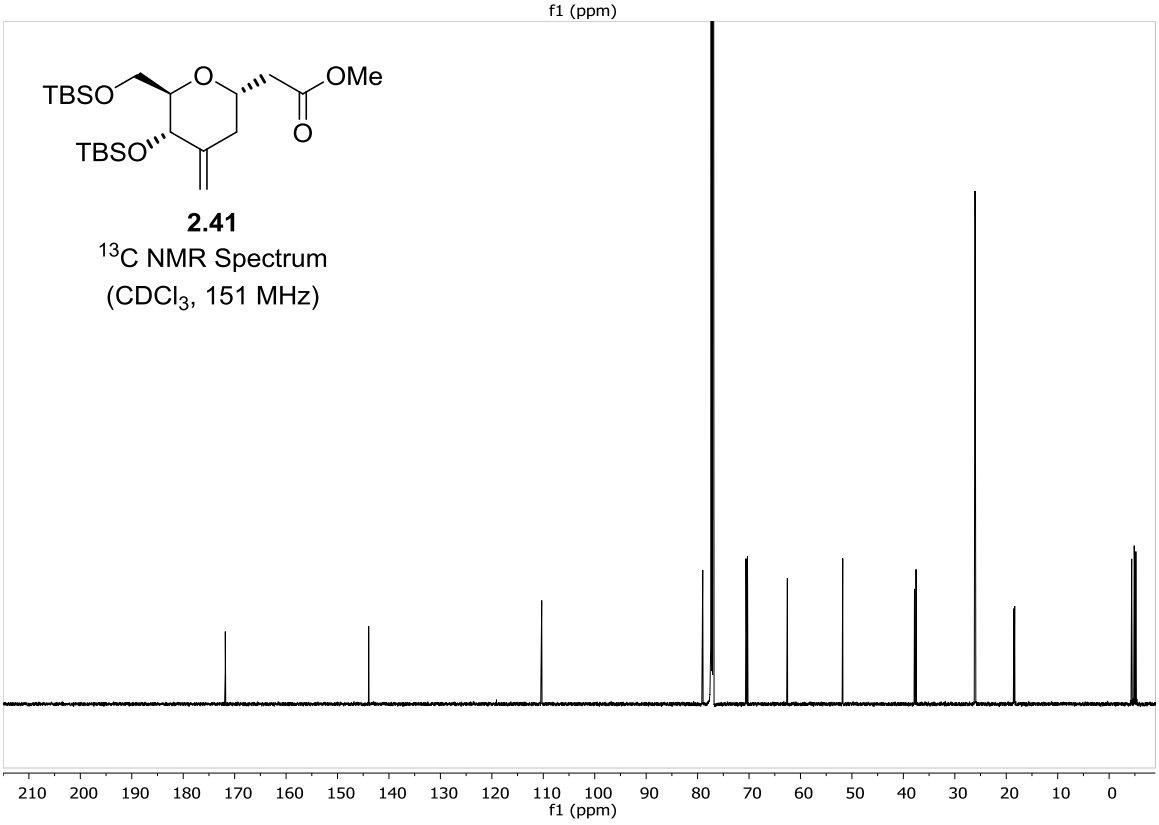
Spectra **2.22**: Compound **2.16**: ^{1}H and ^{13}C NMR



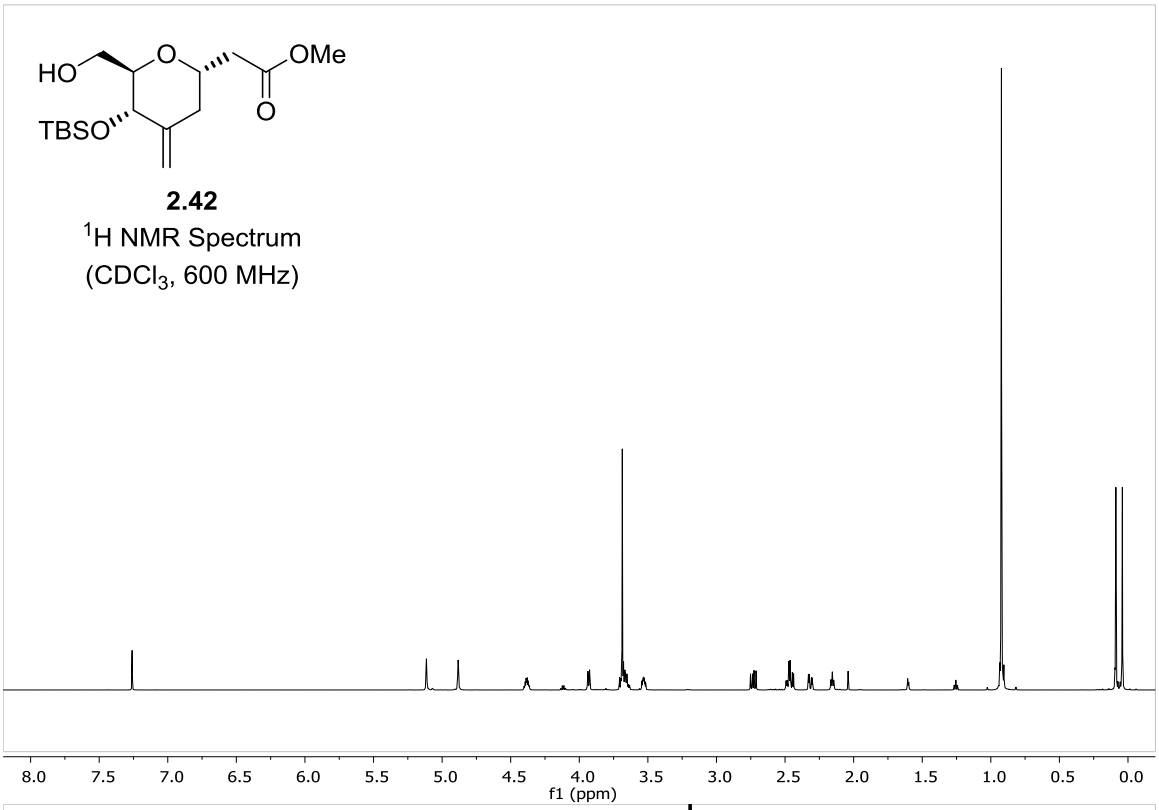


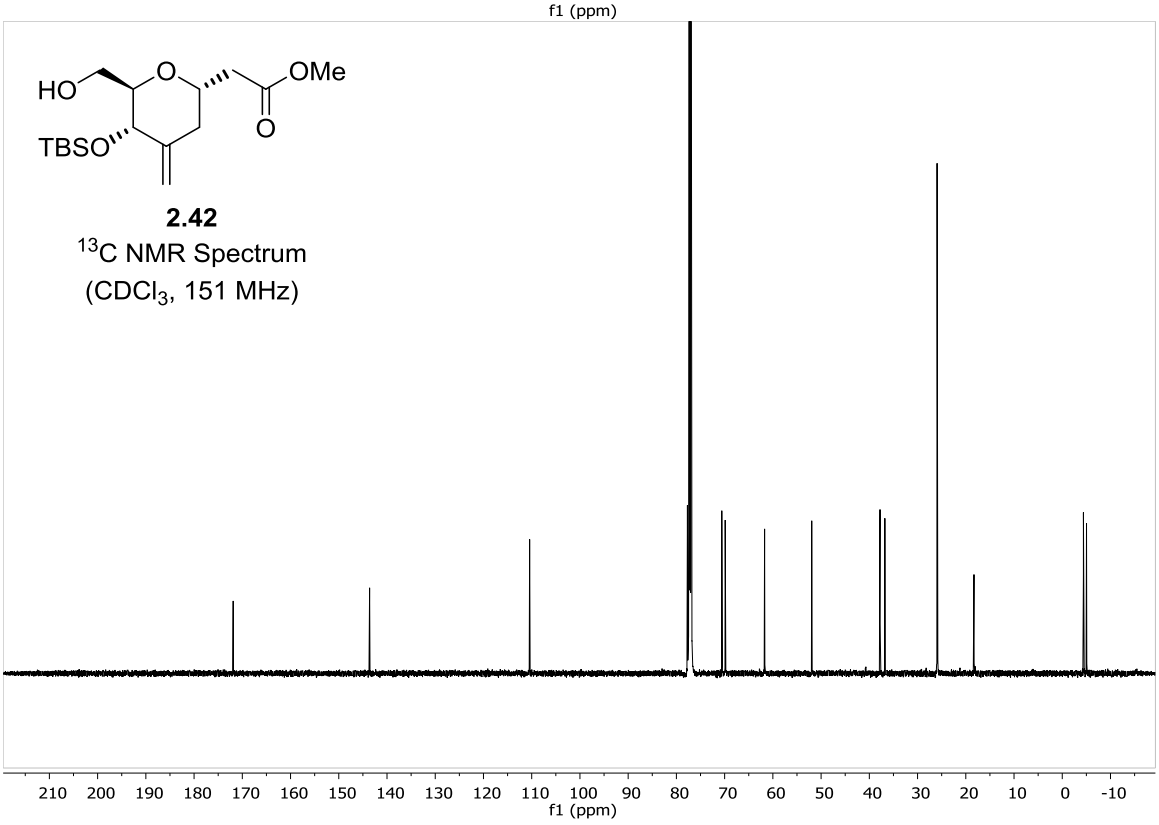
Spectra **2.23**: Compound **2.40**: ^{1}H and ^{13}C NMR



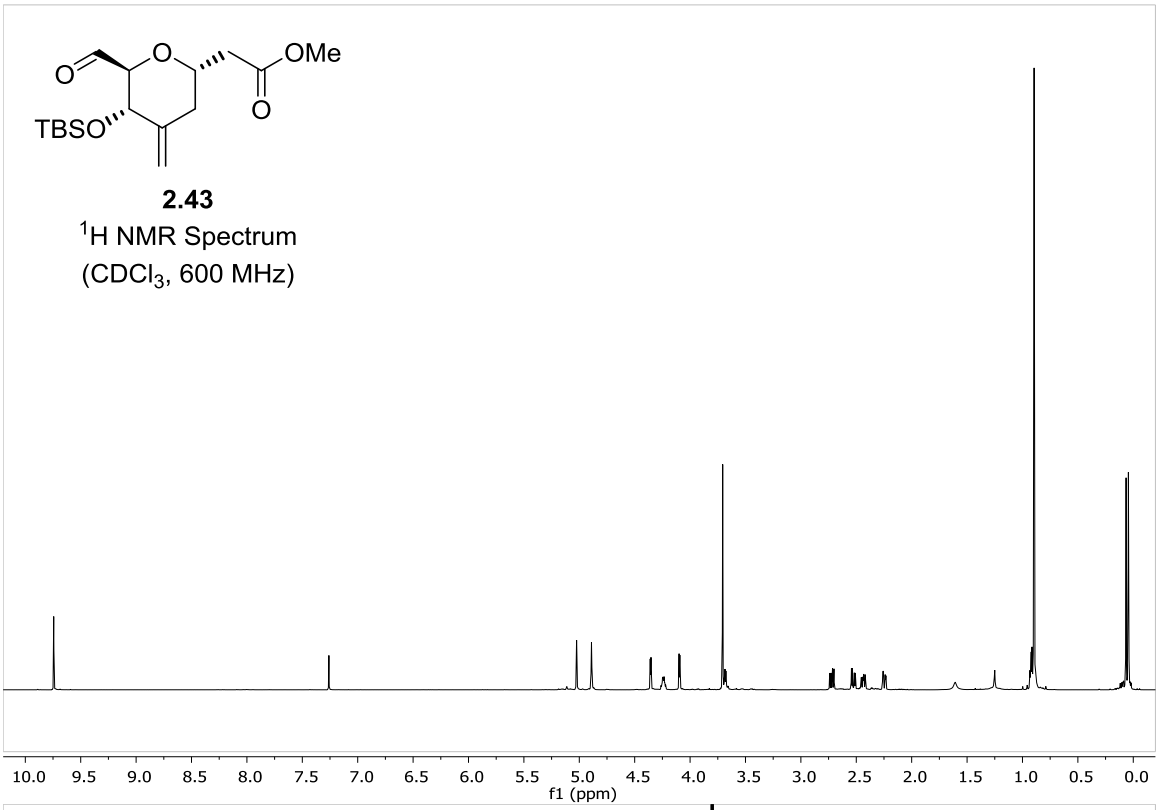


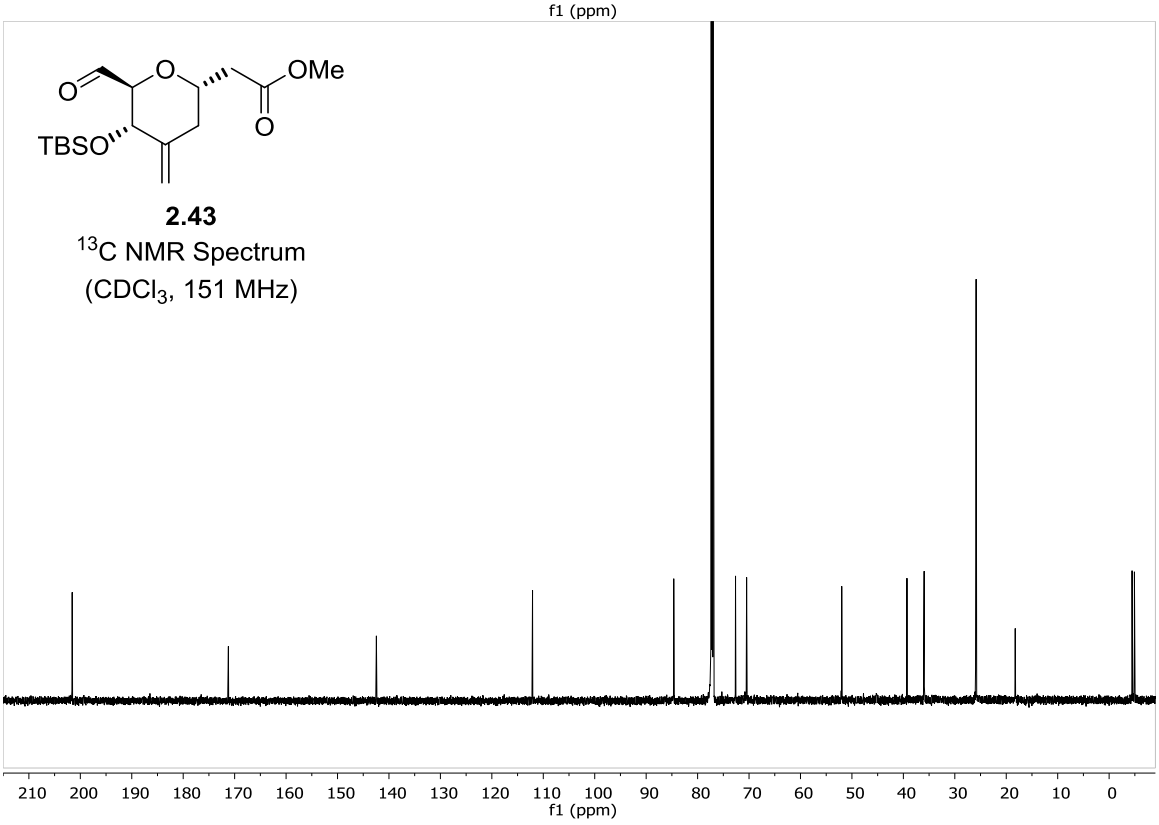
Spectra **2.24**: Compound **2.41**: ^{1}H and ^{13}C NMR



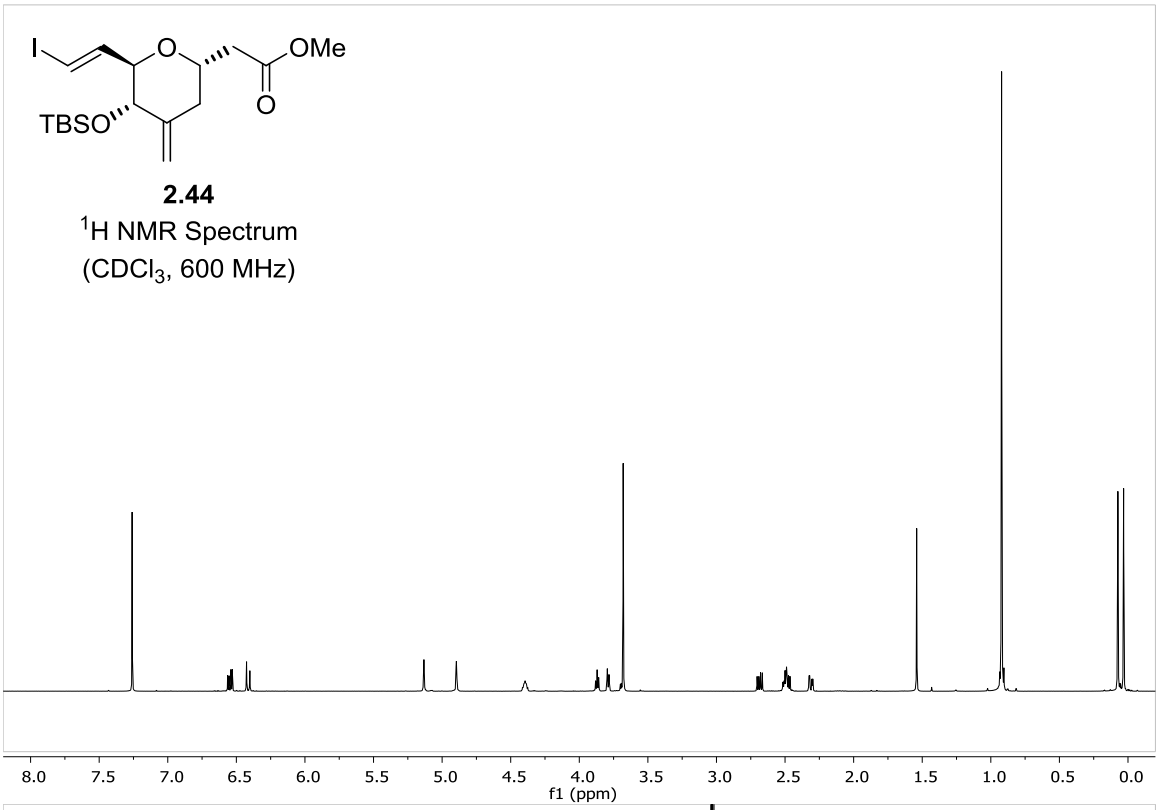


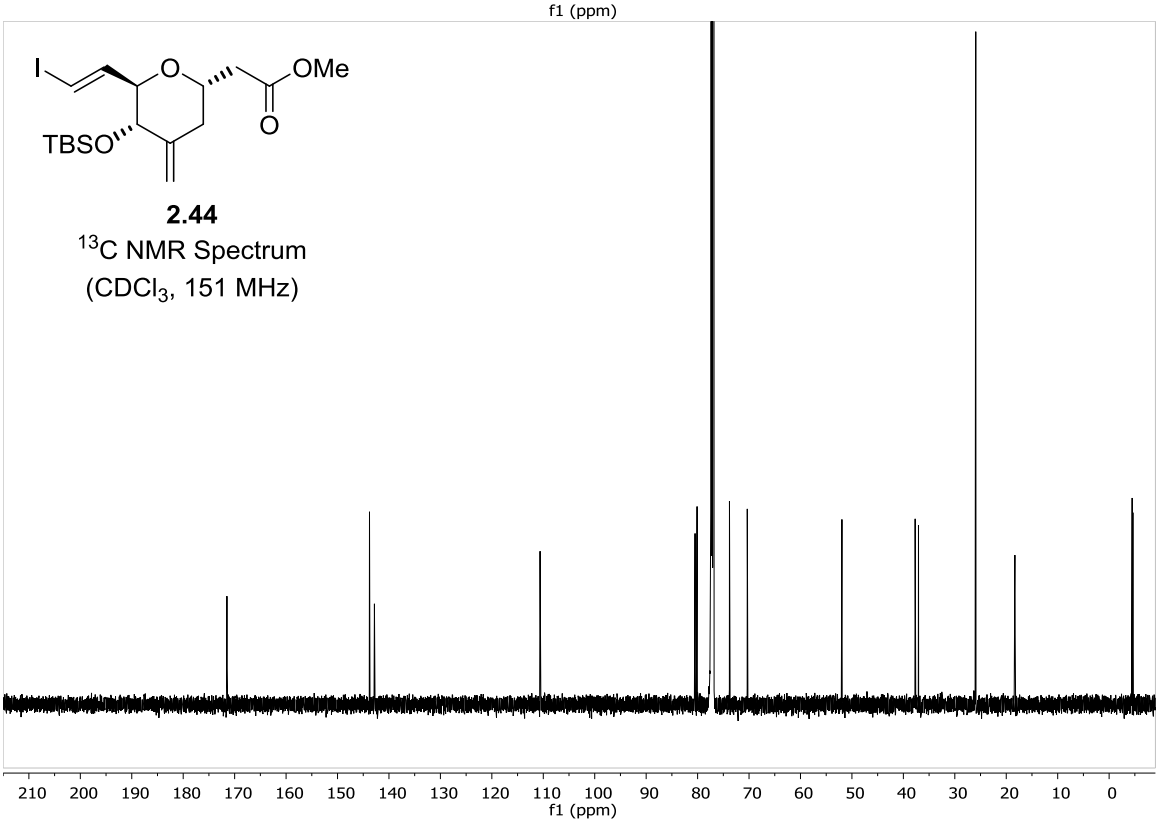
Spectra **2.25**: Compound **2.42**: ^{1}H and ^{13}C NMR



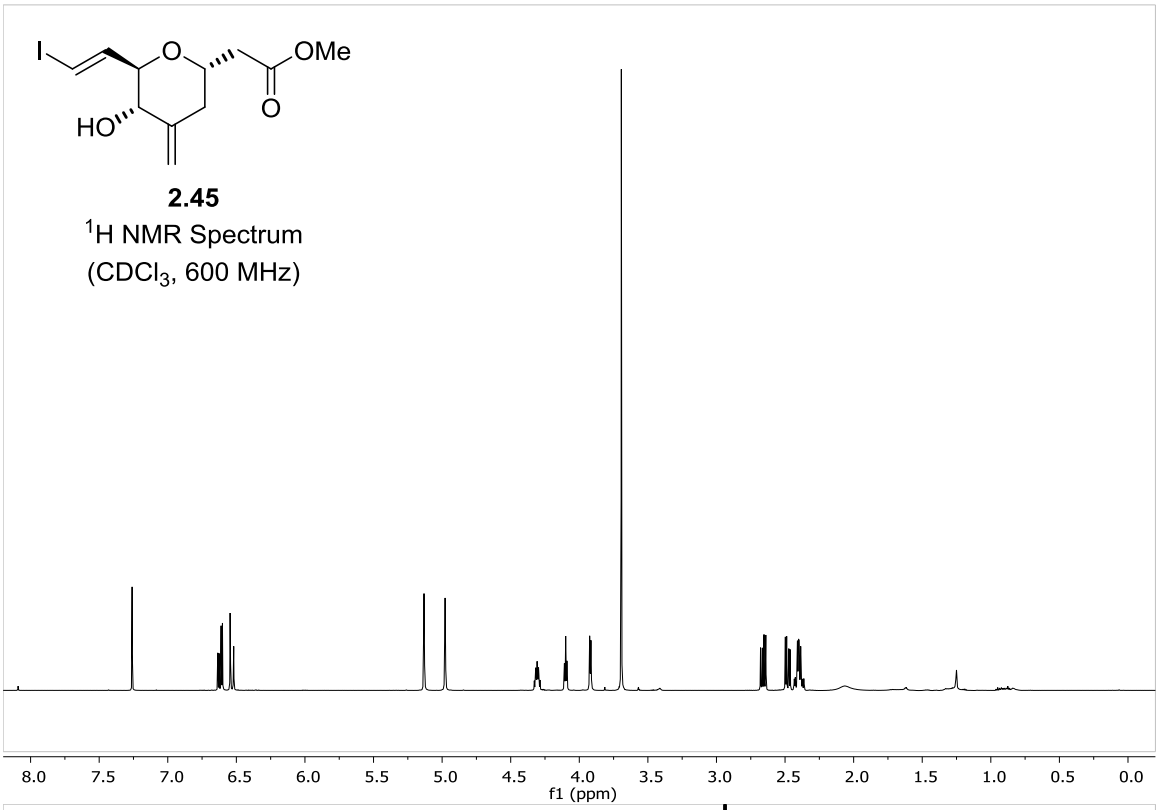


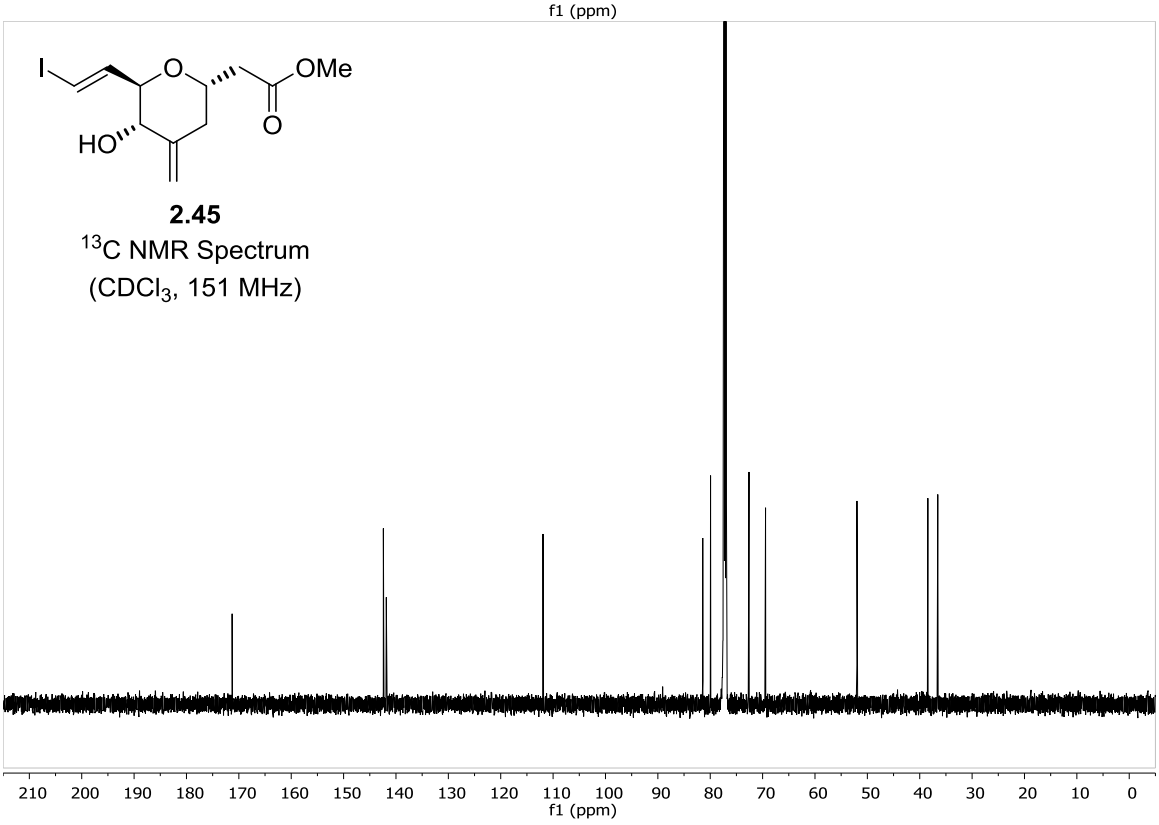
Spectra **2.26**: Compound **2.43**: ^{1}H and ^{13}C NMR



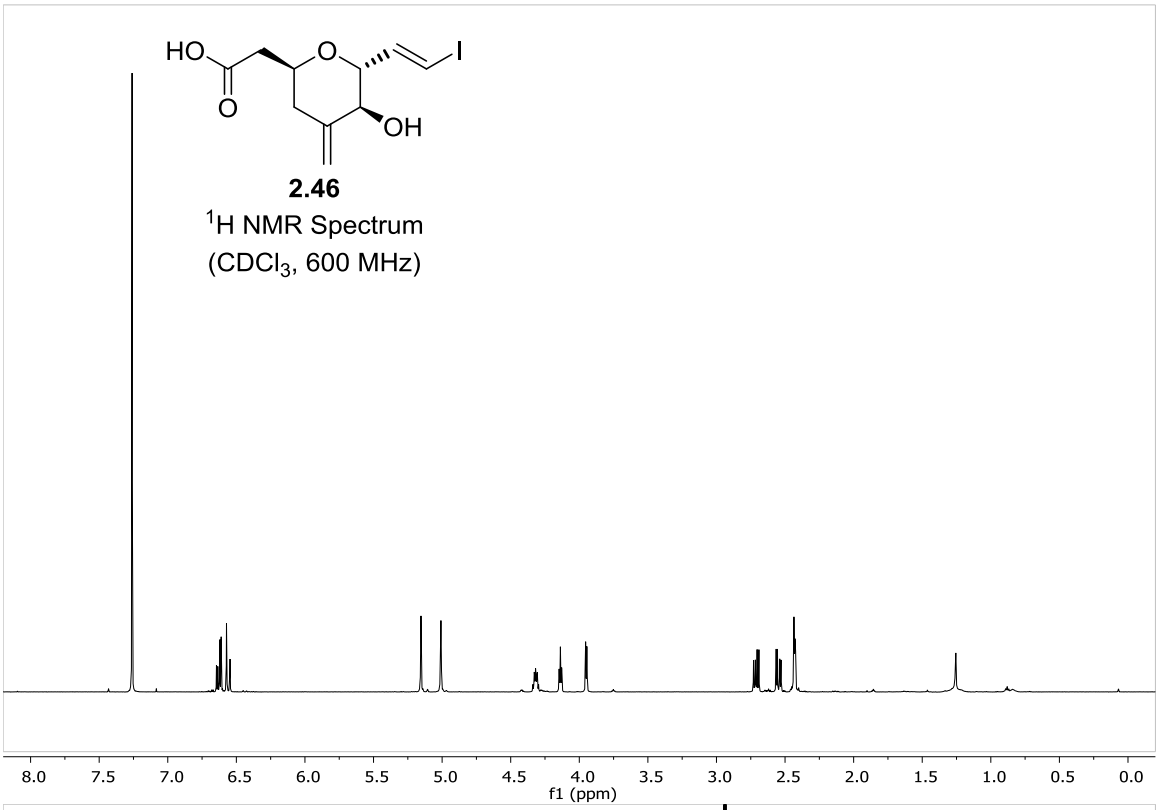


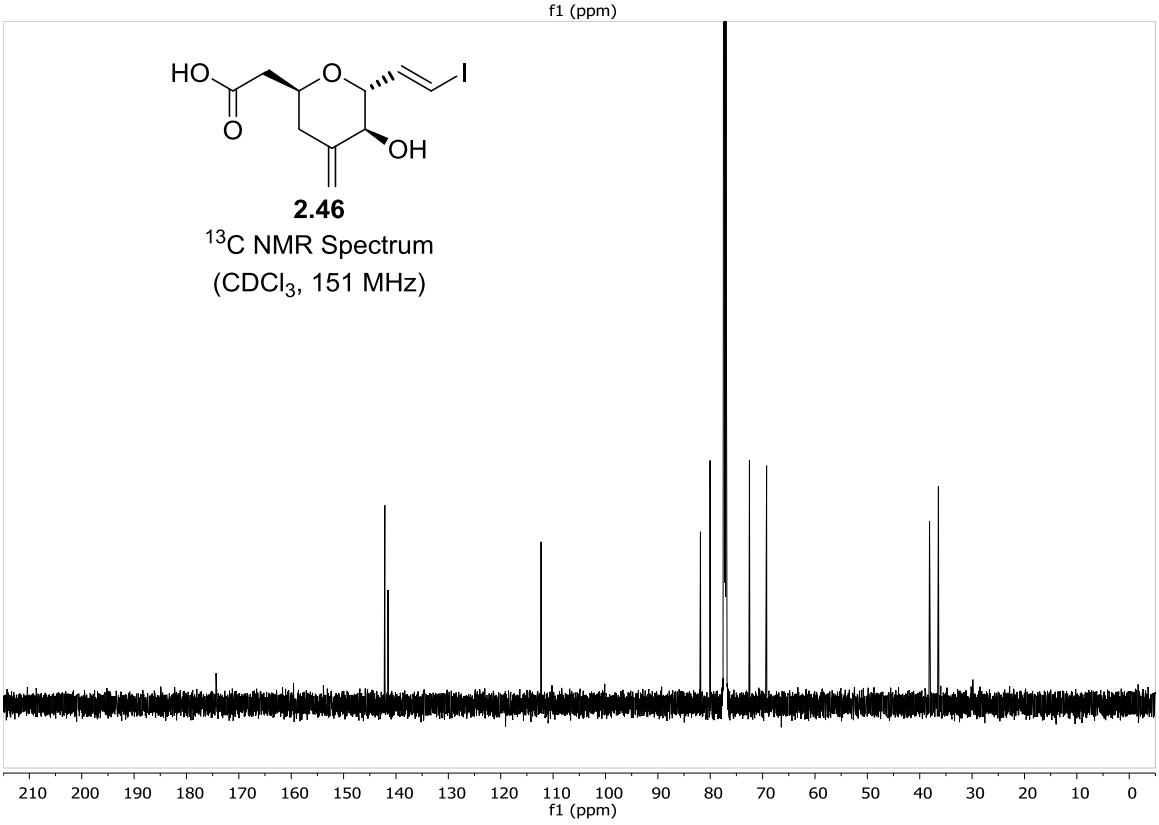
Spectra **2.27**: Compound **2.44**: ^{1}H and ^{13}C NMR



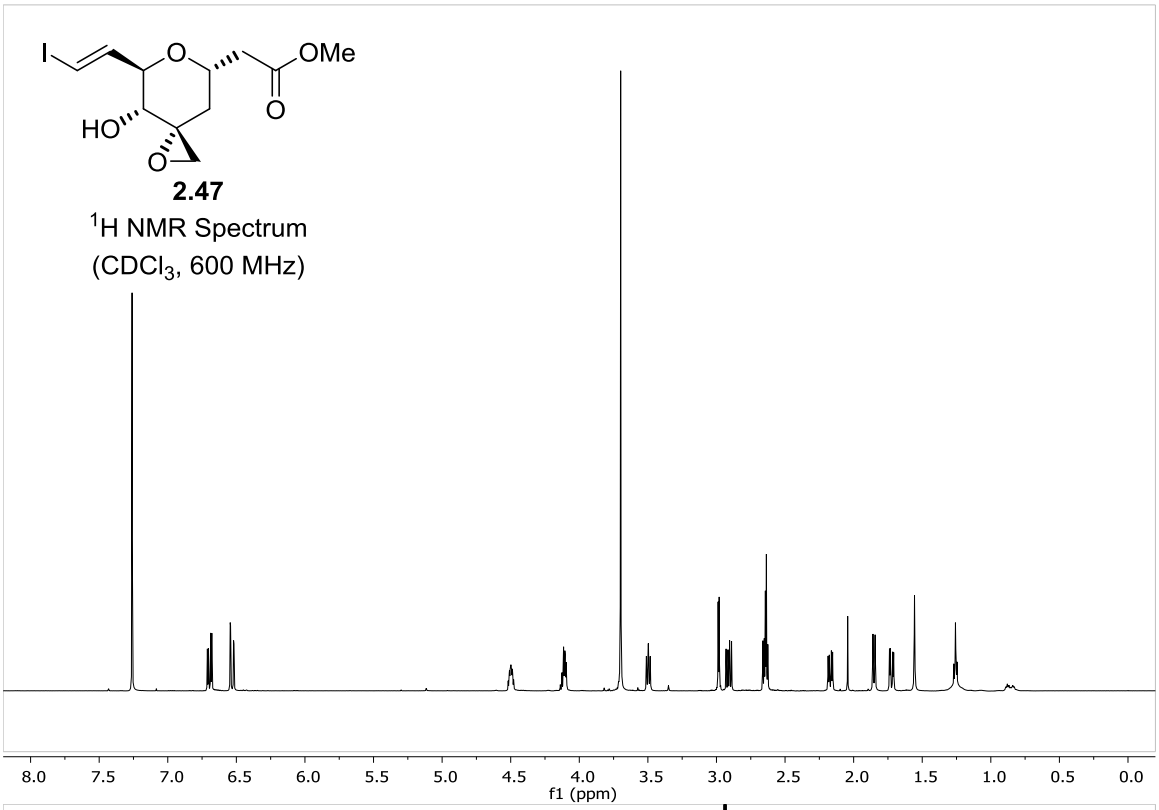


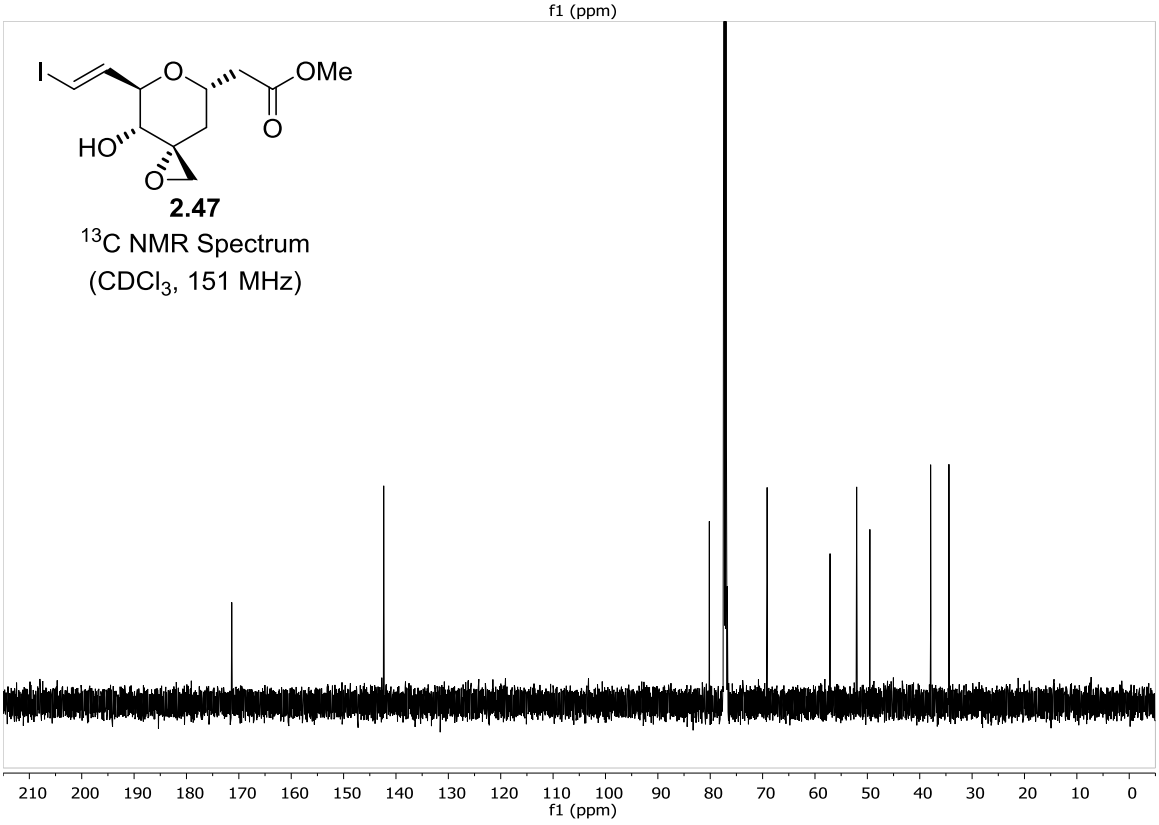
Spectra **2.28**: Compound **2.45**: ^{1}H and ^{13}C NMR



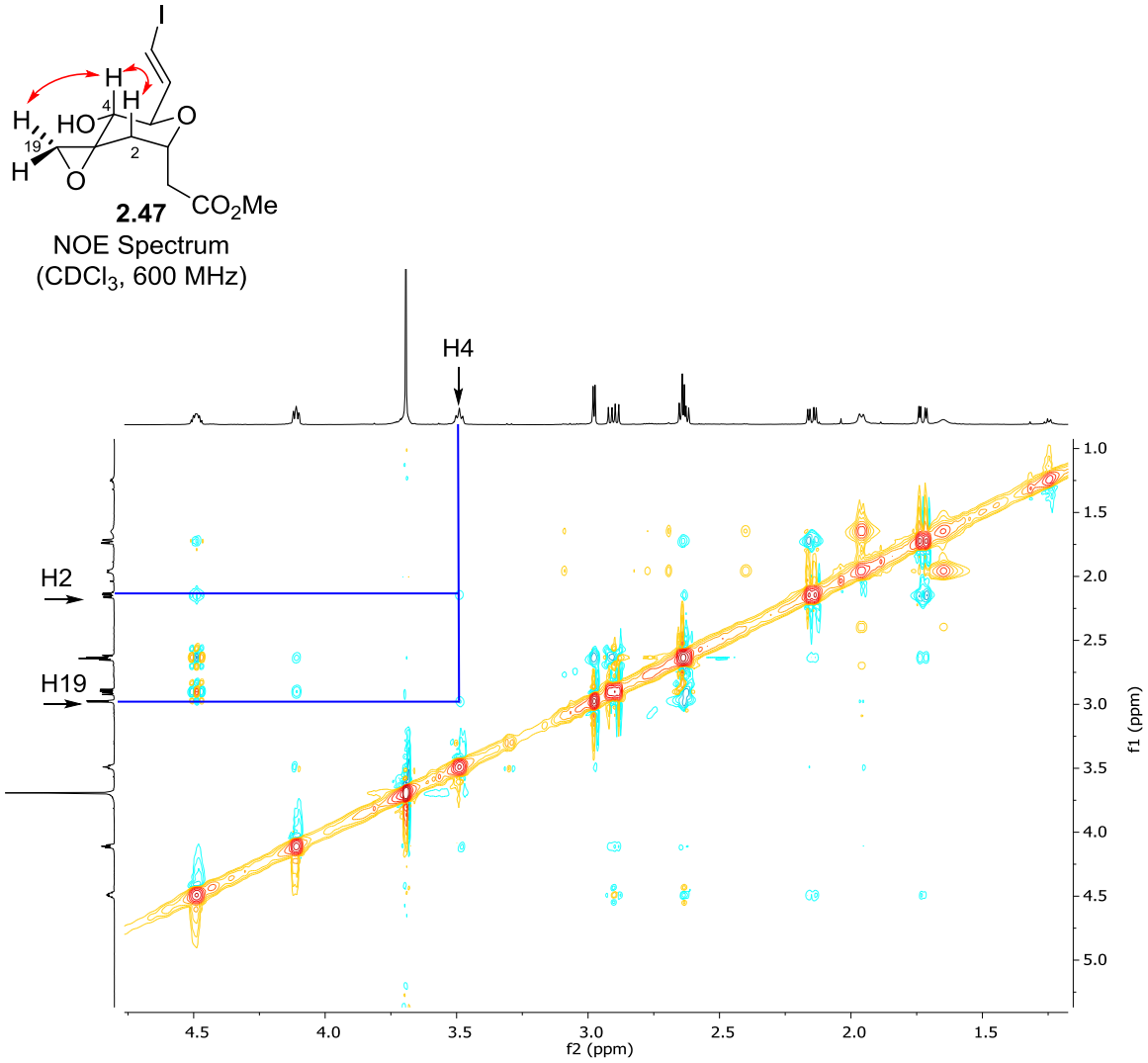


Spectra **2.29**: Compound **2.46**: ^{1}H and ^{13}C NMR

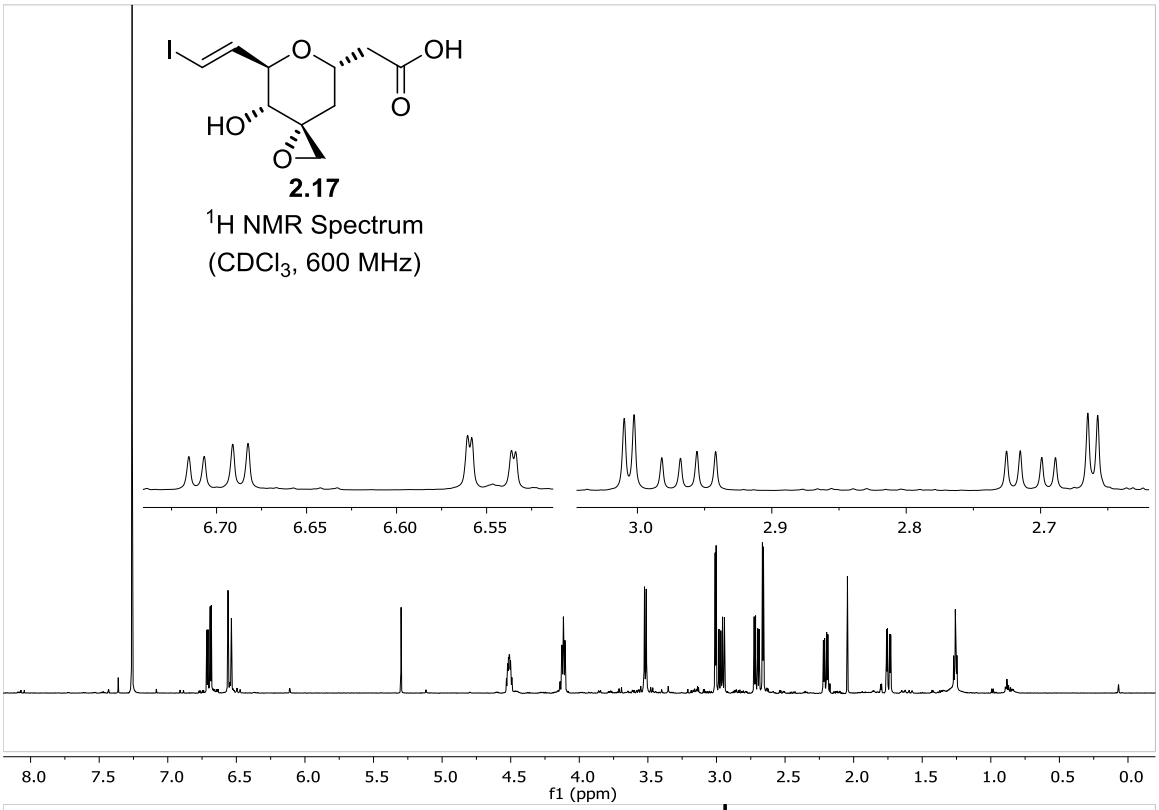


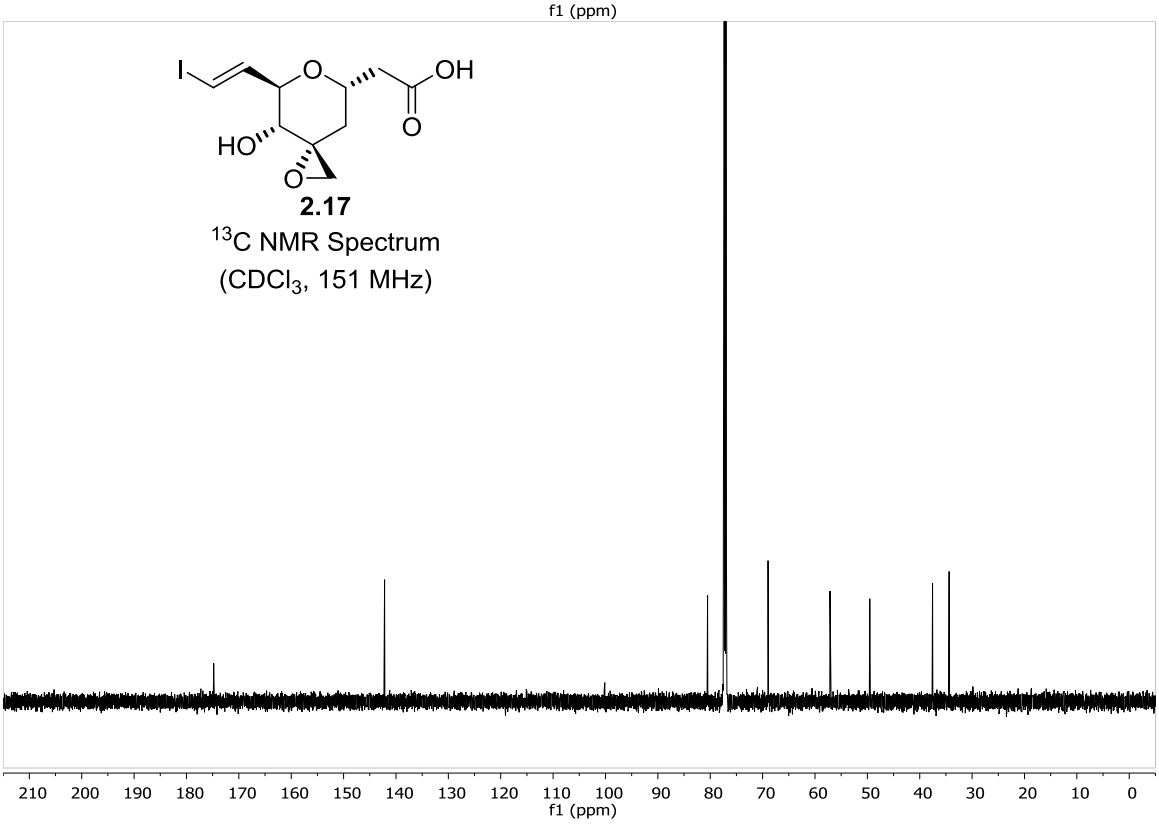


Spectra **2.30**: Compound **2.47**: ^{1}H and ^{13}C NMR

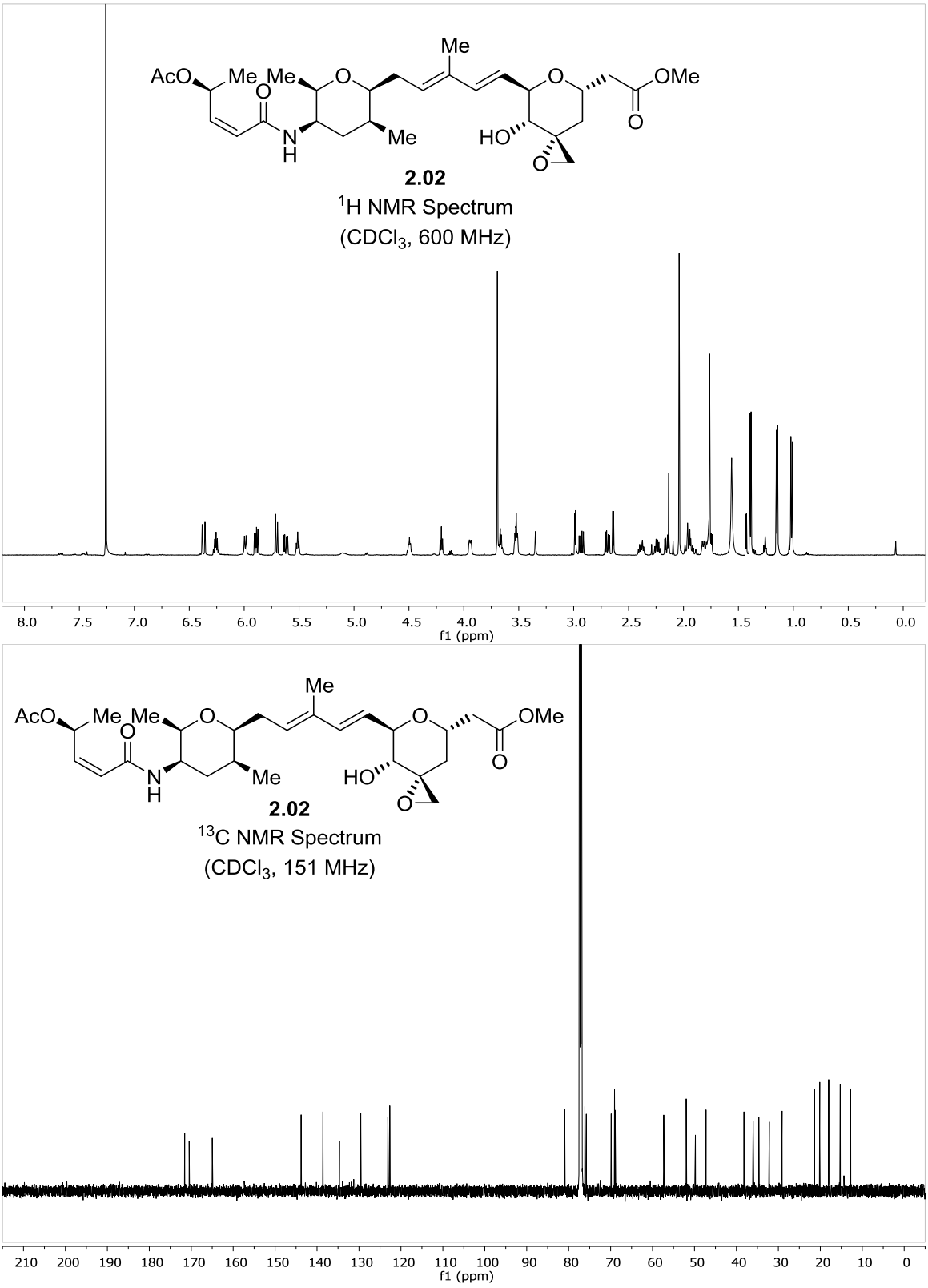


Spectrum **2.31**: Compound **2.47**: ^{1}H NOESY NMR

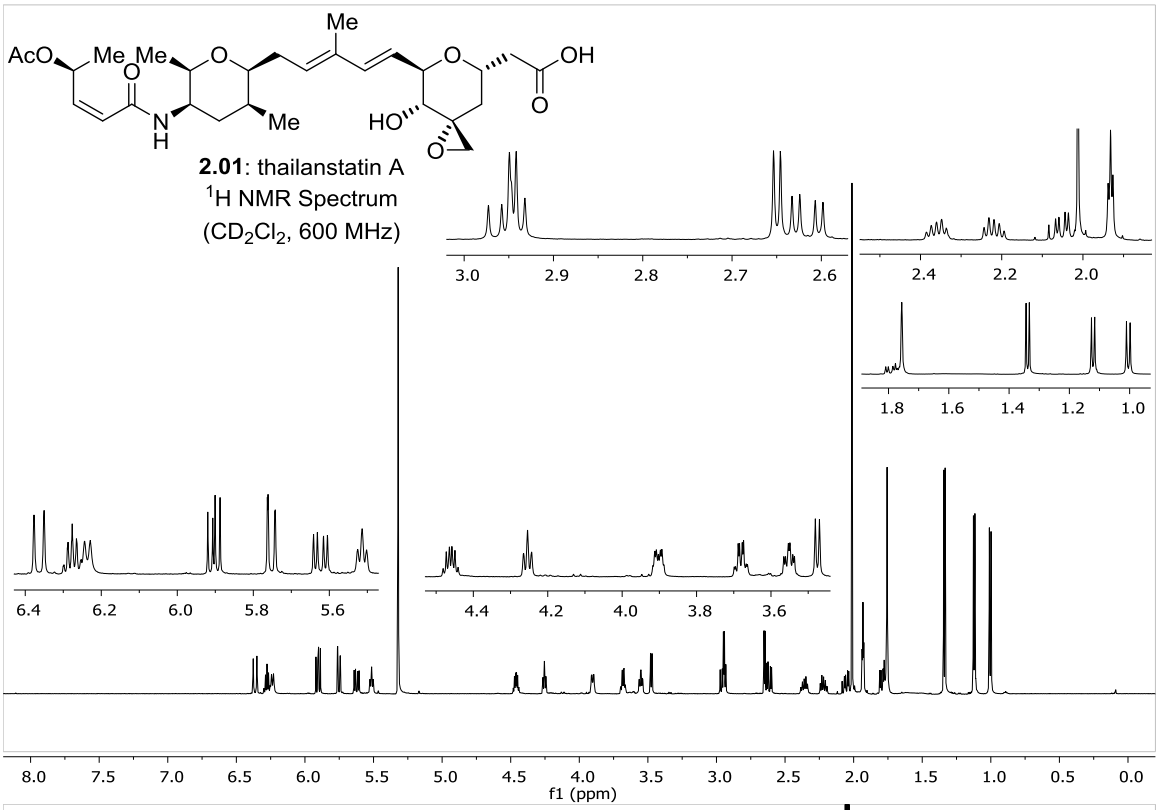


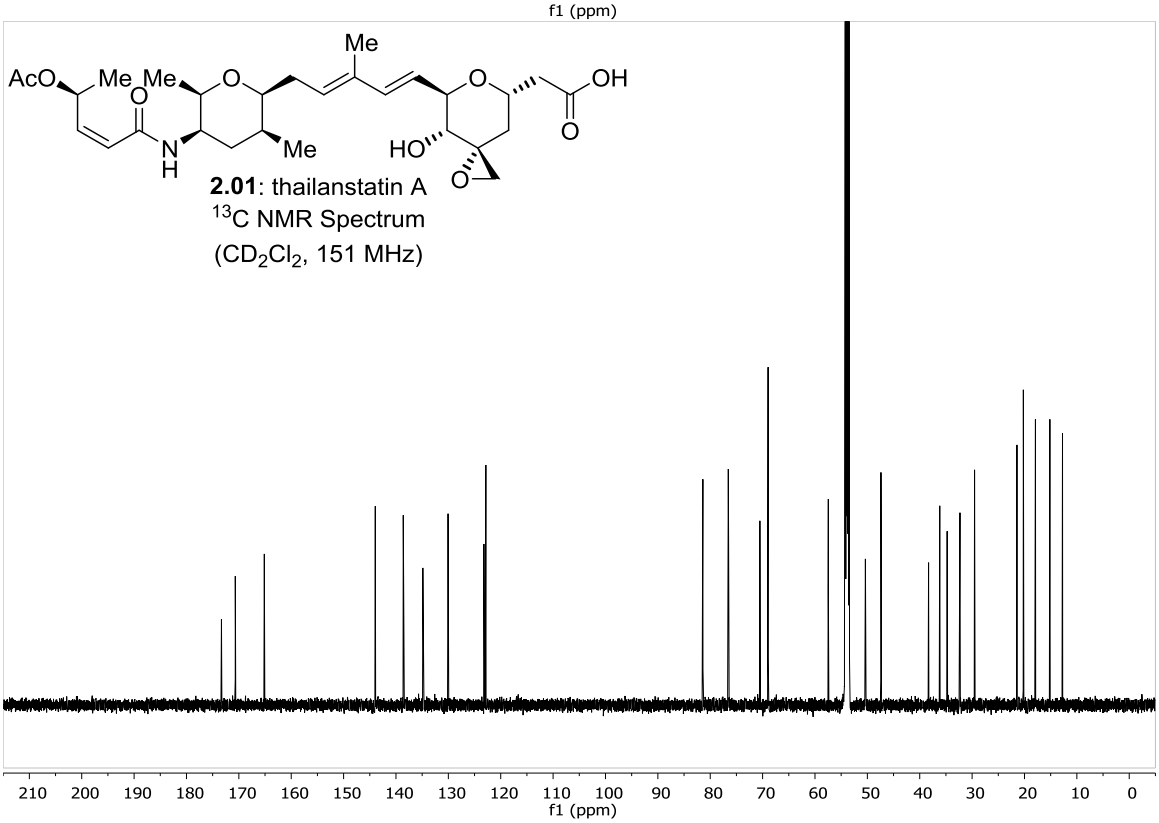


Spectra **2.32**: Compound **2.17**: ^{1}H and ^{13}C NMR



Spectra **2.33**: Compound **2.02**: ^{1}H and ^{13}C NMR





Spectra **2.34**: Compound **2.01**: ^{1}H and ^{13}C NMR

5. X-Ray derived ORTEP of **2.46**

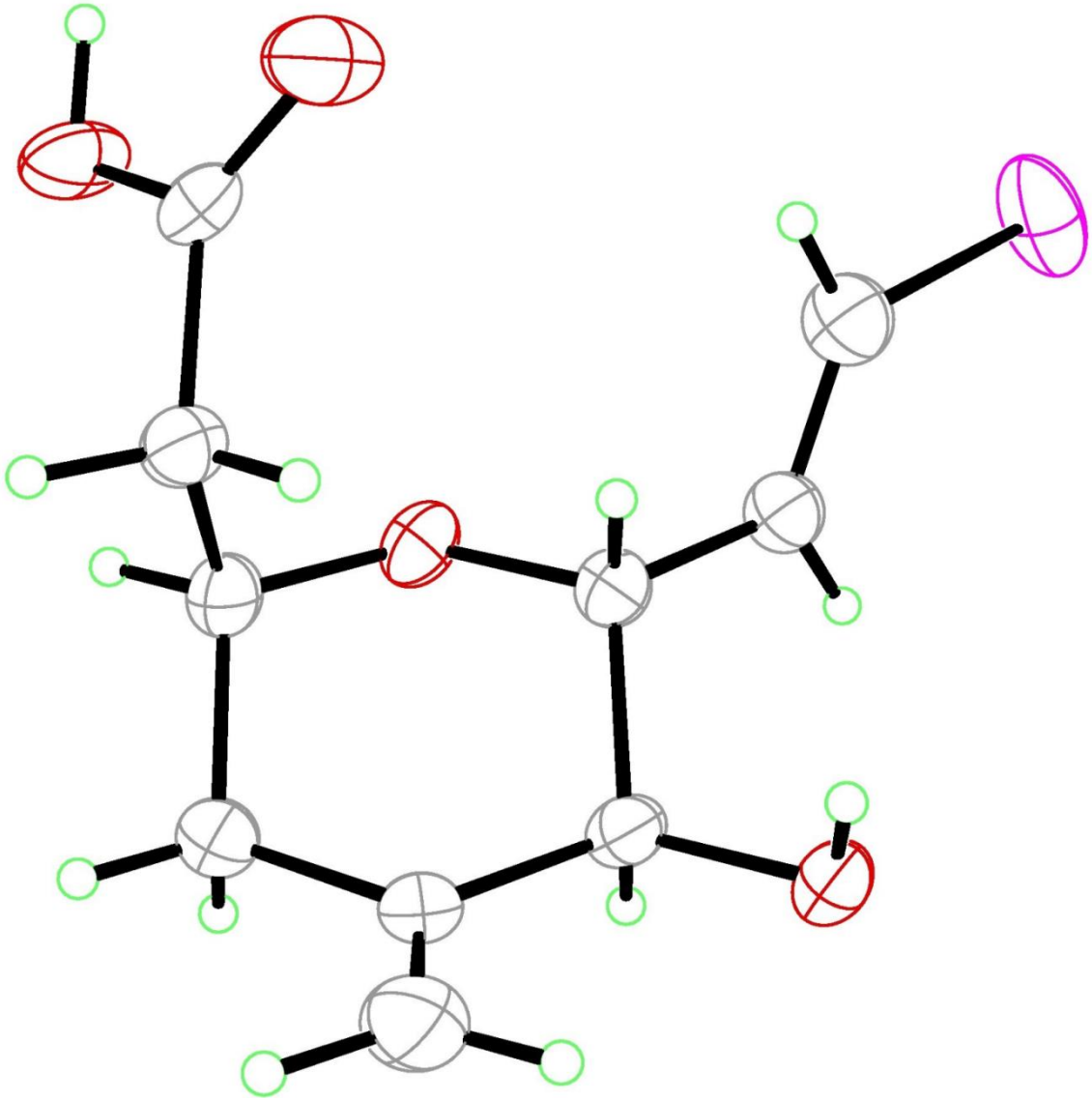


Figure 2.08: X-Ray derived ORTEP of Compound **2.46.**

Chapter 2 is a partial reprint as it appears in "Total Synthesis of Thailanstatin A, K.C. Nicolaou, D. Rhoades, M. Lamani, M.R. Pattanayak, S.M. Kumar, *J. Am. Chem. Soc.* **2016**, *138*, 7532–7535 (D. Rhoades did all of the synthetic chemistry)."

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