DISSERTATION

PART I: THE TOTAL SYNTHESIS OF (±)-SECURININE AND (±)-ALLOSECURININE AND SYNTHETIC STRATEGIES FOR A SECOND GENERATION SYNTHESIS OF THE SECURINEGA ALKALOIDS

AND

PART II: THE USE OF (+)-K252A IN THE SEMI-SYNTHESIS OF INDOLOCARBAZOLE NATURAL PRODUCTS AND NOVEL ANALOGS THEREOF

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ABSTRACT

PART I: THE TOTAL SYNTHESIS OF (±)-SECURININE AND (±)-ALLOSECURININE AND SYNTHETIC STRATEGIES FOR A SECOND GENERATION SYNTHESIS OF THE SECURINEGA ALKALOIDS

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PART II: THE USE OF (+)-K252A IN THE SEMI-SYNTHESIS OF INDOLOCARBAZOLE NATURAL PRODUCTS AND NOVEL ANALOGS THEREOF

In part I, the total syntheses of (±)-securinine (**(±)-1.001**) and (±)-allosecurinine (**(±)-1.003**) are described. The syntheses feature the use of a Rh-initiated O−H insertion/Claisen rearrangement/1,2-allyl migration, which would allow for an enantioselective synthesis when an enantioenriched allylic alcohol (ie: **(+)-1.137**) is used. Three more steps generates the common intermediate imine **1.144**, which upon reduction gives a pair of diastereomers. Protection of the free amine and a second reduction gives **1.146a** and **1.146b**, which were advanced to **(±)-1.003** and **(±)-1.001** respectively. Additional investigations into improving the endgame and devising a more streamlined synthesis were conducted. This focused on reducing the number of oxidation state changes at C13.

Part II of this dissertation details efforts to employ (+)-K252a (**2.016**) as a starting material for the synthesis of potential Hox-A14 inhibitors based on the indolocarbazole scaffold. It also covers the development of a novel method of selectively protecting the amide of **1.016** with a DMB group. This protected analog was employed as the starting material for a potential synthesis of the recently isolated indolocarbazoles Streptocarbazole A (**2.019**) and B (**2.020**). The proposed route to these compounds is via C−N bond migration on ketone **2.138** or

dimethylketal **2.158**. Substrates **2.138** and **2.158** have been synthesized. Preliminary investigations into conditions for the desired rearrangement have been conducted.

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ramblings when I got lonely in D301. Jenn, you rid me of any inclination I might have had to ask taller people to move things for me; my future lab-mates will be suitably grateful. As "group mom", Sarah made me feel welcome right from the start. Dave, thanks for making me laugh at the absurdity of life in general and grad school in particular. Monica and Aaron, you two put in a lot of work editing this dissertation on a short deadline. Thank you for the fantastic job.

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To my mom, you called me once a week and always asked how my chemistry was going. Even when I said "badly", you optimistically asked again the next week. Your support has always been unwavering, thank you. My sister—who commiserated with me as only another grad student could—always provided good advice, even if I did not always follow it. My brother—who reminded me that there was more to life than grad school—had an unshakable confidence that I would finish eventually. I could not have hoped for better siblings, thank you.

AUTOBIOGRAPHY

The daughter of Karen and Dennis Levine, Samantha was born in 1985. The oldest of three children, she grew up in Mahwah, New Jersey. After attending the local elementary and middle schools, she went to a public magnet school, the Academy for the Advancement of Science and Technology, for high school. The summer after her sophomore year, Samantha worked for Professor Robert Mentore at Ramapo College studying surface chemistry. During her senior year, she was a research assistant in inorganic chemistry for Professor Jing Li at Rutgers University.

In 2003 she entered Caltech as a freshman chemistry major. Dennis died in September of 2004, and after struggling with her classes, Samantha took a leave of absence from Caltech for the winter and spring quarters of 2005. After taking time off, she decided that she still wanted to be a chemist and re-enrolled at Caltech in fall 2005. In the winter of 2007 she joined the lab of Professor Brian M. Stoltz as an undergraduate research assistant. Under the supervision of Michael R. Krout she worked on their total synthesis of (+)-Carissone.

In August 2008, Samantha left Caltech and Stoltz group to start graduate school at Colorado State University (CSU). In January 2009 she joined the lab of Professor John L. Wood, where she worked on two short-lived projects prior to joining the *Securinega* alkaloid team. In May of 2012, she re-started the indolocarbazole project at CSU. When the lab moved in August 2013, she remained at CSU under the supervision of Professor Eric M. Ferreira. Samantha defended her dissertation in January 2014. In the spring, she will be starting her post-doctoral research in the lab of Professor Kimberly Beatty at Oregon Health and Science University.

DEDICATION

For my father, who always said I would be a doctor.

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18-c-6	18-crown-6
*p*ABSA	*p*-acetamidobenzenesulfonyl azide
Ac	acetyl
AIBN	azoisobutyronitrile
app	apparent
APCI	atmospheric pressure chemical ionization
aq.	aqueous
BMP	bone morphogenic protein
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOM	benzyloxymethyl
bp	boiling point
n-Bu	*n*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
calcd.	calculated
cat.	catalytic amount
CDI	1,1'-carbonyldiimidazole
*m*CPBA	*m*-chloroperbenzoic acid
CSA	camphorsulfonic acid
d	doublet
d.r. (dr)	diastereomeric ratio
DBU	1,8-diazabicyclo[2.2.2]-octane
DCC	dicyclohexylcarbodiimide
DIC	diisopropylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DHP	dihydropyran
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMB	3,4-dimethoxybenzyl
DMBOPy	2-(3,4-dimethoxybenzyl)oxypyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyltetrahydropyrimidin-2(1*H*)-one
DMS	dimethylsulfide

DMSO	dimethylsulfoxide
e.e. (ee)	enantiomeric excess
e.r. (er)	enantiomeric ratio
EDAC (EDCI)	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ESI	electrospray ionization
equiv (eq)	equivalents
Et	ethyl
g	grams
GABA	*gamma*-aminobutyric acid
h	hour
hν	light
HOBt	hydroxybenzotriazole
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoric triamide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IBX	*o*-iodoxybenzoic acid
imid	imidazole
IR	infrared spectroscopy
KHMDS	potassium bis(trimethylsilyl)amide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamine
LiHMDS	lithium bis(trimethylsilyl)amide
m	multiplet or medium
m/z	mass to charge ratio
Me	methyl
Mes	mesityl
MHz	megahertz
min	minutes
mL	milliliters
mmol	millimole
mp	melting point
Ms	mesyl (methanesulfonyl)
m.s. (ms)	molecular sieves
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
[O]	oxidation
Ph	phenyl
PhH	benzene
PhMe	toluene
PKA	protein kinase A
PKC	protein kinase C

PMB	*p*-methoxybenzyl
ppm	parts per million
i-Pr	*iso*-propyl
py (pyr)	pyridine
q	quartet
R_f	retention factor
rt	room temperature
s	singlet or strong
SEM	2-(trimethylsilyl)ethoxymethyl
t	triplet
TBAAz	tetra-*n*-butylammonium azide
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TCA	trichloroacetimidate
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	*p*-toluenesulfonyl (tosyl)
p-TSA	*p*-toluenesulfonic acid
w	weak
Δ	heat

PART I

THE TOTAL SYNTHESIS OF (±)-SECURININE AND (±)-ALLOSECURININE AND SYNTHETIC STRATEGIES FOR A SECOND GENERATION SYNTHESIS OF THE SECURINEGA ALKALOIDS

CHAPTER 1

Introduction to the *Securinega* Alkaloids

1.1 Background

1.1.1 Securinega Alkaloids

The class of natural products known as the *Securinega* alkaloids[1] consists of more than 40 bridged, tetracyclic molecules isolated from a variety of plants in the Euphorbiaceae subtribe Flueggeinae.[2] These compounds can be further subdivided into two major classes, the securinanes and the norsecurinanes (Figure 1.1). The securinanes take their name from (−)-securinine (**(−)-1.001**) and contain an indolizidine core, while the norsecurinanes take their name from (−)-norsecurinine (**(−)-1.002**) and contain a pyrrolizidine core. Both of these skeletons have a central azabicyclo[3.2.1]octane system, which is proposed to undergo a rearrangement via an aziridinium intermediate to give the azabicyclo[2.2.2]octane skeletons of neosecurinane and neonorsecurinane.[3]

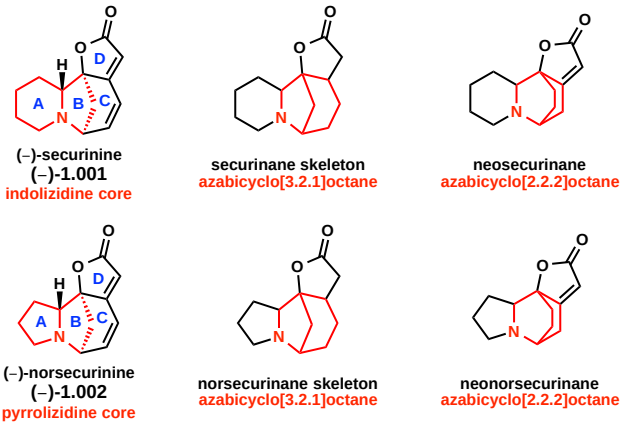


Figure 1.1

Though **1.001** is the most commonly isolated securinane,[2] the other three possible diastereomers, virosecurinine (**(+)-1.001**), allosecurinine (**(−)-1.003**), and viroallosecurinine (**(+)-1.003**) are also natural products (Figure 1.2). Many derivatives of these compounds are also natural products, including the C4 oxidized securitinine (**1.004**) and phyllanthine (**1.005**). Similar

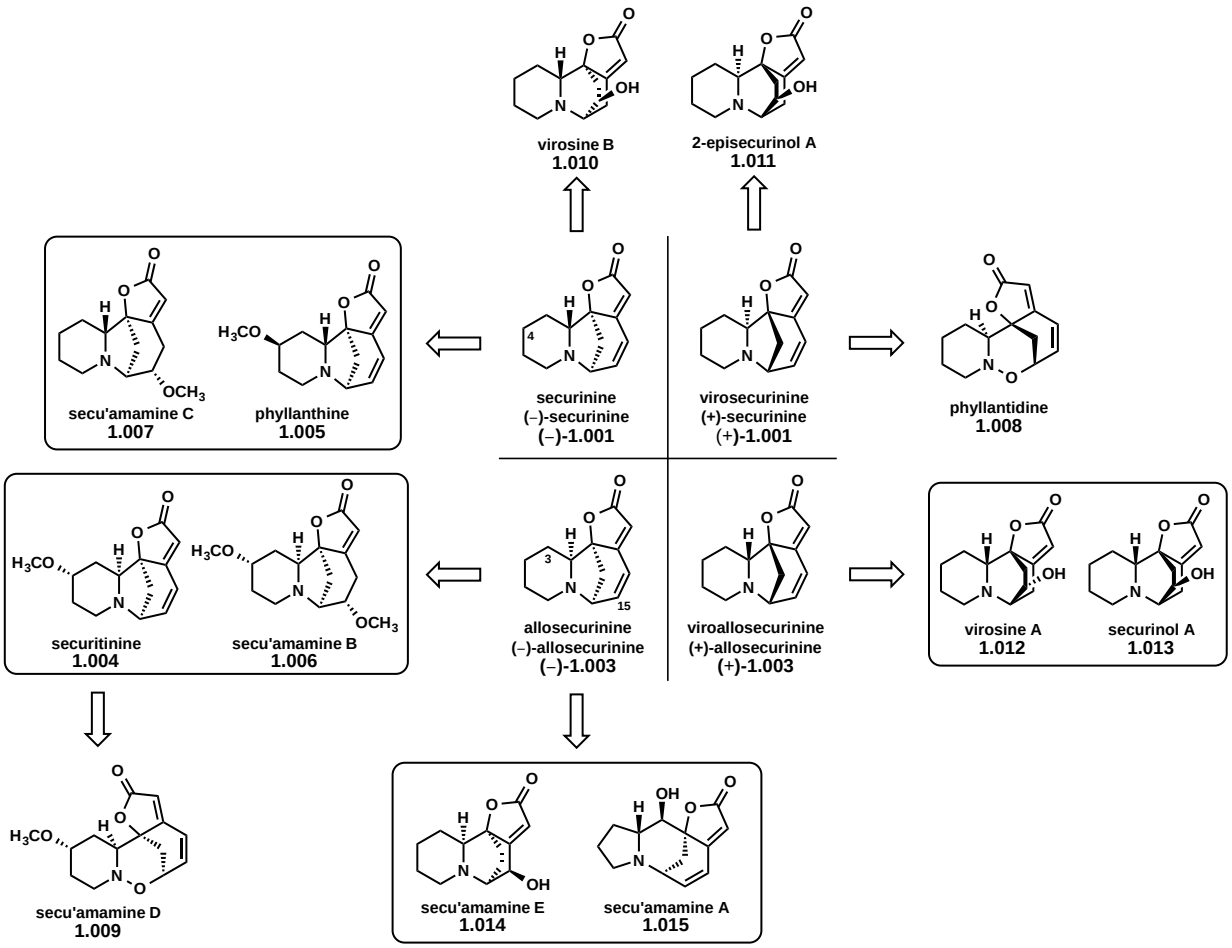
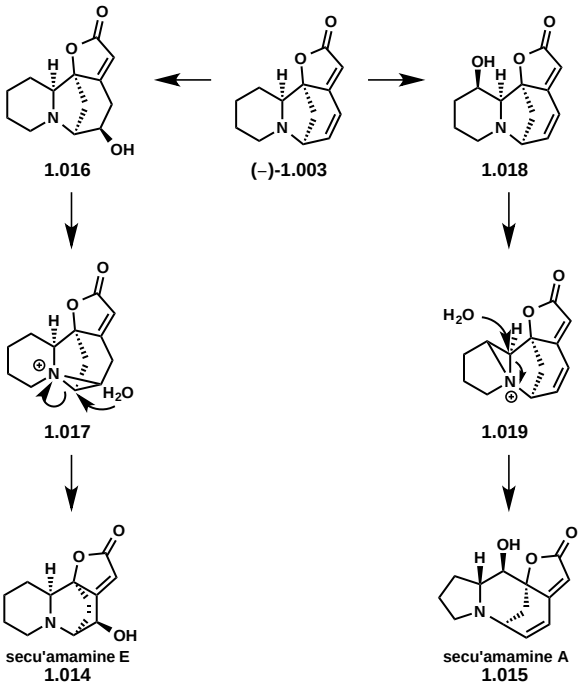


Figure 1.2

compounds with oxygenated skeletons include secu'amamine B (**1.006**) and secu'amamine C (**1.007**). Phyllantidine (**1.008**) and secu'amamine D (**1.009**) are *N*-oxidized derivatives of **(+)-1.001** and **1.004,** respectively. Neosecurinane natural products, derived from a skeletal rearrangement of their parent securinane, include virosine B (**1.010**)[4] from **(−)-1.001**, 2-episecurinol A (**1.011**)[5] from **(+)-1.001**, virosine A (**1.012**)[4] and securinol A (**1.013**) from **(+)-1.003**, and secu'amamines A (**1.015**)[6] and E (**1.014**)[7] from **(−)-1.003**. These last two natural products are generated from the rearrangement of two different aziridinium intermediates of **1.003** (Scheme 1.1).[3,8] First, if **(−)-1.003** is hydrated to give the C15 alcohol **1.016**, attack by the nitrogen gives aziridinium **1.017**. Otherwise, oxidation of **(−)-1.003** at C3 can give alcohol **1.018**, and attack by the nitrogen gives aziridinium **1.019**. Attack by water then generates either

1.014 or **1.015** depending on the aziridinium intermediate.

Scheme 1.1



Unlike the securinanes, only the parent norsecurinanes **(**−)-**1.002** and its enantiomer ((+)-**1.002**) have been isolated as natural products (Figure 1.3). However, apparent derivatives of the unnatural[9] diastereomers (−)-allonorsecurinine (−)-**1.020** and (+)-allonorsecurinine ((+)-**1.020**) have been isolated. The neonorsecurinanes epibubbialine[10] (**1.021**), bubbialidine[11] (**1.022**), and bubbialine[11] (**1.023**) arise from an aziridinium rearrangement analogous to that proposed for the generation of the neosecurinanes. Further derivatization of **1.021** gives nirurine (**1.024**). Interestingly, the *N*-oxidized derivatives of the pyrrolizidine compounds appear to undergo a [1,3]-dipolar cycloaddition to give compounds such as virosaine A[12] (**1.025**) and virosaine B[12] (**1.026**). The hydrated form of (−)-**1.002** is fluggeainol[13] (**1.027**), which is a precursor to at least one of the dimeric *Securinega* alkaloids. These dimers (Figure 1.4) include the (−)-**1.002** dimer flueggenine A[14] (**1.028**), the (−)-**1.002**/**1.027** dimer flueggine A[15] (**1.029**), the (−)-**1.002**/**1.023** dimer flueggine B[15] (**1.030**) and the partial dimer of (+)-**1.003** suffruticosine[16] (**1.031**).

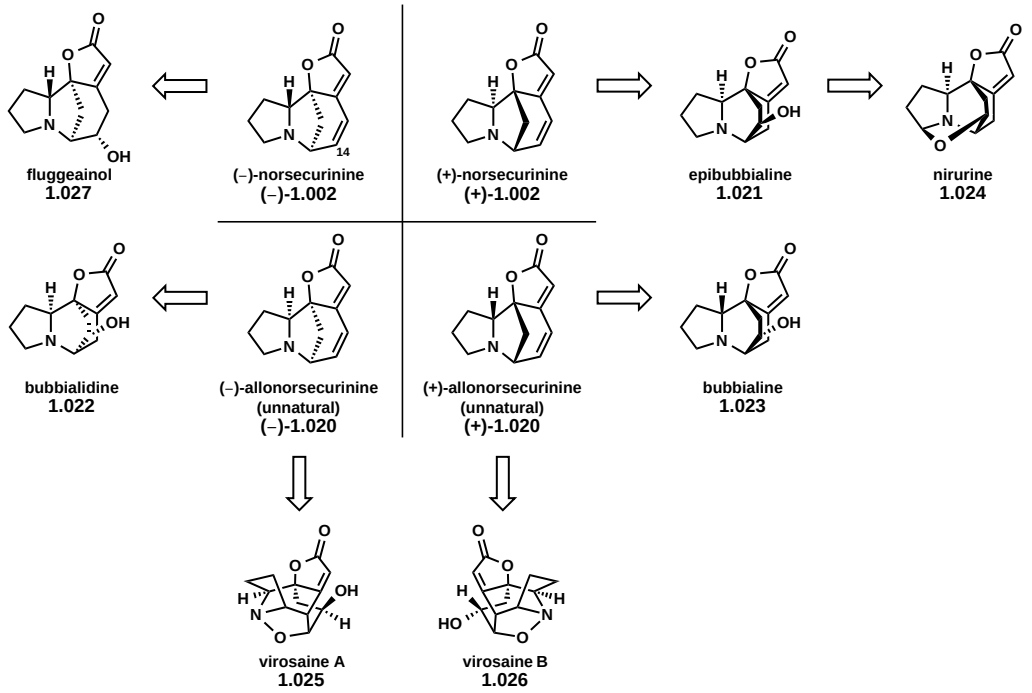


Figure 1.3

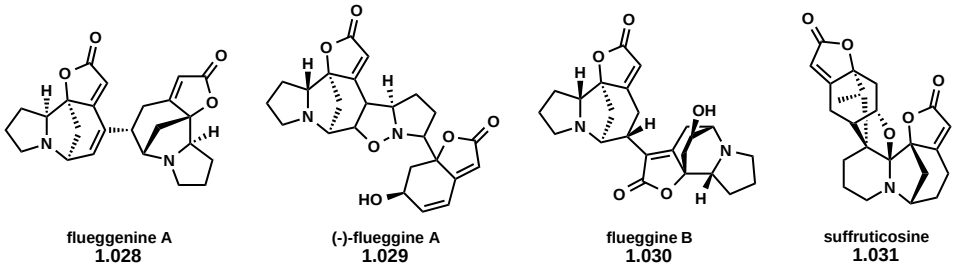


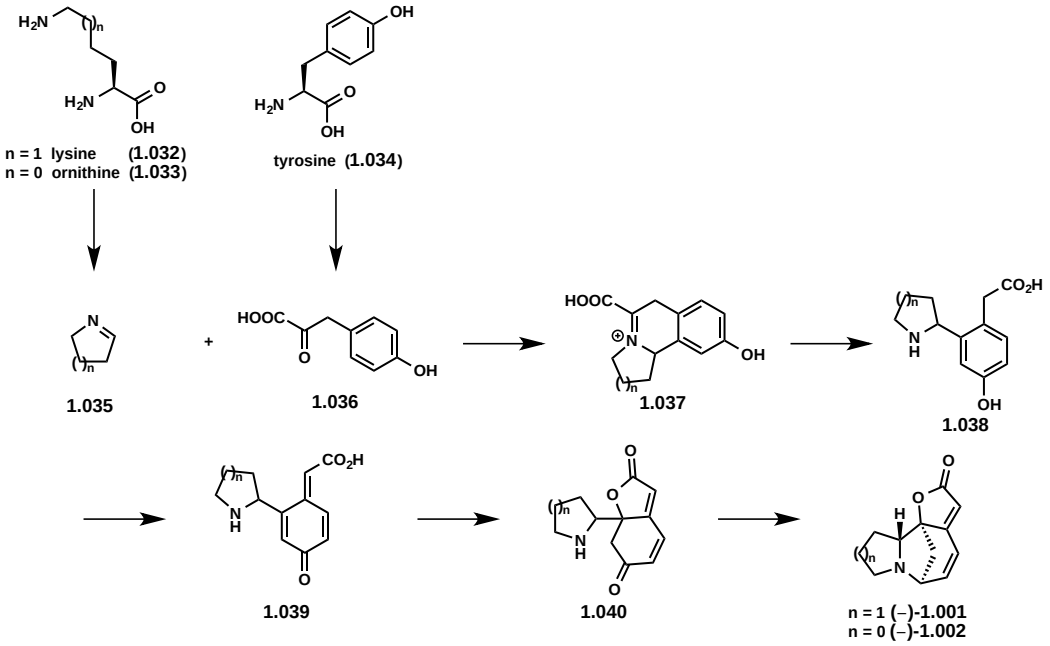
Figure 1.4

1.1.2 Biosynthesis

Early reports of the unusual structure of these alkaloids led to the theory that the piperidine A-ring in **(−)-1.001** was derived from lysine (**1.032**, Scheme 1.2), the commonly proposed biosynthetic precursor of such a ring.[17] Similarly, the pyrrolidine ring in **(−)-1.002** was predicted to originate from ornithine (**1.033**). Feeding studies later confirmed this,[18] leaving only the biosynthetic source of the remaining eight core carbon atoms in question. Additional feeding and degradation studies led to the conclusion that these originated with tyrosine (**1.034**).[19] The generally accepted biosynthetic pathway[1] for the synthesis of **(−)-1.001** therefore starts with the

condensation of the lysine derivative Δ^1-piperidine (**1.035**) with the tyrosine derivative 4'-hydroxyphenylpyruvic acid (**1.036**) to yield iminium ion **1.037**, which could be reductively opened to phenol **1.038**. Oxidation to the quinone methide **1.039** and lactonization would then afford butenolide **1.040**. In the final step, **(−)-1.001** would be produced from the reductive cyclization of tricycle **1.040**.

Scheme 1.2



1.1.3 Biological Activity

Taken together, these molecules have a broad spectrum of biological activity, particularly for a family of so few members. Studies have indicated antimalarial[20] and antibacterial[21] properties for various *Securinega* alkaloids. In addition to antimalarial activity, recent studies have indicated that (−)-securinine (**(−)-1.001)** exhibits inhibitory activity and encystation effects on *Toxoplasma gondii*,[22] possibly due to its activity as an immune system adjuvant.[23] **(−)-1.001** has also been studied as a gamma-aminobutyric acid (GABA) antagonist for use as a potential treatment for or prevention of various neurodegenerative diseases including ALS and

Alzheimer's disease.[24] The fact that **(−)-1.001** is only available at 0.2-0.9% dry weight from *F. suffruticosa* has hindered its clinical use. Its convulsive activity as a GABA antagonist poses an additional problem. **(−)-1.001** binds to the $GABA_A$ receptor through interactions with the amine and lactone functional groups.[24a] The shape of the binding pocket has little tolerance for steric bulk below the plane containing these moieties. Molecular modeling and *in vitro* studies have indicated that steric restrictions prevent (+)-securinine (**(+)-1.001**), (−)-allosecurinine (**(−)-1.003**), and (+)-allosecurinine (**(+)-1.003**) from binding to the receptor (Figure 1.5). For **(+)-1.001** and **(−)-1.003** the position of the A-ring is problematic and for **(+)-1.003** the C-ring causes steric interference.

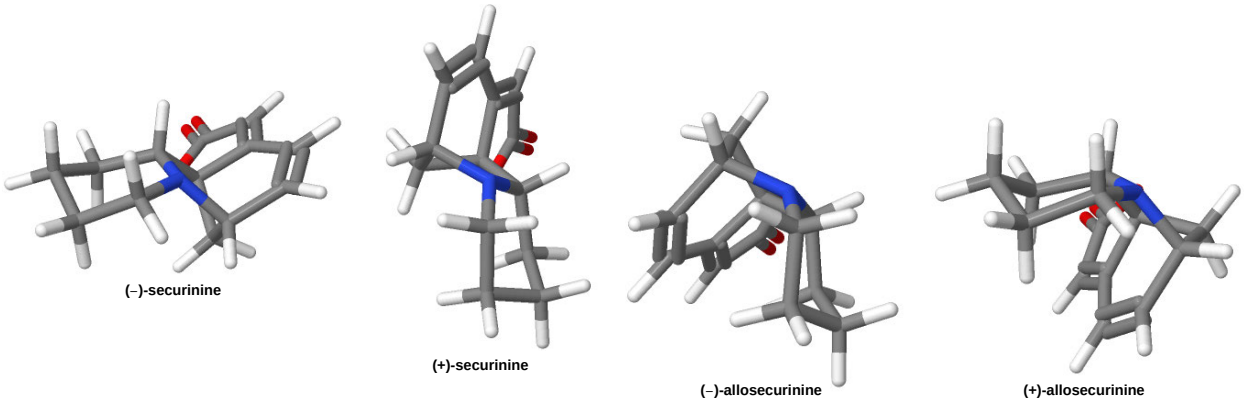


Figure 1.5

A recent report indicating that **(−)-1.001** can induce cell death preferentially in p53-null cells has heightened interest in these compounds.[25] Since a significantly higher percentage of cancerous cells are p53-null compared to noncancerous cells,[26] there exists the heretofore-underexplored possibility for the development of chemotherapeutic agents that exploit this difference and selectively target cancerous cells. The mechanism behind the preferentially induced apoptosis appears to be up-regulation of proapoptosis protein p73. This is a particularly attractive target for chemotherapeutic agents since p73 mutations are extremely rare in cancer cells.[27] **(+)-1.001** and **(−)-1.003** are similarly active against certain p53-null cell lines.[25b]

1.2 Other Syntheses of *Securinega* Alkaloids

1.2.1 Overview

Due to their wide range of biological activities and interesting molecular architecture, there are twenty-one completed approaches to the synthesis of the *Securinega* alkaloids. These have been summarized in Table 1.1. Of particular interest is that eighteen of these approaches start with at least one ring already formed in the starting material. Furthermore, seven of those eighteen approaches make use of proline or its derivatives as the starting material. Also of note is that the bulk of this work has focused on the eight "core" structures, with only a single synthesis of a neosecurinane (**1.010**) and only four of neonorsecurinanes (**1.022, 1.024**, **1.025**, and **1.026**). Syntheses of the securinanes and the Wood group's synthesis of the norsecurinanes **(+)-1.002** and **(+)-1.020** are briefly reviewed below.

1.2.2 Synthesis of Indolizidine Securinega Alkaloids

*1.2.2.1 Horii's Synthesis of (±)-securinine (**(±)-1.001**)*

Horii *et al*. reported the first total synthesis of a *Securinega* alkaloid in 1966 with their synthesis of **(±)-1.001** (Scheme 1.3).[28] Setting a precedent that many later approaches would follow, the synthesis commenced with the nitrogen containing A ring already formed in 2-lithio pyridine (**1.041**). This was added into carbonyl **1.042** to give alcohol **1.043**. Reduction of the pyridine ring of **1.043** to a piperidine was followed by the deprotection of the remaining ketone and *N*-acetylation to give keto-alcohol **1.044**. While the yield over these three steps is quite good, the newly formed stereocenter led to a mixture of diastereomers, whose ratio is unspecified. These are separable, however, and the desired diastereomer was transformed into enone **1.045** via a bromination/dehydrohalogenation sequence. Enone **1.045** was then treated with lithiated ethoxyacetylene and hydrolyzed to generate the D ring in **1.046**. Preliminary work had indicated

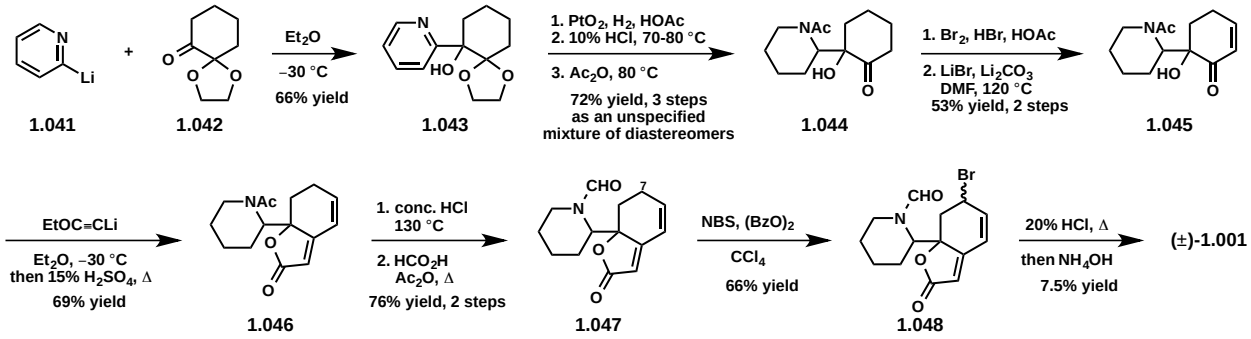
Table 1.1[a]

Group	Compound(s)	Steps	Yield	Notes	Ring order[b]	Purchased rings	Ref.
Horii	**(±)-1.001**	11	1%		A + B, C, D	A, B	28
Heathcock	**(±)-1.002**	14	2%		A, B, C, D	A	29
Jacobi	**(−)-1.002** and **(+)-1.002**	11	5%		A, B/C, D	A (proline deriv.)	30
Magnus	**(±)-1.024**	15	1%	common intermediate	B, C/D, A	B	31
	(±)-1.002	13	12%				
Weinreb	**(−)-1.002**	22	2%		B, C, A, D	B (proline deriv.)	32
	1.005	18	5%				
	1.015	16	8%		A, C, B, D	A (proline deriv.)	33
Honda	**(±)-1.001**	16	1%	formal	A, C/D, B	A	34a
	(−)-1.001	9	17%		A, C/D, B	A (pipecolic acid deriv.)	34b,c
	(+)-1.003	11	24%				
Liras	**(±)-1.001**	9	10%		A, D, C, B	A, D	35
Alibes & de March	**(−)-1.001**	13	3%		A, D, C, B	A (pipecolic acid deriv.)	36
	(−)-1.020	11	2%				
Figueredo	**(−)-1.002**	9	14%	stereochemistry set catalytically	A + D, B/C	A, D	37
Kerr	**1.008**	12	6%		B, C, D, A		38
	(−)-1.003	22	4%		B, D, C, A		39
Busque & de March	**(−)-1.003** and **(+)-1.003**	7	42%		C/D + A, B	A, C/D (menisdaurilide)	40
Thadani	**(−)-1.001**	14	17%		B, A, D, C	B (proline deriv.)	41
Wood	**(+)-1.002**	13	2%	common intermediate, stereochemistry set catalytically	A, C, B, D		42
	(+)-1.020	13	2%				
Bélanger	**1.012**	13	3%	stereochemistry set catalytically	C, D, A/B	C	43
Srihari	**(−)-1.020**	10	7%		A, C, D, B	A (proline deriv.)	44
Yang & Li	**(−)-1.002**	7	10%		A, C/D, B	A (proline deriv.)	45
	(+)-1.020	7	11%				
	1.029	4	57%	from (−)-norsecurinine			
	1.026	3	62%	from (+)-allonorsecurinine			
Gademann	**1.025**	19	1%	common intermediate, stereochemistry set via enzymatic resolution	C, D, A, B	A, C	46
	1.022	16	1%				
Snyder	**(±)-3-deshydroxy-secu'amamine A**	9	6%		B, C/D, A	B	47

[a]Approaches are listed in chronological order, except when the same group has developed a second distinct synthetic route.

[b]The notation should be read as follows: "A, B " is the formation of ring A followed by the formation of ring B, "A + B" is the coupling of ring A with ring B after A and B have been formed independently, and "A/B" is the formation of those two rings in the same step.

Scheme 1.3

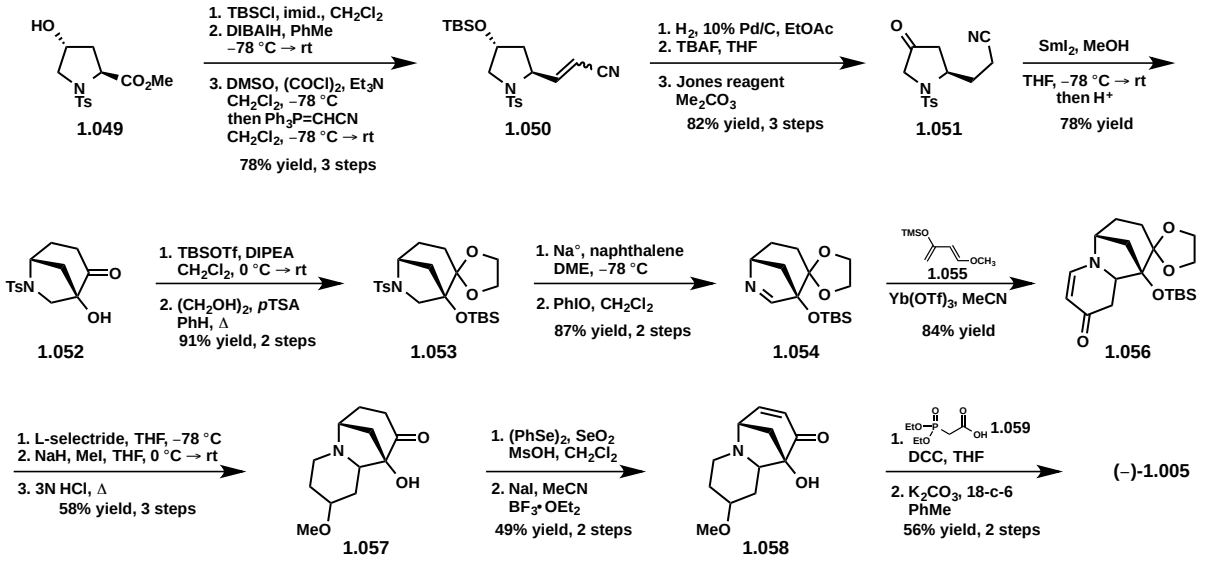


that acetate removal would be challenging at later stages, so it was removed and replaced with a formate group at this point. Unsaturated lactone **1.047** was then brominated at C7 to give **1.048**. Formamide **1.048** was subjected to acid hydrolysis conditions to remove the formyl protecting group. The resulting amine salt was then free-based, leading to concomitant cyclization to form **(±)-1.001**. This final step was quite low yielding, however the question of whether the problem lay with the deprotection or the cyclization was not answered until Honda's synthesis of **(−)-1.001** in 2004.

*1.2.2.2 Weinreb's Synthesis of (−)-phyllanthine (**1.005**)*

The first synthesis of any securinane as a single enantiomer was reported by Weinreb *et al.* in 2000. Their synthesis of **1.005** starts with known L-proline derivative **1.049** (Scheme 1.4), which they protect as the TBS ether.[32] The methyl ester was then reduced to the alcohol, which in turn was oxidized to give an aldehyde. The aldehyde was then treated with (cyanomethyl)-triphenylphosphine to give Wittig product **1.050**, and subsequent hydrogenation delivered a single stereoisomer. Alcohol deprotection and subsequent oxidation yielded ketone **1.051**. The formation of the C ring occurred by treating nitrile **1.051** with samarium diiodide to promote a pinacol-type coupling generating azabicyclo[3.2.1]octane **1.052**. The alcohol of **1.052** was then protected as the TBS ether and the ketone protected as the acetal to give tosylamide **1.053**. Nitrogen deprotection and oxidation to the imine with iodosobenzene gave **1.054**. The A ring

Scheme 1.4

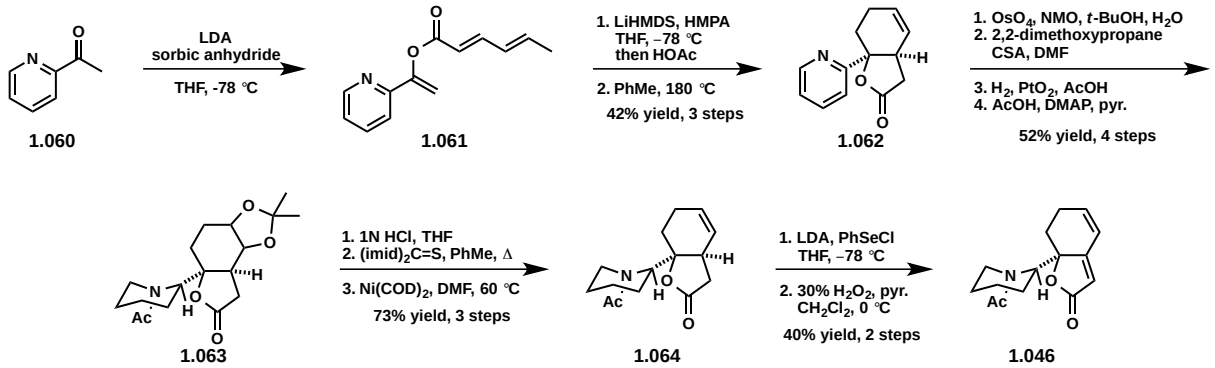


was formed via a hetero-Diels-Alder reaction with Danishefsky's diene (**1.055**) generating **1.056**. Enone **1.056** also has the desired C2 stereochemistry due to the reaction going entirely in an *exo* fashion. The vinylogous amide of **1.056** was then reduced to an amino alcohol, which was subsequently methylated. The TBS ether was then cleaved to reveal alcohol **1.057**. The C ring olefin was then generated by the formation of an α-selenoketone and subsequent deselenation to give enone **1.058**. Conversion to the phosphonate ester with **1.059** and a Horner-Wadsworth-Emmons olefination produced **1.005**.

*1.2.2.3 Honda's Synthesis of (±)-securinine (**(±)-1.001**)*

Honda *et al.*'s first synthesis of a securinane was the formal synthesis of **(±)-1.001**[34] (Scheme 1.5), where they intercepted the final *N*-acetyl compound (**1.046**) in Horii's synthesis.[28] Also starting with a pyridine, the first step was the *O*-acylation of 2-acetylpyridine (**1.060**) with sorbic anhydride to give enol ether **1.061**. Deconjugation of the diene from the carbonyl occurred upon deprotonation of **1.061** with LiHMDS and subsequent kinetic reprotonation. The resulting triene undergoes an intramolecular Diels-Alder reaction to give lactone **1.062**. Dihydroxylation and acetonide formation mask the olefin in **1.062**, allowing for the hydrogenation of the pyridine

Scheme 1.5

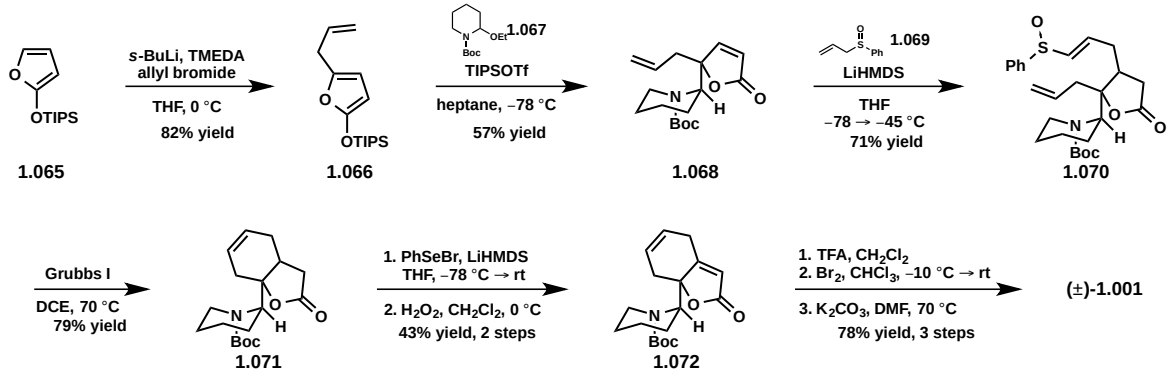


ring and subsequent acetylation to give **1.063**. The yield over four steps was 87%; however the hydrogenation yielded a 3:2 mixture of diastereomers. While separable, this poor diastereoselectivity led to a low yield of **1.063**. Acetonide cleavage was followed by thionocarbonate formation, and subsequent reduction regenerated the alkene in **1.064**. Formation of the α- selenoketone and elimination provided the α, β, γ, δ-unsaturated lactone **1.046**.

*1.2.2.4 Liras' Synthesis of (±)-securinine (**(±)-1.001**)*

In 2001, Liras *et al.* published their synthesis of **(±)-1.001**.[35] Starting with what would later become the D ring, siloxyfuran **1.065** was allylated to give **1.066** (Scheme 1.6). Allylic furan **1.066** was condensed with piperidine **1.067** to deliver butenolide **1.068** with a 57% yield of the desired diastereomer. Conjugate addition of allylphenylsulfoxide (**1.069**) into **1.068**, generated lactone **1.070**. Treatment of diene **1.070** with Grubbs' first generation catalyst formed

Scheme 1.6

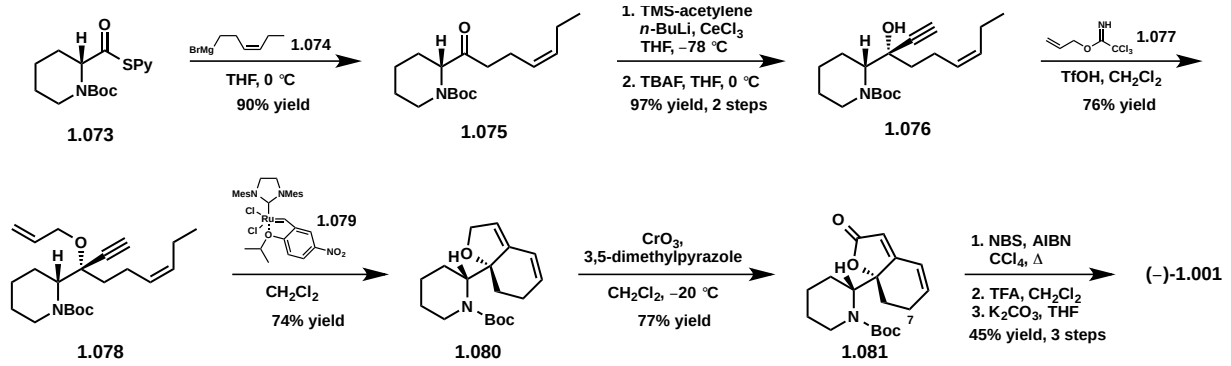


cyclohexene **1.071**. Lactone **1.071** was treated with phenylselenium bromide to give an α-selenoketone. Oxidation/elimination generated the α,β-unsaturated lactone **1.072**. Deprotection of the nitrogen and dibromination of the unconjugated olefin afforded a compound that underwent cyclization and concomitant dehydrohalogenation to yield **(±)-1.001**.

*1.2.2.5 Honda's Synthesis of (−)-securinine (**(−)-1.001**)*

Four years after their initial report of the synthesis of **(±)-1.001**, Honda *et al.* reported the synthesis of **(−)-1.001** (Scheme 1.7).[34b] Once again they started with a preformed A ring, in this case a derivative of *R*-(+)-pipecolic acid (**1.073**). Thioester **1.073** was exposed to (*Z*)-3-hexenylmagnesium bromide (**1.074**) to give ketone **1.075**. TMS-acetylide addition to the ketone occurs to form the Felkin-Anh product, which was desilylated to produce alcohol **1.076**. Treatment with allyl trichloroacetimidate (**1.077**) produced allylic ether **1.078**. In the presence of active ruthenium catalyst **1.079**, allylic ether **1.078** underwent a tandem ring-closing metathesis to produce diene **1.080**. Lactone **1.081** was formed via a chromate oxidation. Bromination at C7 then allowed Honda *et al.* to intercept Horii and co-workers' synthesis.[28] In this case, however the yield of **(−)-1.001** was considerably higher, presumably due to the use of a Boc protecting group rather than the formyl one used by Horii.

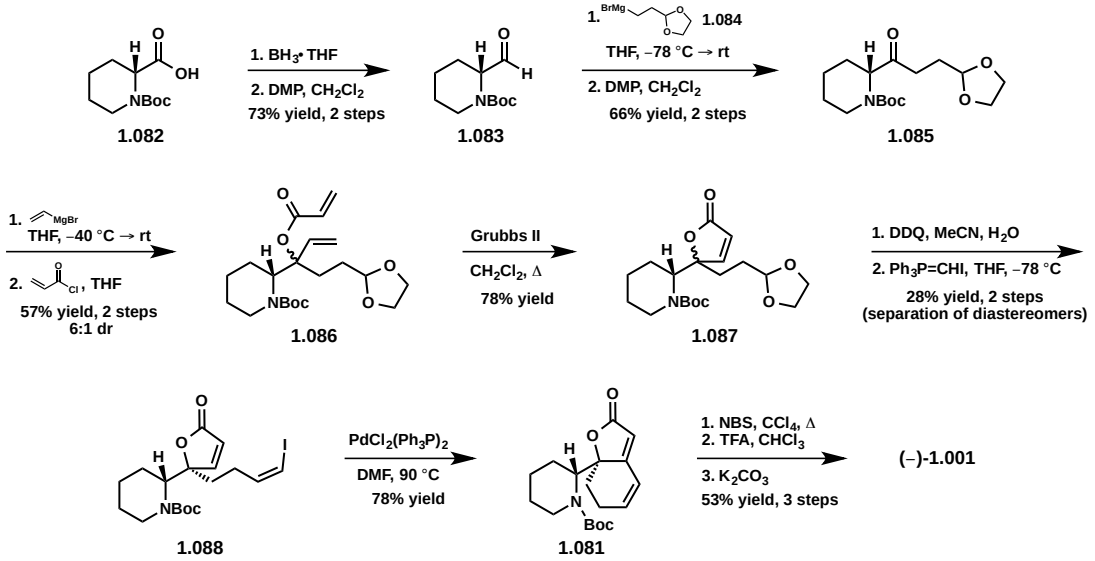
Scheme 1.7



*1.2.2.6 Alibes/de March Synthesis of (−)-securinine (**(−)-1.001**)*

In 2004, Alibes and De March published their synthesis of **(−)-1.001**,[36] following a route (Scheme 1.8) fairly similar to Honda *et al.*[34b] Starting with a different derivative (**1.082**) of *R*-(+)-pipecolic acid, reduction and oxidation afforded aldehyde **1.083**. Addition of Grignard reagent **1.084** to aldehyde **1.083** and subsequent Dess-Martin oxidation gave ketone **1.085**. Addition of vinylmagnesium bromide to the ketone occurred with 6:1 diastereoselectivity for the Felkin-Anh product, and the resulting mixture of alcohols was esterified to give diene **1.086**. Exposure of this diene to Grubbs' second-generation catalyst generated butenolide **1.087**, as a mixture of diastereomers. Deprotection of the aldehyde and a subsequent Wittig reaction produced a vinyl iodide **1.088**. A Heck reaction closes the C ring in cyclohexene **1.081**. This compound (**1.081**) is an intermediate in Honda's synthesis. A similar bromination, deprotection, and ring-closure sequence formed **(−)-1.001**.

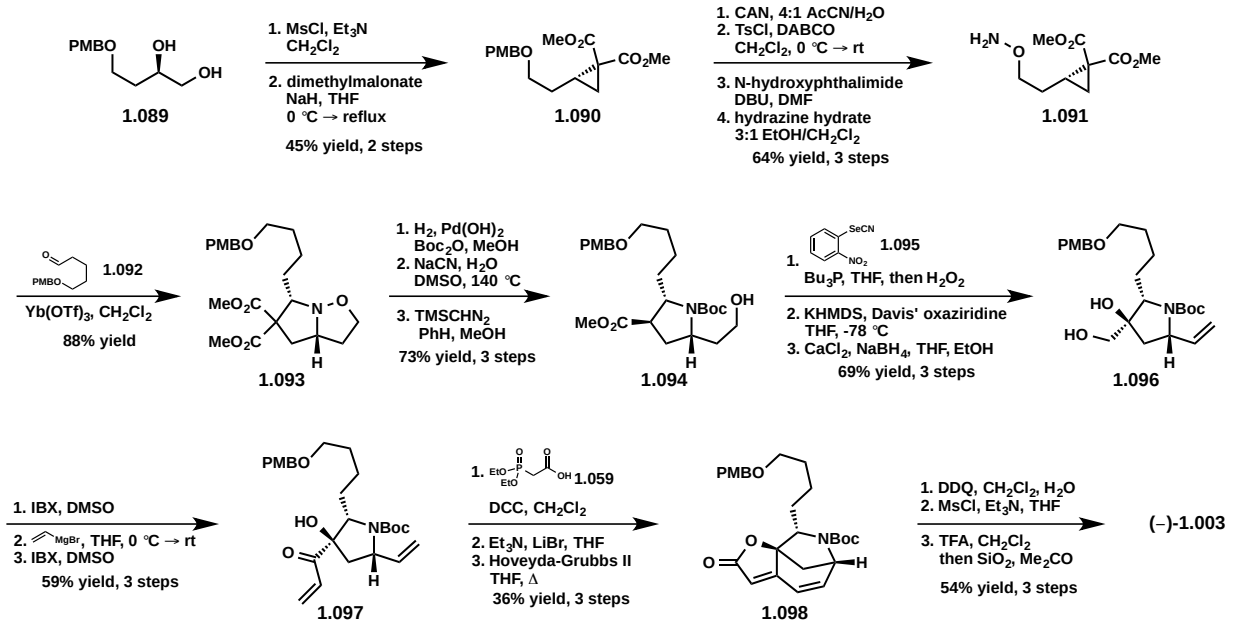
Scheme 1.8



*1.2.2.7 Kerr's Synthesis of (−)-allosecurinine (**(−)-1.003**)*

Kerr *et al.*'s synthesis of **(−)-1.003** in 2008 was the first to employ acyclic starting materials (Scheme 1.9).[39] Beginning with enantioenriched diol **1.089** (available via a Sharpless asymmetric dihydroxylation), a bismesylation and subsequent double displacement with

Scheme 1.9



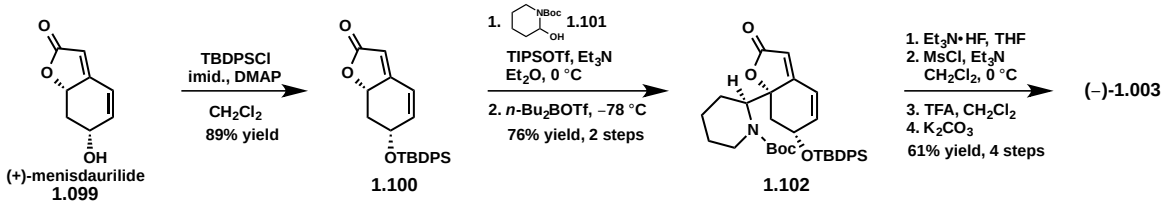
dimethyl malonate gave cyclopropane **1.090**. A four-step sequence consisting of PMB-ether cleavage, tosylation of the resulting alcohol, displacement with *N*-hydroxyphthalimide, and cleavage to the *O*-substituted hydroxylamine generated *O*-substituted hydroxylamine **1.091**. When hydroxylamine **1.091** and aldehyde **1.092** were combined in the presence of ytterbium triflate, the resulting oxime ether underwent an intramolecular addition with the cyclopropane diester to generate pyrroloisoxazolidine **1.093** with excellent *cis* stereoselectivity. The N−O bond of **1.093** was then cleaved via hydrogenolysis in the presence of Boc_2O to give a protected pyrrolidine. This was followed by a Krapcho decarboxylation, which resulted in a mixture of desired monoester **1.094** and the acid. The mixture was treated with TMS-diazomethane to convert the acid to **1.094**. Utilizing Grieco's conditions, the primary alcohol was converted to the alkene. Treatment with KHMDS and Davis' oxaziridine gave an α-hydroxy ester, which was reduced to diol **1.096**. Oxidation of the primary alcohol to the aldehyde, treatment with vinyl Grignard, and reoxidation yielded enone **1.097**. Esterification with **1.059** allowed for an intramolecular Horner-Wadsworth-Emmons reaction, delivering an unstable butenolide

intermediate, which was immediately subjected to ring-closing metathesis conditions to make tricycle **1.098**. Replacement of the PMB-ether with a mesylate is followed by the deprotection of the nitrogen and subsequent amine displacement of the mesyl generating **(−)-1.003**.

*1.2.2.8 Busque/de March Synthesis of (−)-allosecurinine (**(−)-1.003**)*

In a stark contrast to Kerr's somewhat lengthy synthesis from acyclic starting materials,[39] Busque *et al.* were able to synthesize **(−)-1.003** in only seven steps by starting with unnatural (+)-menisdaurilide (**1.099**) (Scheme 1.10).[40] Already containing the C and D rings, **1.099** is a fairly advanced intermediate which itself takes seven steps to produce from commercially available materials.[48] An initial treatment with TBDPSCl gave silyl ether **1.100**. When **1.100** was treated with triethylamine in the presence of TIPSOTf it formed a siloxy furan. With the addition of piperidine **1.101,** the siloxyfuran undergoes a vinylogous Mannich reaction to give a 4:1 mixture of diastereomers. The desired diastereomer (**1.102**) was separable in 76% yield. At this point, their final B-ring formation resembled a number of others. Removal of the TBDPS group and subsequent mesylation provided them with a good leaving group. Boc removal, followed by neutralization led to **(−)-1.003**.

Scheme 1.10

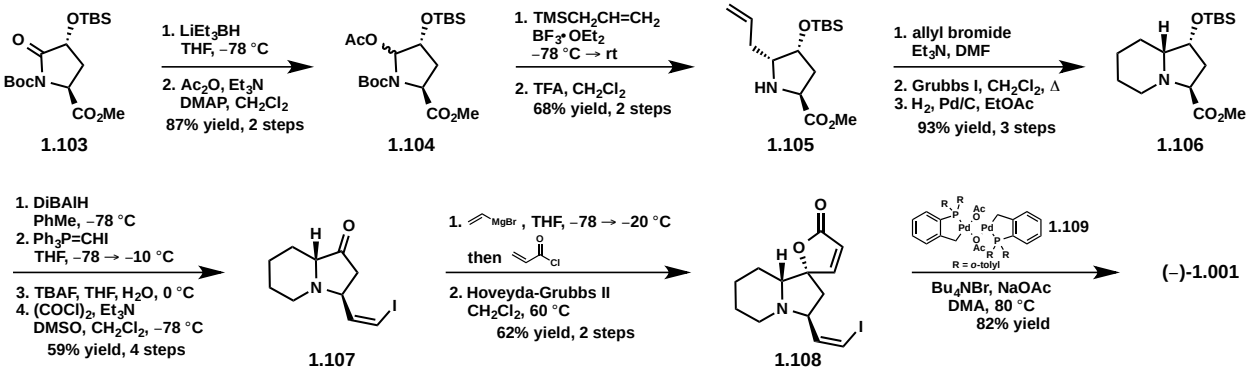


*1.2.2.9 Thadani's Synthesis of (−)-securinine (**(−)-1.001**)*

The most recent synthesis of a securinane was Thadani *et al.*'s completion of **(−)-1.001** (Scheme 1.11) in 2009.[41] While once again starting with a nitrogen containing heterocycle—in this case pyrrolidine **1.103**—they employed a novel B, A, D, C approach to ring formation. L-Proline derivative **1.103**, which will eventually be the B ring in **(−)-1.001**, was partially reduced

to a hemiaminal, which was acylated to give acetate **1.104**. Acetate **1.104** was then used to form an *N*-acyliminium ion, which could be alkylated with allyltrimethylsilane (4:1 dr). Cleavage of the Boc group and subsequent separation of the diastereomers afforded free amine **1.105**. Allylation of the nitrogen, followed by a ring-closing metathesis and hydrogenation of the remaining olefin gave indolizidine **1.106**. Reduction of the ester to an aldehyde and a subsequent Wittig reaction generated a vinyl iodide. Deprotection of the alcohol and a Swern oxidation produced ketone **1.107**. A stereoselective Grignard reaction on this ketone was followed by an esterification with acryloyl chloride. The resulting triene underwent a ring-closing metathesis selective for the terminal alkenes to generate butenolide **1.108**. An intramolecular Heck reaction was effected with the Herrmann-Beller palladium catalyst (**1.109**) to give **(−)-1.001**.

Scheme 1.11



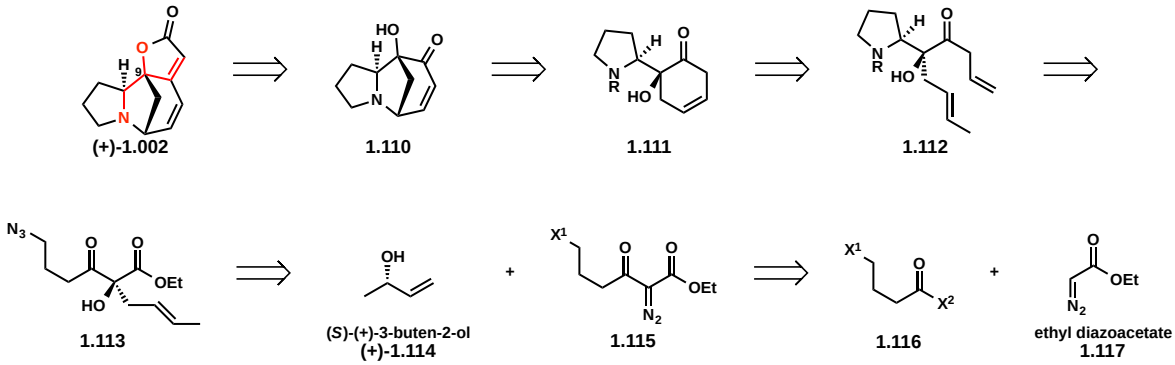
1.2.3 Prior Art in the Wood Group

1.2.3.1 Retrosynthetic Analysis

Our early interest in this class of molecules was piqued by the presence of a masked tertiary alcohol flanked by two carbonyls (highlighted in **(+)-1.002**, Scheme 1.12), a feature which makes these seemingly simple structures challenging synthetic targets. Initial efforts in this area focused on the synthesis of **(+)-1.002**,[42] which could be used as an entry to and model for the synthesis of other pyrrolizidine *Securinega* alkaloids. Upon examining **(+)-1.002**, we

thought that setting the stereochemistry at C9 would be the key to a stereocontrolled synthesis. We also recognized that the enantioselective rhodium carbenoid-initiated O–H insertion/Claisen rearrangement/1,2-allyl migration methodology developed in our lab[49] would be a good method for an enantioselective synthesis of **(+)-1.002**. A review of prior syntheses led to the simplification of norsecurinine to α-hydroxy enone **1.110** (Scheme 1, n = 0). Tricyclic enone **1.110** was envisioned to arise from the halogenation and subsequent cyclization/β-elimination of ketone **1.111**. Cyclohexenone **1.111** itself could originate from the ring-closing metathesis of diene **1.112**. Deconstruction of the A-ring suggested that it could arise from the reductive amination of an α-hydroxy-β-ketoester **1.113**, and this linear tertiary alcohol would be the product of the key reaction between allylic alcohol (+)-**1.114** and α-diazo-β-ketoester **1.115**, thus setting the stereochemistry of the molecule. (+)-**1.114** is a known compound and **1.115** could be readily accessed from commercially available starting materials.

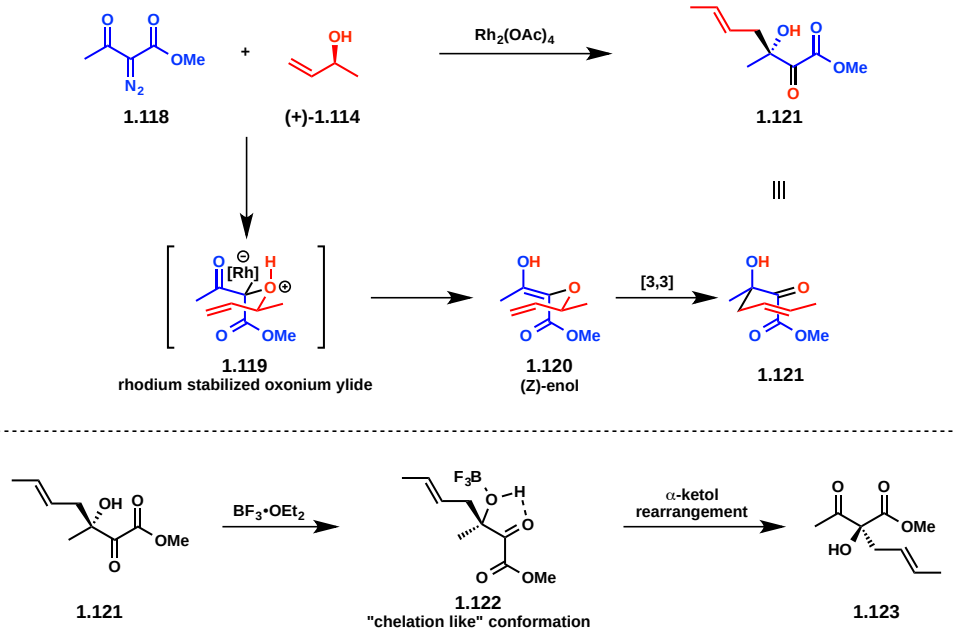
Scheme 1.12



1.2.3.2 The Rh-initiated O−H Insertion/Claisen Rearrangement/1,2-allyl Migration

The aforementioned rhodium carbenoid-initiated O–H insertion/Claisen rearrangement/1,2-allyl migration methodology is a two-step one-pot process that starts with an α-diazo-β-ketoester such as **1.118** and an allylic alcohol such as (+)-**1.114** (Scheme 1.13). The reaction commences with the formation of a rhodium carbenoid through the loss of N_2. The

Scheme 1.13

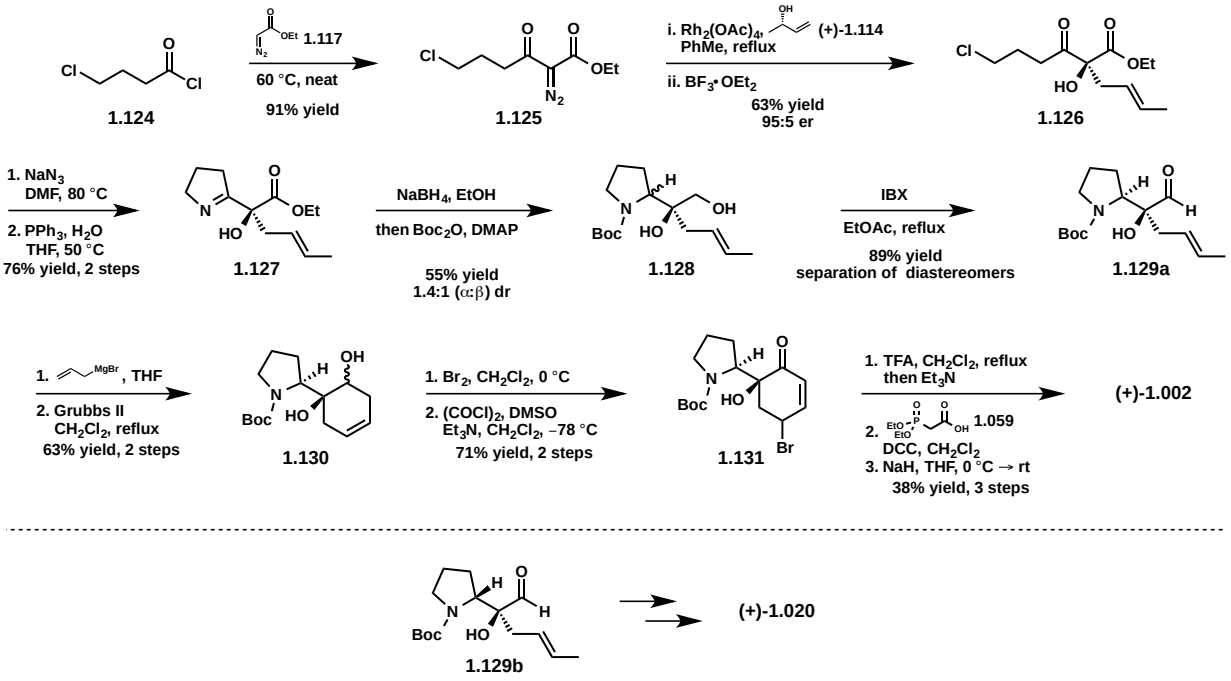


rhodium carbenoid then coordinates to the allylic alcohol to give a rhodium stabilized oxonium ylide (**1.119**). This is followed by the [1,4] shift of an acidic proton and rhodium dissociation to generate a *Z*-enol. Enol **1.120** then undergoes a [3,3]-sigmatropic rearrangement to give an α-keto-β-hydroxyester (**1.121**). The subsequent 1,2-allyl migration occurs upon the addition of BF_3•OEt_2. The α-ketol rearrangement occurs with the migration of the allyl group to the opposite face of the molecule to give α-hydroxy-β-ketoester **1.123**. Since BF_3 contains only a single open coordination site this result appears contradictory.[50] It has therefore been hypothesized that the coordination of BF_3 to the alcohol might be resulting in a greater tendency toward intramolecular proton transfer. This hydrogen bond formation (**1.122**) enforces a syn-periplanar relationship, which directs allyl migration to the observed face.

*1.2.3.3 Total Synthesis of (+)-Norsecurinine (**(+)-1.002**) and (+)-Allonorsecurinine (**(+)-1.020**)*

As can be seen in the retrosynthesis above (Scheme 1.12) unlike all but one other synthesis, it starts with acyclic substrates and constructs all of the rings. It does however follow

Scheme 1.14



the common practice of forming the A ring first. In the forward sense, 4-chlorobutyryl chloride (**1.124**) was coupled with ethyl diazoacetate (**1.117**) to give α-diazo-β-keotester **1.125** (Scheme 1.14). This substrate was then combined with the enantioenriched allylic alcohol (+)-**1.114** in the presence of 0.1 mol% $Rh_2(OAc)_4$ in toluene at reflux to yield the product of the Claisen rearrangement. After cooling to room temperature the 1,2-allyl migration[51] was initiated with the addition of BF_3•OEt_2 to generate tertiary alcohol **1.126** in 63% yield and 95:5 er. Treatment of chloride **1.126** with sodium azide and a subsequent Staudinger reduction/aza-Wittig reaction supplied imine **1.127**. With imine **1.127** in hand, reduction and Boc protection delivered the desired amine **1.128** in 55% yield, over two steps, with a diastereomeric ratio of 1.4:1 (α:β). Oxidation of the primary alcohol to aldehyde **1.129** allowed for the separation of the two diastereomers. **1.129a** and **1.129b** were advanced separately for the synthesis of **(+)-1.002** and **(+)-1.020** respectively. The diene necessary to close the C-ring was generated from the treatment of aldehyde **1.129a** with allylmagnesium bromide. Subsequent ring-closing metathesis afforded

cyclohexene **1.130**. At this point in the synthesis, the strategy similar to the one devised by Liras *et al*. was employed. Treatment of cyclohexene **1.130** with bromine resulted in the dibromination product, which was oxidized to cyclic enone **1.130** under Swern conditions. Boc removal, followed by the DCC mediated esterification of the tertiary alcohol with diethylphosphonoacetic acid (**1.059**) and an intramolecular Horner-Wadsworth-Emmons reaction afforded **(+)-1.002**. Starting with **1.129b**, **(+)-1.020** was synthesized via the same route.

1.3 Conclusions

With the recent reports that *Securinega* alkaloids have the potential to be active anti-cancer compounds[25] and immune system adjuvants,[22,23] there has been an upswing in the number of syntheses of these molecules. Many of these recent syntheses seek to apply modern catalytic methods. In particular the Wood group's route used a rhodium carbenoid-initiated O–H insertion/Claisen rearrangement/1,2-allyl migration domino sequence in order to set the stereochemistry at the key C9 position. In a class of molecules with so many members, one of the hallmarks of a well-designed synthesis is its flexibility for adaptation to different target molecules. With this in mind a sentence from the conclusion of Dr. Matthew R. Medeiros' thesis is particularly apt: "As designed, the route could be applied to the synthesis of (+)- and (–)-securinine and (+)- and (–)-allosecurinine simply by starting with 5-chlorovaleryl chloride and (*R*)-(–)-3-buten-2-ol."[52]

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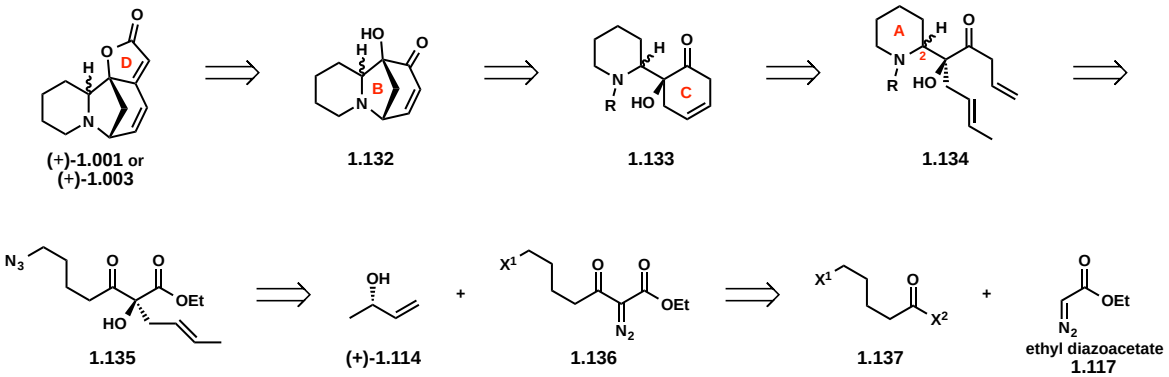
Chapter 2

The Synthesis of (±)-Securinine (1.001) and (±)-Allosecurinine (1.003)

2.1 Retrosynthetic Analysis of the Securinanes

Our previously reported[1] syntheses of **(+)-1.002** and **(+)-1.020** established a route to the norsecurinanes. As a continuation of these studies, we set out to synthesize the securinanes **(+)-1.001** and **(+)-1.003** following the same synthetic plan. To this end, we employed the retrosynthesis shown in Scheme 2.1. The initial disconnection was across the D ring, leading back to hydroxyketone **1.132**. Tricyclic compound **1.132** was envisioned to arise via the oxidative ring closure of the B ring in a bicyclic compound such as **1.133**. The C ring in **1.133** would arise from a ring-closing metathesis of diene **1.134**. The remaining A ring was then disconnected along the N−C2 bond to give masked amine **1.135**. The α-hydroxy-β-ketoester motif in **1.135** is common to the products of the rhodium initiated O−H insertion/Claisen rearrangement/1,2-allyl migration sequence developed by our lab.[2] In previous studies, the stereodefining transformations were initiated by combining allylic alcohol **(+)-1.114** with a variety of α-diazo-β-ketoesters (**1.136**, X = OBz, OTs, Cl, etc.). The β-ketoester **1.129** in turn could be synthesized from commercially available starting materials with the general structure of **1.137** and ethyl diazoacetate (**1.117**).

Scheme 2.1



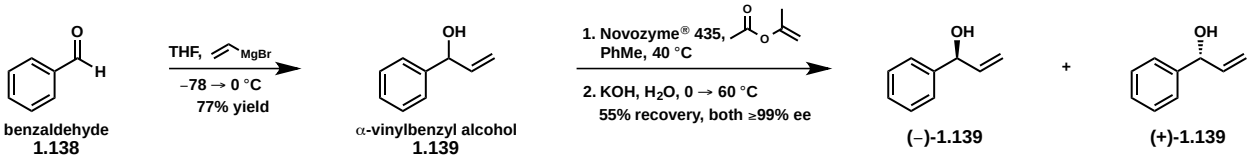
2.2 Modification of the Allylic Alcohol

2.2.1 Why Change the Allylic Alcohol?

Altough our previous studies had proven successful employing allylic alcohol **1.114**, its preparation was problematic. Due to the relative similarity in size of the methyl and vinyl units, neither enzymatic [3] nor metal catalyzed [4] resolution is effective to reach the level of enantioenrichment we desired. Stereoselective reductions of methyl vinyl ketone are similarly ineffective.[5] Those syntheses which are effective are either somewhat lengthy (4 steps)[6] or start with a prohibitively expensive starting material.[7] These reactivity issues coupled with the difficulty in handling the relatively volatile alcohol (**1.116**) eventually led us to consider employing a different substrate.

With this in mind, we decided to employ an allylic alcohol that was readily available from inexpensive starting materials. Outside of availability, our primary criterion in choosing a new alcohol was that the substituent not be likely to interfere with the future ring-closing metathesis. Since the second generation Grubbs catalyst, employed in the prior work, initiates with a loss of styrene we felt that a styryl group would be tolerated in the substrate. Additionally, syntheses of (+)-Didemniserinolipid B[8] and (+)-Neopeltolide[9] have demonstrated that a ring-closing methathesis can occur with a loss of styrene. This led us to target α-vinylbenzyl alcohol **1.139**. While **1.139** is somewhat expensive, it is readily available via the Grignard reaction of vinylmagnesium bromide with benzaldehyde (**1.136**, Scheme 2.3).[10] An enzymatic resolution gives access to both enantiomers of **1.139** in ≥99% ee.[11]

Scheme 2.2

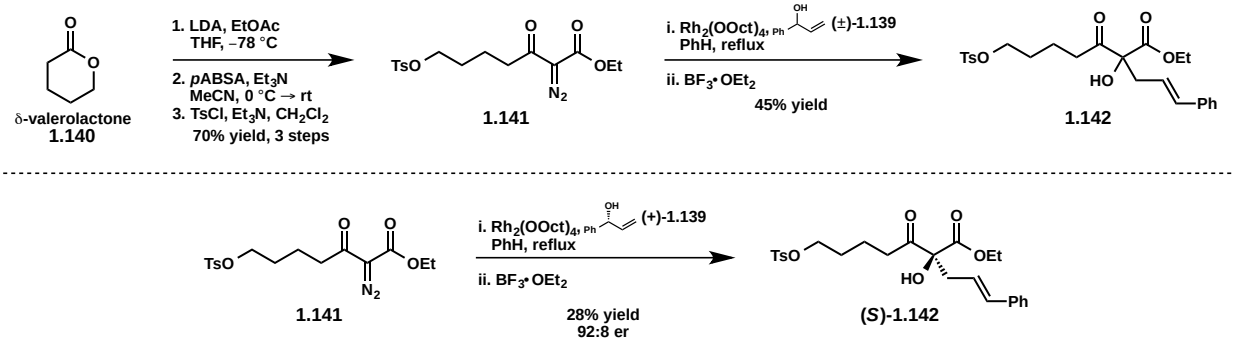


2.2.2 Synthesis of the Tosylate Substrate and the Rhodium Initiated Reaction

Having accessed the requisite allylic alcohol component, we turned our attention to the α-diazo-β-ketoester unit. In an earlier iteration of the syntheses of the norsecurinanes it was shown that X^1 in **1.115** (Scheme 1.12) could be either a chloride or a tosylate. The use of the tosylate was discontinued in favor of the chloride due to problems preparing the substrate; however, yields in the subsequent chemistry with the tosylate were slightly higher (69% vs. 63%). Thus, in continuing our efforts to improve upon our prior work we chose to revisit using the corresponding tosylate. In previous efforts **1.115** (X^1 = OTs) was prepared via ring-opening of the butyrolactone with ethyl lithiodiazoacetate[1,12] followed by the tosylation of the resulting primary alcohol. In this approach, the synthetic difficulties were attributed to the initial ring opening, thus we decided to employ a two-step procedure wherein δ-valerolactone (**1.140**) would be reacted with the lithium enolate of ethyl acetate to give the corresponding β-ketoester (Scheme 2.3).[13] This resulting mixture of linear β-ketoester and cyclic hemiacetal was then treated crude with *p*ABSA[14] to furnish an α-diazoester, which also existed as a mixture of linear and cyclic forms. Tosylation of the primary alcohol generated the desired α-diazo-β-diketoester **1.141** in a reproducible 72% yield.

With a ready source of the desired substrate we treated **1.141** and **(±)-1.139** with

Scheme 2.3

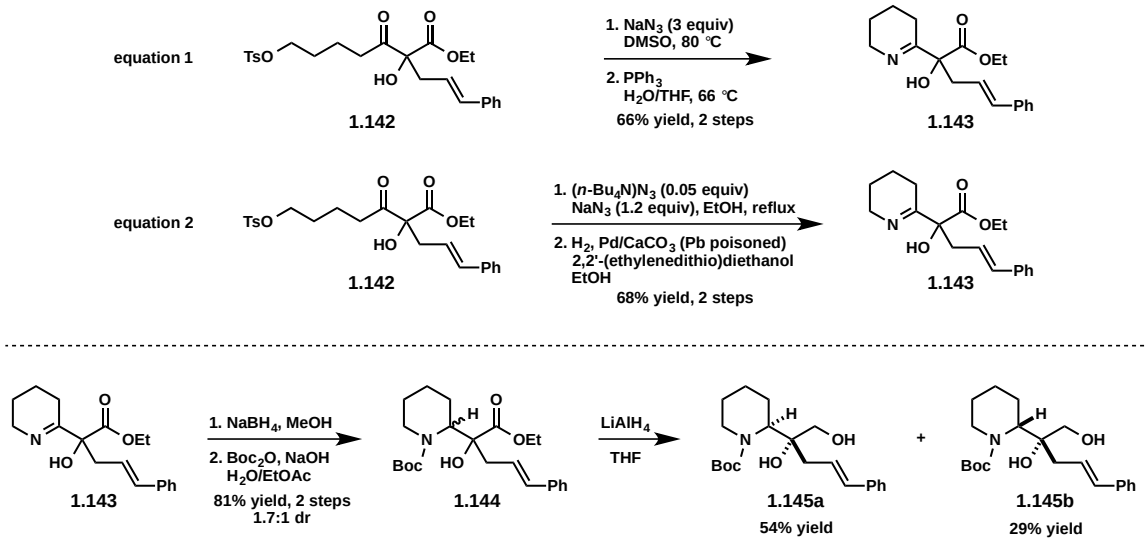


$Rh_2(OAc)_4$ followed by BF_3•OEt_2. To our delight, we found that not only did we observe the desired product (**1.142**), but also that it did was readily separated from residual alcohol (**1.139**). Optimization of the reaction led to the use of $Rh_2(OOct)_4$ as a more soluble rhodium dimer, which helped to suppress the undesired Wolff rearrangement and led to moderate, but consistent yields of **1.142**. As proof of concept we also employed enantioenriched **(+)-1.139**. This afforded the desired enantioenriched[2] product **(*S*)-1.142** with an enantiomeric ratio of 92:8.

2.3 Synthesis of a Common Intermediate En Route to (±)-1.001 and (±)-1.003

Having found a solution to the problem of the limited availability of **(+)-1.114**, we were able to synthesize significant amounts of the α-hydroxy-β-ketoester. With **1.142** in hand, imine **1.143** was readily accessible via a tosylate displacement/Staudinger reaction sequence (Scheme 2.4). Unfortunately, on large scale, the use of 3 equivalents of NaN_3 and the production of Ph_3PO presented waste disposal[15] and purification issues, respectively (equation 1, Scheme 2.4). To address the first issue we devised an alternative set of conditions where 5 mol% of tetrabutylammonium azide was employed as a phase transfer catalyst. This reduced the amount of NaN_3 to a slight (20%) excess (equation 2, Scheme 2.4). In the second step, the conditions[16]

Scheme 2.4



that gave the best results were a reduction with Lindlar's catalyst that had been further poisoned with 2,2'-(ethylenedithio)diethanol (equation 2, Scheme 2.4).[17]

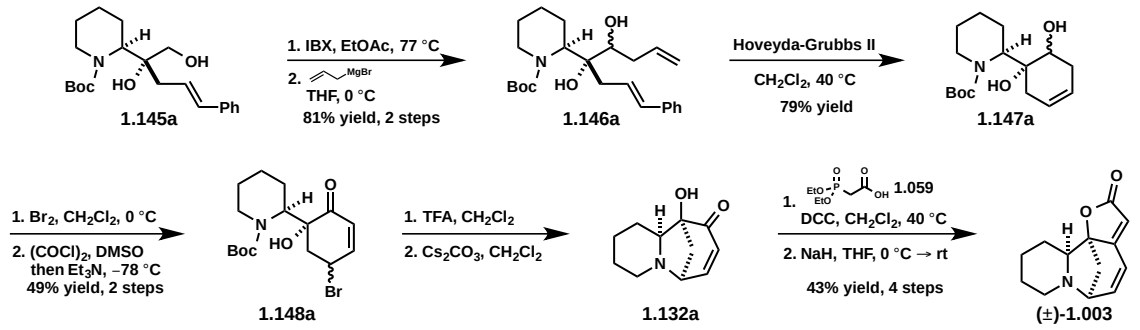
Imine **1.143** was then reduced with $NaBH_4$ and the crude reaction mixture treated with Boc_2O under basic conditions, generating Boc-protected amine **1.144** as an inseparable mixture of diastereomers. A second reduction, this time with $LiAlH_4$, then afforded a mixture of **1.145a** and **1.145b**. Although the diastereomers were separable, the structural assignments illustrated in Scheme 2.4 were not made initially, but followed from the completed syntheses (*vide infra*). Since both **1.145a** and **1.145b** were precursors to natural products, we advanced them independently.

2.4 Completion of the Syntheses

2.4.1 The Synthesis of (±)-1.003

Advancing the major diastereomer (**1.145a**) commenced with the oxidation of the primary alcohol to its corresponding aldehyde with IBX (Scheme 2.5).[18] Subsequent exposure to allylmagnesium bromide provided alcohol **1.146a** as an inconsequential mixture of stereoisomers. Diene **1.146a** was then subjected to ring-closing metathesis conditions with the Hoveyda-Grubbs second generation catalyst[19] forming cyclohexene **1.147a**. The alkene was then treated with bromine to provide the dibromide. A Swern oxidation with concomitant bromide elimination yielded enone **1.148a**. Removal of the Boc group from **1.148a** and treatment with

Scheme 2.5

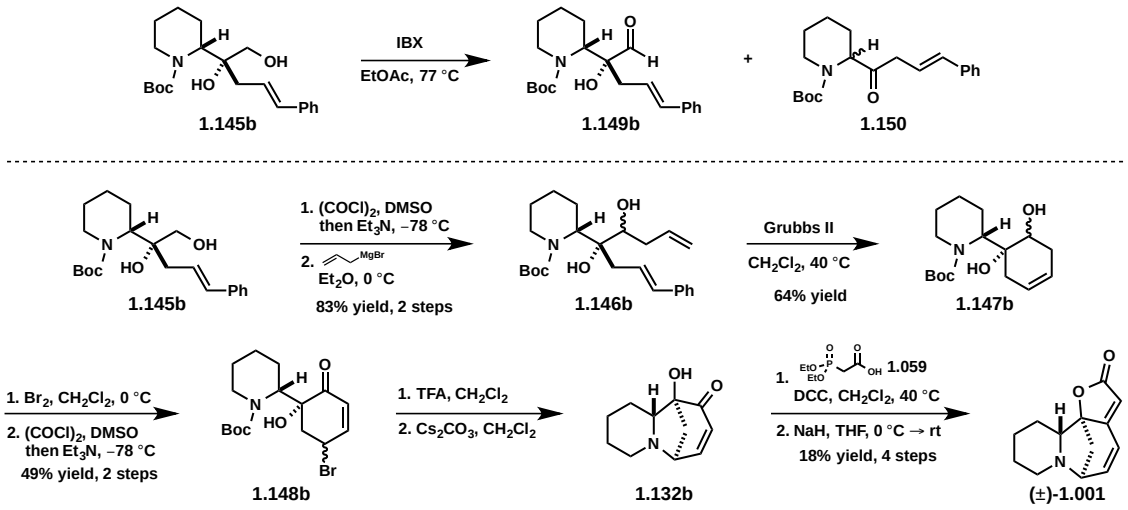


Cs_2CO_3 led to the formation of the B ring in **1.132a**. A Steglich esterification[20] with diethylphosphonoacetic acid (**1.059**) was followed by an intramolecular Horner-Wadsworth-Emmons olefination to generate the final product. A comparison of the spectral data available in the literature indicated that this compound was (±)-allosecurinine (**(±)-1.003**).

2.4.2 The Synthesis of (±)-1.001

With the knowledge that we had synthesized (±)-allosecurinine (**(±)-1.003**) from **1.145a**, we knew the relative stereochemistry of **1.145b** and set out to synthesize (±)-securinine (**(±)-1.001**). We initially attempted to synthesize **1.146b** via the same set of reactions used to synthesize **1.146a** (Scheme 2.6); however only half of the material recovered from the IBX oxidation was aldehyde **1.149b**. We tentatively assigned the other half of the recovered material as **1.150** by crude ^{1}H-NMR. Ketone **1.150** is the product of an oxidative cleavage reaction.[21] As illustrated in Scheme 2.8 (bottom) the formation of side product **1.150** could be circumvented by the use of Swern conditions for the oxidation. Treatment of **1.149b** with allylmagnesium bromide then yielded **1.146b**. This diene provided cyclohexene **1.147b** upon ring-closing metathesis. Bromination of the olefin was followed by an oxidation/elimination to give enone

Scheme 2.6



1.148b. Employing the same strategy as in the diastereomeric system, generation of the free amine was followed by an intramolecular cyclization to give tricyclic compound **1.132b**. The alcohol in **1.132b** was then esterified with diethylphosphonoacetic acid (**1.059**). The intermediate underwent a Horner-Wadsworth-Emmons olefination to provide (±)-securinine (**(±)-1.001**).

2.6 Conclusions

The total syntheses of the securinanes **(±)-1.001** and **(±)-1.003** were completed by a route modeled after our earlier work with norsecurinanes. While synthesized racemically, our use of a rhodium initiated O−H insertion/Claisen rearrangement/1,2-allyl migration would allow for C2 stereocontrol had an enantioenriched sample of **1.135** been used. In the course of this work, we demonstrated the use of a more accessible allylic alcohol **1.135** in the aforementioned key step. We were also able to improve upon some of the steps from a preparatory standpoint.

2.7 Experimental

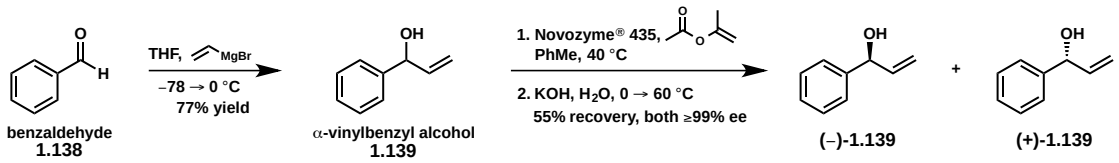
Unless otherwise stated, reactions were magnetically stirred in flame- or oven-dried glassware and inert atmosphere operations were conducted under an atmosphere of nitrogen, which was passed through a drying tube containing Drierite. Triethylamine, diisopropylamine, and methanol were dried over calcium hydride and freshly distilled. Benzene, tetrahydrofuran, dichloromethane, toluene, and diethyl ether were dried using a solvent purification system manufactured by SG Water U.S.A., LLC. Anhydrous acetonitrile, dimethylsulfoxide, and methanol were purchased and used without further purification from Macron Chemicals, EMD Chemicals and Fischer Scientific respectively. All other commercial reagents were used as received, unless noted otherwise.

Unless otherwise stated, all reactions were monitored by thin-layer chromatography (TLC) using Silicycle glass-backed extra hard layer, 60 Å plates (indicator F-254, 250 μm).

Preparatory TLC was performed on the same plates. Flash column chromatography was performed with the indicated solvents using Silicycle SiliaFlash. P60 (230-400 mesh) silica gel as the stationary phase. Infrared spectra (IR) were obtained on an FTIR spectrophotometer and are reported in wavenumbers (cm^{-1}). High-resolution mass spectra were acquired on an electrospray ionization (ESI) spectrometer and obtained by peak matching.

^{1}H-NMR spectra were recorded at ambient temperature at 400 MHz. ^{13}C-NMR spectra were recorded at ambient temperature at 101 MHz. All spectra were acquired in $CDCl_3$. For ^{1}H-NMR chemical shifts are reported as δ values in ppm and are calibrated according to residual $CHCl_3$ (7.26 ppm). For ^{13}C-NMR chemical shifts are reported as δ values in ppm and are calibrated according to residual $CHCl_3$ (77.16 ppm). Coupling constants (*J*) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as: s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintuplet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, br = broad, app = apparent, par = partial.

alcohol 1.139



In a 3-necked 1 L flask topped with two septa and a dropping addition funnel containing vinylmagnesium bromide (300 mL, 1.0 M in THF, 1.01 equiv), a solution of **1.138** (30 mL, 295 mmol, 1 equiv) in THF (200 mL, 1.48 M) was cooled to −78 °C. The Grignard reagent was then added dropwise over 75 min. After an additional 30 min the flask was warmed to 0 °C and stirred for 15 min. The reaction was quenched by the addition of a saturated NH_4Cl solution (45 mL) and additional water (55 mL) and diluted with Et_2O. The aqueous phase was extracted with

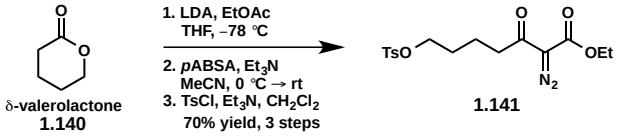
Et_2O (2 x 100 mL) and the combined organic phases were washed with brine (2 x 50 mL) and dried over $MgSO_4$. The resulting solution was filtered and concentrated *in vacuo* to give a cloudy, yellow oil. Purification on SiO_2 (0→20% EtOAc/hexanes) afforded **(±)-1.139** as a clear, pale yellow oil (30.6 g, 77%) whose spectral data matched the literature.[10,11]

In a 50 mL round-bottom flask, **(±)-1.139** (0.4 mL, 3.0 mmol, 1 equiv) was combined with ground 4Å molecular sieves (0.41 g, 100% by weight) and toluene (10 mL, 0.3 M). The Novozyme 435 (0.0613 g, 15% by weight) was then added, followed by the remaining toluene (5 mL, 0.2 M total). The heterogeneous reaction mixture was then heated to 40 °C for 17 h. After cooling to room temperature the mixture was filtered through a fritted funnel and concentrated *in vacuo*. Separation by column chromatography (SiO_2, 5% EtOAc/hexanes) gave **(−)-1.136** (0.0921 g, 23%) as a clear, pale yellow oil. The acetylated material was then transferred to a 25 mL round-bottom flask. A solution of KOH (0.0875 g, 1.56 mmol, 0.52 equiv) in water (5 mL) was then added and the flask heated to 60 °C overnight. After cooling to room temperature the reaction mixture was diluted with EtOAc (10 mL) and water (5 mL). The aqueous layer phase was extracted with EtOAc (2 x 10 mL) and the combined organic phases were washed with brine and dried over $MgSO_4$. Filtration and concentration *in vacuo* gave **(+)-1.139** as a clear, pale yellow oil (0.1309 g, 32%).

(−)-1.136: HPLC trace (OD-H column) ≥99% ee.

(+)-1.136: HPLC trace (OD-H column) 99% ee.

α-diazo-β-ketoester 1.141



To a solution of diisopropylamine (21 mL, 149 mmol, 1.05 equiv) in THF (200 mL) was added *n*-BuLi (1.75 M in hexanes, 82 mL, 144 mmol, 1.01 equiv) dropwise at −78 °C and the mixture allowed to stir for 30 min at this temperature. EtOAc (13.9 mL, 142 mmol, 1 equiv) was then added and the solution stirred for another 30 min at −78 °C, after which δ-valerolactone (13.5 mL, 142 mmol, 1 equiv) was added. The mixture was stirred for 90 min at −78 °C, then the reaction was quenched by addition of acetic acid (17 mL) and allowed to warm to room temperature. The reaction mixture was then diluted with diethyl ether and concentrated *in vacuo* to remove the THF. The resulting slurry was diluted with water and EtOAc. The aqueous phase was extracted with EtOAc (3 x) and the combined organic phases washed with brine and dried over $MgSO_4$. The organics were filtered and concentrated *in vacuo* to give the crude product as a yellow-orange oil, which was used without further purification. To a solution of the crude keto ester (28.6 g, 142 mmol, 1 equiv) in MeCN (350 mL) was added *p*ABSA (34.1 g, 142 mmol, 1 equiv) at 0 °C. The mixture was stirred for five minutes before triethylamine (60 mL, 426 mmol, 3 equiv) was added and the flask slowly warmed to room temperature and stirred 3.5 h. The resulting thick suspension was then concentrated *in vacuo* to removed the MeCN. Diethyl ether was added to the slurry, which was filtered through a fritted funnel and concentrated *in vacuo*. This cloudy, orange oil was then filtered through a plug of SiO_2 (50→75% hexanes/diethyl ether) to give the crude diazo ester as a clear, yellow oil. A 1L flask containing a solution of the crude diazo ester (26.0 g, 121 mmol, 1 equiv), and 4-toluenesulfonyl chloride (25.5 g, 134 mmol, 1.1 equiv) in CH_2Cl_2 (200 mL) was warmed to 35 °C and triethylamine (50 mL. 364 mmol, 3 equiv) was added. The flask was allowed to cool to room temperature overnight. The reaction mixture was then concentrated *in vacuo* to give an orange-brown oil. The crude oil was dry-loaded onto celite and purified via column chromatography on SiO_2 (0→25% EtOAc/hexanes) to give **1.141**

as a viscous yellow oil (36.7 g, 70% over 3 steps).

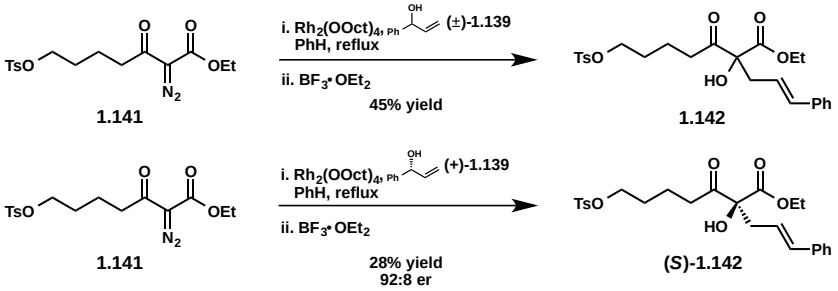
^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.72-7.69 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.96 (t, *J* = 6.0 Hz, 2H), 2.74 (t, *J* = 6.9 Hz, 2H), 2.37 (s, 3H), 1.64-1.57 (m, 4H), 1.25 (t, *J* = 7.1 Hz, 3H)

^{13}C-NMR (101 MHz, $CDCl_3$): δ 192.1, 161.3, 144.8, 133.2, 129.9, 127.9, 70.2, 61.5, 39.3, 28.3, 21.7, 20.2, 14.4

IR (thin film) 2982, 2136, 1715, 1656, 1359, 1305, 1176 cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{16}H_{20}N_2NaO_6S$ $(M+Na)^+$ 391.0934, found 391.0953

α-keto-β-hydroxyester 1.142



To a solution of ester **1.141** (5.00 g, 13.6 mmol, 1 equiv) in 80 mL of benzene was added a solution of allylic alcohol **(±)-1.139** (1.91 g, 14.3 mmol, 1.05 equiv) in benzene (10 mL) followed by rhodium(II) octanoate dimer (0.0210 g, 0.027 mmol, 0.2 mol%). The mixture was immediately immersed in an oil bath preheated to 80 °C and stirred for 30 min. After cooling to room temperature BF_3•OEt_2 (2.1 mL, 17.0 mmol, 1.25 equiv) was added dropwise via syringe and the brownish solution was stirred for two hours at room temperature. The reaction was quenched by addition of Et_3N (3 mL), the solvent was removed *in vacuo*, and the residue purified by flash chromatography (SiO_2, 25%→33% EtOAc/hexanes) to yield **1.142** as a colorless oil (2.91 g, 45%).

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.76-7.74 (m, 2H), 7.33-7.18 (m, 6H), 6.47 (d, *J* = 15.9 Hz, 1H),

6.05 (dt, *J* = 15.6, 7.6 Hz, 1H), 4.23 (qq, *J* = 10.9, 7.2 Hz, 2H), 4.14 (s, 1H), 3.99-3.96 (m, 2H), 2.94 (ddd, *J* = 14.4, 7.2, 1.2 Hz, 1H), 2.78 (ddd, *J* = 14.4, 7.5, 1.1 Hz, 1H), 2.73-2.66 (m, 1H), 2.52-2.44 (m, 1H), 2.42 (s, 3H), 1.61-1.58 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 3H)

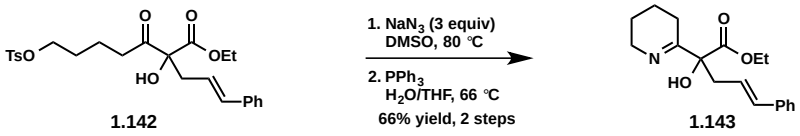
^{13}C-NMR (101 MHz, $CDCl_3$): δ 205.8, 170.7, 144.9, 136.9, 134.8, 133.1, 129.9, 128.6, 127.9, 127.7, 126.3, 122.2, 83.7, 70.0, 63.0, 39.0, 36.3, 28.1, 21.7, 19.5, 14.2

IR (thin film) 3479, 2979, 1721, 1598, 1450, 1358, 1176 cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{25}H_{31}O_7S$ $(M+H)^+$ 475.1785, found 475.1806

(*S*)-1.142: HPLC trace (OD-H column) 84% ee

imine 1.143



To a solution of tosylate **1.142** (15.3 g, 32.2 mmol, 1 equiv) in anhydrous DMSO (60 mL) was added sodium azide (6.29 g, 96.7 mmol, 3 equiv) and the mixture heated at 80 °C for 1 h. After cooling to room temperature diethyl ether (200 mL) and water (200 mL) were added and the aqueous phase was extracted with diethyl ether (2 x 50 mL). The combined organic phases were washed with water (3 x 50 mL) and brine (50 mL). After drying over $MgSO_4$ the solution was filtered and concentrated *in vacuo*. The crude oil (10.4 g, 30.1 mmol, 1 equiv) was dissolved in THF (200 mL) and triphenylphosphine (8.69 g, 33.1 mmol, 1.1 equiv) was added, followed by 10 mL of water. The mixture was heated to reflux for 18 h. After cooling to room temperature the solvent was removed *in vacuo* and the residue purified by flash chromatography (SiO_2, 20% EtOAc/hexanes) to yield **1.143** as a colorless oil (6.44 g, 66%, two steps).

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.15 (t, *J* = 7.1 Hz, 1H), 6.44 (d, *J* = 15.9 Hz, 1H), 6.16-6.08 (m, 1H), 6.01 (s, 1H), 4.23-4.12 (m, 2H), 3.60 (d, *J* = 5.4 Hz, 2H), 3.60 (t, *J* = 5.5 Hz, 2H), 2.95

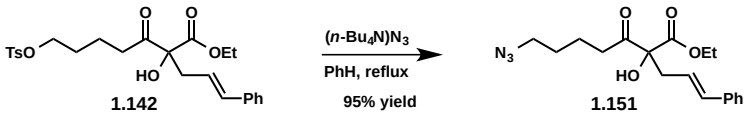
(ddd, *J* = 14.4, 6.3, 1.0 Hz, 1H), 2.73 (dd, *J* = 14.4, 8.0 Hz, 1H), 2.31-2.16 (m, 2H), 1.61 (dt, *J* = 12.9, 6.7 Hz, 2H), 1.57-1.46 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H)

^{13}C-NMR (101 MHz, $CDCl_3$): δ 172.1, 167.3, 137.2, 133.1, 128.3, 127.1, 126.0, 123.9, 79.5, 61.5, 48.3, 39.5, 24.8, 21.8, 18.9, 14.1

IR (thin film) 3252, 3027, 2939, 2861, 1733, 1670, 1447, 1258 cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{18}H_{24}NO_3$ $(M+H)^+$ 302.1751, found 302.1757

azide 1.151 (alternate preparation)



A 2-neck, 50 mL round-bottom flask with a reflux condenser was charged with **1.142** (0.990 g, 2.09 mmol, 1 equiv) in PhH (11 mL, 0.19 M). The TBAAz (0.712 g, 2.50 mmol, 1.2 equiv) was added with the remaining PhH (10 mL, 0.1 M total) and the reaction mixture heated to reflux for 30 min. The flask was then cooled to room temperature and the reaction mixture poured directly onto an SiO_2 plug. The plug was washed with EtOAc, and the resulting solution concentrated *in vacuo*. Azide **1.151** was an orange oil (0.683 g, 95%).

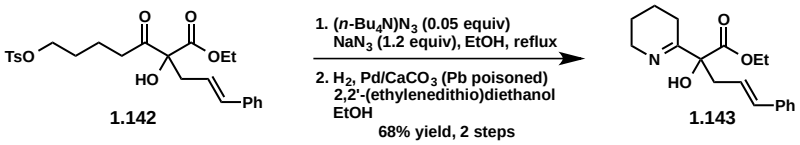
^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.33-7.27 (m, 4H), 7.24-7.20 (m, 1H), 6.50 (d, *J* = 15.9 Hz, 1H), 6.08 (dt, *J* = 15.7, 7.5 Hz, 1H), 4.27 (qq, *J* = 10.5, 7.1 Hz, 2H), 4.16 (s, 1H), 3.26 (t, *J* = 6.7 Hz, 2H), 2.99 (ddd, *J* = 14.4, 7.2, 1.2 Hz, 1H), 2.83 (ddd, *J* = 14.3, 7.5, 1.1 Hz, 1H), 2.78 (dt, *J* = 11.9, 6.3 Hz, 1H), 2.55 (dt, *J* = 18.2, 6.9 Hz, 1H), 1.71-1.64 (m, 2H), 1.60-1.52 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H)

^{13}C-NMR (75 MHz; $CDCl_3$): δ 206.0, 171.2, 136.9, 134.9, 128.7, 127.8, 126.42, 126.33, 122.2, 84.0, 53.7, 51.2, 39.3, 36.7, 28.3, 20.7

IR (thin film) 3852 (w), 3747 (m), 3673 (w), 3648 (w), 2929 (br m), 2360 (s), 2342 (s), 2096 (s), 1718 (s), 1651 (m), 1558 (m), 1540 (m), 1456 (m), 1261 (br m), 695 (m), 521 (w)

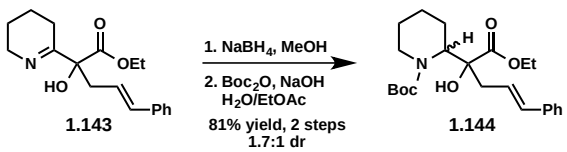
HRMS (ESI−APCI) m/z calcd. for $C_{18}H_{23}N_3NaO_4$ $(M+Na)^+$ 368.1581, found 368.1576

imine 1.143 (alternate preparation)



A 200 mL pear-shaped flasked with a reflux condenser was charged with a solution of **1.142** (1.8 g, 3.79 mmol, 1 equiv), sodium azide (0.30 g, 4.55 mmol, 1.2 equiv), and TBAAz (0.054 g, 0.19 mmol, 0.05 equiv) in EtOH (40 mL, 0.1 M). After heating to reflux for 25 h, the flask was cooled to room temperature. The reaction mixture was then dry loaded onto SiO_2 and added to the top of an SiO_2 plug. The plug was run with EtOAc and the resulting solution concentrated *in vacuo* to an orange oil. The crude azide (**1.151**) was then transferred to a 200 mL round bottom flask with EtOH (20 mL, 0.2 M). The Pb poisoned Pd/$CaCO_3$ (0.20 g, 15% by weight) and the 2,2'-(ethylenedithio)diethanol (0.0066 g, 0.05% by weight) were then added, followed by the remaining EtOH (20 mL, 0.1 M total). A balloon of H_2 was attached to the flask, and the headspace was evacuated and backfilled 3 x H_2. The heterogeneous reaction mixture was then stirred vigorously. After 21 h, the reaction mixture was filtered through celite with EtOAc and concentrated *in vacuo* to an orange-brown oil. Purification by cholumn chromatography (basified[22] SiO_2, 5→20% acetone/hexanes) afforded **1.143** as a yellow oil (0.7708 g, 68% over 2 steps).

***t*-butylcarbamate 1.144**



To a solution of imine **1.143** (6.40 g, 21.2 mmol, 1 equiv) in MeOH (50 mL) was added $NaBH_4$ (1.21 g, 31.9 mmol, 1.5 equiv) over 5 min. After stirring for 1 h at room temperature, the solvent was removed *in vacuo*. The residue was then dissolved in EtOAc (100 mL) and Boc_2O (9.27 g, 42.5 mmol, 2 equiv) and an aqueous sodium hydroxide solution (0.5 M, 425 mL, 10 equiv) were added. This biphasic mixture was stirred vigorously for 24 h. The mixture was then diluted with water (100 mL) and CH_2Cl_2 (300 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic phase was washed with water (50 mL) and brine (50 mL). After drying over $MgSO_4$ the solution was filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2, 11→17% EtOAc/hexanes) to give **1.144** as a mixture of diastereomers and rotamers (6.93 g, 81% over two steps).

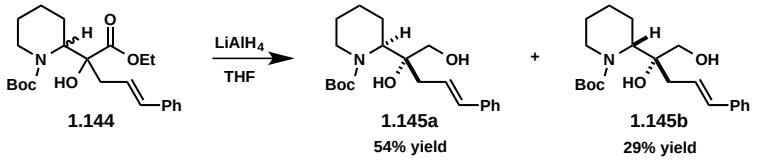
^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.31-7.24 (m, 4H), 7.18 (t, *J* = 7.0 Hz, 1H), 6.45 (dd, *J* = 15.6, 10.6 Hz, 1H), 6.15 (ddd, *J* = 15.5, 8.2, 7.0 Hz, 1H), 4.68-4.47 (m, 1H), 4.29-4.15 (m, 2H), 4.08 (dtd, *J* = 15.6, 8.4, 3.7 Hz, 1H), 3.98-3.72 (m, 2H), 3.53-3.22 (m, 2H), 3.42-3.22 (m, 1H), 2.71-2.60 (m, 2H), 2.00 (dt, *J* = 12.3, 6.0 Hz, 2H), 1.66-1.56 (m, 2H), 1.53-1.45 (m, 9H), 1.28 (t, *J* = 7.2 Hz, 3H)

^{13}C-NMR (101 MHz, $CDCl_3$): δ 175.1, 155.3, 137.1, 133.9, 128.3, 127.1, 126.0, 123.6, 83.4, 82.1, 79.2, 61.9, 55.4, 40.4, 28.2, 24.5, 19.9, 14.0

IR (thin film) 3502, 2976, 2934, 1726, 1688, 1450, 1253, 1149 cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{23}H_{33}NNaO_5$ $(M+Na)^+$ 426.2251, found 426.2267

diol 1.145a and diol 1.145b



A solution of ester **1.144** (0.820 g, 2.03 mmol, 1 equiv) in THF (1 mL) was slowly added to a suspension of $LiAlH_4$ (0.244 g, 6.10 mmol, 3 equiv) in THF (10 mL). The mixture was stirred for 1 h and then quenched with EtOAc (10 mL) and saturated aqueous Rochelle's salt. The resulting biphasic mixture was stirred overnight and the aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were washed with brine (20 mL) and dried over $MgSO_4$. After filtration the solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO_2, 17→20% EtOAc/hexanes). The major isomer **1.145a** eluted first and was obtained as a white solid (0.389 g, 54%). The minor isomer **1.145b** was obtained as a clear, viscous oil (0.206 g, 29%).

1.145a: ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.37 (d, *J* = 7.4 Hz, 2H), 7.31-7.27 (m, 2H), 7.23-7.18 (m, 1H), 6.49 (d, *J* = 15.9 Hz, 1H), 6.36 (dt, *J* = 15.3, 7.4 Hz, 1H), 4.18-4.17 (m, 1H), 4.09 (t, *J* = 6.1 Hz, 1H), 3.85 (dd, *J* = 10.6, 0.5 Hz, 1H), 3.45-3.42 (m, 1H), 3.24 (dq, *J* = 20.9, 8.0 Hz, 2H), 2.64 (dd, *J* = 13.0, 6.4 Hz, 1H), 2.42 (dd, *J* = 14.7, 9.1 Hz, 2H), 1.92 (t, *J* = 4.9 Hz, 2H), 1.71-1.69 (m, 1H), 1.58 (dt, *J* = 11.4, 5.7 Hz, 2H), 1.43 (s, 9H)

^{13}C-NMR (101 MHz, $CDCl_3$): δ 158.1, 137.2, 134.3, 128.6, 127.4, 126.3, 124.8, 80.5, 78.9, 65.1, 55.0, 41.3, 38.4, 28.5, 23.7, 22.6, 19.8

IR (thin film) 3419, 3026, 2935, 1654, 1422, 1279, 1252, 1154 cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{21}H_{31}NNaO_4$ $(M+Na)^+$ 384.2145, found 384.2160

1.145b: ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.35 (d, *J* = 7.3 Hz, 2H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 6.45-6.33 (m, 2H), 3.97 (s, 1H), 3.85 (s, 2H), 3.71 (s, 1H), 3.53-3.41 (m, 2H), 3.05 (ddd, *J* = 13.8, 10.7, 5.3 Hz, 1H), 2.62-2.59 (m, 1H), 2.36-2.34 (m, 1H), 1.90-1.83 (m, 1H), 1.76-1.75 (m, 2H), 1.63-1.54 (m, 2H), 1.47 (s, 9H)

^{13}C-NMR (101 MHz, $CDCl_3$): δ 158.0, 137.4, 132.7, 128.5, 127.1, 126.1, 125.7, 80.6, 65.3, 56.8,

41.6, 37.6, 28.5, 23.5, 21.8, 20.2

IR (thin film) 3421, 2932, 1657, 1420, 1276, 1252, 1153 cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{21}H_{31}NNaO_4$ $(M+Na)^+$ 384.2145, found 384.2162

diene 1.146a

To a solution of alcohol **1.145a** (0.375 g, 1.04 mmol, 1 equiv) in EtOAc (7 mL) was added IBX (0.871 g, 3.11 mmol, 3 equiv) and the suspension heated to reflux for 3 h. The mixture was cooled to room temperature and filtered through a plug of celite. The filtrate was then concentrated *in vacuo*. The crude aldehyde was used in the next step without further purification. To a solution of the crude aldehyde (1.04 mmol, 1 equiv) in THF (5 mL) was added allylmagnesium bromide (1.0 M in diethyl ether, 3.1 mL, 3.12 mmol, 3 equiv) at 0 °C. The mixture was stirred at 0 °C for 1 h and was quenched by the addition of saturated aqueous NH_4Cl solution (5 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL), the combined organic phases were washed with brine (20 mL) and dried over $MgSO_4$. The solution was filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 9% EtOAc/hexanes) yielded diene **1.146a** as a mixture of diastereomers and rotamers (0.339 g, 81% over two steps).

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.35 (t, *J* = 6.3 Hz, 2H), 7.29 (dd, *J* = 9.6, 5.4 Hz, 2H), 7.22-7.18 (m, 1H), 6.59-6.22 (m, 2H), 6.08-5.82 (m, 1H), 5.12 (td, *J* = 17.3, 12.2 Hz, 2H), 4.17 (dt, *J* = 21.6, 6.4 Hz, 2H), 3.76-3.65 (m, 2H), 3.32-3.25 (m, 1H), 2.66-2.34 (m, 5H), 2.21-2.16 (m, 1H), 1.89-1.73 (m, 3H), 1.51-1.46 (m, 9H)

^{13}C-NMR (101 MHz, $CDCl_3$): δ 158.5, 157.7, 137.4, 137.1, 136.5, 134.5, 132.39, 132.30, 128.52, 128.45, 128.43, 127.16, 127.10, 126.1, 117.9, 117.0, 116.1, 80.6, 80.20, 80.17, 79.81,

79.72, 79.3, 74.8, 74.3, 57.5, 55.9, 41.6, 41.3, 38.3, 37.7, 36.4, 35.51, 35.42, 28.48, 28.43, 28.37, 23.6, 23.2, 22.4, 20.0, 19.6

IR (thin film) 3395, 3078, 2975, 2931, 2868, 1654, 1421, 1367, 1275, 1154 cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{24}H_{35}NNaO_4$ $(M+Na)^+$ 424.2458, found 424.2475

diene 1.146b

A solution of oxalyl chloride (606 mL, 6.92 mmol, 2.5 equiv) in CH_2Cl_2 (25 mL) was cooled to −78 °C, then DMSO (2 mL, 27.7 mmol, 10 equiv) was added slowly and the mixture stirred for 10 min. A solution of alcohol **1.145b** (1.00 g, 2.77 mmol, 1 equiv) in CH_2Cl_2 (2 mL) was added and the solution was stirred for 10 min before the addition of triethylamine (3.9 mL, 27.7 mmol, 10 equiv). The mixture was stirred for an additional 10 min at −78 °C and then allowed to warm to room temperature. CH_2Cl_2 (25 mL) and saturated aqueous NH_4Cl solution (50 mL) were added and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic phases were washed with water (30 mL) and brine (30 mL). Drying over $MgSO_4$ followed by filtration and concentration *in vacuo* yielded the aldehyde, which was used in the next step without further purification. To a solution of the crude aldehyde (1.37 g, 3.81 mmol, 1 equiv) in diethyl ether (20 mL) at 0 °C was added allylmagnesium bromide (1.0 M in diethyl ether, 9.5 mL, 9.53 mmol, 2.5 equiv). The mixture was stirred at 0 °C for 30 min and then quenched with saturated aqueous NH_4Cl solution (10 mL). The aqueous phase was extracted with EtOAc (2 x 20 mL) and the combined organic phases were washed with brine (50 mL) and dried over $MgSO_4$. The solution was filtered, concentrated *in vacuo*, and the residue purified by flash chromatography (SiO_2, 14→20% EtOAc/hexanes) to yield diene

1.146b as a mixture of diastereomers and rotamers (1.11 g, 83% over two steps).

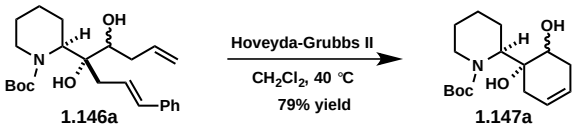
^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.29-7.27 (m, 2H), 7.22 (td, *J* = 7.5, 1.7 Hz, 2H), 7.13 (tt, *J* = 7.1, 1.8 Hz, 1H), 6.39-6.26 (m, 2H), 5.90-5.71 (m, 1H), 5.06 (d, *J* = 16.5 Hz, 2H), 4.06-3.95 (m, 2H), 3.76-3.50 (m, 3H), 3.29-2.99 (m, 2H), 2.56-1.97 (m, 5H), 1.78-1.48 (m, 5H), 1.39-1.18 (m, 9H)

^{13}C-NMR (101 MHz, $CDCl_3$): δ 158.0, 157.7, 137.67, 137.55, 136.28, 136.15, 132.7, 128.7, 127.2, 126.36, 126.21, 117.9, 117.1, 80.44, 80.25, 79.4, 78.6, 75.2, 73.6, 59.1, 56.7, 41.2, 37.5, 37.1, 36.78, 36.66, 36.2, 29.8, 28.6, 24.8, 24.0, 23.7, 23.1, 21.0, 20.0

IR (thin film) 3421, 2975, 2933, 1656, 1478, 1276, 1252, 1151 cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{24}H_{36}NO_4$ $(M+H)^+$ 402.2639, found 402.2659

cyclohexene 1.147a



To a solution of diene **1.146a** (0.339 g, 0.844 mmol, 1 equiv) in CH_2Cl_2 (8.5 mL) was added the second generation Hoveyda-Grubbs catalyst (0.053 g, 0.084 mmol, 0.1 equiv). The green solution was heated to reflux for 3 h and then cooled to room temperature. Concentration *in vacuo* and purification by flash chromatography (SiO_2, 17→25% EtOAc/hexanes) afforded diol **1.147a** as a mixture of diastereomers (0.194 g, 79%). For analytical purposes the two diastereomers were separated by flash chromatography and analyzed separately.

Higher R_f diastereomer: ^{1}H-NMR (400 MHz; $CDCl_3$): δ 5.64-5.53 (m, 2H), 4.89 (t, *J* = 0.9 Hz, 1H), 4.03 (t, *J* = 6.1 Hz, 1H), 3.81 (d, *J* = 13.0 Hz, 1H), 3.59 (s, 1H), 3.23-3.15 (m, 1H), 2.37-2.15 (m, 3H), 1.99 (dd, *J* = 17.9, 4.7 Hz, 1H), 1.88-1.83 (m, 2H), 1.61-1.46 (m, 4H), 1.39-1.35 (m, 9H)

^{13}C-NMR (101 MHz, $CDCl_3$): δ 158.1, 124.7, 122.6, 80.5, 66.6, 54.5, 41.2, 32.1, 29.6, 28.6, 24.0, 22.5, 19.7

IR (thin film) 3450, 3026, 2972, 2930, 1686, 1663, 1416, 1366, 1253, 1153 cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{16}H_{27}NNaO_4$ $(M+Na)^+$ 320.1832, found 320.1849

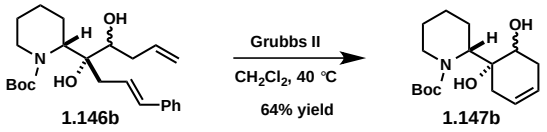
Lower R_f diastereomer: ^{1}H-NMR (400 MHz; $CDCl_3$): δ 5.56-5.47 (m, 2H), 5.35-5.28 (m, 1H), 3.90-3.79 (m, 1H), 3.68 (t, *J* = 7.8 Hz, 1H), 3.50-3.42 (m, 1H), 3.28-3.15 (m, 1H), 2.37-2.23 (m, 2H), 2.28-2.19 (m, 1H), 2.19-2.10 (m, 2H), 1.84-1.67 (m, 2H), 1.65-1.44 (m, 3H), 1.44-1.34 (m, 9H)

^{13}C-NMR (101 MHz, $CDCl_3$): δ 158.7, 124.4, 124.0, 80.9, 75.9, 69.4, 60.9, 43.6, 32.5, 31.7, 28.5, 23.4, 23.2, 20.8

IR (thin film) 3418, 3026, 2973, 2930, 1653, 1423, 1391, 1278, 1252, 1151 cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{16}H_{28}NO_4$ $(M+H)^+$ 298.2013, found 298.2025

cyclohexene 1.147b



To a solution of the second generation Grubbs catalyst (0.233 g, 0.274 mmol, 0.1 equiv) in CH_2Cl_2 (30 mL) was added a solution of diene **1.146b** (1.10 g, 2.74 mmol, 1 equiv) in CH_2Cl_2 (3 mL). The mixture was heated to reflux for 3 h and then cooled to room temperature. The solvent was removed *in vacuo* and the residue purified by flash chromatography (SiO_2, 20→25% EtOAc/hexanes) to yield diol **1.147b** as a brown oil (0.523 g, 64%), which was an inseparable mixture of diastereomers.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 5.54-5.45 (m, 2H), 5.37 (m, 1H), 4.02 (t, *J* = 7.3 Hz, 1H), 3.84-3.79 (m, 1H), 3.66-3.62 (m, 1H), 2.88-2.87 (m, 1H), 2.31-2.23 (m, 2H), 2.18-2.08 (m, 2H), 1.85-

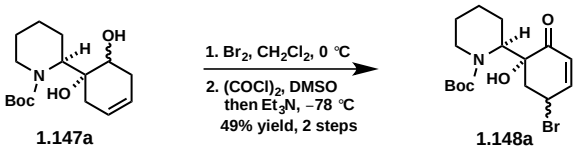
1.65 (m, 4H), 1.53 (m, J = 6.9 Hz, 3H), 1.41 (s, 9H)

^{13}C-NMR (101 MHz, $CDCl_3$): δ 158.4, 124.6, 123.4, 81.0, 75.3, 67.3, 56.1, 40.9, 31.7, 29.8, 28.5, 23.2, 21.0, 19.5

IR (thin film) 3409, 3026, 2929, 2866, 1684, 1654, 1408, 1366, 1342, 1272, 1253, 1170, 1150, 1032 cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{16}H_{27}NNaO_4$ $(M+Na)^+$ 320.1832, found 320.1842

enone 1.148a



1.147a 1.148a

To a solution of diol **1.147a** (0.194 g, 0.663 mmol, 1 equiv) in CH_2Cl_2 (66 mL) at 0 °C was added a solution of bromine (0.158 g, 0.663 mmol, 1.5 equiv) in CH_2Cl_2 (10 mL). The resulting orange solution was stirred for 10 min and then quenched with aqueous sodium bisulfite solution. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were washed with brine (100 mL). Drying over $MgSO_4$ and concentration *in vacuo* yielded the crude dibromide, which was used in without further purification. A solution of DMSO (470 mL, 6.63 mmol, 10 equiv) in CH_2Cl_2 (6.6 mL) was cooled to −78 °C, and oxalyl chloride (140 mL, 1.66 mmol, 2.5 equiv) was added. The mixture was then stirred for 10 min before a solution of the crude dibromide (0.663 mmol, 1 equiv) in CH_2Cl_2 (2.2 mL) was added. After an additional ten minutes triethylamine (920 mL, 6.63 mmol, 10 equiv) was added. The mixture was stirred for 10 min then slowly warmed to room temperature and stirred for 60 min. CH_2Cl_2 (10 mL) and household bleach (15 mL) were then added and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification

by flash chromatography (SiO_2, 9% EtOAc/hexanes) yielded enone **1.148a** as a mixture of diastereomers (0.122 g, 49% over two steps).

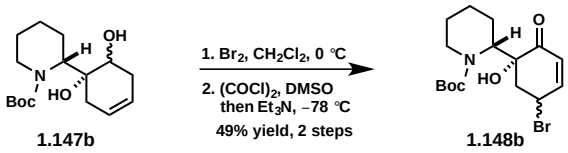
^{1}H-NMR (400 MHz; $CDCl_3$): δ 6.83 (d, *J* = 10.1 Hz, 1H), 6.02 (dd, *J* = 10.1, 1.8 Hz, 1H), 4.85 (m, 1H), 4.24 (t, *J* = 6.2 Hz, 1H), 3.80-3.75 (m, 2H), 3.11 (dt, *J* = 12.5, 6.4 Hz, 1H), 2.91 (ddd, *J* = 13.8, 5.3, 1.9 Hz, 1H), 2.30 (dd, *J* = 13.6, 11.2 Hz, 1H), 1.98-1.92 (m, 1H), 1.89-1.83 (m, 1H), 1.66-1.59 (m, 1H), 1.54-1.39 (m, 3H), 1.35-1.26 (m, 9H)

^{13}C-NMR (101 MHz, $CDCl_3$): δ 199.5, 155.6, 146.9, 127.7, 81.0, 80.0, 53.0, 45.1, 41.2, 29.8, 28.3, 23.81, 23.66, 19.2

IR (thin film) 3463, 2932, 2870, 1686, 1413, 1366, 1253, 1154 cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{16}H_{24}BrNNaO_4$ $(M+Na)^+$ 396.0781, found 396.0804

enone 1.148b



To a solution of diol **1.147b** (0.490 g, 1.648 mmol, 1 equiv) in CH_2Cl_2 (40 mL) at 0 °C was added a solution of bromine (1.10 g, 2.74 mmol, 1 equiv) in CH_2Cl_2 (1 mL). The resulting orange solution was stirred for 10 min and then quenched with aqueous sodium bisulfite solution. The aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude dibromide, which was used without further purification. To a solution of oxalyl chloride (360 mL, 4.119 mmol, 2.5 equiv) in CH_2Cl_2 (15 mL) at −78 °C was slowly added DMSO (1.2 mL, 16.48 mmol, 10 equiv), and the mixture stirred for 10 min. A solution of the crude dibromide (1.648 mmol, 1 equiv) in CH_2Cl_2 (2 mL) was added and the solution was stirred for an additional 10 min before the triethylamine (2 mL, 14.83 mmol, 9

equiv) was added. The mixture was stirred for another 10 min and then slowly warmed to room temperature and stirred for 90 min. CH_2Cl_2 (15 mL) and a saturated aqueous NH_4Cl solution (20 mL) were added and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic phases were washed with household bleach (20 mL), water (30 mL), and brine (30 mL). The solution was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 9% EtOAc/hexanes) yielded enone **1.148b** as a mixture of diastereomers (0.304 g, 49% over two steps).

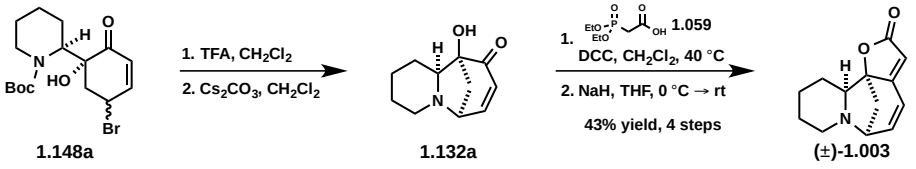
^{1}H-NMR (400 MHz; $CDCl_3$): δ 6.96 (d, *J* = 10.1 Hz, 1H), 5.96 (dd, *J* = 10.1, 2.3 Hz, 1H), 5.63 (ddt, *J* = 10.0, 5.3, 2.5 Hz, 1H), 4.25 (t, *J* = 4.6 Hz, 1H), 3.89-3.78 (m, 2H), 3.35-3.24 (m, 1H), 2.86 (ddd, *J* = 13.4, 5.6, 1.6 Hz, 1H), 2.20 (dd, *J* = 13.4, 10.1 Hz, 1H), 1.86-1.73 (m, 1H), 1.59-1.49 (m, 1H), 1.48 (s, 9H), 1.39-1.31 (m, 4H)

^{13}C-NMR (101 MHz, $CDCl_3$): δ 201.1, 156.5, 152.3, 125.3, 82.7, 80.4, 51.6, 45.2, 41.73, 41.54, 28.5, 24.8, 24.0, 20.4

IR (thin film) 3472, 2957, 2927, 2855, 1678, 1433, 1366, 1274, 1157 cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{16}H_{24}BrNNaO_4$ $(M+Na)^+$ 396.0781, found 396.0794.

(±)-allosecurinine ((±)-1.003)



TFA (250 mL, 3.26 mmol, 10 equiv) was added to a solution of enone **1.148a** (0.122 g, 0.326 mmol, 1 equiv) in CH_2Cl_2 (3.3 mL), and the mixture stirred for 1.75 h. The solvent was removed *in vacuo* and the residue redissolved in fresh CH_2Cl_2 (3.3 mL). Cs_2CO_3 (0.212 g, 0.652 mmol, 2 equiv) was added, and the suspension stirred overnight. The reaction mixture was then filtered, the solid washed with CH_2Cl_2 (3 mL), and the filtrate concentrated *in vacuo* to yield

indolizidine **1.132a**, which was used in the next step without further purification. DCC (0.135 g, 0.652 mmol, 2 equiv) and **1.059** (10 mL, 0.652 mmol, 2 equiv) were added to a solution of **1.132a** (0.326 mmol, 1 equiv) in CH_2Cl_2 (3.3 mL). The mixture was then heated to reflux for 30 min. After cooling to room temperature, the byproducts were filtered off, washed with CH_2Cl_2 (3 mL), and the filtrate concentrated *in vacuo*. The crude ester was then dissolved in THF (0.8 mL) and added to a suspension of sodium hydride (60% in mineral oil, 0.060 g, 1.496 mmol, 2 equiv) in THF (2.5 mL) at 0 °C. The mixture was stirred for 15 minutes at 0 °C, then warmed to room temperature and allowed to stir for another 90 min. It was then quenched with water (5 mL). The aqueous phase was extracted with EtOAc (4 x 5 mL) and the combined organic phases were washed with saturated aqueous $NaHCO_3$ solution (20 mL), brine (20 mL), and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue purified by flash chromatography (two consecutive columns; 2→3% MeOH/CH_2Cl_2, then 2% Et_3N/EtOAc) to give **(±)-1.003** as a yellow solid (0.0300 g, 43% over 4 steps).

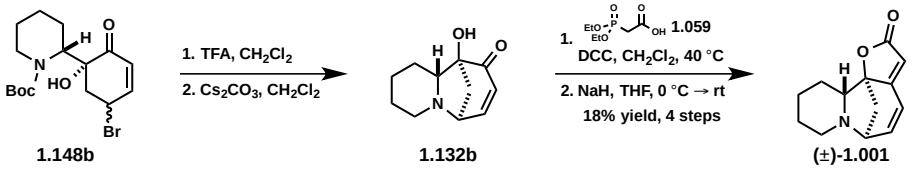
^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.81 (dd, *J* = 9.1, 5.3 Hz, 1H), 6.64 (dd, *J* = 9.1, 0.8 Hz, 1H), 5.72 (s, 1H), 3.90-3.88 (m, 1H), 3.66 (dd, *J* = 13.1, 3.5 Hz, 1H), 2.75 (dd, *J* = 6.3, 4.7 Hz, 2H), 2.68 (dd, *J* = 9.8, 4.4 Hz, 1H), 1.92 (d, *J* = 9.8 Hz, 1H), 1.69-1.67 (m, 3H), 1.45-1.39 (m, 1H), 1.38-1.32 (m, 1H), 1.14 (qd, *J* = 12.9, 5.9 Hz, 1H).

^{13}C-NMR (101 MHz; $CDCl_3$): δ 172.8, 167.6, 148.9, 122.7, 109.1, 91.9, 60.9, 58.9, 43.8, 42.8, 22.4, 21.2, 18.6

IR (thin film) 2934, 2850, 1756, 1630, 1457, 1253, 1178 cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{13}H_{16}NO_2$ $(M+H)^+$ 218.1176, found 218.1184

(±)-securinine ((±)-1.001)



TFA (570 mL, 7.48 mmol, 10 equiv) was added to a solution of enone **1.148b** (0.280 g, 0.748 mmol, 1 equiv) in CH_2Cl_2 (7.5 mL) and the solution stirred for 4 h. The solvent was removed *in vacuo* and the residue redissolved in fresh CH_2Cl_2 (7.5 mL). Cs_2CO_3 (0.488 g, 1.496 mmol, 2 equiv) was added, and the suspension stirred overnight. The reaction mixture was then filtered, the solid washed with CH_2Cl_2 (5 mL), and the filtrate concentrated *in vacuo* to yield indolizidine **1.132b**, which was used in the next step without further purification. DCC (0.309 g, 1.496 mmol, 2 equiv) and **1.059** (20 mL, 1.496 mmol, 2 equiv) were added to a solution of **1.132b** (0.748 mmol, 1 equiv) in CH_2Cl_2 (7.5 mL). The mixture was then heated to reflux for 90 min. After cooling to roomer temperature, the byproducts were filtered off, washed with CH_2Cl_2 (5 mL) and the filtrate concentrated *in vacuo*. The crude ester was then dissolved in THF (1 mL) and added to a suspension of sodium hydride (60% in mineral oil, 0.060 g, 1.496 mmol, 2 equiv) in THF (4 mL) at 0 °C. The mixture was stirred for 15 min at 0 °C, then warmed to room temperature and allowed to stir for another 90 min. It was then quenched with water (5 mL). The aqueous phase was extracted with EtOAc (2 x 5 mL) and the combined organic phases were washed with brine (15 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue purified by flash chromatography (SiO_2, 33% EtOAc/hexanes) to yield **(±)-1.001** as a yellow solid (0.0292 g, 18% over 4 steps).

^{1}H-NMR (400 MHz; $CDCl_3$): δ 6.53 (d, *J* = 9.1 Hz, 1H), 6.34 (dd, *J* = 9.2, 5.3 Hz, 1H), 5.47 (s, 1H), 3.74 (t, *J* = 4.7 Hz, 1H), 2.90 (dt, *J* = 10.6, 3.8 Hz, 1H), 2.44 (dd, *J* = 9.3, 4.1 Hz, 1H), 2.39-2.32 (m, 1H), 2.05-2.02 (m, 1H), 1.81 (ddt, *J* = 13.6, 6.9, 3.4 Hz, 2H), 1.71 (d, *J* = 9.2 Hz, 1H),

1.64-1.43 (m, 4H)

^{13}C-NMR (101 MHz, $CDCl_3$): δ 173.8, 170.2, 140.3, 121.6, 105.3, 89.7, 63.2, 59.0, 48.9, 42.4, 27.4, 26.0, 24.6

IR (thin film) 2927, 2851, 1754, 1631, 1256, 1108, 899, 844 cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{13}H_{16}NO_2$ $(M+H)^+$ 218.1176, found 218.1186

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CHAPTER 3

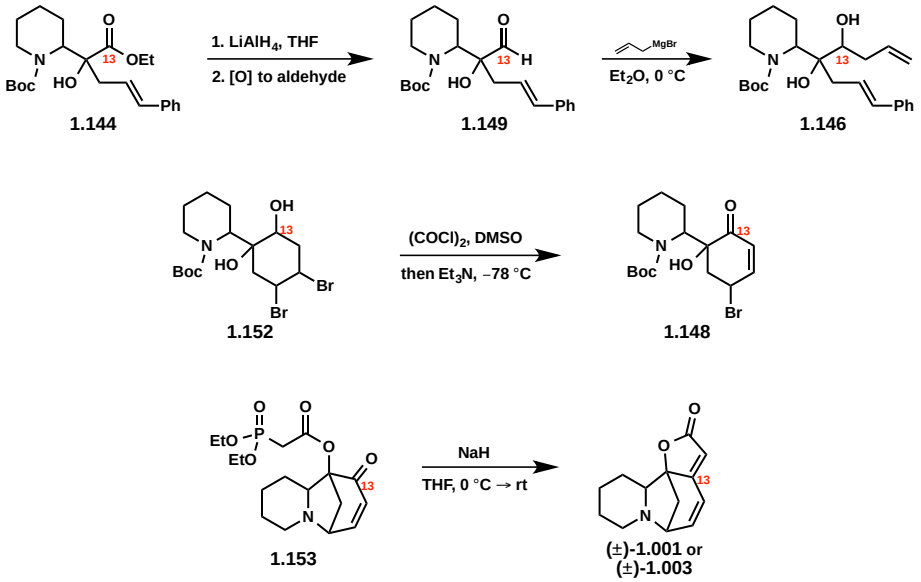
Investigations into a More Streamlined Route to the Securinega Alkaloids

3.1 Drawbacks to the First Generation Synthesis

3.1.1 An Analysis of Oxidation State Changes

While the synthesis of **(±)-1.003** had a yield 43% over the final four steps, the yield over those same steps in the synthesis of **(±)-1.001** was only 18%. The final acylation and butenolide formation remained inefficient, as it had in the earlier syntheses of **(+)-1.002** and **(+)-1.020**. The other drawback to our synthetic route was the number of oxidation state changes[1] at C13 due to the method used to install the C and D rings (Scheme 3.1). In reviewing the synthetic sequence, one finds that the synthesis begins with C13 in the ester oxidation state, and through subsequent steps this state changes five times. From **1.144** a reduction to the alcohol and reoxidation to aldehyde **1.149** was necessary to give a suitable substrate for allylmagnesium bromide addition.[2] The Grignard reaction itself results in a reduction to the alcohol oxidation state in **1.146**. In order to close the D ring with a Horner-Wadsworth-Emmons olefination—a reducing reaction—it was

Scheme 3.1

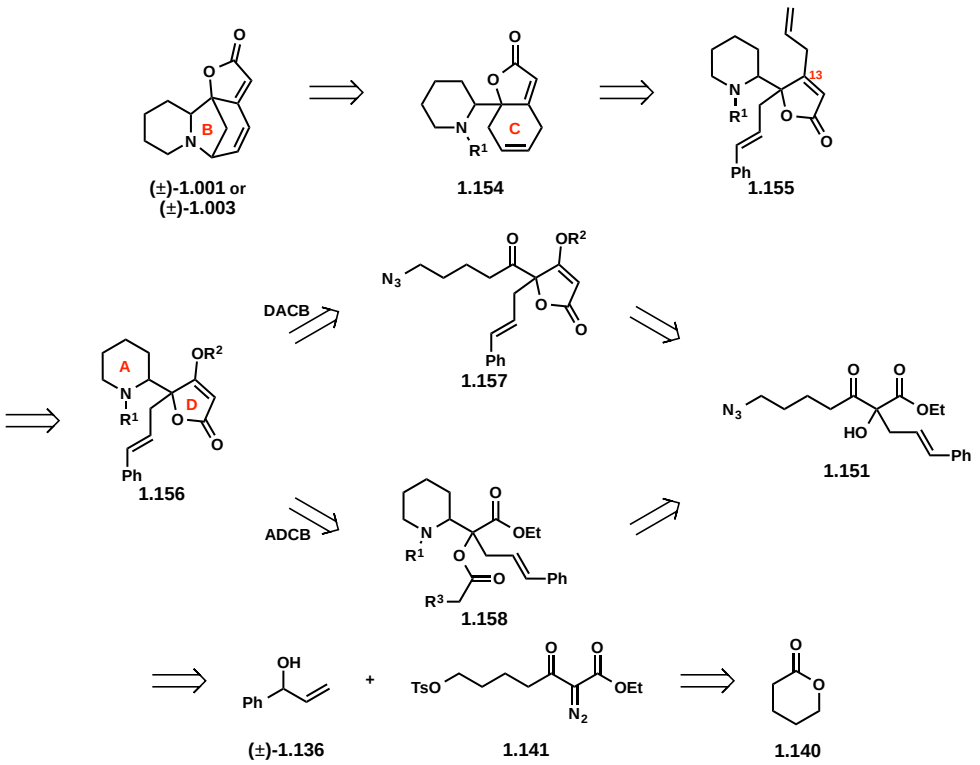


necessary to first oxidize alcohol **1.152** to ketone in **1.148**. The final reaction transforms the ketone in **1.153** to an olefin (alcohol oxidation state) in the final product.

3.1.2 Revision of the Retrosynthesis

Wanting to overcome the dual obstacles of the low yielding D ring formation and the high number of oxidation state changes at C13 we reevaluated the retrosynthesis. To this end, it was envisioned that assembly of the D ring at an earlier stage in the synthesis in the form of a tetronic acid would deliver C13 at an oxidation state level suitable for the Grignard addition of the allyl group. This would set the stage for construction of the C ring. Retrosynthetically, our first disconnection would be of the B ring to a tricyclic compound such as **1.154** (Scheme 3.2), reminiscent of the final step from other synthetic efforts.[3] The C ring of **1.154** could arise from a ring closing metathesis analogous to our previous syntheses, simplifying the compound back to **1.155**. The allyl group at C13 would derive from a Grignard addition or coupling reaction on a

Scheme 3.2



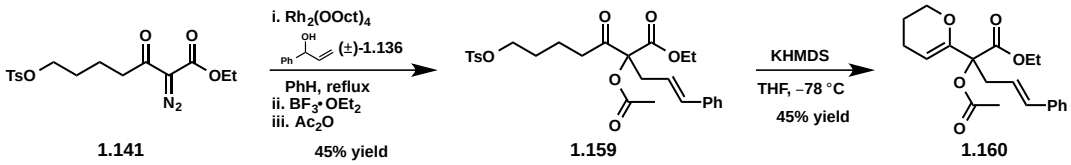
tetronic acid such as **1.156**. We envisioned that **1.156** could be synthesized from alcohol **1.151**; however there appeared to be two distinct routes by which this could occur. In one, we thought that the D ring might be formed before the A ring, leading back to tetronic acid **1.157**. In the other, we thought that the A ring might be formed before the D ring, leading back to ester **1.158**. Both tetronic acid **1.159** and amine **1.158** could arise from azide **1.151**, a compound in our previous synthesis.

3.2 The DACB Ring Formation Order

3.2.1 Tosylate Substrates

Our earliest efforts were directed toward forming the D ring first. We envisioned this occurring via a Dieckmann cyclization of an acetate with the ethyl ester in a substrate such as **1.159**. Since it was previously known that BF_3•OEt_2 was capable of catalyzing the acylation of alcohols[4] we decided to take advantage of the fact that we already employed it in the 1,2-allyl migration. To this end after the completion of the migration, we added acetic anhydride to the reaction mixture (Scheme 3.3). This resulted in the formation of the desired diester (**1.159**). Unfortunately, when treated with a base the only product recovered was an enolate displacement of the tosylate to give **1.160**. The use of additional base to deprotonate at the desired position did not lead to a Dieckmann cyclization.

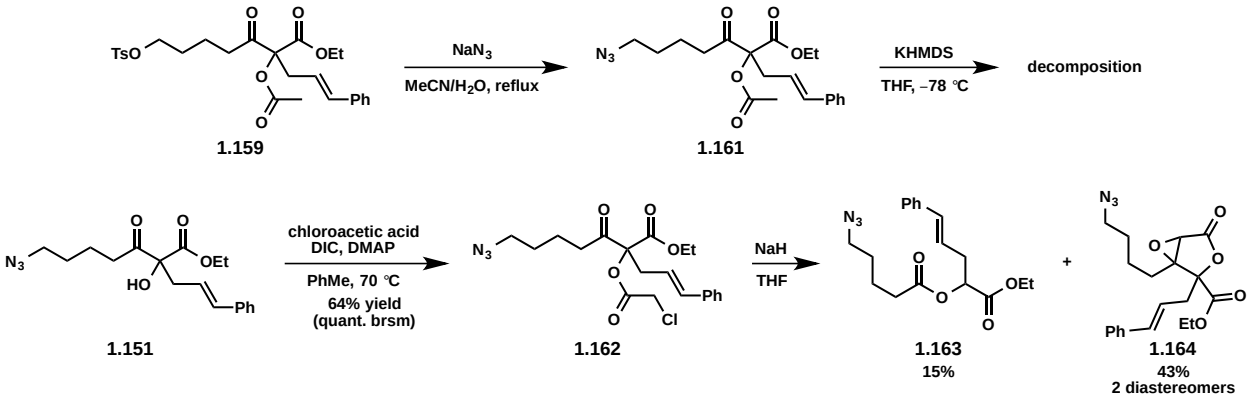
Scheme 3.3



3.2.2 Azide Substrates

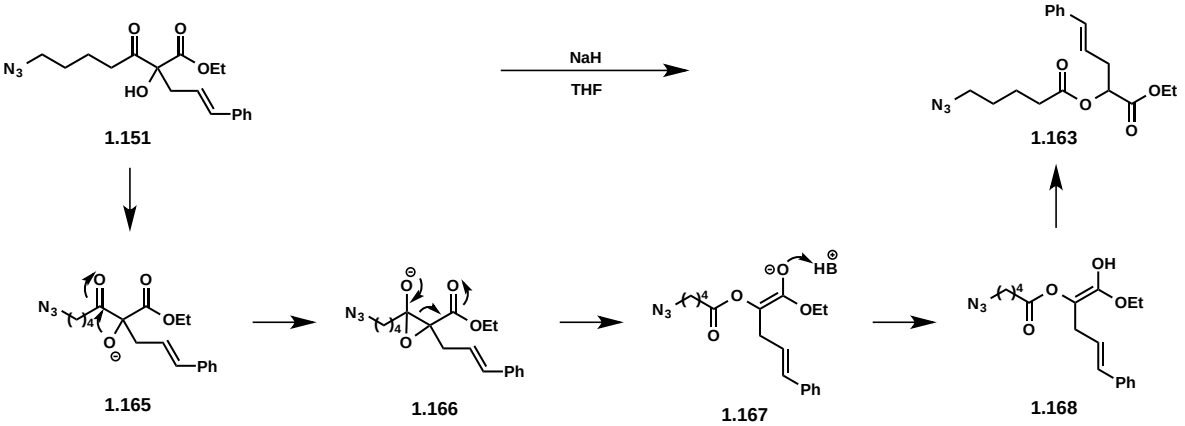
In order to avoid the undesired cyclization we then displaced the tosylate from **1.160** to give azide **1.161** (Scheme 3.4). Once again, treatment with base did not afford the desired

Scheme 3.4

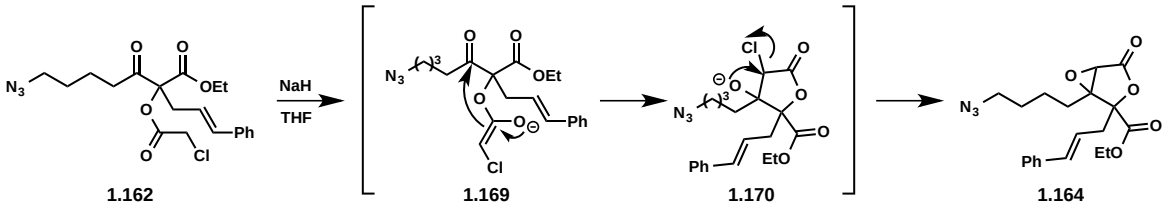


product. In an effort to lower the pK_a of the acetate protons relative to the pK_a of the α-keto protons we also synthesized chloroacetate **1.162**. When **1.162** was exposed to base, three compounds were isolated. We identified the minor component as diester **1.163**, the product of an α-hydroxy-β-ketoester rearrangement[5] (Scheme 3.5). Diester **1.163** is formed when chloroacetate **1.162** reverts to alcohol **1.151**, most likely due to the presence of trace NaOH. In the presence of base **1.151** forms alkoxide **1.165**. Addition of the oxygen to the ketone produces epoxide **1.166**. Opening of epoxide **1.166** leads to ester enolate **1.167**, which is then protonated to form enol **1.168**. Tautomerization of **1.168** produces diester **1.163**. The major products from the reaction of **1.162** with NaH were a pair of epoxide diastereomers (**1.164**). These appear to be the product of a Darzens glycidic ester condensation (Scheme 3.6). While we were pleased to observe the

Scheme 3.5



Scheme 3.6



desired deprotonation to alkoxide **1.169**, the resulting addition into the ketone yielded lactone **1.170**. Halohydrin **1.170** then underwent an S_Ni reaction to form epoxide **1.164**, a product that could not be used in our synthesis.

3.3 The ADCB Ring Formation Order

3.3.1 The Imine Substrate

3.3.1.1 Dieckmann Condensation

Based on the data from the acetate substrates **1.159** and **1.161** (Figure 3.1) we concluded that the C3 position α to a ketone was too acidic. In addition, our results with chloroacetate **1.162** established that the ketone was too reactive compared with the ester. With this in mind, we turned to the ADCB order of ring formation. We first considered substrates such as **1.171**, where the α-imine C3 position might be less acidic and the imine itself less reactive than a ketone. To this end, we initially sought to convert **1.161** to the desired imine (**1.171**, Scheme 3.7). Reduction under either Staudinger or hydrogenolysis conditions afforded a mixture of the desired acetate **1.171** and alcohol **1.143**. Alternatively, **1.143** could be synthesized in the usual way (Scheme 2.6) and then esterified to give **1.171** in moderate yield. Posing an additional difficulty was the fact that **1.171** proved to be quite unstable and as a result could never be fully characterized.

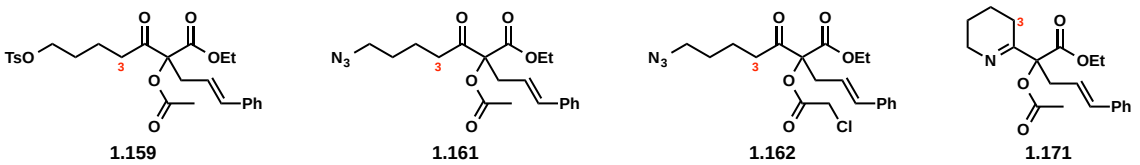
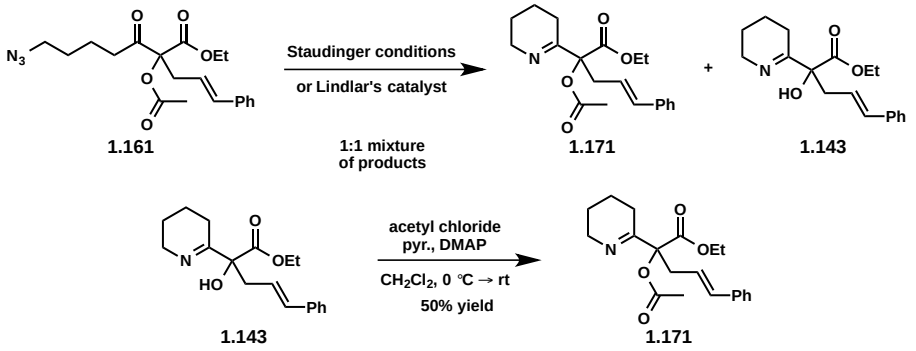


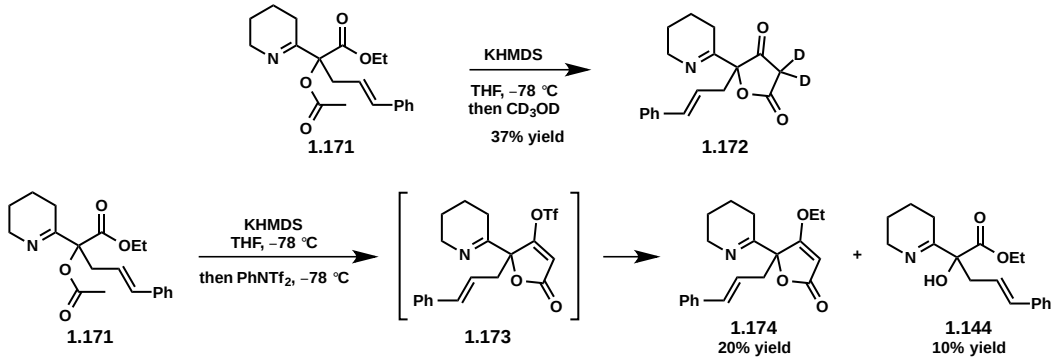
Figure 3.1

Scheme 3.7



With some of the desired acetate in hand, we attempted a Dieckmann cyclization on **1.171** (Scheme 3.8). While there appeared to be some product in ^{1}H-NMR's of the crude reaction mixture, chromatography led to decomposition, and it was not possible to obtain a clean sample of **1.172**. We then tried to trap the tetronic acid as the enol triflate with $PhNTf_2$, hoping that the resulting product would be more stable. Though the desired cyclization was observed, the desired product (**1.173**) appeared to have undergone nucleophilic attack since vinylogous carbonate **1.174** was the only isolable cyclization product.

Scheme 3.8

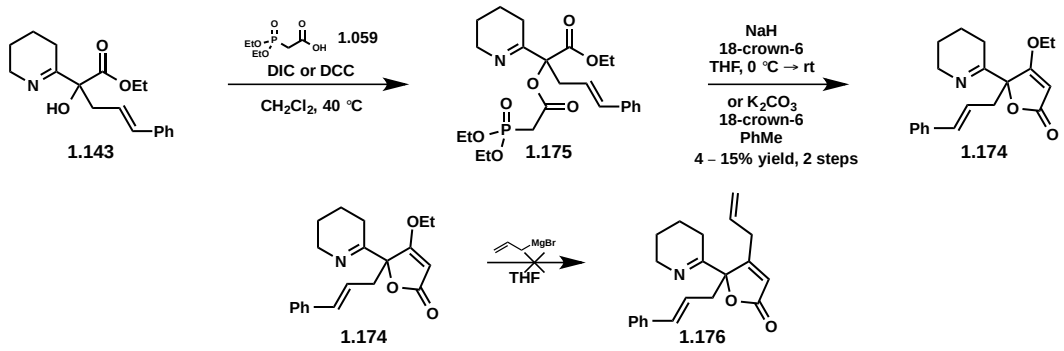


3.3.1.2 Horner-Wadsworth-Emmons Olefination

Since **1.143** was readily accessible, we also esterified it with triethylphosphonoacetic acid to give **1.175** (Scheme 3.9). The crude phosphonate ester was then exposed to NaH for a Horner-Wadsworth-Emmons reaction to give a small amount of the desired **1.174**. From the low and

variable yields, it became clear that both steps were problematic. In particular, both phosphonate ester **1.175** and the desired enol ether **1.174** appeared to be unstable. With access to a small amount of **1.174**, we tested the relative reactivities of the imine and the tetronic acid. To our chagrin, the reaction failed to produce any of the desired product (**1.176**).

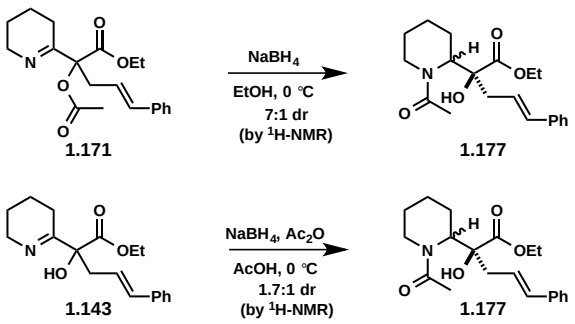
Scheme 3.9



3.3.2 Dieckmann Condensation with Amine Substrates

Having failed at advancing the imine-containing tetronic acid, we decided to explore a route wherein the potentially reactive imine would be reduced an amine (Scheme 3.10). Since we were still planning to construct the tetronic acid via a Dieckmann cyclization, our initial studies were performed with **1.171**, wherein the resident acetate moiety would serve in a subsequent cyclization. Unfortunately, when **1.171** was exposed to the standard imine reduction protocol, the product was not the desired amine, but rather acetamide **1.177**. We attempted to preserve the acetate by running the reaction under conditions known to provide acetamides from imines;

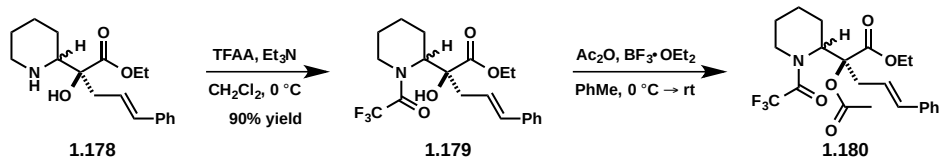
Scheme 3.10



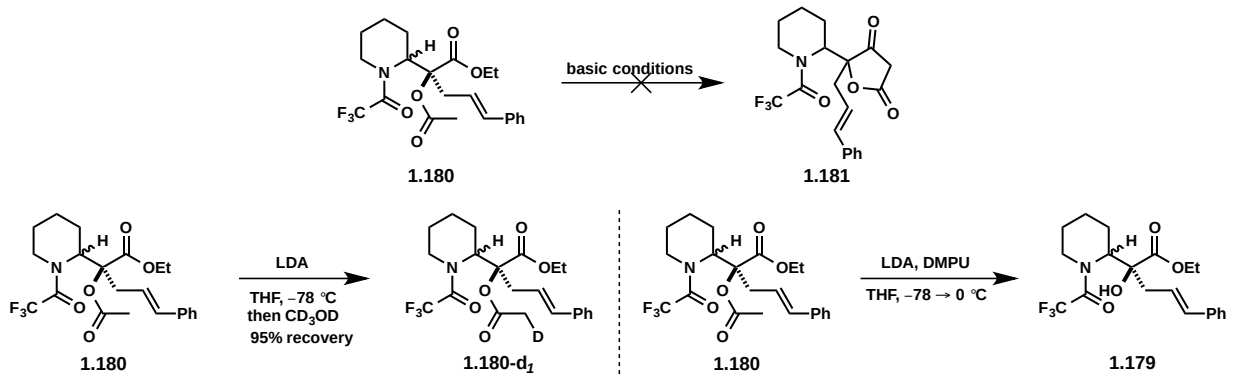
however, the intramolecular transfer was so favorable that this proved futile and the only product was alcohol **1.177**.[6] Although not productive in terms of our synthetic effort these reactions were interesting in that, the diastereomeric ratio of derived acetamide products **1.178** was quite dependent on the nature of the starting material.[7]

With **1.177** on hand, we were able to screen acetylation conditions. Unfortunately, it appeared that the only conditions that transformed the tertiary alcohol into an ester employed super-stoichiometric BF_3•OEt_2. Since the Boc group we previously employed would most likely be cleaved under these conditions, we instead decided to protect the amine as a trifluoroacetamide (Scheme 3.11). Treatment of amine **1.178** with TFAA in the presence of Et_3N gave trifluoracetamide **1.179**. The diastereomers of **1.179** could be separated on smaller scale for analytical purposes, but were typically taken on as a mixture. The alcohol was then acetylated to provide acetate **1.180** as a mixture of diastereomers. These were also separable for analytical purposes. Despite screening a wide variety of conditions, however, we obtained none of the desired tetronic acid (**1.181**, Scheme 3.12). The only results we observed with **1.180** as the substrate for a Dieckmann condensation were recovery of the starting material, deacetylation to give alcohol **1.179**, or decomposition. This was quite disappointing, and we sought to determine where the problem lay in the reaction. To this end we treated **1.180** with LDA and quenched the reaction with CD_3OD at −78 °C. The resulting deuterium incorporation at the acetate on **1.180-d*1*** indicated that deprotonation was occurring at the desired location. Efforts to promote cyclization by allowing the enolate to warm resulted only in loss of the ester moiety to furnish **1.180**.

Scheme 3.11



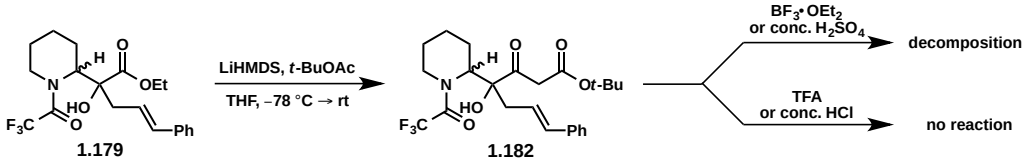
Scheme 3.12



3.3.3 Claisen Condensations with Amine Substrates

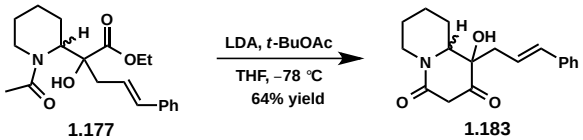
When our attempts to prepare the desired tetronic acid via an esterification/condensation sequence failed, we decided to try reversing the order of the reactions. To that end, we combined ester **1.180** and *t*-BuOAc with base to give the Claisen condensation product **1.182** (Scheme 3.13). All of our attempts at lactone formation via intramolecular transesterification with the crude alcohol (**1.182**) led to either decomposition or no reaction.

Scheme 3.13



With the harsh conditions that were employed we thought that decomposition might be due in part to trifluoroacetamide cleavage. In order to test this theory we decided to employ **1.177** as the substrate (Scheme 3.14). Unfortunately, the product of the first reaction did not contain the desired *t*-butyl ester moiety. Instead, it appeared to be bicyclic compound **1.183**. Rather than adding into the ester, the lithium enolate of *t*-BuOAc had served to deprotonate the

Scheme 3.14



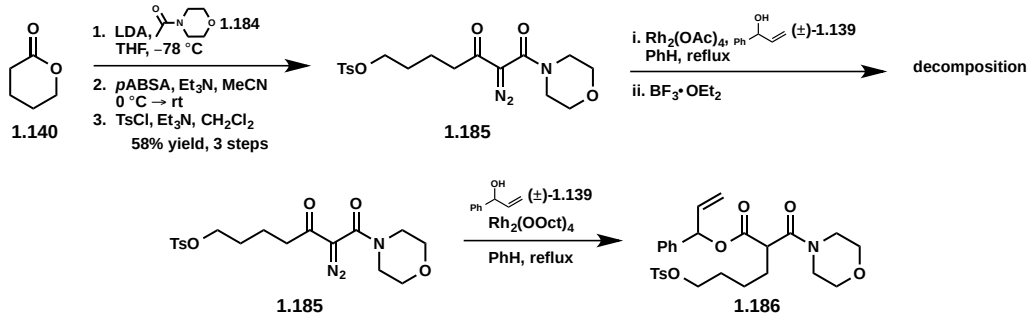
amide. While pleased to finally have the product of a Dieckmann condensation, the connectivity in **1.183** does not map onto the securinane natural products we had targeted.

3.4 Reevaluating the ACBD Ring Formation Order

3.4.1 Modification of the Ester Substrate

Resigned to the fact that D ring formation would have to occur as the final step in the synthesis, we sought a different method to limit the number of oxidation state changes at C13. We therefore directed our efforts toward the synthesis of a substrate containing a Weinreb amide surrogate (Scheme 3.15). Following a route analogous to the synthesis of α-diazoketone **1.141** (Scheme 2.5), we added the lithium enolate of **1.184** into lactone **1.140**. A Regitz diazo transfer was followed by the conversion of the alcohol into the tosylate to give **1.185**.

Scheme 3.15



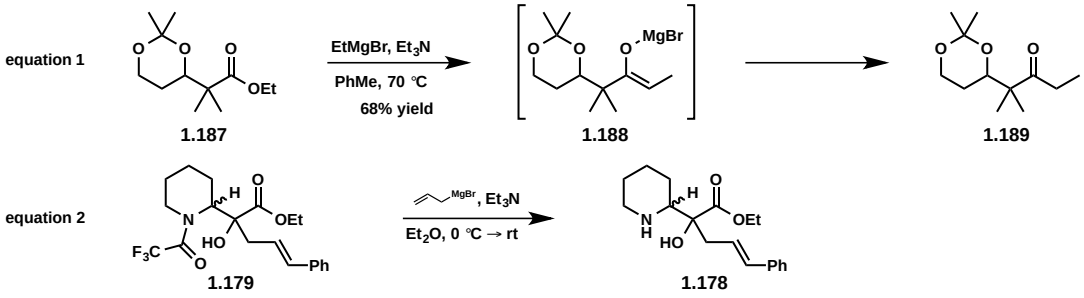
When we first attempted the Rh initiated O−H insertion/Claisen rearrangement/1,2-allyl migration all we observed was decomposition. Stopping the reaction prior to the addition of BF_3•OEt_2 however, allowed us to isolate diester **1.186**, presumably from a Wolff rearrangement generating a ketene that was trapped by **(±)-1.139**. We therefore ran the reaction with both the original allylic alcohol **(±)-1.114** and allyl alcohol itself in place of **(±)-1.139**. In both cases, only the product of a Wolff rearrangement was observed; this indicated that our more sterically hindered alcohol (**(±)-1.139**) was not the problem. Since the Wolff rearrangement is promoted by heat we attempted the reaction at lower temperatures (rt, 40 °C); however, the only compounds

recovered were **1.185** and **1.186**. Additionally, while **1.185** appeared to decompose over time, the rate at which it did so was on the order of weeks at room temperature. This led us to the conclusion that the morpholine moiety was coordinating to the rhodium after the initial rhodium carbenoid formation, preventing the O–H insertion. The resulting carbene then readily undergoes a Wolff rearrangement.

3.4.2 Modification of the Conditions for a Grignard Reaction

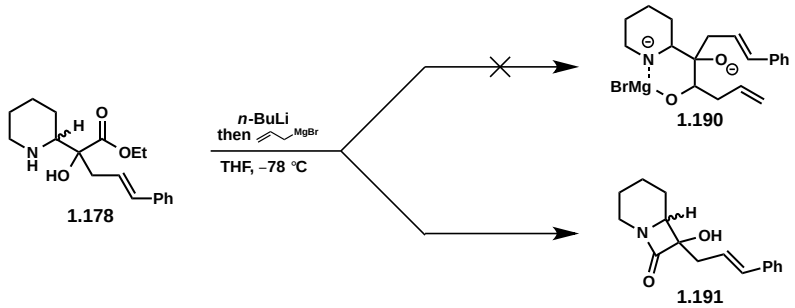
With modification of the diazo substrate itself ruled out, we moved our focus to modification of the conditions of the Grignard reaction. Our goal was to obtain a mono-addition product with an ester substrate such as **1.179**. It had previously been demonstrated by Fürstner *et al.* that an ester such as **1.187** undergoes a monoalkylation with ethylmagnesium bromide in the presence of Et_3N (equation 1, Scheme 3.16).[8] Ketone **1.189** was presumably generated via an enolate intermediate such as **1.188**.[8b] We therefore attempted to perform an analogous reaction by treating **1.179** with allylmagnesium bromide in the presence of Et_3N (equation 2, Scheme 3.16). Unfortunately, we only recovered amine **1.178**, the product of trifluoroacetamide cleavage.

Scheme 3.16



We also attempted to use an amine such as **1.178** to form an internal chelate such as **1.190** that would prevent the second addition (Scheme 3.17). Ester **1.178** was therefore treated with allylmagnesium bromide in the presence of 2 equivalents of *n*-BuLi. Much to our dismay,

Scheme 3.17



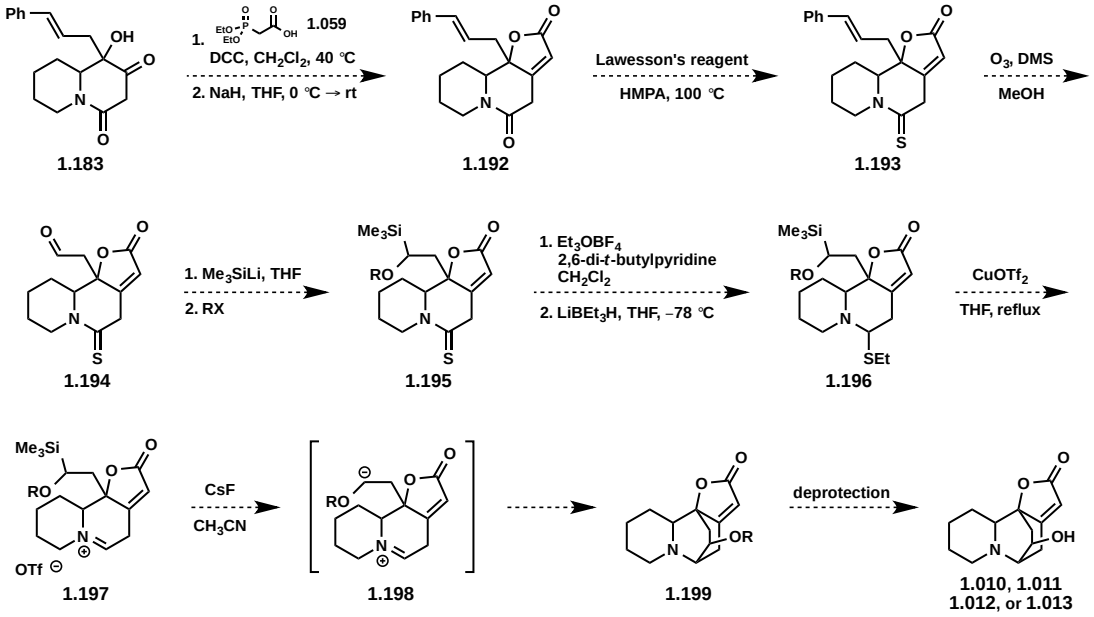
the observed product was β-lactam **1.191**, the product of intramolecular amide addition into the ester. We envisioned that **1.191** might undergo a monoaddition to open the β-lactam and afford the desired ketone; however, treatment of **1.191** with additional allylmagnesium bromide resulted only in decomposition.

3.5 Conclusions

Our goal in this work had been to revise our synthesis of the *Securinega* alkaloids to limit the number of oxidation state changes and improve the yields in the synthesis of the D ring. While we were unsuccessful in accomplishing this, we did inadvertently discover a potential route to the neosecurinane sub-family. Since bicycle **1.183** is a product of a reaction which follows the rhodium initiated O−H insertion/Claisen rearrangement/1,2-allyl migration we could synthesize **1.010**, **1.011**, **1.012**, or **1.013** enantioselectively from that intermediate (Scheme 3.14).

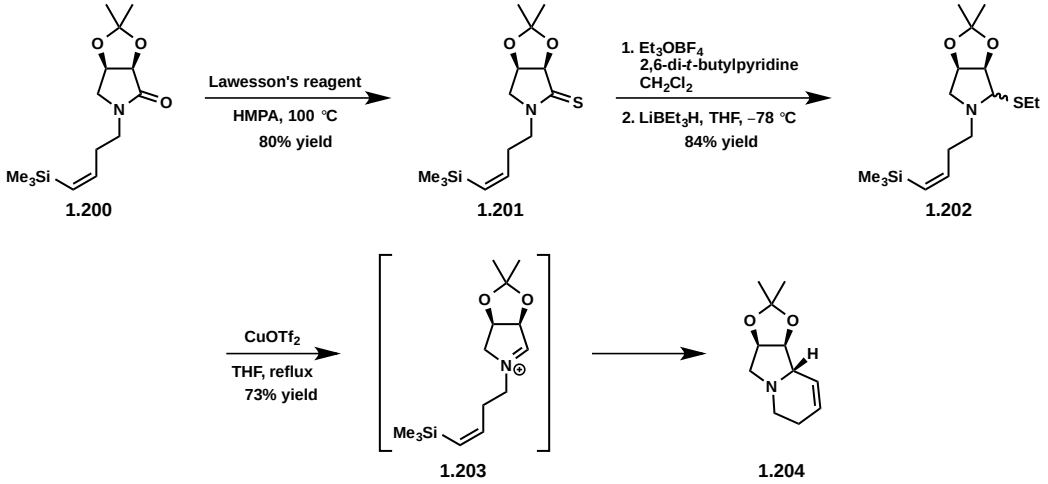
The synthesis would commence with esterification of alcohol **1.183** with **1.059** to give a phosphonate ester (Scheme 3.18). The intramolecular Horner-Wadsworth-Emmons reaction should then occur readily with the adjacent ketone to give butenolide **1.192**. The amide could then be converted to thioamide **1.193**. Ozonolysis of alkene **1.193** would be selective for the styrene over the α,β-unsaturated lactone to give aldehyde **1.194**. Addition of trimethylsilyllithium to aldehyde **1.194** and protection of the alcohol—most likely as a carbonate—would provide **1.195**. Thioamide **1.195** can then be transformed into iminium ion

Scheme 3.18



1.197, via thioaminal **1.196**. This sequence of reactions follows work by Overman *et al.* in their synthesis of hydroxylated indolizidines (Scheme 3.19).[9] In that work, they found that the direct reduction/iminium ion formation of **1.200** did not produce the desired intermediate **1.203**. Instead, they consistently observed the overreduction of the lactam to the pyrrolidine. This led them to the use of thioamide **1.201**, which was converted to a thioimidate salt. The intermediate salt was then reduced to 2-(ethylthio)pyrrolidine **1.202**. Thioaminal **1.202** underwent iminium-ion formation to generate **1.203**. *In situ* vinylsilane cyclization then formed the desired

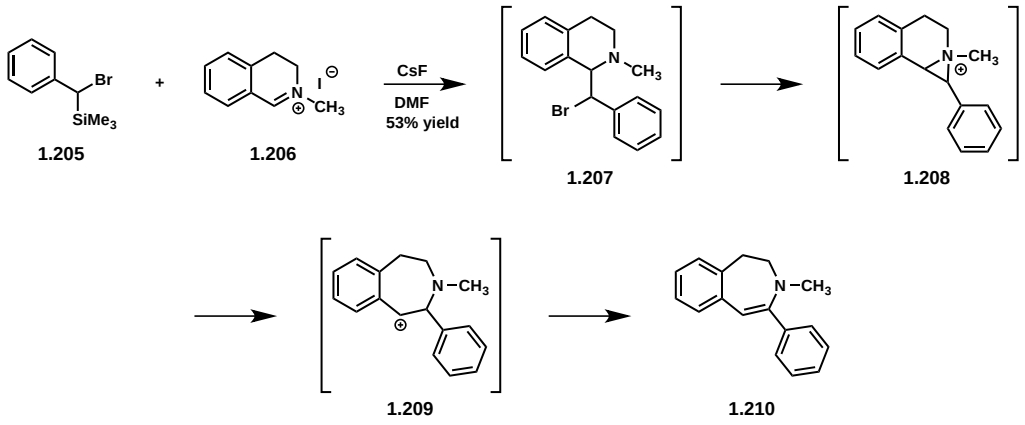
Scheme 3.19



tetrahydroindolizidine **1.204**. Because **1.196** has an alkylsilane rather than a vinylsilane, it is anticipated that the product isolated would be the iminium salt **1.197** analogous to **1.203**.

In order to induce the desired cyclization, we looked to a paper by Kessar *et al.* that described the intermolecular coupling of an iminium salt with an α-halo silane.[10] By combining an α-halo silane such as **1.205** with an iminium such as **1.206** in the presence of cesium fluoride, they generate the carbanion, which adds into the iminium to yield enamine **1.210** (Scheme 3.20). The route to the formation of **1.210** commences with the formation of amine **1.207**. The β-halo amine then undergoes a ring expansion via aziridinium intermediate **1.208** to give carbocation **1.209**. A final elimination generates the observed product. With a substrate lacking a good leaving group β to the amine however, we anticipate that the reaction would halt after the generation of an intermediate analogous to **1.207**. To this end, iminium **1.197** could be exposed to cesium fluoride, generating intermediate carbocation **1.198**. An intramolecular addition into the iminium would deliver amine **1.199**. Tetracycle **1.199** would then only require a deprotection to give a neosecurinane as a mixture of epimers at the alcohol position. The identity of the final product(s) would vary based on the relative and absolute stereochemistry of **1.183**.

Scheme 3.20



3.6 Experimental

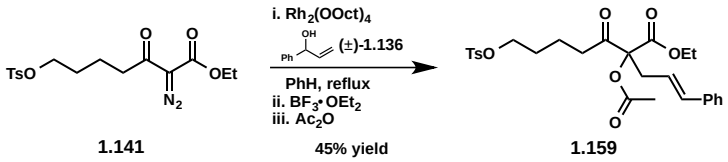
Unless otherwise stated, reactions were magnetically stirred in flame- or oven-dried glassware and inert atmosphere operations were conducted under an atmosphere of nitrogen, which was passed through a drying tube containing Drierite. Triethylamine, diisopropylamine, and methanol were dried over calcium hydride and freshly distilled. Benzene, tetrahydrofuran, dichloromethane, toluene, and diethyl ether were dried using a solvent purification system manufactured by SG Water U.S.A., LLC. Anhydrous acetonitrile, dimethylsulfoxide, and methanol were purchased and used without further purification from Macron Chemicals, EMD Chemicals and Fischer Scientific respectively. All other commercial reagents were used as received, unless noted otherwise.

Unless otherwise stated, all reactions were monitored by thin-layer chromatography (TLC) using Silicycle glass-backed extra hard layer, 60 Å plates (indicator F-254, 250 μm). Preparatory TLC was performed on the same plates. Flash column chromatography was performed with the indicated solvents using Silicycle SiliaFlash. P60 (230-400 mesh) silica gel as the stationary phase. Infrared spectra (IR) were obtained on an FTIR spectrophotometer and are reported in wavenumbers (cm^{-1}). High-resolution mass spectra were acquired on an electrospray ionization (ESI) spectrometer and obtained by peak matching.

Unless otherwise stated, ^{1}H-NMR spectra were recorded at ambient temperature at 400 or 300 MHz. ^{13}C-NMR spectra were recorded at ambient temperature at 101 or 75 MHz. ^{19}F-NMR spectra were recorded at ambient temperature at 376 or 282 MHz. Chemical shifts (δ) are reported in parts per million (ppm) relative to internal residual solvent peaks from the indicated deuterated solvents. Coupling constants (*J*) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as: s = singlet, d = doublet, t = triplet, q = quartet,

quint. = quintuplet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, br = broad, app = apparent, par = partial.

diester 1.159



In a 25 mL, 2-neck, round-bottomed flask fitted with a reflux condenser, **1.141** (0.2519 g, 0.68 mmol, 1 equiv) and **(±)-1.136** (0.0936 g, 0.70 mmol, 1.02 equiv) were dissolved in PhH (4 mL, 0.17 M). The rhodium octanoate (0.0011 g, 0.0014 mmol, 0.002 equiv) was added, followed by the remaining PhH (1.8 mL, 0.1M total). The flask was placed in a pre-heated (80 °C) oil bath and heated for 17 min. After cooling to room temperature, BF_3•OEt_2 (0.11 mL, 0.85 mmol, 1.25 equiv) was added via syringe. The reaction mixture was stirred for 110 min. Ac_2O (0.13 mL, 1.36 mmol, 2 equiv) was then added via syringe. After stirring at room temperature over night, the reaction mixture was diluted with CH_2Cl_2 and concentrated *in vacuo*. The reaction mixture was run through a plug of SiO_2 and reconcentrated *in vacuo*. Purification via column chromatography (SiO_2, 10→20% EtOAc/hexanes) afforded 0.16 g (45%) of **1.159** as a light yellow oil.

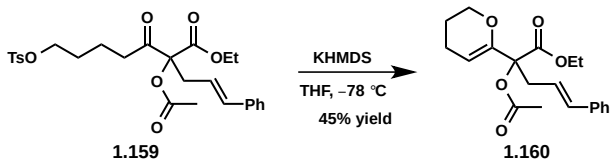
^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 4.4 Hz, 4H), 7.24 (t, *J* = 4.2 Hz, 1H), 6.42 (d, *J* = 15.8 Hz, 1H), 5.97 (dt, *J* = 15.6, 7.7 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.99 (t, *J* = 5.7 Hz, 2H), 3.07 (dd, *J* = 7.5, 1.1 Hz, 2H), 2.70 (d, *J* = 6.4 Hz, 2H), 2.44 (s, 3H), 2.16 (s, 3H), 1.62 (t, *J* = 2.9 Hz, 4H), 1.25 (t, *J* = 7.1 Hz, 3H)

^{13}C-NMR (101 MHz; $CDCl_3$): δ 202.5, 169.7, 167.0, 144.9, 136.8, 135.1, 133.2, 130.0, 128.7, 128.02, 127.87, 126.4, 121.7, 87.8, 70.3, 62.5, 38.2, 37.6, 28.1, 21.8, 20.9, 19.4, 14.2

IR (thin film) 2936 (m), 1744 (s), 1598 (w), 1448 (s), 1361 (s), 1249 (s), 1176 (s), 1097 (m), 1020 (m), 932 (m), 816 (m), 751 (m), 693 (m), 663 (m), 575 (w), 554 (m), 521 (w) cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{27}H_{36}NO_8S$ $(M+NH_4)^+$ 534.2156, found 534.2163

enol ether 1.160



In a 25 mL, 2-neck, round-bottomed flask, **1.159** (0.0908 g, 0.176 mmol, 1 equiv) was dissolved in THF (4 mL, 0.044 M). NaH (0.0127 g, 0.527 mmol, 3 equiv) was added, followed by the remaining THF (1 mL, 0.035 M total). The suspension was stirred for 3 h, and then addition NaH (0.0127 g, 0.527 mmol, 3 equiv) was added. After another 40 min, 18-crown-6 (0.003 g, 0.0114 mmol, 0.06 equiv) was added. After another 130 min, the reaction mixture was quenched by the addition of 1M $HCl_{(aq.)}$ (1 mL). The reaction mixture was then diluted with Et_2O (5 mL) and H_2O (5 mL). The phases were separated, and the aqueous layer was then extracted with EtOAc (2 x 5 mL), and the combined organic layers washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Preparative TLC afforded a sample of **1.160**.

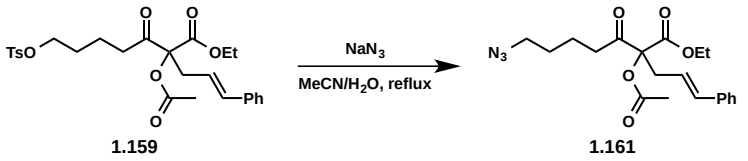
^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.34-7.27 (m, 4H), 7.21 (tt, *J* = 6.9, 2.1 Hz, 1H), 6.40 (d, *J* = 15.8 Hz, 1H), 6.08 (ddd, *J* = 15.5, 8.5, 6.8 Hz, 1H), 5.14 (t, *J* = 3.9 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.01 (t, *J* = 5.1 Hz, 2H), 3.21-3.10 (m, 2H), 2.10 (dt, *J* = 6.4, 3.2 Hz, 2H), 2.08 (s, 3H), 1.81 (dt, *J* = 11.0, 5.8 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H)

^{13}C-NMR (101 MHz; $CDCl_3$): δ 169.42, 169.26, 149.2, 137.7, 133.5, 128.6, 127.3, 126.3, 124.2, 98.3, 82.1, 77.5, 77.2, 76.9, 66.9, 61.8, 35.8, 22.3, 21.2, 20.1, 14.2

IR (thin film) 2979 (br m), 2932 (br m), 1747 (s), 1672 (m), 1558 (s), 1540 (s), 1457 (m), 1369 (m), 1252 (s), 1223 (s), 1067 (br m) 758 (w), 695 (m), 420 (s) cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{20}H_{24}NaO_5$ $(M+Na)^+$ 367.1516, found 367.1510

azide 1.161



1.159 **1.161**

In a 25 mL, 2-neck, round-bottomed flask, **1.159** (0.0325 g, 0.063 mmol, 1 equiv) was dissolved in MeCN (6.3 mL, 0.01 M). NaN_3 (0.0045 g, 0.069 mmol, 1.1 equiv) was added, followed by H_2O (0.7 mL, 0.09 M). The reaction mixture was then heated to reflux for 22 h. After cooling to room temperature and dilution with EtOAc, the reaction mixture was concentrated *in vacuo* to give **1.161**.

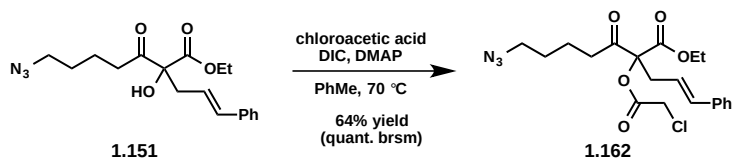
^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.31-7.30 (m, 4H), 7.25-7.21 (m, 1H), 6.43 (d, *J* = 15.8 Hz, 1H), 5.99 (dt, *J* = 15.6, 7.7 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.25 (t, *J* = 6.7 Hz, 2H), 3.10 (d, *J* = 7.4 Hz, 2H), 2.82-2.68 (m, 2H), 2.18 (s, 3H), 1.71-1.63 (m, 2H), 1.60-1.53 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H)

^{13}C-NMR (101 MHz; $CDCl_3$): δ 202.6, 169.7, 167.0, 136.8, 135.0, 128.68, 128.63, 127.8, 126.3, 121.7, 87.8, 62.4, 51.3, 38.4, 37.6, 28.18, 28.16, 20.8, 20.52, 20.46, 14.1

IR (thin film) 2937 (br m), 2096 (s), 1746 (s), 1721 (s), 1651 (m), 1558 (m), 1541 (m), 1457 (m), 1370 (m), 1248 (s), 1098 (br m), 746 (m), 695 (m) cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{20}H_{25}N_3NaO_5$ $(M+Na)^+$ 410.1686, found 410.1690

azide 1.162



1.151 **1.162**

In a 25 mL round-bottomed flask, **1.151** (0.2273 g, 0.658 mmol, 1 equiv) and DMAP (catalytic chip) were dissolved in CH_2Cl_2 (6.8 mL, 0.097 M). DIC (0.124 mL, 0.79 mmol, 1.2 equiv) was then added via syringe, followed by chloroacetic acid (0.0746 g, 0.79 mmol, 1.2 equiv) in CH_2Cl_2 (1 mL) and the remaining CH_2Cl_2 (1 mL, 0.075 M total). After 1 d the reaction mixture was filtered through a SiO_2 plug using Et_2O as the eluent, and the filtrate was concentrated *in vacuo*. Purification via column chromatography (SiO_2, 15→20% Et_2O/hexanes) gave 0.0797 g (29%) of **1.162** as a clear, colorless oil. An additional 0.1927 g of a 1:1 mixture of **1.151** and **1.162** was also recovered (>95% brsm).

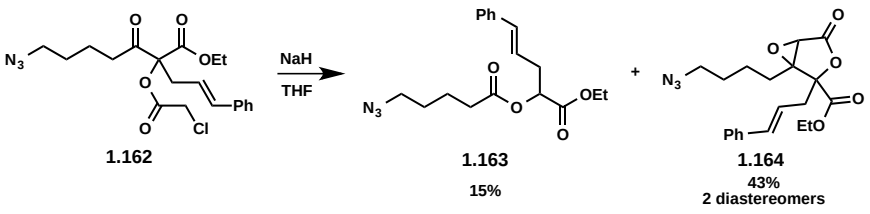
^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.31 (app d, *J* = 4.4 Hz, 4H), 7.26-7.23 (m, 1H), 6.45 (d, *J* = 15.8 Hz, 1H), 5.97 (dt, *J* = 15.6, 7.7 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 4.18 (s, 2H), 3.25 (t, *J* = 6.7 Hz, 2H), 3.15-3.12 (m, 2H), 2.78 (td, *J* = 6.9, 1.6 Hz, 2H), 1.72-1.64 (m, 2H), 1.61-1.53 (m, 2H), 1.45 (d, *J* = 6.9 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz; $CDCl_3$): δ 201.8, 166.3, 166.0, 136.6, 135.5, 128.8, 128.0, 126.4, 121.0, 89.0, 62.8, 51.3, 40.6, 38.6, 37.6, 28.2, 20.5, 20.0, 14.1

IR (thin film) 3853 (m), 3748 (m), 3673 (m), 3649 (m), 2937 (br m), 2360 (s), 2096 (s), 1748 (s), 1735 (s), 1720 (s), 1651 (m), 1558 (m), 1541 (m), 1508 (m), 1457 (m), 1259 (br m), 1161 (br m), 748 (m), 441 (m) cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{20}H_{28}ClN_4O_5$ $(M+NH_4)^+$ 439.1743, found 439.1746

diester 1.163 and epoxide 1.164



In a 25 mL, 2-neck round-bottomed flask, **1.162** (0.0597 g, 0.142 mmol, 1 equiv) was dissolved in THF (4 mL, 0.036 M). NaH (0.0102 g, 0.425 mmol, 3 equiv) was added, followed by additional THF (1 mL, 0.028 M total). This suspension was stirred for 45 min, before additional NaH (0.0068 g, 0.284 mmol, 2 equiv) was added. After 24 h, additional NaH (0.0068 g, 0.284 mmol, 2 equiv) was added. After an additional 18 h, the reaction mixture was cooled to 0 °C and quenched with 1−2 mL 1M $HCl_{(aq.)}$. After warming to room temperature the reaction mixture was diluted with EtOAc (5 mL) and H_2O (5 mL). The phases were separated, and the aqueous layer was then extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. An SiO_2 plug (run with CH_2Cl_2) was followed by an SiO_2 column (10→17.5% acetone/hexanes) to give 0.0075 g (15%) of **1.163**, 0.0125 g (23%) of the diastereomer of **1.164** with the higher R_f, and 0.0107 g (20%) of the diastereomer of **1.164** with the lower R_f.

1.163: ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.35-7.29 (m, 4H), 7.23 (tt, *J* = 6.9, 2.1 Hz, 1H), 6.49 (d, *J* = 15.8 Hz, 1H), 6.14 (dt, *J* = 15.7, 7.2 Hz, 1H), 5.14 (dd, *J* = 7.4, 5.1 Hz, 1H), 4.21 (dtt, *J* = 10.8, 7.2, 3.6 Hz, 2H), 3.26 (t, *J* = 6.6 Hz, 2H), 2.82-2.69 (m, 2H), 2.51-2.39 (m, 2H), 1.78-1.70 (m, 2H), 1.64 (dtd, *J* = 10.0, 7.5, 4.9 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H)

^{13}C-NMR (101 MHz; $CDCl_3$): δ 172.7, 169.7, 137.0, 133.9, 128.7, 127.7, 126.4, 123.6, 72.0, 61.6, 51.2, 35.0, 33.5, 29.9, 28.3, 22.2, 14.3

IR (thin film) 3837 (m), 3747 (m), 3673 (m), 3648 (m), 2925 (s), 2857 (m), 2360 (m), 2338 (m), 20945 (s), 1739 (s), 1558 (m), 1540 (m), 1457 (m), 1375 (br m), 1154 (br m), 745 (m), 695 (m), 420 (m) cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{18}H_{27}N_4O_4$ $(M+NH_4)^+$ 363.2027, found 363.2025

1.164 diastereomer 1: ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.35-7.28 (m, 4H), 7.22 (t, *J* = 7.1 Hz, 1H), 6.54 (d, *J* = 15.9 Hz, 1H), 6.21-6.13 (m, 1H), 4.29 (dtt, *J* = 10.7, 7.1, 3.5 Hz, 2H), 3.69 (s, 1H), 3.33-3.23 (m, 2H), 3.06 (dd, *J* = 14.7, 7.7 Hz, 1H), 2.88 (ddd, *J* = 14.4, 6.5, 1.0 Hz, 1H), 2.07 (ddd, *J* = 15.2, 10.6, 4.8 Hz, 1H), 1.83 (ddd, *J* = 15.3, 10.2, 5.3 Hz, 1H), 1.58 (q, *J* = 6.9 Hz, 2H), 1.48 (tdd, *J* = 10.3, 5.1, 2.6 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H)

^{13}C-NMR (101 MHz; $CDCl_3$): δ 169.6, 168.3, 136.9, 135.1, 128.7, 127.7, 126.4, 121.8, 87.2, 67.6, 63.0, 53.4, 51.1, 34.8, 28.7, 25.5, 21.4, 14.2

IR (thin film) 3852 (w), 3747 (m), 3672 (w), 3648 (w), 2931 (br m), 2359 (m), 2096 (s), 1793 (s), 1757 (s), 1749 (s), 1734 (s), 1651 (m), 1558 (m), 1540 (m), 1456 (m), 1263 (br m), 1195 (m), 1095 (m), 747 (m), 696 (m) cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{20}H_{27}N_4O_5$ $(M+NH_4)^+$ 403.1976, found 403.1978

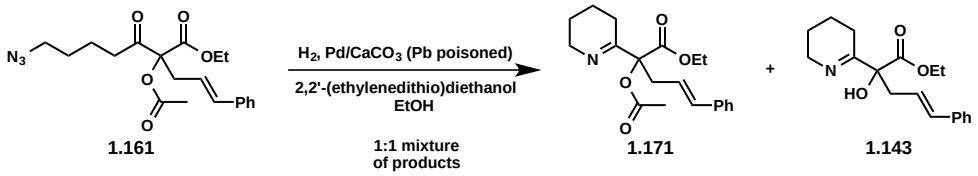
1.164 diastereomer 2: ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.35-7.29 (m, 4H), 7.28-7.22 (m, 1H), 6.57 (d, *J* = 15.8 Hz, 1H), 6.07 (dt, *J* = 15.5, 7.6 Hz, 1H), 4.28 (dtt, *J* = 10.5, 7.0, 3.4 Hz, 2H), 3.67 (s, 1H), 3.30 (td, *J* = 6.7, 2.1 Hz, 2H), 3.01 (dd, *J* = 14.4, 7.4 Hz, 1H), 2.78 (dd, *J* = 14.4, 6.8 Hz, 1H), 2.43 (ddd, *J* = 15.2, 10.6, 4.9 Hz, 1H), 2.22 (ddd, *J* = 15.3, 10.3, 5.2 Hz, 1H), 1.68-1.57 (m, 2H), 1.49-1.39 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H)

^{13}C-NMR (101 MHz; $CDCl_3$): δ 168.5, 167.7, 136.7, 136.4, 128.80, 128.67, 128.2, 126.53, 126.44, 119.6, 87.3, 68.7, 62.6, 53.8, 51.1, 38.4, 28.7, 24.8, 20.9, 14.3

IR 3852 (w), 3747 (m), 3673 (w), 3648 (w), 2936 (br m), 2360 (m), 2097 (s), 1796 (s), 1745 (s), 1699 (m), 1651 (m), 1558 (m), 1540 (m), 1507 (m), 1456 (m), 1269 (br m), 1193 (m), 1095 (m), 1030 (m), 969 (m), 858 (w), 748 (m), 697 (w), 420 (m) cm^{-1}

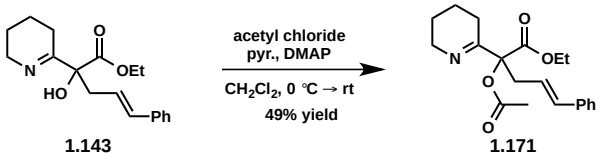
HRMS (ESI−APCI) m/z calcd. for $C_{20}H_{27}N_4O_5$ $(M+NH_4)^+$ 403.1976, found 403.1973

imine 1.171



In a 50 mL round-bottomed flask, **1.161** (0.1190 g, 0.307 mmol, 1 equiv) was dissolved in EtOH (10 mL, 0.03 M). 2,2'-(Ethylenedithio)diethanol (0.000036 g, 0.1% by weight of Pd) was added as a solution in EtOH (0.071 mL), followed by the palladium (0.0357 g, 30% by weight) and the remaining EtOH (2 mL, 0.025 M total). A balloon containing H_2 was attached and the headspace was evacuated and backfilled (4 x). The black suspension was stirred at room temperature for 2 h. The reaction mixture was then filtered through a plug of celite with EtOAc as the eluent, and the filtrate was concentrated *in vacuo*. The pale yellow oily solid obtained was a 1:1 mixture of **1.171** and **1.143**. Due to its instability, it was not possible to isolate a pure sample of **1.171**.

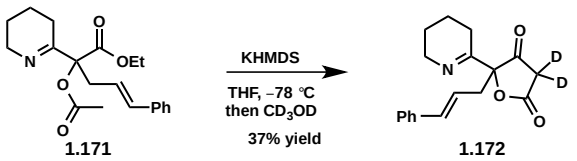
alternate preparation of imine 1.171



In a 100 mL pear-shaped flask, **1.143** (0.4250 g, 1.41 mmol, 1 equiv), pyridine (0.45 mL, 5.64 mmol, 4 equiv), and DMAP (catalytic chip) were dissolved in CH_2Cl_2 (27.5 mL, 0.05 M). This solution was then cooled to 0 °C. The acetyl chloride (0.11 mL, 1.55 mmol, 1.1 equiv) was was dissolved in CH_2Cl_2 (0.5 mL), and this solution was added dropwise to the reaction mixture. After 55 min the bath was removed and the flask allowed to warm to room temperature. The reaction mixture was quenched with H_2O (25 mL) and sat'd. $NaHCO_{3(aq.)}$ (5 mL). The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined

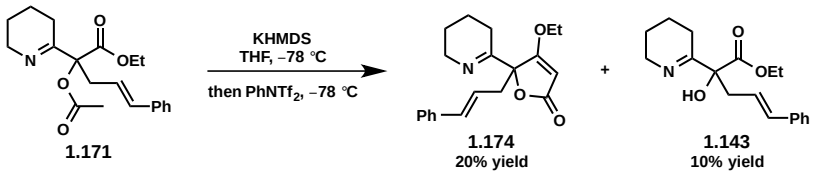
organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (basified SiO_2,[11] 25% Et_2O/hexanes then 10 → 25% EtOAc/hexanes) gave 0.2367 g (49%) of **1.171** as a light yellow oil. An additional 0.03 g (7%) of **1.143** was recovered.

tetronic acid 1.172



A 50 mL pear-shaped flask containing **1.171** (0.0628 g, 0.18 mmol, 1 equiv) in THF (18 mL, 0.01 M) was cooled to −78 °C. The KHMDS (0.54 mL, 0.51 M in PhMe, 0.27 mmol, 1.5 equiv) was then added dropwise over 7 min. After 2.25 h the flask was warmed to −40 °C and stirred for an additional 50 min. The reaction mixture was then quenched with CD_3OD (20 μM) and stirred for 10 min, before being warmed to room temperature. The reaction mixture was then diluted with MeOH and concentrated *in vacuo*. Column chromatography (SiO_2, 10% MeOH/CH_2Cl_2) afforded 0.0198 g (37%) of **1.172**. Due to its instability, it was not possible to isolate a pure sample of **1.172**.

tetronic acid ethyl ester 1.174



A 50 mL round-bottomed flask containing **1.171** (0.0255 g, 0.074 mmol, 1 equiv) and THF (6.4 mL, 0.01 M) was cooled to −78 °C. KHMDS (0.22 mL, 0.5 M in PhMe, 0.11 mmol, 1.5 equiv) was then added dropwise via syringe over 1 min. After 90 min, $PhNTf_2$ (0.0463 g, 0.13 mmol, 1.75 equiv) in THF (0.8 mL) was added dropwise via syringe over 8 min. After 70

min the flask was transferred to a bath at 0 °C. The bath was allowed to expire over 3.5 h. The reaction mixture was then quenched with sat'd. $NaHCO_{3(aq.)}$ and diluted with CH_2Cl_2 (5 mL) and H_2O (5 mL). The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification was performed via preparative thin layer chromatography (basified SiO_2 plate, 100% PhH, then 10% acetone/PhH). The fourth band contained 0.0022 g (10%) of the free alcohol **1.143**. The sixth band contained 0.0048 g (20%) of tetronic acid ester **1.174**.

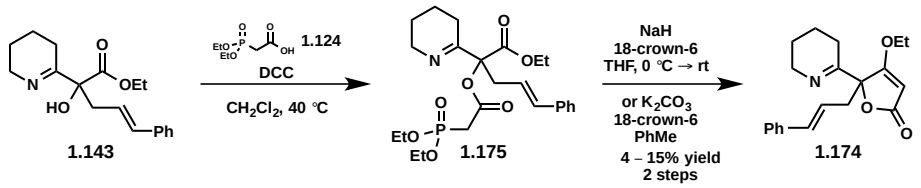
^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.30-7.14 (m, 5H), 6.47 (d, *J* = 15.8 Hz, 1H), 6.02 (dt, *J* = 15.6, 7.7 Hz, 1H), 5.05 (s, 1H), 4.16-4.00 (m, 2H), 3.79-3.65 (m, 2H), 3.04-2.94 (m, 2H), 2.32-1.92 (m, 2H), 1.74-1.63 (m, 2H), 1.57 (td, *J* = 11.1, 5.3 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H)

^{13}C-NMR (75 MHz; $CDCl_3$): δ 172.2, 165.8, 137.7, 134.7, 128.6, 127.5, 126.4, 122.3, 89.7, 89.3, 69.1, 49.9, 36.7, 24.0, 21.7, 19.3, 14.1

IR 3339 (br m), 3026 (w), 2932 (m), 2854 (m), 1759 (s), 1663 (m), 1628 (s), 1494 (w), 1449 (m), 1375 (m), 1338 (m), 1256 (w), 1226 (m), 1160 (w), 1090 (w), 1031 (m), 969 (w), 937 (w), 871 (w), 804 (m), 737 (m), 699 (m) cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{20}H_{24}NO_3$ $(M+H)^+$ 326.1751, found 326.1749

alternate preparation of tetronic acid ethyl ester 1.174

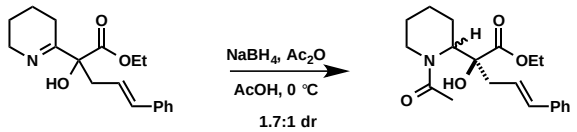


In a 25 mL pear-shaped flask, **1.143** (0.1060 g, 0.35 mmol, 1 equiv) and **1.124** (0.0724 g, 0.37 mmol, 1.05 equiv) were dissolved in CH_2Cl_2 (4 mL, 0.09 M). DCC (0.0794 g, 0.39 mmol, 1.1 equiv) was dissolved in CH_2Cl_2 (0.5 mL) and added dropwise to the flask, followed by the

remaining CH_2Cl_2 (0.5 mL, 0.07 M total). After 20 min additional DCC (0.01 g, 0.048 mmol, 0.14 equiv) was added and the reaction mixture stirred for another 15 min. It was then filtered through sand and cotton with CH_2Cl_2 and concentrated *in vacuo*. **1.175** was isolated as 0.1913 g of an orange-brown oil containing a colorless solid (presumably dicyclohexylurea byproducts). This material was used in the next step without further purification.

In a 50 mL 2-neck, round-bottomed flask, 18-crown-6 (0.0012 g, 0.0044 mmol, 0.05 equiv) and NaH (0.0063 g, 0.264 mmol, 3 equiv) were combined in THF (3 mL, 0.029 M). The flask was cooled to 0 °C and **1.175** (0.0422 g, 0.088 mmol, 1 equiv) in THF (0.5 mL) was added, followed by the remaining THF (1.5 mL, 0.018 M total). After 1 h the flask was allowed to warm to room temperature. After 16.5 h the reaction mixture was quenched with 5% $NaOH_{(aq.)}$ (1−2 mL) and diluted with Et_2O (3 mL) and H_2O (5 mL). The aqueous layer was then extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. ^{1}H-NMR of the crude material indicated that the majority was **1.174**. Attempts to purify the compound (via preparative thin-layer chromatography and column chromatography on basified SiO_2) led to decomposition and variable yields.

acetamide 1.177



1.143 **1.177**

In a 10 mL pear-shaped flask, **1.143** (0.10 g, 0.33 mmol, 1 equiv) was dissolved in a 1:1 mixture of Ac_2O and AcOH (3 mL, 0.11 M) and cooled to 0 °C. $NaBH_4$ (0.0377 g, 1 mmol, 3 equiv) was then added, and the reaction mixture stirred for 20 min. It was then quenched with 40% $NaOH_{(aq.)}$ (3 mL), diluted with CH_2Cl_2, and allowed to warm to room temperature. After

gas evolution had ceased, the reaction mixture was diluted with EtOAc (5 mL) and $NaHCO_{3(aq.)}$ (5 mL). The phases were separated, and the organic layer was washed with H_2O (1 x 10 mL) and sat'd. $NaHCO_{3(aq.)}$ (1 x 10 mL). The combined aqueous layers were then extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was then dissolved in PhH and filtered through an SiO_2 plug (50% Et_2O/hexanes, then Et_2O, then EtOAc as the eluent) and concentrated *in vacuo* to give 0.0666 g (58%) of **1.177** as a mixture of diastereomers. These could be separated for analytical purposes via column chromatography.

diastereomer 1: ^{1}H-NMR (300 MHz; 393 K; DMSO-d_6): δ 7.37-7.19 (m, 5H), 6.40 (d, *J* = 15.9 Hz, 1H), 6.19 (ddd, *J* = 15.9, 7.8, 6.6 Hz, 1H), 4.24-4.14 (m, 2H), 2.61 (ddd, *J* = 14.2, 7.8, 1.1 Hz, 1H), 2.47 (dd, *J* = 15.7, 7.0 Hz, 1H), 2.24 (d, *J* = 21.8 Hz, 1H), 2.07 (s, 3H), 2.03-1.90 (m, 1H), 1.74-1.37 (m, 6H), 1.28 (t, *J* = 7.1 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 2H)

^{13}C-NMR (75 MHz; 393 K; DMSO-d_6): δ 173.4, 141.0, 136.9, 132.0, 127.82, 127.71, 127.59, 127.41, 126.6, 126.3, 125.3, 124.4, 82.1, 80.2, 60.4, 60.1, 32.4, 31.4, 23.77, 23.65, 20.7, 18.97, 18.88, 13.32, 13.27

IR 3491 (br m), 2934 (m), 1728 (s), 1637 (s), 1496 (w), 1423 (s), 1366 (m), 1266 (s), 1196 (m), 1142 (m), 1072 (m), 1027 9m), 980 (m), 914 (w), 858 (w), 744 (m), 696 (m) cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{20}H_{28}NO_4$ $(M+H)^+$ 346.2013, found 346.2004

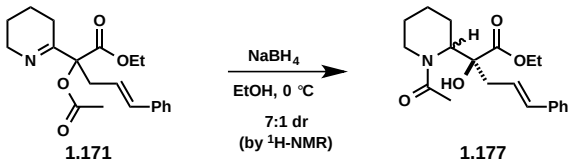
diastereomer 2: ^{1}H-NMR (300 MHz; 393 K; DMSO-d_6): δ 7.35-7.15 (m, 5H), 6.47 (d, *J* = 15.9 Hz, 1H), 6.19 (dt, *J* = 15.8, 7.2 Hz, 1H), 4.80 (br s, 1H), 4.12-4.01 (m, 2H), 2.64 (d, *J* = 7.0 Hz, 2H), 2.03-1.97 (m, 5H), 1.80-1.40 (m, 6H), 1.22-1.15 (m, 3H)

^{13}C-NMR (75 MHz; 393 K; DMSO-d_6): δ 173.1, 136.9, 132.4, 127.87, 127.78, 127.5, 126.4, 125.3, 124.3, 60.1, 23.8, 20.6, 19.1, 13.2

IR 3494 (br m), 2934 (s), 2867 (m), 1725 (s), 1644 (s), 1495 (w), 1422 (s), 1373 (m), 1260 (s), 1197 (m), 1149 (m), 1136 (m), 1082 (m), 1031 (m), 972 (m), 914 (w), 866 (w), 747 (m), 695 (m) cm^{-1}

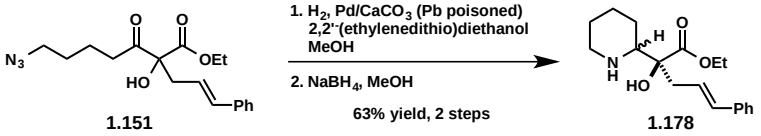
HRMS (ESI−APCI) m/z calcd. for $C_{20}H_{28}NO_4$ $(M+H)^+$ 346.2013, found 346.2018

alternate preparation of acetamide 1.177



In a 25 mL round-bottomed flask, **1.171** (0.0321 g, 0.093 mmol, 1 equiv) was dissolved in EtOH (3 mL, 0.03 M) and the flask cooled to 0 °C. $NaBH_4$ (0.0106 g, 0.28 mmol, 3 equiv) was added, followed by the remaining EtOH (2 mL, 0.19 M total). After 20 min the reaction mixture was concentrated *in vacuo*. It was then redissolved in MeOH and filtered through a plug of basic alumina and concentrated *in vacuo*. The crude material was suspended in $CHCl_3$, filtered through a fiberglass filter paper, and concentrated *in vacuo*. The diastereomeric ratio was determined by ^{1}H-NMR of crude **1.177**.

amine 1.178



In a 1 L pear-shaped flask, azide **1.151** (2.33 g, 6.74 mmol, 1 equiv) and 2,2'-(ethylenedithio)diethanol (0.00000035 g, 0.7 mL of a 0.0005 mg/mL solution, 0.0001% by weight of Pd) were dissolved in MeOH (50 mL, 0.13 M). The Pb poisoned $Pd/CaCO_3$ (0.3495 g, 15% by weight) was then added, followed by the remaining MeOH (100 mL, 0.05 M total). A balloon of H_2 was attached to the flask, and the headspace was evacuated and backfilled 3 x H_2.

The heterogeneous reaction mixture was then stirred vigorously for 3 h. The flask was then cooled to 0 °C. $NaBH_4$ (0.1275 g, 3.37 mmol, 0.5 equiv) was then added, and the reaction mixture was stirred for 30 min. It was then filtered through a plug of celite with Et_2O as the eluent, and the filtrate concentrated *in vacuo*. Purification via column chromatography (basified SiO_2,[11] 30→100% EtOAc/hexanes) gave 1.28 g (63%) of **1.178** as a yellow oil, which was a mixture of diastereomers.

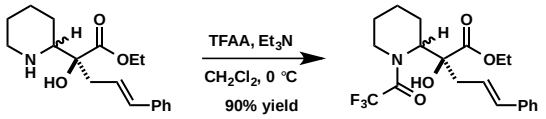
^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.33-7.15 (m, 5H), 6.44 (dd, *J* = 15.8, 3.7 Hz, 1H), 6.22-6.09 (m, 1H), 4.31-4.17 (m, 2H), 3.11 (ddt, *J* = 24.5, 12.9, 1.9 Hz, 1H), 2.87-2.73 (m, 1H), 2.68-2.49 (m, 3H), 1.94-1.75 (m, 2H), 1.58-1.33 (m, 3H), 1.32-1.23 (m, 3H)

^{13}C-NMR (101 MHz; $CDCl_3$): δ 175.9, 174.9, 137.41, 137.34, 133.84, 133.75, 128.6, 127.36, 127.32, 126.3, 124.4, 124.1, 80.1, 79.7, 77.5, 77.2, 76.8, 62.5, 62.03, 61.97, 61.80, 47.20, 47.04, 39.6, 39.3, 27.45, 27.28, 26.9, 26.15, 26.12, 24.86, 24.79, 14.5

IR 3495 (br m), 3304 (br w), 3025 (w), s931 (s), 2853 (m), 1727 (s), 1598 (w), 1496 (w), 1448 (m), 1366 (w), 1250 (br m), 1212 (m), 1196 (m), 1160 (w), 1120 (m), 1026 (w), 968 (m), 852 (w), 790 (w), 743 (m), 694 (m), 668 (w) cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{18}H_{26}NO_3$ 304.1907, found 304.1900

trifluoroacetamide 1.179



A 200 mL 2-neck, round-bottomed flask containing **1.178** (1.0499 g, 3.46 mmol, 1 equiv) and triethylamine (0.6 mL, 4.33 mmol, 1.25 equiv) in CH_2Cl_2 (35 mL, 0.1 M) was cooled to 0 °C. Trifluoroacetic anhydride (0.51 mL, 3.63 mmol, 1.05 equiv) was then added portionwise. After 35 min the flask was allowed to warm to room temperature and dry loaded onto SiO_2.

Purification by column chromatography (5% Et_2O/25% CH_2Cl_2/70% hexanes) afforded 1.2484 g (90%) of **1.179** as a nearly colorless oil. This mixture of diastereomers was separated for analytical purposes.

diastereomer 1: ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.30-7.18 (m, 5H), 6.42 (d, *J* = 15.8 Hz, 1H), 6.04 (ddd, *J* = 15.5, 8.8, 6.5 Hz, 1H), 4.99 (dd, *J* = 6.6, 3.1 Hz, 1H), 4.35-4.21 (m, 2H), 3.85 (t, *J* = 4.8 Hz, 2H), 3.67 (s, 1H), 2.67 (dd, *J* = 14.0, 8.6 Hz, 1H), 2.49 (ddd, *J* = 13.9, 6.3, 1.5 Hz, 1H), 2.13-2.04 (m, 1H), 1.80-1.75 (m, 1H), 1.68 (ddt, *J* = 11.5, 7.4, 4.0 Hz, 2H), 1.61-1.53 (m, 2H), 1.33-1.28 (m, 3H)

^{13}C-NMR (75 MHz; $CDCl_3$): δ 174.9, 157.5 (q, *J* = 35), 137.2, 134.5, 128.6, 127.5, 126.3, 122.9, 117.0 (q, *J* = 288), 82.8, 63.0, 54.0, 43.19, 43.14, 40.3, 25.53, 25.49, 20.0, 14.5

^{19}F-NMR (376 MHz; $CDCl_3$): δ −67.3, −68.52, −68.56

IR 3838 (w), 3748 (w), 3673 (w), 3648 (w), 3628 (w), 2931 (br w), 1732 (m), 1721 (m), 1684 (s), 1651 (w), 1558 (w), 1540 (w), 1507 (w), 1456 (m), 1195 (m), 1140 (m), 744 (w), 694 (w), 419 (m) cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{20}H_{25}F_3NO_4$ $(M+H)^+$ 400.1730, found 400.1733

diastereomer 2: ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.33-7.19 (m, 5H), 6.48 (dt, *J* = 15.8, 1.2 Hz, 1H), 6.07 (ddd, *J* = 15.8, 8.0, 6.7 Hz, 1H), 4.84 (dd, *J* = 6.8, 3.4 Hz, 1H), 4.29-4.04 (m, 2H), 3.75 (br dd, *J* = 10.1, 2.9 Hz, 2H), 3.59 (s, 1H), 2.76-2.62 (m, 2H), 2.14 (ddt, *J* = 12.4, 6.6, 3.2 Hz, 2H), 1.84-1.72 (m, 2H), 1.62-1.53 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H)

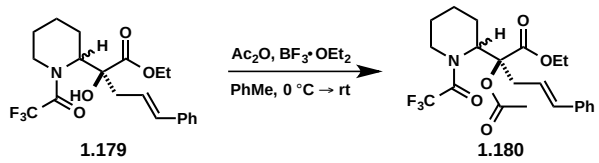
^{13}C-NMR (75 MHz; $CDCl_3$): δ 174.7, 156.7 (q, *J* = 35), 137.0, 134.9, 128.6, 127.6, 126.3, 122.7, 116.8 (q, *J* = 288), 81.7, 62.8, 55.0, 43.26, 43.22, 43.17, 40.9, 25.5, 23.8, 19.5, 14.1

^{19}F-NMR (282 MHz; CDCl3): δ −67.8, −69.31, −69.33

IR 3852 (w), 3747 (w), 3673 (w), 3648 (w), 2927 (br w), 1731 (m), 1718 (m), 1686 (s), 1651 (w), 1558 (w), 1540 (w), 1507 (w), 1455 (m), 1213 (s), 1193 (s), 1132 (s), 745 (w), 694 (w), 420 (m) cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{20}H_{25}F_3NO_4$ $(M+H)^+$ 400.1730, found 400.1729

diester 1.180



A 100 mL 2-neck, round-bottomed flask containing **1.179** (1.2452 g, 3.12 mmol, 1 equiv) in PhMe (20 mL, 0.15 M) was cooled to 0 °C. In a 10 mL collection flask, BF_3•OEt_2 (0.78 mL, 6.24 mmol, 2 equiv) was dissolved in PhMe (1 mL). Ac_2O (1.47 mL, 15.6 mmol, 5 equiv) was added to the BF_3•OEt_2 solution, and the resulting mixture stirred for 7 min. Half of the volume of this solution was added to the flask containing **1.179**, and the reaction mixture was stirred for 10 min. The remaining BF_3•OEt_2/Ac_2O solution was then added to the flask, and the reaction mixture stirred for 15 min. The flask was then allowed to warm to room temperature and stirred for 22 h. Additional BF_3•OEt_2 (0.2 mL, 1.6 mmol, 0.5 equiv) was then added. After an additional 23 h the reaction mixture was diluted with CH_2Cl_2 and concentrated *in vacuo*. It was then filtered through an SiO_2 plug to give 1.2915 g of **1.180** as a dark yellow oil. The diastereomers could be separated via column chromatography for analytical purposes. Both were mixtures of rotamers.

diastereomer 1: ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.31-7.05 (m, 5H), 6.40 (d, *J* = 15.7 Hz, 1H), 6.06 (dt, *J* = 15.5, 7.7 Hz, 1H), 5.03-5.00 (m, 0.75 H), 4.92 (s, 0.25 H), 4.31-4.23 (m, 1.5 H), 4.18 (dt, *J* = 13.6, 6.4 Hz, 0.5 H), 3.85-3.72 (m, 1H), 3.56-3.48 (m, 1H), 3.43-3.35 (m, 1H), 2.92 (ddd, *J* = 15.4, 7.2, 1.1 Hz, 1H), 2.28 (app d, *J* = 1.8 Hz, 1H), 2.11-2.05 (m, 2H), 1.92-1.47 (m, 6H), 1.32 (t, *J* = 7.1 Hz, 2H), 1.24 (t, *J* = 7.0 Hz, 1H)

^{13}C-NMR (75 MHz; $CDCl_3$): δ 170.5, 169.9, 169.4, 169.1, 157.6 (q, *J* = 36), 144.7, 141.5, 137.2, 135.9, 134.5, 129.35, 129.30, 128.68, 128.60, 127.92, 127.82, 127.76, 127.65, 127.55, 126.3, 122.7, 117.0 (q, *J* = 289), 85.6, 84.7, 62.3, 62.0, 54.6, 53.6, 51.3, 43.3, 37.1, 32.5, 29.9, 29.1, 25.3, 24.9, 24.4, 23.4, 21.52, 21.38, 21.1, 19.6, 19.1, 14.14, 14.01

^{19}F-NMR (282 MHz; $CDCl_3$): δ −67.1, −68.99, −69.15

IR 3474 (br w), 3026 (w), 2958 (m), 1742 (s), 1688 (s), 1599 (w), 1513 (w), 1494 (w), 1449 (m), 1369 (m), 1213 (s), 1170 (s), 1143 (s), 1120 (s), 1063 (m), 1026 (m), 1002 (m), 969 (m), 940 (w), 864 (w), 754 (m), 699 (m), 646 (w), 598 (w), 551 (w), 502 (w), 433 (w), 419 (w) cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{22}H_{27}F_3NO_5$ $(M+H)^+$ 442.1836, found 442.1832

diastereomer 2: ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.37-7.15 (m, 5H), 7.13-7.06 (m, 1H), 6.46 (d, *J* = 16.1 Hz, 0.5 H), 6.38 (ddd, *J* = 15.7, 8.6, 5.5 Hz, 0.5 H), 4.84 (ddd, *J* = 17.5, 9.5, 4.0 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 1H), 4.08 (q, *J* = 7.1 Hz, 1H), 3.84-3.76 (m, 1H), 3.64-3.53 (m, 1H), 3.34-3.29 (m, 0.5 H), 2.98 (dd, *J* = 15.0, 8.5 Hz, 0.5 H), 2.70-2.51 (m, 0.5 H), 2.41-2.19 (m, 0.5 H), 2.30 (app d, *J* = 6.4 Hz, 1H), 2.12-2.07 (m, 2H), 2.03-1.86 (m, 2H), 1.83-1.73 (m, *J* = 6.9, 3.6 Hz, 2H), 1.64-1.53 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 2H), 1.23 (t, *J* = 7.4 Hz, 1H)

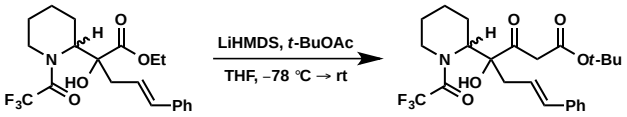
^{13}C-NMR (75 MHz; $CDCl_3$): δ 169.71, 169.56, 169.37, 169.22, 169.11, 157.1 (q, *J* = 36), 144.9, 144.5, 141.8, 141.6, 141.2, 137.2, 135.96, 135.87, 134.2, 129.38, 129.30, 128.87, 128.77, 128.70, 128.58, 128.53, 128.51, 128.45, 128.36, 127.94, 127.84, 127.77, 127.68, 127.63, 126.49, 126.37, 126.30, 126.1, 124.2, 116.7 (q, *J* = 288), 86.3, 85.9, 62.30, 62.11, 53.6, 52.9, 52.5, 51.6, 43.0, 38.1, 36.3, 33.8, 33.1, 30.6, 29.8, 26.6, 25.01, 24.96, 24.06, 24.00, 23.88, 21.68, 21.63, 21.13, 21.08, 19.8, 13.86, 13.83

^{19}F-NMR (282 MHz; $CDCl_3$): δ −67.8, −69.27, −69.34

IR 3025 (w), 2939 (m), 1745 (s), 1687 (s), 1600 (w), 1494 (w), 1450 (m), 1369 (m), 1259 (m), 1233 (s), 1211 (s), 1144 (s), 1118 (m), 1029 (m), 1002 (m), 976 (w), 939 (w), 865 (w), 756 (m), 699 (m), 642 (w), 603 (w), 540 (w), 430 (w), 407 (w) cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{22}H_{27}F_3NO_5$ $(M+H)^+$ 442.1836, found 442.1837

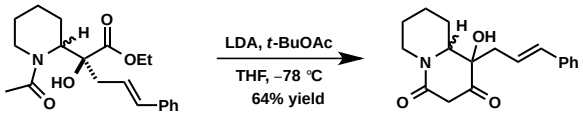
β-ketoester 1.182



1.179 **1.182**

A 250 mL, 3-neck, round-bottomed flask containing LiHMDS (27 mL, 1 M in THF, 27 mmol, 5 equiv) and THF (60 mL) was cooled to −78 °C. *t*-BuOAc (3.6 mL, 27 mmol, 5 equiv) was then added via a dropping addition funnel over 5 min. After 20 min the flask was warmed to 0 °C, stirred for 5 min, and cooled back to −78 °C. A solution of **1.179** (2.1576 g, 5.4 mmol, 1 equiv) in THF (7 mL) was added via a dropping addition funnel over 16 min, followed by the remaining THF (5 mL, 0.075 M total). The bath was allowed to expire overnight. The flask was then cooled to 0 °C and the reaction mixture quenched with citric acid (5.2 g, 27 mmol, 5 equiv) in H_2O (10 mL). The flask was then warmed to room temperature and the reaction mixture diluted with H_2O (10 mL) and Et_2O (20 mL). The phases were separated, and the organic layer was washed with H_2O (20 mL). The combined aqueous layers were then extracted with EtOAc (3 x 15 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. **1.182** was an orange oil, which was used without further purification.

bicycle 1.183



1.177 **1.183**

A 100 mL 2-neck, round-bottomed flask containing diisopropylamine (0.82 mL, 5.79 mmol, 10 equiv) and THF (10 mL) was cooled to −78 °C. *n*-BuLi (1.8 mL, 2.1 M in hexanes, 3.78 mmol and 1.2 mL, 1.18 M in hexanes, 1.42 mmol, 9 equiv total) was then added in two portions. After 5 min the flask was stirred at 0 °C for 10 min, and then cooled back to −78 °C. *t*-BuOAc (0.39 mL, 2.89 mmol, 5 equiv) in THF (5 mL) was then added via a dropping addition funnel over 8 min. After an additional 3 min at −78 °C the flask was stirred at 0 °C for 7 min, and then cooled back to −78 °C. A solution of **1.177** (0.2103 g, 0.61 mmol, 1 equiv) in THF (6 mL) was added via the dropping addition funnel over 24 min. The remaining THF (4 mL, 0.024 M total) was then added and the reaction mixture stirred for 30 min. The flask was then warmed to 0 °C, and the reaction mixture was quenched with sat'd. $NH_4Cl_{(aq.)}$ and diluted with Et_2O (10 mL) and H_2O (10 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (3 x 15 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 100% Et_2O) gave 0.1170 g (64%) of **1.183** as a pink oil. The diastereomers could be separated via preparative thin-layer chromatography for analytical purposes. Both were mixtures of conformers.

diastereomer 1: ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.30-7.21 (m, 5H), 6.51 (d, *J* = 15.9 Hz, 1H), 6.04 (ddd, *J* = 15.8, 8.8, 6.1 Hz, 1H), 4.59 (dt, *J* = 13.8, 1.6 Hz, 1H), 3.84 (s, 1H), 3.51 (d, *J* = 19.2 Hz, 1H), 3.47 (d, *J* = 19.1 Hz, 1H), 3.19-3.15 (m, 1H), 2.79 (ddd, *J* = 14.5, 6.0, 1.6 Hz, 1H), 2.72-2.64 (m, 2H), 2.09-1.98 (m, 2H), 1.80 (app dt, *J* = 9.0, 1.9 Hz, 1H), 1.51-1.43 (m, 3H)

^{13}C-NMR (101 MHz; $CDCl_3$): δ 204.0, 166.0, 136.5, 135.0, 128.7, 128.0, 126.4, 121.8, 79.2, 62.6, 45.4, 43.8, 36.4, 25.8, 24.5, 23.8

IR 3343 (br m), 2939 (m), 2858 (m), 1732 (s), 1630 (s), 1468 (m), 1445 (m), 1383 (w), 1336 (w), 1274 (m), 1202 (w), 1127 (w), 1053 (w), 964 (w), 910 (w), 849 (w), 733 (m), 694 (m), 668 (w) cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{18}H_{22}NO_3$ $(M+H)^+$ 300.1594, found 300.1593

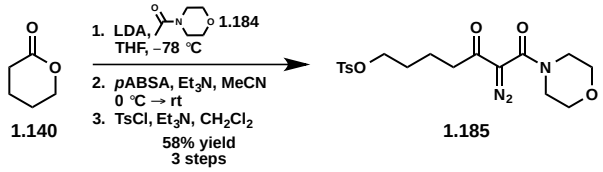
diastereomer 2: ^{1}H-NMR (400 MHz; DMSO-d_6): δ 7.30 (t, *J* = 27.3 Hz, 5H), 6.55 (d, *J* = 15.9 Hz, 0.8 H), 6.42 (d, *J* = 15.9 Hz, 0.2 H), 6.31-6.18 (m, 1H), 5.72 (s, 0.6 H), 5.45 (s, 0.2 H), 4.86 (s, 0.2 H), 4.45-4.41 (app dt, *J* = 12.4, 2.1 Hz, 0.6 H), 4.39-4.35 (app dt, *J* = 12.7, 2.2 Hz, 0.2 H), 4.23 (dd, *J* = 13.0, 3.9 Hz, 0.2 H), 3.69 (d, *J* = 19.6 Hz, 0.8 H), 3.65 (d, *J* = 19.6 Hz, 0.2 H), 3.45 (dd, *J* = 12.2, 2.1 Hz, 0.8 H), 3.36 (dd, *J* = 12.1, 2.0 Hz, 0.2 H), 3.14 (d, *J* = 19.9 Hz, 0.8 H), 3.06 (d, *J* = 19.9 Hz, 0.2 H), 2.75 (d, *J* = 6.6 Hz, 0.8 H), 2.66-2.57 (m, 2H), 2.55-2.52 (m, 0.2 H), 1.97-1.91 (m, 1H), 1.83-1.78 (m, 1H), 1.72-1.63 (m, 0.4 H), 1.56-1.48 (m, 1.6 H), 1.32-1.20 (m, 1H), 0.81 (qd, *J* = 12.5, 3.9 Hz, 0.8 H), 0.73 (qd, *J* = 12.5, 3.7 Hz, 0.2 H)

^{13}C-NMR (101 MHz; DMSO-d_6): δ 204.1, 164.4, 136.9, 133.2, 128.5, 128.25, 128.20, 127.3, 126.06, 125.96, 123.7, 79.1, 71.6, 63.9, 63.2, 45.3, 44.6, 40.3, 36.4, 35.0, 27.6, 24.8, 24.2

IR 3387 (br m), 3025 (w), 2938 (m), 2857 (m), 1729 (s), 1646 (s), 1496 (w), 1464 (m), 1441 (m), 1385 (w), 1313 (w), 1275 (m), 1222 (w), 1197 (w), 1139 (w), 1120 (w), 1052 (w), 972 (w), 911 (w), 846 (w), 734 (m), 696 (m) cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{18}H_{22}NO_3$ $(M+H)^+$ 300.1594, found 300.1585

morpholine amide 1.185



A 50 mL 2-neck, round-bottomed flask containing diisopropylamine (0.78 mL, 5.6 mmol, 1.04 equiv) and THF (10 mL) was cooled to −78 °C. *n*-BuLi was added dropwise via syringe and the reaction mixture stirred for 34 min. A solution of **1.184**[12] (0.62 mL, 5.39 mmol, 1 equiv) in THF (2.5 mL) was added via syringe. After 1 h, **1.140** in THF (2.5 mL, 0.35 M total) was then added dropwise via syringe. The bath was allowed to expire overnight. The reaction mixture was quenched with a solution of AcOH (3.5 mL, 1 M in THF) and diluted with H_2O (10 mL) and EtOAc (10 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL), CH_2Cl_2 (2 x 10 mL), and $CHCl_3$ (1 x 10 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. This orange oil was used crude in the next step.

In a 100 mL pear-shaped flask, the material from the first step (0.9882 g, 4.3 mmol, 1 equiv) and *p*ABSA (1.0330 g, 4.3 mmol, 1 equiv) were dissolved in MeCN (17 mL, 0.25 M). The flask was then cooled to 0 °C and triethylamine (1.8 mL, 12.9 mmol, 3 equiv) was added. After 30 min the bath was removed and the flask allowed to warm to room temperature. After 3.5 h the reaction mixture was then filtered through a fritted funnel with Et_2O. The crude material was used in the next step without further purification.

In a 50 mL pear-shaped flask, the material from the second step (1.0977 g, 4.3 mmol, 1 equiv) and tosyl chloride (1.2297 g, 6.45 mmol, 1.5 equiv) were dissolved in CH_2Cl_2 (17 mL, 0.25 M). Triethylamine (1.8 mL, 12.9 mmol, 3 equiv) was added, and the reaction mixture stirred for 20 h. It was then diluted with sat'd. $NaHCO_{3(aq.)}$ (15 mL) and CH_2Cl_2 (5 mL). The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in*

vacuo. Purification by column chromatography (SiO_2, 100% Et_2O) afforded 1.2752 g (58%, 3 steps) of **1.185** as a yellow oil.

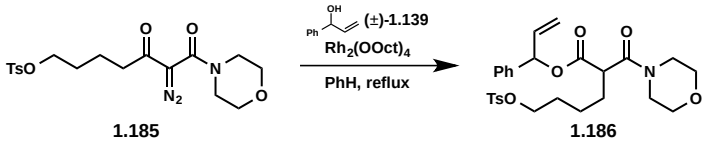
^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.75-7.73 (m, 2H), 7.33-7.31 (m, 2H), 4.01-3.98 (m, 2H), 3.70-3.67 (m, 4H), 3.46 (s, 4H), 2.56 (s, 2H), 2.42 (s, 3H), 1.71-1.62 (m, 4H)

^{13}C-NMR (101 MHz; $CDCl_3$): δ 160.4, 144.9, 133.0, 129.9, 127.9, 70.1, 66.7, 46.1, 38.2, 28.2, 21.7, 20.3

IR 2966 (m), 2924 (m), 2859 (m), 2110 (s), 1633 (s), 1449 (m), 1425 (m) 1356 (s), 1277 (M), 1212 (w), 1175 (s), 1114 (m), 1067 (w), 1017 (w), 934 (m), 817 (m), 732 (w), 664 (m), 577 (m), 555 (m), 428 (w) cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{18}H_{24}N_3O_6S$ $(M+H)^+$ 410.1380, found 410.1379

ester 1.186



1.185 **1.186**

In a 25 mL 2-neck, round-bottomed flask fitted with a reflux condenser, **1.185** (0.0707 g, 0.173 mmol, 1 equiv) and **(±)-1.139** (0.0236 g, 0.176 mmol, 1.02 equiv) were dissolved in PhH (4.8 mL). $Rh_2(OOct)_4$ (0.0003 g, 0.0004 mmol, 0.002 equiv) was added, followed by the remaining PhH (1 mL, 0.03 M total). The flask was transferred to a pre-heated (80 °C) oil bath and stirred for 78 min. After cooling to room temperature the reaction mixture was filtered through a SiO_2 plug with Et_2O. After concentrating *in vacuo*, purification via preparative thin-layer chromatography afforded **1.186** as a pair of diastereomers.

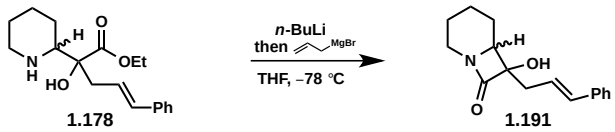
^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.77-7.75 (m, 2H), 7.38-7.29 (m, 6H), 6.26 (t, J = 5.8 Hz, 1H), 6.04-5.93 (m, 1H), 5.34-5.24 (m, 2H), 3.97 (td, J = 6.4, 3.0 Hz, 2H), 3.77-3.33 (m, 9H), 2.44 (s, 2.5 H), 2.17 (s, 0.5 H), 1.96-1.87 (m, 2H), 1.69-1.61 (m, 2H), 1.37-1.25 (m, 2H)

^{13}C-NMR (101 MHz; $CDCl_3$): δ 168.81, 168.71, 166.5, 144.9, 138.40, 138.26, 135.57, 135.54, 133.2, 130.0, 128.78, 128.66, 128.0, 127.4, 117.79, 117.74, 70.2, 66.8, 66.47, 66.43, 49.31, 49.28, 46.35, 46.32, 42.8, 28.9, 28.5, 23.6, 21.8

IR 2959 (m), 2924 (m), 2858 (m), 1738 (s), 1648 (s), 1598 (w), 1494 (w), 1454 (s), 1435 (s), 1357 (s), 1271 (s), 1242 (s), 1176 (s), 1115 (s), 1069 (w), 1030 (m), 935 (br m), 818 (m), 762 (m), 702 (m), 664 (m), 577 (m), 555 (m), 524 (w) cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{27}H_{33}NNaO_7S$ $(M+Na)^+$ 538.1870, found 538.1871

b-lactam 1.191



A 100 mL pear-shaped flask containing **1.178** (0.3046 g, 1 mmol, 1 equiv) in THF (20 mL, 0.05 M) was cooled to −78 °C. *n*-BuLi (3.1 mL, 4 mmol, 4 equiv) was added via syringe and the reaction mixture stirred for 1 h. It was then quenched with MeOH (2−4 mL) and $NH_4Cl_{(aq.)}$ (5 mL). The flask was allowed to warm to room temperature and the reaction mixture diluted with Et_2O (10 mL) and H_2O (15 mL). The phases were separated, and the aqueous layer was extracted with Et_2O (2 x 10 mL) and EtOAc (1 x 15 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification occurred via preparative thin-layer chromatography. This afforded samples of both diastereomers of **1.191**.

diastereomer 1: ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.38-7.18 (m, 5H), 6.54 (d, *J* = 15.9 Hz, 1H), 6.27 (dt, *J* = 15.5, 7.6 Hz, 1H), 3.82 (dd, *J* = 13.4, 4.8 Hz, 1H), 3.66 (br s, 1H), 3.36 (dd, *J* = 10.8, 4.7 Hz, 1H), 2.79 (ddd, *J* = 14.3, 7.1, 1.1 Hz, 1H), 2.74-2.66 (m, 2H), 1.93-1.89 (m, 1H), 1.76 (dq, *J* = 12.8, 3.9 Hz, 1H), 1.66-1.59 (m, 2H), 1.49-1.36 (m, 2H)

^{13}C-NMR (101 MHz; $CDCl_3$): δ 169.7, 137.1, 134.5, 128.7, 127.6, 126.5, 123.4, 85.6, 58.7, 39.5, 38.6, 24.75, 24.57, 21.6

IR 3341 (br m), 2939 (m), 2858 (w), 1725 (s), 1439 (w), 1447 (m), 1417 (m), 1282 (w), 1223 (w), 1151 (w), 1083 (m), 969 (m), 830 (w), 750 (m), 693 (m) cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{16}H_{19}NNaO_2$ $(M+Na)^+$ 280.1308, found 280.1309

diastereomer 2: ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.40-7.36 (m, 2H), 7.31-7.28 (m, 2H), 7.23-7.17 (m, 1H), 6.54 (d, *J* = 15.9 Hz, 1H), 6.31 (ddd, *J* = 15.9, 8.1, 6.3 Hz, 1H), 3.80 (dd, *J* = 13.0, 3.9 Hz, 1H), 3.66 (br s, 1H), 3.46 (dt, *J* = 7.1, 3.6 Hz, 1H), 2.83-2.76 (m, 2H), 2.67-2.62 (m, 1H), 1.92-1.90 (m, 2H), 1.69-1.66 (m, 1H), 1.42-1.35 (m, 3H)

^{13}C-NMR (101 MHz; $CDCl_3$): δ 168.1, 137.0, 134.80, 134.77, 128.6, 127.6, 126.42, 126.35, 123.26, 123.23, 123.19, 86.6, 62.33, 62.29, 38.73, 38.69, 35.4, 26.2, 24.6, 22.1

IR 3344 (br m), 2940 (m), 2857 (w), 1727 (s), 1447 (m), 1421 (m), 744 (m), 693 (m) cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{16}H_{19}NNaO_2$ $(M+Na)^+$ 280.1308, found 280.1311

REFERENCES AND NOTES

[1] For a review of the importance of "redox economy" in total synthesis see: Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem. Int. Ed.* **2009**, *48*, 2854−2867.

[2] Attempts were made to perform a DIBAL reduction directly to the aldehyde in both the prior synthesis of the norsecurinanes and in the present work. The yields were low however, and the product often contaminated with the alcohol.

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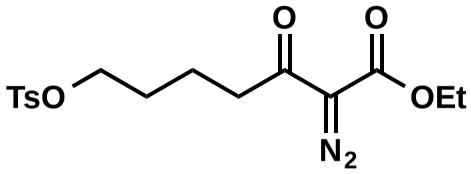
[9] Heitz, M.-P.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 2591−2596.

[10] Kessar, S. V.; Singh, P.; Pal Kaur, N.; Chawla, U.; Shukla, K.; Aggarwal, P.; Venugopal, D. *J. Org. Chem.* **1991**, *56*, 3908−3912.

[11] For the use of basified SiO_2 to purify amines see: Smith, A. B., III; Kim, D.-S. *J. Org. Chem.* **2006**, *71*, 2547−2557.

[12] This was prepared following the procedure described in: Lambert, J. B.; Wharry, S. M. *J. Org. Chem.* **1982**, *47*, 3890−3893.

APPENDIX 1: SPECTRA RELEVANT TO CHAPTER 2



1.141

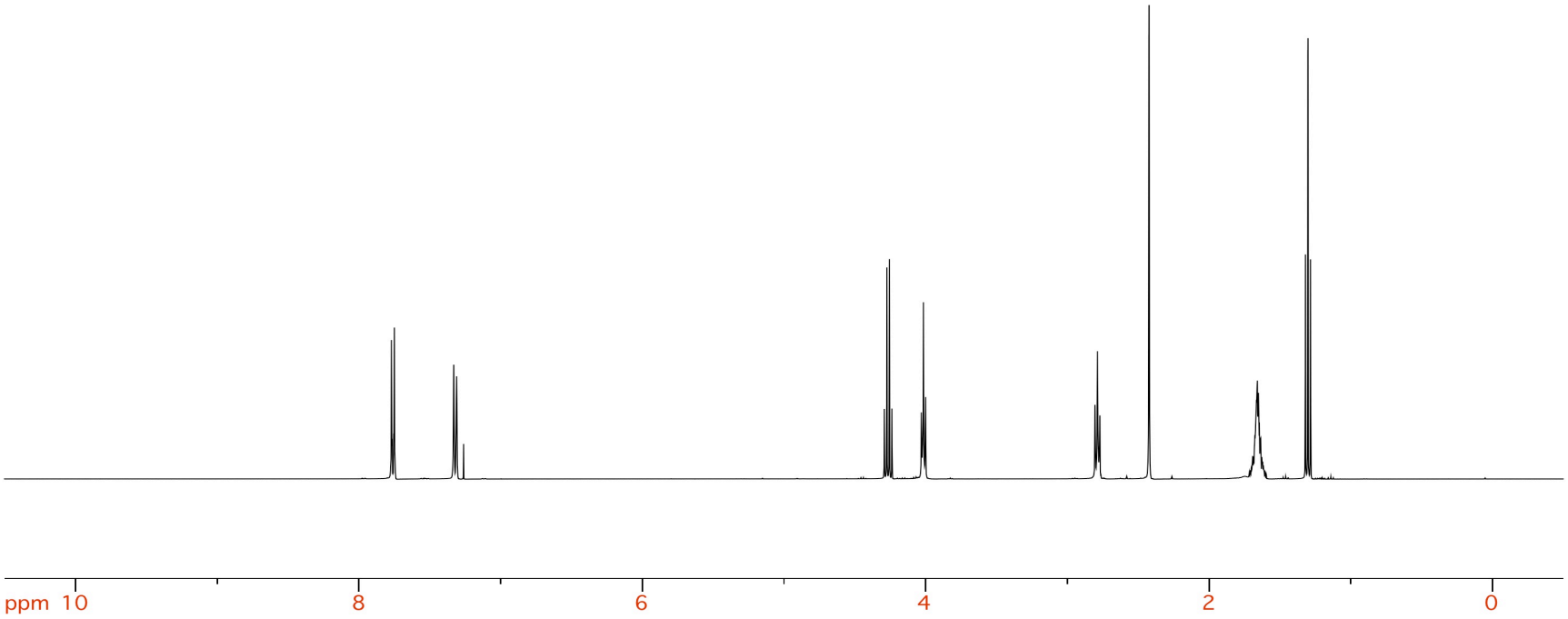


Figure A.1.1a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.141**

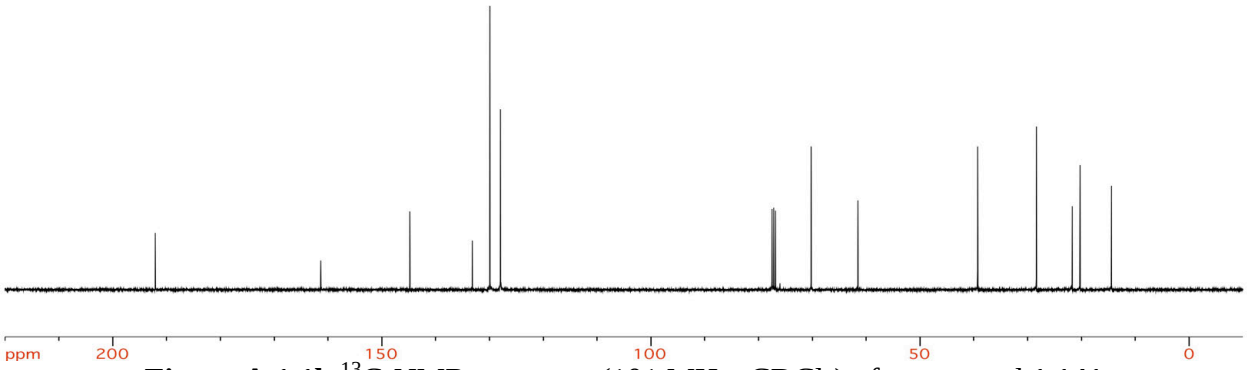


Figure A.1.1b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **1.141**

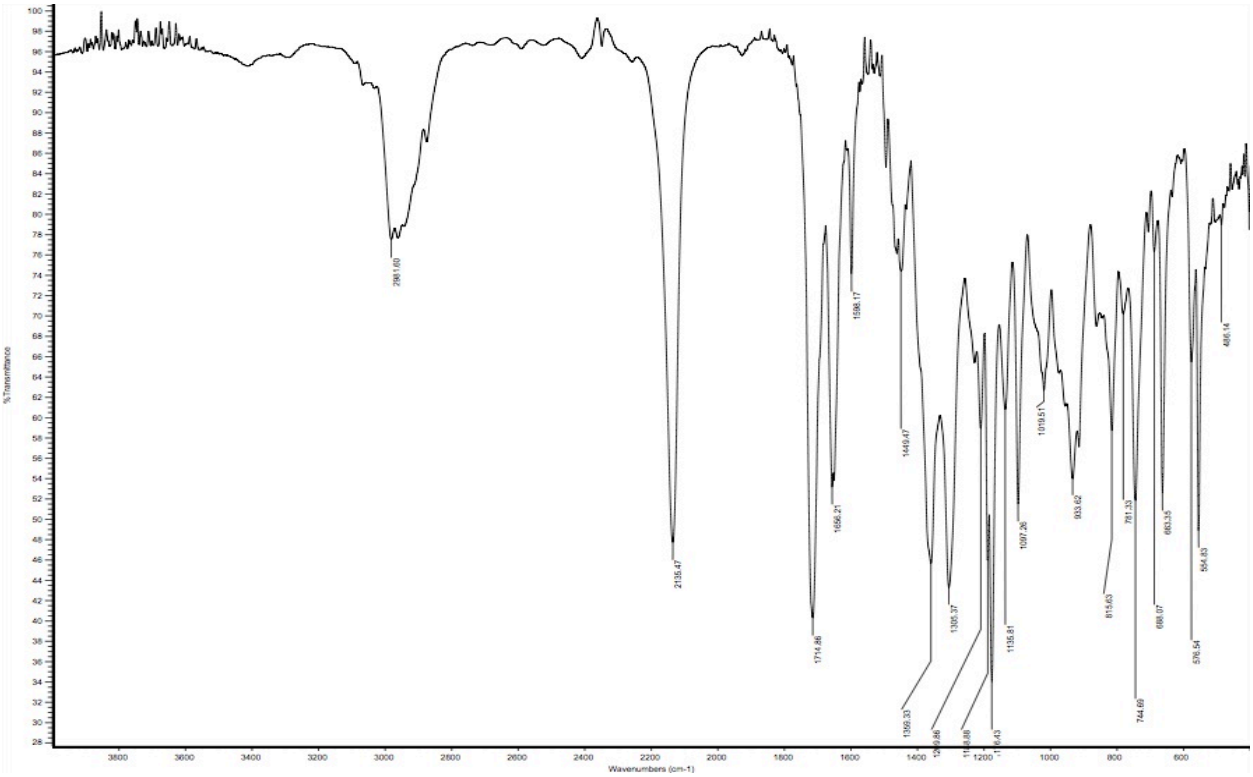


Figure A.1.1c IR spectrum (thin film) of compound **1.141**

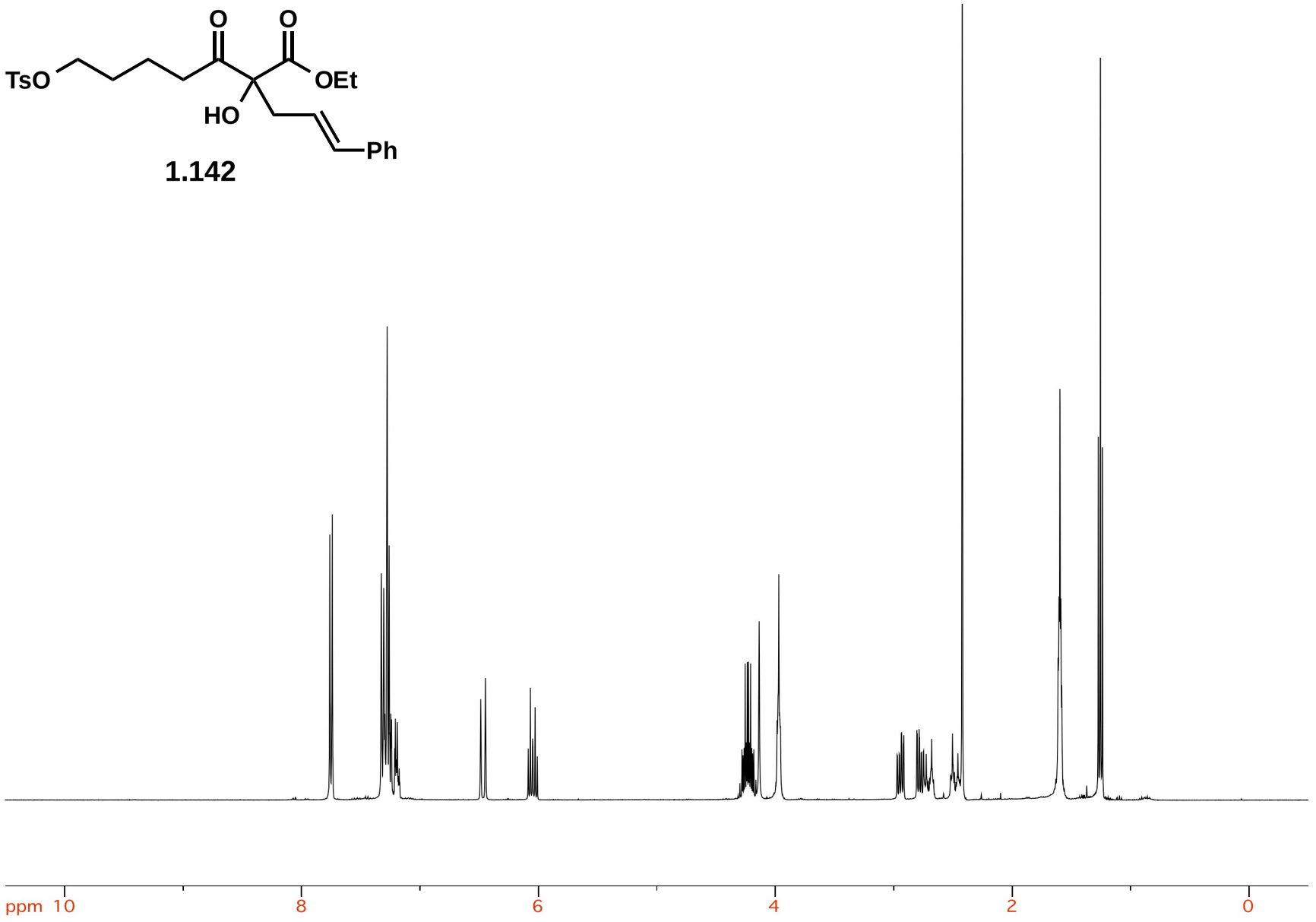


Figure A.1.2a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.142**

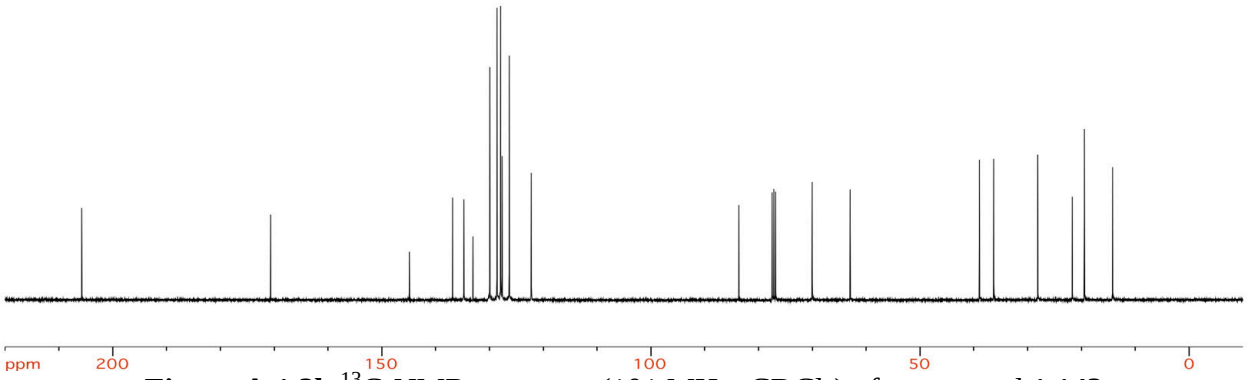


Figure A.1.2b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **1.142**

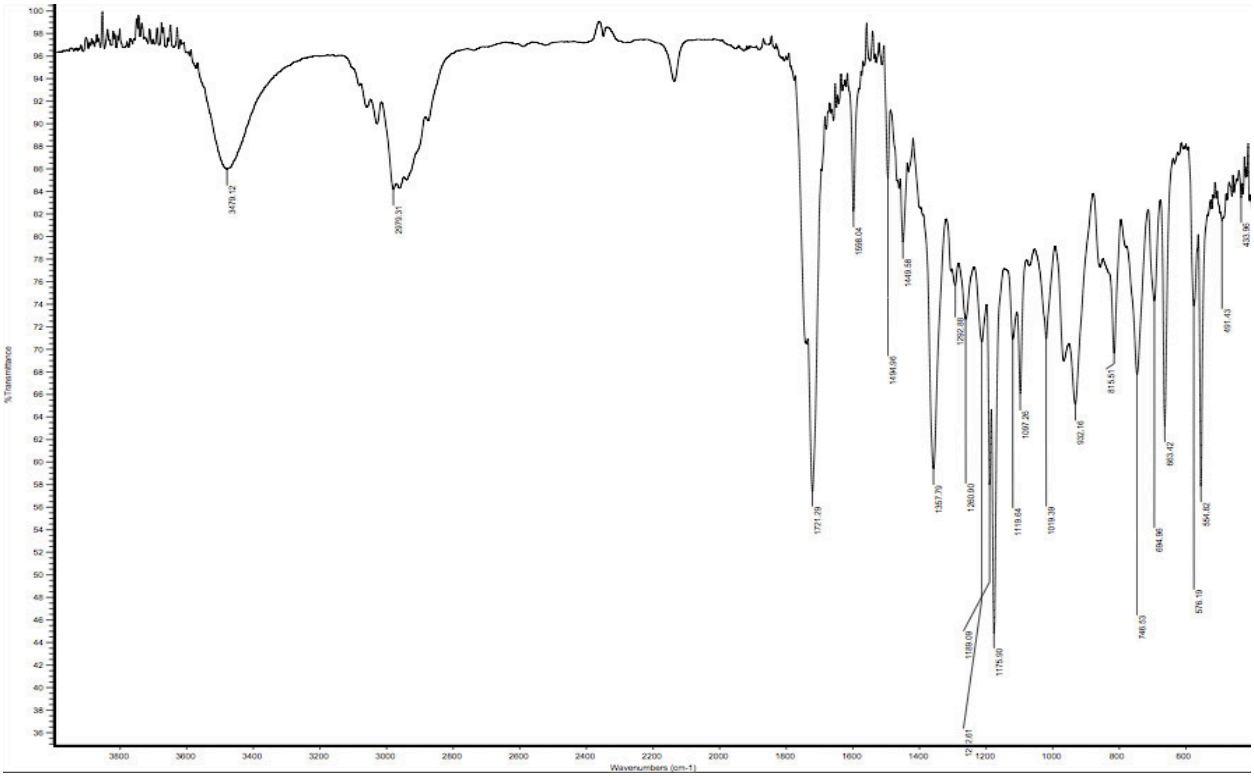
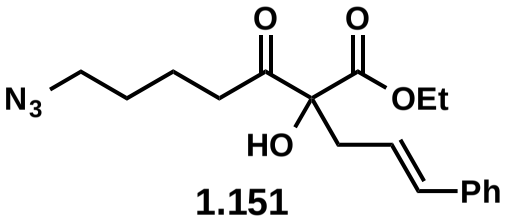


Figure A.1.2c IR spectrum (thin film) of compound **1.142**



1.151

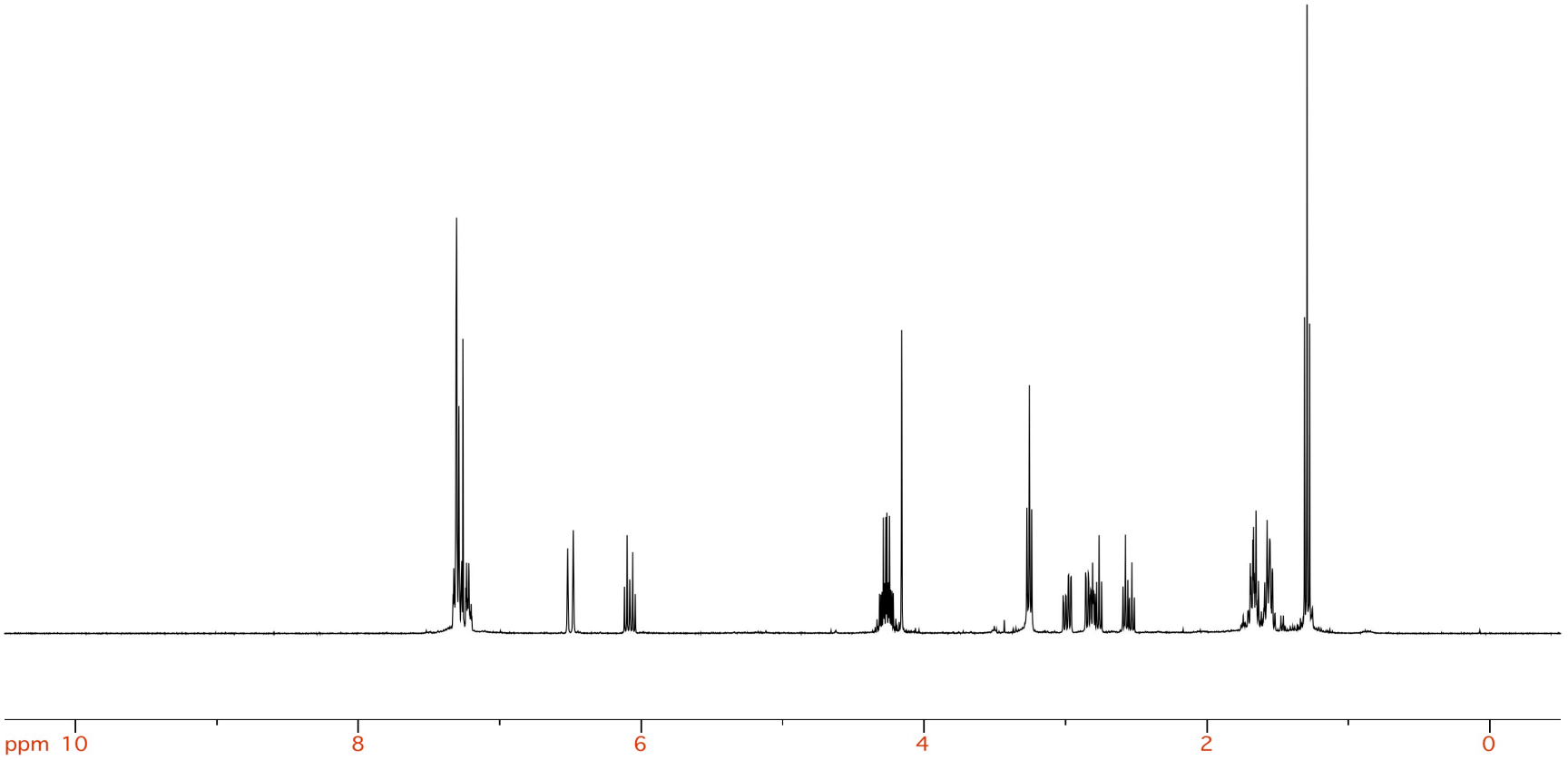


Figure A.1.3a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.151**

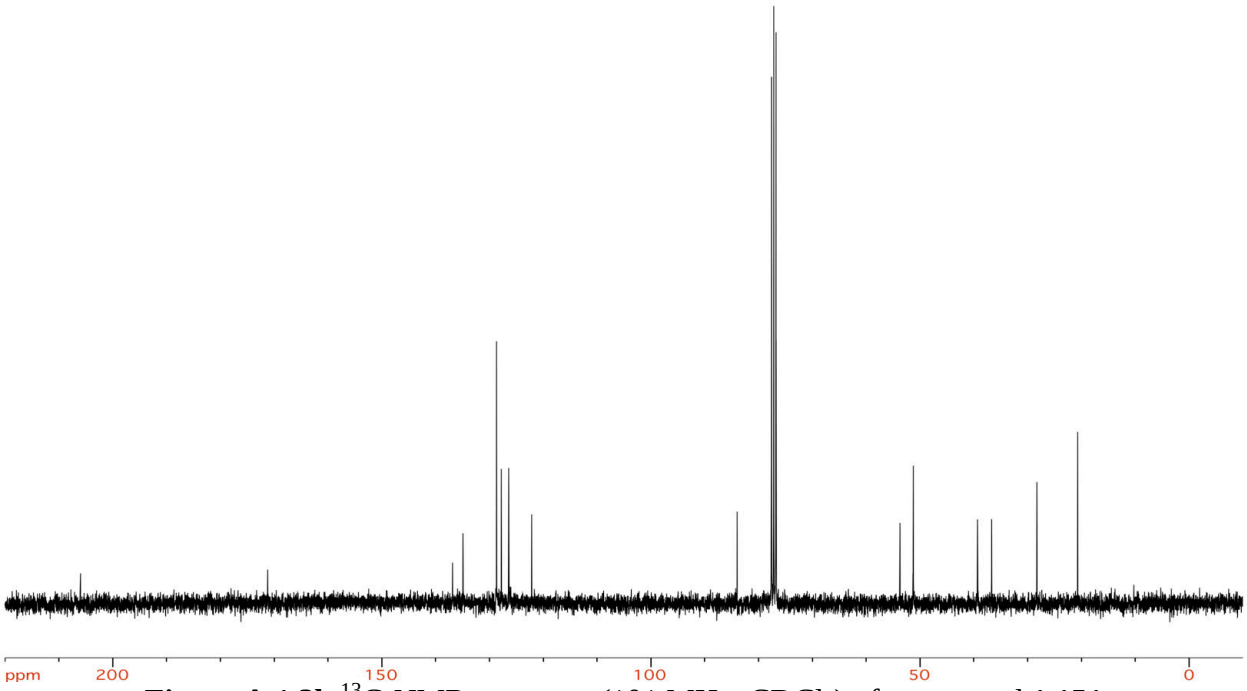


Figure A.1.3b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **1.151**

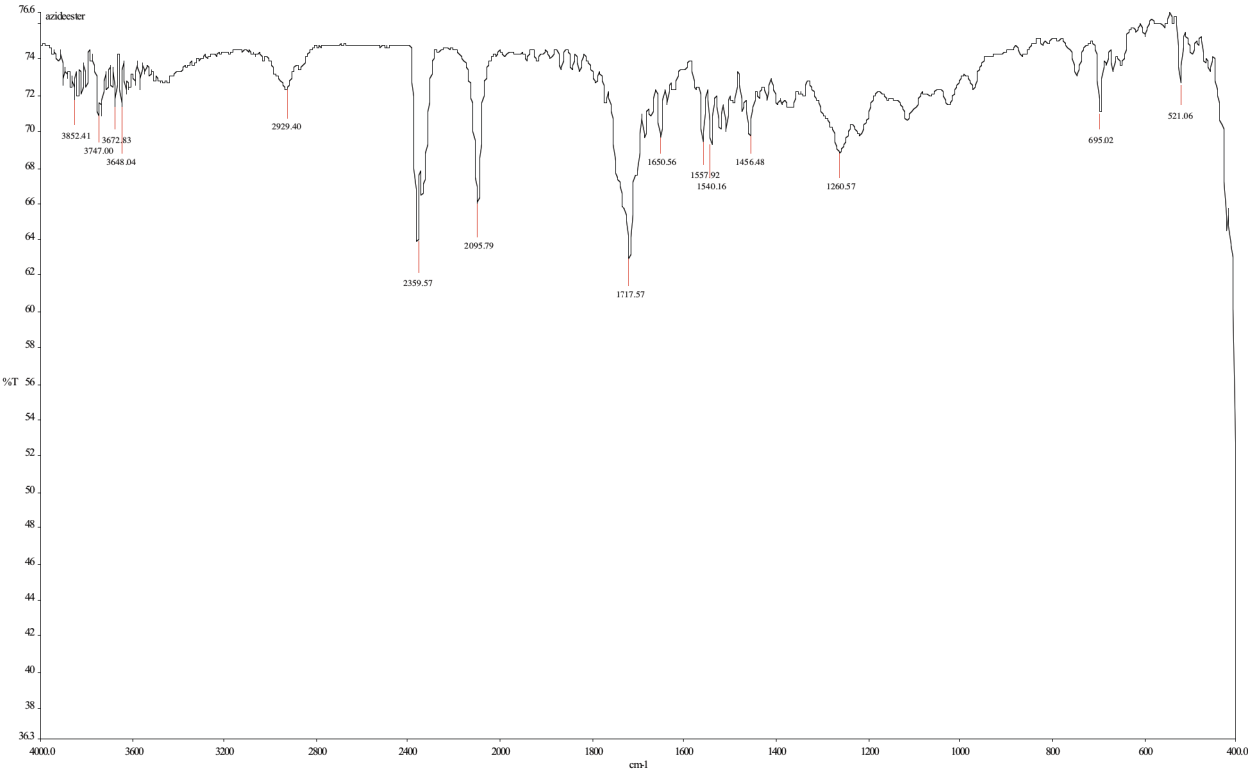
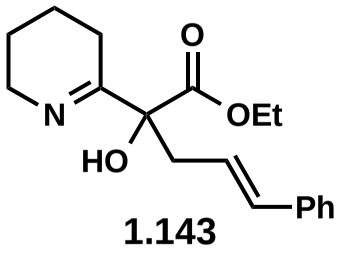


Figure A.1.3c IR spectrum (thin film) of compound **1.151**



1.143

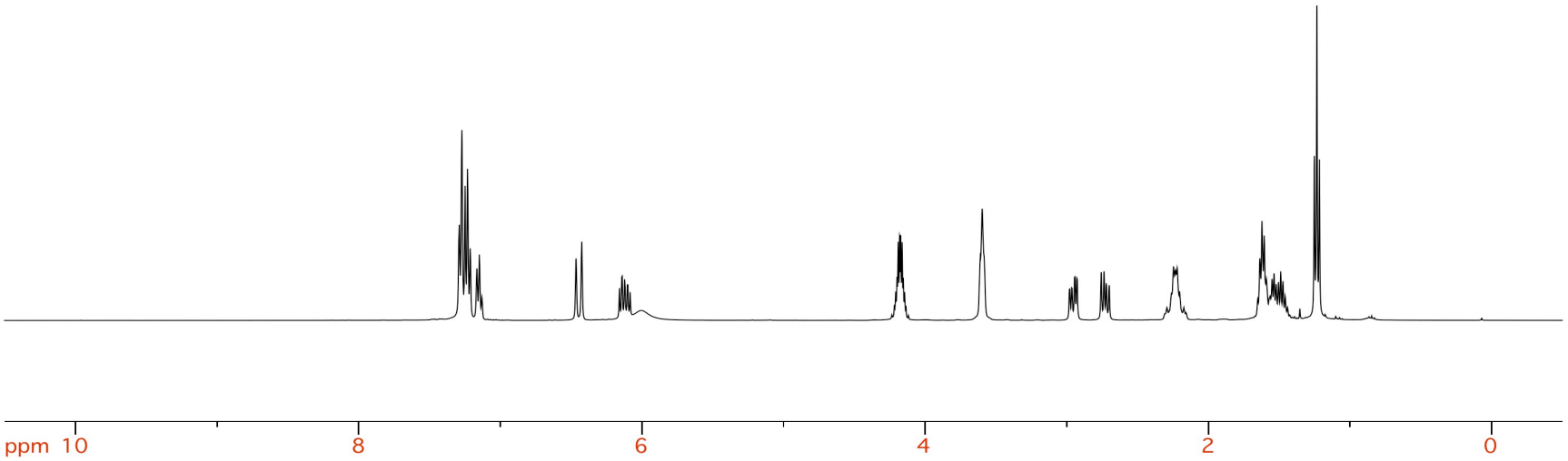


Figure A.1.4a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.143**

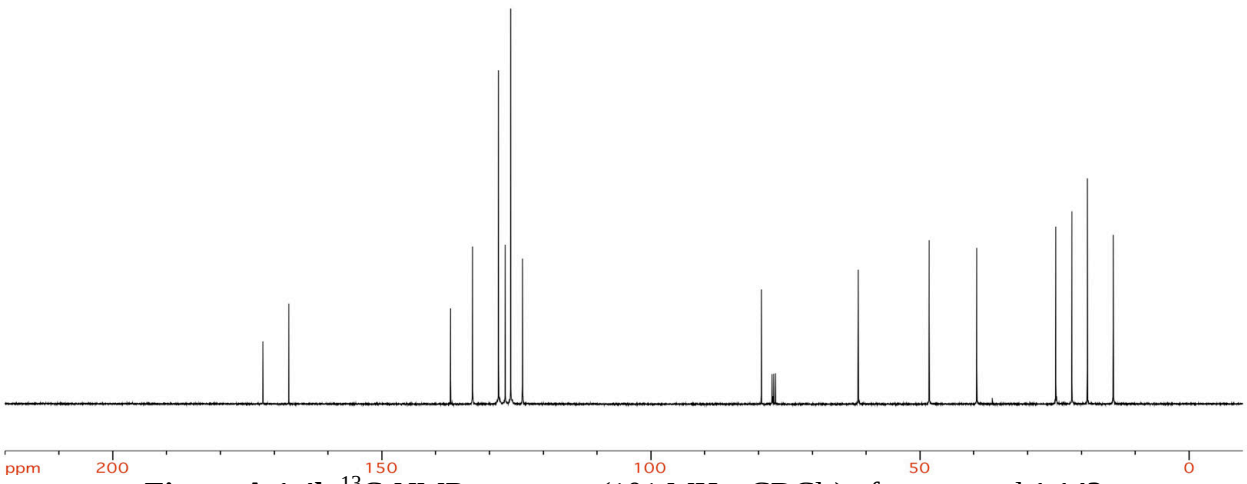


Figure A.1.4b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **1.143**

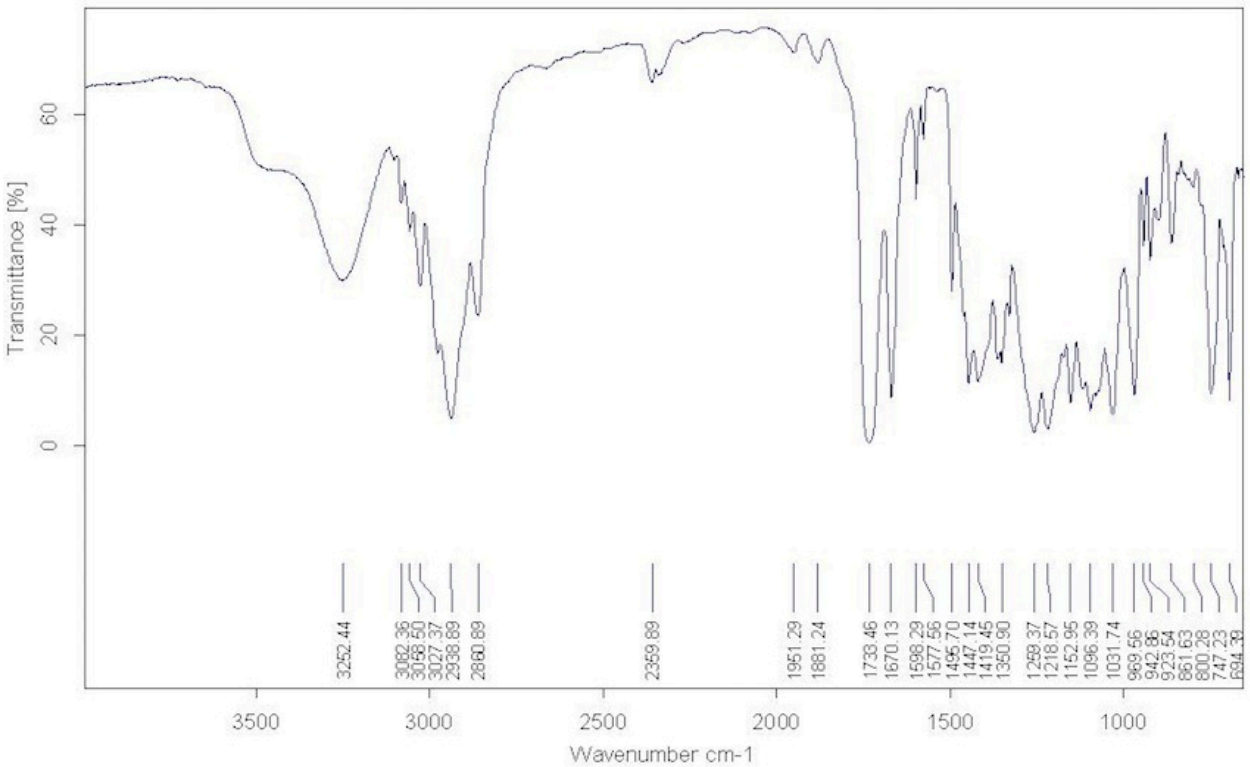
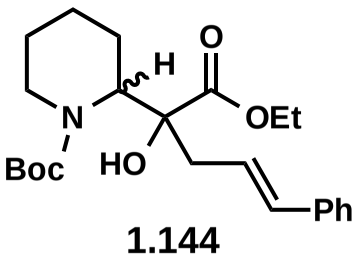


Figure A.1.4c IR spectrum (thin film) of compound **1.143**



1.144

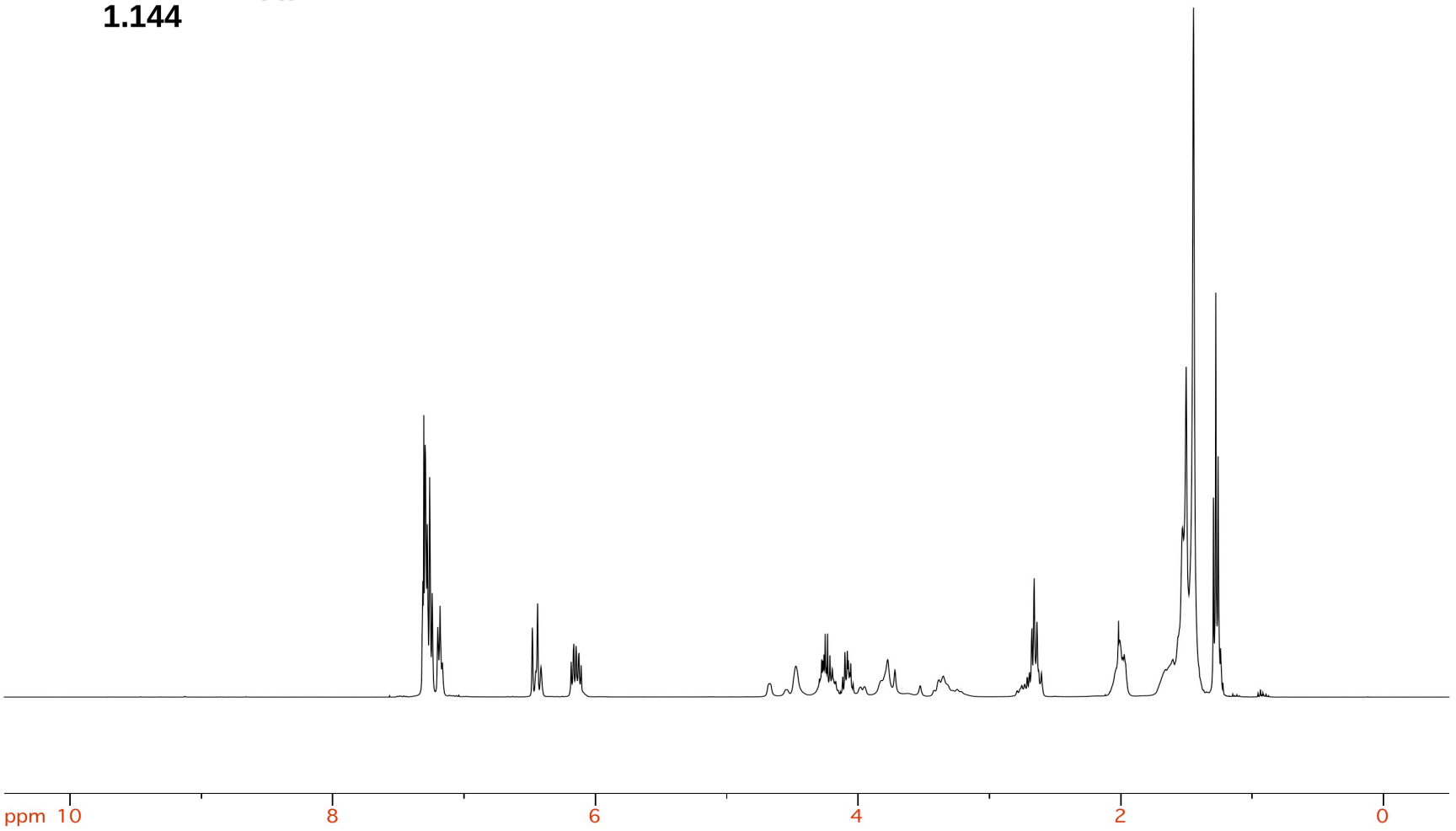


Figure A.1.5a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.144**

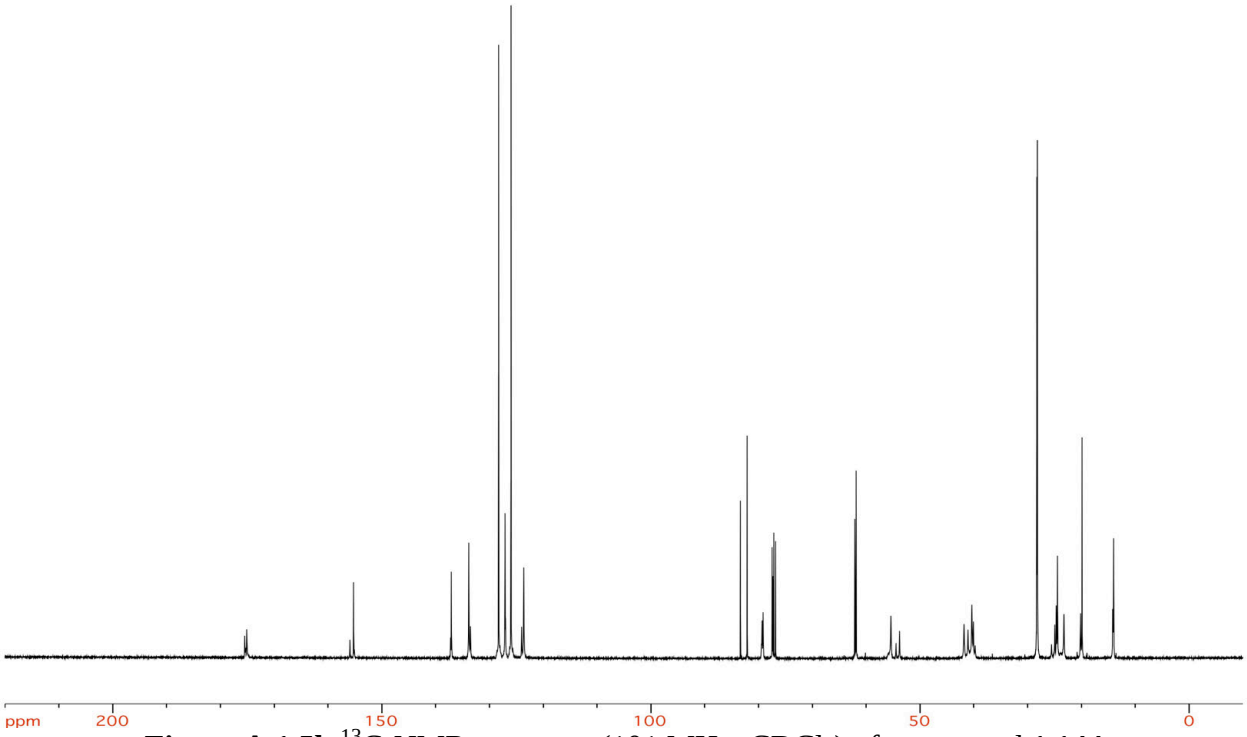


Figure A.1.5b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **1.144**

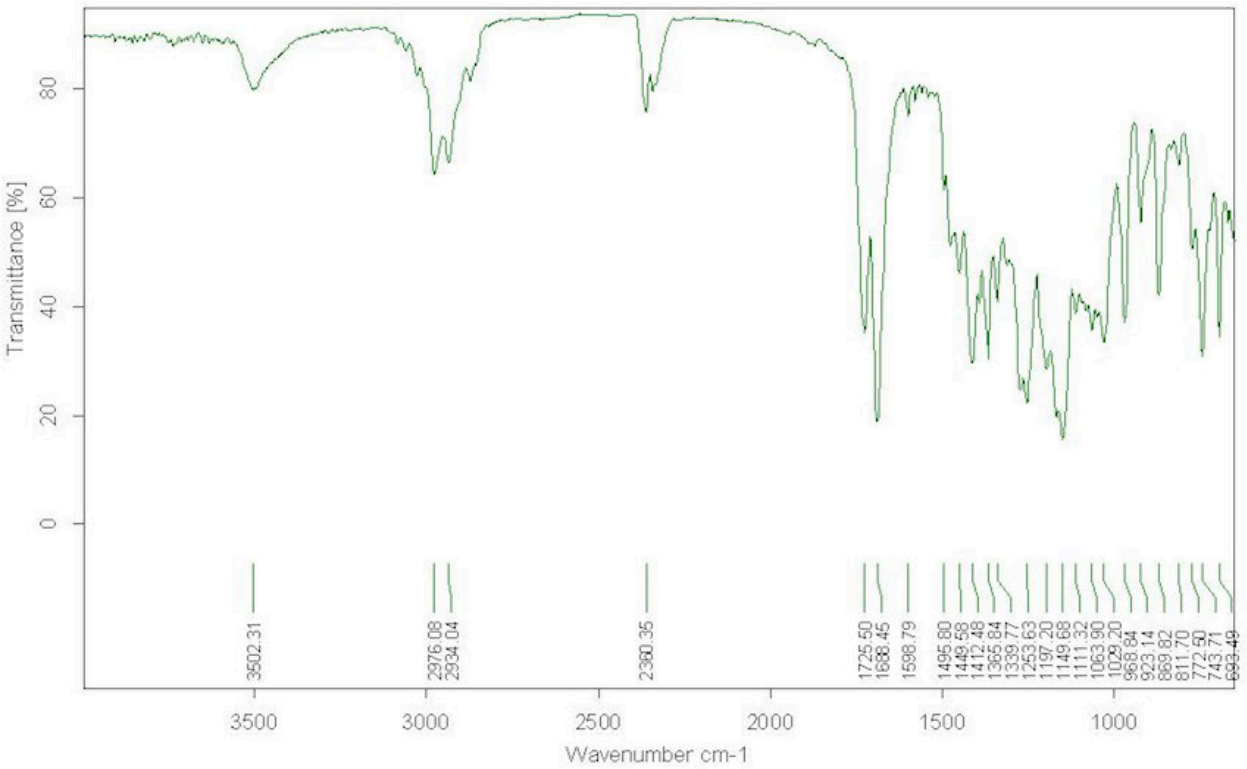
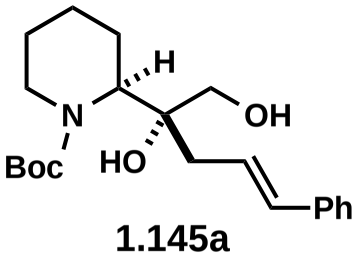


Figure A.1.5c IR spectrum (thin film) of compound **1.144**



1.145a

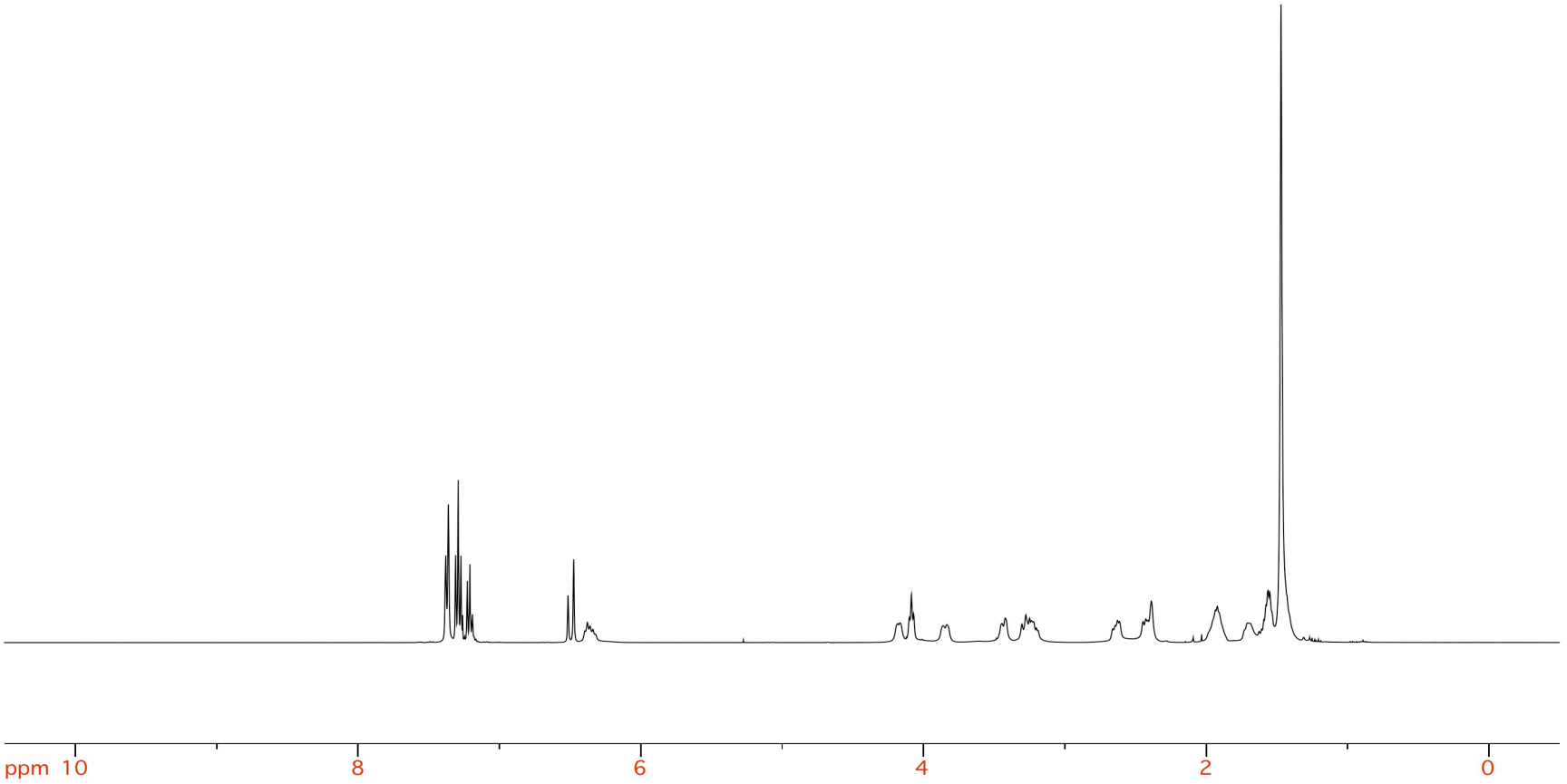


Figure A.1.6a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.145a**

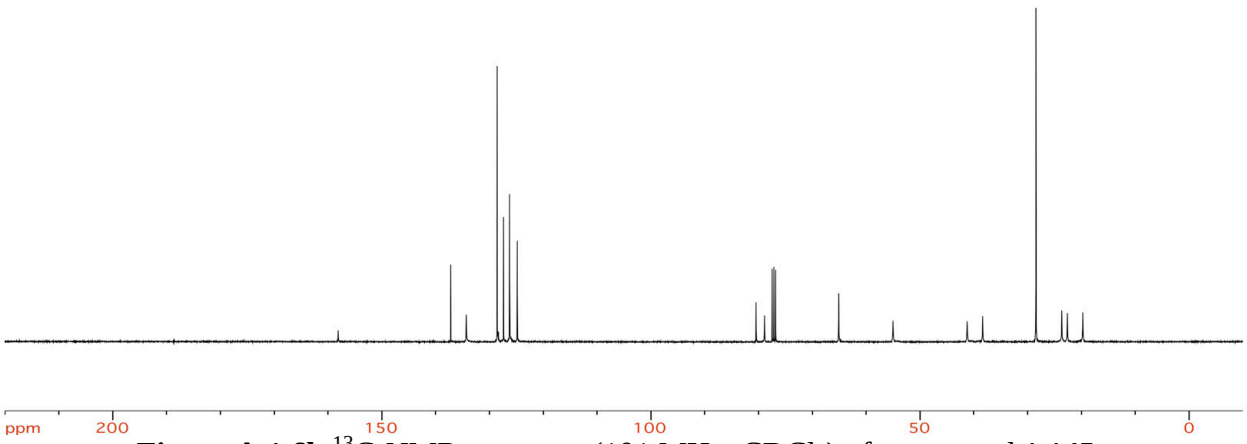


Figure A.1.6b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **1.145a**

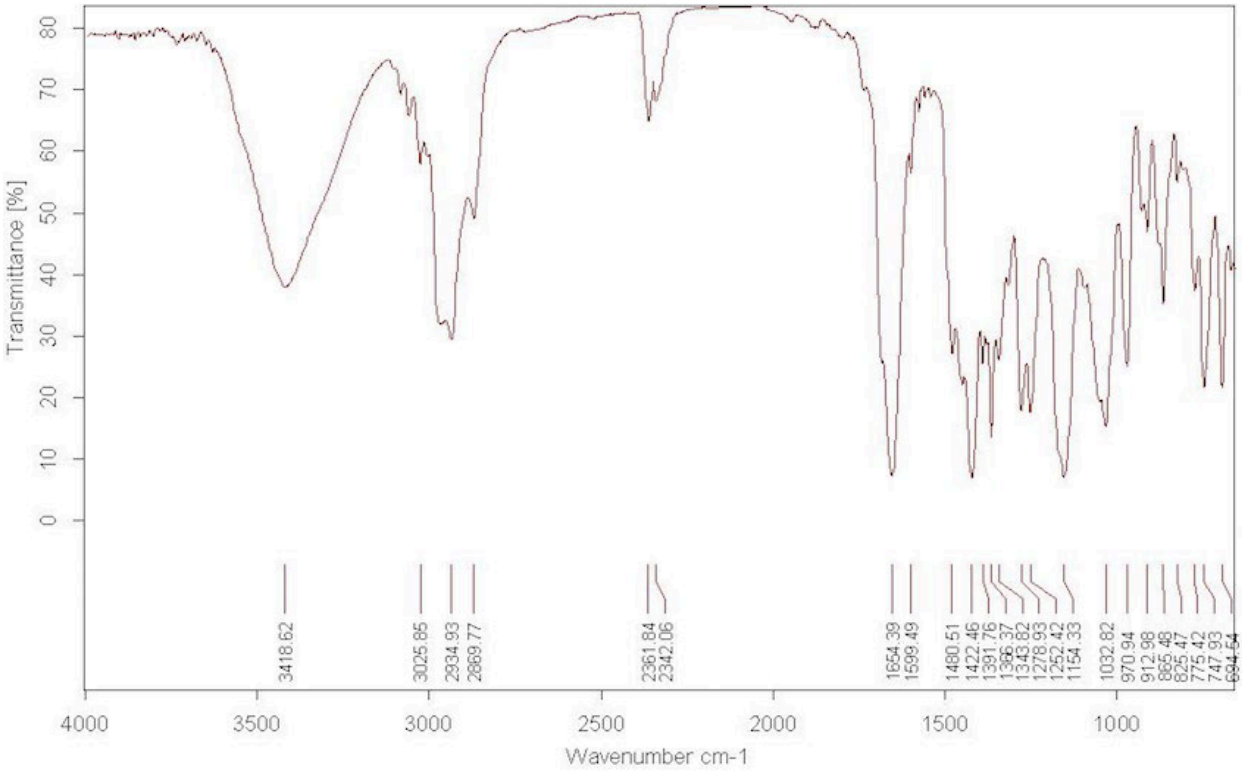
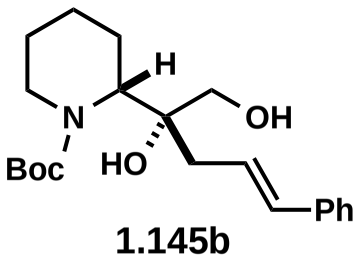


Figure A.1.6c IR spectrum (thin film) of compound **1.145a**



1.145b

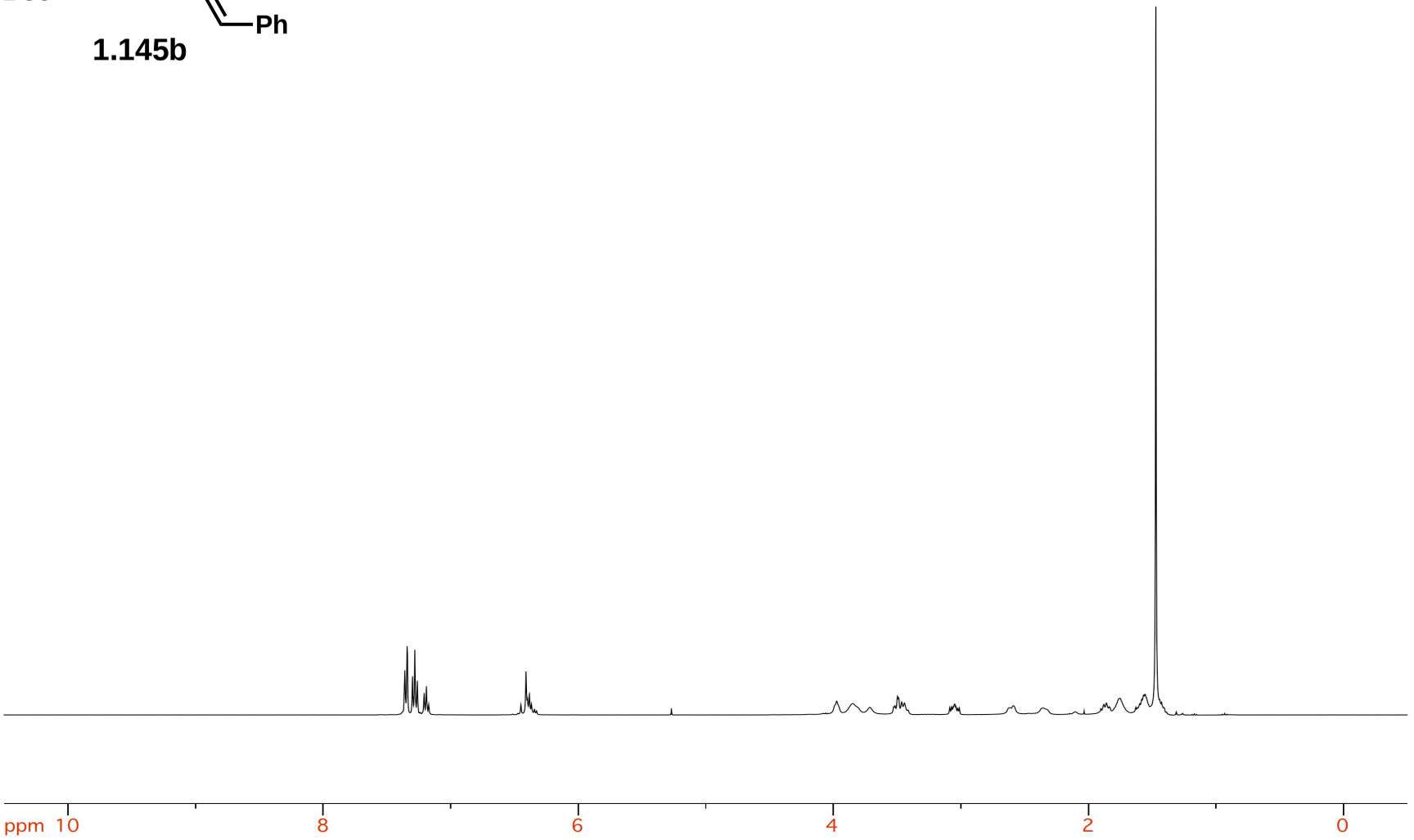


Figure A.1.7a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.145b**

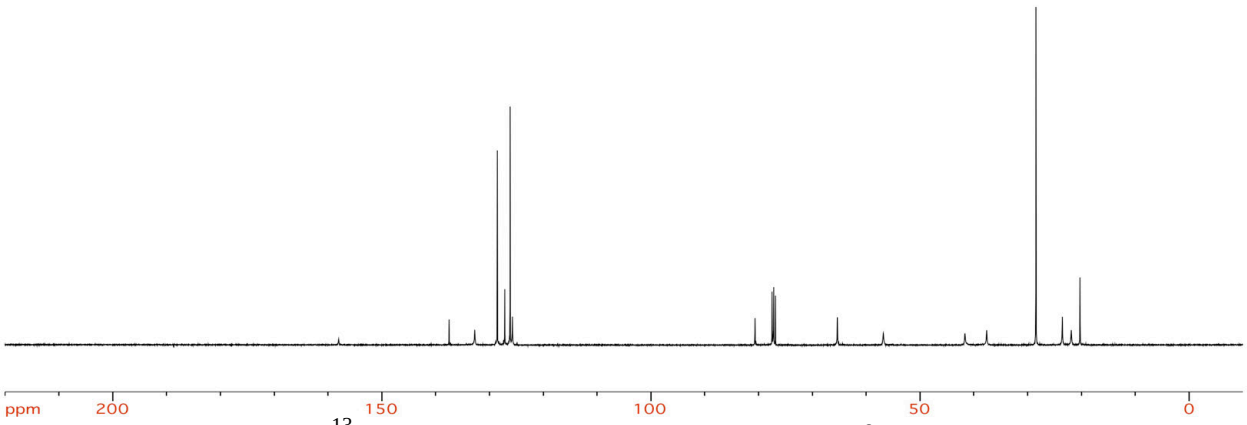


Figure A.1.7b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **1.145b**

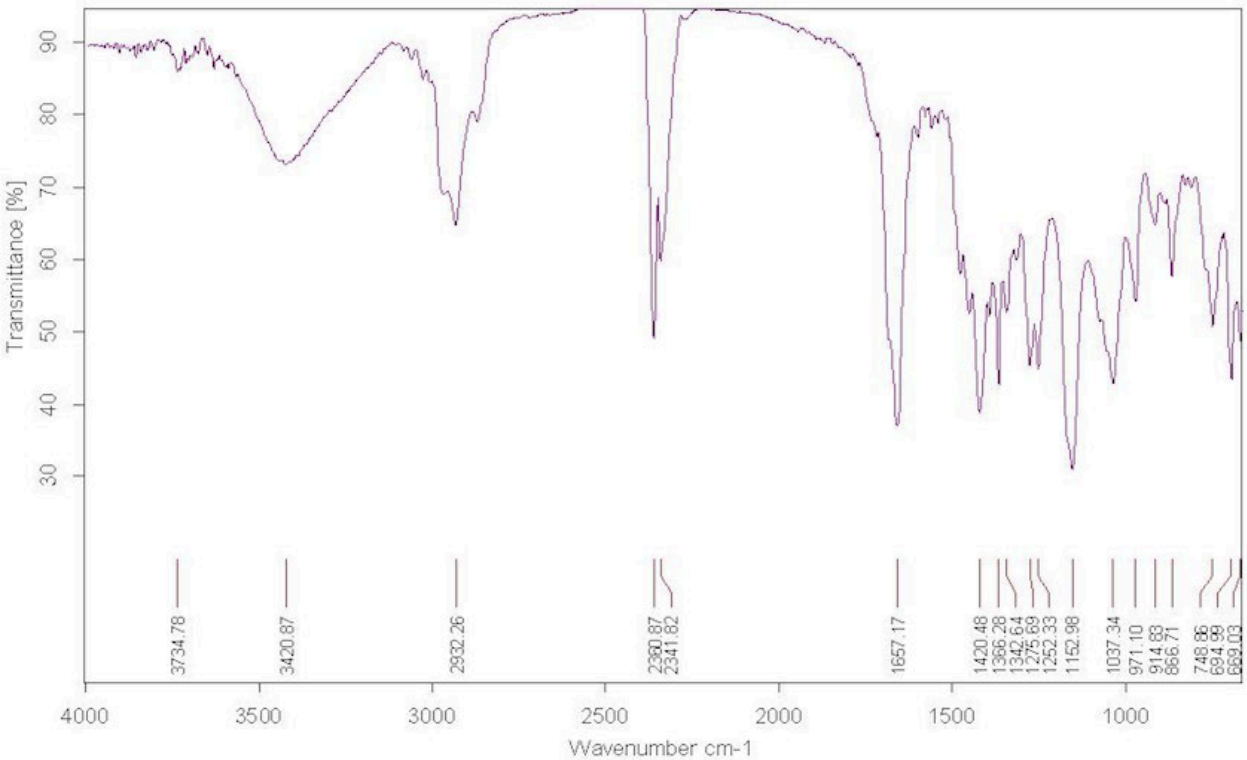
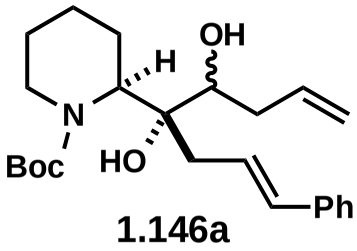


Figure A.1.7c IR spectrum (thin film) of compound **1.145b**



1.146a

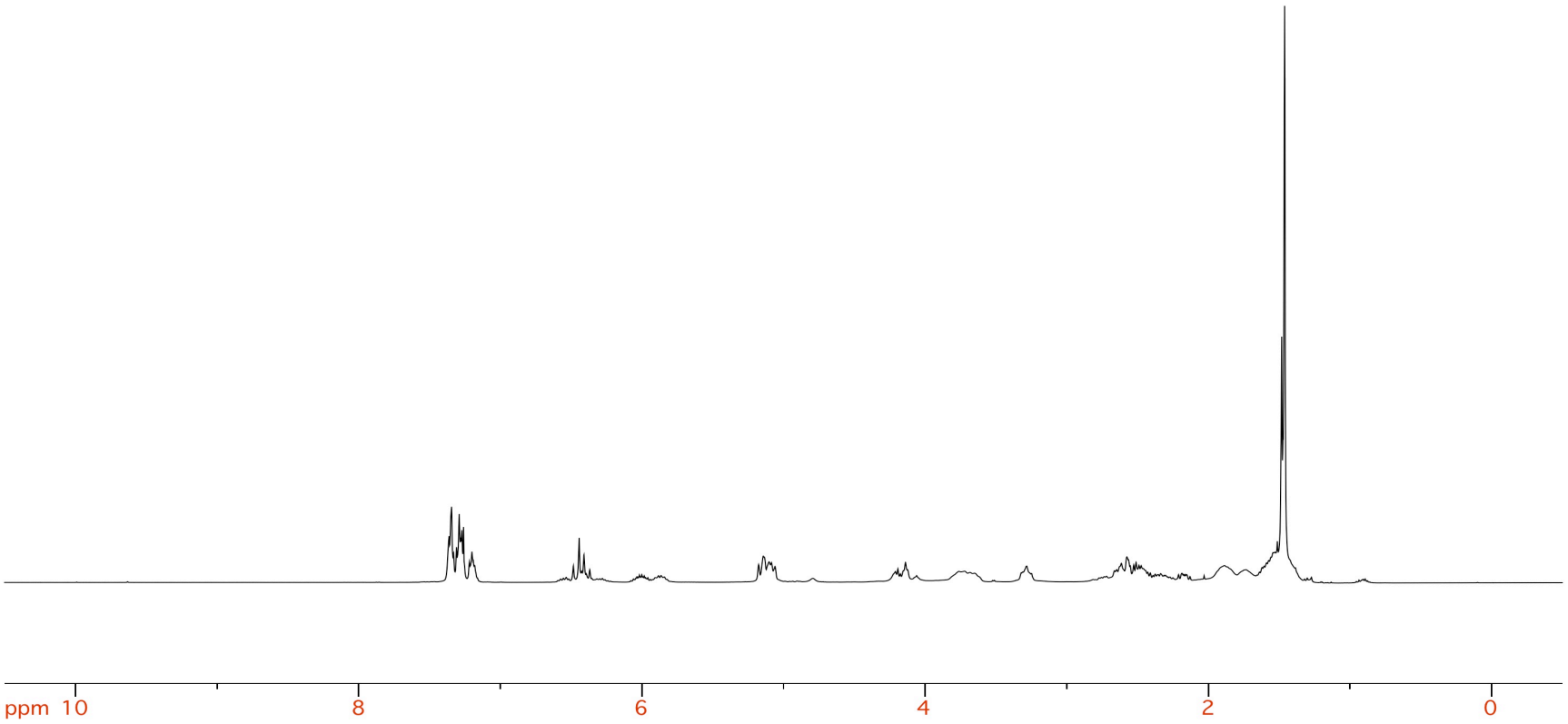


Figure A.1.8a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.146a**

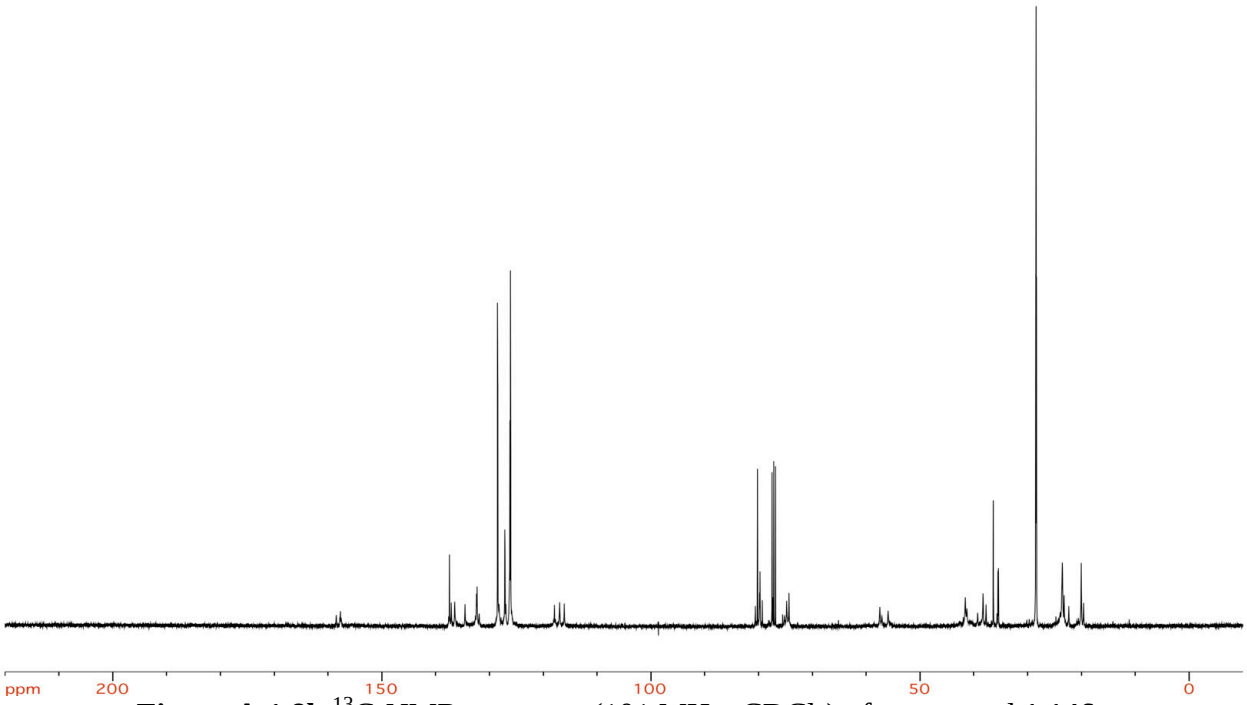


Figure A.1.8b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **1.146a**

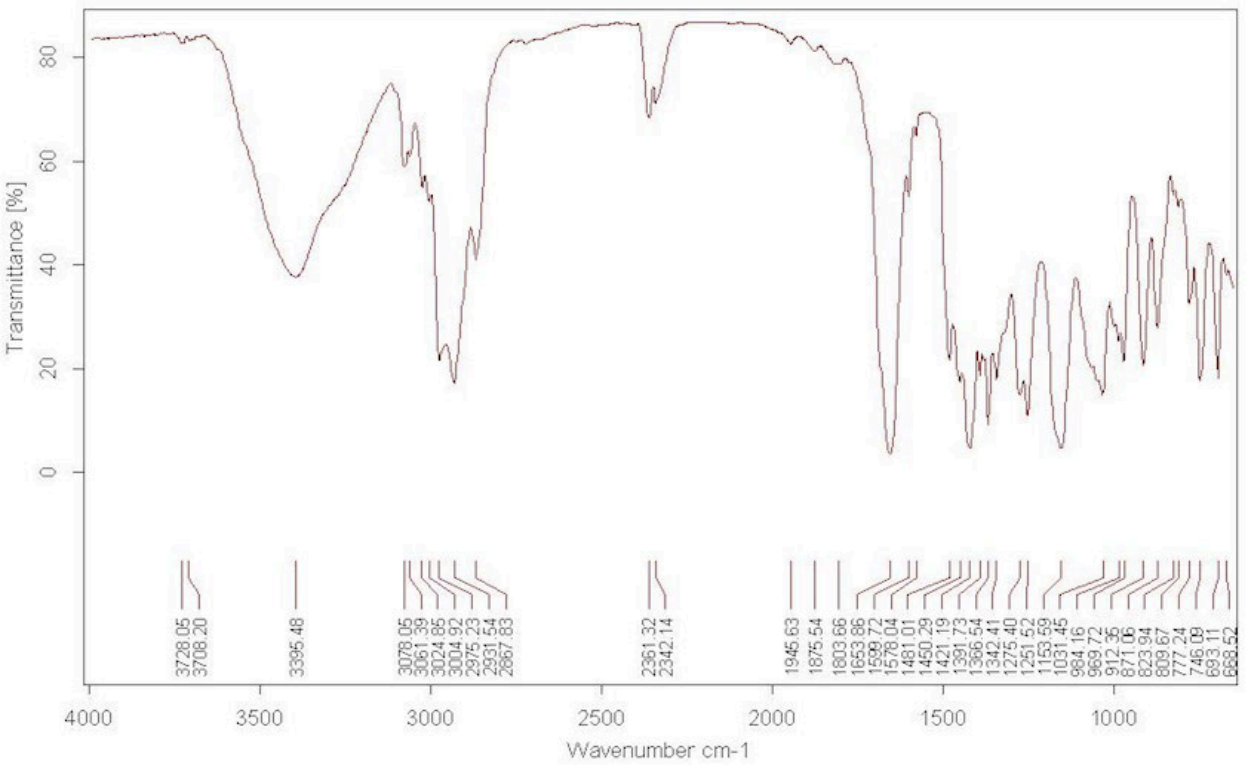
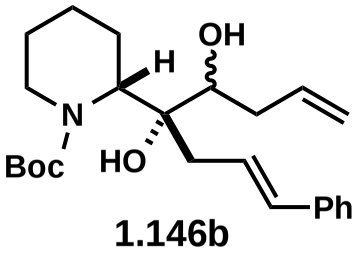


Figure A.1.8c IR spectrum (thin film) of compound **1.146a**



1.146b

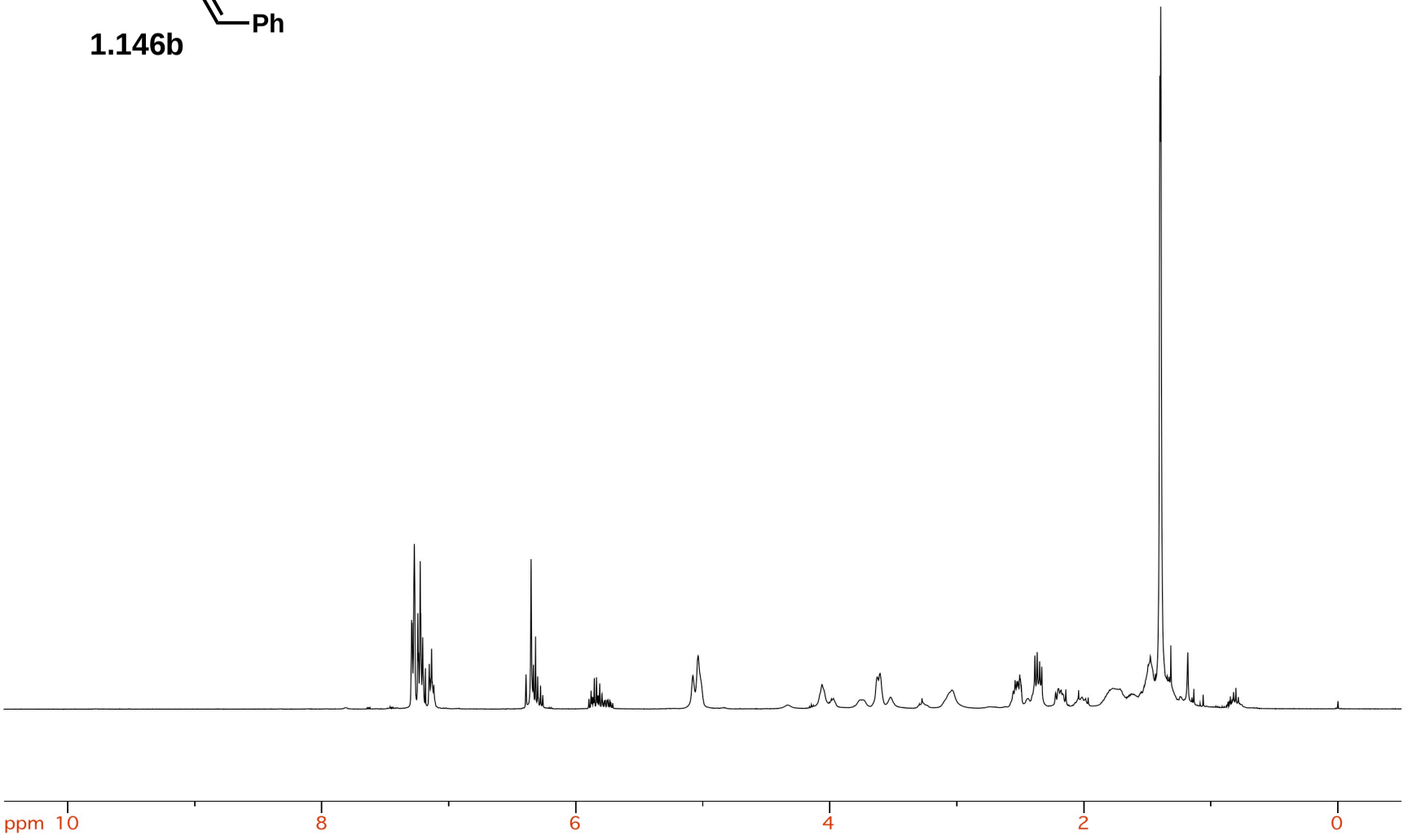


Figure A.1.9a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.146b**

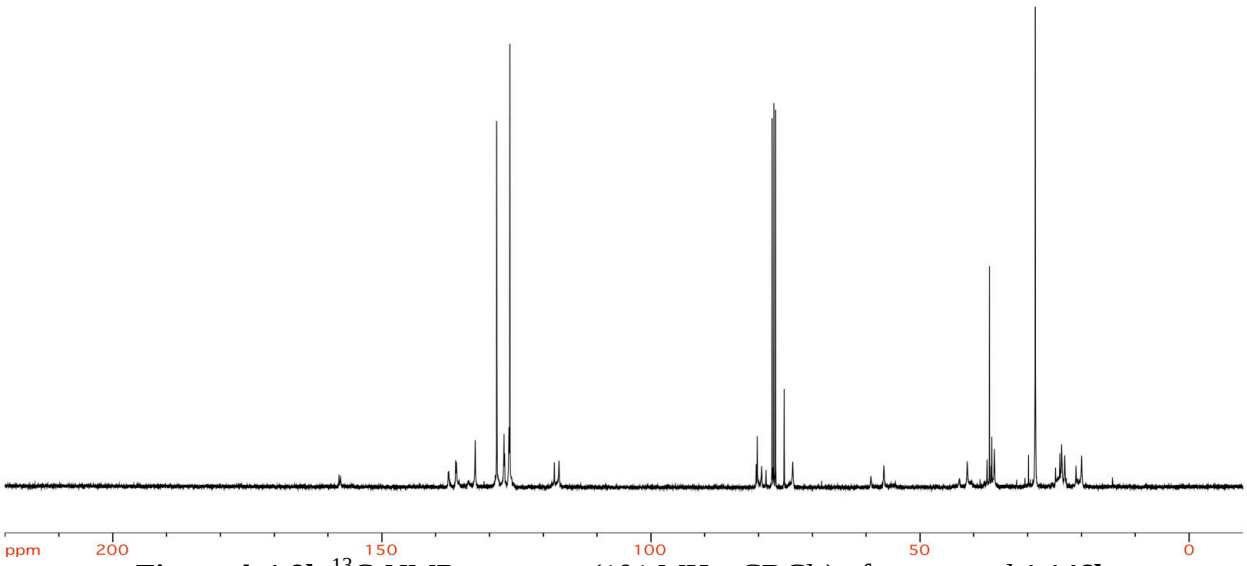


Figure A.1.9b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **1.146b**

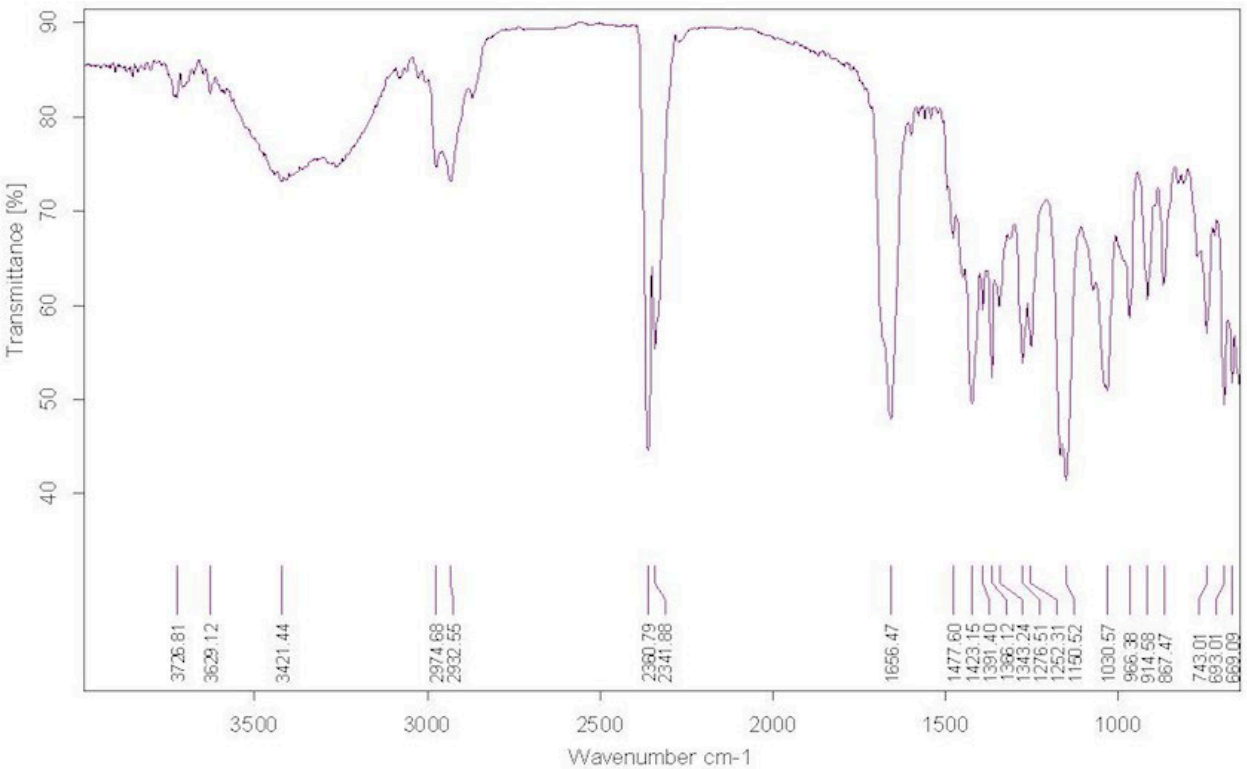
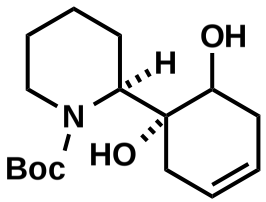


Figure A.1.9c IR spectrum (thin film) of compound **1.146b**



1.147a

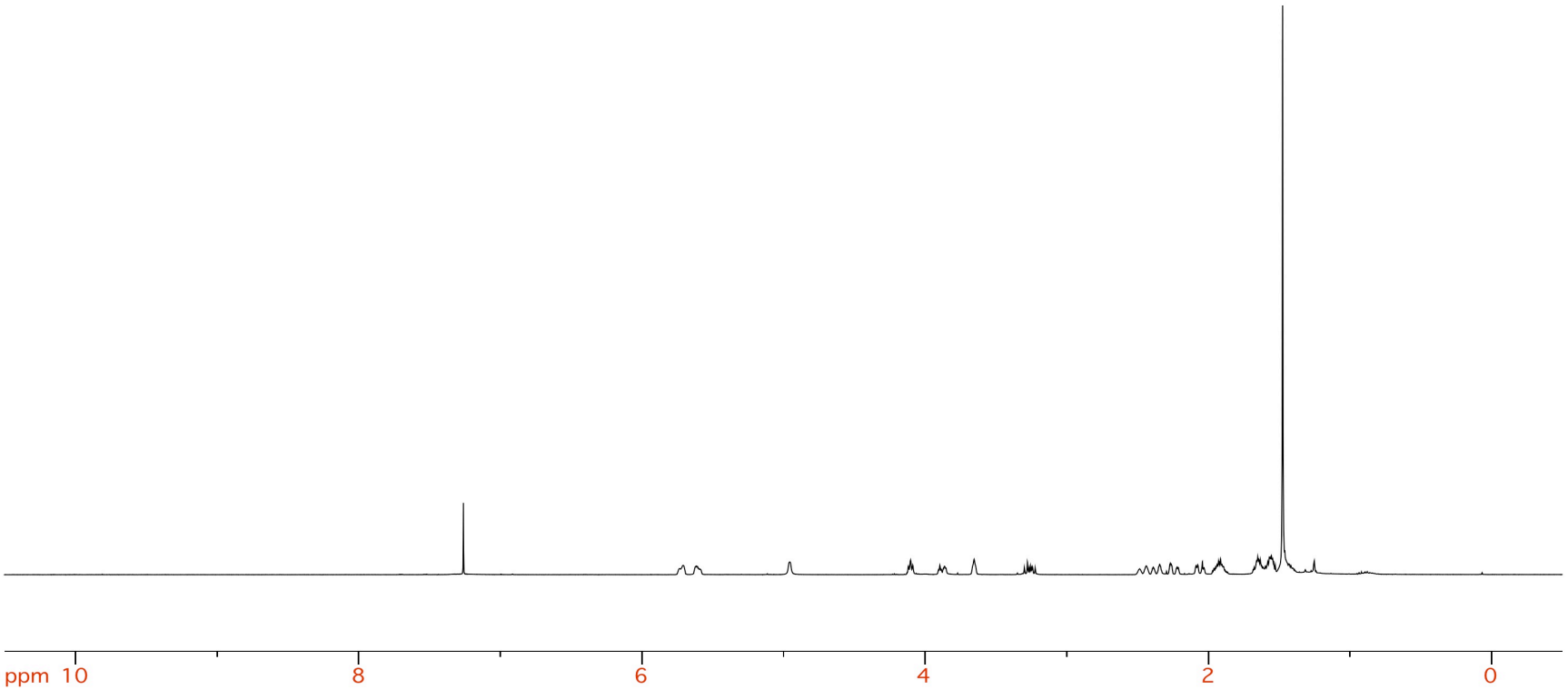


Figure A.1.10a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.147a** (Higher R_f diastereomer)

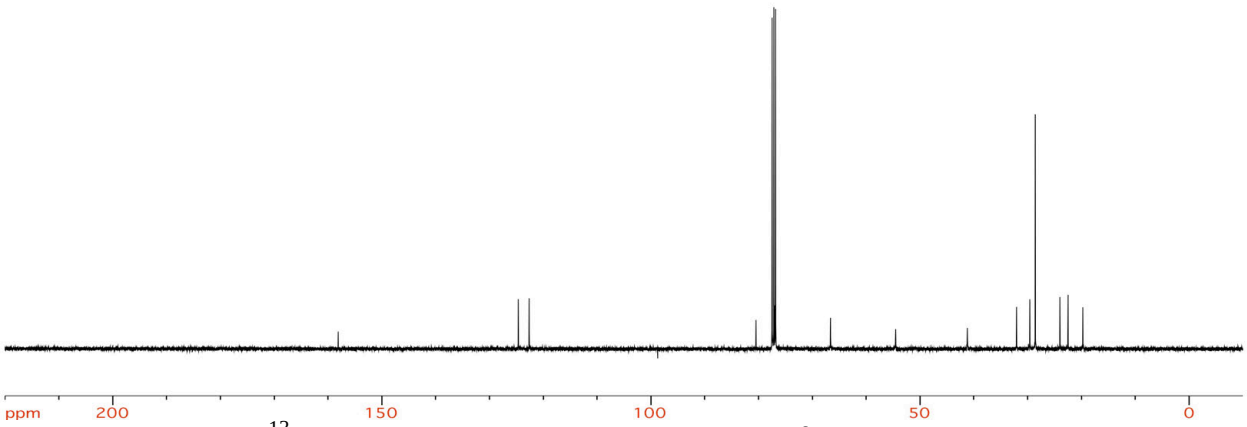


Figure A.1.10b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **1.147a** (Higher R_f diastereomer)

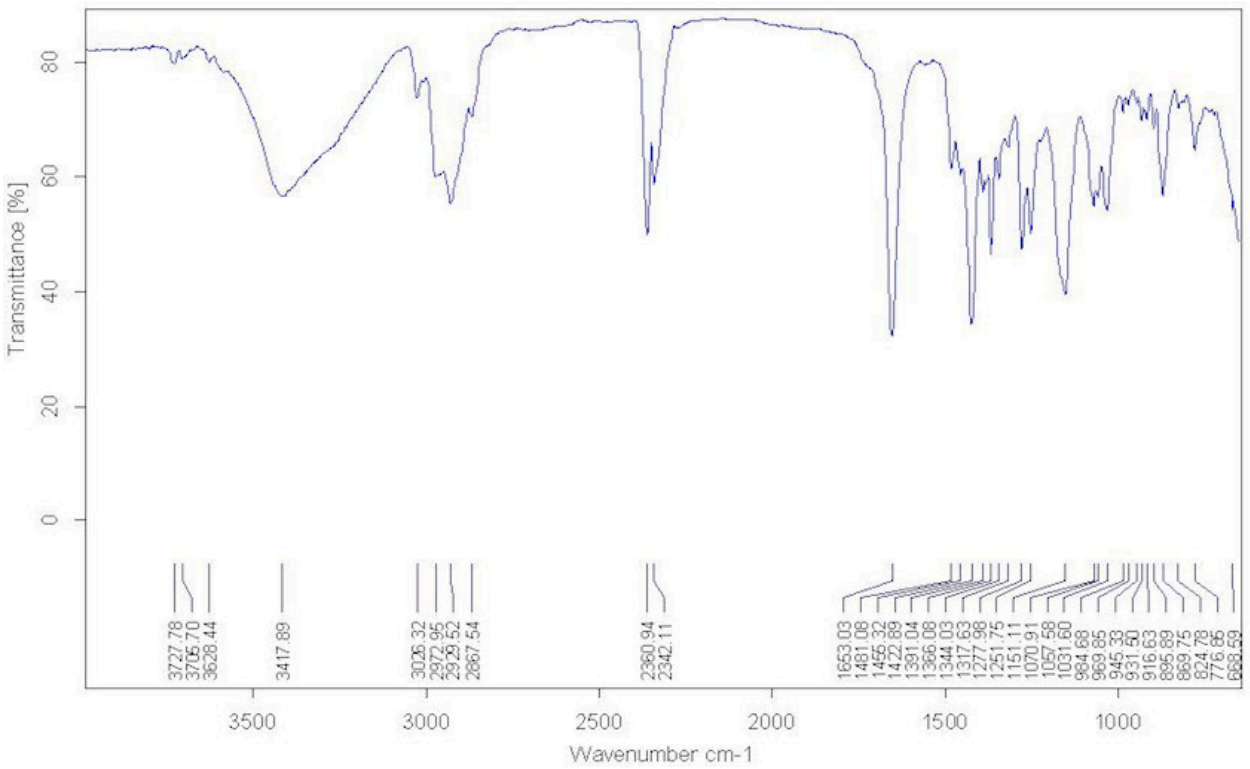
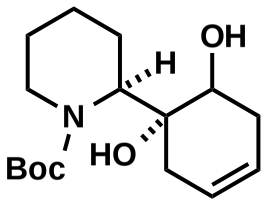


Figure A.1.10c IR spectrum (thin film) of compound **1.147a** (Higher R_f diastereomer)



1.147a

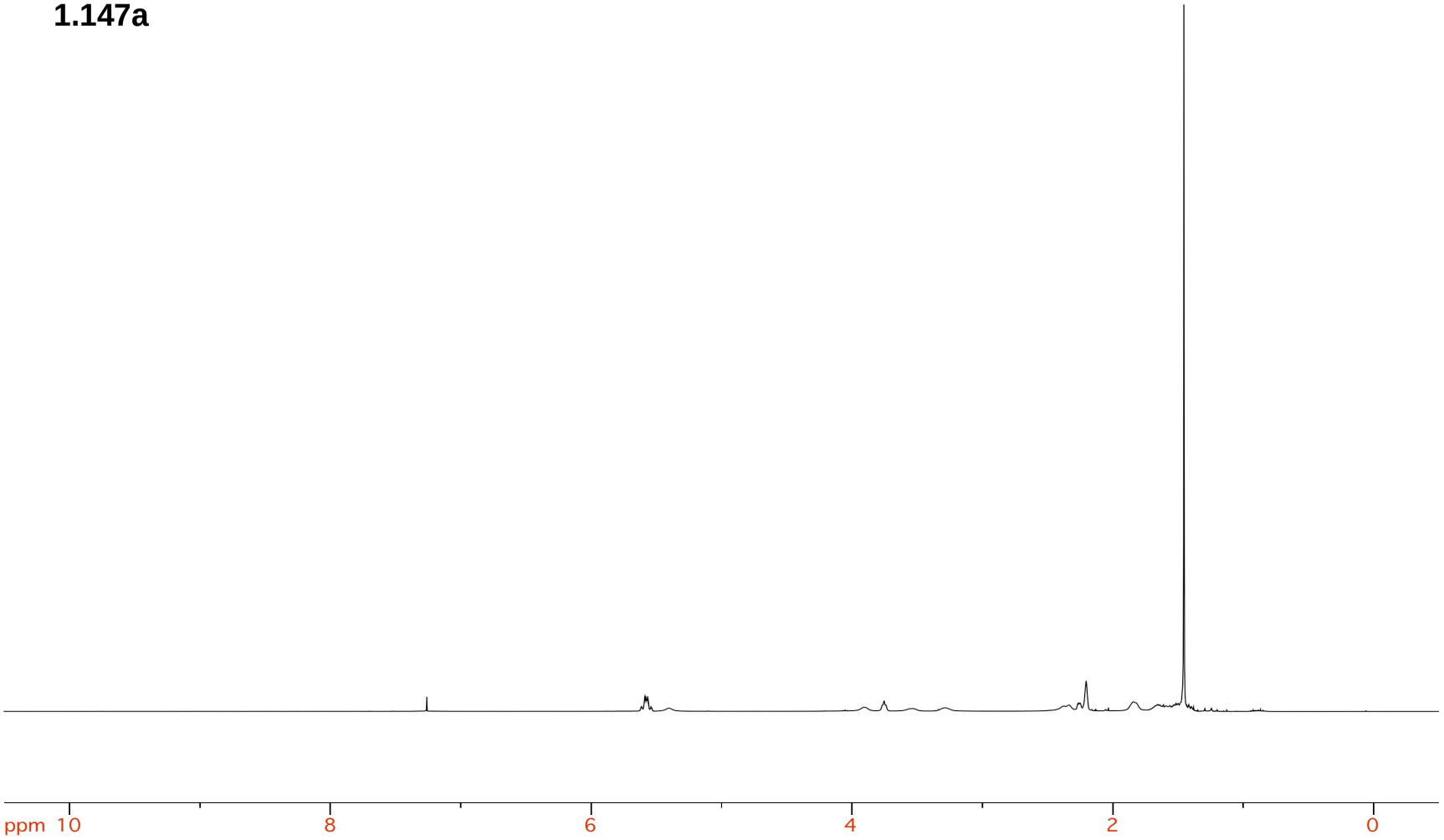


Figure A.1.11a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.147a** (Lower R_f diastereomer)

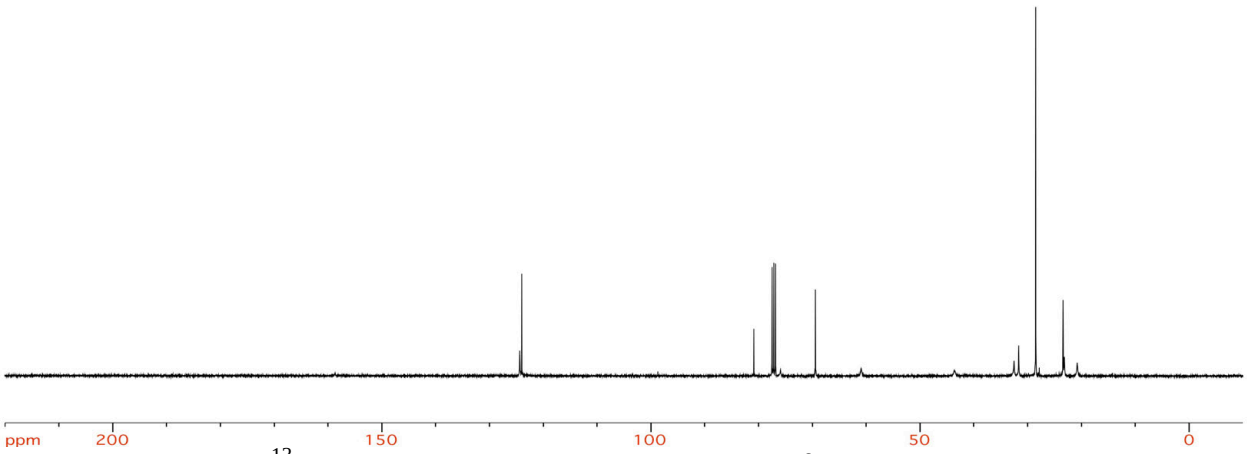


Figure A.1.11b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **1.147a** (Lower R_f diastereomer)

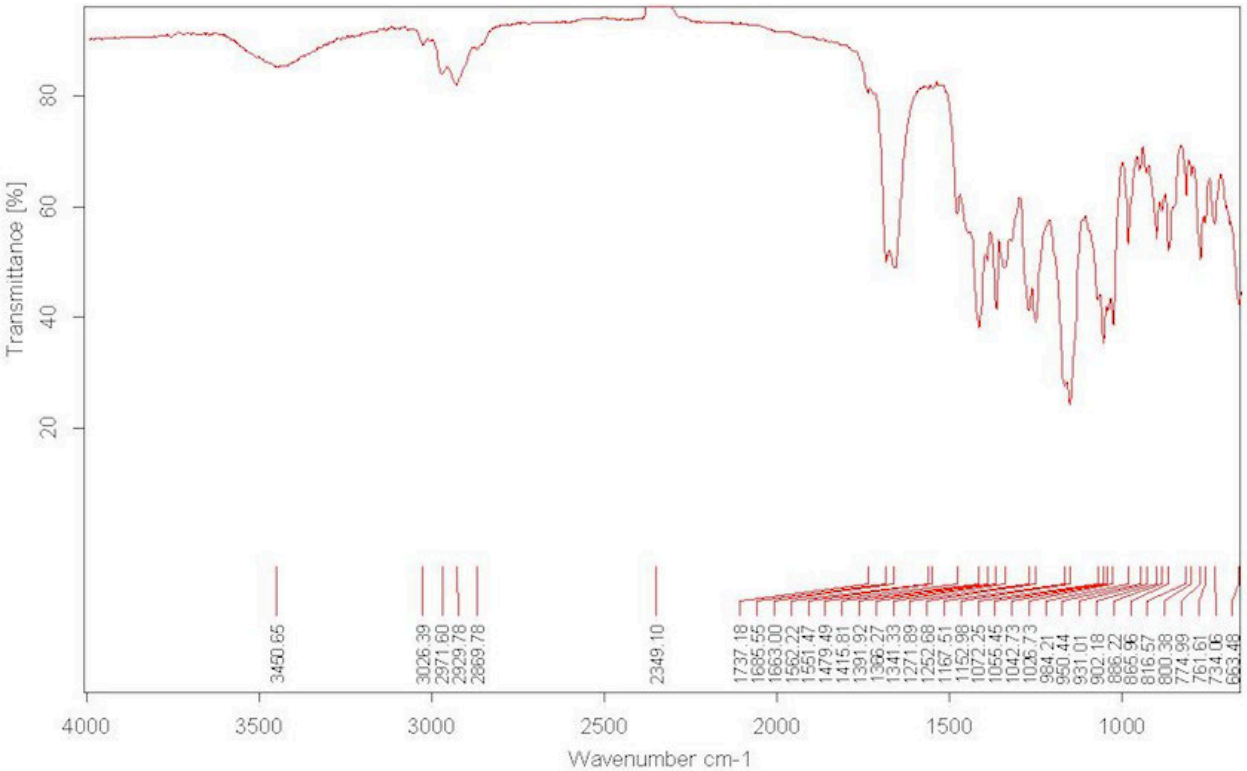
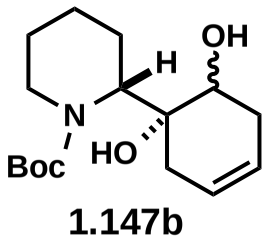


Figure A.1.11c IR spectrum (thin film) of compound **1.147a** (Lower R_f diastereomer)



1.147b

Figure A.1.12a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.147b**

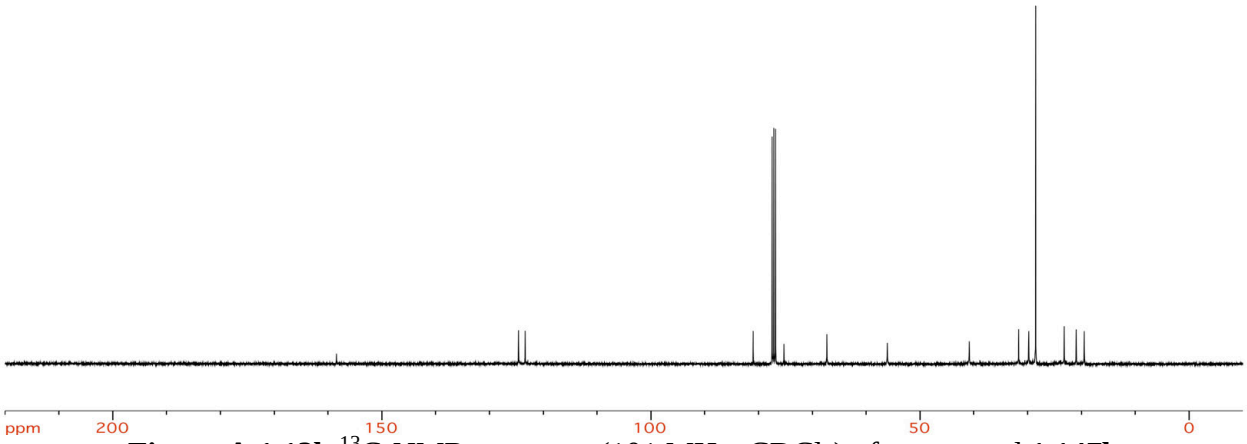


Figure A.1.12b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **1.147b**

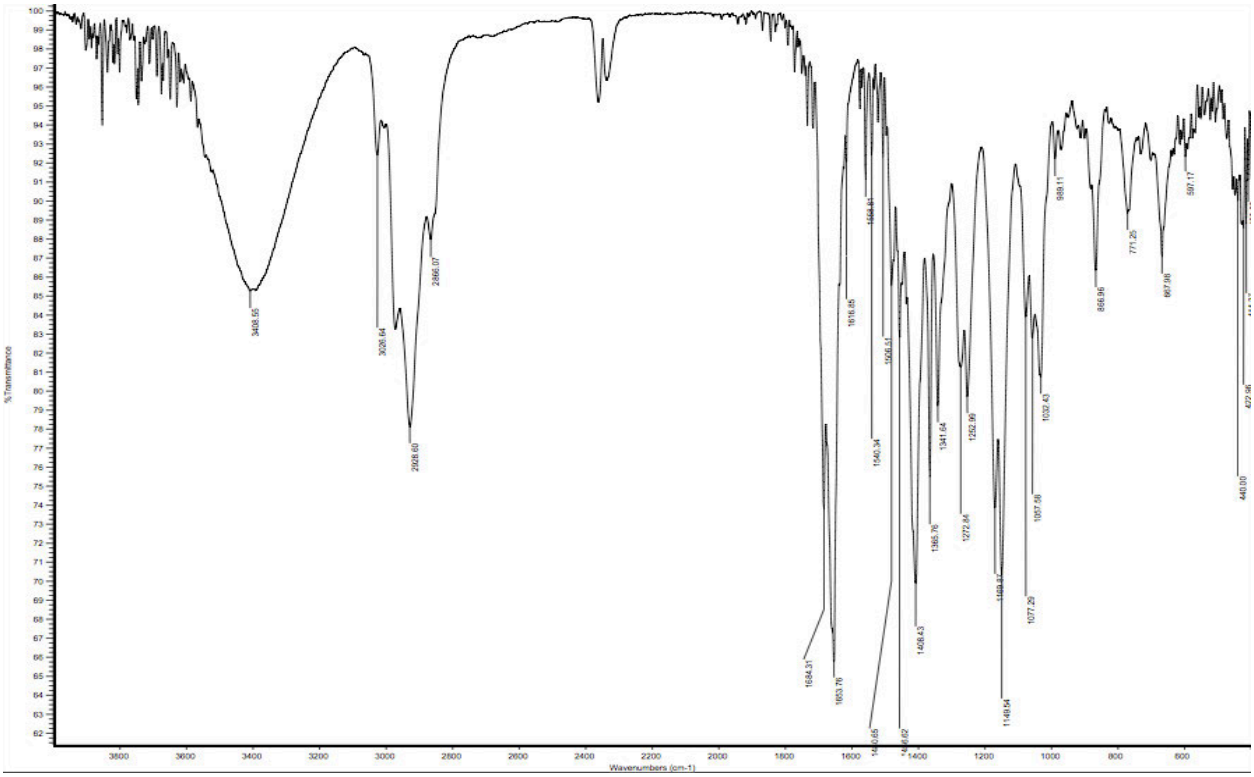
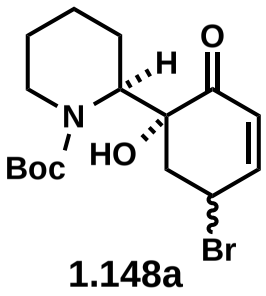


Figure A.1.12c IR spectrum (thin film) of compound **1.147b**



1.148a

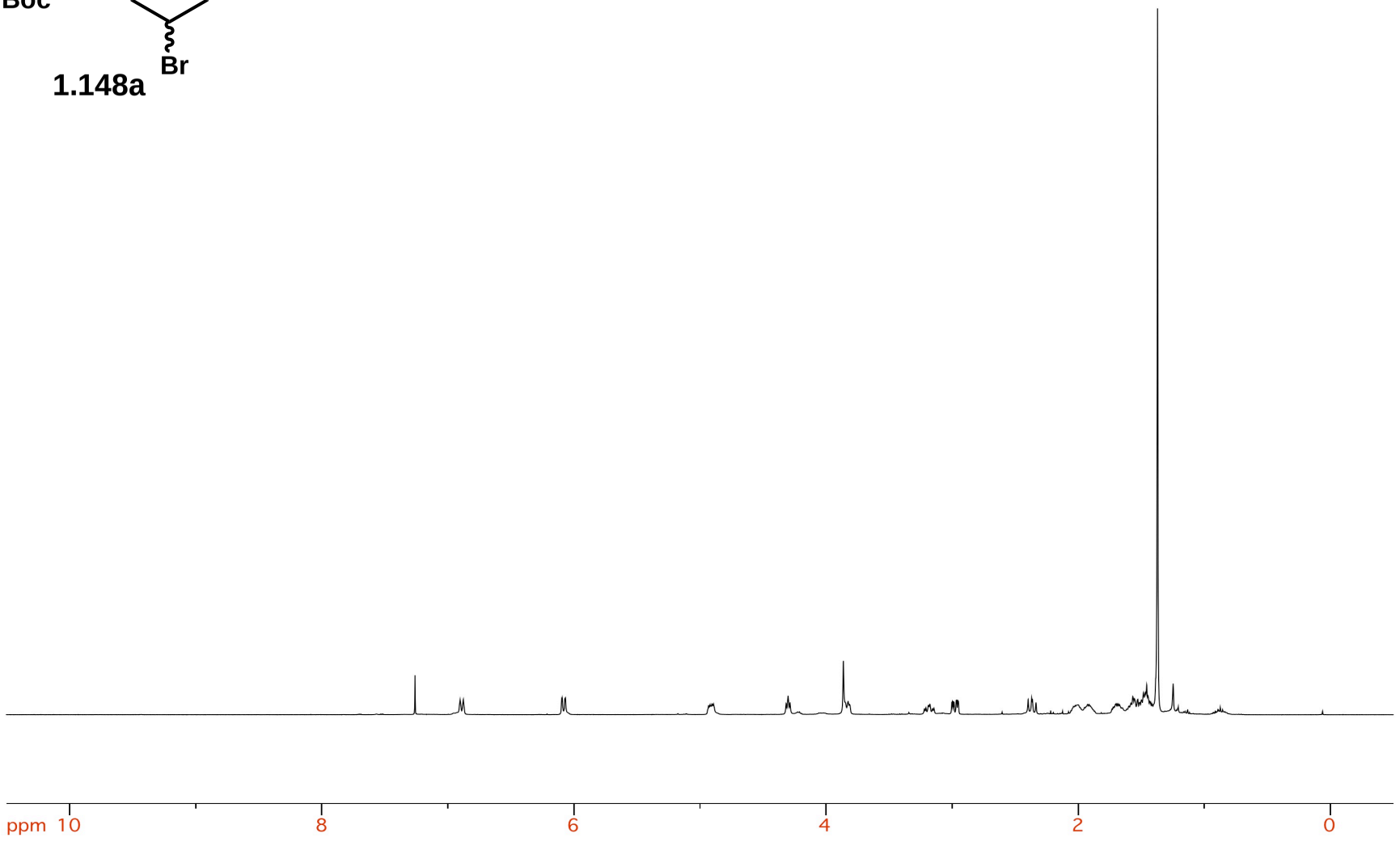


Figure A.1.13a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.148a**

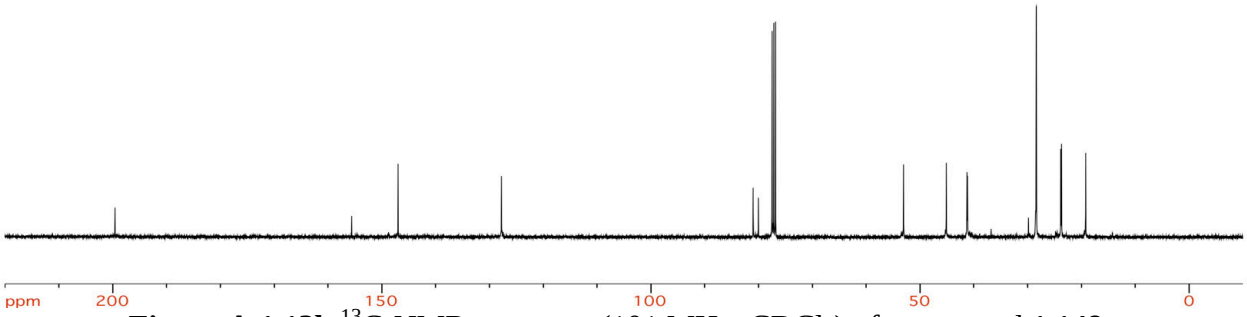


Figure A.1.13b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **1.148a**

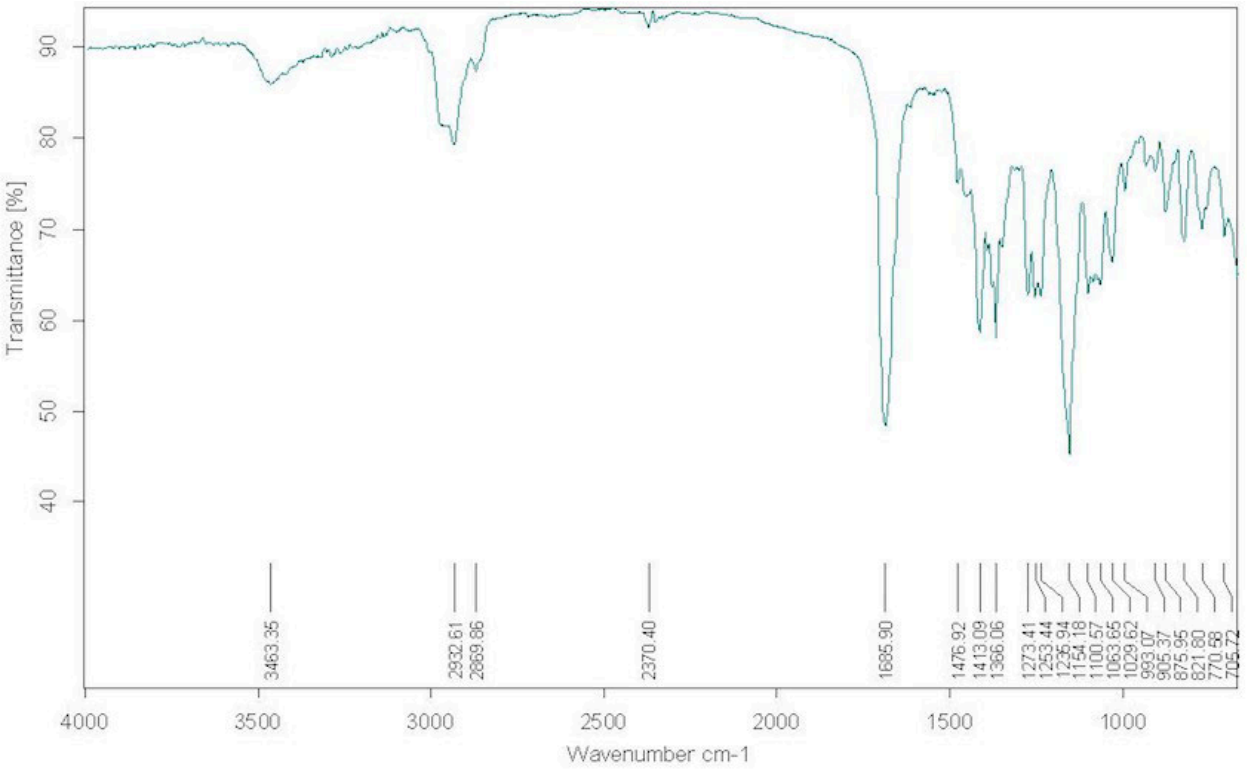
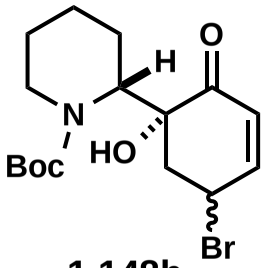


Figure A.1.13c IR spectrum (thin film) of compound **1.148a**



1.148b

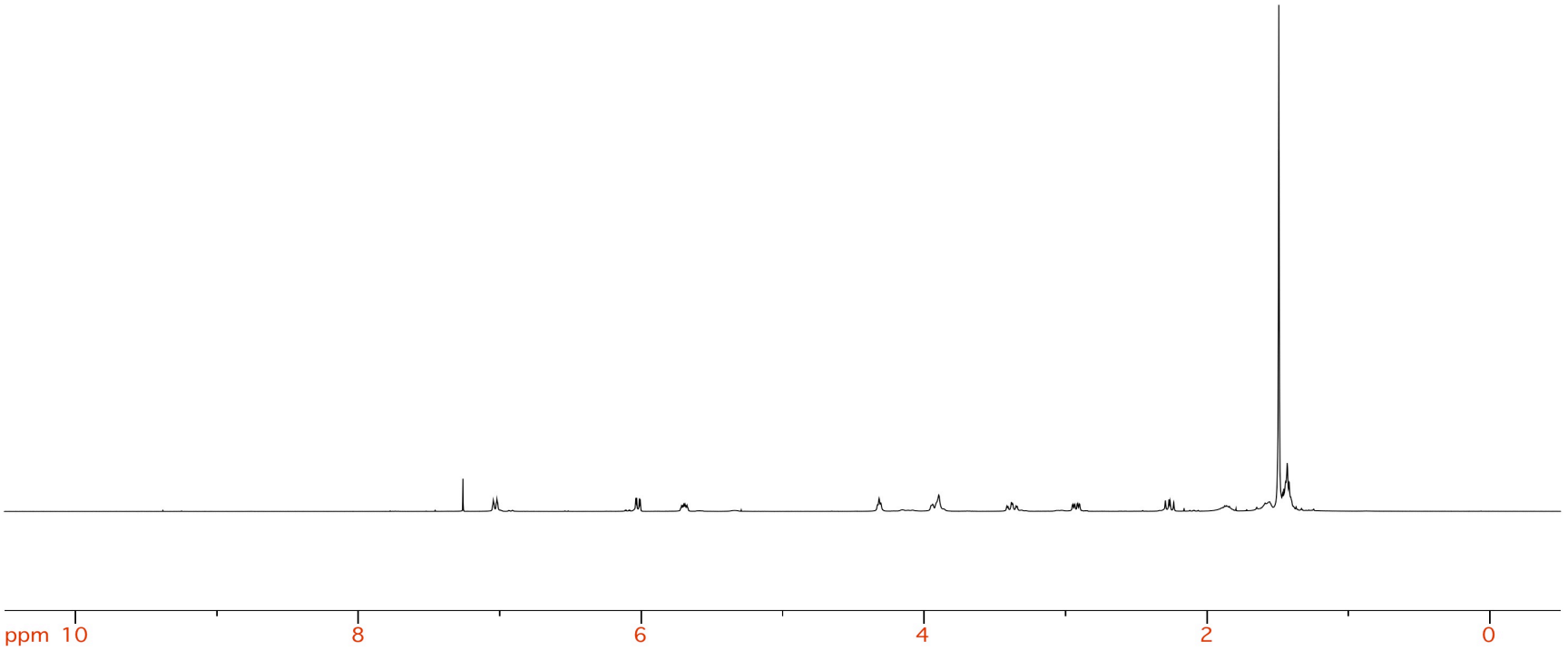


Figure A.1.14a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.148b**

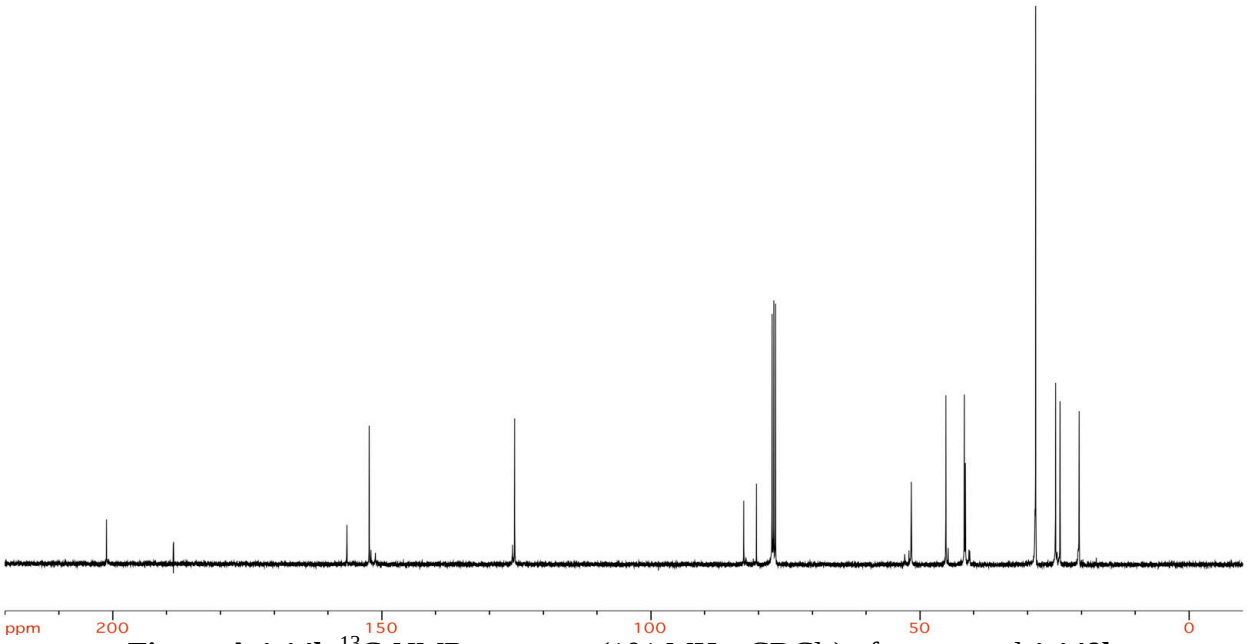


Figure A.1.14b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **1.148b**

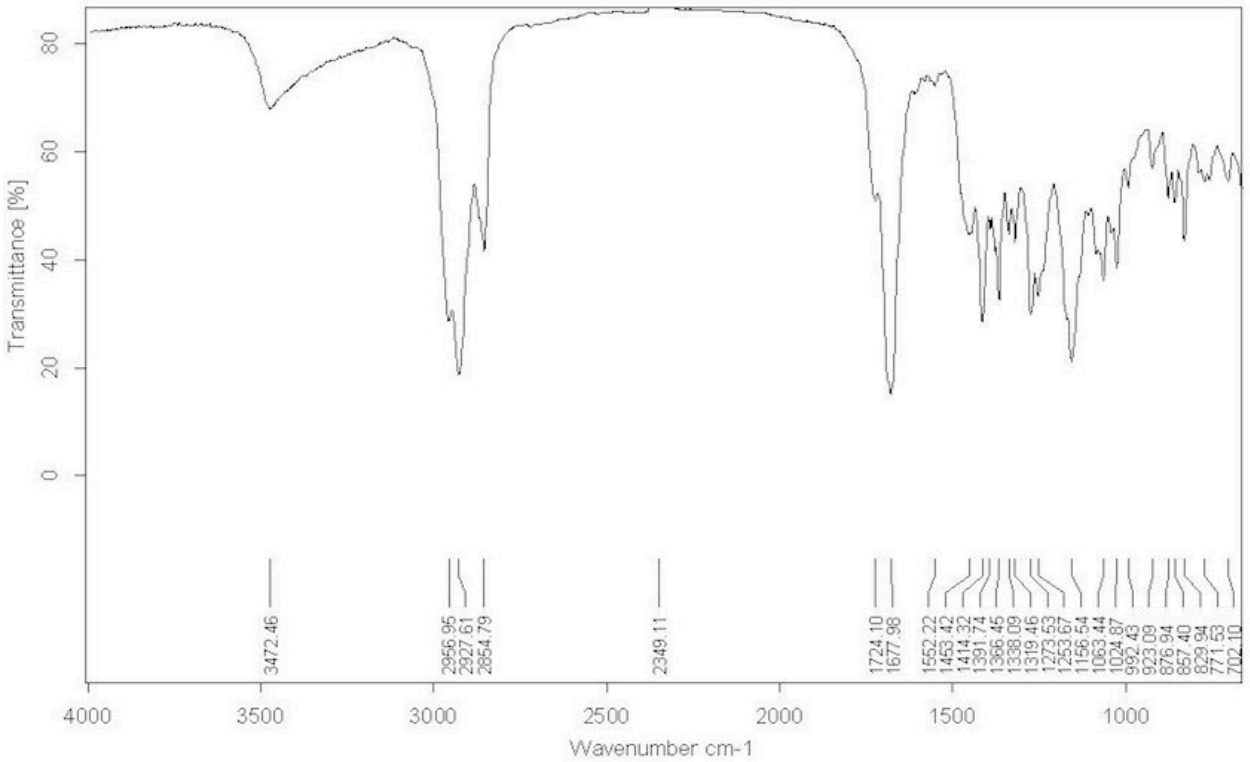
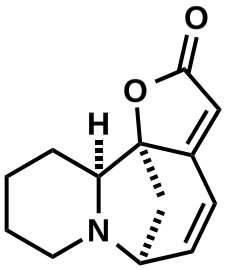


Figure A.1.14c IR spectrum (thin film) of compound **1.148b**



(±)-1.003

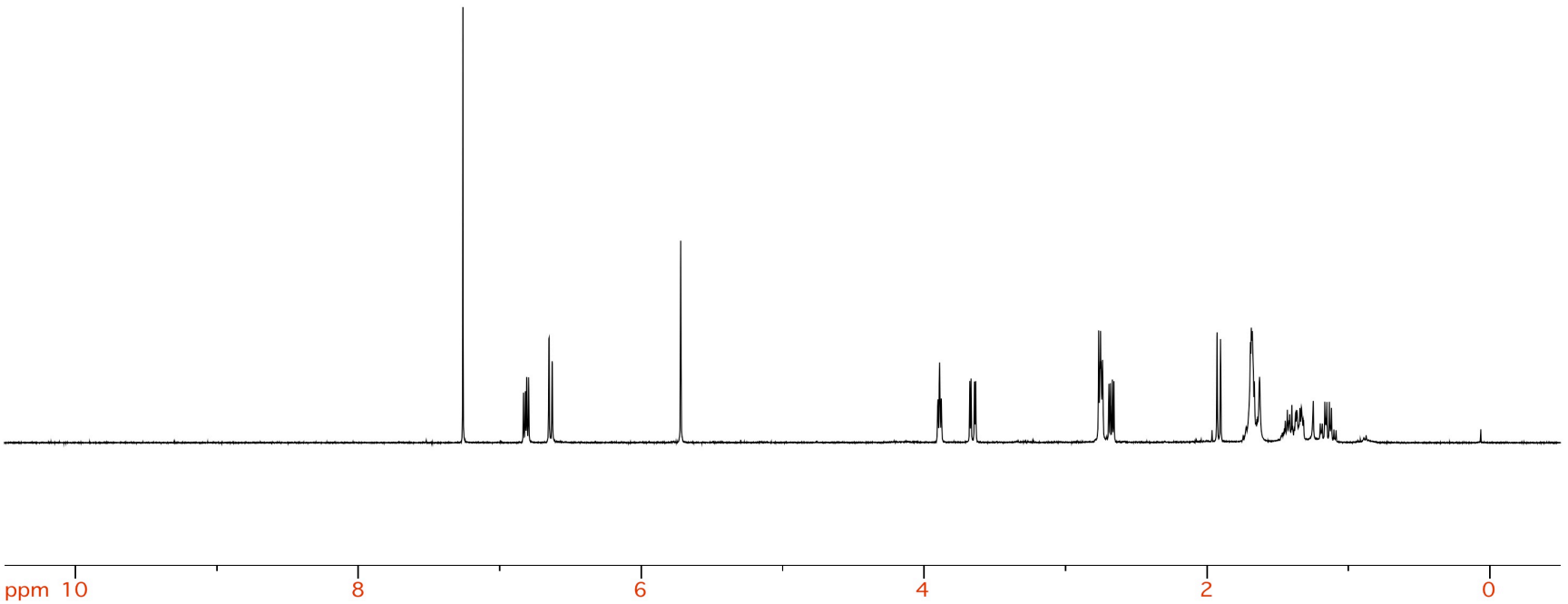


Figure A.1.15a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **(±)-1.003**

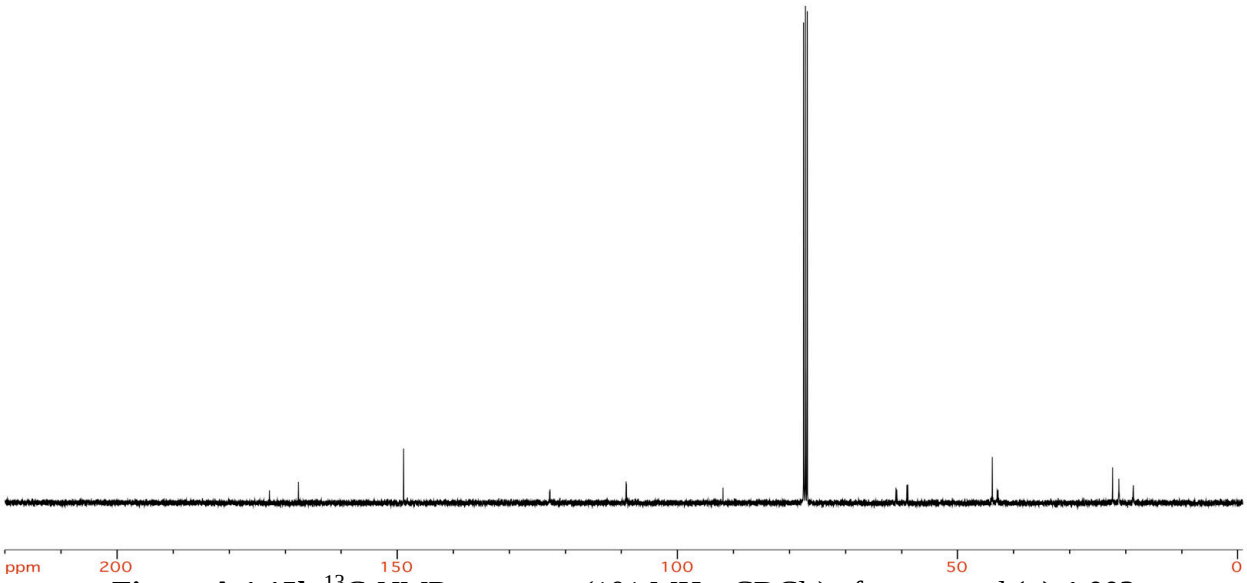


Figure A.1.15b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **(±)-1.003**

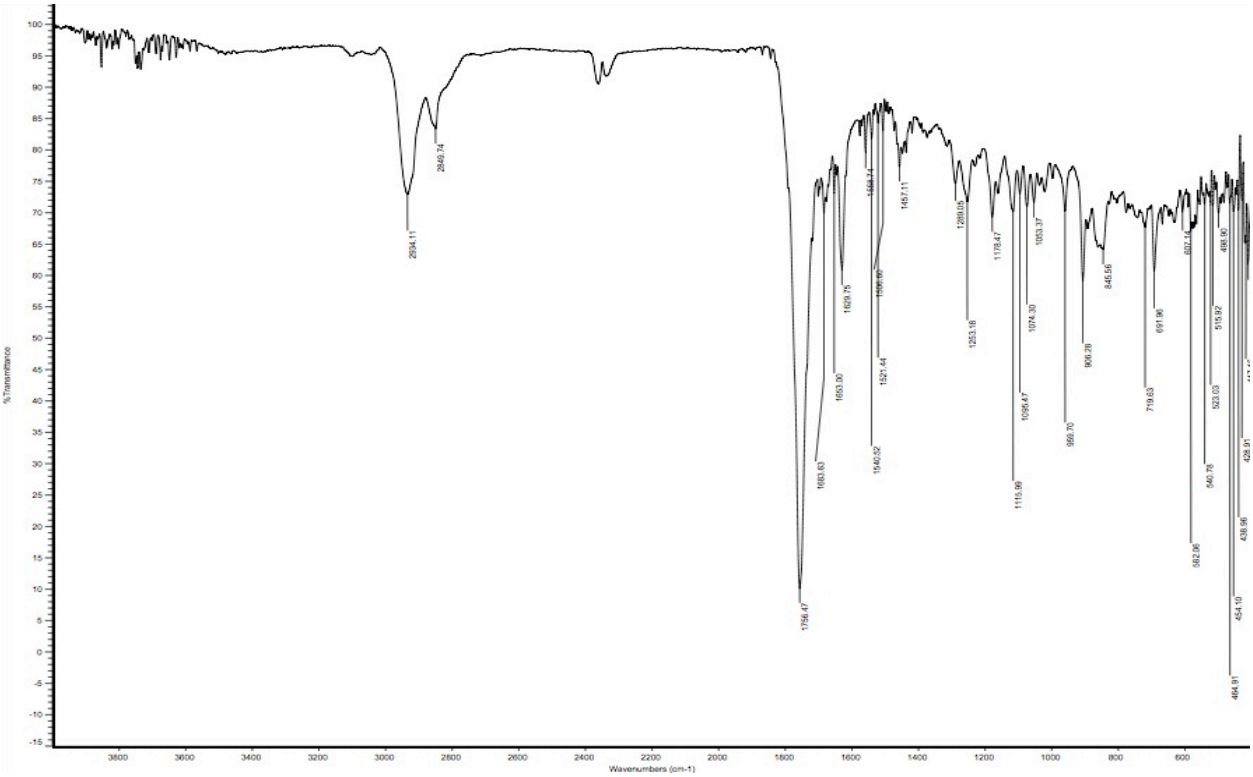
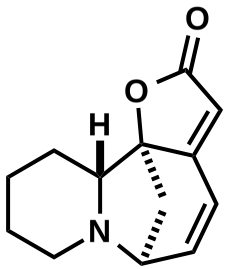


Figure A.1.15c IR spectrum (thin film) of compound **(±)-1.003**



(±)-1.001

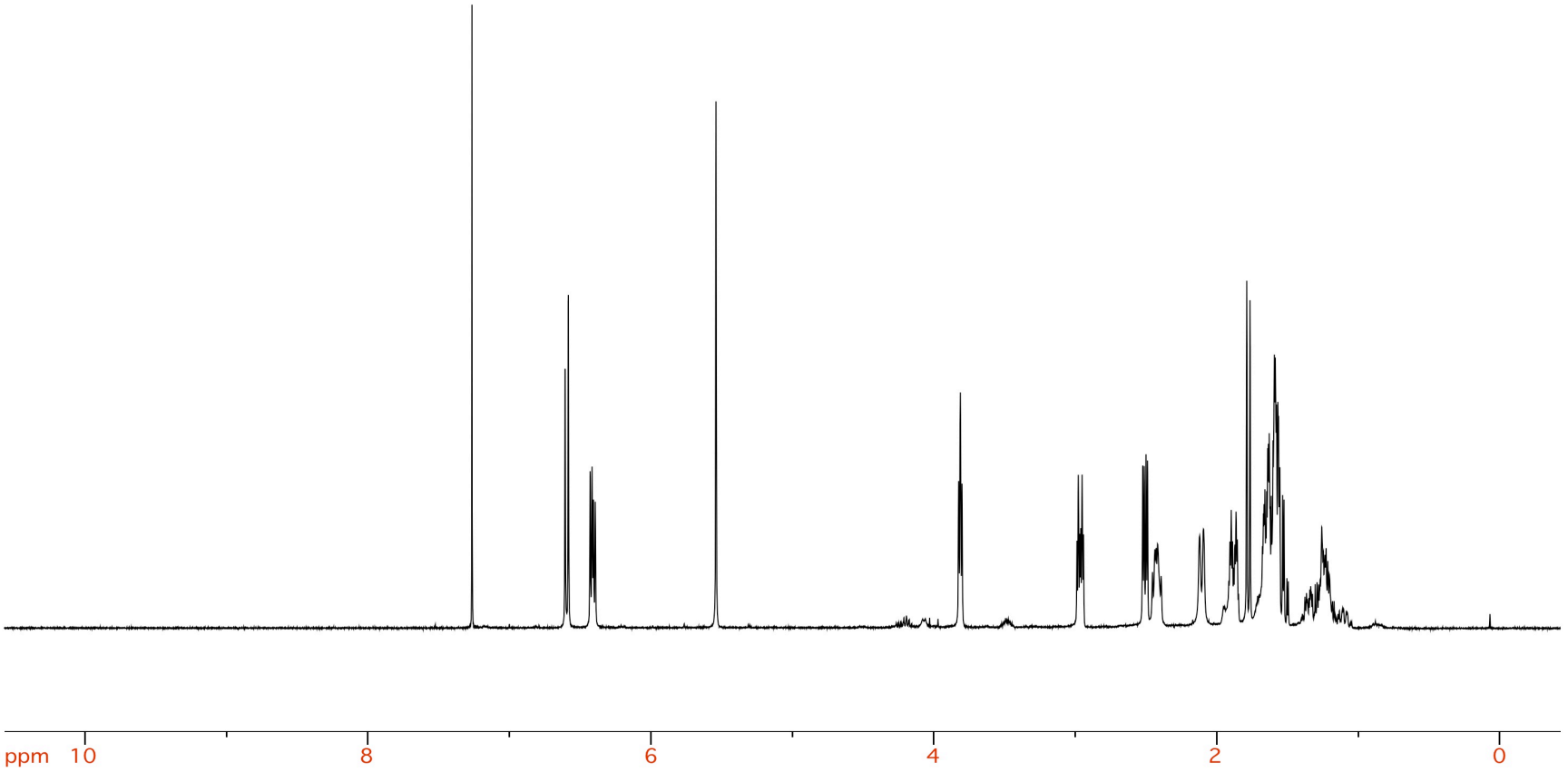


Figure A.1.16a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **(±)-1.001**

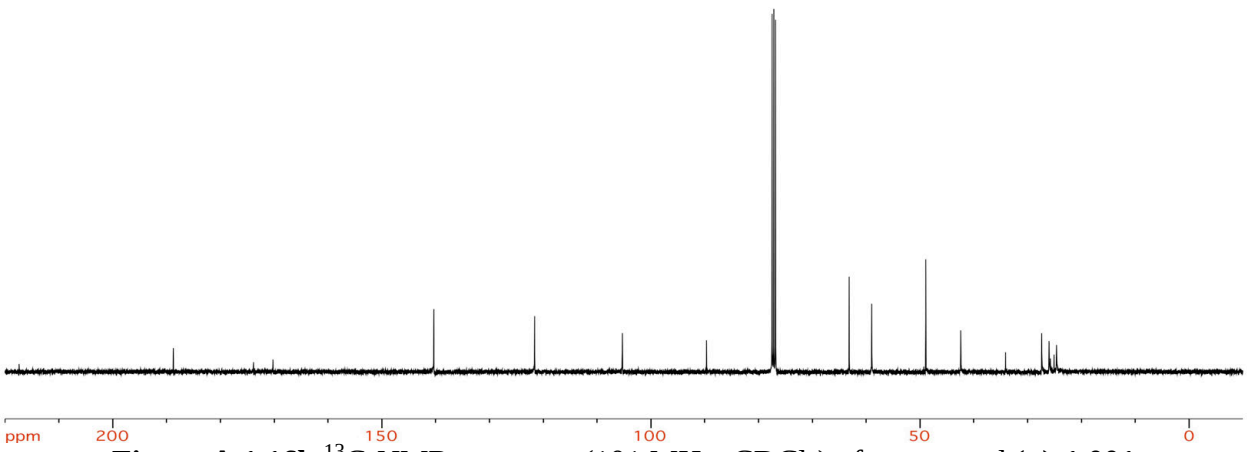


Figure A.1.16b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **(±)-1.001**

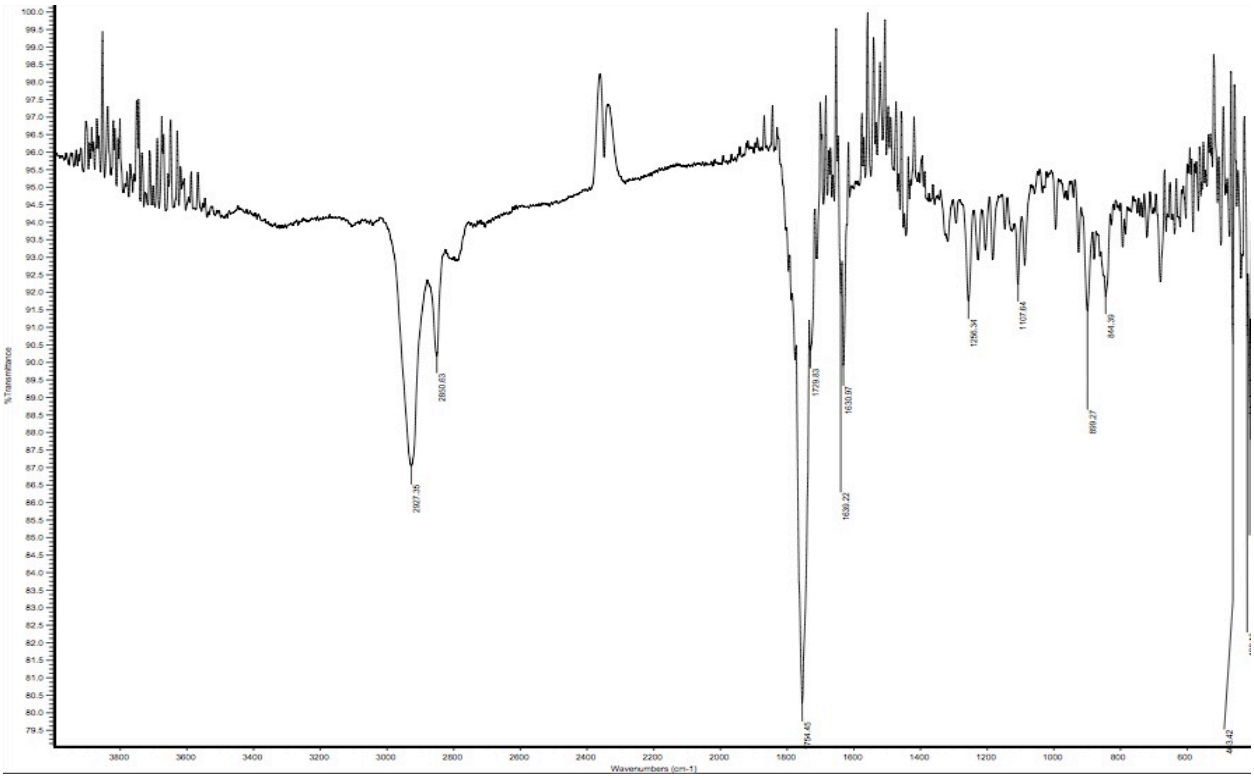
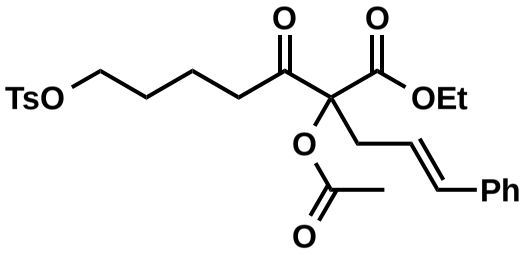


Figure A.1.16c IR spectrum (thin film) of compound **(±)-1.001**

APPENDIX 2: SPECTRA RELEVANT TO CHAPTER 3



1.159

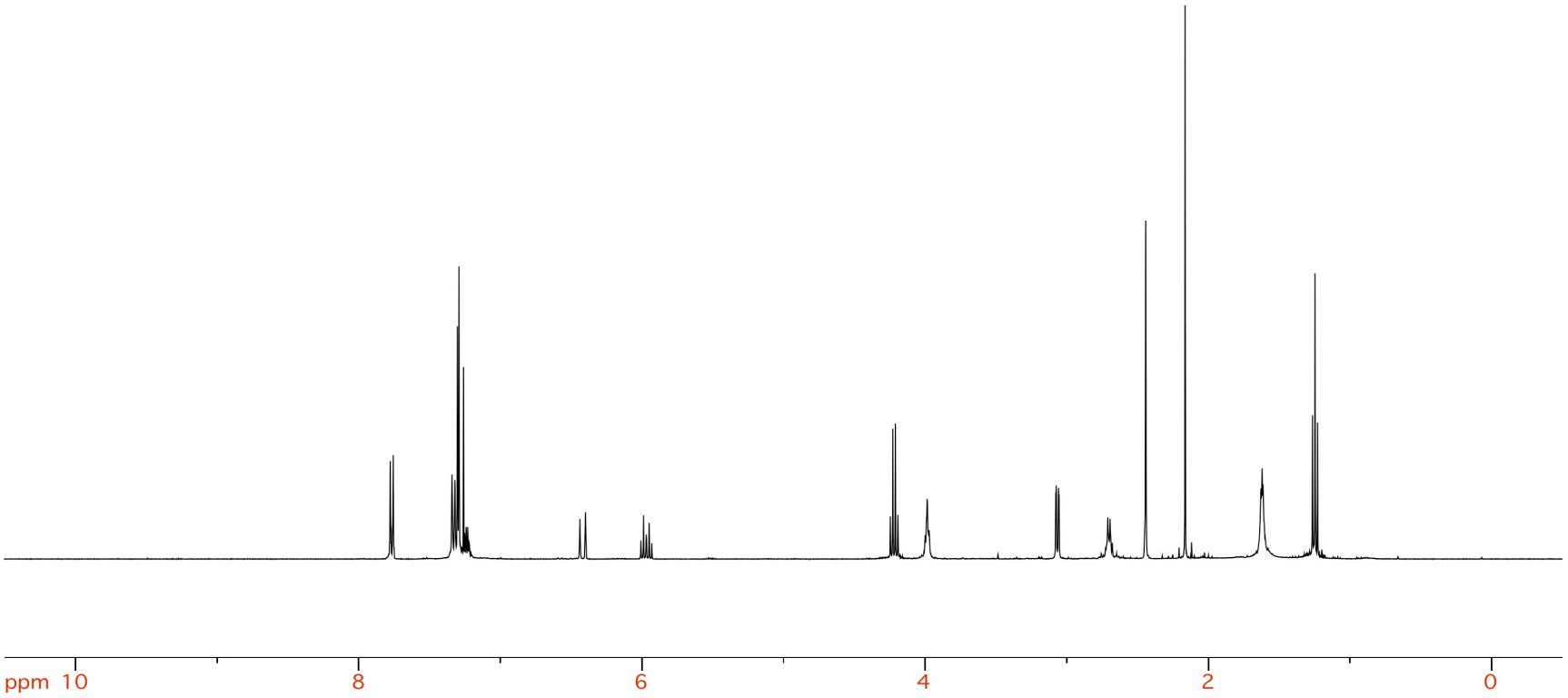


Figure A2.1a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.159**

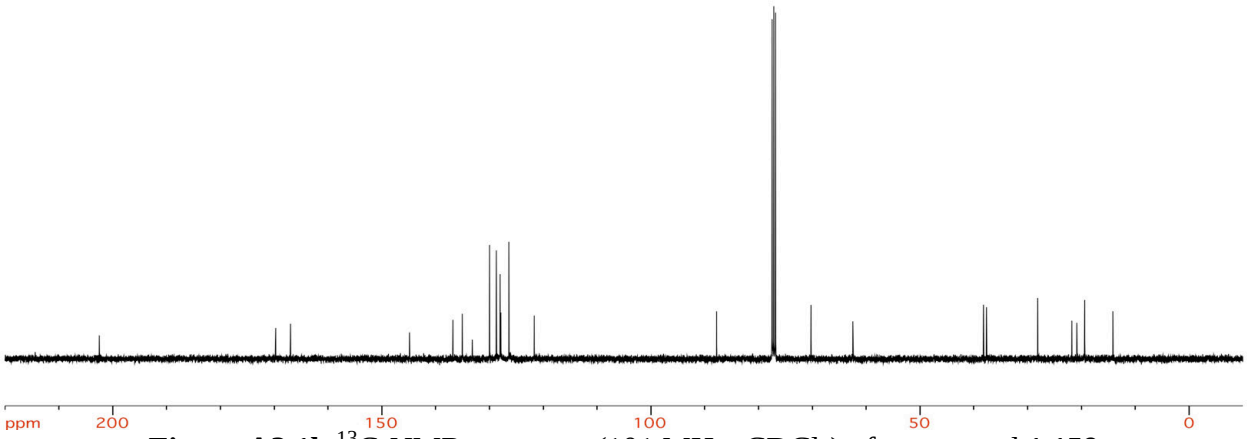


Figure A2.1b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **1.159**

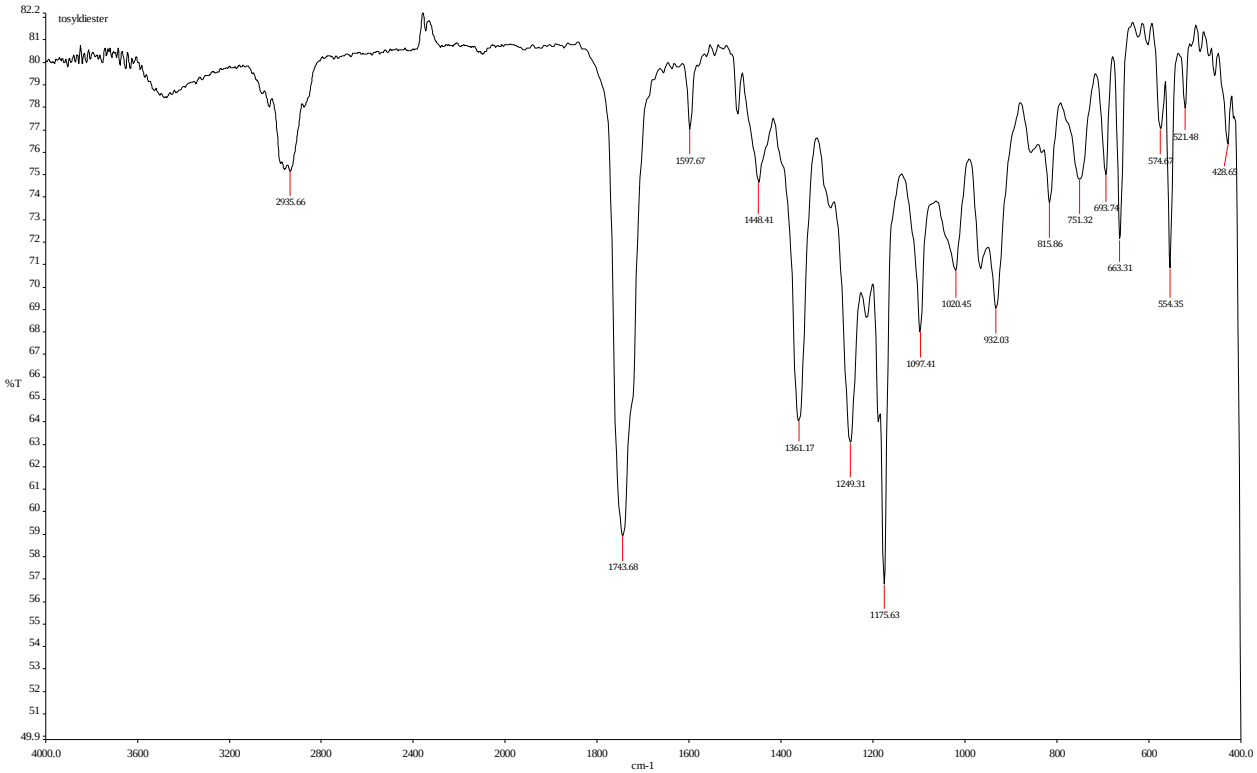
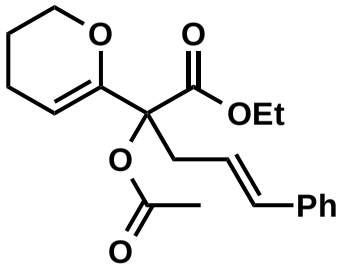


Figure A2.1c IR spectrum (thin film) of compound **1.159**



1.160

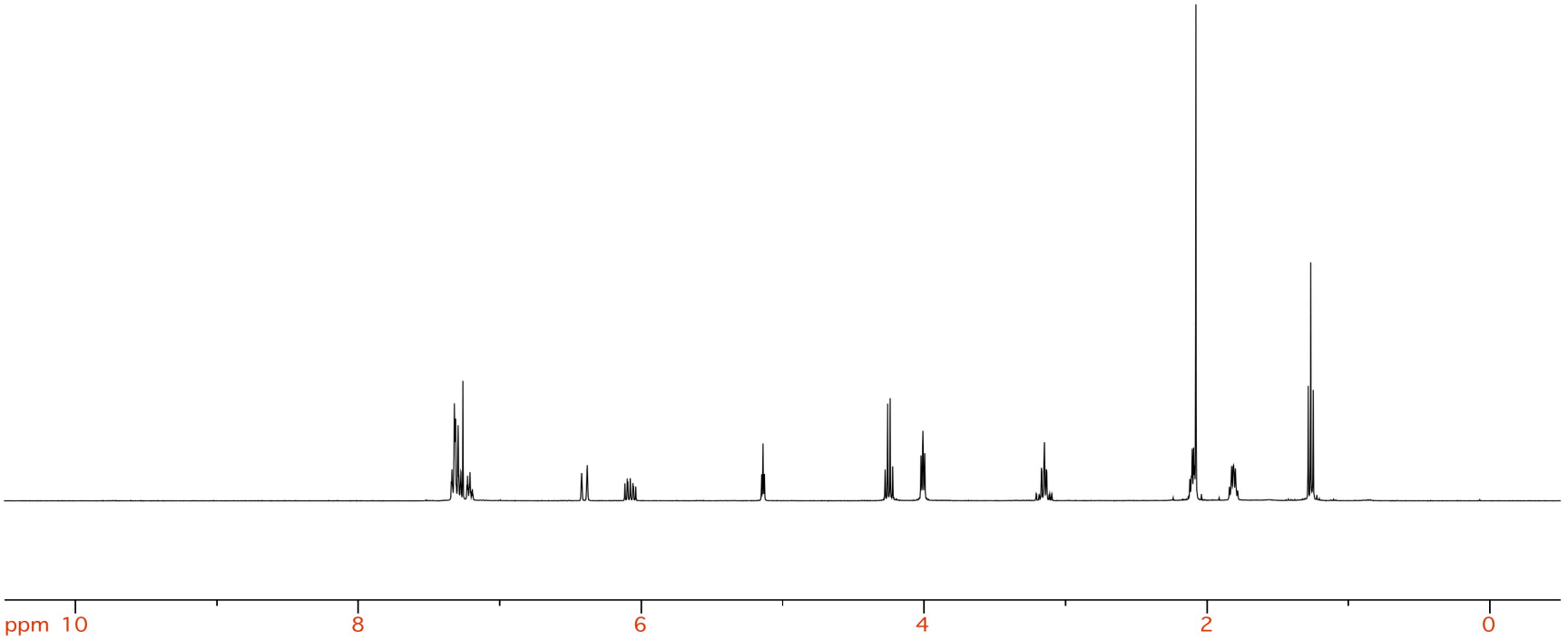


Figure A2.2a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.160**

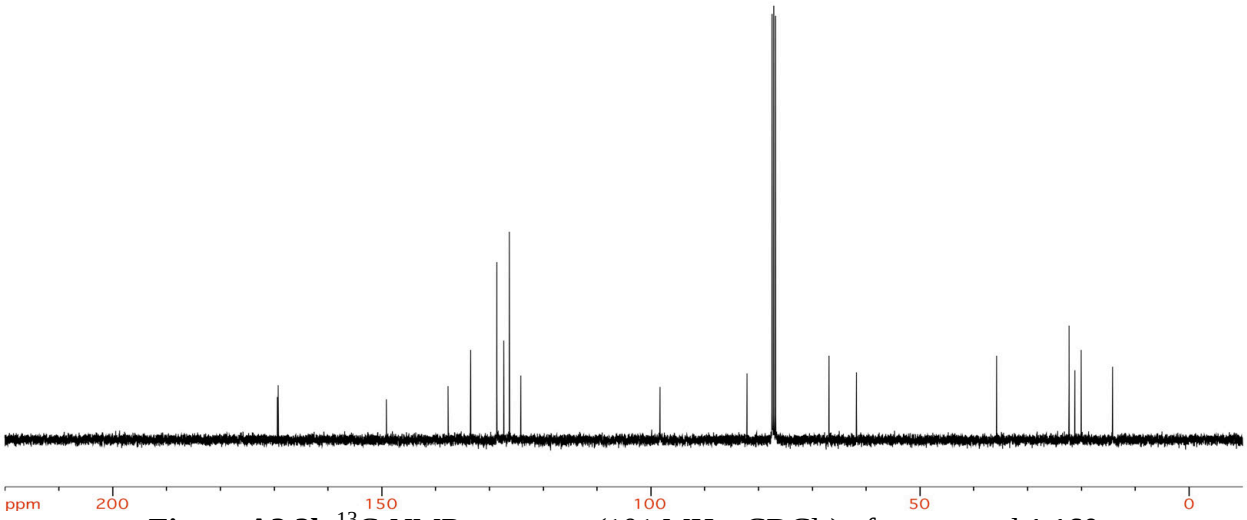
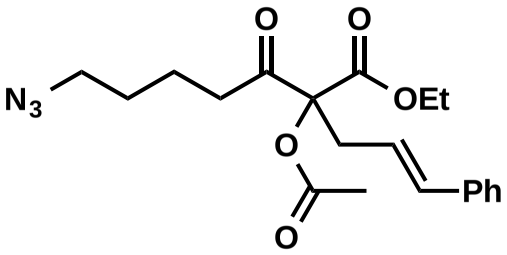


Figure A2.2b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **1.160**

Figure A2.2c IR spectrum (thin film) of compound **1.160**



1.161

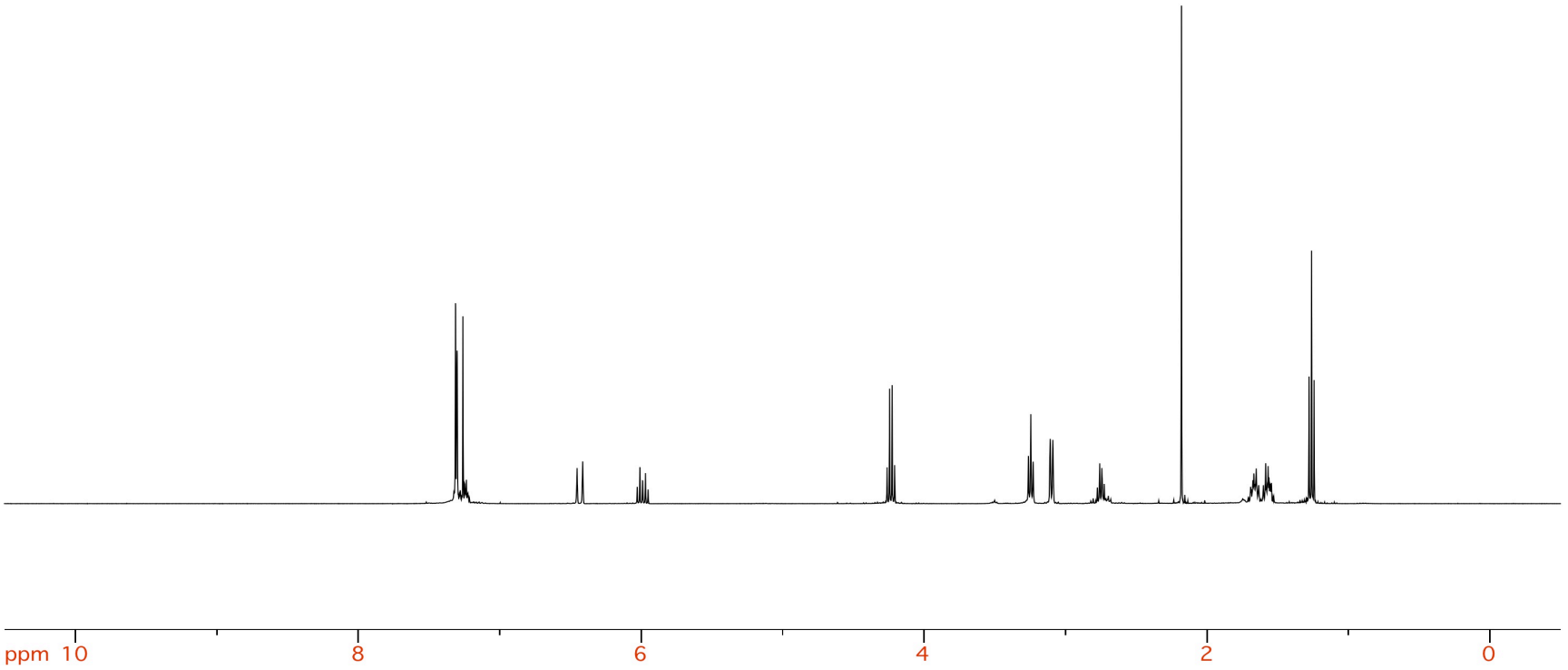


Figure A2.3a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.161**

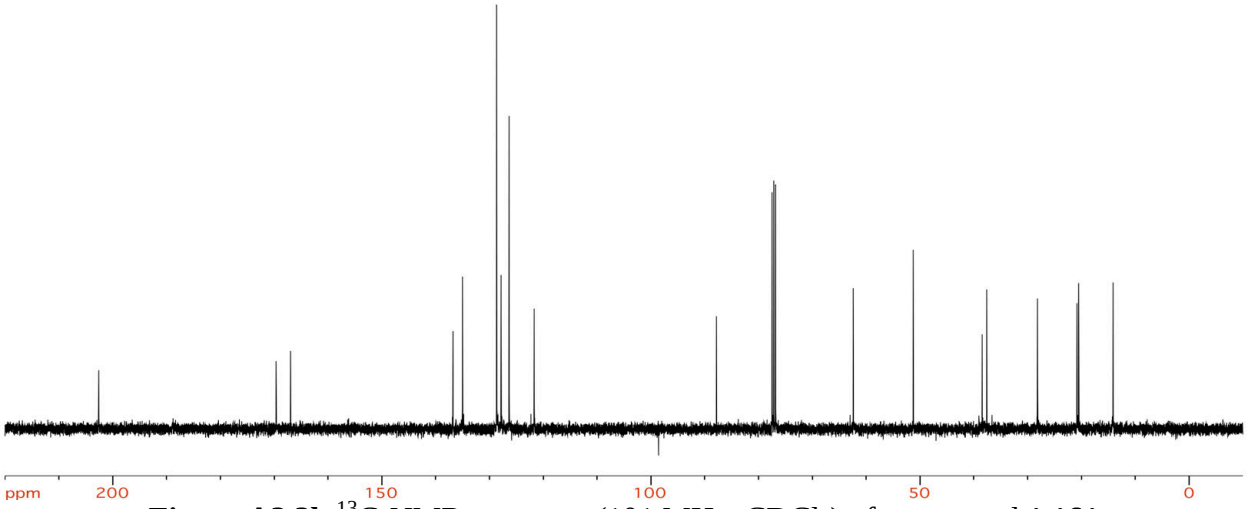


Figure A2.3b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **1.161**

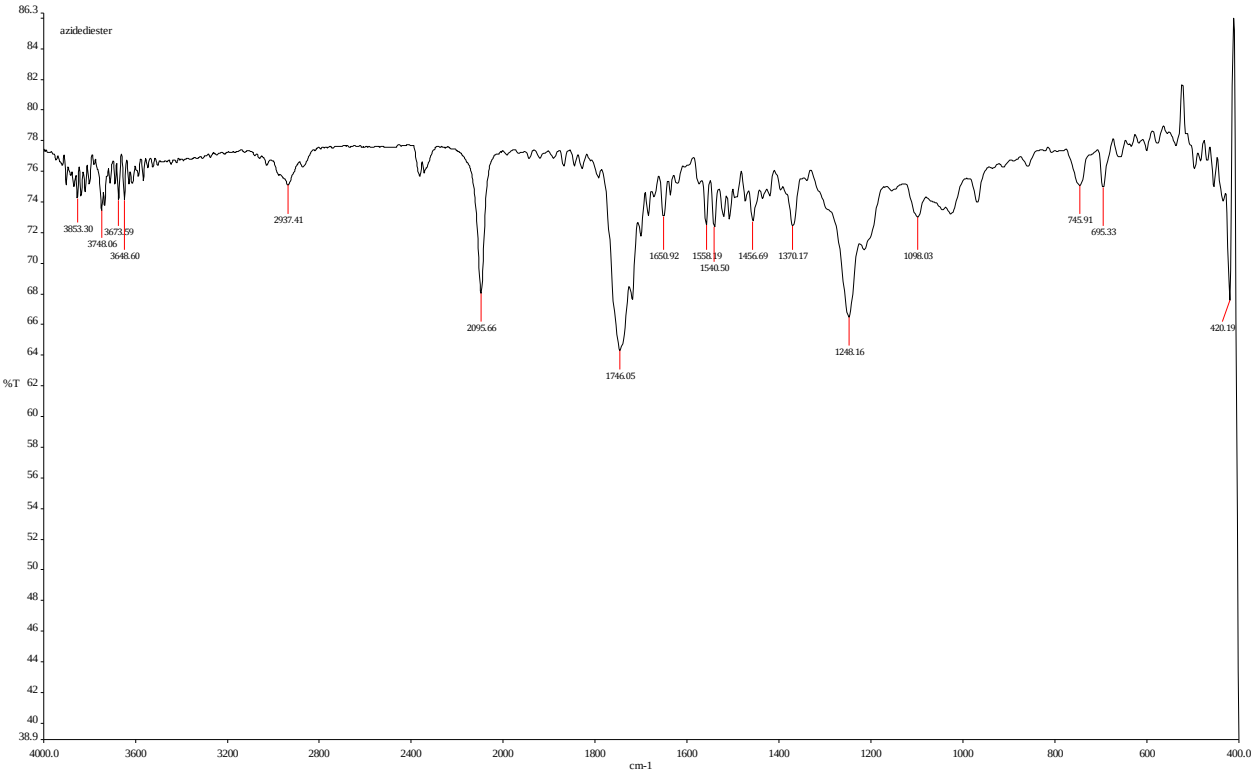
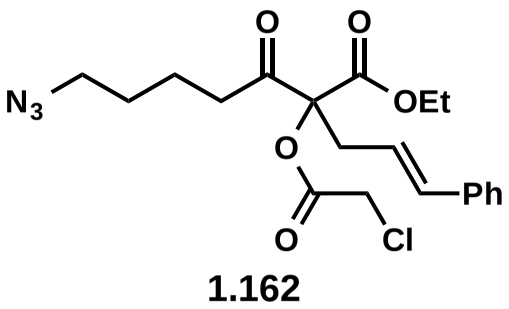


Figure A2.3c IR spectrum (thin film) of compound **1.161**



1.162

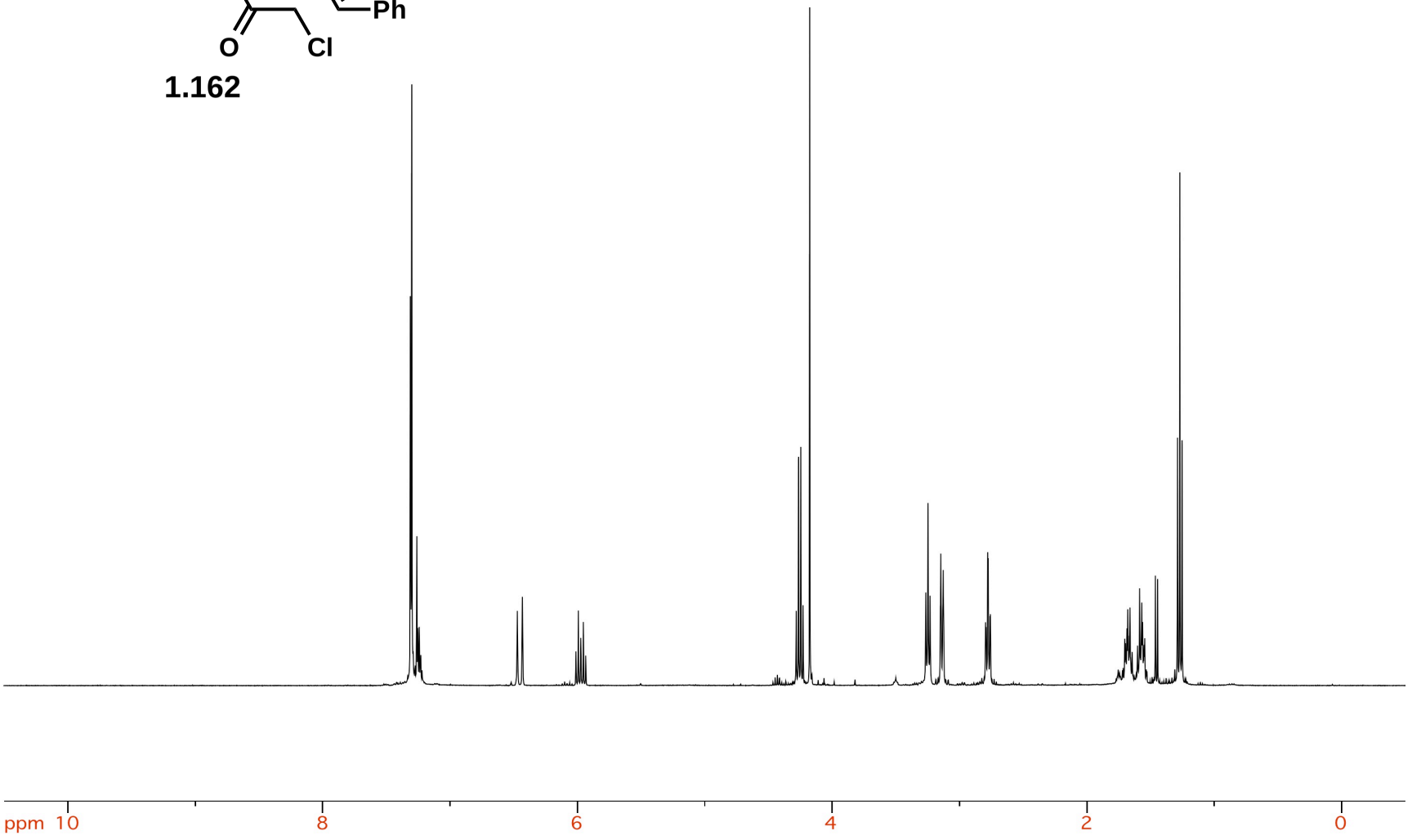


Figure A2.4a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.162**

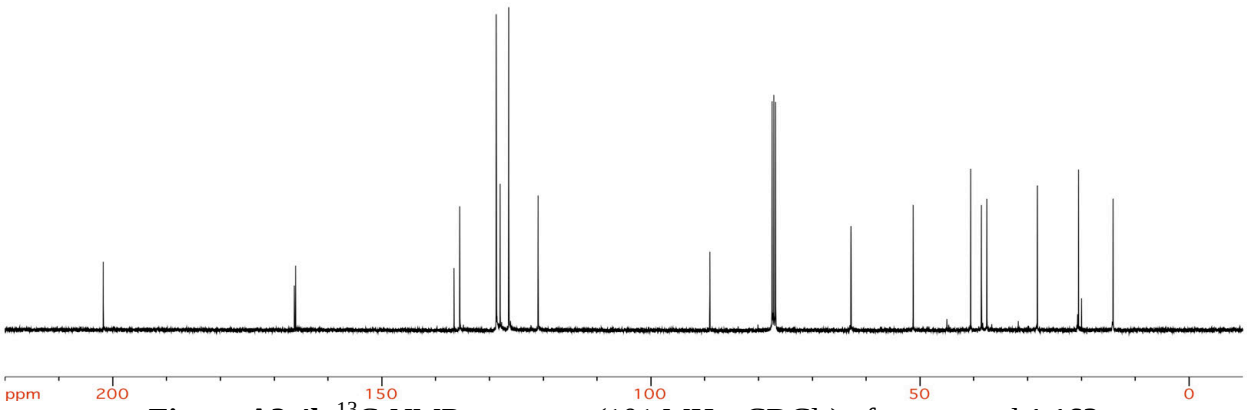


Figure A2.4b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **1.162**

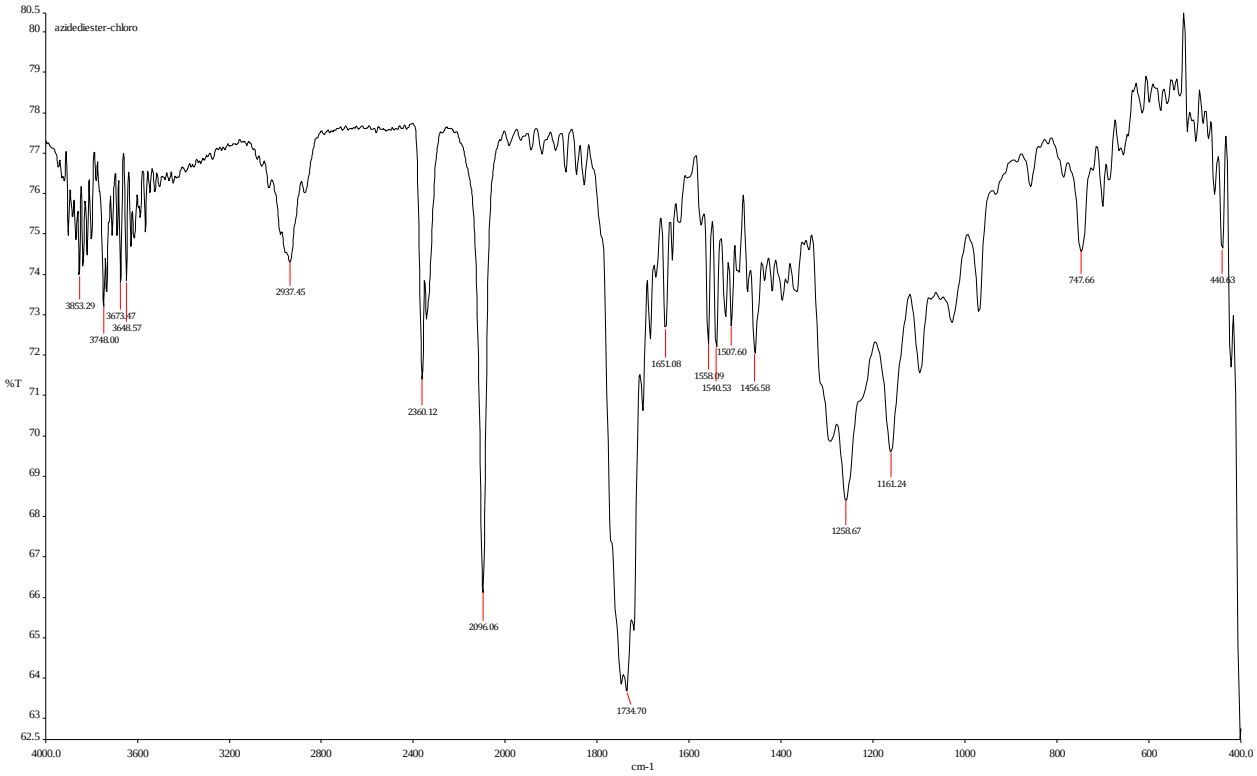
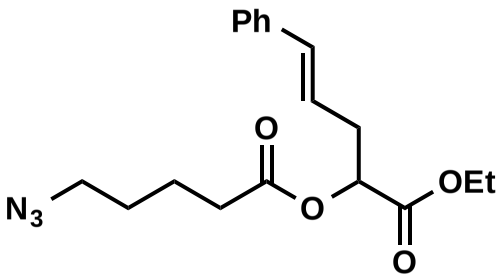


Figure A2.4c IR spectrum (thin film) of compound **1.162**



1.163

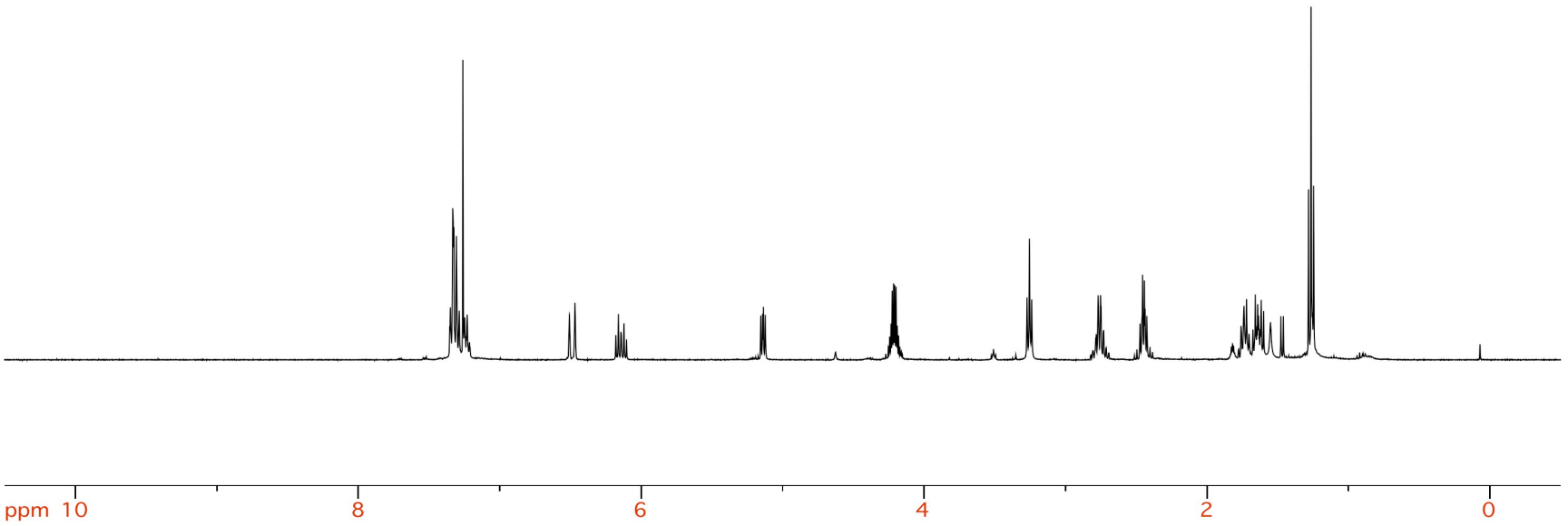


Figure A2.5a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.163**

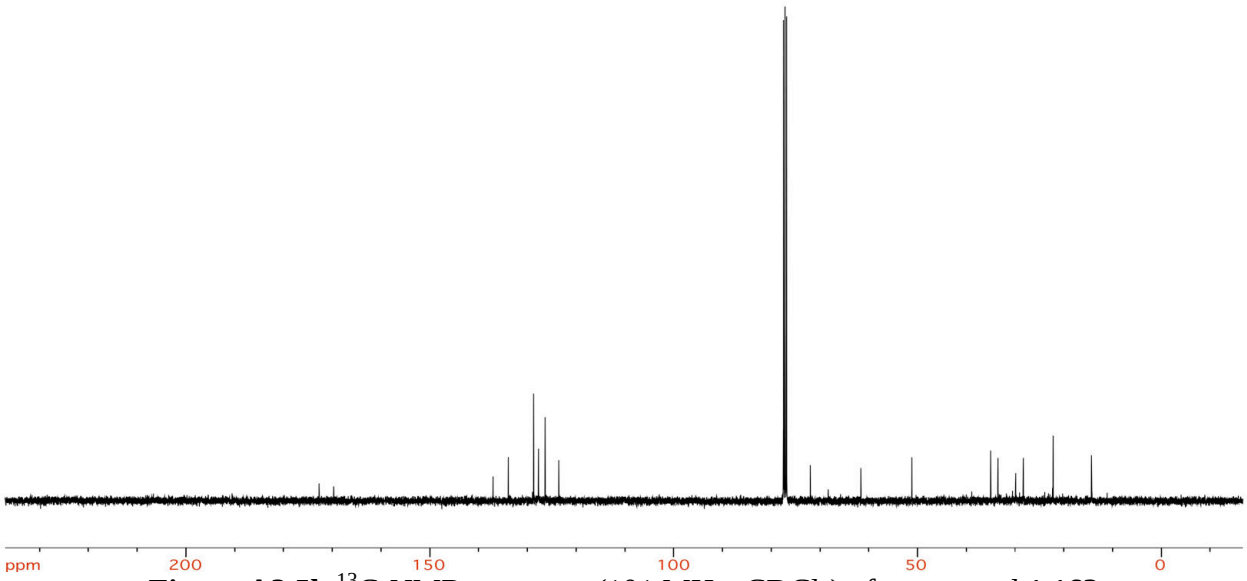


Figure A2.5b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **1.163**

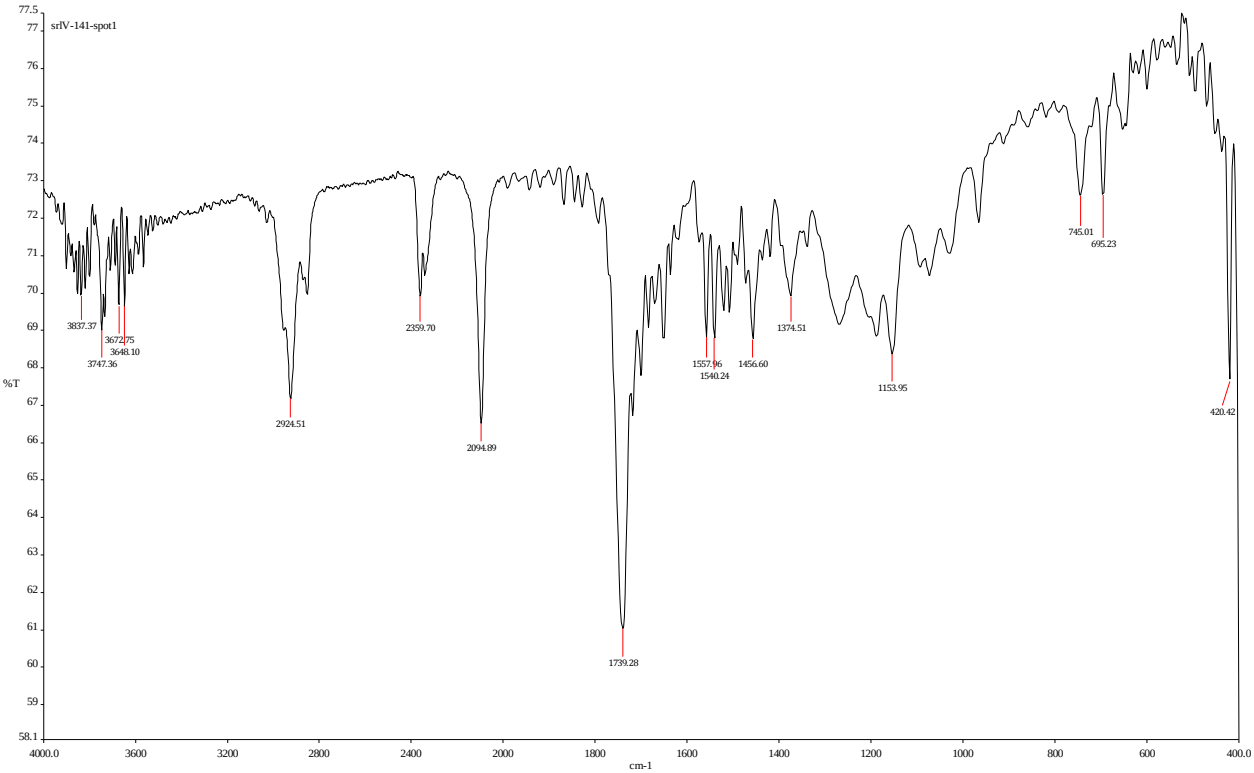
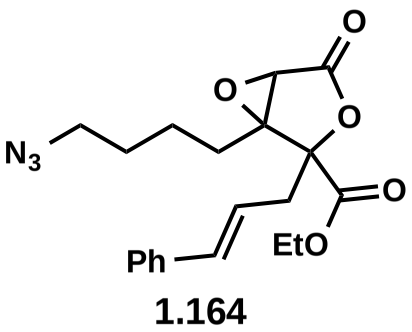


Figure A2.5c IR spectrum (thin film) of compound **1.163**



1.164

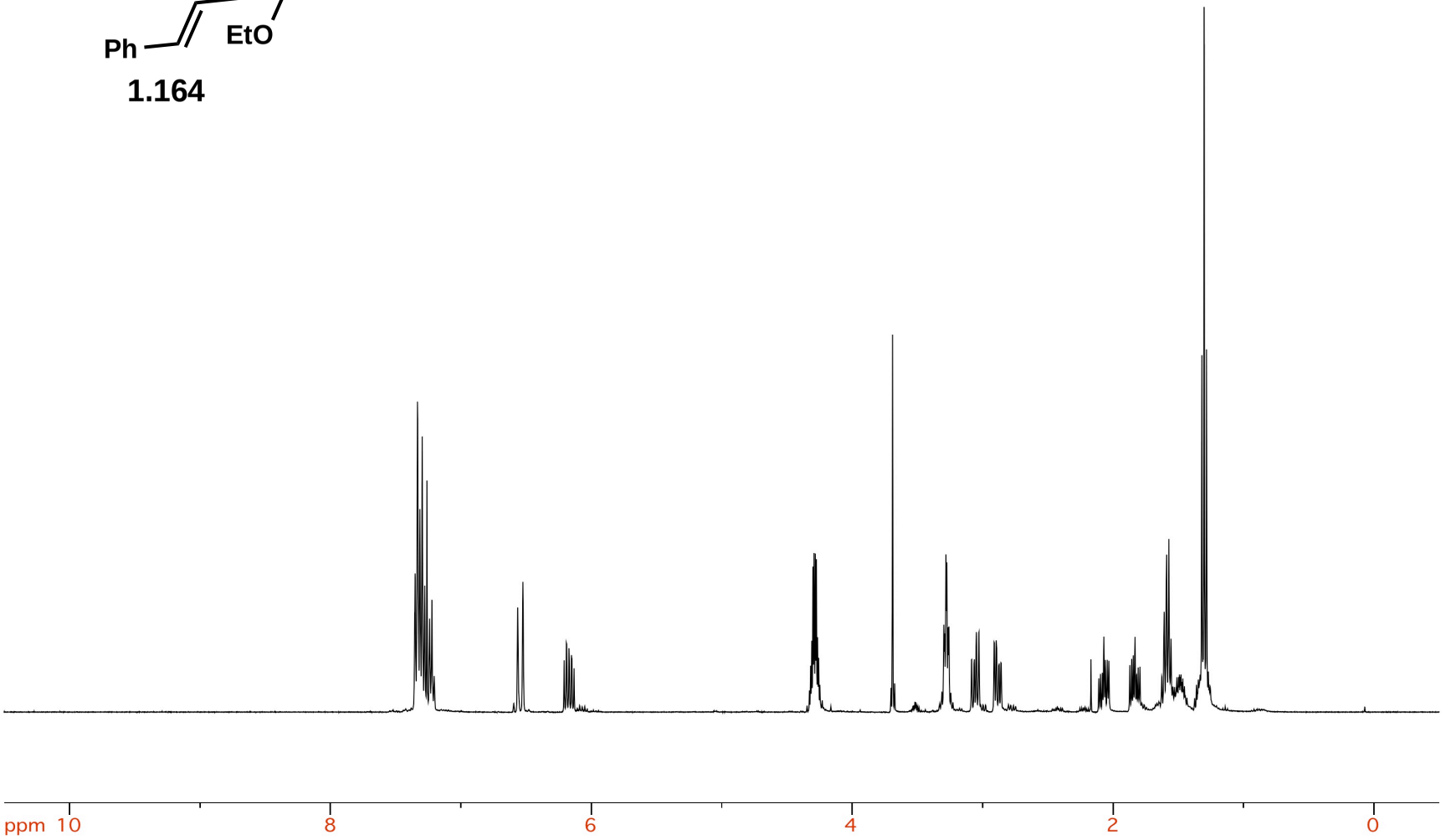


Figure A2.6a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.164** (Higher R_f diastereomer)

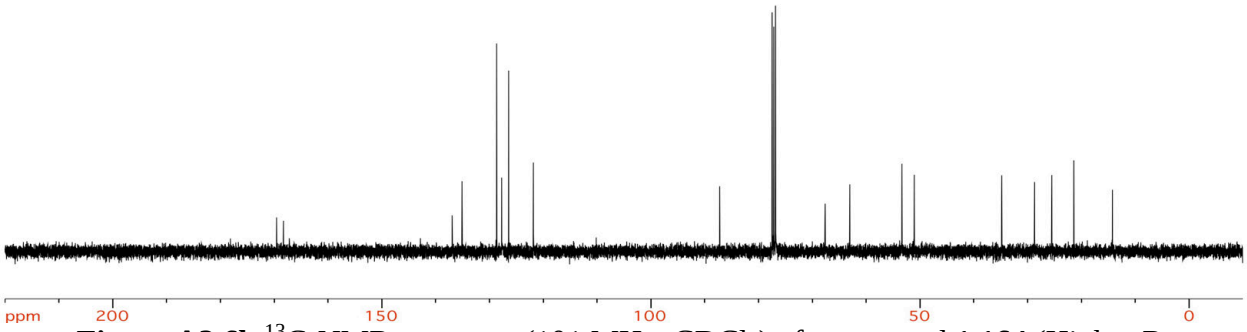


Figure A2.6b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **1.164** (Higher R_f diastereomer)

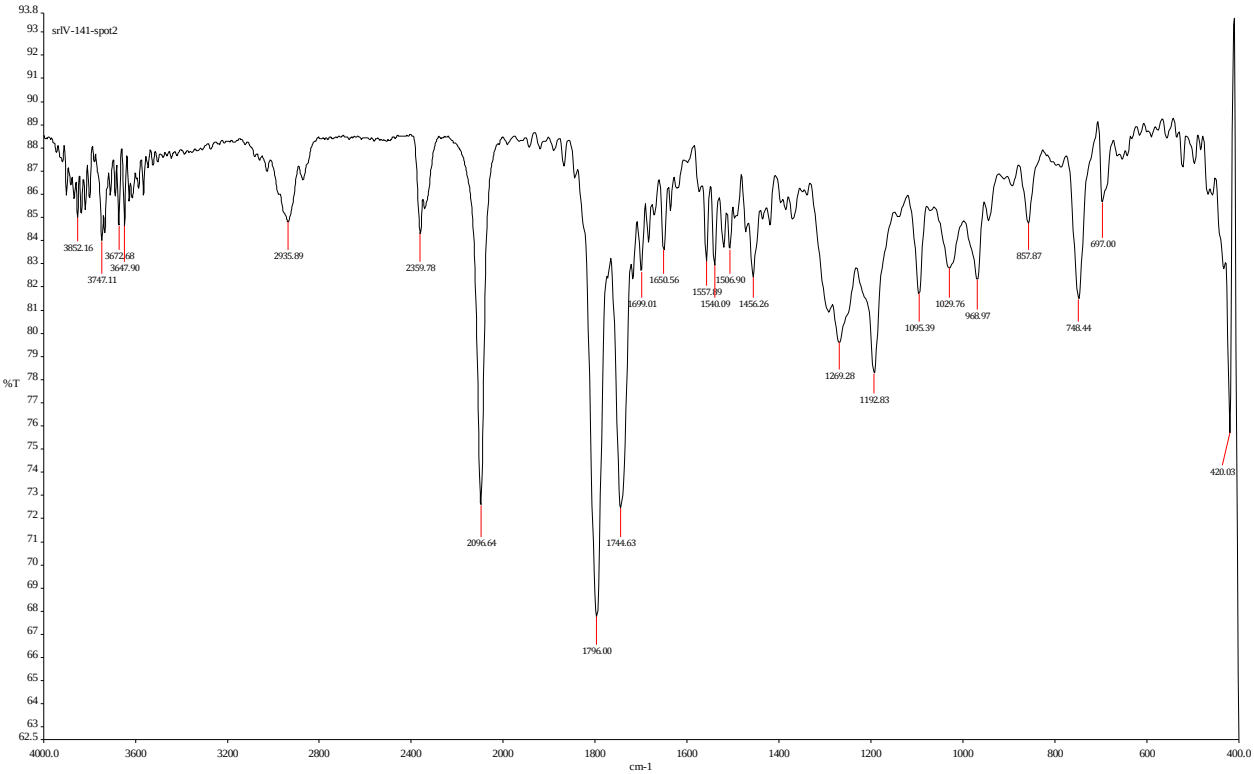
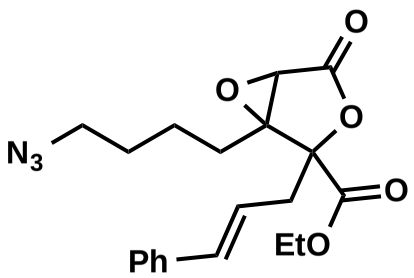


Figure A2.6c IR spectrum (thin film) of compound **1.164** (Higher R_f diastereomer)



1.164

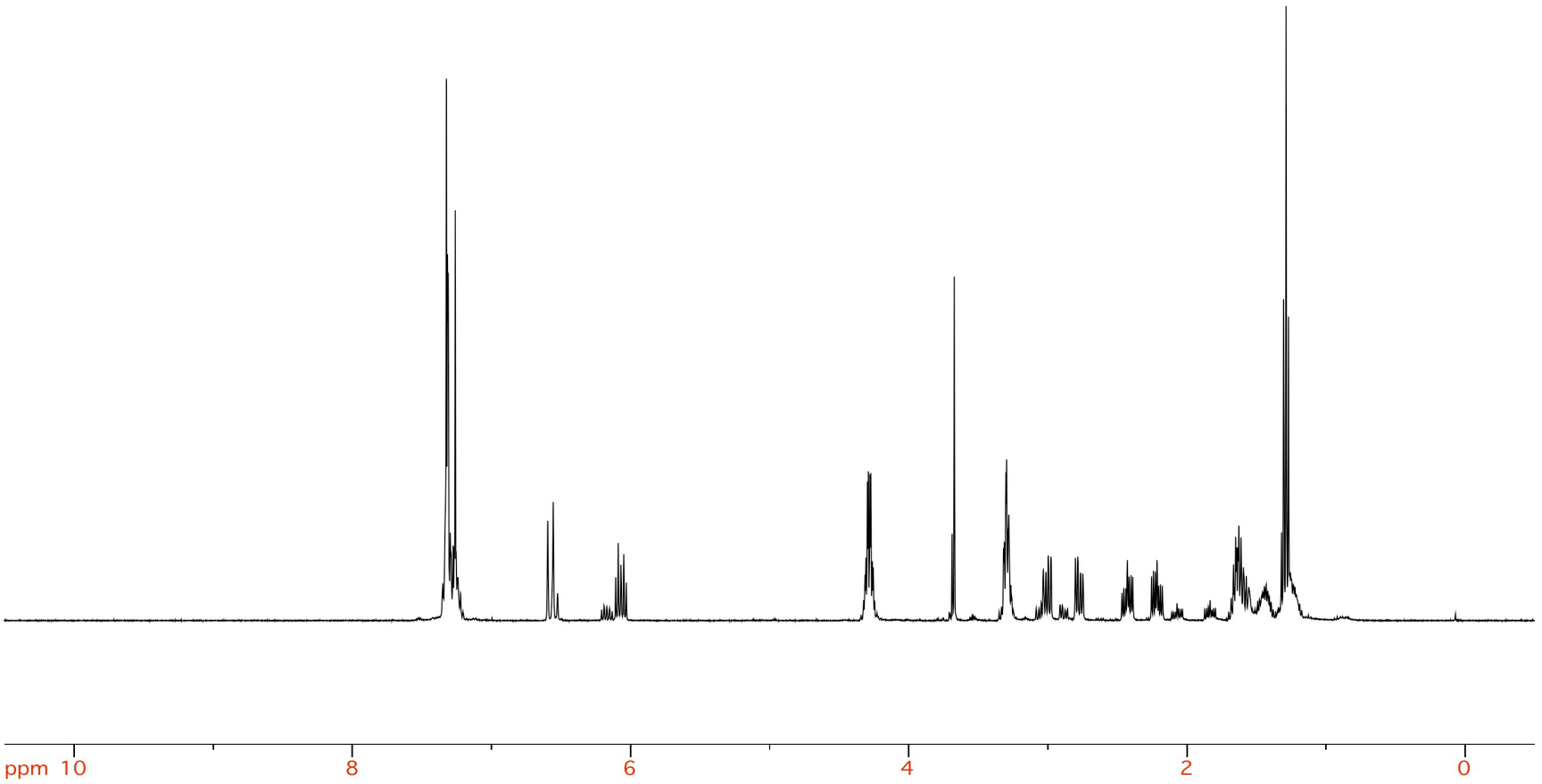


Figure A2.7a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.164** (Lower R_f diastereomer)

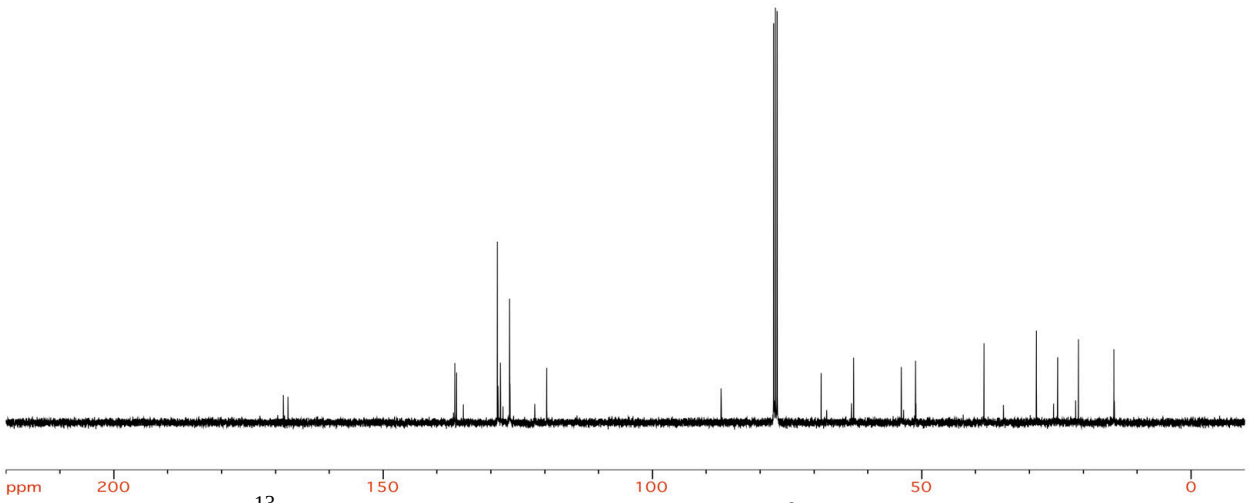


Figure A2.7b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **1.164** (Lower R_f diastereomer)

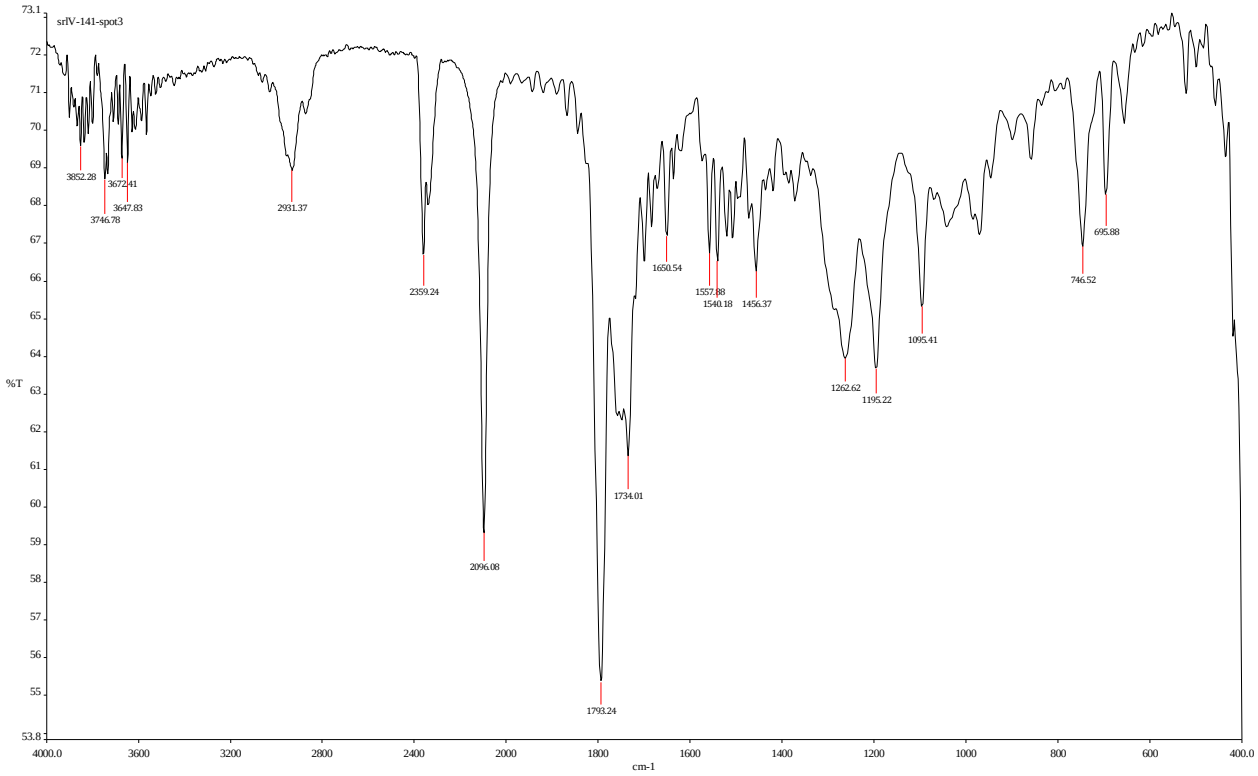
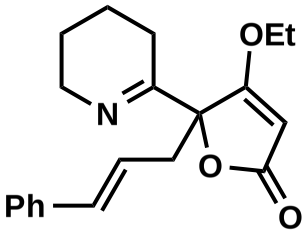


Figure A2.7c IR spectrum (thin film) of compound **1.164** (Lower R_f diastereomer)



1.174

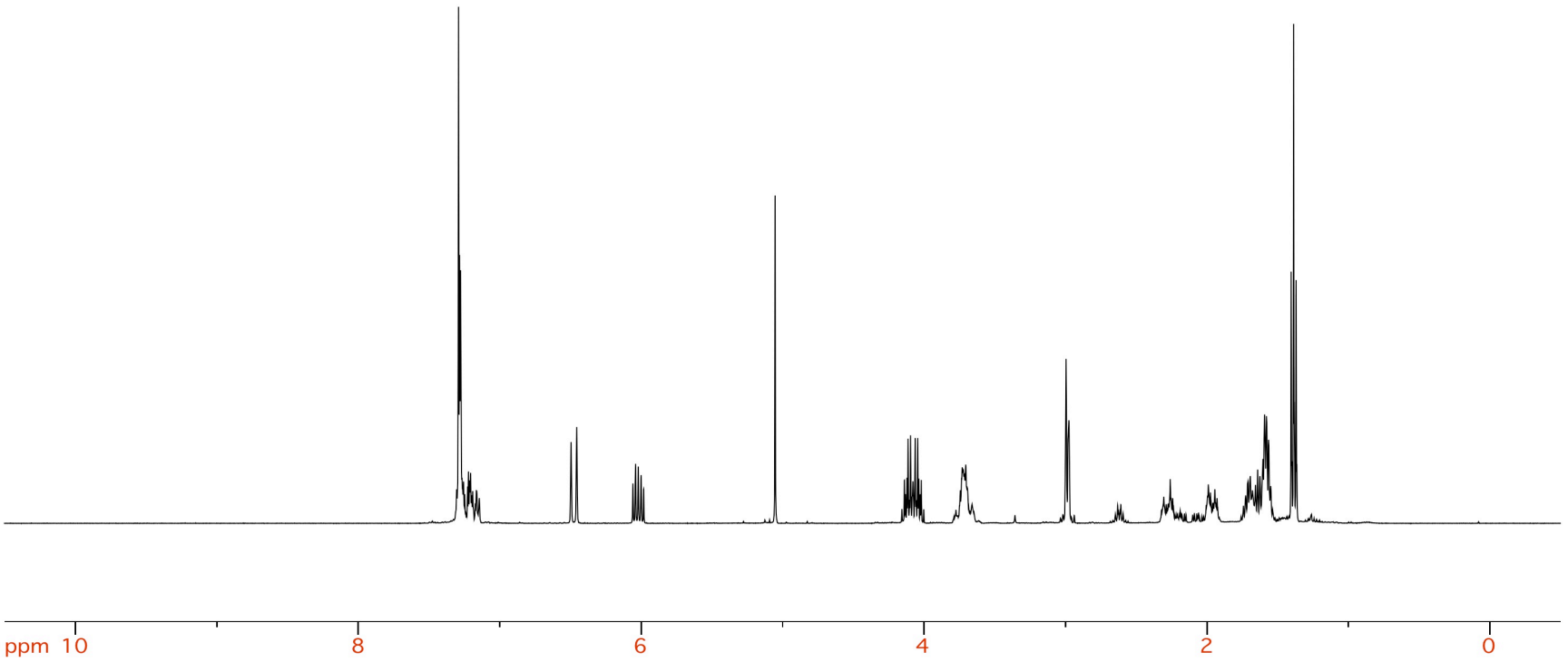


Figure A2.8a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.174**

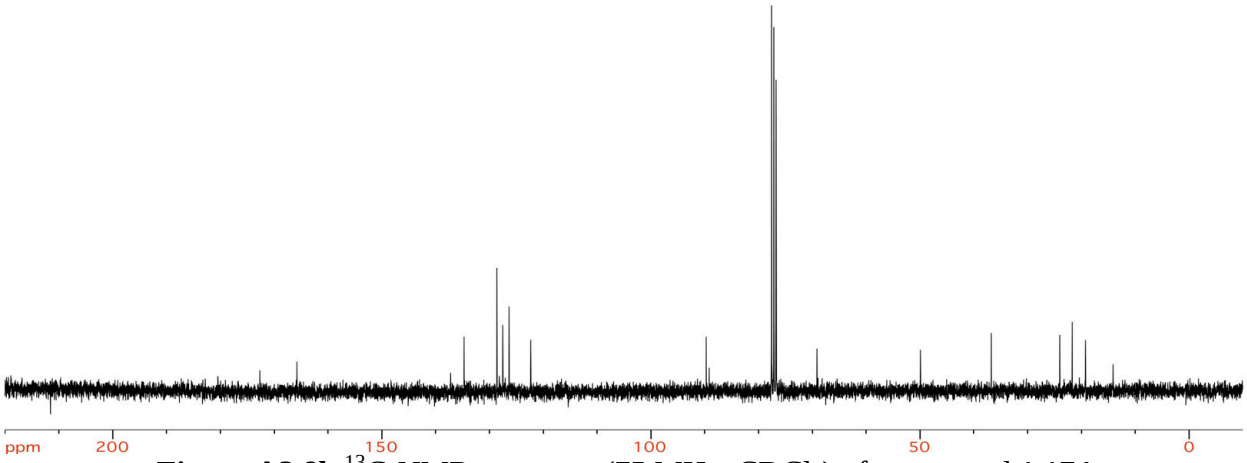


Figure A2.8b ^{13}C-NMR spectrum (75 MHz; $CDCl_3$) of compound **1.174**

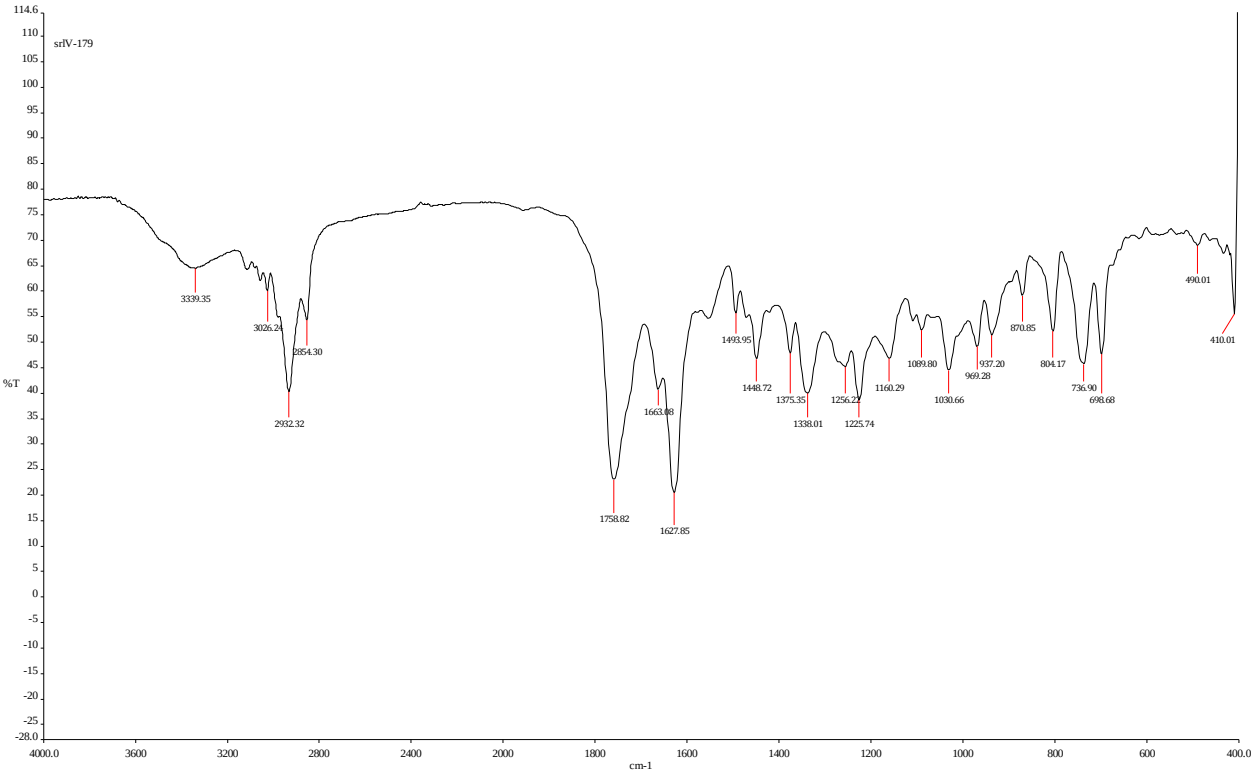
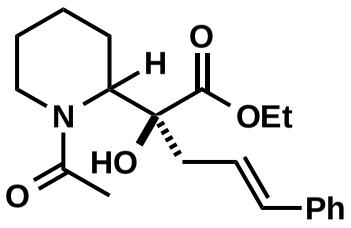


Figure A2.8c IR spectrum (thin film) of compound **1.174**



1.177

Figure A2.9a ^{1}H-NMR spectrum (300 MHz; 393 K; $CDCl_3$) of compound **1.177** (Higher R_f diastereomer)

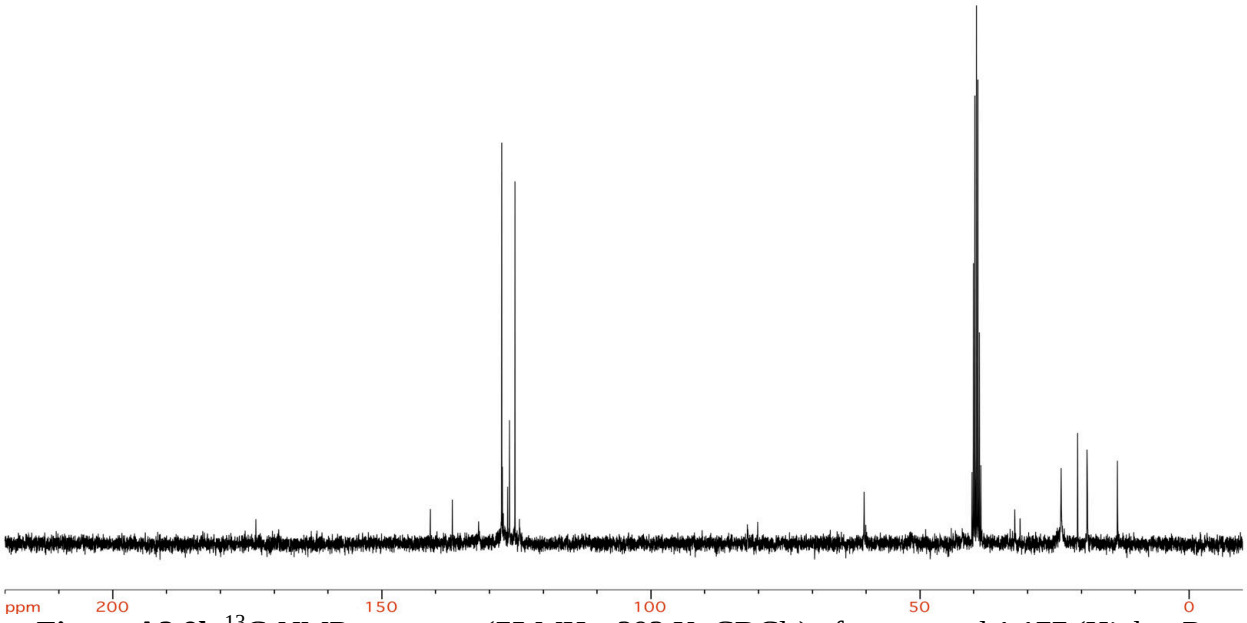


Figure A2.9b ^{13}C-NMR spectrum (75 MHz; 393 K; $CDCl_3$) of compound **1.177** (Higher R_f diastereomer)

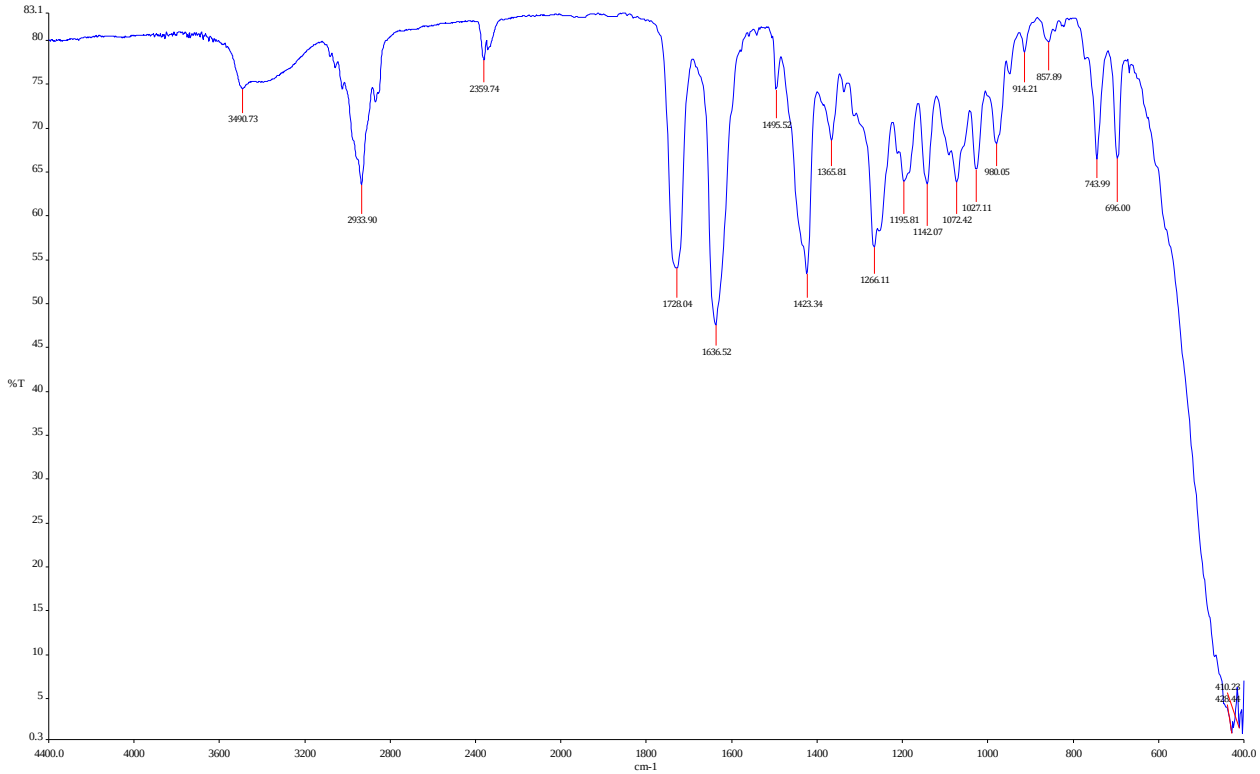
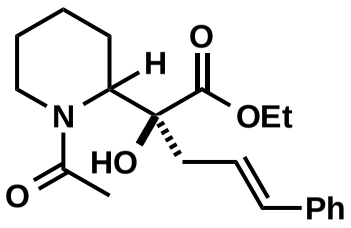


Figure A2.9c IR spectrum (thin film) of compound **1.177** (Higher R_f diastereomer)



1.177

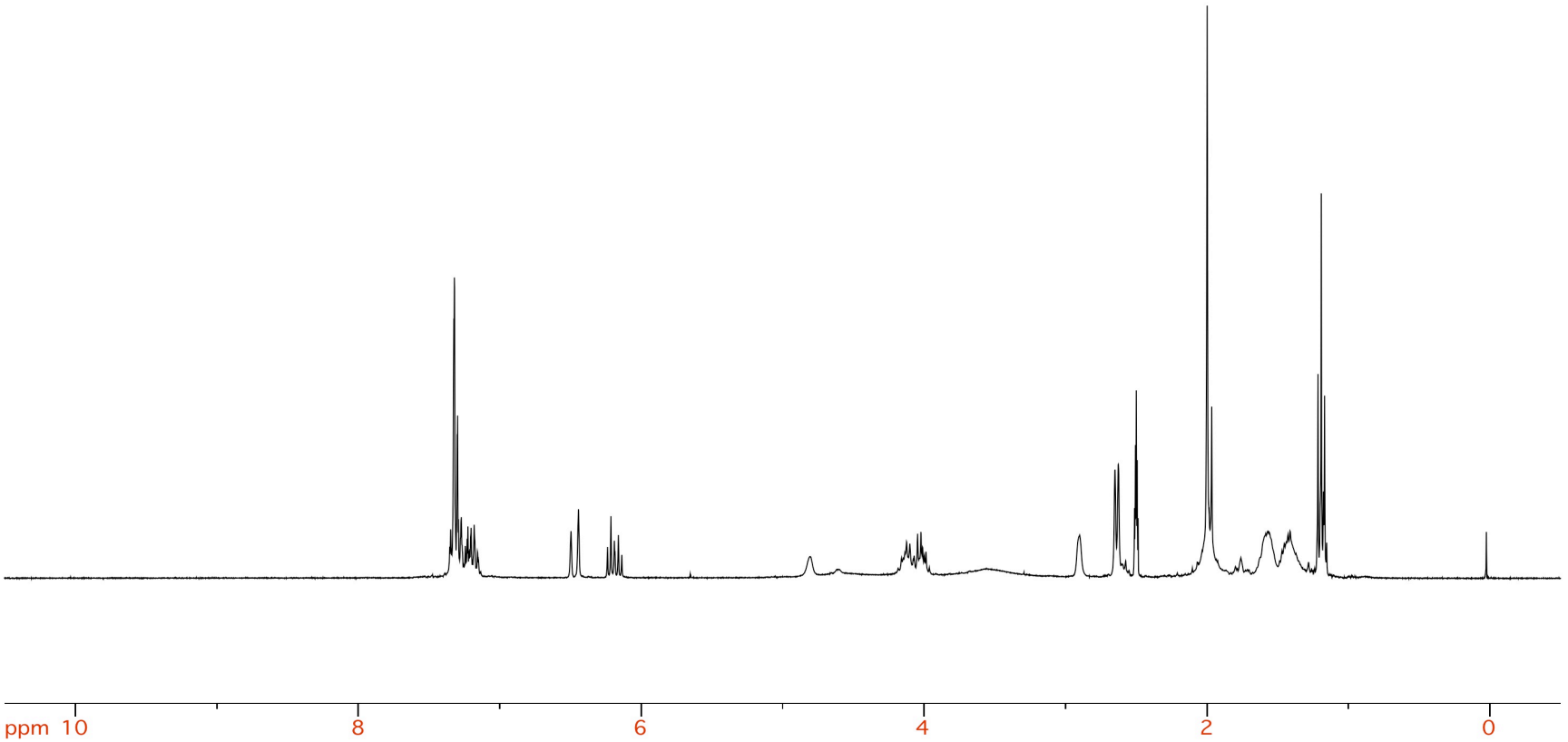


Figure A2.10a ^{1}H-NMR spectrum (300 MHz; 393 K; $CDCl_3$) of compound **1.177** (Lower R_f diastereomer)

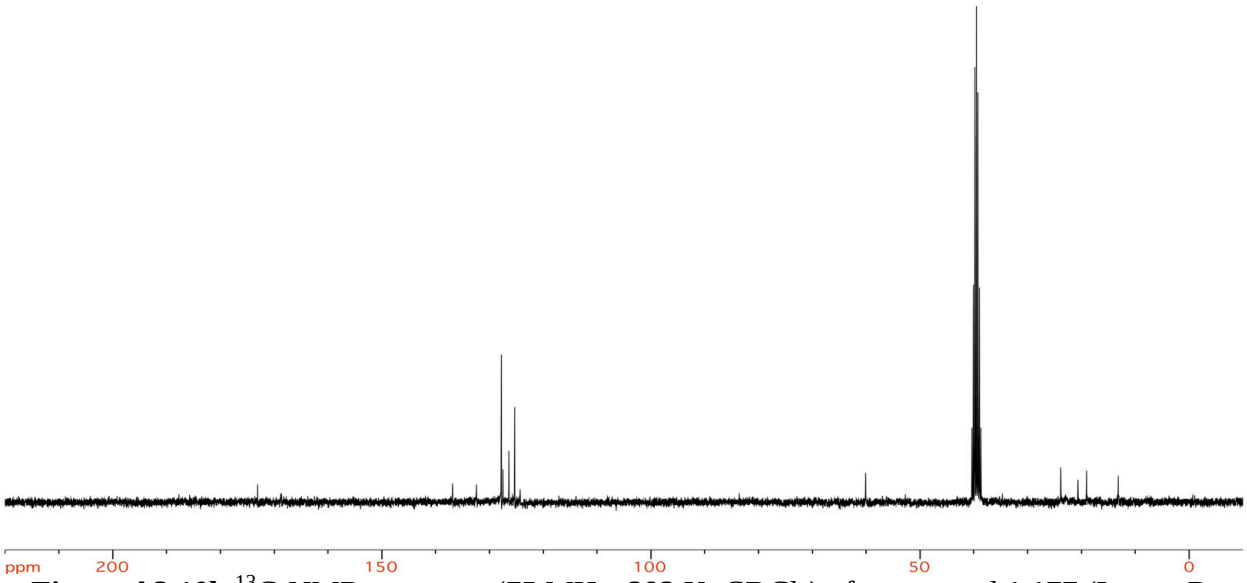


Figure A2.10b ^{13}C-NMR spectrum (75 MHz; 393 K; $CDCl_3$) of compound **1.177** (Lower R_f diastereomer)

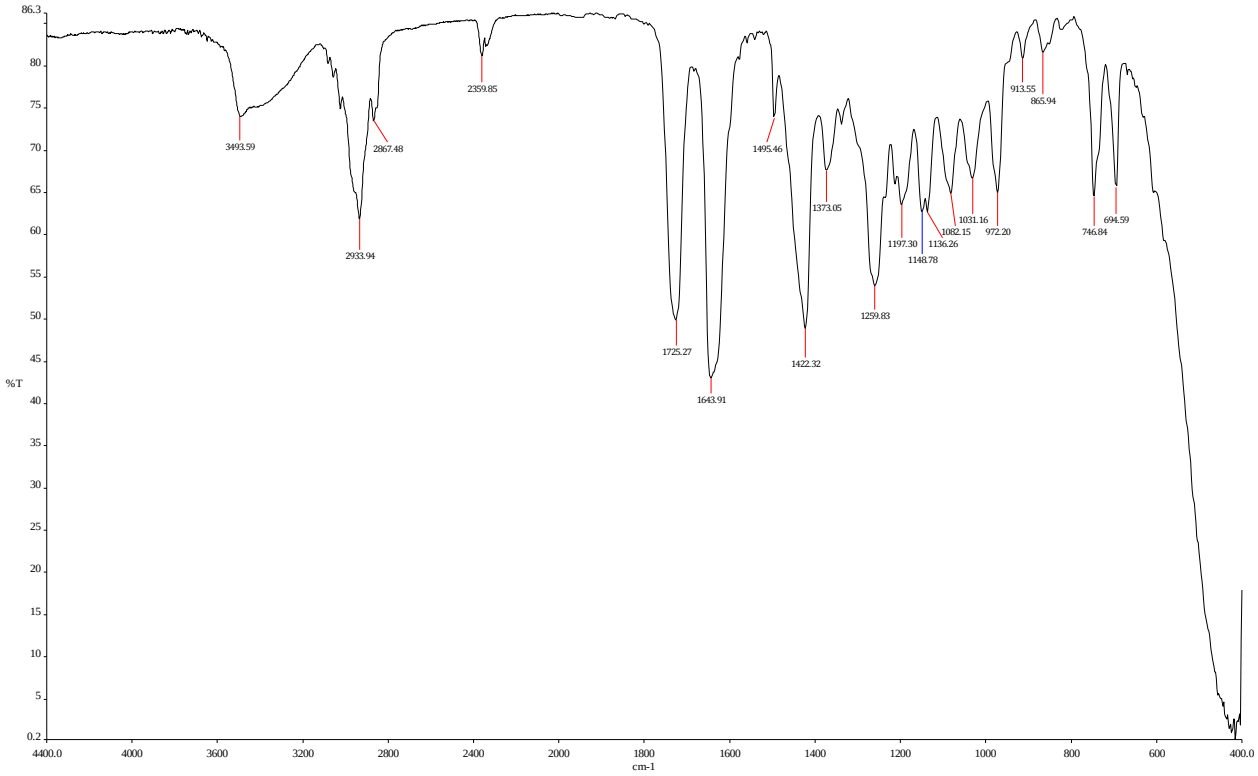
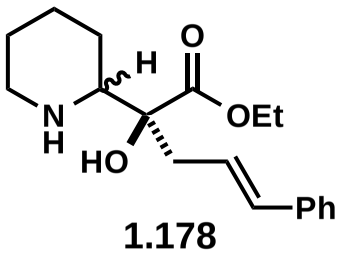


Figure A2.10c IR spectrum (thin film) of compound **1.177** (Lower R_f diastereomer)



1.178

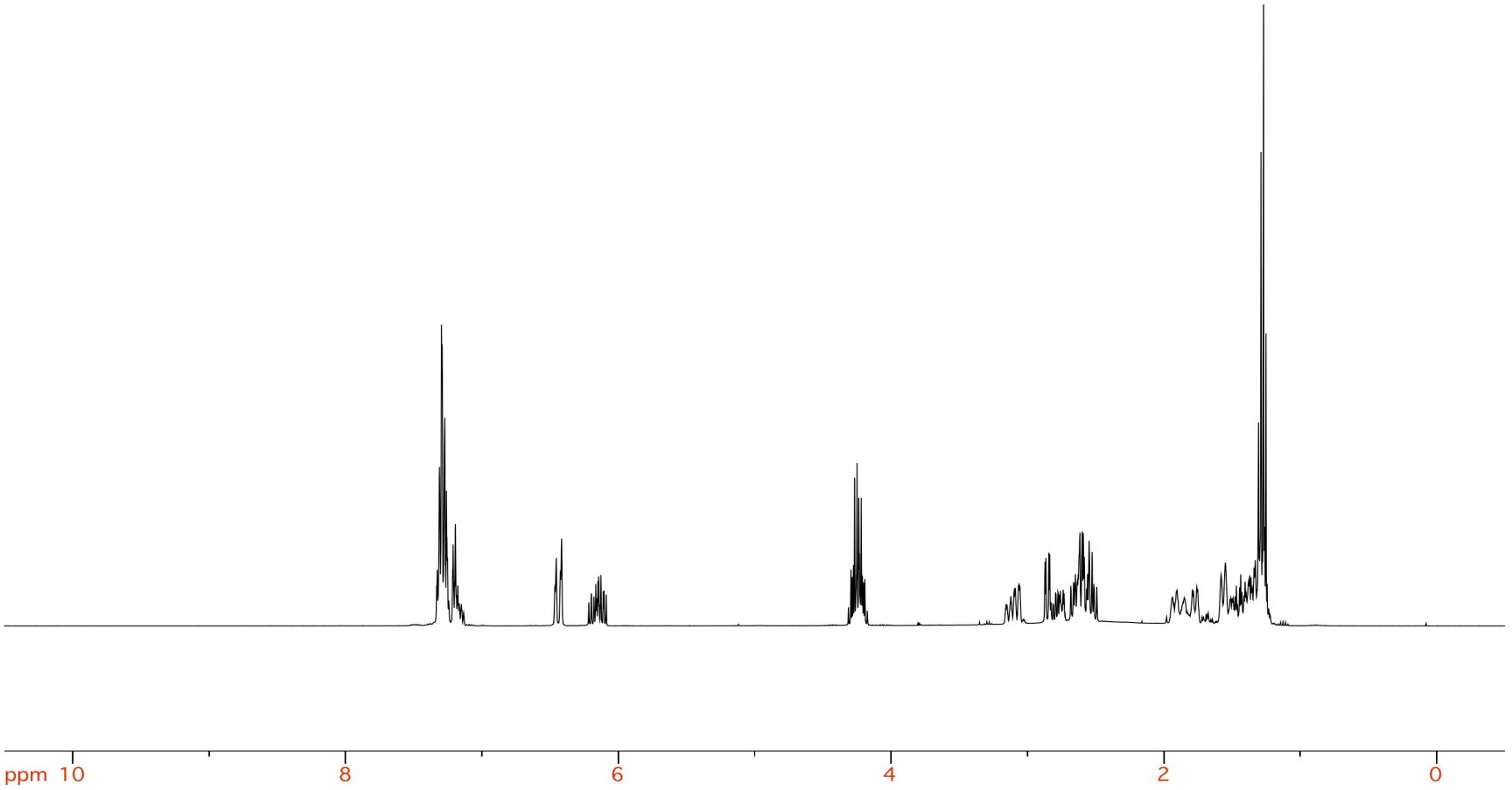


Figure A2.11a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.178**

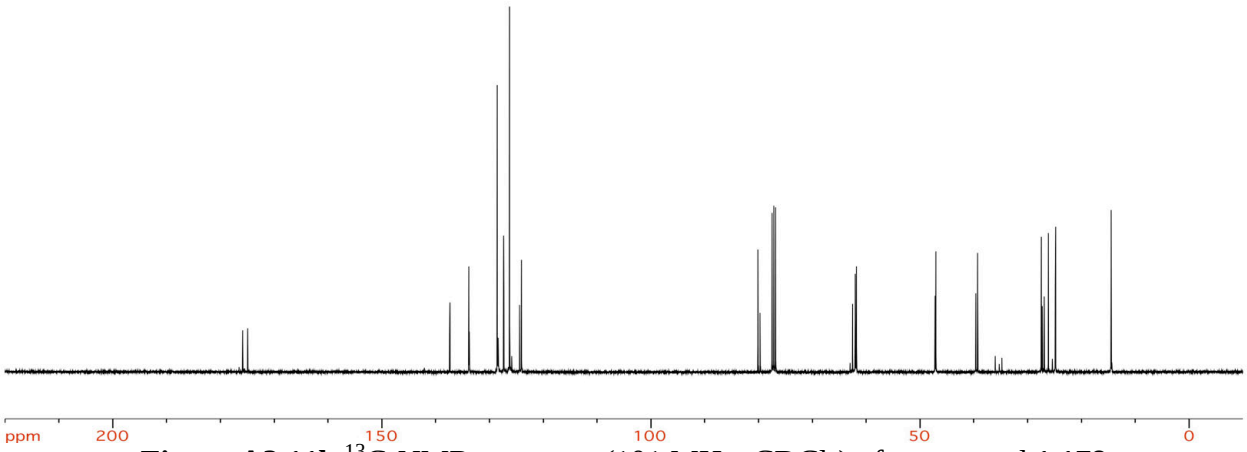


Figure A2.11b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **1.178**

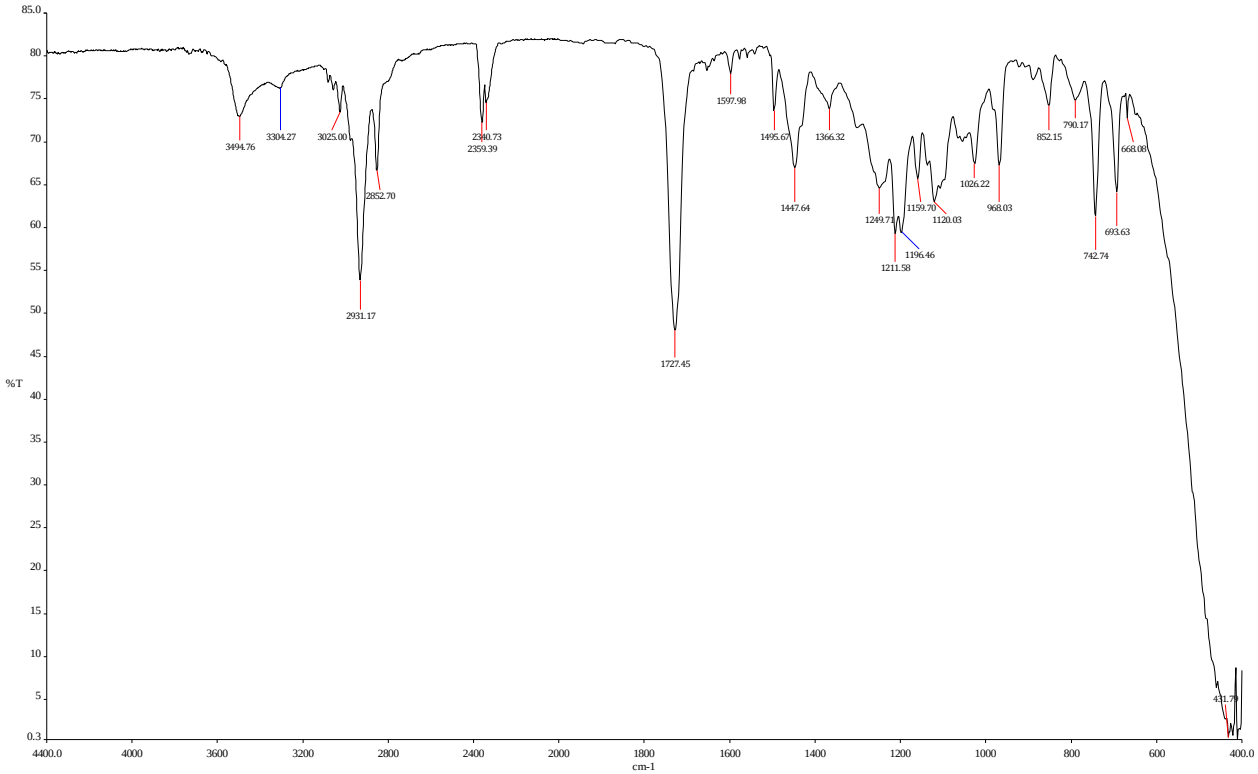
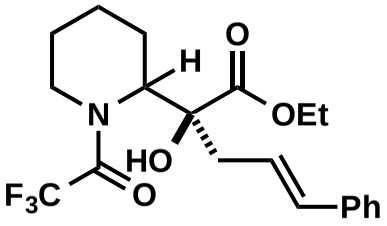


Figure A2.11c IR spectrum (thin film) of compound **1.178**



1.179

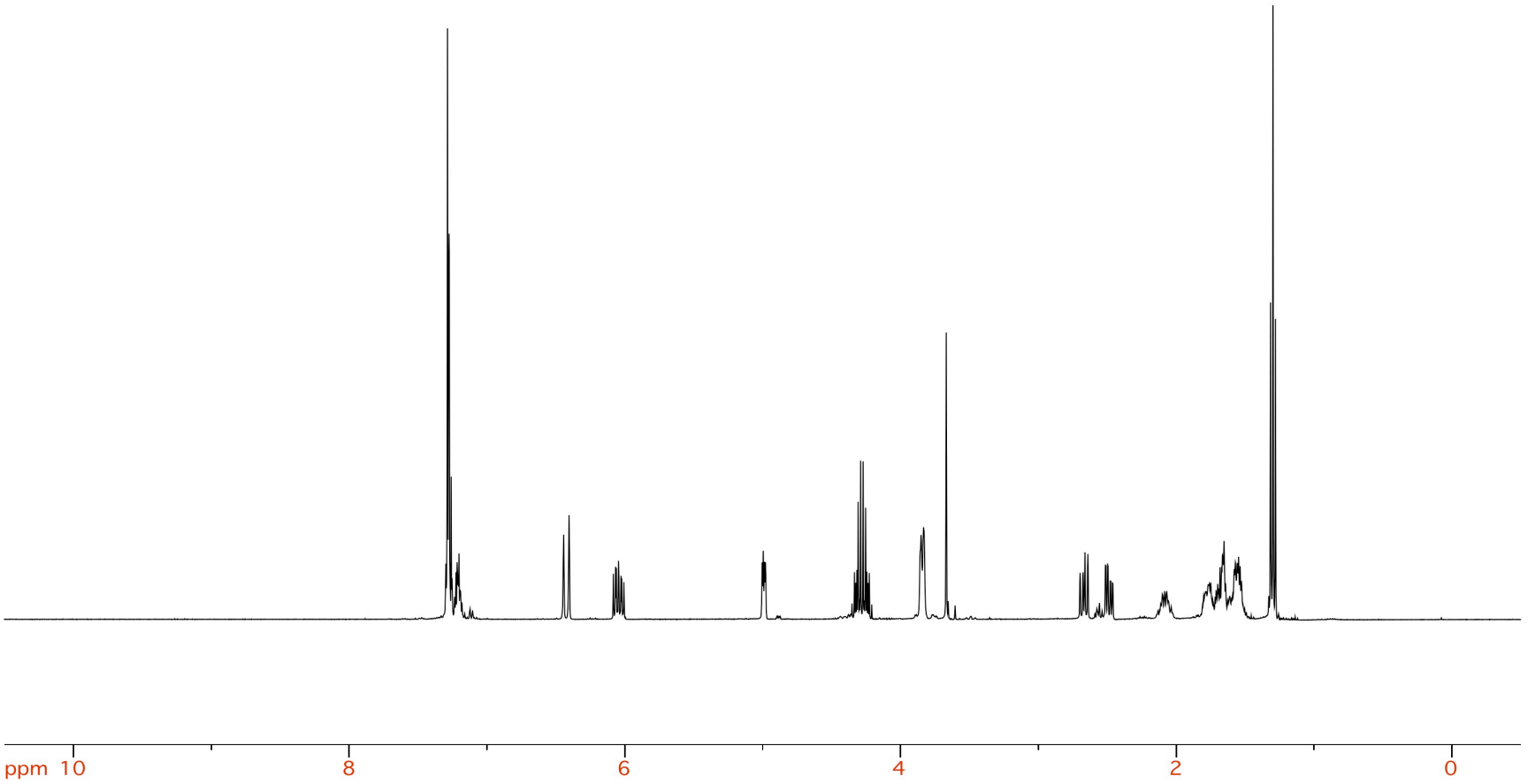


Figure A2.12a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.179** (Higher R_f diastereomer)

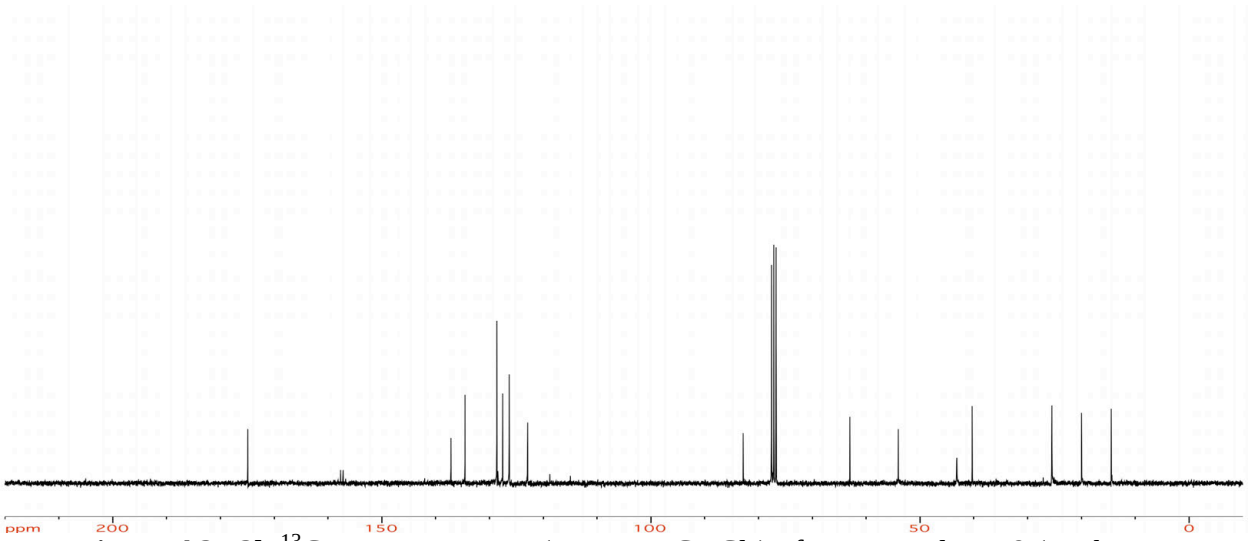


Figure A2.12b ^{13}C-NMR spectrum (75 MHz; $CDCl_3$) of compound **1.179** (Higher R_f diastereomer)

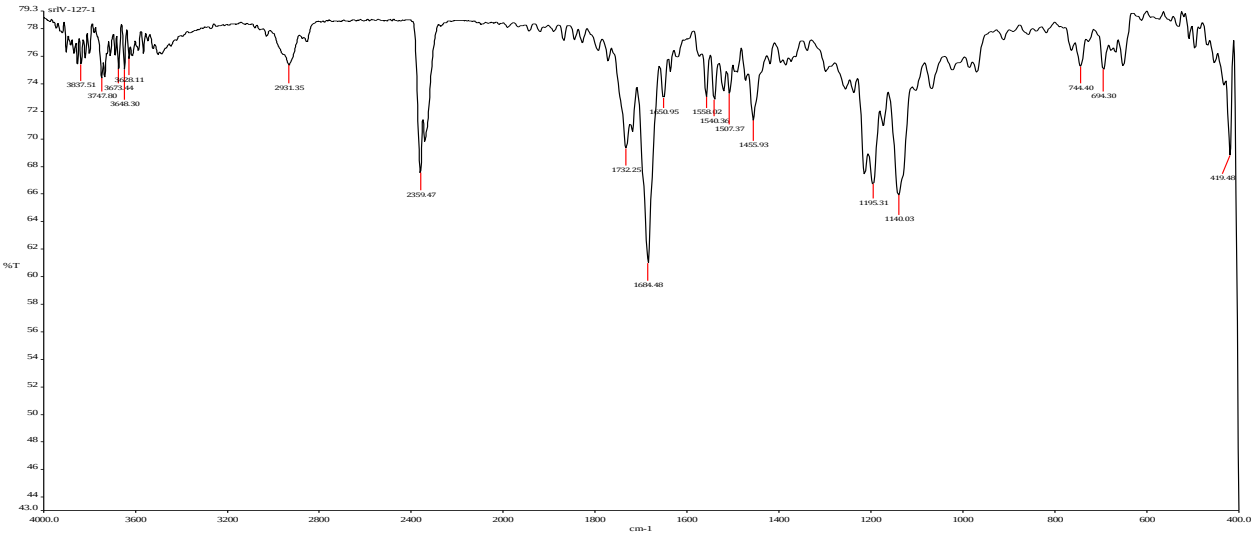


Figure A2.12c IR spectrum (thin film) of compound **1.179** (Higher R_f diastereomer)

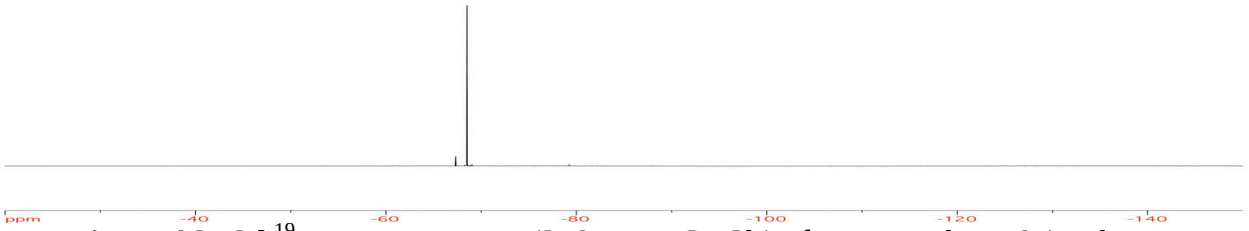
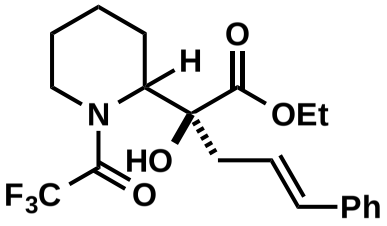


Figure A2.12d ^{19}F-NMR spectrum (376 MHz; $CDCl_3$) of compound **1.179** (Higher R_f diastereomer)



1.179

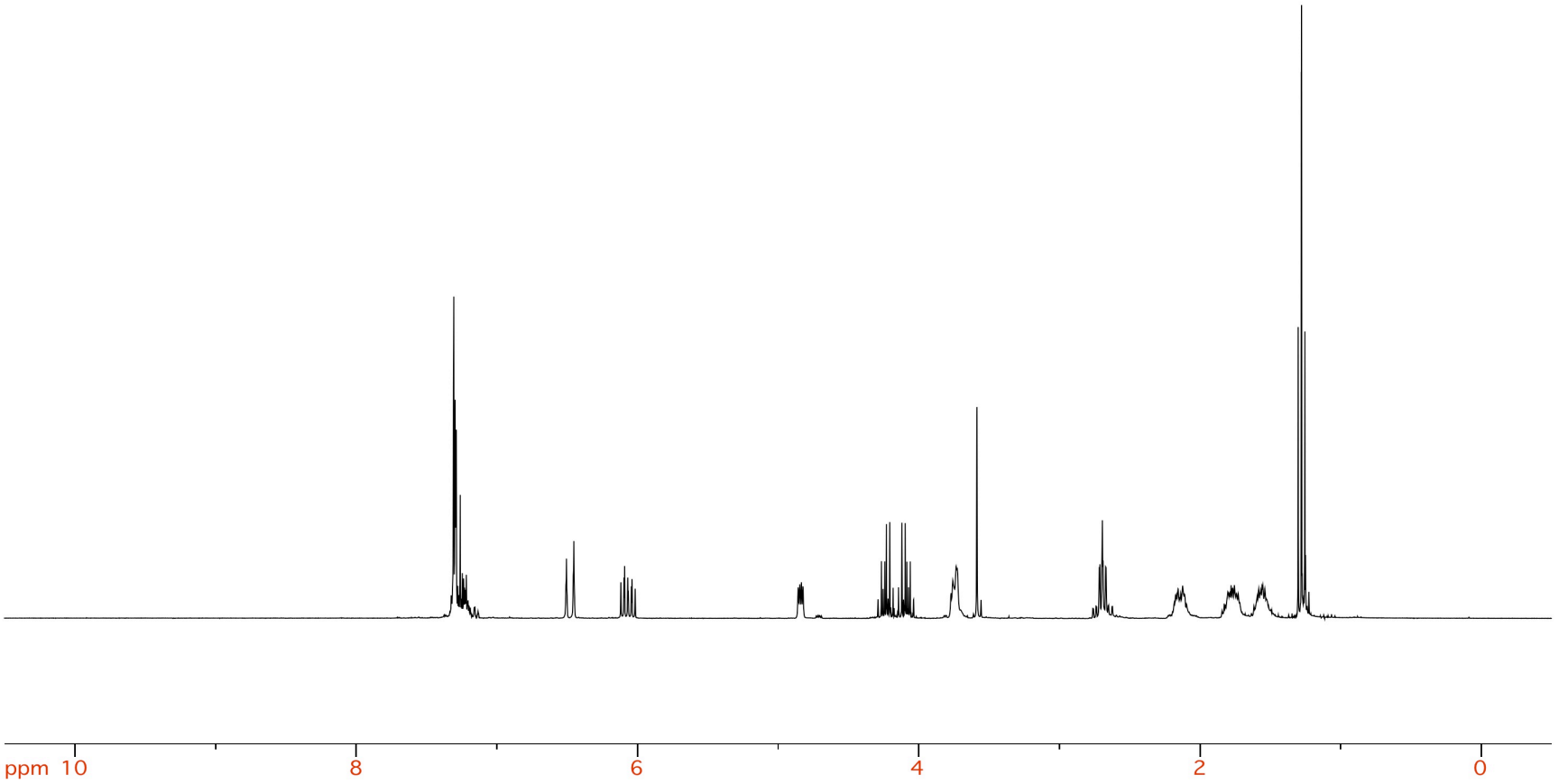


Figure A2.13a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.179** (Lower R_f diastereomer)

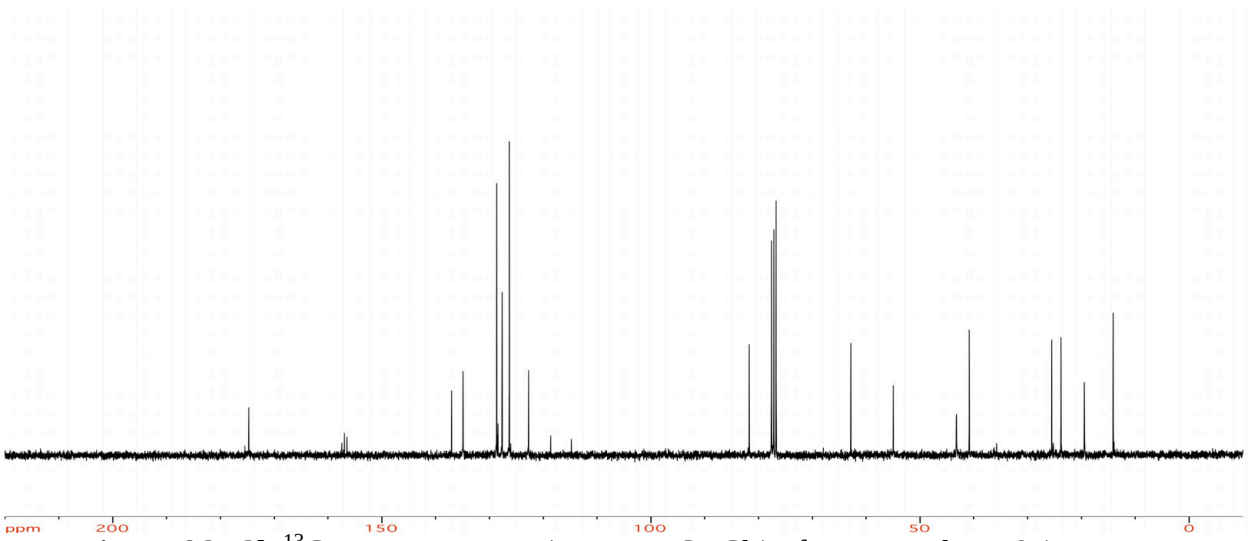


Figure A2.13b ^{13}C-NMR spectrum (75 MHz; $CDCl_3$) of compound **1.179** (Lower R_f diastereomer)

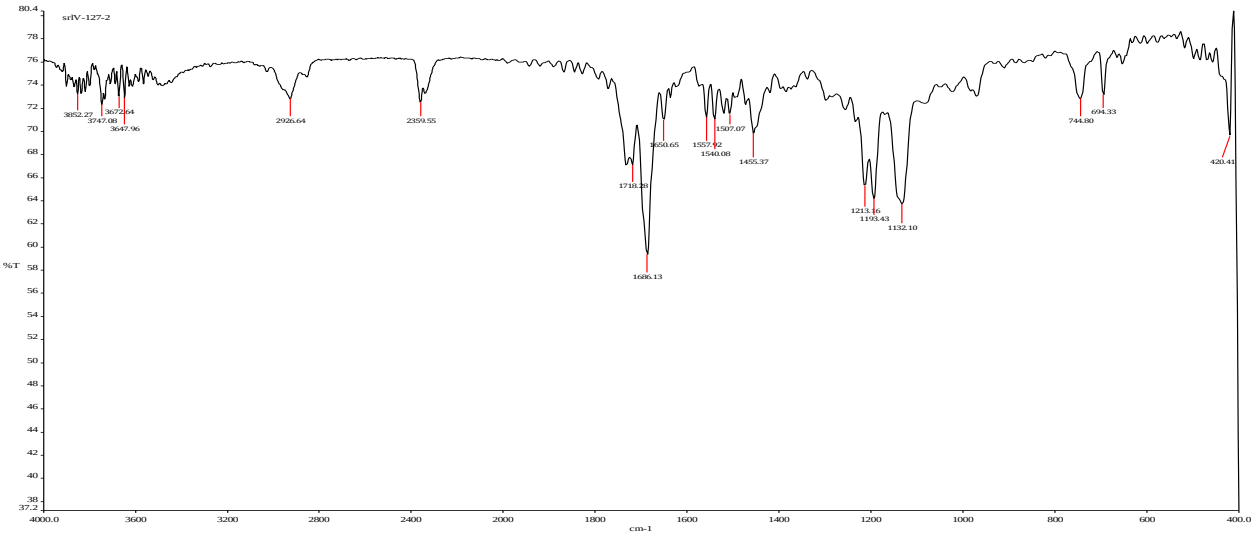


Figure A2.13c IR spectrum (thin film) of compound **1.179** (Lower R_f diastereomer)

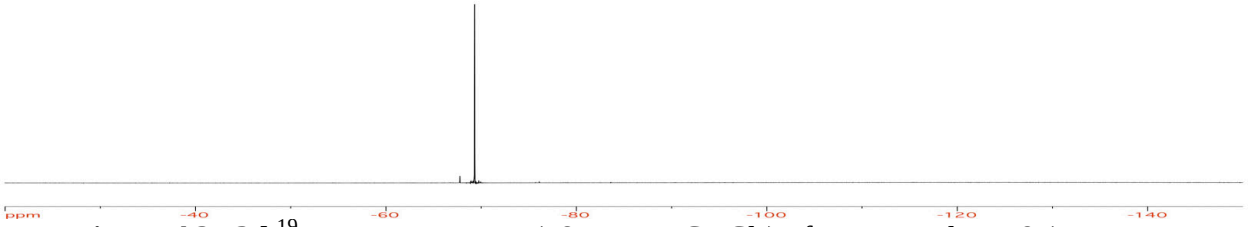
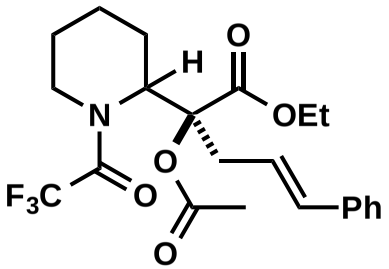


Figure A2.13d ^{19}F-NMR spectrum (282 MHz; $CDCl_3$) of compound **1.179** (Lower R_f diastereomer)



1.180

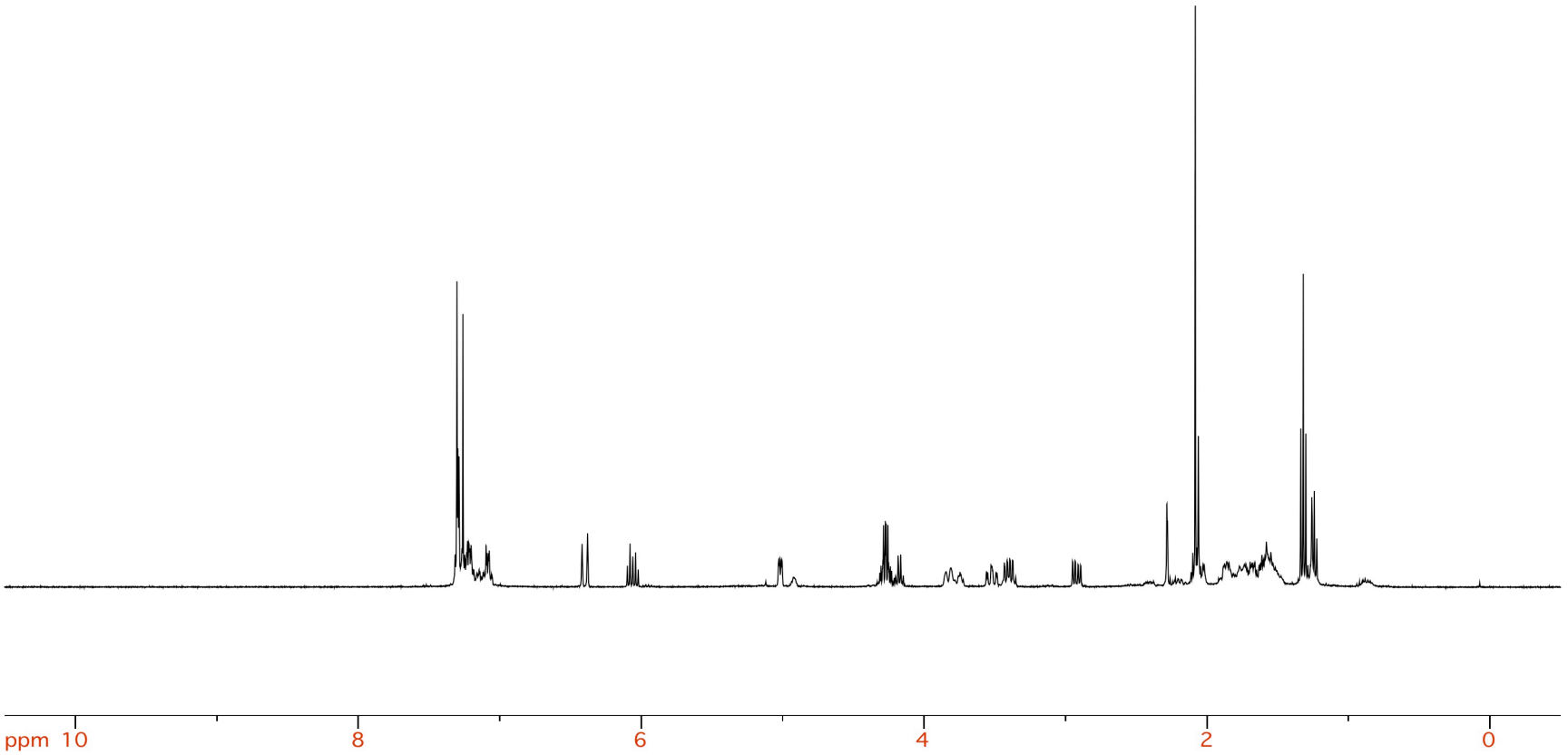


Figure A2.14a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.180** (Higher R_f diastereomer)

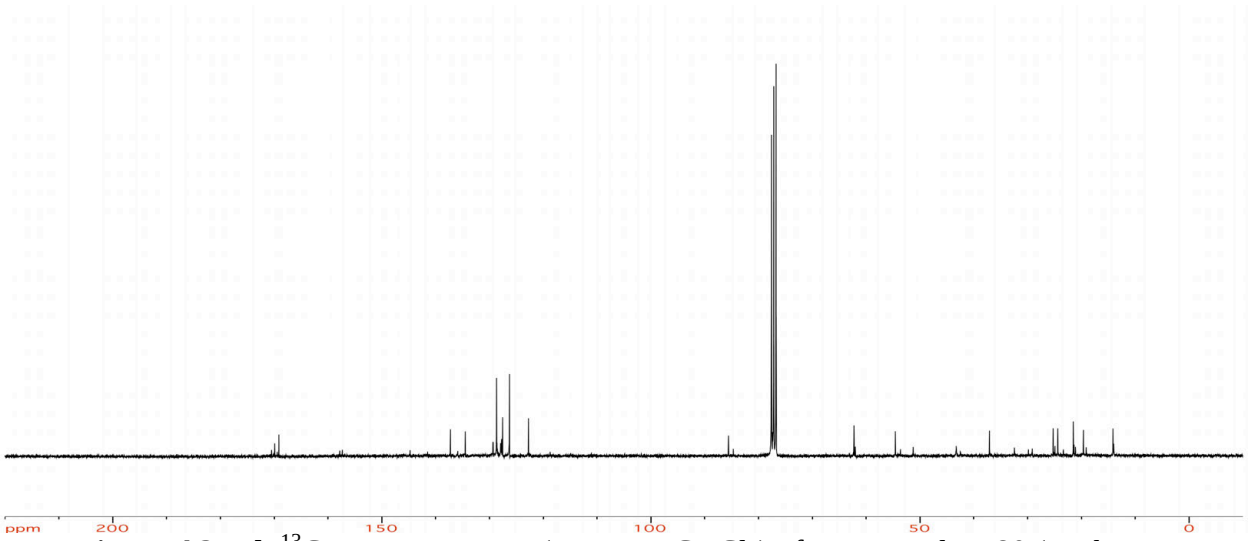


Figure A2.14b ^{13}C-NMR spectrum (75 MHz; $CDCl_3$) of compound **1.180** (Higher R_f diastereomer)

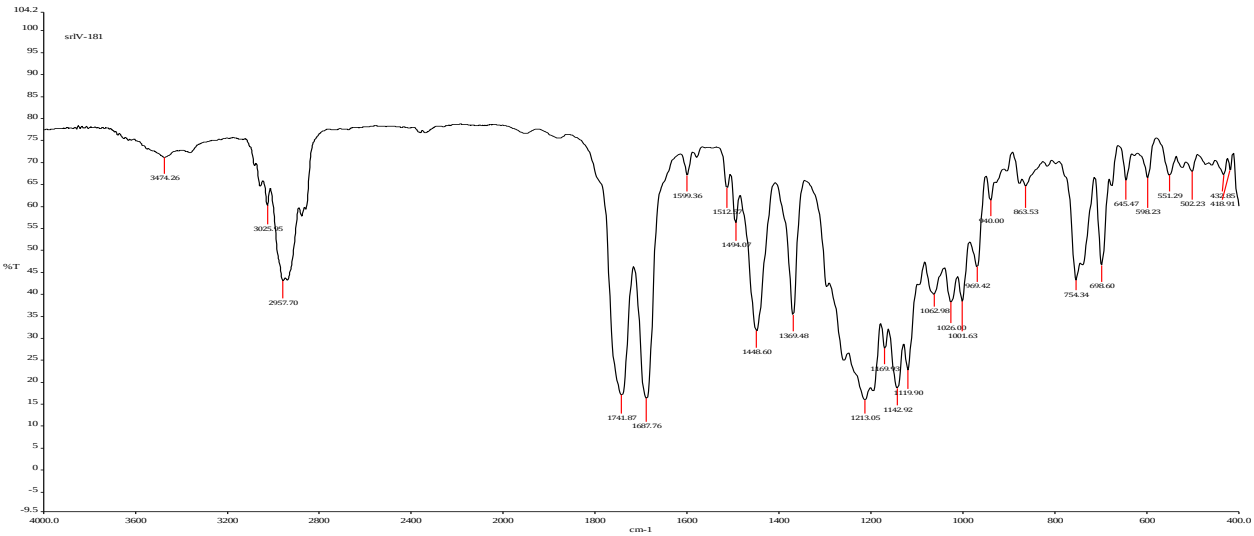


Figure A2.14c IR spectrum (thin film) of compound **1.180** (Higher R_f diastereomer)

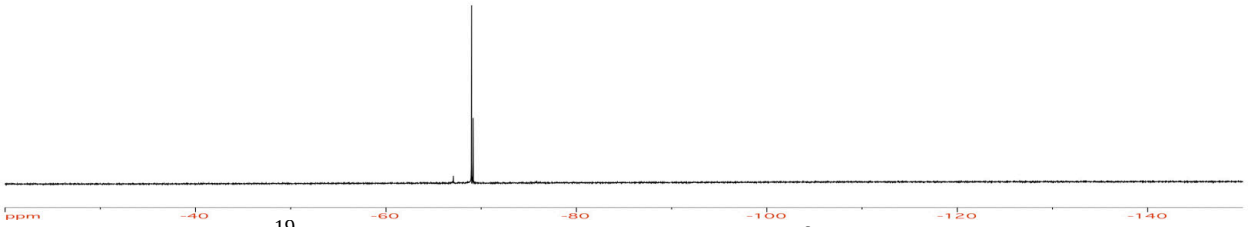
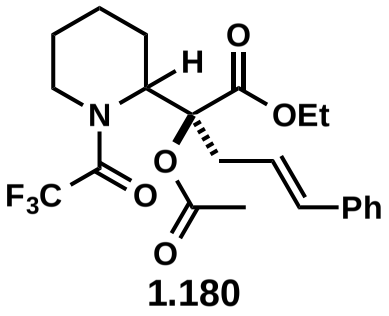


Figure A2.14d ^{19}F-NMR spectrum (282 MHz; $CDCl_3$) of compound **1.180** (Higher R_f diastereomer)



1.180

Figure A2.15a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.180** (Lower R_f diastereomer)

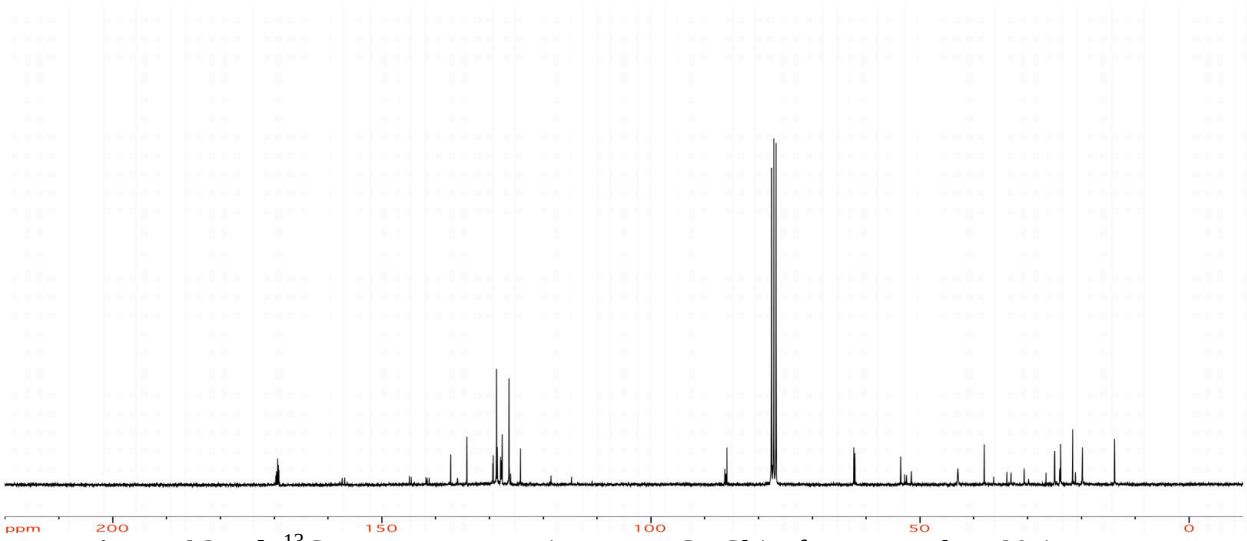


Figure A2.15b ^{13}C-NMR spectrum (75 MHz; $CDCl_3$) of compound **1.180** (Lower R_f diastereomer)

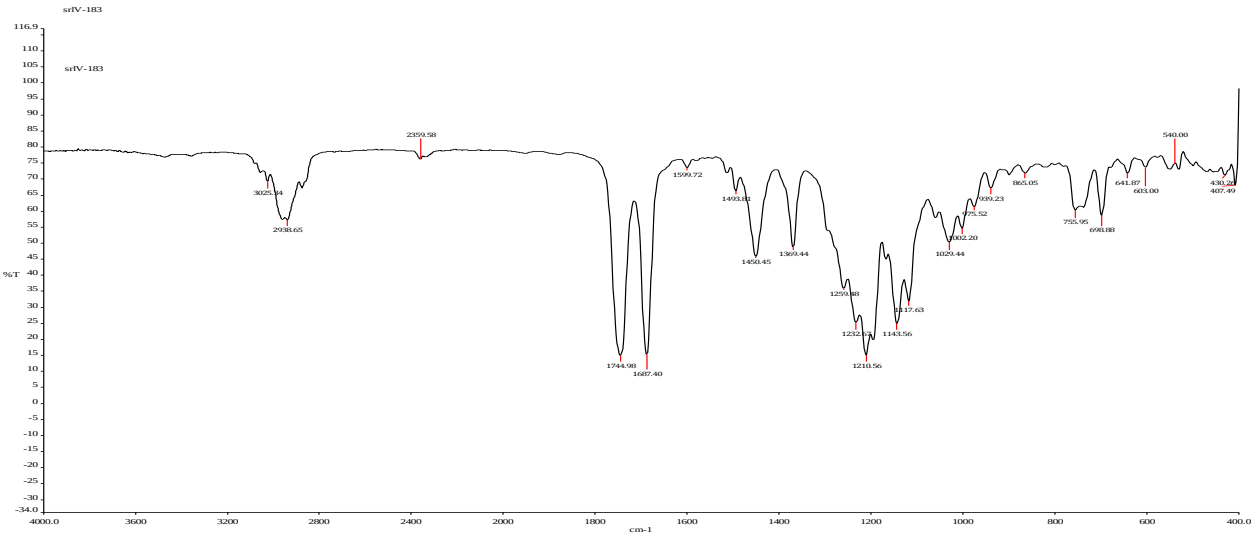


Figure A2.15c IR spectrum (thin film) of compound **1.180** (Lower R_f diastereomer)

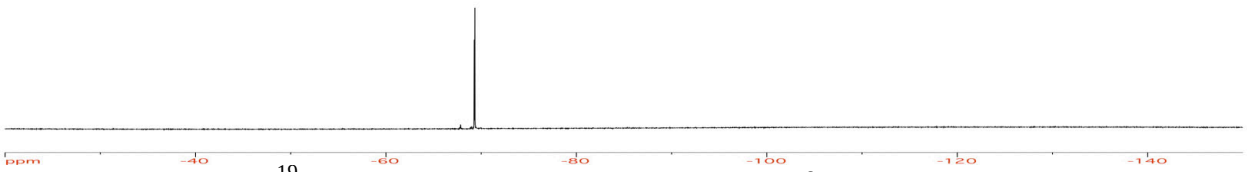
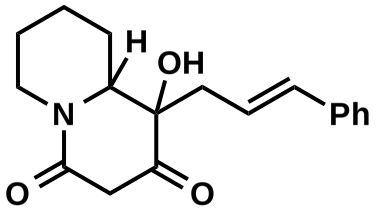


Figure A2.15d ^{19}F-NMR spectrum (282 MHz; $CDCl_3$) of compound **1.180** (Lower R_f diastereomer)



1.183

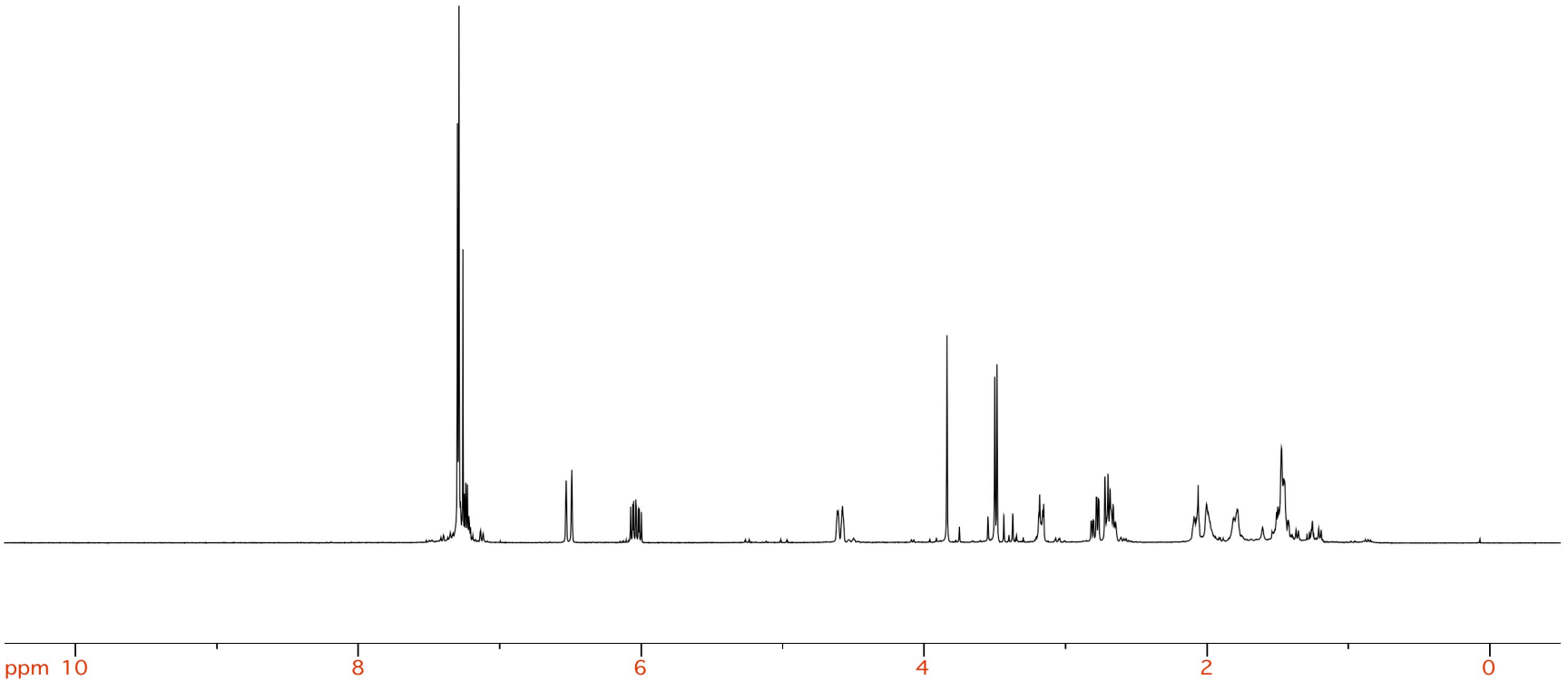


Figure A2.16a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.183** (Higher R_f diastereomer)

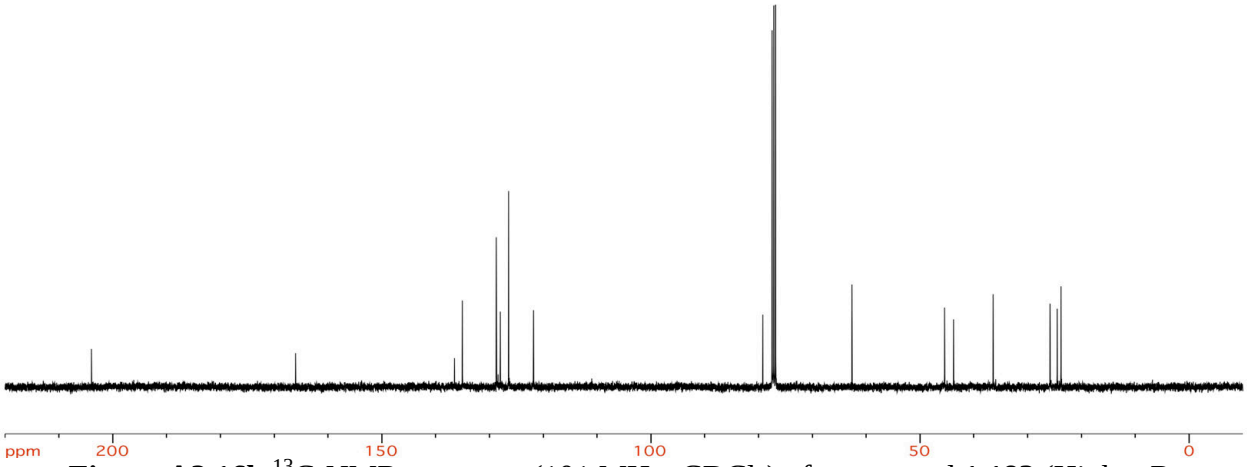


Figure A2.16b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **1.183** (Higher R_f diastereomer)

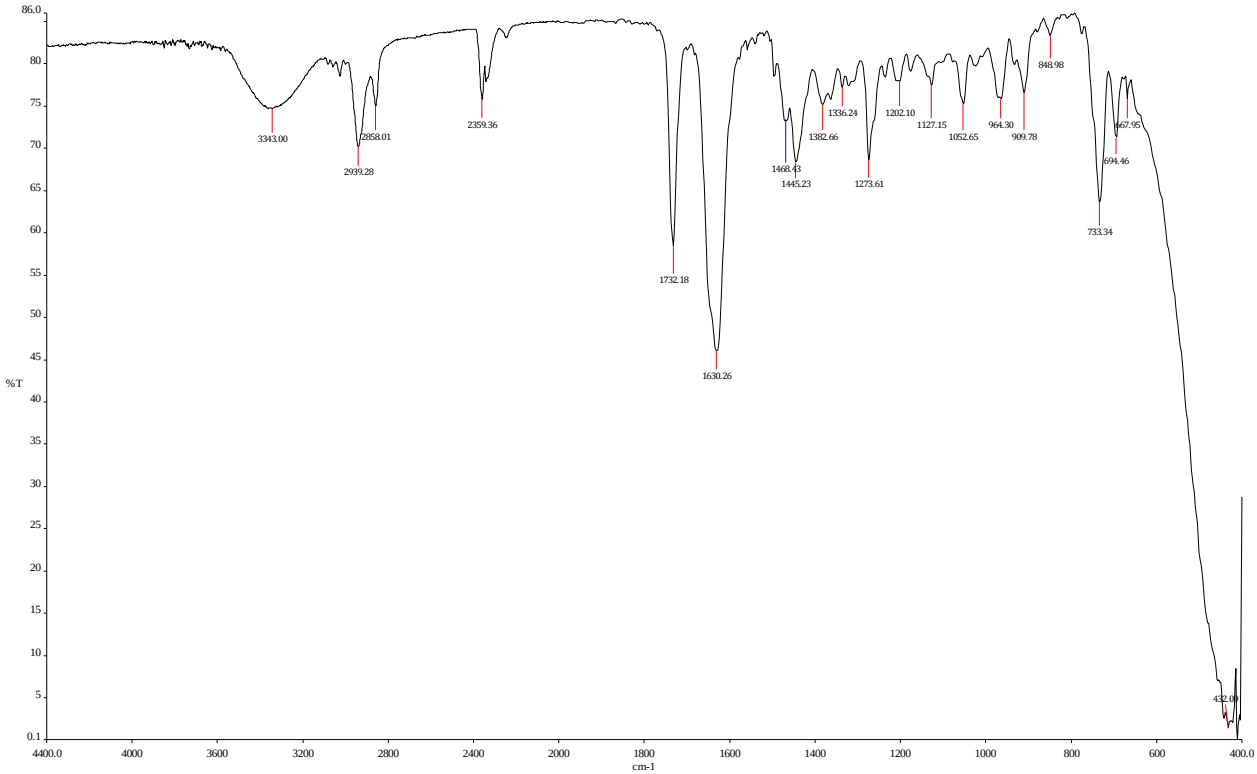
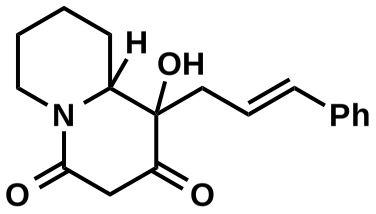


Figure A2.16c IR spectrum (thin film) of compound **1.183** (Higher R_f diastereomer)



1.183

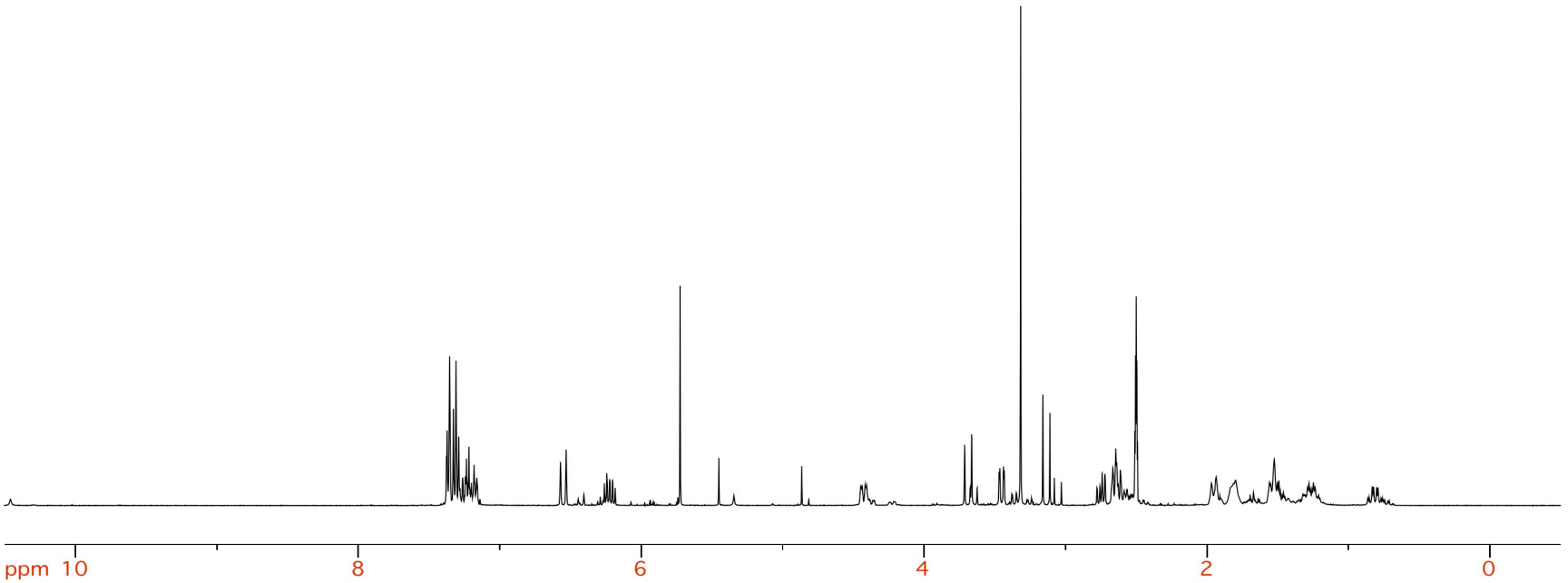


Figure A2.17a ^{1}H-NMR spectrum (400 MHz; DMSO-d_6) of compound **1.183** (Lower R_f diastereomer)

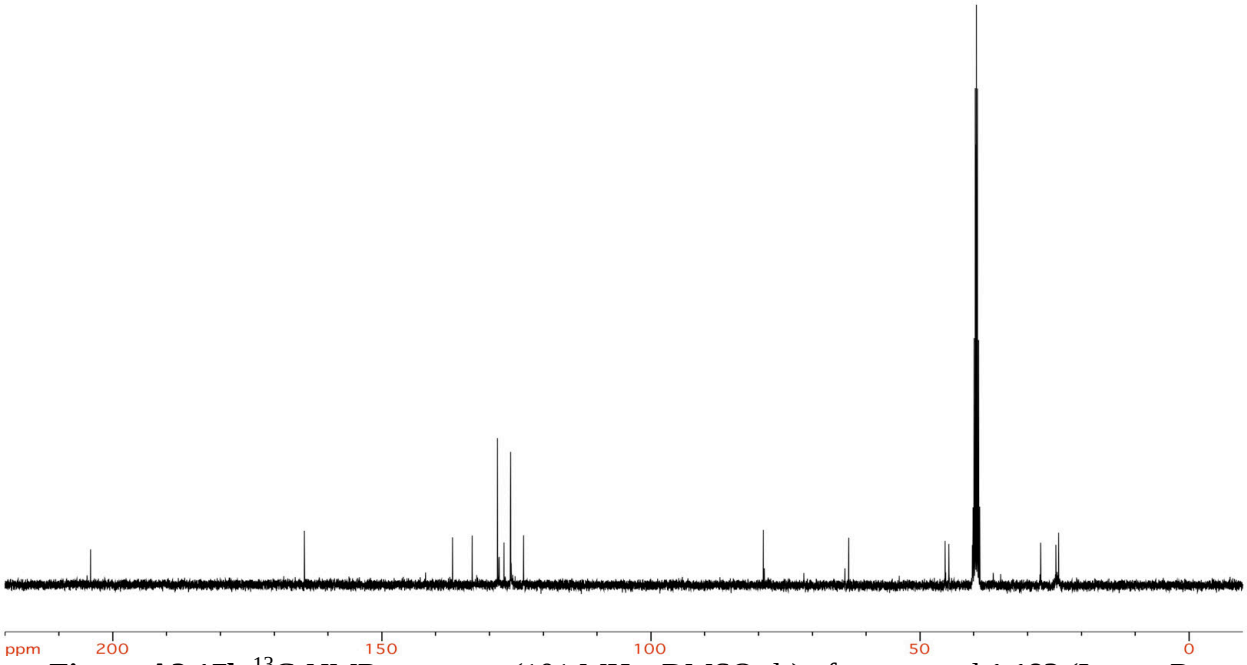


Figure A2.17b ^{13}C-NMR spectrum (101 MHz; DMSO-d_6) of compound **1.183** (Lower R_f diastereomer)

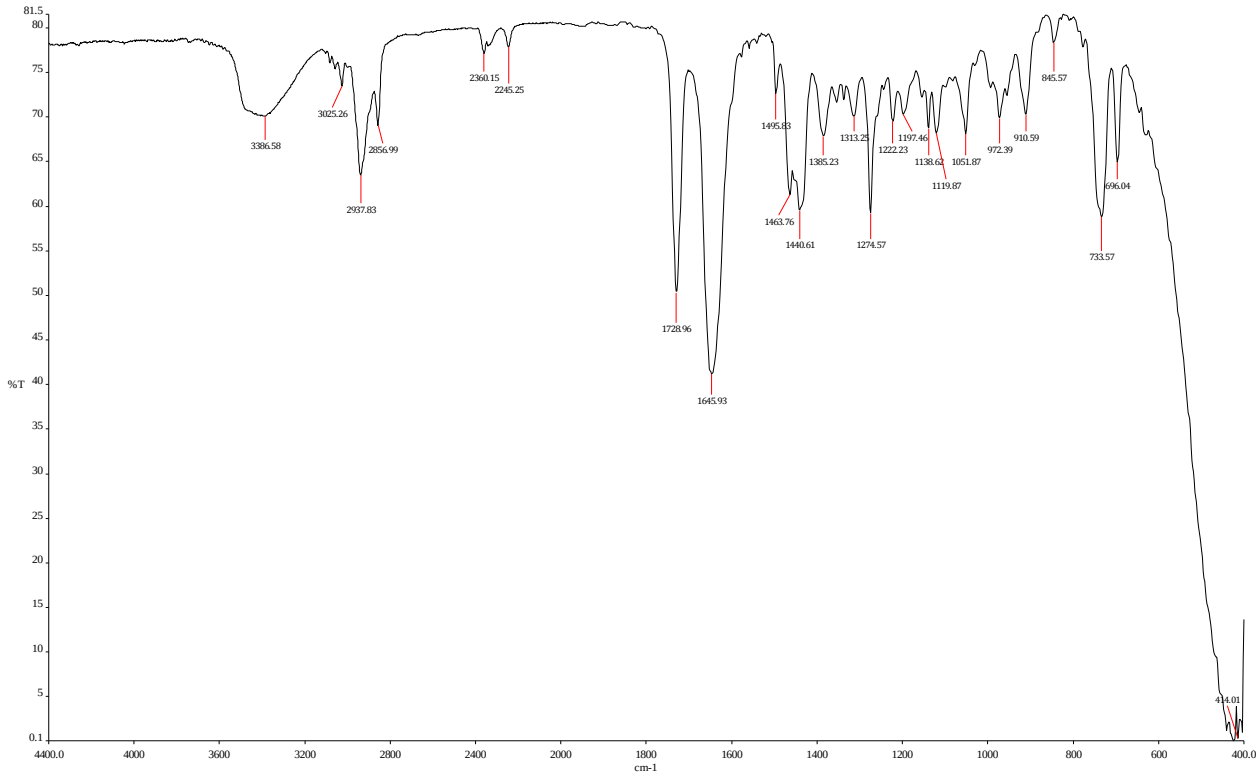
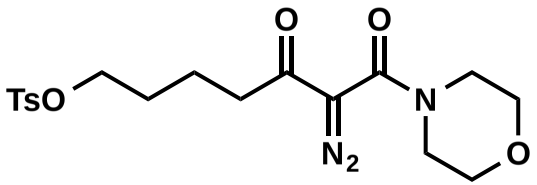


Figure A2.17c IR spectrum (thin film) of compound **1.183** (Lower R_f diastereomer)



1.185

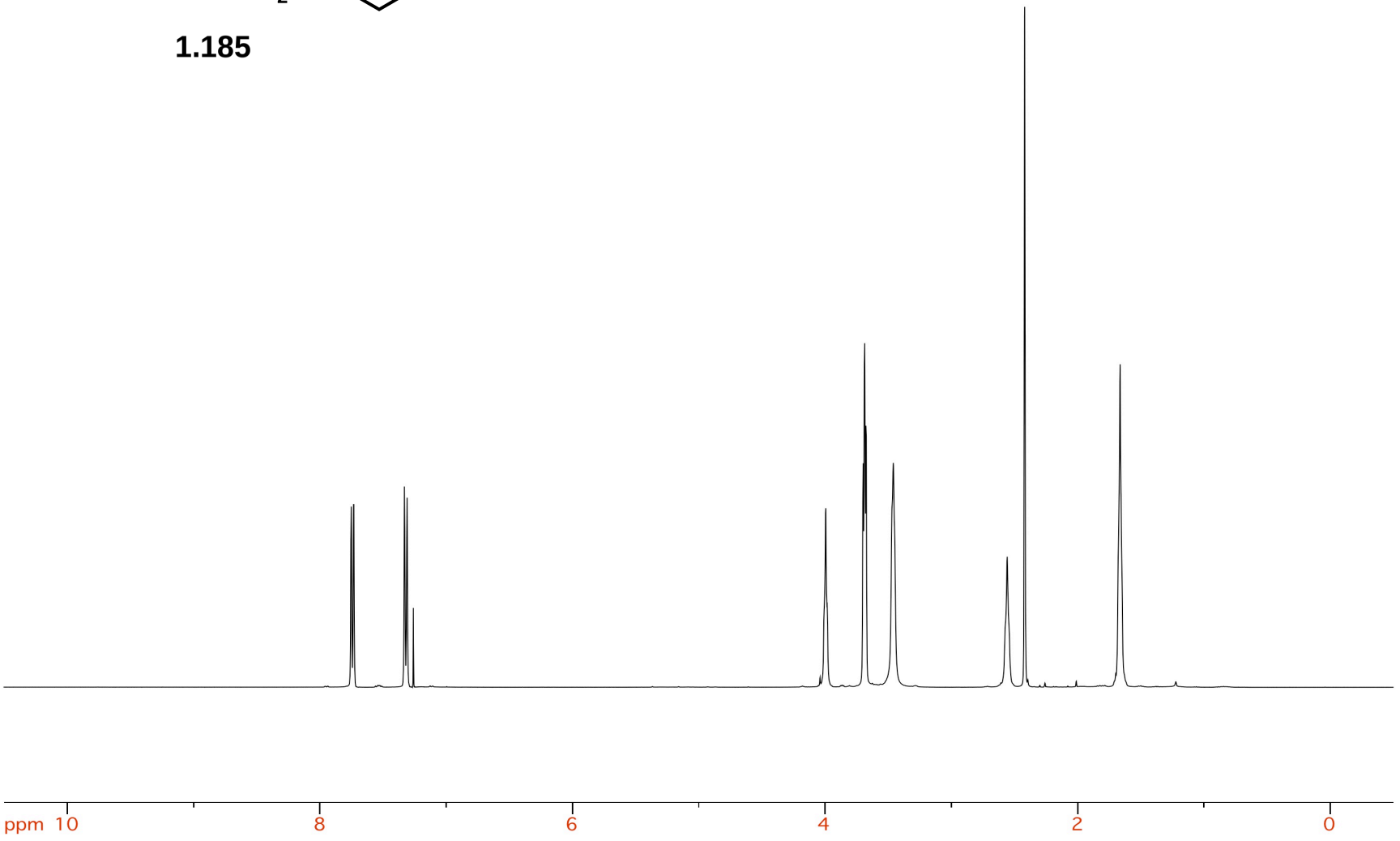


Figure A2.18a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.185**

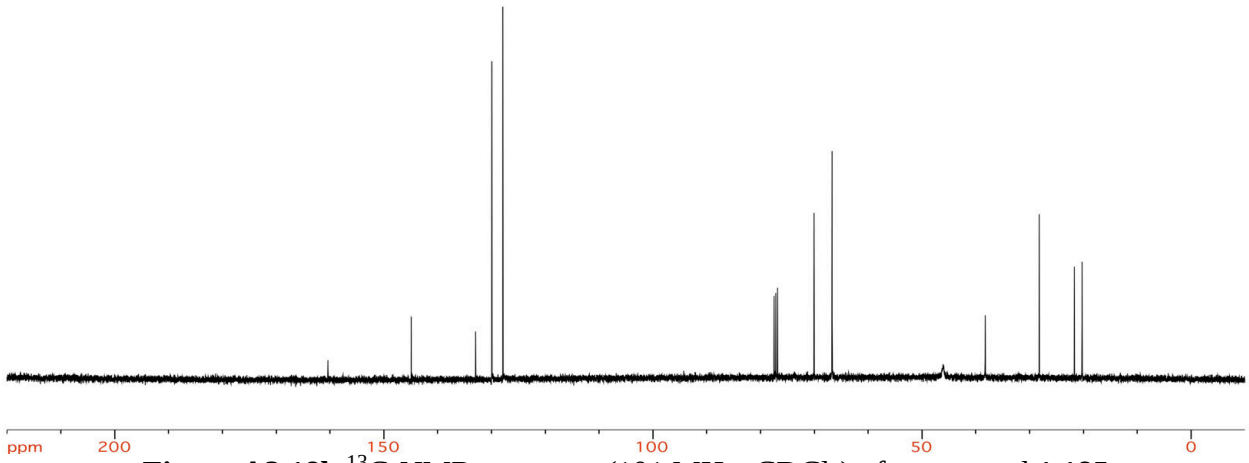


Figure A2.18b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **1.185**

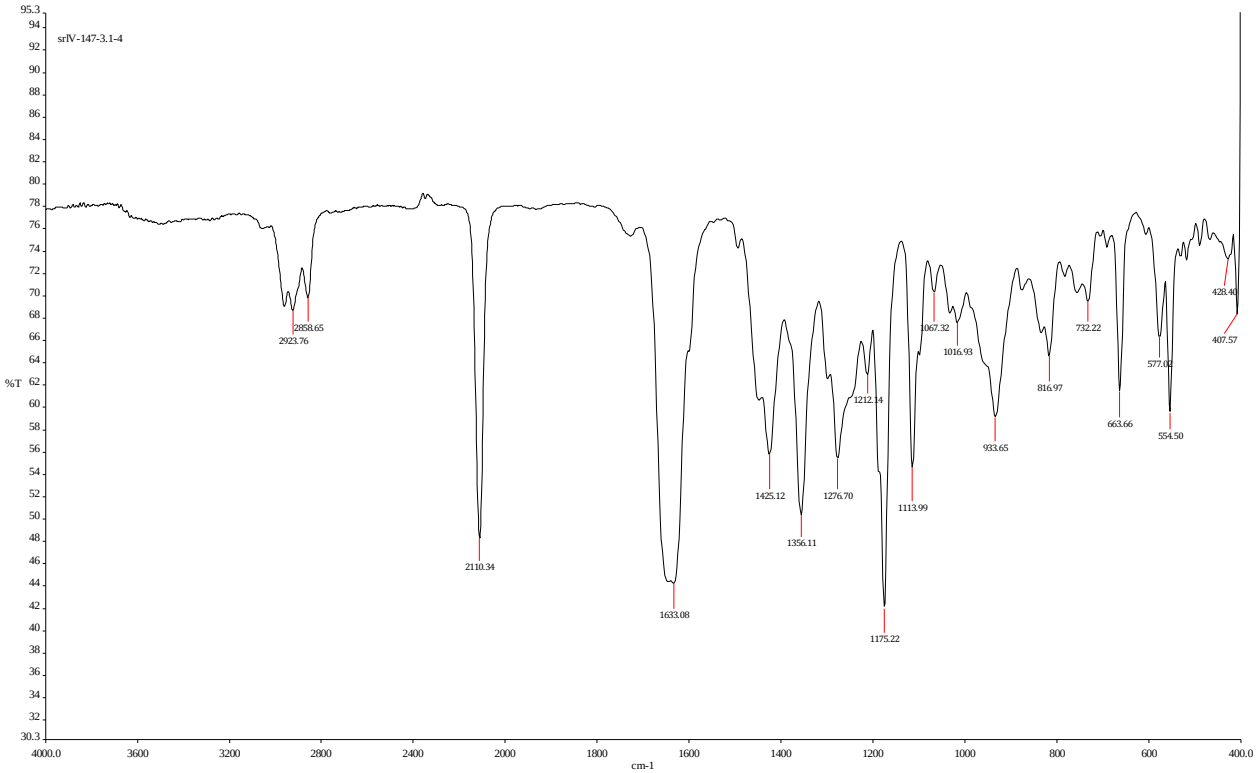
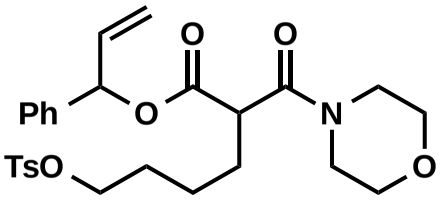


Figure A2.18c IR spectrum (thin film) of compound **1.185**



1.186

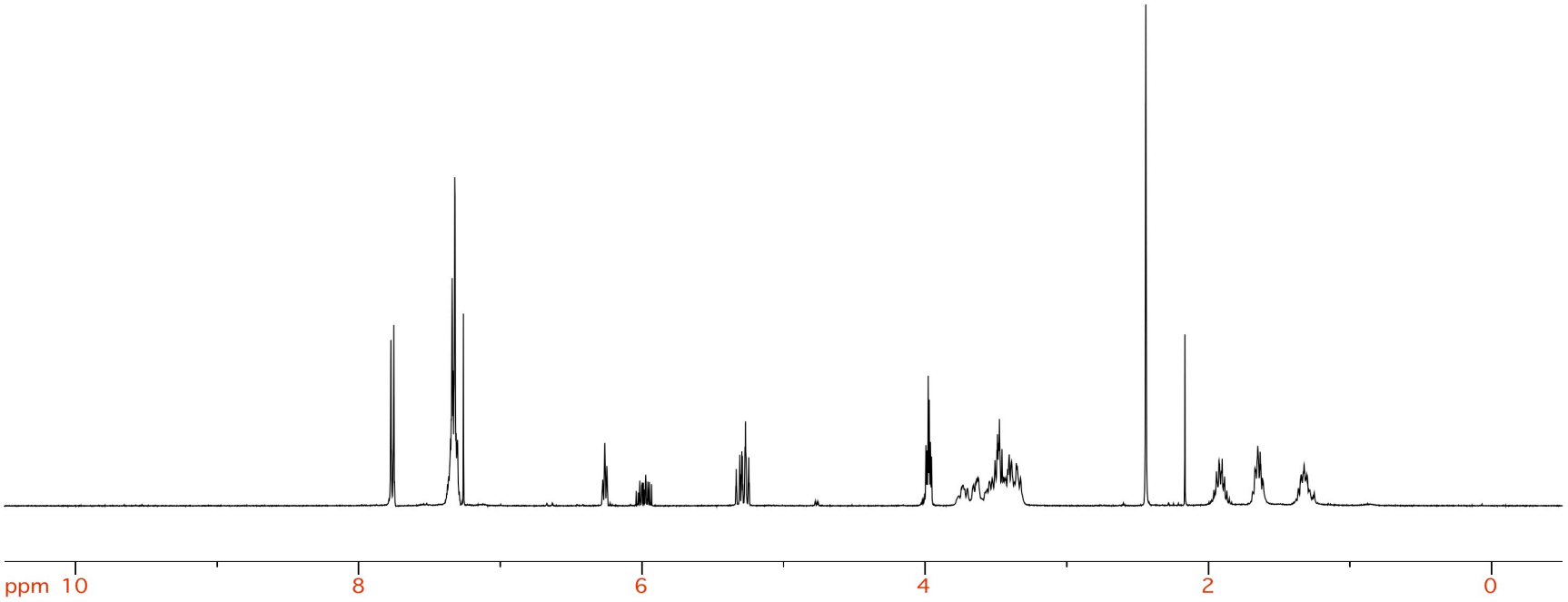


Figure A2.19a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.186**

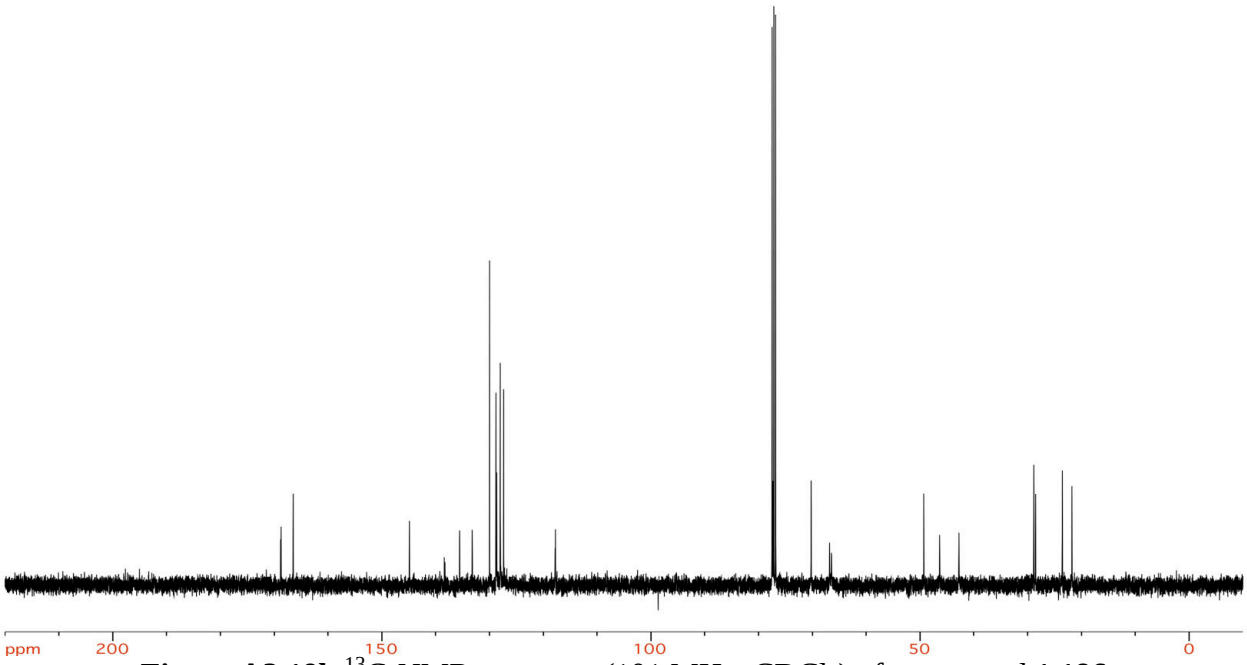


Figure A2.19b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **1.186**

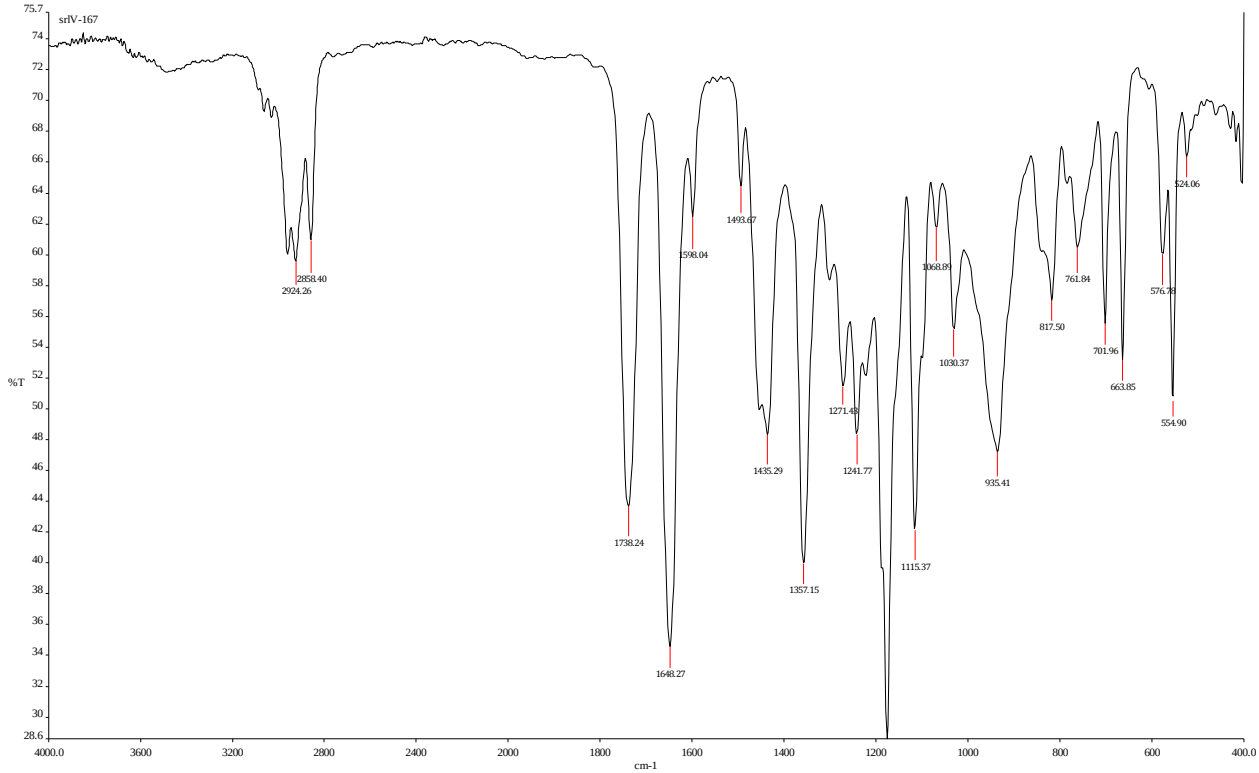
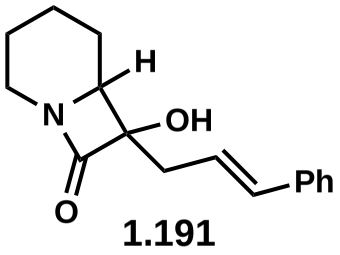


Figure A2.19c IR spectrum (thin film) of compound **1.186**



1.191

Figure A2.20a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.191** (Higher R_f diastereomer)

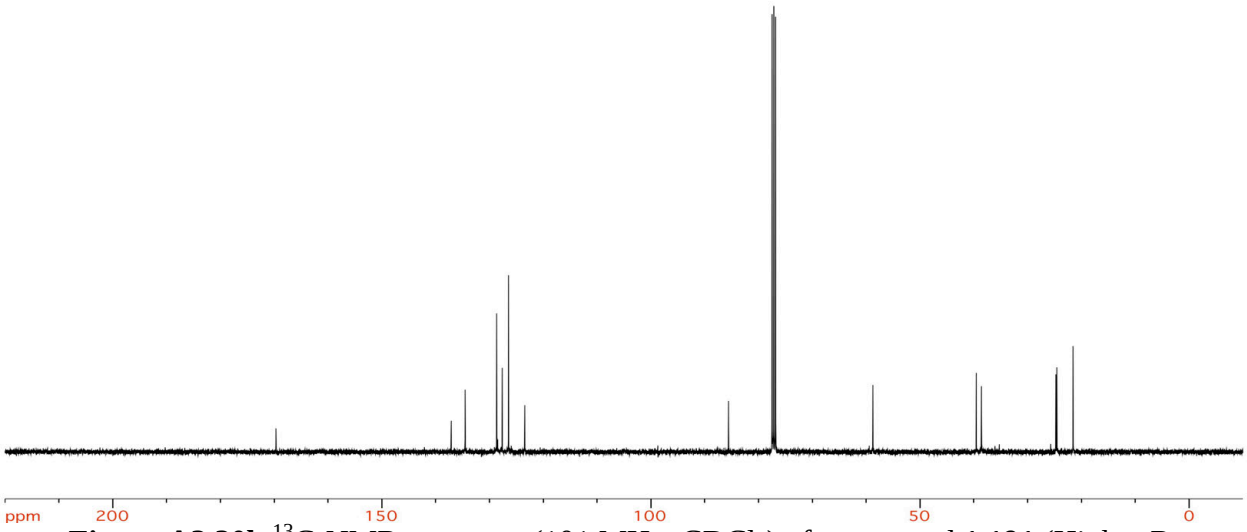


Figure A2.20b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **1.191** (Higher R_f diastereomer)

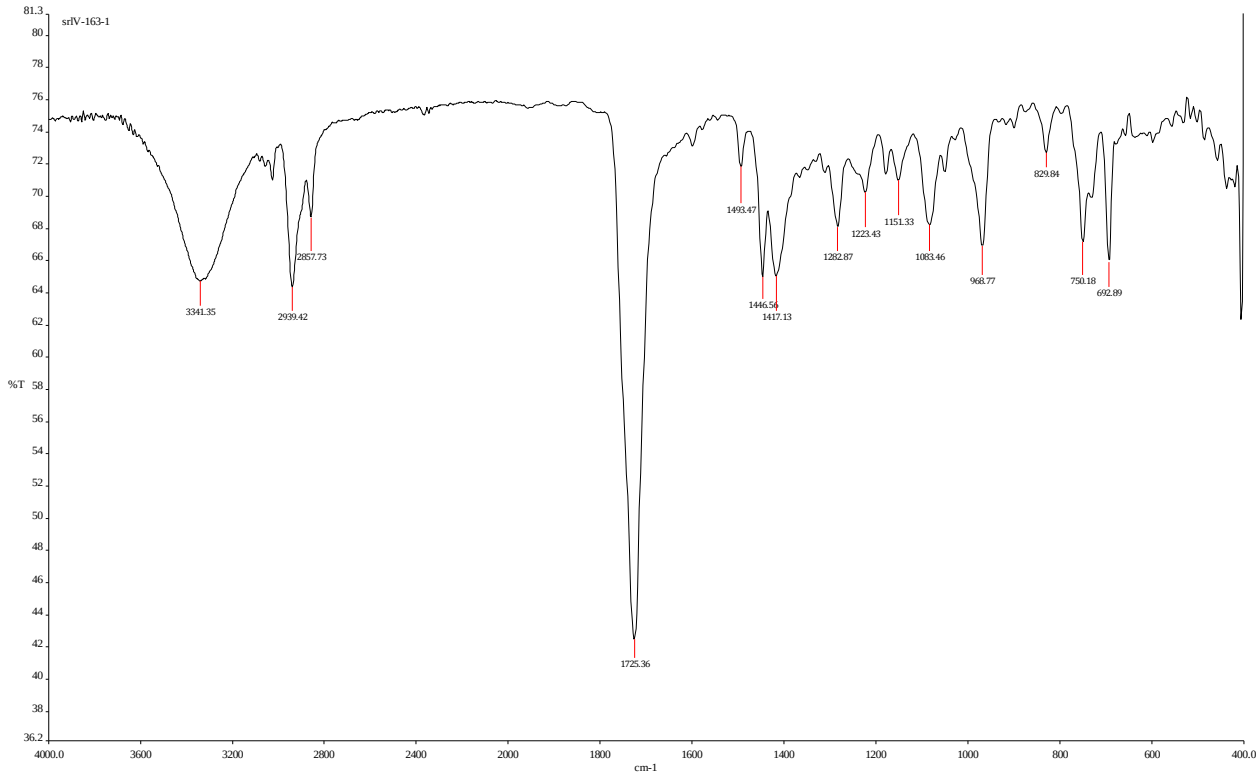
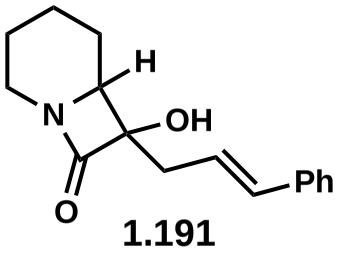


Figure A2.20c IR spectrum (thin film) of compound **1.191** (Higher R_f diastereomer)



1.191

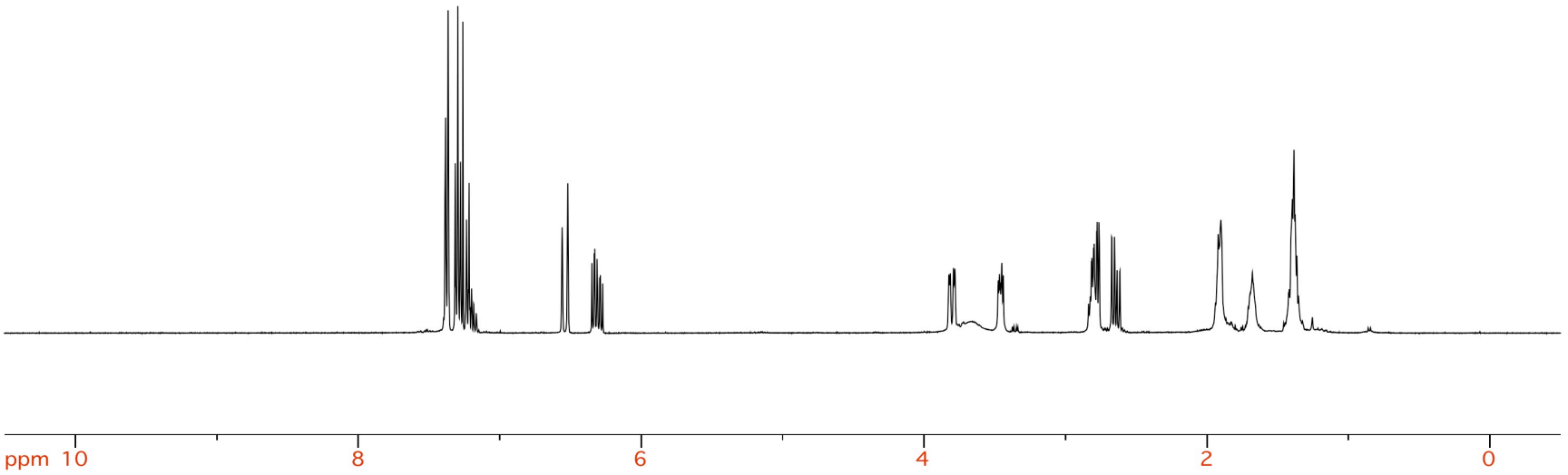


Figure A2.21a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **1.191** (Lower R_f diastereomer)

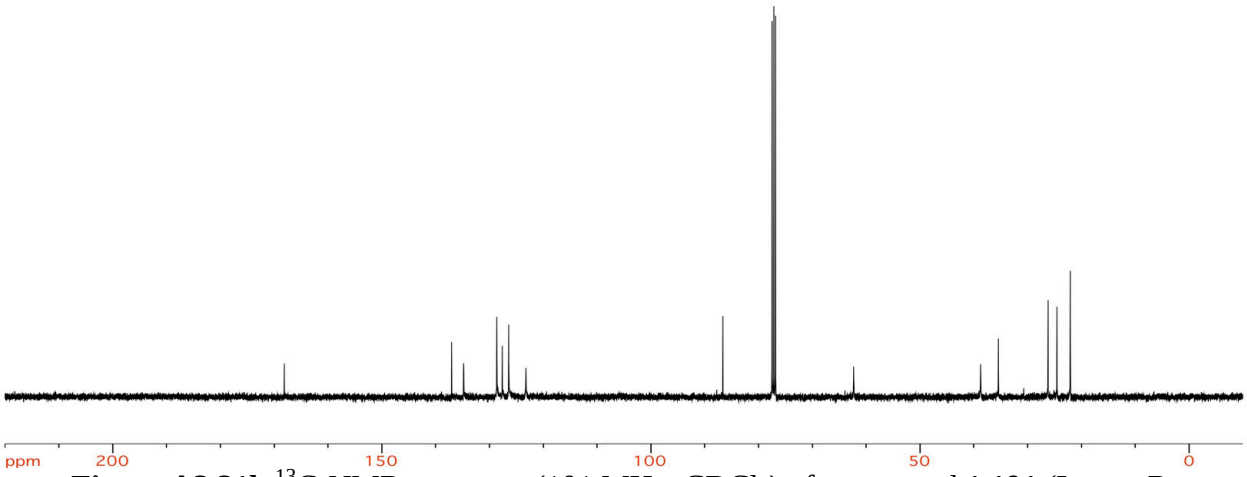


Figure A2.21b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **1.191** (Lower R_f diastereomer)

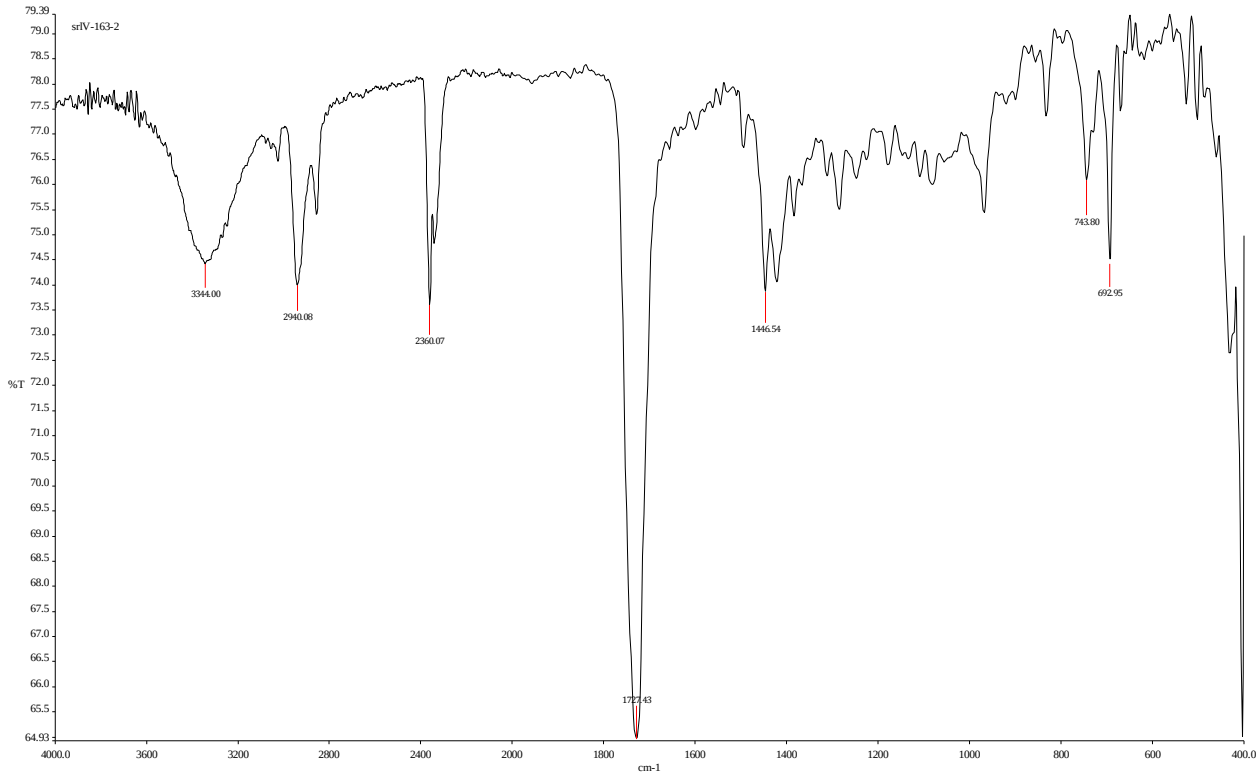
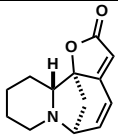
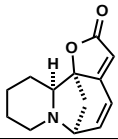
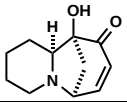
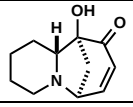
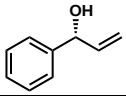
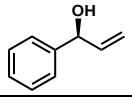
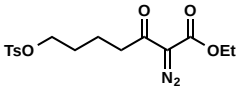
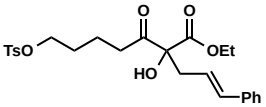
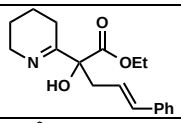
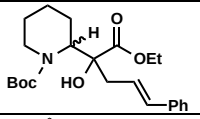
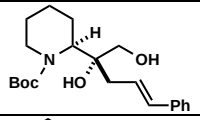
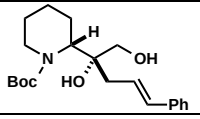


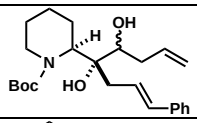
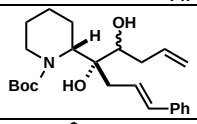
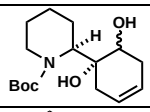
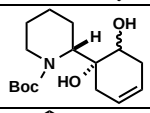
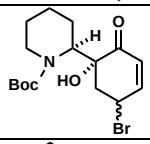
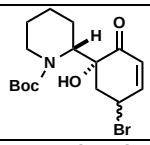
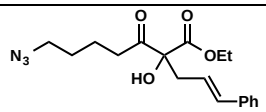
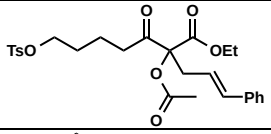
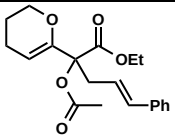
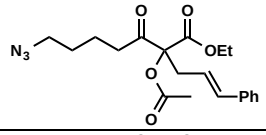
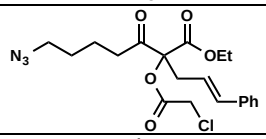
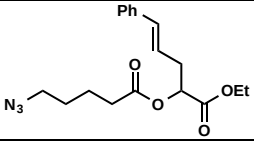
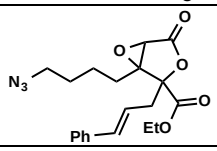
Figure A2.21c IR spectrum (thin film) of compound **1.191** (Lower R_f diastereomer)

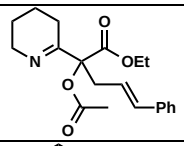
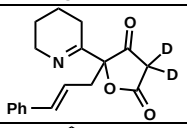
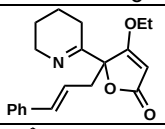
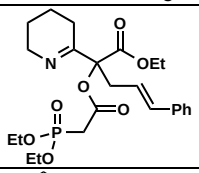
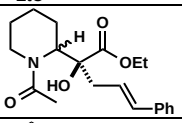
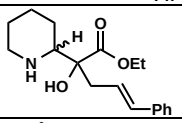
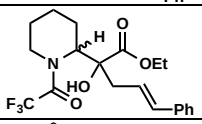
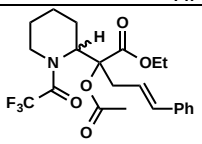
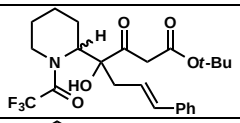
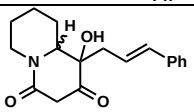
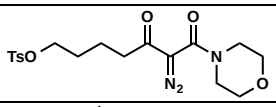
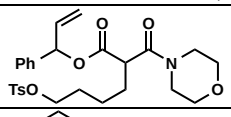
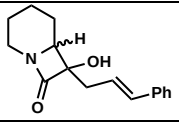
APPENDIX 3: NOTEBOOK CROSS-REFERENCE

The following table contains information to facilitate access to the original spectral data and experimental procedures for compounds mentioned in the experimental sections of this dissertation. Compounds used without further purification or which were unable to be characterized due to decomposition are noted as such.

Table A.3.1

Number	Structure	Characterization Data	Reference Preparation
(±)-1.001		JFB-iii-125securinine	JHC, JFB
(±)-1.003		TCME022	JHC, TCM
1.132a		used without purification	JHC
1.132b		used without purification	JHC
(+)-1.139		hplc trace: SRLII-167	SRLIV-095 (synthesis) SRLII-167 (resolution)
(-)-1.139		hplc trace: SRLII-167	SRLIV-095 (synthesis) SRLII-167 (resolution)
1.141		JHC, TCM0diazo	SRLIV-237, 241, 245
1.142		JHC, JFB-iii-101 hplc trace of **(*S*)-1.142**: SRLII-189	JHC SRLII-189
1.143		JHC-imine	JHC SRLIII-135
1.144		JHC-boc	JHC
1.145a		JHC-OH-A	JHC
1.145b		JHC-OH-B	JHC

Number	Structure	Characterization Data	Reference Preparation
1.146a		JHC-allyl-A	JHC
1.146b		JHC-allyl-B	JHC
1.147a		JHC-ene-A1 JHC-ene-A2	JHC
1.147b		JHC, JFB7Bene	JHC
1.148a		JHC-Br-A	JHC
1.148b		JHC-Br-B	JHC
1.151		SRLV-azideester	SRLII-287 SRLIII-135
1.159		SRLV-tosyldiester	SRLIII-219
1.160		SRLV-151	SRLV-151
1.161		SRLV-azidediester	SRLIII-227
1.162		SRLV-azidediester-chloro	SRLIII-254
1.163		SRLV-141	SRLV-141
1.164		SRLV-141	SRLV-141

Number	Structure	Characterization Data	Reference Preparation
1.171		unable to characterize due to decomposition	SRLIV-085 SRLIII-193
1.172		unable to characterize due to decomposition	SRLIII-175
1.174		SRLV-179 SRLIII-195	SRLIII-195 SRLV-177
1.175		used without purification	V-175
1.177		SRLVIII-acetamide1 SRLVIII-acetamide2	SRLIV-197 SRLIV-189
1.178		SRLVIII-amine	SRLIV-281
1.179		SRLV-127-1 SRLV-127-2	SRLV-023
1.180		SRLV-181 SRLV-183	SRLV-025
1.183		used without purification	SRLV-083
1.183		SRLVIII-147-2 SRLVIII-149-4	SRLV-091 SRLV-099
1.185		SRLV-147-3.1-4.4	SRLII-147, 149, 151
1.186		SRLV-167	SRLV-167
1.191		SRLV-163-1 SRLV-163-2	SRLV-163

PART II

THE USE OF (+)-K252A IN THE SEMI-SYNTHESIS OF INDOLOCARBAZOLE NATURAL PRODUCTS AND NOVEL ANALOGS THEREOF

CHAPTER 1

Introduction to Indolocarbazole Natural Products

1.1 Background and Introduction

1.1.1 Structure

Structures with a condensed heterocyclic moiety consisting of an indole (**2.001**) fused to a carbazole (**2.002**) are broadly referred to as indolocarbazoles (ICZs, Figure 1.1), of which there are five possible isomers (**2.003**–**2.007**).[1] In both natural products and biologically active synthetic analogs, **2.003** is by far the most common motif. A subset of these are the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles (**2.008**), which contain an additional fused pyrrole ring.

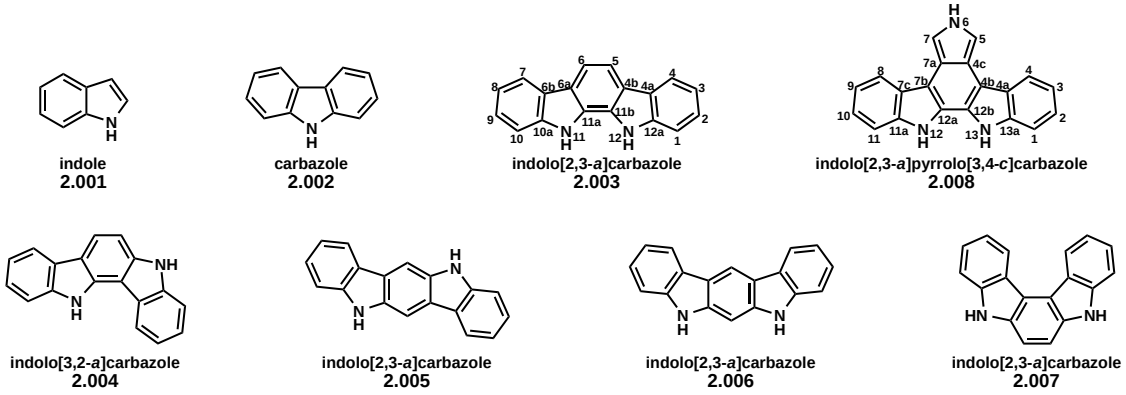


Figure 1.1

Compounds with the **2.008** skeleton can be further divided into three classes based on the oxidation state of C7 (Figure 1.2). When C7 is at the same oxidation state as **2.008**, the parent compound is K252c (**2.009**),[2] when C7 is one oxidation level higher than **2.008** the parent compound is 7-hydroxy-K252c (**2.010**),[3] and when C7 is two oxidation levels higher than **2.008** the parent compound is acyriaflavin A (**2.011**).[4] An alternate way to classify ICZs is to consider the glycosylation pattern. The open form—represented by tjipanazole A1 (**2.012**)[5] and rebeccamycin (**2.015**)[6]—has a single bond between the sugar moiety and one of the indole or carbazole nitrogens. The closed form—represented by staurosporine (**2.013**)[7] and UCN-01

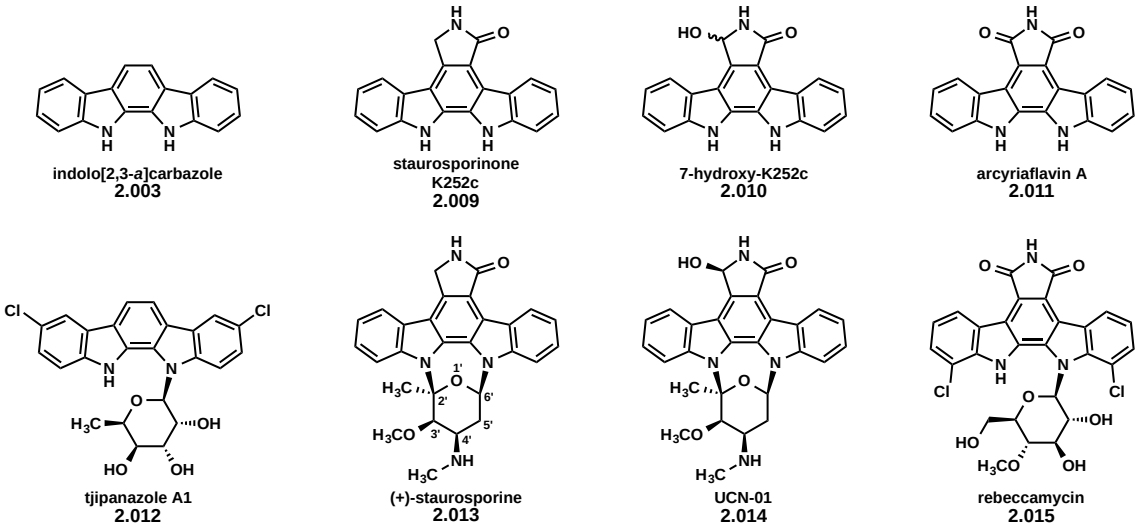


Figure 1.2

(**2.014**)[8]—has bonds connecting both the indole and carbazole nitrogens to the sugar. Other natural products that will be relevant to later discussion (Figure 1.3) include the furanosylated (+)-K252a (**2.016**)[9] and the pyranosylated compounds **2.017**[10] and (+)-RK-286c (**2.018**).[11] These ICZs have been isolated from a variety of organisms including bacteria (actinomycetes, cyanobacteria), fungi (myxomycetes), and marine invertebrates (tunicates), although the majority are isolated from the *Streptomyces* strain of actinomycetes.[12]

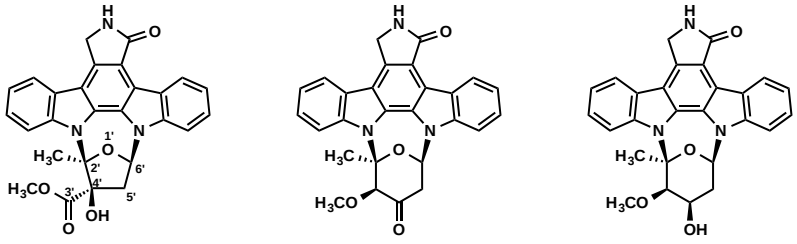


Figure 1.3

1.1.2 Recently Isolated Natural Products

While there have been over 130 ICZ natural products discovered since Ōmura *et al.*'s initial report on staurosporine (**2.013**),[7] the majority of these are only very minor variations on the structures depicted in Figures 1.2 and 1.3. The two most recent reports[13,14] on the isolation of

ICZs depict compounds with some unique structural features. In the earlier paper, Zhu *et al.* reported the isolation of streptocarbazoles A (**2.019**) and B (**2.020**) (Figure 1.4). These two compounds represent the only known natural products with closed form ICZ glycosides where the sugar is not attached at the C2' and C6' positions. In a second paper, the same group reported the isolation of fradcarbazoles A (**2.021**), B (**2.022**), and C (**2.023**). Fradcarbazoles A and B are the only ICZ natural products that contain a sulfurated sugar moiety.

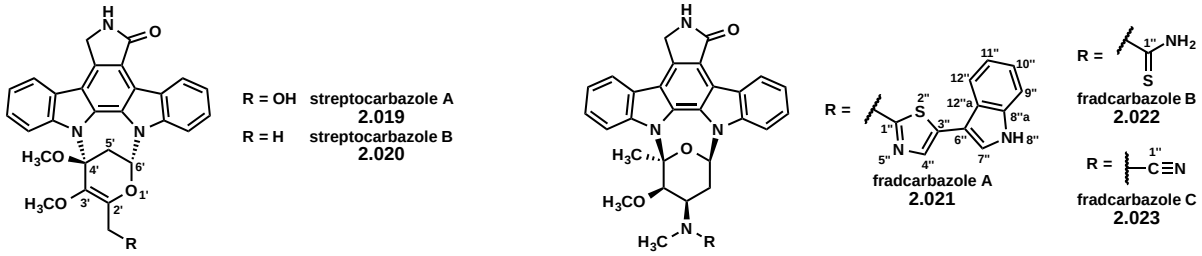


Figure 1.4

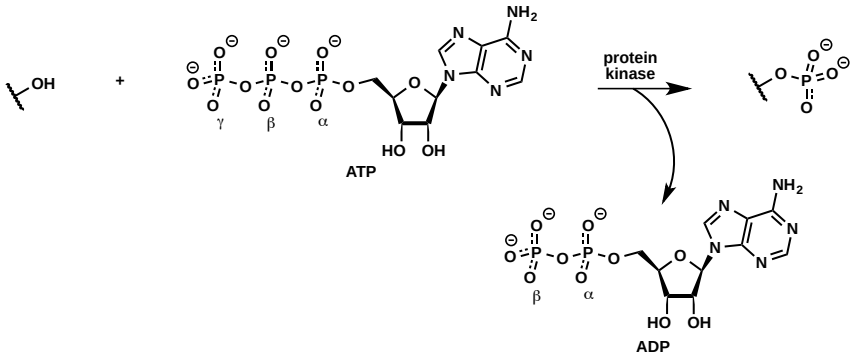
1.1.3 Biological Activity

Despite the fact that staurosporine (**2.013**) was initially identified as a potential antifungal and hypotensive agent,[7a] recent studies on the biological activity of ICZs have focused on their potential anti-cancer properties. This is primarily due to the observation that ICZs have more than one mechanism of action in mammalian cells. Not only do ICZs as a class have multiple modes of action, but there is evidence that the biological activity of some ICZs might also be occurring through more than one mechanism. The two most prevalent modes of action are the inhibition of protein kinases and DNA topoisomerase I inhibition.

1.1.3.1 Protein Kinase Inhibition

The addition of a phosphate group to a hydroxyl containing side chain of an amino acid is catalyzed by protein kinases. These enzymes transfer the γ-phosphate from ATP to a serine, threonine, or tyrosine side chain on the target protein (Scheme 1.1).[15] At any given time, more than 30% of all proteins in a cell are phosphorylated, many of which mediate signal transduction

Scheme 1.1



pathways. Phosphorylation events are a good target for anticancer agents, since cancer progression and metathesis are correlated with dysregulation of cell signaling pathways.[16] There are at least 519 protein kinases in the human genome, most of which have a highly conserved 240 residue "kinase core",[17] which makes targeting specific kinases challenging. There are currently 18 FDA approved kinase inhibitors, all of which are ATP competitive inhibitors.[16]

Co-crystal structures of staurosporine (**2.013**) with various protein kinases indicate that the sugar ring is in a boat configuration and perpendicular to the plane of the ICZ (Figure 1.5).[18] The sugar takes up the same space in the binding pocket that is occupied by the ribose subunit of ATP. The aromatic portion of the ICZ is stacked with the same hydrophobic residues that have van der Waals interactions with the adenine of ATP. This positions the amide to hydrogen bond to the same residues as the adenine of ATP.

Protein kinase C (PKC) is a serine/threonine kinase that exists in at least 12 different isoforms. Various isoforms are involved in signal transduction pathways for cell proliferation, differentiation, and gene expression.[19] Of particular interest as an anticancer target is the regulation of angiogenesis, invasiveness, and programmed cell death by PKC. Both staurosporine (**2.013**) and (+)-K252a (**2.016**) were identified early on as potent[20] PKC inhibitors; both proved to be potent non-selective ATP-competitive kinase inhibitors however.

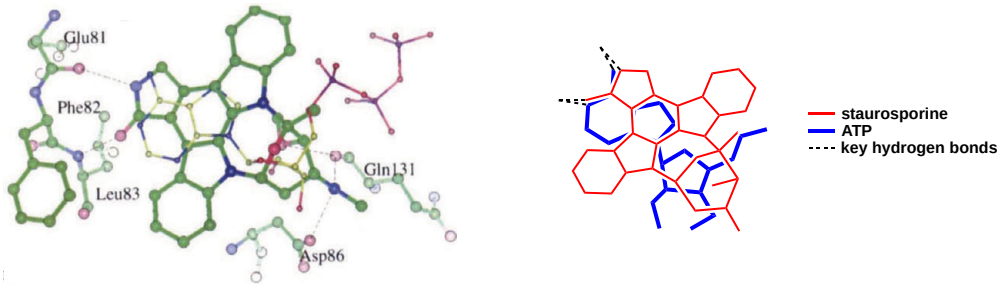


Figure 1.5

In the pursuit of more selective ICZ based protein kinase inhibitors, many medicinal chemistry groups—both industrial and academic—have synthesized analogs of the natural products. Thousands of compounds with modifications to the ICZ or the sugar have been screened, six of which are currently in clinical trials as protein kinase inhibitors (Figure 1.6). Of these seven, UCN-01 (**2.014**) is a natural product in its own right. Other effective modifications to the ICZ include the loss of the C12a−C12b bond in enzastaurin (**2.024**) and the C4/C8 methyl thioethers in CEP-1347 (**2.025**), which is a possible treatment for Parkinson's disease. CEP-1347 (**2.025**) is the only ICZ in clinical trials as something other than an anticancer agent.

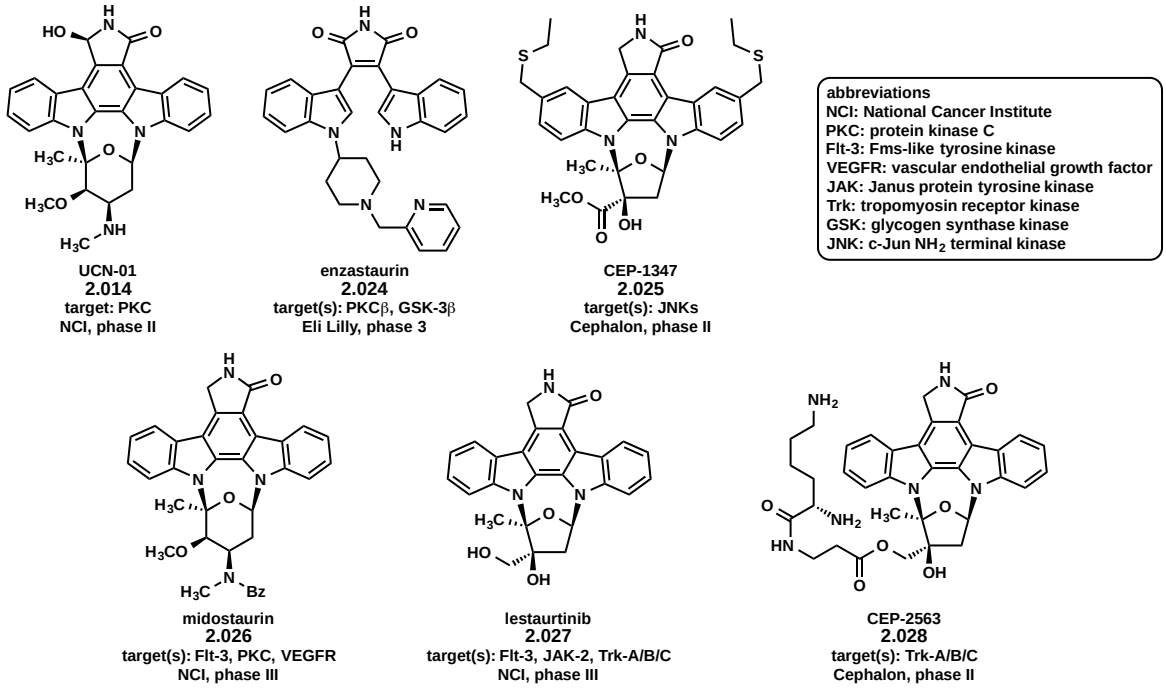


Figure 1.6

Modifications to the sugar moiety include midostaurin (**2.026**), the benzoylated form of staurosporine (**2.013**), and two modifications of (+)-K252a (**2.016**). These are lestaurtinib (**2.027**) and CEP-2563 (**2.028**).

1.1.3.2 DNA Topoisomerase I Inhibition

DNA topoisomerase I (Top1) is an enzyme that mediates many cellular processes via its control of DNA topology. In particular, it relaxes duplex DNA by making a transient nick in one of the strains and subsequently religating the DNA. Compounds that act to stabilize the Top1−DNA complex are called Top1 poisons. The stabilization of the Top1−DNA complex leads to DNA lesions, and eventually apoptosis. This conversion of Top1 into a DNA damaging agent is thought to occur more often in cancerous cells, because the level of Top1 in non-proliferating cells is relatively low.[12] ICZs that are primarily cytotoxic via Top1 inhibition are rebeccamycin (**2.015**) and others with only a single β-glycosidic linkage and C7 in the acid oxidation state.[19b] There are two ICZ Top1 inhibitors currently in clinical trials as anticancer agents (Figure 1.7), edotecarin (**2.029**)[21] and becatecarin (**2.030**).[16]

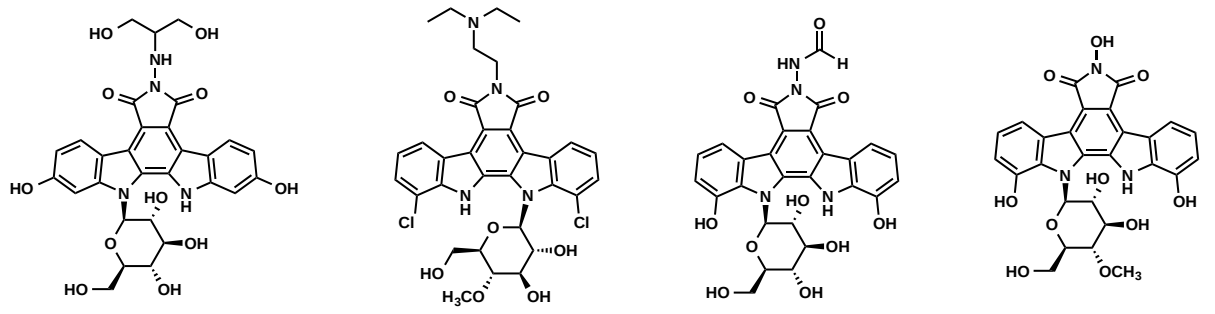


Figure 1.7

Top1 is a "dual enzyme", with protein kinase activity independent of its primary activity on DNA. Since this secondary activity results in the phosphorylation of proteins involved in spliceosome formation, it represents an alternate target for anti-cancer drugs. Compounds such as

NB-506 (**2.031**)[22] and R-3 (**2.032**)[23] have been shown to inhibit tumor growth both as standard Top1 inhibitors and via a secondary pathway.[24] Interestingly, evidence suggests that NB-506 (**2.031**) and R-3 (**2.032**) bind to the kinase domain of Top1, but not in the ATP binding pocket. Allosteric inhibition of a protein kinase is otherwise unknown in ICZs.

1.2 Biosynthesis of Glycosylated Indolocarbazoles

1.2.1 Metabolic Precursors

Prior to the identification of the genes responsible for the synthesis of staurosporine (**2.013**) and other glycosylated ICZs, feeding studies were conducted with isotope-labeled precursors. This led to the determination that the ICZ itself was derived from two molecules of L-tryptophan (**2.033**), while the sugar moiety was derived from D-glucose (**2.034**) (Figure 1.8). However, the origin of the nitrogen in the pyrrole[3,4-*c*] unit could not be determined from these initial feeding studies.[12]

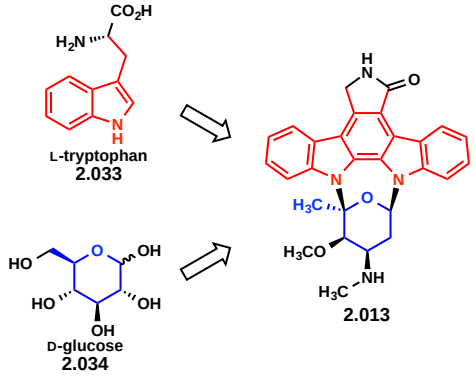


Figure 1.8

1.2.2 Biosynthetic Pathways to (+)-K252a and (+)-Staurosporine

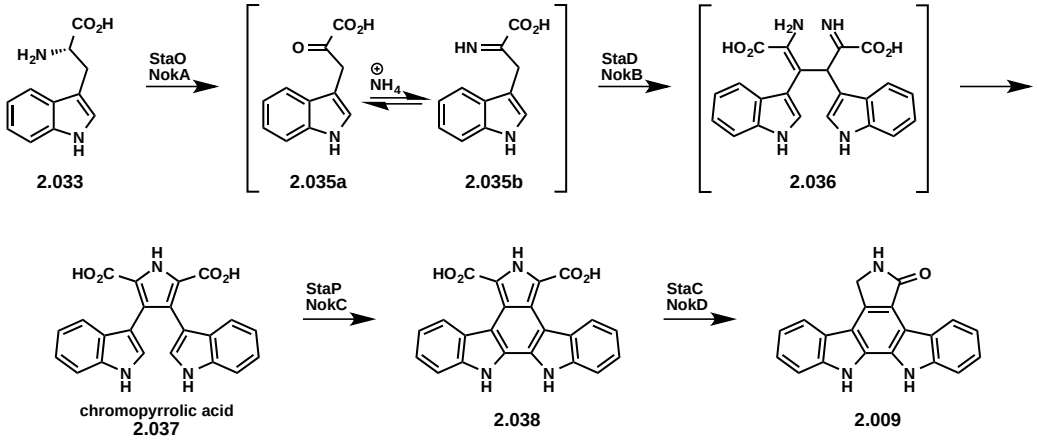
While the metabolic precursors for these compounds had been studied in the 1980−90s, the details of the mechanism by which they were converted to staurosporine and related natural products were not elucidated until more recently. The biosynthesis of the aglycone was initially studied in rebeccamycin producing organisms.[25] Cloning of gene clusters and the use of knockout strains allowed for the determination of the biosynthetic pathway that led to the

aglycone. Analogous genes were later identified in organisms that produced staurosporine and (+)-K252a.[12] The genes that encoded the synthesis of the sugar were fully identified shortly thereafter.[26]

1.2.2.1 Biosynthesis of K252c

Starting with tryptophan, analogous enzymes synthesize K252c (**2.009**) in organisms that produce staurosporine (**2.013**) (enzymes whose names start with Sta[12]) or (+)-K252a (**2.016**) (enzymes whose names start with Nok[27,28]).[29] An initial oxidation of tryptophan by StaO/NokA generates pyruvic acid **2.035a** (Scheme 1.2), which is in equilibrium with its imine **2.035b**. A dimerization with StaD/NokB then gives **2.036**, which spontaneously collapses to chromopyrrolic acid (**2.037**). A StaP/NokC catalyzed aryl−aryl bond formation then generates pentacyclic compound **2.038**. Exposure of **2.038** to StaC/NokD causes a final decarboxylation to give K252c (**2.009**).

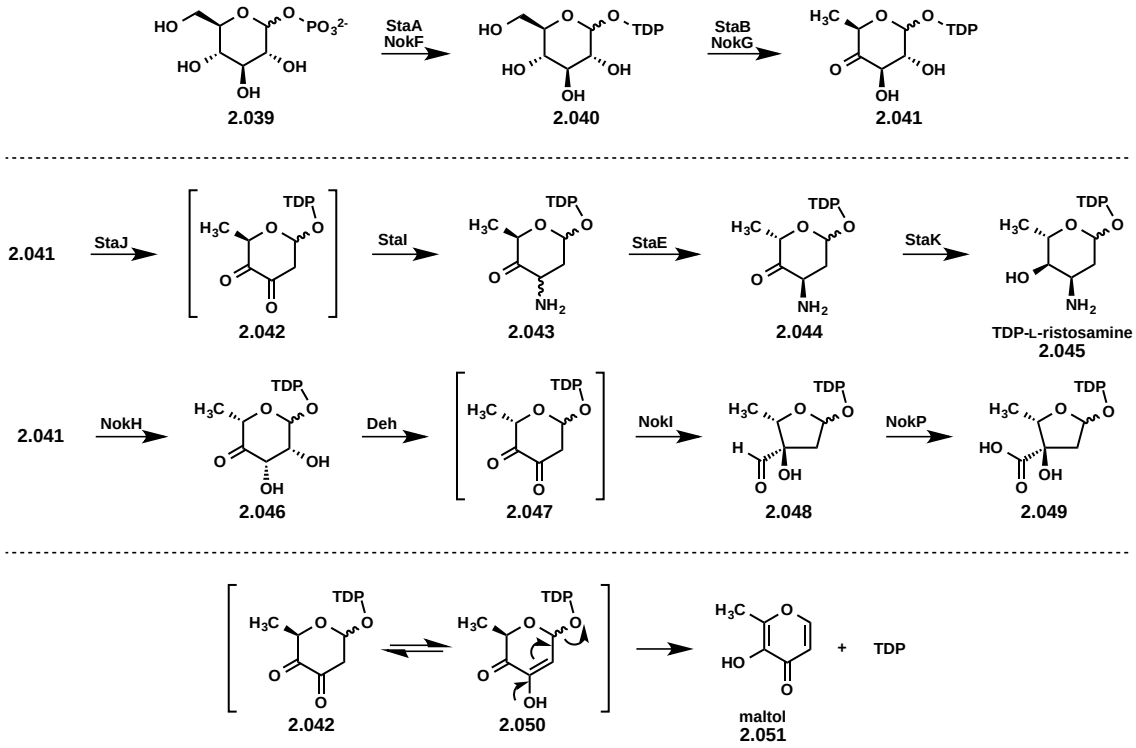
Scheme 1.2



1.2.2.2 Biosynthesis of the Sugars[30]

The sugars that are incorporated into staurosporine (**2.013**) and (+)-K252a (**2.016**) appear to be derived from a common intermediate, with analogous enzymes present in the producing organism. Starting from glucose-1-phosphate (**2.039**), exposure to the thymidyltransferase

Scheme 1.3



StaA/NokF generates the thymidine diphosphate (TDP) compound **2.040** (Scheme 1.3). Dehydratase StaB/NokG then oxidizes **2.040** to common intermediate **2.041**.

For the synthesis of staurosporine (**2.013**), the common intermediate then undergoes a C2 deoxygenation by StaJ, and the transient intermediate **2.042** is reductively aminated by StaI to give amine **2.043**. StaE is a 3,5-epimerase enzyme, which converts **2.043** to **2.044**. A final reduction by StaK gives TDP-L-ristosamine (**2.045**). In the case of (+)-K252a (**2.016**), common intermediate **2.041** undergoes a 3,5-epimerization with NokH to give **2.046**. This is then converted to the transient intermediate **2.047** by Deh.[31] Diketone **2.047** immediately undergoes a ring contraction mediated by the dihydrostreptose synthase NokI to generate furanose **2.048**. An oxidation of the aldehyde produces acid **2.049**.

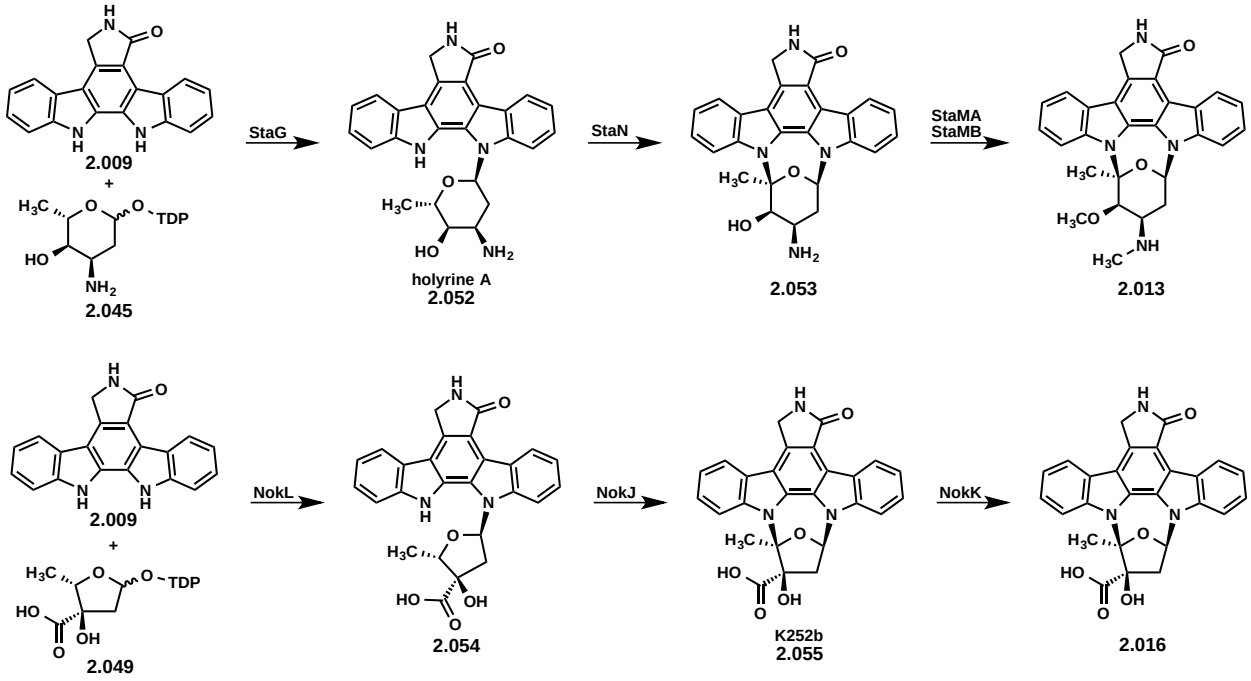
While the exact order of events in the sugar biosynthesis is debatable,[32] it is clear that 3,4-diketone intermediates **2.042** and **2.047** are transitory. In the biosynthesis of other sugars[33] it

has been observed that **2.042** is equilibrium with enol **2.050**. This enol readily undergoes the spontaneous loss of TDP to produce maltol (**2.051**). The enzymes StaJ/Deh and StaI/NokI therefore must work together in order for the necessary sugar to be synthesized.

1.2.2.3 Completion of the Biosynthesis

In the presence of the *N*-glycosyltransferase StaG K252c (**2.009**) and TDP-L-ristosamine (**2.045**) are coupled to give holyrine A[34] (**2.052**) (Scheme 1.4). Formation of the second glycosidic bond is catalyzed by the cytochrome P450 homolog StaN. Finally, **2.053**[35] is converted to staurosporine (**2.013**) via the work of two methyl transferase enzymes. The order of these methylations is unclear. In the biosynthesis of (+)-K252a (**2.016**), K252c (**2.009**) and furanose **2.049** are coupled by NokL to give **2.054**. NokJ then forms the second glycosidic bond to give K252b[12] (**2.055**). The aklanonic acid methyl transferase analog NokK then converts K252b to (+)-K252a (**2.016**). In both cases,[36] the only modifications of the glycoside that occur after the attachment to K252c (**2.009**) are methylations.

Scheme 1.4



1.2.3 Compounds Synthesized by Combinatorial Biosynthesis

Once the ICZ biosynthetic gene cluster was relatively well understood, studies indicated that there was some flexibility in the substrates tolerated by the glycosyltransferase enzymes.[37] *S. albus* was genetically engineered to contain two novel plasmids. One plasmid contained the gene cluster for the biosynthesis of K252c (**2.009**) and the glycosyl transferase enzymes, while the other plasmid contained a gene cluster for deoxysugar biosynthesis. This gene cluster could then be varied to generate ICZs containing a variety of sugars (Figure 1.9) not previously observed in ICZ natural products. Of particular interest is the fact that they were unable to form the second C−N bond when D-deoxysugars such as D-olivose were used.

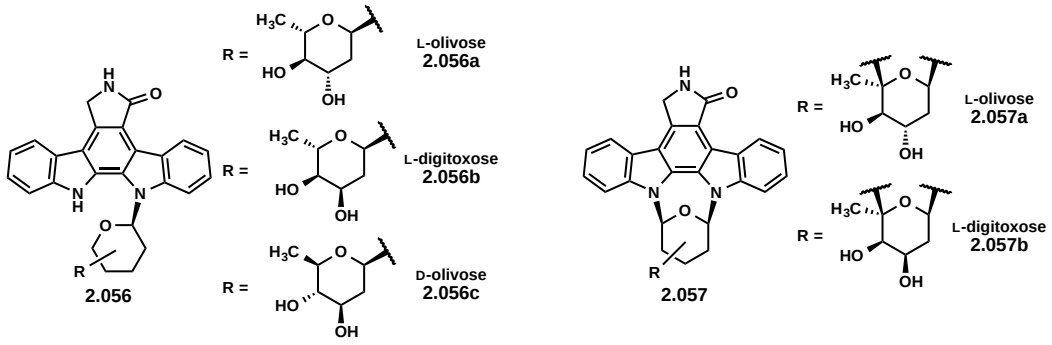
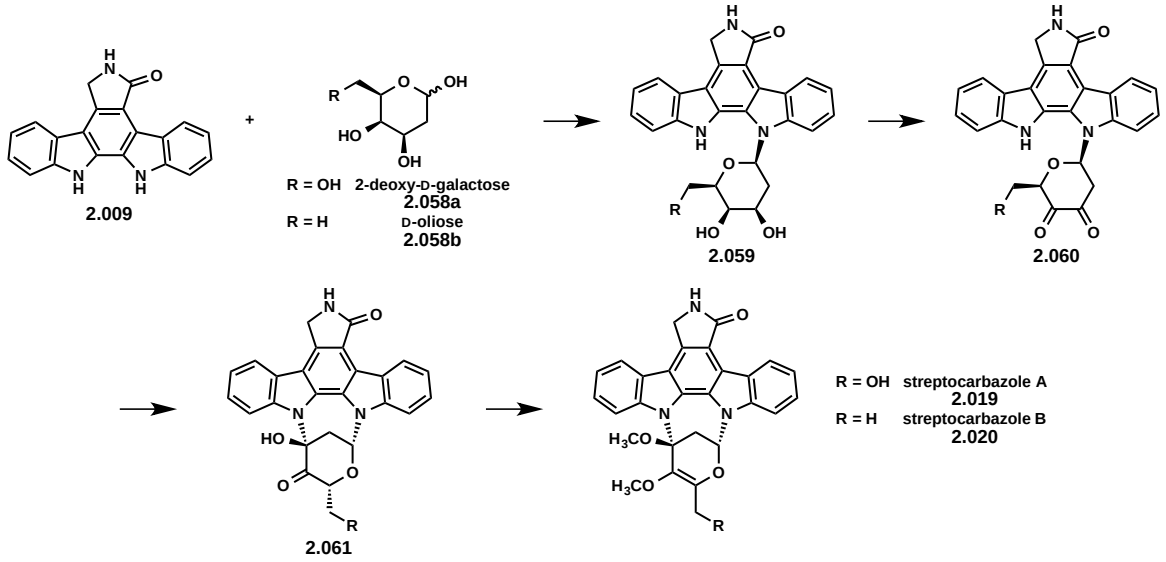


Figure 1.9

1.2.4 Hong & Zhu's Proposed Biosynthesis of Streptocarbazoles A and B

In the paper detailing the isolation of streptocarbazole A (**2.019**) and streptocarbazole B (**2.020**),[13,14] the authors also proposed a biosynthesis for these unique compounds (Scheme 1.5).[38] Starting with the TDP form of **2.058** and K252c (**2.009**), a glycotransferase enzyme would generate **2.059**. Since **2.058** is a D-deoxysugar, the second glycosidic bond would not form. An oxidation would give diketone **2.060**. Subsequent attack by N12 on the 4' ketone would give hemiaminal **2.061**. Dimethylation of the enol form of **2.061** would produce streptocarbazoles A (**2.019**) and B (**2.020**).

Scheme 1.5

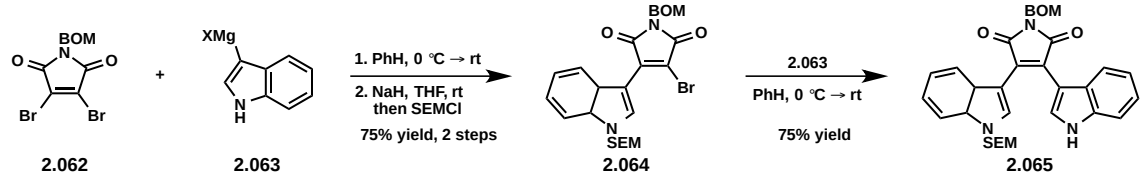


1.3 Prior Syntheses of Glycosylated Indolocarbazole Natural Products

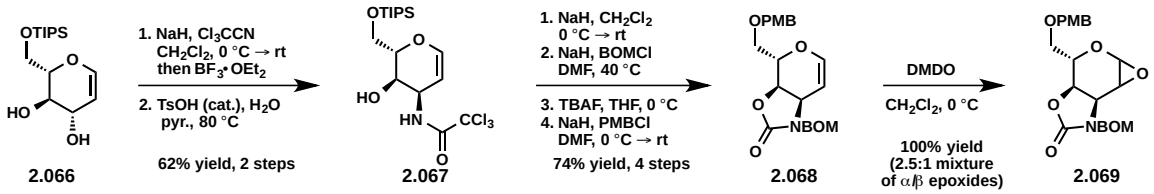
1.3.1 Danishefsky's Synthesis of (+)-Staurosporine

The first total synthesis of a glycosylated ICZ was published by Danishefsky *et al.* in 1995.[39] Their synthesis of the precursor to the aglycone commenced with the addition of indole Grignard (**2.063**) to imide **2.062** (Scheme 1.6). This resulted in a tricyclic compound, where the indole nitrogen could be protected to give **2.064**. The vinyl bromide of **2.064** was then exposed to another equivalent of **2.063** to give bisindolemaleimide **2.065**. The glycoside precursor originated with glucal **2.066** (Scheme 1.7). Conversion to the bis(trichloroacetimidate) and an *in situ* conversion to an oxazoline was followed by ring opening to give trichloroacetamide **2.067**. Exposure to base afforded an oxazolidinone, which was protected as its BOM derivative, and the TIPS ether was replaced with a PMB. Protected oxazolidinone **2.068** was then treated with DMDO to give **2.069** as a mixture of epoxides.

Scheme 1. 6



Scheme 1.7

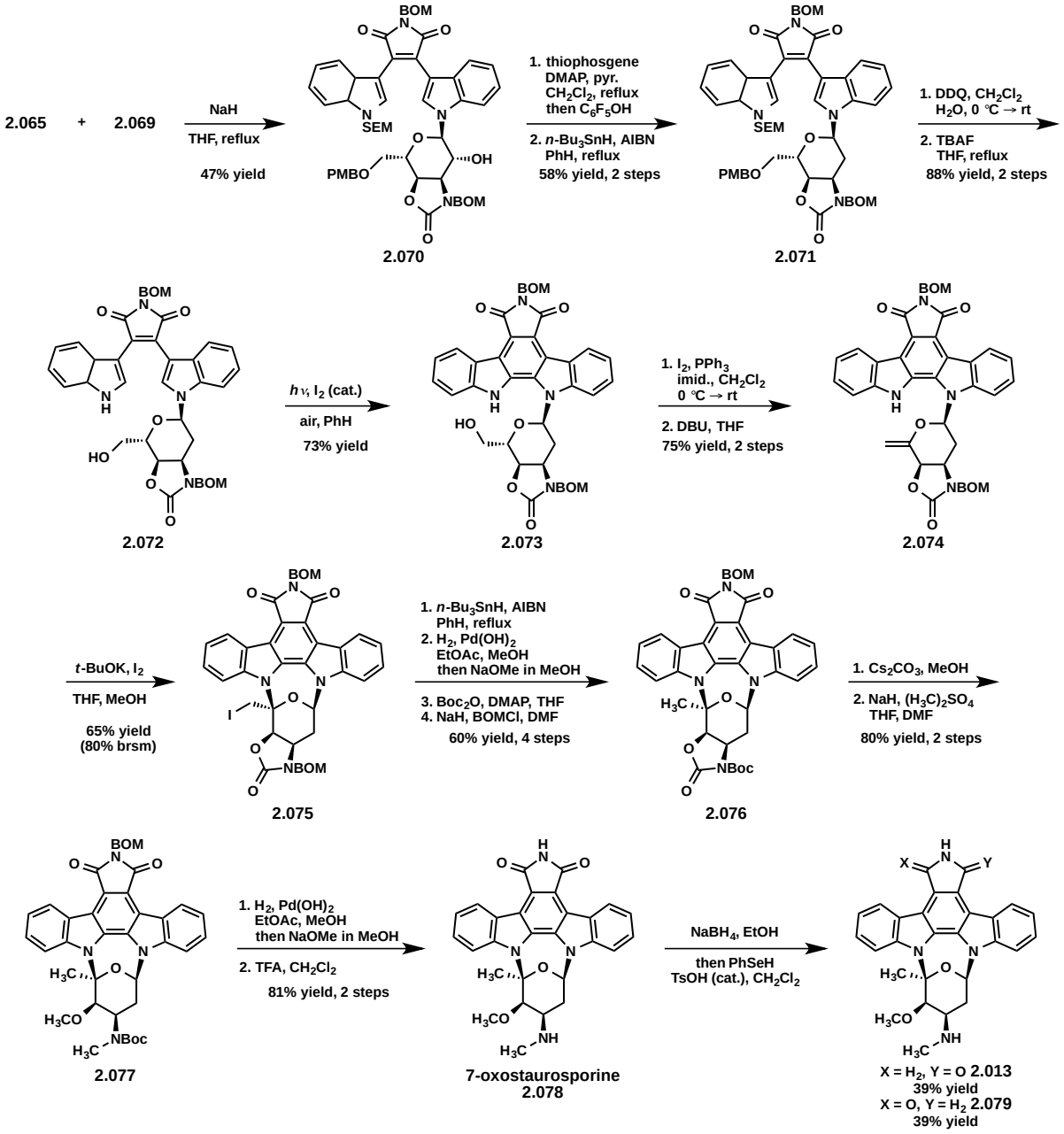


Aglycone **2.065** was coupled with pyran **2.069** in the presence of NaH to give **2.070** (Scheme 1.8). Bisindole glycoside **2.070** was then exposed to Barton radical deoxygenation conditions to give **2.071**. Cleavage of the PMB and SEM protecting groups yielded free indole **2.072**. A photolytic oxidative cyclization then formed ICZ **2.073**. In order to prepare a suitable substrate for the formation of the second glycosidic bond, the free alcohol in **2.073** was exchanged for an iodide. Subsequent elimination gave alkene **2.074**. Treatment of **2.074** with iodine in the presence of *t*-BuOK afforded iodide **2.075**. Reductive removal of the iodide was followed by BOM removal. A selective Boc protection of the oxazolidinone nitrogen and the BOM reprotection of the imide nitrogen gave **2.076**. Exposure of **2.076** to Cs_2CO_3 cleaved the oxazolidinone, which allowed for methylation and the generation of **2.077**. The BOM and Boc group were then removed to give 7-oxostaurosporine (**2.078**). A reduction with $NaBH_4$ was followed by a deoxygenation of the resulting carbanolamide furnished staurosporine (**2.013**) and **2.079** as a separable 1:1 mixture of regioisomers.

1.3.2 Fukuyama's Synthesis of (+)-K252a

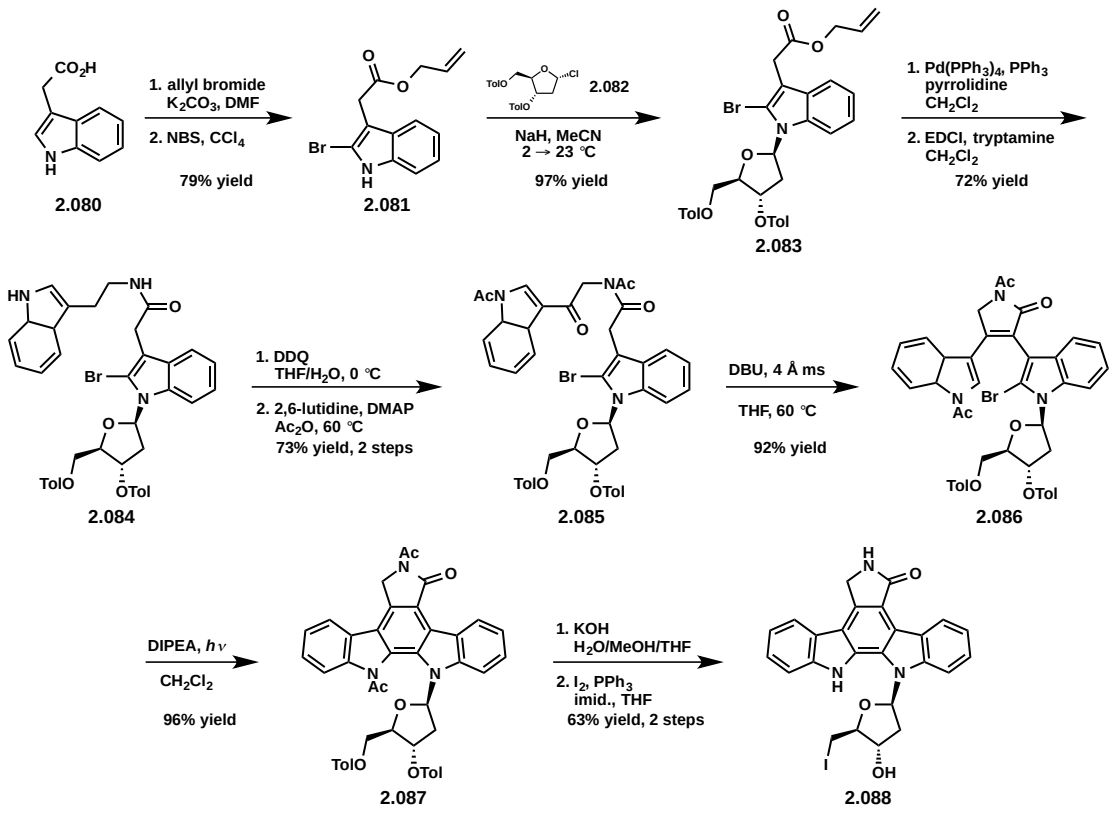
In their synthesis of (+)-K252a (**2.016**),[40] Fukuyama *et al.* used an approach similar to that of Danishefsky where they brought together the precursors to the aglycone and the sugar before fully cyclizing the ICZ. Starting from indole-3-acetic acid (**2.080**, Scheme 1.9), allylation and subsequent bromination of the indole provided **2.081**. The sugar precursor **2.082** is readily available from 2-deoxy-D-ribose. Deprotonation of **2.081** and exposure to chloride **2.082** gave β-*N*-glycoside **2.083**. Cleavage of the allyl ester to the acid and treatment with tryptamine afforded

Scheme 1.8



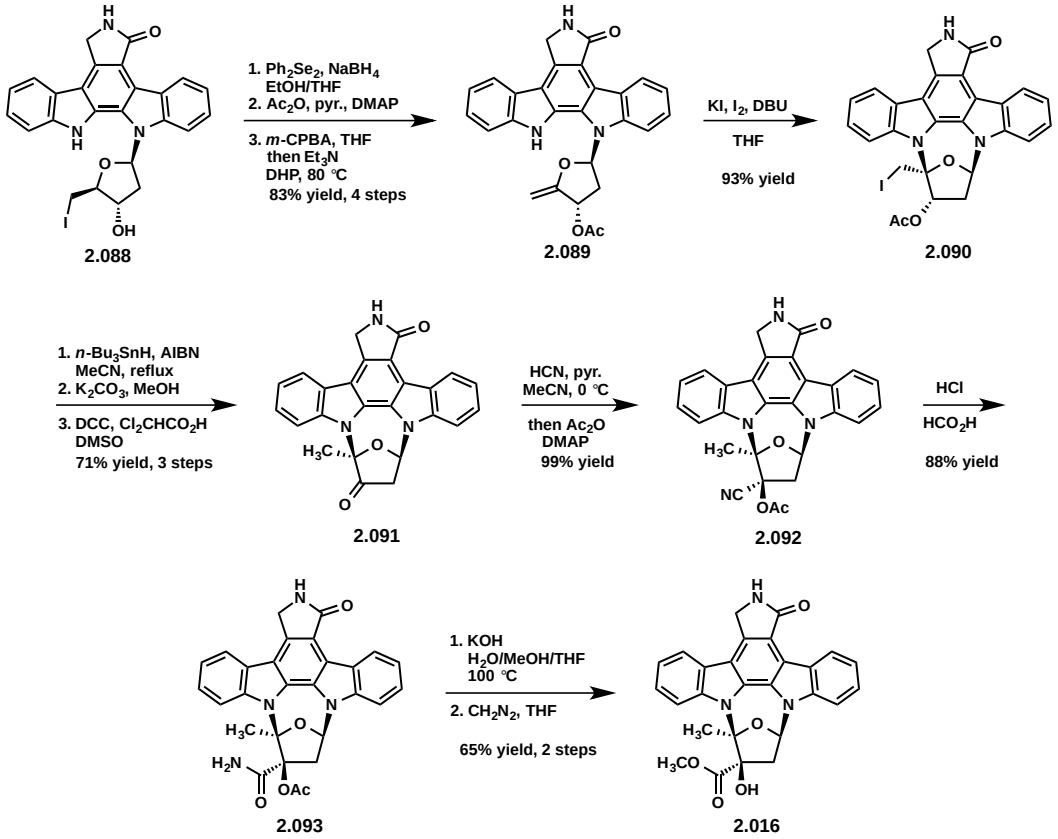
bisindole **2.084**. The more reactive benzylic position was then oxidized, and the nitrogens were acetylated to give **2.085**. Amide **2.085** was then cyclized in the presence of DBU to yield lactam **2.086**, which underwent a photocyclization to give ICZ **2.087**. With the ICZ core of the molecule complete, universal deprotection and the replacement of the primary alcohol with an iodide furnished **2.088**.

Scheme 1.9



Treatment of iodide **2.088** with Ph_2Se_2 converted it to the selenide, and exposure to Ac_2O protected the alcohol as an acetate (Scheme 1.10). The selenide was then oxidized with *m*-CPBA and elimination gave enol ether **2.089**. An iodoglycosidation then formed the second glycosidic linkage to give **2.090**. Iodide **2.090** was deiodinated under radical conditions and the alcohol deprotected and oxidized to yield **2.091**. Exposure of this ketone to hydrogen cyanide followed by acetic anhydride produced cyanohydrin acetate **2.092**. Conversion of **2.092** to amide **2.093** was effected by gaseous HCl. **2.093** was then hydrolyzed, and the resulting acid esterified with diazomethane to afford the desired final product, (+)-K252a (**2.016**).

Scheme 1.10

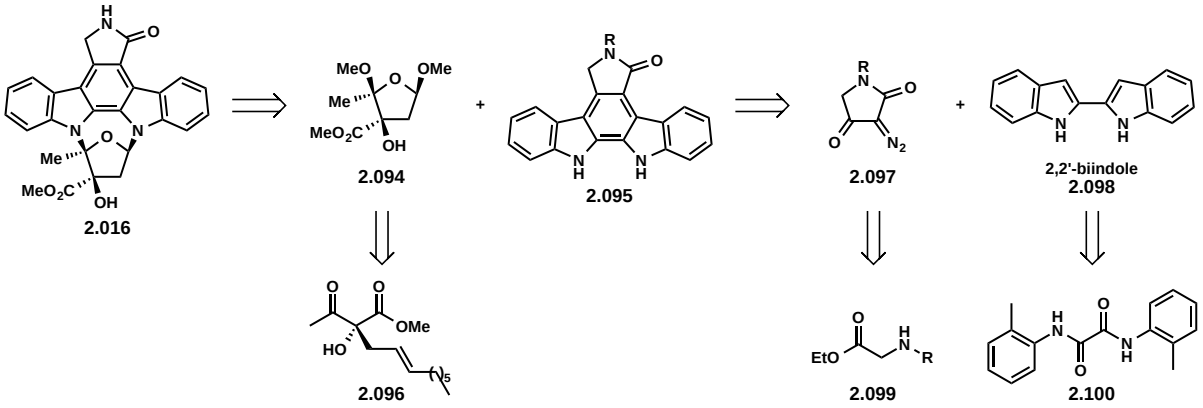


1.3.3 The Wood Group's Synthesis of Indolocarbazole Natural Products

1.3.3.1 Synthesis of (+)-K252a

Shortly after Danishefsky's group published their synthesis of staurosporine, the Wood group published its synthesis of (+)-K252a (**2.016**).[41,42] When considering (+)-K252a they determined that the most efficient route would be one in which both glycosidic bonds were formed in a single cycloglycosidation step. With this in mind, their retrosynthetic analysis started with disconnections across the N12−C2' and N13−C5' bonds (Scheme 1.11) to give glycoside **2.094** and aglycone **2.095**, a protected form of K252c (**2.009**). The sugar was envisioned to arise from an α-hydroxy-β-ketoester such as **2.096**, which contains the desired stereochemistry at C3'. In turn, the ICZ unit would arise from the coupling of protected diazotetramic acid **2.097** with 2,2'-biindole (**2.098**). **2.097** was disconnected at the amide bond to result in protected glycine

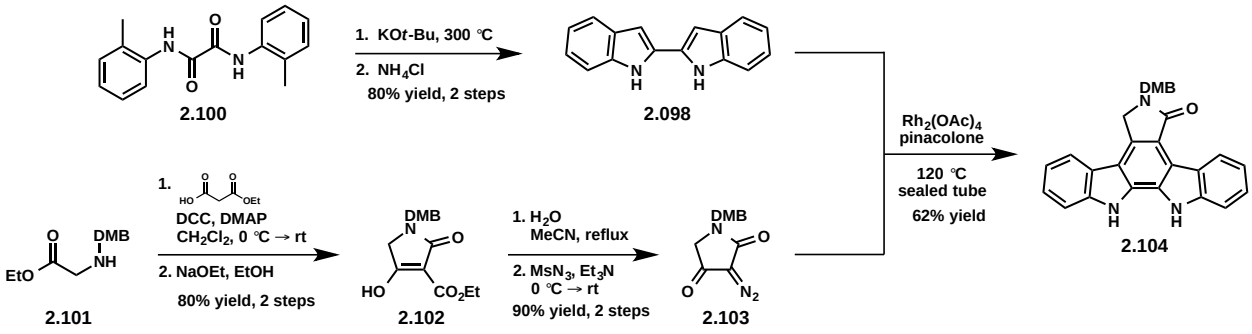
Scheme 1.11



ester **2.099**. It was known that **2.098** could be synthesized from **2.100** via a double Madelung cyclization.[43]

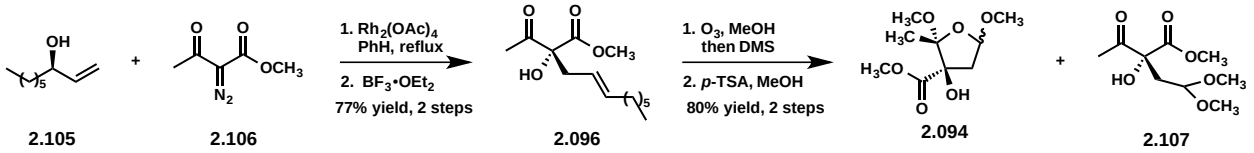
In the forward direction, the DMB-protected glycine ester (**2.101**) was coupled with ethyl hydrogen malonate (Scheme 1.12). A Dieckmann condensation produced **2.102**. Tetramic acid **2.102** then underwent a decarboethoxylation and Regitz diazo transfer to give **2.103**. **2.098** was synthesized from **2.100** following the literature precedent, and coupled with **2.103** in the presence of $Rh_2(OAc)_4$ at elevated temperature produced DMB protected aglycone **2.104**.

Scheme 1.12



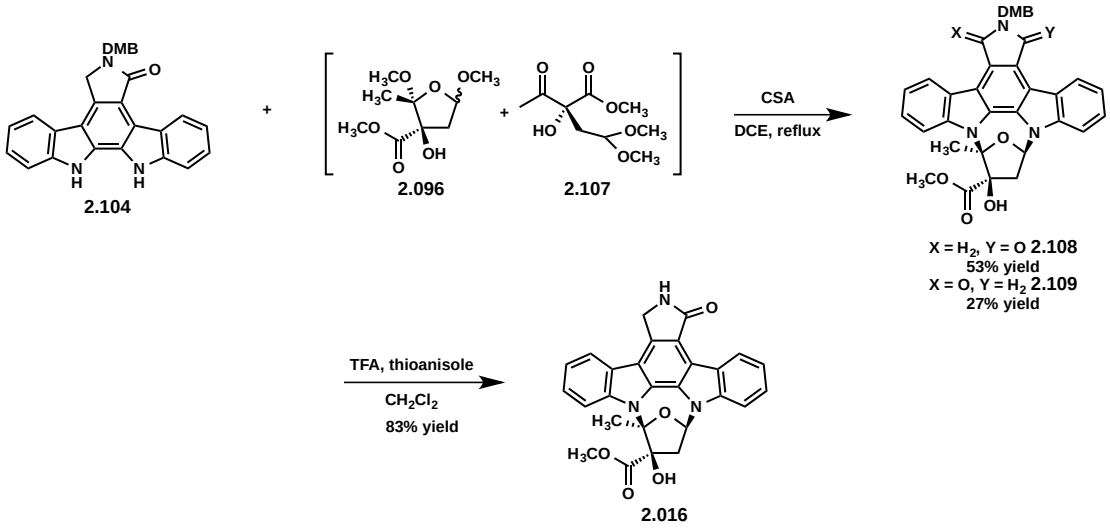
In parallel, the synthesis of **2.094** started with a rhodium initiated O−H insertion/Claisen rearrangement/1,2-allyl migration.[44] Allylic alcohol **2.105** was combined with α-diazo-β-ketoester **2.106** in the presence of $Rh_2(OAc)_4$ to give an α-keto-β-hydroxyester (Scheme 1.13).

Scheme 1.13



This intermediate was then treated with BF_3•OEt_2 to give α-hydroxy-β-ketoester **2.096**. Ozonolysis of the alkene and quenching with DMS gave an aldehyde, which upon exposure to acid formed a mixture of **2.094** and **2.107**. The cyclized product was itself a mixture of diastereomers at C5'. The mixture of carbohydrates proved to be inconsequential when they were combined with **2.104** in the presence of CSA (Scheme 1.14). The resulting product was a mixture of regioisomers **2.108** and **2.109**, with the desired **2.108** predominating. The final step was the removal of the DMB group under acidic conditions to give (+)-K252a (**2.016**).

Scheme 1.14

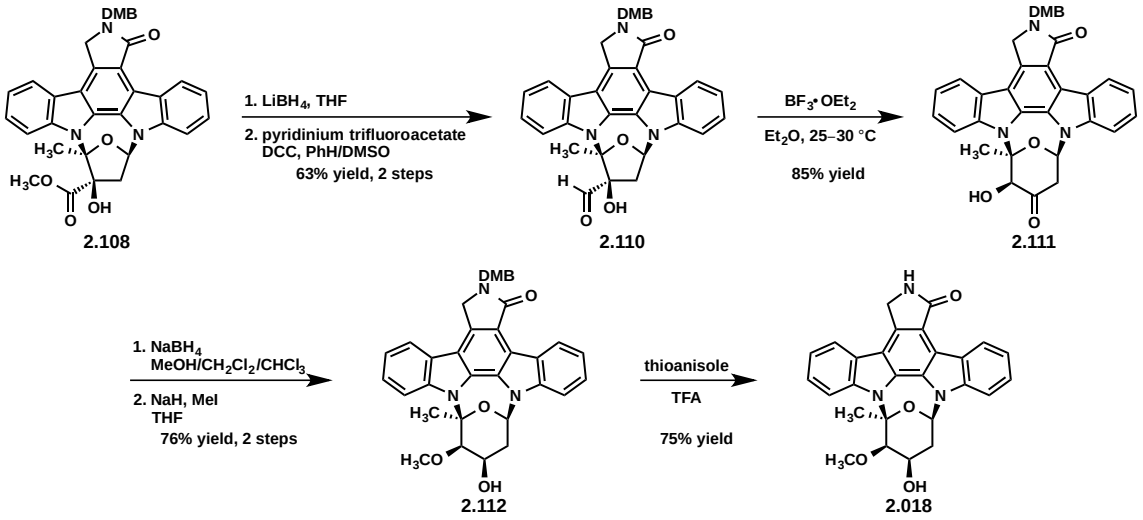


1.3.3.2 Synthesis of (+)-RK-286c

While (+)-K252a (**2.016**) was a furanosylated compound, the Wood group realized that the C3' ester could be incorporated into the ring in order to synthesize pyranosylated ICZs.[45] The way they decided to effect this transformation was via an α-ketol rearrangement. To that end the DMB protected compound **2.108** was converted to aldehyde **2.110** (Scheme 1.15). Upon

exposure to BF_3•OEt_2, the desired transformation occurred, affording pyran **2.111**. Reduction of the ketone occurred with complete selectivity for the desired diastereomer, which was then mono-methylated to give **2.112**. DMB removal provided (+)-RK-286c (**2.018**). They were also able to synthesize staurosporine (**2.013**) along with two other ICZ natural products from ketone **2.111**.

Scheme 1.15



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CHAPTER 2

The Synthesis of 7-oxo-(+)-K252a and Derivatives as Potential Hox-A13 Inhibitors

2.1 Hox-A13

The Hox genes are a subset of homeobox genes, which encode a highly conserved set of transcription factor proteins.[1] These proteins are critical in directing embryonic development. They are divided into four linkage groups (A−D) based on the chromosome where they appear. The HOXA13 gene codes for the Hox-A13 protein, a transcription factor required for the normal development of limb and genitourinary tissues. Hox-A13 is associated with the regulation of the SOSTDC1 gene (Figure 2.1).[2] SOSTDC1 encodes for a protein of the same name, which is a bone morphogenic protein (BMP) antagonist. BMPs are responsible for skeletal growth and cartilage formation during embryonic development. Inhibition of the binding between Hox-A13 and the SOSTDC1 gene leads to overproduction of the SOSTDC1 protein, which in turn disrupts

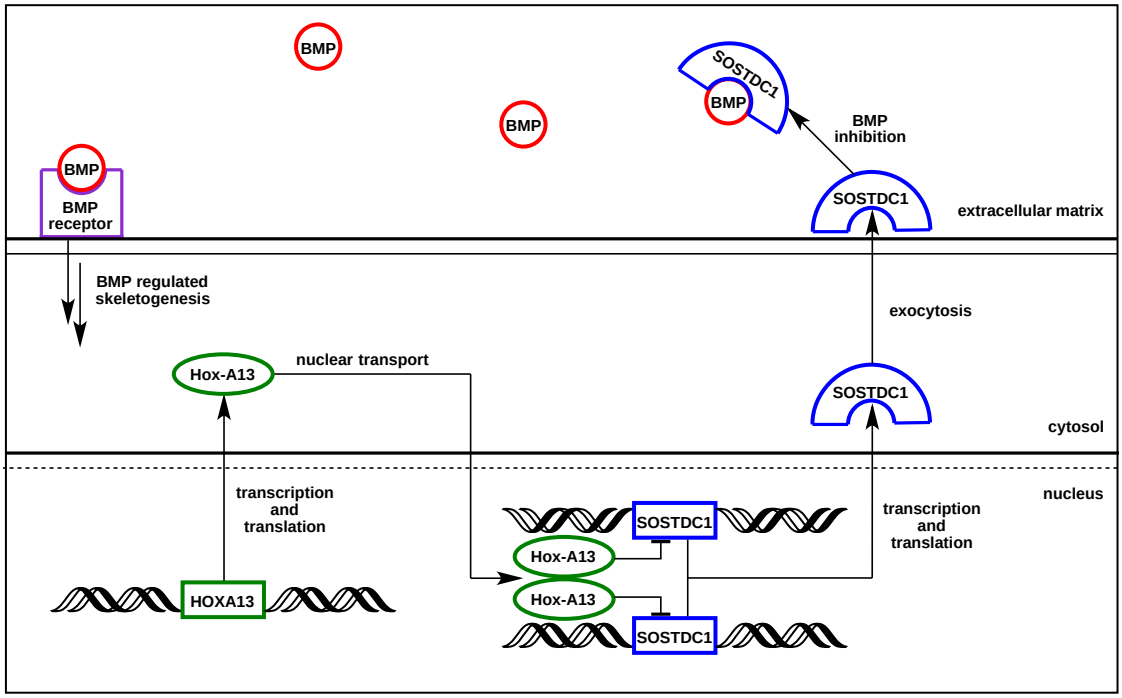


Figure 2.1

the interaction between BMPs and BMP receptors. This leads to malformations in the appendicular skeleton, digit loss, syndactyly, and hypospadias. Specifically, mutations in HOXA13 have been associated with Hand-Foot-Genital-Syndrome (HFGS) and Guttmacher syndrome (GS). A specific inhibitor of Hox-A13 would allow it to be blocked at a particular phase of embryonic development, increasing our understanding of its role. Additionally, Hox proteins are often aberrantly expressed in cancerous tissues; so, a small molecule inhibitor could potentially be a treatment.

2.1.1 *Known Inhibitors of Hox-A13*

When Stadler and co-workers at Oregon Health and Science University (OHSU) initially identified their need for an inhibitor of Hox-A13, they screened a library of small molecules.[3] The compounds were evaluated based on their IC_{50} for the disruption of a Hox-A13-DNA complex.[4] The lowest IC_{50} was found with SB-218078 (**2.113**) (Figure 2.2). Based on this result, they decided to screen a library of lactams generated by Shaw *et al.*[5] The best compound from this screen was lactam **2.114**, whose IC_{50} value was an order of magnitude greater than that of **2.113**. With this information in hand, they decided to screen commercially available ICZs. In this screen, they found another lead compound in stauprimide (**2.115**). Unfortunately, both **2.113** and **2.115** are known to have significant off-target activity against protein kinases.[6]

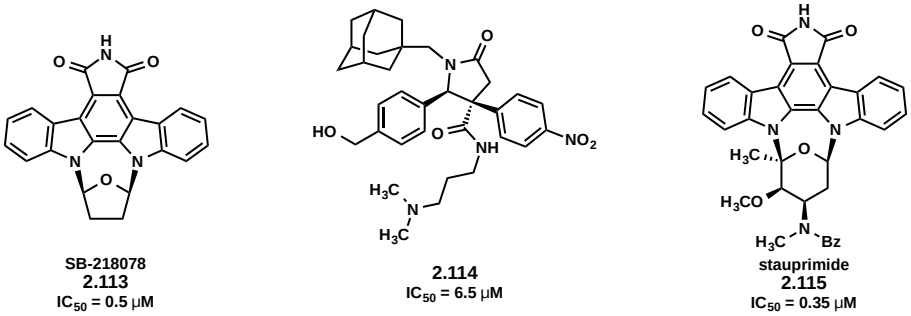
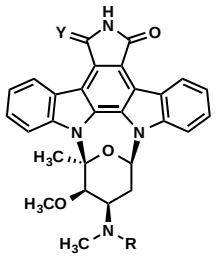


Figure 2.2

2.1.2 *Designing New Hox-A13 Inhibitors*

When considering what compounds to target as potential Hox-A13 inhibitors there were two main factors. The first was a compound's similarity to the known inhibitors SB-218078 (**2.113**) and stauprimide (**2.115**). The second was to avoid off target activity against protein kinases. In terms of optimizing for the first factor, it was clear that the desired compound would contain a 7-oxo-ICZ bonded to a glycoside. In consideration of the second factor, reported values for protein kinase inhibition were compared for some known compounds (Figure 2.3). Midostaurin (**2.026**),[7] which is currently in clinical trials, is considerably more selective and somewhat less active than staurosporine (**2.013**). **2.115**, which also has an N-Bz substituent, is not as selective as **2.026**, but also has attenuated activity compared with **2.013**. This indicated that the presence of a hydrogen-bond acceptor, rather than a donor, on the sugar provided better target selectivity. Additionally, the sterically crowded **2.116** was found to be fairly selective, but exhibited poor actitivity.[6b] Since the furanosylated ICZs are typically less potent protein kinase inhibitors than the analogous pyranosides, **2.113** was compared with (+)-K252a (**2.016**). While there is only limited data available for **2.113**, it appears to be somewhat more potent than **2.016**.



compound	Y	R	PKC IC_{50} (μM)	PKA IC_{50} (μM)
(+)-staurosporine **(+)-2.013**	H_2	H	0.006	0.015
midostaurin **2.026**	H_2	Bz	0.05	2.4
stauprimide **2.115**	O	Bz	0.095	0.75
N-Boc-RK-1409 **2.116**	O	Boc	1.5	>100

compound	PKC IC_{50} (μM)
(+)-K252a **(+)-2.016**	0.028
SB-218078 **2.113**	0.019

Figure 2.3

With this information, Stadler and co-workers chose 7-oxo-K252a (**2.117**) as the initial target compound (Figure 2.4).[3] Since amide analogs of (+)-K252a (**2.016**) had been shown to enhance protein kinase specificity,[8] they also wanted to screen amides such as **2.118a−f**.

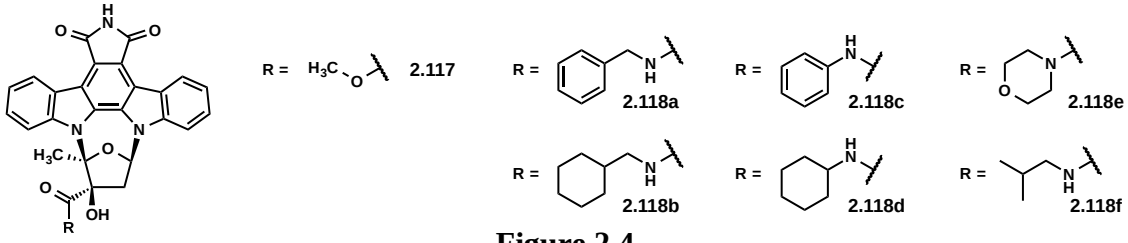
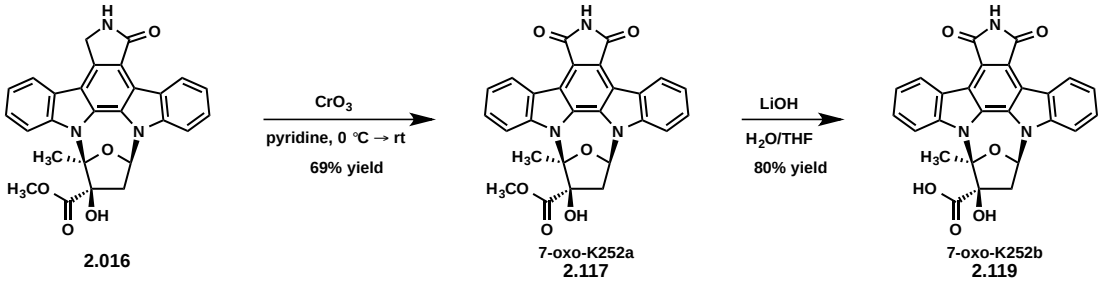


Figure 2.4

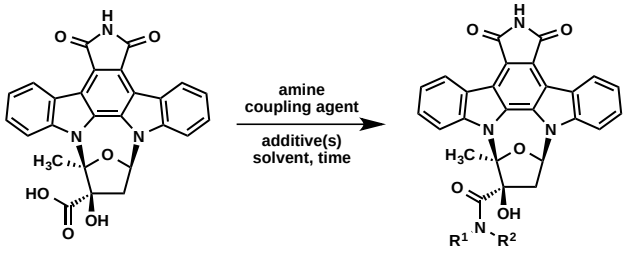
2.2 Synthesis of 7-oxo-K252a (2.117) and Derivatives

With a supply of (+)-K252a (**2.016**) in hand, our first task was to synthesize 7-oxo-K252a (**2.117**) following a procedure by Murakata *et al*.[9] This was accomplished by exposing **2.016** to CrO_3 for four days, after which **2.117** was recovered (Scheme 2.1). In order to synthesize the desired amides we would need 7-oxo-K252b (**2.119**) as a precursor. This was formed by treatment of **2.117** with LiOH in the presence of H_2O.[10]

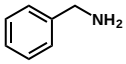
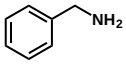
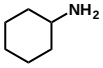
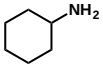
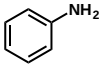
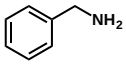
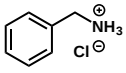
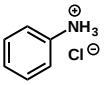
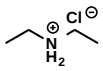
Scheme 2.1



In our initial attempts to make the amide analogs, we focused on EDAC/HOBt conditions (Figure 2.5).[11] We were able to couple the primary amines benzylamine and cyclohexylamine under these conditons to give amides **2.118a** and **2.118d**. We also observed the coupling of the secondary amine morpholine (**2.118f**), though we were unable to purify the product. Converting acid **2.119** to the corresponding acid chloride with $SOCl_2$ appeared to be successful, but treatment with benzylamine did not afford any of the desired amide. Following a procedure known to be effective in a related system,[8] we were able to synthesize **2.118a** in better yield by using CDI as the coupling agent. Unfortunately, our attempts to use the same procedure to make the aniline amide (**2.118c**) or the diethyl amide (**2.118g**) did not succeed.



2.119 2.118

entry	amine	coupling agent	additive(s)	solvent	time	yield
1		EDAC	HOBt, DIPEA	DMF	24 h	15%
2		EDAC	HOBt, DIPEA	EtOAc	20 h	40%
3		EDAC	HOBt, DIPEA	CH_2Cl_2	76 h	8%
4		EDAC	HOBt, DIPEA	CH_2Cl_2	9 days	35%
5		EDAC	HOBt, DIPEA	THF	21 h	0%
6		EDAC	HOBt, DIPEA	THF	21 h	21%[a]
7			$SOCl_2$	THF	29 h	0%
8		CDI	Et_3N	DMF/CH_2Cl_2	18 h	54%
9		CDI	Et_3N	DMF/CH_2Cl_2	19 h	trace
10		CDI	Et_3N	DMF/CH_2Cl_2	18 h	0%

[a]It was not possible to purify this compound.

Figure 2.5

2.3 Conclusions

We were able to synthesize amides **2.118a** and **2.118d** from 7-oxo-K252b (**2.119**) and the corresponding amines. Both amides and 7-oxo-K252a (**2.117**) were sent to OHSU for testing as Hox-A13 inhibitors. Amides **2.118b** and **2.118f** should be readily available using our conditions (entry 8, Figure 2.5). Conditions for the synthesis of phenolic and tertiary amides will require additional screening. We recently received data that indicated that **2.117** would not be a viable

Hox-A13 inhibitor for studying embryonic development, however. It appears that this compound functions as a general DNA binding antagonist, rather than a specific Hox-A13−DNA interrupter. There is an ongoing study to determine if **2.117** has enough specificity to be useful as an anticancer agent in liver cancer tumors expressing Hox-A13.[12] We have not yet received any data pertaining the Hox-A13 binding ability of amides **2.118a** and **2.118d**.

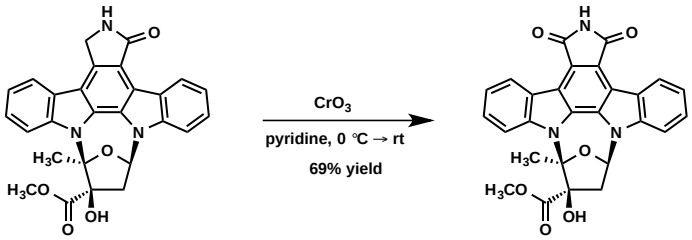
2.4 Experimental

Unless otherwise stated, reactions were magnetically stirred in flame- or oven-dried glassware and inert atmosphere operations were conducted under an atmosphere of nitrogen, which was passed through a drying tube containing Drierite. Triethylamine, diisopropylamine, and methanol were dried over calcium hydride and freshly distilled. Benzene, tetrahydrofuran, dichloromethane, toluene, and diethyl ether were dried using a solvent purification system manufactured by SG Water U.S.A., LLC. Anhydrous acetonitrile, dimethylsulfoxide, and methanol were purchased and used without further purification from Macron Chemicals, EMD Chemicals and Fischer Scientific respectively. All other commercial reagents were used as received, unless noted otherwise.

Unless otherwise stated, all reactions were monitored by thin-layer chromatography (TLC) using Silicycle glass-backed extra hard layer, 60 Å plates (indicator F-254, 250 μm). Preparatory TLC was performed on the same plates. Flash column chromatography was performed with the indicated solvents using Silicycle SiliaFlash. P60 (230-400 mesh) silica gel as the stationary phase. Infrared spectra (IR) were obtained on an FTIR spectrophotometer and are reported in wavenumbers (cm^{-1}). High-resolution mass spectra were acquired on an electrospray ionization (ESI) spectrometer and obtained by peak matching.

^{1}H-NMR spectra were recorded at ambient temperature at 400 MHz. ^{13}C-NMR spectra were recorded at ambient temperature at 101 MHz. For ^{1}H-NMR chemical shifts are reported as δ values in ppm and are calibrated according to the residual solvent peak. For ^{13}C-NMR chemical shifts are reported as δ values in ppm and are calibrated according to the residual solvent peak. Coupling constants (*J*) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as: s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintuplet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, br = broad, app = apparent, par = partial.

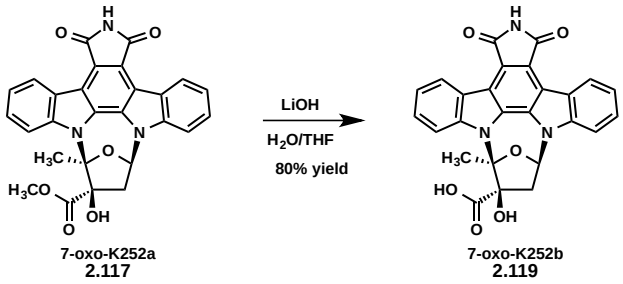
7-oxo-K252a (2.117)



In a 2-neck 25 mL round bottom flask, CrO_3 (0.048 g, 0.48 mmol, 2.2 equiv) was dissolved in 2.7 mL pyridine, and the solution cooled to 0 °C and stirred for 10 min. **(+)-2.016** (0.1038 g, 0.222 mmol, 1 equiv) was added, followed by 1.1 mL pyridine. A solution of CrO_3 (0.020 g, 0.20 mmol, 0.9 equiv) in pyridine (0.9 mL) was cooled to 0 °C and then added to the reaction mixture. The flask was allowed to warm to room temperature. After 24 h a solution of CrO_3 (0.040 g, 0.40 mmol, 1.8 equiv) in pyridine (1.6 mL) at 0 °C was added to the reaction mixture. After 24 h the reaction mixture was filtered through a plug of celite and the resulting solution concentrated *in vacuo*. Column chromatography on SiO_2 (20 →100% EtOAc/hexanes,

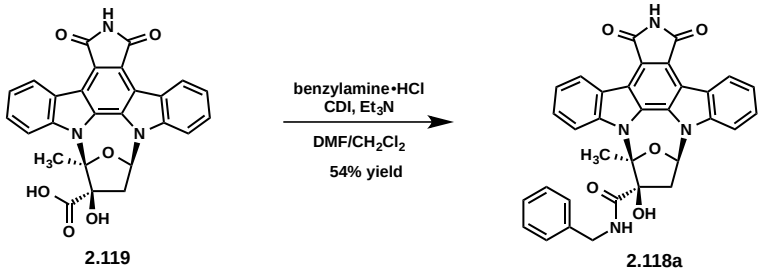
then 10% acetone/$CHCl_3$) afforded **2.117** (0.0741 g, 69%) as a bright yellow solid whose spectral data matched the values given in the literature.[9]

7-oxo-K252b (2.119)



In a 100 mL round bottom flask, **2.117** (0.0741 g, 0.154 mmol, 1 equiv) was dissolved in THF (13 mL, 0.012 M, not dry). LiOH (0.0089 g, 0.37 mmol, 2.4 equiv) was added to this solution, followed by H_2O (1.9 mL). After 16 h the reaction mixture was diluted with EtOAc (20 mL) and H_2O (20 mL). The pH of the aqueous layer was adjusted to 6 with 1M HCl and the layers were separated. The aqueous phase was then extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give **2.119** (0.0572 g, 80%) as a yellow solid, which was used crude in subsequent steps.

amide 2.118a



In a 2-neck 25 mL round bottom flask, **2.119** (0.0108 g, 0.023 mmol, 1 equiv) was dissolved in DMF (0.9 mL). CH_2Cl_2 (2.6 mL) was then added, followed by CDI (0.0101 g, 0.062 mmol, 2.7 equiv). After 95 min Et_3N (0.036 mL, 0.26 mmol, 11.6 equiv) was added, followed by

the benzylamine salt (0.0350 g, 0.24 mmol, 10.6 equiv). After 18 h the reaction mixture was diluted with EtOAc (10 mL) and 1M HCl (5 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were then washed with H_2O (5 x 30 mL), washed with brine, and dried over Na_2SO_4. Filtration was followed by dry loading on SiO_2. Column chromatography with SiO_2 (5 → 20% EtOAc/PhH, then 1% AcOH in 10% MeOH/CH_2Cl_2) yielded **2.118a** (0.0068 g, 54%) as a yellow film.

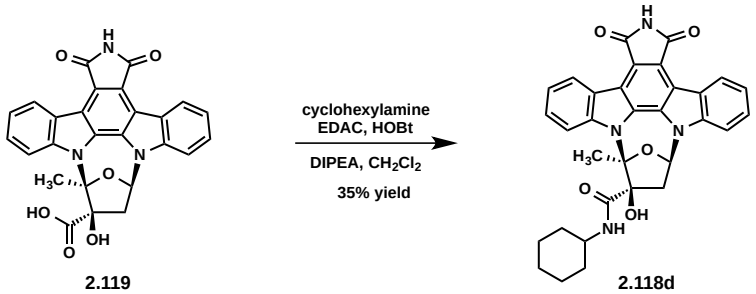
^{1}H-NMR (400 MHz; acetone-d_6): δ 9.92 (br s, 1H), 9.30 (d, *J* = 7.6 Hz, 1H), 9.15 (d, *J* = 8.0 Hz, 1H), 8.53 (t, *J* = 6.2 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 3H), 7.43-7.35 (m, 5H), 7.29 (d, *J* = 14.6 Hz, 1H), 7.11 (dd, *J* = 7.5, 4.7 Hz, 1H), 5.81 (s, 1H), 4.71-4.56 (m, 2H), 3.50 (dd, *J* = 13.7, 7.6 Hz, 1H), 2.44 (dd, *J* = 13.6, 4.8 Hz, 1H), 2.20 (s, 3H)

^{13}C-NMR (101 MHz; acetone-d_6): δ 171.6, 170.4, 170.1, 141.3, 139.4, 138.5, 130.2, 128.3, 128.01, 127.83, 127.06, 126.94, 126.4, 125.3, 125.1, 123.9, 121.9, 120.8, 120.6, 120.2, 117.1, 116.3, 114.7, 109.1, 100.8, 85.6, 85.4, 42.76, 42.57, 22.1

IR 3338 (br m), 2956 (m), 1748 (m), 1703 (s), 1656 (s), 1570 (m), 1459 (m), 1343 (s), 1318 (s), 1269 (m), 1071 (s), 802 (w), 748 (m), 700 (w), 488 (w), 422 (w) cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{33}H_{24}ClN_4O_5$ $(M+Cl)^-$ 591.1441, found 591.1447

amide 2.118d



2.119 **2.118d**

In a 10 mL flask, **2.119** (0.0150 g, 0.032 mmol, 1 equiv) was dissolved in CH_2Cl_2 (3 mL, 0.01 M). Cyclohexylamine (0.009 mL, 0.078 mmol, 2.5 equiv), HOBt (0.0093 g, 0.069 mmol, 2.2 equiv), EDAC (0.0147 g, 0.077 mmol, 2.4 equiv), and DIPEA (0.013 mL, 0.075 mmol, 2.3 equiv) were then added sequentially. After stirring at room temperature for 9 d, the reaction mixture was diluted with EtOAc (10 mL) and H_2O (5 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were then washed with bring, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Column chromatography on SiO_2 (5 → 20% EtOAc/PhH, then 1% AcOH in 10% MeOH/CH_2Cl_2) afforded **2.118d** (0.0061 g, 35%) as a yellow film.

^{1}H-NMR (400 MHz; acetone-d_6): δ 9.92 (s, 1H), 9.31 (d, *J* = 8.0 Hz, 1H), 9.16 (d, *J* = 7.9 Hz, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 8.3 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.64 (t, *J* = 7.1 Hz, 1H), 7.52 (t, *J* = 7.1 Hz, 1H), 7.43-7.35 (m, 2H), 7.09 (dd, *J* = 7.5, 4.7 Hz, 1H), 5.74 (s, 1H), 3.89 (s, 1H), 3.46 (dd, *J* = 13.7, 7.5 Hz, 1H), 2.41 (dd, *J* = 13.7, 4.7 Hz, 1H), 2.26 (s, 2H), 1.96-1.92 (m, 1H), 1.85-1.78 (m, 2H), 1.70-1.66 (m, 1H), 1.48 (dt, *J* = 19.8, 10.6 Hz, 5H)

^{13}C-NMR (101 MHz; acetone-d_6): δ 171.44, 171.35, 171.1, 142.3, 139.5, 131.3, 129.13, 129.02, 128.1, 127.4, 126.3, 126.1, 124.9, 122.9, 121.8, 121.6, 121.2, 118.1, 117.3, 115.8, 110.0, 101.7, 86.4, 49.3, 43.5, 33.5, 33.3, 26.4, 26.00, 25.95, 23.0

IR 3368 (br s), 3932 (s), 1749 (m), 1703 (s), 1655 (m), 1572 (w), 1526 (w), 1460 (m), 1387 (w), 1343 (s), 1318 (s), 1271 (w), 1237 (w), 1192 (w), 1139 (w), 1070 (m), 961 (w), 887 (w), 801 (w), 747 (m), 646 (w), 522 (w), 488 (w), 442 (w), 422 (w) cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{32}H_{28}ClN_4O_5$ $(M+Cl)^-$ 583.1752, found 583.1752

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[2] Zhang, Y.; Larsen, C. A.; Stadler, H. S.; Ames, J. B. *PLoS One* **2011**, *6*, e23069.

[3] Stadler, H. S. Oregon Health and Science University, Portland, OR. Personal communication, 2012.

[4] Knosp, W. M.; Saneyoshi, C.; Shou, S.; Bächinger, H. P.; Stadler, H. S. *J. Biol. Chem.* **2007**, *282*, 6843−6853.

[5] Ng, P. Y.; Yang, Y.; Knosp, W. M.; Stadler, H. S.; Shaw, J. T. *Angew. Chem. Int. Ed.* **2007**, *46*, 5352−5355.

[6] a) McCombie, S. W.; Bishop, R. W.; Carr, D.; Dobek, E.; Kirup, M. P.; Kirschmeier, P.; Lin, S.-I.; Petrin, J.; Rosinski, K.; Shankar, B. P.; Wilson, O. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1537−1542. b) Caravatti, G.; Meyer, T.; Fredenhagen, A.; Trinks, U.; Mett, H.; Fabbro, D. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 399−404.

[7] a) Bharate, S. B.; Sawant, S. D.; Singh, P. P.; Vishwakarma, R. A. *Chem. Rev.* **2013**, *113*, 6761−6815. b) Anastassiadis, T.; Deacon, S. W.; Devarajan, K.; Ma, H.; Peterson, J. R. *Nat. Biotech.* **2011**, *29*, 1039−1045.

[8] Schneider, T. L.; Mathew, R. S.; Rice, K. P.; Tamaki, K.; Wood, J. L.; Schepartz, A. *Org. Lett.* **2005**, *7*, 1695−1698.

[9] Murakata, C.; Sato, A.; Takahashi, M.; Kobayashi, E.; Morimoto, M.; Akinaga, S.; Hirata, T.; Mochida, K.; Kase, H.; Yamada, K.; Iwashashi, K. Derivatives of Physiologically Active Substance K252. U.S. Patent 4,923,986, May 8, 1990.

[10] Due to the presence of both acidic and basic functionalities in this compound, we were unable to purify it via chromatography. This also led to an extremely poor solubility profile and recrystallization was not attempted.

[11] For the use of EDAC/HOBt with 7-oxo-ICZ derivatives see: Wilson, L. J.; Murray, W. V.; Yang, S.-M.; Yang, C.; Wang, B. U.S. Patent 2007/0249590A1, October 25, 2007.

[12] Healthy liver tissue does not express Hox-A13. In hepatocellular carcinoma (HCC), Hox-A13 expression has been linked to very poor prognoses.

CHAPTER 3

Progress Toward the Synthesis of Streptocarbazoles A and B

3.1 Background

While streptocarbazole A **2.019** and streptocarbazole B **2.020** (Figure 3.1)[1] were not found to exhibit a significant inhibitory effect on protein kinases,[2] both demonstrated activity against various tumor cell lines (Table 3.1). While a larger screen of protein kinases would be necessary to rule out that mode of action, these results indicate that these compounds may have unique activity among ICZs, or at least specificity for a particular protein kinase. Coupled with the fact that they have sugar connectivity unique in naturally occurring ICZs, **2.019** and **2.020** make appealing targets for total synthesis.

Table 3.1

	IC_{50} (μM) Against Tumor Cell Lines			
	HL-60	A-549	P388	HeLa
2.019	1.4	5.0	18.9	34.5
2.020	>50	>50	12.8	22.5

3.1.1 Syntheses of Indolocarbazoles with Unusual Glycosidic Linkages

As was discussed in chapter 1, except for the streptocarbazoles, naturally occurring glycosylated ICZs come in two forms. One form, exemplified by rebeccamycin (**2.015**), has a single indole-*N* bond to the C6' position of the sugar (Figure 3.1). The other, typified by staurosporine (**2.013**), has indole-*N* bonds to both the C2' and the C6' positions on the sugar.

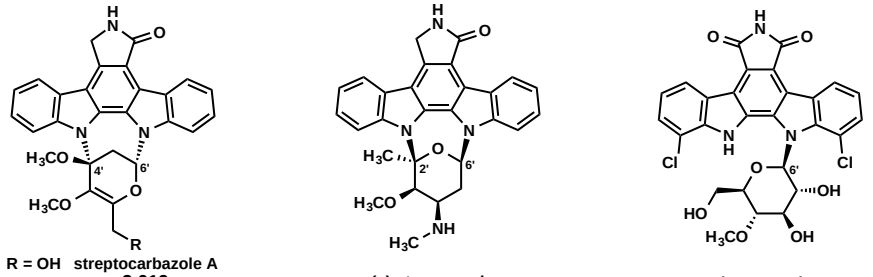


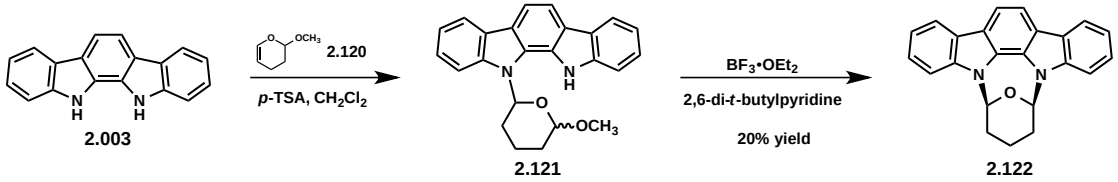
Figure 3.1

There have been three reports of synthetic glycosylated ICZs with alternate connectivity however.

3.1.1.1 C4'/C6' Connectivity

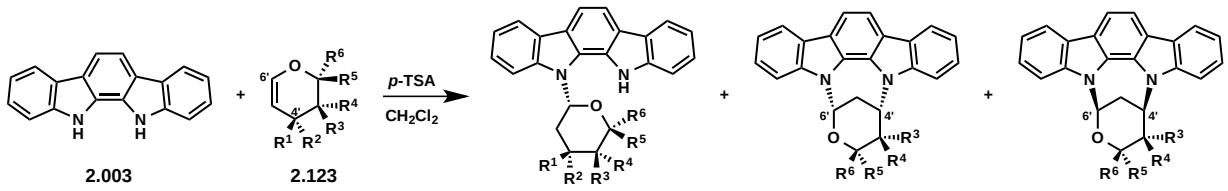
The only examples in the literature of glycosylated ICZs with C4'/C6' connectivity, other than the streptocarbazoles, are some undesired byproducts synthesized by Shankar and McCombie at Schering-Plough.[3] Working with **2.003** as a model system (Scheme 3.1), they were able to synthesize **2.121** via a glycosidation with **2.120**. Acetal **2.121** then underwent a second glycosidic bond formation under Lewis acidic conditions to give the desired pyranose **2.122**. When they switched to a more substituted unsaturated glycal (**2.123a**), they found that the desired mono-bonded glycoside **2.124a** was only formed in trace amounts (Figure 3.2). Instead, the major products appeared to be diastereomers of the dual-bonded glycoside, **2.125a** and **2.126a**. This C4'/C6' substitution product had previously only been observed in reactions which occurred at high temperatures, which could lead to sigmatropic or allylic rearrangements of more typical substitution products. While they found that they could shift the ratio of products so that the desired **2.124** was the major product, they were unable to prevent the formation of **2.125** and **2.126** while C4' was OAc substituted. This led them to conclude that the reaction was likely occurring via an allylic carbonium intermediate such as **2.127**.

Scheme 3.1



3.1.1.2 C5'/C6' Connectivity

The first report of glycosylated ICZs with C5'/C6' connectivity was from Prudhomme *et al.*[4] With **2.128**—which was available in a single step from **2.015**—as the substrate, they were



glycal	R^1	R^2	R^3	R^4	R^5	R^6	2.124	2.125	2.126
2.123a	H	OAc	OAc	H	H	CH_2OAc	trace	20%	40%
2.123b	OAc	H	H	OAc	CH_3	H	10%	15%	7%
2.123c	OAc	H	H	H	CH_3	H			15%
2.123d	H	OAc	H	OAc	H	H	30%	10%	5%
2.123e	H	OAc	H	OAc	H	CH_2OAc	40%	7%	4%

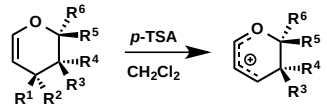
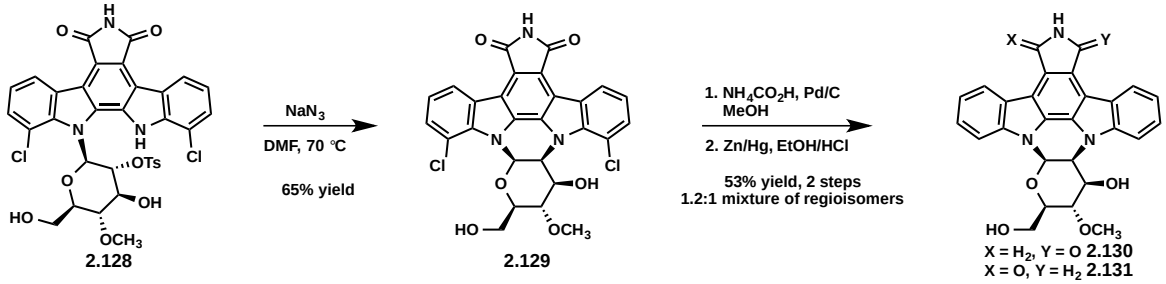


Figure 3.2

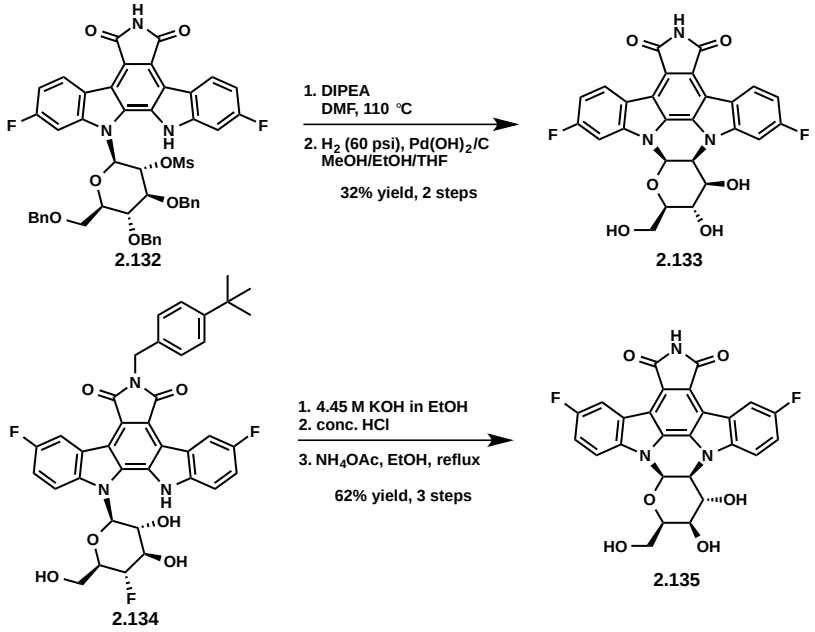
able to synthesize **2.129** (Scheme 3.2). Dehalogenation and subsequent reduction of the imide to the lactam gave an inseparable mixture of the regioisomers **2.130** and **2.131**. Compound **2.129** was found to have only weak activity against PKC-α (IC_{50} 118 μM), but did exhibit activity against the P388 tumor cell line (IC_{50} 5.44 μM). The mixture of **2.130**/**2.131** was not active toward PKC-α (IC_{50} >213 μM); however it was also a moderate antiproliferative agent for P388 cells (IC_{50} 6.82 μM).

Scheme 3.2



A second report on the formation of glycosylated ICZs with C5'/C6' connectivity was in a patent held by Bristol-Myers Squibb.[5] There it was found that mesylate **2.132** would undergo a second glycosylation when heated in the presence of base (Scheme 3.3). The crude material was

Scheme 3.3



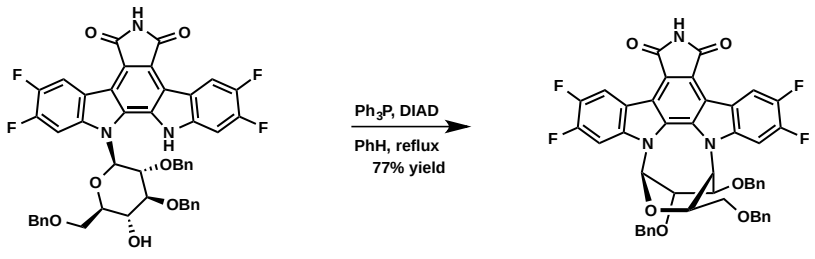
2.132 **2.133** **2.134** **2.135**

then subjected to hydrogenolysis to give **2.133**. They also reported a similar reaction with fluoride **2.134** as the substrate.[6] This substrate gives the same C5'/C6' connectivity via the formation of an epoxide intermediate, followed by a Payne rearrangement and nucleophilic epoxide opening.

3.1.1.3 C3'/C6' Connectivity

The only examples of glycosylated ICZs with C3'/C6' connectivity were reported by Saulnier *et al*. in the same patent as their report of C5'/C6' connectivity.[5] In this case, alcohol **2.136** was exposed to Mitsunobu conditions to give bridged glycoside **2.137** (Scheme 3.4). The other examples of this system are derivatizations of **2.137**.

Scheme 3.4



2.136 **2.137**

3.2 Retrosynthetic Analysis

When streptocarbazoles A (**2.019**) and B (**2.020**) were initially analyzed, we ruled out a route modeled on the prior synthesis of ICZs with unusual sugar connectivity for two reasons. The first was the observation by Danishefsky *et al*. that pyranosylation was substantially more difficult with the lactam when compared with the imide or the ICZ lacking the pyrrole ring.[7] The second reason was that Shankar and McCombie had observed a mixture of diastereomers (**2.125** and **2.126**, Figure 3.2).[3] Since the desired diastereomer (**2.126**) was the minor one of the 2:1 mixture, there would be a significant loss of material if this strategy were to be employed. Additionally, the presence of the asymmetric lactam moiety could generate two regioisomers.[8]

This analysis led to the conclusion that the best synthesis of streptocarbazoles A (**2.019**) and B (**2.020**) would occur via the same route as our prior syntheses of the pyranosylated ICZs.[9] In considering this idea further, it was noted that these new compounds contained the same oxidation state pattern as **2.017** (Figure 3.3). This compound is itself an oxidized form of **2.018**, which we had previously synthesized. In fact, **2.017** had been produced in minute quantities during the work on that synthesis.[8] With this in mind, we developed the retrosynthesis shown in Scheme 3.5.

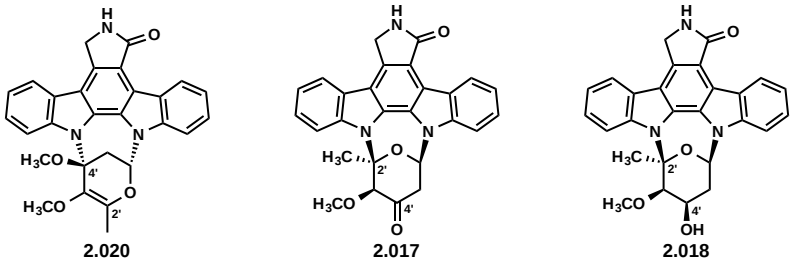
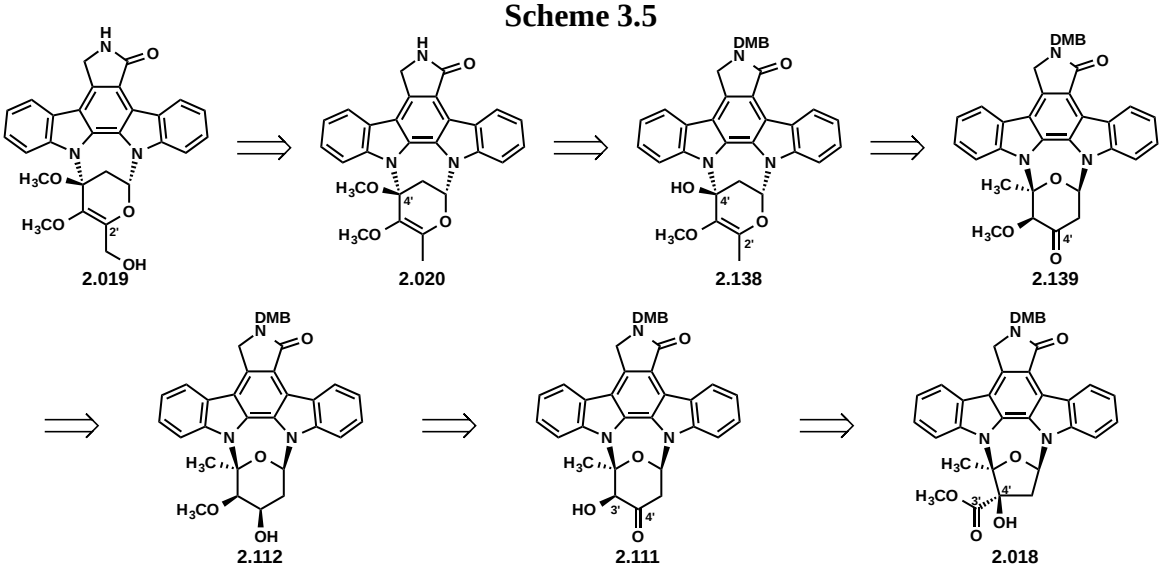


Figure 3.3

Retrosynthetically, we envisioned **2.019** deriving from **2.020** via an allylic oxidation. In turn, **2.020** would come from the methylation of **2.138**. This key intermediate would originate from a rearrangement of **2.139**. We felt that a substantially better yield of **2.139** could be

Scheme 3.5



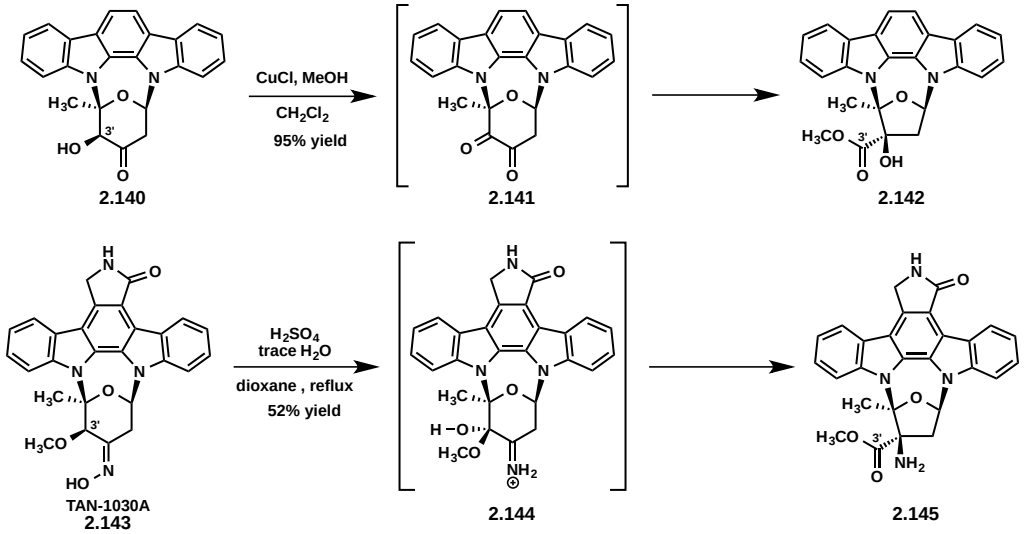
achieved by first synthesizing **2.112** and then oxidizing C4' back to the ketone. **2.112** was available via **2.111** following our previous synthesis from the DMB protected form of **(+)-2.016** (**2.018**). We were optimistic about the key transformation of **2.139** to **2.138** given that rearrangements of the glycoside were already known. Furthermore, the desired C2' to C4' migration was essentially an intramolecular hemiaminal formation, examples of which exist in the literature.

3.2.1 Known Rearrangements of Indolocarbazole Glycosides

When considering the known rearrangements of the glycoside they can be divided into two main groups. The first of these are those that do not involve the migration of an indole nitrogen (Scheme 3.6). Both known examples of this type involve an oxidative ring contraction of a pyranose to a furanose. In the case of Wood and co-workers, in their attempt to methylate model system **2.140**, migration of the indole nitrogen was not observed.[8,9] They found that when α-hydroxyketone **2.140** was treated with CuCl in the presence of methanol, the resulting product was α-hydroxyester **2.142**. They speculated that this reaction occurred via a diketone such as **2.141**, though they found that their "attempts to prepare [the diketone] by direct oxidation of

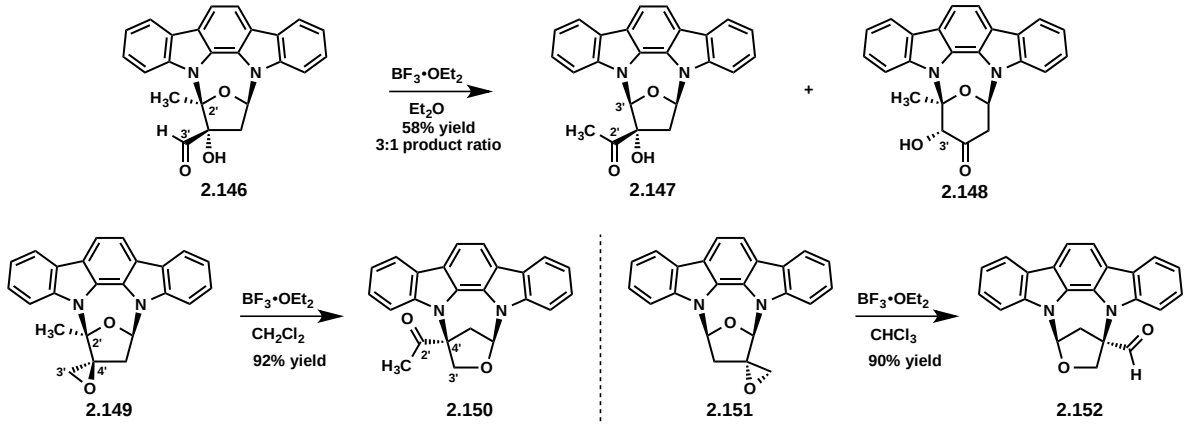
[the] hydroxyketone have been unsuccessful". Fredenhagen and Peter also observed ring contraction without migration of the indole nitrogen. They reported that when the natural product TAN-1030A (**2.143**) was exposed to H_2SO_4, the product was the amine analog of **(+)-2.016** (**2.145**).[10] They proposed a mechanism, where the ring contraction occurred via protonated imine intermediate **2.144**.

Scheme 3.6



The second group of known rearrangements are those in which migration of the indole nitrogen is observed (Scheme 3.7). In one case, aldehyde **2.146** was exposed to the conditions for an α-ketol rearrangement.[8] With the stereochemistry at C4' inverted compared to the natural product, only a small amount of the expected product (**2.148**) was formed. Instead, the major product was α-hydroxyketone **2.147**, which likely arises from an acetal exchange. During the course of the reaction, one of the indole nitrogens has migrated from C2' to C3'. Similarly, when epoxide **2.149** was exposed to related Lewis acid conditions, the product was found to be ketone **2.150**.[8] Based on studies with epoxide **2.151** by Shankar *et al.*,[11] the mechanism appears to involve the ring opening of the epoxide via a C2' to C4' migration of the indole nitrogen.

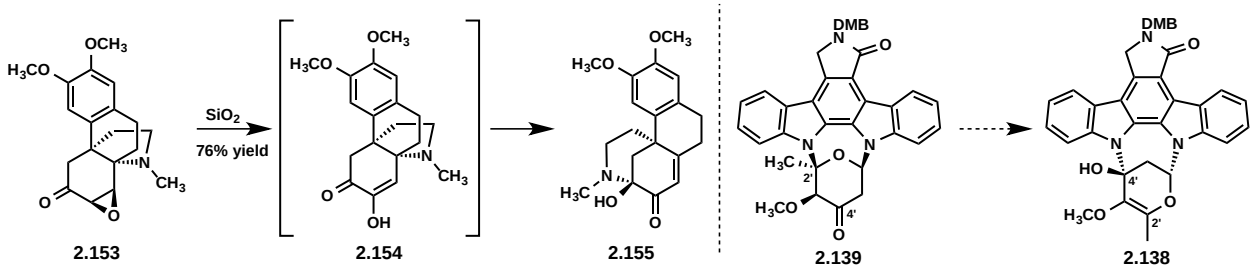
Scheme 3.7



3.2.2 Aminal/Hemiaminal Formations via Intramolecular Migration

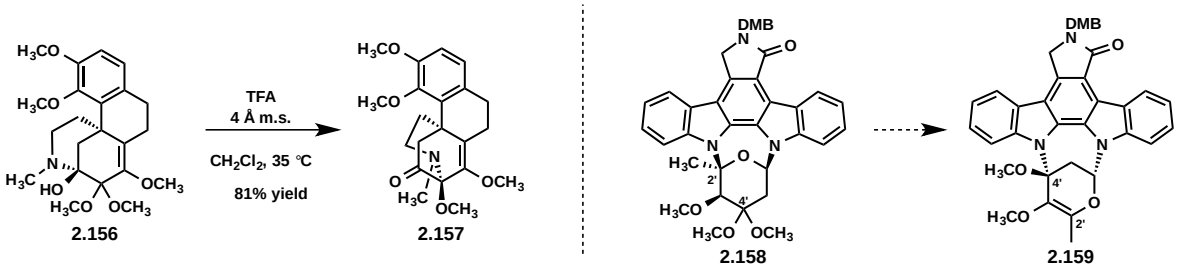
Since the desired C2' to C4' migration is essentially an intramolecular hemiaminal formation, we examined the literature precedent for such a reaction. The intramolecular formation of an aminal or hemiaminal commonly occurs with a secondary amine and without any C–N bond migration. However, there are some examples of tertiary amines undergoing C−N bond migration to give aminals or hemiaminals,[12] particularly as observed in the syntheses of the related hasubanan and cepharatine alkaloids.[13] Two representative examples of this last group appear in Scheme 3.8. In the first, Reisman *et al.* found that when they attempted to purify epoxide **2.153** on SiO_2, they recovered a mixture of products, one of which was not present in the crude material.[13d] Optimization afforded only the new compound in 76% yield. The new compound was assigned as hemiaminal **2.155**. The mechanism proposed for its formation is an acid promoted rearrangement of epoxide **2.153** to corresponding enol **2.154**. We envisioned that

Scheme 3.8



this might be possible with a substrate such as ketone **2.139**. In the second example (Scheme 3.9), Castle *et al.* demonstrated the formation of an aminal via C−N bond migration.[13b] When hemiaminal **2.156** was treated with TFA, the resulting product (**2.157**) contained an aminal in place of the acetal present in the starting material. If we employed this route, dimethylacetal **2.158** would be synthesized and used as the substrate for the rearrangement. The resulting product (**2.159**) would not need to be subsequently methylated.

Scheme 3.9

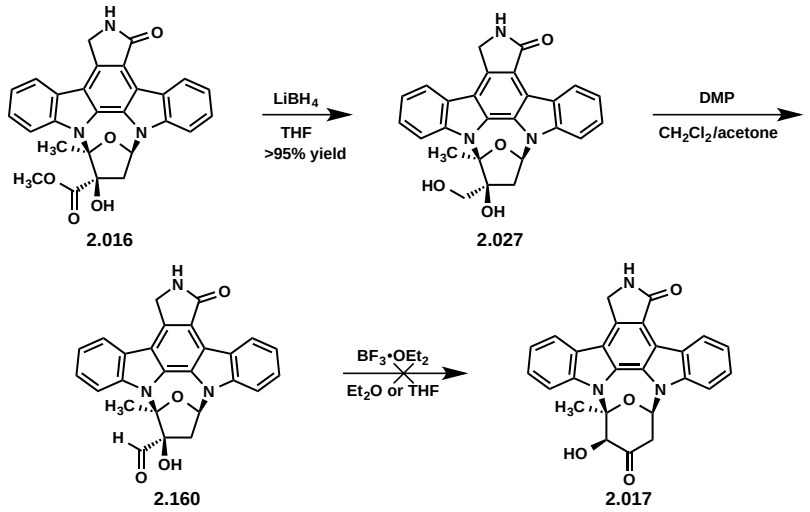


3.3 Preliminary Investigations

3.3.1 The Use of Unprotected (+)-K252a

Since we had a supply of (+)-K252a (**2.016**) on hand, we initially chose to attempt the syntheses of streptocarbazole A (**2.019**) and B (**2.020**) without protecting the lactam. The first step was the reduction of **2.016** to **2.027**, which went smoothly with a large excess of $LiBH_4$ (Scheme 3.10). However, oxidation of alcohol **2.027** was problematic and the yields varied widely. The DMB protected form of the aldehyde (**2.110**) was known to decompose fairly rapidly, and compound **2.160** appeared to have the same problem. However, the poor solubility profile of **2.160** proved to be a greater issue. Previous work[8,14] had shown that the α-ketol rearrangement was only successful in ethereal solvents. Although the α-ketol rearrangement was a heterogeneous reaction, a minimal amount of the aldehyde had to dissolve in order for the reaction to take place. Since the unprotected lactam **2.160** was more polar than its DMB

Scheme 3.10

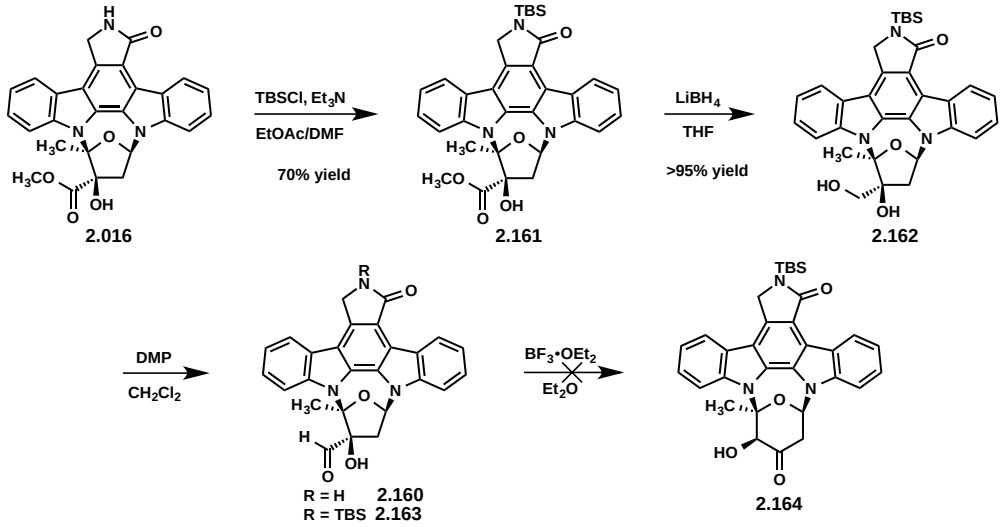


protected counterpart **2.110**, it decomposed before it could dissolve in Et_2O, and we were unable to isolate the desired product (**2.017**). The use of THF provided trace amounts of the product, and a superstochiometric amount of BF_3•OEt_2 led to polymerization of the solvent. We were unable to separate the trace of **2.017** observed by ^{1}H-NMR from the polymeric THF and consequently abandoned the idea of using an unprotected lactam in the synthesis.

3.3.2 Attempts with Alternate Protecting Groups

Previous reports in the literature indicated that late-stage protection of the lactam nitrogen over the oxygen could only be accomplished selectively with installation of a *t*-butyldimethylsilyl group.[15] While we doubted its long-term stability toward the conditions necessary for the α-ketol rearrangement, we thought that if the nonpolar protecting group increased the solubility of the substrate the reaction might proceed more rapidly. Following the literature procedure, we protected (+)-K252a (**2.016**) as the TBS-lactam (**2.161**, Scheme 3.11). Once again, the $LiBH_4$ reduction went smoothly when a large excess of the reagent was used. The resulting diol (**2.162**) was then treated with Dess-Martin periodinane. The desired product (**2.163**) was unfortunately contaminated with the unprotected lactam (**2.160**). This presumably

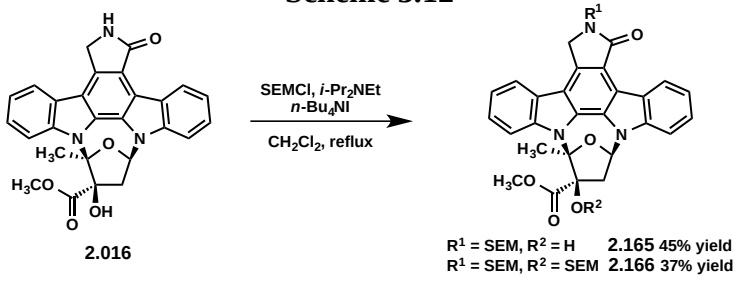
Scheme 3.11



resulted from the generation of acetic acid during the oxidation. While some test reactions in the presence of base to neutralize the acid appeared to be effective, when we attempted to use **2.163** in the α-ketol rearrangement we were unable to obtain any of the desired **2.164**. This was assumed to be due to TBS cleavage and subsequent decomposition of **2.160**.

We also tested the use of the SEM protecting group for the lactam. Unfortunately, the initial protection step provided the two products in a 1.2:1 ratio (Scheme 3.12). Separation of the of the desired **2.165** from the bis-SEM compound **2.166** proved to be quite challenging. The small amount of **2.165** we were able to isolate was competent in the $LiBH_4$ reduction; however we decided that the lack of selectivity in the initial protection reaction made its use unfeasible.

Scheme 3.12



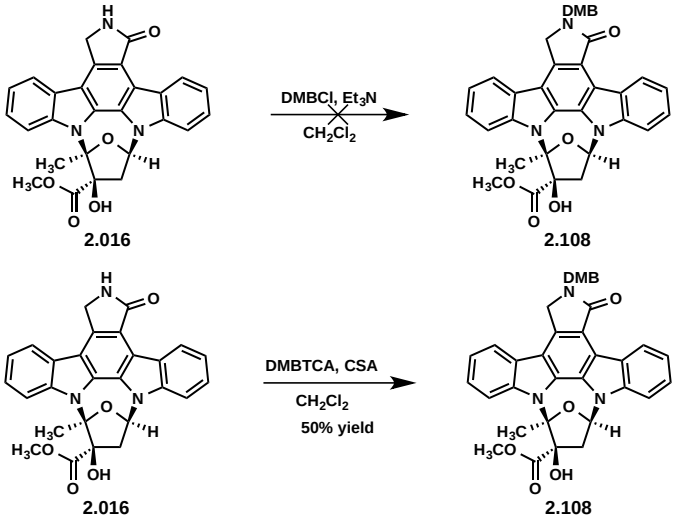
3.4 Synthesis of Substrates for the Desired C−N Bond Migration

3.4.1 Synthesis of DMB Protected (+)-K252a

3.4.1.1 Preliminary Investigations

As was mentioned in the previous section, the selective protection of the lactam of (+)-K252a (**2.016**) over the alcohol was only known to occur with TBSCl. Since we determined that a more stable protecting group was needed, we turned our attention to the DMB group used in our earlier work.[8,9] Our initial attempt was with the analogous reagent, DMBCl[16] (Scheme 3.13), although we isolated only starting material. The next reagent we tried was DMB-trichloroacetimidate[17] (DMBTCA) and we were pleased to observe the formation of the desired **2.108**, albeit in a modest yield. Since the stability of DMBTCA is questionable at room temperature,[18] we elected to try another reagent before attempting to optimize that reaction.

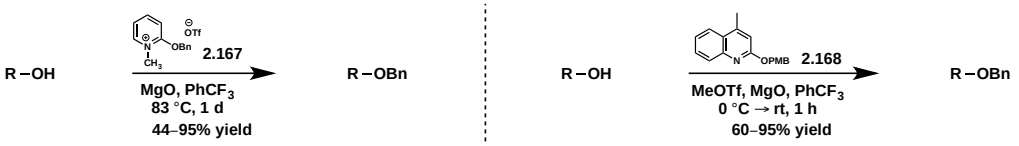
Scheme 3.13



3.4.1.2 Development of DMBOPy

Relatively recently, Dudley *et al.* developed a new reagent for the benzyl protection of alcohols (Scheme 3.14).[19] Although Dudley's reagent (**2.167**) has proven to be effective for a wide range of alcohols, they found that the PMB variant (**2.169**, Figure 3.4) rapidly decomposed

Scheme 3.14



above 0 °C.[20] This led to the development of a process for the *in situ* generation of **2.170** from a modified precursor (**2.168**). Later, Paquette *et al.* found that the same precursor could be used as a PMB transfer reagent without the need to form the salt.[21] A related compound (**2.171**) has also been used as a PMB transfer reagent.[22] In terms of DMB transfer, compound **2.172** has been used by Halcomb and co-workers and compound **2.173** has been used by Burkart *et al.*[23] However, there are only a few cases in the literature where reagents of this type have been used to protect amines or amides rather than alcohols.[24]

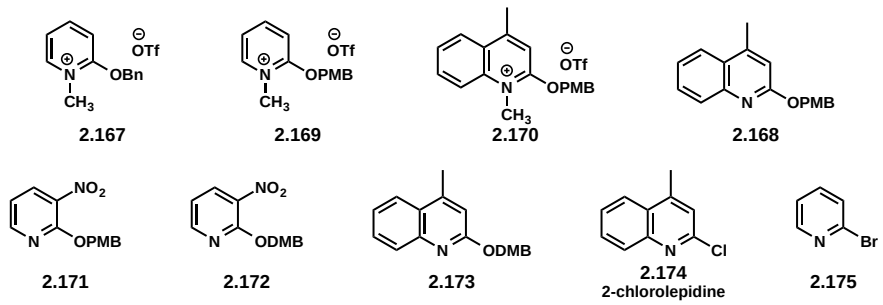
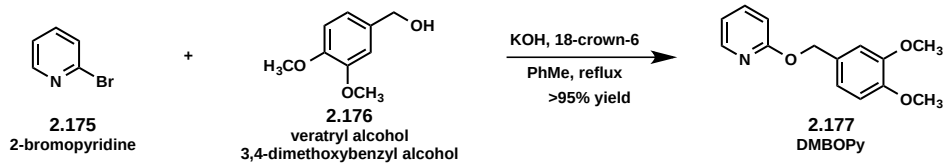


Figure 3.4

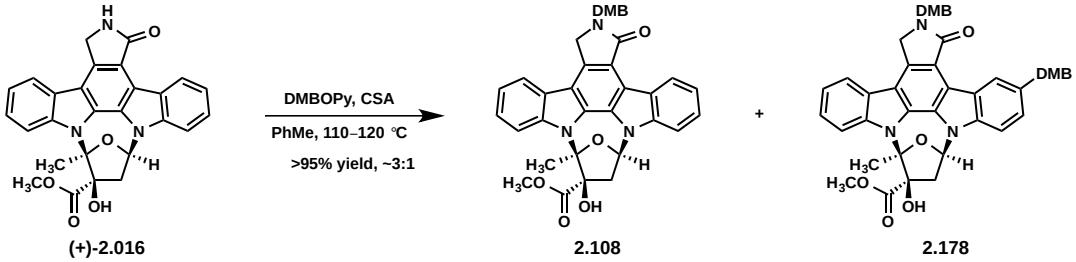
Since **2.171** had previously proven ineffective on an ICZ substrate,[25] we ruled out using the 3-nitropyridine core for a DMB transfer reagent. While **2.173** was a known transfer reagent, we would have to use 2-chlorolepidine (**2.174**) to make it. Since **2.174** was considerably more expensive than **2.175**,[26] we decided to first test the pyridine version. Combining **2.175** with **2.176** in the presence of potassium hydroxide and 18-crown-6 afforded DMBOPy (**2.175**, Scheme 3.15). With **2.177** in hand, we attempted to make the DMB analog of Dudley's reagent. It quickly became apparent that this salt was no more stable than the PMB versions (**2.169**, **2.170**).[20] Since the reagent was unstable above 0 °C, but our substrate (**2.016**) was not soluble at 0 °C, we turned to Paquette's acid catalyzed conditions. Using **2.177**, which was stable at elevated temperatures,

Scheme 3.15



we were able to produce the desired protected amide (**2.108**, Scheme 3.16). Further study determined that running the reaction at a relatively high concentration (0.4 M) at elevated temperatures improved the yield to nearly quantitative.

Scheme 3.16



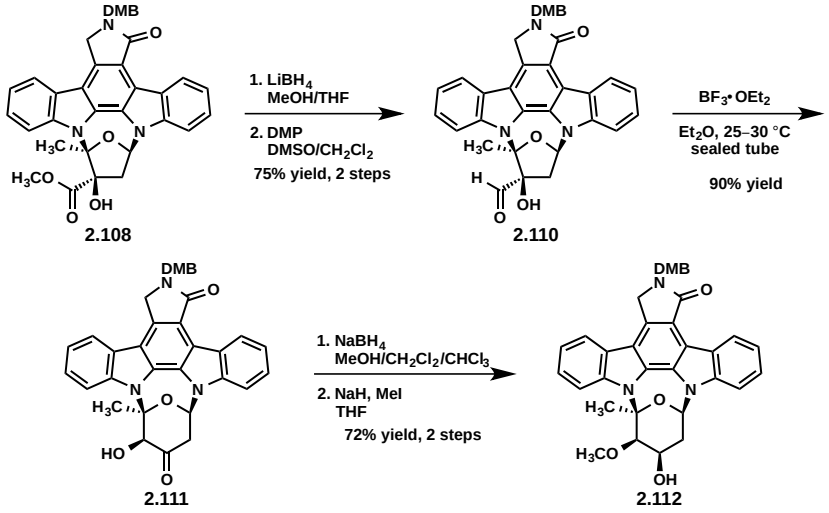
3.4.1.3 An Unexpected Side Product

While the mass recovery was >95%, an examination of the spectral data of product indicated that 20−25% of the material was not the desired compound. Careful chromatography could afford ~60% of pure **2.108**. Further analysis of the side-product indicated that rather than the expected protection of the tertiary alcohol, it was instead compound **2.178**.[27] This appears to result from a Friedel-Crafts alkylation of **2.108** by the dimethoxybenzyl cation derived from **2.177**. Preliminary investigations with DMBTCA in the presence of the cation scavenger thioanisole did not result in the suppression of this undesired side reaction.

3.4.2 Use of DMB Protected (+)-K252a

With the DMB protected **2.108** in hand, a $LiBH_4$ reduction gave the desired diol, which was oxidized to aldehyde **2.110** with Dess-Martin periodinane (Scheme 3.17). The α-ketol rearrangement was less straightforward to reproduce. The original work in this system required a

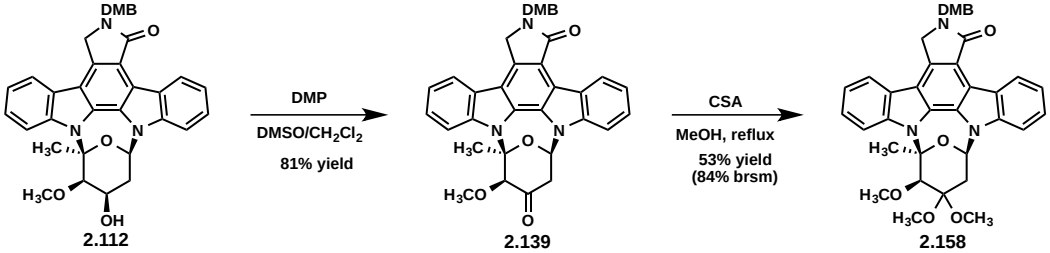
Scheme 3.17



slight elevation above room temperature (25−30 °C) for the reaction to proceed efficiently. However, that work had been conducted at a considerably lower altitude, where the boiling point of Et_2O was 35 °C. We found that in order for the reaction to proceed efficiently, and to effectively keep the concentration constant, it was necessary to run the reaction in a completely closed system.[28] With pyranose **2.111** in hand, the subsequent reduction of the ketone and selective mono-methylation gave methyl ether **2.112**.[29] **2.112** is the DMB protected form of (+)-RK-286c (**2.018**).

Oxidation of alcohol **2.112** with the Dess-Martin reagent afforded ketone **2.139** (Scheme 3.18), the first of our desired substrates. Formation of the dimethyl acetal (**2.158**) with CSA in methanol appeared to be efficient; however, upon work-up and isolation a considerable amount of the starting ketone (**2.139**) was recovered consistently.

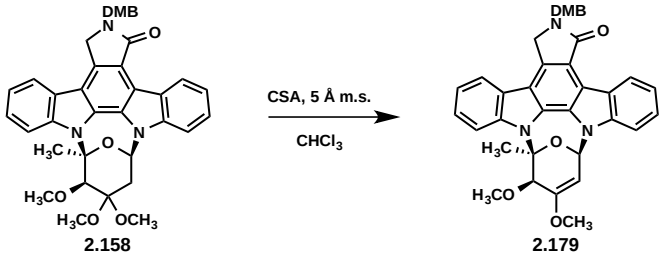
Scheme 3.18



3.5 Screening Potential Rearrangement Conditions

Ketone **2.139** and acetal **2.163** were subjected to a variety of Brønsted (HCl•MeOH, TFA, AcOH, CSA) and Lewis acidic conditions (BF_3•OEt_2, $La(OTf)_3$, $CeCl_3$, BF_3•MeOH), but none of the desired C−N bond migration was observed. When **2.139** was the substrate, we observed no reaction, formation of the aglycone (**2.104**), or decomposition. With **2.158** as the substrate in most cases we observed the same range of results seen with **2.139**. In a few reactions, however, a small amount of a new compound was isolated. Unfortunately, spectral analysis led to the conclusion that this compound was in fact **2.179** (Scheme 3.19). This enol ether is the product of the acid catalyzed elimination of half of the dimethyl acetal in **2.158**.

Scheme 3.19



3.6 Conclusions

In summary, we have developed a method to protect (+)-K252a (**2.016**) with the stable and removable DMB group. The reaction is selective for protection of the amide over the tertiary alcohol, to give **2.108** as the major product. It uses a unique, inexpensive variation of the precursor to Dudley's reagent. Following his convention, we have termed this reagent (**2.177**) DMBOPy.

While the synthesis of the streptocarbazoles remains unfinished, we developed a new method of protecting ICZ lactams and were able to synthesize substrates likely to undergo the desired rearrangement. With the isolation of enol ether **2.179**, it is clear that activation is occurring at the desired location—the C4' substituent—under acidic conditions. Future work on

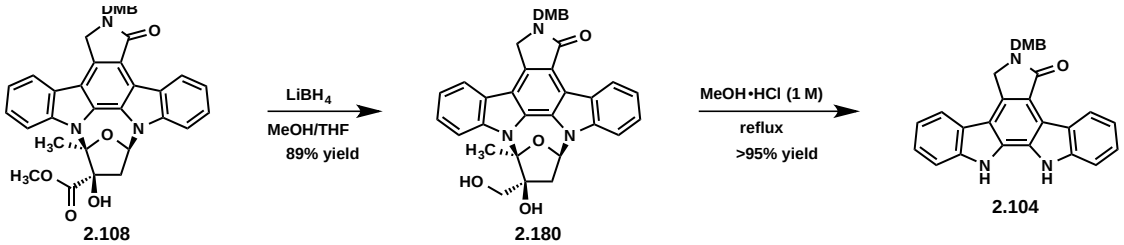
this project should focus on screening a larger variety of rearrangement conditions. A considerable number of the conditions already tested included methanol for solubility; however the desired bond migration may only occur in an aprotic solvent, so some of those reactions should be re-run in a different solvent (THF, CH_2Cl_2, $CHCl_3$). A survey of the literature[12,13] indicates that the following conditions would also be worth testing: dry-loading onto SiO_2, non-nucleophilic acids (ie: HBF_4, H_2SO_4), and other Lewis acids (ie: $MgBr_2 \bullet OEt_2$, SmI_2).

3.7 Other Investigations

3.7.1 Use of Natural (+)-K252a as a Source of DMB-protected K252c

In the course of our work on the synthesis of ICZs, we have been fortunate to have access to (+)-K252a (**2.016**) from a biological source. We did not however have any of the DMB protected aglycone (**2.104**) on hand. While our synthesis of this compound is efficient,[8,9] we sought a way to generate it from the material we possessed. After synthesizing **2.108**, we attempted to cleave the glycoside while leaving the ICZ intact and DMB protected. Unfortunately, all of our attempts led to either no reaction or complete decomposition of **2.108**. We had observed traces of the aglycone (**2.104**) in our efforts toward the streptocarbazoles however, so we knew that this reaction was possible when the sugar was modified. We then reduced **2.108** to diol **2.180** as in our previous work (Scheme 3.20). Here we were able to cleave the sugar under acidic conditions. Optimization of this reaction afforded the desired aglycone (**2.104**) in >95% yield.

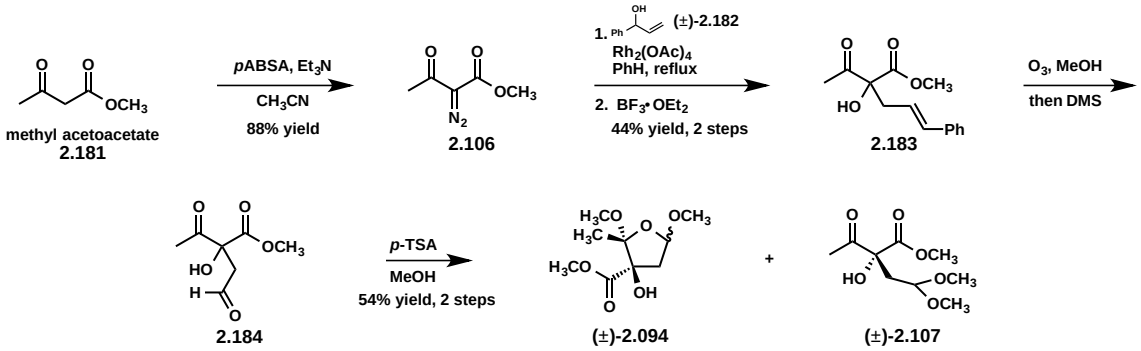
Scheme 3.20



3.7.2 An Alternate Synthesis of Racemic Furan (±)-2.094

While there are two syntheses of **(±)-2.094** in the literature, neither is particularly optimized.[9,30] Since our synthesis of enantioenriched **2.107** was efficient[8,9] we decided to adapt it for the synthesis of the racemic material. Starting from methyl acetoacetate (**2.181**), we synthesized **2.106** in good yield (Scheme 3.21). The Rh-initiated O−H insertion/Claisen rearrangement/1,2-allyl migration[31] was then performed with racemic alcohol **2.182**. The moderate yield of this reaction is tempered by the fact that both **2.106** and **2.182** are each only a single step from cheap, readily available starting materials. With α-hydroxy-β-ketoester ester **2.183** in hand, an ozonolysis could be performed. Quenching with DMS gave aldehyde **2.184**. This crude material was then exposed to *p*TSA to give the expected mixture of furanose diastereomers (**(±)-2.094a** and **(±)-2.094b**) and linear acetal **(±)-2.107**.

Scheme 3.21



3.7.3 Summary

We have also devised an efficient technique by which to cleave the sugar from a DMB-protected ICZ, while leaving the protecting group intact. The resulting aglycone (**2.104**) is a suitable substrate for coupling with furanose **(±)-2.094**. This furanose can be synthesized from inexpensive starting materials via a route that we have demonstrated on a multi-gram scale.

3.8 Experimental

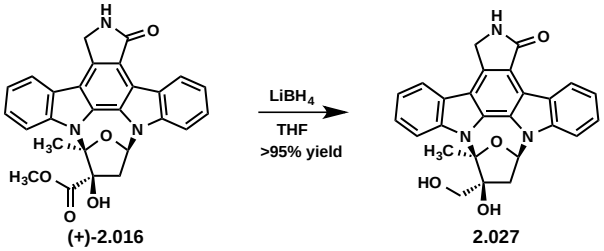
Unless otherwise stated, reactions were magnetically stirred in flame- or oven-dried glassware and inert atmosphere operations were conducted under an atmosphere of nitrogen, which was passed through a drying tube containing Drierite. Triethylamine, diisopropylamine, and methanol were dried over calcium hydride and freshly distilled. Benzene, tetrahydrofuran, dichloromethane, toluene, and diethyl ether were dried using a solvent purification system manufactured by SG Water U.S.A., LLC. Anhydrous acetonitrile, dimethylsulfoxide, and methanol were purchased and used without further purification from Macron Chemicals, EMD Chemicals and Fischer Scientific respectively. All other commercial reagents were used as received, unless noted otherwise.

Unless otherwise stated, all reactions were monitored by thin-layer chromatography (TLC) using Silicycle glass-backed extra hard layer, 60 Å plates (indicator F-254, 250 μm). Preparatory TLC was performed on the same plates. Flash column chromatography was performed with the indicated solvents using Silicycle SiliaFlash. P60 (230-400 mesh) silica gel as the stationary phase. Infrared spectra (IR) were obtained on an FTIR spectrophotometer and are reported in wavenumbers (cm^{-1}). High-resolution mass spectra were acquired on an electrospray ionization (ESI) spectrometer and obtained by peak matching.

^{1}H-NMR spectra were recorded at ambient temperature at 400 or 500 MHz. ^{13}C-NMR spectra were recorded at ambient temperature at 101 or 126 MHz. For ^{1}H-NMR chemical shifts are reported as δ values in ppm and are calibrated according to the residual solvent peak. For ^{13}C-NMR chemical shifts are reported as δ values in ppm and are calibrated according to the residual solvent peak. Coupling constants (*J*) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as: s = singlet, d = doublet, t = triplet, q = quartet,

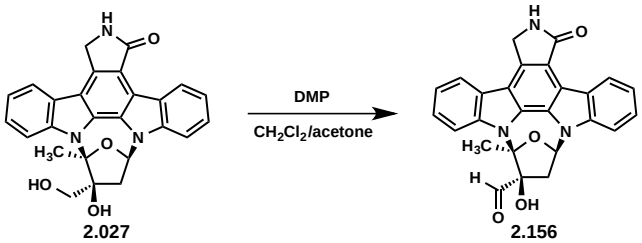
quint. = quintuplet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, br = broad, app = apparent, par = partial.

diol 2.027



In a 25 mL pear-shaped flask, **(+)-2.016** (0.0452 g, 0.097 mmol, 1 equiv) and $LiBH_4$ (0.0084 g, 0.387 mmol, 4 equiv) were combined. THF (4.5 mL, 0.02 M) was added and the reaction mixture stirred for 1.5 h at room temperature. The flask was then cooled to 0 °C and the reaction quenched with 0.13 M citric $acid_{(aq.)}$ (4−5 mL). It was then diluted with EtOAc (5 mL) and H_2O (5 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (3 x 5 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and filtered. Concentration *in vacuo* gave a quantitative yield of **2.027** as an off-white solid, whose spectral data matched that found in the literature.[32]

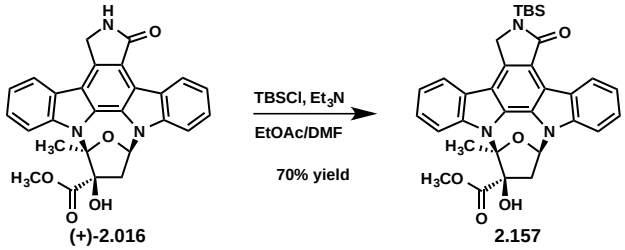
aldehyde 2.156



In a 25 mL, 2-neck, round-bottomed flask, **2.027** (0.0439 g, 0.1 mmol, 1 equiv) was dissolved in a mixture of CH_2Cl_2 (5 mL, 0.02 M) and acetone (3 mL, 0.03M). The Dess-Martin

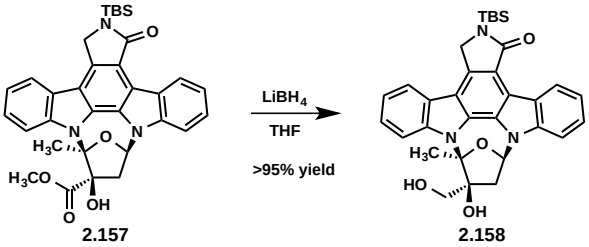
reagent (0.0467 g, 0.11 mmol, 1.1 equiv) was added, and the reaction mixture stirred for 19 h. It was then quenched by the addition of a 1:1 mixture of 10% $Na_2S_2O_{3(aq.)}$ and sat'd. $NaHCO_{3(aq.)}$ and diluted with H_2O (5 mL) and CH_2Cl_2 (5 mL). The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting material (**2.156**) was a light yellow solid, whose spectral data matched that reported in the literature.[32]

silylamide 2.157



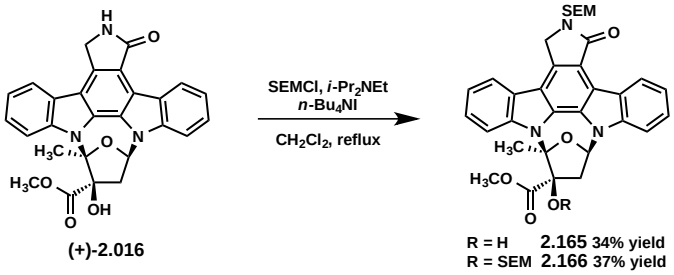
In a 35 mL round-bottomed flask, **(+)-2.016** (0.0475 g, 0.1 mmol, 1 equiv) was suspended in EtOAc (4 mL, 0.025 M). Triethylamine (0.042 mL, 0.3 mmol, 3 equiv) and DMF (0.05 mL) were then added, followed by a solution of TBSCl (0.0452 g, 0.3 mmol, 3 equiv) in EtOAc (0.5 mL) and the remaining EtOAc (0.5 mL, 0.02 M total). After 2.75 h additional DMF was added (0.2 mL). After another 1.5 h the flask was heated to 30 °C and stirred overnight. Additional TBSCl (0.0904 g, 0.6 mmol, 6 equiv), triethylamine (0.126 mL, 0.9 mmol, 9 equiv), and EtOAc (1 mL) were then added, and the reaction mixture stirred for an additional 24 h. It was then concentrated *in vacuo* and purified via column chromatography (SiO_2, 10 → 20% acetone/$CHCl_3$). 0.0407 g (70%) of **2.157** was isolated as a light yellow solid, whose spectral data matched that reported in the literature.[15]

diol 2.158



In a 25 mL, 2-neck, round-bottomed flask, **2.157** (0.0317 g, 0.054 mmol, 1 equiv) was dissolved in THF (4 mL, 0.014 M). The $LiBH_4$ (0.0030 g, 0.109 mmol, 2 equiv) was then added, followed by the remaining THF (0.4 mL, 0.012 M total). After 2 h the flask was cooled to 0 °C and the reaction quenched with 0.13 M citric $acid_{(aq.)}$ (1 mL). The reaction mixture was then diluted with brine (5 mL) and EtOAc (5 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. **2.158** was quantitatively isolated as a yellow solid.[33]

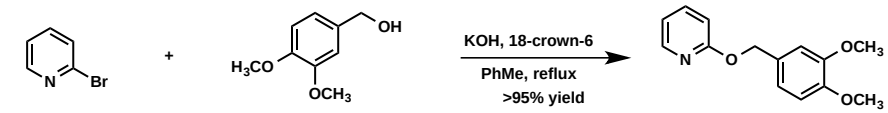
silylamide 2.165 and silylether 2.166



In a 25 mL, 2-neck, round-bottomed flask with a reflux condenser, **(+)-2.016** (0.0212 g, 0.045 mmol, 1 equiv) and *n*-Bu_4NI (0.0218 g, 0.059 mmol, 1.3 equiv) were stirred in CH_2Cl_2 (2.5 mL, 0.17 M). *i*-Pr_2NEt (1 mL, 0.043 M) was added, and the solution stirred for 5 min. SEMCl (0.25 mL, 0.17 M) was then added dropwise via syringe. The flask was then heated to reflux and the reaction mixture stirred for 32 h. After cooling to room temperature, the reaction

mixture was diluted with EtOAc (5 mL) and H_2O (5 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (4 x 3 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Column chromatography (SiO_2, 20 → 50% → 100% EtOAc/hexanes) afforded 0.0121 g (37%) of **2.166** as a yellow oil and 0.0240 g (34%) of **2.165** as a light yellow solid.[34] An additional 0.0059 g (28%) of **(+)-2.016** was also recovered.

DMBOPy (2.177)



2.175
2-bromopyridine

2.176
veratryl alcohol
3,4-dimethoxybenzyl alcohol

2.177
DMBOPy

A 100 mL round bottom flask containing a stir bar was charged with KOH (2.14 g, 38.2 mmol, 4.1 equiv), 18-crown-6 (0.1231 g, 0.47 mmol, 0.05 equiv), and PhMe (10 mL). **2.175** (1.81 mL, 9.3 mmol, 1 equiv) was added, followed by **2.176** (1 mL, 10.3 mmol, 1.1 equiv) and the remaining PhMe (8.6 mL, 0.5M total). A Dean-Stark trap filled with PhMe was affixed to the top of the flask and the system was heated to reflux for 3 h. After cooling to room temperature the reaction mixture was diluted with H_2O (20 mL) and EtOAc (10 mL). The phases were separated, and the organic layer was washed with H_2O (5 mL) and brine (2 x 5 mL). The combined aqueous washes were extracted with EtOAc (3 x 15 mL). The combined organic layers were then washed a final time with brine and dried over Na_2SO_4. Filtration and concentration *in vacuo* gave an oily white solid. Purification by column chromatography on SiO_2 (5 → 30% EtOAc/hexanes gradient) gave 2.27g (>95% yield) of **2.177** as a white solid.[35]

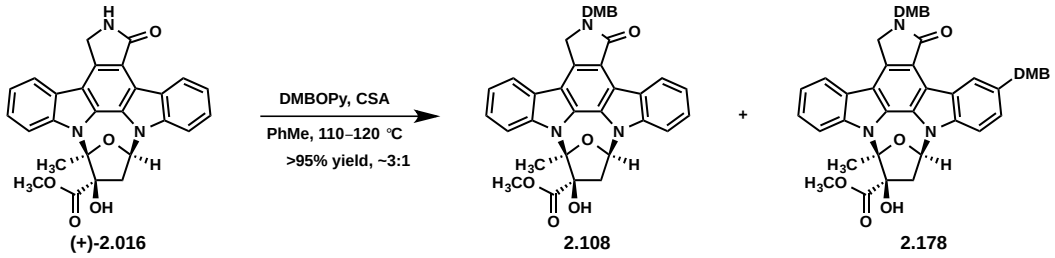
^{1}H-NMR (400 MHz; $CDCl_3$): δ 8.18 (dt, *J* = 5.1, 1.0 Hz, 1H), 7.58 (ddd, *J* = 8.5, 6.9, 1.8 Hz, 1H), 7.03-7.01 (m, 2H), 6.90-6.86 (m, 2H), 6.79 (d, *J* = 8.4 Hz, 1H), 5.31 (s, 2H), 3.89 (d, *J* = 5.4 Hz, 6H)

^{13}C-NMR (101 MHz; $CDCl_3$): δ 163.8, 149.14, 148.97, 147.0, 138.7, 129.9, 121.0, 117.0, 111.7, 111.5, 111.2, 67.8, 56.08, 56.01

IR 3064 (w), 3000 (w), 2935 (m), 2834 (w), 1734 (w), 1596 (s), 1568 (m), 1517 (s), 1474 (s), 1432 (s), 1418 (m), 1367 (m), 1309 (m), 1265 (s), 1238 (s), 1159 (m), 1140 (m), 1028 (m), 987 (m), 871 (w), 805 (w), 781 (m), 738 (w) 668 (w) cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{14}H15NNaO_3$ $(M+Na)^+$ 268.0944, found 268.0937

DMB-K252a (2.108) and dimethoxybenzylated indolocarbazole 2.178



A 1 dram vial containing a stir bar was charged with **(+)-2.016** (0.1504 g, 0.322 mmol, 1 equiv), DMBOPy (0.2367 g, 0.965 mmol, 3 equiv), and PhMe (0.61 mL) was heated to 115 °C for 2 min (until the DMBOPy had dissolved) and then cooled to room temperature. CSA (0.0074 g, 0.032 mmol, 0.1 equiv) was added, followed by the remaining PhMe (0.2 mL, 0.4M total). Argon was blown into the vial, which was then sealed with a septum cap and heated to 115 °C for 2 h. The reaction mixture was then transferred directly onto a SiO_2 column for purification (1% MeOH/CH_2Cl_2, then 50% EtOAc/hexanes). 0.1890 g (95% yield) of a light yellow solid contained a ~3:1 mixture of **2.108** and **2.178**. The remaining 5% of the mass was recovered **(+)-2.016**. The spectral data for **2.108** matched that reported in the literature.[8,9]

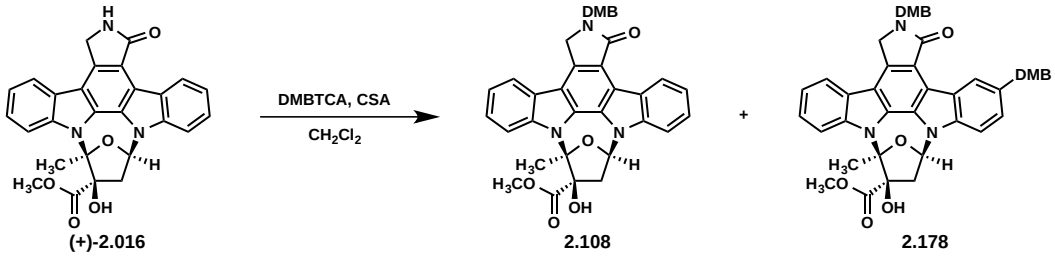
2.178: ^{1}H-NMR (400 MHz; acetone-d_6): δ 9.24 (d, *J* = 1.2 Hz, 1H), 7.98 (t, *J* = 8.1 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.45 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.34-7.28 (m, 3H), 7.05 (dd, *J* = 7.4, 4.9 Hz, 1H), 7.00-6.98 (m, 2H), 6.89-6.81 (m, 4H), 5.46 (s, 1H), 4.86 (s, 2H), 4.74 (d, *J* = 15.0 Hz, 1H), 4.38 (d, *J* = 14.9 Hz, 1H), 4.12 (s, 2H), 4.00 (s, 3H), 3.79 (s, 3H), 3.75 (t, *J* = 0.9 Hz, 9H), 3.50 (dd, *J* = 14.1, 7.4 Hz, 1H), 2.47 (dd, *J* = 14.1, 4.9 Hz, 1H), 2.19 (s, 3H)

^{13}C-NMR (101 MHz; acetone-d_6): δ 173.9, 170.0, 150.6, 150.4, 149.8, 148.7, 141.3, 136.9, 136.1, 133.8, 131.6, 131.0, 129.6, 127.6, 126.8, 125.9, 125.60, 125.54, 124.1, 122.0, 121.7, 121.4, 121.0, 120.3, 117.4, 115.8, 115.5, 114.0, 113.01, 112.85, 112.76, 109.0, 100.4, 86.39, 86.30, 86.16, 56.19, 56.16, 56.13, 56.10, 53.4, 50.4, 46.3, 43.4, 42.4, 23.5

IR 3269 (br w), 3055 (w), 2997 (w), 2952 (w), 2933 (w), 2834 (w), 1731 (m), 1674 (m), 1645 (s), 1589 (m), 1513 (s), 1462 (s), 1418 (m), 1363 (m), 1348 (m), 1308 (m), 1257 (s), 1234 (s), 1205 (m), 1137 (s), 1082 (m), 1026 (s), 971 (m), 953 (m), 920 (w), 874 (m), 802 (m), 734 (s), 697 (m), 654 (w) cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{45}H_{42}N_3O_9$ $(M+H)^+$ 768.2916, found 768.2936

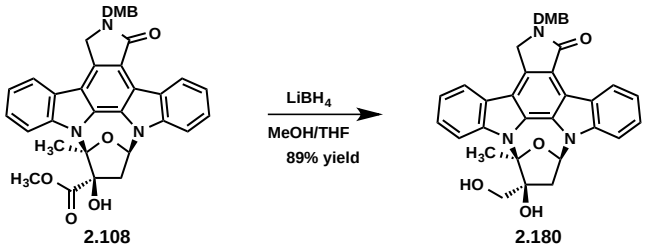
alternate preparation of dimethoxybenzylated indolocarbazole 2.178



A 1 mL micro reaction vial with a septum cap was charged with **(+)-2.016** (0.0095 g, 0.02 mmol, 1 equiv) and CSA (0.0005 g, 0.002 mmol, 0.1 equiv) in CH_2Cl_2 (0.3 mL, 0.07M). A solution of DMBTCA (0.0070 g, 0.022 mmol, 1.1 equiv) in CH_2Cl_2 (0.1 mL) was added dropwise via syringe, followed by the remaining CH_2Cl_2 (0.1 mL, 0.04 M). After being allowed

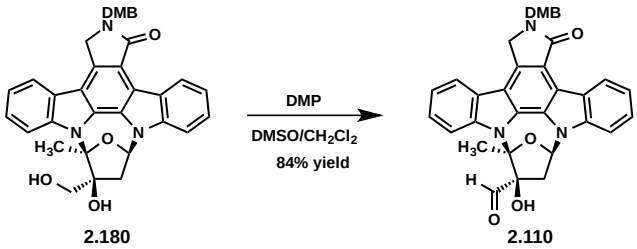
to stir overnight, TLC indicated that the reaction had stopped at ~50% conversion to spots corresponding with **2.108** and **2.178**.

diol 2.180



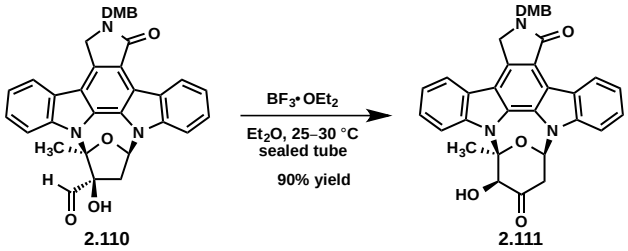
To a stirred solution of **2.108** (0.1390 g, 0.225 mmol, 1 equiv) in THF (6 mL, 0.038 M) was added $LiBH_4$ (0.0196 g, 0.9 mmol, 4 equiv) in one portion. This was followed by the addition of MeOH (2 mL, 0.11 M), and the reaction mixture was stirred at room temperature for 50 min. The flask was cooled to 0 °C and a 0.13M (10 mL) citric acid solution was added. After gas evolution had ceased (~20 min), EtOAc was added and the biphasic reaction mixture separated. The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were then washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give an oily yellow solid. Purification via column chromatography on SiO_2 (10 → 40% EtOAc/CH_2Cl_2 gradient) gave **2.180** as a light yellow solid (0.1180 g, 89% yield). The spectral data for **2.180** matched that reported in the literature.[8,9]

aldehyde 2.110



In a 50 mL 2-neck round-bottom flask, DMP (0.1029g, 0.25 mmol, 1.21 equiv) was left under vacuum for 5−10 min. After back filling 3 times with N_2, CH_2Cl_2 (5 mL) was added. This suspension was stirred for 30 min. **2.180** (0.1180g, 0.2 mmol, 1 equiv) was dissolved in a mixture of CH_2Cl_2 (2 mL) and DMSO (0.5 mL) and was added to the flask via pipet, followed by the remaining CH_2Cl_2 (3 mL, 0.02 M). After 5 min additional DMSO (1 mL) was added. After 5 h the reaction was quenched with a 10:10:1 mixture of sat'd. $NaHCO_{3(aq.)}$, H_2O, and sat'd. $Na_2S_2O_{3(aq.)}$ (10 mL) and stirred vigorously at room temperature for 20−30 min. The phases were separated, and the organic layer was then washed with H_2O (3 x 5 mL). The aqueous layers were combined and extracted with CH_2Cl_2 (2 x 5 mL) and EtOAc (1 x 5 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification via column chromatography (SiO_2, 10% EtOAc/CH_2Cl_2) gave **2.110** as a yellow solid (0.0989g, 84% yield), whose spectral data matched that reported in the literature.[8,9]

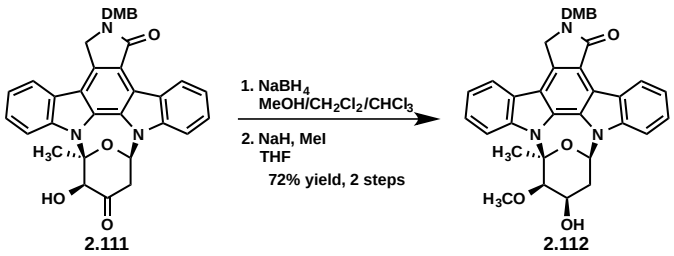
ketone 2.111



A 50 mL round-bottomed flask containing **2.110** (0.1892 g, 0.322 mmol, 1 equiv) in Et_2O (32 mL, 0.01 M) was fitted with a 3-way stopcock whose joints were greased. BF_3•OEt_2 (0.14 mL, 1.11 mmol, 3.5 equiv) was then added via syringe. The system was sealed, heated to 25−30 °C, and stirred vigorously for 21 h. Additional BF_3•OEt_2 (0.15 mL, 1.19 mmol, 3.7 equiv) was then added. After 3.5 h the flask was cooled to room temperature. The reaction mixture was then filtered through a plug of celite and washed with Et_2O. The product was recovered with 10% MeOH/CH_2Cl_2 as the eluent. Et_3N was added to this solution, which was then concentrated *in*

vacuo to give 0.1707 g (90%) of **2.111** as a dark yellow solid, whose spectral data matched that reported in the literature.[8,9]

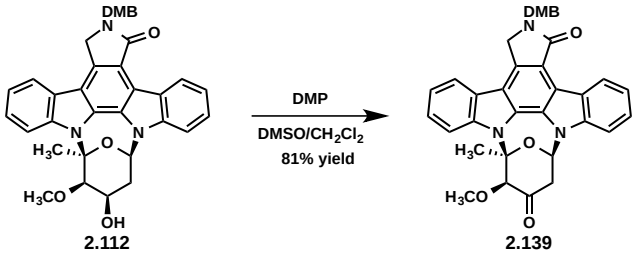
methyl ether 2.112



In a 50 mL round-bottomed flask, **2.111** (0.1707 g, 0.29 mmol, 1 equiv) was dissolved in a mixture of 1:1:2 MeOH (2 mL), CH_2Cl_2 (2 mL), and $CHCl_3$ (4 mL). $NaBH_4$ (0.0440 g, 1.16 mmol, 4 equiv) was added, followed by the remaining 8 mL of the solvent mixture (0.018 M total). After 30 min, the reaction mixture was concentrated *in vacuo* and filtered through a plug of SiO_2 with 10% MeOH/CH_2Cl_2 as the eluent. Concentration *in vacuo* gave 0.1586 g (93%) of the diol as a yellow solid. This was used without further purification in the next reaction.

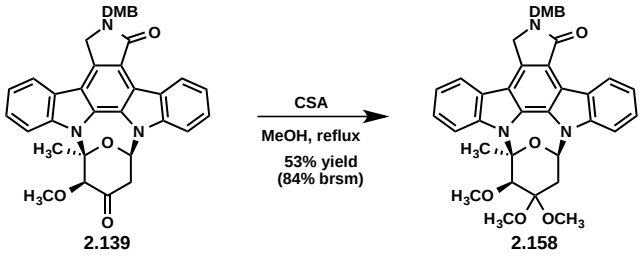
In a 2-neck, round-bottomed flask, NaH (0.0292 g, 1.22 mmol, 4.2 equiv) was suspended in THF (10 mL) and stirred for 10 min. The crude diol (0.1586 g, 0.269 mmol, 1 equiv) was dissolved in THF (5 mL) and added dropwise to the flask via syringe. This was followed by the addition of the remaining THF (15 mL, 0.01 M). After 3 h, methyl iodide (17.6 μL, 0.282 mmol, 1.05 equiv) was added. After 2.5 h, the flask was cooled to 0 °C and quenched with 0.13 M citric $acid_{(aq.)}$ (15 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2) afforded 0.1255 g (72%) of **2.112** as a yellow solid whose spectral data matched that reported in the literature.[8,9]

ketone 2.139



In a 50 mL 2-neck round-bottom flask, DMP (0.0970g, 0.229 mmol, 1.1 equiv) was left under vacuum for 5−10 min. After back filling 3 times with N_2, CH_2Cl_2 (4 mL) was added. This suspension was stirred for 15 min. **2.112** (0.1255 g, 0.208 mmol, 1 equiv) was dissolved in a mixture of CH_2Cl_2 (2 mL) and DMSO (0.5 mL). This suspension was added to the flask via pipet, followed by the remaining CH_2Cl_2 (4 mL, 0.02 M total). After 3 min additional DMSO (0.5 mL) was added. After another 6 min additional DMSO was added (1 mL). After 22 h, the reaction was quenched with a 10:10:1 mixture of sat'd. $NaHCO_{3(aq.)}$, H_2O, and sat'd. $Na_2S_2O_{3(aq.)}$ (10 mL) and stirred vigorously at room temperature for 65 min. The reaction mixture was then diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL), and the phases were separated. The organic layer washed with H_2O (3 x 20 mL). The combined aqueous layers were extracted with CH_2Cl_2 (1 x 15 mL) and $CHCl_3$ (2 x 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 2.5 → 5% acetone/$CHCl_3$) gave 0.1011 g (81%) of **2.139** as a yellow solid, whose spectral data matched that reported in the literature.[8,9]

ketal 2.158



A 25 mL pear-shaped flask with a reflux condenser was charged with **2.139** (0.0662 g, 0.11 mmol, 1 equiv) and CSA (0.0026 g, 0.011 mmol, 0.1 equiv). MeOH was then added and the flask heated to 65 °C. After 3 h, additional CSA (0.028 g, 0.12 mmol, 1.1 equiv) was added and the reaction mixture allowed to stir overnight. After 19 h CH_2Cl_2 (2 mL) was added. At 23 h the reaction mixture was cooled to room temperature and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 25 → 62.5% EtOAc/hexanes) gave 0.0378 g (53%) of **2.158**. An additional 0.0206 g (31%) of **2.139** was recovered.

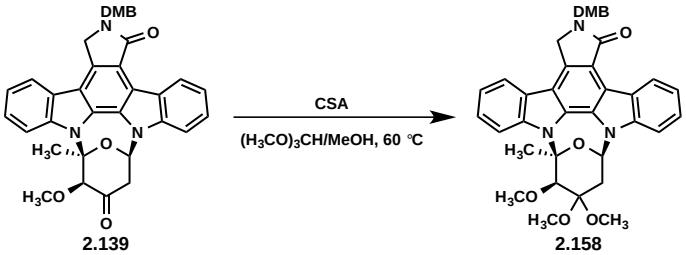
^{1}H-NMR (400 MHz; $CDCl_3$): δ 9.55 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 8.6 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.41-7.37 (m, 2H), 7.26 (d, *J* = 15.1 Hz, 2H), 7.01-6.99 (m, 2H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.70 (s, 1H), 4.95 (s, 2H), 4.86 (s, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.10 (s, 3H), 2.77 (d, *J* = 13.8 Hz, 1H), 2.40 (dd, *J* = 13.7, 5.6 Hz, 1H), 2.35 (s, 3H), 2.20 (s, 3H)

^{13}C-NMR (101 MHz; $CDCl_3$): δ 169.2, 149.5, 148.6, 130.8, 126.96, 126.88, 125.3, 124.5, 120.81, 120.79, 120.6, 120.13, 120.07, 120.04, 119.4, 111.46, 111.31, 96.7, 88.7, 81.6, 73.1, 63.0, 56.15, 56.09, 50.4, 50.0, 47.6, 46.6

IR 3369 (br w), 3052 (w), 2934 (m), 2835 (m), 1692 (s), 1638 (m), 1587 (m), 1515 (s), 1458 (s), 1417 (m), 1396 (m), 1351 (s), 1318 (s), 1300 (m), 1264 (s), 1239 (s), 1228 (s), 1125 (s), 1064 (m), 1028 (m), 962 (w), 932 (w), 854 (w), 797 (m), 744 (s), 704 (m), 692 (m), 669 (w) cm^{-1}

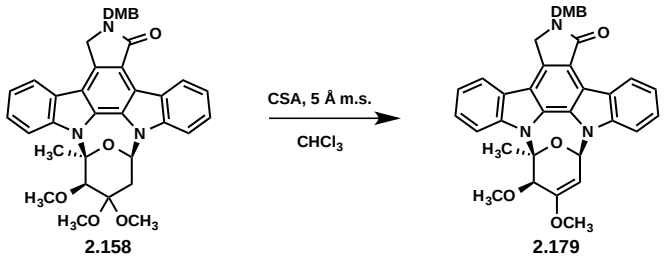
HRMS (ESI−APCI) m/z calcd. for $C_{38}H_{37}N_3O_7$ $(M+Na)^+$ 670.2524, found 670.2524

alternate preparation of ketal 2.158



A 1 dram vial was charged with **2.139** (0.0199 g, 0.033 mmol, 1 equiv) and CSA (0.0077 g, 0.033 mmol, 1 equiv). MeOH (1 mL, 0.03 M) and trimethylorthoformate (0.5 mL, 0.07M) were then added, and the vial sealed with a septum cap. The vial was placed in a sand bath (60 °C) and the reaction mixture allowed to stir for 12 h. The reaction mixture was then concentrated *in vacuo*. Purification via column chromatography (SiO_2, 15 → 25%, then 37.5%, then 50%, then 100% EtOAc/hexanes) gave **2.158**.

enol ether 2.179



A 1 dram vial was charged with **2.158** (0.01 g, 0.015 mmol, 1 equiv) and ground 5Å molecular sieves (0.1 g, 10 wt. equiv). $CHCl_3$ (1 mL, 0.015 M) was added, followed by a solution of CSA (0.32 mL, 0.0017 g/ 1 mL in $CHCl_3$, 0.002 mmol, 0.15 equiv). The vial was sealed with a septum cap and placed in a sand bath (65 °C). After 14 h the reaction mixture was cooled to room temperature, filtered, and concentrated *in vacuo*. Column chromatography (SiO_2, 5 → 10% EtOAc/CH_2Cl_2) gave a sample of **2.179**.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 9.49 (d, *J* = 7.9 Hz, 1H), 8.03 (d, *J* = 8.6 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.54-7.47 (m, 2H), 7.43-7.36 (m, 2H), 7.27 (t, *J* = 7.4 Hz, 1H), 6.98-6.95 (m, 3H), 6.86 (d, *J* = 8.1 Hz, 1H), 4.94 (s, 2H), 4.83 (s, 2H), 4.62 (s, 1H), 4.44 (s, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.34 (s, 3H), 2.28 (s, 3H)

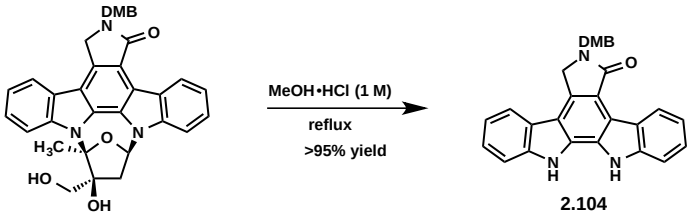
^{13}C-NMR (101 MHz; $CDCl_3$): δ 170.0, 154.1, 149.3, 148.4, 140.5, 136.4, 130.4, 129.90, 129.74, 126.7, 125.40, 125.36, 124.84, 124.65, 123.8, 120.63, 120.46, 120.27, 120.1, 119.4, 116.73,

116.55, 115.2, 111.12, 111.07, 107.3, 92.2, 91.6, 81.2, 79.5, 62.3, 55.93, 55.90, 55.0, 49.9, 46.4, 29.7, 27.9

IR 3357 (br w), 3053 (w), 2925 (m), 2853 (m), 1720 (m), 1676 (s), 1590 (m), 1515 (m), 1460 (s), 1399 (m), 1348 (m), 1326 (m), 1262 (s), 1238 (s), 1137 (s), 1071 (w), 1028 (m), 935 (w), 855 (w), 805 (w), 745 (m), 672 (w) cm^{-1}

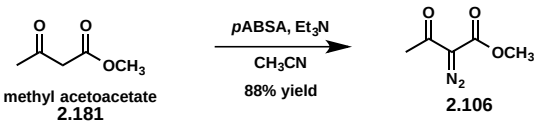
HRMS (ESI−APCI) m/z calcd. for $C_{37}H_{34}N_3O_6$ $(M+H)^+$ 616.2442, found 616.2434

DMB-K252c (2.104)



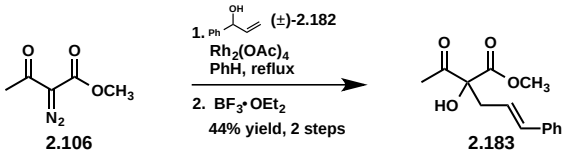
A 20 mL scintillation vial was charged with **2.180** (0.18g, 0.29 mmol, 1 equiv) and 1M methanolic HCl (5.8 mL, 0.05M) was added. The resulting suspension was heated to reflux for 1 h. After cooling to room temperature the reaction mixture was diluted with EtOAc and quenched with a saturated $NaHCO_3$ solution (10 mL). The phases were separated, and the organic layer was washed with additional sat'd. $NaHCO_{3(aq.)}$ (10 mL). The combined aqueous layers were extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a viscous brown oil. Purification via column chromatography on SiO_2 (25 → 75% EtOAc/hexanes) provided 0.13 g (>95% yield) of **2.104** as an oily orange solid. The spectral data for **2.104** matched that reported in the literature.[8,9]

α-diazo-β-ketoester 2.106



A 250 mL round bottom flask was charged with **2.181** (2.25 mL, 20.8 mmol, 1 equiv), *p*ABSA (5.0 g, 20.8 mmol, 1 equiv), and MeCN (52 mL, 0.4 M) and cooled to 0 °C. Et_3N (8.7 mL, 62.4 mmol, 3 equiv) was added via pipet. The bath was allowed to expire and the reaction mixture stirred overnight. The reaction mixture was then partially concentrated via rotary evaporation (250 torr, 0 to 25 °C) until it was a thick white slurry. The contents of the flask were then suspended in a 1:1 ether/petroleum ether (bp = 35 to 60 °C) solution (100 mL) and filtered through a fritted funnel. The solid was rinsed with the same solution (3 x 100 mL). The crude product was then concentrated *in vacuo* (250 torr, 0 °C) and loaded onto an SiO_2 plug (25% ether/petroleum ether) for purification. 2.54 g (86%) of **2.106** was isolated as a somewhat volatile, colorless oil, whose spectral data matched what had been reported in the literature.[36]

α-hydroxy-β-ketoester 2.183



In a 2-neck 500 mL round bottom flask fitted with a reflux condenser (dry, under N_2), diazo **2.106** (2.54 g, 17.9 mmol, 1 equiv) and allylic alcohol **(±)-2.182**[37] (2.64 g, 19.7 mmol, 1.1 equiv) were dissolved in PhH (85 mL, 0.2 M total). $Rh_2(OOct)_4$ (0.0278 g, 0.036 mmol, 0.002 equiv) was added in one portion via the side arm and rinsed down with the remaining 5 mL PhH. The flask was then immediately transferred to a pre-heated (80 °C) oil bath. After 20 min, the bath was removed and the flask allowed to cool to room temperature. $BF_3•OEt_2$ (2.80 mL, 22.4 mmol, 1.25 equiv) was then added dropwise via syringe and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was transferred to a single neck flask with CH_2Cl_2 (30 mL) and concentrated *in vacuo* until only a small amount of solvent remained. This

viscous brown solution was purified by column chromatography on SiO_2 (5 → 15 % EtOAc/hexanes) to afford 1.92 g (43%) of **2.183**.

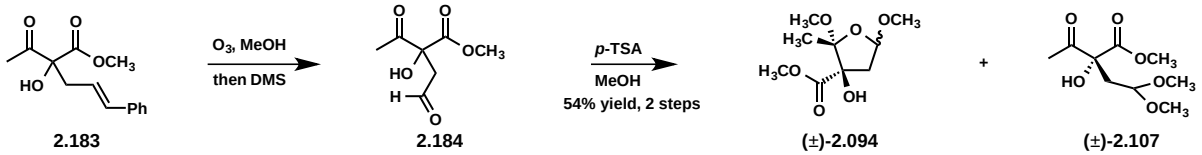
^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.33-7.27 (m, 4H), 7.22 (tt, *J* = 7.1, 1.7 Hz, 1H), 6.52 (d, *J* = 15.9 Hz, 1H), 6.09 (dt, *J* = 15.7, 7.4 Hz, 1H), 4.26 (s, 1H), 3.81 (s, 3H), 3.00 (ddd, *J* = 14.4, 7.0, 1.3 Hz, 1H), 2.86 (ddd, *J* = 14.4, 7.7, 1.0 Hz, 1H), 2.31 (s, 3H)

^{13}C-NMR (126 MHz; $CDCl_3$): δ 204.2, 171.0, 136.9, 134.8, 128.6, 127.7, 126.4, 122.1, 84.1, 53.5, 39.1, 25.0

IR 3467 (br w), 3027 (w), 2955 (w), 1717 (s), 1496 (w), 1435 (m), 1356 (m), 1265 (s), 1219 (s), 1125 (s), 968 (s), 912 (w), 795 (w), 737 (s), 693 (s), 564 (w), 492 (m), 440 (m) cm^{-1}

HRMS (ESI−APCI) m/z calcd. for $C_{14}H_{16}NaO_4$ $(M+Na)^+$ 271.0941, found 271.0948

furanose (±)-2.094 and acetal (±)-2.107



2.183 **2.184** **(±)-2.094** **(±)-2.107**

A 100 mL round bottomed flask containing **2.183** (0.6939 g, 2.79 mmol, 1 equiv) in MeOH (18.6 mL, 0.15 M) was cooled to −78 °C. Ozone was bubbled into the solution until the reaction mixture turned pale blue (3−6 min). The solution was then sparged with N_2 for 10 min. The reaction was then quenched with DMS (7.9 mL, 100 mmol, 26 equiv) and immediately warmed to 0 °C. The reaction mixture was then stirred for 3 h, and the bath allowed to expire. Concentration *in vacuo* afforded **2.184**, which was used without purification in the next step.

In a 100 mL 3-neck, round bottomed flask, **2.184** was dissolved in PhH (18.6 mL, 0.15 M). *p*TSA (catalytic spatula tip) was added and the reaction mixture allowed to stir at room temperature overnight. The reaction mixture was then concentrated *in vacuo* to a volume of 1−2 mL. Purification via column chromatography (SiO_2, 20% EtOAc/hexanes) afforded a pale

yellow oily solid. This product was a mixture consisting of **(±)-2.107** and both diastereomers of **(±)-2.094**, whose spectral data matched those reported in the literature.[8,9]

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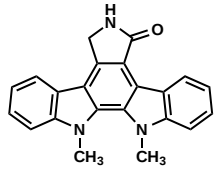
[25] In our own group the PMB protection of the compound shown below was attempted with this reagent; however it did not form the desired *N*-protected product. The product that was formed was not identified. See notebook TSI, page 104 (Takayuki Sawada).



[26] ~$10/gram vs. $0.25-0.75/gram depending on the halide.

[27] This compound has also been observed when the DMB group is cleaved from **2.108** in the absence of a cation scavenger such as anisole or thioanisole. See ref. 8, pp. 118, compound iii.

[28] If the Et_2O is allowed to evaporate to a considerable extent, both the starting material and the product start to decompose in the presence of the remaining BF_3.

[29] Prior work indicated that O-methylation α to the ketone of **2.111** was not possible. See reference 8.

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[34] Both sets of spectral data matched the characterization data from Dr. Takayuki Sawada. See reference 25.

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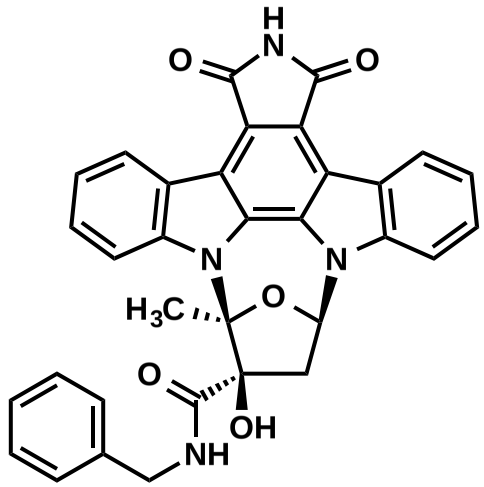
[37] For the synthesis of this compound see part I, chapter 2 of this dissertation.

APPENDIX 1: SPECTRA RELEVANT TO CHAPTER 2



2.118a

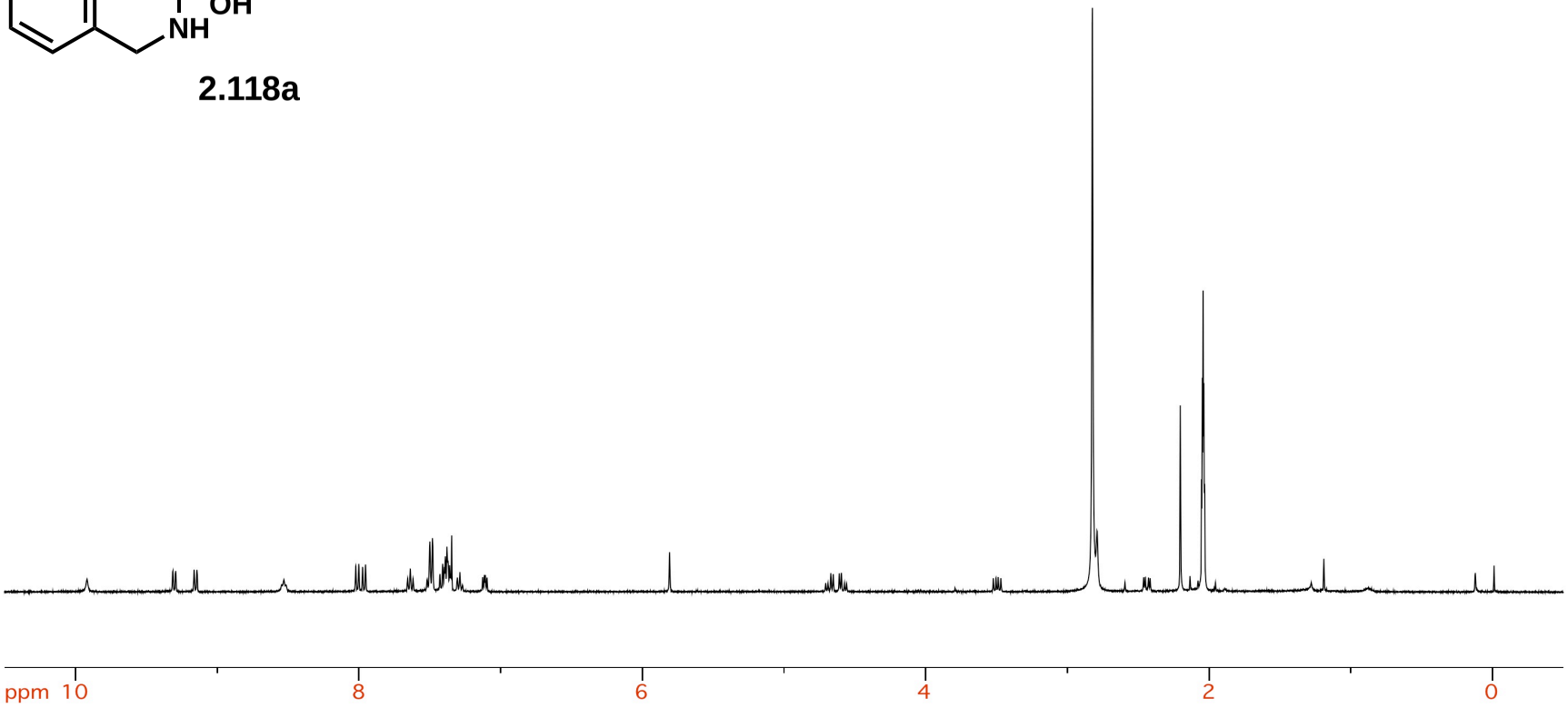


Figure A1.1a ^{1}H-NMR spectrum (400 MHz; acetone-d_6) of compound **2.118a**

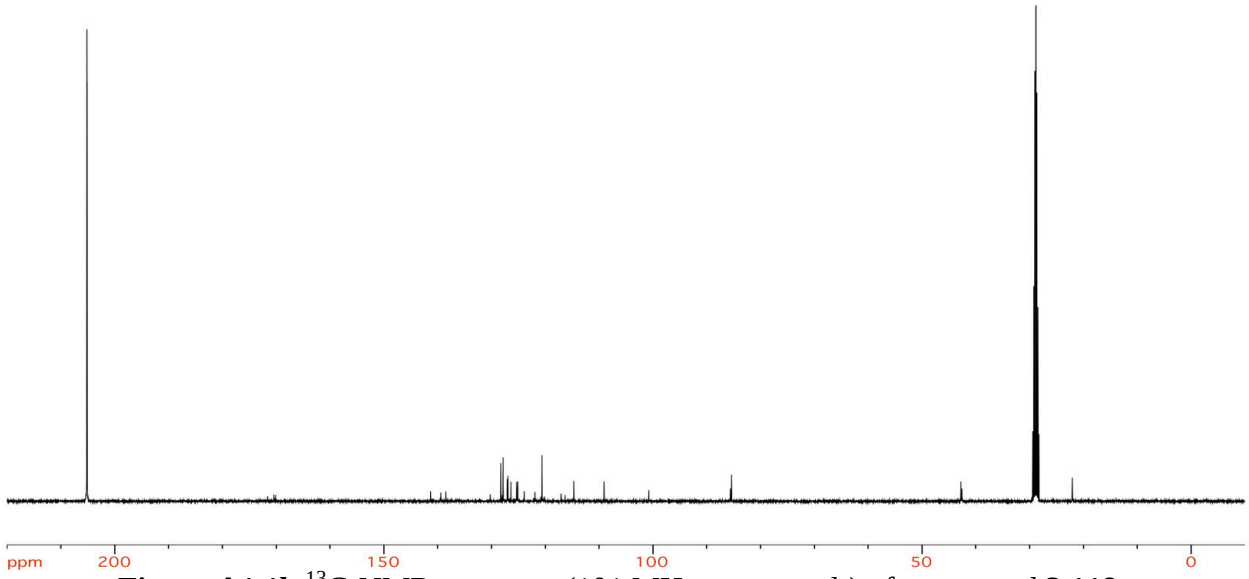


Figure A1.1b ^{13}C-NMR spectrum (101 MHz; acetone-d_6) of compound **2.118a**

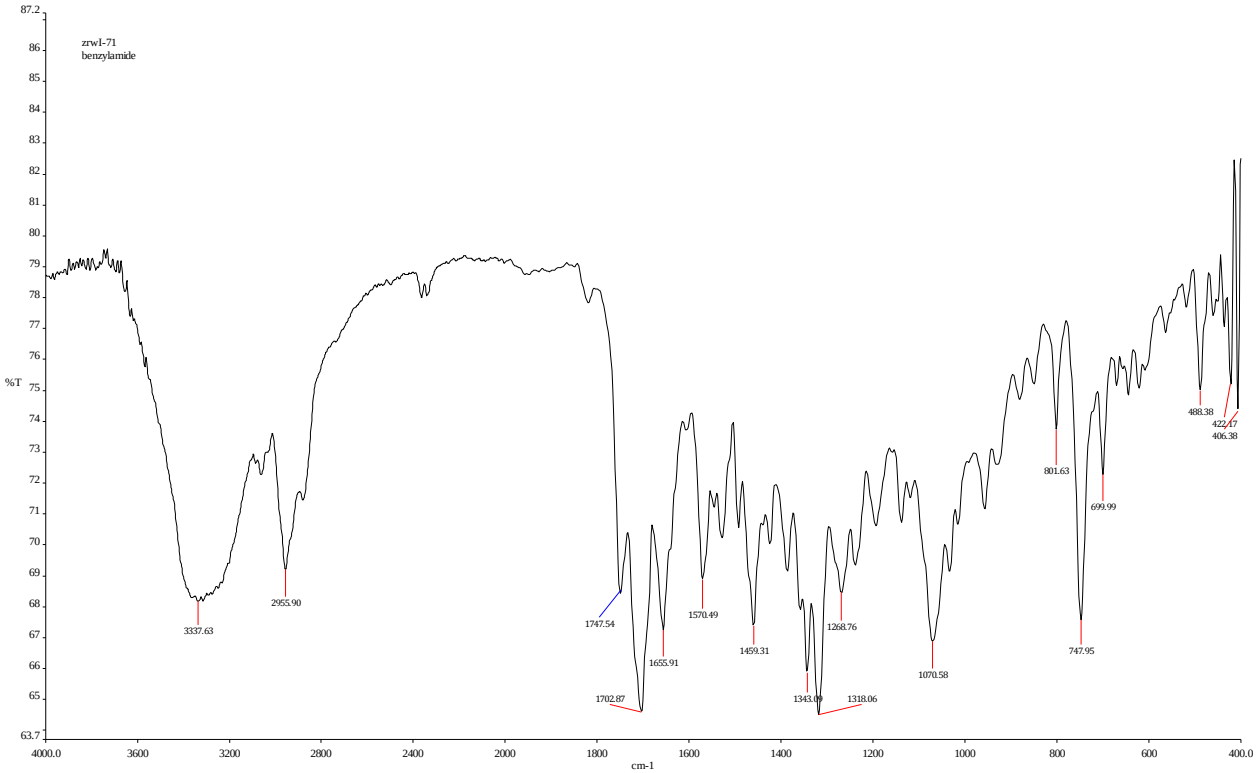


Figure A1.1c IR spectrum of compound **2.118a**

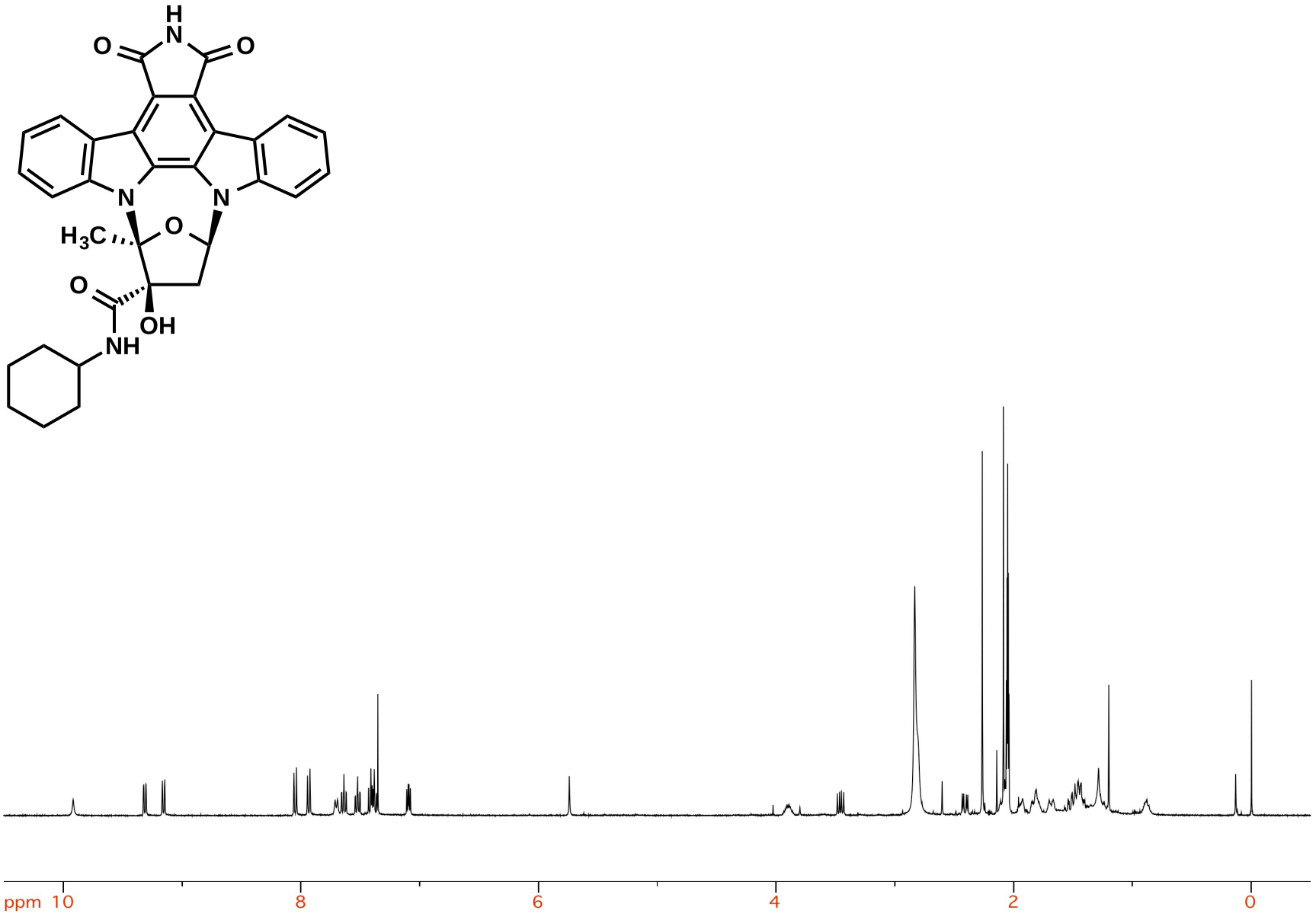


Figure A1.2a ^{1}H-NMR spectrum (400 MHz; acetone-d_6) of compound **2.118d**

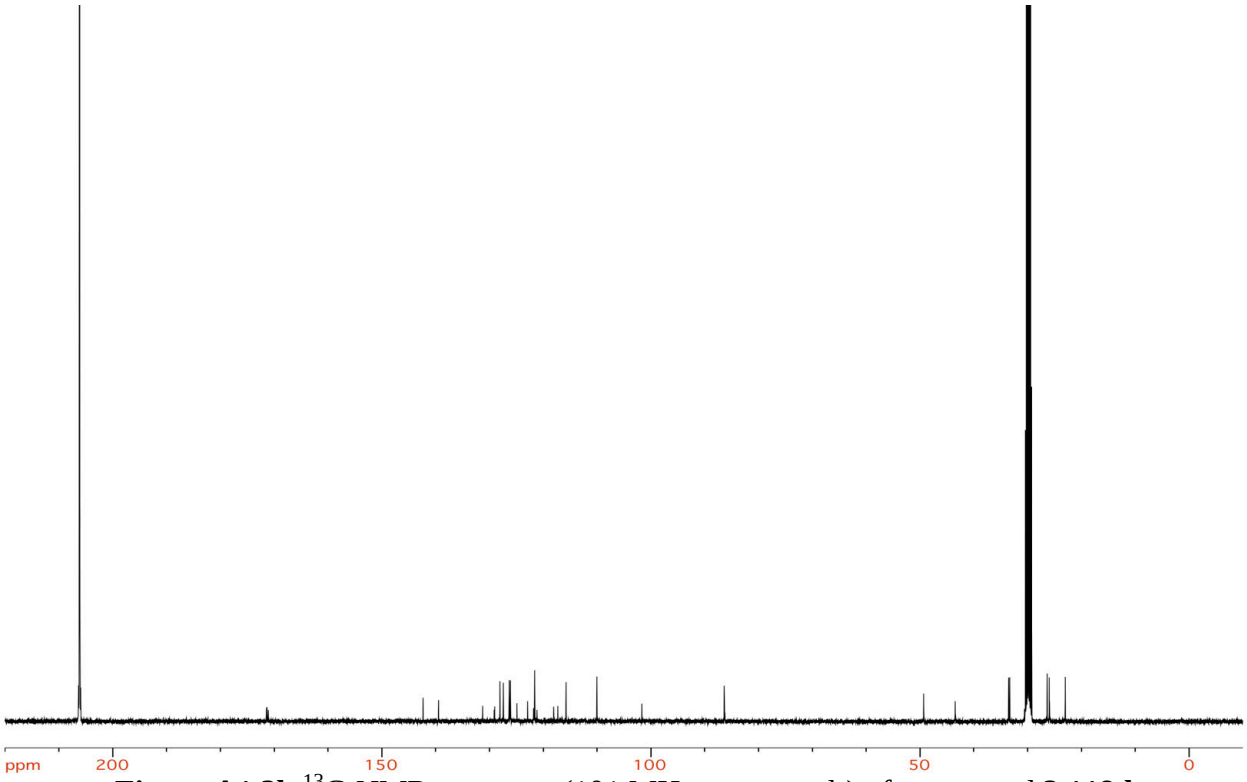


Figure A1.2b ^{13}C-NMR spectrum (101 MHz; acetone-d_6) of compound **2.118d**

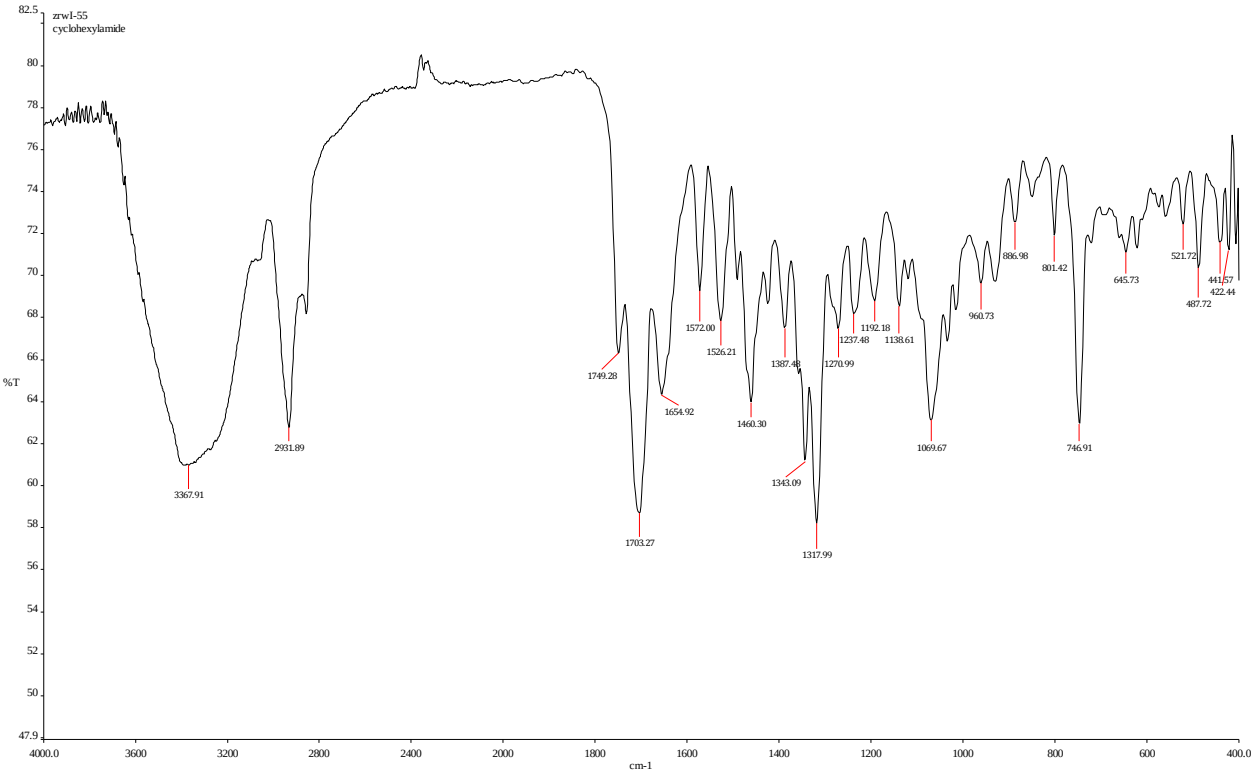
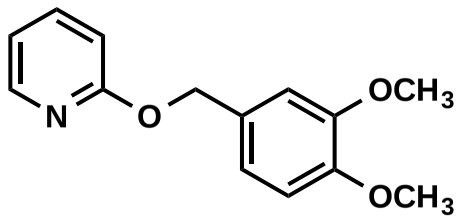


Figure A1.2c IR spectrum of compound **2.118d**

APPENDIX 2: SPECTRA RELEVANT TO CHAPTER 3



2.177
DMBOPy

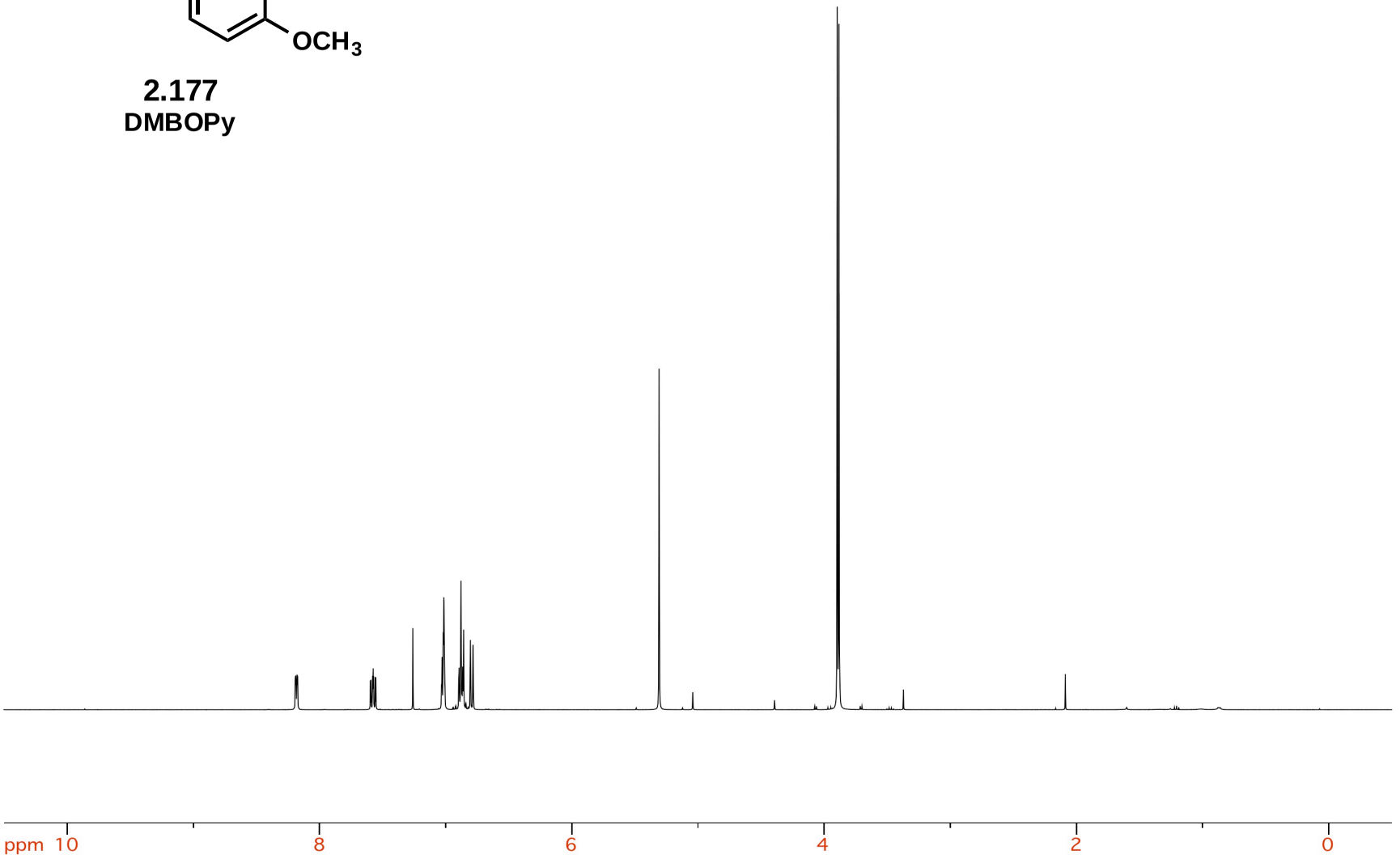


Figure A2.1a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **2.177**

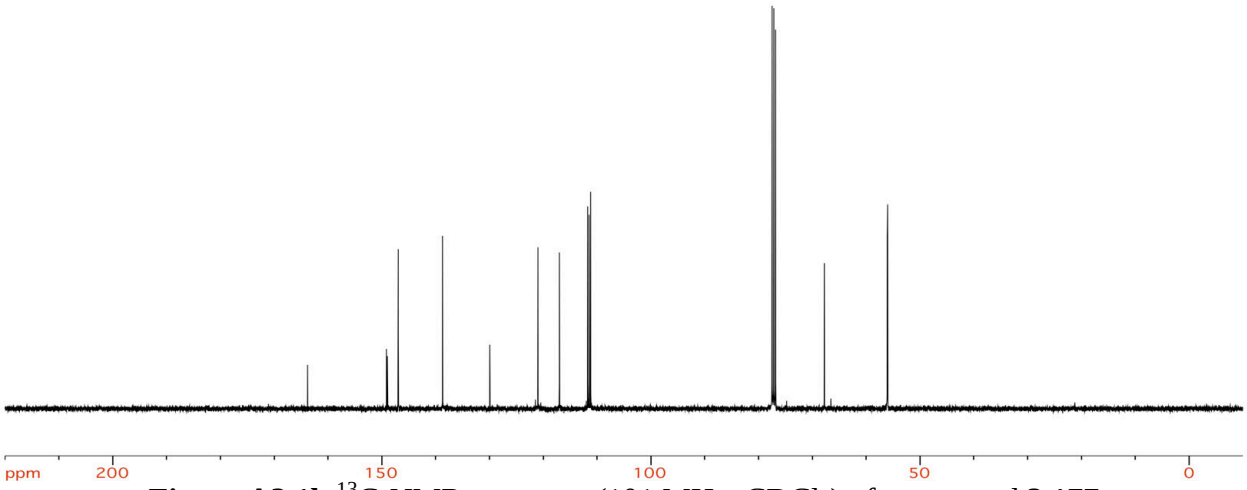


Figure A2.1b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **2.177**

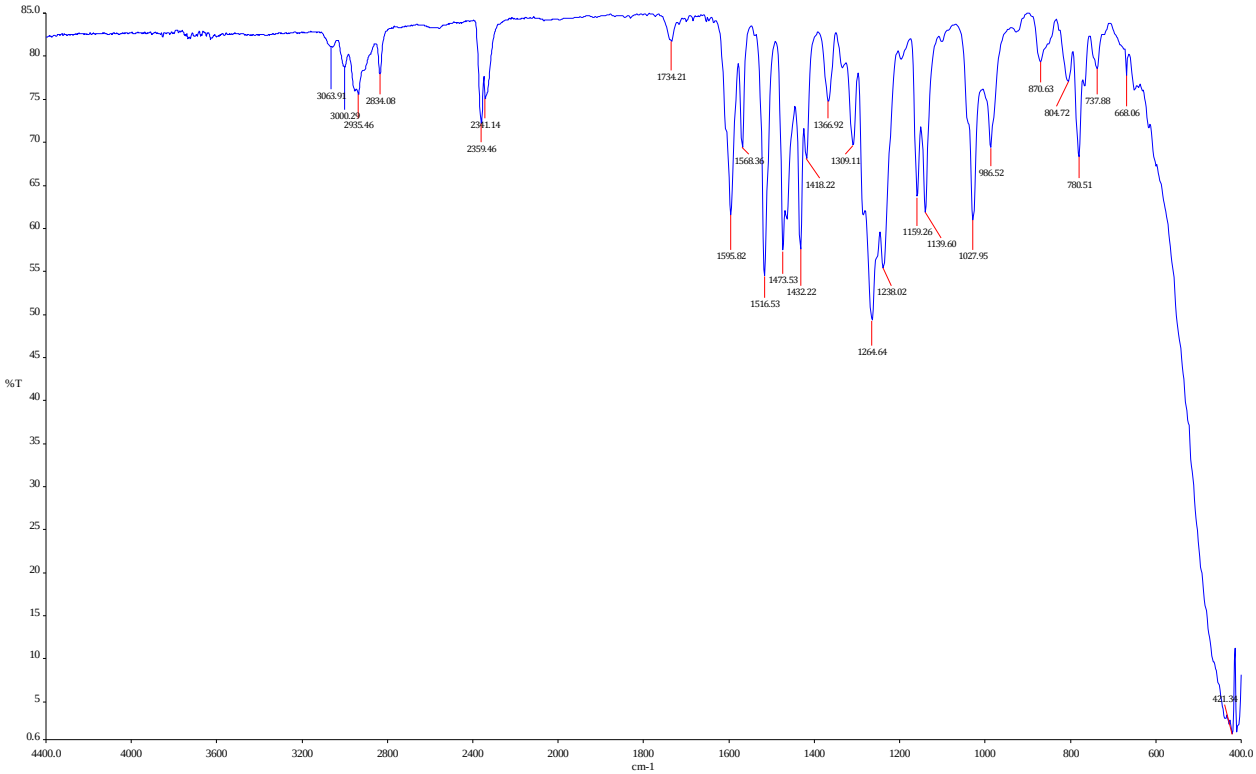
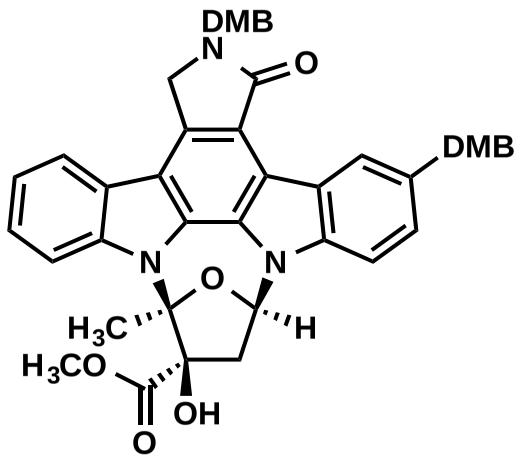


Figure A2.1c IR spectrum of compound **2.177**



2.178

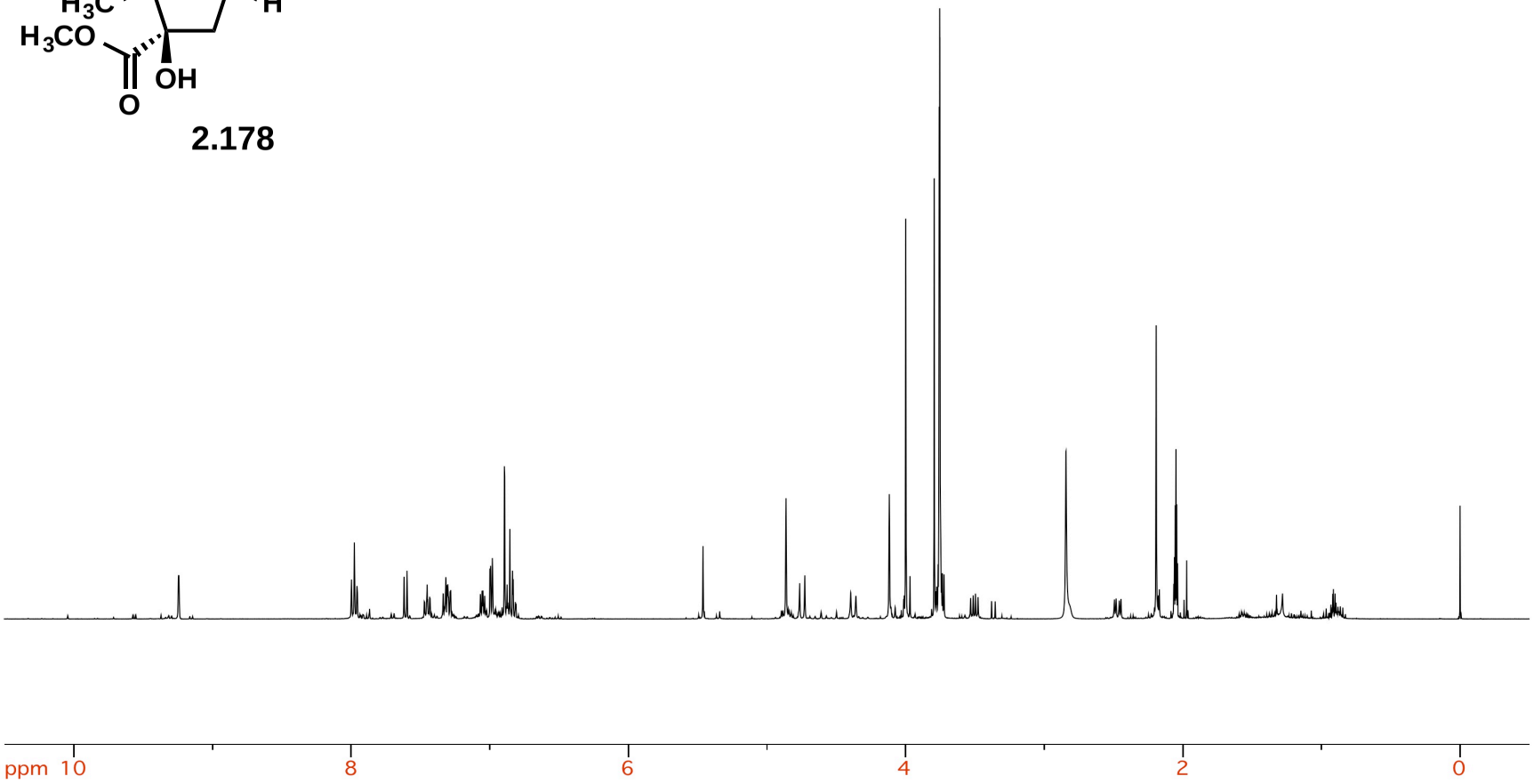


Figure A2.2a ^{1}H-NMR spectrum (400 MHz; acetone-d_6) of compound **2.178**

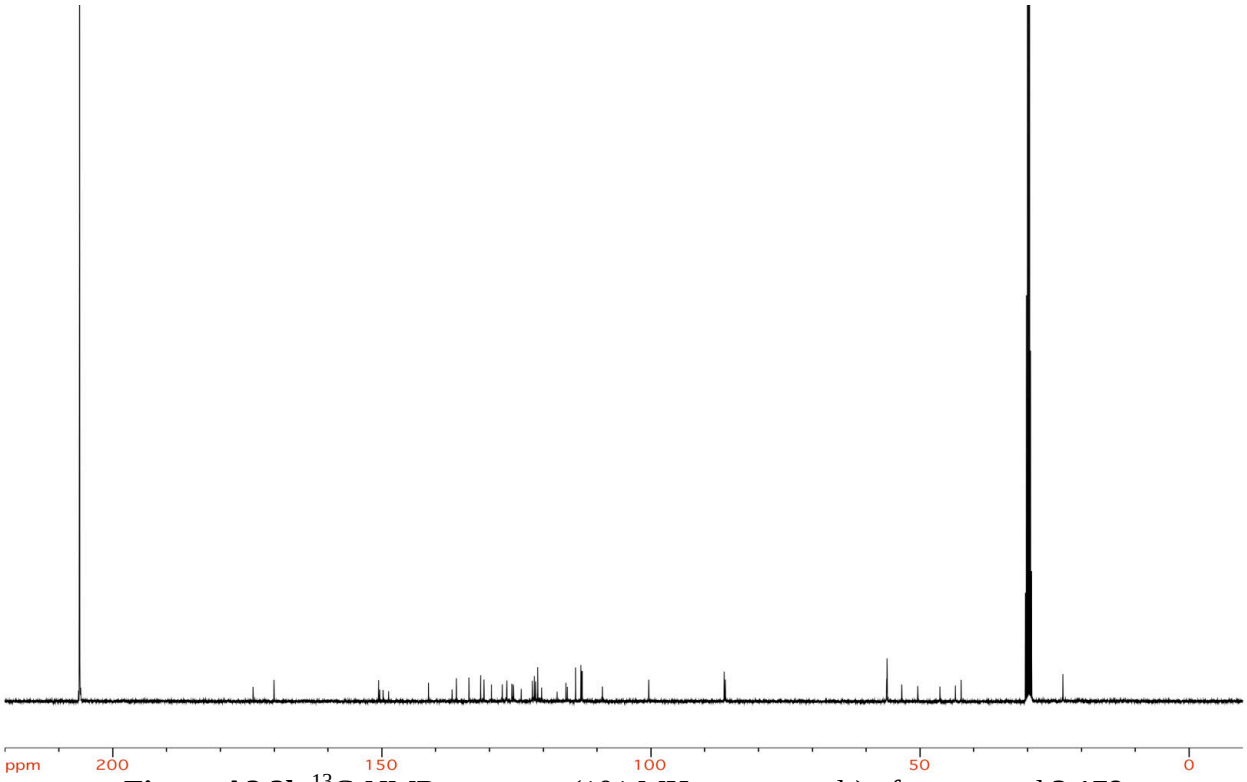


Figure A2.2b ^{13}C-NMR spectrum (101 MHz; acetone-d_6) of compound **2.178**

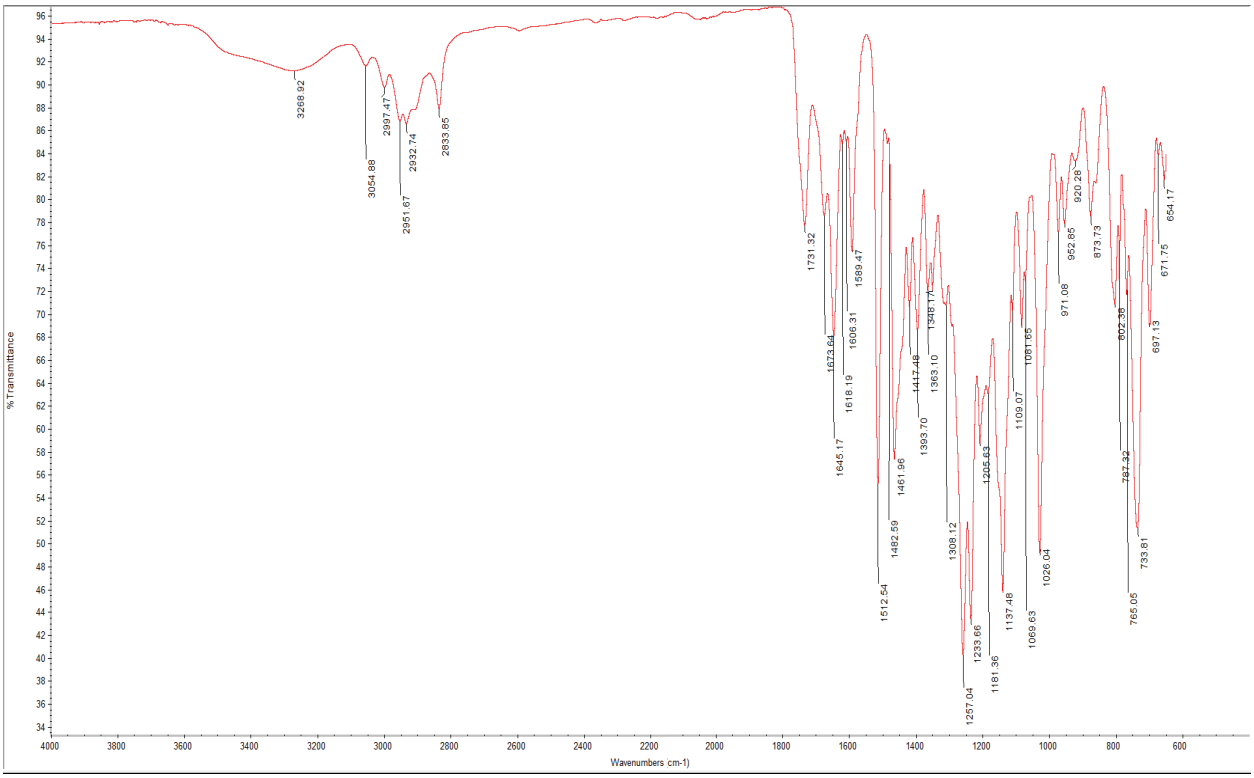


Figure A2.2c IR spectrum of compound **2.178**

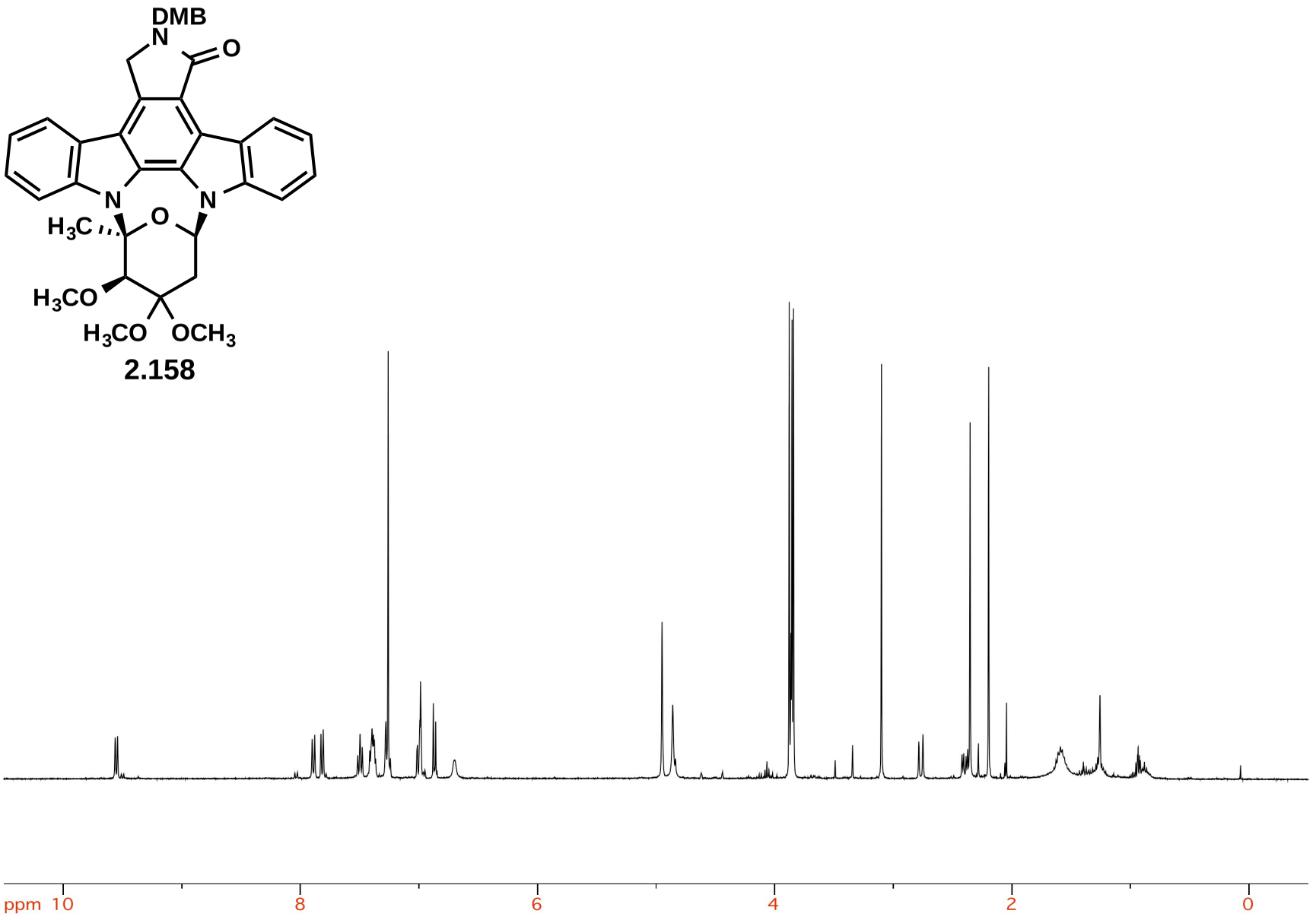


Figure A2.3a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **2.158**

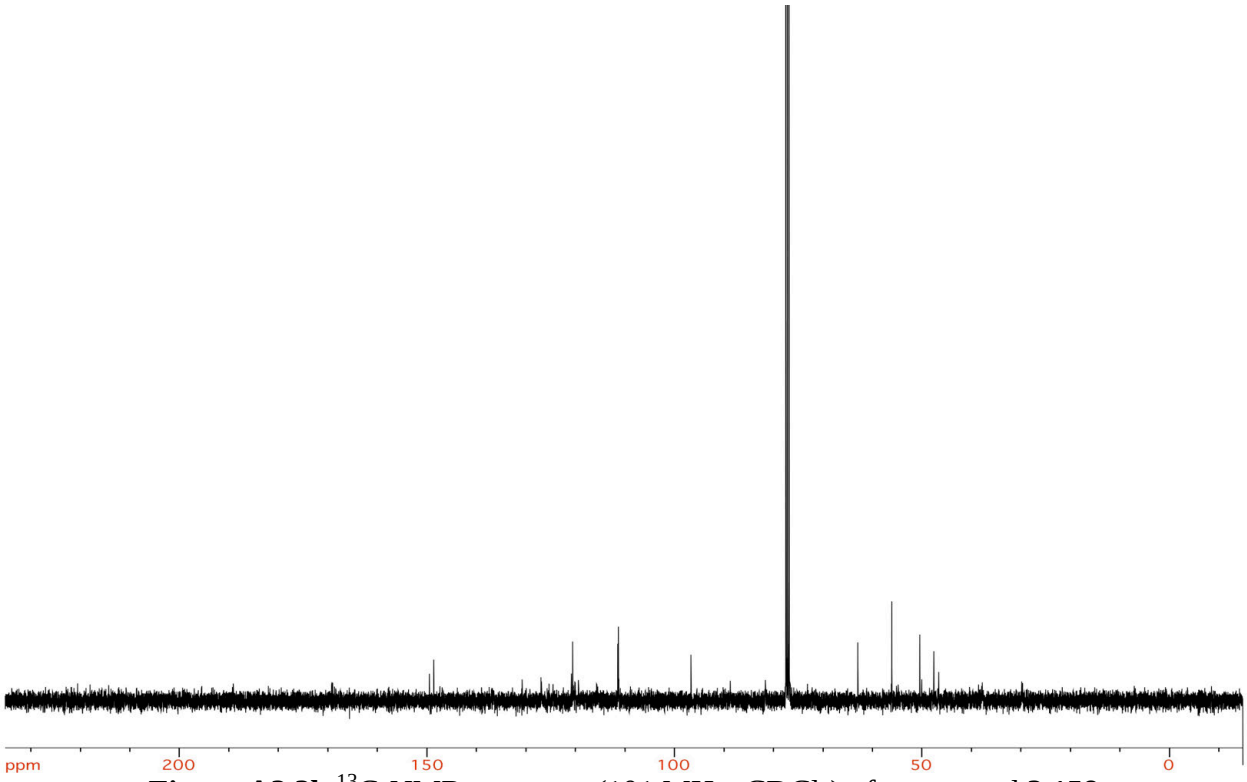


Figure A2.3b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **2.158**

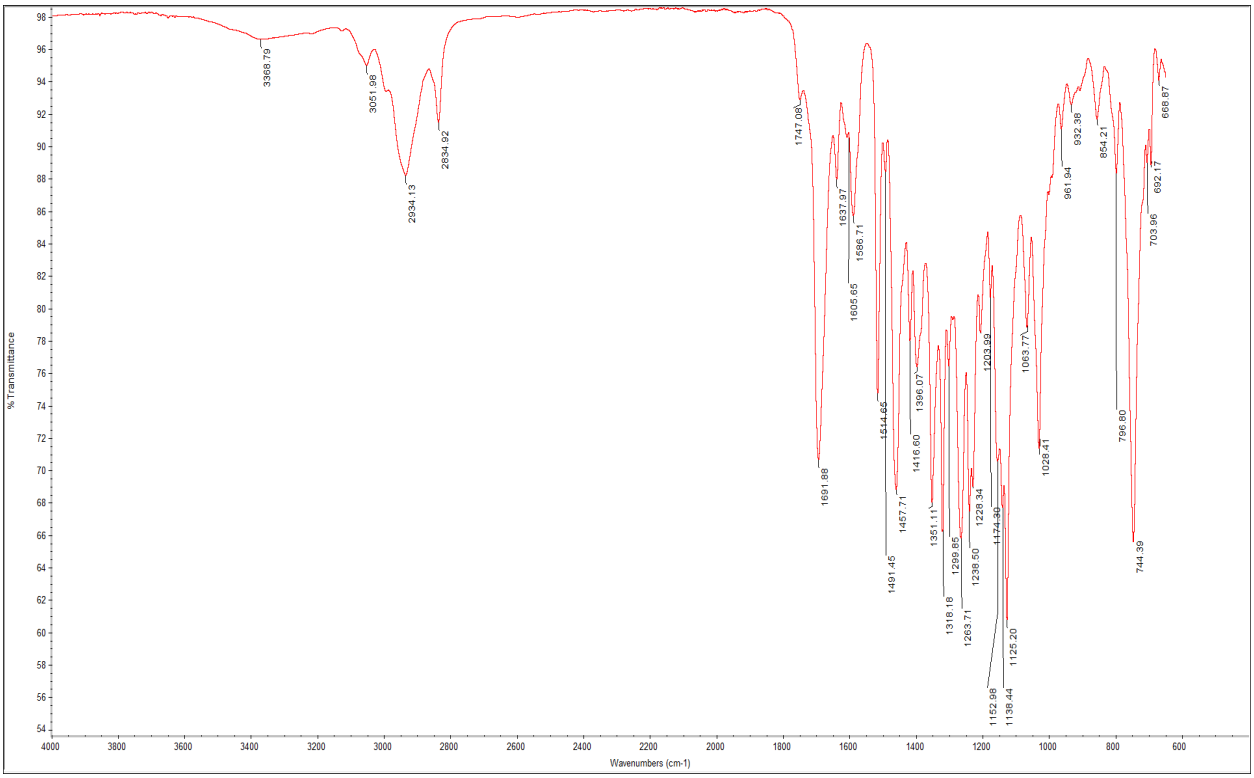
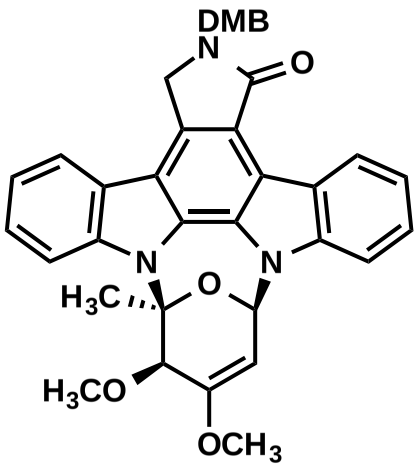


Figure A2.3c IR spectrum of compound **2.158**



2.179

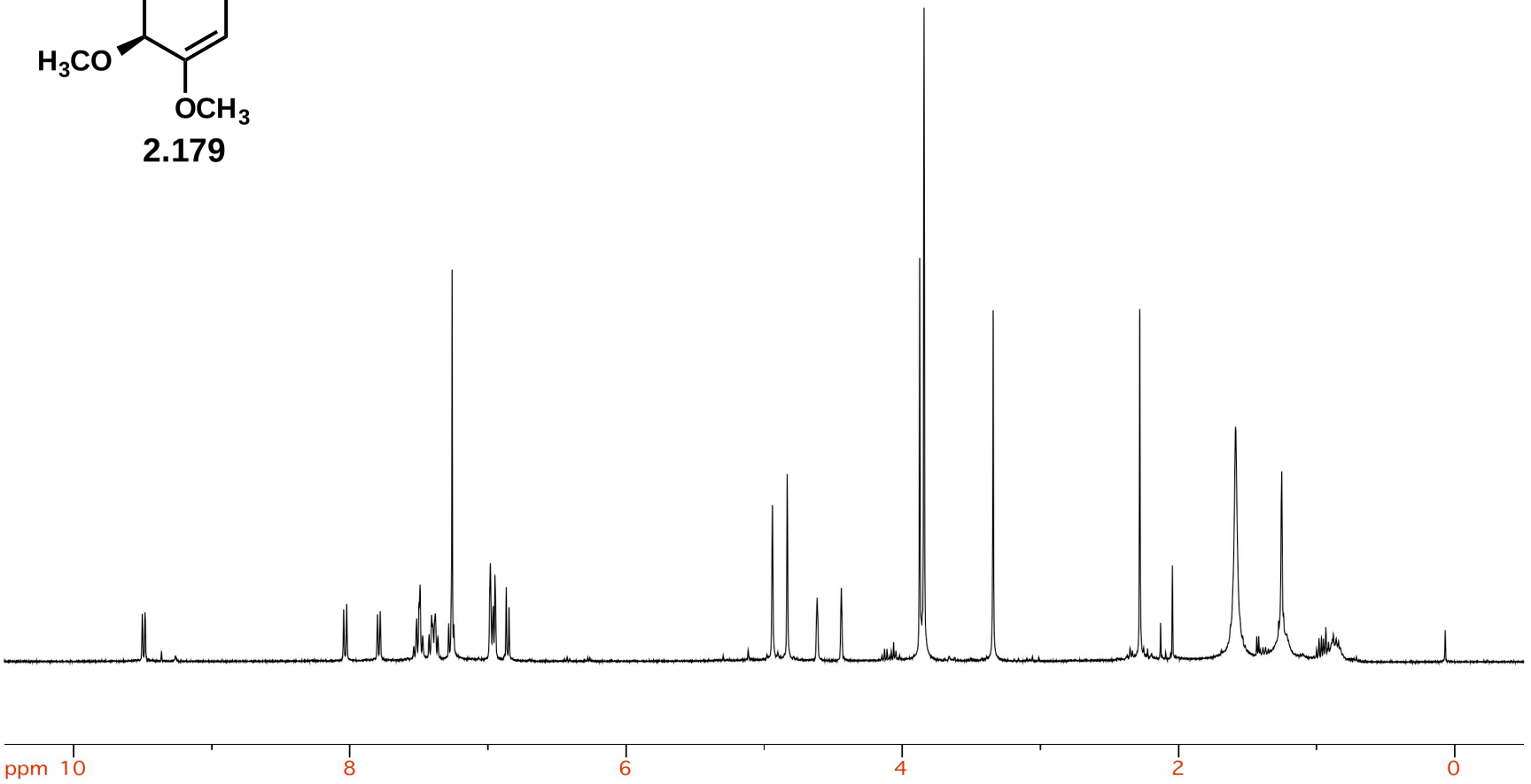


Figure A2.4a ^{1}H-NMR spectrum (400 MHz; $CDCl_3$) of compound **2.179**

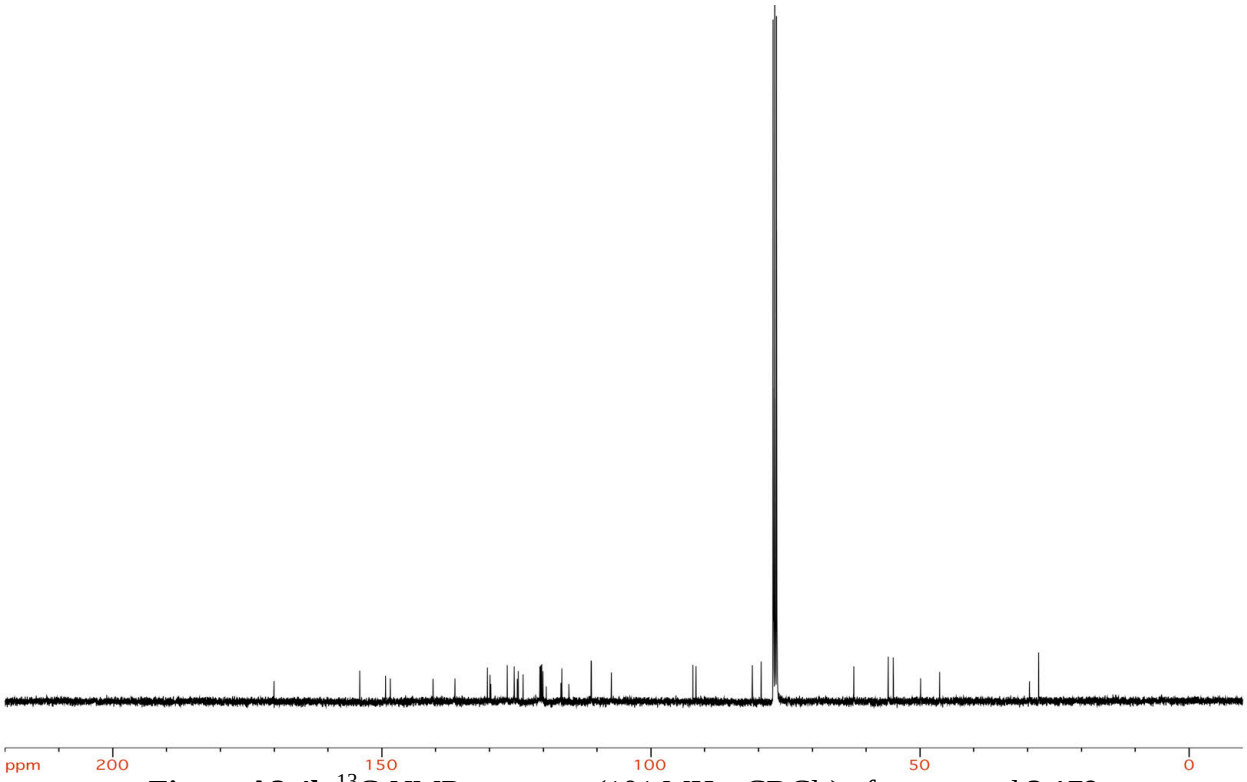


Figure A2.4b ^{13}C-NMR spectrum (101 MHz; $CDCl_3$) of compound **2.179**

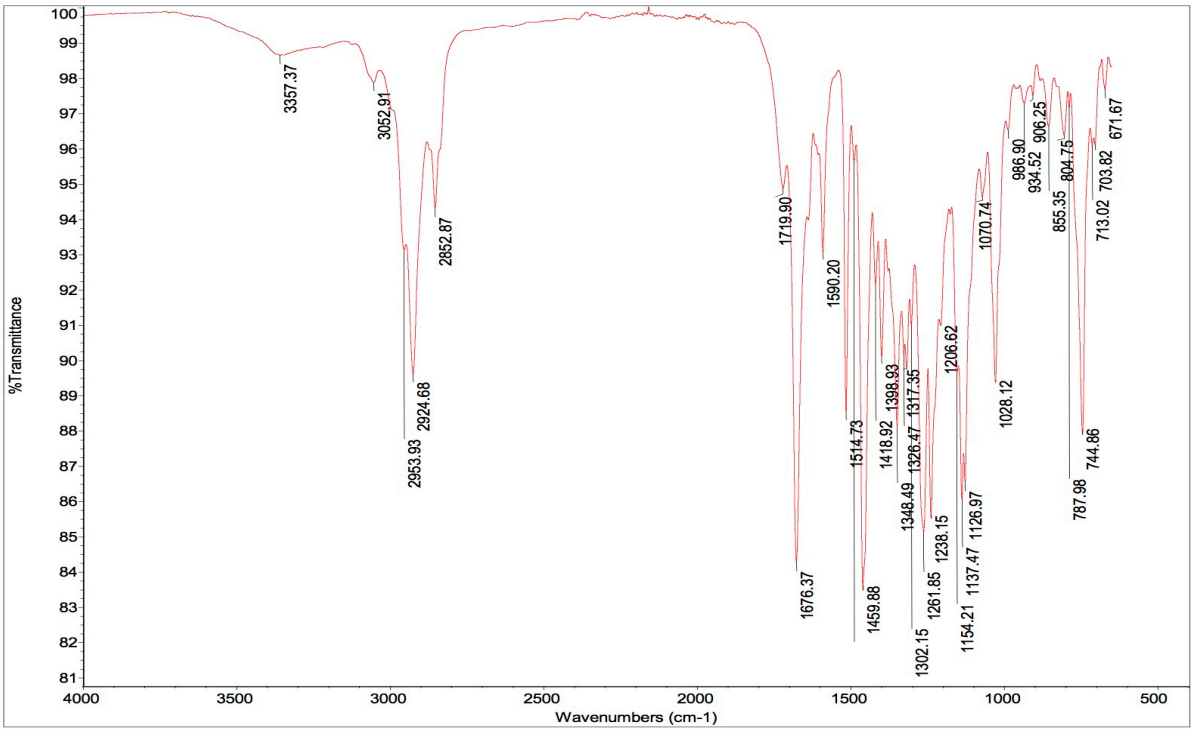


Figure A2.4c IR spectrum of compound **2.179**

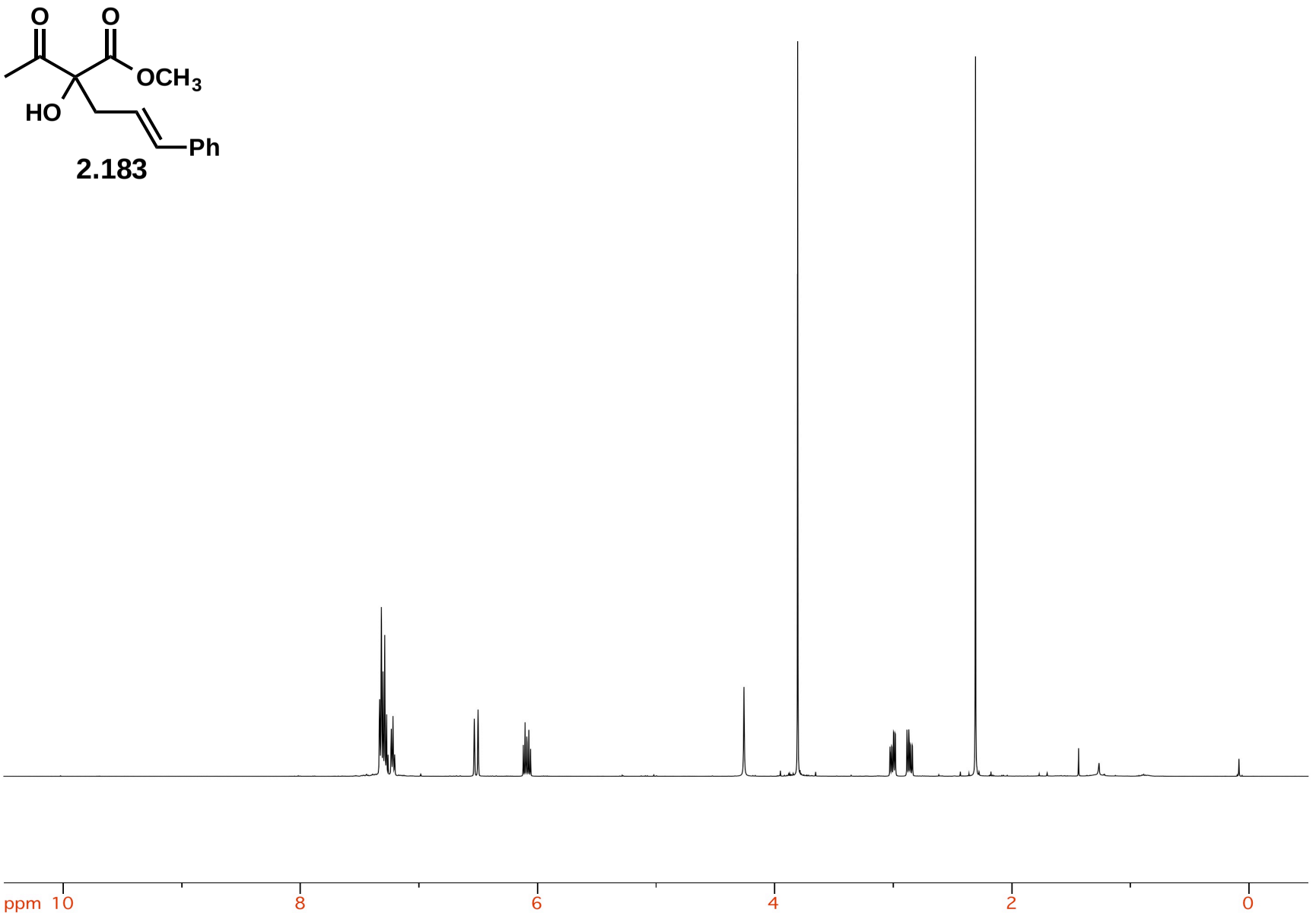


Figure A2.5a ^{1}H-NMR spectrum (500 MHz; $CDCl_3$) of compound **2.183**

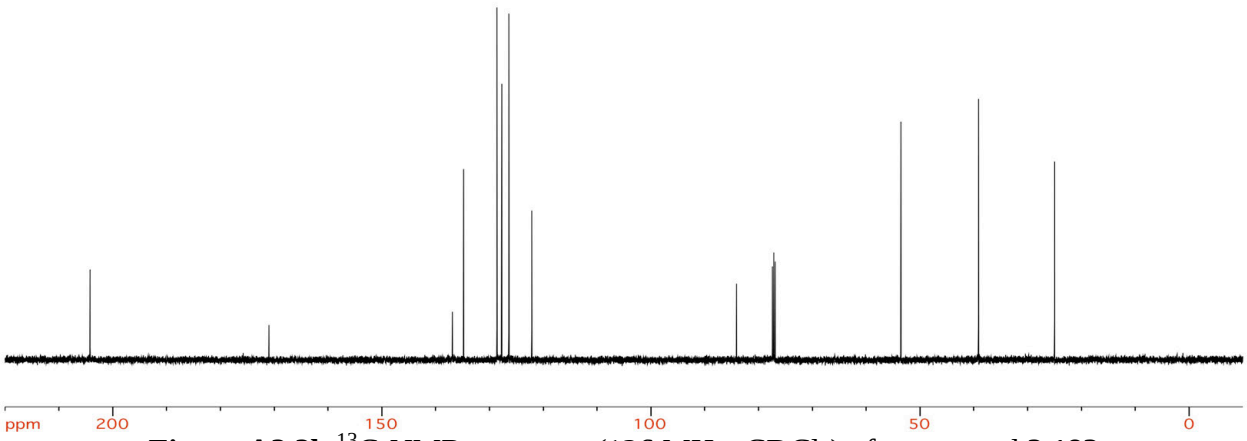


Figure A2.2b ^{13}C-NMR spectrum (126 MHz; $CDCl_3$) of compound **2.183**

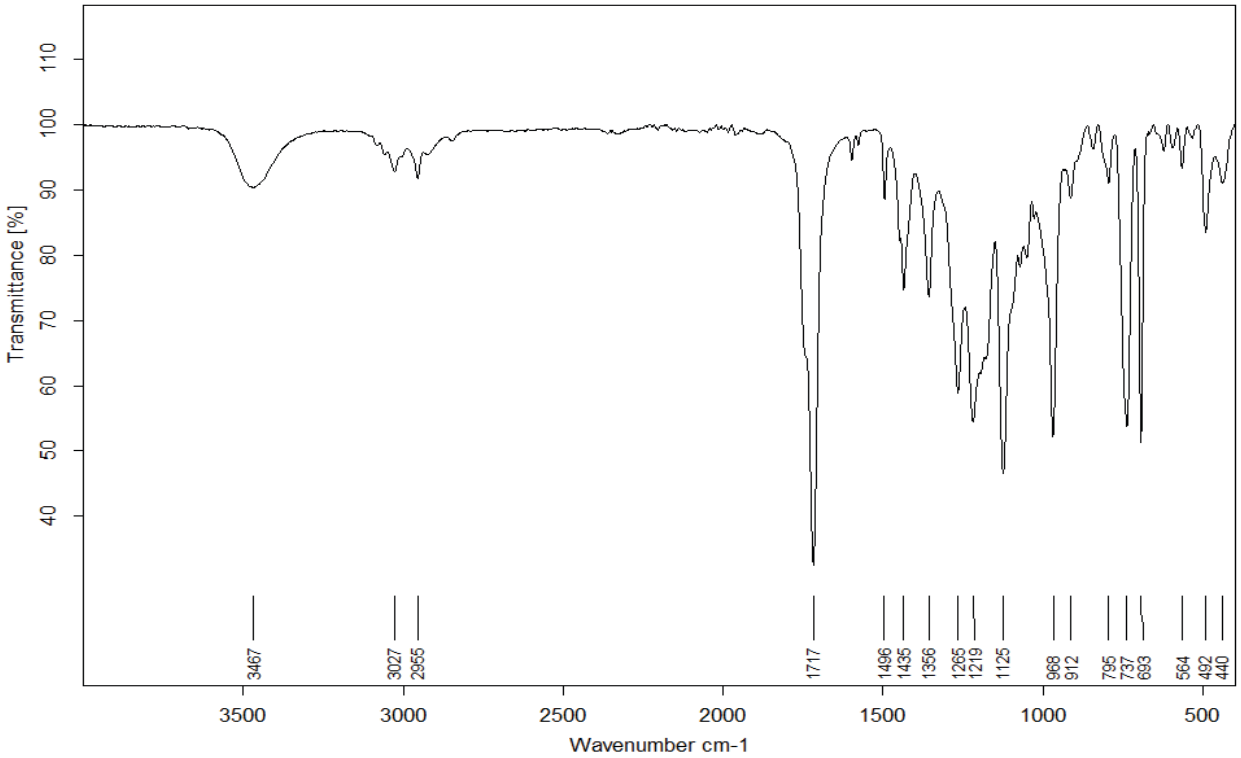
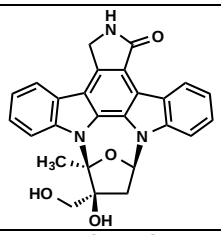
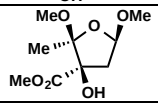
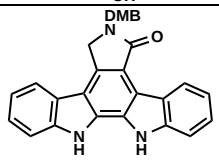
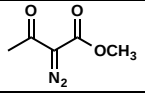
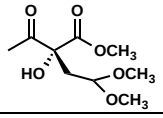
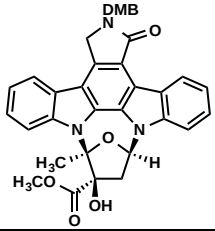
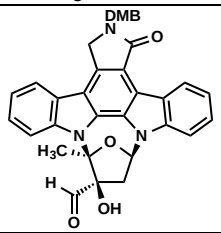


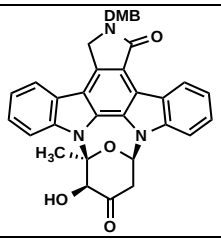
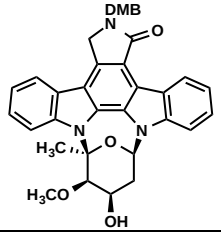
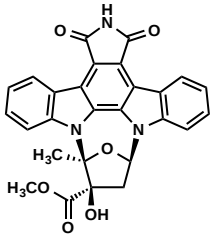
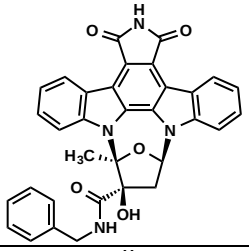
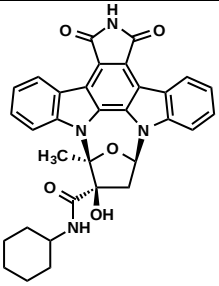
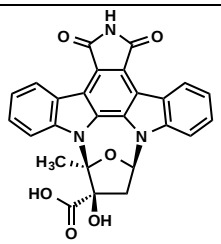
Figure A2.2c IR spectrum of compound **2.183**

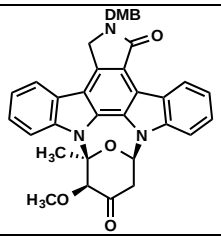
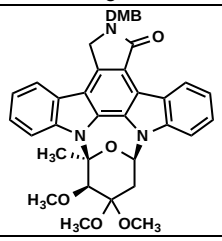
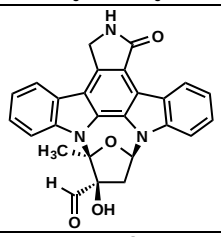
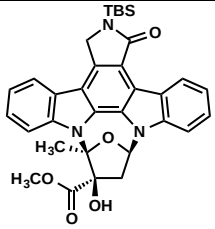
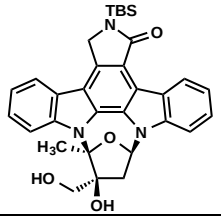
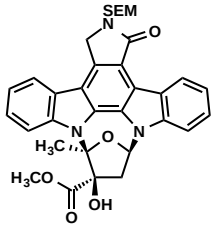
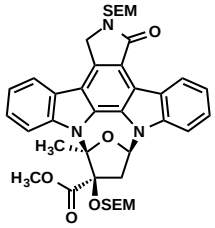
APPENDIX 3: NOTEBOOK CROSS-REFERENCE

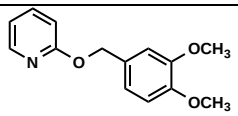
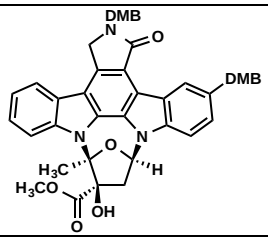
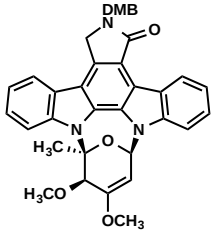
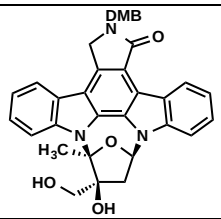
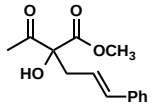
The following table contains information to facilitate access to the original spectral data and experimental procedures for compounds mentioned in the experimental sections of this dissertation. Compounds which were used without further purification, unable to be characterized due to decomposition, or whose spectral data is available in the literature are noted as such.

Table A3.1

Number	Structure	Characterization data	Reference preparation
2.027		literature	SRLV-221
2.094		literature	BJRI-073
2.104		literature	SRLVIII-069
2.106		literature	BJRI-063
2.107		literature	BJRI-073
2.108		literature	SRLVII-153
2.110		literature	SRLVII-025

Number	Structure	Characterization data	Reference preparation
2.111		literature	SRLVII-159
2.112		literature	SRLVII-165
2.117		literature	ZRWI-063
2.118a		ZRWI-045-p ZRWI-benzylamidechar ZRWI-071	ZRWI-071
2.118d		ZRWI-055-carb	ZRWI-055
2.119		used without purification	ZRWI-067

Number	Structure	Characterization data	Reference preparation
2.139		literature	SRLVII-169
2.158		SRLVIII-133-5.1-5.5	SRLVII-293 SRLVIII-133
2.160		literature	SRLV-289
2.161		literature	SRLV-249
2.162		literature	SRLV-241, 253
2.165		literature	SRLVI-061
2.166		literature	SRLVI-061

Number	Structure	Characterization data	Reference preparation
2.177		SRLVIII-DMBOpy	WHI-039
2.178		SRLVII-273-3.2-4.4	SRLVII-273
2.179		SRLVIII-119-3.3-7.4	SRLVIII-119
2.180		literature	SRLV-281, 289 SRLVII-023
2.183		YK	BJRI-069