Organocatalytic Asymmetric Michael, Mannich and aza-Michael Reactions in the Synthesis of Selected Quinolizidines, Indolizidines and Piperidines

by

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Abstract

Quinolizidines, indolizidines and substituted piperidines are ubiquitous structural motifs present in several naturally occurring alkaloids, pharmaceuticals and other compounds which exhibit a broad range of biological activities. Though many methods have been reported for their construction, there is still a need for novel approaches, especially in terms of high efficiency, good modularity and excellent stereoselectivity. A general introduction to the research work described in this thesis has been provided in Chapter 1.

An enantioselective, biomimetic organocatalytic synthesis of 4-arylquinolizidin-2-ones, key intermediates in the synthesis of several *Lythraceae* alkaloids, was developed. The methodology features *S*-proline-mediated Mannich/aza-Michael reactions of readily available arylideneacetones and Δ^1-piperideine. The total syntheses of (−)-lasubine II and (+)-subcosine II as well as the formal syntheses of structurally related *Lythraceae* alkaloids were achieved. The use of Δ^1-pyrroline in the Mannich/aza-Michael reaction provides enantiomerically enriched 5-arylindolizidin-7-ones, which are precursors to nonopiate antinociceptive agents. Details of these studies are described in Chapter 2.

An organocatalytic, enantioselective Mannich reaction of α,β unsaturated β'-ketoesters with *N*-carbamoyl imines was developed. The Mannich reaction uses an aminothiourea catalyst (*S*,*S*-Takemoto catalyst), and this was followed by a Pd(0) mediated deallylative decarboxylation, to provide enantiomerically enriched β-amino ketones. The conversion of these β-amino ketones to 2,6-diaryl substituted piperidinones was achieved. These results are described in Chapter 3.

The diarylindolizidine alkaloids (-)-fistulopsine A and (+)-fistulopsine B, isolated from the bark and the leaves of *Ficus fistulosa*, have potent *in vitro* antiproliferative activity against breast

(MCF7) and colon (HCT 116) carcinoma cell lines. Several 2-Indolinone-based analogues of (+)-fistulopsine B, with structural variation in the diaryl substitution, were prepared and examined for their biological activity. The synthesis of the analogues, by employing an organocatalytic Michael addition as a key step, and the biological activity studies are described in Chapter 4.

Acknowledgements

My sincere gratitude to my Ph.D. supervisor Prof. Sunil V. Pansare for being the guiding light all throughout my time at Memorial as a doctoral student. Your invaluable suggestions, appreciation for hard-work and the encouragement to do better made this seemingly long arduous journey more of an adventurous learning experience of a lifetime. Thank you, Dr. Pansare, for providing me an atmosphere most conducive to my learning and research. It could not have been better!

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To St. John’s, Newfoundland and Memorial University- thank you for giving me 5 eventful years of life. I cherish the days I spent here in an endeavour to earn my doctorate degree.

In the words of Guru Nanak, ' Let no man in the world lie in delusion. Without a Guru none can cross over to the other shore'. Thankyou to all my mentors who made this momentous achievement possible.

Dedication

This thesis is dedicated to:

The almighty, Waheguru; for blessing me with much more than I deserve,

My alma mater, St. Stephen's School; my teachers for laying a strong foundation for higher education,

Panjab University; I wish I could go back in time and live those glorious years once again,

My family, for their unconditional love and support in countless ways,

My dearest husband, who has a significant contribution during my Grad school years,

My in-laws, who have always stood by my side in all my major life decisions; particularly my grand-mother-in-law, her strength, character and contributions to the family back in those days, are inspirational.

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List of abbreviations

Ac	Acetyl
AIBN	Azobisisobutyronitrile
Alloc	allyloxycarbonyl
APCI	atmospheric pressure chemical ionization
APPI	atmospheric pressure photoionization
aq.	Aqueous
BINOL	1,1′-dinaphthalene-2,2′-diol
BnBr	benzyl bromide
Boc	*tert*-butoxycarbonyl
br	broad
BzCl	benzoyl chloride
CAN	ceric ammonium nitrate
cat.	catalytic
Cbz	benzyloxycarbonyl
CDI	1,1'-carbonyldiimidazole
CI	chemical ionization
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DCE	1,2-dichloroethylene
DCM	dichloromethane

DIBAL-H	diisobutylaluminum hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
EDG	electron donating group
ee	enantiomeric excess
EI	electron impact
eq.	equivalent (s)
er	enantiomeric ratio
ESI	electrospray ionization
EtOAc	ethyl acetate
EWG	electron withdrawing group
g	gram (s)
h	hour (s)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons
Hz	Hertz
i-Bu	isobutyl
IMAMR	intramolecular aza-Michael reaction

IR	infrared
J	coupling constant
L	ligand
LAH	lithium aluminum hydride
LDA	lithium diisopropyl amide
LHMDS	lithium hexamethyldisilazide
LiHMDS	lithium bis(trimethylsilyl)amide
M	molar
M^+	molecular ion
Me	methyl
mg	milligram(s)
min	minute(s)
mL	milliliter(s)
mmol	millimole(s)
mp	melting point
MS	mass spectrometry
MsCl	methanesulfonyl chloride
MVK	methyl vinyl ketone
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million

PTSA/*p*-TsOH	*para*-toluenesulfonic acid
R_f	retention factor
rt	room temperature
TBDMS/TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TMSOTf	trimethylsilyl trifluoromethanesulfonate
UV	ultraviolet

Chapter 1

Introduction

The research described in this thesis is focused on the synthesis of selected naturally occurring alkaloids and their analogues of pharmacological relevance. The alkaloids identified in this thesis have been of interest to several research groups leading to the development of a number of synthetic routes, however the novelty of our work lies in its brevity and the construction of molecular complexity from simple starting materials. This has been achieved by the strategic use of Mannich and intramolecular aza-Michael reactions under organocatalytic conditions. These reactions are powerful tools for C−C and C−N bond construction, respectively. The organocatalytic Mannich reaction between *N*-carbamoyl imines and α,β-unsaturated β'-keto-esters and the application of this methodology in the synthesis of substituted piperidines were also investigated. The purpose of this introduction is to provide a background for the organocatalyzed versions of the Mannich and the aza-Michael reactions and to present a literature review for the use of these reactions in tandem since the year 2000.

1.1 The Mannich Reaction

Asymmetric Mannich reactions are well-known C−C bond forming reactions employed for the synthesis of β-amino carbonyl compounds. In general, it is the addition of enolates (or enolate synthetic equivalents) to the electrophilic carbon of an imine and generates amine-containing chiral compounds also known as Mannich bases (Figure 1.1).

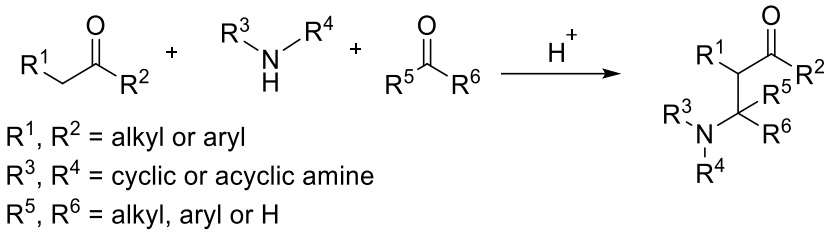
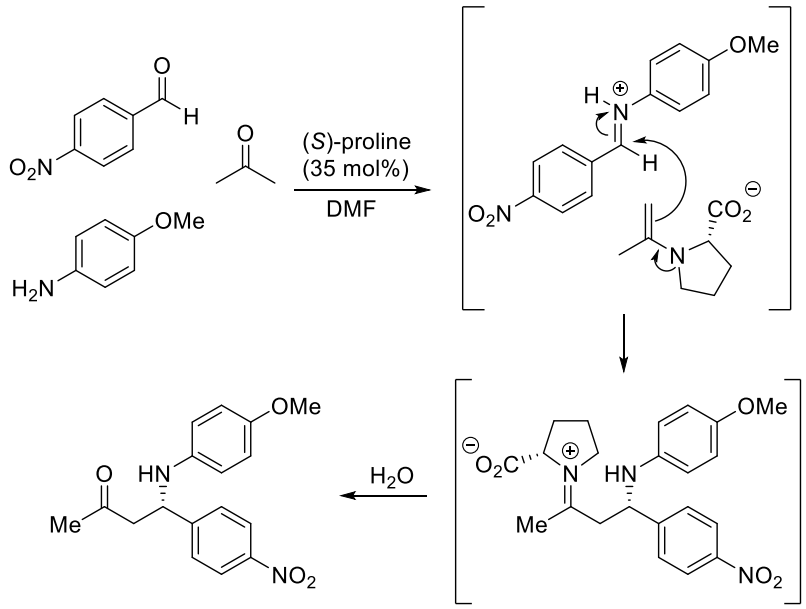


Figure 1.1: The Mannich Reaction

There is an enormous amount of literature on the organocatalytic Mannich reaction since its inception in the year 2000 when List[1] discovered that (*S*)-proline can effectively catalyse the asymmetric Mannich addition in a three-component reaction involving *p*-nitrobenzaldehyde, *p*-anisidine and acetone to provide the Mannich adduct in 50% yield and 94% ee (Scheme 1.01).



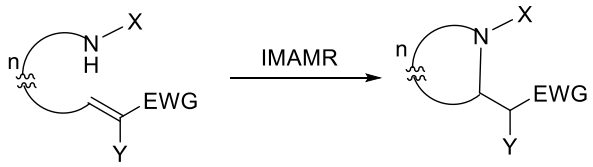
Scheme 1.01

Shortly after, significant advances were reported by Barbas, Cordova, Hayashi, and others and significant progress in this area still continues to be made. The organocatalytic asymmetric Mannich reaction has been a topic for several reviews[2] from 2000 to the most recent one in 2021.

1.2 The Intramolecular Aza-Michael Reaction (IMAMR)

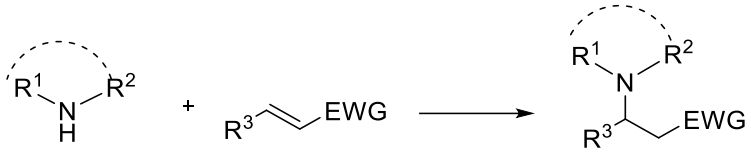
The Michael addition is one of the most important and versatile methods for C−C bond formation in organic chemistry. It is the 1,4-conjugate addition of carbon nucleophiles to olefins with electron-withdrawing groups (EWGs) as substituents. This reaction received recognition from the scientific community in 1887 when A. Michael reported his pioneering work on the addition of sodium malonate/acetoacetate esters to α,β-unsaturated esters. What makes this reaction so useful is that a large variety of acceptors and nucleophiles can participate in it. Particularly interesting is the use of heteroatom nucleophiles, especially those containing oxygen and nitrogen, in this reaction. Such reactions are termed oxa-Michael and aza-Michael reactions, respectively. Aza-Michael reactions, which result in C−N bond formation, are a key step in the synthesis of nitrogen heterocycles of pharmacological and synthetic significance and hence are of great value in alkaloid chemistry.

Aza-Michael reactions can further be categorized as intra- and intermolecular versions depending on whether the nucleophilic and electrophilic counterparts are from the same molecule or are present in two different molecules, respectively. Several reviews are available on organocatalytic aza-Michael reactions[3] and some recent reviews on intramolecular aza-Michael reactions[4] (IMAMR), as a special class of reactions for the synthesis of piperidines and pyrrolidines, have been published.



EWG = CHO, COR, CO_2R, NO_2, SO_2Ar, $PO(OR)_2$
X = H, CO_2R, OR, NR_2, SO_2Ar, COR
Y = H, COR, CO_2R, SO_2Ar; n =2, 3

Figure 1.2: General Scheme for an Intramolecular Aza-Michael Reaction



EWG = CHO, COR, CO_2R, $CONR_2$, CN, $PO(OR)_2$, SO_2R, NO_2, heterocycle etc.
R^1-R^3 = alkyl, aryl, heteroaryl etc.

Figure 1.3: General Scheme for an Intermolecular Aza-Michael Reaction

1.3 Enantioselective Organocatalysis

The use of chiral organic molecules in catalytic amounts to synthesize complex chiral organic frameworks from achiral reactants, is how one would define enantioselective organocatalysis in simple words. The growing demands on the pharmaceutical industry to fight new and already prevailing diseases requires the synthesis of therapeutics with high levels of selectivity, modularity, and low levels of toxicity.[5] Traditionally, enantiopure molecules were obtained using resolution, a technique used to separate a racemic mixture into individual enantiomers. However, only 50% of each enantiomer could be obtained following a resolution procedure, and nonetheless, less than satisfactory yields and time constraints involved gave organic chemists the incentive to strive for better methods to obtain enantiomerically enriched target molecules.

The dramatic influence of chirality on biochemical properties can best be depicted by the example of the drug thalidomide, a sedative given in the 1950s to pregnant women to alleviate

morning sickness.[5] It was discovered later that only the (+)-enantiomer was an effective sedative while the (−)-enantiomer was an active teratogen. The consumption of the drug (as a mixture of enantiomers) resulted in numerous birth abnormalities when taken in the early stages of pregnancy. There are several chiral compounds for which different enantiomers exhibit different culinary and olfactory effects; however, differences in therapeutic effects where one enantiomer is the benefactor while the other one is a malefactor, demand that modern organic chemists exploit the fast-growing field of enantioselective synthesis for the needs of society. Most drugs we know of today are non-racemic/chiral and to achieve the synthesis of such biologically active organic molecules, enantioselective organocatalysis plays a key role. Organocatalytic methods score over metal-based enantioselective syntheses for reasons such as operational simplicity, low levels of toxicity[5] and ready availability, all of which align with facets of environmentally benign green chemistry and thus have great potential in the realm of drug discovery.

Both Mannich and intramolecular aza-Michael reactions work with several organocatalyts which can be broadly classified into three categories**:**

i) Chiral amines

ii) Chiral Brønsted bases

iii) Chiral Brønsted acids

1.3.1 Organocatalytic Mannich Reactions

(a) Using enamine forming chiral amines[2]

Chiral amines react with aldehydes and ketones (donors) to form enamines which then undergo nucleophilic addition to the electrophilic carbon of imines (acceptors), thus generating 1

or 2 chiral centers in the product. The catalytic cycle is terminated by the regeneration of the amine catalyst via hydrolysis.

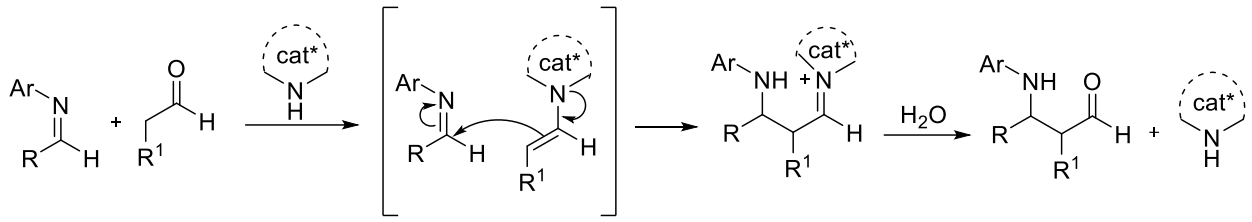


Figure 1.4: Mode of activation in Mannich reactions using chiral amines

(b) Using chiral Brønsted bases[2]

Chiral Brønsted bases can be used to catalyze Mannich reactions of active methylene nucleophiles with neutral imines (with the EWG on the imine nitrogen to enhance electrophilicity) via a mode of activation in which the chiral base deprotonates the nucleophile to form a chiral ion pair, the anion of which adds to the Mannich acceptor in an enantioselective manner. In such catalysts, the presence of a thiourea motif enhances the reaction via double hydrogen bonding with the imine, thus facilitating nucleophilic attack by increasing the electrophilic character of the imine carbon.

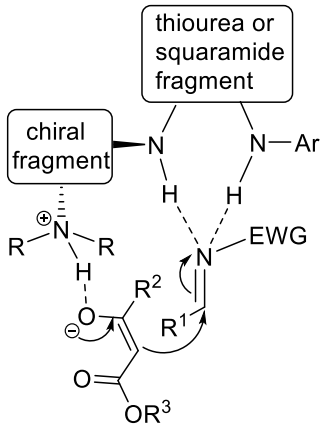


Figure 1.5: Mode of activation in Mannich reactions using chiral Brønsted base catalysis

(c) Using chiral Brønsted acids[2]

The use of chiral Brønsted acids for enantioselective Mannich reactions operates via the protonation of the imine nitrogen with the chiral acid generating an iminium ion alongside an enantiopure counterion. This chiral counterion orients the nucleophilic species and the Mannich acceptor such that the attack of the nucleophile generates enantiomerically enriched Mannich products.

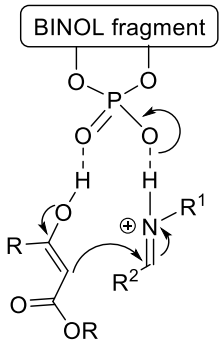


Figure 1.6: Mode of activation in Mannich reactions using chiral Brønsted acid catalysis

1.3.2 Organocatalytic Intramolecular aza-Michael Reactions (IMAMR)

(a) Using chiral amines[3]

Primary and secondary amine catalysts such as proline, pyrrolidine derivatives and cinchona alkaloid derived amines act as Lewis bases, reversibly forming iminium ions with α, β-unsaturated carbonyl compounds. These iminium ions have lower LUMO energies and thus have increased reactivity towards a nitrogen nucleophile present in the molecule. The use of chiral secondary amine catalysis is a well-established synthetic tool for the enantioselective functionalization of aldehydes; however, the same is not true for ketones. This is due to the inherent difficulty in formation of congested iminium ions from ketones along with other unfavorable issues such as generally poor control over iminium ion geometry and the lower

electrophilicity of ketones towards iminium ion formation as compared to aldehydes.[6] For the same reason, stereoselective addition to α, β-unsaturated ketones is also a challenging objective in organocatalysis. The use of primary amine catalysts, which have been unpopular because of the notion of an unfavorable imine-enamine equilibrium, has been shown to circumvent the issues associated with secondary amine catalysis of ketones.[6] However, efficient iminium ion activation of ketones via chiral amine catalysis is still an area of ongoing research.

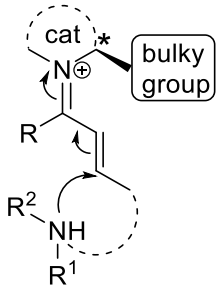


Figure 1.7: Mode of activation in aza-Michael reactions using chiral amines

(b) Brønsted base catalysis[3]

Usually, tertiary amine containing squaramide and thiourea catalysts fall under this category. The thiourea/squaramide participates in double hydrogen bonding to the EWG on the Michael acceptor thereby enhancing its electrophilicity for conjugate addition, while the tertiary amine abstracts a proton to yield an ion pair in which the nucleophile is placed in space in a fashion leading to stereoselective addition of the nitrogen nucleophile.

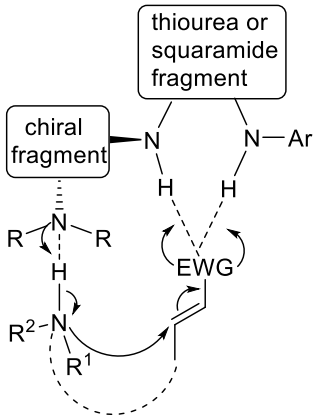


Figure 1.8: Mode of activation in aza-Michael reactions using chiral Brønsted base catalysis

(c) Brønsted acid catalysis[3]

BINOL-derived phosphoric acids act by protonating the α,β-unsaturated carbonyl compound to enhance its electrophilic character while the chiral counterion steers the nucleophilic nitrogen towards an intramolecular stereoselective ring closure.

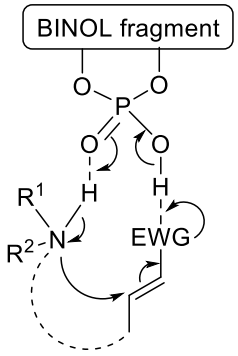


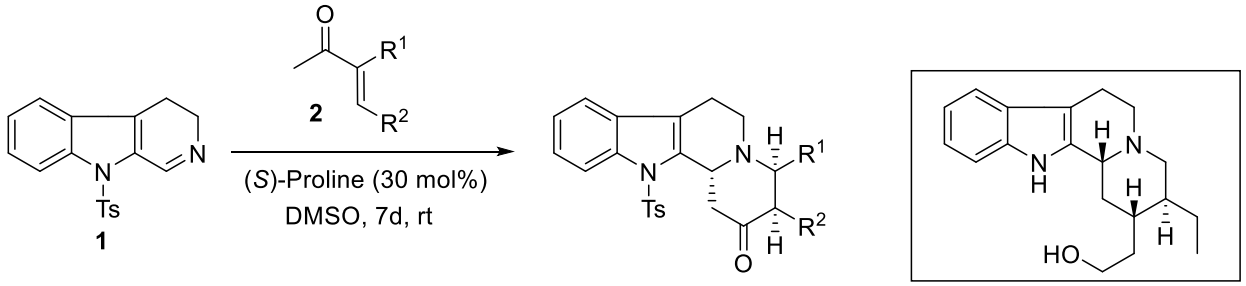
Figure 1.9: Mode of activation in aza-Michael reactions using chiral Brønsted acid catalysis

1.4 Tandem Mannich/Intramolecular Aza-Michael reactions

The blend of a Mannich reaction with an IMAMR yields products analogous to that from an aza-Diels-Alder reaction. However, the sequence occurs stepwise rather than in a concerted

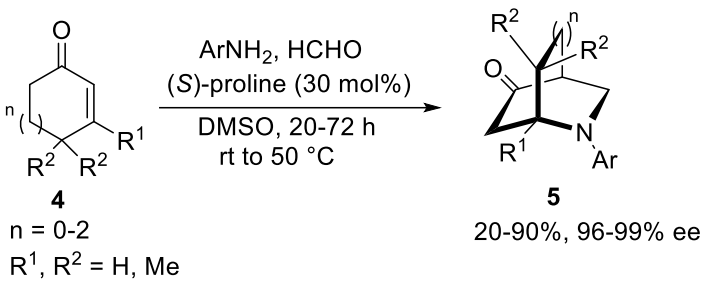
fashion as for the Diels-Alder reaction. The Michael acceptor containing a nucleophilic nitrogen center is generated in situ via an organocatalytic Mannich reaction, which then undergoes an IMAMR in tandem to yield complex organic molecules in a single step. These reactions[2-4] have been reviewed independently by several researchers in the past; however, the tandem Mannich/IMAMR has not been reviewed as a single topic for the synthesis of several functionalized nitrogen heterocycles. This thesis provides the references for all such organocatalyzed cascade reactions in chronological order since the year 2003, the year when the first example of these reactions was reported.

The first report on a Mannich/aza-Michael sequence was reported in 2003 by Ohsawa[7,8] and co-workers. (*S*)-Proline catalysed the reaction of 9-tosyl-3,4-dihydro-*β*-carboline **1** with methyl vinyl ketone (MVK) **2** to provide a tetracyclic derivative **3a** in good yield and excellent enantiomeric excess (ee) after 7 days at room temperature (Scheme 1.02). The methodology was extended in 2006 by reacting substituted conjugated enones **2** with the imine **1** to yield the desired pyridone rings **3b-c** as single diastereomers with good yields. The application of this methodology was demonstrated in the total synthesis of the natural product *ent*-dihydrocorynantheol.



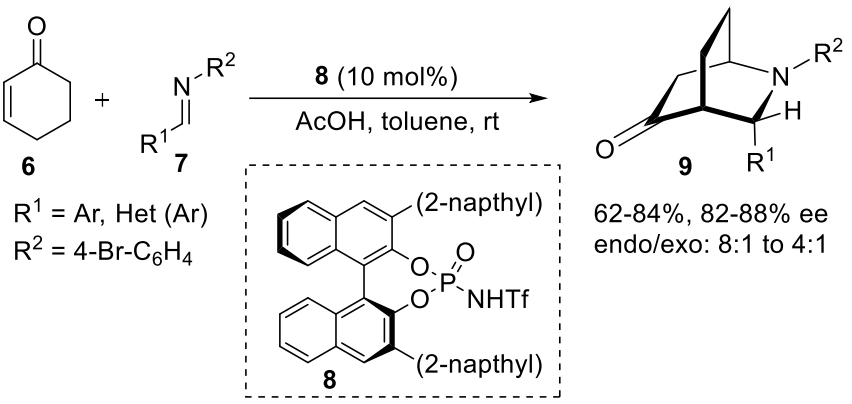
Scheme 1.02

Cordova's work[9] used (*S*)-proline as a catalyst in DMSO for the reaction between aqueous formaldehyde, aromatic imines and cyclic enones **4**, providing nitrogen containing bicycles **5** in low to high yields and excellent ee. The ring size of the cyclic enone had a dramatic effect on the yields of the desired product with cyclopentenone providing the product in only 10% yield. Additionally, it was found that steric hindrance at the enone β-position (substituent R^1), did not allow the aza-Michael addition step to occur and Mannich adducts were isolated instead. In terms of the effect of substitution in the aromatic amines, electron rich anilines provided better yields of the cyclized products as compared to electron deficient analogues (Scheme 1.03).



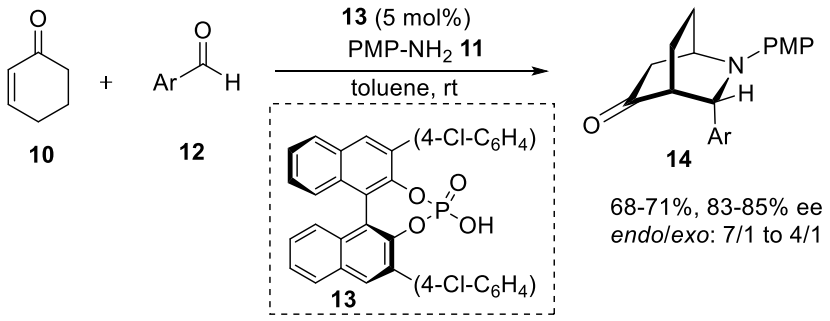
Scheme 1.03

Later, Rueping[10] discovered that the use of chiral BINOL derived catalyst **8** along with acetic acid as a co-catalyst in the reaction of cyclohexenone **6** and aromatic/hetero-aromatic imines **7** in toluene at room temperature provided isoquinuclidines **9** in good yields and with moderate diastereoselectivity and good enantioselectivity (Scheme 1.04).



Scheme 1.04

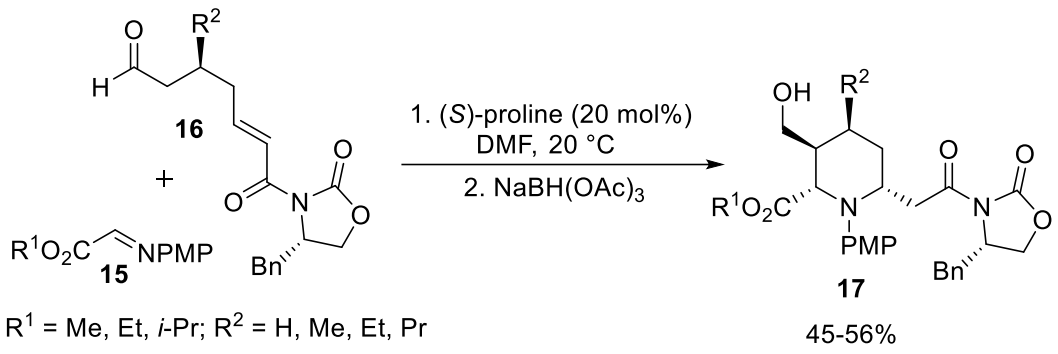
Almost at the same time, another report using chiral BINOL phosphoric acids to afford azabicyclic ketones **14** in a stereoselective Mannich/aza-Michael fashion came from the group of Gong.[11] The difference was that the procedure used the substituted BINOL phosphoric acid **13** as a catalyst, with no need for the addition of the acid co-catalyst to provide the desired products. Also, the reaction could be efficiently performed using a three-component protocol (cyclohexenone **10**, *p*-anisidine **11** and aromatic aldehydes **12**) to give final products in comparable yields to those formed using preformed imines (Scheme 1.05).



Scheme 1.05

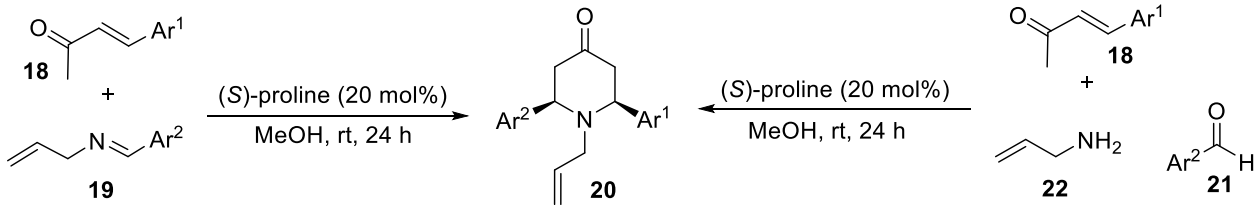
In 2008, the synthesis of highly substituted pipecolic esters **17** using an organocatalyzed Mannich/aza-Michael cascade reaction was reported by Schneider[12] and co-workers. Chiral 7-oxo-2-enimides **16** containing an aldehyde along with an α,β-unsaturated imide were reacted

with glyoxyl imines **15** at -20 °C for 20 hours in the presence of (*S*)-proline as a catalyst, after which the aldehyde functionality in the product was immediately reduced to provide pipecolic esters **17** as single diastereomers in moderate yields. The product contained four chiral centers, three of which were formed during the reaction with absolute stereocontrol (Scheme 1.06). Experimental evidence for the Mannich reaction being under catalyst control and the subsequent aza-Michael reaction being under substrate control was also reported.



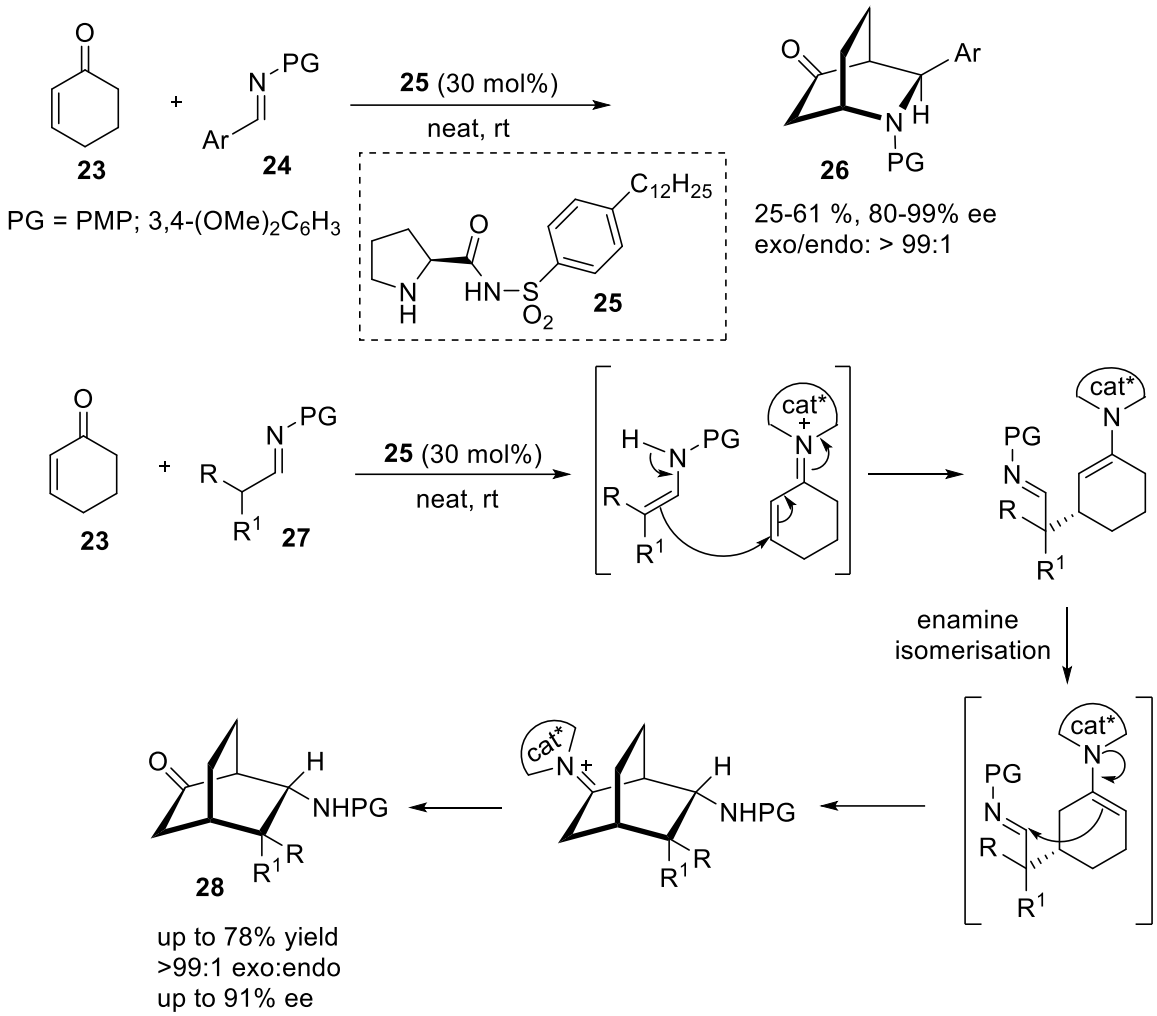
Scheme 1.06

Around the same time, Aznar and co-workers[13] reported (*S*)-proline to be an efficient catalyst in the stereoselective synthesis of *cis*- and *meso*-2,6-diarylpiperidin-4-ones **20** from (*E*)-4-phenylbut-3-en-2-one **18** and *N*-allylbenzaldimine **19** in methanol as solvent. The effect of the protecting group on nitrogen was significant and only low conversions were seen when *N*-alkyl or *N*-aryl imines were employed. However, the diastereoselectivity remained high in all cases. This methodology could also be carried out as a 3-component, one-pot protocol using the enone **18**, amine **22** and benzaldehyde **21** as starting materials in the presence of (*S*)-proline in methanol, affording the Mannich/aza-Michael reaction products in good yields and with diastereoselectivities comparable to those obtained with preformed imines (Scheme 1.07).



Scheme 1.07

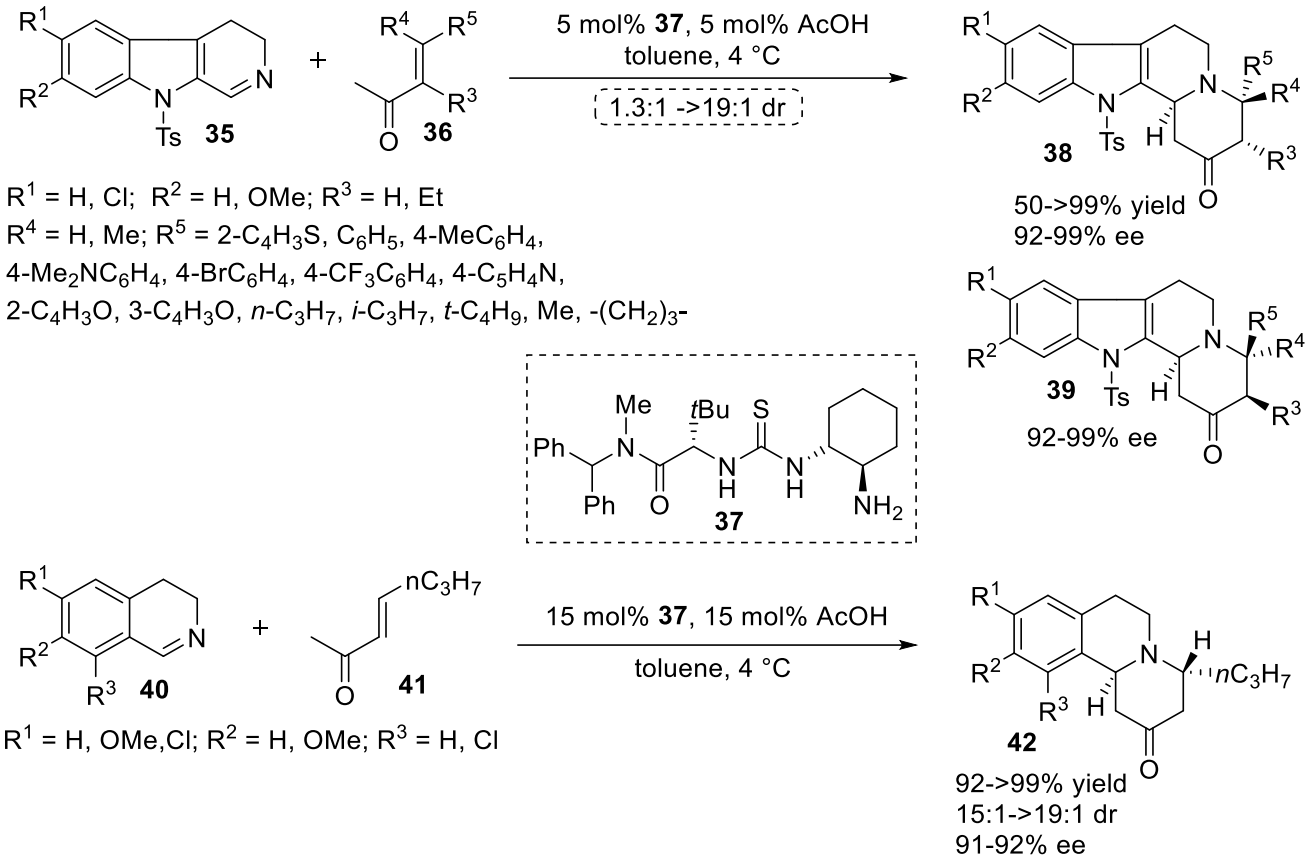
Carter's report[14] on the synthesis of azabicyclic ketones **26**, was complementary to earlier work by Gong[11] and Rueping.[10] The use of *p*-dodecylphenylsulfonamide based proline derivative **25** as a catalyst in the neat reaction of cyclohexenone **23** and aromatic imines **24**, provided exclusively the *exo*-substituted isomers of the isoquinuclidines **26** in moderate yields, but with excellent diastereoselectivity and enantioselectivity (Scheme 1.08). This observation contrasts the results obtained by Gong (Scheme 1.05) and Rueping (Scheme 1.04) wherein the endo-substituted isoquinuclidines were obtained as major products. Reactions involving aliphatic imines followed a different reaction pathway, forming bicyclo [2.2.2] octanes **28** instead via the reaction of cyclohexenone **23** and imine **27** in the presence of catalyst **25**. The formation of the all-carbon bicycle **28** was rationalized as the Michael addition of an enamine derived from the enolisable aliphatic imine **27** to the iminium ion of cyclohexenone **23** (Michael acceptor). Subsequent enamine isomerization followed by an intramolecular Mannich cyclization and finally hydrolysis provided the bicyclic product **28** and regenerated the catalyst.



Scheme 1.08

In 2010, Enders[15] reported the synthesis of highly functionalized pyrrolidines **32** in good yields and with excellent diastereo- and enantioselectivities from the reaction of γ-malonate substituted α,β-unsaturated esters **29** with *N*-carbamoyl protected imines **30** in the presence of the aminothiourea catalyst **31** (the Takemoto catalyst). The presence of two electron-withdrawing ester moieties in the Michael acceptor was a vital requirement for the aza-Michael reaction to occur in tandem. Only the Mannich products were isolated with analogues of **29**

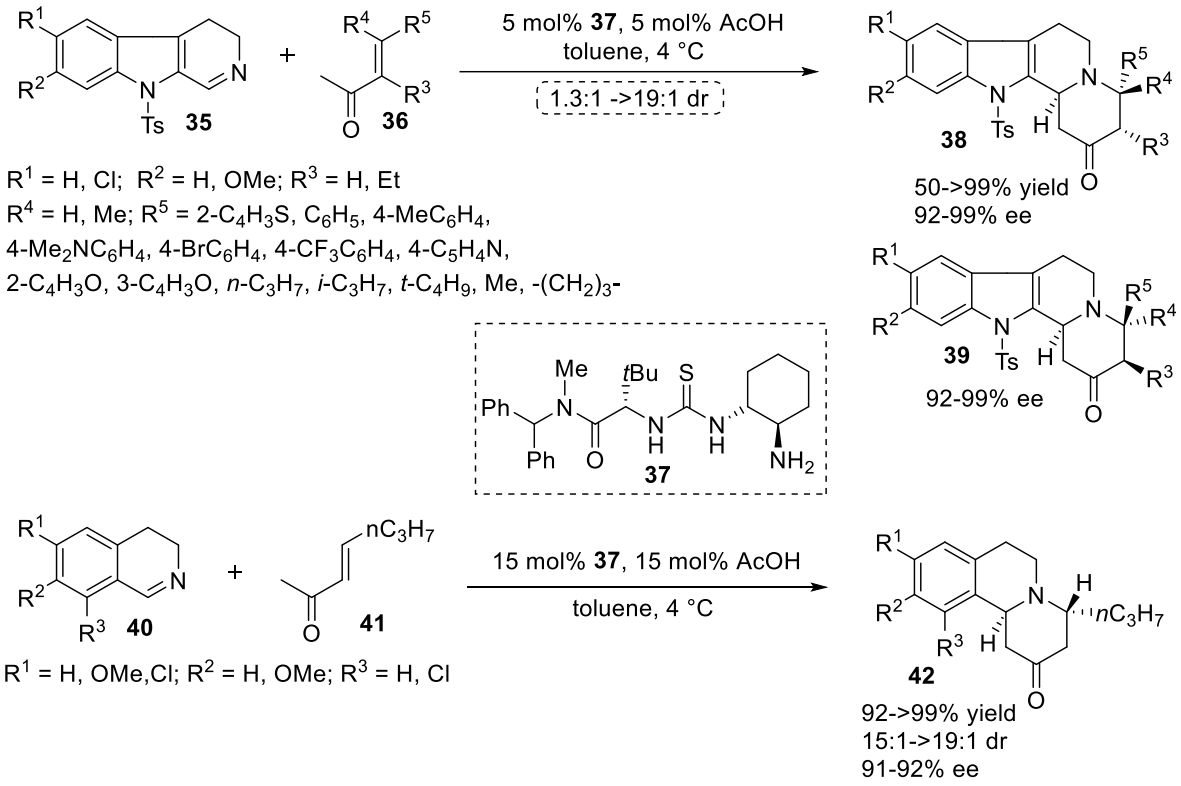
lacking one of the two ester moieties on the Michael acceptor such as from the reaction of **33** with imine **30** to provide Mannich product **34** (Scheme 1.09).



Scheme 1.09

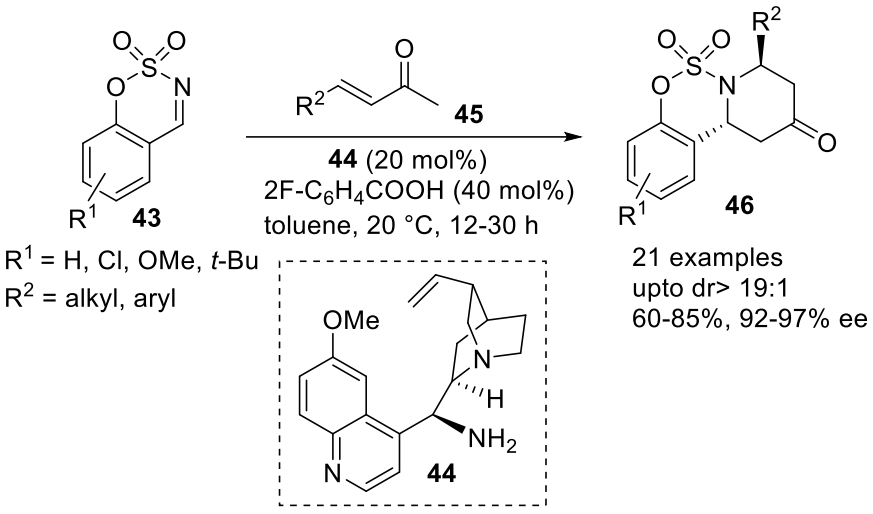
In 2013, Jacobsen[16] and co-workers reported an enantio- and diastereoselective synthesis of indolo- and benzoquinolizidine compounds using a primary aminothiourea **37** catalysed Mannich/aza-Michael cascade reaction of cyclic imines **35** and enones **36** (Scheme 1.10). The methodology worked equally well for 9-tosyl-3,4-dihydro-*β*-carboline imines as well as 3, 4-dihydroisoquinolines (however a higher catalyst loading was required) providing the cyclised adducts in good yields via the simultaneous activation of the imine and the enone by the chiral primary aminothiourea employed as catalyst. Although the enantioselectivity of the reaction was unaffected, the absence of catalytic AcOH resulted in very low turnover of the primary amine

thiourea catalyst **37**. The reaction scope was studied with 22 examples covering a range of acyclic enones with heteroaryl, *β*-aryl, linear and branched alkyl substituents as well as cyclic enones which reacted well with electron rich and electron deficient imines to provide products in a highly stereoselective fashion.



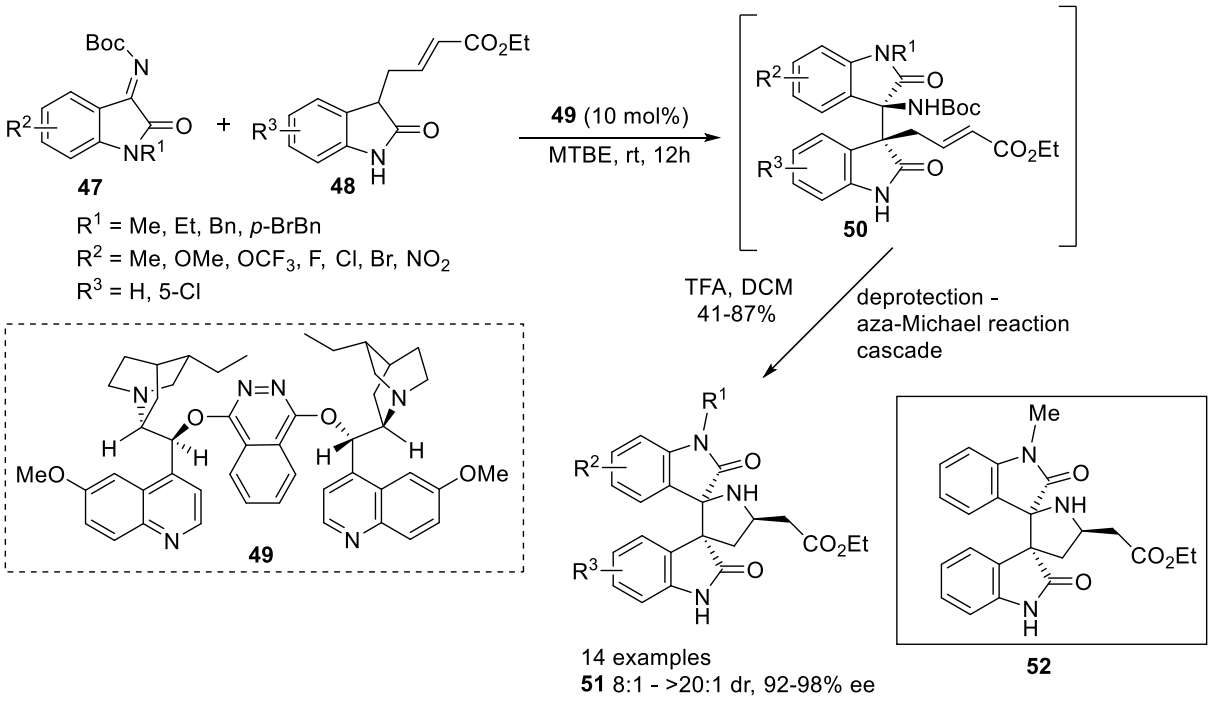
Scheme 1.10

In 2013, He and co-workers[17] reported the reaction of cyclic *N*-sulfonyl imines **43** with *β*-aryl or *β*-alkyl enones **45** in the presence of a quinidine derived primary amine **44** and *o*-fluorobenzoic acid as co-catalyst at room temperature in toluene provided sulfamate fused 2, 6-disubstituted piperidin-4-ones **46** in good yields and with excellent diastereo- and enantioselectivities. The reaction was very tolerant to both electron-withdrawing and electron-donating groups on the enone (Scheme 1.11).



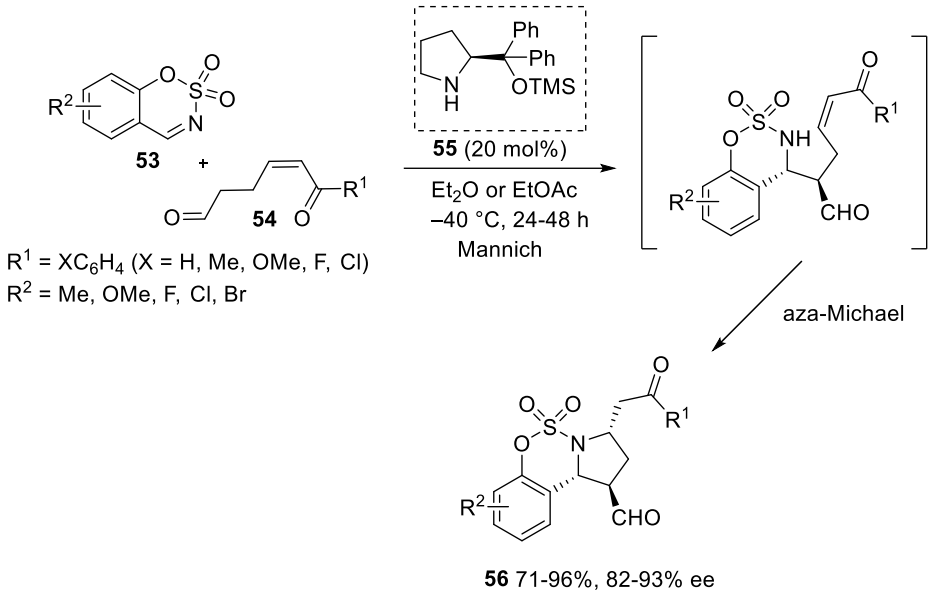
Scheme 1.11

In 2016, Enders et al. reported[18] an elegant one-pot stereoselective synthesis of 3, 3′-pyrrolidinyl-dispirooxindoles **51**, compounds which are known to exhibit interesting anti-cancer and anti-microbial properties. Their methodology featured $(DHQD)_2PHAL$ **49**, a commercially available catalyst for the Mannich addition of crotonate bearing oxindoles **48** to *N*-Boc protected isatin derived ketimines **47**. The intermediates were subsequently deprotected in the same pot thus triggering the diastereoselective aza-Michael cascade reaction to form the desired heterocyclic scaffolds in moderate to high yields and excellent diastereo- and enantioselectivities (Scheme 1.12). The scope of substrates that can usefully undergo the Mannich/deprotection/aza-Michael reaction cascade was studied with 14 examples and the methodology was tested successfully for the gram scale synthesis of **52** as well.



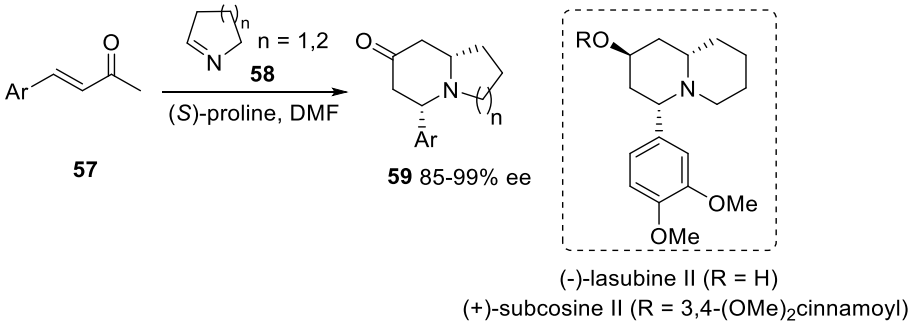
Scheme 1.12

Kim and co-workers[19] described a stereoselective synthesis of benzosulfamidate-fused pyrrolidines using diphenylprolinol TMS ether **55** to catalyse the reaction of δ-formyl-α,β-unsaturated ketones **54** with cyclic *N*-sulfinimines **53**. The confirmed stereochemistry of the final product sulfamidate **56** was evidence for Mannich addition on the *re*-face of the imine followed by a spontaneous aza-Michael ring closure to the *si*-face of the Michael acceptor to give the desired heterocycles in good yields and with high diastereo- and enantioselectivities (Scheme 1.13).



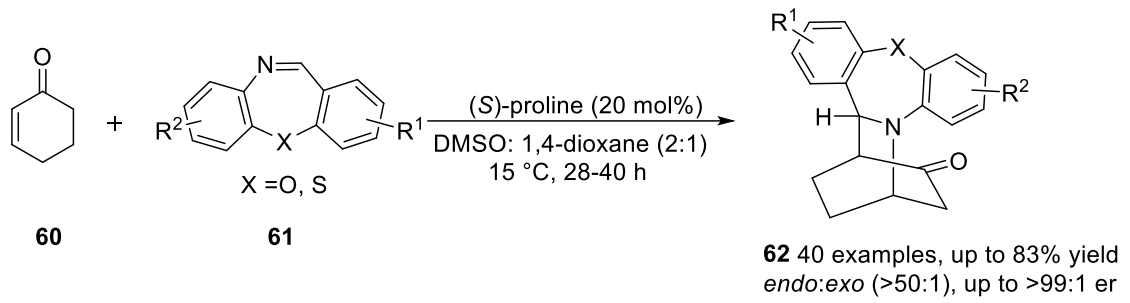
Scheme 1.13

In 2019, the Pansare group described[20] a biomimetic enantioselective approach to several 4-arylquinolizidine alkaloids and 5-arylindolizidinones. These studies resulted in the total synthesis of (-)-lasubine II and (+)-subcosine II along with the formal synthesis of several *Lythraceae* alkaloids (Scheme 1.14). The key steps of this methodology involved a dienamine mode of activation of the enone **57** resulting in a Mannich/aza-Michael reaction with the cyclic imine **58** in tandem stereoselectively from the aza-bicycle **59** in one pot. The details of this study are given in Chapter 2 of this thesis.



Scheme 1.14

The most recent report on Mannich/aza-Michael reaction cascades came in 2020 from Kumar[21] and co-workers. They implemented a (*S*)-proline catalysed enantioselective synthesis of dibenzoxazepine/thiazepine fused [2.2.2] isoquinuclidines utilizing 2-cyclohexen-1-ones **60** and various tricyclic imines **61** (dibenzoxazepines and thiazepines) as starting materials. Mannich reaction followed by an aza-Michael intramolecular ring closure in tandem afforded the endo-isoquinuclidines **62** in high yields and with excellent enantioselectivity (Scheme 1.15).



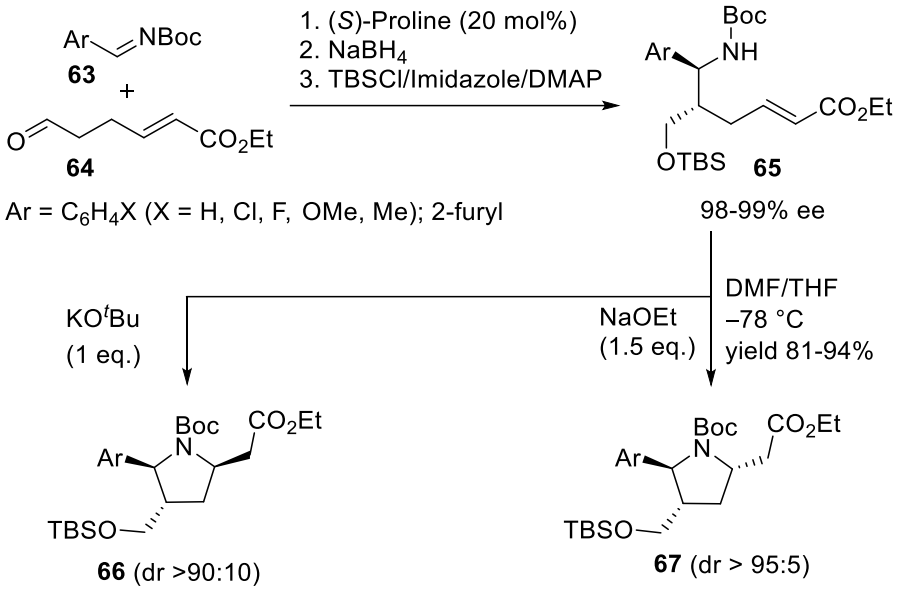
Scheme 1.15

1.5 Stepwise Mannich and Intramolecular Aza-Michael Reactions

There is only one report in the literature where the synthesized Mannich product is cyclized in a separate aza-Michael reaction. In this case, the Mannich product itself is isolable due to two reasons; 1) low nucleophilicity of the amine generated via the Mannich reaction (effect of the protecting group on the imine nitrogen), and 2) the presence of a weak Michael acceptor in the molecule. Under such conditions, the product of the first step (Mannich reaction) is isolated and subjected to a second reaction in which ring closure occurs.

Following their previous work on the synthesis of highly substituted piperidine rings, Schneider et al.[22] reported, in 2009, a stereodivergent synthesis of trisubstituted pyrrolidines using 6-oxo-2-enoate **64** and *N*-Boc protected imines **63** in an (*S*)-proline catalyzed Mannich

reaction followed by insitu reduction to give the reduced Mannich products as single diastereomers in good yields and excellent enantioselectivities. Silylation followed by base-catalyzed intramolecular aza-Michael ring closure provided the 2,5-*cis*- and 2,5-*trans*- isomers of the target pyrrolidines. The diastereoselectivity of the aza-Michael step is dependent on the base that is employed. The use of a strong base such as KO^{t}Bu promoted epimerization and resulted in the thermodynamically stable 2,5-*cis* form **66** (dr > 90:10), while NaOEt, a weaker base, provided the 2,5-*trans* isomer **67** with excellent diastereoselectivity (dr > 95:5, Scheme 1.16). The fact that the aza-Michael step needed a separate base treatment in fact offered stereodivergence to the protocol, which would not have been possible had the cyclization reaction been spontaneous.



Scheme 1.16

While the above reports highlight the utility of the organocatalytic Mannich and aza-Michael reactions, only a few examples of the application of these reactions in the catalytic enantioselective synthesis of natural products are reported. Some of the studies described in this thesis are aimed at addressing this limitation.

1.6 References

1. List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336.
2. Reviews on Organocatalytic Mannich reactions: (a) Bagheri, I.; Mohammadi, L.; Zadsirjan, V.; Heravi, M. M. *ChemistrySelect*. **2021**, *6*, *1008*. (b) Cheng, D.-J.; Shao, Y.-D. *ChemCatChem*. **2019**, *11*, 2575. (c) Cai, X.-H.; Xie, B. *ARKIVOC* **2013**, 264. (d) Verkade, J. M. M.; Hemert, L. J. C. V.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29.
3. Reviews on organocatalytic aza-Michael reactions: (a) Vinogradov, M. G.; Turova, O. V.; Zlotin, S. G. *Org. Biomol. Chem.* **2019**, *17*, 3670. (b) Amara, Z.; Caron, J.; Joseph, D. *Nat. Prod. Rep*. **2013**, *30*, 1211. (c) Enders, D.; Wang, C.; Liebich, J. X. *Chem. Eur. J.* **2009**, *15*, 11058.
4. Reviews on organocatalyzed IMAMRs: (a) Bates, R. W.; Ko, W.; Barat, V. *Org. Biomol. Chem*. **2020**, *18*, 810. (b) Sanchez-Rosello, M.; Acena, J. L.; Simon-Fuentes, A.; Pozo, C. D. *Chem. Soc. Rev.* **2014**, *43*, 7430.
5. Gaunt, M. J.; Johansson, C. C. C.; Mcnally, A.; Vo, N. T. *Drug Discov. Today* **2007**, *12*, 8.
6. Bartoli, G.; Melchiorre, P. *Synlett* **2008**, *12*, 1759.
7. Itoh, T.; Yokoya, M.; Miyauchi, K.; Nagata, K.; Ohsawa, A. *Org. Lett*. **2003**, *5*, 4301.
8. Itoh, T.; Yokoya, M.; Miyauchi, K.; Nagata, K.; Ohsawa, A. *Org. Lett*. **2006**, *8*, 1533.
9. Sunden, H.; Ibrahem, I.; Eriksson, L.; Cordova, A. *Angew. Chem. Int. Ed*. **2005**, *44*, 4877.
10. Rueping, M.; Azap, C. *Angew. Chem. Int. Ed*. **2006**, *45*, 7832.
11. Liu, H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2006**, *8*, 6023.

12. Khaliel, S.; Nandakumar, M. V.; Krautscheid, S.; Schneider, C. *Synlett*, **2008**, 2705.

13. Aznar, F.; Garcia, A-B.; Quinones, N.; Cabal, M-P. *Synthesis*. **2008**, *3*, 479.

14. Yang, H.; Carter, R. G. *J. Org. Chem*. **2009**, *74*, 5151.

15. Enders, D.; Goddertz, D. P.; Beceno, C.; Raabe, G. *Adv. Synth. Catal*. **2010**, *352*, 2863.

16. Lalonde, M. P.; McGowan, M. A.; Rajapaksa, N. S.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2013**, *135*, 1891.

17. Liu, Y.; Kang, T.-R.; Liu, Q.-Z.; Chen, L.-M.; Wang, Y.-C.; Liu, J.; Xie, Y.-M.; Yang, J.-L.; He, L. *Org. Lett*. **2013**, *15*, 6090.

18. Zhao, K.; Zhi, Y.; Li, X.; Puttreddy, R.; Rissanen, K.; Enders, D. *Chem. Commun.* **2016**, *52*, 2249.

19. Kim, H.; Kim, Y., Kim, S.-G. *J. Org. Chem.* **2017**, *82*, 8179.

20. Virk, S.; Pansare, S. V. *Org. Lett.* **2019**, *21*, 5524.

21. Yadav, J.; Pawar, A. P.; Nagare, Y. K.; Iype, E.; Rangan, K.; Ohshita, J.; Kumar, D.; Kumar, I. *J. Org. Chem.* **2020**, *85*, 14094.

22. Enkisch, C.; Schneider, C. *Eur. J. Org. Chem.* **2009**, 5549.

Chapter-2

Biomimetic Organocatalytic Approach to 4-Arylquinolizidine Alkaloids and Application in the Synthesis of (−)-Lasubine II and (+)-Subcosine II

The work described in this chapter has been published in Organic Letters.

Virk, S.; Pansare, S. V. *Org. Lett*. **2019**, *21,* 5524-5528.

2.1 Introduction

The *Lythraceae* plant family is a rich source of quinolizidine alkaloids (the *Lythracea*e alkaloids). These alkaloids, in general, are known to exhibit a wide range of biological activities such as anti-inflammatory, antispasmodic, and sedative properties. They also have a widespread folk reputation for their efficacy in the treatment of slow-healing ulcers and wounds, dysentery, indigestion, and bronchitis.[1] A few of these alkaloids such as lythrine and decinine have proven useful for treating Addison's disease and general nephrosis.[1]

The *Lythraceae* alkaloids incorporate the quinolizidine ring system with an aryl substituent at C-4 (see **1** for quinolizidine numbering, Figure 2.1). A significant number of naturally occurring 4-arylquinolizidines have the *trans*-decalin-type structure in which the ring junction methine hydrogen and the aryl substituent are *trans* to each other. Representative examples of *Lythraceae* alkaloids such as 4-arylquinolizidin-2-one **1**,[2] (−)-lasubine II (**2**),[3] (+)-subcosine II (**3**),[3] and (+)-abresoline (**4**)[4] are shown in Figure 2.1. Further modification of the lasubine motif adds structural complexity to provide (+)-lythrine (**5**),[5] (+)-dihydrolyfoline (**6**),[7] (−)-decinine (**7**),[6] and decaline (**8**),[6] all of which are characterized by a 4-hydroxycinnamic acid derived macrolactone subunit that spans the 4-aryl substituent and the C2 hydroxy group.

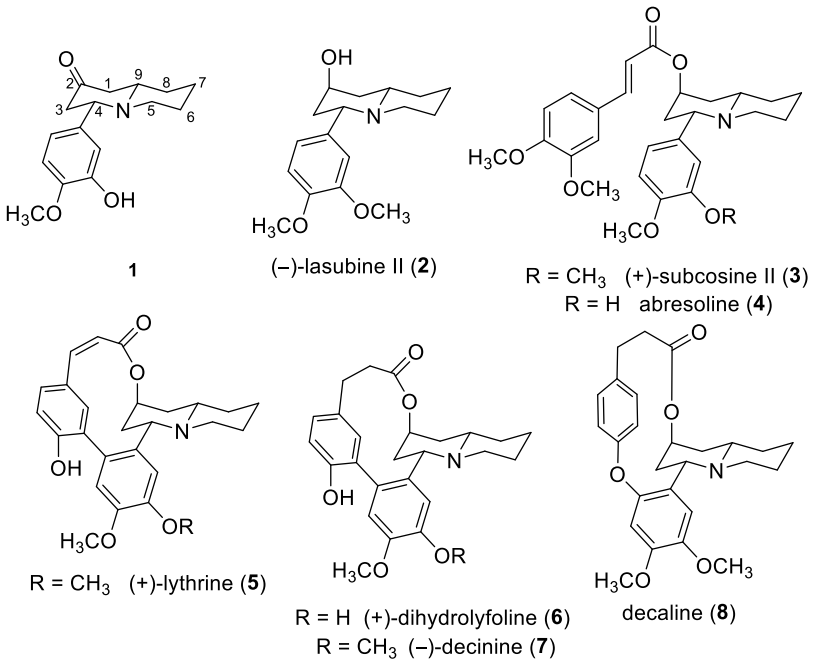


Figure 2.1 Representative examples of *Lythraceae* alkaloids

The biosynthesis[8] of the *Lythraceae* alkaloids is known to involve Δ^1-piperideine (**11**) and ring-oxygenated versions of (*E*)-3-oxo-5-phenylpent-4-enoic acid (**14**) which are obtained from L-lysine (**9**) and L-phenylalanine (**12**) via the intermediacy of cadaverine (**10**) and cinnamic acid (**13**), respectively, as shown in Figure 2.2. Mannich reaction of the phenylalanine-derived component and Δ^1-piperideine, followed by an intramolecular conjugate addition of the piperideine intermediate **15** (Figure 2.2), provides quinolizidinone **16** which is the key biosynthetic precursor for the 4-arylquinolizidine alkaloids. Notably, one such quinolizidinone (**1**, Figure 2.1) and the alkaloids derived from it have been isolated from the same plant.[9]

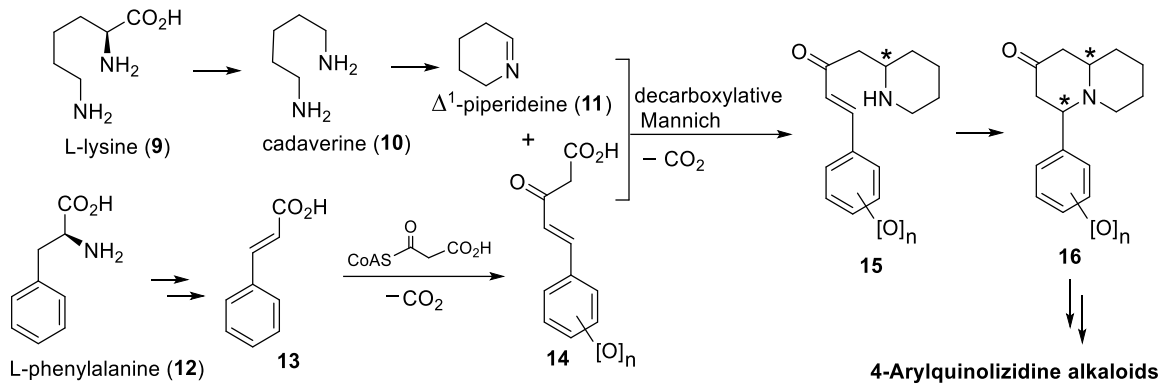


Figure 2.2 Biosynthesis of *Lythraceae* alkaloids

2.2 Our work

As a rapidly emerging research field, biomimetic synthesis has attracted intensive interest in natural product synthesis.[10] Given the lack of a mild and efficient enantioselective synthesis for lasubine II, our immediate objective was to develop a nature-inspired, concise, and highly stereocontrolled synthesis of lasubine II. Notably, despite the simplicity of the biosynthetic route, none of the reported enantioselective syntheses of 4-arylquinolizidine alkaloids have adopted a biosynthetic strategy in the sense that they do not employ Δ^1-piperideine and a β-aryl enone derivative as the starting materials. Thus, we were intrigued by the idea of developing a biomimetic synthesis of the arylquinolizidine core as a one-pot synthesis. Soon, our goal broadened into developing not just a biomimetic enantioselective synthesis of representative 4-arylquinolizidine alkaloids, but also advanced intermediates leading to the macrolactone family of *Lythraceae* alkaloids, and advanced intermediates for arylindolizidines with antinociceptive properties.

We reasoned that substituted piperidines similar to **16** (Figure 2.2) could probably be prepared by a biomimetic reaction of Δ^1-piperideine (**11**) with aryl enones. Only a few studies have examined the utility of Δ^1-piperideine in Mannich reactions with either acetone[11a] or functionalized nitroalkanes.[11b] Similarly, although reactions of enones with dihydro-*β*-

carbolines are known,[11c,d] organocatalytic reactions of enones and Δ^1-piperideine have not been reported. Accordingly, our synthetic approach involves an enamine/iminium ion mediated organocatalytic Mannich/aza-Michael strategy that relies on readily available β-aryl enones **17** and Δ^1-piperideine (**11**) as the key components (Figure 2.3).

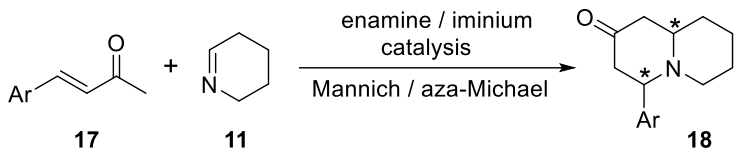


Figure 2.3 Our enamine/iminium ion mediated organocatalytic Mannich/aza-Michael strategy

Since the primary objective of the present study was to develop a succinct, enantioselective protocol for synthesizing suitable 4-arylquinolizidine skeletons which can further be transformed into *Lythraceae* alkaloids, it was informative to survey previous reports on the synthesis of 4-arylindolizidinones and to calculate the number of synthetic steps required and the overall yields of the reported syntheses. Specifically, a brief survey of the shortest known syntheses of the 4-arylquinolizidinones that have been employed as advanced intermediates in the synthesis of lasubine II (**2**), dihydrolyfoline (**6**), lythrine (**5**), abresoline (**4**), and decalin (**8**) is provided in the following section.

2.3 Previous Work

The 4-arylquinolizidine alkaloids have previously been synthesised using different methodologies but a common theme in all these syntheses[12-16] is the multistep construction of a suitable 4-arylquinolizidin-2-one **16** (Figure 2.4) as the key starting material followed by reduction to the corresponding 4-aryl-2-hydroxyquinolizidine **19** (Figure 2.4). Synthesis of the macrolactone-containing target **20** was then achieved by linking the 4-aryl substituent and the

hydroxy group with the appropriate carboxylic acid that was either directly incorporated or was constructed in the ring-closing step (Figure 2.4).

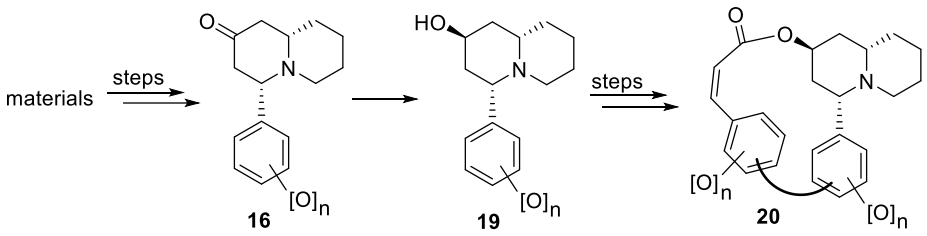
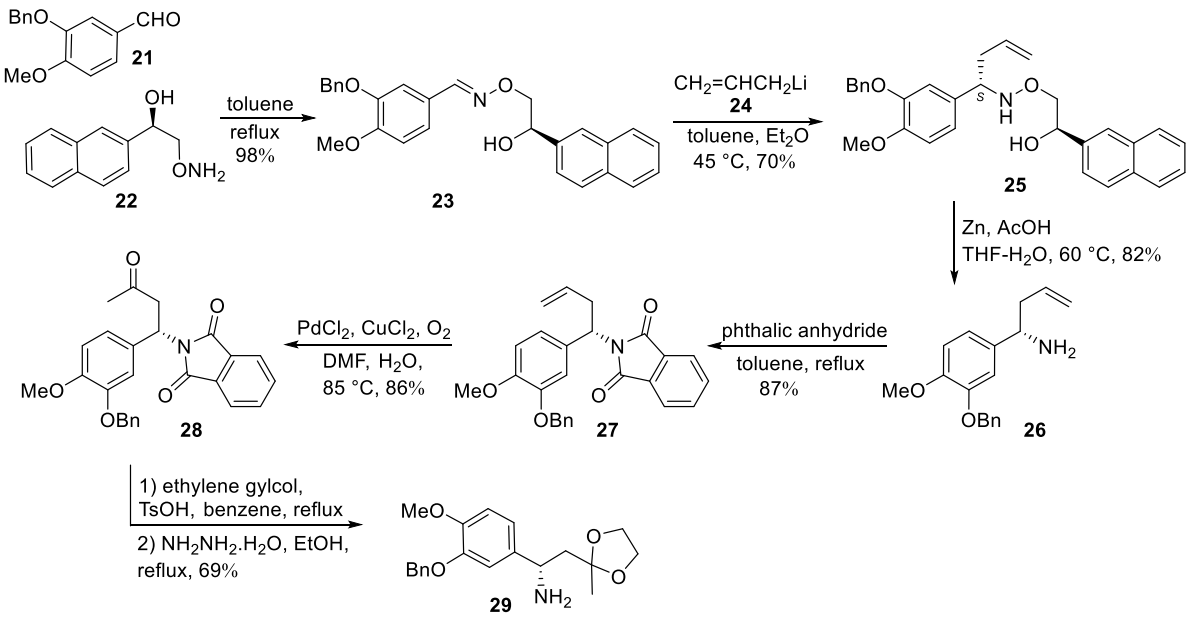


Figure 2.4 Multi-step synthesis of the advanced *Lythraceae* alkaloids

In the following subsections, the shortest reported [12,13,15,21a,21e] syntheses of 4-arylquinolizidinone cores is discussed.

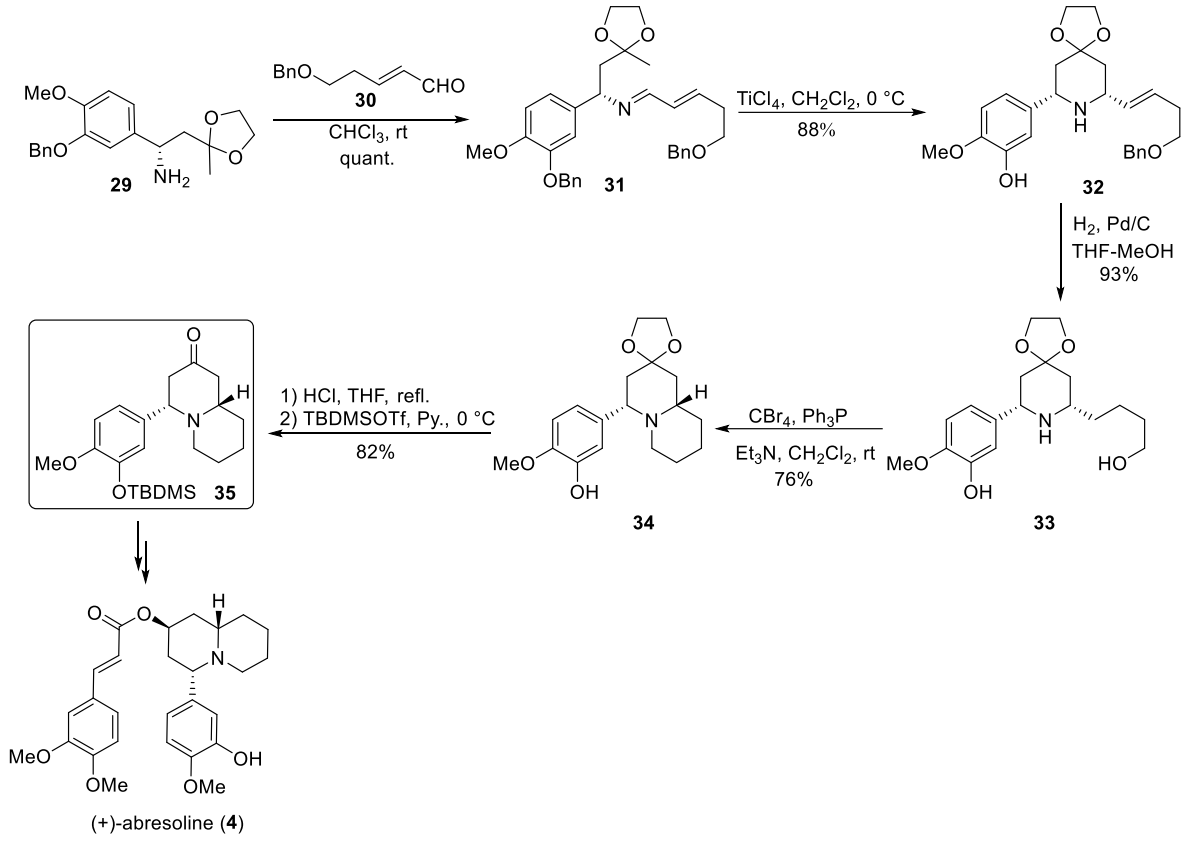
2.3.1 Kibayashi's[12] total synthesis of (+)-abresoline

Kibayashi's route to (+)-abresoline starts with the condensation of *O*-benzylisovanilline (**21**) with (*R*)-1-(2-naphthyl) aminooxy ethanol (**22**) to provide the oxime ether **23** in 98% yield. Treatment of the ether with allyllithium (**24**) at 45 ^{o}C afforded the (*S*)-adduct **25** as the major diastereomer in a 4:1 ratio and 70% combined yield. The chiral auxiliary was removed by the reductive N-O bond cleavage with zinc and acetic acid to give the (*S*)-homoallylic amine **26** in 82% yield. After protection of the amino group as the phthalimide, Wacker oxidation of the terminal alkene **27** proceeded with 86% yield to give the methyl ketone **28**, which was then converted to the ketal amine **29** by acetalization followed by phthalimide cleavage in 69% yield.



Scheme 2.01

Condensation of the amine **29** with 5-benzyloxypent-2-enal (**30**) provided the imine **31** in quantitative yield (Scheme 2.02). Treatment of **31** with $TiCl_4$ in dichloromethane at 0 ^oC gave the intramolecular Mannich-type cyclisation product, the *cis*-2,6-disubstituted piperidine **32** as a single isomer in 88% yield. Catalytic hydrogenation of the alkene in **32** proceeded with simultaneous cleavage of the benzyl ether to provide the amino alcohol **33** in 93% yield. This was followed by CBr_4/PPh_3-induced cyclodehydration to afford the *trans*-4-arylquinolizidine **34** in 76% yield. The deprotection of the ketal and silylation of the phenol provided the desired quinolizidin-2-one **35** in 82% yield. This intermediate was converted to (+)-abresoline (4) in 3 more steps. Thus, Kibayashi's 2005 work on the asymmetric synthesis of (+)-abresoline reported the construction of intermediate quinolizidin-2-one (**35**) in 12 steps with an overall yield of 14.8%.

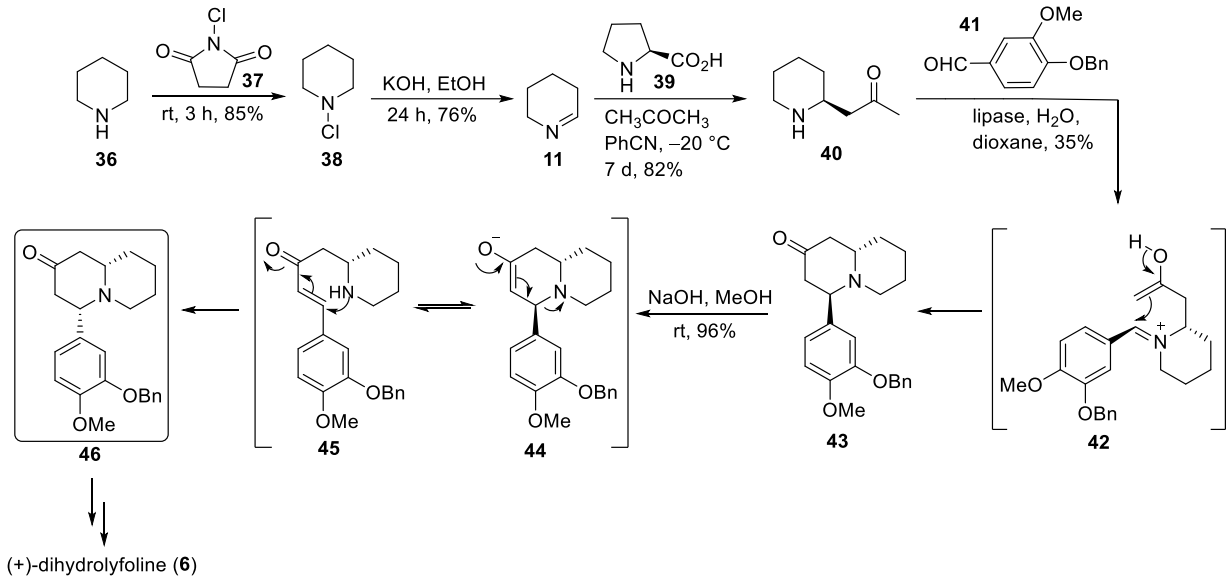


Scheme 2.02

2.3.2 She's[13] total synthesis of (+)-dihydrolyfoline

The She synthesis of (+)-dihydrolyfoline (**6**) involves the use of 4-arylquinolizidinone **46** (Scheme 2.03) as the key intermediate that was incorporated into the target alkaloid. Lipase (a class of hydrolase enzymes) catalysed the formation of iminium ion intermediate **42** in the reaction of (+)-pelletierine (**40**) and aldehyde **41** under optimal conditions which led to a subsequent intramolecular Mannich reaction to afford quinolizidin-2-one **43** as the only product in 35% yield. (+)-Pelletierine (**40**, 87% ee), used for the key reaction, was obtained from piperidine **36** in 3 steps and in overall 44% yield according to the procedure reported by Bella.[11a] The quinolizidin-2-one **43** had to be isomerised to **46** (96% yield) by employing a base-induced (NaOH/MeOH, rt, 72 h) retro-aza-Michael/intramolecular aza-Michael addition protocol, and **46** was subsequently converted to (+)-dihydrolyfoline (**6**) in four steps.

In this synthesis, the key intermediate **46** was obtained from piperidine in 5 steps with 14.7% overall yield.

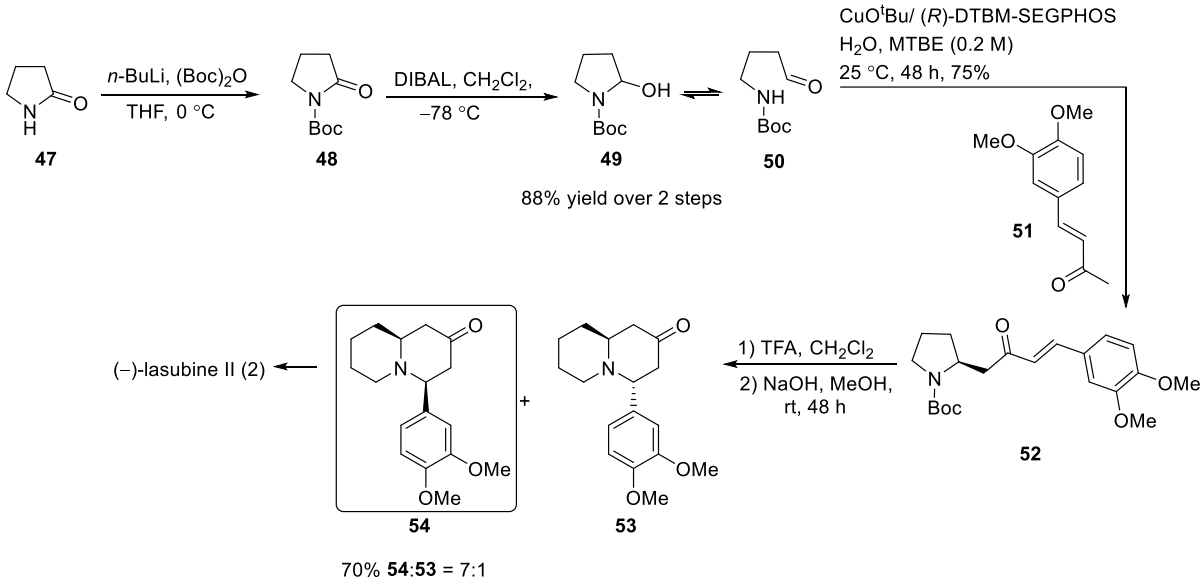


Scheme 2.03

2.3.3 Kanai's formal synthesis of (−)-lasubine II[21e]

Kanai's formal synthesis of (−)-lasubine II begins with the pyrrolidone **47**[17] which is converted into the cyclic hemiaminal **49** in 2 steps (88% yield). Reaction of **49** and the enone **51** using a chiral copper (I) catalyst provided **52** (75% yield, 97% ee). The formation of **52** proceeds via a one-pot three step aldol/dehydration/aza-Michael reaction pathway. Removal of the Boc protecting group in **52** (TFA in dichloromethane) followed by base catalysed cyclization of the secondary amine product provided a mixture of diastereomers **53** and **54**. Notably, the relative amounts of **53** and **54** depend on the choice of base that is employed for the cyclization step. Using NaOH in MeOH for this transformation, **54** was obtained as the major isomer in 61% yield and 92% ee. Stereoselective reduction of the ketone **54** could afford (−)-lasubine II (**2**).

Thus, Kanai's synthesis of the quinolizidin-2-one **54** employed a total of 5 steps with an overall 40% yield for the reaction sequence. This intermediate could be converted in one step to (−)-lasubine II.

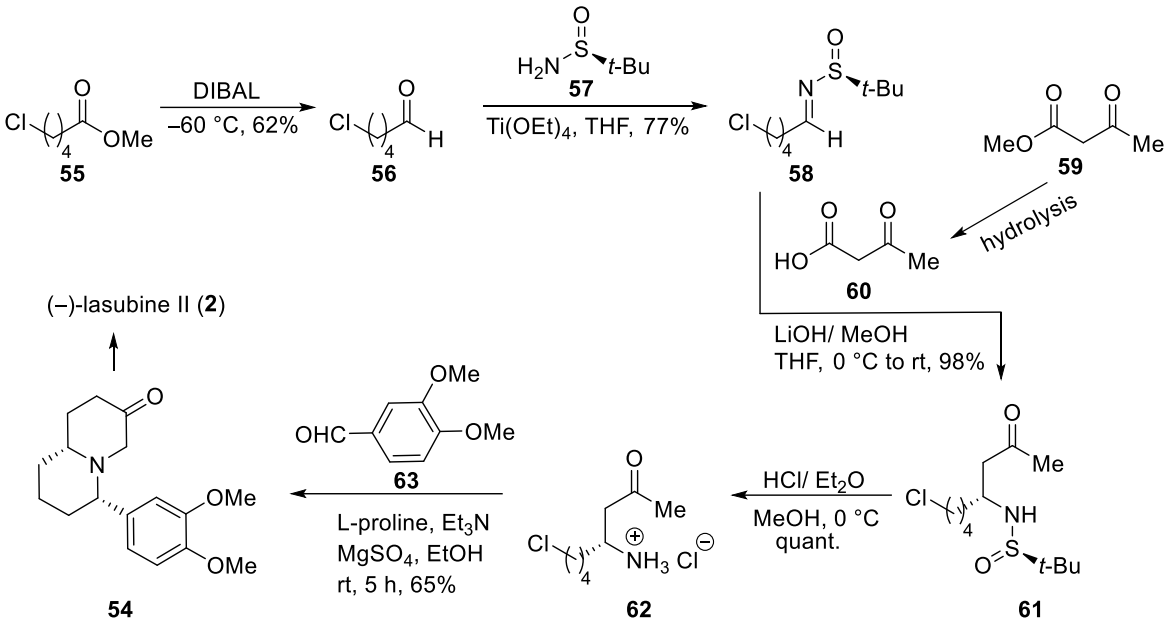


Scheme 2.04

2.3.4 Foubelo's total synthesis of (−)-lasubine II[21a]

In 2019, Foubelo reported the total synthesis of (−)-lasubine II (**2**) using a decarboxylative Mannich reaction followed by an intramolecular Mannich condensation/*N*-alkylation reaction sequence employing chiral starting materials. The chiral *N*-*tert*-butylsulfinyl imine[18] **58** was obtained in 77% yield by the condensation of the aldehyde **56** (obtained by the DIBAL reduction of methyl-5-chloropentanoate **55**) with (*R*)-*tert*-butanesulfinamide **57** in the presence of titanium tetraethoxide. The decarboxylative Mannich reaction of **58** with *β*-ketoacid **60** (obtained by LiOH/MeOH hydrolysis of the ester **59**) provided **61** in 98% yield with 95:5 dr. Removal of the *tert*-butylsulfinyl group using acidic conditions followed by the (*S*)-proline catalysed condensation of the amine hydrochloride **62** with veratraldehyde **63** afforded the quinolizidin-2-one **54** (via a Mannich and concomitant

intramolecular *N*-alkylation reaction) in 65% yield with 95:5 er. Later, **54** was stereo-selectively reduced with L-selectride® to give (−)-lasubine II in 70% yield.



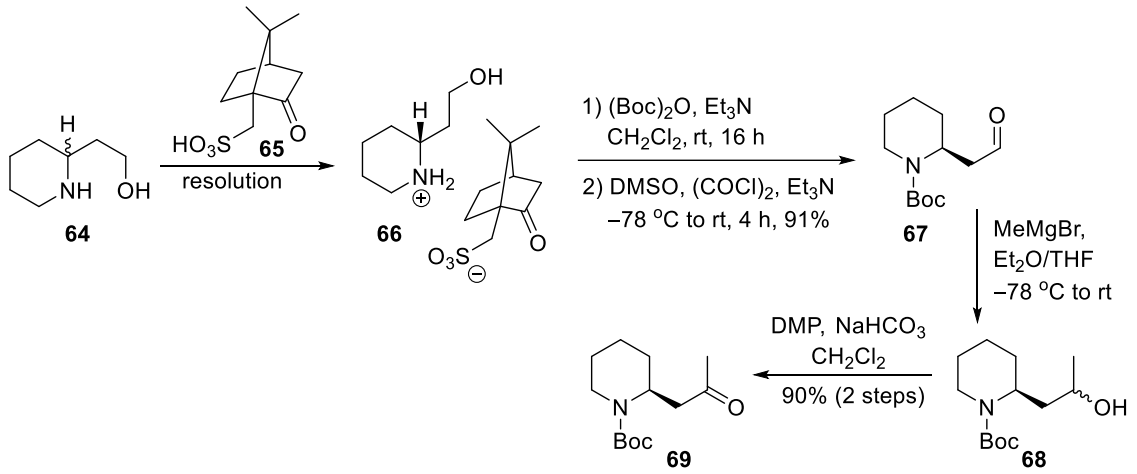
Scheme 2.05

Thus, Foubelo's work provided the desired quinolizidin-2-one **54** in 6 steps from commercially available materials (methyl-5-chloropentanoate **55** and the *β*-ketoester **59**) in an overall yield of 30%.

2.3.5 Kündig's total synthesis of (+)-lythrine[15]

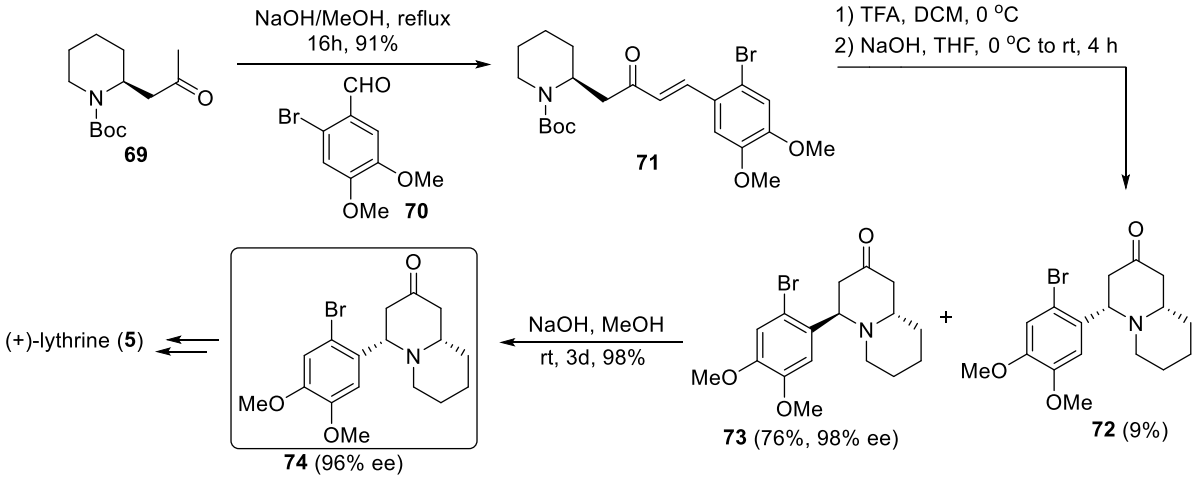
Kündig's approach to (+)-lythrine (**5**, Scheme 2.07) involved the synthesis of quinolizidin-2-one (**74**, Scheme 2.07) as a key intermediate and its multi-step conversion into (+)-lythrine. The key starting material in this synthesis is enantioenriched *N*-Boc pelletierine (**69**) which was synthesized using Hou's resolution protocol.[19] Racemic 2-piperidineethanol (**64**) was resolved using (*R*)-10-camphorsulfonic (**65**) acid to obtain the salt of (*S*)-(**66**). Neutralization of the salt, protection of the free amino alcohol as a carbamate and Swern oxidation of the alcohol provided the aldehyde **67**. Reaction of **67** with a methyl Grignard

reagent gave the secondary alcohol **68** which was oxidised using DMP to obtain the desired *N*-Boc-protected piperidine **69** in 90% yield over 2 steps.



Scheme 2.06

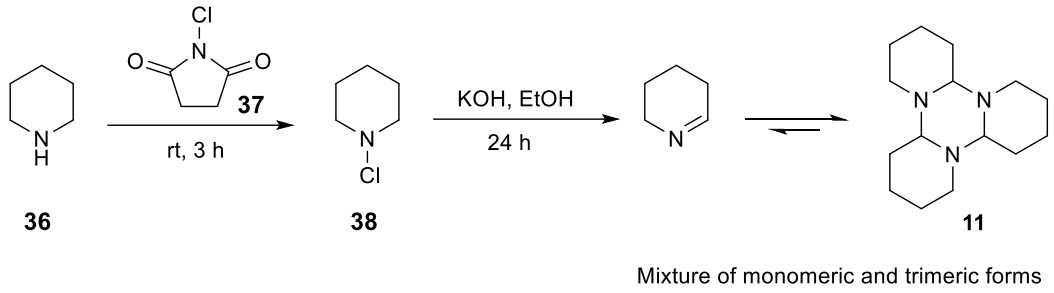
Aldol condensation of **69** and 6-bromoveratraldehyde (**70**) afforded the *β*-aminoketone **71** in 91% yield. Deprotection of **71** with TFA and cyclisation under basic conditions provided a diastereomeric mixture of quinolizidin-2-ones **72** and **73** in a 1:8 ratio. Chromatographic separation of **73** and subsequent isomerization using NaOH in methanol at rt for 3 days provided **74** in 98% yield. Thus, the quinolizidin-2-one **74** in Kündig's work was obtained in overall 28% yield over 9 steps from **64** as the starting material.



Scheme 2.07

2.4 Results and Discussion

Our studies began with the investigation of an organocatalytic Mannich/aza-Michael reaction of β-aryl enones with Δ^1-piperideine as hypothesised in Figure 2.3. For this, the Δ^1-piperideine **11** was synthesised using Bella's reported[11a] procedure (Scheme 2.08) which involves *N*-chlorination of piperidine (**36**) followed by treatment of the product *N*-chloropiperidine **38** with base. Notably, although Δ^1-piperideine is easily prepared[11] from piperidine, it can be isolated only as the minor component in a mixture with tripiperideine since it trimerizes spontaneously. However, as shown by Bella,[11a] this trimer is a convenient source of Δ^1-piperideine which is generated by dissociation in solution (Scheme 2.08).

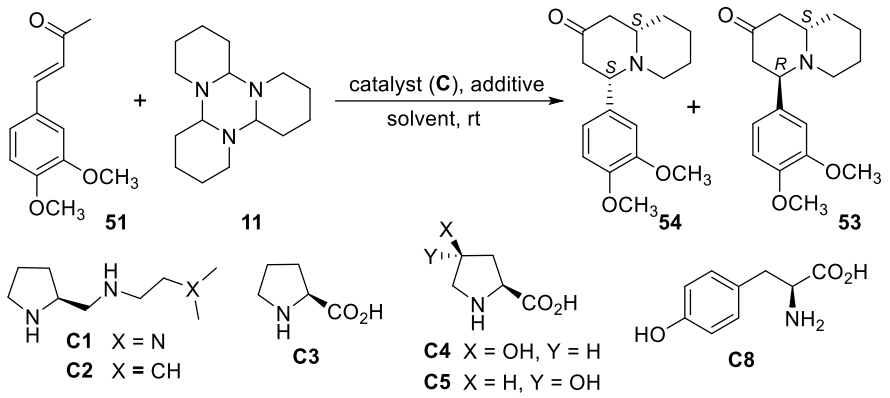


Scheme 2.08

2.4.1 Synthesis of 4-aryl quinolizidinones as intermediates for 4-aryl quinolizidine alkaloids

For the synthesis of the 4-arylquinolizidinone leading to (-)-lasubine II, we chose 3,4-dimethoxybenzylidene acetone (**51**) as the enone (commercially available, bench stable) and a selection of enamine-forming amines, the pyrrolidine-based secondary amines **C1**−**C5** and (*S*)-tyrosine (**C8**) for exploratory reactions with tripiperideine **11** (as a source of Δ^1-piperideine). The results of these studies are summarized in Table 2.1.

Table 2.1 Reaction of 3, 4- dimethoxy benzylidene acetone (**51**) with Δ^1-piperideine (**11**)



Entry	Catalyst[a]	Acid[b]	Solvent	Time (h)	Yield	dr	%ee (54)[c]
1	C1	-	DMF	96	22	≥99/1	19
2		TsOH	DMF	24	22	≥99/1	8
3		TsOH	DMF	48	26	≥99/1	7
4	C2	-	DMF	120	9	0.6:1	20
5		TsOH	DMF	120	24	≥99/1	27
6	C3	TsOH	DMF	96	7	≥99/1	96
7		-	DMF	43	35	≥99/1	96
8		-	DMF	96	54	≥99/1	96
9		-	DMF	144	60	≥99/1	96
10		-	MeOH	144	15	≥99/1	82
11		-	CH_3CN	144	22	2.6/1	>99
12		-	DMSO	144	58	≥99/1	96
13		-	CH_2Cl_2	144	14	1/0.4	97
14		-	$CHCl_3$	144	31	0.7/1	96
15		-	THF	144	-	-	-

16		-	Toluene	144	-	-	-
17	C4	-	DMF	48	2	-	-
18		TsOH	DMF	96	7	≥99/1	-
19	C5	-	DMF	48	-	-	-
20		TsOH	DMF	96	7	≥99/1	-
21	C6	-	DMF	48	-	-	-
22		TsOH	DMF	96	10	≥99/1	-

[a]20 mol%, [b]20 mol%, [c]chiral phase HPLC analysis

The proline-derived triamine **C1**[20] and the diamine **C2**[20] were examined first, either with or without the use of an acid co-catalyst. Encouragingly, the 4-aryl quinolizidin-2-one **54** was obtained from these reactions, albeit in low yield (20−26% yield). Notably, neither the diastereomeric 4-aryl quinolizidin-2-one **53** nor the amino enone (product of the Mannich reaction) could be detected in these reactions. The stereochemistry of **53** and **54** was determined by comparison of their ^{1}H NMR data with those reported (Figure 2.5).[21d] The chemical shift and the coupling constants of the C4 hydrogen atoms in **53** and **54** are distinct. These resonances were used as diagnostic features to determine the diastereomer ratios of **53** and **54** in product mixtures obtained in the optimization studies and also for stereochemical assignments of structurally related 4-aryl quinolizidine-2-ones obtained in subsequent substrate-scope studies.

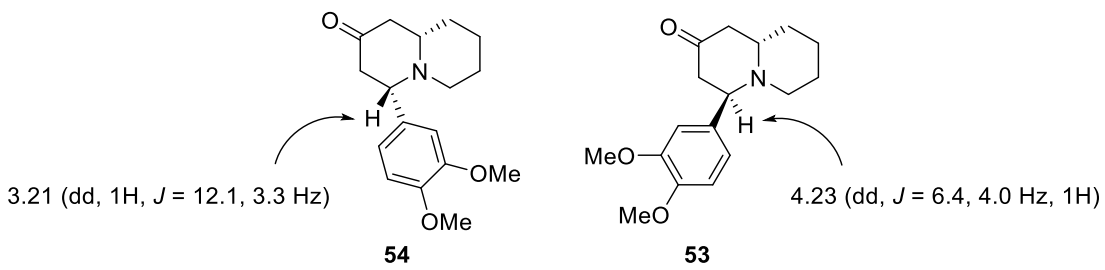


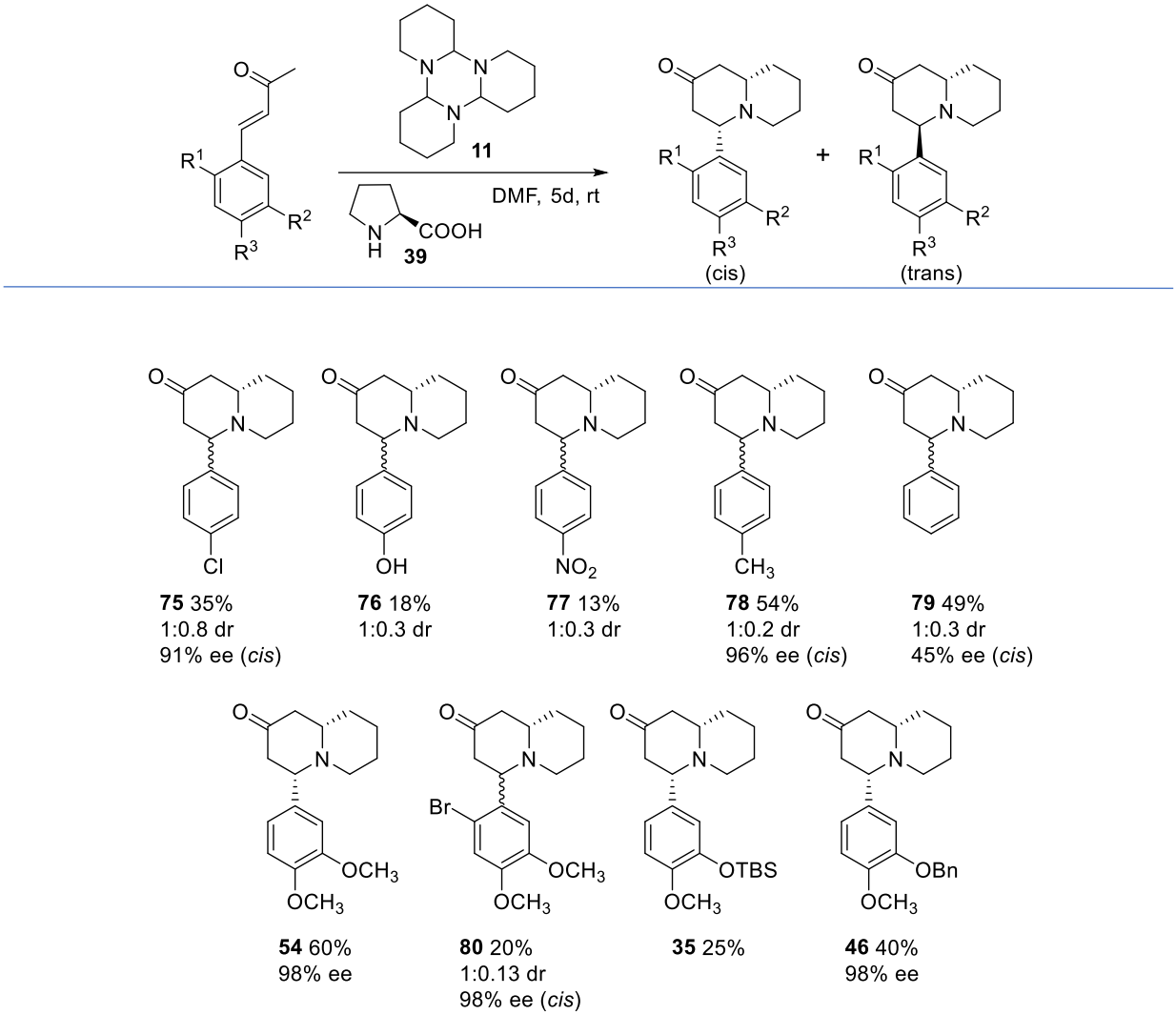
Figure 2.5 Assignment of stereochemistry of **53** and **54** based on reported ^{1}H NMR data[21d]

The absolute configuration of **54** was assigned as (*S*,*S*) by comparison of the sign of its optical rotation (levorotatory) to that reported[21d] for (*S*,*S*)-**54**. This assignment was subsequently confirmed by the optical rotation of (−)-lasubine II that was obtained by the reduction of **54**. The absolute configuration of **53** is based on the assumption that both **53** and **54** are both derived from the β-amino enone obtained from the initial Mannich reaction.

The diamine **C2**, without an acid co-catalyst, provided a mixture of **54** and **53** (54:53 = 0.6:1) in low yield (9%). The use of TsOH as a co-catalyst with **C2** was marginally beneficial, providing only **54** in 24% yield. Interestingly, the use of (*S*)-proline (**C3**) as the catalyst provided the best results (Table 2.1, entry 9), and **54** was obtained in 60% yield as a single diastereomer with 96% ee. Increasing the reaction time beyond 144 h was only marginally beneficial (yield of **54** after 240 h is 63%). Notably, the use of TsOH acid as a co-catalyst with proline was detrimental to the yield of the reaction (Table 2.1, entry 6). Having identified (*S*)-proline as the catalyst of choice in DMF, we conducted a brief solvent survey (Table 2.1, entries 10−16). Except for DMSO, the yield of **54** was adversely affected in all of the other solvents examined. Notably, the enantiomeric excess of **54** was uniformly high (96−99% ee), with methanol being the only exception (82% ee of **54**). However, the diastereoselectivity of the reaction was sensitive to the solvent used, and it was particularly low in acetonitrile, dichloromethane and chloroform (Table 2.1, entries 11, 13, and 14). Since there is no apparent correlation of the diastereoselectivity and the polarity of the solvent (high diastereoselectivity in methanol but low in acetonitrile), the reasons for this trend in diastereoselectivity have not been elucidated at this time. Quinolizidinone **54** was obtained in very low yield when hydroxyprolines **C4** and **C5** or (*S*)-tyrosine (**C8**) were used as catalysts.

To study the substrate scope of the reaction, other *β*-aryl enones were reacted with tripiperideine **11** using (*S*)-proline (**39**) as catalyst under the optimized reaction conditions

described above. These studies revealed that the diastereoselectivity of the reaction depended on the substitution in the aryl portion of the enone (Scheme 2.09).



Scheme 2.09

A plausible mechanism that explains the stereoselectivity of the Mannich-conjugate addition reaction and the sense of asymmetric induction is provided in Figure 2.6. Addition of the enamine **A** derived from proline and the enone to the *re* face of the imine **B** generates the iminium ion **D**. The facial selectivity of this addition is governed by hydrogen bonding of the imine with the carboxylic acid functionality in proline. Intramolecular conjugate addition of the amine to the *si* face of the iminium ion generates the enamine **E** which provides the observed (*S*,*S*) diastereomer **F** of the 4-arylquinolizidinone.

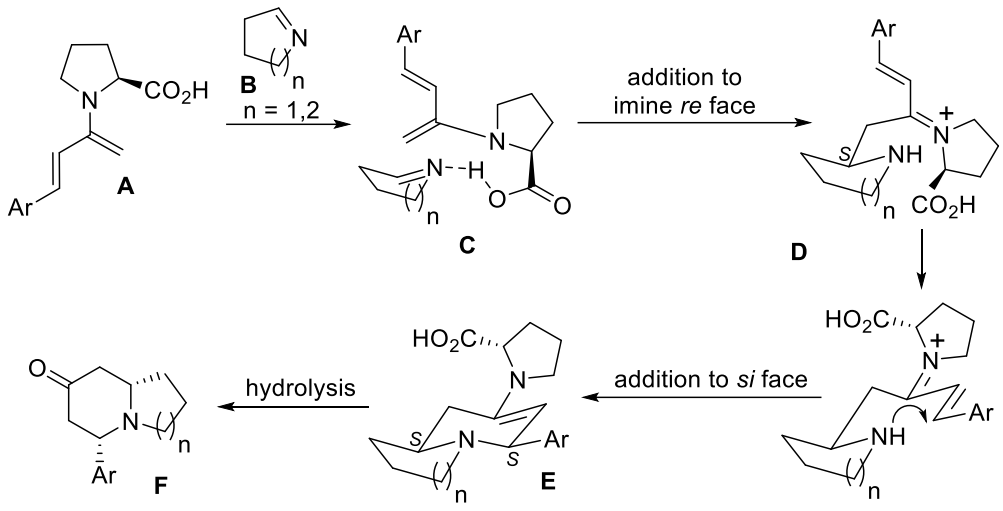


Figure 2.6 Plausible reaction mechanism of the Mannich/aza-Michael reaction

The intramolecular aza-Michael reaction is also a component of other syntheses of 4-arylquinolizidine alkaloids.[21c,d,f,g,22] However, the diastereoselectivity of C−N bond formation in the other syntheses is low (dr for required diastereomer = 1.2:1,[21c] 7:1,[21e] and 0.7:1[21g]). In addition, opposite diastereoselectivity is observed when the aza-Michael reaction is mediated by a bifunctional catalyst (4*S*,9a*R* quinolizidinone is obtained)[22] and when *β*-alkyl enones,[11c,d] and enones with a *β*-aryl group lacking electron-rich substituents[11d] are employed.

While it is likely that formation of the C4 stereocenter in the 4-arylquinolizidinones is thermodynamically controlled, it should be mentioned that the diastereomer **53** was not observed at any time during the reaction of **51** and **11** in DMF under optimized conditions. However, rapid equilibration of **E** and **D** via a retro-aza-Michael process, and the resultant conversion of **53** to **54** under thermodynamic control, cannot be ruled out.

The quinolizidinones **35**, **46**, **54** and **80** were obtained with good diastereomeric excess in favour of the *cis* quinolizidinone, while the quinolizidinones **75-79** provided products with low to moderate diastereomeric ratios. This observation can be explained by resonance stabilisation of the iminium ion **81** formed from the Mannich reaction (Figure 2.7). Presumably, electron donating substituents stabilize a partial positive charge at the benzylic position. This

reduces the reactivity of the iminium ion which in turn increases the selectivity of the aza-Michael addition reaction. The opposite is true for electron-deficient or neutral aryl groups.

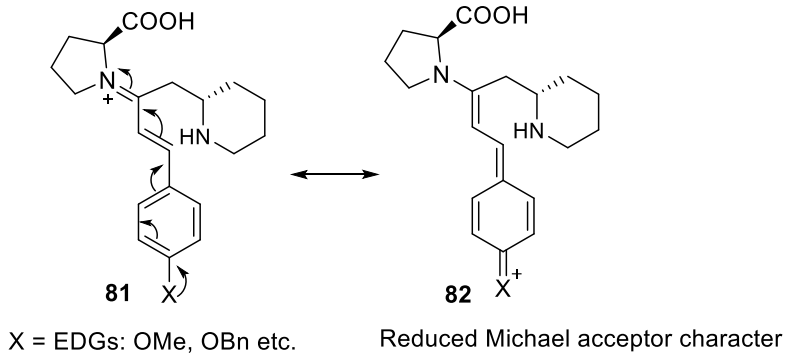
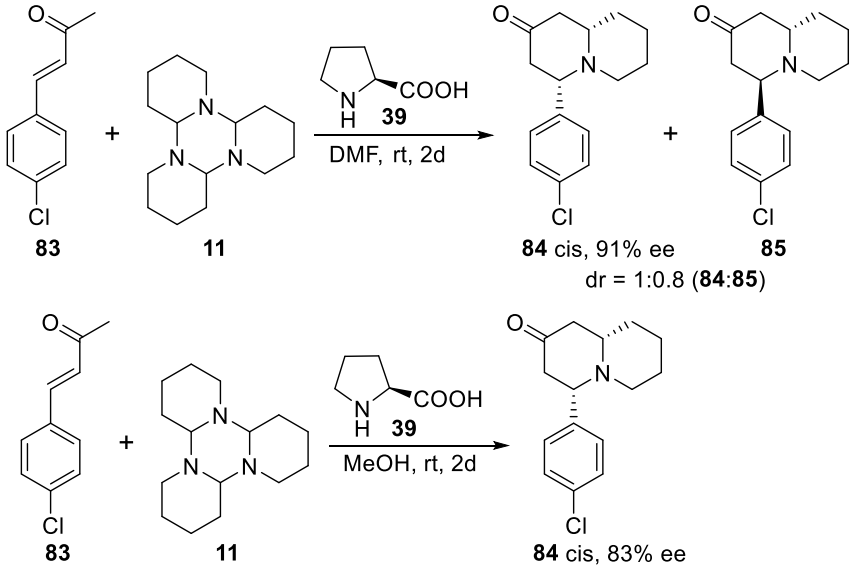


Figure 2.7 Resonance stabilisation in the Mannich reaction intermediate **81**

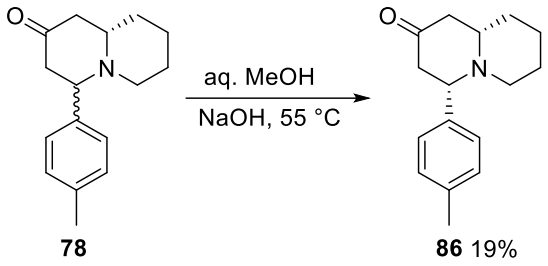
To address the issue of diastereoselectivity, we conducted an experiment to study the effect of the solvent on the diastereoselectivity wherein we switched the optimal solvent, DMF (polar aprotic), to methanol (a polar protic solvent). This resulted in the exclusive formation of the cis isomer but with a decreased enantioselectivity for the reaction (Scheme 2.10).



Scheme 2.10

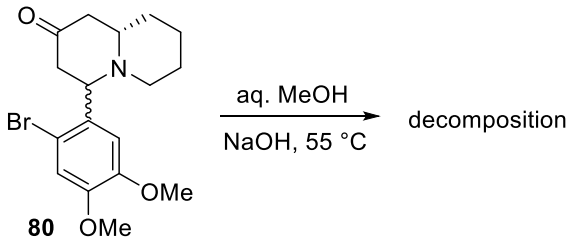
In addition, the possibility of a base-mediated isomerization (see Scheme 2.11) of the *trans* isomer to the *cis* isomer was also examined.[21g,23]

Initially, a solution of **78** (5:1, favouring the cis isomer) in aq. MeOH was stirred at ambient temperature for 6 hours, but no epimerisation at C4 was observed. Later, 1M NaOH was added, and the reaction mixture was heated at 55 ^{o}C overnight. This resulted in conversion of **78** to the *cis* isomer **86**, but in low yield (19%, Scheme 2.11).



Scheme 2.11

A solution of **80** in methanol (5:1, favouring the *cis* isomer) was also treated with aqueous NaOH (2M) at ambient temperature for 7 h, but no change in diastereomeric composition was observed by ^{1}H NMR. The reaction mixture was then heated but, unfortunately, this resulted in complete decomposition of **80**.



Scheme 2.12

Considering the low diastereoselectivity for enones lacking electron-rich aryl groups and the observation that the stereochemistry of the major product (4-aryl quinolizidinone **54**) is (4*S*, 9a*S*), it is likely that the reaction of *β*-aryl enones and piperideine, under our optimized conditions, proceeds via a stepwise Mannich/aza-Michael reaction and not via a concerted [4+2] reaction pathway (aza-Diels Alder reaction) since the latter should provide the diastereomeric (4*R*, 9a*S*) quinolizidinone **I** or its enantiomer (Figure 2.8) as the major product.

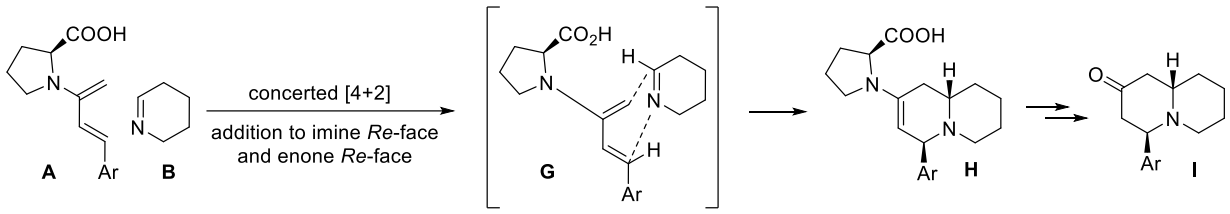
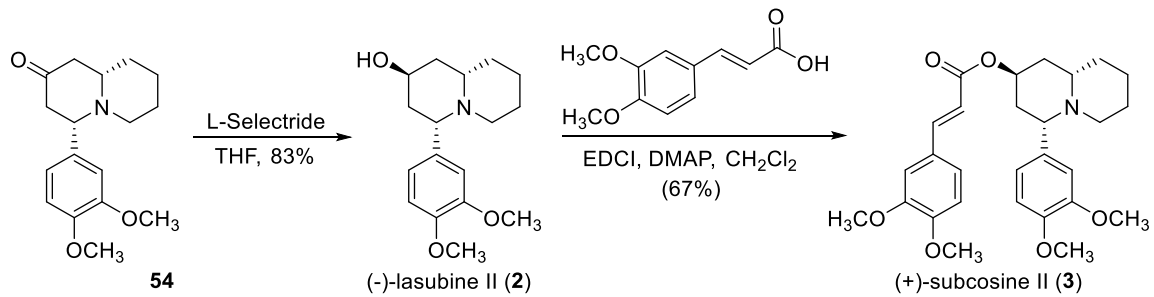


Figure 2.8 Predicted stereochemistry for the aza-Diels Alder reaction pathway

It may be noted that (*S*,*S*)-**54** obtained in our studies is a direct precursor of the naturally occurring alkaloid (−)-lasubine II (**2**, Figure 2.1).[21] Thus, the stereoselective reduction of **54** provides (−)-lasubine II (**2**, 83%), and subsequent acylation of **2** with 3,4-dimethoxycinnamic acid generates (+)-subcosine II (**3**, 67%, Scheme 2.13).[24] To the best of our knowledge, these are the shortest reported syntheses of (**2**) (three steps) and (**3**) (four steps) from commercially available starting materials.



Scheme 2.13

As noted previously, several other alkaloids share the 4-aryl quinolizidine unit present in **1** and **2** (Figure 2.1). Examples of such alkaloids include **4**, a structural variant of **2**, and also the alkaloids **5**−**8** (Figure 2.1) that incorporate a macrolactone moiety. Over the years, the synthesis of these alkaloids has also been extensively investigated.

Clearly, syntheses of **5**−**8** that rely on a 4-arylindolizidin-2-one would benefit from a concise enantioselective synthesis of this starting material. The present synthesis of **54** is relevant in this context. Figure 2.9 shows key 4-aryl quinolizidinones and the alkaloids that have been synthesized from them.

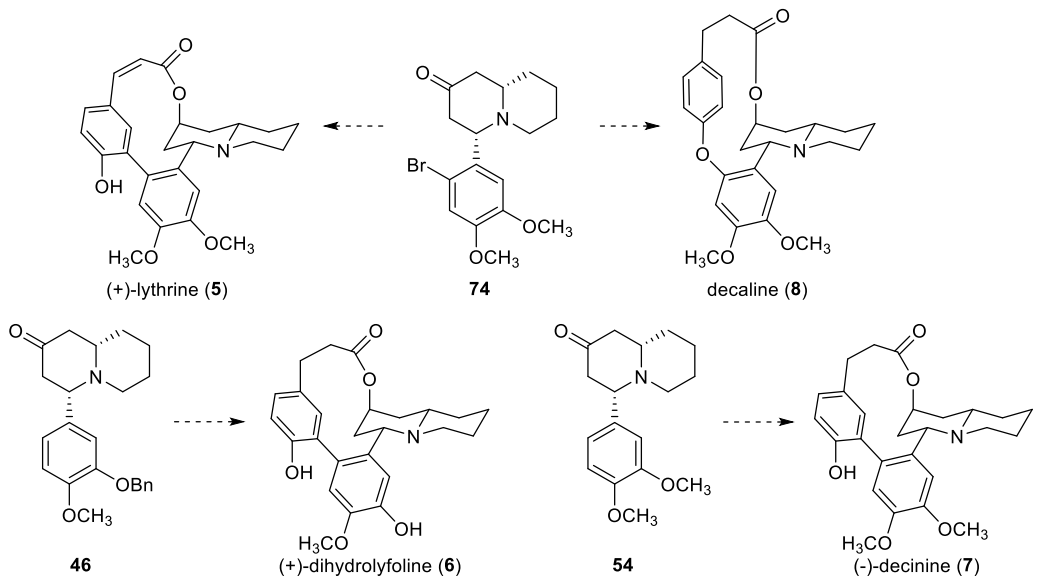
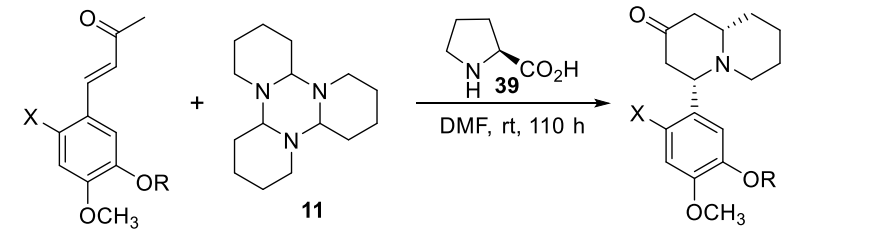


Figure 2.9 Quinolizidinones **74**, **46** and **54** as advanced intermediates for other *Lythraceae* alkaloids

We reasoned that the choice of a suitable enone in our Mannich/aza-Michael protocol would enable single step syntheses of advanced intermediates to the *Lythraceae* alkaloids **5**–**8**. Accordingly, the reaction of enones **87**, **88**, and **89** with **11**, under the reaction conditions optimized for **54**, provided the 4-arylquinolizidinones **1** (40%, 85% ee), **46** (40%, 98% ee), and **74** (32%, 98% ee), respectively (Scheme 2.14). The stereochemistry of **1**, **46**, and **74** is assigned by analogy to **54**.

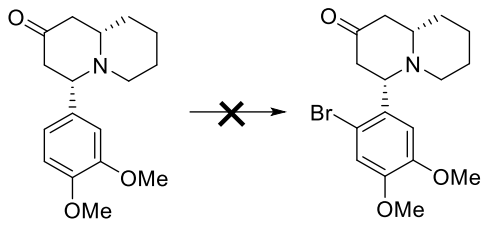


Scheme 2.14

In an attempt to improve the overall yield of the quinolizidinone **74**, we also investigated the direct bromination and the iodination of the activated aryl ring in **54**. The

results of these studies are provided in Table 2.2. Unfortunately, none of the reactions provided the desired bromo- or iodoaryl products.

Table 2.2 Attempted late-stage bromination or iodination of **54**



54 **74**

Entry	Reaction Conditions	Observation
1.	*N*-Iodosuccinimide (1.1eq), TFA (0.3eq), CH_3CN, rt to reflux overnight[25]	Decomposition; some starting material recovered
2.	Iodine (1.5 eq), Hg $(OAc)_2$ (1.5 eq), DCM, rt to reflux overnight	Decomposition; some starting material recovered
3.	KI (1.2 eq), oxone (1.2 eq), MeOH, rt[26]	Starting material recovered
4.	In $(OTf)_3$ (0.5 eq), ICl (1 eq), DCM, rt[27]	Starting material recovered
5.	48% HBr soln. (2.1 eq), DMSO (1.1 eq) K_2CO_3, EtOAc, 60 ^oC[28]	Complex reaction mixture, required product not obtained
6.	NH_4I (1.2 eq), DMSO (3 eq), H_2SO_4 (1.5 eq), EtOAc, 60 ^oC	Starting material recovered
7.	48% HBr (2.1 eq), DMSO (1.1 eq), EtOAc	Starting material recovered

The synthesis of quinolizidinone **35** which is a known advanced intermediate[12] in Kibayashi's total synthesis of (+)-abresoline (shown in Figure 2.10) was also investigated.

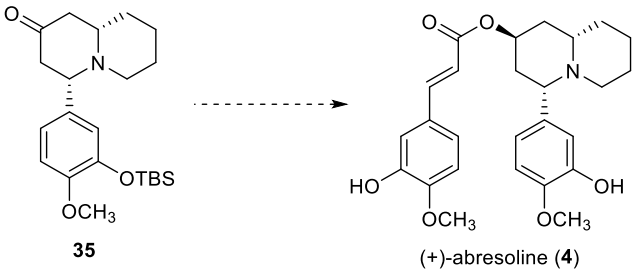
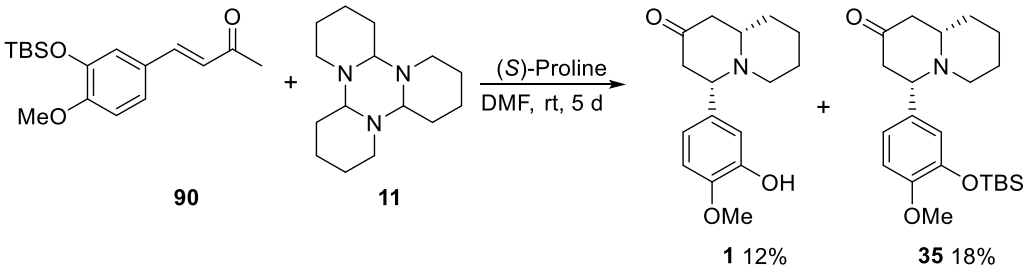


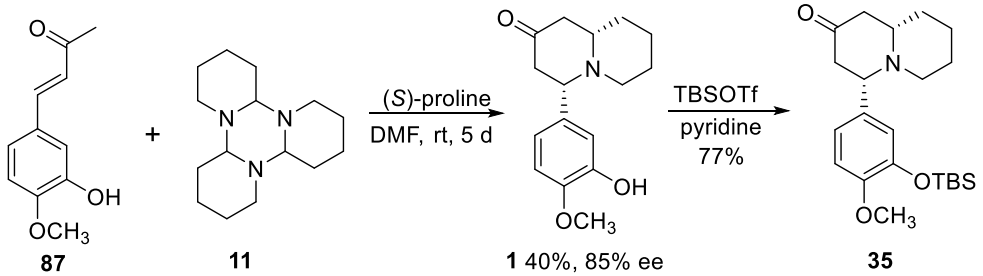
Figure 2.10 Quinolizidinone **35** as advanced intermediate for (+)-abresoline

Under our optimised Mannich/aza-Michael reaction conditions, the enone **90** provided a mixture of the required, diastereomerically pure, 4-aryl quinolizidinone **35** and the quinolizidinone **1** which is presumably obtained by the desilylation of **35** or **90** under the reaction conditions shown below (Scheme 2.15). The use of DMSO as the solvent instead of DMF was not beneficial and the yield of **35** as well as **1** remained unaffected.



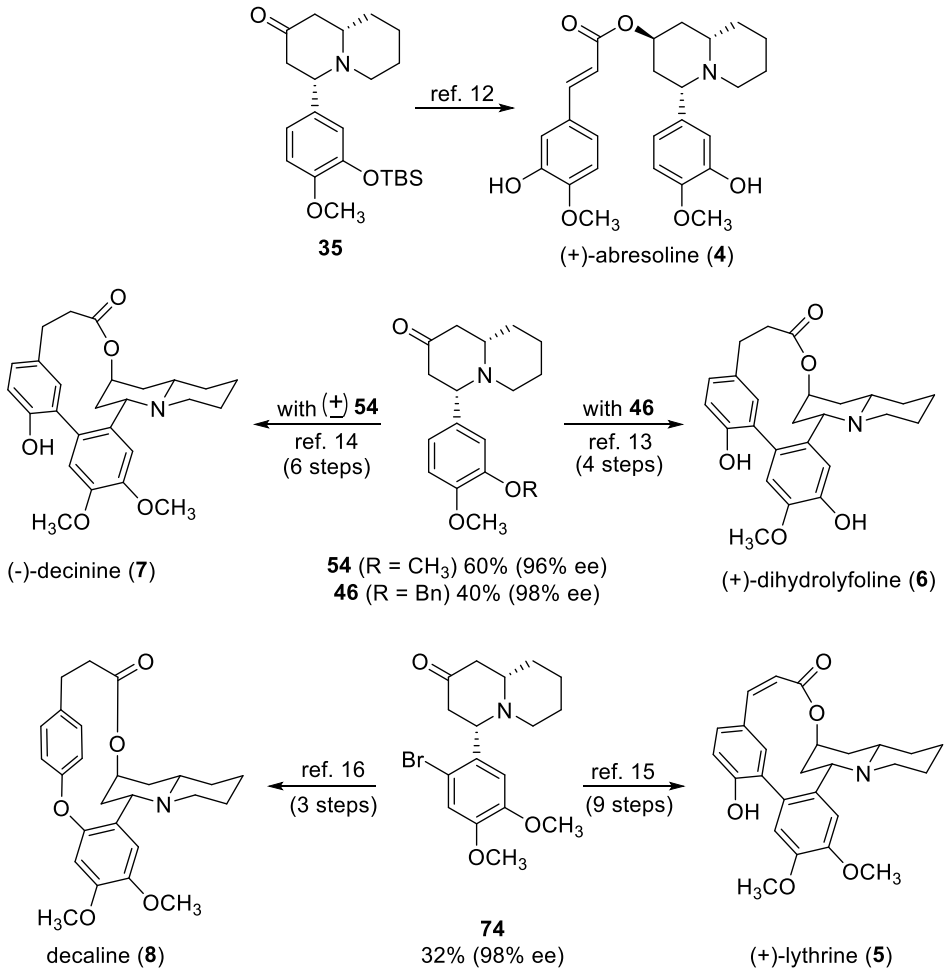
Scheme 2.15

Alternatively, quinolizidinone **35** could be obtained more efficiently by the reaction of enone **87** and compound **11** under optimised reaction conditions and the subsequent silylation of **1** (77%, Scheme 2.16).



Scheme 2.16

As noted previously, the conversion of **35** to (+)-abresoline (**4**),[12] **46** to (+)-dihydrolyfoline (**6**),[13] **54** to (−)-decinine (**7**, via **2**),[14] and **74** to lythrine (**5**)[15] and decalin (**8**)[16] has been reported (Scheme 2.17).



Scheme 2.17

The present one-step syntheses of **54**, **46**, and **74** and the two-step synthesis of **35** compare favorably with the overall yields of the shortest multistep syntheses of these quinolizidinones reported to date (**54**: five steps from 2-pyrrolidone, 40% overall,[21e] or five steps from methyl 5-chloropenanoate, 30% overall;[21a] **46**: five steps from piperidine, 15% overall;[13] **74**: six steps from piperidine, 2% overall;[15] **35**: twelve steps from 3-(benzyloxy)-4-methoxybenzaldehyde, 15% overall[12]). These results have also been tabulated below (Table 2.3).

Table 2.3 Comparison of our syntheses of **35**, **46, 54** and **74** with previous reports

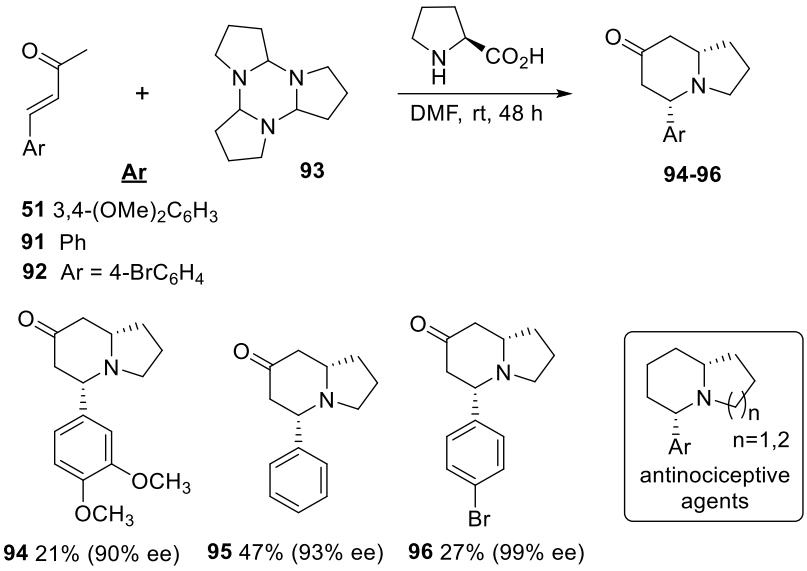
Entry	Quinolizidinone	Previous reports			Present work	
		Reference	No. of steps	Overall yield (%)	No. of steps	Overall yield (%)
1.	**54**	Kanai[21e]	5	40	1	60
2.		Foubelo[21a]	5	30		
4.	**74**	Kundig[15]	6	2	3	26
5.	**46**	She[13]	5	15	3	23
6.	**35**	Kibayashi[12]	12	15	3	30

In addition, with the exception of **35**, the reported syntheses require separation of the undesired diastereomeric 4-arylquinolizidin-2-one products that are invariably obtained and their subsequent isomerization to the diastereomers that are required for the natural product targets. Thus, the synthesis of 4-aryl quinolizidinones **35**, **46**, **54** and **74** developed in the present studies offers a shorter and a more efficient synthetic route to several 4-aryl quinolizidine alkaloids.

2.4.2 Synthesis of 5-aryl indolizidinones as intermediates to 5-aryl indolizidine alkaloids

We also examined the possibility of applying the above methodology to the synthesis of arylindolizidinones. Preliminary results of these studies are promising. The reaction of 1-pyrroline[29] with selected enones, under the reaction conditions optimized for Δ^1-piperideine, provided 5-arylindolizidin-7-ones[30] with good enantioselectivity (Scheme 2.18), but with low yields. The reasons for the low yields observed in these reactions are not clear at this time. It is noteworthy that 5-aryl indolizidines and 4-arylquinolizidines, which can be easily obtained

by reduction of the corresponding 5-aryl indolizidinones and 4-aryl quinolizidinones,[31] are of interest as nonopiate antinociceptive agents.[31]



Scheme 2.18

2.4.3 Preliminary studies on the synthesis of 3-aryl quinolizidin-2-ones as intermediates to phenanthroquinolizidine alkaloids

Phenanthroquinolizidine alkaloids possess a pentacyclic structure in which a phenanthrene ring is fused to a quinolizidine ring. These alkaloids display a wide variety of biological activities, including antitumor, antiamoebic, and antifungal activities.[32] Despite the biological relevance of these alkaloids, there are only a small number[33] of synthetic approaches developed so far for their synthesis. Thus, there is a need for an efficient approach for the synthesis of target phenanthroquinolizidine alkaloids, a few examples of which are shown in Figure 2.11.

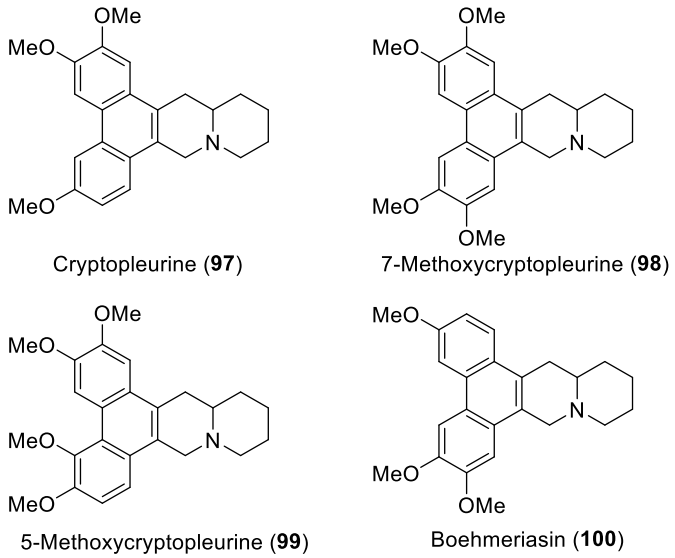


Figure 2.11 Examples of phenanthroquinolizidine alkaloids

Previous studies[33e] in the Pansare group had established that 3-aryl quinolizidin-2-ones such as **101** (Figure 2.12) can provide access to secophenanthroquinolizidine alkaloids (**102,** Figure 2.12) which, upon oxidative cyclisation, yield phenanthroquinolizidines **103** (Figure 2.12).

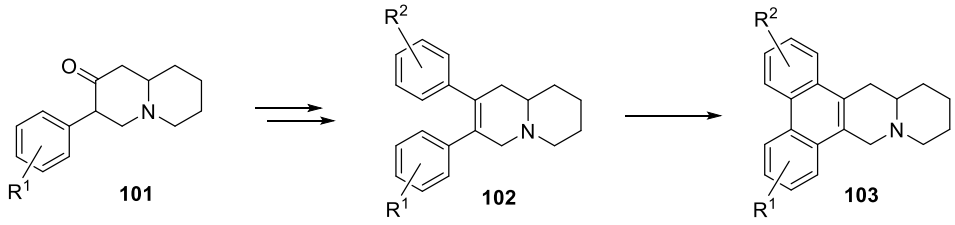


Figure 2.12 Synthesis of phenanthroquinolizidines from 3-aryl quinolizidin-2-ones

As part of our ongoing studies on improving the synthesis of 3-aryl quinolidin-2-ones, such as **101**, we hypothesised that an enamine/iminium ion mediated organocatalytic Mannich/aza-Michael reaction between α-methylene ketones **104** and Δ^1-piperideine (**11**) could provide enantioselective access to the target 3-aryl quinolizidinone framework (Figure 2.13).

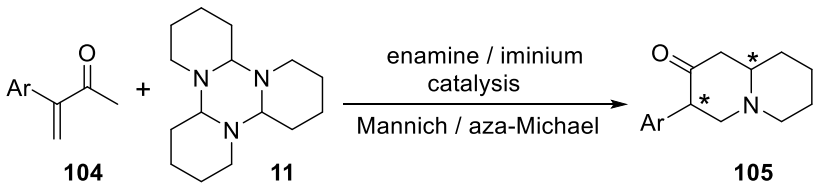
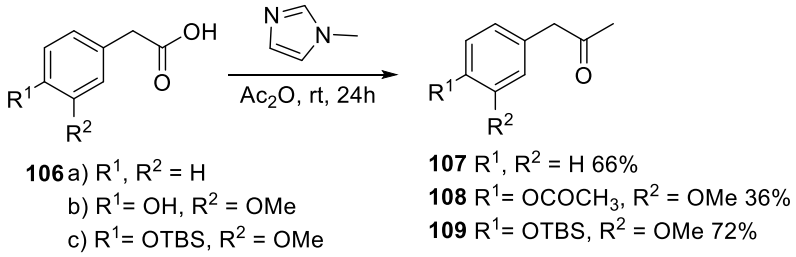


Figure 2.13 Our enamine/iminium ion mediated organocatalytic Mannich/aza-Michael strategy

The α-methylene ketones used for these studies were synthesised from the corresponding ketones which were either commercially available or were prepared from arylacetic acids using the less commonly known Dakin West reaction[34] (Scheme 2.19). The required carboxylic acids **106**a-c were prepared using a reported procedure.[35] Following the reported procedure, the arylacetic acids were treated with acetic anhydride and *N*-methyl imidazole at ambient temperature to provide the required 3-aryl propanones. Heating had a detrimental effect on the yield of the reaction and a free hydroxyl group in the aryl ring also reduced the yield of the required product (36% for **108** compared to 72% for **109**, Scheme 2.19).

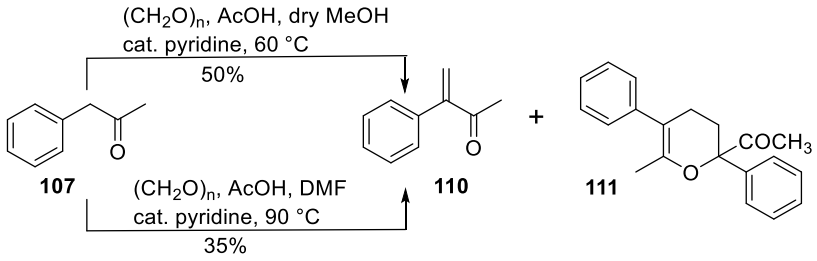


Scheme 2.19

The conversion of the ketone to the enone was achieved using two different literature protocols shown in Schemes 2.20 and 2.21.

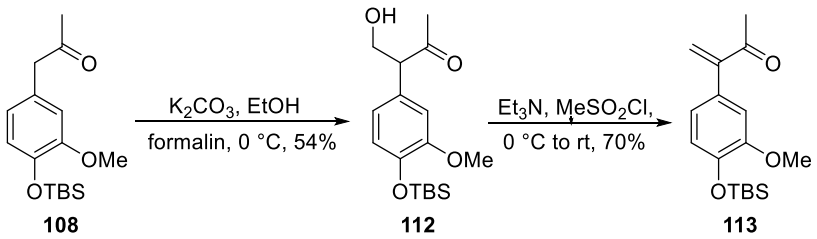
Ketone **107** was treated with paraformaldehyde and acetic acid in the presence of a catalytic amount of pyridine[36,37] in DMF to yield the desired enone **110** in 35% yield under

reflux conditions. The undesired side product dimer **111** formed as a result of an oxa-Diels Alder reaction of **110** with itself was obtained as the major product (Scheme 2.20). The use of methanol as solvent compared to DMF and lowering the temperature from 90 ºC to 60 ºC was beneficial for the reaction (improvement in yield by 15%). However, the formation of **111** (22%) could not be avoided.



Scheme 2.20

In an alternative attempt to optimise the reaction for a higher yield of the desired enone, the ketone **108** was converted to the β-hydroxy ketone[38] **112** in 54% yield. Subsequent conversion to enone[39] **113** was achieved by mesylation of **112** and subsequent elimination of the mesylate at ambient temperature (70% yield, Scheme 2.21). The higher overall yield of **113** from **108** (38%, Scheme 2.21) compares favourably with only 10% yield of enone **110** obtained according to the conditions shown in Scheme 2.20.

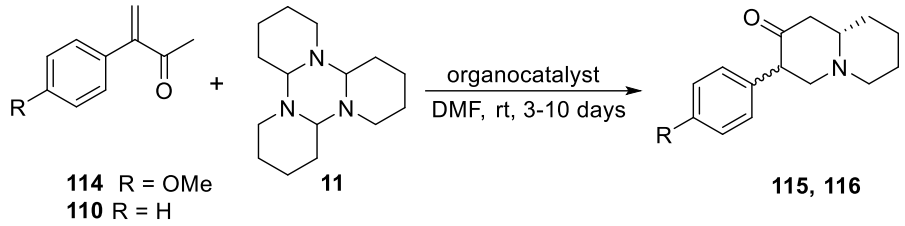


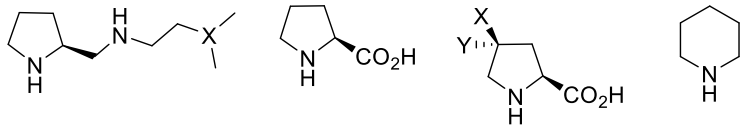
Scheme 2.21

Initial studies were conducted with the enone **110** and piperideine **11**. A Mannich/aza-Michael reaction between Δ^1-piperideine (**11**) and enones **110** and **114** provided

quinolizidinones **115** as a diastereomeric mixture under organocatalytic reaction conditions. The results for this study are listed in the Table 2.4.

Table 2.4 Reactions of α-methylene ketones with **11** under enamine/iminium ion mediated organocatalytic Mannich/aza-Michael reaction conditions





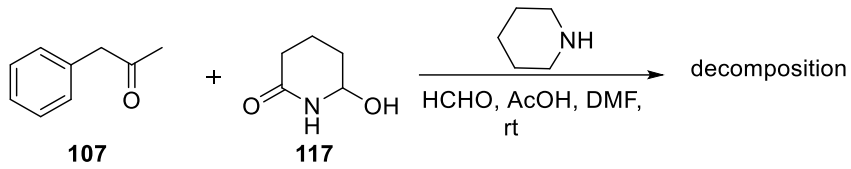
Entry[a]	Enone	Catalyst	Solvent	Time (days)	Yield (%)
1.	**114**	**C3**	DMF	10	13
2.	**114**	**C3**	CH_3CN[b]	3	No reaction
3.	**114**	**C4**	DMF	6	Traces
4.	**114**	**C5**	DMF	6	Traces
5.	**114**	**C6**	DMF	6	No reaction
6.	**110**	**C1**:p-TsOH = 1:2	DMF	5	22
7.	**110**	**C1**:p-TsOH = 1:2	DMF	3	16
8.	**110**	**C3**	DMSO	4	10
9.	**110**	**C2**:p-TsOH = 1:1	DMF	3	7
10.	**110**	**C1**:p-TsOH = 1:1	DMF	3	7

a: all reactions performed at rt except when mentioned. b: 0℃ to rt

Preliminary results suggest that the presence of an acid co-catalyst had a beneficial effect on the product yields. The best result was obtained with enone **110** in the presence of 20

mol% of triamine catalyst **C1** and 40 mol% of p-TsOH. (entry 6, Table 2.4). The reactions worked better in DMF as compared to DMSO while acetonitrile was not a suitable solvent for the reaction. Increasing the reaction time was also favourable for the reaction (entries 6 and 7, Table 2.4).

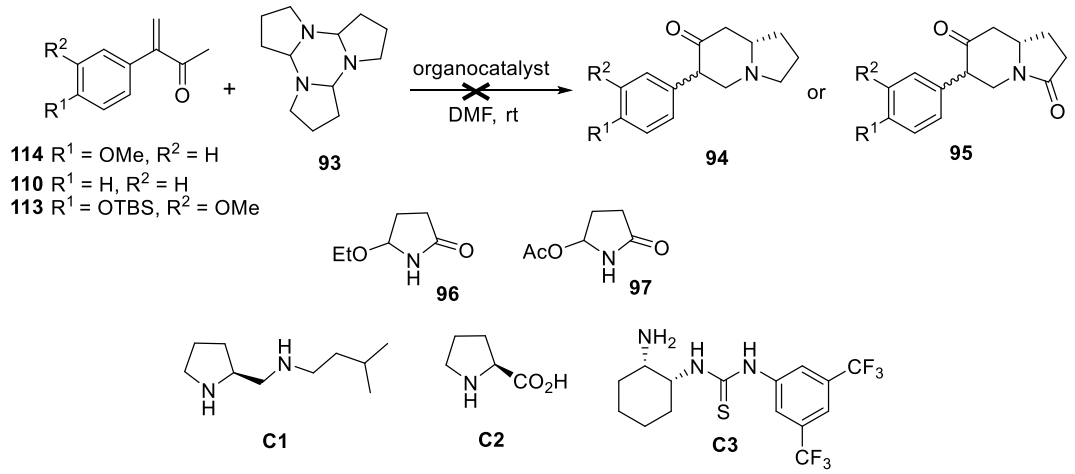
Reasoning that the low yields of the quinolizidinone products could be due to the inevitable dimerization of the starting material (observed in the crude product mixture by ^{1}H NMR), we attempted a one-pot reaction where both the enone and the imine would be formed in-situ (Scheme 2.22). Unfortunately, this reaction provided a complex mixture of products in which the desired quinolizidinone could not be detected.



Scheme 2.22

Experiments were also conducted for the synthesis of 4-arylindolizidinones. Reactions of α-methylene ketones were performed with trimer **93**, and also with precursors **96** and **97** which were hypothesised to generate reactive iminium ions insitu. However, under the different conditions tried (Table 2.5), none of the reactions afforded desired products **94** or **95**.

Table 2.5 Unsuccessful attempts for the synthesis of 4-arylindolizidinone **94** or **95** under enamine/iminium ion mediated organocatalytic Mannich/aza-Michael reaction conditions



Entry	Enone	Imine	Catalyst	Time (days)	Observation
1.	**113**	**93**	**C2**	4	No reaction
2.	**113**	**96**	**C2**	4	No reaction
3.	**113**	**96**	**C2**: p-TsOH = 1:1	4	Complex mixture
4.	**113**	**96**	**C3**	2	No reaction
5.	**113**	**97**	**C2** +10 mol% HCl	2	Complex mixture
6.	**114**	**93**	**C2**	10	No reaction
7.	**110**	**93**	**C1**	5	No reaction

2.5 Conclusion

In conclusion, we have developed a biomimetic, organocatalytic strategy for the synthesis of 4-arylquinolizidin-2-ones and 5-arylindolizidin-4-ones. The 4-aryl quinolizidinone synthesis involves a Mannich reaction of β-aryl enones with piperideine followed by an intramolecular aza-Michael reaction. This methodology was applied in the enantioselective synthesis of (−)-lasubine II and (+)-subcosine II. The strategy also provides

the shortest enantioselective route to several 4-arylquinolizidinones that are key intermediates in the synthesis of macrolactone-containing *Lythraceae* alkaloids. The use of pyrroline in the Mannich reaction provides 5-arylindolizidinones in moderate yields but with excellent diastereoselectivity and enantioselectivity. We also have preliminary results on the extension of the Mannich/aza-Michael strategy to methylidene ketones for the synthesis of 3-arylquinolizidinones. Further exploration of the initial observations in this study are planned.

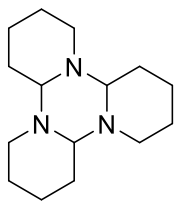
2.6 Experimental Section

General

All commercially available reagents were used without purification. All reactions requiring anhydrous conditions were performed under an atmosphere of dry nitrogen using oven dried glassware. CH_2Cl_2 was distilled from CaH_2. Commercial precoated silica gel plates were used for TLC. All melting points are uncorrected. Silica gel used for flash column chromatography was 230-400 mesh. IR spectra were recorded on a Bruker TENSOR 27 FT-IR instrument. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE III 300 or an AVANCE 500 instrument. Mass spectra were obtained on an Agilent 1100 series LC/MSD (Trap) or an Agilent 6200 LC/MSD (TOF) chromatographic system. HPLC analyses were performed on a Waters chromatographic system using the Breeze software.

Enones **51** and **91** are commercially available and enones **87**[40] and **92**[41] were prepared according to the literature procedures. The synthesis of enones **88, 89** and **90** is provided.

Dodecahydro-1H,6H,11H-tripyrido[1,2-a:1',2'-c:1'',2''-e][1,3,5]triazine (11)[11a]



To a solution of *N*-chlorosuccinimide (3.78 g, 27.9 mmol) in diethyl ether (75 mL) was added a solution of distilled piperidine (2.48 mL, 25.2 mmol) in ether (50 mL) over 30 min at room temperature. The reaction mixture was stirred for 3 h at ambient temperature after which it was filtered through a pad of Celite® and the residue was washed with ether (1 x 25 mL). The combined filtrates were washed with water (3 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated without heating to give *N*-chloropiperidine.

An ethereal solution of the above *N*-chloropiperidine was added dropwise to ethanolic KOH (prepared by heating 2.1 mol of solid KOH in ethanol (15.0 mL) to 85°C) at room temperature and the reaction was left to stir overnight. The white precipitate of KCl formed was then separated by filtration through a pad of Celite®. The filtrate was concentrated to remove ethanol and the residue was diluted with ethyl acetate. The resulting solution was washed with water (3 x 20 mL) to provide the piperideine **11** (1.45 g, 70% yield over two steps). This is a mixture of monomeric (minor) and trimeric (major) forms (^{1}H NMR). This material was used as such without purification.

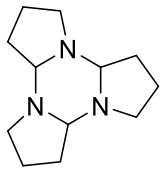
^{1}H NMR (300 MHz, $CDCl_3$): Trimer: 3.18-3.06 (m, 3H), 2.80 (dd, 3H, *J* = 7.2, 3.0 Hz), 2.07-1.95 (m, 3H), 1.80-1.61 (m, 9H), 1.60-1.51 (m, 6H), 1.38-1.20 (m, 3H). Visible peaks for the monomer: δ 7.83-7.78 (m, 1H, N=C*H*), 3.61-3.53 (m, 1H), 2.21-2.12 (m, 2H), 1.80-1.61 (m, 1H)

^{13}C NMR (75 MHz, $CDCl_3$): Trimer δ 82.0 (N*C*H), 46.4, 29.2, 25.8, 22.3. Visible peaks for the monomer: δ 163.2 (N=*C*H), 49.3, 28.8, 18.7.

IR (neat): 2924, 2850, 2812, 2775, 2730, 2701, 1446, 1379, 1238, 1131, 1107, 1024, 889, 796 cm^{-1}.

HRMS (ESI, pos.): *m/z* 249.2198 (249.2205 calc. for $C_{15}H_{27}N_3$ (M^+)), 250.2275 (250.2283 calc. for $C_{15}H_{28}N_3$ $[M+H]^+$.

Dodecahydrotripyrrolo[1,2-a:1',2'-c:1'',2''-e][1,3,5]triazine (93)[29]



To a stirred mixture of pyrrolidine (24.35 mmol, 2 mL), $AgNO_3$ (21.25 mg) and NaOH (2 g) in water (25 mL) at 0 °C was added dropwise a 25% aqueous solution of sodium peroxodisulfate $Na_2S_2O_8$ (6.25 g in 25 mL water). The reaction mixture was stirred for 2.5 h after which it was extracted with dichloromethane (3 x 10 mL). The organic layer was first washed with brine and then dried overnight over Na_2SO_4-K_2CO_3 in the refrigerator. The organic layer was then concentrated without heating to provide **93** as a mixture of monomeric (minor) and trimeric (major) forms distinguished by ^{1}H NMR. The crude material was used as such without purification.

^{1}H NMR (300 MHz, $CDCl_3$): Trimer: δ 3.07-2.95 (m, 6H, NC*H*N and NCH_2), 2.37-2.26 (m, 3H, NCH_2), 1.97-1.63 (m, 12H, CH_2). Visible peaks for the monomer: δ 7.63-7.59 (m, 1H, N=C*H*), 3.89-3.80 (m, 2H, NCH_2), 2.58-2.48 (m, 2H, N=CH*C*H2), 1.97-1.63 (m, 2H, CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): Trimer: δ 82.0 (N*C*H), 45.9 (N*C*H_2), 27.9 (NCH*C*H_2), 20.3 (NCH$_2$*C*H$_2$). Visible peaks for monomer: 166.9 (N=*C*H), 61.2 (N*C*H_2), 36.6 (N=CH*C*H_2), 20.4 (NCH$_2$*C*H$_2$).

IR (neat): 2955, 2871, 2784, 1677, 1613, 1458, 1391, 1337, 1292, 1232, 1194, 1178, 1141, 1065 cm^{-1}.

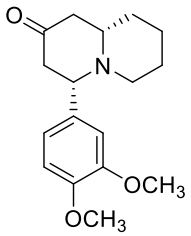
HRMS (ESI, pos.): *m/z* 207.1734 (207.1735 calc. for $C_{12}H_{21}N_3$ (M^+)), m/z 208.1816 (208.1814 calc. for $C_{12}H_{22}N_3$ $[M+H]^+$

General procedure for the Mannich/aza-Michael reaction:

To either **11** or **93** in a vial was added *S*-proline, the enone and DMF at room temperature. The reaction mixture was stirred at ambient temperature for the specified period.

Aqueous HCl (1M) was added and the mixture was extracted with EtOAc. The aqueous layer was made basic to pH 10 with solid NaOH and then extracted with dichloromethane. The combined extracts were dried and concentrated and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 99:1) to provide the required 4-arylquinolizidinone or 5-arylindolizidinone.

(4*S*,9a*S*)-4-(3,4-Dimethoxyphenyl) hexahydro-1H-quinolizin-2(6H)-one (54):



Synthesis of 54 on >1 mmol scale:

Reaction of (*E*)-4-(3,4-dimethoxyphenyl) but-3-en-2-one (**51**, 1.48 g, 7.20 mmol) and **11** (0.30 g, 1.20 mmol) in the presence of *S*-proline (83 mg, 0.12 mmol) in DMF (3.5 mL) according to the general procedure gave, after purification by flash chromatography on silica gel, 605 mg (58%) of **54** as a pale yellow foam.

The reaction of **51** and **11** on a smaller scale provided a slightly higher yield of **54**.

Reaction of **51** (247 mg, 1.2 mmol) and (50.0 mg, 0.2 mmol) **11** in the presence of *S*-proline (13.8 mg, 0.12 mmol) in DMF (0.5 mL) according to the general procedure gave, after purification by flash chromatography on silica gel, 104 mg (60%) of **54** as a pale yellow foam.

R_f = 0.36 (EtOAc/MeOH, 80:20), $[\alpha]_D^{20}$ = −87.2 (c 0.83, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): 6.92 (br s, 1H, Ar*H*), 6.87-6.78 (br m, 2H, Ar*H*), 3.90 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.21 (dd, 1H, NC*H*, *J* = 12.1, 3.3 Hz), 2.84-2.62 (m, 2H), 2.57-2.21 (m, 4H), 1.80-1.18 (m, 7H)

^{13}C NMR (75 MHz, $CDCl_3$): 207.8 (*C*=O), 149.3 (C_{ipso}), 148.3 (C_{ipso}), 135.2 (C_{ipso}), 119.5 (Ar*C*), 111.1 (Ar*C*), 109.8 (Ar*C*), 70.0 (Ar*C*HN), 62.5 (N*C*HCH$_2$CO), 56.0 (O*C*H$_3$), 55.9

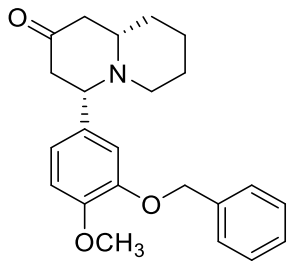
(O*C*H$_3$), 52.8 (ArCH*C*H$_2$CO or NCH*C*H$_2$CO), 50.9 (ArCH*C*H$_2$CO or NCH*C*H$_2$CO), 48.7 (N*C*H2CH2), 34.3 (NCH*C*H$_2$), 25.8 (NCH$_2$*C*H$_2$ or NCH$_2$CH$_2$*C*H$_2$), 24.2 (NCH$_2$*C*H$_2$ or NCH$_2$CH$_2$*C*H$_2$)

IR (neat): 2927, 2850, 2835, 2796, 1717, 1593, 1508, 1461, 1443, 1256, 1231, 1146, 1076, 1024, 812 cm^{-1}.

HRMS (ESI, pos.): *m*/*z* 289.1692 (289.1678 calc. for $C_{17}H_{23}NO_3$ [M$^+$]), m/z 290.1764 (290.1756 calc. for $C_{17}H_{24}NO_3$ [M+H]$^+$).

HPLC: Chiralpak OJ-H (hexane/*i*-PrOH, 80/20, flow rate 1 mL/min, λ = 254 nm), t_{major} = 6.85 min., t_{minor} = 9.82 min., 98% ee.

(4*S*,9a*S*)-4-(3-(Benzyloxy)-4-methoxyphenyl) hexahydro-1H-quinolizin-2(6H)-one (46):



Reaction of **11** (50 mg, 0.2 mmol) and (*E*)-4-(3-(benzyloxy)-4-methoxyphenyl) but-3-en-2-one (**88**, 338 mg, 1.2 mmol) in the presence of *S*-proline (13.8 mg, 0.12 mmol) in DMF (1 mL) according to the general procedure gave, after purification by flash chromatography on silica gel, 84 mg (40%) of **46** as a pale-yellow foam.

R_f = 0.25 (EtOAc/MeOH, 90:10), $[\alpha]_D^{20}$ = -65.9 (c 0.62, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): 7.46-7.42 (m, 2H, Ar*H*), 7.38-7.28 (m, 3H, Ar*H*), 6.94 (broad s, 1H, Ar*H*), 6.83 (m, 2H, Ar*H*), 5.16 (s, 2*H*, PhC*H*$_2$), 3.87 (s, 3H, OC*H*$_3$), 3.15 (dd, 1H, *J* = 12.0, 3.2 Hz, NC*H*), 2.72-2.18 (m, 6H), 1.75-1.18 (m, 7H)

^{13}C NMR (75 MHz, $CDCl_3$): 208.0 (*C*=O), 149.2 (*C*$_{ipso}$), 148.4 (*C*$_{ipso}$), 137.0 (*C*$_{ipso}$), 135.2 (*C*$_{ipso}$), 128.5 (2 x Ar*C*), 127.9 (Ar*C*), 127.5 (2 x Ar*C*), 120.2 (Ar*C*), 113.1 (Ar*C*), 111.8 (Ar*C*), 71.1 (Ph*C*H$_2$), 69.8 (Ar*C*HN), 62.4 (N*C*HCH$_2$CO), 56.1 (O*C*H$_3$), 52.7 (ArCH*C*H$_2$CO or

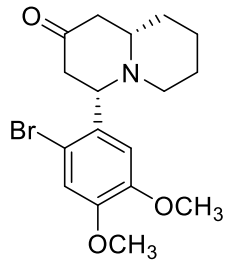
NCH*C*H$_2$CO), 50.9 (ArCH*C*H$_2$CO or NCH*C*H$_2$CO), 48.8 (N*C*H$_2$CH$_2$), 34.4 (NCH*C*H$_2$), 25.9 (NCH$_2$*C*H$_2$ or NCH$_2$CH$_2$*C*H$_2$), 24.2 (NCH$_2$*C*H$_2$ or NCH$_2$CH$_2$*C*H$_2$).

IR (neat): 2930, 1714, 1521, 1510, 1263, 1248, 1238, 1223, 1163, 1141, 1044, 831 cm^{-1}

HRMS (ESI, pos.): *m*/*z* 365.1998 (365.1991 calc. for $C_{23}H_{27}NO_3$ [M$^+$]), m/z 366.2071 (366.2069 calc. for $C_{23}H_{28}NO_3$ [M+H]$^+$), 388.1889 (388.1889 calc. for $C_{23}H_{27}NO_3Na$ [M+Na]$^+$).

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 97/3, flow rate 1 mL/min, λ = 254 nm), t_{major} = 17.69 min., t_{minor} = 20.89 min., 95% ee.

(4*S*,9a*S*)-4-(2-Bromo-4,5-dimethoxyphenyl) hexahydro-1H-quinolizin-2(6H)-one (74)



Reaction of **11** (50 mg, 0.2 mmol) and (*E*)-4-(2-bromo-4,5-dimethoxyphenyl)but-3-en-2-one (**89**, 342 mg, 1.2 mmol) in the presence of *S*-proline (13.8 mg, 0.12 mmol) in DMF (0.5 mL) according to the general procedure gave, after purification by flash chromatography on silica gel, unreacted **89** (244 mg) and 45 mg (20%, 35% based on recovered starting material) of **74** as a pale yellow foam.

R_f = 0.29 (EtOAc/MeOH, 95:5), $[\alpha]_D^{20}$ = -90.7 (c 0.57, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): 7.14 (s, 1H, Ar*H*), 6.96 (s, 1H, Ar*H*), 3.91 (s, 3H, OC*H*$_3$), 3.86 (s, 3H, OC*H*$_3$), 3.82 (dd, 1H, NC*H*, *J* = 10.2, 5.2 Hz), 2.83-2.74 (m, 1H, C*H*CH$_2$), 2.55-2.29 (m, 5H, C*H*$_2$), 1.81-1.66 (m, 3H, C*H*$_2$), 1.62-1.22 (m, 4H, C*H*$_2$).

^{13}C NMR (75 MHz, $CDCl_3$): 207.3 (*C*=O), 149.3 (*C*$_{ipso}$), 148.6 (*C*$_{ipso}$), 133.3 (Ar*C*), 115.1 (Ar*C*), 113.2 (*C*$_{ipso}$), 110.4 (Ar*C*), 67.2 (Ar*C*HN), 62.0 (N*C*HCH$_2$CO), 56.2 (OC*H*$_3$), 56.1 (OC*H*$_3$), 52.3 (ArCH*C*H$_2$CO or NCH*C*H$_2$CO), 48.9 (ArCH*C*H$_2$CO or NCH*C*H$_2$CO), 48.6

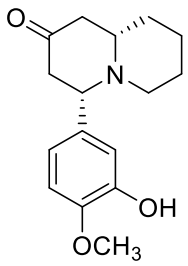
(N*C*H$_2$*C*H$_2$), 34.4 (NCH*C*H$_2$), 25.8 (NCH$_2$*C*H$_2$ or NCH$_2$CH$_2$*C*H$_2$), 24.2 (NCH$_2$*C*H$_2$ or NCH$_2$CH$_2$*C*H$_2$).

IR (neat): 2931, 2842, 1720, 1500, 1461, 1439, 1378, 1363, 1343, 1323, 1276, 1246, 1207, 1160, 1119, 1076, 1027 cm^{-1}

HRMS (ESI, pos.): *m/z* 367.0776 (367.0783 calc. for $C_{17}H_{22}BrNO_3$ [M$^+$]), m/z 368.0848 (368.0861 calc. for $C_{17}H_{23}Br^{79}NO_3$ [M+H]$^+$), m/z 370.083 (370.0841 calc. for $C_{17}H_{23}Br^{81}NO_3$ [M+H]$^+$)

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 97/3, flow rate 1 mL/min, λ = 254 nm), t_{major} = 16.82 min., t_{minor} = 16.12 min., 98% ee.

(4*S*,9a*S*)-4-(3-Hydroxy-4-methoxyphenyl) hexahydro-1H-quinolizin-2(6H)-one (1)



Reaction of **11** (200 mg, 0.8 mmol) and (*E*)-4-(3-hydroxy-4-methoxyphenyl) but-3-en-2-one **87** (920 mg, 4.8 mmol) in the presence of *S*-proline (55.2 mg, 0.48 mmol) in DMF (2 mL) according to the general procedure gave, after purification by flash chromatography on silica gel, 265 mg (40%) of **1** as a pale-yellow foam.

R_f = 0.3 (EtOAc/MeOH, 90:10), $[\alpha]_D^{20}$ = -67.0 (c 0.56, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): 6.97 (br d, 1H, Ar*H*, *J* = 1.4 Hz), 6.82-6.76 (m, 2H, Ar*H*), 5.65 (broad s, 1H, O*H*), 3.88 (s, 3H, OC*H*$_3$), 3.17 (dd, 1H, *J* = 12.1, 3.3 Hz, NC*H*), 2.84-2.75 (m, 1H), 2.71-2.59 (m, 1H), 2.55-2.43 (m, 1H), 2.43-2.20 (m, 3H), 1.78-1.38 (m, 6H), 1.34-1.17 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): 208.0 (*C*=O), 145.9 (2 x C_{ipso}), 136.0 (C_{ipso}), 118.9 (Ar*C*), 113.2 (Ar*C*), 110.6 (Ar*C*), 69.8 (Ar*C*HN), 62.4 (N*C*HCH$_2$CO), 56.0 (O*C*H$_3$), 52.8 (ArCH*C*H$_2$CO or

NCH*C*H$_2$CO), 50.9 (ArCH*C*H$_2$CO or NCH*C*H$_2$CO), 48.8 (N*C*H$_2$CH$_2$), 34.5 (NCH*C*H$_2$), 25.9 (NCH$_2$*C*H$_2$ or NCH$_2$CH$_2$*C*H$_2$), 24.2 (NCH$_2$*C*H$_2$ or NCH$_2$CH$_2$*C*H$_2$).

IR (neat): 3392, 3010, 2931, 2841, 2795, 1715, 1592, 1441, 1323, 1270, 1218, 1123, 1026, 879, 806, 754 cm^{-1}

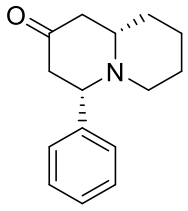
HRMS (ESI, pos.): *m*/*z* 275.1533 (275.1521 calc. for $C_{16}H_{21}NO_3$ [M$^+$]), m/z 276.1606 (276.1600 calc. for $C_{16}H_{22}NO_3$ [M+H]$^+$), 298.1399 (298.1419 calc. for $C_{16}H_{21}NO_3Na$ [M+Na]$^+$).

HPLC: Chiralpak OJ-H (hexane/*i*-PrOH, 80/20, flow rate 1 mL/min, λ = 254 nm), t_{major} = 10.95 min., t_{minor} = 8.72 min., 82% ee.

4-Phenylhexahydro-1*H*-quinolizin-2(6*H*)-one (79)

Reaction of **11** (100 mg, 0.2 mmol) and (E)-4-phenylbut-3-en-2-one (352 mg, 2.4 mmol) in the presence of (*S*)-proline (27.6 mg, 0.24 mmol) in DMF (1 mL) according to the general procedure gave **79** as a mixture of diastereomers (dr = 1:0.6 for cis: trans). These were separated by flash chromatography on silica gel (CH_2Cl_2/MeOH, 95.5:0.5 → CH_2Cl_2/MeOH, 98:2) to provide 63 mg (23%) of (*cis*) 4-phenylhexahydro-1*H*-quinolizin-2(6*H*)-one as a pale-yellow foam and 45.5 mg (17%) of the (*trans*) phenylhexahydro-1*H*-quinolizin-2(6*H*)-one as a pale yellow gum.

(*cis*) 4-Phenylhexahydro-1*H*-quinolizin-2(6*H*)-one



R_f = 0.33 (EtOAc/MeOH, 90:10), $[\alpha]_D^{20}$ = -111.4 (c 0.88, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): 7.36-7.32 (m, 4H, Ar*H*), 7.32- 7.26 (m, 1H, Ar*H*), 3.27 (dd, 1H, *J* = 12.1, 3.3 Hz, NC*H*), 2.80-2.63 (m, 2*H*), 2.57-2.46 (m, 1H), 2.45-2.23 (m, 3H), 1.78-1.38 (m, 6H), 1.35-1.17 (m, 1H).

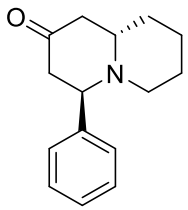
^{13}C NMR (75 MHz, $CDCl_3$): 207.9 (*C*=O), 142.7 (C_{ipso}), 128.8 (2 x Ar*C*), 127.6 (Ar*C*), 127.3 (2 x Ar*C*), 70.3 (Ar*C*HN), 62.5 (N*C*HCH$_2$CO), 53.0 (ArCH*C*H$_2$CO or NCH*C*H$_2$CO), 50.8 (ArCH*C*H$_2$CO or NCH*C*H$_2$CO), 48.8 (N*C*H$_2$CH$_2$), 34.5 (NCH*C*H$_2$), 25.9 (NCH$_2$*C*H$_2$ or NCH$_2$CH$_2$*C*H$_2$), 24.2 (NCH$_2$*C*H$_2$ or NCH$_2$CH$_2$*C*H$_2$).

IR (neat): 2931, 2857, 2791, 2754, 1718, 1492, 1452, 1409, 1324, 1294, 1253, 1128, 1117, 1072, 1031, 1019, 775, 751, 701 cm^{-1}

HRMS (ESI, pos.): *m*/*z* 229.1468 (229.1467 calc. for $C_{15}H_{19}NO$ [M^+]), m/z 230.1540 (230.1545 calc. for $C_{15}H_{20}NO$ $[M+H]^+$)

HPLC: Chiralpak OJ-H (hexane/*i*-PrOH, 80/20, flow rate 1 mL/min, λ = 254 nm, t_{major} = 5.73 min, t_{minor} = 4.92 min., 99% ee.

(*trans*) 4-Phenylhexahydro-1*H*-quinolizin-2(6*H*)-one



R_f = 0.25 EtOAc/MeOH, 95:5)

^{1}H NMR (300 MHz, $CDCl_3$): 7.36-7.27 (m, 3H, Ar*H*), 7.16-7.11 (m, 2H, Ar*H*), 4.28 (dd, 1H, *J* = 6.4, 3.7 Hz, NC*H*), 2.97-2.81 (m, 3*H*), 2.67-2.54 (m, 2H), 2.42-2.32 (m, 1H), 2.13 (td, 1H, *J* = 11.6, 3.4 Hz), 1.73-1.06 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): 209.5 (*C*=O), 138.8 (C_{ipso}), 128.7 (2 x Ar*C*), 128.2 (2 x Ar*C*), 127.6 (Ar*C*), 64.3 (Ar*C*HN), 54.0 (N*C*HCH$_2$CO), 51.5 (ArCH*C*H$_2$CO or NCH*C*H$_2$CO), 47.7 (ArCH*C*H$_2$CO or NCH*C*H$_2$CO), 46.5 (N*C*H$_2$CH$_2$), 32.2 (NCH*C*H$_2$), 24.3 (NCH$_2$*C*H$_2$ or NCH$_2$CH$_2$*C*H$_2$), 23.4 (NCH$_2$*C*H$_2$ or NCH$_2$CH$_2$*C*H$_2$).

IR (neat): 2929, 2855, 2814, 1710, 1493, 1451, 1411, 1385, 1368, 1336, 1313, 1294, 1278, 1241, 1181, 1153, 1120, 1077, 1038, 775, 760, 738, 701 cm^{-1}

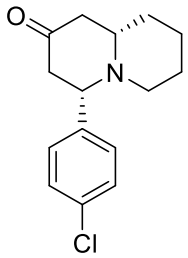
HRMS (ESI, pos.): *m*/*z* 229.1478 (229.1467 calc. for $C_{15}H_{19}NO$ [M^+]), m/z 230.1551(230.1545 calc. for $C_{15}H_{20}NO$ [$M+H]^+$)

HPLC: Chiralpak OJ-H (hexane/*i*-PrOH, 98/2, flow rate 1 mL/min, λ = 254 nm, t_{major} = 11.77 min., t_{minor} = 10.27 min., 87% ee.

4-(4-Chlorophenyl) hexahydro-1*H*-quinolizin-2(6*H*)-one (75)

Reaction of **11** (100 mg, 0.4 mmol) and (*E*)-4-(4-chlorophenyl) but-3-en-2-one (432 mg, 2.4 mmol) in the presence of L-proline (27.6 mg, 0.24 mmol) in DMF (1 mL) according to the general procedure gave **75** as a 1:1 mixture of diastereomers. These were separated by flash chromatography on silica gel to provide 38 mg (12%) of *cis*-diastereomer **84** as a pale-yellow foam and 40 mg (13%) of the *trans* 4-(4-chlorophenyl) hexahydro-1*H*-quinolizin-2(6*H*)-one **85** diastereomer as a pale yellow gum.

(*cis*) 4-(4-Chlorophenyl) hexahydro-1*H*-quinolizin-2(6*H*)-one (84)



R_f = 0.31 (EtOAc/MeOH, 95:5), $[\alpha]_D^{20}$ = -88.8 (c 0.84, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): 7.35-7.27 (m, 4H, Ar*H*), 3.26 (dd, 1H, *J* = 12.0, 3.3 Hz, NC*H*), 2.77-2.68 (m, 1*H*), 2.66-2.24 (m, 5H), 1.78-1.36 (m, 6H), 1.35-1.17 (m, 1H)

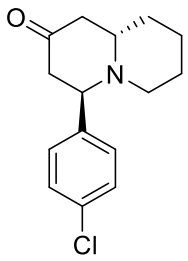
^{13}C NMR (75 MHz, $CDCl_3$): 207.4 (*C*=O), 141.3 (C_{ipso}), 133.2 (C_{ipso}), 129.0 (2 x Ar*C*), 128.6 (2 x Ar*C*), 69.5 (Ar*C*HN), 62.4 (N*C*HCH$_2$CO), 52.9 (ArCH*C*H$_2$CO or NCH*C*H$_2$CO), 50.7 (ArCH*C*H$_2$CO or NCH*C*H$_2$CO), 48.7 (N*C*H$_2$CH$_2$), 34.4 (NCH*C*H$_2$), 25.8 (NCH$_2$*C*H$_2$ or NCH$_2$CH$_2$*C*H$_2$), 24.1 (NCH$_2$*C*H$_2$ or NCH$_2$CH$_2$*C*H$_2$).

IR (neat): 2922, 2909, 1714, 1488, 1411, 1341, 1324, 1299, 1285, 1277, 1154, 1114, 1089, 1074, 1015, 818 cm^{-1}

HRMS (ESI, pos.): *m*/*z* 263.1075 (263.1077 calc. for $C_{15}H_{18}ClNO$ [M^+]), m/z 264.1143 (264.1155 calc. for $C_{15}H_{19}NOCl$ [M+H]$^+$)

HPLC: Chiralpak OJ-H (hexane/*i*-PrOH, 95/5, flow rate 1 mL/min, λ = 254 nm, t_{major} = 7.75 min., t_{minor} = 8.47 min., 95% ee.

(*trans*) 4-(4-Chlorophenyl) hexahydro-1*H*-quinolizin-2(6*H*)-one (85)



R_f = 0.24 (EtOAc/MeOH, 95:5)

^{1}H NMR (300 MHz, $CDCl_3$): 7.33-7.27 (apparent d, 2H, *J* = 8.5 Hz, Ar*H*), 7.12-7.05 (apparent d, 2H, *J* = 8.5 Hz, Ar*H*), 4.27 (dd, 1H, *J* = 6.4, 3.8 Hz, NC*H*), 2.95-2.77 (m, 3*H*), 2.64-2.51 (m, 2H), 2.44-2.32 (m, 1H), 2.23-2.07 (m, 1H), 1.73-1.08 (m, 6H).

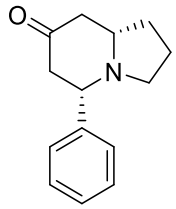
^{13}C NMR (75 MHz, $CDCl_3$): 209.2 (*C*=O), 137.4 (C_{ipso}), 133.4 (C_{ipso}), 129.9 (2 x Ar*C*), 128.4 (2 x Ar*C*), 63.6 (Ar*C*HN), 54.1 (N*C*HCH$_2$CO), 51.3 (ArCH*C*H$_2$CO or NCH*C*H$_2$CO), 47.4 (ArCH*C*H$_2$CO or NCH*C*H$_2$CO), 46.2 (N*C*H$_2$CH$_2$), 32.0 (NCH*C*H$_2$), 24.1 (NCH$_2$*C*H$_2$ or NCH$_2$CH$_2$*C*H$_2$), 23.2 (NCH$_2$*C*H$_2$ or NCH$_2$CH$_2$*C*H$_2$).

IR (neat): 2929, 2856, 1713, 1491, 1444, 1410, 1385, 1368, 1335, 1306, 1292, 1280, 1242, 1229, 1180, 1152, 1115, 1095, 1039, 1013 cm^{-1}

HRMS (ESI, pos.): *m*/*z* 263.1077 (263.1077 calc. for $C_{15}H_{18}ClNO$ [M^+])

HPLC: Chiralpak OJ-H (hexane/*i*-PrOH, 95/5, flow rate 1 mL/min, λ = 254 nm, t_{major} = 8.66 min., t_{minor} = 11.13 min., 93% ee.

(5*S*, 8a*S*)-5-Phenylhexahydroindolizin-7(1H)-one (95):



Reaction of **93** (50 mg, 0.24 mmol) and (*E*)-4-phenylbut-3-en-2-one (**91**, 204 mg, 1.4 mmol) in the presence of *S*-proline (16.1 mg, 0.14 mmol) in DMF (0.5 mL) according to the general procedure gave, after purification by flash chromatography on silica gel, 70 mg (47%) of **95** as a pale-yellow gum.

R_f = 0.35 (EtOAc/MeOH, 90:10), $[\alpha]_D^{20}$ = -100.6 (c 0.76, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): 7.40-7.24 (m, 5H, Ar*H*), 3.32 (dd, 1H, NC*H*, *J* = 11.4, 3.6 Hz), 2.86-2.77 (m, 1H), 2.68-2.53 (m, 2H), 2.52-2.36 (m, 3H), 2.05-1.55 (m, 5H)

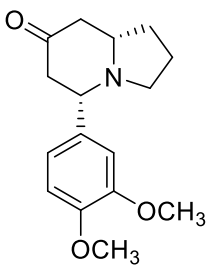
^{13}C NMR (75 MHz, $CDCl_3$): 208.6 (*C*=O), 142.2 (C_{ipso}), 128.6 (2 x Ar*C*), 127.7 (Ar*C*), 127.1 (2 x Ar*C*), 66.9 (N*C*HAr or N*C*HCH_2), 64.1 (N*C*HAr or N*C*HCH_2), 51.5 (NCH*C*H_2CO or ArCH*C*H_2CO), 49.7 (NCH*C*H_2CO or ArCH*C*H_2CO), 47.3 (N*C*H_2CH_2), 31.1 (NCH$_2$*C*H_2 or NCH*C*H_2), 21.5 (NCH$_2$*C*H_2 or NCH*C*H_2).

IR (neat): 2960, 2819, 2781, 1711, 1371, 1348, 1302, 1290, 1245, 1152, 1029, 765, 701 cm^{-1}

HRMS (ESI, pos.): *m*/*z* 215.1304 (215.1310 calc. for $C_{14}H_{17}NO$ [M^+])

HPLC: Chiralpak OJ-H (hexane/*i*-PrOH, 80/20, flow rate 1 mL/min, λ = 254 nm), t_{major} = 5.87 min., t_{minor} = 5.10 min., 94% ee.

(5*S*, 8a*S*)-5-(3,4-Dimethoxyphenyl) hexahydroindolizin-7(1H)-one (94):



Reaction of **93** (50 mg, 0.24 mmol) and (*E*)-4-(3,4-Dimethoxyphenyl) but-3-en-2-one (**51**, 288 mg, 1.4 mmol) in the presence of *S*-proline (16.1 mg, 0.14 mmol) in DMF (0.5 mL)

according to the general procedure gave, after purification by flash chromatography on silica gel, 40 mg (21%) of **94** as a yellow gum.

R_f = 0.17 (EtOAc/MeOH, 90:10), $[\alpha]_D^{20}$ = -87.2 (c 0.83, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): 6.94 (d, 1H, *J* = 1.9 Hz, Ar*H*), 6.88 (dd, 1H, *J* = 8.2, 1.9 Hz, Ar*H*), 6.81 (d, 1H, *J* = 8.2 Hz, Ar*H*), 3.91 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.26 (dd, 1H, NC*H*, *J* = 11.4, 3.5 Hz), 2.87-2.80 (m, 1H), 2.68-2.55 (m, 2H), 2.52-2.34 (m, 3H), 2.07-1.56 (m, 5H)

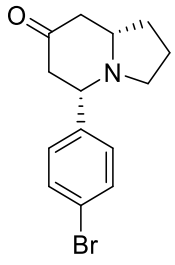
^{13}C NMR (75 MHz, $CDCl_3$): 208.7 (*C*=O), 149.2 (C_{ipso}), 148.4 (C_{ipso}), 134.9 (C_{ipso}), 119.3 (Ar*C*), 110.9 (Ar*C*), 109.8 (Ar*C*), 66.6 (N*C*HAr or N*C*HCH_2), 64.1 (N*C*HAr or N*C*HCH_2), 56.0 (O*C*H_3), 55.9 (O*C*H_3), 51.5 (NCH*C*H_2CO or ArCH*C*H_2CO), 49.9 (NCH*C*H_2CO or ArCH*C*H_2CO), 47.3 (N*C*H_2CH_2), 31.1 (NCH$_2$*C*H_2 or NCH*C*H_2), 21.5 (NCH$_2$*C*H_2 or NCH*C*H_2)

IR (neat): 2958, 2834, 2796, 1715, 1592, 1511, 1259, 1234, 1157, 1136, 1025, 728 cm^{-1}

HRMS (ESI, pos.): m/z 275.1526 (275.1521 for $C_{16}H_{21}NO_3$ [M^+]), m/z 276.1594 (276.1600 for $C_{16}H_{22}NO_3$ [M+H]$^+$)

HPLC: Chiralpak OJ-H (hexane/*i*-PrOH, 80/20, flow rate 1 mL/min, λ = 254 nm), t_{major} = 8.60 min., t_{minor} = 10.62 min., 90% ee.

(5*S*, 8a*S*)-5-(4-Bromophenyl) hexahydroindolizin-7(1H)-one (96):



Reaction of **93** (50 mg, 0.24 mmol) and (*E*)-4-(4-bromophenyl) but-3-en-2-one (**92**, 315 mg, 1.4 mmol) in the presence of L-proline (16.1 mg, 0.14 mmol) in DMF (0.5 mL)

according to the general procedure gave, after purification by flash chromatography on silica gel, 56 mg (27%) of **96** as a yellow gum.

R_f = 0.23 (EtOAc/MeOH, 90:10), $[\alpha]_D^{20}$ = -66.7 (c 0.51, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): 7.47(apparent d, 2H, *J* = 8.5 Hz, ArC*H*), 7.26 (apparent d, 2H, *J* = 8.5 Hz, 2H, ArC*H*), 3.29 (dd, 1H, NC*H*, *J* = 11.2, 3.8 Hz), 2.84-2.75 (m, 1H), 2.63-2.38 (m, 5H), 2.06-1.53 (m, 5H)

^{13}C NMR (75 MHz, $CDCl_3$): 208.0 (*C*=O), 141.4 (C_{ipso}), 131.8 (2 x Ar*C*), 128.8 (2 x Ar*C*), 121.4 (C_{ipso}), 66.2 (N*C*HAr or N*C*HCH_2), 64.0 (N*C*HAr or N*C*HCH_2), 51.5 (NCH*C*H_2CO or ArCH*C*H_2CO), 49.6 (NCH*C*H_2CO or ArCH*C*H_2CO), 47.3 (N*C*H_2CH_2), 31.1 (NCH$_2$*C*H_2 or NCH*C*H_2), 21.5 (NCH$_2$*C*H_2 or NCH*C*H_2)

IR (neat): 2948, 2923, 2780, 2702, 1717, 1488, 1365, 1347, 1301, 1282, 1159, 1147, 1070, 1008, 838, 811 cm^{-1}.

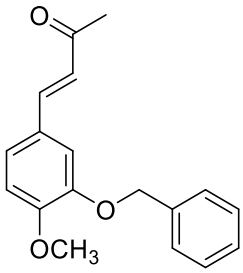
HRMS (ESI, pos.): m/z 293.0419 (293.0415 for $C_{14}H_{16}BrNO$ [M^+]), m/z 294.0492 (294.0494 for $C_{14}H_{17}Br^{79}NO$ [M+H^+]), m/z 296.0474 (296.0473 for $C_{14}H_{17}Br^{81}NO$ [M+H]$^+$)

HPLC: Chiralpak OJ-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, λ = 254 nm), t_{major} = 7.02 min., t_{minor} = 7.60 min., 99% ee.

General procedure for the synthesis of enones 88, 89 and 90:

To a solution of 1-(triphenylphosphoranylidene)-2-propanone in dichloromethane at 0°C was added a solution of the aldehyde in dichloromethane and the mixture was left to stir overnight at room temperature. After consumption of the aldehyde (as shown by TLC), the solvent was removed in vacuo and the crude product was purified using flash column chromatography on silica gel (hexane/EtOAc, 9:1).

(*E*)-4-(3-(Benzyloxy)-4-methoxyphenyl) but-3-en-2-one (88)



Reaction of 3-(benzyloxy)-4-methoxybenzaldehyde (1.3 g, 5.4 mmol) with 1-(triphenylphosphoranylidene)-2-propanone (2.4 g, 8.1 mmol) in CH_2Cl_2 for 48 h according to the general procedure gave, after purification by flash chromatography on silica gel, 818 mg (55%) of **88** as a white solid.

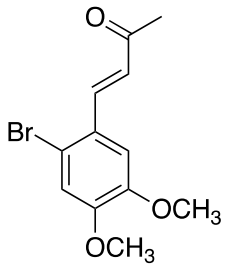
^{1}H NMR (300 MHz, $CDCl_3$): 7.48-7.29 (m, 6H, Ar*H* and COCHC*H*), 7.13 (dd, 1H, Ar*H*, *J* = 8.5, 2.1 Hz), 7.10 (d, 1H, Ar*H*, *J* = 2.1 Hz), 6.90 (d, 1H, Ar*H*, *J* = 8.5 Hz), 6.52 (d, 1H, COC*H*, *J* = 16.4 Hz), 5.17 (s, 2H, CH_2Ph), 3.91 (s, 3H, OCH_3), 2.34 (s, 3H, COCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): 198.3 (*C*=O), 152.1 (C_{ipso}), 148.4 (C_{ipso}), 143.4 (Ar*C*), 136.6 (C_{ipso}), 128.6 (2 x Ar*C*), 128.0 (Ar*C*), 127.3 (2 x Ar*C*), 127.2 (Ar*C*), 125.2 (Ar*C*), 123.3 (Ar*C*), 112.7 (Ar*C*H), 111.6 (ArCH*C*HCO), 71.1 (O*C*H_2Ph), 56.0 (O*C*H_3), 27.4 (CO*C*H_3).

IR (neat): 3065, 3030, 2933, 2874, 2846, 1660, 1640, 1622, 1595, 1511, 1425, 1363, 1380, 1249, 1220, 1160, 1136, 1009, 980, 807, 739, 698 cm^{-1}.

HRMS (ESI, pos.): *m*/*z* 282.1262 (282.1256 calc. for $C_{18}H_{18}O_3$ [M^+]).

(*E*)-4-(2-bromo-4,5-dimethoxyphenyl) but-3-en-2-one (89)



To a solution of veratraldehyde (3.3 g, 20 mmol) in methanol (30 mL), was added bromine (1 mL, 1.05 mol). The reaction was left to stir overnight at room temperature. After consumption of the starting material, the methanol was removed *in vacuuo* and the residue was

dissolved with dichloromethane (50 mL). The resulting solution was washed with a saturated aqueous solution of sodium thiosulphate (2 x 50 mL) and then with brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to provide 2-bromo-4,5-dimethoxybenzaldehyde (4.5 g, 92%) as a white solid which was shown to be pure by ^{1}H NMR and was used in the next step without purification.

Reaction of 2-bromo-4,5-dimethoxybenzaldehyde (2.8 g, 11.4 mmol) with 1-(triphenylphosphoranylidene)-2-propanone (5.1 g, 17.1 mmol) in CH_2Cl_2 for 48 hours according to the general procedure gave, after purification by flash chromatography on silica gel, 2.27 g (78%) of **89** as a beige solid.

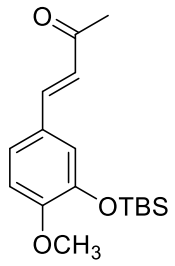
^{1}H NMR (300 MHz, $CDCl_3$): 7.83 (d, 1H, *J* = 16.3 Hz, COCHC*H*), 7.09 (s, 1H, Ar*H*), 7.06 (s, 1H, Ar*H*), 6.53 (d, 1H, COC*H*, *J* = 16.3 Hz), 3.91 (s, 3H, OCH_3), 3.90 (s, 3H, COCH_3), 2.41 (s, 3H, COCH_3)

^{13}C NMR (75 MHz, $CDCl_3$): 198.4 (*C*=O), 151.6 (C_{ipso}), 148.8 (C_{ipso}), 142.0 (COCH*C*H), 127.9 (CO*C*H), 126.2 (C_{ipso}), 117.6 (C_{ipso}), 115.6 (Ar*C*), 109.2 (Ar*C*), 56.3 (O*C*H_3), 56.1 (O*C*H_3), 26.9 (CO*C*H_3)

IR (neat): 2963, 2935, 2919, 2836, 1660, 1637, 1591, 1502, 1435, 1357, 1253, 1210, 1165, 1024, 972 cm^{-1}.

HRMS (ESI, pos.): *m/z* 284.0037 (284.0048 calc. for $C_{12}H_{13}O_3Br$ [M^+]), m/z 285.0109 (285.0126 calc. for $C_{12}H_{14}O_3Br^{79}$ $[M+H]^+$), m/z 287.0090 (287.0106 calc. for $C_{12}H_{14}O_3Br^{81}$ $[M+H]^+$)

(*E*)-4-(3-(*tert*-Butyldimethylsilyloxy)-4-methoxyphenyl) but-3-en-2-one (90)



Reaction of 3-(tert-butyldimethylsilyloxy)-4-methoxybenzaldehyde (1.4 gm, 5.4 mmol) with 1-(triphenylphosphoranylidene)-2-propanone (2.4 g, 8.1 mmol) in CH_2Cl_2 for 48 h according to the general procedure gave, after purification by flash chromatography on silica gel, 996 mg (71 %) of **90** as a white solid.

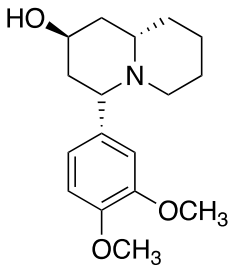
^{1}H NMR (300 MHz, $CDCl_3$): 7.42 (d, 1H, *J* = 16.2 Hz, COCHC*H*), 7.12 (dd, 1H, Ar*H*, *J* = 8.4, 2.2 Hz), 7.07 (d, 1H, Ar*H*, *J* = 2.2 Hz), 6.85 (d, 1H, Ar*H*, *J* = 8.4 Hz), 6.56 (d, 1H, COC*H*, *J* = 16.2 Hz), 3.85 (s, 3H, OCH_3), 2.36 (s, 3H, COCH_3), 1.01 (s, 9H, C(CH_3)$_3$), 0.17 (s, 6H, Si(CH_3)$_2$).

^{13}C NMR (75 MHz, $CDCl_3$): 198.5 (*C*=O), 153.4 (C_{ipso}), 145.4 (C_{ipso}), 143.5 (COCH*C*H), 127.4 (C_{ipso}), 125.2 (CO*C*H), 123.4 (ArC), 119.9 (Ar*C*), 111.8 (Ar*C*), 55.5 (O*C*H$_3$), 27.3 (CO*C*H$_3$), 25.7 (C(*C*H$_3$)$_3$), 18.5 (Si*C*(CH$_3$)$_3$), -4.6 (Si(*C*H$_3$)$_2$)

IR (neat): 2954, 2931, 2897, 2856, 1664, 1640, 1510, 1253, 1231, 1133, 979, 836, 779 cm^{-1}.

HRMS (ESI, pos.): *m*/*z* 306.1653 (306.1651 calc. for $C_{17}H_{26}O_3Si$ [M$^+$]), m/z 307.1724 (307.1729 calc. for $C_{17}H_{27}O_3Si$ [M+H]$^+$).

(-)-Lasubine II (2)



To a solution of **54** (106 mg, 0.37 mmol) in anhydrous THF (1.5 mL) at -78 ^{o}C, was added dropwise a solution of L-Selectride (1.0 M in THF, 0.74 mL, 0.74 mmol). The mixture was stirred at -78 °C for 3 h after which it was warmed to 0 °C and 1M NaOH (2 mL) was added. The resulting mixture was stirred at room temperature for 1 h and the THF was removed under reduced pressure. The residue was dissolved in EtOAc (10 mL) and the solution was washed with brine (1 x 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and

concentrated. The residue was purified by flash chromatography on silica gel using gradient elution (EtOAc→EtOAc/MeOH 8:2) to provide 81 mg (76%) of (-)-lasubine (II) as a white foam. Spectroscopic data is in agreement with reported data.[21d]

R_f = 0.2 (EtOAc/MeOH, 90:10), Mp: 96-98 ºC

$[\alpha]_D^{21}$ = -76.5 (c 0.67, $CHCl_3$), lit.[42] $[\alpha]_D^{20}$ = +43.4 (c 1.0, $CHCl_3$) for (+)-lasubine II.

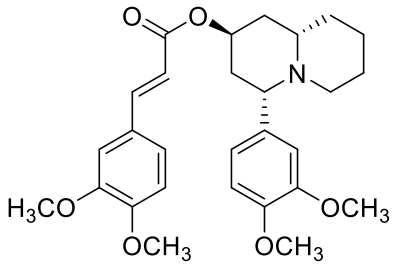
^{1}H NMR (300 MHz, $CDCl_3$): 6.91 (br s, 1H, Ar*H*), 6.86 (d, 1H, *J* = 8.2 Hz, Ar*H*), 6.79 (d, 1H, *J* = 8.2 Hz, Ar*H*), 4.17-4.12 (br m, 1H, C*H*OH), 3.88 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.31 (dd, 1H, NC*H*, *J* = 11.8, 3.3 Hz), 2.72-2.66 (m, 1H), 2.43-2.35 (m, 1H), 1.90-1.83 (m, 1H), 1.83-1.77(m, 1H), 1.74-1.64 (m, 4H), 1.59-1.23 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$: 149.0 (C_{ipso}), 147.8 (C_{ipso}), 137.3 (C_{ipso}), 119.7 (Ar*C*), 111.0 (Ar*C*), 110.5 (Ar*C*), 65.1 (Ar*C*HN), 63.4 (*C*HOH), 56.5 (N*C*HCH$_2$COH), 56.0 (O*C*H$_3$), 55.9 (O*C*H$_3$), 53.2 (ArCH*C*H$_2$COH or NCH*C*H$_2$COH), 42.9 (ArCH*C*H$_2$COH or NCH*C*H$_2$COH), 40.4 (N*C*H2CH2), 33.7 (NCH*C*H$_2$), 26.2 (NCH$_2$*C*H$_2$ or NCH$_2$CH$_2$*C*H$_2$), 24.9 (NCH$_2$*C*H$_2$ or NCH$_2$CH$_2$*C*H$_2$).

IR (neat): 3388 (br), 2924, 1592, 1512, 1462, 1444, 1259, 1228, 1130, 1026 cm^{-1}

HRMS (ESI, pos.): *m*/*z* 291.1830 (291.1834 calc. for $C_{17}H_{25}NO_3$ [M$^+$]), m/z 292.1903 (292.1913 calc. for $C_{17}H_{26}NO_3$ [M+H]$^+$).

(+)-Subcosine (II) (3)



(*E*)-3,4-Dimethoxycinnamic acid (33.3 mg, 0.16 mmol) was added to a solution of crude (-)-lasubine II (48.2 mg, 0.16 mmol) in dichloromethane (2 mL) under nitrogen at ambient temperature. To the resulting solution was added EDCI (36.4 mg, 0.19 mmol) and

DMAP (19.5 mg, 0.16 mmol) and the mixture was stirred 19 h at ambient temperature. Water (5 mL) was added and the organic layer was separated, diluted with CH_2Cl_2 (2 mL) and again washed with water (5 mL) and then with brine (5 mL). The organic layer was dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography on silica gel (EtOAc) provided 51.3 mg (67%) of **3** as a white foam. Spectroscopic data is in agreement with reported data.[24a]

R_f = 0.41 (EtOAc/MeOH, 90:10), $[\alpha]_D^{21}$= +89.3 (c 0.56, MeOH); lit.[21d] $[\alpha]_D^{20}$= +85.3 (c 0.64, MeOH)

^{1}H NMR (300 MHz, $CDCl_3$): 7.67 (d, 1H, *J* = 15.9 Hz, COCHC*H*Ar), 7.16 (dd, 1H, *J* = 8.2, 2.0 Hz, Ar*H*), 7.12 (d, 1H, *J* = 2.0 Hz, Ar*H*), 6.94- 6.83 (m, 2H, Ar*H*), 6.90 (d, 1H, *J* = 8.2 Hz, Ar*H*), 6.79 (d, 1H, *J* = 8.2 Hz, Ar*H*), 6.41(d, 1H, J = 15.9 Hz, COC*H*), 5.22-5.18 (m, 1H), 3.95 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.29 (dd, 1H, J = 11.1, 3.8 Hz), 2.77-2.67 (m, 1H), 2.43-2.31 (m, 1H), 2.15-1.81 (m, 3H), 1.79-1.19 (m, 8H).

^{13}C NMR (125 MHz, $CDCl_3$): 166.6, 151.2, 149.3, 149.2, 147.9, 144.6, 137.1, 127.5, 122.8, 116.4, 111.1, 109.7, 68.4, 64.2, 57.2, 56.0, 55.9, 53.2, 39.9, 37.5, 33.7, 26.2, 24.9

IR (neat): 2931, 2836, 1702, 1631, 1597, 1511, 1256, 1229, 1156, 1137, 1024, 729 cm^{-1}.

HRMS (ESI, pos.): *m*/*z* 481.2472 (481.2464 calc. for $C_{28}H_{35}NO_6$ [M^+]), m/z 482.2544 (482.2543 calc. for $C_{28}H_{36}NO_6$ $[M+H]^+$).

Comparison of observed and reported ^{1}H and ^{13}C NMR data for (-)-lasubine II and for (+)-subcosine II.

(-)-Lasubine II

^{1}H NMR observed (300 MHz)	**^{1}H NMR reported[43] (300 MHz)**
6.91 (br s, 1H), 6.86 (d, 1H, *J* = 8.2 Hz)	7.00 – 6.82 (2H, m)
6.79 (d, 1H, *J* = 8.2 Hz)	6.79 (1H, d, *J* = 8.0 Hz)
4.17- 4.12 (br m, 1H)	4.19 – 4.12 (1H, m),

3.88 (s, 3H)	3.89 (s, 3H)
3.86 (3H, s),	3.86 (s, 3H)
3.31 (dd, 1H, *J* = 11.8, 3.3 Hz)	3.32 (1H, br d, J = 10.5 Hz),
2.72-2.66 (m, 1H)	2.70 (1H, br d, J = 11.0 Hz),
2.43-2.35 (m, 1H)	2.47 – 2.33 (m, 1H)
1.90-1.83 (m, 1H), 1.83-1.77(m, 1H), 1.74-1.64 (m, 4H), 1.59-1.23 (m, 6H)	2.00 – 1.20 (m, 12H)

^{13}C NMR observed (125 MHz)	**^{13}C NMR reported[43] (100 MHz)**
149.0	148.9
147.8	147.7
137.3	137.1
119.7	119.7
111.0	110.8
110.5	110.4
65.1	65.0
63.4	63.4
56.5	56.4
56.0	55.9
55.9	55.8
53.2	53.2
42.9	42.7
40.4	40.3
33.7	33.6

26.2	26.1
24.9	24.8

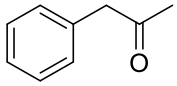
(+)-Subcosine II

^{1}H NMR observed (300 MHz)	**^{1}H NMR reported[24a] (500 MHz)**
7.67 (d, 1H, *J* = 15.9 Hz)	δ 7.67 (dd, 1H, *J* = 16.0, 2.5 Hz)
7.16 (dd, 1H, *J* = 8.2, 2.0 Hz), 7.12 (d, 1H, *J* = 2.0 Hz)	7.18 – 7.08 (m, 2H)
6.94-6.83 (m, 2H), 6.90 (d, 1H, *J* = 8.2 Hz), 6.79 (d, 1H, *J* = 8.2 Hz)	6.94 – 6.75 (m, 4H)
6.41 (d, 1H, *J* = 15.9 Hz)	6.40 (dd, 1H, *J* = 15.5, 2.0 Hz)
5.22- 5.18 (m, 1H)	5.20 (m, 1H)
3.95 (s, 3H)	3.96 (s, 3H)
3.93 (s, 3H)	3.94 (s, 3H)
3.90 (s, 3H)	3.90 (s, 3H)
3.86 (s, 3H)	3.86 (s, 3H)
3.29 (dd, 1H, *J* = 11.1, 3.8 Hz)	3.28 (d, 1H, *J* = 11.5 Hz)
2.77- 2.67 (m, 1H)	2.72 (d, 1H, *J* = 11.5 Hz)
2.43- 2.31 (m, 1H)	2.37 (t, 1H, *J* = 10.0 Hz)
2.15- 1.81 (m, 3H)	2.06 – 1.85 (m, 3H)
1.79-1.19 (m, 8H)	1.79 – 1.20 (m, 8H)

^{13}C NMR observed (125 MHz)	**^{13}C NMR reported[24a] (125 MHz)**
166.6	166.6

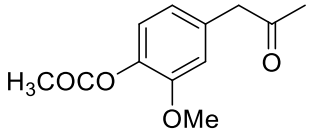
151.2	151.2
149.3	149.3
149.2	149.1
147.9	147.9
144.6	144.6
137.1	137.0
127.5	127.5
122.8	122.7
116.4	116.4
111.1	111.0
109.7	109.6
68.4	68.4
64.2	64.1
57.2	57.2
56.0	56.1
56.0	55.9
55.9	55.8
53.2	53.2
39.9	39.9
37.4	37.4
33.7	33.6
26.2	26.2
24.9	24.9

1-Phenylpropan-2-one (107)[34]



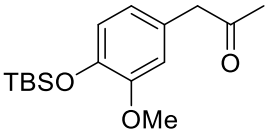
^{1}H NMR (300 MHz, $CDCl_3$): 7.37-7.17 (m, 5H, Ar*H*), 3.70 (s, 2H, ArCH_2CO), 2.15 (s, 3H, COCH_3). Data matched with that reported in literature.[34]

2-Methoxy-4-(2-oxopropyl)phenyl acetate (108)[34]



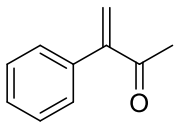
^{1}H NMR (300 MHz, $CDCl_3$): 6.98 (d, 1H, *J* = 7.87 Hz, Ar*H*), 6.81-6.74 (m, 2H, Ar*H*), 3.80 (s, 3H, OCH_3), 3.66 (s, 2H, ArCH_2CO), 2.29 (s, 3H, OCOCH_3), 2.16 (s, 3H, COCH_3). Data matched with that reported in literature.[34]

1-(4-((*tert*-Butyldimethylsilyl)oxy)-3-methoxyphenyl)propan-2-one (109)[34]



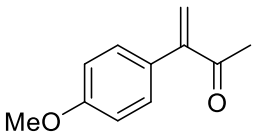
^{1}H NMR (300 MHz, $CDCl_3$): 6.68-6.62 (m, 1H, Ar*H*), 6.55-6.48 (m, 2H, Ar*H*), 3.63 (s, 3H, OCH_3), 3.44 (s, 2H, ArCH_2CO), 1.97 (s, 3H, COCH_3), 0.84 (s, 9H, C(CH_3)$_3$), 0.00 (s, 6H, Si(CH_3)$_2$). Data matched with that reported in literature.[34]

3-Phenylbut-3-en-2-one (110)[36]



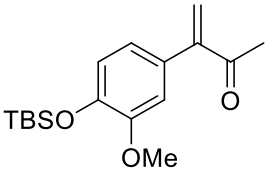
^{1}H NMR (300 MHz, $CDCl_3$): 7.40-7.27 (m, 5H, Ar*H*), 6.17 (d, 1H, *J* = 0.64 Hz, C=CH_2), 5.96 (d, 1H, *J* = 0.64 Hz, C=CH_2), 2.44 (s, 3H, COCH_3). Data matched with that reported in literature.[36]

3-(4-Methoxyphenyl) but-3-en-2-one (114)[36]



^{1}H NMR (300 MHz, $CDCl_3$): 7.27-7.22 (m, 2H, Ar*H*), 6.91-6.85 (m, 2H, Ar*H*), 6.08 (br s, 1H, C=CH_2), 5.91 (br s, 1H, C=CH_2), 3.80 (s, 3H, OCH_3), 2.43 (s, 3H, COCH_3). Data matched with that reported in literature.[36]

3-(4-((*tert*-Butyldimethylsilyl) oxy)-3-methoxyphenyl) but-3-en-2-one (113)[36]

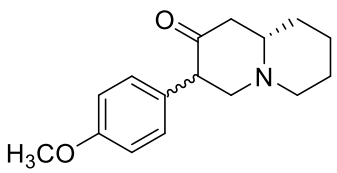


^{1}H NMR (300 MHz, $CDCl_3$): 6.68-6.59 (m, 3H, Ar*H*), 5.89 (s, 1H, C=CH_2), 5.73 (s, 1H, C=CH_2), 3.64 (s, 3H, OCH_3), 2.26 (s, 3H, COCH_3), 0.83 (s, 9H, C(CH_3)$_3$), 0.00 (s, 6H, Si(CH_3)$_2$). Data matched with that reported in literature.[36]

General procedure for the synthesis of 3-arylquinolizidinones

To **11** in a vial was added *S*-proline, the enone and DMF at room temperature. The reaction mixture was stirred at ambient temperature for the specified period. Aqueous HCl (1M) was added and the mixture was extracted with EtOAc. The aqueous layer was made basic to pH 10 with solid NaOH and then extracted with dichloromethane. The combined extracts were dried and concentrated and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 99:1) to provide the required 3-arylquinolizidinone.

3-(4-Methoxyphenyl) hexahydro-1H-quinolizin-2(6H)-one (115)



Reaction of **114** (247 mg, 1.2 mmol) and (50.0 mg, 0.2 mmol) of **11** in the presence of *S*-proline (13.8 mg, 0.12 mmol) in DMF (0.5 mL) according to the general procedure gave, after purification by flash chromatography on silica gel, 17 mg (10%) of **115**.

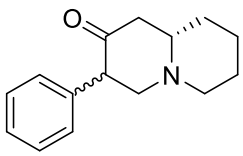
^{1}H NMR (300 MHz, $CDCl_3$): 7.10-7.02 (m, 2H, Ar*H*), 6.92-6.83 (m, 2H, Ar*H*), 3.90 (dd, 1H, *J* = 12.6, 6.9 Hz, ArC*H*CO), 3.79 (s, 3H, OCH_3), 3.19 (dd, 1H, *J* = 11.5, 5.9 Hz, CH_2), 3.03-2.94 (m, 1H, NC*H*), 2.63-2.38 (m, 3H, CH_2), 2.33-2.20 (m, 1H, NC*H*), 2.11 (dt, 1H, *J* = 11.5, 3.4 Hz, CH_2), 1.84-1.57 (m, 4H, CH_2), 1.50-1.19 (m, 2H, CH_2)

^{13}C NMR (125 MHz, $CDCl_3$): 207.5 (*C*O), 158.8 (ArC_{ipso}), 130.1 (2xAr*C*), 128.0 (ArC_{ipso}), 113.9 (2xAr*C*), 63.3 (*C*H_2), 62.7 (Ar*C*H), 56.1 (O*C*H_3), 55.3 (N*C*H), 55.0 (*C*H_2), 48.4 (*C*H_2), 33.6 (*C*H_2), 25.6 (*C*H_2), 23.4 (*C*H_2)

IR (neat): 2932, 1710, 1609, 1513, 1446, 1346, 1287, 1251, 1225, 1179, 1109, 1027 cm^{-1}

HRMS (ESI, pos.): *m*/*z* 260.1642 (260.1651 calc. for $C_{16}H_{22}NO_2$ $(M+H)^+$)

3-Phenylhexahydro-1H-quinolizin-2(6H)-one (116)



Reaction of **110** (176 mg, 1.2 mmol) and (100 mg, 0.2 mmol) **11** in the presence of *S*-proline (13.8 mg, 0.12 mmol) in DMF (0.5 mL) according to the general procedure gave, after purification by flash chromatography on silica gel, 34 mg (13%) of **116**.

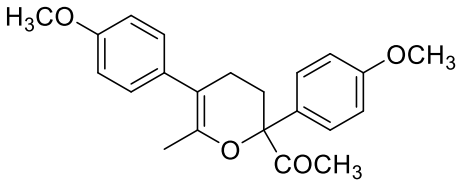
^{1}H NMR (300 MHz, $CDCl_3$): 7.37-7.26 (m, 3H, Ar*H*), 7.16-7.11 (m, 2H, Ar*H*), 3.94 (dd, 1H, *J* = 12.44, 5.82 Hz, ArC*H*CO), 3.21 (dd, 1H, *J* = 11.51, 5.87 Hz, CH_2), 3.04-2.93 (m, 1H, CH_2), 2.60 (dd, 1H, *J* = 12.47, 11.56 Hz, CH_2), 2.55-2.39 (m, 2H, CH_2), 2.33-2.22 (m, 1H, NC*H*), 2.17-2.02 (m, 1H, CH_2), 1.85-1.59 (m, 4H, CH_2), 1.50-1.21 (m, 2H, CH_2)

^{13}C NMR (125 MHz, $CDCl_3$): 207.0 (*C*O), 135.9 (ArC_{ipso}), 129.2 (2xAr*C*), 128.4 (2xAr*C*), 127.3 (Ar*C*), 63.1 (Ar*C*HCO), 62.6 (*C*H_2), 56.9 (N*C*H), 55.0 (*C*H_2), 48.4 (*C*H_2), 33.6 (*C*H_2), 25.5 (*C*H_2), 23.3 (*C*H_2)

IR (neat): 2931, 1715, 1602, 1496, 1446, 1364, 1281, 1222, 1154, 1108, 1026 cm^{-1}

HRMS (ESI, pos.): *m/z* 230.1539 (230.1545 calc. for $C_{15}H_{20}NO$ $(M+H)^+$)

1-(2,5-bis(4-Methoxyphenyl)-6-methyl-3,4-dihydro-2H-pyran-2-yl) ethanone[44]



This compound was obtained as a side product in the synthesis of enone **114**.

^{1}H NMR (300 MHz, $CDCl_3$): 7.46-7.39 (m, 2H, Ar*H*), 7.06-6.99 (m, 2H, Ar*H*), 6.93-6.86 (m, 2H, Ar*H*), 6.85-6.79 (m, 2H, Ar*H*), 3.81 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 2.65-2.51 (m, 1H, CH_2), 2.33-2.18 (m, 1H, CH_2), 2.13-2.00 (m, 2H, CH_2), 1.96-1.92 (m, 3H, CH_3)

^{13}C NMR (125 MHz, $CDCl_3$): 209.5 (*C*O), 159.3 (ArC_{ipso}), 158.0 (ArC_{ipso}), 145.6 (ArC_{ipso}), 133.8 (ArC_{ipso}), 131.4 (Ar*C*=C), 129.8 (2xAr*C*), 126.4 (2xAr*C*), 113.9 (2xAr*C*), 113.5 (2xAr*C*), 110.8 (C=C_{ipso}), 85.4 (ArC_{ipso}COCH$_3$), 52.3 (2xOCH$_3$), 29.9 (*C*H$_2$), 25.0 (*C*H$_2$), 24.3 (COCH$_3$), 18.1 (*C*H$_3$)

2.7 References

(1) Rother, A.; Malone, M. H. *J. Ethnopharmacol.* ***1994****, 42,* 135.

(2) Rother, A.; Schwarting, A. E. *Experientia* **1974**, *30*, 222.

(3) Fuji, K.; Yamada, T.; Fujita, E.; Murata, H. *Chem. Pharm. Bull*. **1978**, *26*, 2515.

(4) Horhammer, R. B.; Schwarting, A. E.; Edwards, J. M. *J. Org. Chem.* **1975**, *40*, 656.

(5) Blomster, R. N.; Schwarting, A. E.; Bobbitt, J. M. *Lloydia* **1964**, *27*, 15.

(6) Ferris, J. P. *J. Org. Chem.* **1962**, *27*, 2985.

(7) Appel, H.; Rother, A.; Schwarting, A. E. *Lloydia* **1965**, *28*, 84.

(8) (a) Rother, A.; Schwarting, A. E. *Phytochemistry* **1972**, *11*, 2475. (b) Rother, A.; Schwarting, A. E. J. Chem. Soc. D: *Chem. Commun.* **1969**, 1411. (c) Koo, S. H.; Comer,

F; Spenser, I. D. J. Chem. Soc. D: *Chem. Commun.* **1970**, 897. (d) Koo, S. H.; Gupta, R. N.; Spenser, I. D.; Wrobel, J. T. J. Chem. Soc. D: *Chem. Commun.* **1970**, 396. (e) Gupta, R. N.; Horsewood, P.; Koo, S. H.; Spenser, I. D. *Can. J. Chem.* **1979**, *57*, 1606. (f) Horsewood, P.; Golebieweski, W. M.; Wrobel, J. T.; Spenser, I. D.; Cohen, J. F.; Comer, F. *Can. J. Chem.* **1979**, *57*, 1615. (g) Hedges, S. H.; Herbert, R. B.; Wormald, P. C. *J. Nat. Prod.* **1993**, *56*, 1259.

(9) Rother, A.; Schwarting, A. E. *Lloydia* **1975**, *38*, 477.

(10) Bulger, P. G.; Bagal, S. K.; Marquez, R. *Nat. Prod. Rep.* **2008**, *25*, 254.

(11) (a) Monaco, M. R.; Renzi, P.; Scarpino Schietroma, D. M.; Bella, M. *Org. Lett.* **2011**, *13*, 4546. (b) Jakubec, P.; Cockfield, D. M.; Helliwell, M.; Raftery, J.; Dixon, D. *Beilstein J. Org. Chem.* **2012**, *8*, 567. (c) Itoh, T.; Yokoya, M.; Miyauchi, K.; Nagata, K.; Ohsawa, A. *Org. Lett.* **2006**, *8*, 1533. (d) Lalonde, M. P.; McGowan, M. A.; Rajapaksa, N. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2013**, *135*, 1891.

(12) Atobe, N.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **2005**, *46*, 2669.

(13) Mei, R.; Xu, D.; Hu, H.; Song, D.; Zhang, H.; Ma, D.; Xie, X.; She, X. *Org. Lett.* **2015**, *17*, 2230.

(14) Shan, Z.-H.; Liu, J.; Xu, L.-M.; Tang, Y.-F.; Chen, J.-H.; Yang, Z. *Org. Lett.* **2012**, *14*, 3712.

(15) Chausset-Boissarie, L.; Àrvai, R.; Cumming, G. R; Guénée, L.; Kündig, P. E. *Org. Biomol. Chem.* **2012**, *10*, 6473.

(16) Hanaoka, M.; Ogawa, N.; Arata, Y. *Chem. Pharm. Bull.* **1975**, *23*, 2140.

(17) Tayama, E.; Otoyama, S.; Isaka, W. *Chem. Commun.* **2008**, *35*, 4216.

(18) Cutter, A. C.; Miller, I. R.; Keily, J. F.; Bellingham, R. K.; Light, M. E.; Brown, R. C. D. *Org. Lett.* **2011**, *13*, 3988.

(19) Cheng, H. Y.; Hou, D. R. *Tetrahedron* **2007**, *63*, 3000.

(20) Pansare, S. V.; Pandya, K. *J. Am. Chem. Soc.* **2006**, *128*, 9624.

(21) Selected, recent, enantioselective syntheses of lasubine II: (a) Lahosa, A.; Yus, M.; Foubelo, F. *J. Org. Chem.* **2019**, *84*, 7331. (b) Formal synthesis: Aslam, N. F. M.; Simon, O.; Bates, R. W. *Tetrahedron* **2018**, *74*, 5032. (c) Reddy, A. A.; Reddy, P. O.; Prasad, K. R. *J. Org. Chem.* **2016**, *81*, 11363. (d) Trost, B. M.; Hung, C.-I. *J. Am. Chem. Soc.* **2015**, *137*, 15940. (e) Shi, S.-L.; Wei, X.-F.; Shimizu, Y.; Kanai, M. *J. Am. Chem. Soc.* **2012**, *134*, 17019. (f) Lim, J.; Kim, G. *Tetrahedron Lett.* **2008**, *49*, 88. (g) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *J. Org. Chem.* **1995**, *60*, 717.

(22) Hirama, T.; Umemura, T.; Kogure, N.; Kitajima, M.; Takayama, H. *Tetrahedron Lett.* **2017**, *58*, 223.

(23) Quick, J.; Meltz, C. *J. Org. Chem.* **1979**, *44*, 573.

(24) Enantioselective syntheses of subcosine II: (a) Cui, L.; Li, C.; Zhang, L. *Angew. Chem. Int. Ed.* **2010**, *49*, 9178. (b) Chalard, P.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C. *Tetrahedron: Asymmetry* **1998**, *9*, 4361.

(25) Castanet, A. S.; Colobert, F.; Broutin, P. E. *Tetrahedron Lett.* **2002**, *43*, 5047.

(26) Narender, N.; Srinivasu, P.; Kulkarni, S. J.; Raghavan, K.V. *Synth. Commun.* **2002**, *32*, 2319.

(27) Johnsson, R.; Meijer, A.; Ellervik, U. *Tetrahedron* **2005**, *61*, 11657.

(28) Song, S.; Sun, X.; Li, X.; Yuan, Y.; Jiao, N. *Org. Lett*. **2015**, *17*, 2886.

(29) (a) 1-Pyrroline was prepared by oxidation of pyrrolidine, see: Nomura, Y.; Ogawa, K.; Takeuchi, Y.; Tomoda, S. *Chem. Lett.* **1977**, 693. The crude product was purified by precipitation, see: (b) Baker, J. D.; Heath, R. R.; Millar, J. G. *J. Chem. Ecol.* **1992**, *18*, 1595.

(30) Selected reports on the synthesis of 9-aryindolizidinones: (a) Trost, B. M.; Biannick, B. *Org. Lett.* **2015**, *17*, 1433. (b) Pearson, W. H.; Walawalkar, R. A. *Tetrahedron* **2001**, *57*, 5081. (c) Pearson, W. H.; Gallagher, B. M. *Tetrahedron* **1996**, *52*, 12039.

(31) Carson, J. R.; Carmosin, R. J.; Vaught, J. L.; Gardocki, J. F.; Costanzo, M. J.; Raffa, R. B.; Almond, H. R. *J. Med. Chem.* **1992**, *35*, 2855.

(32) Wang, Z.; Wu, M.; Wang, Y.; Li, Z.; Wang, L.; Han, G.; Chen, F.; Liu, Y.; Wang, K.; Zhang, A.; Meng, L.; Wang, Q. *Eur. J. Med. Chem.* **2012**, *51*, 250.

(33) (a) Cui, M.; Wang, Q. *Eur. J. Org. Chem.* **2009**, 5445. b) Wang, Z.; Wang, Q. *Tetrahedron Lett.* **2010**, *51*, 1377. (c) Anton-Torrecillas, C.; Bosque, I.; Gonzalez-Gomez, J. C.; Loza, M. I.; Brea, J. *J. Org. Chem.* **2015**, *80*, 1284. (d) Stoye, A.; Opatz, T. *Eur. J. Org. Chem.* **2015**, 2149. (e) Pansare, S. V.; Dyapa, R. *Org. Biomol. Chem.* **2012**, *10*, 6776.

(34) Tran, K. V.; Bickar, D. *J. Org. Chem.* **2006**, *71*, 6640.

(35) Hashimoto, S.; Katoh, S.; Kato, T.; Urabe, D.; Inoue, M. *J. Am. Chem. Soc.* **2017**, *139*, 16420.

(36) Michailidis, F. R.; Sedillo, K. F.; Neely, J. M.; Rovis, T. *J. Am. Chem. Soc.* **2015**, *137*, 8892.

(37) Wang, Q.; Gao, W.; Lv, H.; Zhang, X. *Chem. Commun.* **2016**, *52*, 11850.

(38) Lancelot, S. F.; Cozens, F. L.; Schepp, N. P. *Org. Biomol. Chem.* **2003**, *1*, 1972.

(39) Hasegawa, E.; Arai, S.; Tayama, E.; Iwamoto, H. *J. Org. Chem.* **2015**, *80*, 1593.

(40) Chuprajob, T.; Changtam, C.; Chokchaisiri, R.; Chunglok, W.; Sornkaew, N.; Suksamrarn, A. *Bioorg. Med. Chem. Lett.* **2014**, *24,* 2839.

(41) Bakos, M.; Dobi, Z.; Fegyverneki, D.; Gyömöre, A.; Fernández, I.; Soós, T. *ACS Sustainable Chem. Eng.* **2018**, *6,* 10869.

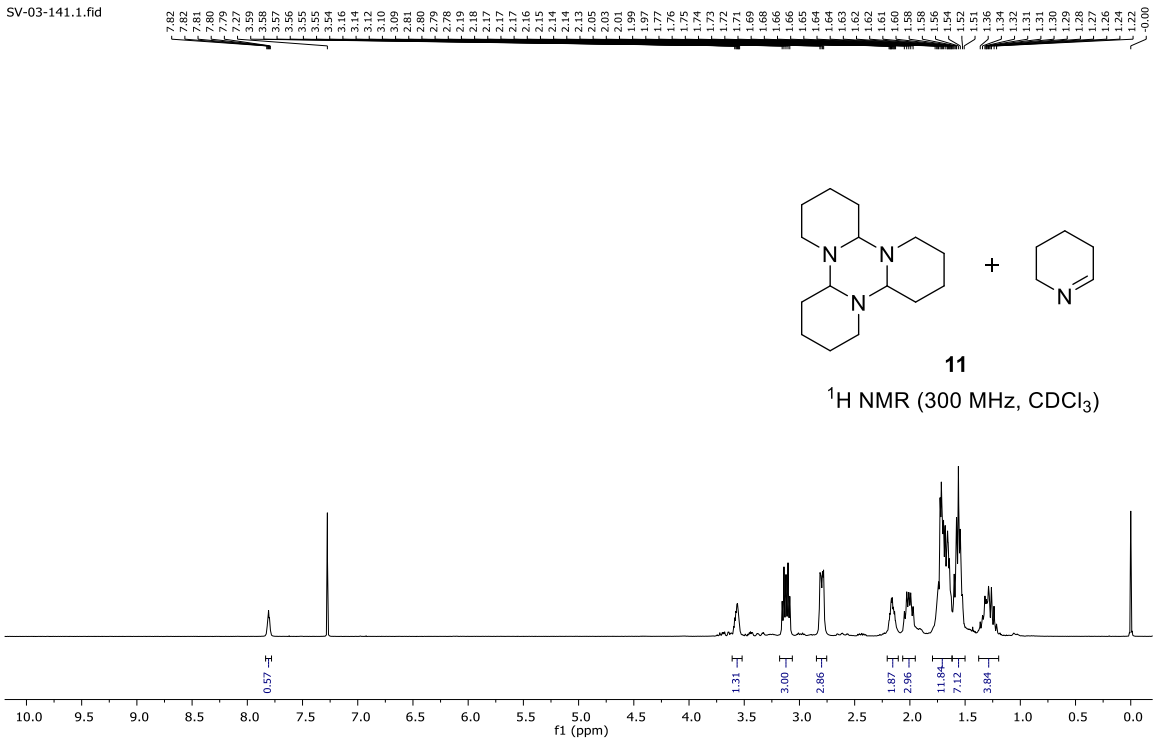
(42) Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128,* 12370.

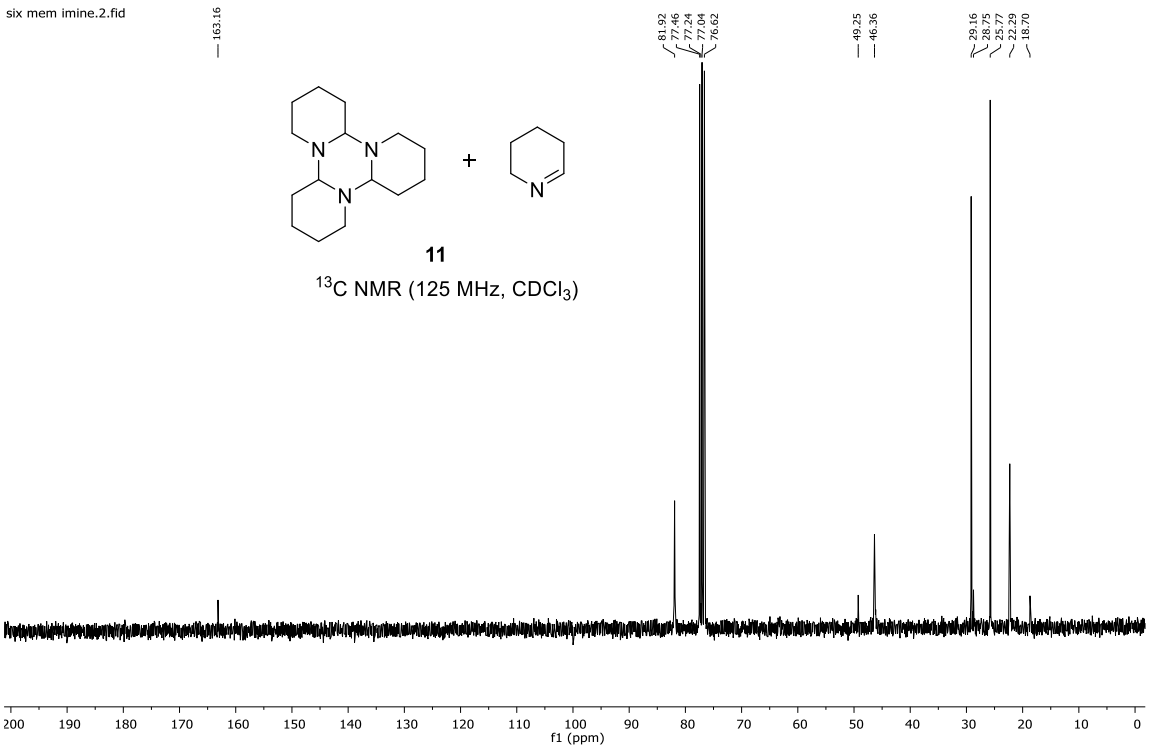
(43) James, M. J.; Grant, N. D.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. *Org. Lett.* **2016***, 18,* 6256.

(44) Lin, H.-C.; Tsai, R.-T.; Wu, H.-P.; Lee, H.-Y.; Lee, G.-A. *Tetrahedron* **2016**, *72*, 184.

(45) Prasun, K. P.; Sumit, D.; Parasuraman, J.; Venkatachalam, S. G. *Synth. Commun.* **2005**, *35*, 913.

2.8 Selected ^{1}H and ^{13}C NMR spectral data





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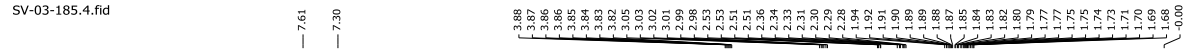
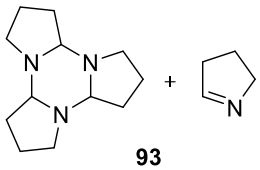
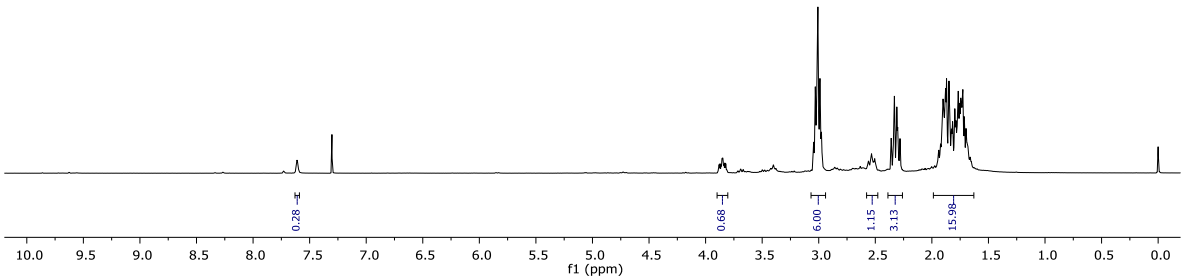




93

^{1}H NMR (300 MHz, $CDCl_3$)



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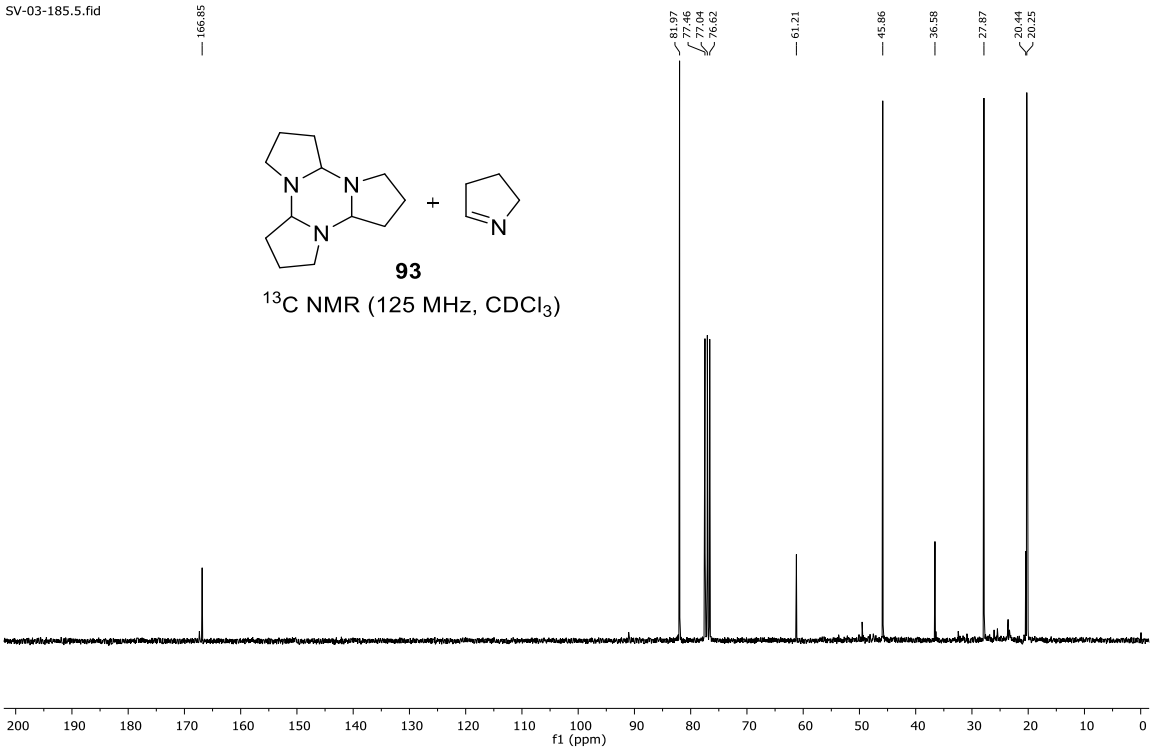
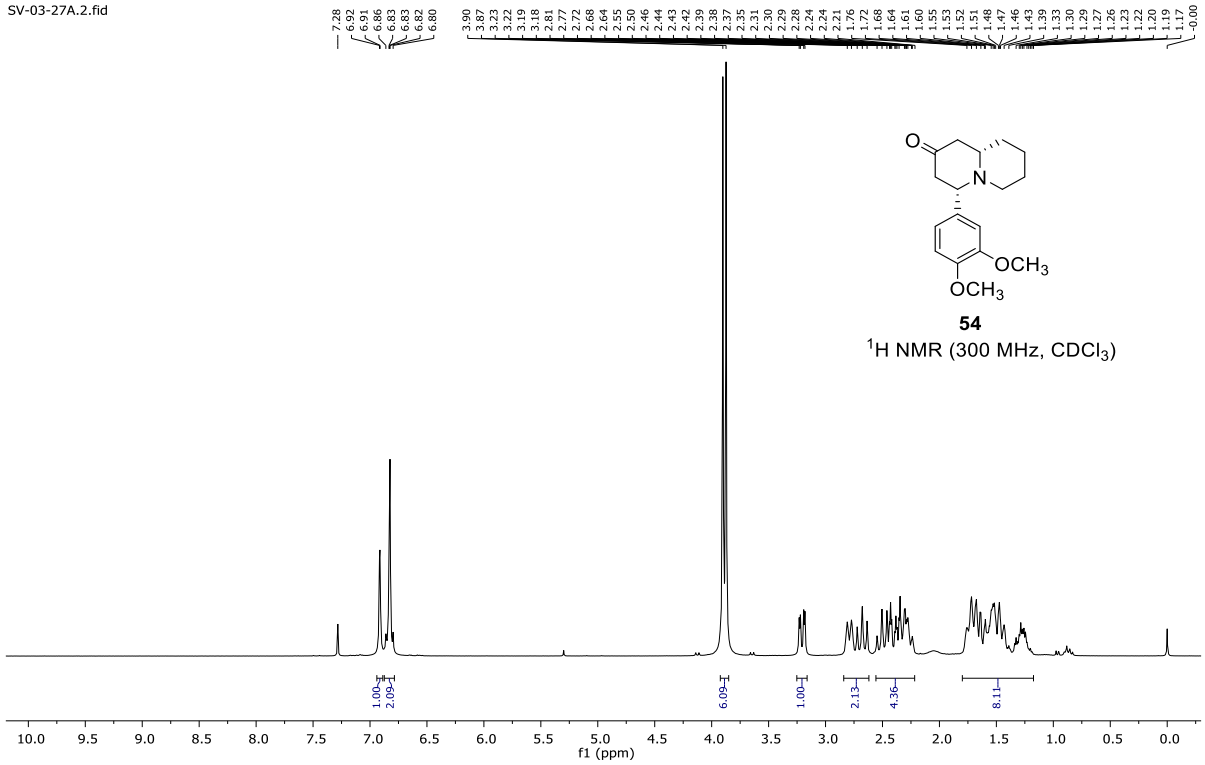


93

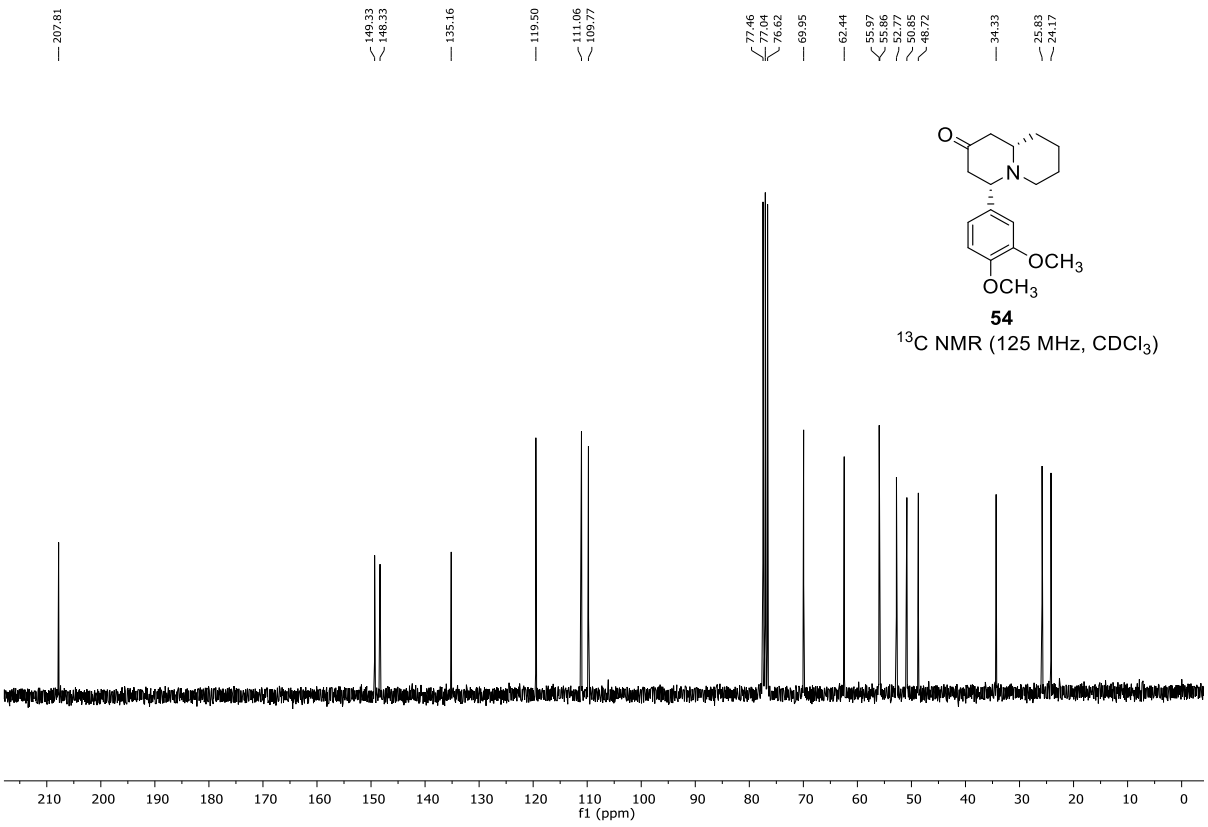
^{13}C NMR (125 MHz, $CDCl_3$)

SV-03-27A.2.fid



54

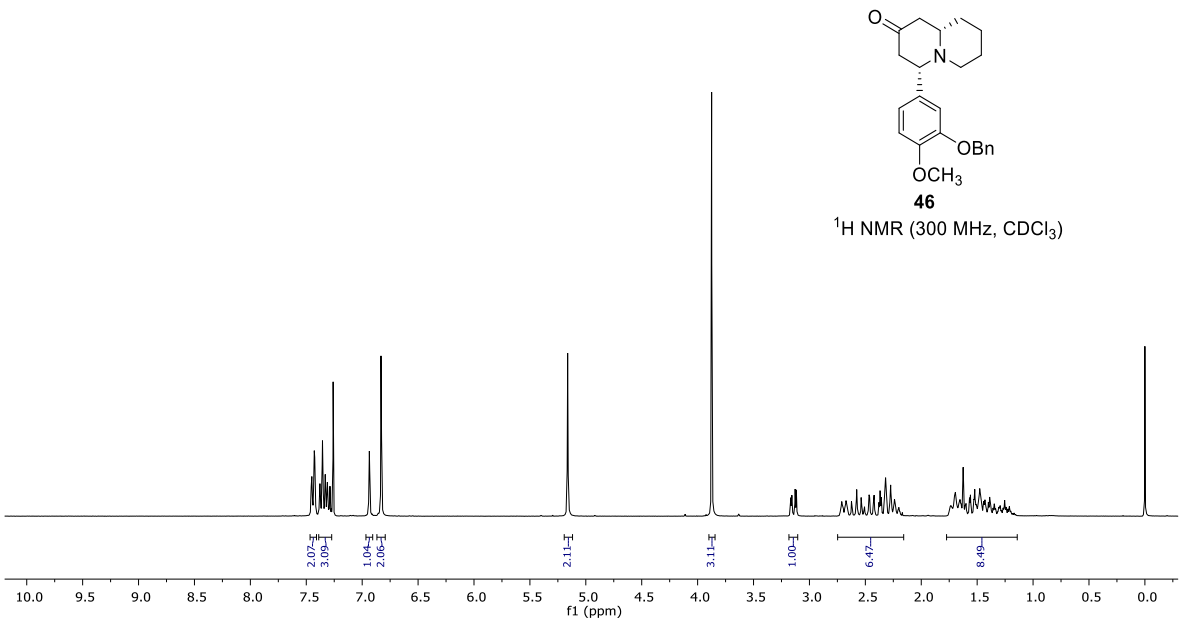
^{1}H NMR (300 MHz, $CDCl_3$)

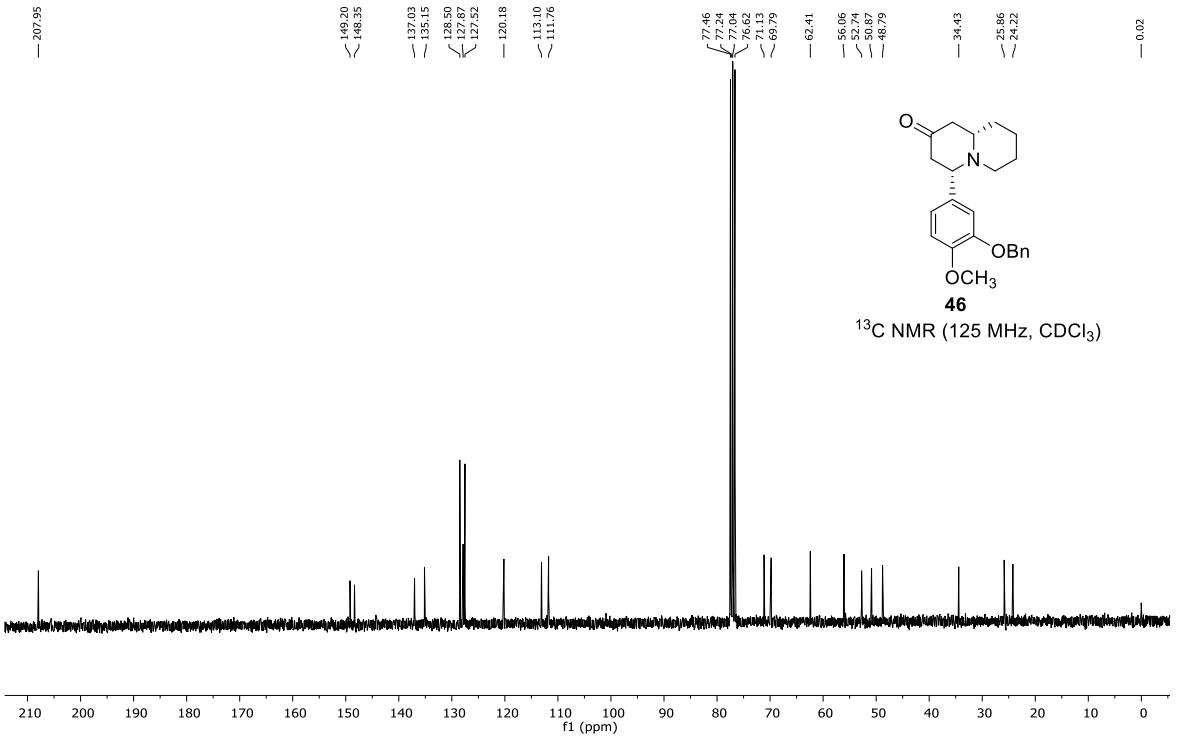


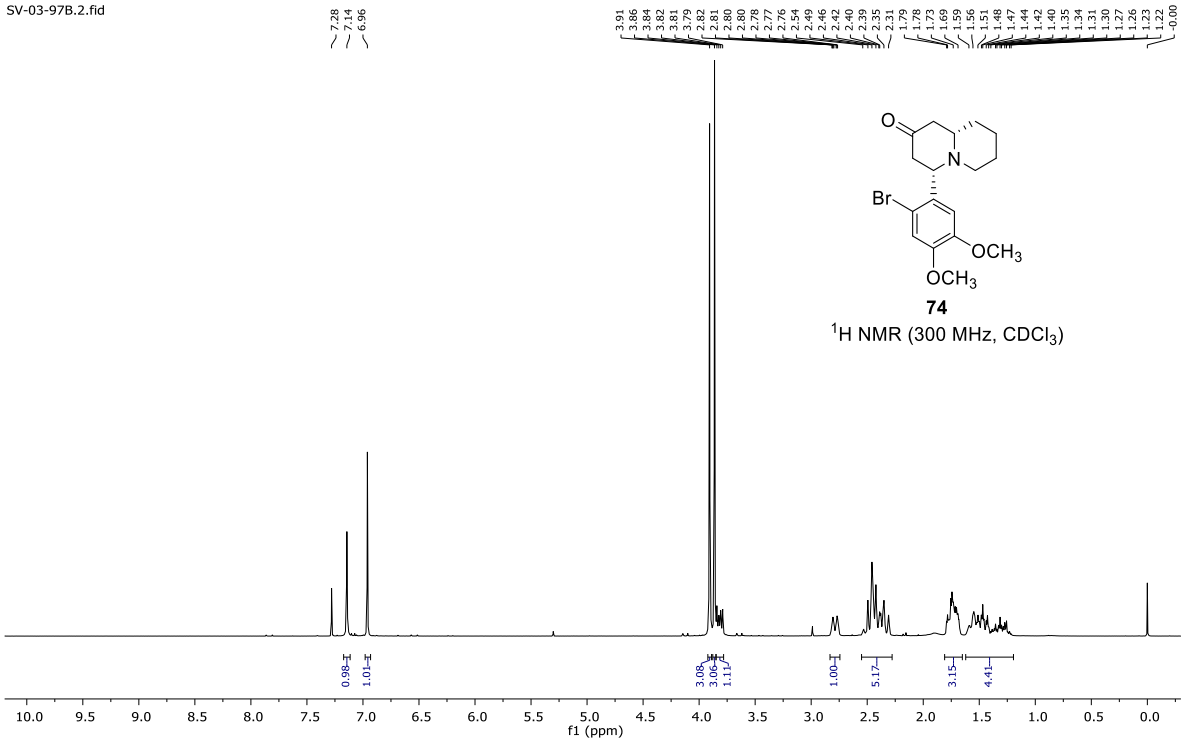
54

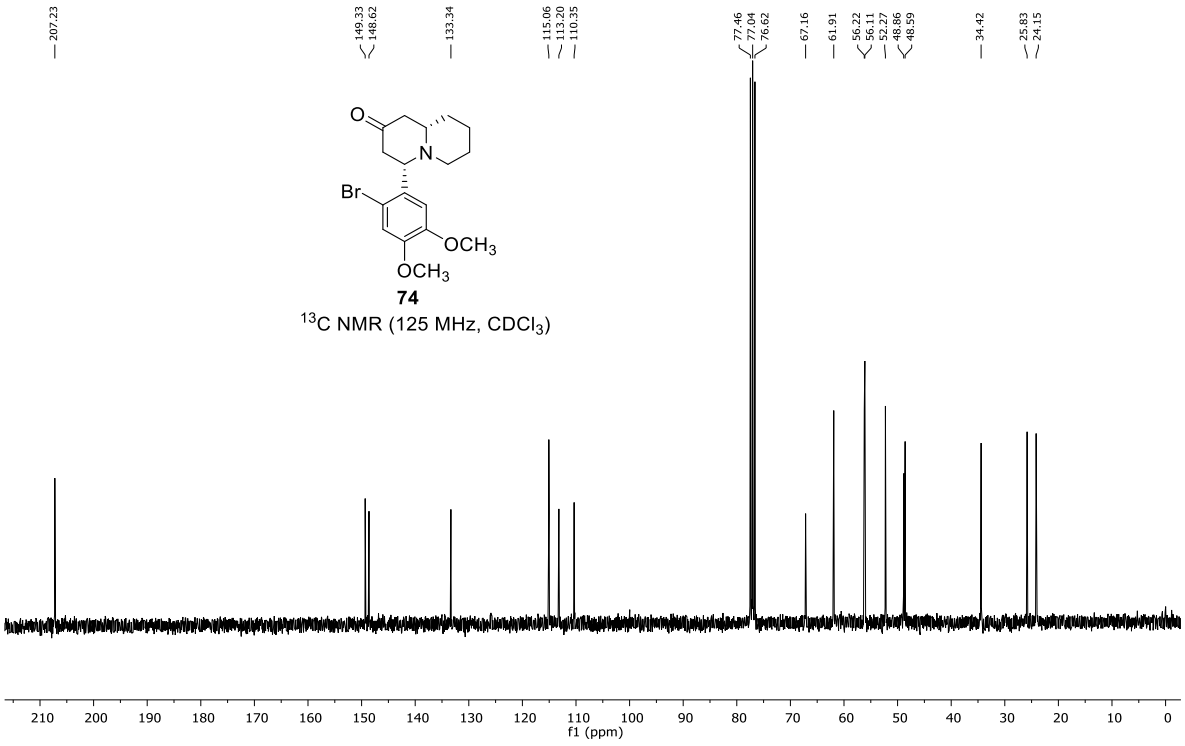
^{13}C NMR (125 MHz, $CDCl_3$)

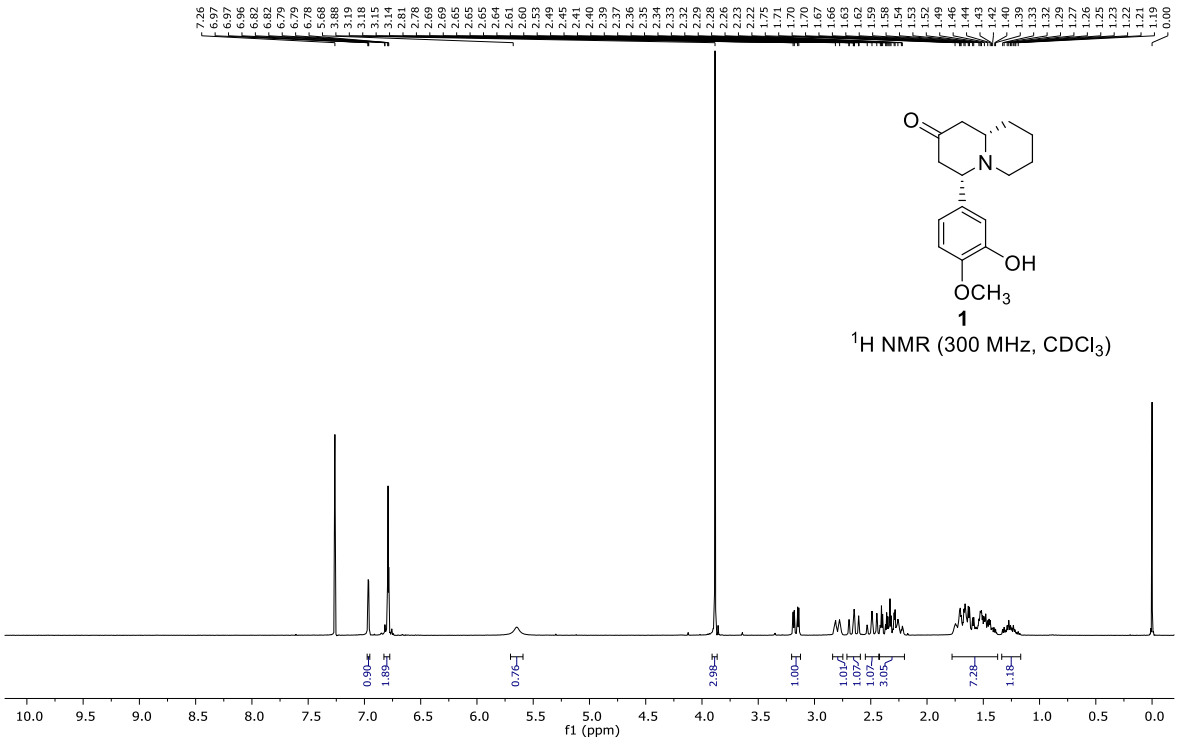
SV-03-69A.1.fid

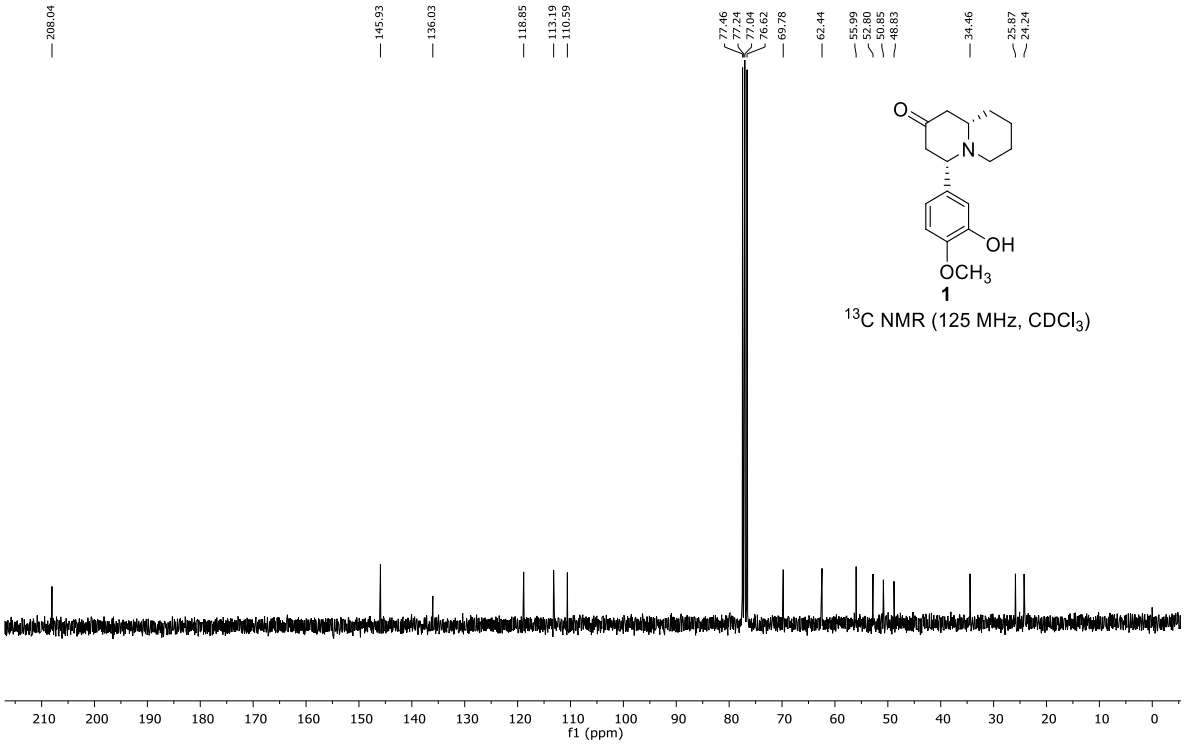




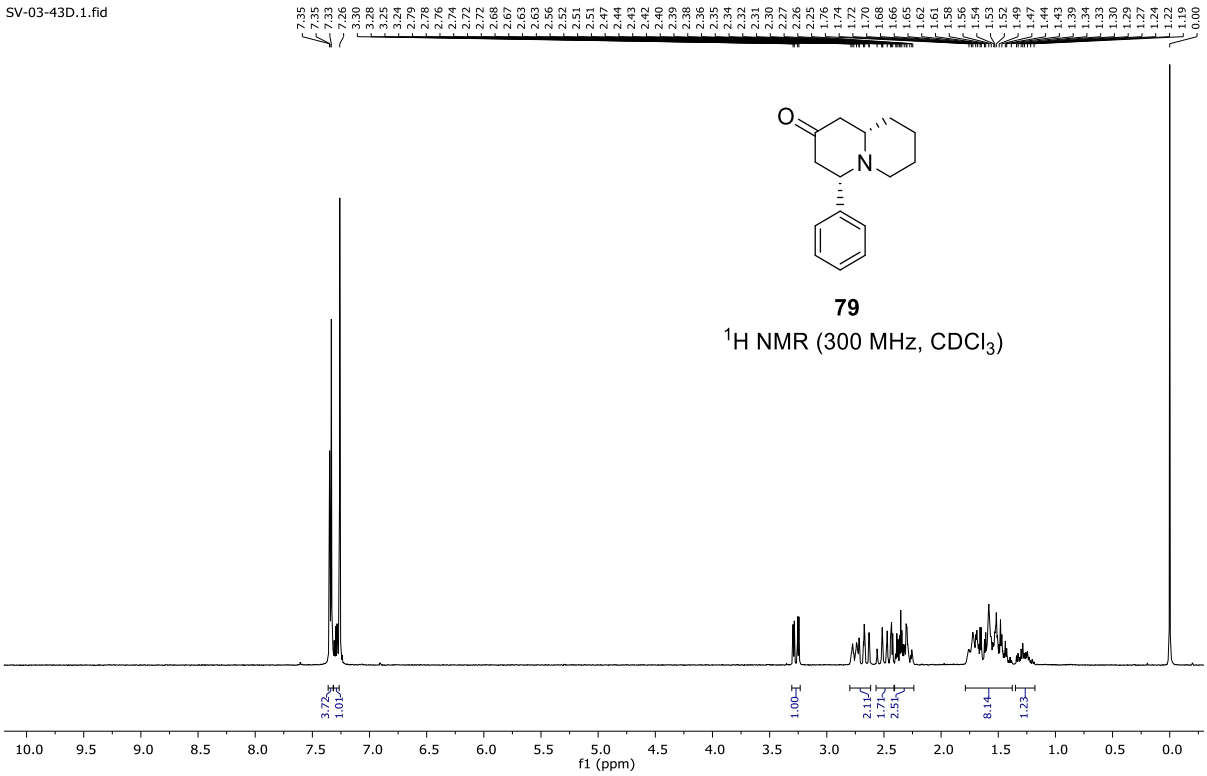

SV-03-97B.2.fid
7.28
7.14
6.96
3.91
3.86
3.84
3.82
3.81
3.79
2.82
2.81
2.80
2.80
2.78
2.77
2.76
2.54
2.49
2.46
2.42
2.40
2.39
2.35
2.31
1.79
1.78
1.73
1.69
1.59
1.56
1.51
1.48
1.47
1.44
1.42
1.40
1.35
1.34
1.31
1.30
1.27
1.26
1.23
1.22
-0.00
O
N
Br
OCH3
OCH3
74
1H NMR (300 MHz, CDCl3)
0.98
1.01
3.08
3.06
1.11
1.00
5.17
3.15
4.41
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

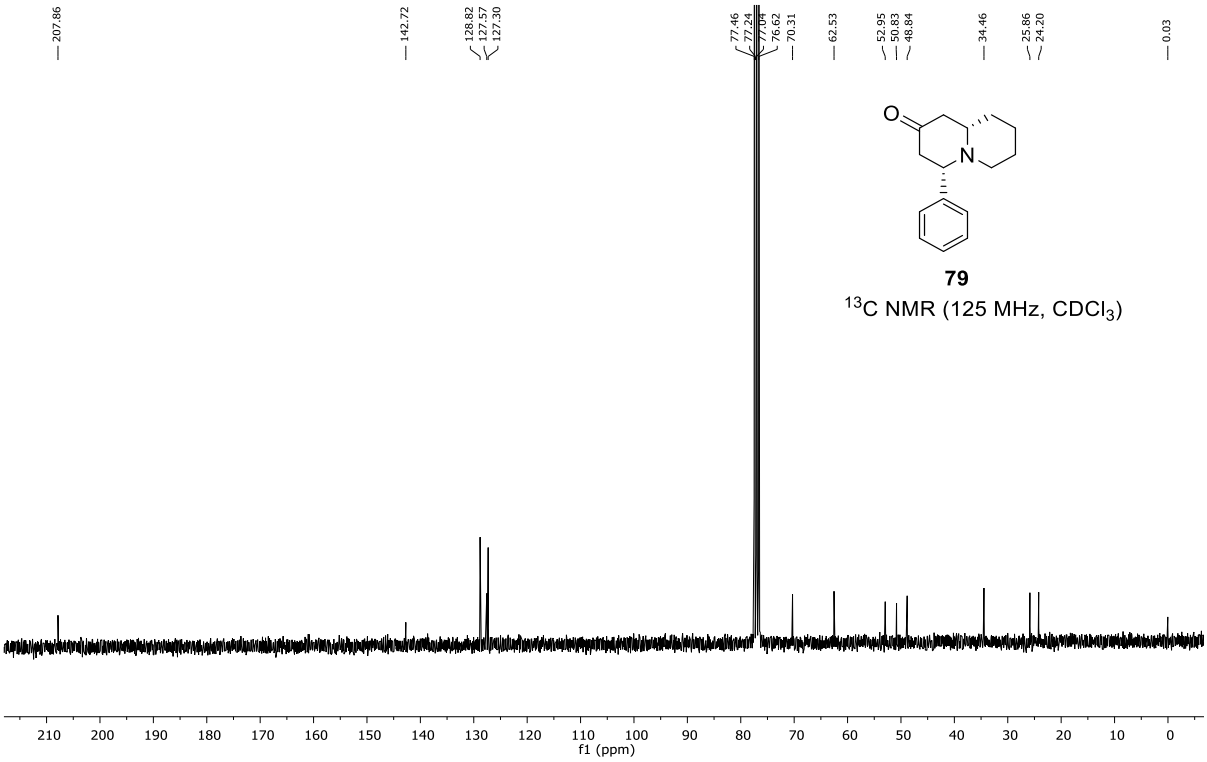

207.23
149.33
148.62
133.34
115.06
113.20
110.35
77.46
77.04
76.62
67.16
61.91
56.22
56.11
52.27
48.86
48.59
34.42
25.83
24.15
O
N
Br
OCH3
OCH3
74
13C NMR (125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

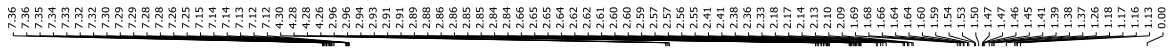

7.26 6.97 6.97 6.96 6.82 6.82 6.79 6.79 6.78 5.68 3.88 3.19 3.18 3.15 3.14 2.81 2.78 2.69 2.69 2.65 2.65 2.64 2.61 2.60 2.53 2.49 2.45 2.41 2.40 2.39 2.37 2.36 2.35 2.34 2.33 2.32 2.29 2.28 2.26 2.23 2.22 1.75 1.71 1.70 1.70 1.67 1.66 1.63 1.62 1.59 1.58 1.54 1.53 1.52 1.49 1.46 1.44 1.43 1.42 1.40 1.39 1.33 1.32 1.29 1.27 1.26 1.25 1.23 1.22 1.21 1.19 0.00
O
N
OH
OCH3
1
1H NMR (300 MHz, CDCl3)
0.90 1.89 0.76 2.98 1.00 1.01 1.07 1.07 3.05 7.28 1.18
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

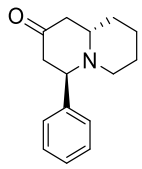

208.04 145.93 136.03 118.85 113.19 110.59 77.46 77.24 77.04 76.62 69.78 62.44 55.99 52.80 50.85 48.83 34.46 25.87 24.24
O
N
OH
OCH3
1
13C NMR (125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

SV-03-43D.1.fid



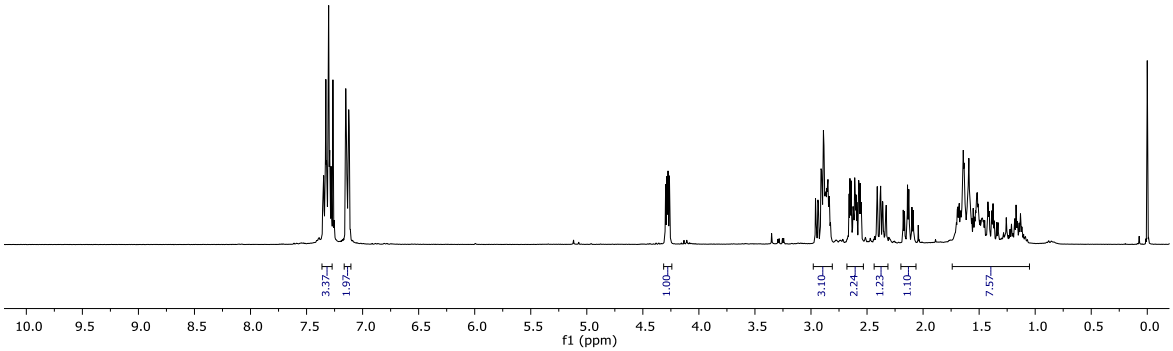


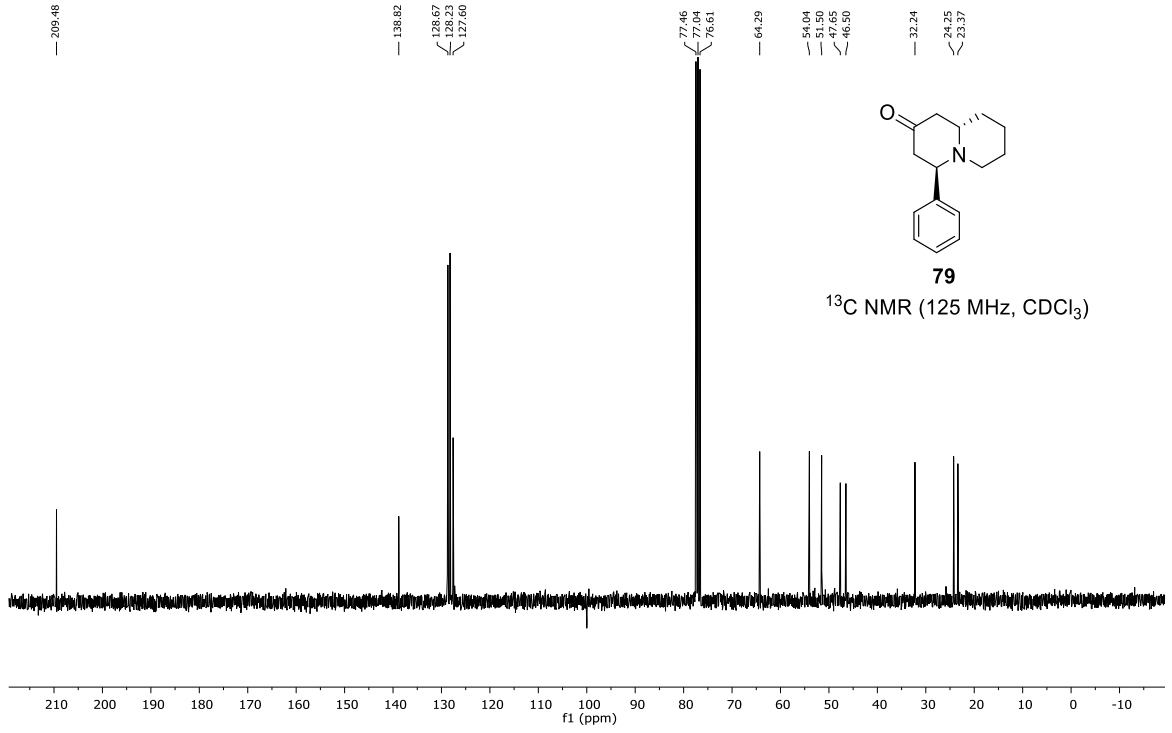




79

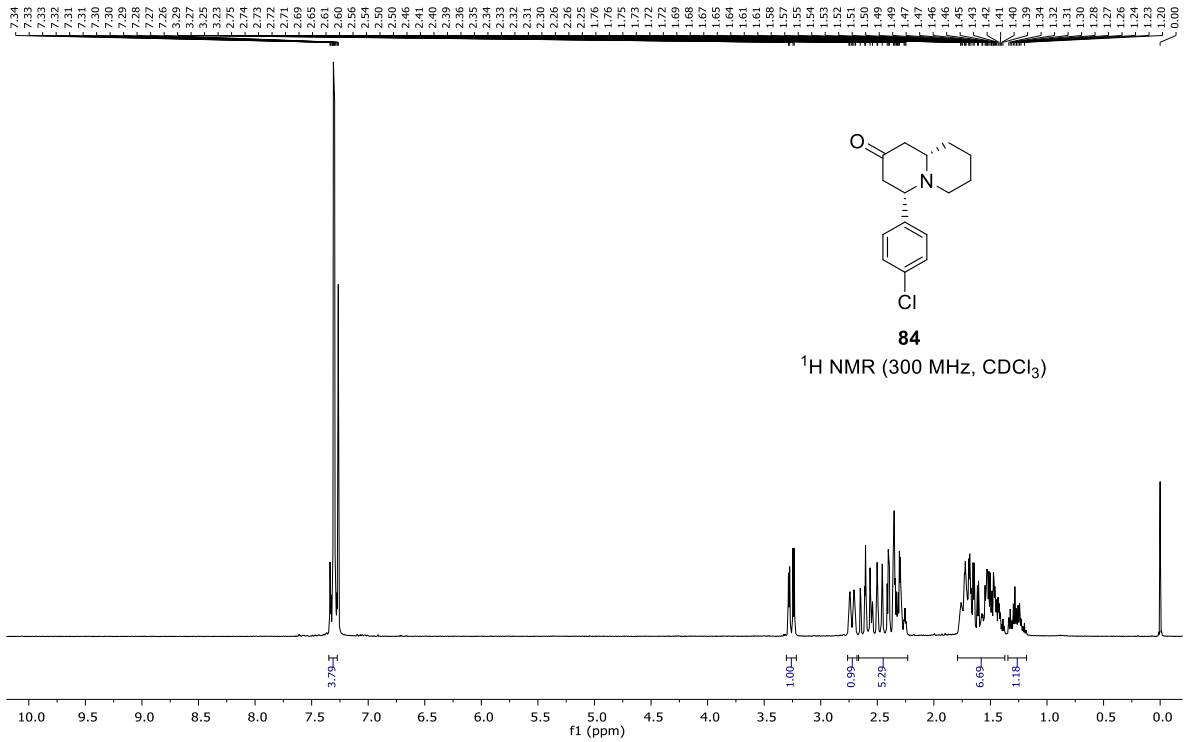
^{1}H NMR (300 MHz, $CDCl_3$)





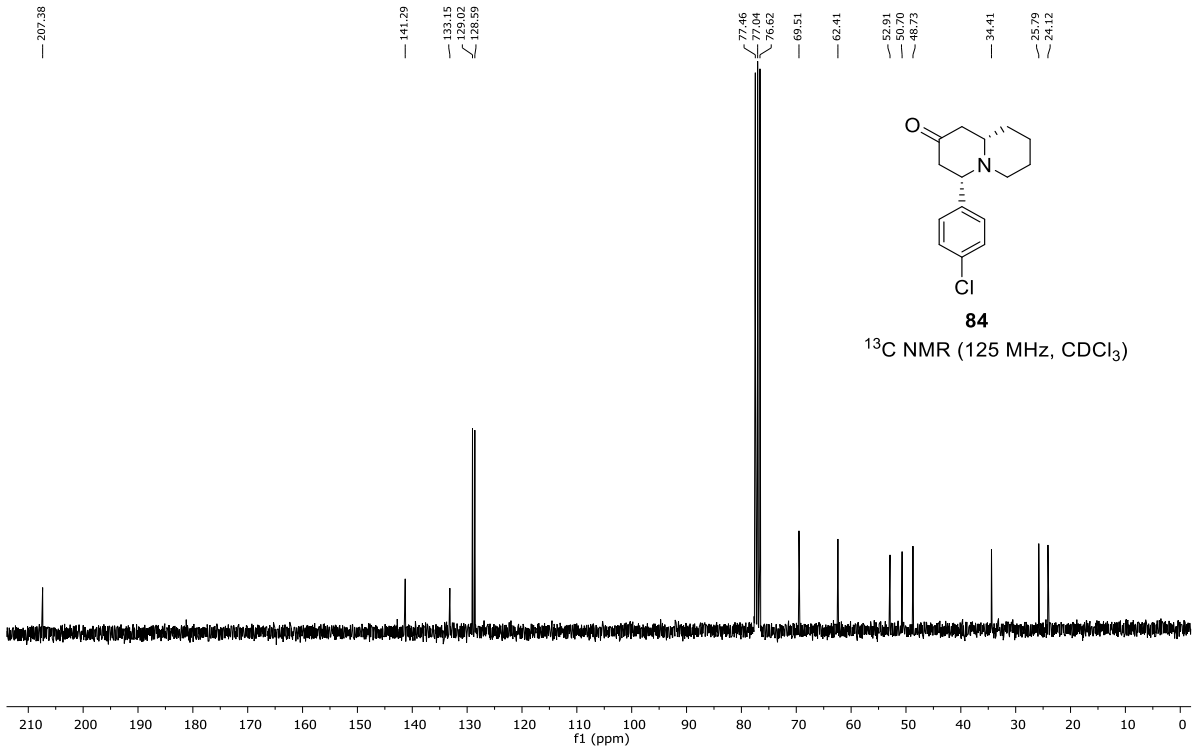
79

^{13}C NMR (125 MHz, $CDCl_3$)



84

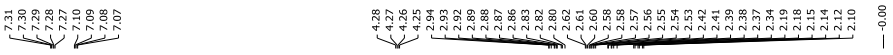
^{1}H NMR (300 MHz, $CDCl_3$)

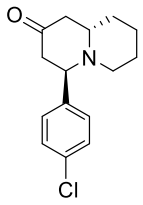


84

^{13}C NMR (125 MHz, $CDCl_3$)

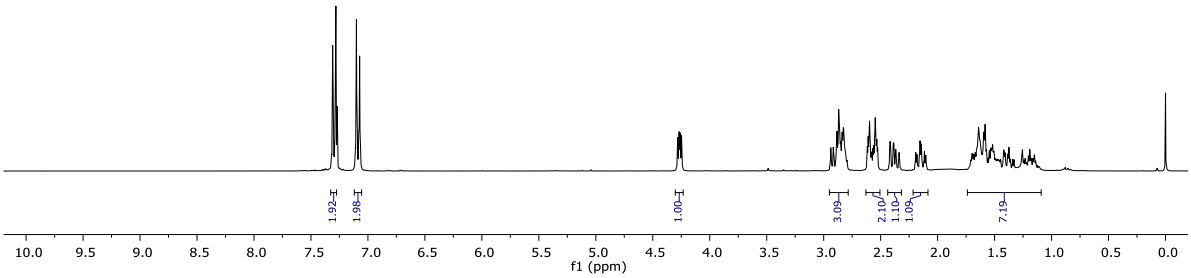
SV-03-41C.2.fid

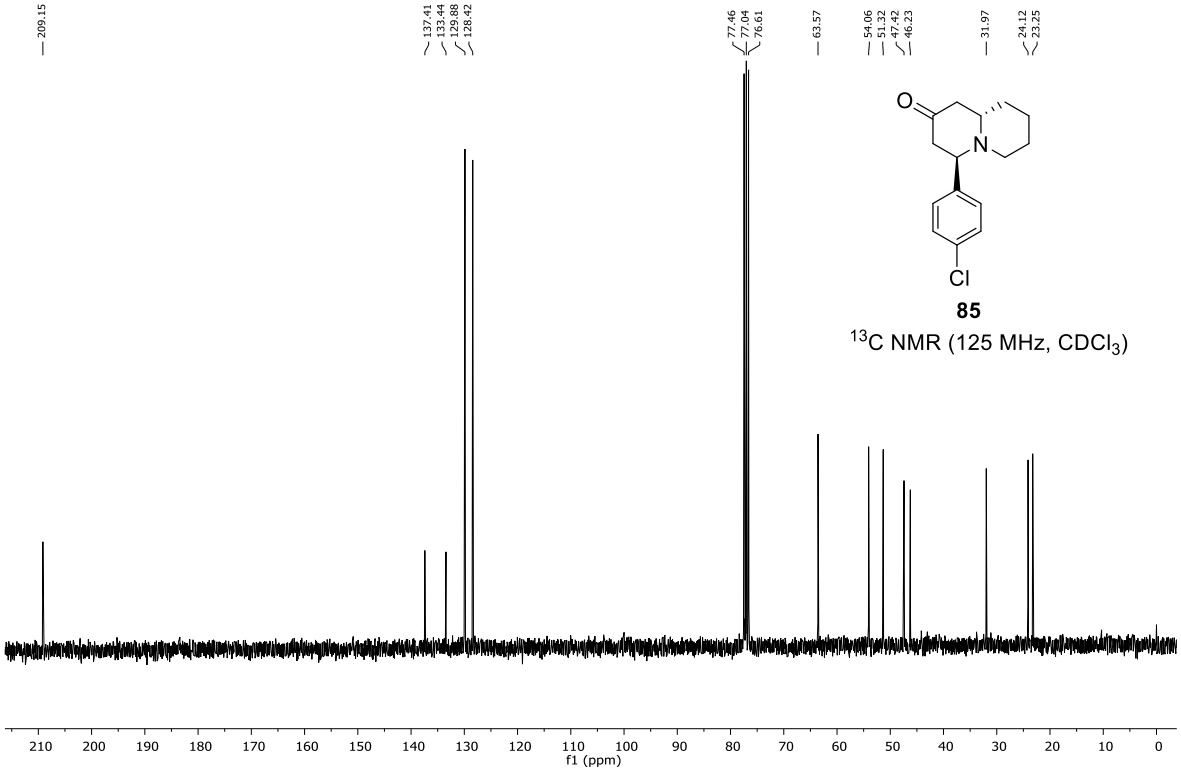




85

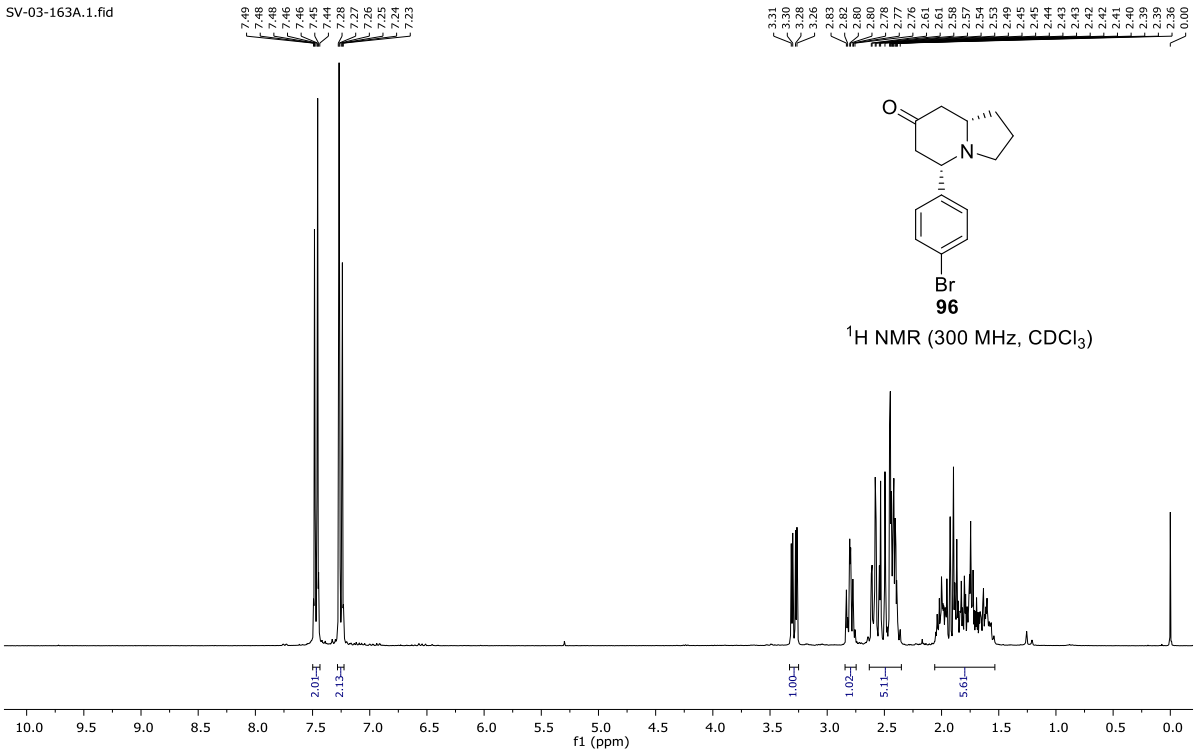
^{1}H NMR (300 MHz, $CDCl_3$)

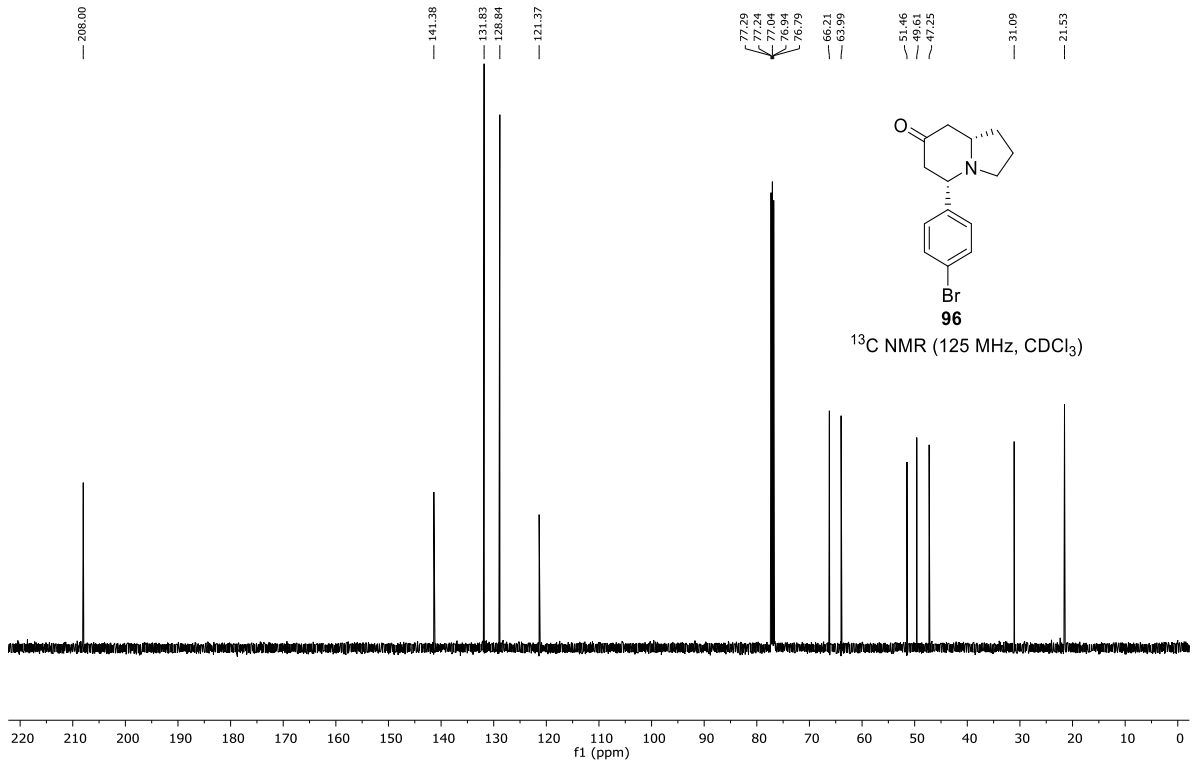


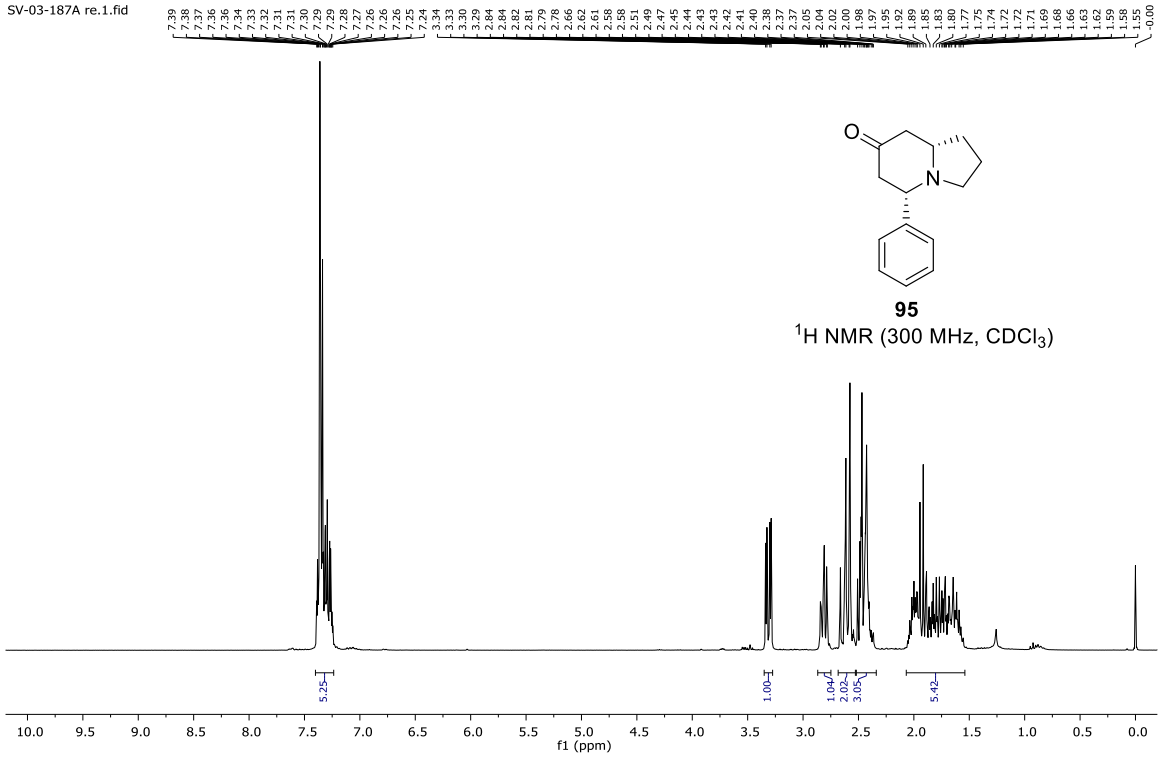


85

^{13}C NMR (125 MHz, $CDCl_3$)


SV-03-163A.1.fid
O
N
Br
96
^{1}H NMR (300 MHz, $CDCl_3$)
f1 (ppm)


O
N
Br
96
^{13}C NMR (125 MHz, $CDCl_3$)
f1 (ppm)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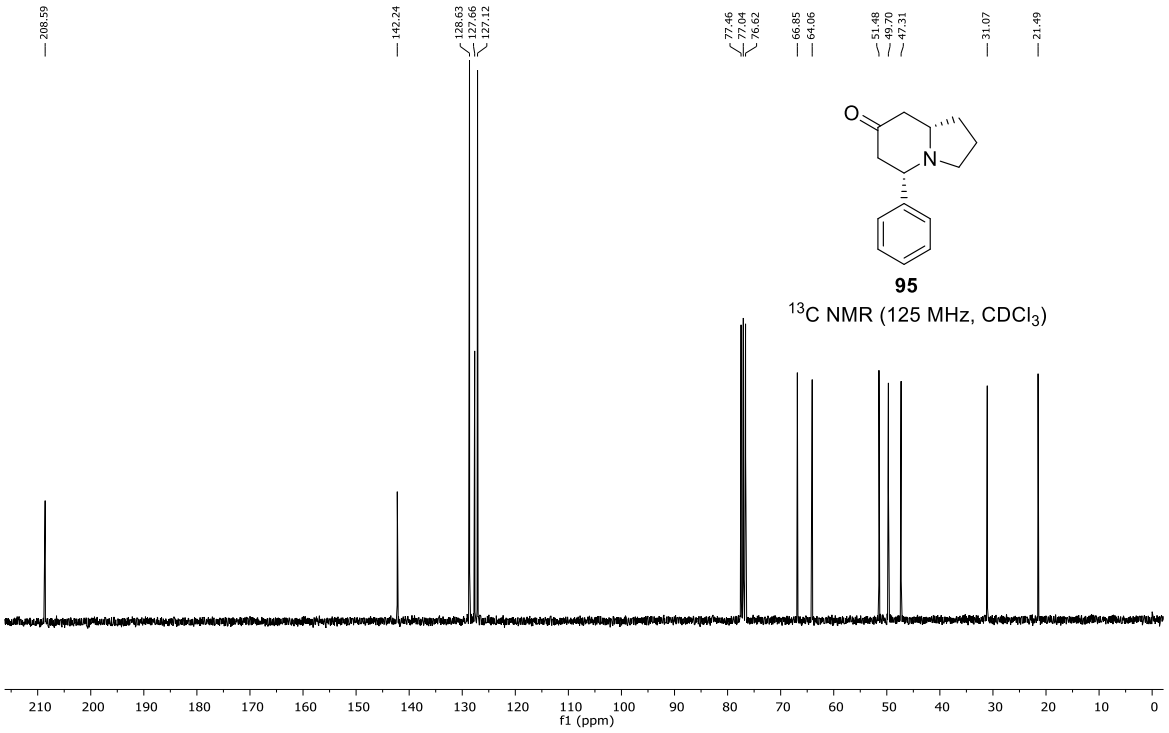
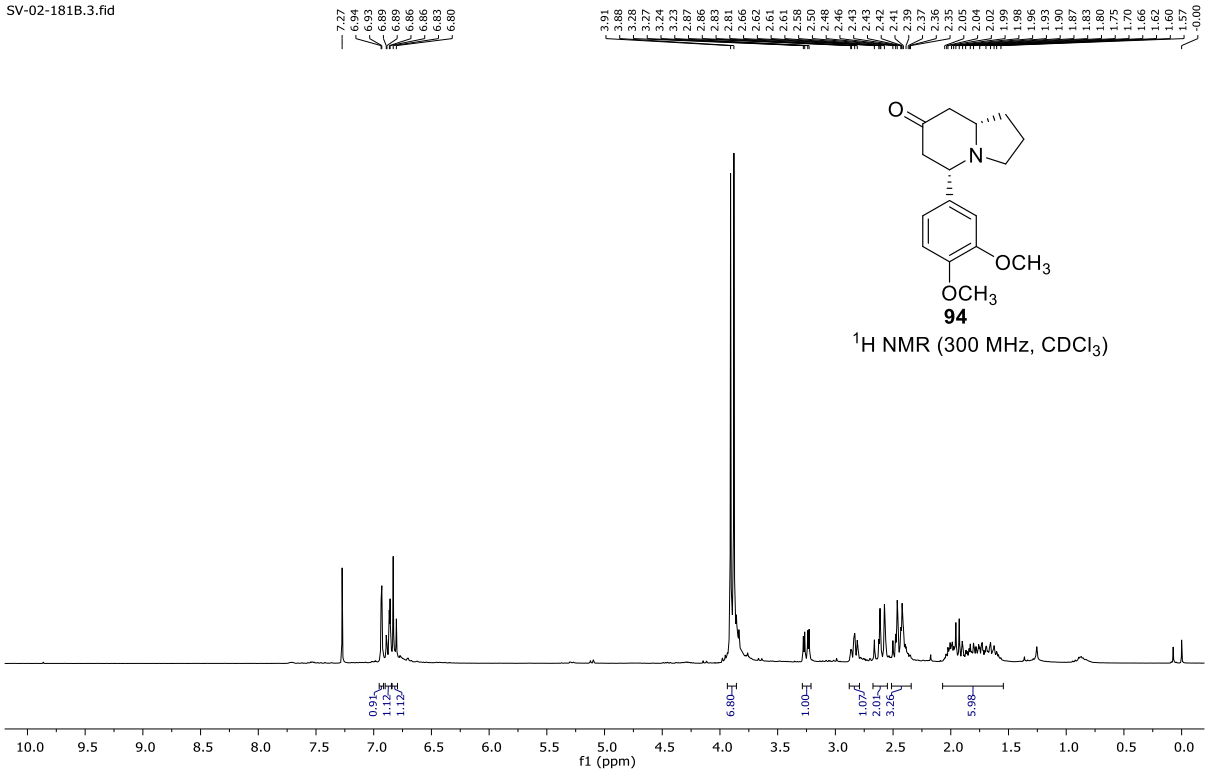
3.34 3.33 3.30 3.29 2.84 2.84 2.82 2.81 2.79 2.78 2.66 2.62 2.61 2.58 2.58 2.51 2.49 2.47 2.45 2.44 2.43 2.43 2.42 2.41 2.40 2.38 2.37 2.37 2.05 2.04 2.02 2.00 1.98 1.97 1.95 1.92 1.89 1.85 1.83 1.80 1.77 1.75 1.74 1.72 1.72 1.71 1.69 1.68 1.66 1.63 1.62 1.59 1.58 1.55 -0.00
O
N
95
^{1}H NMR (300 MHz, $CDCl_3$)
5.25
1.00
1.04
2.02
3.05
5.42
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

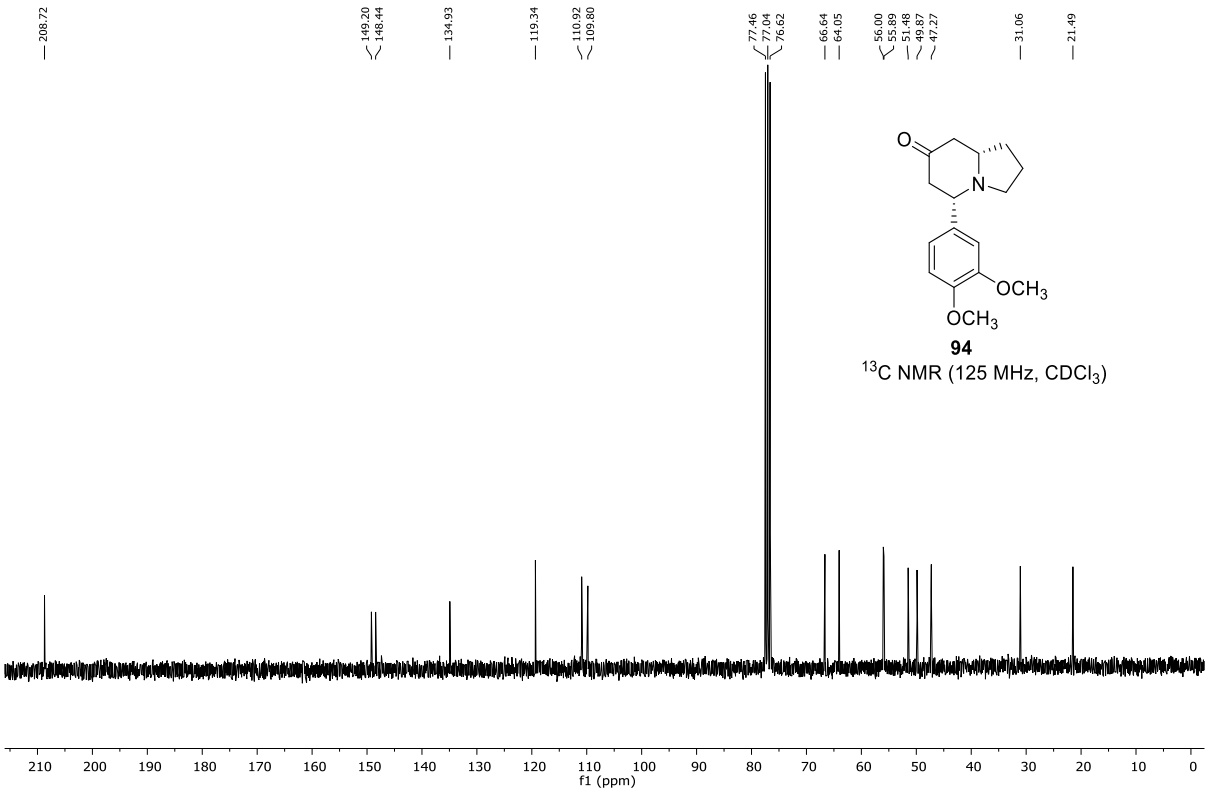

208.59
142.24
128.63
127.66
127.12
77.46
77.04
76.62
66.85
64.06
51.48
49.70
47.31
31.07
21.49
O
N
95
^{13}C NMR (125 MHz, $CDCl_3$)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

SV-02-181B.3.fid



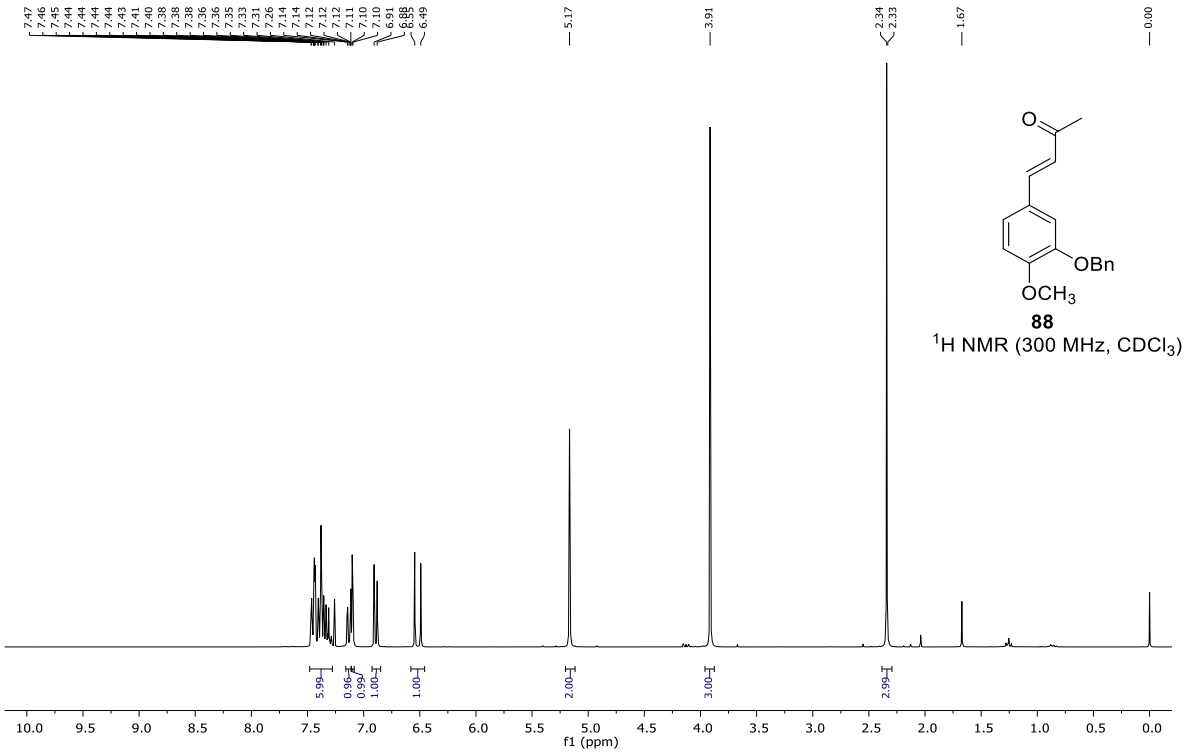
94

^{1}H NMR (300 MHz, $CDCl_3$)



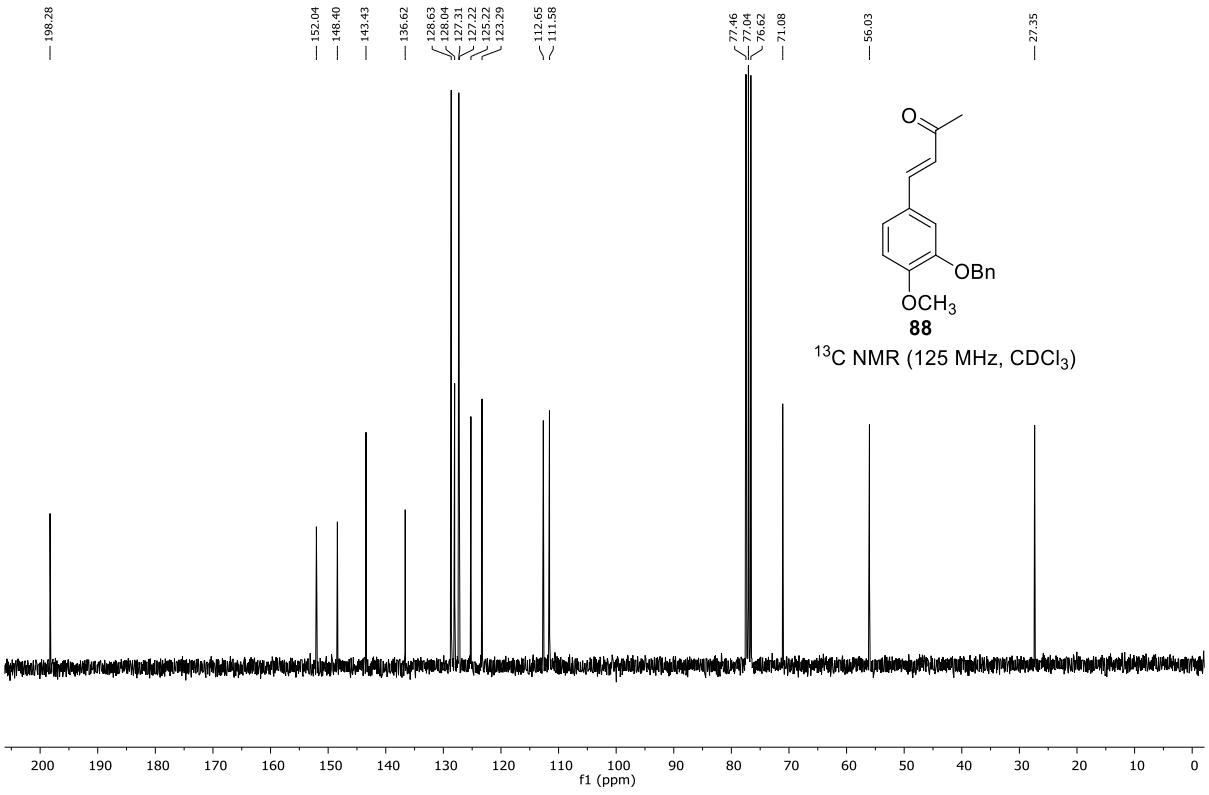
94

^{13}C NMR (125 MHz, $CDCl_3$)



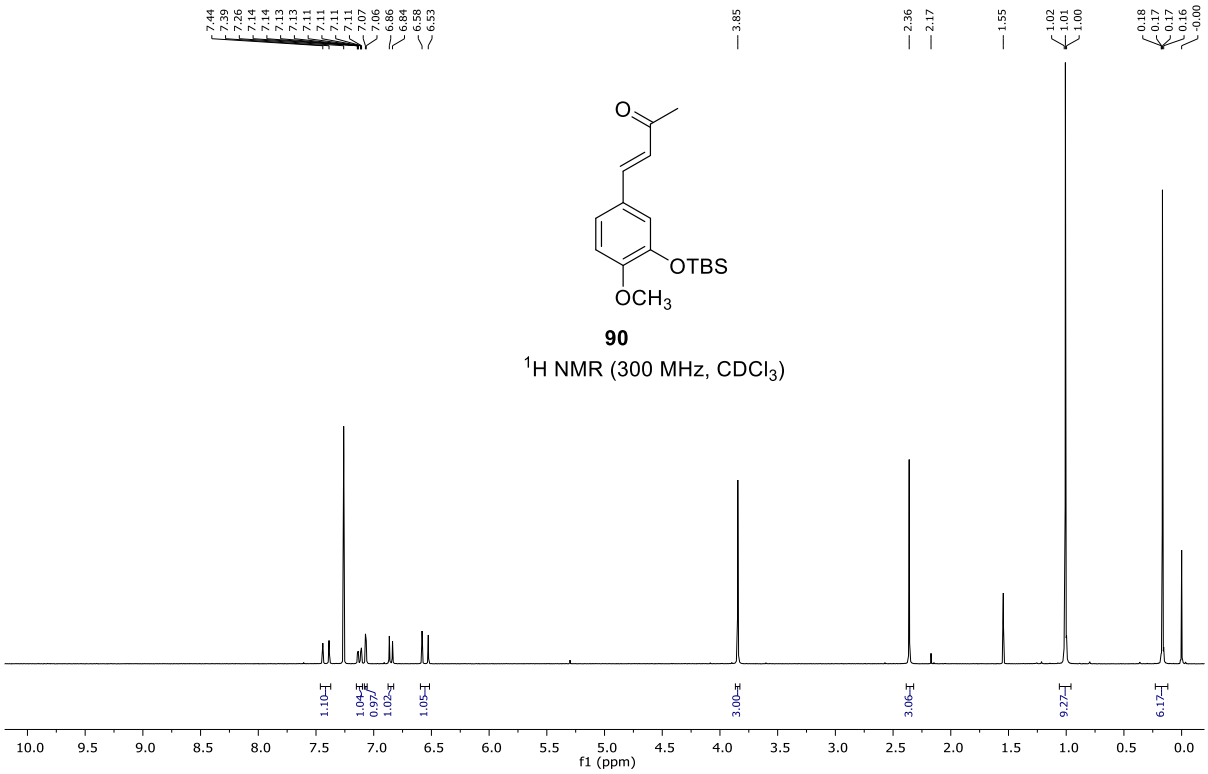
88

^{1}H NMR (300 MHz, $CDCl_3$)



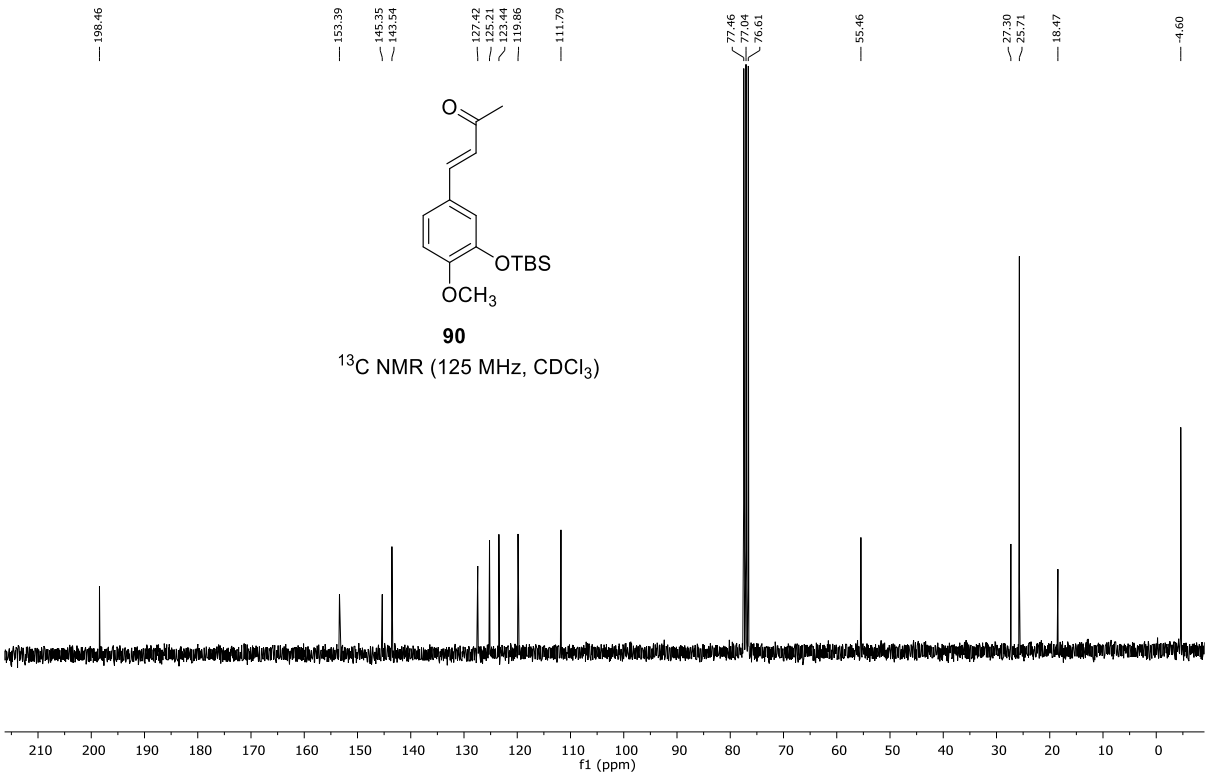
88

^{13}C NMR (125 MHz, $CDCl_3$)



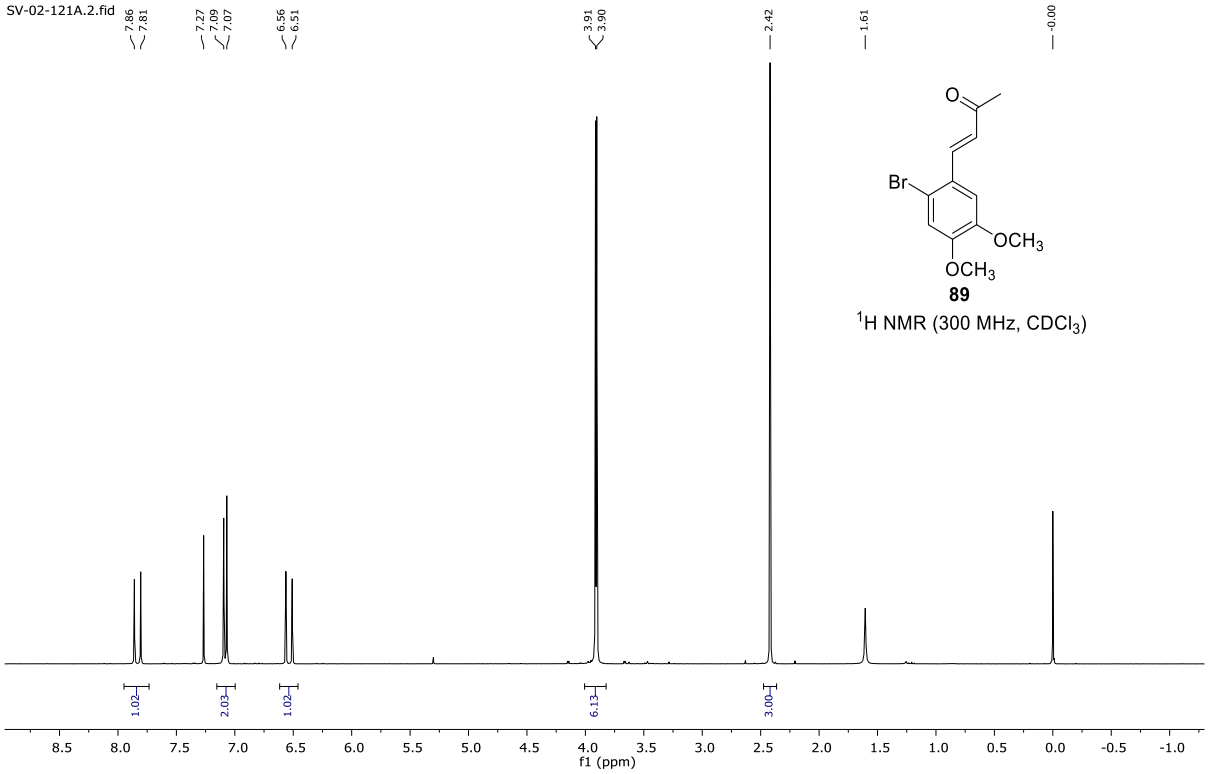
90

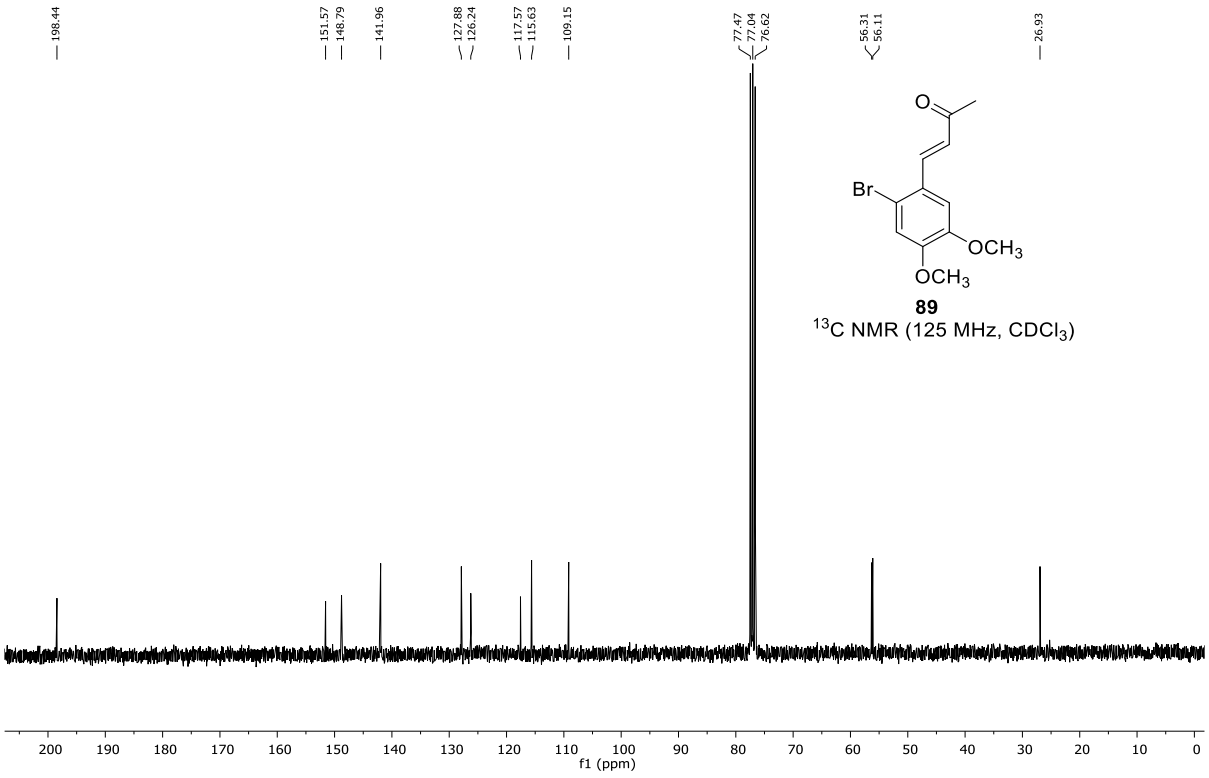
^{1}H NMR (300 MHz, $CDCl_3$)

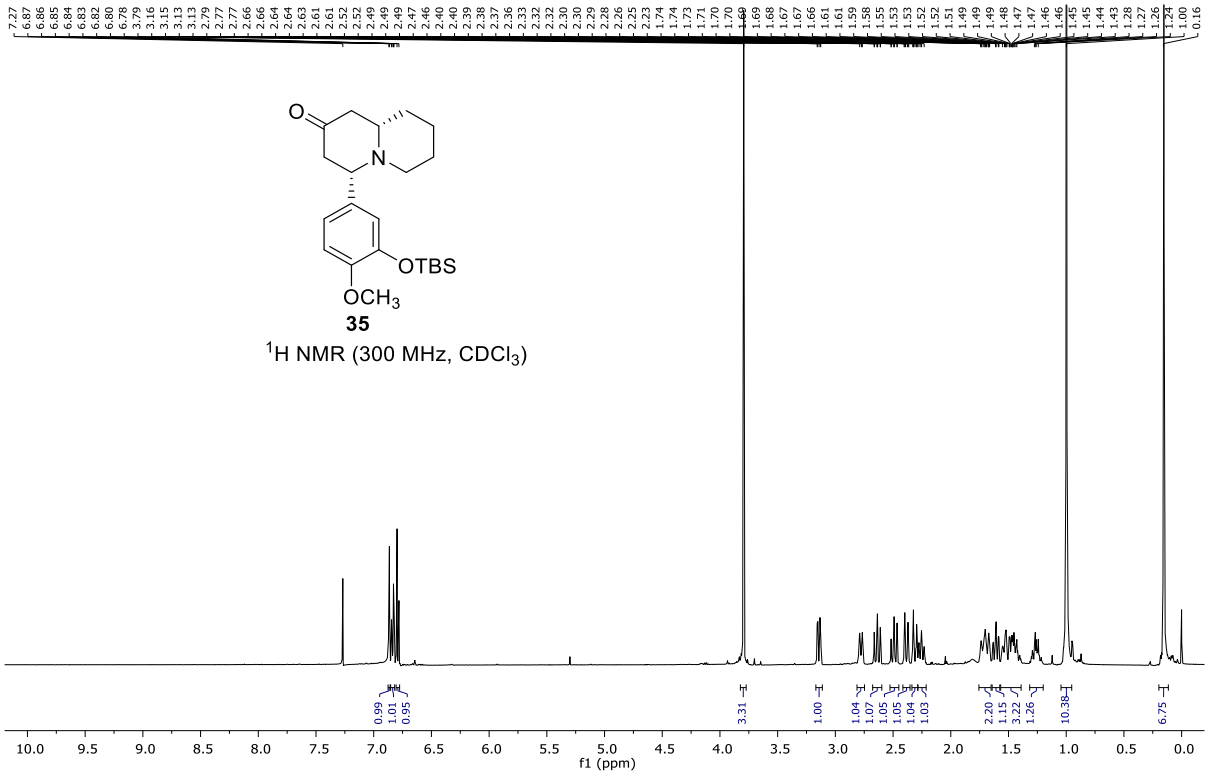


90

^{13}C NMR (125 MHz, $CDCl_3$)

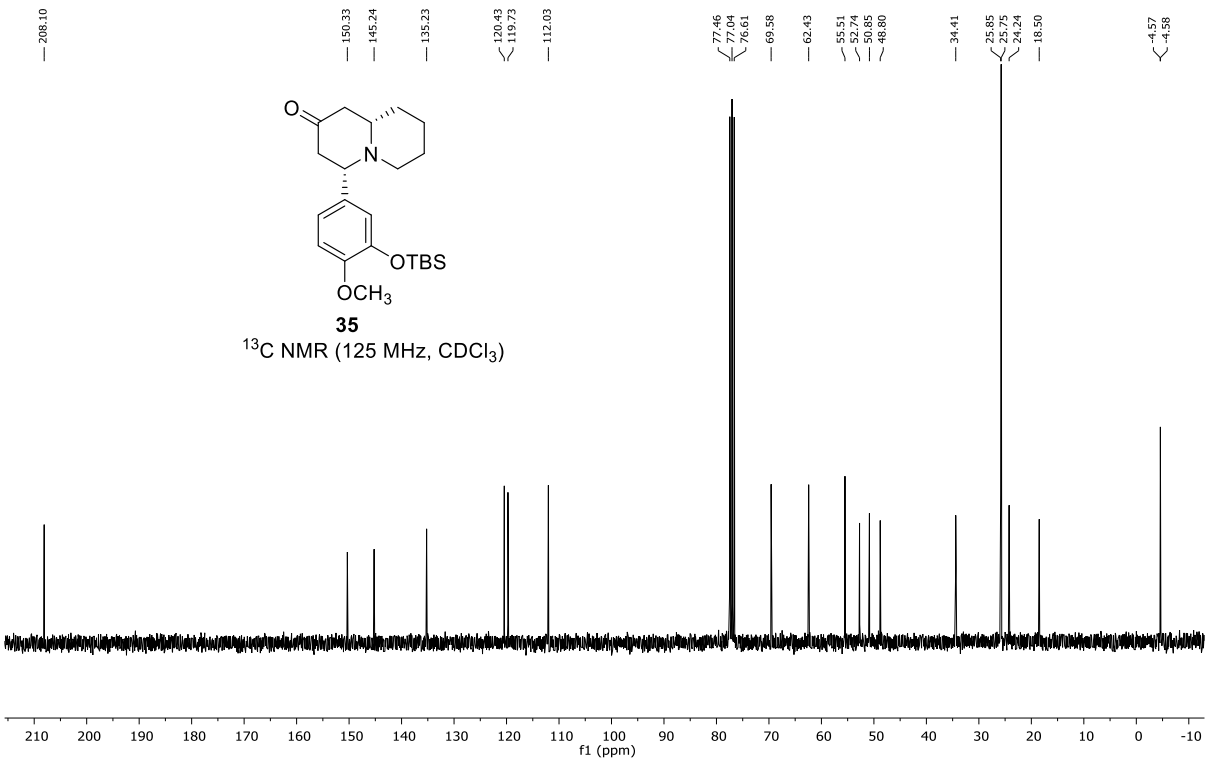

SV-02-121A.2.fid
7.86
7.81
7.27
7.09
7.07
6.56
6.51
3.91
3.90
2.42
1.61
-0.00
1.02
2.03
1.02
6.13
3.00
f1 (ppm)
O
Br
OCH3
OCH3
89
1H NMR (300 MHz, CDCl3)


198.44
151.57
148.79
141.96
127.88
126.24
117.57
115.63
109.15
77.47
77.04
76.62
56.31
56.11
26.93
f1 (ppm)
O
Br
OCH3
OCH3
89
13C NMR (125 MHz, CDCl3)



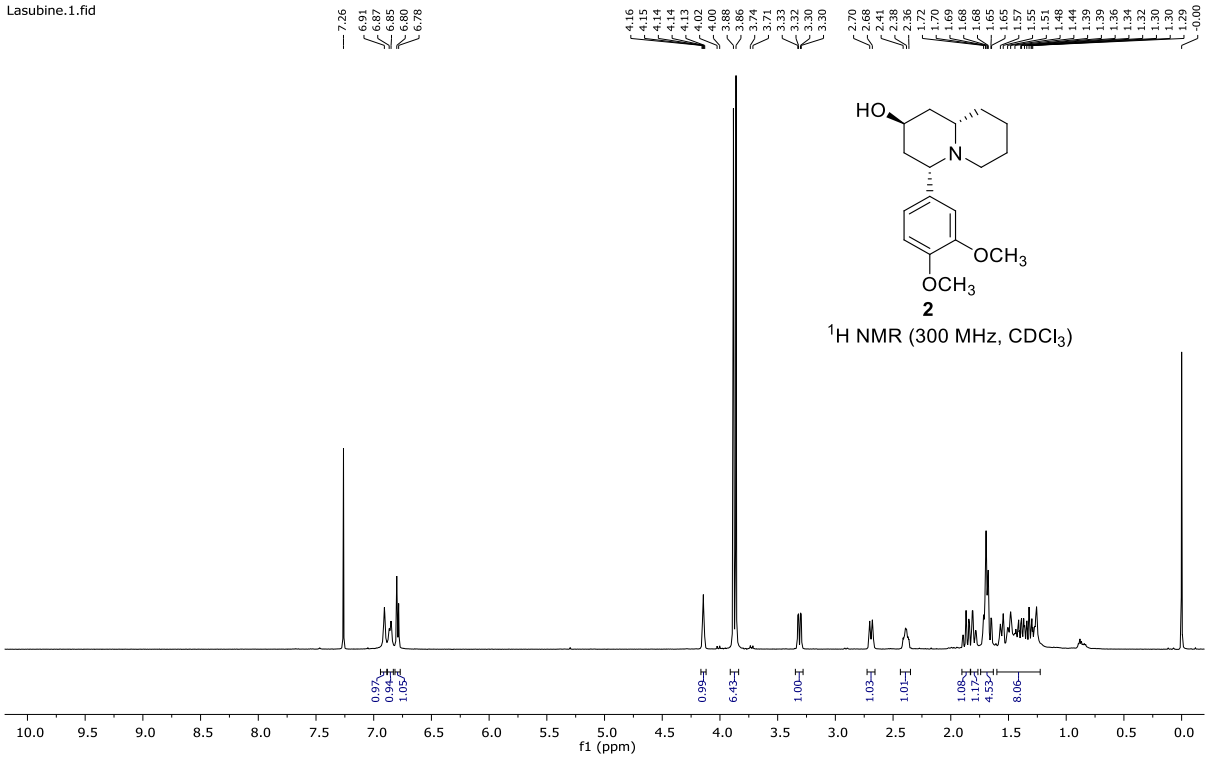
35

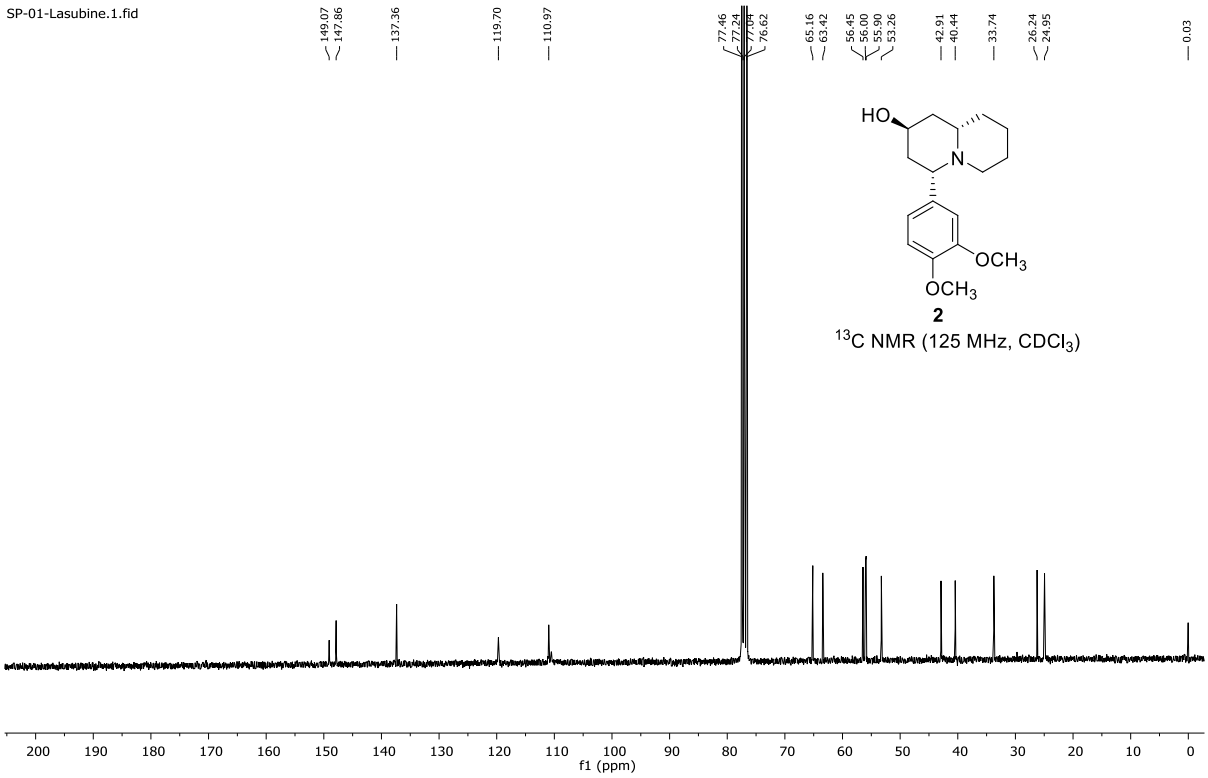
^{1}H NMR (300 MHz, $CDCl_3$)



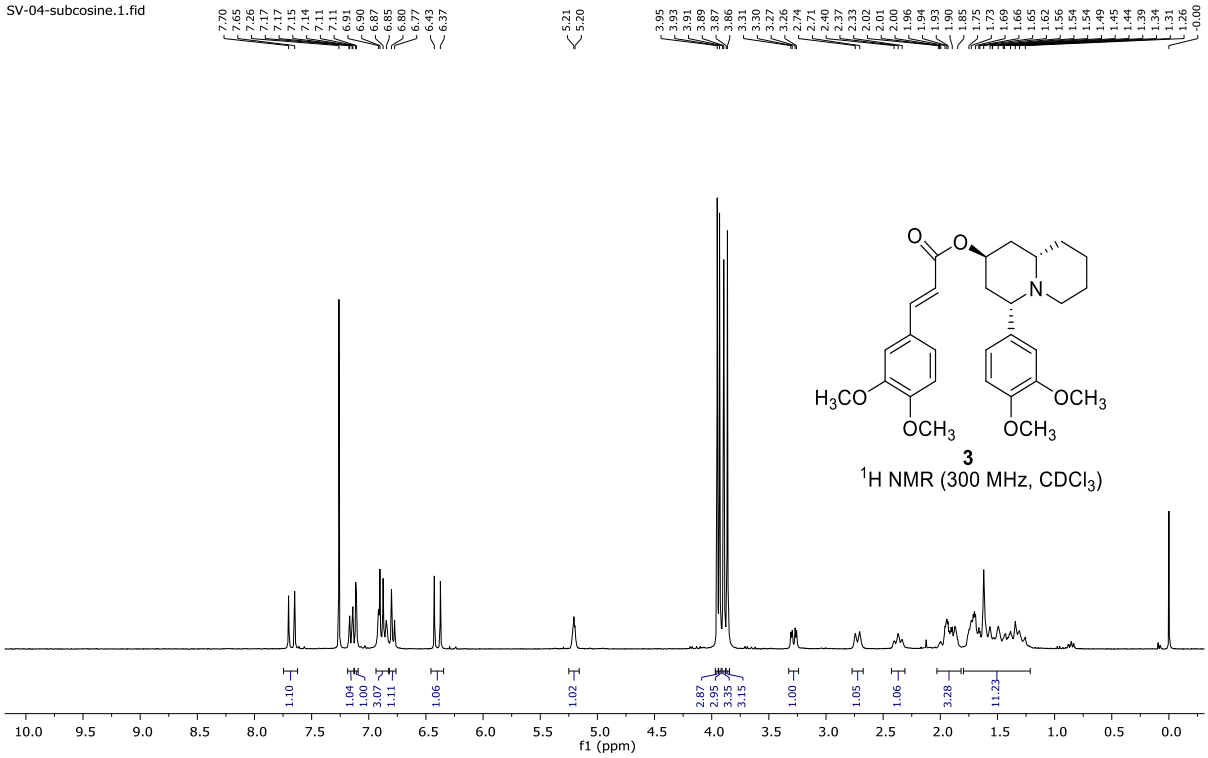
35

^{13}C NMR (125 MHz, $CDCl_3$)


Lasubine.1.fid
HO
N
OCH3
OCH3
2
1H NMR (300 MHz, CDCl3)
f1 (ppm)


SP-01-Lasubine.1.fid
HO
N
OCH3
OCH3
2
13C NMR (125 MHz, CDCl3)
f1 (ppm)

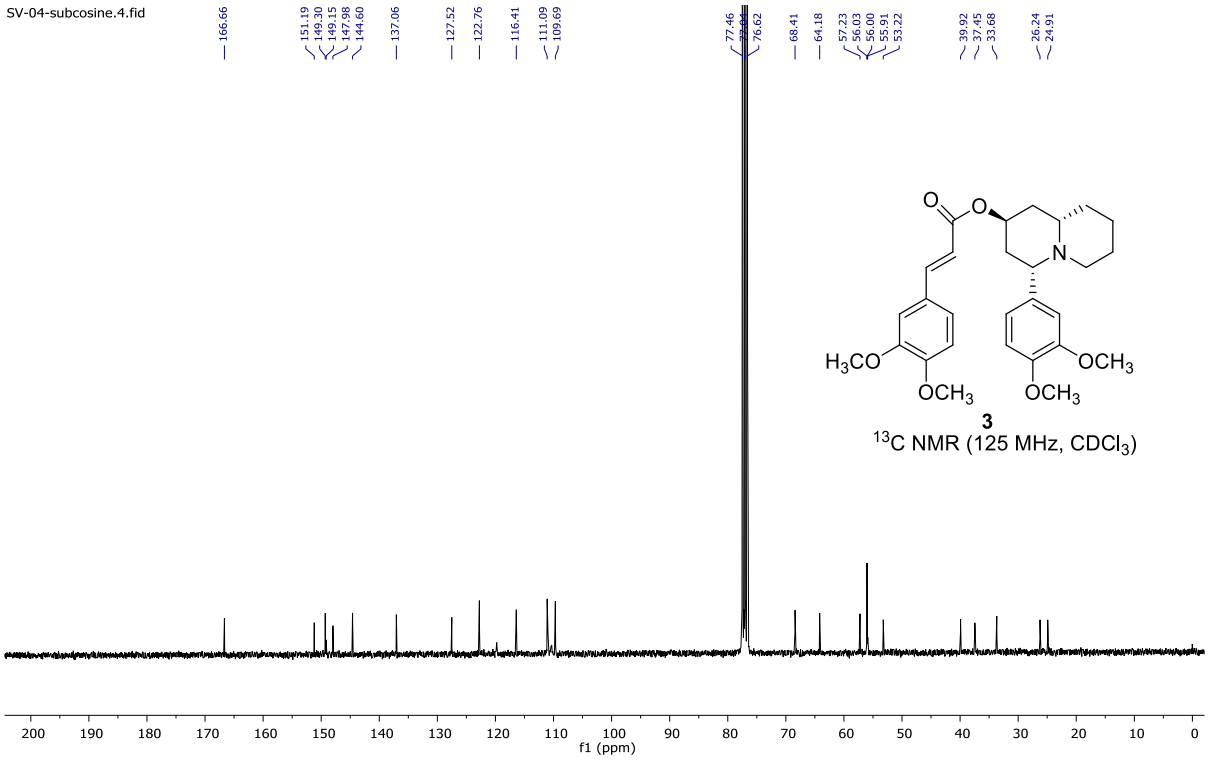
SV-04-subcosine.1.fid



3

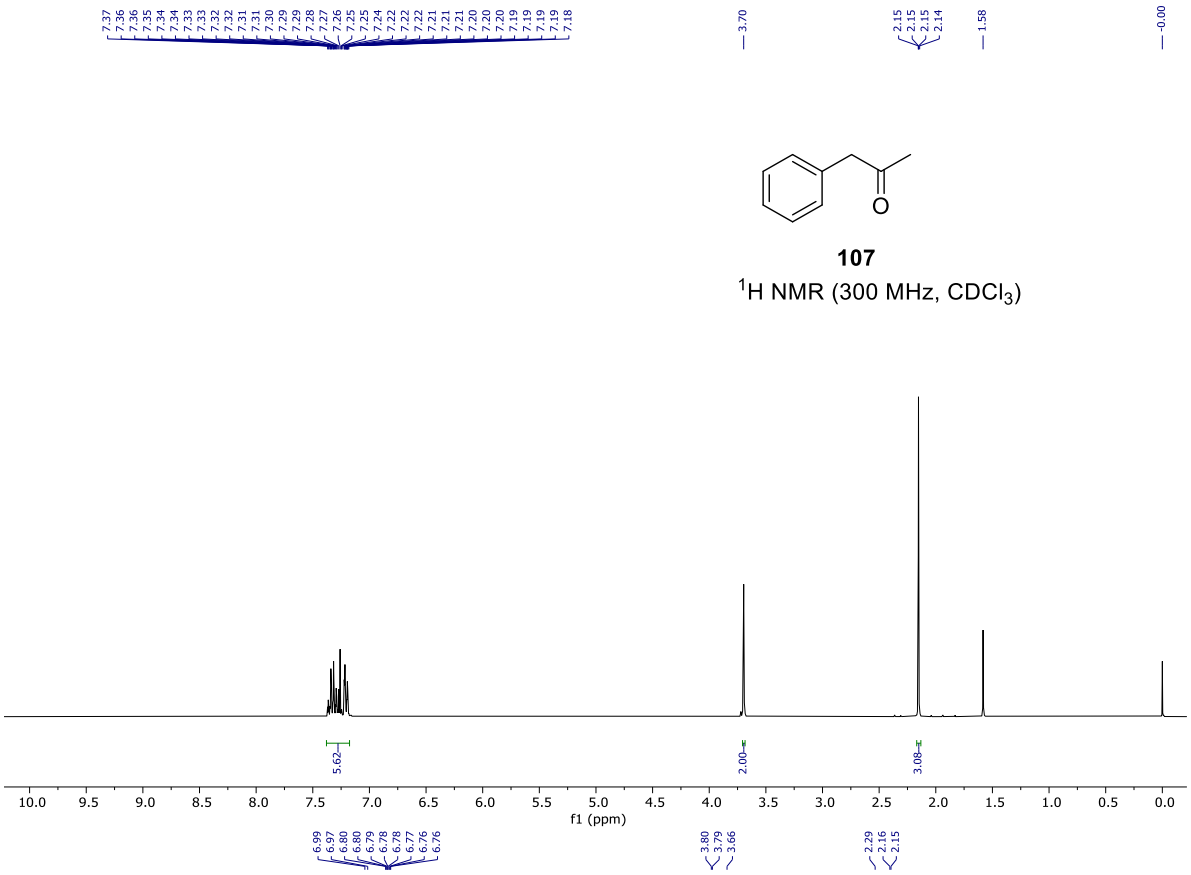
^{1}H NMR (300 MHz, $CDCl_3$)

SV-04-subcosine.4.fid



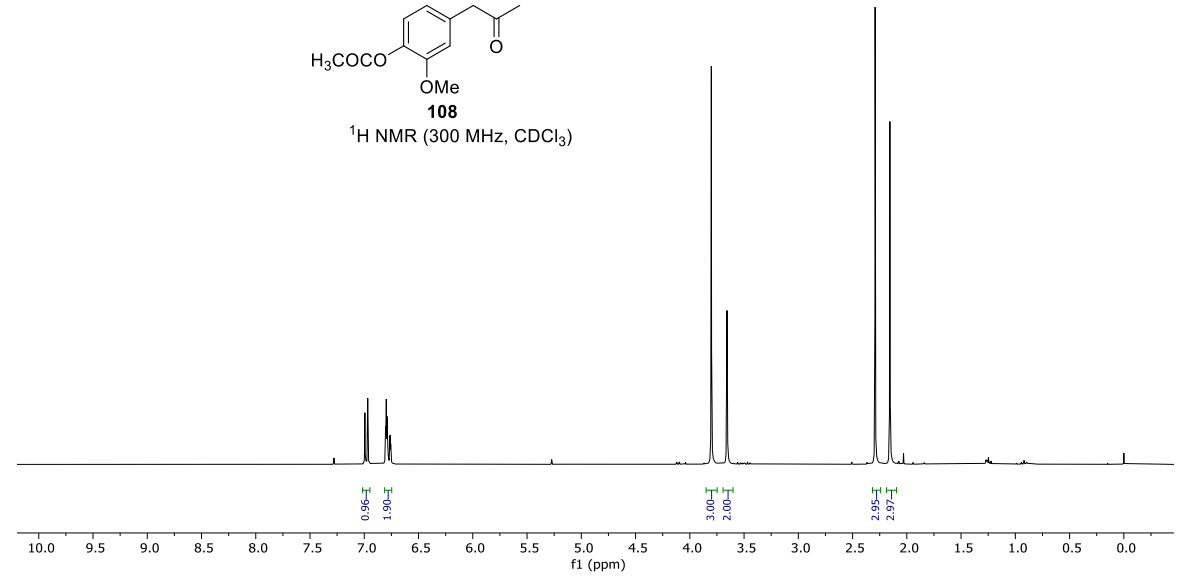
3

^{13}C NMR (125 MHz, $CDCl_3$)



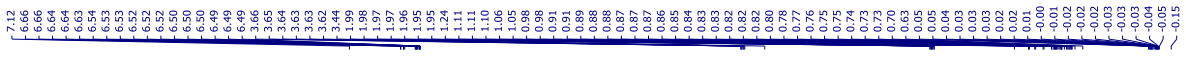
107

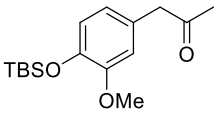
^{1}H NMR (300 MHz, $CDCl_3$)



108

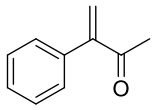
^{1}H NMR (300 MHz, $CDCl_3$)





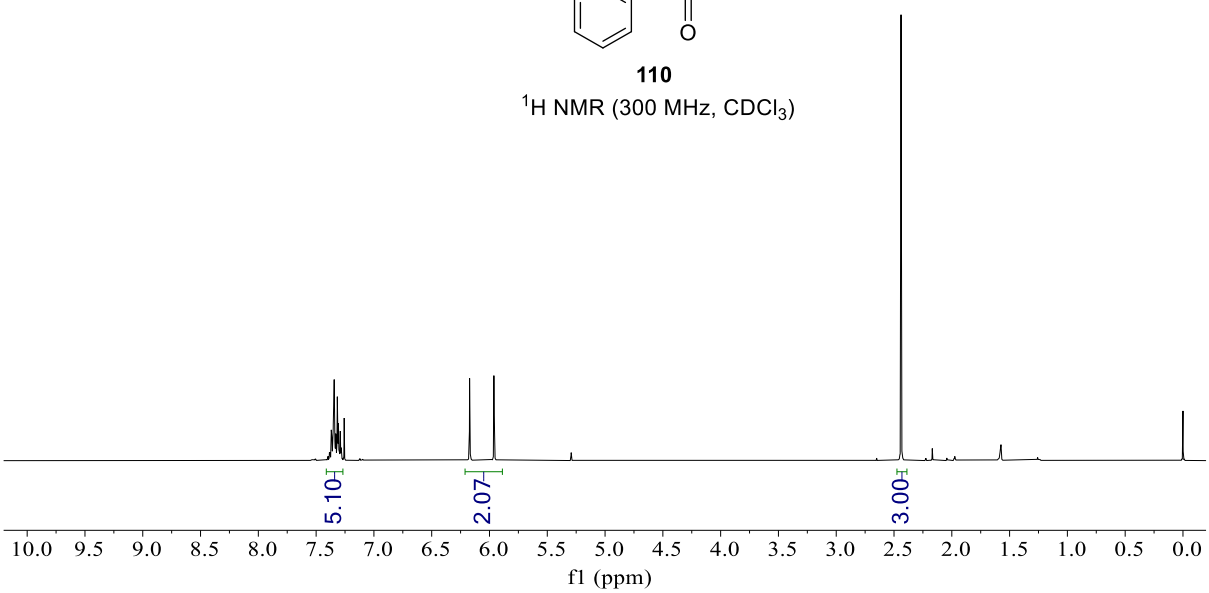
109

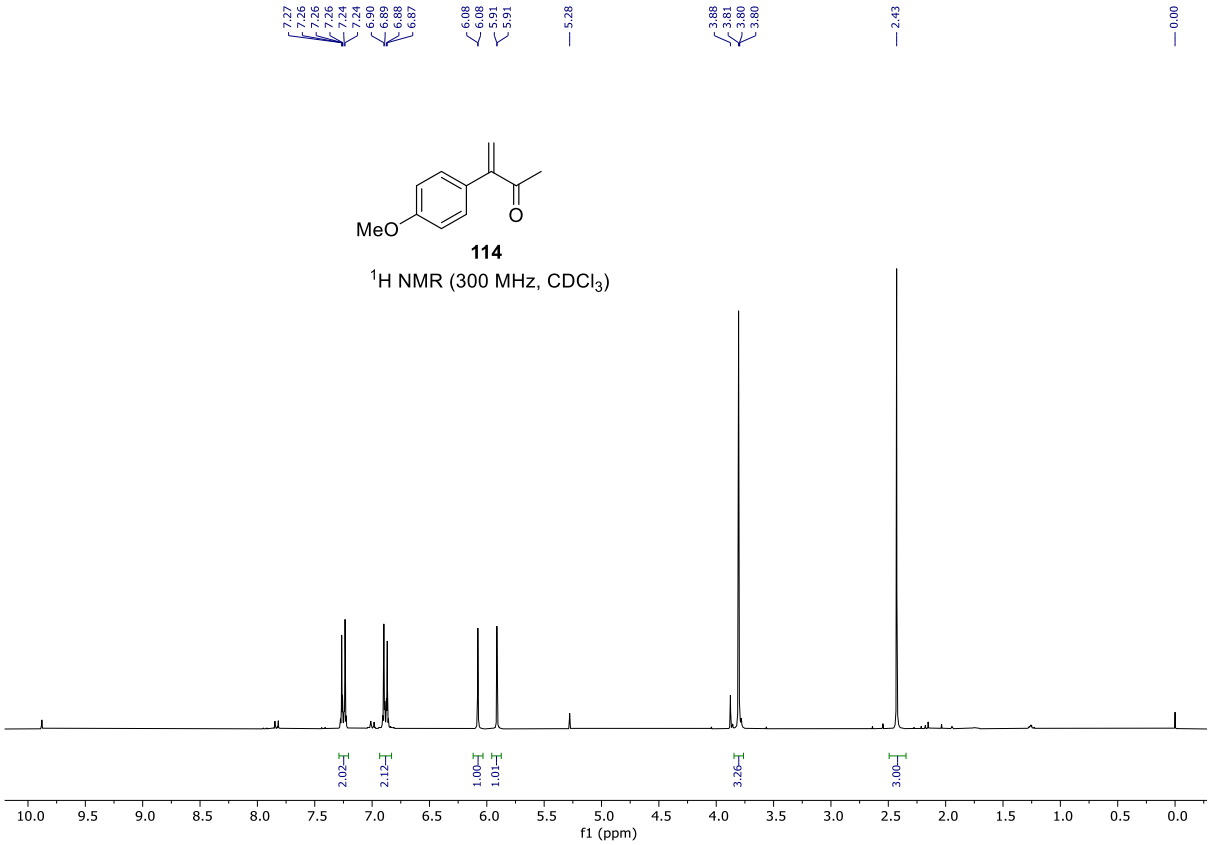
^{1}H NMR (300 MHz, $CDCl_3$)



110

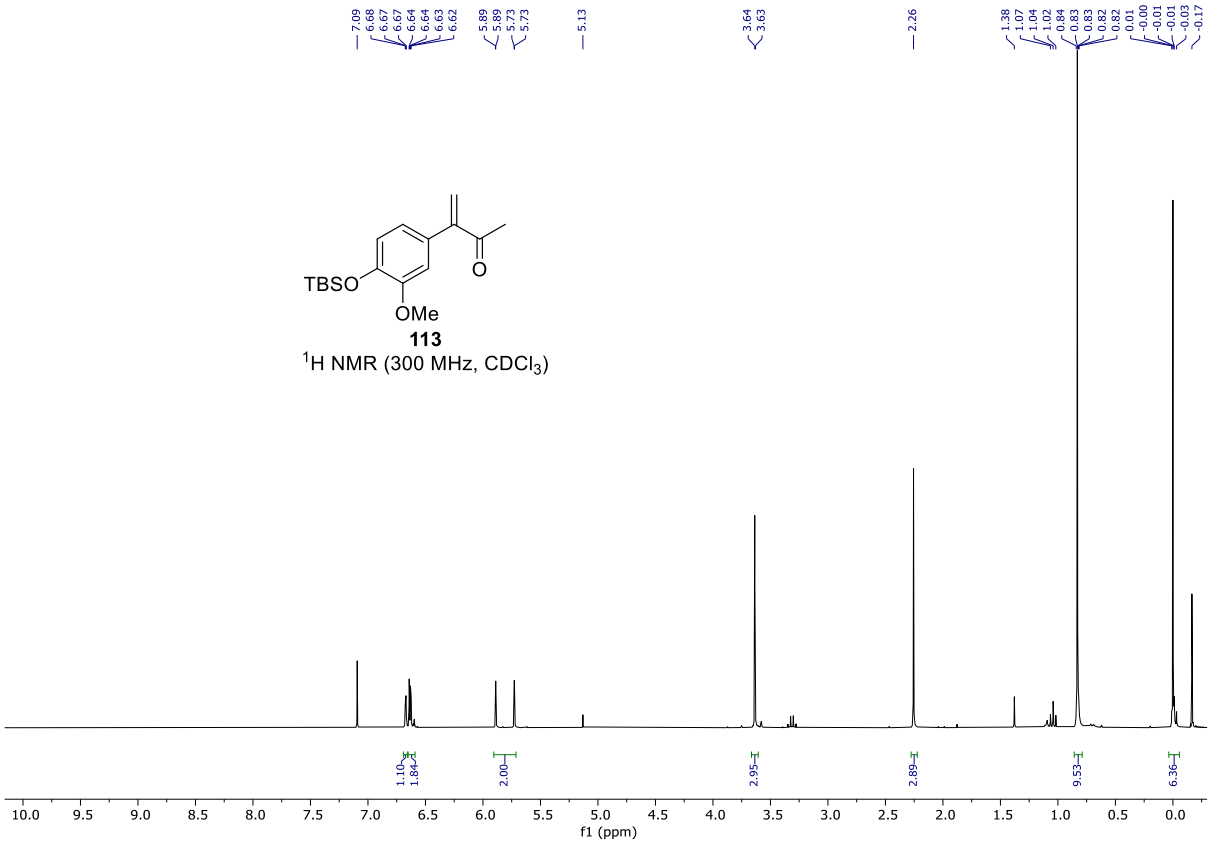
^{1}H NMR (300 MHz, $CDCl_3$)





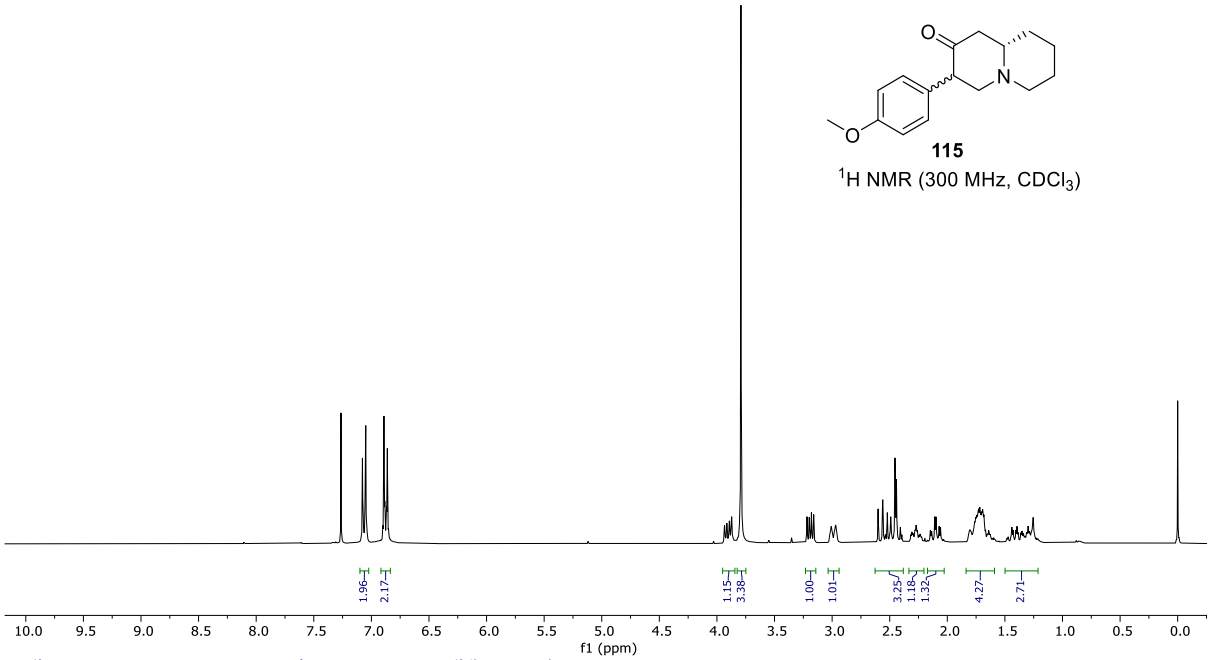
114

^{1}H NMR (300 MHz, $CDCl_3$)



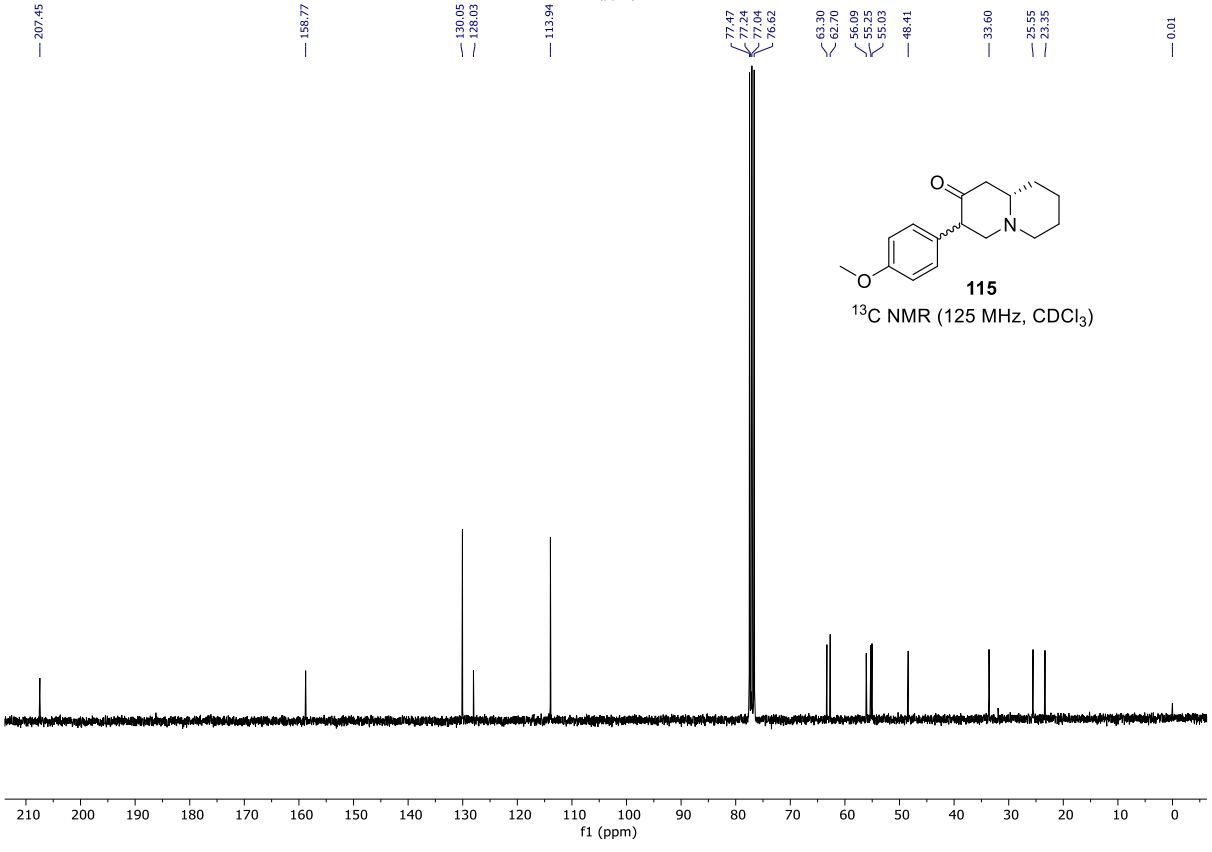
113

^{1}H NMR (300 MHz, $CDCl_3$)



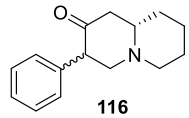
115

^{1}H NMR (300 MHz, $CDCl_3$)



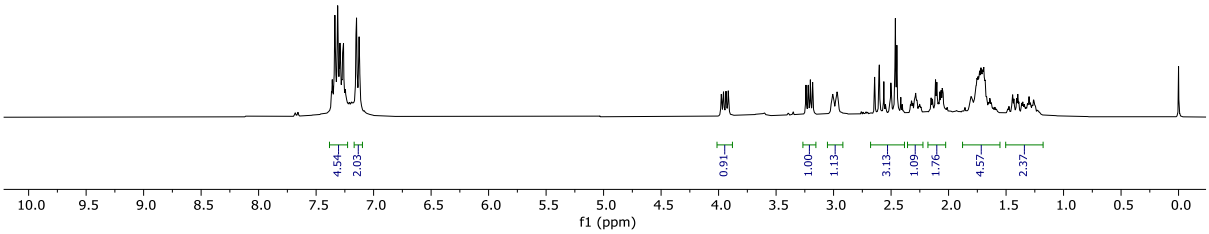
115

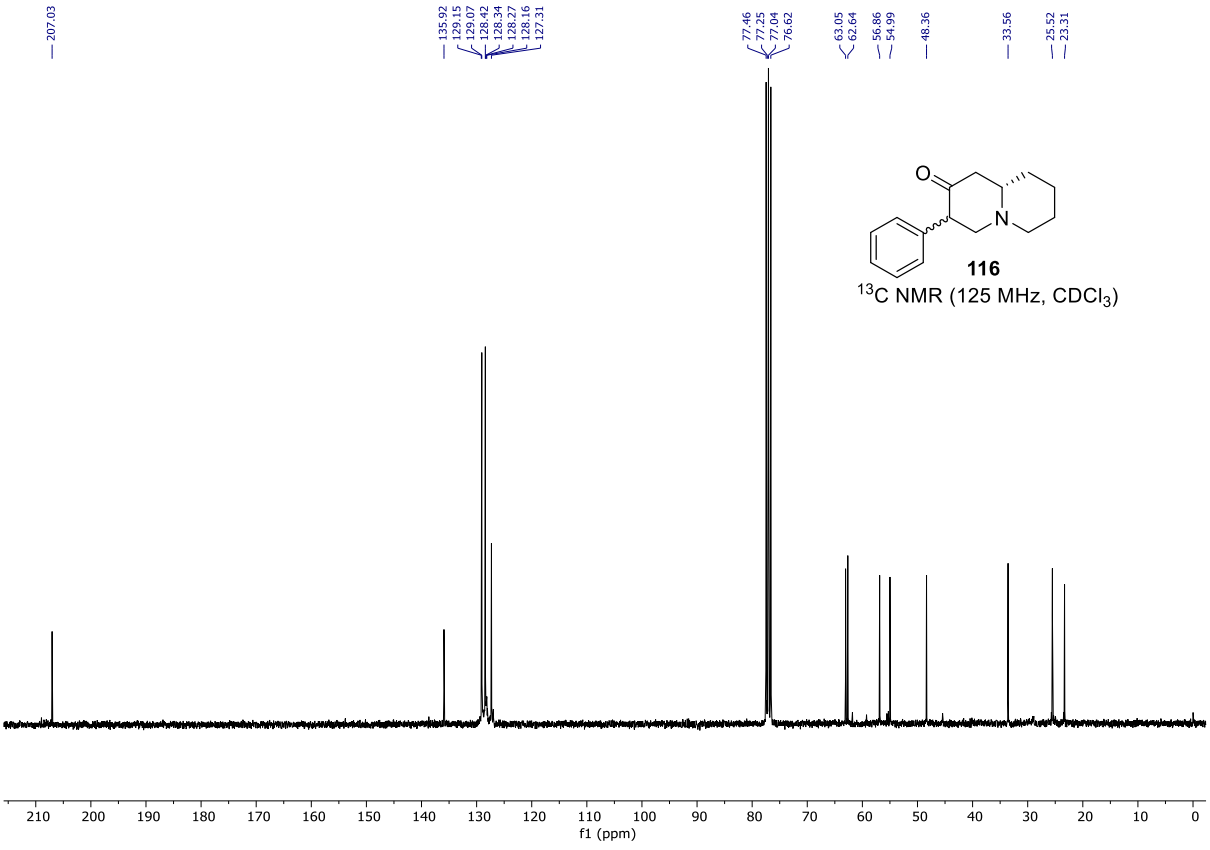
^{13}C NMR (125 MHz, $CDCl_3$)



116

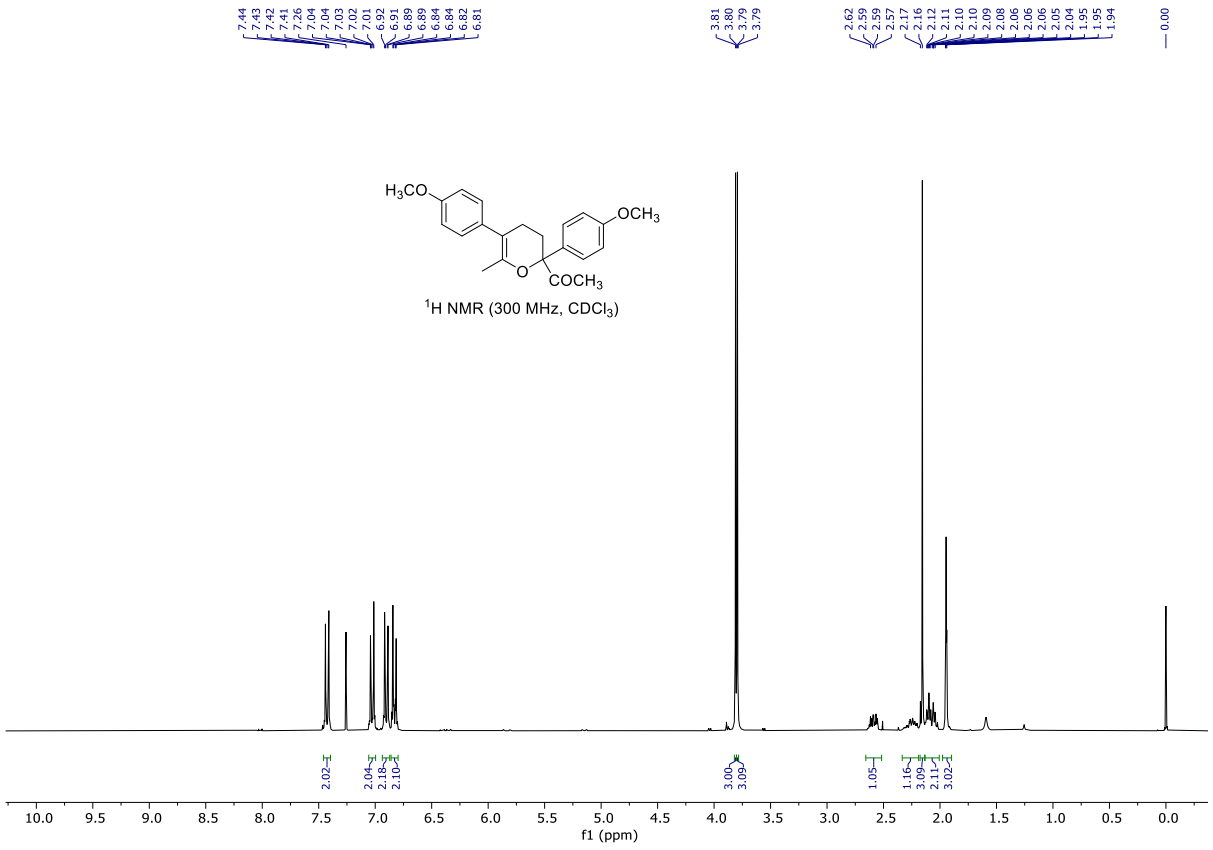
^{1}H NMR (300 MHz, $CDCl_3$)

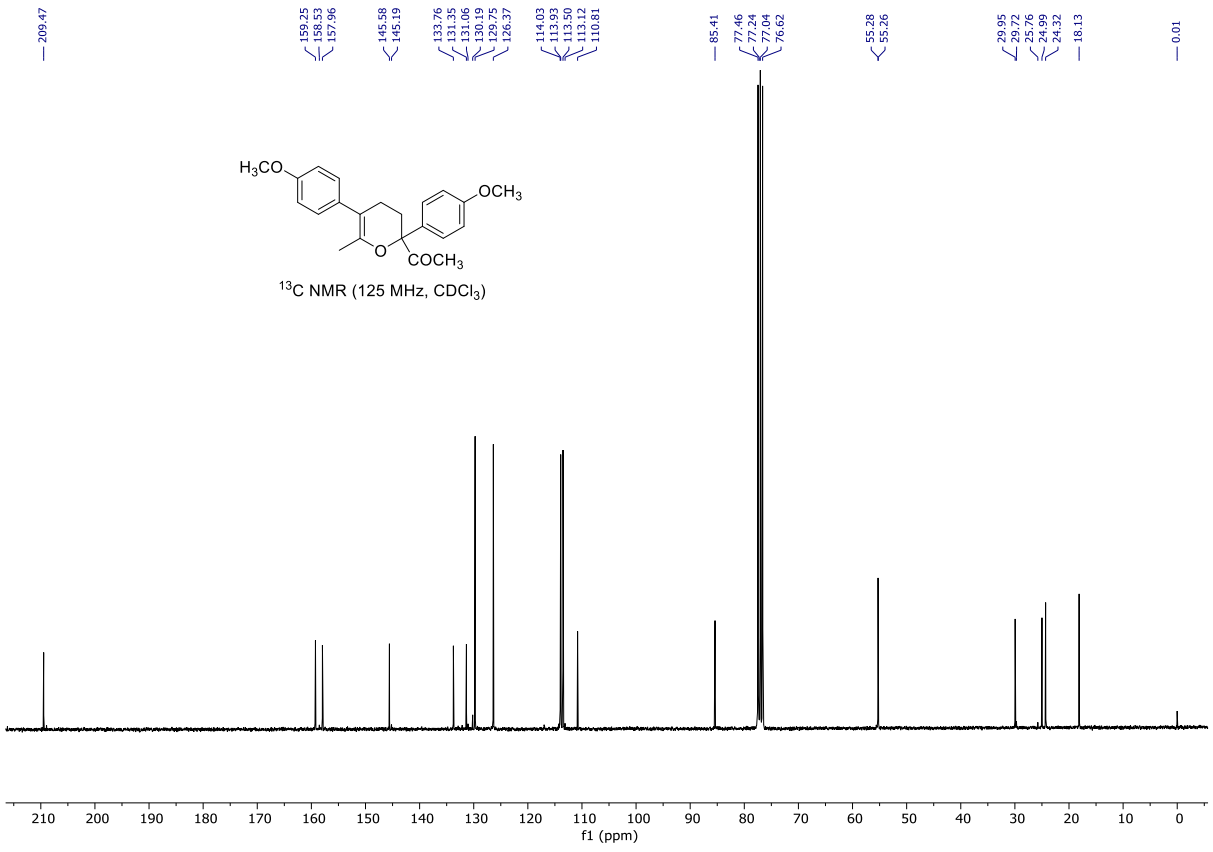




116

^{13}C NMR (125 MHz, $CDCl_3$)


7.44 7.43 7.42 7.41 7.26 7.04 7.04 7.03 7.02 7.01 6.92 6.91 6.89 6.89 6.84 6.84 6.82 6.81
3.81 3.80 3.79 3.79
2.62 2.59 2.59 2.57 2.17 2.16 2.12 2.11 2.10 2.10 2.09 2.08 2.06 2.06 2.06 2.05 2.04 1.95 1.95 1.94
0.00
H3CO
OCH3
O
COCH3
1H NMR (300 MHz, CDCl3)
2.02 2.04 2.18 2.10 3.00 3.09 1.05 1.16 3.09 2.11 3.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


209.47
159.25 158.53 157.96 145.58 145.19 133.76 131.35 131.06 130.19 129.75 126.37 114.03 113.93 113.50 113.12 110.81
85.41
77.46 77.24 77.04 76.62
55.28 55.26
29.95 29.72 25.76 24.99 24.32
18.13
0.01
H3CO
OCH3
O
COCH3
13C NMR (125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

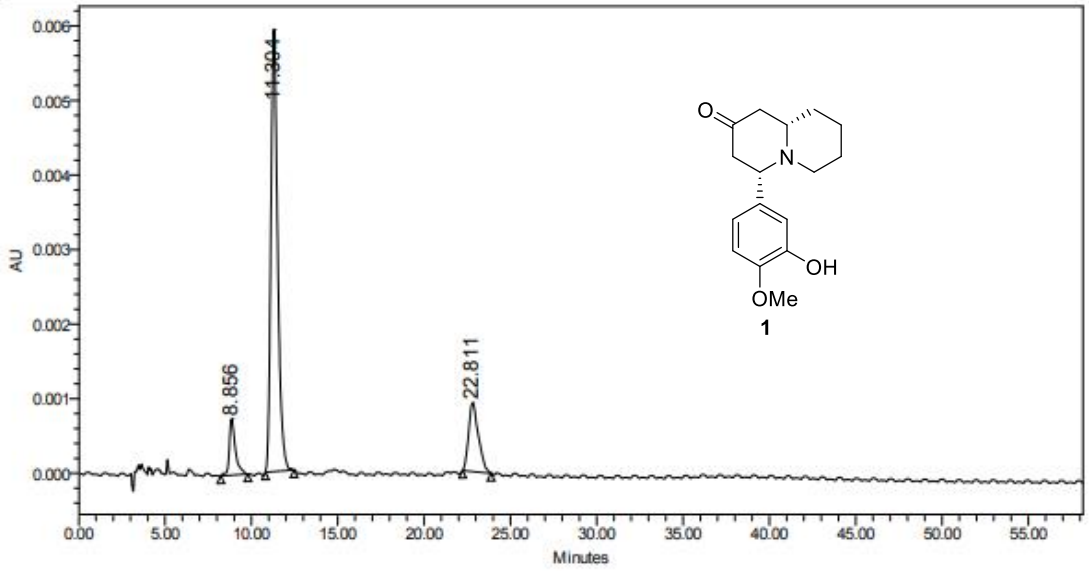
2.9 Selected HPLC traces

Memorial University
Project Name SEERAT
Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	SV-02- 191B	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	10/04/2018 11:18:23 AM NDT
Vial:	1	Acq. Method:	OJ_H 80% HEX 20%IPA
Injection #:	1	Date Processed:	17/04/2018 4:06:21 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	60.00 Minutes	Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	8.856	18441	8.51	754	9.92
2	11.304	161824	74.68	5930	78.03
3	22.811	36414	16.81	916	12.06

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Memorial University

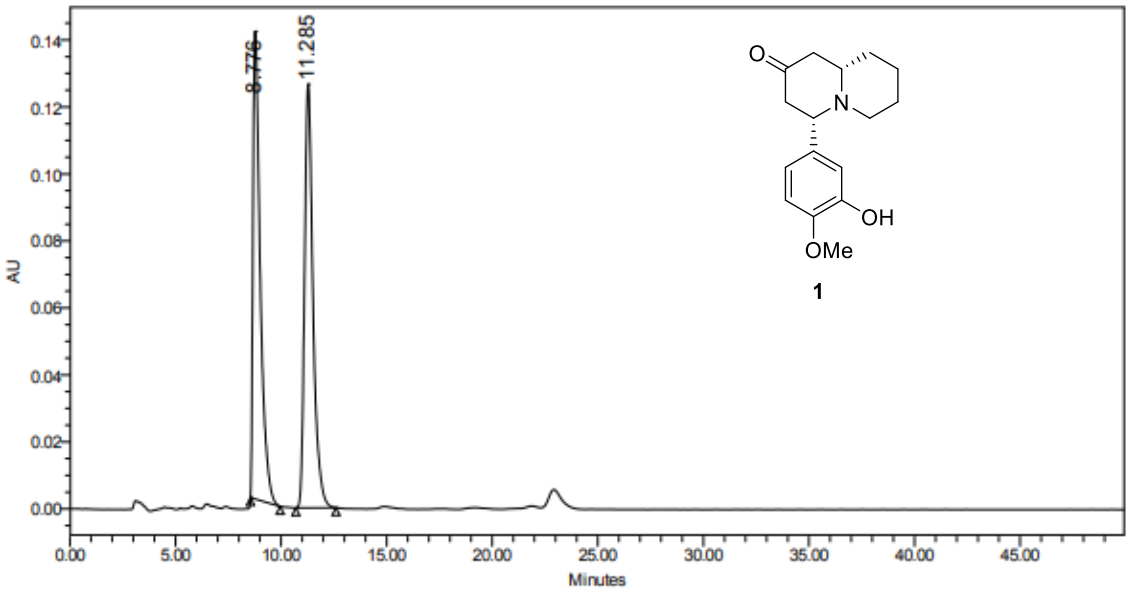
Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	SV-02- 193B	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	09/04/2018 3:40:38 PM NDT
Vial:	1	Acq. Method:	OJ_H 80% HEX 20%IPA
Injection #:	1	Date Processed:	17/04/2018 4:04:51 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	60.00 Minutes	Sample Set Name	



1

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	8.776	3330788	48.59	139772	52.49
2	11.285	3523655	51.41	126527	47.51

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Memorial University

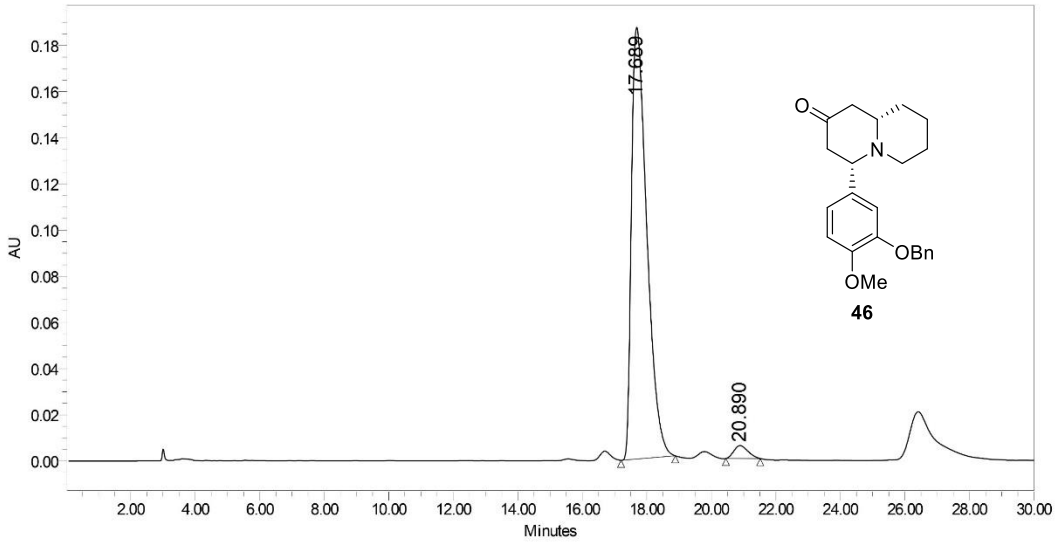
Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	SV-02-171C	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	22/08/2018 11:30:10 AM NDT
Vial:	1	Acq. Method:	AD_H 97%HEX 3%IPA
Injection #:	1	Date Processed:	22/08/2018 4:15:53 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	30.00 Minutes	Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	17.689	6178862	97.32	187042	97.09
2	20.890	170136	2.68	5605	2.91

Report Method: Untitled

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Memorial University

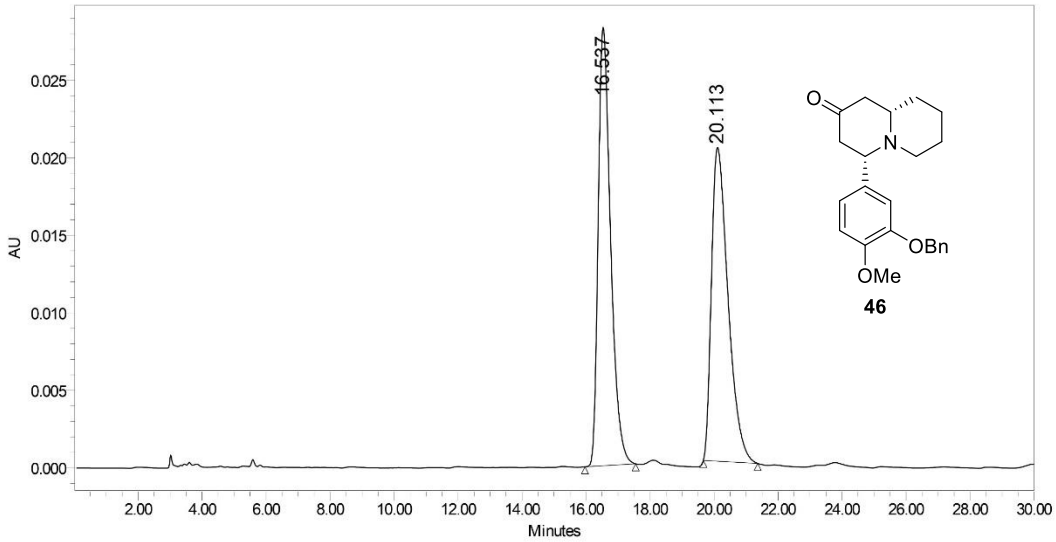
Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	SV-02-185A fridge	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	22/08/2018 4:50:45 PM NDT
Vial:	1	Acq. Method:	AD_H 97%HEX 3%IPA
Injection #:	1	Date Processed:	19/09/2018 12:59:08 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	30.00 Minutes	Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	16.537	760923	51.10	28279	58.27
2	20.113	728147	48.90	20249	41.73

Report Method: Untitled

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Memorial University

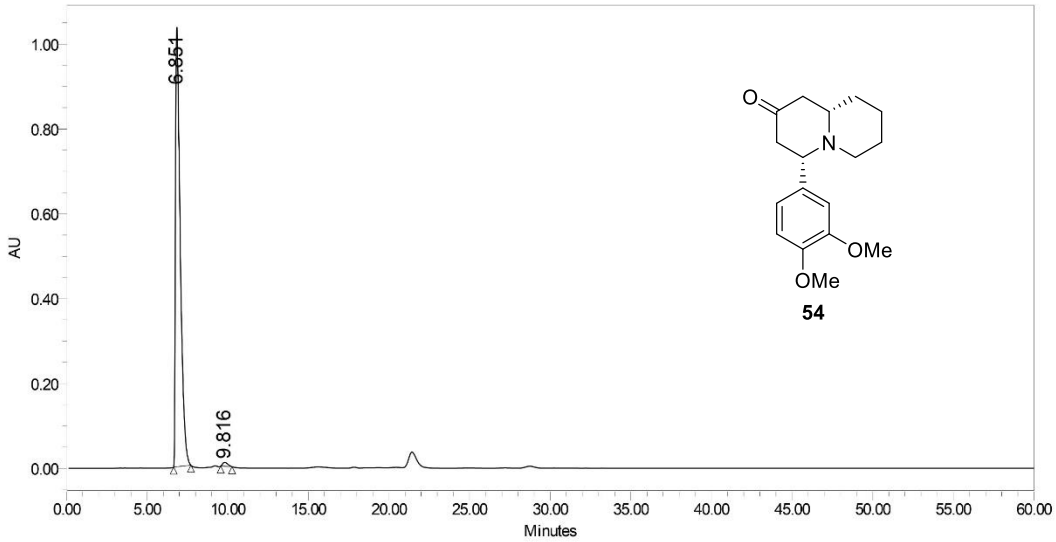
Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	SV-03-27A	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	23/05/2018 2:32:06 PM NDT
Vial:	1	Acq. Method:	OJ_H 80% HEX 20%IPA
Injection #:	2	Date Processed:	23/05/2018 5:01:39 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	60.00 Minutes	Sample Set Name	



54

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	6.851	21382860	99.04	1035780	99.12
2	9.816	207001	0.96	9200	0.88

Memorial University

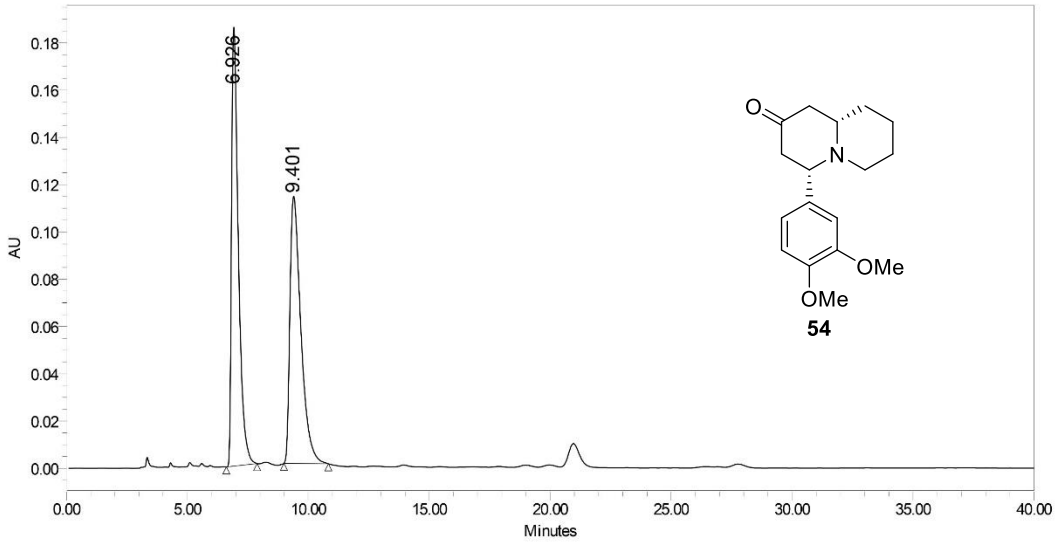
Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	SV-02-59A	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	21/09/2017 3:01:51 PM NDT
Vial:	1	Acq. Method:	OJ_H 80% HEX 20%IPA
Injection #:	1	Date Processed:	21/09/2017 3:43:50 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	6.926	3654516	50.67	186275	62.25
2	9.401	3557390	49.33	112948	37.75

Memorial University

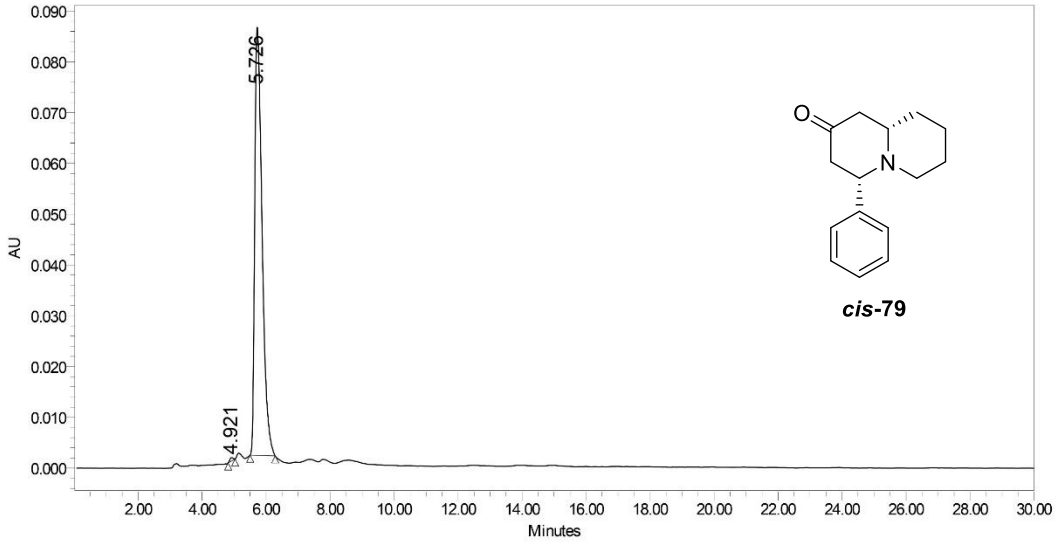
Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	SV-02-101B	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	03/01/2019 1:39:02 PM NST
Vial:	1	Acq. Method:	OJ_H 80% HEX 20%IPA
Injection #:	1	Date Processed:	03/01/2019 2:59:01 PM NST
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	30.00 Minutes	Sample Set Name	



***cis*-79**

	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	4.921	4922	0.37	673	0.79
2	5.726	1340105	99.63	84745	99.21

Memorial University

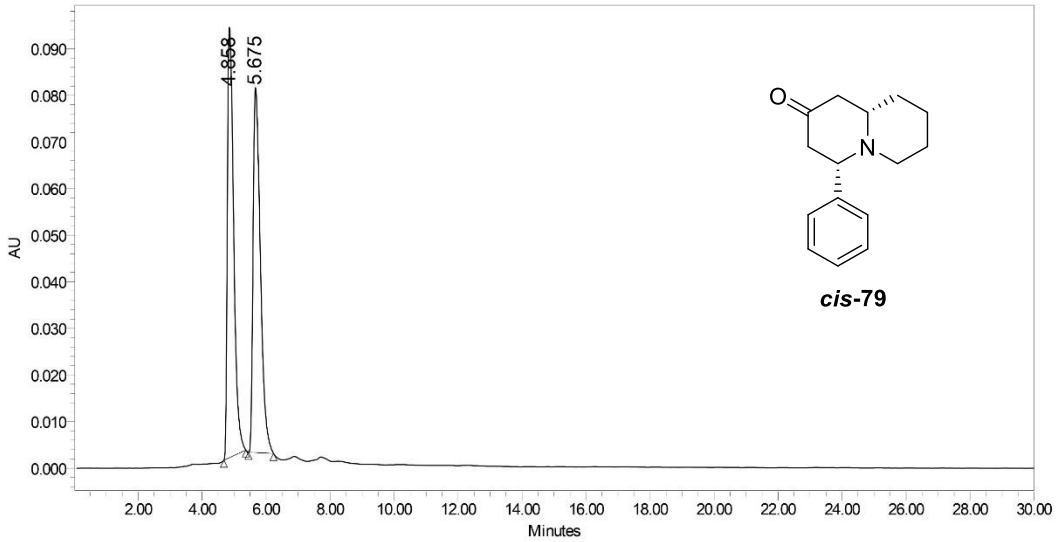
Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	SV-03-43D	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	03/01/2019 2:13:22 PM NST
Vial:	1	Acq. Method:	OJ_H 80% HEX 20%IPA
Injection #:	2	Date Processed:	03/01/2019 2:57:20 PM NST
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	30.00 Minutes	Sample Set Name	



***cis*-79**

	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	4.858	1257020	50.31	92799	54.14
2	5.675	1241401	49.69	78597	45.86

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Memorial University

Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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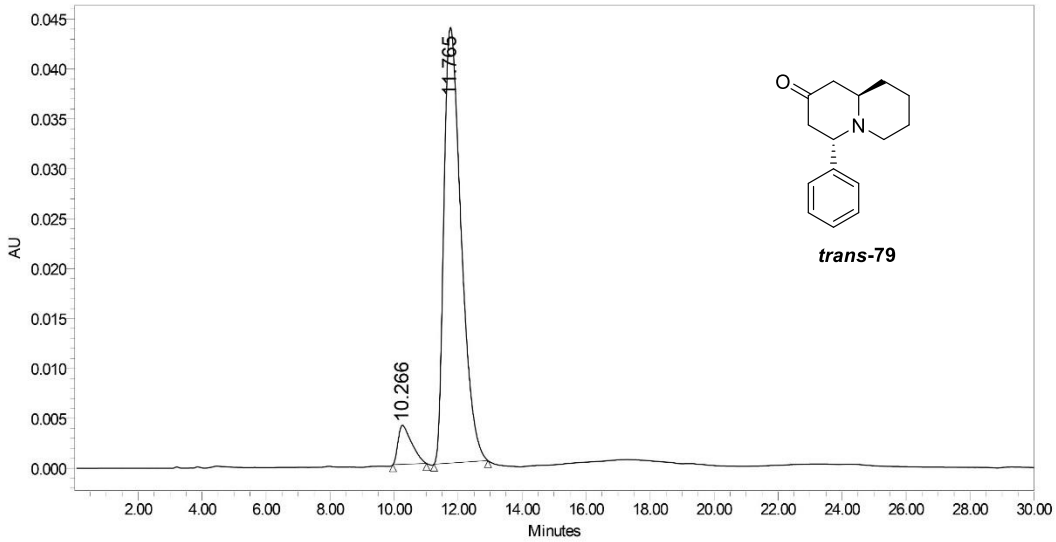

***trans*-79**

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Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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Sample Type:	Unknown	Date Acquired:	19/06/2018 12:03:57 PM NDT
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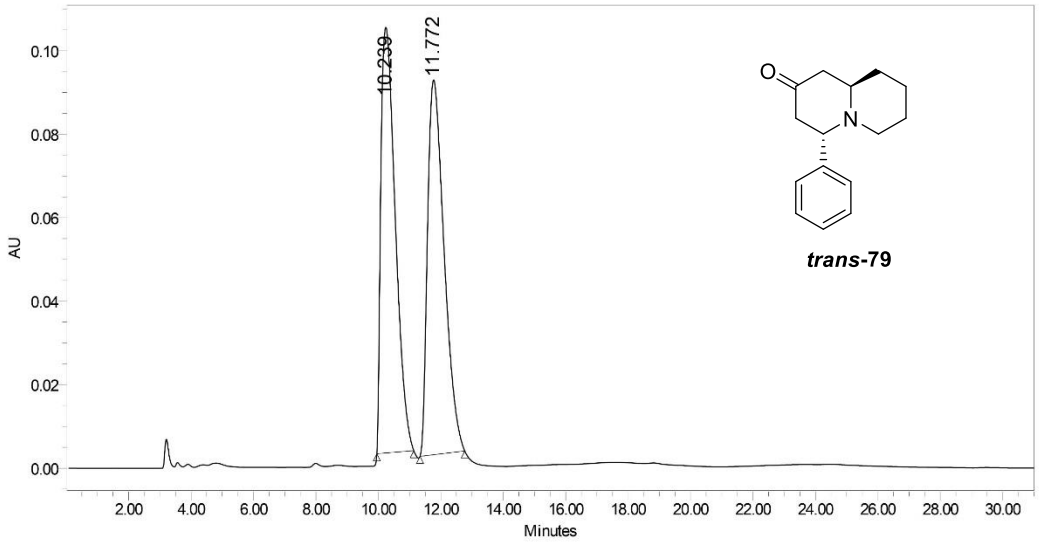

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Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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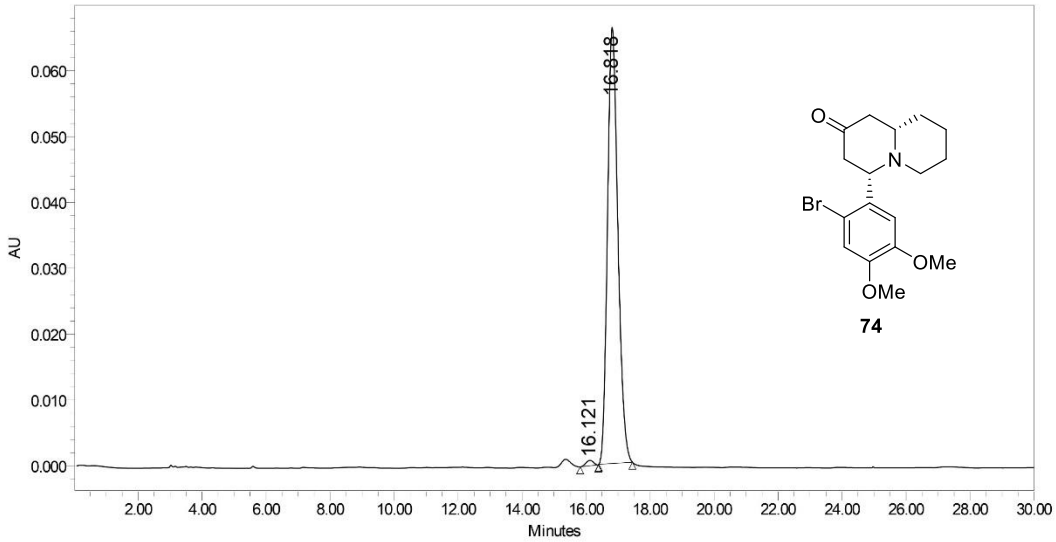

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Report Method: Untitled

Page: 1 of 1

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Memorial University

Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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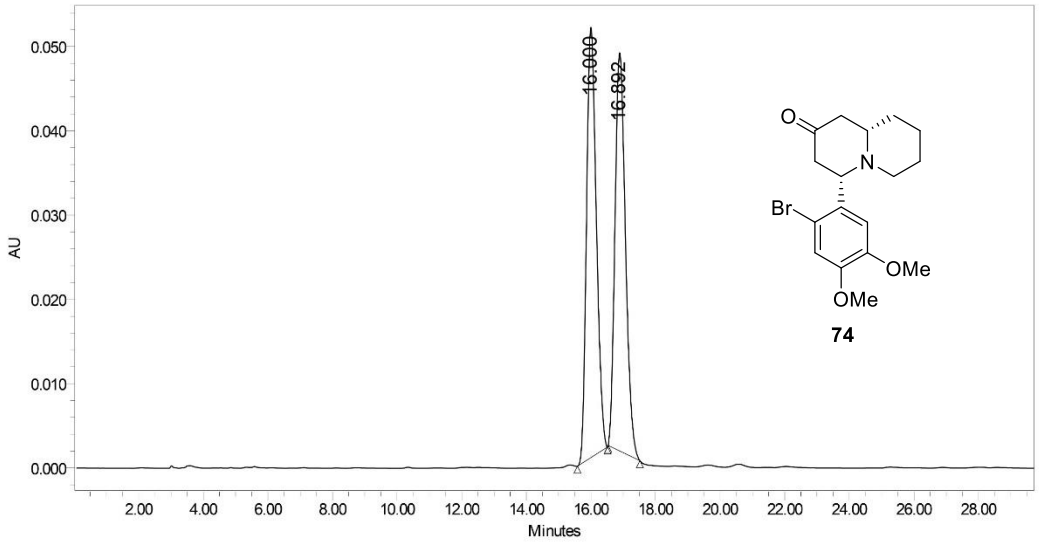

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Printed: 01/05/2019

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Memorial University

Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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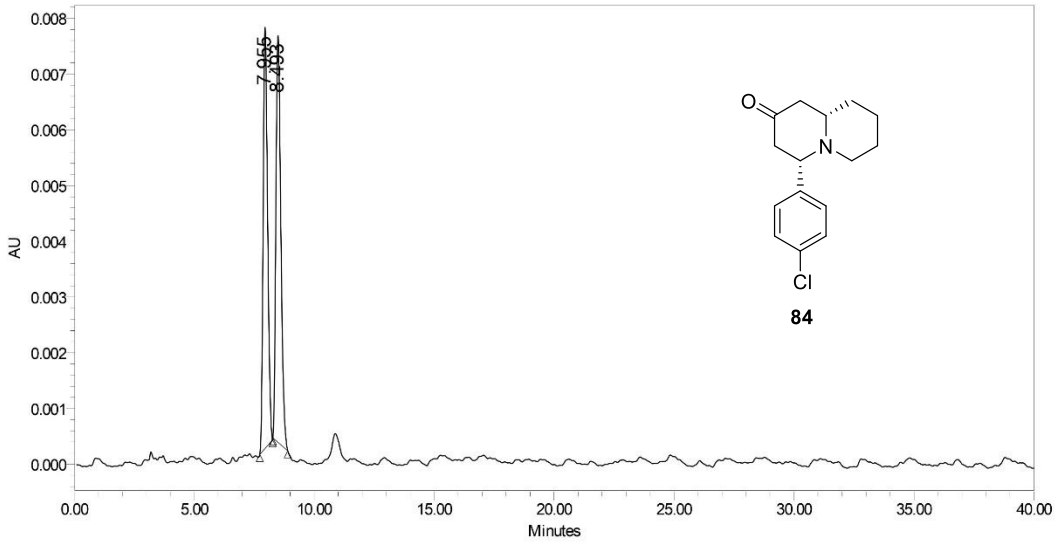

84

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Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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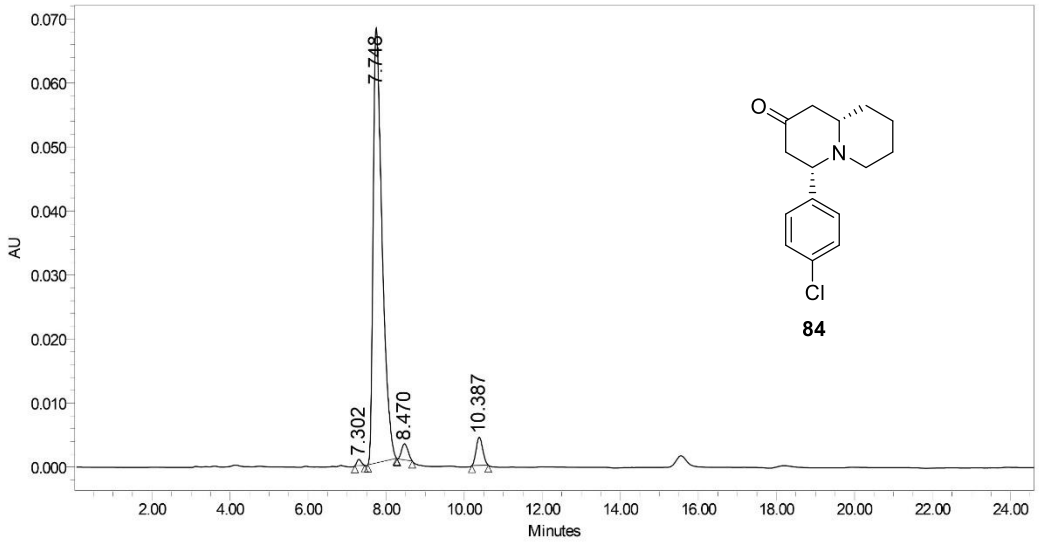
Run Time:	40.00 Minutes	Sample Set Name	



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2	7.748	1077411	92.53	68061	89.59
3	8.470	28249	2.43	2523	3.32
4	10.387	51302	4.41	4409	5.80

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Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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Sample Type:	Unknown	Date Acquired:	18/06/2018 12:44:58 PM NDT
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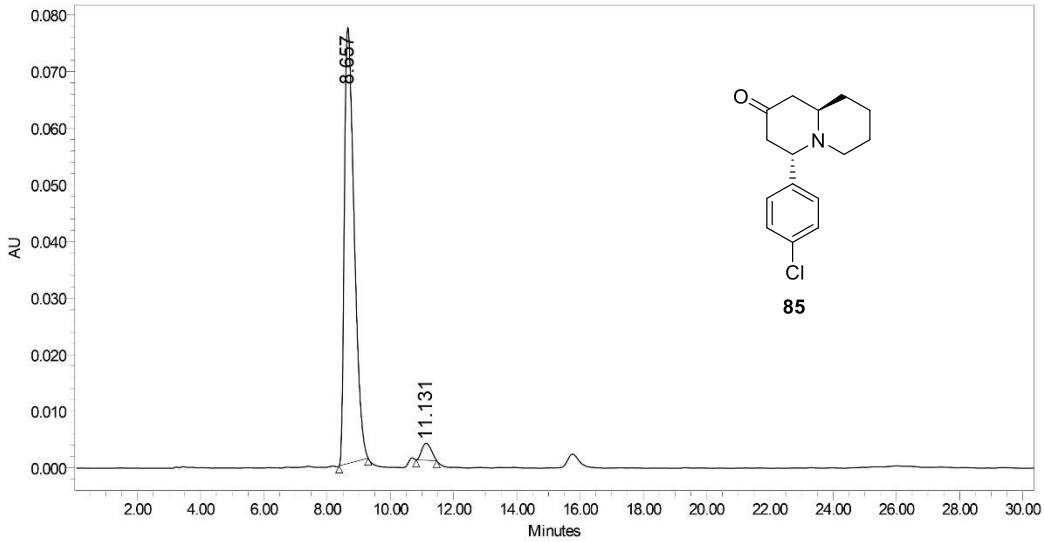

85

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Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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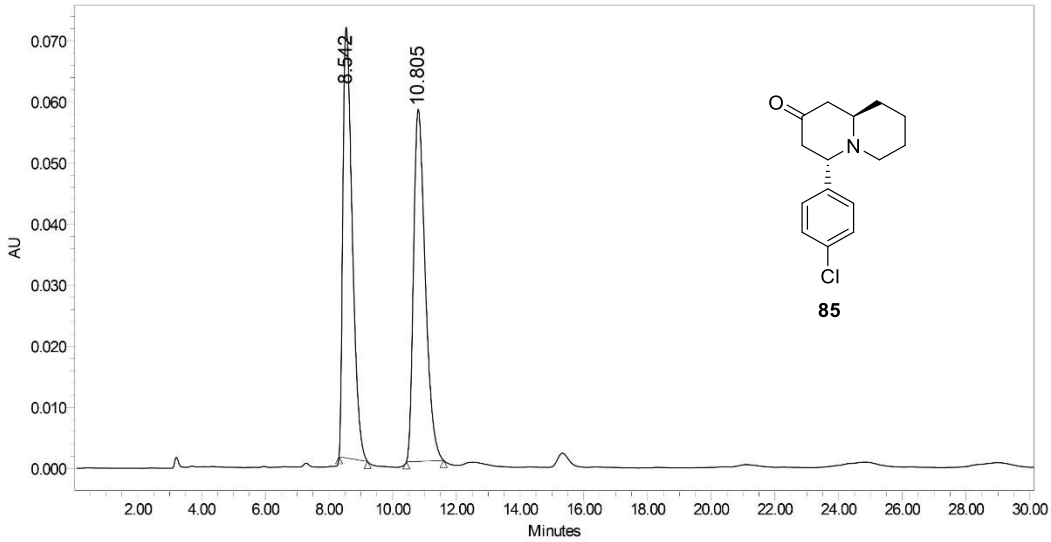

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Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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Sample Type:	Unknown	Date Acquired:	15/03/2018 2:29:30 PM NDT
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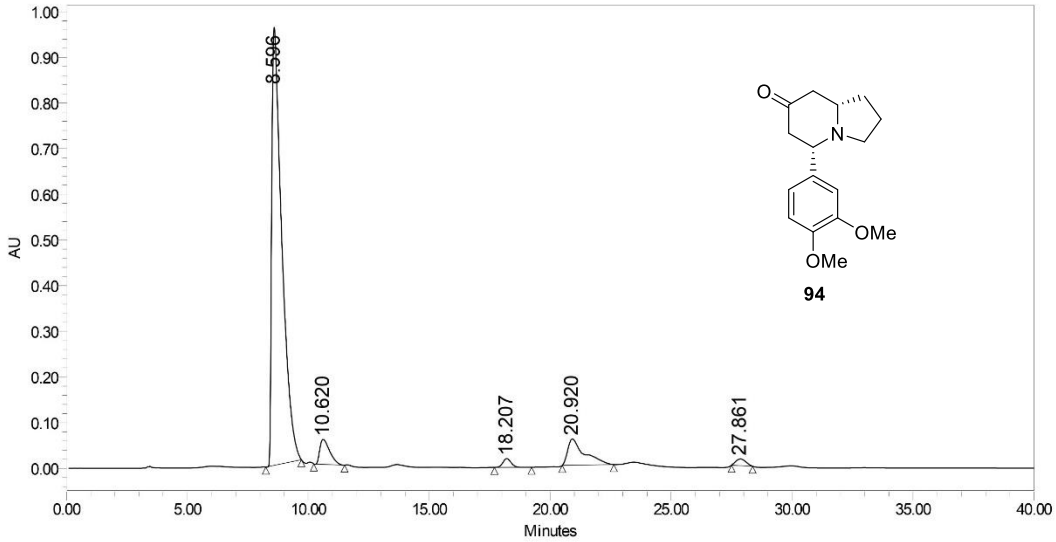

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
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2	10.620	1548895	4.68	54536	4.93
3	18.207	449821	1.36	19255	1.74
4	20.920	2764595	8.36	57662	5.21
5	27.861	422941	1.28	14706	1.33

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Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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Vial:	1	Acq. Method:	OJ_H 80% HEX 20%IPA
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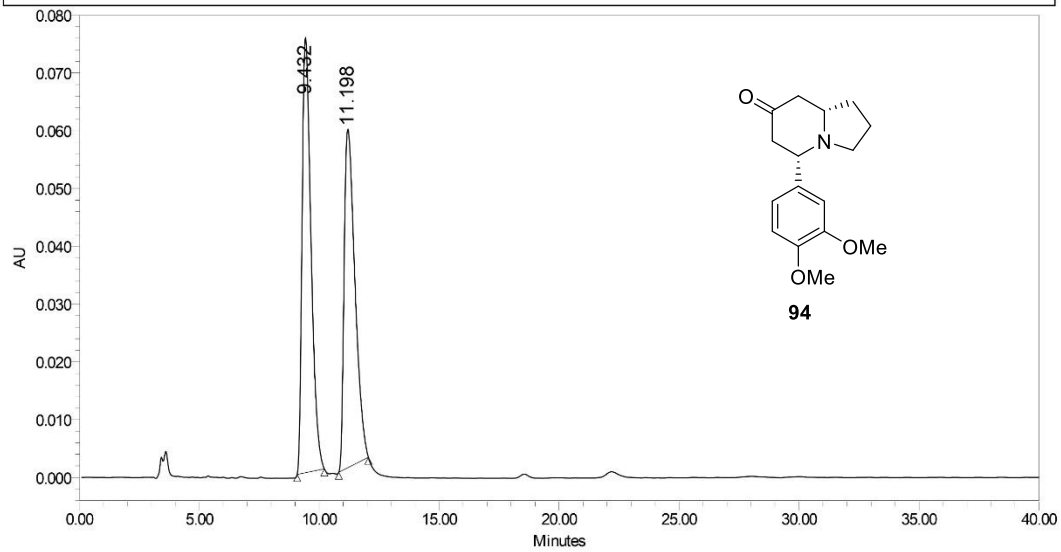

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Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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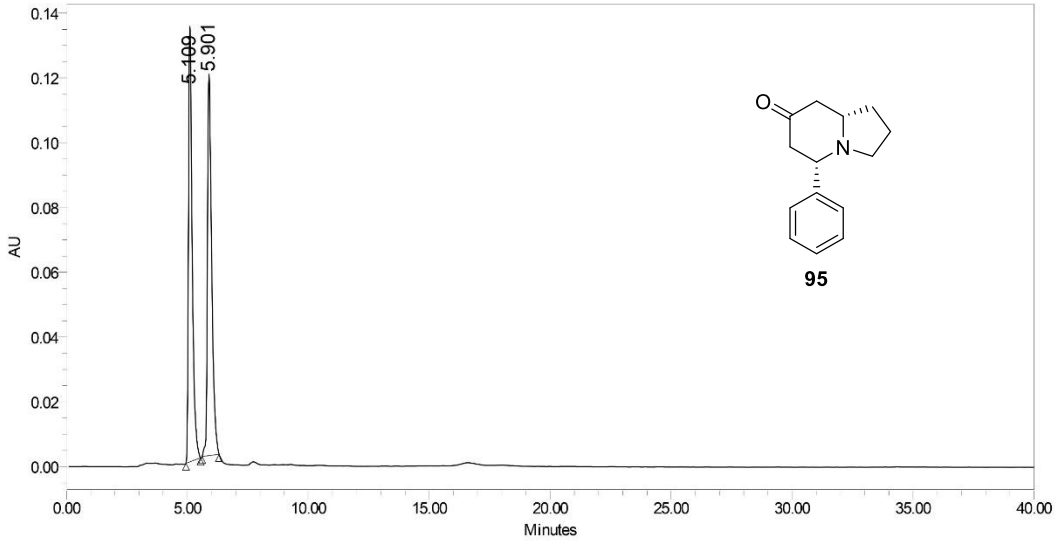

95

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	5.109	1444119	50.34	135498	53.52
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Memorial University

Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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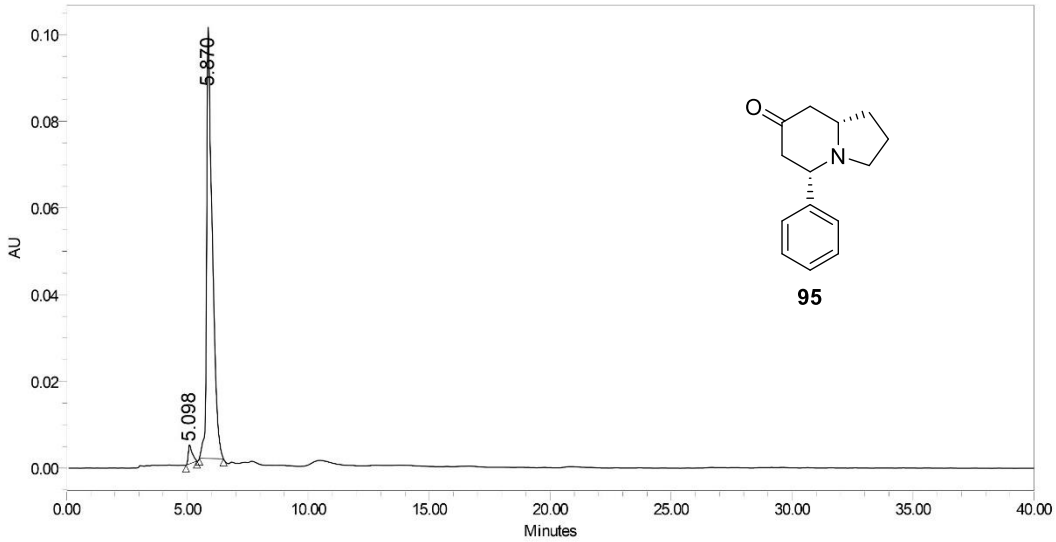

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2	5.870	1608134	96.99	99479	95.80

Memorial University

Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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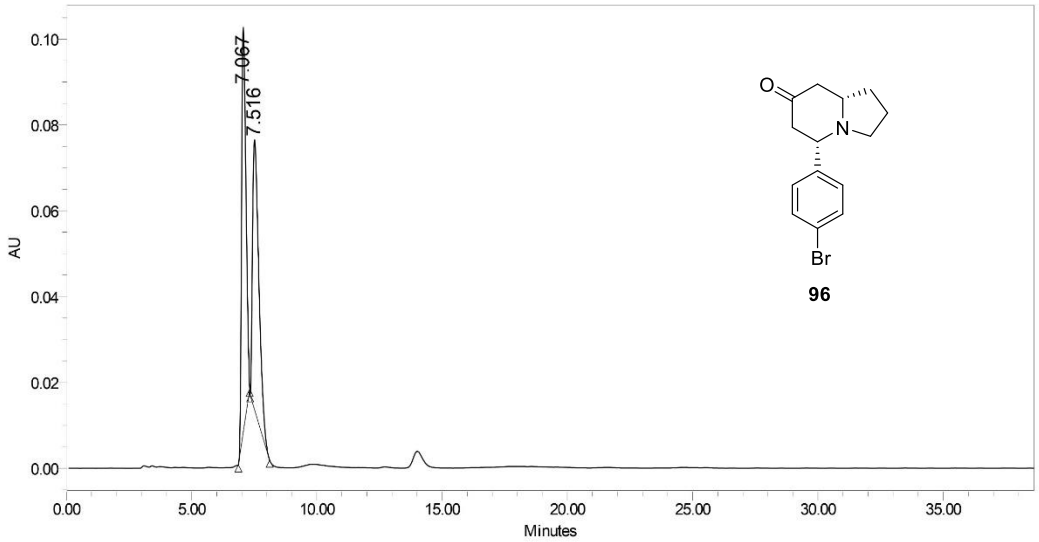

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	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	7.067	1140232	50.88	94126	59.90
2	7.516	1100638	49.12	63000	40.10

Report Method: Untitled

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Memorial University

Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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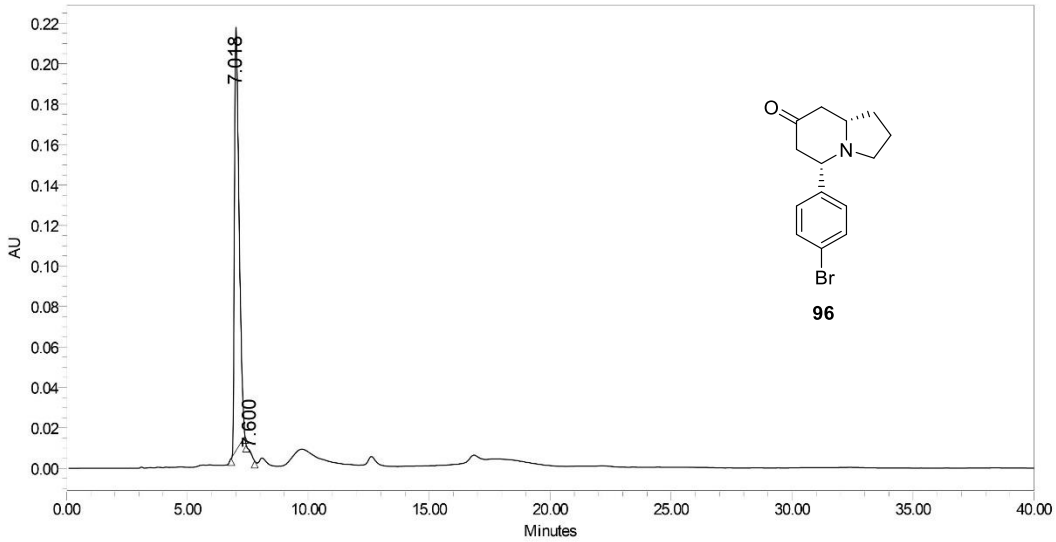
Run Time:	40.00 Minutes	Sample Set Name	



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2	7.600	5724	0.20	565	0.27

Report Method: Untitled

Page: 1 of 1

Printed: 02/05/2019

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Chapter 3

Organocatalytic Asymmetric Mannich Reaction of *α*, *β*-Unsaturated *β′*-Keto Esters and *N*-Carbamoyl Imines and Application in the Synthesis of Substituted Piperidinones

3.1 Introduction

Asymmetric Mannich reactions[1] are one of the most powerful approaches to synthesize chiral β-amino ketones which are prevalent in many natural products of medicinal importance.[2] There are numerous reports on the synthesis of β-amino ketone moiety containing compounds (**A**-**D**, Figure 3.1) employing Mannich reactions between imines and carbonyl compounds via both enamine[3] and enolate[4-7] reaction pathways. Enantioselective Mannich reactions following the latter pathway include enol silanes,[4] β-dicarbonyl compounds,[5] β-keto esters[6] and malonate esters[7] as nucleophiles. β'-Amino α, β-unsaturated enones (**E**, Figure 3.1) are yet another important class of nitrogen containing compounds which have been utilized in the synthesis of piperidinones,[8,9] 1,2,3,6-tetrahydropyridines (TPs),[10] 4-aminocyclopentenones[11] and conformationally rigid pyrazoloquinazoline α-amino acids[8] and β-pyridyl α-amino acids.[8]

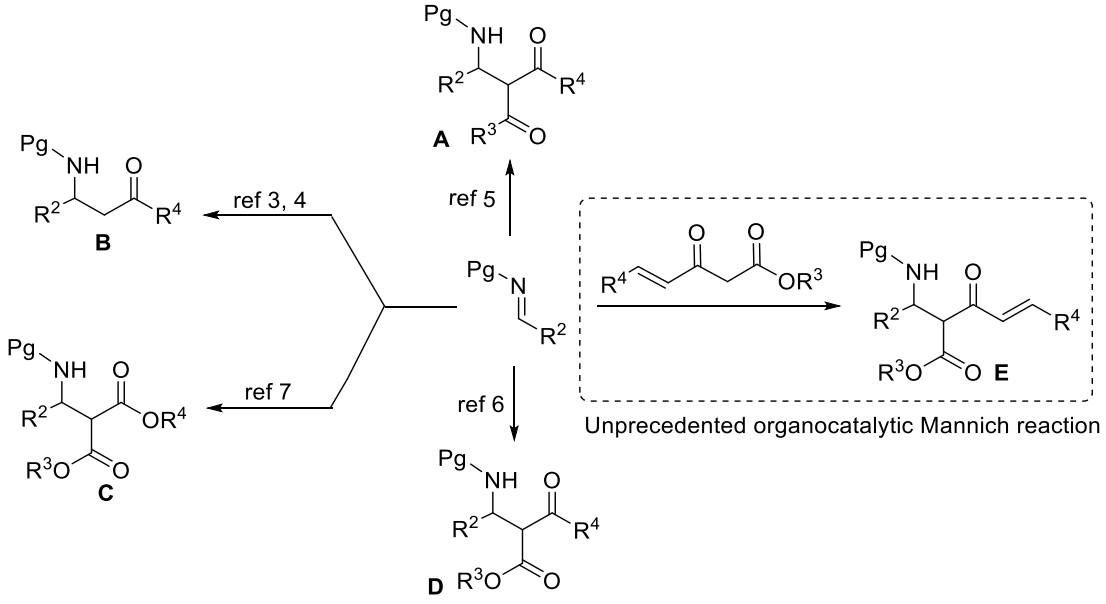


Figure 3.1: Past and present work on the direct Mannich reaction of imines with different carbonyl nucleophiles

However, to the best of our knowledge, only five asymmetric syntheses (described in Section 3.2 of this thesis) for these synthetically versatile *β′*-amino *α*,*β*-unsaturated enones have been reported to date, and none of the reports makes use of an organocatalytic approach. Thus, the development of an efficient enantioselective organocatalytic Mannich methodology for *β′*-amino, *α*,*β*-unsaturated enones is both an exciting and challenging task.

β′-Amino *α*,*β*-unsaturated enones are good candidates for an intramolecular aza-Michael reaction to provide 2,6-disubstituted piperidinones and, subsequently, the corresponding piperidines by the reduction of the piperidinones. The piperidine motif is found in several naturally occurring alkaloids and selected examples (**5**-**10**) are shown in Figure 3.2. These are of particular interest due to their wide range of biological activities such as anti-HIV, antibacterial and antifungal properties.[12] Compounds **3** and **4** are capable of binding to chemokine receptors[12,13] (particularly CXCR4 receptors) and have applications in the treatment of HIV, cancer, rheumatoid arthritis and inflammation. *N*-Amidinopiperidines **2** are reported to be neuroprotectants,[14] and compounds of type **1** are *γ*-secretase inhibitors[15] for the treatment of neurodegenerative diseases.

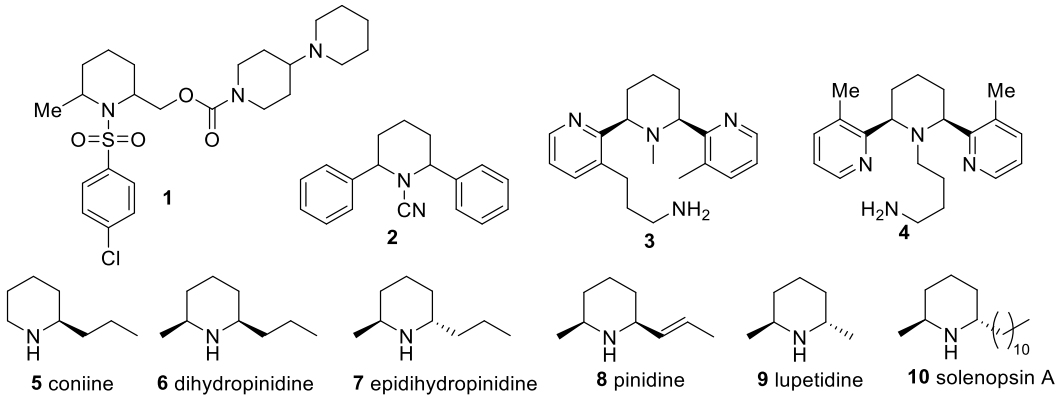
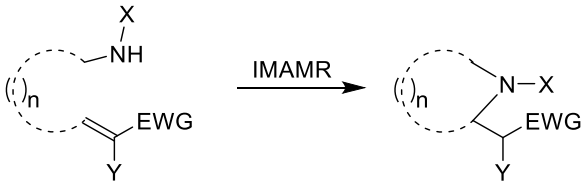


Figure 3.2 Examples of biologically relevant 2,6-disubstituted piperidines

Although there are several reports in the literature for the asymmetric synthesis of substituted piperidines,[16] none of these involve the use of an organocatalytic Mannich reaction followed by an intramolecular aza-Michael reaction. Thus, the development of such a synthetic approach can significantly improve on the earlier known syntheses of piperidines and at the same time, add to the utility of these two reactions in the field of asymmetric natural products synthesis.

Notably, most of the present-day work on aza-Michael[17] reactions is focused on the intermolecular version and only a few reports involving enantioselective organocatalytic intramolecular reactions[18] have been published, especially for *α,β*-unsaturated ketones.[19] Figure 3.3 shows the general scheme for an intramolecular aza-Michael reaction (IMAMR). The following section provides a summary of the known methods for the synthesis of *β′*-amino *α, β*-unsaturated enones, a class of IMAMR substrates that is the focus of our studies.



EWG = CHO, COR, CO_2R, NO_2, SO_2Ar, $PO(OR)_2$
X = H, CO_2R, OR, NR_2, SO_2Ar, COR
Y = H, COR, CO_2R, SO_2Ar; n = 2, 3

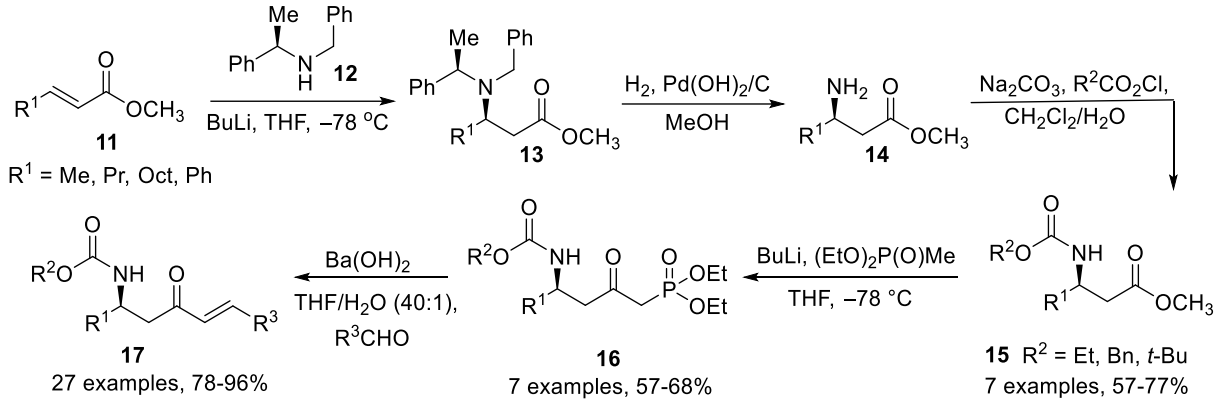
Figure 3.3: General scheme for an intramolecular aza-Michael reaction (IMAMR)

3.2 Previous reports on the synthesis of *β′*-amino *α,β*-unsaturated enones

3.2.1 A five-step conversion of *α,β*-unsaturated methyl esters[9a]

Troin and co-workers reported, in 2013, the synthesis of *β′*-amino *α,β*-unsaturated enones **17** employing five steps from *β*-substituted *α,β*-unsaturated methyl esters **11**. The synthesis

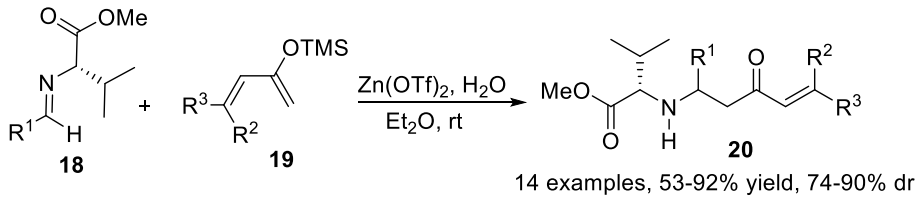
began with the addition of enantiopure lithium *N*-benzyl-*N*-α-methylbenzylamide (derived from *N*-benzyl-*N*-α-methylbenzylamine **12**, the Davies amine) to **11**. Hydrogenolysis of **13** provided the corresponding primary amine **14**. Protection as a carbamate resulted in β-amino methylester **15**, which was then converted into ketophosphonate **16** in moderate yields. Wittig-Horner-Emmons reaction of **16** with a variety of aldehydes using 1.3 equivalents of $Ba(OH)_2$ in a biphasic medium (THF/H_2O, 40:1) provided the target compounds **17** in good to excellent yield (Scheme 3.01).



Scheme 3.01

3.2.2 Mannich reaction of 2-silyloxybutadienes with chiral aldimines[20]

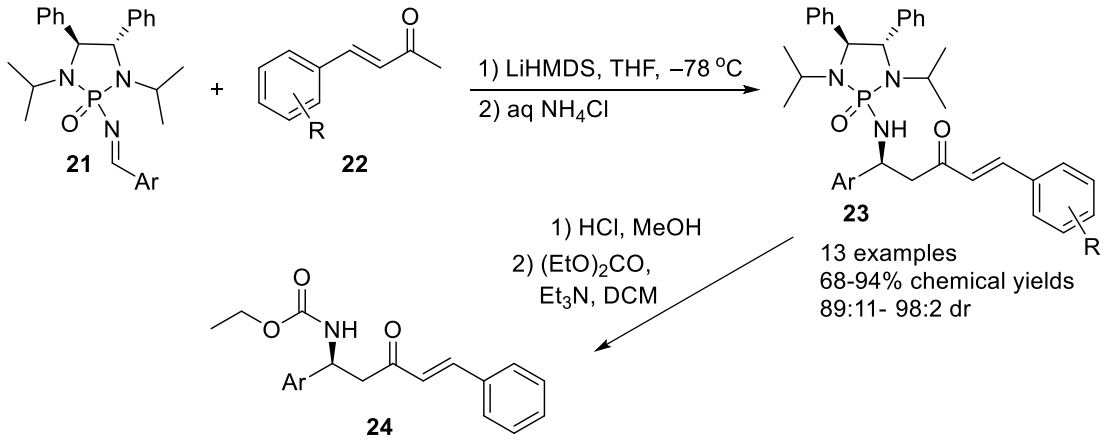
Ishimaru et al. reported the synthesis of β'-amino-α,β-unsaturated enones **20** by the reaction of chiral aldimines **18** with silyloxydienes **19** in diethyl ether in the presence of zinc triflate and water. The products were obtained in 53-92 % yields with 74-90% dr (Scheme 3.02).



Scheme 3.02

3.2.3 Addition of *α*, *β*-unsaturated ketone enolates to chiral *N*-phosphonyl imines[21]

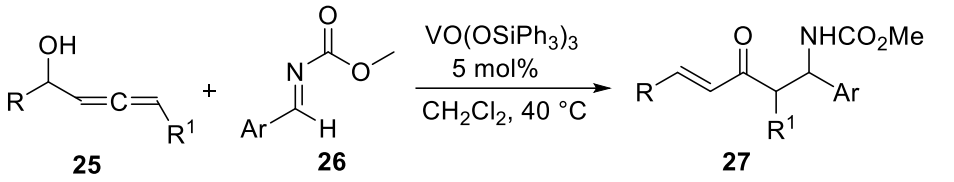
In 2014, Pan and coworkers reported an asymmetric Mannich reaction of benzylidene acetone-derived enolates **22** with *N*-phosphonyl imines **21** to yield *β*′-amino-*α*,*β*-unsaturated enones **23** with good yields and excellent diastereoselectivities (13 examples, 68-94% yields and 89:11-98:2 dr). Removal of the chiral auxiliary followed by protection of the amine as a carbamate provided **24** in good yields. It is worth noting that this is the only report of a Mannich reaction of an acyclic enone derived enolate to an imine, in this case the imine being a specialized phosphonyl imine[17] (Scheme 3.03).



Scheme 3.03

3.2.4 Vanadium-catalyzed additions of allenols to imines[22]

In 2003, Trost et al. reported the first vanadium-catalyzed *anti*-selective addition of allenic alcohols **25** to imines. Best results were obtained with *N*-carbamoyl imines **26** and allenols (**25**, R = aliphatic group) to provide *β*′-amino *α*, *β*-unsaturated enones **27** in good yields. (Scheme 3.04).

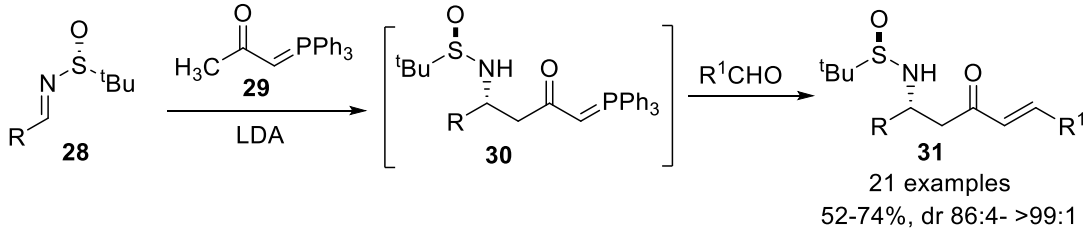


R, R^1 = aryl, CH_3: 7 examples, 40-85%, *anti*/*syn*: 1.5 to 9.0
R, R^1 = aryl, H: 1 example, 78%, *anti*/*syn*: NA (not applicable)
R, R^1 = alkyl, CH_3: 4 examples, 66-86%, *anti*/*syn*: 1.9 to 32.3

Scheme 3.04

3.2.5 Addition of lithium enolate of (acetylmethylene)triphenylphosphorane to chiral sulfinimines[23]

Prasad and co-workers reported a diastereoselective addition of the lithium enolate of (acetylmethylene) triphenylphosphorane **29** to non-racemic sulfinimines **28**. Further reaction of the formed sulfinimidophosphorane **30** with several aldehydes afforded the *β*-sulfinamido substituted enones **31** in good yields. The resultant enones were employed in the synthesis of alkaloid (+)-241D and aminocyclopentenol and in the formal total synthesis of (–)-preussin (Scheme 3.05).



Scheme 3.05

3.3 Objective

The objective of this study was to develop an asymmetric organocatalytic methodology for the synthesis of substituted piperidinones. As described in Chapter 2 of this thesis, we have

developed a methodology for the synthesis of 4-aryl quinolizidinones using a domino Mannich/aza-Michael reaction sequence by reacting a cyclic imine **F** with functionalized enones **G** under enamine/iminium ion catalysis (Figure 3.4). A logical extension of this methodology is to react a stabilized acyclic imine **I** with an α,β-unsaturated ketone **J**, or a nucleophilic synthon for such an enone, under organocatalytic conditions. The product of such an organocatalytic reaction was anticipated to be either a β'-amino-α,β-unsaturated ketone **K** (Mannich product) or a piperidinone **L** that could be obtained via a ring closure reaction of the initial Mannich product. For the former case, the Mannich product would have to be subjected to an intramolecular ring closure protocol to form the piperidone (Figure 3.4). This methodology could also provide an enantioselective route to chiral 2,6-disubstituted piperidines by reduction of the piperidinones.

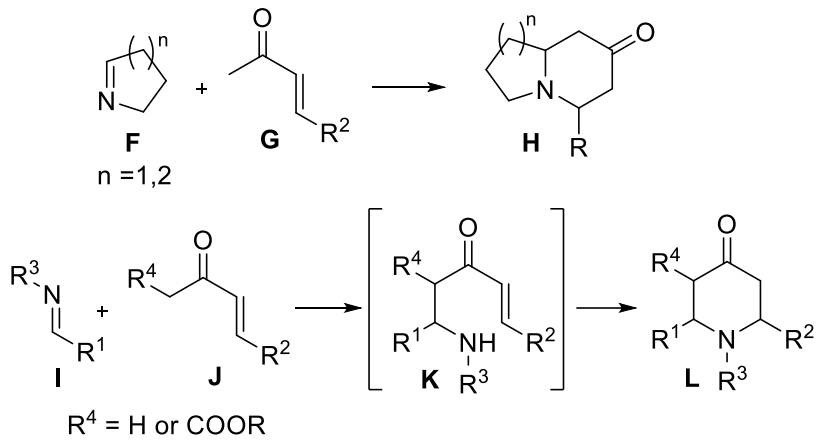


Figure 3.4 Our previous work with cyclic imines and the proposed synthesis of substituted piperidinones with acyclic imines

3.4 Results and discussion

We began our studies by investigating the reactivity of stable acyclic imines **32-38** and imine precursors **39-41** with enone **42** under (*S*)-proline catalysis in DMF (the optimized Mannich reaction conditions described in Chapter 2). Unfortunately, none of the reactions

afforded the desired product **43** or **44**. Apart from that, other reaction conditions were also tested, however with no success. The acyclic imines examined for reaction with enone **42** are shown in Figure 3.5 and the reaction conditions tried are listed in Table 3.1.

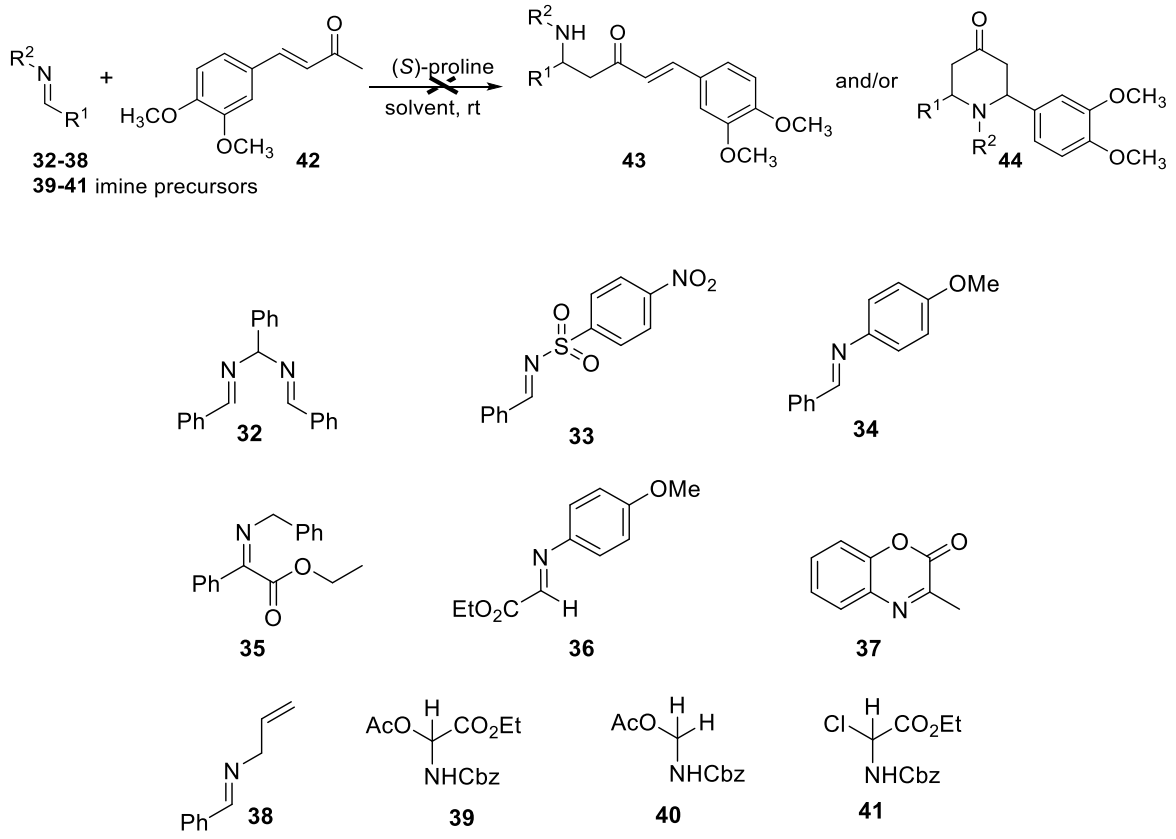
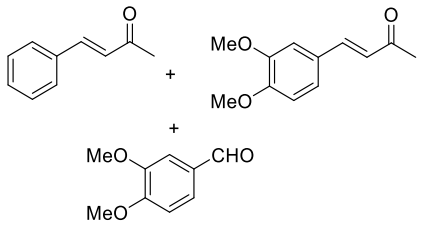


Figure 3.5 The acyclic imines and imine precursors examined for reaction with enone **42**

Table 3.1 Unsuccessful attempts at the reaction of enone **42** with imines **32-38** and precursors **39-41** shown above in Figure 3.5

Entry	Imine/Imine precursor	Solvent	Observation
1.	**32**	DMF	No reaction
2.	**33**	DMF	No reaction
3.	**34**	DMF	No reaction

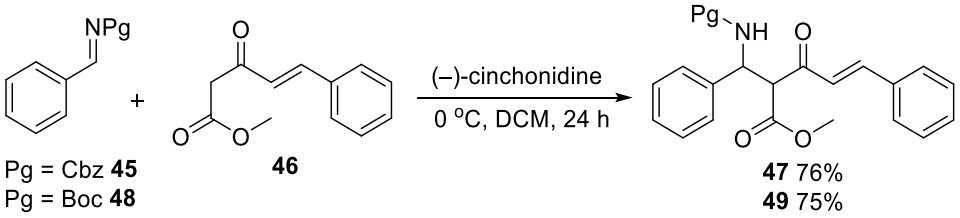
4.	**34**	MeOH	
5.	**35**	DMF	No reaction
6.	**36**[a]	DMF	No reaction
7.	**36**	MeOH	No reaction
8.	**36**	DMSO	No reaction
9.	**36**	1-butyl 3-imidazolium tetrafluoroborate	No reaction
10.	**36**	$CHCl_3$	No reaction
11.	**36**	*p*-TsOH, DMF	Enone unreacted, imine decomposed
12.	**36**	DMF[b]	No reaction
13.	**37**	DMF[b]	No reaction
14.	**38**	MeOH	Cyclised product **44** (22%) formed as a racemic mixture
15.	**39**	DMF	No reaction
16.	**40**	DMF	No reaction
17.	**41**	DMF	Imine decomposed, enone recovered

a: With this imine, L-tryptophan[24] was also tried as a catalyst in DMSO, however no reaction was observed.
b: reaction temperature 40 ^oC

As can be seen from the results shown in the Table 3.1, no reaction was observed with imines **32-38** and precursors **39-41** using (*S*)-proline as the catalyst in DMF. The effect of solvent was studied for imine **36** (entries 6-10), however no beneficial change in outcome was seen. Imine **36** was also subjected to L-tryptophan mediated[24] organocatalysis in DMSO, however no reaction was observed. The effect of temperature was studied using imines **36** and

37, but it was found to be ineffective in bringing about the desired reaction (entries 12,13). Addition of an acid additive resulted in decomposition of imine **36** (entry 11). Decomposition was also noticed for imine precursor **41** under organocatalytic conditions at ambient temperature, even without an acid additive (entry 17). Clearly, the reaction between the acyclic imines and enone **42** was not working under organocatalytic conditions. The only exception is the reaction of the *N*-allyl imine **38** (entry 14, Table 3.1) where the cyclized product **44** was formed as a racemic mixture, as was also seen in Aznar's report.[16c]

We then turned our attention to *N*-carbamoyl imines[25] as electrophiles and α, β-unsaturated β'-keto-esters (unprecedented in Mannich reactions) as nucleophiles for the direct Mannich reaction. Gratifyingly, the organocatalytic Mannich reaction between *N*-Cbz imine **45** and methyl ester **46** in the presence of 10 mol% of cinchonidine[25] at 0 °C afforded the product **47** in 76% yield as a 1:1 mixture of diastereomers (Scheme 3.06). Similar results were obtained with the *N*-Boc imine **48** as well yielding the corresponding product **49** in 75% yield. The piperidinone derived by cyclization of **47** or **49** was not observed in the reaction mixtures. The enantiomeric excess of **47** and **49** was not determined.



Scheme 3.06

The Mannich products **47** and **49** were obtained as an inseparable mixture of diastereomers. In addition, the carbamate functionality in **47** and **49** causes atropisomerism and hence the ^{1}H NMR spectra for **47** and **49** are quite complex. The decarboxylation of **47** and **49**

seemed a reasonable solution as it would simplify the analysis of ^{1}H NMR spectra. However, since the decarboxylation of methyl esters using the Krapcho[26] reaction would require drastic conditions, we chose to use the corresponding allyl ester **51**, anticipating that deallylative decarboxylation would be possible under mild (Pd(0) catalysis) reaction conditions.

The ketoester **51** and the imine **50** were chosen for initial studies aimed at identifying a suitable catalyst for the Mannich reaction. The catalysts selected for the study are shown in Figure 3.6 and Table 3.2 summarizes the results of the study. The product **52** was then subjected to deallylative decarboxylation using $Pd(PPh_3)_4$ and morpholine in THF at ambient temperature[27] to obtain the product **53** for which enantiomeric excess was measured.

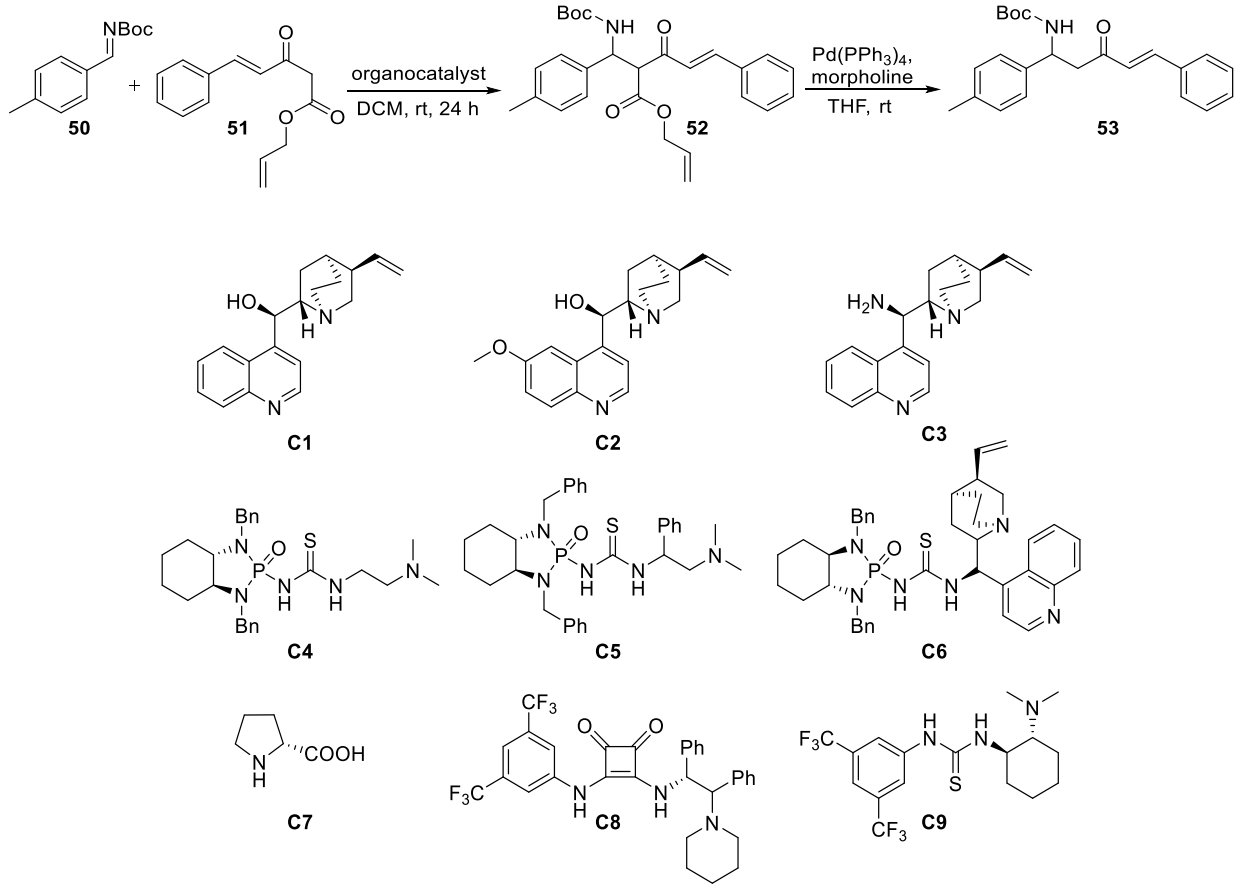


Figure 3.6 The catalysts studied for the Mannich reaction between imine **50** and keto-ester **51**

Table 3.2 Results for the catalyst survey of the Mannich reaction

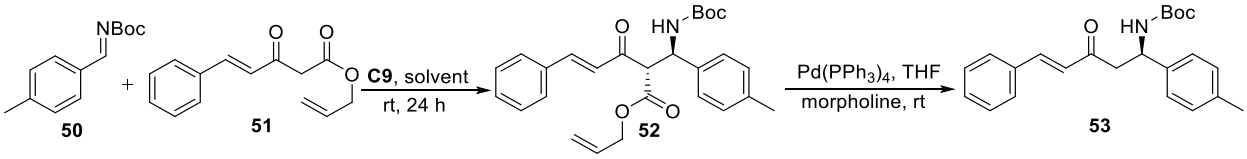
Entry	Organocatalyst	Yield[b] (52) %	Yield (53) %	% ee (53)
1.	**C1**	98	92	60
2.	**C2**	86	93	52
3.	**C3**	82	89	2
4.	**C4**	93	91	3
5.	**C5**	80	92	2
6.	**C6**	62	85	5
7.	**C7**	50	85	6
8.	**C8**	62	86	47
9.	**C9**	75	90	80
10.[a]	**C9**	80	86	66

a: reaction in the presence of 5 mol% catalyst, b: all Mannich products are approximately 1:1 mixture of diastereomers.

Of all the catalysts studied, **C9** (the (*S*,*S*)-Takemoto catalyst) provided product with the highest enantiomeric excess of 80% at ambient temperature (entry 9, Table 3.2). Cinchonidine **C1** and quinine **C2** gave higher yields for the product but lower enantioselectivity (entries 1 and 2, Table 3.2). The use of (*S*)-proline **C7** (entry 7, Table 3.2) and other phosphoramide based catalysts **C4**, **C5** and **C6** (entries 4-6, Table 3.2) afforded nearly racemic products. The use of **C3**, a primary amine catalyst also resulted in a racemic mixture (entry 3, Table 3.2). Lowering the catalyst loading to 5 mol% for **C9** at 0 ^{o}C for 24 h led to a decrease in ee to 66% but a slight increase in yield to 80% (entry 10, Table 3.2).

The above studies identified **C9** as the catalyst of choice and a brief survey of reaction solvents was conducted with this catalyst. The results of this survey are provided in Table 3.3.

Table 3.3 Solvent survey for the reaction of **50** and **51** catalyzed by **C9**



Entry	Solvent	Yield (52)	Yield (53)	% ee (53)
1.	$PhCH_3$	64	87	60
2.	CH_3CN	60	85	86
3.	THF	77	87	68
4.	CH_3CN[a]	85	83	91[c]
5.	CH_3CN[a]	93 (84)[d]	89	99[e]
6.	CH_3CN[b]	98	89	72

a: at 0 ^oC, b: at −10 ^oC, c: deallylative decarboxylation performed on a 1:1 mixture of diastereomers, d: yield of major diastereomer which precipitates from the reaction mixture e: deallylative decarboxylation performed on a single diastereomer.

The reaction performed in acetonitrile at 0 ^oC provided the best result, desirable both in terms of yield and enantiomeric excess (entry 5, Table 3.3). At −10 ^oC, the enantiomeric excess for the product **53** dropped to 72% (entry 6, Table 3.3) in comparison to the reaction done at 0 ^oC where it was 91%. In the other solvents studied, both the yield and ee were lower in comparison to acetonitrile, thus it was determined to be the solvent of choice for the Mannich reaction. Notably, the reaction performed in the absence of any catalyst in acetonitrile at 0 ^oC also provided the Mannich product **52** in 80% yield. Taking this into account, it is interesting that the enantioselectivity of our Mannich reaction is high. This observation suggests that, under the

optimized conditions, the uncatalyzed background reaction does not contribute to an extent that significantly affects the enantioselectivity of the process.

At this stage, the Mannich product **52** (single diastereomer) and the corresponding amino ketone **53** (99% ee), obtained by deallylative decarboxylation of **52** (entry 5, Table 3.3) were subjected to X-ray crystallographic analysis. This established the absolute configuration of **52** and **53** as shown in Figure 3.7 (*S* at the ketoester stereocenter and *R* at the amine stereocenter for **52** and *R* for **53**).

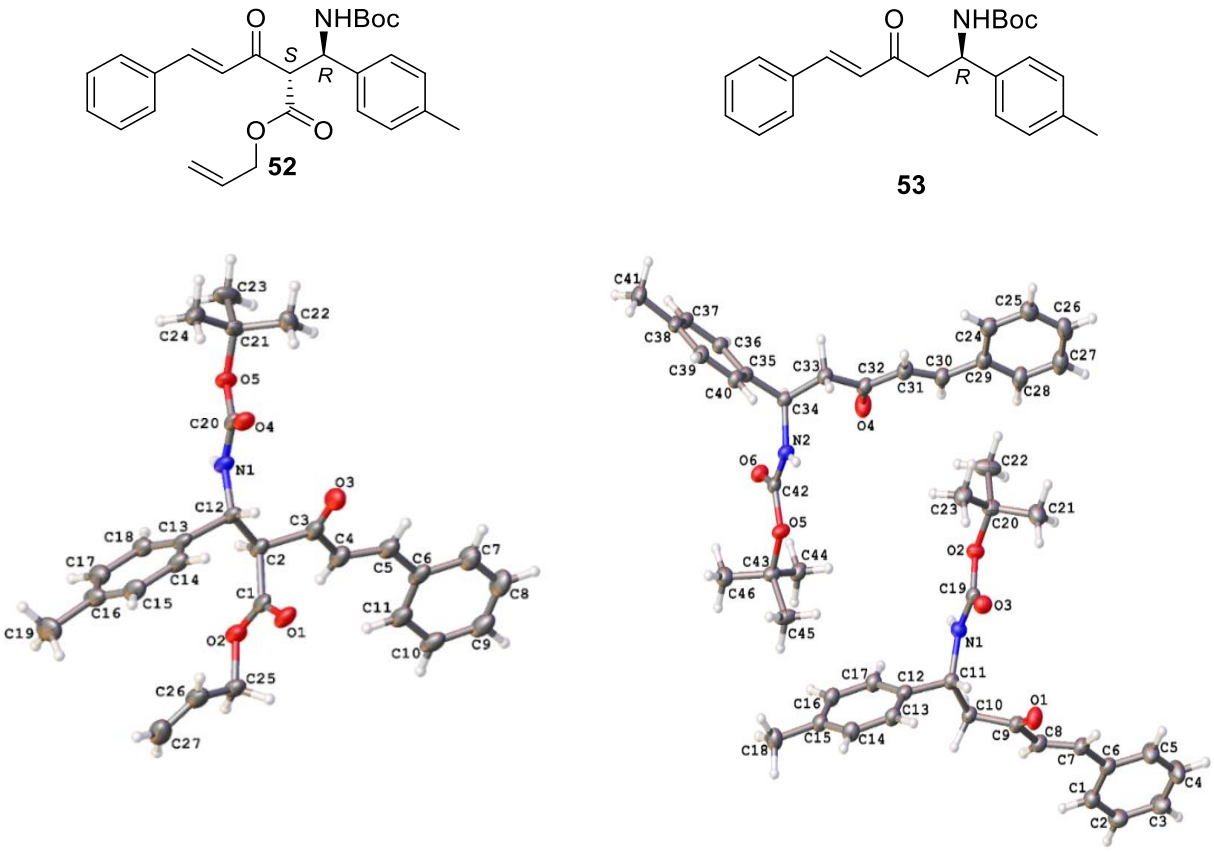


Figure 3.7 Crystal structures for **52** and **53**

A possible transition state assembly for the reaction of **50** and **51** to provide **52** in the presence of catalyst **C9** is shown in Figure 3.8. The proposed model involves hydrogen bonding

of the alkoxy moiety in the ester enolate with the protonated tertiary amine in **C9**, and also of the imine nitrogen and the Boc group with the thiourea N−H groups. The resulting arrangement promotes a reaction of the *si* face of ester enolate with the *re* face of the imine (Figure 3.8).

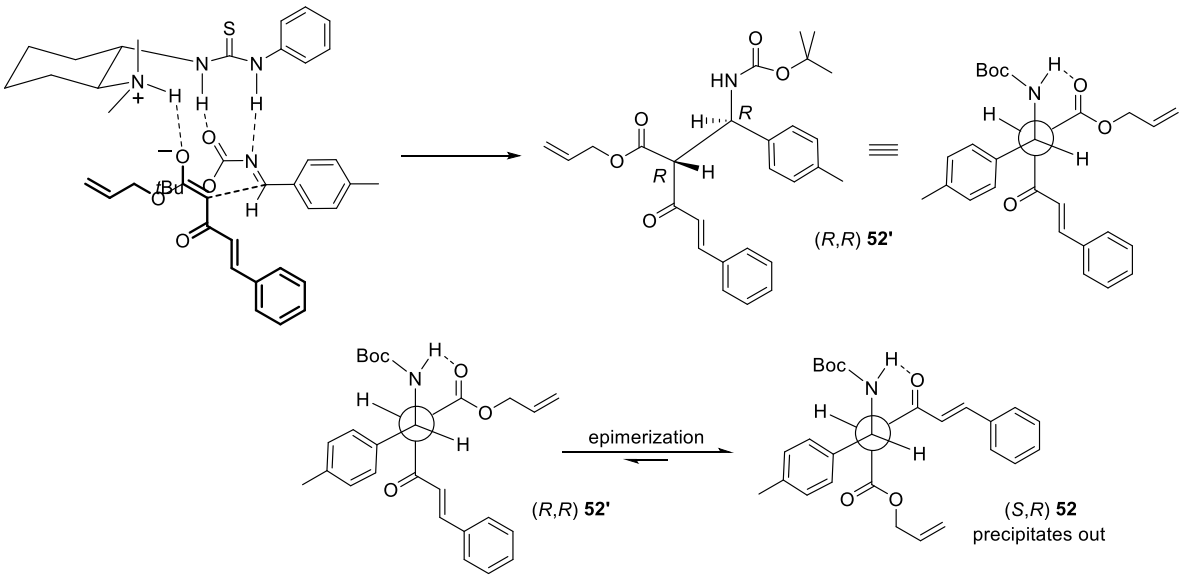


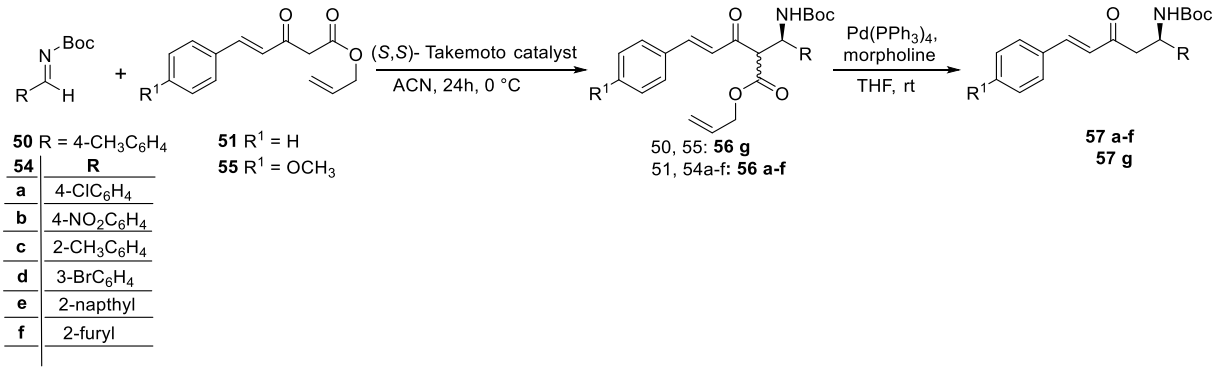
Figure 3.8 Proposed transition state assembly for the Mannich reaction of **50** and **51** and epimerization of the Mannich product (*R*,*R*)-**52′** to (*S*,*R*)-**52**.

The proposed transition state model predicts the formation of the (*R*,*R*) Mannich product **52′** whereas (*S*,*R*)-**52** is the major product that was isolated and analyzed by X-ray crystallography. It is likely that (*R*,*R*)-**52′** undergoes rapid epimerization under the reaction conditions to provide (*S*,*R*)-**52** which precipitates out of the reaction mixture. Notably, the supernatant solution of the reaction mixture contains a mixture of diastereomers, one of which is (*S*,*R*)-**52** and the other is presumably (*R*,*R*)-**52′**. The high enantiomeric excess of **53** supports our hypothesis that the diastereomers are formed due to epimerization of the labile ketoester stereocenter in (*R*,*R*)-**52′** and not due to low facial selectivity for addition to the imine **50**. Since the Newman projections (Figure 3.8) of internally hydrogen-bonded (*R*,*R*)-**52′** and (*S*,*R*)-**52** do

not indicate any notable differences that would stabilize one over the other, we assume that (*S*,*R*)-**52** is obtained as the major product because it gradually precipitates out of the reaction mixture and is thus unavailable for equilibration to (*R*,*R*)-**52′**. Selective precipitation of one of the diastereomers was also observed with a few other imines (see Table 3.4). It should be mentioned that if the Mannich product does not precipitate out of the reaction mixture, it is isolated as a mixture of diastereomers.

Having established an optimized protocol for the Mannich reaction and for the deallylative decarboxylation reaction, we next investigated the substrate scope of our methodology (Table 3.4).

Table 3.4 Substrate scope for the optimized Mannich reaction



54	R
a	4-ClC$_6$H$_4$
b	4-NO$_2$C$_6$H$_4$
c	2-CH$_3$C$_6$H$_4$
d	3-BrC$_6$H$_4$
e	2-napthyl
f	2-furyl

Entry	56, 57	yield (56) %	dr (56)	yield (57)%	% ee (57)
1.[c]	**a**	88	4:1	88	97[a]
2.	**b**	58	1:1.3	89	>99
3.	**c**	85	1:0.9	89	81
4.	**d**	74	1:0.9	87	73
5.[c]	**e**	91	4:1	88	39[a]
6.[b]	**f**	68	1:0.9	85	25

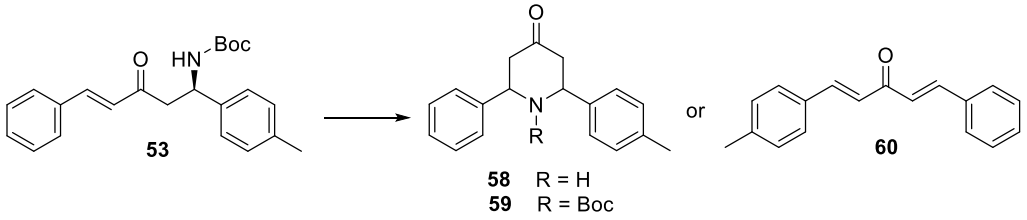
7.	**g**	58	1:1	76	94

a: deallylative decarboxylation performed on single diastereomer, b: worked up after 60h c: major diastereomer precipitated out and chromatography was not necessary.

3.5 Intramolecular aza-Michael reaction of *β′*-*N*-carbamoyl-*α*,*β*-unsaturated ketones to provide 2,6-disubstituted piperidinones

Having developed an enantioselective synthesis of *β′*-amino *α*,*β*-unsaturated enones, we turned our attention to their conversion to substituted piperidin-4-ones by employing the IMAMR. We soon realized that this apparently simple cyclisation was quite difficult, and our initial attempts yielded very little of the required piperidinones. Table **3.5** summarizes the unsuccessful attempts at the 6-endo trig cyclisation using **53** as the starting material.

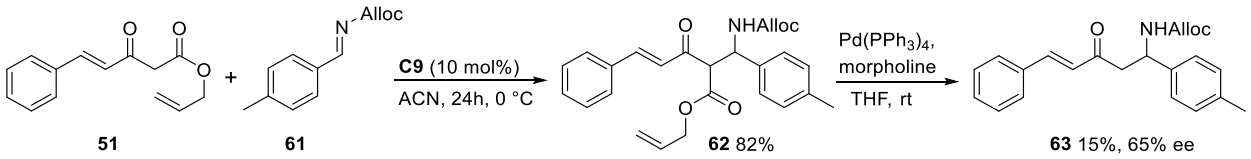
Table 3.5 Unsuccessful attempts to cyclize the Mannich product **53**



Entry	Reaction conditions	Observation
1.	NaH (1 eq.) in THF at rt	Starting material consumed, but complex mixtures obtained after purification
2.	DBU (1 eq.) in THF at rt	Starting material unreacted
3.	4M HCl in dioxane at rt	**60** along with decomposed material obtained
4.	(*S*)-proline, DMF, rt to 60 ^{o}C	Starting material unreacted
5.	K_2CO_3, DMSO, rt	Starting material unreacted
6.	20 mol% Cu $(OTf)_2$ in DCM	Starting material unreacted

7.	H_3PO_4 (85%), DCM, rt to reflux[28]	Decomposition of starting materials
8.	**C3** (0.2 eq.), TFA (0.2 eq.), $CHCl_3$	Starting material unreacted
9.	**C3** (0.2 eq.), DPP (0.2 eq.), $CHCl_3$	Starting material unreacted at rt but on heating elimination product formed
10.	$Cu(acac)_2$, THF, rt	Starting material unreacted
11.	TfOH (0.1 eq.), DCM, 0 ^oC	Starting material and elimination product recovered
12.	$Et_2O.BF_3$, DCE	Starting material unreacted at rt, but complete decomposition when heated to 60 °C
13.	Cu(I)Cl, PPh_3, K(O^tBu), toluene, rt[29]	Starting material unreacted
14.	Cu(I)Cl, DPPE, K(O^tBu), toluene, rt to 60 ^oC	Starting material unreacted
15.	$HC(OCH_3)_3$ (5 eq.), ethylene glycol (5 eq.), PTSA.H_2O (0.2 eq.)[9a]	Complete decomposition

We also examined the effect of changing the *N*-protecting group. Thus, we reacted allyl ester **51** with *N*-alloc imine **61** under the optimized conditions to obtain the Mannich product **62** in 82% yield (shown in Scheme 3.07). Deallylative decarboxylation gave the desired product **63** in 15% yield along with the corresponding free amine resulting from the simultaneous removal of the *N*-Alloc group.

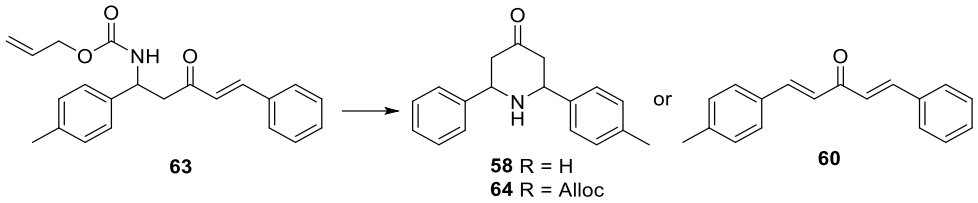


51 61 **62** 82% **63** 15%, 65% ee

Scheme 3.07

A few attempts were made to convert **63** to the corresponding piperidinone, but none was successful. These have been listed in Table 3.6 below.

Table 3.6 Unsuccessful attempts at cyclisation of product **63**

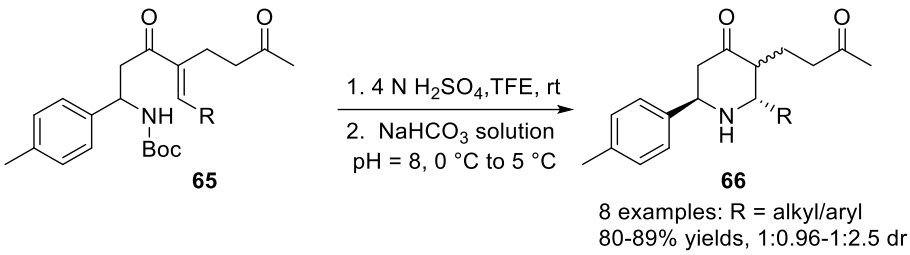


Entry	Reaction condition	Observation
1.	$Pd(PPh_3)_4$, THF, rt to reflux (1 to 2d)	No progress at rt, **60** formed upon heating (checked by TLC)
2.	$Pd(PPh_3)_4$, TEA, HCOOH, THF, 1d, rt	**60** (22%) and multiple other products isolated
3.	$Pd(PPh_3)_4$, N-TMS morpholine, DCM, rt	**60** (18%) and multiple other products isolated

Given the lack of piperidinone formation and also the low enantiomeric excess (65%) of the *N*-Alloc product **63**, studies with the *N*-Alloc imine were discontinued.

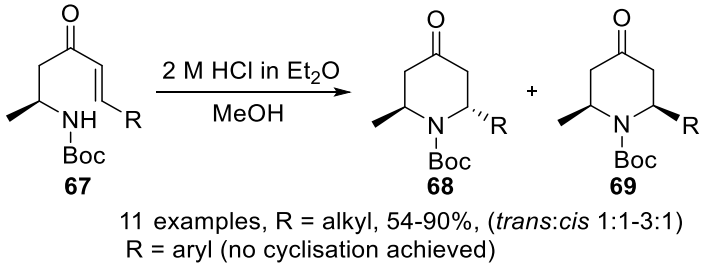
The above studies underscore the challenging nature of the intramolecular aza-Michael reaction of our *β*-amino ketones transformation, and it is therefore instructive to summarize the previously reported procedures for similar conversions.

Recently (2019), a base-catalysed cyclisation protocol involving a 6-*endo* activated cyclisation for the synthesis of trisubstituted piperidinones (Scheme 3.08) was reported by reported Trost.[16a] Diastereomeric piperidinone products **66** were obtained in 80-89% overall yields with 1:0.96-1:2.5 dr for aryl/ alkyl *β*-substituents on the enone.



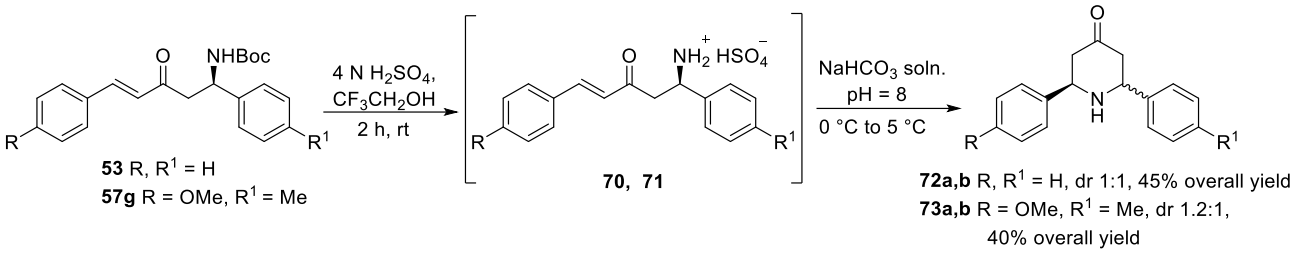
Scheme 3.08

Prior to this, in 2018, Sutherland et al.[16d] reported acid-catalysed cyclisation of aminoketones **67**. Although the required piperidinones **68** and **69** were obtained as a mixture of diastereomers when the enone β-substituent was an alkyl group, the piperidinone products were not obtained when β-aryl enones were used (Scheme 3.09).



Scheme 3.09

When Trost's conditions were employed for the deprotection and cyclization of our Mannich products **53** and **57g**, the corresponding piperidinones **72a**,**b** and **73a**,**b** were indeed obtained as mixtures of *cis* and *trans* isomers, but in modest yields (Scheme 3.10) compared to the reported examples. The reasons for this are not clear at this time, but it is possible that the absence of an α-substituent in the enone affects the cyclization step.

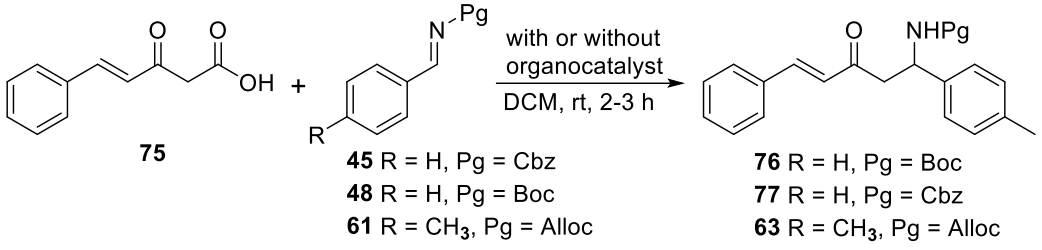


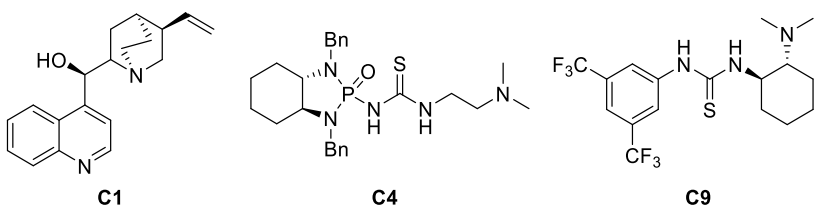
Scheme 3.10

3.6 Decarboxylative Mannich Reaction

Although there are a few reports[30-32] on the use of decarboxylative Mannich reactions in the synthesis of chiral amino compounds, this reaction has not been employed in the synthesis of *β′*-amino *α,β*-enones. We have observed a decarboxylative Mannich reaction[33] of *N*-carbamoyl imines **45, 48 and 61** and the *α, β*-unsaturated *β′*-keto acid **75** to provide corresponding Mannich products **63, 76** and **77** in good yields. This reaction worked well for Boc, Cbz and Alloc imines, however only racemic products were obtained using a selection of chiral organocatalysts. Table 3.7 summarizes the reactions examined using the decarboxylative Mannich reaction.

Table 3.7 Decarboxylative Mannich Reaction between *N*-carbamoyl imine and the *α,β*-unsaturated *β′*-keto acid





Entry	Product	Organocatalyst	Yield %	%ee
1.	**76**	**C9**	90	2
2.	**76**	**C1**	89	5
3.	**76**	**C4**	78	5
4.	**63**	**C9**	96	1
5.	**76**	**-**	88	NA
6.	**63**	**-**	96	NA
7.	**77**	**-**	74	NA

The reaction between the imine and the ketoacid gave equally good yields in the absence of a catalyst (entries 5, 6 and 7 in Table 3.7). This decarboxylative Mannich protocol is by far the most operationally facile method to obtain α,β-unsaturated Mannich products **63, 76** and **77** in good yields.

3.7 Conclusion and future work

We have developed an organocatalytic asymmetric Mannich reaction of α,β-unsaturated β'-keto esters with *N*-carbamoyl imines. The reaction provides moderate to good yields of the required products and proceeds with good enantioselectivity. Deallylative decarboxylation of the Mannich products provides enantiomerically enriched β-amino ketones which can be cyclized to the corresponding 2,6-diaryl piperidin-4-ones. These studies provide the first examples of the synthesis of the target compounds using a direct organocatalytic Mannich reaction. Apart from this, we have also developed a decarboxylative Mannich reaction of β-ketoacids and

N-carbamoyl imines. While the yields of these reactions are high, they provided only racemic products even in the presence of a chiral amine catalyst.

Future studies will focus on the substrate scope and on optimizing the enantioselectivity of the described Mannich reaction.

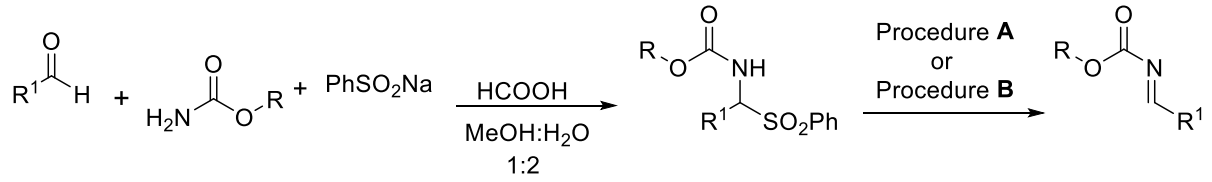
3.8 Experimental Section

General

All commercially available reagents were used without purification. All reactions requiring anhydrous conditions were performed under an atmosphere of dry nitrogen using oven dried glassware. CH_2Cl_2 were distilled from CaH_2. Commercial precoated silica gel plates were used for TLC. All melting points are uncorrected. Silica gel for flash column chromatography was 230-400 mesh. IR spectra were recorded on a Bruker TENSOR 27 FT-IR instrument. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE III 300 or an AVANCE 500 instrument. Mass spectra were obtained on an Agilent 1100 series LC/MSD (Trap) or an Agilent 6200 LC/MSD (TOF) chromatographic system. HPLC analyses were performed on a Waters chromatographic system using the Breeze software.

Imine Preparation

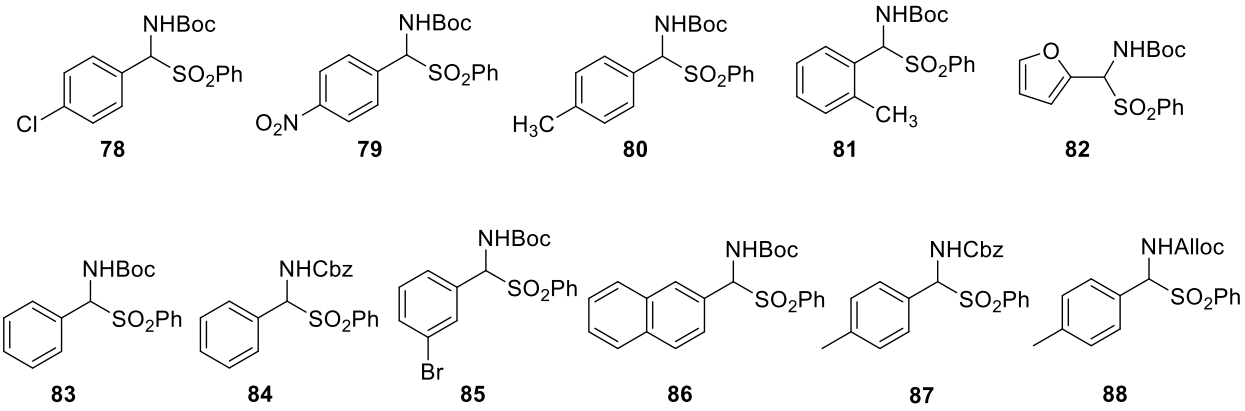
The required imines were prepared by following a two-step protocol as shown below:



General Procedure[34] **for the synthesis of sulfones**

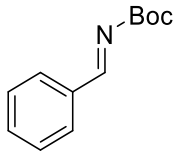
The corresponding carbamate was added to a solution of the sodium salt of benzene sulfinic acid in a methanol:water (1:2) mixture. The resulting white suspension was vigorously stirred followed by the addition of the aldehyde and later formic acid. At this stage, the reaction mixture became a clear solution. With time, a precipitate began forming and after stirring at rt for 3 days, the reaction mixture was suction filtered and the residue was thoroughly washed, first with water and then with ethyl ether (3 times each) to obtain the pure sulfone.

The sulfones **78**,[35] **79**,[36] **80-86**,[37] **87**,[36] **and 88**[36] synthesised for these studies are all known compounds and their spectroscopic data was in agreement with reported data.



General Procedure[36] **A**: The sulfone was added to a 1:1 ratio of 1.4 M K_2CO_3 and DCM. The reaction mixture was stirred vigorously (such that the mixture no longer looked like a bilayer) at rt for 4-5 hrs. Upon completion of the reaction (^{1}H NMR), the layers were separated, and the organic layers collected, dried over anhydrous sodium sulfate to give the corresponding pure imine.

(*E*)-*tert*-Butyl benzylidenecarbamate (48)



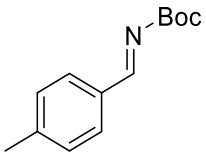
The reaction of sulfone **83** (1 g, 2.9 mmol) with 1.4 M K_2CO_3 (45.8 mL) in DCM (45.8 mL), according to the general procedure A, provided 587 mg (99%) of the pure imine **48**.

^{1}H NMR (300 MHz, $CDCl_3$): 8.88 (s, C*H*=N), 7.95-7.89 (m, 2H, Ar*H*), 7.60-7.53 (m, 1H, Ar*H*), 7.51-7.44 (m, 2H, Ar*H*), 1.59 (s, 9H, OC(CH_3)$_3$).

IR (neat): 2973, 1702, 1629, 1601, 1348, 1250, 1218, 1141 cm^{-1}.

HRMS (ESI, pos.): m/z 206.1179 (206.1181 calc. for $C_{12}H_{16}NO_2$ $(M+H)^+$)

(*E*)-*tert*-Butyl 4-methylbenzylidenecarbamate (50)



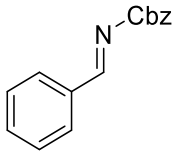
The reaction of sulfone **80** (763 mg, 2.1 mmol) with 1.4 M K_2CO_3 (33.6 mL) in DCM (33.6 mL), according to the general procedure A, provided 442 mg (96%) of the pure imine **50**.

^{1}H NMR (300 MHz, $CDCl_3$): 8.88 (s, 1H, C*H*=N), 7.82 (d, 2H, *J* = 9.4 Hz, Ar*H*), 7.30-7.24 (m, 2H, *J* = 9.4 Hz, Ar*H*), 2.42 (s, 3H, CH_3), 1.59 (s, 9H, OC(CH_3)$_3$).

IR (neat): 2980, 1706, 1636, 1607, 1368, 1250, 1218, 1148 cm^{-1}.

HRMS (ESI, pos.): m/z 220.1341 (220.1338 calc. for $C_{13}H_{18}NO_2$ $(M+H)^+$)

(*E*)-Benzyl benzylidenecarbamate (45)



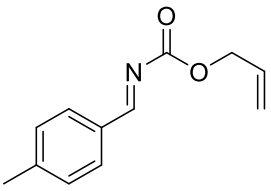
The reaction of sulfone **84** (500 mg, 1.26 mmol) with 1.4 M K_2CO_3 (20.2 mL) in DCM (20.2 mL), according to the general procedure A, provided 287 mg (95 %) of the pure imine **45**.

^{1}H NMR (300 MHz, $CDCl_3$): 8.93 (s, 1H, C*H*=N), 7.92 (m, 2H, Ar*H*), 7.58-7.54 (m, 1H, Ar*H*), 7.47 (d, 2H, *J* = 8.0 Hz, Ar*H*), 7.45-7.42 (m, 2H, Ar*H*), 7.39-7.31 (m, 3H, Ar*H*), 5.30 (s, 2H, CH_2Ph)

IR (neat): 3296, 2971, 1695, 1528, 1455, 1337, 1250, 1024, 951 cm^{-1}.

HRMS (ESI, pos.): m/z 240.1007 (240.1025 calc. for $C_{15}H_{14}NO_2$ $(M+H)^+$)

(*E*)-Allyl 4-methylbenzylidenecarbamate (61)



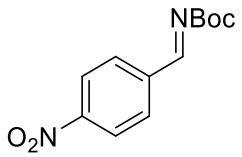
The reaction of sulfone **88** (1 g, 2.9 mmol) with 1.4 M K_2CO_3 (44 mL) in DCM (44 mL), according to the general procedure A, provided 515 mg (87%) of the pure imine **61**.

^{1}H NMR (300 MHz, $CDCl_3$): 8.95 (s, 1H, C*H*=N), 7.84 (d, 2H, *J* = Hz, Ar*H*), 7.29 (d, 2H, *J* = Hz, Ar*H*), 6.11-5.96 (m, 1H, OCH_2CH=CH_2), 5.46-5.37 (m, 1H, OCH_2CH=CH_2), 5.33-5.26 (m, 1H, OCH_2CH=CH_2), 4.79-4.75 (m, 2H, OCH_2CH=CH_2), 2.43 (s, 3H, OCH_3)

IR (neat): 3294, 3025, 2360, 1711, 1553, 1512, 1310, 1233, 1132 cm^{-1}.

HRMS (ESI, pos.): m/z 204.1020 (204.1025 calc. for $C_{12}H_{14}NO_2$ $(M+H)^+$)

***tert*-Butyl 4-nitrobenzylidenecarbamate (54b)**



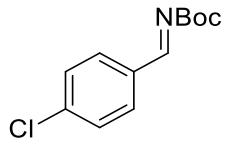
The reaction of sulfone **79** (677 mg, 1.73 mmol) with 1.4 M K_2CO_3 (30 mL) in DCM (30 mL), according to the general procedure A, provided 355 mg (82%) of the pure imine **54b**.

^{1}H NMR (300 MHz, $CDCl_3$): 8.88 (s, 1H, C*H*=N), 8.36-8.30 (m, 2H, Ar*H*), 8.12-8.06 (m, 2H, Ar*H*), 1.60 (s, 9H, OC(CH_3)$_3$).

IR (neat): 3324, 2980, 2934, 2359, 1719, 1639, 1602, 1524, 1460, 1369, 1250, 1214, 1147 cm^{-1}.

HRMS (ESI, pos.): m/z 251.1025 (251.1032 calc. for $C_{12}H_{15}N_2O_4$ $(M+H)^+$)

***tert*-Butyl 4-chlorobenzylidenecarbamate (54a)**



The reaction of sulfone **78** (1.08 g, 2.83 mmol) with 1.4 M K_2CO_3 (45 mL) in DCM (45 mL), according to the general procedure A, provided 609 mg (90%) of the pure imine **54a**.

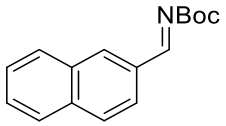
^{1}H NMR (300 MHz, $CDCl_3$): 8.84 (s, 1H, C*H*=N), 7.86 (d, 2H, *J* = 8.48 Hz, Ar*H*), 7.46 (d, 2H, *J* = 8.48 Hz, Ar*H*), 1.59 (s, 9H, OC(CH_3)$_3$).

IR (neat): 3334, 2979, 2932, 2361, 1702, 1630, 1593, 1572, 1506, 1490, 1390, 1251, 1216, 1154, 1087 cm^{-1}.

HRMS (ESI, pos.): m/z 240.0781 (240.0791 calc. for $C_{12}H_{15}NO_2Cl$ $(M+H)^+$)

General Procedure B:[37] Anhydrous potassium carbonate and anhydrous sodium sulfate were flame dried under vacuum. Once cool, the solid sulfone was added to this flask under a positive stream of nitrogen. To the flask containing all the solids was added dry THF and the reaction mixture was heated to reflux under nitrogen until the reaction was complete (^{1}H NMR). After completion, the reaction mixture was suction filtered, and the filtrate was collected and concentrated in vacuo to obtain the pure imine.

***tert*-Butyl naphthalen-2-ylmethylenecarbamate (54e)**

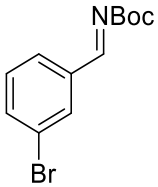


The reaction of sulfone **86** (944 mg, 2.37 mmol) with anhydrous K_2CO_3 (1.97 g, 14.22 mmol) and Na_2SO_4 (2.37 g) in dry THF (30 mL), according to the general procedure **B**, provided 556 mg (92%) of the pure imine **54e**.

^{1}H NMR (300 MHz, $CDCl_3$): 9.04 (s, 1H, C*H*=N), 8.28 (s, 1H, Ar*H*), 8.09 (d, 1H, Ar*H*), 7.93 (d, 1H, Ar*H*), 7.88 (t, 2H, Ar*H*), 7.59 (t, 1H, Ar*H*), 7.54 (t, 1H, Ar*H*), 1.60 (s, 9H, OC(CH_3)$_3$).

IR (neat): 3401, 3062, 2980, 1710, 1621, 1573, 1469, 1438, 1393, 1269, 1249, 1153, 1119 cm^{-1}. HRMS (ESI, pos.): m/z 256.1328 (256.1338 calc. for $C_{16}H_{18}NO_2$ $(M+H)^+$).

***tert*-Butyl 3-bromobenzylidenecarbamate (54d)**



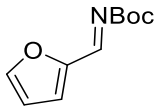
The reaction of sulfone **85** (2.4 g, 5.6 mmol) with anhydrous K_2CO_3 (4.6 g, 33.6 mmol) and Na_2SO_4 (5.6 g) in dry THF (48 mL), according to the general procedure **B**, provided 1.55 g (97%) of the pure imine **54d**.

^{1}H NMR (300 MHz, $CDCl_3$): 8.79 (s, 1H, C*H*=N), 8.12 (t, 1H, *J* = 1.86 Hz, Ar*H*), 7.82-7.77 (m, 1H, Ar*H*), 7.71- 7.66 (m, 1H, Ar*H*), 7.35 (t, 1H, *J* = 7.86 Hz, Ar*H*), 1.59 (s, 9H, OC(CH_3)$_3$).

IR (neat): 3369, 2979, 1710, 1639, 1566, 1475, 1432, 1392, 1367, 1253, 1205, 1150 cm^{-1}.

HRMS (ESI, pos.): m/z 284.0272 (284.0286 calc. for $C_{12}H_{15}NO_2Br$ $(M+H)^+$), m/z 286.0254 (286.0266 calc. for $C_{12}H_{15}NO_2Br$ $(M+H)^+$)

***tert*-Butyl furan-2-ylmethylenecarbamate (54f)**



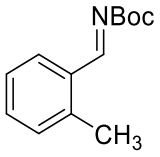
The reaction of sulfone **82** (629 mg, 1.86 mmol) with anhydrous K_2CO_3 (1.54 g, 11.2 mmol) and Na_2SO_4 (1.86 g) in dry THF (24 mL), according to the general procedure **B**, provided 333 mg (92%) of the pure imine **54f**.

^{1}H NMR (300 MHz, $CDCl_3$): 8.78 (s, 1H, C*H*=N), 7.71-7.67 (m, 1H, Ar*H*), 7.24 (d, 1H, *J* = 3.61 Hz, Ar*H*), 6.61 (dd, 1H, *J* = 3.61, 1.71 Hz, Ar*H*), 1.57 (s, 9H, OC(CH_3)$_3$).

IR (neat): 3351, 2979, 1710, 1619, 1476, 1394, 1368, 1345, 1243, 1150 cm^{-1}.

HRMS (ESI, pos.): m/z 196.0964 (196.0974 calc. for $C_{10}H_{14}NO_3$ $(M+H)^+$)

***tert*-Butyl 2-methylbenzylidenecarbamate (54c)**



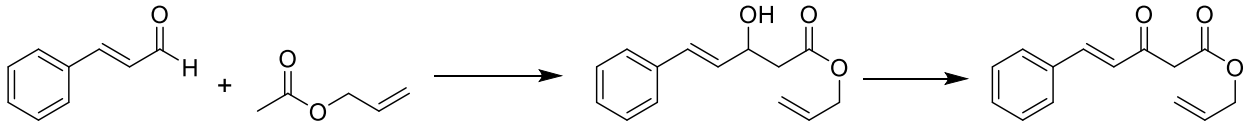
The reaction of sulfone **81** (744 mg, 2.1 mmol) with anhydrous K_2CO_3 (1.74 g, 12.6 mmol) and Na_2SO_4 (2.1 g) in dry THF (24 mL), according to the general procedure **B**, provided 429 mg (93%) of the pure imine **54c**.

^{1}H NMR (300 MHz, $CDCl_3$): 9.23 (s, 1H, C*H*=N), 8.09 (dd, 1H, *J* = 8.2, 1.4 Hz, Ar*H*), 7.43 (td, 1H, *J* = 7.46, 1.4 Hz, Ar*H*), 7.31-7.21 (m, 2H, Ar*H*, merged with $CDCl_3$ signal), 2.59 (s, 3H, CH_3), 1.60 (s, 9H, OC(CH_3)$_3$).

IR (neat): 3355, 3062, 2980, 2934, 1712, 1693, 1622, 1574, 1504, 1468, 1367, 1269, 1249, 1158 cm^{-1}.

HRMS (ESI, pos.): m/z 220.1327 (220.1338 calc. for $C_{13}H_{18}NO_2$ $(M+H)^+$)

General Procedure[38] **for the synthesis of allyl esters**

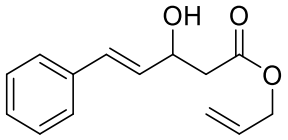


A solution of LDA was prepared by adding *n*-BuLi (1.16 eq) to a solution of diisopropylamine (1.22 eq) in dry THF (5 mL) at 0 °C under nitrogen. After 30 min, the reaction mixture was cooled to −78 °C and allyl acetate (1.1 eq) was slowly added. The resulting mixture was stirred at −78 °C for 50 min, after which the corresponding aldehyde (1.0 eq) was added. The reaction mixture was warmed to 0 °C and stirred for 3 h after which a saturated solution of aqueous NH_4Cl was added. The THF was removed by rotary evaporation and the residual

aqueous layer was extracted thrice with ethyl ether. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc/Hexanes) to provide the product alcohol as a pale-yellow oil.

The oxidation was done using DDQ instead of MnO_2. DDQ (1 eq) was added to a solution of the above alcohol (1 eq) in dichloromethane at rt. The reaction mixture was stirred for 2 h at rt, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/Hexanes) on silica gel to provide the ketoester as a pale-yellow oil (a mixture of keto/enol forms by ^{1}H NMR).

(*E*)-Allyl 3-hydroxy-5-phenylpent-4-enoate (89)



The addition of *n*-BuLi (2.2 M in hexanes, 9.8 mL, 21.5 mmol) to a solution of diisopropylamine (3.15 mL, 22.5 mmol) in dry THF (5 mL) was done according to the general procedure. The reaction of LDA with allyl acetate (2.25 mL, 20.5 mmol) and cinnamaldehyde (2.32 mL, 18.5 mmol), according to the general procedure provided upon purification by flash chromatography (Hexanes/EtOAc, 90:10) on silica gel, 3.4 g (79%) of the alcohol **89** as a pale-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): 7.40-7.21 (m, 5H, Ar*H*), 6.66 (dd, 1H, *J* = 15.9, 1.3 Hz, C=C*H*Ph), 6.22 (dd, 1H, *J* = 15.9, 6.1 Hz, *H*C=CHPh), 5.92 (ddt, 1H, *J* = 17.2, 10.4, 5.8 Hz, CH_2CH=CH_2),

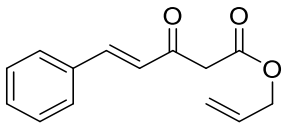
5.33 (dq, 1H, *J* = 17.2, 1.5 Hz, $CH_2CH=CH_2$), 5.25 (dq, 1H, *J* = 10.4, 1.2 Hz, $CH_2CH=CH_2$), 4.79-4.70 (m, 1H, C*H*OH), 4.63 (dt, 1H, *J* = 5.8, 1.4 Hz, $CH_2CH=CH_2$), 3.05 (dd, 1H, *J* = 4.3, 0.8 Hz, O*H, confirmed by D_2O exchange*), 2.69 (d, 1H, *J* = 1.2 Hz, CH_2CO), 2.67 (d, 1H, *J* = 3.5 Hz, CH_2CO)

^{13}C NMR (75 MHz, $CDCl_3$): 171.9 (*C*O), 136.4 (ArC_{ipso}), 131.8 ($COOCH_2CH$), 130.9 (C=C*H*Ph), 129.8, 128.6 (2xAr*C*), 127.9 (C=C*H*CO), 126.6 (2xAr*C*), 118.7 ($C=CH_2$), 68.9 (*C*HOH), 65.5 ($OCH_2CH=CH_2$), 41.5 (CH_2CO)

IR (neat): 3436, 3027, 1729, 1373, 1276, 1157, 967 cm^{-1}.

HRMS (ESI, pos.): m/z 232.1125 (232.1099 calc. for $C_{14}H_{16}O_3$ $(M)^+$)

(*E*)-Allyl 3-oxo-5-phenylpent-4-enoate (51)



The reaction of DDQ (681 mg, 3 mmol) with a solution of alcohol **89** (702 mg, 3 mmol) in dichloromethane (20.0 mL), according to the general procedure, provided, after purification by flash chromatography (Hexanes/EtOAc, 90:10) on silica gel, 352 mg (50% yield) of the keto-ester **51** as a pale-yellow oil (in a mixture of keto/enol forms).

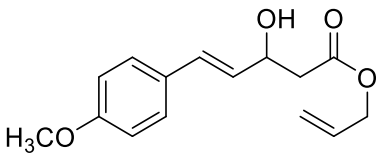
^1H NMR (300 MHz, $CDCl_3$): Mixture of the keto and enol forms. 11.90 (d, *J* = 1.5 Hz), 7.64-7.29 (m), 6.81 (d, *J* = 16.1 Hz), 6.45 (dd, *J* = 15.9, 1.5 Hz), 6.05-5.85 (m), 5.40-5.31 (m), 5.30-5.22 (m), 5.21 (s), 4.68 (tt, *J* = 5.7, 1.4 Hz), 3.74 (s)

^{13}C NMR (75 MHz, $CDCl_3$): Mixture of the keto and enol forms. 191.7, 172.4, 169.5, 167.0, 144.7, 137.0, 135.3, 134.0, 132.1, 131.6, 131.0, 129.4, 129.0, 128.8, 128.5, 127.6, 125.2, 121.8, 118.8, 118.3, 91.6, 66.0, 64.8, 47.5

IR (neat): 3026, 1741, 1633, 1594, 1447, 1409, 1224, 1144, 1028 cm^{-1}.

HRMS (ESI, pos.): m/z 231.1014 (231.1021 calc. for $C_{14}H_{15}O_3$ $(M+H)^+$)

(*E*)-Allyl 3-hydroxy-5-(4-methoxyphenyl) pent-4-enoate (90)



The addition of *n*-BuLi (1.6 M in hexanes, 4.48 mL, 7.16 mmol) to a solution of diisopropylamine (1.06 mL, 7.53 mmol) in dry THF (5 mL) was done according to the general procedure. The reaction of LDA with allyl acetate (0.74 mL, 6.79 mmol) and 4-methoxy cinnamaldehyde (1 g, 6.17 mmol), according to the general procedure provided upon purification by flash chromatography (Hexanes/EtOAc, 80:20) on silica gel, 921 g (57%) of the alcohol **90** as a pale-yellow oil.

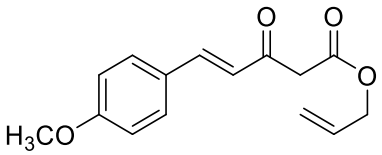
^{1}H NMR (300 MHz, $CDCl_3$): 7.35-7.28 (m, 2H, Ar*H*), 6.89-6.82 (m, 2H, Ar*H*), 6.60 (d, 1H, *J* = 15.9 Hz, C=C*H*Ph), 6.09 (dd, 1H, *J* = 15.9, 6.4 Hz, *H*C=CHPh), 5.92 (ddt, 1H, *J* = 17.1, 10.5, 5.8 Hz, CH_2CH=CH_2), 5.33 (dq, 1H, *J* = 17.2, 1.5 Hz, CH_2CH=CH_2), 5.25 (dq, 1H, *J* = 10.4, 1.2 Hz, CH_2CH=CH_2), 4.77-4.67 (m, 1H, C*H*OH), 4.63 (dt, 1H, *J* = 5.8, 1.4 Hz, CH_2CH=CH_2), 3.81 (s, 3H, OCH_3), 2.95 (d, 1H, *J* = 4.0 Hz, O*H*), 2.68 (s, 1H, CH_2CO), 2.66 (d, 1H, *J* = 2.6 Hz, CH_2CO)

^{13}C NMR (75 MHz, $CDCl_3$): 171.9 (*C*O), 159.4 (ArC_{ipso}), 131.8 (COOCH$_2$*C*H), 130.5 (C=C*H*Ph), 129.1 (ArC_{ipso}), 127.8 (2xAr*C*), 127.6 (C=C*H*CO), 118.7 (C=*C*H$_2$), 114.0 (2xAr*C*), 69.1 (*C*HOH), 65.5 (O*C*H$_2$CH=CH$_2$), 55.3 (O*C*H$_3$), 41.6 (*C*H$_2$CO)

IR (neat): 3470, 2976, 1728, 1605, 1511, 1247, 1167, 1030 cm^{-1}.

HRMS (ESI, pos.): m/z 245.1162 (245.1178 calc. for $C_{15}H_{17}O_3$ (M+H)-$H_2O)^+$)

(*E*)-Allyl 5-(4-methoxyphenyl)-3-oxopent-4-enoate (55)



The reaction of DDQ (86.3 mg, 0.38 mmol) with a solution of alcohol **90** (100 mg, 0.38 mmol) in dichloromethane (4 mL), according to the general procedure, provided, after purification by flash chromatography (Hexanes/EtOAc, 80:20) on silica gel, 66 mg (66% yield) of the keto-ester **55** as a pale-yellow oil (in a mixture of keto/enol forms).

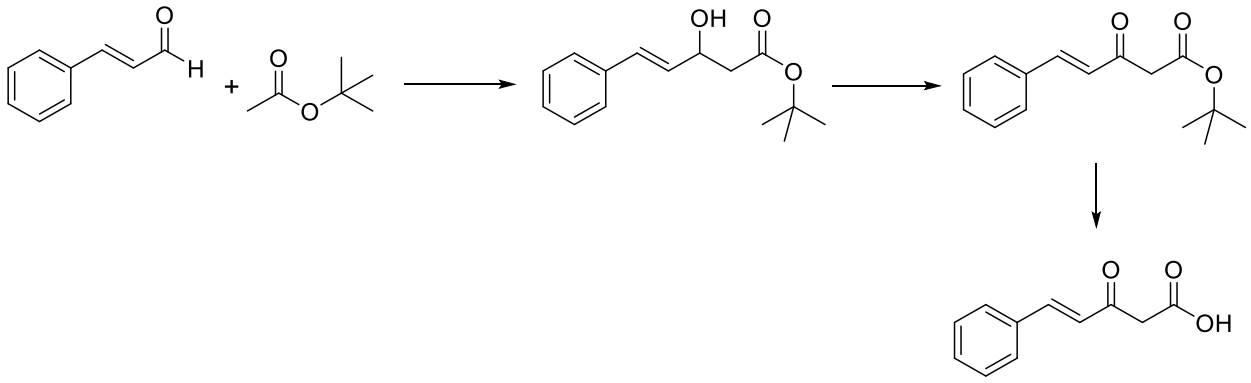
^{1}H NMR (300 MHz, $CDCl_3$): Mixture of the keto and enol forms. 11.94-11.90 (m), 7.60-7.36 (m), 6.95-6.85 (m), 6.69 (d, *J* = 16.0 Hz), 6.32 (dd, *J* = 15.8, 1.5 Hz), 6.04-5.84 (m), 5.40-5.30 (m), 5.29-5.22 (m), 5.17 (s), 4.71-4.63 (m), 3.85 (s), 3.83 (s), 3.72 (s)

^{13}C NMR (75 MHz, $CDCl_3$): Mixture of the keto and enol forms. 191.6, 172.5, 170.0, 167.2, 162.0, 160.7, 144.6, 136.7, 132.2, 131.7, 130.3, 129.1, 128.0, 126.7, 122.9, 119.4, 118.7, 118.2, 114.5, 114.3, 90.7, 65.9, 64.7, 55.4, 55.3, 47.4

IR (neat): 2937, 2362, 1741, 1649, 1596, 1512, 1413, 1307, 1253, 1173, 1144, 1029 cm^{-1}

HRMS (ESI, pos.): m/z 261.1113 (261.1127 calc. for $C_{15}H_{17}O_4$ $(M+H)^+$)

Procedure[39] for the synthesis of *β*-ketoacid 75

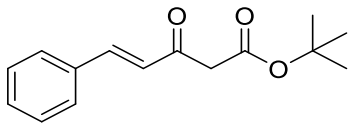


A solution of LDA was prepared by adding *n*-BuLi (3.6 mL, 7.2 mmol, 2M solution in hexanes) to diisopropylamine (1.1 mL, 8.4 mmol) in dry THF (5 mL) at -78 °C. The solution was stirred for 10 min after which *t*-butyl acetate (0.96 mL, 7.2 mmol) was added. 30 min later, cinnamaldehyde (0.9 ml, 7.2 mmol) was added, and reaction mixture was stirred at 0 °C for another 2 h. Upon completion, the reaction was quenched with saturated aqueous NH_4Cl solution and THF was removed under reduced pressure. The quenched reaction mixture was extracted with diethyl ether (3x15 mL), combined organic extracts washed with water and dried over anhydrous Na_2SO_4. The crude alcohol obtained was used without purification in the next step.

The oxidation was conducted with DDQ instead of MnO_2 as described in ref. 39. To the solution of crude alcohol (1.26g, 5.1 mmol) in DCM (8.0 mL) was added DDQ (1.27 g, 5.61 mmol) in portions slowly. The reaction mixture was stirred for 2 h at room temperature and then filtered, concentrated under reduced pressure. The crude was purified by flash chromatography (10% EtOAc/Hexanes) to provide 1g of the keto-ester **91** in 79% yield as a pale-yellow oil which slowly solidified in the freezer overtime (in a mixture of keto/enol forms).

To a solution of the pure *β*-keto *t*-butyl ester (971 mg) in DCM (92 mL) was added TFA (13.6 mL) at 0 °C according to literature protocol.[40] The reaction mixture was stirred for 3 h at 0°C and then concentrated under reduced pressure. The crude residue was purified using trituration with DCM and hexane followed by filtration to provide 476 mg of the *β*-keto-acid **75** in 63.5% yield.

(*E*)-*tert*-Butyl 3-oxo-5-phenylpent-4-enoate (91)



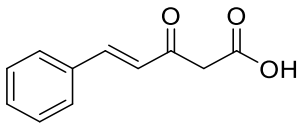
^{1}H NMR (300 MHz, $CDCl_3$): mixture of keto and enol forms 12.13 (d, 1H, *J* = 1.5 Hz, enol O*H*), 7.63-7.45 (m, 6H, Ar*H* and ArC*H*=CH), 7.45-7.28 (m, 6H, Ar*H*), 6.80 (d, 1H, *J* = 16.2 Hz, ArCH=C*H*), 6.41 (dd, 1H, *J* = 15.9, 1.5 Hz, ArCH=C*H*), 5.09 (s, 1H, C=C*H*COOH), 3.61 (s, 2H, COCH_2COOH), 1.52 (s, 9H, OC(CH_3)$_3$), 1.48 (s, 9H, OC(CH_3)$_3$)

^{13}C NMR (75 MHz, $CDCl_3$): Mixture of the keto and enol forms. 192.5 (*C*O), 172.8, 166.6, 144.3, 136.1, 135.5 (ArC_{ipso}), 134.2 (ArC_{ipso}), 130.8, 129.2, 129.0 (2xAr*C*), 128.8, 128.5 (2xAr*C*), 127.5, 125.4, 122.2, 93.6, 82.0 (O*C*(CH$_3$)$_3$), 81.1 (O*C*(CH$_3$)$_3$), 49.1 (*C*H$_2$CO), 28.4 (OC(*C*H$_3$)$_3$), 28.0 (OC(*C*H$_3$)$_3$)

IR (neat): 2975, 1645, 1597, 1450, 1410, 1365, 1273, 1252, 1142 cm^{-1}

HRMS (ESI, pos.): m/z 247.1324 (247.1334 calc. for $C_{15}H_{19}O_3$ $(M+H)^+$)

(*E*)-3-Oxo-5-phenylpent-4-enoic acid (75)



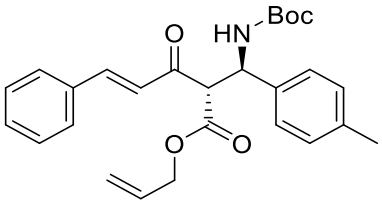
^{1}H NMR (300 MHz, $CDCl_3$): mixture of keto and enol forms 11.76 (s, 1H, enol O*H*), 7.72 (d, 1H, *J* = 16.2 Hz, ArC*H*=CH), 7.63-7.57 (m, 2H, Ar*H*), 7.55-7.49 (m, 2H, Ar*H*), 7.49-7.34 (m, 7H, Ar*H* and ArC*H*=CH), 6.82 (d, 1H, *J* = 16.1 Hz, ArCH=C*H*), 6.48 (d, 1H, *J* = 15.8 Hz, ArCH=C*H*), 5.23 (s, 1H, C=C*H*COOH), 3.80 (s, 2H, COCH_2COOH)

IR (neat): 3019, 2979, 1653, 1621, 1563, 1447, 1300, 1246, 1154 cm^{-1}

HRMS (ESI, pos.): m/z 191.0700 (191.0708 calc. for $C_{11}H_{11}O_3$ $(M+H)^+$)

General procedure for the Mannich reaction: To the corresponding imine (1 eq.) was added *S*,*S*-Takemoto catalyst (0.1 eq), *β*-keto ester (1 eq) and acetonitrile. The reaction was stirred at 0°C for 24 h after which solvent was removed from the reaction mixture under reduced pressure. The crude product was purified using flash chromatography (85:15 hexanes/EtOAc) on silica gel to obtain the required Mannich product as an inseparable mixture of diastereomers.

(*E*)-Allyl 2-((tert-butoxycarbonylamino) (p-tolyl) methyl)-3-oxo-5-phenylpent-4-enoate (52)



The reaction of imine **50** (267 mg, 1.22 mmol) and *β*-keto ester **51** (280 mg, 1.22 mmol) in the presence of *S*,*S*-Takemoto catalyst (50.4 mg, 0.122 mmol) in acetonitrile (7.5 mL) for 24 h according to the general procedure provided, after precipitation from the crude reaction mixture, 460 mg (84%) of **52** as a single diastereomer and 105.5 mg of the yellow filtrate which contained

the catalyst, and a mixture of the two diastereomers (dr = 1:1.12). The slow evaporation of a solution of single diastereomer **52** in DMSO, provided X-ray quality crystals for analysis.

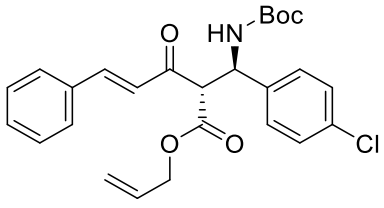
^{1}H NMR (300 MHz, $CDCl_3$): 7.56-7.47 (m, 3H, Ar*H* and C=C*H*Ph), 7.42-7.34 (m, 3H, Ar*H*), 7.23 (d, 2H, *J* = 7.98Hz, Ar*H*), 7.11 (d, 2H, *J* = 7.91 Hz, Ar*H*), 6.78 (d, 1H, *J* = 16.02 Hz, ArCH=C*H*CO), 6.03-5.90 (m, 1H, N*H*Boc, exchangeable H), 5.89-5.74 (m, 1H, $COOCH_2CHCH_2$), 5.57-5.45 (m, 1H, NHC*H*Ar), 5.30-5.14 (m, 2H, $COOCH_2CHCH_2$), 4.61-4.55 (m, 2H, $COOCH_2CHCH_2$), 4.35 (d, 1H, *J* = 6.18 Hz, $COCHCO_2$Allyl), 2.28 (s, 3H, CH_3), 1.37 (s, 9H, $OC(CH_3)_3$)

^{13}C NMR (75 MHz, $CDCl_3$): 193.7 ($CHCOCH=CHAr$), 167.3 (*C*OOAllyl), 155.0 (NH*C*OO), 144.7 (Ar*C*H=CHCO), 137.2 (ArC_{ipso}), 137.0 (ArC_{ipso}), 134.0 (ArC_{ipso}), 131.3 ($COOCH_2CH=CH_2$), 131.0 (Ar*C*), 129.3 (2xArC), 128.9 (2xAr*C*), 128.7 (2xAr*C*), 126.5 (2xAr*C*), 124.9 (CO*C*H=CH), 118.9 ($COOCH_2CHCH_2$), 79.6 ($OC(CH_3)_3$), 66.3 ($COOCH_2CH$), 61.2 (CO*C*HCOO), 53.9 (*C*HNH), 28.3 ($OC(CH_3)_3$), 21.0 (CH_3)

IR (neat): 3396, 2976, 1725, 1687, 1609, 1514, 1449, 1364, 1292, 1247, 1161, 983 cm^{-1}

HRMS (ESI, pos.): m/z 450.2275 (450.2280 calc. for $C_{27}H_{32}NO_5$ $(M+H)^+$)

(*E*)-Allyl 2-((tert-butoxycarbonylamino) (4-chlorophenyl) methyl)-3-oxo-5-phenylpent-4-enoate (56a)



The reaction of imine **54a** (100 mg, 0.42 mmol) and *β*-keto ester **51** (96.6 mg, 0.42 mmol) in the presence of *S*,*S*-Takemoto catalyst (17.4 mg, 0.042 mmol) in acetonitrile (2.6 mL) for 24 h according to the general procedure provided, after precipitation from the crude reaction mixture, 58 mg (30%) of **56a** as a light yellow solid (dr =1:0.1) and 133 mg of yellow filtrate containing the catalyst alongwith a mixture of diastereomers (dr 1:1.2).

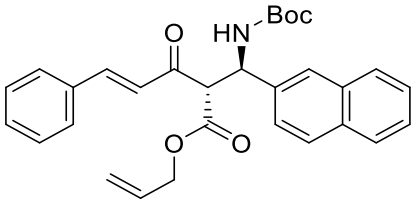
^{1}H NMR (300 MHz, $CDCl_3$): 7.59-7.47 (m, 3H, Ar*H* and ArC*H*=CH), 7.44-7.35 (m, 3H, ArH), 7.32-7.25 (m, 4H, ArH (merged with C*H*Cl_3 signal)), 6.76 (d, 1H, *J* = 16.02 Hz, COC*H*=CHAr), 6.15-5.95 (m, 1H, N*H*Boc), 5.91-5.71 (m, 1H, $COOCH_2CHCH_2$), 5.58-5.42 (m, 1H, NHC*H*Ar), 5.32-5.15 (m, 2H, $COOCH_2CHCH_2$), 4.64-4.55 (m, 2H, $COOCH_2CHCH_2$), 4.35 (d, 1H, *J* = 5.94 Hz, COC*H*CO_2Allyl), 1.38 (s, 9H, $OC(CH_3)_3$)

^{13}C NMR (75 MHz, CDCl3): 193.5 (CH*C*OCH=CHAr), 167.1 (*C*OOAllyl), 155.0 (NH*C*OO), 145.1 (Ar*C*H=CHCO), 138.6 (ArC_{ipso}), 133.9 (ArC_{ipso}), 133.4 (ArC_{ipso}), 131.21 (Ar*C or* $COOCH_2CH=CH_2$), 131.18 (Ar*C* or $COOCH_2CH=CH_2$), 129.0 (2xAr*C*), 128.7 (4xAr*C*), 128.1 (2xAr*C*), 124.8 (CO*C*H=CH), 119.1 ($COOCH_2CHCH_2$), 80.0 ($OC(CH_3)_3$), 66.5 ($COOCH_2CH$), 60.7 (*C*HNH), 53.7 (CO*C*HCOO), 28.3 ($OC(CH_3)_3$)

IR (neat): 3393, 2976, 2939, 2359, 1725, 1685, 1612, 1576, 1516, 1493, 1450, 1331, 1286, 1165 cm^{-1}

HRMS (ESI, pos.): m/z 470.1722 (470.1734 calc. for $C_{26}H_{29}ClNO_5$ $(M+H)^+$)

(*E*)-Allyl 2-((tert-butoxycarbonylamino) (naphthalen-2-yl) methyl)-3-oxo-5-phenylpent-4-enoate (56e)



The reaction of imine **54e** (100 mg, 0.39 mmol) and *β*-keto ester **51** (89.7 mg, 0.39 mmol) in the presence of *S*,*S*-Takemoto catalyst (16.1 mg, 0.039 mmol) in acetonitrile (2.4 mL) for 24 h according to the general procedure provided, after precipitation from the crude reaction mixture, 119.8 mg (63%) of **56e** as a single diastereomer and 68 mg of filtrate containing the catalyst alongwith a mixture of diastereomers (dr 1:0.96).

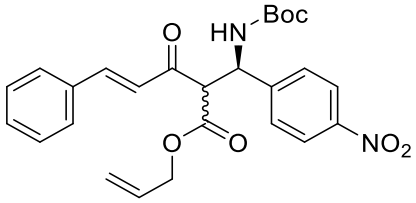
^{1}H NMR (300 MHz, $CDCl_3$): 7.85-7.74 (m, 4H, Ar*H*), 7.53 (d, 1H, *J* = 16.0 Hz, ArC*H*=C), 7.49-7.40 (m, 5H, Ar*H*), 7.39-7.31 (m, 3H, Ar*H*), 6.78 (d, 1H, *J* = 16.0 Hz, COC*H*=CHAr), 6.22-6.06 (m, 1H, N*H*), 5.89-5.64 (m, 2H, $COOCH_2CHCH_2$ and NHC*H*Ar), 5.30-5.11 (m, 2H, $COOCH_2CHCH_2$), 4.62-4.54 (m, 2H, $COOCH_2CHCH_2$), 4.48 (d, 1H, *J* = 6.2 Hz, COC*H*CO_2Allyl), 1.38 (s, 9H, $OC(CH_3)_3$)

^{13}C NMR (75 MHz, $CDCl_3$): 193.6 (CH*C*OCH=CHAr), 167.3 (*C*OOAllyl), 155.1 (NH*C*OO), 144.9 (Ar*C*H=CHCO), 137.4 (ArC_{ipso}), 134.0 (ArC_{ipso}), 133.2 (ArC_{ipso}), 132.8 (ArC_{ipso}), 131.3 (Ar*C* or COOCH2*C*H=CH2), 131.1 (Ar*C* or COOCH2*C*H=CH2), 128.9 (2xAr*C*), 128.7 (2xAr*C*), 128.5 (Ar*C*), 128.1 (Ar*C*), 127.6 (Ar*C*), 126.2 (Ar*C*), 126.0 (Ar*C*), 125.7 (Ar*C*), 124.8 (Ar*C*), 124.6 (CO*C*H=CH), 119.0 (COOCH2CH*C*H2), 79.8 (O*C*$(CH_3)_3$), 66.4 ($COOCH_2CH$), 61.1 (*C*HNH), 54.5 (COO*C*HCO), 28.3 ($OC(CH_3)_3$)

IR (neat): 3394, 2977, 1730, 1688, 1608, 1514, 1248, 1212, 1164, 990 cm^{-1}

HRMS (ESI, pos.): m/z 508.2090 (508.2100 calc. for $C_{30}H_{31}NO_5Na$ $(M+Na)^+$)

(*E*)-Allyl 2-((tert-butoxycarbonylamino) (4-nitrophenyl) methyl)-3-oxo-5-phenylpent-4-enoate (56b)



The reaction of imine **54b** (100 mg, 0.4 mmol) and *β*-keto ester **51** (92 mg, 0.4 mmol) in the presence of *S*,*S*-Takemoto catalyst (16.5 mg, 0.04 mmol) in acetonitrile (2.5 mL) for 24 h according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 90:10), 110.7 mg (58%) of **56b** as an inseparable mixture of diastereomers (dr 1:1.3).

^{1}H NMR (300 MHz, $CDCl_3$): 8.27-8.08 (m, 4H, Ar*H*), 7.72 (d, 1H, *J* = 15.73 Hz, ArC*H*=C), 7.61-7.47 (m, 9H, Ar*H* and CH=C*H*Ar), 7.46-7.33 (m, 6H, Ar*H*), 6.92 (d, 1H, *J* = 15.65 Hz, COC*H*=CHAr), 6.74 (d, 1H, *J* = 15.98 Hz, COC*H*=CHAr), 6.30-6.09 (m, 2H, N*H*), 5.91-5.70 (m, 2H, $COOCH_2CH$=CH_2), 5.69-5.54 (m, 2H, CHN*H*), 5.34-5.15 (m, 4H, $COOCH_2CHCH_2$), 4.68-4.49 (m, 4H, $COOCH_2CHCH_2$), 4.43 (d, 1H, *J* = 5.29 Hz, COC*H*COO), 4.33 (d, 1H, *J* = 5.26 Hz, COC*H*COO), 1.39 (s, 9H, $OC(CH_3)_3$), 1.36 (s, 9H, $OC(CH_3)_3$)

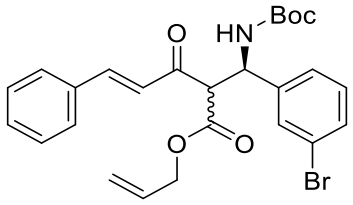
^{13}C NMR (75 MHz, $CDCl_3$): 193.1 (2x*C*O), 168.0 (*C*OOallyl), 166.9 (*C*OOallyl), 155.1 (2xNH*C*OO), 147.5 (2xArC_{ipso}), 147.4 (ArC_{ipso}), 147.3 (ArC_{ipso}), 145.8 (Ar*C*H=CHCO), 145.6 (Ar*C*H=CHCO), 133.8 (ArC_{ipso}), 133.6 (ArC_{ipso}), 131.5 (Ar*C* or $COOCH_2CH$=CH_2), 131.4 (Ar*C* or $COOCH_2CH$=CH_2), 131.0 (Ar*C* or $COOCH_2CH$=CH_2), 130.96 (Ar*C* or $COOCH_2CH$=CH_2), 129.1 (2xAr*C*), 128.95 (Ar*C*), 128.83 (2xAr*C*), 128.79 (2xAr*C*), 127.7 (2xAr*C*), 127.6 (2xAr*C*), 126.5 (Ar*C*), 124.6 (CO*C*H=CH), 123.9 (2xAr*C*), 123.8 (2xAr*C*), 122.5 (CO*C*H=CH), 119.4

(2xCOO*C*H_2CH=CH_2), 80.5 (O*C*(CH_3)$_3$), 80.3 (O*C*(CH_3)$_3$), 66.7 (COOCH$_2$CH=*C*H$_2$), 66.5 (COOCH$_2$CH=*C*H$_2$), 62.0 (*C*HNH), 60.0 (*C*HNH), 53.3 (CO*C*HCOO), 53.0 (CO*C*HCOO), 28.3 (OC(*C*H_3)$_3$), 28.2 (OC(*C*H_3)$_3$)

IR (neat): 3303, 2973, 1698, 1605, 1523, 1346, 1254, 1162, 1095 cm^{-1}.

HRMS (ESI, pos.): m/z 481.1957 (481.1975 calc. for $C_{26}H_{29}N_2O_7$ $(M+H)^+$)

(*E*)-Allyl 2-((3-bromophenyl) (tert-butoxycarbonylamino) methyl)-3-oxo-5-phenylpent-4-enoate (56d)



The reaction of imine **54d** (346.5 mg, 1.22 mmol) and *β*-keto ester **51** (280 mg, 1.22 mmol) in the presence of *S*,*S*-Takemoto catalyst (50.4 mg, 0.122 mmol) in acetonitrile (7.5 mL) for 24 h according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 85:15), 460 mg (74%) of **56d** as a 1:1 inseparable mixture of diastereomers.

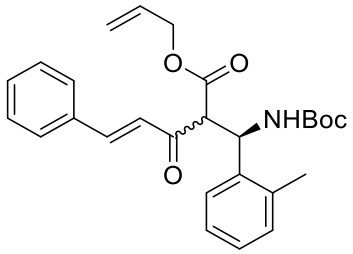
^{1}H NMR (300 MHz, $CDCl_3$): 7.70 (d, 1H, *J* = 15.8 Hz, C=C*H*Ar), 7.61-7.54 (m, 2H, CH=C*H*Ar and Ar*H*), 7.53-7.47 (m, 3H, Ar*H*), 7.45-7.33 (m, 7H, Ar*H*), 7.32-7.26 (m, 2H, Ar*H*), 7.24-7.12 (m, 2H, Ar*H*), 6.93 (d, 1H, *J* = 15.8 Hz, C*H*=CHAr), 6.76 (d, 1H, *J* = 16.0 Hz, COC*H*=CHAr), 6.22-5.99 (m, 2H, C*H*NH), 5.91-5.70 (m, 2H, COOCH$_2$C*H*=CH$_2$), 5.62-5.42 (m, 2H, N*H*), 5.32-5.17 (m, 4H, HC=CH_2), 4.68-4.51 (m, 4H, COOCH_2), 4.35 (d, 1H, *J* = 5.8 Hz, COC*H*COO), 4.26 (d, 1H, *J* = 5.3 Hz, COC*H*COO), 1.39 (s, 9H, OC(CH_3)$_3$), 1.36 (s, 9H, OC(CH_3)$_3$)

^{13}C NMR (75 MHz, $CDCl_3$): 191.4 (2xCH*C*OCH=CHAr), 168.3 (*C*OOAllyl), 167.1 (*C*OOAllyl), 155.0 (2xNH*C*OO), 145.3 (Ar*C*H=CHCO), 145.2 (Ar*C*H=CHCO), 142.4 (ArC_{ipso}), 142.3 (ArC_{ipso}), 134.0 (ArC_{ipso}), 133.9 (ArC_{ipso}), 131.21 (Ar*C* or $COOCH_2CH=CH_2$), 131.18 (2x(Ar*C* or $COOCH_2CH=CH_2$)), 131.14 (Ar*C* or $COOCH_2CH=CH_2$), 130.81 (Ar*C*), 130.76 (Ar*C*), 130.21 (Ar*C*), 130.16 (Ar*C*), 129.9 (Ar*C*), 129.6 (Ar*C*), 129.0 (4xAr*C*), 128.8 (2xAr*C*), 128.75 (2xAr*C*), 125.3 (Ar*C*), 125.2 (Ar*C*), 124.8 (CO*C*H=CH), 122.8 (2xArC_{ipso}), 122.7 (CO*C*H=CH), 119.2 ($COOCH_2CHCH_2$), 119.17 ($COOCH_2CHCH_2$), 80.1 (2xO*C*$(CH_3)_3$), 66.5 (COO*C*H_2CH), 66.3 (COO*C*H_2CH), 62.4 (*C*HNH), 60.6 (*C*HNH), 52.8 (2xCO*C*HCOO), 28.3 (OC(*C*$H_3)_3$), 28.2 (OC(*C*$H_3)_3$)

IR (neat): 3353, 2978, 1736, 1687, 1601, 1522, 1495, 1279, 1248, 1161, 987 cm^{-1}

HRMS (ESI, pos.): m/z 514.1215 (514.1229 calc. for $C_{26}H_{29}BrNO_5$ $(M+H)^+$)

(*E*)-Allyl 2-((tert-butoxycarbonylamino) (o-tolyl) methyl)-3-oxo-5-phenylpent-4-enoate (56c)



The reaction of imine **54c** (211.7 mg, 0.97 mmol) and *β*-keto ester **51** (105.8 mg, 0.97 mmol) in the presence of *S*,*S*-Takemoto catalyst (222.2 mg, 0.097 mmol) in acetonitrile (5.9 mL) for 24 h according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 85:15), 413 mg (95%) of **56c** as a 1.1:1 inseparable mixture of diastereomers.

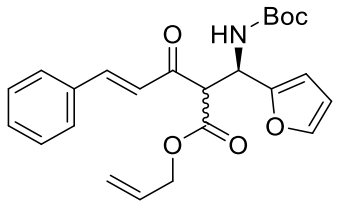
^{1}H NMR (300 MHz, $CDCl_3$): 7.68 (d, 1H, *J* = 15.8 Hz, C=C*H*Ar), 7.58-7.46 (m, 5H, Ar*H* and C=C*H*Ar), 7.44-7.33 (m, 6H, Ar*H*), 7.32-7.27 (m, 2H, Ar*H*), 7.20-7.08 (m, 6H, Ar*H*), 6.90 (d, 1H, *J* = 15.7 Hz, C*H*=CHAr), 6.79 (d, 1H, *J* = 16.0 Hz, C*H*=CHAr), 6.05-5.87 (m, 2H, N*H*), 5.86-5.66 (m, 4H, C*H*NH and $COOCH_2CH$=CH_2), 5.28-5.11 (m, 4H, HC=CH_2), 4.65-4.49 (m, 4H, COOCH_2), 4.29 (d, 1H, *J* = 6.5 Hz, COC*H*COO), 4.19 (d, 1H, *J* = 5.9 Hz, COC*H*COO), 2.54 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 1.37-1.32 (m, 18H, OC(CH_3)$_3$)

^{13}C NMR (75 MHz, $CDCl_3$): 202.4 (CH*C*OCH=CHAr), 191.6 (CH*C*OCH=CHAr), 168.3 (*C*OOAllyl), 167.3 (*C*OOAllyl), 154.9 (2xNH*C*OO), 145.0 (Ar*C*H=CHCO), 144.7 (Ar*C*H=CHCO), 138.3 (2xArC_{ipso}), 135.3 (ArC_{ipso}), 135.1 (ArC_{ipso}), 134.1 (2xArC_{ipso}), 131.34 (Ar*C* or $COOCH_2CH$=CH_2), 131.31 (Ar*C* or $COOCH_2CH$=CH_2), 131.1 (Ar*C* or $COOCH_2CH$=CH_2), 131.0 (Ar*C* or $COOCH_2CH$=CH_2), 130.9 (Ar*C*), 130.8 (Ar*C*),129.0 (2xAr*C*), 128.9 (2xAr*C*), 128.7 (4xAr*C*), 127.7 (Ar*C*), 127.6 (Ar*C*), 126.3 (2xAr*C*), 126.2 (Ar*C*), 125.8 (Ar*C*), 124.9 (CO*C*H=CH), 122.9 (CO*C*H=CH), 118.9 ($COOCH_2CHCH_2$), 118.8 ($COOCH_2CHCH_2$), 79.7 (2xO*C*(CH$_3$)$_3$), 66.3 ($COOCH_2CH$), 66.2 ($COOCH_2CH$), 61.6 (*C*HNH), 60.2 (*C*HNH), 50.1 (2xCO*C*HCOO), 28.3 (2xOC(*C*H$_3$)$_3$), 19.5 (*C*H$_3$), 19.4 (*C*H$_3$)

IR (neat): 3368, 2978, 1697, 1605, 1494, 1365, 1163, 983 cm^{-1}

HRMS (ESI, pos.): m/z 450.2276 (450.2281 calc. for $C_{27}H_{32}NO_5$ $(M+H)^+$)

(*E*)-Allyl 2-((tert-butoxycarbonylamino) (furan-2-yl) methyl)-3-oxo-5-phenylpent-4-enoate (56f)



The reaction of imine **54f** (100 mg, 0.51 mmol) and *β*-keto ester **51** (118 mg, 0.51 mmol) in the presence of *S*,*S*-Takemoto catalyst (21.2 mg, 0.051 mmol) in acetonitrile (3.2 mL) for 60 h according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 85:15), 154 mg (68%) of **56f** as a 1:0.9 inseparable mixture of diastereomers.

^{1}H NMR (300 MHz, $CDCl_3$): 7.68 (d, 1H, *J* = 15.9 Hz, C=C*H*Ar), 7.64-7.51 (m, 5H, Ar*H* and C=C*H*Ar), 7.43-7.34 (m, 6H, Ar*H*), 7.30 (ddd, 2H, *J* = 10.5, 1.8, 0.9 Hz, Ar*H*), 6.89 (d, 1H, *J* = 15.9 Hz, C*H*=CHAr), 6.83 (d, 1H, *J* = 16.0 Hz, C*H*=CHAr), 6.27-6.32 (m, 2H, Ar*H*), 6.26-6.22 (m, 2H, Ar*H*), 5.94-5.77 (m, 4H, C*H*NH and $COOCH_2CHCH_2$), 5.69-5.56 (m, 2H, N*H*), 5.34-5.18 (m, 4H, $CH=CH_2$), 4.67-4.59 (m, 4H, $COOCH_2$), 4.55 (d, 1H, *J* = 6.0 Hz, COOC*H*CO), 4.47 (d, 1H, *J* = 5.6 Hz, COOC*H*CO), 1.40 (s, 9H, $OC(CH_3)_3$), 1.39 (s, 9H, $OC(CH_3)_3$)

^{13}C NMR (75 MHz, $CDCl_3$): 193.3 (CH*C*OCH=CHAr), 191.5 (CH*C*OCH=CHAr), 168.2 (*C*OOAllyl), 167.1 (*C*OOAllyl), 155.0 (2xNH*C*OO), 152.6 (ArC_{ipso}), 152.4 (ArC_{ipso}), 145.0 (Ar*C*H=CHCO), 144.8 (Ar*C*H=CHCO), 142.0 (Ar*C*), 141.9 (Ar*C*), 134.07 (ArC_{ipso}), 134.04 (ArC_{ipso}), 131.4 (Ar*C* or $COOCH_2CH=CH_2$), 131.3 (Ar*C* or $COOCH_2CH=CH_2$), 131.0 (2x(Ar*C* or $COOCH_2CH=CH_2$)), 129.0 (4xAr*C*), 128.74 (2xAr*C*), 128.71 (2xAr*C*), 124.8 (CO*C*H=CH), 123.3 (CO*C*H=CH), 118.92 ($COOCH_2CHCH_2$), 118.86 ($COOCH_2CHCH_2$), 110.60 (Ar*C*), 110.56 (Ar*C*), 107.0 (Ar*C*), 106.9 (Ar*C*), 80.0 (2xO*C*$(CH_3)_3$), 66.4 ($COOCH_2CH$), 66.2 ($COOCH_2CH$), 59.8 (*C*HNH), 58.2 (*C*HNH), 48.8 (2xCO*C*HCOO), 28.3 ($OC(CH_3)_3$), 28.2 ($OC(CH_3)_3$)

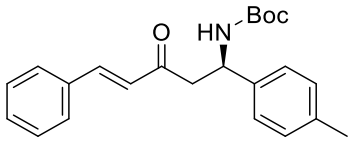
IR (neat): 3354, 2978, 1720, 1689, 1608, 1517, 1246, 1165, 985 cm^{-1}

HRMS (ESI, pos.): m/z 426.1902 (426.1917 calc. for $C_{24}H_{28}NO_6$ $(M+H)^+$)

General procedure[41] for the deallylative decarboxylation:

To the Mannich product in dry THF was added morpholine (10 eq) and later Pd $(PPh_3)_4$ (0.05 eq). The reaction mixture was stirred at rt for 30 minutes after which THF was removed under reduced pressure and the crude was purified using flash chromatography (85:15 hexanes/ EtOAc) on silica gel to afford the product in 80-90% yield.

(*E*)-*tert*-Butyl 3-oxo-5-phenyl-1-p-tolylpent-4-enylcarbamate (53)



The reaction of Mannich product **52** (45.9 mg, 0.102 mmol) with morpholine (88.8 μL, 1.02 mmol) and $Pd(PPh_3)_4$ (5.8 mg, 0.005 mmol) in THF (1 mL) for 30 min according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 85:15), 33.1 mg (89%) of **53** as a white solid. The evaporation of a solution of **52** in hot hexanes, provided X-ray quality crystals for analysis.

$[\alpha]_D^{20}$ = 29.4 (c 0.62, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): 7.55-7.45 (m, 3H, Ar*H* and C=C*H*Ph), 7.42-7.35 (m, 3H, Ar*H*), 7.22 (apparent d, 2H, *J* = 8.1 Hz, Ar*H*), 7.13 (apparent d, 2H, *J* = 8.0 Hz, Ar*H*), 6.67 (d, 1H, *J* = 16.2 Hz, C=C*H*CO), 5.62-5.41 (m, 1H, N*H*, confirmed with D_2O exchange), 5.20-5.08 (m, 1H, C*H*NH), 3.39-3.22 (m, 1H, CH_2CO), 3.11 (dd, 1H, *J* = 15.9, 6.2 Hz, CH_2CO), 2.30 (s, 3H, CH_3), 1.41 (s, 9H, OC(CH_3)$_3$)

^{13}C NMR (75 MHz, $CDCl_3$): 198.6 (*C*O), 155.2 (NH*C*OO), 143.4 (C=*C*HPh), 138.7 (ArC_{ipso}), 137.0 (ArC_{ipso}), 134.3 (ArC_{ipso}), 130.7 (Ar*C*), 129.3 (2xAr*C*), 128.9 (2xAr*C*), 128.4 (2xAr*C*),

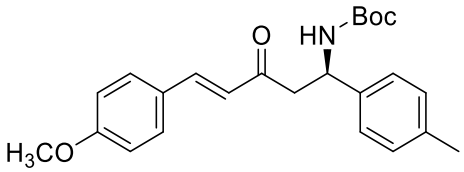
126.2 (2xAr*C*), 126.1 (C=*C*HCO), 79.5 (O*C*$(CH_3)_3$, 46.6 (*C*H_2CO), 51.3 (*C*HNH), 28.4 (OC(*C*$H_3)_3$), 21.1 (*C*H_3)

IR (neat): 3387, 2925, 2361, 1684, 1608, 1510, 1452, 1363, 1253, 1167 cm^{-1}

HRMS (ESI, pos.): m/z 366.2048 (366.2069 calc. for $C_{23}H_{28}NO_3$ $(M+H)^+$)

HPLC: Chiralpak IA (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, λ = 254 nm), t_{major} = 13.49 min., t_{minor} = 15.12 min., 99% ee.

(*E*)-*tert*-Butyl 5-(4-methoxyphenyl)-3-oxo-1-p-tolylpent-4-enylcarbamate (57g)



The reaction of Mannich product **56g** (309 mg, 0.64 mmol) with morpholine (0.6 mL, 6.4 mmol) and $Pd(PPh_3)_4$ (37.9 mg, 0.032 mmol) in THF (10 mL) for 30 min according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 85:15), 192 mg (76%) of **57g** as a white solid.

$[\alpha]_D^{20}$ = 5.5 (c 0.29, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): 7.50-7.42 (m, 3H, Ar*H* and C=C*H*Ph), 7.22 (apparent d, 2H, *J* = 8 Hz, Ar*H*), 7.12 (apparent d, 2H, *J* = 8Hz, Ar*H*), 6.90 (d, 2H, *J* = 8.7 Hz, Ar*H*), 6.56 (d, 1H, *J* = 16.1 Hz, C=C*H*), 5.65-5.46 (m, 1H, N*H*), 5.18-5.07 (m, 1H, C*H*NH), 3.84 (s, 3H, OCH_3), 3.33-3.18 (m, 1H, CH_2CO), 3.08 (dd, 1H, *J* = 15.8, 6.1 Hz, CH_2CO), 2.30 (s, 3H, CH_3), 1.41 (s, 9H, OC(C$H_3)_3$)

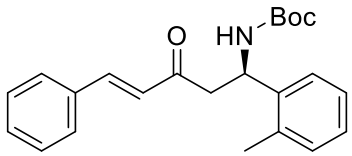
^{13}C NMR (75 MHz, $CDCl_3$): 198.0 (CO), 161.7 (ArC_{ipso}), 155.2 (NHCOO), 143.2 (C=*C*HPh), 138.9 (ArC_{ipso}), 136.9 (ArC_{ipso}), 130.2 (2xAr*C*), 129.3 (2xAr*C*), 127.0 (ArC_{ipso}), 126.2 (2xAr*C*), 123.9 (C=*C*HCO), 114.4 (2xAr*C*), 79.5 (O*C*$(CH_3)_3$), 55.4 (O*C*H_3), 51.4 (*C*HNH), 46.5 (*C*H_2CO), 28.4 (OC(*C*$H_3)_3$), 21.1 (*C*H_3)

IR (neat): 3374, 2979, 1683, 1638, 1601, 1511, 1255, 1168, 1087 cm^{-1}.

HRMS (ESI, pos.): m/z 396.2155 (396.2175 calc. for $C_{24}H_{30}NO_4$ $(M+H)^+$)

HPLC: Chiralpak IA (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, λ = 254 nm), t_{major} = 10.93 min., t_{minor} = 11.63 min., 94% ee.

(*E*)-*tert*-Butyl 3-oxo-5-phenyl-1-o-tolylpent-4-enylcarbamate (57c)



The reaction of Mannich product **56c** (58.6 mg, 0.13 mmol) with morpholine (0.12 mL, 1.3 mmol) and $Pd(PPh_3)_4$ (7.6 mg, 0.006 mmol) in THF (1 mL) for 30 min according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 85:15), 33.1 mg (89%) of **57c** as a white solid.

$[\alpha]_D^{20}$ = 29.4 (c 0.62, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): 7.53-7.44 (m, 3H, Ar*H* and C=C*H*Ph), 7.41-7.34 (m, 3H, Ar*H*), 7.33-7.26 (m, 1H, Ar*H*), 7.21-7.10 (m, 3H, Ar*H*), 6.66 (d, 1H, *J* = 16.2 Hz, C=C*H*CO), 5.48-5.30 (m, 2H, C*H*NH and CHN*H*), 3.31-3.01 (m, 2H, CH_2CO), 2.46 (s, 3H, CH_3), 1.39 (s, 9H, OC(C$H_3)_3$)

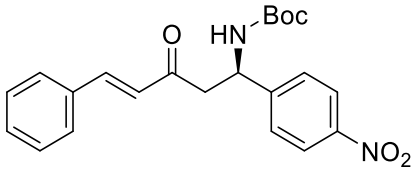
^{13}C NMR (75 MHz, $CDCl_3$): 197.8 (*C*O), 155.0 (NH*C*OO), 143.4 (C=*C*HPh), 139.8 (ArC_{ipso}), 135.3 (ArC_{ipso}), 134.3 (ArC_{ipso}), 130.7 (Ar*C*), 130.6 (Ar*C*), 128.9 (2xAr*C*), 128.4 (2xAr*C*), 127.3 (Ar*C*), 126.3 (Ar*C*), 126.0 (C=*C*HCO), 125.3 (Ar*C*), 79.6 (O*C*(CH_3)$_3$), 48.6 (*C*HNH), 45.9 (*C*H_2CO), 28.3 (OC(*C*H_3)$_3$), 19.3 (*C*H_3)

IR (neat): 3370, 2979, 2934, 1713, 1681, 1639, 1517, 1367, 1251, 1164 cm^{-1}

HRMS (ESI, pos.): m/z 366.206 (366.2069 calc. for $C_{23}H_{28}NO_3$ $(M+H)^+$)

HPLC: Chiralpak IA (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, λ = 254 nm), t_{major} = 11.55 min., t_{minor} = 17.16 min., 81% ee.

(*E*)-*tert*-Butyl 1-(4-nitrophenyl)-3-oxo-5-phenylpent-4-enylcarbamate (57b)



The reaction of Mannich product **56b** (46.7 mg, 0.097 mmol) with morpholine (84.5 μL, 0.97 mmol) and $Pd(PPh_3)_4$ (5.7 mg, 0.005 mmol) in THF (0.5 mL) for 30 min according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 85:15), 32.4 mg (84%) of **57b** as a white solid.

$[\alpha]_D^{20}$ = -38.4 (c 0.95, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): 8.19 (apparent d, 2H, *J* = 8.76 Hz, Ar*H*), 7.56-7.47 (m, 5H, Ar*H* and C=C*H*Ph), 7.43-7.34 (m, 3H, Ar*H*), 6.67 (d, 1H, *J* = 16.2 Hz, C=C*H*CO), 5.94-5.78 (m, 1H, N*H*), 5.31- 5.19 (m, 1H, C*H*NH), 3.44-3.29 (m, 1H, CH_2CO), 3.19 (dd, 1H, *J* = 16.9, 5.6 Hz, CH_2CO), 1.42 (s, 9H, OC(CH_3)$_3$)

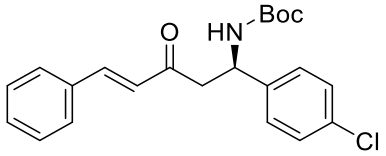
^{13}C NMR (75 MHz, $CDCl_3$): 197.4 (*C*O), 155.1 (NH*C*OO), 149.5 (ArC_{ipso}), 147.1 (ArC_{ipso}), 144.2 (C=*C*HPh), 133.9 (ArC_{ipso}), 131.1 (Ar*C*), 129.1 (2xAr*C*), 128.5 (2xAr*C*), 127.2 (2xAr*C*), 125.5 (C=*C*HCO), 123.8 (2xAr*C*), 80.2 (O*C*$(CH_3)_3$), 50.8 (*C*HNH), 45.6 (*C*H_2CO), 28.3 (OC(*C*$H_3)_3$)

IR (neat): 3362, 2958, 2925, 2854, 2360, 1677, 1603, 1516, 1344, 1269, 1251, 1156 cm^{-1}

HRMS (ESI, pos.): m/z 397.1757 (397.1763 calc. for $C_{22}H_{25}N_2O_5$ $(M+H)^+$)

HPLC: Chiralpak IA (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, λ = 254 nm), t_{major} = 31.19 min., t_{minor} = 36.32 min., >99% ee.

(*E*)-*tert*-Butyl 1-(4-chlorophenyl)-3-oxo-5-phenylpent-4-enylcarbamate (57a)



The reaction of Mannich product **56a** (31.4 mg, 0.067 mmol) with morpholine (58.4 μL, 0.67 mmol) and $Pd(PPh_3)_4$ (3.8 mg, 0.003 mmol) in THF (1 mL) for 30 min according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 85:15), 21.8 mg (84%) of **57a** as a white solid.

$[\alpha]_D^{20}$ = -9.4 (c 0.63, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): 7.77-7.20 (m, 10H, Ar*H* and C=C*H*Ph), 6.66 (d, 1H, *J* = 16.2 Hz, C=C*H*CO), 5.80-5.53 (m, 1H, N*H*), 5.23-5.05 (m, 1H, C*H*NH), 3.30 (d, 1H, *J* = 16.1 Hz, CH_2CO), 3.11 (dd, 1H, *J* = 16.6, 5.9 Hz, CH_2CO), 1.41 (s, 9H, OC(C$H_3)_3$)

^{13}C NMR (75 MHz, $CDCl_3$): 197.8 (*C*O), 155.1 (NH*C*OO), 143.8 (C=*C*HPh), 140.4 (ArC_{ipso}), 134.1 (ArC_{ipso}), 133.0 (ArC_{ipso}), 130.9 (Ar*C*), 129.0 (2xAr*C*), 128.7 (2xAr*C*), 128.4 (2xAr*C*),

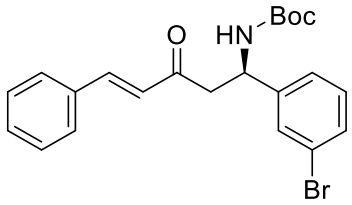
127.7 (2xAr*C*), 125.9 (C=*C*HCO), 79.9 (O*C*(CH_3)$_3$), 51.0 (*C*HNH), 46.1 (*C*H_2CO), 28.4 (OC(*C*H_3)$_3$)

IR (neat): 3392, 2978, 2929, 2360, 1684, 1450, 1364, 1251, 1612, 1169, 1088 cm^{-1}

HRMS (ESI, pos.): m/z 386.1509 (386.1523 calc. for $C_{22}H_{25}NO_3Cl$ $(M+H)^+$)

HPLC: Chiralpak IA (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, λ = 254 nm), t_{major} = 14.20 min., t_{minor} = 15.69 min., 97% ee.

(*E*)-*tert*-Butyl 1-(3-bromophenyl)-3-oxo-5-phenylpent-4-enylcarbamate (57d)



The reaction of Mannich product **56d** (45.4 mg, 0.088 mmol) with morpholine (76.6 μL, 0.88 mmol) and $Pd(PPh_3)_4$ (5.08 mg, 0.004 mmol) in THF (0.8 mL) for 30 min according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 85:15), 32.8 mg (87%) of **57d** as a white solid.

$[\alpha]_D^{20}$ = 11.4 (c 0.42, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): 7.55-7.46 (m, 4H, Ar*H* and C=C*H*Ph), 7.43-7.32 (m, 4H, Ar*H*), 7.30-7.25 (m, 1 H, Ar*H* (merged with C*H*Cl3 signal)), 7.18 (t, 1H, *J* = 7.8 Hz, Ar*H*), 6.66 (d, 1H, *J* = 16.2 Hz, C=C*H*CO), 5.75-5.55 (m, 1H, N*H*), 5.20-5.07 (m, 1H, C*H*NH), 3.37-3.22 (m, 1H, C*H*$_2$CO), 3.11 (dd, 1H, *J* = 16.4, 5.8 Hz, C*H*$_2$CO), 1.42 (s, 9H, OC(C*H*$_3$)$_3$)

^{13}C NMR (75 MHz, $CDCl_3$): 197.6 (*C*O), 155.1 (NH*C*OO), 144.4 (ArC_{ipso}), 143.8 (C=*C*HPh), 134.1 (ArC_{ipso}), 130.9 (Ar*C*), 130.4 (Ar*C*), 130.2 (Ar*C*), 129.4 (Ar*C*), 129.0 (2xAr*C*), 128.5

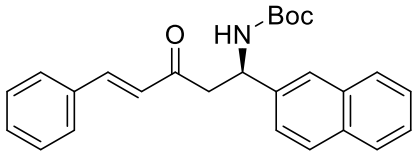
(2xAr*C*), 125.9 (C=*C*HCO), 125.0 (Ar*C*), 122.7 (ArC_{ipso}), 79.9 (O*C*$(CH_3)_3$), 50.9 (*C*HNH), 46.0 (*C*H_2CO), 28.4 (OC(*C*$H_3)_3$)

IR (neat): 3399, 2976, 2928, 2361, 1688, 1613, 1517, 1365, 1346, 1250, 1170 cm^{-1}

HRMS (ESI, pos.): m/z 430.1002 (430.1018 calc. for $C_{22}H_{25}NO_3Br$ $(M+H)^+$), m/z 432.0984 (432.0997 calc. for $C_{22}H_{25}NO_3Br$ $(M+H)^+$)

HPLC: Chiralpak IA (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, λ = 254 nm), t_{major} = 11.37 min., t_{minor} = 13.12 min., 73% ee.

(*E*)-*tert*-Butyl 1-(naphthalen-2-yl)-3-oxo-5-phenylpent-4-enylcarbamate (57e)



The reaction of Mannich product **56e** (30.1 mg, 0.062 mmol) with morpholine (54 μL, 0.62 mmol) and $Pd(PPh_3)_4$ (3.6 mg, 0.003 mmol) in THF (0.5 mL) for 30 min according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 85:15), 22 mg (85%) of **57e** as a white solid.

$[\alpha]_D^{20}$ = -34.1 (c 0.23, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): 7.85-7.75 (m, 4H, Ar*H*), 7.55-7.42 (m, 6H, Ar*H* and C=C*H*Ph), 7.41-7.30 (m, 3H, Ar*H*), 6.68 (d, 1H, *J* = 16.2 Hz, C=C*H*CO), 5.77-5.60 (m, 1H, N*H*), 5.41-5.28 (m, 1H, C*H*NH), 3.47-3.34 (m, 1H, CH_2CO), 3.22 (dd, 1H, *J* = 16.1, 6.0 Hz, CH_2CO), 1.42 (s, 9H, OC(C$H_3)_3$)

^{13}C NMR (75 MHz, $CDCl_3$): 198.0 (*C*O), 155.2 (NH*C*OO), 143.6 (C=*C*HPh), 134.2 (ArC_{ipso}), 133.3 (ArC_{ipso}), 132.7 (ArC_{ipso}), 130.7 (Ar*C*), 128.9 (2xAr*C*), 128.5 (Ar*C*), 128.4 (2xAr*C*), 128.3

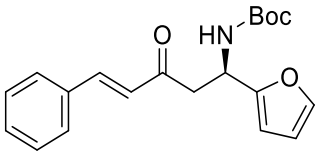
(ArC_{ipso}), 128.0 (Ar*C*), 127.6 (Ar*C*), 126.2 (Ar*C*), 126.0 (C=*C*HCO), 125.9 (Ar*C*), 125.0 (Ar*C*), 124.6 (Ar*C*), 79.7 (O*C*(CH_3)$_3$), 51.7 (*C*HNH), 46.4 (*C*H_2CO), 28.4 (OC(*C*H_3)$_3$)

IR (neat): 3393, 2972, 2926, 1686, 1605, 1508, 1247, 1168 cm^{-1}

HRMS (ESI, pos.): m/z 402.206 (402.2069 calc. for $C_{26}H_{28}NO_3$ $(M+H)^+$)

HPLC: Chiralpak IA (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, λ = 254 nm), t_{major} = 15.01 min., t_{minor} = 17.15 min., 39% ee.

(*E*)-*tert*-Butyl 1-(furan-2-yl)-3-oxo-5-phenylpent-4-enylcarbamate (57f)



The reaction of Mannich product **56f** (48.4 mg, 0.114 mmol) with morpholine (99.3 μL, 1.14 mmol) and $Pd(PPh_3)_4$ (6.6 mg, 0.006 mmol) in THF (0.6 mL) for 30 minutes according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 85:15), 34.1 mg (88%) of **57f** as a white solid.

$[\alpha]_D^{20}$ = 7.6 (c 1.34, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): 7.61-7.49 (m, 3H, Ar*H* and C=C*H*Ph), 7.44-7.36 (m, 3H, Ar*H*), 7.31 (d, 1H, *J* = 1.8 Hz, Ar*H*), 6.71 (d, 1H, *J* = 16.2 Hz, C=C*H*CO), 6.29 (dd, 1H, *J* = 3.3, 1.8 Hz, Ar*H*), 6.21 (d, 1H, *J* = 3.3 Hz, Ar*H*), 5.64-5.46 (m, 1H, N*H*), 5.33-5.20 (m, 1H, C*H*NH), 3.38 (d, 1H, *J* = 16.6 Hz, C*H*$_2$CO), 3.15 (dd, 1H, *J* = 16.3, 6.2 Hz, C*H*$_2$CO), 1.44 (s, 9H, OC(C*H*$_3$)$_3$)

^{13}C NMR (75 MHz, $CDCl_3$): 197.7 (*C*O), 155.1 (NH*C*OO), 153.9 (ArC_{ipso}), 143.5 (C=*C*HPh), 141.7 (Ar*C*), 134.3 (ArC_{ipso}), 130.7 (Ar*C*), 129.0 (2xAr*C*), 128.4 (2xAr*C*), 126.0 (C=*C*HCO), 110.4 (Ar*C*), 106.1 (Ar*C*), 79.8 (O*C*$(CH_3)_3$), 45.8 (*C*HNH), 43.7 (*C*H_2CO), 28.4 (OC(*C*$H_3)_3$)

IR (neat): 3343, 2978, 2929, 2251, 1698, 1609, 1495, 1366, 1165 cm^{-1}

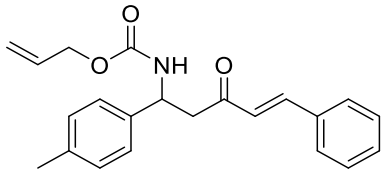
HRMS (ESI, pos.): m/z 342.1697 (342.1705 calc. for $C_{20}H_{24}NO_4$ $(M+H)^+$)

HPLC: Chiralpak IC (hexane/*i*-PrOH, 90/10, flow rate 1 mL/min, λ = 254 nm), t_{major} = 41.23 min., t_{minor} = 43.47 min., 25% ee.

General procedure for the Decarboxylative Mannich reaction

To the corresponding imine (1 eq.) was added *β*-keto acid (1 eq) and dichloromethane. The reaction was stirred at ambient temperature for 12 h after which solvent was removed from the reaction mixture under reduced pressure. The crude was purified using flash chromatography (85:15 hexanes/EtOAc) on silica gel to obtain the pure product in 75-96% yields.

(*E*)-Allyl 3-oxo-5-phenyl-1-p-tolylpent-4-enylcarbamate (63)



The reaction of imine **61** (400 mg, 1.97 mmol) and *β*-keto acid **75** (453.1 mg, 1.97 mmol) in dichloromethane (8 mL) for 12 h according to the general procedure provided, after flash column chromatography on silica gel (hexanes/EtOAc, 85:15), 663 mg (96%) of **63** as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): 7.55-7.45 (m, 3H, Ar*H* and C=C*H*Ph), 7.42-7.35 (m, 3H, Ar*H*), 7.23 (apparent d, 2H, *J* = 8 Hz, Ar*H*), 7.13 (apparent d, 2H, *J* = 7.9 Hz, Ar*H*), 6.66 (d, 1H, *J* =

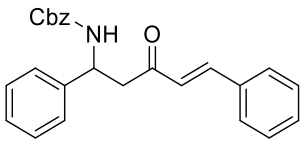
16.2 Hz, C=C*H*CO), 5.98-5.74 (m, 2H, N*H* and COOCH$_2$C*H*), 5.34-5.14 (m, 3H, C*H*NH and C*H*$_2$=CH), 4.55 (apparent dt, 2H, *J* = 5.6, 1.5 Hz, COOC*H*$_2$), 3.35 (apparent dd, 1H, *J* = 16.1, 5.8 Hz,C*H*$_2$CO), 3.14 (dd, 1H, *J* = 16.2, 6.1 Hz, C*H*$_2$CO), 2.30 (s, 3H, C*H*$_3$)

^{13}C NMR (75 MHz, $CDCl_3$): 198.0 (*C*O), 155.5 (NH*C*OO), 143.6 (C=*C*HPh), 138.3 (Ar*C*$_{ipso}$), 137.2 (Ar*C*$_{ipso}$), 134.2 (Ar*C*$_{ipso}$), 132.8 (*C*H=CH$_2$), 130.7 (Ar*C*), 129.3 (2xAr*C*), 129.0 (2xAr*C*), 128.4 (2xAr*C*), 126.2 (CH=*C*HCO), 126.0 (2xAr*C*), 117.7 (*C*H$_2$=CH), 65.6 (COO*C*H$_2$), 51.7 (*C*HNH), 46.1 (*C*H$_2$CO), 21.1 (*C*H$_3$)

IR (neat): 3328, 2953, 1711, 1650, 1524, 1450, 1257, 1175 cm^{-1}.

HRMS (ESI, pos.): m/z 350.1747 (350.1756 calc. for $C_{22}H_{24}NO_3$ $(M+H)^+$)

(*E*)-Benzyl 3-oxo-1,5-diphenylpent-4-enylcarbamate (77)



The reaction of imine **45** (355 mg, 1.5 mmol) and *β*-keto acid **75** (328.5 mg, 1.5 mmol) in dichloromethane (10 mL) for 12 h according to the general procedure provided, after flash column chromatography on silica gel (hexanes/EtOAc, 85:15), 428 mg (74%) of **77** as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): 7.53-7.43 (m, 3H, Ar*H* and C=C*H*Ph), 7.41-7.19 (m, 13H, Ar*H*), 6.65 (d, 1H, *J* = 16.2 Hz, C=C*H*CO), 6.03-5.85 (m, 1H, N*H*), 5.31-5.20 (m, 1H, C*H*NH), 5.13-5.03 (m, 2H, C*H*$_2$Ph), 3.42-3.26 (m, 1H, C*H*$_2$CO), 3.13 (dd, 1H, *J* = 16.3, 5.9 Hz, C*H*$_2$CO)

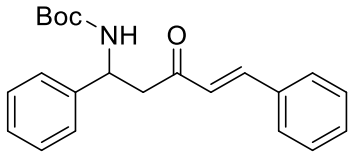
^{13}C NMR (75 MHz, $CDCl_3$): 197.8 (*C*O), 155.7 (NH*C*OO), 143.6 (C=*C*HPh), 141.3 (Ar*C*ipso), 136.4 (Ar*C*ipso), 134.1 (Ar*C*ipso), 130.7 (2xAr*C*), 128.9 (2xAr*C*), 128.6 (2xAr*C*), 128.44

(2xAr*C*), 128.37 (2xAr*C*), 128.1 (Ar*C*), 128.0 (Ar*C*), 127.5 (2xAr*C*), 126.3 (C=*C*HCO), 125.9 (Ar*C*), 66.8 (*C*H_2Ph), 51.8 (*C*HNH), 46.0 (*C*H_2CO)

IR (neat): 3326, 3032, 1687, 1536, 1254 cm^{-1}.

HRMS (ESI, pos.): m/z 386.1764 (386.1756 calc. for $C_{25}H_{24}NO_3$ $(M+H)^+$)

(*E*)-*tert*-Butyl 3-oxo-1,5-diphenylpent-4-enylcarbamate (76)



The reaction of imine **48** (469 mg, 2.28 mmol) and *β*-keto acid **75** (524.4 mg, 2.28 mmol) in dichloromethane (10 mL) for 12 h according to the general procedure provided, after flash column chromatography on silica gel (hexanes/EtOAc, 85:15), 646 mg (81%) of **76** as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): 7.54-7.45 (m, 3H, Ar*H* and C=C*H*Ph), 7.42-7.35 (m, 3H, Ar*H*), 7.35-7.27 (m, 4H, Ar*H*), 7.25-7.19 (m, 1H, Ar*H*), 6.67 (d, 1H, *J* = 16.2 Hz, C=C*H*CO), 5.70-5.46 (m, 1H, N*H*), 5.24-5.11 (m, 1H, C*H*NH), 3.40-3.25 (m, 1H, CH_2CO), 3.13 (dd, 1H, *J* = 16.0, 6.1 Hz, CH_2CO), 1.41 (s, 9H, OC(CH_3)$_3$)

^{13}C NMR (75 MHz, $CDCl_3$): 198.0 (*C*O), 155.2 (NH*C*OO), 143.5 (C=*C*HPh),141.7 (ArC_{ipso}) 134.2 (ArC_{ipso}), 130.7 (Ar*C*), 129.0 (2xAr*C*), 128.6 (2xAr*C*), 128.4 (2xAr*C*), 127.4 (Ar*C*), 126.3 (2xAr*C*), 126.0 (C=*C*HCO), 79.7 (O*C*(CH$_3$)$_3$), 51.5 (*C*HNH), 46.5 (*C*H_2CO), 28.4 (OC(*C*H_3)$_3$)

IR (neat): 3390, 3028, 2975, 1686, 1606, 1503, 1169 cm^{-1}

HRMS (ESI, pos.): m/z 352.1903 (352.1913 calc. for $C_{22}H_{26}NO_3$ $(M+H)^+$)

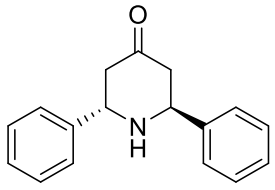
General procedure for the base-catalysed cyclization of β'-amino α,β-unsaturated enones to 2,6-Diarylpiperidin-4-ones

To a solution of the decarboxylated Mannich product (β'-amino α,β-unsaturated enone) in trifluoroethanol was added 4 N H_2SO_4 and the reaction mixture was stirred at room temperature for 3 hours. Then the reaction mixture was cooled between 0-5 ^oC and basified upto pH = 8 by dropwise addition of saturated $NaHCO_3$ solution. The reaction mixture was allowed to stir at 0-5°C for 6-18 hours. Later, the organic part was extracted with DCM and dried over anhydrous Na_2SO_4. Evaporation of the organic solvent followed by flash chromatography (95:5 to 60:40 gradient elution of hexanes/EtOAc) on silica gel afforded the separate piperidone diastereomers.

2,6-Diphenylpiperidin-4-ones (72a and 72b)

This was isolated as a liquid with a diastereomeric ratio of 1:1. The diastereomers were separated by flash chromatography on silica gel (95:5 to 60:40 hexanes/EtOAc) to provide overall 64 mg (45%) of **72**.

(2*RS*, 6*RS*) 2,6-Diphenylpiperidin-4-one (72a)



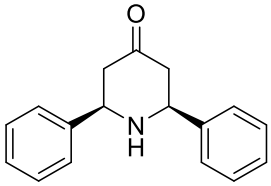
^{1}H NMR (300 MHz, $CDCl_3$): 7.38-7.24 (m, 10H, Ar*H*), 4.36 (t, 2H, *J* = 5.9 Hz, ArC*H*NH), 2.80 (d, 4H, *J* = 5.9 Hz, CH_2CO)

^{13}C NMR (75 MHz, $CDCl_3$): 209.3 (*C*O), 142.4 (2xAr*C*$_{ipso}$), 128.8 (2xAr*C*), 127.7 (2xAr*C*$_{ipso}$), 126.9 (2xAr*C*), 55.3 (Ar*C*HNH), 47.3 (*C*H_2CO)

IR (neat): 2920, 2850, 1700, 1600, 1471, 1283, 1221 cm^{-1}.

HRMS (ESI, pos.): m/z 252.1383 (252.1388 calc. for $C_{17}H_{18}NO$ $(M+H)^+$)

(2*RS*, 6*SR*) 2,6-Diphenylpiperidin-4-one (72b)[42]



^{1}H NMR (300 MHz, $CDCl_3$): 7.43-7.37 (m, 4H, Ar*H*), 7.33-7.17 (m, 6H, Ar*H*), 4.05-3.97 (m, 2H, ArC*H*NH), 2.62-2.45 (m, 4H, CH_2CO)

^{13}C NMR (75 MHz, $CDCl_3$): 208.2 (*C*O), 142.7 (2xAr*C*$_{ipso}$), 128.8 (2xAr*C*), 128.0 (2xAr*C*$_{ipso}$), 126.6 (2xAr*C*), 61.2 (Ar*C*HNH), 50.4 (*C*H_2CO)

IR (neat): 2922, 2853, 1713, 1602, 1492, 1452, 1293, 1242 cm^{-1}.

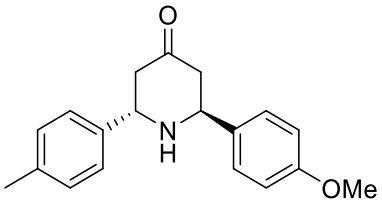
HRMS (ESI, pos.): m/z 252.1383 (252.1388 calc. for $C_{17}H_{18}NO$ $(M+H)^+$)

The observed NMR data is in agreement with reported data.[42]

2-(4-Methoxyphenyl)-6-*p*-tolylpiperidin-4-ones (73a and 73b)

This was isolated as a liquid with a diastereomeric ratio of 1.2:1. The diastereomers were was separated by flash chromatography on silica gel (95:5 to 60:40 hexanes/EtOAc) to provide overall 37 mg (40%) of **73**.

(2*RS*, 6*RS*) 2-(4-Methoxyphenyl)-6-*p*-tolylpiperidin-4-one (73a)



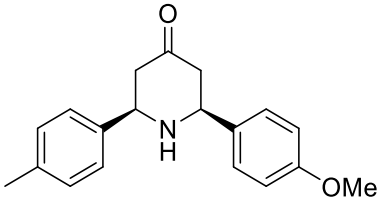
^{1}H NMR (300 MHz, $CDCl_3$): 7.28-7.11 (m, 6H, Ar*H*), 6.89-6.82 (m, 2H, Ar*H*), 4.31 (t, 2H, *J* = 5.9 Hz, ArC*H*NH), 3.79 (s, 3H, OCH_3), 2.77 (d, 4H, *J* = 6.6 Hz, CH_2CO), 2.33 (s, 3H, CH_3)

^{13}C NMR (75 MHz, $CDCl_3$): 209.6 (*C*O), 159.0 (ArC_{ipso}), 139.4 (ArC_{ipso}), 137.3 (ArC_{ipso}), 134.5 (ArC_{ipso}), 129.4 (2xAr*C*), 128.1 (2xAr*C*), 126.8 (2xAr*C*), 114.0 (2xAr*C*), 55.3 (O*C*H_3), 55.0 (Ar*C*HNH), 54.7 (Ar*C*HNH), 47.4 (*C*H_2), 47.3 (*C*H_2), 21.1 (*C*H_3)

IR (neat): 2947, 2900, 1710, 1619, 1511, 1450, 1417, 1303, 1287, 1170, 1031 cm^{-1}

HRMS (ESI, pos.): m/z 296.1644 (296.1651 calc. for $C_{19}H_{22}NO_2$ $(M+H)^+$)

(2*RS*, 6*SR*) 2-(4-Methoxyphenyl)-6-*p*-tolylpiperidin-4-one (73b)



The 2,6-*cis* stereochemistry is tentatively assigned by comparison of the ^{1}H NMR data to structurally related 2,6-*cis* disubstituted piperidinones.[42]

^{1}H NMR (300 MHz, $CDCl_3$): 7.41-7.32 (m, 4H, Ar*H*), 7.19-7.14 (m, 2H, Ar*H*), 6.91-6.86 (m, 2H, Ar*H*), 4.04 (t, 1H, *J* = 3.4 Hz, ArC*H*NH)), 4.01 (t, 1H, *J* = 3.5 Hz, ArC*H*NH), 3.80 (s, 3H, OCH_3), 2.66-2.48 (m, 4H, CH_2CO), 2.33 (s, 3H, CH_3)

^{13}C NMR (75 MHz, $CDCl_3$): 208.6 (*C*O), 159.2 (Ar*C*$_{ipso}$), 139.9 (Ar*C*$_{ipso}$), 137.6 (Ar*C*$_{ipso}$), 135.0 (Ar*C*$_{ipso}$), 129.4 (2xAr*C*), 127.7 (2xAr*C*), 126.5 (2xAr*C*), 114.1 (2xAr*C*), 60.9 (Ar*C*HNH), 60.7 (Ar*C*HNH), 55.3 (O*C*H$_3$), 50.6 (*C*H$_2$), 50.5 (*C*H$_2$), 21.1 (*C*H$_3$)

IR (neat): 2955, 2910, 1700, 1609, 1511, 1450, 1417, 1313, 1237, 1175, 1030 cm^{-1}

HRMS (ESI, pos.): m/z 296.1644 (296.1651 calc. for $C_{19}H_{22}NO_2$ $(M+H)^+$)

3.9 X-ray crystallographic data for 52

Experimental details

Single-crystal X-ray diffraction data was collected at 100(2) K on a XtaLAB Synergy-S, Dualflex, HyPix-6000HE diffractometer using Cu *K*α radiation (λ = 1.5406 Å). Crystal was mounted on nylon CryoLoops with Paraton-N. The data collection and reduction were processed within *CrysAlisPro* (Rigaku OD, 2021). A multi-scan absorption correction was applied to the collected reflections. Using Olex^2 [1], the structure was solved with the ShelXT [2] structure solution program using Intrinsic Phasing and refined with the ShelXL [3] refinement package using Least Squares minimisation. All non-hydrogen atoms were refined anisotropically. The carbamate hydrogen atoms were located in difference Fourier maps and refined by using the DFIX and HTAB commands. All other organic hydrogen atoms were generated geometrically.

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), *J. Appl. Cryst*. 42, 339-341.
2. Sheldrick, G.M. (2015). *Acta Cryst*. A71, 3-8.
3. Sheldrick, G.M. (2015). *Acta Cryst*. C71, 3-8.

Table 1. Crystal data and structure refinement

Identification code	SV-07-155
Empirical formula	$C_{27}H_{31}NO_5$
Formula weight	449.53
Temperature/K	100(2)
Crystal system	monoclinic
Space group	*I*2

a/Å	27.8463(2)
b/Å	5.41710(10)
c/Å	32.3710(3)
β/°	97.9280(10)
Volume/Å^3	4836.37(11)
Z	8
ρ_{calc}g/cm^3	1.235
μ/mm^{-1}	0.685
F(000)	1920.0
Crystal size/mm^3	0.27 × 0.06 × 0.05
Radiation	Cu $K\alpha$ (λ = 1.54184)
2θ range for data collection/°	4.506 to 159.686
Index ranges	$-34 \leq h \leq 35$, $-6 \leq k \leq 6$, $-41 \leq l \leq 41$
Reflections collected	60277
Independent reflections	10346 [R_{int} = 0.0779, R_{sigma} = 0.0488]
Data/restraints/parameters	10346/3/639
Goodness-of-fit on F^2	1.060
Final R indexes [I>=2σ (I)]	R_1 = 0.0432, wR_2 = 0.1146
Final R indexes [all data]	R_1 = 0.0481, wR_2 = 0.1199
Largest diff. peak/hole / e Å^{-3}	0.24/-0.23
Flack parameter	-0.04(10)

Table 2. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3). U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Atom	***x***	***y***	***z***	**U(eq)**
O1	4078.7(6)	7402(5)	7294.2(6)	42.1(5)
O2	4290.8(6)	3509(4)	7150.6(6)	41.0(5)
O3	4947.0(7)	8564(5)	8158.6(6)	46.6(5)
O4	5787.2(6)	12022(4)	7572.6(6)	35.9(4)

Atom	*x*	*y*	*z*	U(eq)
O5	6369.2(6)	9303(4)	7853.9(6)	35.1(4)
N1	5673.5(7)	7850(5)	7543.6(6)	33.1(5)
C1	4371.8(8)	5751(6)	7318.7(7)	36.2(6)
C2	4883.9(8)	5968(6)	7553.3(7)	35.2(6)
C3	4831.6(9)	6567(7)	8006.2(8)	38.8(7)
C4	4613.5(9)	4562(7)	8231.6(8)	41.9(7)
C5	4509.0(9)	4885(7)	8616.9(8)	40.4(6)
C6	4258.9(8)	3151(7)	8861.0(8)	41.0(7)
C7	4215.5(11)	3722(8)	9275.6(9)	47.7(7)
C8	3963.7(11)	2188(8)	9511.0(9)	52.2(8)
C9	3745.0(10)	87(8)	9335.6(10)	49.9(8)
C10	3783.6(9)	-543(7)	8925.3(9)	46.7(8)
C11	4041.0(9)	983(7)	8689.0(9)	43.6(7)
C12	5170.1(7)	7943(6)	7345.2(7)	32.7(6)
C13	5114.5(7)	7507(6)	6876.7(7)	32.7(5)
C14	4844.5(8)	9156(7)	6607.8(8)	38.7(6)
C15	4756.4(9)	8667(7)	6181.7(8)	43.4(7)
C16	4930.8(10)	6550(7)	6015.9(8)	43.2(7)
C17	5210.1(10)	4935(7)	6286.9(8)	41.5(6)
C18	5300.3(9)	5395(6)	6712.4(7)	36.6(6)
C19	4815.8(13)	5979(9)	5556.2(9)	59.9(10)
C20	5930.4(8)	9915(6)	7650.6(7)	31.4(5)
C21	6722.9(8)	11218(6)	8019.5(8)	36.5(6)
C22	6515.5(10)	12866(7)	8330.4(8)	42.2(7)
C23	7132.7(10)	9645(7)	8245.0(11)	51.6(8)
C24	6890.2(10)	12657(7)	7666.6(9)	45.0(7)
C25	3814.0(9)	3102(7)	6908.2(8)	43.6(7)
C26	3788.7(9)	4236(8)	6484.9(9)	48.8(8)

Atom	*x*	*y*	*z*	U(eq)
C27	3655.6(11)	2986(10)	6134.8(10)	60.6(10)
O6	3447.1(7)	7311(6)	5302.2(6)	53.6(6)
O7	3302.6(6)	11169(5)	5053.9(6)	46.9(6)
O8	2362.1(8)	5514(5)	5533.6(6)	49.8(6)
O9	1825.3(6)	2761(5)	4556.4(6)	44.2(5)
O10	1214.1(6)	5588(4)	4411.0(6)	40.8(5)
N2	1955.7(7)	6922(6)	4606.0(7)	39.9(6)
C28	3169.1(9)	8923(7)	5161.8(7)	42.0(7)
C29	2621.5(8)	8623(7)	5081.6(8)	40.0(7)
C30	2459.5(9)	7682(7)	5489.7(8)	42.6(7)
C31	2444.5(9)	9566(7)	5816.3(8)	43.2(7)
C32	2253.8(9)	9035(7)	6166.3(8)	43.0(7)
C33	2223.5(9)	10706(7)	6517.4(7)	41.2(7)
C34	1899.6(9)	10148(8)	6800.0(8)	44.8(7)
C35	1849.5(10)	11726(8)	7128.2(8)	47.6(8)
C36	2129.0(10)	13840(8)	7190.4(8)	47.1(8)
C37	2461.1(10)	14399(8)	6916.2(8)	46.7(8)
C38	2500.4(9)	12850(7)	6580.7(8)	43.7(7)
C39	2483.3(8)	6798(7)	4719.2(7)	39.3(7)
C40	2753.6(8)	7332(6)	4349.8(7)	36.9(6)
C41	2667.8(9)	9448(6)	4110.9(8)	39.2(7)
C42	2932.2(9)	9936(7)	3784.3(7)	39.4(6)
C43	3291.2(9)	8310(7)	3690.8(8)	41.5(7)
C44	3372.3(9)	6186(7)	3929.2(8)	43.0(7)
C45	3107.5(9)	5681(7)	4255.9(8)	38.9(6)
C46	3582.7(12)	8877(8)	3342.2(10)	55.9(9)
C47	1679.2(9)	4891(7)	4526.9(8)	39.4(7)
C48	823.1(9)	3747(7)	4299.1(8)	42.5(7)

Atom	*x*	*y*	*z*	U(eq)
C49	761.0(11)	2168(8)	4669.6(9)	50.1(8)
C50	923.9(10)	2224(8)	3926.7(9)	50.1(8)
C51	385.6(10)	5419(8)	4185.0(12)	56.0(9)
C52	3823(4)	11340(20)	5096(4)	40(2)
C52A	3820(7)	12180(40)	5047(6)	35(3)
C53	4017(2)	10151(17)	4732(2)	39.0(16)
C53A	3992(5)	11130(30)	4653(5)	43(3)
C54	4231.7(18)	11365(12)	4461.3(17)	47.4(17)
C54A	4430(3)	10290(20)	4657(3)	50(3)

Table 3. Selected Bond Distances (Å)

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C1	1.206(4)	O7	C52	1.438(11)
O2	C1	1.337(4)	O7	C52A	1.545(19)
O2	C25	1.463(3)	O8	C30	1.218(5)
O3	C3	1.213(4)	O9	C47	1.223(4)
O4	C20	1.224(4)	O10	C47	1.352(3)
O5	C20	1.347(3)	O10	C48	1.484(4)
O5	C21	1.479(3)	N2	C39	1.466(3)
N1	C12	1.460(3)	N2	C47	1.347(5)
N1	C20	1.347(4)	C28	C29	1.520(3)
C1	C2	1.525(3)	C29	C30	1.540(4)
C2	C3	1.528(3)	C29	C39	1.542(4)
C2	C12	1.543(4)	C30	C31	1.474(4)
C3	C4	1.484(4)	C31	C32	1.347(4)
C4	C5	1.331(4)	C32	C33	1.464(4)
C5	C6	1.464(4)	C33	C34	1.403(4)

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C6	C7	1.399(4)	C33	C38	1.394(5)
C6	C11	1.402(5)	C34	C35	1.386(5)
C7	C8	1.382(5)	C35	C36	1.384(6)
C8	C9	1.376(6)	C36	C37	1.400(4)
C9	C10	1.390(5)	C37	C38	1.389(4)
C10	C11	1.390(4)	C39	C40	1.526(3)
C12	C13	1.521(3)	C40	C41	1.385(5)
C13	C14	1.393(4)	C40	C45	1.395(4)
C13	C18	1.391(4)	C41	C42	1.395(4)
C14	C15	1.393(4)	C42	C43	1.397(4)
C15	C16	1.382(5)	C43	C44	1.386(5)
C16	C17	1.397(4)	C43	C46	1.510(4)
C16	C19	1.511(4)	C44	C45	1.397(4)
C17	C18	1.388(4)	C48	C49	1.502(5)
C21	C22	1.518(4)	C48	C50	1.519(4)
C21	C23	1.527(4)	C48	C51	1.522(4)
C21	C24	1.509(4)	C52	C53	1.508(15)
C25	C26	1.494(4)	C52A	C53A	1.53(3)
C26	C27	1.328(5)	C53	C54	1.304(10)
O6	C28	1.213(4)	C53A	C54A	1.301(19)
O7	C28	1.333(5)			

Table 4. Selected Bond Angles

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C1	O2	C25	116.4(2)	C47	O10	C48	121.5(3)
C20	O5	C21	121.2(2)	C47	N2	C39	122.5(3)
C20	N1	C12	121.9(2)	O6	C28	O7	124.7(3)

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O1	C1	O2	124.9(2)	O6	C28	C29	124.1(3)
O1	C1	C2	123.6(3)	O7	C28	C29	111.3(3)
O2	C1	C2	111.5(2)	C28	C29	C30	107.1(2)
C1	C2	C3	106.73(19)	C28	C29	C39	109.7(2)
C1	C2	C12	109.9(2)	C30	C29	C39	111.6(3)
C3	C2	C12	113.3(3)	O8	C30	C29	121.0(3)
O3	C3	C2	121.6(3)	O8	C30	C31	123.7(3)
O3	C3	C4	123.8(2)	C31	C30	C29	115.3(3)
C4	C3	C2	114.6(3)	C32	C31	C30	120.6(3)
C5	C4	C3	121.4(3)	C31	C32	C33	126.3(3)
C4	C5	C6	127.1(3)	C34	C33	C32	118.9(3)
C7	C6	C5	119.1(3)	C38	C33	C32	122.6(2)
C7	C6	C11	118.4(3)	C38	C33	C34	118.4(3)
C11	C6	C5	122.4(3)	C35	C34	C33	120.6(3)
C8	C7	C6	120.9(4)	C36	C35	C34	120.5(3)
C9	C8	C7	120.0(3)	C35	C36	C37	119.6(3)
C8	C9	C10	120.6(3)	C38	C37	C36	119.7(3)
C9	C10	C11	119.6(3)	C37	C38	C33	121.1(3)
C10	C11	C6	120.5(3)	N2	C39	C29	107.3(2)
N1	C12	C2	107.8(2)	N2	C39	C40	112.4(2)
N1	C12	C13	113.12(18)	C40	C39	C29	112.1(3)
C13	C12	C2	109.9(2)	C41	C40	C39	121.9(2)
C14	C13	C12	119.7(3)	C41	C40	C45	118.8(2)
C18	C13	C12	121.1(2)	C45	C40	C39	119.3(3)
C18	C13	C14	119.1(2)	C40	C41	C42	120.8(2)
C15	C14	C13	120.2(3)	C41	C42	C43	120.9(3)
C16	C15	C14	121.3(3)	C42	C43	C46	120.5(3)
C15	C16	C17	118.1(3)	C44	C43	C42	118.0(2)

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C15	C16	C19	121.0(3)	C44	C43	C46	121.5(2)
C17	C16	C19	121.0(3)	C43	C44	C45	121.4(3)
C18	C17	C16	121.3(3)	C40	C45	C44	120.1(3)
C17	C18	C13	120.1(3)	O9	C47	O10	125.5(3)
O4	C20	O5	125.3(3)	O9	C47	N2	125.5(2)
O4	C20	N1	125.1(2)	N2	C47	O10	109.0(3)
O5	C20	N1	109.6(2)	O10	C48	C49	110.4(2)
O5	C21	C22	110.9(2)	O10	C48	C50	110.4(2)
O5	C21	C23	101.4(2)	O10	C48	C51	101.2(3)
O5	C21	C24	110.3(2)	C49	C48	C50	112.2(3)
C22	C21	C23	109.8(2)	C49	C48	C51	110.9(3)
C24	C21	C22	112.5(3)	C50	C48	C51	111.1(2)
C24	C21	C23	111.2(2)	O7	C52	C53	111.3(9)
O2	C25	C26	110.8(2)	C53A	C52A	O7	106.3(12)
C27	C26	C25	123.1(4)	C54	C53	C52	123.8(8)
C28	O7	C52	110.3(4)	C54A	C53A	C52A	121.5(14)
C28	O7	C52A	128.5(7)				

Table 5. Selected Torsion Angles

A	B	C	D	Angle/°	A	B	C	D	Angle/°
O1	C1	C2	C3	59.3(3)	O7	C28	C29	C30	-127.7(3)
O1	C1	C2	C12	-63.8(3)	O7	C28	C29	C39	110.9(3)
O2	C1	C2	C3	-119.9(3)	O7	C52	C53	C54	114.1(8)
O2	C1	C2	C12	116.9(2)	O7	C52A	C53A	C54A	-137.4(16)
O2	C25	C26	C27	126.6(3)	O8	C30	C31	C32	-9.4(4)
O3	C3	C4	C5	3.2(4)	N2	C39	C40	C41	53.3(4)
N1	C12	C13	C14	-129.2(3)	N2	C39	C40	C45	-128.5(3)

A	B	C	D	Angle/°	A	B	C	D	Angle/°
N1	C12	C13	C18	55.3(3)	C28	O7	C52	C53	79.0(6)
C1	O2	C25	C26	78.0(3)	C28	O7	C52A	C53A	77.3(13)
C1	C2	C3	O3	-111.4(3)	C28	C29	C30	O8	-101.7(3)
C1	C2	C3	C4	66.3(3)	C28	C29	C30	C31	76.9(3)
C1	C2	C12	N1	-172.4(2)	C28	C29	C39	N2	-169.9(3)
C1	C2	C12	C13	-48.7(3)	C28	C29	C39	C40	-46.0(3)
C2	C3	C4	C5	-174.5(2)	C29	C30	C31	C32	172.0(2)
C2	C12	C13	C14	110.2(3)	C29	C39	C40	C41	-67.7(3)
C2	C12	C13	C18	-65.2(3)	C29	C39	C40	C45	110.5(3)
C3	C2	C12	N1	68.3(3)	C30	C29	C39	N2	71.5(3)
C3	C2	C12	C13	-168.0(2)	C30	C29	C39	C40	-164.7(2)
C3	C4	C5	C6	174.6(3)	C30	C31	C32	C33	178.9(2)
C4	C5	C6	C7	174.8(3)	C31	C32	C33	C34	162.1(3)
C4	C5	C6	C11	-8.2(4)	C31	C32	C33	C38	-17.2(4)
C5	C6	C7	C8	177.1(3)	C32	C33	C34	C35	-177.9(3)
C5	C6	C11	C10	-176.4(3)	C32	C33	C38	C37	179.7(3)
C6	C7	C8	C9	-1.0(5)	C33	C34	C35	C36	-2.0(5)
C7	C6	C11	C10	0.7(4)	C34	C33	C38	C37	0.4(4)
C7	C8	C9	C10	1.4(5)	C34	C35	C36	C37	0.7(5)
C8	C9	C10	C11	-0.8(5)	C35	C36	C37	C38	1.1(5)
C9	C10	C11	C6	-0.3(4)	C36	C37	C38	C33	-1.7(5)
C11	C6	C7	C8	0.0(5)	C38	C33	C34	C35	1.5(4)
C12	N1	C20	O4	-4.8(3)	C39	N2	C47	O9	3.3(4)
C12	N1	C20	O5	175.58(19)	C39	N2	C47	O10	-176.9(2)
C12	C2	C3	O3	9.7(4)	C39	C29	C30	O8	18.5(3)
C12	C2	C3	C4	-172.6(2)	C39	C29	C30	C31	-162.9(2)
C12	C13	C14	C15	-174.5(2)	C39	C40	C41	C42	177.7(3)
C12	C13	C18	C17	174.6(2)	C39	C40	C45	C44	-177.5(3)

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C13	C14	C15	C16	0.3(4)	C40	C41	C42	C43	-0.2(4)
C14	C13	C18	C17	-0.9(4)	C41	C40	C45	C44	0.8(4)
C14	C15	C16	C17	-1.6(4)	C41	C42	C43	C44	0.7(4)
C14	C15	C16	C19	177.4(3)	C41	C42	C43	C46	-178.8(3)
C15	C16	C17	C18	1.8(4)	C42	C43	C44	C45	-0.5(5)
C16	C17	C18	C13	-0.5(4)	C43	C44	C45	C40	-0.3(5)
C18	C13	C14	C15	1.0(4)	C45	C40	C41	C42	-0.5(4)
C19	C16	C17	C18	-177.3(3)	C46	C43	C44	C45	179.0(3)
C20	O5	C21	C22	59.2(3)	C47	O10	C48	C49	63.9(3)
C20	O5	C21	C23	175.8(2)	C47	O10	C48	C50	-60.9(3)
C20	O5	C21	C24	-66.2(3)	C47	O10	C48	C51	-178.6(2)
C20	N1	C12	C2	-136.8(2)	C47	N2	C39	C29	-136.5(3)
C20	N1	C12	C13	101.5(3)	C47	N2	C39	C40	99.8(3)
C21	O5	C20	O4	2.2(3)	C48	O10	C47	O9	-0.8(4)
C21	O5	C20	N1	-178.14(19)	C48	O10	C47	N2	179.4(2)
C25	O2	C1	O1	2.2(3)	C52	O7	C28	O6	4.6(6)
C25	O2	C1	C2	-178.50(19)	C52	O7	C28	C29	-174.7(6)
O6	C28	C29	C30	52.9(4)	C52A	O7	C28	O6	5.2(10)
O6	C28	C29	C39	-68.5(3)	C52A	O7	C28	C29	-174.2(9)

Table 6. Hydrogen Bonds

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
N1	H1	O4[1]	0.89(2)	2.36(3)	3.173(3)	151(3)
N2	H2	O9[2]	0.87(2)	2.38(3)	3.185(4)	154(4)

[1]+X,-1+Y,+Z; [2]+X,1+Y,+Z

3.10 X-ray crystallographic data for 53

Experimental details

Single-crystal X-ray diffraction data was collected at 100(2) K on a XtaLAB Synergy-S, Dualflex, HyPix-6000HE diffractometer using Cu *K*a radiation (λ = 1.5406 Å). Crystal was mounted on nylon CryoLoops with Paraton-N. The data collection and reduction were processed within *CrysAlisPro* (Rigaku OD, 2020). A multi-scan absorption correction was applied to the collected reflections. Using Olex^2 [1], the structure was solved with the ShelXT [2] structure solution program using Intrinsic Phasing and refined with the ShelXL [3] refinement package using Least Squares minimisation. All non-hydrogen atoms were refined anisotropically. The carbamate hydrogen atoms were located in difference Fourier maps and refined by using the HTAB command. All other organic hydrogen atoms were generated geometrically.

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), *J. Appl. Cryst*. 42, 339-341.
2. Sheldrick, G.M. (2015). *Acta Cryst*. A71, 3-8.
3. Sheldrick, G.M. (2015). *Acta Cryst*. C71, 3-8.

Table 1. Crystal data and structure refinement

Empirical formula	$C_{23}H_{27}NO_3$
Formula weight	365.45
Temperature/K	100(2)
Crystal system	monoclinic
Space group	*I*2
a/Å	17.8536(3)
b/Å	5.40730(10)
c/Å	41.7782(6)
β/°	93.3630(10)
Volume/Å^3	4026.31(12)
Z	8

ρ_{calc}g/cm^3	1.206
μ/mm^{-1}	0.630
F(000)	1568.0
Crystal size/mm^3	0.352 × 0.053 × 0.045
Radiation	Cu $K\alpha$ (λ = 1.54184)
2θ range for data collection/°	4.238 to 159.774
Index ranges	$-22 \leq h \leq 22$, $-6 \leq k \leq 6$, $-53 \leq l \leq 50$
Reflections collected	49436
Independent reflections	8601 [R_{int} = 0.0641, R_{sigma} = 0.0365]
Data/restraints/parameters	8601/1/501
Goodness-of-fit on F^2	1.090
Final R indexes [I>=2σ (I)]	R_1 = 0.0436, wR_2 = 0.1187
Final R indexes [all data]	R_1 = 0.0476, wR_2 = 0.1234
Largest diff. peak/hole / e Å^{-3}	0.28/-0.29
Flack parameter	-0.05(12)

Table 2. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3). U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Atom	***x***	***y***	***z***	**U(eq)**
O1	8793.1(11)	9578(3)	5272.5(4)	34.1(4)
O2	6363.6(9)	9286(3)	5758.6(4)	27.8(3)
O3	7325.2(9)	12071(3)	5816.8(4)	30.6(4)
N1	7525.4(11)	7889(4)	5815.9(5)	26.1(4)
C1	9480.1(14)	2663(5)	4489.8(6)	32.4(5)
C2	9629.7(15)	1339(6)	4216.4(7)	38.2(6)
C3	9357.6(16)	2155(7)	3917.0(7)	43.6(7)
C4	8946.9(18)	4318(7)	3890.1(6)	46.9(7)
C5	8806.4(16)	5679(6)	4161.7(6)	39.4(6)

Atom	*x*	*y*	*z*	U(eq)
C6	9067.0(13)	4855(5)	4465.6(6)	29.7(5)
C7	8918.9(13)	6360(5)	4747.8(6)	29.3(5)
C8	8930.5(13)	5586(5)	5050.9(6)	29.0(5)
C9	8800.3(12)	7347(5)	5314.2(5)	27.3(4)
C10	8709.9(13)	6234(5)	5642.5(5)	27.3(5)
C11	8340.1(12)	8000(4)	5873.8(5)	25.6(4)
C12	8602.2(12)	7417(4)	6219.7(5)	25.4(4)
C13	9096.4(13)	9036(5)	6383.1(6)	29.5(5)
C14	9398.7(14)	8464(5)	6688.3(6)	32.8(5)
C15	9209.8(13)	6290(5)	6840.1(5)	29.4(5)
C16	8696.4(14)	4717(5)	6678.5(6)	30.0(5)
C17	8399.1(13)	5255(5)	6371.6(6)	29.6(5)
C18	9541.1(16)	5645(6)	7170.8(6)	39.4(6)
C19	7092.4(13)	9946(4)	5800.4(5)	24.6(4)
C20	5760.3(13)	11160(5)	5723.7(6)	30.7(5)
C21	5846.6(16)	12691(6)	5424.4(6)	38.9(6)
C22	5063.5(15)	9556(6)	5687.6(9)	47.3(7)
C23	5745.9(15)	12756(6)	6023.6(6)	36.6(5)
O4	6052.9(11)	1578(4)	3667.1(4)	37.2(4)
O5	3950.2(9)	872(3)	3062.0(4)	28.2(4)
O6	4938.8(9)	-1726(3)	3000.5(4)	28.8(3)
N2	5080.9(10)	2462(4)	3018.8(5)	25.6(4)
C24	7125.7(14)	9136(5)	4321.5(6)	32.7(5)
C25	7378.0(15)	10678(5)	4571.5(7)	37.2(6)
C26	7230.5(16)	10094(6)	4884.7(6)	39.1(6)
C27	6836.4(17)	7961(6)	4949.4(6)	39.8(6)
C28	6588.5(15)	6401(5)	4700.4(6)	34.3(5)
C29	6730.8(13)	6972(5)	4382.9(6)	29.6(5)

Atom	*x*	*y*	*z*	U(eq)
C30	6472.5(13)	5245(5)	4129.4(5)	29.6(5)
C31	6456.1(14)	5636(5)	3813.7(6)	30.1(5)
C32	6222.0(13)	3651(5)	3583.2(5)	28.1(5)
C33	6243.0(13)	4354(5)	3233.4(5)	27.1(4)
C34	5895.7(11)	2437(4)	3000.4(5)	24.5(4)
C35	6148.9(12)	2895(4)	2664.6(5)	24.7(4)
C36	6632.1(12)	1233(5)	2529.9(6)	27.4(5)
C37	6898.6(13)	1668(5)	2229.0(6)	30.5(5)
C38	6692.3(13)	3776(5)	2054.3(5)	28.7(5)
C39	6196.5(13)	5428(5)	2190.1(5)	28.8(5)
C40	5928.9(13)	5000(5)	2490.4(5)	28.1(5)
C41	7007.0(16)	4312(6)	1734.3(6)	37.2(6)
C42	4680.1(12)	349(4)	3025.5(5)	24.5(4)
C43	3393.6(13)	-1131(5)	3086.1(6)	27.9(5)
C44	3589.2(14)	-2787(5)	3373.3(6)	32.1(5)
C45	2680.0(14)	315(6)	3138.6(7)	38.7(6)
C46	3314.0(15)	-2569(6)	2772.0(6)	36.2(5)

Table 3. Selected Bond Distances (Å)

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C9	1.219(3)	O4	C32	1.218(3)
O2	C19	1.351(3)	O5	C42	1.351(3)
O2	C20	1.480(3)	O5	C43	1.477(3)
O3	C19	1.222(3)	O6	C42	1.220(3)
N1	C11	1.462(3)	N2	C34	1.461(3)
N1	C19	1.354(3)	N2	C42	1.349(3)

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C1	C2	1.387(4)	C24	C25	1.391(4)
C1	C6	1.397(4)	C24	C29	1.397(4)
C2	C3	1.387(4)	C25	C26	1.386(4)
C3	C4	1.381(5)	C26	C27	1.386(5)
C4	C5	1.388(4)	C27	C28	1.391(4)
C5	C6	1.399(4)	C28	C29	1.400(3)
C6	C7	1.469(3)	C29	C30	1.466(3)
C7	C8	1.333(3)	C30	C31	1.335(3)
C8	C9	1.484(3)	C31	C32	1.486(3)
C9	C10	1.515(3)	C32	C33	1.513(3)
C10	C11	1.535(3)	C33	C34	1.528(3)
C11	C12	1.526(3)	C34	C35	1.519(3)
C12	C13	1.393(3)	C35	C36	1.388(3)
C12	C17	1.388(3)	C35	C40	1.395(3)
C13	C14	1.390(4)	C36	C37	1.390(3)
C14	C15	1.387(4)	C37	C38	1.392(4)
C15	C16	1.395(4)	C38	C39	1.401(3)
C15	C18	1.511(3)	C38	C41	1.509(3)
C16	C17	1.389(3)	C39	C40	1.388(3)
C20	C21	1.515(4)	C43	C44	1.522(3)
C20	C22	1.517(4)	C43	C45	1.522(3)
C20	C23	1.523(4)	C43	C46	1.525(4)

Table 4. Selected Bond Angles

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C19	O2	C20	121.47(19)	C42	O5	C43	120.78(18)

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C19	N1	C11	122.3(2)	C42	N2	C34	121.6(2)
C2	C1	C6	120.3(2)	C25	C24	C29	120.6(2)
C3	C2	C1	120.3(3)	C26	C25	C24	120.1(3)
C4	C3	C2	119.9(3)	C27	C26	C25	120.0(2)
C3	C4	C5	120.2(3)	C26	C27	C28	120.1(2)
C4	C5	C6	120.4(3)	C27	C28	C29	120.5(3)
C1	C6	C5	118.8(2)	C24	C29	C28	118.7(2)
C1	C6	C7	122.1(2)	C24	C29	C30	122.8(2)
C5	C6	C7	119.1(2)	C28	C29	C30	118.5(2)
C8	C7	C6	126.5(2)	C31	C30	C29	126.9(2)
C7	C8	C9	120.6(2)	C30	C31	C32	121.0(2)
O1	C9	C8	122.0(2)	O4	C32	C31	123.0(2)
O1	C9	C10	121.5(2)	O4	C32	C33	122.0(2)
C8	C9	C10	116.5(2)	C31	C32	C33	115.0(2)
C9	C10	C11	113.3(2)	C32	C33	C34	114.4(2)
N1	C11	C10	109.33(18)	N2	C34	C33	109.15(18)
N1	C11	C12	113.29(17)	N2	C34	C35	113.46(17)
C12	C11	C10	110.39(18)	C35	C34	C33	110.25(18)
C13	C12	C11	119.0(2)	C36	C35	C34	119.7(2)
C17	C12	C11	122.2(2)	C36	C35	C40	118.6(2)
C17	C12	C13	118.7(2)	C40	C35	C34	121.7(2)
C14	C13	C12	120.7(2)	C35	C36	C37	120.8(2)
C15	C14	C13	121.1(2)	C36	C37	C38	121.2(2)
C14	C15	C16	117.8(2)	C37	C38	C39	117.7(2)
C14	C15	C18	121.4(2)	C37	C38	C41	121.4(2)
C16	C15	C18	120.8(2)	C39	C38	C41	120.9(2)
C17	C16	C15	121.6(2)	C40	C39	C38	121.3(2)
C12	C17	C16	120.1(2)	C39	C40	C35	120.4(2)

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O2	C19	N1	109.4(2)	O6	C42	O5	125.1(2)
O3	C19	O2	125.3(2)	O6	C42	N2	125.0(2)
O3	C19	N1	125.3(2)	N2	C42	O5	110.0(2)
O2	C20	C21	110.29(19)	O5	C43	C44	111.17(19)
O2	C20	C22	101.9(2)	O5	C43	C45	101.86(19)
O2	C20	C23	110.7(2)	O5	C43	C46	110.14(19)
C21	C20	C22	110.7(2)	C44	C43	C46	112.6(2)
C21	C20	C23	112.1(2)	C45	C43	C44	110.1(2)
C22	C20	C23	110.7(2)	C45	C43	C46	110.5(2)

Table 5. Selected Torsion Angles

A	B	C	D	Angle/°	A	B	C	D	Angle/°
O1	C9	C10	C11	20.6(3)	O4	C32	C33	C34	11.1(3)
N1	C11	C12	C13	-129.5(2)	N2	C34	C35	C36	-126.6(2)
N1	C11	C12	C17	54.3(3)	N2	C34	C35	C40	55.7(3)
C1	C2	C3	C4	1.1(5)	C24	C25	C26	C27	0.5(4)
C1	C6	C7	C8	-22.3(4)	C24	C29	C30	C31	-12.0(4)
C2	C1	C6	C5	0.2(4)	C25	C24	C29	C28	0.6(4)
C2	C1	C6	C7	-177.8(2)	C25	C24	C29	C30	-178.1(2)
C2	C3	C4	C5	0.1(5)	C25	C26	C27	C28	0.1(4)
C3	C4	C5	C6	-1.2(5)	C26	C27	C28	C29	-0.3(4)
C4	C5	C6	C1	1.0(4)	C27	C28	C29	C24	0.0(4)
C4	C5	C6	C7	179.0(3)	C27	C28	C29	C30	178.7(2)
C5	C6	C7	C8	159.7(3)	C28	C29	C30	C31	169.3(2)
C6	C1	C2	C3	-1.3(4)	C29	C24	C25	C26	-0.8(4)
C6	C7	C8	C9	177.4(2)	C29	C30	C31	C32	176.2(2)
C7	C8	C9	O1	-11.4(4)	C30	C31	C32	O4	-1.8(4)

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C7	C8	C9	C10	171.2(2)	C30	C31	C32	C33	-179.1(2)
C8	C9	C10	C11	-161.93(19)	C31	C32	C33	C34	-171.62(19)
C9	C10	C11	N1	82.9(2)	C32	C33	C34	N2	72.1(2)
C9	C10	C11	C12	-151.80(19)	C32	C33	C34	C35	-162.68(19)
C10	C11	C12	C13	107.5(2)	C33	C34	C35	C36	110.7(2)
C10	C11	C12	C17	-68.7(3)	C33	C34	C35	C40	-67.1(3)
C11	N1	C19	O2	-177.37(18)	C34	N2	C42	O5	176.35(18)
C11	N1	C19	O3	3.6(3)	C34	N2	C42	O6	-4.0(3)
C11	C12	C13	C14	-174.4(2)	C34	C35	C36	C37	-177.1(2)
C11	C12	C17	C16	175.2(2)	C34	C35	C40	C39	177.0(2)
C12	C13	C14	C15	-0.9(4)	C35	C36	C37	C38	0.2(4)
C13	C12	C17	C16	-1.1(3)	C36	C35	C40	C39	-0.7(3)
C13	C14	C15	C16	-1.1(4)	C36	C37	C38	C39	-1.0(3)
C13	C14	C15	C18	179.5(2)	C36	C37	C38	C41	177.2(2)
C14	C15	C16	C17	2.0(4)	C37	C38	C39	C40	1.0(3)
C15	C16	C17	C12	-0.9(4)	C38	C39	C40	C35	-0.1(4)
C17	C12	C13	C14	2.0(3)	C40	C35	C36	C37	0.7(3)
C18	C15	C16	C17	-178.5(2)	C41	C38	C39	C40	-177.3(2)
C19	O2	C20	C21	63.0(3)	C42	O5	C43	C44	60.3(3)
C19	O2	C20	C22	-179.4(2)	C42	O5	C43	C45	177.6(2)
C19	O2	C20	C23	-61.7(3)	C42	O5	C43	C46	-65.2(3)
C19	N1	C11	C10	-135.6(2)	C42	N2	C34	C33	-136.6(2)
C19	N1	C11	C12	100.9(2)	C42	N2	C34	C35	100.0(2)
C20	O2	C19	O3	0.8(3)	C43	O5	C42	O6	2.2(3)
C20	O2	C19	N1	-178.20(18)	C43	O5	C42	N2	-178.22(19)

Table 6. Hydrogen Bonds

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
N1	H1	O3[1]	0.91(4)	2.31(4)	3.167(3)	156(3)
N2	H2A	O6[2]	0.89(4)	2.35(4)	3.153(3)	151(3)

[1]+X,-1+Y,+Z; [2]+X,1+Y,+Z

3.11 References

1. For reviews on Organocatalytic Mannich reactions: (a) Bagheri, I.; Mohammadi, L.; Zadsirjan, V.; Heravi, M. M. *ChemistrySelect* **2021**, *6*, 1008. (b) Cai, X.-H.; Xie, B. *ARKIVOC* **2013**, *(i)*, 264. (c) Verkade, J. M. M.; Hemert, L. J. C. V.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29.
2. Nguyen, N. H.; Hughes, A. B.; Sleebs, B. E. *Curr. Org. Chem.* **2014**, *18*, 260.
3. For a review, see: Benohoud, M.; Hayashi, Y. In *Science of Synthesis: Asymmetric Organocatalysis 1*; List, B., Ed.; Georg Thieme Verlag: Stuttgart, 2012; pp 73−134. Examples of enamine catalysis in Mannich reactions leading to *β*-amino ketones: (a) Cordova, A.;́ Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F. *J. Am. Chem. Soc.* **2002**, *124*, 1842. (b) Yang, J. W.; Stadler, M.; List, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 609.
4. Selected enantioselective Mannich reactions with enol silanes: (a) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474. (b) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548. (c) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964. (d) Nakamura, Y.; Matsubara, R.; Kiyohara, H.; Kobayashi, S. *Org. Lett.* **2003**, *5*, 2481. (e) Kobayashi, S.; Arai, K.; Shimizu, H.; Ihori, Y.; Ishitani, H.; Yamashita, Y. *Angew. Chem. Int. Ed.* **2005**, *44*, 761. (f) Wang, Q.; Leutzsch, M.; van Gemmeren, M.; List, B. *J. Am. Chem. Soc.* **2013**, *135*, 15334.

5. Selected Enantioselective Mannich reactions with *β*-dicarbonyl compounds: (a) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. (b) Hatano, M.; Maki, T.; Moriyama, K.; Arinobe, M.; Ishihara, K. *J. Am. Chem. Soc.* **2008**, *130*, 16858. (c) Hatano, M.; Moriyama, K.; Maki, T.; Ishihara, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 3823. (d) Hatano, M.; Horibe, T.; Ishihara, K. *J. Am. Chem. Soc.* **2010**, *132*, 56. (e) Terada, M.; Sorimachi, K.; Uraguchi, D. *Synlett* **2006**, *1*, 133. (f) Puglisi, A.; Benaglia, M.; Annunziata, R.; Rossi, D. *Tetrahedron: Asymmetry* **2008**, *19*, 2258. See also ref 6(b).
6. Selected Enantioselective Mannich reactions with *β*-keto esters: (a) Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. *J. Am. Chem. Soc.* **2005**, *127*, 11256. (b) Tillman, A. L.; Ye, J.; Dixon, D. J. *Chem. Commun.* **2006**, 1191. (c) Ting, A.; Lou, S.; Schaus, S. E. *Org. Lett.* **2006**, *8*, 2003. (d) Kang, Y. K.; Kim, D. Y. *J. Org. Chem.* **2009**, *74*, 5734. (e) Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1525. (f) With *β*-cyano esters: Poulsen, T. B.; Alemparte, C.; Saaby, S.; Bella, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 2896. See also ref 5(d).
7. For a review, see: Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29. Selected enantioselective Mannich reactions with malonate esters: (a) Marigo, M.; Kjærsgaard, A.; Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Chem. Eur. J.* **2003**, *9*, 2359. (b) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048. (c) Song, J.; Shih, H.-W.; Deng, L. *Org. Lett.* **2007**, *9*, 603. (d) Hatano, M.; Horibe, T.; Ishihara, K. *Org. Lett.* **2010**, *12*, 3502. See also ref 6(b).
8. (a) Harkiss, A. H.; Bell, J. D.; Knuhtsen, A.; Jamieson, A. G.; Sutherland, A. *J. Org. Chem.* **2019**, *84*, 2879. (b) Bell, J. D.; Harkiss, A, H.; Nobis, D.; Malcolm, E.; Knuhtsen,

A.; Wellaway, C. R.; Jamieson, A. G.; Magennis, S. W.; Sutherland, A. *Chem. Commun.* **2020**, *56*, 1887. (c) Harkiss, A. H.; Sutherland, A. *J. Org. Chem.* **2018**, *83*, 535. (d) Bell, J. D.; Harkiss, A. H.; Wellaway, C. R.; Sutherland, A. *Org. Biomol. Chem.* **2018**, *16*, 6410.

9. (a) Abrunhosa-Thomas, I.; Plas, A.; Vogrig, A.; Kandepedu, N.; Chalard, P.; Troin, Y. *J. Org. Chem.* **2013**, *78*, 2511. (b) Abrunhosa-Thomas, I.; Plas, A.; Kandepedu, N.; Chalard, P.; Troin, Y. *Beilstein J. Org. Chem.* **2013**, *9*, 486.
10. Visseq, A.; Boibessot, T.; Nauton, L.; Thery, V.; Anizon, F.; Abrunhosa-Thomas, I. *Eur. J. Org. Chem.* **2019**, 7686.
11. Davis, F. A.; Wu, Y. *Org. Lett.* **2004**, *6*, 1269.
12. Bourque, E. M. J.; Skerlj, R. WO 2020264292.
13. Bridger, G. J.; McEachern, E. J.; Skerlj, R.; Schols, D. WO 2004093817.
14. Graham, J. D.; Michael, M.; Jun Q. G. WO 9806401.
15. Pissarnitski, D. A.; Josien, H. B.; Smith, E. M.; Clader, J. W.; Asberom, T.; Guo, T.; Hobbs, D. W. US 20050085506.
16. For the synthesis of substituted piperidines: (a) Trost, B. M.; Sarkar, D.; Bera, N. *Adv. Synth. Catal.* **2019**, *361*, 5648. (b) Lahosa, A.; Yus, M.; Foubelo, F. *J. Org. Chem.* **2019**, *84*, 7331. (c) Aznar, F.; Garcia, A-B.; Quinones, N.; Cabal, M-P. *Synthesis*. **2008**, *3*, 479. (d) Bell, J. D.; Harkiss, A. H.; Wellaway, C. R.; Sutherland, A. *Org. Biomol. Chem.* **2018**, *16*, 6410.
17. For reviews on organocatalytic aza-Michael reactions: (a) Vinogradov, M. G.; Turova, O. V.; Zlotin, S. G. *Org. Biomol. Chem.* **2019**, *17*, 3670. (b) Amara, Z.; Caron, J.; Joseph, D.

Nat. Prod. Rep. **2013**, *30*, 1211. (c) Enders, D.; Wang, C.; Liebich, J. X. *Chem. Eur. J.* **2009**, *15*, 11058.

18. For reviews on organocatalyzed IMAMRs: (a) Bates, R. W.; Ko, W.; Barat, V. *Org. Biomol. Chem*. **2020**, *18*, 810. (b) Sanchez-Rosello, M.; Acena, J. L.; Simon-Fuentes, A.; Pozo, C. D. *Chem. Soc. Rev.* **2014**, **43**, 7430.
19. Stereoselective conjugate additions to α,β-unsaturated ketones using organocatalysis are a challenging objective because of issues such as difficulty of formation of congested iminium ions from ketones, along with other unfavorable issues such as poor control over iminium ion geometry and lower electron affinity of ketones towards iminium ion formation as compared to aldehydes. The use of primary amine catalysts, which have been unpopular because of the notion of an unfavorable imine-enamine equilibria, has, to some extent, been able to circumvent the issues associated with secondary amine catalysis of ketones. See: Bartoli, G.; Melchiorre, P. *Synlett*, **2008**, *12*, 1759.
20. Ishimaru, K.; Kojima, T. *J. Org. Chem.* **2000**, *65*, 8395.
21. Xiong, Y.; Mei, H.; Han, J.; Li, G.; Pan, Y. *Tetrahedron. Lett.* **2014**, *55*, 2476.
22. Trost, B. M.; Jonasson, C. *Angew. Chem. Int. Ed.* **2003**, *42*, 2063.
23. Khandare, S. P.; Reddy, P. O.; Prasad, K. R. *Org. Lett.* **2020**, *22*, 7273.
24. Valero, G.; Leon, C. M.; Moyano, A. *Asymm. Catal.* **2015**, *2*, 7-16.
25. For a review on enantioselective organocatalytic reactions with *N*-carbamoyl imines, see: Vesely, J.; Rios, R. *Chem. Soc. Rev.* **2014**, *43*, 611. Reports on *N*-carbamoyl imines in Mannich or Mannich/aza-Michael reactions: See ref 6a and also (b) Enders, D.; Goddertz, D. P.; Beceno, C.; Raabe, G. *Adv. Synth. Catal.* **2010**, *352*, 2863.

26. Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen Jr., E. G. E.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138.

27. Casy, G.; Sutherland, A. G.; Taylor, R. J. K.; Urben, P. G. *Synthesis* **1989**, *10*, 767.

28. Li, B.; Berliner, M.; Buzon, R.; Chiu, C. K.-F.; Colgan, S. T.; Kaneko, T.; Keene, N.; Kissel, W.; Le, T.; Leeman, K. R.; Marquez, B.; Morris, R.; Newell, L.; Wunderwald, S.; Witt, M.; Weaver, J.; Zhang, Z.; Zhang, Z. *J. Org. Chem.* **2006**, *71*, 9045.

29. Kim, S.; Kang, S.; Kim, G.; Lee, Y. *J. Org. Chem.* **2016**, *81*, 4048.

30. Jiang, C.; Zhong, F.; Lu, Y. *Beilstein J. Org. Chem.* **2012**, *8*, 1279.

31. Pelletier, J. C.; Cava, M. P. *Synthesis.* **1987**, 474.

32. Zhou, Y.; You, Y.; Wang, Z-H.; Zhang, X-M.; Xu, X-Y.; Yuan, W-C. *Eur. J. Org. Chem.* **2019**, 3112.

33. Bohm, M.; Proksch, K.; Mahrwald, R. *Eur. J. Org. Chem.* **2013**, 1046.

34. Tillman, A. L.; Ye, J.; Dixon, D. J. *Chem. Commun.* **2006**, 1191.

35. Goodman, C. G.; Do, D. T.; Johnson, J. S. *Org. Lett.* **2013**, *15*, 2446.

36. Mbofana, C. T.; Miller, S. J. *J. Am. Chem. Soc.* **2014**, *136*, 3285.

37. Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964.

38. Wu, Y-. K.; Rawal, V. H. *Org. Biomol. Chem.* **2019**, *17*, 8827.

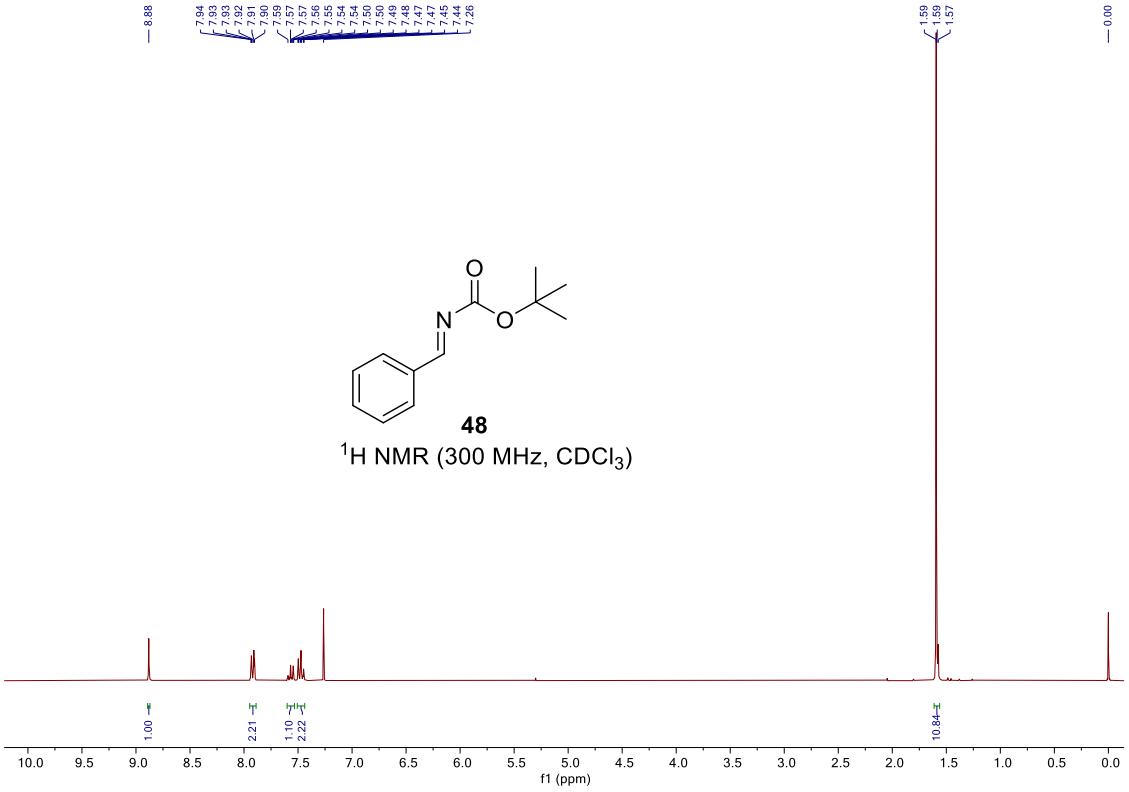
39. Loy, N. S. Y.; Singh, A.; Xu, X.; Park, C-. M. *Angew. Chem. Int. Ed*. **2013**, *52*, 2212.

40. Massaro, N. P.; Stevens, J. C.; Chatterji, A.; Sharma, I. *Org. Lett.* **2018**, *20*, 7585.

41. Casy, G.; Sutherland, A.G.; Taylor, R. J. K.; Urben, P. G. *Synthesis*, **1989**, *10*, 767.

42. Adriaenssens, L. V.; Hartley, R. C. *J. Org. Chem.* **2007**, *72*, 10287.

3.12 Selected ^{1}H and ^{13}C NMR spectral data



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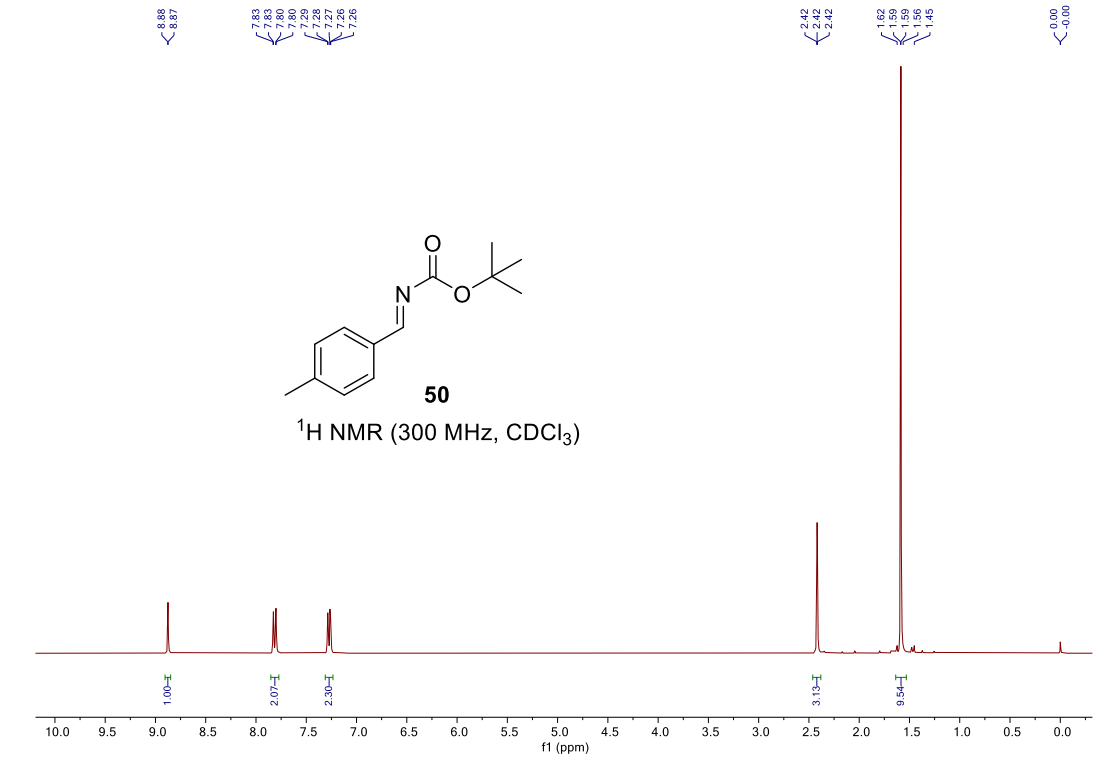

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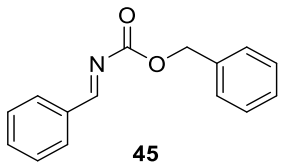

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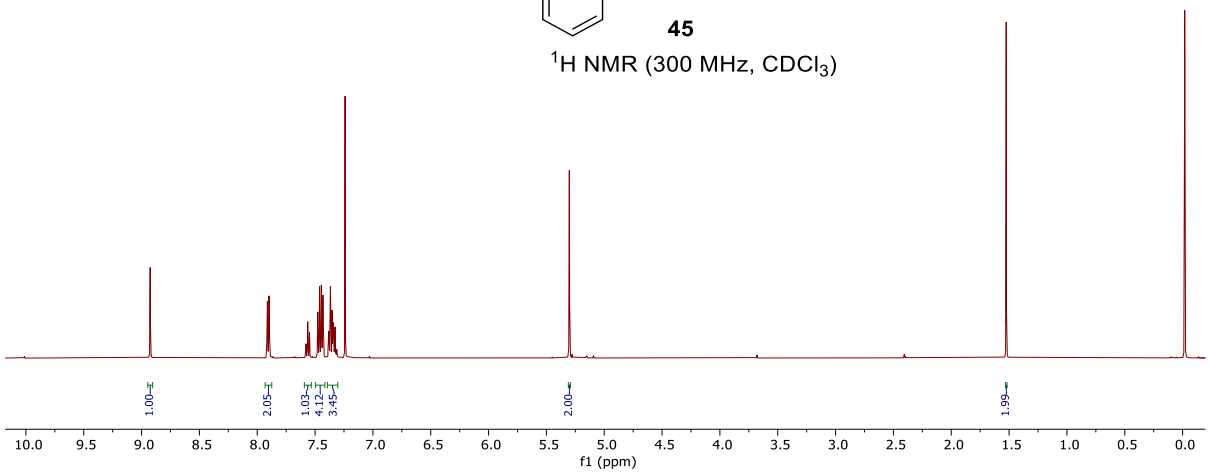

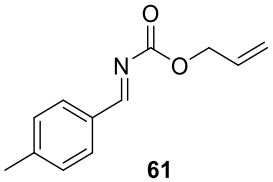

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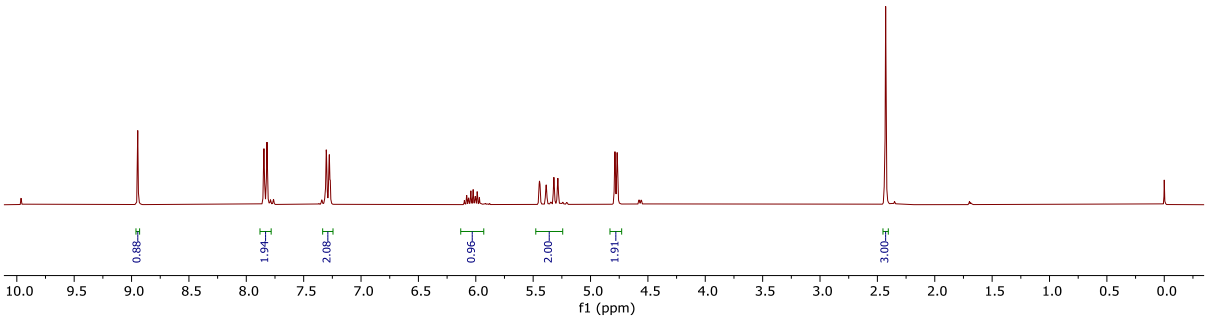

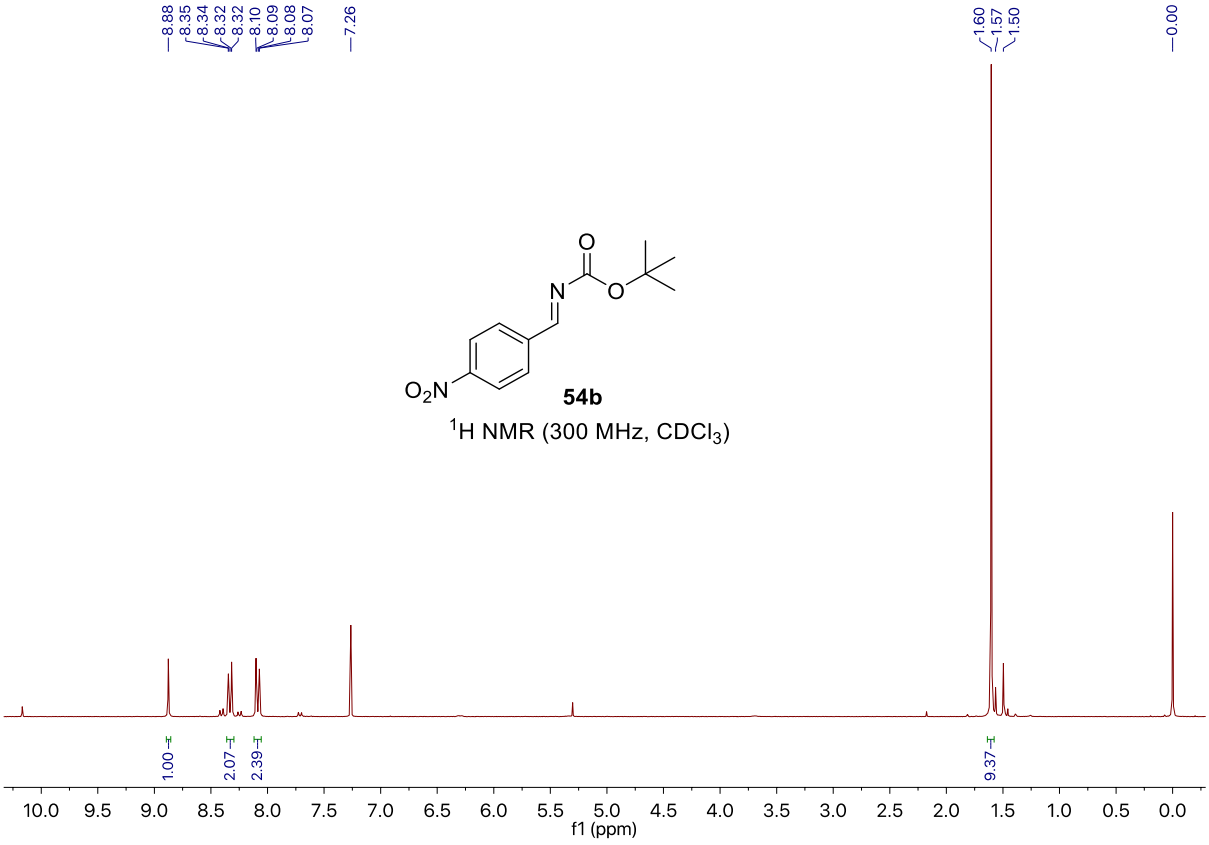

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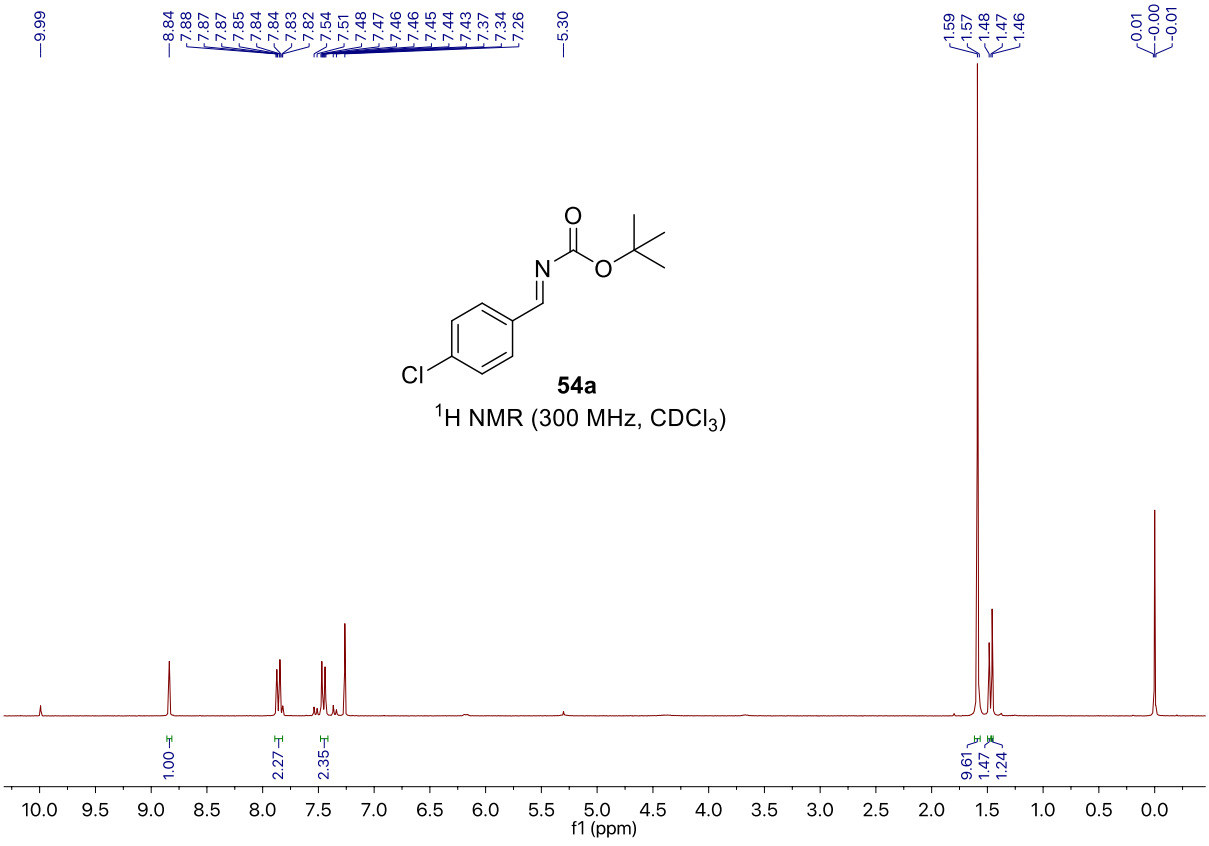

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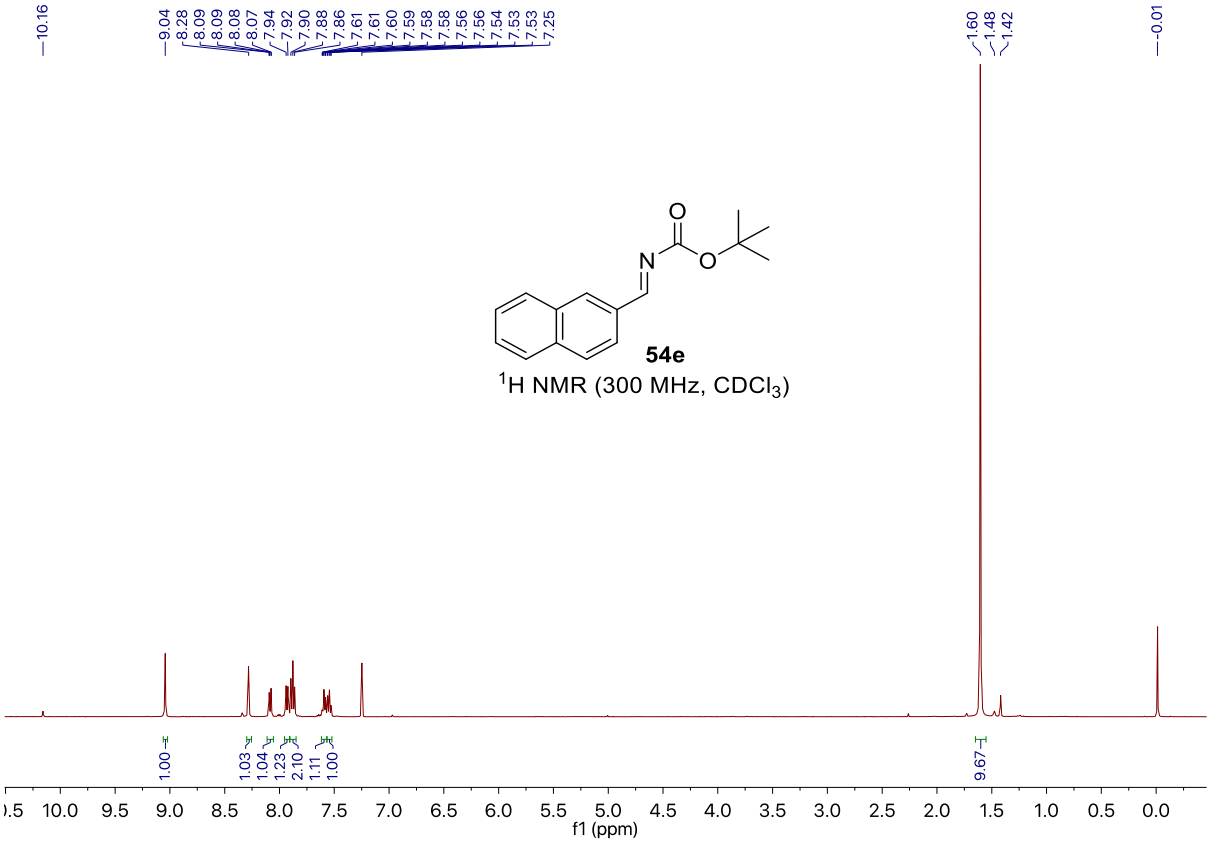

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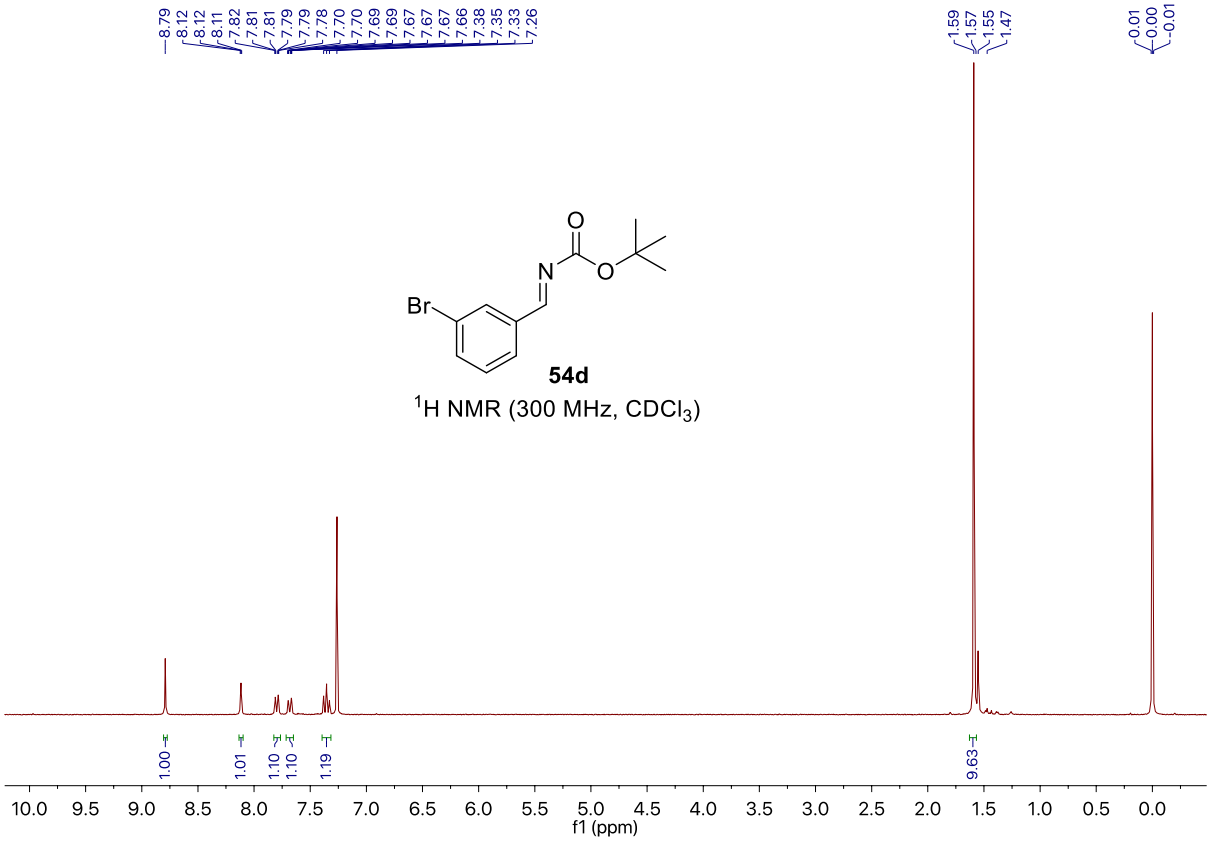

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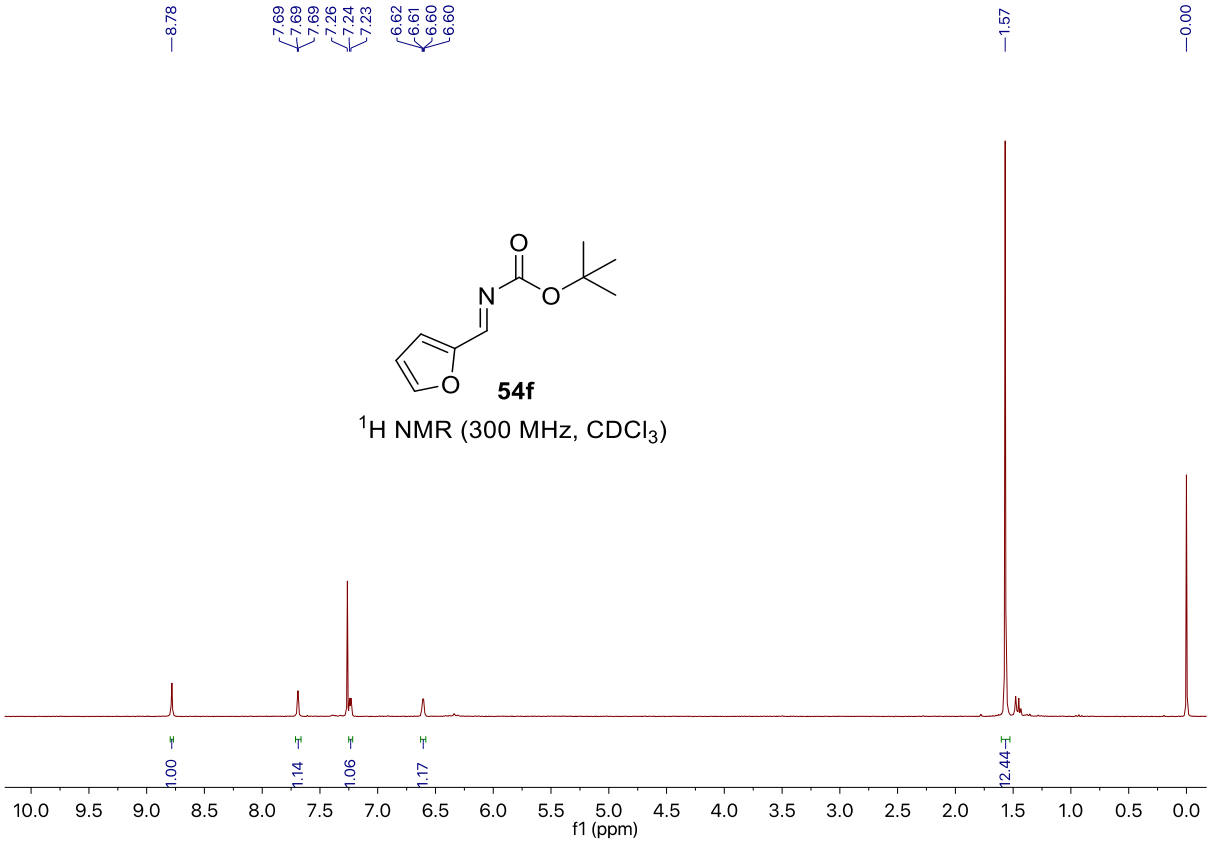

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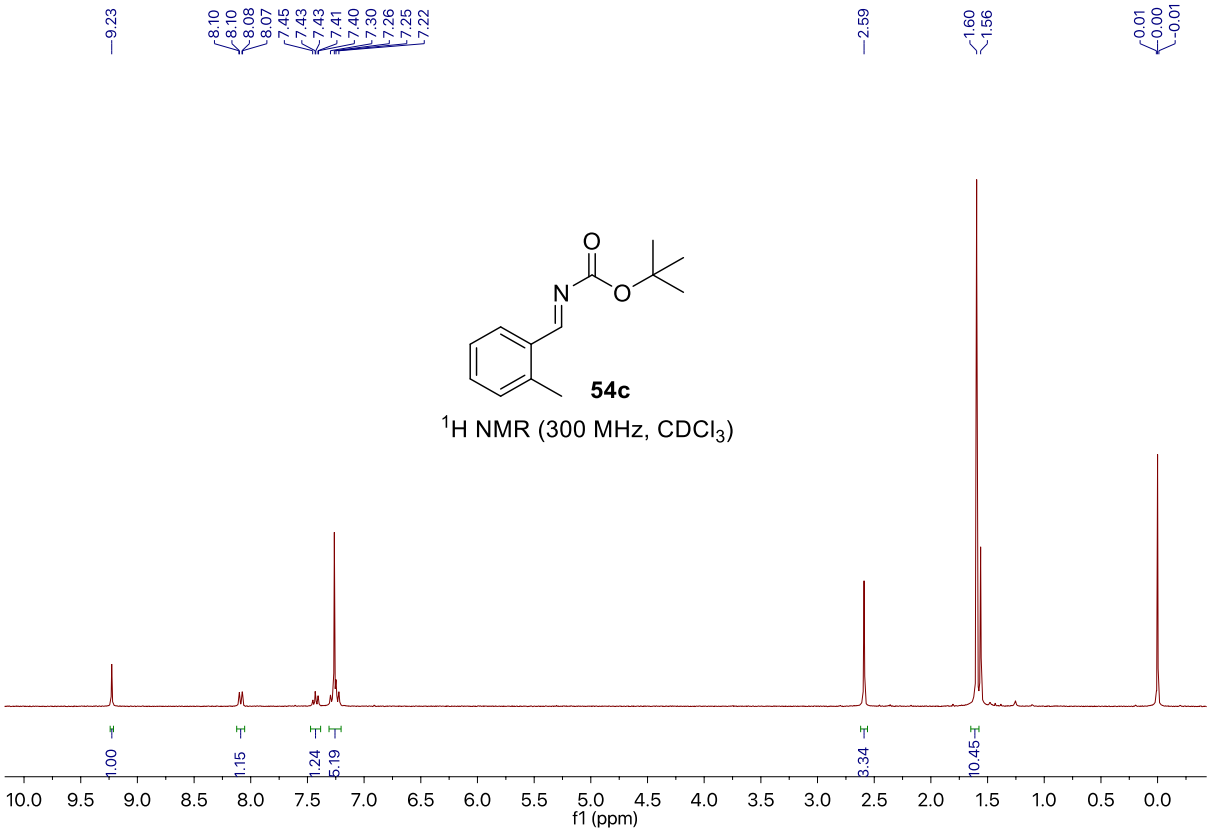

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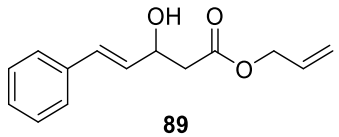

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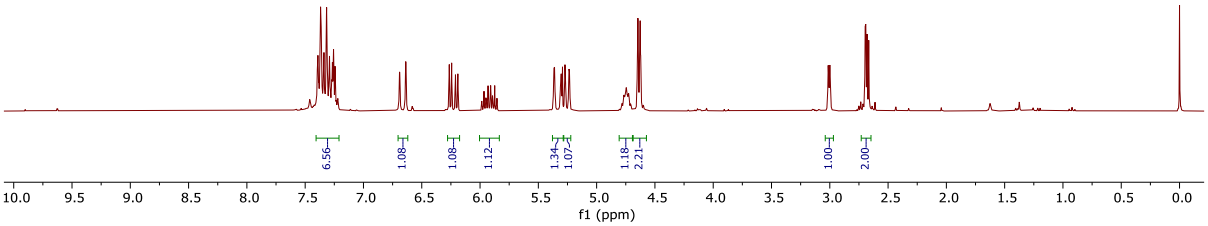

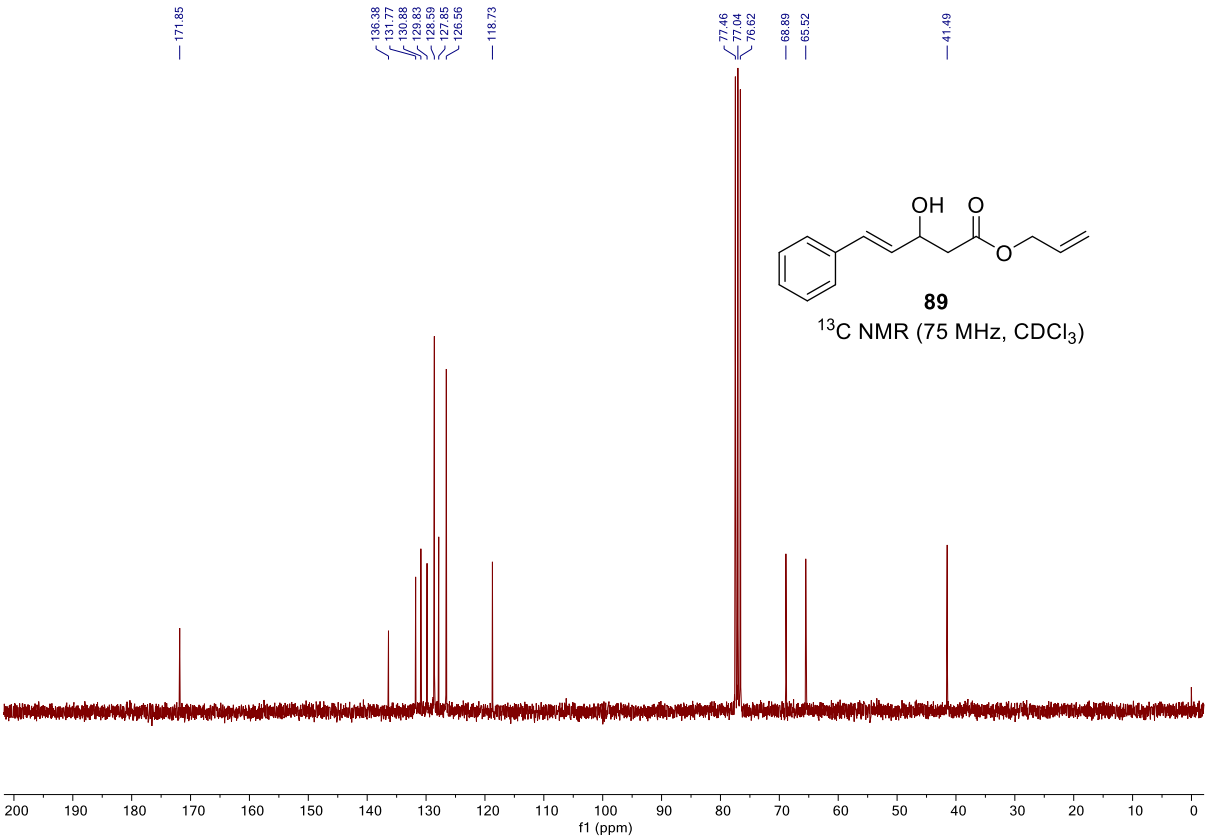

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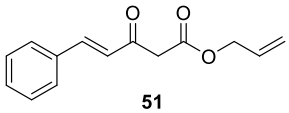

51

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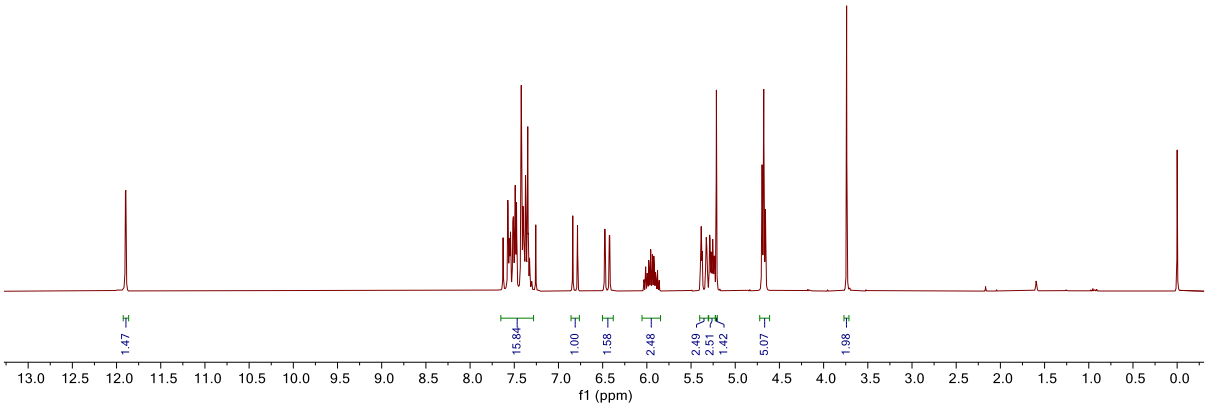

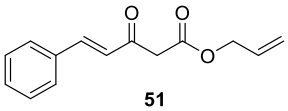

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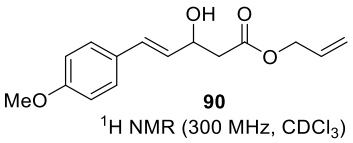

90

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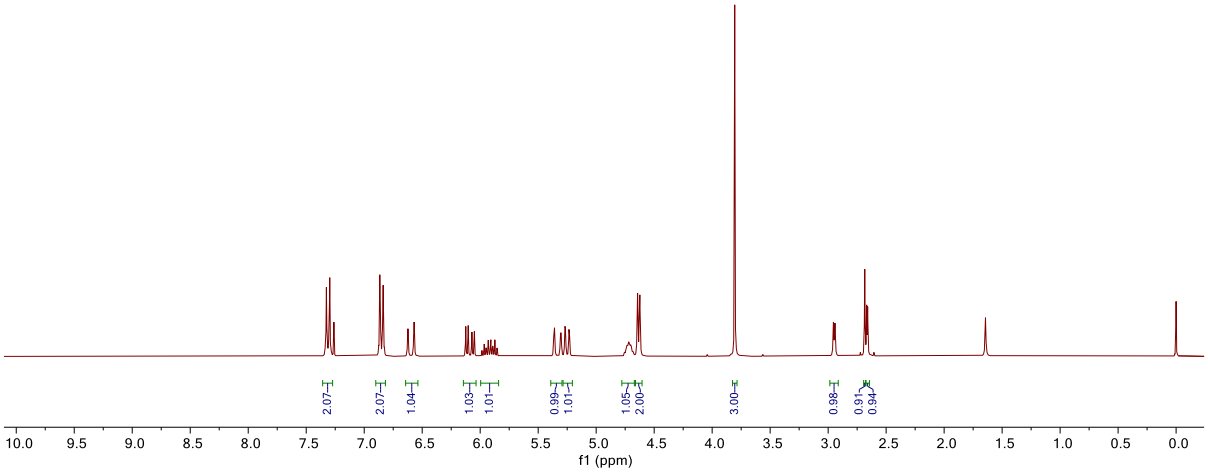

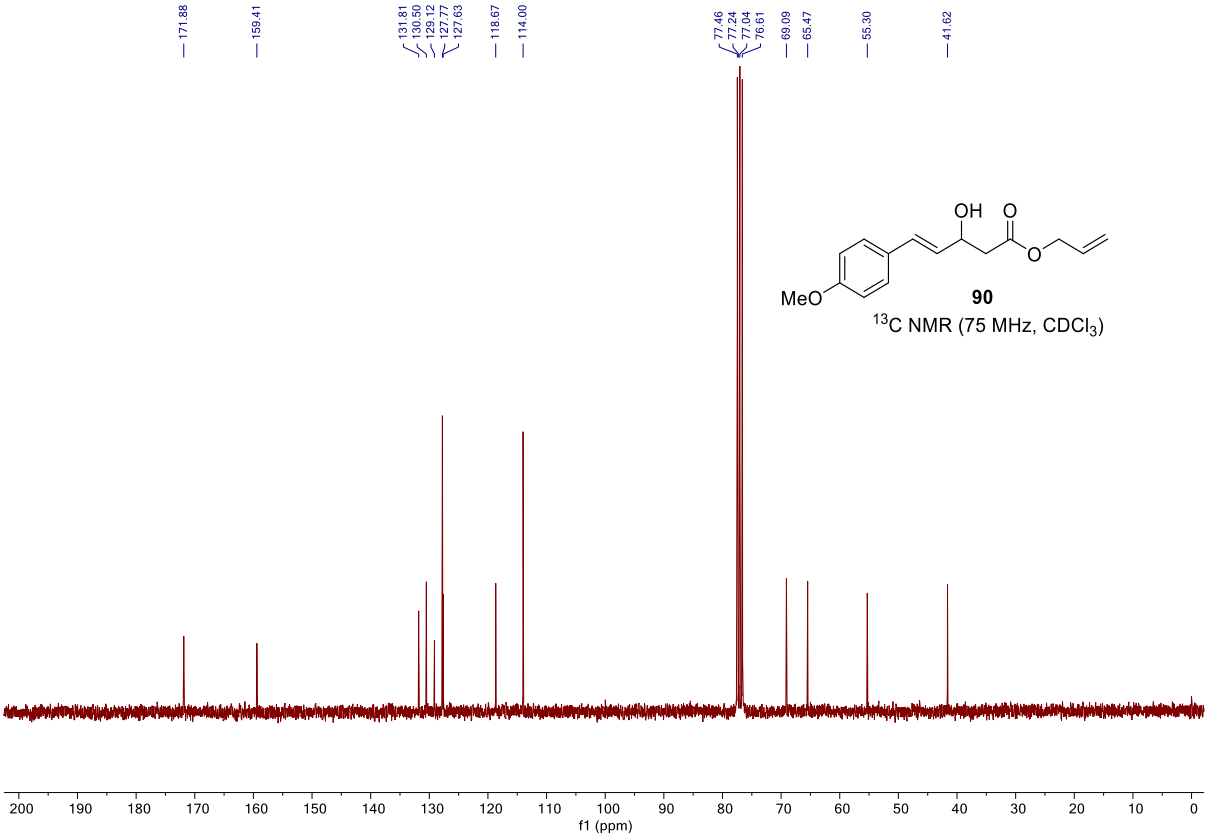

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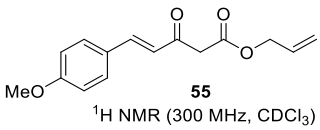

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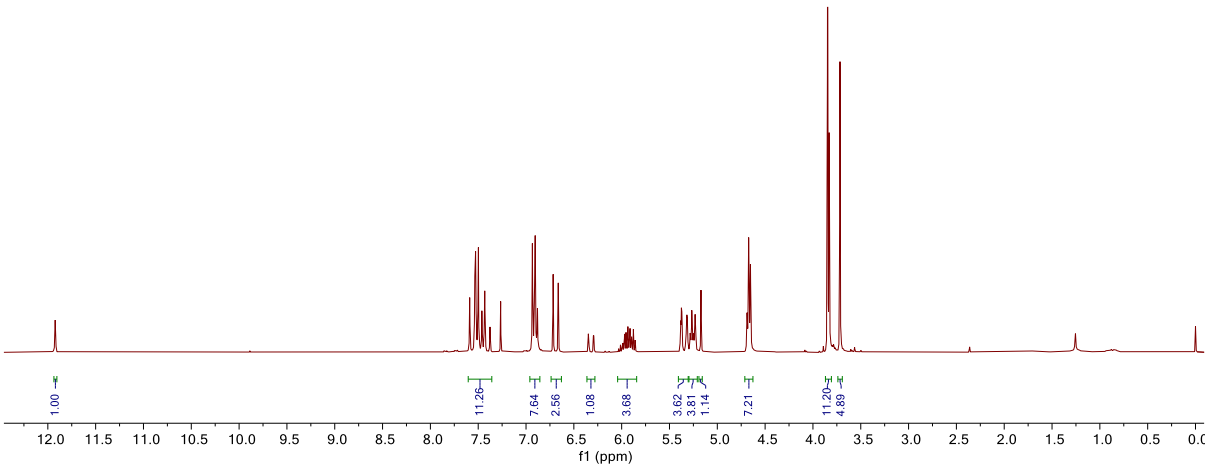

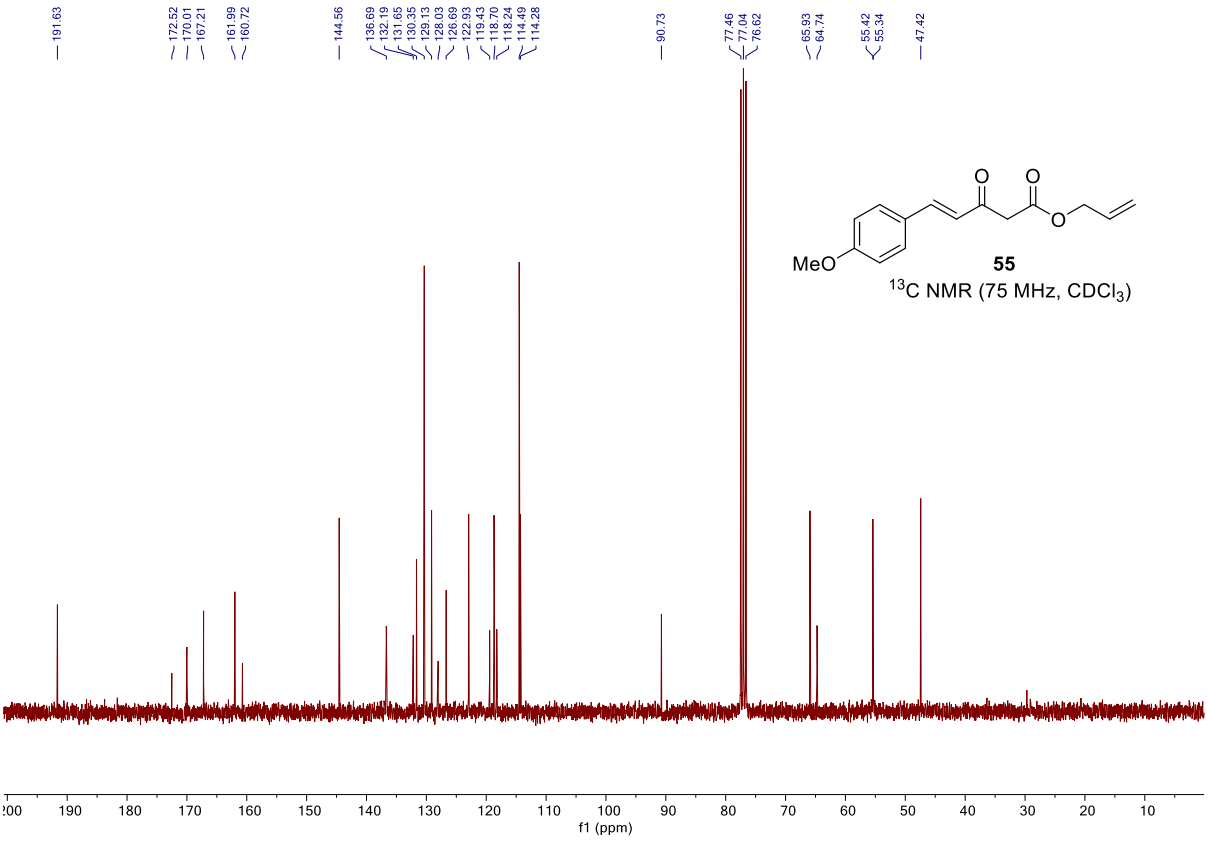

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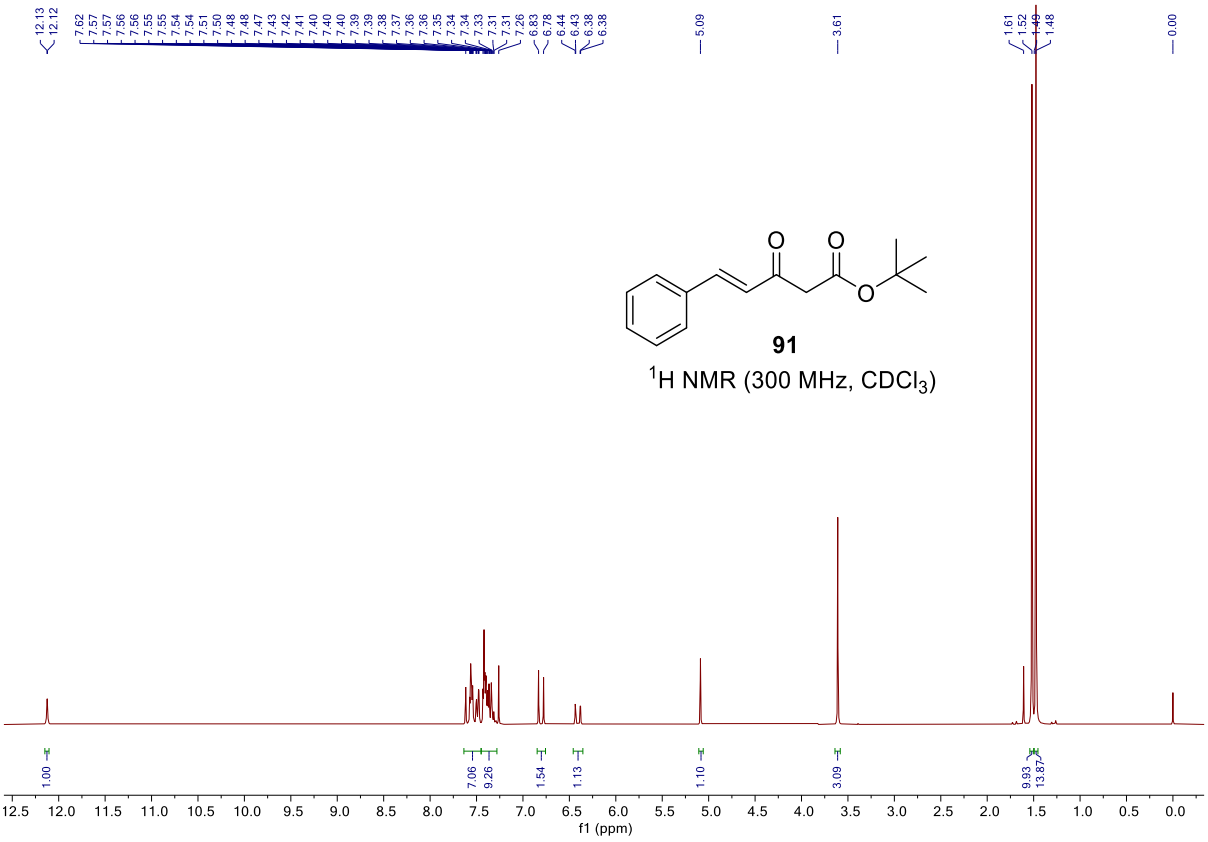
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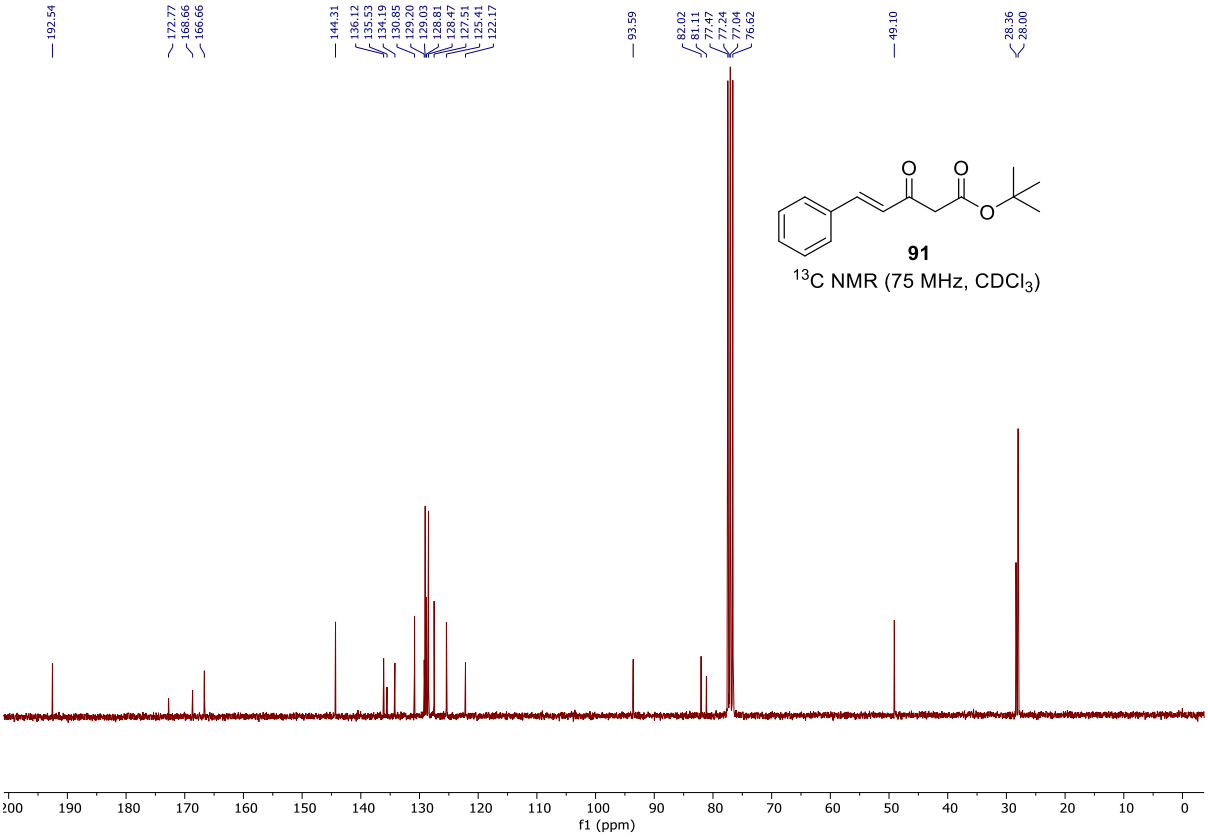
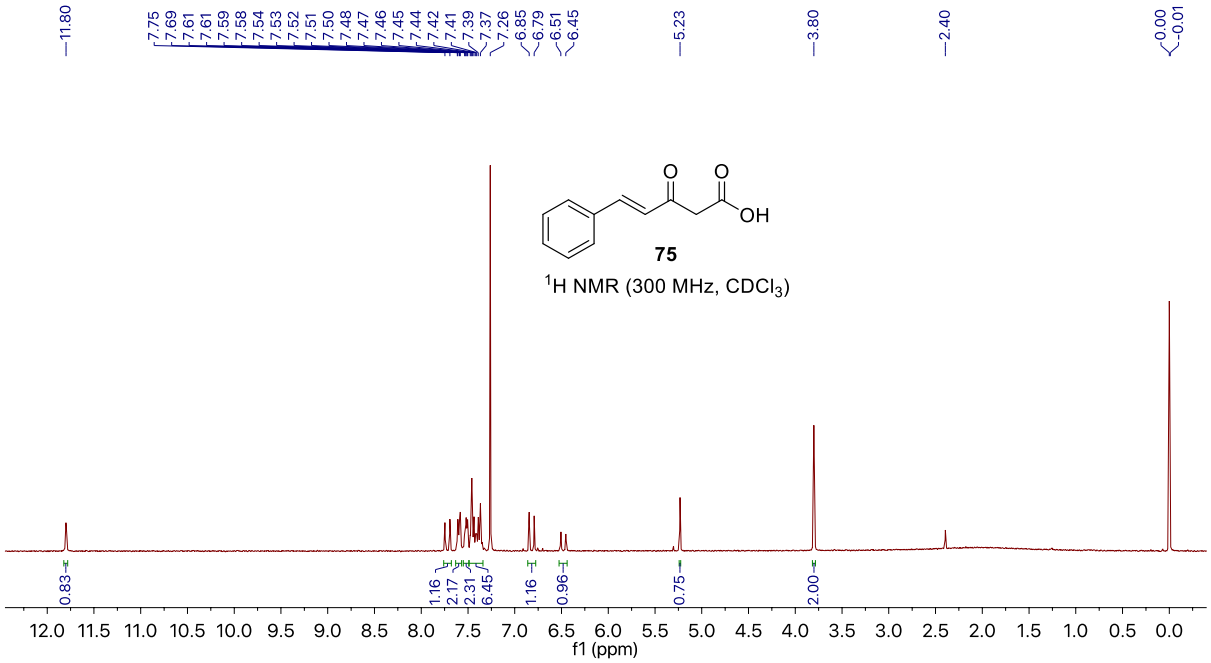
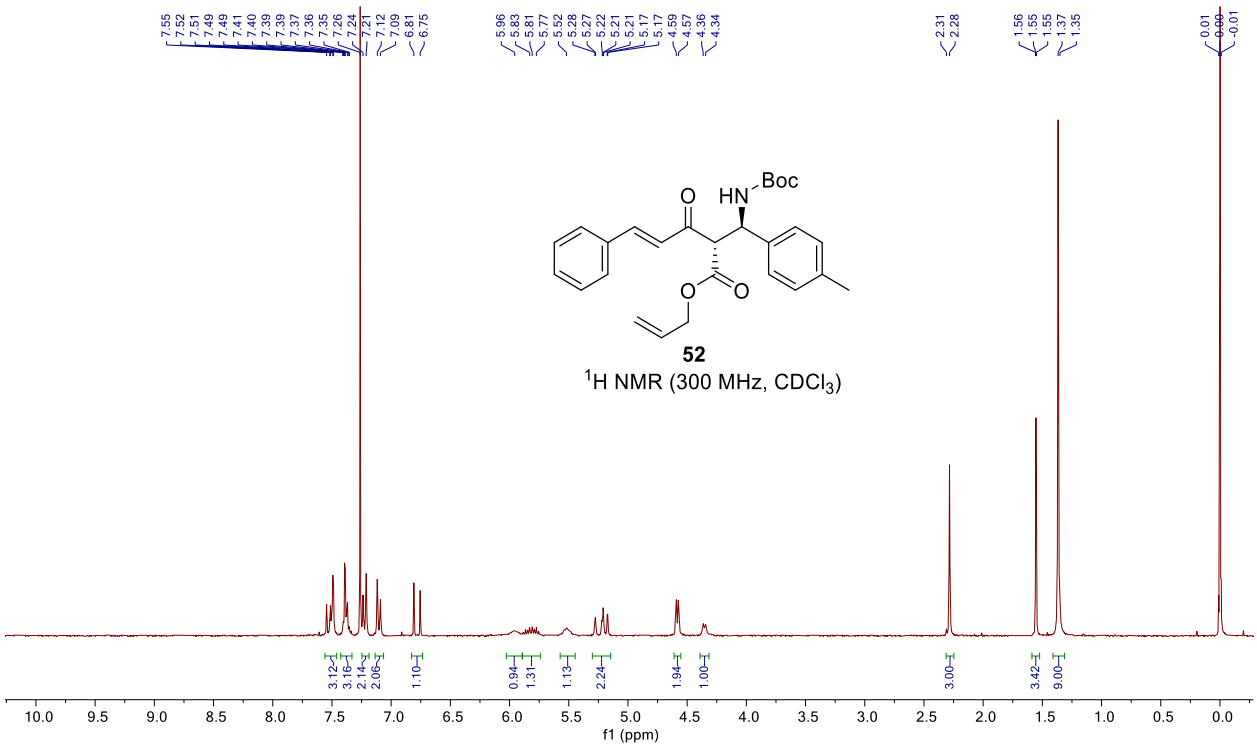
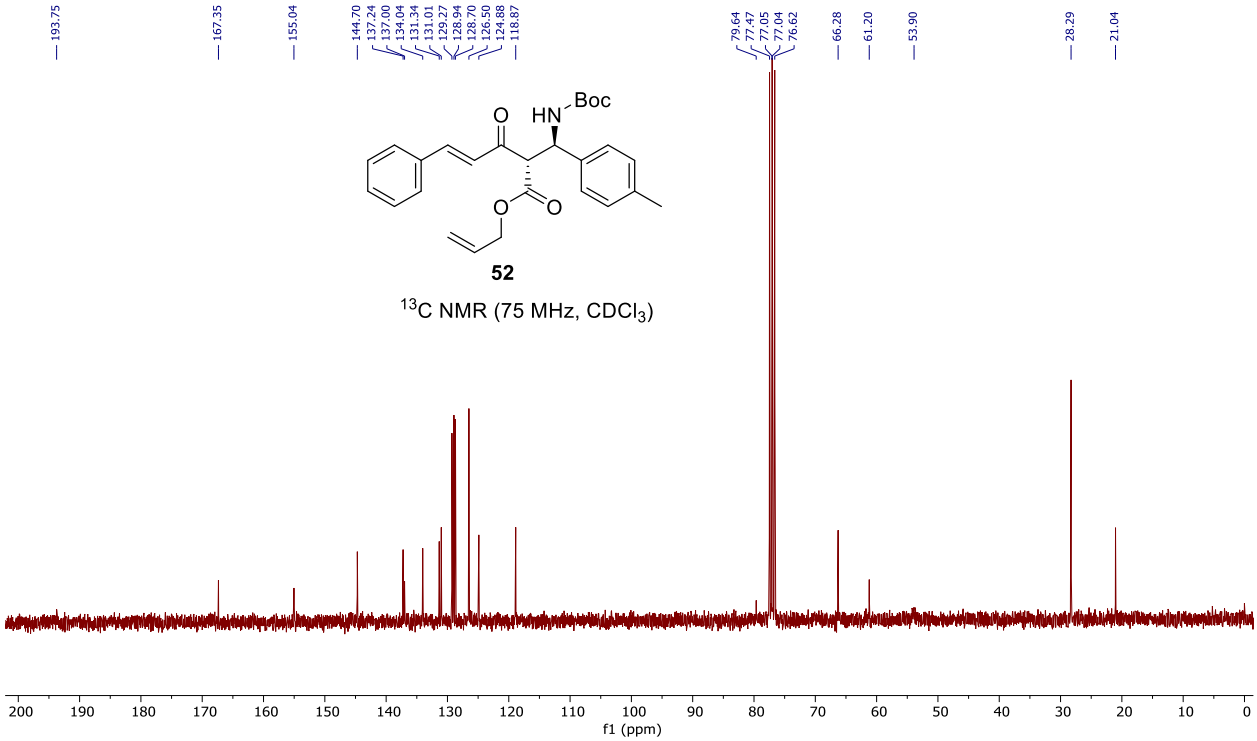
7.54
7.54
7.51
7.50
7.48
7.48
7.47
7.43
7.42
7.41
7.40
7.40
7.40
7.39
7.39
7.38
7.37
7.36
7.36
7.35
7.34
7.34
7.33
7.31
7.31
7.26
6.83
6.78
6.44
6.43
6.38
6.38
5.09
3.61
1.61
1.52
1.49
1.48
0.00
O
O
O
91
1H NMR (300 MHz, CDCl3)
1.00
7.06
9.26
1.54
1.13
1.10
3.09
9.93
13.87
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


192.54
172.77
168.66
166.66
144.31
136.12
135.53
134.19
130.85
129.20
129.03
128.81
128.47
127.51
125.41
122.17
93.59
82.02
81.11
77.47
77.24
77.04
76.62
49.10
28.36
28.00
O
O
O
91
13C NMR (75 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

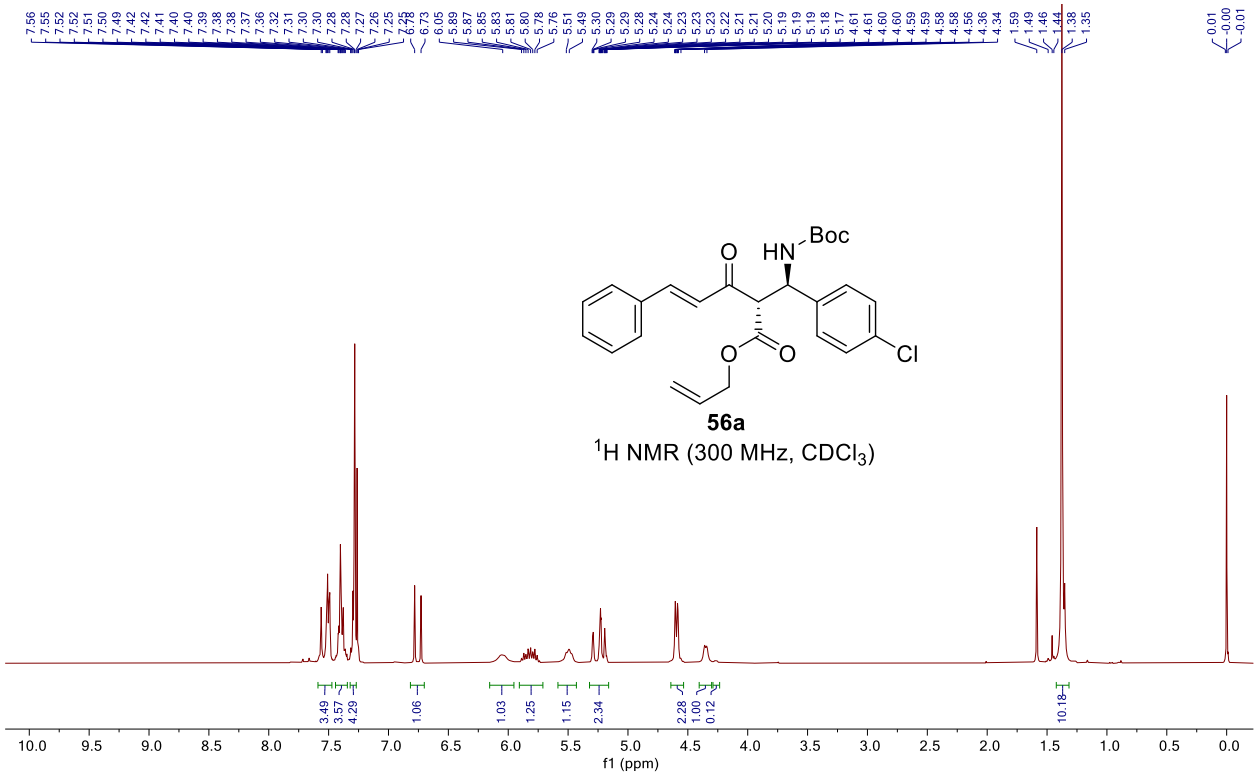

11.80
7.75
7.69
7.61
7.61
7.59
7.58
7.54
7.53
7.52
7.51
7.50
7.48
7.47
7.46
7.45
7.44
7.42
7.41
7.39
7.37
7.26
6.85
6.79
6.51
6.45
5.23
3.80
2.40
0.00
-0.01
O
O
OH
75
1H NMR (300 MHz, CDCl3)
0.83
1.16
2.17
2.31
6.45
1.16
0.96
0.75
2.00
f1 (ppm)


7.55
7.52
7.51
7.49
7.49
7.41
7.40
7.39
7.39
7.37
7.36
7.35
7.26
7.24
7.21
7.12
7.09
6.81
6.75
5.96
5.83
5.81
5.77
5.52
5.28
5.27
5.22
5.21
5.21
5.17
5.17
4.59
4.57
4.36
4.34
2.31
2.28
1.56
1.55
1.55
1.37
1.35
0.01
0.00
-0.01
O
HN
Boc
O
O
52
1H NMR (300 MHz, CDCl3)
3.12
3.16
2.14
2.06
1.10
0.94
1.31
1.13
2.24
1.94
1.00
3.00
3.42
9.00
f1 (ppm)



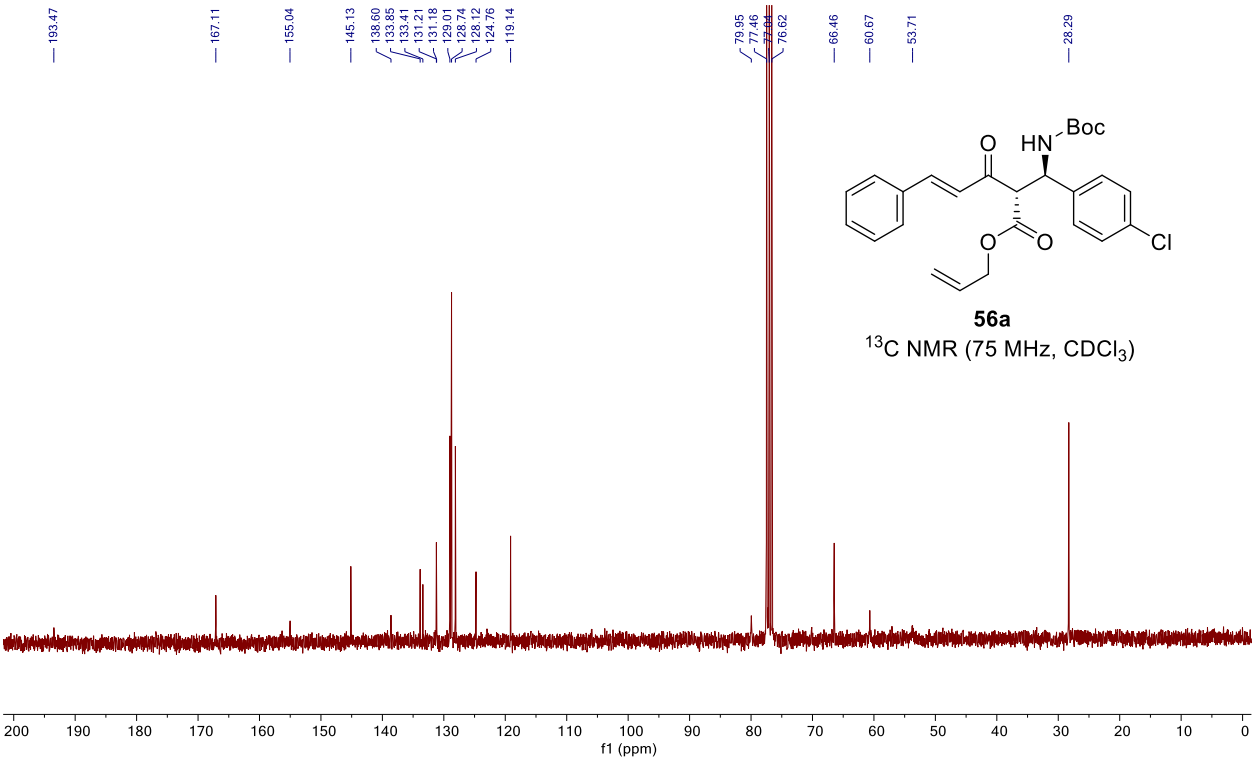
52

^{13}C NMR (75 MHz, $CDCl_3$)



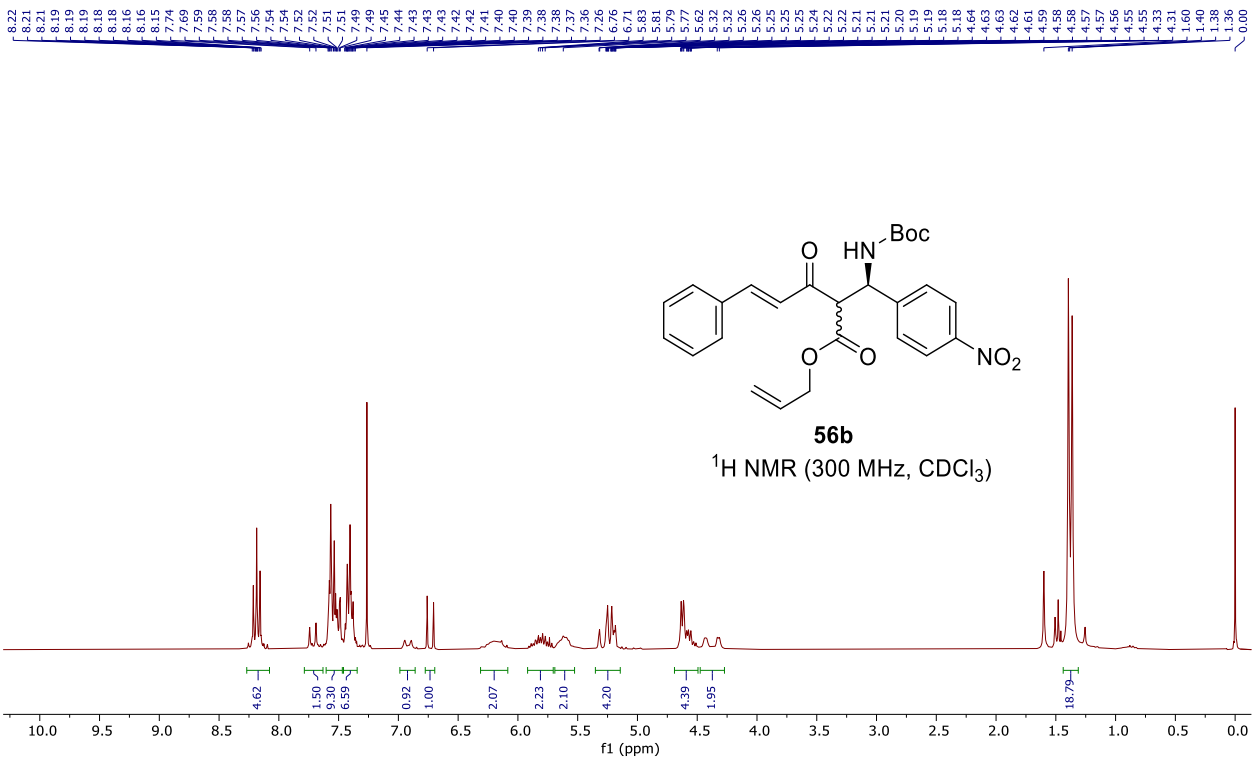
56a

^{1}H NMR (300 MHz, $CDCl_3$)



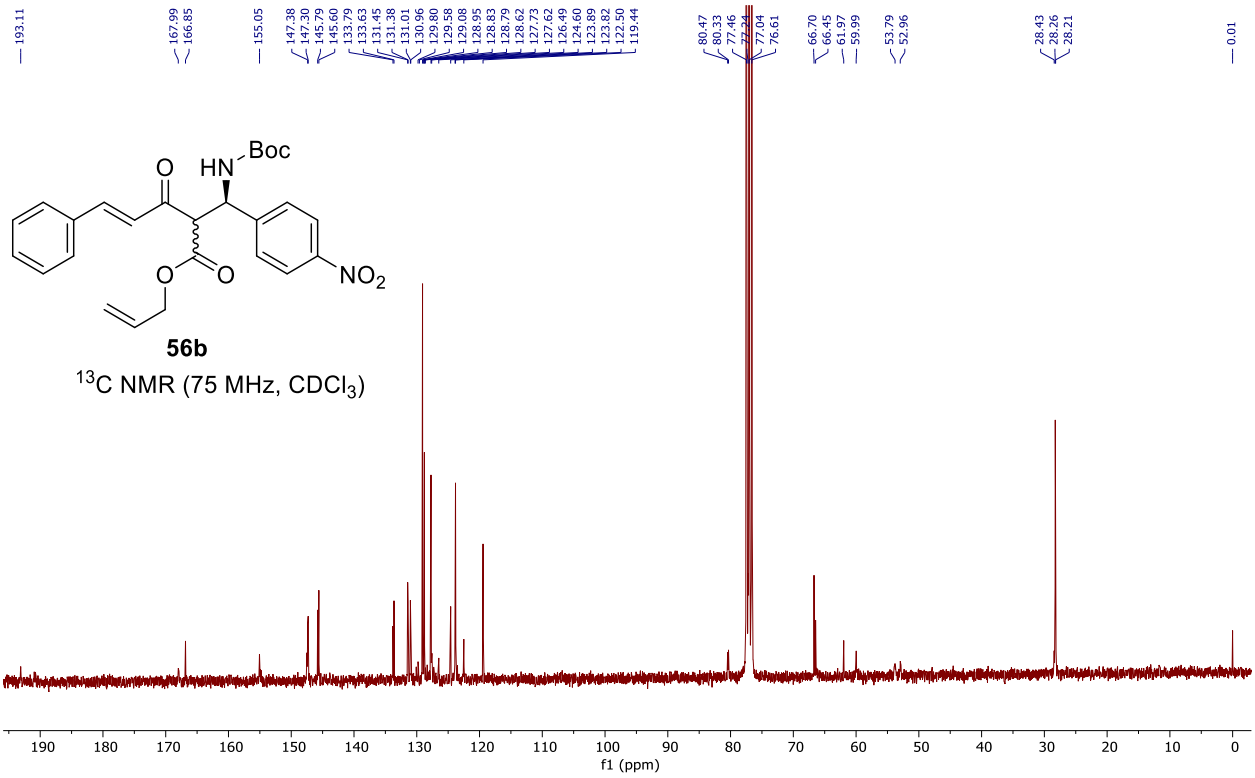
56a

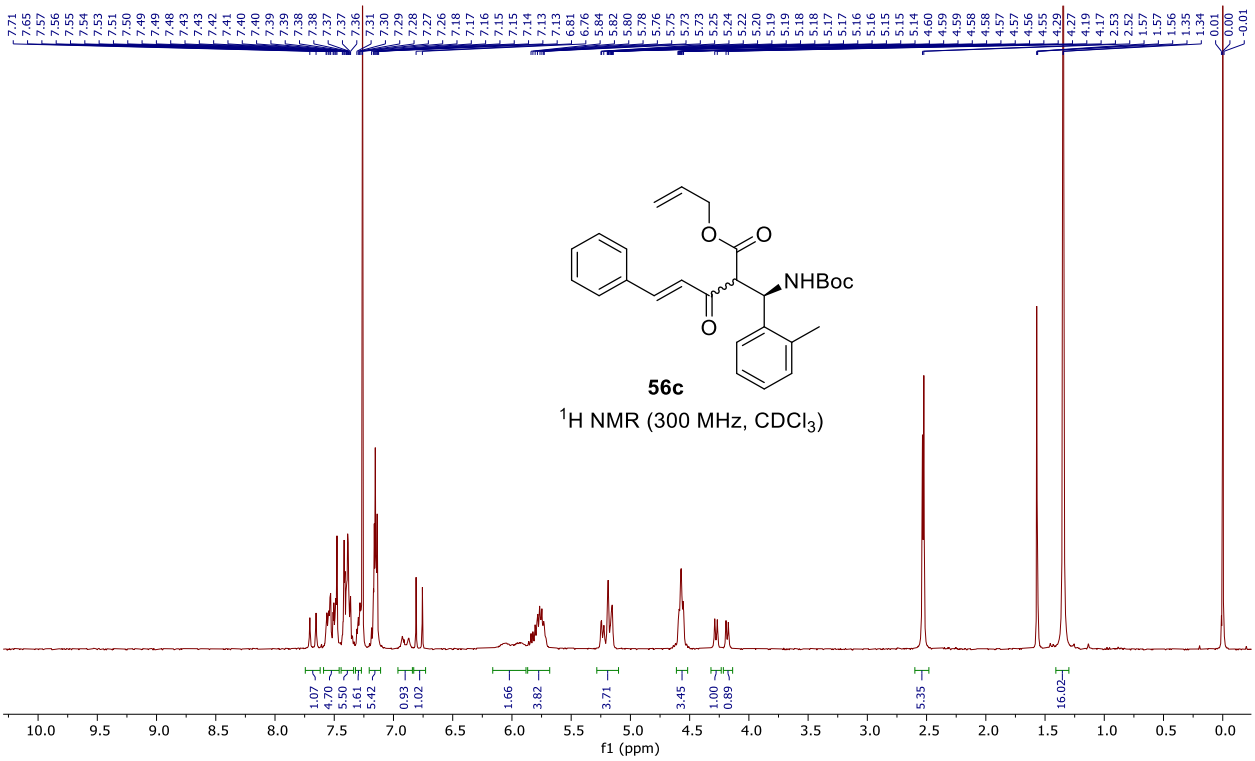
^{13}C NMR (75 MHz, $CDCl_3$)

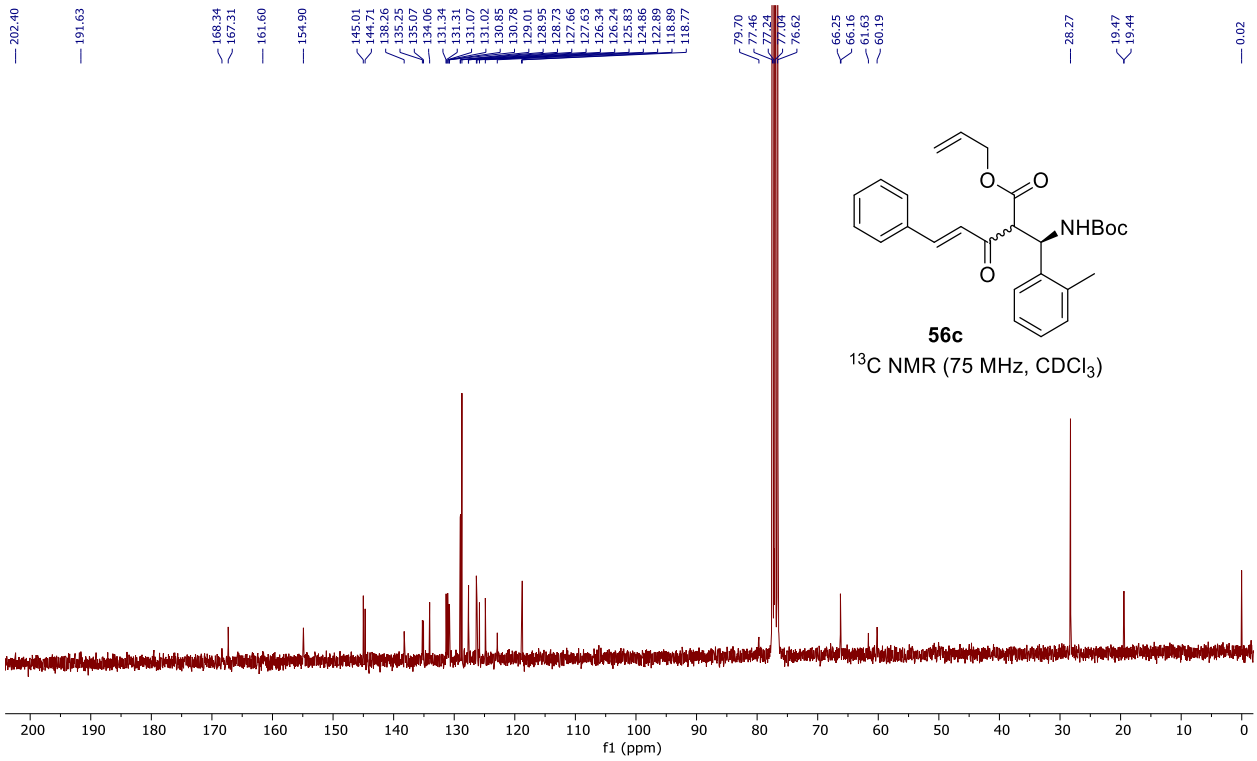


56b

^{1}H NMR (300 MHz, $CDCl_3$)

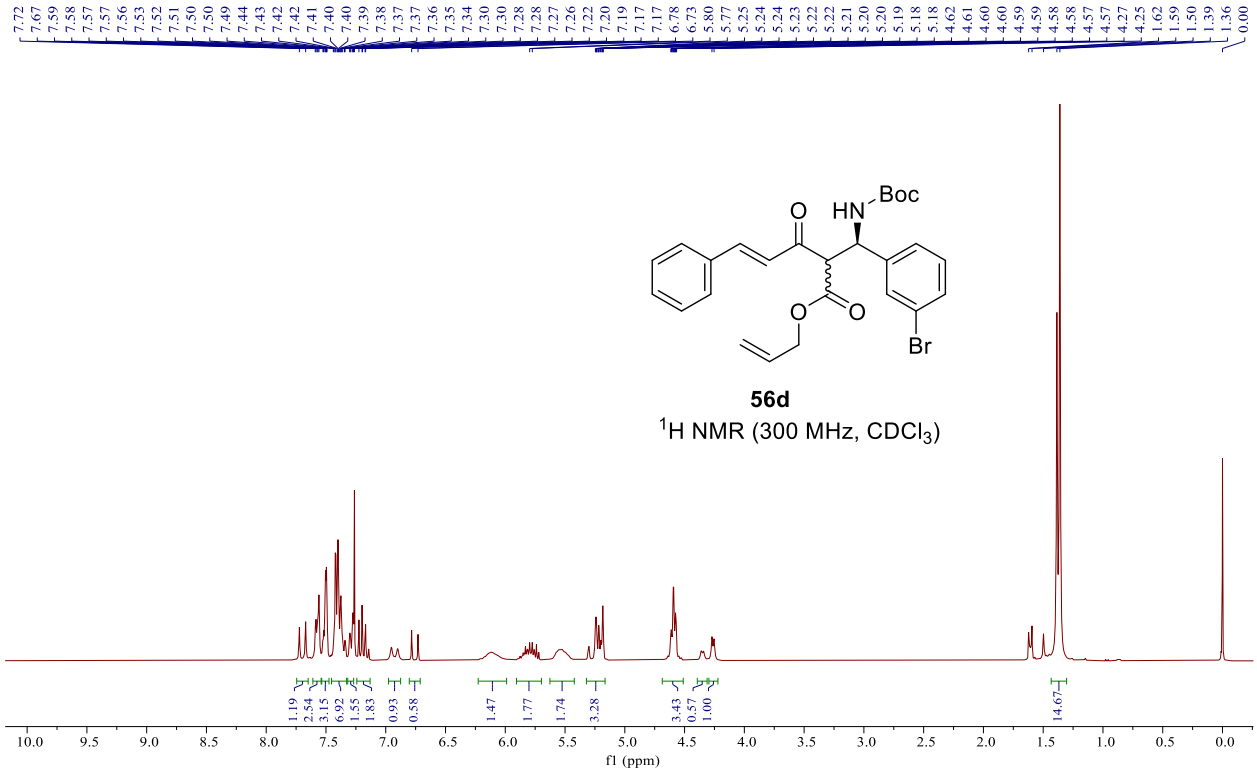

193.11
167.99
166.85
155.05
147.38
147.30
145.79
145.60
133.79
133.63
131.45
131.38
131.01
130.96
129.80
129.58
129.08
128.95
128.83
128.79
128.62
127.73
127.62
126.49
124.60
123.89
123.82
122.50
119.44
80.47
80.33
77.46
77.24
77.04
76.61
66.70
66.45
61.97
59.99
53.79
52.96
28.43
28.26
28.21
0.01
O
HN
Boc
O
O
O
NO2
56b
13C NMR (75 MHz, CDCl3)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.71
7.65
7.57
7.56
7.55
7.54
7.53
7.51
7.50
7.49
7.49
7.48
7.43
7.43
7.42
7.41
7.40
7.40
7.39
7.39
7.38
7.38
7.37
7.37
7.36
7.31
7.30
7.29
7.28
7.27
7.26
7.18
7.17
7.16
7.15
7.15
7.14
7.13
7.13
6.81
6.76
5.84
5.82
5.80
5.78
5.76
5.75
5.73
5.73
5.25
5.24
5.22
5.20
5.19
5.19
5.18
5.18
5.17
5.17
5.16
5.16
5.15
5.15
5.14
4.60
4.59
4.59
4.58
4.58
4.57
4.57
4.56
4.55
4.29
4.27
4.19
4.17
2.53
2.52
1.57
1.57
1.56
1.35
1.34
0.01
0.00
-0.01
O
O
O
NHBoc
56c
1H NMR (300 MHz, CDCl3)
1.07
4.70
5.50
1.61
5.42
0.93
1.02
1.66
3.82
3.71
3.45
1.00
0.89
5.35
16.02
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



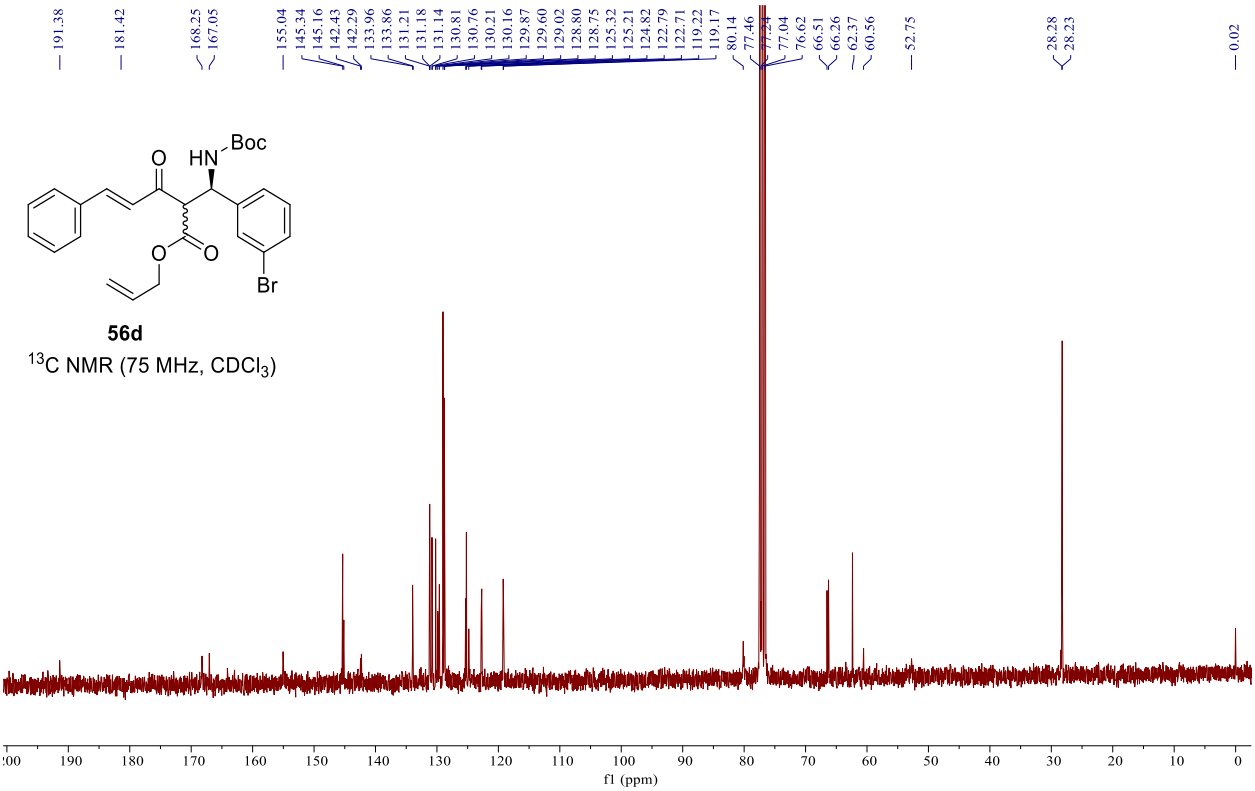
56c

^{13}C NMR (75 MHz, $CDCl_3$)



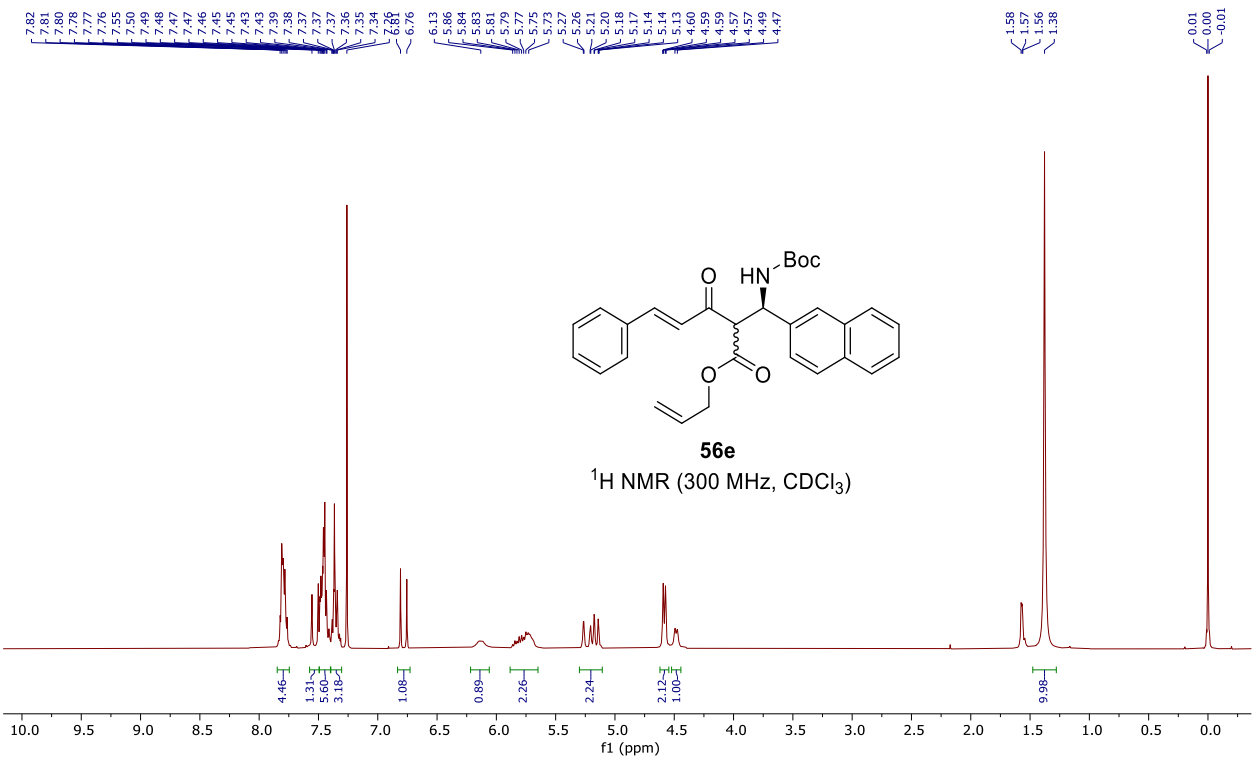
56d

^{1}H NMR (300 MHz, $CDCl_3$)



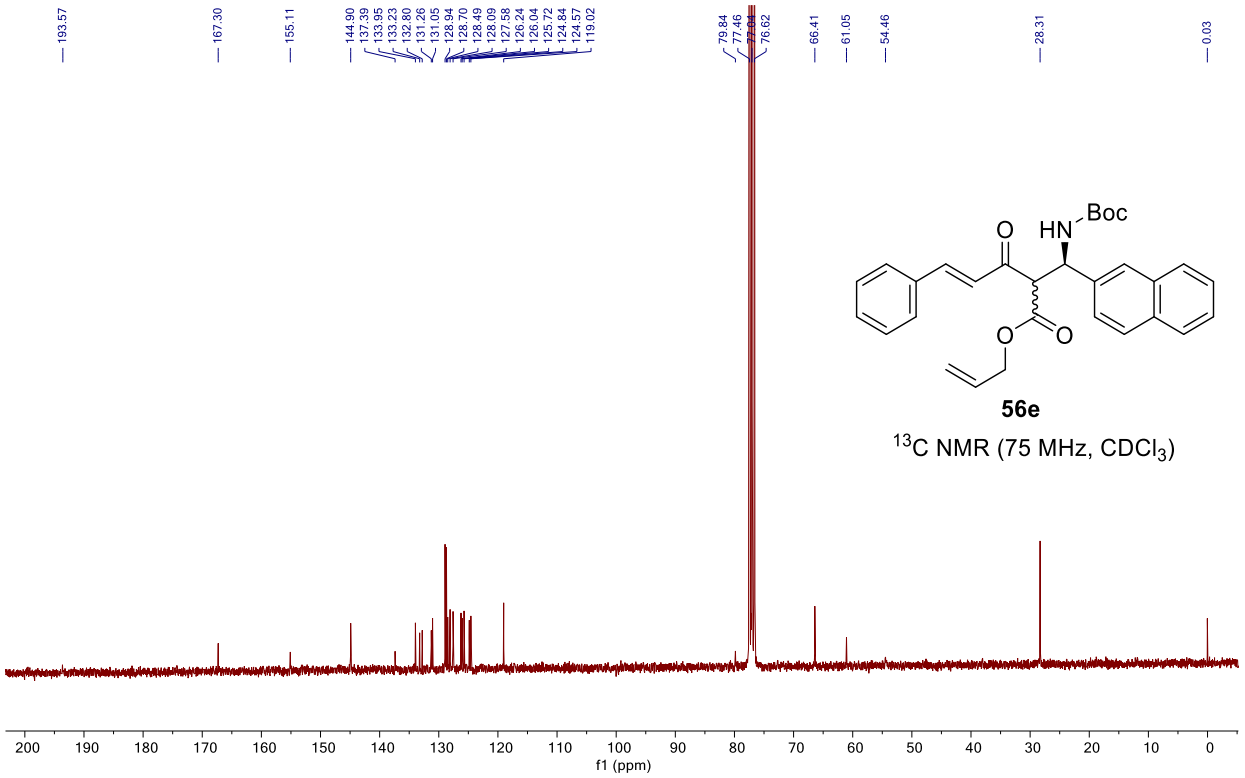
56d

^{13}C NMR (75 MHz, $CDCl_3$)



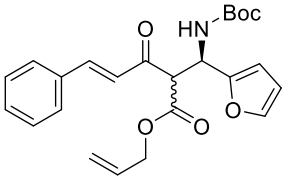
56e

^{1}H NMR (300 MHz, $CDCl_3$)



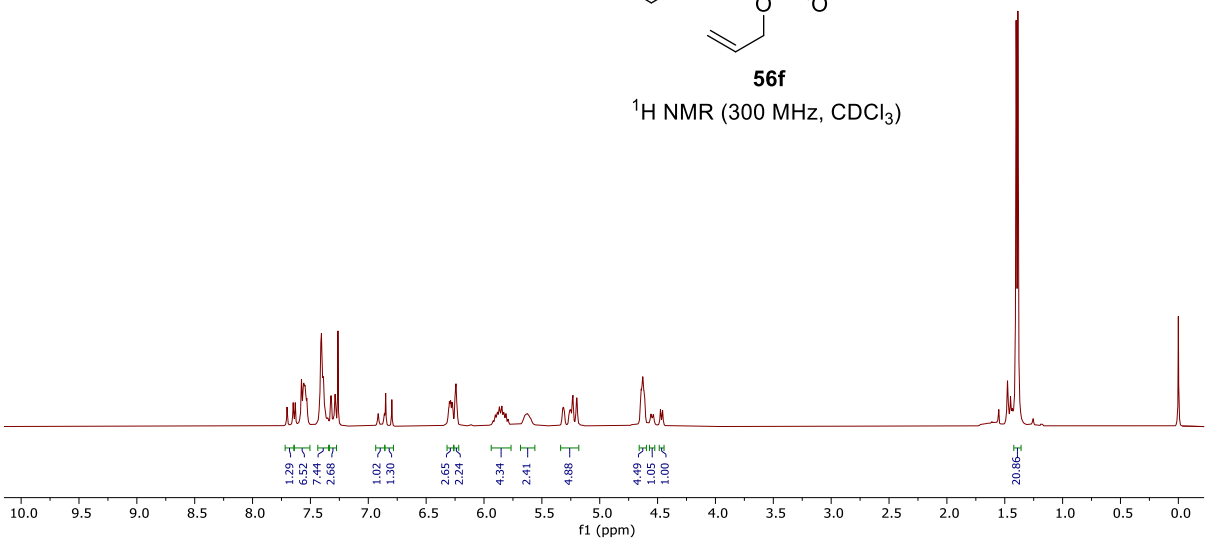
56e

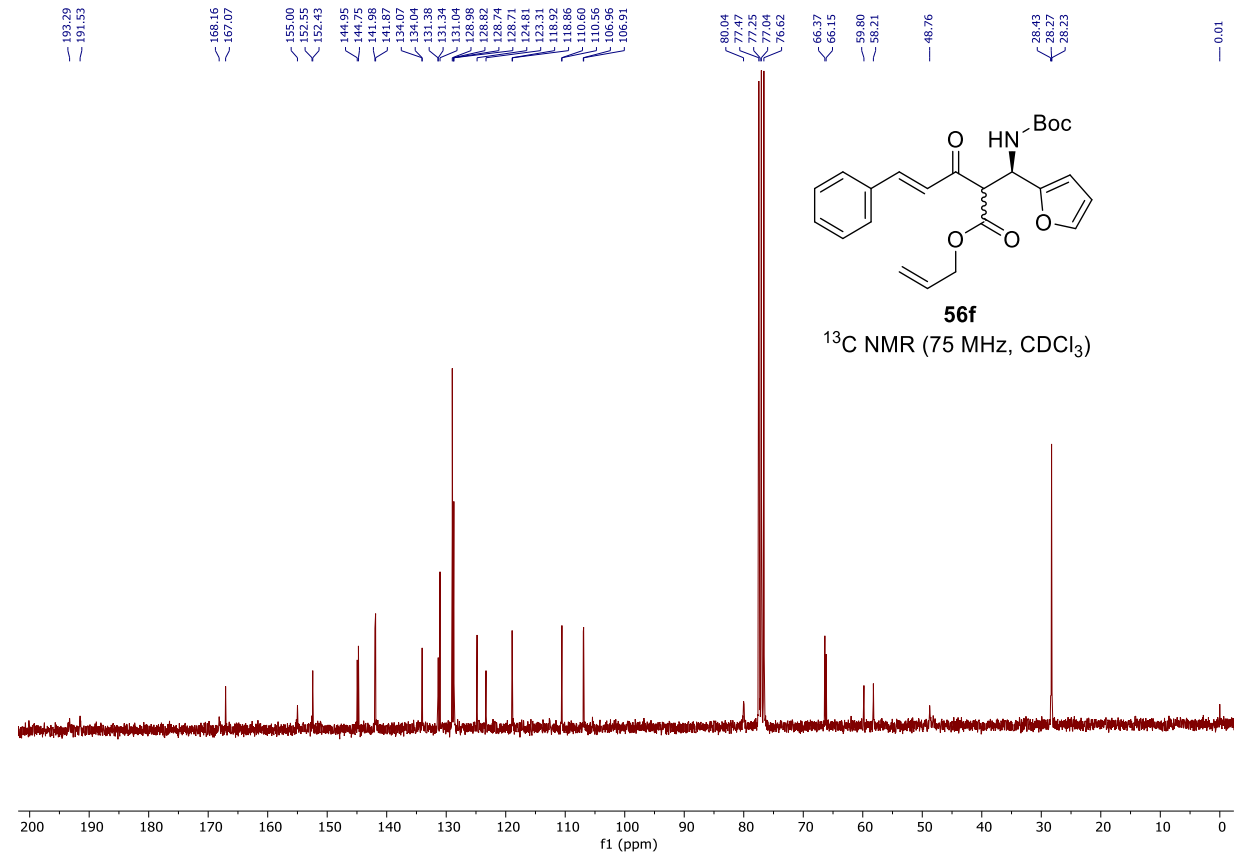
^{13}C NMR (75 MHz, $CDCl_3$)

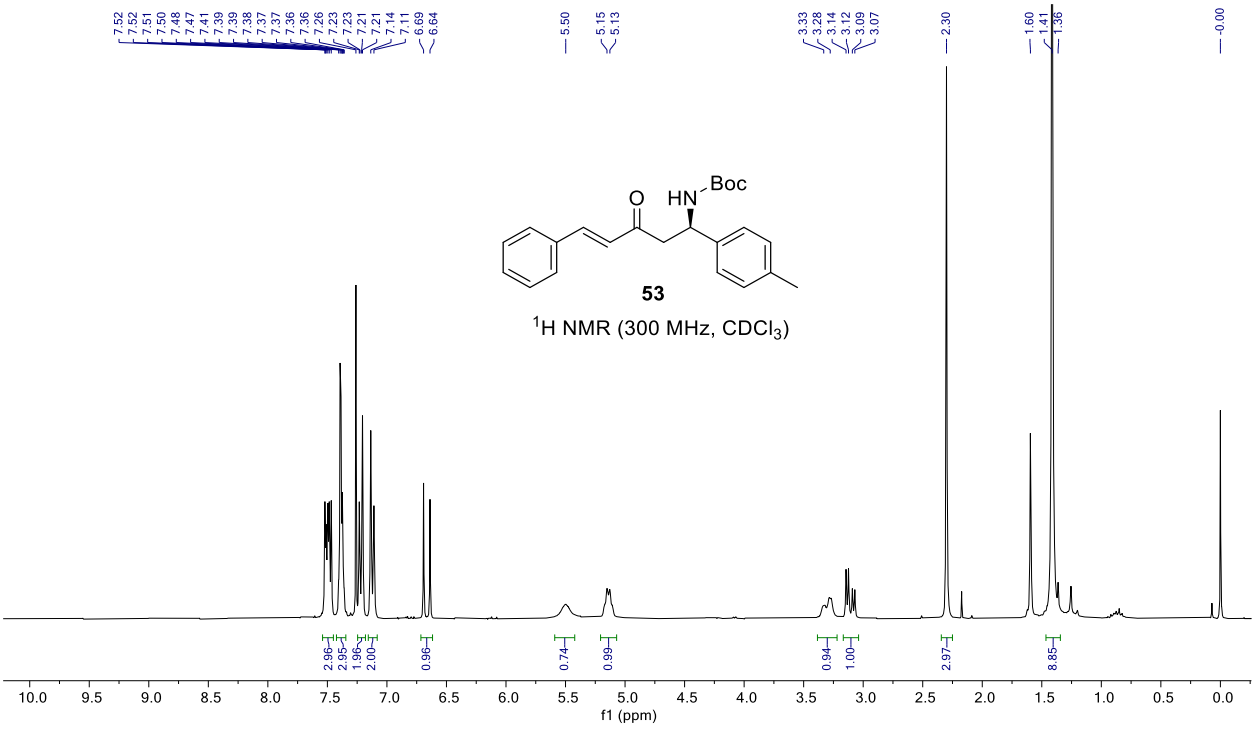


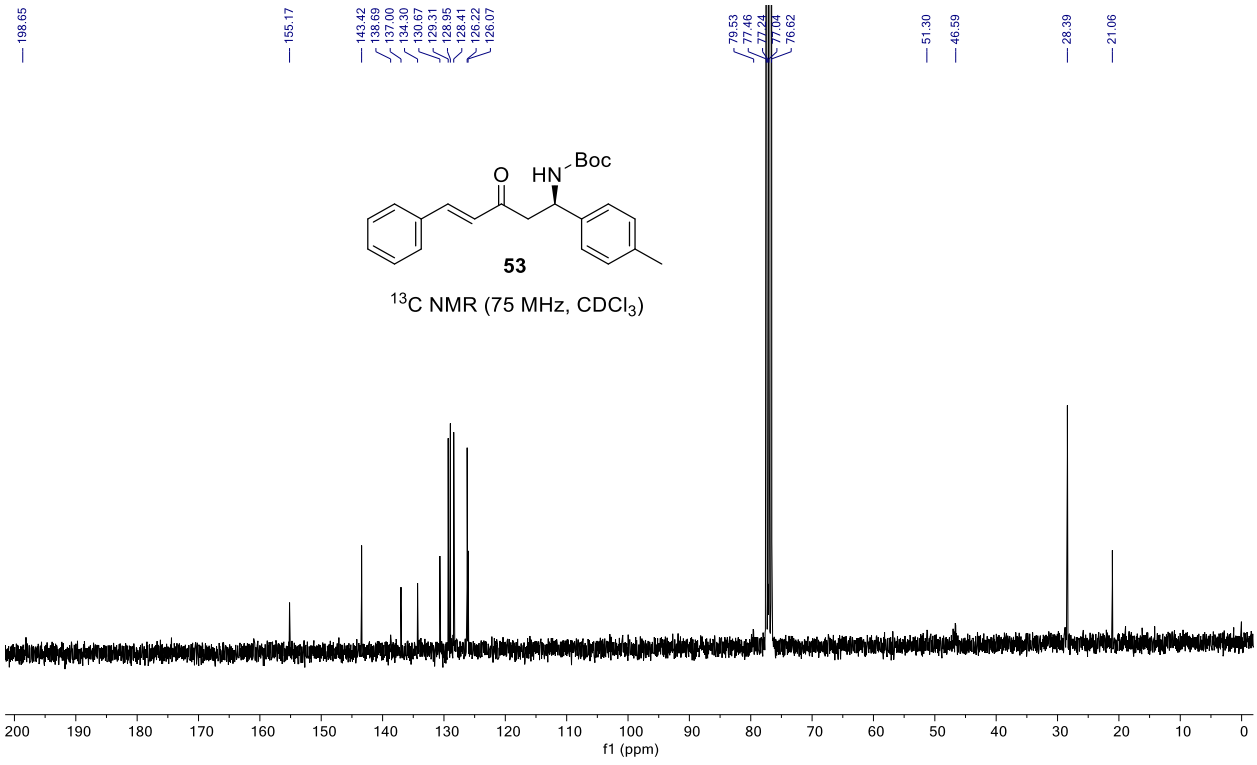
56f

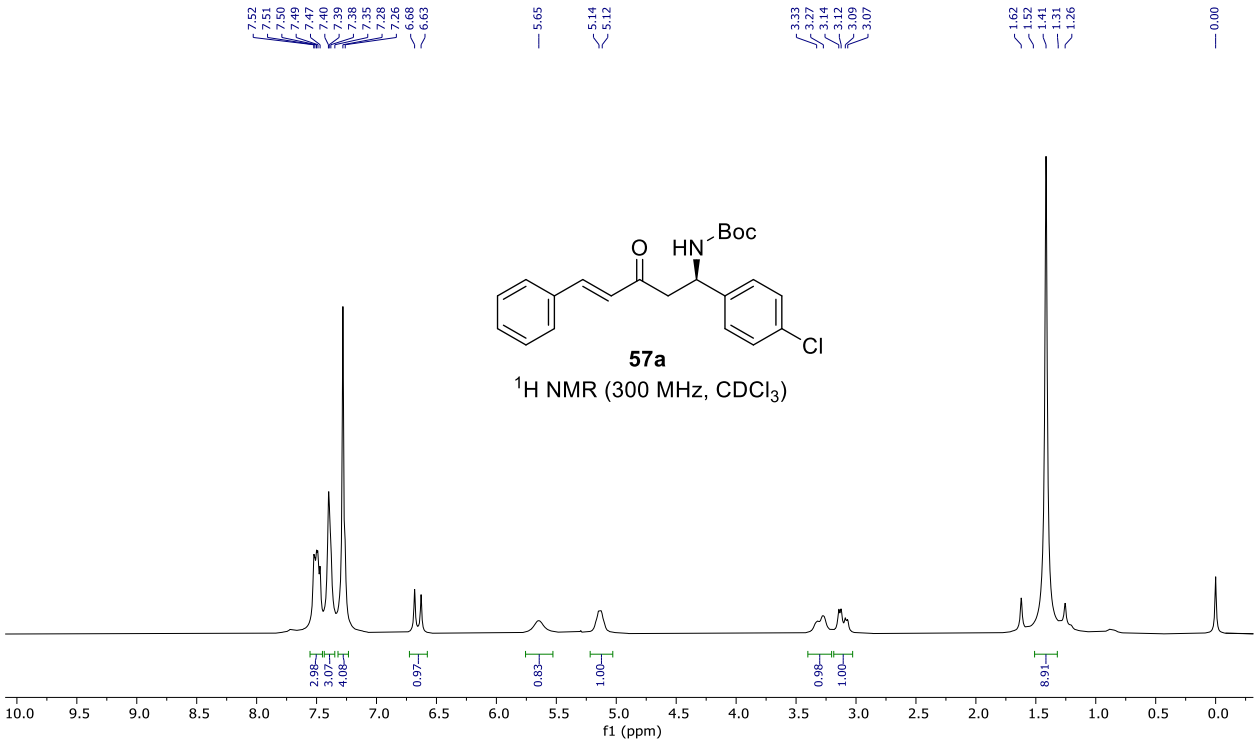
^{1}H NMR (300 MHz, $CDCl_3$)

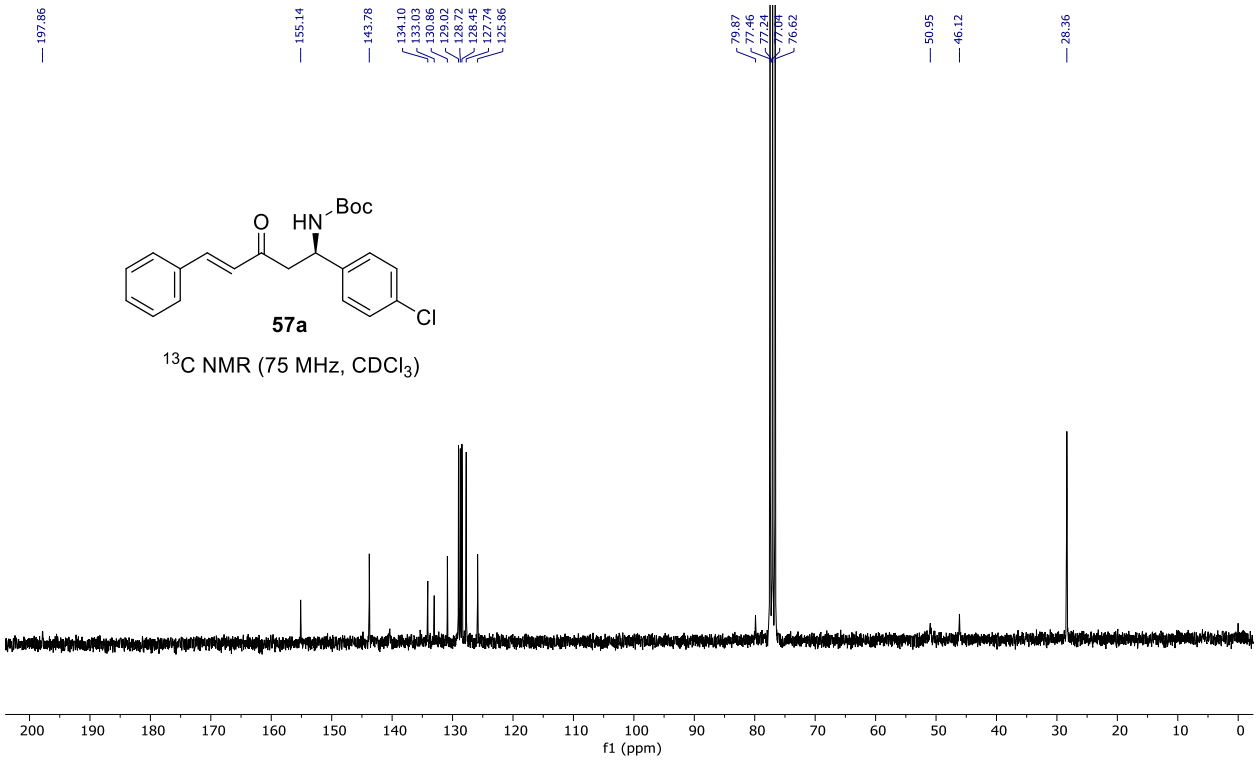


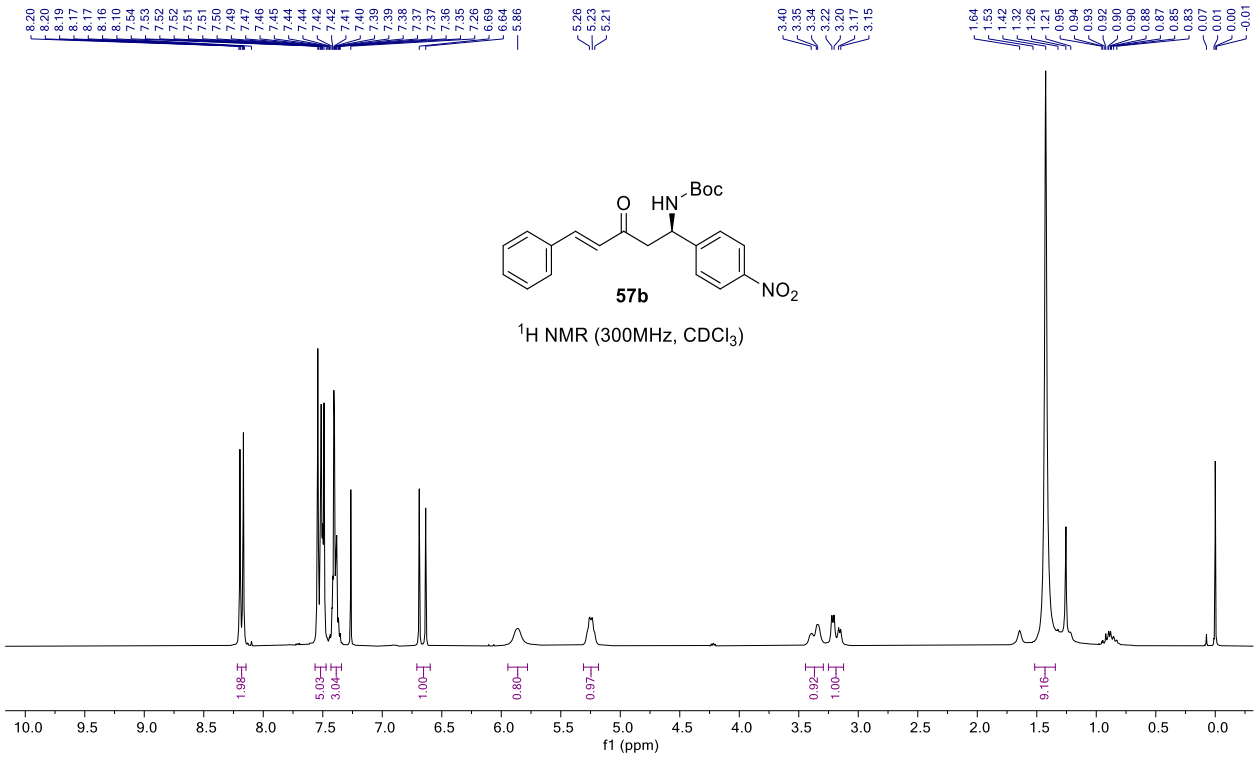

193.29
191.53
168.16
167.07
155.00
152.55
152.43
144.95
144.75
141.98
141.87
134.07
134.04
131.38
131.34
131.04
128.98
128.82
128.74
128.71
124.81
123.31
118.92
118.86
110.60
110.56
106.96
106.91
80.04
77.47
77.25
77.04
76.62
66.37
66.15
59.80
58.21
48.76
28.43
28.27
28.23
0.01
O
HN
Boc
O
O
O
56f
13C NMR (75 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

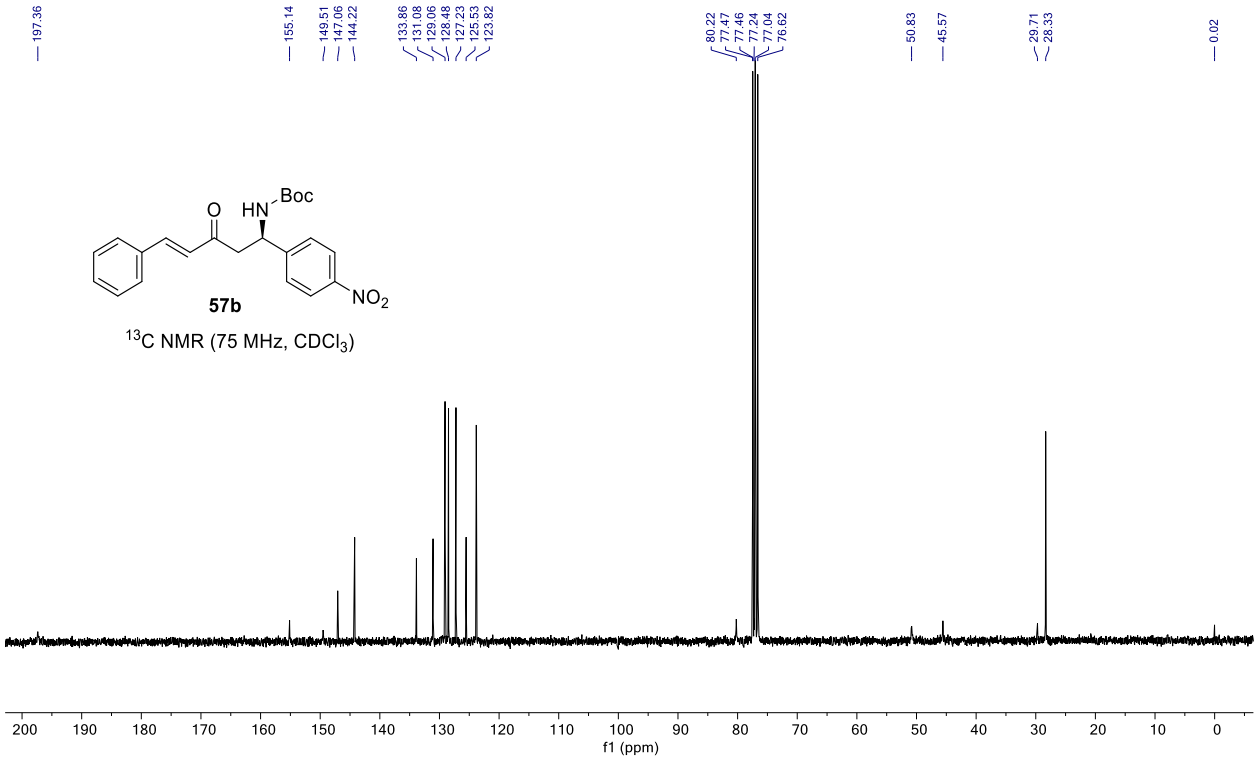

7.52
7.52
7.51
7.50
7.48
7.47
7.41
7.39
7.39
7.38
7.37
7.37
7.36
7.36
7.26
7.23
7.23
7.21
7.21
7.14
7.11
6.69
6.64
5.50
5.15
5.13
3.33
3.28
3.14
3.12
3.09
3.07
2.30
1.60
1.41
1.36
0.00
O
HN
Boc
53
1H NMR (300 MHz, CDCl3)
2.96
2.95
1.96
2.00
0.96
0.74
0.99
0.94
1.00
2.97
8.85
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

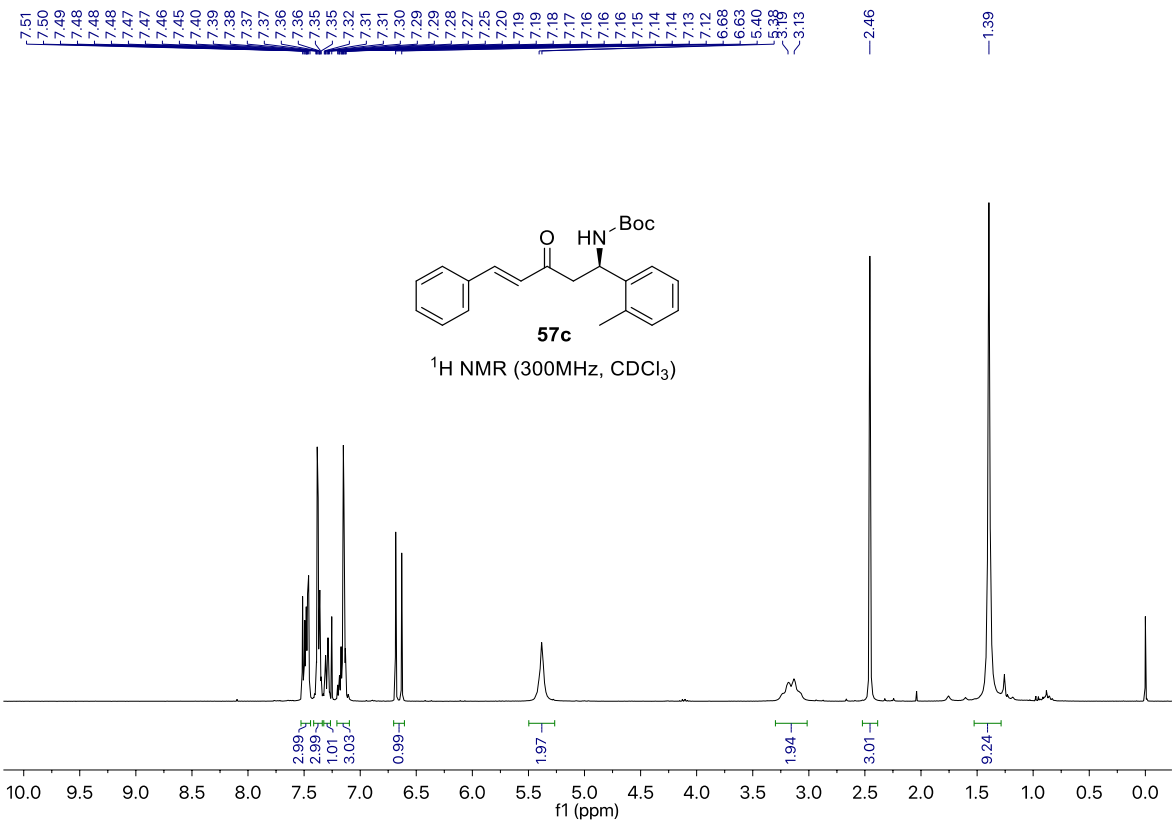

198.65
155.17
143.42
138.69
137.00
134.30
130.67
129.31
128.95
128.41
126.22
126.07
79.53
77.46
77.24
77.04
76.62
51.30
46.59
28.39
21.06
O
HN
Boc
53
13C NMR (75 MHz, CDCl3)
f1 (ppm)

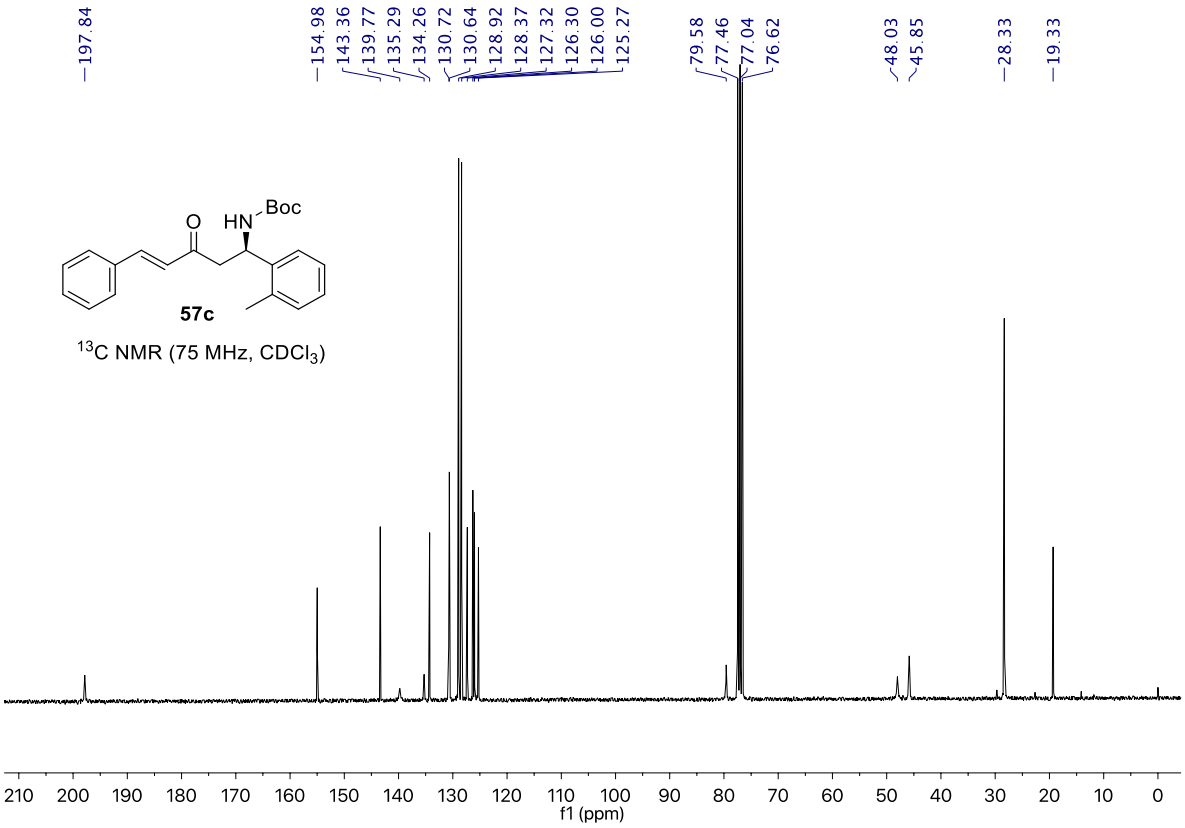

7.52
7.51
7.50
7.49
7.47
7.40
7.39
7.38
7.35
7.28
7.26
6.68
6.63
5.65
5.14
5.12
3.33
3.27
3.14
3.12
3.09
3.07
1.62
1.52
1.41
1.31
1.26
0.00
O
HN
Boc
Cl
57a
1H NMR (300 MHz, CDCl3)
2.98
3.07
4.08
0.97
0.83
1.00
0.98
1.00
8.91
f1 (ppm)

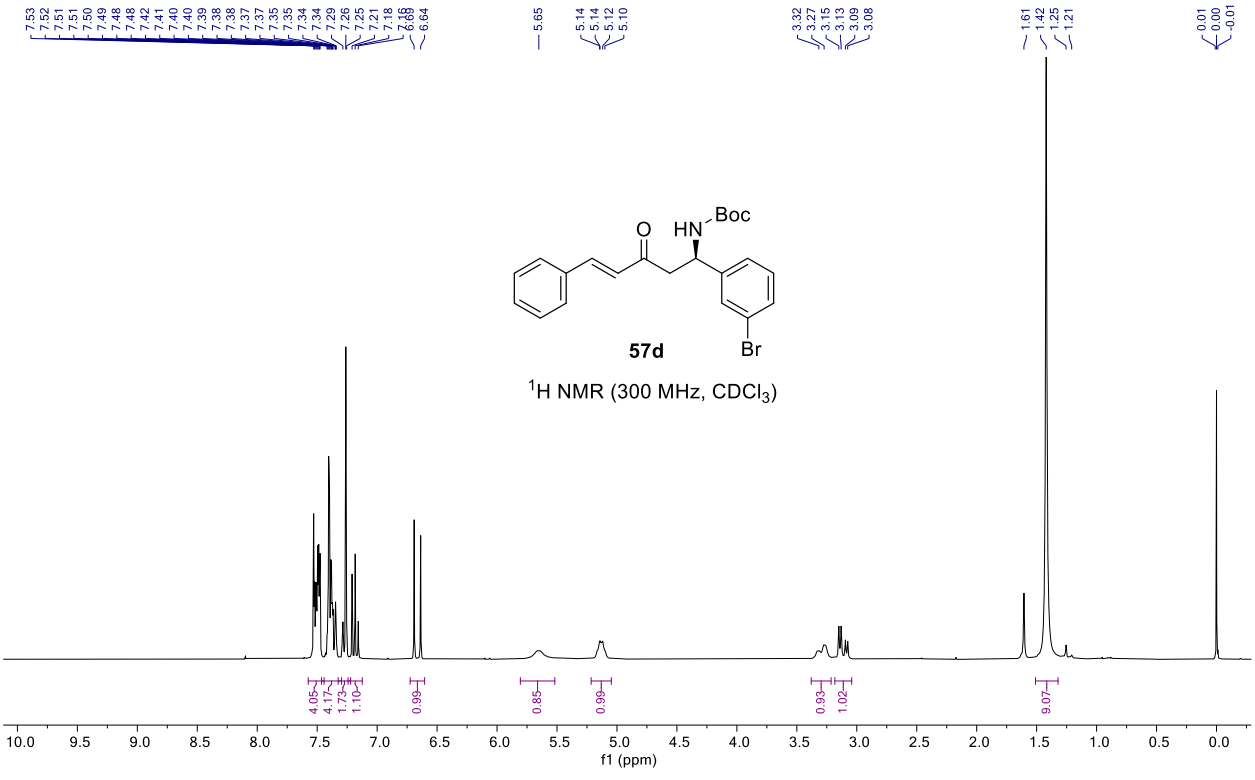

197.86
155.14
143.78
134.10
133.03
130.86
129.02
128.72
128.45
127.74
125.86
79.87
77.46
77.24
77.04
76.62
50.95
46.12
28.36
O
HN
Boc
Cl
57a
13C NMR (75 MHz, CDCl3)
f1 (ppm)

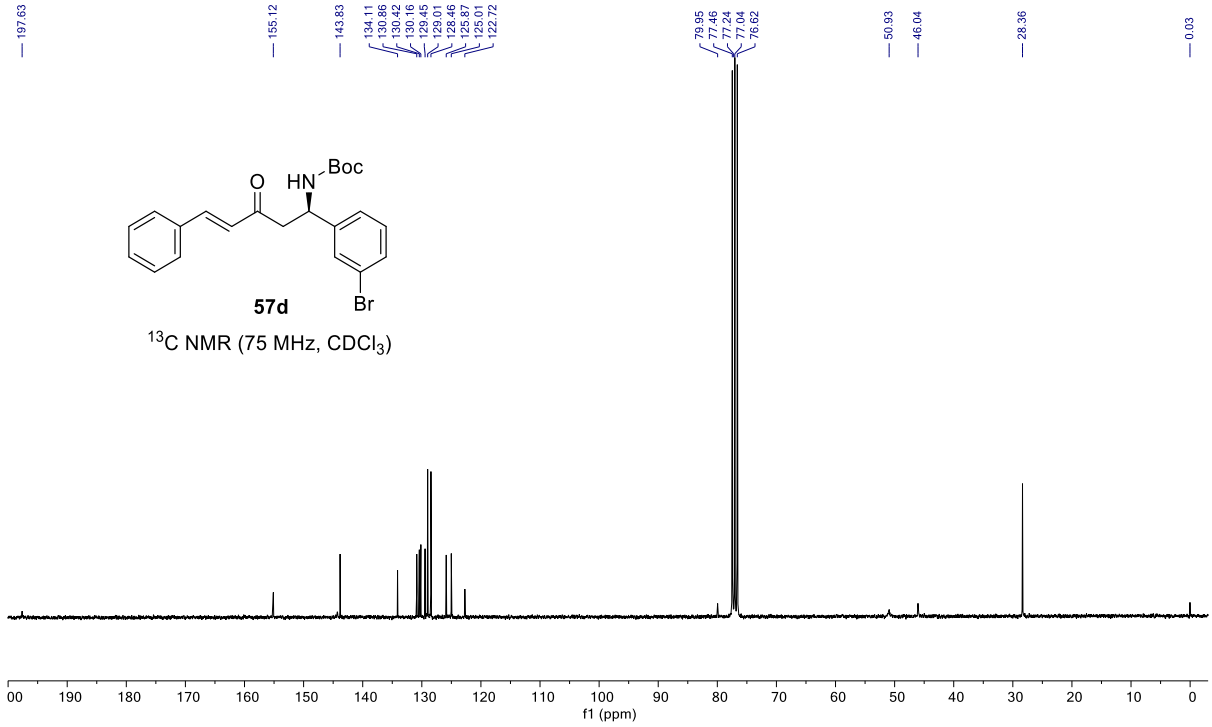

8.20
8.20
8.19
8.17
8.17
8.16
8.10
7.54
7.53
7.52
7.52
7.51
7.51
7.50
7.49
7.47
7.46
7.45
7.44
7.44
7.42
7.42
7.41
7.40
7.39
7.39
7.38
7.37
7.37
7.36
7.35
7.26
6.69
6.64
5.86
5.26
5.23
5.21
3.40
3.35
3.34
3.22
3.20
3.17
3.15
1.64
1.53
1.42
1.32
1.26
1.21
0.95
0.94
0.93
0.92
0.90
0.90
0.88
0.87
0.85
0.83
0.07
0.01
0.00
-0.01
O
HN
Boc
NO2
57b
1H NMR (300MHz, CDCl3)
1.98
5.03
3.04
1.00
0.80
0.97
0.92
1.00
9.16
f1 (ppm)

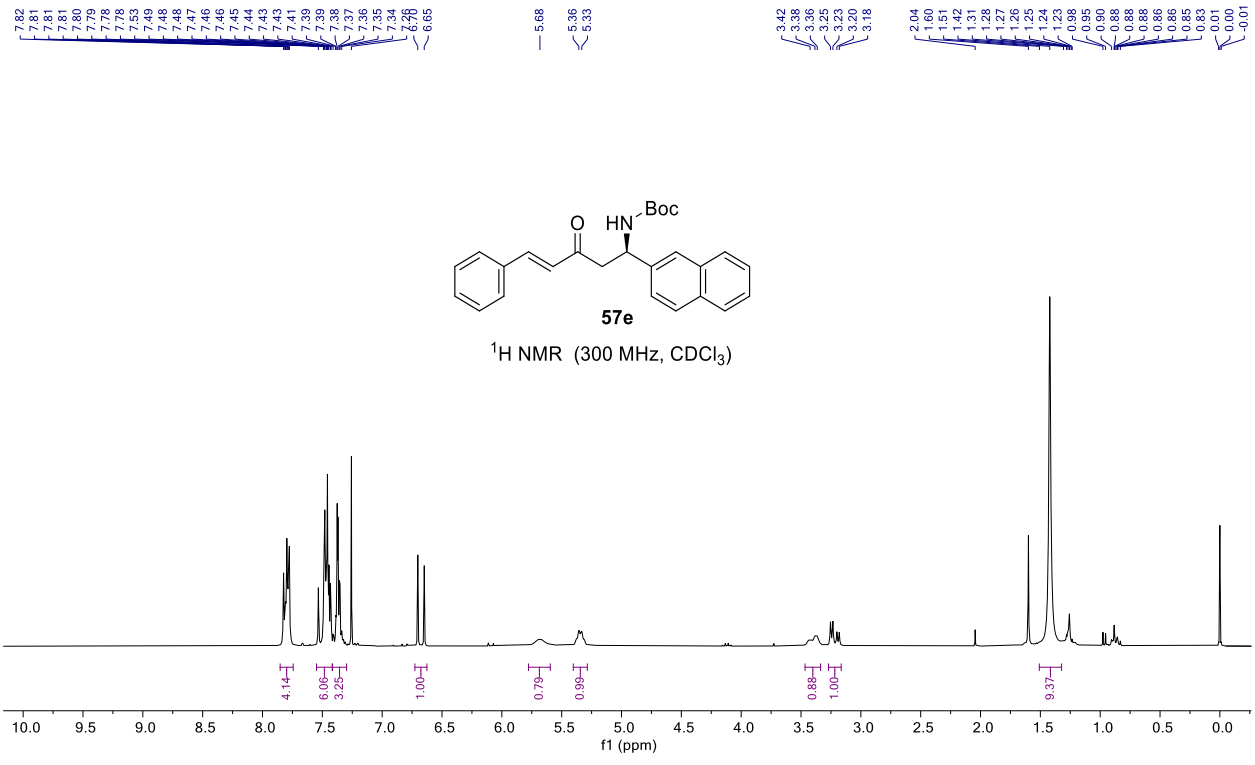

197.36
155.14
149.51
147.06
144.22
133.86
131.08
129.06
128.48
127.23
125.53
123.82
80.22
77.47
77.46
77.24
77.04
76.62
50.83
45.57
29.71
28.33
0.02
O
HN
Boc
NO2
57b
13C NMR (75 MHz, CDCl3)
f1 (ppm)

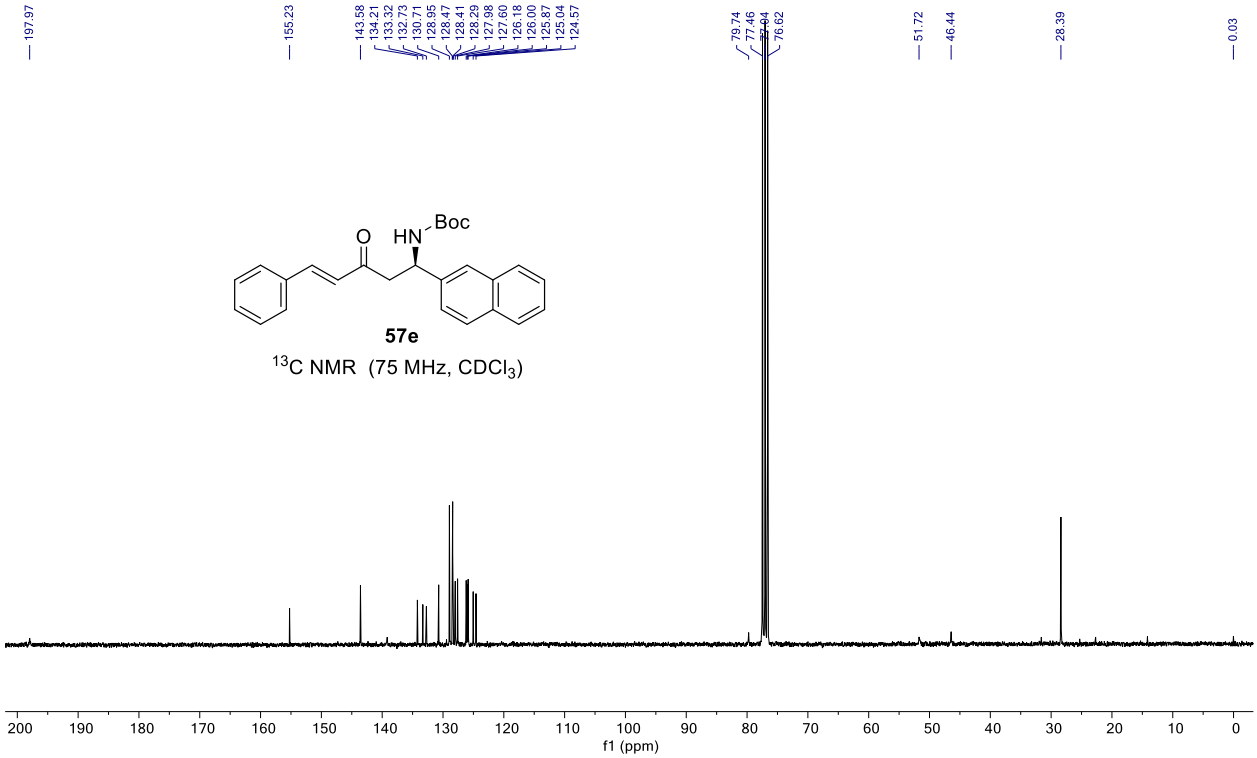

7.51
7.50
7.49
7.48
7.48
7.48
7.47
7.47
7.46
7.45
7.40
7.39
7.38
7.37
7.37
7.36
7.36
7.35
7.35
7.32
7.31
7.31
7.30
7.29
7.29
7.28
7.27
7.25
7.20
7.19
7.19
7.18
7.17
7.16
7.16
7.16
7.15
7.14
7.14
7.13
7.12
6.68
6.63
5.40
3.19
3.13
2.46
1.39
O
HN
Boc
57c
1H NMR (300MHz, CDCl3)
2.99
2.99
1.01
3.03
0.99
1.97
1.94
3.01
9.24
f1 (ppm)


197.84
154.98
143.36
139.77
135.29
134.26
130.72
130.64
128.92
128.37
127.32
126.30
126.00
125.27
79.58
77.46
77.04
76.62
48.03
45.85
28.33
19.33
O
HN
Boc
57c
13C NMR (75 MHz, CDCl3)
f1 (ppm)


7.53
7.52
7.51
7.51
7.50
7.49
7.48
7.48
7.42
7.41
7.40
7.40
7.39
7.38
7.38
7.37
7.37
7.35
7.35
7.34
7.34
7.29
7.26
7.25
7.21
7.18
6.68
6.64
5.65
5.14
5.14
5.12
5.10
3.32
3.27
3.15
3.13
3.09
3.08
1.61
1.42
1.25
1.21
0.01
0.00
-0.01
O
HN
Boc
Br
57d
1H NMR (300 MHz, CDCl3)
4.05
4.17
1.73
1.10
0.99
0.85
0.99
0.93
1.02
9.07
f1 (ppm)

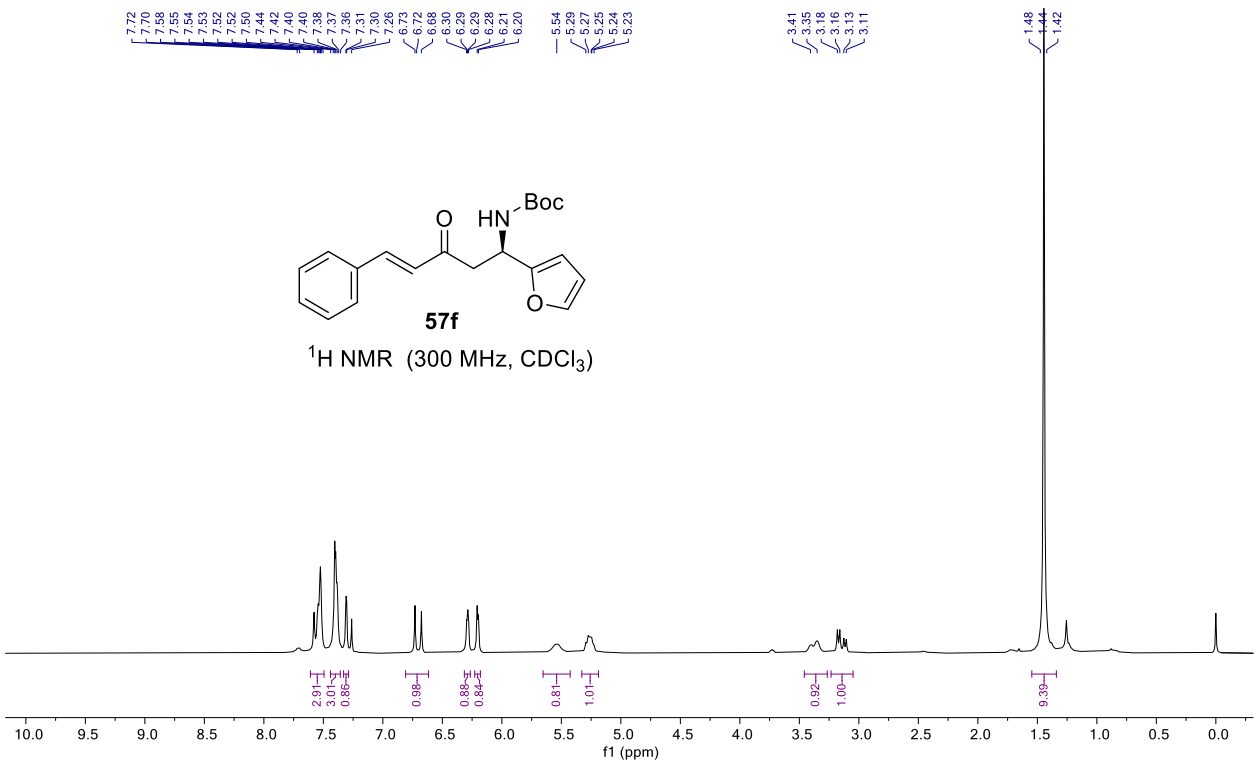

197.63
155.12
143.83
134.11
130.86
130.42
130.16
129.45
129.01
128.46
125.87
125.01
122.72
79.95
77.46
77.24
77.04
76.62
50.93
46.04
28.36
0.03
O
HN
Boc
Br
57d
13C NMR (75 MHz, CDCl3)
f1 (ppm)


7.82
7.81
7.81
7.81
7.80
7.79
7.78
7.78
7.53
7.49
7.48
7.48
7.47
7.46
7.46
7.45
7.44
7.43
7.43
7.41
7.39
7.39
7.38
7.37
7.36
7.35
7.34
6.70
6.65
5.68
5.36
5.33
3.42
3.38
3.36
3.25
3.23
3.20
3.18
2.04
1.60
1.51
1.42
1.31
1.28
1.27
1.26
1.25
1.24
1.23
0.98
0.95
0.90
0.88
0.88
0.88
0.86
0.86
0.85
0.83
0.01
0.00
-0.01
O
HN
Boc
57e
1H NMR (300 MHz, CDCl3)
4.14
6.06
3.25
1.00
0.79
0.99
0.88
1.00
9.37
f1 (ppm)



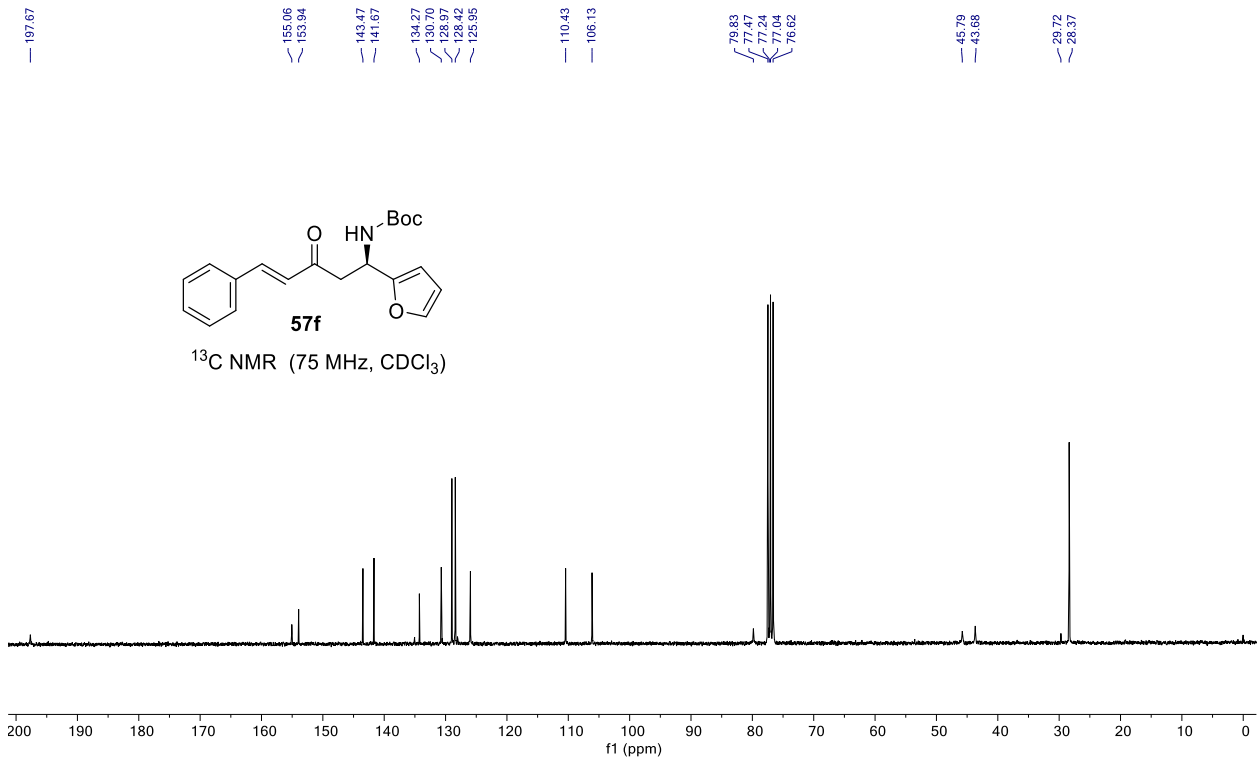
57e

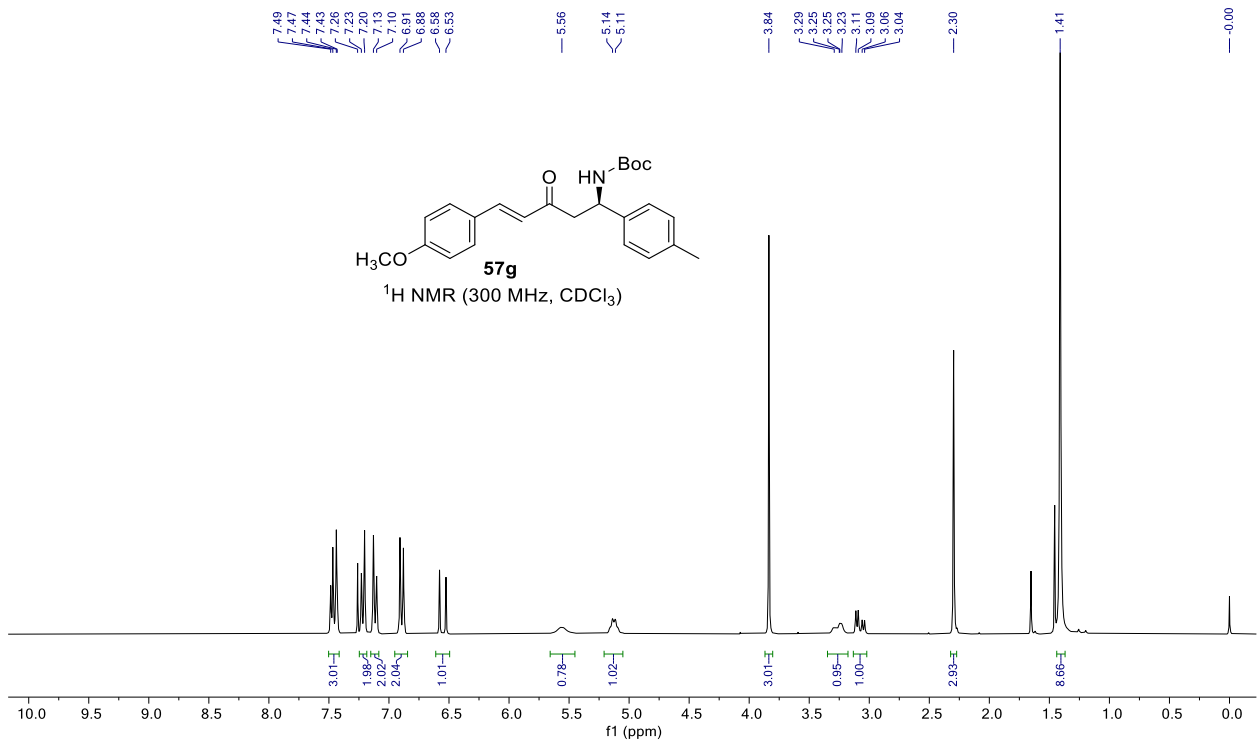
^{13}C NMR (75 MHz, $CDCl_3$)

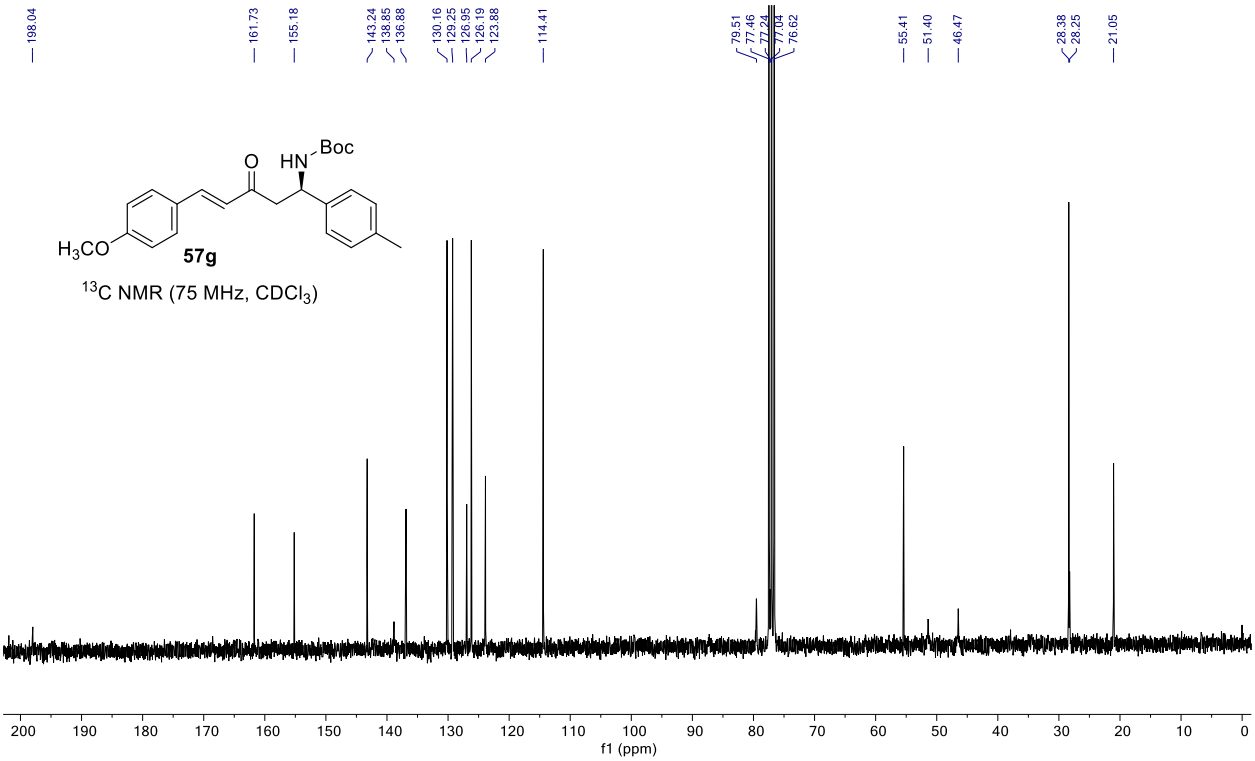


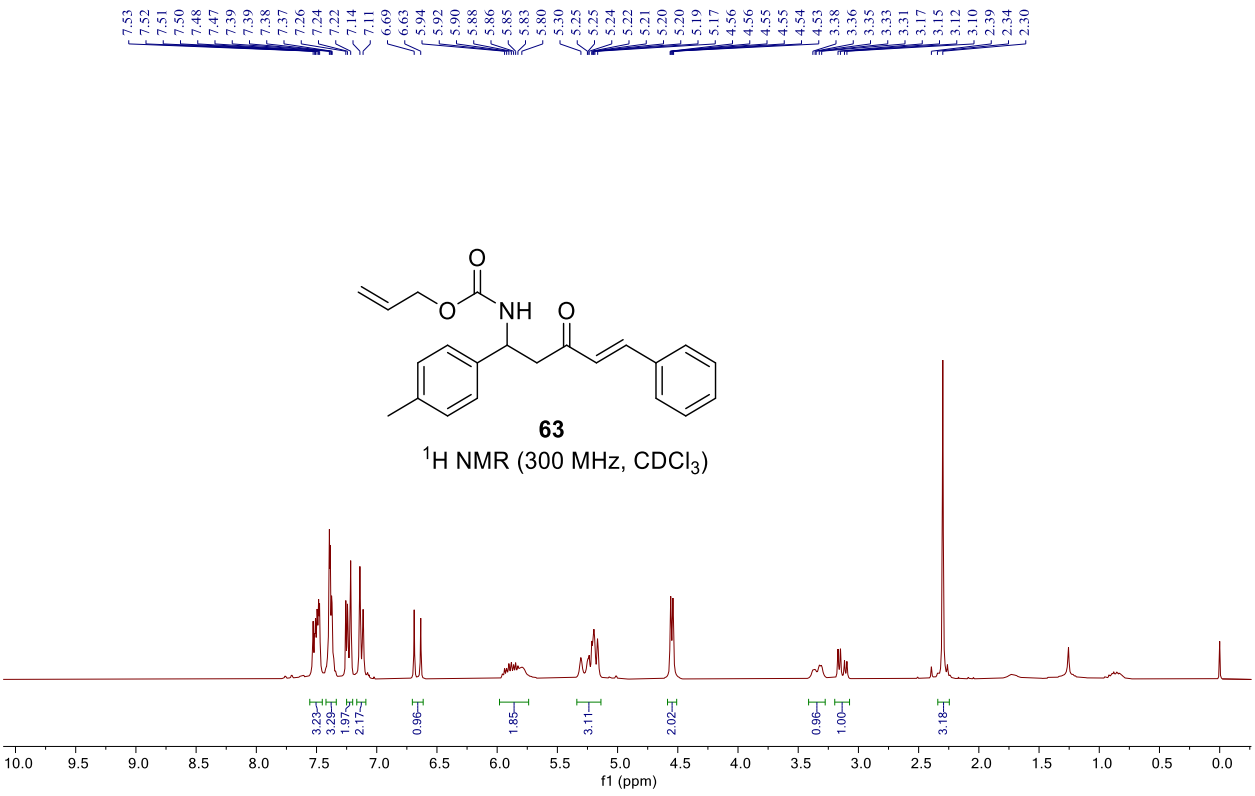
57f

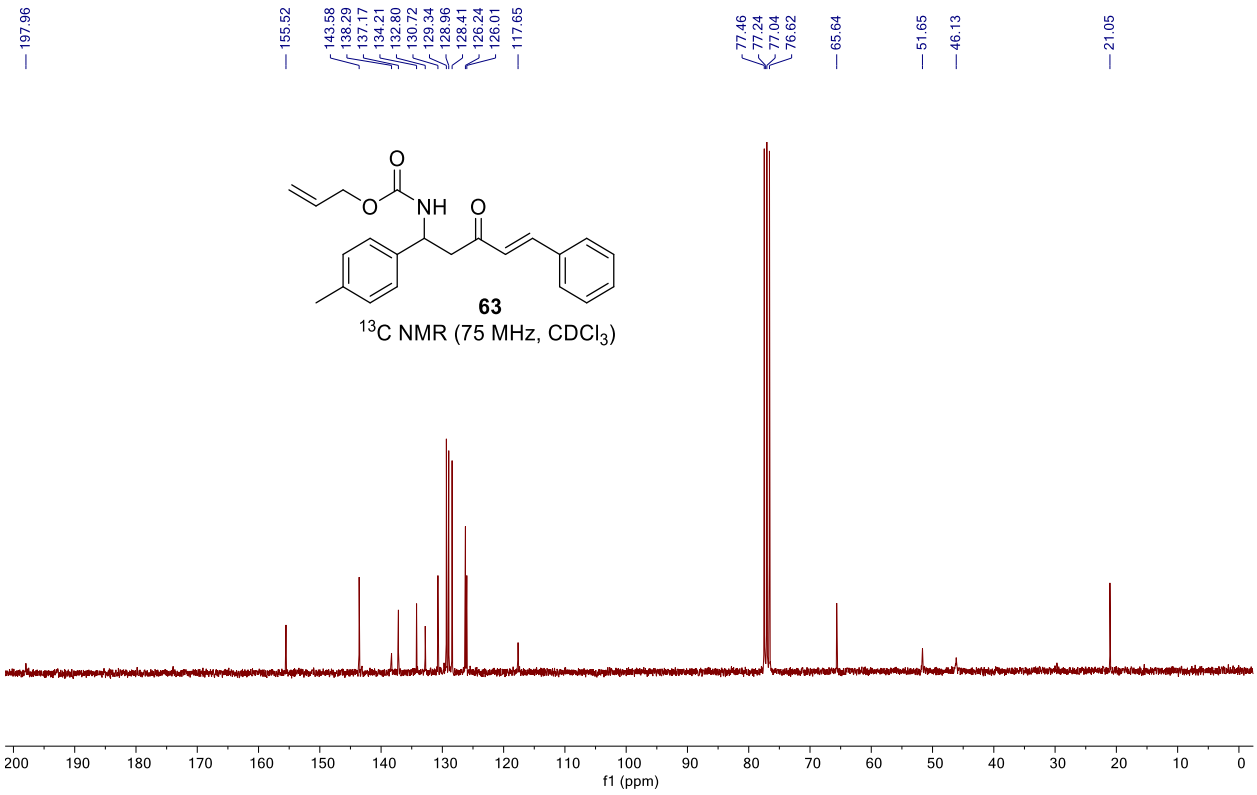
^{1}H NMR (300 MHz, $CDCl_3$)

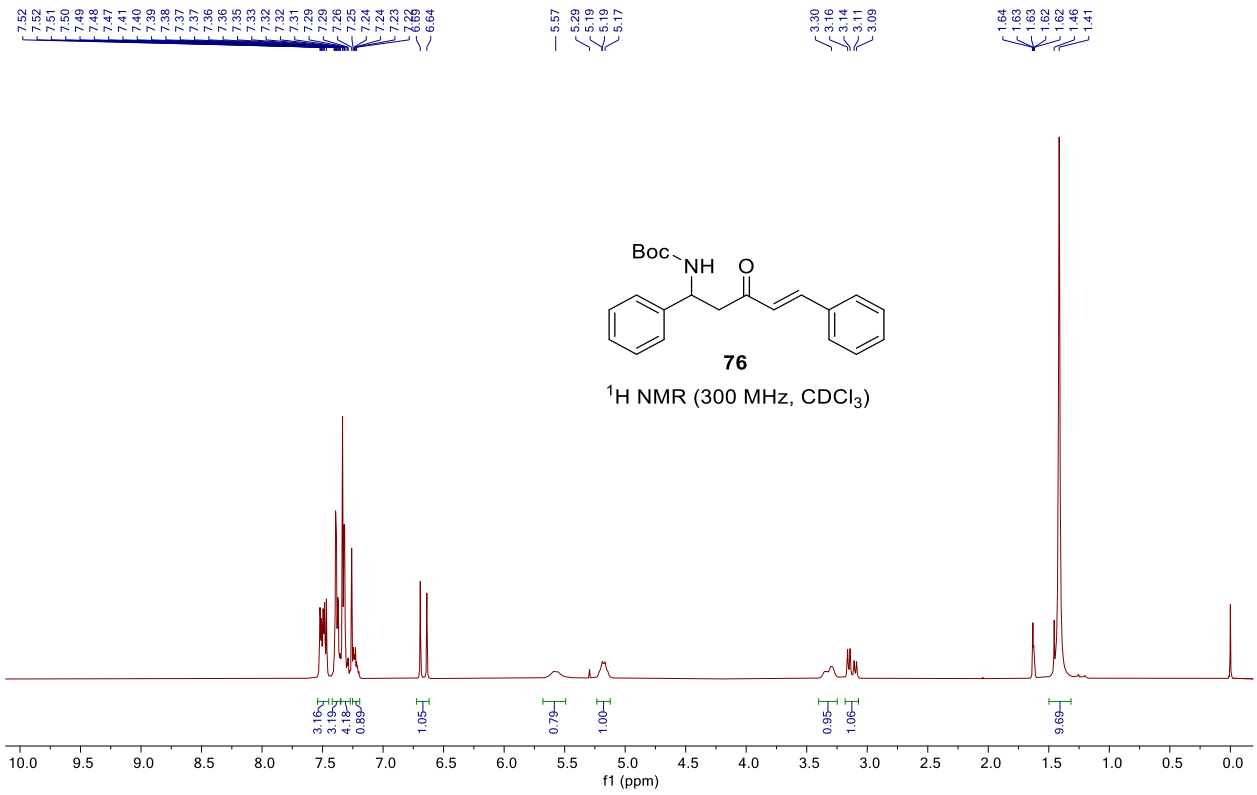

197.67
155.06
153.94
143.47
141.67
134.27
130.70
128.97
128.42
125.95
110.43
106.13
79.83
77.47
77.24
77.04
76.62
45.79
43.68
29.72
28.37
O
HN
Boc
O
57f
13C NMR (75 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

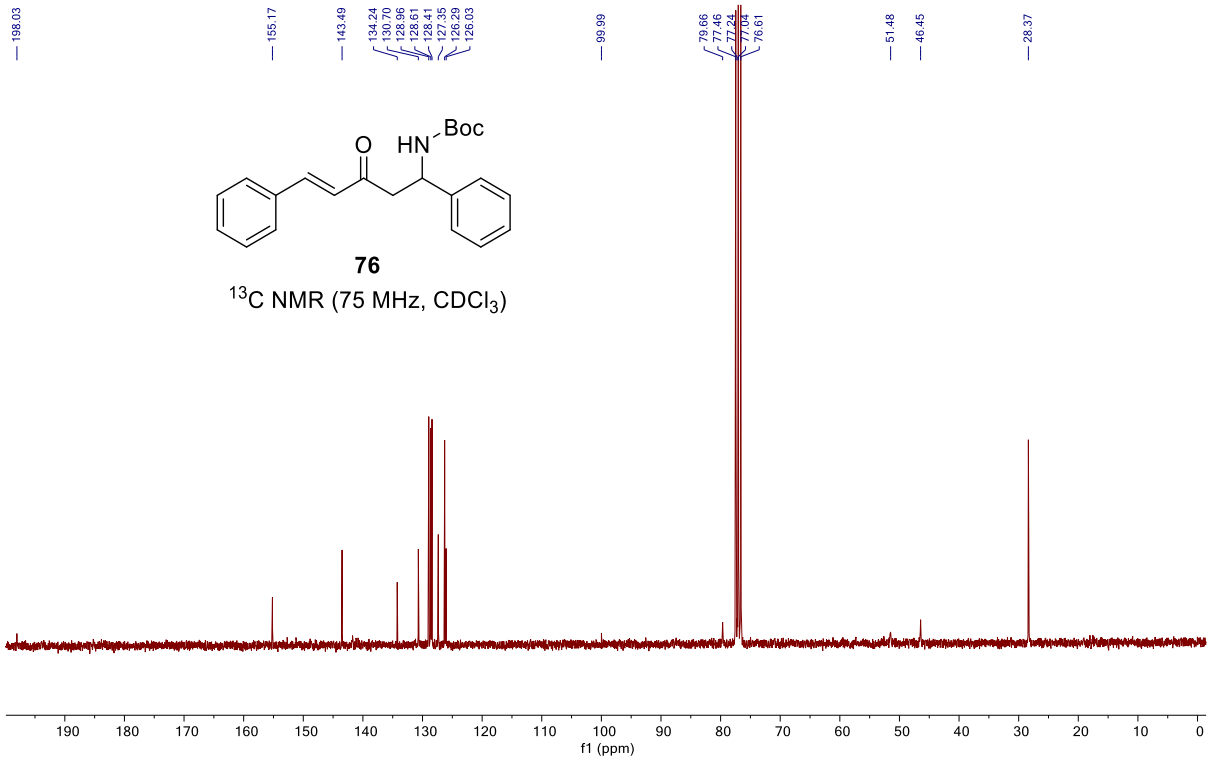

7.49
7.47
7.44
7.43
7.26
7.23
7.20
7.13
7.10
6.91
6.88
6.58
6.53
5.56
5.14
5.11
3.84
3.29
3.25
3.25
3.23
3.11
3.09
3.06
3.04
2.30
1.41
-0.00
O
HN
Boc
H3CO
57g
1H NMR (300 MHz, CDCl3)
3.01
1.98
2.02
2.04
1.01
0.78
1.02
3.01
0.95
1.00
2.93
8.66
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


198.04
161.73
155.18
143.24
138.85
136.88
130.16
129.25
126.95
126.19
123.88
114.41
79.51
77.46
77.24
77.04
76.62
55.41
51.40
46.47
28.38
28.25
21.05
O
HN
Boc
H3CO
57g
13C NMR (75 MHz, CDCl3)
f1 (ppm)


7.53
7.52
7.51
7.50
7.48
7.47
7.39
7.39
7.38
7.37
7.26
7.24
7.22
7.14
7.11
6.69
6.63
5.94
5.92
5.90
5.88
5.86
5.85
5.83
5.80
5.30
5.25
5.25
5.24
5.22
5.21
5.20
5.20
5.19
5.17
4.56
4.56
4.55
4.55
4.54
4.53
3.38
3.36
3.35
3.33
3.31
3.17
3.15
3.12
3.10
2.39
2.34
2.30
O
O
NH
O
63
1H NMR (300 MHz, CDCl3)
3.23
3.29
1.97
2.17
0.96
1.85
3.11
2.02
0.96
1.00
3.18
f1 (ppm)

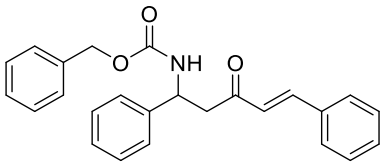

197.96
155.52
143.58
138.29
137.17
134.21
132.80
130.72
129.34
128.96
128.41
126.24
126.01
117.65
77.46
77.24
77.04
76.62
65.64
51.65
46.13
21.05
O
O
NH
O
63
13C NMR (75 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.52
7.52
7.51
7.50
7.49
7.48
7.47
7.41
7.40
7.39
7.38
7.37
7.37
7.36
7.36
7.35
7.33
7.32
7.32
7.31
7.29
7.29
7.26
7.25
7.24
7.24
7.23
6.69
6.64
5.57
5.29
5.19
5.19
5.17
3.30
3.16
3.14
3.11
3.09
1.64
1.63
1.63
1.62
1.62
1.46
1.41
Boc
NH
O
76
1H NMR (300 MHz, CDCl3)
3.16
3.15
4.18
0.89
1.05
0.79
1.00
0.95
1.06
9.69
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



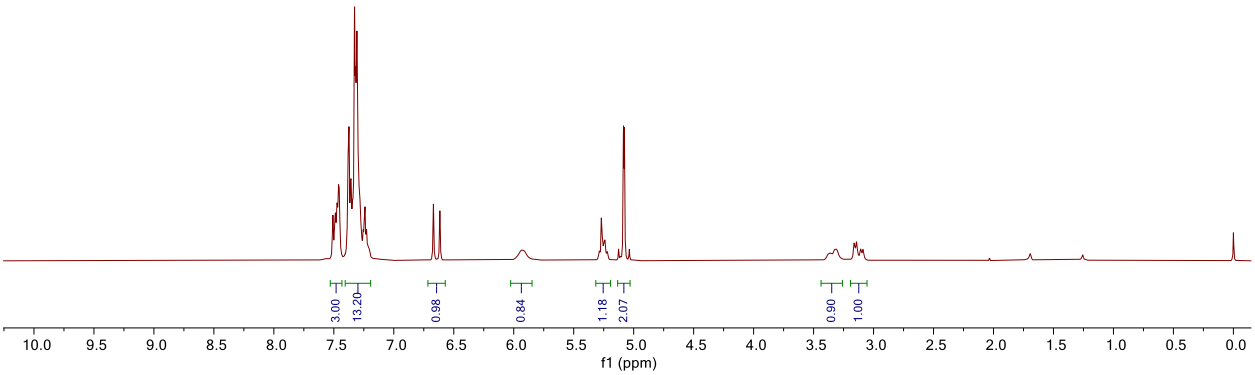
76

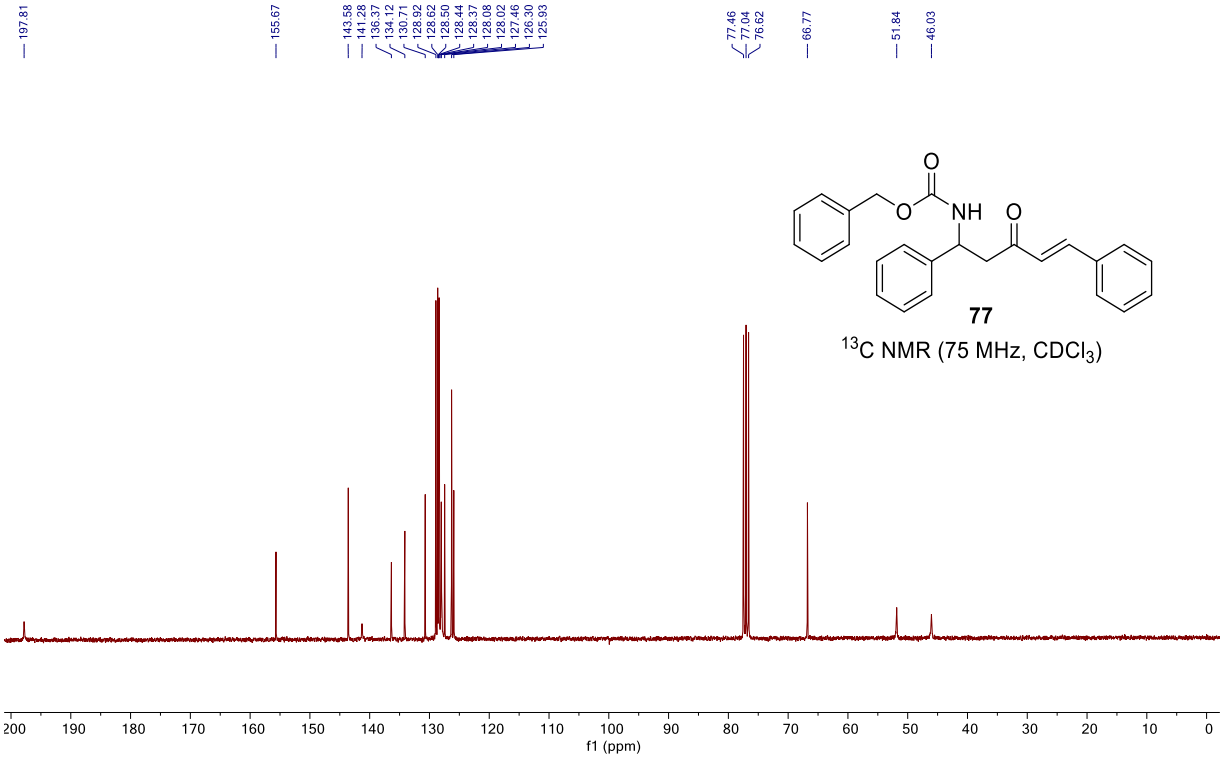
^{13}C NMR (75 MHz, $CDCl_3$)



77

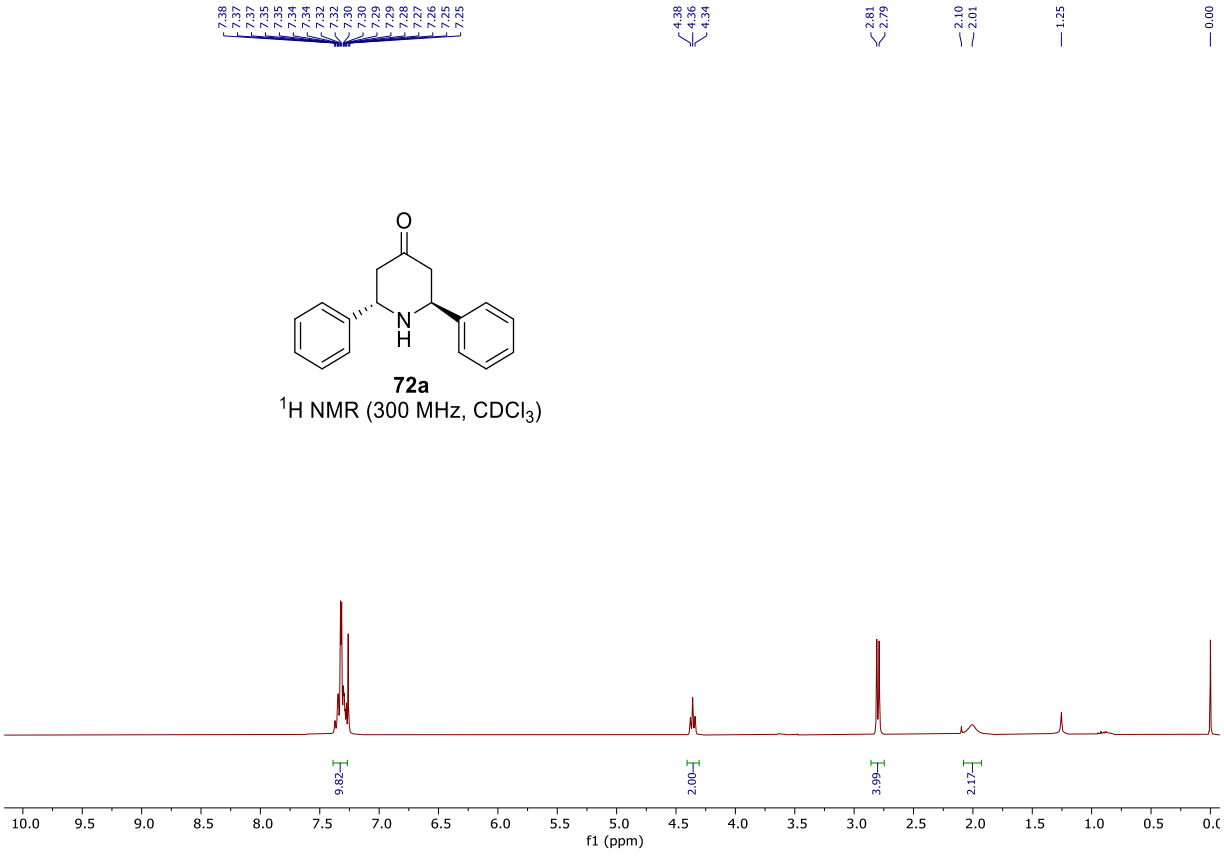
^{1}H NMR (300 MHz, $CDCl_3$)





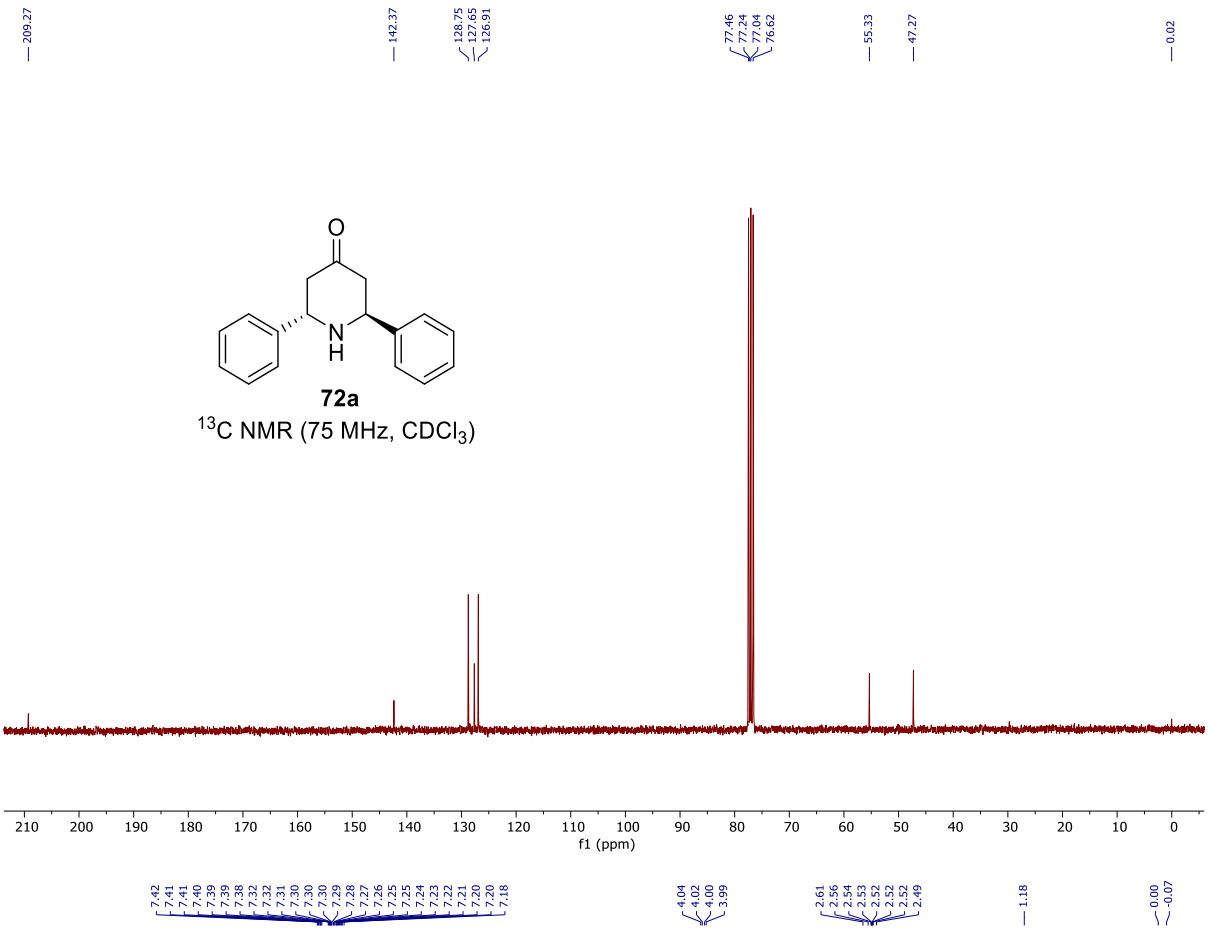
77

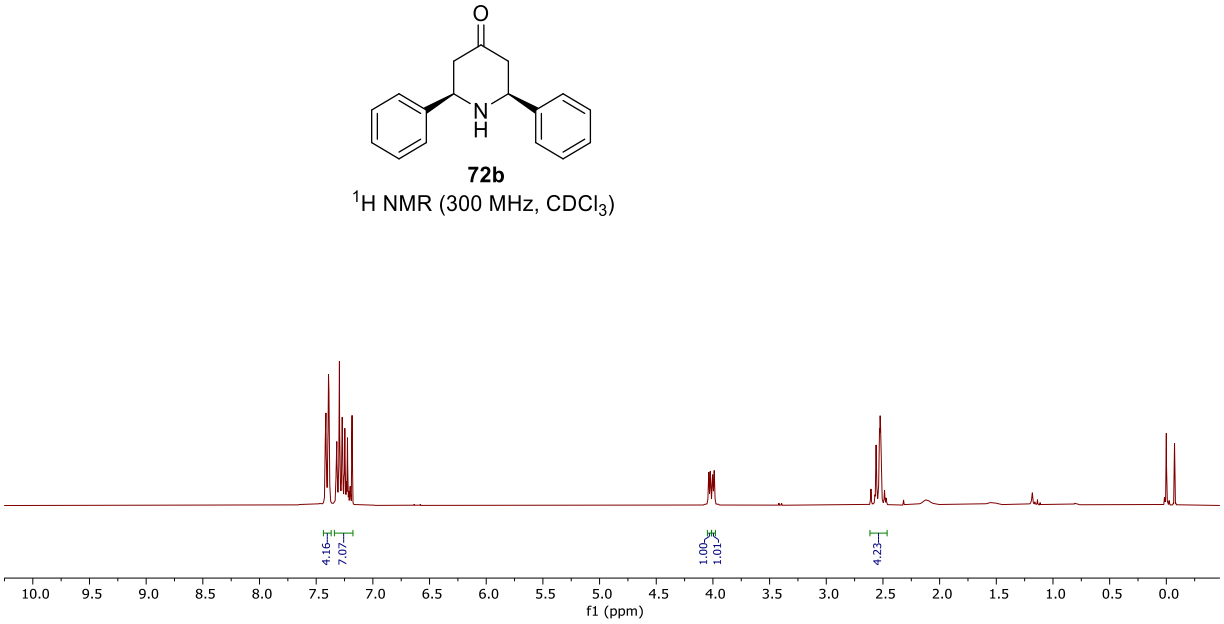
^{13}C NMR (75 MHz, $CDCl_3$)

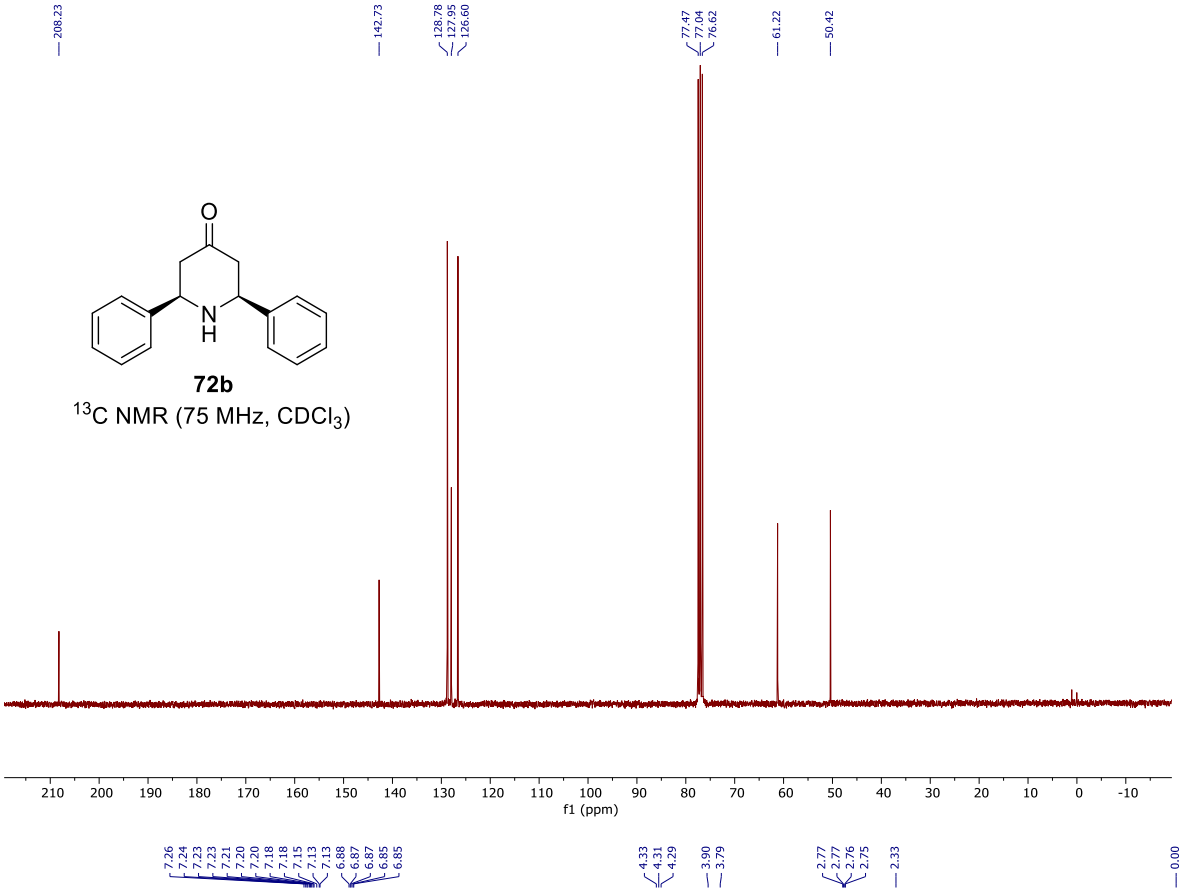


72a

^{1}H NMR (300 MHz, $CDCl_3$)

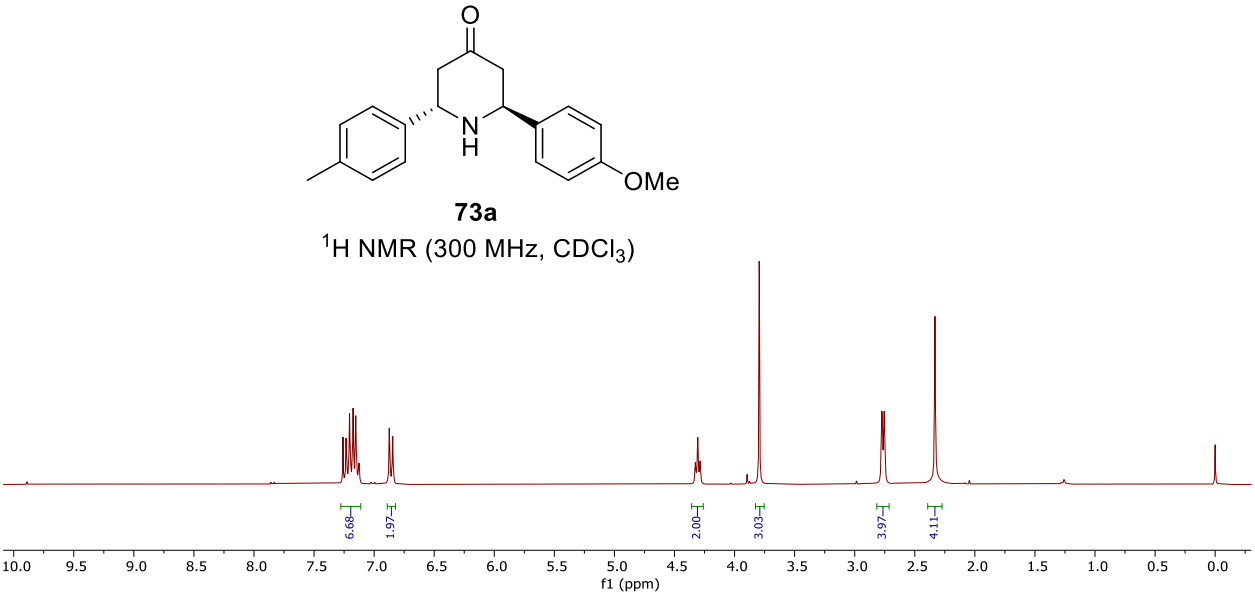

209.27
142.37
128.75
127.65
126.91
77.46
77.24
77.04
76.62
55.33
47.27
0.02
O
N
H
72a
13C NMR (75 MHz, CDCl3)
f1 (ppm)
7.42
7.41
7.41
7.40
7.39
7.39
7.38
7.32
7.32
7.31
7.30
7.30
7.30
7.29
7.28
7.27
7.26
7.25
7.25
7.24
7.23
7.22
7.21
7.20
7.20
7.18
4.04
4.02
4.00
3.99
2.61
2.56
2.54
2.53
2.52
2.52
2.52
2.49
1.18
0.00
-0.07


O
N
H
72b
1H NMR (300 MHz, CDCl3)
4.16
7.07
1.00
1.01
4.23
f1 (ppm)



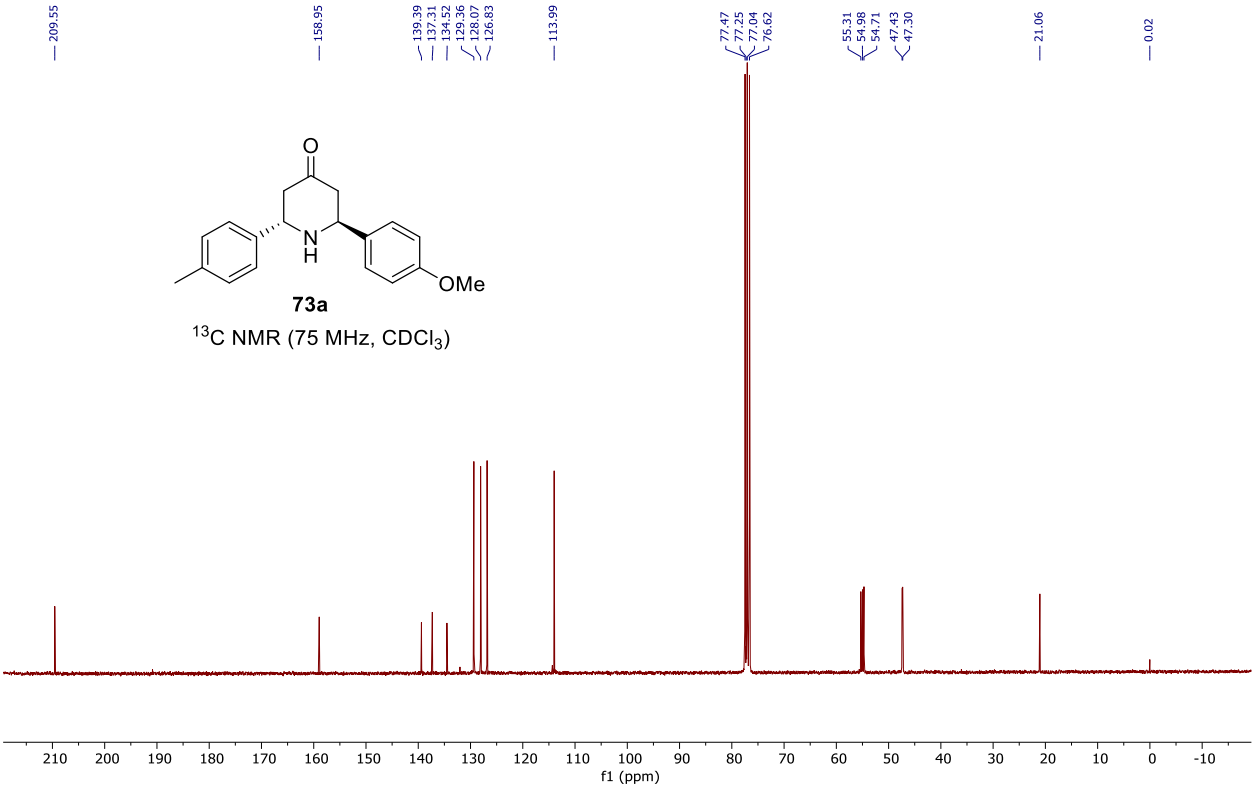
72b

^{13}C NMR (75 MHz, $CDCl_3$)



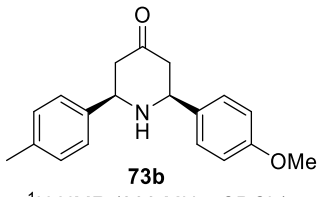
73a

^{1}H NMR (300 MHz, $CDCl_3$)



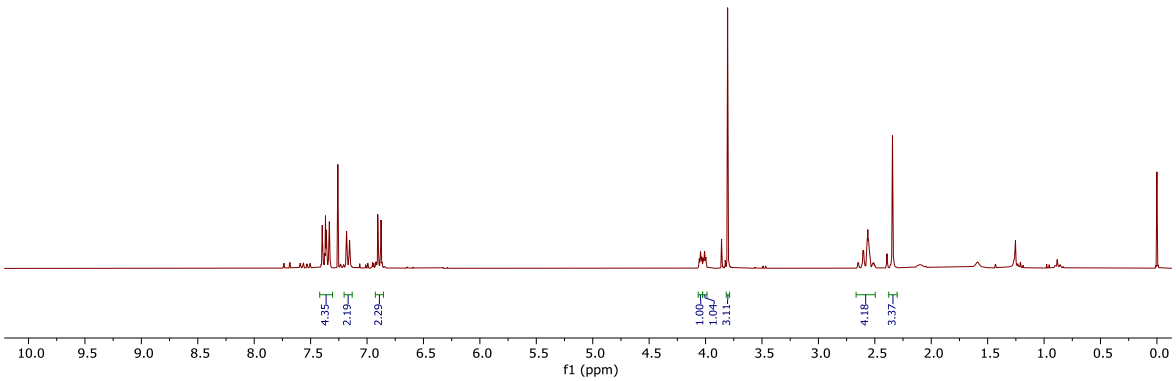
73a

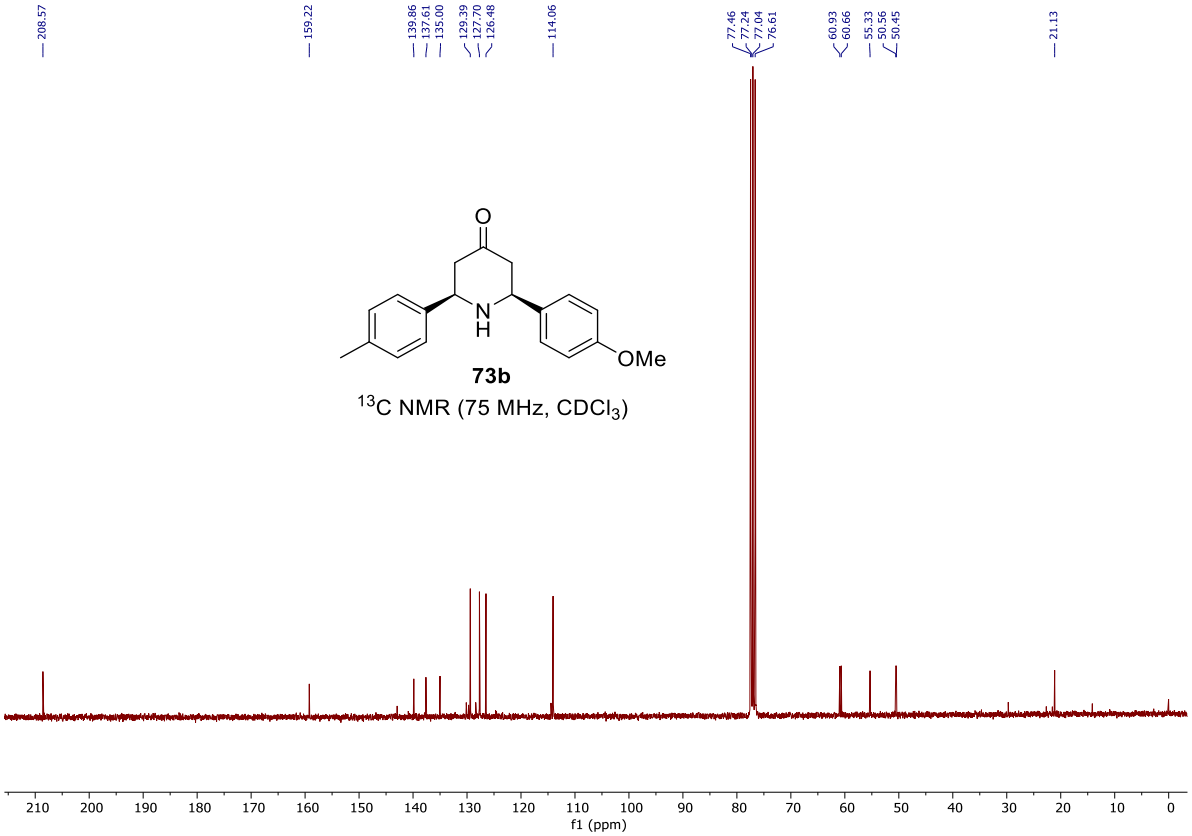
^{13}C NMR (75 MHz, $CDCl_3$)



73b

^{1}H NMR (300 MHz, $CDCl_3$)




208.57
159.22
139.86
137.61
135.00
129.39
127.70
126.48
114.06
77.46
77.24
77.04
76.61
60.93
60.66
55.33
50.56
50.45
21.13
O
N
H
OMe
73b
^{13}C NMR (75 MHz, CDCl$_3$)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

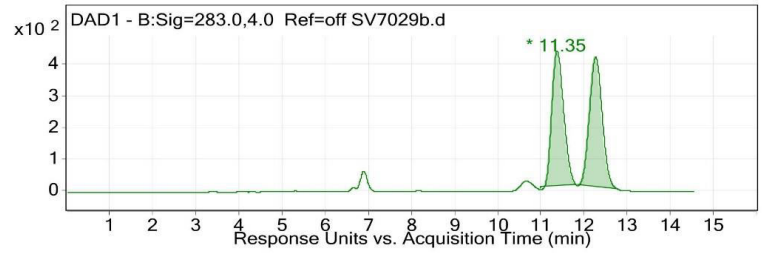
3.13 Selected HPLC traces

Qualitative Analysis Report

Data Filename	SV7029b.d	**Sample Name**	SV-07-69A racemic
Sample Type	Sample	**Position**	Vial 2
Instrument Name	LCMS 1260_6230	**User Name**	crit-TOF\agilent
Acq Method	SVirk_HPLC.m	**Acquired Time**	12/14/2020 12:20:14 PM
IRM Calibration Status	Success	**DA Method**	N.m
Comment			

Sample Group	**Info.**
Acquisition SW Version	6200 series TOF/6500 series Q-TOF B.05.01 (B5125.3)

User Chromatograms



Integration Peak List

Peak	Start	RT	End	Height	Area
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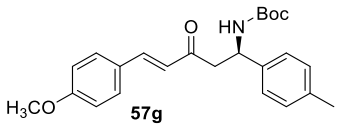
2	11.85	12.24	12.79	410.39	8522.31

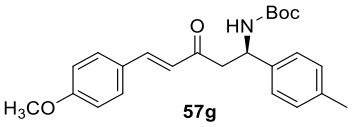


57g

--- End Of Report ---

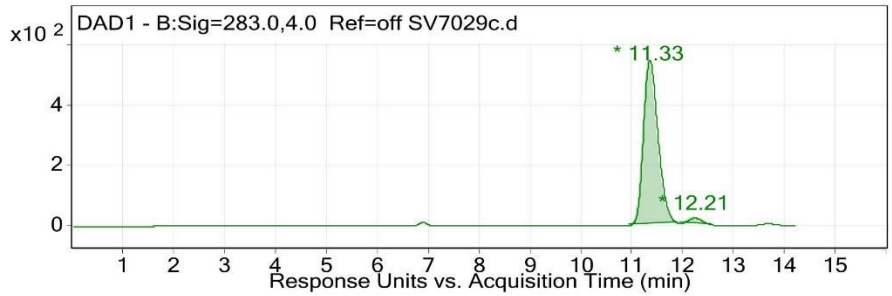
Qualitative Analysis Report

Data Filename	SV7029c.d	**Sample Name**	SV-07-05B recolumn
Sample Type	Sample	**Position**	Vial 3
Instrument Name	LCMS 1260_6230	**User Name**	crit-TOF\agilent
Acq Method	SVirk_HPLC.m	**Acquired Time**	12/14/2020 12:50:08 PM
IRM Calibration Status	Success	**DA Method**	N.m
Comment			
Sample Group		**Info.**	
Acquisition SW Version	6200 series TOF/6500 series Q-TOF B.05.01 (B5125.3)		



57g

User Chromatograms



Integration Peak List

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2	11.93	12.21	12.57	20.11	367.86	3.39

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Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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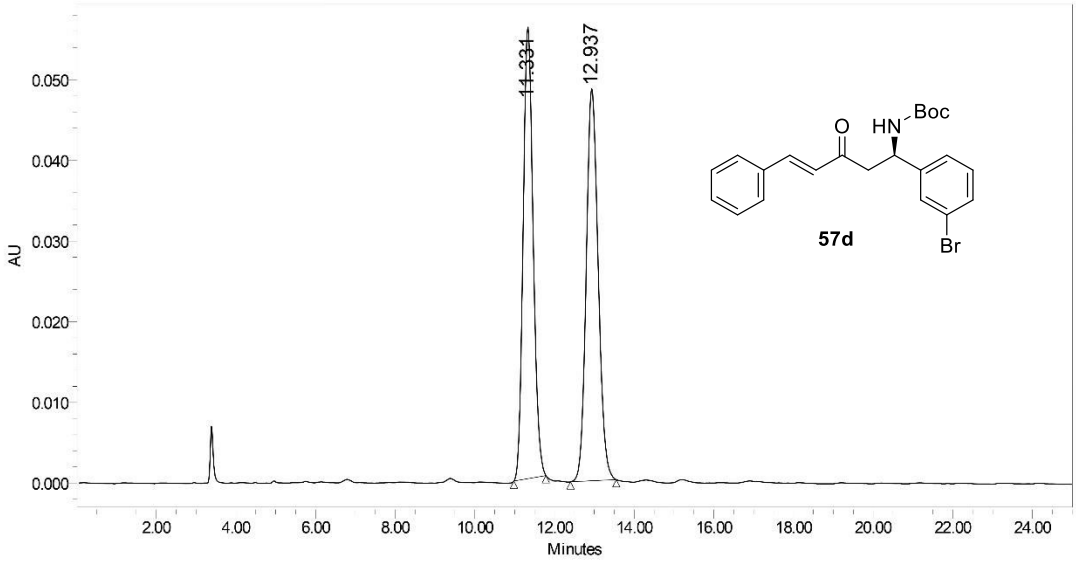

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Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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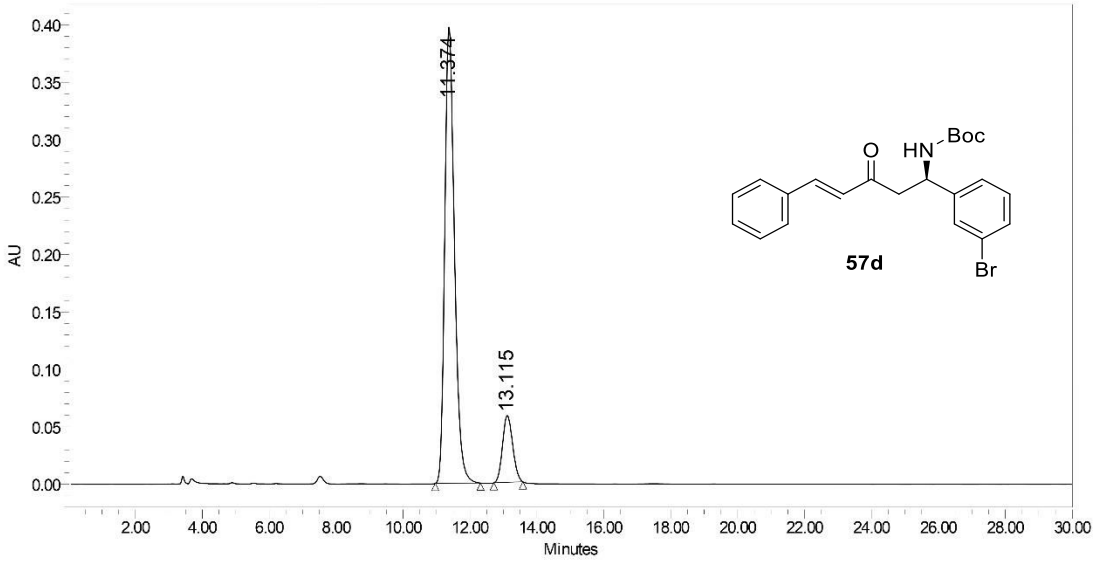

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Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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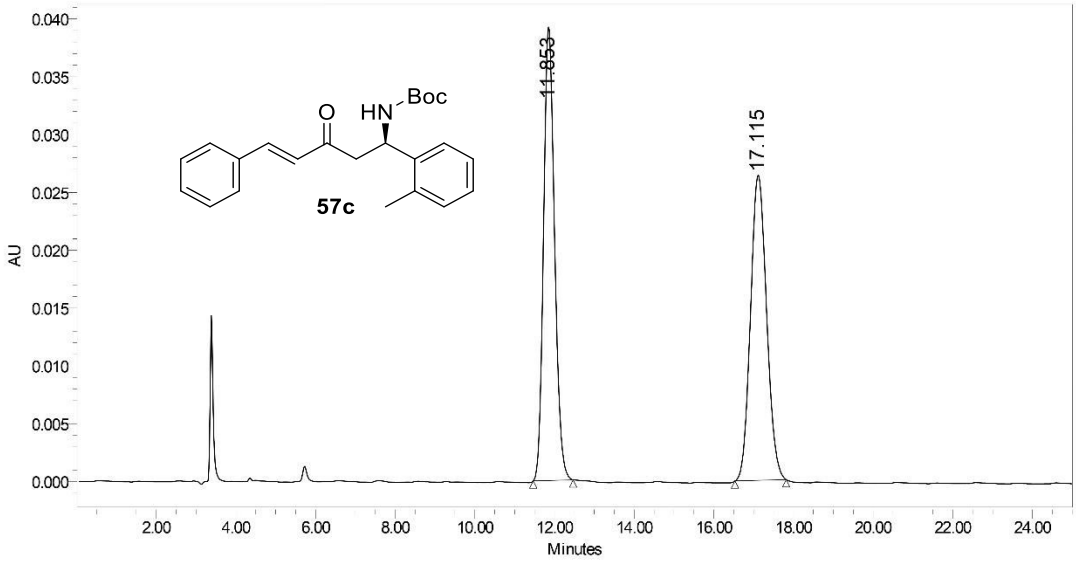

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Report Method: Individual Control Report

Page: 1 of 1

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Memorial University

Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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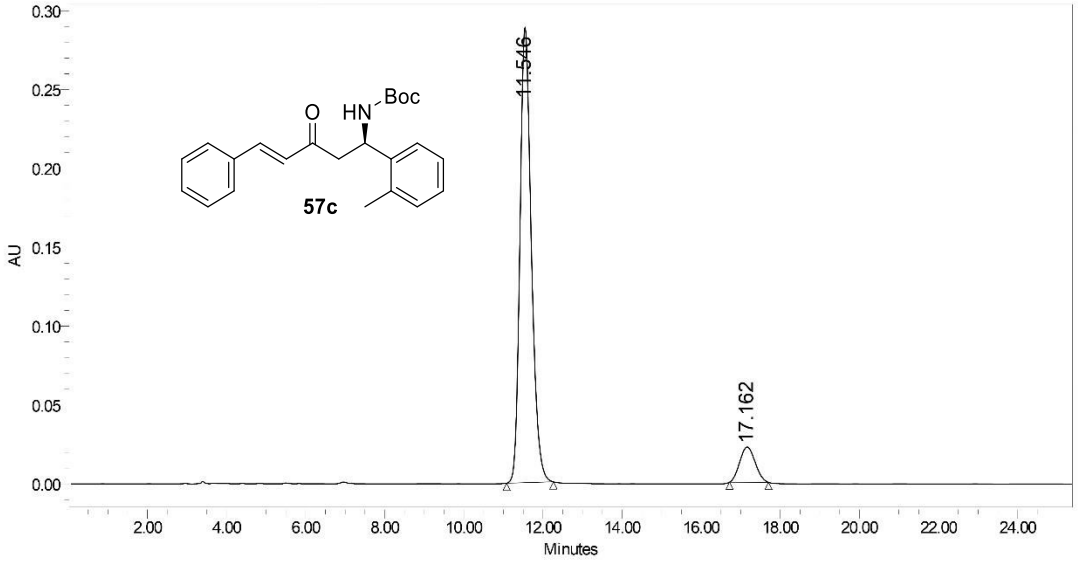

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Report Method: Individual Control Report

Page: 1 of 1

Printed: 06/04/2021

12:25:30 PM Canada/Newfoundland

Memorial University

Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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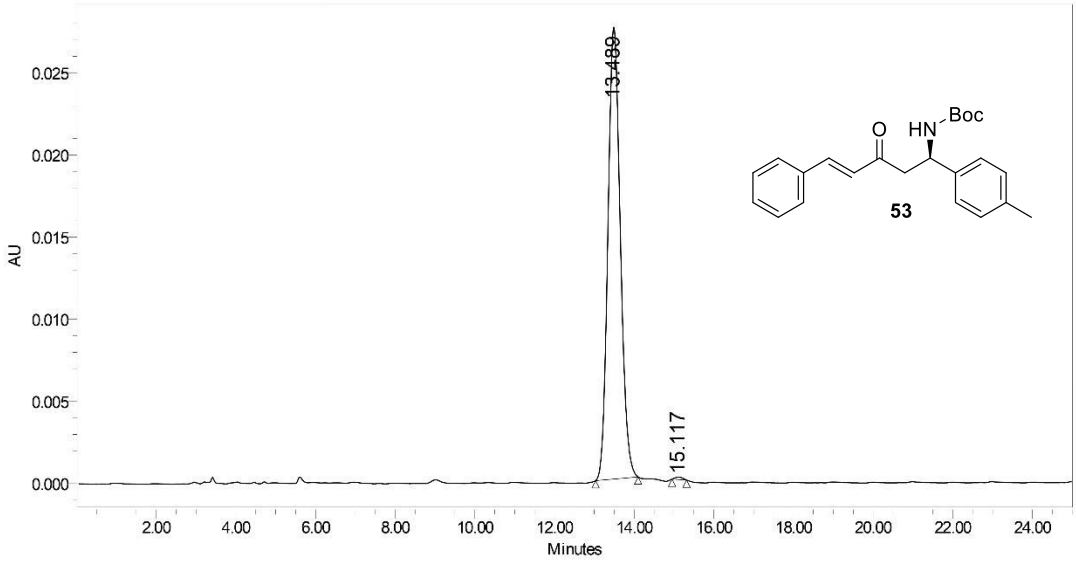

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2	15.117	1933	0.32	143	0.52

Report Method: Individual Control Report

Page: 1 of 1

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Memorial University

Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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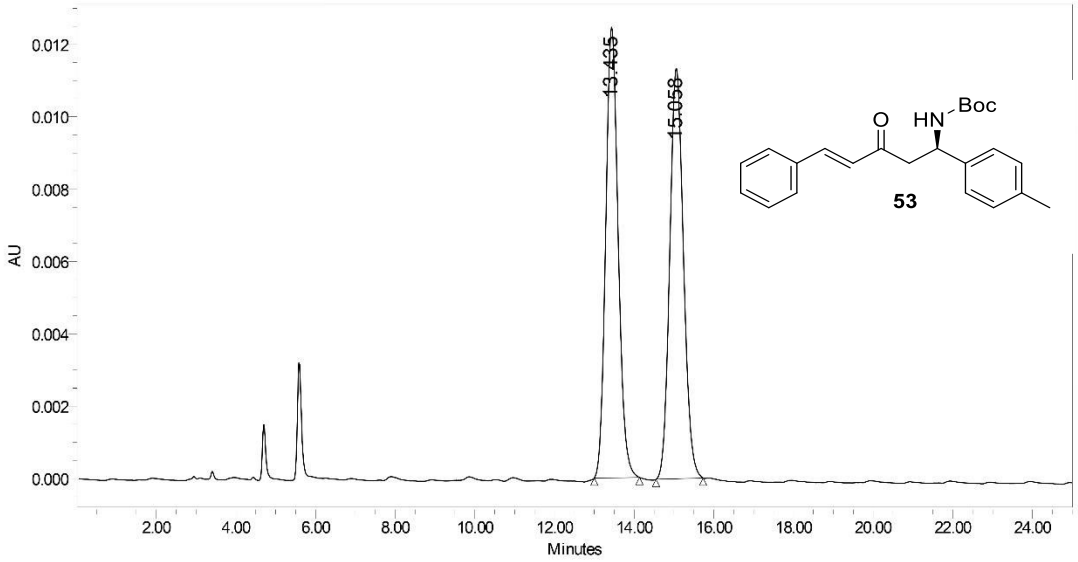

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Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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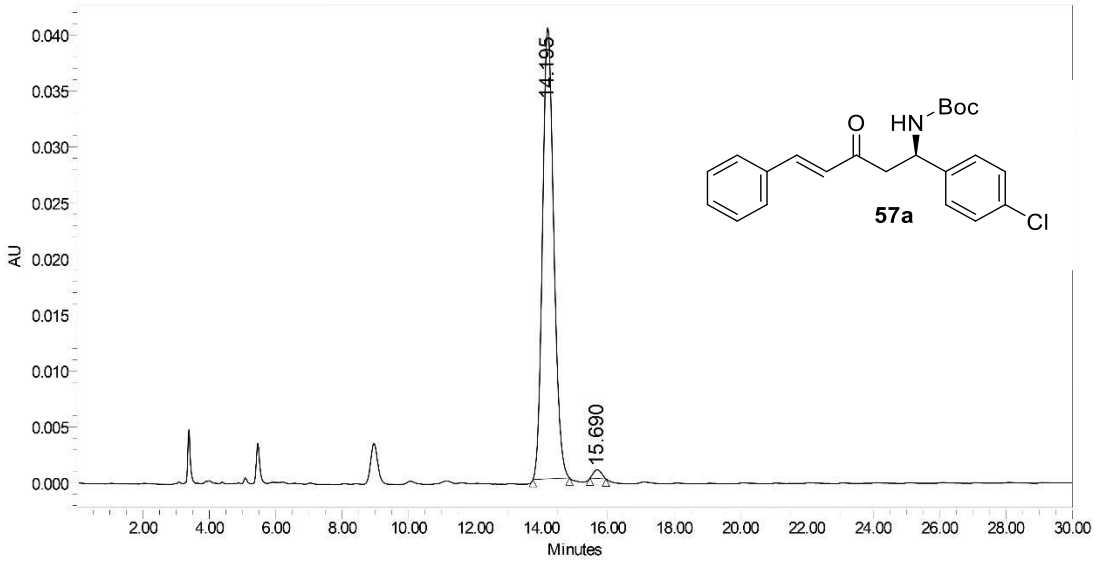

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Report Method: Individual Control Report

Page: 1 of 1

Printed: 07/04/2021

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Memorial University

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Breeze 2 HPLC System

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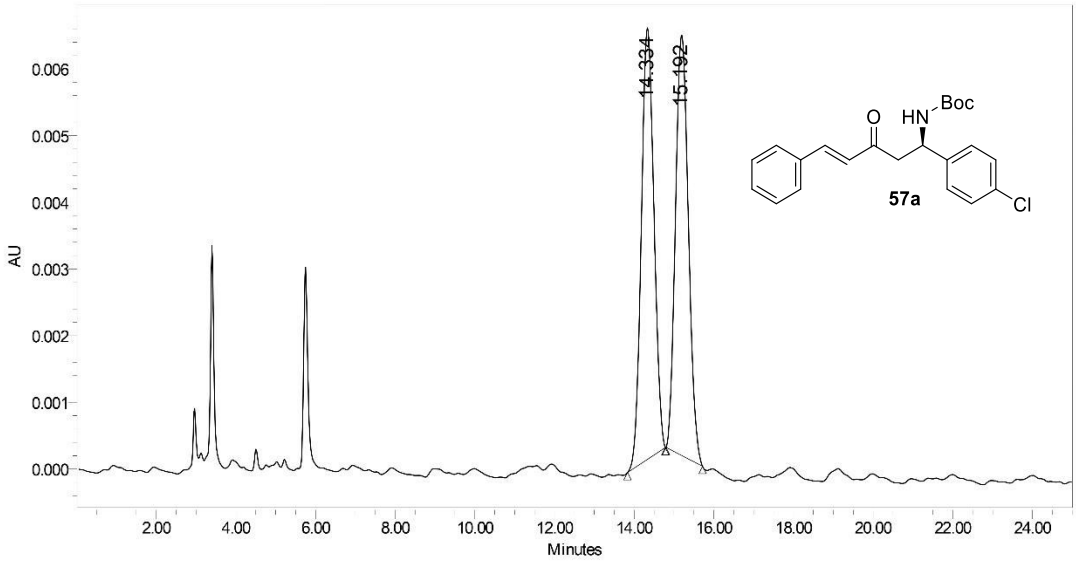

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1	14.334	142054	50.01	6469	50.65
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Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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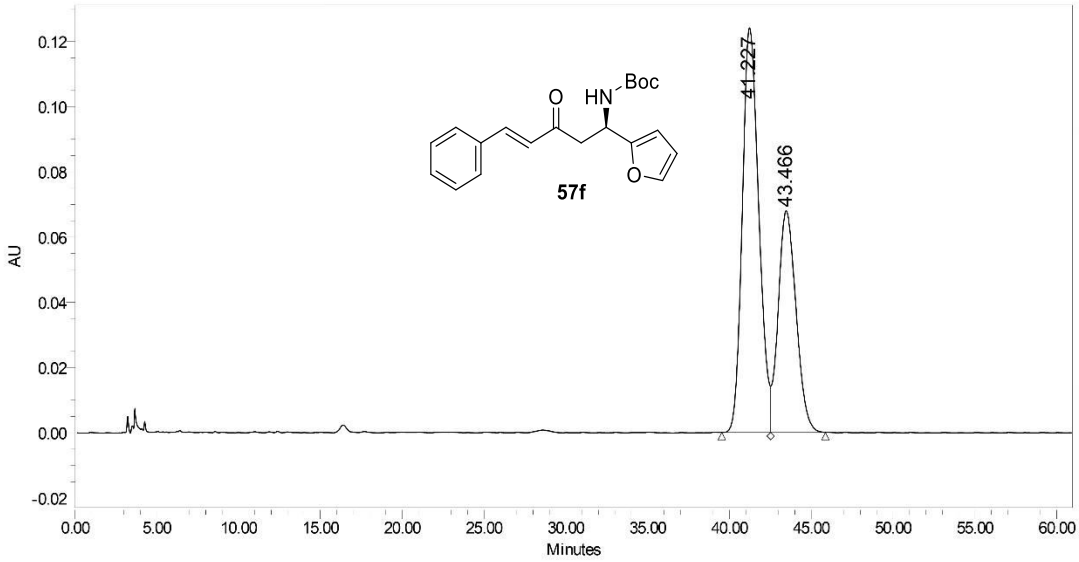

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1	41.227	8676106	62.61	124046	64.60
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Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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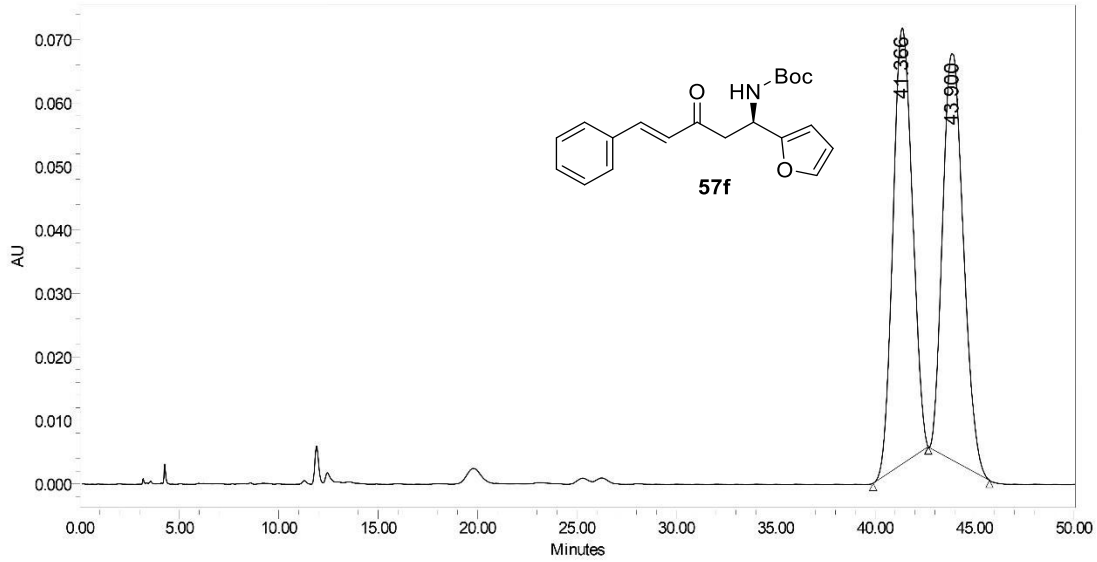

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1	41.366	4659153	50.03	68680	51.77
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Report Method: Individual Control Report

Page: 1 of 1

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Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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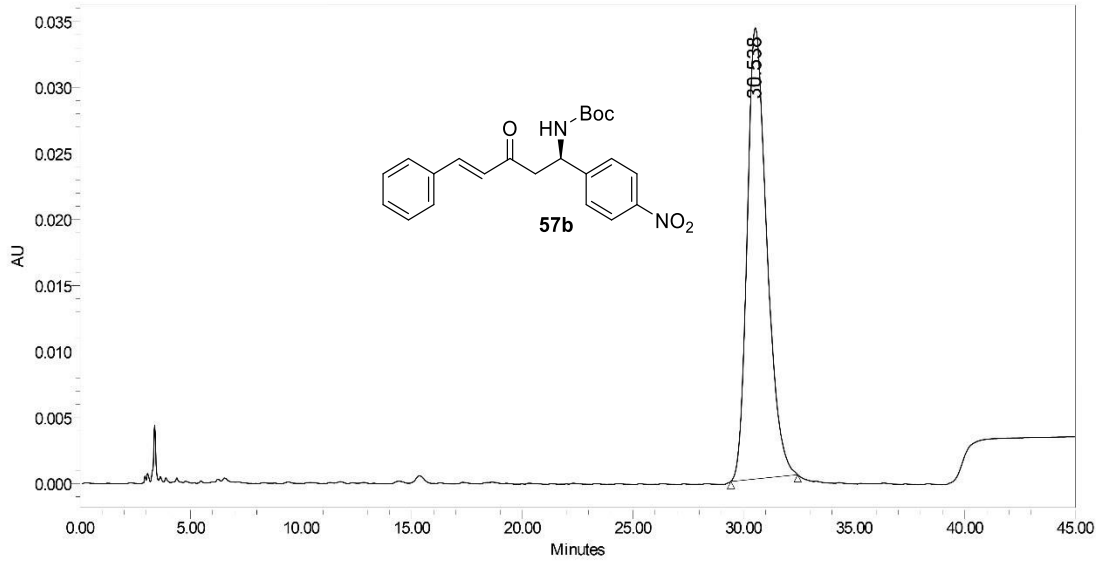

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1	30.538	2115051	100.00	34163	100.00

Report Method: Individual Control Report

Page: 1 of 1

Printed: 09/04/2021

2:16:09 PM Canada/Newfoundland

Memorial University

Project Name SEERAT

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Breeze 2 HPLC System

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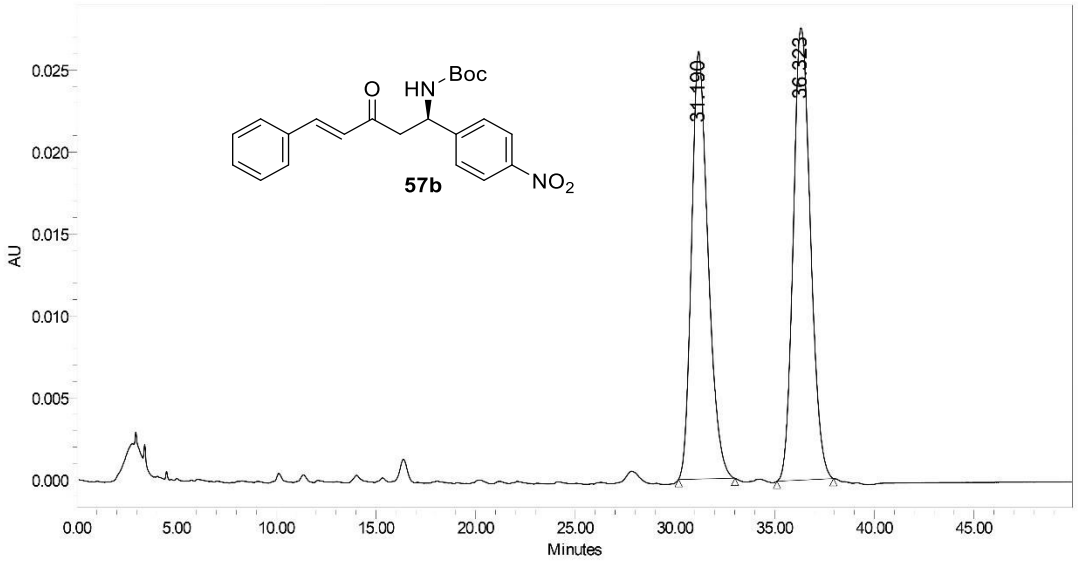

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2	36.323	1661048	52.45	27591	51.40

Memorial University

Project Name SEERAT

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Breeze 2 HPLC System

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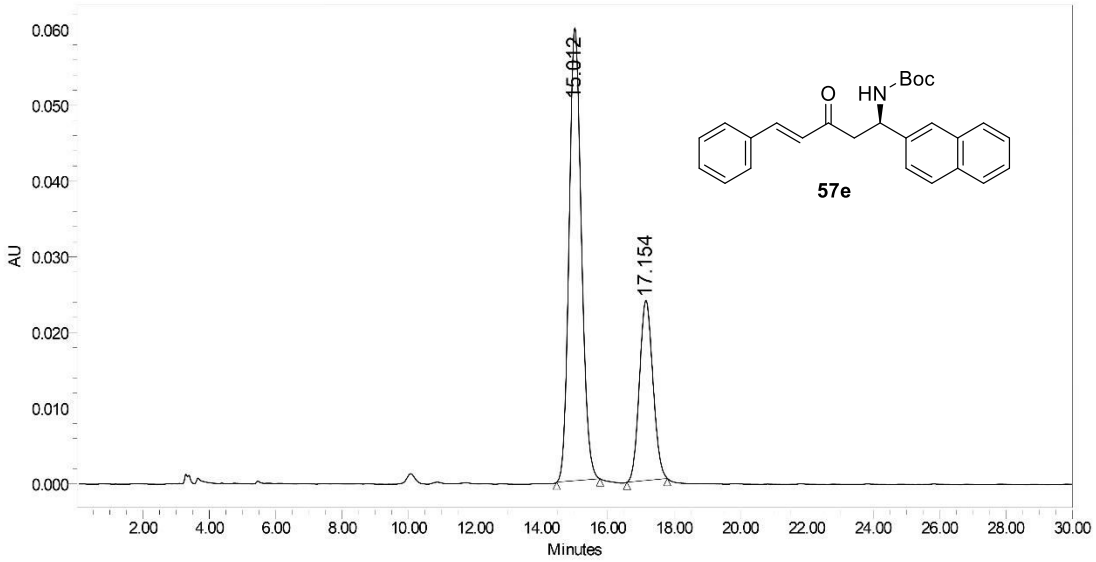

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	15.012	1539568	69.56	59825	71.55
2	17.154	673863	30.44	23787	28.45

Memorial University

Project Name SEERAT

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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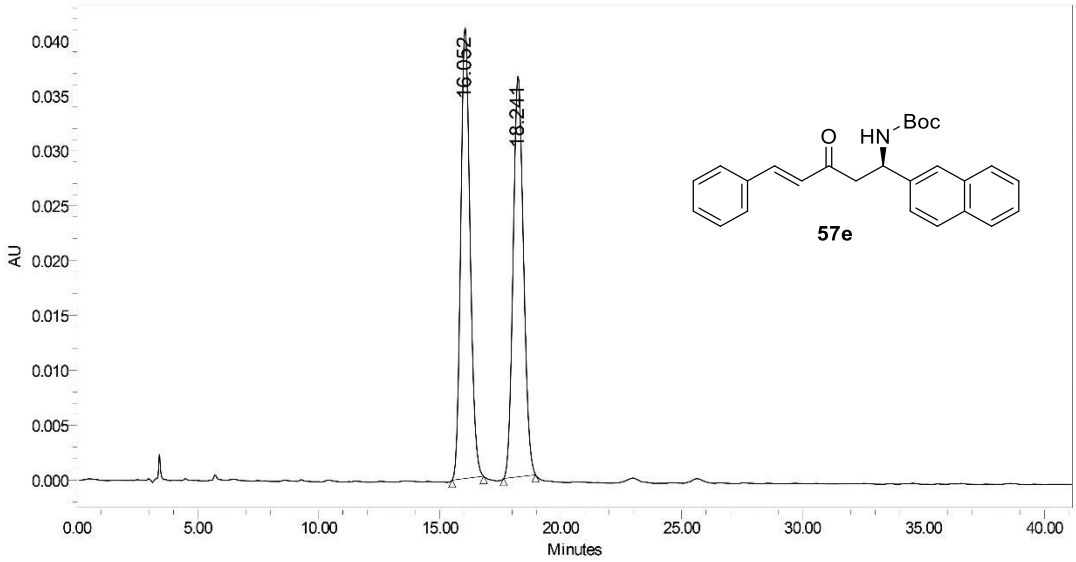


	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	16.052	1096236	50.28	41023	52.94
2	18.241	1084107	49.72	36467	47.06

Chapter 4

Synthesis of 2-Indolinone-based Analogues of (+)-Fistulopsine B and Their Biological Activity

4.1 Introduction

Indolizidine alkaloids[1] exhibit a wide array of biological activities and have been of interest because of their anticancer, antiviral, anti-inflammatory, and antidiabetic properties.[2] Selected diarylindolizidine and phenanthroindolizidine alkaloids include phyllostemine (**1**), secoantofine (**2**), ipalbidine (**3**), antofine (**4**) and tylophorine (**5**) (Figure 4.1). Aryl-substituted indolizidines are of interest as bioactive natural products[3] and as peptidomimetics.[4] Several synthetic strategies for aryl-fused[5] or aryl-substituted indolizidines[6] as well as other functionalized indolizidines[7] have been reported[8] and the field continues to develop rapidly.[9] The arylindolizidine alkaloids (-)-fistulopsine A (**6**) and (+)-fistulopsine B (**7**, Figure 4.1) have been isolated from the bark and leaves of the plant *Ficus Fistulosa*[10] and they are the most recent additions to the family of diarylindolizidine alkaloids. Structurally, these alkaloids resemble (+)-septicine (**8**) and they are of interest due to their *in vitro* antiproliferative activity against breast (MCF7) and colon (HCT 116) cancer cell lines.[11] The chemical synthesis of these alkaloids and their analogues will help in the study of their structure-activity relationships (SARs) to better harness their beneficial properties to treat several diseases.

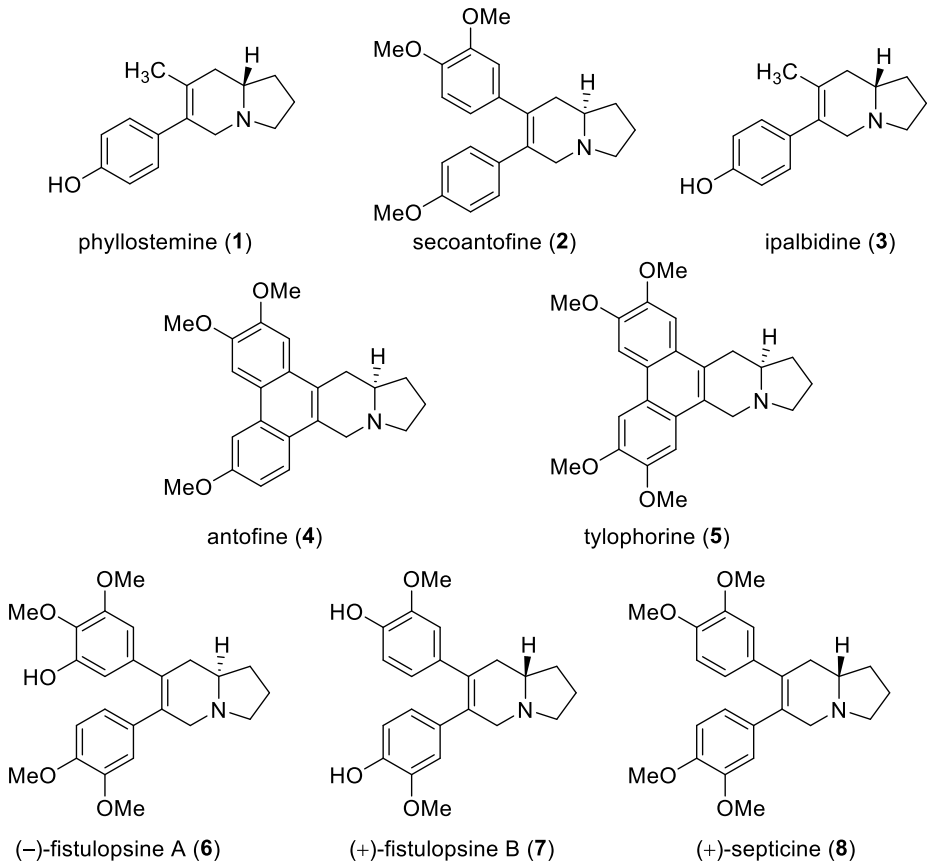


Figure 4.1: Selected diarylindolizidine and phenanthroindolizidine alkaloids

4.2 Objective

The primary objective of this study was the synthesis of analogues of (+)-fistulopsine B with structural variation in terms of a) the diaryl substitution on the indolizidine core (this would include the use of a protected phenol functionality) and b) the use of a cyclic amide instead of the pyrrolidine subunit. These variations are highlighted in Figure 4.2.

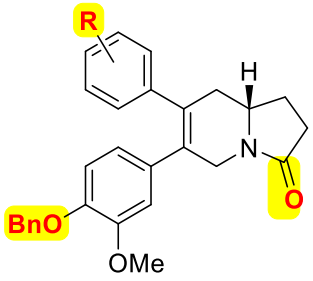


Figure 4.2 Structure of (+)-fistulopsine B showing the planned variations

We reasoned that having more rigidified structures due to the presence of an amide functionality and more lipophilic character due to the presence of the benzyl group would have a significant influence on the biological activity compared to fistulopsine. Whether this influence would be positive or negative, would be best articulated once these compounds are synthesized and tested.

4.3 Results and Discussion

These analogs of (+)-fistulopsine B with structural diversity in the aryl rings on the indolizidine were synthesized using a strategy previously devised in the Pansare group for the total synthesis of (+)-fistulopsine B.[12] The retrosynthetic analysis of our synthesis is provided in Figure 4.3.

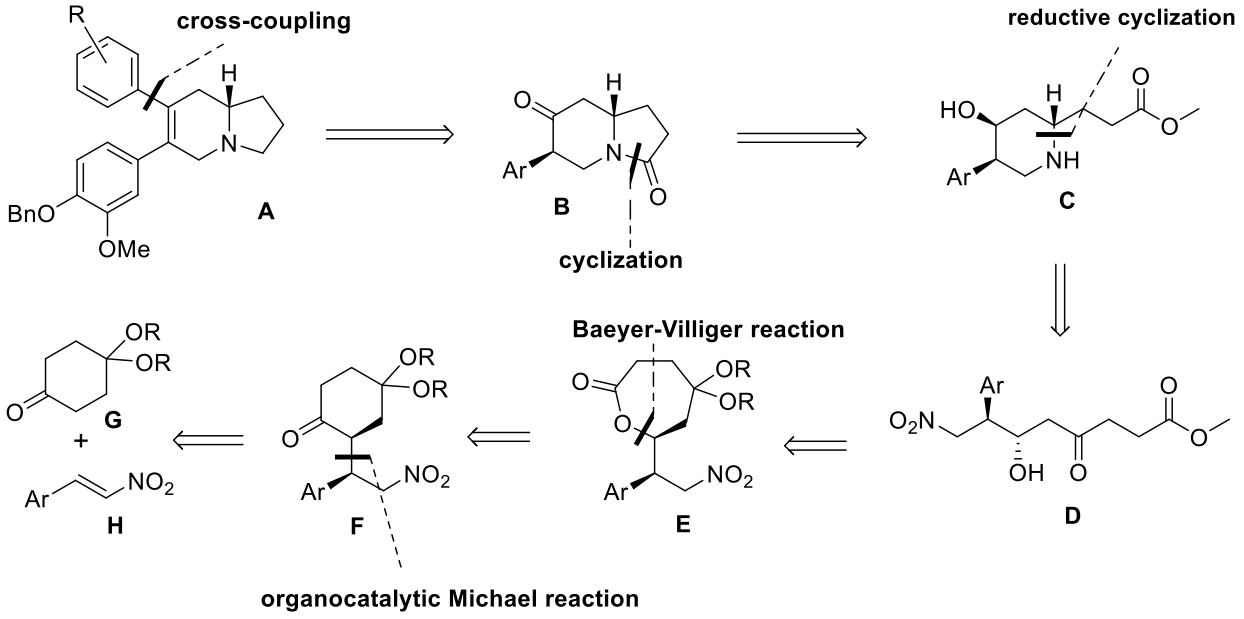
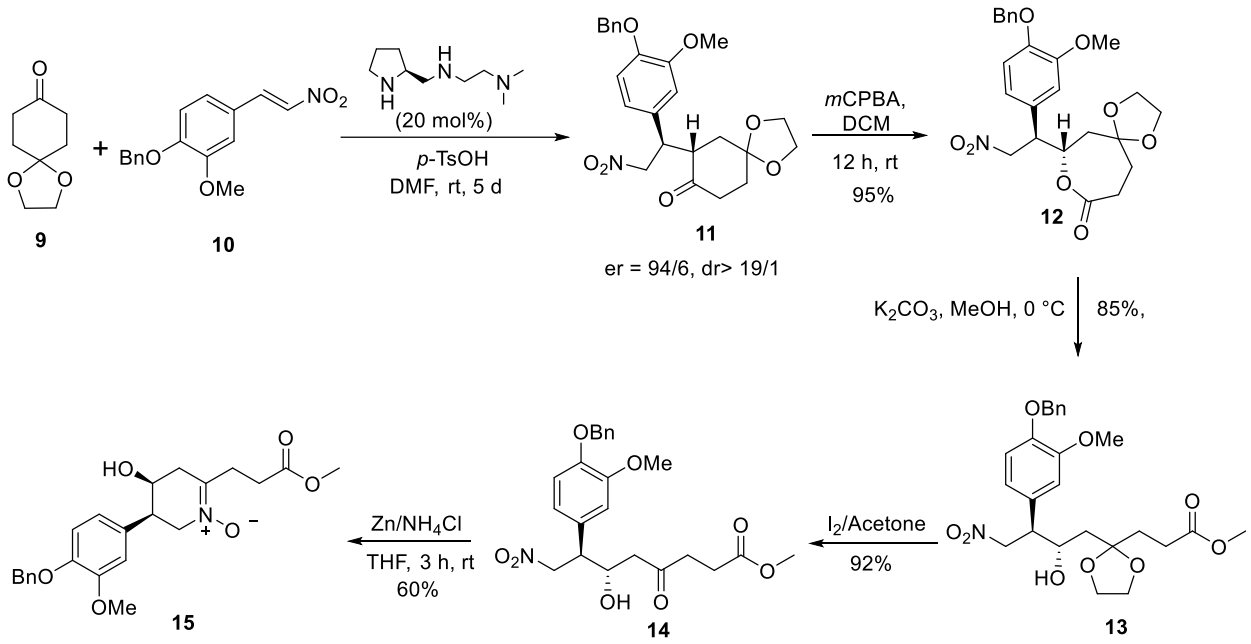


Figure 4.3 Retrosynthetic analysis for the synthesis of fistulopsine B analogues

According to our synthetic plan, fistulopsine B analog **A** could be obtained from the ketone **B** by converting it to an enol triflate followed by cross-coupling with the desired aryl

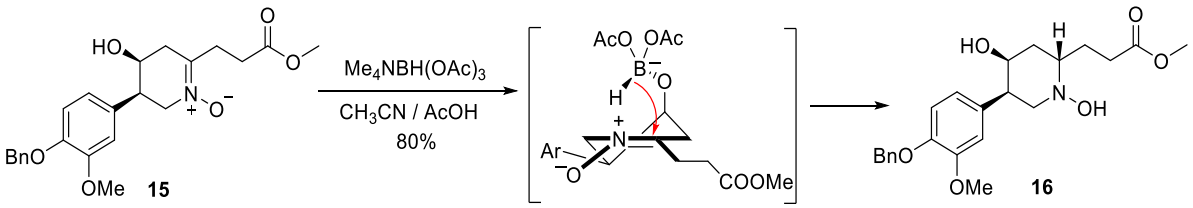
partner. Compound **B** could be synthesized from piperidine **C** by the cyclisation of a suitable side chain, and later by the oxidation of the alcohol. The synthesis of compound **C** could be achieved by reductive cyclization involving the nitro and the ketone groups of a diastereomerically pure acyclic precursor **D**. Compound **D** derives from the ring opening of lactone **E** followed by methanolysis and susbsequent removal of the ketal protecting group. Finally, lactone **E** derives from a Baeyer-Villiger oxidation of the γ-nitroketone **F** which, in turn, could be synthesised from the organocatalytic Michael addition of a monoprotected 1,4-cyclohexanedione **G** to a β-nitrostyrene **H** (Figure 4.3).

The synthetic sequence began with the organocatalytic Michael addition of cyclohexane-1,4-dione monoethylene ketal **9** to 4-benzyloxy-3-methoxy-β-nitrostyrene **10** employing our triamine catalyzed protocol,[12b] providing the γ-nitroketone **11** in good yield and stereoselectivity (er = 94/6, *dr*> 19/1, Scheme 4.01). The need for a robust protecting group such as a benzyl ether was realized during the development of the total synthesis of (+)-fistulopsine B wherein further reactions such as reductive cyclisation and ketal deprotection were found to be incompatible with either the free phenol or other ester protecting groups. Baeyer-Villiger oxidation of **11** provided the lactone **12** in 95% yield. Methanolysis of **12** followed by removal of the ketal protecting group gave the functionalized octanoate **14** (Scheme 4.01, 78% over two steps) containing the required number of carbon atoms for the formation of an indolizidine framework. Reductive cyclization of the octanoate **14** using zinc in aqueous ammonium chloride gave the nitrone **15** in 60% yield (Scheme 4.01).



Scheme 4.01

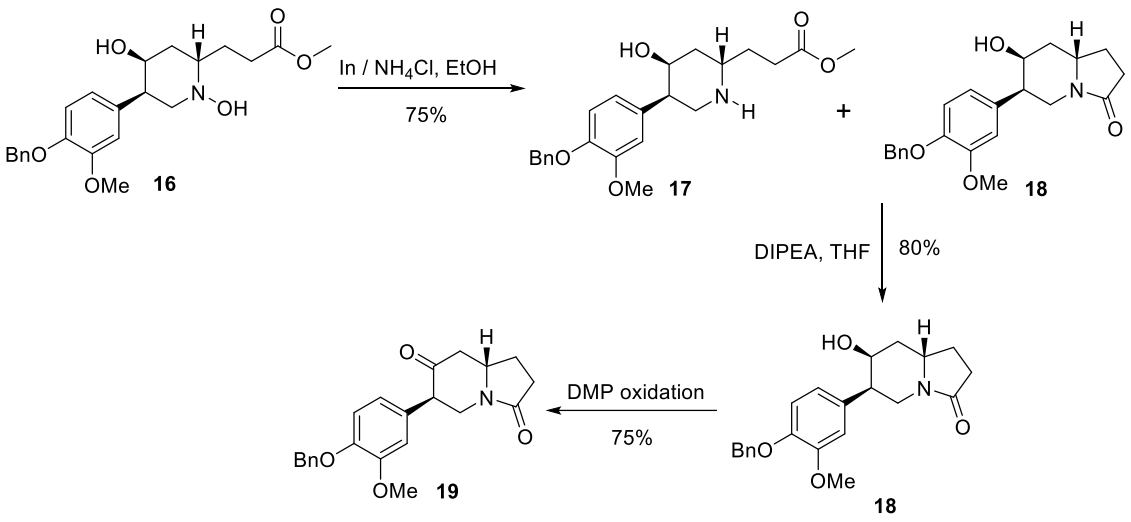
Nitrone **15** was stereoselectively reduced with $Me_4NBH(OAc)_3$ to obtain hydroxyl amine **16** in 80% yield and as a single diastereomer, presumably via an intramolecular hydroxyl-directed reduction[13] (Scheme 4.02). This step created a stereocenter which would ultimately be retained in fistulopsine B and its analogs.



Scheme 4.02

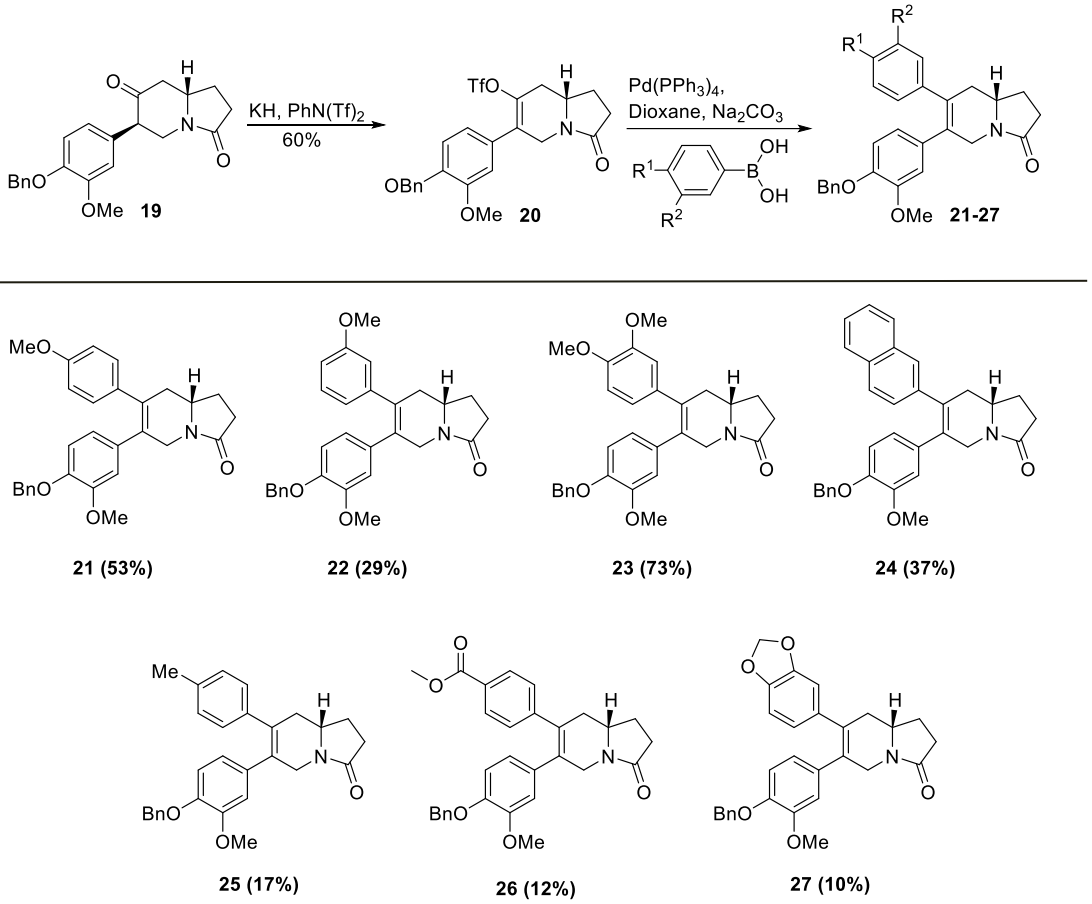
Once we had the key piperidine **16** in hand, the next step was its conversion to the indolizidine framework. Indium metal-based reduction of the N−O bond in **16** provided a mixture of the uncyclized amino ester **17** and the cyclised indolizidine **18**. This mixture was

treated with DIPEA in refluxing THF to achieve full conversion to the cyclised product **18** in 80% yield. Dess-Martin periodinane (DMP) oxidation of **18** provided the ketolactam **19** in 75% yield. (Scheme 4.03)



Scheme 4.03

Conversion of **19** to the enol triflate **20** followed by a Suzuki-Miyaura coupling[14] of **20** with a variety of boronic acids provided the corresponding fistulopsine B analogs (**21**-**27**) in varying 10-73% yields (Scheme 4.04).



Scheme 4.04

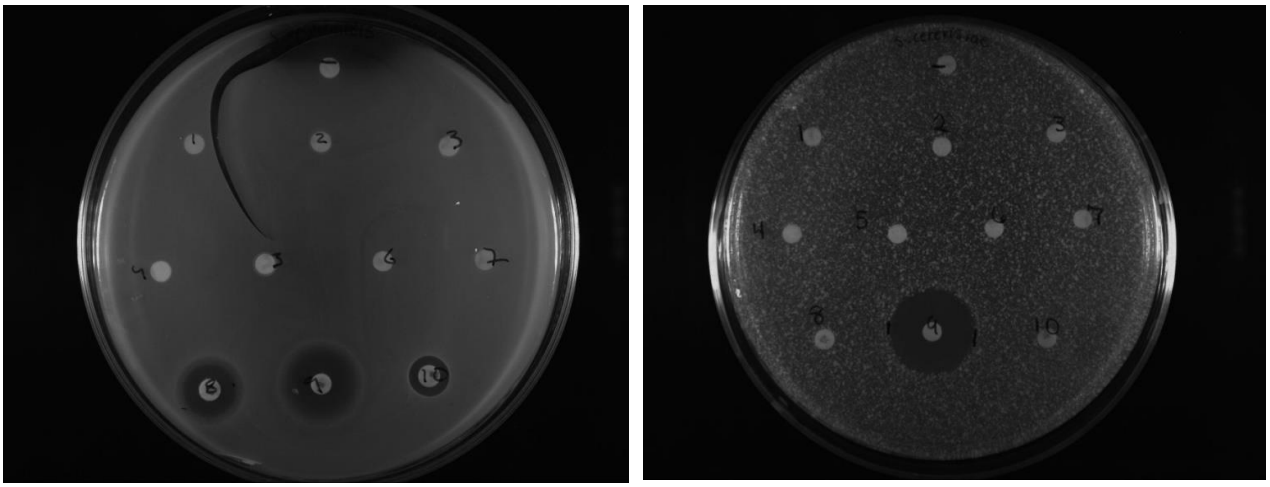
4.4 Biological testing

With the fistulopsine B analogs **21**-**27** in hand, we proceeded to examine their biological activity. These studies were conducted by Ms. Clarissa McIsaac in the laboratory of Dr. Kapil Tahlan in the Department of Biology at MUN.

Results:

An estimate of the activity of our compounds was obtained by examining the petri dishes for lack of microorganism growth in the immediate vicinity of the paper discs that were treated with our compounds. A lack of microorganism growth, and hence an indication of compound activity, appears as a clear ring around the paper disc (as compared to the uniform growth of the

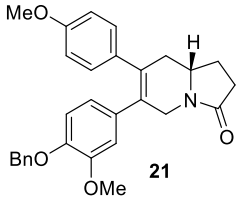
organism which appears as the general background). The principle is best explained by examining photographs of the petri dishes (Figure 4.4). The observations of the testing experiments (shown in Figure 4.4) are summarized in Table 4.1.

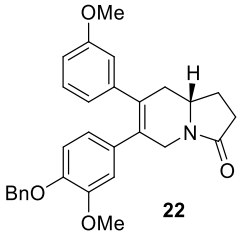
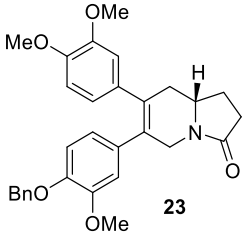
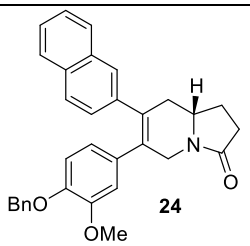
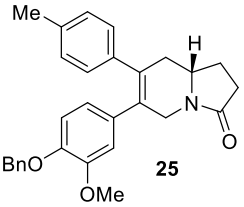
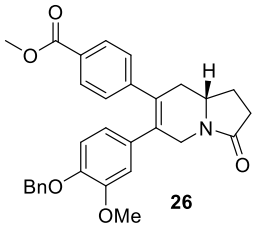
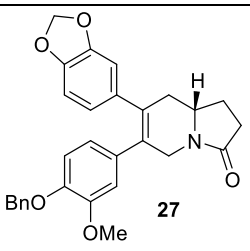


Photograph A Photograph B

Figure 4.4 Photographs of the testing results against *S. epidermidis* (A) and *S. cerevisiae* (B)

Table 4.1 Observations and conclusions for the results seen in Figure 4.4

Disc no. (Fig. 4.4)	**Compound**	**Observation**	**Conclusion**
0	DMSO (negative control)	No ring of inhibition	DMSO is not responsible for any activity
1	 **21**	No ring of inhibition	Inactive

2	 **22**	No ring of inhibition	Inactive
3	 **23**	No ring of inhibition	Inactive
4	 **24**	No ring of inhibition	Inactive
5	 **25**	No ring of inhibition	Inactive
6	 **26**	No ring of inhibition	Inactive
7	 **27**	No ring of inhibition	Inactive

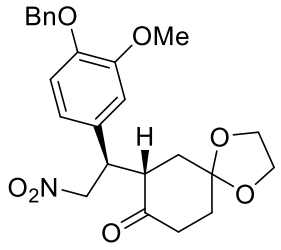
8	Gentamycin	Shows ring of inhibition (photograph A) No ring of inhibition (photograph B)	The inhibition of bacterial/fungi growth confirms that the results are accurate and the experimental conditions for the study are appropriate.
9	Tetracycline (photograph A) Nystatin (photograph B)	Show ring of inhibition	
10	Vancomycin	Shows ring of inhibition (photograph A) No ring of inhibition (photograph B)	

4.5 Conclusion

In conclusion, seven analogs of (+)-fistulopsine B were synthesized and tested for their biological activity. None of the synthesized analogs exhibited any antifungal or antibacterial activity. Although the reasons for the lack of activity can be numerous, we presume that the absence of a free phenolic –OH group in our analogs could be of significance since it would affect the polarity, and hence the uptake, of our compounds by the test organisms. Future efforts will therefore focus on the debenzylation of **21**-**27**. In addition, since (−)-fistulopsine A and (+)-fistulopsine B exhibit activity against certain cancer cell lines,[11] we plan to test our analogs for anticancer activity as well. Although none of the analogs show antifungal or antibacterial activity, their synthesis establishes access to a planned library of fistulopsine analogues.

4.6 Experimental section

(*S*)-7-((*R*)-1-(4-(Benzyloxy)-3-methoxyphenyl)-2-nitroethyl)-1,4-dioxaspiro[4.5]decan-8-one (11):

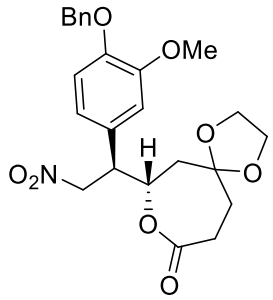


To a solution of 1,4-cyclohexanedione monoethylene ketal (16.4 g, 105 mmol), N^1,N^1-dimethyl-N^2-(((*S*)-pyrrolidin-2-yl)methyl)ethane-1,2-diamine (720 mg, 4.2 mmol) and *p*-toluene sulfonic acid monohydrate (800 mg, 4.2 mmol) was added a solution of 4-benzyloxy-3-methoxy-*β*-nitrostyrene **5** (6.0 g, 21 mmol) in DMF (60 mL) and the resulting solution was stirred at ambient temperature for 5 d. Ethyl acetate (200 mL) was added and the resulting solution washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The residue obtained was purified by flash column chromatography on silica gel (70/30 hexanes/EtOAc) to provide 8.3 g (89%) of **11** as a white foam.

IR (neat): 2925, 1709, 1548, 1510, 1257, 1232, 1139, 1117, 1011, 948 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.45-7.29 (m, 5H, Ar*H*), δ 6.82 (d, 1H, *J* = 8.2, Ar*H*), 6.68 (d, 1H, *J* = 2.1, Ar*H*), 6.64 (d, 2H, *J* = 8.2, 2.1, Ar*H*), 5.11 (s, 2H, OCH_2Ph), 4.90 (dd, 1H, *J* = 12.4, 4.7, CH_2NO_2), 4.60 (dd, 1H, *J* = 12.4, 9.8, CH_2NO_2), 4.00-3.83 (m, 4H, OCH_2CH_2O), 3.86 (s, 3H, OCH_3), 3.79-3.7 (dt, 1H, *J* = 13.4, 6.6, ArC*H*), 3.07-2.93 (m, 1H, COC*H*), 2.76-2.62 (dt, 1H, *J* = 13.8, 6.6, COCH_2), 2.50-2.39 (m, 1H, COCH_2), 2.09-1.86 (m, 2H, CHCH_2), 1.74-1.64 (m, 1H, CH_2CH_2), 1.54 (t, 1H, *J* = 13.0, CH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.5 (*C*O), 149.8 (ArC_{ipso}), 147.8 (ArC_{ipso}),

137.0 (ArC_{ipso}), 130.2 (ArC_{ipso}), 128.6 (2 x Ar*C*), 127.9 (Ar*C*), 127.4 (2 x Ar*C*), 120.2 (Ar*C*), 114.2 (Ar*C*), 112.0 (Ar*C*), 107.1 (O*C*O), 79.0 (*C*H_2NO_2), 71.1 (*C*H_2OPh), 64.8 (O*C*$H_2C H_2$O), 64.6 (OCH_2*C*H_2O), 56.1 (O*C*H_3), 48.3 (CO*C*H), 43.1 (*C*HCH_2NO_2), 39.3 (CO*C*H_2), 38.7 (*C*H_2), 35.1 (*C*H_2); HRMS (APPI, pos.) *m/z* 441.1801 (441.1788 calc. for $C_{24}H_{27}NO_7$ $[M]^+$); HPLC (Chiralpak AS-H, hexanes/2-propanol, 90/10, flow rate 1.0 mL/min, 254 nm): t_{minor} = 12.55 min, t_{major} = 17.54 min, ee = 95%, dr = 20:1 (average value from multiple reactions).

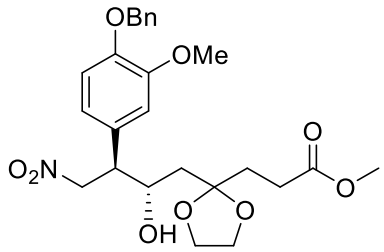
(*S*)-7-((*R*)-1-(4-(Benzyloxy)-3-methoxyphenyl)-2-nitroethyl)-1,4,8-trioxaspiro[4.6]undecan-9-one (12):



To a solution of nitroketone **11** (3.0 g, 6.8 mmol) in anhydrous dichloromethane (50 mL) at ambient temperature was added solid sodium phosphate (2.36 g, 8.80 mmol) followed by *m*-chloroperoxybenzoic acid (~77%, 3.63 g, 21 mmol). The resulting white slurry was stirred vigorously for 16 h at ambient temperature. Dichloromethane (100 mL) was added and the mixture was washed with aqueous $NaHCO_3$ (2 x 60 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue obtained was purified by flash column chromatography on silica gel (60/40 EtOAc/hexanes) to provide 2.9 g (93%) of **12** as a yellow foam.

IR (neat): 2936, 2887, 1734, 1551, 1513, 1378, 1327, 1260, 1232, 1144, 1099, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ 7.44-7.31 (m, 5H, Ar*H*), 6.85 (d, 1H, *J* = 8.2, Ar*H*), 6.73 (d, 1H, *J* = 2.1, Ar*H*), 6.70 (dd, 1H, *J* = 8.2, 2.1, Ar*H*), 5.13 (s, 2H, OCH_2Ph), 4.93 (dd, 1H, *J* = 12.7, 4.7, CH_2NO_2), 4.72 (dd, 1H, *J* = 12.7, 9.3, CH_2NO_2), 4.74-4.63 (m, 1H (CO)OC*H*), 3.89 (s, 3H, OCH_3), 3.87-3.73 (m, 3H, OCH_2CH_2O), 3.56 (dt, 1H, *J* = 9.3, 4.7, ArC*H*), 3.47-3.41 (m, 1H, OCH_2CH_2O), 2.88-2.80 (m, 1H, CH_2CO), 2.66-2.56 (m, 1H, CH_2CO), 1.93-1.87 (m, 2H, CH_2(C)CH_2), 1.82-1.80 (m, 2H, CH_2(C)CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6 (*C*O), 150.0 (ArC_{ipso}), 148.1 (ArC_{ipso}), 136.8 (ArC_{ipso}), 128.9 (ArC_{ipso}), 128.6 (2 x Ar*C*), 128.0 (Ar*C*), 127.4 (2 x Ar*C*), 120.5 (Ar*C*), 114.3 (Ar*C*), 111.8 (Ar*C*), 107.2 (O*C*O), 77.8 (*C*H_2NO_2), 75.8 (*C*OC(O)), 70.9 (O*C*H_2Ph), 65.0 (O*C*H_2CH_2O), 64.3 (OCH_2*C*H_2O), 56.1 (O*C*H_3), 48.5 (OCH*C*H_2), 41.4 (*C*HCH_2NO_2), 33.1 (*C*H_2(C)CH_2), 29.4 (CH_2(C)*C*H_2); HRMS (APPI, pos.): *m/z* 457.1749 (457.1737 calc. for $C_{24}H_{27}NO_8$ $[M]^+$), *m/z* 475.2086 (475.2080 calc. for $C_{24}H_{31}N_2O_8$ $[M+NH_4]^+$).

Methyl 3-(2-((2*S*, 3*R*)-3-(4-(benzyloxy)-3-methoxyphenyl)-2-hydroxy-4-nitrobutyl)-1,3-dioxolan-2-yl) propanoate (13):

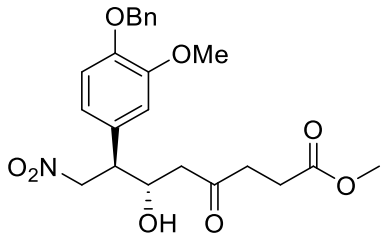


A solution of the lactone **12** (3.3 g, 7.2 mmol) in methanol (70 mL) was cooled to 0 °C and potassium carbonate (2.00 g, 14.4 mmol) was added. The mixture was stirred at ambient temperature for 2 h. The mixture was then cooled to 0 °C, neutralized with aqueous HCl (0.5 M)

and the resulting solution was extracted with dichloromethane (2 x 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to provide 3.0 g, (85%) of the nitroketal **13** as a light brown gum. This material was pure by ^{1}H NMR and was directly used as is.

IR (neat): 3499, 2953, 1732, 1549, 1515, 1453, 1436, 1379, 1261, 1233, 1141, 1024 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) : δ 7.44-7.29 (m, 5H, Ar*H*), 6.83 (d, 1H, *J* = 8.2, Ar*H*), 6.70 (d, 1H, *J* = 2.1, Ar*H*), 6.65 (dd, 1H, *J* = 8.2, 2.1, Ar*H*), 5.12 (s, 2H, OC*H*$_2$Ph), 5.02 (dd, 1H, *J* = 12.9, 5.3, C*H*$_2$NO$_2$), 4.59 (dd, 1H, *J* = 12.9, 9.5, C*H*$_2$NO$_2$), 4.08-3.98 (m, 1H, ArC*H*), 3.98-3.90 (m, 4H, OC*H*$_2$C*H*$_2$O), 3.86 (s, 3H, ArOC*H*$_3$), 3.63 (s, 3H, CO_2C*H*$_3$), 3.37 (dt, 1H, *J* = 9.3, 5.3, C*H*OH), 2.25-2.17 (m, 2H, CO_2C*H*$_2$), 2.05-1.95 (m, 1H, C*H*$_2$(C)CH$_2$), 1.87-1.77 (m, 1H, C*H*$_2$(C)CH$_2$), 1.66-1.62 (m, 2H, CH$_2$(C)C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6 (*C*O_2CH_3), 149.9 (Ar*C*$_{ipso}$), 147.9 (Ar*C*$_{ipso}$), 137.0 (Ar*C*$_{ipso}$), 130.3 (Ar*C*$_{ipso}$), 128.6 (2 x Ar*C*), 127.9 (Ar*C*), 127.3 (2 x Ar*C*), 120.1 (Ar*C*), 114.3 (Ar*C*), 111.8 (Ar*C*), 110.9 (O*C*O), 78.4 (*C*H$_2$NO$_2$), 71.0 (O*C*H$_2$Ph), 70.0 (*C*HOH), 65.1 (O*C*H$_2$*C*H$_2$O), 64.6 (O*C*H$_2$*C*H$_2$O), 56.1 (ArO*C*H$_3$), 51.7 (CO_2CH$_3$), 50.6 (HO-C*C*H$_2$), 40.5 (Ar*C*H), 31.8 (*C*H$_2$CH$_2$COOCH$_3$), 28.5 (*C*H$_2$CO$_2$CH$_3$); HRMS (APPI, pos.): *m/z* 489.2016 (489.1999 calc. for $C_{25}H_{31}NO_9$ $[M]^+$), *m/z* 507.2317 (507.2343 calc. for $C_{25}H_{35}N_2O_9$ $[M+NH_4]^+$).

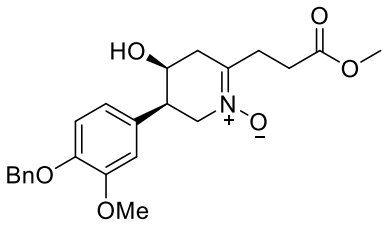
(6*S*,7*R*)-Methyl 7-(4-(benzyloxy)-3-methoxyphenyl)-6-hydroxy-8-nitro-4-oxooctanoate (14):



To a solution of nitroketal **13** (2.9 g, 5.9 mmol) in acetone (55 mL) was added iodine (150 mg, 0.6 mmol) and the solution was stirred at ambient temperature for 1 h. The acetone was removed under reduced pressure and the residue was diluted with dichloromethane (2 x 50 mL). The resulting solution was washed with aqueous $Na_2S_2O_3$ (5% w/v, 2 x 10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. This procedure was repeated one more time with the same amount of materials to finally provide 2.4 g (92%) of the nitroketone **14** as a white, fluffy solid. This material was pure by ^{1}H NMR and was directly used in the next step.

IR (neat): 3441, 2939, 2900, 1732, 1711, 1549, 1519, 1379, 1366, 1262, 1205, 1139, 1105, 1026 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) : δ 7.44-7.29 (m, 5H, Ar*H*), 6.83 (d, 1H, *J* = 8.2, Ar*H*), 6.71 (d, 1H, *J* = 2.1, Ar*H*), 6.65 (dd, 1H, *J* = 8.2, 2.1, Ar*H*), 5.11 (s, 2H, OC*H*$_2$Ph), 5.05 (dd, 1H, *J* = 12.8, 5.0, C*H*$_2$NO$_2$), 4.6 (dd, 1H, *J* = 12.8, 9.7, C*H*$_2$NO$_2$), 4.24-4.18 (m, 1H, Ar-C*H*), 3.87 (s, 3H, OC*H*$_3$), 3.65 (s, 3H, CO$_2$C*H*$_3$), 3.65 (s, 1H, CHO*H*), 3.50-3.42 (dt, 1H, *J* = 9.9, 5.2, C*H*OH), 2.61-2.55 (m, 4H, C*H*$_2$COC*H*$_2$), 2.54-2.45 (m, 2H, C*H*$_2$CO$_2$CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): 209.8 (*C*O), 173.2 (*C*O$_2$CH$_3$), 150.0 (Ar*C*$_{ipso}$), 148.1 (Ar*C*$_{ipso}$), 136.9 (Ar*C*$_{ipso}$), 129.8 (Ar*C*$_{ipso}$), 128.6 (2 x Ar*C*), 128.0 (Ar*C*), 127.4 (2 x Ar*C*), 120.1 (Ar*C*), 114.3 (Ar*C*), 111.7 (Ar*C*), 78.4 (*C*H$_2$NO$_2$), 71.0 (*C*H$_2$OPh), 69.9 (*C*HOH), 56.1 (O*C*H$_3$), 52.0 (CO$_2$*C*H$_3$), 49.6 (HOC-*C*H$_2$CO), 47.1 (Ar*C*H), 37.8 (CO*C*H$_2$), 27.5 (*C*H$_2$CO$_2$CH$_3$); HRMS (APPI, pos.): *m/z* 445.1754 (445.1737 calc. for $C_{23}H_{27}NO_8$ $[M]^+$), *m/z* 463.2087 (463.2080 calc. for $C_{23}H_{31}N_2O_8$ $[M+NH_4]^+$).

(3*R*, 4*S*)-3-(4-(Benzyloxy)-3-methoxyphenyl)-4-hydroxy-6-(3-methoxy-3-oxopropyl)-2,3,4,5-tetrahydropyridine-1-oxide (15):

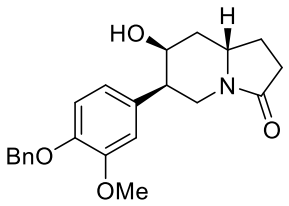


A solution of NH_4Cl (252 mg, 4.70 mmol) in water (11.5 mL) was added to a solution of the nitroketone **14** (2.1 g, 4.7 mmol) in THF (32 mL). Activated Zn powder (3.10 g, 47.1 mmol) was added and the mixture was stirred vigorously at room temperature under nitrogen for 3 h. The mixture was filtered (Celite), the filter cake was washed with THF, and the combined filtrates were concentrated under reduced pressure. Dichloromethane (50 mL) was added to the residue and the resulting mixture was washed with water (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (98/2 Dichloromethane/MeOH) to provide 1.2 g (63%) of the nitrone **15** as a purple-brown foam.

IR (neat): 2948, 1735, 1511, 1453, 1435, 1265, 12124, 1196, 1173, 1133, 1070, 1007 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.45-7.30 (m, 5H, Ar*H*), 6.87-6.85 (m, 2H, Ar*H*), 6.75 (dd, 1H, *J* = 8.4, 2.0, Ar*H*), 5.15 (s, 2H, OCH_2Ph), 4.29 (br t, 1H, *J* = 13.6, ArC*H*), 4.19 (br s, 1H, C*H*OH), 3.92 (dd, 1H, *J* = 13.6, 5.7, CH_2N), 3.88 (s, 3H, OCH_3), 3.66 (s, 3H, CO_2CH_3), 3.21 (dd, 1H, *J* = 13.6, 5.7, CH_2N), 2.91-2.66 (m, 6H, CH_2C=N, $COCH_2CH_2$, COCH_2), 2.36 (br s, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) : 173.7 (*C*O), 149.7 (ArC_{ipso}), 147.6 (ArC_{ipso}), 145.4 (*C*=NO), 137.03 (ArC_{ipso}), 130.9 (ArC_{ipso}), 128.6 (2 x Ar*C*), 127.9 (Ar*C*), 127.3 (2 x Ar*C*), 119.8 (Ar*C*), 114.0

(Ar*C*), 111.8 (Ar*C*), 71.0 (*C*H_2OPh), 64.9 (*C*H_2NO), 57.7 (Ar*C*H), 56.0 (O*C*H_3), 51.9 ($CO_2C H_3$), 44.0 (*C*HOH), 38.8 (*C*$H_2CO_2CH_3$), 28.3 (N=C*C*H_2), 27.4 (N=C*C*H_2); HRMS (APPI): *m/z* 413.1828 (413.1838 calc. for $C_{23}H_{27}NO_6$ $[M]^+$), *m/z* 414.1901 (414.1917 calc. for $C_{23}H_{28}NO_6$ $[M+H]^+$).

(6*R*,7*S*, 8a*S*)-6-(4-(Benzyloxy)-3-methoxyphenyl)-7-hydroxyhexahydroindolizin-3(5*H*)-one (16):



To a solution of tetramethylammonium triacetoxyborohydride (891 mg, 3.39 mmol) in acetonitrile (4 mL) was added glacial acetic acid (2.26 mL). The mixture was stirred at 0 °C for 5 min and a solution of nitrone **15** (700 mg, 1.69 mmol) in acetonitrile (6 mL) was added. The mixture was stirred at 0 °C for 1 h and the pH of the solution was adjusted (pH 7 to 8) with aqueous NaOH (5% solution). The resulting mixture was extracted with dichloromethane (50 mL) and the combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give 630 mg (90%) of **16** as a purple foam. This crude material was used further without purification.

^{1}H NMR (300 MHz, $CDCl_3$): 7.45-7.29 (m, 5H, ArC*H*), 6.84 (d, 1H, *J* = 8.2, ArC*H*), (m, 1H, ArC*H*), 6.70-6.64 (m, 2H, ArC*H*), 5.13 (s, 2H, OC*H*$_2$Ph), 3.92 (br s, 1H, ArC*H*), 3.87 (s, OCH_3), 3.67 (s, OCH_3), 3.46 (m, 1H, C*H*OH), 3.27-3.21 (m, 1H, ArC*H*CH_2), 2.99-2.87 (m, 1H, ArC*H*CH_2), 2.50-2.41 (m, 2H, COC*H*$_2$), 2.17-2.04 (m, 1H, NC*H*), 1.93-1.87 (m, 1H, OHCHC*H*$_2$), 1.71-1.62 (m, 1H, OHCHC*H*$_2$), 1.54-1.50 (m, 2H, NCHC*H*$_2$); HRMS (APPI, pos.):

m/z 415.1982 (415.2000 calc. for $C_{23}H_{29}NO_6$ $[M]^+$) *m/z* 416.2055 (416.2100 calc. for $C_{23}H_{30}NO_6$ $[M+H]^+$);

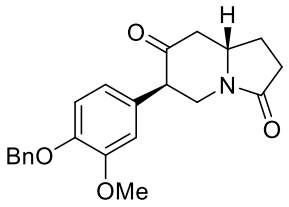
The hydroxylamine **16** (720 mg, 1.73 mmol) was dissolved in a mixture of ethanol (15 mL) and saturated aqueous NH_4Cl (3.6 mL). Indium powder (378 mg, 3.30 mmol) was added and the mixture was heated to reflux for 4 h. The mixture was cooled, filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. Dichloromethane (25 mL) was added to the residue and the aqueous layer was separated. The organic layer was washed with saturated aqueous $NaHCO_3$ solution (2 × 10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 630 mg of a yellow gum. This material is a mixture of the amino ester **17** and the cyclisation product (lactam **18**, ~30%) (^{1}H NMR analysis). The crude mixture was directly converted to the lactam as follows:

To a solution of crude aminoester and lactam mixture (280 mg) in THF (7 mL) was added diisopropylethylamine (24µL, 0.14 mmol) and the solution was heated to reflux for 5 h. The THF was removed under reduced pressure, the residue dissolved in dichloromethane (15 mL) and the resulting solution washed with aqueous HCl (0.5 M, 10 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to provide 200 mg (78%) of the lactam **18** as a pale yellow foam. This material was pure by ^{1}H NMR and was directly used further without purification.

IR (neat): 3341, 2961, 2931, 1654, 1512, 1454, 1419, 1259, 1220, 1140, 1019 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43 (d, 1H, *J* = 7.4, Ar*H*), 7.36 (t, 2H, *J* = 7.4, ArH), 7.29-7.22 (m, 1H, *J* = 7.4, Ar*H*), 6.80 (d, 1H, *J* = 8.3, Ar*H*), 6.75 (d, 1H, *J* = 2.1, Ar*H*), 6.66 (dd, 1H, *J* = 8.3, 2.1, ArC*H*), 5.1 (s, 2H, OC*H*$_2$Ph), 4.11 (br s, 1H, NC*H*), 4.05 (dd, 1H, *J* = 12.7, 4.8 , NC*H*$_2$), 3.94-3.88 (m, 1H, ArC*H*), 3.85 (s, 3H, OC*H*$_3$), 3.31 (t, 1H, *J* = 12.7, NC*H*$_2$), 2.73-2.70 (ddd, 1H, *J* =

12.5, 4.8, 2.0, C*H*OH), 2.36 (br t, 2H, *J* = 7.0, COCH_2), 2.30 (br s, 1H, CH_2CHOH), 2.24-2.17 (m, 1H, CH_2CHOH), 2.16-2.12 (m, 1H, CH_2CH$_2$C(O)), 1.60-1.54 (m, 1H, CHCH_2CH), 1.45 (dt, 1H, *J* = 11.0, 2.1, NCHCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): 173.7 (N*C*O), 149.7 (ArC_{ipso}), 147.3 (ArC_{ipso}), 137.1 (ArC_{ipso}), 133.0 (ArC_{ipso}), 128.6 (2 x Ar*C*), 127.9 (Ar*C*), 127.3 (2 x Ar*C*), 119.6 (Ar*C*), 114.1 (Ar*C*), 111.7 (Ar*C*), 71.0 (O*C*H$_2$Ph), 68.8 (*C*HOH), 56.0 (O*C*H$_3$), 50.9 (N*C*H), 45.2 (N*C*H$_2$), 39.8 (Ar*C*H), 38.3 (HOCH*C*H$_2$), 30.6 (NCO*C*H$_2$), 24.7 (NCH*C*H$_2$); HRMS (APPI, pos.): *m/z* 367.1779 (367.1784 calc. for $C_{22}H_{25}NO_4$ $[M]^+$), *m/z* 368.1851 (368.1862 calc. for ($C_{22}H_{26}NO_4$ $[M+H]^+$).

(6*R*, 8a*S*)-6-(4-(Benzyloxy)-3-methoxyphenyl) hexahydroindolizine-3,7-dione (19):

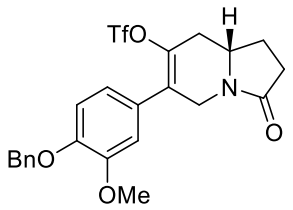


To a stirred solution of amidoalcohol **18** (200 mg, 0.540 mmol) in dichloromethane (4 mL) was added Dess-Martin periodinane (462 mg, 1.08 mmol) and the mixture was stirred at ambient temperature for 3 h. Saturated aqueous $NaHCO_3$ (10 mL) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (15 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate) to provide 164 mg (83%) of **19** as a white solid.

IR (neat): 2934, 1680, 1514, 1454, 1419, 1262, 1220, 1142, 1029, 912 cm^{-1}; ^{1}H NMR (300 MHz,$CDCl_3$): δ 7.45-7.29 (m, 5H, Ar*H*), 6.86 (d, 1H, *J* = 8.2, Ar*H*), 6.66 (d, 1H, *J* = 2.1, Ar*H*), 6.62 (dd, 1H, *J* = 8.2, 2.1, Ar*H*), 5.14 (s, 2H, OCH_2Ph), 4.6 (dd, 1H, *J* = 12.5, 6.9, ArCC*H*),

4.03-3.94 (m, 1H, NC*H*), 3.86 (s, 3H, OCH_3), 3.60 (dd, 1H, *J* = 12.5, 6.9, NCH_2), 3.09 (t, 1H, *J* = 12.5, NCH_2), 2.73 (dd, 1H, *J* = 13.6, 3.9, COCH_2), 2.58-2.51 (m, 2H, COCH_2, NCOCH_2), 2.48-2.33 (m, 2H, NCOCH_2, NCOCH$_2$CH_2), 1.86-1.74 (m, 1H, NCOCH$_2$CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): □ 205.5 (*C*O), 173.6 (N*C*O), 149.6 (ArC_{ipso}), 147.8 (ArC_{ipso}), 137.1 (ArC_{ipso}), 128.6 (2 x Ar*C*), 127.9 (Ar*C*), 127.4 (Ar*C*), 127.3 (2 x Ar*C*), 121.1 (Ar*C*), 113.9 (Ar*C*), 112.8 (Ar*C*), 71.0 (O*C*H$_2$Ph), 57.1 (N*C*H), 56.1 (O*C*H$_3$), 55.3 (ArC*C*H), 48.6 (*C*H$_2$N), 45.1 (*C*H$_2$CO), 29.7 (*C*H$_2$CH$_2$CO), 24.7 (*C*H$_2$CO); HRMS (ESI, pos.) *m/z* 365.1639 (365.1627 calc. for $C_{22}H_{23}NO_4$ $[M]^+$), *m/z* 366.1709 (366.1705 calc. for $C_{22}H_{24}NO_4$ $[M+H]^+$).

(*S*)-6-(4-(Benzyloxy)-3-methoxyphenyl)-3-oxo-1,2,3,5,8,8a-hexahydroindolizin-7-yl trifluoromethanesulfonate (20):

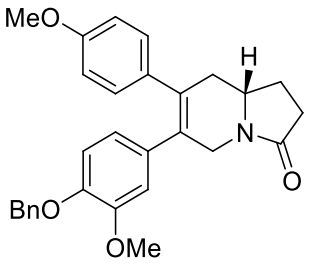


To a suspension of KH (73 mg, 0.54 mmol) in THF (2 mL) was added ketone **19** (100 mg, 0.27 mmol) at 0 °C. The mixture was stirred at 0 °C for 45 mins and then warmed to room temperature for 1 h. *N*-phenyl-bis(trifluoromethanesulfonimide) (105 mg, 0.29 mmol) was added in one portion and the mixture stirred for 1 h at ambient temperature. Water (2 mL) was added and the mixture extracted with EtOAc (5 mL). The combined layers were dried (Na_2SO_4) and concentrated under reduced pressure to provide 121 mg (89%) of triflate **20** as a yellow foam. This was used further without purification. An analytical sample was obtained by flash column chromatography on silica gel (ethyl acetate).

IR (neat): 2940, 2843, 1694, 1514, 1413, 1263, 1243, 1206, 1139, 1035, 947 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.30 (m, 5H, Ar*H*), 6.91-6.78 (m, 3H, Ar*H*), 5.16 (s, 2H, OCH_2Ph), 4.75 (br d, 1H, *J* = 18.1, NCH_2), 3.88 (s, 3H, OCH_3), 3.93-3.88 (m, 1H, NC*H*), 3.71 (br d, 1H, *J* = 18.1, NCH_2), 2.67-2.39 (m, 5H, COCH_2, C=CCH_2, $COCH_2CH_2$), 1.87-1.80 (m, 1H, $COCH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): 173.8 (*C*O), 155.1 (TfO*C*=C), 149.5 (ArC_{ipso}), 148.7 (ArC_{ipso}), 139.6 (ArC_{ipso}), 136.7 (ArC_{ipso}), 128.6 (2 x Ar*C*), 127.9 (2 x Ar*C*), 127.3 (2 x Ar*C*), 125.5 (TfOC=*C*), 120.8 (Ar*C*), 115.2 (q, *J* = 109.4, *C*F_3), 113.7 (Ar*C*), 111.9 (Ar*C*), 70.9 (O*C*H_2Ph), 56.1 (O*C*H_3), 53.3 (N*C*H), 42.9 (N*C*H_2), 35.4 (C=C*C*H_2CH), 29.6 ($COCH_2CH_2$), 24.2 (CO*C*H_2); HRMS (APPI): *m/z* 497.1106 (497.1120 calc. for $C_{23}H_{23}F_3NO_6S$ $[M]^+$).

General procedure for the Suzuki-Miyaura Coupling: To the enol triflate **20** was added the corresponding boronic acid and degassed dioxane. A saturated solution of Na_2CO_3 made in degassed water was added followed by $Pd(PPh_3)_4$. The reaction mixture was heated to reflux at 85°C for 20 min. The mixture was cooled to room temperature, diluted with ethyl acetate, and washed with water. The organic layers were collected, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using EtOAc/hexanes as the eluent. The eluent was removed under reduced pressure to obtain the pure products as sticky gums in varying yields.

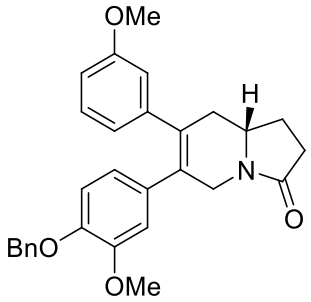
(*S*)-6-(4-(Benzyloxy)-3-methoxyphenyl)-7-(4-methoxyphenyl)-1,2,8,8a-tetrahydroindolizin-3(5H)-one (21)



Reaction of the purified triflate **20** (30 mg, 0.06 mmol) with 4-methoxy phenyl boronic acid (9.95 mg, 0.065 mmol) in dioxane (1 mL) and aqueous Na_2CO_3 (21.6 mg dissolved in 0.1 mL of water) followed by $Pd(PPh_3)_4$ (3.5 mg) according to the general procedure, provided 14 mg (52%) of **21** as a yellow gum.

IR (neat): 2957, 2924, 2853, 1683, 1605, 1509, 1453, 1417, 1245, 1031cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.27 (m, 5H, Ar*H*), 6.92 (d, 2H, *J* = 8.8 Hz, Ar*H*), 6.73-6.66 (m, 3H, Ar*H*), 6.59 (dd, 1H, *J* = 8.3, 2.0 Hz, Ar*H*), 6.49 (d, 1H, *J* = 2.0 Hz, Ar*H*), 5.07 (s, 2H, -CH_2Ph), 4.73 (dd, 1H, *J* = 18.4, 2.8 Hz, -NCH_2), 3.95-3.84 (m, 1H, -NC*H*), 3.81-3.71 (m (overlaps with methoxy singlet), 1H, -NCH_2), 3.74 (s, 3H, -OCH_3), 3.58 (s, 3H, -OCH_3), 2.72 (dd, 1H, *J* = 17.2, 4.1 Hz, -COCH_2), 2.55-2.33 (m, 4H, -CH_2), 1.86-1.73 (m, 1H, -CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): 173.9 (N*C*O), 158.2 (Ar*C*), 148.9 (Ar*C*), 147.0 (Ar*C*), 137.1 (Ar*C*), 134.3 (Ar*C*), 132.4 (Ar*C*), 131.7 (C=*C*), 130.4 (C=*C*), 129.9 (2xAr*C*), 128.5 (2xAr*C*), 127.8 (Ar*C*), 127.4 (2xAr*C*), 121.1 (Ar*C*), 113.5 (3xAr*C*), 113.4 (Ar*C*), 70.9 (*C*H_2Ph), 55.7 (O*C*H_3), 55.2 (O*C*H_3), 53.3 (N*C*H), 44.2 (N*C*H_2), 39.0 (C=C*C*H_2CH), 30.1 (CO*C*H_2), 24.9 (COCH$_2$*C*H_2); HRMS (APPI, +ve): m/z 455.2076 (455.2097 calc. for $C_{29}H_{29}NO_4$ $[M]^+$) and 456.2148 (456.2175 calc. for $C_{29}H_{30}NO_4$ $[M+H]^+$)

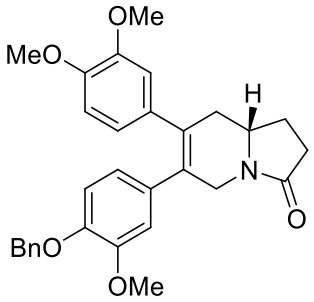
(*S*)-6-(4-(Benzyloxy)-3-methoxyphenyl)-7-(3-methoxyphenyl)-1,2,8,8a-tetrahydroindolizin-3(5H)-one (22)



Reaction of the crude triflate **20** (47 mg, 0.09 mmol) with 3-methoxy phenyl boronic acid (15.5 mg, 0.10 mmol) in dioxane (1.7 mL) and aqueous Na_2CO_3 (34.4 mg dissolved in 0.17 mL of water) followed by $Pd(PPh_3)_4$ (5.4 mg) according to the general procedure, provided 12 mg (29%) of **22** as a yellow gum.

IR (neat): 2927, 2854, 2835, 1686, 1600, 1579, 1511, 1453, 1420, 1286 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.42-7.27 (m, 5H, Ar*H*), 7.08 (t, 1H, *J* = 7.9 Hz, Ar*H*), 6.74-6.58 (m, 4H, Ar*H*), 6.52-6.47 (m, 2H, Ar*H*), 5.07 (s, 2H, -C*H*$_2$Ph), 4.73 (dd, 1H, *J* = 18.5, 2.3 Hz, -NC*H*$_2$), 3.95-3.84 (m, 1H, -NC*H*), 3.83-3.72 (m, 1H, -NC*H*$_2$), 3.59 (s, 3H, -OC*H*$_3$), 3.56 (s, 3H, -OC*H*$_3$), 2.73 (dd, 1H, *J* = 16.8, 3.4 Hz, -COC*H*$_2$), 2.55-2.33 (m, 4H, -C*H*$_2$), 1.86-1.73 (m, 1H, -C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): 173.9 (N*C*O), 159.3 (Ar*C*), 148.9 (Ar*C*), 147.1 (Ar*C*), 143.5 (Ar*C*), 137.0 (Ar*C*), 132.15 (Ar*C*), 132.13 (Ar*C*), 131.1 (Ar*C*), 129.1 (Ar*C*), 128.5 (2xAr*C*), 127.8 (Ar*C*), 127.3 (2xAr*C*), 121.1 (Ar*C*), 120.9 (Ar*C*), 114.5 (Ar*C*), 113.5 (*C*=C), 113.4 (C=*C*), 112.3 (Ar*C*), 70.9 (*C*H$_2$Ph), 55.8 (O*C*H$_3$), 55.1 (O*C*H$_3$), 53.3 (N*C*H), 44.1 (N*C*H$_2$), 38.9 (C=C*C*H$_2$CH), 30.1 (CO*C*H$_2$), 24.9 (COCH$_2$*C*H$_2$); HRMS (APPI, +ve): m/z 455.2082(455.2097 calc. for $C_{29}H_{29}NO_4[M]^+$) and 456.2153 (456.2175 calc. for $C_{29}H_{30}NO_4[M+H]^+$)

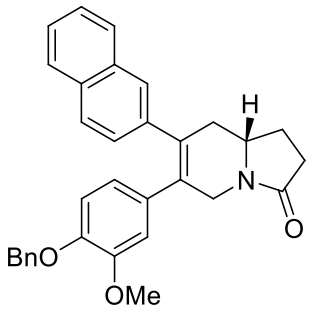
(*S*)-6-(4-(Benzyloxy)-3-methoxyphenyl)-7-(3,4-dimethoxyphenyl)-1,2,8,8a-tetrahydroindolizin-3(5H)-one (23)



Reaction of the pure triflate **20** (30 mg, 0.06 mmol) with 3, 4-dimethoxy phenyl boronic acid (11.9 mg, 0.065 mmol) in dioxane (1 mL) and aqueous Na_2CO_3 (21.6 mg dissolved in 0.1 mL of water) followed by $Pd(PPh_3)_4$ (3.5 mg) according to the general procedure, provided 21 mg (73%) of **23** as a yellow gum.

IR (neat): 2931, 2833, 1679, 1509, 1443, 1415, 1258, 1240 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.42-7.28 (m, 5H, Ar*H*), 6.70 (dd, 2H, *J* = 8.3, 1.7 Hz, Ar*H*), 6.66-6.56 (m, 2H, Ar*H*), 6.52 (d, 1H, *J* = 1.9 Hz, Ar*H*), 6.43 (d, 1H, *J* = 1.9 Hz, Ar*H*), 5.08 (s, 2H, -CH_2Ph), 4.73 (dd, 1H, *J* = 18.5, 2.7 Hz, -NCH_2), 3.92-3.86 (m, 1H, -NC*H*), 3.82 (s, 3H, -OCH_3), 3.80-3.71 (m, 1H, -NCH_2), 3.60 (s, 3H, -OCH_3) , 3.54 (s, 3H, -OCH_3), 2.75 (dd, 1H, *J* = 16.9, 4.3 Hz, - COCH_2), 2.54-2.37 (m, 4H, -CH_2), 1.86-1.75 (m, 1H, -CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9, 149.0, 148.2, 147.6, 147.0, 137.0, 134.4, 132.5, 131.8, 130.7, 128.5, 127.9, 127.3, 121.1, 120.7, 113.4, 113.3, 112.8, 110.6, 70.8, 55.8, 55.7, 53.3, 44.2, 38.7, 30.1, 24.9; HRMS (APPI, +ve): m/z 485.2201 (485.2202 calc. for $C_{30}H_{31}NO_5[M]^+$) and 486.2273 (486.2280 calc. for $C_{30}H_{32}NO_5[M+H]^+$)

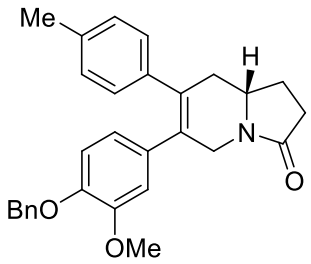
(*S*)-6-(4-(Benzyloxy)-3-methoxyphenyl)-7-(naphthalen-2-yl)-1,2,8,8a-tetrahydroindolizin-3(5H)-one (24)



Reaction of the crude triflate **20** (55.8 mg, 0.11 mmol) with 2-napthalene boronic acid (21.0 mg, 0.12 mmol) in dioxane (2 mL) and aqueous Na_2CO_3 (41.1 mg dissolved in 0.2 mL of water) followed by $Pd(PPh_3)_4$ (6.3 mg) according to the general procedure, provided 20 mg (37%) of **24** as a yellow gum.

IR (neat): 3056, 2927,1686, 1511, 1453, 1419, 1260 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.76-7.64 (m, 2H, Ar*H*), 7.61-7.52 (m, 2H, Ar*H*), 7.45-7.27 (m, 7H, Ar*H*), 7.05 (dd, 1H, *J* = 8.5, 1.8 Hz, Ar*H*), 6.68-6.58 (m, 2H, Ar*H*), 6.53 (d, 1H, *J* = 1.8 Hz, Ar*H*), 5.02 (s, 2H, -CH_2Ph), 4.79 (dd, 1H, *J* = 18.4, 1.9 Hz, -NCH_2), 4.01-3.90 (m, 1H, -NC*H*), 3.89-3.78 (m, 1H, -NCH_2), 3.44 (s, 3H, -OCH_3), 2.86 (dd, 1H, *J* = 16.6, 4.0 Hz, -COCH_2), 2.60-2.36 (m, 4H, -CH_2), 1.90-1.76 (m, 1H, -CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): 174.0 (N*C*O), 148.9, 147.1, 139.6, 137.0, 133.2, 132.1, 132.0, 131.6, 128.5 (2xAr*C*), 127.81, 127.76, 127.5, 127.4, 127.3 (2xAr*C*), 127.2, 126.0, 125.8, 121.3, 113.5, 113.4, 70.9 (*C*H_2Ph), 55.7 (O*C*H_3), 53.4 (N*C*H), 44.3 (N*C*H_2), 39.1 (C=C*C*H_2CH), 30.1 (CO*C*H_2), 24.9 (COCH$_2$*C*H_2); HRMS (APPI, +ve): m/z 475.2138 (475.2147 calc. for $C_{32}H_{29}NO_3[M]^+$), 476.2209 (476.2226 calc. for $C_{32}H_{30}NO_3[M+H]^+$)

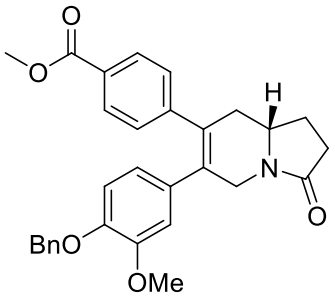
(*S*)-6-(4-(Benzyloxy)-3-methoxyphenyl)-7-p-tolyl-1,2,8,8a-tetrahydroindolizin-3(5H)-one (25)



Reaction of the crude triflate **20** (47 mg, 0.09 mmol) with 4-methyl phenyl boronic acid (13.9 mg, 0.10 mmol) in dioxane (1.7 mL) and aqueous Na_2CO_3 (34.4 mg dissolved in 0.16 mL of water) followed by $Pd(PPh_3)_4$ (5.4 mg) according to the general procedure, provided 7 mg (17%) of **25** as a yellow gum.

IR (neat): 3030, 2923, 1683, 1510, 1452, 1418, 1258 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.42-7.27 (m, 5H, Ar*H*), 6.96 (d, 2H, *J* = 8.5 Hz, Ar*H*), 6.88 (d, 2H, *J* = 8.2 Hz, Ar*H*), 6.71 (d, 1H, *J* = 8.3 Hz, Ar*H*), 6.60 (dd, 1H, *J* = 8.3, 2.0 Hz, Ar*H*), 6.46 (d, 1H, *J* = 2.0 Hz, ArH), 5.07 (s, 2H, -CH_2Ph), 4.73(dd, 1H, *J* = 18.5, 2.7 Hz, -NCH_2), 3.95-3.85 (m, 1H, -NC*H*), 3.82-3.71 (m, 1H, -NCH_2), 3.54 (s, 3H, -OCH_3), 2.72 (dd, 1H, *J* = 16.8, 4.4 Hz, -COCH_2), 2.54-2.32 (m, 4H, -CH_2), 2.25 (s, 1H, CH_3), 1.85-1.72 (m, 1H, -CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): 173.9 (*C*=O), 148.8 (ArC_{ipso}), 147.0 (ArC_{ipso}), 139.1 (ArC_{ipso}), 137.1 (ArC_{ipso}), 136.2 (ArC_{ipso}), 132.3 (C=C), 132.1 (C=C), 130.6 (Ar*C*), 128.8 (2 x Ar*C*), 128.7 (2 x Ar*C*), 128.5 (2 x Ar*C*), 127.8 (Ar*C*), 127.4 (2 x Ar*C*), 121.0 (Ar*C*), 113.6 (Ar*C*), 113.3 (Ar*C*), 70.9 (*C*H_2Ph), 55.7 (OCH_3), 53.3 (NCH), 44.2 (NCH_2), 39.0 (C=C*C*H_2CH), 30.1 (COCH_2), 24.9 (COCH_2*C*H_2), 21.1 (*C*H_3); HRMS (APPI, +ve): m/z 439.2142 (439.2147 calc. for $C_{29}H_{29}NO_3[M]^+$) and 440.2213 (440.2226 calc. for $C_{29}H_{30}NO_3[M+H]^+$)

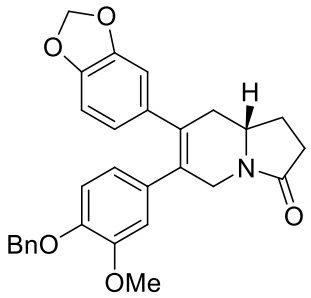
(*S*)-Methyl 4-(6-(4-(benzyloxy)-3-methoxyphenyl)-3-oxo-1,2,3,5,8,8a-hexahydroindolizin-7-yl) benzoate (26)



Reaction of the crude triflate **20** (212 mg, 0.43 mmol) with 4-methoxycarbonyl phenyl boronic acid (81.6 mg, 0.46 mmol) in dioxane (7 mL) and aqueous Na_2CO_3 (150 mg dissolved in 0.7 mL of water) followed by $Pd(PPh_3)_4$ (24 mg) according to the general procedure, provided 25 mg (12%) of **26** as a yellow gum.

IR (neat): 2926, 2853, 1718, 1687, 1605, 1512, 1436, 1419, 1311, 1277 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, 2H, *J* = 8.5 Hz, Ar*H*), 7.42-7.27 (m, 5H, Ar*H*), 7.07 (d, 2H, *J* = 8.4 Hz, Ar*H*), 6.69 (d, 2H, *J* = 8.3 Hz, Ar*H*), 6.56 (dd, 1H, *J* = 8.2, 2.1 Hz, Ar*H*), 6.45 (d, 1H, *J* = 2.0 Hz, Ar*H*), 5.06 (s, 2H, -CH_2Ph), 4.74 (dd, 1H, *J* = 18.7, 2.7 Hz, -NCH_2), 3.97-3.89 (m, 1H, -NC*H*), 3.88 (s, 3H, COOCH_3), 3.85-3.74 (m, 1H, -NCH_2), 3.56 (s, 3H, -OCH_3), 2.73 (dd, 1H, *J* = 16.8, 4.4 Hz, -COCH_2), 2.55-2.34 (m, 4H, -CH_2), 1.88-1.72 (m, 1H, -CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): 173.9 (*C*OOCH$_3$), 166.8 (*C*ON), 149.0 (Ar*C*), 147.4 (Ar*C*), 147.0 (Ar*C*), 136.9 (Ar*C*), 132.7 (Ar*C*), 131.5 (C=C), 131.4 (C=C), 129.4 (2xAr*C*), 128.9 (2xAr*C*), 128.5 (2xAr*C*), 128.1(Ar*C*), 127.9 (Ar*C*), 127.4 (2xAr*C*), 121.2 (Ar*C*), 113.5 (Ar*C*), 113.3 (Ar*C*), 70.9 (*C*H$_2$Ph), 55.8 (O*C*H$_3$), 53.2 (N*C*H), 52.1 (COO*C*H$_3$) , 44.3 (N*C*H$_2$), 38.5 (C=C*C*H$_2$CH), 30.0 (CO*C*H$_2$), 24.9 (COCH$_2$*C*H$_2$); HRMS (APPI, +ve): m/z 483.2038 (483.2046 calc. for $C_{30}H_{29}NO_5[M]^+$) and 484.2109 (484.2124 calc. for $C_{30}H_{30}NO_5[M+H]^+$)

(*S*)-7-(Benzo[d][1,3] dioxol-5-yl)-6-(4-(benzyloxy)-3-methoxyphenyl)-1,2,8,8a-tetrahydroindolizin-3(5H)-one (27)



Reaction of the crude triflate **20** (62.5 mg, 0.126 mmol) with 3, 4-methylenedioxy phenyl boronic acid (22.2 mg, 0.137 mmol) in dioxane (2.3 mL) and aqueous Na_2CO_3 (46 mg dissolved in 0.2 mL of water) followed by $Pd(PPh_3)_4$ (7 mg) according to the general procedure, provided 6 mg (10%) of **27** as a yellow gum.

IR (neat): 3032, 2926, 1683, 1510, 1487, 1439, 1420, 1241, 1218 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.43-7.28 (m, 5H, Ar*H*), 6.72 (d, 1H, *J* = 8.3 Hz, Ar*H*), 6.64-6.57 (m, 2H, Ar*H*), 6.52 (d, 1H, *J* = 2.0 Hz, Ar*H*), 6.49-6.45 (m, 2H, Ar*H*), 5.88 (s, 2H, -OCH_2O), 5.08 (s, 2H, -CH_2Ph), 4.71 (dd, 1H, *J* = 18.4, 2.4 Hz, -NCH_2), 3.95-3.83 (m, 1H, -NC*H*), 3.80-3.69 (m, 1H, -NCH_2), 3.63 (s, 3H, -OCH_3), 2.67 (dd, 1H, *J* = 16.7, 4.4 Hz, -COCH_2), 2.54-2.33 (m, 4H, -CH_2), 1.85-1.72 (m, 1H, -CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): 173.9 (N*C*O), 149.0 (Ar*C*), 147.3 (Ar*C*), 147.1 (Ar*C*), 146.1 (Ar*C*), 137.0 (Ar*C*), 136.0 (Ar*C*), 132.2(C=*C*), 131.8 (C=*C*), 130.9 (Ar*C*), 128.5 (2xAr*C*), 127.8 (Ar*C*), 127.4 (2xAr*C*), 122.2 (Ar*C*), 121.1 (Ar*C*), 113.5 (Ar*C*), 113.3 (Ar*C*), 109.4 (Ar*C*), 108.0 (Ar*C*), 100.9 (O*C*H_2O), 70.9 (*C*H_2Ph), 55.8 (O*C*H_3), 53.3 (N*C*H), 44.2 (N*C*H_2), 39.2 (C=C*C*H_2CH), 30.1 (CO*C*H_2), 24.9 (COCH$_2$*C*H_2); HRMS (APPI, +ve): m/z 469.1884 (469.1889 calc. for $C_{29}H_{27}NO_5[M]^+$) and 470.1995 (470.1968 calc. for $C_{29}H_{28}NO_5[M+H]^+$)

4.7 Bio-assay protocol

All the experiments were performed in a fume hood. The general procedure for conducting the biological activity tests is as follows:

1. Each test organism was streaked onto the respective solid media (in a petri dish) for single colonies and the petri dish was incubated at the appropriate temperature overnight.
2. Single colonies of each test organism that were obtained were inoculated into 2 mL of respective liquid media and the mixture was incubated overnight at the appropriate temperature.
3. 20% Glycerol stocks were made of each culture by combining 600 µL of culture with 600 µl of 40% glycerol. The resulting stock solutions were stored at -80°C.
4. For each organism, 500 µL of culture was combined with 50 mL of the respective solid media (in deionized water) and poured onto a bio-assay plate.
5. Autoclaved paper discs (made by hole-punching filter paper) were placed on the solidified agar and a 5 µL sample of a 100 µM solution of each compound in DMSO was pipetted onto the discs.
6. The plates were incubated for approximately 20 h at the appropriate temperatures and the lawn of growth was assessed for 'clearing' in the immediate vicinity of the paper disc

Organisms studied:

Staphylococcus epidermidis – Gram positive bacteria

Saccharomyces cerevisiae – Fungus

Media:

Organism	Solid	Liquid

S. epidermidis	Trypticase Soy Agar[15]	Luria-Bertani Broth[15]
S. cerevisiae	Yeast/Peptone/Dextrose[15]	Yeast/Peptone/Dextrose

Controls:

1. For all organisms, DMSO was used as a negative control.
2. For *S. epidermidis*; the antibiotics gentamicin (sample 8), tetracycline (sample 9), and vancomycin (sample 10) were used as positive controls.
3. For *S. cerevisiae*; gentamicin, nystatin, and vancomycin (samples 8-10) were used as positive controls.

4.8 References:

1) (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139. and previous reviews on indolizidine and quinolizidine alkaloids in the series; (b) Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556.

2) a) Wong, C.–H.; Halcomb, R. L.; Ichibaka, Y.; Kajimoto, T. *Angew. Chem.* **1995**, *107*, 569. (b) Compain, P.; Martin, O. R. *Curr. Top. Med. Chem.* **2003**, *3*, 541.

3) Chemler, S. R. *Curr. Bioact. Compd.* **2009**, *5*, 2.

4) Cluzeau, J.; Lubell, W. D.; *J. Org. Chem.* **2004**, *69*, 1504.

5) Reviews on phenanthroindolizidine alkaloids: (a) Li, Z.; Jin, Z.; Huang, R. *Synthesis* **2001**, 2365. (b) Bick, I.; Ralph, C.; Sinchai, W. *Alkaloids* **1981**, *19*, 193. (c) Govindachari, T. R.; Vishwanathan, N. *Heterocycles* **1978**, *11*, 587. Selected recent reports: (d) Banwell, M. G.; Sydnes, M. O. *Aust. J. Chem.* **2004**, *57*, 537. (e) Sharma, V. M.; AdiSeshu, K. V.; Krishna, C. V.; Prasanna, P.; Shekhar, V. C.; Venkateswarlu, A.; Rajagopal, S.; Ajaykumar, R.; Deevi, D. S.; Mamidi, N. V. S. R.; Rajagopalan, R.

Bioorg. Med. Chem. Lett. **2003**, *13*, 1679. (f) Zhu, W.; Cai, G.; Ma, D. *Org. Lett.* **2005**, *7*, 5545. (g) Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2782. (h) Boto, A.; De, L.; Yolanda, G.; Juan, A.; Hernandez, R. *Eur. J. Org. Chem.* **2005**, 3461.

6) Reviews: (a) Brandi, A.; Cardona, F.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Eur. J.* **2009**, *15*, 7808. (b) Perreault, S.; Rovis, T. *Chem. Soc. Rev.* **2009**, *38*, 3149. (c) Toure, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439. (d) *Beilstein J. Org. Chem.* **2007**, *3*, No. 27, thematic series on indolizidines and quinolizidines. (e) Jefford, C. W. *Curr. Org. Chem.* **2000**, *4*, 205. (f) Rajeswari, S.; Chandrasekharan, S.; Govindachari, T. R. *Heterocycles* **1987**, *25*, 659. Selected recent reports: (g) Iza, A.; Carrillo, L.; Vicario, J. L.; Badia, D.; Reyes, E.; Martinez, J. *Org. Biomol.Chem.* **2010**, *8*, 2238. (h) Sirisha, N.; Raghunathan, R. *Tetrahedron Lett.* **2010**, *51*, 2515. (i) Yang, D.; Micalizio, G. C. *J. Am. Chem. Soc.* **2009**, *131*, 17548. (j) Affani, R.; Comesse, S.; Daich, A.; Hamon, L.; Kadouri-Puchot, C. *Heterocycles* **2009**, *78*, 2193. (k) Barbe, G.; Pelletier, G.; Charette, A. B. *Org. Lett.* **2009**, *11*, 3398. (l) Katoh, M.; Mizutani, H.; Honda, T. *Heterocycles* **2006**, *69*, 19.

7) (a) Min, H.-Y.; Chung, H.-J.; Kim, E.-H.; Kim, S.; Park, E.-J.; Lee, S. K.; *Biochem. Pharmacol.* **2010**, *80*, 1356. (b) Gao, W.; Chen, A. P. C.; Leung, C. H.; Gullen, E. A.; Furstner, A.; Shi, Q.; Wei, L.; Lee, K. H.; Cheng, Y. C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 704.

8) Baumgartner, B. J.; Erdelmeier, C. A.; Wright, A. D.; Rali, T.; Sticher, O. *Phytochemistry* **1990**, *29*, 3330.

9) (a) Tian G.; Song, L.; Li, Z.; Robeyns, K.; Meervelt, L. V.; Eycken, E. V. V. *Org. Lett.* **2020**, *22*, 8441. (b) Renner, J.; Thakur, A.; Rutz, P. M.; Cowley, J. M.; Evangelista, J. L.; Kumar,

P.; Prater, M. B.; Stolley, R. M.; Louie, J. *Org. Lett.* **2020**, *22*, 924. (c) Zhang, C.; Wang, Y.; Song, Y.; Gao, H.; Sun, Y.; Sun, X.; Yang, Y.; He, M.; Yang, Z.; Zhan, L.; Yu, Z-X.; Yu, R. *CCS Chem.* **2019**, *1*, 352.

10) Tuyen, N. V.; Kim, D. S. H. L.; Fong, H. S.; Soejarto, D. D.; Khanh, T. C.; Tri, M. V.; Xuan, L. T. *Phytochemistry* **1999**, *50*, 467.

11) Yap, V. A.; Qazzaz, M. E.; Raja, V. J.; Bradshaw, T. D.; Loh, H. –S.; Sim, K. –S.; Yong, K. –T.; Low, Y. –Y.; Lim, K.–H. *Phytochemistry* **2016**, *15*, 136.

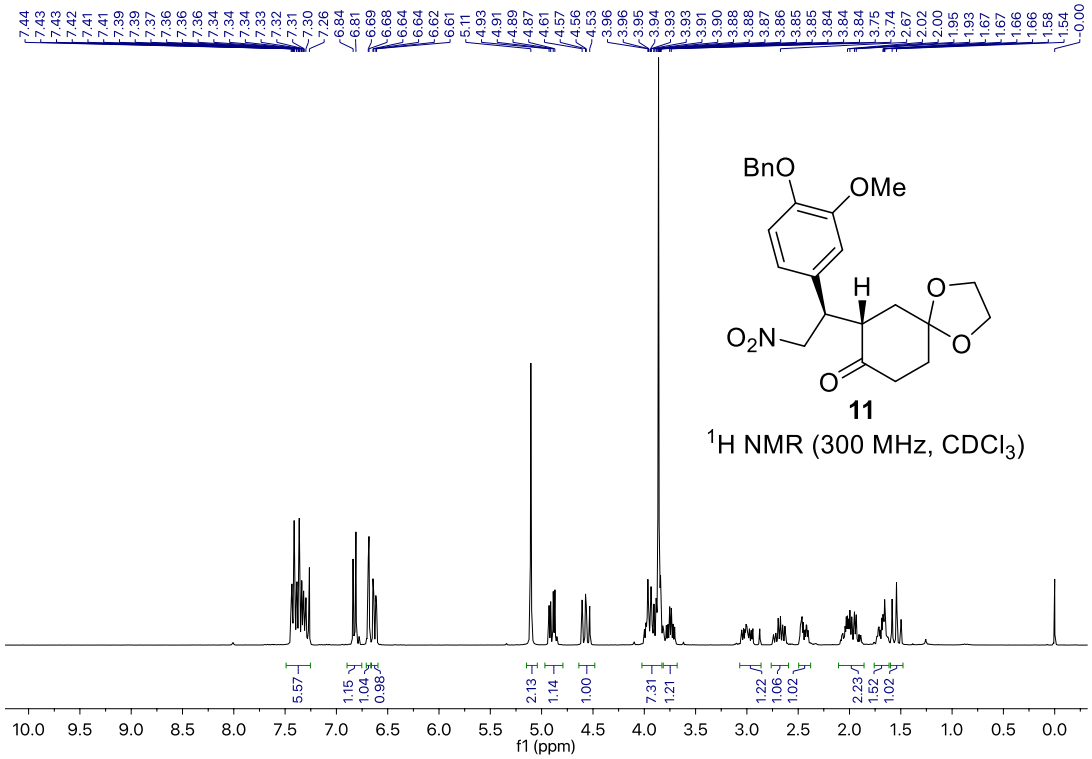
12) (a) Moorthy, N. V. G.; Pansare, S. V. *Tetrahedron*, **2018**, *74*, 1422. (b) Pansare, S. V.; Pandya, K. *J. Am. Chem. Soc.* **2006**, *128*, 9624. (c) Pansare, S.V., Kirby R. L. *Tetrahedron* **2009**, *65*, 4557. (d) Pansare, S. V.; Lingampally, R.; Dyapa, R. *Eur. J. Org. Chem.* **2011**, *12*, 2235.

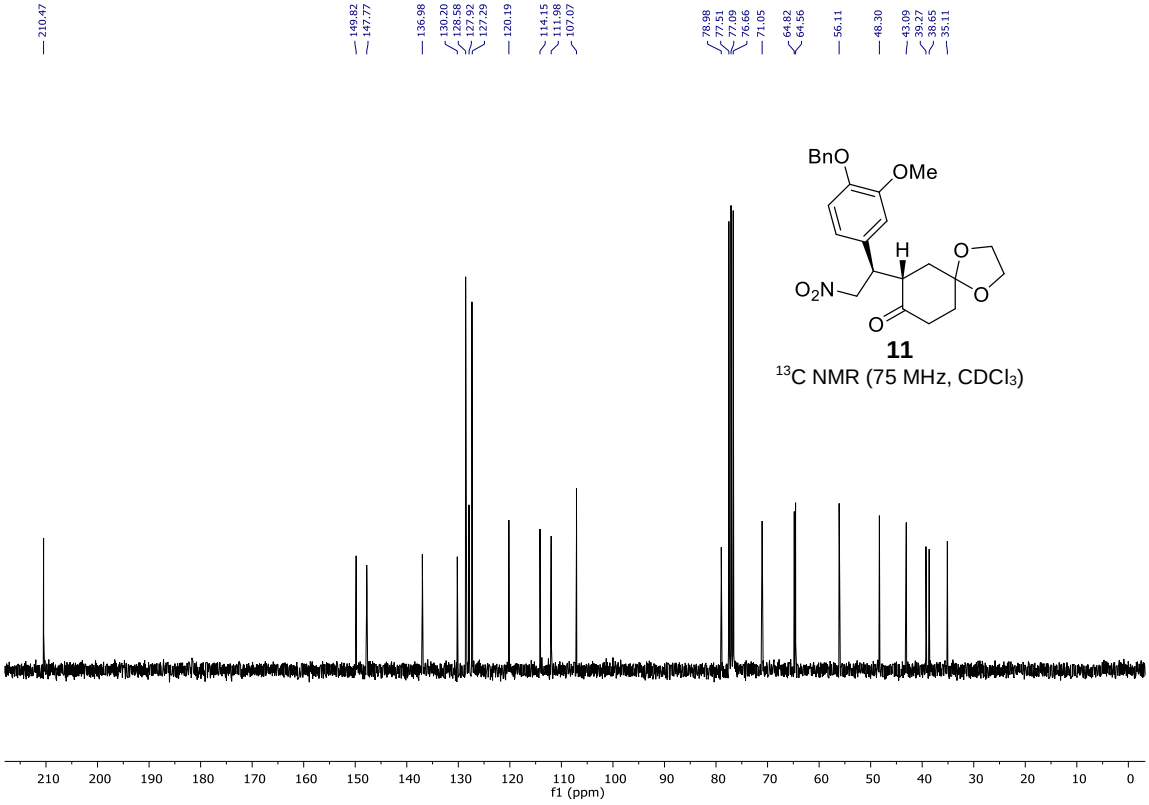
13) Evans, D. A.; Chapman, K. T.; Carriera, E. A. *J. Am. Chem. Soc*. **1988**, *110*, 3560.

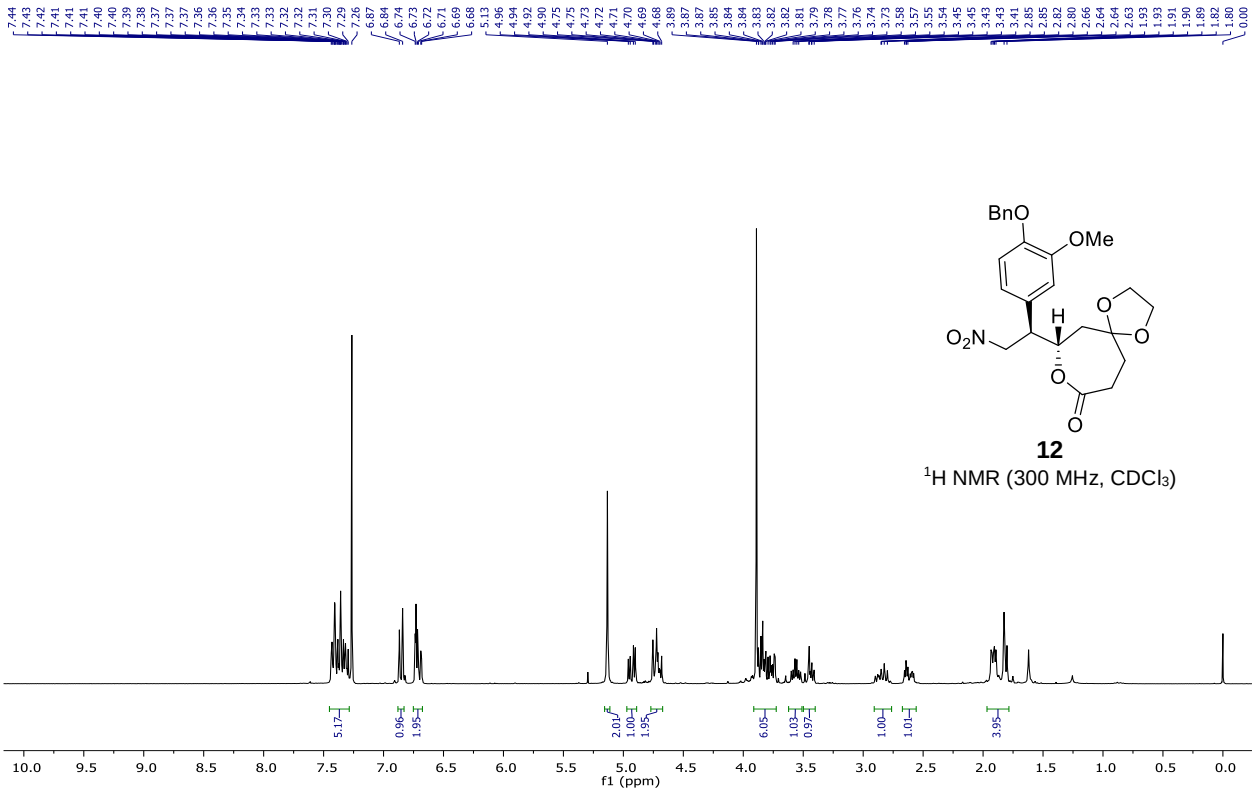
14) (a) Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201. (b) Miyaura, N. Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

15) Bonnet, M.; Lagier, J. C.; Raoult, D.; Khelaifia, S. *New Microbes New Infect.* **2020**, *34*, 100622.

4.9 Selected ^{1}H and ^{13}C NMR spectral data



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O
O
O
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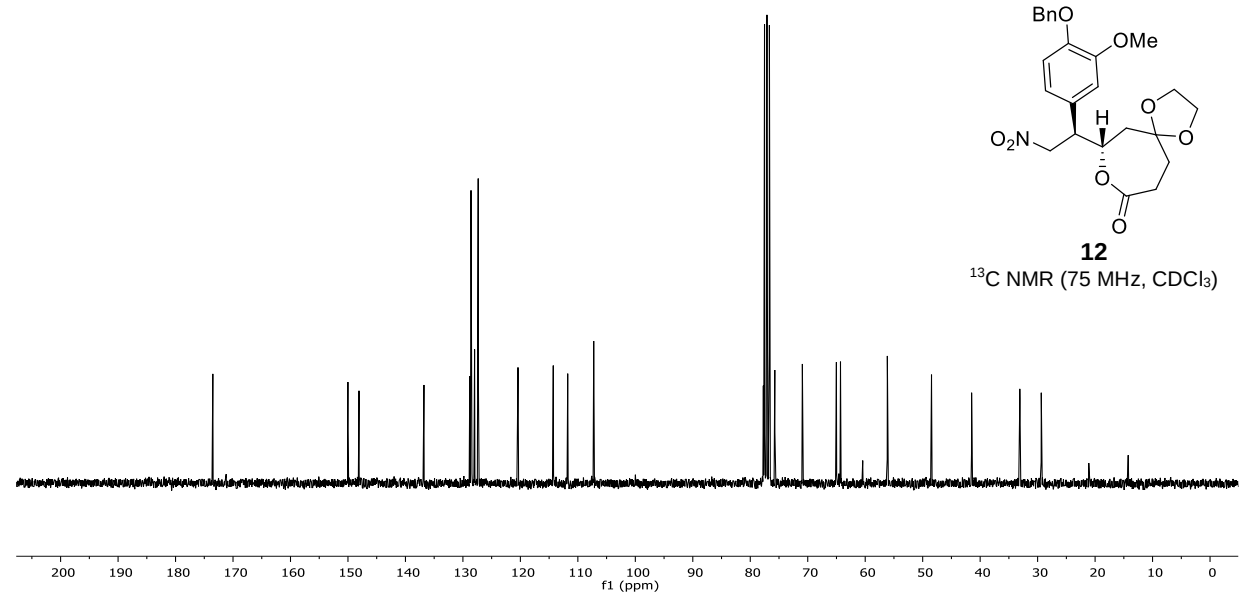
f1 (ppm)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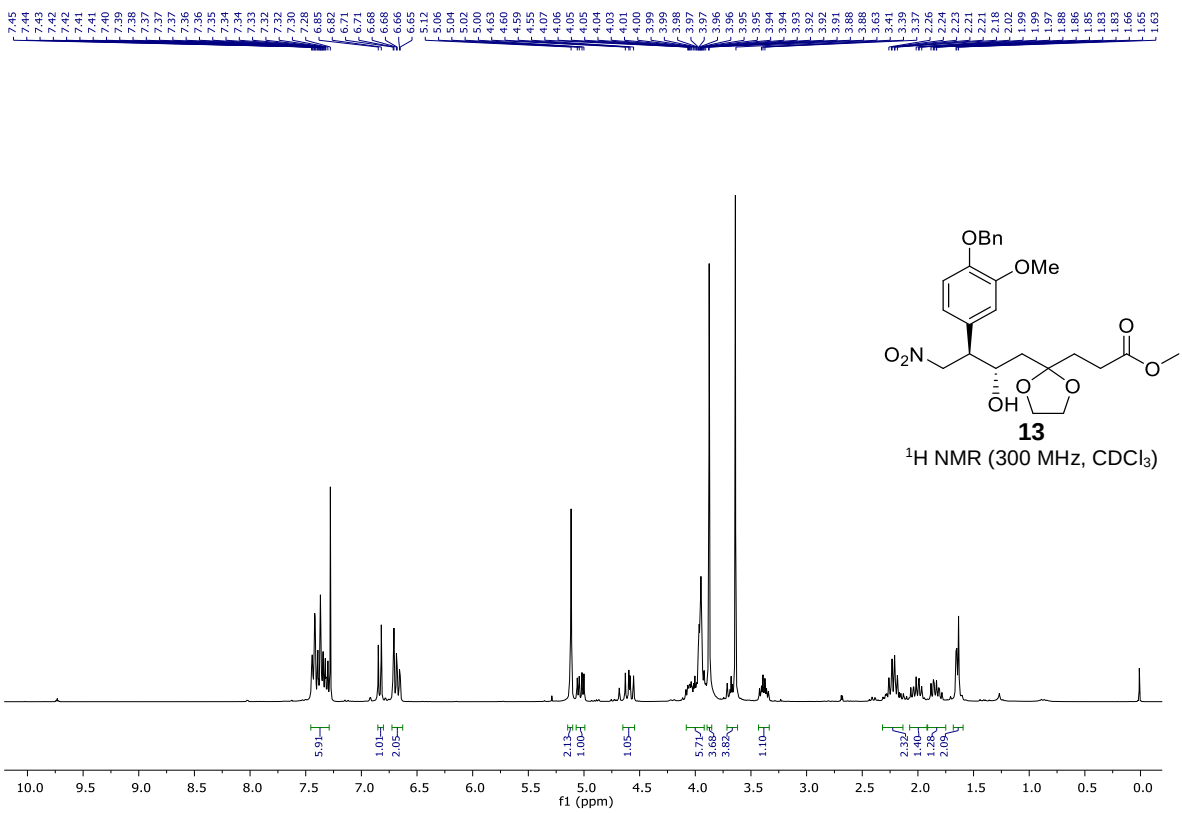
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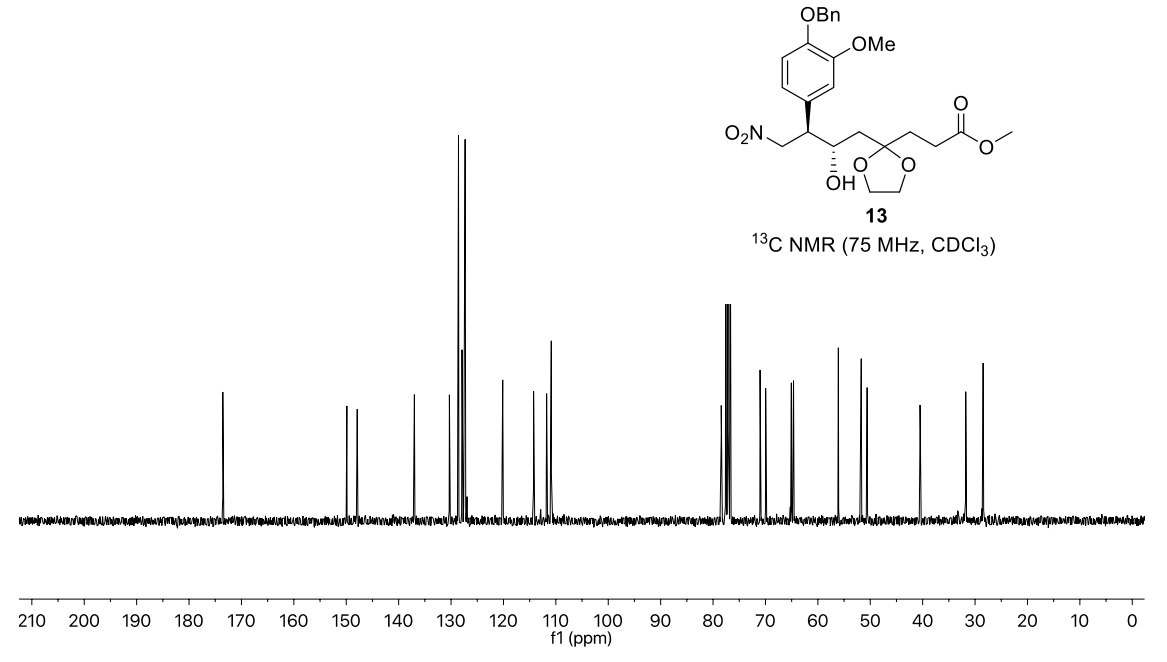
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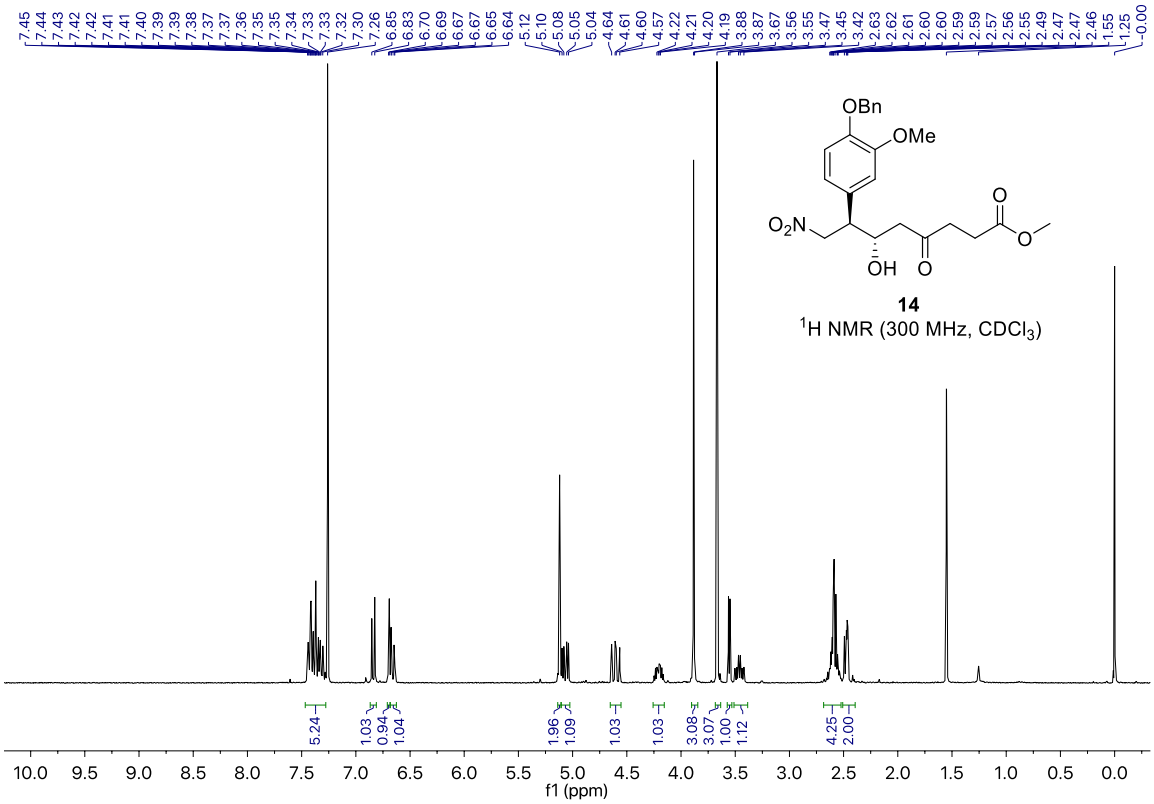
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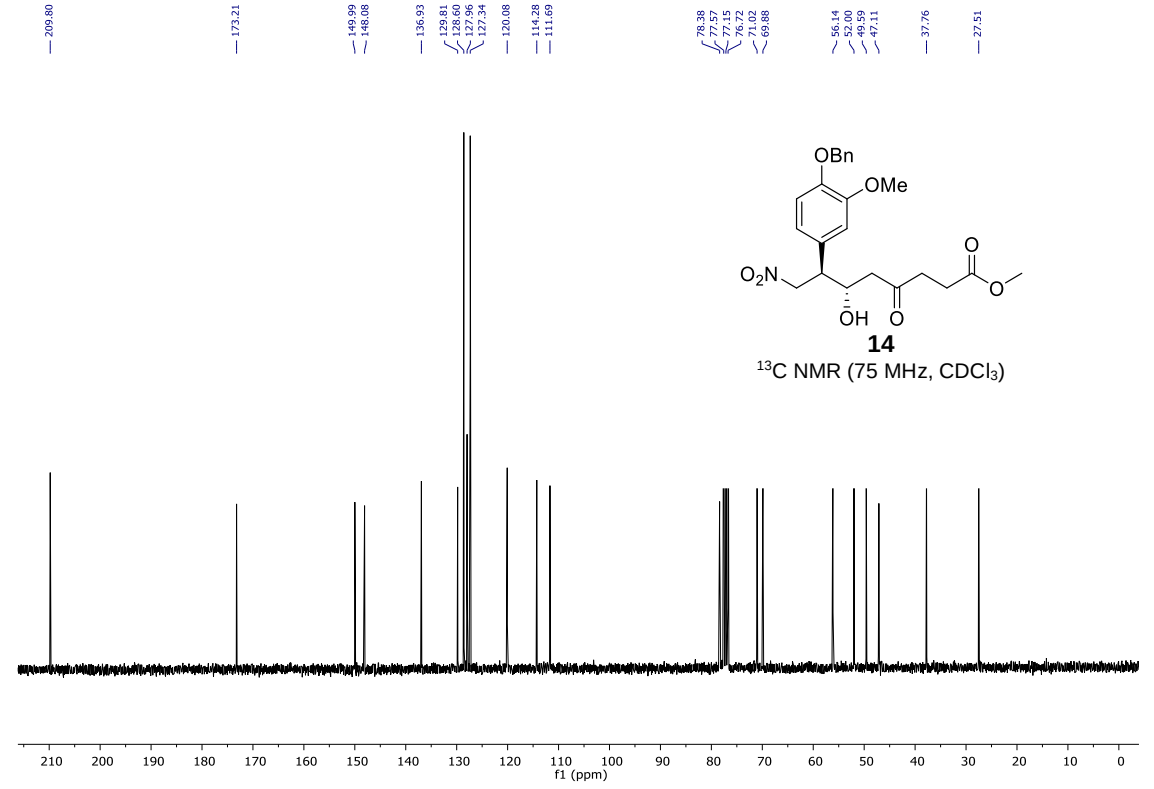
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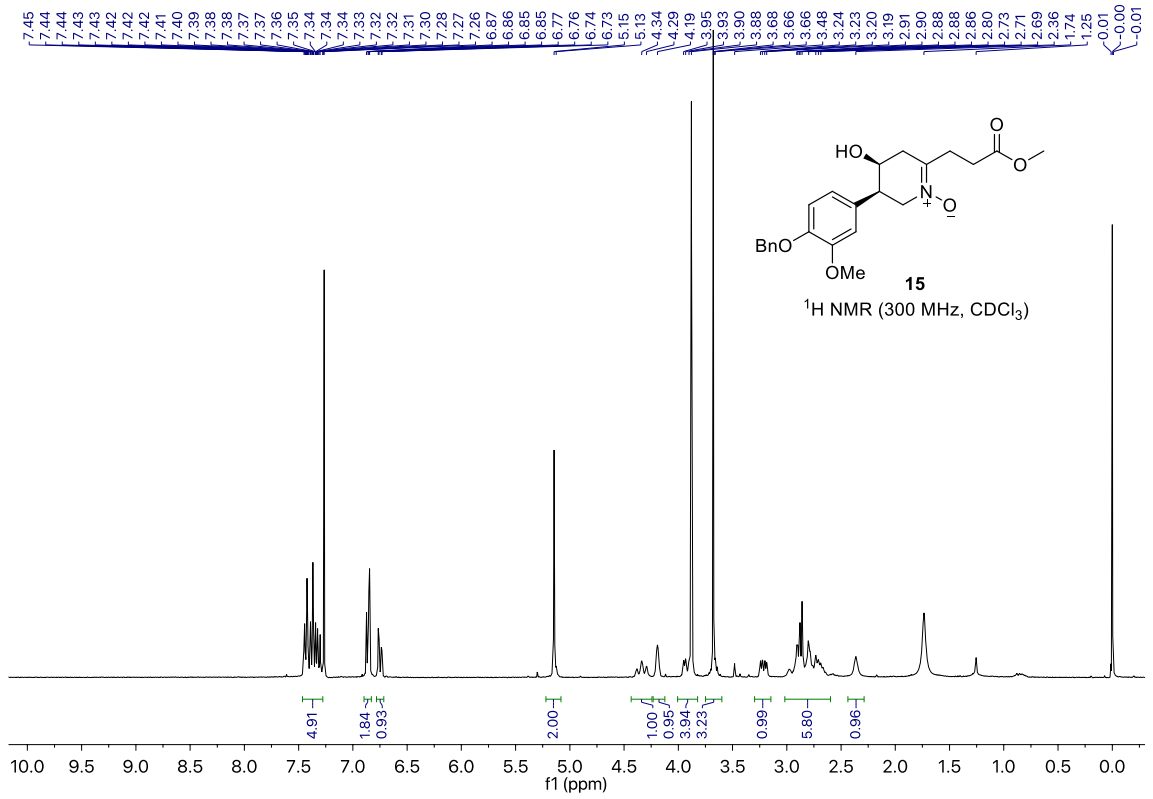
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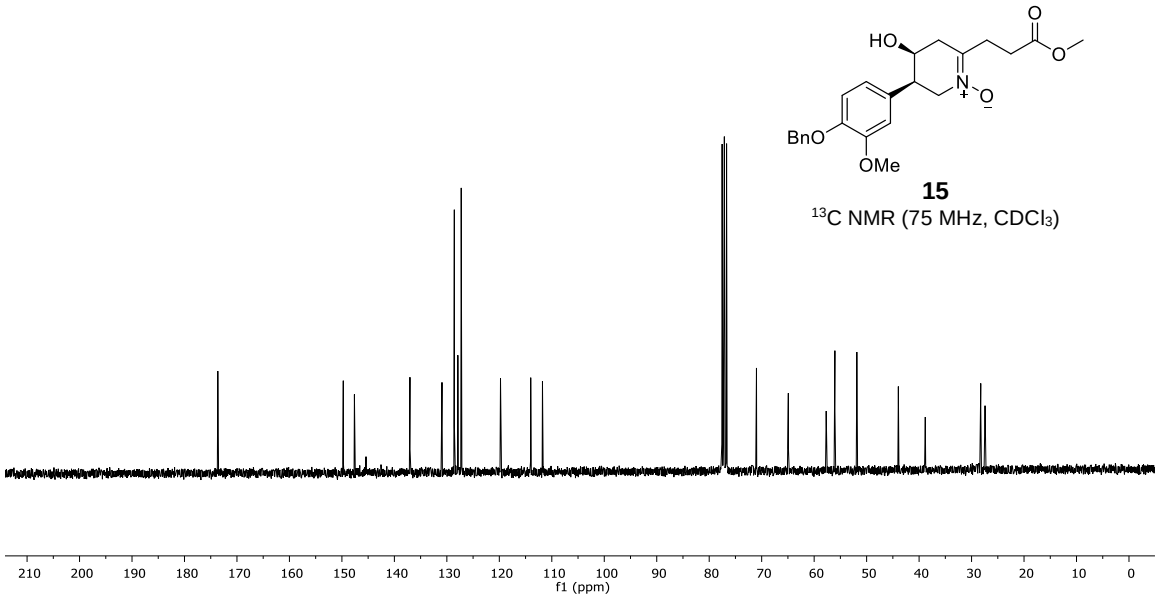
f1 (ppm)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O
O
N
O
BnO
OMe
15
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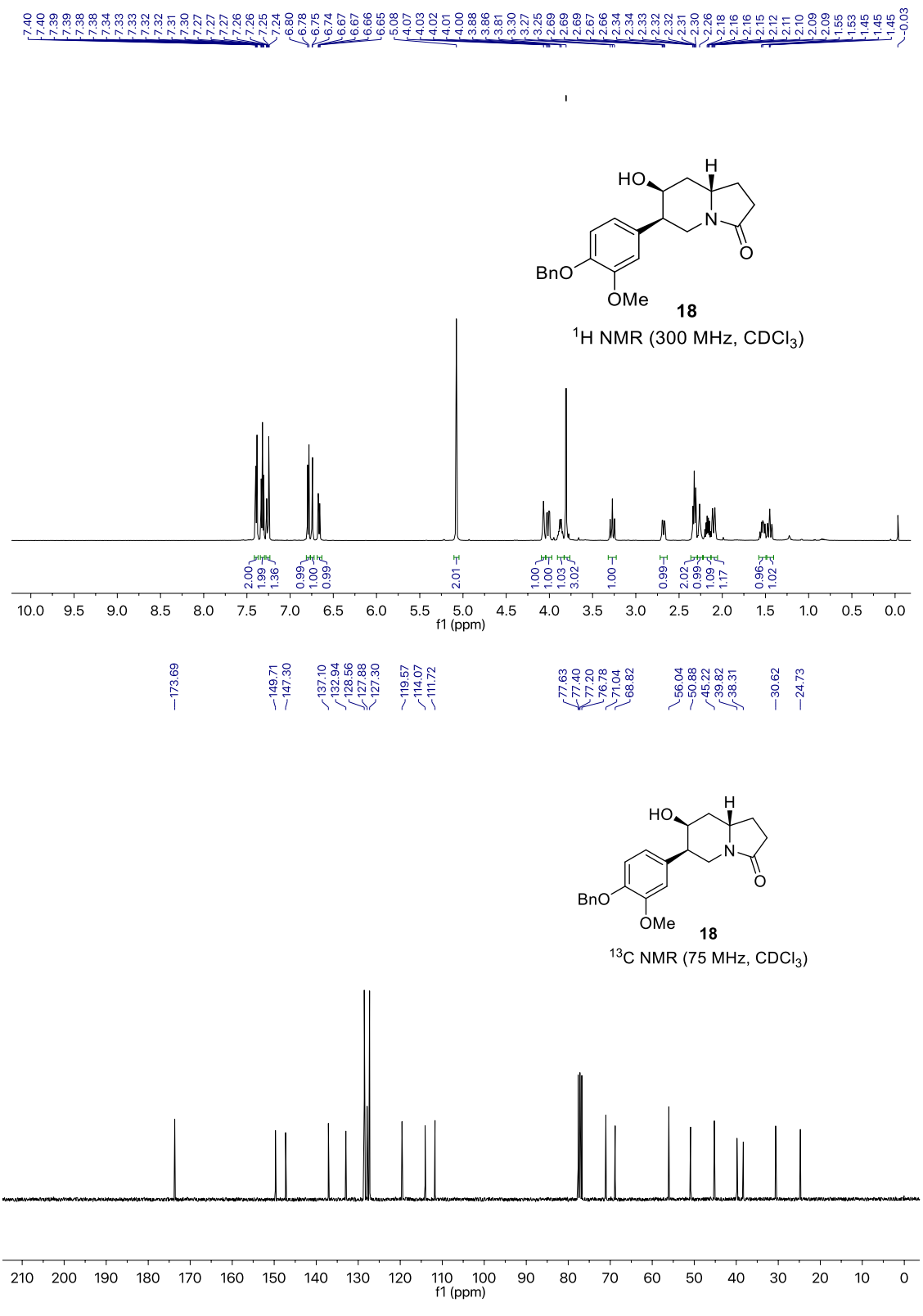
f1 (ppm)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H
N
O
BnO
OMe
18
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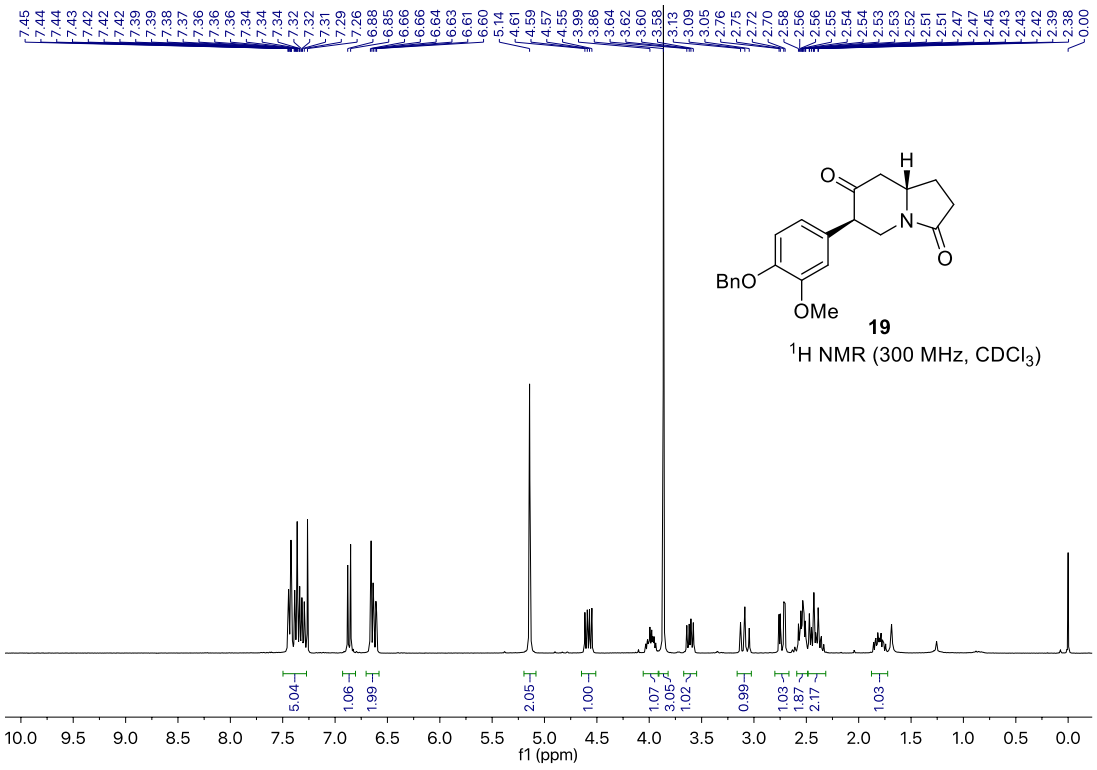
f1 (ppm)
13C NMR (75 MHz, CDCl3)
f1 (ppm)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OMe
19
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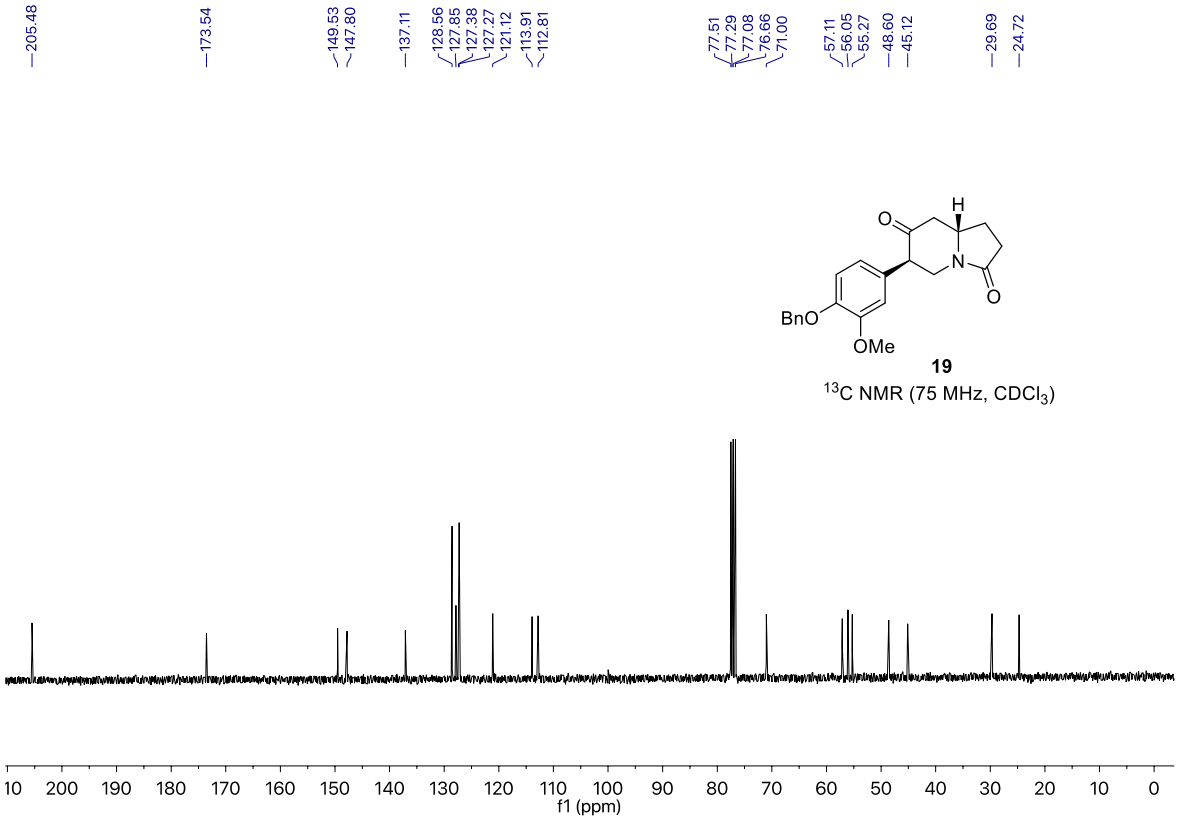
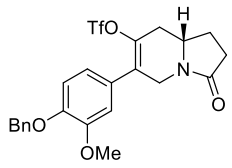
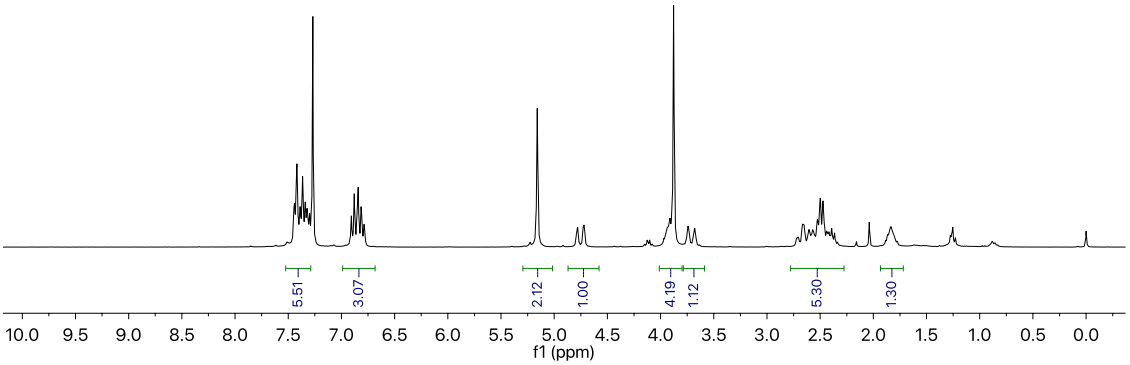
f1 (ppm)

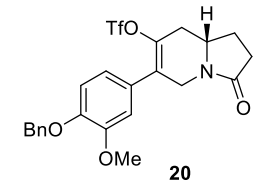

BnO
OMe
19
^{13}C NMR (75 MHz, CDCl$_3$)
f1 (ppm)



20

^{1}H NMR (300 MHz, $CDCl_3$)





20

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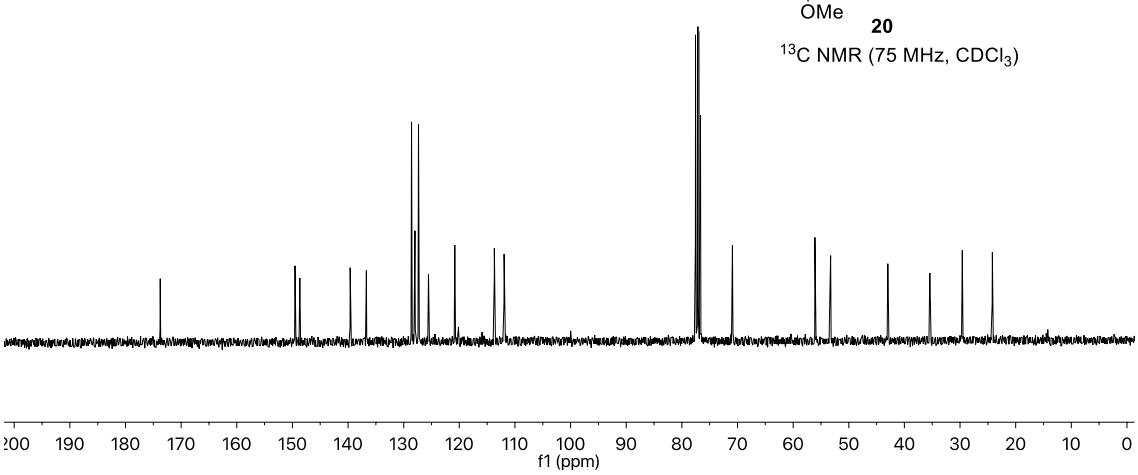

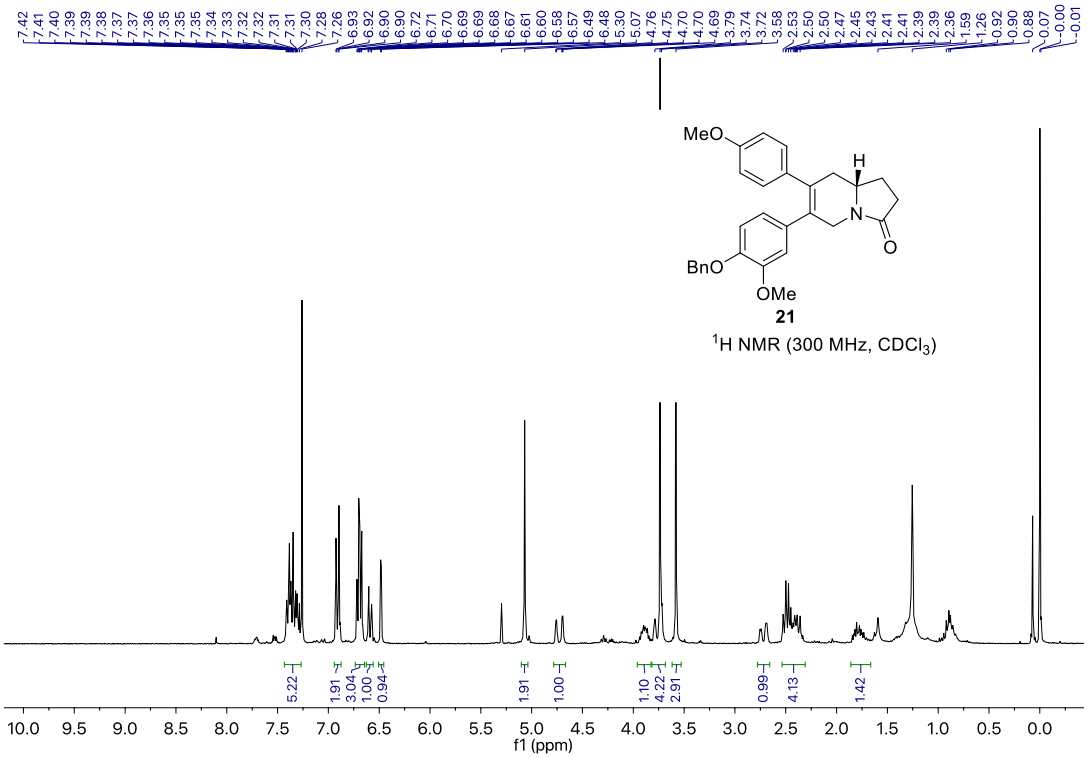
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H
N
O
BnO
OMe
21
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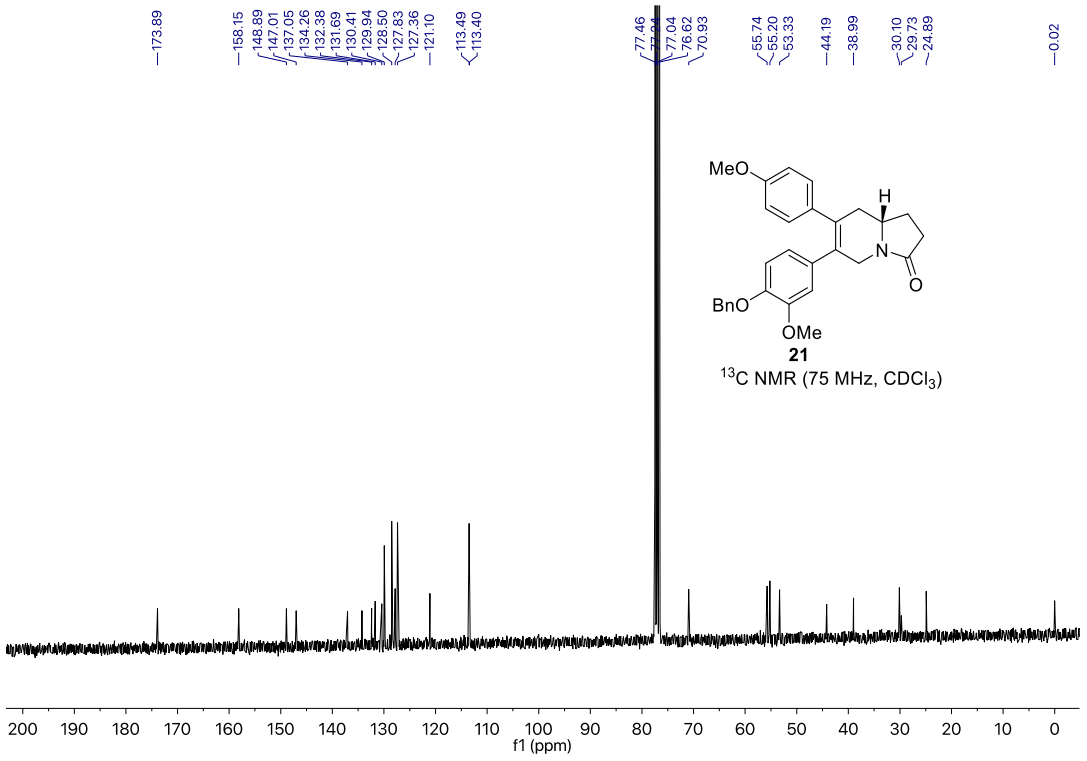
f1 (ppm)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BnO
OMe
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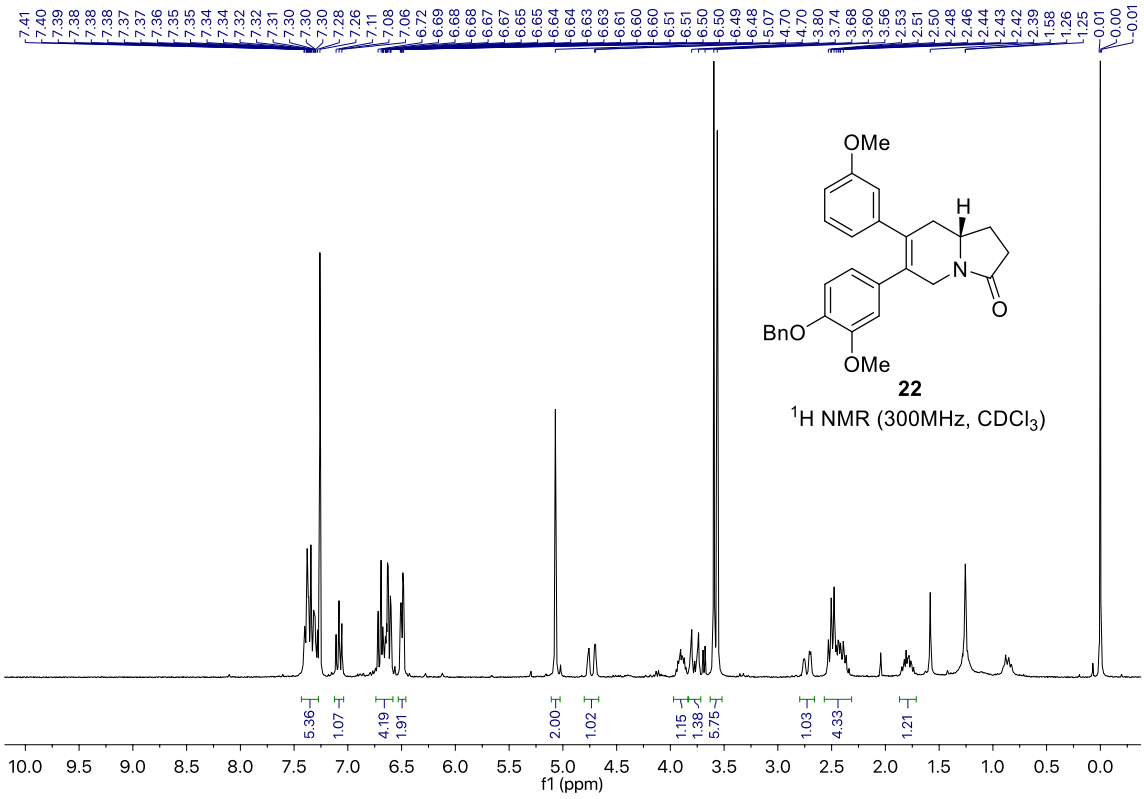
f1 (ppm)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O
BnO
OMe
22
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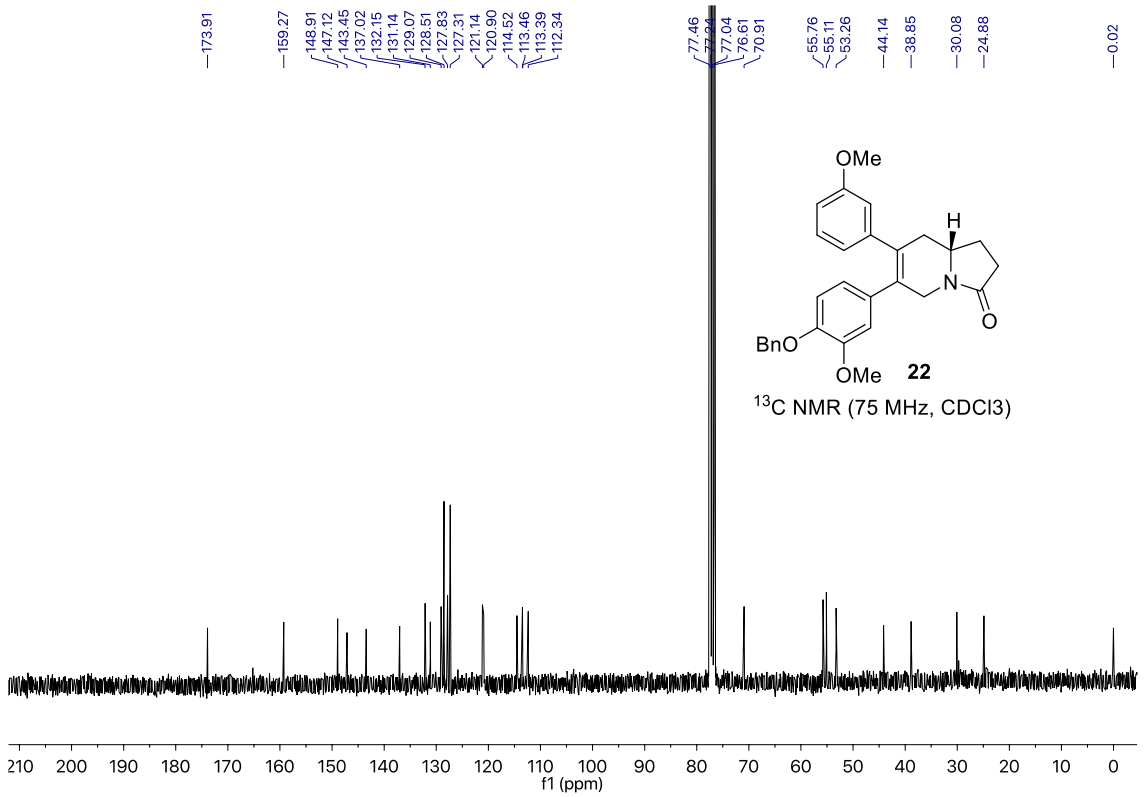
f1 (ppm)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H
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O
BnO
OMe
22
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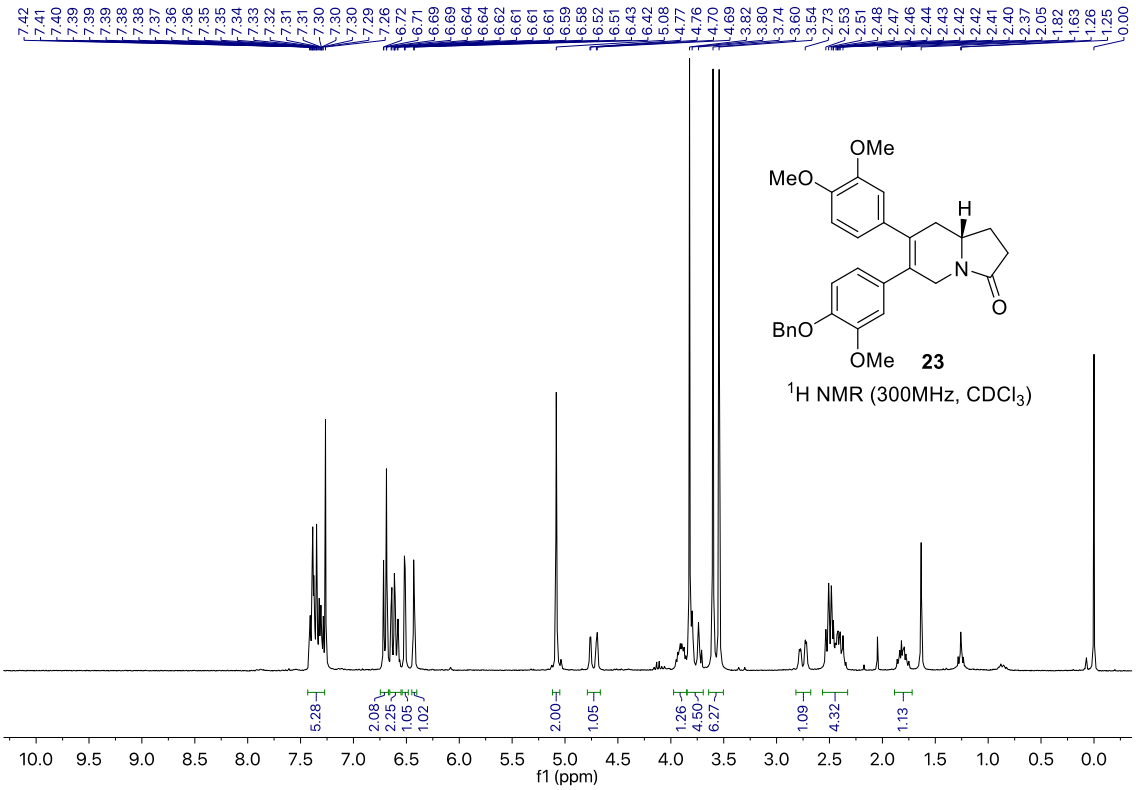
f1 (ppm)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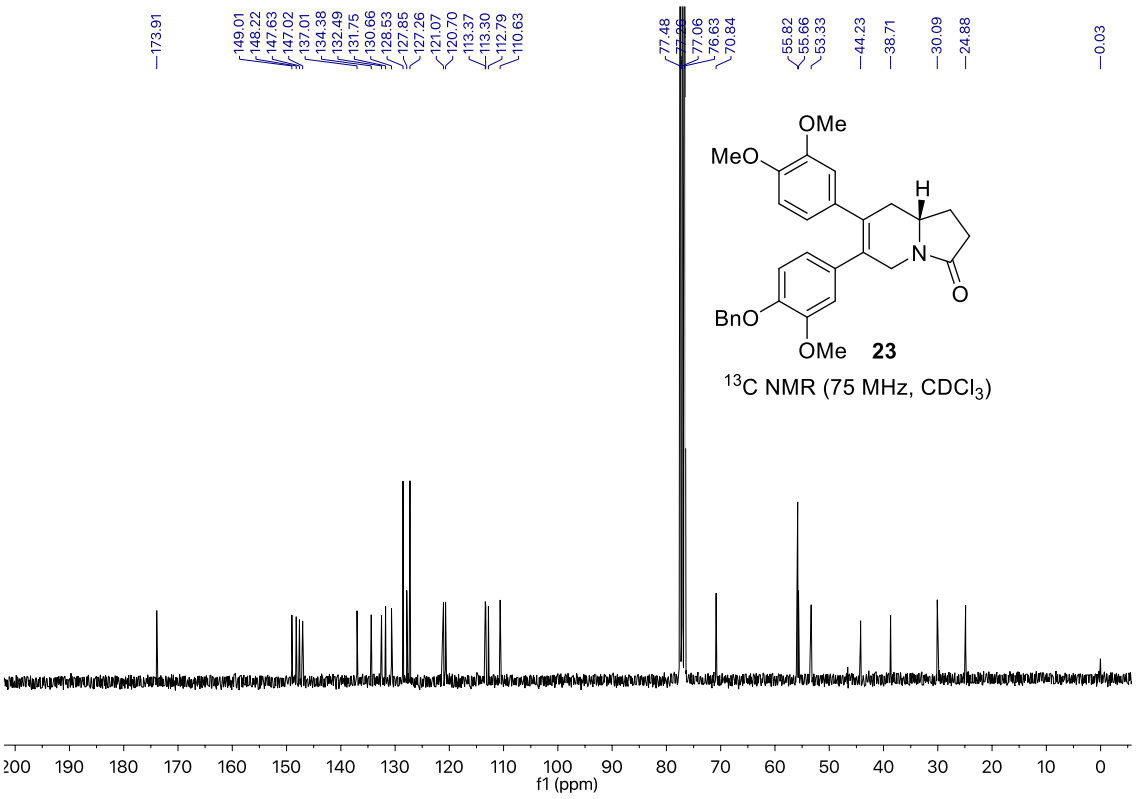
^{1}H NMR (300MHz, CDCl$_3$)
f1 (ppm)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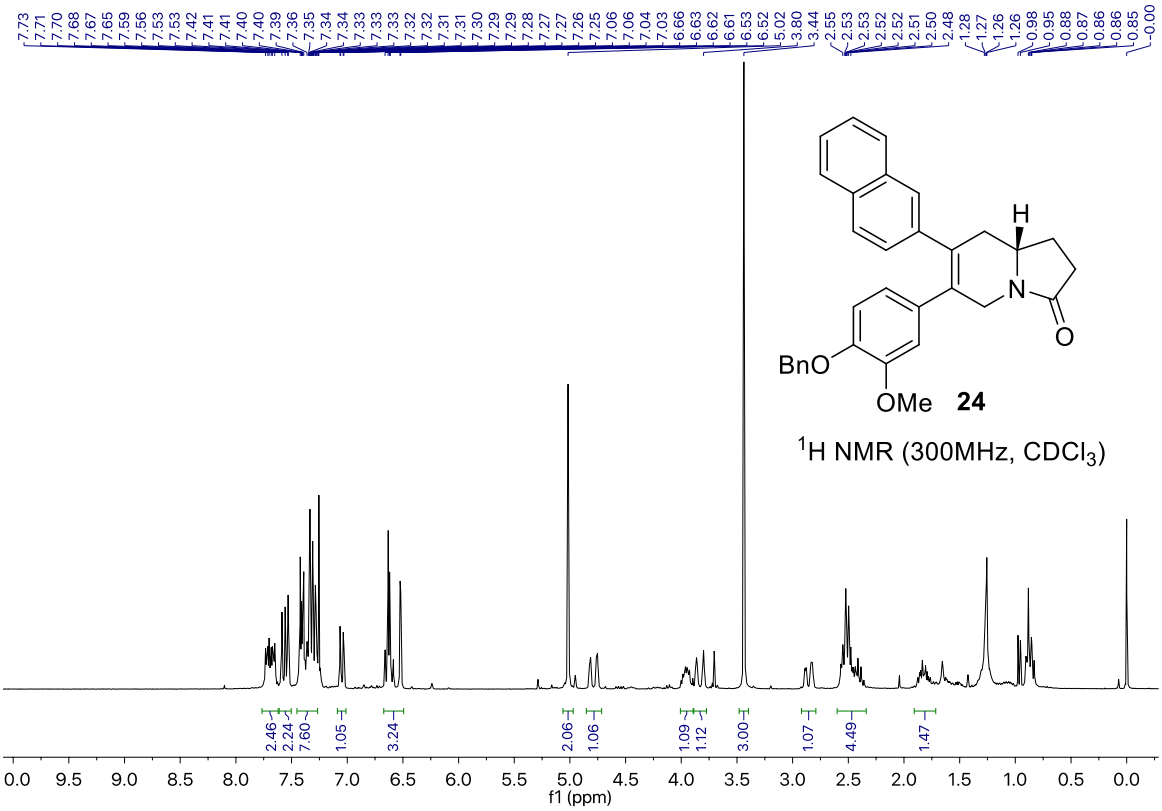
f1 (ppm)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BnO
OMe
24
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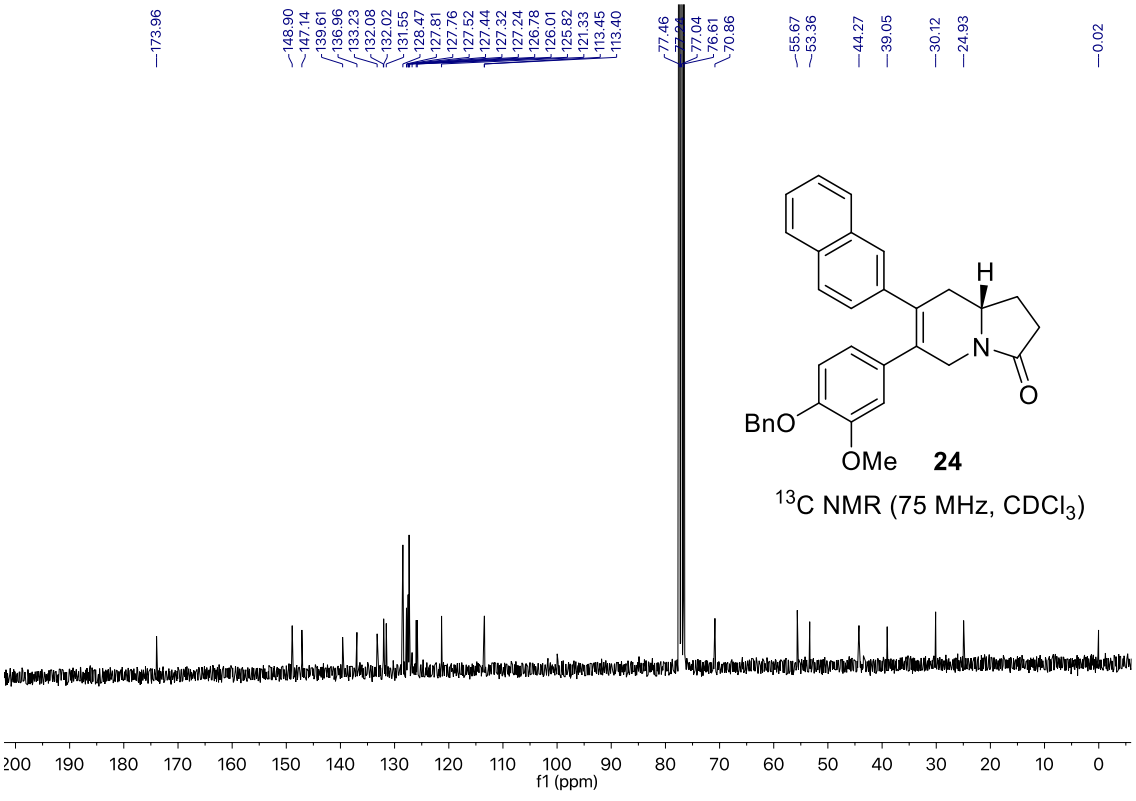
f1 (ppm)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BnO
OMe
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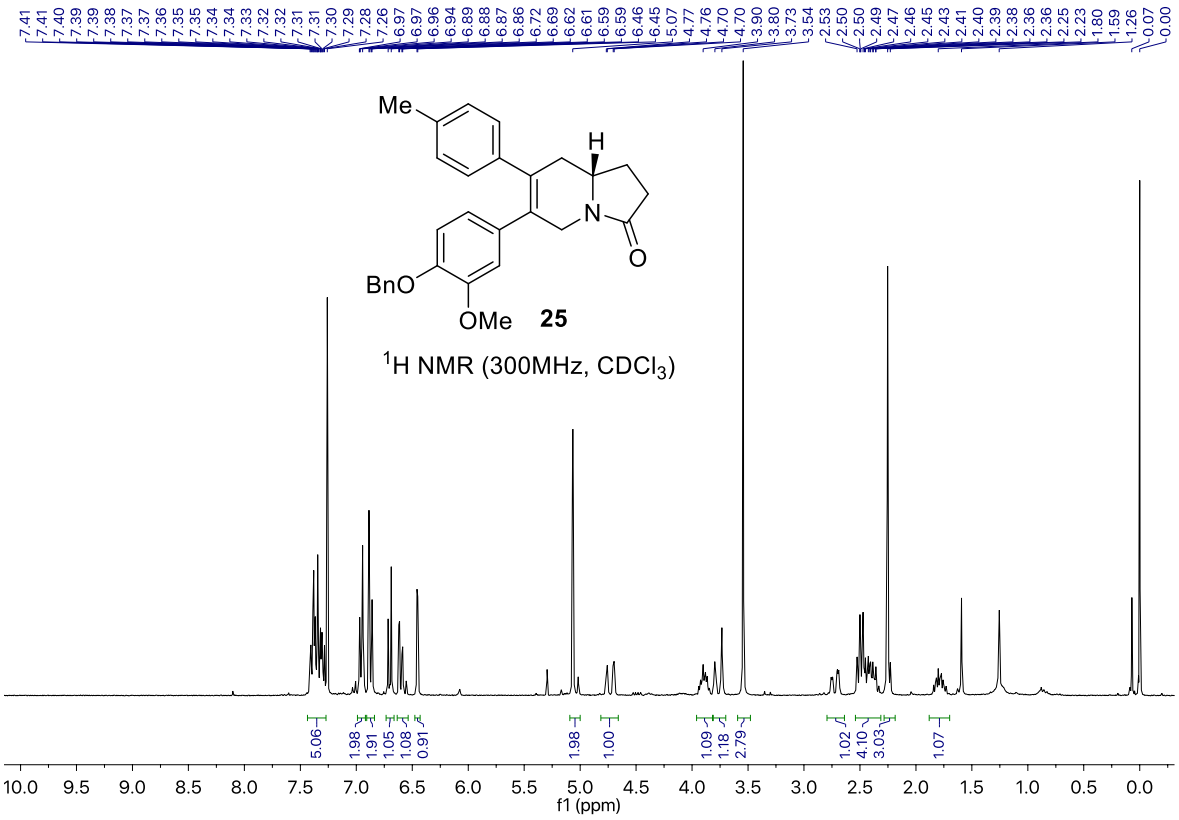
^{13}C NMR (75 MHz, CDCl$_3$)
f1 (ppm)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BnO
OMe
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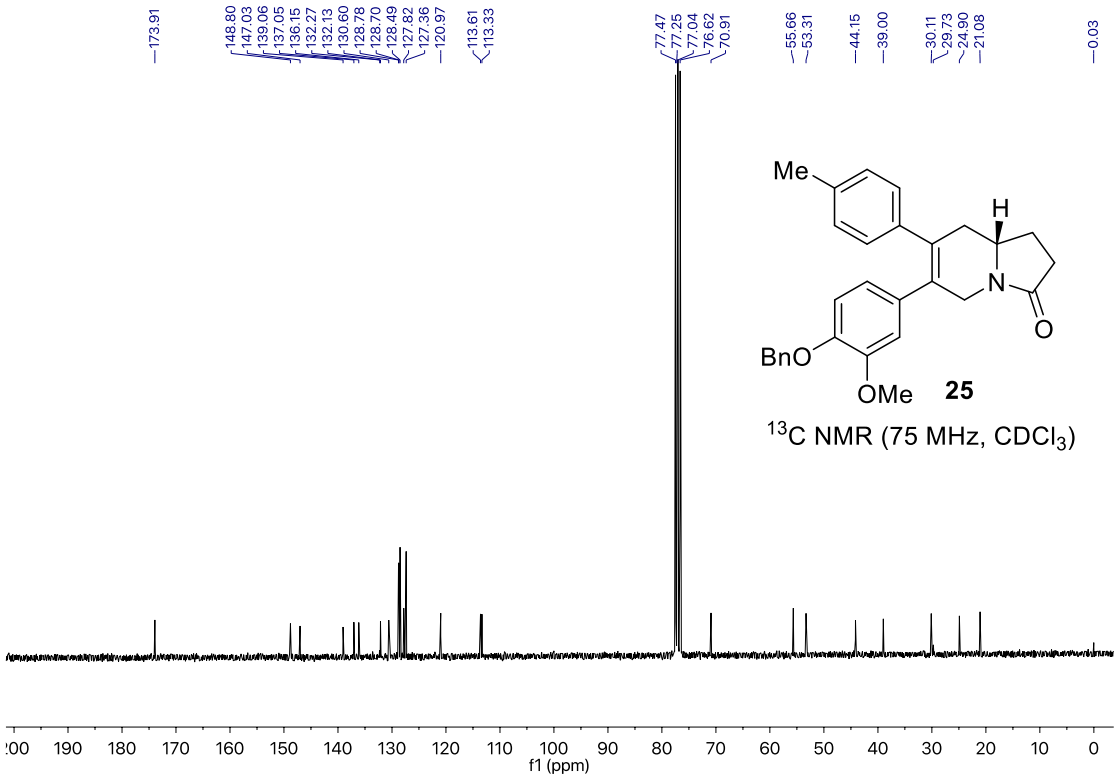
f1 (ppm)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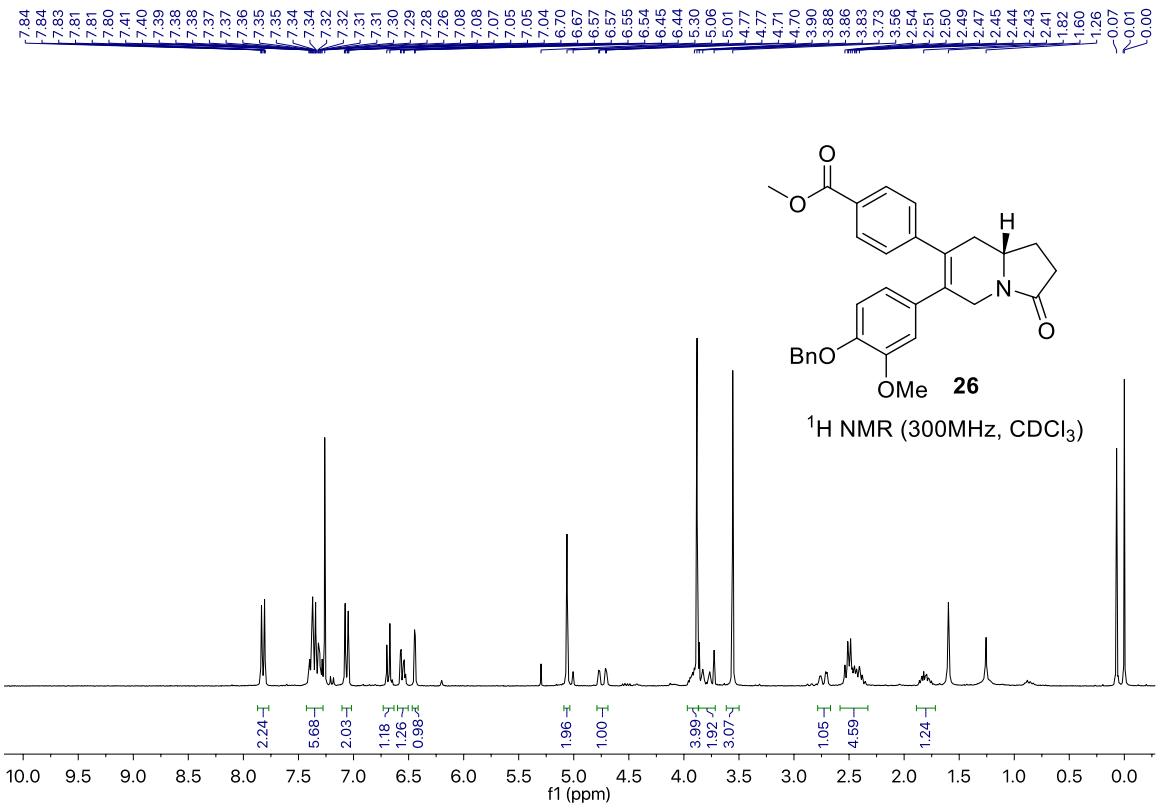
f1 (ppm)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OMe
26
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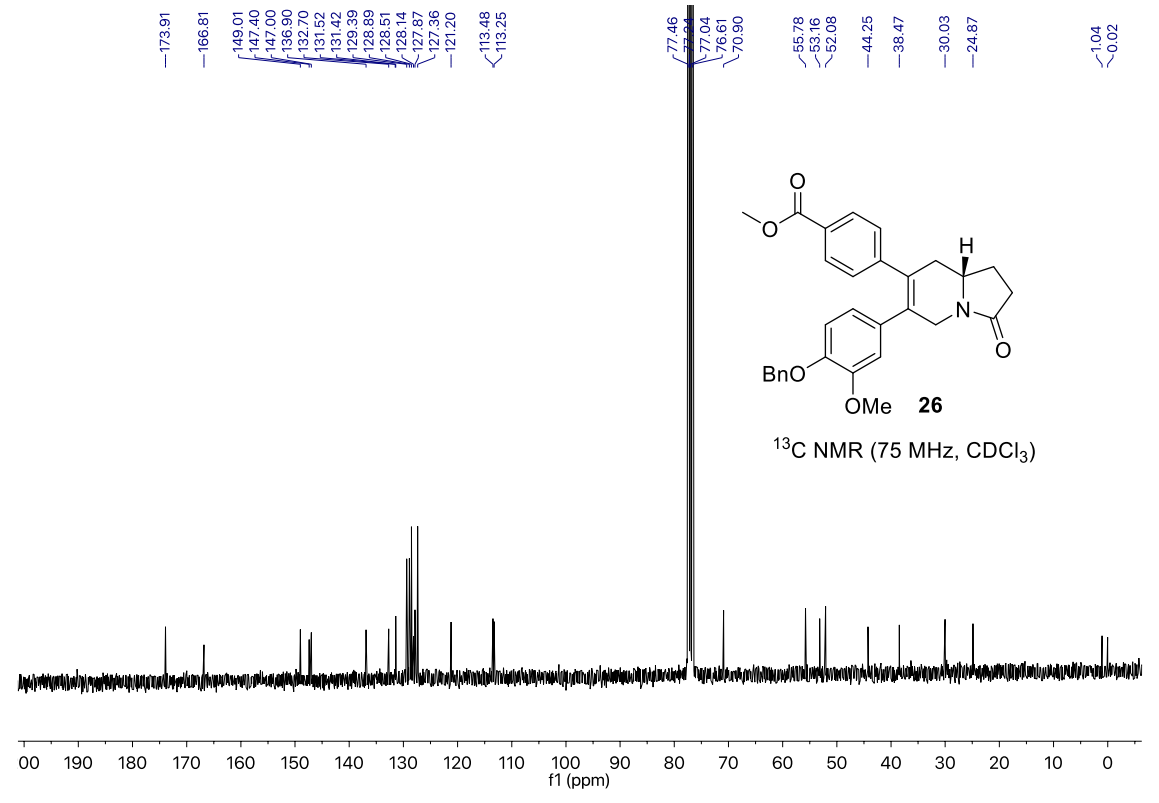
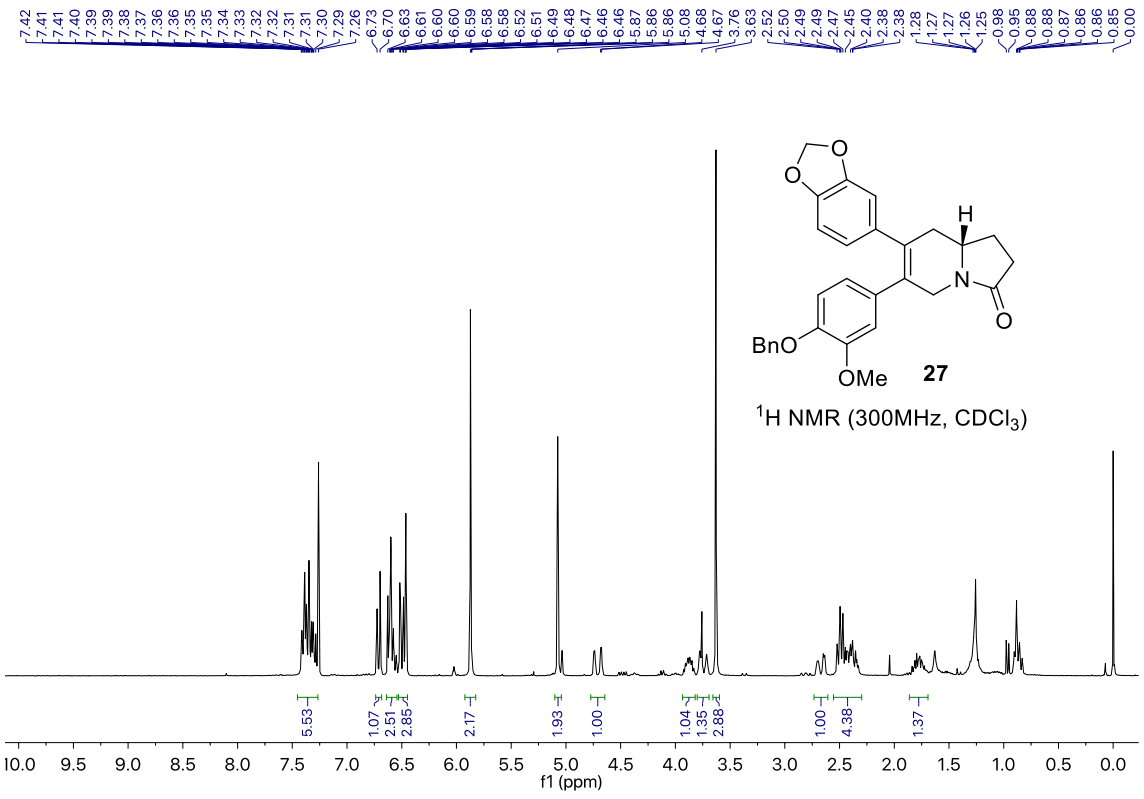
f1 (ppm)


BnO
OMe
26
^{13}C NMR (75 MHz, CDCl$_3$)
f1 (ppm)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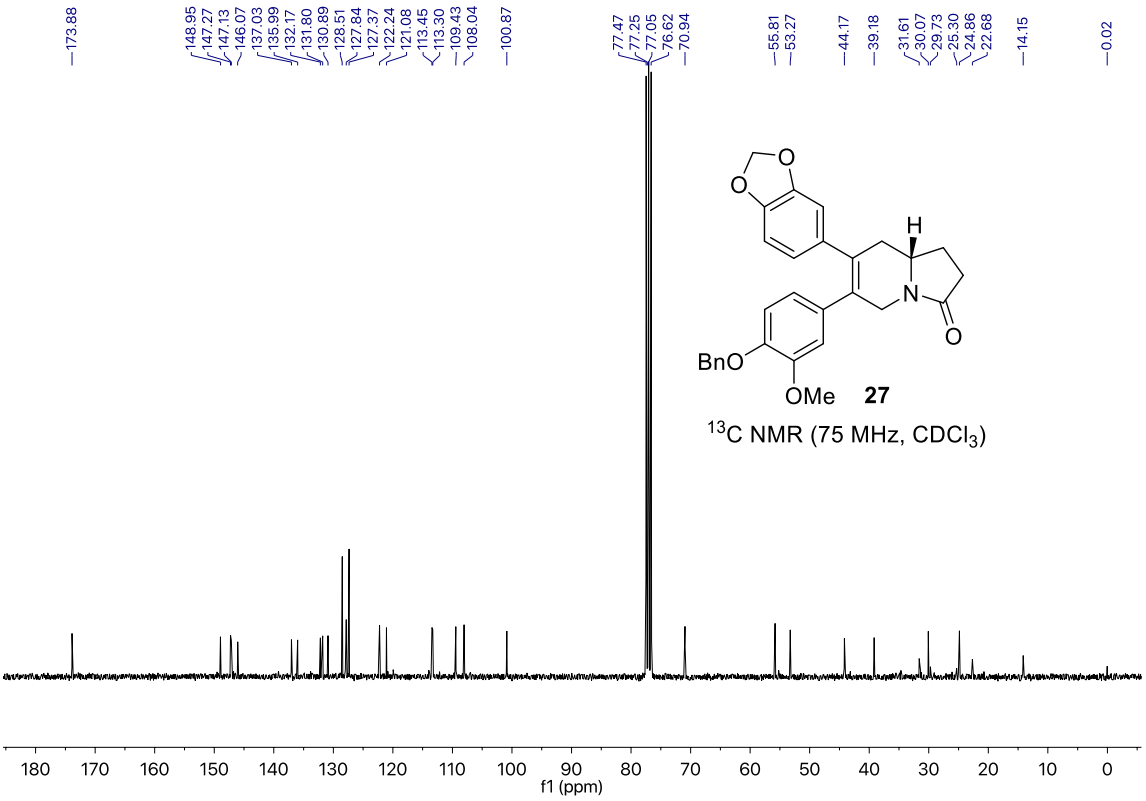
^{1}H NMR (300MHz, CDCl$_3$)
f1 (ppm)

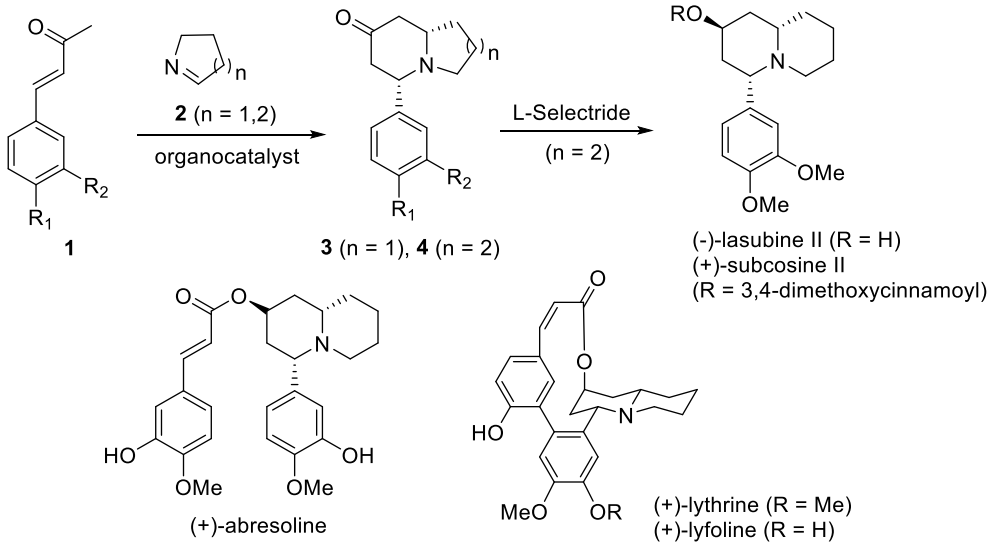

BnO
OMe
27
^{13}C NMR (75 MHz, CDCl$_3$)
f1 (ppm)

Chapter 5

Summary and Future Work

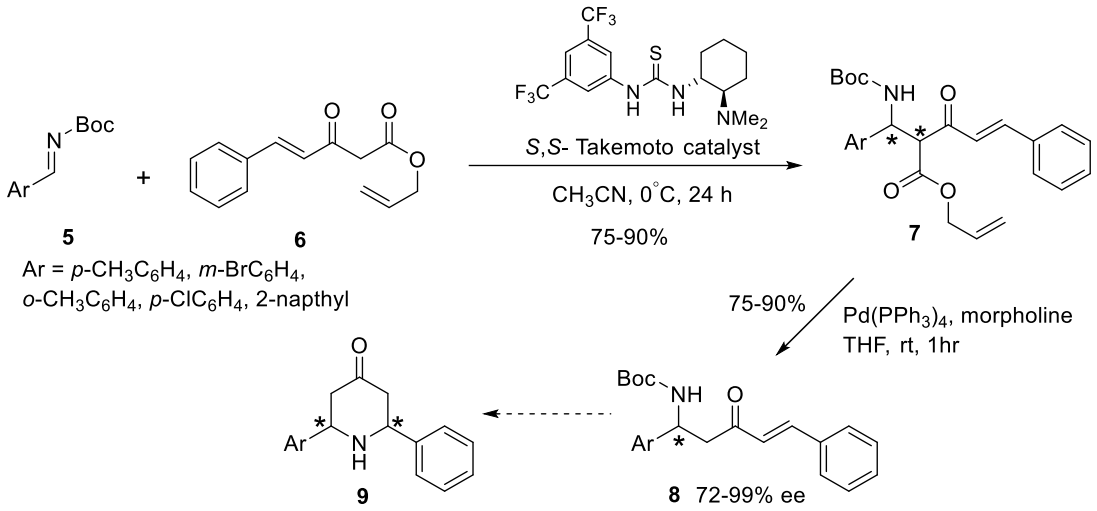
5.1 Summary

A stereoselective synthesis of 5-arylindolizidinones (**3**) and 4-arylquinolizidinones (**4**) was developed. The approach involves an organocatalyzed formal aza-Diels Alder reaction of a variety of chalcones **1** and unstabilized cyclic imines **2**. The methodology was applied in a biomimetic, two-step, enantio- and diastereoselective synthesis of the 4-arylquinolizidine alkaloid (-)-lasubine II (a *Lythraceae* alkaloid) which was easily converted into (+)-subcosine II by acylation. Key 4-arylquinolizidinone intermediates to other *Lythraceae* alkaloids such as (+)-abresoline, (+)-lythrine and (+)-lyfoline were also prepared by this method. Details of these studies are described in Chapter 2.



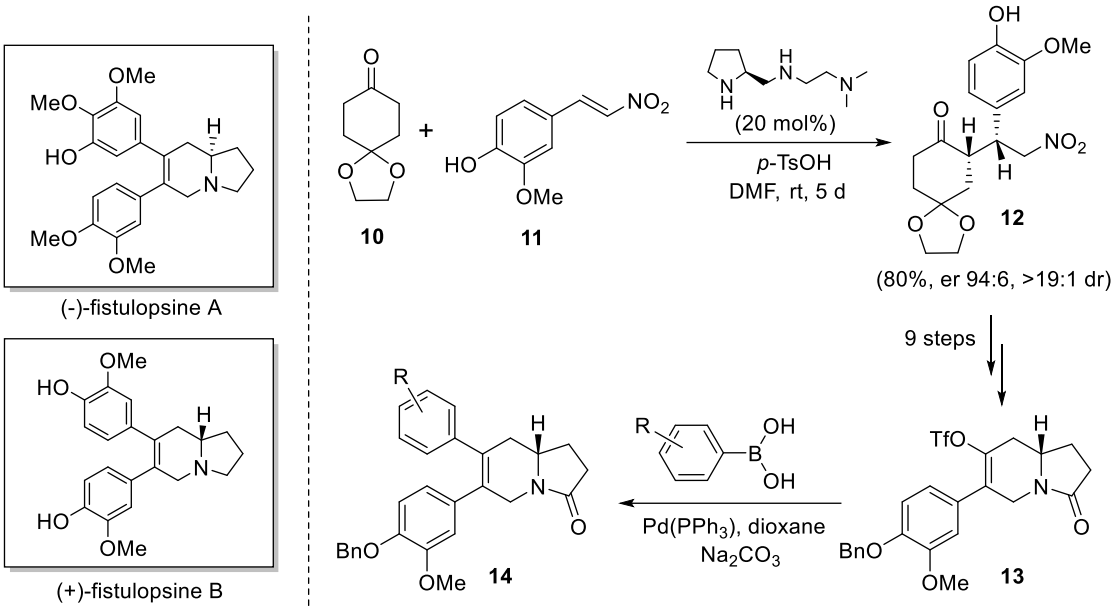
Scheme 5.01

An organocatalyzed asymmetric Mannich reaction of α,β unsaturated β'-ketoesters with *N*-carbamoyl imines was investigated as a potential route to 2,6-disubstituted piperidinone derivatives. The reaction of imines **5** with the ketoester **6** in the presence of an aminothiourea catalyst (*S*,*S*-Takemoto catalyst) provided the Mannich products **7** in 75-90 % yields as a mixture of diastereomers. Pd(0) mediated deallylative decarboxylation of **7** provided the desired β-amino ketones **8** in 75-90% yield and with 72-99% ee. These results and studies on the conversion of **8** to the 2,6-diarylpiperidinones **9** are described in Chapter 3.



Scheme 5.02

Several 2-indolinone-based analogues of (+)-fistulopsine B were synthesized, with structural variation in terms of a) the diaryl substitution on the indolizidine core and b) the use of a cyclic amide instead of the pyrrolidine subunit. These analogues were tested against *S. epidermidis* and *S. cerevisiae* for their biological activity, however, were found to be inactive. The synthesis of the analogues, by employing an organocatalytic Michael addition as a key step, and the biological activity studies are described in Chapter 4.



Scheme 5.03

5.2 Future work

Given the importance of Mannich and aza-Michael reactions in alkaloids chemistry, it would be interesting to explore these reactions as tools to construct focused libraries of alkaloid analogues for biological evaluation. However, the relative instability and problematic synthesis of activated imines, especially alkyl imines, is a limitation. The use of an oxidative Mannich reaction, in which stable amines are used for in situ generation of activated imines oxidatively, can circumvent these issues. It will be particularly interesting to develop domino reactions using oxidative Mannich/aza-Michael reaction processes. The application of these processes to synthesize azepane/azocine containing compounds which are frequently found in biologically active compounds will also be interesting.