Stereoselective Reactions of Ephedrine-Derived Alkylidene Morpholinones for the Synthesis of (+)-Epilupinine, (+)-Epitashiromine and Functionalized Quaternary Stereocenters

by

© **Rakesh G. Thorat**

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To my family

ABSTRACT

The stereoselective 1,3-dipolar cycloaddition reaction of cyclic nitrones with ephedrine-derived alkylidene morpholinones provided the corresponding spiro isoxazolidines which were converted to naturally occurring indolizidine and quinolizidine alkaloids. A detailed investigation of the cycloaddition reaction and the conversion of the isoxazolidine intermediates to (+)-epilupinine and (+)-epitashiromine is described in Chapter 2. In a separate study, haloalkylidene morpholinones were used as substrates for metal-catalyzed cross-coupling reactions to provide diastereomerically pure, substituted alkylidene morpholinones. These were subjected to a stereoselective Prins reaction to provide diastereomerically pure spirodioxolane intermediates which were converted to β-hydroxy carboxylic acids with a quaternary stereocenter at the α carbon. This methodology is described in Chapter 3. Investigations of alkylidene dioxolanones, as potential substitutes for the ephedrine-derived alkylidene morpholinones employed in Chapters 2 and 3, are described in Chapter 4.

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List of Abbreviations and Symbols

4 Å MS	4 angstrom molecular sieves
Ac	acetyl
APCI	atmospheric pressure chemical ionization
AIBN	azobisisobutyronitrile
aq.	aqueous
BnBr	benzyl bromide
BzCl	benzoyl chloride
Boc	*tert*-butoxycarbonyl
br	broad
cat.	catalytic
CAN	ceric ammonium nitrate
CI	chemical ionization
dr	diastereomeric ratio
1,2-DME	1,2-dimethoxyethane
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEAD	diethylazodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide

DMSO	dimethyl sulfoxide
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
ee	enantiomeric excess
eq.	equivalent(s)
EDG	electron donating group
EI	electrospray ionization
EtOAc	ethyl acetate
EWG	electron withdrawing group
g	gram(s)
h	hour(s)
HRMS	high resolution mass spectrum
Hz	Hertz(s)
IR	infrared
i-Bu	isobutyl
J	coupling constant
L	ligand
LAH	lithium aluminium hydride
LD_{50}	lethal dose, 50%
LDA	lithiumdiisopropyl amide
LiHMDS	lithium bis(trimethylsilyl)amide
M	molar
M+	molecular ion
m-CPBA	*meta*-chloroperoxybenzoic acid

Me	methyl
mg	milligram(s)
min	minute(s)
mL	milliliter(s)
mmol	millimole(s)
mp	melting point
MsCl	methanesulfonyl chloride
MS	mass spectrum
MW	microwave
Na_2EDTA	disodium ethylenediamine tetraacetate
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
Oxone®	potassium peroxymonosulfate
ppm	parts per million
PCC	pyridinium chlorochromate
Ph	phenyl
PTSA/*p*-TsOH	*para*-toluenesulphonic acid
RCM	ring-closing metathesis
rt	room temperature
t-BuOH	*tert*-butyl alcohol
TfOH	trifluoromethanesulfonic acid

TBAI	tetra-*n*-butylammonium iodide
TBDMS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMS	tetramethylsilane
TMSOTf	trimethylsilyl trifluoromethanesulfonate
^{o} C	degree Celsius
δ	chemical shift (spectroscopy)
α	alpha
β	beta
γ	gamma

Chapter 1

Introduction

1. Indolizidine and Quinolizidine Alkaloids

A large number of alkaloids which contain indolizidine and quinolizidine frameworks exhibit notable biological activities.[1] The wide array of biological activities includes antiviral,[2] antiarrhythmic,[2c] antimalarial,[2d,2e] and platelet antiaggregating activities.[2f] The structural diversity arising from varying degrees of substitution on either ring of the bicyclic core makes these alkaloids interesting targets for the development of new synthetic strategies.[3]

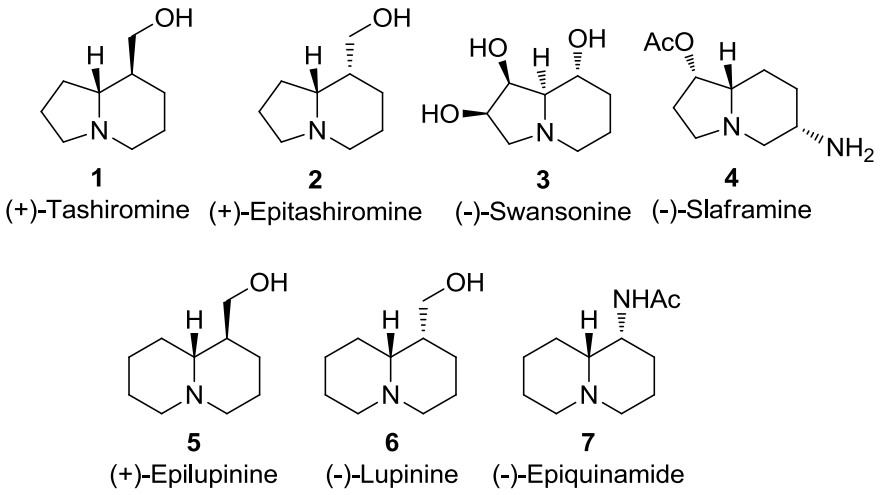


Figure 1.1 Examples of indolizidine and quinolizidine alkaloids.

A review of the classical literature reveals several methodologies for the synthesis of indolizidine and quinolizidine alkaloids, each focused on a specific reaction to install the required stereochemistry in the target molecule. Since a vast amount of literature is available on the subject, the focus of the following literature survey is only on methodologies reported after 2008. In addition, since one of the objectives, which will be

described in this thesis, is the synthesis of targets **1**, **2**, **5** and **6**, the total syntheses or formal syntheses of any one or more of these target alkaloids (Figure 1.1) will be presented. Individual studies have addressed the total synthesis of various target alkaloids, as well as analogs or congeners of the natural product. Hence, a synthetic tactic-based analysis is presented as follows:

1.1. Ring formation via nucleophilic displacement or addition reactions:

1.1.1. Nitrogen-carbon cyclization reactions

1.1.2. Carbon-carbon cyclization reactions

1.2 Ring formation employing ring closing metathesis reaction

1.3 Asymmetric cycloaddition based strategies

1.4 Iminium ion-based approaches

1.5 Organocatalytic approaches

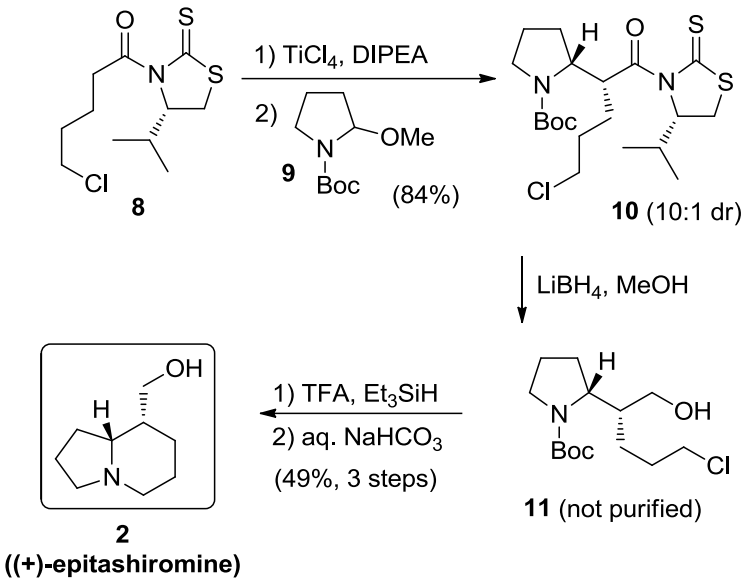
1.1 Ring formation via nucleophilic displacement or addition reactions

1.1.1 Nitrogen-carbon cyclizations

1.1.1.1 Nitrogen-carbon cyclization with preformed azacycles as starting materials

Pilli and coworkers[4] have reported a synthesis of (+)-epitashiromine which begins with stereoselective nucleophilic functionalization of *N*-Boc-2-methoxypyrrolidine (**9**) using a chiral thiazolidinone derived nucleophile (Scheme 1.1). The titanium enolate generated from **8**, reacts with **9**, to provide the intermediate **10** (10:1 dr). This reaction installs the two stereocenters in epitashiromine. Reduction of **10** with lithium borohydride provided **11** as a mixture. Treatment of the crude product with acid removed the *N*-Boc group. Basification of the resulting salt provided (+)-epitashiromine (**2**). An analog of **8**

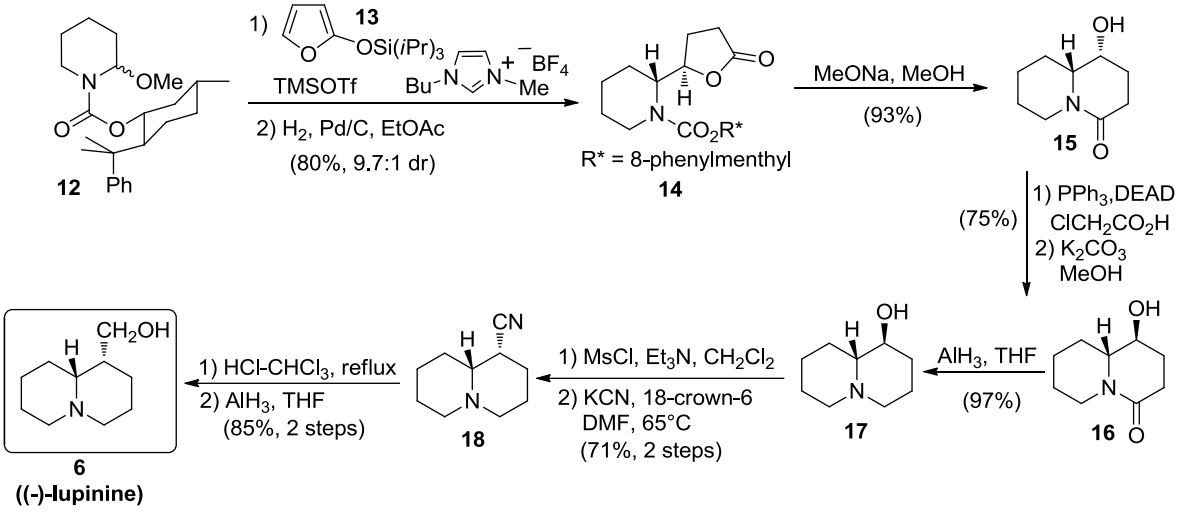
bearing an *N*-chlorobutyryl group was converted to (+)-isoretronecanol following a similar synthetic sequence.



Scheme 1.1 Synthesis of (+)-epitashiromine (**2**) by nucleophilic alkylation of *N*-Boc-2-methoxypyrrolidine.

An asymmetric vinylogous Mannich reaction was employed by Santos in a synthesis of (−)-lupinine (**6**) (Scheme 1.2).[5] The 2-methoxypiperidine derivative **12** when treated with the silyloxyfuran **13** in the presence of trimethylsilyl triflate provides the corresponding Mannich product (9.7:1 dr), hydrogenation of which generates **14**. Use of 1-butyl-3-methylimidazolium tetrafluoroborate (BMI·BF_4) as an additive is necessary for good diastereoselectivity in the Mannich reaction. Removal of the protecting group in **14** with sodium methoxide resulted in intramolecular acylation of the piperidine with the butyrolactone moiety to provide **15**. Mitsunobu inversion of the secondary alcohol in **15** provided **16** which was reduced to **17** with alane. Cyanation of **17** by conversion to the mesylate and treatment with potassium cyanide gave **18**. Hydrolysis of the nitrile followed

by reduction of the corresponding acid provided (−)-lupinine (**6**). This asymmetric vinylogous Mannich reaction strategy was also employed in a synthesis of (−)-epiquinamide.



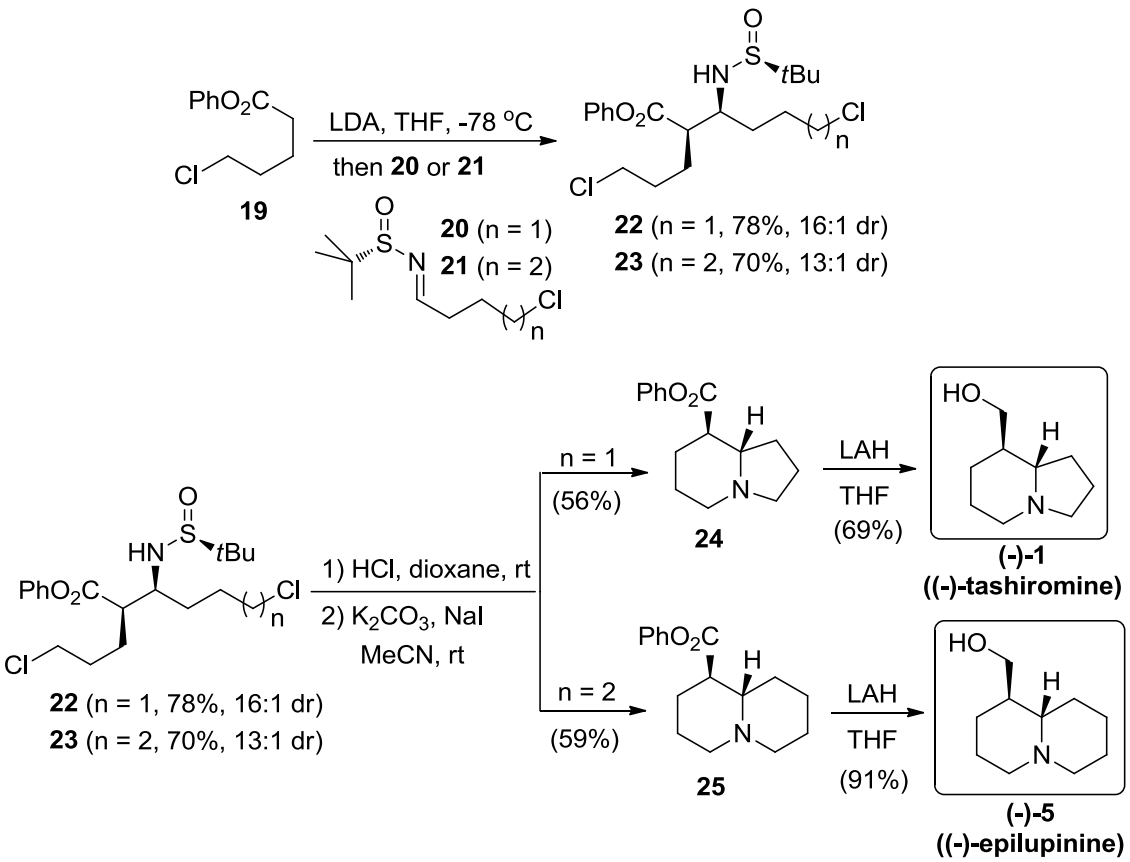
Scheme 1.2 Synthesis of (−)-lupinine (**6**) employing a chiral carbamate-protected methoxypiperidine as the starting material.

1.1.1.2 Nitrogen-carbon cyclizations with open chain precursors

The methodologies utilizing cyclization of open chain precursors to the target ring systems appear more frequently in the literature compared to the cyclization reactions using preformed azacycles. This is probably due to the ready availability of starting materials for the synthesis of appropriately functionalized precursors. These precursors provide access to a wide variety of fused ring systems ([5, 5], [5, 6], [6, 6], [6, 7]) with varying degrees of substitution.

An efficient strategy using an imino-aldol reaction was reported by Brown and coworkers for the synthesis of (−)-epilupinine and (−)-tashiromine.[6] A stereoselective imino-aldol reaction of (*S*)-*tert*-butylsulfinyl imines **20** and **21** (Scheme 1.3) with the

enolate of phenyl 5-chloropentanoate, generates *syn* imino-aldol products **22** and **23** respectively, with good yield and high diastereoselectivity.



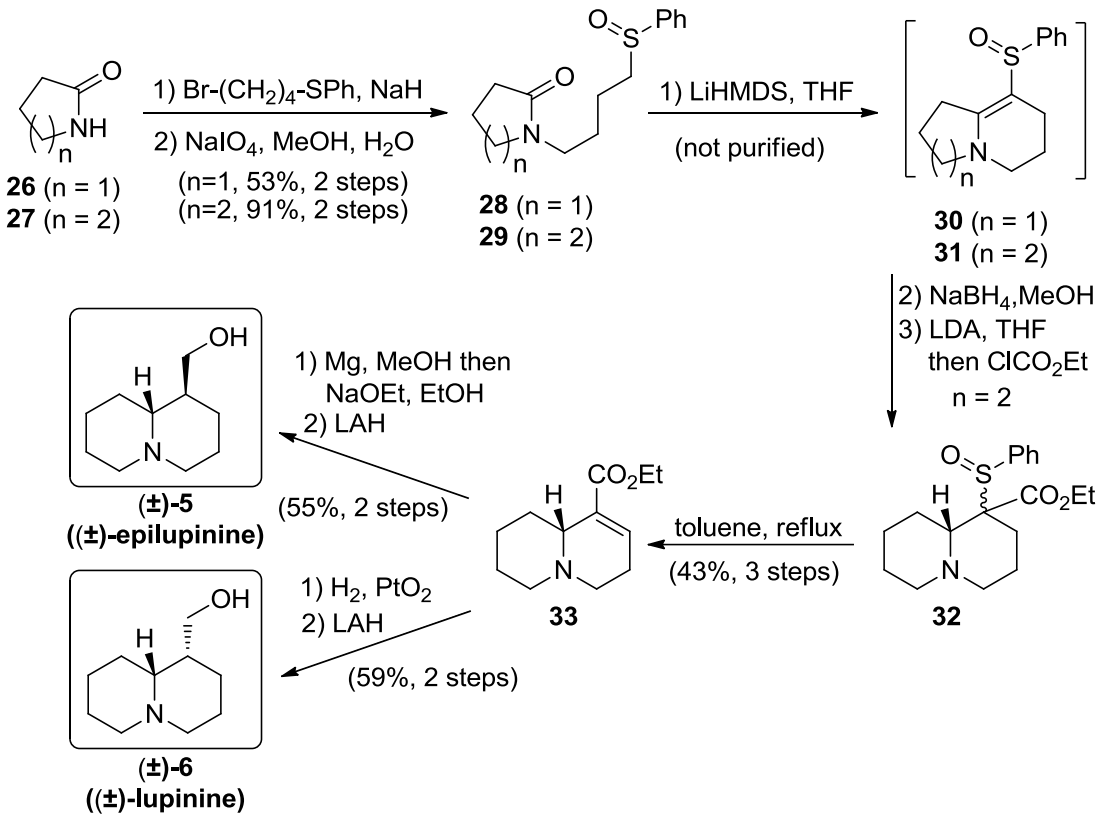
Scheme 1.3 Stereoselective imino-aldol strategy for the synthesis of (−)-tashiromine (**1**) and (−)-epilupinine (**5**).

Removal of the *tert*-butylsulfinyl protection in **22** and **23** followed by sequential cyclization of the primary amine onto the chloroalkyl side chains provided **24** and **25**. These were converted into (−)-tashiromine and (−)-epilupinine respectively by reduction of the phenyl ester to a primary alcohol.

1.1.2 Carbon-carbon cyclizations

1.1.2.1 Carbon-carbon cyclizations with preformed azacycles as starting materials

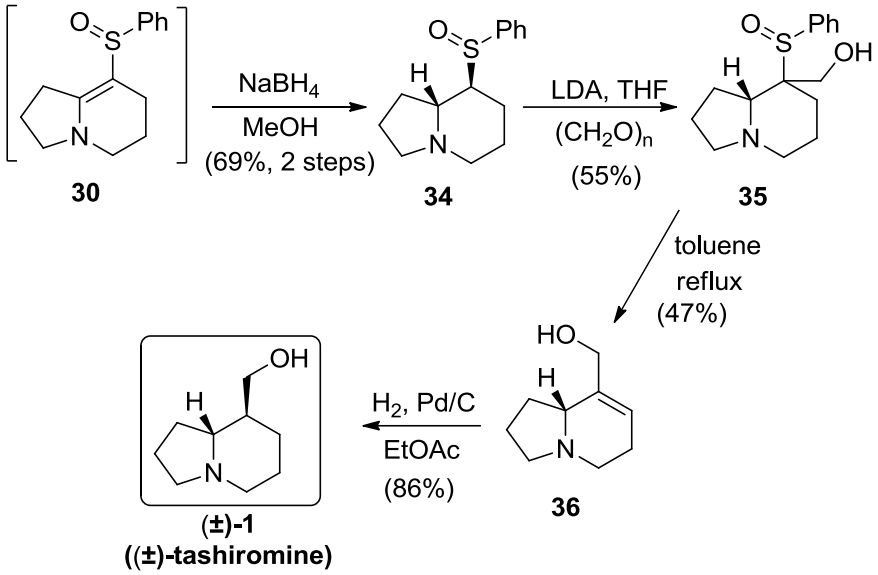
Pohmakotr et al. have reported a general synthetic route to 1-azabicyles by using α-sulfinyl carbanions for intramolecular carbon-carbon bond forming reactions.[7] This tactic relies on the susceptibility of cyclic amides to nucleophilic addition reactions.



Scheme 1.4 Sulfinyl-carbanion cyclization-based approaches to (±)-lupinine (**6**) and (±)-epilupinine (**5**).

N-Alkylation of 2-pyrrolidinone (**26**) and 2-piperidinone (**27**) with 4-bromobutylphenylsulfane followed by oxidation, provided the sulfoxides **28** and **29** respectively (Scheme 1.4). Deprotonation of the sulfoxides followed by cyclization generated **30** and **31**. The reduction of **31** followed by acylation α to the sulfoxide provided **32** as a mixture of diastereomers. A sulfoxide elimination in **32** provided **33**, which was

converted to (±)-epilupinine and (±)-lupinine by following two different reduction protocols. Hydrogenation of **33** followed by reduction of the ester with LAH provided (±)-lupinine as a single diastereomer. Alternatively, reduction of **33** with Mg in MeOH followed by epimerization of the ester and reduction with LAH provided (±)-epilupinine as a single diastereomer. This strategy relies on epimerization of the reduction product obtained from **33** to the thermodynamically stable β-form of the ester.

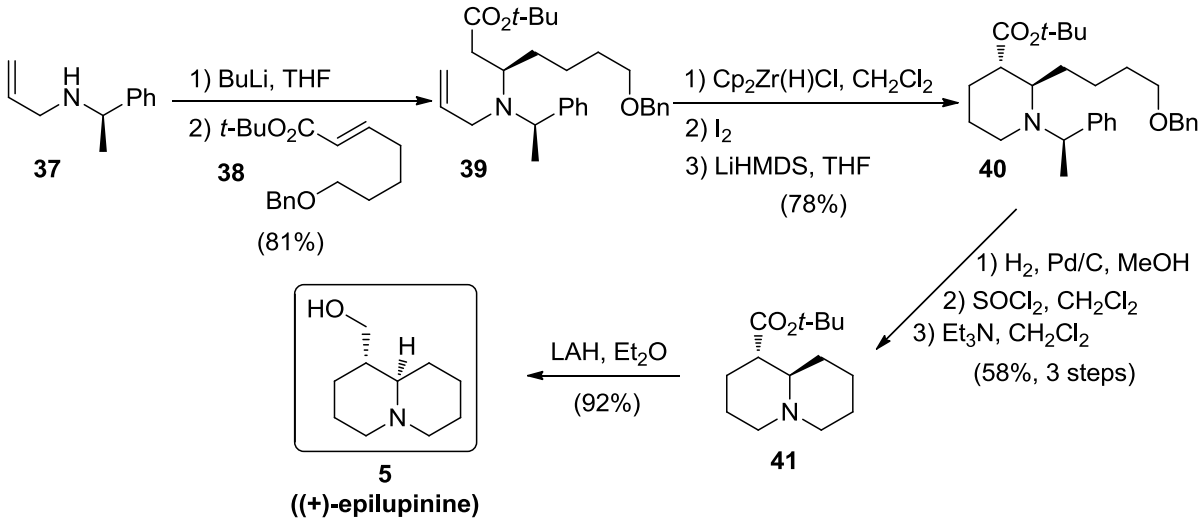


Scheme 1.5 Sulfinyl-carbanion cyclization-based approaches to (±)-tashiromine (**1**).

As with **31**, the reduction of **30** provided **34**, which was converted to **35** in an aldol-type reaction with paraformaldehyde (Scheme 1.5). Sulfoxide elimination in **35** followed by hydrogenation provided diastereomerically pure (±)-tashiromine. This strategy was also applied to the syntheses of related indolizidine alkaloids.

1.1.2.2 Carbon-carbon cyclizations via azacyclic intermediates

Szymoniak and coworkers reported a synthetic strategy that follows a hydrozirconation / iodination / cyclization protocol for the formation of the piperidine ring in (+)-epilupinine (**5**).[8] The same group has also reported a synthesis of (±)-lupinine by employing a hydrozirconative cyclization of a functionalized pyridine moiety.[8b] For the synthesis of epilupinine, enantiomerically enriched amine **37** was used as the starting material. Conjugate addition of lithiated **37** to the enoate **38** generated **39** as a single diastereomer (Scheme 1.6).



Scheme 1.6 A hydrozirconation / iodination / cyclization approach to (+)-epilupinine (**5**).

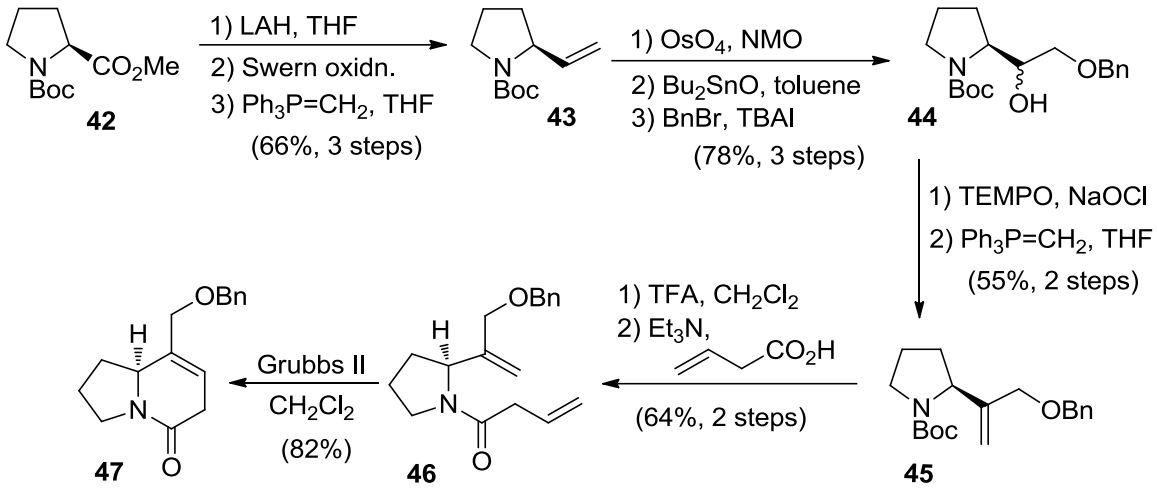
Hydrozirconation of the *N*-allyl group in **39** followed by treatment with iodine generated the corresponding primary iodide. Treatment of this iodoester intermediate with LiHMDS resulted in an intramolecular alkylation of the ester enolate to provide **40**. This strategy was also used in the synthesis of other *trans*-2,3-disubstituted piperidines. Hydrogenation of **40** generated the corresponding amino alcohol. This was converted to

the corresponding primary chloride which cyclized to provide **41**. Reduction of the ester in **41** provided (+)-epilupinine (**5**).

1.2 Syntheses employing ring closing metathesis as a key transformation

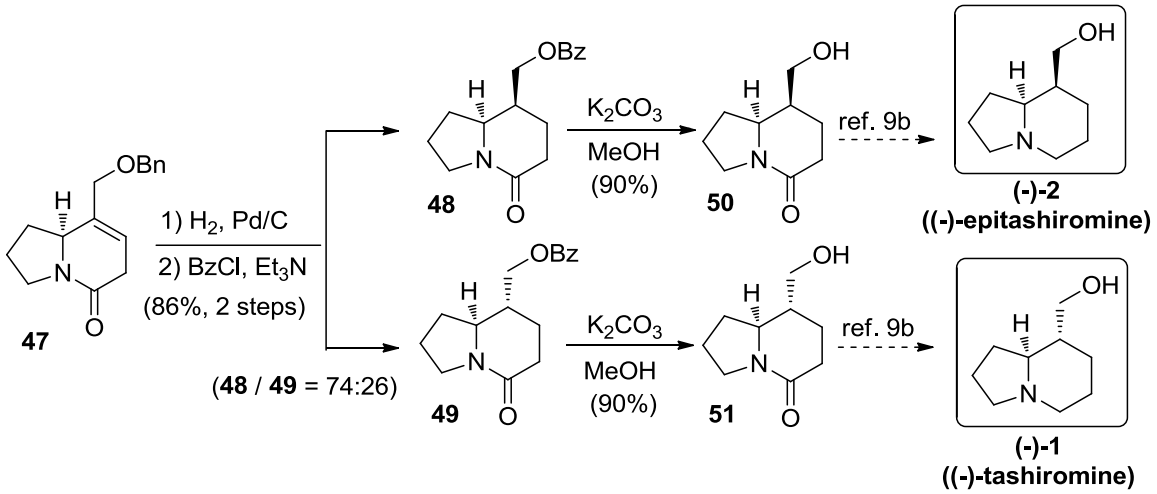
Various research groups have investigated a ring closing metathesis (RCM) strategy for construction of azabicyclo alkaloid motifs. Most of the RCM strategies involve construction of one (for indolizidine motifs) or both (for quinolizidine motifs) of the six membered rings. Strategies involving construction of a five membered ring using RCM are rare.

Rao and coworkers[9] reported (*S*)-proline-based formal syntheses of the indolizidine alkaloids (−)-tashiromine and (−)-epitashiromine employing RCM as a key step (Scheme 1.7). Their approach begins with (*S*)-Boc methyl prolinate **42**. The stereocenter in proline becomes the ring junction stereocenter in the target. Reduction of **42** with LAH followed by Swern oxidation gave the corresponding aldehyde. Wittig methylenation of the aldehyde furnished **43**. Dihydroxylation of **43** followed by chemoselective protection of the diol provided **44** which furnished **45** on oxidation to the ketone and Wittig methylenation. Replacing the Boc group with an appropriate *N*-acyl group provided the RCM precursor **46** which, upon treatment with the Grubbs II catalyst, furnished **47**.



Scheme 1.7 (*S*)-Proline-based approach to (−)-tashiromine (**1**) and (−)-epitashiromine (**2**) involving RCM.

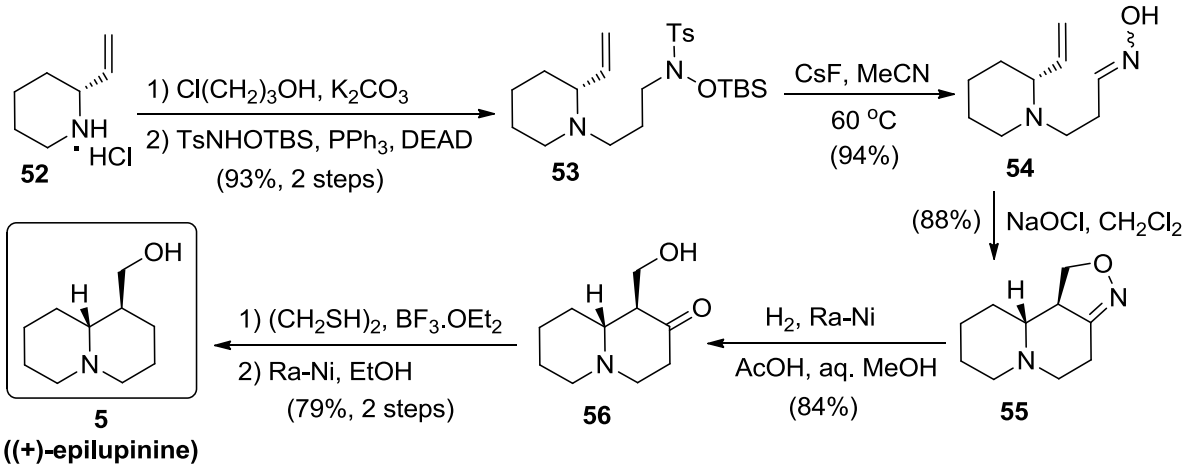
Hydrogenation of **47** followed by benzoylation of the resulting primary alcohol provided a mixture of separable diastereomers **48** and **49** (Scheme 1.8). Debenzoylation of **48** and **49** provided **50** and **51** respectively. These can be converted to the targets by reduction of the cyclic amide.



Scheme 1.8 Conversion of **47** to (−)-epitashiromine and (−)-tashiromine.

1.3 Asymmetric cycloaddition-based strategies

In view of the numerous syntheses of aza sugars and their analogs employing cycloaddition reactions of functionalized nitrones, it is surprising that similar strategies involving cycloaddition reactions for the synthesis of indolizidine and quinolizidine motifs are not as common. The few studies reported rely on [2+2],[10] and [4+2][11] cycloaddition reactions of alkenes, nitrile oxide cycloaddition reactions[12] and inter-[13] and intramolecular 1,3-dipolar cycloaddition reactions of acyclic nitrones[14]. Hu, Wang and coworkers reported a synthesis of (+)-epilupinine (**5**) starting with the enantiomerically enriched 2-vinyl piperidine **52** and utilizing a nitrile oxide cycloaddition as the pivotal step (Scheme 1.9).[12,15] The piperidine **52** was prepared in four steps by a procedure reported by the same authors.[15]



Scheme 1.9 Synthesis of (+)-epilupinine (**5**) via an intramolecular nitrile oxide cycloaddition reaction.

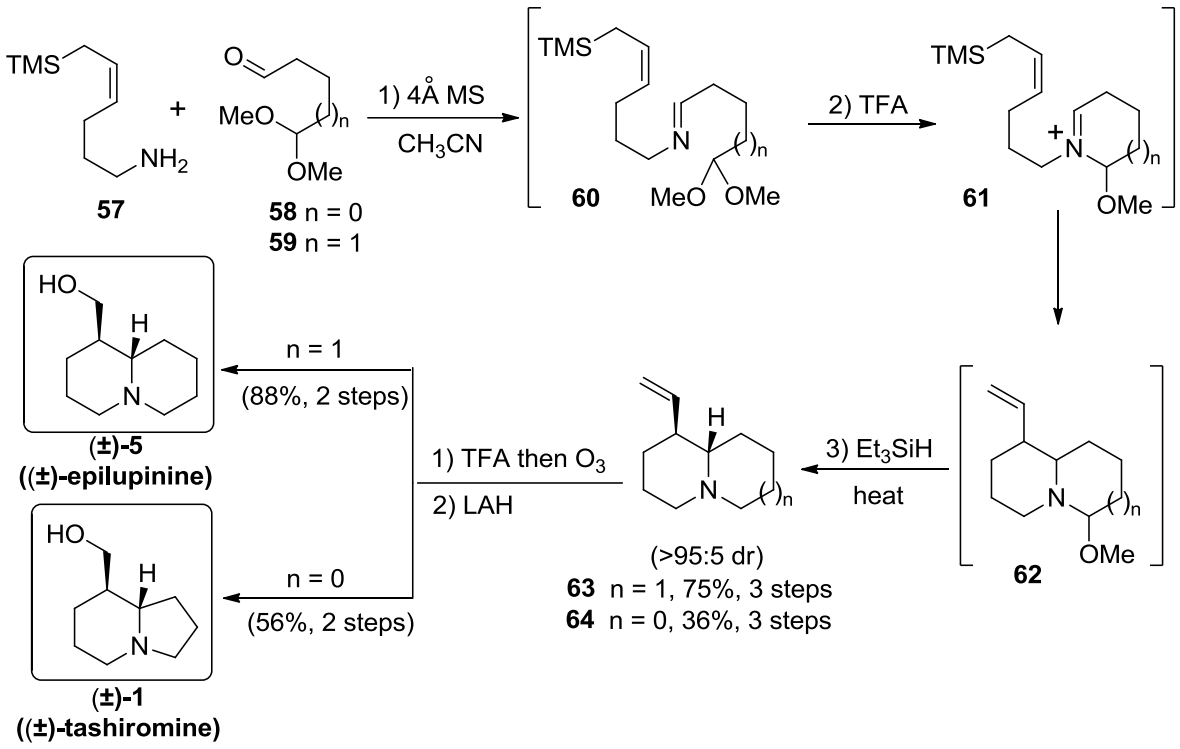
N-Alkylation of **52** with 3-chloropropanol, elaboration of the alcohol into the *N*-tosyl-*O*-TBS hydroxyl amine derivative **53** (Fukuyama procedure[16]), followed by treatment with CsF generated the oxime **54**. The nitrile oxide generated on oxidation of **54**

with NaOCl underwent an intramolecular [3+2] cycloaddition to provide the isoxazoline **55** as a single diastereomer. Reductive N-O bond cleavage in **55** followed by *in situ* hydrolysis of the resulting imine furnished the intermediate **56**. Conversion of **56** to (+)-epilupinine (**5**) was achieved by reducing the dithiolane obtained from the ketone.

1.4 Iminium ion-based approaches

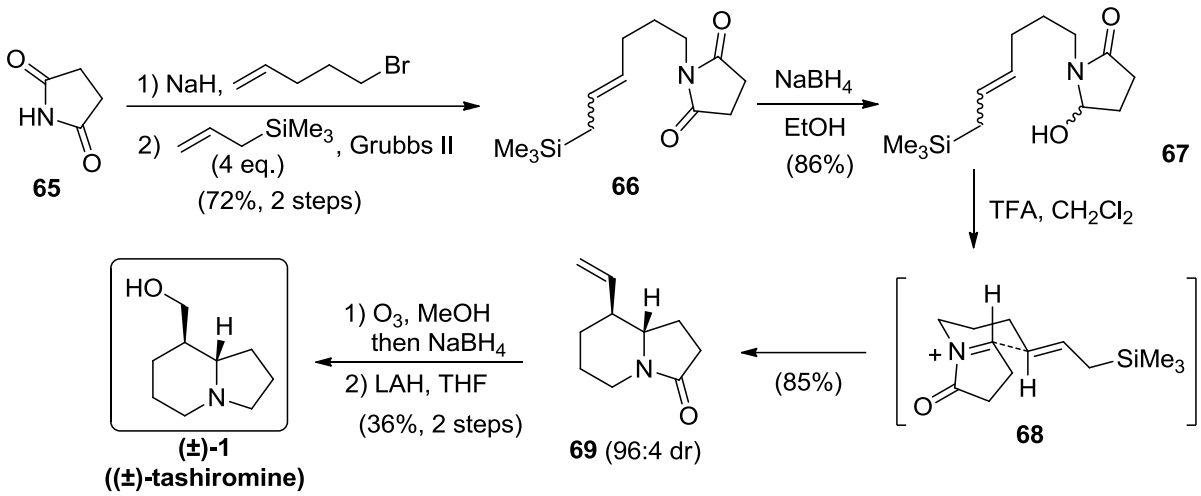
Remuson has recently reviewed the applications of *N*-acyliminium ions in the synthesis of alkaloids containing a piperidine ring[3d] and hence only studies reported after this review will be summarized below. Strategies utilizing *N*-acyliminium ions are among the most concise and are unique for their rapid assembly of the heterocyclic rings from acyclic precursors.

Martin and coworkers[17] have developed a strategy for the syntheses of (±)-epilupinine, (±)-tashiromine and (−)-epimyrtene (Scheme 1.10), which relies on the intramolecular *N*-alkylation and allylation of a preformed imine. Their synthetic sequence begins with the aminosilane **57** which was condensed with the monoprotected dialdehyde **58** or **59** to provide the corresponding imine **60**. Treatment of **60** with TFA generated an oxonium ion that reacted further with the adjacent imine moiety to form compound **61**. The resulting iminium ion underwent an intramolecular allylation to provide the bicyclic *N*,*O*-acetal **62**. The iminium ion obtained from **62** was reduced with triethylsilane to provide either **63** or **64** depending on the aldehyde used (**58** or **59**). Ozonolysis of **63** and **64** followed by reduction of the corresponding aldehydes provided (±)-epilupinine and (±)-tashiromine, respectively.



Scheme 1.10 Intramolecular, iminium ion silylation strategy for (±)-epilupinine (**5**), (±)-tashiromine (**1**).

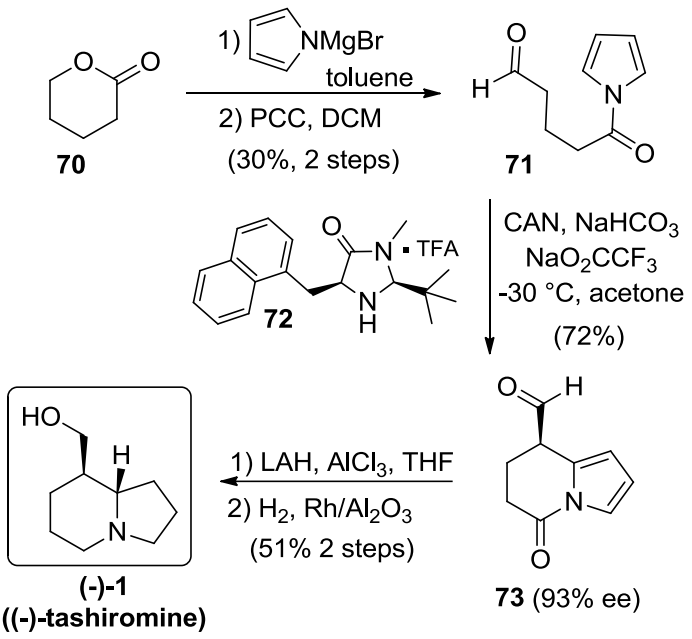
Marsden and McElhinney reported a synthesis of (±)-tashiromine which uses an *N*-acyliminium ion-based intermediate for construction of the six membered ring.[18] The iminium ion precursor was prepared from succinimide **65** (Scheme 1.11). *N*-Alkylation of **65** with 5-bromo-1-pentene followed by cross metathesis of the resultant *N*-alkenyl succinimide with allyltrimethylsilane provided **66**. The hydroxy lactam (**67**) obtained by partial reduction of **66** furnished the indolizidinone **69** on treatment with TFA. The authors suggested that the intramolecular capture of the iminium ion generated from **67** proceeded via a chair-like transition state **68** to provide **69** with the shown stereochemistry. Reductive ozonolysis of **69** and subsequent reduction provided (±)-tashiromine.



Scheme 1.11 Stereoselective intramolecular *N*-acyliminium ion capture in the synthesis of (±)-tashiromine (**1**).

1.5 Organocatalytic Approaches

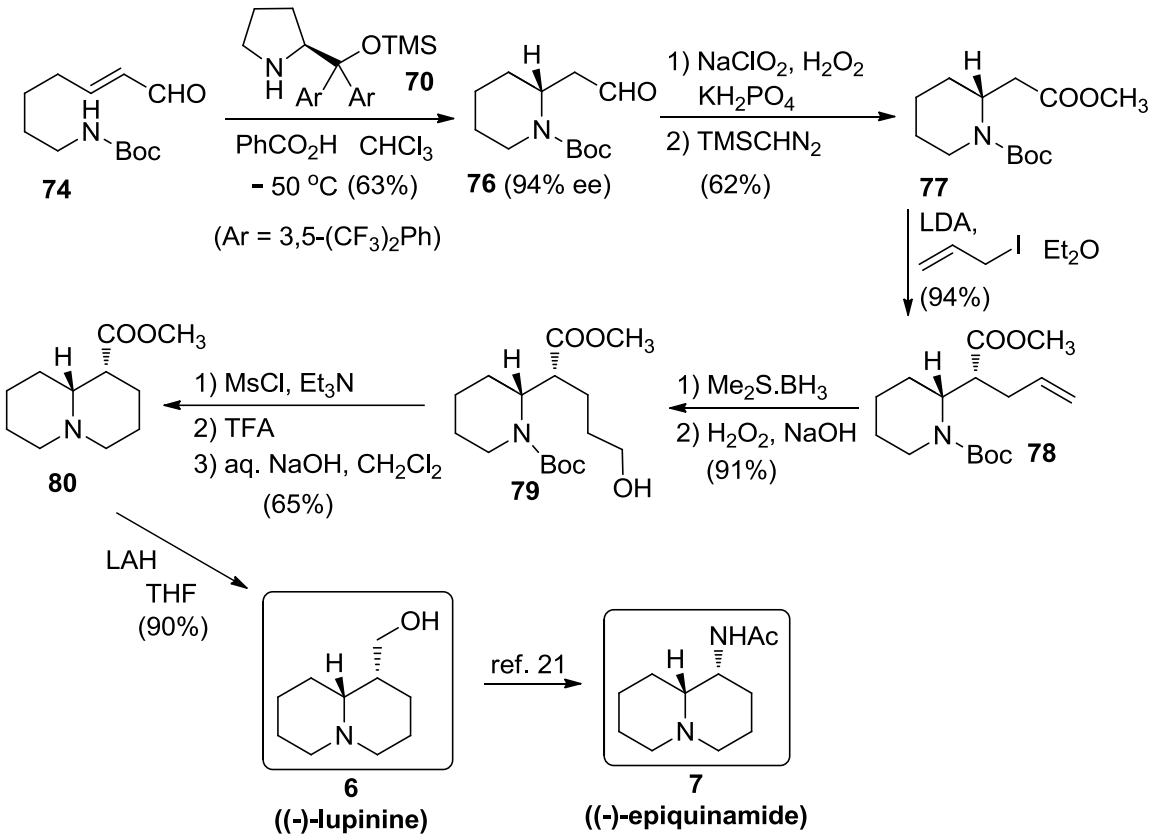
MacMillan and coworkers reported a short synthesis of (−)-tashiromine based on organo-SOMO catalysis.[19] Lactone **70** on treatment with the magnesium salt of pyrrole (prepared in situ by deprotonation of pyrrole with MeMgBr) followed by oxidation of the alcohol product provided aldehyde **71** (Scheme 1.12). The key step of the synthesis, α-arylation of the aldehyde, was performed by converting the aldehyde to the corresponding iminium ion by exposure to a catalytic amount of the imidazolidinone salt **72** and oxidizing the iminium ion with ceric ammonium nitrate.



Scheme 1.12 Enantioselective intramolecular aldehyde α-arylation-based synthesis of (−)-tashiromine (**1**).

The resulting radical cation underwent an enantioselective, intramolecular α-arylation reaction to ultimately provide the tetrahydroindolizinone **73** (93% *ee*) after rearomatization. Reduction of the aldehyde and the lactam followed by hydrogenation of the pyrrole in **73** provided (−)-tashiromine.

Fustero, del Pozo and coworkers reported syntheses of (−)-lupinine (**6**), (+)-myrtene and a formal synthesis of (−)-epiquinamide (**7**) by using an enantiomerically pure piperidine as the starting material.[20] An intramolecular *aza*-Michael reaction of the *N*-Boc amino enal **74** catalyzed by the (*S*)-diarylprolinol derivative **75** furnished the 2-(2-oxoethyl)piperidine derivative **76** with high enantioselectivity (Scheme 1.13).



Scheme 1.13 Synthesis (−)-lupinine (**6**) relying on an organocatalytic intramolecular *aza*-Michael reaction.

Oxidation of the aldehyde to the acid followed by esterification provided the intermediate **77**. A highly diastereoselective allylation of **77** provided **78** with both of the stereocenters in the target. Primary alcohol **79**, obtained from **78**, on activation and cyclization provided the quinolizidine **80**. Reduction of the ester in **80** provide (−)-lupinine (**6**) which has been converted to (−)-epiquinamide (**7**), via oxidation of the primary alcohol followed by Curtius rearrangement, by Fitch et al.[21] Hence, the above synthetic route constitutes a synthesis of (−)-lupinine (**6**) as well as a formal synthesis of (−)-epiquinamide (**7**).

All of the methodologies presented in the sections **1.1-1.5** and all of the reported methodologies in the literature deal with the synthesis of stereochemically related alkaloids *i.e.* tashiromine (**1**)/epilupinine (**5**) or epitashiromine (**2**)/lupinine (**6**). Strategies giving easy access to diastereomeric alkaloids (**1** and **6** or **2** and **5**) are very few, and they rely on one of two strategies: i) the separation of diastereomeric intermediates at an early stage in the synthesis, or ii) a thermodynamically favorable enolization of an intermediate to one of the alkaloids. In addition, the lack of cycloaddition strategies employing cyclic nitrones is surprising. It may be noted that a cycloaddition with cyclic nitrones can install the contiguous stereocenters as well as more than half of the required bicyclic framework of the target molecules (Figure 1.2) in a single step. Based on these considerations, our objective was to examine the utility of nitrone cycloaddition reactions with chiral alkenes as the pivotal step in the synthesis of **1**, **2**, **5** and **6**.

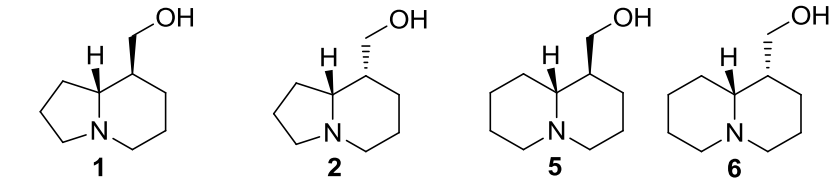
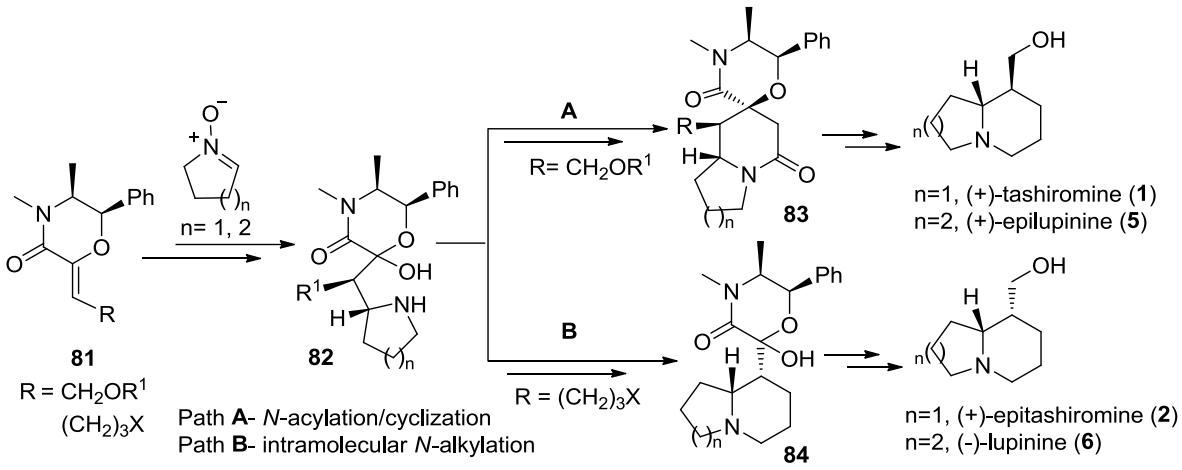


Figure 1.2 Synthetic targets in this thesis work.

We chose to examine these cycloaddition reactions with ephedrine-derived alkylidene morpholinones. Apart from cycloaddition reactions, our second objective was to develop a unique strategy that can give access to diastereomeric alkaloids without the need of separation of diastereomeric intermediates or enolization (Scheme 1.14). Details of these studies are provided in Chapter 2 of this thesis.



Scheme 1.14 Stereochemically flexible strategy for the synthesis of **1**, **2**, **5** and **6**.

1.6 Quaternary Stereocenters

The structural complexity of many natural products poses challenges to synthetic chemists, and is an impetus to develop new and efficient synthetic strategies.[22] The development of new synthetic methodologies has made many syntheses possible, which could not have been accomplished decades ago.[23] Many natural products contain one or more quaternary stereocenters, the synthesis of which have attracted the interest of many research groups. The enantioselective synthesis of quaternary stereocenters is a continuing challenge for synthetic chemists due to steric demands during the successive construction of new carbon-carbon bonds and the reliability of these carbon-carbon bond forming reactions.[24]

A variety of strategies for constructing quaternary stereocenters have appeared in the literature. These strategies can be generally divided into two major types: enantioselective and diastereoselective approaches.[25] The enantioselective C-C bond

formation from prochiral substrates is involved in reactions such as Diels-Alder reactions, catalytic asymmetric conjugate addition reactions, and alkylation reactions. Although the enantioselective synthesis of quaternary stereocenters has been investigated extensively, most of the strategies require specialized substrates and reactants. The diastereoselective approach is more attractive and widely applicable provided the preparation of enantiomerically enriched starting materials is easy. Examples of diastereoselective approaches include the Claisen rearrangement, auxiliary mediated alkylation and conjugate addition reactions.[25]

Of the various C-C bond-forming reactions, the reactions listed below[23,26] appear frequently in synthetic methodologies reported for the construction of quaternary stereocenters.

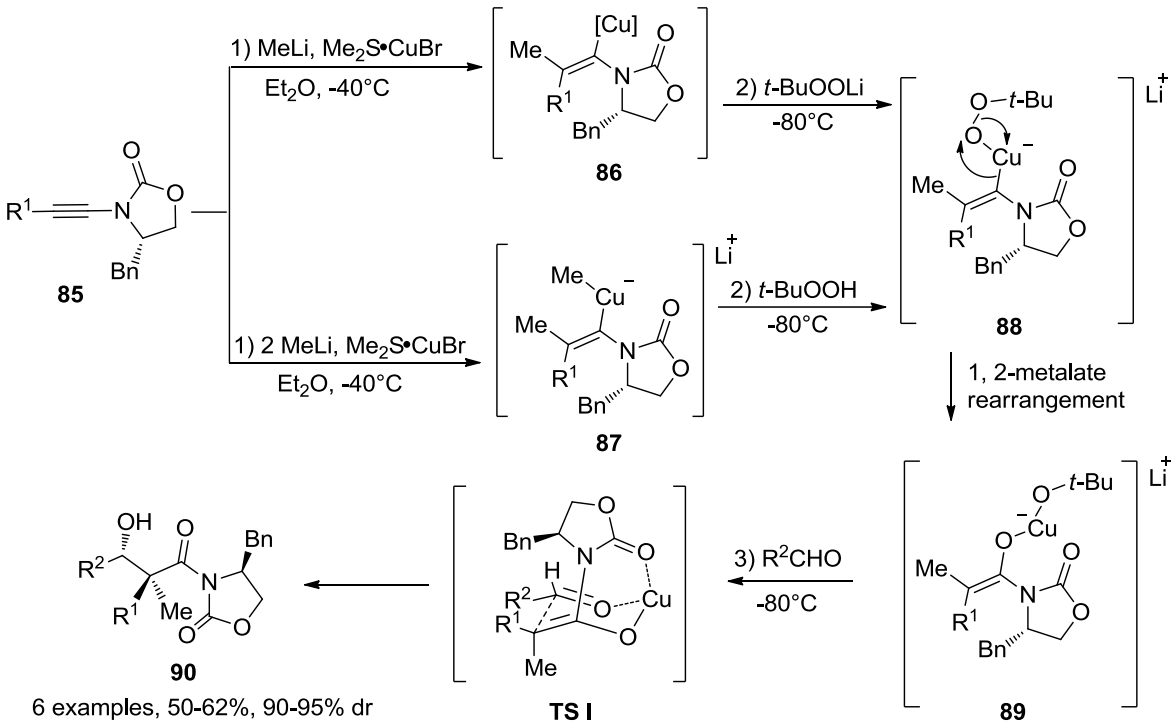
1) Aldol and Mannich reactions
2) Addition to chiral carbon electrophiles
3) Carbonyl α-alkylation reactions
4) Conjugate addition reactions
5) Cycloaddition reactions
6) Cyclopropanations
7) Metal catalyzed cyclizations
8) The Heck reaction

The key reaction in our approach to quaternary stereocenters is a Prins reaction which closely resembles an aldol reaction. Hence, the following literature review covers only the aldol-type approaches to quaternary stereocenters.

1.6.1 Aldol Reactions

Strategies that employ an aldol reaction for the synthesis of quaternary stereocenters are relatively few. In general, the aldol reactions suffer from low stereoselectivity and poor yields when a quaternary stereocenter is formed in the product. This is due to steric congestion in the aldol products with quaternary stereocenters which favours the retroaldol reaction under acidic or basic conditions.[27] In view of these limitations, modified aldol reactions have been devised. These methods allow the construction of quaternary stereocenters in good yield as well as good stereoselectivity. Nonetheless, it should be noted that due to the specialized nature of these reactions, most of them do not provide the classical aldol products which can be obtained by a conventional intermolecular aldol reaction of carbonyl substrates.

Marek and coworkers recently reported a strategy that gives access to acyclic systems with quaternary stereocenters. Their method uses enolates formed from ynamides such as **85** (Scheme 1.15). Conjugate addition of a cuprate to the ynamide **85** generates **86** or **87** which furnishes intermediate **88** on treatment with *t*-butyl hydroperoxide. 1,2-Metalate rearrangement of **88** furnishes the enolate **89**. Reaction of the enolate with an aldehyde provides the corresponding aldol product **90** with a quaternary stereocenter.[28] In a related process, reaction of **89** with an imine provides the corresponding Mannich product.

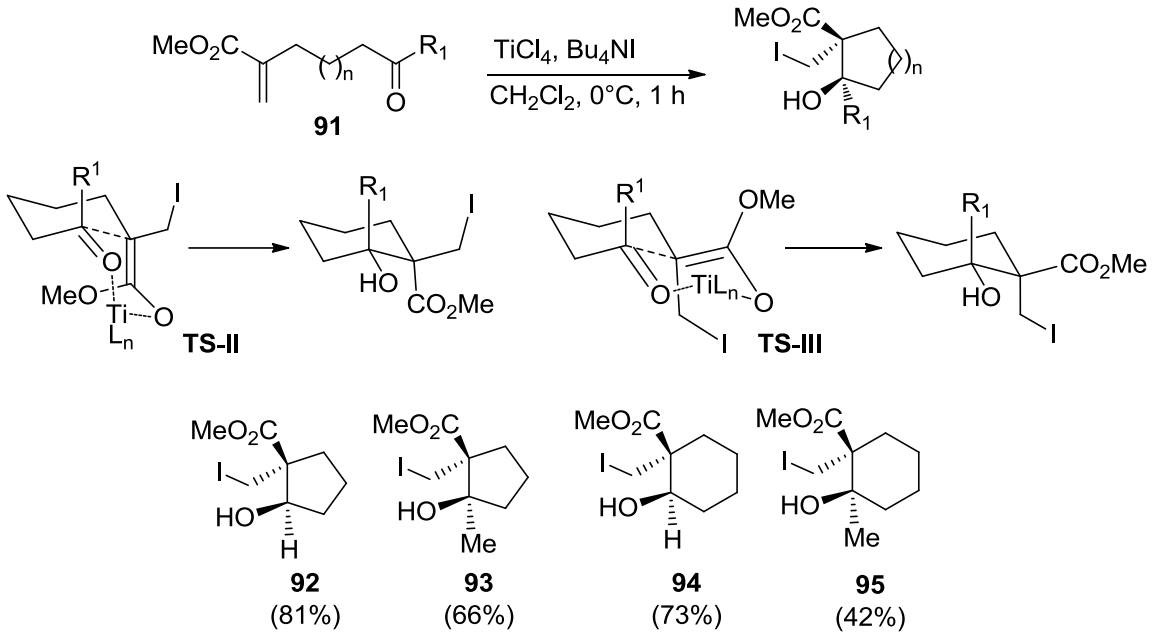


Scheme 1.15 Synthesis of quaternary stereocenters from ynamides.

The transition state assembly (**TS I**) involved in the formation of aldol adducts is shown in Scheme 1.15. The authors suggest that the oxazolidine moiety chelates with copper forming a 'second pseudo-heterocycle' and then the approach of the aldehyde from the *Re* face of the enolate (*anti* to the benzyl group in the oxazolidinone) and with the R^2 group of the aldehyde in a pseudo-equatorial position, leads to the observed diastereoselectivity.

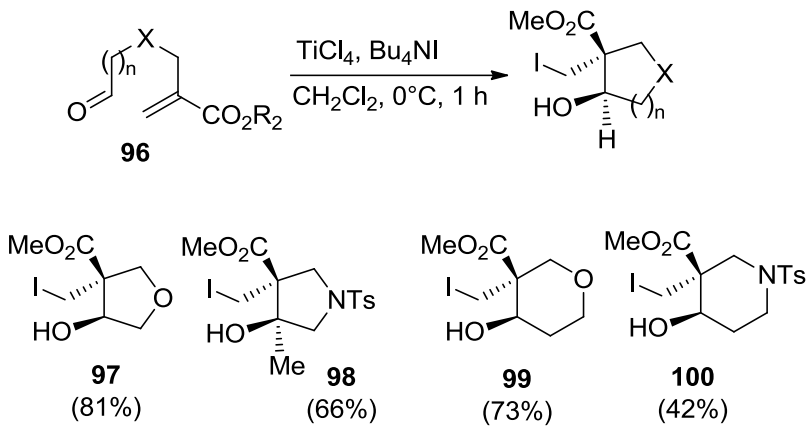
Greaney and coworkers[29] reported the synthesis of carbocycles and heterocycles with vicinal quaternary and tertiary stereocenters using an intramolecular iodo-aldol reaction. The iodo-aldol reaction is synthetically useful due to its excellent atom economy, and its generation of complex structures in a single step with the incorporation of up to three chiral centers. The strategy employed by Greaney utilizes α-substituted enolates for

the construction of cyclopentanes or cyclohexanes bearing a quaternary stereocenter. Accordingly, the substrate **91** furnished carbocycles **92-95** in good yields. Aldehydes were particularly good substrates in this reaction. In all of the reactions only a single diastereomer of the product was observed. This can be explained from the transition state models shown in Scheme 1.16.



Scheme 1.16 Synthesis of carbocycles with vicinal tertiary and quaternary stereocenters.

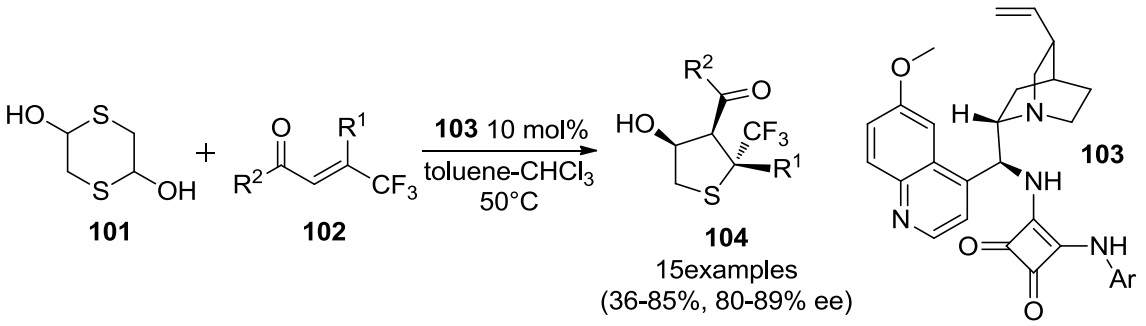
In **TS-II**, the bulky CH_2I group is placed in a pseudo-equatorial position, which is more favored than the pseudo-axial position in **TS-III**. Hence, **TS-II** leads to the products with the observed diastereoselectivity. The strategy was also employed in the synthesis of heterocycles (Scheme 1.17). The substrates for these reactions were prepared in two steps from ethyl or methyl α-bromomethylacrylates. The use of simple prochiral substrates and formation of heterocycles with functional groups for further conversion to complex natural products makes this strategy a versatile tool.



Scheme 1.17 Synthesis of heterocycles containing vicinal tertiary and quaternary stereocenters.

Xu and coworkers[30] reported cascade sulfa-Michael/aldol reactions of β-disubstituted enones to synthesize quaternary stereocenters bearing a trifluoromethyl substituent. The incorporation of a -CF_3 group into organic molecules remarkably alters their biological properties and such compounds have potential applications in agricultural and medicinal chemistry.[30] Thus, research activity has increased in the area of asymmetric synthesis of functionalized molecules with incorporation of a -CF_3 group. Xu and coworkers developed a strategy to trifluoromethylated tetrahydrothiophenes using a trifluoromethyl-activated enone as the starting material.

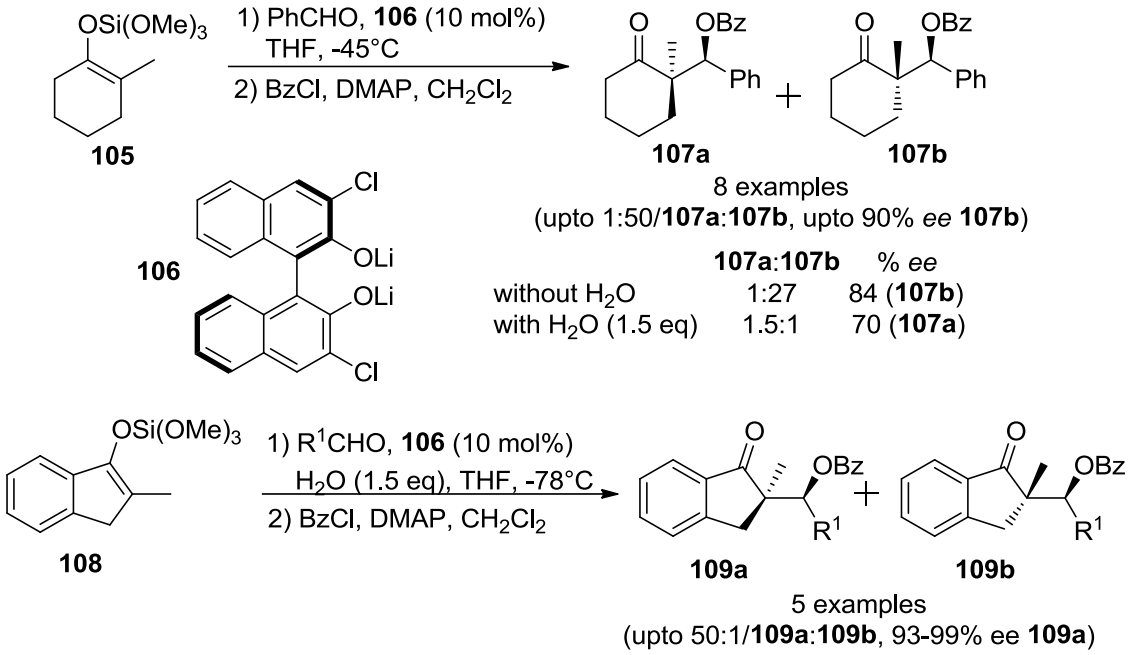
1,4-Dithiane-2,5-diol (**101**) reacted with different β-aryl-β-trifluoromethyl enones **102** to furnish tetrahydrothiophenes **104** in moderate to good yields and high enantioselectivity (up to 89% *ee*). The reaction proceeds smoothly in the presence of various bifunctional squaramides as catalysts with the quinine-derived squaramide catalyst **103** giving the best results (Scheme 1.18).



Scheme 1.18 Synthesis of quaternary stereocenters with trifluoromethyl substituent.

The reaction tolerates various aryl substituents, heteroatomic rings as well as sterically demanding naphthyl rings in the enone **102**. The substitution pattern on the aryl rings has no effect on enantioinduction, but has a small effect on the yield.[30]

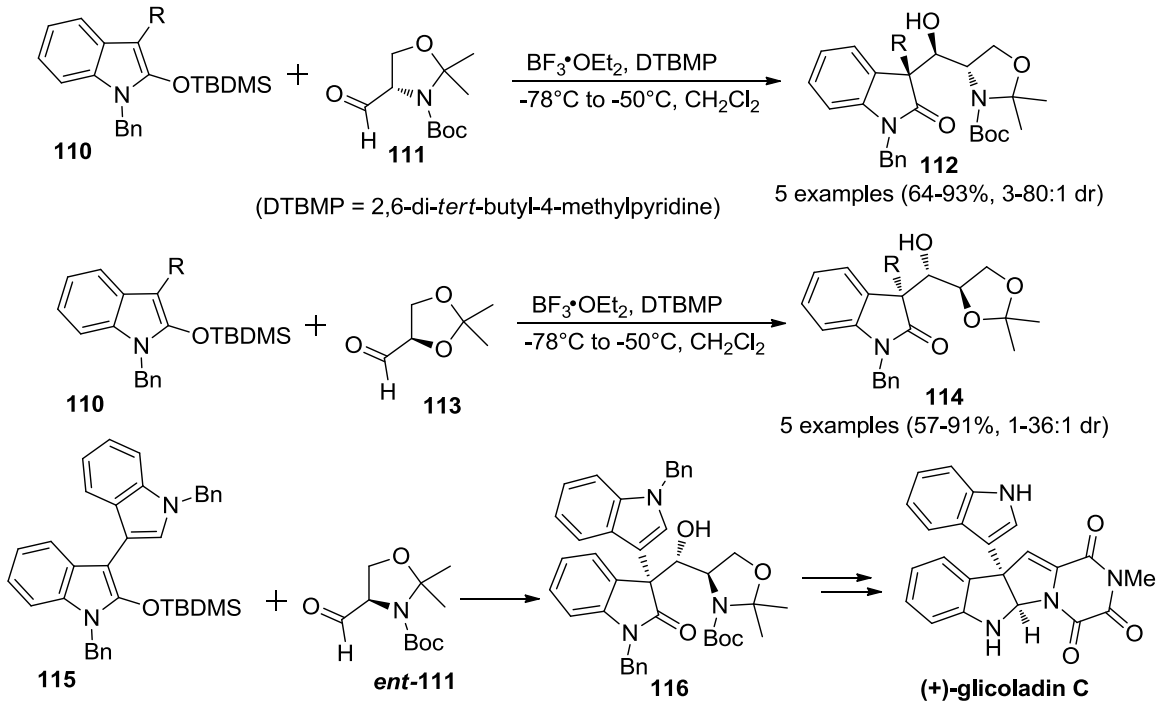
Enantioselective strategies using aldol reactions of trimethylsilyl enol ethers with aldehydes, i.e. the Mukaiyama aldol reaction, have attracted considerable attention in recent years. Many examples are reported for Lewis acid-catalyzed Mukaiyama aldol reactions.[31] Following a similar trend, Lewis base-catalyzed aldol reactions are also being investigated with considerable success. Nakajima and coworkers reported aldol reactions of trichlorosilyl enol ethers catalyzed by chiral *N*-oxides[32] and phosphine oxides[33] for the synthesis of quaternary, as well as tertiary stereocenters. However, trichlorosilyl enol ethers are extremely sensitive to moisture, which limits the application of this methodology. Recently, Nakajima and coworkers reported lithium binaphtholate catalyzed aldol reactions of trimethoxysilyl enol ethers with aldehydes (Scheme 1.19).[27]



Scheme 1.19 Mukaiyama aldol reaction for the synthesis of quaternary stereocenters.

The trimethoxysilyl enol ether derived from 2-methylcyclohexanone (**105**) furnished *anti* **107b** as the major aldol product under anhydrous conditions while a slight excess of the *syn* aldol product **107a** was obtained in the presence of water. Nakajima also reported an improved synthesis for the trimethoxysilyl enol ethers. The substrate **108** furnished *syn* aldol products in good yields and excellent stereoselectivity.

Overman et al.[34] reported the synthesis of 3,3-disubstituted oxindoles by employing a Mukaiyama aldol reaction of 3-substituted 2-siloxyindoles with enantiopure aldehydes (Scheme 1.20). The 3-substituted 2-siloxyindoles **110** (prepared from corresponding isatin in three steps) furnished the aldol product **112**, with Garner's aldehyde, in good to excellent yields with high diastereoselectivity.

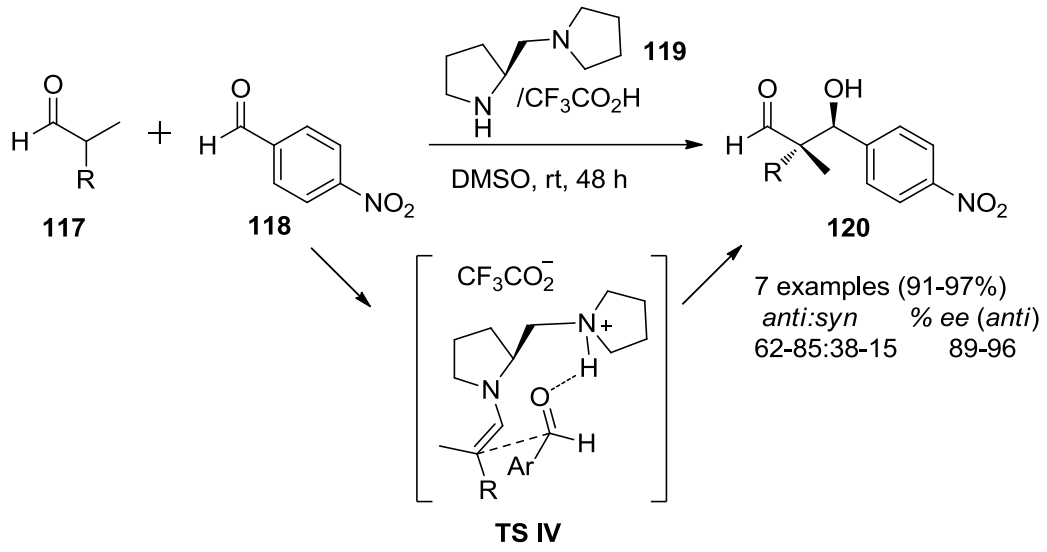


Scheme 1.20 Mukaiyama aldol reaction of 3-alkyl 2-siloxyindoles.

In a related reaction, the substrate **110** furnished the aldol adduct **114**, with (*R*)-glyceraldehyde acetonide **113**, in good yield and high diastereoselectivity. In both of these reactions, the stereoselectivity of product formation was very high when the substituent at C3 in the indole was an electron-rich aryl substituent. Later, Overman and Shin reported the synthesis of (+)-glicoaladin C employing the Mukaiyama aldol reaction of **115** and *ent*-**111** to set the quaternary stereocenter in the target alkaloid (Scheme 1.20).[35]

The synthesis of quaternary stereocenters using organocatalytic aldol reactions employing *S*-proline derived enamines has received limited attention. Tanaka, Barbas III and Mase[36] reported a direct aldol reaction catalyzed by a diamine salt for the synthesis of quaternary stereocenters. Various combinations of chiral amines and Lewis, Brønsted and organic acids were screened. The use of carboxylic acids as additives favored the formation

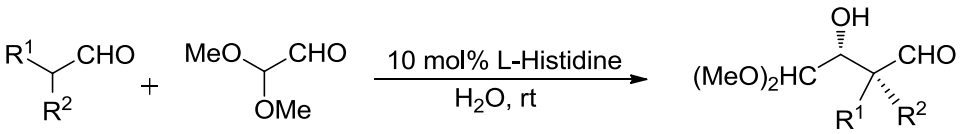
of the key enamine intermediate. The catalysts were screened using a high-throughput fluorescence-based screening.



Scheme 1.21 Organocatalytic aldol reaction using bifunctional chiral amine/acid catalyst.

Following the optimized reaction conditions, α, α-dialkyl aldehydes **117** furnished the aldol products **120** with a quaternary stereocenter at the α-carbon atom in high yields and enantioselectivities (Scheme 1.21). The stereochemistry of aldol adducts was assigned *S* by the Mosher ester derivation method.[37] Thus, the enamine attacks the *Re*-face of the aldehyde as shown in the proposed transition state **TS IV** by Tanaka et al. A limitation of this methodology is the need for a non-enolizable aldehyde as one of the reactants. To address this limitation of the organocatalytic aldol reactions, Mahrwald and coworkers reported a cross-aldol reaction using 2,2-dimethoxyacetaldehyde (**121**, an enolizable aldehyde) as the electrophile in the aldol reaction.[38] The use of L-histidine as the catalyst furnished aldol adducts **122** with high stereoselectivities (Scheme 1.22). The aldol adducts obtained using this strategy are not accessible by other organocatalytic approaches. This

methodology gives an easy access to poly-functionalized intermediates as well as branched-chain carbohydrates.



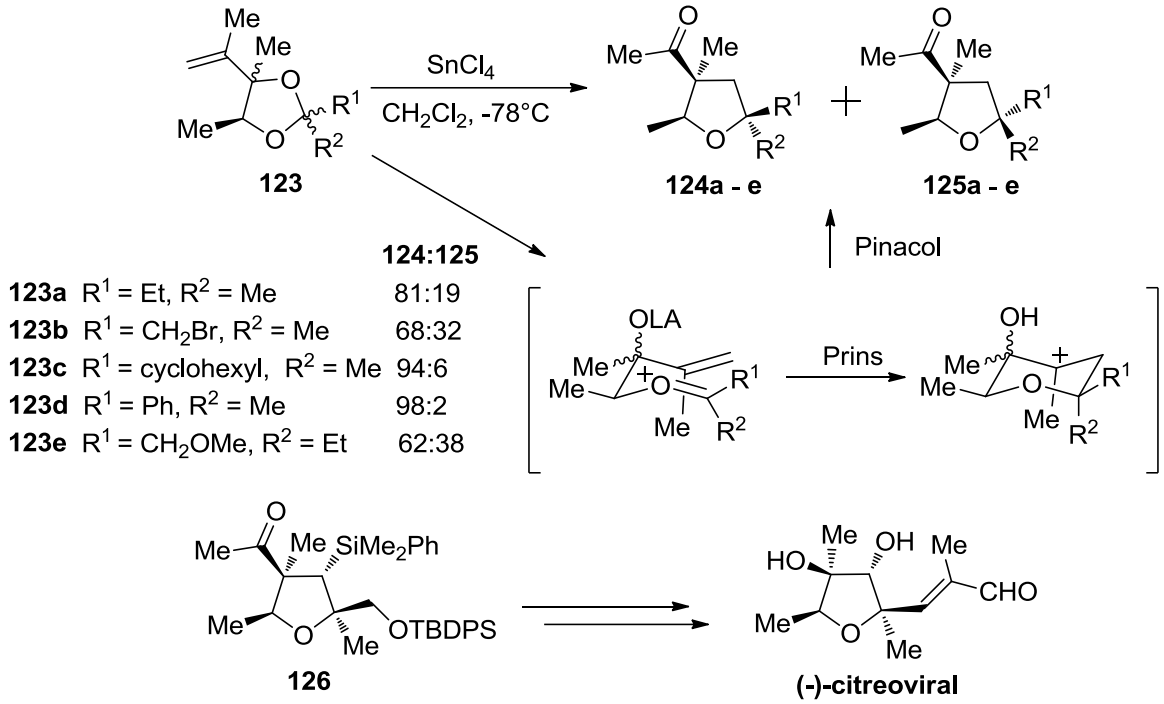
120a - b **121**

	R^1	R^2	Yield(%)	% *de*	% *ee*
122a	Me	Et	78	50	90
122b	Me	Ph	89	57	41

Scheme 1.22 Asymmetric aldol addition of dimethoxyacetaldehyde to enolizable aldehydes.

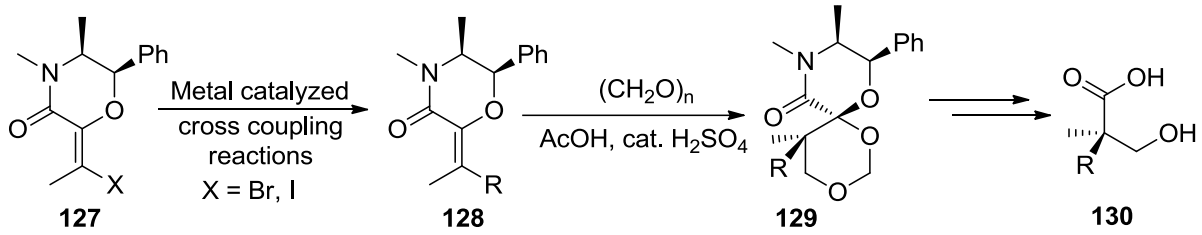
Mahrwald and coworkers employed their methodology in the syntheses of (*R*)-pantolactone, 2-hydroxymethyl-*D*-lyxose and 5-deoxy-2-methyl-*L*-lyxose.

Overman and coworkers[39] reported a Prins-pinacol methodology for the stereoselective synthesis of acetyltetrahydrofurans bearing a quaternary stereocenter. The acetals of unsymmetrical ketones with 3,4-dimethyl-4-penten-2,3-diol were used as substrates in this method. The acetals **123a-e** rearranged respectively to acyltetrahydrofurans **124a-e**, with a quaternary stereocenter at C2, in the presence of $SnCl_4$ with good stereoselectivity (Scheme 1.23). The stereoselectivity of the reaction was controlled by the size of the R^1 group in the methyl ketone series **124a - d**. The observed stereoselectivity was in accordance with the proposed transition state models. Thus, the substituent R^1 prefers a pseudo-equitorial position in the Prins cyclization step, leading to the formation of the observed products. The methodology was applied in the synthesis of (−)-citreoviral from the intermediate **126** prepared by a Prins-pinacol rearrangement.[39]



Scheme 1.23 Prins-pinacol rearrangement of acetals of unsymmetrical ketones.

The Pansare group approach to quaternary stereocenters is based upon two pivotal reactions of haloalkylidene morpholinones **127** (Scheme 1.24).



Scheme 1.24 Synthetic strategy for the synthesis of functionalized quaternary stereocenters.

These reactions are: i) synthesis of diastereomerically pure, unsymmetrical alkylidene morpholinones **128** employing a cross-coupling reaction, and ii) an asymmetric Prins reaction of the alkylidene morpholinone. The second reaction is the key C-C bond

forming reaction which installs the fourth carbon atom to form the quaternary stereocenter in **129**. Details of this methodology are provided in Chapter 3 of this thesis.

1.7 References

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Chapter 2

Synthesis of (+)-Epitashiromine and (+)-Epilupinine

2.1 Introduction

The indolizidine and quinolizidine alkaloids constitute a prominent group of alkaloids containing nitrogen-bridged bicyclic ring systems.[1] These alkaloids are isolated from natural sources including various animals and plants,[1a] and are known for their notable biological activities such as antiviral,[2] antiarrythmic,[3] antimalarial,[4] and platelet antiaggregating activities.[5] In particular, (−)-epilupinine is known for its *in vitro* inhibitory activity against P-388 (LD_{50} = 28 μg/mL) and L1210 (LD_{50} = 20 μg/mL) cell lines.[6] In addition, it is also used as an intermediate in drug discovery where molecules containing the epilupinyl unit can be used as ligands for 5-HT_3, 5-HT_4 or Sigma receptors.[7] The indolizidine alkaloids are also known for their insecticidal, fungicidal and antibacterial acitivities.[8] In addition to these biological properties, these alkaloids also serve as potential targets for validation of synthetic methodologies which adds to their synthetic importance.[8b]

The objective of this investigation was the development of a synthetic route to the diastereomeric indolizidine alkaloids (+)-tashiromine (**1**) and (+)-epitashiromine (**2**) and the structurally related, diastereomeric quinolidine alkaloids (+)-epilupinine (**3**) and (−)-lupinine (**4**, Figure. 2.1).

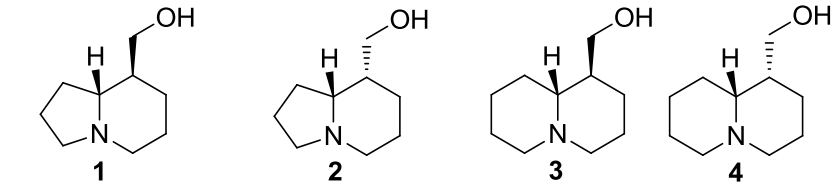


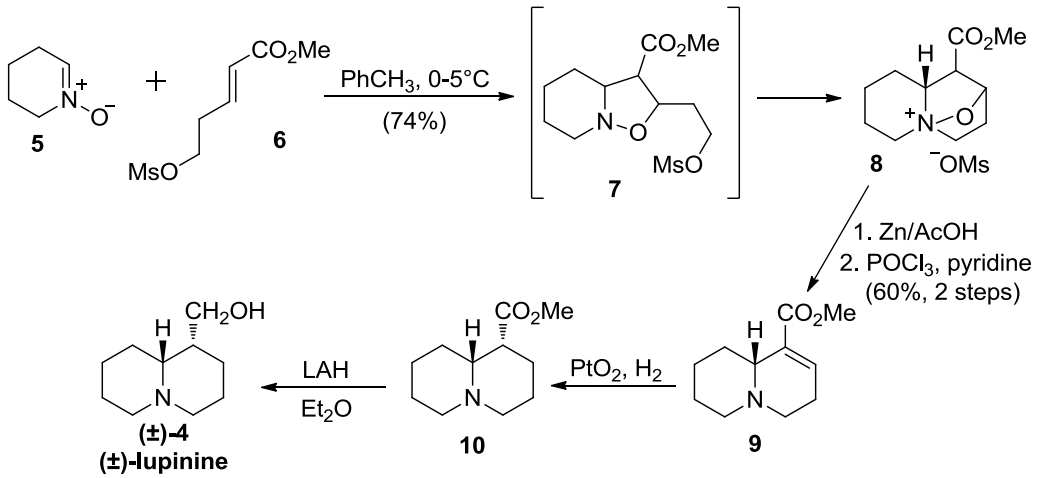
Figure 2.1 Diastereomeric pairs of indolizidine and quinolizidine alkaloids.

The strategy employed for the synthesis of **1**-**4** is based on an asymmetric nitrone/alkene 1,3-dipolar cycloaddition reaction. Interestingly, there are no methodologies reported for the synthesis of alkaloids **1** and **2** using 1,3-dipolar cycloaddition reactions of nitrones. Hence, only the strategies employed by others that resulted in the synthesis of the target alkaloids **3** and/or **4** are presented. Notably none of these methods are enantioselective.

2.2 Nitrone/Alkene 1,3-Dipolar Cycloaddition for the Synthesis of 3 and 4

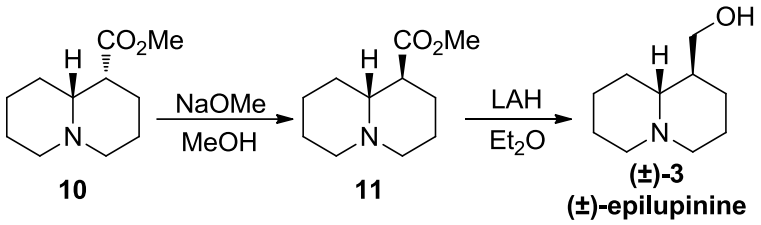
2.2.1 Tufariello's Synthesis of (±)-Epilupinine and (±)-Lupinine

Tufariello and Tegeler reported a synthesis of (±)-epilupinine (**3**) and (±)-lupinine (**4**) using a piperidine-derived cyclic nitrone **5**.[9] Their synthesis begins with a cycloaddition reaction between the nitrone **5** and (*E*)-methyl-5-((methylsulfonyl)oxy)pent-2-enoate (**6**, Scheme 2.1). The cycloaddition reaction afforded the adduct **7** which spontaneously cyclized to provide the salt **8** in good yield.



Scheme 2.1

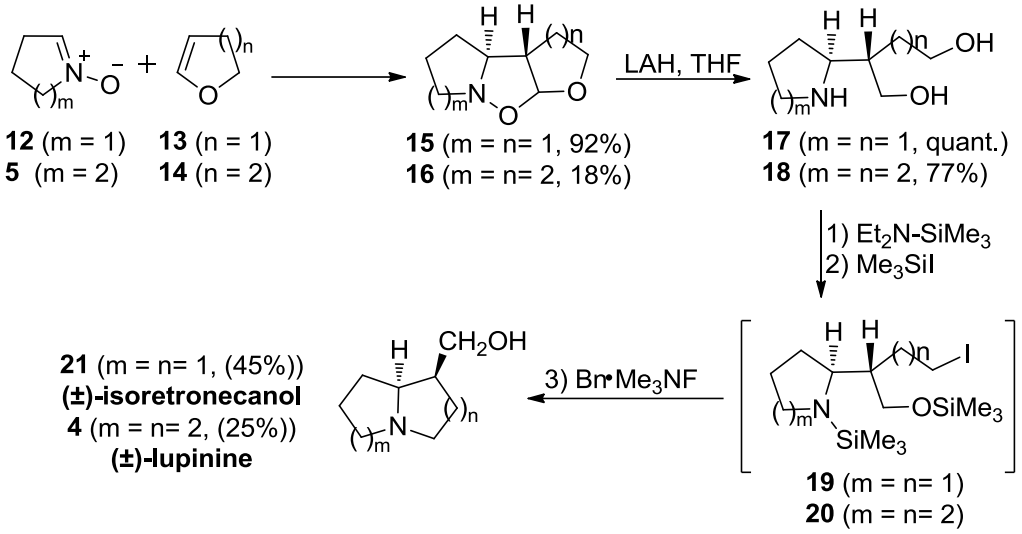
The mesylate salt **8** was reduced to the corresponding *β*-hydroxy ester which, on dehydration with $POCl_3$, furnished the *α*,*β*-unsaturated ester **9**. Catalytic hydrogenation of **9** furnished (±)-methyl lupinate **10**. Further reduction of **10** with lithium aluminum hydride provided (±)-lupinine (**4**, Scheme 2.1). (±)-Epilupinine (**3**) was obtained by reduction of methyl epilupinate **11** which was obtained by epimerisation of (±)-methyl lupinate **10** using sodium methoxide in methanol (Scheme 2.2).



Scheme 2.2

2.2.2 Kakisawa's Synthesis of (±)-Isoretronecanol and (±)-Lupinine

Kakisawa and co-workers employed a nitrone cycloaddition reaction for the syntheses of (±)-lupinine (**4**) and (±)-isoretroneacanol (**21**, Scheme 2.3).[10]



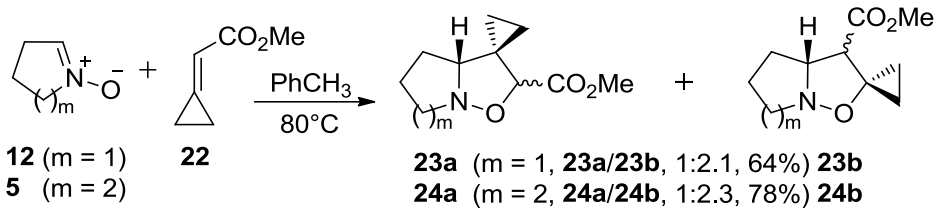
Scheme 2.3

The cycloaddition reaction of dihydrofuran **13** with nitrone **12** furnished the adduct **15** in good yield as a mixture of diastereomers (*exo*:*endo* 31:1). In a related sequence of reactions, dihydropyran **14** furnished the adduct **16** on reaction with nitrone **5**. Reduction of cycloadducts **15** and **16** with lithium aluminium hydride furnished the amino diols **17** and **18** respectively. These were silylated using *N*,*N*-diethyl-1,1,1-trimethylsilanamine and the resulting silyl ethers were then converted to primary iodides **19** and **20**. The selective formation of iodides **19** and **20** is due to reaction of the iodide at the sterically less-hindered carbon. Treatment of crude **19** or **20** with benzyltrimethylammonium fluoride furnished the alkaloids (±)-isoretronecanol (**21**) and (±)-lupinine (**4**, Scheme 2.3), respectively.

2.2.3 Brandi's Formal Syntheses of (±)-Epilupinine and (±)-Lupinine

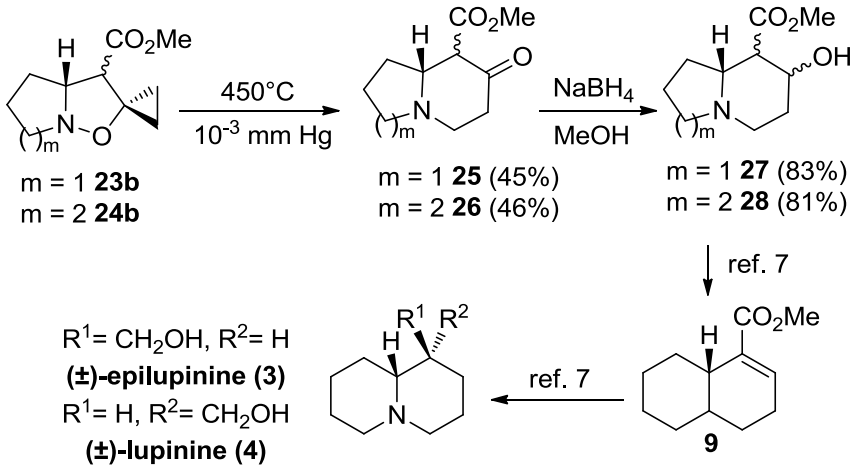
Brandi and co-workers reported a methodology employing the cycloaddition of cyclic nitrones **12** and **5**, with methylenecyclopropane **22**.[11] Nitrone cycloaddition provided the regioisomeric isoxazolidines **23a**/**23b** and **24a**/**24b** (Scheme 2.4), each as a mixture of

diastereomers (**23a**/**23b,** 1:2.1 and **24a**/**24b**, 1:2.3). The regioisomeric adducts were separated and **23b** and **24b** were carried further.



Scheme 2.4

Adducts **23b** and **24b** rearranged to compounds **25** and **26** under flash vacuum pyrolysis conditions (Scheme 2.5). Reduction of the ketone with sodium borohydride provided the corresponding *β*-hydroxy esters **27** and **28**. The ester **28** has been converted to the alkaloids (±)-epilupinine (**3**) and (±)-lupinine (**4**) by Tufariello and co-workers as shown in Schemes 2.1 and 2.2.[9]

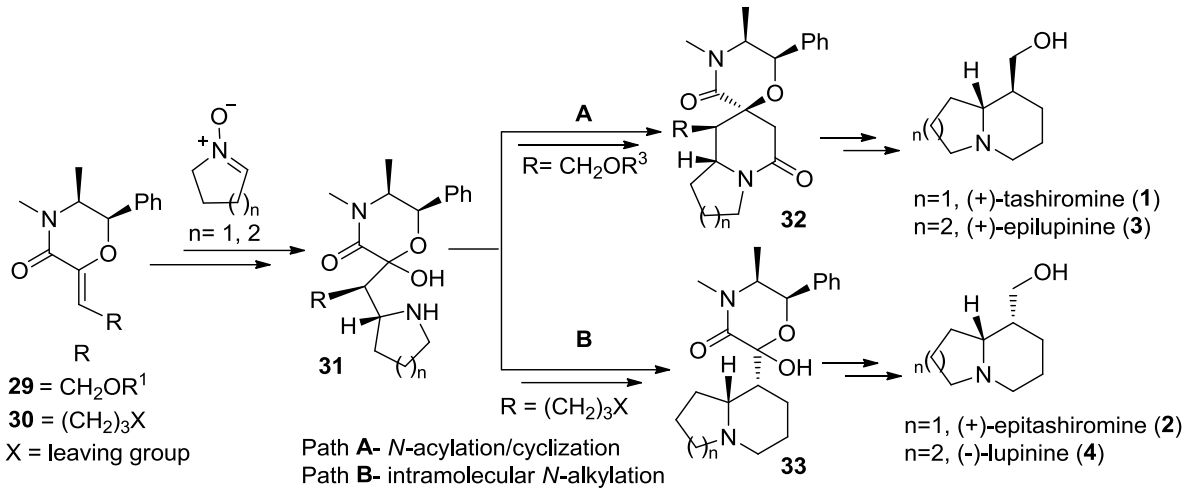


Scheme 2.5

2.3 Objectives

The synthetic strategies presented in Chapter 1 and Section 2.2 highlight the early synthetic interest in the indolizidine and quinolizidine alkaloids. As is evident, most of the reported studies towards **1**-**4** have addressed the synthesis of stereochemically-related targets; namely **1** and **3** or **2** and **4**. This is an inherent limitation, since the structural variety of indolizidine and quinolizidine alkaloids derives not only from differences in substitution on the rings but also from the stereochemistry of the stereogenic carbons. For the synthesis of diastereomeric alkaloids, namely **1** and **2** or **3** and **4**, the reported methods rely on one of one of two strategies: 1) a thermodynamically favorable isomerization of enolizable intermediates[12] or 2) separation of stereoisomeric intermediates at an early stage in the synthesis.[8,13] Syntheses that provide access to diastereomeric alkaloids without employing these two strategies are rare.[14] The synthetic strategy described in this Chapter addresses this limitation.[15]

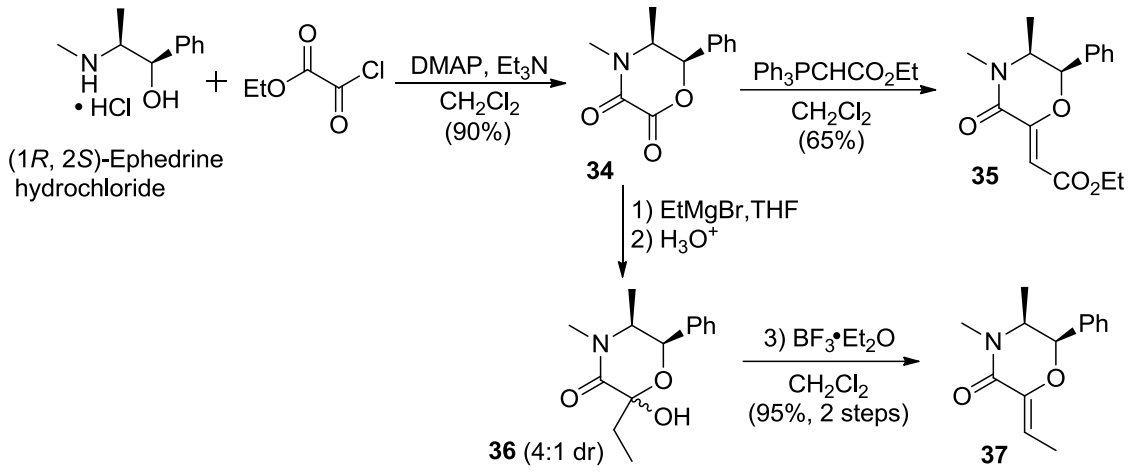
The approach described in this thesis relies on stereoselective, 1,3-dipolar cycloaddition reactions of cyclic nitrones with chiral alkylidene morpholinones to install contiguous stereocenters in the targets (Scheme 2.6). The cycloadducts obtained were converted to the corresponding alkaloids by following two different modes of ring construction (Path **A** or **B**, Scheme 2.6). A change in the mode of cyclization gives easy access to diastereomeric alkaloids without the need for diastereomeric cycloadducts. Thus, even though only one set of contiguous stereocenters is constructed, the approach ultimately provides access to either diastereomer of the targets.[15]



Scheme 2.6 Synthetic strategy employed in this Chapter.

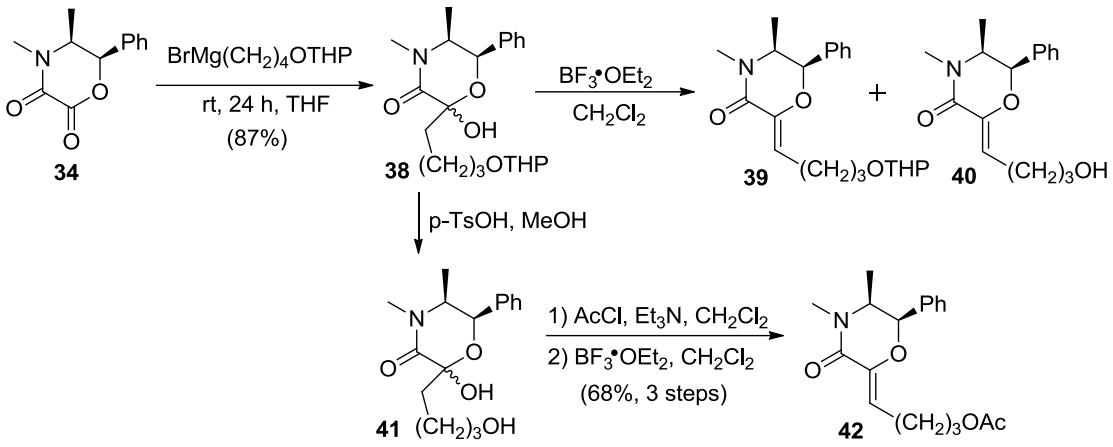
2.4 Results and Discussion

The study began with the synthesis of chiral alkylidene morpholinones which were obtained from the ephedrine-derived morpholine dione **34**[16] (Scheme 2.7). Dione **34** was readily prepared from (1*R*,2*S*)-ephedrine hydrochloride and ethyl-2-chloro-2-oxoacetate. Reaction of dione **34** with carbethoxymethylenetriphenylphosphorane provided alkene **35**.[16c] The alkene **37** was obtained by dehydration of hemiacetal **36** (dr = 4:1) obtained from a reaction of dione **34** with ethylmagnesium bromide.[17]



Scheme 2.7 Synthesis of alkylidene morpholinones.

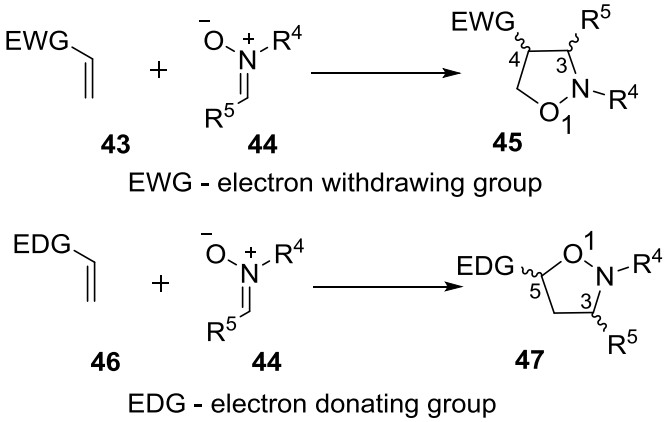
In a related sequence of reactions, dione **34** was converted to the alkylidene morpholinone **42** (Scheme 2.8). Treatment of **34** with the Grignard reagent obtained from the THP-protected 4-bromobutanol furnished hemiacetal **38** as a mixture of diastereomers (4:1) in good yield. However, dehydration of hemiacetal **38** suffered from competitive cleavage of the tetrahydropyranyl ether in **38**, to generate the alcohol **40**. In addition, column chromatography was not effective for separation of dihydropyran-derived impurities from the desired product **39**. Hence a change of the hydroxyl protecting group was necessary. Accordingly, replacement of the THP protection by an acetate group and dehydration of the hemiacetal provided the alkylidene morpholinone **42** (Scheme 2.8).



Scheme 2.8 Synthesis of alkylidene morpholinone **42**.

The alkylidene morpholinones **35**, **37** and **42** were assigned the *Z* stereochemistry by analogy to other alkylidene morpholinones prepared in the Pansare group.[18]

The 1,3-dipolar cycloaddition reactions of alkenes **35** and **37** were then examined. It should be noted here that the cycloaddition of a nitrone and an alkene can proceed with the formation of regioisomeric products, the regiochemistry of the nitrone addition being dependent on the nature of the alkene (Scheme 2.9).

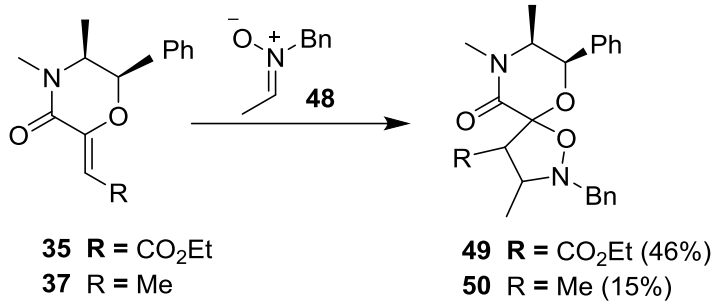


Scheme 2.9. Regiochemistry of 1, 3-dipolar cycloaddition of nitrones to alkenes.

For electron-deficient alkenes such as **43**, the nitrone oxygen adds to the β-carbon of the dipolarophile giving a 3,4-substituted isoxazolidine **45** as the major product (Scheme 2.9). For electron-rich alkenes such as **46**, the nitrone oxygen adds to the α-carbon of the dipolarophile giving a 3,5-substituted isoxazolidine **47** as the major product. The formation of a particular regioisomeric isoxazolidine may or may not be favoured over the other, and results may vary depending on individual alkenes. For example, the cycloaddition reactions summarized in Sections 2.2.1 and 2.2.2 proceed with formation of only one regioisomer (Scheme 2.1 and 2.3). However, the cycloaddition reaction reported by Brandi and co-workers provided both regioisomers of the product isoxazolidine (Scheme 2.4).

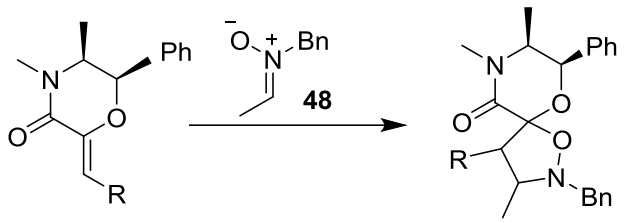
For the alkylidene morpholinones examined in this study, it was predicted that cycloaddition of nitrones with alkenes **35** and **37** would give cycloadducts **49** and **50** (Scheme 2.10). This outcome was based on the observation that, although alkenes **35**, **37** and **42** could be considered to be enamides, the reactivity of these alkenes resembles those of enol ethers rather than enamides. For example, alkylidene morpholinones related to **35**, **37** and **42** can be epoxidized with *m*-CPBA[17] and can also undergo Prins reactions.[16a] As anticipated, the cycloaddition of alkenes **35** and **37** with nitrone **48**[19] furnished the spiroisoxazolidines **49** and **50** (Scheme 2.10). Based on a characteristic resonance at ~100 ppm for the spiroacetal carbon in the spiroisoxazolidines, and the predicted reactivity of alkylidene morpholinones **35** and **37**, the regiochemistry of the nitrone cycloaddition was assigned as shown. The regioisomeric cycloadducts would have a spiro carbon which is expected to appear at ~75-80 ppm (as seen for compounds **74**, **76** and **85**). Attempts to assign the stereochemistry and diastereomeric excess of the spiroisoxazolidines **49** and **50**

by ^{1}H NMR spectroscopy were not successful. This was due to line brodening in the ^{1}H NMR spectra of spiroisoxazolidines **49** and **50** due to pyramidal inversion at the nitrogen.[20]



Scheme 2.10 1, 3-Dipolar cycloaddition reactions of alkenes **12** and **14** with the acyclic nitrone **48**.

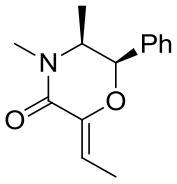
Given the low yields of spiroisoxazolidines **49** and **50**, we decided to optimize the conditions for the cycloaddition reaction and explore the use of different catalysts in order to improve the yield.[21] It may be noted that, since the alkenes **35** and **37** behave like enol ethers, the electron-deficient component in the 1,3-dipolar cycloaddition is most likely the nitrone. The Lewis acid could, in principle, coordinate with the alkylidene morpholinone or the nitrone. If it coordinates with the nitrone, an increase in the electrophilicity of the nitrone is expected. However, the use of Lewis acids known to catalyze nitrone cycloadditions[21a] had no beneficial effect on the reaction of nitrone **48** with alkenes **35** or **37**. In fact, the use of $Ti(O^iPr)_4$ in toluene at 60 °C had a detrimental effect on the thermal reaction and only unreacted **37** was recovered. This may indicate deactivation of the alkene in the presence of $Ti(O^iPr)_4$. These results with the use of different catalysts and conditions are summarized in Table 2.1.



35 **R =** CO_2Et
37 R **=** Me

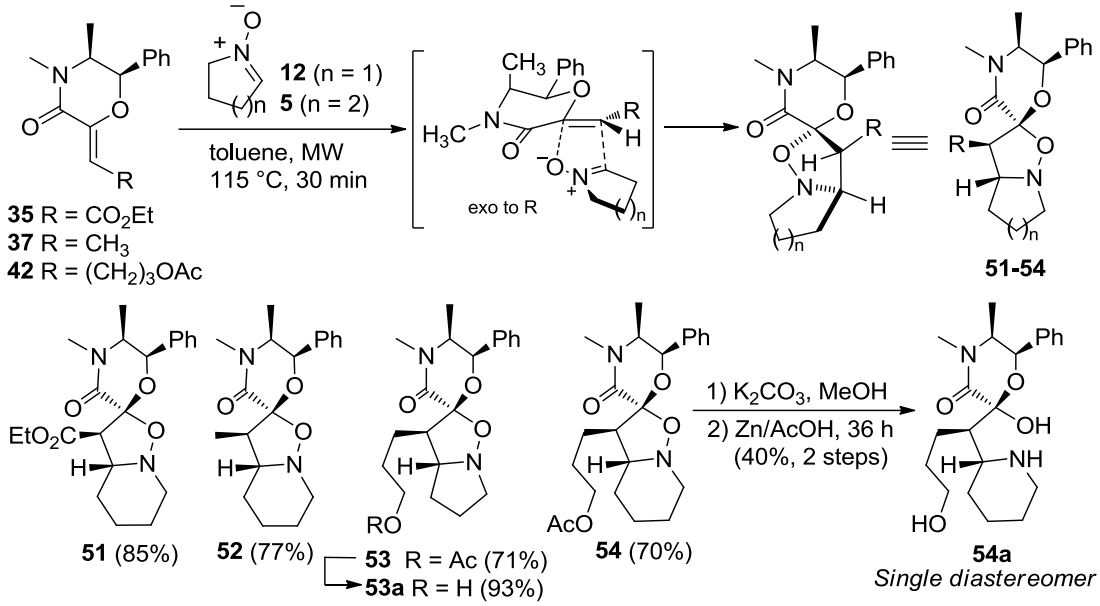
49 **R =** CO_2Et
50 R **=** Me

Table 2.1 Survey of catalysts and different reaction conditions for the 1, 3-dipolar cycloaddition reaction of nitrone **48**.

Substrates	Catalyst	Time	Solvent	Result
35	none[a]	24 h	toluene	**49** (46%)
	$ZnCl_2$[b]	5 d	CH_2Cl_2	**35** recovered
	microwave[a]	30 min	toluene	**49** (40%)
 **37**	none[a]	24 h	toluene	**50** (15%)
	$ZnCl_2$[b]	5 d	CH_2Cl_2	**37** recovered
	$Sc(OTf)_3$[b]	5 d	CH_2Cl_2	**37** recovered
	$In(OTf)_3$[b]	5 d	CH_2Cl_2	**37** recovered
	$Ti(O^iPr)_4$[c]	24 h	toluene	**37** recovered
	$MgBr_2.OEt_2$[b]	5 d	CH_2Cl_2	**37** recovered
	microwave[a]	30 min	toluene	**50** (20%)

[a] reflux. [b] room temperature. [c] toluene, 60 °C.

A few reports on nitrone cycloaddition reactions suggest the use of microwave irradiation to increase the reaction rate.[21b,22] For the reactions of **35** and **37**, the use of microwave irradiation reduced the reaction time to 30 minutes with a marginal effect on the yields. Hence, we decided to use these conditions for the reactions of **35**, **37** and **42** with the cyclic nitrones **12** and **5**. Nitrones **12** and **5** were prepared by the oxidation of pyrrolidine and piperidine respectively, according to the reported procedure.[23]

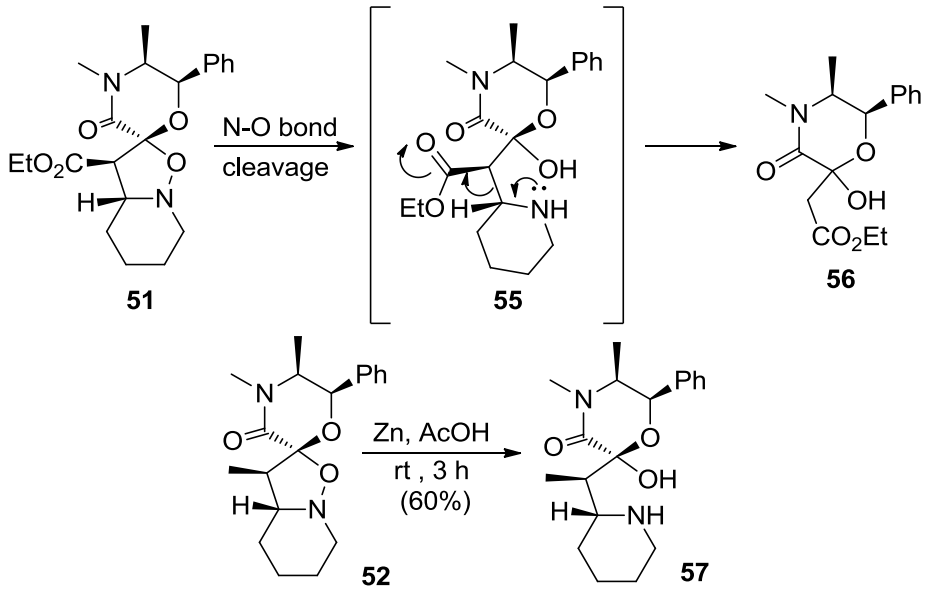


Scheme 2.11 1, 3-Dipolar cycloaddition reactions of alkene **35**, **37** and **42** with cyclic nitrones **12** and **5**.

Thus, following the optimized reaction conditions, alkenes **35**, **37** and **42** furnished spiroisoxazolidines **51** – **54** (Scheme 2.11) with nitrones **12** and **5**. The tentative stereochemical assignments for the spiroisoxazolidines **51** – **54** were based on two assumptions: 1) approach of the nitrone *exo* to the alkene substituent ('R' as shown in Scheme 2.11) to minimize steric interactions, and 2) reaction of the alkene from the face opposite to the methyl and phenyl groups in the morpholinone. The facial selectivity of the alkene is based on other transformations of the ephedrine-derived morpholinone system which have indicated a strong preference for reactions from the less-hindered face of the morpholinone.[17-18] As seen previously for the spiroisoxazolidines **49** and **50**, attempts to determine the diastereomeric excess for spiroisoxazolidines **51** – **54** were unsuccessful due to line brodening of ^{1}H NMR spectra. However, the diastereomeric excess of **53** and **54** was readily determined by conversion of **53** to **53a** by deacetylation (Scheme 2.11), and of

54 to **54a** by deacetylation and reduction (Scheme 2.11), since these derivatives did not show line broadening in their ^{1}H NMR spectra.

The next step in the sequence was N-O bond cleavage in the spiroisoxazolidines to the obtain the corresponding amino alcohols. Curiously, spiroisoxazolidine **51** did not furnish the amino alcohol **55** under various N-O bond cleavage conditions (Table 2.2). Instead, in most of these reactions, only the formation of compound **56** (Scheme 2.12) was observed by ^{1}H NMR analysis of the crude product. Although the precise reasons for the formation of **56** are unclear, it seemed possible that the electron-withdrawing ester group in **28** favored a cleavage of the C-N bond resulting in loss of the piperidine ring (Scheme 2.12). Some evidence for this hypothesis was provided by the formation of **57** from **52** in which the ester is replaced by a methyl group (Scheme 2.12).

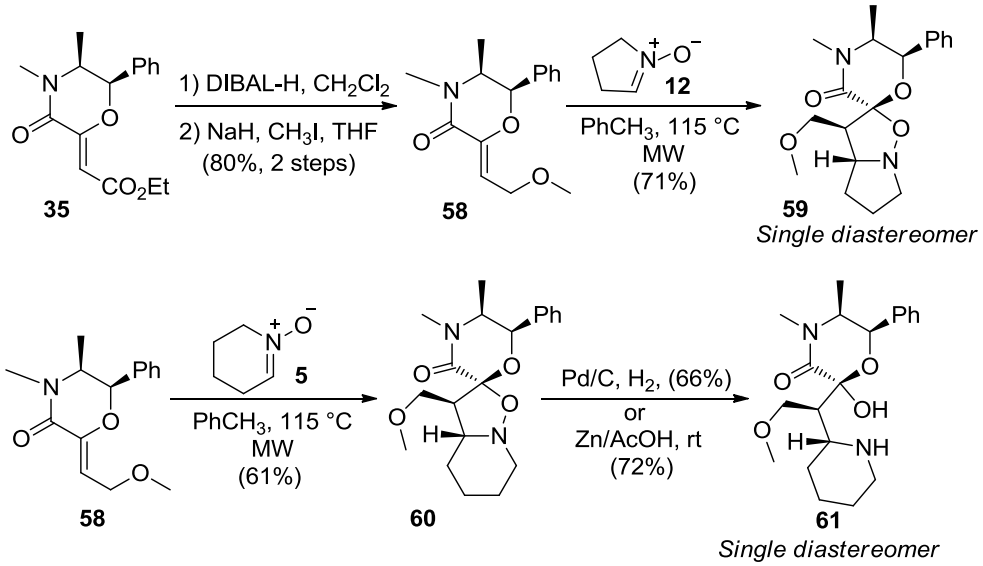


Scheme 2.12 N-O Bond cleavage studies.

Table 2.2 N-O Bond cleavage studies of spiroisoxazolidine **51**.

Reagent	Conditions	Result
Indium powder	reflux, 15 h, THF	**51** recovered
Zn/AcOH	80 °C, 2 h	**56** major
Pd/C, H_2	rt, 15 h, EtOH	**56** major
Raney Ni, H_2	rt, 15 h, EtOH	**51** recovered
$Pd(OH)_2/C$, H_2	rt, 15 h, EtOH	**56** major
SmI_2	-40 °C, 9 h, THF	complex mixture

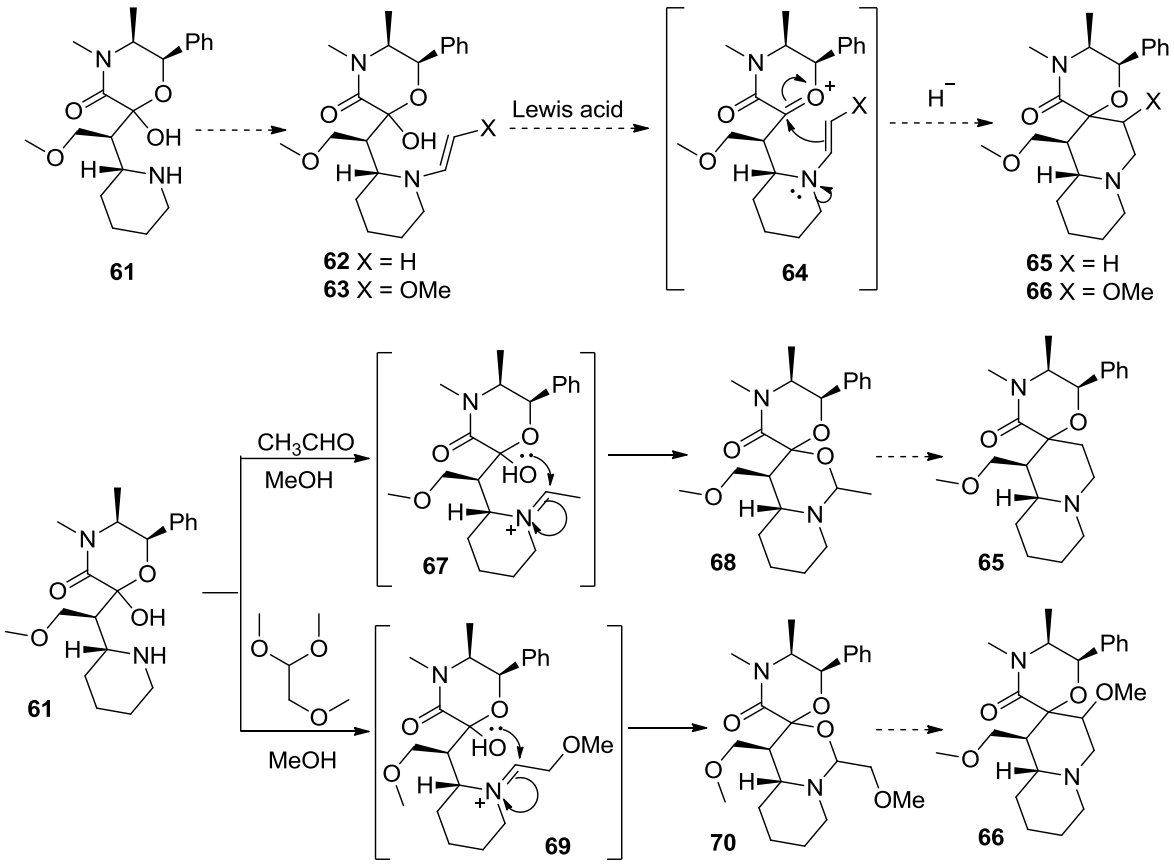
As a result of these observations, the ester group in **35** was reduced to a primary alcohol which, upon methylation, provided the methyl ether **58**. The alkene **58** provided spiroisoxazolidines **59** and **60** on cycloaddition reactions with nitrones **12** and **5**, respectively. Spiroisoxazolidine **60** provided the amino hemiacetal **61** as a single diastereomer on reduction (Scheme 2.13).[24]



Scheme 2.13

2.4.1 Synthesis of (+)-Epilupinine (3)

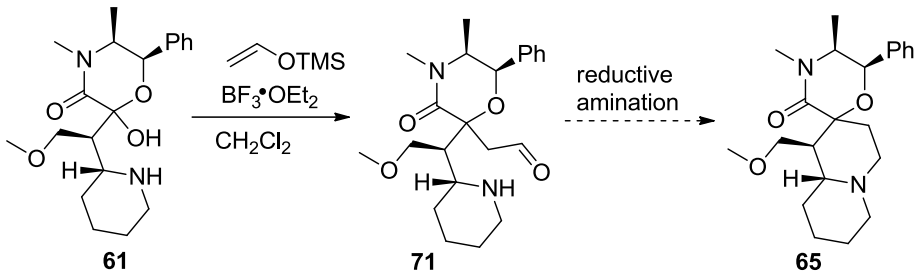
The synthesis of (+)-epilupinine (**3**) was now initiated from **61**, and the immediate objective was the construction of the second six-membered ring in the epilupinine quinolizidine ring system. Initially, we decided to pursue an enamine-based approch for construction of the second ring. We reasoned that, in the presence of a Lewis acid, the hemiacetal in **61** may form an oxocarbenium ion which can be trapped by an internal nucleophile.[16c,17-18,25] Hence, the objective was to convert the amine in **61** to an enamine **62** or **63** (Scheme 2.14), which would serve as an internal nucleophile for capturing the oxocarbenium ion **64** obtained from the hemiacetal in **62** (Scheme 2.14). Reduction of the iminium ion generated after cyclization of **64** would furnish the tricyclic intermediate **65** or **66** with the required azabicyclic framework for (+)-epilupinine. Treatment of **61** with acetaldehyde resulted in formation of the *N*,*O*-acetal **68**. The probable mechanism for formation of **68** through the iminium ion **67** is shown in Scheme 2.14. Unfortunately, **68** was stable to a variety of Lewis acids and hence its conversion to **65** was not achieved.



Scheme 2.14

In a related reaction, treatment of **61** with 1,1,2-trimethoxyethane in methanol also resulted in formation of the *N*,*O*-acetal **70** (through intermediate **69**) which was also stable to a variety of Lewis acids ($ZnCl_2$, $InCl_3$, $Sc(OTf)_3$, $In(OTf)_3$, $MgBr_2 \bullet OEt_2$). The enamine-mediated cyclization strategy was therefore not pursued further.

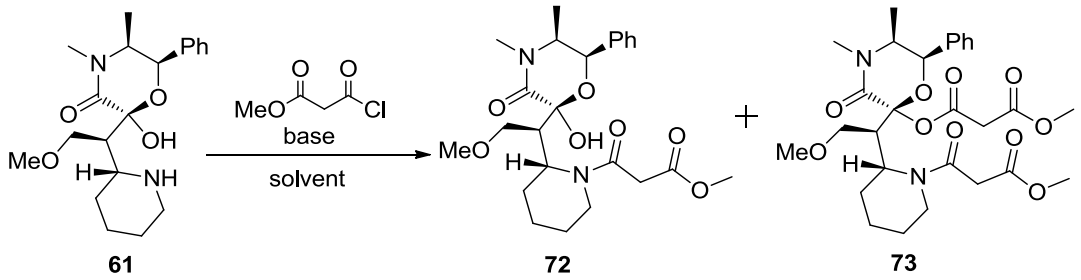
The use of a reductive amination strategy which would require an intermediate such as **71** was next explored (Scheme 2.15). However, the reaction of **61** with vinyloxy trimethylsilane was unsuccessful and **71** was not obtained (Scheme 2.15).



Scheme 2.15

As an alternative to the approaches described above, the possibility of intramolecular C-C bond formation by reaction of an oxocarbenium ion with an enolate was pursued. To this effect, the conversion of **61** to **72** was investigated (Scheme 2.16). Treatment of amino hemiacetal **61** with methyl-3-chloro-3-oxopropanoate under a variety of conditions generated a mixture of mono-acyl **72** and bis-acyl **73** (Scheme 2.16 and Table 2.3) that was separable by column chromatography. Efforts to obtain either **72** or **73** exclusively were unsuccessful. In all of these attempts, longer reaction times did not result in the conversion of **72** to **73**. The exact reasons behind the formation of a mixture of **72** and **73** are unclear. Ultimately, acylation of **61** in CH_2Cl_2 with aqueous 10% K_2CO_3 solution (entry 3, Table 2.3) as a base[26] proved to be the best conditions for a maximum yield of **73** (50%). A brief solvent survey for this conversion indicated that the reaction proceeds only in halogenated solvents, with CH_2Cl_2 being the solvent of choice in terms of conversion, and the ratio of **73** to **72** (entries 3-6, Table 2.3). Optimization of the base revealed that using aqueous K_2CO_3 as the base (10% solution, entry 3, Table 2.3) provided the best yield of **73** (50%). Increasing the concentration of this base (30% solution, entry 6, Table 2.3) reduced the reaction time from 12 h to less than 3 h with minimal effect on the yield of **73**. Although, acylation of **61** in CH_2Cl_2 with aqueous 10% K_2CO_3 solution

(entry 3, Table 2.3) as a base[26] provided a marginally higher yield of **73** (50%), 30% aq. K_2CO_3 was used as the base for all subsequent reactions due to the significantly shorter reaction times with only a negligible reduction in the yield of **73** (47%).



Scheme 2.16

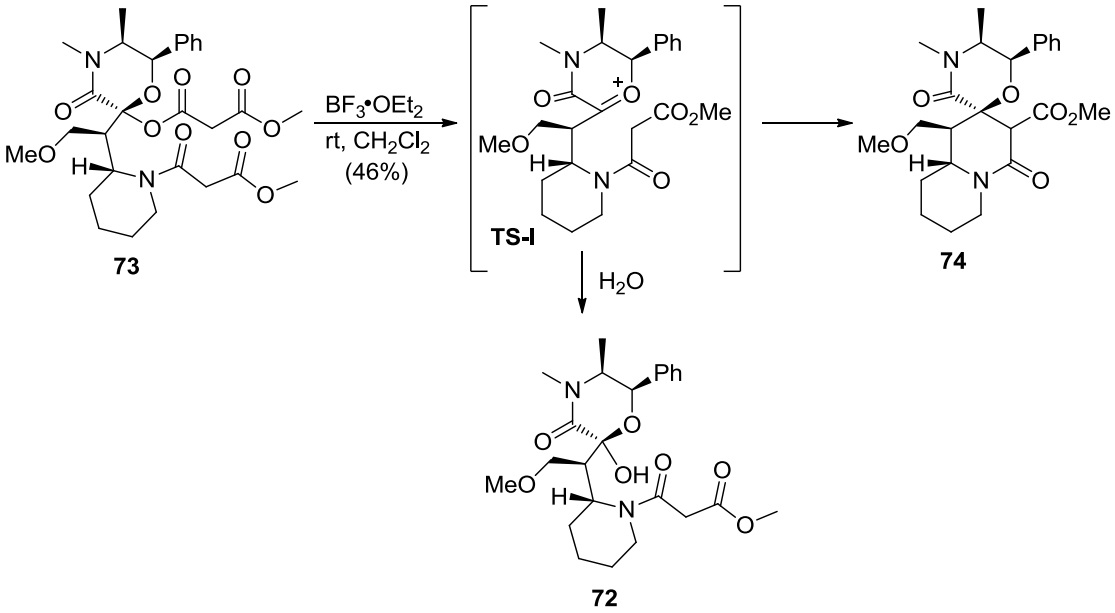
Table 2.3 Optimization studies for the acylation of **61**.

No	Base	Conditions	Time (h)	Yields (%)	
				72	**73**
1	Et_3N	DMAP, CH_2Cl_2, rt	24	18	9
2	Hunig's base	DMAP, THF, rt	24	9	2
3	10% aq. K_2CO_3	CH_2Cl_2, rt	12	20	50
4		$CHCl_3$, rt	12	55[a]	45[a]
5		THF, rt	12	**61** recovered	
6		EtOAc, rt	12	**61** recovered	
7	30% aq. K_2CO_3	CH_2Cl_2, rt	3	21	47

[a] ^{1}H NMR of the crude product.

Gratifyingly, the bis-acyl morpholinone **73** provided tricyclic compound **74** as a single diastereomer on treatment with BF_3•OEt_2 in CH_2Cl_2. The stereochemistry of the newly-formed spiro-stereocenter in **74** was assumed to be as shown, and is based on the known preference for the oxocarbenium ion such as TS-1 to react from the *Re* face.[16c,17-

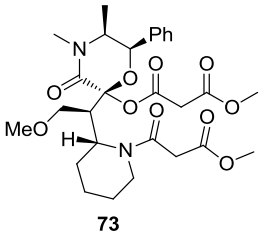
[18,25] The stereochemistry at the ester-bearing carbon was not determined in this study. In addition to **74**, the deacylation product **72** was also formed as a byproduct in this reaction (Scheme 2.17). The formation of **72** was an indication of complete oxocarbenium ion formation from the acetal in **73**, but an incomplete intramolecular capture of this oxocarbenium ion.



Scheme 2.17

A brief survey of various Lewis acids for the cyclization reaction was also conducted. However, only BF_3•OEt_2 was effective as a catalyst for the conversion of **73** to **74** (Table 2.4). The use of other metal-based Lewis acids resulted only in deacylation of **73** to provide **72** as the sole product. In addition, the cyclization reaction proceeded only in CH_2Cl_2 as the solvent. These results are summarized in Table 2.4.

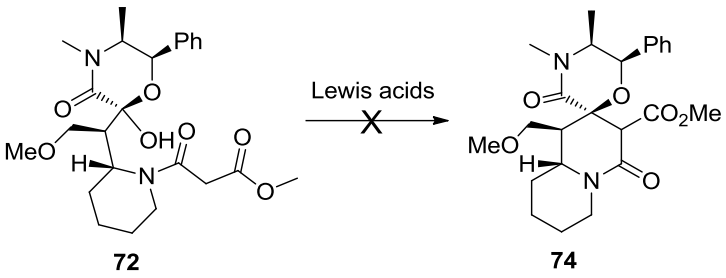
Table 2.4. Catalyst survey for the cyclization of **73** to **74**.

No	Substrate	Catalyst	Solvent	Time	Result
1	 **73**	BF_3•OEt_2[a]	CH_2Cl_2	24 h	**74** (46%) + **72** (49%)
2		$ZnCl_2$[a]	THF	24 h	**72** [c]
3		$InCl_3$[a]	THF	24 h	**72** [c]
4		$In(OTf)_3$[a]	CH_2Cl_2	24 h	**72** [c]
5		$Sc(OTf)_3$[a]	CH_2Cl_2	24 h	**72** [c]
6		$MgBr_2.OEt_2$[a]	CH_2Cl_2	24 h	**72** [c]
7		$TiCl_4$[b]	CH_2Cl_2	24 h	complex mixture
8		BF_3•OEt_2[d]	BF_3•OEt_2[d]	5 d	**72** [c] + **74** (20%) [f]
			+ CH_2Cl_2[e]	5 d	

[a] room temp., [b] -78 °C to room temp., [c] analysis of ^{1}H NMR of crude product, [d] room temp., [e] added after 5 days. [f] formed after addition of CH_2Cl_2.

In a related reaction, we attempted to suppress the formation of **72** by carrying out cyclization reaction of **73** in neat BF_3•OEt_2 (entry 8, Table 2.4). Surprisingly, analysis of an aliquot of this reaction indicated complete conversion to the deacylation product **72** after 5 days. Interestingly, the addition of CH_2Cl_2 to this reaction mixture resulted in cyclization of some of the deacylation product to the required product **74** (20%) after an additional 5 days. While this result highlights the importance of CH_2Cl_2 for the formation of **74**, it is unclear why the reactions that are initiated with CH_2Cl_2 as the solvent provide **74** at a faster rate.

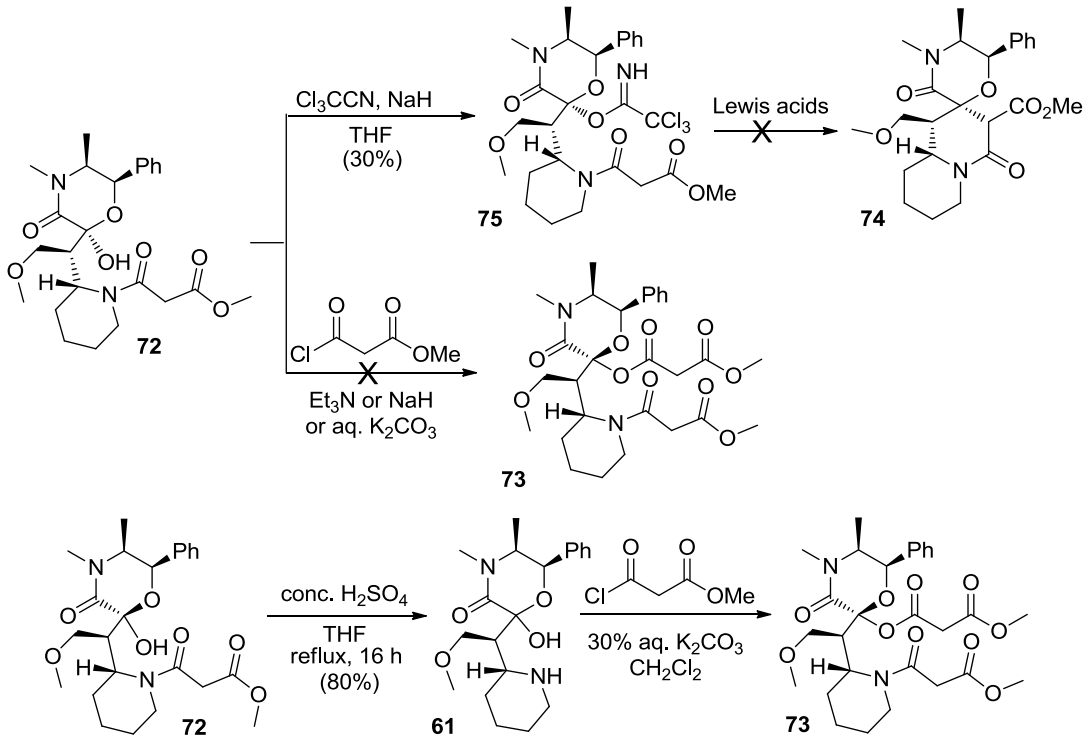
In order to maximize the overall conversion of **61** to **74**, attempts were undertaken to cyclize the mono-acyl compound **72** to **74**. However, exposure of **72** to a variety of Lewis acids failed to furnish any of the cyclized product **74** (Scheme 2.18).



72 74

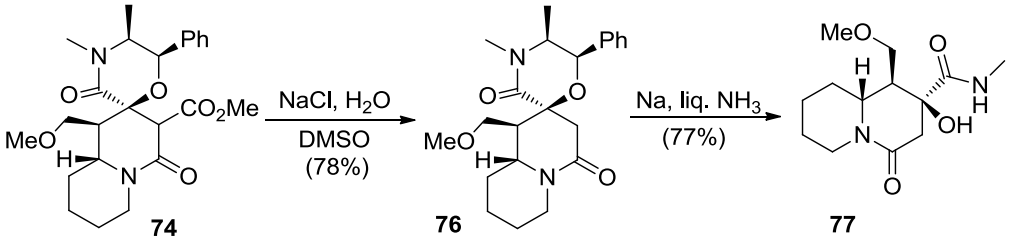
Scheme 2.18

In order to facilitate oxocarbenium ion formation from **72**, its conversion into an acetimidate derivative was attempted.[27] Deprotonation of **72** followed by treatment with trichloacetonitrile furnished the acetimidate derivative **75** (Scheme 2.19) only in low yield. Surprisingly, treatment of **75** with various Lewis acids did not furnish any of the cyclized product **74**. Attempts to recycle **72** by acylation to obtain the bis-acyl compound **73** were also unsuccessful. The only effective transformation of **72** was its hydrolysis to the amino hemiacetal **61**, which was recycled by conversion to **73** (Scheme 2.19).



Scheme 2.19

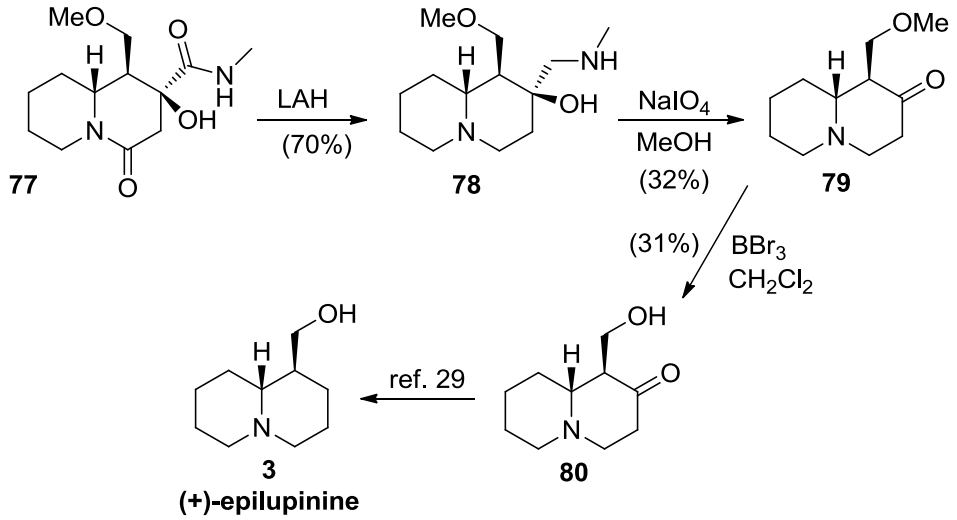
The synthetic efforts towards epilupinine were now continued further. Krapcho decarboxylation[28] of **74** provided **76** which has the required azabicylic framework for epilupinine (Scheme 2.20). Removal of the ephedrine portion from **76** was achieved by a dissolving-metal reduction (Na/NH_3) to provide the hydroxy amide **77**.



Scheme 2.20

Reduction of **77** ($LiAlH_4$) furnished the aminoalcohol **78**, oxidative cleavage of which provided the aminoketone **79**. Demethylation of **79** furnished **80** which is a known

intermediate to (+)-epilupinine (**3**, Scheme 2.21). Since (+)-Epilupinine (**3**) can be obtained by reduction of the dithiolane derived from **80**,[29] the synthesis outlined in Scheme 2.21 constitutes a formal synthesis of (+)-epilupinine (**3**).

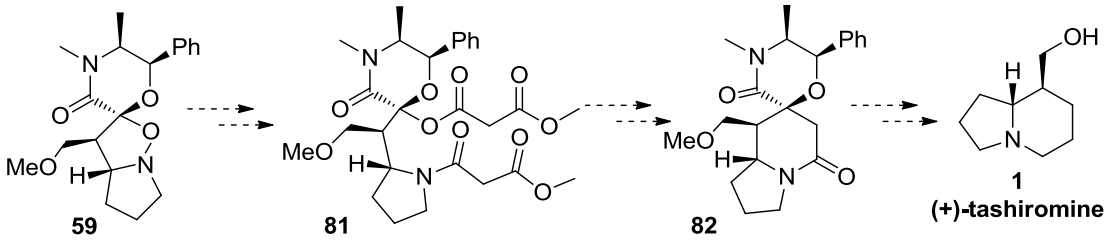


Scheme 2.21

The stereochemistry of **80** confirms the stereochemistry of the spiroisoxazolidine **60** (Scheme 2.13) and it also validates the stereochemical assumptions regarding the [3+2] cycloaddition of the alkylidene morpholinones and nitrones examined in this study (Schemes 2.11 and 2.13).

As a logical extension of the studies described above, it is reasonable to expect that the spiroisoxazolidine **59** will provide the indolizidine alkaloid (+)-tashiromine (**1**, Scheme 2.22). N-O Bond cleavage in **59** should provide the corresponding amino hemiacetal which upon bis-acylation to **81** and subsequent cyclization, will yield **82**. Reductive removal of the ephedrine portion in **82** and further transformations as outlined for **77** (Scheme 2.21)

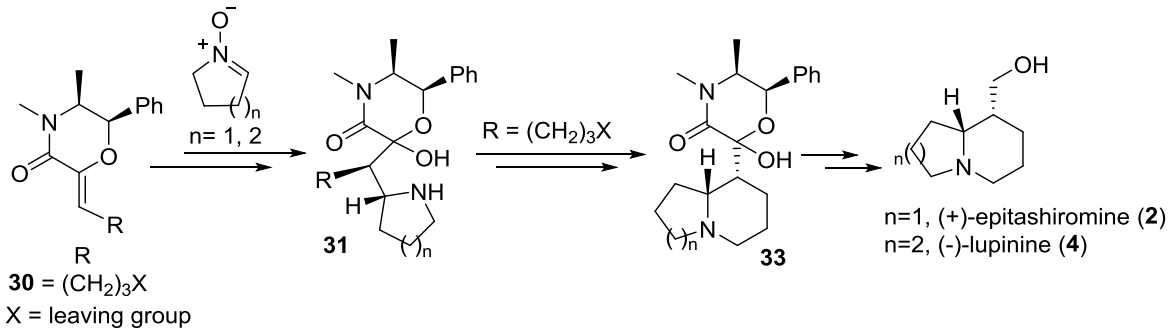
will lead to (+)-tashiromine (**1**). In general, the construction of the second ring in the azabicycle through the intramolecular oxonium ion capture procedure should provide access to indolizidine and quinolizidine alkaloids with *cis* orientation of the ring junction hydrogen and the adjacent hydroxymethyl group.



Scheme 2.22

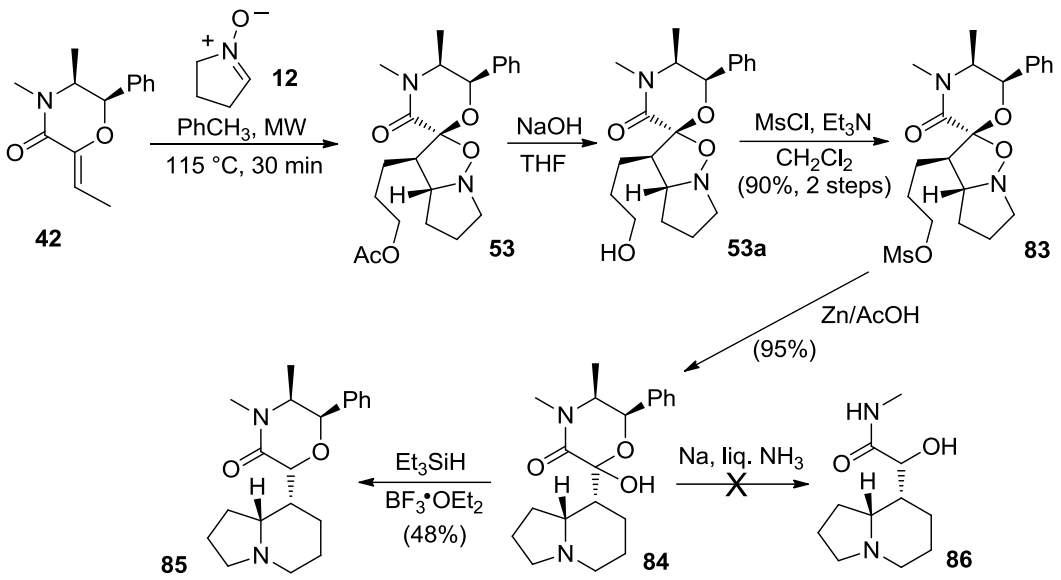
2.4.2 Synthesis of (+)-Epitashiromine (2)

As mentioned earlier, one of the objectives of this investigation was to develop a stereochemically flexible route to diastereomeric indolizidine and quinolizidine alkaloids. To this effect, the utility of the nitrone cycloaddition strategy, described above, in the synthesis of (+)-epitashiromine (**2**) was examined. In this approach, construction of the six membered ring of epitashiromine by an intramolecular *N*-alkylation reaction was chosen (Scheme 2.23). The substituent ('R') in the alkene **31** serves as the alkyl fragment for intramolecular *N*-alkylation to construct one ring of the target alkaloid. Depending on the length of the carbon chain, a five- or a six-membered ring can be constructed.



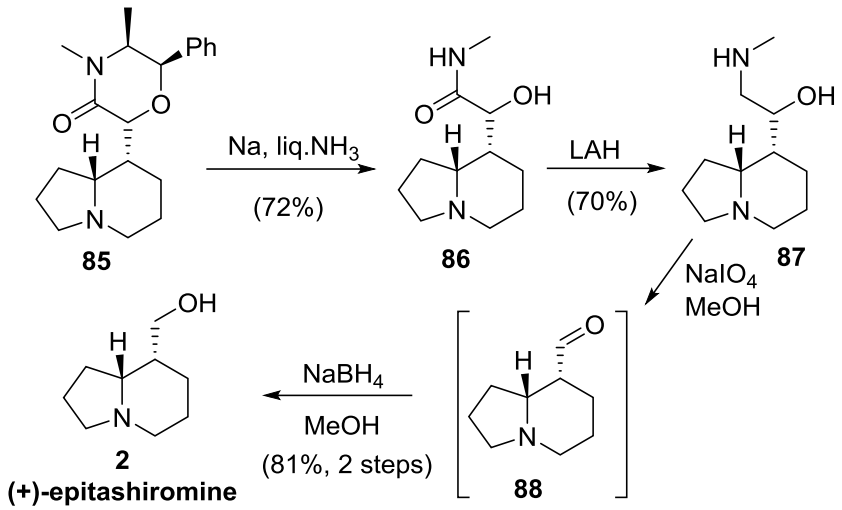
Scheme 2.23

The synthesis of (+)-epitashiromine was initiated with the preparation of the spiroisoxazolidine **53** (Scheme 2.11) by the reaction of alkylidene morpholinone **52** and the nitrone **12**. Hydrolysis of the acetate in **53** and subsequent mesylation of the alcohol provided **83**. Due to the unstable nature of **83**, the crude mesylate was immediately reduced with Zn-AcOH. During the reduction, an *in-situ* cyclization of the secondary amine, obtained after N-O bond cleavage in **83**, furnished the indolizidine **84** (Scheme 2.24). With the required azabicylic framework for (+)-epitashiromine (**2**) available in **84**, it was subjected to a dissolving metal reduction (Na/NH_3), the usual protocol for removal of the ephedrine portion. However, it was observed that **84** was resistant to the reduction. Previous studies in the Pansare group had indicated that morpholinone derivatives with free hydroxy groups were not good substrates for the dissolving-metal reduction protocol. It was therefore decided that reduction of the hemiacetal in **84** was necessary. Accordingly, treatment of **84** with $BF_3 \bullet OEt_2$ and Et_3SiH furnished **85**.



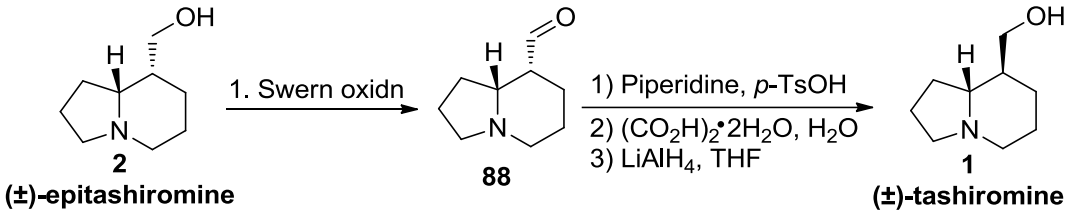
Scheme 2.24

As anticipated, the dissolving-metal reduction of **85** successfully generated the hydroxy amide **86** (Scheme 2.25). Conversion of **86** to (+)-epitashiromine (**2**) was achieved by reduction of the hydroxy amide to the amino alcohol **87**, oxidative cleavage of the amino alcohol **87** to the aldehyde **88** and *in situ* reduction of **88** to the primary alcohol (Scheme 2.25). The formation of (+)-epitashiromine confirms the stereochemistry of **53**.



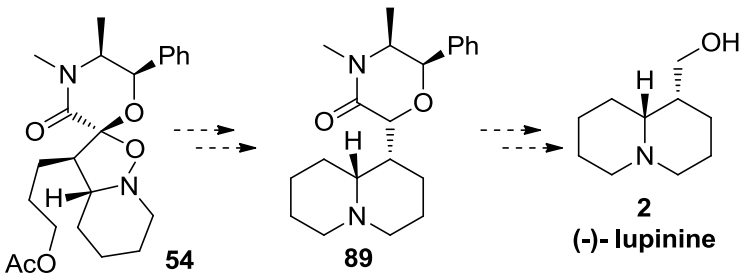
Scheme 2.25

The racemic version of the aldehyde intermediate obtained from **88** has previously been converted to (±) tashiromine *via* epimerization (Scheme 2.26) by Stille and Paulvannan.[12a] Thus, the present synthesis of (+)-epitashiromine (**2**) also constitutes a formal synthesis of (+)-tashiromine (**1**).



Scheme 2.26

It is reasonable to expect that the quinolizidine **89** will be obtained by following a synthetic sequence similar to the one described above for (+)-epitashiromine (**2**), but starting with the spiroisoxazolidine compound **54** (Scheme 2.11). Compound **89** should provide (−)-lupinine (**4**, Scheme 2.27) by following the sequence of reactions described in Scheme 2.25 for (+)-epitashiromine (**2**).



Scheme 2.27

2.5 Conclusions

In conclusion, a stereodivergent synthetic strategy, employing a 1,3-dipolar cycloaddition reaction of achiral nitrones with chiral dipolarophiles, was developed for the synthesis of selected indolizidine and quinolizidine alkaloids. The methodology was applied in the total synthesis of (+)-epitashiromine (**2**, 6.2% yield over 14 linear steps) and in the formal syntheses of (+)-epilupinine (**3**) and (+)-tashiromine (**1**).

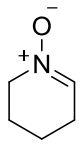
2.6 Experimental Section

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 and THF were distilled from CaH_2 and sodium/benzophenone respectively. Commercial precoated silica gel plates were used for TLC. Silica gel for flash column chromatography was 230-400 mesh. For column chromatographic purifications employing CH_2Cl_2/MeOH/aq. NH_3, the eluent was dried over Na_2SO_4 before use. All melting points are uncorrected. Optical rotations were measured at the sodium D line on a digital polarimeter at ambient temperature. A CEM Discover® microwave reactor was used for the microwave experiments. All reactions involving microwave heating were conducted in sealed reaction vessels. The temperature of the reaction mixture was monitored with an infrared sensor and the mixture reached the preset temperature (110 ^oC) in approximately 60s. Compounds **34**,[16a] **35**,[16c] and **37**[17] were prepared according to literature methods.

General procedure for the preparation of cyclic nitrones 5 and 12:[23]

To the solution of amine (10 mmol) in acetone (25 mL) was added SeO_2 (0.5 mmol) at 0 °C under nitrogen. To this mixture was added dropwise an aqueous solution of H_2O_2 (50% soln., 1.5 mL, 22 mmol) and the reaction mixture was warmed to room temperature and stirred for 3 h at room temperature. Acetone was removed under reduced pressure and the resulting mixture was extracted with CH_2Cl_2 (5 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure.

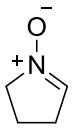
2,3,4,5-Tetrahydropyridine 1-oxide (5):



This was prepared according to the general procedure. The crude product was purified by flash chromatography (9:1 CH_2Cl_2/MeOH) to obtain 285 mg of **5** (25%) as a yellowish solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (m, 1H, =C*H*), 3.80 (m, 2H, NCH_2), 2.44 (m, 2H, =CCH_2), 1.98 (m, 2H, CH_2), 1.74 (m, 2H, CH_2).

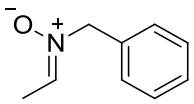
3,4-dihydro-2H-pyrrole-1-oxide (12):



This was prepared according to the general procedure. The crude product was of sufficient purity and was directly used in the reactions with alkylidene morpholinones.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.91 (m, 1H, =C*H*), 3.99-3.98 (m, 2H, NCH_2), 2.76-2.73 (m, 2H, =CCH_2), 2.32-2.22 (m, 2H, CH_2).

(*Z*)-*N*-Ethylidene-1-phenylmethanamine oxide (48):[19]



To a solution of benzaldehyde (10.0 g, 0.094 mol) and hydroxylamine hydrochloride (21.81 g, 0.314 mol) in ethanol (90%, 315 mL) was added powdered NaOH (34 g, 0.85 mol) in small portions. The mixture was allowed to stir at 25 °C for 30 min and then heated to reflux for additional 30 min. The reaction mixture was then cooled to 25 °C and poured into a mixture of concentrated HCl (38 mL) and water (145 mL). The acidic solution was carefully concentrated to one third of the original volume and extracted with CH_2Cl_2 (3 x 50 mL). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product (yellow oil) was purified by Kugelrohr distillation (b.p. 71 °C, 0.5 mmHg) to give 5.5 g (48%) benzaldehyde oxime as a colorless oil which slowly crystallized below 20 °C.

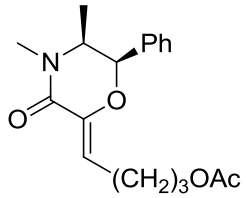
To a solution of benzaldehyde oxime (5.4 g, 0.045 mol) and $NaBH_3CN$ (4.776 g, 0.076 mol) in 60 mL MeOH at 0 °C, HCl (12 N, 7.5 mL, 0.09 mol) was added drop wise. The reaction mixture was then stirred at 25 °C for 4 h and basified to pH ~ 9 with NaOH (6 M). The mixture was concentrated under reduced pressure and the product was extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue obtained was recrystallized

(hexanes/MeOH, 4:1) to provide 4.8 g (87%) of *N*-benzyl-hydroxylamine as colorless crystals.

To a solution of *N*-benzyl hydroxylamine (4.71 g, 38.2 mol), in CH_2Cl_2 (100 mL) at 0 °C under an argon atmosphere, were added freshly distilled acetaldehyde (10.7 mL, 76.4 mol), Na_2SO_4 (5.42 g, 38.2 mol) and $NaHCO_3$ (0.178 g, 1.91 mol) and the mixture was stirred for 1 h. The mixture was then filtered and the filtrate was concentrated under reduced pressure to afford 5.5 g (97%) of (*Z*)-*N*-ethylidene benzylamine *N*-oxide (**48**) as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41-7.38 (m, 5H, Ar*H*), 6.73-6.70 (q, 1H, *J* = 5.8, NC*H*), 4.89 (s, 2H, PhCH_2), 2.00-1.99 (d, 3H, *J* = 5.8, CH_3).

(*Z*)-4-((5*S*,6*R*)-4,5-Dimethyl-3-oxo-6-phenylmorpholin-2-ylidene)butyl acetate (42):



To a suspension of the dione **34** (1.4 g, 6.4 mmol) in THF (25 mL) at 0 ^{o}C, was added the Grignard reagent prepared from 2-(4-bromobutoxy)tetrahydro-2H-pyran (3.77 g, 15.9 mmol) and magnesium metal (388 mg, 15.9 mmol) in THF (10 mL) and the mixture was stirred at ambient temperature for 12 h. A saturated aqueous solution of ammonium chloride was added and the mixture was extracted with ethyl acetate (3 x 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated to provide 2.2 g (91 %) of the hemiacetal **38**. This was pure (^{1}H NMR) and was used further without purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.29 (m, 5H, Ar*H*), 5.52-5.51 (d, 1H, *J* = 2.9, PhC*H*), 4.62-4.59 (m, 1H, OC*H*O), 3.92-3.74 (m, 2H, ring OCH_2 or alkyl OCH_2), 3.54-3.40 (m overlapped with dq, 3H, C*H*CH_3 and ring OCH_2 or alkyl OCH_2), 3.15 (br s, 1H, O*H*), 3.04 (s, 3H, NCH_3), 2.20-2.07 (m, 1H, CH_2), 2.02-1.93 2.20-2.07 (m, 1H, CH_2), 1.88-1.47 (m, 12H, CH_2), 0.97 (d, 3H, *J* = 6.5, CHCH_3).

Visible peaks of minor diastereomer: 5.19-5.18 (d, 1H, *J* = 2.8, PhC*H*), 4.55-4.51 (m, 1H, OC*H*O), 3.03 (s, 3H, NCH_3), 1.35 (d, 3H, *J* = 6.5, CHCH_3).

A solution of the hemiacetal **38** (2.1 g, 5.6 mmol) in MeOH (10 mL) was cooled to 0 ^{o}C and *p*-TsOH (2.64 g, 13.9 mmol) was added. The solution was stirred at room temperature for 12 h and the MeOH was removed under reduced pressure. The residue was taken up in water and the mixture was neutralized with saturated aqueous $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2 (3 x 30 mL) and the combined extracts were dried (Na_2SO_4) and concentrated to provide the 1.5 g (92%) of the primary alcohol **41**. This was dissolved in CH_2Cl_2 (15 mL) and the solution was cooled to 0°C. To this were added DMAP (0.03 g, 0.3 mmol), followed by triethylamine (1.78 mL, 12.8 mmol) and acetyl chloride (0.55 mL, 7.74 mmol) and the mixture was stirred for 12 h at ambient temperature. Water (5 ml) was added, the mixture extracted with CH_2Cl_2 (3 x 15 mL) and the combined extracts washed with water and sat. $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated to provide 1.54 g (90%) of the crude acetate.

The acetate was dissolved in CH_2Cl_2 (10 mL), the solution was cooled to -78 ^{o}C and $BF_3.OEt_2$ (1.70 mL, 13.8 mmol) was added. The solution was stirred at ambient temperature for 12 h and cold water (5 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 30 mL) and the combined extracts were dried (Na_2SO_4) and concentrated. The

residue was purified by flash chromatography on silica gel (1:1 EtOAc/hexane) to provide 1.15 g (79%, 65% from the OTHP hemiacetal) of **42** as a colorless gum.

IR (neat): 1732, 1633, 1481, 1447, 1400, 1304, 1241, 1209, 1164, 1045, 1014 cm^{-1}.

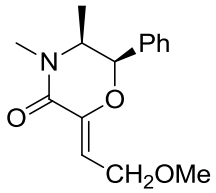
^1H NMR (300 MHz, $CDCl_3$): δ 7.44-7.28 (m, 5H, Ar*H*), 6.05 (t, 1H, *J* = 7.8, C*H*CH_2), 5.23-5.22 (d, 1H, *J* = 2.7, PhC*H*), 4.15-4.03 (m, 2H, OC*H*$_2$), 3.59-3.51 (dq, 1H, *J* = 2.7, 6.6, C*H*CH_3), 3.09 (s, 3H, NC*H*$_3$), 2.41-2.28 (m, 2H, C*H*$_2$CH), 1.97 (s, 3H, C*H*$_3$CO), 1.84-1.74 (m, 2H, C*H*$_2$$CH_2$), 0.98 (d, 3H, *J* = 6.6, CHC*H*$_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1 (O*C*=O), 159.5 (N*C*=O), 144.6 (C=*C*-C=O), 137.0 (ArC_{ipso}), 128.5 (2 x Ar*C*), 128.0 (Ar*C*), 125.5 (2 x Ar*C*), 115.0 (C=*C*H), 77.1 (Ph-*C*H), 63.9(*C*H_2OAc), 58.6 (N*C*H), 33.6 (N*C*H_3), 27.8 (*C*H_2), 21.3 (*C*H_2), 20.9 (*C*H_3CO), 11.7 (CH*C*H_3).

MS (APCI, pos.): *m/z* 318.1 $(M+H)^+$.

HRMS (EI): *m/z* 317.1630 (317.1627 calc. for $C_{18}H_{23}NO_4$ (M^+)).

(*Z*,5*S*,6*R*)-2-(2-Methoxyethylidene)-4,5-dimethyl-6-phenylmorpholin-3-one (58):



To a stirred solution of (Z)-ethyl-2-((5S,6R)-4,5-dimethyl-3-oxo-6-phenylmorpholin-2-ylidene)acetate (**35**, prepared from the morpholine dione **34** and carbethoxymethylenetriphenylphosphorane,[16c] 2.20 g, 7.60 mmol) in CH_2Cl_2 (10 mL) at -78 ºC was added DIBAL-H (27.3 mL of 1 M soln. in CH_2Cl_2, 27.3 mmol) drop wise. The

resulting mixture was stirred at room temperature for 5 h, then cooled to 0 °C and aqueous HCl (3 M, 5 mL) was added. The resulting mixture was warmed to room temperature and then extracted with CH_2Cl_2 (4 x 25mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate) to provide 1.15 g (61%) of (*Z*,5*S*,6*R*)-2-(2-Hydroxyethylidene)-4,5-dimethyl-6-phenylmorpholin-3-one as a colorless oil.

IR (neat): 3393 (br), 1624, 1444, 1397, 1303, 1157, 1038, 998 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.42-7.30 (m, 5H, Ar*H*), 6.21 (t, 1H, *J* = 6.5, C*H*CH_2), 5.27 (d, 1H, *J* = 2.6, PhC*H*), 4.50-4.36 (dd, 2H, *J* = 6.5, 14.5, OC*H*$_2$), 3.57-3.53 (dq, IH, *J* = 2.6, 6.6, C*H*CH_3), 3.10 (s, 3H, NC*H*$_3$), 1.95 (br s, 1H, O*H*), 1.00 (d, 3H, *J* = 6.6, CHC*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1 (*C*=O), 144.3 (*C*-C=O), 136.5 (ArC_{ipso}), 128.5 (2 x Ar*C*), 128.1 (Ar*C*), 125.4 (2 x Ar*C*), 115 (C=*C*H), 77.3 (Ph-*C*H), 58.6 (N*C*H), 57.0 (*C*H_2OH), 33.7 (N*C*H_3), 11.8 (CH*C*H_3).

MS (APCI, pos.): *m/z* 248.1 $(M+H)^+$.

HRMS (EI): *m/z* 247.1216 (247.1208 calc. for $C_{14}H_{17}NO_3$ (M^+)).

To a suspension of NaH (323 mg (95%), 12.8 mmol) in THF (5 mL), was added a solution of the above alcohol (2.10 g, 8.49 mmol) in THF (10 mL) at 0 °C. The mixture was stirred for 30 min at 0 °C and MeI (0.74 mL, 11.9 mmol) was added. The mixture was stirred at ambient temperature for 3 h and water (5 mL) was added. The resulting mixture was extracted with EtOAc (3 x 25 mL), the combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give 1.9 g (85%) of the ether **58** as a colorless oil. This was pure by ^1H NMR and was used further without purification. An analytical sample was obtained by flash chromatography on silica gel (EtOAc/hexanes, 7:3).

IR (neat): 2980, 2929, 1634, 1488, 1445, 1394, 1307, 1157, 1112, 1073, 1025 cm^{-1}.

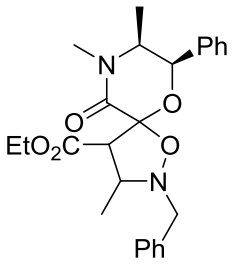
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.33 (m, 5H, Ar*H*), 6.16 (t, 1H, *J* = 6.7, C*H*CH_2), 5.27 (d, 1H, *J* = 2.6, PhC*H*), 4.29-4.18 (dd, 2H, *J* = 6.7, 13.4, C*H*$_2$O), 3.57-3.53 (dq, 1H, *J* = 2.6, 6.6, C*H*CH_3), 3.37 (s, 3H, OC*H*$_3$), 3.10 (s, 3H, NC*H*$_3$), 1.00 (d, 3H, *J* = 6.6, CHC*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 158.9 (*C*=O), 145.2 (*C*-C=O), 136.6 (ArC_{ipso}), 128.6 (2 x Ar*C*), 128.1 (Ar*C*), 125.4 (2 x Ar*C*), 111.9 (C=*C*H), 77.4 (Ph-*C*H), 66.1 (O*C*H_2), 58.6 (O*C*H_3), 58.1 (N*C*H), 33.7 (N*C*H_3), 11.7 (CH*C*H_3).

MS (APCI, pos.): *m/z* 262.1 $(M+H)^+$.

HRMS (EI): *m/z* 261.1375 (261.1365 calc. for $C_{15}H_{19}NO_3$ (M^+)).

(7*R*,8*S*)-Ethyl-2-benzyl-3,8,9-trimethyl-10-oxo-7-phenyl-1,6-dioxa-2,9-diazaspiro[4.5]decane-4-carboxylate (49):



A solution of **35** (0.05 g, 0.17 mmol) and nitrone **48** (0.052 g, 0.35 mmol) in toluene (2 mL) was heated by microwave irradiation in a sealed reaction vessel for 30 min at 110 °C. The mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 5:5) to afford 0.033 g (40%) of the spiroisoxazolidine **49** as a pale yellow foam.

IR (neat): 1735, 1666, 1495, 1450, 1377, 1243, 1197, 1024, 892, 746 cm^{-1}.

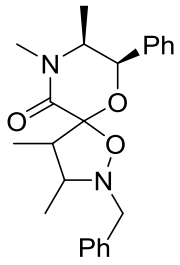
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40-7.31 (m, 3H, Ar*H*), 7.25-7.15 (m, 7H, Ar*H*), 5.51-5.50 (d, 1H, *J* = 2.9, PhC*H*), 4.34-4.27 (m, 1H, OCH_2), 4.15-4.10 (m, 1H, OCH_2), 4.07 (d, 1H, *J* = 11.3, PhCH_2), 4.04 (d, 1H, *J* = 9.9, PhCH_2), 3.84 (br s, 1H, NC*H*), 3.47 (dq, 1H, *J* = 3.2, 6.5, NC*H*CH_3), 3.02, (s, 3H, NCH_3), 1.32 (d, 3H, *J* = 6.2, CHCH_3), 1.28 (t, 3H, *J* = 7.2, CH_2CH_3), 0.89 (d, 3H, *J* = 6.5, CHCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 168.0 (O*C*=O), 162.6 (N*C*=O), 137.1 (ArC_{ipso}), 136.9 (ArC_{ipso}), 129.1 (2 x Ar*C*), 128.5 (2 x Ar*C*), 128.1 (2 x Ar*C*), 127.8 (Ar*C*), 127.2 (Ar*C*), 125.4 (2 x Ar*C*), 104 (O*C*-C(O)), 76.04 (OCH_2), 71.3 (Ph*C*H), 61.6 (N*C*H), 61.1 (PhCH_2), 58.9 (C(O)N*C*H), 34.2 (NCH_3), 18.26 (CH*C*H_3), 14.1 (CH_2CH_3), 12.4 (CH*C*H_3).

MS (APCI, pos.): *m/z* 439.4 $(M+H)^+$.

HRMS (EI): *m/z* 438.2145 (438.2155 calc. for $C_{25}H_{30}N_2O_5$ (M^+)).

(7*R*,8*S*)-2-Benzyl-3,4,8,9-tetramethyl-7-phenyl-1,6-dioxa-2,9-diazaspiro[4.5]decan-10-one (50):



A solution of **37** (0.05 g, 0.22 mmol) and nitrone **48** (0.065 g, 0.44 mmol) in toluene (2 mL) was heated by microwave irradiation in a sealed reaction vessel for 30 min at 110 °C. The mixture was cooled to ambient temperature and concentrated under reduced

pressure. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 4:6) to afford 0.020 g (20%) of the spiroisoxazolidine **50** as a yellowish foam.

IR (neat): 1654, 1550, 1495, 1453, 1320, 1252, 1151, 1029, 917 cm^{-1}.

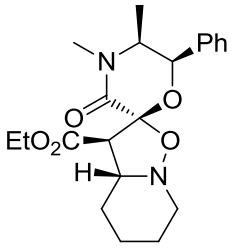
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43-7.38 (m, 2H, Ar*H*), 7.35-7.31 (m, 3H, Ar*H*), 7.24-7.23 (br d, 2H, Ar*H*), 7.20-7.13 (m, 3H, Ar*H*), 5.55-5.54 (d, 1H, *J* = 2.8, PhC*H*), 4.02-3.99 (d, 1H, *J* = 13.7, PhCH_2), 3.97-3.94 (d, 1H, *J* = 13.7, PhCH_2), 3.47 (m, 1H, NC*H*CH_3), 3.05-3.02 (br m, 2H, NC*H*, C*H*CH_3), 3.00, (s, 3H, NCH_3), 1.18-1.17 (d, 3H, *J* = 5.5, CHCH_3), 1.14-1.13 (d, 3H, *J* = 6.6, CHCH_3), 0.93 (d, 3H, *J* = 6.4, CHCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 137.7 (ArC_{ipso}), 137.4 (ArC_{ipso}), 129.1 (2 x Ar*C*), 128.4 (2 x Ar*C*), 128.1 (2 x Ar*C*), 127.7 (Ar*C*), 127.1 (Ar*C*), 125.5 (2 x Ar*C*), 104.2 (*C*-C(O)), 70.7 (Ph*C*H), 66 (PhCH_2), 58.9 (C(O)N*C*H), 50.7 (CH*C*H), 34.1 (NCH_3), 16.61 (*C*H), 13.0 (CH_2CH_3), 10.3 (CHCH_3).

MS (APCI, pos.): *m/z* 381.4 $(M+H)^+$.

HRMS (EI): *m/z* 380.2103 (380.2100 calc. for $C_{23}H_{28}N_2O_3$ (M^+)).

(5'*S*,6'*R*)-Ethyl-4',5'-dimethyl-3'-oxo-6'-phenylhexahydrospiro[isoxazolo[2,3-a]pyridine-2,2'-morpholine]-3-carboxylate (51):



A solution of **35** (0.145 g, 0.501 mmol) and nitrone **5** (0.100 g, 1.002 mmol) in toluene (2 mL) was heated by microwave irradiation in a sealed reaction vessel for 30 min

at 110 °C. The mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 4:6) to afford 0.165 g (85%) of the spiroisoxazolidine **51** as a yellowish foam.

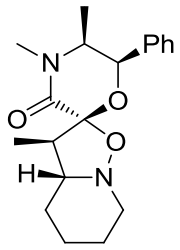
IR (neat): 2935, 1736, 1662, 1449, 1379, 1309, 1237, 1191, 1145, 995, 754 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.34-7.19 (m, 5H, Ar*H*), 5.53 (br s, 1H, PhC*H*), 4.34-4.25 (m, 1H, OCH_2), 4.16-4.11 (m, 1H, OCH_2), 3.81-3.75 (m, 1H), 3.70-3.43 (m, 2H), 3.50 (m, 1H, NC*H*), 3.22-3.20 (m, 1H, NC*H*), 3.00, (s, 3H, NCH_3), 2.20-2.14 (br m, 1H, CH_2) 2.01(br m, 1H, CH_2), 1.74 (br s, 2H, CH_2), 1.58-1.52 (br m, 2H, CH_2), 1.42-1.41 (m, 1 H, CH_2), 1.29-1.22 (m, 4H, CH_2), 0.90 (d, 3H, *J* = 6.6, CHCH_3).

MS (APCI, pos.): *m/z* 389.2 $(M+H)^+$.

HRMS (CI): *m/z* 388.1989 (388.1998 calc. for $C_{21}H_{28}N_2O_5$ (M^+)).

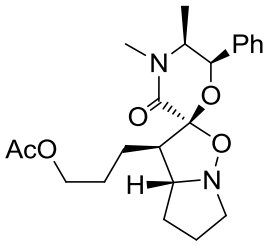
(5'*S*,6'*R*)-3,4',5'-Trimethyl-6'-phenylhexahydrospiro[isoxazolo[2,3-a]pyridine-2,2'-morpholin]-3'-one (52):



A solution of **37** (0.1 g, 0.43 mmol) and nitrone **5** (0.086 g, 0.86 mmol) in toluene (2 mL) was heated by microwave irradiation in a sealed reaction vessel for 30 min at 110 °C. The mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 4:6) to afford 0.11 g (77%) of the spiroisoxazolidine **52** as a colorless foam.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.26 (m, 5H, Ar*H*), 5.52 (br s, 1H, PhC*H*), 3.49-3.44 (m, 1H, NC*H*), 3.34 (m, 1H, NC*H*), 3.21 (m, 1H, NCH_2), 3..06 (s, 3H, NCH_3), 2.00-1.91 (br m, 2H, CH_2), 1.74-1.68 (br d, 4H, CH_2), 1.49 (br m, 1H, CH_2), 1.39-1.37 (br m, 1H, CH_2), 1.26 (br s, 1H, CH_2), 1.13 (d, 3H, *J* = 6.6, CHCH_3), 0.95-0.94 (d, 3H, *J* = 6.6, CHCH_3).

3-((5*S*,6*R*)-4,5-Dimethyl-3-oxo-6-phenyltetrahydro-3'H-spiro[morpholine-2,2'-pyrrolo[1,2-b]isoxazol]-3'-yl)propyl acetate (53):



A solution of **42** (2.00 g, 6.29 mmol) and nitrone **12** (1.07 g, 12.6 mmol) in toluene (8 mL) was heated by microwave irradiation in a sealed reaction vessel for 30 min at 110 °C. The mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 6:4) to afford 1.82 g (71%) of the spiroisoxazolidine **53** as a pale yellow foam.

IR (neat): 1735, 1659, 1449, 1236, 1148, 1040 cm^{-1}.

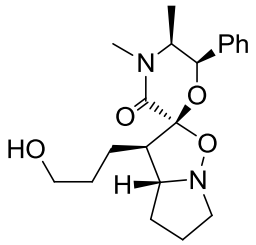
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.25 (m, 5H, Ar*H*), 5.62-5.61 (d, 1H, *J* = 3.2, PhC*H*), 4.17-4.04 (m, 2H, OCH_2), 3.68-3.62 (m, 1H, C*H*NO), 3.55-3.48 (dq, 1H, *J* = 3.2, 6.5, C*H*CH_3), 3.38-3.30 (m, 1H), 3.11-3.07 (m, 1H), 3.04 (s, 3H, NCH_3), 3.03-2.97 (m, 1H), 2.06 (s, 3H, CH_3CO), 1.97-1.92 (m, 1H, CH_2CH), 1.89-1.78 (m, 3H, CH_2CH_2), 1.72-1.61 (m, 4H, CH_2CH_2) 0.94 (d, 3H, *J* = 6.5, CHCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1 (O*C*=O), 164.0 (N*C*=O), 137.4 (ArC_{ipso}), 128.3 (2 x Ar*C*), 127.6 (Ar*C*), 125.6 (2 x Ar*C*), 104.9 (O*C*O), 70.9 (Ph-*C*H), 69.6 (N*C*H), 64.4 (*C*H_2OAc), 59.0 (N*C*H), 56.9 (N*C*H_2), 55.2 (*C*HCH*$_2$*), 34.3 (N*C*H_3), 29.9 (*C*H_2), 27.2 (*C*H_2), 24.2 (*C*H_2), 23.0 (*C*H_2), 21.0 (*C*H_3CO), 12.9 (CH*C*H_3).

MS (APCI, pos.): *m/z* 403.2 $(M+H)^+$.

HRMS (EI): *m/z* 402.2150 (402.2155 calc. for $C_{22}H_{30}N_2O_5$ (M^+)).

(5*S*,6*R*)-3'-(3-Hydroxypropyl)-4,5-dimethyl-6-phenyltetrahydro-3'H-spiro[morpholine-2,2'-pyrrolo[1,2-b]isoxazol]-3-one (53a):



To the solution of the spiroisoxazolidine **53** (1.82 g, 4.52 mmol) in THF (10 mL) was added NaOH (18.1 mL of 2.5 M soln. 45.24 mmol) and the mixture was heated to reflux for 16 h (monitored by TLC). The mixture was then cooled to ambient temperature and extracted with CH_2Cl_2 (5 x 20 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to provide 1.52 g (93%) of the alcohol **53a** as a white foam. This was pure by ^{1}H NMR and was used further without purification.

IR (neat): 3395, 1650, 1448, 1189, 1146, 1017 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.29 (m, 5H, Ar*H*), 5.62-5.61 (d, 1H, *J* = 3.2, PhC*H*), 3.69-3.61 (m, 3H, OC*H*$_2$ and C*H*NO), 3.54-3.46 (dq, 1H, *J* = 3.2, 6.5, C*H*CH_3), 3.37-3.29 (m, 1HNC*H*), 3.11-3.06 (m, 1H, NC*H*$_2$) 3.03 (s, 3H, NC*H*$_3$), 3.03-2.97 (m, 1H, C*H*CH_2),

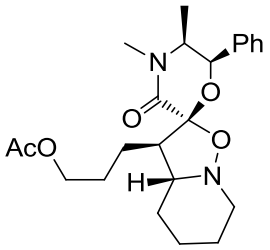
2.1-2.01 (m, 1H, C*H*$_2$), 1.98-1.86 (m, 4H, C*H*$_2$), 1.81-1.68 (m, 2H, C*H*$_2$CH$_2$), 1.66-1.55 (m, 2H, C*H*$_2$CH$_2$), 0.95 (d, 3H, *J* = 6.5, CHC*H*$_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 164.2 (N*C*=O), 137.5 (Ar*C*$_{ipso}$), 128.3 (2 x Ar*C*), 127.6 (Ar*C*), 125.7 (2 x Ar*C*), 105.2 (O*C*O), 70.9 (Ph-*C*H), 69.7 (N*C*H), 62.7 (*C*H$_2$OH), 59.0 (N*C*H), 56.9 (NCH$_2$), 55.3 (*C*HCH$_2$) 34.3 (NCH$_3$), 31.0 (*C*H$_2$), 39.0 (*C*H$_2$), 24.0 (*C*H$_2$), 23.0 (*C*H$_2$), 13.0 (CH*C*H$_3$).

MS (APCI, pos.): *m/z* 361.1 $(M+H)^+$.

HRMS (EI): *m/z* 360.2048 (360.2049 calc. for $C_{20}H_{28}N_2O_4$ (M^+)).

3-((3*R*,3a*R*,5'*S*,6'*R*)-4',5'-Dimethyl-3'-oxo-6'-phenylhexahydrospiro[isoxazolo[2,3-a]pyridine-2,2'-morpholin]-3-yl)propyl acetate (54):



A solution of **42** (100 mg, 0.32 mmol) and nitrone **5** (63.0 mg, 0.64 mmol) in toluene (3 mL) was heated by microwave irradiation in a sealed reaction vessel for 30 min at 110 °C. The mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 6:4) to afford 90 mg (70%) of the spiroisoxazolidine **54** as a pale yellow foam.

IR (neat): 2938, 1734, 1655, 1447, 1237, 1146, 1100, 986 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.28 (m, 5H, Ar*H*), 5.60 (br s, 1H, PhC*H*), 4.11-4.02 (br m, 2H, OC*H*$_2$), 3.57-3.47 (m, 2H, NC*H* and NC*H*CH$_2$), 3.42-3.27 (m, 1H), 3.11-2.99

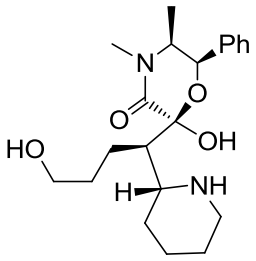
(s superimposed on a m, 4H), 2.51-2.35 (m, 3H), 2.08-2.02 (s superimposed on a m, 4H), 1.97-1.92 (m, 2H), 1.77-1.69 (m, 5H), 0.94 (d, 3H, J = 6.5).

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1 (*C*OOCH$_3$), 165.4 (*C*ONCH$_3$), 137.5 (Ar*C*$_{ipso}$), 128.3 (2 x Ar*C*H), 127.6 (Ar*C*H), 125.5 (2 x Ar*C*H), 104.5 (O*C*O), 70.8 (Ph-*C*H), 69.3 (O*C*H$_2$), 64.5 (N*C*HCH$_2$), 58.6 (N*C*HCH$_3$), 52.2 (N*C*H$_2$), 47.3 (*C*HCH$_2$), 34.2 (N*C*H$_3$), 27.1 (*C*H$_2$), 24.45 (*C*H$_2$), 22.35 (*C*H$_2$), 21.7 (*C*H$_2$), 20.9 (*C*H$_3$CO), 18.6 (*C*H$_2$), 12.8 (CH*C*H$_3$).

MS (APCI, pos.): *m/z* 417.3 $(M+H)^+$.

HRMS (CI): *m/z* 416.2309 (416.2311 calc. for $C_{23}H_{32}N_2O_5$ (M^+)).

2-Hydroxy-2-((*R*)-4-hydroxy-1-((*R*)-piperidin-2-yl)butyl)-4,5-dimethyl-6-phenylmorpholin-3-one (54a):



To the solution of **54** (42 mg, 0.101 mmol) in MeOH (2 mL) was added K_2CO_3 (138 mg, 1.01 mmol) at room temperature, reaction was stirred for 3 h at room temperature. The solvent was removed under reduced pressure, the residue was dissolved in water (2 mL) and was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layer was dried (Na_2SO_4) and concentrated to afford crude alcohol (37 mg, 98%). This was used further without purification.

To a stirred solution of alcohol (37 mg, 0.99 mmol) in acetic acid (2 mL) was added activated zinc powder (65.0 mg, 9.88 mmol) in two portions at ambient temperature. The

mixture was stirred vigorously at ambient temperature for 36 h (monitored by TLC), CH_2Cl_2 (5 mL) was added and the mixture was filtered. The solvent was removed under reduced pressure and the mixture was basified (pH=12) with NaOH solution (10%). The basic mixture was extracted with CH_2Cl_2 (3 x 20 mL) and the combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 8:2) to provide 15 mg (41%) of **54a** as colorless foam.

IR (neat): 3400, 3246, 1641, 1445, 1395, 1161, 1076, 994, 735 cm^{-1}.

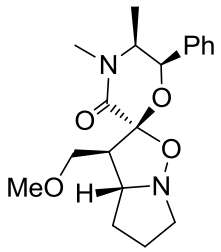
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.29 (m, 5H, Ar*H*), 5.80-5.79 (d, 1H, *J* = 3.1, PhC*H*), 3.82-3.74 (m, 1H, OCH_2), 3.63-3.52 (m, 2H, NC*H* and OCH_2), 3.34-3.27 (br t, 1H, *J* = 10.2, NCH_2), 3.22-3.17 (br d, 1H, *J* = 14, NC*H*), 3.02 (s, 3H, NCH_3), 2.72-2.63 (m, 1H, NCH_2), 2.60-2.55 (br t, 1H, *J* = 7.6, CH_2C*H*), 1.98-1.95 (br m, 2H, CH_2CH_2), 1.75-1.63 (m, 2H, CH_2CH_2), 1.59-1.48 (m, 5H, CH_2CH_2), 1.38-1.26 (m, 3H, CH_2CH_2), 0.93 (d, 3H, *J*= 6.6, CHCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8 (*C*=O), 138.6 (ArC_{ipso}), 128.3 (2 x Ar*C*H), 127.4 (Ar*C*H), 125.7 (2 x Ar*C*H), 101.8 (O*C*O), 69.5 (Ph*C*H), 61.3 (O*C*H_2), 59.2 (N*C*H), 58.6 (N*C*H_2), 45.56 (N*C*H_2), 44.1 (CH*C*H), 33.9 (N*C*H_3), 31.9 (CH_2*C*H_2), 31.2 (CH_2*C*H_2), 27.3 (CH_2*C*H_2), 24.86 (CH_2*C*H_2), 24.74 (CH_2*C*H_2), 12.8 (CH*C*H_3).

MS (APCI, pos.): *m/z* 377.1 $(M+H)^+$.

HRMS (CI): *m/z* 376.2366 (376.2362 calc. for $C_{21}H_{32}N_2O_4$ (M^+)).

(3'*S*,3a'*R*,5*S*,6*R*)-3'-(Methoxymethyl)-4,5-dimethyl-6-phenyltetrahydro-3'H-spiro[morpholine-2,2'-pyrrolo[1,2-b]isoxazol]-3-one (59):



A solution of **58** (0.15 g, 0.57 mmol) and the nitrone **12** (0.097 g, 1.14 mmol) in toluene (4 mL) was subjected to microwave irradiation in a sealed microwave reaction vessel for 30 min at 110°C. The mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 1:1) to afford 0.141 g (71%) of the spiroisoxazolidine **59** as a colorless foam.

IR (neat): 2930, 1720, 1658, 1449, 1246, 1196, 1144, 1105, 1006 cm^{-1}.

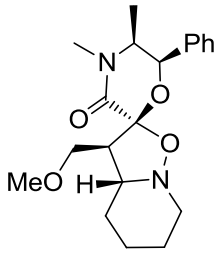
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.33 (m, 2H, Ar*H*), 7.31-7.27 (m, 3H, Ar*H*), 5.57-5.56 (d, 1H, *J* = 3.0, PhC*H*), 3.82-3.79 (t, 1H, *J* = 9, OCH_2), 3.68-3.64 (m, 1H, NC*H*), 3.59-3.56 (dd, 1H, *J* = 6.6, 9.3, OCH_2), 3.47 (dq, 1H, *J* = 3.0, 6.5, NC*H*CH_3), 3.40-3.37 (m, 2H, NCH_2), 3.35 (s, 3H, OCH_3), 3.08-3.05 (m, 1H, CH_2C*H*), 3.05, (s, 3H, NCH_3), 2.14-2.05 (m, 1H, CH_2CH_2), 1.95-1.91 (m, 2H, CH_2CH_2), 1.79-1.72 (m, 1H, CH_2CH_2), 0.95 (d, 3H, *J* = 6.5, CHCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 163.9 (*C*=O), 137.6 (ArC_{ipso}), 128.2 (2 x Ar*C*), 127.5 (Ar*C*), 125.7 (2 x Ar*C*), 104.4 (*C*-C=O), 71.4 (Ph*C*H), 70.4 (OCH_2), 67.6 (OCH_3), 58.96 (N*C*H), 58.85 (O*C*H_3), 57.0 (N*C*H_2), 55.7 (CH*C*H), 34.2 (N*C*H_3), 29.9 (CH_2*C*H_2), 23.0 (CH_2*C*H_2), 12.2 (CH*C*H_3).

MS (APCI, pos.): *m/z* 347.1 $(M+H)^+$.

HRMS (EI): *m/z* 346.1890 (346.1893 calc. for $C_{19}H_{26}N_2O_4$ (M^+)).

(2*R*,3*S*,3a*S*,5'*S*,6'*R*)-3-(Methoxymethyl)-4',5'-dimethyl-6'-phenylhexahydrospiro[isoxazolo[2,3-a]pyridine-2,2'-morpholin]-3'-one (60):



A solution of **58** (1.90 g, 7.27 mmol) and nitrone **5** (1.45 g, 14.6 mmol) in toluene (8 mL) was subjected to microwave irradiation in a sealed microwave reaction vessel 30 min at 110°C. The mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 1:1) to afford 1.59 g (61%) of the spiroisoxazolidine **60** as a pale yellow foam.

IR (neat): 2933, 1658, 1489, 1143, 1100, 990 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 7.45-7.25 (m, 5H, Ar*H*), 5.53 (br s, 1H, PhC*H*), 3.81-3.75 (m, 1H, NC*H*), 3.70-3.43 (m, 2H, OCH_2), 3.47 (dq, 1H, *J* = 3.0, 6.6, NC*H*CH_3), 3.34 (s, 3H, OCH_3), 3.34-3.13 (m, 2H, NCH_2), 3.05, (s, 3H, NCH_3), 2.00-1.90 (br m, 2H, CH_2), 1.80-1.65 (br m, 2H, CH_2), 1.55-1.40 (br m, 2H, CH_2), 0.95 (d, 3H, *J* = 6.6, CHCH_3).

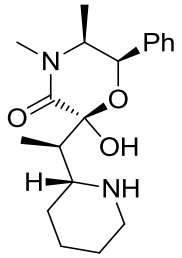
^{13}C NMR (125 MHz, $CDCl_3$): δ 165.4 (*C*O), 137.7 (ArC_{ipso}), 128.3 (2 x Ar*C*H), 127.5 (Ar*C*H), 125.6 (2 x Ar*C*H), 104.6 (O*C*O), 71.4 (Ph-*C*H), 69.7 (O*C*H_2), 61.4 (O*C*H_2), 58.9,

58.7 (N*C*HCH$_3$, N*C*HCH$_2$), 52.5 (N*C*H$_2$), 48.1 (*C*HCH$_2$OCH$_3$), 34.1 (N*C*H$_3$), 24.8 (*C*H$_2$), 24.5 (*C*H$_2$), 18.9 (*C*H$_2$), 12.2 (CH*C*H$_3$).

MS (APCI, pos.): *m/z* 361.2 $(M+H)^+$.

HRMS (CI): *m/z* 360.2058 (360.2049 calc. for $C_{20}H_{29}N_2O_4$ $(M+H)^+$).

(5*S*,6*R*)-2-Hydroxy-4,5-dimethyl-6-phenyl-2-(1-(piperidin-2-yl)ethyl)morpholin-3-one (57):



To a stirred solution of cycloadduct **52** (0.10 g, 0.03 mmol) in acetic acid (3 mL) was added activated zinc powder (0.198 g, 0.302 mmol) in two portions at ambient temperature. The mixture was stirred vigorously at ambient temperature for 5 h (monitored by TLC), CH_2Cl_2 (15 mL) was added and the mixture was filtered. The solvent was removed under reduced pressure and the mixture was basified (pH=12) with NaOH solution (10%). The basic mixture was extracted with CH_2Cl_2 (3 x 20 mL) and the combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to provide 0.06 g (60%) of the amino alcohol **53** as a white foam.

IR (neat): 3440, 1641, 1445, 1387, 1169, 1097, 893, 750 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39-7.27 (m, 5H, Ar*H*), 5.69-5.68 (d, 1H, *J* = 3.1, PhC*H*), 3.50-3.44 (dq, 1H, *J* = 3.6, 6.9, NC*H*CH$_3$), 3.11-3.06 (dt, 1H, *J* = 2.6, 10.7, NC*H*), 3.01-2.99 (s overlapped with m, 4H, NC*H*$_3$ and NC*H*$_2$), 2.61-2.55 (dt, 1H, *J* = 2.6, 11.8, NC*H*$_2$),

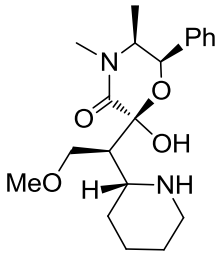
2.40-2.34 (m, 1H, CH_3CH), 1.91-1.84 (m, 2H, CH_2), 1.63-1.54 (m, 2H, CH_2), 1.34-1.24 (m, 2H, CH_2), 1.13-1.05 (m, 2H, CH_2), 0.90 (d, 3H, *J*= 6.4, $CHCH_3$), 0.88 (d, 3H, *J*= 6.9, $CHCH_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8 (*C*=O), 138.8 (ArC_{ipso}), 128.2 (2 x Ar*C*), 127.3 (Ar*C*), 125.8 (2 x Ar*C*), 101.1 (O*C*O), 69.8 (Ph*C*H), 59.1 (N*C*H*C*H_3), 57.8 (ring N*C*H), 45.4 (N*C*H_2), 41.9 (*C*HCH_3), 33.6 (N*C*H_3), 31.0 (*C*H_2), 26.9 (*C*H_2), 24.3 (*C*H_2), 13.4 ($CH*C*H_3$), 12.8 ($CH*C*H_3$).

MS (APCI, pos.): *m/z* 333.3 $(M+H)^+$.

HRMS (CI): *m/z* 333.2183 (333.2178 calc. for $C_{19}H_{29}N_2O_3$ $(M+H)^+$).

(5*S*,6*R*)-2-Hydroxy-2-(2-methoxy-1-(piperidin-2-yl)ethyl)-4,5-dimethyl-6-phenylmorpholin-3-one (61):



To a stirred solution of cycloadduct **60** (1.75 g, 4.85 mmol) in acetic acid (10 mL) was added activated zinc powder (3.176 g, 48.57 mmol) in two portions at ambient temperature. The mixture was stirred vigorously at ambient temperature for 5 h (monitored by TLC), CH_2Cl_2 (15 mL) was added and the mixture was filtered. The solvent was removed under reduced pressure and the mixture was basified (pH=12) with NaOH solution (10%). The basic mixture was extracted with CH_2Cl_2 (3 x 20 mL) and the combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to

provide 1.62 g (92%) of the amino alcohol **61** as a white foam. This was pure by ^{1}H NMR and was used further without purification.

IR (neat): 3429, 1654, 1447, 1398, 1117, 1067, 999, 760 cm^{-1}.

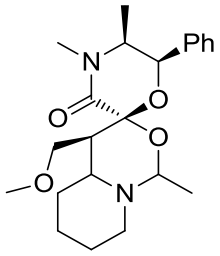
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39-7.26 (m, 5H, Ar*H*), 5.70 (d, 1H, *J* = 3.2, PhC*H*), 3.50-3.44 (dq, 1H, *J* = 3.2, 6.6, C*H*CH_3), 3.39-3.31 (ABM system, 2H, *J* = 10.4, 6.4, OC*H*$_2$), 3.26-3.22 (s overlapped with m, 4H, OC*H*$_3$ and NC*H*CH_2), 3.04-3.01 (s overlapped with m, 4H, NC*H*$_3$ and C*H*CH_2), 2.66-2.57 (m, 2H, NC*H*$_2$), 1.93-1.83 (m, 2H, C*H*$_2$), 1.63-1.52 (m, 2H, C*H*$_2$), 1.38-1.26 (m, 2H, C*H*$_2$), 0.90 (d, 3H, *J*= 6.6, CHC*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.0 (*C*=O), 139.0 (Ar*C*$_{ipso}$), 128.2 (2 x Ar*C*), 127.3 (Ar*C*), 125.8 (2 x Ar*C*), 99.5 (O*C*O), 71.1 (O*C*H_2), 69.9 (Ph*C*H), 59.0 (O*C*H_3), 58.5 (N*C*HCH_3), 56.7 (*C*HCH_2OCH_3), 46.1 (N*C*HCH_2), 45.4 (N*C*H_2), 33.8 (N*C*H_3), 31.0 (*C*H_2), 26.9 (*C*H_2), 24.3 (*C*H_2), 12.4 (CH*C*H_3).

MS (APCI, pos.): *m/z* 363.1 $(M+H)^+$.

HRMS (CI): *m/z* 363.2293 (363.2284 calc. for $C_{20}H_{31}N_2O_4$ $(M+H)^+$).

(5*S*,6*R*)-4'-(Methoxymethyl)-1',4,5-trimethyl-6-phenylhexahydro-1'H-spiro[morpholine-2,3'-pyrido[1,2-c][1,3]oxazin]-3-one (68):



To a solution of **61** (0.363 g, 1.002 mmol) in MeOH (2 mL) was added acetaldehyde (0.17 mL, 3.01 mmol). The reaction mixture was stirred at ambient temperature for 12 h

and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$, 6:94) to afford 232 mg (60%) of **68** as a colorless foam.

IR (neat): 1649, 1559, 1495, 1394, 1243, 1146, 1075, 1004, 740 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.42-7.31 (m, 5H, Ar*H*), 5.52 (d, 1H, *J* = 3.1, PhC*H*), 4.52-4.51 (m, 1H, OC*H*N), 3.50 (dq, 1H, *J* = 3.4, 6.6, NC*H*), 3.42 (dd, 1H, *J* = 10.1, 17.4, OCH_2), 3.38 (dd, 1H, *J* = 10.1, 15.5, OCH_2), 3.25-3.19 (s overlapped with m, 4H, OCH_3 and NC*H*), 3.02-2.97 (s overlapped with m, 5H, NCH_3 and NCH_2), 2.39 (br m, 1H, CH_2C*H*), 1.76-1.69 (m, 2H, CH_2), 1.91-1.84 (m, 2H, CH_2), 1.67-1.61 (m, 2H, CH_2), 1.56-1.50 (m, 1H, CH_2), 1.45-1.37 (m, 1H, CH_2), 1.24 (d, 3H, *J* = 5.8, CH_3), 0.92 (d, 3H, *J* = 6.6, CHCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.7 (*C*=O), 137.9 (ArC_{ipso}), 128.5 (2 x Ar*C*), 127.6 (Ar*C*), 125.5 (2 x Ar*C*), 98.35 (O*C*O), 82.5 (O*C*HN), 71.0 (O*C*H_2), 69.5 (Ph*C*H), 58.81 (N*C*HCH_3), 58.67 (N*C*HCH), 56.62 (*C*H), 33.9 (N*C*H_3), 28.3 (*C*H_2), 25.3 (*C*H_2), 21 (*C*H_2), 19 (CH*C*H_3), 12 (CH*C*H_3).

MS (APCI, pos.): *m/z* 389.2 $(M+H)^+$.

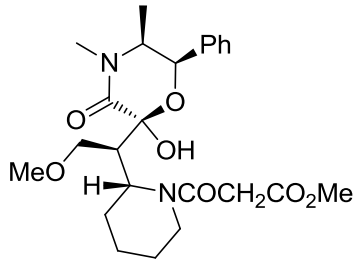
HRMS (CI): *m/z* 389.2426 (389.2440 calc. for $C_{22}H_{33}N_2O_4$ $(M+H)^+$).

Acylation of amino alcohol 61:

To a cooled (0 °C) solution of **61** (1.34 g, 3.69 mmol) in CH_2Cl_2 (10 mL) was added an aqueous solution of K_2CO_3 (30%, 6.81 mL, 14.8 mmol) followed by addition of methyl malonyl chloride (1.19 mL, 11.1 mmol). The mixture was stirred for 3 h at room temperature and the biphase was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated under

reduced pressure to a pale yellow foam. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 98:2) to provide 360 mg (21%) of **72** as a colorless foam and 980 mg (47%) of **73** as a colorless foam.

Methyl-3-((*S*)-2-((*S*)-1-((2*S*,5*S*,6*R*)-2-hydroxy-4,5-dimethyl-3-oxo-6-phenylmorpholin-2-yl)-2-methoxyethyl)piperidin-1-yl)-3-oxopropanoate (72):



IR: 3404, 1736, 1642, 1445, 1249, 1009, 759 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): major diastereomer: δ 7.38-7.34 (m, 2H, Ar*H*), 7.34-7.26 (m, 3H, Ar*H*), 7.06 (s, 1H, O*H*), 5.69 (d, 1H, *J* = 3.2, PhC*H*), 4.91 (br m, 1H, NC*H*CH_2), 3.72 (s, 3H, CO_2CH_3), 3.62-3.35 (m, 6H, NC*H*CH_3, OCH_2, NC*H*CH_2, NCH_2,), 3.35-3.25 (m, 3H, OCH_3, C(O)$CH_2CO_2CH_3$), 3.02 (s, 4H, NCH_3), 2.90-2.85 (m, 1H, C*H*CH_2O), 2.05-1.95 (m, 1H, ring CH_2), 1.90-1.75 (m, 2H, ring CH_2), 1.75-1.65 (m, 2H, ring CH_2), 1.60-1.50 (m, 1H, ring CH_2), 0.90 (d, 3H, CHCH_3); visible resonances for the minor diastereomer: d 5.63 (br s, PhC*H*), 3.02 (m, 2H), 0.81 (br d, CHCH_3).

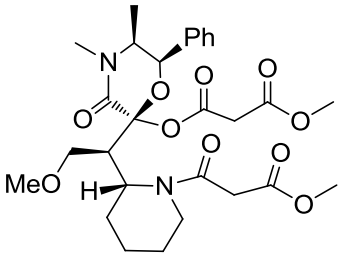
^{13}C NMR (125 MHz, $CDCl_3$): δ 167.9 (N-*C*(O)$CH_2CO_2CH_2$), 167.3 (*C*O2CH_3), 137.9 (ArC_{ipso}), 128.3 (2 x Ar*C*), 127.4 (Ar*C*), 125.6 (2 x Ar*C*), 98.2 (O*C*O), 70.4 (OCH_2), 70.2 (Ph*C*H), 58.9 (CH_2OCH_3), 58.2 (N*C*HCH_3), 52.5 (CO_2CH_3), 49.5 (*C*HCH_2OCH_3), 48.6

(N*C*HCH$_2$), 42.0 (C(O)*C*H$_2$C(O), or N*C*H$_2$), 41.4 (C(O)*C*H$_2$C(O), or N*C*H$_2$), 33.8 (N*C*H$_3$), 25.1 (ring *C*H$_2$), 24.5 (ring *C*H$_2$), 19.2 (ring *C*H$_2$), 12.7 (CH*C*H$_3$).

MS (ESI, neg.): *m/z* 461.2 $(M-H)^-$.

HRMS (CI, pos.): *m/z* 462.2386 (462.2366 calc. for $C_{24}H_{32}N_2O_7$ (M^+)).

(2*R*,5*S*,6*R*)-2-((*S*)-2-Methoxy-1-((*S*)-1-(3-methoxy-3-oxopropanoyl)piperidin-2-yl)ethyl)-4,5-dimethyl-3-oxo-6-phenylmorpholin-2-yl methyl malonate (73):



IR (neat): 2941, 1738, 1664, 1634, 1442, 1151, 1111, 1016, 963 cm^{-1}.

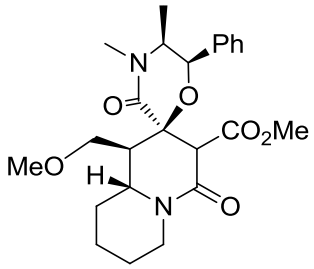
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.27 (m, 5H, Ar*H*), 5.83 (br s, 1H, PhC*H*), 4.68-4.56 (m, 1H, NC*H*CH$_2$), 3.68 (s, 3H, CO$_2$C*H*$_3$), 3.51 (s, 3H, CO$_2$C*H*$_3$), 3.25 (s, 3H, NC*H*$_3$), 3.09 (s, 3H, CH$_2$OC*H*$_3$), 3.75-3.10 (br m, 9H, 2 x C*H*$_2$CO$_2$CH$_3$, NC*H*CH$_3$, OC*H*$_2$, NC*H*$_2$), 2.75 (apparent br t, 1H, *J* =12.7, C*H*CH$_2$O), 1.91 (apparent br d, 1H, *J* = 12.4, ring C*H*$_2$), 1.75-1.45 (br m, 5H, ring C*H*$_2$), 1.00 (d, 3H, *J* = 6.3, CHC*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.7 (N-*C*(O)CH$_2$C(O)), 166.5 (*C*O$_2$CH$_3$), 166.4 (*C*O$_2$CH$_3$), 165.2 (O-*C*(O)CH$_2$C(O)), 163.3 (CH$_3$N*C*(O)), 136.5(Ar*C*$_{ipso}$), 128.4 (2 x Ar*C*), 128.2 (Ar*C*), 125.9 (Ar*C*), 102.3 (O*C*O), 74.0 (PhCH), 69.5 (O*C*H2), 58.9 (CH$_2$O*C*H$_3$), 58.7 (N*C*HCH$_3$), 52.4 (O*C*H$_3$), 51.9 (O*C*H$_3$), 51.1 (*C*HCH$_2$), 42.7 (NCHCH$_2$), 41.2 (C(O)*C*H$_2$C(O)N), 40.5 (C(O)*C*H$_2$C(O), 36.9 (N*C*H$_2$), 33.9 (N*C*H$_3$), 28.4 (ring *C*H$_2$), 25.3 (ring *C*H$_2$), 19.9 (ring *C*H$_2$), 12.4 (CH*C*H$_3$).

MS (APCI, pos.): *m/z* 563.3 $(M+H)^+$.

HRMS (EI): 563.2605 *m/z* (563.2605 calc. for $C_{28}H_{39}N_2O_{10}$ $(M+H)^+$).

(1'*S*,5*S*,6*R*,9a'*S*)-Methyl-1'-(methoxymethyl)-4,5-dimethyl-3,4'-dioxo-6-phenyloctahydrospiro- [morpholine-2,2'-quinolizine]-3'-carboxylate (74):



To a solution of **73** (700 mg, 1.25 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added BF_3•OEt_2 (1.53 mL, 12.5 mmol). The mixture was warmed to room temperature and stirred for 12 h. Water (2 mL) was added, the biphase separated, the aqueous layer extracted with CH_2Cl_2 (3 x 5 mL) and combined organic layer dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 98:2) to give provide 236 mg (46%) of **74** as a white foam.

IR (neat): 2937, 1740, 1650, 1574, 1496, 1438, 1367, 1345, 1209, 1152, 1113, 1037 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.47-7.32 (br t, 2H, *J* = 7.2, Ar*H*), 7.30-7.25 (br d, 1H, *J* =7.2, Ar*H*), 7.20-7.18 (br d, 2H, *J* =7.2, Ar*H*), 5.06 (d, 1H, *J* = 3.2, PhC*H*), 4.70 (br d, 1H, *J* = 12.1, CH_2NCO), 3.93 (s, 3H, CO_2CH_3), 3.62-3.55 (dt, 1H, *J* = 2.9, 11.2, NC*H*CH_2), 3.55-3.47 (m, 3H, OCH_2, NC*H*CH_3), 3.27 (s, 3H, OCH_3), 3.07 (s, 3H, NCH_3), 2.75-2.67 (dt, 1H, *J* = 2.6, 12.7, C*H*CH_2O), 2.55-2.50 (m, 1H, CH_2NCO), 2.30 (br m, 1H, *J* = 14.2,

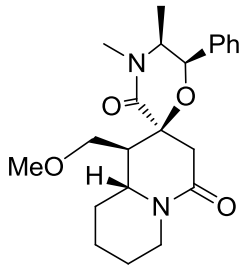
C*H*$_2$), 1.95-1.90 (br m, 1H, ring C*H*$_2$), 1.83-1.75 (br m, 1H, ring *C*H$_2$), 1.55-1.50 (m, 2H, ring *C*H$_2$), 1.39-1.29 (m, 2H, ring *C*H$_2$), 0.93 (d, 3H, *J* = 6.5, CHC*H*$_3$).

^{13}C NMR (125 MHz, CDCl$_3$): δ 168.4 (*C*(O)NCH$_3$), 168.4 (*C*(O)NCH$_2$), 164.5 (*C*O$_2$CH$_3$), 137.9 (Ar*C*$_{ipso}$), 128.3 (2 x Ar*C*), 127.6 (Ar*C*), 125.5 (2 x Ar*C*), 79.5 (O*C*C(O)), 71.8 (O*C*H$_2$), 70.9 (Ph*C*H), 58.6 (CO$_2$*C*H3, *C*HNCH$_3$, *C*H(C=O)$_2$), 55.3, 55.2 (O*C*H$_3$, *C*HNCH$_2$), 46.4 (*C*HCH$_2$O), 44.4 (*C*H$_2$NC(O), 34.1 (N*C*H$_3$), 31.4 (ring *C*H$_2$), 24.6 (ring *C*H$_2$)), 23.2 (ring *C*H$_2$), 13.4 (CH*C*H$_3$).

MS (ESI, pos.): *m/z* 445.3 (M+H)$^+$.

HRMS (EI): *m/z* 444.2255 (444.2260 calc. for $C_{24}H_{32}N_2O_6$ (M^+)).

(1'*S*,5*S*,6*R*,9a'*S*)-1'-(Methoxymethyl)-4,5-dimethyl-6-phenylhexahydrospiro-[morpholine-2,2'-quinolizine]-3,4'-(3'H)-dione (76):



To a solution of **74** (370 mg, 0.83 mmol) in DMSO (3 mL) was added NaCl (53.8 mg, 0.92 mmol) and H$_2$O (60.0 µL, 3.33 mmol). The solution was then heated at 110 °C for 1 h. The DMSO was removed under reduced pressure and water was added to the residue (3 mL). The mixture was extracted with CH$_2$Cl$_2$ (4 x 5 mL) and the combined extracts were washed with water (30mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure to provide 250 mg (78%) of **76** as a pale brown foam. This was pure by ^{1}H NMR

and was used further without purification. An analytical sample (white foam) was obtained by flash chromatography on silica gel (CH_2Cl_2/MeOH, 98:2).

IR: 1636, 1482, 1444, 1266, 1146, 1107, 1022, 754 cm^{-1}.

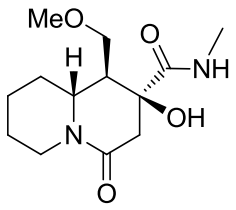
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (t, 2H, *J* = 7.9, Ar*H*), 7.30-7.25 (m, 1H, Ar*H*), 7.22-7.21 (d, 2H, *J* = 7.6, Ar*H*), 5.15 (br d, *J* = 2.8, 1H, PhC*H*), 4.76 (br d, 1H, *J* = 13.2, C*H*$_2$NC(O)), 3.7 (dd, 1H, *J* = 6.7, 10.2, OC*H*$_2$), 3.55-3.50 (m, 1H, NC*H*CH_3), 3.5-3.45 (dd, 1H, *J* = 4.8, 10.2, OC*H*$_2$), 3.29-3.25 (m, 1H, NC*H*CH_2), 3.27 (s, 3H, OC*H*$_3$), 3.02 (s, 3H, NC*H*$_3$), 3.02-2.87 (AB system, 2H, *J* = 17.5, C*H*$_2$C(O)), 2.65-2.57 (m, 1H, OCH_2C*H*), 2.41 (dt, 1H, *J* = 2.4, 12.8, C(O)NC*H*$_2$), 2.15 (br d, 1H, *J* = 11.5, ring C*H*$_2$), 1.90 (br d, 1H, *J* = 12.1, ring C*H*$_2$), 1.70 (br d, 1H, *J* = 11.0, ring C*H*$_2$), 1.55-1.40 (m, 2H, 1.40-1.25 (m, 1H, ring C*H*$_2$), 0.95 (d, 3H, *J* = 6.5, CHC*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.9 (*C*=O), 165.9 (*C*=O), 137.5 (Ar*C*$_{ipso}$), 128.3 (2 x Ar*C*), 127.6 (Ar*C*), 125.4 (2 x Ar*C*), 78.2 (O*C*C(O)), 71.6 (Ph*C*H), 71.5 (O*C*H_2), 58.9 (N*C*H_3), 58.7 (N*C*H), 56.8 (O*C*H_3), 45.4 (OCH_2*C*H), 42.4 (N*C*H_2), 38.4 (*C*H_2C(O), 34.0 (N*C*H_3), 33.3 (ring *C*H_2), 25.1 (ring *C*H_2), 24.5 (ring *C*H_2), 12.6 (CH*C*H_3).

MS (APCI, pos.): *m/z* 387.1 $(M+H)^+$.

HRMS (CI): *m/z* 386.2216 (386.2206 calc. for $C_{22}H_{30}N_2O_4$ (M^+)).

(1*S*,9a*R*)-Octahydro-2-hydroxy-1-(methoxymethyl)-N-methyl-4-oxo-1H-quinolizine-2-carboxamide (77):



To anhydrous liquid ammonia (6 mL, distilled over sodium) was added Na metal (88.3 mg, 3.84 mmol) at -78 °C and the mixture was stirred for 15 min. To the resulting blue solution was added a solution of compound **76** (185 mg, 0.48 mmol) in anhydrous THF (1.5 mL) and the mixture was stirred for 30 min at -78 °C. A mixture of MeOH/H_2O (3/1, 2 mL) was added and the reaction mixture was brought to ambient temperature and stirred for 30 min to remove ammonia. The resulting solution was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 96:4) to provide 100 mg, (77%) of **77** as a white solid.

IR: 3439, 3334, 2858, 1641, 1526, 1450, 1407, 1246, 1112, 1077, 1021, 971, 906 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16 (br s, 1H, NH), 4.85 (br m, 1H, NC*H*$_2$), 4.58 (d, 1H, *J* = 2.2, O*H*), 3.67-3.62 (ABM system, 2H, OC*H*$_2$), 3.48 (dt, 1H, *J* =2.5, 11, NC*H*), 3.34 (s, 3H, OC*H*$_3$), 2.89 (d, 3H, *J* = 5.0, NC*H*$_3$), 2.77 (br dd, 1H, *J* = 2.2, 16.9, C(O)C*H*$_2$), 2.46 (br dt, 1H, *J* = 3, 13, C*H*CH_2O), 2.43 (d, 1H, *J* = 16.9, C(O)C*H*$_2$), 2.30 (br d, 1H, *J*= 10.6, NC*H*$_2$), 2.06-2.0 (br m, 1H, ring C*H*$_2$), 1.93-1.90 (br m, 1H, ring C*H*$_2$), 1.78-1.75 (br m, 1H, ring C*H*$_2$), 1.52-1.40 (br m, 2H, ring C*H*$_2$), 1.30-1.20 (br m, 1H, ring C*H*$_2$).

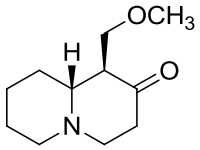
^{13}C NMR (125 MHz, $CDCl_3$): δ 174.5 (*C*=O), 166.4 (*C*=O), 76.8 (*C*-OH), 70.8 (O*C*H_2), 59.6 (N*C*H), 53.9 (O*C*H_3), 43.3 (N*C*H_3), 42.4 (N*C*H_2 or C(O)*C*H_2), 42.3 (N*C*H_2 or C(O)*C*H_2), 32.1 (*C*H_2), 26.1 (*C*HCH_2O), 25.1 (ring *C*H_2), 24.2 (ring *C*H_2).

MS (APCI, pos.): *m/z* 271.1 $(M+H)^+$.

HRMS (CI): *m/z* 270.1590 (270.1580 calc. for $C_{13}H_{22}N_2O_4$ (M^+)).

$[\alpha]_D^{20}$ = −10.3 (c 1, CH_2Cl_2).

(1*S*,9a*R*)-Hexahydro-1-(methoxymethyl)-1H-quinolizin-2(6H)-one (79):



To a stirred solution of the hydroxy amide **77** (136 mg, 0.51 mmol) in 1,2-dimethoxyethane (3 mL) at 0 ºC was slowly added lithium aluminum hydride (191 mg, 5.1 mmol) in small portions. The mixture was then brought to room temperature and heated to reflux for 72 h. The reaction mixture was then cooled to 0 °C and water (0.1 mL), NaOH (2.2 mL, 2.5 M soln.) and water (0.3 mL) were added sequentially at 5 min intervals. The resulting mixture was filtered and the solid residue was washed with CH_2Cl_2 (30 mL). The combined filtrates were dried (Na_2SO_4) and concentrated under reduced pressure to provide 70 mg (57%) of (1*S*,9a*R*)-octahydro-1-(methoxymethyl)-2-((methylamino)methyl)-1H-quinolizin-2-ol (**78**). This was used further without purification.

IR (neat): 3443, 1448, 1105, 734, 695 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.70-3.65 (ABM system, 2H, OC*H*$_2$), 3.31 (s, 3H, OC*H*$_3$), 3.30-3.28 (m, 1H, NC*H*), 2.91-2.85 (m, 1H, NC*H*$_2$), 2.70 (d, 1H, *J* = 11.6, NC*H*$_2$), 2.65-

2.60 (m, 1H, C*H*CH_2O), 2.56 (d, 1H, *J* = 11.6, NC*H*$_2$), 2.46 (s, 3H, NC*H*$_3$), 2.35-2.20 (m, 2H, C*H*$_2$), 2.18-2.09 (m, 1H, C*H*$_2$), 1.90 (br d, 1H, C*H*$_2$), 1.80 (br d, 1H, C*H*$_2$), 1.68-1.55 (m, 5H, C*H*$_2$), 1.43 (br d, 1H, C*H*$_2$), 1.35-1.25 (m, 2H, C*H*$_2$), 1.18-1.08 (m, 1H, C*H*$_2$), 0.95-0.85 (m, 1H, C*H*$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 71.8 (*C*-OH), 69.8 (O*C*H$_2$), 61.6 (N*C*H$_2$), 59.1 (O*C*H$_3$), 58.4 (N*C*H), 56.7 (N*C*H$_2$), 51.4 (N*C*H$_2$), 47.7 (*C*HCH$_2$), 37.4 (N*C*H$_3$), 35.1 (*C*H$_2$C-OH), 29.8 (*C*H$_2$), 25.6 (*C*H$_2$), 24.6 (*C*H$_2$).

MS (APCI, pos.): *m/z* 243.3 $(M+H)^+$.

HRMS (EI): *m/z* 242.2000 (242.1994 calc. for $C_{13}H_{26}N_2O_2$ (M^+)).

$[\alpha]_D^{20}$ = +6.5 (c 1.6, $CHCl_3$).

To a stirred solution of the amino alcohol **78** (70 mg, 0.29 mmol) in MeOH/H_2O (100/1, 2 mL) at 0 ºC was added $NaIO_4$ (247 mg, 1.16 mmol). The reaction mixture was stirred at 0 ºC for 15 min and then warmed to room temperature and stirred for 30 min. A cold, saturated aqueous solution of sodium bicarbonate was added and the mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/MeOH, 99:1) to provide the ketone **79** (18 mg, 32%) as a yellow liquid.

IR (neat): 2927, 1717, 1454, 1357, 1294, 1154, 1111 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.76-3.71 (dd, 1H, *J* = 2.8, 9.7, OC*H*$_2$), 3.62-3.57 (dd, 1H, *J* = 3.6, 9.7, OC*H*$_2$), 3.32 (s, 3H, OC*H*$_3$), 3.07-2.96 (m, 2H, C*H*CO and NC*H*), 2.73-2.65 (m, 1H, C(O)C*H*$_2$), 2.46-2.38 (m, 2H, NC*H*$_2$ and C*H*$_2$CO), 2.28-1.98 (m, 4H, C*H*$_2$), 1.80-1.62 (m, 3H, C*H*$_2$), 1.36-1.22 (m, 2H, C*H*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.8 (*C*=O),

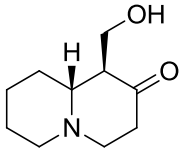
67.1 (O*C*H_2), 63.5 (*C*H-C=O), 59.2 (O*C*H_3), 56.0 (N*C*H_2), 55.4 (N*C*H), 55.2 (N*C*H_2), 41.2 (*C*H_2-C=O), 31.4 (*C*H_2), 25.5 (*C*H_2), 23.5 (*C*H_2).

MS (APCI, pos.): *m/z* 198.1 $(M+H)^+$.

HRMS (CI): *m/z* 197.1418 (197.1416 calc. for $C_{11}H_{19}NO_2$ (M^+)).

$[\alpha]_D^{20}$ = +17.3 (c 2, $CHCl_3$).

(1*S*,9a*R*)-Hexahydro-1-(hydroxymethyl)-1H-quinolizin-2(6H)-one (80):



To a stirred solution of the ketone **79** (21 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) at 0 ºC was added BBr_3 (1.0 M soln. in CH_2Cl_2, 43 μL, 0.43 mmol). The reaction mixture was warmed to room temperature and stirred for 30 min (monitored by TLC). An aqueous solution of ammonia (30%, 3 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/MeOH, 85:15) to provide the hydroxy ketone **80** (6 mg, 31%) as a white solid.

IR (neat): 3169, 1709, 1091 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.97-3.92 (dd, 1H, *J* = 2.8, 11.9, OC*H*$_2$), 3.74-3.68 (dd, 1H, *J* = 5.7, 11.9, OC*H*$_2$), 3.14-3.07 (m, 1H, C*H*C(O)), 3.01-2.97 (br m, 1H, NC*H*), 2.83-2.72 (m, 1H, C*H*$_2$C(O)), 2.47-2.35 (m, 3H, C*H*$_2$C(O) and C*H*$_2$), 2.18-2.07 (m, 2H, C*H*$_2$), 1.99-1.94 (m, 1H, C*H*$_2$), 1.85-1.75 (m, 1H, C*H*$_2$), 1.75-1.55 (m, 2H, C*H*$_2$), 1.42-1.17 (m, 3H, C*H*$_2$).

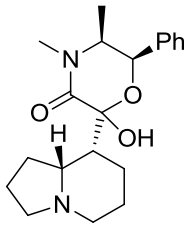
^{13}C NMR (75 MHz, $CDCl_3$): δ 212.1 (*C*=O), 63.1 (O*C*H_2), 58.5 (*C*HC(O) or N*C*H), 56.6 (*C*HC(O) or N*C*H), 55.77 (N*C*H_2), 55.75 (N*C*H_2), 41.7 (C(O)*C*H_2), 31.1 (*C*H_2), 25.3 (*C*H_2), 23.3 (*C*H_2).

MS (APCI, pos.): *m/z* 184.1 $(M+H)^+$.

HRMS (EI): *m/z* 183.1256 (183.1259 calc. for $C_{10}H_{17}NO_2$ (M^+)).

$[\alpha]_D^{20}$ = +16.7 (c 0.6, $CHCl_3$, lit.[29] $[\alpha]_D^{20}$ = +8.8 (c 0.04, $CHCl_3$).

(2*S*,5*S*,6*R*)-2-((8*R*,8a*R*)-Octahydroindolizin-8-yl)-2-hydroxy-4,5-dimethyl-6-phenylmorpholin-3-one (84):



To the solution of the alcohol **53a** (1.52 g, 4.22 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (1.47 mL, 10.5 mmol) followed by MsCl (0.36 mL, 4.64 mmol) at -20 °C. The reaction mixture was stirred at -20 °C for 3 h and water (5 mL) was added. The mixture was warmed to ambient temperature and was extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (2 x 10 mL), water (4 x 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure to provide 1.35 g (73%) of the mesylate **83** as a yellowish foam. Due to its instability, the mesylate **83** was immediately used further without any purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39-7.28 (m, 5H, Ar*H*), 5.64-5.63 (d, 1H, *J* = 3.2, PhC*H*), 4.27 (t, 2H, *J* = 6.0, OC*H*$_2$), 3.66-3.61 (m, 1H, C*H*NO), 3.55-3.47 (dq, 1H, *J* = 6.5, 3.2,

C*H*CH_3), 3.37-3.29 (m, 1H, NC*H*$_2$) 3.09 (m, 1H, NC*H*$_2$), 3.02 (s, 3H, NC*H*$_3$), 3.00 (s, 3H, C*H*$_3SO_2$), 2.11-1.90 (m, 2H, C*H*$_2CH_2$), 1.89-1.69 (m, 7H, C*H*$_2CH_2$), 0.94 (d, 3H, *J* = 6.5, CHC*H*$_3$).

To a stirred solution of the mesylate **83** (1.35 g, 3.08 mmol) in acetic acid (10 mL) was added activated zinc powder (2.02 g, 30.8 mmol) in two portions at ambient temperature. The mixture was stirred at 55 °C for 5 h and then cooled to ambient temperature. CH_2Cl_2 (15 mL) was added and the mixture was filtered. The solvent was removed under reduced pressure and the mixture was basified (pH = 12) with aqueous NaOH solution (10%). The basic mixture was extracted with CH_2Cl_2 (3 x 20 mL) and the combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to provide 1.14 g of crude product as a pale yellow foam. This was purified by extraction into aqueous acid followed by neutralization to the free base and extraction into CH_2Cl_2 to provide 1.0 g (94%) of the amino hemiacetal **84**. This was pure by ^{1}H NMR and was used further without purification.

IR (neat): 3396 (br), 1632, 1470, 1377, 1287, 1168, 1107, 1046 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.29 (m, 5H, Ar*H*), 5.73-5.72 (d, 1H, *J* = 3.2, PhC*H*), 3.55-3.49 (dq, 1H, *J* = 3.2, 6.6, C*H*CH_3), 3.01-2.95 (s superimposed on a m, 5H, NC*H*$_3$ and NC*H*$_2$), 2.76-2.70 (br m, 3H, NC*H*$_2$), 2.39-2.20 (br m, 3H, C*H*$_2$), 2.03-1.92 (m,2H, C*H*$_2$), 1.84-1.81 (m, 2H, C*H*$_2$), 1.71-1.64 (m, 2H, C*H*$_2$), 1.37-1.29 (m, 1H, C*H*$_2$), 0.90 (d, 3H, *J*= 6.6, CHC*H*$_3$).

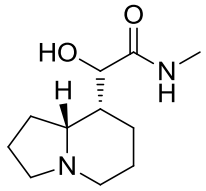
^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1 (*C*=O), 137.4 (Ar*C*$_{ipso}$), 128.3 (2 x Ar*C*), 127.7 (Ar*C*), 125.7 (2 x Ar*C*), 97.6 (O-*C*-OH), 70.9 (Ph*C*H), 65.0 (N*C*H), 59.2 (N*C*H*C*H_3), 53.7 (N*C*H_2),

52.6 (N*C*H_2), 48.6 (CH*C*HCH$_2$), 33.8 (N*C*H_3), 28.9 (*C*H_2), 24.7 (*C*H_2), 23.8 (*C*H_2), 20.6 (*C*H_2), 12.5 (CH*C*H_3).

MS (ESI, pos.): *m/z* 345.2 $(M+H)^+$.

HRMS (CI): *m/z* 345.2188 (345.2178 calc. for $C_{20}H_{29}N_2O_3$ $(M+H)^+$).

(*R*)-2-Hydroxy-*N*-methyl-2-((8*R*,8a*R*)-octahydroindolizin-8-yl)acetamide (86):



To a solution of **84** (1.00 g, 2.90 mmol) in triethylsilane (4.64 mL, 29.0 mmol) was added BF_3•OEt_2 (3.6 mL, 29 mmol) at 0 °C. The mixture was warmed to ambient temperature and stirred vigorously for 72 h. Water (3 mL) was added at 0 °C, the mixture warmed to room temperature and then extracted with CH_2Cl_2 (5 x 20 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/aq. NH_3, 8/2/1) to provide 460 mg (48%) of (2*S*,5*S*,6*R*)-2-((8*R*,8a*R*)-octahydroindolizin-8-yl)-4,5-dimethyl-6-phenylmorpholin-3-one (**84**) as a white foam.

IR (neat): 1644, 1489, 1449, 1377, 1153, 1112, 1075, 1012 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.28 (m, 5H, Ar*H*), 4.99 (d, 1H, *J* = 3.0, PhC*H*), 4.33 (d, 1H, *J* = 3.0, *H*C-C=O), 3.53-3.46 (dq, 1H, *J* = 3.0, 6.5, NC*H*CH_3), 3.03 (s, 3H, NC*H*$_3$), 2.93-2.80 (m, 3H, NC*H* and NC*H*$_2$) 2.64-2.56 (m, 2H, NC*H*$_2$), 2.41-2.35 (m, 1H, CH_2C*H*),

1.99-1.78 (m, 4H, CH_2), 1.75-1.59 (m, 3H, CH_2), 1.49-1.40 (m, 1H, CH_2), 0.95 (d, 3H, *J* = 6.5, CHCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3 (N*C*=O), 138.1 (ArC_{ipso}), 128.3 (2 x Ar*C*), 127.5 (Ar*C*), 125.4 (2 x Ar*C*), 79.7 (H*C*-C=O), 76.6 (Ph*C*H), 64.6 (CON*C*H), 58.7 (N*C*H), 54.4 (N*C*H_2), 49.6 (N*C*H_2), 38.9 (CH_2*C*H), 33.8 (N*C*H_3), 25.1 (*C*H_2), 24.1 (*C*H_2), 21.55 (*C*H_2), 21.46 (*C*H_2), 13.2 (CH*C*H_3).

MS (ESI, pos.): *m/z* 329.2 $(M+H)^+$.

HRMS (TOF, EI+): *m/z* 328.2142 (328.2151 calc. for $C_{20}H_{28}N_2O_2$ (M^+)).

HRMS (TOF, CI+): *m/z* 329.2234 (329.2229 calc. for $C_{20}H_{29}N_2O_2$ $(M+H)^+$).

$[\alpha]_D^{20}$ = −176.3 (c 1, $CHCl_3$).

To anhydrous liquid ammonia (6 mL, distilled over sodium) was added sodium metal (193 mg, 8.40 mmol) at -78 °C and the mixture was stirred for 15 min. To the resulting blue solution was added a solution of **85** (460 mg, 1.40 mmol) in anhydrous THF (1.5 mL) and the mixture was stirred for 3 hr at -78 °C. A mixture of MeOH/H_2O (3:1, 2 mL) was added and the reaction mixture was brought to ambient temperature and stirred for 30 min to remove ammonia. The resulting solution was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/NH_3, 96:4:1) to provide 210 mg (71%) of **86** as a white solid.

IR: 3358, 3151, 2927, 2868, 1645, 1528, 1458, 1396, 1335, 1248, 1150, 1087, 1016 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.07 (br s, 1H, CON*H*), 4.60 (br d, 1H, *J* = 3.4, C*H*OH), 3.15-3.12 (br dd, 1H, *J* = 4.5, 10.7, NCH_2), 3.08-3.04 (m, 1H, NC*H*), 2.88-2.87(d, 3H, *J* = 5.0, NCH_3), 2.41-2.37 (m, 1H, C*H*CH_2), 2.31 (br m, 1H, NCH_2), 2.06-2.00 (m, 2H,

C*H*$_2$CH$_2$), 1.98-1.91 (m, 1H, C*H*$_2$CH$_2$), 1.90-1.85 (m, 2H, C*H*$_2$CH$_2$), 1.83-1.78 (m, 3H, C*H*$_2$CH$_2$), 1.69-1.62 (m, 1H, C*H*$_2$CH$_2$), 1.57-1.53 (br m, 1H, C*H*$_2$CH$_2$), 1.40-1.33 (m, 1H, C*H*$_2$CH$_2$).

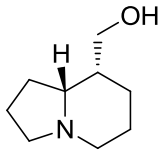
^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5 (*C*=O), 74.2 (*C*H-OH), 67.3 (N*C*H), 54.1 (N*C*H$_2$), 53.5 (N*C*H$_2$), 35.2 (N*C*H$_3$), 26.2 (*C*H$_2$CH$_2$), 25.5 (*C*H$_2$CH$_2$ and *C*HCH$_2$), 23.2 (*C*H$_2$), 20.9 (*C*H$_2$).

MS (APCI, pos.): *m/z* 213.1 $(M+H)^+$.

HRMS (TOF, CI+): *m/z* 213.1606 (213.1603 calc. for $C_{11}H_{21}N_2O_2$ $(M+H)^+$).

$[\alpha]_D^{20} = -51.8$ (c 1, $CHCl_3$).

((8*R*,8a*R*)-Octahydroindolizin-8-yl)-methanol (2):



To a stirred solution of the hydroxy amide **86** (135 mg, 0.64 mmol) in 1,2-dimethoxyethane (3 mL) at 0 ºC was slowly added lithium aluminum hydride (242 mg, 6.40 mmol) in small portions. The mixture was then brought to room temperature and heated to reflux for 30 h. The reaction mixture was then cooled to 0 °C and water (0.12 mL), NaOH (2.55 mL, 2.5 M soln.) and water (0.36 mL) were added sequentially at 5 min intervals. The resulting mixture was filtered and the solid residue was washed with CH_2Cl_2 (30 mL). The combined filtrates were dried (Na_2SO_4) and concentrated under reduced pressure to provide 88 mg (70%) of the amino alcohol **87**. This was used further without purification.

To a stirred solution of the above amino alcohol **87** (88 mg, 0.44 mmol) in MeOH/H_2O (100/1, 2 mL) at 0 °C was added $NaIO_4$ (380 mg, 1.76 mmol). The mixture was stirred at 0 ºC for 15 min and then warmed to room temperature and stirred for 30 min. The solution was then cooled to 0 °C and $NaBH_4$ (42.0 mg, 1.11 mmol) was added. The mixture was stirred at ambient temperature for 1.5 h. Water (2 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/NH_3, 80:20:1) to provide 35 mg (36% from **86**) of (+)-epitashiromine (**2**) as a colorless liquid.

IR: 3175, 3071, 1659, 1278, 1038 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.17 (dd, 1H, *J* = 10.7, 3.3, C*H*$_2$OH), 3.74 (br d, 1H, *J* = 10.7, C*H*$_2$OH), 3.12 (m, 1H, NC*H*), 2.96 (m, 1H, NC*H*$_2$), 2.35-2.25 (br m, 1H, NC*H*$_2$), 2.18-2.00 (m, 2H, NC*H*$_2$), 2.00-1.75 (m, 6H, C*H*$_2$), 1.75-1.50 (m, 2H, C*H*$_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 66.8 (O*C*H$_2$), 65.6 (N*C*H), 54.5 (N*C*H$_2$), 53.6 (N*C*H$_2$), 35.3 (*C*H$_2$), 30.3 (*C*H$_2$), 25.9 (*C*H$_2$), 23.3 (*C*H$_2$), 20.7 (*C*H$_2$).

MS (APCI, pos.): *m/z* 156.1 $(M+H)^+$.

2 is reported to have a very low specific rotation (~1^o) which is also known to change with sample history. Hence, the specific rotation of **2**.HCl was measured, $[\alpha]_D^{20}$ = +26.0 (c 0.5, EtOH); lit.[13b] $[\alpha]_D^{20}$ = +29.1 (c 0.45, EtOH).

2.7 References

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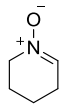
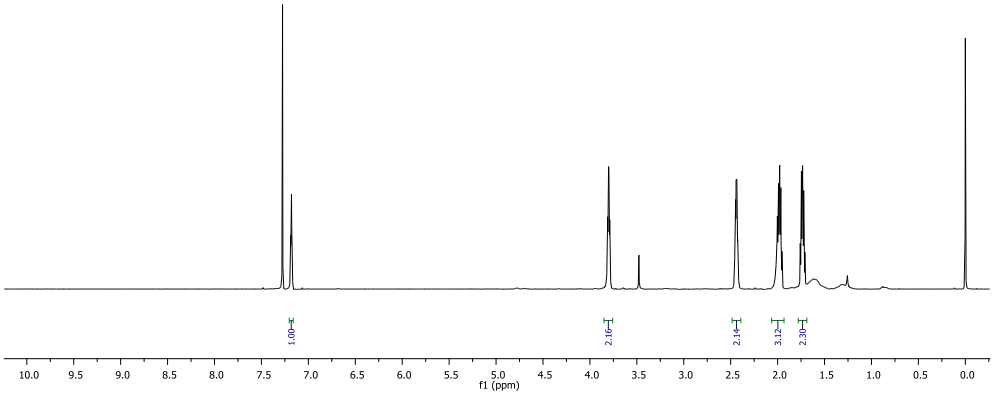
2.8 Selected ^{1}H NMR and ^{13}C NMR Spectra

RT 3335A
RGT-I-78C

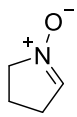


5

$CDCl_3$, 500 MHz

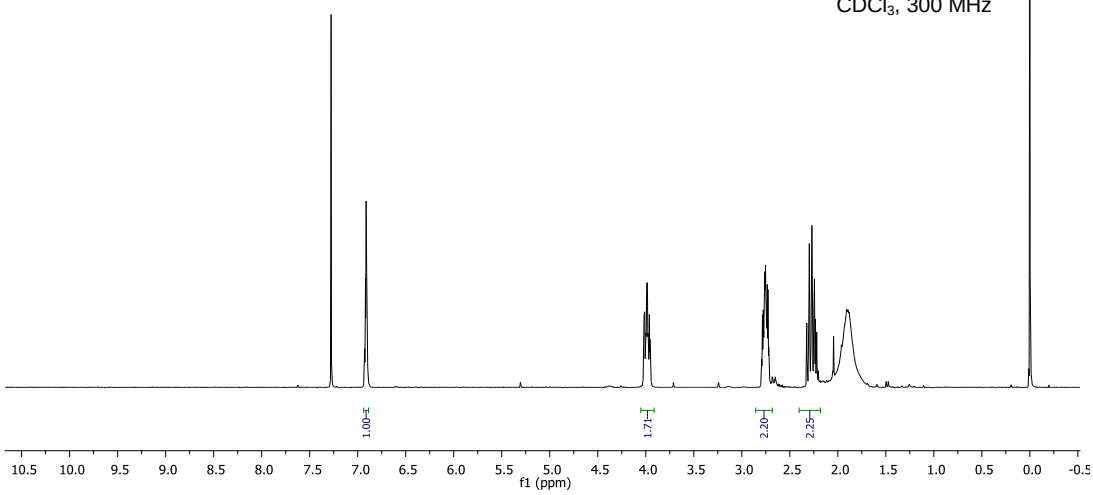


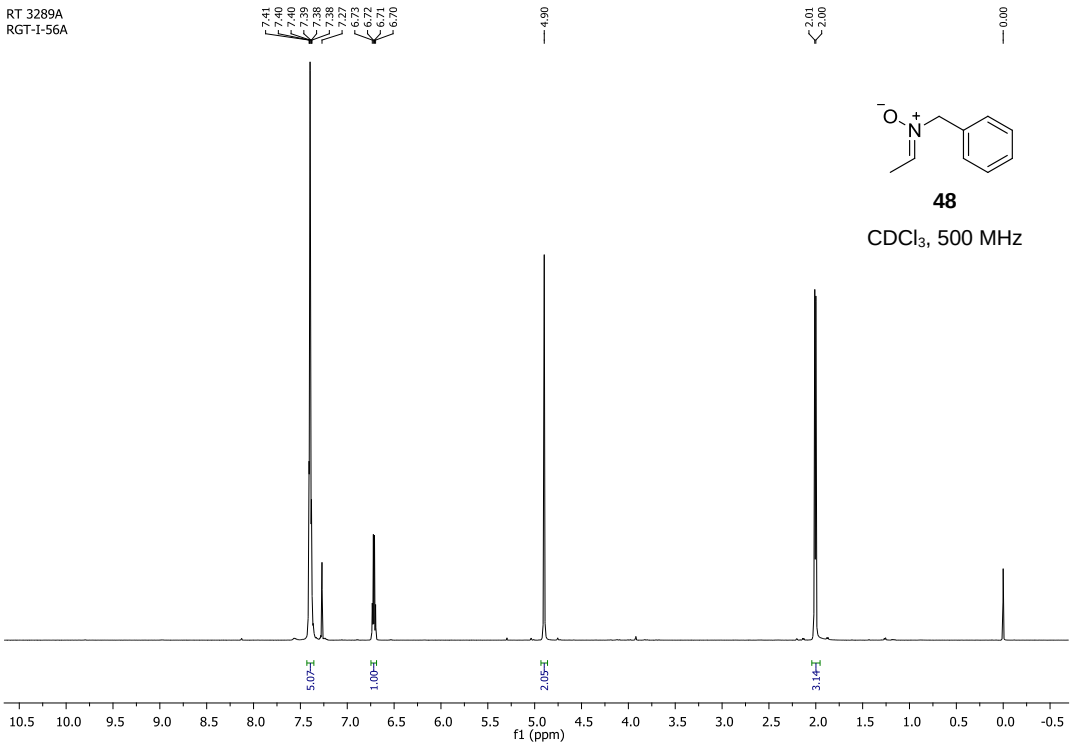
RGT-VI-2.5GM NITRONE
PYRROLIDINE NITRONE



12

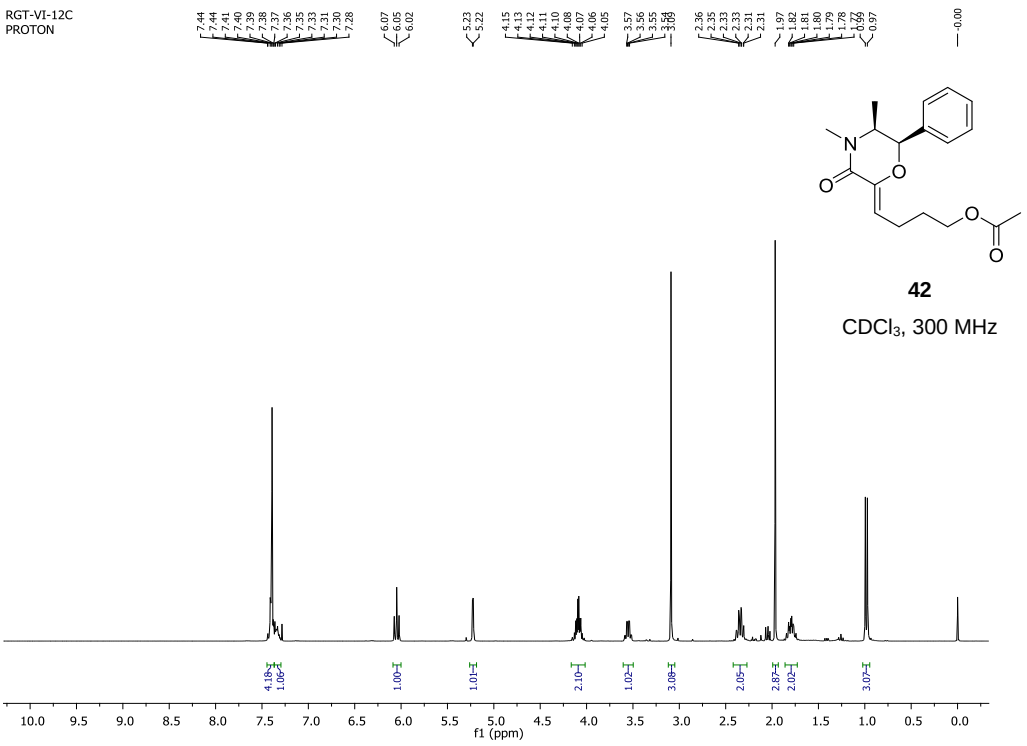
$CDCl_3$, 300 MHz





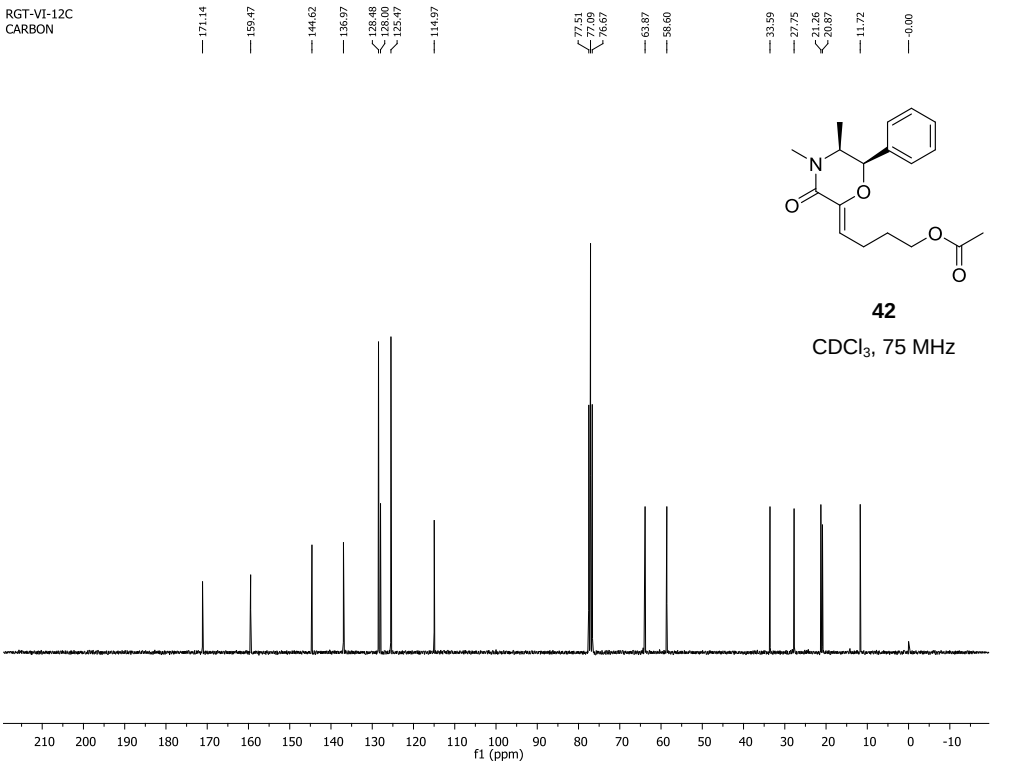
48

$CDCl_3$, 500 MHz



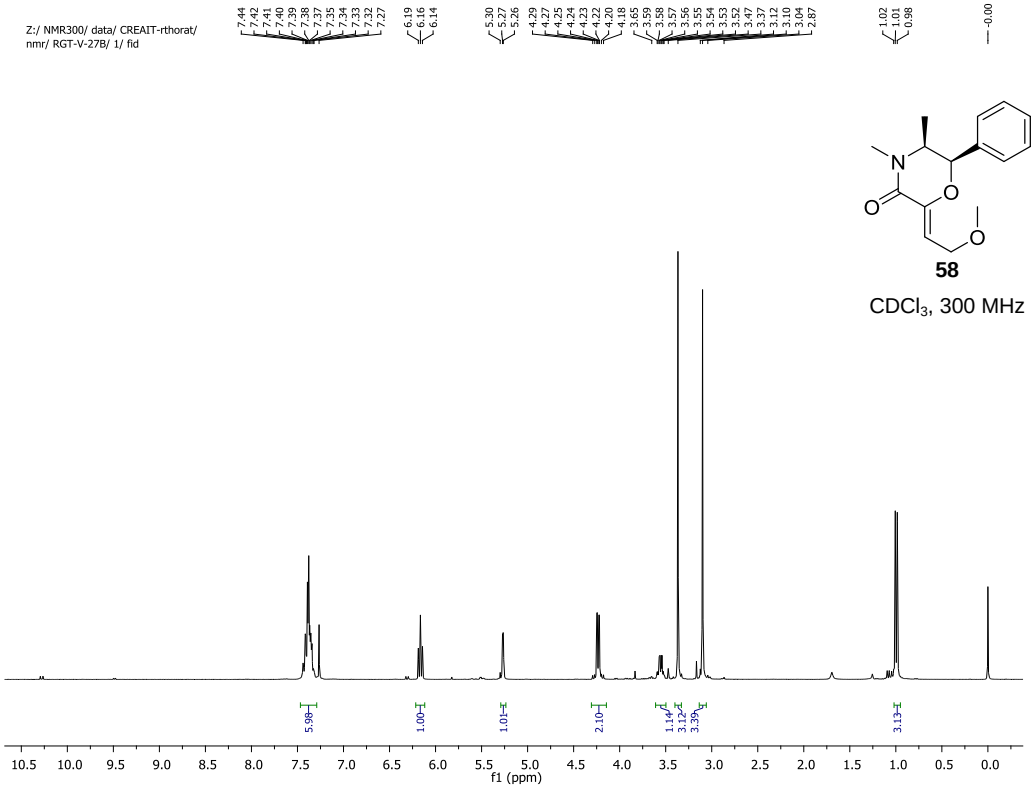
42

$CDCl_3$, 300 MHz



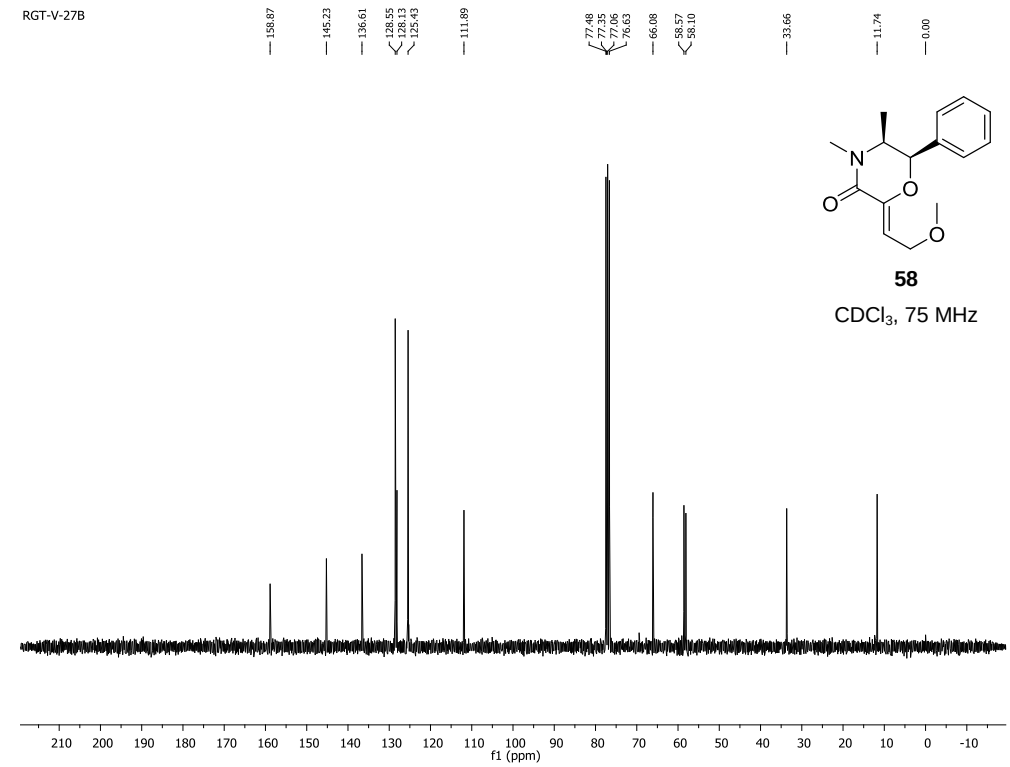
42

$CDCl_3$, 75 MHz



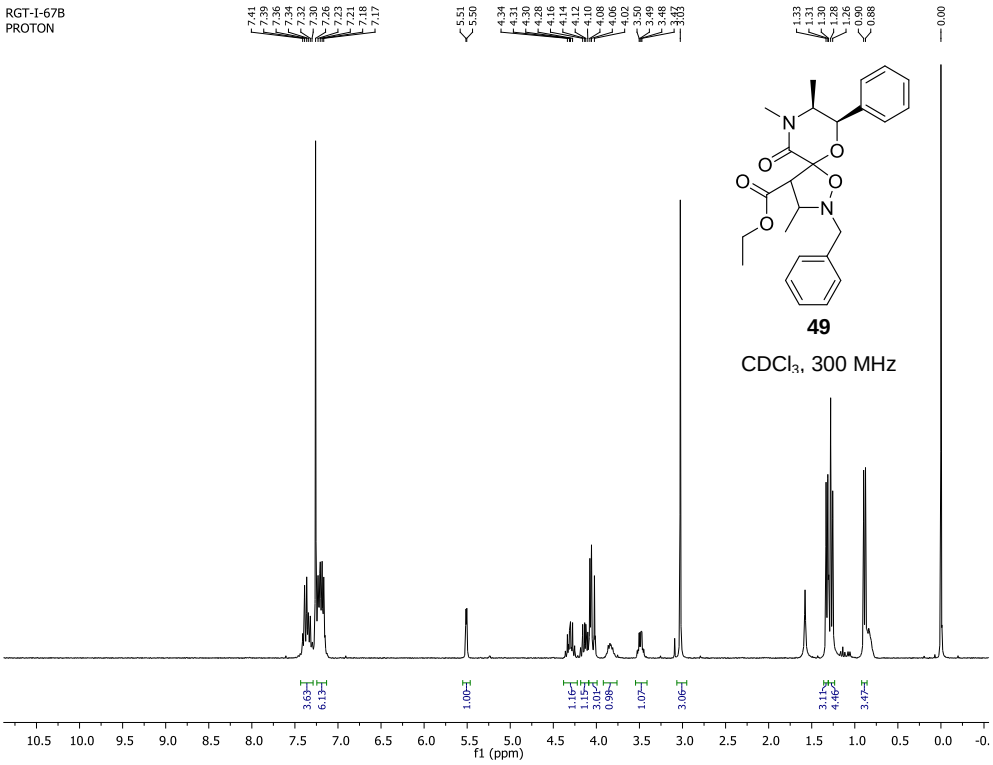
58

$CDCl_3$, 300 MHz



58

$CDCl_3$, 75 MHz


RGT-I-67B
PROTON
7.41
7.39
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7.34
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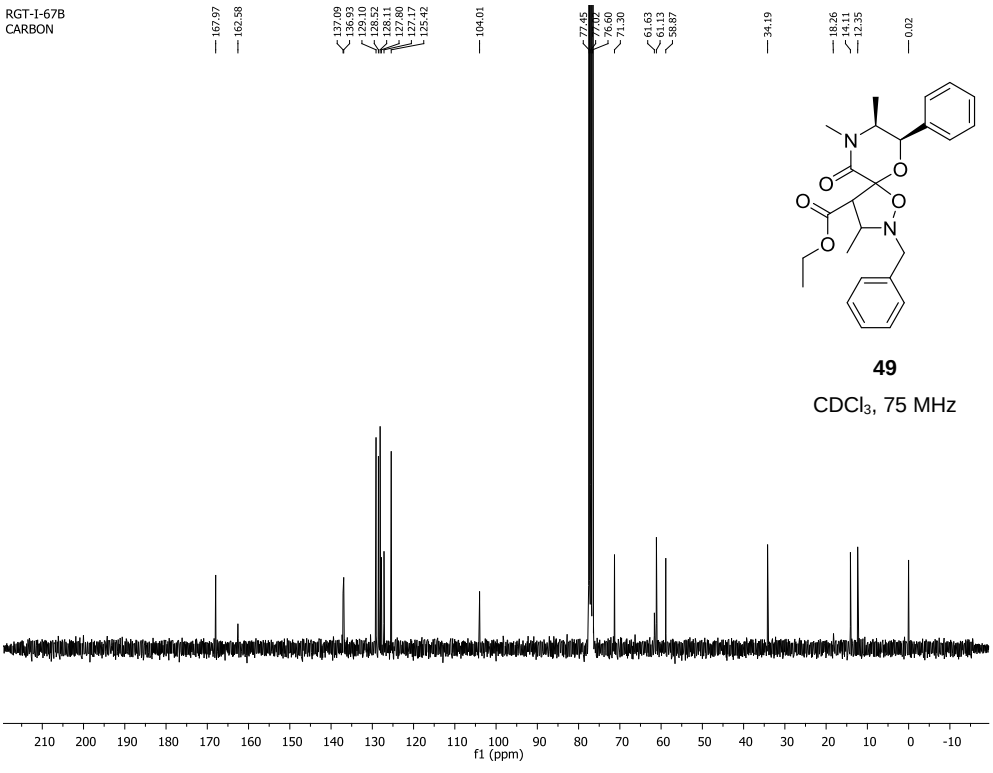
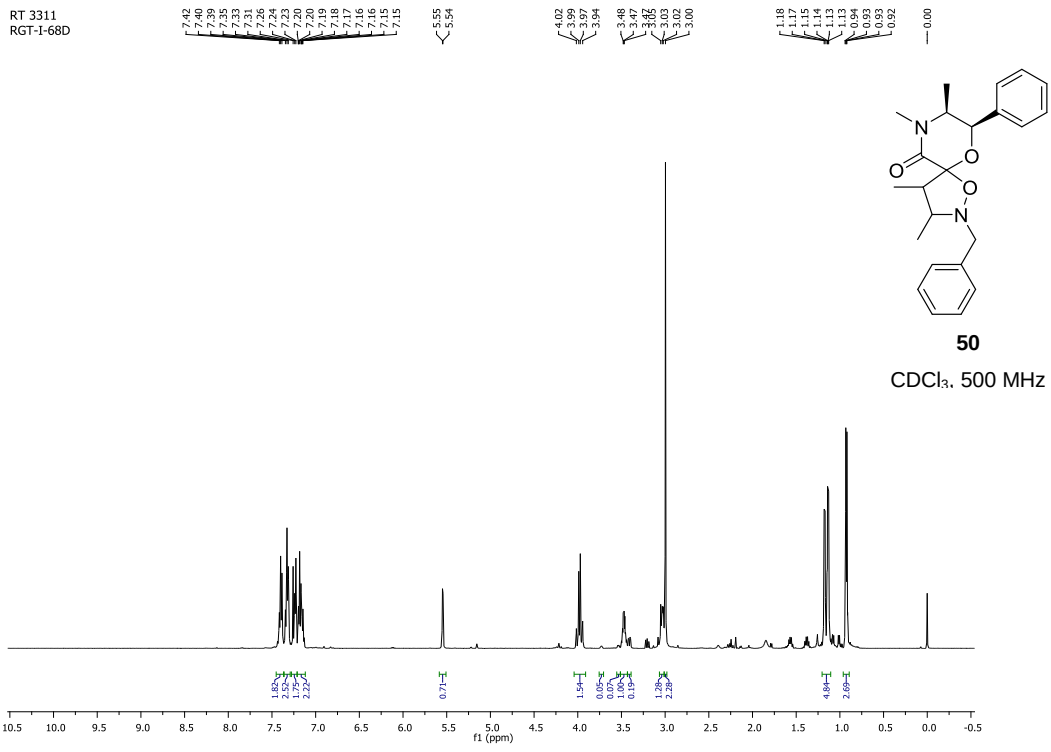
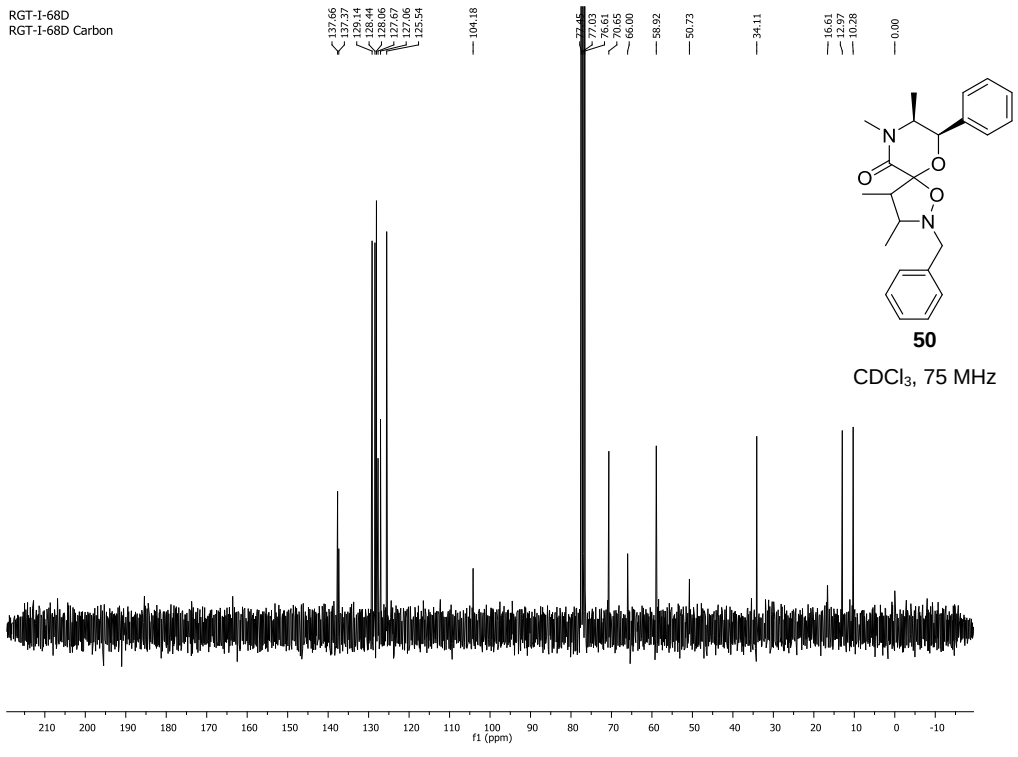
7.17
5.51
5.50
4.34
4.31
4.30
4.28
4.16
4.14
4.12
4.10
4.08
4.06
4.02
3.50
3.49
3.48
3.47
3.03
1.33
1.31
1.30
1.28
1.26
0.90
0.88
0.00
3.63
6.13
1.00
1.16
1.15
3.01
0.98
1.07
3.06
3.11
4.46
3.47
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)
49
CDCl3, 300 MHz


RGT-I-67B
CARBON
167.97
162.58
137.09
136.93
129.10
128.52
128.11
127.80
127.17
125.42
104.01
77.45
77.02
76.60
71.30
61.63
61.13
58.87
34.19
18.26
14.11
12.35
0.02
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
49
CDCl3, 75 MHz



50

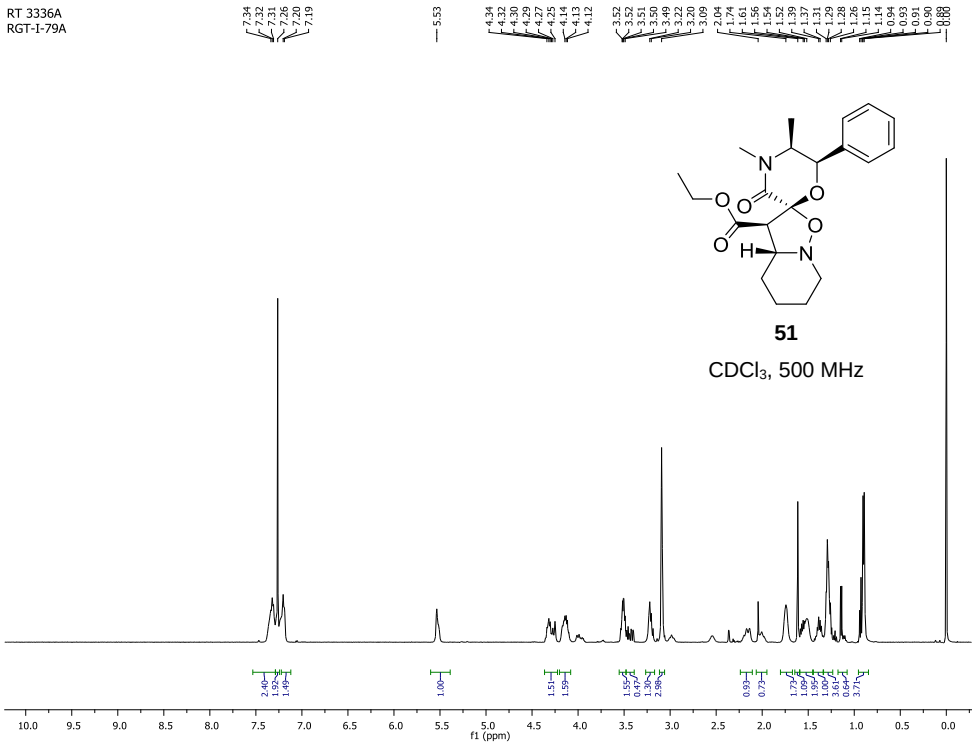
$CDCl_3$, 500 MHz



50

$CDCl_3$, 75 MHz

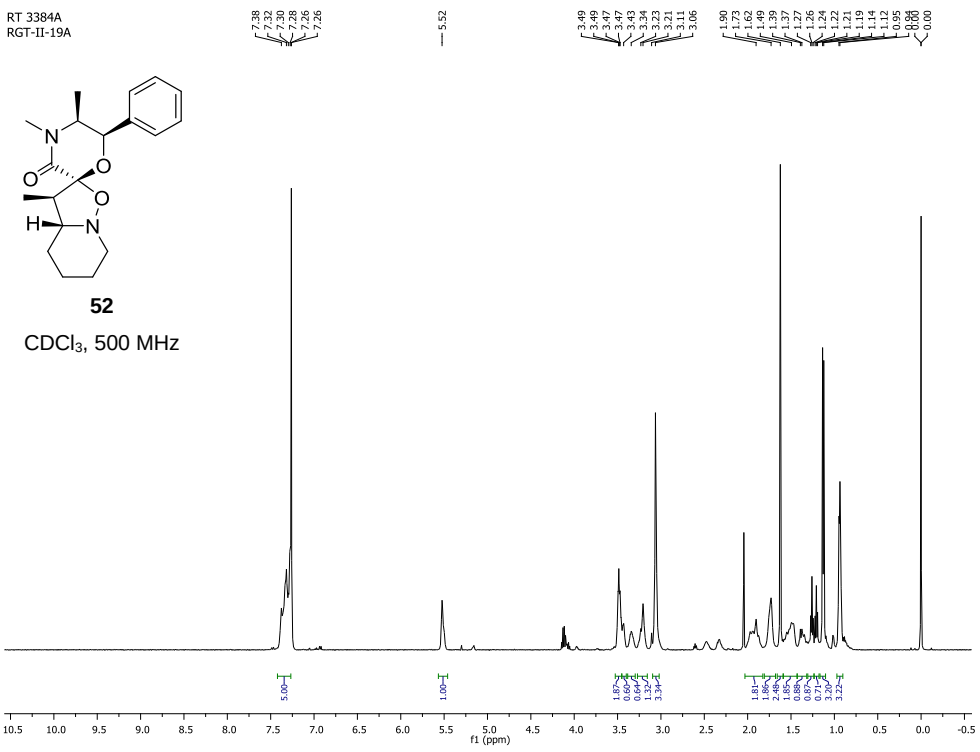
RT 3336A
RGT-I-79A



51

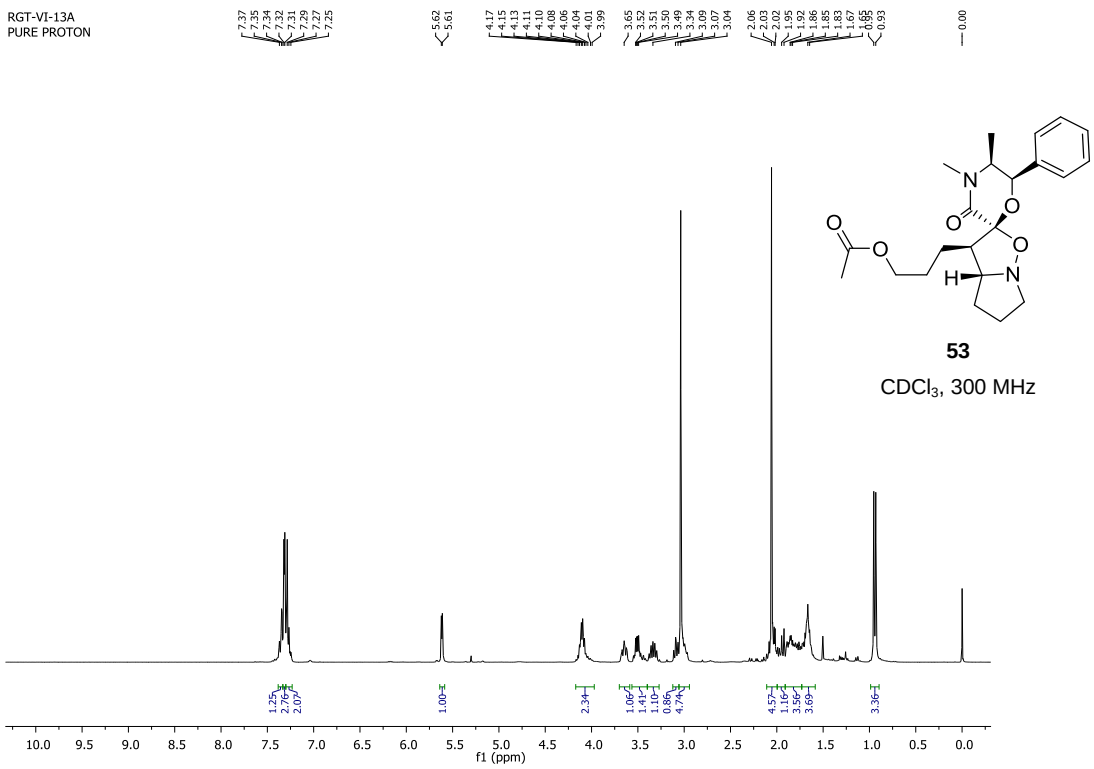
$CDCl_3$, 500 MHz

RT 3384A
RGT-II-19A



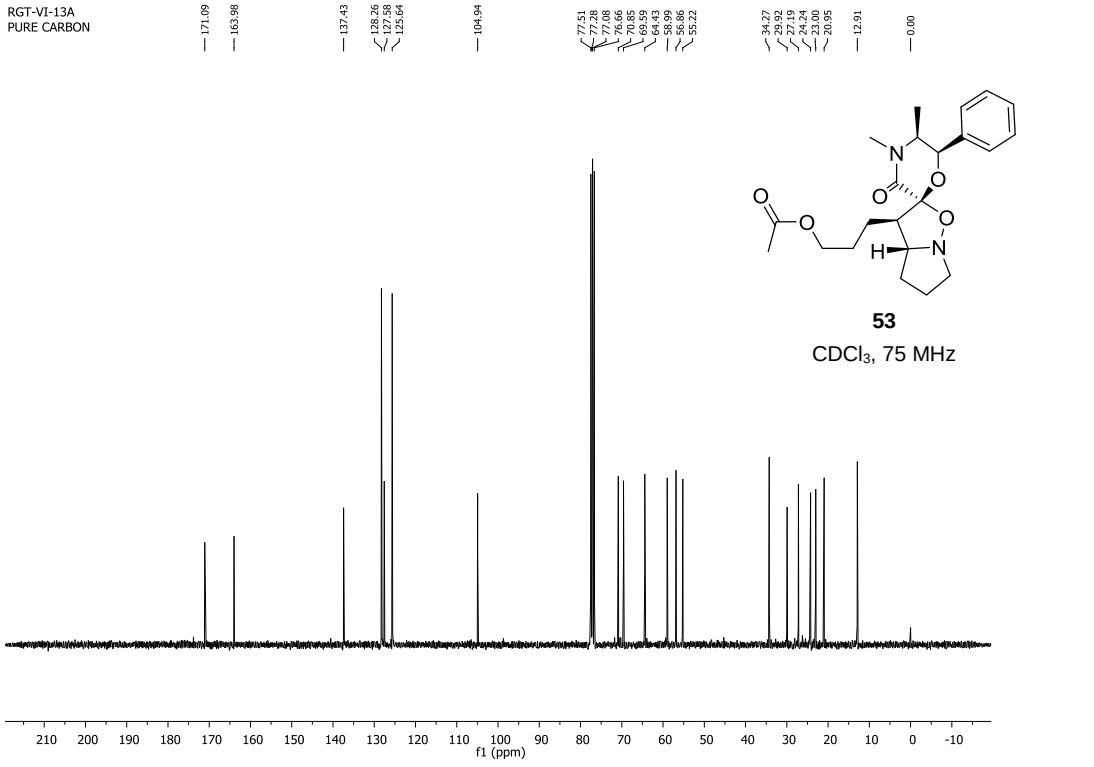
52

$CDCl_3$, 500 MHz



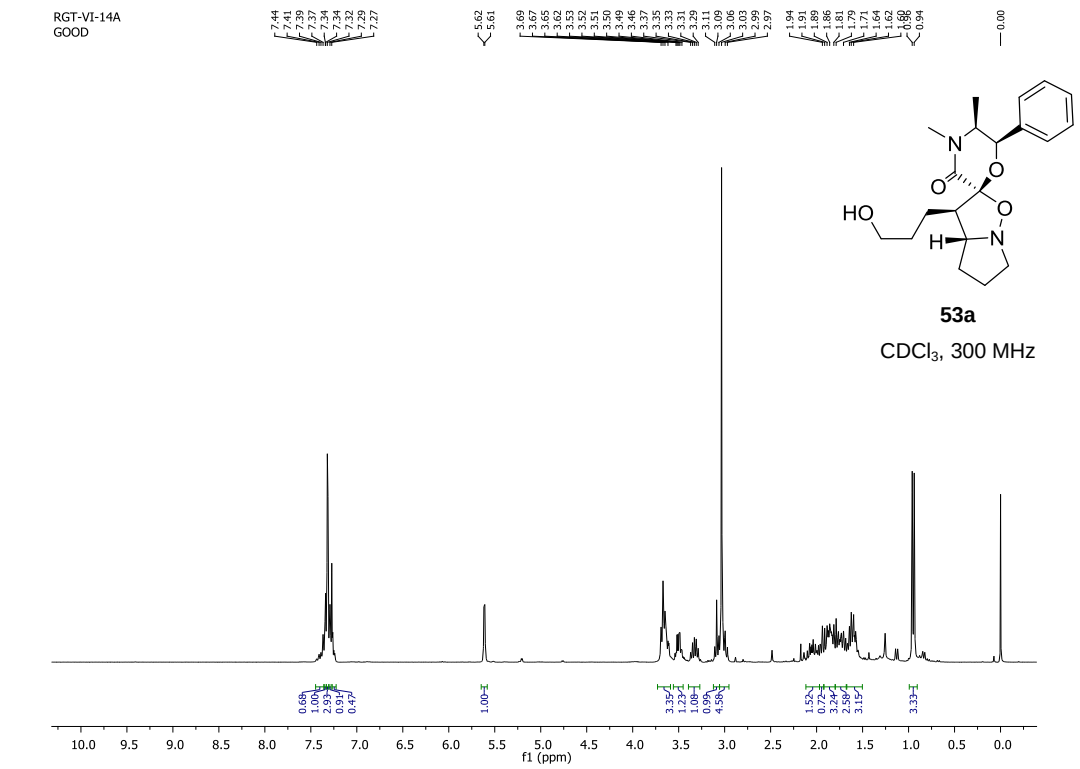
53

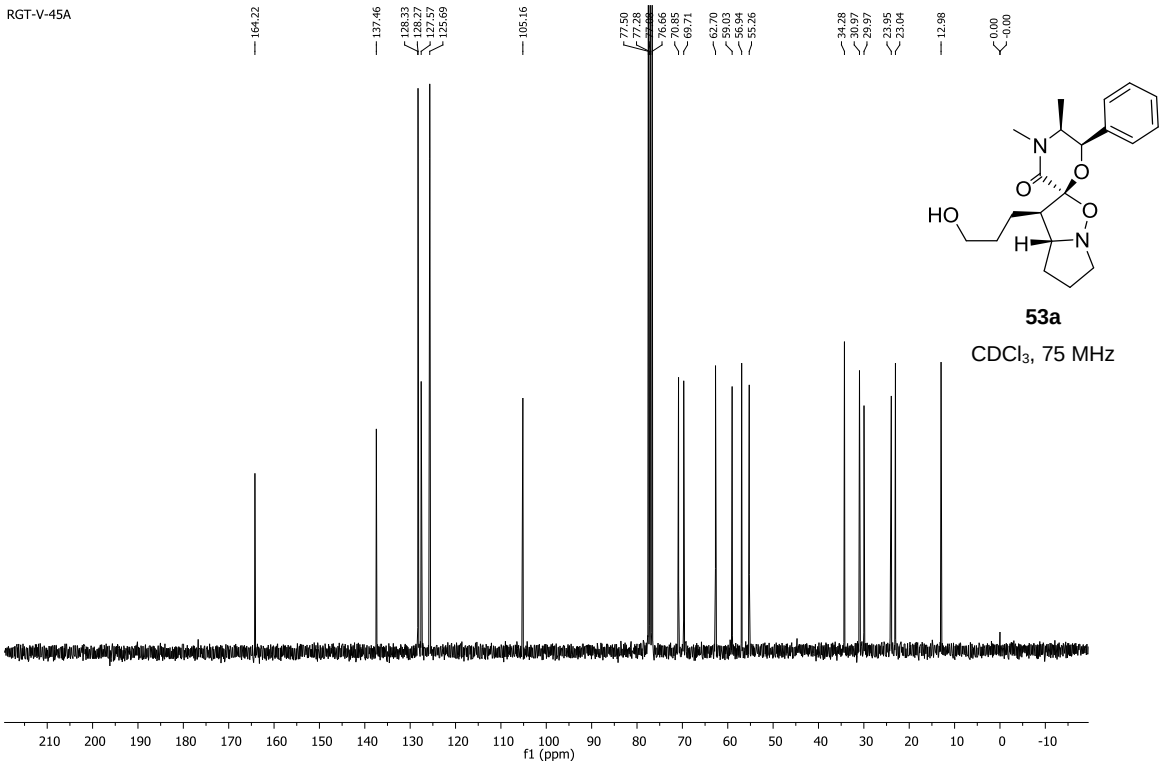
$CDCl_3$, 300 MHz

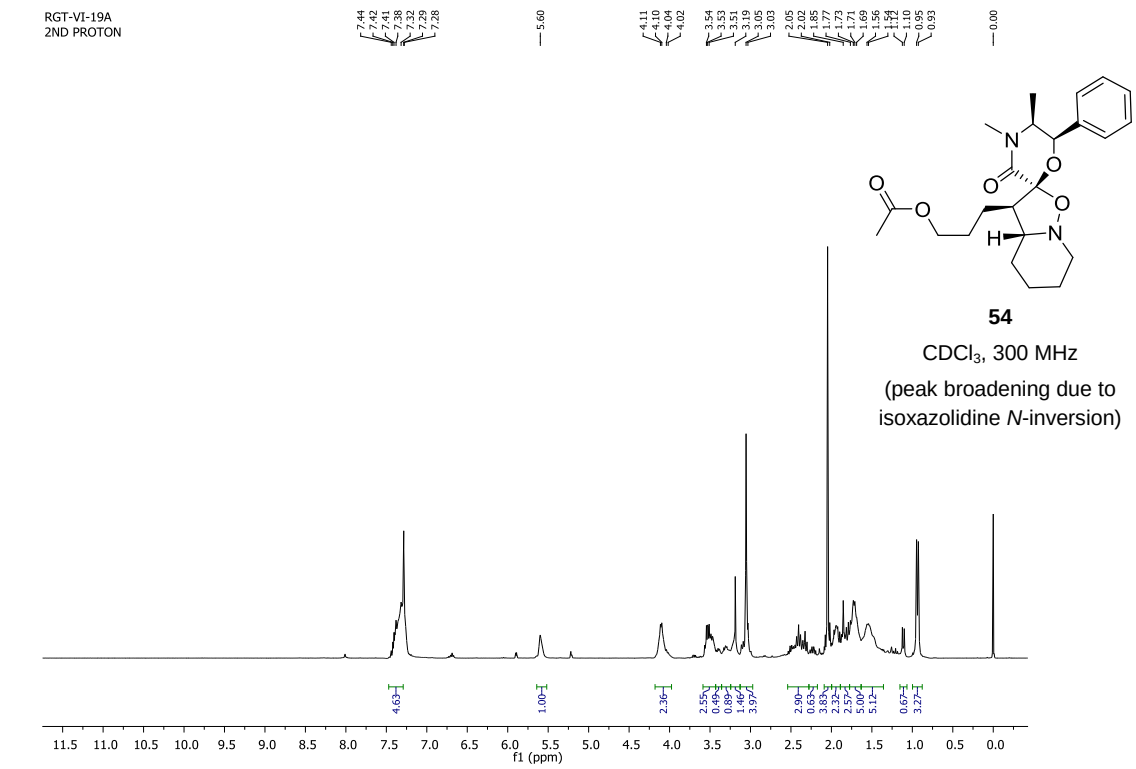


53

$CDCl_3$, 75 MHz


RGT-VI-14A
GOOD
HO
H
N
O
O
O
N
53a
CDCl3, 300 MHz
f1 (ppm)

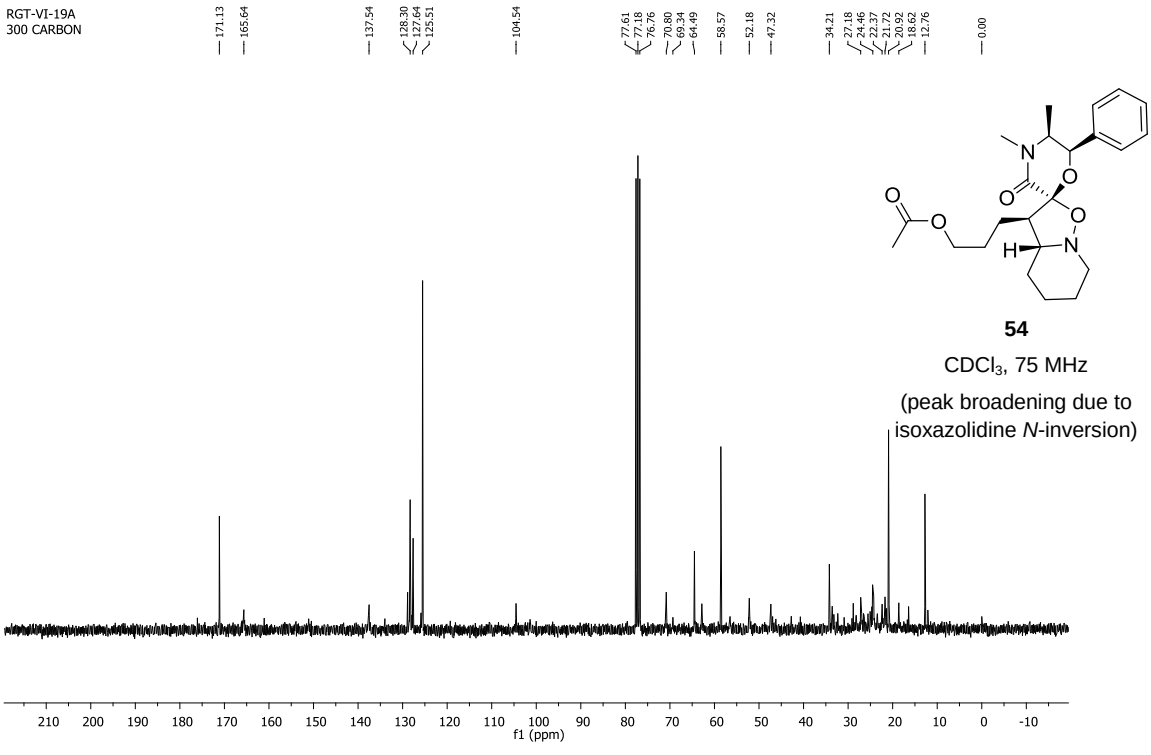

RGT-V-45A
HO
H
N
O
O
O
N
53a
CDCl3, 75 MHz
f1 (ppm)



54

$CDCl_3$, 300 MHz

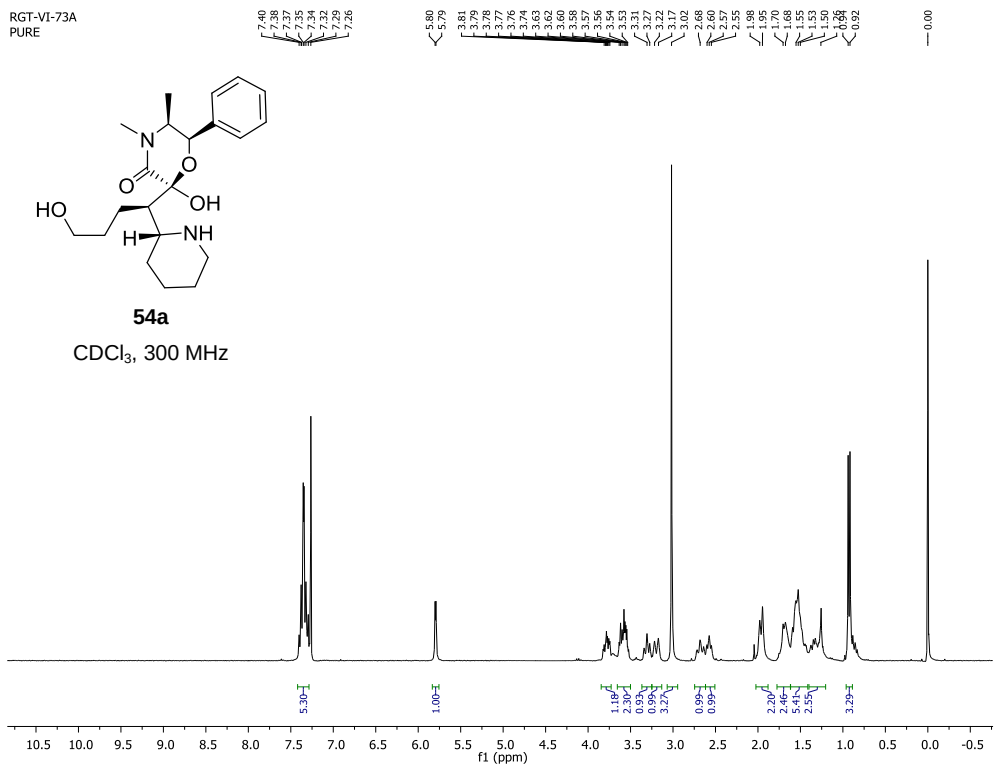
(peak broadening due to isoxazolidine *N*-inversion)

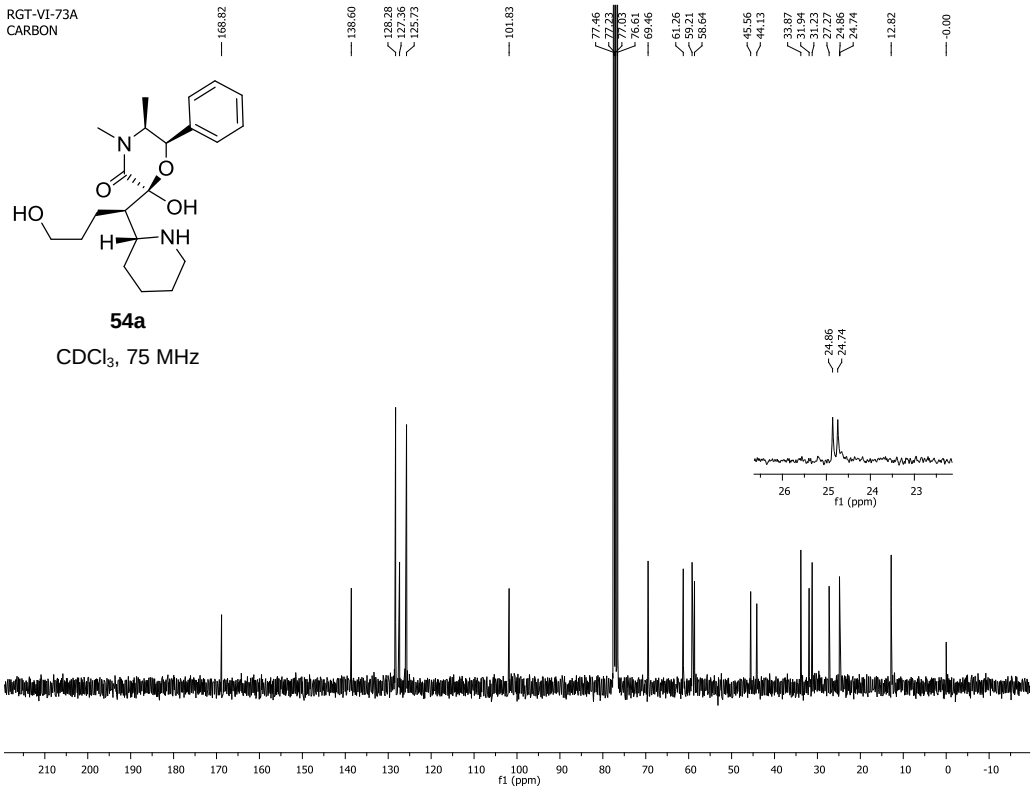


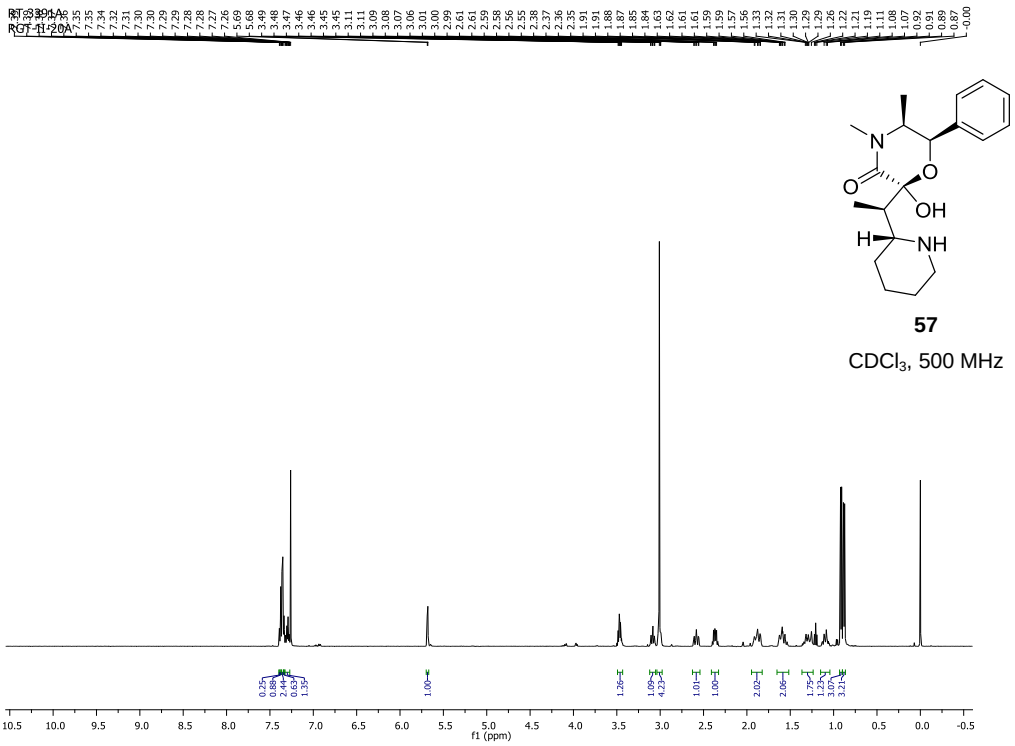
54

$CDCl_3$, 75 MHz

(peak broadening due to isoxazolidine *N*-inversion)

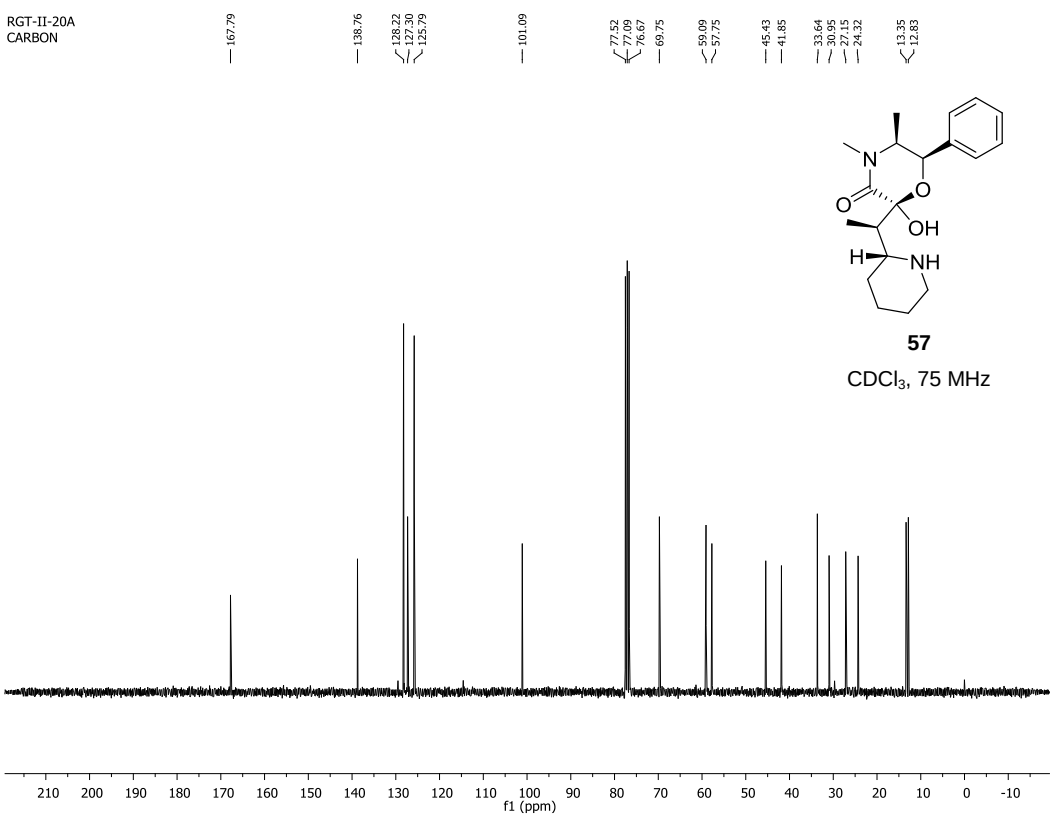

RGT-VI-73A
PURE
HO
OH
NH
H
O
N
54a
CDCl3, 300 MHz
f1 (ppm)


RGT-VI-73A
CARBON
HO
OH
NH
H
O
N
54a
CDCl3, 75 MHz
f1 (ppm)



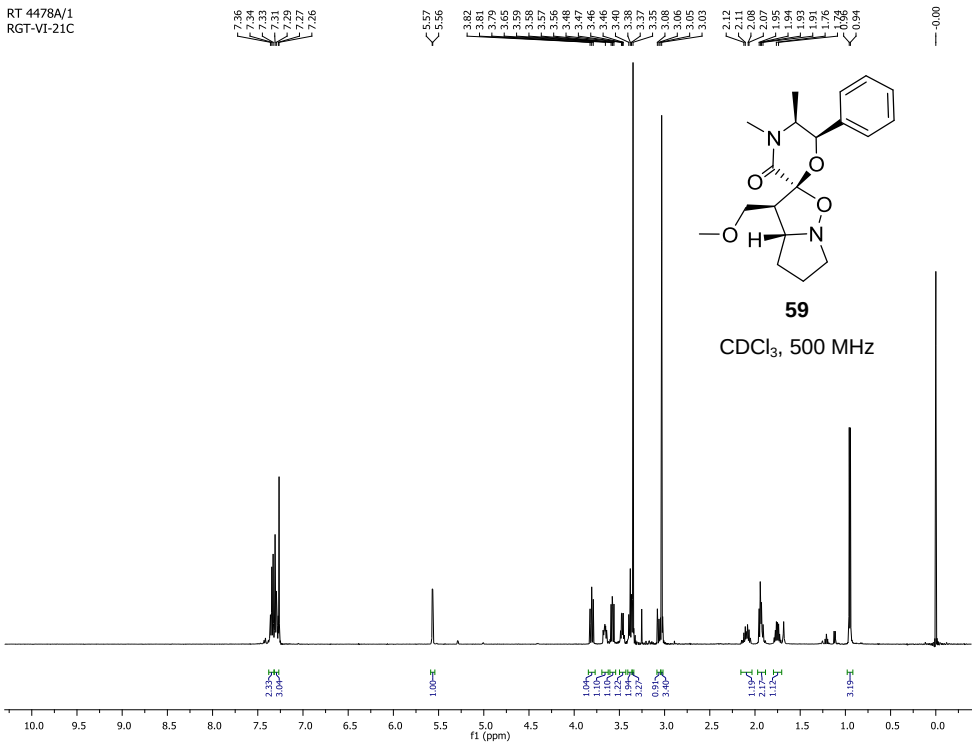
57

$CDCl_3$, 500 MHz



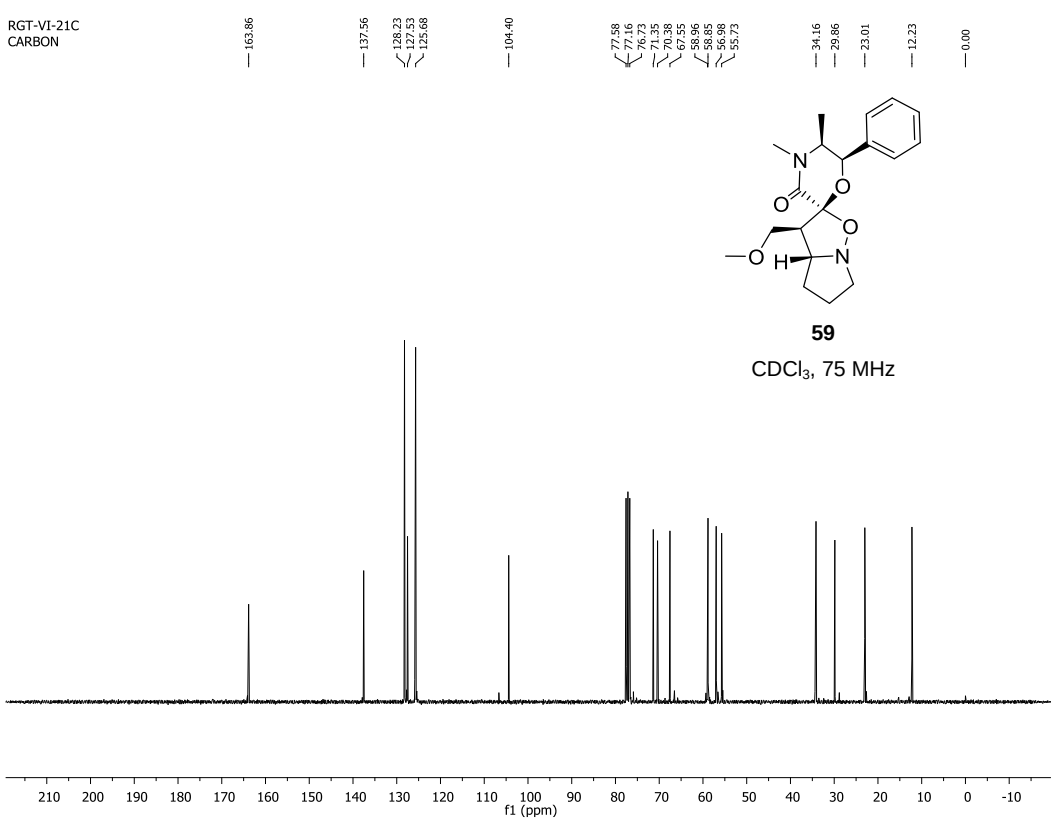
57

$CDCl_3$, 75 MHz



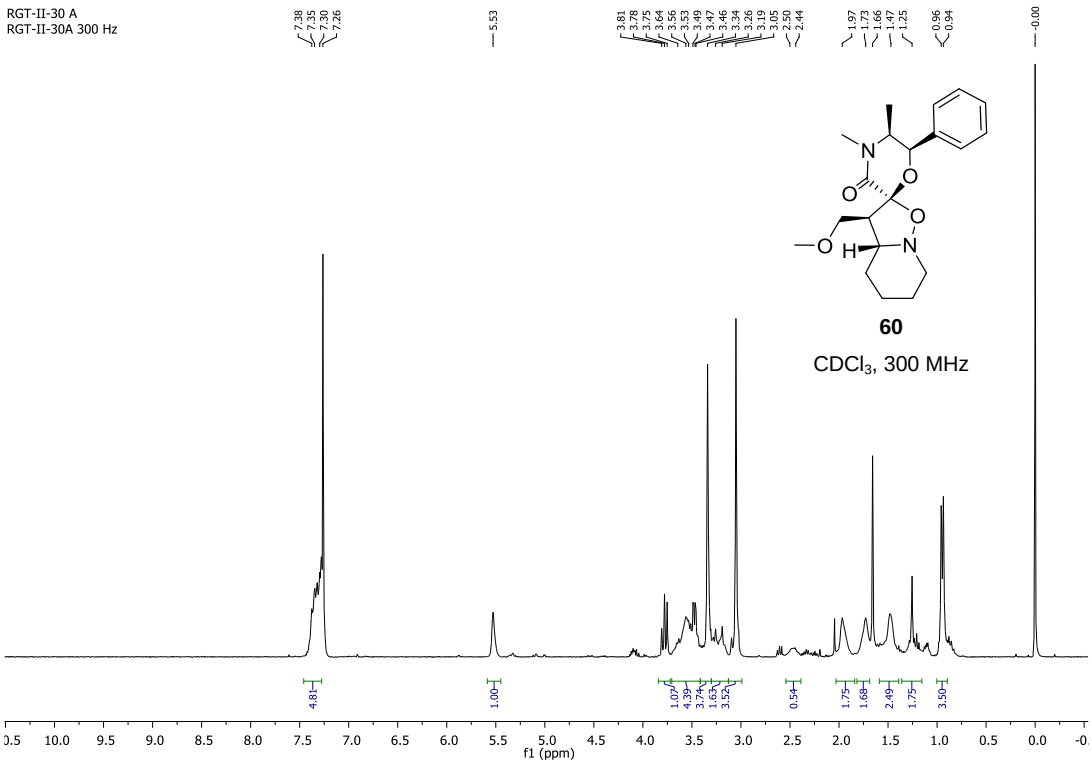
59

$CDCl_3$, 500 MHz



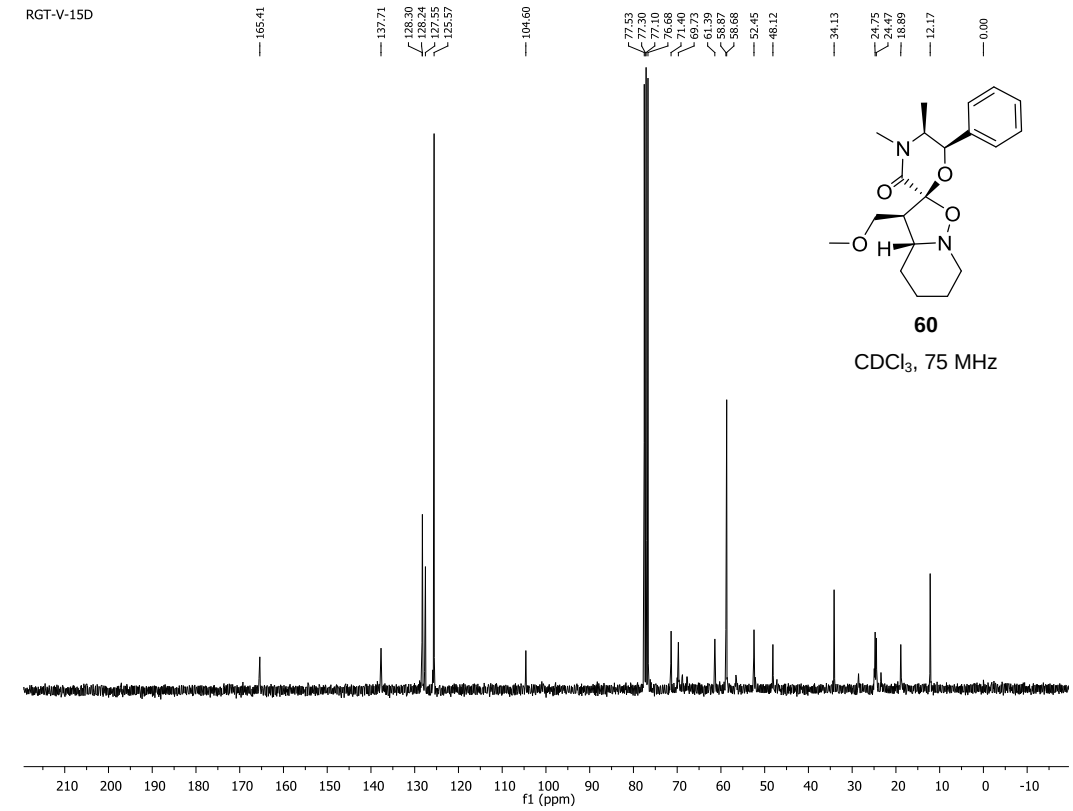
59

$CDCl_3$, 75 MHz



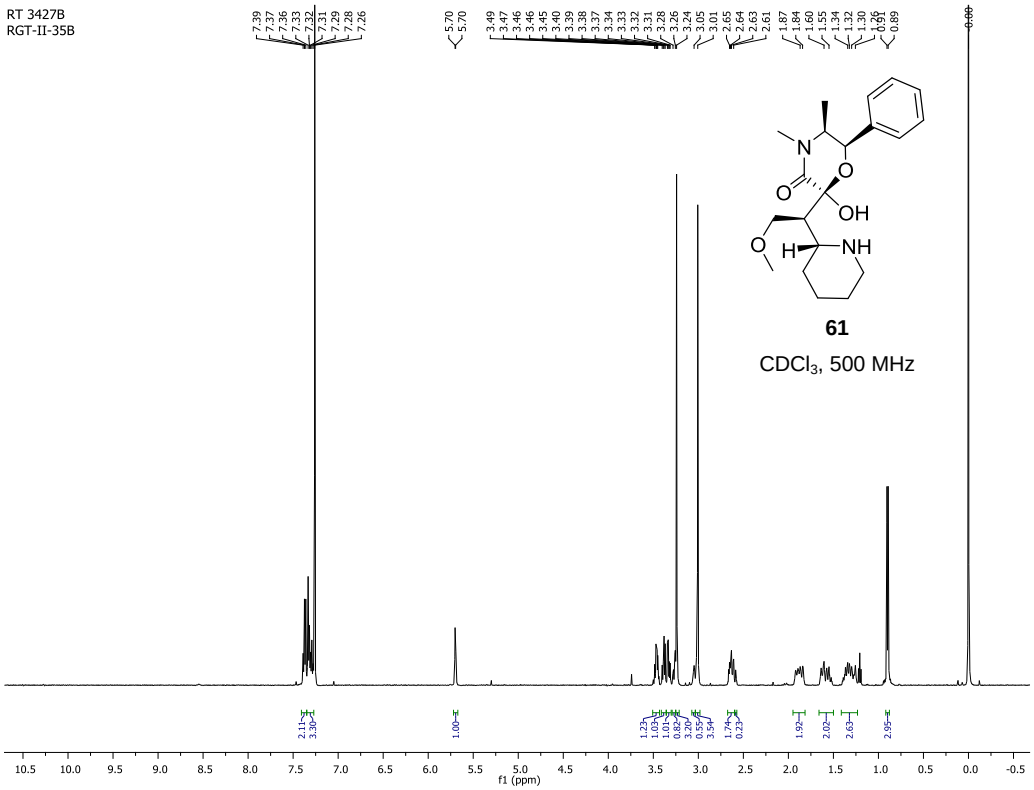
60

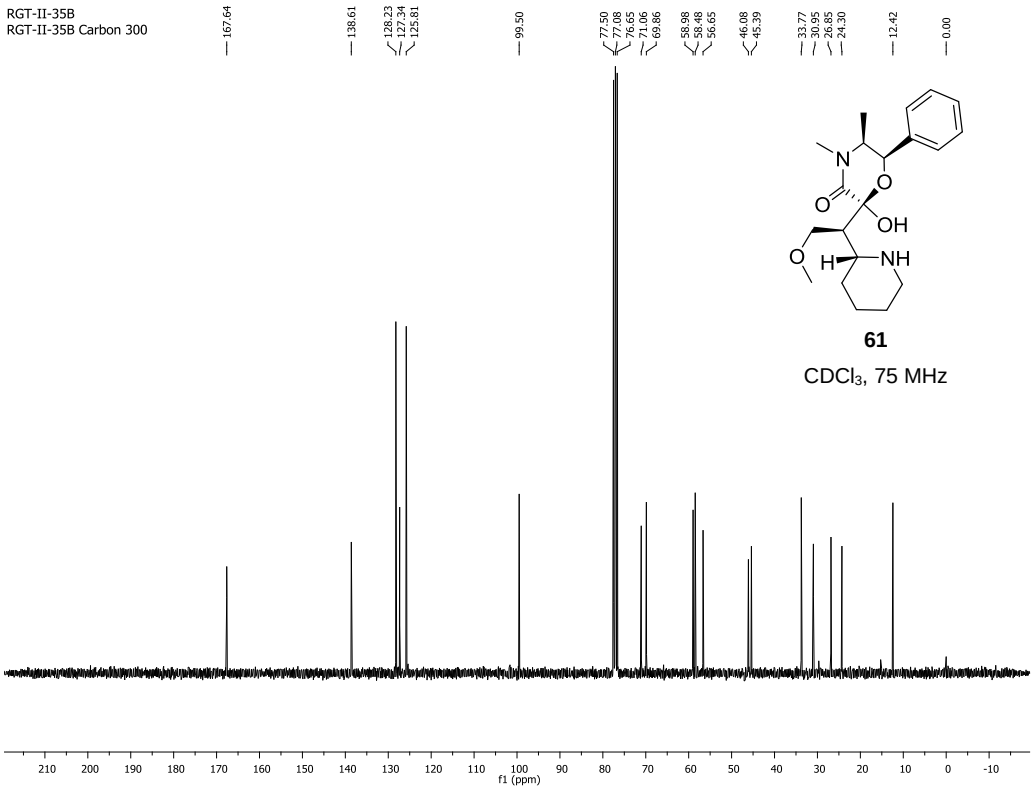
$CDCl_3$, 300 MHz

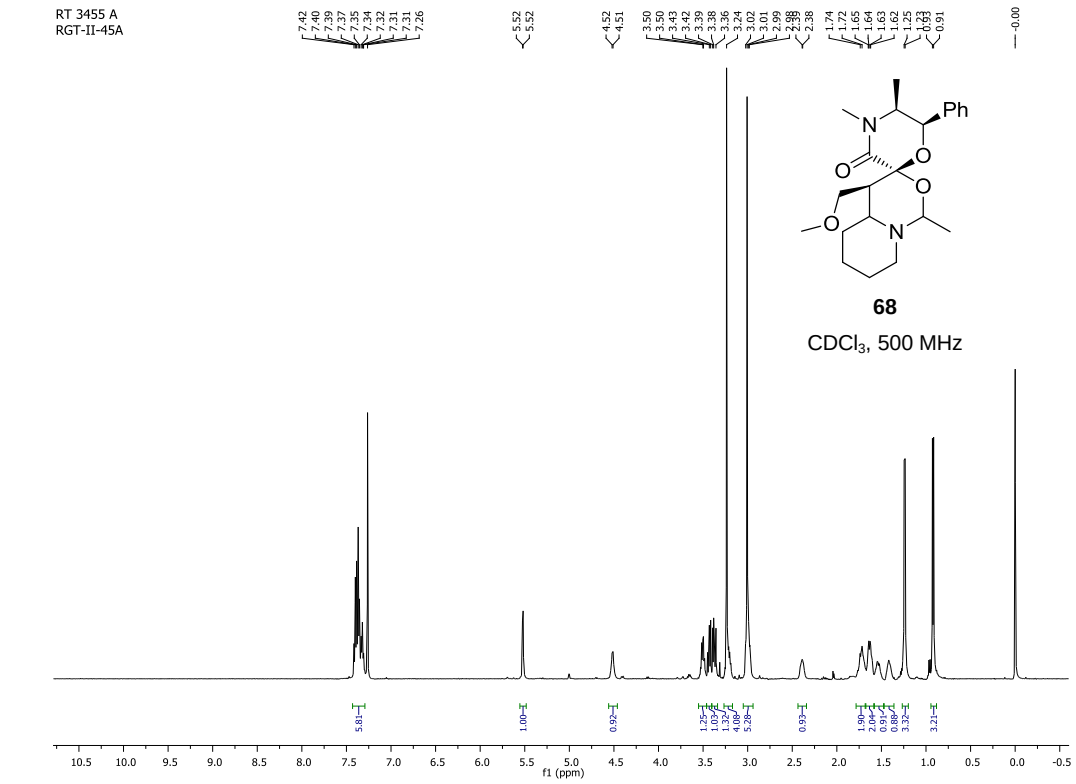


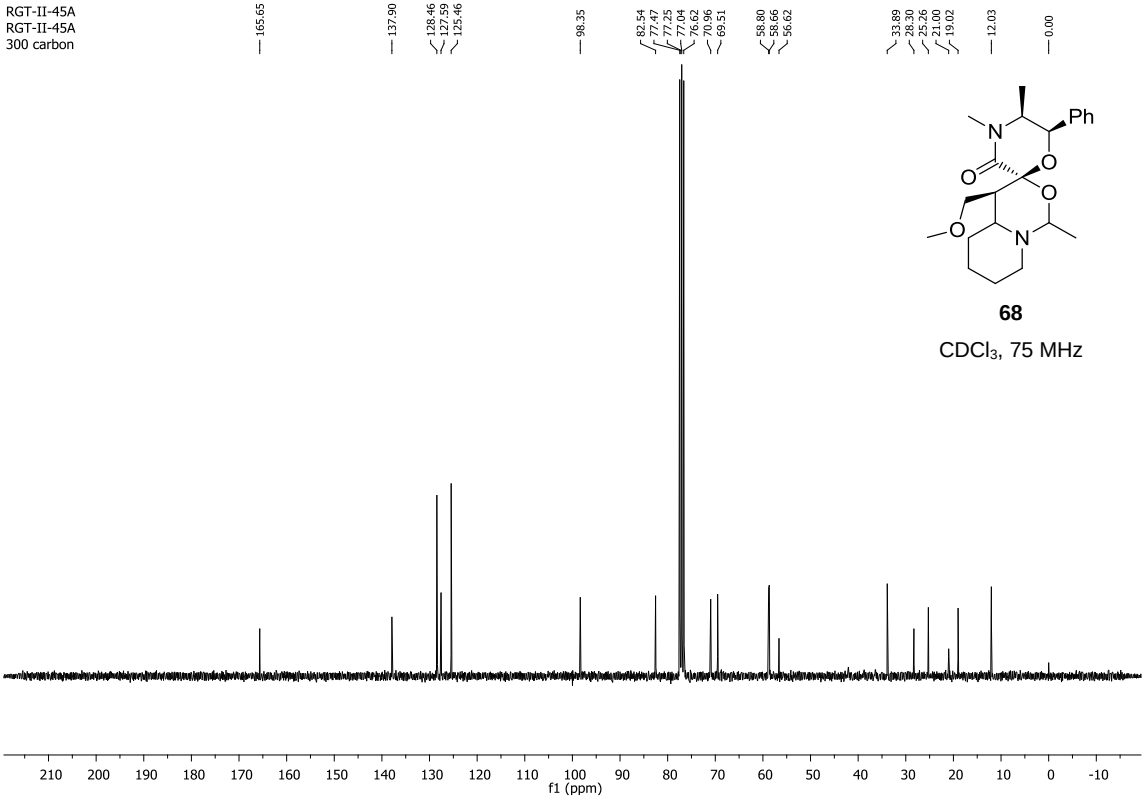
60

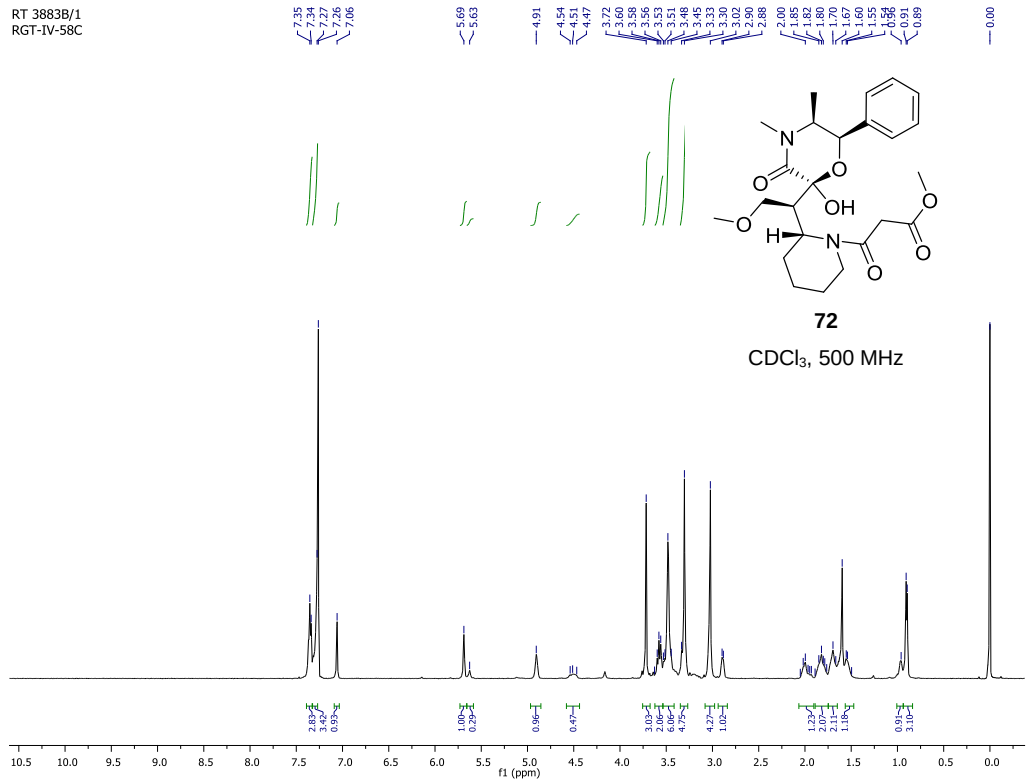
$CDCl_3$, 75 MHz

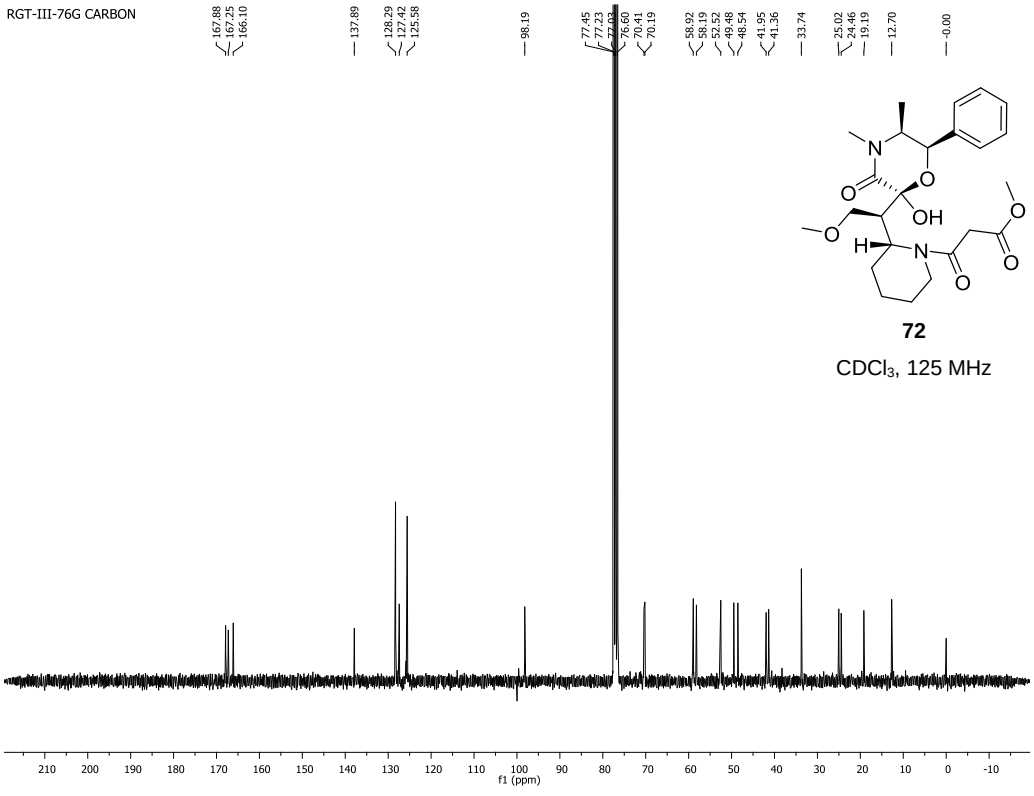

RT 3427B
RGT-II-35B
7.39
7.37
7.36
7.33
7.32
7.31
7.29
7.28
7.26
5.70
5.70
3.49
3.47
3.46
3.46
3.45
3.40
3.39
3.38
3.37
3.34
3.33
3.32
3.31
3.28
3.26
3.24
3.05
3.01
2.65
2.64
2.63
2.61
1.87
1.84
1.60
1.55
1.34
1.32
1.30
0.91
0.89
0.00
N
O
O
OH
O
H
NH
61
CDCl3, 500 MHz
2.11
3.39
1.00
1.23
1.03
1.01
0.82
3.20
0.55
3.94
1.74
0.23
1.92
2.02
2.63
2.95
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
-0.5
f1 (ppm)

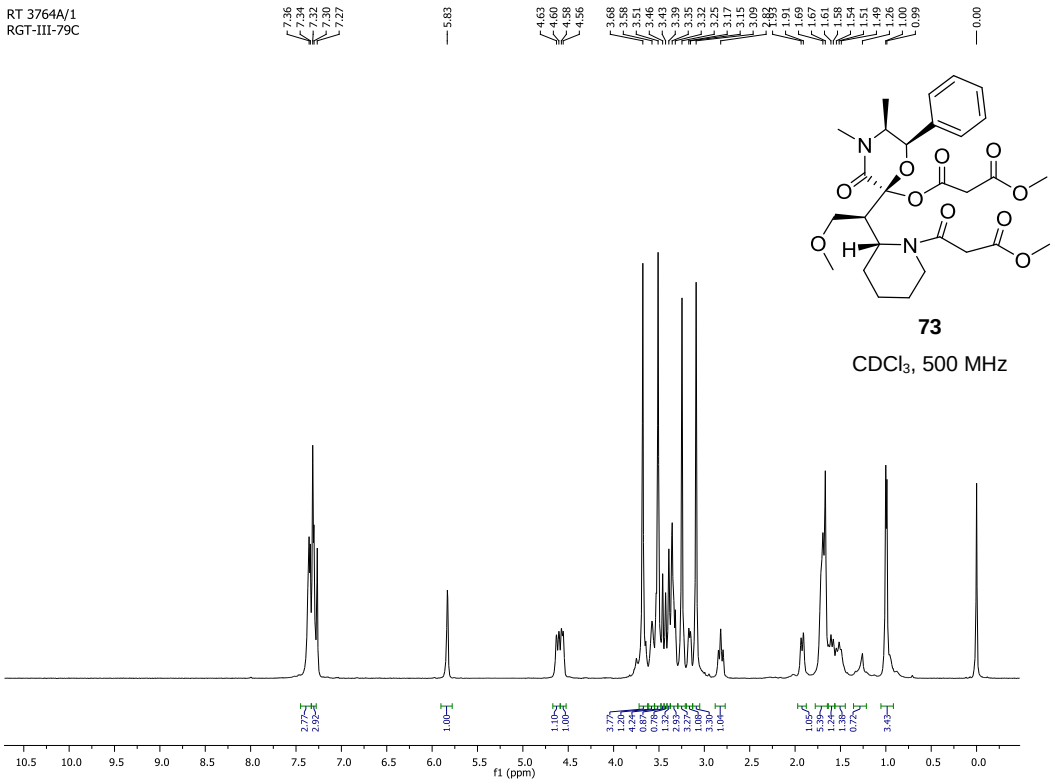

RGT-II-35B
RGT-II-35B Carbon 300
167.64
138.61
128.23
127.34
125.81
99.50
77.50
77.08
76.65
71.06
69.86
58.98
58.48
56.65
46.08
45.39
33.77
30.95
26.85
24.30
12.42
0.00
N
O
O
OH
O
H
NH
61
CDCl3, 75 MHz
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


RT 3455 A
RGT-II-45A
Ph
N
O
O
O
O
N
68
CDCl3, 500 MHz
f1 (ppm)


RGT-II-45A
RGT-II-45A
300 carbon
Ph
N
O
O
O
O
N
68
CDCl3, 75 MHz
f1 (ppm)

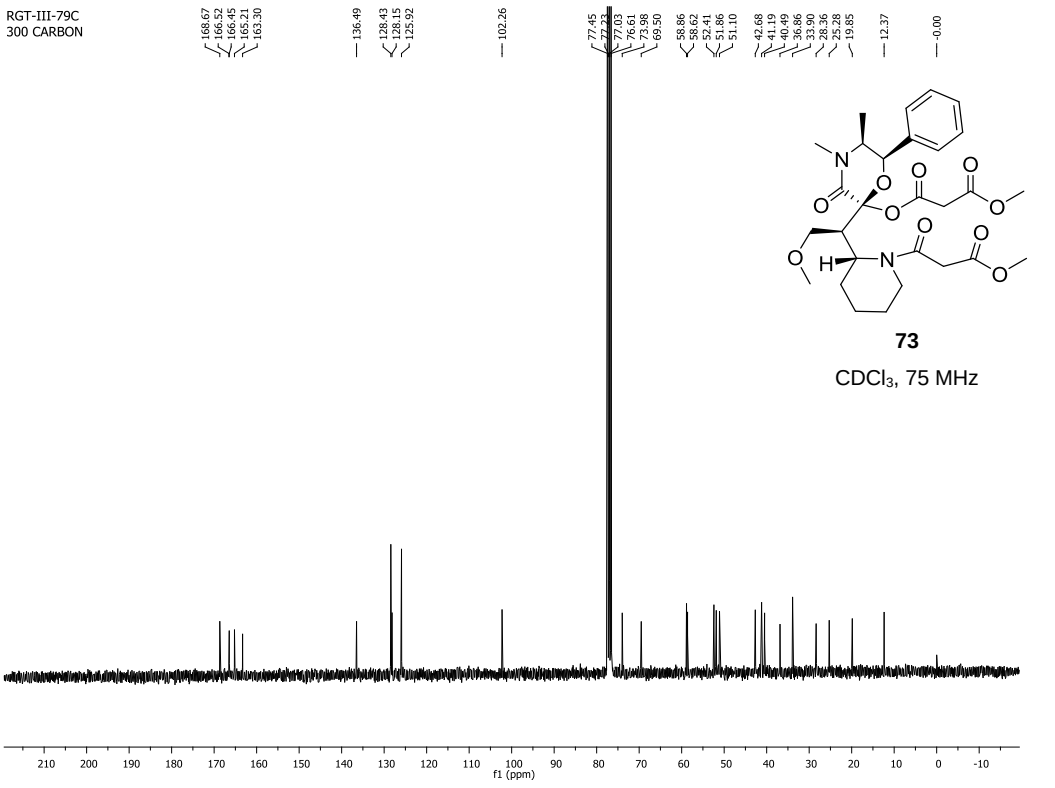

RT 3883B/1
RGT-IV-58C
7.35
7.34
7.27
7.26
7.06
5.69
5.63
4.91
4.54
4.51
4.47
3.72
3.60
3.58
3.56
3.53
3.51
3.48
3.45
3.33
3.30
3.02
2.99
2.88
2.00
1.85
1.82
1.80
1.70
1.67
1.60
1.55
1.54
0.96
0.91
0.89
0.00
N
O
O
OH
O
O
H
N
O
O
O
72
CDCl3, 500 MHz
2.83
3.42
0.93
1.00
0.29
0.96
0.47
3.03
2.06
6.06
4.79
4.27
1.02
1.23
2.07
2.11
1.18
0.91
3.10
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)


RGT-III-76G CARBON
167.88
167.25
166.10
137.89
128.29
127.42
125.58
98.19
77.45
77.23
77.02
76.60
70.41
70.19
58.92
58.19
52.52
49.48
48.54
41.95
41.36
33.74
25.02
24.46
19.19
12.70
-0.00
N
O
O
OH
O
O
H
N
O
O
O
72
CDCl3, 125 MHz
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



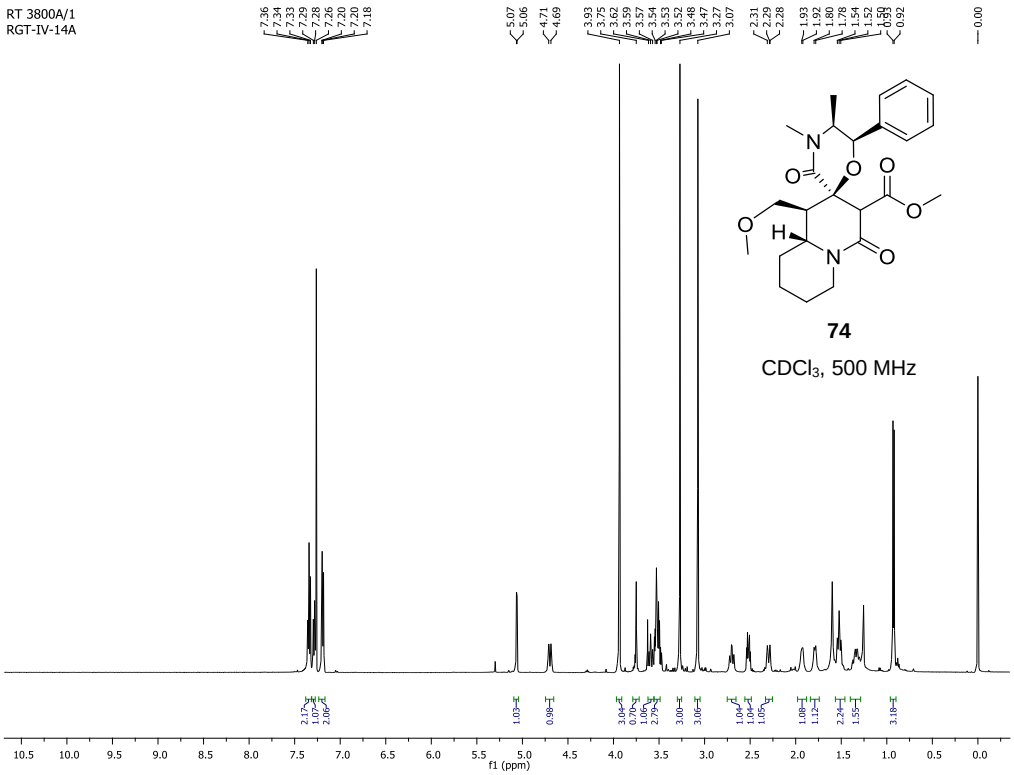
73

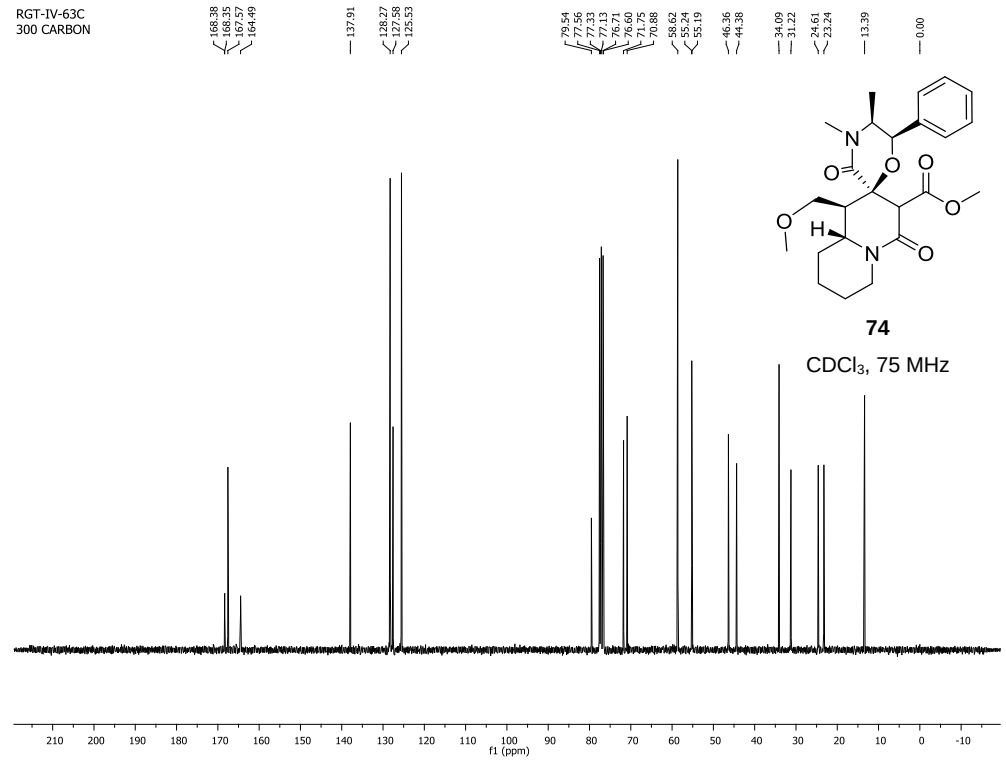
$CDCl_3$, 500 MHz

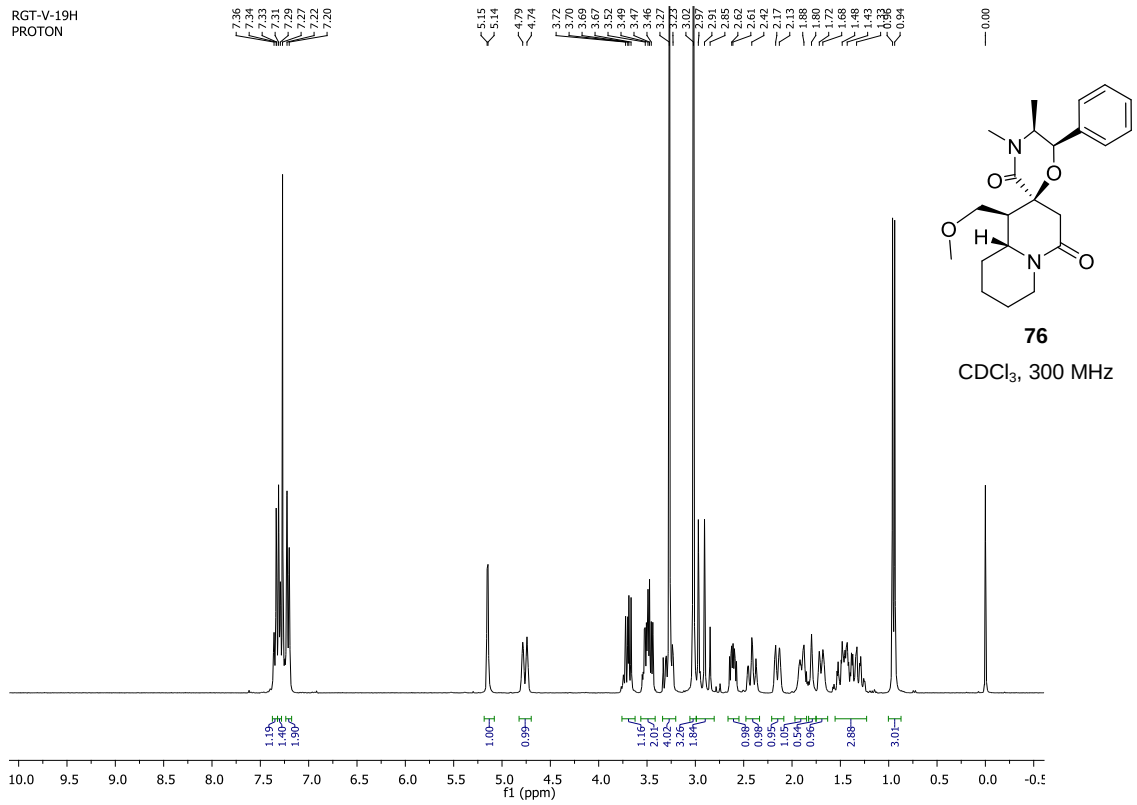


73

$CDCl_3$, 75 MHz

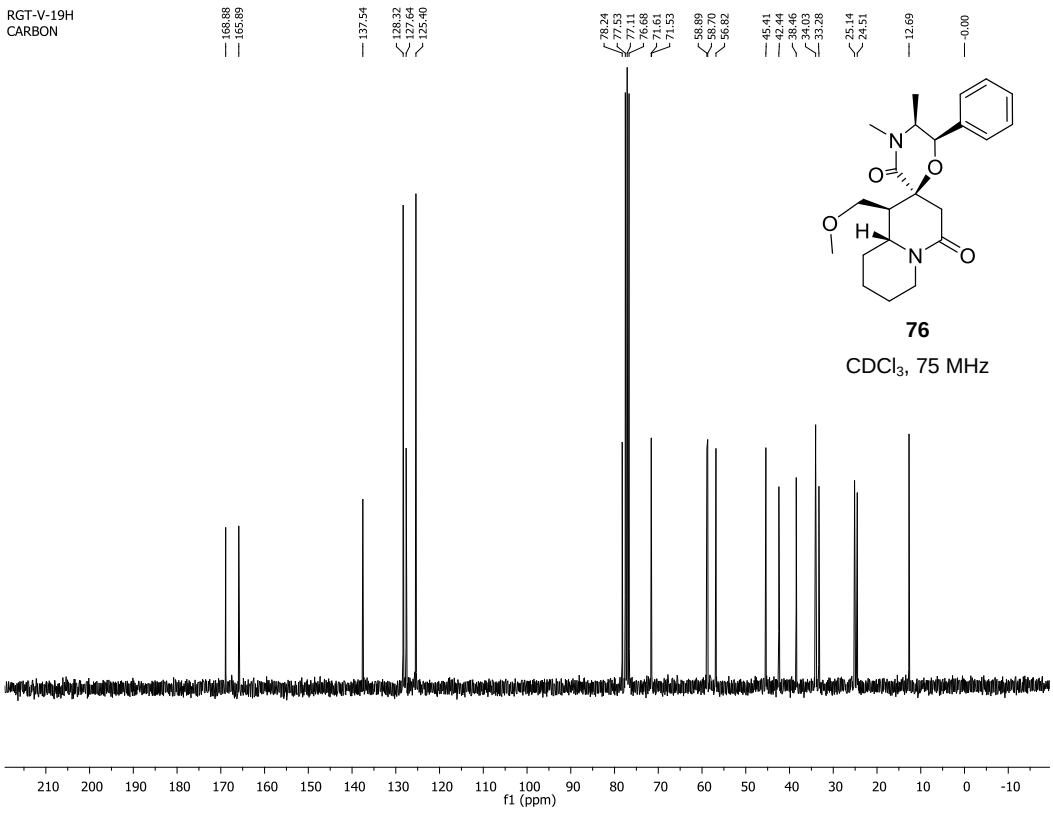

RT 3800A/1
RGT-IV-14A
74
CDCl3, 500 MHz
f1 (ppm)


RGT-IV-63C
300 CARBON
74
CDCl3, 75 MHz
f1 (ppm)



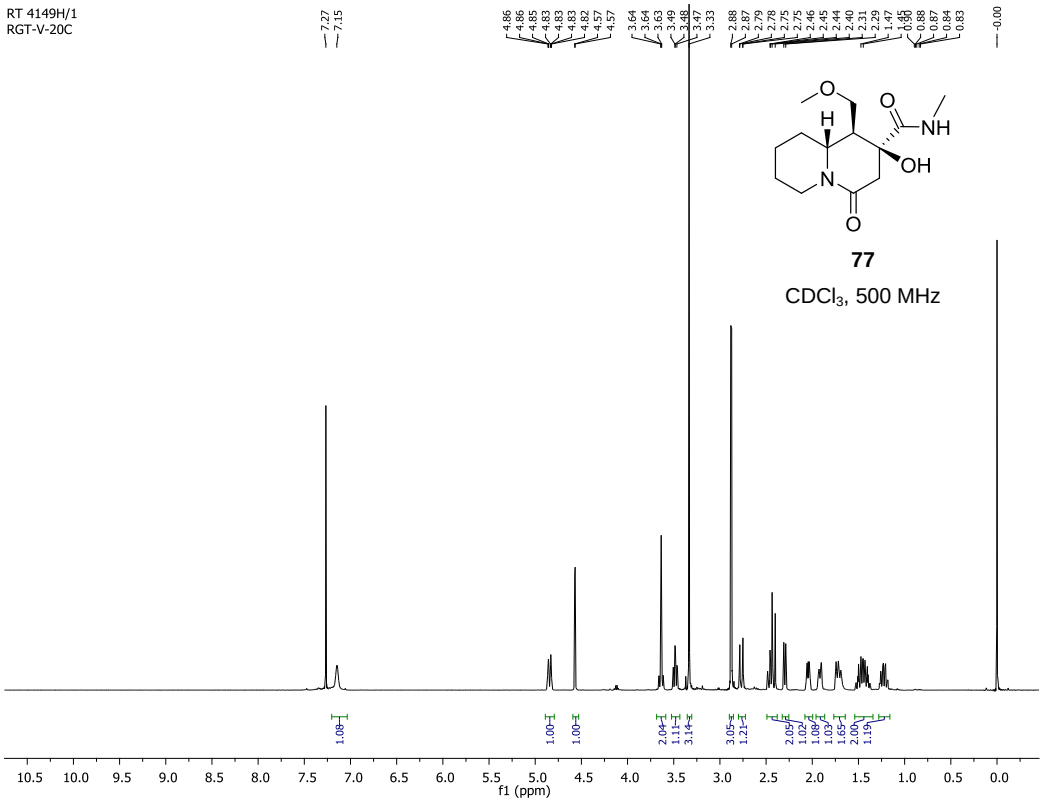
76

$CDCl_3$, 300 MHz



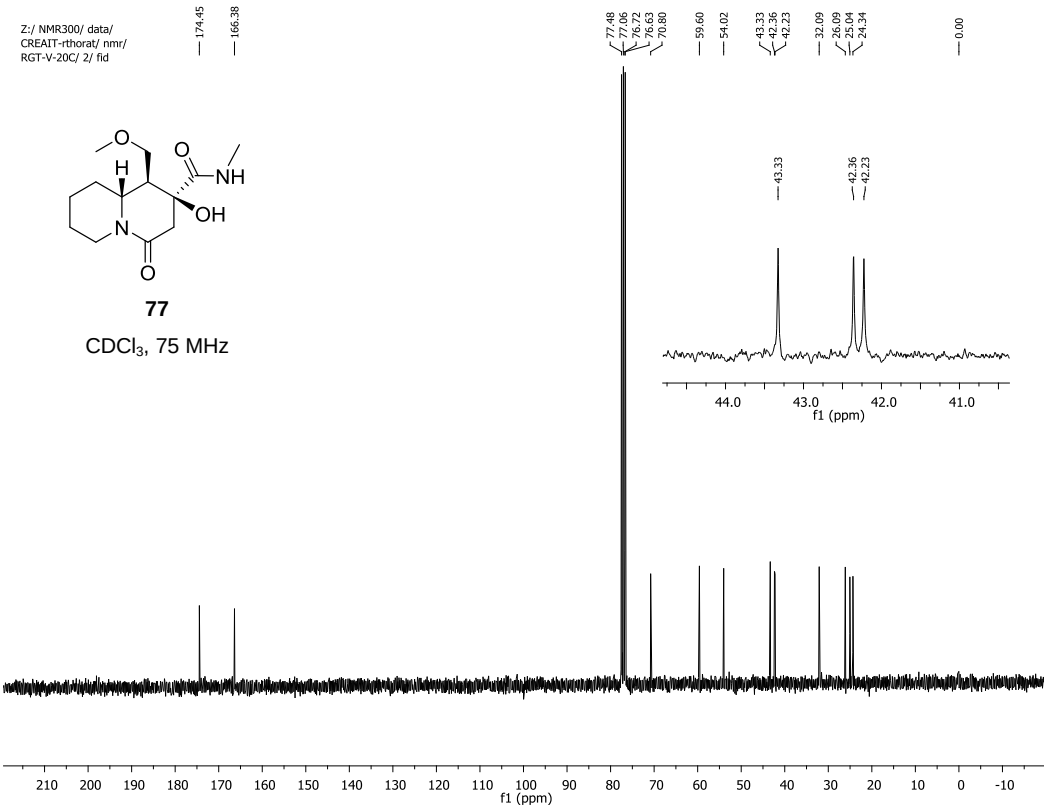
76

$CDCl_3$, 75 MHz



77

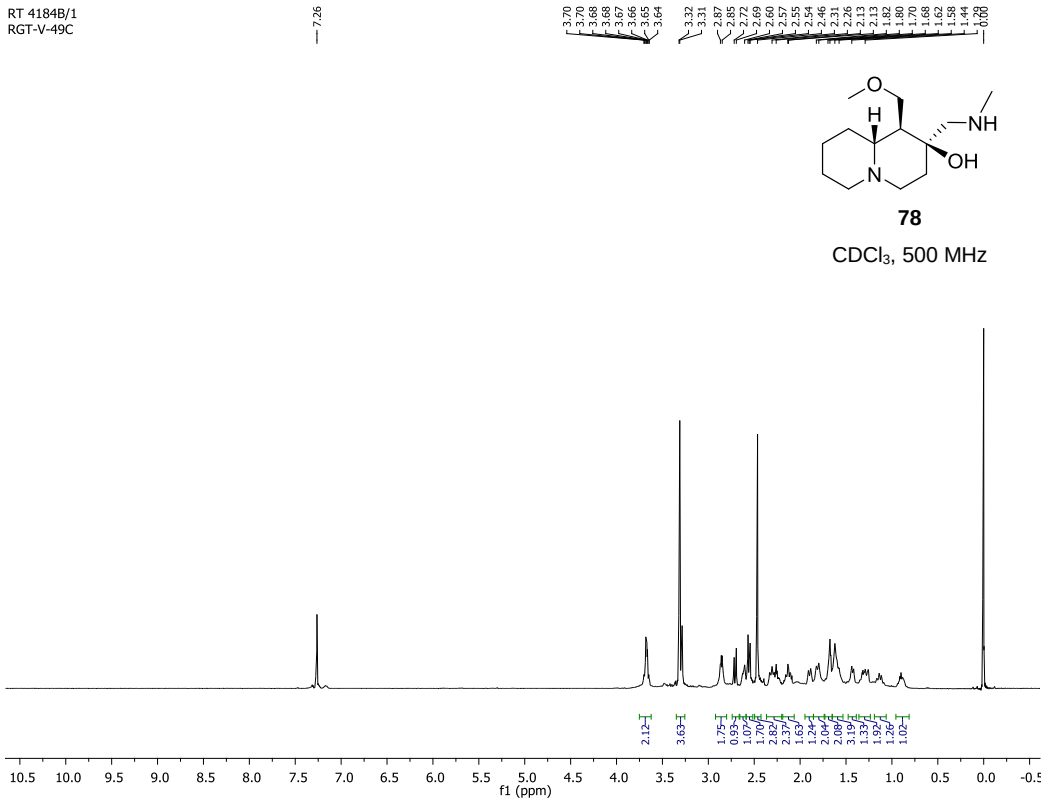
$CDCl_3$, 500 MHz



77

$CDCl_3$, 75 MHz

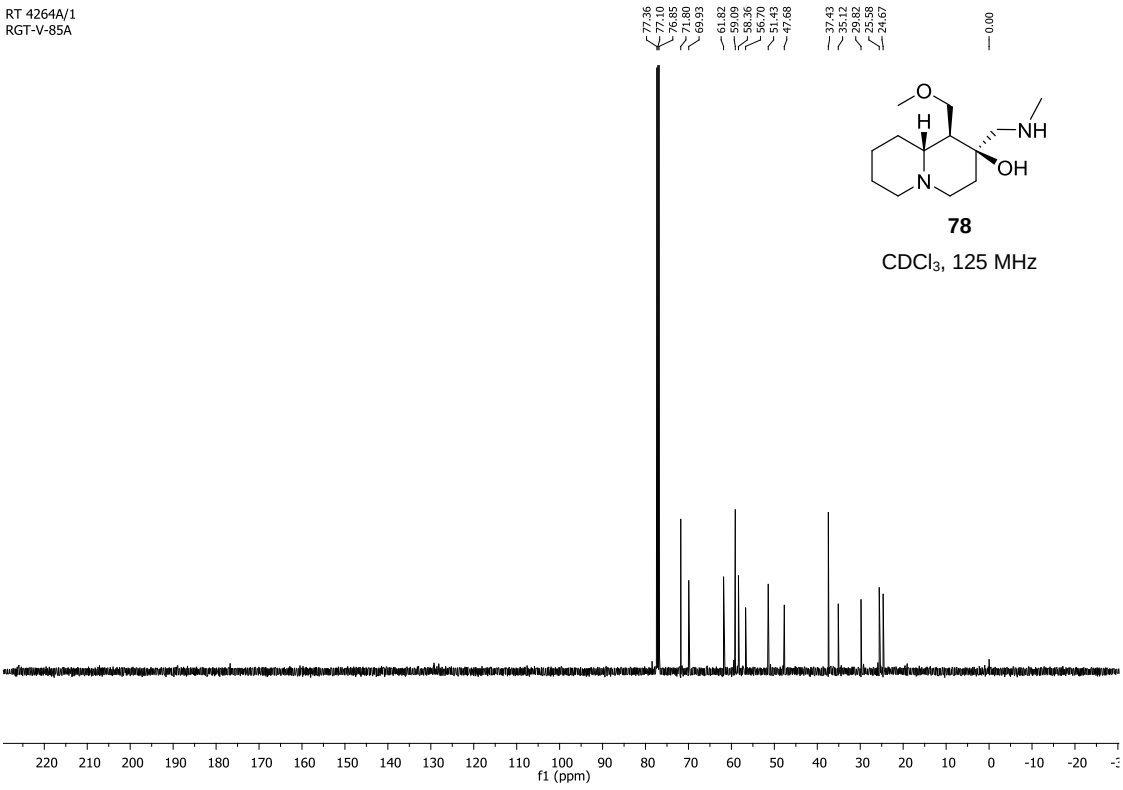
RT 4184B/1
RGT-V-49C



78

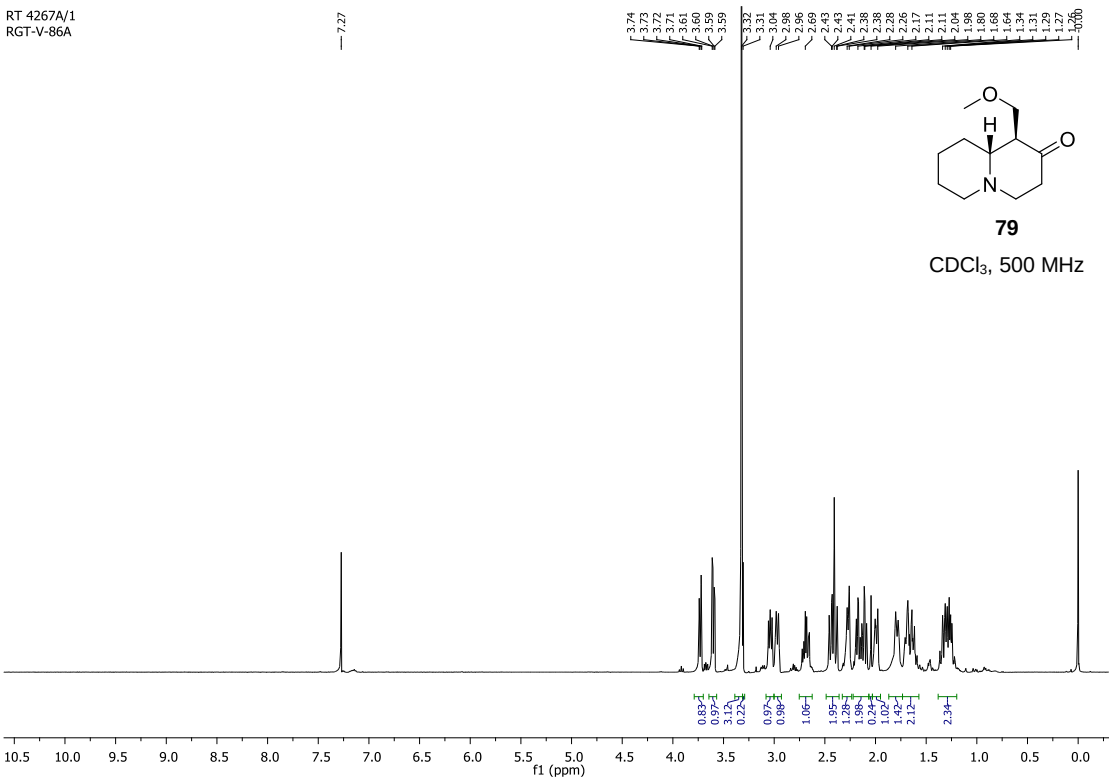
$CDCl_3$, 500 MHz

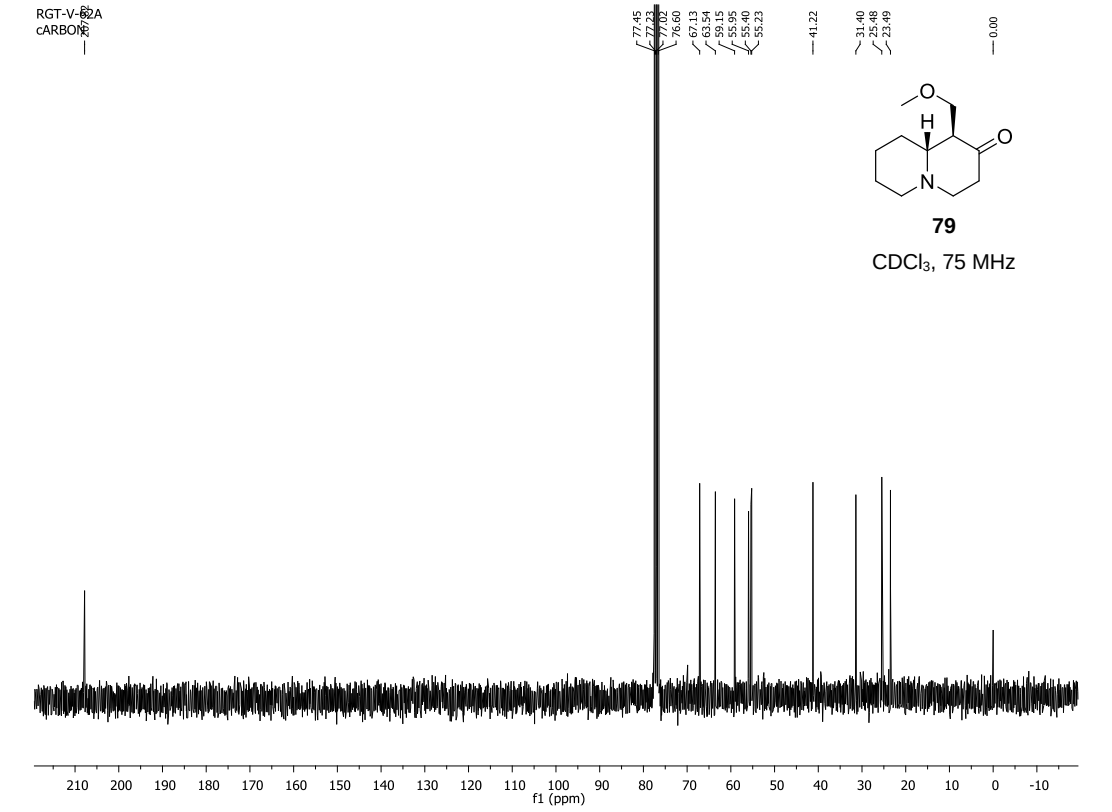
RT 4264A/1
RGT-V-85A

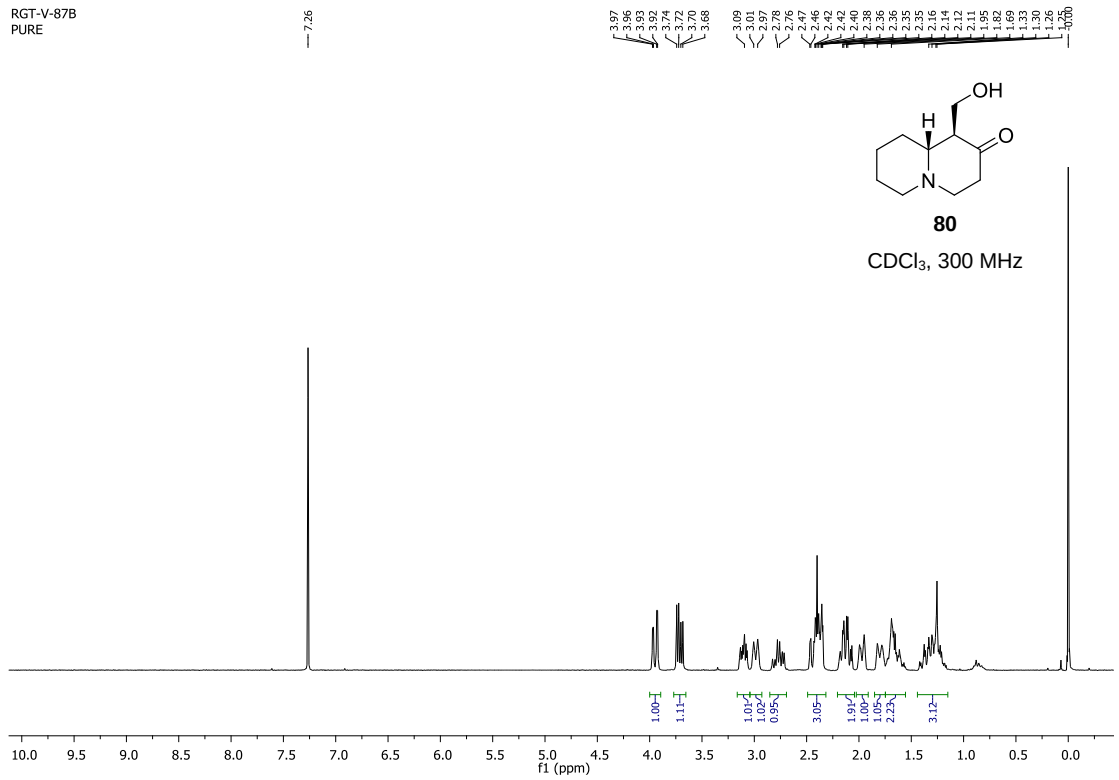


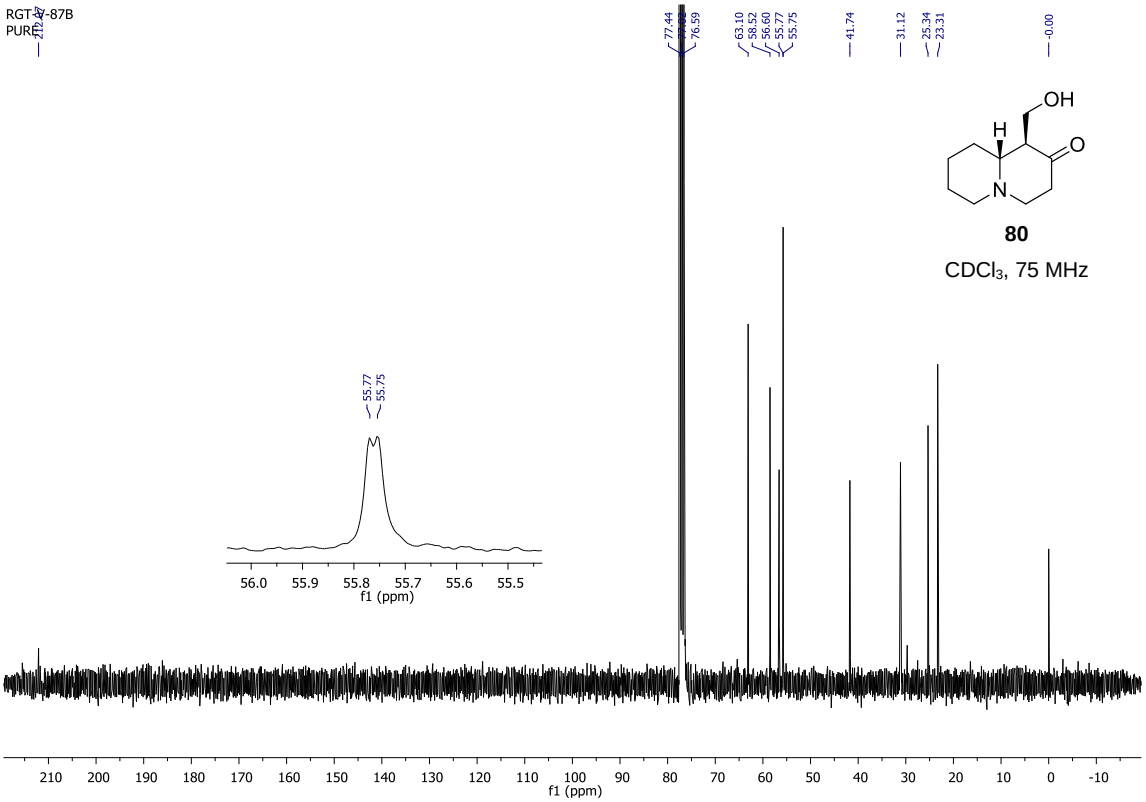
78

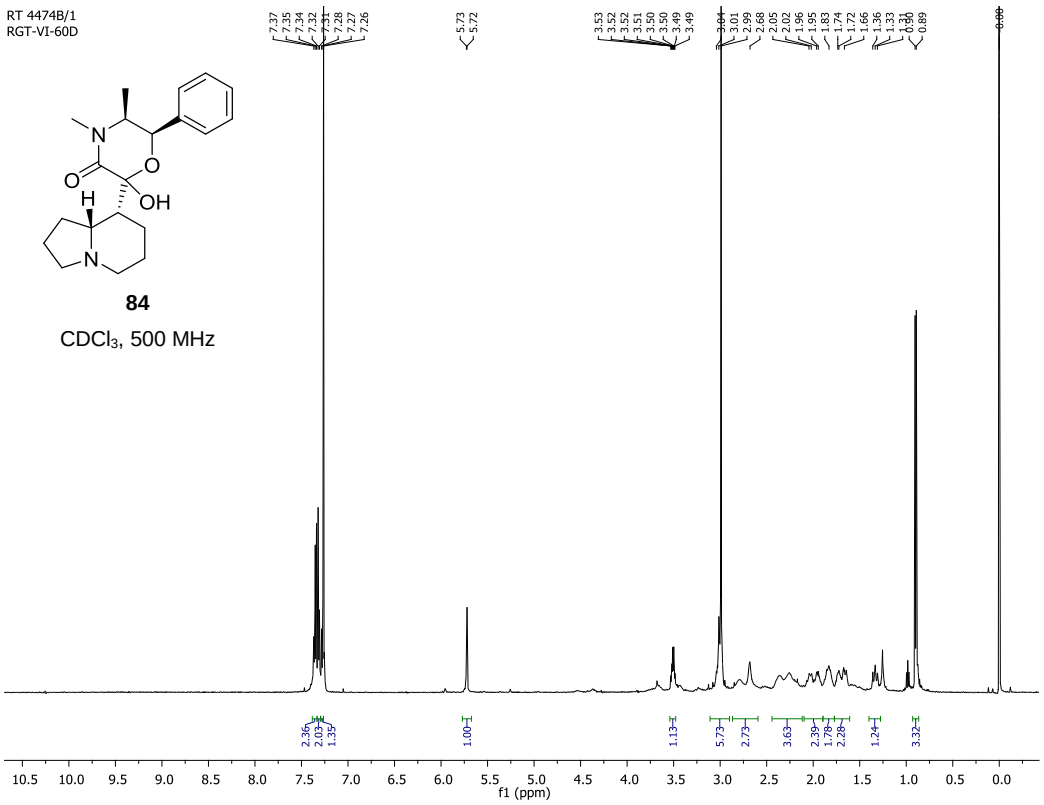
$CDCl_3$, 125 MHz


RT 4267A/1
RGT-V-86A
7.27
3.74
3.73
3.72
3.71
3.61
3.60
3.59
3.59
3.32
3.31
3.04
2.98
2.96
2.69
2.43
2.43
2.41
2.38
2.38
2.28
2.26
2.17
2.11
2.11
2.04
1.98
1.80
1.68
1.64
1.34
1.31
1.29
1.27
1.26
0.00
O
H
O
N
79
CDCl3, 500 MHz
0.83
0.97
3.12
0.22
0.97
0.99
1.06
1.95
1.28
1.98
0.94
1.02
1.42
2.12
2.34
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)


RGT-V-82A
cARBON
77.45
77.23
77.02
76.60
67.13
63.54
59.15
55.95
55.40
55.23
41.22
31.40
25.48
23.49
0.00
O
H
O
N
79
CDCl3, 75 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


RGT-V-87B
PURE
OH
H
O
N
80
CDCl3, 300 MHz
f1 (ppm)


RGT-V-87B
PURE
OH
H
O
N
80
CDCl3, 75 MHz
f1 (ppm)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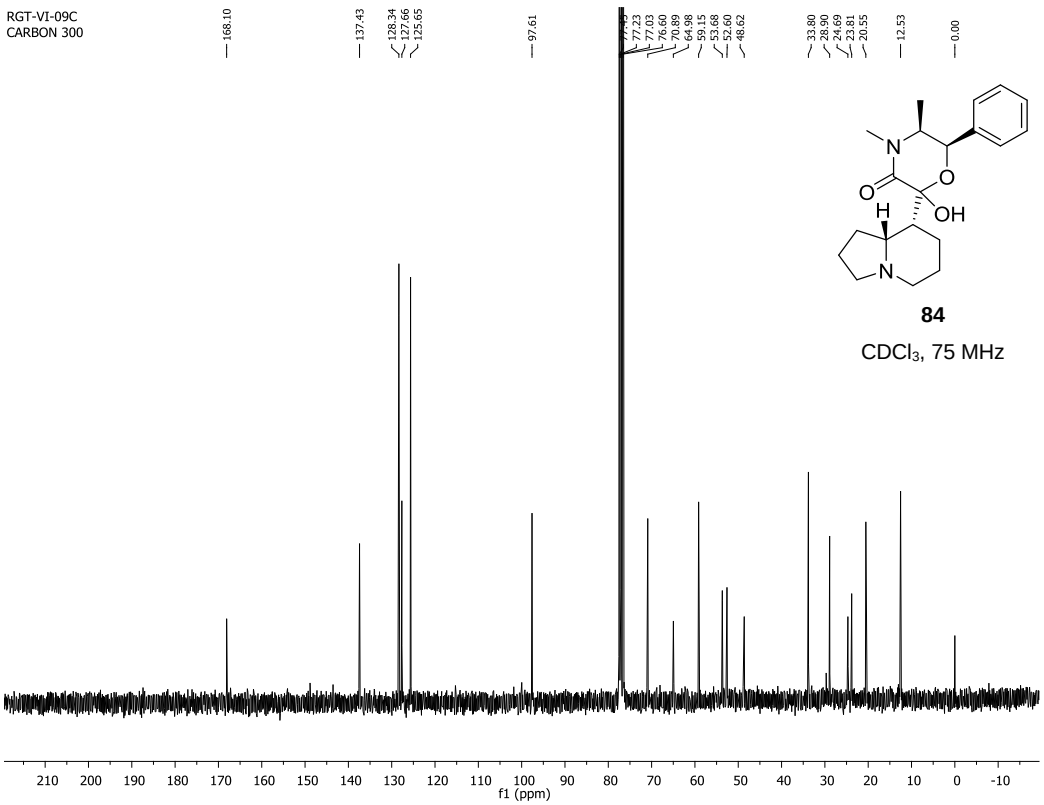
RGT-VI-60D
84
CDCl3, 500 MHz
f1 (ppm)


RGT-VI-09C
CARBON 300
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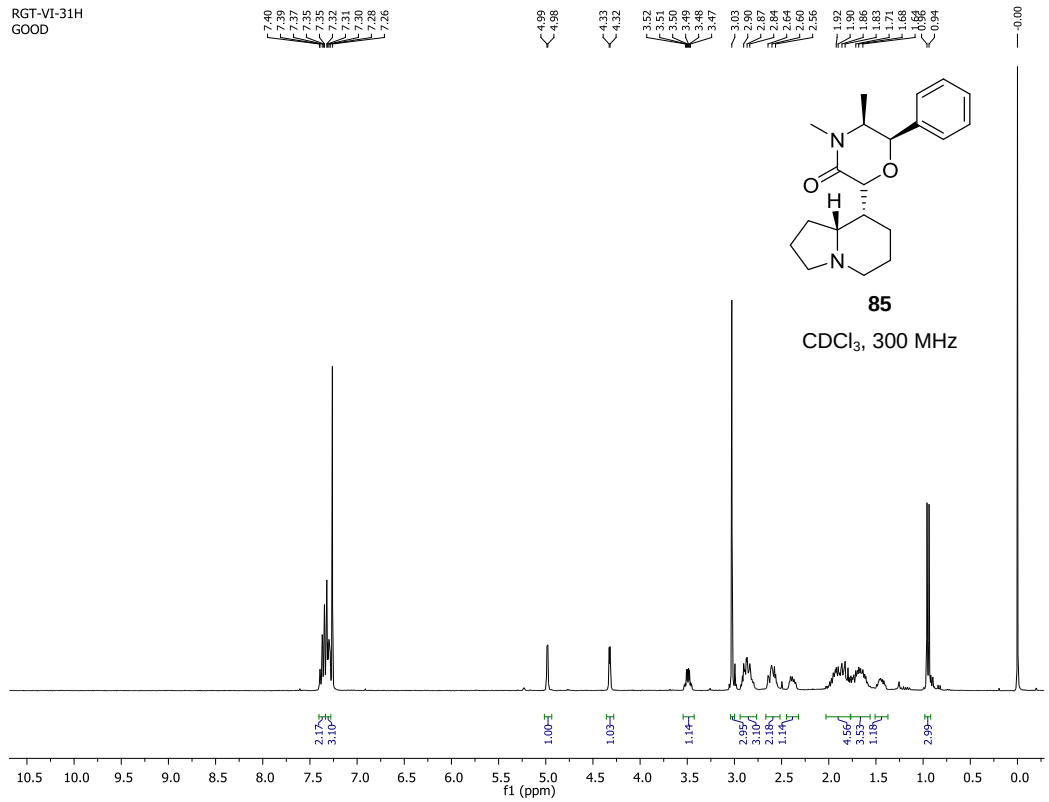
CDCl3, 75 MHz
f1 (ppm)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7.39
7.37
7.35
7.35
7.32
7.31
7.30
7.28
7.26
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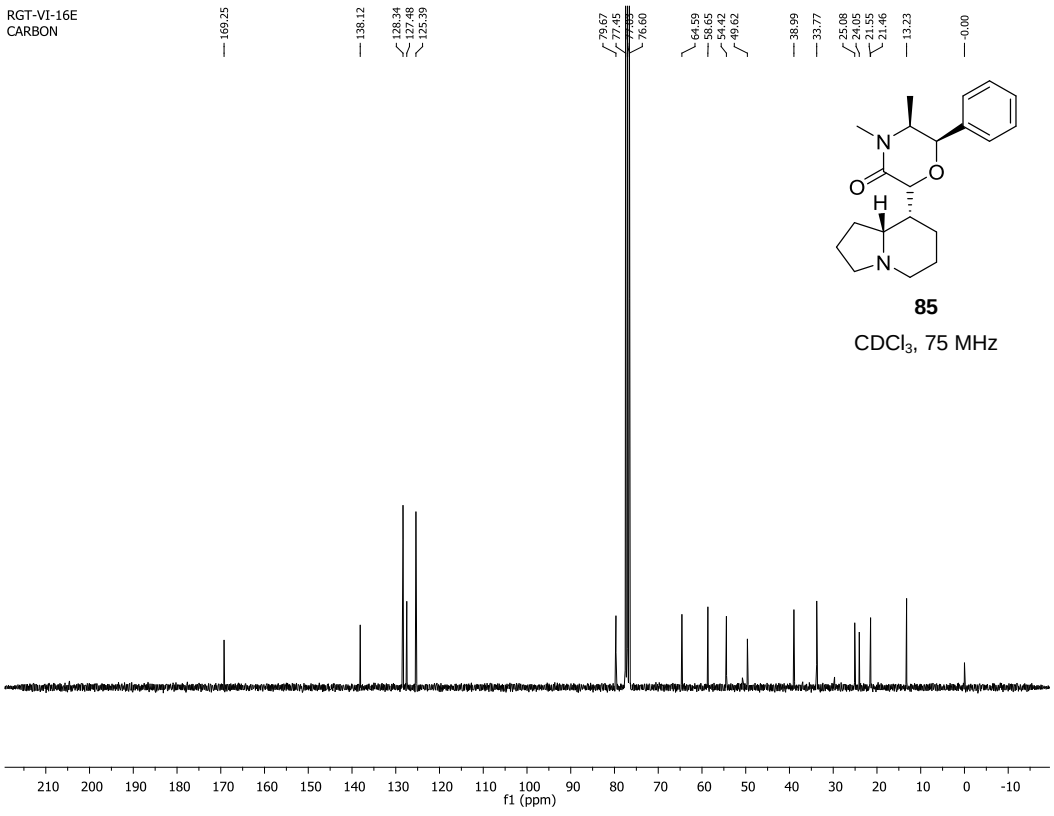
4.98
4.33
4.32
3.52
3.51
3.50
3.49
3.48
3.47
3.03
2.90
2.87
2.84
2.64
2.60
2.56
1.92
1.90
1.86
1.83
1.71
1.68
0.96
0.94
-0.00
N
O
O
H
N
85
CDCl3, 300 MHz
2.17
3.10
1.00
1.03
1.14
2.99
3.10
2.18
1.14
4.58
3.53
1.18
2.99
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


RGT-VI-16E
CARBON
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128.34
127.48
125.39
79.67
77.45
77.03
76.60
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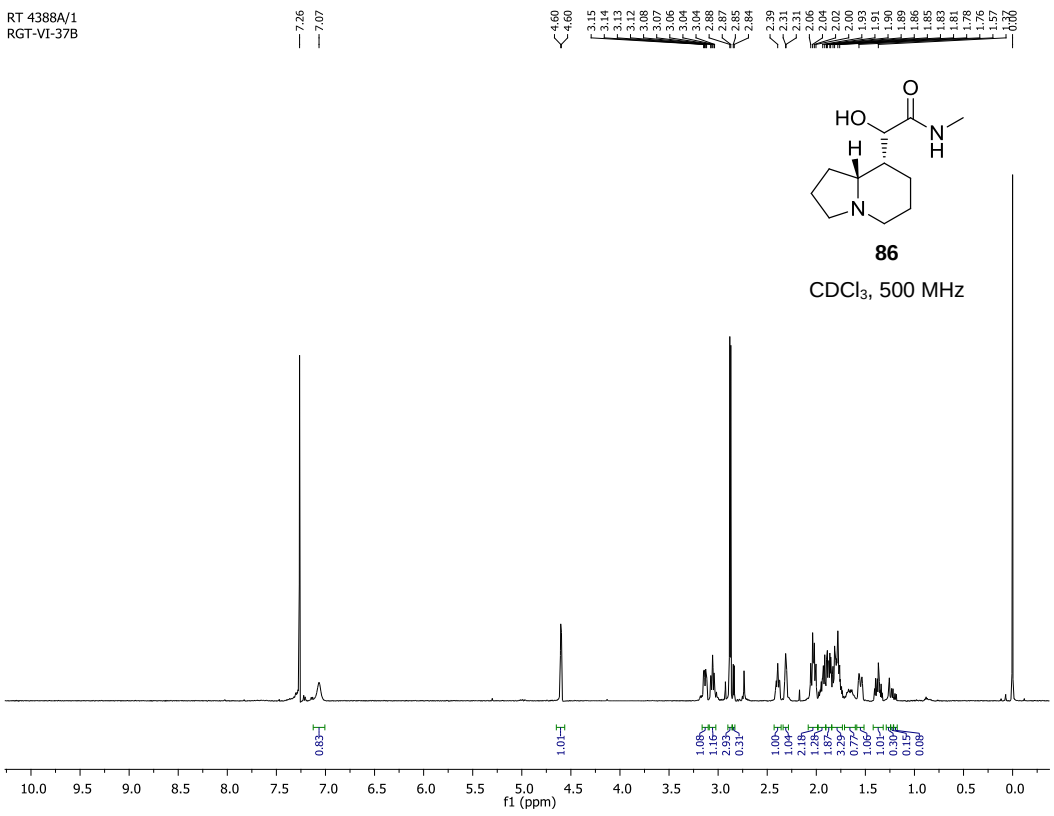
58.65
54.42
49.62
38.99
33.77
25.08
24.05
21.55
21.46
13.23
-0.00
N
O
O
H
N
85
CDCl3, 75 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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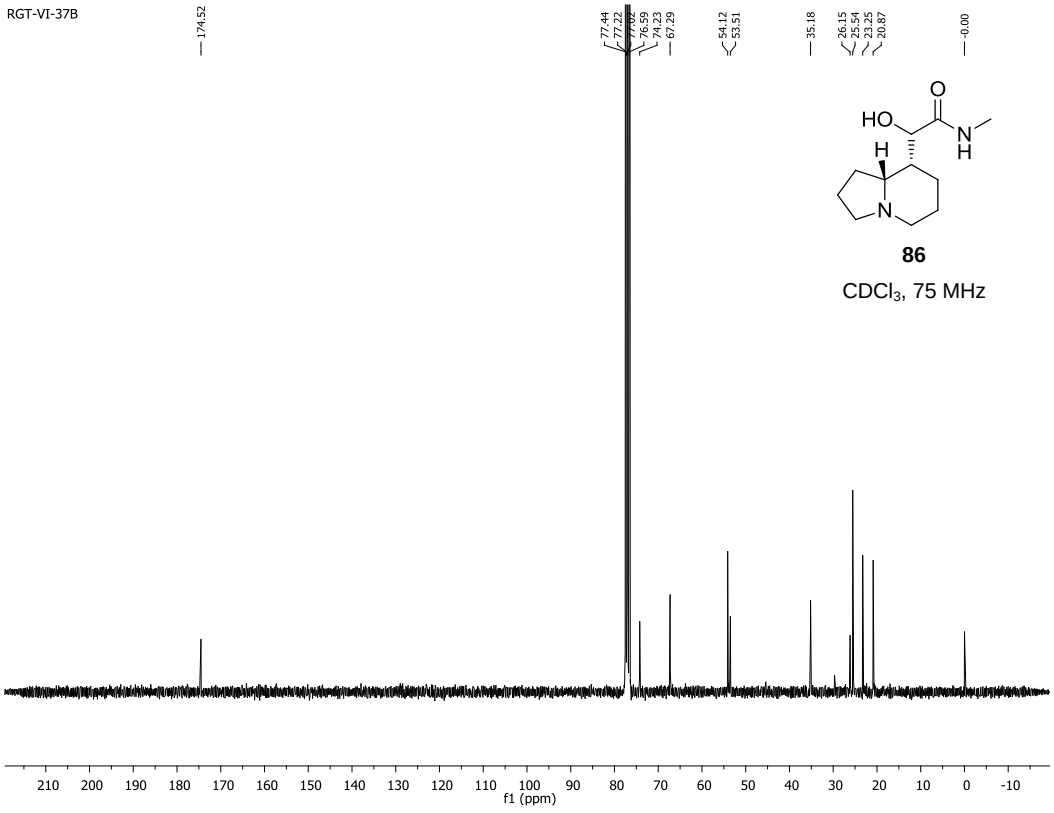
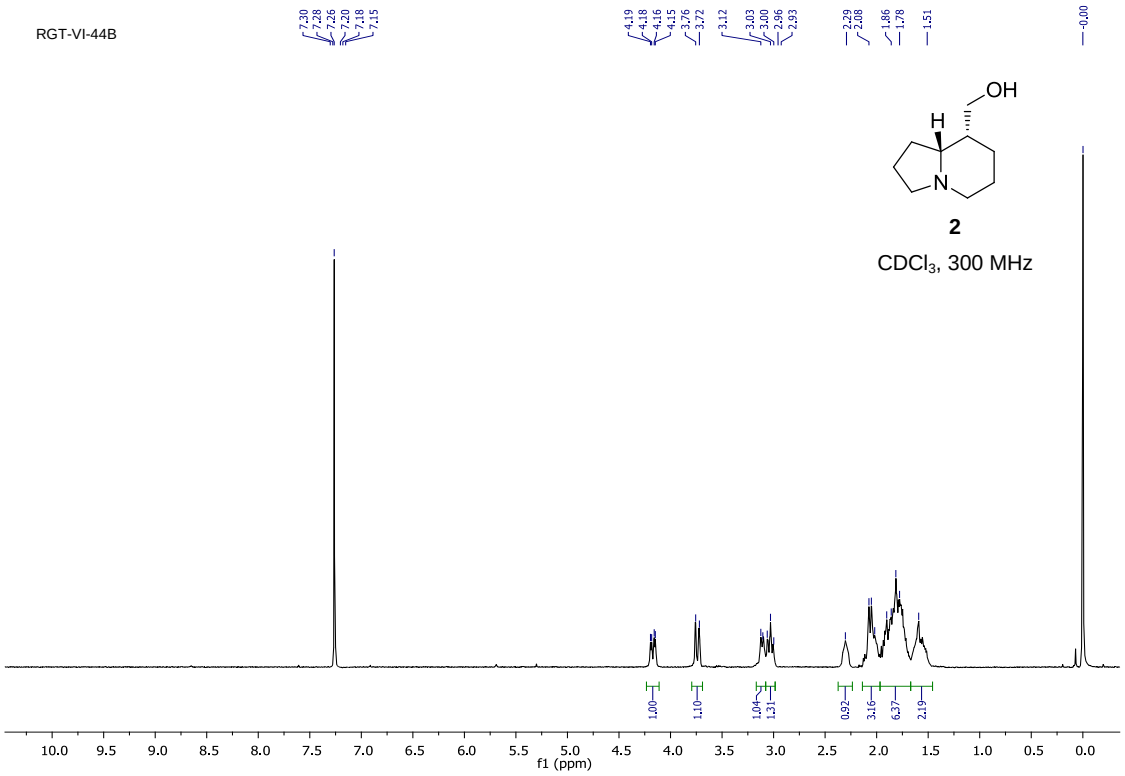
RGT-VI-37B
HO
O
N
H
H
N
86
CDCl3, 500 MHz
f1 (ppm)


RGT-VI-37B
HO
O
N
H
H
N
86
CDCl3, 75 MHz
f1 (ppm)

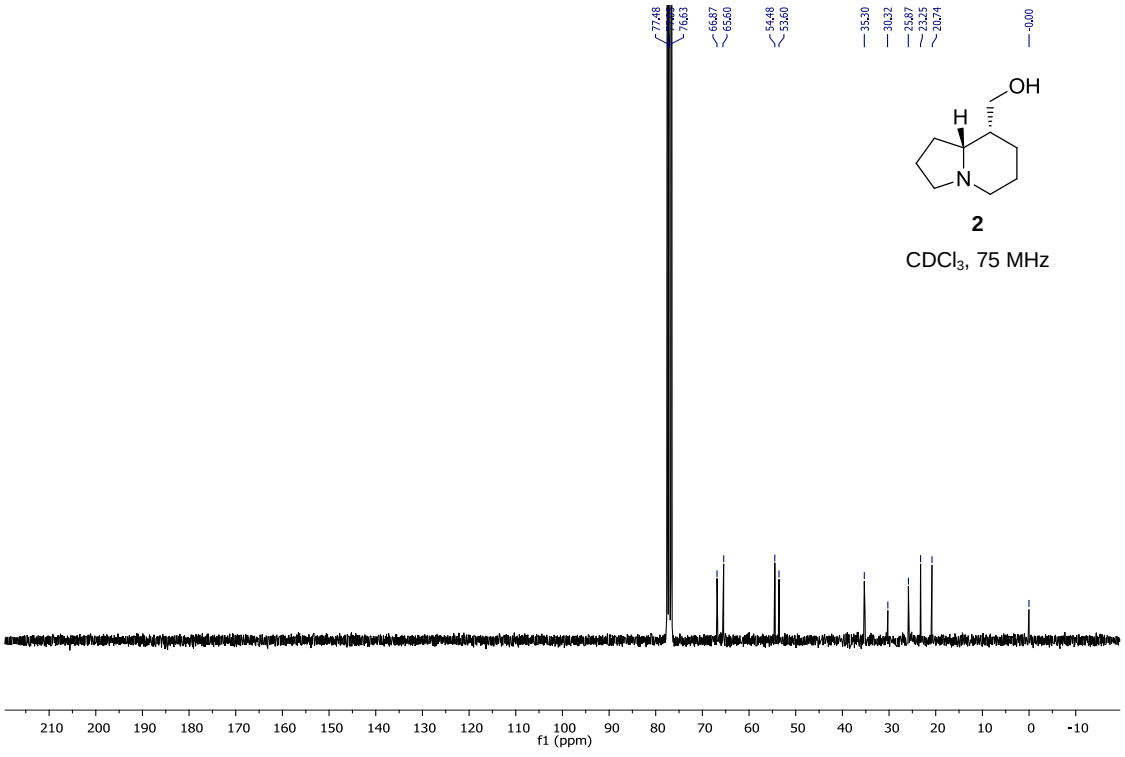
RGT-VI-44B



2

$CDCl_3$, 300 MHz

RGT-VI-56B



2

$CDCl_3$, 75 MHz

Chapter 3

Enantioselective Synthesis of Functionalized Quaternary Stereocenters

3.1 Introduction

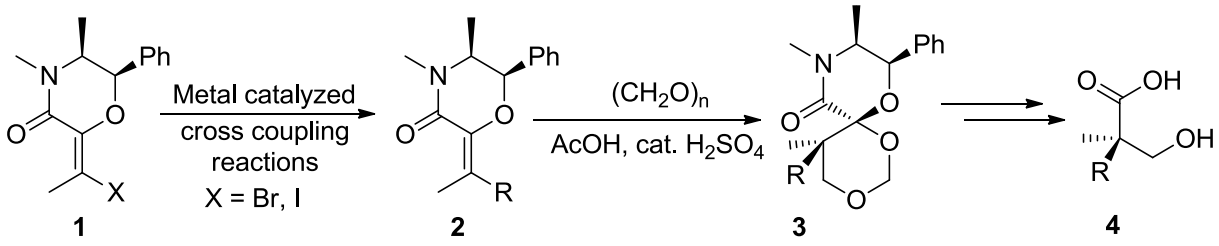
Many natural products and pharmaceuticals contain one or more quaternary stereocenters.[1] The structural complexity and diversity of these compounds combined with notable biological activities drive the need for new and efficient methods for their synthesis.[2] From a methodology-development standpoint, the stereoselective synthesis of quaternary stereocenters is challenging due to issues with reliability of any carbon-carbon bond forming reaction that is part of the synthetic protocol. This is due to steric congestion during formation of the carbon-carbon bond leading to a quaternary stereocenter.[1] Over the years, various methodologies for the construction of quaternary stereocenters have appeared in the literature. These include carbon-carbon bond-forming reactions such as the aldol reaction, the Mannich reaction, carbanion alkylation reactions, and metal-catalyzed reactions such as the Heck reaction. Among these, the aldol reaction is most closely related to the methodology described in this chapter and hence aldol-based syntheses of quaternary stereocenters have been summarized in Chapter 1.

3.2 Objective

The objective of the work reported in this Chapter was to develop a methodology for the construction of functionalized quaternary stereocenters. These can be used as precursors for the synthesis of small organic molecules with quaternary stereocenters or they can be incorporated into more complex structures. Given the difficulties in the

synthesis of quaternary stereocenters, it may or may not be possible to construct a quaternary stereocenter in a complex molecule at a later stage of the synthetic sequence. In this regard, functionalized quaternary stereocenters are of great importance due to the availability of functional groups for further transformations.

Our approach to the synthesis of quaternary stereocenters relies on two pivotal reactions of halo-alkylidene morpholinones **1** (Scheme 3.1): (1) a metal-catalyzed cross coupling reaction for the synthesis of diastereomerically pure alkylidene morpholinones **2**; and (2) a stereoselective Prins reaction of alkylidene morpholinones **2** (Scheme 3.1) which constructs the quaternary stereocenter.



Scheme 3.1 Synthetic strategy applied in this Chapter.

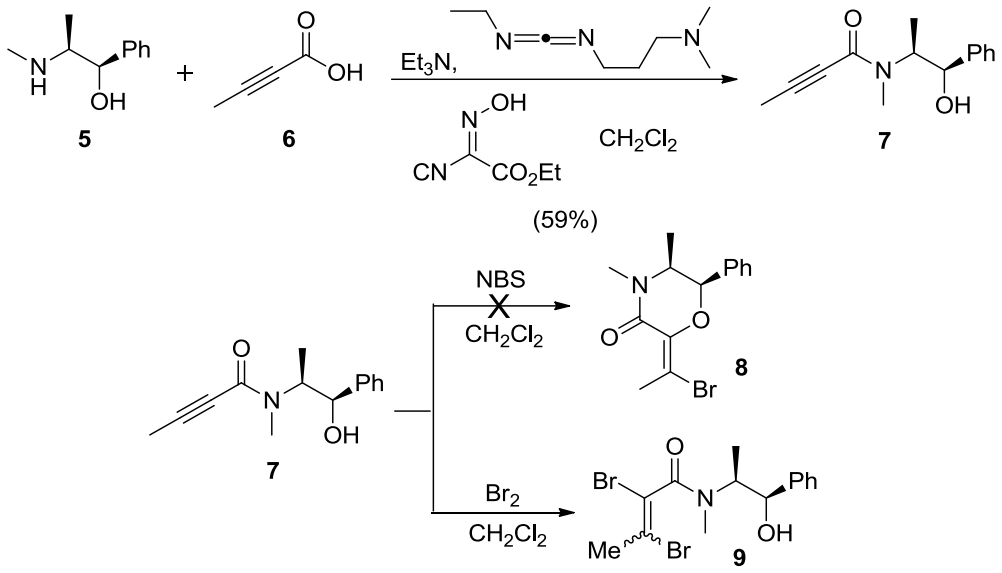
Previously in the Pansare group, Prins adducts such as **3** have been used as important intermediates for the synthesis of medium-sized oxacycles,[3] (*S*)-(+)-pantolactone[3b] and its analogues[3c] and *β*, *β*-dialkyl *α*-hydroxy-*γ*-butyrolactones.[3d] Lessons learned from these and other reactions of alkylidene morpholinones were that the addition at the carbon-carbon double bond takes place from the less-hindered face of the morpholinone, i.e. the face opposite to the methyl and phenyl groups. Hence, the focus of this investigation was the stereoselective synthesis of alkylidene morpholinones such as **2** and their conversion to **3** and **4**. Details of these studies are presented in this Chapter.

3.3 Results and Discussion

To access functionalized quaternary stereocenters with a variety of substituents, it was necessary to prepare stereochemically defined alkylidene morpholinones with different substituents on the alkene. Methods previously developed in the Pansare group for the preparation of alkylidene morpholinones **2** (Scheme 3.1) provide access only to isomeric mixtures of disubstituted alkylidene morpholinones such as **2**. Hence, a new method had to be developed which would provide either the *E* or *Z* isomers of **2** as required. Towards this objective, it was decided to explore metal-catalyzed cross-coupling reactions to synthesize the required diastereomerically pure alkylidene morpholinones. Accordingly, an immediate goal was the synthesis of haloalkylidene morpholinones **1**, which would be used as substrates for metal-catalyzed cross coupling reactions.

3.3.1 Synthesis of Haloalkylidene Morpholinones

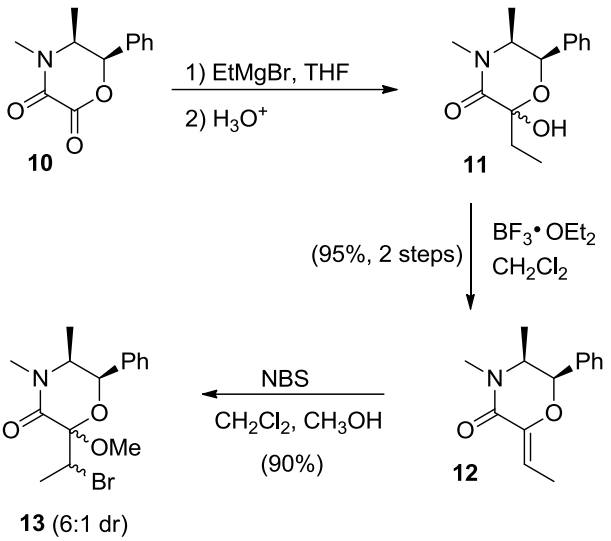
Initially, we reasoned that a strategy involving alkynoic amides as substrates for a haloetherification reaction to form haloalkylidene morpholinones would be suitable, since the related, halolactonization reactions of alkynoic acids have been reported.[4] Hence, the plan was to prepare the alkynoic amide derivative from (1*R*, 2*S*)-ephedrine (**5**) and but-2-ynoic acid (**6**) and then subject this alkynoic amide to an intramolecular haloetherification reaction.[5] Accordingly, acylation of **5** with **6**, employing 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) as the coupling agent, in the presence of ethyl 2-cyano-2-(hydroxyimino)acetate (Oxyma®) as an acyl-transfer agent, provided the required amide **7** (Scheme 3.2).



Scheme 3.2

Treatment of **7** with *N*-bromosuccinimide did not result in formation of either bromoalkene **8**, or the corresponding *E* isomer (Scheme 3.2) and **7** was recovered unreacted. However, treatment of **7** with a solution of bromine in CH_2Cl_2 generated the product **9** arising from the dibromination of the alkyne group in **7**. These observations suggested that accessing the conformer of **7** required for cyclization, namely, the conformer in which the acyl group and the ephedrine portion are *syn*, is difficult. Hence, the haloetherification approach was not pursued further. As an alternative, we reasoned that dehydration of a bromohydrin, or elimination of the elements of an alcohol from a bromo acetal, may be a more fruitful strategy for accessing **8**. To this effect, a bromoacetal derivative was prepared from the alkylidene morpholinone **12** (Scheme 3.3) which was readily made by dehydration of the hemiacetal **11** obtained from a reaction of the ephedrine-derived morpholinedione **11** with ethylmagnesium bromide. Treatment of **12**

with *N*-bromosuccinimide in CH_2Cl_2/MeOH provided the bromoacetal **13** as a 6:1 mixture of diastereomers (Scheme 3.3).



Scheme 3.3

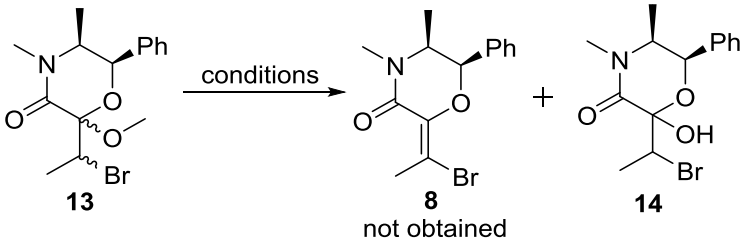


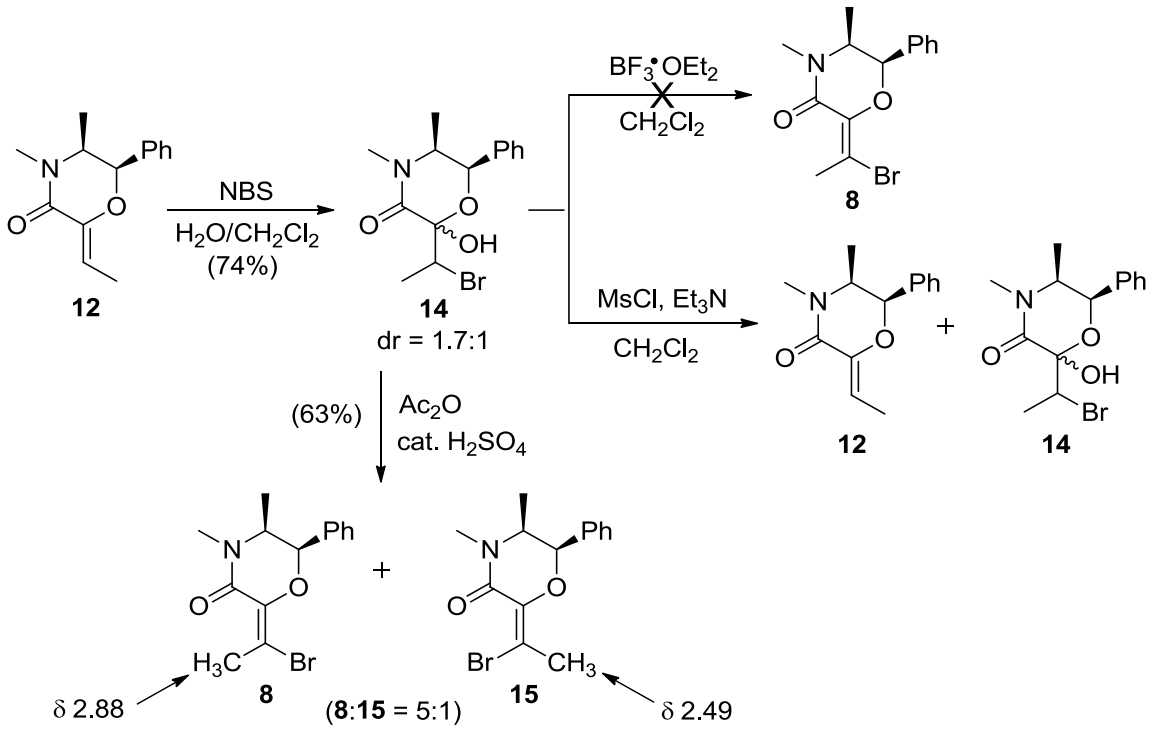
Table 3.1 Elimination studies of bromoacetal **13**.

No	Reagents	Solvent	Results
1	$BF_3 \cdot OEt_2$[a]	CH_2Cl_2	**14** (80%)
2	conc. H_2SO_4[b]	THF	**14** (73%)
3	CF_3CO_2H[b]	THF	**14** (84%)
4	$TiCl_4$[a]	CH_2Cl_2	**13** recovered
5	$ZnCl_2$[b]	CH_2Cl_2	**13** recovered
6	$InCl_3$[b]	THF	**13** recovered
7	LDA[a]	THF	**13** recovered

[a] -78 °C to room temperature, 24 h. [b] room temperature, 24 h.

With the bromoacetal **13** in hand, the possibility was examined of converting it into **8** by generating an oxonium ion from the acetal in **13**, followed by the loss of a proton, a process that would be similar to the BF_3•OEt_2 mediated conversion of **11** to **12** (as in Scheme 3.3). Surprisingly, the reaction of bromoacetal **13** with BF_3•OEt_2 provided only the hemiacetal **14** instead of the required bromoalkene **8** (entry 1, Table 3.1). Protic acid-mediated reactions of **13** were also unsuccessful and the treatment of **13** with concentrated H_2SO_4 or trifluoroacetic acid (entry 2 and 3, Table 3.1) also resulted in the formation of the hemiacetal **14**. In addition, treatment of **13** with selected metal-based Lewis acids also did not generate bromoalkene **8** (entries 3-6, Table 3.1) and unreacted **13** was recovered from these reactions. The formation of **14** in some of these reactions indicates ionization of the acetal to provide an oxocarbenium ion which is stable under the reaction conditions, and its subsequent reaction with water generates **14**. An attempted elimination of the elements of methanol from **13** under basic conditions, by treatment with LDA, was also unsuccessful, presumably due to the low acidity of the methine proton in the bromomethyl side chain in **13**.

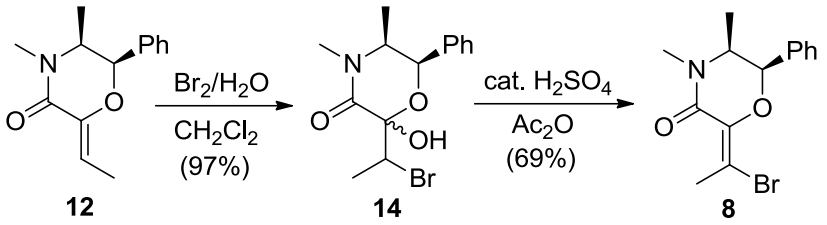
Next, the bromohemiacetal **14** (dr 1.7:1) was prepared by treating alkene **12** with *N*-bromosuccinimide in CH_2Cl_2/H_2O (Scheme 3.4). The bromohydrin **14** was then subjected to dehydration conditions. Interestingly, **14** was also resistant to dehydration under Lewis acidic conditions. It was reasoned that activation of the hemiacetal as a mesylate would facilitate oxocarbenium ion formation from **14**. Surprisingly, treatment of **14** with methanesulfonyl chloride in the presence of triethylamine as a base afforded a mixture of **12** (45%, ^{1}H NMR of the crude product, Scheme 3.4) and unreacted **14** (55%). The exact reasons for the formation of alkene **12** are unclear.



Scheme 3.4

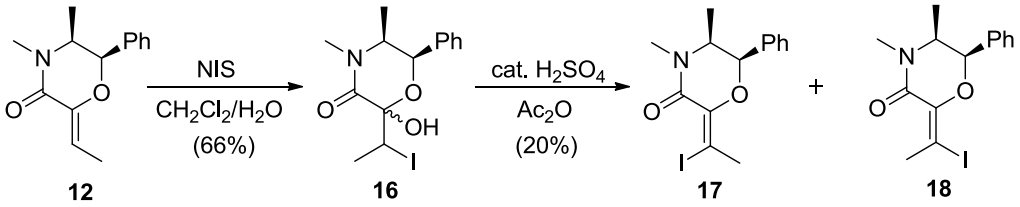
However, when the bromohydrin **14** was treated with acetic anhydride in the presence of catalytic amounts of concentrated H_2SO_4, a dehydration protocol reported by Mamedov et al.,[6] the bromoalkene was obtained as mixture of isomers **8** and **15** (*E*:*Z* = 1:5, Scheme 3.4). The stereochemistry of alkene **8** was assigned as *Z* on the basis of a downfield resonance of the olefinic methyl group (2.88 ppm), compared to the corresponding methyl group resonance (2.49 ppm) for the isomeric *E* alkene **15**.[3c,7] Morpholinones **8** and **15** are not separable by flash chromatography and the bromohemiacetal **14** is always obtained as an inseparable mixture with succinimide that is obtained from NBS during the preparation of **14**. In order to simplify the preparation of the bromoalkene, the bromohemiacetal synthesis was modified by treating **12** with a solution of bromine in water to provide **14**. Interestingly, the dehydration of **14** obtained by this procedure provided **8** as the only

product. The precise reasons for the formation of both **8** and **15** from **14** obtained from the NBS reaction are not known. It is possible that the succinimide contaminant in **14** influences the stereochemical course of the dehydration step, but this has not been verified. Thus, the optimal procedure for the conversion of **12** to **8** involves treating **12** with a solution of bromine in water to provide **14**, followed by dehydration of crude **14** with Ac_2O/H_2SO_4 (Scheme 3.5). This two-step protocol provides **8** in 67% yield from **12**.



Scheme 3.5

In related studies, the treatment of **12** with *N*-iodosuccinimide in CH_2Cl_2/H_2O provided the iodohemiacetal **16**. However, dehydration of **16** furnished a mixture of the *E*-iodoalkene **17** and *Z*-iodoalkene **18** in poor yield (Scheme 3.6). Although the *E* and *Z* iodoalkenes were separable by column chromatography, the *E*-iodoalkene **17** was always obtained as a mixture with unreacted iodohemiacetal **16**.



Scheme 3.6

The formation of both **17** and **18** in the dehydration of **16** is surprising, as only the *Z*-alkene is obtained in the dehydration of the bromohemiacetal **14**. The exact reasons for this difference in reactivity are unclear, but one probable cause could be the carbon-iodine bond length. Since the carbon-iodine bond (2.10 Å) is longer than a carbon-bromine bond (1.88 Å),[8] it is plausible that electronic repulsion between iodine and the lone pair on the carbonyl group in **17** is less severe as compared to a similar repulsion between bromine and the carbonyl lone pair in **15**. Assignment of the *E* and *Z* stereochemistry of **17** and **18** is based on the resonance of the olefinic methyl protons (2.40 ppm for **17** (*E*) vs 3.08 ppm for **18** (*Z*)) in the ^{1}H NMR spectrum.

A brief study was conducted to optimize the selective formation of **17** or **18** by variation of the dehydration conditions. In the best result, the use of trifluoromethanesulfonic acid (entry 8, Table 3.2) offered a mixture of iodoalkenes **17** and **18** with moderate selectivity (*E*:*Z* = 5:1) and no side-product formation. For further studies, **17** and **18** were separated by flash column chromatography. These results are summarized in Table 3.2.

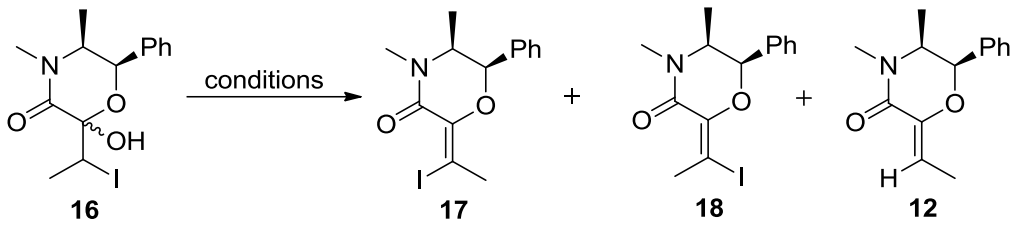


Table 3.2 Survey of dehydration conditions for **16**.

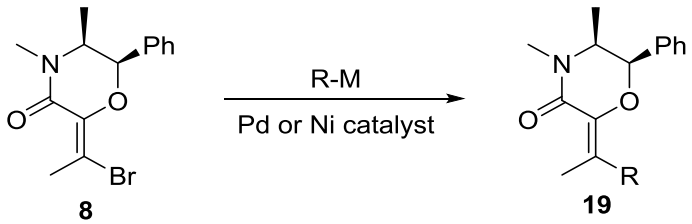
No.	Conditions[a]	Solvent	Result	Yield (%) or product ratio
1	TFA	CH_2Cl_2	**12**	90
2	Et_3N, MsCl	CH_2Cl_2	**12**	95
3	$TiCl_4$[c]	CH_2Cl_2	**12**	62
4	conc. H_2SO_4	CH_2Cl_2	**12**	90
5	pyridine, AcCl	CH_2Cl_2	**16**	-
6	AcCl	pyridine	**16**	-
7	Ac_2O, H_2SO_4	CH_2Cl_2	**12**	90
8	TfOH	Ac_2O	**17** + **18**	5:1[b]
9	TFA	Ac_2O	**12** + **16**	2.8:1[b]
10	CSA	Ac_2O	**12**	83
11	CH_3SO_3H	Ac_2O	**12** + **17** + **18**	2.5:2.5:1[b]
12	*p*-TsOH	Ac_2O	**12** + **17**	4:1[b]
13	$(CF_3CO)_2O$	Ac_2O	**16**	-
14	$HClO_4$	THF	**16**	-
15	2,4-dinitrobenzenesulfonic acid	Ac_2O	**17** + **18**	2:1[b]
16	2,4,6-triisopropylbenzene sulfonic acid	Ac_2O	**12**	69

[a] room temp., 24 h., [b] ^1H NMR spectrum of crude product., [c] -78 °C to room temp., 4 h.

3.3.2 Cross-Coupling Reactions of Haloalkylidene Morpholinones

3.3.2.1 Negishi Coupling Reactions

With the haloalkenes **8** and **18** in hand, their metal-catalyzed cross-coupling reactions were investigated. First, the reactivity of haloalkylidene morpholinones under Negishi coupling conditions was explored. Alkenyl halides are known to undergo Negishi coupling reactions with various organozinc reagents to produce substituted alkenes.[9] However, attempted Negishi coupling of the bromoalkene **8** in the presence of $Ni(acac)_2$ or a variety of Pd catalysts did not furnish the desired coupled product.



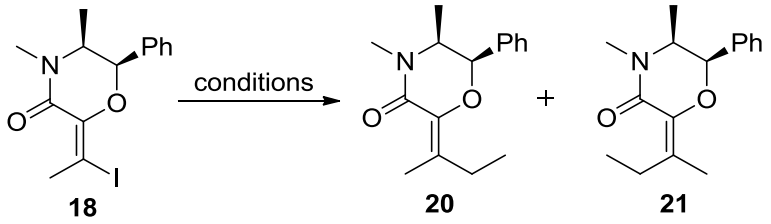
Scheme 3.7 Negishi coupling reaction of bromoalkene **8**.

Table 3.3 Survey of reaction conditions for Negishi coupling reaction of **8**.

No	Conditions[a]	Catalysts	Result
1	EtZnBr, TMEDA	$PdCl_2(PPh_3)_2$	**8** recovered
2	EtZnBr	$PdCl_2(PPh_3)_2$	**8** recovered
3	EtZnBr[b]	$Pd(PPh_3)_4$	**8** recovered
4	EtZnI	$Ni(acac)_2$	**8** recovered
5	*i*-PrZnBr	$PdCl_2$(dppf)	**8** recovered
6	*n*-BuLi, $ZnBr_2$	$PdCl_2(PPh_3)_2$	**8** recovered
7	cyclohexylZnBr	$PdCl_2$(dppf)	**8** recovered

[a] room temp., THF, 24 h., [b] room temp., 16 h, 60 °C, 12 h, THF.

In all of these reactions unreacted bromoalkene **8** was recovered. These results are summarized in Table 3.3. In related studies, the iodoalkene **18** was also subjected to the Negishi coupling reaction. In initial studies, iodoalkene **18** generated the expected products **20** and **21** as a mixture of isomers (*E*:*Z* 1:2.4-2.7) with nickel or palladium catalysts (entries 3 and 4, Table 3.4). Unfortunately, these results could not be reproduced in repeated attempts.



18 **20** **21**

Scheme 3.8 Negishi coupling reaction of iodoalkene **13**.

Table 3.4 Survey of reaction conditions for Negishi coupling of **18**.

No.	Conditions [a]	Catalysts	Result
1	EtZnBr, TMEDA [b]	$PdCl_2(PPh_3)_2$	**18** recovered
2	EtZnBr, THF	$Pd(PPh_3)_4$	**18** recovered
3	EtZnI, THF, rt	$PdCl_2$(dppf)	**20**:**21** 2.4:1 [c]
4	EtZnI, TMEDA	$Ni(acac)_2$	**20**:**21** 2.7:1 [c]

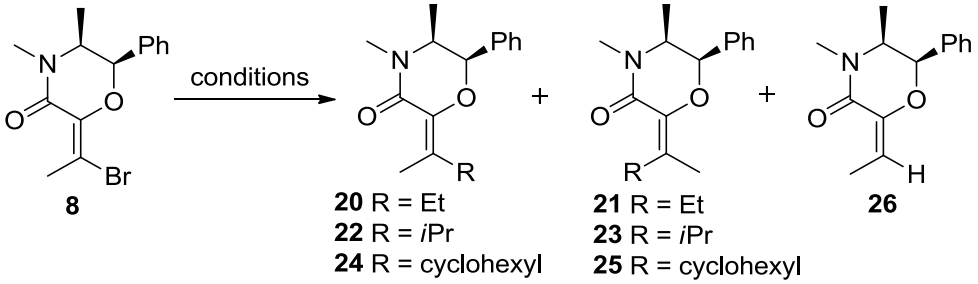
[a] room temp., THF, 24 h., [b] room temp., THF, 24 h and 16 h, 60 °C., [c] ^{1}H NMR of crude product.

The mechanistic aspects involved in the formation of product **21** are unclear, since the starting iodoalkene **18** is diastereomerically pure. Furthermore, it is surprising that the reaction was not reproducible. Considering the lack of reactivity of **8** and the capricious

reactivity of **18**, Negishi coupling reactions for the preparation of alkylidene morpholinones from **8** and **18** were not examined further.

3.3.2.2 Kumada Coupling Reactions of bromoalkylidene morpholinone 8

Kumada coupling reactions of bromoalkene **8** with selected Grignard reagents were next investigated.[10] The results of this study are summarized in Table 3.5. The bromoalkene **8** failed to form any of the expected cross-coupled products in the presence of nickel catalysts (entries 1-3, Table 3.5). Bromoalkene **8** also failed to generate any coupling products with cyclohexylmagnesium bromide in the presence of palladium catalysts (entries 10-12, Table 3.5). A coupling reaction of **8** with ethylmagnesium bromide did not provide any of the coupled products with $Pd(OAc)_2$ as catalyst (entry 6, Table 3.5). Treatment of **8** with isopropylmagnesium chloride in presence of $PdCl_2(PPh_3)_2$ as a catalyst provided the coupled product **22** as a mixture with reduction product **26**, and unreacted **8** (30%) was also recovered (entry 5, Table 3.5). Bromoalkene **8** also furnished the coupled product **20** (with EtMgBr) as a mixture with the reduction product **26** and unreacted **8** (entry 7, Table 3.5). An increase in catalyst loading for this reaction resulted in complete consumption of bromoalkene **8**, but **20** was once again obtained as a mixture with **26** (entry 8, Table 3.5). Interestingly, bromoalkene **8** furnished exclusively the coupled product **20** in the presence of $PdCl_2(dppf)\bullet CH_2Cl_2$ as a catalyst, albeit in low yield (30%, entry 9, Table 3.5). It is evident from these studies that bromoalkene **8** is less reactive with sterically demanding Grignard reagents under the Kumada coupling conditions.



Scheme 3.9 Kumada coupling reactions of bromoalkene **8**.

Table 3.5 Catalyst survey for Kumada coupling reaction of bromoalkene **8**.

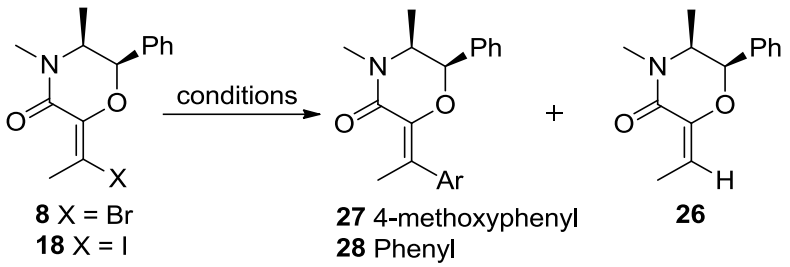
No.	RMgX	Catalysts[a]	Results	Ratio of Products
1		$NiCl_2$	**8**	-
2		$Ni(acac)_2$	**8**	-
3	*i*PrMgCl	$Ni(acac)_2$[b]	**8**	-
4		$Pd(PPh_3)_4$	**8**	-
5		$PdCl_2(PPh_3)_2$	**22** + **26** + **8**	3:1:1
6		$Pd(OAc)_2$	**8**	-
7		$PdCl_2(PPh_3)_2$	**20** + **26** + **8**	4.3:1:3
8	EtMgBr	$PdCl_2(PPh_3)_2$[c]	**20** + **26**	3:1
9		$PdCl_2$(dppf)	**20**	30%[d]
10		$Pd(OAc)_2$[c]	**8**	-
11	cyclohexylMgBr	$PdCl_2$(dppf)	**8**	-
12		$PdCl_2(PPh_3)_2$[c]	**8**	-

[a] 10 mol% catalyst, THF, 24 h, room temp., [b] 10 mol% TMEDA as additive,
[c] 30 mol% catalyst, [d] isolated yield.

Although Kumada coupling reactions of **8** did produce the required coupled products **20** and **22**, their yields were a major concern. In order to obtain alkylidene morpholinones in higher yields, as well as to improve the substrate scope, the bromoalkene **8** and iodoalkene **18** were also tested in Suzuki-Miyaura coupling reactions.

3.3.2.3 Suzuki-Miyaura Coupling Reactions

In initial studies, the Suzuki-Miyaura coupling reactions of **8** and **18** with 4-methoxyphenylboronic acid were investigated. Iodoalkene **18** failed to provide any of the expected product **27** (entry 1, Table 3.6). Instead, the only product obtained was the *E*-alkene **26**, presumably arising from reduction of the iodoalkene **18**. Under similar reaction conditions, with $Pd(PPh_3)_4$ as a catalyst the bromoalkene **8** provided the alkene **27** (entry 2, Table 3.7). However, this reaction was incomplete even after 48 h of heating. In a related reaction, alkene **26** was obtained in good yield (75%, entry 3, Table 3.7) from bromoalkene **8** using $PdCl_2(dppf)\cdot CH_2Cl_2$ as the catalyst and Cs_2CO_3 as the base. Fortunately, in these coupling reactions of **8**, there was no formation of alkene **26** (as was seen with **18**). Following the optimized reaction conditions (entry 3, Table 3.6), the alkylidene morpholinone **28** was prepared from **8** and phenylboronic acid (entry 5, Table 3.6).



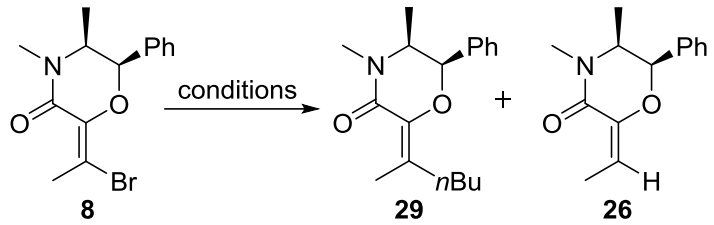
Scheme 3.10 Suzuki-Miyaura coupling reactions of alkenes **8** and **17**.

Table 3.6 Survey of catalysts and reaction conditions for Suzuki-Miyaura coupling reactions of **8** and **18**.

No	Substrate	Catalysts	Base	Solvent[a]	Time	Result
1	**18**	$Pd(PPh_3)_4$	Na_2CO_3	1,4-dioxane	6 h	**26** (81%)
2	**8**	$Pd(PPh_3)_4$	Na_2CO_3	1,4-dioxane	48 h	**8** + **27**
3		$PdCl_2(dppf)•CH_2Cl_2$	Cs_2CO_3	CH_3CN	2 h	**27** (75%)
4		$PdCl_2(dppf)•CH_2Cl_2$	Cs_2CO_3	THF	5 h	**27** (70%)
5		$PdCl_2(dppf)•CH_2Cl_2$	Cs_2CO_3	CH_3CN	5 h	**28** (75%)

[a] All reactions were carried at the reflux temperature of the corresponding solvent.

With the alkenes **27** and **28** in hand, the synthesis of alkylidene morpholinones with alkyl substituents such as the morpholinone **20** (Scheme 3.9) through Suzuki-Miyaura coupling reactions were evaluated. Treatment of bromoalkene **8** with butylboronic acid under a variety of Suzuki-Miyaura conditions furnished the required product **29** as a mixture with **26** (Scheme 3.11). These results are summarized in Table 3.7.



8 **29** **26**

Scheme 3.11 Suzuki-Miyaura coupling reaction of alkene **8** with butylboronic acid.

Table 3.7 Survey of reaction conditions for Suzuki-Miyaura coupling of **8** with butylboronic acid.

No	Catalysts	Base	Solvent[a]	Time	Result	Ratio of Products[b]
1	$PdCl_2(dppf)$	Cs_2CO_3	CH_3CN	2 h	**8**	-
2	$PdCl_2(PPh_3)_2$	Cs_2CO_3	THF	24 h	**8**	-
3	$PdCl_2(PPh_3)_2$	K_2CO_3	CH_3CN	5 h	**8**	-
4	$Pd(OAc)_2$	K_2CO_3	THF	48 h	**8**	-
5	$Pd(OAc)_2$	Cs_2CO_3	THF	48 h	**8**	-
6	$Pd(PPh_3)_4$	K_2CO_3	THF	48 h	**29** + **26** + **8**[c]	2.7:2.3:1
7	$Pd(PPh_3)_4$	Cs_2CO_3	CH_3CN	24 h	**29** + **26**[c]	2.5:1
8	$Pd(PPh_3)_4$	K_2CO_3	1,2-DME	5 h	**29** + **26**	3.3:1
9	$Pd(PPh_3)_4$	Cs_2CO_3	1,2-DME	5 h	**29** + **26**	1.3:1

[a] All reactions were conducted at the reflux temperature for the solvent used., [b] ^1H NMR analysis of crude., [c] isolated yield (42%).

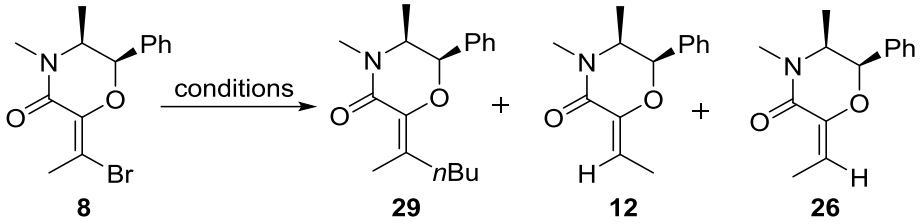
Notably, Palladium (II) catalysts such as $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$ or $PdCl_2(dppf)\cdot CH_2Cl_2$ did not provide any of the coupled product **29** (entries 1-5, Table 3.7). This was unexpected because the use of Palladium (II) salts (as a source of Pd (0)) in Suzuki-Miyaura coupling reactions is well known.[11] In a related reaction, bromoalkene **8**

provided the cross-coupled product **29** in the reaction catalyzed by $Pd(PPh_3)_4$ (entries 6-9, Table 3.7). The reaction was incomplete when K_2CO_3 was used as a base (entry 6, Table 3.7) but complete consumption of bromoalkene **8** was observed when Cs_2CO_3 was used as base (entry 7, Table 3.8). Although the yield of product **29** was identical for these two reactions (42%), when Cs_2CO_3 was employed, higher amounts of reduction product **26** were obtained. The use of 1,2-dimethoxyethane reduced the reaction time to 5 hours (entries 8-9, Table 3.8), but resulted in higher amounts of the reduction product **26** (entry 7, (26%) and entry 9, (43%)).

Microwave assisted Suzuki-Miyaura coupling reactions are known, and the most important effect of microwave heating on a Suzuki-Miyaura reaction is a reduction in reaction times.[12] Apart from reduced reaction times, a sealed microwave reaction vessel provides an opportunity to carry out reactions at high temperatures and pressures. Hence, the possibility of microwave heating for the cross-coupling of bromoalkene **8** with butylboronic acid were explored and the results of these studies are summarized in Table 3.8.

Attempted cross-coupling of **8** and butylboronic acid in THF (entry 1 and 2, Table 3.8) with $Pd(PPh_3)_4$ as the catalyst and with microwave irradiation did not result in the formation of **29**. The bromoalkene **8** was recovered from these reactions. A similar reaction performed in 1,2-dimethoxyethane as the solvent with 10 mol% of $Pd(PPh_3)_4$ as the catalyst furnished the cross-coupled product **29** (65%) in good yield and with minimal formation of reduction products (entry 3, Table 3.8). In an attempt to suppress the side product formation completely, the catalyst loading was lowered. However, it was observed that at lower catalyst loadings (entries 4 and 5, Table 3.8) side product formation was more than

under the standard conditions (10 mol% catalyst loading, entry 3, Table 3.8). The reasons for the formation of **12** and **26** in these reactions are not known at this time. Therefore 10 mol% catalyst loadings were employed for the Suzuki-Miyaura coupling reactions of **8** with selected alkylboronic acids.



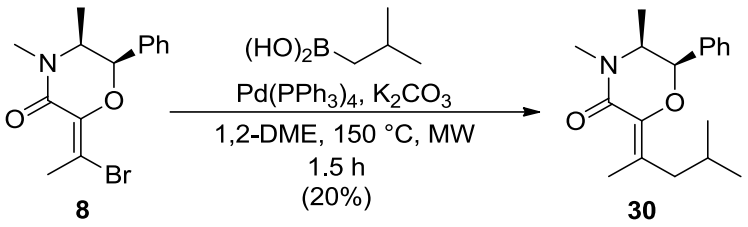
8 **29** **12** **26**

Table 3.8 Optimization studies for microwave assisted Suzuki-Miyaura coupling reaction of **8**.

No	Catalyst loading	Base	Solvent	Temp.	Time	Ratio of products[a]		
						12	**26**	**29**
1	10 mol%	K_2CO_3	THF	100 °C	4 h	-	-	-
2	10 mol%	Cs_2CO_3	THF	100 °C	4 h	-	-	-
3	10 mol%	K_2CO_3	1,2-DME	150 °C	1.5 h	1	1.7	33
4	1 mol%	K_2CO_3[c]	1,2-DME	150 °C	1.5 h	1	2.3	10
5	5 mol%	K_2CO_3[d]	1,2-DME	150 °C	1.5 h	1	1.2	3.5

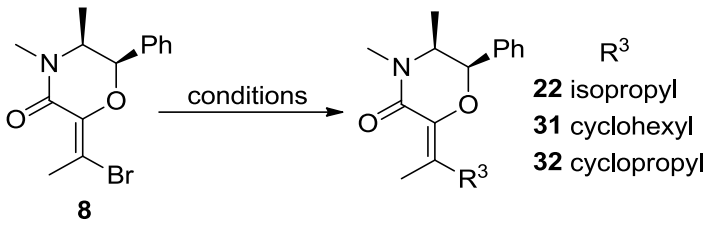
[a] ^{1}H NMR analysis of the crude product.

With the conditions optimized for the coupling reaction, isopropyl-, cyclopropyl-2-methylpropyl- and cyclohexylboronic acids were examined in the cross-coupling reactions of **8**. Of these, only (2-methylpropyl)boronic acid furnished the cross-coupled product **30** in low yield (20%, Scheme 3.12).



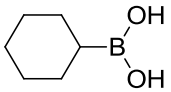
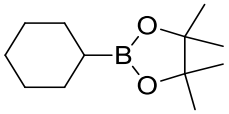
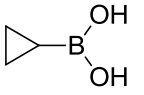
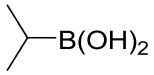
Scheme 3.12 Cross coupling reaction of bromoalkene **8** with (2-methylpropyl) boronic acid.

For the reactions with cyclopropylboronic acid and cyclohexylboronic acid, consumption of bromoalkene **8** was observed, but only the reduction products **12** and **26** were detected and/or isolated. These results are summarized in the Table 3.10. Although the use of microwave irradiation reduces the reaction time, it also provides a very harsh reaction environment and the stability of cyclic boronic acids under microwave heating was in doubt. Hence, a few reactions were also conducted under conventional heating. Unfortunately, none of the reactions provided cross-coupled products (entries 1 and 3-5, Table 3.9). Since alkyl boronate esters are also good coupling partners in Suzuki-Miyaura coupling reactions,[13] cyclohexylboronic acid was converted to the corresponding pinacol boronate which was tested in the coupling reactions. However, the bromoalkene **8** failed to provide any of the expected cross-coupled product with cyclohexyl pinacol boronate under microwave irradiation as well as conventional heating conditions (entries 8 and 9, Table 3.9). Cyclopropylboronic and isopropylboronic acids also failed to give any of the coupling products (entries 10-12, Table 3.9).



Scheme 3.13

Table 3.9 Survey of reaction conditions for alkyl boronic acids.

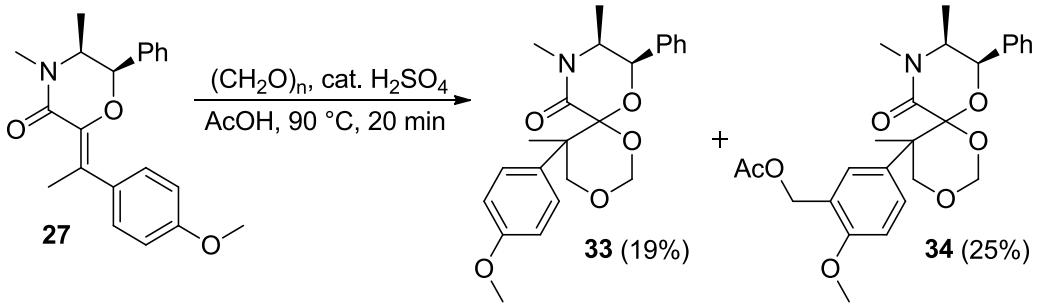
No.	Boronic Acid	Catalysts	Base[a]	Result[b]
1		$Pd(OAc)_2$	K_2CO_3[c]	**8**
2		$Pd(PPh_3)_4$	K_2CO_3	**12** + **26**
3		$Pd(PPh_3)_4$	K_2CO_3[c]	**12** + **26**
4		$PdCl_2(PPh_3)_2$	K_2CO_3[c]	**12** + **26**
5		$PdCl_2(dppf)$	K_2CO_3[c]	**12** + **26**
6		$Pd(PPh_3)_4$	DBU[d]	**8**
7		$Pd(PPh_3)_4$	DBU[e]	**12** + **26**
8		$Pd(PPh_3)_4$	K_2CO_3	**12** + **26**
9			K_2CO_3[c]	**12** + **26**
10		$Pd(PPh_3)_4$	K_2CO_3[c]	No reaction
11		$Pd(PPh_3)_4$	Cs_2CO_3[f]	**12** + **26**
12		$Pd(PPh_3)_4$	K_2CO_3	No reaction

[a] 1,2-DME, MW, 150 °C, 1.5 h., [b] analysis of ^1H NMR of crude [c] 1,2-DME, reflux, 24 h., 6 h., [d] THF, MW, 100 °C, 7 h., [e] 1,2-DME, MW, 120 °C, [f] 1,2-DME, reflux, 6 h.

The use of an organic base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, entries 6 and 7, Table 3.9) instead of K_2CO_3 or Cs_2CO_3 failed to provide any coupling product with cyclohexylboronic acid.

3.3.3 Synthesis of Prins Adducts and Quaternary Stereocenters

With the requisite alkylidene morpholinones **27**, **28** and **29** in hand, the next task was to perform the carbon-carbon bond forming reaction which would construct the quaternary stereocenter, namely the Prins reaction. Initially, alkene **27** was chosen as the substrate for the Prins reaction. Alkene **27** on treatment with paraformaldehyde in acetic acid in the presence of a catalytic amount of sulphuric acid afforded a mixture of products **33** (19%) and **34** (25%, Scheme 3.14) as single diastereomers which were separable by column chromatography. Careful analysis of compound **34** suggested that it was the expected Prins product, but with an acetoxymethyl substituent on the anisyl ring.

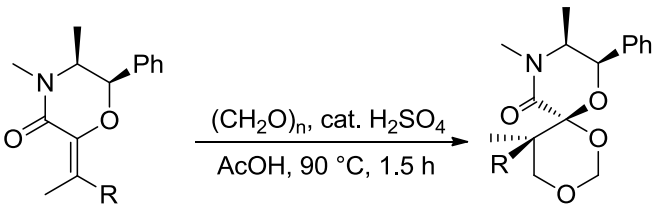


Scheme 3.14 Prins reaction of alkene **27**.

The electron-rich nature of the 4-methoxyphenyl group and the high reaction temperature may have promoted the formation of **34**. In order to suppress the formation of **34**, the Prins

reaction was conducted at room temperature. Although this suppressed the formation of **34**, it also affected the formation of **33** which was obtained in very low yield (7%).

In related reactions, alkenes **28** and **29** furnished the Prins products **36** (58%) and **37** (57%, Scheme 3.15) in moderate yields. Although the yields for the conversion of **28** and **29** were moderate, these reactions were reproducible.



Scheme 3.15

At this stage, the stereochemistry of **33**, **35** and **36** was tentatively assigned as shown, on the basis of a stereoselective reaction of the alkylidene morpholinone and formaldehyde from the less hindered face of the alkene to provide **37a** (Fig. 3.1). Further reaction of **37a** with formaldehyde and subsequent capture of the oxocarbenium ion from the *Re* face generates the spiromorpholinones.

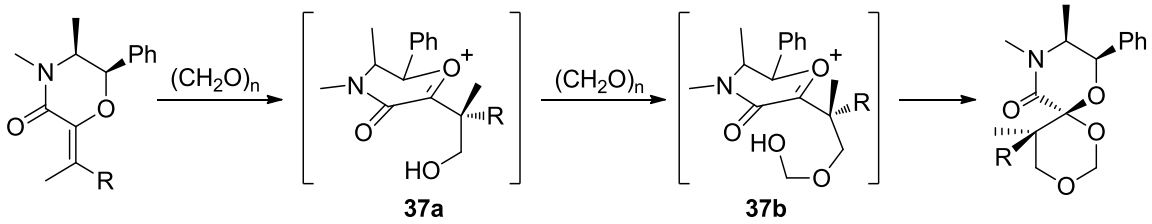
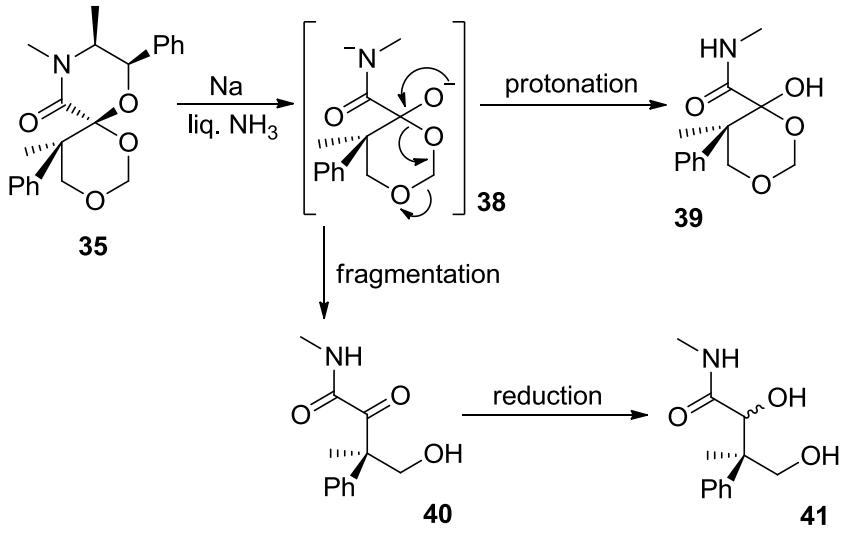


Figure 3.1 Proposed model for stereoselectivity in Prins reaction.

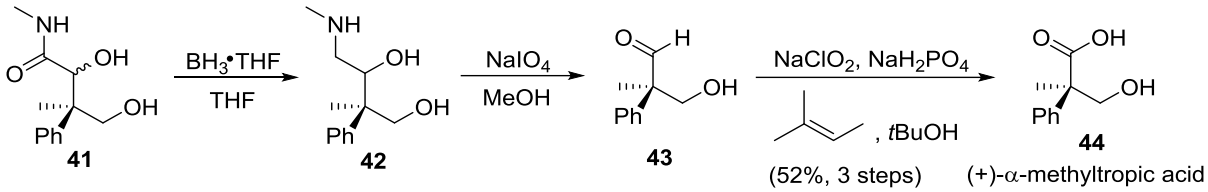
With **35** and **36** in hand, efforts were now focused on isolating the key, quaternary carbon-bearing structural unit in these compounds. Accordingly, removal of the ephedrine portion in **35** was accomplished by means of a dissolving-metal reduction reaction. It was

expected that the dissolving-metal reduction would furnish the hydroxy amide **39** (Scheme 3.16), but instead, amide **40** was obtained. Formation of **40** was unexpected but much appreciated, as it saved a few synthetic steps. Presumably, the alkoxide intermediate **38**, formed in the dissolving-metal reduction of **35**, undergoes fragmentation to provide the α-ketoamide **40** which is reduced *in situ* to the hydroxy amide **41**. In repeated reactions, **41** was obtained either as a single diastereomer or as a 2:1 mixture of diastereomers. The stereochemistry at the α-carbon in **41** was not established in this study.



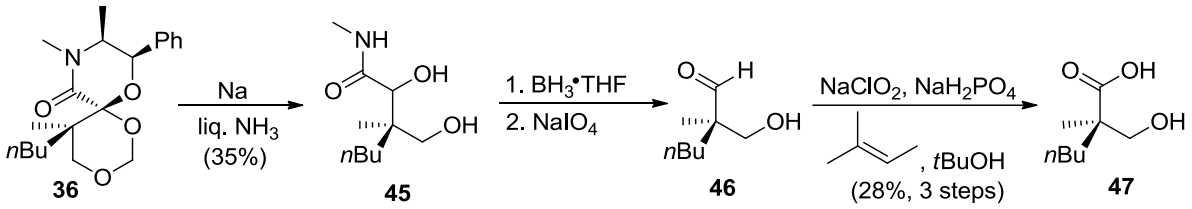
Scheme 3.16

The amide **41** was reduced with borane to provide the aminoalcohol **42** (Scheme 3.17). Oxidative cleavage of **42** generated the aldehyde **43**, which was oxidized to provide α-methyltropic acid **44**. Comparison of the observed optical rotation of **44** (+23.6) with that reported[14] for the *R* enantiomer of **44** (+27.0) confirmed that the stereochemistry at the quaternary stereocenter in **44** was *R*. The formation of *R*-**44** also confirms the stereochemical course of the Prins reaction (Fig. 3.1).



Scheme 3.17 Synthesis of α–methyltropic acid **44**.

Following a similar reaction sequence, the spiromorpholinone **36** was converted to the acid **47** (Scheme 3.18). Dissolving-metal reduction of adduct **36** produced the hydroxy amide **45** as a single diastereomer. The stereochemistry at the α-carbon in **45** was not determined. Reduction of **45** to the corresponding aminoalcohol followed by an oxidative cleavage provided the aldehyde **46**. Pinnick oxidation of **46** provided (*R*)-2-(hydroxymethyl)-2-methylhexanoic acid (**47**, Scheme 3.18). The *R* configuration of **47** was assigned by analogy to **44**.



Scheme 3.18

3.4 Conclusions

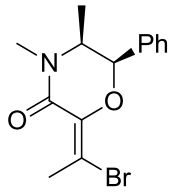
Isomerically pure haloalkylidene morpholinones **8**, **17** and **18** were prepared from alkene **12**. Stereoselective cross-coupling reactions of **8** provides access to the diastereomerically pure alkylidene morpholinones **27**, **28** and **29**. The Suzuki-Miyaura coupling protocol is the method of choice for this conversion, but optimization of reaction conditions as well as extensive catalyst screening is required. A Prins reaction of the

alkylidene morpholinones afforded the expected spiromorpholinones in moderate yields. Conversion of the spiromorpholinone **35** to (*R*)-α-methyltropic acid **44** confirmed the stereochemistry of the Prins reaction.

3.5 Experimental Section

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. Dichloromethane and tetrahydrofuran were distilled from CaH_2 and sodium/benzophenone respectively. Commercial precoated silica gel plates were used for TLC. Silica gel for flash column chromatography was 230-400 mesh. For column chromatographic purifications employing CH_2Cl_2/MeOH/aq. NH_3, the eluent was dried over Na_2SO_4 before use. All melting points are uncorrected. Optical rotations were measured at the sodium D line on a digital polarimeter at ambient temperature. A CEM Discover® microwave reactor was used for the microwave experiments. All reactions involving microwave heating were conducted in sealed reaction vessels. The temperature of the reaction mixture was monitored with an infrared sensor and the mixture reached the preset temperature (150 ^oC) in approximately 90 s. Compounds **10** and **12** were prepared according to literature methods.

(5*S*,6*R*,*Z*)-2-(1-Bromoethylidene)-4,5-dimethyl-6-phenylmorpholin-3-one (8):



To a solution of the alkene **12** (2.50 g, 10.8 mmol) in CH_2Cl_2 (10 mL) at room temperature was added a solution of bromine (6.50 mL of a 2.00 M soln. in H_2O, 13.0 mmol). The mixture was stirred for 30 min at room temperature (monitored by TLC) and

then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with aqueous saturated $Na_2S_2O_3$ (3 x 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure to provide 3.43 g (97%) of the crude bromohemiacetal **14**.

Major diastereomer:

^{1}H NMR (300Hz, $CDCl_3$)): δ 7.46-7.31 (m, 5H, Ar*H*), 5.60 (d, 1H, *J* = 3.2, PhC*H*), 5.11 (q, 1H, *J* = 6.9, C*H*Br), 3.72-3.68 (m, 1H, NC*H*), 3.08 (s, 3H, NCH_3), 2.13 (d, 3H, *J* = 6.9, BrCHCH_3), 1.12 (d, 3H, *J* = 6.7, CHCH_3).

Minor diastereomer:

^{1}H NMR (300Hz, $CDCl_3$)): δ 7.46-7.31 (m, 5H, Ar*H*), 5.64 (d, 1H, *J* = 3.2, PhC*H*), 4.91 (q, 1H, *J* = 6.7, C*H*Br), 3.72-3.68 (m, 1H, NC*H*), 3.07 (s, 3H, NCH_3), 2.02 (d, 3H, *J* = 6.9, BrCHCH_3), 1.05 (d, 3H, *J* = 6.7, CHCH_3).

The hemiacetal **14** (3.43 gm, 10.5 mmol) was dissolved in acetic anhydride (10 mL) and conc. H_2SO_4 (0.25 mL) was added to the solution. The mixture was stirred at room temperature for 16 h and the acetic anhydride was removed under reduced pressure. The residue was basified with an aqueous NaOH (10%) and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 7:3) to provide 2.30 g (69%) of (5*S*,6*R*,*Z*)-2-(1-bromoethylidene)-4,5-dimethyl-6-phenylmorpholin-3-one (**8**) as a pale yellow gum.

IR (neat): 1660, 1610, 1441, 1389, 1284, 1212, 1151, 1065, 1023 cm^{-1}.

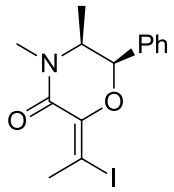
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.39 (m, 4H, Ar*H*), 7.36-7.32 (m, 1H, Ar*H*), 5.28 (d, 1H, *J* = 2.8, PhC*H*), 3.60 (dq, 1H, *J* = 2.8, 6.5, NC*H*), 3.08 (s, 3H, NCH_3), 2.88 (s, 3H, C=CH_3), 0.99 (d, 3H, *J* = 6.5, CHCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.5 (*C*=O), 140.2 (*C*-C=O), 136.4 (Ar*C*), 128.5 (2 x Ar*C*), 128.0 (Ar*C*), 125.5 (2 x Ar*C*), 117.2 (C=*C*Br), 77.02 (Ph-*C*), 58.8 (N*C*H), 33.6 (N*C*H_3), 24.9 (C=*C*H_3), 11.9 (CH*C*H_3).

MS (EI, pos.): *m*/*z* 310.1 and 312.1 $(M+H)^+$.

HRMS (CI): *m*/*z* 310.0436 (310.0443 calc. for $C_{14}H_{17}{}^{79}BrNO_2$ $(M+H)^+$) and 312.0423 (312.0422 calc. for $C_{14}H_{17}{}^{81}BrNO_2$ $(M+H)^+$).

(5*S*,6*R*,*Z*)-2-(1-Iodoethylidene)-4,5-dimethyl-6-phenylmorpholin-3-one (18):



To a solution of the alkene **12** (0.200 g, 0.865 mmol) in CH_2Cl_2/H_2O (1:1, 5 mL) at room temperature was added *N*-iodosuccinimide (0.234 g, 1.04 mmol). The mixture was stirred for 30 min at room temperature (monitored by TLC) and extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were washed with saturated aqueous $Na_2S_2O_3$ (3 x 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to provide the crude iodohemiacetal **16**. This was dissolved in acetic anhydride (10 mL) and conc. H_2SO_4 (0.25 mL) was added to the solution. The reaction was stirred at room temperature for 16 h and the acetic anhydride was removed under reduced pressure. The residue was basified with aqueous NaOH (10%) and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 7:3) to provide

0.6 g (20%) of (5*S*,6*R*,*Z*)-2-(1-iodoethylidene)-4,5-dimethyl-6-phenylmorpholin-3-one (**18**) as a pale yellow gum.

IR (neat): 1655, 1603, 1440, 1387, 1283, 1262, 1211, 1193, 1063, 1021 cm^{-1}.

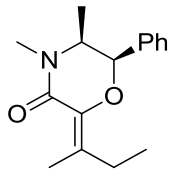
^1H NMR (300 MHz, $CDCl_3$): δ 7.49-7.46 (m, 2H, Ar*H*), 7.43-7.38 (m, 2H, Ar*H*), 7.35-7.30 (m, 1H, Ar*H*), 5.29 (d, 1H, *J* = 2.7, PhC*H*), 3.60 (dq, 1H, *J* = 2.7, 6.6, C*H*CH_3), 3.11 (s, 3H, NC*H*$_3$), 3.08 (s, 3H, C=C*H*$_3$C), 0.97 (d, 3H, *J* = 6.6, CHC*H*$_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 157.2 (*C*=O), 142.9 (*C*-C=O), 136.3 (ArC_{ipso}), 128.6 (2 x Ar*C*), 128.0 (Ar*C*), 125.6 (2 x Ar*C*), 94.5 (C=*C*I), 78.1 (Ph*C*), 58.9 (N*C*H), 33.4 (N*C*H_3), 28.9 (C=*C*H_3), 11.9 (CH*C*H_3).

MS (CI, pos.): *m*/*z* 358.0 $(M+H)^+$.

HRMS (EI): *m*/*z* 357.0217 (357.0226 calc. for $C_{14}H_{16}INO_2$ (M^+)).

(5*S*,6*R*,*Z*)-2-(Butan-2-ylidene)-4,5-dimethyl-6-phenylmorpholin-3-one (20):



To a solution of the bromoalkene **8** (35.0 mg, 0.11 mmol) in THF (2 mL) was added $PdCl_2$(dppf)•CH_2Cl_2 (9.60 mg 0.01 mmol) followed by ethylmagnesium bromide (0.34 mL, 1.00 M solution, 0.34 mmol). The reaction was stirred at room temperature for 24 h and aqueous saturated NH_4Cl (2 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 5 mL) and the combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 95:5) to provide 10 mg (35%) of (5*S*,6*R*,*Z*)-2-(butan-2-ylidene)-4,5-dimethyl-6-

phenylmorpholin-3-one **20** as colorless gum. The spectral data was in agreement with the reported data.[3c]

IR (neat): 1660, 1616, 1448, 1387, 1295, 1167, 1070, 1015 cm^{-1}.

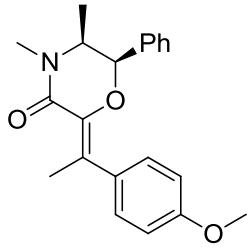
^1H NMR (300 MHz, $CDCl_3$): δ 7.42-7.28 (m, 5H, Ar*H*), 5.13 (d, 1H, *J* = 2.7, PhC*H*), 3.54 (dq, 1H, *J* = 2.7, 6.6, NC*H*), 3.06 (s, 3H, NCH_3), 2.38-2.28 (m, 2H, CH_2CH_3), 2.25 (s, 3H, C=CCH_3), 1.05 (t, 3H, *J* = 7.5, CH_2CH_3), 0.95 (d, 3H, *J* = 6.6, CHCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 161.0 (*C*=O), 138.0 (*C*-C=O), 137.7 (ArC_{ipso}), 132.5 (C=*C*CH_3), 128.4 (2 x Ar*C*), 127.7 (Ar*C*), 125.4 (2 x Ar*C*), 76.8 (Ph*C*H), 58.9 (N*C*H), 33.5 (N*C*H_3), 26.9 (C*C*H_3), 17.9 (*C*H_2CH_3), 11.97 (CH_2*C*H_3), 11.89 (CH*C*H_3).

MS (CI, pos.): *m*/*z* 260.2 $(M+H)^+$.

HRMS (EI): *m*/*z* 259.1579 (259.1572 calc. for $C_{16}H_{21}NO_2$ (M^+)).

(5*S*,6*R*,*Z*)-2-(1-(4-Methoxyphenyl)ethylidene)-4,5-dimethyl-6-phenylmorpholin-3-one (27):



To a solution of the bromoalkene **8** (0.13 g, 0.42 mmol) in THF (3 mL) were added 4-methoxyphenylboronic acid (0.076 g, 0.50 mmol), Cs_2CO_3 (0.41 g, 1.26 mmol) and $PdCl_2$(dppf)•CH_2Cl_2 (0.035 mg 0.042 mmol). The mixture was heated to reflux for 5 h, cooled to room temperature and aqueous saturated NH_4Cl (5 ml) was added to the reaction mixture. The mixture was extracted with EtOAc (3 x 10 mL) and the combined extracts

were washed with aqueous HCl (10%), followed by aqueous NaOH (10%) and then dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 1:1) to provide 110 mg (78%) of (5*S*,6*R*,*Z*)-2-(1-(4-methoxyphenyl)ethylidene)-4,5-dimethyl-6-phenylmorpholin-3-one (**27**) as a colorless gum.

IR (neat): 1654, 1606, 1508, 1438, 1386, 1289, 1246, 1175, 1107, 1026, 830, 758, 696 cm^{-1}.

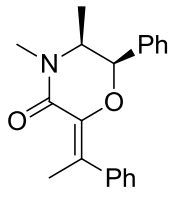
^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (m, 2H, Ar*H*), 7.33-7.23 (m, 3H, Ar*H*), 7.21-7.15 (m, 2H, Ar*H*), 6.90-6.83 (m, 2H, Ar*H*), 5.18 (d, 1H, *J* = 2.7, PhC*H*), 3.81 (s, 3H, OCH_3), 3.60 (dq, 1H, *J* = 2.7, 6.5, NC*H*), 3.11 (s, 3H, NCH_3), 2.56 (s, 3H, C=CCH_3), 0.96 (d, 3H, *J* = 6.5, CHCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 161.3 (*C*=O), 158.4 (*C*-C=O), 138.5 (ArC_{ipso}), 137.0 (ArC_{ipso}), 133.8 (ArC_{ipso}), 129.8 (2 x Ar*C*), 128.3 (2 x Ar*C*), 127.7 (Ar*C*), 127.5 (Ar*C*), 125.3 (2 x Ar*C*), 113.0 (C=*C*CH_3), 77.1 (Ph*C*H), 58.8 (N*C*H), 55.2 (O*C*H_3), 33.7 (N*C*H_3), 20.1 (C*C*H_3), 11.9 (CH*C*H_3).

MS (CI, pos.): *m*/*z* 338.3 $(M+H)^+$.

HRMS (EI pos.): *m*/*z* 337.1677 (337.1678 calc. for $C_{21}H_{23}NO_3$ (M^+)).

(5*S*,6*R*,*Z*)-4,5-Dimethyl-6-phenyl-2-(1-phenylethylidene)morpholin-3-one (28):



To a solution of the bromoalkene **8** (0.10 g, 0.32 mmol) in CH_3CN (3 mL) was added phenylboronic acid (0.078 g, 0.645 mmol), Cs_2CO_3 (0.21 g, 0.64 mmol) and $PdCl_2(dppf)•CH_2Cl_2$ (27.0 mg 0.032 mmol). The mixture was heated to reflux for 2 h, cooled to room temperature and aqueous saturated NH_4Cl (5 mL) was added. The mixture was extracted with EtOAc (3 x 10 mL) and the combined extracts were washed with aqueous HCl (10%), followed by aqueous NaOH (10%) and then dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 1/1) to provide 99.0 mg (75%) of (5*S*,6*R*,*Z*)-4,5-dimethyl-6-phenyl-2-(1-phenylethylidene)morpholin-3-one (**28**) as a light brown gum.

IR (neat): 1649, 1606, 1490, 1440, 1295, 1256, 1176, 912 cm^{-1}.

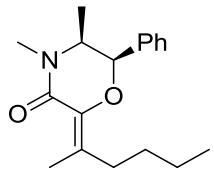
^1H NMR (300 MHz, $CDCl_3$): δ 7.42-7.34 (m, 3H, Ar*H*), 7.34-7.29 (m, 2H, Ar*H*), 7.29-7.19 (m, 4H, Ar*H*), 7.14-7.09 (m, 2H, Ar*H*), 5.18 (d, 1H, *J* = 2.7, PhC*H*), 3.60 (dq, 1H, *J* = 2.7, 6.5, NC*H*), 3.12 (s, 3H, NCH_3), 2.57 (s, 3H, C=CCH_3), 0.96 (d, 3H, *J* = 6.5, CHCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 161.2 (*C*=O), 141.7 (*C*-C=O), 138.7 (ArC_{ipso}), 137.0 (C=*C*CH_3), 128.4 (2 x Ar*C*), 128.3 (2 x Ar*C*), 128.1 (Ar*C*), 127.7 (2 x Ar*C*), 127.6 (Ar*C*), 126.9 (Ar*C*), 125.3 (2 x Ar*C*), 77.03 (Ph*C*H), 58.8 (N*C*H), 33.7 (N*C*H_3), 20.1 (C=C*C*H_3), 12.0 (CH*C*H_3).

MS (CI, pos.): *m*/*z* 308.4 $(M+H)^+$.

HRMS (EI): *m*/*z* 307.1574 (307.1572 calc. for $C_{20}H_{21}NO_2$ (M^+)).

(5*S*,6*R*,*Z*)-2-(Hexan-2-ylidene)-4,5-dimethyl-6-phenylmorpholin-3-one (29):



To a solution of the bromoalkene **8** (1.00 g, 3.22 mmol) in DME (10 mL, purged with N_2 for 10 min) was added butylboronic acid (986 mg, 9.66 mmol), K_2CO_3 (0.89 g, 6.44 mmol) and $Pd(PPh_3)_4$ (372 mg 0.32 mmol). The mixture was subjected to microwave irradiation in a sealed microwave reaction vessel for 90 min at 150 °C and then cooled to room temperature. Aqueous saturated NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (3 x 10 mL). The combined extracts were washed with aqueous HCl (10%), followed by aqueous NaOH (10%) and then dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 7/3) to provide 620 mg (67%) of (5*S*,6*R*,*Z*)-2-(hexan-2-ylidene)-4,5-dimethyl-6-phenylmorpholin-3-one (**29**) as pale yellow gum.

IR (neat): 1659, 1617, 1443, 1386, 1286, 1211, 1165 cm^{-1}.

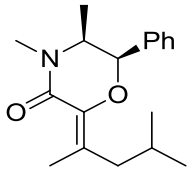
^1H NMR (300 MHz, $CDCl_3$): δ 7.40-7.28 (m, 5H, Ar*H*), 5.12 (d, 1H, *J* = 2.7, PhC*H*), 3.58-3.50 (dq, 1H, *J* = 2.7, 6.6, NC*H*), 3.06 (s, 3H, NCH_3), 2.39-2.24 (m, 2H, C=CCH_2), 2.24 (s, 3H, C=CCH_3), 1.52-1.40 (m, 2H, CH_2CH_2), 1.38-1.28 (m, 2H, CH_2CH_2), 0.95 (d, 3H, *J* = 6.6, CHCH_3), 0.90 (t, 3H, *J* = 7.2, CH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 161.0 (*C*=O), 138.4 (*C*-C=O), 137.7 (ArC_{ipso}), 131.2 (C=*C*CH_2CH_3), 128.4 (2 x Ar*C*), 127.7 (Ar*C*), 125.4 (2 x Ar*C*), 76.8 (Ph*C*H), 58.9 (N*C*H), 33.44 (NCH_3), 33.42 (C=C*C*H_2), 29.6 (*C*H_2), 22.6 (*C*H_2), 18.4 (C=C*C*H_3), 14.0 (CH_2*C*H_3), 11.9 (CH*C*H_3).

MS (CI, pos.): *m*/*z* 288.3 $(M+H)^+$.

HRMS (EI pos.): *m*/*z* 287.1887 (287.1885 calc. for $C_{18}H_{25}NO_2$ (M^+)).

(5*S*,6*R*,*Z*)-4,5-Dimethyl-2-(4-methylpentan-2-ylidene)-6-phenylmorpholin-3-one (30):



To the solution of bromoalkene **8** (70.0 mg, 0.23 mmol) in DME (3 mL) was added (2-methylpropyl)boronic acid (70.0 mg, 0.69 mmol), K_2CO_3 (63 mg, 0.46 mmol) and $Pd(PPh_3)_4$ (26.0 mg 0.02 mmol). The reaction was subjected to microwave irradiation in a sealed microwave reaction vessel for 90 min at 150 °C and then cooled to room temperature. Aqueous saturated NH_4Cl (2mL) was added and the mixture was extracted with EtOAc (3 x 10 mL). The combined extracts were washed aqueous HCl (10%), followed by aqueous NaOH (10%) and then dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 7:3) to provide 14.0 mg (20%) of (5*S*,6*R*,*Z*)-4,5-dimethyl-2-(4-methylpentan-2-ylidene)-6-phenylmorpholin-3-one (**30**) as a gum.

IR (neat): 1658, 1616, 1446, 1385, 1292, 1243, 1165 cm^{-1}.

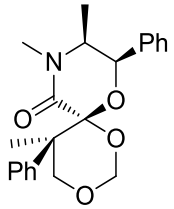
^1H NMR (300 MHz, $CDCl_3$): δ 7.43-7.29 (m, 5H, Ar*H*), 5.10 (d, 1H, *J* = 2.7, PhC*H*), 3.57-3.50 (dq, 1H, *J* = 2.7, 6.5, NC*H*), 3.06 (s, 3H, NCH_3), 2.28-2.14 (m, 5H, C=CCH_2), 2.22 (s, 3H, C=CCH_3), 1.95-1.82 (m, 1H, CH_2C*H*), 0.96 (d, 3H, *J* = 6.6, CHCH_3), 0.94 (d, 3H, *J* = 6.6, CHCH_3), 0.89 (d, 3H, *J* = 6.5, CHCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 161.0 (*C*=O), 138.8 (*C*-C=O), 137.7 (ArC_{ipso}), 130.5 (C=*C*CH_3), 128.4 (2 x Ar*C*), 127.7 (Ar*C*), 125.4 (2 x Ar*C*), 76.8 (Ph*C*H), 58.9 (N*C*H), 42.9 (CH*C*H_2), 33.5 (N*C*H_3), 27.1 (C=C*C*H_3), 22.7 (2 x CH*C*H_3), 18.9 (CH_2*C*H), 12.0 (CH*C*H_3).

MS (APCI, pos.): *m*/*z* 288.3 $(M+H)^+$.

HRMS (EI pos.): *m*/*z* 287.1883 (287.1885 calc. for $C_{18}H_{25}NO_2$ (M^+)).

(8*R*,9*S*)-5,9,10-Trimethyl-5,8-diphenyl-1,3,7-trioxa-10-azaspiro[5.5]undecan-11-one (35):



To a solution of the alkene **28** (360 mg, 1.17 mmol) and paraformaldehyde (176 mg, 5.86 mmol) in glacial acetic acid (3 mL) was added conc. H_2SO_4 (two drops) and the mixture was heated for 45 min in a preheated oil bath set at 85 °C. The mixture was cooled to room temperature and the acetic acid was removed under reduced pressure. The residue was neutralized with aqueous NaOH (10%) and then was extracted with CH_2Cl_2 (4 x 5 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 6:4) to provide 270 mg (63%) of **35** as a colorless foam.

IR (neat): 1656, 1493, 1448, 1383, 1238, 1161, 1091, 1029, 986 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.29 (m, 7H, Ar*H*), 7.22-7.20 (m, 3H, Ar*H*), 5.23 (d, 1H, *J* = 2.9, PhC*H*), 5.14 (d, 1H, *J* = 5.7, OCH_2), 5.03 (d, 1H, *J* = 10.3, OCH_2), 4.92 (d,

1H, *J* = 5.7, OC*H*$_2$), 3.83 (d, 1H, *J* = 10.3, OC*H*$_2$), 3.22 (dq, 1H, *J* = 2.9, 6.6, NC*H*), 2.93 (s, 3H, NC*H*$_3$), 2.04 (s, 3H, C-C*H*$_3$), -0.07 (d, 3H, *J* = 6.6, CHC*H*$_3$).

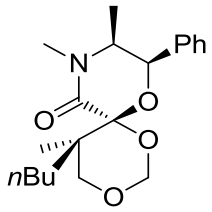
^{13}C NMR (75 MHz, $CDCl_3$): δ 164.2 (*C*=O), 142.2 (Ar*C*$_{ipso}$), 137.0 (Ar*C*$_{ipso}$), 128.5 (2 x Ar*C*), 128.2 (2 x Ar*C*), 127.8 (Ar*C*), 126.9 (2 x Ar*C*), 126.8 (Ar*C*), 125.4 (2 x Ar*C*), 99.8 (O-*C*-O), 86.9 (O*C*H$_2$O), 71.8 (O*C*H$_2$), 71.3 (Ph*C*H), 59.1 (NC*H*), 44.8 (Ph-*C*-CH$_3$), 33.9 (N*C*H$_3$), 22.2 (C-*C*H$_3$), 10.6 (CH*C*H$_3$).

MS (CI, pos.): *m*/*z* 368.4 $(M+H)^+$.

HRMS (CI pos.): *m*/*z* 368.1862 (368.1862 calc. for $C_{22}H_{26}NO_4$ $(M+H)^+$).

$[\alpha]_D^{20}$ = + 11.0 (c 1, CH_2Cl_2).

(8*R*,9*S*)-5-Butyl-5,9,10-trimethyl-8-phenyl-1,3,7-trioxa-10-azaspiro[5.5]undecan-11-one (36):



To a solution of the alkene **29** (50.0 mg, 0.17 mmol) and paraformaldehyde (30.0 mg, 0.87 mmol) in glacial acetic acid (3 mL) was added conc. H_2SO_4 (two drops) and the mixture was heated for 15 min in a preheated oil bath set at 85 °C. The mixture was cooled to room temperature and the acetic acid was removed under reduced pressure. The residue was neutralized with aqueous NaOH (10%) and the mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced

pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 7:3) to provide 31.0 mg (57%) of **36** as a colorless foam.

IR (neat): 1656, 1457, 1380, 1288, 1139, 1090, 1024, 976 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42-7.33 (m, 5H, Ar*H*), 5.42 (d, 1H, *J* = 3.0, PhC*H*), 5.00 (d, 1H, *J* = 5.6, OC*H*$_2$O), 4.97 (d, 1H, *J* = 5.6, OC*H*$_2$O), 4.03 (d, 1H, *J* = 10.8, OC*H*$_2$), 3.72 (d, 1H, *J* = 10.8, OC*H*$_2$), 3.50 (dq, 1H, *J* = 3.0, 6.5, NC*H*), 3.00 (s, 3H, NC*H*$_3$), 1.51-1.48 (m, 2H, C*H*$_2$), 1.44 (s, 3H, C-C*H*$_3$), 1.32-1.21 (m, 4H, C*H*$_2$), 1.18-1.15 (m, 1H, C*H*$_2$), 0.98 (d, 3H, *J* = 6.5, CHC*H*$_3$), 0.90 (t, 3H, *J* = 7.1, C*H*$_2$C*H*$_3$).

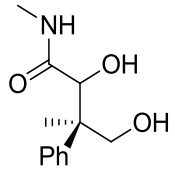
^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8 (*C*=O), 137.1 (Ar*C*$_{ipso}$), 128.6 (2 x Ar*C*), 127.8 (Ar*C*), 125.4 (2 x Ar*C*), 99.8 (O-*C*-O), 87.5 (O*C*H$_2$O), 73.0 (O*C*H$_2$), 70.5 (Ph*C*H), 59.0 (N*C*H), 41.0 (*C*CH$_3$), 33.9 (N*C*H$_3$), 33.6 (C-*C*H$_2$), 25.3 (*C*H$_2$), 23.7 (*C*H$_2$), 19.4 (C-*C*H$_3$), 14.1 (CH*C*H$_3$), 12.5 (CH$_2$*C*H$_3$).

MS (CI, pos.): *m*/*z* 348.3 $(M+H)^+$.

HRMS (EI): *m*/*z* 347.2105 (347.2097 calc. for $C_{20}H_{29}NO_4$, (M^+)); 348.2172 (348.2175 calc. for $C_{20}H_{30}NO_4$ $(M+H)^+$).

$[\alpha]_D^{20}$ = – 46.8 (c 1, CH_2Cl_2).

(3*R*)-2,4-Dihydroxy-*N*,3-dimethyl-3-phenylbutanamide (41):



To anhydrous liquid ammonia (6 mL, distilled over sodium) was added sodium metal (25.0 mg, 1.09 mmol) at –78 °C and the mixture was stirred for 15 min. To the

resulting blue solution was added a solution of **35** (50.0 mg, 0.14 mmol) in anhydrous THF (1.5 mL) and the mixture was stirred for 10 min at –78°C. A mixture of MeOH/H_2O (3:1, 2 mL) was added and the reaction mixture was brought to ambient temperature and stirred for 30 min to remove ammonia. The resulting solution was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (hexane/EtOAc, 2:8) to provide 15.0 mg (50%) of **41** as a white solid (dr = 2:1)

Minor diastereomer:

IR (neat): 3351 (br), 2935, 1643, 1541, 1455, 1409, 1371, 1247, 1155, 1081, 1028, 910 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 7.54-7.51 (m, 2H, Ar*H*), 7.41-7.36 (m, 2H, Ar*H*), 7.32-7.29 (m, 1H, Ar*H*), 6.80 (br s, 1H, N*H*), 4.59 (br s, 1H, C*H*OH), 4.32-4.29 (br t, 1H, *J* = 5.8, O*H*), 4.00 (br dd, 1H, *J* = 3.3, 11.5, OCH_2), 3.64 (br dd, 1H, *J* = 5.5, 11.5, OCH_2), 2.87 (d, 3H, *J* = 5.0, NCH_3), 1.60 (br s, 1H, O*H*), 1.30 (s, 3H, C-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1 (*C*=O), 143.6 (ArC_{ipso}), 129.0 (2 x Ar*C*), 127.3 (Ar*C*), 126.6 (2 x Ar*C*), 77.0 (C(O)*C*H), 70.3 (O*C*H_2), 47.8 (Ph-*C*), 25.8 (N*C*H_3), 15.8 (C*C*H_3).

$[\alpha]_D^{20}$ = – 52.2 (c 1, CH_2Cl_2).

Major diastereomer:

IR (neat): 3353 (br), 2932, 1645, 1539, 1453, 1408, 1290, 1246, 1159, 1085, 1023 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 7.47-7.38 (m, 4H, Ar*H*), 7.35-7.29 (m, 1H, Ar*H*), 5.05 (br s, 1H, N*H*), 4.52 (br s, 1H, C*H*OH), 4.12 (d, 1H, *J* = 11.3, OCH_2), 3.82 (s, 1H, O*H*), 3.65 (d, 1H, *J* = 11.3, OCH_2), 3.10 (s, 1H, O*H*), 2.63 (d, 3H, *J* = 4.9, NCH_3), 1.40 (s, 3H, C-CH_3).

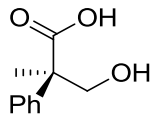
^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6 (*C*=O), 141.9 (ArC_{ipso}), 129.1 (2 x Ar*C*), 127.6 (Ar*C*), 126.9 (2 x Ar*C*), 76.9 (Ph*C*H), 70.7 (OCH_2), 47.2 (Ph-*C*), 26.2 (NCH_3), 16.7 (C-CH_3).

MS (CI, pos.): *m*/*z* 206.1 (M–OH); 224.1 $(M+H)^+$.

HRMS (CI): *m*/*z* 224.1292 (224.1287 calc. for $C_{12}H_{18}NO_3$ $(M+H)^+$).

$[\alpha]_D^{20}$ = – 31.5 (c 1, CH_2Cl_2).

(*R*)-3-hydroxy-2-methyl-2-phenylpropanoic acid (44):



To a stirred solution of the hydroxy amide **41** (45.0 mg, 0.20 mmol) in THF (1 mL) at 0 ºC was added a solution of BH_3•THF (1.21 mL of 1M solution in THF, 1.21 mmol) and the mixture was heated to reflux for 24 h. The mixture was cooled to 0 °C, aqueous HCl (3M, 2 mL) was added, the mixture was stirred at room temperature for 45 min and then concentrated under reduced pressure. The residue was basified (pH >10) with aqueous NaOH then extracted with CH_2Cl_2 (4 x 5 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to provide 30.0 mg (71%) of the amino alcohol (**42**). This was used further without purification.

To a stirred solution of the amino alcohol **42** (30.0 mg, 0.14 mmol) in MeOH/H_2O (100/1, 2 mL) at 0 ºC was added $NaIO_4$ (122 mg, 5.73 mmol). The mixture was stirred at 0 ºC for 30 min and cold, aqueous saturated sodium bicarbonate was added. The mixture was extracted with ethyl acetate (3 x 15 mL) and the combined extracts were dried (Na_2SO_4)

and concentrated under reduced pressure to provide 21.0 mg of the aldehyde **43** as colorless oil. This was used further without any purification.

To a solution of the aldehyde **43** (21.0 mg, 0.13 mmol) in *t*-butyl alcohol (3 mL) were added a solution of 2-methyl-2-butene (0.07 mL of 2 M solution in THF, 1.40 mmol) followed by a solution of $NaClO_2$ (80%, 64.0 mg, 0.56 mmol) and NaH_2PO_4 (67.0 mg, 1.40 mmol) in H_2O (1 mL). The resulting solution was stirred at room temperature for 12 h and the mixture was then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (3 mL), and aqueous HCl (10%, 0.75 ml) and brine (0.75 mL) were added. The resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to provide 19.0 mg (52% from **41**) of (*R*)-3-hydroxy-2-methyl-2-phenylpropanoic acid (**44**) as a colorless solid.

IR (neat): 3061 (br), 1701, 1498, 1454, 1379, 1254, 1157, 1122, 1027 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.29 (m, 5H, Ar*H*), 4.12 (d, 1H, *J* = 11.5, OCH_2), 3.70 (d, 1H, *J* = 11.5, OCH_2), 1.70 (s, 3H, CH_3).

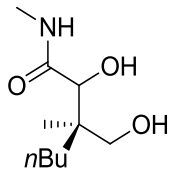
^{13}C NMR (75 MHz, $CDCl_3$): δ 180.9 (*C*=O), 139.6 (ArC_{ipso}), 128.7 (2 x Ar*C*), 127.7 (Ar*C*), 126.3 (2 x Ar*C*), 69.1 (O*C*H_2), 52.4 (Ph-*C*), 20.1 (C-*C*H_3).

MS (CI, neg.): *m*/*z* 179.1 $(M–H)^-$.

HRMS (CI pos.): *m*/*z* 181.0872 (181.0865 calc. for $C_{10}H_{13}O_3$ $(M+H)^+$).

$[\alpha]_D^{20}$ = +23.6 (c 1.9, EtOH), lit.[15] $[\alpha]_D^{20}$ = +26.6 (c 2, EtOH), lit.[14] $[\alpha]_D^{20}$ = +27.0 (c 2, EtOH).

(3*R*)-2-Hydroxy-3-(hydroxymethyl)-*N*,3-dimethylheptanamide (45):



To anhydrous liquid ammonia (6 mL, distilled over sodium) was added sodium metal (100 mg, 4.32 mmol) at –78 °C and the mixture was stirred for 15 min. To the resulting blue solution was added a solution of **36** (250 mg, 0.72 mmol) in anhydrous THF (1.5 mL) and the mixture was stirred for 10 min at –78°C. A mixture of MeOH/H_2O (3:1, 2 mL) was added and the reaction mixture was brought to ambient temperature and stirred for 30 min to remove ammonia. The resulting solution was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (hexane/EtOAc, 2:8) to provide 51.0 mg (35%) of **45** as a colorless solid.

IR (neat): 3353, 2930, 1642, 1540, 1462, 1409, 1297, 1027 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.85 (br s, 1H, N*H*), 4.06 (s, 1H, C*H*OH), 3.76 (br s, 1H, CO_2H), 3.57 (dd, 2H, *J* = 11.5, OCH_2), 2.86 (d, 3H, *J* = 5.0, NCH_3), 1.50-1.42 (m, 1H, CH_2), 1.39-1.16 (m, 5H, 3 x CH_2), 0.98 (s, 3H, C-CH_3), 0.90 (t, 3H, *J* = 6.7, CH_2CH_3).

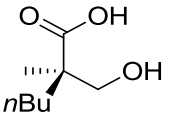
^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0 (*C*=O), 78.0 (*C*HOH), 69.1 (OCH_2), 41.8 (*C*-CH_3), 32.9 (NCH_3), 25.8 (*C*H_2), 25.6 (C-*C*H_3), 23.6 (CH_2CH_3), 19.1 (*C*H_2), 14.1 (*C*H_2).

MS (CI, pos.): *m*/*z* 186.1 $(M–OH)^+$; 204.1 $(M+H)^+$.

HRMS (CI): *m*/*z* 204.1600 (204.1600 calc. for $C_{10}H_{22}NO_3$ $(M+H)^+$).

$[\alpha]_D^{20}$ = + 15.5 (c 1.3, CH_2Cl_2).

(*R*)-2-(Hydroxymethyl)-2-methylhexanoic acid (47):



To a stirred solution of the hydroxy amide **45** (43.0 mg, 0.21 mmol) in THF (1 mL) at 0 ºC was added a solution of BH_3•THF (2.1 mL of 1 M solution in THF, 2.1 mmol). The mixture was heated to reflux for 24 h. The reaction mixture was cooled to 0 °C and a solution of 3M HCl (2 mL) was added. The reaction mixture was stirred at room temperature for 45 min and the solvent was removed under reduced pressure. The residue was basified (pH >10) with aqueous NaOH and the mixture was extracted with CH_2Cl_2 (4 x 5 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to provide 20.0 mg (50%) of the amino alcohol. This was used further without purification.

To a stirred solution of the amino alcohol (20.0 mg, 0.11 mmol) in MeOH/H_2O (100/1, 2 mL) at 0 ºC was added $NaIO_4$ (90.0 mg, 0.42 mmol) and the mixture was stirred at 0 ºC for 30 min. A cold, saturated aqueous solution of sodium bicarbonate was added and the mixture was extracted with ethyl acetate (3 x 5 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to provide 15.0 mg of the aldehyde **46** as a colorless oil. This was used further without any purification.

To a solution of the aldehyde **46** in *t*-butyl alcohol (3 mL) was added a solution of 2-methyl-2-butene (0.06 mL, 2 M solution in THF, 0.12 mmol) followed by a solution of $NaClO_2$ (80%, 38.0 mg, 0.42 mmol) and NaH_2PO_4 (51.0 mg, 0.42 mmol) in H_2O (1 mL). The solution was stirred at room temperature for 12 h and the resulting mixture was

concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (3 mL), and aqueous HCl (10%, 0.75 mL) and brine (0.75 mL) were added. The mixture was extracted with CH_2Cl_2 (3 × 5 mL) and the combined extracts were dried (Na_2SO_4) and concentrated to provide 6.0 mg (18% from **45**) of (*R*)-2-(hydroxymethyl)-2-methylhexanoic acid (**47**) as a colorless oil.

IR (neat): 3439 (br), 2929, 1699, 1461, 1407, 1381, 1282, 1220, 1160, 1032 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 7.0-5.5 (br, CO_2H), 3.77-3.76 (br d, 1H, *J* = 9.5, OCH_2), 3.54-3.53 (br d, 1H, *J* = 9.5, OCH_2), 1.69-1.53 (m, 2H, CH_2), 1.30-1.26 (m, 4H, CH_2) 1.22 (s, 3H, C-CH_3), 0.90 (t, 3H, *J* = 6.5, CH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 182.9 (*C*=O), 68.0 (OCH_2), 47.7 (*C*-C=O), 35.5 (C-CH_3), 26.3 (CH_2), 23.2 (CH_2), 19.4 (CH_2), 13.9 (CH_2CH_3).

MS (CI, neg.): *m*/*z* 159.1 $(M–H)^-$.

HRMS (CI neg.): *m*/*z* 159.1028 (159.1021 calc. for $C_8H_{15}O_3$ $(M–H)^-$).

$[\alpha]_D^{20}$ = –16.7 (c 0.6, CH_2Cl_2).

3.6 References

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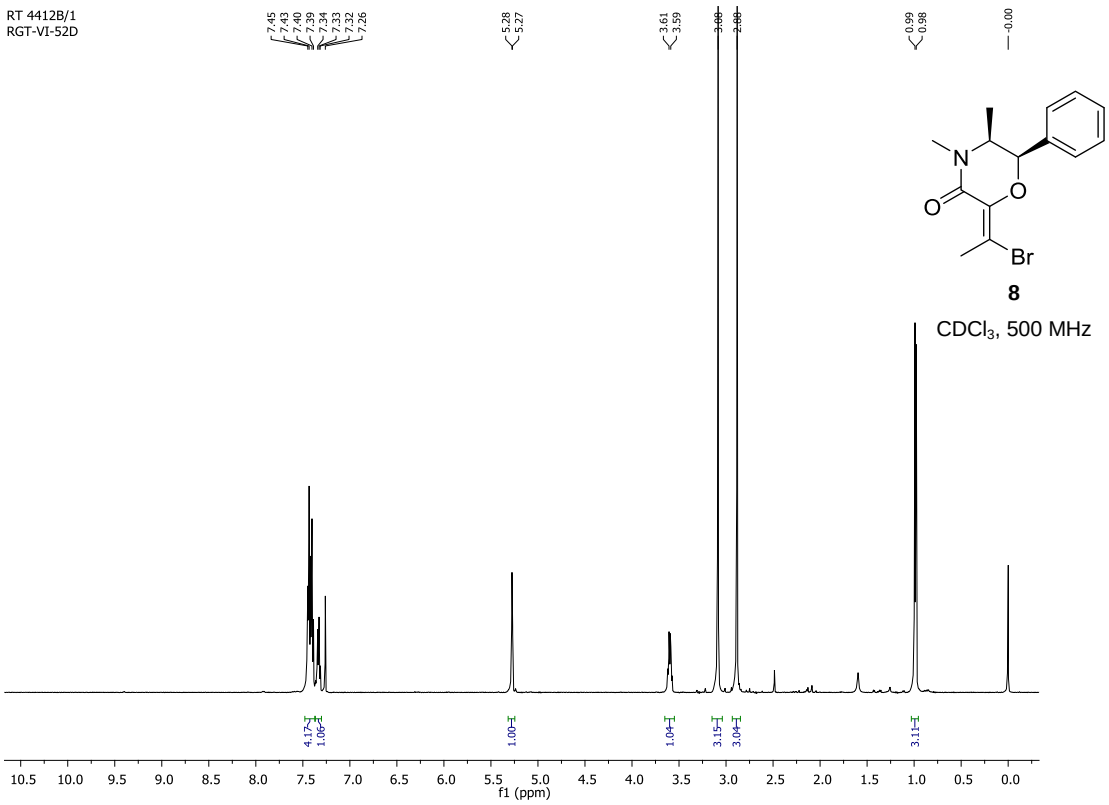
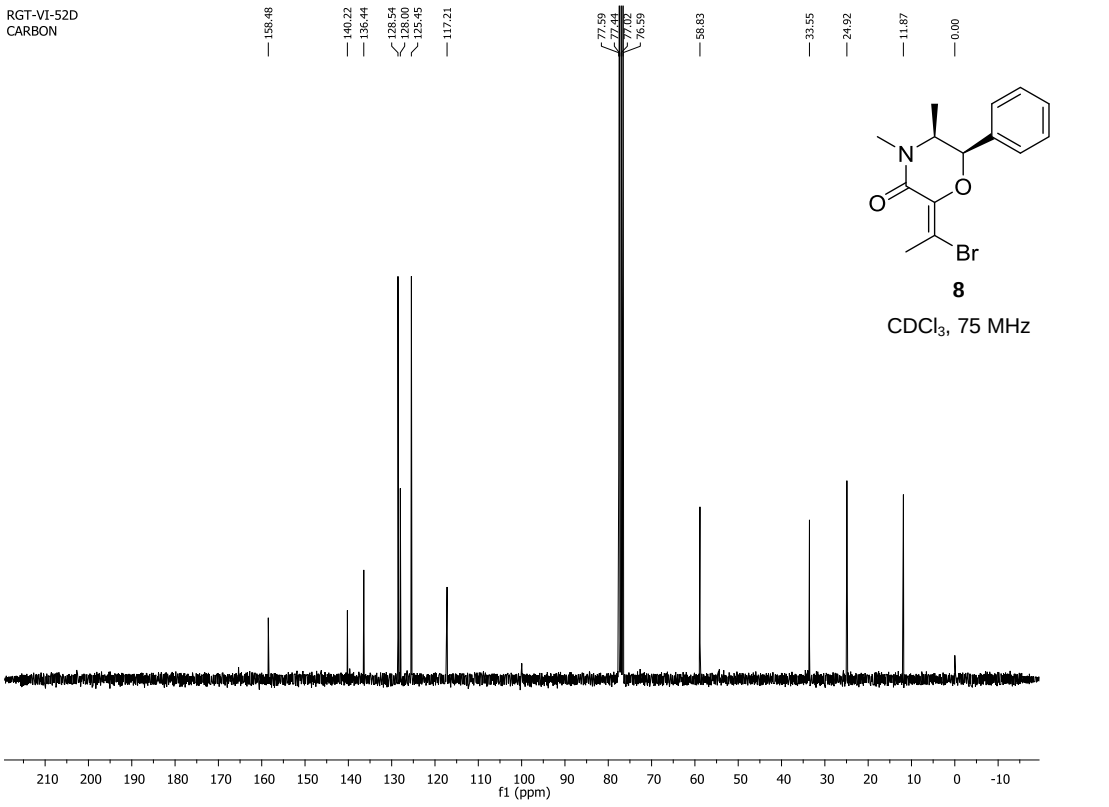
3.7 Selected ^{1}H NMR and ^{13}C NMR Spectra



8

$CDCl_3$, 500 MHz



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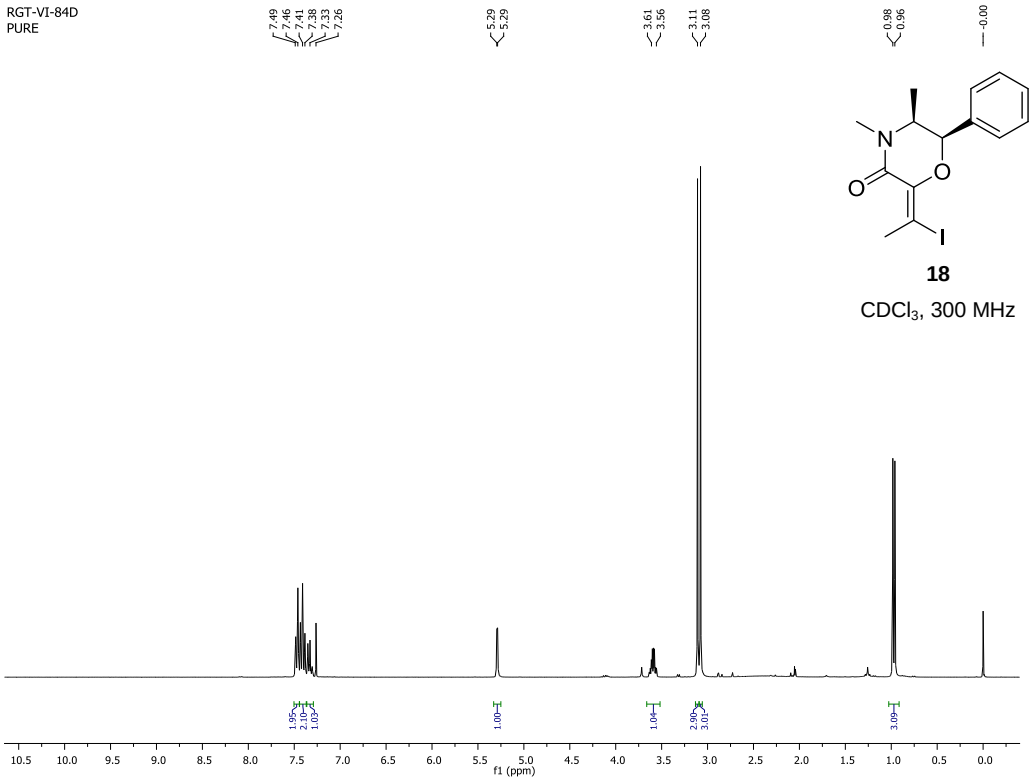

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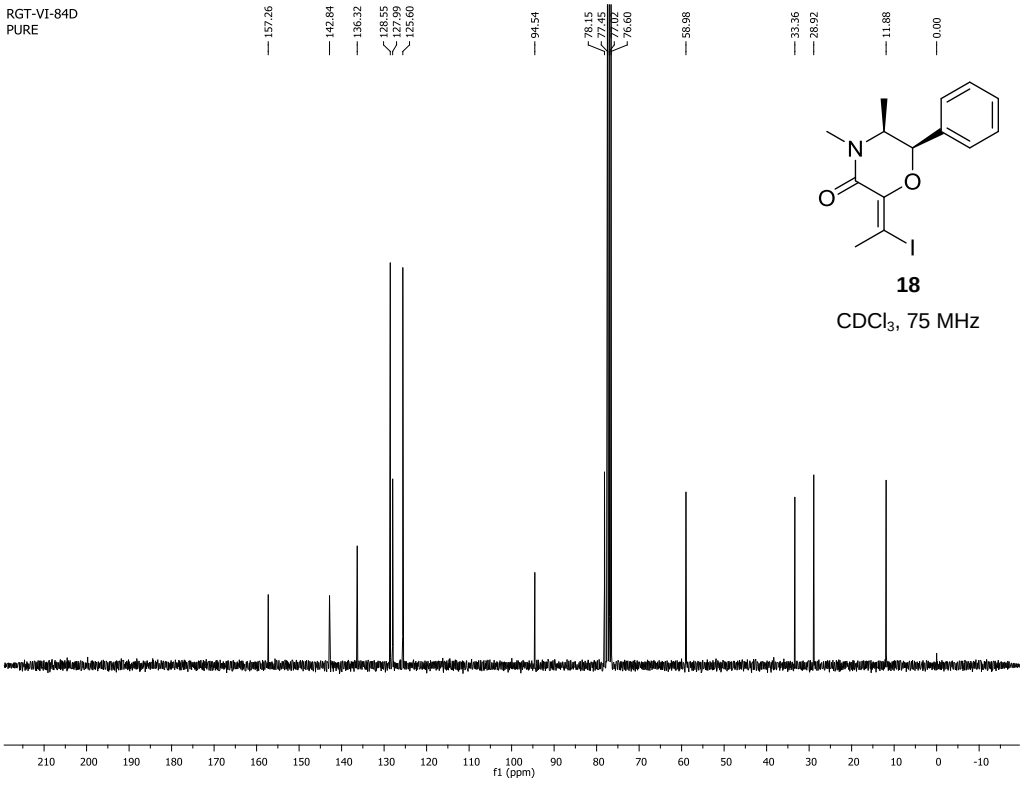

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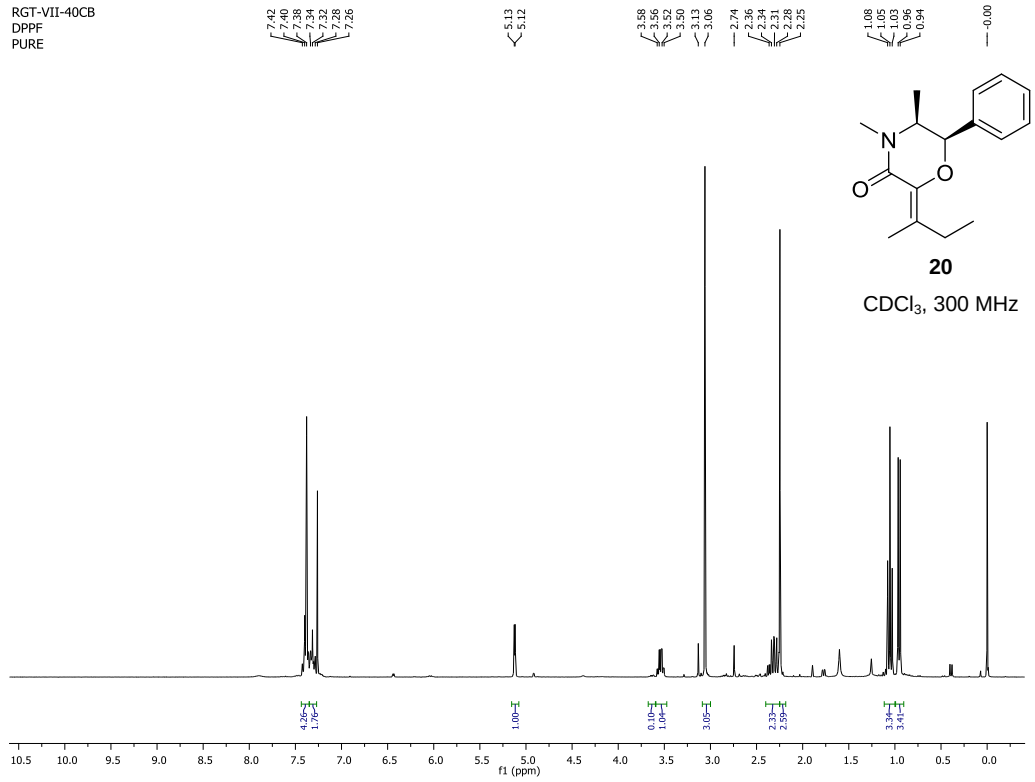

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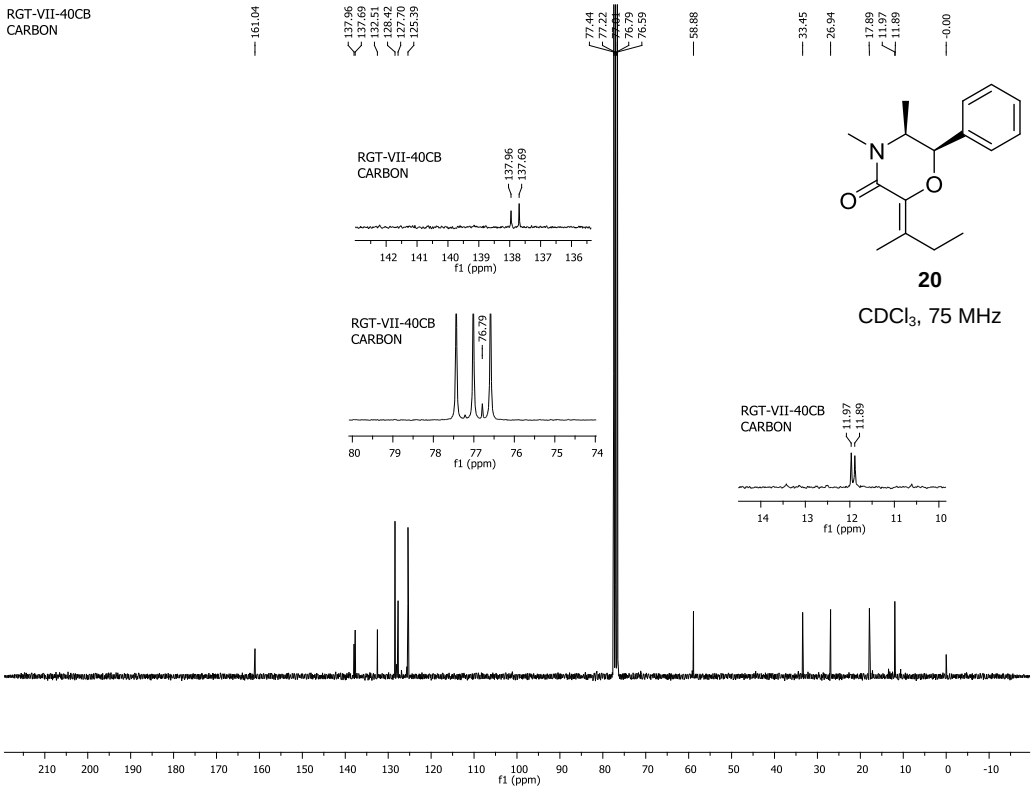

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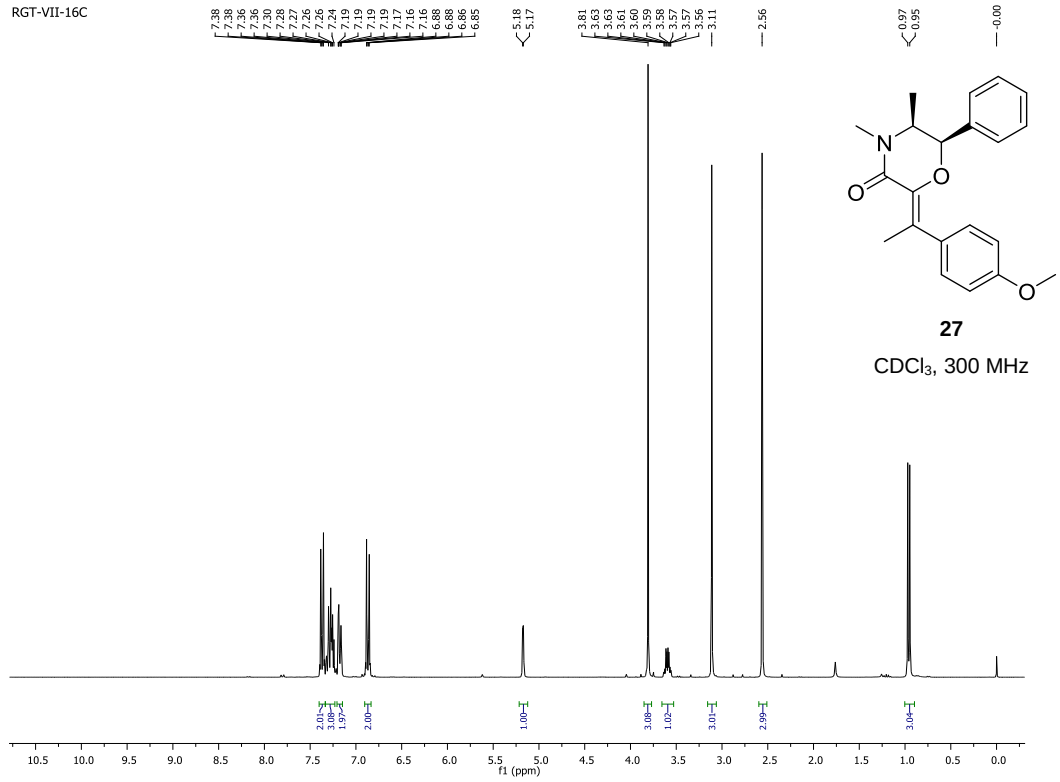

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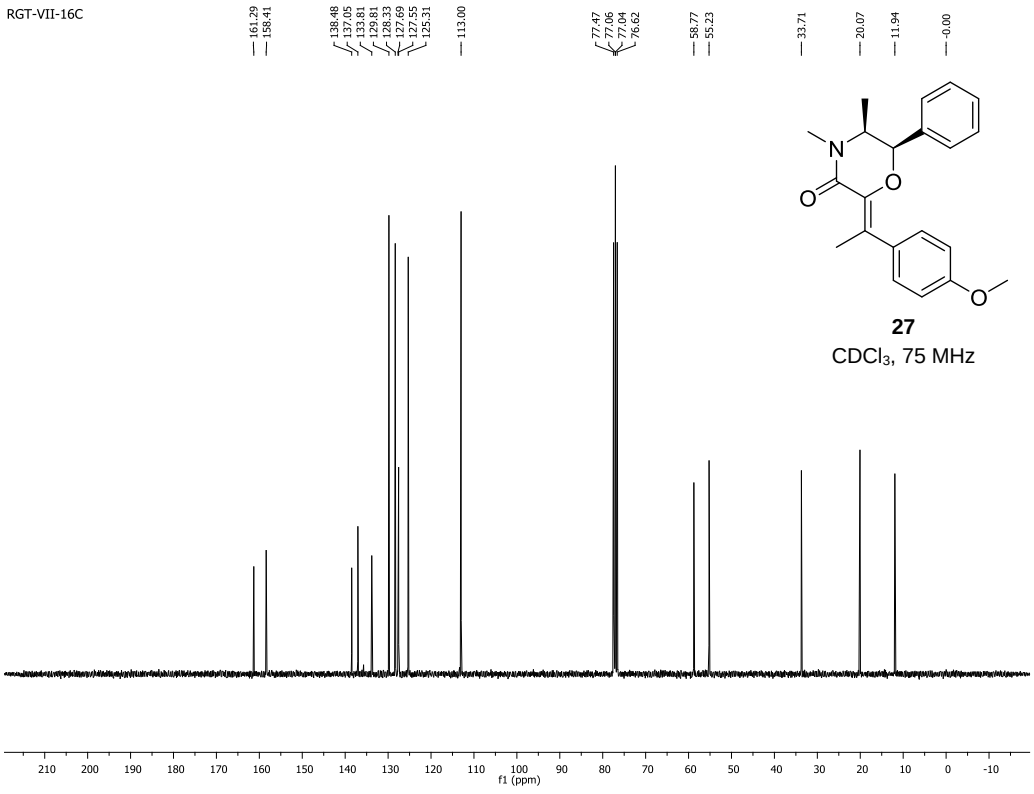

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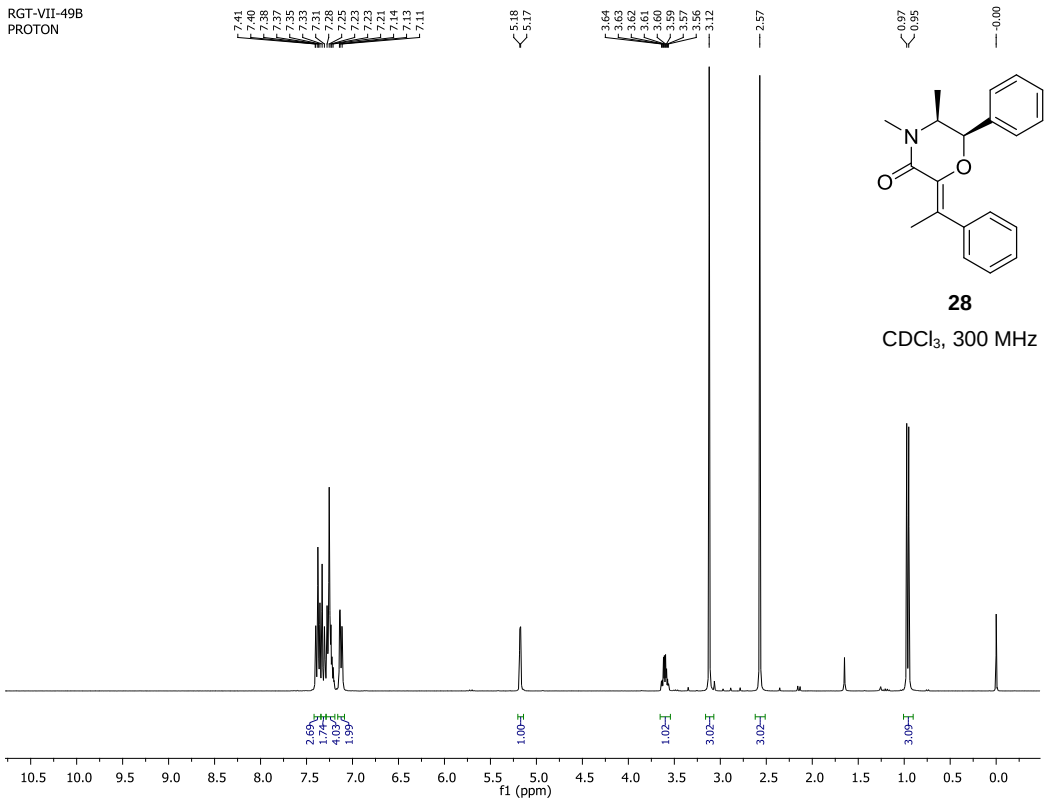

28

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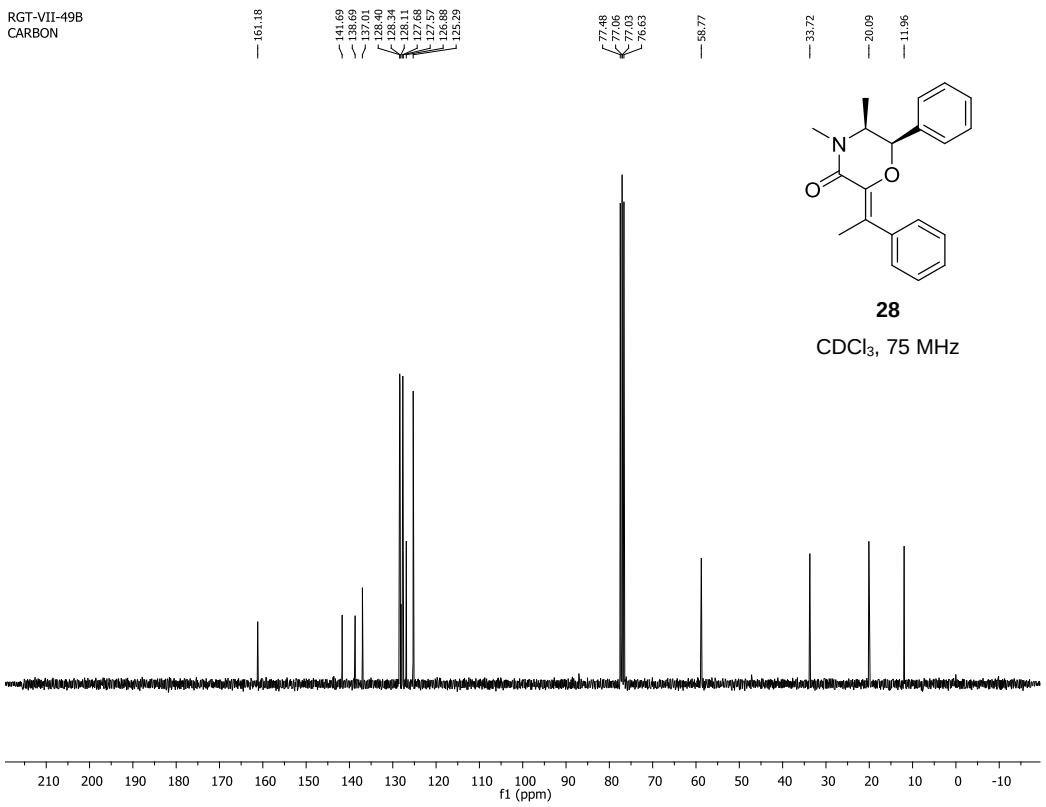
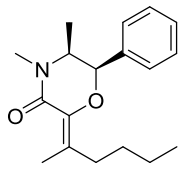


28

$CDCl_3$, 75 MHz

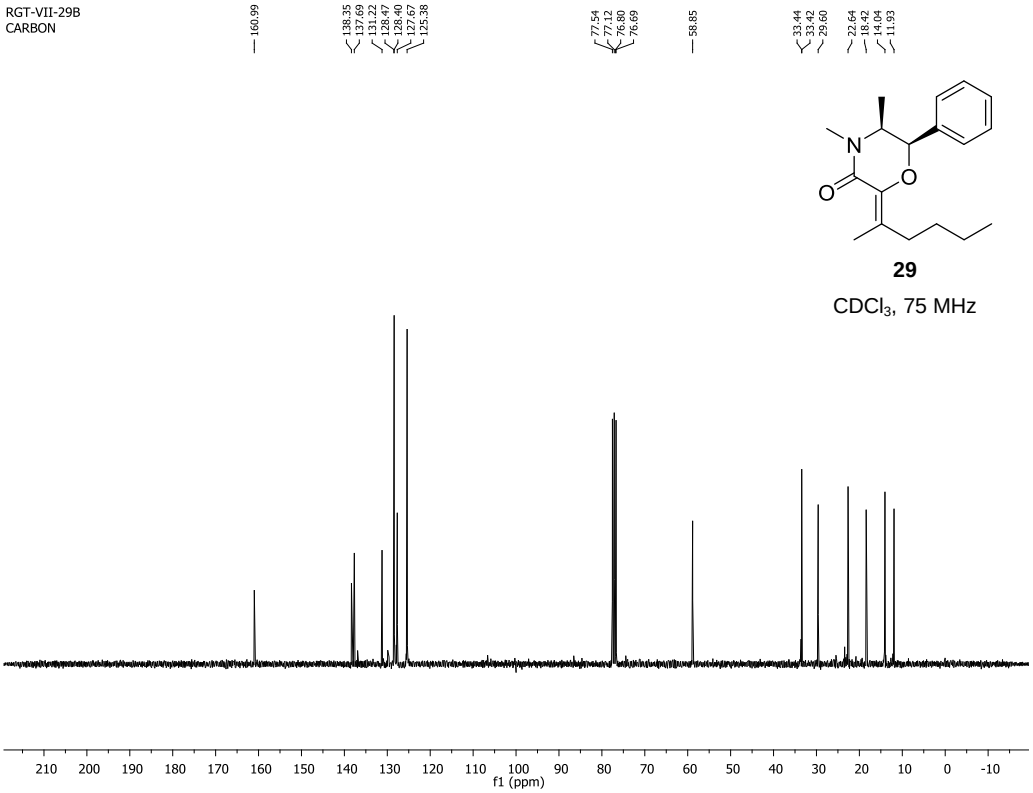
RGT-VII-50B



29

$CDCl_3$, 300 MHz

RGT-VII-29B
CARBON



29

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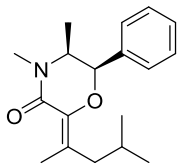

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$CDCl_3$, 300 MHz

RGT-VII-42B
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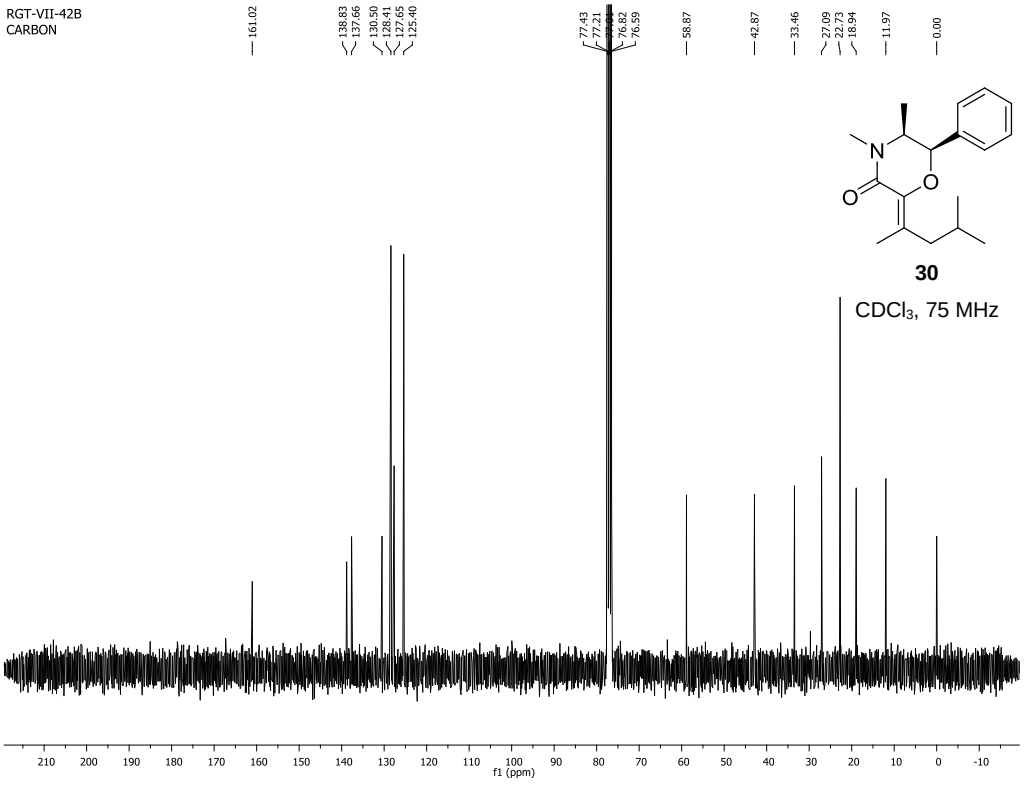

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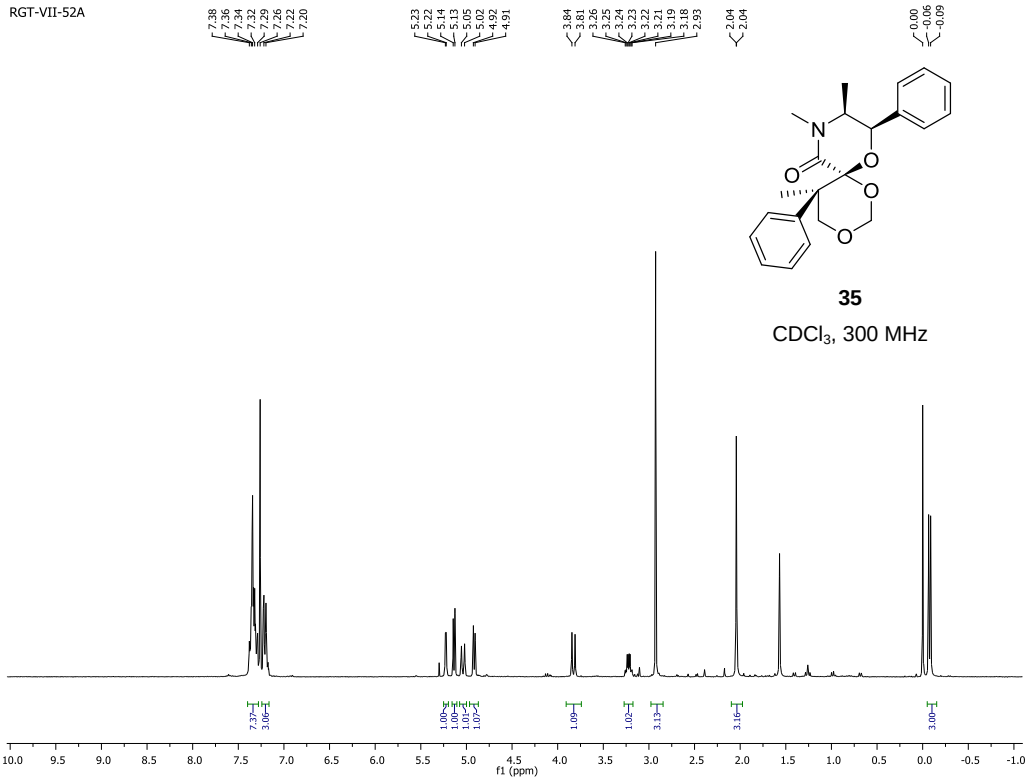

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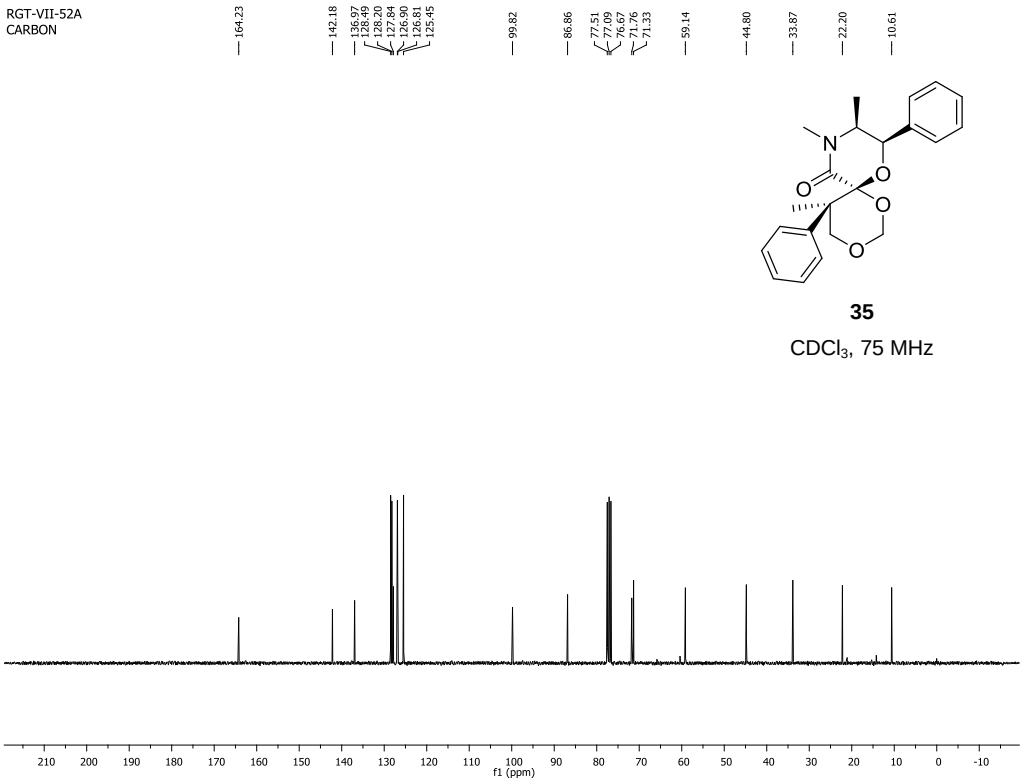
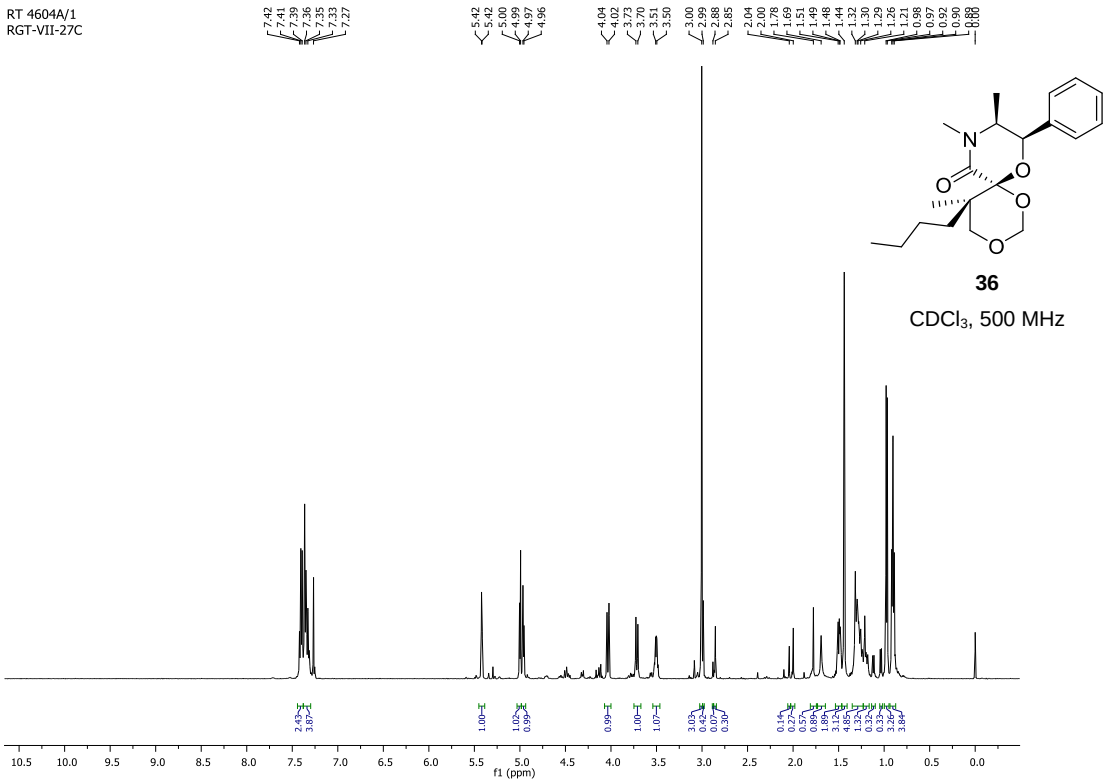
$CDCl_3$, 300 MHz



35

$CDCl_3$, 75 MHz



36

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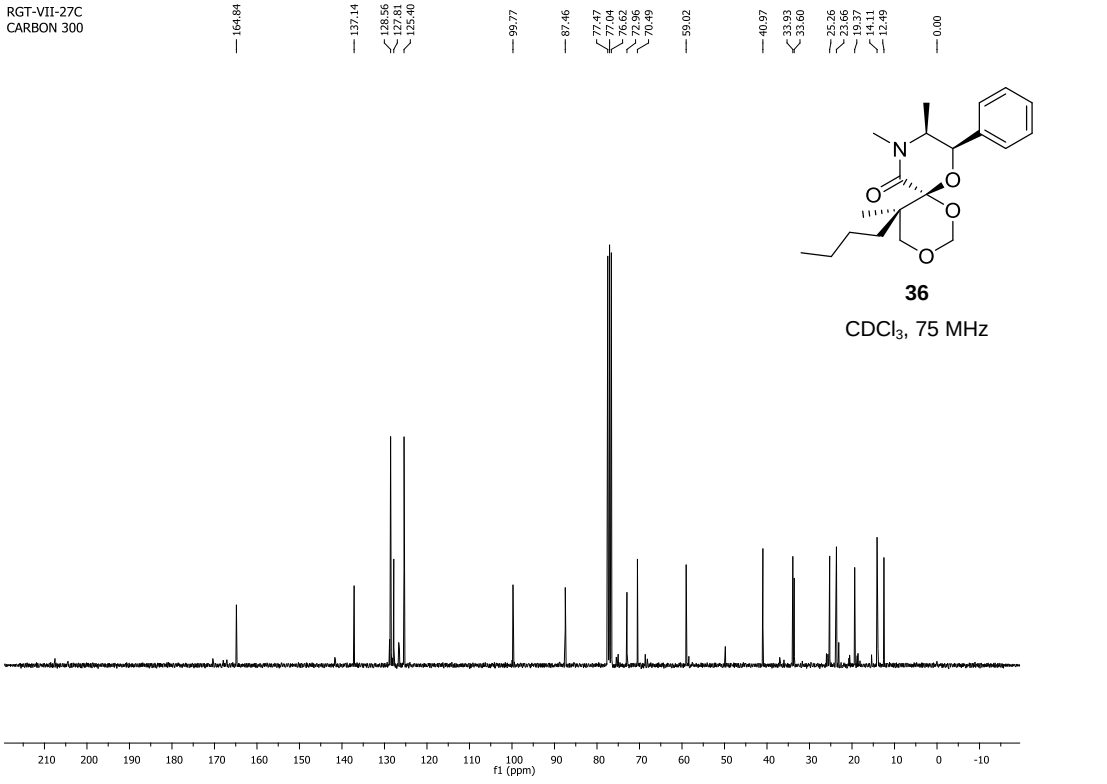
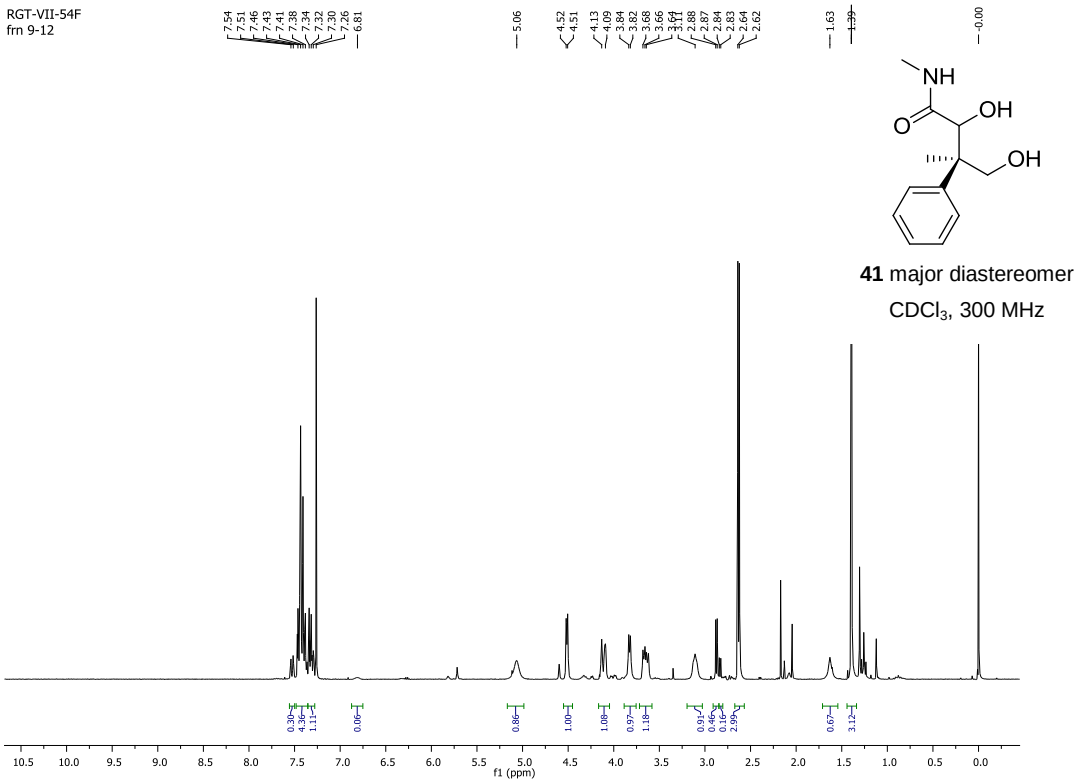


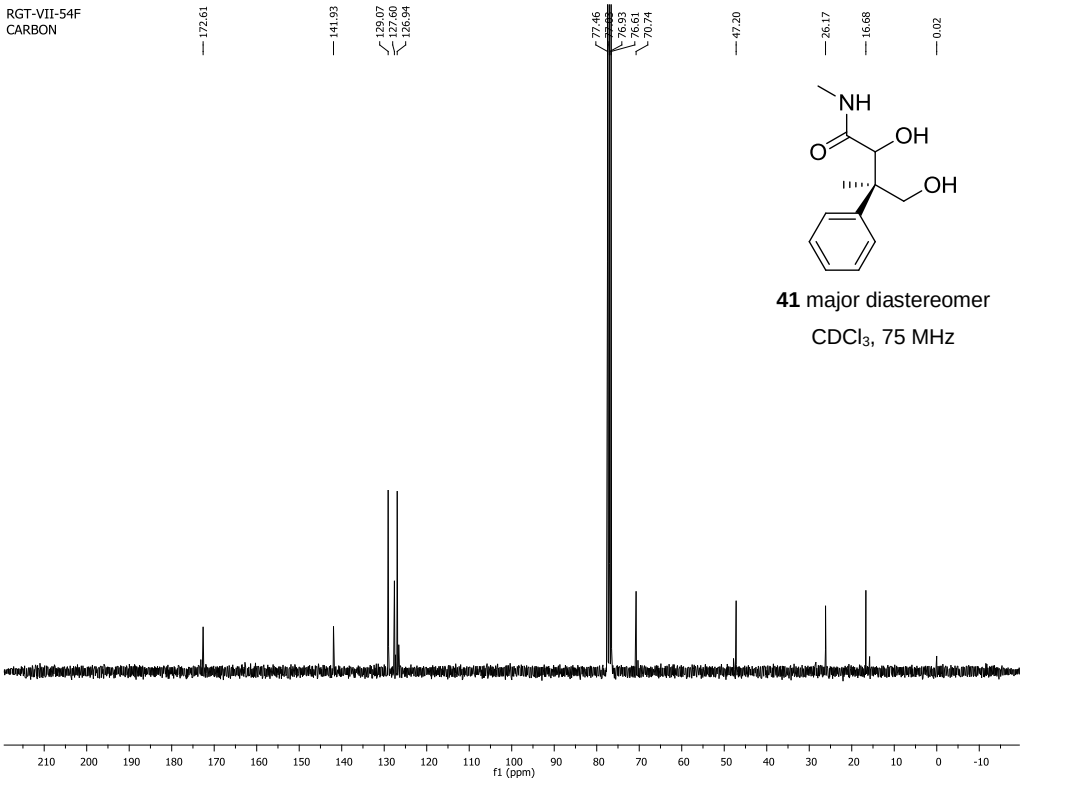
36

$CDCl_3$, 75 MHz



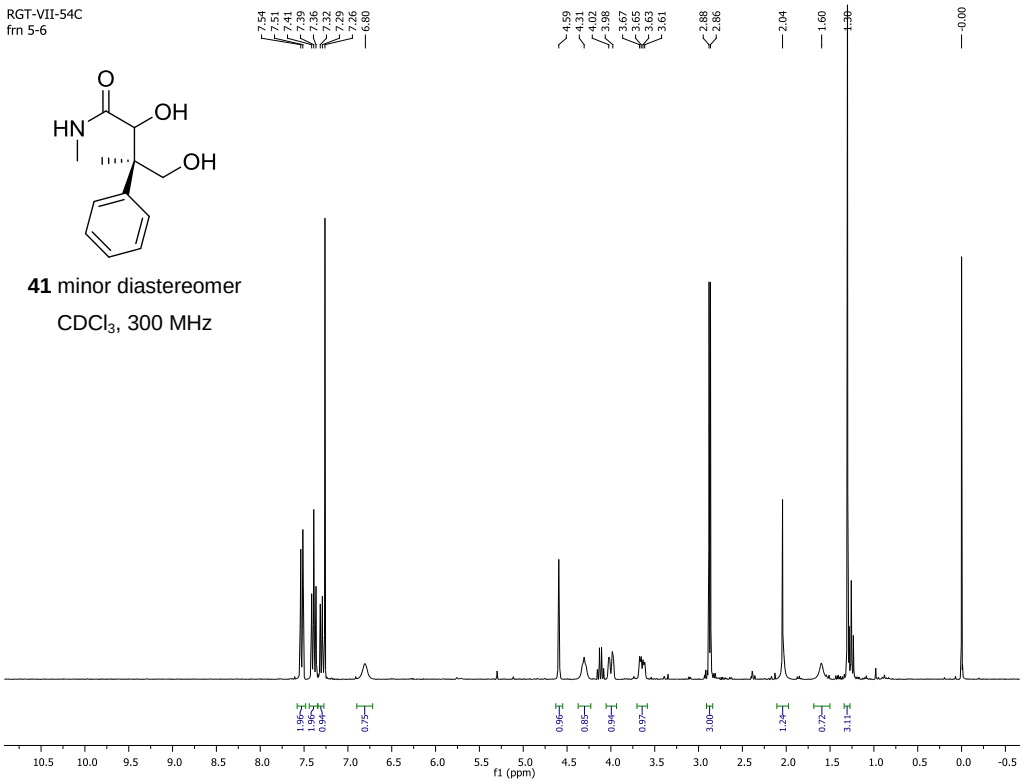
41 major diastereomer

$CDCl_3$, 300 MHz



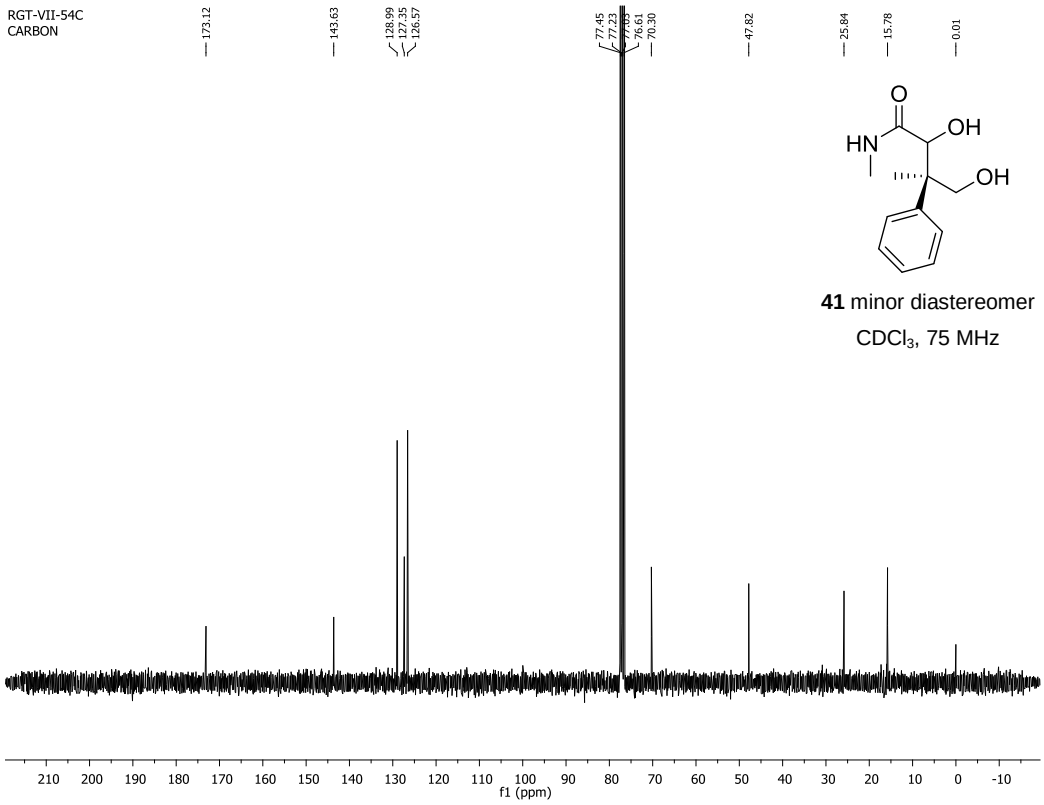
41 major diastereomer

$CDCl_3$, 75 MHz



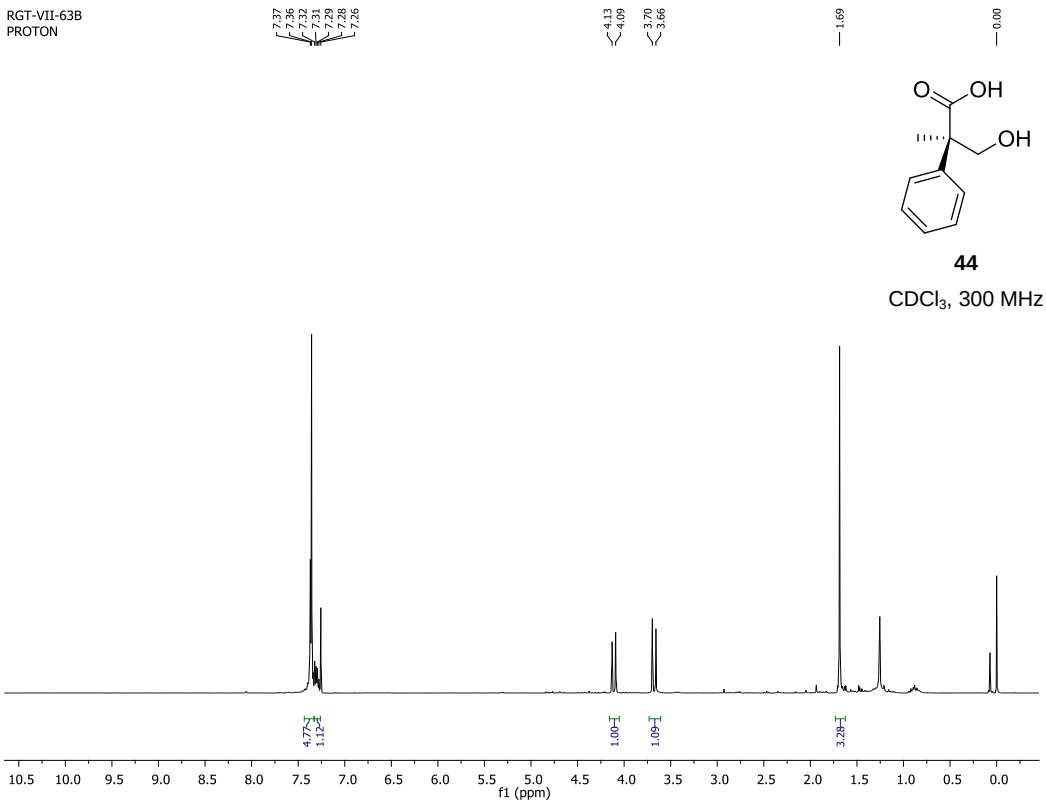
41 minor diastereomer

$CDCl_3$, 300 MHz



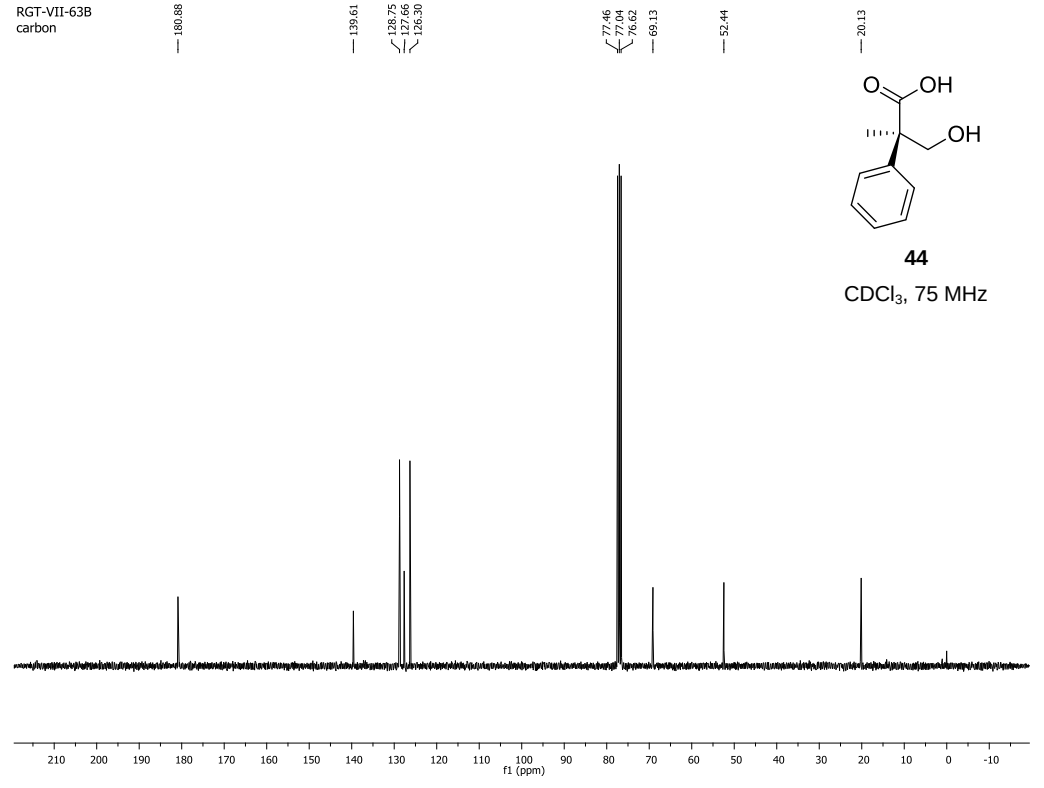
41 minor diastereomer

$CDCl_3$, 75 MHz



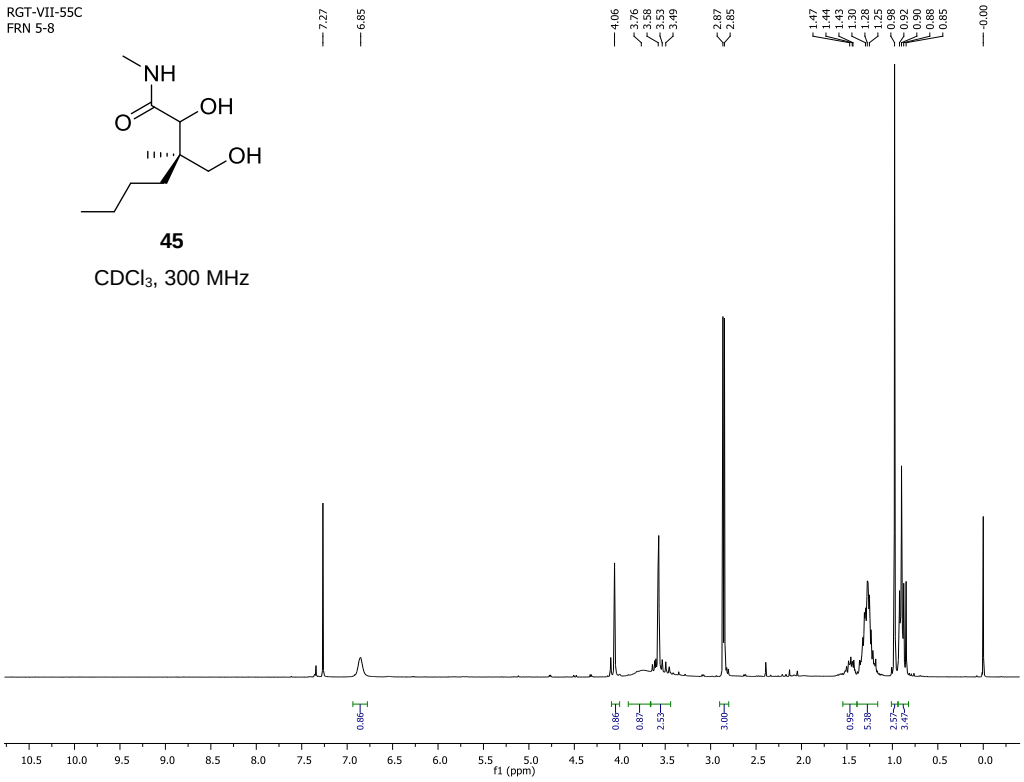
44

$CDCl_3$, 300 MHz



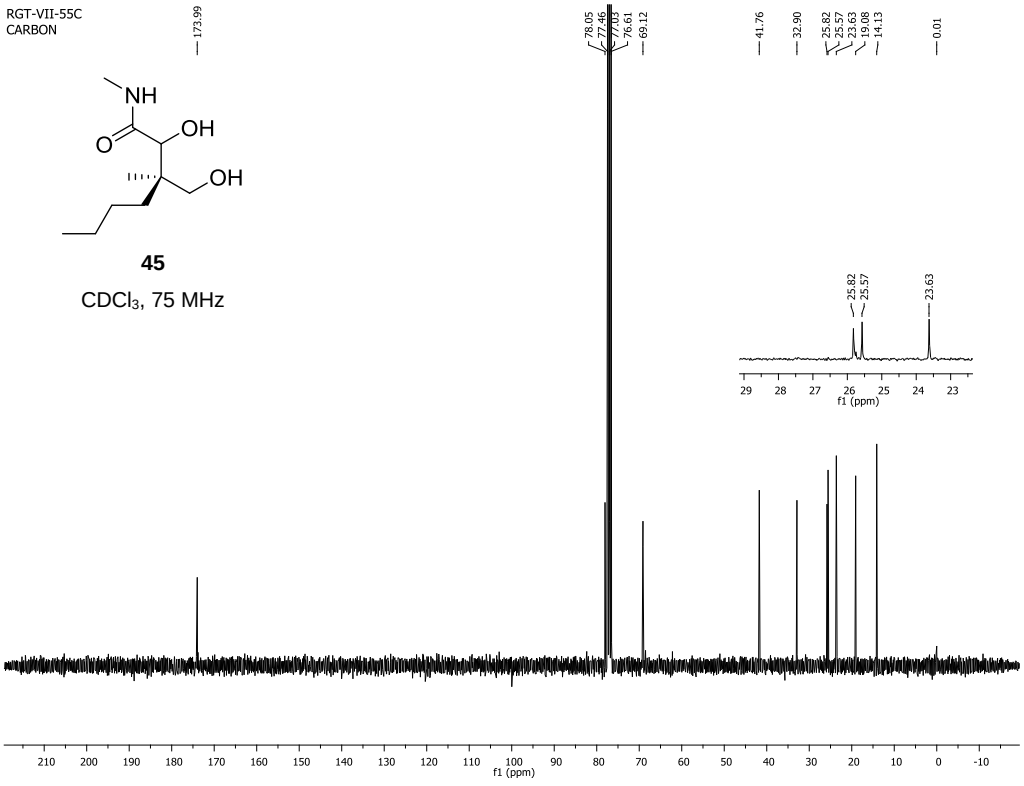
44

$CDCl_3$, 75 MHz



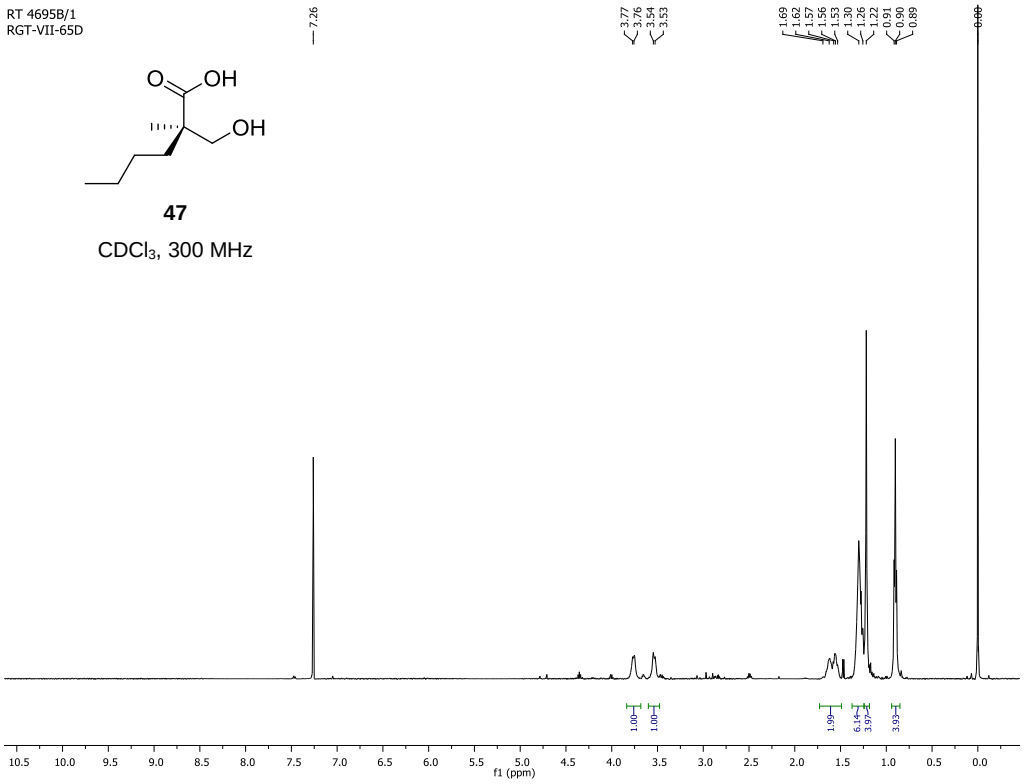
45

$CDCl_3$, 300 MHz



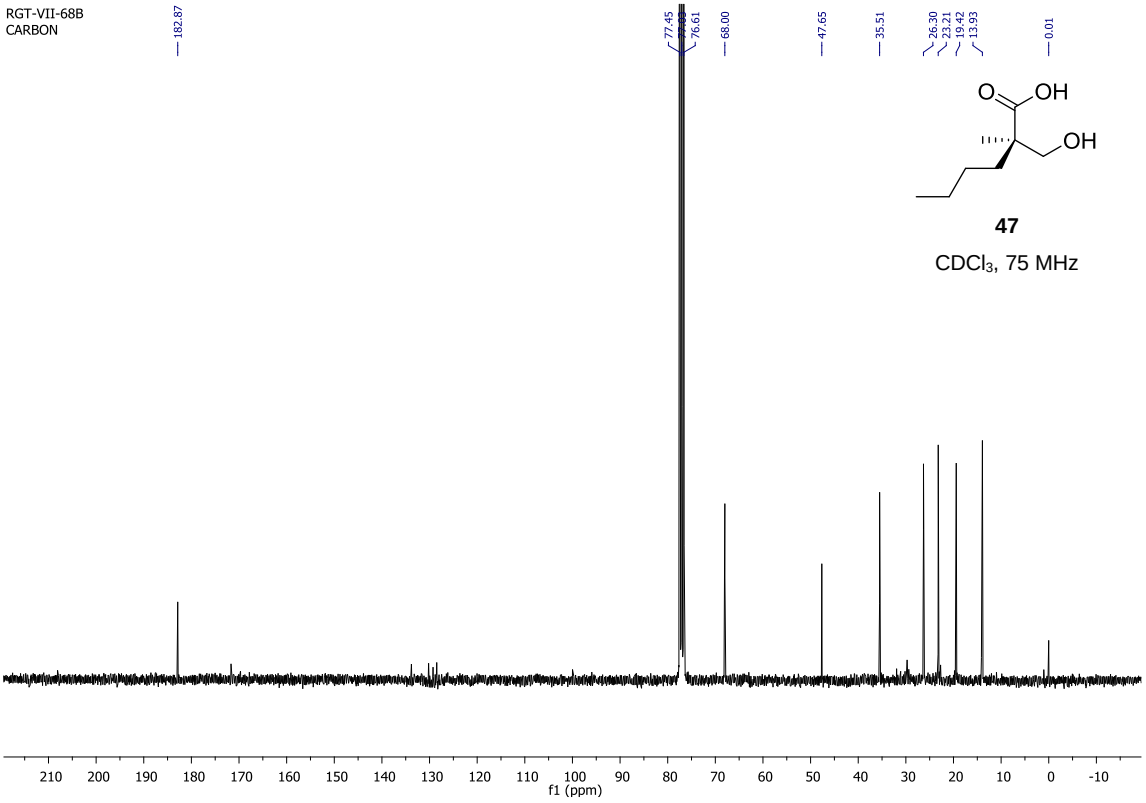
45

$CDCl_3$, 75 MHz



47

$CDCl_3$, 300 MHz



47

$CDCl_3$, 75 MHz

Chapter 4

Studies on Alkylidene Dioxolanones as Potential Substitutes for Ephedrine-Derived Alkylidene Morpholinones

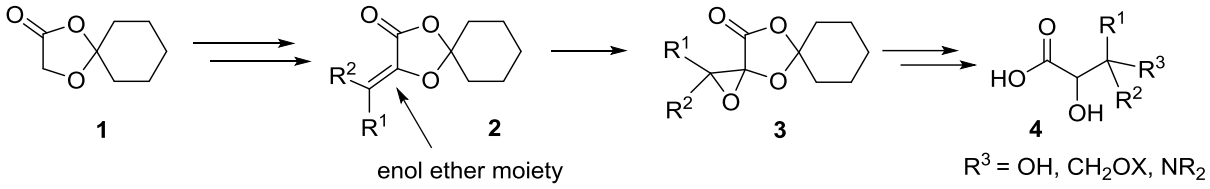
4.1 Introduction

In addition to the chemistry described in Chapter 2 and Chapter 3 of this thesis, the Pansare group has explored the synthetic utility of (1*R*,2*S*)-ephedrine hydrochloride as an efficient chiral controller in the synthesis of a variety of enantiomerically pure, functionalized molecules. Examples of such applications include the synthesis of enantiomerically-enriched α-hydroxy acid derivatives, (*S*)-pantalactone and its analogues,[1] functionalized medium-sized oxacycles,[1c] an advanced intermediate to the marine natural product Laurencin,[1d] (-)-quinic acid,[1e] and a variety of *β*-substituted *γ*-butyrolactones.[1f] However, a limitation of this methodology is the destructive removal of ephedrine at the end of the synthetic sequence. In addition, ephedrine has gone from being a cheap and easily available substance to a controlled substance which can no longer be purchased from the usual suppliers of research chemicals. In light of this, it is necessary to find either a replacement for ephedrine, or to develop an alternative synthetic methodologies that are based on the knowledge derived from the ephedrine-based system. Investigations aimed at both these objectives are ongoing in the Pansare group.

4.2 Objective

The objective of the present study was to investigate the synthesis of α-hydroxy acid derivatives from alkylidene dioxolanone derivatives rather than ephedrine-derived

morpholinones. It was reasoned that achiral spirodioxolanones such as **2** could be used as substrates for asymmetric epoxidation reactions (Scheme 4.1) to provide enantiomerically enriched epoxides **3**. This assumption was based on the known reactivity of the corresponding alkylidene morpholinones in which the exocyclic double bond functions as an enol ether (Chapter 2 and Chapter 3 of this thesis) and not as an electron-deficient acrylate. The enantiomerically-enriched epoxide intermediates can potentially be converted into α,β-difunctionalized α-hydroxy acids or β-functionalized α-hydroxy acids as shown in Scheme 4.1.



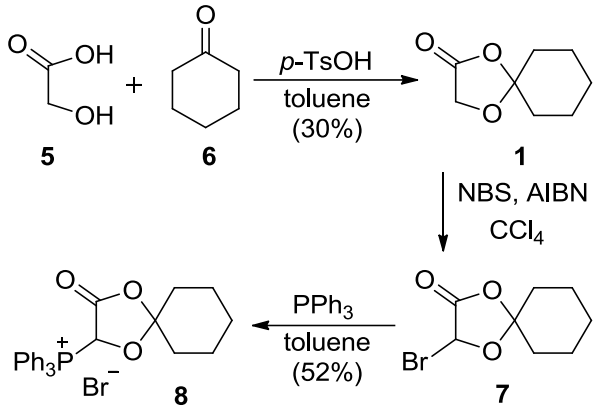
Scheme 4.1 Proposed synthesis of functionalized hydroxy acids from epoxy dioxolanones

Such hydroxy acids have numerous synthetic applications[2] and are important building blocks for natural product synthesis.[3] Notably, α-hydroxy β-amino acids constitute an important class of amino acids with a wide range of applications. They are present in many natural products and are also key components of many pharmaceuticals.[4] β-Amino acids are also used as building blocks for chiral heterocycles[4c] and in peptides with biological and catalytic properties.[5]

4.3 Results and Discussion

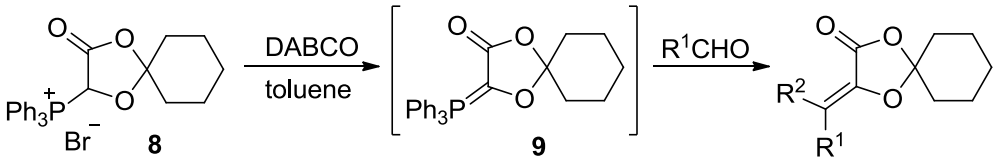
Synthesis of the required alkylidene dioxolanones was initiated by condensation of glycolic acid (**5**) and cyclohexanone (**6**) according to the literature procedure[6] to provide

the spirodioxolanone **1**. Bromination of **1** using *N*-bromosuccinimide (NBS)[6] followed by treatment of the crude bromide **7** with triphenylphosphine provided the phosphonium salt **8** (Scheme 4.2).



Scheme 4.2

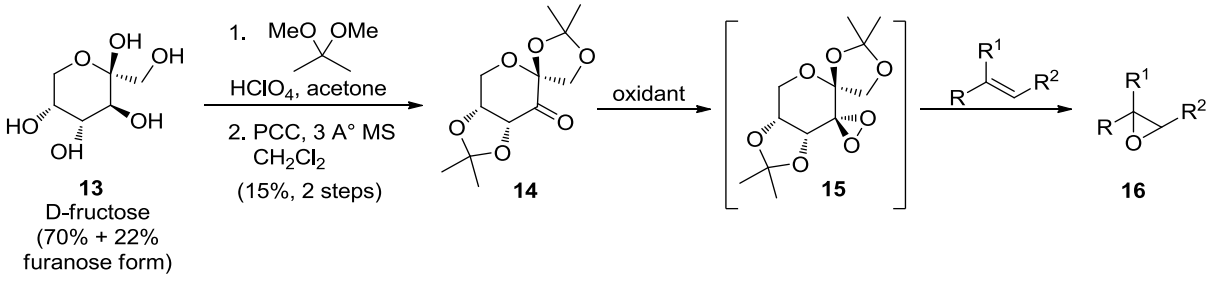
Conversion of **8** into the alkylidene dioxolanones was achieved via a conventional Wittig reaction. Treatment of **8** with DABCO (1,4-diazabicyclo[2.2.2]octane) generated the phosphorane **9** which was treated *in situ* with benzaldehyde to obtain the *Z*-alkene **10** (Scheme 4.3) as the only product. However, treatment of **9** with isobutyraldehyde furnished a mixture of the *Z*-alkene **11** and the *E*-alkene **12**. Separation of **11** and **12** by chromatography is difficult and, although some separation was achieved, **11** and **12** are both obtained as mixtures which contain approximately 10% of the isomeric alkene.



	R^1	R^2	Yield
10	Ph	H	67%
11	*i*Pr	H	66%
12	H	*i*Pr	

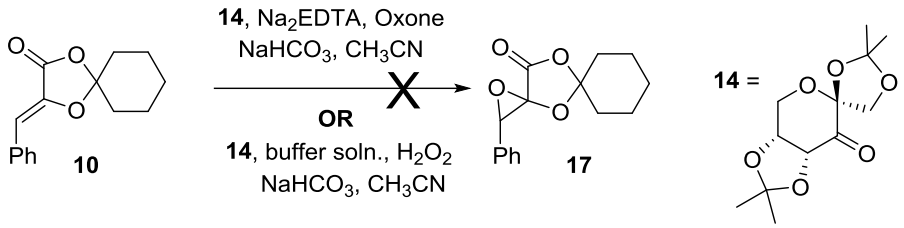
Scheme 4.3

With the alkylidene dioxolanones in hand, the next task was to test the feasibility of conducting an asymmetric epoxidation reaction of the double bond. It was decided to employ the Shi epoxidation[7] for this purpose since it is known to work for electron-rich as well as electron-deficient alkenes. In the Shi epoxidation, the epoxidizing agent is a chiral dioxirane which is formed *in situ* using an oxidant and the chiral ketone **14**. This ketone was prepared from D-fructose (**13**) in two steps (Scheme 4.4) following the reported procedure.[8] In the presence of Oxone®[9] ($KHSO_5$•1/2$KHSO_4$•1/2K_2SO_4) or H_2O_2[10] as an oxidant, **14** forms the chiral dioxirane **15** which can epoxidize a variety of alkenes (Scheme 4.4). This catalyst system also shows tolerance to a wide range of functional groups on the alkene.[7]



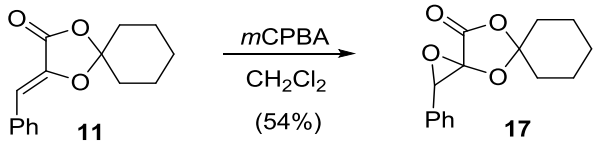
Scheme 4.4 Epoxidation of alkenes using dioxirane **16**.

Unfortunately, alkene **10** did not furnish the required epoxide **17** under the Shi epoxidation conditions and starting alkene **10** was recovered. It may be noted that the Shi epoxidation of electron-deficient alkenes as well as electron-rich alkenes is known[11] and hence, the reasons for the lack of reactivity of **10** are not clear. The epoxidation of alkenes **11** and **12** was not examined because these alkenes could not be obtained as single diastereomers.



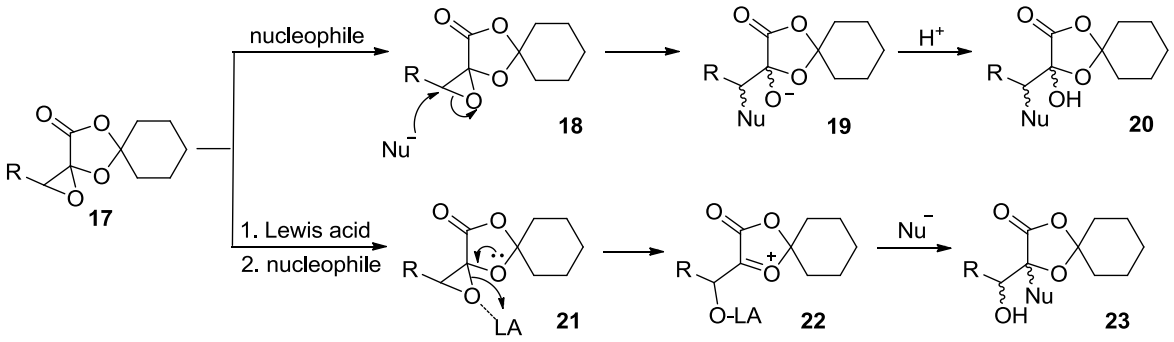
Scheme 4.5. Attempted epoxidation of alkene **11** with Shi's catalyst **14**.

In spite of the difficulties in obtaining an enantiomerically enriched epoxy spirodioxolanone, it was decided to examine the epoxidation of alkene **11** with traditional epoxidation reagents with the intention of investigating the reactivity of the epoxy dioxolanone system. Interestingly, **11** furnished the epoxide **17** in moderate yield (54%, Scheme 4.7) on treatment with *m*-CPBA.



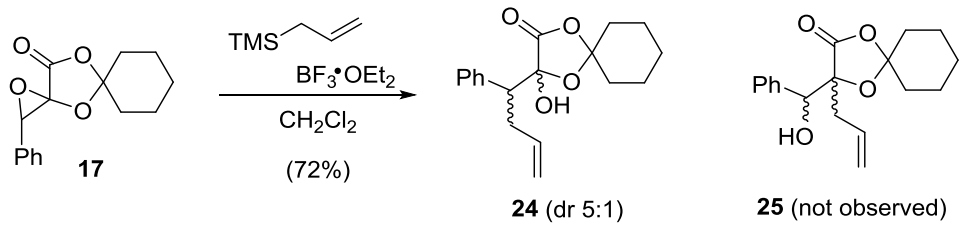
Scheme 4.6 Epoxidation of **11** with *m*-CPBA.

It was anticipated that the epoxide **17** would function as an ambident electrophile. Treatment of **17** with nucleophiles was expected to provide ring-opening products such as **20** arising from addition to the 'terminal' carbon of the epoxide,[12] whereas nucleophilic addition in the presence of a Lewis acid was anticipated to proceed at the acetal carbon end of the epoxide (**23**, Scheme 4.7).[1c]



Scheme 4.7

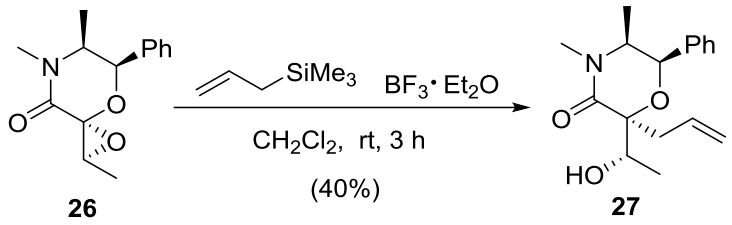
However, treatment of epoxide **17** with nitrogen nucleophiles ($BnNH_2$, Bu_4NSCN) lead to complex mixtures, presumably due to competing reactions of the amine with the lactone carbonyl. The expected ring-opened products **20** or **23** could not be detected by ^1H NMR spectroscopy of the crude products. Furthermore, a Lewis acid mediated allylation of **17** resulted in allylation at the non-acetal end of the epoxide to provide **24** (5:1 mixture of diastereomers) instead of the anticipated product **25** (Scheme 4.8). The mixture of diastereomers may arise either from an S_N1-type substitution at the benzylic carbon or due to a thermodynamically controlled equilibration of the hemiacetal stereocenter.



Scheme 4.8 Allylation of epoxide **17**.

The formation of **24** was confirmed by analysis of its ^1H NMR spectrum in which the benzylic methine appeared as a doublet of doublet due to coupling with the allylic methylene group. In addition, the COSY ^1H NMR spectrum of **24** showed a correlation between the benzylic methine and the allylic methylene group. These interactions are not

possible for the isolated benzylic methine in **25**. The formation of **24** from **17** is unexpected and is in contrast to the reactivity of the spiro epoxide **26** obtained from an ephedrine-derived alkylidene morpholinones. Allylation of **26** proceeds at the acetal carbon to provide **27** as the only isolable product (Scheme 4.9).[1c]



26 **27**

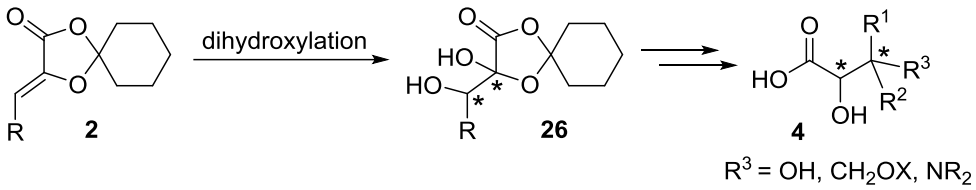
Scheme 4.9

It is plausible that the benzylic position in **17** is activated towards nucleophilic addition which leads to the formation of **24** before the generation of an oxonium ion from the ring oxygen-assisted opening of the epoxide. The reactivity of an alkyl analog of **17**, in which the phenyl group is replaced by an alkyl group, needs to be explored to gain insight into the observed reactivity of **17**.

Due to the difficulties encountered in the stereoselective synthesis of dialkyl alkylidene spirodioxolanones such as **11** and **12** and the unreactivity of the spirodioxolanone **10** in the Shi epoxidation, further studies with **10**, **11** and **12** were discontinued.

4.4 Conclusion

Although the alkylidene dioxolanones **10**, **11**, and **12** prepared in this study may have synthetic potential, as evidenced by the conversion of **17** to **24**, an extensive screening of the reactivity of these alkylidene dioxolanones is required. Asymmetric epoxidation methods such as the Jacobson epoxidation or epoxidation under phase transfer conditions can be explored to access enantiomerically enriched epoxides such as **17**. Apart from epoxidation, asymmetric dihydroxylation also presents an interesting way to prepare β-functionalized α-hydroxy acids **4** from alkenes **10**, **11** and **12**.

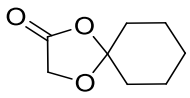


Scheme 4.10

4.5 Experimental Section

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 and THF were distilled from CaH_2 and sodium/benzophenone respectively. Commercial precoated silica gel plates were used for TLC. Silica gel for flash column chromatography was 230-400 mesh. All melting points are uncorrected. Optical rotations were measured at the sodium D line on a digital polarimeter at ambient temperature. Compounds **10** and **12** were prepared according to literature methods.[8]

1,4-Dioxaspiro[4.5]decan-2-one (1):



To a solution of cyclohexanone (32.01 g, 0.326 mol) and *p*-TsOH (0.075 g, 0.4 mmol) in toluene (150 mL) was added, dropwise over 1 h, a solution of glycolic acid (20 g, 0.262 mol) in water (10 mL). The mixture was heated to reflux for a further 5 h (the water produced in the reaction was removed *via* a Dean and Stark apparatus) and cooled to ambient temperature. Anhydrous sodium acetate (0.119 g, 1.45 mmol) was added and the mixture was stirred for 1 h. The mixture was filtered and the filtrate was evaporated under reduced pressure to provide a yellow oil which was fractionally distilled to yield cyclohexanone (b.p. 20 °C, 0.5 mmHg), followed by the dioxolanone **1** (15.4 g, 38%) as a colourless liquid which solidified upon storage in the referigerator.

B.p. 70 °C, 0.5 mm Hg.

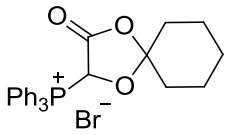
IR (neat): 1788, 1451, 1371, 1269, 1215, 1150, 1080, 1037 920 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.33 (s, 2H, C(O)CH_2), 1.87-1.82 (m, 2H, CH_2), 1.77-1.72 (m, 2H, CH_2), 1.70-1.64 (m, 4H, CH_2), 1.52-1.41 (m, 2H, CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6 (*C*=O), 113.5 (O-*C*-O), 63.2 (C(O)*C*H_2), 35.3 (2 x *C*H_2), 24.4 (*C*H_2), 22.9 (2 x *C*H_2).

MS (EI, pos.): *m*/*z* 157.1 $(M+H)^+$.

(3-Oxo-1,4-dioxaspiro[4.5]decan-2-yl)triphenylphosphonium bromide (8):



A mixture of *N*-bromosuccinimide (3.89 g, 21.8 mmol), freshly-distilled dioxolanone **1** (3.10 g, 19.8 mol) and AIBN (8 mg, 0.05 mmol) in CCl_4 (30 mL) was heated to reflux and irradiated with a 300 W tungsten lamp. The ensuing vigorous reaction was controlled by switching off the lamp occasionally. After 30 min, the resulting pale yellow suspension was cooled to 5 °C and the colorless precipitate of succinimide was filtered off and washed with CCl_4 (2 x 20 mL). The filtrate and the washings were combined and the solution was concentrated under reduced pressure to provide 4.51 g (97%) of the bromide **7** as a pale yellow, lachrymatory oil. This was pure by ^{1}H NMR and was used further without any purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.52 (s, 1H, C*H*Br), 2.20-2.08 (m, 2H, CH_2), 1.82-1.72 (m, 6H, CH_2), 1.56-1.44 (m, 2H, CH_2).

The bromide **7** (4.51 g, 19.2 mmol) was dissolved in toluene (50 mL) and a solution of triphenylphosphine (5.03 g, 19.2 mmol) in toluene (25 ml) was added dropwise over 1 h. The resulting solution was stirred overnight and the colourless precipitate was filtered and washed with toluene (2 x 100 ml), and ether (3 x 100 mL). The residue was purified by dissolution in ethanol followed by precipitation with ether to provide 5.1 g (52%) of phosphonium bromide **8** as a colourless solid.

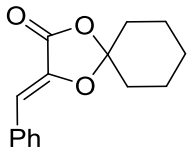
IR (neat): 1783, 1436, 1266, 1204, 1150, 1106, 1057, 920 cm^{-1}.

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 8.07-8.03 (m, 9H, Ar*H*), 7.91-7.87 (m, 7H, Ar*H* and C*H*C(O)), 2.10-2.08 (m overlapped with $(CD_3)_2CO$, 2H, CH_2), 1.78-1.71 (m, 1H, CH_2), 1.64-1.58 (m, 1H, CH_2), 1.56-1.50 (m, 1H, CH_2), 1.49-1.40 (m, 3H, CH_2), 1.38-1.35 (m, 1H, CH_2), 1.33-1.28 (m, 1H, CH_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7 (*C*=O), 135.7 (Ar*C*), 134.8 (Ar*C*), 130.4 (Ar*C*), 116.1 (ArC_{ipso}), 114.9 (O*C*O), 71.2 (d, *J* = 63.0, *C*HPPh$_3$), 36.2 (*C*H$_2$), 35.5 (*C*H$_2$), 24.2 (*C*H$_2$), 23.08 (*C*H$_2$), 23.04 (*C*H$_2$).

MS (EI, pos.): *m*/*z* 417.5 $(M\text{-}Br)^+$.

(*Z*)-3-Benzylidene-1,4-dioxaspiro[4.5]decan-2-one (10):



To the solution of phosphonium bromide **8** (1 g, 2.012 mmol) was added a solution of DABCO (0.237 g, 2.112 mmol) in toluene (25 mL) at 110 °C under nitrogen. The yellow colour of the phosphorane **9** was seen immediately and the mixture was stirred for 3-5 min.

Freshly distilled benzaldehyde (0.20 mL, 1.91 mmol) was added and the solution was heated to reflux for 1 h. The mixture was cooled to 5 °C and filtered to remove the precipitated DABCO hydrobromide. The filtrate was concentrated under reduced pressure to provide with an oily residue which was triturated with petroleum ether (5 x 10 mL) to remove most of the triphenylphosphine oxide. The resulting oily solid was purified by flash chromatography (hexane/ether, 4:1) to give a pale yellow solid. This was crystallized from ethanol-water to provide 0.330 g (67%) of (*Z*)-3-benzylidene-1,4-dioxaspiro[4.5]decan-2-one (**10**) as a colorless solid.

IR (neat): 1781, 1669, 1448, 1367, 1271, 1239, 1188, 1114, 1039 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, 2H, *J* = 7.5, Ar*H*), 7.39 (t, 2H, *J* = 7.5, Ar*H*), 7.31 (t, 1H, *J* = 7.5, Ar*H*), 6.45 (s, 1H, C=C*H*), 1.94-1.86 (m, 4H, CH_2), 1.84-1.75 (m, 4H, CH_2), 1.59-1.50 (m, 2H, CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ 163.8 (*C*=O), 137.0 (*C*-C=O), 133.1 (ArC_{ipso}), 129.6 (2 x Ar*C*), 128.7 (2 x Ar*C*), 128.5 (Ar*C*), 112.7 (C=*C*H), 108.1 (O-*C*-O), 36.3 (2 x *C*H_2), 24.2 (*C*H_2), 23.0 (2 x *C*H_2).

MS (EI, pos.): *m*/*z* 245.1 $(M+H)^+$.

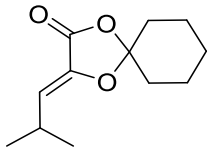
(*E*)-3-(2-Methylpropylidene)-1,4-dioxaspiro[4.5]decan-2-one (11) and

(*Z*)-3-(2-methylpropylidene)-1,4-dioxaspiro[4.5]decan-2-one (12):

To a solution of the phosphonium bromide **8** (2.74 g, 5.51 mmol) (70 mL) was added a solution of DABCO (0.65 g, 5.79 mmol) in toluene (5 mL) at 110 °C under nitrogen. The yellow colour of the phosphorane **9** was seen immediately and the mixture was stirred for 3-5 min. Isobutyraldehyde (2.01 g, 27.9 mmol) was added and the solution

was heated to reflux for 1.5 h. The mixture was cooled to 5 °C and filtered to remove the precipitated DABCO hydrobromide. The filtrate was concentrated under reduced pressure to provide with an oily residue which was triturated with petroleum ether (5 x 10 mL) to remove most of the triphenylphosphine oxide. The resulting oil was purified by flash chromatography (hexane/ether, 4:1) gave 30 mg (2%) of **11**, 25 mg (2%) of **12** and 710 mg of mixture of **11** and **12** (61%) all as a colourless oils.

(*Z*)-3-(2-Methylpropylidene)-1,4-dioxaspiro[4.5]decan-2-one (11):



IR (neat): 1789, 1454, 1368, 1299, 1224, 1148, 1104, 1036, 940 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.50 (d, 1H, *J* = 9.0, C=C*H*), 2.73-2.66 (m, 1H, CH_3CH), 2.33-2.17 (m, 1H, CH_2), 1.83-1.72 (m, 10H, CH_2), 1.07 (d, 6H, *J* = 6.7, 2 x CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5 (*C*=O), 136.9 (*C*-C=O), 117.4 (C=*C*H), 111.5 (O-*C*-O), 36.1 (CH_3CH), 25.7 (2 x CH_2), 24.3 (2 x CH_2), 22.8 (CH_3 overlapped with CH_2), 22.1 (CH_3).

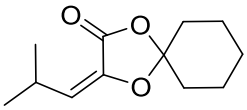
MS (EI, pos.): *m*/*z* 211.1 $(M+H)^+$.

Visible peaks of **12**:

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.36 (d, 1H, *J* = 10.6, C=C*H*), 3.55-3.45 (m, 1H, CH_3CH), 1.02 (d, 6H, *J* = 6.7, 2 x CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 122.1 (C=*C*H), 110.6 (O*C*O), 36.1 (CH_3CH), 24.0, 23.4, 22.8.

(*E*)-3-(2-Methylpropylidene)-1,4-dioxaspiro[4.5]decan-2-one (12):



IR (neat): 1782, 1454, 1368, 1306, 1207, 1139, 1046, 977, 935 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.36 (d, 1H, *J* = 10.6, C=C*H*), 3.55-3.45 (m, 1H, CH_3CH), 1.84-1.68 (m, 9H, CH_2), 1.51-1.42 (m, 2H, CH_2), 1.02 (d, 6H, *J* = 6.7, 2 x CH_3).

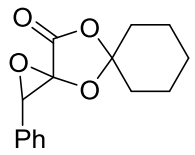
^{13}C NMR (75 MHz, $CDCl_3$): δ 162.5 (*C*=O), 136.0 (*C*-C=O), 122.0 (C=*C*H), 110.6 (O-*C*-O), 36.1 (CH_3CH), 24.2 (2 x CH_2), 24.0 (2 x CH_2), 23.4 (CH_3), 22.8 (CH_3 overlapped with CH_2).

Visible peaks of **11**:

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.50 (d, 1H, *J* = 9, C=C*H*), 2.73-2.66 (m, 1H, CH_3CH), 1.07 (d, 6H, *J* = 6.7, 2 x CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 117.4 (C=*C*H), 111.4 (O*C*O), 25.7, 22.8, 22.1.

2-Phenyl-1,4,11-trioxadispiro[2.1.5^{5}.2^{3}]dodecan-12-one (17):



To a solution of (*Z*)-3-benzylidene-1,4-dioxaspiro[4.5]decan-2-one (**10**) (310 mg, 1.27 mmol) in DCM (5 mL) was added *m*-chloroperbenzoic acid (426 mg, 1.91 mmol) at – 78°C. The reaction mixture was then warmed to room temperature and stirred for 12 h. An aqueous saturated $NaHCO_3$ was added and the mixture was extracted with ethyl acetate (3x10mL). The combined organic layers were dried (Na_2SO_4) and concentrated under

reduced pressure to provide a white solid which was purified by flash chromatography on silica gel (EtOAc/hexanes, 1:9) to provide 180 mg (54%) of **17** as a white solid.

IR (neat): 1805, 1448, 1369, 1273, 1179, 1130, 1091, 1042, 944, 906 cm^{-1}.

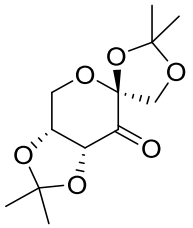
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39-7.44 (m, 5H, Ar*H*), 4.42 (s, 1H, ArC*H*), 2.03-1.94 (m, 2H, CH_2), 1.84-1.79 (m, 1H, CH_2), 1.77-1.70 (m, 3H, 2-CH_2), 1.68-1.61 (m, 1H, CH_2), 1.60-1.56 (m, 1H, CH_2), 1.50-1.42 (m, 2H, CH_2).

^{13}C NMR (125.5 MHz, $CDCl_3$): δ 166.3 (*C*=O), 131.5 (Ar*C*ipso), 129.1 (Ar*C*), 128.4 (2 x Ar*C*), 127.7 (2 x Ar*C*), 112.1 (O-*C*-O), 84.1 (O=C-*C*-O), 60.9 (Ar*C*-O), 36.9 (*C*H_2CO), 36.1 (*C*H_2CO), 24.1(*C*H_2CH_2CO), 22.9 (*C*H_2CH_2CO), 22.(CH$_2$*C*H$_2$CH$_2$).

MS (EI, pos.): *m*/*z* 261.5 (M^+).

HRMS (CI, pos): *m*/*z* 261.1126 (261.1127 calc. For $C_{15}H_{17}O_4$ $(M+H)^+$).

(3a*R*,4'*S*,7a*R*)-2,2,2',2'-Tetramethyldihydrospiro[[1,3]dioxolo[4,5-c]pyran-6,4'-[1,3]dioxolan]-7(7aH)-one (14):



Perchloric acid (70%, 4.3 mL) was added to a suspension of D-fructose (18.01 g, 99.96 mmol) in acetone (350 mL) and 2,2-dimethoxypropane (7.4 mL, 59.98 mmol) at 0 °C. The resulting mixture was stirred under nitrogen at 0 °C for 6 h and concentrated ammonium hydroxide was added until pH was ~7-8. The resulting mixture was stirred for 5 min and the solvent was removed under reduced pressure. The solid residue was

dissolved in CH_2Cl_2 (200 mL) and the solution was washed with a saturated solution of brine (2 x 50 mL), dried (Na_2SO_4) and concentrated under reduced pressure to a volume of 40 mL. Boiling hexane was added to this solution and the mixture was cooled to ambient temperature followed by cooling at -25 °C for 4 h. The solids obtained were filtered, washed with cold hexane and dried to provide 5.74 g (22%) of **13a**.

IR (KBr) 3454, 1376, 1216, 1070, 973 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 4.21 (dd, 1H, *J* = 5.8, 2.4), 4.20 (d, 1H, *J* = 8.8), 4.14 (d, 1H, *J* = 6.8), 4.11 (dd, 1H, *J* = 10.9, 3.2), 4.00 (d, 1H, *J* = 14.9), 3.98 (d, 1H, *J* = 8.9), 3.67 (dd, 1H, *J* = 8.1, 7.1), 2.01 (d, 1H, *J* = 8.3), 1.54 (s, 3H), 1.52 (s, 3H), 1.44 (s, 3H), 1.37 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 111.9, 109.4, 104.6, 77.32, 73.4, 72.2, 70.4, 60.7, 28.0, 26.4, 26.3, 26.0.

MS (EI, pos.): *m*/*z* 260.1 (M^+), 243.1 $(M-17)^+$.

PCC (4.14 g, 19.2 mmol) was added in small portions over 15 min to a mixture of alcohol **13a** (2.01 g, 7.69 mmol) and powdered 3 Å molecular sieves (3 g, activated at 180-200 °C under vacuum) in CH_2Cl_2 (40 mL). The reaction mixture was stirred for 3 h under nitrogen and filtered through Celite. The residue was washed carefully with ether. The combined filtrates were concentrated under reduced pressure and the residue was purified on short flash silica gel column (hexane/ether, 1:1) to provide 1.1 g (55%) of **14** as a colorless solid.

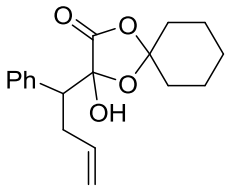
IR (KBr) 1746, 1377, 1218, 1098, 1061, 1001, 965 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.72 (d, 1H, *J* = 5.8, C*H*C(O)), 4.61 (d, 1H, *J* = 9.6, OCH_2), 4.54 (ddd, 1H, *J* = 5.8, 1.3, 0.64, OC*H*), 4.38 (dd, 1H, *J* = 13.5, 1.9, OCH_2), 4.11 (d, 1H, *J* = 13.5, OCH_2), 3.99 (d, 1H, *J* = 9.6, OCH_2), 1.55 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.40 (s, 6H, 2 x CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 197.0 (*C*=O), 113.8 (O*C*CO), 110.6 (O*C*O), 104.1 (O*C*O), 77.9 (O*C*C=O), 75.9 (O*C*CH_2), 70.0 (O*C*H_2), 60.1 (O*C*H_2), 27.1 (*C*H_3), 26.5 (*C*H_3), 26.04 (*C*H_3), 26.00 (*C*H_3).

MS (EI, pos.): *m*/*z* 259.2 $(M+H)^+$.

3-Hydroxy-3-(1-phenylbut-3-en-1-yl)-1,4-dioxaspiro[4.5]decan-2-one (24):



To a solution of **17** (0.19 g, 0.73 mmol) in CH_2Cl_2 (5 mL) at -78 ºC was added allytrimethylsilane (0.69 mL, 4.38 mmol) followed by BF_3•Et_2O (0.55 mL, 4.38 mmol). The mixture was stirred at -78 ºC for 15 min and then warmed to ambient temperature and stirred for 2 h. Cold water (3 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 9:1) to provide 0.160 g (72%) of **24** as a colorless gum.

IR (neat): 3521, 1780, 1448, 1371, 1282, 1210, 1158, 1078, 948, 911 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68-7.66 (m, 2H, Ar*H*), 7.40-7.32 (m, 3H, Ar*H*), 5.76-5.68 (m, 1H, C=C*H*), 5.13-5.04 (m, 2H, C=CH_2), 4.13-4.09 (m, 1H, ArC*H*), 2.11-2.02 (m, 1H, CH_2), 2.01-1.95 (m, 3H, CH_2), 1.83-1.77 (m, 1H, CH_2), 1.74-1.69 (m, 4H, CH_2), 1.63-1.58 (m, 1H, CH_2), 1.53-1.46 (m, 2H, CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3 (*C*O), 136.8 (Ar*C*ipso), 134.1 (C=*C*H), 128.5 (2 x Ar*C*), 128.4 (Ar*C*), 125.1 (2 x Ar*C*), 118.4 (C=*C*H_2), 111.6 (O-*C*-O), 85.9 (O-*C*-C=O), 74.9 (Ar*C*H), 37.5 (C=C-*C*H_2), 36.8 (*C*H_2), 34.7 (*C*H_2), 24.5 (*C*H_2), 23.2 (*C*H_2), 22.1(*C*H_2).

MS (EI, pos.): *m*/*z* 325.2 $(M+Na)^+$.

HRMS (CI): *m*/*z* 303.1592 (303.1596 calc. for $C_{18}H_{23}O_4$ $(M+H)^+$), 301.1440 (301.1440 calc. For $C_{18}H_{21}O_4$ $(M-H)^+$).

4.6 References

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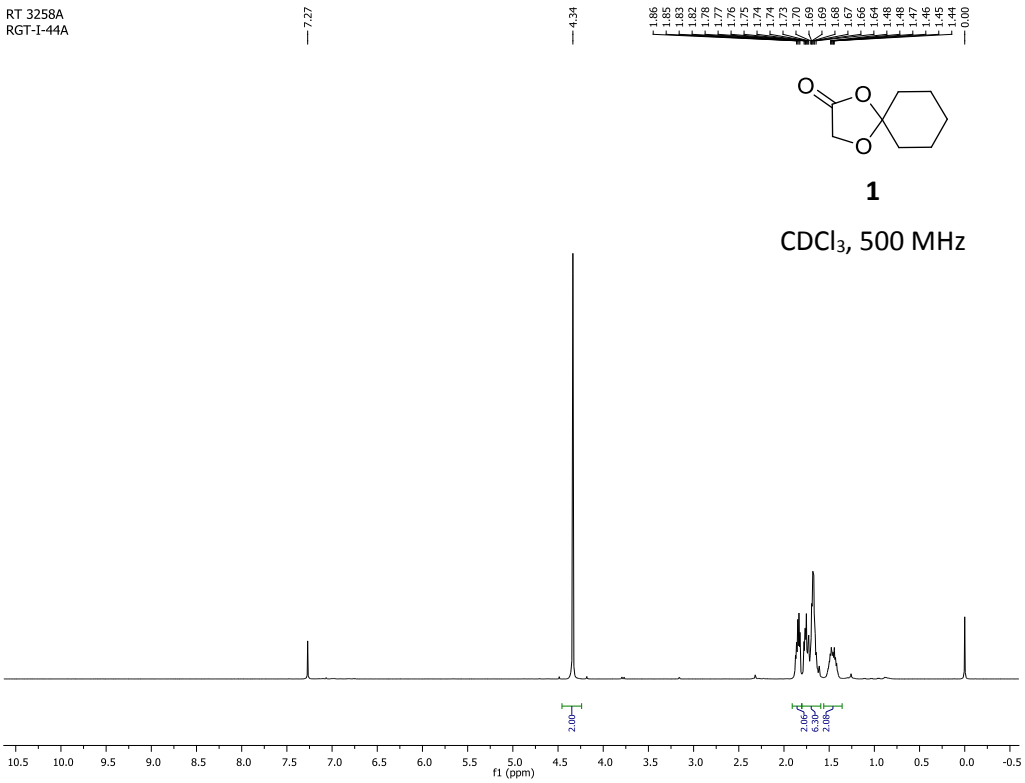
4.6 Selected ^{1}H NMR and ^{13}C NMR Spectra


RT 3258A
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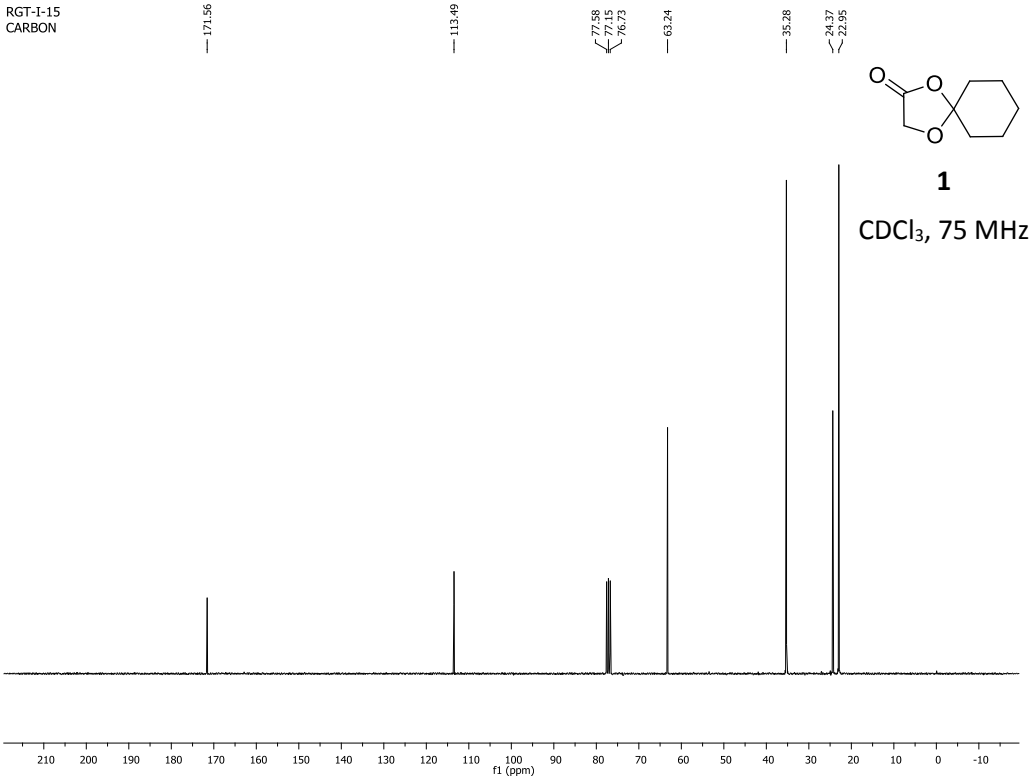
7.27
4.34
1.86
1.85
1.83
1.82
1.78
1.77
1.76
1.75
1.74
1.74
1.73
1.70
1.69
1.69
1.68
1.67
1.66
1.64
1.48
1.48
1.47
1.46
1.45
1.44
0.00
O
O
O
1
CDCl3, 500 MHz
2.00
2.06
6.30
2.08
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


RGT-I-15
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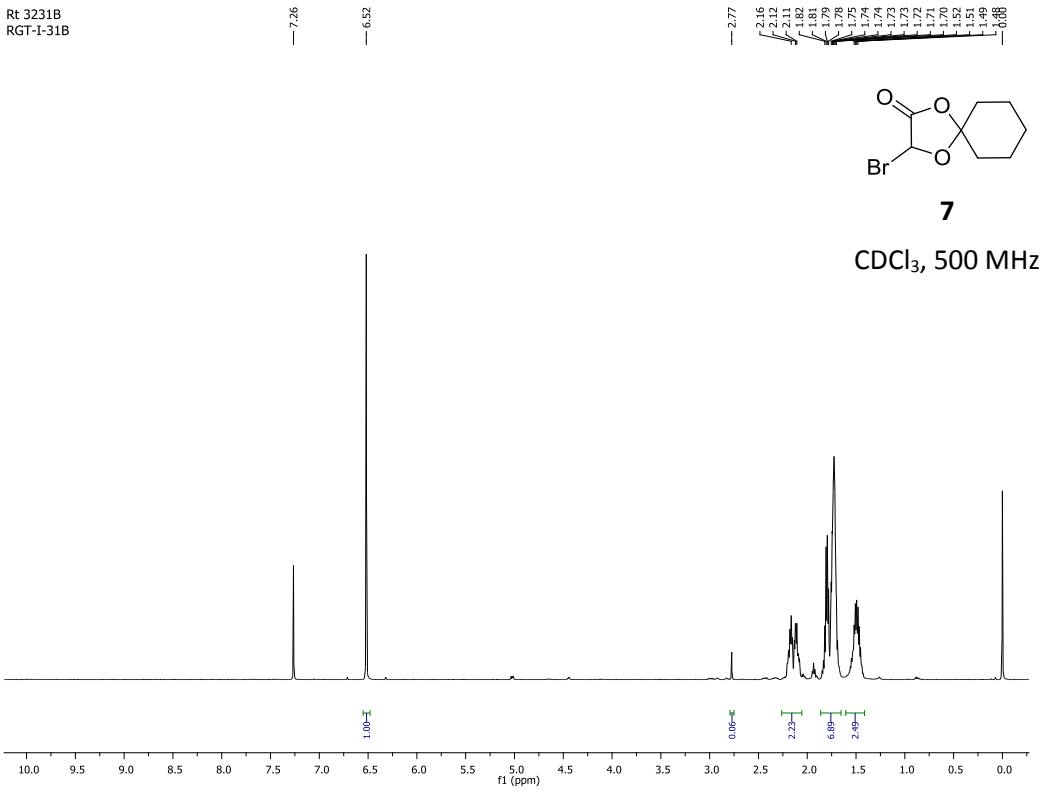
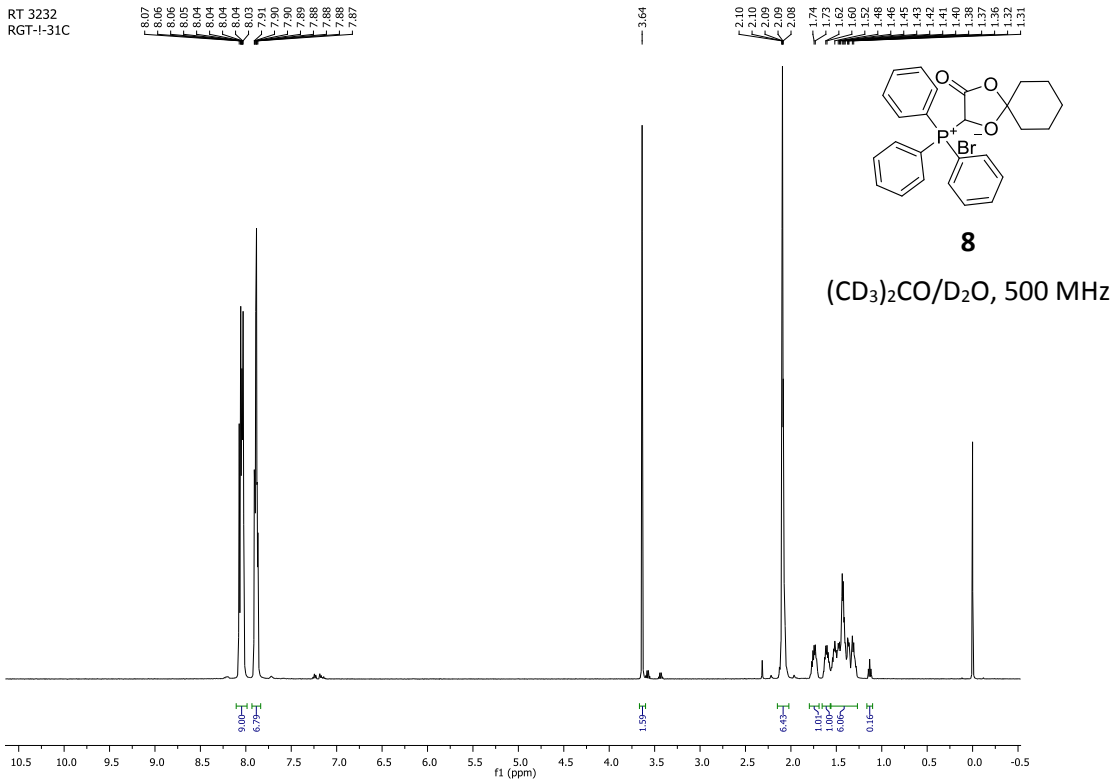
171.56
113.49
77.58
77.15
76.73
63.24
35.28
24.37
22.95
O
O
O
1
CDCl3, 75 MHz
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



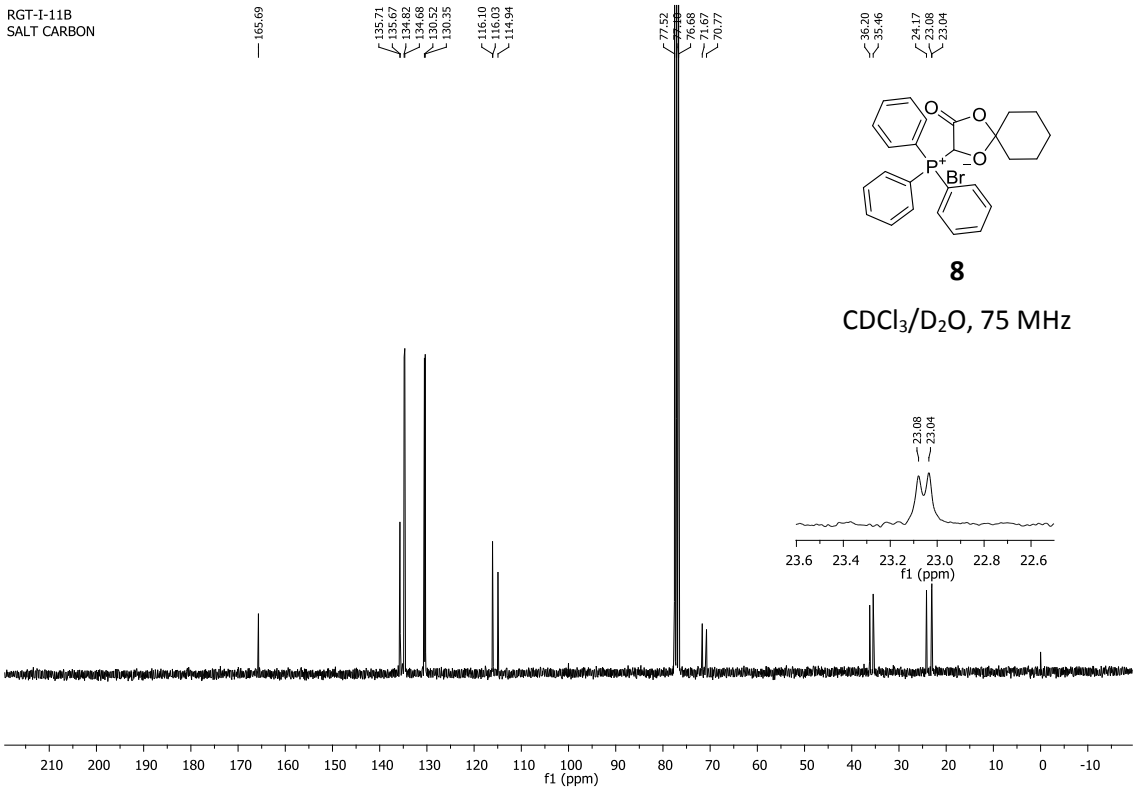
7

$CDCl_3$, 500 MHz



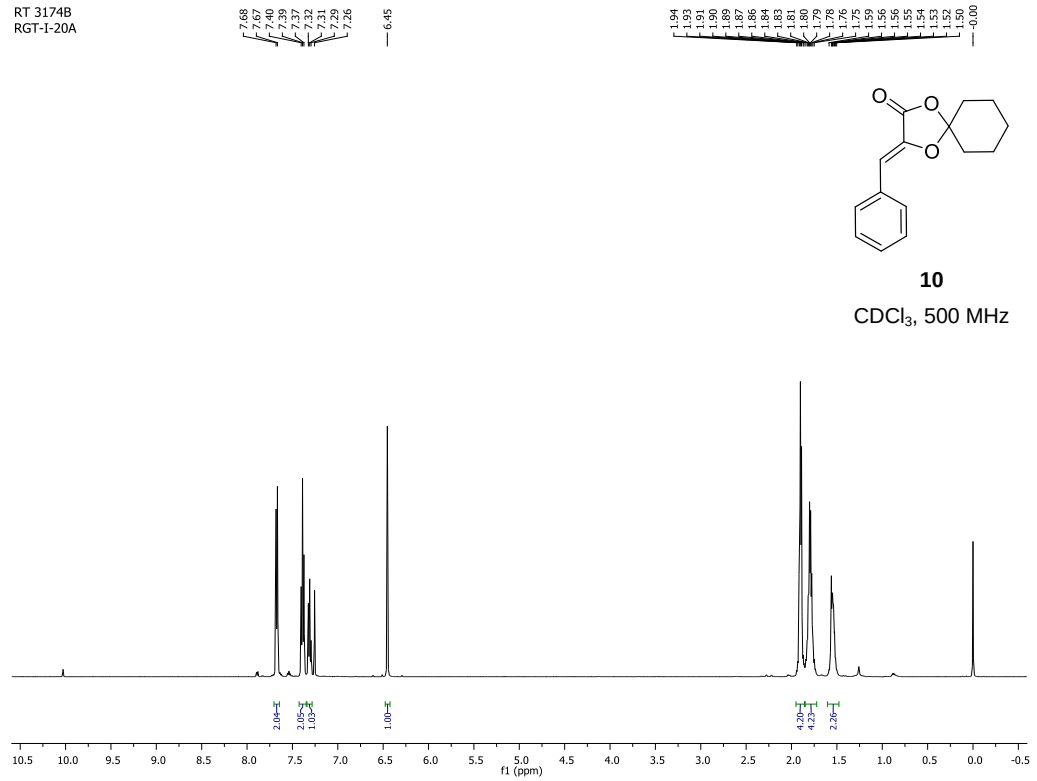
8

$(CD_3)_2CO/D_2O$, 500 MHz



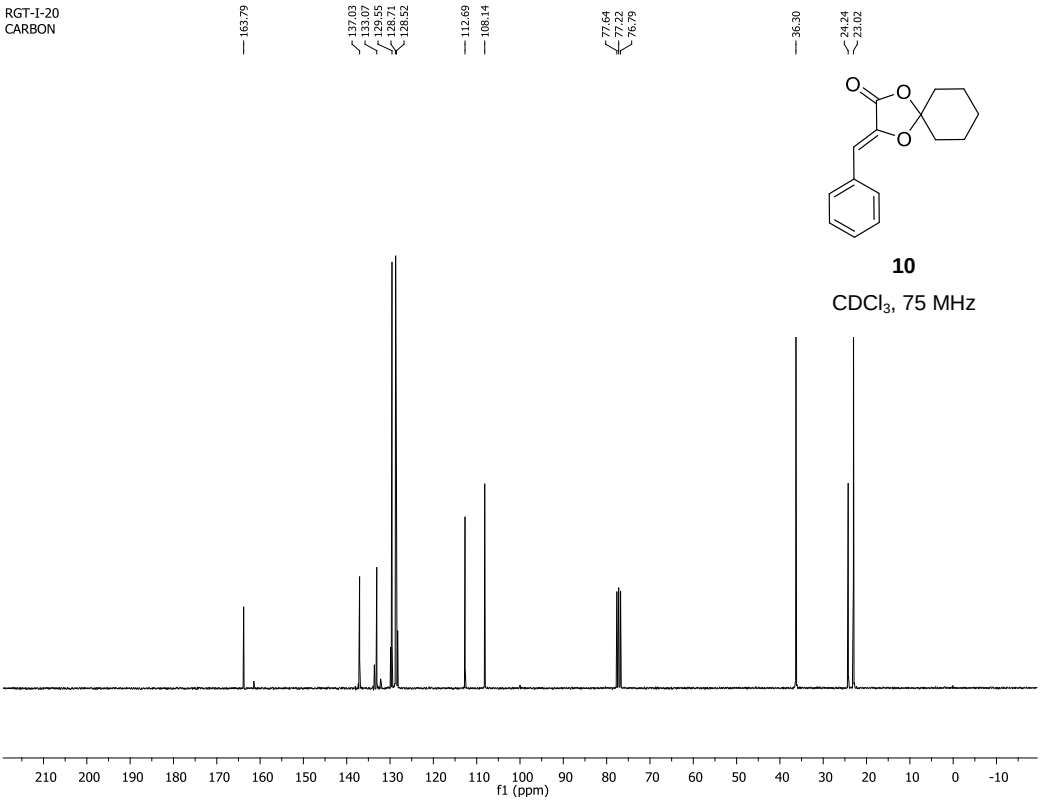
8

$CDCl_3/D_2O$, 75 MHz



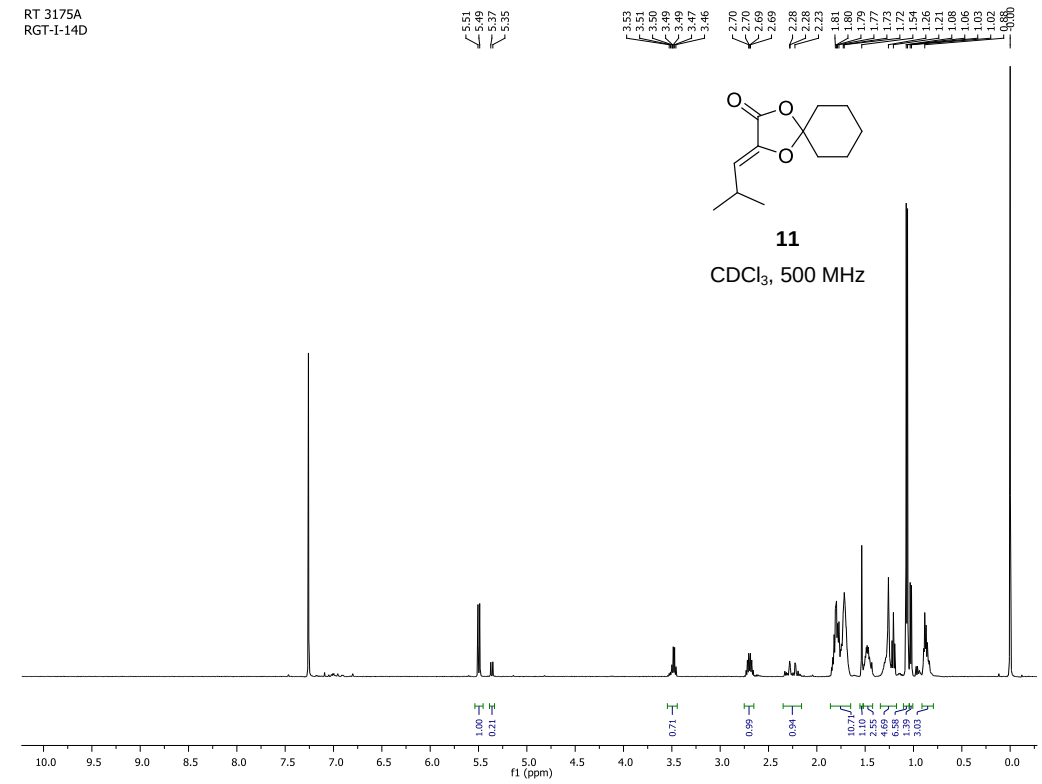
10

$CDCl_3$, 500 MHz



10

$CDCl_3$, 75 MHz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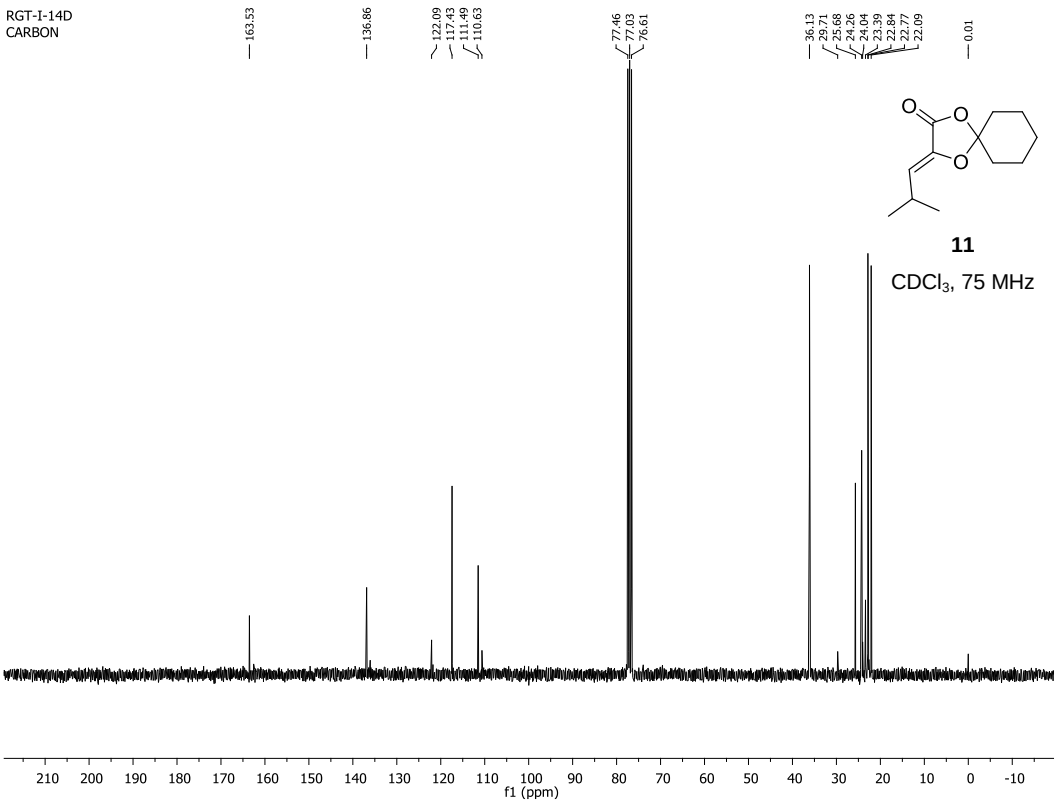
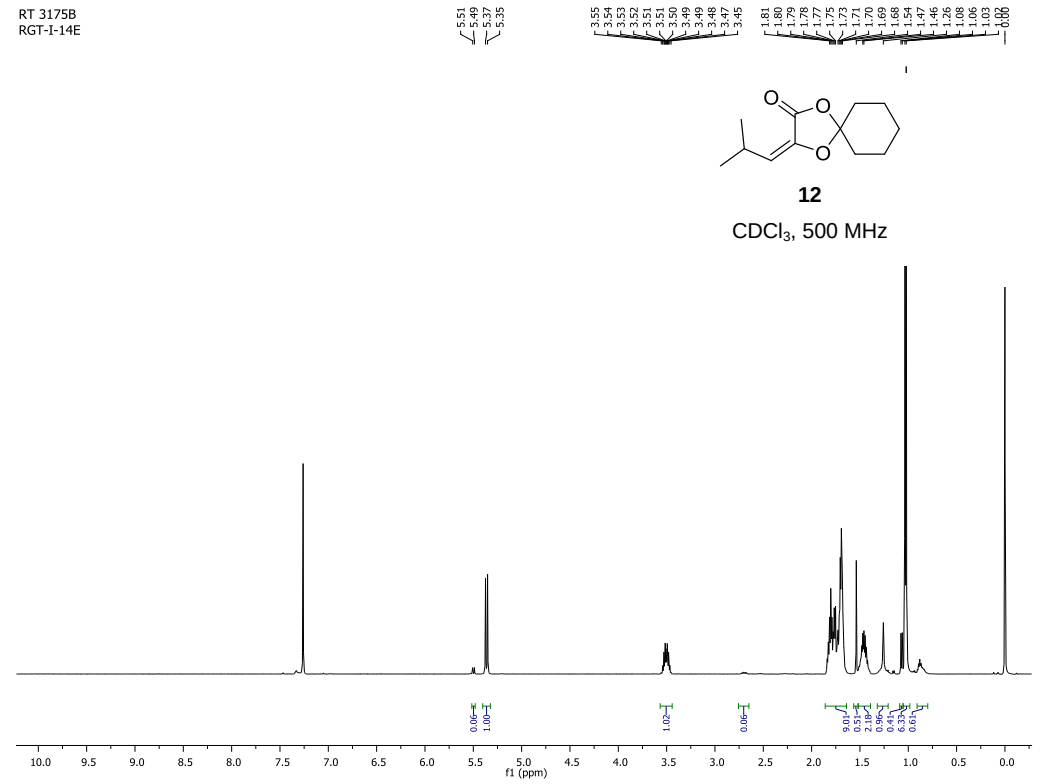
11
CDCl3, 500 MHz
f1 (ppm)


RGT-I-14D
CARBON
11
CDCl3, 75 MHz
f1 (ppm)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5.37
5.35
3.55
3.54
3.53
3.52
3.51
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3.49
3.49
3.48
3.47
3.47
3.45
1.81
1.80
1.79
1.78
1.77
1.75
1.73
1.71
1.70
1.69
1.68
1.54
1.47
1.46
1.26
1.08
1.06
1.03
1.02
1.00
O
O
O
12
CDCl3, 500 MHz
0.06
1.00
1.02
0.06
9.01
0.51
2.18
0.94
6.33
0.61
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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3.5
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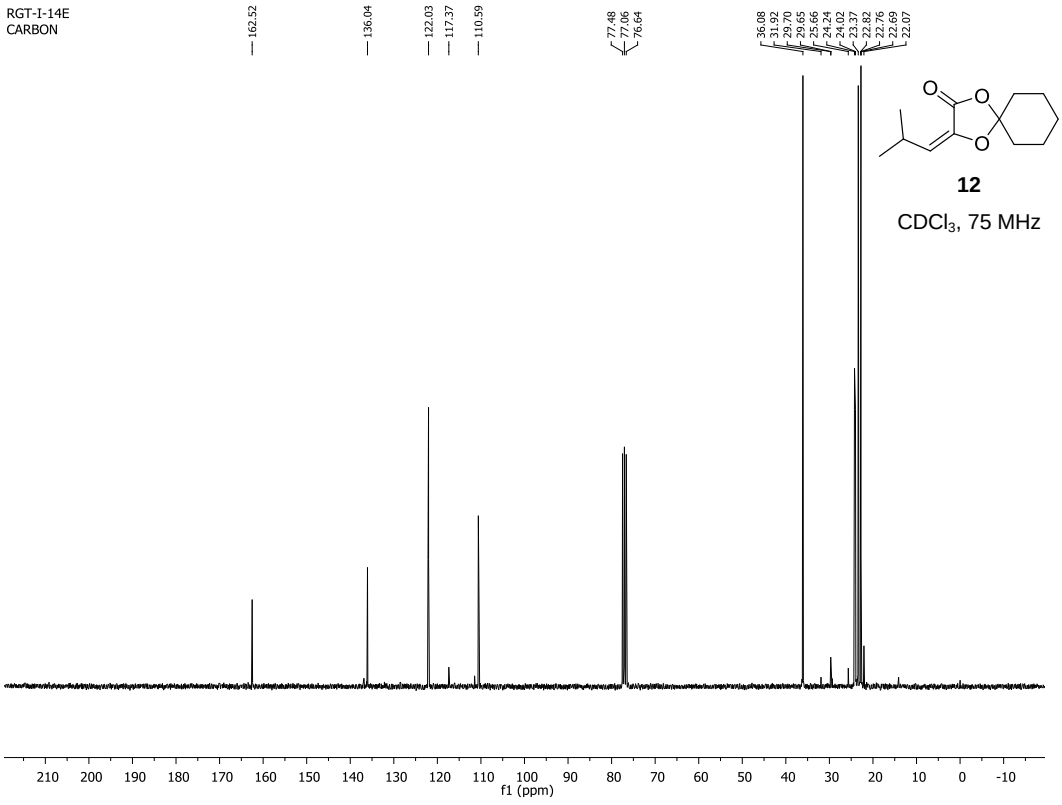
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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CARBON
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136.04
122.03
117.37
110.59
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77.06
76.64
36.08
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29.70
29.65
25.66
24.24
24.02
23.37
22.82
22.76
22.69
22.07
O
O
O
12
CDCl3, 75 MHz
210
200
190
180
170
160
150
140
130
120
110
100
90
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60
50
40
30
20
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0
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f1 (ppm)

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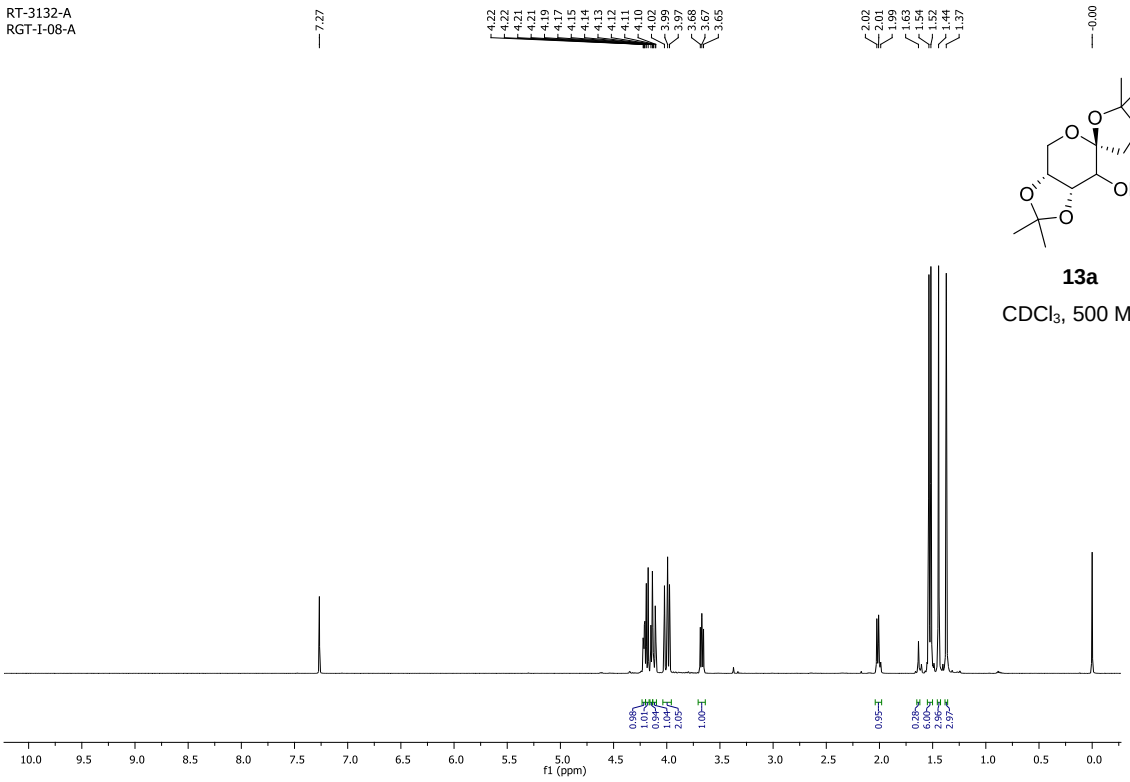
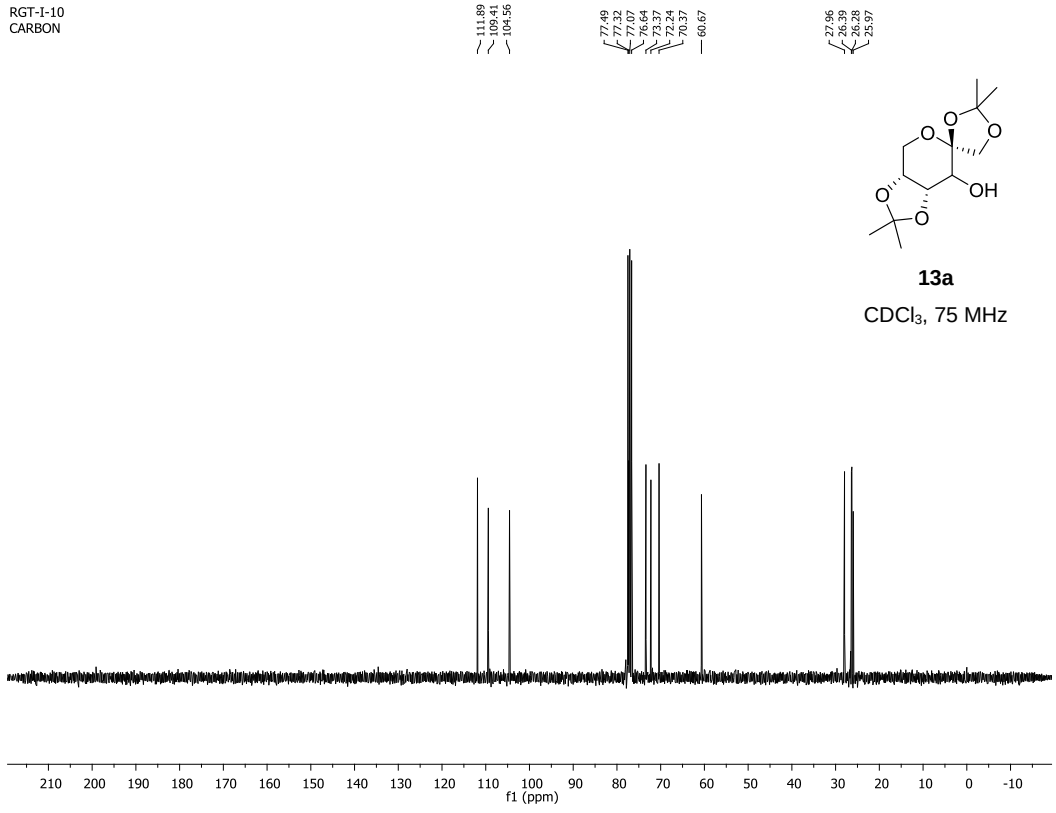


13a

$CDCl_3$, 500 MHz

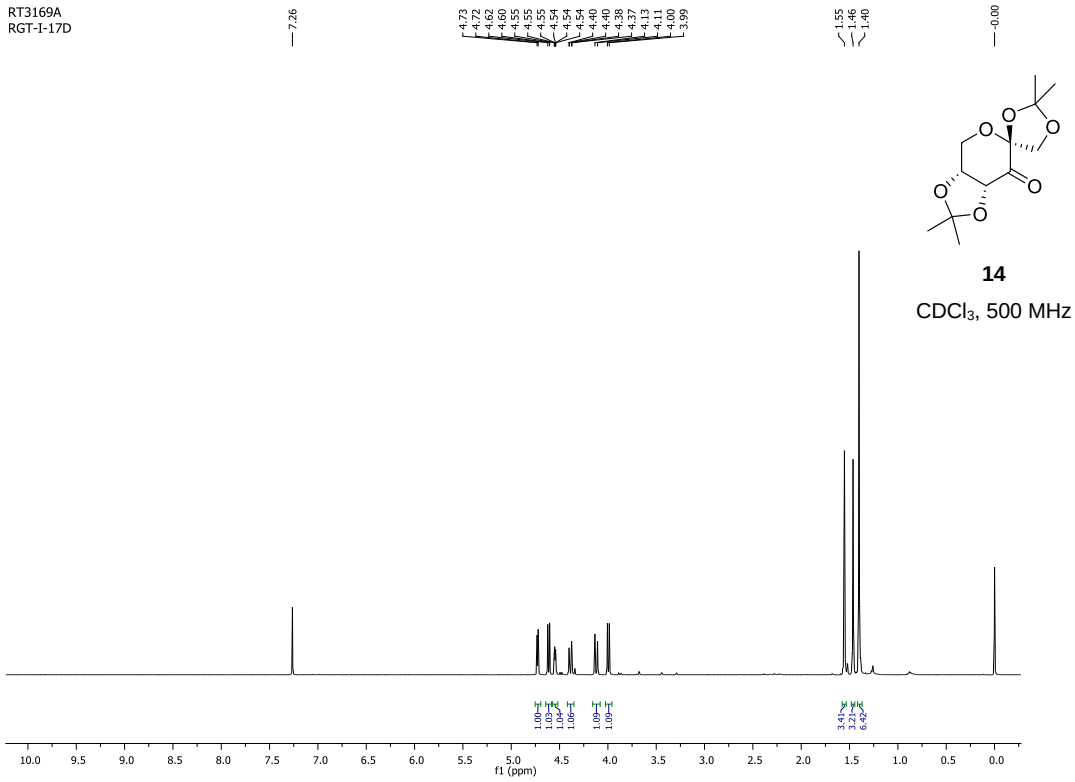
RGT-I-10
CARBON



13a

$CDCl_3$, 75 MHz

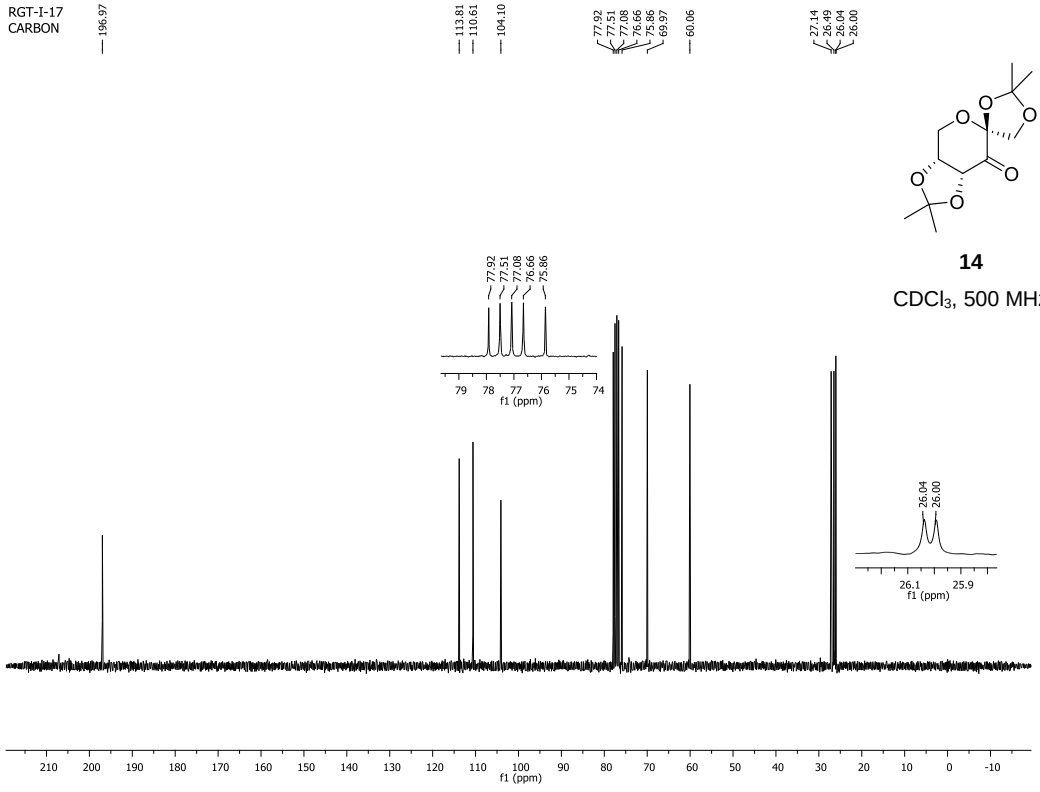
RT3169A
RGT-I-17D



14

$CDCl_3$, 500 MHz

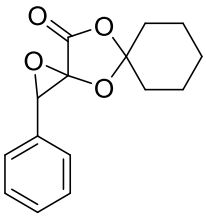
RGT-I-17
CARBON



14

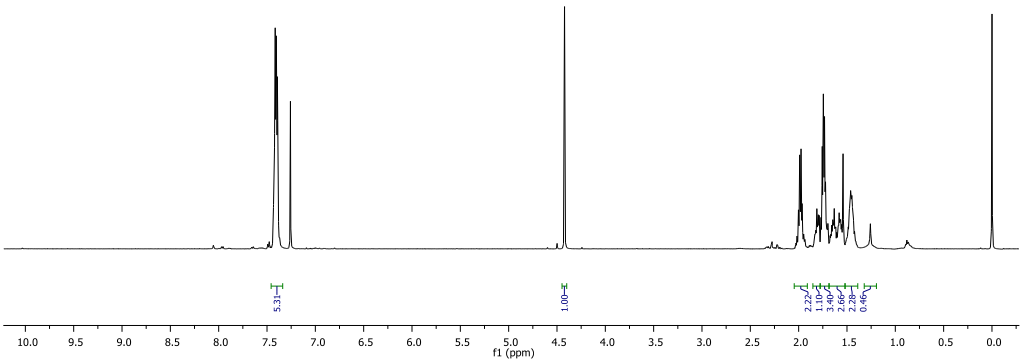
$CDCl_3$, 500 MHz

RT 3207
RGT-I-27A

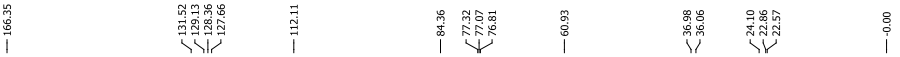


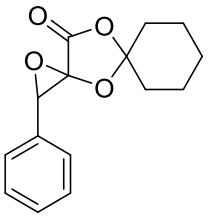
17

$CDCl_3$, 500 MHz



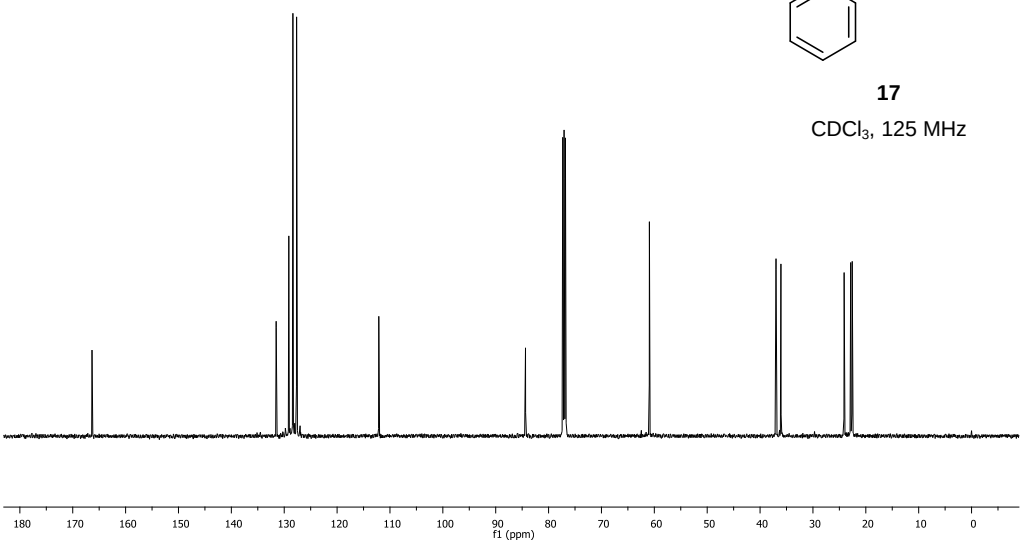
RT 3208
RGT-I-27A



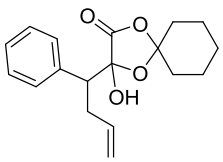


17

$CDCl_3$, 125 MHz

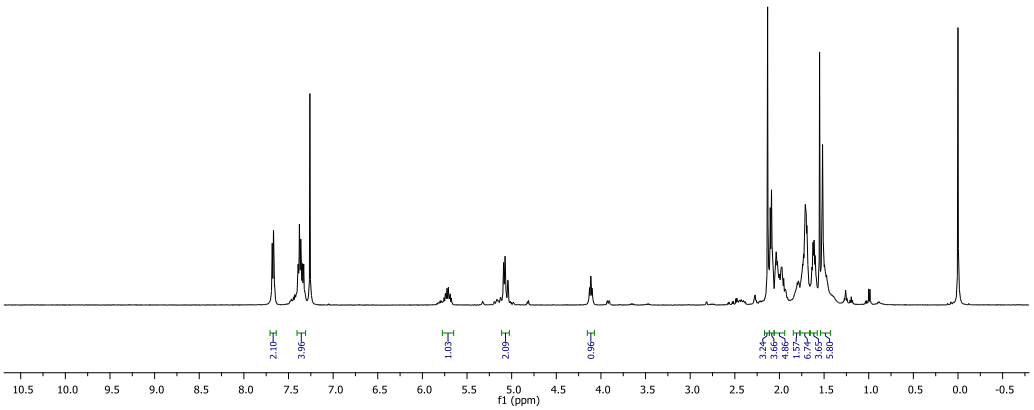


RT 3246A
RGT-I-38A

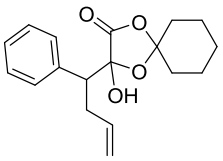


24

$CDCl_3$, 500 MHz

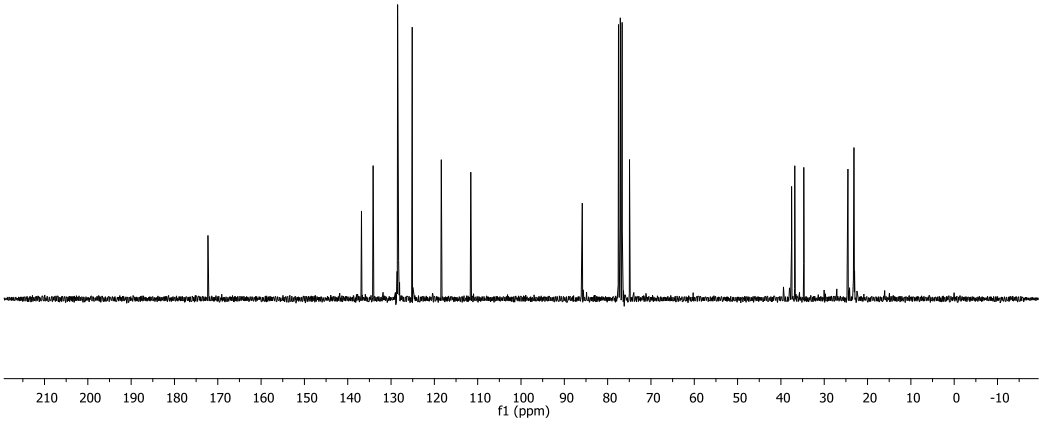


RGT-I-38A
CARBON



24

$CDCl_3$, 75 MHz



Chapter 5

Conclusions

5.1 Summary of the Thesis

A regio- and stereoselective 1,3-dipolar cycloaddition of achiral nitrones with ephedrine-derived alkylidene morpholinones (**5** and **6**) provided the intermediate isoxazolidines which are converted into either an indolizidine or a quinolizidine alkaloid depending on the nitrone and the substituent on the chiral alkene. The methodology was applied to the synthesis of (+)-epitashiromine (**1**) and the formal syntheses of (+)-epilupinine (**2**) and (+)-tashiromine (**3**, Figure 5.1). Details of these syntheses are provided in Chapter 2 of this thesis. The synthesis begins with the morpholine dione **4** which was converted into the alkylidene morpholinones **5** or **6** either by addition of a carbon nucleophile to the lactone carbonyl followed by dehydration (as for **5**) or by a Wittig reaction of the lactone carbonyl (as for **6**, Scheme 5.1). Cycloaddition reactions of **5** and **6** with cyclic nitrones **7** and **8**, under microwave irradiation, provided the spiro isoxazolidines **9** and **10** respectively, both as single diastereomers. The assignment of stereochemistry for the isoxazolidines was based on two assumptions: i) addition of the nitrone *exo* to the alkene substituent and ii) reaction of the alkene from the face opposite to the methyl and phenyl groups in the morpholinone.

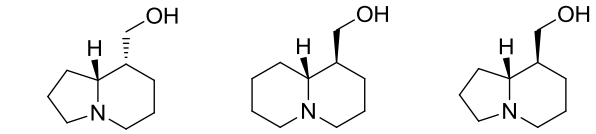
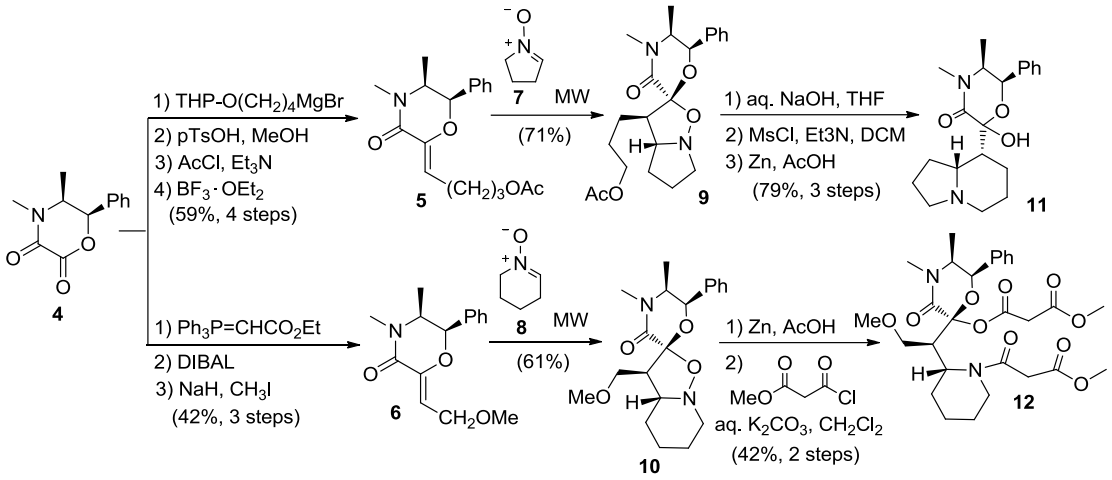


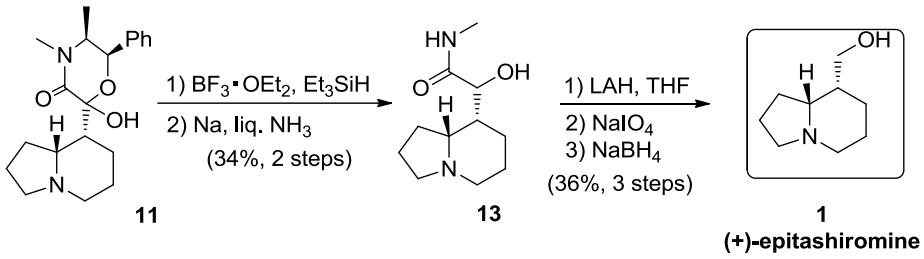
Figure 5.1 Our synthetic targets.



Scheme 5.1

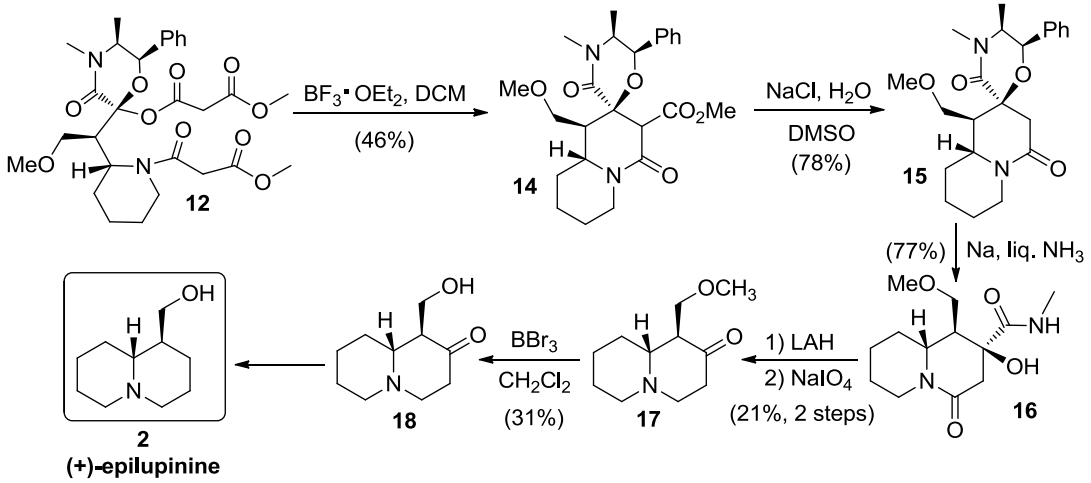
The strategy for converting **9** into the indolizidine motif involved a ring formation of the nitrone-derived pyrrolidine ring with the alkyl group on the dipolarophile and hence, the side chain in **9** was first activated as a mesylate. Reductive cleavage of isoxazolidine ring in **9** liberated the secondary amine which cyclized *in situ* to provide the functionalized indolizidine **11**. Conversely, the tactic for building the quinolizidine core from **10** involved ring formation with the morpholinone section. In this approach, the methoxymethyl group from the dipolarophile would eventually become a substituent in the target. Accordingly, **10** was first reduced and then bis-acylated to provide **12**.

Reduction of the hemiacetal in **11** followed by a reductive removal of the ephedrine portion provided **13** (Scheme 5.2). Conversion of the hydroxy amide side chain into a hydroxymethyl group was achieved by reduction to the amino alcohol, oxidative cleavage to the aldehyde and reduction to the alcohol. This three-step procedure provided (+)-epitashiromine (**1**) from **13**.



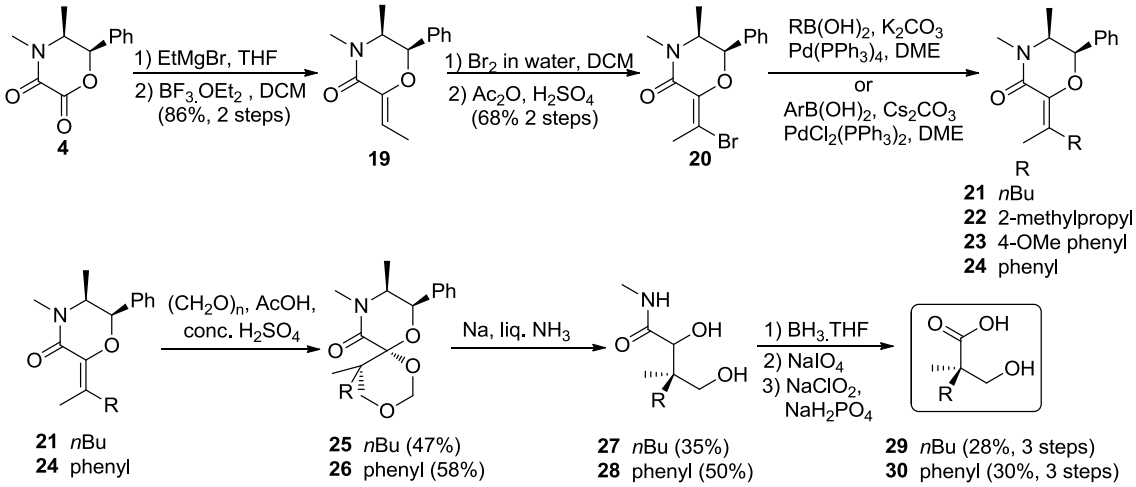
Scheme 5.2

In the other synthetic route, generation of an oxonium ion from the activated hemiacetal in **12** and its intramolecular capture provided **14** which was decarboxylated to **15** (Scheme 5.3). Reductive removal of the ephedrine portion and oxidative removal of the hydroxy amide functionality provided **17** which was converted to the ketone **18**, a known precursor to (+)-epilupinine (**2**, shown in Scheme 5.3). This constitutes a formal synthesis of (+)-epilupinine (**2**). Notably, this is the only synthetic strategy that provides access to either isomer (*syn* or *anti*) of the hydroxymethyl-substituted indolizidines and quinolizidines. Completion of both synthetic routes confirms our initial stereochemical assignments for isoxazolidines **9** and **10**.



Scheme 5.3

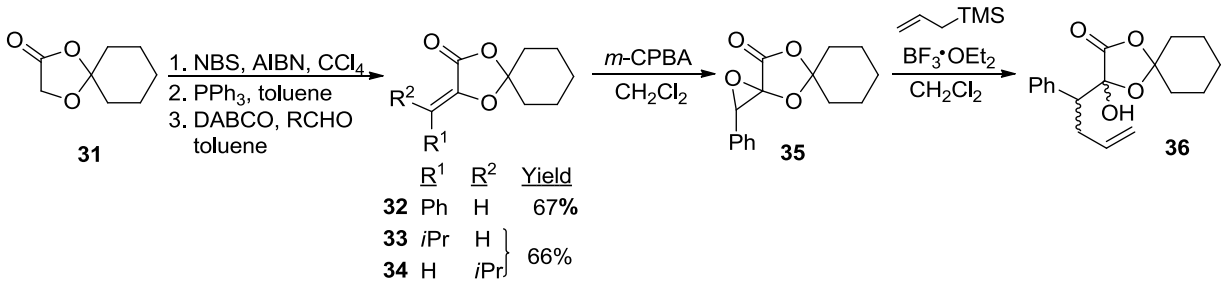
The methodology for the synthesis of quaternary stereocenters is described in Chapter 3. The strategy for the synthesis of quaternary stereocenters involves two key transformations of alkylidene morpholinones: i) metal catalyzed, stereoselective cross coupling reactions and ii) an asymmetric Prins reaction. Alkylidene morpholinone **19** was prepared by addition of ethylmagnesium bromide to dione **4** followed by dehydration. Halohydrin formation from alkene **19** (bromine/water) and subsequent dehydration furnished the *Z*-alkenyl bromide **20** (Scheme 5.4). This smoothly furnished tetrasubstituted alkenes (**21**-**24**) under Suzuki and/or Kumada cross coupling conditions in moderate to good yields. The alkylidene morpholinones **21** and **24** were subjected to a Prins reaction with paraformaldehyde in acetic acid. The Prins adducts **25** and **26**, on dissolving metal reduction, furnished the corresponding α, γ-dihydroxy amides **27** and **28** with an all-carbon quaternary stereocenter at the β carbon.



Scheme 5.4

Reduction of the amide in **28** followed by oxidative cleavage using $NaIO_4$ furnished the β-hydroxy aldehyde. Oxidation of the aldehyde provided the (*R*)-(+)-α-methyltropic acid (**30**). Following a similar reaction sequence acid **29** was prepared from amide **27**.

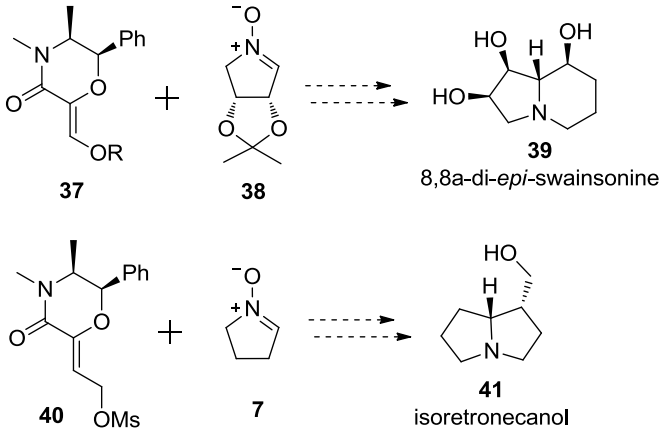
Chapter 4 of this thesis describes the efforts directed towards identifying possible substitutes for ephedrine in the synthesis of α-hydroxy acid derivatives. Studies on alkylidene dioxolanones as a possible substitute for ephedrine-derived alkylidene morpholinones was undertaken. The alkylidene dioxolanones **32**, **33** and **34** were successfully prepared from dioxolanone **31** (Scheme 5.5). Alkene **32** furnished the epoxide **35** on treatment with *m*-CPBA but it failed to react under Shi epoxidation conditions. Because of side reactions during nucleophilic epoxide ring opening reactions and the unexpected reactivity of epoxide **35**, to yield **36** during Lewis acid catalyzed epoxide ring opening, further studies with alkenes **32**, **33** and **34** were discontinued. If further studies of alkylidene dioxolanones are to be carried out, a thorough survey of asymmetric epoxidation as well as dihydroxylation methods using **32-34** as substrates is necessary.



Scheme 5.5

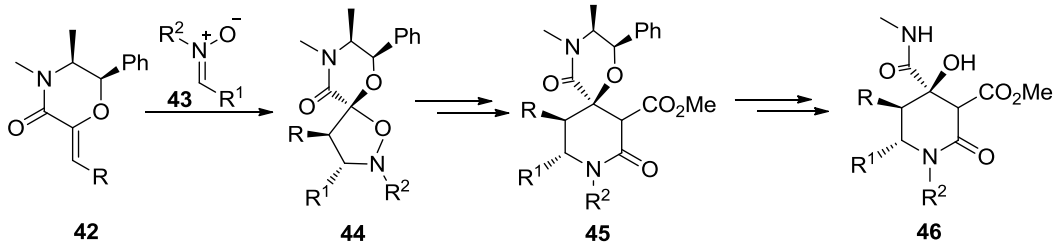
5.2 Future Work

The use of a functionalized cyclic nitrone such as **38** in the 1,3-dipolar cycloaddition reaction with alkylidene morpholinones can lead to alkaloids with ring substitution (Scheme 5.6).



Scheme 5.6

The methodology described in Chapter 2 can also be applied to the synthesis of polysubstituted piperidines **46** (Scheme 5.7) by using acyclic nitrones in the cycloaddition reaction (Scheme 5.7). The piperidines obtained by this method can be used as synthetic intermediates or they can be tested for biological activity.[1]



Scheme 5.7

For the synthesis of quaternary stereocenters, an extensive survey of metal-catalyzed cross-coupling reactions of the bromoalkylidene morpholinone starting material

is necessary. Optimization of the Prins reaction conditions to improve the overall yield of the target compounds is also worth pursuing.

5.3 References

1) (a) Mani, T.; Liu, D.; Zhou, D.; Li, L.; Knabe, W. E.; Wang, F.; Oh, K.; Meroueh, S. O. *ChemMedChem* **2013**, *8*, 1963; (b) Anwar, M. T.; Ali, S.; Shahzadi, S.; Shahid, M. *Russ. J. Gen. Chem.* **2013**, *83*, 2380.