ENANTIOSELECTIVE SYNTHESIS WITH AN EPHEDRINE-DERIVED MORPHOLINE-DIONE: NEW METHODS AND APPLICATIONS IN TARGET-ORIENTED SYNTHESIS

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Enantioselective Synthesis with an Ephedrine-Derived Morpholine-Dione: New Methods and Applications in Target-Oriented Synthesis

by

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To my family

Abstract

Enantiomerically pure α-hydroxy acids and their derivatives are an important class of organic compounds due to their utility as building blocks for the asymmetric synthesis of natural products and biologically active molecules. As a result, several synthetic strategies towards these targets have been reported in recent years. This thesis describes the applications of an ephedrine-based morpholine-dione as a chiral controller for the asymmetric synthesis of α-hydroxy acid derivatives. The methodology has been applied in enantioselective synthetic approaches to functionalized oxacycles as well as selected natural products such as (-)-quinic acid, (*R*)-homocitric acid lactone and (+)-laurencin.

A formal, enantioselective synthesis of (-)-quinic acid was achieved from a (1*S*,2*R*)-ephedrine-derived morpholine-dione which was converted to a dialkyl morpholinone via a highly diastereoselective allylation reaction. Using a similar strategy and by employing the enantiomeric (1*R*,2*S*)-ephedrine-derived dione, a concise and highly enantioselective synthesis of (*R*)-homocitric acid lactone was achieved.

Enantioselective routes to functionalized, seven-, eight-, and nine-membered oxacycles that are amenable to further elaboration have been developed. Salient features of the methodology include highly diastereoselective and regioselective transformations of an ephedrine-derived epoxy-morpholinone to functionalized precursors of the oxacycles. The ephedrine scaffold exerts remote stereocontrol in the functionalization of the appended oxacycle.

An application of the strategy for the enantioselective synthesis of medium-sized oxacycles has been demonstrated in a convergent, enantioselective route to an advanced intermediate for the synthesis of the marine natural product (+)-laurencin. The methodology employs ring-opening of an ephedrine-based spiro-epoxide with a chiral secondary alcohol,

hemiacetal allylation and ring closing metathesis as the key steps for elaboration of the functionalized medium-ring ether moiety in laurencin.

Studies on applications of the epoxy-morpholinone in the synthesis of funtionalized pyrrolidines were also conducted. The methodology, which is currently under development, employs ring-opening of an ephedrine-based spiroepoxide with a primary amine. Ring-closing of the amine side-chain on the resulting hemiacetal should provide functionalized pyrrolidines.

In the investigations described above, removal of the ephedrine portion has been achieved by reductive cleavage (dissolving metal reduction), which results in destruction of the ephedrine portion. Hence, potentially recoverable chiral amino alcohols were examined as alternatives to ephedrine. This study has identified diphenyl alaninol as a potential substitute for ephedrine and has also provided some insights into the morpholinone structural elements that are necessary for good diastereoselection.

Acknowledgements

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List of Abbreviations:

APC	allylpalladium chloride
aq.	aqueous
BOM	benzyloxymethyl
br	broad
CAN	cerric ammonium nitrate
cat.	catalytic
Cbz	benzyloxycarbonyl
CI	chemical ionization
CPME	cyclopentyl methyl ether
CSA	camphor-10-sulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DET	diethyl tartarate
DIBAL	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide

dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
ds	diastereoselectivity
ee	enantiomeric excess
EI	electrospray ionization
equiv.	Equivalent(s)
Et	ethyl
g	gram
h	hour
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrum
Hünig's base	*N*,*N*-diisopropylethylamine
Hz	hertz
IR	infrared
i-Bu	isobutyl
i-Pr	isopropyl
J	coupling constant
KHMDS	potasium hexamethyldisilazide
LHMDS	lithium hexamethyldisilazide
LAH	$LiAlH_4$, lithium aluminium hydride
LDA	lithium diisopropylamide
M	molar

M+	molecular ion
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
min	minute
mL	milliliter
mmol	millimole
mp	melting point
MS	mass spectrum
NaHMDS	sodium hexamethyldisilazide
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser enhancement
dmdba	3,5,3',5'-dimethoxydibenzylideneacetone
Ph	phenyl
PLE	porcine liver esterase
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
PPTS	*para*-toluenesulphonic acid
Pr	propyl
DVS	divinyltetramethyldisiloxane

PTSA	*para*-toluenesulphonic acid
Pv	trimethylacetyl
rt	room temperature
s	second
t-Bu	tertiary butyl
TBAF	tetra-*N*-butylammonium fluoride
TBAT	tetra-butylammonium triflate
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydrogenperoxide
TEA	triethylamine
TES	triethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TPS	triphenylsilyl
Ts	*p*-toluenesulphonyl
V-BrPO	vanadium bromoperoxidase

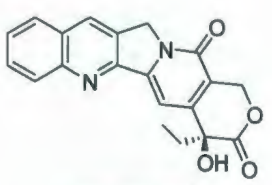
List of Appendices

Chapter 1

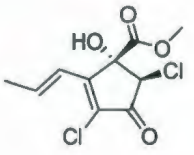
Stereoselective Approaches for the Synthesis of α,α-Disubstituted α-Hydroxy Acids : An Overview

Introduction

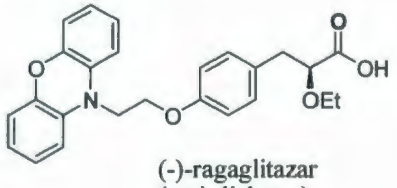
The stereoselective synthesis of α-hydroxy carboxylic acids is one of the most actively investigated areas in organic synthesis.[1] The α-hydroxycarboxyl group is found in several biologically important natural products such as the anti-cancer agent camptothecin,[2] the antifungal agent cryptoporiopsin[3] and also in pharmaceutical agents such as the anti-diabetes drug (-)-ragaglitazar.[4] In addition, the biological activities of several other complex natural products such as the cytotoxic leiodolide,[5a] anti-cancer agents in the harringtonine series[5b] and drugs from the taxane category, are dependent on their α-hydroxyester side chains.[5c] Moreover, α-hydroxy carboxylic acid derivatives are important building blocks in the asymmetric synthesis of biologically relevant molecules.[6] (Figure 1).



camptothecin
(anti-cancer agent)



cryptoporiopsin
(anti-fungal)



(-)-ragaglitazar
(anti-diabetes)

Figure 1. Examples of biologically active α-hydroxy carboxylic acid derivatives.

A survey of the literature reveals that though several methods for the synthesis of α-hydroxy caroboxylic acids have been reported[7] relatively few methods are suitable for

the synthesis of α,α-dialkyl α-hydroxy acids. This chapter aims at providing a brief overview of the developments in this field.

Stereoselective synthesis of α,α-disubstituted-α-hydroxy acids

From a retrosynthetic perspective, α,α-dialkyl-α-hydroxy acids can be envisioned to be accessed by four major routes, which are

- nucleophilic alkylation of α-keto acid derivatives (**A**)
- electrophilic alkylation of glycolic acid derivatives (**B**)
- hydrocyanation of ketones followed by hydrolysis (**C**)
- α-hydroxylation of enolates derived from esters and amides (**D**)

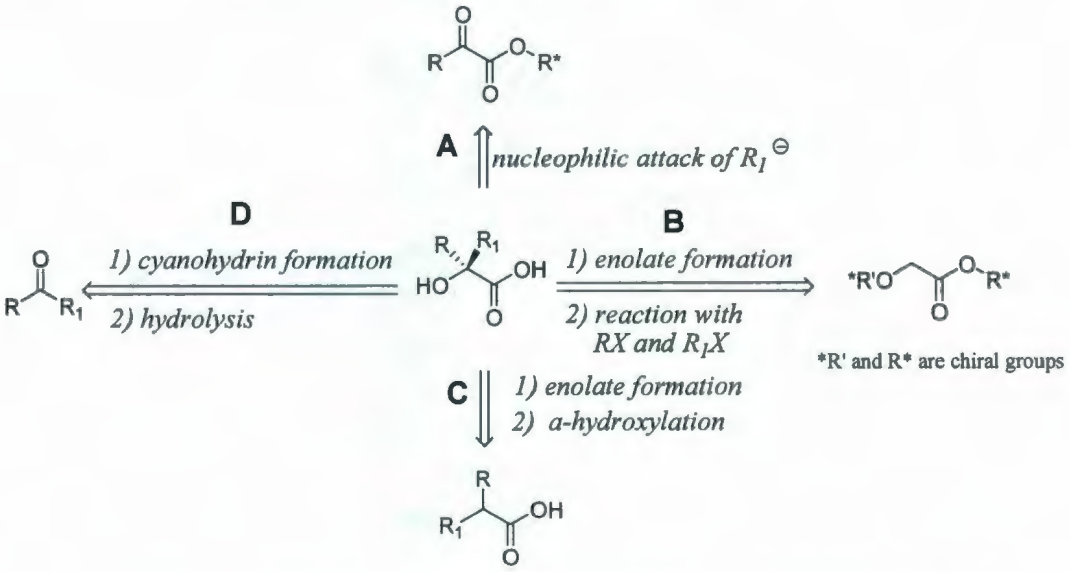


Figure 2. Retrosynthetic routes to α,α-dialkylated-α-hydroxy acids.

The first two routes mentioned above, namely the nucleophilic alkylation of α-keto acid derivatives (route A) and the electrophilic alkylation of glycolic acid derivatives (route B) employ chiral auxiliaries to modify the substrate. From a historical perspective, these routes have been at a preeminent position for the synthesis of α,α-dialkylated-α-

hydroxy acids. The work reported in this thesis is also based on a similar concept. The asymmetric synthesis of α,α-dialkylated-α-hydroxy acids via the α-hydroxylation of enolates (route C) has been largely explored by a chiral reagent-based approach and the topic was last reviewed in 1992.[8] Also, cyanohydrin formation from ketones (route D) for the asymmetric synthesis α,α-dialkylated-α-hydroxy acids remains an active area of research.[9]

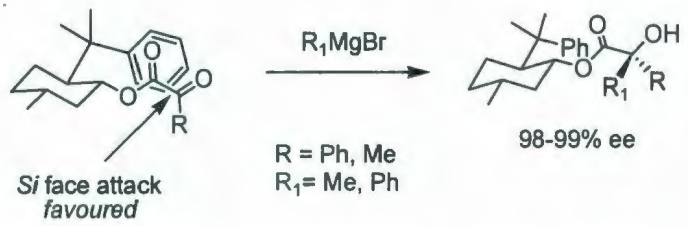
A brief review of the major developments in the field of auxiliary-mediated reactions of glycolates and α-ketoacid derivatives follows.

Route A:

Diastereoselective nucleophilic addition to chiral α-ketoacid derivatives

More than a century ago, McKenzie and co-workers discovered that the addition of Grignard reagents to α-ketoesters of chiral alcohols was a stereoselective process.[10] In 1971, Morrison and Mosher examined the addition of Grignard reagents to α-keto esters of (-)-menthol.[11] Following this report, an asymmetric allylation of menthyl pyruvate and phenyl glyoxylate using allyltrimethylsilane as the nucleophile was disclosed by Ojima (16-55% ee).[12] In a notable development, Whitesell and Bhattacharya examined (-)-8-phenylmenthol[13] as a chiral auxiliary.[14] They reported that addition of Grignard reagents to α-ketoesters of (-)-8-phenylmenthol yielded the corresponding tertiary alcohols in high diastereomeric excess (>90%). The sense of asymmetric induction was rationalized by assuming a *syn* conformation for the α-ketoester in which the *Re* face of the ketone is shielded by the phenyl ring in the auxiliary (Scheme 1).

Scheme 1.

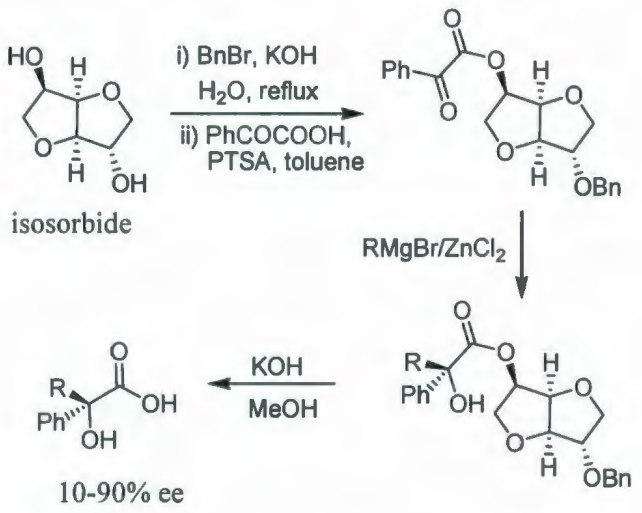


After the initial reports on the use of menthol and (-)-8-phenylmenthol, several other cyclohexane-based chiral auxiliaries such as *chiro*-inositol derivatives (96-98% ee),[15] *trans*-2-phenylcyclohexanol (82-91% ee),[16,17] (1*R*,2*R*)-2-nitrooxycyclohexan-1-ol (82- 86% ee),[18] and 2-aryloxycyclohexan-1-ols (83-97% ee)[19] were reported. Also, other chiral auxiliaries that are described in the literature include 2'-substituted-1,1'-binapthalen-2-ols (4-52% de),[20] 2,5-bis(methoxymethoxymethyl)pyrrolidine (10-90% de),[21] chiral hydrobenzoin mono-*tert*-butyl ethers (45->98% de),[22] and (-)-quinine.[23] In 1981, Myers reported the alkylation of ketooxazolines (9-87% ee) by using chiral amino alcohols as chiral auxiliaries to prepare enantiomerically enriched α,α-dialkyl α-hydroxy acids.[24] Allylation of α-keto amides derived from proline esters has also been explored. However, the diastereoselectivities observed in these studies were not uniformly high (2-92% ee).[25]

In a recent development, Loupy and Monteux used selectively protected isomannide and isosorbide as chiral auxiliaries (Scheme 2).[26] The chiral auxiliary was prepared by protecting one of the two hydroxyl groups in isosorbide as a benzyl ether and the second alcohol was esterified with benzoylformic acid. The ketone in the resulting substrate was shown to react with various organozinc reagents in a stereoselective fashion. Hydrolysis yielded the corresponding α-hydroxy acids. The stereochemical

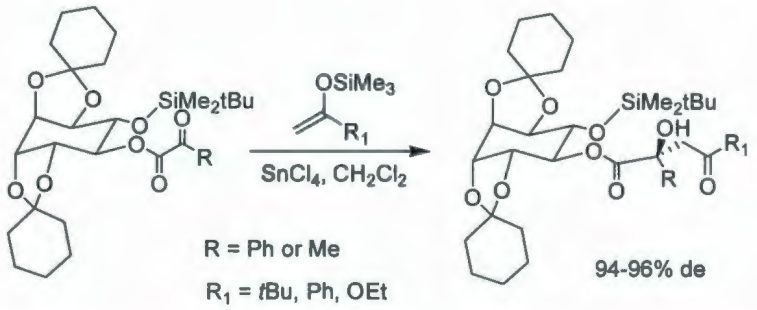
outcome was found to vary for different nuclophiles (e.g. R = Et, 94% ee, R = *i*Bu, 60% ee).

Scheme 2.



Notably, this was the first report in which the introduction of groups other than methyl and phenyl as nucleophiles was demonstrated with good stereocontrol. On the other hand, metal-complex promoted asymmetric pyruvate Mukaiyama aldol reactions[27] have been reported with a variety of silyl enol ethers which have been used as nucleophiles. In these reports, (-)-8-phenylmenthol[27b] and (-)-menthol[27c] have been examined as auxiliaries. The stereoselectivities observed were low to moderate (24-76% de for (-)-8-phenylmenthol and 18-68% de for (-)-menthol). In 1994, Akiyama and co-workers[27a] reported a synthesis of functionalized tertiary alcohols by diastereoselective aldol reactions of silyl enol ethers and ketene silyl acetals with α-keto esters bearing *chiro*-inositol as the chiral auxiliary. These reactions provide good yields and excellent stereoselectivities (70-98%, 94-96% de, Scheme 3).

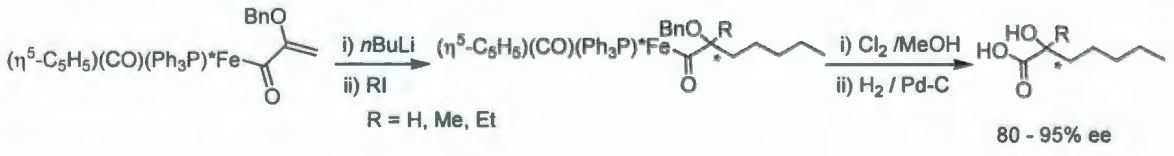
Scheme 3.



Despite these successes, it should be pointed out that all of the studies mentioned above suffer from a common drawback, that is, they all employ either pyruvates or benzoylformates as starting materials. Not surprisingly, this has resulted in limited the use of this approach for the synthesis of α,α-dialkylated α-hydroxy acids and there is a need for new protocols with broader substrate scope and good stereocontrol.

In a conceptually different synthesis of α-hydroxy acids, Tamm and co-workers[28] examined an organometallic chiral auxiliary (Scheme 4). The Michael addition of *n*-BuLi to an enantiomerically pure α-benzyloxyacryliron(II) complex followed by stereospecific protonation (with water) or alkylation (with alkyl halides) of the intermediate enolate provides α-hydroxy carbonyl derivatives with 80-95% diastereoselectivity (Scheme 4). Oxidative cleavage of the iron-carbon bond followed by hydrogenolysis of the benzyl ether provides the α-hydroxy acids.

Scheme 4.

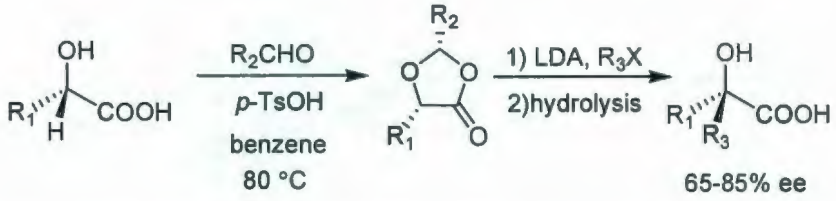


Route B:

Diastereoselective alkylation of chiral glycolates.

In 1981, Frater demonstrated the diastereoselective alkylations of 2-substitituted-1,3-dioxalan-4-ones (65-85% de).[29] It was shown that the α-anions of 2-substitituted-1,3-dioxalan-4-ones derived from mandelic and lactic acid (Scheme 5) could be alkylated with high stereoselectivity. The resulting products were then hydrolysed to the corresponding α,α-disubstituted α-hydroxy acids. This protocol was later termed as the "self regeneration of stereocenters" (SRS) by Seebach. [6f,7b]

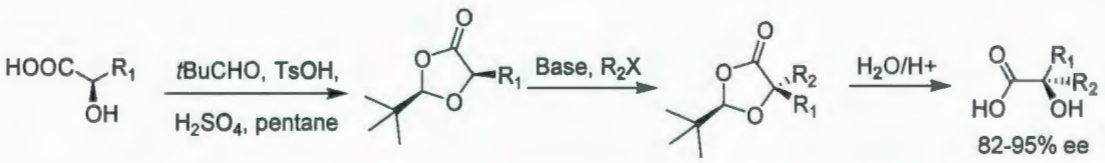
Scheme 5



On similar lines, Seebach reported his protocol for the asymmetric synthesis of α,α-dialkyl α-hydroxy acids.[6f,7b] In this procedure, enantiomerically pure chiral α-hydroxy acids could be reacted with unsymmetrical ketones or aldehydes to obtain chiral cyclic acetals with embedded memory of chirality (Scheme 6). On enolisation, of the α-hydroxy stereocenter (the original chirality of the hydroxy acid) would be lost, but owing to the embedded chirality in the acetal, subsequent alkylation of the enolate is facially selective. The α,α-disubstituted-α-hydroxy acid can then be revealed by hydrolysis of the acetal (Scheme 6). The approach is commonly known as 'self regeneration of stereocenters' .[6f,7b] However, the use of a enantiomerically pure starting material greatly limits the flexibility

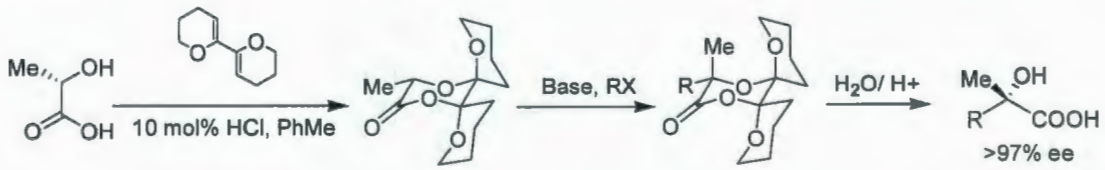
of this approach, especially when the starting enantiopure α-hydroxy acids are not easily available.

Scheme 6



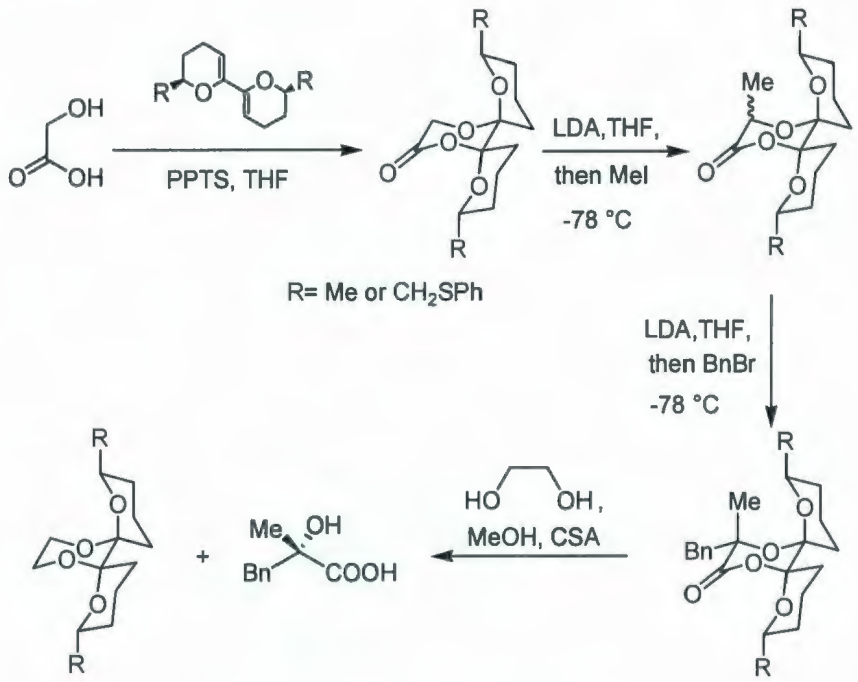
A conceptually similar protocol was disclosed by Ley and co-workers wherein they demonstrated the utility of a lactic acid-derived dispiroketal ("DISPOKE") for the synthesis of α,α-disubstituted-α-hydroxy acids (Scheme 7).[7c] The procedure was based on an observation that the reaction of 1,2-diols with a bis-enol ether gave a single diastereomer of the dispiroketal product, presumably due to the influence of anomeric effects. Alkylation of the spiroketal followed by hydrolysis provided α,α-dialkyl-α-hydroxy acids with >97% ee.[7c,30]

Scheme 7



Later, in an important development of their DISPOKE based protocol, Ley and co-workers reported the synthesis of α,α-dialkyl-α-hydroxy acids by using glycolic acid as a starting material (Scheme 8).[30,31] This approach requires enantiomerically enriched bis(enol ethers) as starting materials.

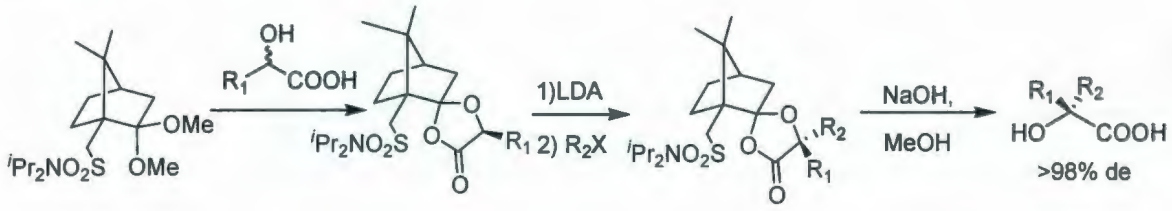
Scheme 8



The enolate of the dispiroketal obtained from glycolic acid (Scheme 8) could be sequentially alkylated to give the dialkylated dispiroketal as a single diastereomer. This could be hydrolysed to yield the α,α-dialkyl α-hydroxy acid product. This improvement circumvented the need to use the enantiomerically pure hydroxy acids as starting materials and hence carries special significance in the synthesis of α,α-dialkyl-α-hydroxy acids.

In another study of approaches toward the targets under discussion, Uang and co-workers employed (1*S*)-(+)-*N,N*-diisopropyl-10-camphorsulfonamide as a chiral auxiliary.[32] In this investigation, they observed that condensation of the dimethoxy acetal of the chiral auxiliary with racemic lactic or mandelic acid proceeded under thermodynamic control to provide the product spiroacetal as a single diastereomer with '*S*' stereochemistry at the α-carbon (Scheme 9).

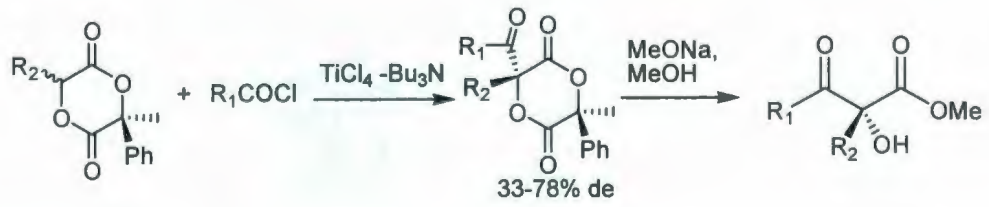
Scheme 9.



Subsequent enolate formation and alkylation with a variety of alkyl halides proceeded with excellent diastereoselectivity (> 98%). Hydrolysis of the dialkylation products provided the α,α-disubstituted-α-hydroxy acids.

In a recent study, Tanabe and co-workers successfully in synthesized α-hydroxy-β-ketoesters in good yields (~90%) by an asymmetric $TiCl_4$-mediated cross-Claisen condensation of a chiral dioxane dione derived from atrolactic acid[33] (Scheme 10).

Scheme 10

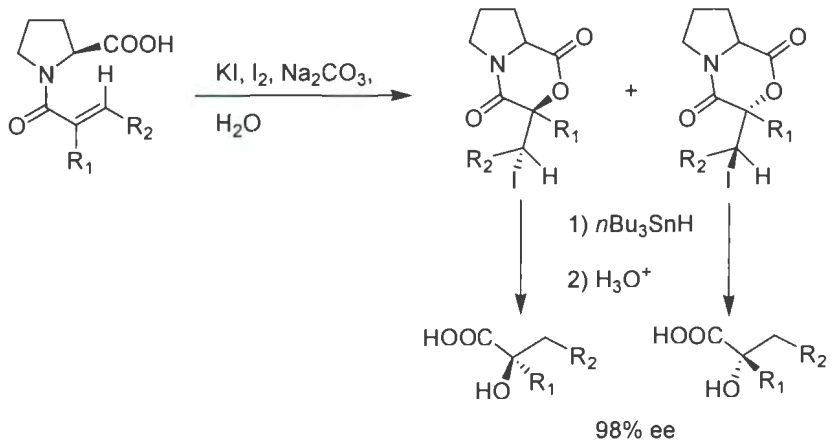


Other routes

In 1979, Terashima and Koga demonstrated a halolactonisation-based strategy for the synthesis of α,α-dialkyl-α-hydroxy acids. This method uses α,β-unsaturated acids and proline as the starting materials.[34] The procedure involves *N*-acylation of proline with the α,β-unsaturated acid chloride and a diastereoselective halolactonisation of the resulting amide. A mixture of halolactones (~95:5) was obtained. The diastereomers were

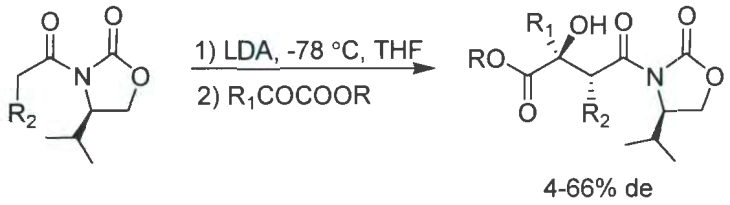
separated and subjected to reductive debromination (nBu$_3$SnH) followed by acidic hydrolysis to provide the target α,α-dialkyl-α-hydroxy acids (Scheme 11).

Scheme 11



In 1996, Jacobson and Reddy[35] described the asymmetric reactions of chiral imide enolates (obtained from Evans' *N*-acyl oxazolidones[36]) on α-ketoesters to generate 2-hydroxy-2,3-trisubstituted succinates, albeit with poor to moderate diastereoselectivities (4-66% de, Scheme 12).

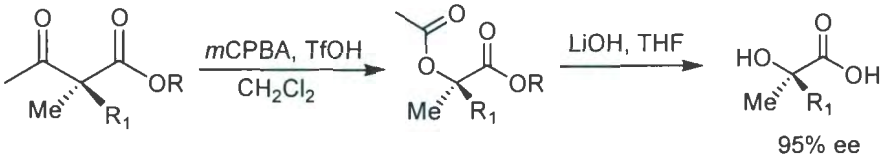
Scheme 12



More recently, it was shown that the Bayer-Villiger rearrangement can be employed for regioselective and stereoselective oxidation of α,α-disubstituted-β-ketoesters to provide α,α-dialkylated-α-hydroxy acid acetates.[37] Thus, utilizing the fact that the Bayer-Villiger rearrangement proceeds with retention of configuration at the

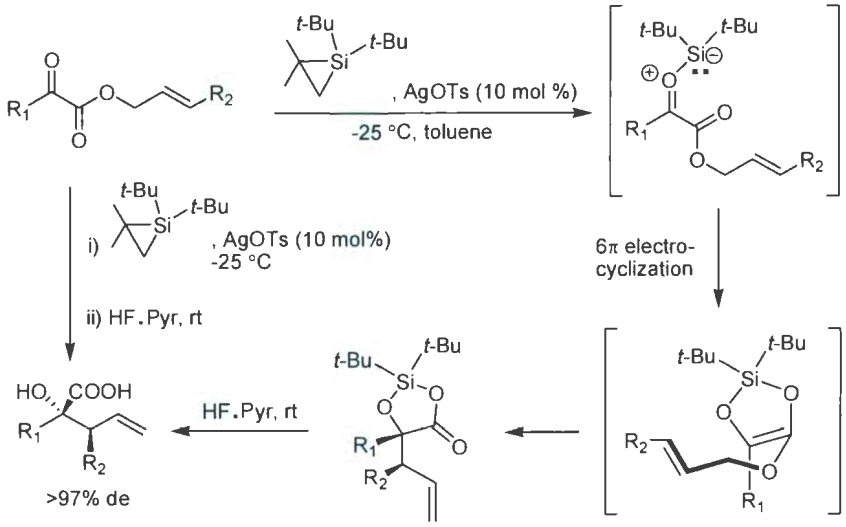
migrating carbon, it was demonstrated that enantiomerically enriched substrates[38] provide enantiomerically enriched α,α-disubstituted-α-hydroxy acids (Scheme 13).

Scheme 13



In 2007, Woerpel unveiled a unique diastereoselective strategy where α-keto-esters were converted into α-hydroxy acids (≥97% de). The methodology involves metal-catalyzed silylene transfer, 6π-electrocyclization, Ireland-Claisen rearrangement, and hydrolysis (Scheme 14).[39]

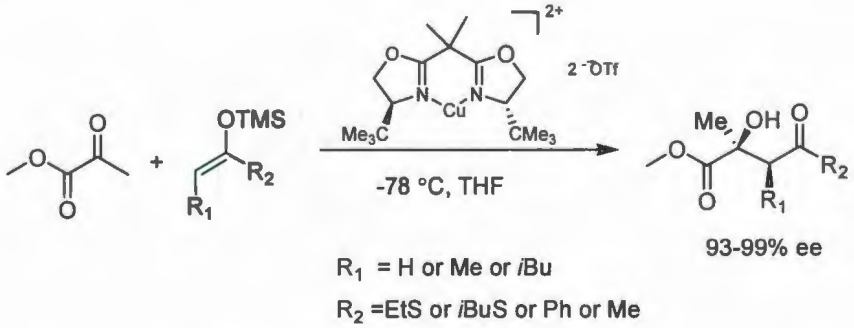
Scheme 14



Importantly, this reaction sequence is stereoselective and tolerates alkyl and aryl substituted α-keto ester substrates. The α-hydroxy acids are obtained in moderate to good yields, and with excellent diastereoselectivites (47-84%, ≥97% de).

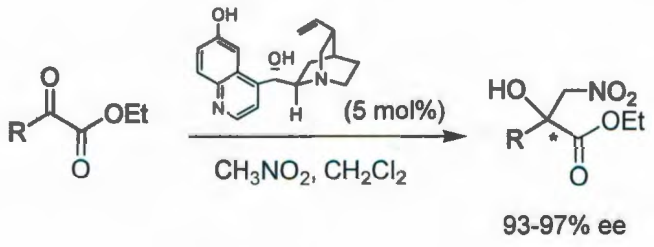
Examples of diastereoselective and chiral metal-complex-promoted asymmetric pyruvate Mukaiyama aldol reactions are also documented.[40] However, only one example of catalytic enantioselective addition of enolsilanes to pyruvate esters is reported.[41,42] In this report, Evans revealed a bidentate bis(oxazolinyl)Cu(II) complex that served as an effective chiral Lewis acid catalyst for the enantioselecitive aldol reaction between enolsilanes and methyl pyruvate (Scheme 15). The aldol adducts were obtained in good to excellent yields (77-97%) and with excellent stereoselectivities (93-99% ee).

Scheme 15



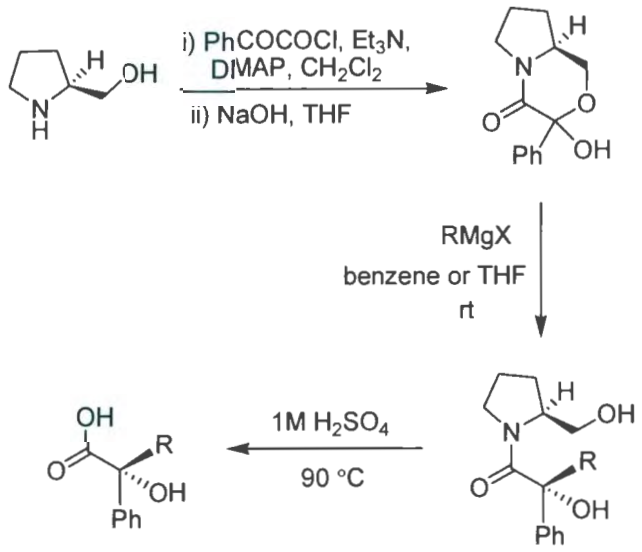
Nitroaldol reactions of α-ketoesters offer another route to the synthesis of α,α-disubstituted-α-hydroxy acids and a few catalytic versions of this approach are reported.[43] Deng and co-workers[43c] have described the use of cinchona alkaloids as organocatalysts for nitroaldol reactions of α-ketoesters to synthesize the α,α-disubstituted-α-hydroxy acids in excellent yields and enantioselectivity (87-98%, 93-97% ee, Scheme 16).

Scheme 16



The Pansare group demonstrated the use of (*S*)-prolinol as a chiral auxiliary for the synthesis of α,α-disubstituted α-hydroxy acids.[44] Bis-acylation of (*S*)-prolinol with benzoylformyl chloride followed by selective ester hydrolysis in the amido ester intermediate gave the corresponding hemiacetal. This hemiacetal could be reacted with a variety of Grignard reagents (*ca.* 10 molar equivalents) to yield the corresponding α-hydroxy amides. Hydrolysis of the amides afforded α-hydroxy acids in good yields and enantioselectivity (62-68%, 82-87% ee, Scheme 17).

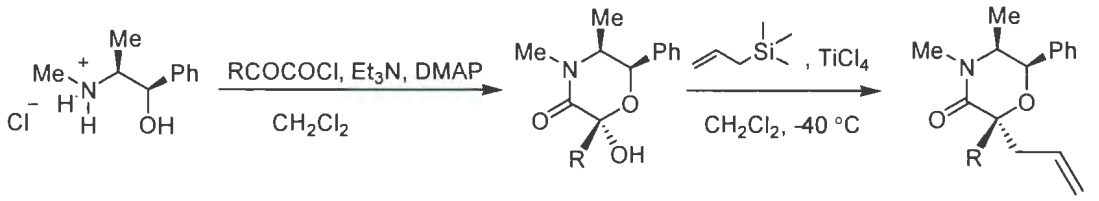
Scheme 17



The Pansare group also reported a synthesis of α-hydroxy acids based on asymmetric carbon-carbon bond formation on an ephedrine-derived template.[45] Using a commercially available and cheap starting material like (1*R*,2*S*)-ephedrine and acylating it with aliphatic α-keto acid chlorides afforded the corresponding hemiacetals (Scheme 18) in good yields (65-71%). The configuration of the hemiacetal stereocenter was established as '*S*', based on X-ray crystallographic analysis. In the pivotal step of this sequence, the hemiacetals were allylated with allyltrimethylsilane/$TiCl_4$ to give the

allylated morpholinones in good to excellent yields (67–97%), and as single diastereomers.

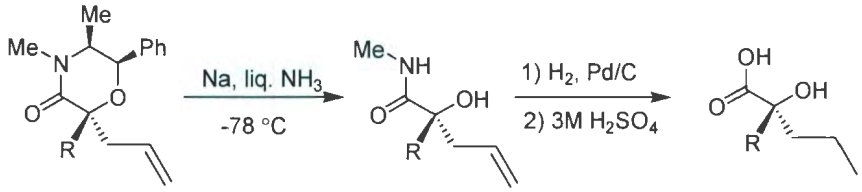
Scheme 18



single diastereomer

Removal of the ephedrine portion followed by reduction of the double bond and hydrolysis of the amide provided α,α-disubstituted chiral α-hydroxy acids (Scheme 19). These products were assigned the '*R*' configuration, by comparison of their optical rotation with reported values.

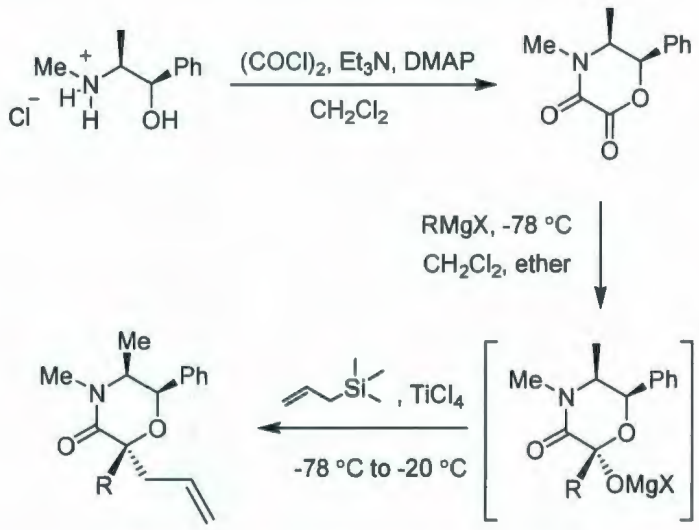
Scheme 19



Later, the group reported a modified one-pot synthesis of the hydroxy acids starting with an ephedrine-derived morpholine-dione.[46] The chiral dione was obtained from (1*R*,2*S*)-ephedrine and oxalyl chloride (65%) and could be reacted with several Grignard reagents (Scheme 20) to generate the corresponding hemiacetal salts. These could then be allylated *in situ* to yield the corresponding dialkylated morpholinones which, in turn, had served as the intermediates in the synthesis of α,α-disubstituted-α-

hydroxy acids.[21] This strategy is significantly different from those reported in the literature and provides excellent stereocontrol.

Scheme 20.



The utility of the ephedrine-based protocol would be highlighted if the methodology can be applied to interesting synthetic targets. Also, an investigation of the origin of stereoselectivity in the ephedrine derived oxazinone would be an important endeavour. Information from such studies could eventually lead to better chiral starting materials. These aspects were identified as goals of the doctoral studies described in this thesis.

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Chapter 2

Formal Total Synthesis of (-)-Quinic Acid and Total Synthesis of (R)-Homocitric Acid Lactone

Part of the work described in this chapter has been published in

Organic Letters **2006**, *8*, 2035

&

Tetrahedron Letters **2007**, *48*, 7099

General introduction

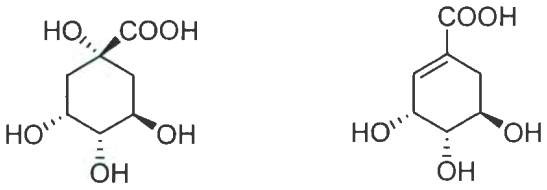
The art of organic synthesis is perhaps best illustrated by the applications of newer and better synthetic protocols towards definite targets. Indeed, development of a synthetic technique can be thought to be complete only when it is explained and applied towards a specific target.

Over the past few years, the Pansare group has devised and reported a unique protocol for the synthesis of α-hydroxy acids[1] by using an ephedrine-derived morpholine-dione as a chiral starting material. This highly enantioselective strategy can serve as a useful alternative to the existing methods reported in the literature. To complete this study and also to elaborate the significance of this protocol, it was decided to apply it towards the synthesis of natural products falling in the class of α-hydroxy acids. Towards this end, (-)-quinic acid and (*R*)- homocitric acid were chosen as the targets.

Chapter 2 is divided into two sections to describe the synthesis of each of the natural products separately along with a literature overview of the known approaches towards these targets.

Part I: A concise and enantioselective formal total synthesis of (-)-quinic acid.

Introduction

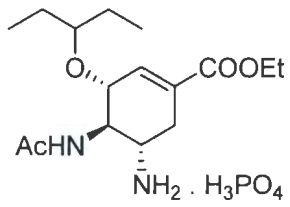


1 (-)-Quinic acid

2 (-)-Shikimic acid

Figure 1. Quinic acid and Shikimic acid.

Over the past few decades (-)-quinic acid (**1**, Figure 1) has proven to be a useful chiral building block in asymmetric synthesis and has been employed as the starting material in numerous syntheses.[2] Recently, the synthetic utility of (-)-quinic acid (**1**) has been highlighted because of its use as a starting material for the synthesis of viral neuraminidase inhibitors for the treatment of influenza.[3] In fact, the current industrial procedure for the synthesis of Oseltamivir (**3**, Figure 2), an antiviral drug manufactured by Hoffmann-La Roche (Roche) under the trade name Tamiflu® uses both (-)-quinic acid (**1**) and (-)-shikimic acid (**2**) as starting materials.[3]



3

Figure 2. Oseltamivir (Tamiflu®)

Incidentally, in 2005, Roche announced a production shortage for Tamiflu®.[4] According to Roche, the major bottleneck in Oseltamivir production was the availability of (-)-quinic acid which cannot be synthesized economically and is isolated from Chinese star anise, an ancient cooking spice. Thus, influenced by its synthetic applicability, we decided to undertake an enantioselective synthesis of (-)-quinic acid.

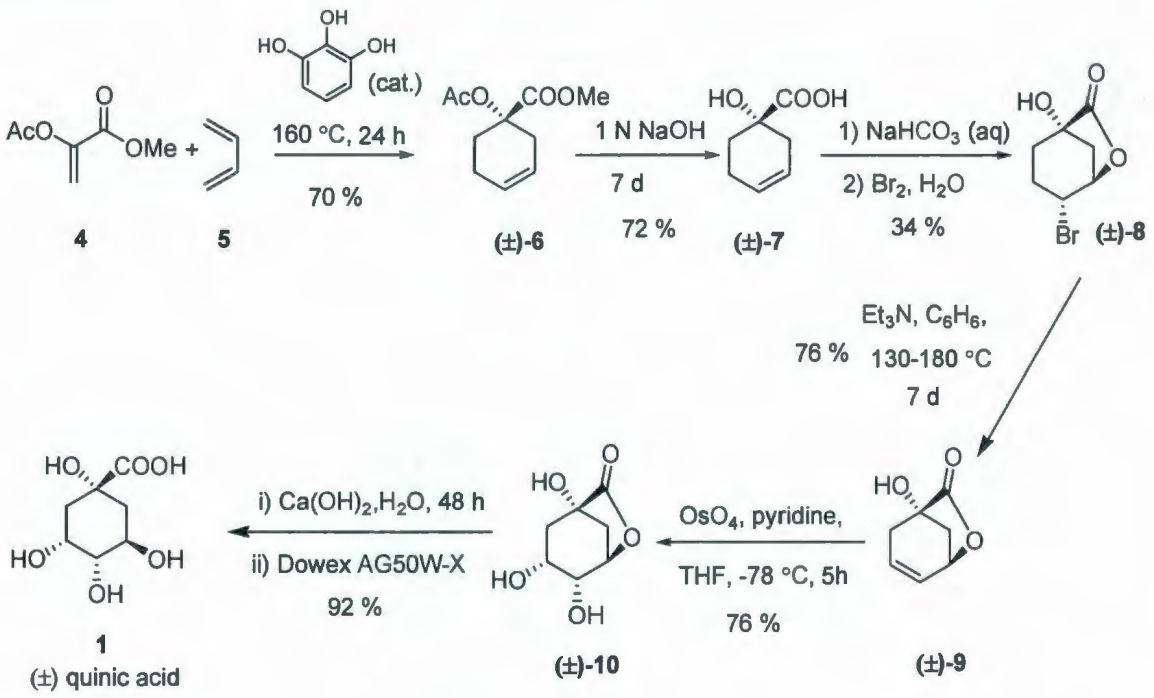
(-)-Quinic acid is found in plants and organisms and has a regulating role in the biosynthesis of aromatic compounds in the shikimate pathway.[5] The biosynthesis of (-)-quinic acid is also being actively investigated as a target in the search of new herbicidal, antifungal, antibacterial and antiparasitic agents that do not affect mammals.[6] Owing to the high level of interest in this natural product, several enantioselective routes toward its synthesis have been described in the literature[7] and a summary depicting key transformations in these reports follows.

Known synthetic routes to (-)-quinic acid

This summary is focused primarily on the enantioselective syntheses of (-)-quinic acid. However, the discussion will start with Wolinsky's synthesis[8] of racemic quinic acid, since some of the formal enantioselective syntheses are aimed at making a key intermediate in Wolinsky's synthesis.

Wolinsky's synthesis starts with a Diels-Alder reaction of methyl-α-acetoxy acrylate (**4**) and 1,3-butadiene (**5**) to provide cyclohexene **6** (Scheme 1).

Scheme 1

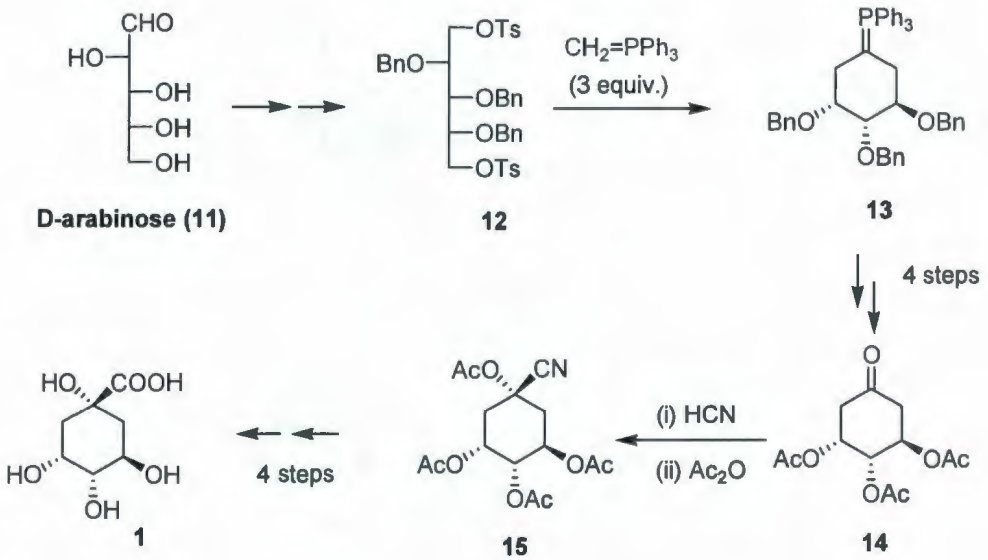


Hydrolysis of **6** followed by bromolactonization afforded bromolactone **8** which was dehydrohalogenated to the bicyclic lactone **9**. Stereoselective dihydroxylation of **9** with osmium tetroxide provided **10**. Finally, hydrolysis of the lactone in **10** provided quinic acid (**1**) in racemic form.

In 1971, Bestmann and Heid reported the first enantioselective synthesis of (-)-quinic acid from D-arabinose (**11**) (Scheme 2).[7a] Using the chemistry previously developed by their group,[9] the authors demonstrate the formation of the functionalized cyclohexene in quinic acid from an arabinose-derived starting material **12**. Treatment of the intermediate **12** with three molar equivalents of methylenetriphenyl phosphorane yielded the ylide **13**. Cyclic ylide **13** was then transformed into ketone **14** over four steps.

The ketone in **14** was stereoselectively converted into the triacetylquinic acid nitrile by treatment with HCN and the resulting tertiary alcohol was acetylated to generate tetracetyl derivative **15**. (-)-Quinic acid was then obtained from **15** (Scheme 2) following the previously reported procedure by Grewe.[10]

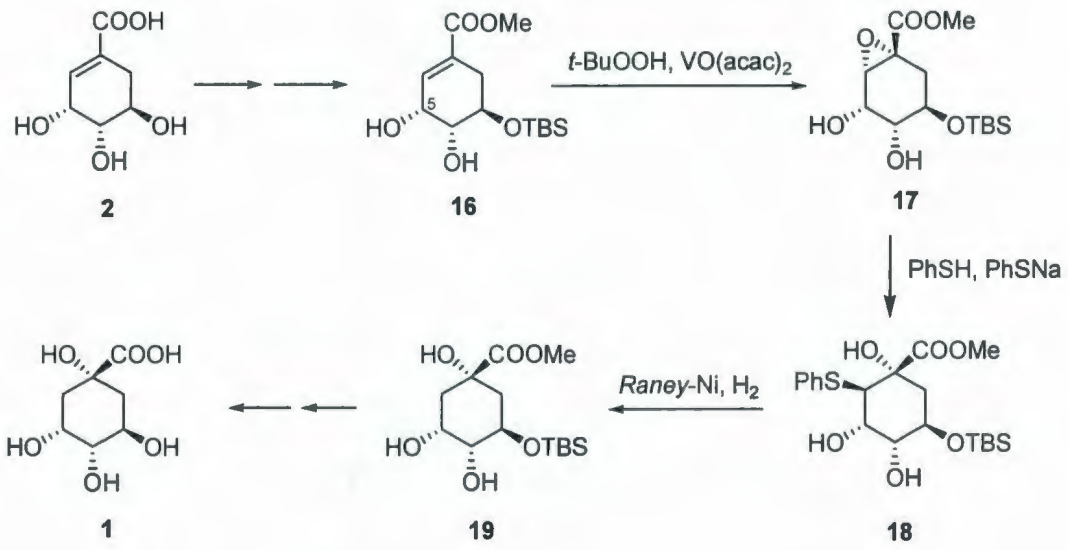
Scheme 2



Nearly two decades after this report, Tamm and Meier reported their synthesis of (-)-quinic acid **1** from (-)-shikimic acid **2** (Scheme 3).[7b] The synthesis was devised around a stereoselective epoxidation[11] of the intermediate **16** (obtained from shikimic acid) by using the *cis*-directing effect of the C-5 hydroxyl group in **16**. Thus, epoxidation of **16** with *t*-butyl hydroperoxide in the presence of vanadium diacetate as a catalyst yielded the epoxide **17**, which, in turn, was subjected to a regioselective ring-opening by sodium thiophenolate to afford tertiary alcohol **18**. Reductive removal of the phenylthio group in

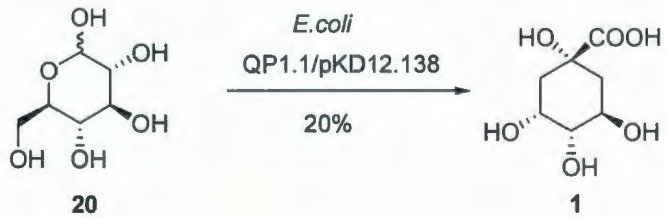
18 gave **19**, which was then deprotected to provide (-)-quinic acid (**1**) in an overall yield of 21-25% from (-)-shikimic acid (**2**).

Scheme 3



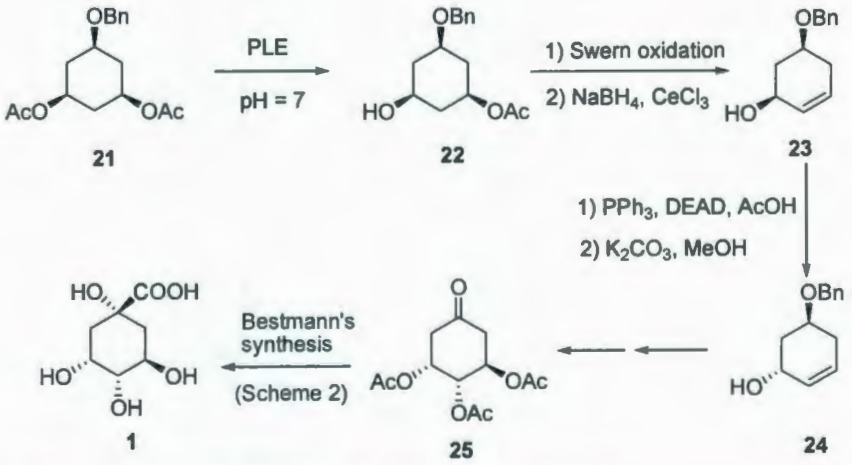
A biocatalytic approach for the synthesis of (-)-quinic acid **1** from D-glucose (**20**) by using an *E. coli* strain (AB2848/pKD136/pTW8090A) was described by Frost in 1992.[7e] Later, the Frost group documented a refined procedure (Scheme 4) to make (-)-quinic acid from glucose by using a different strain of *E. coli* (QP1.1/pKD12.138).[7g] Notably, in this report, the authors admitted that significant optimization of the process is necessary before this route could be used on an industrial scale.

Scheme 4



In another example of a biocatalysis-based approach, Sakai and co-workers reported a porcine liver esterase (PLE) catalyzed asymmetric hydrolysis of the *meso* diester **21** to obtain alcohol **22** (62%, 87% ee, Scheme 5).[7c] Compound **22** was then subjected to Swern oxidation to yield an enone which was stereoselectively reduced by employing Luche reduction conditions ($NaBH_4$, $CeCl_3$) to afford the alcohol **23**. Inversion of the alcohol in **23** under Mitsunobu conditions and hydrolysis of the resulting acetate afforded compound **24** which could then be converted into compound **25**, which is a known intermediate in Bestmann's synthesis of quinic acid[7a] (Scheme 2).

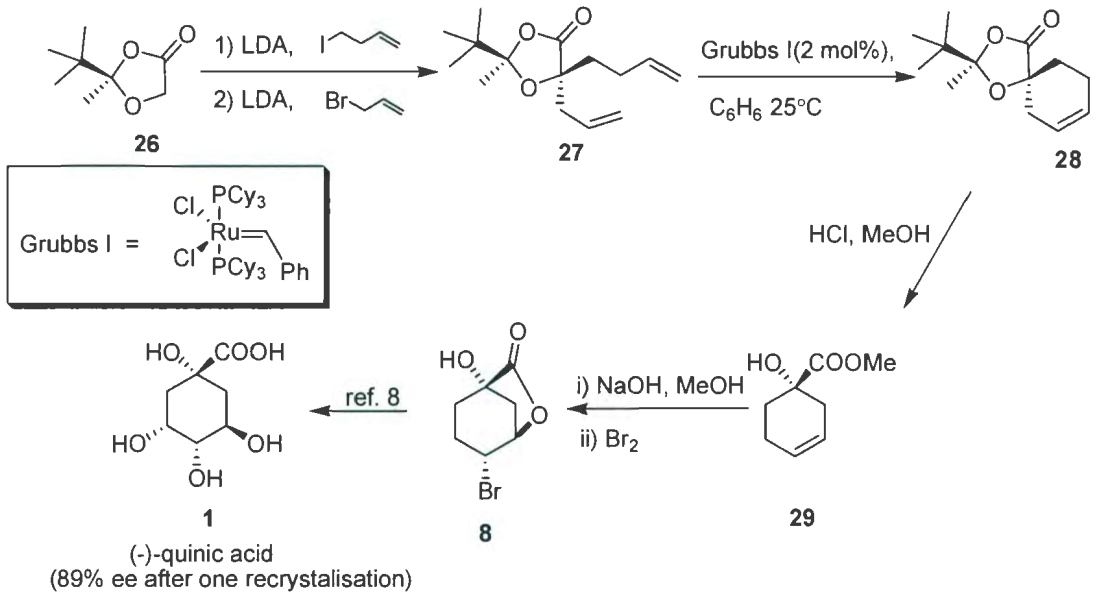
Scheme 5



Renaud and co-workers reported a formal synthesis of (-)-quinic acid (**1**) based on their protocol for double alkylation of the chiral glycolate derivative **26** (Scheme 6).[7f] Double alkylation of **26** (obtained from D-mannitol, 80% ee) provided a 2:1 mixture of diastereomers favoring **27** (51%). A ring closing metathesis reaction of **27** provided cyclohexene **28**. Methanolysis of **28** yielded ester **29** which could then be converted into **8** (82% ee) via hydrolysis and bromolactonization. Since Wolinsky[8] had already reported

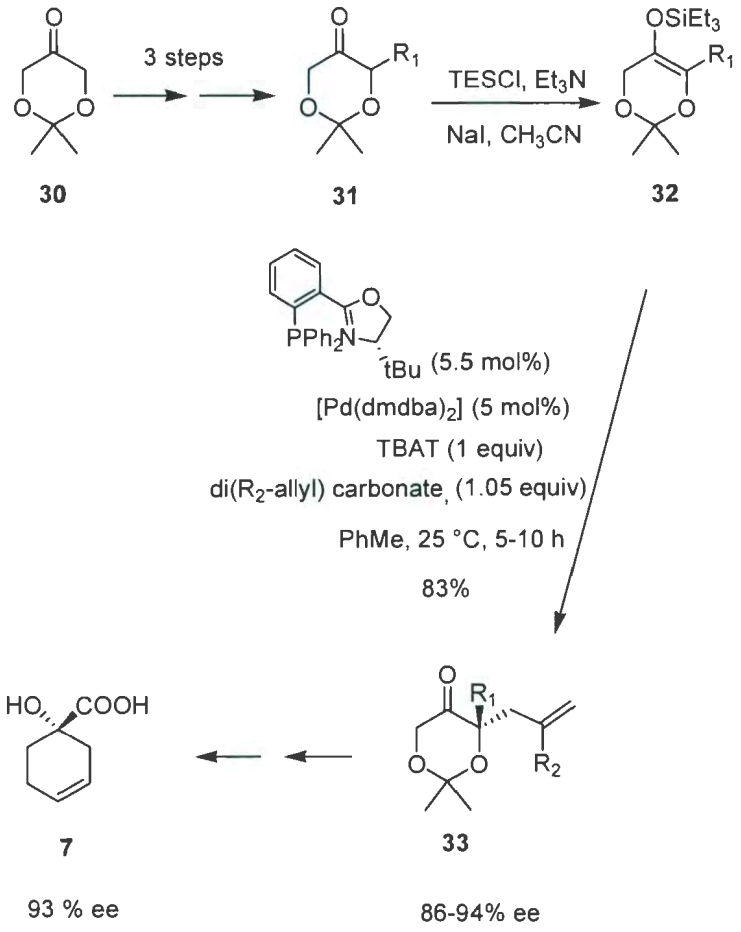
the conversion of the bromolactone **8** into racemic quinic acid (Scheme 1), the above sequence accounts for a formal synthesis of the natural product.

Scheme 6



Very recently, and after we reported our approach to (-)-quinic acid (1),[12] Stoltz and co-workers reported a catalytic enantioselective formal synthesis of (-)-quinic acid **1** (Scheme 7).[13] This synthesis utilized a palladium-catalyzed asymmetric alkylation of the silyl enol ether derivative **32** to obtain dioxanones **33**. An appropriate intermediate (**33**, R = allyl) was converted into the cyclohexene intermediate **7** (Scheme 1) in the Wolinsky synthesis[8] (Scheme 1).

Scheme 7


3 steps
TESCl, Et3N
NaI, CH3CN
OSiEt3
R1
30
31
32
PPh2
tBu (5.5 mol%)
[Pd(dmdba)2] (5 mol%)
TBAT (1 equiv)
di(R2-allyl) carbonate, (1.05 equiv)
PhMe, 25 °C, 5-10 h
83%
HO
COOH
R2
7
33
93 % ee
86-94% ee

Objectives:

A study of the syntheses of (-)-quinic acid reported so far clearly warrants the development of a concise enantioselective route to (-)-quinic acid. The objective of this investigation was the development of an enantioselective formal synthesis of (-)-quinic acid employing the ephedrine-derived morpholine-dione based synthesis of α-hydroxy acids developed in Pansare group.

Results and Discussion:

It was decided to focus on the asymmetric construction of the α-hydroxy acid moiety in (-)-quinic acid, which was envisioned to be obtained from the ephedrine-derived morpholine-dione **36**, as shown in Figure 3.

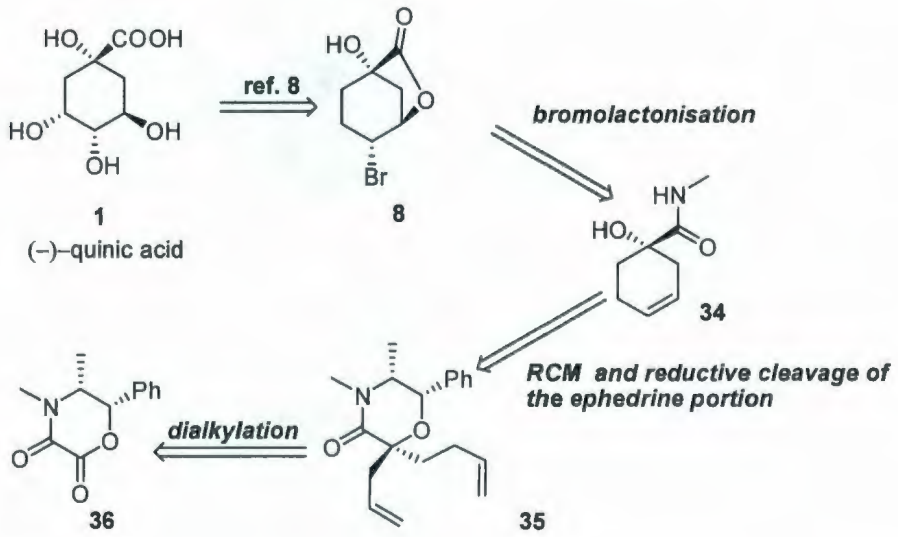
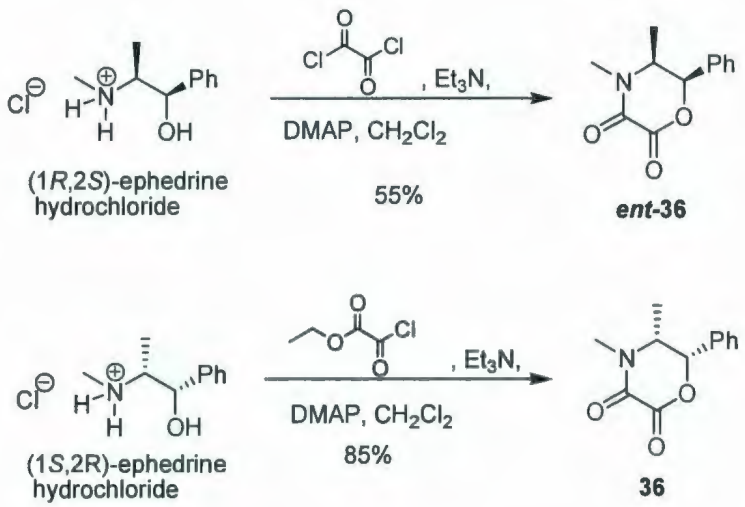


Figure 3. Retrosynthetic analysis for (-)-quinic acid.

It was decided to target the lactone **8** which was an intermediate in the Wolinsky synthesis of quinic acid (Scheme 1). It was reasoned that the lactone could be obtained via a bromolactonisation reaction of the hydroxy amide **34**, which should be accessible from the diene **35**. In the forward sense, this can be achieved by subjecting the diene to a ring closing metathesis reaction followed by removal of the ephedrine portion. The diene **35** should be readily obtained from the dione **36**, by following the dialkylation protocol previously reported by our group.[1]

The previously reported synthesis[1b] of the enantiomer of **36** employed (1*R*,2*S*)-ephedrine and oxalyl chloride to provide the morpholine dione in 55% yield after purification by column chromatography (Scheme 8). In order to eliminate this low yielding step at the beginning of the synthesis it was decided to optimize the reaction conditions. After a brief study, ethyl oxalyl chloride was determined to be a better alternative to oxalyl chloride. This reagent is presumably less electrophilic than oxalyl chloride and this is reflected in an increased reaction time (48 h, as compared to 5 h for oxalyl chloride). However, a significantly improved yield (85%) of **36** was obtained. Moreover, the purification was reduced to a simple trituration of the crude product with 9:1 hexanes:dichloromethane, thus eliminating the need for chromatographic purification. Using this modified procedure, dione **36** could be prepared on a 10 g scale.

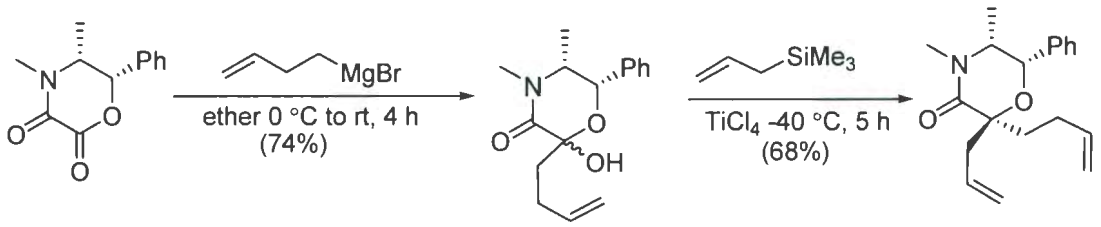
Scheme 8



The dione **36** was then reacted with the Grignard reagent derived from 4-bromo-1-butene (Scheme 9) to yield the hemiacetal **37** (74%). The stereochemistry of the hemiacetal was found to be influenced by the reaction temperature during the addition of the Grignard reagent. Thus, if the Grignard addition was carried out at 0 °C, **37** was obtained as a 5:1 mixture of diastereomers (^{1}H NMR) as compared to a 1:1 mixture when the reaction was carried out at room temperature. The stereochemistry of the major diastereomer was not determined since it was inconsequential in further steps.

In the context of the proposed retrosynthesis (Figure 3), it was now possible to try the crucial allylation reaction. An initial attempt using allyltrimethylsilane and $BF_3 \cdot Et_2O$ at -78 °C provided no product. However, warming the reaction mixture to 0 °C gave the desired product **35** (Scheme 9), albeit in a low yield (20%). The use of allyltributyltin as the nucleophile under identical conditions also provided **35** in a low yield (14%).

Scheme 9



36 **37** **35**

Fortunately, it was determined that using $TiCl_4$ as the Lewis acid and allyltrimethylsilane as the nucleophile at -40 °C, provided the required dialkylated glycolamide derivative **35** in good yield (68%) and excellent diastereoselectivity (single diastereomer by ^1H NMR).

At this stage, the stereochemistry of the newly generated stereocenter in **35** was assigned the '*S*' configuration on the basis of a NOE experiment, which indicated a *syn* orientation of the allyl group and the benzylic hydrogen in the morpholinone ring.

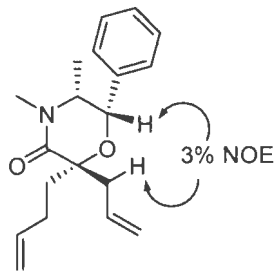
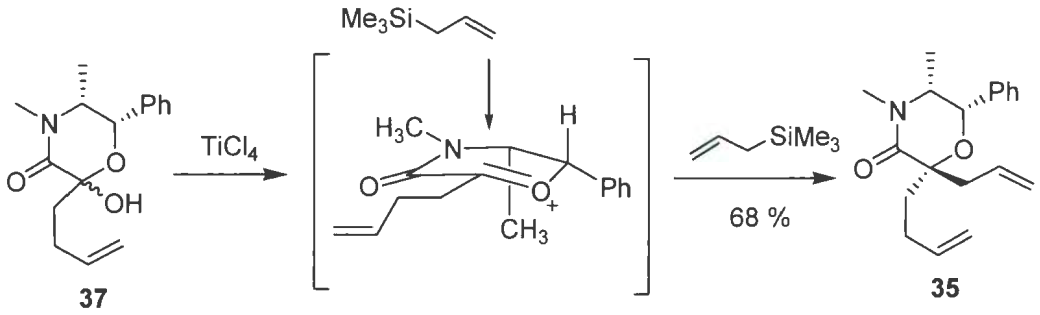


Figure 4. NOE measurement on **35**.

This result was probably the outcome of a stereoelectronically controlled axial allylation of the oxocarbenium ion in a boat-like transition state assembly (Scheme 10).

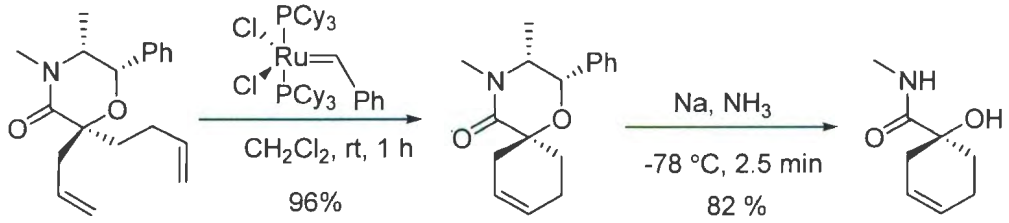
Scheme 10



37 **35**

Having obtained the diene **35,** the stage was set for a ring-closing metathesis reaction to generate the cyclohexene derivative from the diene. Gratifyingly, use of the Grubbs (generation I) catalyst (7 mol%, CH_2Cl_2, room temperature) resulted in a swift and efficient (1 h, 96%) ring-closing metathesis reaction to yield the spirocyclohexene derivative **38** (Scheme 11). Cyclohexene **38** was then subjected to dissolving metal reduction (Na/NH_3, -78 °C) to remove the ephedrine portion and provide hydroxy amide **34** in good yield (82%) and high enantiomeric excess (96%).

Scheme 11



35 **38** **34**

Details of this homobenzylic C-N bond cleavage are not known at present. It is plausible that, at some stage in the reduction, a benzylic carbanion is generated (Figure 5) and it undergoes facile *β*-elimination of the *N*-acyl moiety. [14]

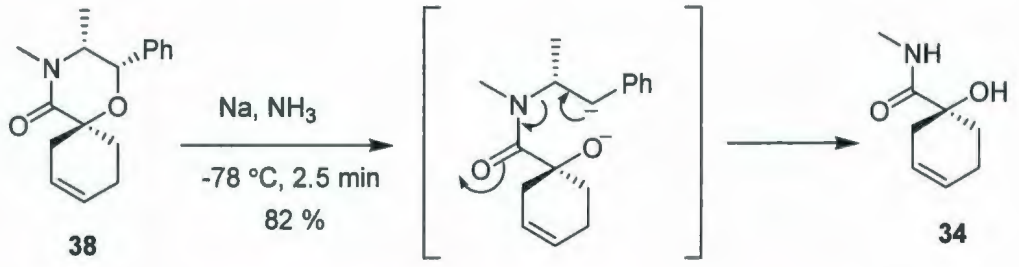
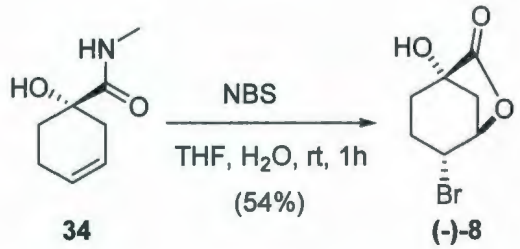


Figure 5. Possible mechanism for the reductive cleavage of the ephedrine portion

The key intermediate to (-)-quinic acid was obtained by bromolactonisation of **34** (Scheme 12). Treatment of **34** with *N*-bromosuccinimide in moist THF at ambient temperature generated the bromolactone **8** (54% (unoptimized), 96% ee).

Scheme 12



Spectroscopic data for lactone **8** were in agreement with those reported earlier,[7f,15] and the optical rotation confirmed the '*S*' configuration at the α-hydroxy carboxylic acid stereocenter in the lactone ($[\alpha]_D$ -11.1, (c 2, CH_2Cl_2); lit.[7f] $[\alpha]_D$ -9.1, (c 1.36, CH_2Cl_2) for material with 82% ee). This observation also confirmed the stereochemistry of the allylation reaction that provided **35** from hemiacetal **37**.

It is noteworthy that the above-mentioned highly stereoselective synthesis of dialkylglycoamide (**35**) from a chiral oxalic acid derivative (**36**) is an alternative to conventional approaches to chiral α,α-dialkylated glycolic acid derivatives that are based on sequential dialkylation of glycolate anions.[16] Importantly, the approach may be

advantageous when the S_N2 reactivity of the electrophile is a limitation in the anion alkylation protocol.

To the best of our knowledge, this is the shortest and most efficient synthesis of enantiomerically enriched (-)-**8**.[12] The only other asymmetric synthesis[7f] of (-)-**8** reported at the time when this work was published, employed an enantiomerically enriched dioxolanone (a chiral glycolate derivative with 80% ee) as the starting material, which was obtained by a multistep synthesis from D-mannitol, and the key dialkylation of the dioxolanone proceeded with low diastereoselectivity (2/1, Scheme 6). The present method represents a significant improvement since it requires fewer steps, and the dialkylglycolamide derivative **35** was easily prepared with high diastereoselectivity. It should be noted that even after the recent report[13] by Stoltz, the method reported in this thesis remains unsurpassed in terms of length and enantioselectivity.

Racemic bromolactone **8**[8] and its iodo-analogue **39**[15] (Figure 6) are easily converted to the oxabicyclooctene derivative **9**[8,15] by dehydrohalogenation and subsequently to racemic quinic acid[8] (two steps) and a racemic, protected 3-phospho-shikimate derivative **40**[15] (four steps). Hence, the present synthetic route to enantiomerically enriched **8** establishes a route to enantiomerically enriched quinic acid and shikimic acid derivatives.

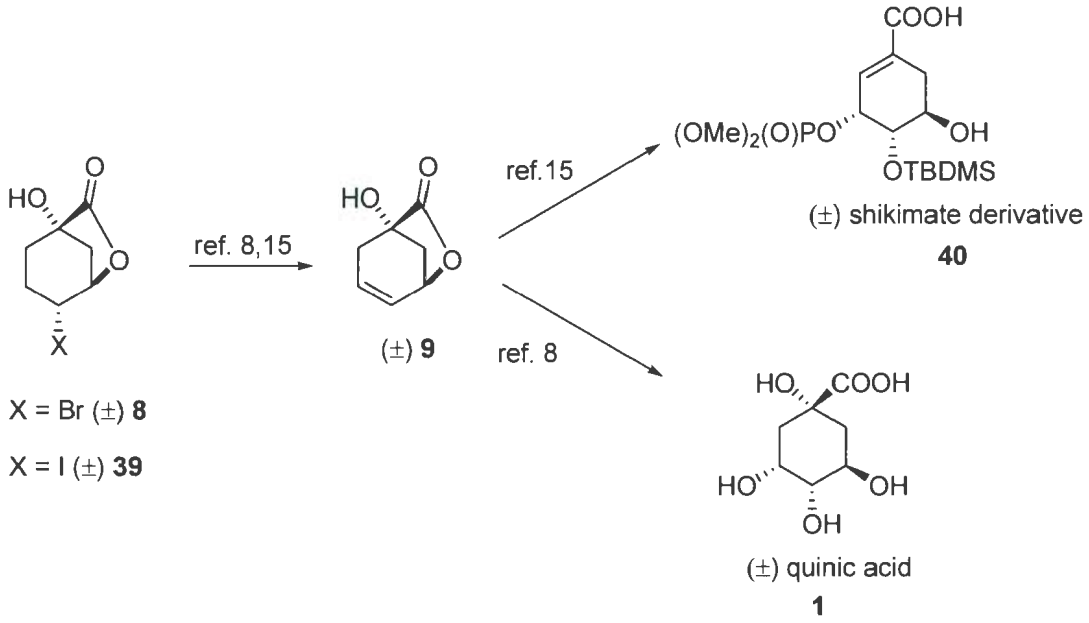


Figure 6. Halolactones **8** and **42** as precursors to quinic acid and shikimates.

Conclusions:

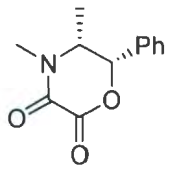
In conclusion, a short, enantioselective route to (-)-quinic acid that is extendable to shikimic acid derivatives has been developed. It is noteworthy that this method can provide access to either enantiomer of these biologically important metabolites since both enantiomers of ephedrine are commercially available. The oxalate dialkylation is an alternative to the conventional dialkylation of glycolate enolates and has potential for applications in the synthesis of polyhydroxylated cyclopentanes and cyclohexanes, as well as functionalized medium-sized carbocycles by variation of the alkenyl groups in morpholinone **38** (Scheme 9).

Experimental:

General

All reactions requiring anhydrous conditions were performed under a positive pressure of nitrogen using oven-dried glassware (120 °C) that was cooled under nitrogen. THF was distilled from sodium benzophenone ketyl and dichloromethane was distilled from calcium hydride. Commercial precoated silica gel (Merck 60F-254) plates were used for TLC. Silica gel for column chromatography was 230-400 mesh. All melting points were uncorrected. IR spectra were recorded on a Bruker TENSOR 27 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE-500 instrument. Coupling constants (*J*) are given in Hz. Mass spectra were obtained on an Agilent 1100 series LC/MSD chromatographic system. High-resolution mass spectra were obtained on a Waters GCT Premier Micromass mass spectrometer. Optical rotations were measured at the sodium D line on a JASCO-DIP 370 digital polarimeter at ambient temperature.

(5*R*,6*S*)-4,5-Dimethyl-6-phenylmorpholine-2,3-dione (36):



To a stirred solution of (1*S*,2*R*)-ephedrine hydrochloride (2.0 g, 9.9 mmol) and DMAP (60 mg, 0.49 mmol) in dichloromethane (200 mL) at 0 °C was added triethylamine (5.5 mL, 40 mmol). The mixture was stirred for 10 min and a solution of oxalyl chloride (1.3 mL, 15 mmol) in dichloromethane (100 mL) was added dropwise over a period of 3.5 h at 0 °C. The mixture was stirred at 0 °C for an hour and water (50

mL) was added. The mixture was warmed to ambient temperature and the biphase was separated. The dichloromethane layer was washed with water (100 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel (1/2 hexane/ethyl acetate) to furnish 1.20 g (55%) of **36** as a white solid.

Mp: 181-182 °C.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.46-7.39 (m, 5H), 5.89 (d, 1H, J = 2.9), 3.71-3.68 (dq, 1H, J = 2.9, 6.8), 3.20 (s, 3H), 1.13 (d, 3H, J = 6.8)

^{13}C NMR (125.8 MHz, $CDCl_3$):

δ 156.6, 153.5, 134.1, 129.2, 129.1, 125.7, 79.8, 58.9, 33.8, 12.3.

IR (solid):

2933, 1752, 1698, 1409, 1290, 1215, 1142, 1001 cm^{-1}

$[\alpha]^{23}_D$ = +185.0 (c 2, CH_2Cl_2).

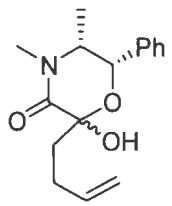
MS (APCI):

220.1 (M+1, 100).

HRMS (CI):

m/z 220.0965 (220.0974 calc. for. $C_{12}H_{14}NO_3$, M+H).

(5*R*, 6S)-2-But-3-enyl-2-hydroxy-4, 5-dimethyl-6-phenylmorpholin-3-one (37):



To a suspension of **36** (219 mg, 1 mmol) in anhydrous ether at 0°C was added 3-butenylmagnesiumbromide (prepared from 720 mg of Mg and 0.35 mL of 4-bromobutene in ether (10 mL) and the mixture was warmed up to ambient temperature. The reaction mixture was stirred 3 h at ambient temperature and the precipitated solids were dissolved with saturated aqueous NH_4Cl solution. The resulting mixture was extracted with ethyl acetate (3 x 10 mL), the combined organic layers was dried (Na_2SO_4) and concentrated. Purification of the crude product by flash chromatography on silica gel (2/1 ethyl acetate/hexanes) gave 204 mg (74%) of **37** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.41-7.30 (m, 5H), 5.87-5.81 (m, 1H), 5.19 (d, 1H, J = 3.4), 5.0 (br m, 1H), 4.9 (d, 1H, J = 10.3), 4.3 (s, 1H), 3.51 (dq, 1H, J = 3.4, 7.3), 3.0 (s, 3H), 2.42-2.37 (m, 1H), 2.25-2.2.1 (m, 3H), 1.05 (d, J = 7.3, 3H).

^{13}C NMR (125.8 MHz, $CDCl_3$):

δ 169.8, 138.4, 137.4, 128.6, 127.9, 125.7, 114.8, 98.2, 73.6, 59.4, 35.1, 34.0, 26.3, 12.7.

Visible peaks of the minor diastereomer:

^{1}H NMR (500 MHz, $CDCl_3$):

δ 5.5 (d, 1H, J = 3.0), 3.04 (s, 3H), 0.99 (d, J = 6.6, 3H).

^{13}C NMR (125.8 MHz, $CDCl_3$):

δ 168.5, 138.2, 137.7, 128.5, 127.8, 125.9, 115.0, 97.8, 71.5, 59.5, 38.7, 33.8, 28.0, 12.8.

IR (solid):

3306, 1645, 902, 735, 695, 668 cm^{-1}.

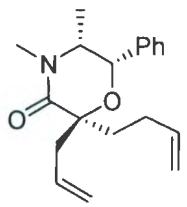
MS (APCI, positive):

m/z 148.1 (25), 164.1 (10), 258.1 (10), 276.1 (M+1, 75).

HRMS (CI):

m/z 276.1587 (276.1599 calc. for. $C_{16}H_{22}NO_3$, M+H).

(2*S*,5*R*,6*S*)-2-Allyl-2-but-3-enyl-4,5-dimethyl-6-phenylmorpholin-3-one (35):



To a solution of **37** (275 mg, 1 mmol) in dichloromethane at –78 °C was added $TiCl_4$ (0.66 mL, 6 mmol) and allyltrimethylsilane (0.95 mL, 6 mmol). The mixture was gradually warmed to – 40 °C and allowed to stir at this temperature for 4.5 h. Saturated NH_4Cl solution was added and the mixture was warmed to ambient temperature. Water was added and the mixture was extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica (2/1 ethyl acetate/hexane) to give 203 mg (68%) of **35** as a colorless gum.

^{1}H NMR ($CDCl_3$):

δ 7.39-7.29 (m, 5H), 5.89-5.80 (m, 2H), 5.26 (d, 1H, *J* = 2.4), 5.10-5.00 (m, 3H), 4.97 (d, 1H, *J* = 10.5), 3.51 (dq, 1H, *J* = 6.5, 2.4), 3.03 (s, 3H), 2.85 (dd, 1H), 2.55 (dd, 1H), 2.42-2.38 (m, 1H), 2.05-2.00 (m, 2H), 1.92-1.85 (m, 1H), 0.98 (d, 3H, J=6.5).

^{13}C NMR (125.8 MHz, CDCl3):

δ 171.4, 138.7, 138.3, 133.1, 128.6, 127.8, 125.8, 118.5, 114.8, 82.0, 71.8, 59.5, 40.4, 37.5, 34.0, 28.8, 13.4.

IR (neat):

2978, 1640, 1146, 913, 759, 700 cm^{-1}.

$[\alpha]^{23}_D$ = + 44 (*c* 1, CH_2Cl_2).

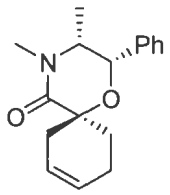
MS (APCI, positive):

m/z 258.1 (7), 300.1 (M+1, 100).

HRMS (CI):

m/z 300.1953 (300.1964 calc. for. $C_{19}H_{26}NO_2$, M+H).

(2*S*,3*R*,6*S*)-3,4-Dimethyl-2-phenyl-1-oxa-4-azaspiro[5.5]undec-8-en-5-one (38):



To a solution of **35** (960 mg, 3.2 mmol) in dichloromethane (350 mL) at room temperature was added Grubbs I catalyst (175 mg, 0.21 mmol, 6.6 mol%). The reaction

mixture was stirred for an hour at room temperature and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (1/1 ethyl acetate/hexane) to give 830 mg (96%) of **38** as a white solid.

Mp: 78-79 °C.

^{1}H NMR ($CDCl_3$):

δ 7.37-7.28 (m, 5H), 5.79-5.77 (m, 1H), 5.57-5.54 (m, 1H), 5.13 (d, 1H, *J* = 2.5), 3.51 (dq, 1H, *J* = 6.4, 2.5), 3.04 (s, 3H), 2.67-2.62 (m, 1H), 2.50-2.42 (m, 1H), 2.42-2.38 (m, 1H), 2.22-2.05 (m, 2H), 1.95-1.91 (m, 1H), 0.98 (d, 3H, *J* = 6.4);

^{13}C NMR (125.8 MHz, $CDCl_3$):

δ 172.4, 138.4, 128.3, 127.4, 126.1, 125.5, 123.2, 77.4, 71.7, 59.1, 33.9, 31.8, 30.8, 21.3, 12.7;

IR (solid):

2934, 2362, 1635, 1092, 700, 668, 656 cm^{-1}.

$[\alpha]^{23}_D$ = -15.6 (c 1, CH_2Cl_2).

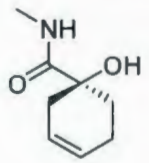
MS (APCI, positive):

m/z 270.1 (7), 372.1 (M+1, 100).

HRMS (CI):

m/z 272.1647 (272.1651 calc. for. $C_{17}H_{22}NO_2$, M+H).

(1*S*)-1-Hydroxy-*N*-methylcyclohex-3-ene-1-carboxamide (34):



34

To anhydrous liquid ammonia (distilled over sodium) was added Na (40 mg, 1.74 mmol) at –78 °C and the mixture was stirred for 15 min. To the resulting blue solution was added a solution of **38** (60 mg, 0.22 mmol) in anhydrous THF (2.5 mL) and the mixture was stirred for 3 min. A mixture of 2/1 methanol/water (3 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 column chromatography on silica gel (8/2 ethyl acetate/hexane) to yield 28 mg (82%) of **34** as a white solid.

Mp: 115-116 °C.

^{1}H NMR ($CDCl_3$):

δ 6.83 (br s, 1H), 5.82-5.79 (m, 1H), 5.69-5.66 (m, 1H), 2.85 (d, 3H, J = 5.3), 2.77-2.71 (m, 2H), 2.57 (s, 1H), 2.22-2.18 (m, 2H), 2.11-2.04 (m, 2H), 1.75-1.70 (m, 1H).

^{13}C NMR (125.8 MHz, $CDCl_3$):

δ 176.4, 126.9, 123.9, 73.5, 35.6, 30.7, 26.2, 21.6.

IR:

3000, 3023, 1645, 1549, 1090, 932, 655 cm^{-1};

$[\alpha]^{23}_D$ = + 44.3 (c 1, CH_2Cl_2);

MS (APCI, positive):

m/z 138.1 (40), 156.1 (M+1, 100).

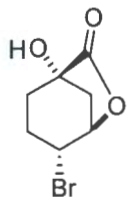
HRMS (CI):

m/z 156.1022 (156.1025 calc. for $C_8H_{14}NO_2$, M+H).

HPLC:

Enantiomeric excess: 95%, Chiralpak AD-H column, hexane/isopropyl alcohol 9/1, flow rate 1 mL/min, tR (major): 6.6 min. t_R (minor): 6.3 min.

(1*S*,4*R*,5*R*)-4-Bromo-1-hydroxy-6-oxabicyclo[3.2.1]octan-7-one (8):



To a solution of **34** (40 mg, 0.26 mmol) in THF (1 mL) was added *N*-bromosuccinimide (70 mg, 0.39 mmol). The reaction mixture was stirred for an hour at room temperature, saturated aqueous $NaHSO_3$ solution (1.5 mL) was added and the mixture was then extracted with ethyl acetate (3 x 3 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel to give 31 mg (54%) of **8** as a white solid.

Mp: 119-120 °C.

^{1}H NMR ($CDCl_3$):

δ 4.83 (t, 1H, *J* = 5), 4.34 (t, 1H, *J* = 4.5), 2.90 (s, 1H), 2.84 (d, 1H, *J* = 12), 2.51-2.47 (m, 1H), 2.42-2.33 (m, 1H), 2.29-2.15 (m, 2H), 1.83-1.80 (m, 1H).

^{13}C NMR (125.8 MHz, $CDCl_3$):

δ 177.8, 77.7, 74.4, 43.4, 38.9, 31.1, 28.6.

IR:

3485, 2925, 1763, 1128, 856, 668 cm^{-1}.

$[\alpha]^{23}_D$ = -11.1 (c 2, CH_2Cl_2).

MS (APCI, positive):

m/z 111.2 (20), 149.1 (46), 177.1 (100), 199 (20), 221 (M+1, 5).

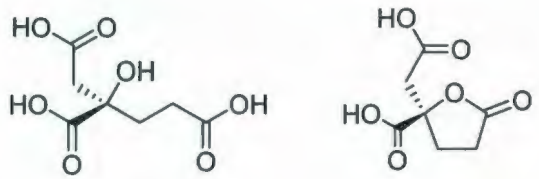
HRMS (CI):

m/z 220.9810 (220.9814 calc. for $C_7H_{10}BrO_3$, M+H); GC: t_R = 51 min, Rt-βDEXsm column, 40-280 °C, 2 °C/min.

Part II: Enantioselective synthesis of (*R*)-homocitric acid lactone.

Introduction

(*R*)-Homocitric acid (**41**, Figure 7) is a key intermediate in the biosynthesis of L-lysine, an essential amino acid in some yeast and fungi,[17] and it is also a component of the Fe–Mo cofactor in nitrogenase enzymes.[18] The unique biological profile of homocitric acid is of interest in the development of antifungal therapies[19] and in the elucidation of the intricacies of nitrogen fixation.[20] Studies toward these objectives require access to enantiomerically enriched (*R*)-homocitric acid and its analogues,[21] neither of which are commercially available in significant amounts. Consequently, the enantioselective synthesis of homocitric acid, invariably isolated as its γ-lactone **42** (Figure 7), has been actively investigated in recent years.[22] Syntheses of the racemate have also been reported recently.[23] In addition, it has been observed that the alkyl citrate, isocitrate, or α-alkyl malate motifs, which are close congeners of homocitrates, are key pharmacophoric units in several bioactive alkaloids, glycosides and antifungal agents.[24] This has added to the interest in substituted α-hydroxy di- and tri-carboxylic acid derivatives in recent years.



41 **42**

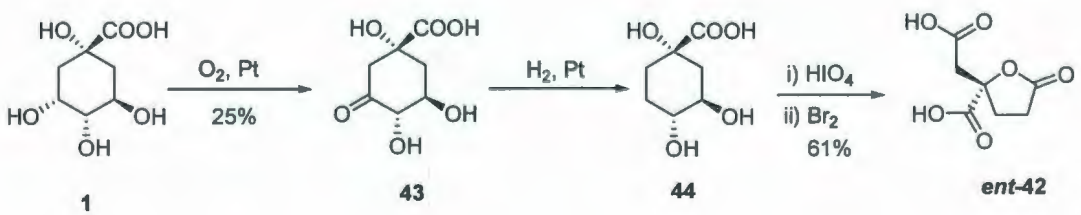
Figure 7. (*R*)-Homocitric acid (**41**) and (*R*)-homocitric acid lactone (**42**).

Structurally, (*R*)-homocitric acid is a deceptively simple target having only a single stereocenter. The favourably positioned alcohol and carboxylic acid functional groups are prone to lactonization, and hence homocitric acid has consistently been isolated as a γ-lactone. Notably, interest in the enantioselective synthesis of (*R*)-homocitric acid has increased over the last few years.[22a-f] The following section will give an overview of the known stereoselective methods for the synthesis of (*R*)-homocitric acid.

Previous syntheses of (*R*)-homocitric acid.

The first enantioselective synthesis of homocitric acid lactone, albeit the antipode of the natural isomer, was reported by Thomas, Kalyanpur and Stevens in 1966 (Scheme 13).[22g] Incidentally, the synthesis was carried out primarily to establish the absolute configuration of (*R*)-homocitric acid by synthesis of its optical isomer, which could be obtained by degradation of (-)-quinic acid. In the first step of this endeavour, quinic acid was oxidised to the ketone **43** using a catalytic oxidation protocol reported by Haslam,[25] followed by complete reduction of the ketone moiety in **43** to generate the diol **44**.[26] Periodate cleavage of the diol followed by *in situ* oxidation of the dialdehyde provided (*S*)-homocitric acid lactone (*ent*-**42**).

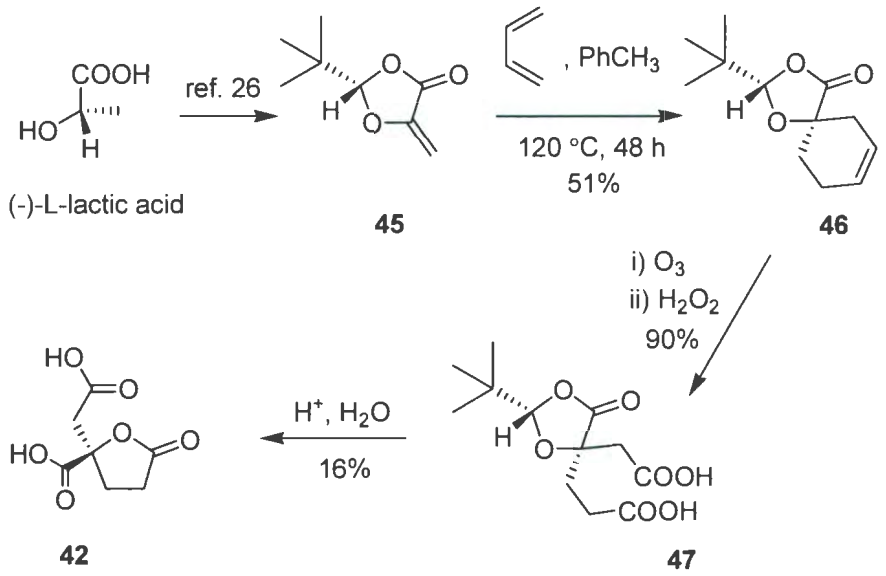
Scheme 13



1 **43** **44** ***ent*-42**

It was not until three decades later that Biellmann and co-workers published the first enantioselective synthesis (Scheme 14) of the natural isomer of homocitric acid lactone **42** starting from (-)-L-lactic acid.[22f] In a sequence centered around a stereoselective Diels-Alder reaction, the authors used reported methods[27] to make the key starting material **45** from lactic acid.

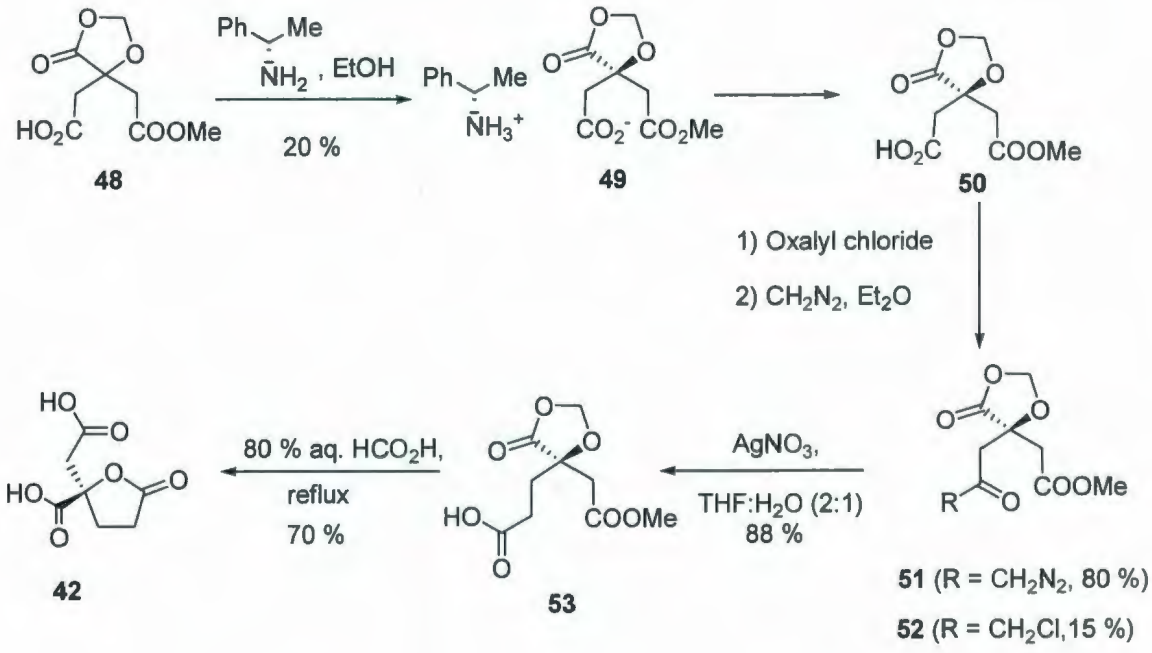
Scheme 14



Dioxolanone **45** was subjected to a Diels-Alder reaction with 1,3-butadiene to obtain the cyclohexene derivative **46**. Ozonolysis of **46** followed by oxidative workup provided the diacid **47**. Hydrolysis of the dioxolanone **47** provided (*R*)-homocitric acid lactone **42** in low yield (16%, 96% ee). In the same report, the authors also describe the synthesis of (*S*)-homocitric acid **41** from *ent*-**45** which was prepared from (*S*)-serine.

In 1997, Russell and co-workers used (*S*)-α-methylbenzylamine for the resolution of the racemic citric acid derivative **48** (50 g scale). The (*S*,*R*) salt **49** (20%) provided the required enantiomer **50** (Scheme 15).[22e]

Scheme 15

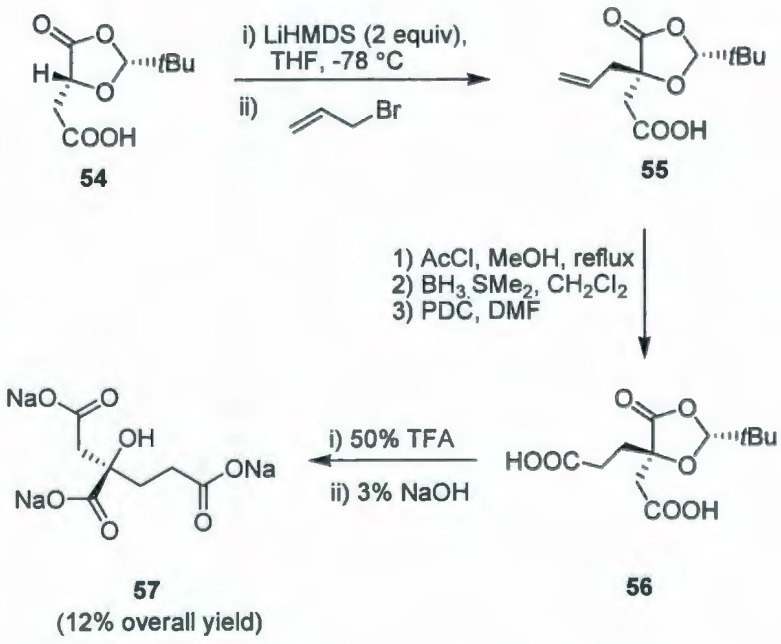


With a dual purpose of confirming the absolute stereochemistry of **50** and demonstrating the usefulness of their protocol, the authors undertook the synthesis of (*R*)-homocitric acid lactone. Homologation of (*R*)-**50** was achieved by using the Arndt-Eistert protocol. Accordingly, the required diazo ketone **51** (80%) was obtained along with a significant amount of chlorinated ketone **52**. The mixture was then converted into the desired homologue by treatment with silver nitrate to afford **53**. The synthesis concluded with the hydrolysis of **53** to give the (*R*)-homocitric acid lactone **42**. A comparison of the

specific rotation value of **42** with the reported value for (*R*)-homocitric acid lactone confirmed the absolute stereochemistry of **50** and also established a route to (*R*)-homocitric acid lactone from citric acid.

Palmer and Ma explored the SRS strategy[27] developed by Seebach for the synthesis of (*R*)-homocitric acid lactone (Scheme 16).[22d] Dioxolanone **54** was synthesized from D-malic acid and stereoselectively alkylated with allyl bromide to yield **55**. Esterification of **55** followed hydroboration of the alkene and oxidative workup gave the diacid **56**. Hydrolysis of dioxolanone **56** followed by basic hydrolysis of the methyl ester yielded the trisodium salt of *R*-homocitric acid (**57**) in an overall yield of 12% from D-malic acid.

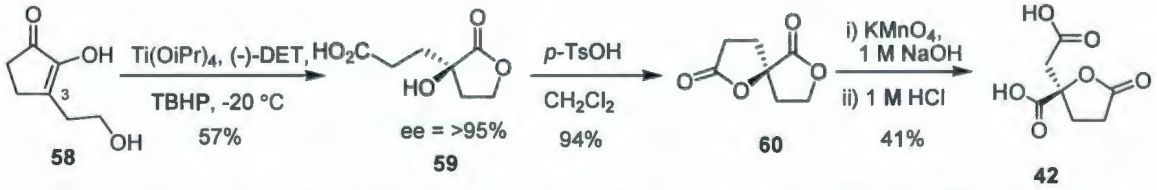
Scheme 16



Paju and co-workers reported an interesting enantioselective synthesis of **42** (Scheme 17).[22c] In an earlier report,[28] the authors had demonstrated the synthesis of

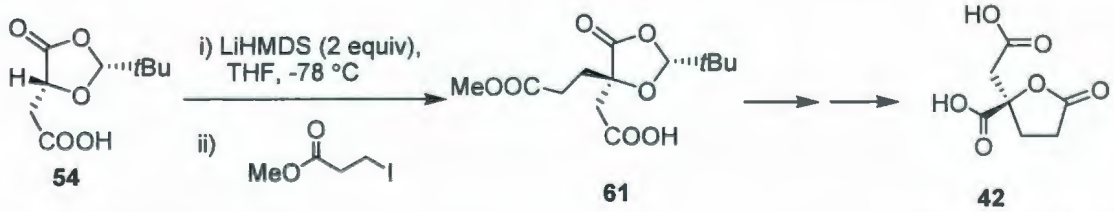
spirodilactone **60** from the lactone **59** (57%, >95% ee), which, in turn, was obtained by asymmetric hydroxylation at the C-3 position of 3-(hydroxyethyl)cyclopentane-1,2-dione (**58**). Using this protocol for the synthesis of **60**, the authors then showcased the utility of their method by demonstrating the oxidation of this spirodilactone to (*R*)-homocitric acid lactone.[22c]

Scheme 17



Tatsumi and co-workers described a slight modification[22b] of Palmer's synthesis[22d] (Scheme 16) of (*R*)-homocitric acid lactone (Scheme 18). In their synthesis, they employed a 3-iodopropionate as an electrophile (Palmer used allyl bromide) to obtain compound **61** from the acid **54**, thus decreasing the number of steps and achieving a higher overall yield.

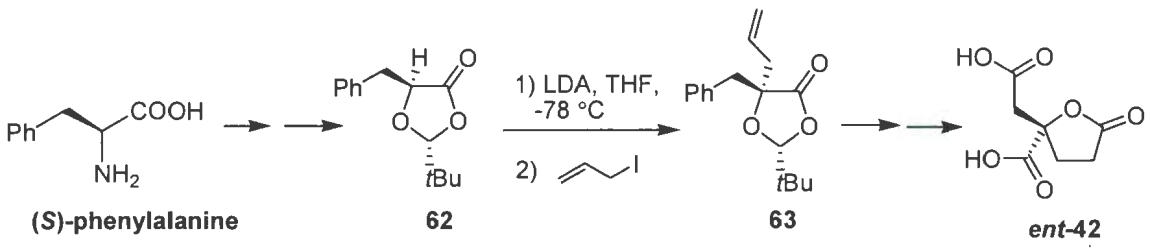
Scheme 18



The third example of a SRS strategy[27] for the synthesis of (*S*)-homocitric acid lactone was described by Huang and Li, who reported a synthesis of *ent*-**42** from (*S*)-

phenylalanine (Scheme 19).[22a] This strategy relied on using the phenyl group as a latent carboxyl group.[29]

Scheme 19



Thus, compound **62** was prepared from (*S*)-phenylalanine using a known procedure[27] and then stereoselectively alkylated with allyl iodide[27] to give dioxolanone **63.** Compound **63** could be converted into the antipode of the naturally occurring homocitric acid lactone (overall yield of 12%) by conversion of the benzyl group in **63** to an acetate side chain and by oxidation of the allyl group to a propionate side chain.

Objectives:

The objective of this study was the enantioselective synthesis of (*R*)-homocitric acid lactone by employing an ephedrine-derived morpholinone as the starting material for the construction of the chiral α-hydroxy carboxylic acid functionality in homocitric acid.

Results and Discussion:

Homocitric acid is invariably isolated as a lactone (**42**). However, from the retrosynthetic perspective, the focus was on the synthesis of the homocitric acid (**41**) and the retrosynthetic analysis is shown below (Figure 8).

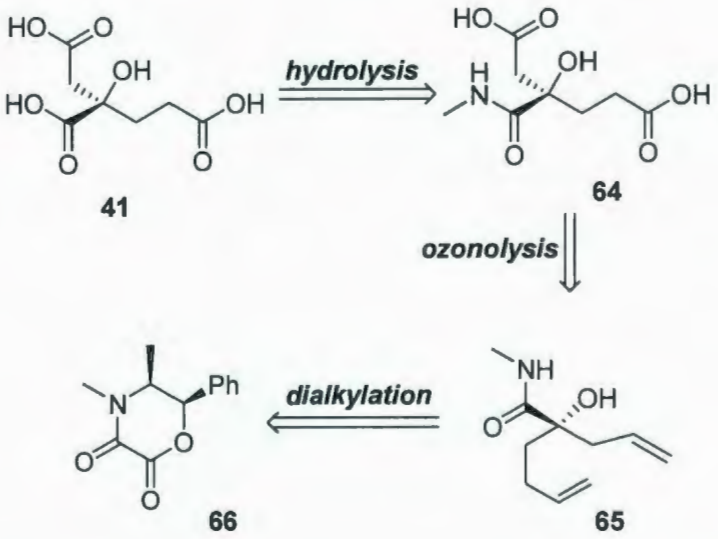
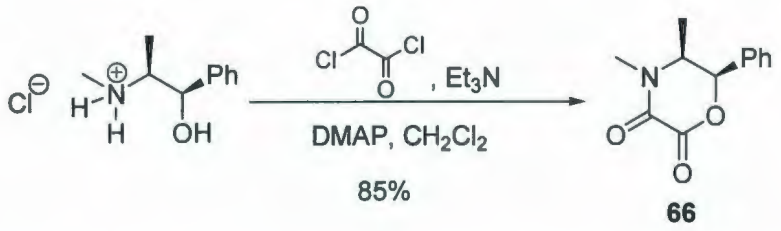


Figure 8: Retrosynthetic analysis of homocitric acid (**41**).

Thus, (*R*)-homocitric acid (**41**) could be obtained by hydrolysis of the amide in **64**. The carboxylic acid funtionalities in **64** can be generated by the oxidative cleavage of the alkene moieties in **65**. The hydroxyl amide **65** should be readily available from the dione **66**, by following the dialkylation protocol previously reported by the Pansare group.[1]

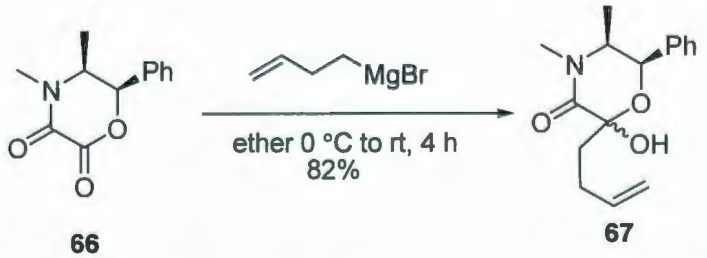
The morpholine-derived ephedrine dione[1b] **66** was chosen as the starting material in this study and was obtained (85%) from commercially available (1*R*, 2*S*) ephedrine and ethyl oxalyl chloride by following the procedure described in Part I (Scheme 8).

Scheme 20



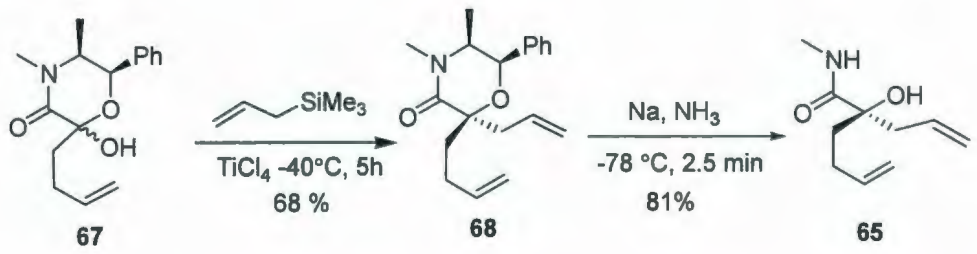
Treatment of **66** with freshly prepared butenylmagnesium bromide generated the hemiacetal **67** (82%, Scheme 21). The diasteroselectivity of the process was moderate (1/1–5/1, depending on the reaction temperature) and the stereochemistry of the major diastereomer was not determined.

Scheme 21



The hemiacetal in **67** was readily allylated ($TiCl_4$, allyltrimethylsilane, -40 °C) to furnish the dialkylmorpholinone **68** (68%) as a single diastereomer (Scheme 22). The newly generated stereocenter in **68** was assigned the '*R*' configuration on the basis of an NOE experiment, which indicated a *syn* orientation of the allyl group and the benzylic hydrogen in the morpholinone ring.

Scheme 22



67 68 65

The α-hydroxy amide in **65** was obtained by subjecting **68** to dissolving metal reduction (Na, NH_3, -78 °C, 81%, Scheme 22). The next objective was conversion of **65** to the lactone **42**. This would require a hydrolysis of the amide in **65** and oxidative cleavage of the alkenes to provide carboxylic acid functional groups.

All attempts to hydrolyze the amide in **65** were unfruitful (Table 1). Heating **65** in aqueous acids led to multiple products, some of which were presumably derived from intramolecular alcohol-alkene etherification reactions of **65**, whereas basic hydrolysis conditions resulted in decomposition. Attempts to activate the amide by *N*-nitrosation[30] were unsuccessful as were efforts to convert the amide into an iminium species or an imidate ester.

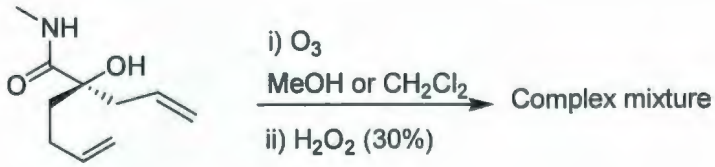
Table 1: Attempted hydrolysis of the amide **65**

65 **69**

Entry	Reagents	Conditions	Result
1	1N HCl	rt/reflux	Decomposition
2	2N LiOH	rt/reflux	No reaction
3	KOH, ethanediol	150 °C	Decomposition
4	2N H_2SO_4	rt/reflux	Decomposition
5	$Me_3O^+BF_4^-$, CH_3CN	rt	No reaction
6	$Me_3O^+BF_4^-$, CH_2Cl_2	rt	No reaction
7	N_2O_4, CH_3CN then LiOOH	0 °C to rt	No reaction
8	Triphosgene	0 °C to rt	Decomposition

An oxidative cleavage of the terminal alkenes in **65** by ozonolysis (Scheme 23) was also attempted. However, ozonation of **65** followed by an oxidative workup yielded a complex mixture of products.

Scheme 23

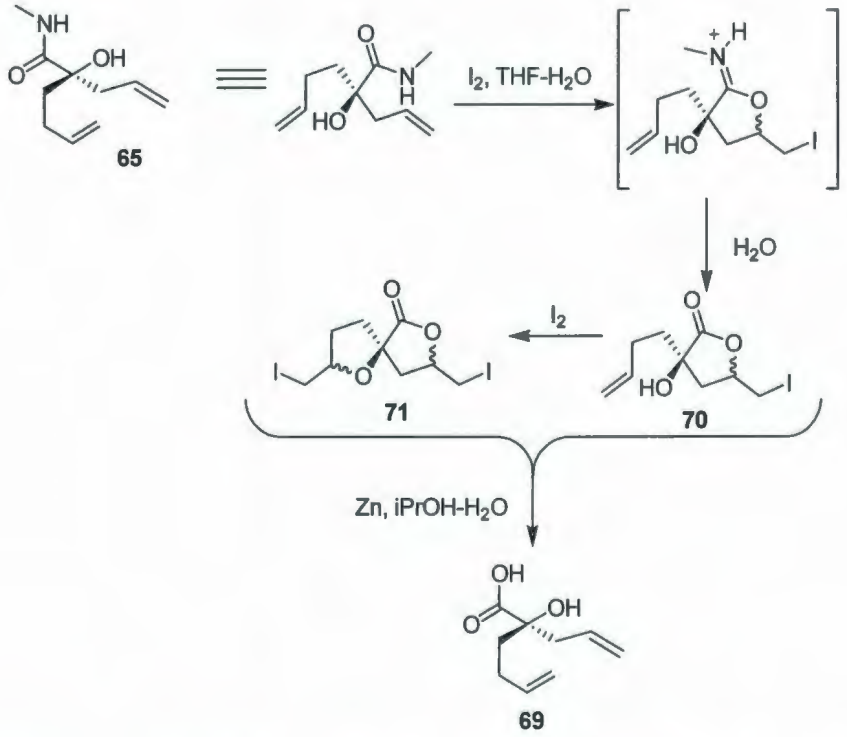


65

The failure of the amide hydrolysis and complications with the alkene oxidation in **65** prompted the exploration of an indirect hydrolytic strategy for conversion of the amide to a carboxylic acid. This involved a two step sequence that is shown in Scheme 24. Treatment of **65** with iodine (2.5 molar equiv.) yielded a mixture of products, which was probably obtained by iodolactonization involving the amide and the allyl group, and

iodoetherification of some of the iodolactone by reaction of the tertiary alcohol with the butenyl group to generate a spiro ring system. The exact sequence of these events is not known. In principle, the lactonization as well as the iodoetherification products should readily generate the required acid **69** after metallation with zinc.

Scheme 24

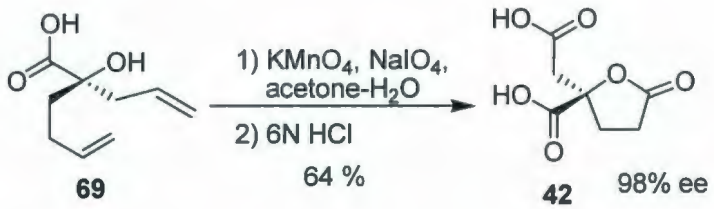


Fortunately, when the mixture of products (**70**, **71**) obtained by iodolactonization/iodoetherification was subjected to dehalogenative elimination with zinc, the hydroxy acid **69** was obtained in excellent yield (91%). This observation provided some credence to the proposed reactions of **65** (Scheme 24) with iodine.

The final step of the synthesis required the oxidative cleavage of the two terminal alkenes in **69** (Scheme 25). This was readily achieved by treating **69** with $KMnO_4$ and

$NaIO_4$ in aqueous acetone. Acidification of a sodium bicarbonate extract of the crude reaction product furnished (*R*)-homocitric acid γ-lactone **42** (64%, 98% ee).

Scheme 25



The specific rotation of the isolated lactone was in agreement with that of the natural product ($[\alpha]^{23}_D$ -57.0 (*c* 1, H_2O); (lit.[6c] $[\alpha]^{23}_D$ -48.9 (*c* 0.38, H_2O)). This new synthesis of (*R*)-homocitric acid γ-lactone proceeds with an overall yield of 20% starting from commercially available (1*R*,2*S*)-ephedrine.

Conclusions:

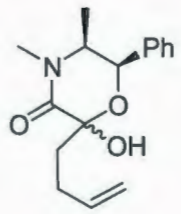
In conclusion, an enantioselective synthesis of (*R*)-homocitric acid γ-lactone by using the ephedrine dione-based protocol for α-hydroxy acid synthesis was demostrated. The approach is flexible and several variations can conceivably be incorporated if desired. For example, the antipode of (*R*)-homocitric acid γ-lactone can be easily made by using the enantiomer of ephedrine. Also, it may be noted that the use of labelled butenyl Grignard reagents[31] prepared from 4-bromobutene deuterated at C-4 should allow the introduction of deuterium into the lactone ring of **42**. Similarly, the use of deuterated allyltrimethylsilanes[32] should provide access to homocitrate that is deuterated in the

acetate side chain. The synthesis is therefore well suited for the preparation of labelled homocitrates[20a] that may be of interest in biological studies.

Lastly, it should be mentioned that this route in conjunction with the stereoselective synthesis of (-)-quinic acid, clearly illustrates the utility of the protocol for the synthesis of α-hydroxy acids.

Experimental:

(5*S*, 6*R*)-2-(But-3-enyl)-2-hydroxy-4,5-dimethyl-6-phenylmorpholin-3-one (67):



To a suspension of **32** (1.75 g, 8.0 mmol) in anhydrous ether (25 mL) at 0 °C was added 3-butenylmagnesiumbromide (prepared from 600 mg of Mg and 2.6 mL of 4-bromo-1-butene in ether (25 mL)) and the mixture was warmed up to ambient temperature. The reaction mixture was stirred 3 h at ambient temperature and the precipitated solids were dissolved with saturated aqueous NH_4Cl solution. The resulting mixture was extracted with ethyl acetate (3 x 30 mL), the combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the crude product by flash chromatography on silica gel (2/1 ethyl acetate/hexane) gave 1.8 g (82%) of **67** as a white solid (1.8/1 mixture of diastereomers).

^{1}H NMR:

δ (500 MHz, $CDCl_3$): 7.4-7.3 (m, 5H), 5.92-5.81 (m, 1H), 5.21 (d, 1H, J = 3.4), 5.1-5.0 (m, 1H), 4.95-4.92 (m, 1H), 3.51 (dq, 1H, J = 3.4, 7.3), 3.4 (bs, 1H), 3.0 (s, 3H), 2.42-2.37 (m, 1H), 2.25-2.21 (m, 3H), 1.05 (d, J = 7.3, 3H).

^{13}C NMR (125.8 MHz, $CDCl_3$):

δ 169.6, 138.2, 137.2, 128.4, 127.7, 125.5, 114.6, 98.0, 73.4, 59.2, 34.9, 33.8, 26.1, 12.5.

Visible peaks of the minor diastereomer:

^{1}H NMR (500 MHz, $CDCl_3$):

δ 5.53 (d, 1H, J = 3.0), 3.04 (s, 3H), 0.99 (d, J = 6.6, 3H).

^{13}C NMR (125.8 MHz, $CDCl_3$):

δ 168.5, 138.2, 137.7, 128.5, 127.8, 125.9, 115.0, 97.8, 71.5, 59.5, 38.7, 33.8, 28.0, 12.8.

IR (solid):

3306, 1645, 902, 735, 695, 668 cm^{-1}.

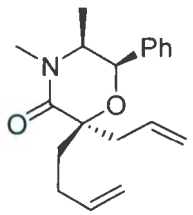
MS (APCI, positive):

m/z 148.1 (25), 164.1 (10), 258.1 (10), 276.1 (M+1, 75).

HRMS (CI, methane):

m/z 276.1603 (276.1600 calc. for $C_{16}H_{22}NO_3$, M+H).

(2*R*,5*S*,6*R*)-2-Allyl-2-but-3-enyl-4,5-dimethyl-6-phenylmorpholin-3-one (68):



To a solution of **67** (1.8 g, 6.6 mmol) in dichloromethane (65 mL) at –78 °C was added $TiCl_4$ (4.3 mL, 39.3 mmol) and allyltrimethylsilane (6.3 mL, 39.3 mmol). The mixture was gradually warmed to – 40 °C and allowed to stir at this temperature for 4.5 h. Saturated NH_4Cl was added and the mixture was warmed to ambient temperature. Water was added, the biphase was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was

purified by flash chromatography on silica (2/1 ethyl acetate/hexane) to give 1.34 g (68%) of **68** as a colorless gum.

^{1}H NMR ($CDCl_3$):

δ 7.38-7.28 (m, 5H), 5.89-5.80 (m, 2H), 5.26 (d, 1H, J = 2.4), 5.10-5.00 (br m, 3H), 4.97 (br d, 1H, J = 10.5), 3.51 (dq, 1H, J = 6.5, 2.4 Hz), 3.03 (s, 3H), 2.86 (dd, 1H, J = 14.7, 6.2,), 2.55 (dd, 1H, J = 14.7, 8.4), 2.42-2.38 (m, 1H), 2.05-2.00 (m, 2H), 1.92-1.85 (m, 1H), 0.98 (d, 3H, J = 6.5).

^{13}C NMR (125.8 MHz, $CDCl_3$):

δ 171.4, 138.7, 138.3, 133.1, 128.6, 127.8, 125.8, 118.5, 114.8, 82.0, 71.8, 59.5, 40.4, 37.5, 34.0, 28.8, 13.4.

IR (neat):

2978, 1640, 1146, 913, 759, 700 cm^{-1}.

MS (APCI, positive):

m/z 258.1 (7), 300.1 (M+1, 100).

HRMS (CI, methane):

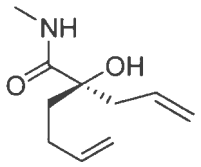
m/z 300.1968 (300.1964 calc. for. $C_{19}H_{26}NO_2$, M+H).

Enantiomeric excess (HPLC):

Chiralpak AD-H column, hexane/isopropyl alcohol 98:2, flow rate 1 mL/min, t_R (major): 7.6 min., t_R (minor): 8.4 min., 98% ee.

$[\alpha]^{23}_D$ = - 48 (c 1, CH_2Cl_2).

(2*R*)-2-Allyl-2-hydroxy-*N*-methylhex-5-enamide (65):



To anhydrous liquid ammonia (distilled over sodium) was added Na (0.68 g, 29.4 mmol) at –78 °C and the mixture was stirred for 15 min. To the resulting blue solution was added a solution of **68** (1.15 g, 4.2 mmol) in anhydrous THF (2.5 mL) and the mixture was stirred for 4.5 min. A mixture of 2/1 methanol/water (3mL) 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 column chromatography on silica gel (3/2 ethyl acetate/hexane) to yield **65** (620 mg, 81%) as a white solid.

Mp: 75-76 °C.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 6.90 (bs, 1H), 5.84-5.73 (m, 2H), 5.17 (br m, 2H), 5.02 (br dd, 1H, J = 8.8, 1.6), 4.95 (br d, 1H, J = 10.1 Hz,), 3.05 (s, 1H), 2.82 (d, 3H, J = 5.4 Hz), 2.68 (dd, 1H, J = 14.3, 6.7), 2.34 (dd, 1H, J = 14.3, 8.2), 2.24-2.16 (m, 1H), 2.03-1.94 (m, 2H), 1.69-1.63 (m, 1H).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 175.2, 138.3, 132.8, 120.0, 114.9, 77.5, 44.2, 38.4, 28.1, 26.0.

IR (solid):

3346, 2949, 1641, 1550, 1127, 993, 953, 903 cm^{-1}.

MS (APCI, positive):

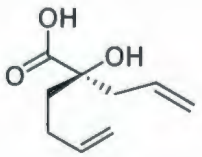
184.1 (M+1, 100).

HRMS (CI, methane):

m/z 184.1335 (184.1338 calc. for $C_{10}H_{18}NO_2$, M+H).

$[\alpha]^{23}_D$ = +14.0 (c 1, CH_2Cl_2).

(2*R*)-2-Allyl-2-hydroxyhex-5-enoic acid (69):



Iodine (610 mg, 2.4 mmol) was added to a solution of **65** (200 mg, 1.1mmol) in 1:1 THF-H_2O (6 mL) and the solution was stirred in the dark for 12 h. The solution was then extracted with ethyl acetate (3 x 10 mL) and the combined organic layers were washed with saturated aqueous sodium thiosulphate, dried (Na_2SO_4) and concentrated under reduced pressure to yield 240 mg of yellow oil. This was dissolved in 3:1 isopropyl alcohol:water (12 mL) and zinc (240 mg, 3.7 mmol) was added. The mixture was heated to reflux for 4 h and cooled to room temperature and filtered. The residue was washed with acetone (4 x 10mL) and the combined filtrates were concentrated under reduced pressure. The resulting solid was dissolved in ethyl acetate (20 mL) and the solution was extracted with saturated aqueous sodium bicarbonate (3 x 10mL). The combined extracts were acidified with 3 N HCl and the acidic solution was extracted with ethyl acetate (3 x 15 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced

pressure to yield 170 mg (91%) of **69** as a white solid. This material was pure (^{1}H NMR) and was used directly in the next step.

Mp: 90-91 °C.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 5.87-5.78 (m, 2H), 5.21-5.00 (br m, 1 H), 5.19 (d, 1H, *J* = 5.9), 5.07 (br dd, 1H, *J* = 15.6, 1.4), 4.99 (dd, 1H, *J* = 8.7, 1.4), 3.00 (broad, 1H), 2.60 (dd, 1H, *J* = 6.8, 13.8), 2.46 (dd, 1H, *J* = 13.8, 7.2), 2.32-2.25 (m, 1H), 2.06 (s, 1H), 2.10-2.01 ((m, 1H), 1.94 (m, 1H), 1.82 (m, 1H).

^{13}C NMR (125.77 MHz, CD_2Cl_2):

δ 177.7, 138.3, 132.4, 120.3, 115.5, 77.7, 44.3, 38.3, 28.5.

IR (solid):

3078, 2954, 1718, 1642, 1094, 995, 915 cm^{-1}.

MS (APCI, negative):

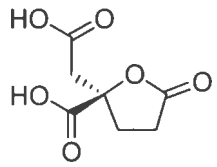
169.1 (M-1, 100).

HRMS (CI, methane):

m/z 169.0866 (169.0865 calc. for. $C_9H_{13}O_3$, M-H).

$[\alpha]^{23}_D$ = -10.6 (c 1, CH_2Cl_2).

(*R*)-5-Carboxy-5-carboxymethyl-dihydrofuran-2(3*H*)-one (42):



To a solution of **69** (120 mg, 0.71 mmol) in acetone (3 mL) was added a solution of $KMnO_4$ (34 mg, 0.22 mmol) in water (20 mL). The mixture was stirred for 10 min, solid $NaIO_4$ (1.8 g, 8.5 mol) was added and the purple mixture was stirred for 48 h at ambient temperature. Methanol (5 mL) and conc. HCl (0.4 mL) were added and the mixture was stirred vigorously for 15 min. The resulting brick red mixture was filtered, the solids were washed with acetone and the combined filtrates were concentrated under reduced pressure. The residue obtained was dissolved in saturated aqueous sodium bicarbonate the solution was washed with ethyl acetate (2 x 15 mL). The aqueous layer was acidified with aqueous 6 N HCl and the acidic solution was concentrated to dryness. The residue was extracted with acetone (3 x 15mL) and the combined acetone extracts were concentrated under reduced pressure. The solid obtained was purified by flash chromatography on a short silica gel column (2/1 hexane/acetone) to yield 85 mg (64%) of **42** as a white solid.

Mp: 146-147 °C (Lit.[1] mp: 146-148 °C;).

^{1}H NMR (500 MHz, D_2O):

δ 3.22 (d, 1H, *J* = 16 Hz), 2.96 (d, 1H, *J* = 16 Hz), 2.72 (br t, 2H, *J* = 7.5), 2.37-2.33 (m, 1H), 2.33-2.29 (m, 1H).

^{1}H NMR (500 MHz, d_6 acetone):

δ 3.21 (d, 1H, J = 17.1), 3.02 (d, 1H, J = 17.1), 2.71-2.68 (m, 2H), 2.57-2.52 (m, 1H), 2.49-2.42 (m, 1H).

^{13}C NMR (125.77 MHz, d_6 acetone):

δ 176.9, 174.2, 171.1, 83.9, 42.3, 32.4, 28.9.

IR (neat):

2952, 1793, 1683, 995, 945 cm^{-1}.

MS (APCI, negative): 187.1 (M-1, 100).

$[\alpha]^{23}_{D}$ = -57.0 (c 1, H_2O); lit.[2] $[\alpha]^{20}_{D}$ = -48.9 (c 0.38, H_2O).

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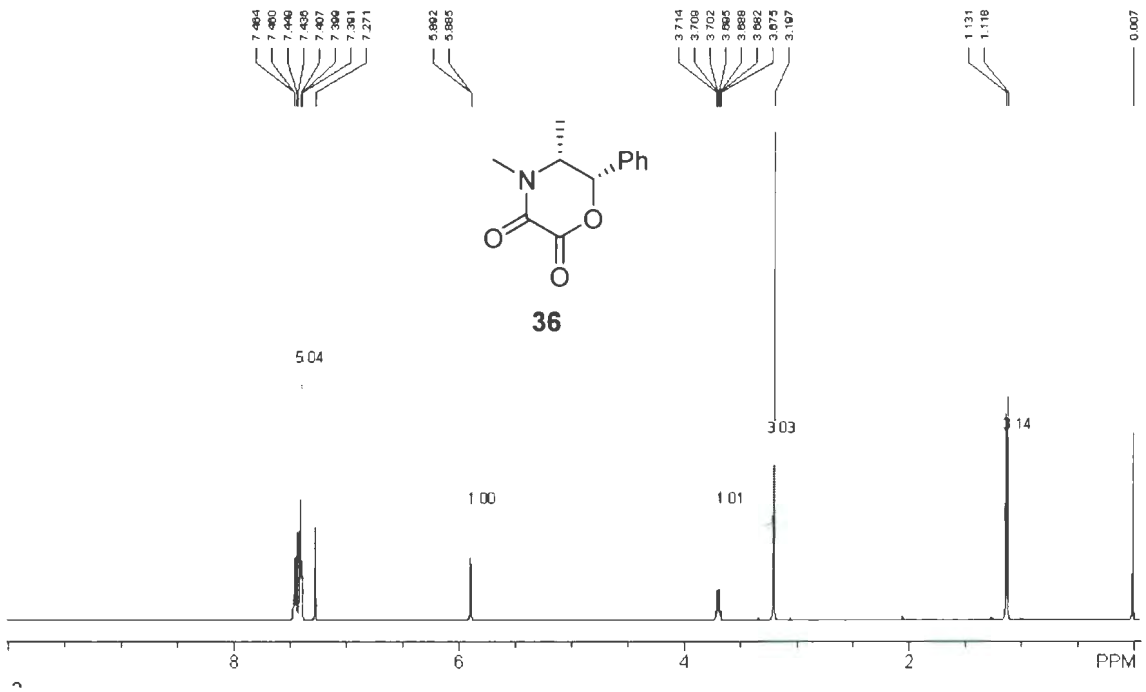
Appendix 1:

^{1}H and ^{13}C NMR Spectra for Chapter 2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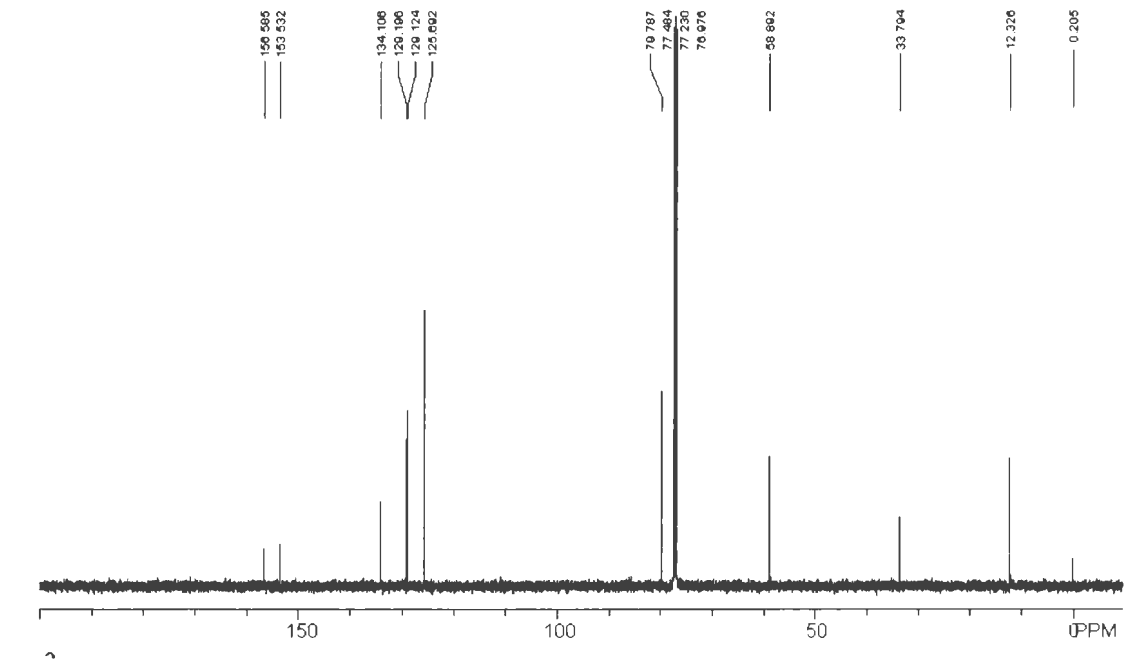
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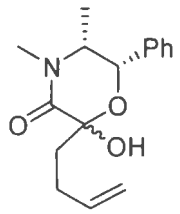
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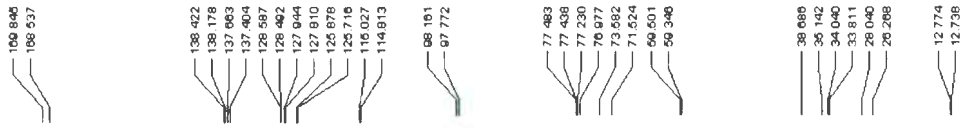
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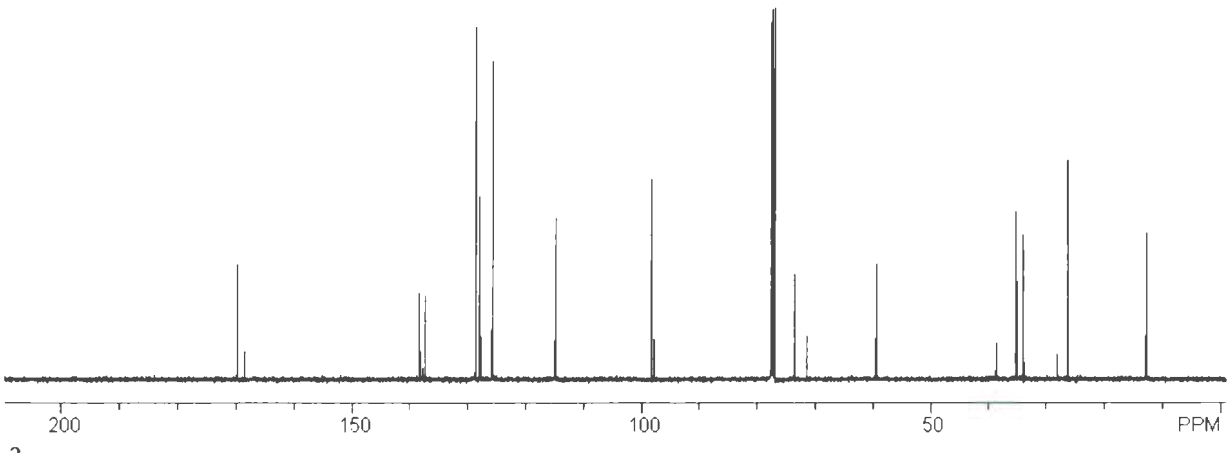
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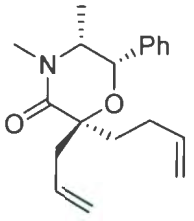
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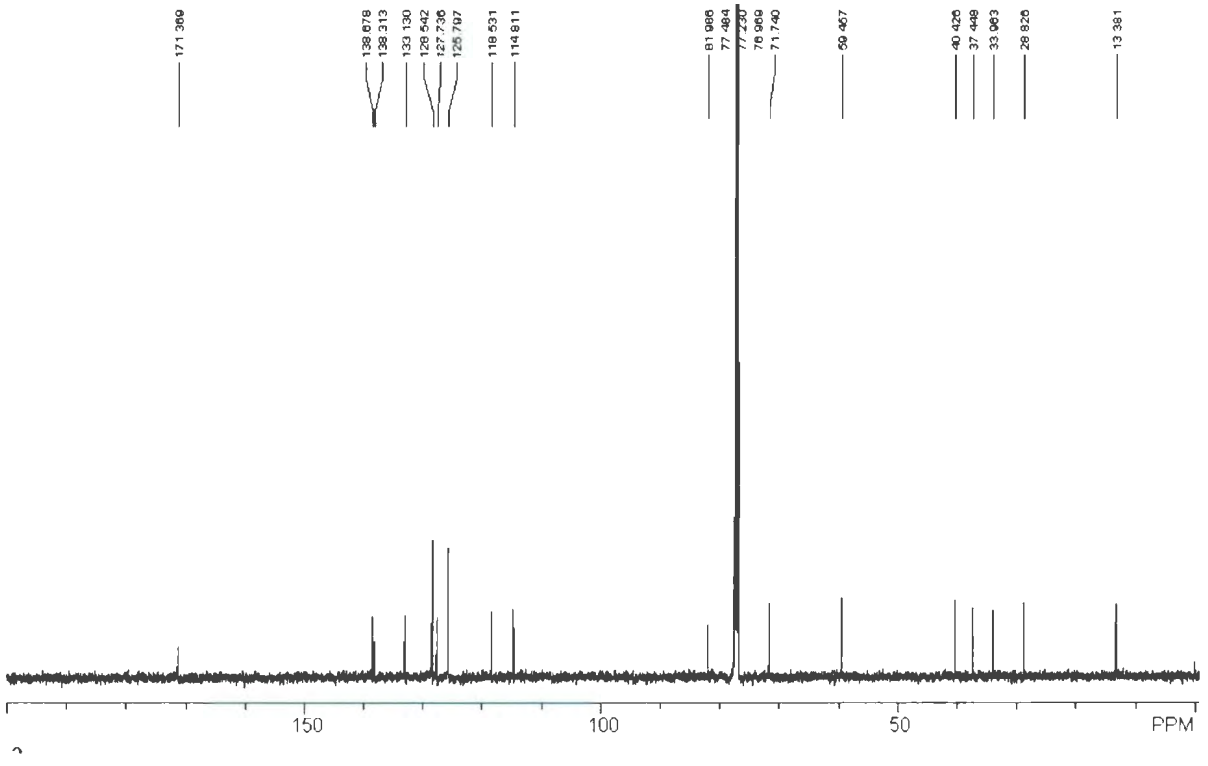
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118.531
114.811
81.966
77.484
77.230
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71.740
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33.963
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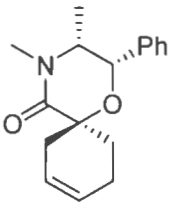
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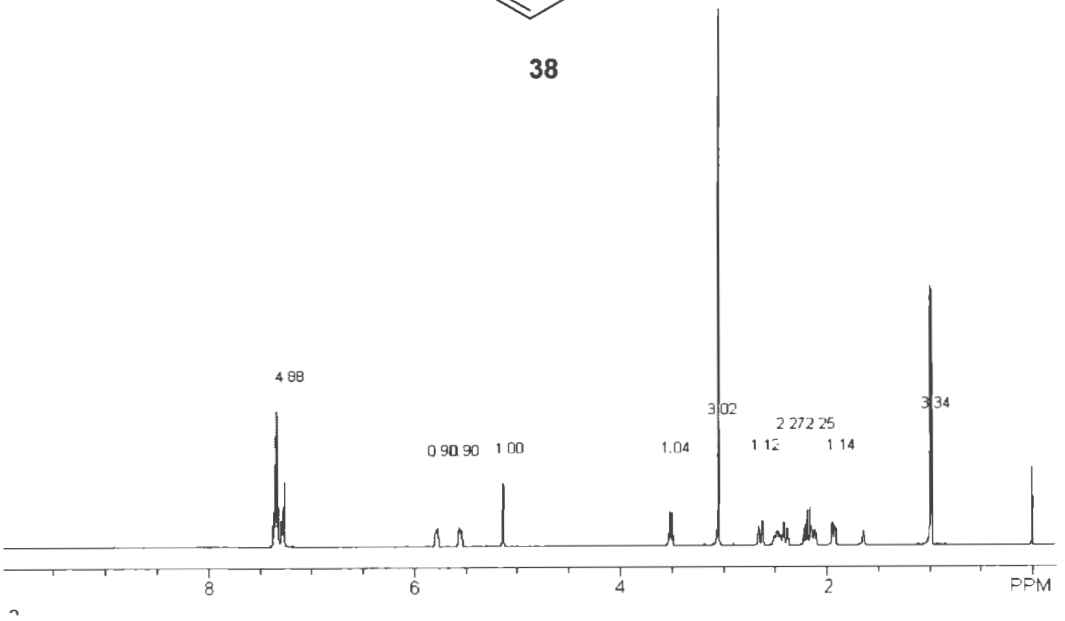
O
O
Ph

38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2.27 2.25
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3.34
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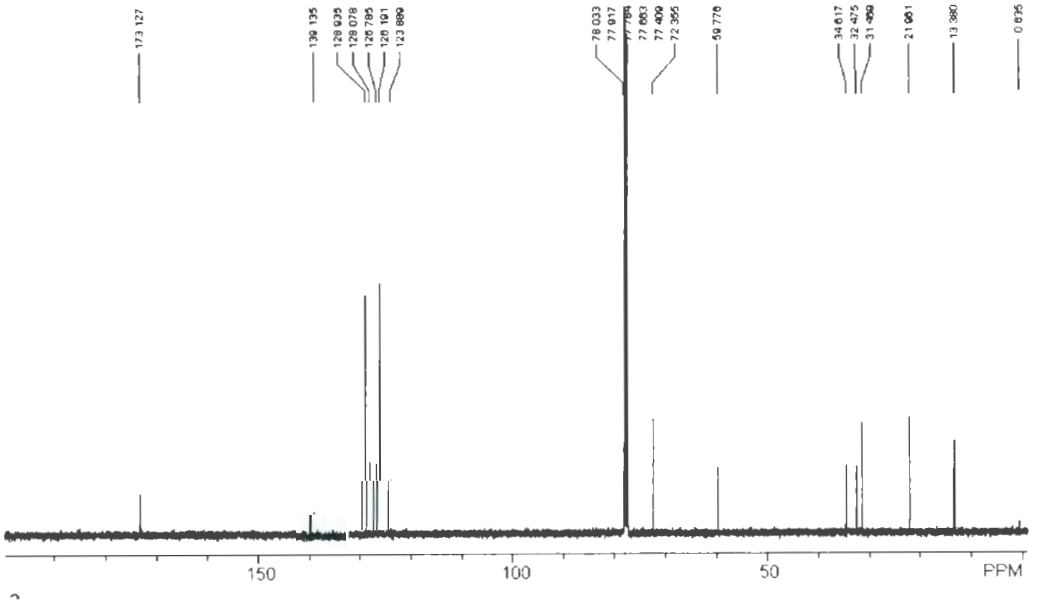
6
4
2
PPM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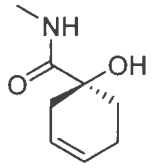
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O
OH

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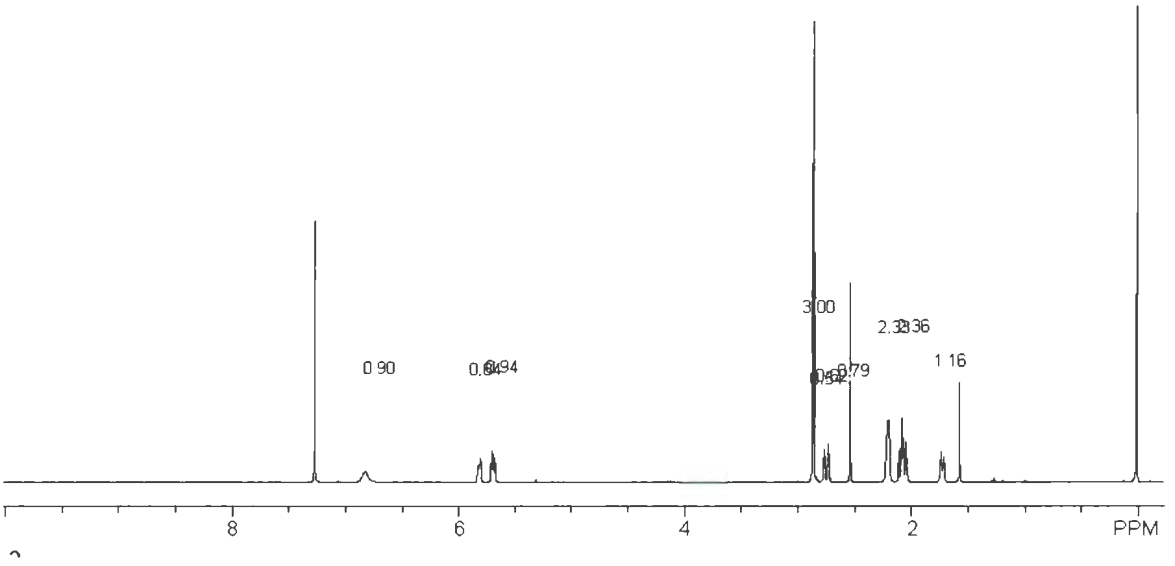
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6
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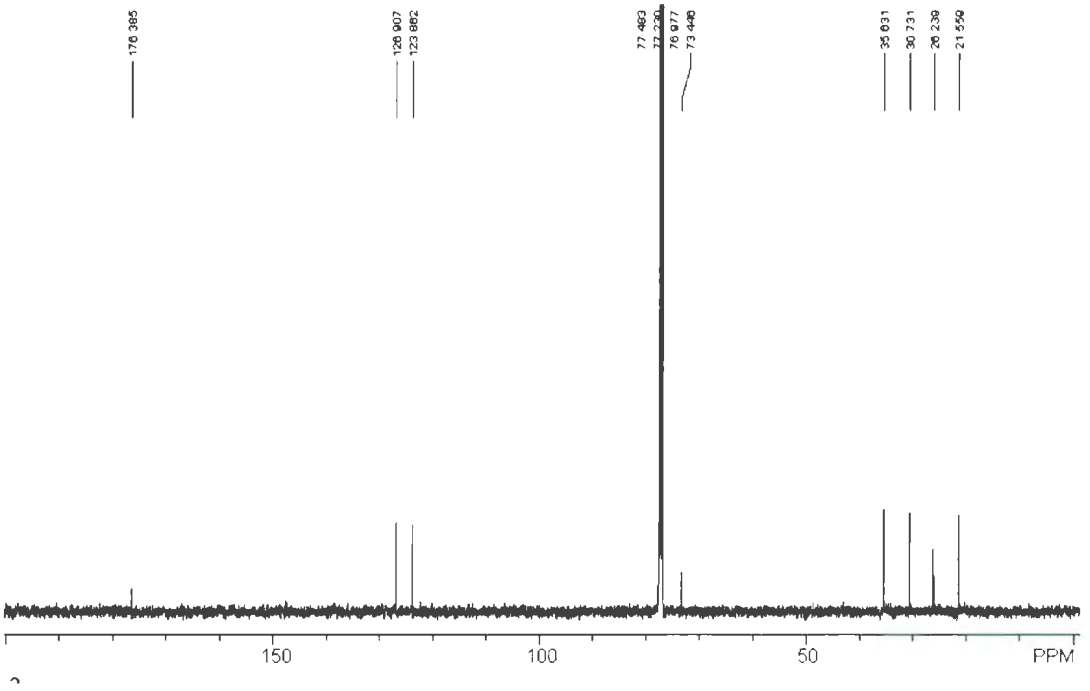
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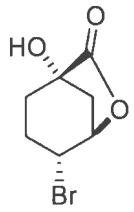
100
50
PPM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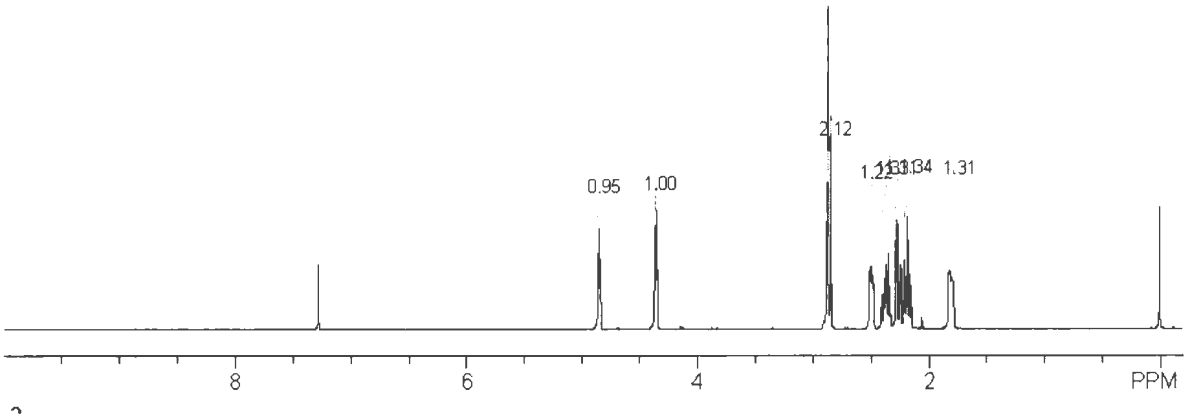
O
O
Br

8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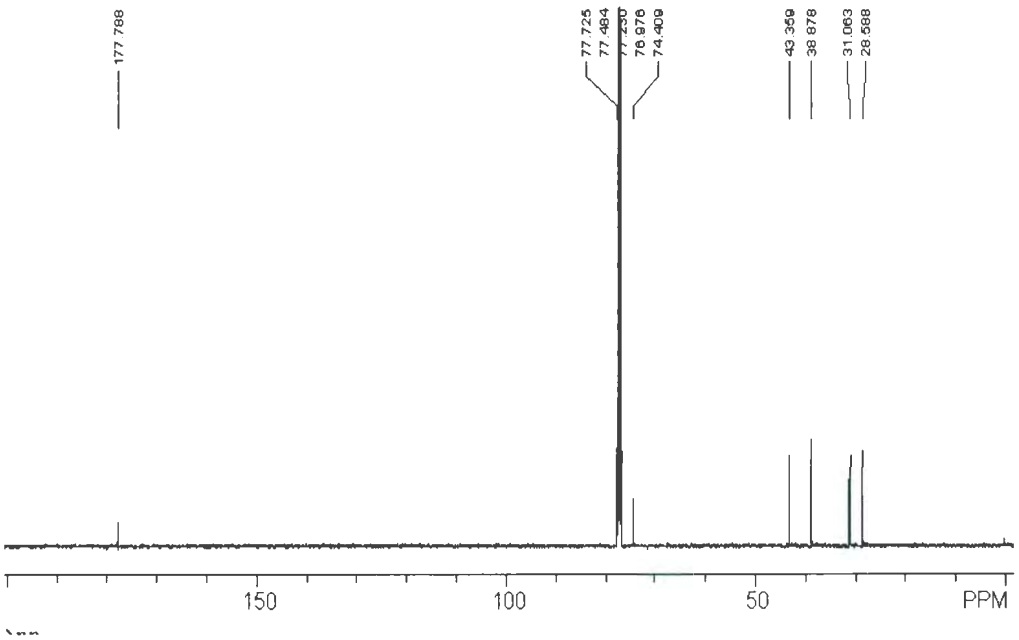
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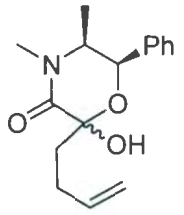

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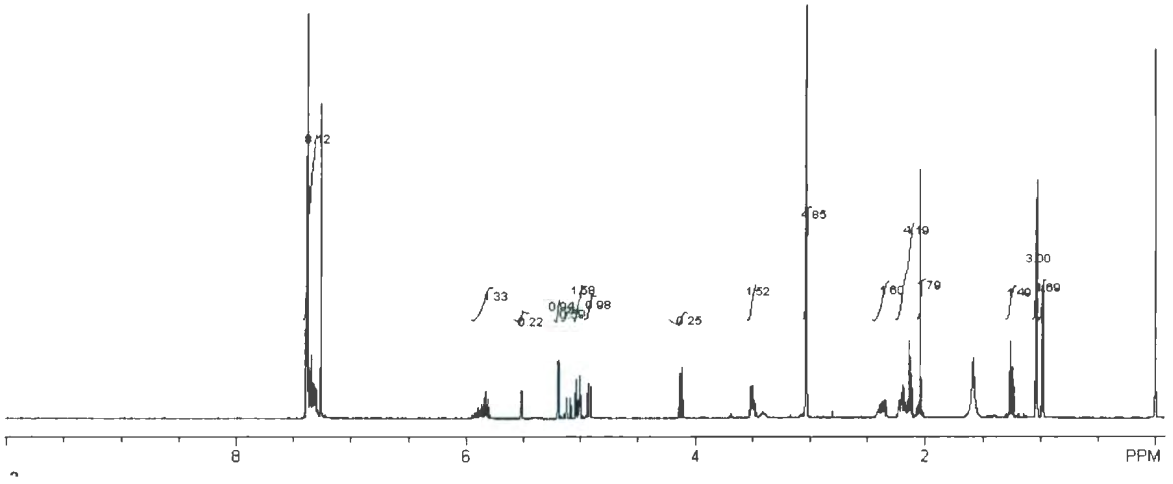
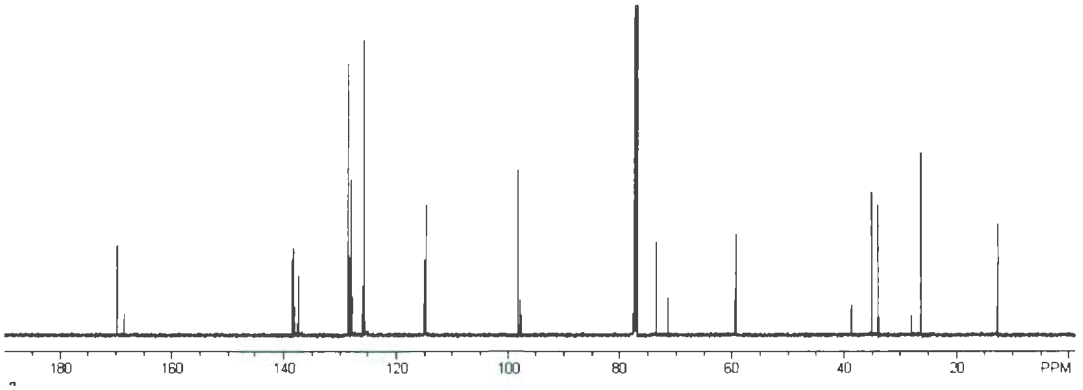
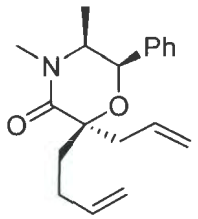
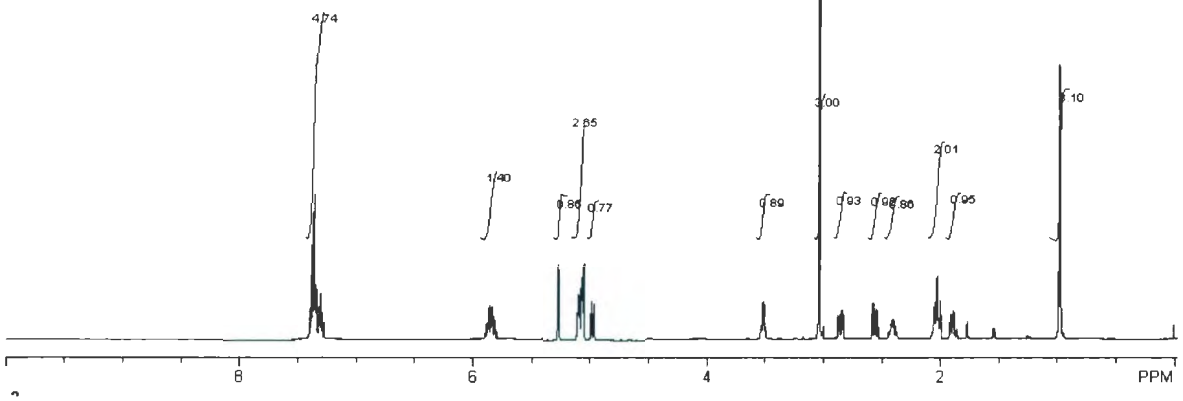





Ph
N
O
O

68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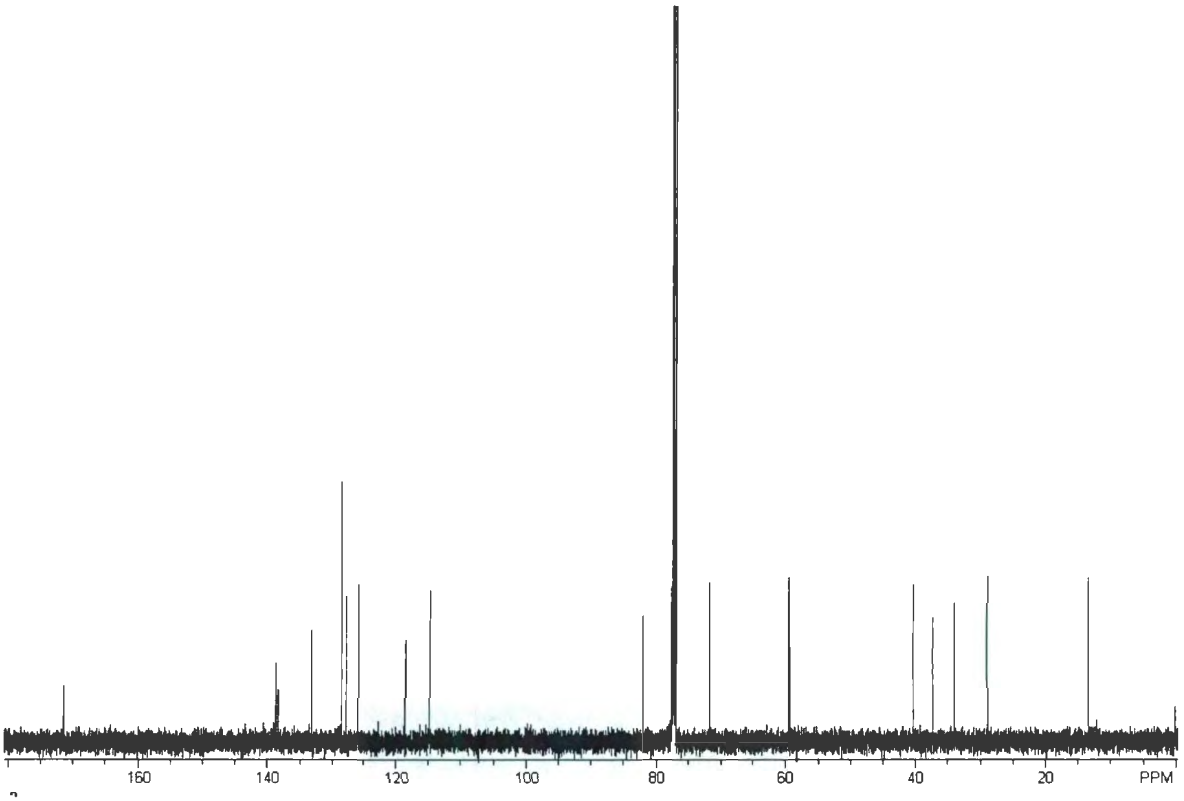
6
4
2
PPM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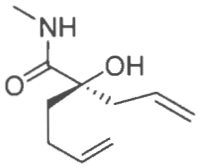
80
60
40
20
PPM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O
OH

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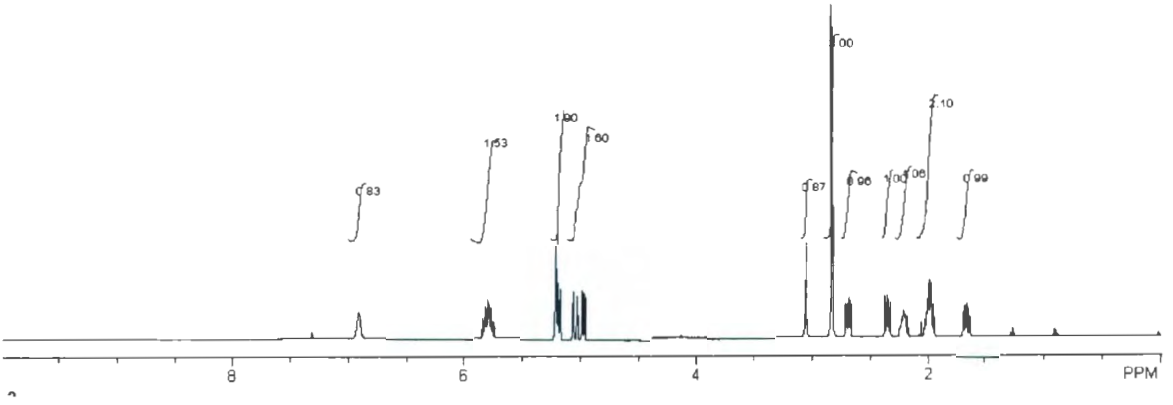
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4
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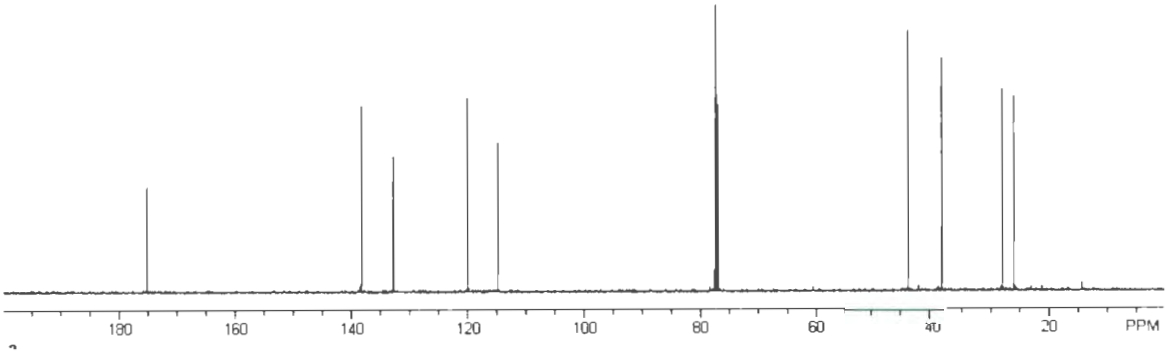
PPM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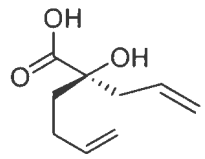
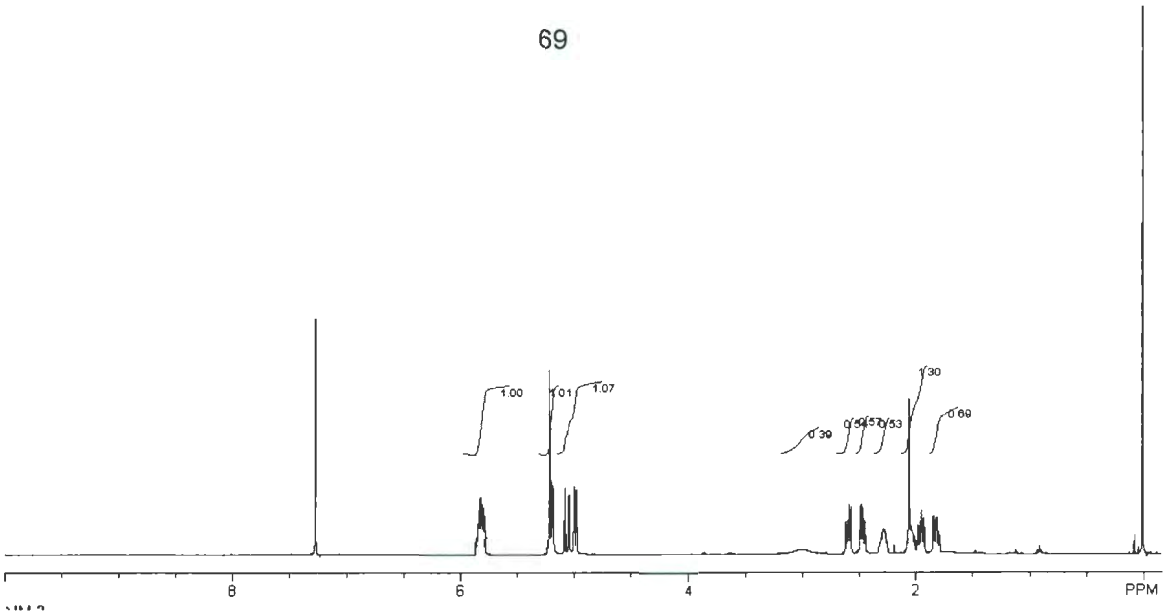
140
120
100
80
60
40
20
PPM


OH
O
OH

69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1.30
0.69
8
6
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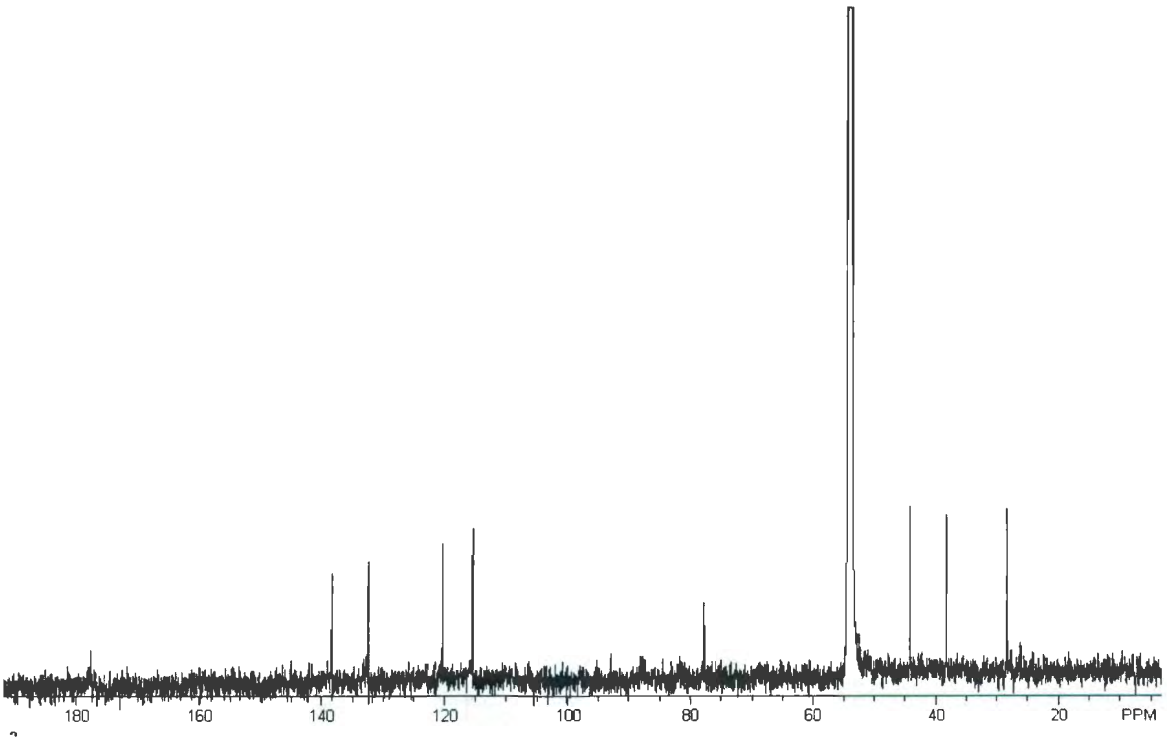
2
PPM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160
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80
60
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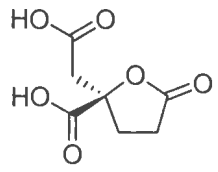

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Chapter 3

Enantioselective Synthesis of Functionalized Medium-Sized Oxacycles

Part of the work described in this chapter has been published in

Organic Letters **2006**, *8*, 5897

Introduction

A significant number of natural products contain medium-sized oxacycles in their molecular framework. These natural products range from complex ladder-like polyethers such as brevetoxin, to other functionalized monocycles such as laurencin, lobatrienol and rogioloxepane (Figure 1). Several members of this class are under pharmacological investigations owing to their high ion-channel blocking,[1] antiviral[2] and antifungal activities.[3]

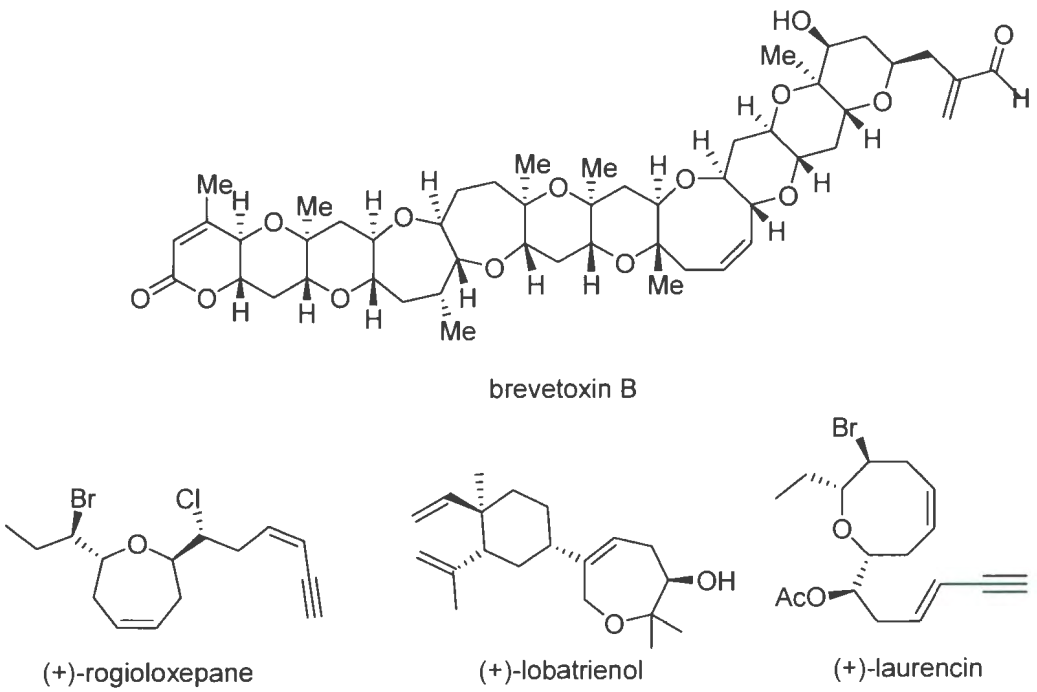


Figure 1. Natural products having the medium-sized oxacycle framework.

From a synthetic perspective, assembling these medium-sized scaffolds (especially eight-membered rings) is difficult primarily due to the following factors:[4]

- Entropic disfavour (making the ends of the ring meet)
- Imperfectly staggered conformations (Pitzer strain)
- Bond angle deformations (Baeyer strain)
- Destabilizing transannular interactions (enthalpic disfavour)

Nevertheless, these issues have been addressed and, both general[5] and target-oriented[6] strategies that address the stereoselective assembly of medium-sized oxacycles are reported in the literature. Several reviews covering this topic are available.[7] The following summary provides an overview of recently reported, general approaches to the stereoselective synthesis of medium-ring ethers.

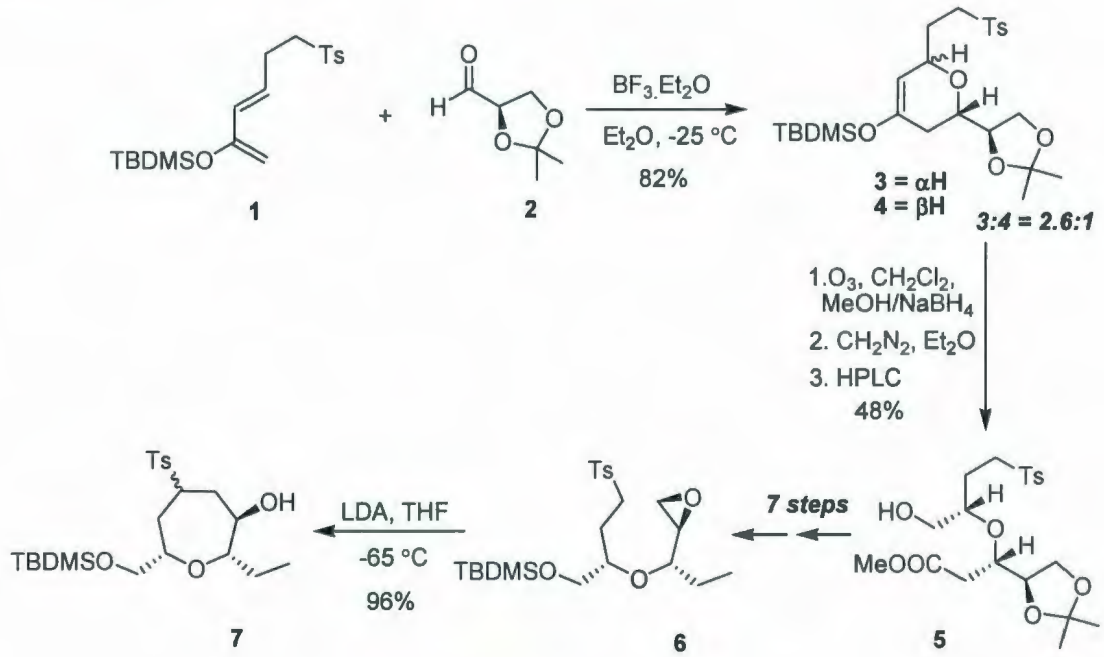
Recent developments in the stereoselective synthesis of medium-ring ethers.

- **Cyclization by C-C bond formation.**

Palenzuela and co-workers[5k] reported an enantioselective synthesis of the α,β,α'-trisubstituted cyclic ethers. Their approach starts with a hetero Diels-Alder reaction and the resulting adduct is transformed into a linear ether which in turn is cyclized to give the corresponding oxacycle. Thus, reaction of the diene **1** with the aldehyde **2** gave the dihydropyrans **3** and **4** as a 2.6:1 mixture of diastereomers (Scheme 1). The cycloaddition products were treated with ozone, followed by $NaBH_4$ reduction, and the resulting mixture was methylated using diazomethane to yield a mixture of diastereomeric hydroxy

esters **5**. At this point the diastereomers were separated by HPLC and the major isomer **5** was converted into the epoxide **6**. Treatment of the linear ether **6** with LDA effected the cyclization to afford the oxepane **7**. Synthesis of an oxocane (8-membered ring) and an oxonane (9-membered ring) related to **7** was also demonstrated by using the appropriate dienes as starting materials.

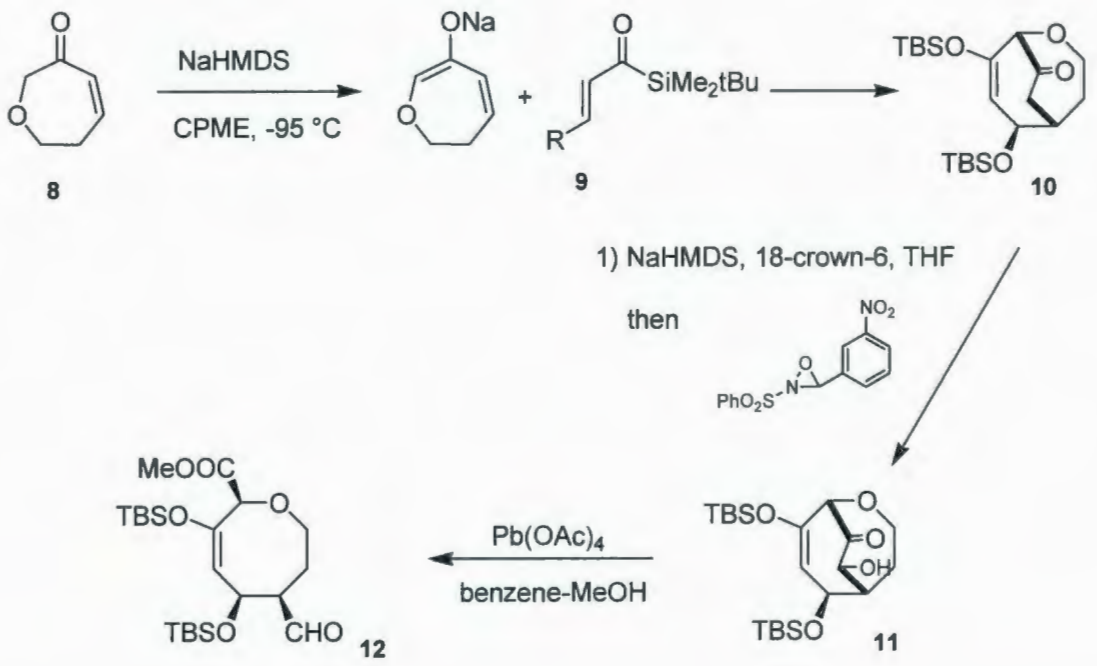
Scheme 1



Takeda[5f] reported a [3+4] annulation-based strategy for the construction of eight-membered oxacycles. In this method, the reaction of β-substituted acryloylsilane **9** and the enolate of 6-oxacyclohept-2-en-1-one **8** (Scheme 2) was utilized to generate the bicyclic derivative **10**. Cleavage of the internal tether in **10** was achieved by sequential α-hydroxylation of the ester and oxidative cleavage thereby generating the eight-membered oxygen heterocycle **12** as a single diastereomer. Although the synthesis is

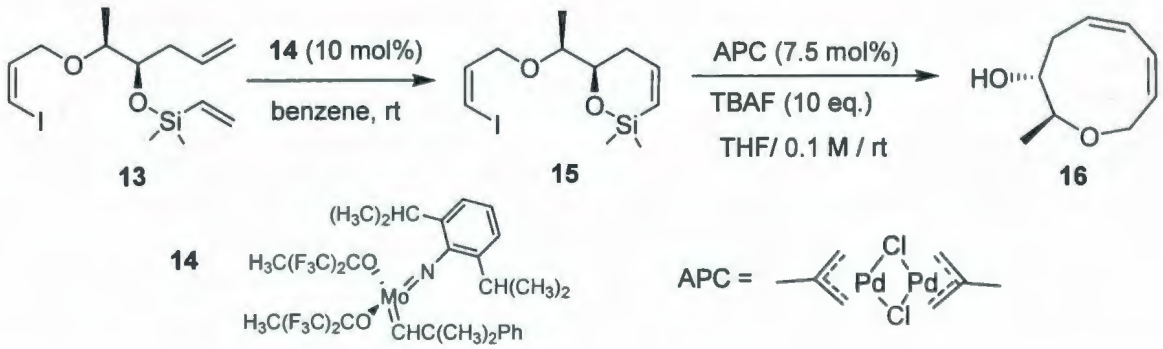
diastereoselective, the development of an enantioselective protocol by using this method has not been demonstrated.

Scheme 2



An intramolecular silicon-assisted cross-coupling reaction for the synthesis of medium-sized rings having a 1,3-*cis*-*cis*-diene unit was revealed by Denmark.[6f] The substrate **13** (prepared in seven steps from propargyl alcohol) was subjected to a RCM reaction using Shrock's molybdenum complex **14** as the catalyst (Scheme 3). The resulting cyclic ether **15** was then subjected to a Pd-catalyzed cross coupling reaction by employing allylpalladium chloride (APC) dimer as the catalyst to obtain the nine-membered heterocycle **16** in good yield (77%). The method employed mild reaction conditions and provided an easy access to medium-sized rings having a 1,3-*cis*-*cis*-diene unit.

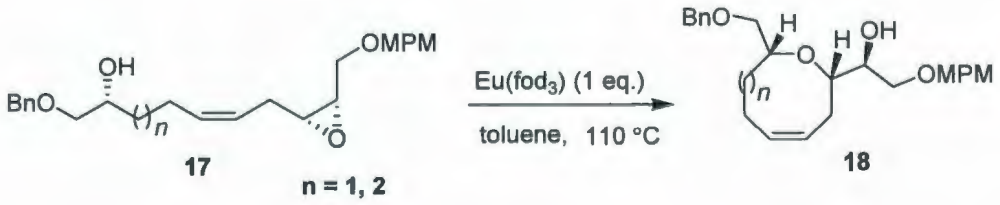
Scheme 3



- **Cyclization by C-O bond formation.**

Suzuki and co-workers[5b] reported a stereospecific synthesis of eight- and nine-membered cyclic ring ethers via Lewis acid mediated cyclization of hydroxy epoxides. This conceptually simple method was demonstrated by treating *cis*-alkenes such as **17** with $Eu(fod)_3$ to provide the corresponding cyclic ethers **18** in good yield (76-97%, Scheme 4).

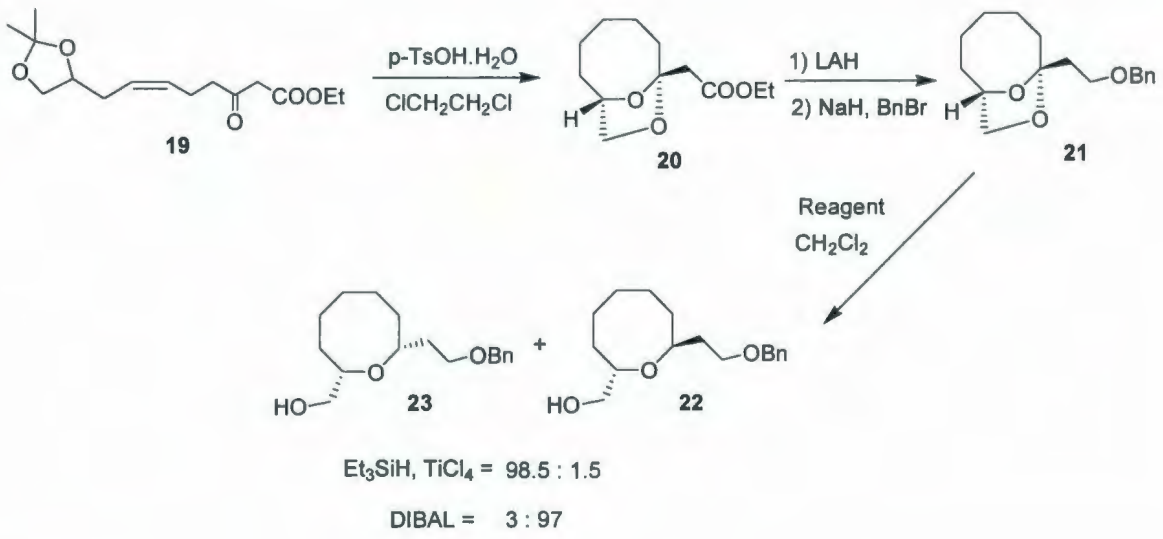
Scheme 4



Kotsuki revealed an interesting route to medium-sized oxacycles via chiral acyclic *cis*-alkene intermediates like **19**.[8] Transformation of **19** to the bicyclic ketal **20** was achieved by treatment of **19** with a catalytic amount of *p*-TsOH. Reduction of the ester in **20** followed by protection of the resulting alcohol as a benzyl ether gave **21**. Interestingly, it was shown that predominant generation of either the *cis* or *trans* α,α'-disubstituted oxacycles could be achieved from **21** by using different reducing reagents. Thus the

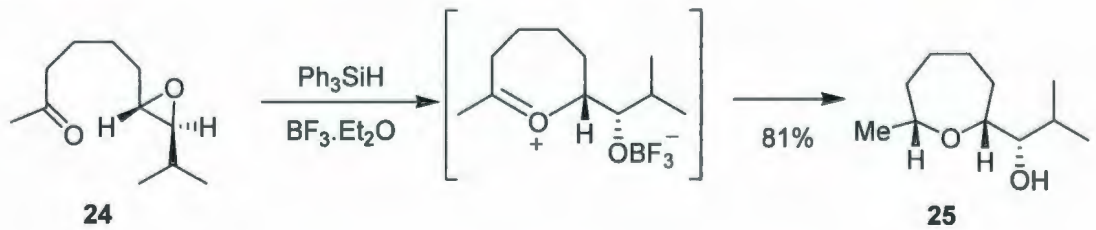
combination of $TiCl_4$ and trimethylsilane gave predominantly the *cis* isomer **23** (71%) whereas DIBAL reduction of **21** gave the *trans* isomer **22** (89%).

Scheme 5



Fotch and Chamberlin[9] have described a method involving intramolecular opening of the epoxide in keto epoxide **24** by the carbonyl oxygen (Scheme 6). The resulting oxocarbenium species is reduced *in situ* to generate the cyclic ether **25** in good yields.

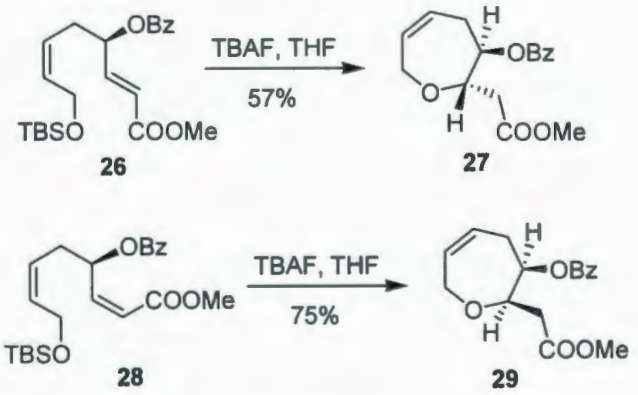
Scheme 6



Martin *and* co-workers[10] have demonstrated the synthesis of oxepanes by an intramolecular hetero-Michael reaction (Scheme 7). Interestingly, the stereochemistry of

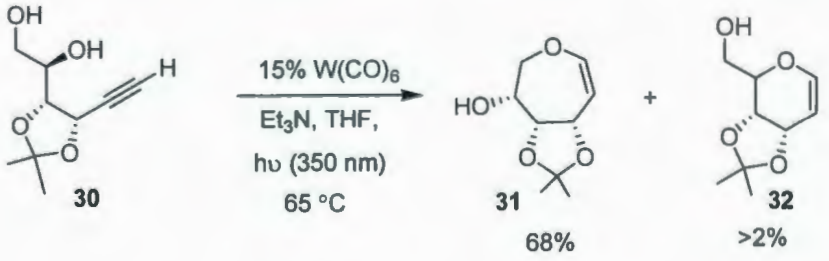
the cyclization could be controlled by the double bond geometry of the Michael acceptor, and therefore either diastereomer of the oxepane can be readily accessed. The *cis*-double bond in the substrate was necessary for successful cyclization.

Scheme 7



MacDonald[5e] reported an accidental discovery of a novel route to seven membered oxacycles via *endo*-selective alkynol cycloisomerization. Attempted cyclization of the alkynyl diol **30** in the presence of $W(CO)_6$ did not provide the expected pyranose glycal analogue **32** (Scheme 8) but rather gave the seven-membered ring glycal **31** in 68% isolated yield. However, this protocol is limited to the synthesis of oxepanes only.

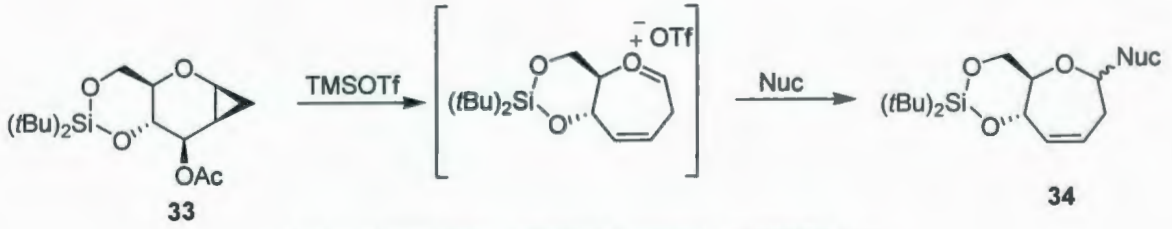
Scheme 8



- **Ring expansion**

Batchelor and Hoberg[6e] demonstrated a diastereoselective synthesis of seven-membered oxacycles by ring-expansion of cyclopropanated galactal. Galactal **33** could be reacted with a nucleophile in the presence of TMSOTf to afford the seven-membered cyclic ethers **34** in good-to-excellent yield, and moderate-to-high diastereoselectivity (68-91%, 43-97% de, Scheme 9).

Scheme 9

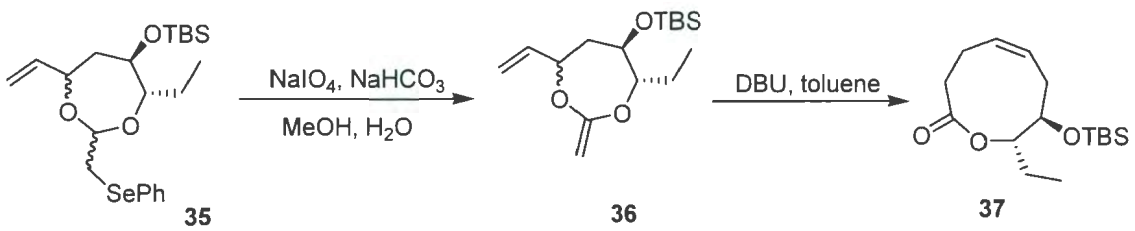


33 **34**

Nuc = Nucleophile = TMSallyl, $TMSN_3$, TMSSPh etc.

The application of a Claisen rearrangement of ketene acetals in the synthesis of nine-membered oxacylces was demonstrated by Holmes.[11] The easily prepared (79% over six steps) selenyl ether **35** was isolated as a mixture of three diastereoisomers. These were oxidized to the selenoxides and immediately heated to give the ketene acetals **36** which underwent Claisen rearrangement to give the lactone **37**. Notably, the ketene acetal (presumably a mixture of diastereoisomers) reacted to give lactone **37** as a single diastereomer (Scheme 10). Recently, the same group has used this method for the synthesis of fused bicyclic medium-ring oxacycles.[12]

Scheme 10



- **Ring-closing metathesis (RCM)**

The scope of the methods described above is limited to specific medium-sized frameworks and is largely defined by the ring-closing transformation. Fortunately, with recent advances in the field of organometallic catalysis for the ring-closing metatheses (RCM) reaction, a more general approach to these systems is now available.[13] In a typical example of RCM, two double bonds in an acyclic precursor **I** undergo metathesis in the presence of an organometallic catalyst to yield **II** with the evolution of ethane gas (Figure 2).

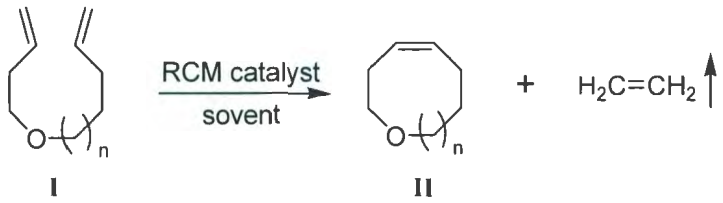


Figure 2. The ring closing metathesis strategy for the synthesis of medium-sized oxacycles.

Thus, with a relatively simple disconnection, one can easily define an acyclic intermediate that can provide the necessary target. Moreover, the reaction conditions are generally mild and product isolation is simple. Indeed, the metathesis protocol has just

been a boon to organic synthesis on a small scale, but also for preparations on industrial scale. Several RCM catalysts are commercially available.[14]

Nonetheless, the challenge of synthesis of the medium-sized oxacycles now lies in the construction of the acyclic RCM substrate and, not surprisingly, this has been the focus of some recent studies.[5b,i,j,6a,c,d] At the outset of these studies towards the synthesis of functionalized medium-sized oxacycles, it was decided to focus on the synthesis of chiral dienes and rely on the RCM reaction for generation of the cyclic ethers.

Objective:

The objective of this investigation was to explore the applicability of the ephedrine-based methodology described earlier (Chapter 1 and Chapter 2) for the enantioselective construction of functionalized seven-, eight-, and nine-membered oxacyles.

Results and discussion

From the viewpoint of retrosynthetic analysis of the medium-sized oxacycles, acyclic diene **V** was identified as the primary target. It was envisioned that the diene **V** could be obtained from epoxide **VI** via an epoxide opening/allylation sequence. The cyclization of the diene **V** can be acheived by employing the RCM protocol to provide the unsaturated oxacycle **IV** (Figure 3).

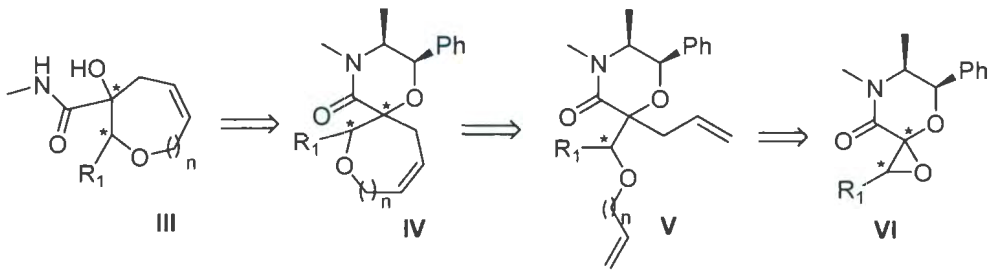


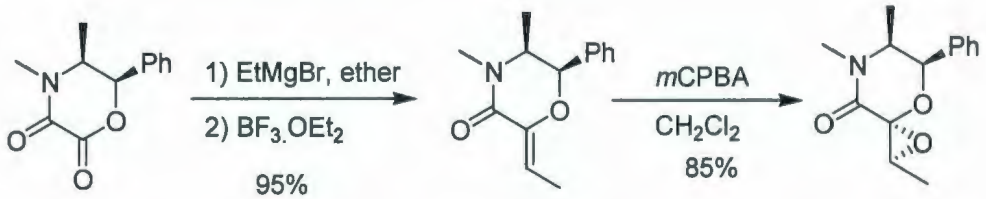
Figure 3. Retrosynthetic strategy for functionalized medium-sized oxacycles.

Removal of the ephedrine portion in **IV** would reveal oxacycle **III** having the versatile chiral α-hydroxy amide functionality, which in turn, can be used as a handle for further functionalization of the framework via transannular reactions.[15]

The first task was the synthesis of the spiro-epoxide **40** (Scheme 11). The synthesis of **40** began with the ephedrine-derived morpholine-dione **38** which was readily

prepared (85%) from commercially available (1*R*,2S)-ephedrine hydrochloride and ethyl oxalyl chloride, as described earlier (Chapter 1).

Scheme 11

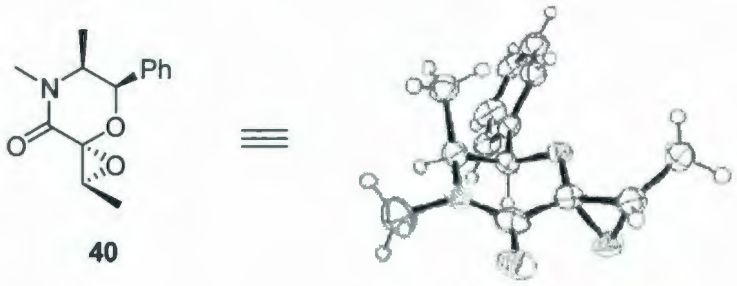


38 **39** **40**

A Grignard reaction of **38** with ethylmagnesium bromide gave the hemiacetal derived from addition to the lactone carbonyl in **38**. Dehydration of the hemiacetal was readily achieved by treatment with $BF_3.Et_2O$ to provide the alkylidene morpholine **39** (Scheme 11). Based on previous studies in this group, the trisubstituted olefin **39** was assigned the *Z* geometry on the basis of the chemical shift of the olefinic methine proton (δ 6.12 in **39**) as compared to its upfield shift in the *E* isomer (δ 5.75).[16,17] With the olefin **39** in hand, the stage was set for an epoxidation reaction. Epoxidation of **39** was readily achieved with *m*-CPBA and provided **40** in excellent yield (85 %).

Notably, the epoxide **40** was found to be quite a stable intermediate, and it could be easily purified by flash column chromatography and stored in the fridge for extended periods (>4 months). The planned transformations of the epoxide necessitated the determination of its absolute stereochemistry. Fortunately, due to its stability and crystalline nature, X-ray crystallographic analysis of epoxide **40** was possible. The ORTEP representation of **40** (**VII**) is shown in Figure 4 (see Appendix 3 for details).[18] As anticipated, the epoxidation of **39** had occurred *anti* to the phenyl and methyl groups in

the morpholine ring. Thus, having developed an easy access to **40** and ascertained its stereochemistry, it was now time to explore various strategies to open the epoxide ring.



40 **VII**

Figure 4. X-ray crystal structure of the epoxide **40**

The spiro epoxide was expected to behave as an ambident electrophile. Nucleophilic ring-opening of the epoxide in **40** was expected to proceed at the less hindered terminal carbon. In addition, in the absence of a Lewis acid, this reaction was anticipated to proceed with inversion of configuration (Figure 5).[19] On the other hand, Lewis acid- mediated ring-opening of **40** (Figure 5) should proceed via an oxocarbenium ion intermediate. The stereochemical course of nucleophilic substitution at this oxocarbenium ion (**IX**) was assumed to be identical to that in related oxocarbenium ions (see Chapter 1 and Chapter 2). In addition, previous studies on related systems also suggested that the stereoselectivity of nucleophilic addition to the oxocarbenium ion was dictated by the chiral morpholinone and not by the exocyclic stereocenter.[20]

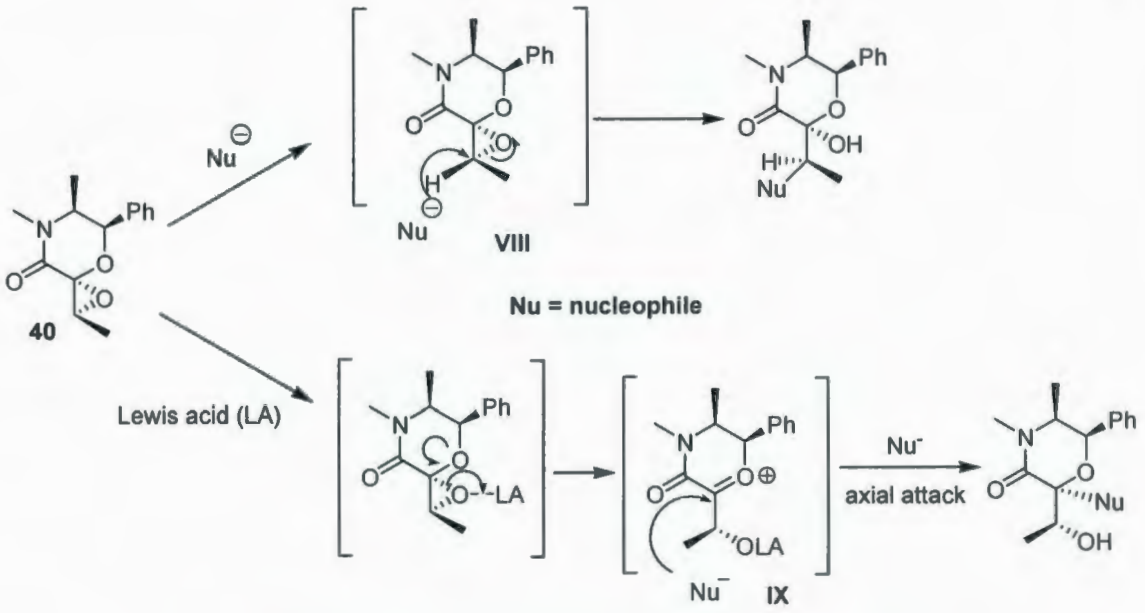
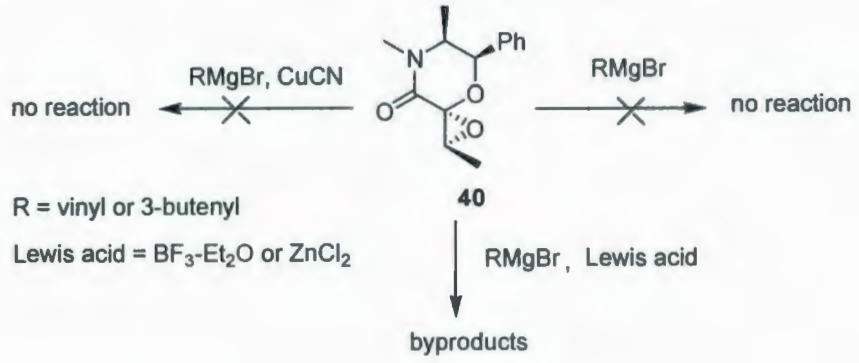


Figure 5. Possible ring opening reactions of epoxide **40**.

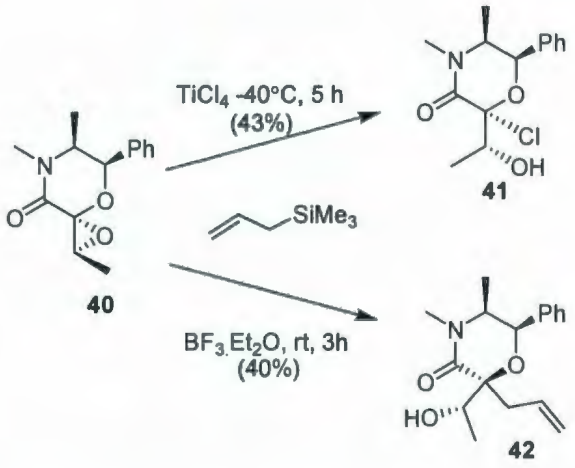
The ring opening of **40** was initially explored with vinyl- and butenyl magnesium bromide at low temperature (-78 °C) was explored first. Surprisingly, no reaction was observed. Organocopper reagents were not beneficial, and byproducts predominated when zinc chloride or BF_3•etherate was employed as a Lewis acid in these reactions (Scheme 12).

Scheme 12



Attempted allylation of **40** with $TiCl_4$/allyltrimethylsilane provided the chloroalcohol **41** arising from epoxide ring-opening with the chloride ion at the hemiacetal carbon (Scheme 13). Fortunately, the use of BF_3-Et_2O as a Lewis acid proved effective. The epoxide could be readily opened at the acetal carbon with excellent diastereocontrol (>19:1, Scheme 13) at ambient temperature to afford the alcohol **42** (40 %)

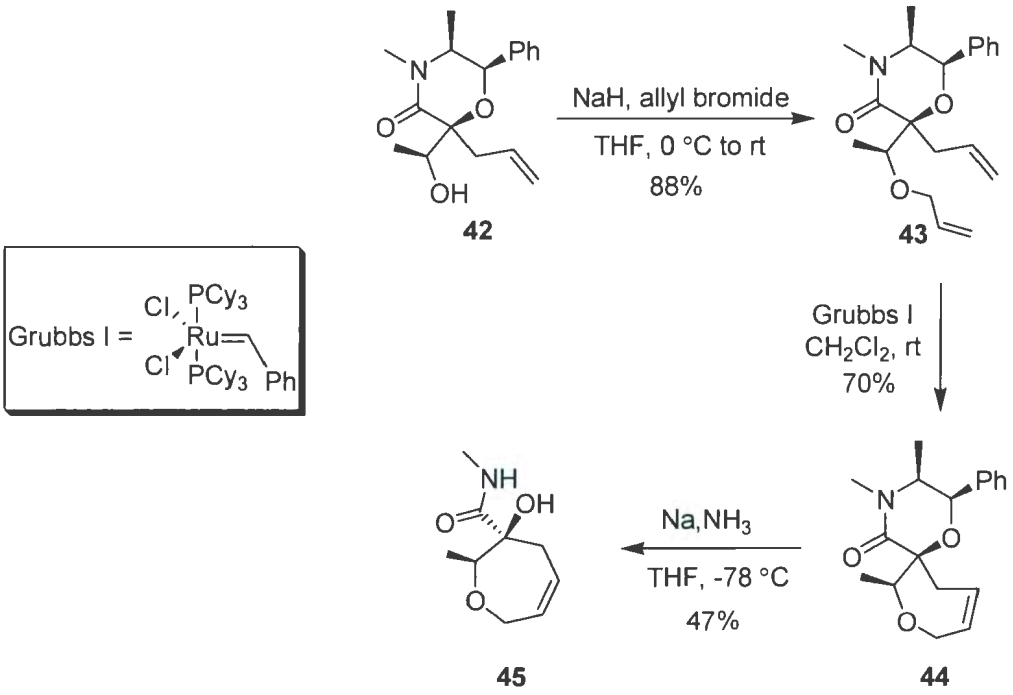
Scheme 13



The secondary alcohol **42** was treated with sodium hydride and the resulting sodium salt was reacted with allyl bromide to furnish the diene **43** (88 %, Scheme 14). The diene **43** was then subjected to a RCM reaction using the Grubbs generation I catalyst to generate the oxepane **44** (70%). At this point, it was unclear whether the allyl ether moiety would survive the usual dissolving metal reduction protocol for removal of the ephedrine portion since the cleavage of allyl ethers under these conditions has been documented in the literature.[21,22] Fortunately, the ephedrine portion in **44** could be removed selectively by subjecting **44** to a dissolving metal reduction, which generated the α-hydroxy amide **45** in moderate yield (47%). Although no other product was isolated, it

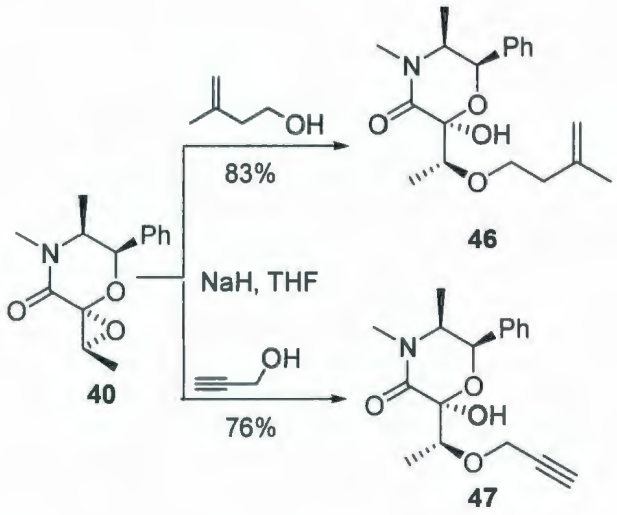
was possible that concomitant allyl ether cleavage was responsible for the diminished yield of **45**.

Scheme 14



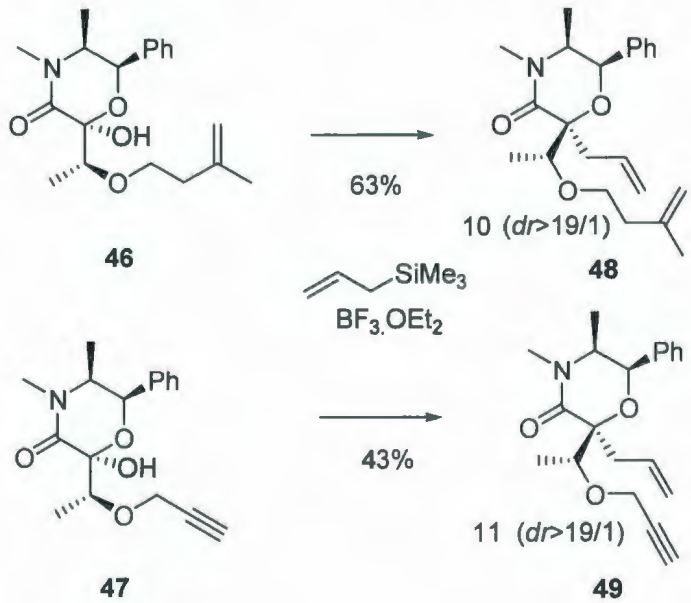
Efforts to open the epoxide **40** at the terminal carbon were successful when alkoxide nucleophiles were used (Scheme 15). Thus treating the epoxide **40** with the sodium salt of 3-methyl-3-buten-1-ol, or propargyl alcohol cleanly generated the hemiacetals **46** and **47**, respectively. It was assumed that the epoxide opening occured with inversion of configuration.

Scheme 15



Ethers **46** and **47** could be allylated by using $BF_3.Et_2O$ and allyltrimethylsilane to generate compounds **48** (63%) and **49** (43%) respectively with excellent diastereomeric excess (>19:1, Scheme 16). The stereochemistry at the spiro center in **48** and **49** was assigned by analogy to the reactions of other ephedrine-derived hemiacetals.[16,20]

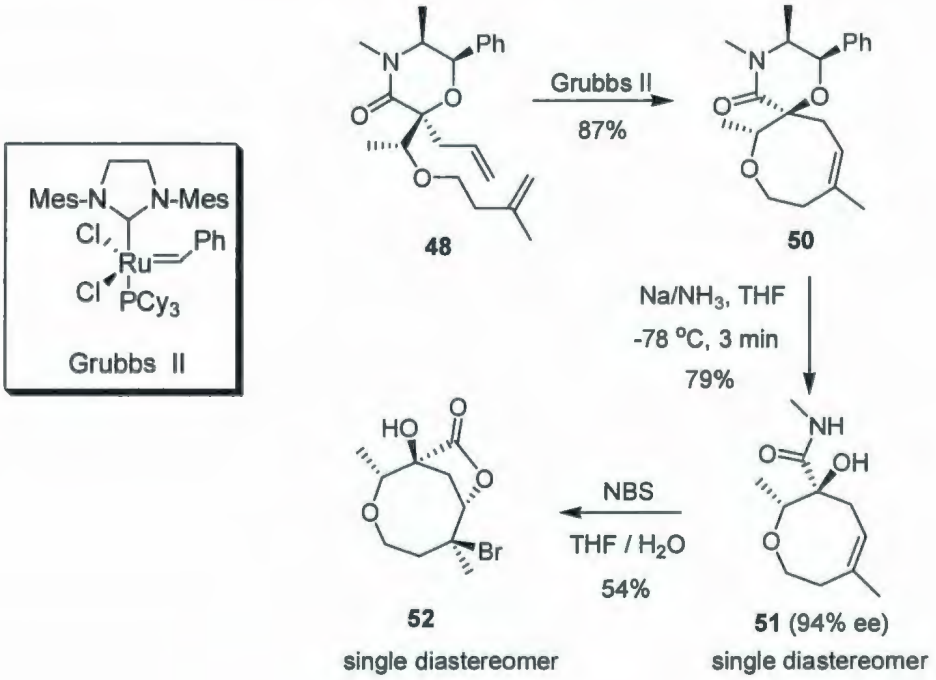
Scheme 16



The above results indicated that the alkoxide opening/allylation procedure could be used to provide the diastereomer of the product obtained by an allylation/*O*-alkylation reaction sequence with **40**. In addition, the use of an enantiomerically pure secondary alcohol in the epoxide opening reaction should allow for the control of two stereocenters adjacent to the ether oxygen, a structural motif that is found in the laurencin, obtusan, and lauthisan classes of marine natural products.[23]

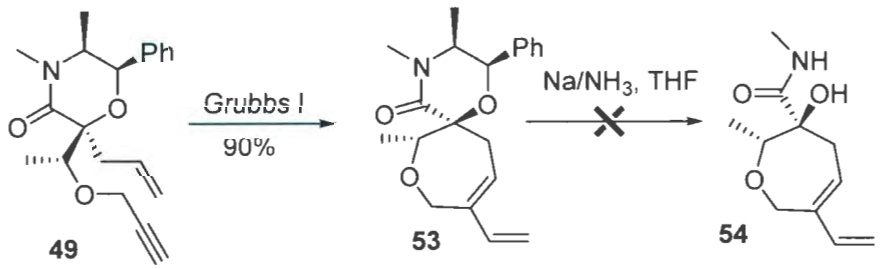
The diene **48** was successfully converted into the oxocane **50** by a RCM reaction (87%) using Grubbs generation II catalyst (Scheme 17). Dissolving metal reduction of **50** gave the hydroxy amide ring **51** (79%) as a single diastereomer (94% ee). At this stage, the utility of the carboxamide for transannular functionalization was demonstrated by bromolactonization of **51** to provide the functionalized dioxabicyclo[5.2.1]decanone **52** as a single diastereomer (Scheme 17).

Scheme 17



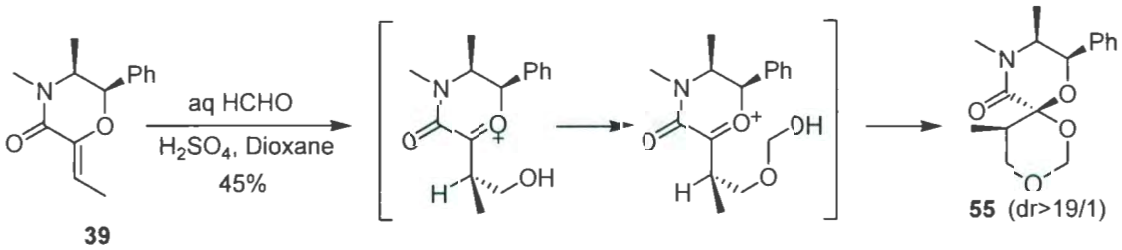
In a related sequence, generation of the diene **53** (90%) via enyne metathesis could be achieved by utilizing the Grubbs generation I catalyst (Scheme 18). Subsequent dissolving metal reduction of **53** generated a complex mixture of products and the required product **54** could not be detected. Presumably, the diene functionality in **53** is susceptible to reduction under the dissolving metal reduction conditions.

Scheme 18



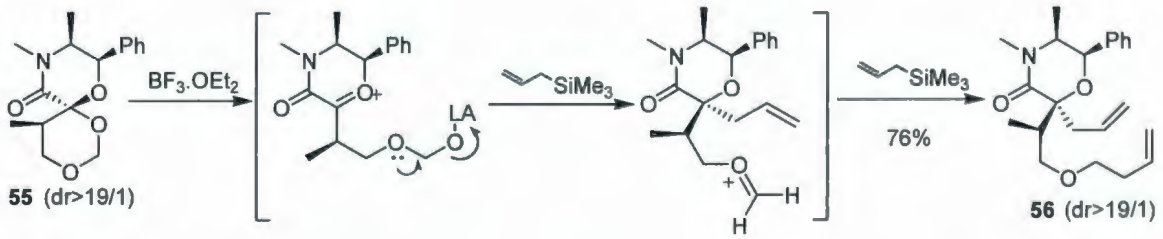
In addition to the epoxide-based routes described above, the utility of the alkylidene morpholinone **39** for the preparation of functionalized dienes has also examined. In this direction, the Prins reaction[24] of **39** with formaldehyde provided the spirodioxane **55** as a single diastereomer (Scheme 19). The absolute configuration of the newly generated stereocenters in **55** is assigned on the basis of earlier studies in Pansare group, which had demonstrated that the Prins reaction of alkylidene morpholinones such as **39** was stereospecific and proceeds with retention of the alkene stereochemistry.[20]

Scheme 19



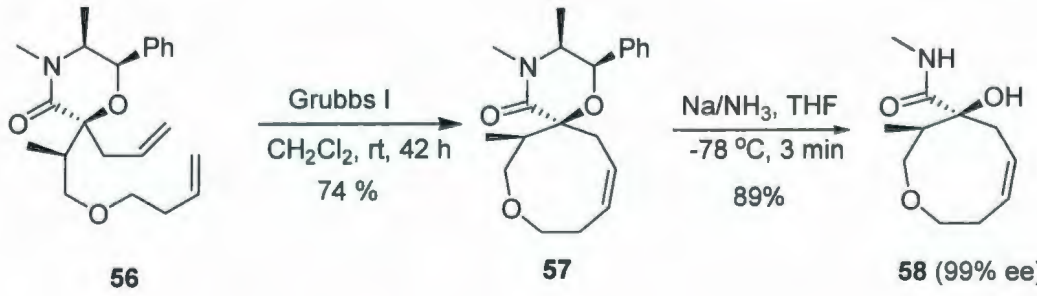
Treatment of **55** with excess allyltrimethylsilane/BF_3 etherate provided the diastereomerically pure bis(allylation) product **56** (76%). The bis(allylation) reaction presumably proceeds through the sequential generation of endocyclic and exocyclic oxocarbenium ions derived from the spiromorpholinone (Scheme 20). The exact sequence of events is not known at present.

Scheme 20



Further in the sequence, the ring closure of **56** by treatment with the Grubbs I catalyst gave the spiro oxonane **57** (74%). Removal of the chiral controller in **57** revealed the nine-membered oxacycle **58** (66% over two steps, 99% ee, Scheme 21).

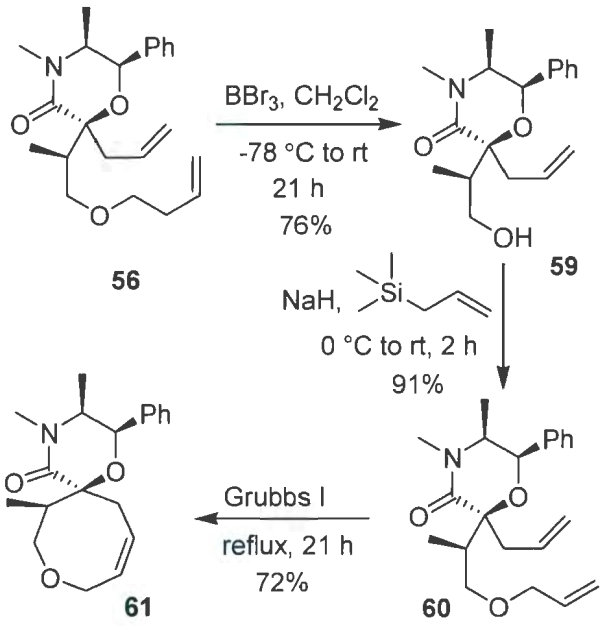
Scheme 21



The spiromorpholinone **56** by treatment with Grubbs I catalyst was also utilized in the synthesis of a functionalized oxocane (74%). To this effect, treatment of **56** with BBr_3 gave the alcohol **59** (76%), which could be converted into ether **60** by alkylation with

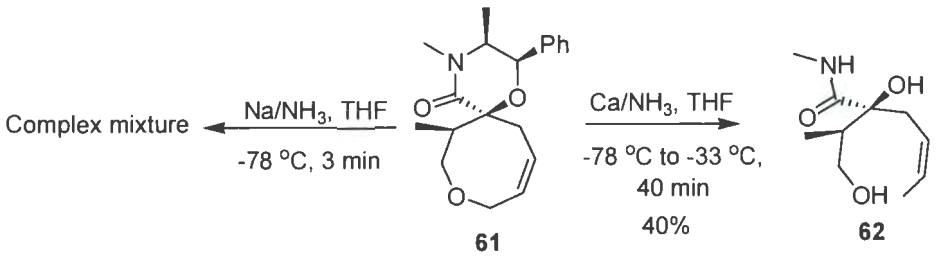
allyl bromide (91%, Scheme 22). As anticipated, the ring-closing metathesis of **60** with the Grubbs I catalyst yielded oxocane **61** (72%).

Scheme 22



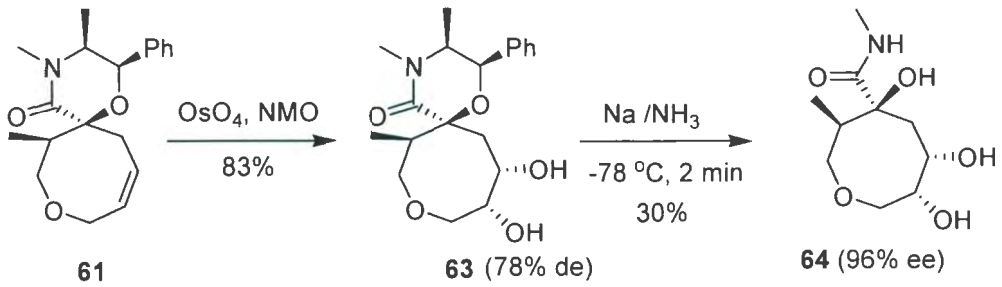
Previous results with oxepane **44** (Scheme 15) had suggested that the allyl ether funtionality in **61** would survive dissolving metal reduction conditions. However, treatment of **61** with Na/NH_3 failed to give the desired product and a complex, inseparable mixture was obtained instead. It was then decided to use calcium as an alternative to sodium in the reduction of oxocane **61**. It is known that Ca in NH_3 is a milder reducing agent that Na in NH_3.[25] For example, Ca/NH_3 exhibits better selectivity for debenzylation in the presence of other reducible functionalities. Therefore, the selective reduction of the phenyl ring in the morpholinone **61** with Ca/NH_3 over the allyl ether was anticipated. However, actual implementation of these conditions yielded the olefin **62** (40%, Scheme 23) instead, suggesting that the reduction of the phenyl ring was accompanied by reduction of the C-O bond in the allylic ether functionality.[26]

Scheme 23



Given the difficulties encountered in the dissolving metal reduction of **61**, it was decided to examine the functionalization of the double bond in **61** prior to the removal of the ephedrine portion. Accordingly, dihydroxylation of **61** (OsO_4, NMO, H_2O/THF) provided the diol **63** in good yield and diastereoselectivity (83%, 78% de, Scheme 24). Exposure of **63** to Na/NH_3 gave triol **64** (30%) as a single diastereomer, possibly due to losses during the isolation/purification process. Notably, triol **64** was found to be highly water soluble.

Scheme 24



The major diastereomer in **63** was assigned the shown stereochemistry on the basis of a preferred conformation for **61** that was determined by molecular modeling studies with the Spartan software (MM2 calculation). In this conformation, the top face of the double bond in **61** is shielded by the phenyl ring in the morpholinone portion of the

spirocycle (Figure 8). The chirality of the ephedrine can thus be utilized not only for stereochemical control in the morpholinone ring but also for remote stereocontrol in the appended oxacycle.

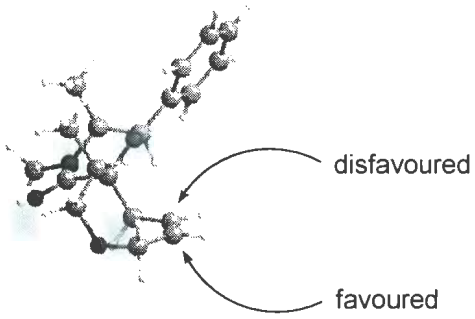


Figure 8. Proposed origin of stereoselectivity for the dihydroxylation of **61**.

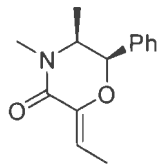
Conclusion:

In conclusion, versatile approaches to functionalized, enantiomerically pure oxacycles have been developed. The overall strategy is quite flexible and permits the construction of seven-, eight- or nine-membered oxacycles from readily available chiral precursors, namely the alkylidene morpholinone **39** and the epoxide **40**. Incorporation of unsaturation and positioning of the ring oxygen at specific locations in the ring are achieved by the judicious choice of starting materials. The overall efficiency of this protocol coupled with the high enantioselectivity strongly advocates an investigation on the application of these methods in the synthesis of selected, naturally occurring oxacycles and their analogues.

Experimental

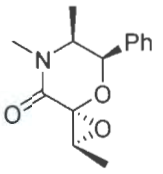
General experimental techniques that have been described in the experimental section of Chapter 2 were followed.

(Z,5*S*,6*R*)-2-Ethylidene-4,5-dimethyl-6-phenylmorpholin-3-one (39):[16]



To a suspension of the dione **38** (2.87 g, 13.2 mmol) in ether (25 mL) was added ethylmagnesium bromide (prepared from magnesium metal (0.740 g, 30.4 mmol) and ethyl iodide (2.22 mL, 27.3 mmol) in ether (10 mL)) at 0 °C and the mixture was stirred at room temperature for 3 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 3.2 g (98%) of the hemiacetal. This was dissolved in dichloromethane (60 mL), the solution was cooled to -78 °C and BF_3 etherate (5 mL, 38.5 mmol) was added. The solution was stirred at room temperature for 18 h. and cold water (35 mL) was added. The mixture was extracted with dichloromethane (3 x 30 mL) and the combined extracts were dried (Na_2SO_4) and concentrated to provide the crude product. Purification by flash chromatography on silica gel (2/1 ethyl acetate/hexane) furnished 2.90 g (95% over 2 steps) of **39** as a pale yellow gum. Spectroscopic data for **39** was identical to the reported data.[16]

(2*S*,3S,5*R*,6*S*)-5-Phenyl-2,6,7-trimethyl-1,4,dioxa-7-azaspiro[2,5]octan-8-one (40):



To a solution of **39** (1.00 g, 4.30 mmol) in dichloromethane (15 mL) was added *m*CPBA (1.20 g, 6.90 mmol) at -78 °C and the mixture was warmed to room temperature and stirred for 45 min. Saturated $NaHCO_3$ solution was added and the mixture was extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were dried and concentrated under reduced pressure. The residue obtained was purified by flash chromatography on silica gel (ethyl acetate) to give 0.860 g (80 %) of **40** as a white, crystalline solid.

Mp: 141-142 °C.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.39-7.36 (m, 2H), 7.33-7.30 (m, 3H), 5.48 (d, 1H, J = 2.2), 3.84 (q, 1H, J = 5.2), 3.64 (dq, 1H, J = 3.5, 6.3), 3.10 (s, 3H), 1.51 (d, 3H, J = 5.2), 1.03 (d, 3H, J = 6.3).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 163.4, 136.6, 128.5, 128.1, 125.4, 82.0, 75.9, 59.2, 58.5, 33.8, 12.8, 12.4.

IR (solid):

2360, 2344, 1665, 1291, 923, 891 cm^{-1}.

MS (APCI):

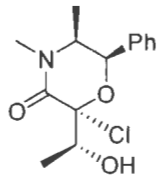
248.1 (M+1, 100).

HRMS (CI):

m/z 247.1202 (247.1208 calc. for $C_{14}H_{17}NO_3$, M+).

$[\alpha]^{23}_D$: -161.9 (c 1, CH_2Cl_2).

(2*R*,5*S*,6*R*)-2-Chloro-2-(1-hydroxyethyl)-4,5-dimethyl-6-phenylmorpholin-3-one (41):



To a solution of **3** (0.710 g, 2.90 mmol) in dichloromethane (35 mL) at –78 °C was added $TiCl_4$ (1.90 mL, 17.4 mmol) and allyltrimethylsilane (2.80 mL, 17.4 mmol). The mixture was gradually warmed to – 40 °C and allowed to stir at this temperature for 9 h. Saturated NH_4Cl was added and the mixture was warmed to ambient temperature. Water was added, the biphase was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica (2/1 ethyl acetate/hexane) to give 0.350 g (43%) of **41** as a colorless gum.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.42-7.29 (m, 1H), 5.65 (d, 1H, J = 3.3), 4.36-4.31 (m, 2H), 3.64 (qd, 1H, J = 3.3, 6.6), 3.08 (s, 1H), 1.44 (d, 1H, J = 6.1), 0.99 (d, 1H, J = 6.6)

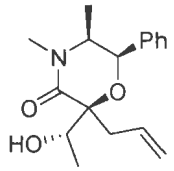
^{13}C NMR (125.8 MHz, $CDCl_3$):

δ 165.2, 135.6, 128.4, 128.2, 125.5, 101.3, 73.8, 71.8, 58.3, 34.1, 16.6, 13.2.

MS (APCI):

284.1 (M+1, 100).

(2*S*,5*S*,6*R*)-2-Allyl-2-((S)-1-hydroxyethyl)-4,5-dimethyl-6-phenylmorpholin-3-one (42):



To a solution of **40** (0.770 g, 3.1 mmol) in dichloromethane (25 mL) at -78 °C was added allytrimethylsilane (3.00 mL, 18.6 mmol) followed by $BF_3.Et_2O$ (2.30 mL, 18.6 mmol). The mixture was stirred at -78 °C for 15 min and then warmed to ambient temperature and stirred for 3 h. Cold water was added and the resulting mixture was extracted with dichloromethane (3 x 25 mL). The combined organic layers were concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (2/1 ethyl acetate/hexane) to provide 0.360 g (40%) of **42** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.40-7.37 (m, 2H), 7.33-7.27 (m, 3H), 5.95 (m, 1H), 5.41 (d, 1H, J = 2.2), 5.17 (dd, 1H, J = 1.4, 16.1), 5.05 (d, 1H, J = 10.3), 4.05 (dq, 1H, J = 6.5, 2.7), 3.88 (d, 1H, J = 2.7), 3.52 (dq, 1H, J = 6.6, 2.2), 3.06 (s, 3H), 2.96 (m, 1H), 2.65 (dd, 1H, J = 7.9, 14.9), 1.37 (d, 3H, J = 6.5), 0.98 (d, 3H, J = 6.6).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 171.6, 137.9, 134.3, 128.6, 127.9, 125.7, 118.4, 81.9, 73.2, 72.0, 59.3, 37.0, 33.9, 16.9, 13.0.

IR (solid):

3394, 2974, 2936, 2896, 1622, 978, 887 cm^{-1}.

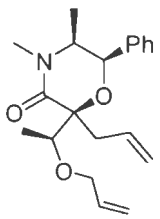
MS (APCI):

290.1 (M+1, 100).

HRMS (CI):

m/z 289.1669 (289.1678 calc. for $C_{17}H_{23}NO_3$, M+).

(2*S*,5*S*,6*R*)-2-Allyl-2-((S)-1-(allyloxy)ethyl)-4,5-dimethyl-6-phenylmorpholin-3-one (43):



To a solution of the alcohol **42** (0.300 g, 1.04 mmol) in THF (15 mL) at 0 °C was added KH (0.0500 g, 1.25 mmol). The mixture was stirred at 0 °C for 15 min and allyl bromide (0.270 mL, 3.12 mmol) was added dropwise. The mixture was then warmed up to ambient temperature, stirred for 3.5 h and cold water was added. The mixture was extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were dried and

concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (2/1 ethyl acetate/hexane) to provide 0.30 g (88 %) of **43** as a yellow gum.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.39-7.29 (m, 5H), 6.0-5.91 (m, 2H), 5.31-5.26 (m, 2H), 5.17-5.02 (m, 3H), 4.20-4.16 (m, 1H), 4.10-4.06 (m, 1H), 3.81 (q, 1H, J = 6.5), 3.50-3.47 (dq, 1H, J = 6.1, 2.9), 3.04 (s, 3H), 2.83 (dd, 1H, 2.6, 6.5), 2.72 (dd, 1H, J = 6.5, 6.7), 1.37 (d, 3H, J = 6.5), 1.02 (d, 3H, J = 6.1).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 169.6, 138.5, 135.6, 133.8, 128.5, 127.7, 125.9, 118.0, 116.9, 84.6, 79.9, 72.4, 71.7, 59.3, 38.8, 34.0, 15.4, 12.9.

IR (neat):

2980, 1636, 1451, 1379, 1071, 1030, 919 cm^{-1}.

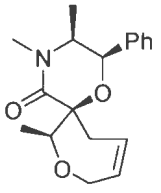
MS (APCI):

330.2 (M+1, 100).

HRMS (CI):

m/z 329.1982 (329.1991 calc. for $C_{20}H_{27}NO_3$, M+).

(2*R*,3*S*,6*S*,7*S*)-2-Phenyl-3,4,7-Trimethyl-1,8-dioxa-4-azaspiro[5.6]dodec-10-en-5-one (44):



To a solution of **43** (0.220 g, 0.670 mmol) in dichloromethane (90 mL) was added Grubbs I catalyst (0.0250 g, 0.0300 mmol, 4.50 mol %). The mixture was stirred at room temperature for 5 h and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel to give 0.140 g (70 %) of **44** as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.37-7.36 (m, 4H), 7.30-7.27 (m, 1H), 5.71-5.68 (m, 1H), 5.65-5.62 (m, 1H), 5.16 (d, 1H, J = 3.5), 4.34-4.46 (m, 2H), 4.26-4.22 (m, 1H), 3.53 (dq, 1H, J = 6.1, 3.4), 3.01 (s, 3H), 2.89 (dq, 2H, J = 6.6, 4.7), 1.31 (d, 3H, J = 6.2), 0.97 (d, 3H, J = 6.1).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 170.5, 138.2, 130.5, 128.5, 127.7, 125.7, 125.4, 83.8, 80.7, 71.2, 69.1, 59.1, 33.9, 33.8, 16.8, 13.4.

IR (neat):

2938, 1628, 1448, 1402, 1380, 1027, 900 cm^{-1}.

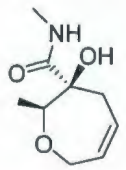
MS (APCI):

302.1 (M+1, 100).

HRMS (CI):

m/z 301.1670 (301.1678 calc. for $C_{18}H_{23}NO_3$, M+).

(*Z*,2*S*,3*S*)-2,3,4,7-Tetrahydro-3-hydroxy-*N*,2-dimethyloxepine-3-carboxamide (45):



To anhydrous liquid ammonia (distilled over sodium) was added Na metal (0.0640 g, 2.79 mmol) at –78 °C and the mixture was stirred for 15 min. To the resulting blue solution was added a solution of **44** (0.120 g, 0.400 mmol) in anhydrous THF (2.5 mL) and the mixture was stirred for 3 min. A mixture of 2/1 methanol/water (3 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 column chromatography on silica gel (3/2, ethyl acetate/hexane) to provide 0.0350 g (47%) of **45** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 6.91 (s, 1H), 5.96-5.91 (m, 1H), 5.76-5.71 (m, 1H), 4.32 (dd, 1H, J = 9.6, 5.8), 4.12 (m, 1H), 3.98 (q, 1H, J = 6.3), 3.12 (s, 1H), 2.94 (m, 1H), 2.83 (d, 3H, J = 4.3), 2.46 (dd, 1H, J = 16.7, 8.1), 1.12 (d, 3H, J = 6.3).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 174.1, 131.3, 128.3, 82.6, 76.4, 69.2, 38.9, 25.8, 17.4.

IR (neat):

3435, 3015, 1737, 1686, 1537, 1215, 745 cm^{-1}.

MS (APCI):

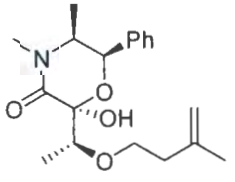
186.1 (M+1, 100).

$[\alpha]^{23}_D$ = +53.6 (*c* 1, CH_2Cl_2).

HRMS (CI):

m/z 185.1043 (185.1052 calc. for $C_9H_{15}NO_3$, M+).

(2*S*,5*S*,6*R*)-2-((*S*)-1-(3-Methylbut-3-enyloxy)ethyl)-2-hydroxy-4,5-dimethyl-6-phenylmorpholin-3-one (46):



To a solution of 3-methyl-3-butene-1-ol (0.442 mL, 4.40 mmol) in THF (35 mL) at 0 °C was added NaH (0.121 g, 5.04 mmol). The mixture was then stirred for 15 min at 0 °C and the epoxide **40** (0.900 g, 3.60 mmol) was added as a solid. The reaction mixture was warmed to ambient temperature, stirred for 3 h, cold water was added, and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by flash

chromatography on silica gel (1/1 ethyl acetate/hexane) to provide 1.00 g (83 %) of **46** as a colorless gum.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.37-7.33 (m, 4H), 7.31-7.27 (m, 1H), 5.38 (d, 1H, J = 2.6), 4.71 (s, 1H), 4.67 (s, 1H), 4.04 (s, 1H), 3.88 (q, 1H, J = 6.4), 3.67 (m, 1H), 3.46-3.41 (m, 2H), 3.02 (s, 3H), 2.23-2.20 (m, 2H), 1.70 (s, 3H), 1.36 (d, 3H, J = 6.4), 1.03 (d, 3H, J = 6.2).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 168.8, 143.0, 137.0, 128.5, 127.8, 126.1, 111.5, 97.6, 79.2, 72.9, 68.3, 59.8, 38.4, 33.7, 22.7, 12.1, 12.0.

IR (neat):

3347, 2940, 1641, 1452, 1109, 1024, 891 cm^{-1}.

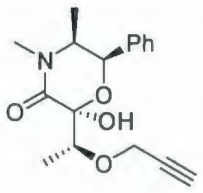
MS (APCI):

334.2 (M+1, 100).

HRMS (CI):

m/z 333.1933 (333.1940 calc. for $C_{19}H_{27}NO_4$, M+).

(2*S*,5*S*,6*R*)-2-Hydroxy-4,5-dimethyl-6-phenyl-2-((*S*)1-(prop-2-ynyloxy)ethyl)morpholin-3-one (47):



To a solution of propargyl alcohol (0.200 mL, 3.40 mmol) in THF (15 mL) at 0 °C was added NaH (0.190 g, 7.94 mmol). The reaction mixture was stirred at 0 °C for 15 min and the epoxide **40** (0.700 g, 2.83 mmol) was added as a solid. The reaction mixture was warmed to ambient temperature, stirred for 2.5 h and cold water was added. The mixture was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were dried and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (1/1 ethyl acetate/hexane) to provide 0.650 g (76%) of **47** as a white solid.

Mp: 133-134 °C.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.37-7.32 (m, 4H), 7.28-7.26 (m, 1H), 5.42 (d, 1H, J = 2.7), 5.1 (s, 1H), 4.15 (d of AB, 2H, J = 15.0, 2.0), 4.07 (q, 1H, J = 6.5), 3.44-3.40 (dq, J = 2.7, 7.1), 3.01 (s, 3H), 2.39 (t, 1H, J = 2.0), 1.43 (d, 3H, J = 6.5), 1.03 (d, J = 7.1).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 168.9, 137.7, 128.4, 127.8, 126.0, 97.2, 80.3, 78.8, 74.0, 72.4, 59.6, 57.7, 33.8, 12.7, 12.0.

IR (solid):

3294, 1658, 1449, 1195, 1148, 1078, 1014, 967 cm^{-1}.

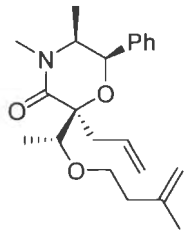
MS (APCI):

304.1 (M+1, 100).

HRMS (CI):

m/z 303.1481 (303.1471 calc. for $C_{17}H_{21}NO_4$, M+).

(2*S*,5*S*,6*R*)-2-((*R*)-1-(3-Methylbut-3-enyloxy)ethyl)-2-allyl-4,5-dimethyl-6-phenylmorpholin-3-one (48):



To a solution of **46** (0.500 g, 1.5 mmol) in dichloromethane (20 mL) at -78 °C was added allytrimethylsilane (1.50 mL, 9 mmol) followed by $BF_3.Et_2O$ (1.10 mL, 9 mmol). The mixture was stirred at -78 °C for 15 min and then warmed to ambient temperature and stirred for 36 h. Cold water was added and the mixture was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (1/1 ethyl acetate/hexane) to provide 0.232 g (43%, 63% based on recovered starting material (0.160 g)) of **48** as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.38-7.34 (m, 4H), 7.30-7.27 (m, 1H), 6.02-5.96 (m, 1H), 5.30 (d,1H, J = 2.5), 5.09 (dd, 1H, J = 13.3, 1.0), 4.70 (d, 1H, J = 10.1), 4.72 (s, 1H), 4.67 (s, 1H), 3.81 (q, 1H, J = 6.3), 3.68-3.63 (m, 1H), 3.46-3.40 (m, 2H), 3.02 (s, 3H), 2.63 (dd, 1H, J = 14.1, 7.4), 2.53 (dd, 1H, J = 14.1, 7.2), 2.21 (*br*t, 2H, J = 6.5), 1.72 (s, 3H), 1.32 (d, 3H, J = 6.3), 1.01 (d, 3H, J = 6.2).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 170.1, 143.2, 138.9, 134.5, 128.4, 127.6, 126.0, 117.8, 111.4, 84.0, 80.4, 73.4, 68.4, 59.5, 40.8, 38.5, 33.8, 22.8, 13.0, 12.2.

IR (neat):

2982, 1737, 1605, 1402, 1310, 1166, 1090, 1068, 852 cm^{-1}.

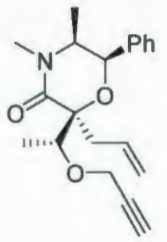
MS (APCI):

358.3 (M+1, 100).

HRMS (CI):

m/z 357.2305 (357.2304 calc. for $C_{22}H_{31}NO_3$, M+).

(2*S*,5*S*,6*R*)-2-Allyl-4,5-dimethyl-6-phenyl-2-((*R*)-1-(prop-2-ynyloxy)ethyl)morpholin-3-one (49):



To a solution of **47** (0.430 g, 1.42 mmol) in dichloromethane (20 mL) at -78 °C was added allyltrimethylsilane (1.35 mL, 8.52 mmol) followed by $BF_3.Et_2O$ (1.10 mL, 8.52 mmol). The mixture was stirred at -78 °C for 15 min and then warmed to ambient temperature and stirred for 3 days. Cold water was added and the resulting mixture was extracted with dichloromethane (3 x 20mL). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (1/1 ethyl acetate/hexane) to provide 0.0600 g (43% based on recovered starting material (0.300 g) of **49** as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.35-7.34 (m, 4H), 7.29-1.27 (m, 1H), 6.01-5.93 (m, 1H), 5.32 (d, 1H, J = 2.6), 5.10 (d, 1H, J = 16.6, 1H5.16 (d, 1H, J = 10, 1H), 4.15 (d of AB, 2H, J = 16, 2.0), 3.96 (q, 1H, J = 6.5), 3.40 (dq, J = 2.6, 7.2), 3.03 (s, 3H), 2.65-2.61 (dd, 1H, J = 14, 7.2), 2.53-2.50 (dd, 1H, J = 14, 7.2), 2.36 (br t, 1H, J = 2), 1.38 (d, 3H, J = 6.5), 1.04 (d, J = 7.2).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 169.8, 138.7, 128.4, 127.7, 126.0, 118.0, 83.9, 80.8, 80.7, 80.6, 73.6, 73.4, 59.9, 40.7, 40.5, 33.9.

IR (solid):

1703, 1580, 1421, 1389, 1135, 1054, 1010 cm^{-1}.

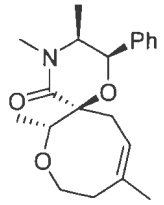
MS (APCI):

328.3 (M+1, 100).

HRMS (CI):

m/z 327.1835 (327.1834 calc. for $C_{20}H_{25}NO_3$, M+).

(2*R*,3*S*,6*S*,7*S*)-3,4,7,11-Tetramethyl-2-phenyl-1,8-dioxa-4-azaspiro[5.7]tridec-11-en-5-one (50):



To a solution of **48** (0.100 g, 0.280 mmol) in dichloromethane (28 mL) was added the Grubbs II catalyst (0.0560 g, 0.0700 mmol, 20 mol %). The reaction mixture was stirred at room temperature for 48 h and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel to give 0.0800 g (87 %) of **50** as colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.39-7.28 (m, 5H), 5.25 (br, 2H), 4.17 (br dt, 1H, *J* = 12.0, 2.8), 3.58 (q, 1H, *J* = 6.3), 3.51 (dq, 1H, *J* = 6.7, 3.1), 3.41 (t, 1H, *J* = 12.0), 3.17 (dd, 1H, *J* = 14, 10.4), 3.01 (s, 3H), 2.89 (br t, 1H, *J* = 12), 2.60 (dd, 1H, *J* = 5.8, 14), 1.78 (s, 3H), 1.75 (dd, 1H, *J* = 12.2, 2.8), 1.19 (d, 3H, *J* = 6.3), 0.92 (d, 3H, *J* = 6.7).

^{13}C NMR (125.77 MHz, $CDCl_3$):

158.9, 145.4, 136.7, 128.6, 128.2, 125.5, 111.9, 77.5, 66.2, 58.6, 58.1, 33.7, 11.8.

IR (neat):

2933, 1642, 1450, 1111, 1093, 959, 900, 847 cm^{-1}.

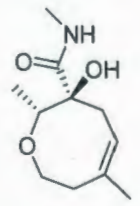
MS (APCI):

330.2 (M+1, 100).

HRMS (CI):

m/z 329.1993 (329.1991 calc. for $C_{20}H_{27}NO_3$, M+).

(*Z*,2*R*,3*S*)-3,4,7,8-Tetrahydro-3-hydroxy-*N*,2,6-trimethyl-2H-oxocine-3-carboxamide (51):



To anhydrous liquid ammonia (distilled over sodium) was added Na metal (0.0380 g, 1.66 mmol) at –78 °C and the mixture was stirred for 15 min. To the resulting blue solution was added a solution of **50** (0.0780 g, 0.240 mmol) in anhydrous THF (2.5 mL) and the mixture was stirred for 3 min. A mixture of 2/1 methanol/water (3 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 column chromatography on silica gel (ethyl acetate) to provide 0.0400 g (79%) of **51** as a white solid.

Mp:

102-103 °C;

^{1}H NMR (500 MHz, $CDCl_3$):

δ 6.72 (br s, 1H), 5.32 (br s, 1H), 4.22 (br s, 1H), 4.01 (br s, 1H), 4.68 (br q, 1H), 3.53 (br t, 1H), 2.89 (d, 3H, J = 5.4), 2.75 (br s, 2H), 2.17 (br s, 1H), 1.84 (br s, 4H), 1.02 (d, 3H, J = 6.3); a satisfactory ^{13}C spectrum could not be obtained due to atropisomerism resulting in peak broadening.

IR (solid):

3354, 2920, 1700, 1684, 1540, 1088, 968, 895 cm^{-1}.

$[\alpha]^{23}_D$: -109 (*c* 1, CH_2Cl_2).

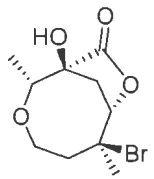
MS (APCI):

214.1 (M+1, 100).

HRMS (CI):

m/z 213.1371 (213.1365 calc. for $C_{11}H_{19}NO_3$, M+).

(1*S*,2*S*,6*R*,7*S*)-2-Bromo-7-hydroxy-2,6-dimethyl-5,9-dioxa-bicyclo[5.2.1]decan-8-one (52):



To a solution of **51** (0.0400 g, 0.190 mmol) in THF (1 mL) was added *N*-bromosuccinimide (0.0500 g, 0.280 mmol) and the solution was stirred for 3 h at room temperature. Saturated aqueous $NaHSO_3$ solution (1.5 mL) was added and the mixture

was extracted with ethyl acetate (3 x 3 mL). The combined organic layers were dried (Na_2SO_4), concentrated and the residue was purified by flash chromatography on silica gel (7/3 ethyl acetate/hexane) to give 0.0270 g (54%) of **52** as a colorless gum.

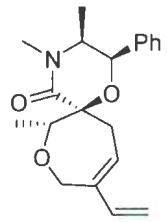
^{1}H NMR (500 MHz, $CDCl_3$):

δ 4.77 (dd, 1H, *J* = 11.5, 1.5), 4.12 (ddd, 1H, *J* = 13, 6, 2), 3.8 (dd, 1H, *J* = 13.0, 9.0), 3.76 (q, 1H, *J* = 6.3), 3.20 (dd, 1H, *J* = 15.5, 2), 2.78 (dd, 1H, *J* = 15.5, 11), 2.72 (br s, 1H), 2.36 (ddd, 1H, *J* = 16.5, 10.0, 2.0), 2.25 (dd, 1H, J = 16.5, 6.0), 1.95 (s, 3H), 1.37 (d, 3H, *J* = 6.3).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 177.7, 83.5, 81.4, 76.4, 68.6, 67.7, 44.4, 38.8, 34.2, 15.9.

(2*R*,3*S*,6*S*,7*S*)-3,4,7-Trimethyl-2-phenyl-10-vinyl-1,8-dioxa-4-azaspiro[5.6]dodec-10-en-5-one (53):



To a solution of **49** (0.0500 g, 0.150 mmol) in dichloromethane (15 mL) was added Grubbs I catalyst (0.0150 g, 0.0200 mmol, 10 mol%). The mixture was stirred at room temperature for 48 h and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel to give 0.045 g (90%) of **53** as colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.39-7.28 (m, 5H), 6.23 (dd, 1H, *J* = 9.2, 6.9), 5.61 (t, *J* = 6.4), 5.16 (d, 1H, *J* = 3.6), 4.93 (d, 1H, J = 13), 4.90 (d, 1H, *J* = 18.5), 4.78 (br d, 2H), 4.54 (dd, 1H, *J* = 13.3, 2.6), 3.79 (q, 1H, *J* = 6.8), 3.51 (dq, *J* = 3.6, 6.5, 1H), 3.47-3.44 (m, 1H), 3.0 (s, 3H), 2.60 (q, 1H, *J* = 15, 9.0), 1.28 (d, 1H, *J* = 6.8), 0.95 (d, 3H, *J* = 6.5).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 169.6, 138.0, 138.0, 128.5, 127.8, 127.0, 125.8, 111.4, 89.3, 79.5, 72.8, 72.3, 59.0, 33.7, 30.5, 17.0, 12.5.

IR (neat):

1646, 1452, 1399, 1380, 1253, 1146, 1123, 1097, 991 cm^{-1}.

$[\alpha]^{23}_D$: +24 (*c* 1, CH_2Cl_2).

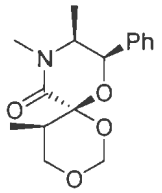
MS (APCI):

28.3 (M+1, 100).

HRMS (CI):

m/z 327.1834 (327.1834 calc. for $C_{20}H_{25}NO_3$, M+).

(5*R*,6*R*,8*R*,9*S*)-8-Phenyl-5,9,10-trimethyl-1,3,7-trioxa-10-azaspiro[5,5]undecan-11-one (55):



To a solution of **39** (0.562 g, 2.40 mmoles) in glacial acetic acid (10 mL) was added formaldehyde (0.406 g, 13.5 mmoles) and H_2SO_4 (0.1 mL). The reaction mixture was stirred at 85 °C for 8 h and saturated $NaHCO_3$ solution was added and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (2/3 ethyl acetate/hexanes) to provide 0.340 g (45%) of **55** as a white solid.

Mp: 134-135 °C.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.44-7.28 (m, 5H), 5.51 (d, 1H, *J* = 3.5), 4.81 (d, 1H, *J* = 5.8), 5.04 (d, 1H, *J* = 5.8), 3.90 (dd, *J* = 11, 5), 3.80 (t, *J* = 11), 3.54 (dq, 1H, *J* = 6.1, 3.5), 3.07 (s, 3H), 3.01 (m, 1H), 0.99 (d, 1H, *J* = 6.1), 0.89 (d, 1H, *J* = 6.7).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 164.7, 137.4, 128.8, 128.1, 125.6, 100.0, 96.8, 70.4, 68.1, 59.2, 34.7, 34.1, 13.0, 11.7.

$[\alpha]^{23}_D$ = - 47.3 (*c* 1, CH_2Cl_2).

IR (neat):

2977, 1756, 1663, 1153, 985, 967, 881 cm^{-1}.

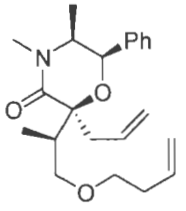
MS (APCI):

292.1 (M+1, 100).

HRMS (CI):

m/z 291.1472 (291.1471 calc. for $C_{16}H_{21}NO_4$, M+).

(2*S*,5*S*,6*R*)-2-Allyl-2-((S)-1-(but-3-enyloxy)propan-2-yl)-4,5-dimethyl-6-phenylmorpholin-3-one (56):



To a solution of **55** (0.310 g, 1.06 mmol) in dichloromethane (3.5 mL) at -78 °C was added allytrimethylsilane (3.40 mL, 21.2 mmol) followed by $BF_3.Et_2O$ (2.65 mL, 21.2 mmol). The mixture was stirred at – 78 °C for 15 min and then at ambient temperature for 96 h. Cold water was added and the resulting mixture was extracted with dichloromethane (3 x 20mL). The combined organic layers were dried, concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (1/1 ethyl acetate/hexane) to provide 0.290 g (76%) of **56** as a yellow oil.

IR (neat):

2978, 1643, 1452, 1398, 1378, 1246, 1103, 1001, 913 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.38-7.27 (m, 5H), 5.99-5.94 (m, 1H), 5.87-5.81 (m, 1H), 5.32 (d, 1H, J = 2.7), 5.09 (d, 2H, J = 16.8), 5.02 (d, 2H, J = 10.5), 3.84 (dd, 1H, J = 4.9, 2.1) 3.54-3.40 (m, 4H), 3.01 (s, 3H), 2.80 (dd, 1H, J = 7, 14.6), 2.72 (dd, 1H, J = 7, 14.6), 2.44-2.41 (m, 1H), 2.36-2.32 (m, 2H), 1.20 (d, 1H, J = 6.5), 0.94 (d, 1H, J = 6.8).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 170.7, 138.4, 135.7, 134.4, 128.5, 127.7, 125.7, 117.7, 116.3, 82.9, 71.7, 71.6, 70.4, 60.6, 59.2, 40.7, 34.5, 33.8, 14.2, 13.2.

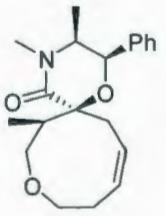
MS (APCI):

358.3 (M+1, 100).

HRMS (CI):

m/z 357.2300 (357.2304 calc. for $C_{22}H_{31}NO_3$, M+).

(2*R*,3*S*,6*S*,7*R*)-3,4,7-Trimethyl-2-phenyl-1,9-dioxa-4-azaspiro[5.8]tetradec-12-en-5-one (57):



To a solution of **56** (0.0500 g, 0.140 mmol) in dichloromethane (36 mL) was added Grubbs I catalyst (0.0350 g, 0.043 mmol, 30.3 mol %). The reaction mixture was heated to relux for 42 h and then concentrated under reduced pressure. The residue was

purified by flash chromatography on silica gel to provide 0.0340 g (74 %) of **57** as pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.4-7.3 (m, 5H), 5.8 (m, 2H), 5.34 (d, 1H, *J* = 3.5), 4.1 (t, 1H, *J* = 11.5), 3.85-3.82 (brm, 1H), 3.54 (dq, 1H, *J* = 6.7, 3.1), 3.35-3.30 (m, 2H), 3.07-3.05 (m, 1H), 3.05 (s, 3H), 2.95-2.89 (m, 1H), 2.68 (m, 1H), 2.32-2.27 (m, 1H), 2.16-2.10 (m, 1H), 0.95 (d, 3H, *J* = 6), 0.80 (d, 3H, *J* = 6.7).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 138.8, 135.7, 129.8, 129.3, 128.4, 128.0, 126.0, 83.3, 73.3, 71.0, 70.7, 60.1, 59.1, 57.7, 34.9, 33.8, 29.5, 13.4.

IR (neat):

2920, 2852, 1742, 1640, 1451, 1379, 1124, 1036 cm^{-1}.

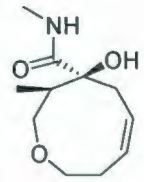
MS (APCI):

330.2 (M+1, 100).

HRMS (CI):

m/z 329.1986 (329.1991 calc. for $C_{20}H_{27}NO_3$, M+).

(*Z*,3*R*,4*S*)-2,3,4,5,8,9-Hexahydro-4-hydroxy-*N*,3-dimethyloxonine-4-carboxamide (58):



To anhydrous liquid ammonia (distilled over sodium) was added Na metal (0.0590 g, 2.50 mmol) at –78 °C and the mixture was stirred for 15 min. To the resulting blue solution was added a solution of ring closing metathesis product **57** (0.0400 g, 0.120 mmol) in anhydrous THF (2.5 mL) and the mixture was stirred for 3 min. A mixture of 2/1 methanol/water (3 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 column chromatography on silica gel (3/2, ethyl acetate/hexane) to provide 0.0230 g (89%) of **58** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 6.72 (bs, 1H), 5.85-5.78 (m, 2H), 3.87-3.83 (m, 1H), 3.69-3.65 (dd, 1H, J = 8.9, 11.8), 3.54-3.50 (dd, 1H, J = 4.6, 11.8), 3.26-3.22 (m, 1H), 2.95-2.91 (m, 2H), 2.84 (d, 3H, J = 5.2), 2.48-2.41 (m, 2H), 2.29-2.21 (m, 2H), 0.70 (d, 3H, J = 6.8).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 176.0, 129.5, 129.2, 79.4, 72.5, 69.9, 38.3, 36.3, 27.8, 25.9, 12.4.

IR (neat):

3422, 2936, 2866, 1656, 1650, 1562, 1121, 958, 911 cm^{-1}.

$[\alpha]^{23}_{D}$ = +16.3 (*c* 1, CH_2Cl_2).

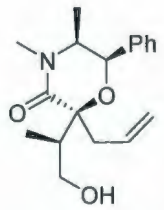
MS (APCI):

214.1 (M+1, 100).

HRMS (CI):

m/z 213.1361 (213.1365 calc. for $C_{11}H_{19}NO_3$, M+).

(2S,5S,6*R*)-2-Allyl-2-[(*S*)-1-(allyloxy)propan-2-yl]-6-phenyl-4,5-dimethylmorpholin-3-one (59):



To a solution of **56** (0.250 g, 0.700 mmol) in dichloromethane at -78 °C was added BBr_3 (0.330 mL, 3.50 mmol) dropwise. The mixture was then brought to ambient temperature and stirred for 21 h. Saturated sodium bicarbonate solution was added and the mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried and concentrated under reduced pressure and the residue obtained was purified by flash chromatography on silica gel to yield 0.180 g (85 %) of the primary alcohol **59** as a white solid.

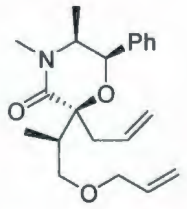
^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.39-7.26 (m, 5H), 5.95 (m, 1H), 5.36 (d, 1H, *J* = 2.8), 5.16-5.06 (m, 2H), 3.96-3.92 (m, 1H), 3.80-3.76 (m, 1H), 3.52-3.45 (m, 1H), 3.04 (s, 3H), 2.83 (m, 2H), 2.61 (m, 1H), 2.31 (m, 1H), 1.20 (d, 3H, *J* = 7.1), 1.01 (d, 3H, *J* = 6.6).

^{13}C NMR (125.8 MHz, $CDCl_3$):

δ 171.0, 137.8, 133.9, 128.7, 128.0, 125.7, 118.4, 84.7, 72.8, 64.6, 59.3, 42.6, 40.1, 34.1, 13.8, 13.2.

(2S,5S,6*R*)-2-Allyl-2-[(*S*)-1-(allyloxy)propan-2-yl]-6-phenyl-4,5-dimethylmorpholin-3-one (60):



To a solution of the alcohol **59** (0.105 g, 0.0350 mmol) in THF (15 mL) at 0 °C was added KH (0.0170 g, 0.420 mmol). The mixture was then stirred at 0 °C for 15 min and allylbromide (0.0900 mL, 1.21 mmol) was added dropwise. The mixture was then warmed up to ambient temperature, stirred for 2 h and cold water was added. The mixture was extracted with ethyl acetate (3 x 10 mL) and the combined organic layers were dried and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (60/40 ethyl acetate/hexane) to provide 0.090 g (75%) of **60** as a yellow gum.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.39-7.28 (m, 5H), 6.0-5.91 (m, 2H), 5.33 (d, 2H, J = 3.3), 5.30 (dd, 1H, J = 17.9, 1.6), 5.17 (dd, 1H, J = 9.8, 1.4), 5.11 (dd, 1H, J = 1.2, 17.9), 5.04 (d, J = 9.8), 4.00-3.98 (m, 2H), 3.87 (dd, 1H, J = 9.3, 4.1), 3.50 (dq, 1H, J = 3.1, 7.0),

3.44 (t, 1H, J = 9.3), 3.02 (s, 3H), 2.81 (dd, 1H, J = 15, 8.2), 2.74 (dd, J = 15, 6.6), 2.46-2.42 (m, 1H), 1.16 (d, 3H, J = 7.4), 0.96 (d, 3H, J = 7.0).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 170.7, 138.4, 135.3, 134.3, 128.5 , 127.7, 125.7, 117.8, 116.6, 82.9, 71.9, 71.8, 71.2, 59.2, 40.8, 40.2, 33.8, 14.2, 13.2.

IR (neat):

2979, 1737, 1643, 1497, 1398, 1379, 1243, 1143, 1088, 1030, 918 cm^{-1}.

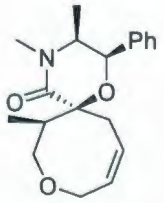
MS (APCI):

344.3 (M+1, 100).

HRMS (CI):

m/z 343.2155 (343.2147 calc. for $C_{21}H_{29}NO_3$, M+).

(2*R*,3*S*,6*S*,7*R*)-3,4,7-Trimethyl-2-phenyl-1,9-dioxa-4-azaspiro[5.7]tridec-11-en-5-one (61):



To a solution of the diene **25** (0.0710 g, 0.210 mmol) in dichloromethane (40 mL) was added the Grubbs I catalyst (0.0510 g, 0.0600 mmol, 30.3 mol %). The mixture was heated to reflux for 21 h and then the solvent was removed under pressure. The residue was purified by flash chromatography on silica gel to give 0.0500 g (77 %) of **61** as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.60-7.47 (m, 5H), 5.83-5.75 (m, 2H), 5.47 (d, 1H, *J* = 3.7), 4.68 (br d, 1H, *J* = 17.4), 4.33 (dd, 1H, *J* = 17.4, 1.8), 4.27 (t, 1H, *J* = 11.8), 3.75 (dq, 1H, *J* = 6.9, 3.2), 3.69 (dd, 1H, *J* = 11.8, 3.7), 3.42-3.38 (m, 1H), 3.24 (s, 3H), 3.23-3.13 (m, 2H), 1.17 (d, 3H, *J* = 9.8), 1.06 (d, 3H, *J* = 6.9).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 172.1, 138.6, 132.0, 128.5, 127.7, 125.7, 123.8, 82.2, 73.7, 71.4, 71.0, 59.1, 37.3, 33.8, 33.7, 13.3, 13.1.

IR (neat):

2940, 1636, 1452, 1380, 1146, 1132, 1037 cm^{-1}.

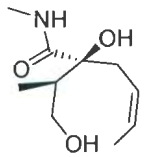
MS (APCI):

316.3 (M+1, 100);

HRMS (CI):

m/z 315.1830 (315.1834 calc. for $C_{19}H_{25}NO_3$, M+).

(*S*,*E*)-2-Hydroxy-2-((*R*)-1-hydroxypropan-2-yl)-*N*-methylhex-4-enamide (62):



To refluxing anhydrous liquid ammonia (distilled over sodium) was added Ca metal (0.0530 g, 1.33 mmol) at –33 °C and the mixture was stirred for 15 min. To the resulting blue solution was added a solution of **61** (0.0600 g, 0.400 mmol) in anhydrous

THF (1 mL) and the refluxing mixture was stirred for 40 min. A mixture of 2/1 methanol/water (3 mL) was added and the reaction mixture was brought to ambient temperature and stirred for 30 min to remove the ammonia. The resulting solution was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (ethyl acetate) to provide 0.0150 g (40%) of **62** as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 6.85 (bs, 1H), 5.66 (m, 1H), 5.41 (m, 1H), 4.07 (m, 1H), 3.91 (s, 1H), 3.73 (m, 1H), 2.82 (d, 3H, J = 5.0), 2.61 (m, 2H), 2.38 (m, 1H), 2.10 (m, 1H), 1.65 (m, 3H), 1.05 (d, 3H, J = 7.2).

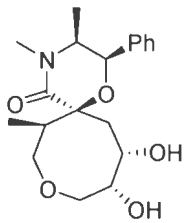
^{13}C NMR (125.8 MHz, $CDCl_3$):

δ 175.3, 128.0, 124.5, 81.3, 65.6, 40.3, 35.2, 25.9, 13.3, 13.0.

MS (APCI):

202.1 (M+1, 100).

(2*R*,3*S*,6*S*,7*R*,11*S*,12*R*)-11,12-Dihydroxy-3,4,7-trimethyl-2-phenyl-1,9-dioxa-4 azaspiro[5.7]tridecan-5-one (63):



To a solution of **61** (0.0600 g, 0.190 mmol) in acetone:water (3:1, 0.400 mL) was added NMO (0.0470 g, 0.400 mmol) followed by OsO_4 (20.0 μL (4% soln. in water) 3.00

μmol). The reaction was stirred for 3 h at room temperature and the solvent was evaporated under reduced pressure. Saturated sodium bicarbonate solution was added to the residue and the resulting mixture was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried and concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (95/5, dichloromethane/methanol) to give 0.0550 g (83%) of **63** as a colourless gum.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.39-7.28 (m, 5H), 5.31 (d, 1H, *J* = 2.8), 4.52 (d, 1H, *J* = 7.3), 4.05 (dd, 1H, *J* = 13.1, 2.43.99 (t, 1H, *J* = 12.1), 3.79 (br s, 1H), 3.60 (dd, 1H, *J* = 1.4, 13.1), 3.52 (dq, 1H, *J* = 7.3, 3.2), 3.40 (dd, 1H, *J* = 12.1, 4.1), 3.02 (s, 3H), 2.83 (br q, 2H, *J* = 8.1), 2.69 (m, 1H), 2.23 (d, 1H), 2.18 (s, 1H), 0.94 (d, 3H, *J* = 6.7), 0.83 (d, 3H, *J* = 7.3).

Visible peaks of the minor diastereomer: δ 5.28 (d), 3.05 (s), 0.97 (d), 0.83 (d).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 172.6, 138.3, 128.5, 127.7, 125.7, 79.8, 72.9, 71.5, 70.8, 70.5, 69.0, 59.3, 39.9, 34.9, 33.8, 13.1, 12.9.

Visible peaks of other isomer:

δ 128.7, 128.0, 71.4, 59.2, 31.1, 13.2.

IR (neat):

3403, 2937, 1626, 1452, 1380, 1258, 1140, 1059, 1039, 755 cm^{-1}.

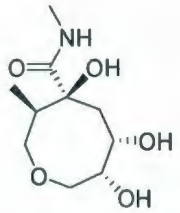
MS (APCI):

350.1 (M+1, 100).

HRMS (CI):

m/z 349.1881 (349.1889 calc. for $C_{19}H_{27}NO_5$, M+).

(3*R*,4*S*,6*S*,7*R*)-4,6,7-Trihydroxy-*N*,3-dimethyloxocane-4-carboxamide (64):



To anhydrous liquid ammonia (distilled over sodium) was added Na (0.0160 g, 0.700 mmol) at –78 °C and the mixture was stirred for 15 min. To the resulting blue solution was added a solution of the dihydroxylation product obtained from **63** (0.350 g, 0.100 mmol) in anhydrous THF (2.5 mL) and the mixture was stirred for 3 min. A mixture of 2/1 methanol/water (3 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 column chromatography on silica gel (3/2, ethyl acetate/hexane) to provide 8.00 mg (34%) of **64** as a colourless gum. This compound is very water soluble.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.16 (br q, 1H, *J* = 5), 5.47 (br s, 1H), 4.7 (br m, 1H), 3.96 (br dd, 1H, *J* = 11.0, 3.0), 3.8 (br s, 1H), 3.68 (br t, 1H, *J* = 11.0), 3.60 (br d, 1H, *J* = 12.0), 3.39 (dd, 1H, *J* = 12.0, 4.0), 2.81 (d, 3H, *J* = 5.0), 2.80 (m, 1H), 2.53-2.48 (m, 1H), 2.02 (s, 1H, OH), 1.77 (br d, 1H), 0.65 (d, 3H, *J* = 7.0).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 177.0, 78.3, 76.4, 72.9, 72.1, 70.5, 69.5, 29.9, 25.9, 11.4.

IR (neat):

3375, 1646, 1540, 1458, 1412, 1264, 1145, 1093, 1055, 1019, 977 cm^{-1}.

MS (APCI):

234.1 (M+1, 100).

HRMS (CI):

m/z 233.1259 (233.1263 calc. for $C_{10}H_{19}NO_5$, M+).

$[\alpha]^{23}_D$ = -3.8 (*c* 0.8, CH_2Cl_2).

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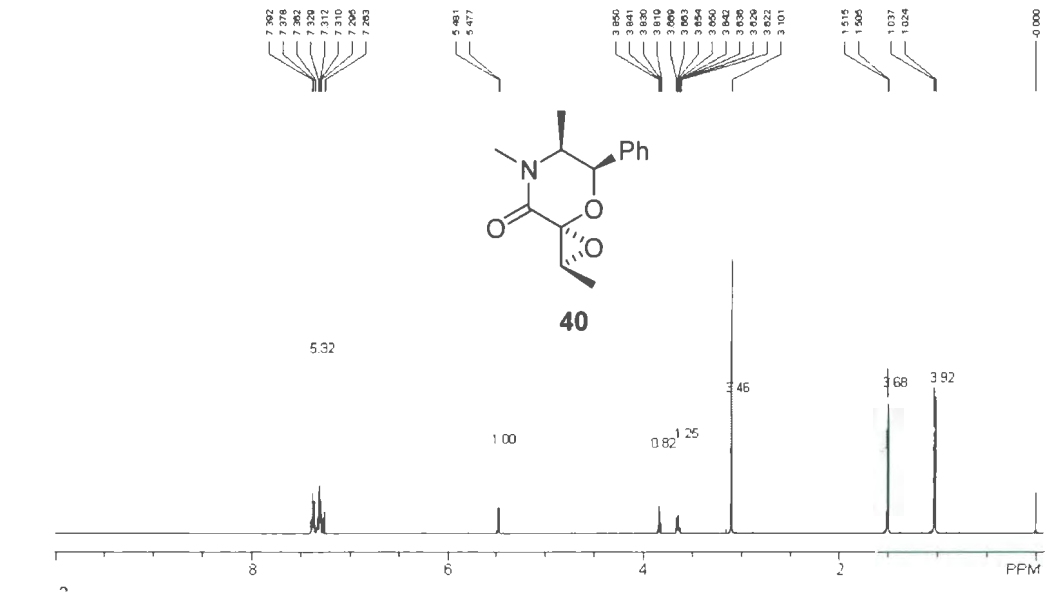
Appendix 2:

^{1}H and ^{13}C NMR Spectra for Chapter 3


7.392
7.378
7.362
7.329
7.312
7.310
7.296
7.283
5.481
5.477
3.850
3.841
3.830
3.810
3.669
3.663
3.654
3.650
3.642
3.638
3.629
3.622
3.101
1.515
1.505
1.037
1.024
0.000
Ph
N
O
O
O
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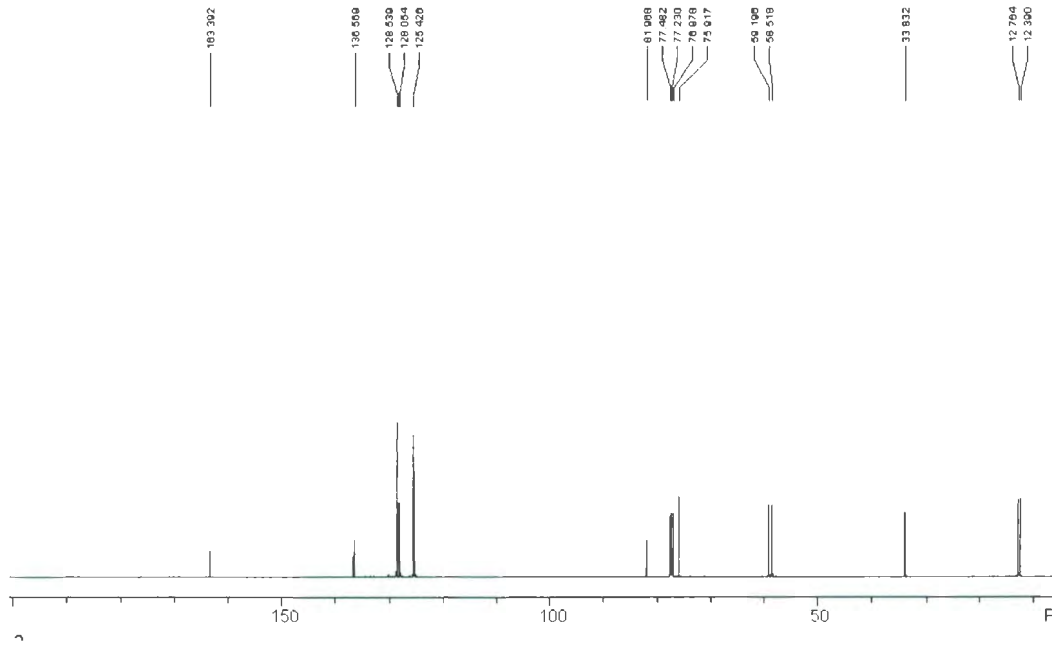
1.00
0.82
1.25
3.46
3.68
3.92
8
6
4
2
PPM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125.426
81.968
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58.519
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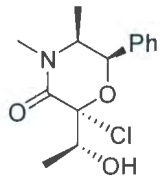
12.764
12.390
150
100
50
PPM



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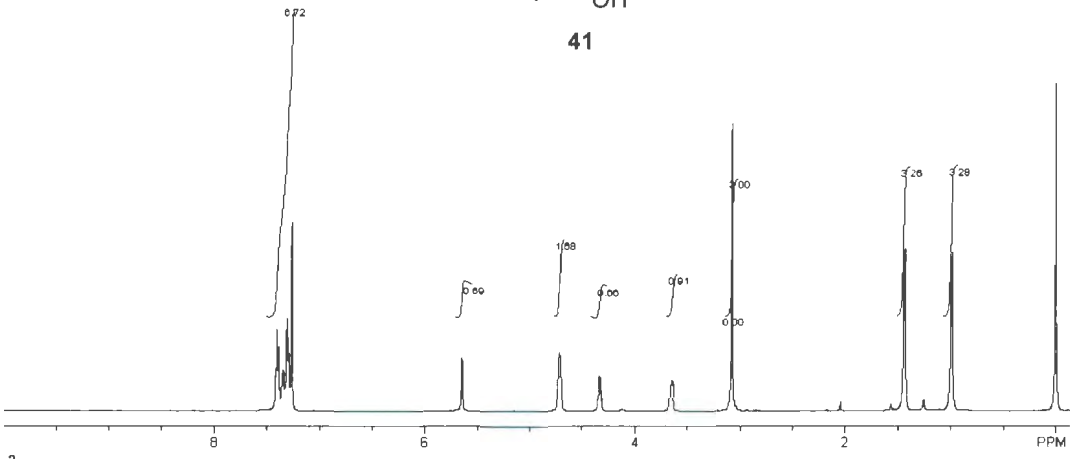

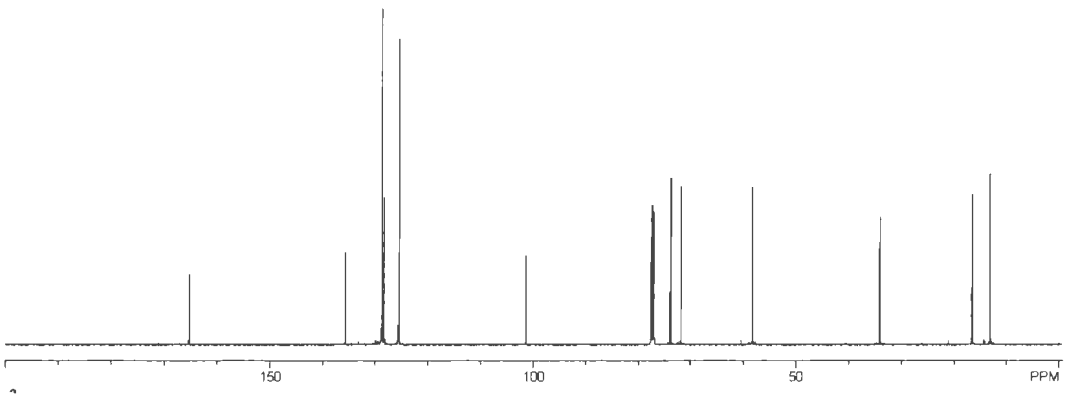

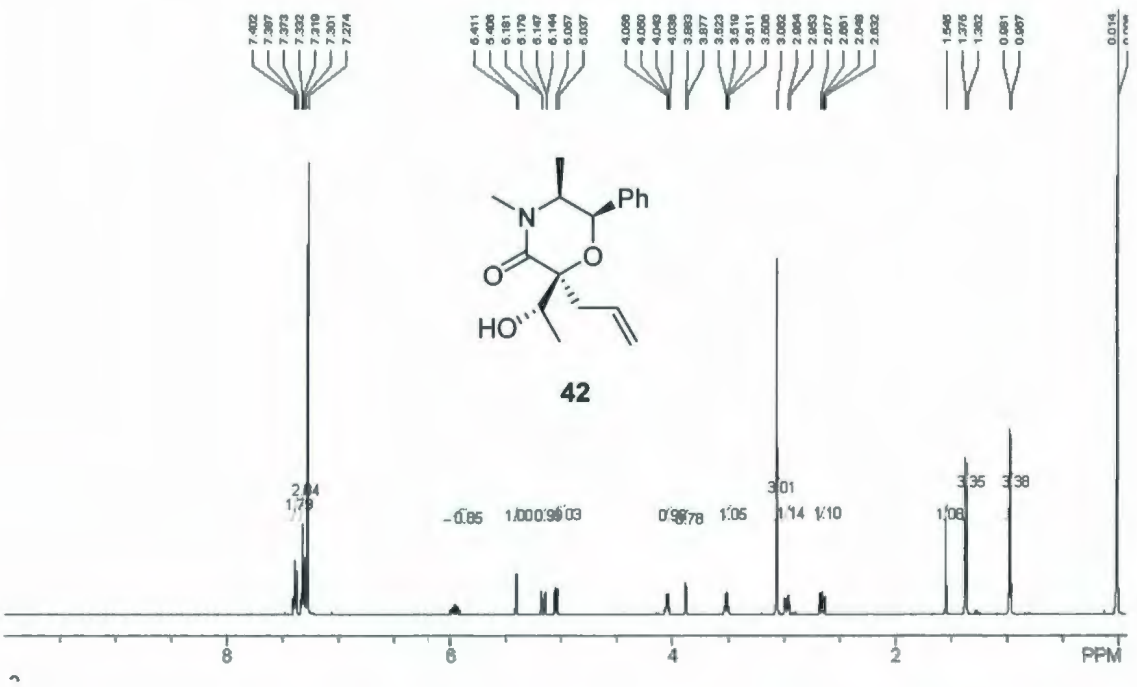
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O
O
HO
42
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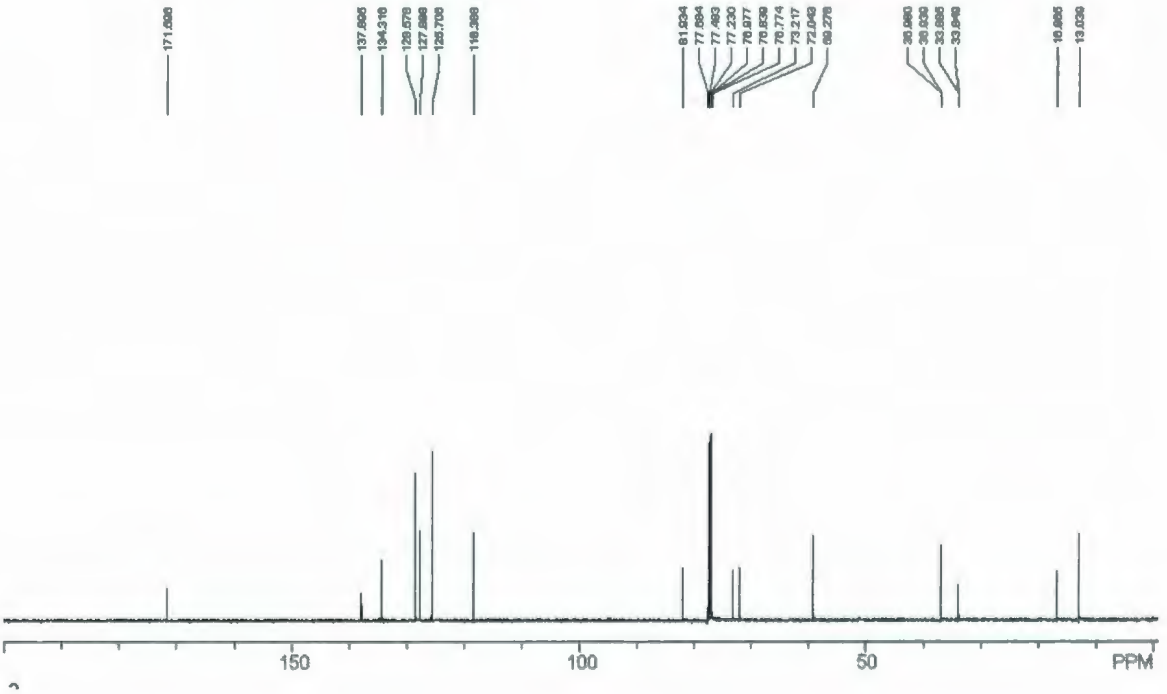
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100
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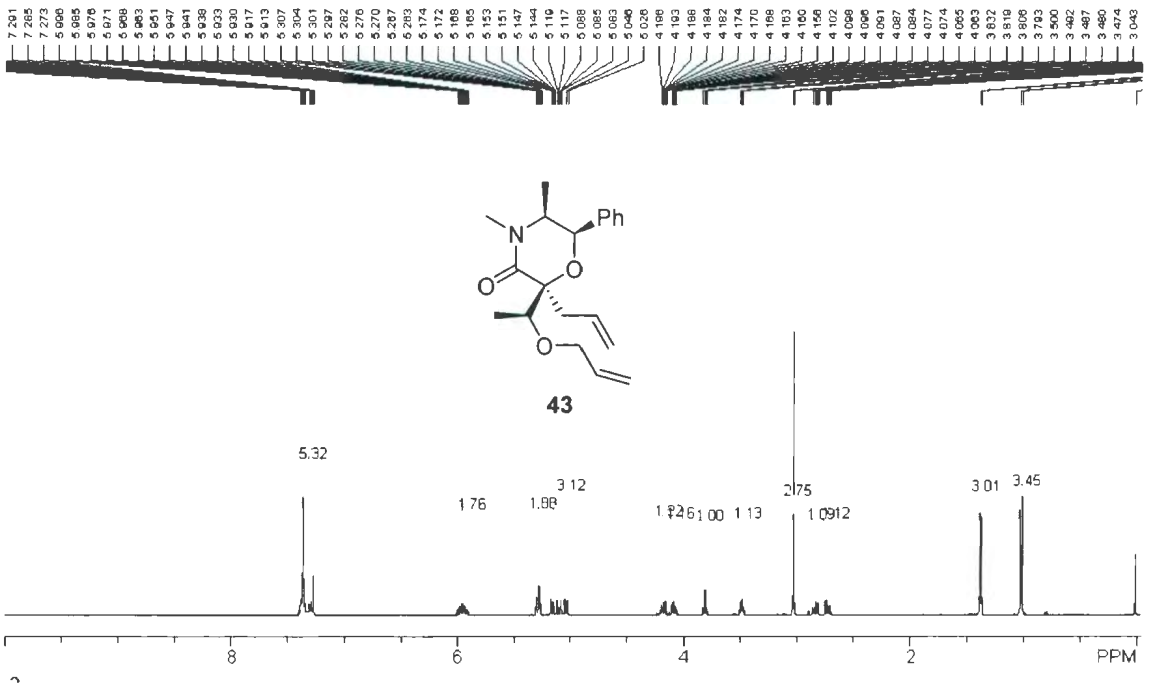
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O
O
O
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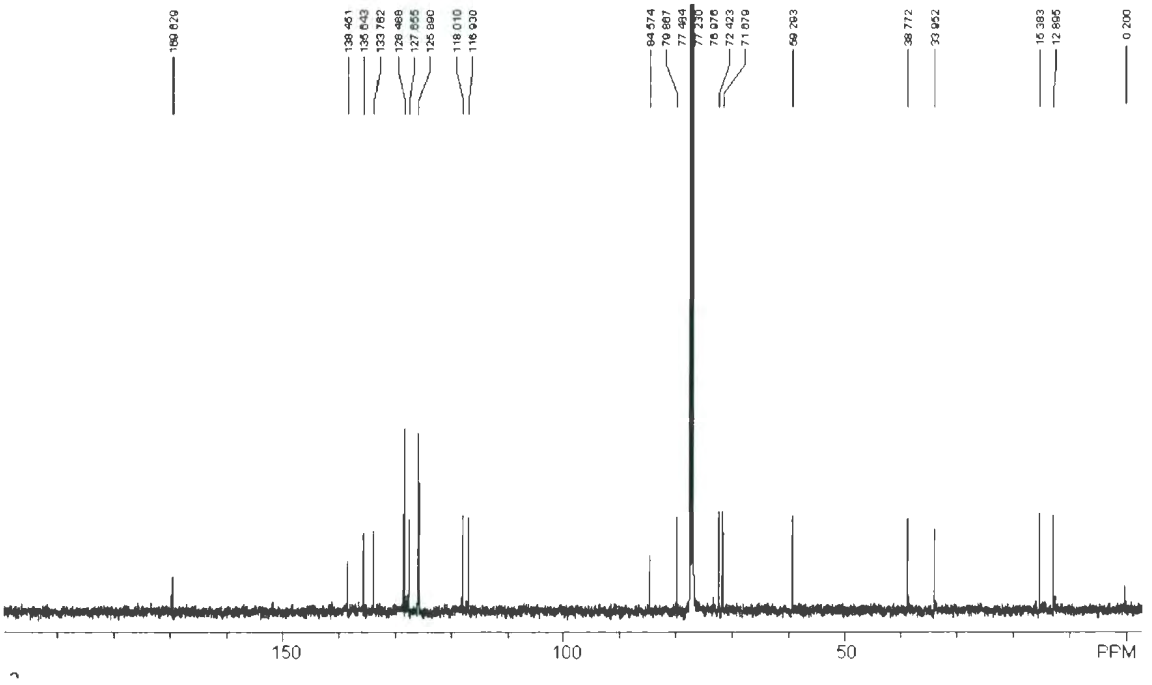
1.13
1.09
12
3.01
3.45
8
6
4
2
PPM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100
50
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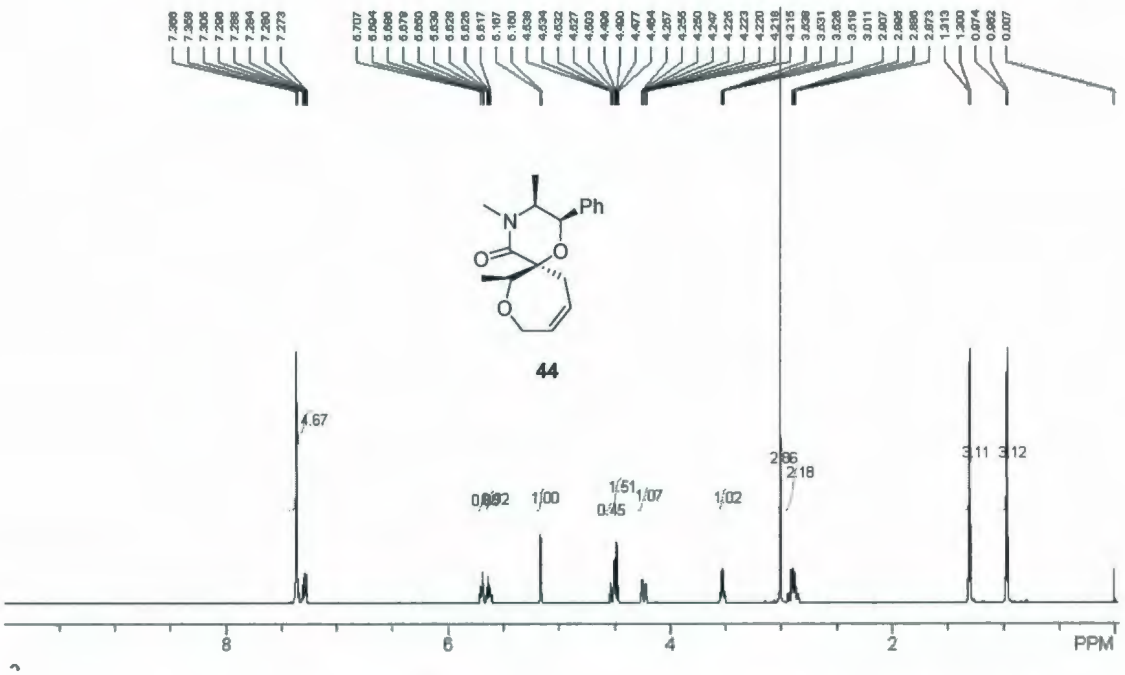
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4
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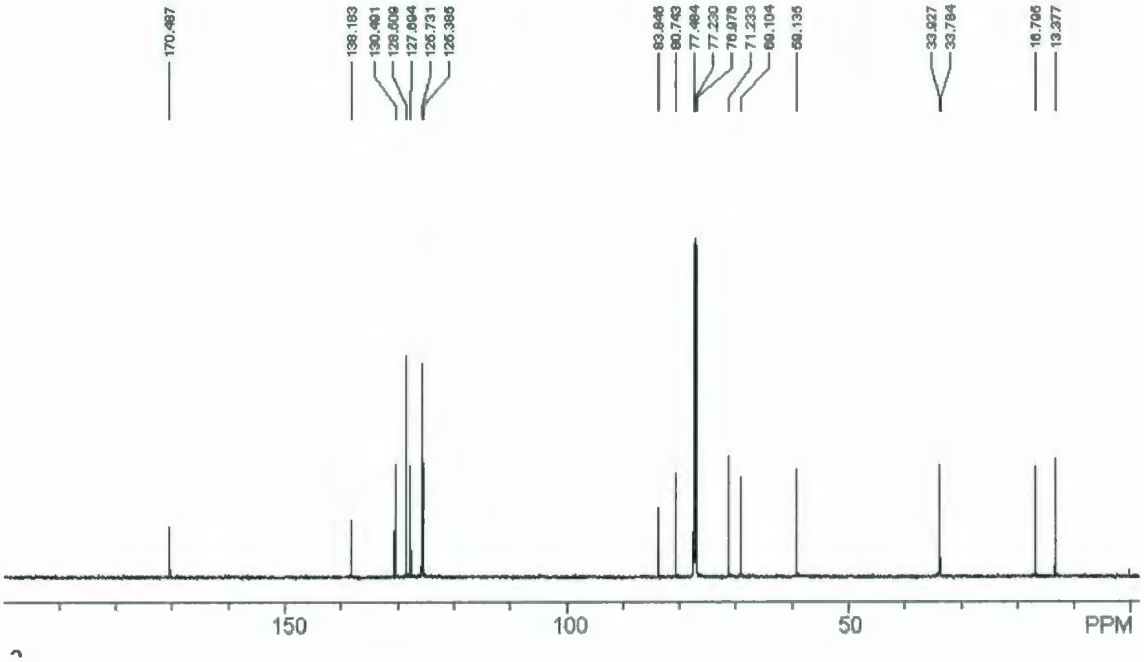
PPM

44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100
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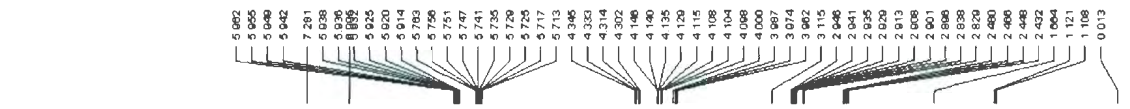
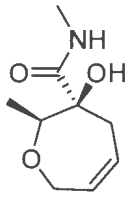
PPM

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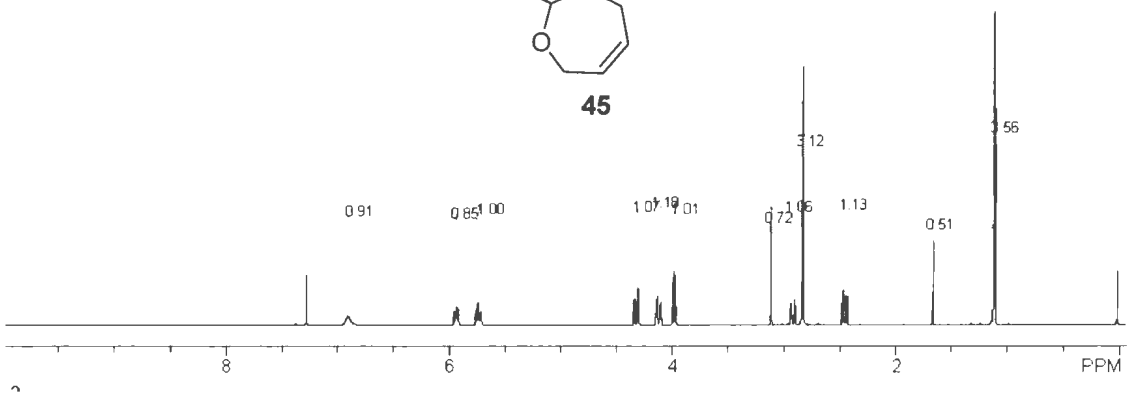
OH
O

45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1.13
0.51
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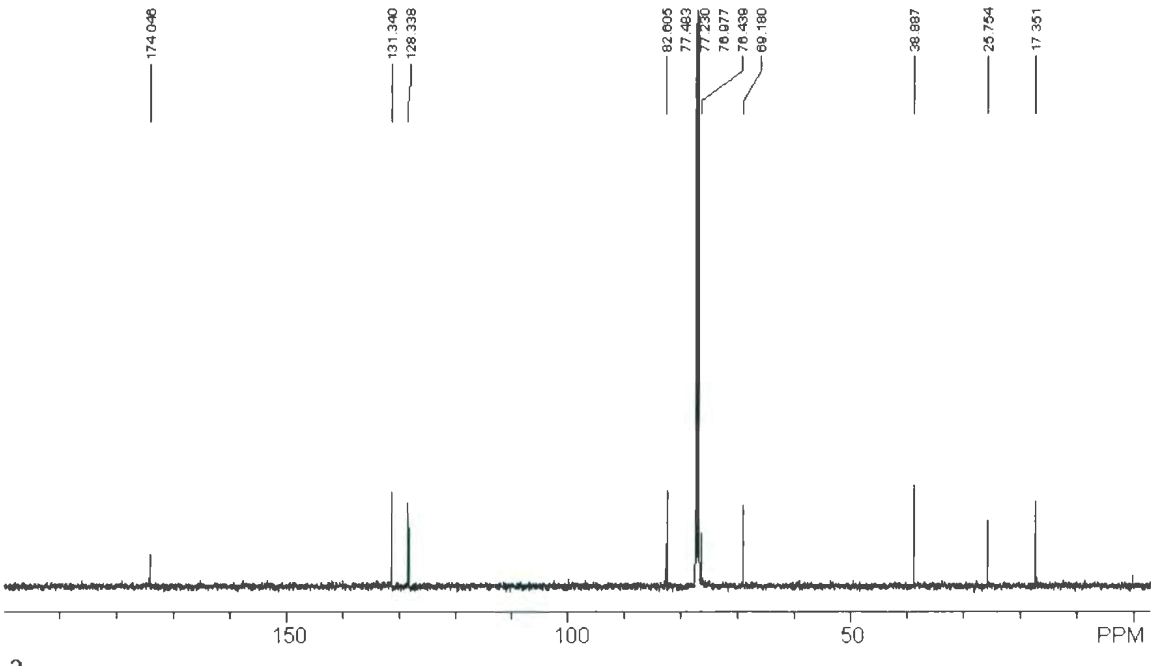
8
6
4
2
PPM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50
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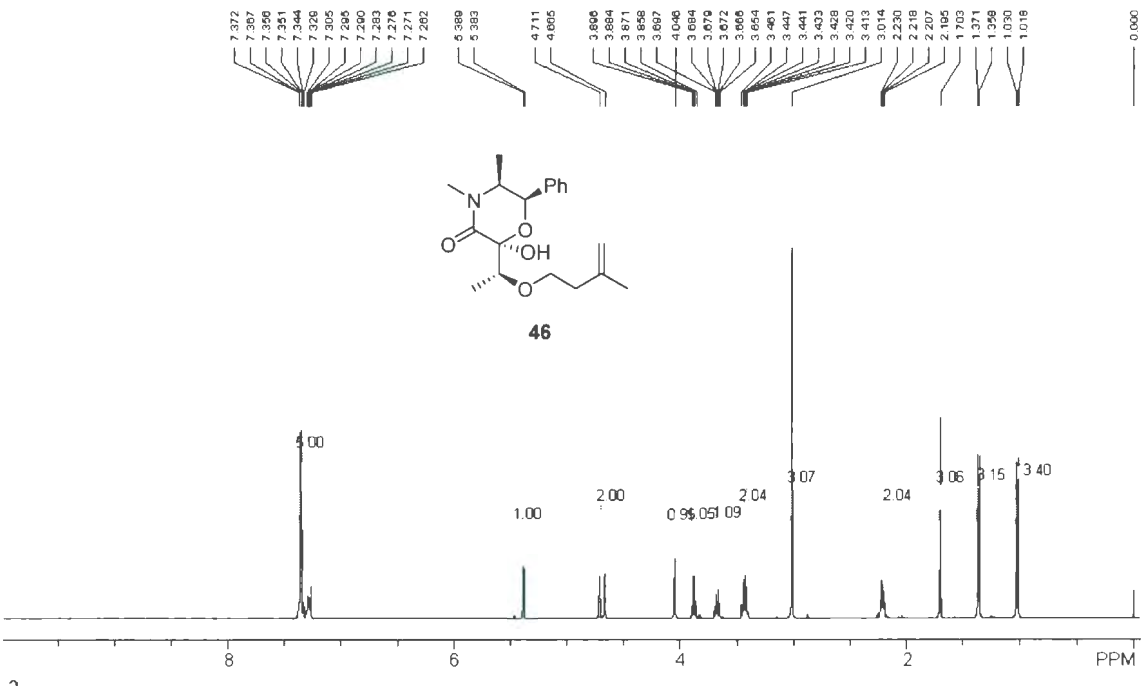
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7.262
5.389
5.383
4.711
4.665
3.896
3.884
3.871
3.858
3.687
4.046
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3.679
3.672
3.666
3.654
3.461
3.447
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3.428
3.420
3.413
3.014
2.230
2.218
2.207
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1.371
1.358
1.030
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0.000
Ph
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O
O
OH
O
46
5.00
1.00
2.00
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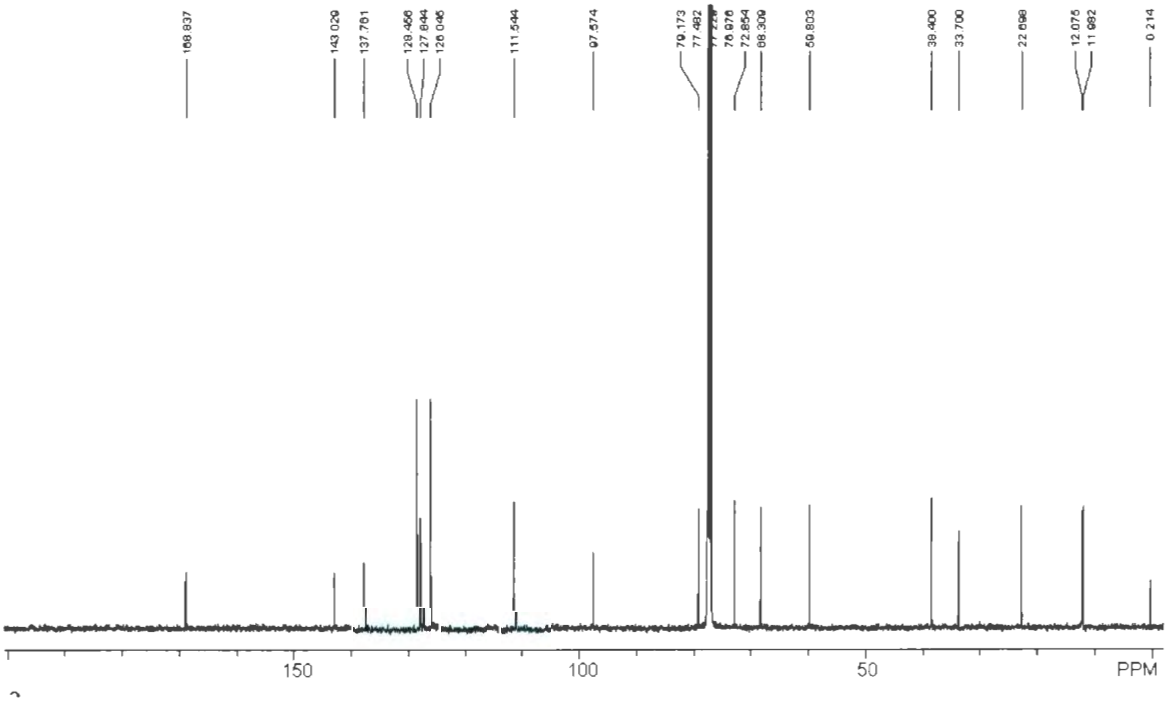
8
6
4
2
PPM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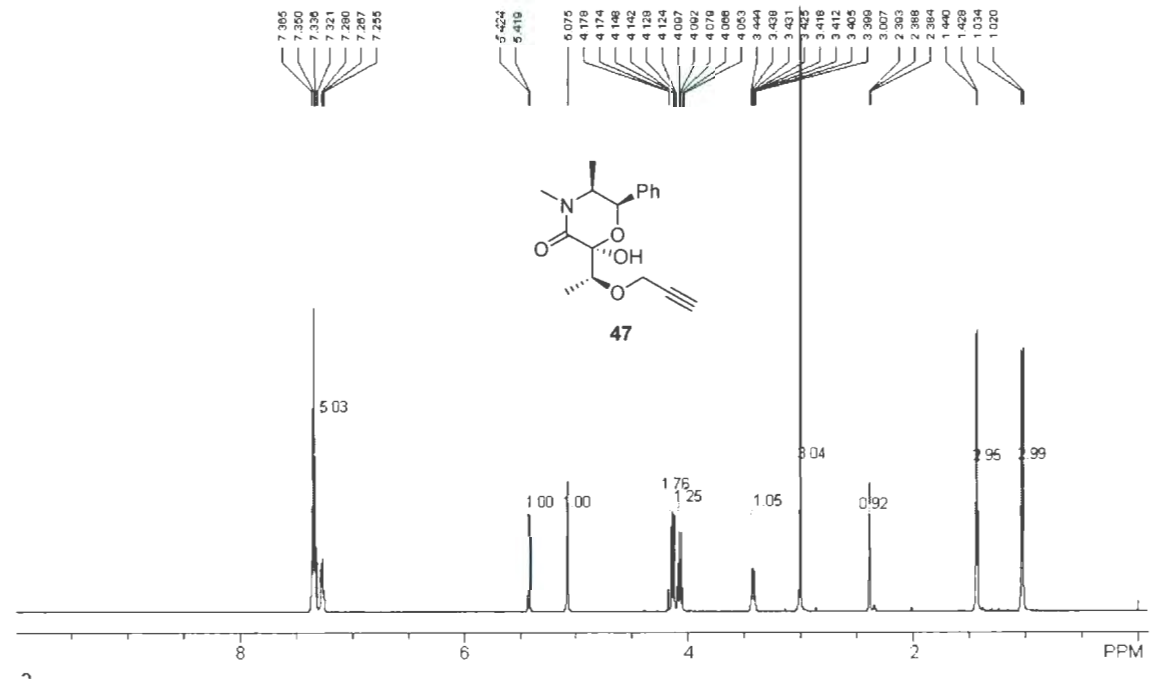
100
50
PPM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4.148
4.142
4.129
4.124
4.097
4.092
4.079
4.066
4.053
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3.438
3.431
3.425
3.418
3.412
3.405
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1.020
Ph
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O
O
OH
O
47
5.03
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2
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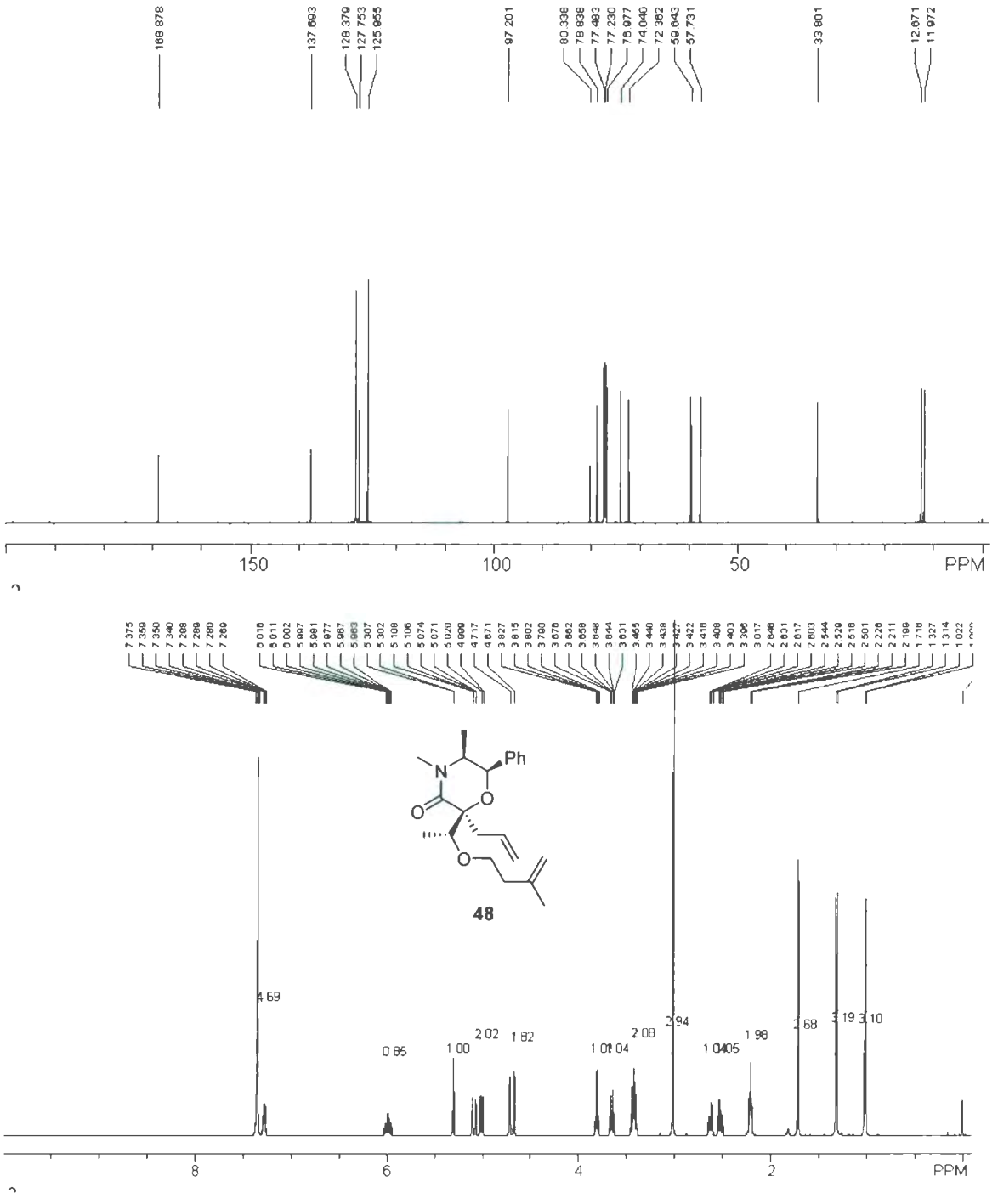
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72.362
59.643
57.731
33.801
12.671
11.972
150
100
50
PPM
Ph
N
O
O
O
48
4.69
0.85
1.00
2.02
1.82
1.01
1.04
2.08
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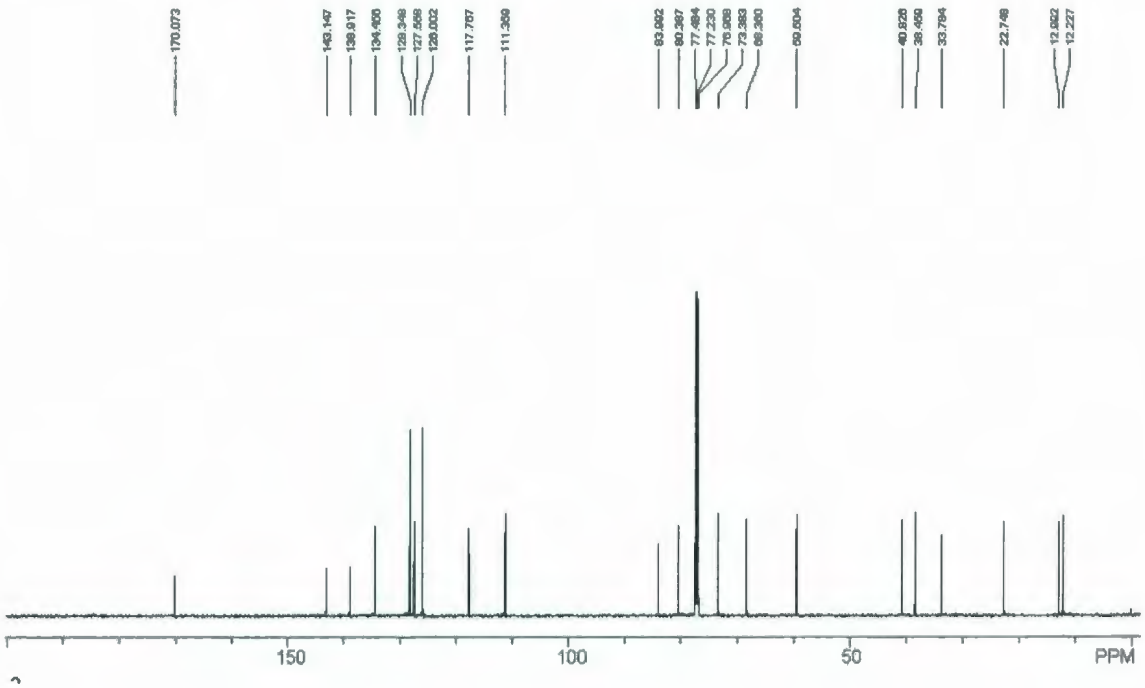
1.98
2.68
3.19
3.10
8
6
4
2
PPM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127.888
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111.399
83.992
80.367
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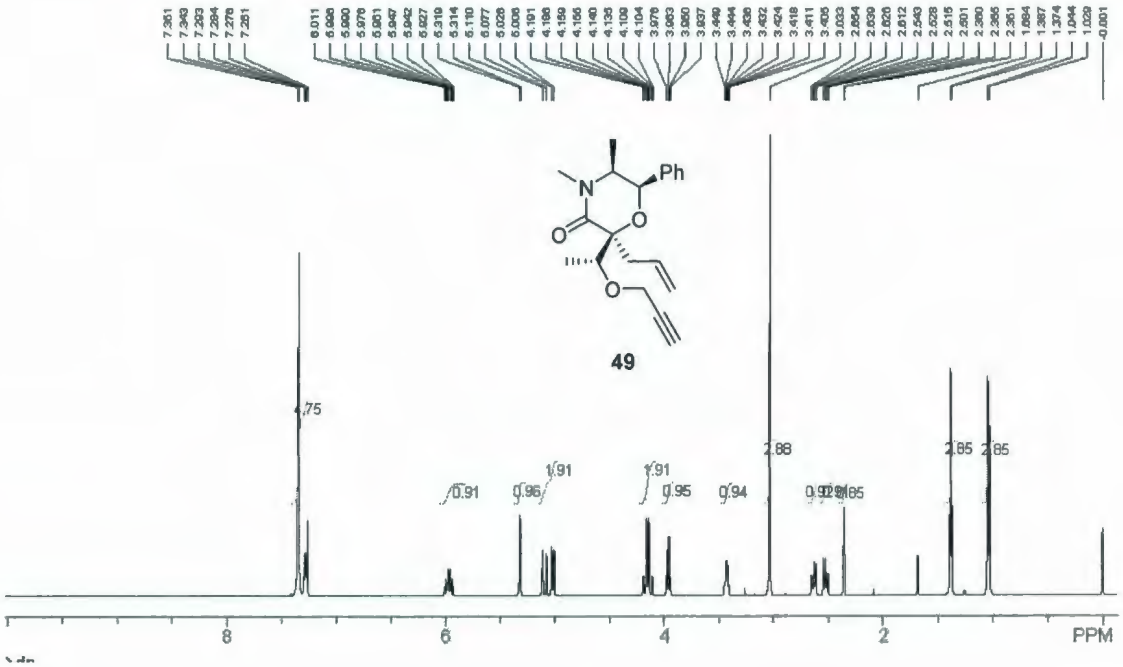
77.230
76.968
73.383
66.360
60.604
40.826
38.459
33.794
22.748
12.922
12.227
150
100
50
PPM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5.942
5.827
5.319
5.314
5.110
5.077
5.026
5.006
4.191
4.186
4.159
4.156
4.140
4.135
4.109
4.104
3.976
3.963
3.950
3.857
3.449
3.444
3.439
3.432
3.424
3.418
3.411
3.406
3.033
2.854
2.839
2.826
2.612
2.543
2.528
2.515
2.501
2.360
2.356
2.351
1.684
1.367
1.374
1.044
1.029
0.001
Ph
N
O
O
O
49
4.75
0.91
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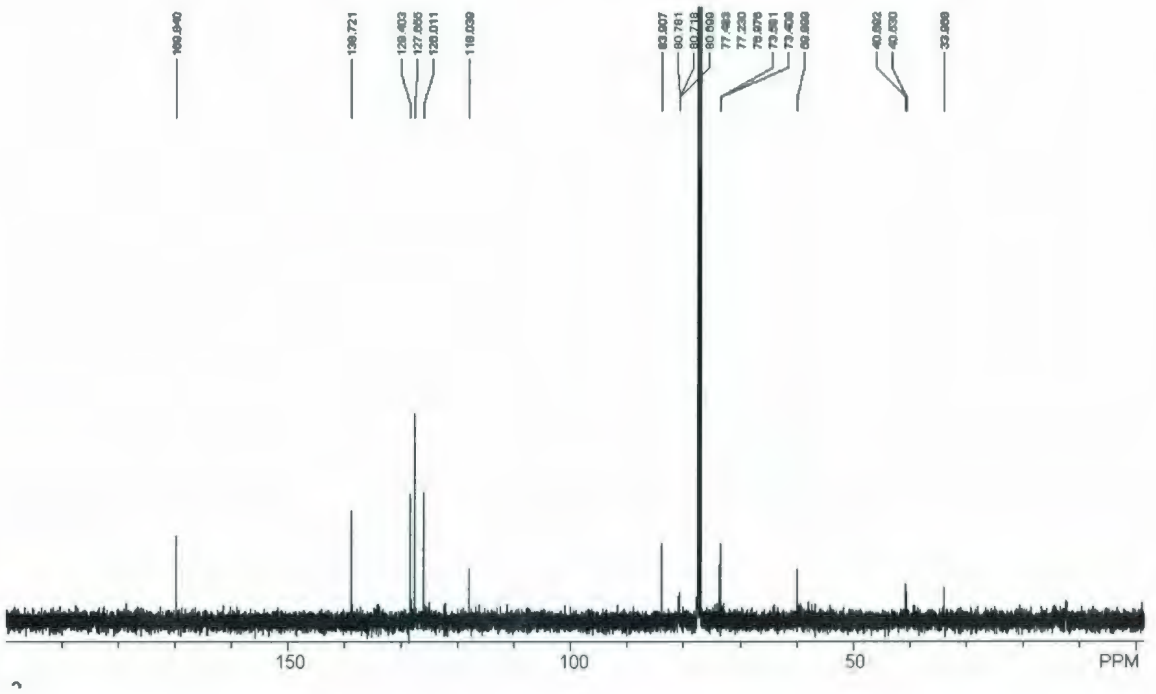
1.91
0.95
0.94
2.88
0.85
2.85
2.85
8
6
4
2
PPM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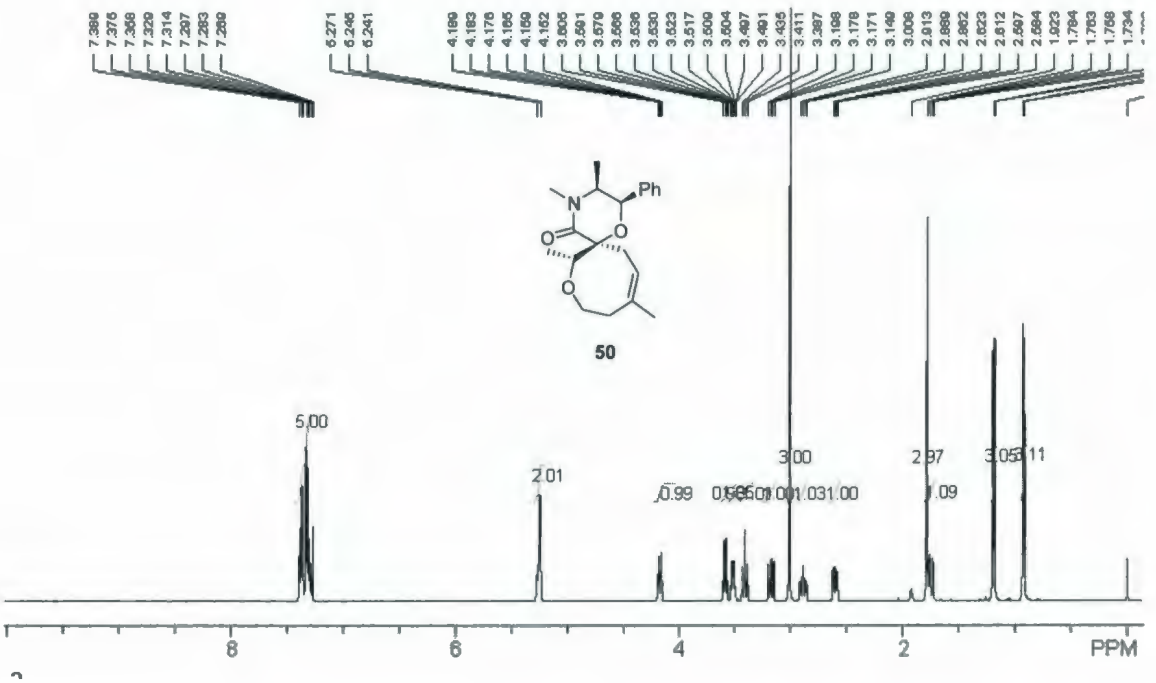
Ph
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O
O
O
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8
6
4
2
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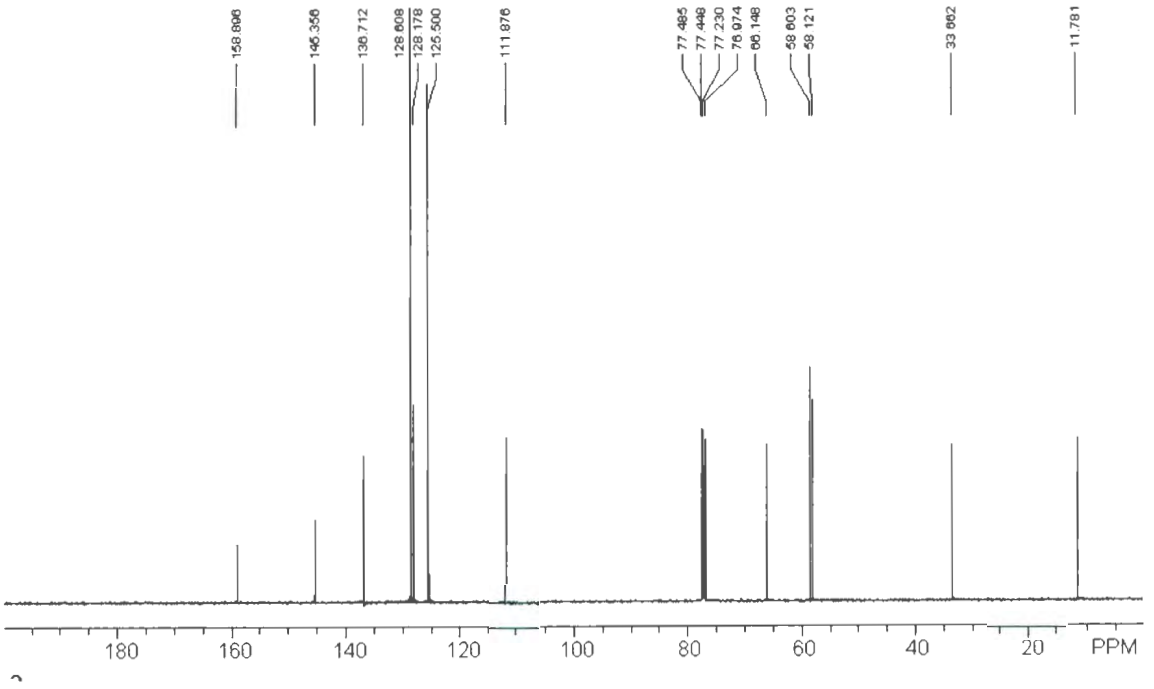
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125.500
111.876
77.485
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77.230
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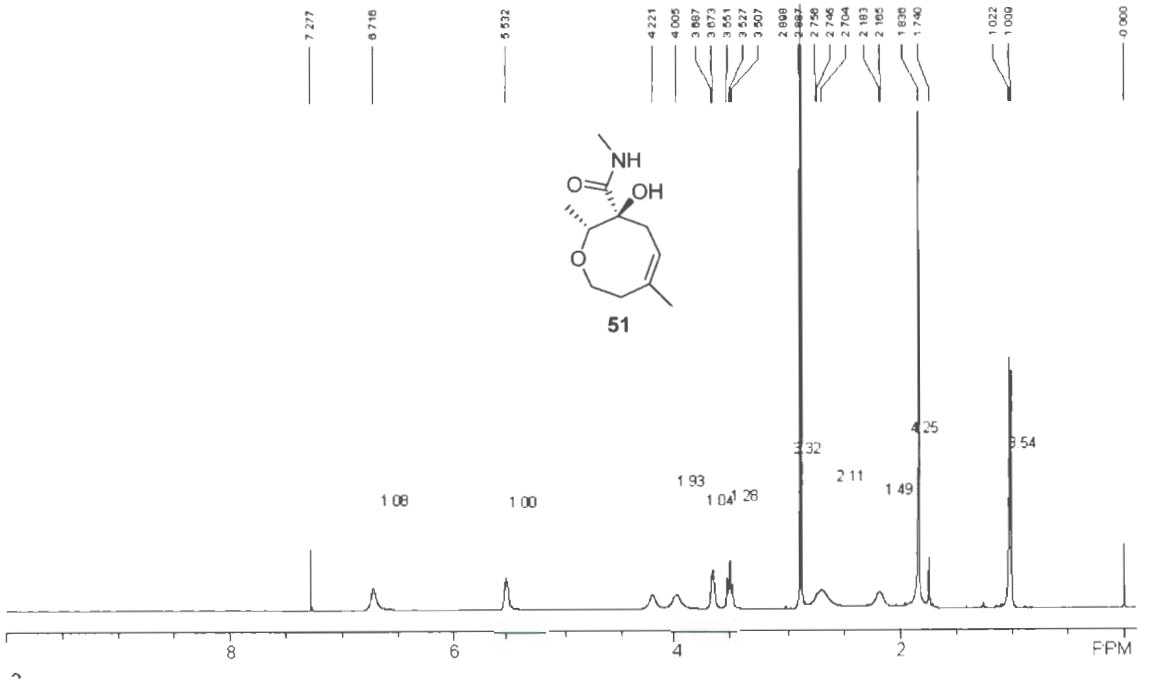
58.121
33.662
11.781
180
160
140
120
100
80
60
40
20
PPM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6.716
5.532
4.221
4.005
3.667
3.673
3.551
3.527
3.507
2.898
2.887
2.756
2.745
2.704
2.193
2.165
1.838
1.740
1.022
1.000
0.000
NH
OH
O
O
51
1.08
1.00
1.93
1.04
1.28
3.32
2.11
1.49
4.25
3.54
8
6
4
2
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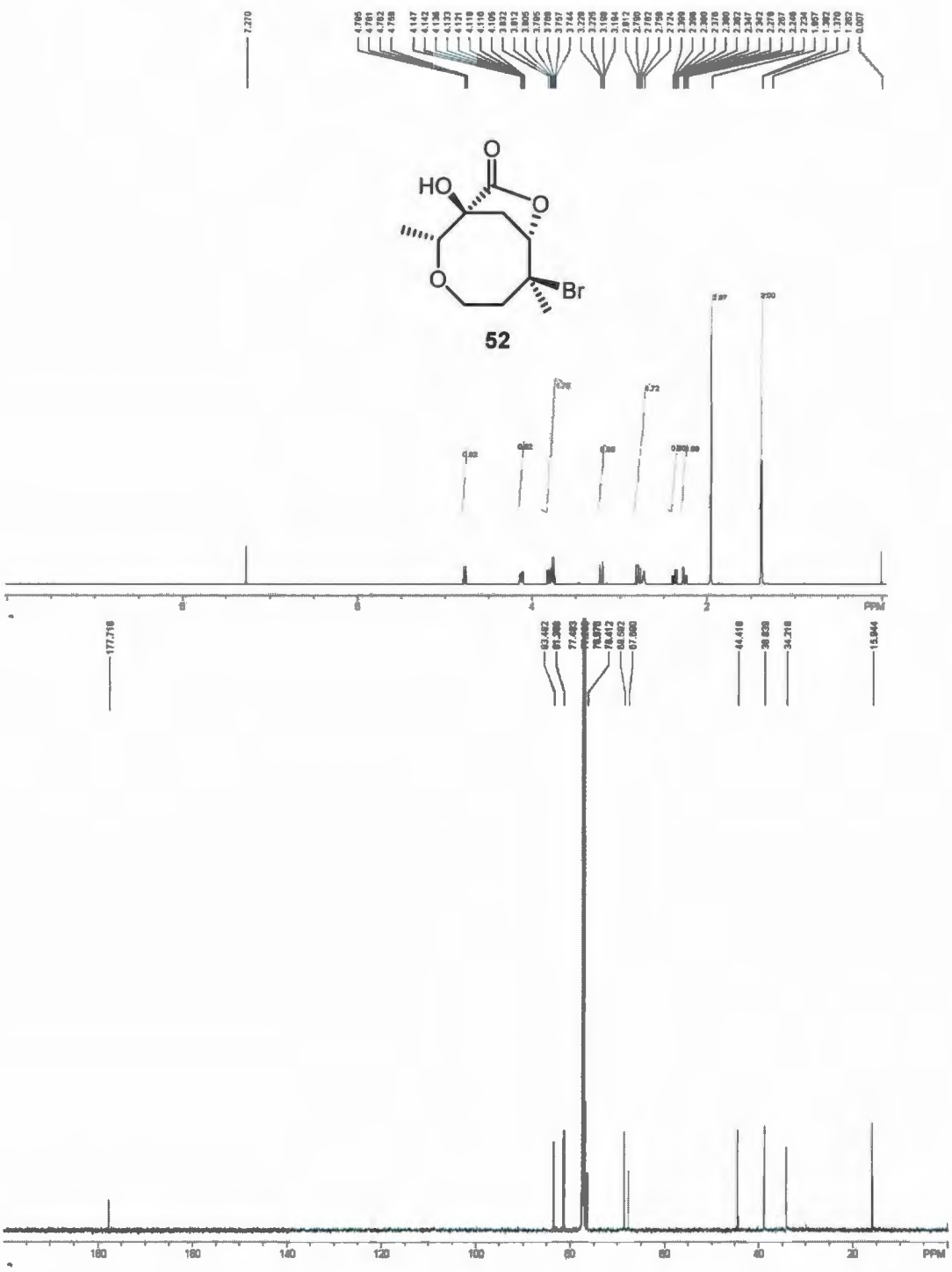

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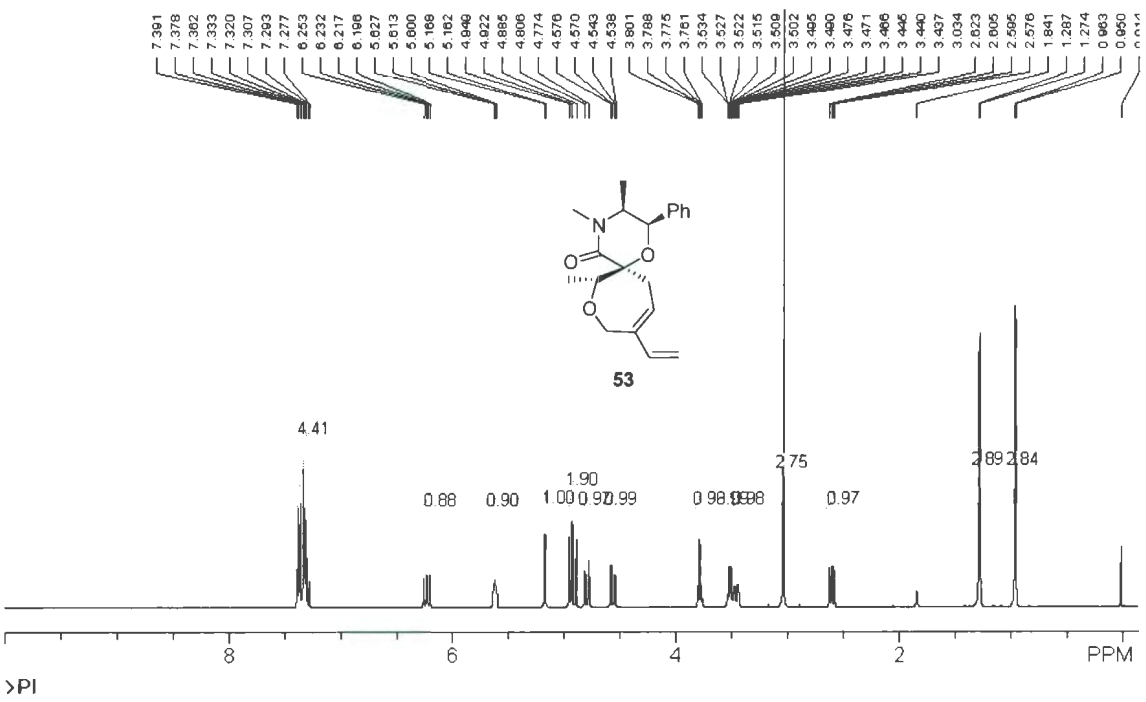
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O
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0.97
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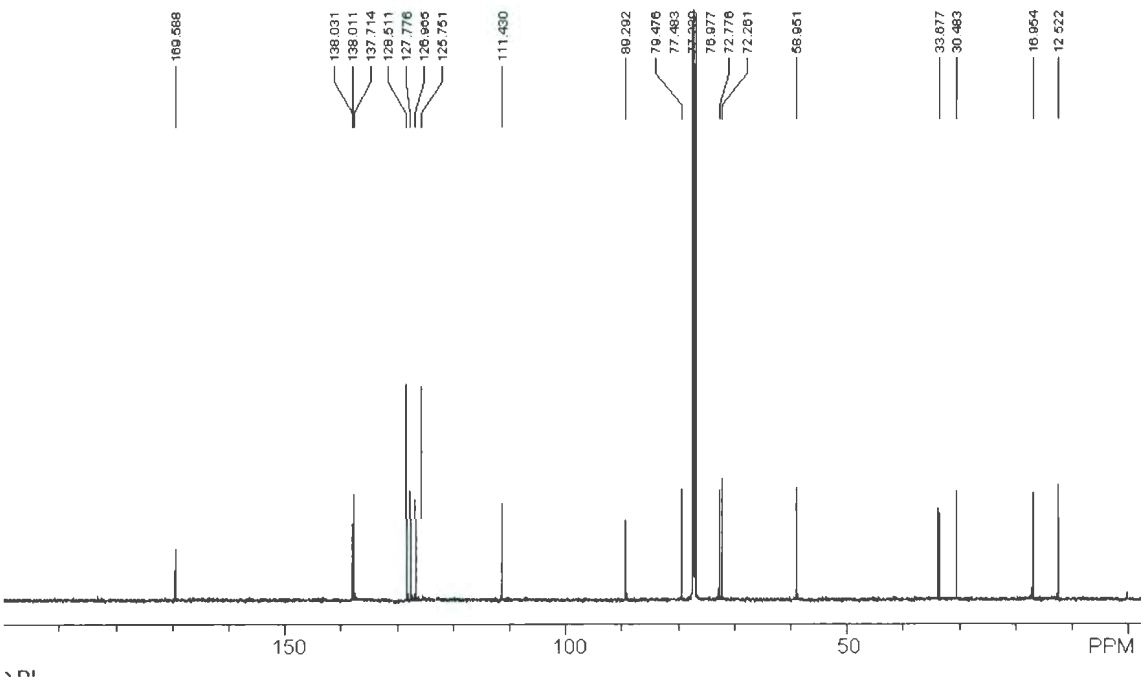
2.84
8
6
4
2
PPM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127.776
126.905
125.751
111.430
89.292
79.476
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72.776
72.261
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33.877
30.483
16.954
12.522
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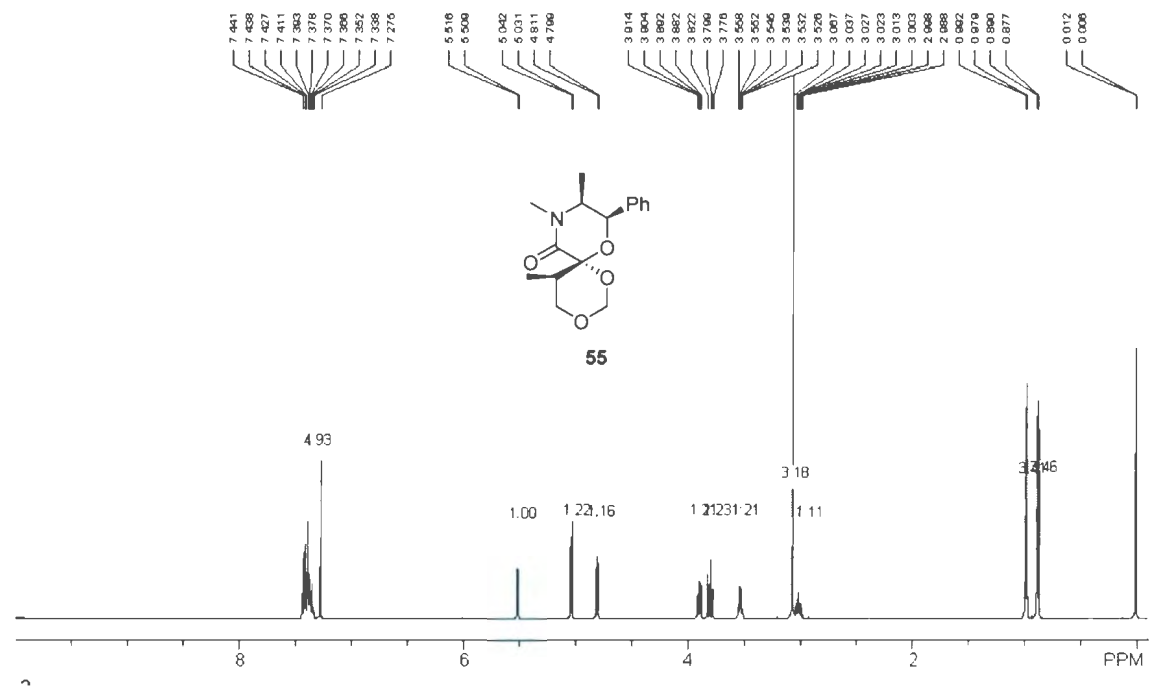
100
50
PPM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O
O
O
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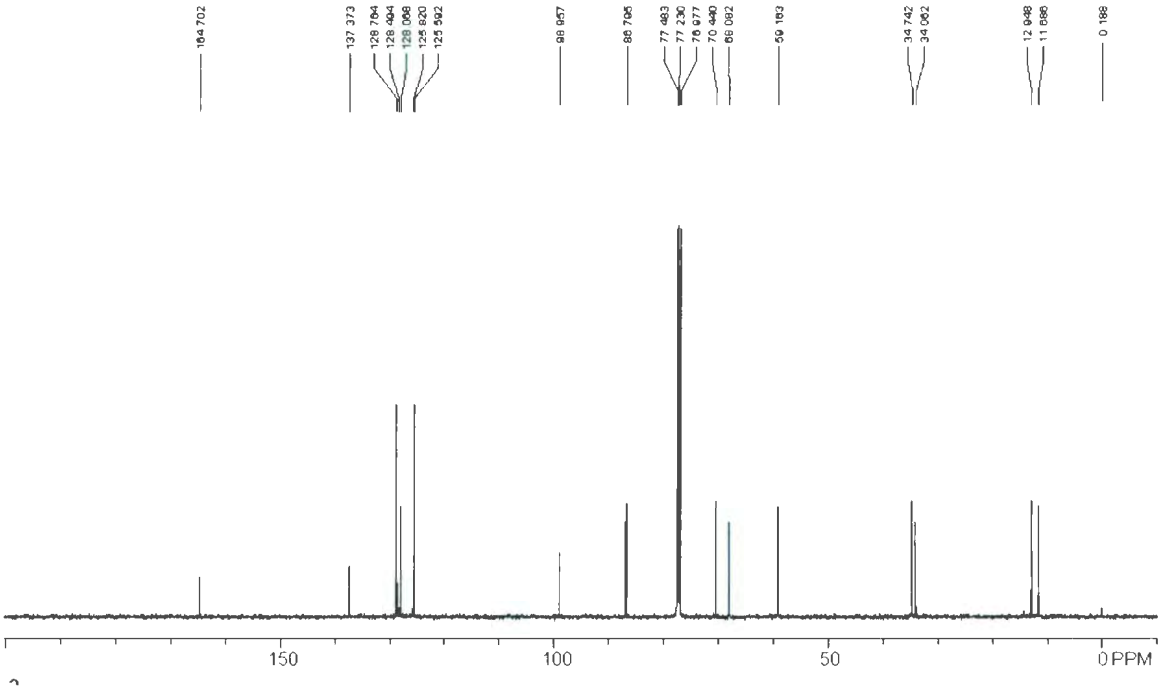
1.22
1.16
3.18
1.11
PPM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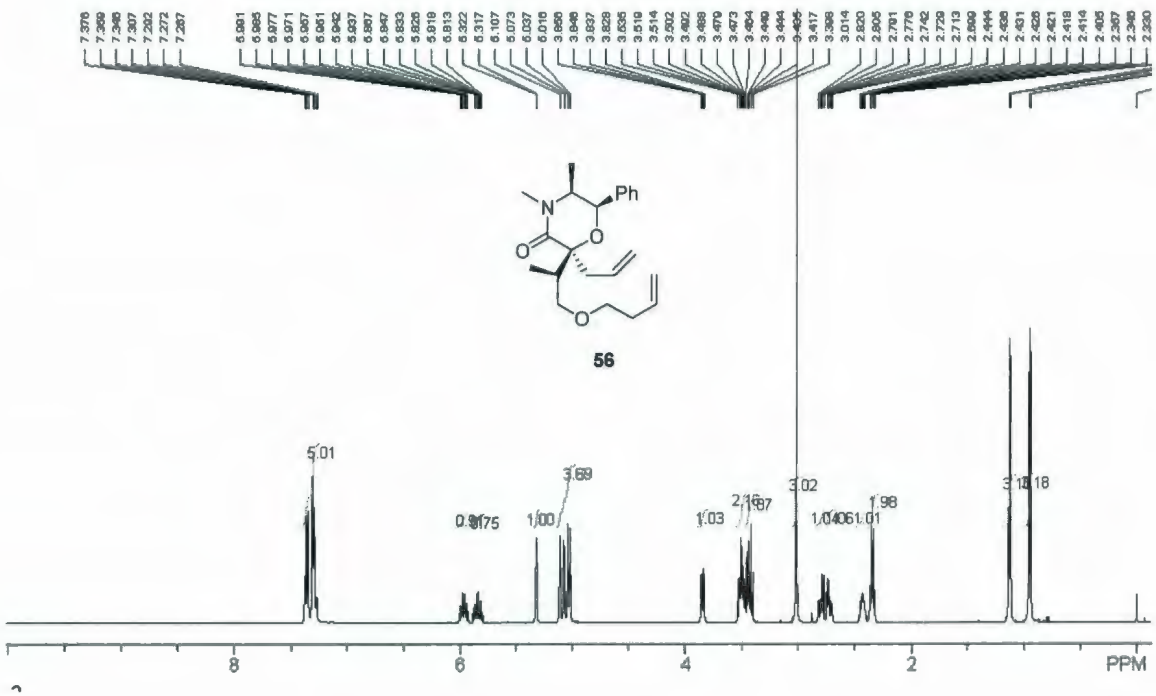
100
50
0 PPM


Ph
N
O
O
O
56
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2.16
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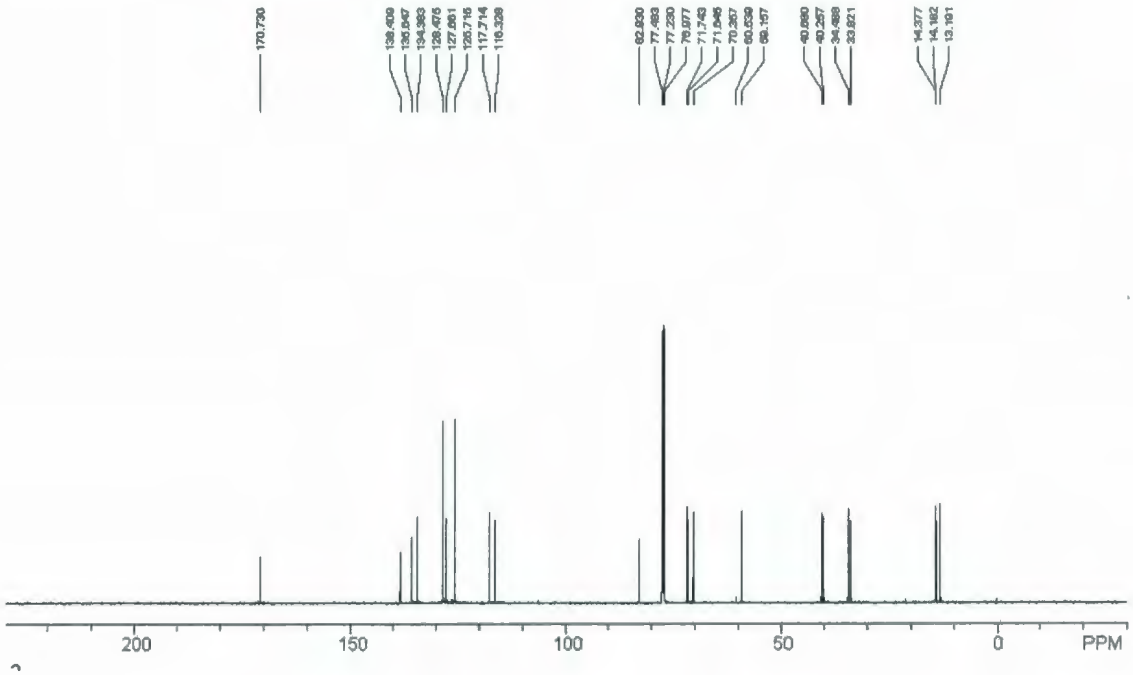
1.03
1.00
1.04
1.01
8
6
4
2
PPM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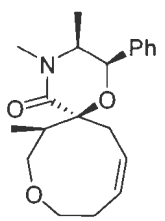
130.547
134.369
128.475
127.661
120.715
117.714
110.338
82.830
77.483
77.230
76.977
71.743
71.545
70.357
60.539
60.157
40.680
40.257
34.488
33.821
14.377
14.162
13.161
200
150
100
50
0
PPM



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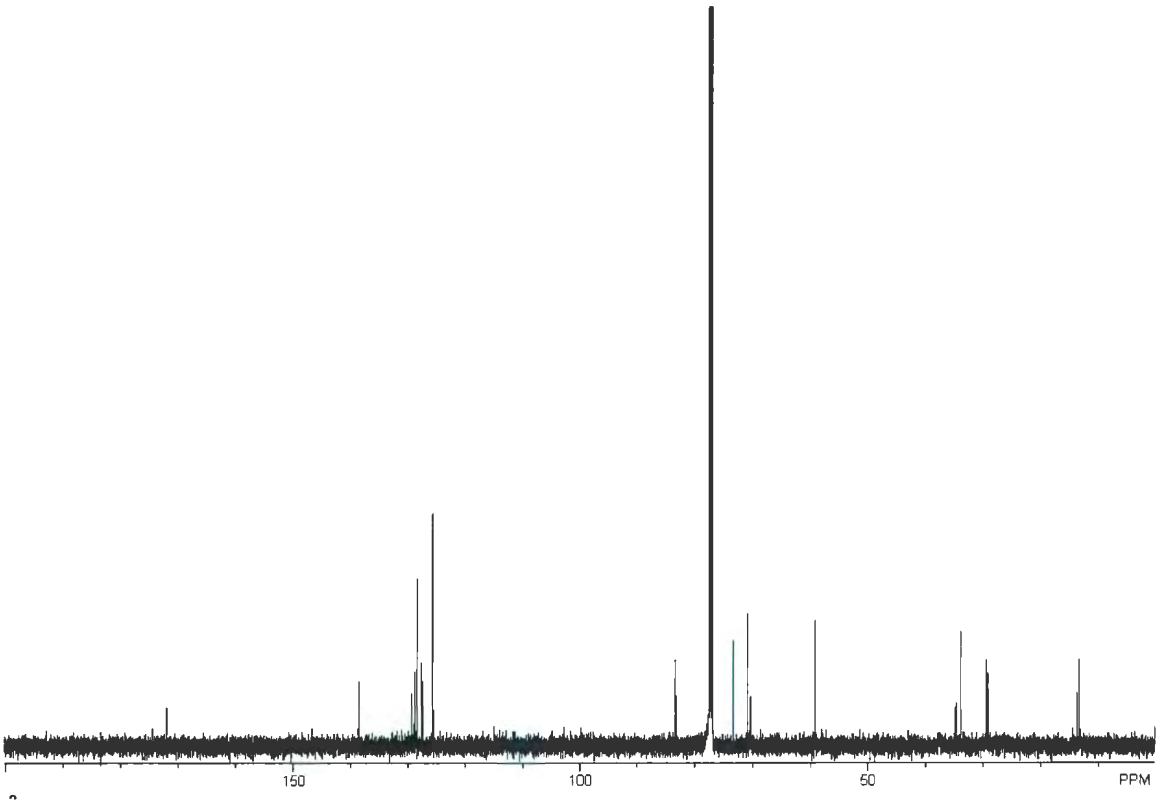

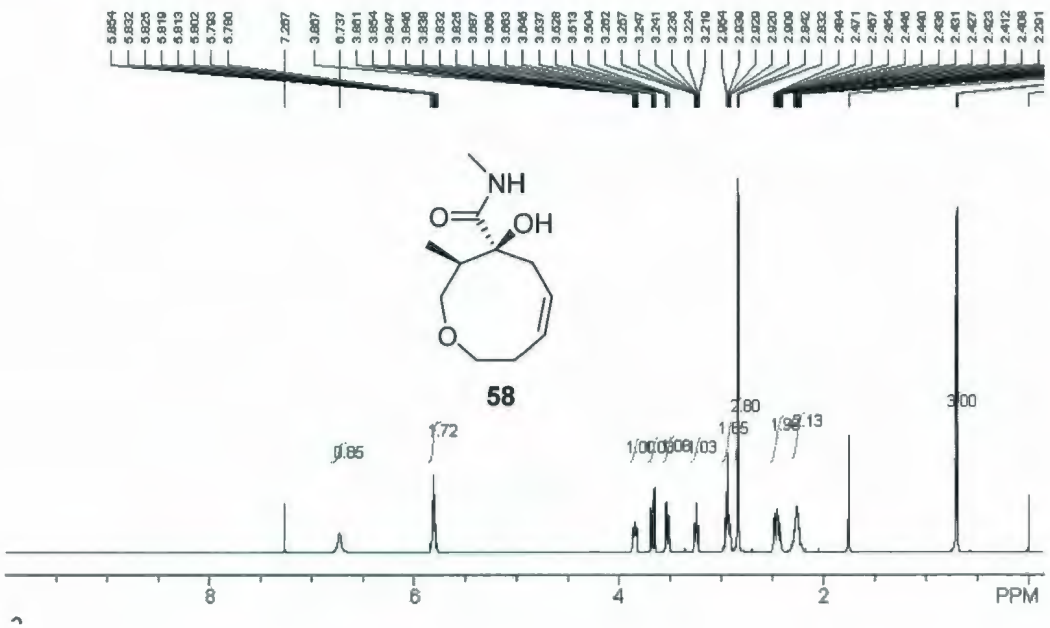
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O
OH
O
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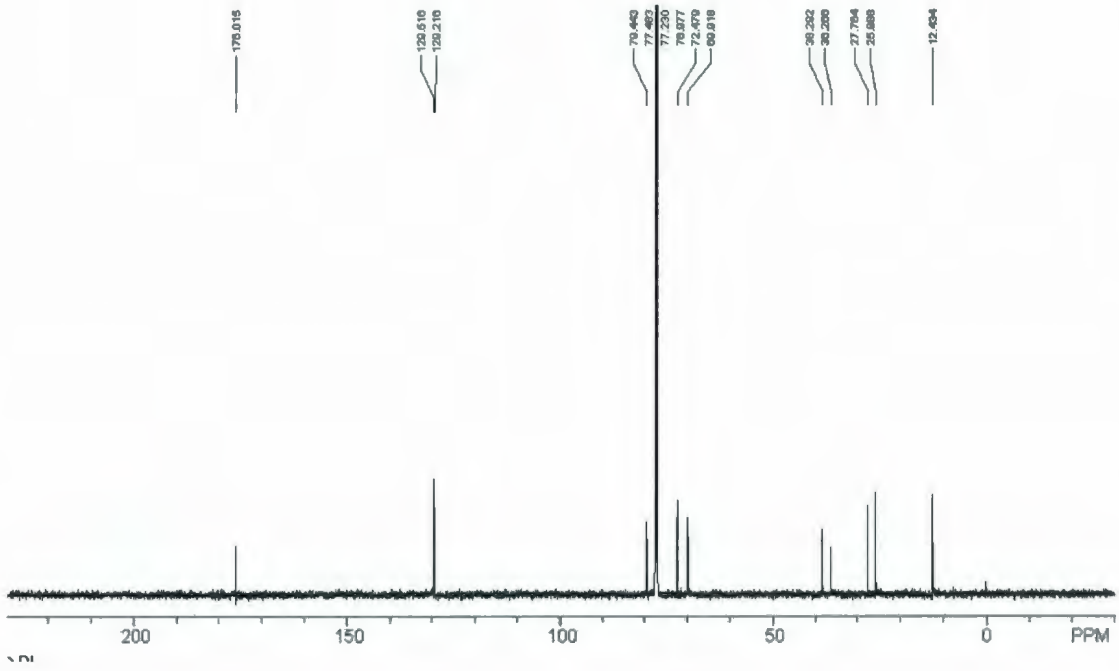
1.72
2.80
3.00
PPM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129.216
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72.479
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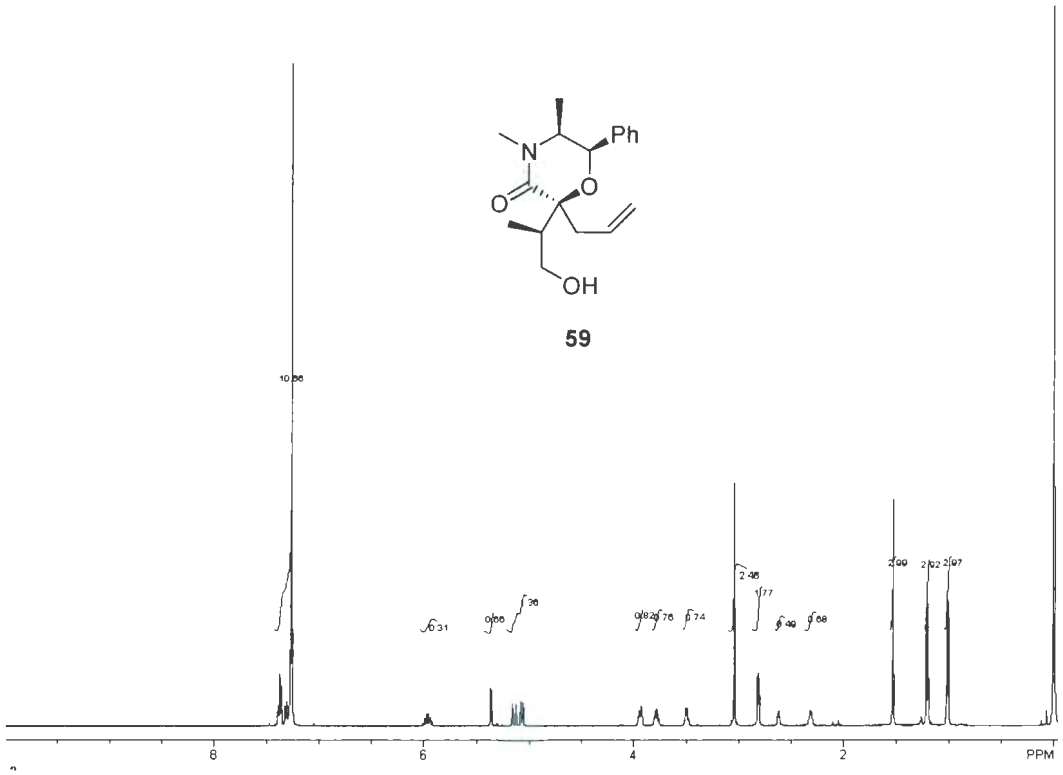
38.269
27.764
25.986
12.434
200
150
100
50
0
PPM



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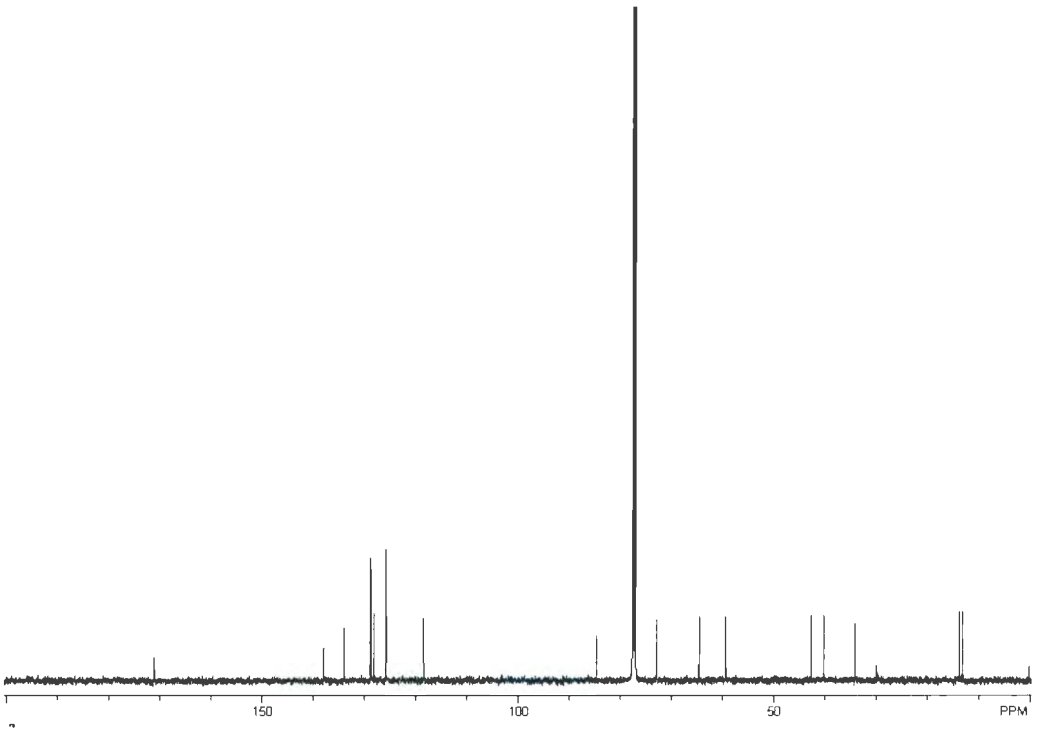

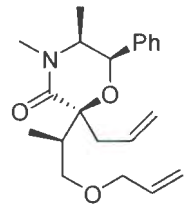
Ph
N
O
O
O

60

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1.68
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1.94
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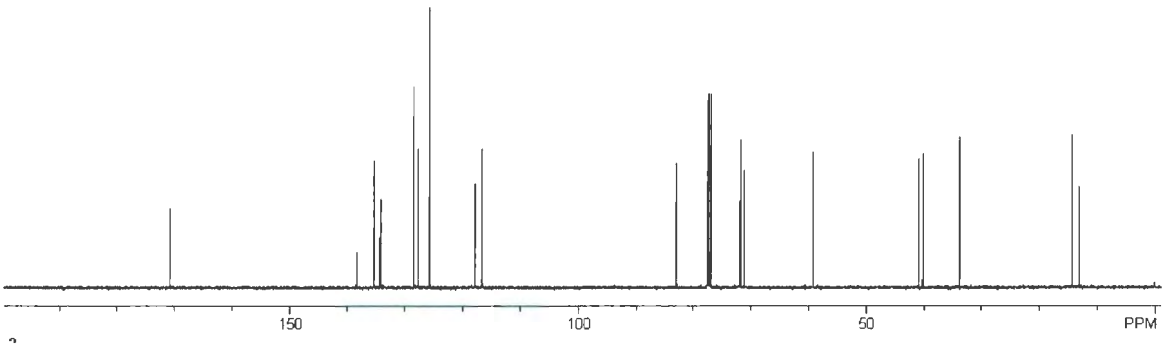
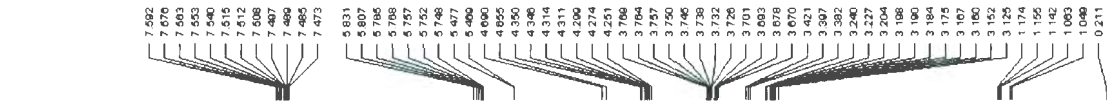
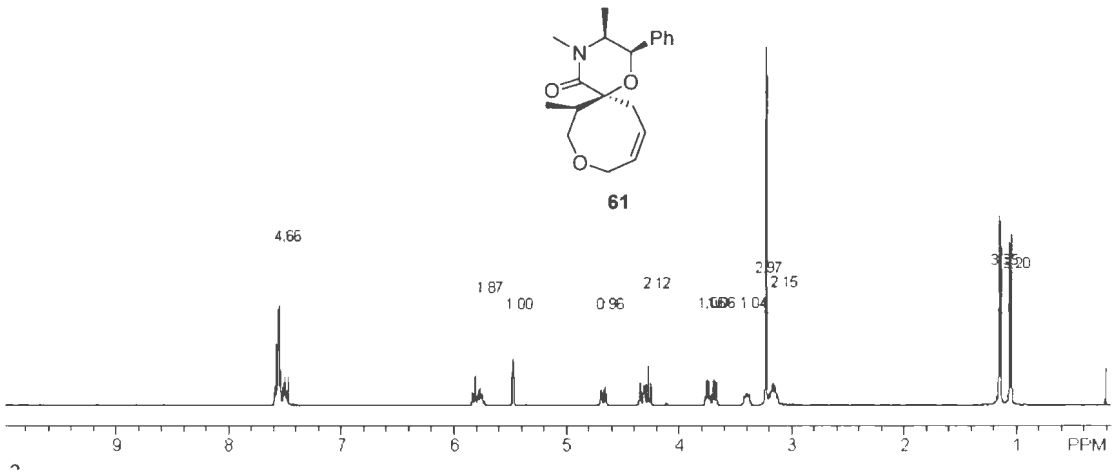
2.75
0.75
3.09
3.17
8
6
4
2
PPM


150
100
50
PPM




Ph
N
O
O
O
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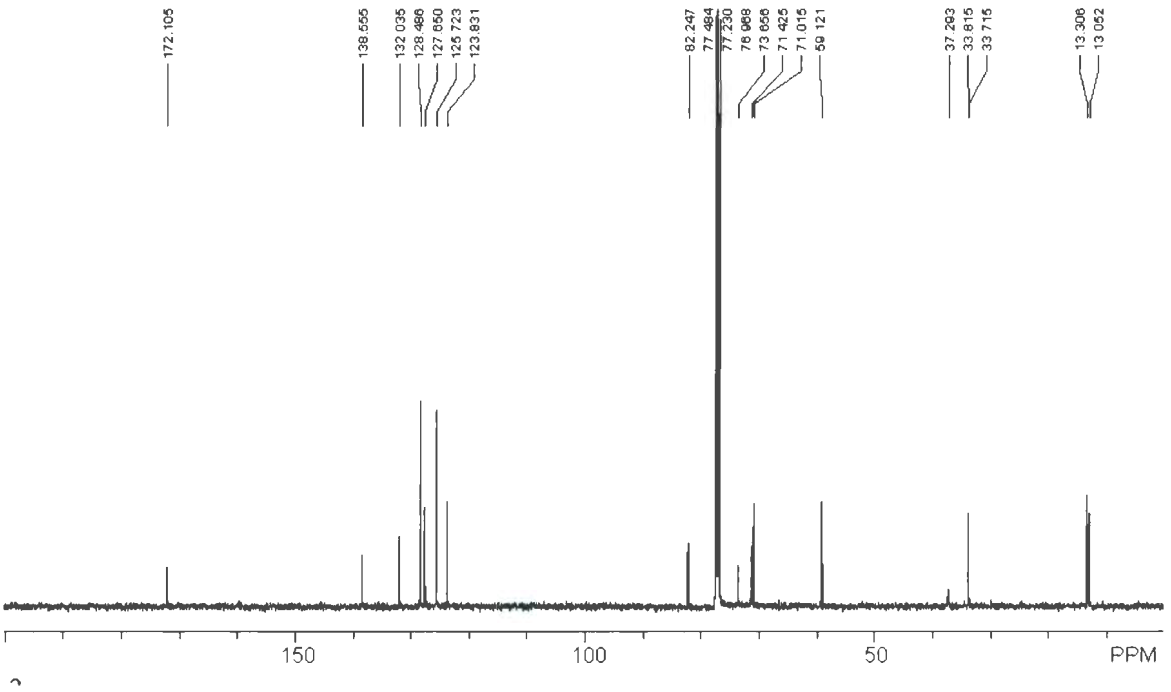
2.15
1.04
9
8
7
6
5
4
3
2
1
PPM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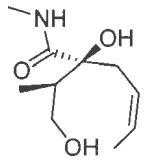
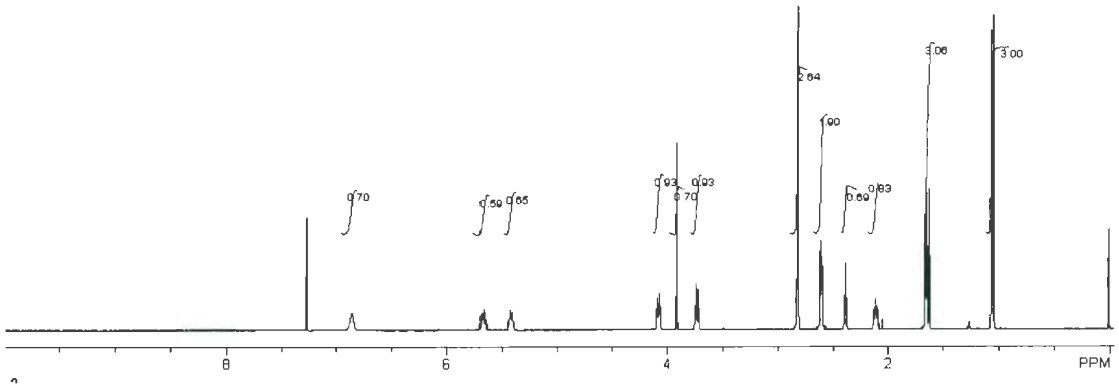
132.035
128.486
127.850
125.723
123.831
82.247
77.484
77.230
76.968
73.656
71.425
71.015
59.121
37.293
33.815
33.715
13.306
13.052
150
100
50
PPM


NH
OH
O
OH

62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0.80
0.83
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3.00
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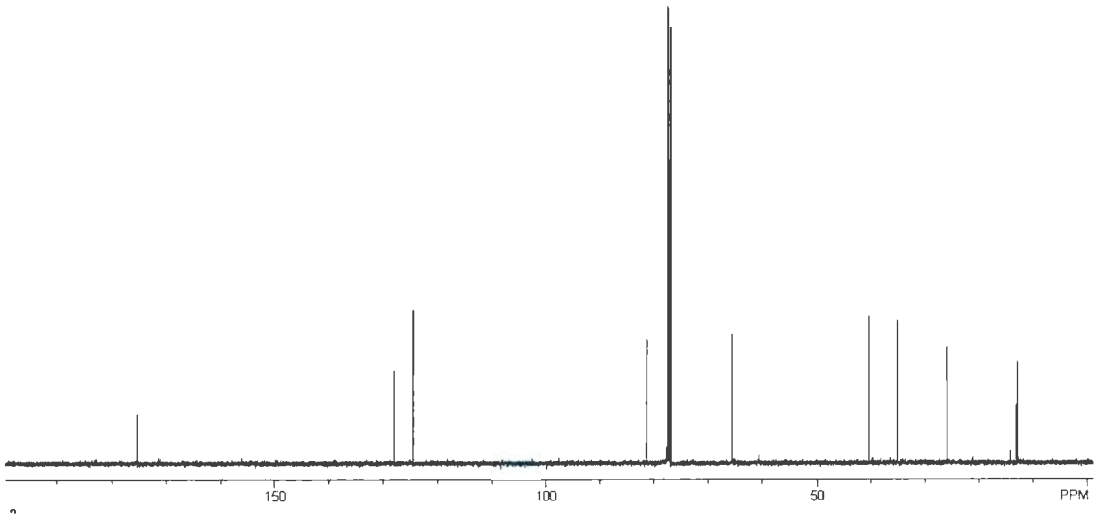
4
2
PPM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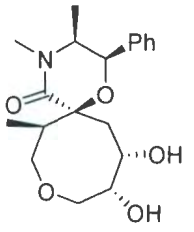
100
50
PPM



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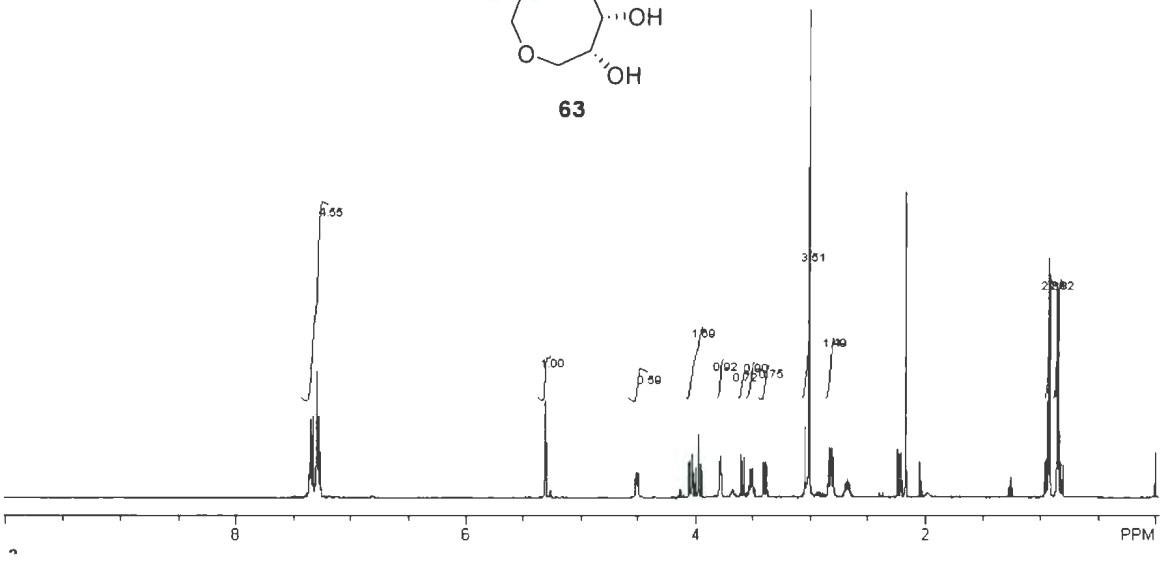
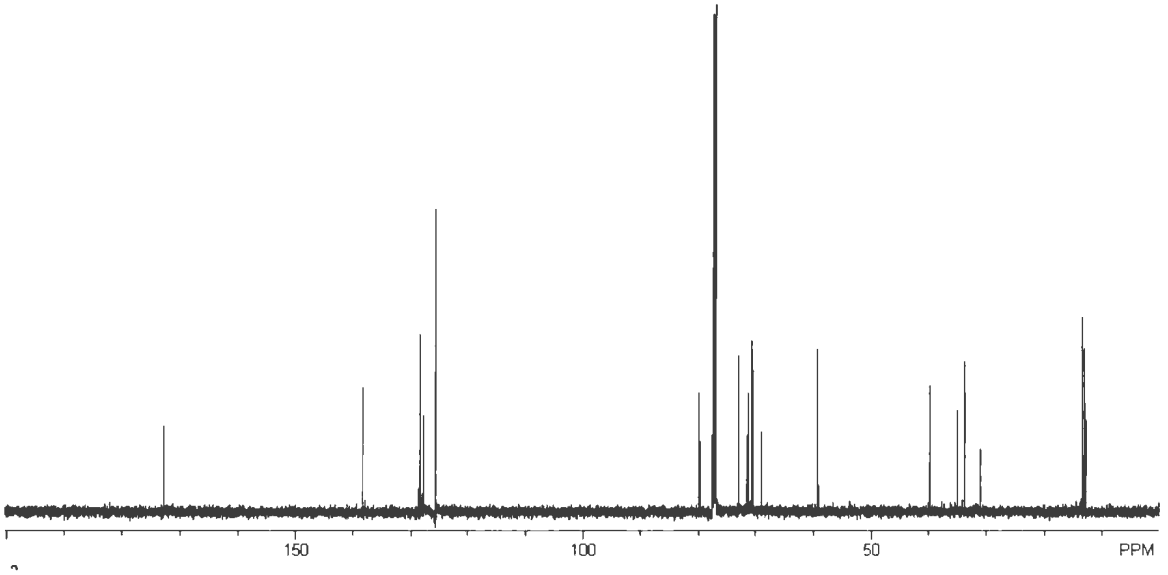
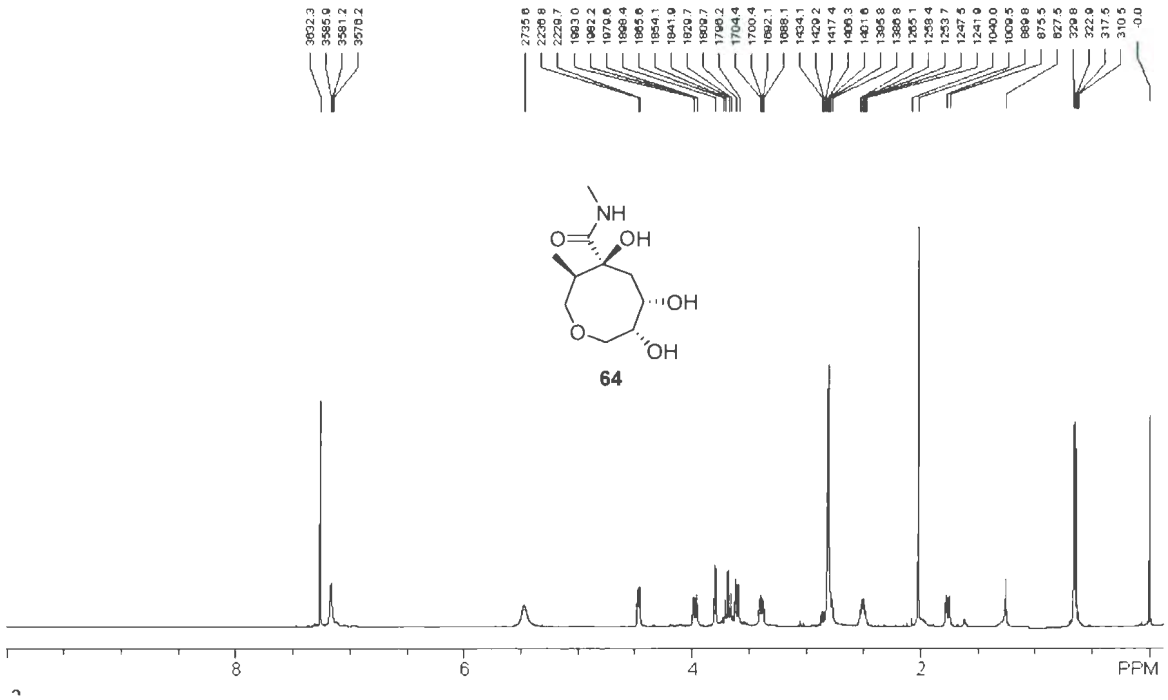
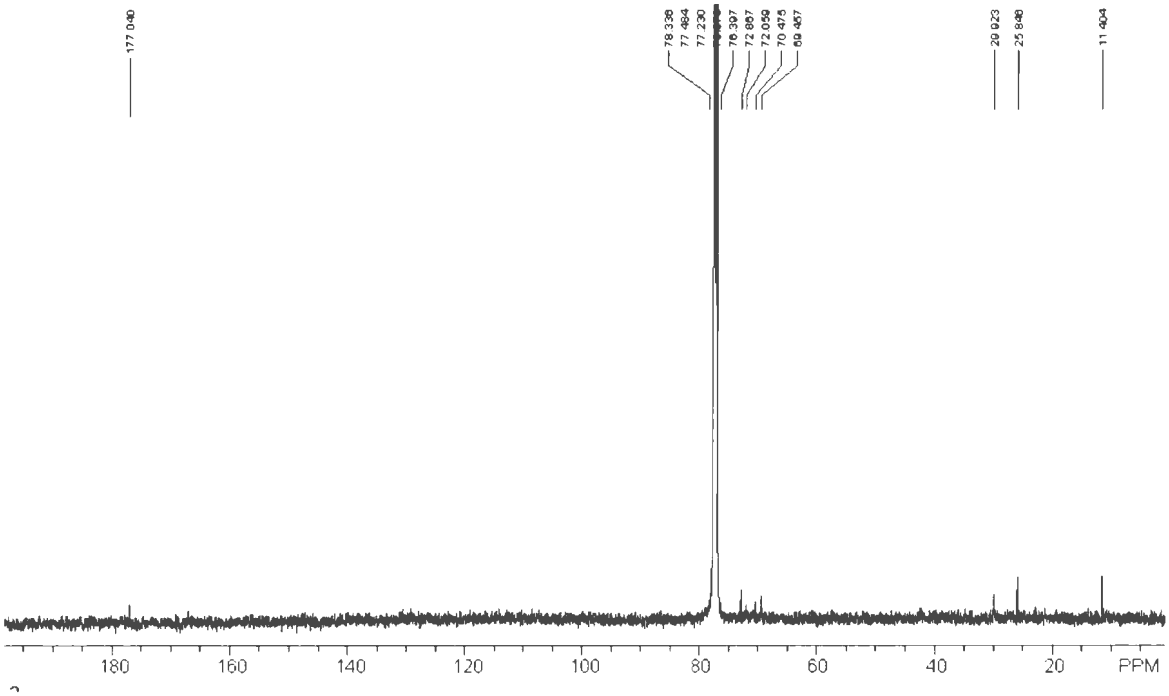





NH
O
OH
OH
O
OH
64
8
6
4
2
PPM


177.040
78.339
77.484
77.230
76.397
72.867
72.059
70.475
64.457
29.923
25.849
11.404
180
160
140
120
100
80
60
40
20
PPM

Chapter 4

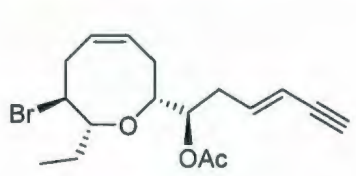
Formal Total Synthesis of (+)-Laurencin

Part of the work described in this chapter has been published in

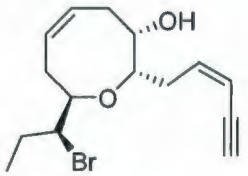
Org. Biomol. Chem. **2008** ,*6,* 2011

Introduction

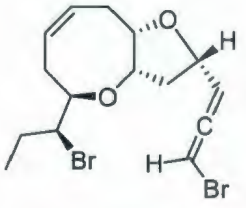
The stereoselective construction of medium-sized oxacycles[1] continues to be an area of active interest and target-oriented[2] as well as general[3] strategies for assembling such ring systems and have been extensively investigated in recent years. In particular, medium-ring ether-containing marine natural products[4] isolated from red algae have attracted considerable synthetic effort. The halogenated oxocenes laurencin[5] (**1**), prelaureatin (**2**),[6] pannosallene[7] (**3**) and laurenyne[8] (**4**) are representative examples of the impressive array of red algae metabolites that have been the focus of intense synthetic investigations in recent years (Figure 1).



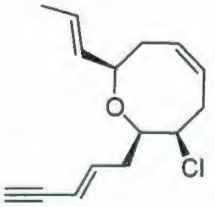
Laurencin (**1**)



Prelaureatin (**2**)



Pannosallene (**3**)



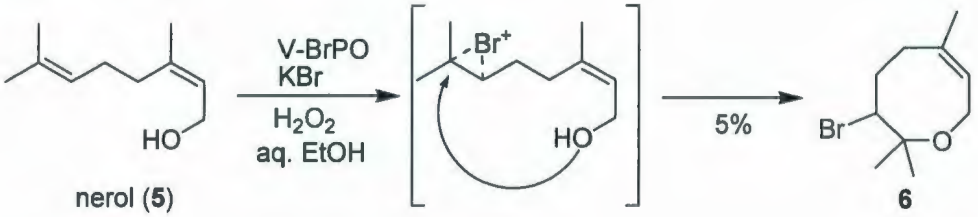
Laurenyne (**4**)

Figure 1. Medium-ring ether-containing halogenated marine natural products.

Apart from the oxocene ring, other structurally salient features of the above-mentioned marine natural products are; 1) the α,α'-disubstituted ether functionality and 2) the presence of a halogen atom at the β position with respect to the ether oxygen. Interestingly, though the elucidation of biosynthesis of these molecules is still incomplete,

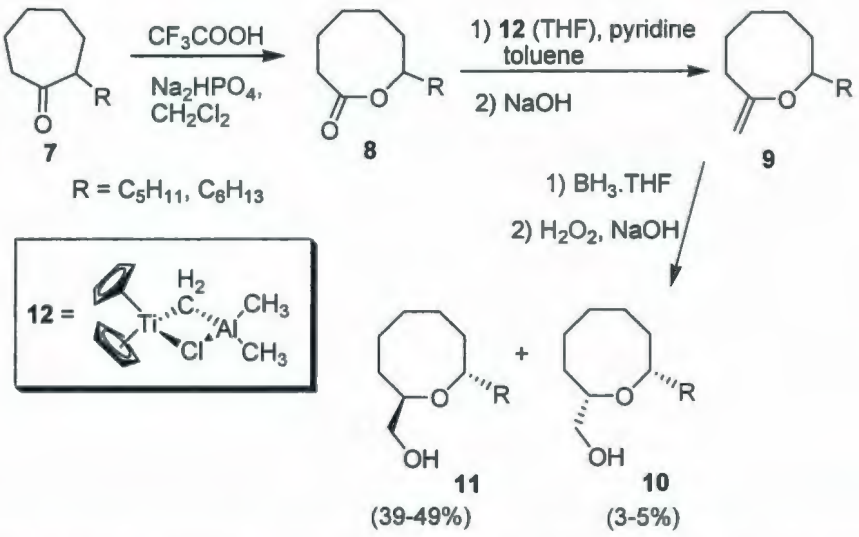
it has now been shown that haloperoxidase enzymes may play a crucial role in the biosynthesis of these molecules from terpenes. Butler and coworkers[9] have shown that the vanadium bromoperoxidase (V-BrPO)-catalyzed bromination of nerol (**5**) leads to cyclization, yielding the monobromo eight-membered cyclic ether **6** (Scheme 1).

Scheme 1.



From a historical perspective, general strategies towards the halogenated oxocene natural products were virtually non-existent until 1986 when Holmes and Carling devised a protocol based on the Baeyer-Villiger oxidation of cycloheptanones for the synthesis of 2,8-disubstituted oxocane derivatives.[10] It was shown that substituted heptanolides **8** obtained from Bayer-Villiger oxidation of cycloheptanones **7**, (Scheme 2) could be methylenated with the Tebbe reagent to provide oxocanes **9**. Hydroboration/oxidation of **9** gave predominantly the *cis*-oxocane **10** (38-49%). The *trans*-isomer **11** was obtained as the minor product.

Scheme 2



In the last decade, several strategies for the enantioselective synthesis of functionalized medium-sized oxacycles have been documented and an overview of these methods was provided in Chapter 3. Although a significant number of natural products with the oxocane core are known, the synthesis of laurencin (**1**) has served to showcase new methodologies for the stereoselective construction of substituted eight-membered oxacycles. Several successful strategies targeting laurencin have been reported and a summary of the reported enantioselective syntheses of (+)-laurencin follows.

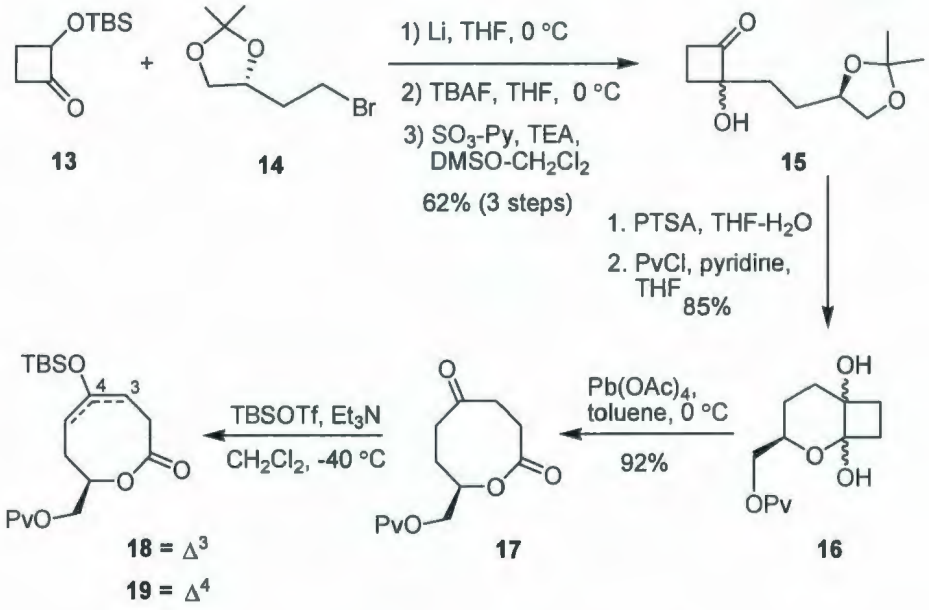
Enantioselective syntheses of (+)-laurencin:

Murai's synthesis of (+)-laurencin [11]

Murai and Tsushima reported the first total synthesis of (+)-laurencin. Their strategy for the construction of the medium-sized oxacycle relied on a ring expansion reaction of a four-membered ring fused to a funtionalized tetrahydropyran. The starting material **15** was obtained from silyloxycyclobutanone **13** and the alkyl bromide **14** in

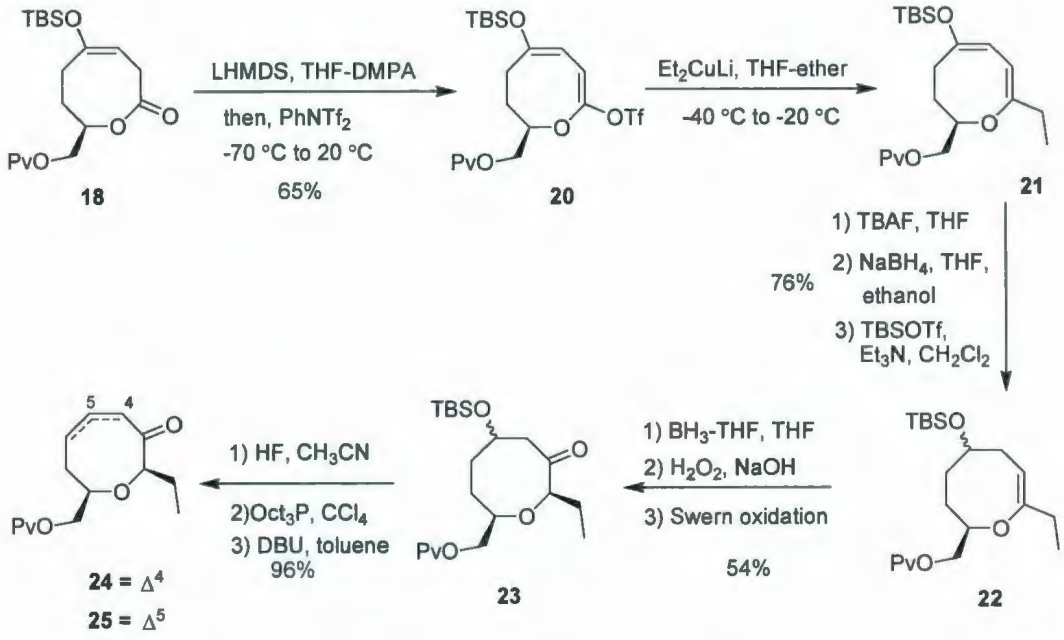
three steps (Scheme 3). Acid hydrolysis of the acetonide in **15** followed by protection of the resulting primary alcohol gave hemiacetal **16**. Oxidative cleavage of **16** yielded the eight-memebered oxacycle **17**. The ketone in **17** was then treated with TBSOTf in presence of Et_3N to give a separable mixture of silyl enol ethers **18** and **19**.

Scheme 3



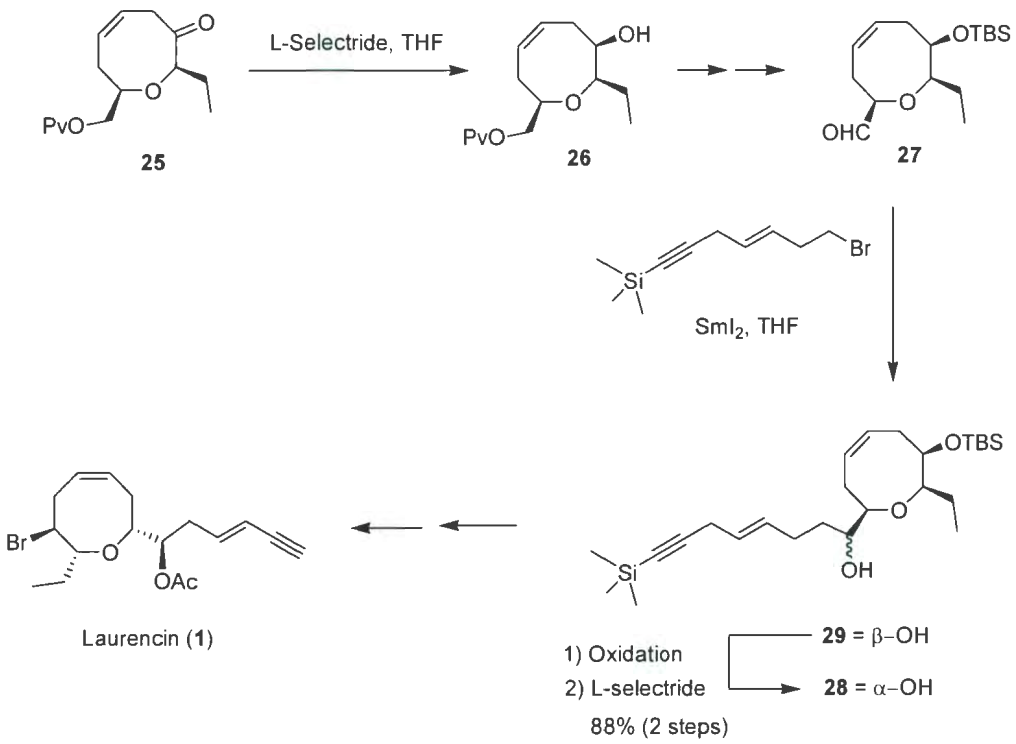
Compound **18** was treated with LHMDS and the resulting enolate reacted with $PhNTf_2$ to give the dienol triflate **20** (Scheme 4). Subsequent treatment of **20** with Et_2CuLi gave the ethyl derivative **21**. A sequence of reactions comprised of removal of silyl protection on the enol ether by exposing it to TBAF, reduction of the resulting ketone with $NaBH_4$, and protection of the alcohol as a silyl ether by reacting it with TBSOTf gave **22**. The double bond in **22** was then subjected to a hydroboration/oxidation sequence followed by oxidation of the resulting secondary alcohol to afford ketone **23**. The *cis*-configuration at the α,α'-postions was thus installed.

Scheme 4



Deprotection of the alcohol in **23** followed by dehydration gave a mixture of unsaturated ketones **24** and **25**. The unwanted product **24** could be converted into the desired compound **25** by treating the former with DBU. Stereoselective reduction of the ketone in **25** was achieved by using L-Selectride® (Scheme 5) to obtain alcohol **26** which in turn could be converted to compound **27** over 3 steps. The aldehyde in **27** was then reacted with (3*E*)-5-bromo-3-pentene-1-ynyltrimethylsilane in the presence of SmI_2 to obtain a mixture of enyne alcohols **28** and **29** in a ratio of 44:55. Oxidation of the undesired isomer **29** followed by reduction with L-Selectride® generated the alcohol **28** in a combined yield of 88%. Compound **28** could then be transformed into **1** over three steps. Thus, the 27-step sequence was carried out with an overall yield of 2.5%.

Scheme 5

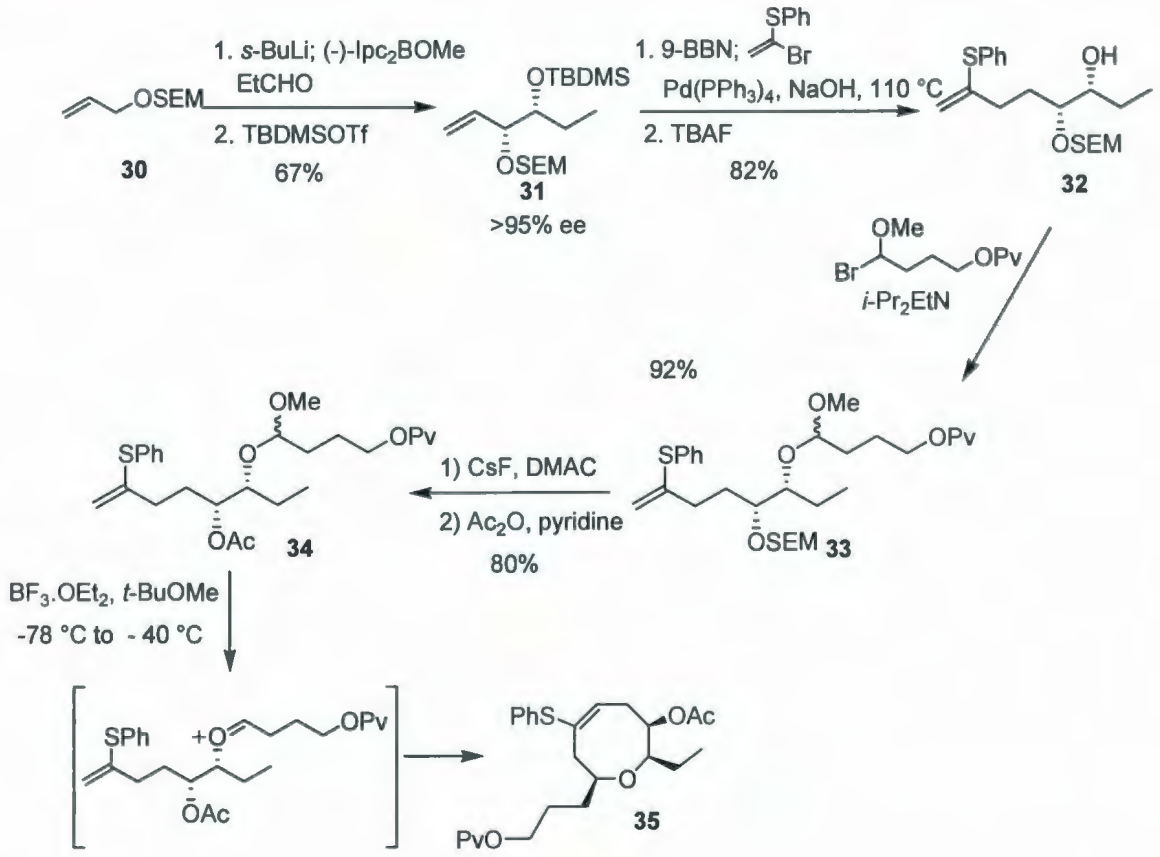


The Overman synthesis of (+)-laurencin[12]

This synthesis starts with asymmetric allylboration of propanal with the allyldiisopinocampheylborane (generated *in situ* by sequential reaction of allyl ether **30** with *s*-BuLi, (-)-*B*-methoxydiisopinocampheylborane, Scheme 6) and the resulting alcohol was converted to the *tert*-butyldimethylsilyl (TBDMS) ether derivative **31**. Suzuki coupling[13] of **31** with (1-bromovinyl)phenylsulfane and removal of the TBDMS protecting group gave **32**. Treatment of the alcohol in **32** with 4-bromo-4-methoxybutyl pivalate gave the mixed acetal **33**. Deprotection of the silyl ether followed by acylation of the resulting alcohol gave **34**. The key acetal-vinyl sulphide cyclization was carried out

by using $BF_3 \cdot Et_2O$ as a Lewis acid in *t*-BuOMe as a solvent at -10 °C to give the oxocene **35** (Scheme 6).[14]

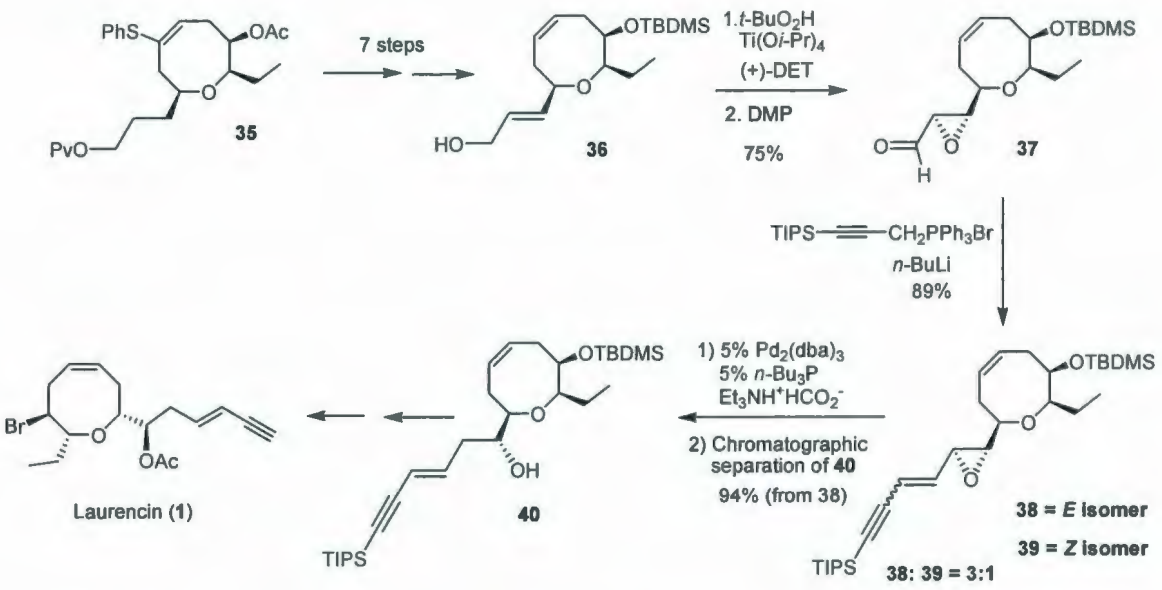
Scheme 6



Oxocane **35** was then transformed to compound **36** in seven steps (Scheme 7). The allyl alcohol in **36** served as a substrate for Sharpless epoxidation to yield the epoxy aldehyde **37** in high yield (85%) and good stereoselectivity. The primary alcohol was then oxidised by using Dess-Martin periodinane[15] to generate the aldehyde **37** which could be condensed with the ylide obtained from the phosphonium salt of (3-bromoprop-1-ynyl)triisopropylsilane to afford the alkenes **38** and **39** as a 3:1 mixture of *E* and *Z* stereoisomers respectively. Palladium catalyzed hydrogenolysis[16] of the epoxides **38** and

39 yielded the alcohols as a 4:1 mixture of *E* and *Z* isomers respectively. The required *E*-alkene **40** was separated and converted to (+)-laurencin over four steps. The target was thus obtained with an overall yield of ~2% (24 steps).

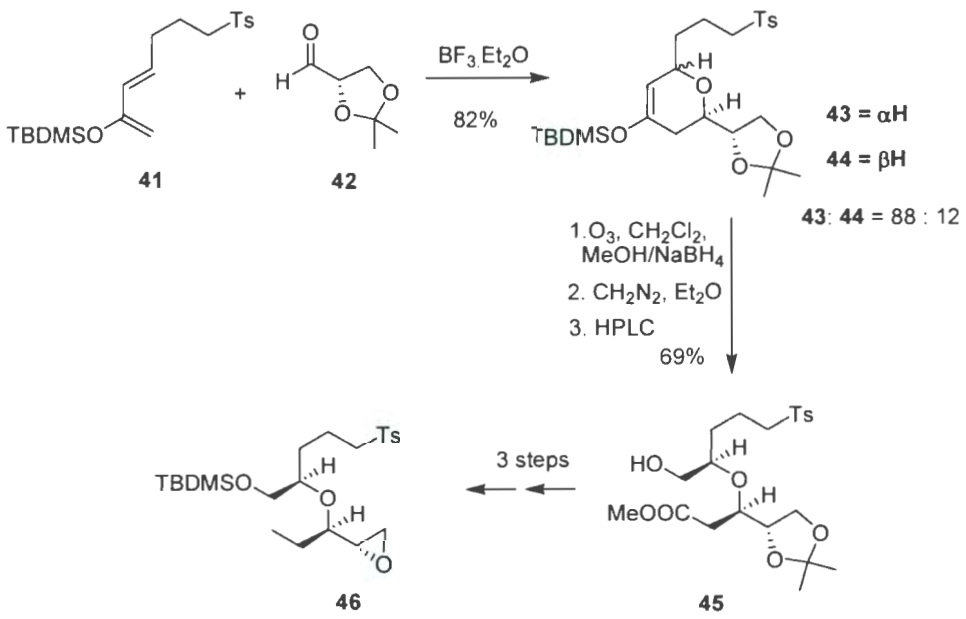
Scheme 7



The Palenzuela approach to (+)-laurencin[17]

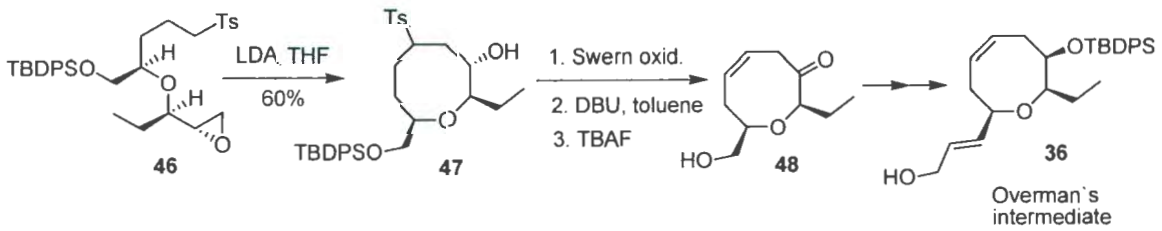
Palenzuela and co-workers reported a synthesis that started with a hetero Diels-Alder reaction between the diene **41** and aldehyde **42**[18] to obtain the cycloadducts **43** and **44** as an 88:12 mixture of isomers (Scheme 8). Ozonolysis of the mixture followed by esterification gave a mixture of stereoisomeric esters which were separated by HPLC to secure the desired isomer **45** in 69% yield. Conversion of compound **45** to the epoxide **46** was then achieved in three steps.

Scheme 8



Epoxide **46** was subjected to a base-induced ring opening at the terminal carbon to form the eight-membered oxacycle **47** (Scheme 9). The alcohol in **47** was then oxidized and the resulting ketone was treated with DBU to afford oxocene **48**. This in turn was transformed to the compound **36** which was also an intermediate in Overman's synthesis[12] of (+)-laurencin (Scheme 7).

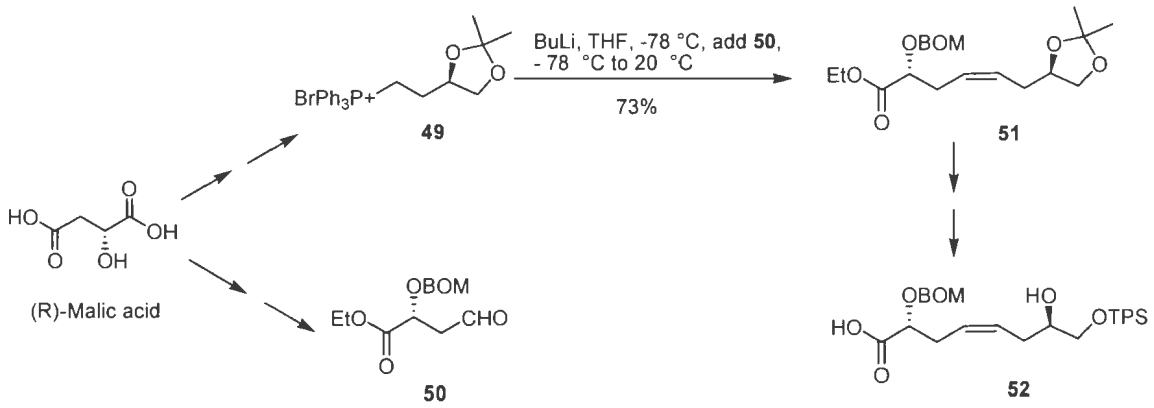
Scheme 9



The Holmes approach to (+)-laurencin[19]

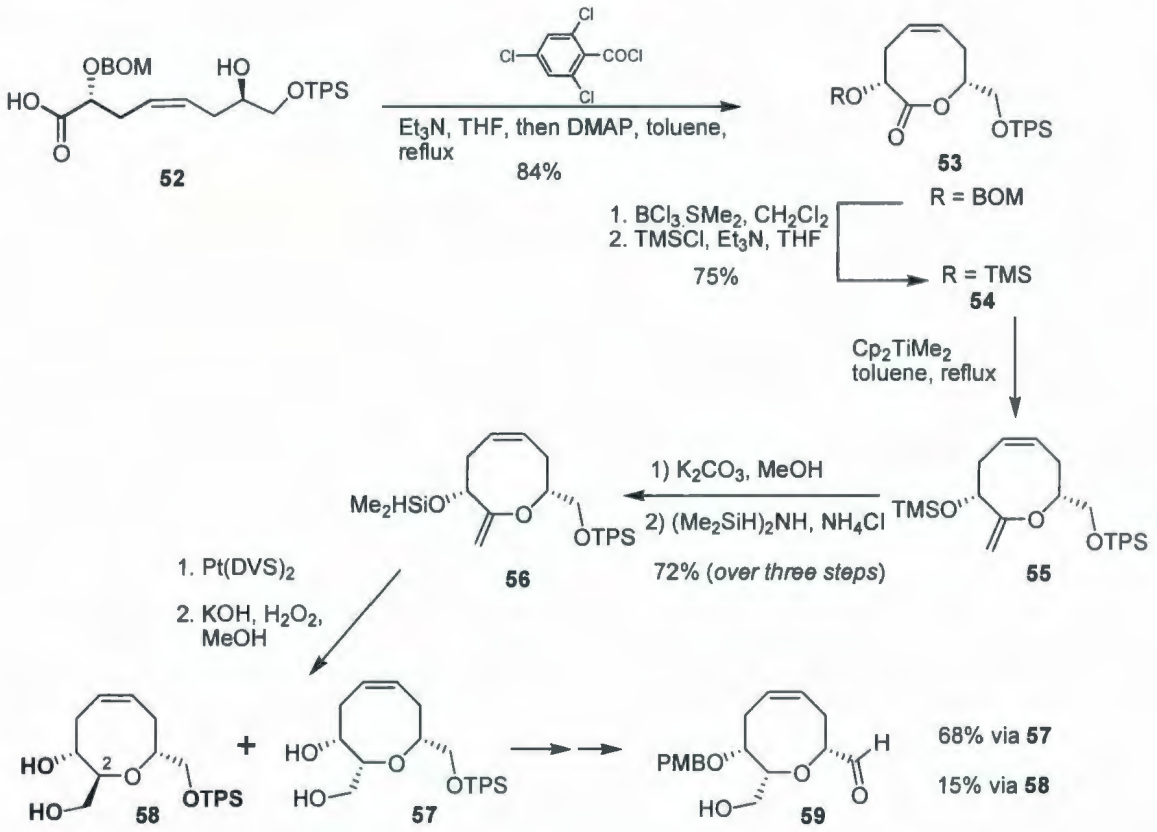
This approach originated with (*R*)-malic acid and both the starting materials **49** and **50** were obtained from this source (Scheme 10). Wittig reaction of **49** with **50** was effected by using *n*BuLi as a base to give the *cis*-alkene **51**. The alcohol **52** was then obtained from **51** via a protection/deprotection sequence.

Scheme 10



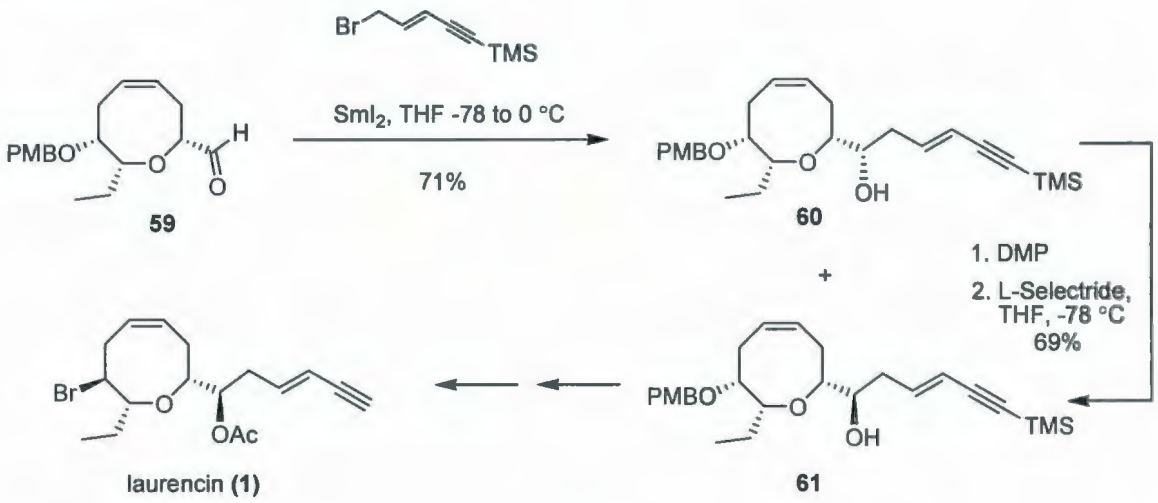
Formation of the eight-membered ring was achieved by subjecting **52** to Yamaguchi lactonization[20] to yield the lactone **53** in excellent yield (84%, Scheme 11). After replacing the BOM group with TMS, the lactone in the resulting compound was converted into the vinyl ether **54** by employing the Petasis reagent. Funtionalization of the double bond was achieved by an intramolecular hydrosilation reaction.[21] Thus, replacing the TMS protection on the secondary alcohol in **55** by dimethylsilyl hydride followed by the treatment of the resulting ether **56** with the platinum complex $[Pt(DVS)_2]$[22] gave compounds **57** and **58** as a 58:42 mixture of diastereomers. Compound **57** was then converted into **59**. Also, it was shown that aldehyde **59** could also be obtained from **58**, albeit in low yield, by oxidation of the secondary alcohol in **58** followed by epimerization of the C2 carbon as shown by Murai[11] and Palenzuela.[17]

Scheme 11



The end game of this synthesis resembles the one in Murai's synthesis of laurencin. A Barbier-type alkylation of the aldehyde **59** (Scheme 12) with (3*E*)-5-bromo-3-pentene-1-ynyltrimethylsilane in the presence of samarium(II) iodide, provided alcohols **60** and **61** as a mixture of diastereomers. These products had to be separated by HPLC and the undesired alcohol **60** could be recycled into the desired alcohol **61** by following an oxidation/reduction sequence. (+)-Laurencin was then obtained from the alcohol **61**.

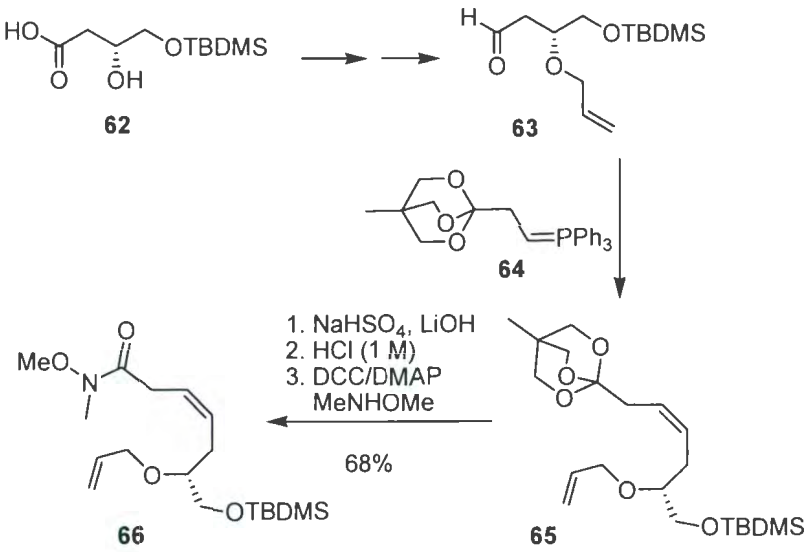
Scheme 12



The Hoffmann approach to (+)-laurencin[23]

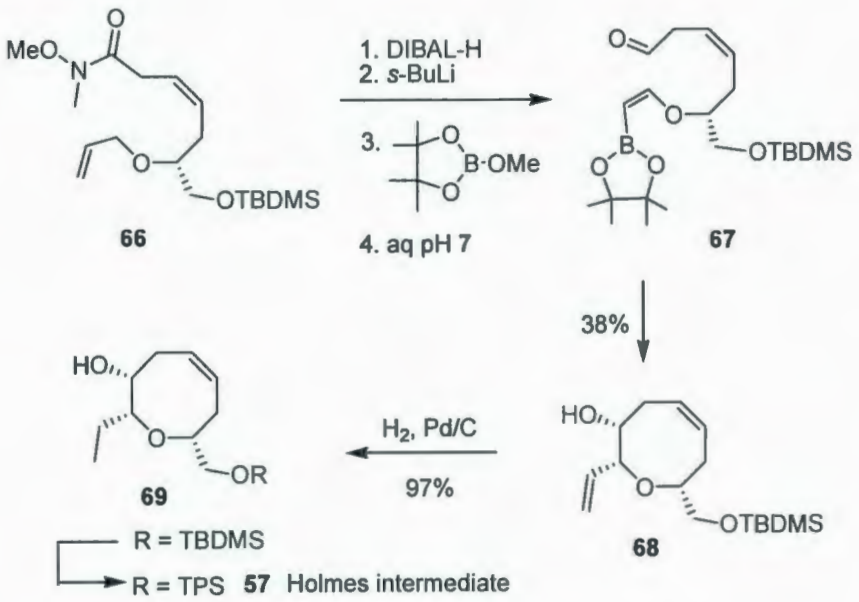
The Hoffmann synthesis started with the known ester **62** (obtained from (*R*)-malic acid)[24] which was transformed into the aldehyde **63** (Scheme 13). A Wittig reaction of **63** with the known phosphorane **64**[25] gave the *cis*-alkene **65**. One-pot conversion of the 4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (**OBO**) ester in **65** to the Weinreb amide was achieved by hydrolysis to the acid and DCC coupling with *N*-methoxy-*N*-methylamine to provide the Weinreb amide **66**.

Scheme 13



DIBAL reduction of the Weinreb amide **66** (Scheme 14) followed by metalation with *sec*-butyllithium, borylation with pinacol borate ester and, finally, liberation of both the aldehyde and allylboronate function by aqueous pH 7 buffer solution generated aldehyde **67** which spontaneously cyclized to the desired oxocane **68**. Selective reduction of the terminal double bond by simple hydrogenation in presence of catalytic amounts of palladium on carbon secured the oxocene **69.** The TBDMS group in **69** was replaced with TPS to give compound **57**. Since the intermediate **57** was previously reported in Holmes synthesis (Scheme 12) of laurencin[19] this synthesis constituted a formal total synthesis of the molecule.

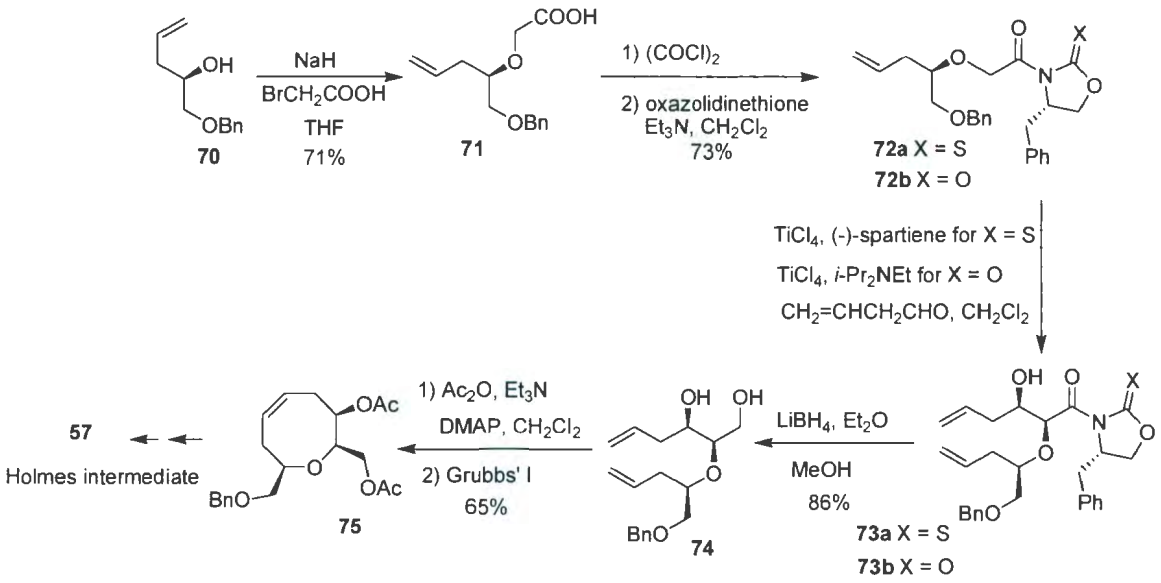
Scheme 14



The Crimmins approach to (+)-laurencin[26]

Crimmins reported a formal synthesis of laurencin utilizing an aldol reaction-RCM strategy. The readily-available alcohol **70**[27] was treated with NaH and the resulting sodium salt was alkylated with the sodium salt of bromoacetic acid to furnish **71** (Scheme 15). The acid **71** was treated with oxalyl chloride, and the resultant acid chloride was added to (*S*)-4-benzyloxazolidine-2-thione and triethylamine to obtain the acyloxazolidinethione **72a**.

Scheme 15

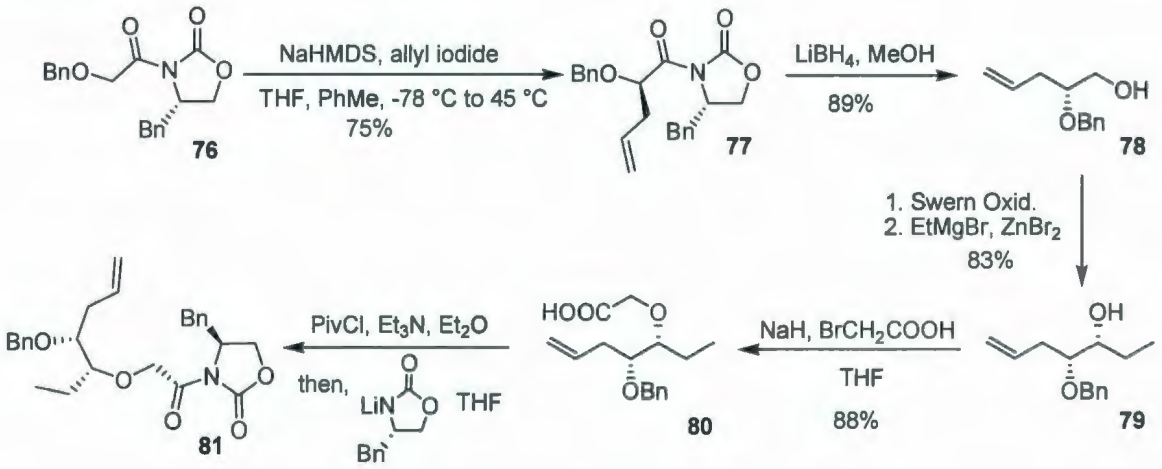


The corresponding oxazolidinone **72b** was prepared similarly by exposure of the acid chloride to the lithium salt of (*S*)-4-benzyloxazolidine-2-one. Enolization of the acyloxazolidinethione **72a** was achieved by using $TiCl_4$ and and (-)-sparteine and that of **72b** with $TiCl_4$ and Hunig's base. Reaction of the enolates of **72a** and **72b** with 3-butenal gave the aldol products **73a** and **73b** in good yields and diastereoselectivity (90% yield at 30% conversion for **73a** and 65% yield for **73b**, >96% de for both **73a** and **73b**). Reductive removal of the chiral auxiliaries in **73a** and **73b** provided the diol **74** in good yield (86%). Acetylation of the diol afforded the diacetate which was then subjected to a RCM reaction to furnish the eight-membered oxacycle **75**, which was then transformed to the intermediate **57** previously reported in the Holmes synthesis (Scheme 11) of laurencin.[19]

The Crimmins synthesis of (+)-laurencin[28]

In the same year, Crimmins reported the total synthesis of laurencin. This route relied on an asymmetric glycolate alkylation[29] protocol for installation of the stereocenters and on a RCM reaction for construction of the the oxocene core. The synthesis started with the oxazolidinone **76** (Scheme 16) which was stereoselectively alkylated to give compound **77**. The chiral auxiliary in **77** was removed by employing $LiBH_4$ as the reducing agent. The resulting primary alcohol **78**, was oxidised to give an aldehyde which, in turn, was subjected to a chelation-controlled addition of ethylmagnesium bromide to provide **79**. *O*-Alkylation of **79** with bromoacetic acid gave **80**.

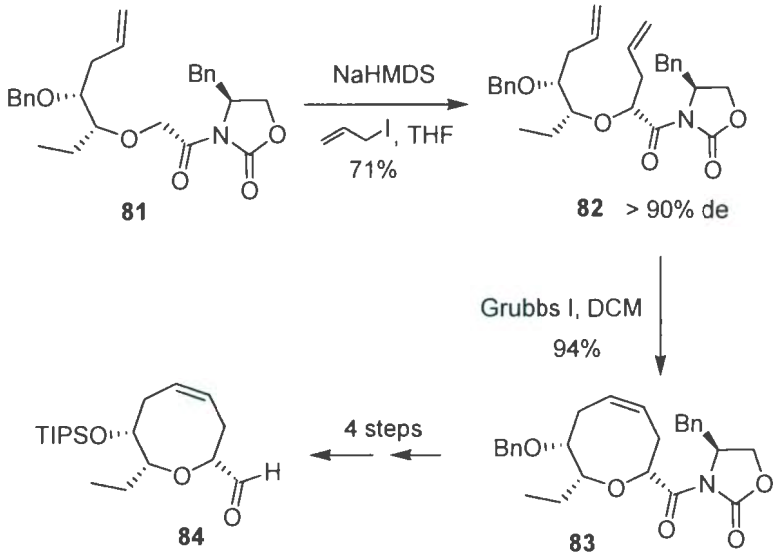
Scheme 16



The acid in **80** was converted to a mixed anhydride which was then exposed to lithiated (*S*)-4-benzyloxazolidine-2-one to give the acyl oxazolidinone **81**. Enolization of **81** with NaHMDS followed by treatment with allyl iodide gave the diene **82** with excellent stereoselectivity (>90% de, Scheme 17). Exposure of the diene **82** to the Grubbs

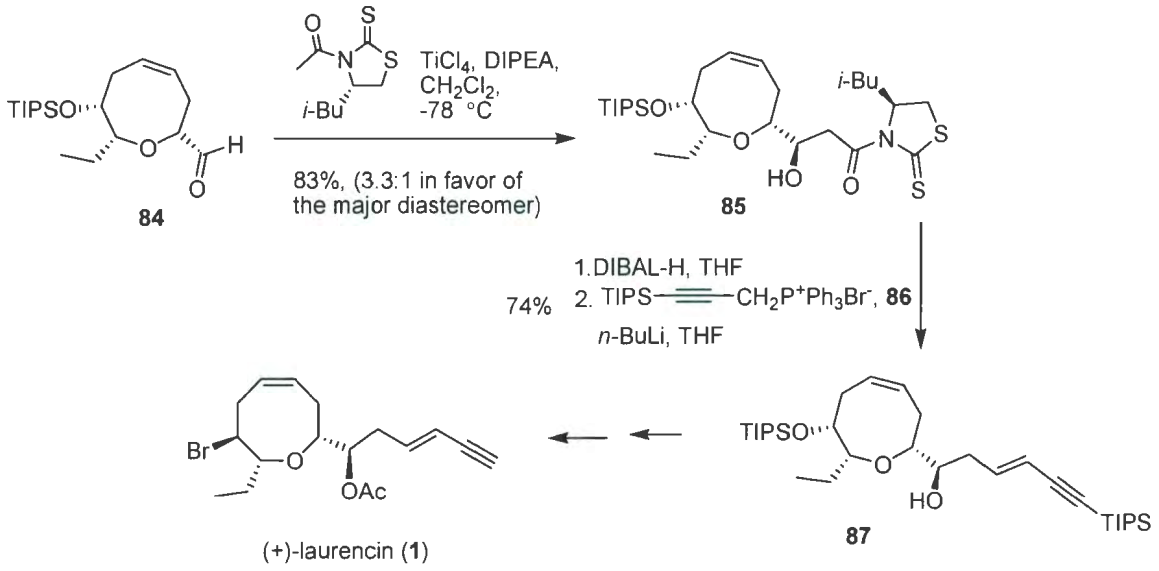
generation I catalyst led to a successful ring closing metathesis reaction to afford the oxocene **83**, which could then be converted into aldehyde **84** in four steps.

Scheme 17



The strategy for installation of the side-chain included an asymmetric acetate aldol reaction of the aldehyde in **84** with (*S*)-(+)-3-acetyl-4-isobutyl-2-thiazolidinethione (Scheme 18) to give a 3.3 : 1 mixture of diastereomers in favour of the desired isomer **85**. Reductive removal of the chiral auxiliary and reaction of the ensuing aldehyde with the phoshonium salt **86** gave a mixture of isomeric alkenes with the desired *trans*-enyne **87** as the major product. The enyne **87** was then converted to (+)-laurencin in three steps.

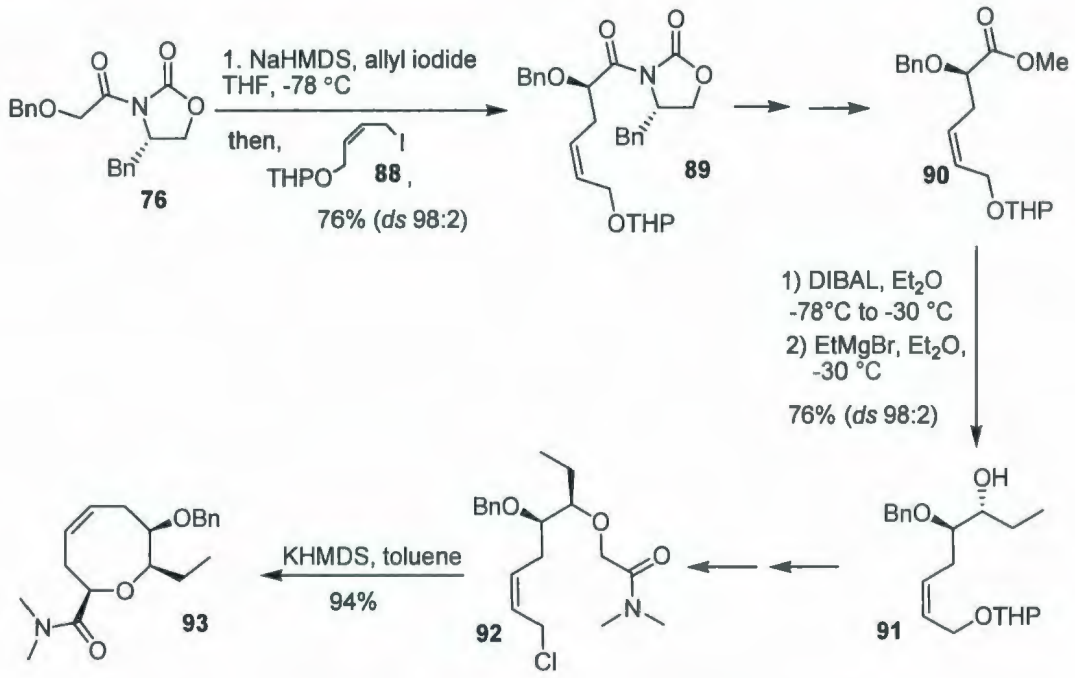
Scheme 18



The Kim synthesis of (+)-laurencin[30]

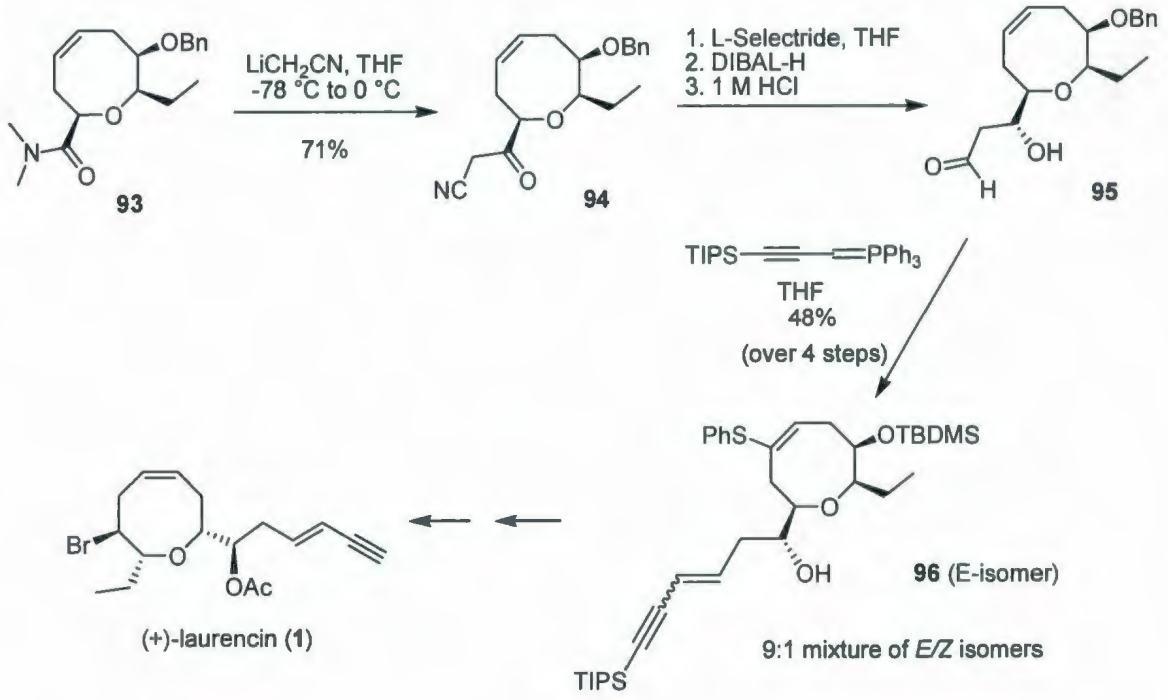
Kim and co-workers started their synthesis (Scheme 19) by using a sequence similar to the Crimmins protocol (chiral glycolate alkylation and chelation-controlled addition of ethylmagnesium bromide, Scheme 16). Alkylation of oxazolidinone **76** (Crimmins approach, Scheme 16) with allylic iodide **88** gave **89**, which could be converted into the methyl ester **90**. A one-pot conversion of **90** to **91** was achieved by DIBAL reduction and *in situ* addition of EtMgBr.[31] The alcohol **91** was then converted to amide **92**, which, in turn, when treated KHMDS gave the oxocene **93** in excellent yield and diastereoselectivity (dr > 25:1, 94%).

Scheme 19



The elaboration of the enyne side chain (Scheme 20) began with a novel transformation. The authors successfully demonstrated the addition of an acetonitrile anion to the α-alkoxy amide in **93** to yield the ketone **94**. Reduction of the ketone followed by conversion of the nitrile function to an aldehyde gave **95**. Reaction of the aldehyde **95** with the phosphorane **86** (Scheme 18, Crimmins approach) gave a 9:1 mixture of *E/Z* isomers in favour of the enyne **96** which was then transformed to (+)-laurencin in three steps (Scheme 20).

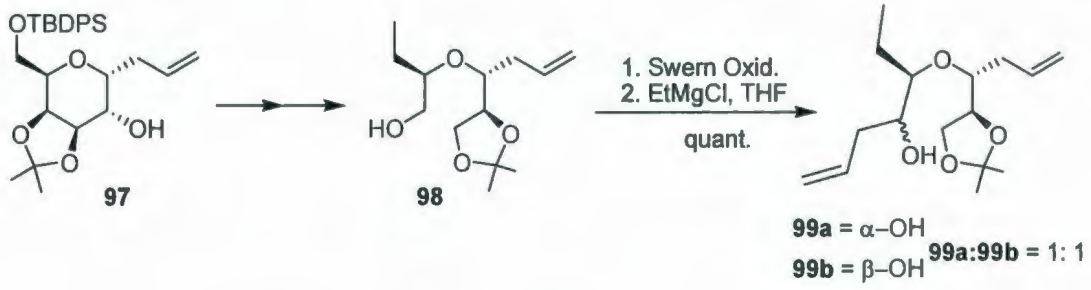
Scheme 20



The Fujiwara synthesis of (+)-laurencin[32]

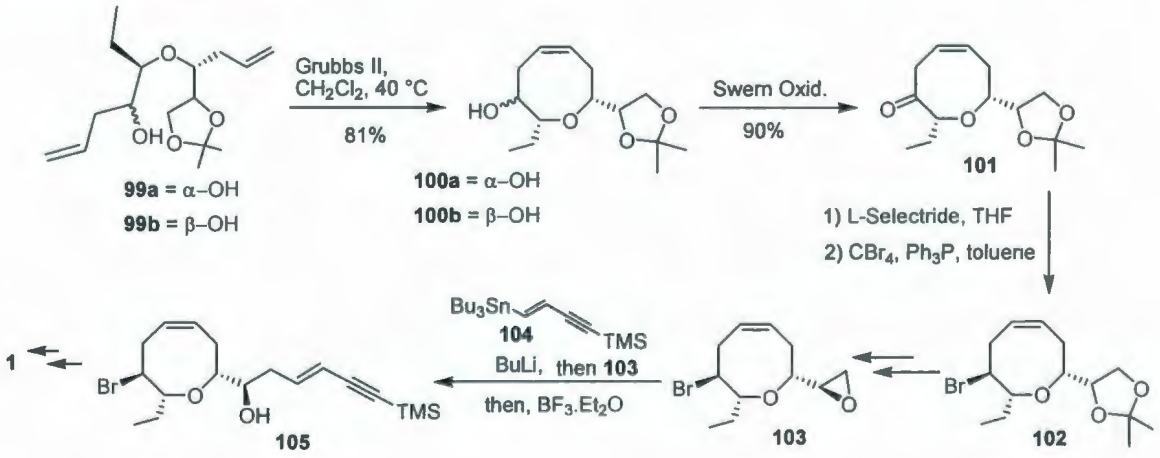
Fujiwara reported a total synthesis of (+)-laurencin by employing a ring-expansion strategy. The chiral *C*-glycoside derivative **97**[33] obtained from D-galactose pentaacetate was transformed into the primary alcohol **98** over six steps (Scheme 21). Swern oxidation of the alcohol in **98** followed by treatment of the resulting aldehyde with excess allylmagnesium chloride yielded a 1:1 mixture of diastereomeric dienes **99a** and **99b** in quantitative yield. Since the stereochemistry of the secondary alcohol was inconsequential to the synthesis, the above mixture was used directly in the next step.

Scheme 21



The diene in **99a** and **99b** was subjected to a ring closing metathesis reaction by using the Grubbs generation II catalyst (Scheme 22) to afford the funtionalized oxacycles **100a** and **100b**. Oxidation of **100a/b** provided the ketone **101** which was stereoselectively reduced using L-Selectride® and the resulting alcohol was treated with PPh_3 and CBr_4 in toluene to provide the bromoether **102**. Epoxide **103** could be obtained from compound **102** in three steps.

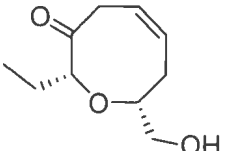
Scheme 22



The enyne side chain was installed next by reaction of **103** with a vinyllithium reagent (obtained from stannane **104** *in situ*) to provide **105**, which was transformed in two steps (desilylation/acetylation) to (+)-laurencin (Scheme 22).

Objectives

The objective of this study was to examine the utility of the epoxide opening / RCM protocol (Chapter 3)[34] for the synthesis of the oxocene core in (+)-laurencin. Specifically, we targeted the ketone (+)-**48** (Fig. 2), which is an advanced intermediate in the Palenzuela synthesis[17] of (+)-laurencin.



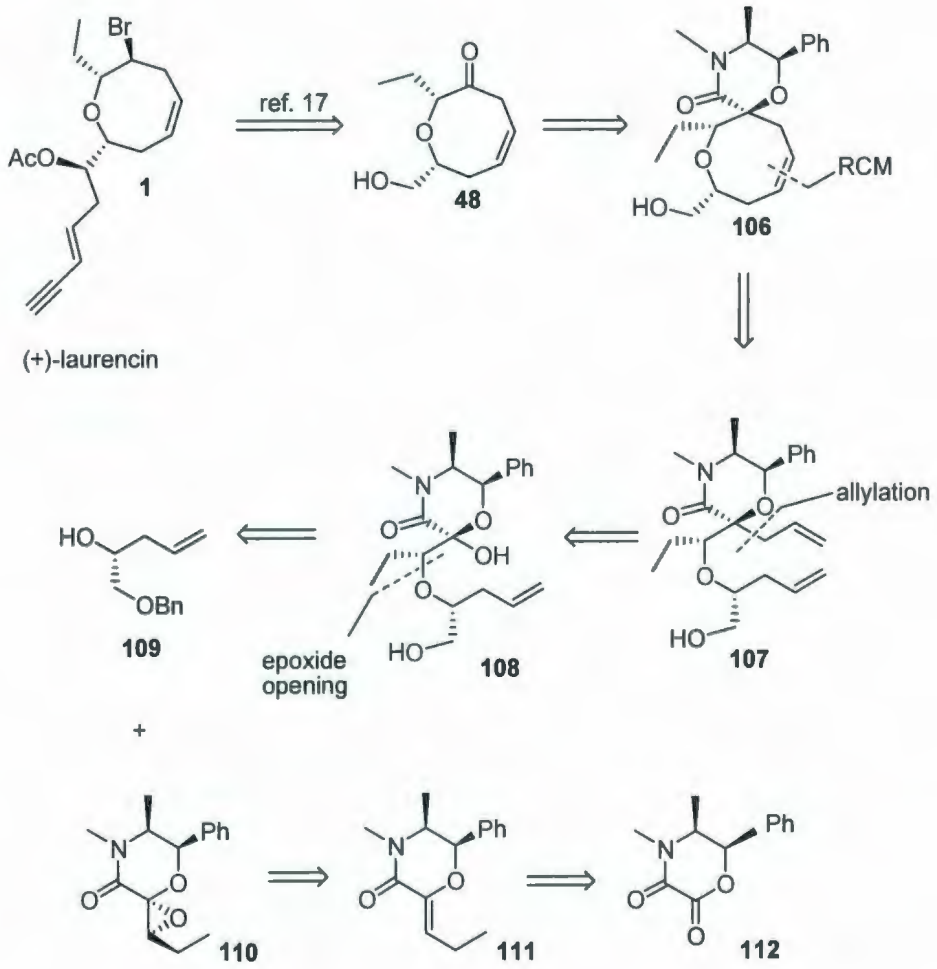
48

Figure 2. The Palenzuela intermediate for the synthesis of (+)-laurencin

Results and discussions

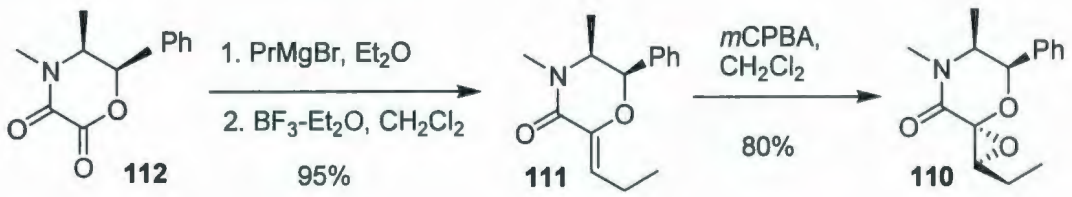
The retrosynthetic plan (Scheme 23) was based on the use of the ephedrine-derived template (Chapter 3) for stereocontrol, and on a ring-closing metathesis reaction to achieve the oxocene formation. It was reasoned that the target ketone **48** could be obtained from the spiro-system **106**, which, in turn, would be the outcome of the ring-closing metathesis reaction of the diene **107** obtained by allylation of the hemiacetal **108**. It was hoped that a direct entry to the α,α'-disubstituted ether motif in **107** could be achieved by an epoxide ring-opening of the spiro-epoxide **110** with a secondary alcohol **109**. Epoxide **110** could be obtained from the alkene **111**,[34] which, in turn, should be accessible from the dione **112**.[35,36]

Scheme 23



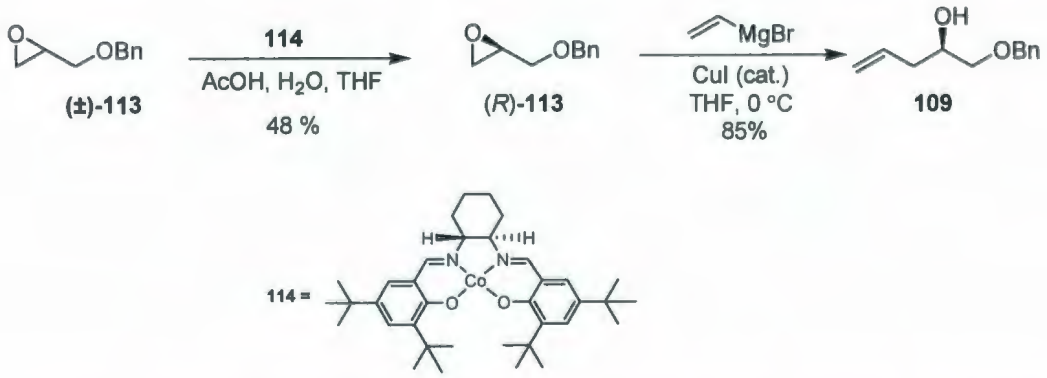
The synthesis of the functionalized oxocene core in laurencin began with the morpholine-dione **112** which was readily prepared (85%) from commercially available (1*R*,2*S*)-ephedrine hydrochloride and ethyloxalyl chloride. Treatment of **112** with propylmagnesium bromide and dehydration of the resulting hemiacetal cleanly generated the alkylidene morpholinone **111** (95%, Scheme 24). Reaction of **111** with *m*CPBA provided the epoxide **110** (85%) as a single diastereomer, which was stable to chromatography. At this stage, the stereochemistry of **110** was assigned by analogy to the epoxidation of a similar substrate (Scheme 11, Chapter 3).

Scheme 24



With epoxide **110** in hand, it was time to examine the proposed epoxide opening with a secondary alcohol such as **109**. The secondary alcohol **109** could be synthesized from racemic benzylglycidyl ether (**113**) by adaptation of the reported procedure (Scheme 25). A hydrolytic kinetic resolution of racemic **113** employing the Jacobsen protocol[37] provided (*R*)-**113** in excellent yield (48%). Treatment of (*R*)-**113** with vinylmagnesium bromide in the presence of a catalytic amount of cuprous iodide provided the secondary alcohol **109** in good yield (85%).[27]

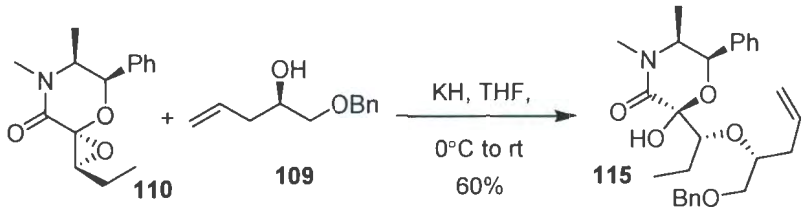
Scheme 25



Several examples of nucleophilic additions of alcohols to epoxides are known.[38] However, practically all of these reactions are conducted in the presence of Lewis acids and, as such, cannot be applied for this synthesis. It may be noted that Lewis acid-

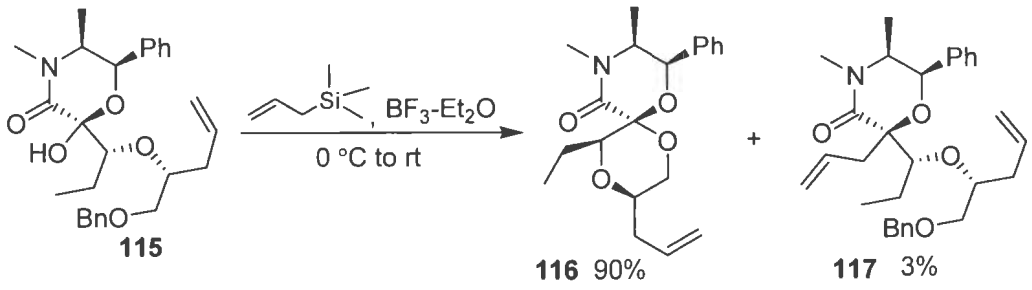
mediated reactions of **110** will almost certainly proceed via nucleophilic addition to the acetal carbon.[38] Consequently, direct nucleophilic ring-opening of epoxide **110** at the terminal carbon was the only alternative. While the ring-opening of substituted epoxides with secondary alkoxides is uncommon, it was gratifying to see that epoxide **110** reacted with the potassium salt of alcohol **109** to furnish the hemiacetal **115** (60%). This key step assembled the two stereocenters adjacent to the oxygen in the oxocene core of laurencin (Scheme 26).

Scheme 26



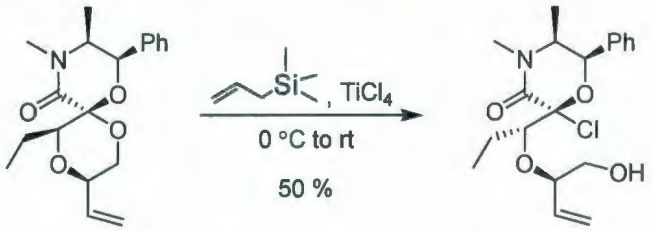
It was anticipated that allylation of the hemiacetal in **115** would provide the diene precursor for the required oxocene. However, attempted allylation of **115** with allyltrimethylsilane in the presence of BF_3•etherate provided the spiro-acetal **116** as the major product (90%, Scheme 27) and only a trace amount (3%) of the desired allylation product **117** was obtained.

Scheme 27



Attempts to allylate the spiroacetal **116** by with allyltrimethylsilane-BF_3•etherate at 40 °C, with allyltributyltin-BF_3•etherate at 0 °C and at 40 °C, with allyltrimethylsilane-$TiCl_4$ at –40 °C and with allyltributyltin-$TiCl_4$ at –40 °C were unsuccessful and unreacted starting material was recovered from these experiments. Formation of the chloro-morpholinone **118** (50%) was observed when $TiCl_4$ was employed as a Lewis acid at room temperature (Scheme 28).

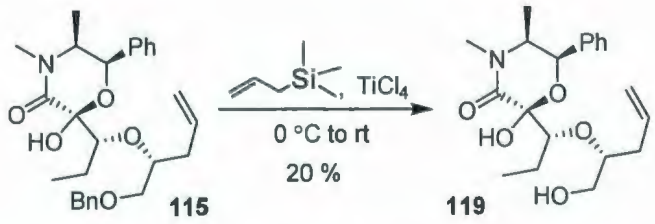
Scheme 28



116 **118**

Attempted allylation of hemiacetal **115** with $TiCl_4$ as the Lewis acid was also not beneficial and provided **119** (arising from debenzylation of **115**) in low yield (Scheme 29).

Scheme 29

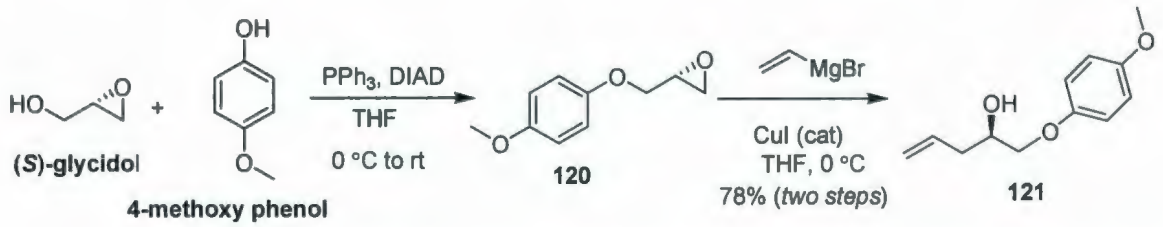


115 **119**

Clearly, the benzyl ether in **115** was unsuitable for the required transformation and an alternative was necessary. At this point, it was decided to employ the *p*-methoxyphenyl (PMP) protecting group as it was expected to be relatively unreactive under the Lewis acidic conditions necessary for the allylation reaction. At the same time deprotection of the PMP-ether was expected to proceed under mild conditions.

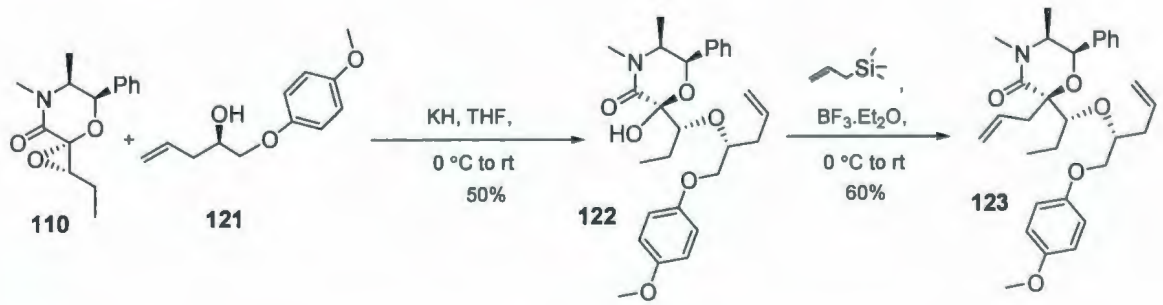
Accordingly, the alcohol **121** was prepared from commercially available (*S*)-glycidol (Scheme 30).[39] A Mitsonobu reaction of (*S*)-glycidol with 4-methoxyphenol provided the epoxyether **120** which was readily converted to the alcohol **121** by a copper-catalyzed reaction with vinylmagnesium bromide (78%).

Scheme 30



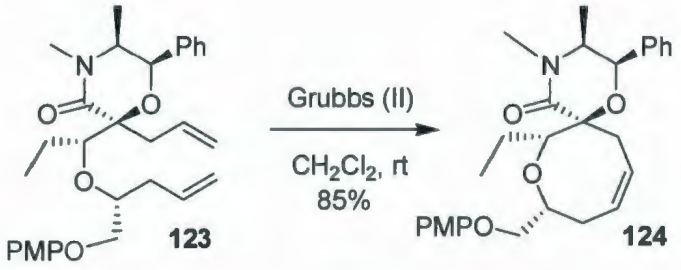
The potassium alkoxide of **121** was reacted with the epoxide **110** to provide the hemiacetal **122** in moderate yield (50%). As projected, allylation of **122** proceeded smoothly to provide the diene **123** (60%, Scheme 31) as a single diastereomer.

Scheme 31



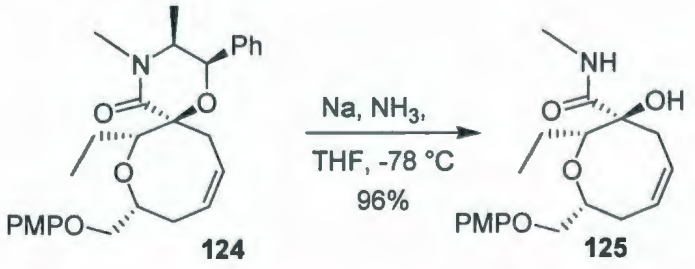
A ring closing metathesis reaction of **123** by using the Grubbs generation II catalyst gave the oxocene **124** in good yield (85%, Scheme 32).

Scheme 32



Having constructed the oxacycle framework, removal the ephedrine portion of the morpholinone in **124** remained. Attention to experimental detail was necessary in this step. Normally, removal of the ephedrine portion in morpholinones such as **124** is readily effected with dissolving metal reduction (Na/NH_3).[34,35] In the present case, competing, albeit slow, reduction of the electron-rich *p*-methoxyphenyl protecting group was a distinct possibility. Indeed, it was observed that benzylic C–O bond cleavage was faster than reduction of the *p*-methoxyphenyl group and a rapid quenching of the reaction (1 min) provided the hydroxy amide **125** in excellent yield (96%, Scheme 33). Longer reaction times resulted in partial reduction of the *p*-methoxyphenyl protecting group as well.

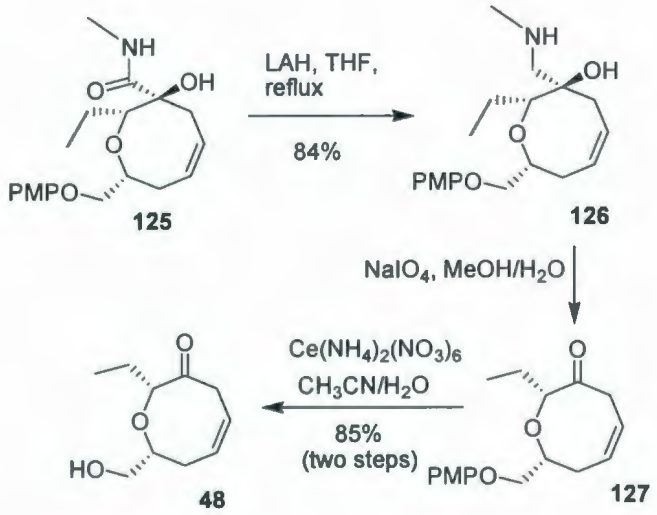
Scheme 33



Only a few functional group transformations were required to reach the target. The α-hydroxy amide in **125** was reduced by LAH to afford the amino alcohol **126** in

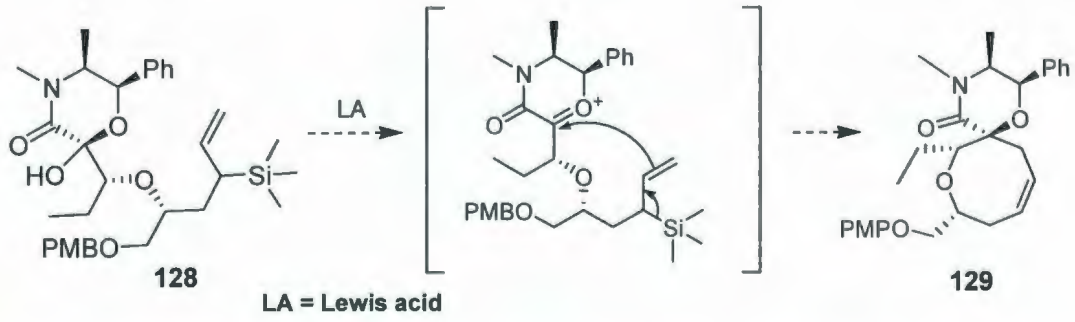
good yield (84%, Scheme 34). Oxidative cleavage of **126** with $NaIO_4$ gave the ketone **127**. Finally, removal of the PMP group by ceric ammonium nitrate provided the target ketone **48** (85% over two steps).

Scheme 34



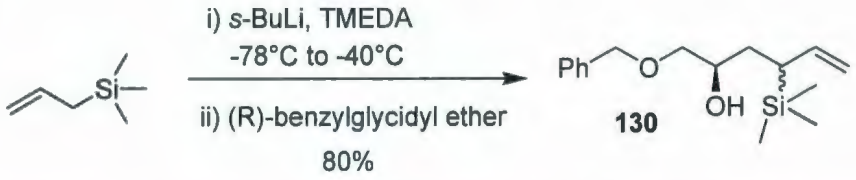
Given the moderate yields of the epoxide opening and allylation reactions, the possibility of employing an intramolecular allylation reaction for a more direct construction of the oxocane target was also explored (Scheme 35).

Scheme 35



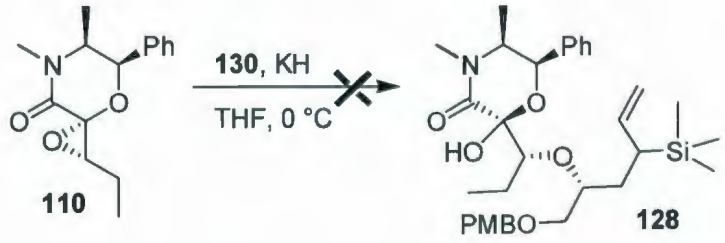
Towards this end the required alcohol **130**[40] was prepared by alkylation of allyltrimethylsilane with (*R*)-benzylglycidyl ether (Scheme 36).

Scheme 36



Unfortunately, all attempts to convert epoxide **110** to **128** were unsuccessful (Scheme 37). It was noted that although unreacted **110** was recovered from these reactions, none of the alcohol **130** could be recovered. It is possible that the alkoxide derived from allylsilane **130** undergoes a C to O silyl group migration (Brook rearrangement[41]), effectively destroying the starting material.

Scheme 37



Conclusion

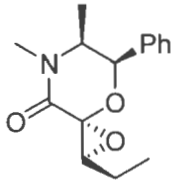
In conclusion, an efficient enantioselective route to an advanced intermediate (**48**) in the synthesis of (+)-laurencin has been established. The present route was shorter (10 steps) and provided **48** in higher overall yield (11.3%) compared to the reported synthesis[10] (21 steps, 4.3% overall yield from commercially available starting materials). A notable advantage of the methodology was the ready availability of both enantiomers of ephedrine and glycidol. This should enable the assembly of all possible stereoisomers of disubstituted oxocenes such as **48** to provide access to analogues of laurencin and its congeners.

Experimental

General

General experimental techniques that have been described in the experimental section of Chapter 2 were followed.

(2*S*,3*S*,5*R*,6*S*)-2-Ethyl-6,7-dimethyl-5-phenyl-1,4-dioxa-7-azaspiro[2.5]octan-8-one (110):



To a solution of **111** (2.00 g, 8.20 mmol) in dichloromethane (30 mL) was added *m*CPBA (1.83 g, 10.6 mmol) at -78 °C and the mixture was warmed to ambient temperature and stirred for 40 min. Saturated aqueous $NaHCO_3$ was added, the mixture was extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were dried and concentrated under reduced pressure. The residue obtained was immediately subjected to purification by flash chromatography on silica gel (3/1 ethyl acetate/hexane) to give 1.70 g (80%) of **110** as a colourless gum.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.39-7.36 (m, 2H), 7.33-7.27 (m, 3H), 5.47 (d, 1H, J = 3.0), 3.69 (t, 1H, J = 6.5), 3.65 (dq, 1H, J = 6.5, 3.0), 3.11 (s, 3H), 1.91-1.80 (m, 2H), 1.12 (t, 3H, J = 7.5), 1.03 (d, 3H, J = 6.5).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 163.6, 136.7, 128.7, 128.2, 125.5, 82.2, 76.0, 63.5, 59.4, 34.0, 21.0, 12.5, 10.3.

IR (neat):

2976, 1669, 1294, 1195, 930, 700 cm^{-1}.

$[\alpha]_D^{23}$ = -115.5 (*c* 2, $CHCl_3$);

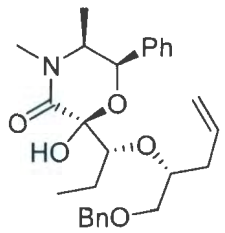
MS (APCI):

262.1 (M+1, 100);

HRMS (CI):

m/z 262.1451 (262.1443 calc. for $C_{15}H_{20}NO_3$, M+H).

(2*S*,5*S*,6*R*)-2-((*R*)-1-((*R*)-1-(benzyloxy)pent-4-en-2-yloxy)propyl)-2-hydroxy-4,5-dimethyl-6-phenylmorpholin-3-one (115):



To a solution of the alcohol **109** (0.880 g, 4.21 mmol) in THF (20 mL) at 0 °C was added KH (0.252 g (obtained by washing a 30 wt.% dispersion in mineral oil with hexane), 6.30 mmol, as a suspension in THF (2 mL)). The mixture was then stirred for 10 min at 0 °C and a solution of the epoxide **110** (1.10 g, 4.20 mmol) in THF (5 mL) was added. The reaction mixture was then warmed up to ambient temperature, stirred for 4.5 h, cold water (10 mL) was added, and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried and concentrated under reduced pressure.

The residue was purified by flash chromatography on silica gel (2/1 ethyl acetate/hexane) to provide 1.00 g (60%) of **115** as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.36-7.22 (m, 10H), 5.85-5.78 (m, 1H), 5.44 (d, 1H, J = 2.7), 5.08-5.02 (m, 2H), 4.90 (br s, 1H), 4.59-4.50 (AB, 2H, J = 12.1), 3.86-3.82 (m, 1H), 3.67-3.64 (m, 1H), 3.52-3.49 (m, 1H), 3.43-3.38 (m, 2H), 2.94 (s, 3H), 2.36-2.34 (m, 2H), 1.92-1.87 (m, 1H), 1.71-1.65 (m, 1H), 1.11 (t, 3H, J = 7.3), 0.98 (d, 3H, J = 7).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 168.3, 138.3, 137.8, 134.5, 128.5, 128.4, 127.9, 127.8, 127.7, 126.0, 117.5, 98.4, 83.9, 79.1, 73.6, 72.5, 72.0, 59.4, 37.0, 33.5, 23.2, 12.3, 11.6.

IR (neat):

3326, 2976, 1739, 1636, 1242, 1086 cm^{-1}.

$[\alpha]_D^{23}$ = -105.6 (*c* 1, $CHCl_3$).

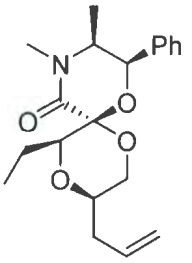
MS (APCI):

454.2 (M+1, 100).

HRMS (EI):

m/z 453.2509 (453.2515 calc. for $C_{27}H_{35}NO_5$, M+).

(3*R*,5*R*,6*S*,8*R*,9*S*)-3-Allyl-9,10-dimethyl-5-ethyl-8-phenyl-1,4,7-trioxa-10-azaspiro[5.5]undecan-11-one (116):



To a solution of **115** (0.320 g, 0.700 mmol) in dichloromethane (15 mL) at -78 °C was added allyltrimethylsilane (0.670 mL, 4.20 mmol) followed by BF_3•etherate (0.520 mL, 4.21 mmol). The mixture was stirred at -78 °C for 15 min and then warmed to ambient temperature and stirred for 22 h. Cold water was added and the mixture was extracted with dichloromethane (3 x 25 mL). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (1/3 ethyl acetate/hexane) to provide 0.220 g (90%) of **116** as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.40-7.36 (m, 3H), 7.34-7.31 (m, 1H), 5.89-5.83 (m, 1H), 5.21 (d, 1H, J = 2.3), 5.16-5.07 (m, 2H), 4.21 (dd, 1H, J = 7.3, 5.5), 4.05-4.00 (apparent t, 1H, J = 10), 3.88-3.82 (m, 1H), 3.67 (dd, 1H, J = 11.2, 2.7), 3.46 (dq, 1H, J = 13.2, 3.0), 3.07 (s, 3H), 2.40-2.34 (m, 1H), 2.22-2.16 (m, 1H), 1.55-1.49 (m, 2H), 1.12 (d, 3H, J = 5.9), 0.98 (t, J = 7.3, 3H).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 165.1, 138, 133.8, 128.6, 128.1, 126.1, 117.3, 95.3, 80.5, 78.0, 74.7, 64.6, 59.4, 36.3, 23.3, 12.3, 10.3.

IR (neat):

2925, 1663, 1496, 1042, 700 cm^{-1}.

$[\alpha]_D^{23}$ = -45.9 (c 1, $CHCl_3$).

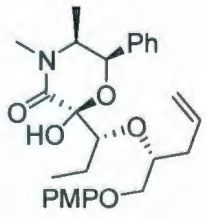
MS (APCI):

346.3 (M+1, 100).

HRMS (EI):

m/z 345.1940 (345.1940 calc. for $C_{20}H_{27}NO_4$, M+).

(2*S*,5*S*,6*R*)-2-((*R*)-1-((*R*)-1-(4-Methoxyphenoxy)pent-4-en-2-yloxy)propyl)-2-hydroxy-4,5-dimethyl-6-phenylmorpholin-3-one (122):



To a solution of (*R*)-1-(4-methoxyphenoxy)-3-buten-2-ol[14] (0.88 g, 4.2 mmol) in THF (20 mL) at 0 °C was added KH (0.252 g, 6.30 mmol). The mixture was then stirred for 10 min at 0 °C and a solution of the epoxide **110** (1.10 g, 4.20 mmol) in THF (5 mL) was added. The reaction mixture was then warmed up to ambient temperature, stirred for 4.5 h, cold water (10 mL) was added, and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried and concentrated under reduced

pressure. The residue was purified by flash chromatography on silica gel (2/1 ethyl acetate/hexane) to provide 1.00 g (50%) of **122** as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.37-7.31 (m, 4H), 7.30-7.26 (m, 1H), 6.85-6.81 (m, 4H) 5.82-5.74 (m, 1H), 5.40 (br s, 1H), 5.09-5.02 (m, 2H), 3.95-3.91 (m, 3H), 3.87-3.84 (m, 1H), 3.75 (s, 3H), 3.47 (dq, 1H, J = 6, 2.5), 3.06 (s, 3H), 2.42-2.32 (m, 2H), 2.03-1.97 (m, 1H), 1.85-1.79 (m, 1H), 1.10 (t, 3H, J = 8), 1.08 (d, 3H, J = 7).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 169 (NC=O), 154.0 ($_{p\text{-}OMe}$ArCOCH$_3$), 153.3 ($_{p\text{-}OMe}$ArCOCH$_2$), 137.7 (ArC*ipso*), 134.4 (CH=CH$_2$), 128.5 (ArCH), 127.9 (ArCH), 126.1 (ArCH), 117.9 ($_{p\text{-}OMe}$ArCH), 115.7 ($_{p\text{-}OMe}$ArCH), 114.8 (CH=CH$_2$), 98.6 (O=CCO), 83.3 (CH$_3$CH$_2$CHO), 78.0 (PhCH), 76.9 ($_{p\text{-}OMe}$ArCH$_2$), 72.8 ($_{p\text{-}OMe}$ArCH$_2$CH), 69.9 (OCH), 59.9 (NCH), 55.9 (OCH$_3$), 36.5 (CH$_2$CH=C), 33.9 (NCH$_3$), 22.3 (CH$_3$CH$_2$), 12.4 (CH$_3$CHN), 11.2 (CH$_3$CH$_2$).

IR (neat):

3327, 2936, 1633, 1507, 1230, 756 cm^{-1};

$[\alpha]_D^{23}$ = -60 (*c* 1, $CHCl_3$).

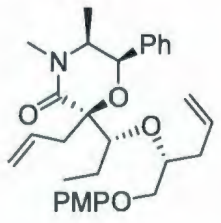
MS (APCI):

470.2 (M+1, 100).

HRMS (EI):

m/z 469.2467 (469.2464 calc. for $C_{27}H_{35}NO_6$, M+).

(2*S*,5*S*,6*R*)-2-Allyl-((*R*)-1-((*R*)-1-(4-methoxyphenoxy)pent-4-en-2-yloxy)propyl)-4,5-dimethyl-6-phenylmorpholin-3-one (123):



To a solution of **122** (0.660 g, 1.40 mmol) in dichloromethane (15 mL) at -78 °C was added allytrimethylsilane (1.40 mL, 8.50 mmol) followed by BF_3•etherate (1.10 mL, 8.50 mmol). The mixture was stirred at -78 °C for 15 min and then warmed to ambient temperature and stirred for 18 h. Cold water was added and the mixture was extracted with dichloromethane (3 x 25 mL). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (1/3 ethyl acetate/hexane) to provide 0.232 g (60%) of **123** as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.36-7.32 (m, 3H), 7.29-7.26 (m, 2H), 6.85-6.80 (m, 4H), 6.04-5.95 (m, 1H), 5.83-5.75 (m, 1H), 5.31 (d, 1H, J = 3.5), 5.11-5.01 (m, 4H), 3.96-3.90 (m, 3H), 3.83 (m, 1H), 3.76 (s, 3H), 3.43 (dq, 1H, J = 3.5, 7.0), 3.05 (s, 3H), 2.68 (dd, 1H, J = 14, 7.5), 2.59 (dd, 1H, J =14.5, 7.5), 2.40-2.37 (m, 2H), 1.95-1.88 (m, 1H), 1.87-1.78 (m, 1H), 1.09 (t, 3H, J = 7), 1.06 (d, 3H, J = 7).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 170.2 (N*C*=O), 154.0 ($_{p\text{-}MeO}$ArCOCH$_3$), 153.4 ($_{p\text{-}MeO}$ArCO), 138.8 (ArCipso), 134.6 (*C*H=CH$_2$), 134.5 (*C*H=CH$_2$), 128.4 (Ar*C*), 127.6 (Ar*C*), 126.1 (Ar*C*), 117.9

($_{p\text{-}MeO}$ArC), 117.6 ($_{p\text{-}MeO}$ArC), 115.7 (CH=CH_2), 114.8 (CH=CH_2), 85.4 (O=CCO), 84.0 (PhCH), 77.4 (OCH_2), 73.7 ($_{p\text{-}OMe}$ArCH_2), 69.8 (CHO), 59.7 (NCH), 55.9 (OCH_3), 41.4 (CH_2CH=C), 36.2 (CH_2CH=C), 34.0 (NCH_3), 22.8 (CH_3CH_2), 12.7 (CH_3CHO), 11.3 (CH_3CHN).

IR (neat):

2934, 1643, 1508, 1230, 1043, 823 cm^{-1}.

$[\alpha]_D^{23}$ = -63 (*c* 1, $CHCl_3$).

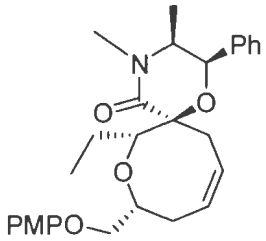
MS (APCI):

494.2 (M+1, 100).

HRMS (EI):

m/z 493.2824 (493.2828 calc. for $C_{30}H_{39}NO_5$, M+).

(2*R*,3*S*,6*S*,7*R*,9*R*,11*Z*)-3,4-Dimethyl-7-ethyl-9-((4-methoxyphenoxy)methyl)-2-phenyl-1,8-dioxa-4-azaspiro[5.7]tridec-11-en-5-one (124):



To a solution of **123** (0.350 g, 0.709 mmol) in dichloromethane (290 mL) was added the Grubbs (II) catalyst (43 mg, 0.05 mmol, 10 mol%). The reaction mixture was stirred at room temperature for 28 h and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (1/1 ethyl acetate/hexane) to give 0.280 g (85%) of **124** as a white solid.

Mp: 67-69 °C.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.41-7.35 (m, 2H), 7.33-7.31 (m, 3H), 6.86-6.82 (m, 4H), 6.02-5.97 (m, 1H), 5.62-5.59 (m, 1H), 5.28 (d, 1H, J = 3.0), 4.19 (dd, 1H, J = 9.0, 5.0), 3.86 (dd, 1H, J = 9.0, 7.5), 3.77 (s, 3H), 3.74-3.72 (m, 1H), 3.56-3.52 (m, 2H), 3.32 (dd, 1H, J = 13.0, 5.5), 3.01(s, 3H), 2.68 (dd, 1H, J = 13.0, 5.5), 2.51-2.47 (m, 1H), 2.43-2.38 (m, 1H), 1.78-1.75 (m, 1H), 1.42-1.37 (m, 1H), 1.10 (t, 3H, J = 7.5), 0.96 (d, 3H, J = 7.0).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 170.3, 154.0, 153.1, 138.1, 130.2, 128.7, 128.6, 127.8, 125.7, 115.4, 115.0, 87.7, 85.7, 83.4, 72.0, 71.5, 58.9, 56.0, 33.6, 32.1, 30.0, 24.9, 13.0, 11.3.

IR (neat):

2958, 1646, 1507, 1230, 823 cm^{-1}.

$[\alpha]_D^{23}$ = +13.5 (*c* 1, $CHCl_3$).

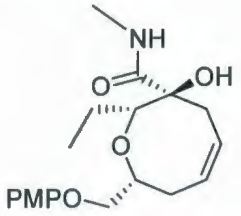
MS (APCI):

466.2 (M+1, 100).

HRMS (EI):

m/z 465.2524 (465.2515 calc. for $C_{28}H_{35}NO_5$, M+).

(2*R*,3*S*,5*Z*,8*R*)-2-Ethyl-8-((4-Methoxyphenoxy)methyl)-3,4,7,8-tetrahydro-3-hydroxy-*N*-methyl-2*H*-oxocine-3-carboxamide (125):



To anhydrous liquid ammonia (15 mL, distilled over sodium) was added Na metal (0.0870 g, 3.78 mmol) at –78 °C and the mixture was stirred for 15 min. To the resulting blue solution was added rapidly a solution of **124** (0.250 g, 0.537 mmol) in anhydrous THF (3 mL) and the mixture was stirred for 1 min. A mixture of methanol/water (3/1, 5 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 column chromatography on silica gel (ethyl acetate) to provide 0.180 g (96%) of **125** as a colourless gum.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 6.88-6.84 (m, 4H), 6.54 (br s, 1H), 6.07-6.02 (m, 1H), 5.91-5.85 (m, 1H), 4.27 (s, 1H), 4.03 (dd, 1H, J = 5, 9.5), 3.95 (dd, 1H, J = 4.5, 9.5), 3.85-3.81 (m, 1H), 3.78 (s, 3H), 3.63 (m, 1H), 2.85 (d, 3H, J = 4), 2.85-2.82 (m, 1H), 2.57-2.51 (m, 1H), 2.35-2.31 (m, 1H), 2.26-2.22 (m, 1H), 1.68-1.63 (m, 1H), 1.16-1.08 (m, 1H), 1.01 (t, 3H, J = 7.0).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 176.3, 154.2 , 153.2, 129.7, 129.4, 115.6, 115.0, 84.1, 82.3, 79.1, 71.9, 56.0, 37.8, 31.4, 26.7, 23.6, 10.9.

IR (neat):

3392, 2928, 1663, 1507, 1231, 1068, 1035, 824 cm^{-1}.

$[\alpha]_D^{23} = +27$ (*c* 1, $CHCl_3$).

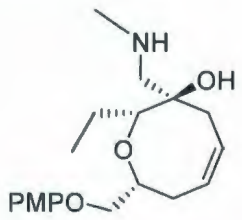
MS (APCI):

350.1 (M+1, 100)

HRMS (EI):

m/z 349.1897 (349.1889 calc. for $C_{19}H_{27}NO_5$, M+).

(2*R*,3*S*,5*Z*,8*R*)-8-((4-Methoxyphenoxy)methyl)-2-ethyl-3,4,7,8-tetrahydro-3-((methylamino)methyl)-2*H*-oxocin-3-ol (126):



To a stirred solution of **125** (0.180 g, 0.514 mmol) in THF (10 mL) at 0 °C was slowly added lithium aluminum hydride (0.157 g, 4.10 mmol). The mixture was then brought to room temperature and heated to reflux for 50 h. The reaction mixture was then cooled to room temperature and 3 M HCl (5 mL) was added. The resulting solution was washed with ethyl acetate (2 x 15 mL). The aqueous layer was cooled (<5 °C), basified (pH = 10) with 6 M sodium hydroxide and concentrated under reduced pressure. The residual solids were extracted with ethyl acetate (5 x 15 mL) and the combined organic layers were dried and concentrated under reduced pressure. The residue was purified by

flash chromatography on silica gel (1/3 ethyl acetate/hexane) to provide 0.145 g (84%) of **126** as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 6.85-6.81 (m, 4H), 5.98-5.93 (m, 1H), 5.89-5.84 (m, 1H), 3.99 (m, 1H), 3.77-3.75 (m, 2H), 3.72 (s, 3H), 3.50 (dd, 1H, J = 10.8, 1.1), 2.70 (d, 1H, J = 13), 2.69 (m, 1H), 2.58 (d, 1H, J = 13.0), 2.46 (s, 3H), 2.38-2.27 (m, 2H), 2.14 (dd, 1H, J = 12.5, 6.5), 1.69-1.65 (m, 1H), 1.27-1.19 (m, 1H), 1.04 (t, 3H, J = 7.0).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 154.0, 153.2, 130.1, 129.2, 115.5, 114.8, 85.4, 80.6, 76.9, 71.7, 56.5, 55.9, 37.7, 36.6, 31.4, 24.0, 11.4.

IR (neat):

2930, 1737, 1507, 1231, 1039, 823 cm^{-1}.

$[\alpha]_D^{23}$ = +85 (*c* 1, $CHCl_3$).

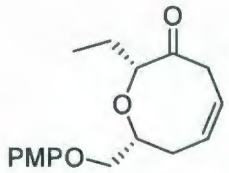
MS (APCI):

336.2 (M+1, 100).

HRMS (CI):

m/z 336.2193 (336.2175 calc. for $C_{19}H_{30}NO_4$, M+H).

(2*R*,5*Z*,8*R*)-2-Ethyl-7,8-dihydro-8-((4-Methoxyphenoxy)methyl)-2H-oxocin-3(4H)-one (127):



To a stirred solution of **126** (0.100 g, 0.298 mmol) in a mixture of methanol-water (100:1, 4 mL) at 0 °C was added $NaIO_4$ (0.255 g, 1.23 mmol). The reaction mixture was maintained at this temperature for 15 min and then warmed to room temperature and stirred for 2.5 h. 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 (sodium sulphate) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (1/3 ethyl acetate/hexane) to provide 0.0850 mg (98%) of the ketone **127** as a colourless gum.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 6.87-6.83 (m, 4H), 5.89-5.84 (m, 1H), 5.71-5.66 (m, 1H), 4.06 (dd, 1H, J = 9.1, 5.9), 3.97-3.90 (m, 2H), 3.82-3.78 (m, 2H), 3.78 (s, 3H), 2.82 (dd, 1H, J = 12, 4.5), 2.45 (dd, 2H, J = 7.1, 4.5), 1.79-1.73 (m, 1H), 1.63-1.57 (m, 1H), 1.02 (t, 3H, J = 7.0).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 213.8, 154.3, 153.0, 128.4, 126.5, 115.7, 114.9, 87.6, 82.1, 71.1, 56.0, 41.3, 30.4, 26.4, 10.4.

IR (neat):

2930, 1715, 1508, 1231, 1044, 823 cm^{-1}.

$[\alpha]_D^{23}$ = +513 (c 1, $CHCl_3$).

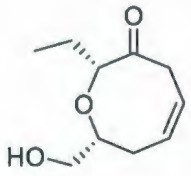
MS (APCI):

291.1 (M+1, 100)

HRMS (CI):

m/z 290.1519 (290.1518 calc. for $C_{17}H_{22}NO_4$, M+).

(2*R*,5*Z*,8*R*)-2-Ethyl-7,8-dihydro-8-(hydroxymethyl)-2*H*-oxocin-3(4*H*)-one (48):[17]



To a stirred solution of the ketone **127** (0.030 mg, 0.103 mmol) in acetonitrile/water (4/1, 2.5 mL) at 0 °C was added ceric ammonium nitrate (0.164 g, 0.314 mmol). The resulting orange coloured reaction mixture was stirred at 0 °C for 10 min and then diluted with dichloromethane (10 mL). The aqueous layer was extracted with dichloromethane (2 x 10 mL) and the combined organic layers were dried (sodium sulphate) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (1/2 ethyl acetate/hexane) to provide 0.0200 g (87%) of **48** as a white solid.

Mp: 71-72 °C;

^{1}H NMR (500 MHz, $CDCl_3$):

δ 5.86-5.81 (m, 1H), 5.68-5.63 (m, 1H), 3.89 (dd, 1H, *J* = 12.5, 7.5), 3.83 (dd, 1H, *J* = 8, 4.5), 3.69-3.62 (m, 2H), 3.60-3.56 (m, 1H), 2.83 (dd, 1H, *J* = 12.5, 7.5),

2.36-2.34 (m, 2H), 2.00 (m, 1H), 1.81-1.74 (m, 1H), 1.73-1.63 (m, 1H), 1.00 (t, 3H, J = 7.5).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 213.2 (C=O), 128.3 ($O=CCH_2\underline{C}H=CH$), 126.2 ($O=CCH_2\underline{C}H=\underline{C}H$), 87.0 ($C_2H_5\underline{C}H$), 84.3 ($O\underline{C}H$), 66.1 ($\underline{C}H_2OH$), 41.2($O=\underline{C}CH_2$), 30.2 ($\underline{C}H_2CH=$), 26.3 ($CH_3\underline{C}H_2$), 10.2 ($\underline{C}H_3CH_2$).

IR (solid):

3440, 3026, 1710, 1645, 1095, 1063, 755 cm^{-1}.

$[\alpha]_D^{23}$ = +610 (*c* 1, $CHCl_3$) (lit.[17] $[\alpha]_D^{25}$ = +568 (*c* 0.81, $CHCl_3$).

MS (APCI):

183.1 (M-1, 100).

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39.Prepared from commercially available (*R*)-glycidol by adapting the literature procedure: Cossy, J.; Pradaux, F.; BouzBouz, S. *Org. Lett.*, **2001**, *3*, 2233.

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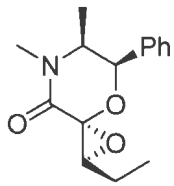
41. Brook, A. G. *J. Am. Chem. Soc.* **1958**, *80*, 1886.

Appendix 3:

^{1}H and ^{13}C NMR Spectra for Chapter 4



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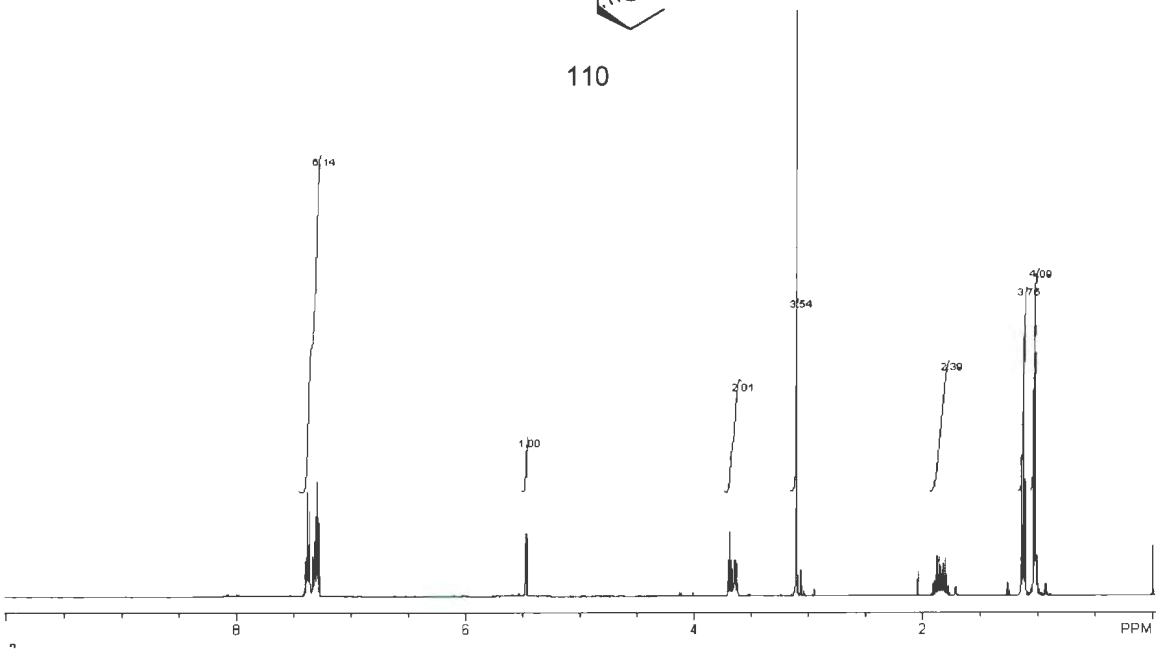

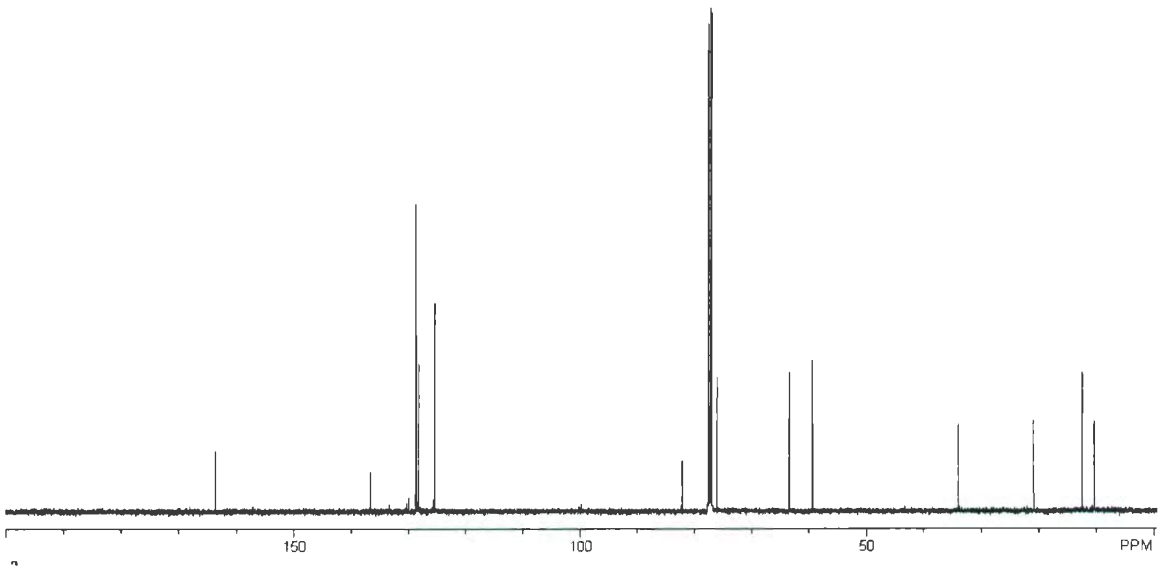

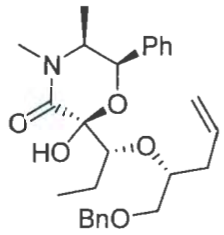

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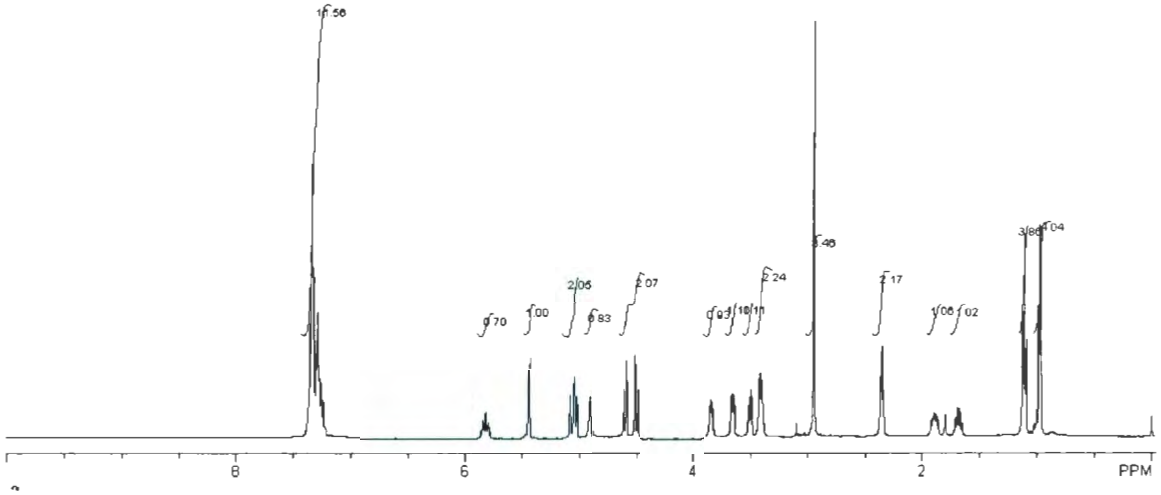

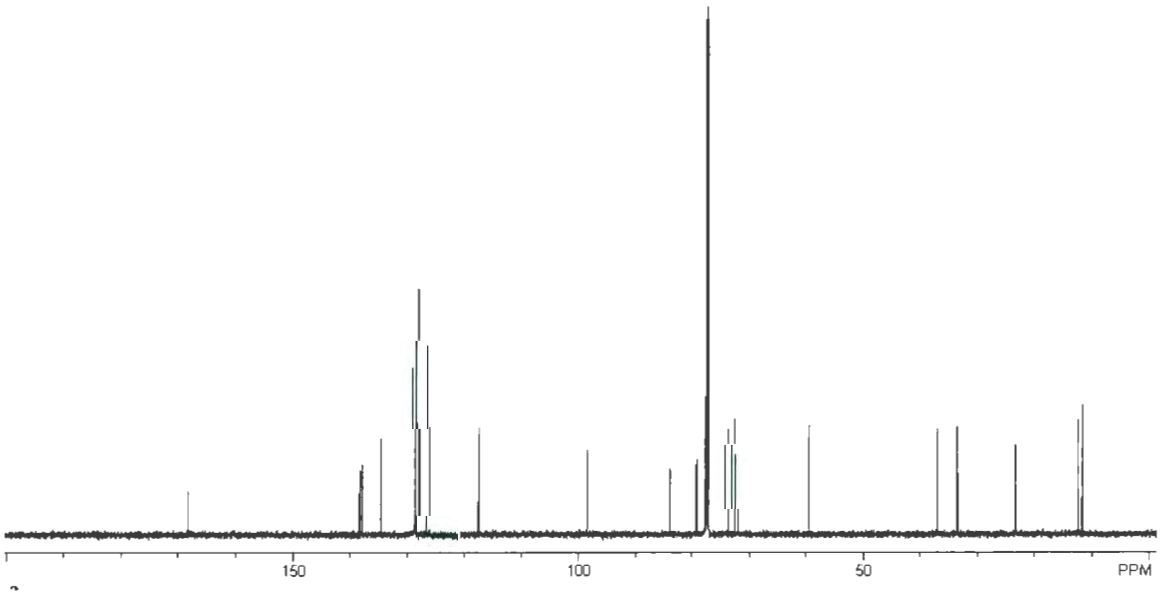

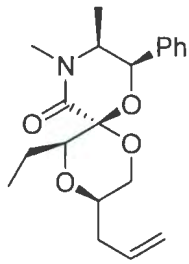
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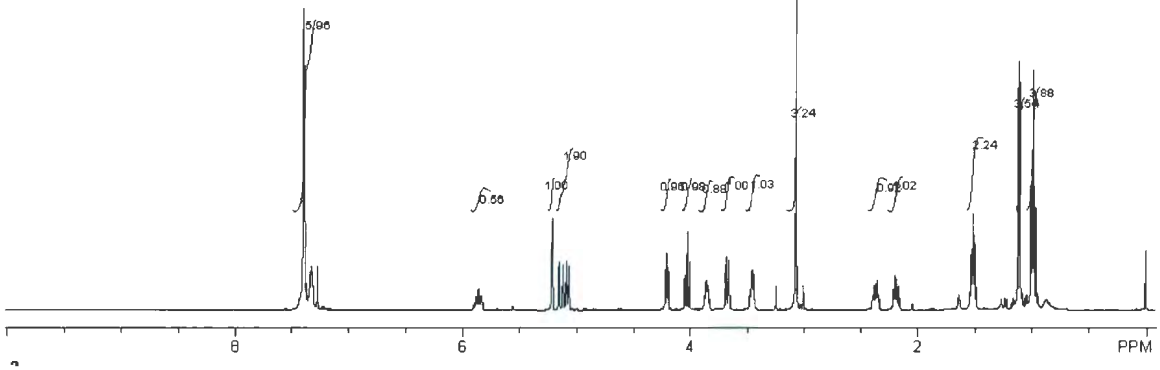
O
O
O

116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2
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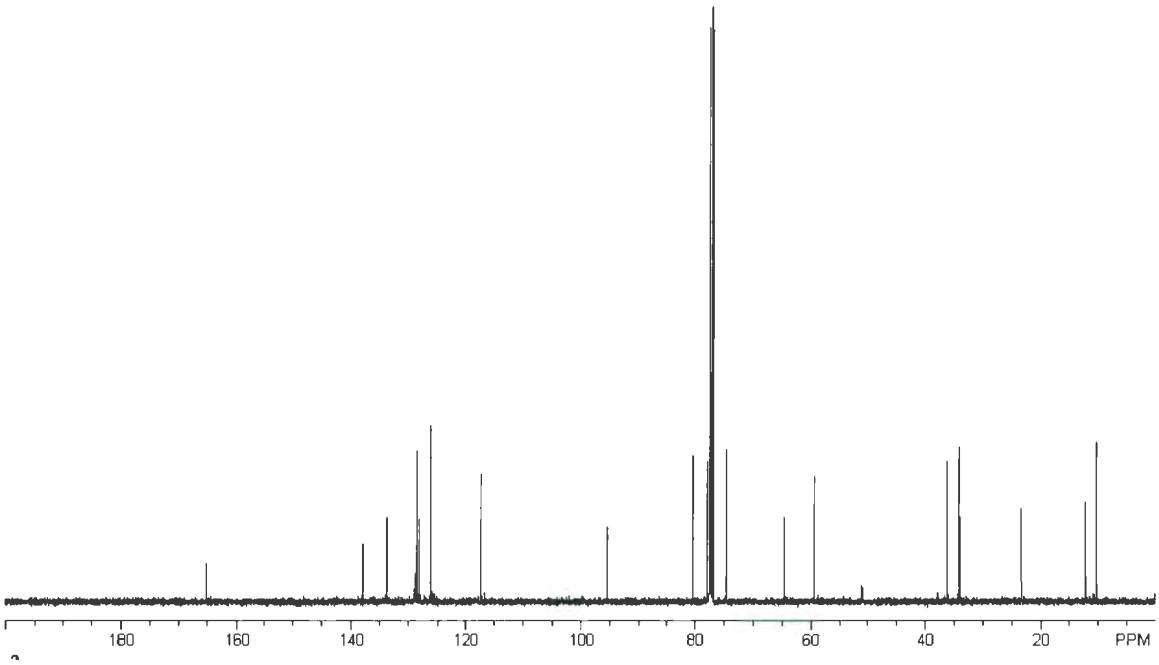
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60
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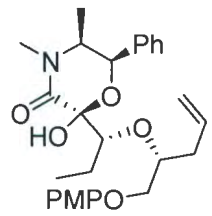
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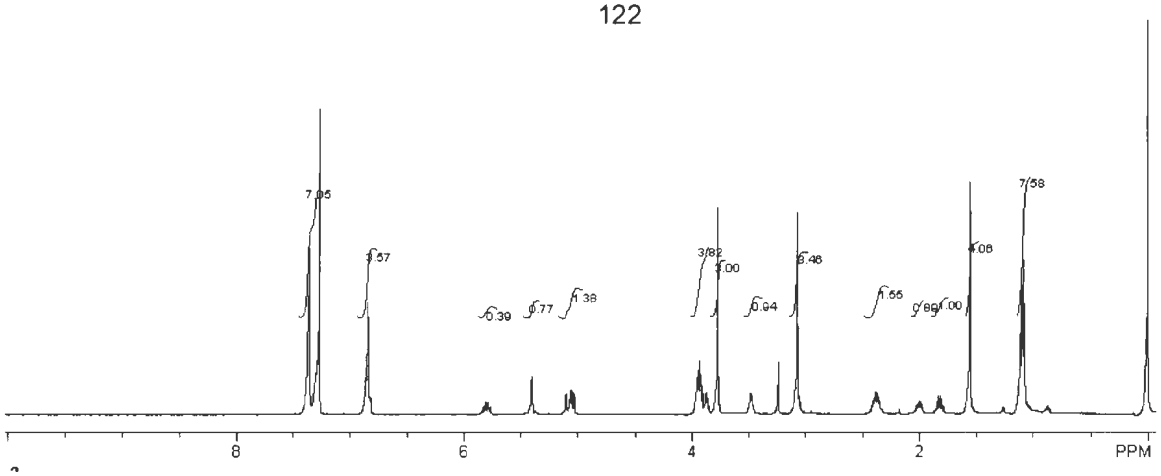
O
HO
O
PMPO

122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6
4
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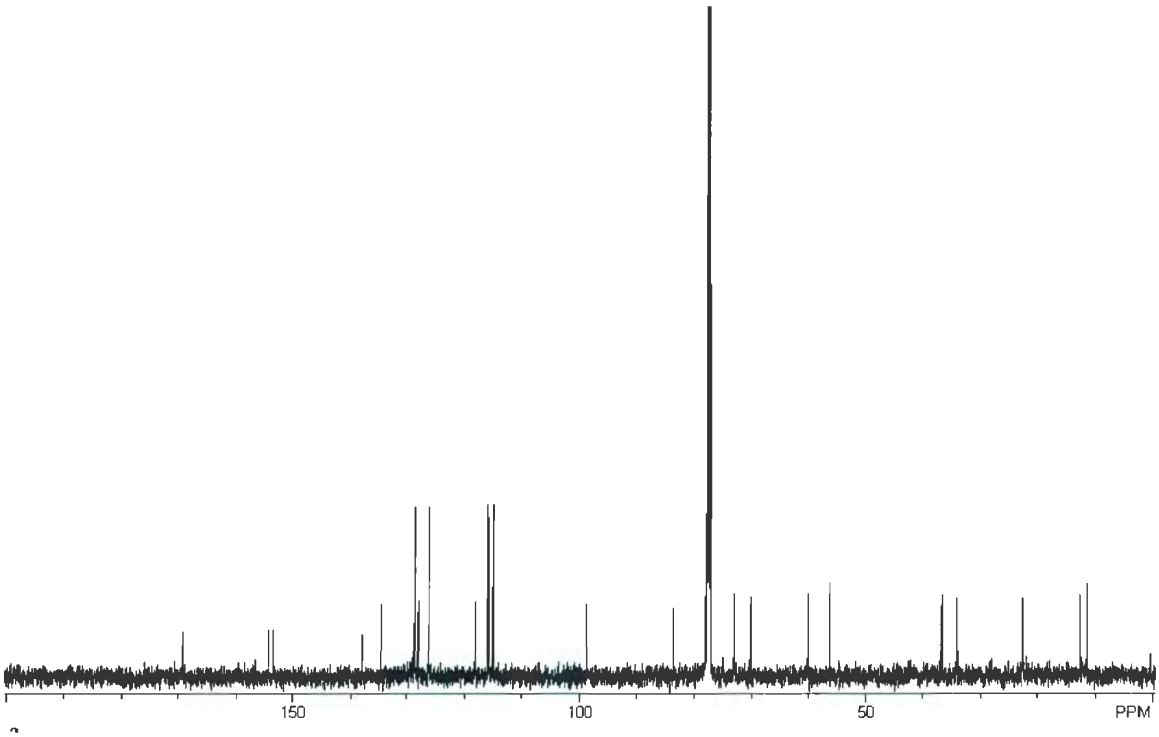
PPM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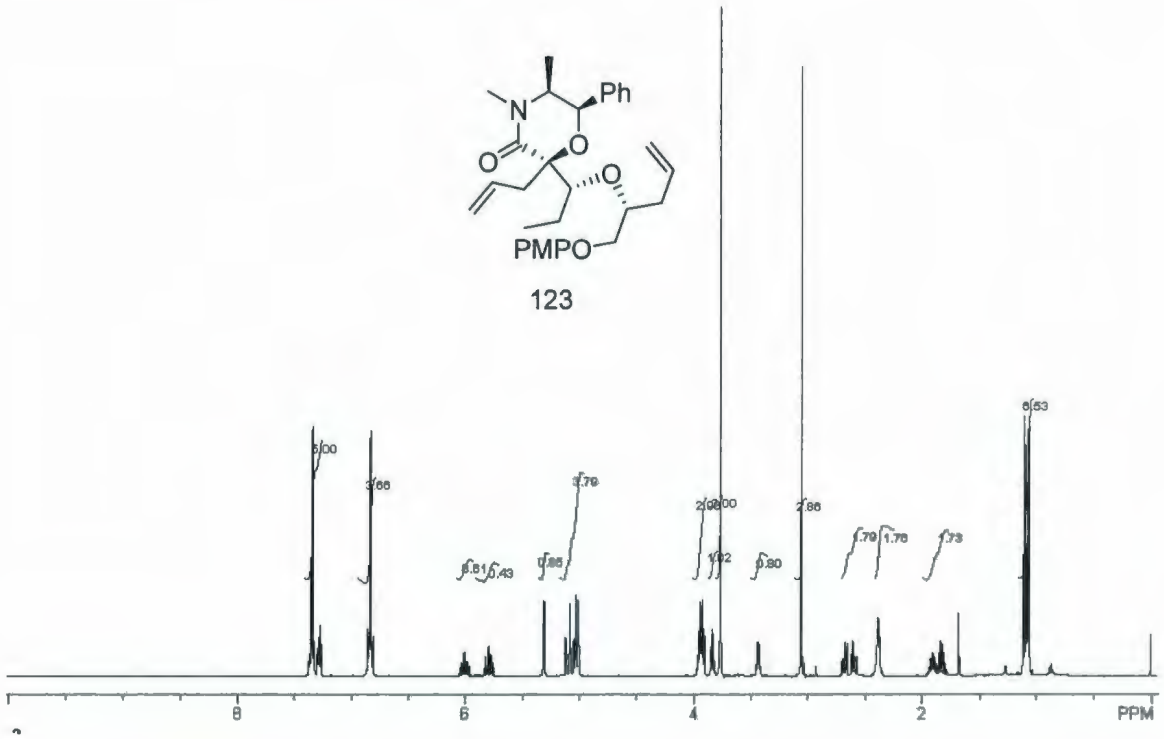

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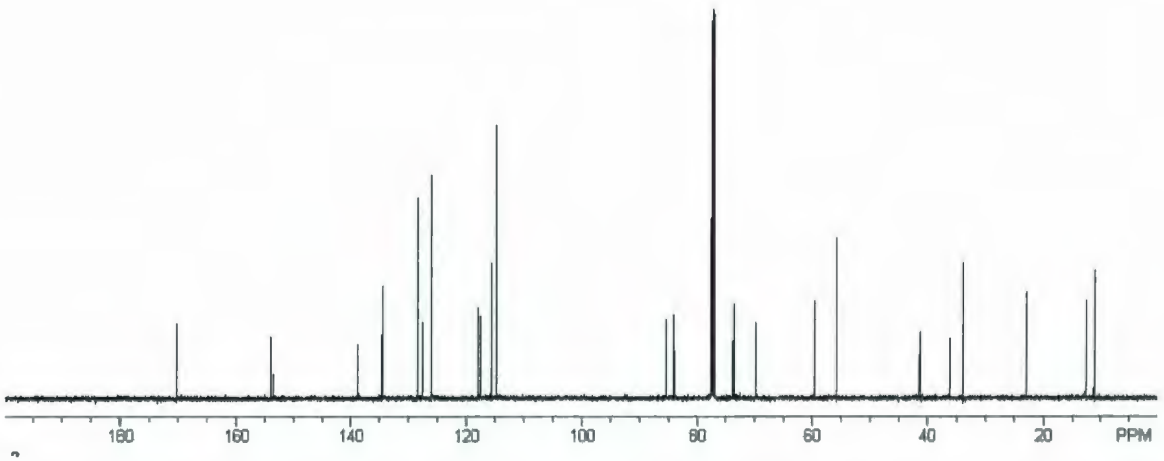

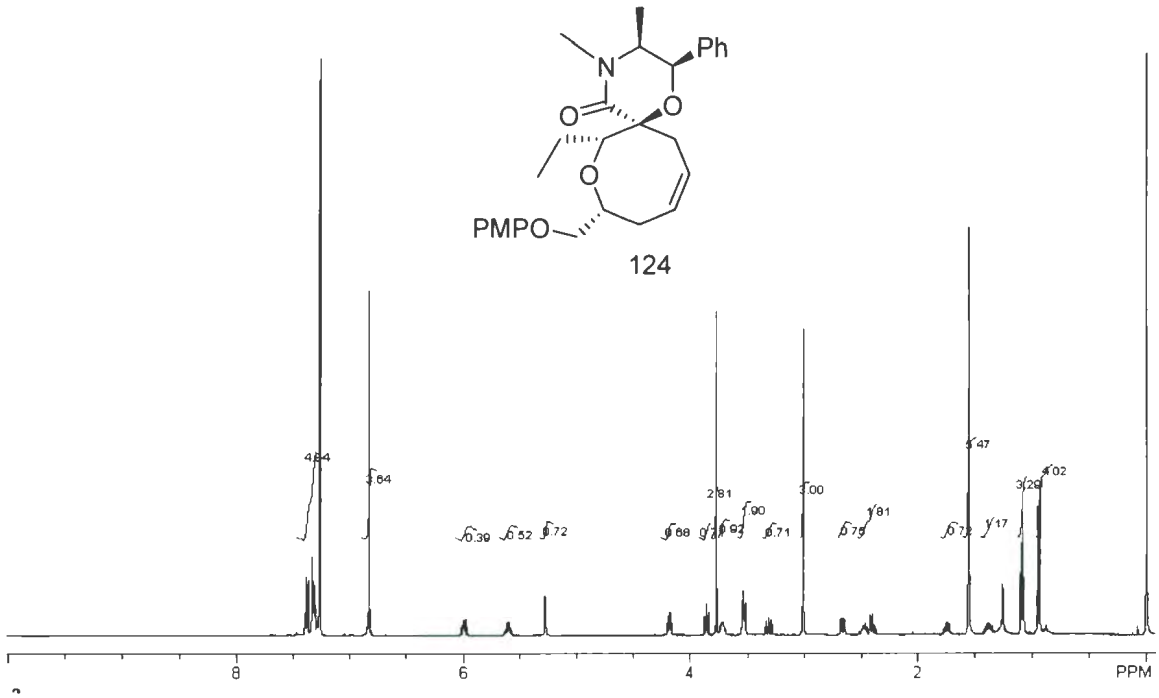

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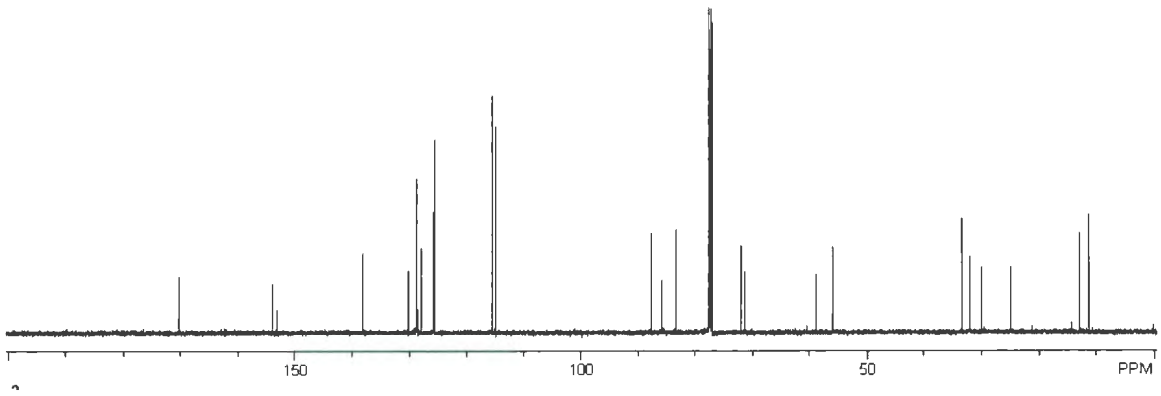

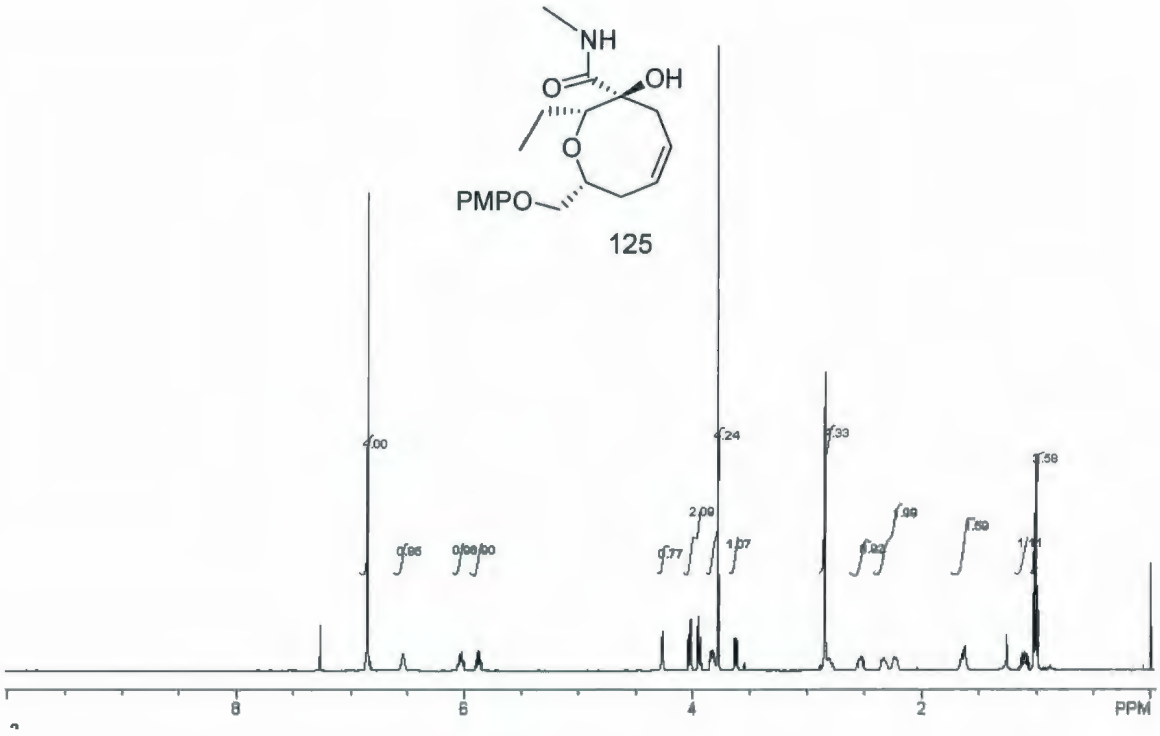
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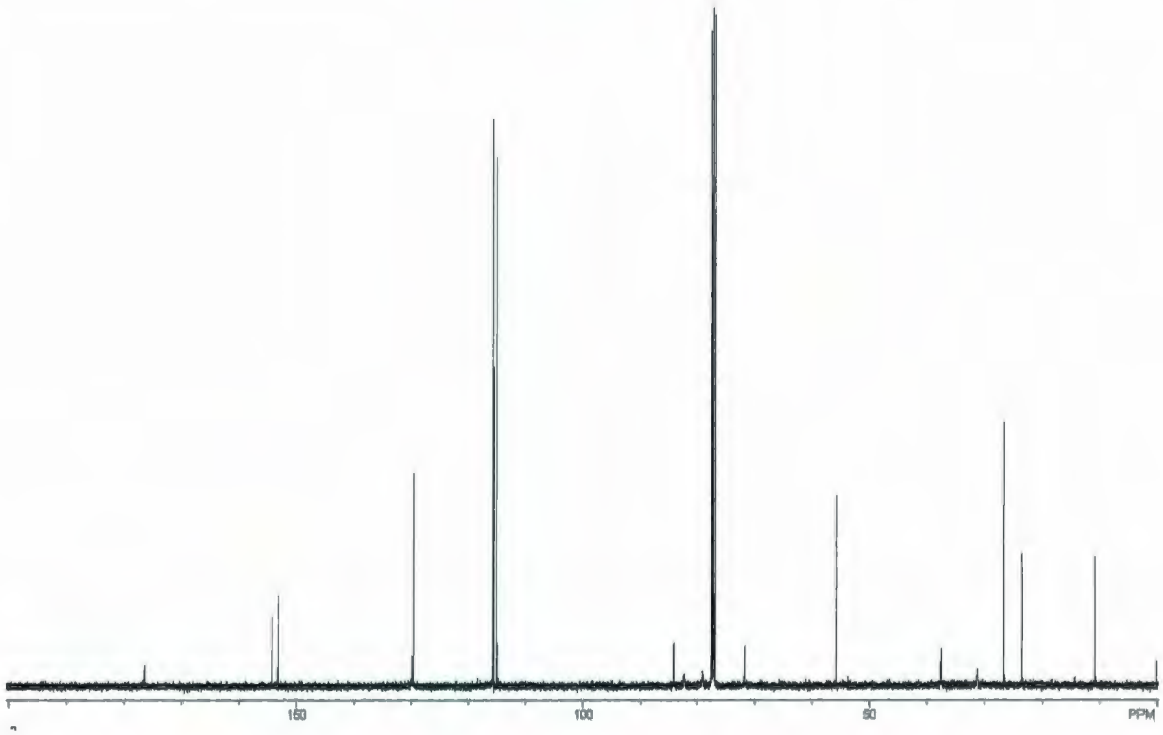
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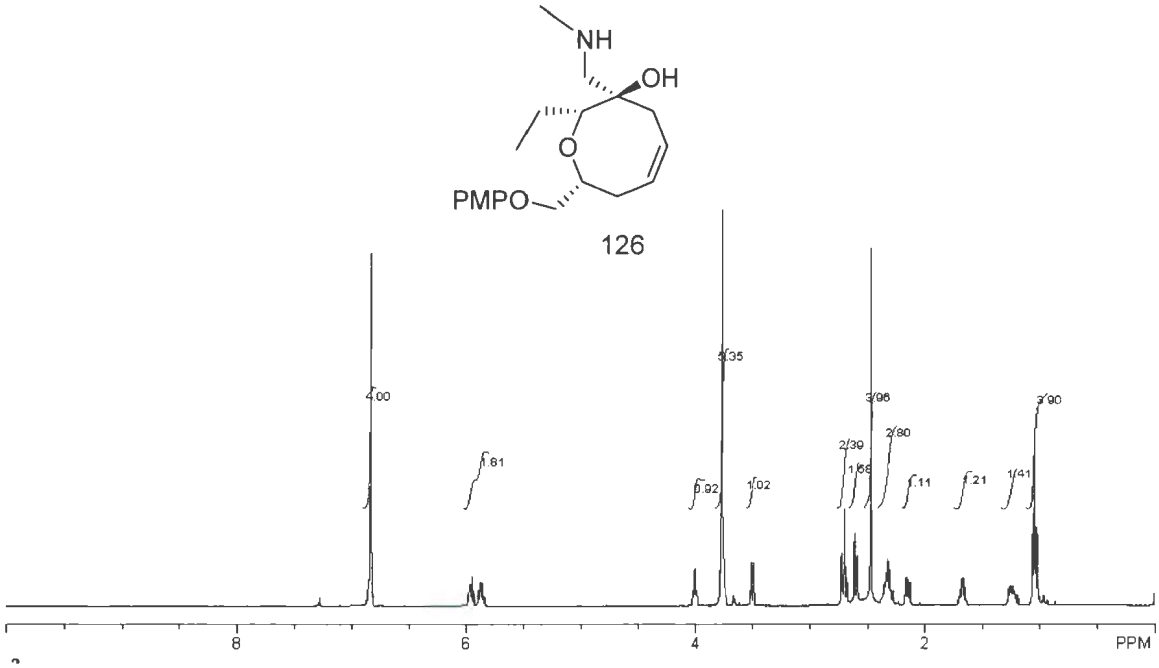
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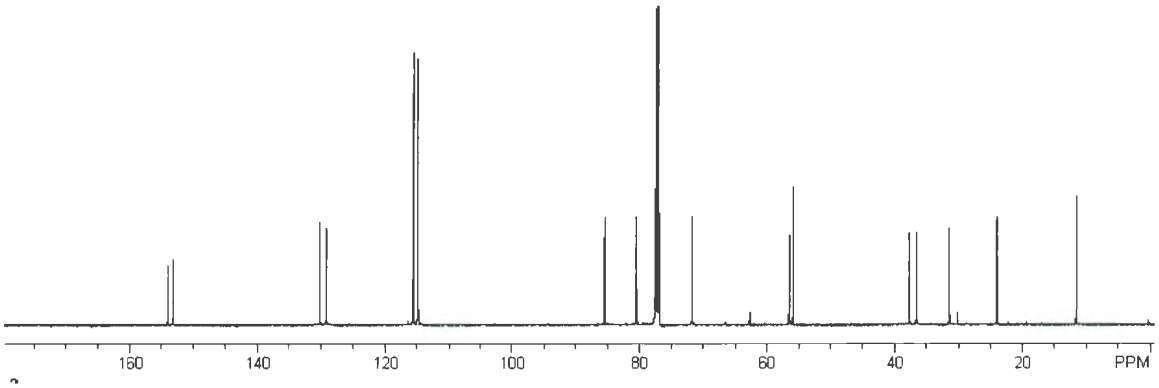
6
4
2
PPM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60
40
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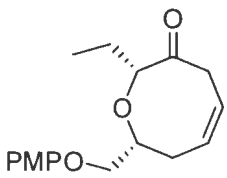
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O
PMPO

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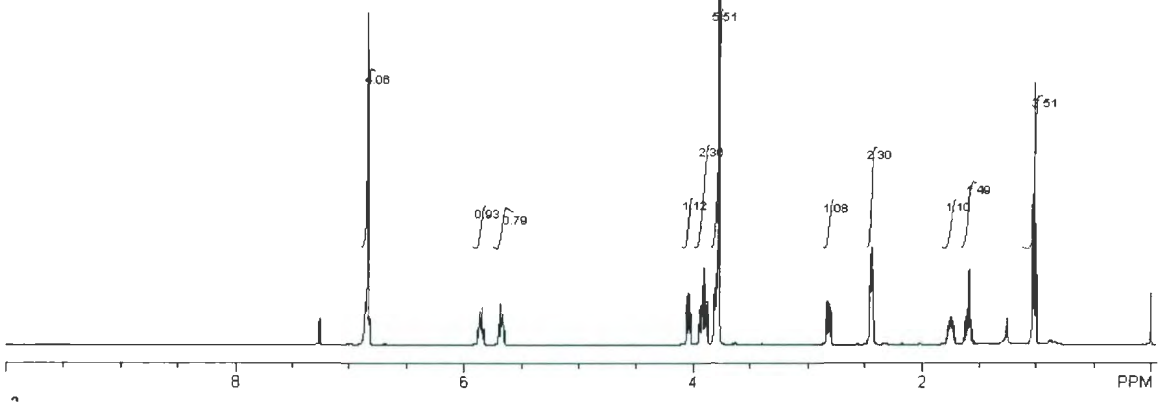
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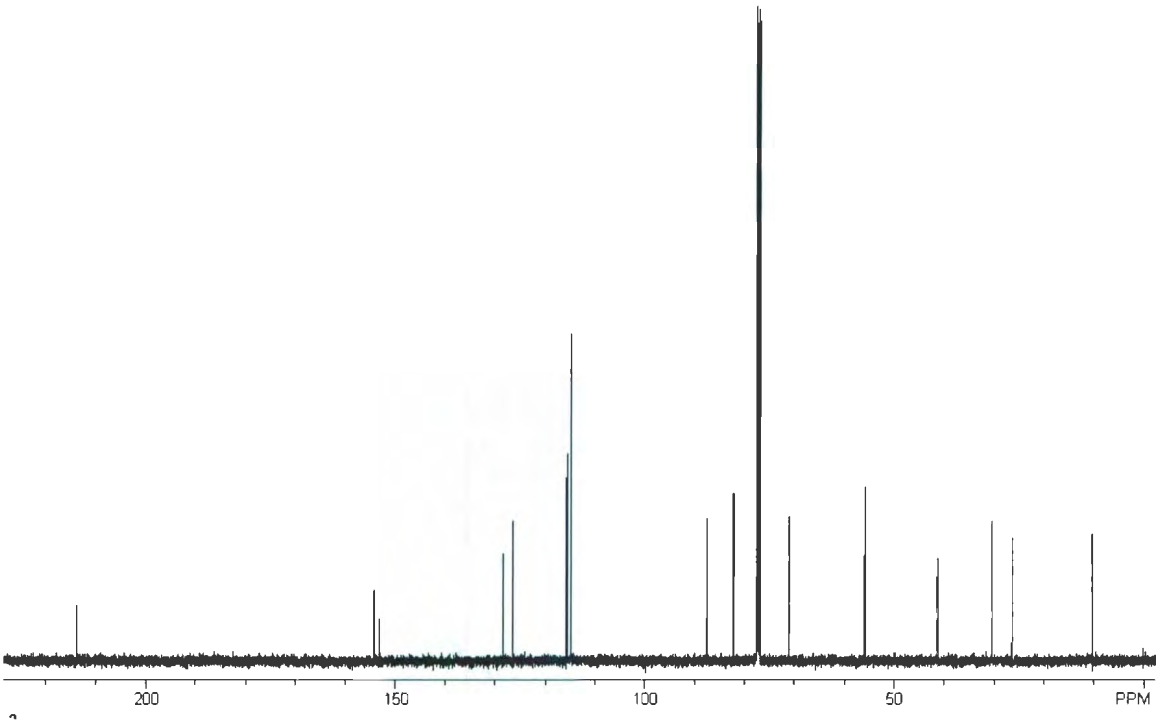
1.10
1.49
8
6
4
2
PPM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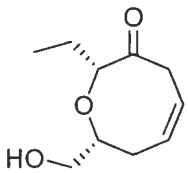
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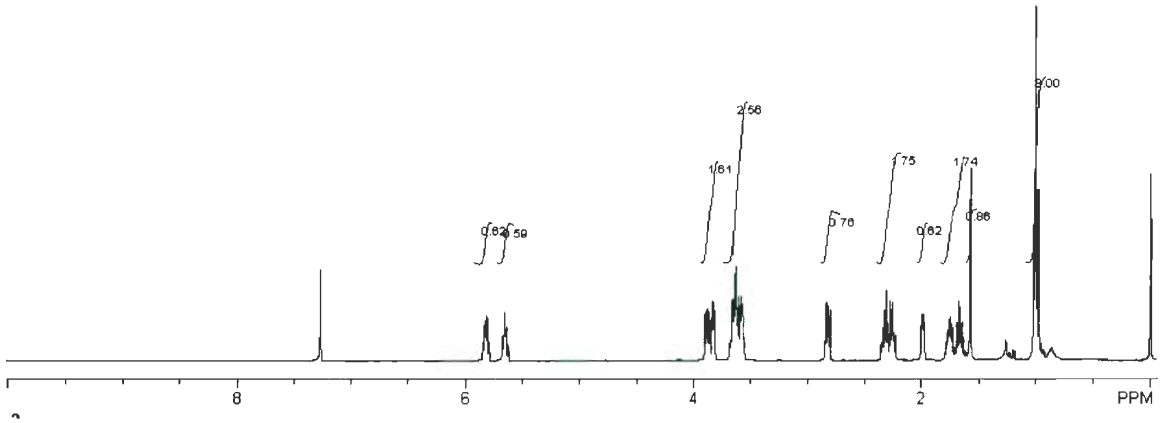
O
HO

48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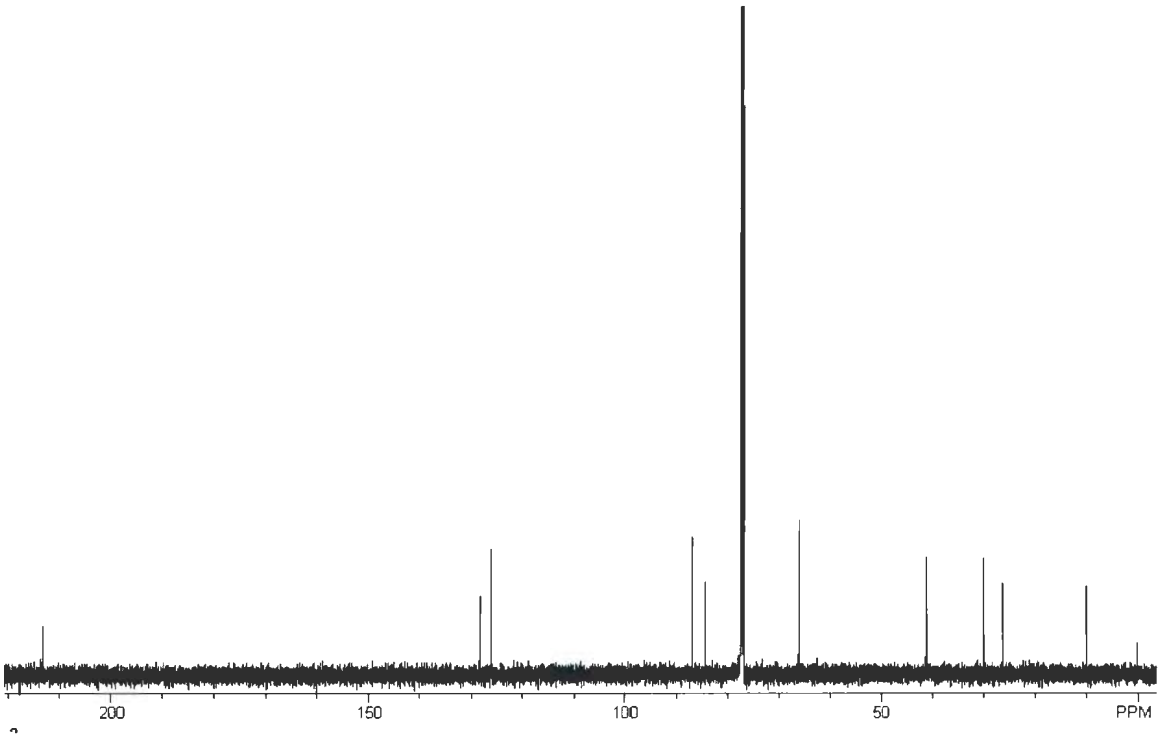
1.74
0.86
3.00
8
6
4
2
PPM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Chapter 5

Studies on Enantioselective Synthesis of Functionalized Pyrrolidines

Introduction.

Nitrogen heterocycles, especially pyrrolidines, are represented in a large class of biologically active natural products.[1] Selected examples are kainic acid,[2] kaitocephalin,[3] plakoridine[4] and anisomycin[5] (Figure 1). Not surprisingly, the synthesis of functionalized pyrrolidines has been actively investigated and several strategies for the synthesis of stereochemically defined, substituted pyrrolidines have been reported in the literature.[6]

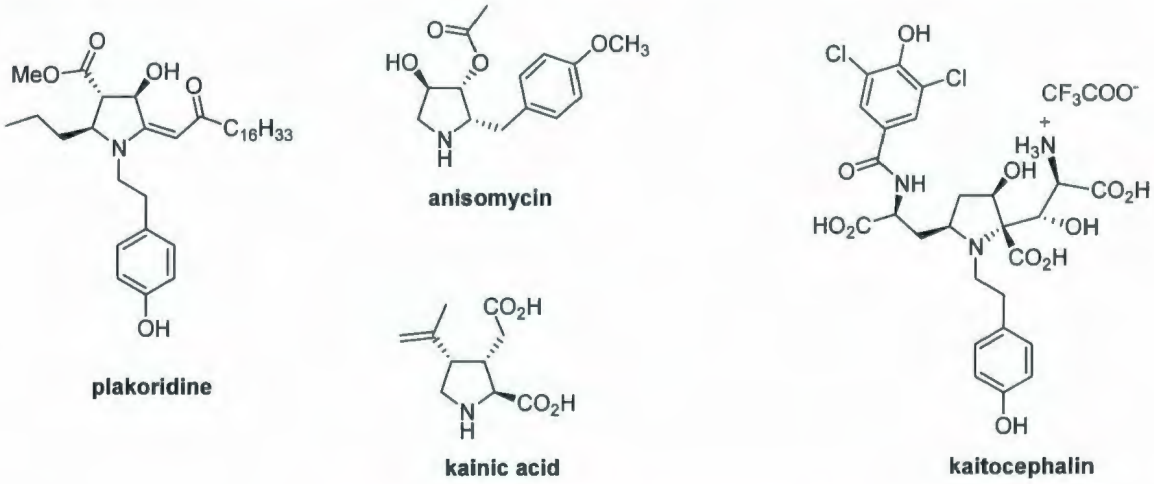
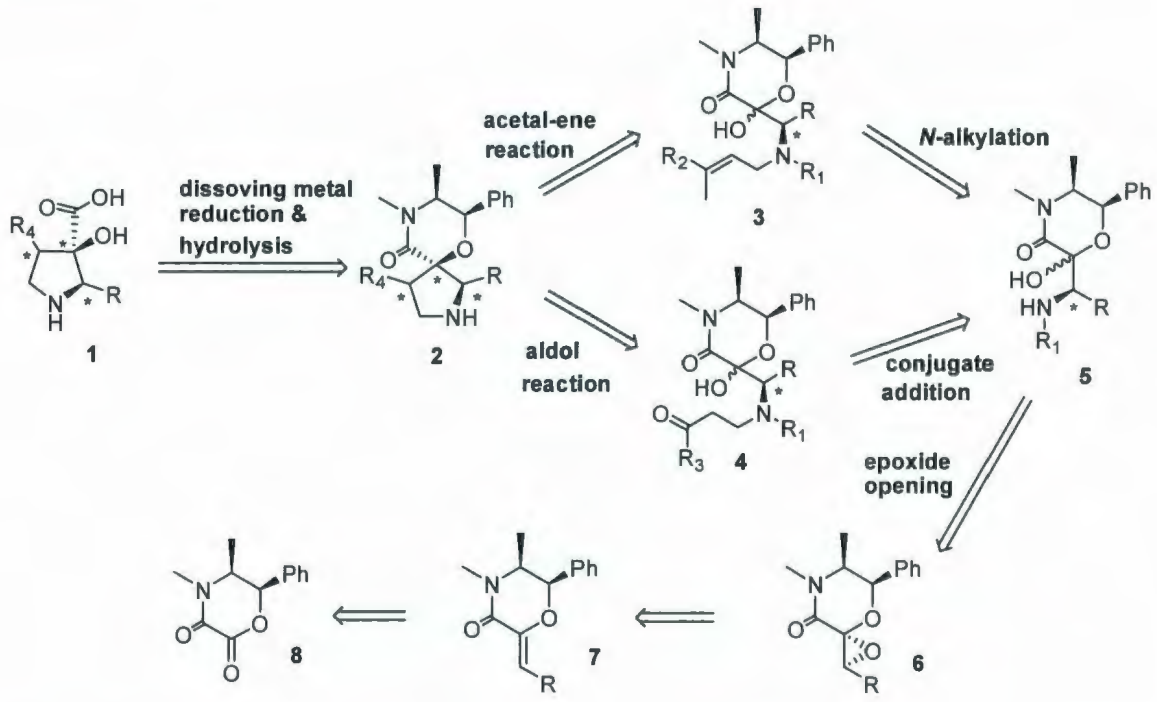


Figure 1. Pyrrolidine-based natural products.

In continuation of the studies on the applications of the ephedrine-derived morpholine-dione template (described in Chapters 2, 3 and 4), it was decided to explore a general route for the enantioselective synthesis of functionalized pyrrolidines via this starting material. From a retrosynthetic perspective, the plan can be explained as follows (Scheme 1): the target compounds such as pyrrolidines **1**, could be obtained by subjecting the morpholinone portion in **2** to dissolving metal reduction. The pyrrolidine ring in the pyrrolidino-morpholinone **2** could be obtained from hemiacetals such as **3** via an intramolecular ene-type ring closing reaction or from hemiacetals such as **4** via an

intramolecular aldol-type reaction. In the synthetic direction, treatment of the hemiacetals **3** or **4** with a Lewis acid could simultaneously achieve the formation of the oxocarbenium ion and activation of the pendant nucleophile thereby facilitating an intramolecular ring-closing reaction. Also, based on the earlier studies (Chapter 3, 4) on nucleophilic additions to chiral morpholinone-based oxocarbenium ions, it was anticipated the proposed intermolecular ring closing to be a highly stereoselective process.

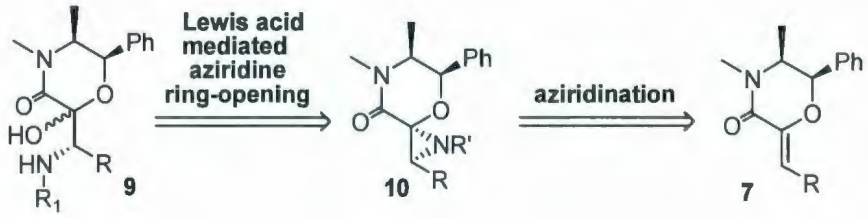
Scheme 1



Hemiacetals **3** can be obtained by alkylation of the amine in **5**. Likewise, a conjugate addition of the amine in **5** to α,β-unsaturated ketones can provide easy access to **4**. The amine **5** can be obtained by the epoxide-opening of **6** by an appropriate amine. As discussed earlier in this thesis (see Chapter 3 and Chapter 4) the epoxide **6** can be obtained from morpholinedione **8** via alkylidene morpholine **7**.

An alternate strategy that involved the aziridine **10** which should be accessible from **7** was also envisioned. Based on the observations with the epoxidation of alkenes such as **7** it was reasonable to assume that aziridination would proceed form the *Si* face of the double bond. Lewis acid-mediated aziridine ring opening would then give **9**. The amine **9** is similar to the amine **5** (Scheme 1) except for the newly-generated stereocenter in **9** which would be opposite in configuration to that in **5**.

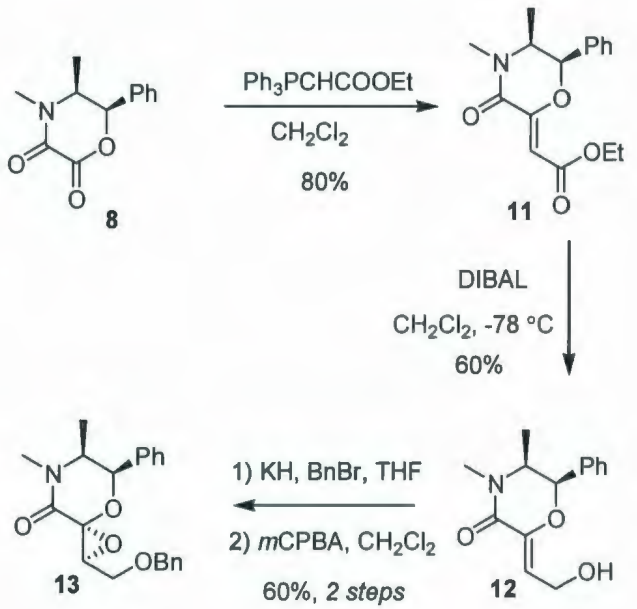
Scheme 2



Results

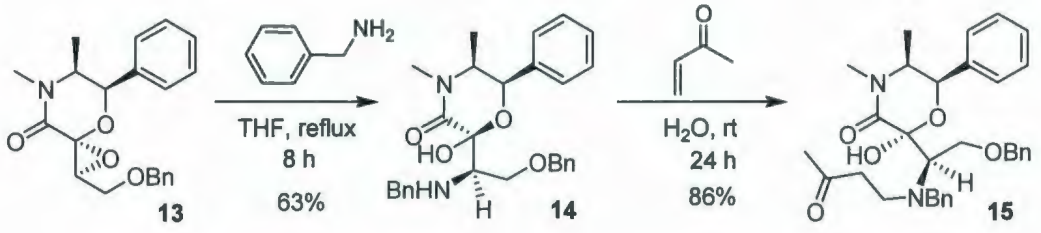
Exploration began with the synthesis of the epoxide **13** (Scheme 3). The alkylidene morpholinone **11** (80%) was prepared from dione **8** by following a procedure previously reported by this group.[7] Reduction of the ester in **11** with DIBAL gave the alcohol **12** (60%). Protection of the alcohol in **12** as a benzyl ether followed by epoxidation of the alkene with *m*-CPBA using the conditions reported earlier (Chapter 3 and Chapter 4) gave the epoxide **13** in reasonable yield (60%).

Scheme 3



The next task was the crucial epoxide-opening with a nitrogen-containing nucleophile. After some experimentation, it was determined that treatment of **13** with benzyl -amine in THF at reflux temperature for 8 h provided the hydroxyamine **14** (63%, Scheme 4). Michael addition of the amine in **14** to 3-butene-2-one in water[8] yielded the aminoketone **15** in good yield (86%).

Scheme 4



At this point, it was reasoned that simultaneous *in situ* generation of the oxocarbenium from the hemiacetal and enolate from the ketone in **15** should be possible by treating **15** with a Lewis acid (Figure 2). The enolate would then react with the

oxocarbenium ion to provide the functionlalized pyrrolidine **16**. It was hoped that the chiral morpholinone ring would influence the stereochemistry at the chiral center in the morpholinone ring. Prediction of the configuration of the α-keto stereocenter was difficult, and was left for experimental evaluation.

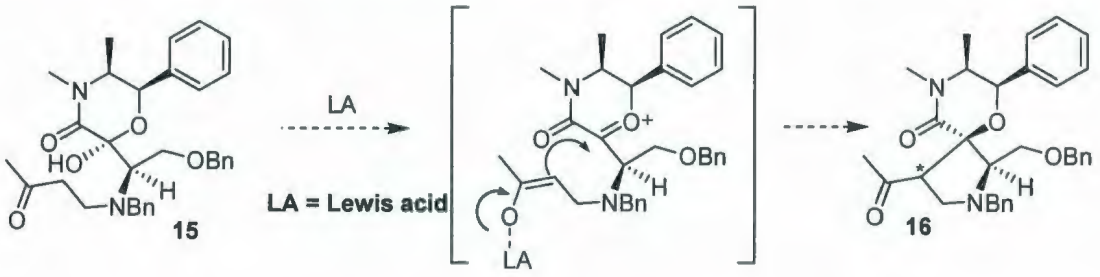
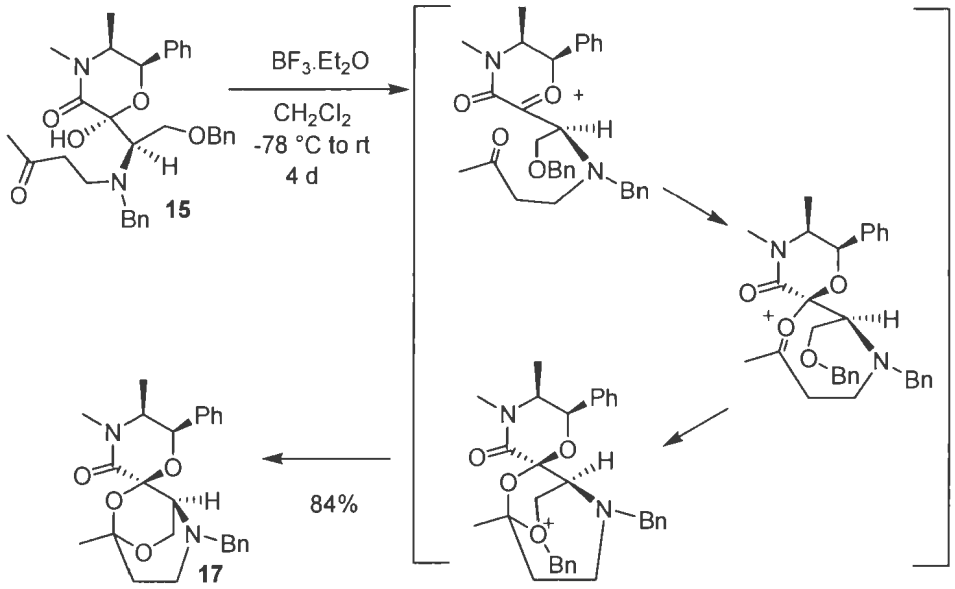


Figure 2. Intramolecular aldol-type reaction of **15**.

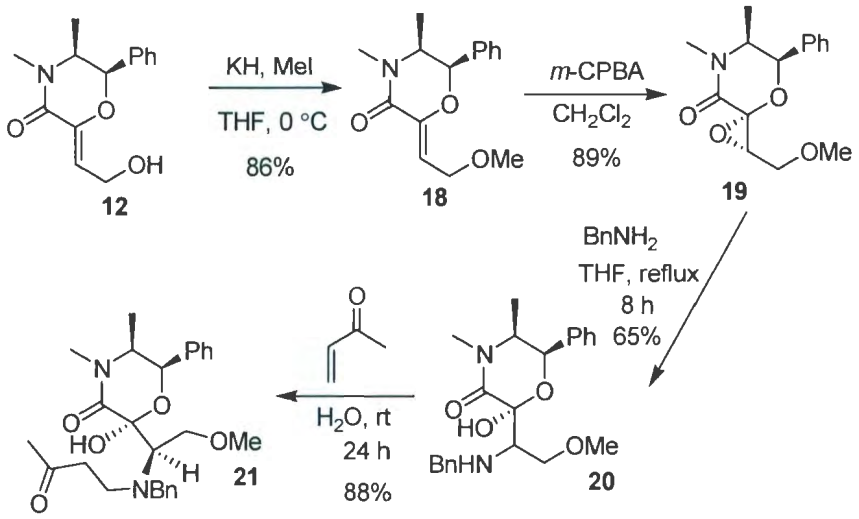
Reaction of **15** with BF_3•etherate (-78 °C to rt) showed a steady progress and complete consumption of the starting material was observed after 4 d (Scheme 5). Disappointingly, none of the required product **16** was formed. Instead, product **17** arising from debenzylation of the ether in **15** was obtained. The stereochemistry at the acetal carbons in **17** was not determined. One of the several possible pathways leading to **17** is shown in Scheme 5.

Scheme 5



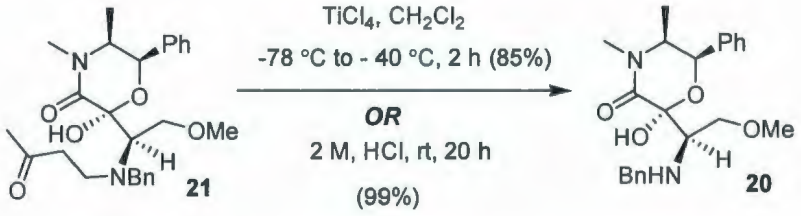
It was therefore decided to use the more robust methyl ether analogue of **15**. The required methyl ether **18** was readily obtained by methylation of the alcohol in **12** (KH, MeI). The aminoketone **21** was then obtained from **18** (Scheme 6) by following a reaction sequence similar to that for aminoketone **15** (Scheme 4).

Scheme 6



Unfortunately, no reaction was observed when **21** was treated with BF_3•etherate at room temperature or under reflux conditions and the starting material could be recovered. Use of $TiCl_4$ or aqueous 2 M HCl resulted in dealkylation of the 2-butanone side-chain to give back the amine **20** (Scheme 7). A survey of other Lewis acids to effect the desired transformation remains to be done.

Scheme 7



An acetal-ene[9] cyclization approach was also explored. It was reasoned that treatment of **22** with a Lewis acid would generate an oxocarbenium ion that would then facilitate the proposed acetal-ene reaction with the 3-methylbut-2-ene side-chain serving as a nucleophile to provide the pyrrolidine **23** (Figure 3).

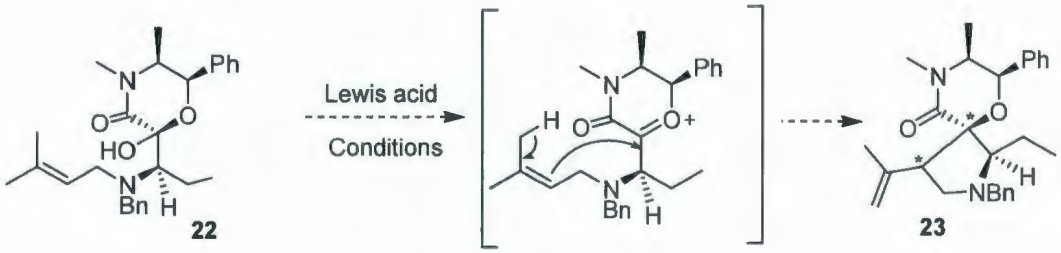
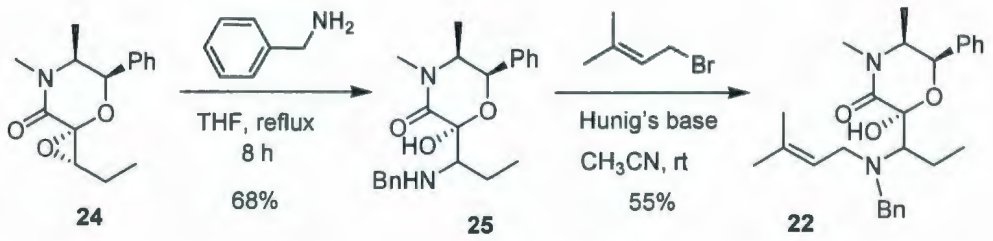


Figure 3. Synthesis of pyrrolidine **23**.

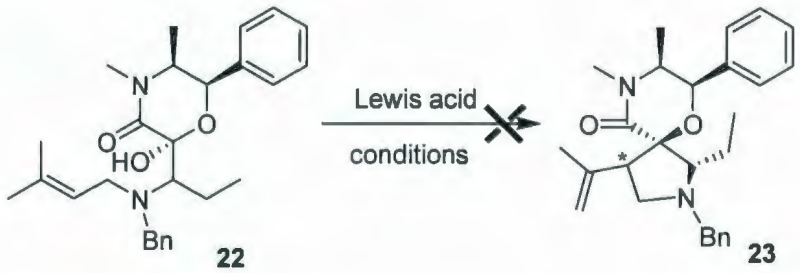
Compound **22** was prepared in moderate yield (55%) by *N*-alkylation[10] of the secondary amine **25**, which was obtained from the epoxide **24** (Scheme 8).

Scheme 8



Unfortunately, treatment of **22** with various Lewis acids (Table 1) failed to provide the desired product and in most of the reactions, the starting material was recovered. The only exception was a reaction with $TiCl_4$ at room temperature, which resulted in *N*-dealkylation of **22** to provide **25**. These studies are still incomplete and will be pursued further in our group.

Table 1: Attempeted acetal-ene reaction of **22**.



Entry	Lewis acid	Conditions	Time	Result
1.	$BF_3•Et_2O$	Ether, reflux	36 h	No reaction
2.	$ZnCl_2$	CH_2Cl_2, reflux	36 h	No reaction
3.	TFA	CH_2Cl_2, reflux	36 h	No reaction
4.	$TiCl_4$	CH_2Cl_2, -40 °C	10 h	No reaction
5.	$TiCl_4$	CH_2Cl_2, rt	2 h	*N*-dealkylation

Aziridination of ephedrine-derived alkylidene-morpholinones.

In a related approach to functionalized pyrrolidines, the stereoselective aziridination of alkylidene morpholinone **24** (Chapters 3,4) was examined. The objective was to prepare aminohemiacetals or aminoacetals similar to **14** or **25** by an aziridination reaction instead of a two-step epoxidation/aminolysis protocol (Figure 4). Asymmetric aziridination of the double bond followed by regioselective ring opening at the acetal would install the β-amino functionality in **26** (Figure 4).

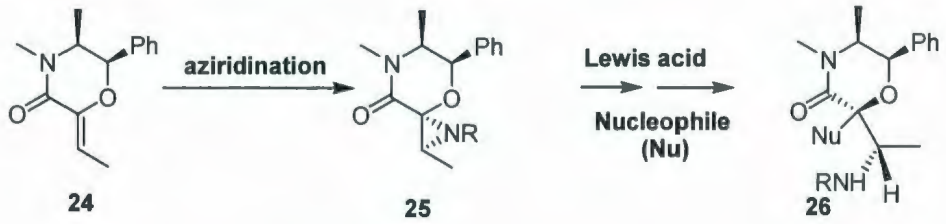
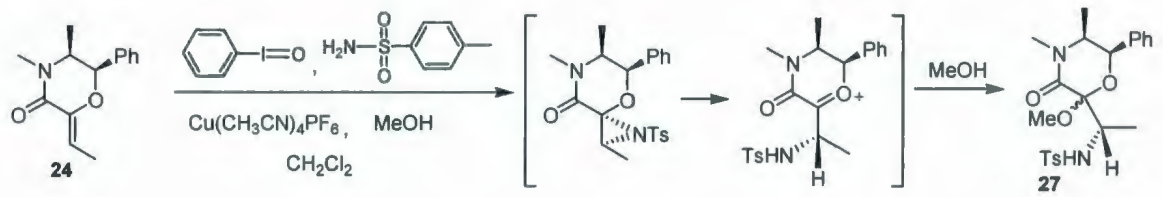


Figure 4. Aziridination of alkene **24** and Lewis Acid mediated reaction of the aziridine.

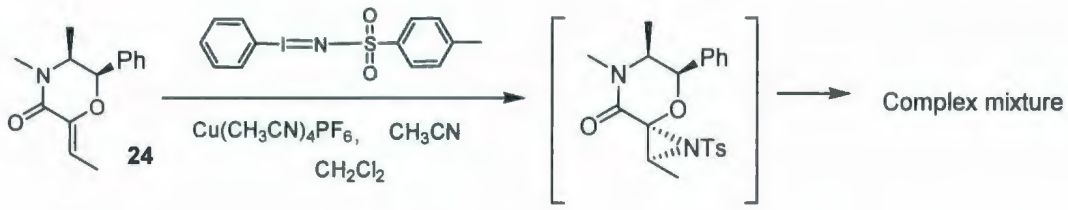
To begin the protocol reported by Dauban[11] for the aziridination of **24** was employed. Thus, reaction of the alkene in **24** with the iminoiodinane generated *in situ* from tosyl amide and iodosobenzene in the presence of methanol gave the aminomethoxy morpholinone **27** as a mixture of diastereomers (Scheme 9). Presumably, the aziridine undergoes *in situ* ring opening to generate an oxocarbenium that is trapped with methanol. Assuming that aziridination of the alkene proceeds at the *Si* face, the β-amino functionality in **27** should have the shown configuration. It may be noted that this configuration was opposite to that of the amine **14** (Scheme 4)

Scheme 9



The use of methanol for the aziridination reaction is necessary for solubilizing iodosobenzene and hence for the *in situ* generation of the aziridinating reagent, (*N*-(*p*-toluenesulfonyl)imino)phenyliodinane (PhI=NTs). It was not clear if methanol was promoting the decomposition of the aziridine, and therefore conducted an experiment with pre-formed iminoiodinane[12] (Scheme 10). However, a complex mixture of products was obtained from this reaction. This observation suggested that the aziridine is unstable under the reaction conditions.

Scheme 10



The aminomethoxylation product **27** was *N*-alkylated with 1-bromo-3-methylbut-2-ene to give **28** (Scheme 11), which was subjected to a variety of Lewis acids in order to induce the acetal-ene reaction. However, as observed for the structurally similar compound **22**, this reaction failed to give the desired product **29**. The results from these studies are summarized in Table 2.

Scheme 11

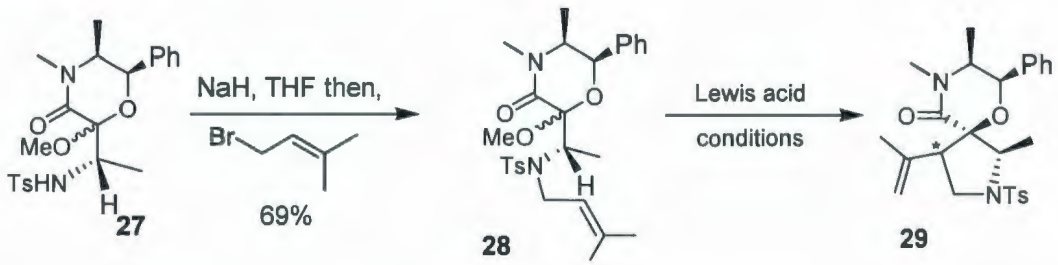


Table 2: Attempeted acetal-ene reaction of **27**.

Entry	Lewis acid	Conditions	Time	Result
1.	BF_3•Et_2O	-78 °C to rt	2.5 h	Decomposition
2.	BF_3•Et_2O	-15 °C	48 h	Starting material + *N*-dealkylation
3.	$ZnCl_2$	CH_2Cl_2, reflux	36 h	No reaction
4.	TFA	CH_2Cl_2, 0 °C	3 h	*N*-dealkylation
5.	$TiCl_4$	CH_2Cl_2, -40 °C	10 h	*N*-dealkylation

An allylation-iodocyclization strategy for the synthesis of pyrrolidines from **27** was also considered. It was anticipated that allylation at the acetal carbon in **27** would give **30**. *N*-Deprotection in **30** followed by iodocyclization would give pyrrolidines **31** (Figure 5). Notably, the suggested iodoamination reaction was known to proceed without the oxidation of the amine by the iodine.[13]

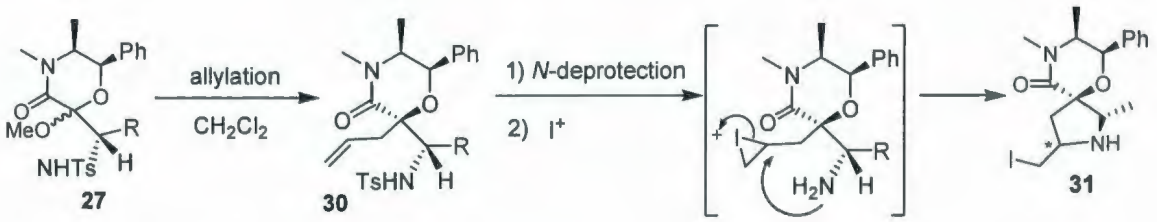
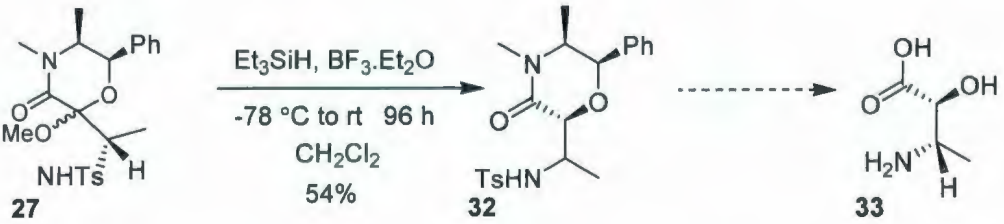


Figure 5. Allylation-haloamination approach to spiro-pyrrolidine **31**.

Unfortunately, the allylation reaction failed to proceed as desired and starting material was recovered in most of the cases. However, the use of triethylsilane in the presence of BF_3•Et_2O gave the reduced product **32** (54%, Scheme 12).[14] This observation suggested that the allylation reaction may have failed for steric reasons. Interestingly, the removal of the ephedrine portion in **32** should provide the α-hydroxy-β-amino acid **33**. α-Hydroxy-β-amino acids such as **33** are of special interest in chemistry and biology due to their applications in peptidomimetics.[15] Preliminary results suggested that the usual dissolving metal reduction protocol was not useful for the conversion of **32** to **33** (Scheme 12). Further studies on this approach to α-hydroxy-β-amino acids are planned.

Scheme 12



Conclusions

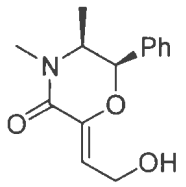
While the target pyrrolidines were not synthesized in this study due to time restriction, further investigations based on this study may be more fruitful. Nevertheless, it should be noted that the epoxide ring-opening and aziridination approaches towards functionalized pyrrolidines have provided interesting intermediates, which may also be useful for the synthesis of other targets such as α-hydroxy-β-aminoacids.

Experimental

General

General experimental techniques that have been described in the experimental section of Chapter 2 were followed.

(Z,5*S*,6*R*)-2-(2-Hydroxyethylidene)-4,5-dimethyl-6-phenylmorpholin-3-one (12)



To a stirred solution of **11** (840 mg, 2.90 mmol) in dichloromethane (10 mL) at -78 °C was added DIBAL-H (1.42 g (10.2 mL of 1 M solution in dichloromethane), 10.2 mmol) dropwise. The resulting mixture was stirred at -78 °C temperature for 6 h and 3 M HCl (5 mL) was added. The resulting mixture was warmed to room temperature and was extracted with ethyl acetate (2 x 25 mL). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate) to provide 395 mg (60%) of **12** as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.43-7.31 (m, 5H), 6.22 (t, J = 6.5), 5.28 (br d, 1H, J = 3.5), 4.43 (dAB-system, 2H, J = 6.5, 14.), 3.56 (dq, 1H, J = 3.5, 6.3), 3.10 (s, 3H), 1.01 (d, 3H, J = 6.3).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 159.2, 145.0, 136.7, 128.8, 128.7, 128.4, 125.7, 114.5, 77.7, 58.8, 57.5, 33.9, 12.0.

IR (neat):

3396, 1623, 1303, 1161, 1002 cm^{-1}.

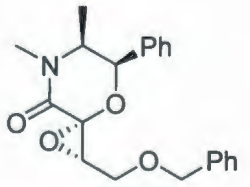
MS (APCI):

248.1 (M+1, 100).

HRMS (CI):

m/z 247.1207 (247.1208 calc. for $C_{14}H_{17}NO_3$, M+).

(2*S*,3*S*,5*R*,6*S*)-2-(2-(Benzyloxy)ethylidene)-6,7-dimethyl-5-phenyl-1,4-dioxa-7-azaspiro[2.5]octan-8-one (13)



To a solution of the alcohol **12** (300 mg, 1.21 mmol) in THF (15 mL) at 0 °C was added KH (71 mg (obtained by washing a 30 wt% dispersion in mineral oil with hexane), 1.82 mmol). The mixture was stirred at 0 °C for 15 min and benzyl bromide (0.190 mL (obtained by washing a 30 wt% dispersion in mineral oil with hexane), 1.57 mmol) was added dropwise. The mixture was then warmed up to ambient temperature, stirred for 3.5 h and cold water was added. The mixture was extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were dried and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate) to provide 300 mg (73%) of the benzyl ether as a colourless gum.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.40-7.21 (m, 10H), 5.46 (br d, 1H, J = 2.5), 4.66 (AB-system, 2H, J = 12.1), 4.02 (t, 1H, J = 5.0), 3.95 (dd, 1H, J = 11.5, 5.0), 3.84 (dd, 1H, J = 11.5, 5.0), 3.64 (dq, 1H, J = 6.5, 2.5), 3.11 (s, 3H), 1.02 (d, 3H, J = 6.5).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 162.4, 137.8, 136.1, 128.6, 128.5, 128.4, 128.1, 127.8, 125.3, 81.3, 76.3, 73.2, 67.0, 60.1, 59.1, 33.9, 12.3.

To a solution of the benzyl ether (281 mg, 0.83 mmol) in dichloromethane (15 mL) was added *m*CPBA (230 mg, 1.33 mmol) at -78 °C and the mixture was warmed to room temperature and stirred for 45 min. Saturated aqueous $NaHCO_3$ was added, the mixture was extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were dried and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate) to give 220 mg (75 %) of **13** as a white, crystalline solid.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.40-7.21 (m, 10H), 5.46 (b rd, 1H, J = 2.5), 4.66 (AB-system, 2H, J = 12.1), 4.02 (t, 1H, J = 5.0), 3.95 (dd, 1H, J = 5.0, 11.5), 3.84 (dd, 1H, J = 11.5, 5.0), 3.64 (dq, 1H, J = 6.5, 2.5), 3.11 (s, 3H), 1.02 (d, 3H, J = 6.5).

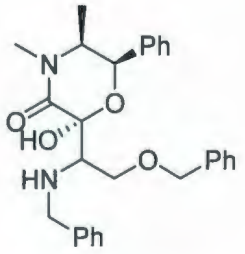
^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 162.4, 137.8, 136.1, 128.6, 128.5, 128.4, 128.1, 127.8, 125.3, 81.3, 76.3, 73.2, 67.0, 60.1, 59.1, 33.9, 12.3.

IR (neat):

2980, 1669, 1246, 731 cm^{-1};

(2*S*,5*S*,6*R*)-2-(1-(Benzylamino)-2-(benzyloxy)ethyl)-2-hydroxy-4,5-dimethyl-6-phenylmorpholin-3-one (14)



To a solution of **13** (300 mg, 0.840 mmol) in THF (5 mL) at 0 °C was added benzyl amine (1.50 mL, 1.38 mmol) at room temperature. The reaction mixture was heated to reflux for 6h and cooled to room temperature. The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography on silica gel (ethyl acetate) to provide 246 mg (63%) of **14** as a pale yellow gum.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.38-7.20 (m, 15H), 5.62 (br d, 1H, *J* = 2.5), 4.56 (AB, 2H, *J* = 12.0), 3.96 (d, 1H, *J* =14.0), 3.91 (dd, 1H, *J* = 8.1, 9.3), 3.86 (d, 1H, *J* = 14.0), 3.73 (dd, 1H, *J* = 5.3, 9.3), 3.54 (dd, 1H, *J* = 5.3, 8.1), 3.48 (dq, 1H, *J* = 2.5, 6.4), 3.11 (s, 3H, NCH_3), 0.90 (d, 3H, *J* = 6.4).

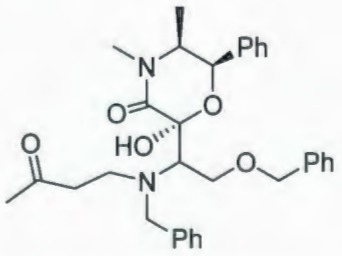
MS (APCI):

461.2 (M+1, 100).

HRMS (CI):

m/z 461.2451 (461.2440 calc. for $C_{28}H_{33}N_2O_4$, $[M+H]^+$).

(2*S*,5*S*,6*R*)-2-(4-(Benzylamino)butan-2-one)-2-(benzyloxy)ethyl)-3-hydroxy-4,5-dimethyl-6-phenylmorpholin-3-one (15)



To a suspension of **14** (0.030 g, 0.07 mmol) in water (1 mL) was added methyl vinyl ketone (0.008 mL), 0.10 mmol) and the reaction mixture was stirred vigorously for 30 h at room temperature. The water was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (ethyl acetate) to provide 0.030 g (86%) of **15** as a pale yellow gum.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.41-7.20 (m, 15H), 5.71 (br d, 1H, J = 3.4), 4.66-4.56 (m, 2H), 4.13 (t, 1H, J = 9.1), 3.98 (dd, 1H, J = 6, 9.1), 3.67 (dd, 1H, J = 6, 9.1), 3.59 (d, 1H, J = 14.4), 3.49 (dq, 1H, J = 3.4, 6.3), 3.12 (s, 3H), 2.97-2.93 (m, 2H), 2.87-2.81 (m, 1H), 2.67-2.60 (m, 1H), 2.07 (s, 3H), 0.72 (d, 2H, J = 6.3).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 208.6, 167.0, 139.8, 138.0, 137.4, 128.7, 128.5, 128.4, 128.1, 127.8, 127.7, 127.1, 125.8, 99.1, 73.9, 71.4, 66.8, 63.7, 59.0, 54.7, 47.0, 42.6, 33.8, 30.5, 12.8.

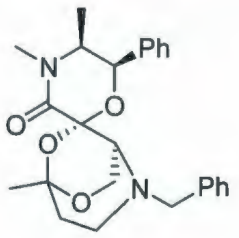
MS (APCI):

531.2 (M+1, 100);

HRMS (EI):

m/z 531.2855 (531.2859 calc. for $C_{32}H_{38}N_2O_5$, $[M+H]^+$).

(5*S*,5'*S*,6*S*,6'*S*)- 4-(Benzyl)-6'-(phenyl)- 1,4',5'-trimethyl-3'*H*-spiro[7,8-dioxa-4-azabicyclo[3.2.2]nonane-6,2'-[1,4]oxazinan]-3'-one (17)



To a solution of **15** (0.030 g, 0.06 mmol) in dichloromethane (1 mL) at -78 °C was added BF_3•etherate (0.06 mL, 0.45 mmol). The mixture was stirred at -78 °C for 15 min and then warmed to ambient temperature and stirred for 48 h. Cold water was added and the mixture was extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate) to provide 0.032 g (84%) of **17** as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.54-7.20 (m, 10H), 5.70 (*br* d, 1H, J = 2.5), 4.76 (dd, 1H, J = 10.5, 3.3), 4.33 (d, 1H, J = 10.5), 3.89 (AB, 2H, J = 14), 3.53 (dq, 1H, J = 6.5, 2.5), 3.14 (d, J =

3.3, 1H), 3.03-3.0 (m, 1H), 2.96-2.91 (m, 1H), 2.94 (s, 3H), 2.42 (ddd, *J*= 4.7, 10.7, 15, 1H), 1.87 (dt, *J* = 4.7, 15, 1H), 1.40 (s, 3H), 0.87 (d, *J* = 6.5, 3H).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 167.0, 139.8, 138.5, 128.9, 128.8, 128.5, 127.7, 127.2, 125.8, 100.6, 96.1, 70.2, 61.5, 60.5, 58.9, 57.9, 48.4, 39.0, 34.1, 29.6, 12.7.

IR (neat);

2925, 1653, 1191, 1046, 934 cm^{-1}.

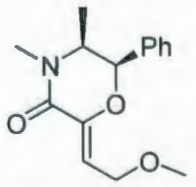
MS (APCI):

423.3 (M+1, 100).

HRMS (EI):

m/z 422.2207 (422.2206 calc. for $C_{25}H_{30}N_2O_4$, M+).

(Z,5S,6R)-2-(2-Methoxyethylidene)-4,5-dimethyl-6-phenylmorpholin-3-one (18)



To a solution of the alcohol **12** (135 mg, 0.55 mmol) in THF (15 mL) at 0 °C was added KH (0.031 g (obtained by washing a 30 wt% dispersion in mineral oil with hexane), 0.770 mmol). The mixture was stirred at 0 °C for 15 min and methyl iodide (0.050 mL, 0.720 mmol) was added dropwise. The mixture was then warmed up to ambient temperature, stirred for 3.5 h and cold water was added. The mixture was extracted with ethyl acetate (3 x 5 mL) and the combined organic layers were dried and

concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate) to provide 123 mg (86 %) of **18** as a colourless gum.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.43-7.27 (m, 5H), 6.16 (t, 1H, J = 6.7), 5.27 (brd, 1H, J = 2.6), 4.24 (dAB-system, 2H, J = 6.7, 18), 3.58-3.56 (dq, 1H, J = 7.5, 2.6), 3.37 (s, 3H), 3.11 (s, 3H), 1.00 (d, 3H, J = 7.5).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 159.1, 145.4, 136.8, 128.7, 128.5, 128.3, 125.6, 112.1, 77.6, 66.3, 58.8, 58.3, 33.8, 11.9.

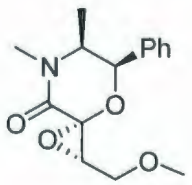
IR (neat);

1636, 1304, 1121, 751 cm^{-1}.

MS (APCI):

262.0 (M+1, 100).

(2*S*,3*S*,5*R*,6*S*)-2-(2-Methoxyethylidene)-6,7-dimethyl-5-phenyl-1,4-dioxa-7-azaspiro[2.5]octan-8-one (19)



To a solution of **18** (100 mg, 0.400 mmol) in dichloromethane (2 mL) was added *m*CPBA (90.0 mg, 0.500 mmol) at -78 °C and the mixture was warmed to room temperature and stirred for 45 min. Saturated aqueous $NaHCO_3$ was added and the

mixture was extracted with ethyl acetate (3 x 2 mL). The combined organic layers were dried and concentrated under reduced pressure. The residue obtained was purified by flash chromatography on silica gel (ethyl acetate) to give 100 mg (89%) of **19** as a white, crystalline solid.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.41-7.27 (m, 5H), 5.49 (br d, 1H, J = 2.5), 3.94 (dd, 1H, J = 4.5, 6.3), 3.88 (dd, 1H, J = 11, 4.5), 3.72 (dd, 1H, J = 6.3, 11), 3.65 (dq, 1H, J =7.0, 2.5), 3.47 (s, 3H), 3.11 (s, 3H), 1.04 (d, 3H, J = 7.0).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 162.6, 136.3, 128.7, 128.3, 125.4, 81.3, 76.4, 69.6, 60.1, 59.3, 59.3, 34.0, 12.5.

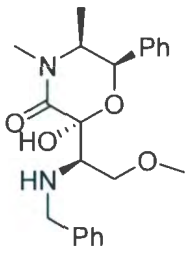
MS (APCI):

278.0 (M+1, 100);

HRMS (EI):

m/z 277.1318 (277.1314 calc. for $C_{15}H_{19}NO_4$, M+).

(2*S*,5*S*,6*R*)-2-(1-(Benzylamino)-2-methoxyethyl)-2-hydroxy-4,5-dimethyl-6-phenylmorpholin-3-one (20)



To a solution of **19** (100 mg, 0.360 mmol) in THF (3 mL at 0 °C) was added benzyl amine (0.060 mL), 0.540 mmol) at room temperature. The mixture was heated to

reflux for 6 h, cooled to room temperature and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate) to provide 101 mg (65%) of **20** as a pale yellow gum.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.38-7.23 (m, 10H), 5.63 (br d, 1H, J = 4.0), 3.98-3.88 (AB-system, 2H, J = 12.5), 3.84 (t, 1H, J = 9.0), 3.66 (dd, 1H, J = 5.5, 9.0), 3.52-3.48 (m, 2H), 3.38 (s, 3H), 3.07 (s, 3H), 0.97 (d, 3H, J = 7.0).

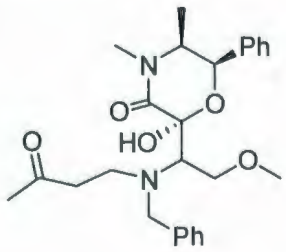
^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 167.4, 140.6, 138.0, 128.5, 128.3, 127.8, 127.2, 125.8, 98.3, 72.9, 71.6, 60.5, 59.4, 59.1, 52.7, 33.8, 12.7.

MS (APCI):

385.1 (M+1, 100).

(2*S*,5*S*,6*R*)-2-(4-(Benzylamino)butan-2-one)-2-methoxyethyl)-2-hydroxy-4,5-dimethyl-6-phenylmorpholin-3-one (21)



To a suspension of **20** (0.050 g, 0.130 mmol) in water (1 mL) was added methyl vinyl ketone (0.002 mL, 0.02 mmol) and the reaction mixture was stirred vigorously at room temperature for 30 h. The water was removed under reduced pressure and the

residue was purified by flash chromatography on silica gel (ethyl acetate) to provide 0.037 g (88%) of **21** as a pale yellow gum.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.39-7.28 (m, 10H), 6.2 (brs, 1H), 5.70 (d, 1H, J = 3.5) , 4.61 (d, 1H, J = 13.0), 4.01 (t, J = 8.5, 1H), 3.89 (dd, 1H, J = 6, 8.5), 3.60 (m, 2H, OCH_2), 3.50 (m, 1H), 3.48 (s, 3H) 3.09 (s, 3H), 2.96 (m, 2H), 2.87-2.81 (m, 1H), 2.67-2.62 (m, 1H), 2.09 (s, 3H), 0.76 (d, 3H, J = 7.0).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 208.5, 167.0, 139.8, 138.1, 128.5, 128.4, 127.7, 127.1, 125.8, 99.0, 71.4, 69.4, 63.6, 59.5, 59.1, 54.8, 47.0, 42.7, 33.8, 30.5, 12.8.

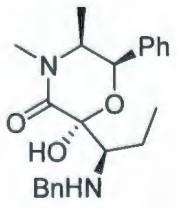
IR (neat):

3380, 2933, 1710, 1654, 1046, 731 cm^{-1}.

MS (APCI):

455.1 (M+1, 100).

(2*S*,5*S*,6*R*)-2-((*R*)-1-(Benzylamino)propyl)-2-hydroxy-4,5-dimethyl-6-phenylmorpholin-3-one (25)



To a solution of **24** (450 mg, 1.72 mmol) in THF (20 mL) at 0 °C was added benzylamine (0.200 mL, 1.72 mmol) at room temperature. The mixture was the heated to

reflux for 6 h and then cooled to room temperature. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (ethyl acetate) to provide 430 mg (68%) of **25** as a pale yellow gum.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.40-7.24 (m, 10H), 5.61 (br d, 1H, J = 2.5), 4.11 (d, 1H, J = 12.5), 3.82 (d, 1H, J = 12.5), 3.50 (dq, 1H, J = 6.5, 2.5), 2.82 (s, 3H), 2.84-2.82 (m, 1H), 1.91-1.85 (m, 1H), 1.75-1.69 (m, 1H), 1.84 (t, 3H, J = 7.0), 1.04 (d, 3H, J = 6.5).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 169.0, 140.3, 137.7, 128.6, 128.5, 128.4, 128.3, 127.7, 127.1, 125.8, 125.4, 97.7, 72.5, 65.6, 58.9, 53.0, 33.3, 23.8, 12.7, 12.6.

IR (neat);

3338, 2973, 1636, 1046, 736 cm^{-1}.

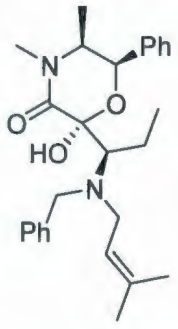
MS (APCI):

369.2 (M+1, 100).

HRMS (EI):

m/z 368.2104 (368.2100 calc. for $C_{22}H_{28}N_2O_3$, M+).

(2*S*,5*S*,6*R*)-2-((*R*)-1-(*N*-Benzyl-3-methylbut-2-en-1-amine)propyl)-2-hydroxy-4,5-dimethyl-6-phenylmorpholin-3-one (22)



To a solution of **25** (260 mg, 0.700 mmol) and DIPEA (0.200 mL, 1.16 mmol) in acetonitrile (2 mL) was added allyl bromide (0.090 mL, 0.770 mmol) and the mixture was stirred vigorously at room temperature for 48 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (2/1, ethyl acetate/hexane) to provide 0.169 g (55%) of **21** as pale yellow gum.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.37-7.21 (m, 10H), 5.61 (br d, 1H), 5.2 (m, 1H), 4.73 (br s, 1H), 3.53-3.32 (m, 3H), 3.01 (s, 3H), 2.00-1.91 (m, 1H), 1.78-1.66 (m, 4H), 1.55 (s, 3H), 1.12 (t, J = 7.5, 3H), 0.77 (d, J = 6.6, 3H).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 168.6, 138.3, 128.5, 128.4, 127.5, 127.1, 125.7, 122.1, 97.6, 72.2, 68.4, 58.9, 33.7, 26.0, 20.5, 18.3, 13.7, 12.6.

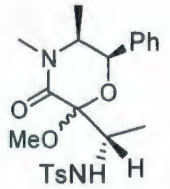
MS (APCI):

437.4 (M+1, 100).

HRMS (CI):

m/z 437.2807 (437.2804 calc. for $C_{22}H_{28}N_2O_3$, $[M+H]^+$).

(5*S*,6*R*,2*S*)-4,5-Dimethyl-6-phenyl-3-(methoxy)-2-(1-(tosylamino)methyl)morpholin-3-one (27)



To a solution of **24** (1.25g, 5.40 mmol) in dichlromethane (30 mL) at room temperature was added *p*-toluenesulfonamide (2.8 g, 16.2 mmol), iodosobenzene (3.54 g, 16.2 mmol), methanol (3 mL) and activated 4 Å molecular sieves (1 g). The mixture was cooled to 0 °C and $Cu(CH_3CN)_4PF_6$ (0.6 g, 1.6 mmol) was added and the mixture was stirred for 2 h at 0 °C. The mixture was then filtered through celite and the filtrate was concentrated. The resulting residue was purified by flash chromatography on silica gel (1/1, ethyl acetate/hexane) to provide 1.42 g (61%) of **27** as pale yellow gum and as a ~3:2 mixture of diastereomers (^{1}H NMR). The diastereomers were separated by flash chromatography on silica gel (4/1, ethyl acetate/hexane) to give 0.850 g (37%) of the major diastereomer and 0.560 g (24%) of the minor diastereomer.

^{1}H NMR (500 MHz, $CDCl_3$):

Major diastereomer; δ 7.71 (d, 2H, J = 7.5), 7.39-7.26 (m, 7H), 5.78 (br d, J = 8, 1H), 5.25 (d, J = 3.0), 3.96 (m, 1H), 3.46 (dq, 1H, J = 3.0, 8.0), 3.36 (s, 3H), 3.02 (s, 3H), 2.37 (s, 3H), 1.16 (d, 3H, J = 6.5), 1.01 (d, 3H, J = 8.0).

Minor diastereomer; δ 7.80 (d, 2H, J = 8.5), 7.40-7.30 (m, 7H), 5.37 (*br* d, 1H, J = 3.5), 4.75 (*br* d, 1H, J = 9.0), 3.91 (m, 1H), 3.45 (dq, J = 3.5, 6.0), 3.15 (s, 3H), 2.97 (s, 3H), 2.42 (s, $3H_3$), 1.24 (d, 3H, J = 6.5), 1.01 (d, 3H, J = 6.0).

IR (neat):

1684, 1652, 1164, 839 cm^{-1}.

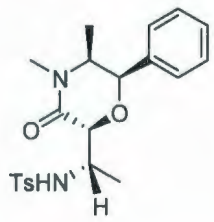
MS (APCI):

431.1 (M-1, 100).

HRMS (CI):

m/z 433.1797 (433.1797 calc. for $C_{22}H_{29}N_2O_5S$, $[M+H]^+$).

(5*S*,6*R*)-4,5-Dimethyl-6-phenyl-2-((*S*)-1-(tosylamino)methyl)morpholin-3-one (32):



To a solution of **27** (0.200 g, 0.460 mmol) in dichloromethane (4 mL) at -78 °C was added triethylsilane (0.740 mL), 0.460 mmol) followed by BF_3•etherate (0.550 mL), 4.6 mmol). The mixture was stirred at -78 °C for 15 min and then warmed to ambient temperature and stirred for 22 h. Cold water was added and the mixture was extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (1/3 ethyl acetate/hexane) to provide 0.178 g (54%) of **32** as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.81 (d, 2H, J = 10, Ar*H*), 7.34 (m, 3H, Ar*H*), 5.24 (d, 1H, J = 9.7, TsN*H*), 4.84 (*br* d, J = 2.6, PhC*H*), 4.16 (s, 1H, C*H*O), 4.16 – 4.12 (m, 2H, TsNC*H*), 3.45 (dq, 1H, J = 6.5, 2.6 C*H*CH_3), 2.98 (s, 3H, ArCH_3), 2.42 (s, 3H, NCH_3), 1.20 (d, 1H, J = 6.6, TsNCHCH_3), 0.93 (d, 3H, J = 6.5, CHCH_3).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 166.4, 143.5, 138.2, 137.3, 129.9, 128.7, 128.3, 127.4, 125.6, 80.0, 76.9, 58.9, 51.3, 33.5, 21.8, 17.1, 13.3.

IR (neat);

3380, 1684, 1653, 1158 cm^{-1}.

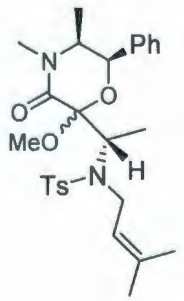
MS (APCI):

403.1 (M+1, 100).

HRMS (EI):

m/z 403.1707 (403.1692 calc. for $C_{21}H_{27}N_2O_4S$, $[M+H]^+$).

(5*S*,6*R*,2*S*)-4,5-Dimethyl-6-phenyl-3-(methoxy)-2-(1-(3-methyl-*N*-tosylbut-2-en-1-amine)methyl)morpholin-3-one (28)



To a solution of the amide **27** (400 mg, 0.900 mmol) in THF (15 mL) at 0 °C was added KH (66 mg (obtained by washing a 30 wt% dispersion in mineral oil with hexane),

1.10 mmol). The mixture was stirred at 0 °C for 15 min and 3,3-dimethylallyl bromide (0.133 mL), 1.00 mmol) was added dropwise. The mixture was then warmed up to 50 °C and stirred at that temperature for 9 h. The reaction mixture was then cooled to 0 °C and cold water was added. The suspension was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were dried and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (2/3, ethyl acetate/hexane) to provide 318 mg (69 %) of **28** as a colourless gum.

^{1}H NMR (500 MHz, $CDCl_3$):

Major diastereomer: δ 7.71 (d, 2H, *J* = 8.3), 7.43-7.36 (m, 7H, Ar*H*), 5.39 (br d, 1H, *J* = 3.2), 5.04-5.01 (brm, 1H), 4.78 (q, 1H, *J* = 7.2), 4.06 (dd, 1H, *J* = 16.7, 6.7), 3.85 (dd, 1H, *J* = 6.7, 15.5), 3.49 (dq, 1H, *J* = 6.6, 3.2), 3.36 (s, 3H), 2.99 (s, 3H), 2.41 (s, 1H), 1.55 (s, 6H), 1.23 (d, 3H, *J* = 7.2), 1.05 (d, 3H, *J* = 6.6).

Visible peaks of minor diastereomer: δ 7.52 (d, 2H, *J* = 8.3), 5.77 (brd, 1H, *J* = 3.2), 4.71 (q, 1H, *J* = 7.2), 3.93 (dd, 1H, *J* = 6.7, 18.3), 3.55 (dq, 1H, *J* = 3.2, 6.6), 3.38 (s, 3H), 3.04 (s, 3H), 2.36 (s, 3H), 1.62 (s, 6H), 1.26 (d, 3H, *J* = 7.2), 1.04 (d, 3H, *J* = 6.6).

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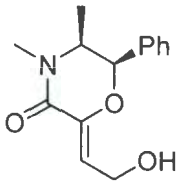
Appendix 4:

^{1}H and ^{13}C NMR Spectra for Chapter 5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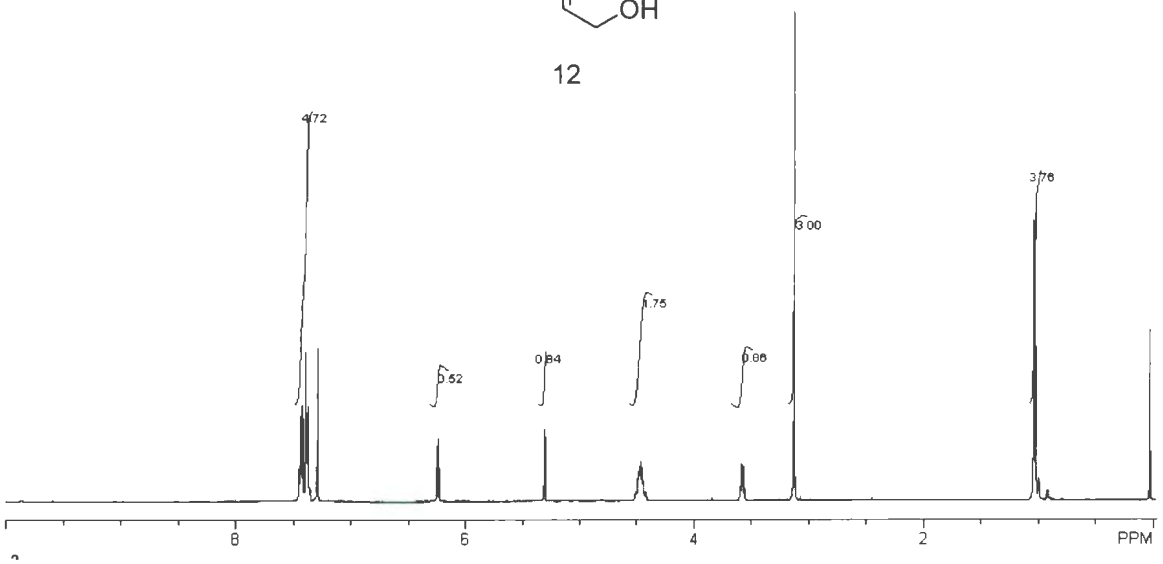
OH

12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8
6
4
2
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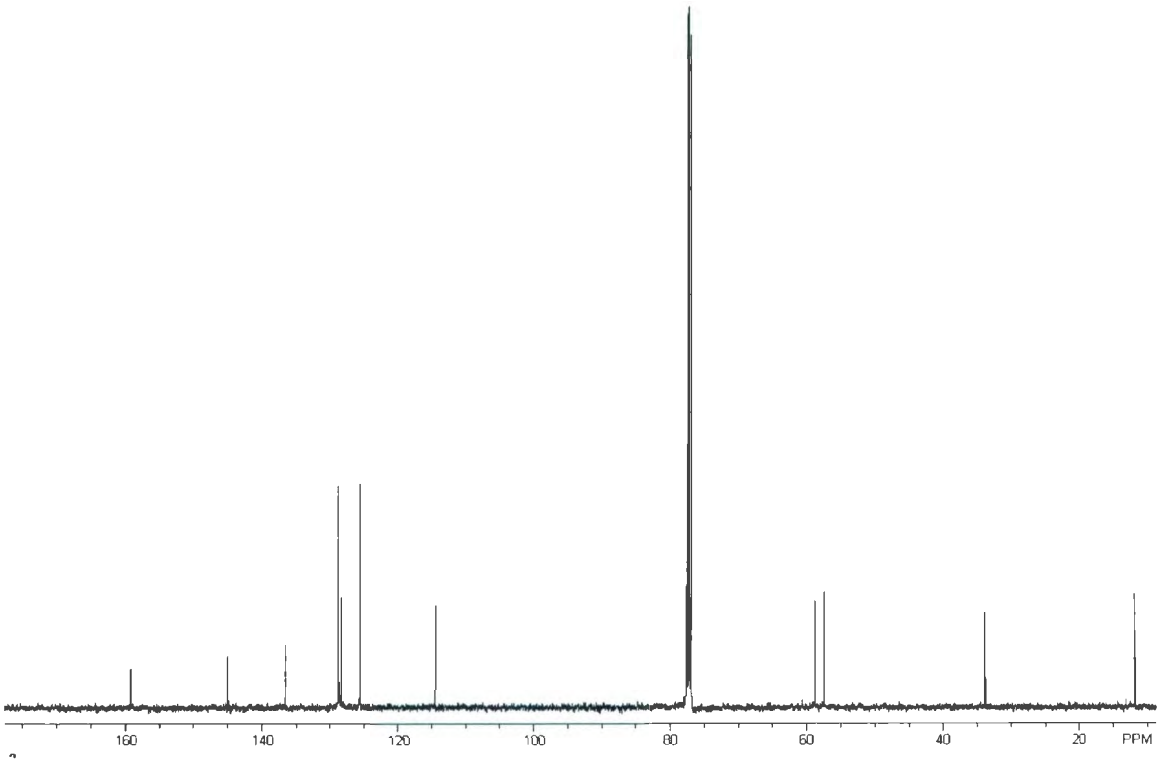
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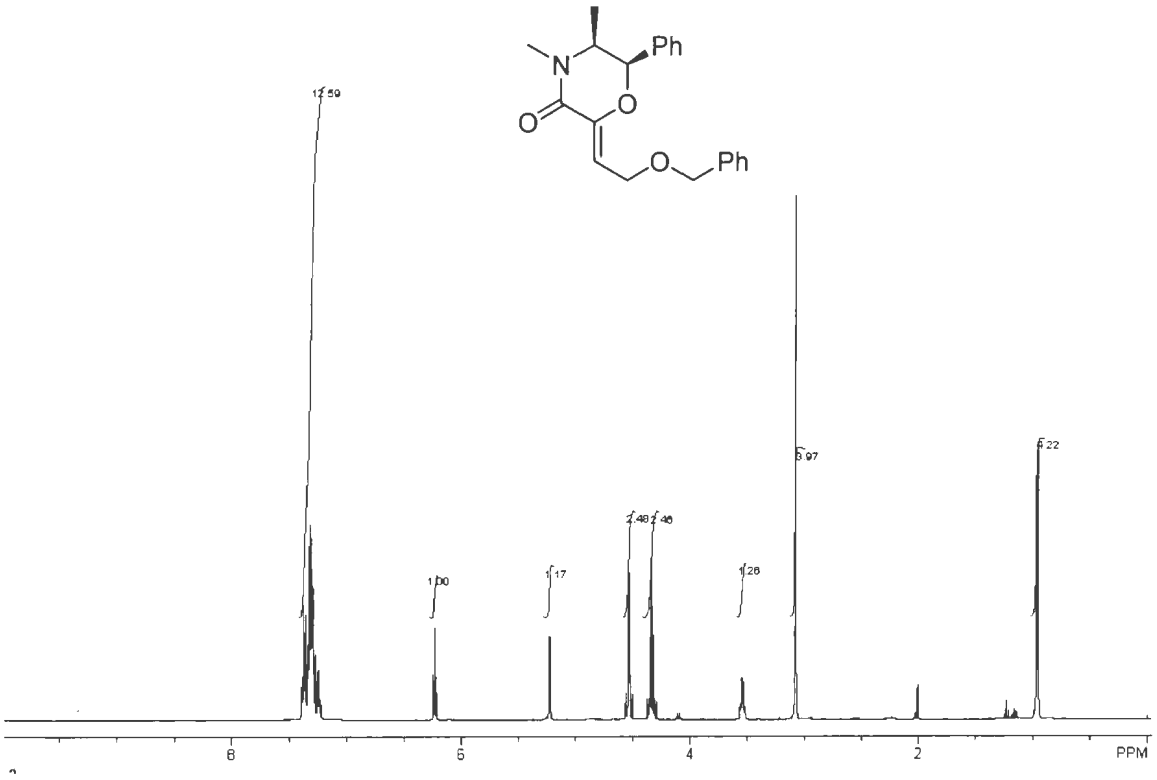
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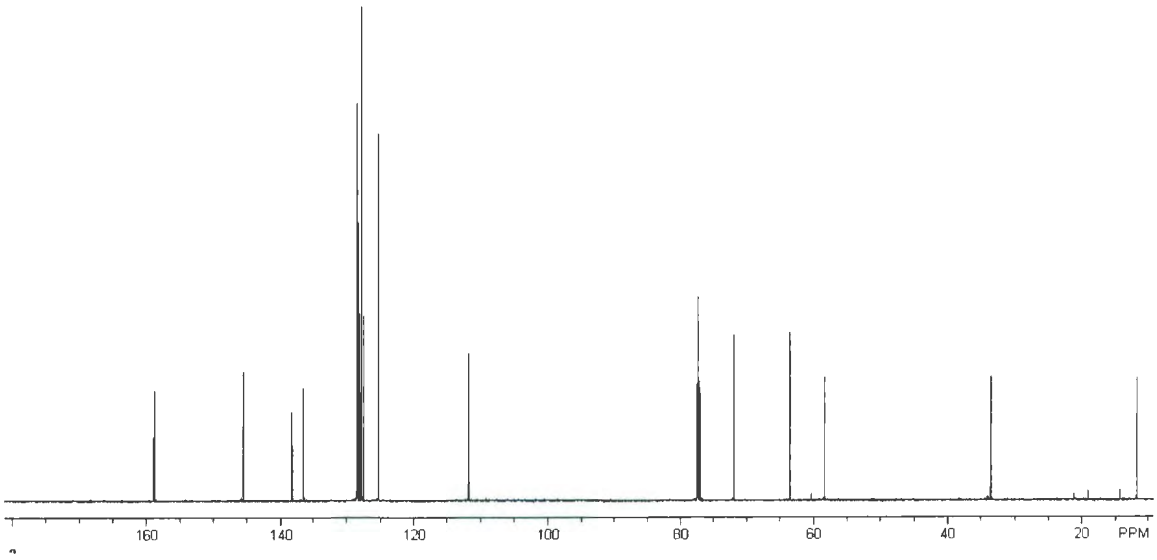
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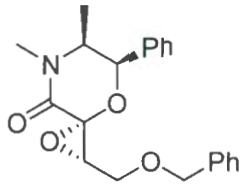
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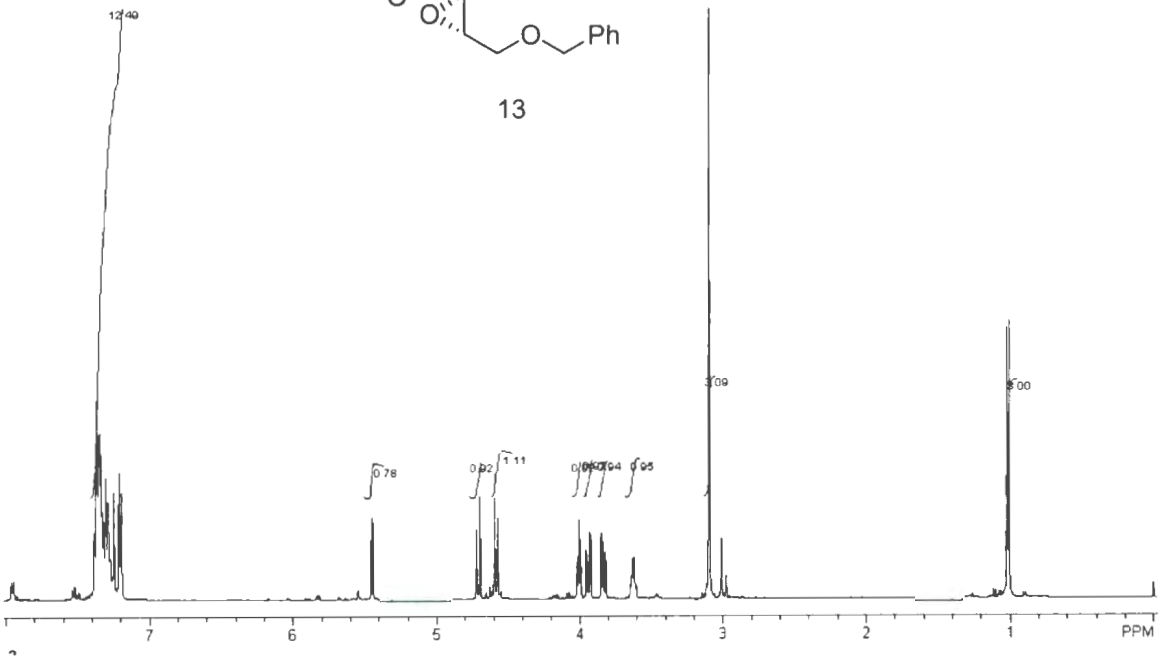
13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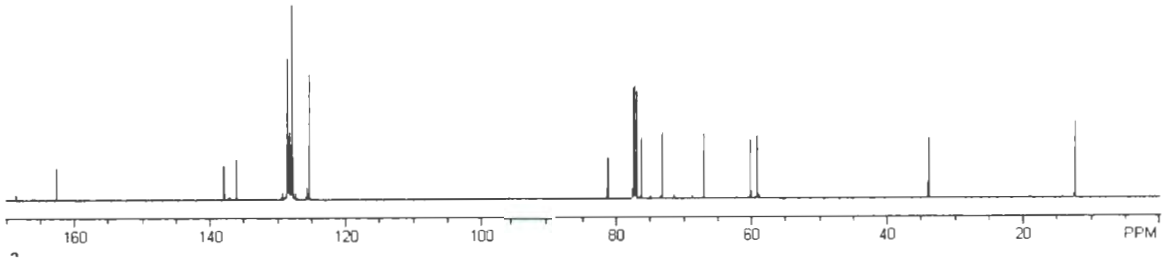
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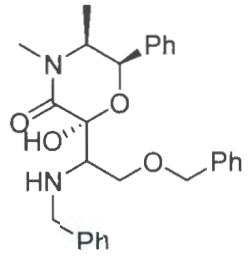

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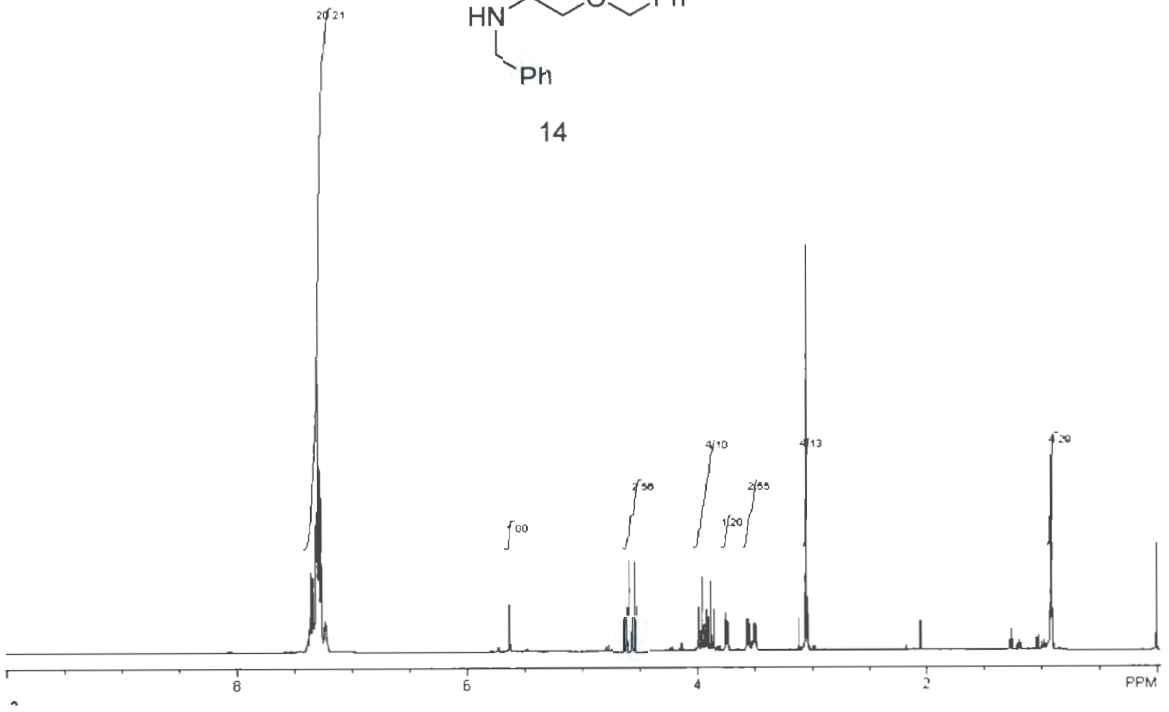

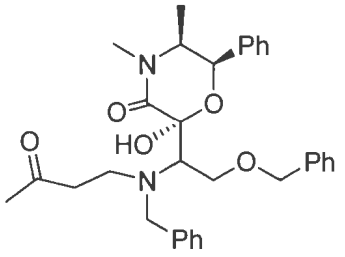

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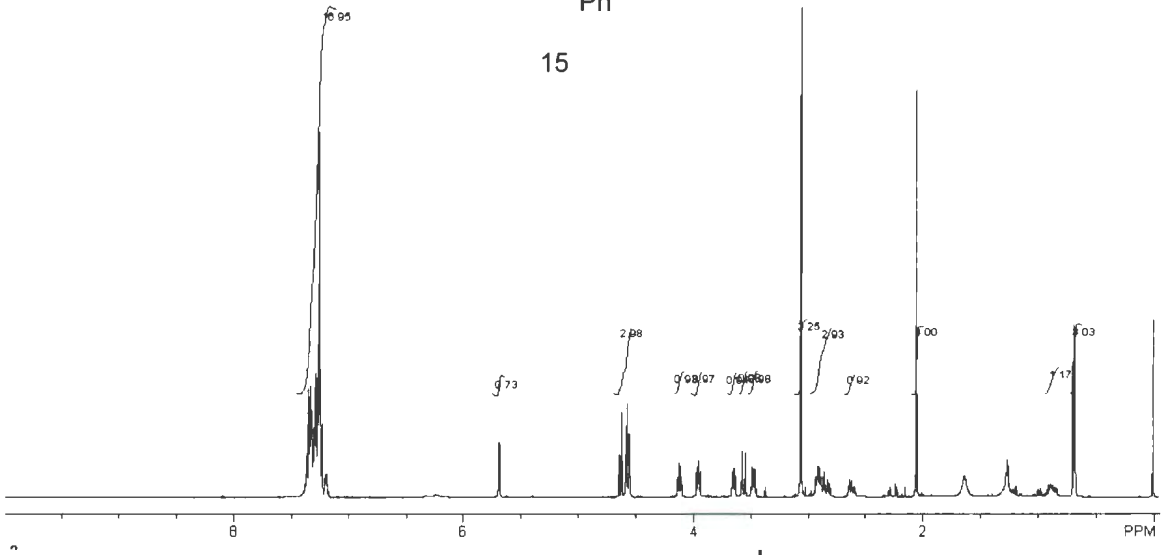

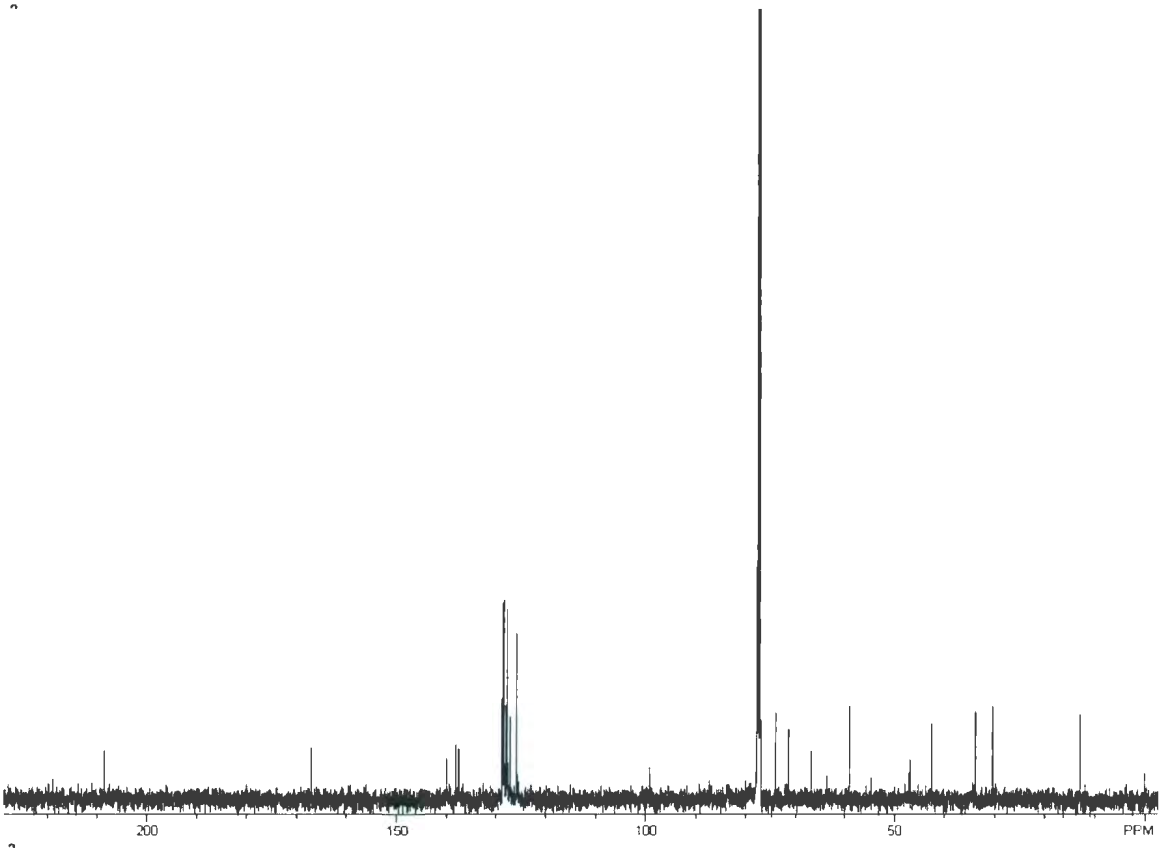

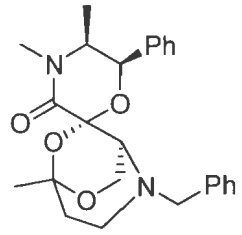
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N
Ph

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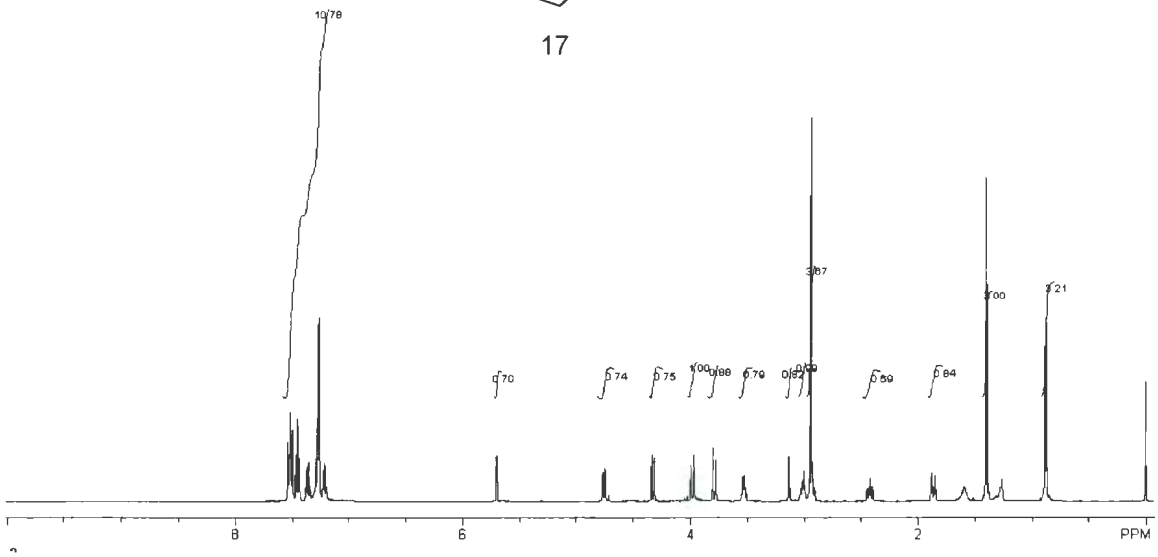
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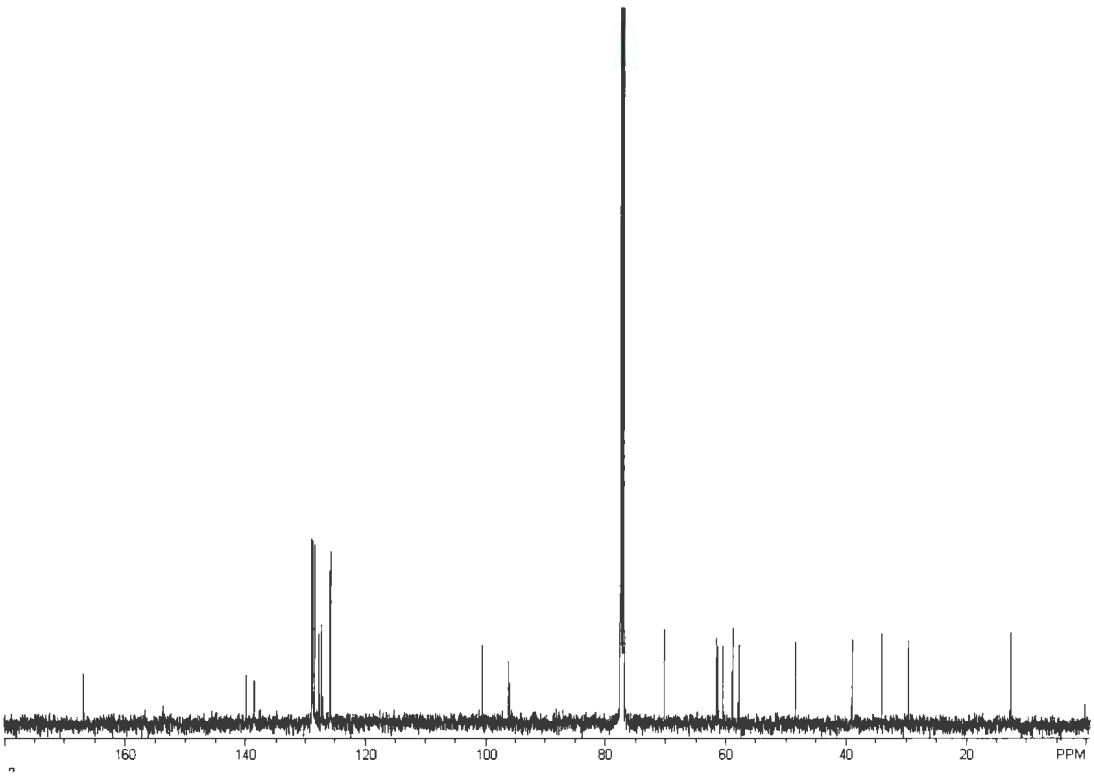
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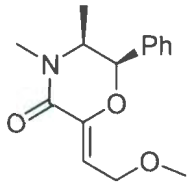
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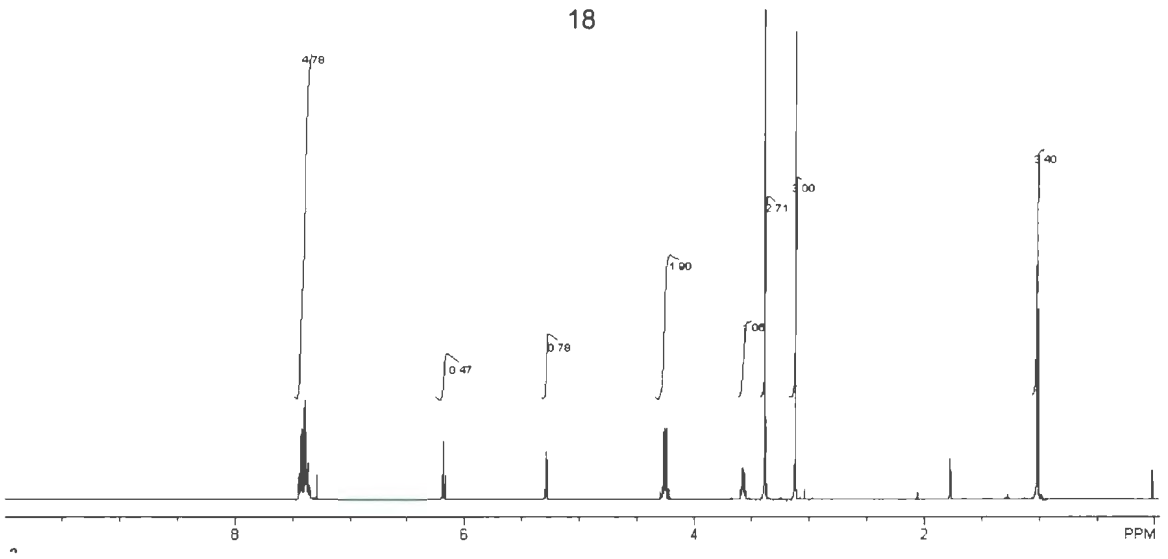
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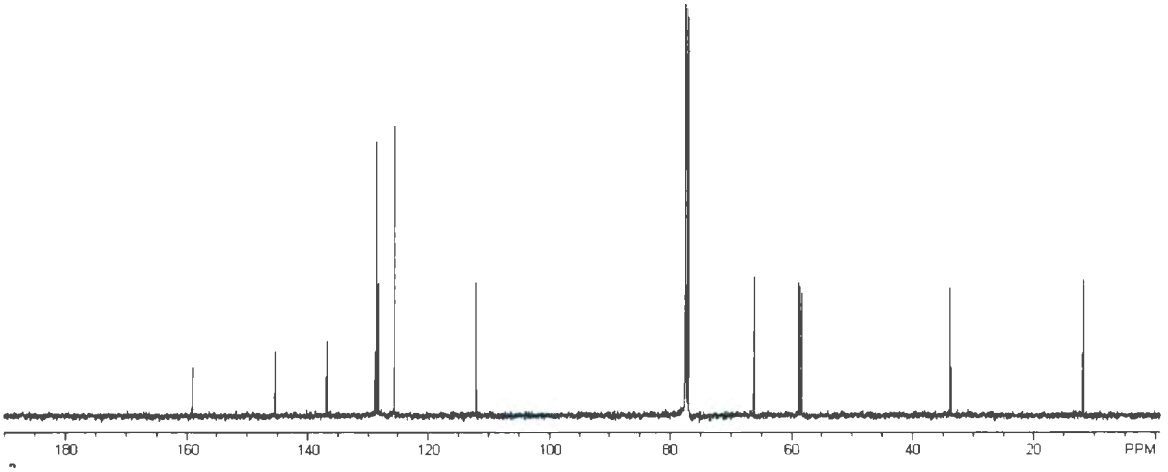
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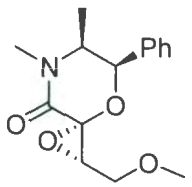

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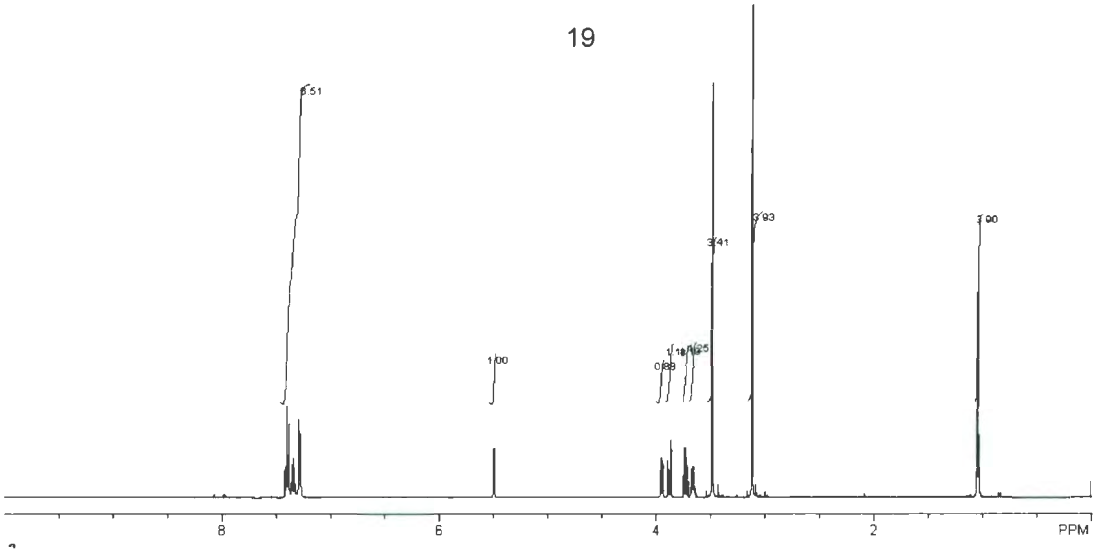

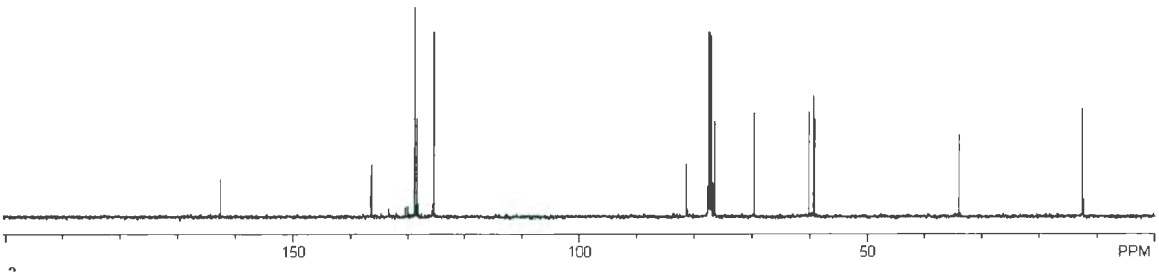

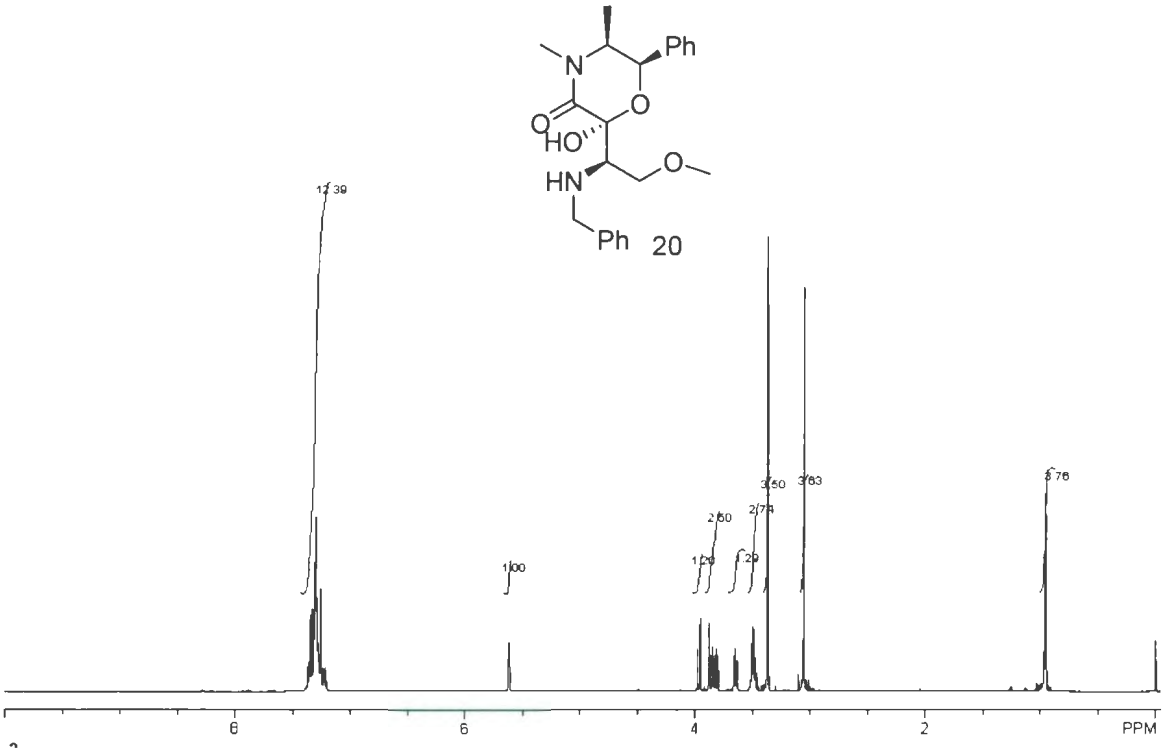
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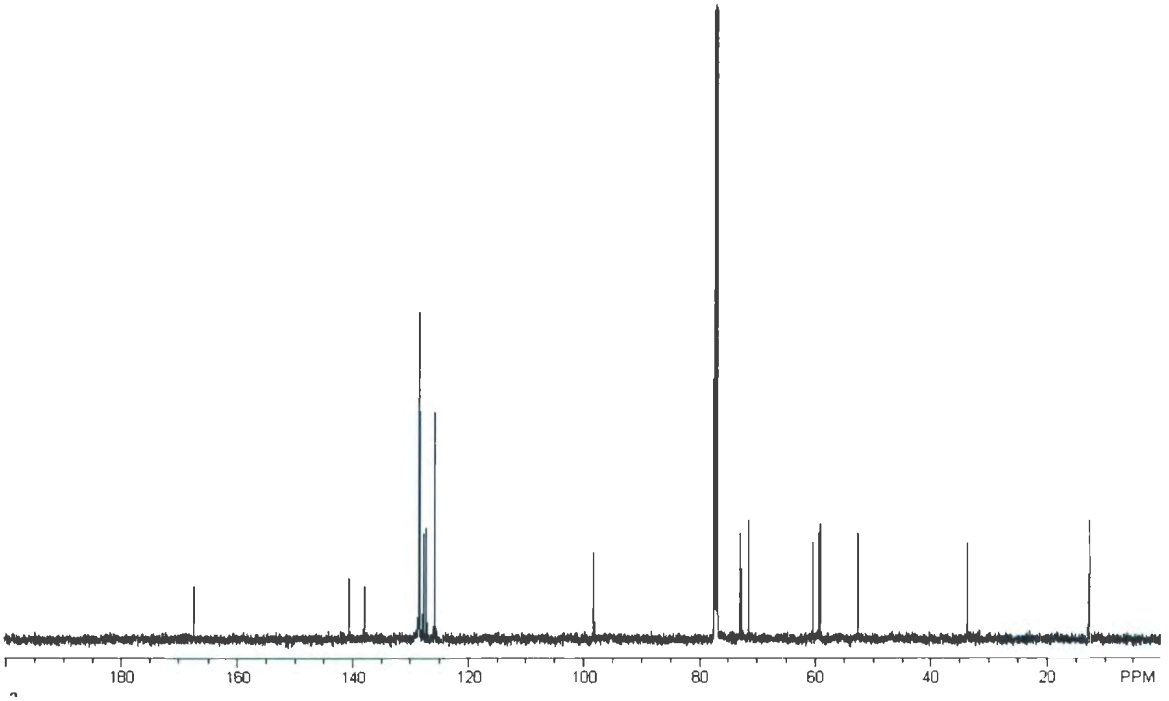
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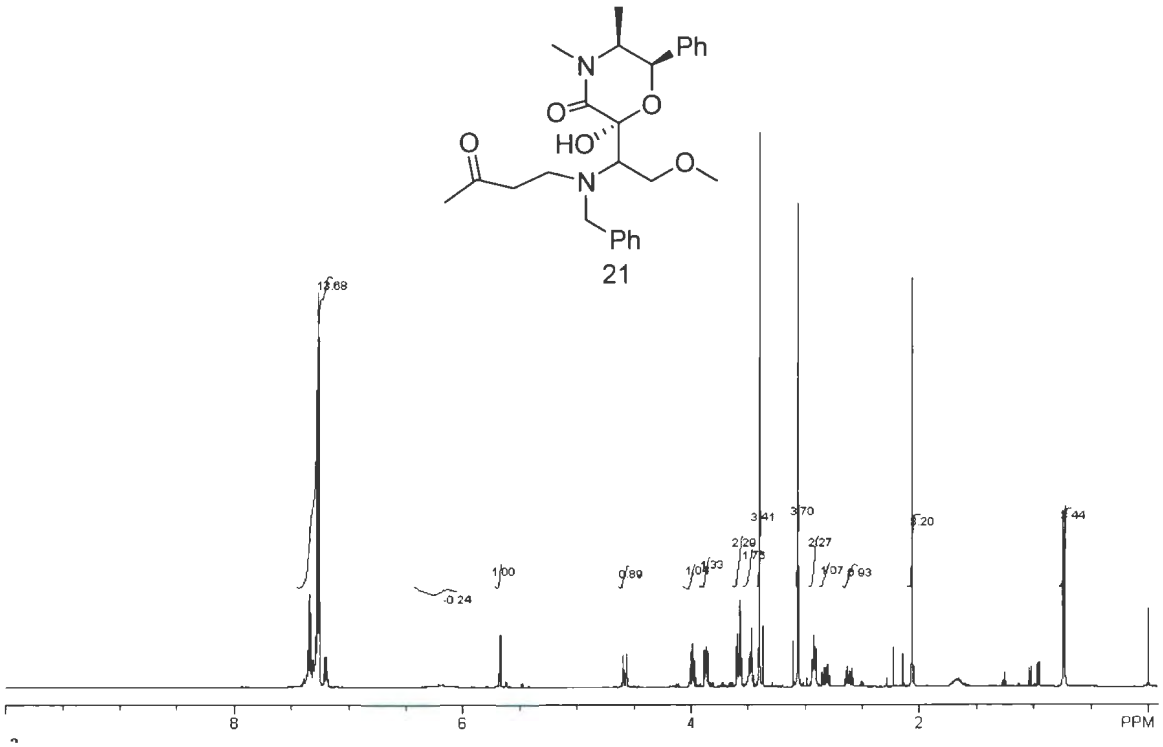
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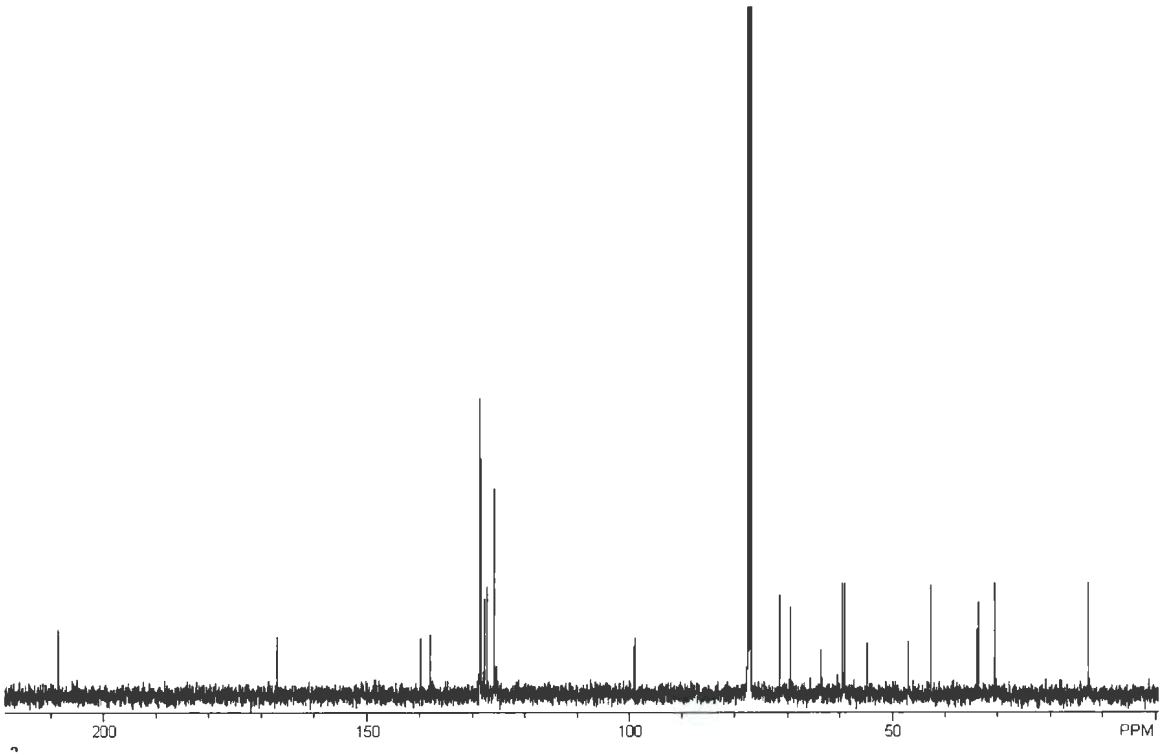
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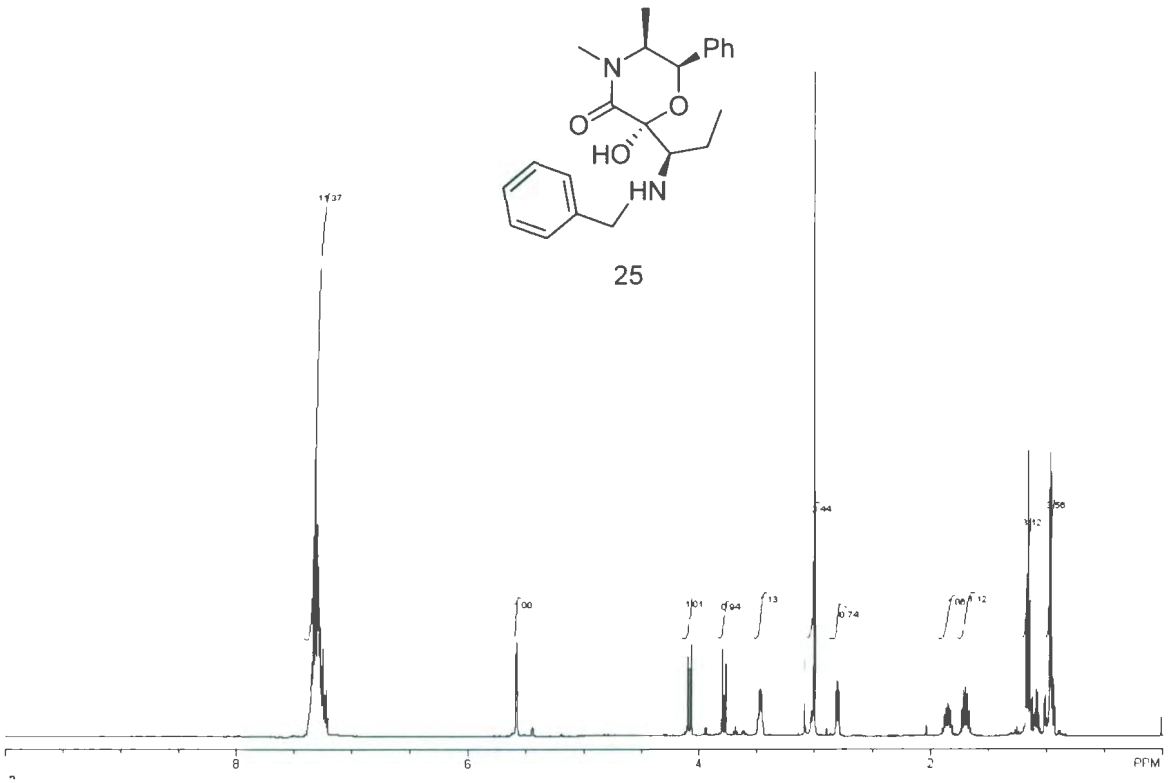
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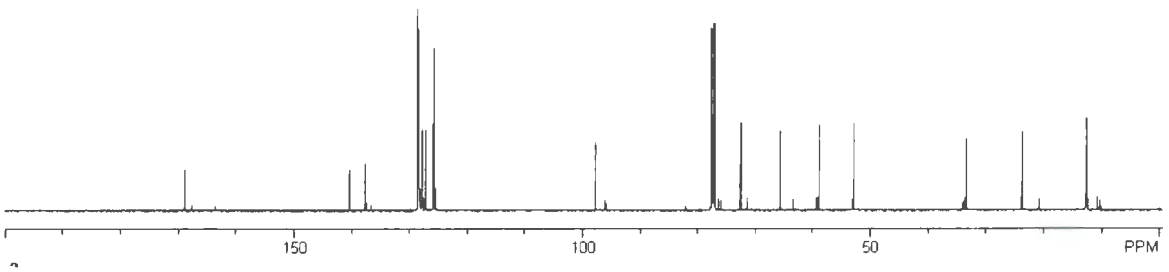
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100
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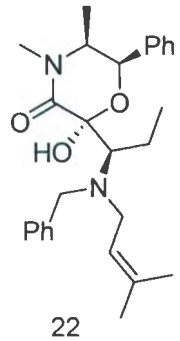

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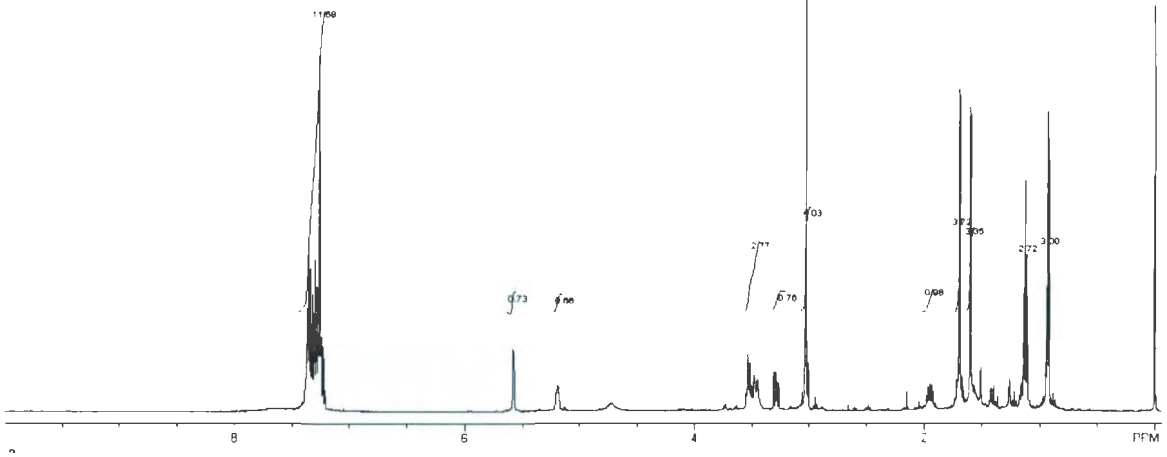

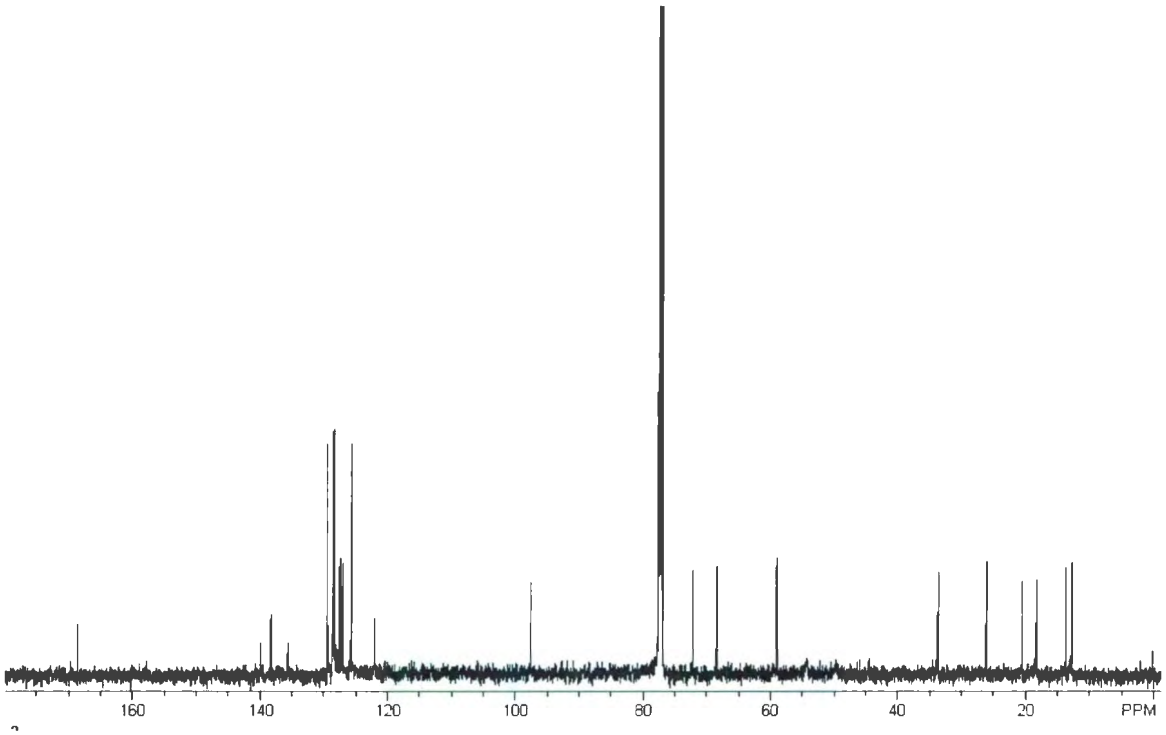

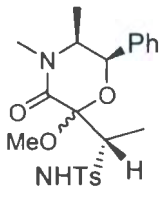

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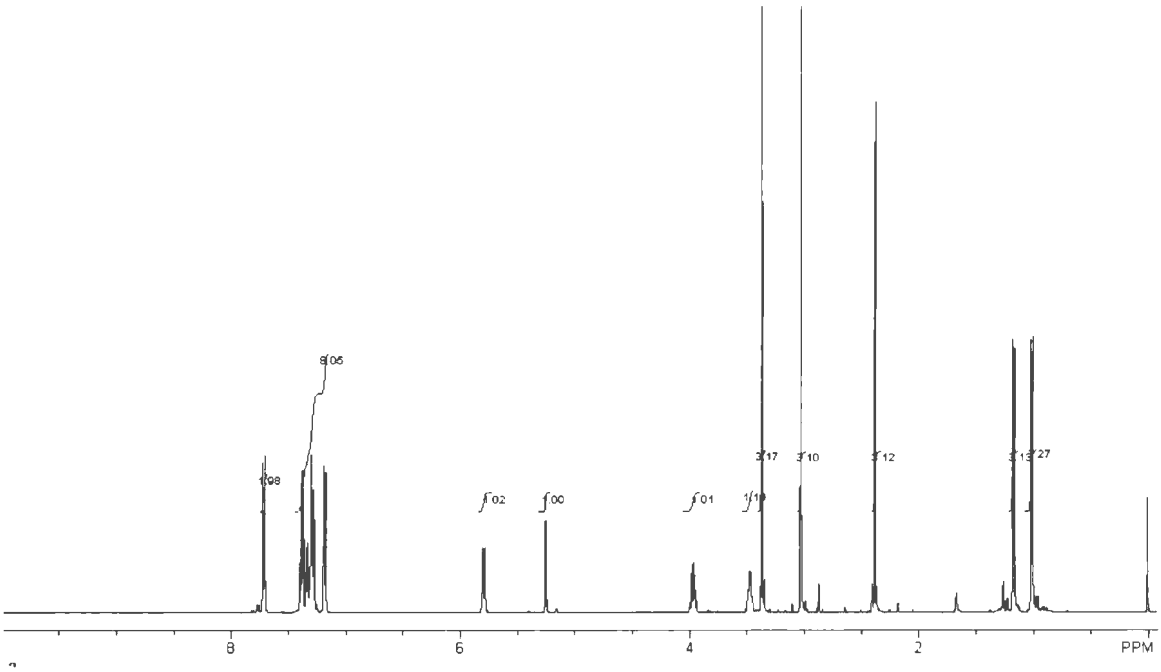

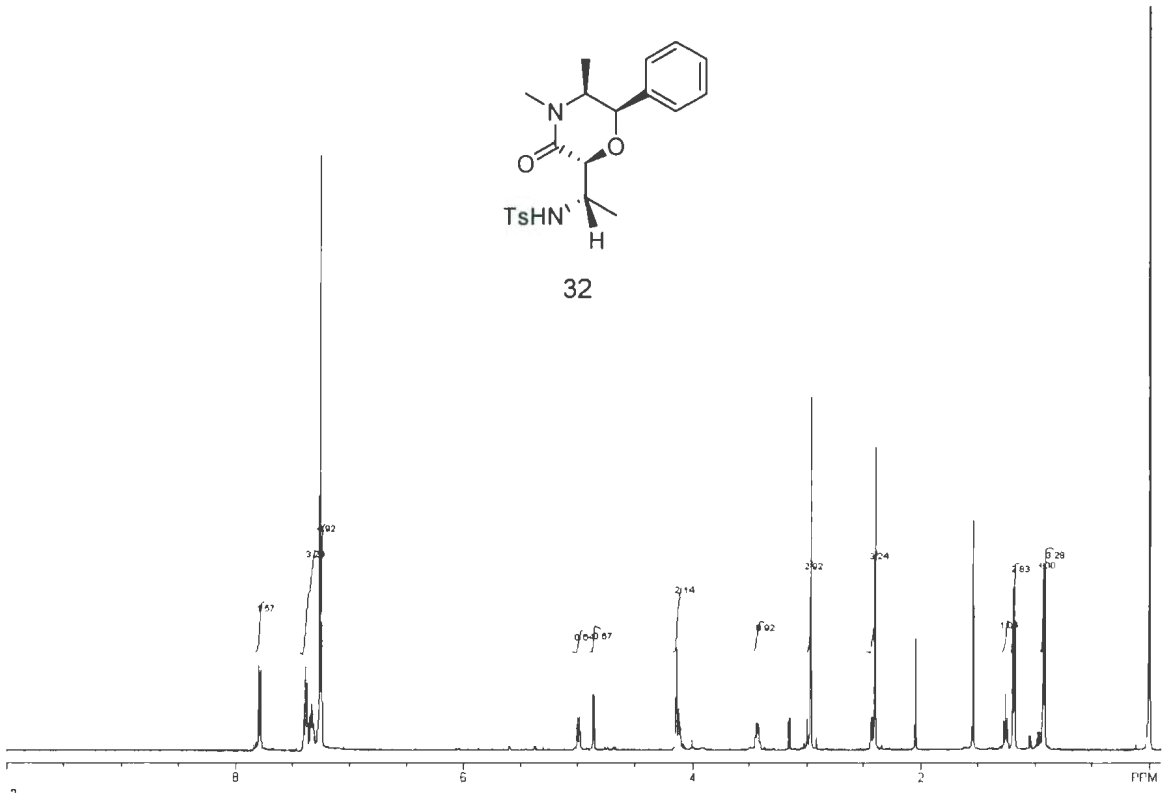

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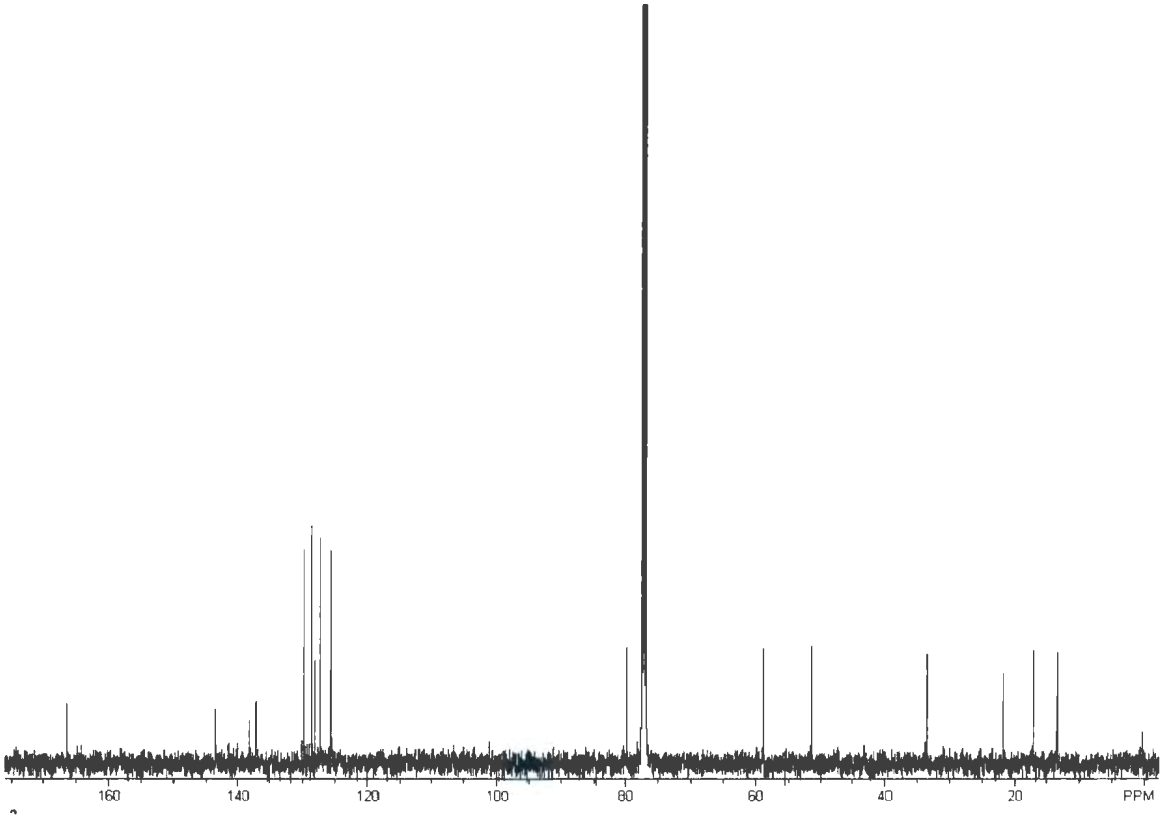

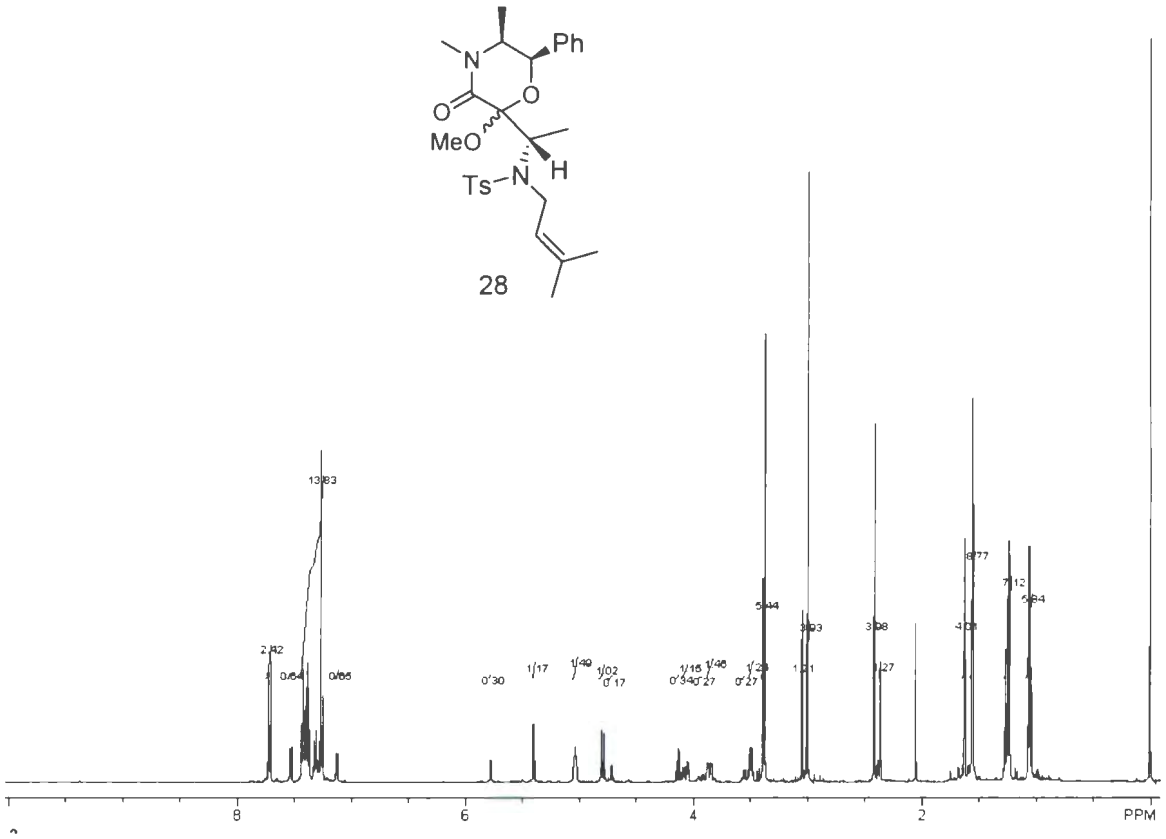
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MeO
Ts
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0.65
0.30
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1.49
1.02
0.17
1.15
0.34
1.46
0.27
1.20
0.27
5.44
3.93
1.21
3.08
1.27
4.08
6.77
7.12
5.84
8
6
4
2
PPM

Chapter 6

Studies on Chiral Amino Alcohol Alternatives to Ephedrine

Introduction

Along with the exploitation of the utility of the ephedrine-derived morpholine-dione as a chiral starting material in asymmetric synthesis, efforts were also directed toward identifying other chiral amino alcohols that may be utilized in place of ephedrine. The search for these amino alcohols focused on two aspects of the ephedrine-based methodology:

1) **Replacing ephedrine with a more accessible alternative**: Both enantiomers of ephedrine can be obtained from commercial sources for synthetic purposes. However, ephedrine is also a controlled substance and hence the use of an alternative amino alcohol is desirable.

2) **Removal of the ephedrine portion**: In the studies described in this thesis, the removal of the ephedrine portion has been achieved by reductive cleavage (dissolving metal reduction). This results in destruction of the ephedrine. Clearly, a recoverable amino alcohol would enhance the utility of the chiralmorpholinone based methodology.

Objective

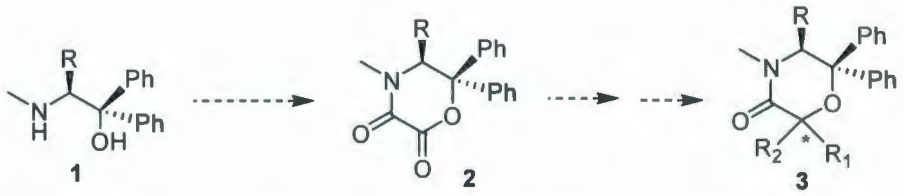
The objective of this study was to survey easily-accessible aminoalcohols for the synthesis of morpholine-diones which could serve as alternatives to the ephedrine-based morpholine-dione. This goal also included a plan to identify an amino alcohol, which could be recovered at the end of the synthesis and thus would serve as a chiral auxiliary rather than a chiral starting material. Importantly, such a study could also provide some understanding of the origin of stereoselectivity in the ephedrine-based template.

Results and discussion

Section 1: Investigations on potentially recoverable chiral amino alcohols.

The initial objective was to identify a chiral amino alcohol that could be recovered easily at the desired stage of the synthesis. It was hoped that synthesis of intermediates such as **3** from the diones **2** could be achieved with stereoselectivities similar to those derived using the ephedrine-derived morpholine-dione (Scheme 1). The dione **2** would, in turn, be obtained from the amino alcohol **1** by using a procedure similar to the ephedrine-based morpholine-dione.

Scheme 1



It is known that diphenylmethyl ethers are readily cleaved under acidic conditions.[1] It was reasoned that in the presence of aqueous acid, diphenylmethyl ether cleavage in **3** may be followed by a N→O acyl transfer reaction. Subsequent hydrolysis of the resulting ester would give the α-hydroxy acid **4** and amino alcohol **1** (Figure 1). Also, heterolytic C-O bond cleavage under anhydrous conditions could result in the formation of a benzylic carbocation which may react further (Figure 1) to provide the required α-hydroxy acid and the aminoalcohol auxiliary.

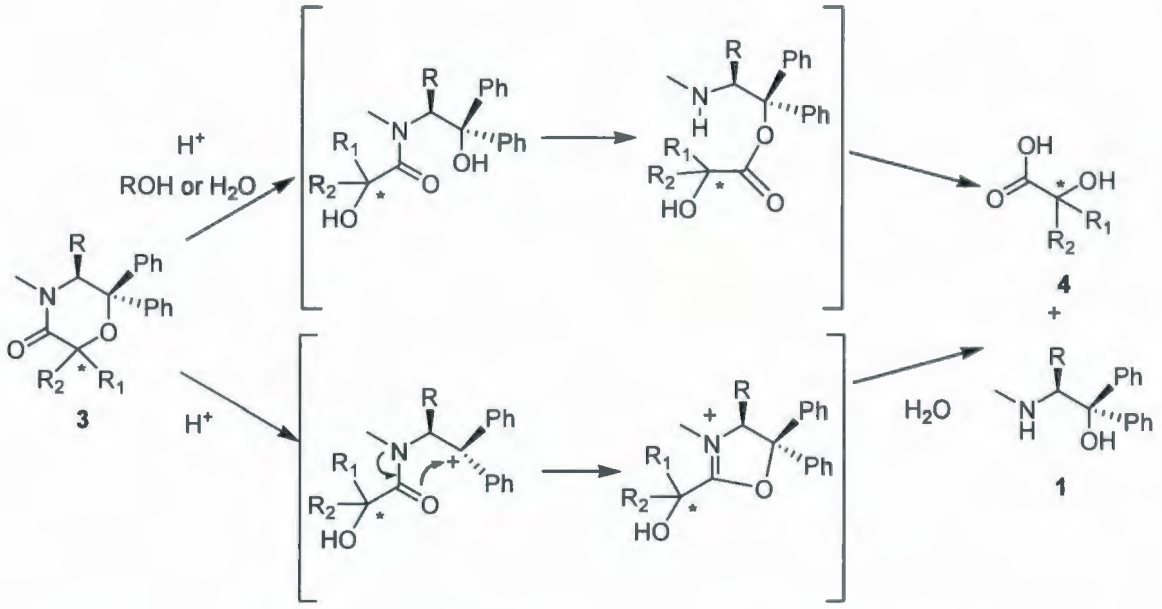
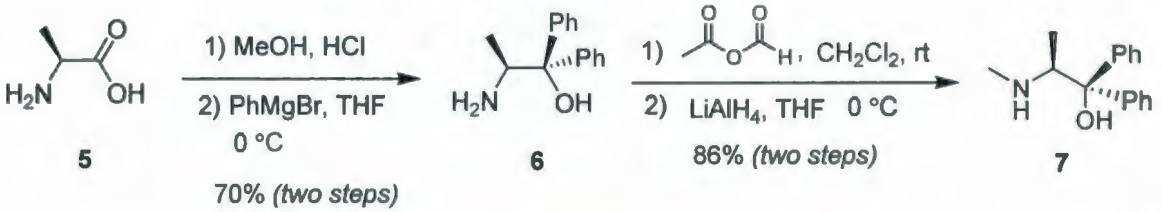


Figure 1. Proposed removal of the chiral auxiliary in **3**.

With these objectives in mind, the diphenylalaninol **7** was prepared from (*S*)-alanine (**5**, Scheme 2).[2] Reaction of (*S*)-alanine **5** with methanolic-HCl gave the corresponding methyl ester which, in turn, was reacted with phenylmagnesium bromide to give the tertiary alcohol **6** (70%).[3] Formylation of the secondary amine in **6** followed by reduction of the resulting amide gave the required amino alcohol **7** (86%, two steps).

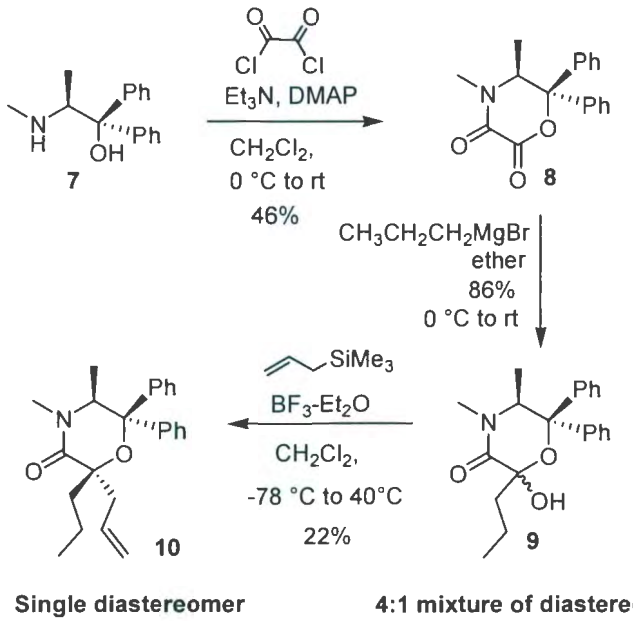
Scheme 2



The reaction of the amino alcohol **7** with oxalyl chloride afforded the dione **8** (46%, Scheme 3). Treatment of **6** with propylmagnesium bromide yielded **9** as a 4/1 mixture of diastereomers (86%). The hemiacetal in **9** was allylated (BF_3•Et_2O,

allyltrimethylsilane, -40 °C) to provide the dialkylated glycolamide derivative **10** (78%) as a single diastereomer. Energy minimization (Spartan software, MM2 calculations) studies on the oxocarbenium ion intermediate derived from **9** suggested a conformation that was very similar to the oxocarbenium ion derived from the corresponding ephedrine-based hemiacetal. Hence, the stereochemistry of the newly formed stereocenter in **10** was tentatively assigned as '*R*'.

Scheme 3



With the dialkyl morpholinone **10** in hand, diphenyl ether cleavage under a variety of acid hydrolysis conditions was examined. However, all attempts to effect the desired transformation were unsuccessful (Scheme 4, Table 1).

Scheme 4

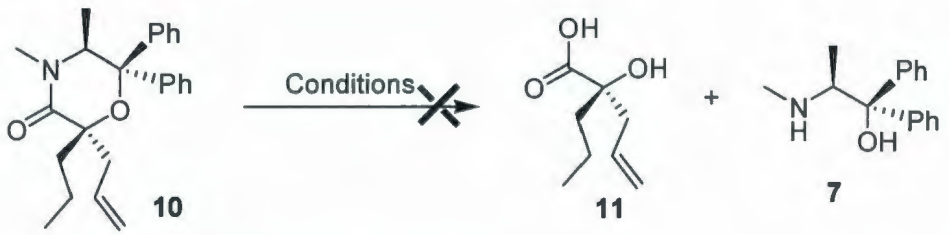
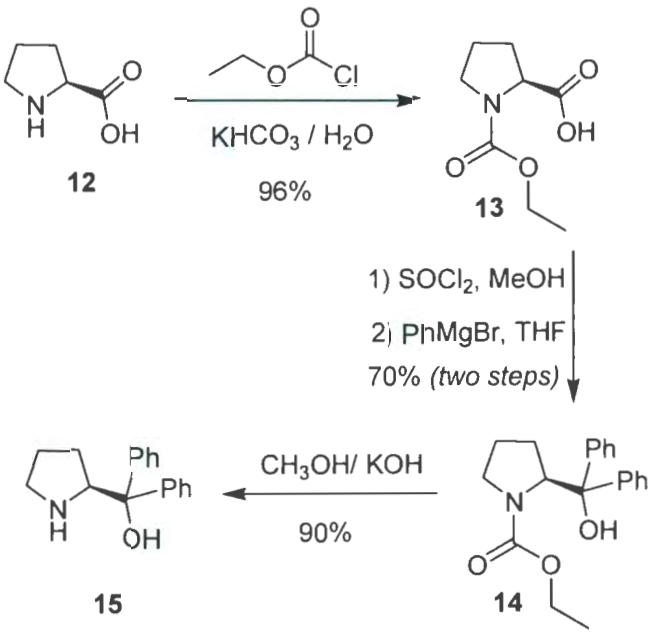


Table 1: Attempted removal of the chiral auxiliary in **10.**

Entry	Reagent and conditions	Time	Result
1	H_2SO_4 (cat), H_2O, reflux	24 h	Decomposition
2	CF_3COOH, DCM, 55 °C	2 h	No reaction
3	HBr (33%wt in acetic acid), rt	18 h	Decomposition
4	H_2SO_4 (cat), $HO(CH_2)_2OH$, 160 °C	4 d	Decomposition

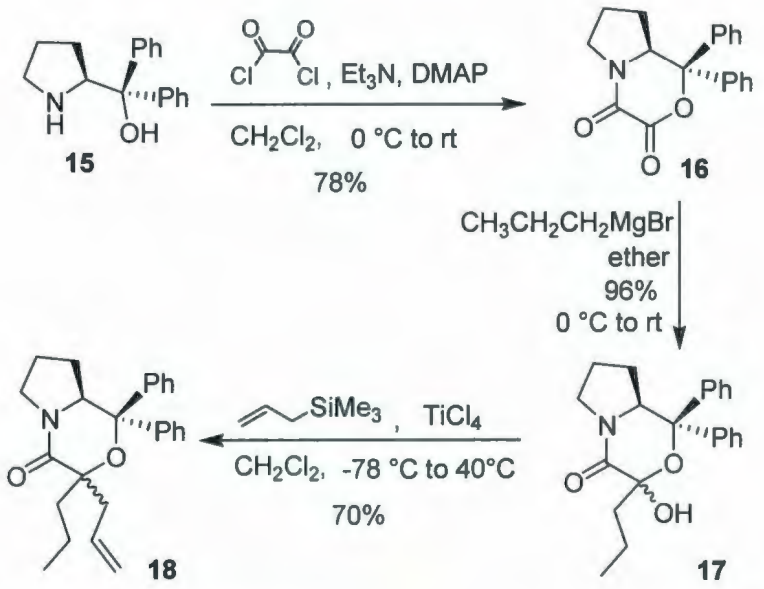
Diphenylprolinol, was also examined as an alternative to the diphenyl alaninol auxiliary (**7**). Diphenyl((*S*)-pyrrolidin-2-yl)methanol (**15**) is commercially available. However, it was also easily made from (*S*)-proline (**12**) by following a procedure reported by Kanth and Periasamy (Scheme 5).[4] Protection of the amine in **12** as an ethylcarbamate gave **13** (96%). Conversion of the carboxylic acid in **13** to a methyl ester followed by its reaction with phenylmagnesium bromide gave the alcohol **14** (74%). Finally, alkaline hydrolysis of the carbamate in **14** afforded the required amino alcohol **15** (92%).

Scheme 5



Treatment of diphenyl((*S*)-pyrrolidin-2-yl)methanol (**15**) with ethyloxalyl chloride gave dione **16** (78%, Scheme 6). Treatment of **16** with propylmagnesium bromide provided hemiacetal **17** (86%) as a 3/1 mixture of diastereomers (^{1}H NMR). The hemiacetal in **17** failed to undergo allylation when BF_3•Et_2O was used as a Lewis acid. Fortunately, however, allylation of the hemiacetal in **17** could be achieved with $TiCl_4$ and allyltrimethylsilane at -40 °C to provide **18** as a 1.7/1 mixture of diastereomers (^{1}H NMR).

Scheme 6



1.7:1 mixture of diastereomers

3:1 mixture of diastereomers

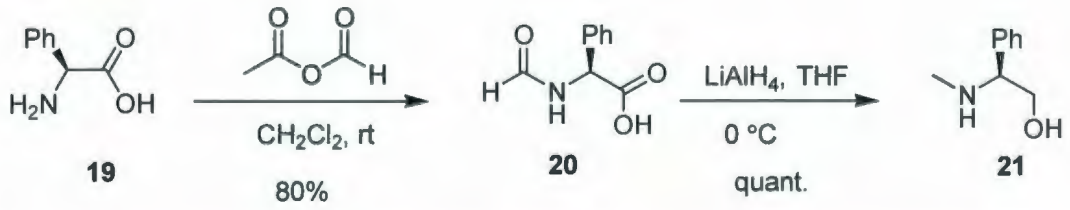
However, as was also seen for compound **10**, the dialkyl morpholinone derivative **18** was remarkably resistant to acid hydrolysis and could not be converted to the required α-hydroxy acid.

Thus, use of the aminoalcohol **7** was partially successful in that it provided excellent stereocontrol. However, the yield of the allylation reaction was low and the chiral auxiliary could not be removed under the attempted conditions. Aminoalcohol **15** provided poor stereoselectivity and the auxiliary could not be removed. It should be noted that the search for conditions to recover the chiral auxiliary from **10** and **18** remains incomplete and will be pursued further in our group.

Section 2: Studies with non-recoverable amino alcohols.

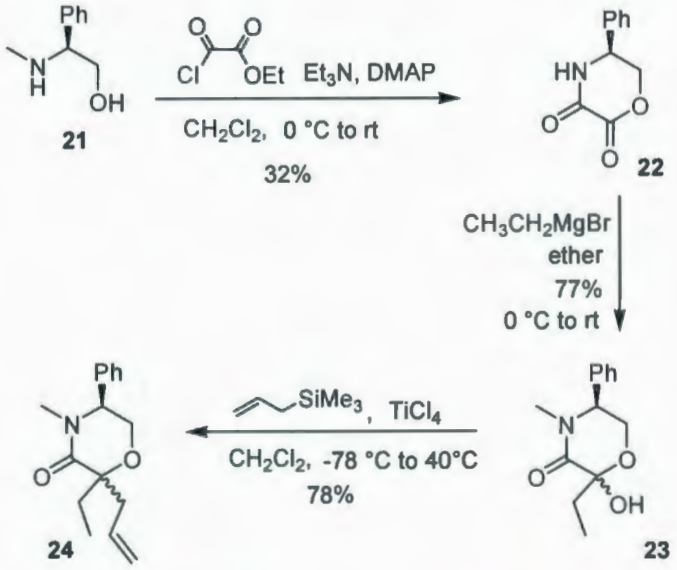
The utility of chiral morpholine-diones similar to the ephedrine-based morpholine-dione in asymmetric allylation reactions was then explored. Recovery of the amino alcohol was not an objective in this particular study. The study commenced with the synthesis of the amino alcohol **21** which was prepared from (*S*)-phenylglycine (**19**) by following a reported procedure (Scheme 7).[5] Thus, formylation of the amine in **19** gave the amide **20** (80%). Simultaneous reduction of the amide and the carboxylic acid group in **20** gave the required amino alcohol **21** in quantitative yield.

Scheme 7



The morpholine-dione **22** was prepared (32%) from aminoalcohol **21** and ethyloxalyl chloride. Treatment of **22** with ethylmagnesium bromide generated the hemiacetal **23** (77%, Scheme 8). The diastereoselectivity of the process was moderate (3/1) and the stereochemistry of the major diastereomer was not determined. The hemiacetal in **23** was readily allylated ($TiCl_4$, allyltrimethylsilane, -40 °C) to provide the dialkylated glycolamide derivative **24** (78%) as a 1/1 mixture of diastereomers (^1H NMR, Scheme 8). This observation emphasizes the importance of the stereocenter adjacent to the oxygen in the ephedrine-derived morpholinone system. The lack of 1,3 stereocontrol may be responsible for the completely unselective allylation of **23**.

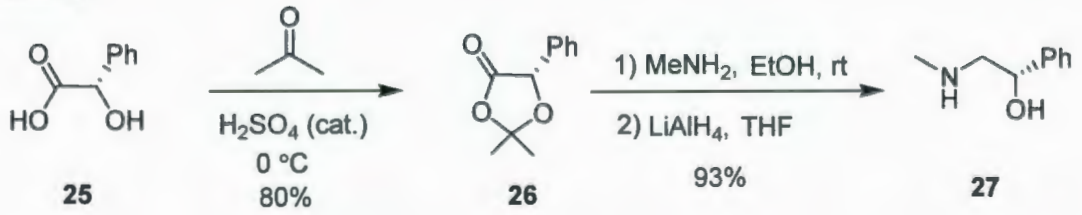
Scheme 8



1:1 mixture of diastereomers **3:1 mixture of diastereomers**

Next, the amino alcohol **27** was made from (*S*)-mandelic acid (**25**) according to the procedure reported by Davies and co-workers (Scheme 9).[6] Reaction of (*S*)-mandelic acid with acetone under acid catalysis generated the dioxolanone derivative **26** (80%). Treatment of **26** with methylamine in ethanol, gave ***N***-methylmandelamide, which in turn, could be reduced with lithium aluminium hydride to yield the amino alcohol **27** (93%).

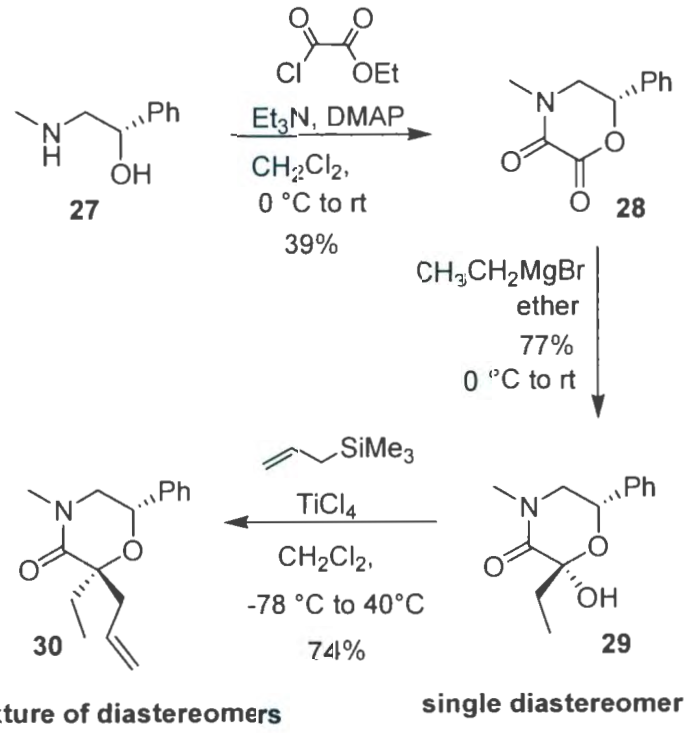
Scheme 9



The dione **28** was synthesized from amino alcohol **27** by using conditions identical to those employed for the dione **22** (39%, Scheme 10). Treatment of **28** with the ethylmagnesium iodide cleanly generated the hemiacetal **29** in 77% yield. The

diastereoselectivity of the process was moderate (5/1) and the stereochemistry at the hemiacetal stereocenter was not determined. The hemiacetal in **29** was readily allylated ($TiCl_4$, allyltrimethylsilane, -40 °C) to provide the dialkylated morpholinone **30** (68%) as a 2/1 mixture of diastereomers (^1H NMR, Scheme 10). Energy minimization (Spartan software) studies on the oxocarbenium ion intermediate derived from **29** suggested a conformation that was very similar to the ephedrine-based oxocarbenium ion. Consequently, the newly formed stereocenter was tentatively assigned the '*S*'configuration.

Scheme 10

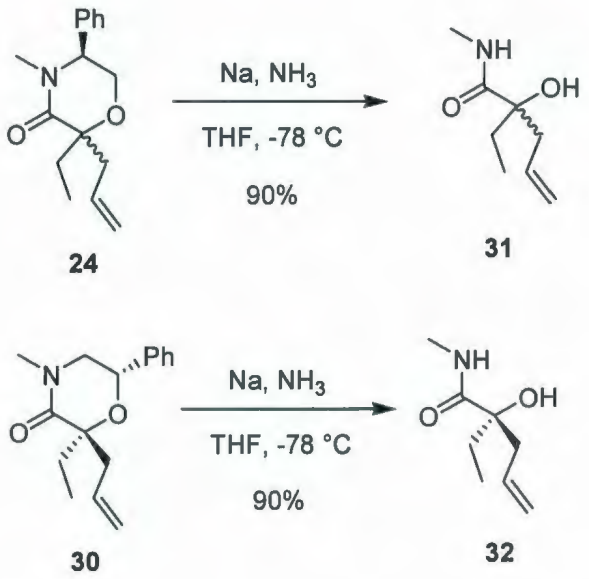


Interestingly, this allylation reaction proceeded with slightly better stereocontrol as compared to that of hemiacetal **23**. This observation suggests that 1,3 stereocontrol definitely plays a role in the reactions of **23** and **29**. However, the ephedrine-based system

is far superior to either of the two systems described above. Clearly, 1,3 stereocontrol is not the only deciding factor.

The dialkyl morpholinones **24** and **30** could be readily cleaved under dissolving metal reduction conditions to afford the hydroxyamides **31** and **32** respectively (Scheme 11). These results are in tune with expectations and supported the proposed mechanism for the removal of the ephedrine portion in the ephedrine-based template (Chapter 2). The configuration of the newly formed stereocenter in the major diastereomer in **30** was confirmed as '*S*' on the basis of the specific rotation of the amide **32** ($[\alpha]^{23}_D$ = -6.5 (c 1.7, H_2O)), which indicated an excess of the '*S*' enantiomer ($[\alpha]^{23}_D$ = +16 (*c* 1.7, H_2O) for (*R*)-**24**[7]).

Scheme 11



Conclusions

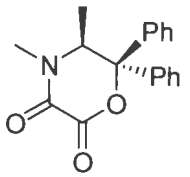
The search for alternatives to ephedrine has provided some insights into the morpholinone structural elements that were necessary for good diastereoselection. It appears that both stereocenters in ephedrine may be important for stereoselectivity. Diphenylalaninol may be a potential alternative to ephedrine and further investigations on this system are currently underway in our laboratories.

Experimental

General

General experimental techniques that have been described in the experimental section of Chapter 2 were followed.

(*S*)-4,5-Dimethyl-6,6-diphenylmorpholine-2,3-dione (8):



To a cold (0 °C), stirred solution of (*S*)-2-(methylamino)-1,1-diphenylpropan-1-ol (1.00 g, 4.1 mmol) in dichloromethane (20 mL) was added DMAP (0.03 g, 0.03 mmol). Triethylamine (0.23 mL, 16.6 mmol) was added followed by dropwise addition of oxalyl chloride (1.05 mL, 12.4 mmol). The mixture was stirred at 0 °C for 1 h and then at ambient temperature for 4 h. Cold water was added and the mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with HCl (2 M, 2 x 20 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give a pale yellow oil. Purification of the crude product by flash chromatography on silica gel (7/3 ethyl acetate/hexane) gave 0.521 g (46%) of **8** as a pale green solid.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.44-7.27 (m, 10H), 4.47 (q, 1H, J = 7.5, 1H), 3.15 (s, 3H), 1.22 (d, 3H, J = 7.5).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 156.6, 153.5, 141.6, 139.7, 129.5, 129.1, 128.8, 128.3, 125.7, 124.8, 87.2, 59.1, 34.1, 15.2.

IR (neat):

2297, 1763, 1681, 1495, 769 cm^{-1}.

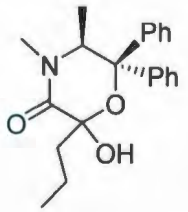
MS (APCI):

296.1 (M+1, 100).

HRMS (CI):

m/z 296.1280 (296.1287 calc. for $C_{18}H_{18}NO_3$, $[M+H]^+$).

(5*S*)-2-Hydroxy-4,5-dimethyl-6,6-diphenyl-2-propylmorpholin-3-one (9)



To a suspension of **8** (0.495 g, 1.70 mmol) in anhydrous ether (10 mL) at 0 °C was added propylmagnesium bromide (prepared from 131 mg of Mg and 0.460 mL of 1-bromopropane in ether (10 mL)) and the mixture was warmed up to ambient temperature. The reaction mixture was stirred 3 h at ambient temperature and saturated aqueous NH_4Cl solution was added. The mixture was stirred to dissolve any precipitated solids and was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the crude product by flash chromatography on silica gel (3/1 ethyl acetate/hexane) gave 0.490 g (86%) of **9** as a pale green oil (5/1

mixture of diastereomers).

^{1}H NMR (500 MHz, $CDCl_3$): Major diastereomer.

δ 7.36-7.19 (m, 10H), 4.28 (q, 1H, J = 6.5), 3.17 (s, 3H), 2.50 (s, 1H), 1.93-1.87 (m, 2H), 1.72-1.67 (m, 1H), 1.66-1.61 (m, 1H), 1.01 (d, 3H, J = 6.5), 1.00 (t, 3H, J = 7.5) .

Visible peaks of the minor diastereomer.

δ 7.36-7.19 (m, 10H), 4.22 (q, 1H, J = 6.6), 3.15 (s, 3H), 2.85 (s, 1H), 1.93-1.87 (m, 2H), 1.72-1.67 (m, 1H), 1.66-1.61 (m, 1H), 1.14 (d, 3H, J = 6.5), 0.08 (t, 3H, J = 7.4)

^{13}C NMR (125.77 MHz, $CDCl_3$): Major diastereomer.

δ 169.6, 144.2, 142.8, 128.7, 128.4, 128.2, 127.3, 125.5, 97.0, 80.1, 58.1, 43.8, 34.3, 16.5, 15.0, 14.5.

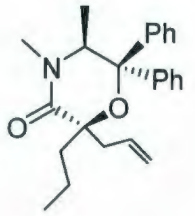
Visible peaks of the minor diastereomer.

δ 168.4, 144.0, 143.1, 128.4, 128.3, 128.0, 127.7, 125.8, 97.5, 81.8, 58.9, 39.2, 34.2, 15.4, 14.9, 14.0.

MS (APCI):

322.1 (M-H_2O, 100).

(2*R*,5S)-2-Allyl-4,5-dimethyl-6,6-diphenyl-2-propylmorpholin-3-one (10)



To a solution of **9** (0.214 g, 0.628 mmol) in dichloromethane (6 mL) at –78 °C was added $BF_3 \cdot Et_2O$ (0.470 mL, 3.8 mmol) and allyltrimethylsilane (0.604 mL, 23.8 mmol). The mixture was gradually warmed to room temperature and allowed to stir at this temperature for 1 h. Water was added and the mixture was warmed to ambient temperature. The biphase was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica (2/1 ethyl acetate/hexane) to give 0.050 g (22%) of **10** as a colourless gum.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.30-7.22 (m, 10H), 5.90-5.85 (m, 1H), 5.01 (br d, 1H), 4.98 (brd, 2H), 4.25 (q, 1H, J = 6.5), 3.21 (s, 3H), 2.08 (dd, 1H, J = 15.0, 8.0), 1.85 (dt, 1H, J = 13.0, 4.0), 1.75 (m, 1H, J = 13.0, 3.7), 1.72-1.68 (m, 1H), 1.48 (dd, 1H, J = 15.0, 5.0), 1.39-1.34 (m, 1H), 0.96 (d, 3H, J = 6.5), 0.92 (t, 3H, J = 7.0) .

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 171.9, 145.5, 144.0, 134.4, 128.5, 128.4, 127.2, 117.4, 81.0, 79.4, 59.2, 42.2, 41.1, 33.9, 18.8, 15.9, 14.5.

IR (neat):

2957, 1648, 1445, 760 cm^{-1}.

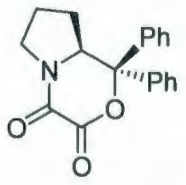
MS (APCI):

364.2 (M+1, 100).

HRMS (CI):

m/z 364.2295 (364.2277 calc. for $C_{24}H_{30}NO_2$, $[M+H]^+$).

(*S*)-Tetrahydro-1,1-diphenyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-3,4-dione (16)



To a cold (0 °C), stirred solution of diphenyl((*S*)-pyrrolidin-2-yl)methanol (0.250 g, 1.0 mmol) in dichloromethane (1 mL) was added DMAP (0.006 g, 0.05 mmol). Triethylamine (0.280 mL, 0.200 mmol) was added followed by dropwise addition of ethyloxalyl chloride (6.7 mL, 0.06 mmol). The mixture was stirred at 0 °C for 1 h and then at ambient temperature for 26 h. Cold water was added and the mixture was extracted with dichloromethane (3 x 5 mL). The combined organic layers were washed with HCl (2M, 3 x 5 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give a pale yellow oil. Purification of the crude product by flash chromatography on silica gel (7/3 ethyl acetate/hexane) gave 0.250 g (78%) of **16** as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.42-7.33 (m, 8H), 7.15-7.11 (m, 2H), 4.76 (t, 1H, J = 8, 1H), 3.78-3.74 (ddd, J = 12.4, 8.7, 2.9 1H), 3.61-3.55 (m, 1H), 2.35-2.2 (m, 2H), 1.97-1.84 (m, 2H).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 158.0, 152.6, 140.7, 137.6, 129.2, 129.1, 128.8, 128.7, 128.6, 127.3, 89.8, 63.3, 46.1, 29.5, 23.1.

IR (neat):

1755, 1689, 1442, 1186, 955 cm^{-1}.

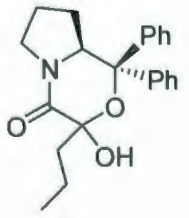
MS (APCI):

308.1 (M+1, 100).

HRMS (EI):

m/z 307.1213 (307.1208 calc. for $C_{19}H_{17}NO_3$, M+).

(8*S*)-Tetrahydro-3-hydroxy-1,1-diphenyl-3-propyl-1H-pyrrolo[2,1-c][1,4]oxazin-4(3H)-one (17)



To a suspension of **16** (0.320 g, 1.04 mmol) in anhydrous THF (10 mL) at 0°C was added propylmagnesiumbromide (prepared from 80 mg of Mg and 0.300 mL of bromopropane in ether (10 mL)) and the mixture was warmed up to ambient temperature. The reaction mixture was stirred 3 h and saturated aqueous NH_4Cl solution was added.

The mixture was stirred to dissolve any precipitated solids and was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the crude product by flash chromatography on silica gel (3/1 ethyl acetate/hexane) gave 0.350 g (96%) of **17** as a colourless gum (3/1 mixture of diastereomers).

^{1}H NMR (500 MHz, $CDCl_3$): Mixture of diastereomers (A and B)

δ 7.51-7.20 (m, 8H), 6.95-6.93 (m, 2H), 5.08 (t, 1H, J = 7), 3.48-3.40 (m, 2H), 2.21-2.28 (m, 1H), 2.33-2.28 (m, 1H), 2.10-2.03 (m, 1H), 1.93-1.90 (m, 1H), 1.76-1.56 (m, 4H), 1.04 (t, 3H, J = 7), 0.97 (t, 3H, J = 7.4).

^{13}C NMR (125.77 MHz, $CDCl_3$): Diastereomer A

δ 166.8, 146.5, 142.9, 129.8, 128.5, 128.2, 127.8, 127.0, 98.2, 83.1, 60.1, 45.0, 39.9, 31.2, 23.0, 16.6, 14.5, 14.3.

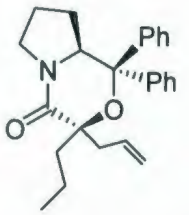
Visible peaks of the diastereomer B.

δ 169.0, 144.8, 140.5, 129.8, 128.5, 128.3, 127.9, 127.7, 97.9, 81.3, 66.4, 46.5, 43.2, 29.7, 22.9, 16.9.

MS (APCI):

334.1 (M-H_2O, 100).

(3*R*,8*S*)-3-Allyl-tetrahydro-1,1-diphenyl-3-propyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-4(3H)-one (18)



To a solution of **17** (0.160 g, 0.460 mmol) in dichloromethane (2 mL) at –78 °C was added $TiCl_4$ (0.310 mL, 2.7 mmol) and allyltrimethylsilane (0.43 mL, 2.7 mmol). The mixture was gradually warmed to – 40 °C and allowed to stir at this temperature for 5.5 h. Saturated NH_4Cl was added and the mixture was warmed to ambient temperature. Water was added, the biphase was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica (1/1 ethyl acetate/hexane) to give 0.120 g (70%) of **18** as a colourless gum (1.7/1 mixture of diastereomers).

^{1}H NMR (500 MHz, $CDCl_3$): Major diastereomer

δ 7.42-7.10 (m, 10H), 5.98-5.90 (m, 1H), 5.21 (br d, 1H), 5.10 (br d, 1H), 4.03-3.97 (m, 1H), 3.84-3.74 (m, 2H), 2.68 (dd, 1H, J = 7.0, 13.8), 2.42 (dd, 1H, J = 7.0, 14.3), 2.19-2.05 (m, 2H), 1.94-1.78 (m, 4H), 1.35-1.19 (m, 2H), 0.50 (t, 3H, J = 7.0).

^{1}H NMR (500 MHz, $CDCl_3$): Visible peaks of the minor diastereomer

δ 7.42-7.10 (m, 10H), 5.74-5.65 (m, 1H), 4.94-4.80 (m, 2H), 4.03-3.97 (m, 1H), 3.84-3.74 (m, 2H), 2.40-2.34 (m, 2H), 1.94-1.78 (m, 4H), 1.54-1.49 (m, $1H_2$), 1.35-1.19 (m, 2H), 0.94 (t, 3H, $J = 6.5$), 0.39-0.33 (m, 1H).

^{13}C NMR (125.77 MHz, $CDCl_3$): Major diastereomer

δ 170.9, 145.8, 141.3, 134.0, 130.1, 128.2, 128.0, 127.1, 118.7, 82.5, 80.3, 66.0, 46.1, 43.4, 38.4, 29.7, 22.6, 15.9, 14.1.

^{13}C NMR (125.77 MHz, $CDCl_3$): Visible peaks of the minor diastereomer.

145.7, 141.1, 134.3, 13.3, 128.3, 128.0, 127.6, 127.1, 117.6, 82.0, 80.4, 66.2, 46.2, 41.8, 40.9, 29.8, 22.7, 17.6, 14.5.

IR (neat):

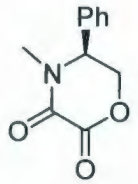
2960, 1647, 1445, 700 cm^{-1}.

MS (APCI):

376.1 (M+1, 100).

HRMS (CI): *m/z* 376.2287 (376.2277 calc. for $C_{25}H_{30}NO_2$, $[M+H]^+$).

(*S*)-4-Methyl-5-phenylmorpholine-2,3-dione (22)



To a cold (0 °C), stirred solution of (*S*)-2-(methylamino)-2-phenylethanol (0.700 mg, 2.00 mmol) in dichloromethane (15 mL) was added DMAP (0.031 g, 0.26 mmol).

Triethylamine (2.20 mL, 15.6 mmol) was added followed by dropwise addition of ethyloxalyl chloride (0.710 mL, 15.6 mmol). The mixture was stirred at 0 °C for 1 h and then at ambient temperature for 48 h. Cold water was added and the mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were washed with HCl (2M, 3 x 15 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give a pale yellow oil. Purification of the crude product by flash chromatography on silica gel (7/3 ethyl acetate/hexane) gave 0.300 g (32%) of **22** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.47-7.43 (m, 3H), 7.29-7.24 (m, 2H), 4.85 (dd, 1H, J = 3.6, 11.7) -4.78 (t, 1H, J = 3.6), 4.51 (dd, J = 3.6, 11.7, 1H), 3.05 (s, 3H).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 156.9, 154.3, 134.1, 129.7, 129.5, 126.8, 70.26, 61.1, 33.9 .

IR (neat):

1752, 1674, 1161 cm^{-1}

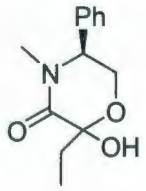
MS (APCI):

206.1 (M+1, 100).

HRMS (CI):

m/z 205.0742 (205.0739 calc. for $C_{11}H_{11}NO_3$, M+).

(5*S*)-2-Ethyl-2-hydroxy-4-methyl-5-phenylmorpholin-3-one (23)



To a suspension of **22** (0.180 g, 0.900 mmol) in anhydrous ether (10 mL) at 0°C was added ethylmagnesiumbromide (prepared from 65 mg of Mg and 0.220 mL of bromoethane in ether (10 mL)) and the mixture was warmed up to ambient temperature. The reaction mixture was stirred 3 h at ambient temperature and the precipitated solids were dissolved with saturated aqueous NH_4Cl solution. The resulting mixture was extracted with ethyl acetate (3 x 5 mL), the combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the crude product by flash chromatography on silica gel (2/1 ethyl acetate/hexane) gave 0.160 g (77%) of **23** as a colourless oil (3/1 mixture of diastereomers by ^{1}H NMR).

^{1}H NMR (500 MHz, $CDCl_3$): Major diastreomer

δ 7.42-7.25 (m, 5H), 4.67 (dd, 1H, J = 6.0, 11.0), 4.22 (dd, 1H, J = 11.0, 12.0), 3.87 (dd, 1H, J = 6.0, 12.0), 2.73 (s, 3H), 2.20-2.11 (m, 1H), 1.92-1.86 (m, 1H), 0.97 (t, 3H, J = 7.5) .

Visible peaks of the minor diastreomer

δ 7.42-7.25 (m, 5H), 4.72 (dd, 1H, J = 9.0, 12.0), 3.78 (d, 1H, J = 12.0), 2.93 (s, 3H), 1.99-1.93 (m, 1H), 1.03 (t, 3H, J = 8.0) .

IR (neat):

1638, 1238, 1191 cm^{-1}.

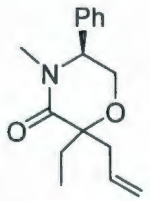
MS (APCI):

218.1 ($M-H_2O$, 100).

HRMS (CI):

m/z 236.1292 (236.1287 calc. for $C_{13}H_{18}NO_3$, $[M+H]^+$)

(5*S*)-2-Allyl-2-ethyl-4-methyl-5-phenylmorpholin-3-one (24)



To a solution of **23** (0.140 g, 6.00 mmol) in dichloromethane (2 mL) at –78 °C was added $TiCl_4$ (0.400 mL, 3.6 mmol) and allyltrimethylsilane (0.6 mL, 3.6 mmol). The mixture was gradually warmed to – 40 °C and allowed to stir at this temperature for 3 h. Saturated NH_4Cl was added and the mixture was warmed to ambient temperature. Water was added, the biphase was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica (2/1 ethyl acetate/hexane) to give 0.120 g (78%) of **24** as a colourless gum (1/1 mixture of diastereomers).

^{1}H NMR (500 MHz, $CDCl_3$): Mixture of diastereomers (A and B).

δ 7.54-7.23 (m, 10H), 5.91-5.82 (m, 2H), 5.15-5.10 (m, 4H), 4.53-4.48 (m, 1H), 4.53 (dd, 1H, J = 4.5, 7.2),4.5 (m, 1H), 4.07 (dAB, J = 4.5, 12.4), 3.83 (dAB, J = 6.8, 12.4), 3.09 (s, 3H), 3.17 (s, 3H), 2.72 (dd, 1H, J = 6.9, 14.2), 2.59-2.50 (m,

1H), 2.10-1.96 (m, 1H), 1.89-1.84 (m, 1H), 1.80-1.74 (m, 1H), 1.00 (t, J = 7.5, 1H), 0.94 (t, J = 7.4, 1H),

^{13}C NMR (125.77 MHz, $CDCl_3$): Diastereomer A.

δ 172.7, 137.3, 133.4, 129.1, 128.6, 127.5, 118.5, 82.1, 65.4, 63.4, 40.6, 32.8, 30.2, 7.9.

^{13}C NMR (125.77 MHz, $CDCl_3$): Visible peaks of diastereomer B.

δ 172.7, 137.8, 128.6, 127.3, 118.4, 81.9, 65.2, 63.3, 40.5, 30.0, 29.1, 8.2.

IR (neat):

2973, 1646, 1122 cm^{-1}.

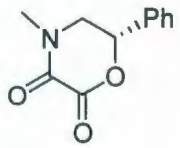
MS (APCI):

260.1 (M+1, 100).

HRMS (EI):

m/z 259.1570 (259.1572 calc. for $C_{16}H_{21}NO_2$, M+).

(*S*)-4-Methyl-6-phenylmorpholine-2,3-dione (28)



To a cold (0 °C), stirred solution of (*S*)-2-(methylamino)-1-phenylethanol (0.300 mg, 2.00 mmol) in dichloromethane (3 mL) was added DMAP (0.013 g, 0.120 mmol). Triethylamine (0.850 mL, 6.00 mmol) was added followed by dropwise addition of ethyloxalyl chloride (0.250 mL, 2.4 mmol). The mixture was stirred at 0 °C for 1 h and

then at ambient temperature for 72 h. Cold water was added and the mixture was extracted with dichloromethane (3 x 5 mL). The combined organic layers were washed with HCl (2 M, 3 x 5 mL), dried (Na_2SO_4) and concentrated under reduced pressure to yield a pale yellow oil. Purification of the crude product by flash chromatography on silica gel (7/3 ethyl acetate/hexane) gave 0.160 g (39%) of **28** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.46-7.41 (m, 4H), 5.73 (dd, 1H, J = 10.0, 3.0 1H), 3.98 (dd, J = 13.0, 10.0, 1H), 3.61 (dd, J = 13.0, 3.0, 1H), 3.15 (s, 3H).

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 156.7, 153.9, 134.4, 129.8, 129.7, 129.2, 126.3 (ArCH), 77.8, 53.5, 35.2.

IR (neat):

2936, 1752, 1690, 1231, 1192 cm^{-1}

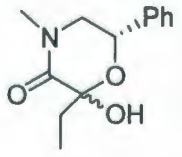
MS (APCI):

206.1 (M+1, 100).

HRMS (CI):

m/z 206.0817 (206.0817 calc. for $C_{11}H_{11}NO_3$, $[M+H]^+$).

(6*S*)-2-Ethyl-2-hydroxy-4-methyl-6-phenylmorpholin-3-one (29)



To a suspension of **28** (0.150 g, 0.700 mmol) in anhydrous ether (10 mL) at 0 °C

was added ethylmagnesium bromide (prepared from 65 mg of Mg and 0.220 mL of bromoethane in ether (10 mL)) and the mixture was warmed up to ambient temperature. The reaction mixture was stirred 3 h at ambient temperature and the precipitated solids were dissolved with saturated aqueous NH_4Cl solution. The resulting mixture was extracted with ethyl acetate (3 x 5 mL), the combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the crude product by flash chromatography on silica gel (2/1 ethyl acetate/hexane) gave 0.160 g (77%) of **29** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.42-7.32 (m, 3H), 5.36 (dd, 1H, J = 3.5, 11.0), 4.07 (brs, 1H), 3.58 (t, 1H, J = 11.0), 3.30 (1H, dd, J = 3.5, 11.0), 3.02 (s, 3H), 2.18-2.12 (m, 1H), 1.93-1.87 (m, 1H), 0.99 (t, 3H, J = 7.7) .

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 168.4, 138.0, 128.7, 128.6, 126.4, 98.5, 69.2, 55.9, 34.8, 33.0, 8.0.

IR (neat):

3383, 1638, 1231, 1184 cm^{-1}.

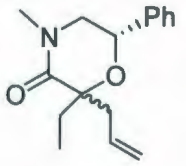
MS (APCI):

218.1 (M-H_2O, 100).

HRMS (EI):

m/z 236.1290 (236.1287 calc. for $C_{13}H_{18}NO_3$, $[M+H]^+$)

(6*S*)-2-Allyl-2-ethyl-4-methyl-6-phenylmorpholin-3-one (30)



To a solution of **29** (0.140 g, 6.00 mmol) in dichloromethane (2 mL) at –78 °C was added $TiCl_4$ (0.400 mL, 3.6 mmol) and allyltrimethylsilane (0.6 mL, 3.6 mmol). The mixture was gradually warmed to – 40 °C and allowed to stir at this temperature for 3.5 h. Saturated aqueous NH_4Cl was added and the mixture was warmed to ambient temperature. Water was added, the biphase was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica (2/1 ethyl acetate/hexane) to give 0.114 g (74%) of **30** as a colourless gum (2/1 mixture of diastereomers).

^{1}H NMR (500 MHz, $CDCl_3$): Major diastereomer

δ 7.42-7.32 (m, 3H), 5.93-5.86 (m, 1H), 5.14-5.10 (m, 3H), 3.61-3.60 (m, 1H), 3.28 (dd, 1H, J = 2.2, 12.2), 3.03 (s, 3H), 2.86 (dd, 1H, J = 6.1, 14.6), 2.54-2.51 (m, 1H) 4.54 (dd, J = 4.1, 7, 1H), 3.04 (s, 3H), 1.96-1.89 (m, 1H), 1.79-1.73 (m, 1H), 0.97 (t, 3H, J = 7.2) .

^{1}H NMR (500 MHz, $CDCl_3$): Visible peaks of minor diastereomer

4.94 (m, 2H), 3.54-3.51 (m, 1H), 3.23 (dd, 1H, J = 3.1, 12.2), 3.03 (s, 3H), 2.10 (m, 1H), 0.97 (t, 3H, J = 7.2).

^{13}C NMR (125.77 MHz, $CDCl_3$): Major diastereomer

δ 171.3, 138.7, 133.5, 128.8, 128.7, 126.4, 126.3, 118.4, 82.8, 70.3, 55.9, 41.4, 34.9, 32.1, 8.4.

^{13}C NMR (125.77 MHz, $CDCl_3$): Visible peaks of minor diastereomer

δ 171.1, 138.6, 133.7, 128.7, 128.5, 118.5, 82.8, 70.5, 55.9, 42.3, 34.8, 29.1, 8.0.

IR (neat):

2935, 1646, 1231 cm^{-1}.

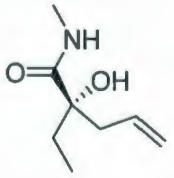
MS (APCI):

260.1 (M+1, 100).

HRMS (EI):

m/z 259.1575 (259.1572 calc. for $C_{16}H_{21}NO_2$, M+H).

(*S*)-2-Ethyl-2-hydroxy-*N*-methylpent-4-enamide (32)



To anhydrous liquid ammonia (distilled over sodium) was added Na (0.044 g, 1.93 mmol) at –78 °C and the mixture was stirred for 15 min. To the resulting blue solution was added a solution of **30** (0.050 g, 0.2 mmol) in anhydrous THF (2.5 mL) and the mixture was stirred for 1.5 min. A mixture of 2/1 methanol/water (1.5mL) 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 column chromatography on silica gel (3/2 ethyl acetate/hexane) to yield **32** 26 mg (90%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 6.70 (br s, 1H), 5.80-5.72 (m, 1H), 5.21-4.16 (m, 2H), 2.83 (d, 3H, *J* = 5.4), 2.71 (dd, 1H, *J* = 6.5, 13.5), 2.71 (dd, 1H, *J* = 9.3, 13.5), 1.92-1.85 (m, 1H), 1.64-1.56 (m, 1H), 0.89 (t, 3H, *J* = 7.5) .

^{13}C NMR (125.77 MHz, $CDCl_3$):

δ 175.2 , 133.0, 120.4, 78.0, 33.9, 32.3, 26.1, 8.0.

IR (neat):

3349, 2935, 1646 cm^{-1}.

MS (APCI):

158.1 (M+1, 100).

HRMS (CI):

m/z 157.1102 (157.1103 calc. for $C_8H_{15}NO_2$, M+).

$[\alpha]^{23}_D$ = -6.5 (c 1.7, H_2O).

A similar reaction of compound **24** provided compound **31** (90%).

References

1. a) Froussios, C.; Kolovos, M. *Synthesis* **1987**, 1106. b) Kolovos, M.; Froussios, C. *Tetrahedron Lett.*, **1984**, *25*, 3909. c) Paredes, R.; Perez, R. *Tetrahedron Lett.*, **1998**, *25*, 3909.
2. Aratani, T.; Hazama, M.; Yoneyoshi, Y.; Suzukamo, G. *Eur. Pat. Appl.* (1983), EP 75868 A2 19830406.
3. Vatcher, B. unpublished observations in these laboratories.
4. Kanth, J. V. B.; Periasamy, M. *Tetrahedron* **1993**, *49*, 5127.
5. Huszthy, P.; Oue, M.; Brandshaw, J. S.; Zhu, C. Y.; Wang, T.; Dalley, N. K.; Curtis, J. C.; Izatt, R. M. *J. Org. Chem.* **1992**, *57*, 5383.
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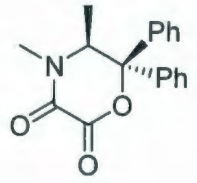
7. Gnana Ravi, R., Ph.D Thesis, **1998**, Pune University.

Appendix 5:

^{1}H and ^{13}C NMR Spectra for Chapter 6



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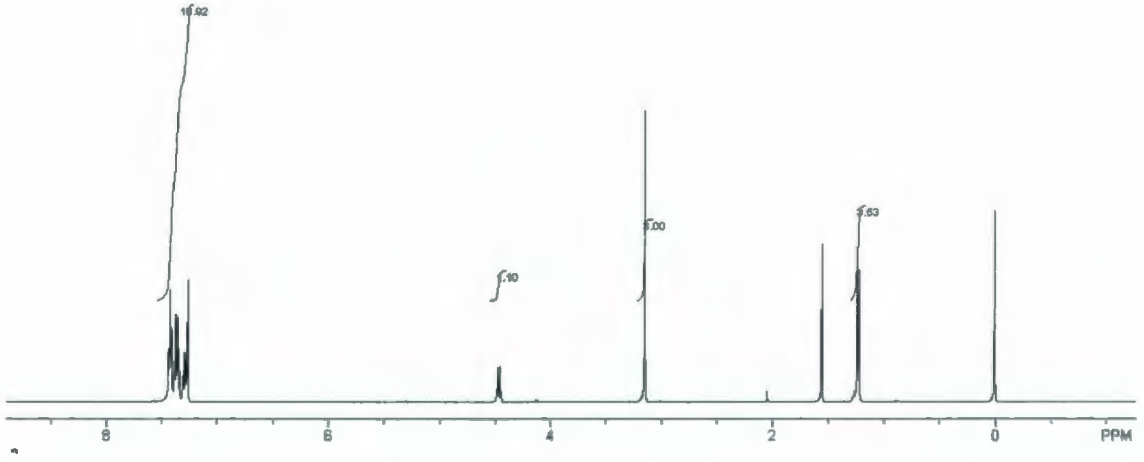
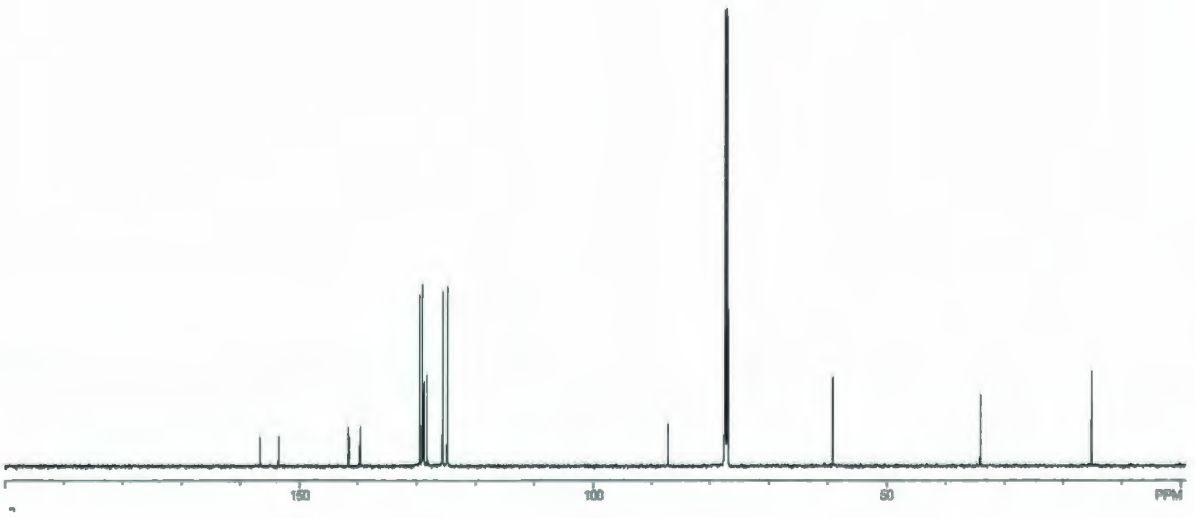
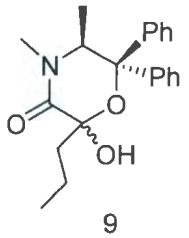
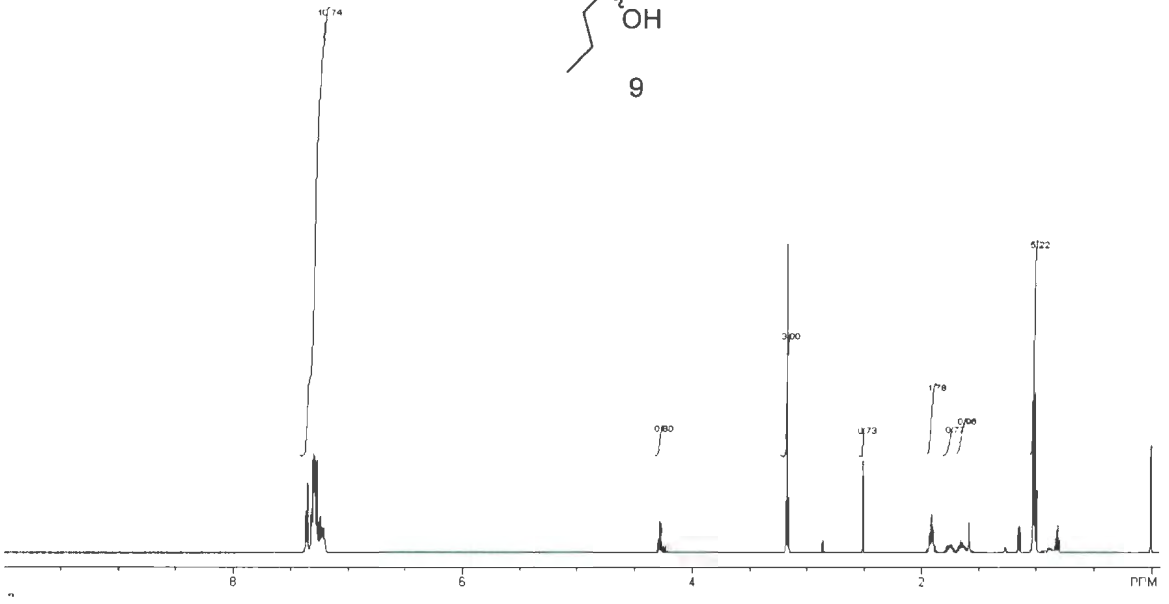





Ph
Ph
N
O
O
OH

9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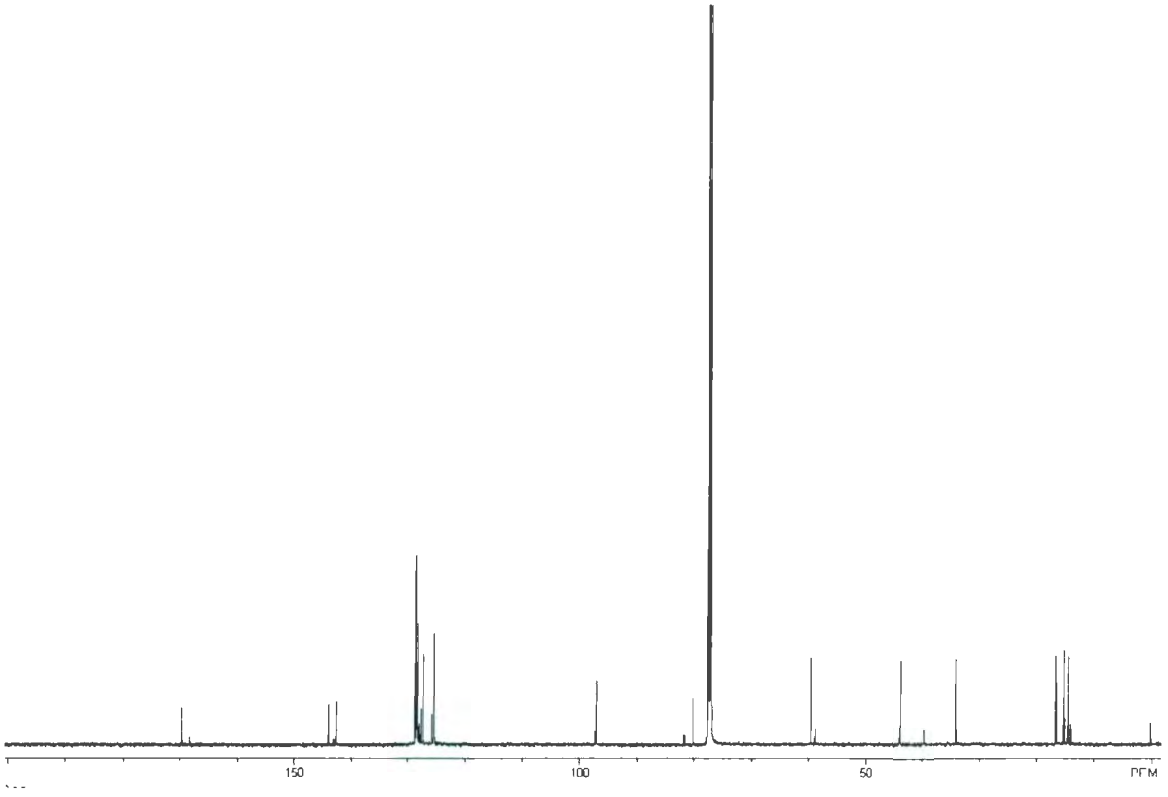
0.96
0.97
5.22
8
6
4
2
PPM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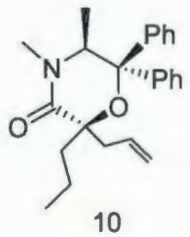
100
50
PPM



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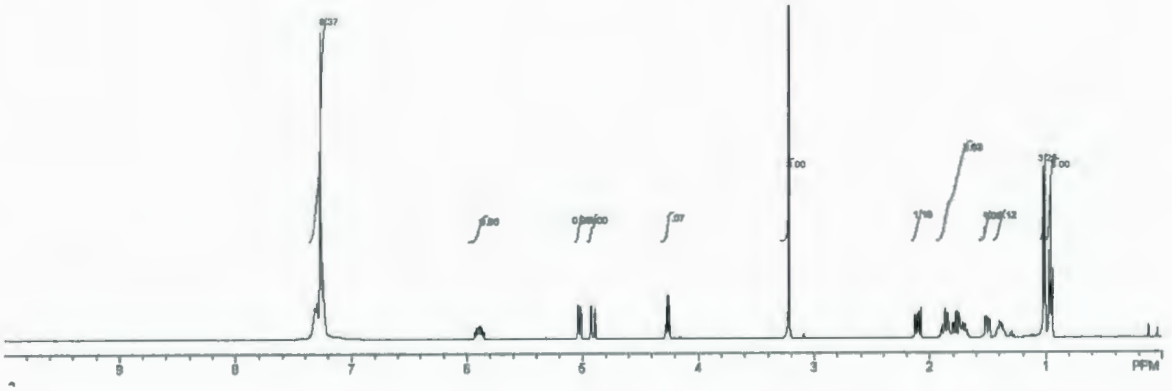

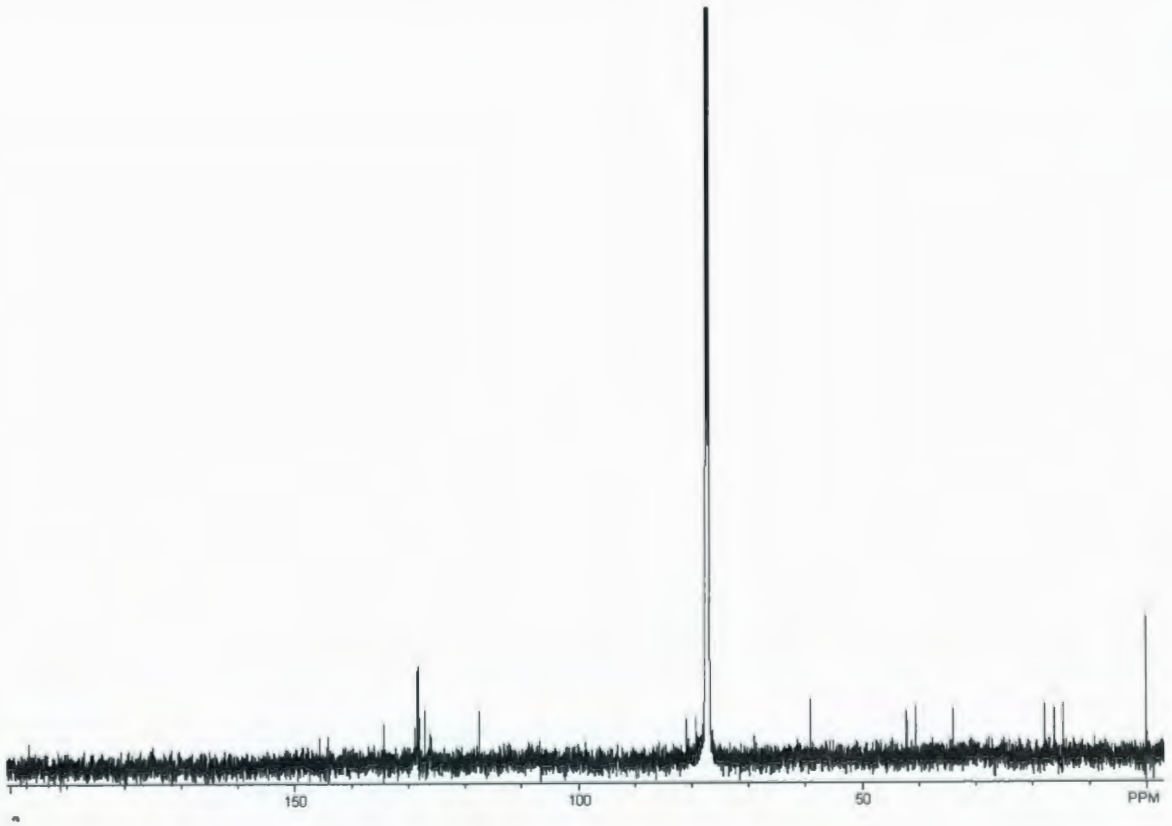

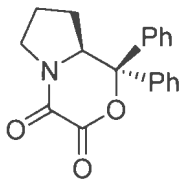

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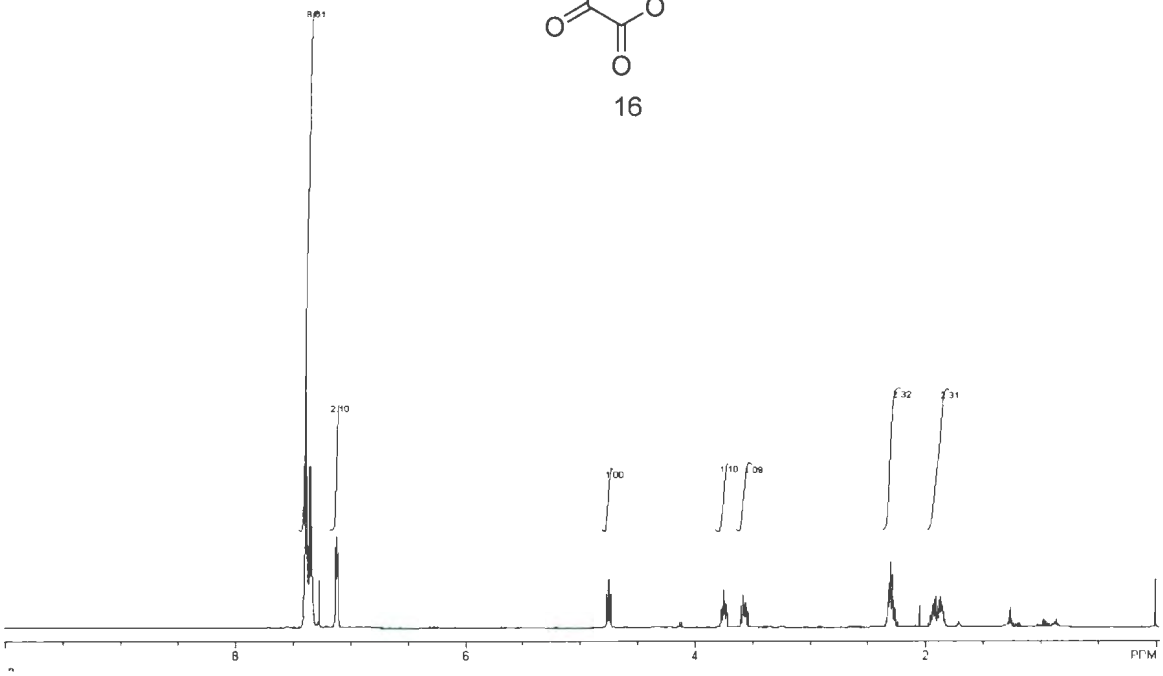

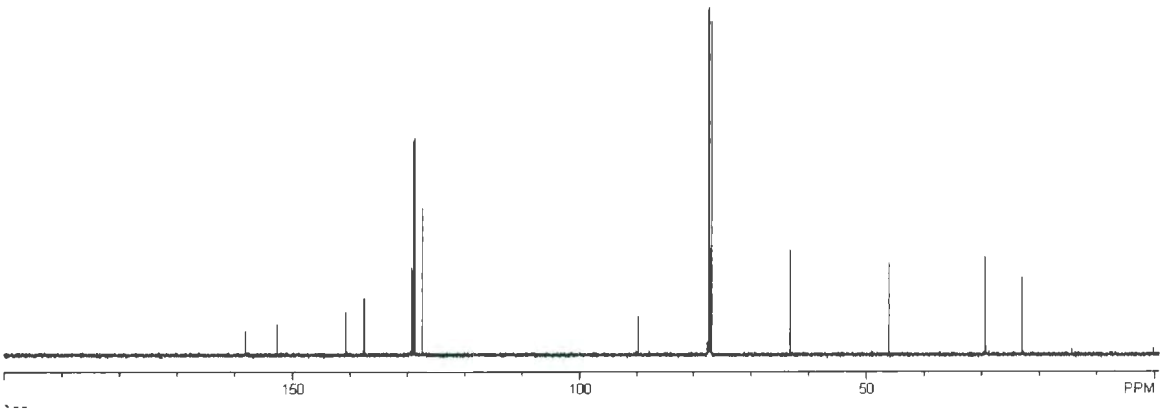

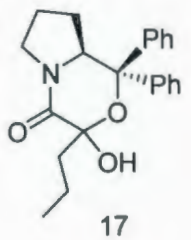

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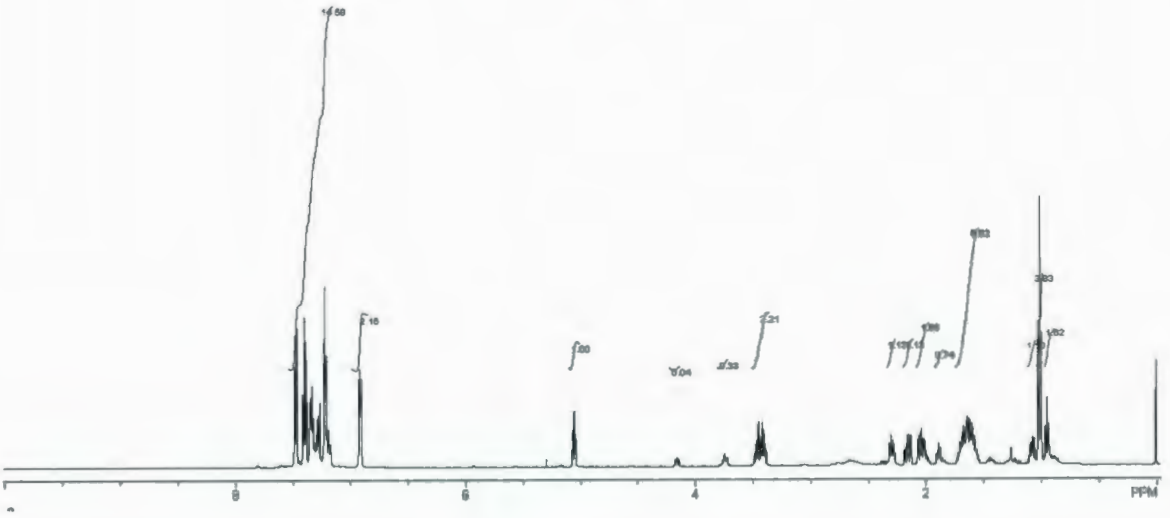

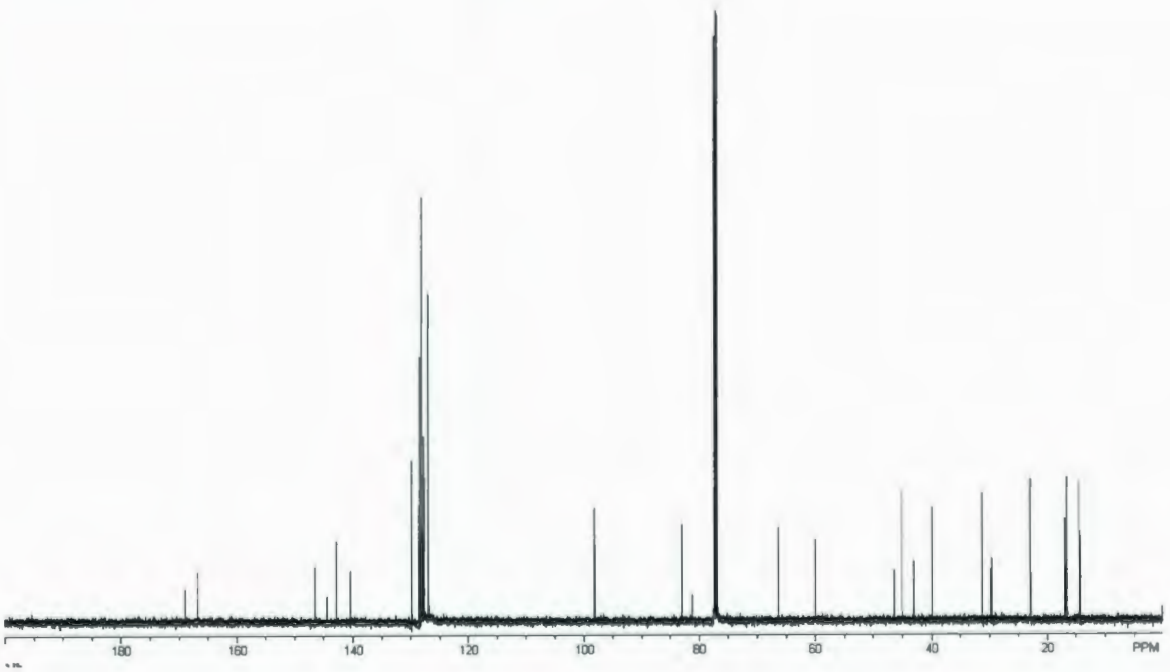

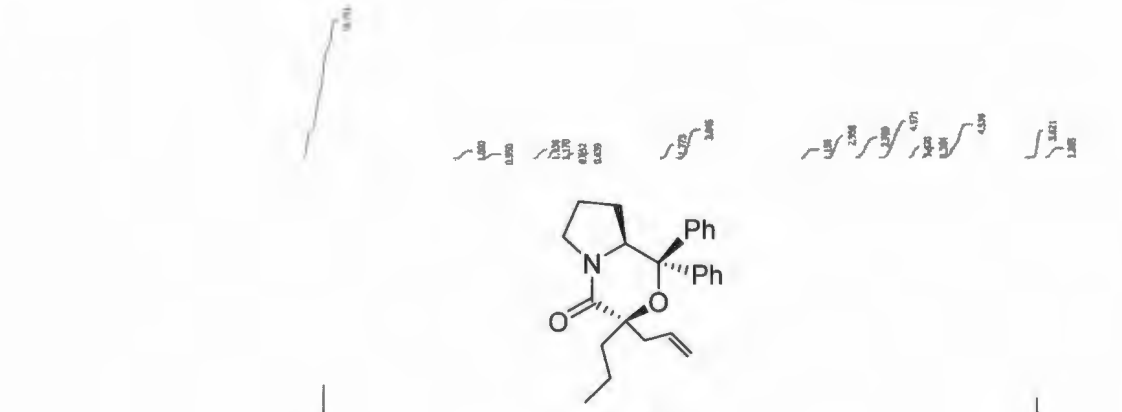
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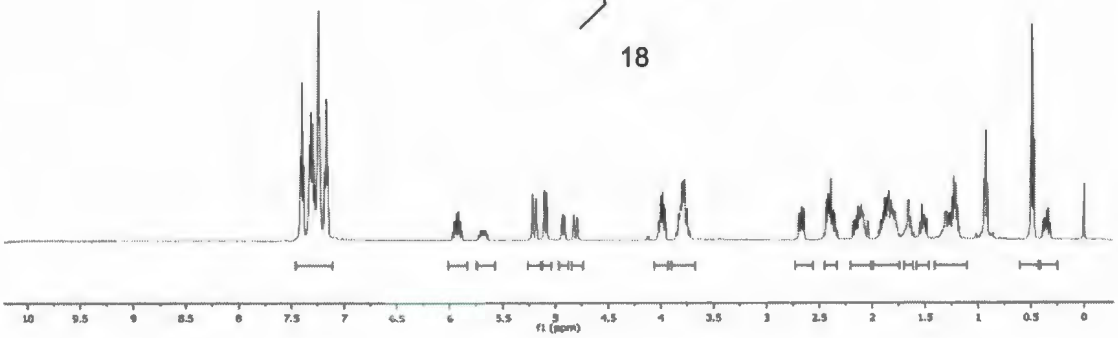
O

18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7
6.5
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5
4.5
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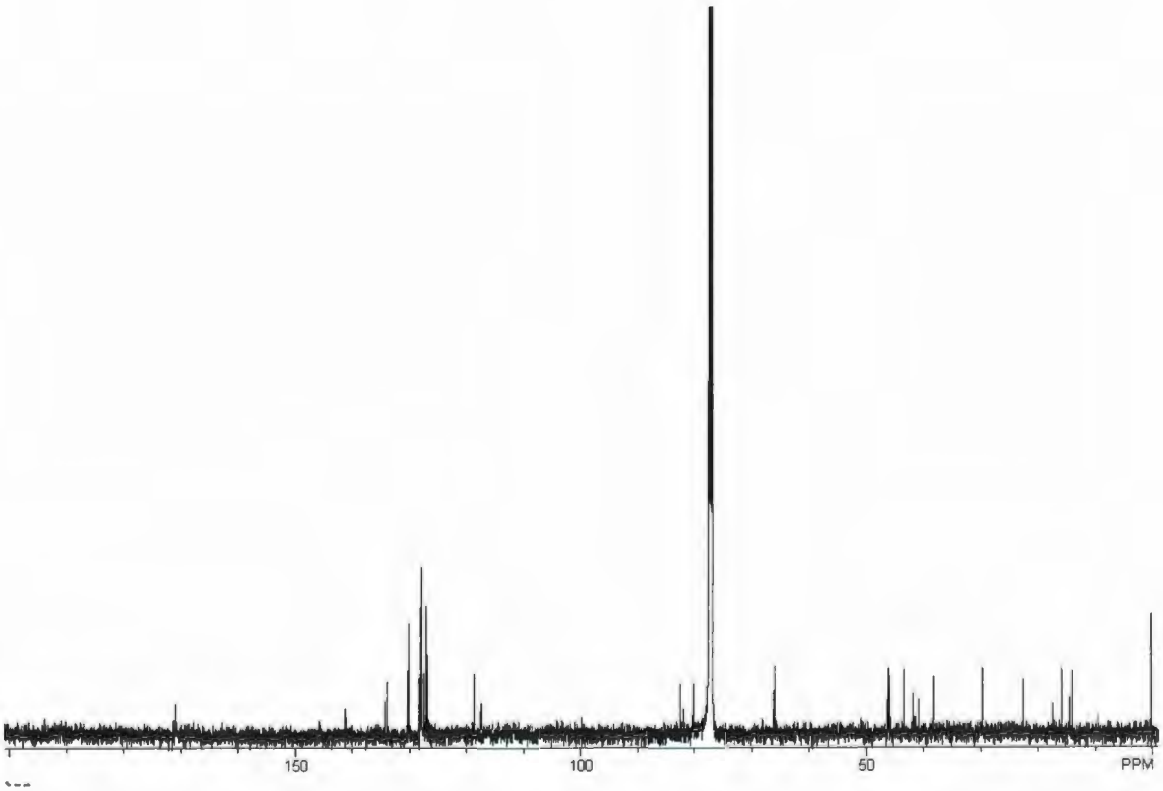
2.5
2
1.5
1
0.5
0
f1 (ppm)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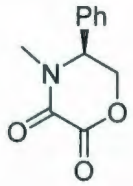

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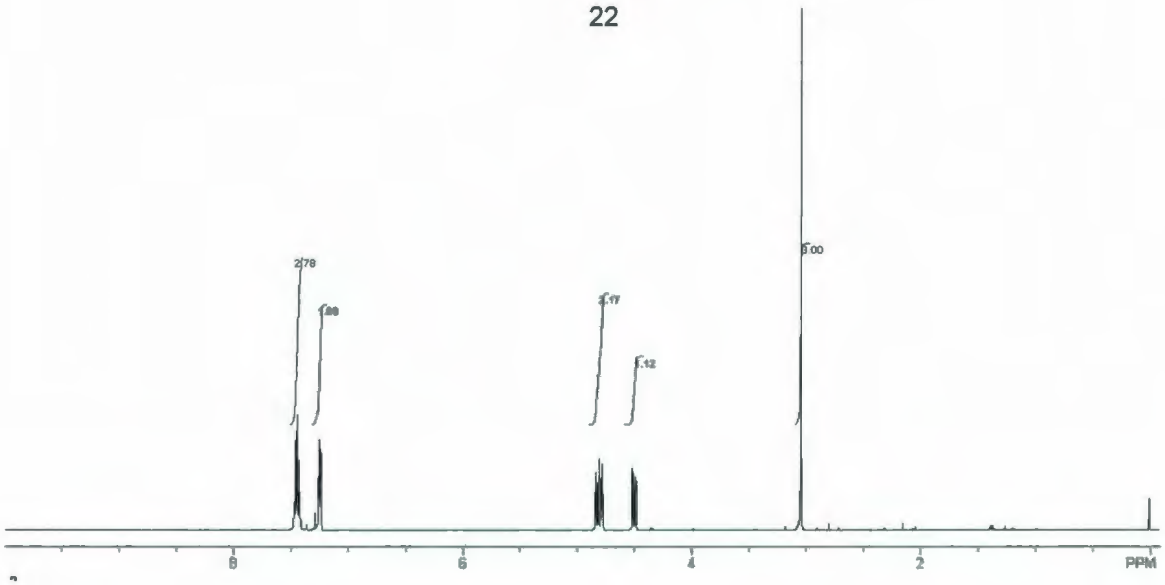

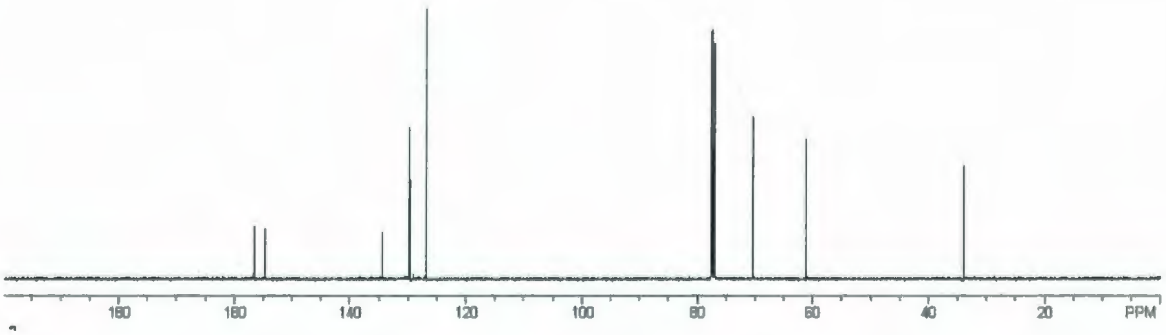

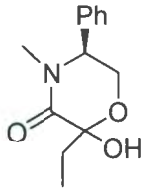
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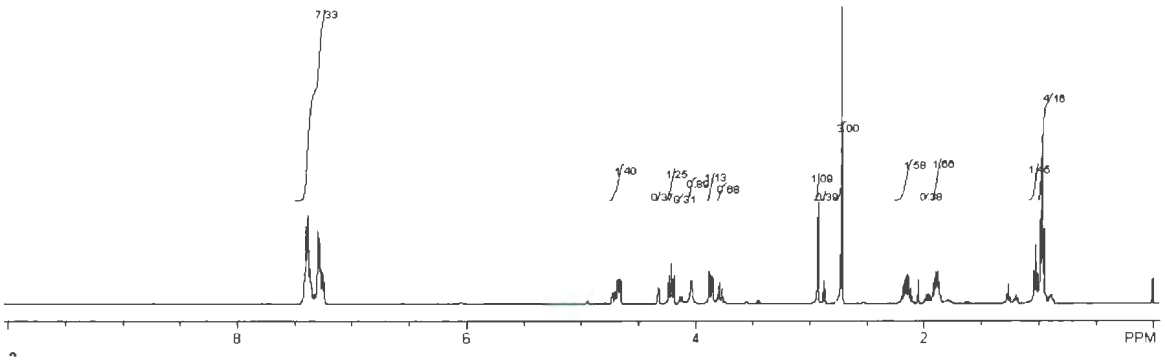
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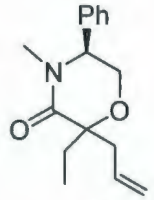
4
2
PPM



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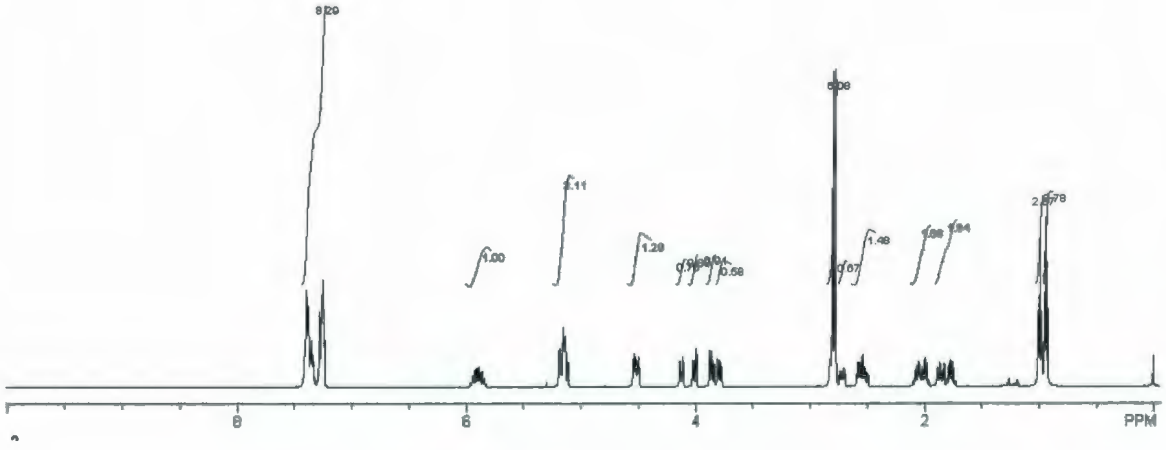

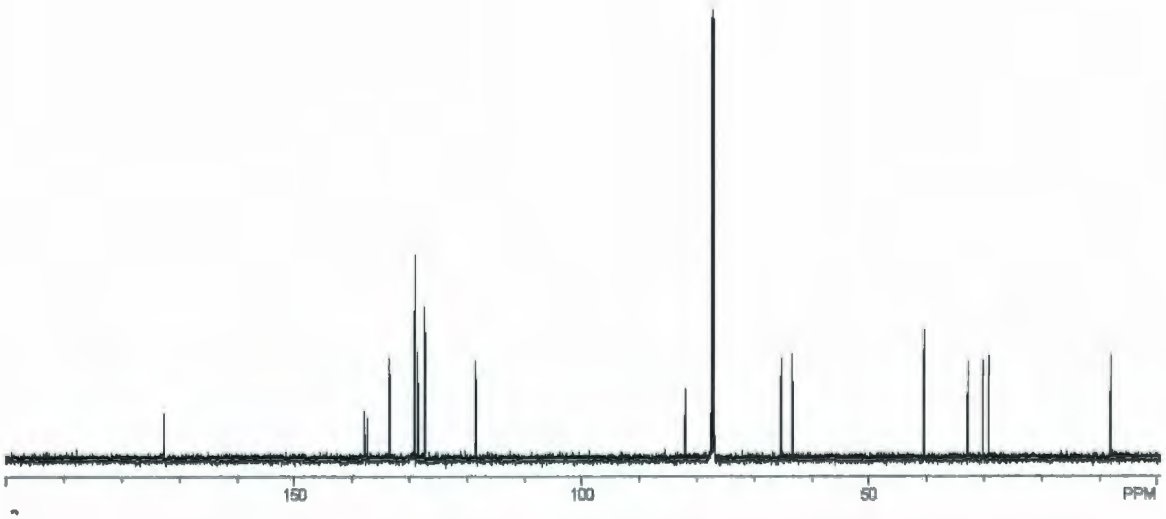

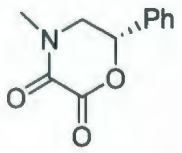

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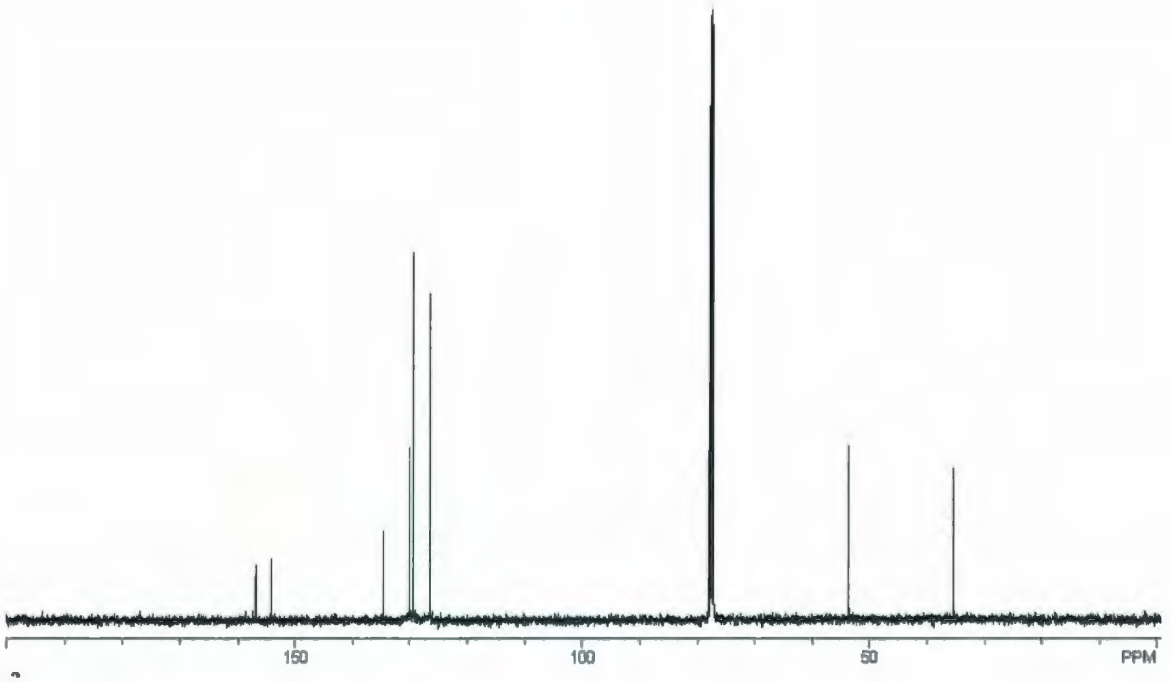

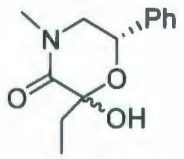

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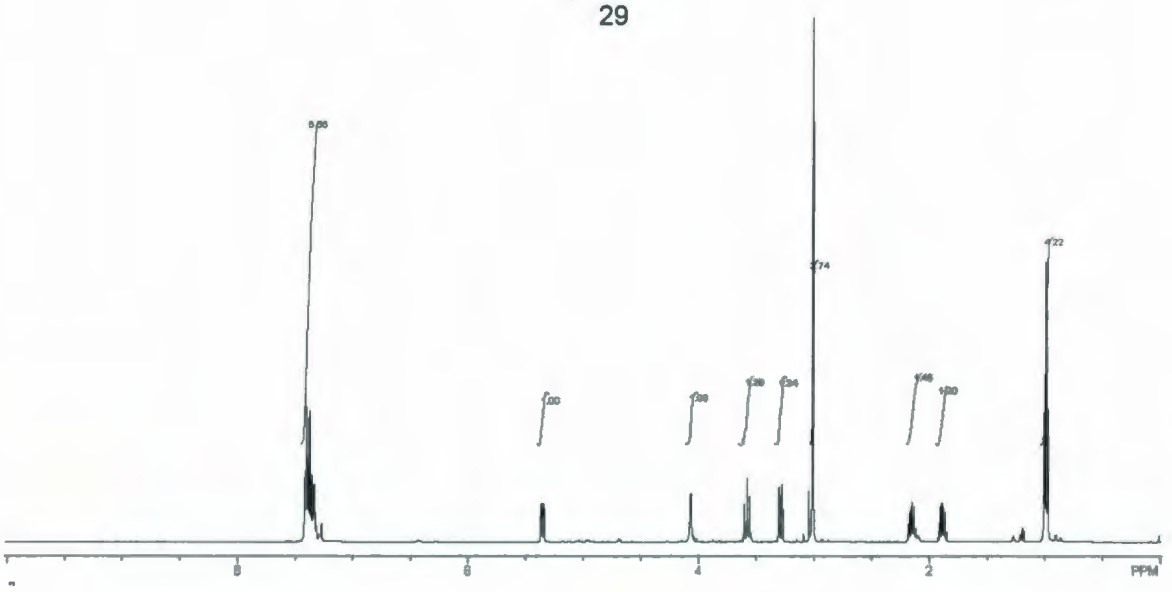

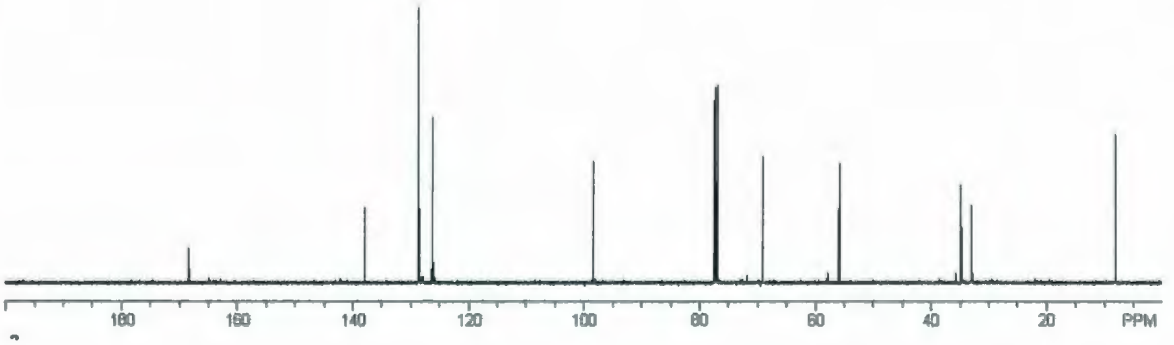

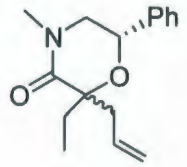

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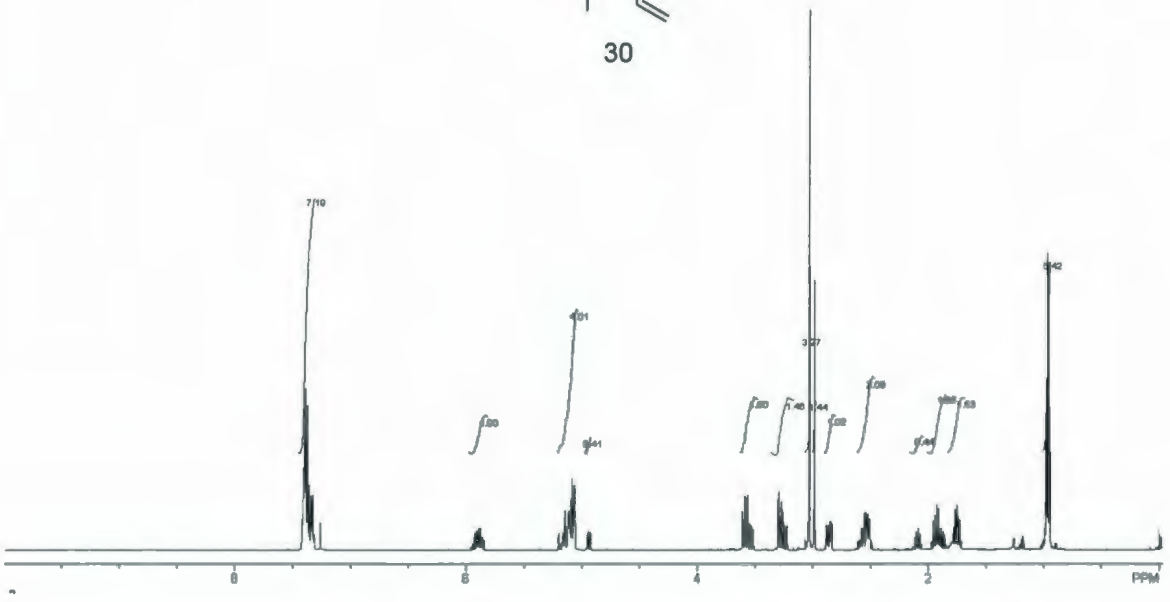

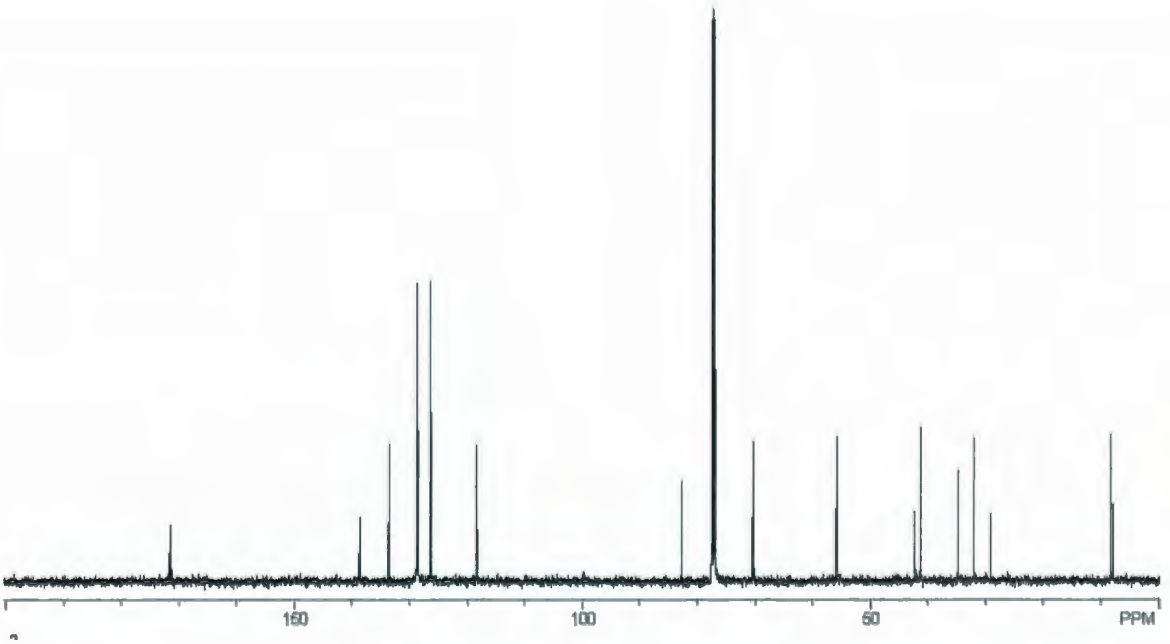

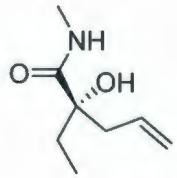

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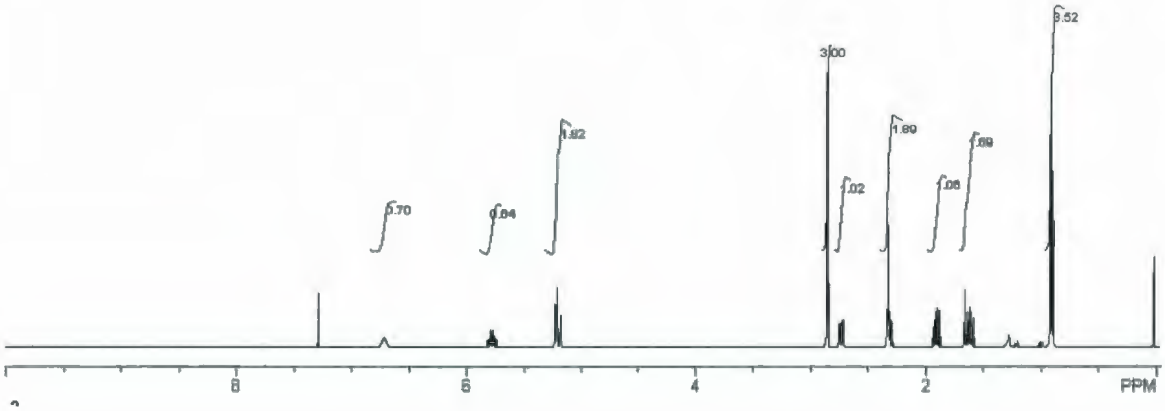

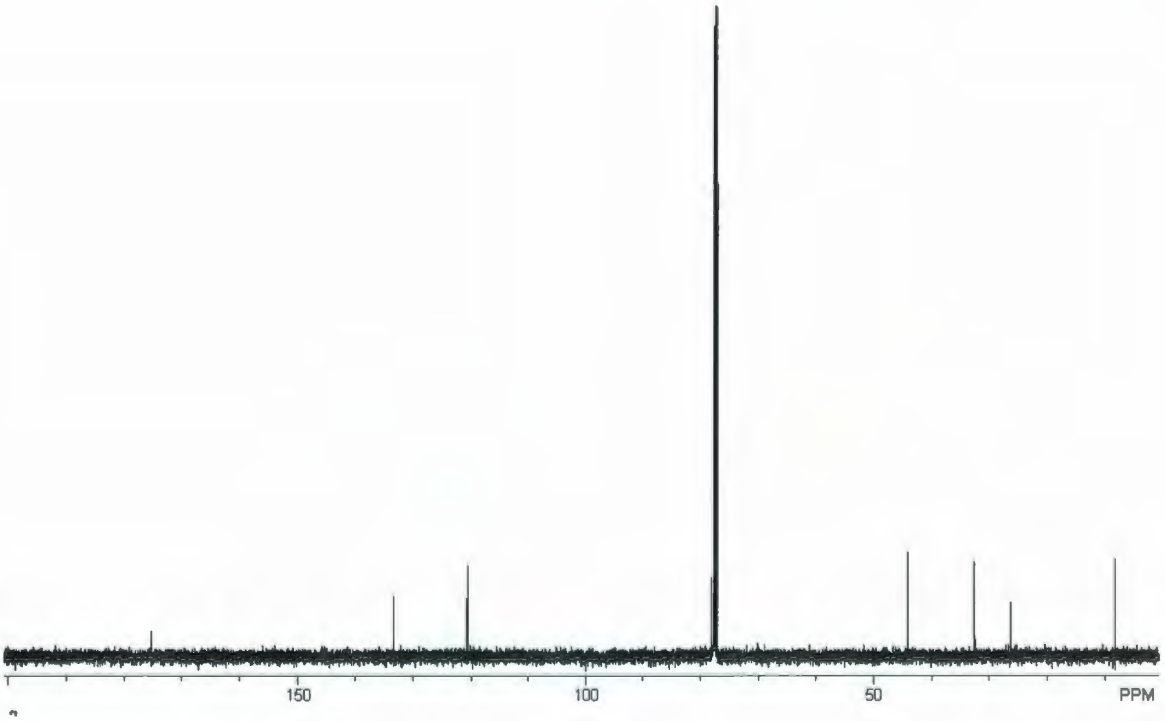

Future plans

This thesis describes the applications of an ephedrine-derived morpholine-dione as a chiral starting material in the enantioselective synthesis of α-hydroxy acids and medium-sized oxacycles. Based on the observations from the present studies, future investigations on morpholine-dione systems could examine, 1) expanding the scope of the morpholine-dione based synthetic methods and 2) the development of an alternative to 1*R*,2*S* ephedrine.

1) Expanding the scope of the morpholine-dione based synthetic methods:

So far, only allyltrimethylsilane and allyltributyltin have been used as nucleophiles in the reactions of ephedrine-based oxocarbenium ions. The use of other carbon nucleophiles will be a useful addition to the existing method. Also, the ring opening of ephedrine-derived spiroepoxides with nitrogen nucleophiles can potentially lead to the synthesis the α-hydroxy-β-amino acids. Similarly, epoxide opening with carbon nucleophiles can lead to α-hydroxy-β,β-dialkylated acids, whereas the use of cyanide as a nucleophile may provide access to α-hydroxy-β-alkyl-γ-amino acids. A synthesis of stereoselectively functionalized tetrahydrofurans, analogous to the pyrrolidine synthesis studies, can also be examined.

2) The development of an alternative to 1*R*,2*S* ephedrine:

Understanding the origin of stereoselectivity in the ephedrine-derived morpholine-dione system may help in the development of a recoverable amino alcohol replacement for ephedrine. Diphenylalaninol has shown some promise and further investigations on related amino alcohols, such as di-*p*-methoxyphenylalaninol, would be interesting.

Appendix 6:

X-ray crystallographic data for compound **40**
(Chapter 3)

X-ray crystallographic data for epoxide 40.

Sample: VA-II-95

X-ray Structure Report

for
Dr. Sunil V. Pansare

Prepared by
Julie L. Collins

August 4, 2006

Introduction

Collection, solution and refinement all proceeded normally. Hydrogen atoms were included in calculated or difference map positions with isotropic parameters set twenty percent greater than those of their bonding partners.

Experimental

Data Collection

A colorless prism crystal of $C_{14}H_{17}NO_3$ having approximate dimensions of 0.20 x 0.15 x 0.10 mm was mounted on a glass fiber. All measurements were made on a Rigaku Saturn CCD area detector with graphite monochromated Mo-Kα radiation.

Indexing was performed from 165 images that were exposed for 50 seconds. The crystal-to-detector distance was 35.01 mm.

Cell constants and an orientation matrix for data collection corresponded to a primitive orthorhombic cell with dimensions:

a = 8.6454(12) Å
b = 10.7876(17) Å
c = 13.704(2) Å
V = 1278.1(3) $Å^3$

For Z = 4 and F.W. = 247.29, the calculated density is 1.285 g/cm^3. The systematic absences of:

h00: h ± 2n
0k0: k ± 2n
00l: l ± 2n

uniquely determine the space group to be:

$P2_12_12_1$ (#19)

The data were collected at a temperature of -120 ± 1°C to a maximum 2θ value of 61.7°. A total of 285 oscillation images were collected. A sweep of data was done using ω scans from -50.0 to 70.0° in 1.0° step, at χ = 0.0° and ϕ = 0.0°. The exposure rate was 50.0 [sec./°]. The detector swing angle was 10.08°. A second sweep was performed using ω scans from -80.0 to 85.0° in 1.0° step, at χ=45.0° and ϕ = 90.0°. The exposure rate was 50.0 [sec./°]. The detector swing angle was 10.08°. The crystal-to-detector distance was 35.01 mm. Readout was performed in the 0.137 mm pixel mode.

Data Reduction

Of the 11571 reflections that were collected, 2916 were unique (R_{int} = 0.032); equivalent reflections were merged. Data were collected and processed using CrystalClear (Rigaku). Net intensities and sigmas were derived as follows:

$$F^2 = [\Sigma(P_i - mB_{ave})] \cdot Lp^{-1}$$

where P_i is the value in counts of the i^{th} pixel
m is the number of pixels in the integration area
B_{ave} is the background average
Lp is the Lorentz and polarization factor

$$B_{ave} = \Sigma(B_j)/n$$

where n is the number of pixels in the background area
B_j is the value of the j^{th} pixel in counts

$$\sigma^2(F^2_{hkl}) = [(\Sigma P_i) + m((\Sigma(B_{ave} - B_j)^2)/(n-1))] \cdot Lp \cdot errmul + (erradd \cdot F^2)^2$$

where erradd = 0.00
errmul = 1.00

The linear absorption coefficient, μ, for Mo-Kα radiation is 0.902 cm^{-1}. The data were corrected for Lorentz and polarization effects. A numerical absorption correction was applied which resulted in transmission factors ranging from 0.9688 to 0.9791. A correction for secondary extinction[2] was applied (coefficient = 0.013370).

Structure Solution and Refinement

The structure was solved by direct methods[3] and expanded using Fourier techniques[4]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement[5] on F^2 was based on 2916 observed reflections and 165 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R1 = \Sigma \, ||Fo| - |Fc|| \, / \, \Sigma \, |Fo| = 0.0446$$

$$wR2 = [\, \Sigma \, (\, w \, (Fo^2 - Fc^2)^2 \,) / \, \Sigma \, w(Fo^2)^2]^{1/2} = 0.1103$$

The standard deviation of an observation of unit weight[6] was 1.07. Unit weights were used. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.14 and -0.17 $e^-/Å^3$, respectively. The absolute structure was deduced based on Flack parameter -0.1(12), refined using Friedel pair 1234.[7]

Neutral atom scattering factors were taken from Cromer and Waber[8]. Anomalous dispersion effects were included in Fcalc[9]; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley[10]. The values for the mass attenuation coefficients are those of Creagh and Hubbell[11]. All calculations were performed using the CrystalStructure[12,13] crystallographic software package except for refinement, which was performed using SHELXL-97[14].

References

(1) CrystalClear: Rigaku Corporation, 1999. CrystalClear Software User's Guide, Molecular Structure Corporation, (c) 2000.J.W.Pflugrath (1999) Acta Cryst. D55, 1718-1725.

(2) Larson, A.C. (1970), Crystallographic Computing, 291-294. F.R. Ahmed, ed. Munksgaard, Copenhagen (equation 22, with V replaced by the cell volume).

(3) SIR92: Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M., Polidori, G., and Camalli, M. (1994) J. Appl. Cryst., 27, 435.

(4) DIRDIF99: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M.(1999). The DIRDIF-99 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(5) Least Squares function minimized: (SHELXL97)

$\Sigma w(F_o^2-F_c^2)^2$ where w = Least Squares weights.

(6) Standard deviation of an observation of unit weight:

$[\Sigma w(F_o^2-F_c^2)^2/(N_o-N_v)]^{1/2}$

where: N_o = number of observations
N_v = number of variables

(7) Flack, H. D. (1983), Acta Cryst. A39, 876-881.

(8) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(9) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(10) Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(11) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(12) CrystalStructure 3.7.0: Crystal Structure Analysis Package, Rigaku and Rigaku/MSC (2000-2005). 9009 New Trails Dr. The Woodlands TX 77381 USA.

(13) CRYSTALS Issue 10: Watkin, D.J., Prout, C.K. Carruthers, J.R. & Betteridge, P.W. Chemical Crystallography Laboratory, Oxford, UK. (1996)

(14) SHELX97: Sheldrick, G.M. (1997).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{14}H_{17}NO_3$
Formula Weight	247.29
Crystal Color, Habit	colorless, prism
Crystal Dimensions	0.20 X 0.15 X 0.10 mm
Crystal System	orthorhombic
Lattice Type	Primitive
Indexing Images	165 images @ 50.0 seconds
Detector Position	35.01 mm
Pixel Size	0.137 mm
Lattice Parameters	a = 8.6454(12) Å b = 10.7876(17) Å c = 13.704(2) Å V = 1278.1(3) Å^3
Space Group	$P2_12_12_1$ (#19)
Z value	4
D_{calc}	1.285 g/cm^3
F_{000}	528.00
μ(MoKα)	0.902 cm^{-1}

B. Intensity Measurements

Detector	Rigaku Saturn
Goniometer	Rigaku AFC8
Radiation	MoKα (λ = 0.71070 Å) graphite monochromated
Detector Aperture	70 mm x 70 mm
Data Images	285 exposures
ω oscillation Range (χ=0.0, ϕ=0.0)	-50.0 - 70.0°
Exposure Rate	50.0 sec./°
Detector Swing Angle	10.08°
ω oscillation Range (χ=45.0, □=90.0)	-80.0 - 85.0°
Exposure Rate	50.0 sec./°
Detector Swing Angle	10.08°
Detector Position	35.01 mm
Pixel Size	0.137 mm
$2\theta_{max}$	61.7°
No. of Reflections Measured	Total: 11571 Unique: 2916 (R_{int} = 0.032)
Corrections	Lorentz-polarization Absorption (trans. factors: 0.9688 – 0.9791) Secondary Extinction (coefficient: 1.33700e-002)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares on F^2
Function Minimized	$\Sigma\ w\ (Fo^2 - Fc^2)^2$
Least Squares Weights	$w = 1/[\ \sigma^2(Fo^2) + (0.0521 \cdot P)^2 + 0.2055 \cdot P\ ]$ where $P = (Max(Fo^2,0) + 2Fc^2)/3$
$2\theta_{max}$ cutoff	55.0^o
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (All reflections)	2916
No. Variables	165
Reflection/Parameter Ratio	17.67
Residuals: R1 ($I>2.00\sigma(I)$)	0.0446
Residuals: R (All reflections)	0.0496
Residuals: wR2 (All reflections)	0.1103
Goodness of Fit Indicator	1.072
Flack Parameter (Friedel pairs = 1234)	-0.1(12)
Max Shift/Error in Final Cycle	0.000
Maximum peak in Final Diff. Map	0.14 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.17 $e^-/Å^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
O(1)	-0.04806(16)	0.29510(12)	0.49274(9)	3.49(2)
O(2)	0.07376(18)	0.11116(12)	0.36193(11)	3.92(3)
O(3)	0.05358(13)	0.44230(11)	0.38061(9)	2.72(2)
N(1)	0.2450(2)	0.25828(12)	0.31235(11)	3.01(2)
C(1)	-0.2701(2)	0.4001(2)	0.40667(14)	3.52(3)
C(2)	-0.1546(2)	0.29754(19)	0.40991(13)	3.27(3)
C(3)	0.0103(2)	0.32095(17)	0.39673(12)	2.83(3)
C(4)	0.1139(2)	0.22086(17)	0.35573(12)	3.05(3)
C(5)	0.3466(2)	0.1652(2)	0.26909(18)	4.43(4)
C(6)	0.2967(2)	0.38778(16)	0.30894(12)	2.76(3)
C(7)	0.2701(2)	0.44345(18)	0.20792(12)	3.25(3)
C(8)	0.21860(19)	0.45775(16)	0.39176(12)	2.52(2)
C(9)	0.2533(2)	0.59407(16)	0.39483(12)	2.62(2)
C(10)	0.3767(2)	0.63576(19)	0.45148(13)	3.30(3)
C(11)	0.4095(2)	0.7618(2)	0.45561(14)	4.03(4)
C(12)	0.3203(2)	0.84583(18)	0.40505(14)	3.90(4)
C(13)	0.1979(2)	0.80583(17)	0.34906(14)	3.47(3)
C(14)	0.1649(2)	0.67922(17)	0.34322(13)	3.07(3)

$B_{eq} = 8/3\ \pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha)$

Table 2. Atomic coordinates and B_{iso} involving hydrogens/B_{eq}

atom	x	y	z	B_{eq}
H(1)	-0.3644	0.3744	0.4409	4.22
H(2)	-0.2950	0.4194	0.3386	4.22
H(3)	-0.2269	0.4738	0.4384	4.22
H(4)	-0.1923	0.2149	0.3869	3.92
H(5)	0.4214	0.1369	0.3180	5.32
H(6)	0.4018	0.2015	0.2136	5.32
H(7)	0.2847	0.0946	0.2467	5.32
H(8)	0.4106	0.3886	0.3216	3.31
H(9)	0.2965	0.3821	0.1579	3.89
H(10)	0.3355	0.5169	0.1999	3.89
H(11)	0.1612	0.4671	0.2011	3.89
H(12)	0.2509	0.4198	0.4551	3.03
H(13)	0.4380	0.5784	0.4871	3.96
H(14)	0.4942	0.7902	0.4937	4.84
H(15)	0.3434	0.9318	0.4088	4.68
H(16)	0.1362	0.8640	0.3146	4.16
H(17)	0.0815	0.6513	0.3038	3.68

$$B_{eq} = 8/3\ \pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha)$$

Table 3. Anisotropic displacement parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(1)	0.0486(7)	0.0498(8)	0.0343(6)	-0.0034(6)	-0.0026(5)	0.0104(5)
O(2)	0.0585(8)	0.0290(6)	0.0614(9)	-0.0015(6)	-0.0151(7)	0.0022(5)
O(3)	0.0311(5)	0.0292(6)	0.0429(6)	-0.0003(5)	0.0002(5)	0.0028(4)
N(1)	0.0460(8)	0.0292(7)	0.0394(7)	0.0064(6)	-0.0009(7)	-0.0040(5)
C(1)	0.0387(9)	0.0528(11)	0.0422(9)	-0.0026(9)	0.0030(8)	0.0097(9)
C(2)	0.0412(9)	0.0427(10)	0.0401(9)	-0.0069(8)	-0.0047(8)	0.0092(8)
C(3)	0.0406(9)	0.0336(9)	0.0335(8)	-0.0039(7)	-0.0050(7)	0.0045(7)
C(4)	0.0461(10)	0.0314(8)	0.0381(9)	0.0003(8)	-0.0139(7)	-0.0003(7)
C(5)	0.0677(14)	0.0388(10)	0.0620(13)	0.0141(10)	0.0064(11)	-0.0114(10)
C(6)	0.0337(8)	0.0317(8)	0.0395(9)	0.0018(7)	-0.0020(7)	-0.0040(7)
C(7)	0.0475(10)	0.0396(9)	0.0363(9)	0.0019(8)	0.0027(8)	-0.0010(7)
C(8)	0.0317(8)	0.0311(8)	0.0331(8)	0.0007(6)	-0.0047(7)	0.0004(6)
C(9)	0.0366(8)	0.0331(8)	0.0299(8)	-0.0017(7)	0.0031(7)	-0.0022(6)
C(10)	0.0453(10)	0.0438(10)	0.0362(9)	-0.0053(8)	-0.0050(8)	0.0001(7)
C(11)	0.0635(13)	0.0504(12)	0.0391(10)	-0.0198(10)	-0.0071(9)	-0.0053(8)
C(12)	0.0753(14)	0.0324(9)	0.0404(10)	-0.0123(9)	0.0089(10)	-0.0035(7)
C(13)	0.0559(11)	0.0327(9)	0.0431(9)	0.0019(8)	0.0063(8)	0.0025(8)
C(14)	0.0417(9)	0.0337(9)	0.0412(9)	0.0018(7)	-0.0002(8)	0.0008(7)

The general temperature factor expression: $\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$

Table 4. Bond lengths (Å)

atom	atom	distance	atom	atom	distance
O(1)	C(2)	1.462(2)	O(1)	C(3)	1.436(2)
O(2)	C(4)	1.236(2)	O(3)	C(3)	1.379(2)
O(3)	C(8)	1.444(2)	N(1)	C(4)	1.342(2)
N(1)	C(5)	1.460(2)	N(1)	C(6)	1.467(2)
C(1)	C(2)	1.491(2)	C(2)	C(3)	1.459(2)
C(3)	C(4)	1.511(2)	C(6)	C(7)	1.526(2)
C(6)	C(8)	1.521(2)	C(8)	C(9)	1.501(2)
C(9)	C(10)	1.394(2)	C(9)	C(14)	1.389(2)
C(10)	C(11)	1.390(2)	C(11)	C(12)	1.377(3)
C(12)	C(13)	1.377(3)	C(13)	C(14)	1.398(2)

Table 5. Bond lengths involving hydrogens (Å)

atom	atom	distance	atom	atom	distance
C(1)	H(1)	0.980	C(1)	H(2)	0.980
C(1)	H(3)	0.980	C(2)	H(4)	1.000
C(5)	H(5)	0.980	C(5)	H(6)	0.980
C(5)	H(7)	0.980	C(6)	H(8)	1.000
C(7)	H(9)	0.980	C(7)	H(10)	0.980
C(7)	H(11)	0.980	C(8)	H(12)	1.000
C(10)	H(13)	0.950	C(11)	H(14)	0.950
C(12)	H(15)	0.950	C(13)	H(16)	0.950
C(14)	H(17)	0.950			

Table 6. Bond angles (°)

atom	atom	atom	angle	atom	atom	atom	angle
C(2)	O(1)	C(3)	60.43(11)	C(3)	O(3)	C(8)	111.15(12)
C(4)	N(1)	C(5)	118.74(15)	C(4)	N(1)	C(6)	123.88(15)
C(5)	N(1)	C(6)	117.34(16)	O(1)	C(2)	C(1)	117.29(16)
O(1)	C(2)	C(3)	58.91(11)	C(1)	C(2)	C(3)	121.49(17)
O(1)	C(3)	O(3)	115.23(14)	O(1)	C(3)	C(2)	60.66(11)
O(1)	C(3)	C(4)	114.20(14)	O(3)	C(3)	C(2)	116.71(15)
O(3)	C(3)	C(4)	117.23(15)	C(2)	C(3)	C(4)	120.10(16)
O(2)	C(4)	N(1)	123.73(17)	O(2)	C(4)	C(3)	119.49(17)
N(1)	C(4)	C(3)	116.77(15)	N(1)	C(6)	C(7)	110.96(14)
N(1)	C(6)	C(8)	108.28(14)	C(7)	C(6)	C(8)	114.50(14)
O(3)	C(8)	C(6)	107.58(13)	O(3)	C(8)	C(9)	108.27(13)
C(6)	C(8)	C(9)	114.72(14)	C(8)	C(9)	C(10)	118.99(15)
C(8)	C(9)	C(14)	121.56(15)	C(10)	C(9)	C(14)	119.45(16)
C(9)	C(10)	C(11)	119.64(18)	C(10)	C(11)	C(12)	120.6(2)
C(11)	C(12)	C(13)	120.31(18)	C(12)	C(13)	C(14)	119.70(18)
C(9)	C(14)	C(13)	120.30(17)				

Table 7. Bond angles involving hydrogens (°)

atom	atom	atom	angle	atom	atom	atom	angle
C(2)	C(1)	H(1)	109.5	C(2)	C(1)	H(2)	109.5
C(2)	C(1)	H(3)	109.5	H(1)	C(1)	H(2)	109.5
H(1)	C(1)	H(3)	109.5	H(2)	C(1)	H(3)	109.5
O(1)	C(2)	H(4)	115.7	C(1)	C(2)	H(4)	115.7
C(3)	C(2)	H(4)	115.7	N(1)	C(5)	H(5)	109.5
N(1)	C(5)	H(6)	109.5	N(1)	C(5)	H(7)	109.5
H(5)	C(5)	H(6)	109.5	H(5)	C(5)	H(7)	109.5
H(6)	C(5)	H(7)	109.5	N(1)	C(6)	H(8)	107.6
C(7)	C(6)	H(8)	107.6	C(8)	C(6)	H(8)	107.6
C(6)	C(7)	H(9)	109.5	C(6)	C(7)	H(10)	109.5
C(6)	C(7)	H(11)	109.5	H(9)	C(7)	H(10)	109.5
H(9)	C(7)	H(11)	109.5	H(10)	C(7)	H(11)	109.5
O(3)	C(8)	H(12)	108.7	C(6)	C(8)	H(12)	108.7
C(9)	C(8)	H(12)	108.7	C(9)	C(10)	H(13)	120.2
C(11)	C(10)	H(13)	120.2	C(10)	C(11)	H(14)	119.7
C(12)	C(11)	H(14)	119.7	C(11)	C(12)	H(15)	119.8
C(13)	C(12)	H(15)	119.8	C(12)	C(13)	H(16)	120.1
C(14)	C(13)	H(16)	120.2	C(9)	C(14)	H(17)	119.9
C(13)	C(14)	H(17)	119.8				

Table 8. Torsion Angles(°)

atom1	atom2	atom3	atom4	angle	atom1	atom2	atom3	atom4	angle
C(2)	O(1)	C(3)	O(3)	107.77(17)	C(2)	O(1)	C(3)	C(4)	-112.22(18)
C(3)	O(1)	C(2)	C(1)	-112.05(19)	C(3)	O(3)	C(8)	C(6)	67.52(16)
C(3)	O(3)	C(8)	C(9)	-167.97(13)	C(8)	O(3)	C(3)	O(1)	98.07(16)
C(8)	O(3)	C(3)	C(2)	166.40(15)	C(8)	O(3)	C(3)	C(4)	-40.70(19)
C(5)	N(1)	C(4)	O(2)	0.5(2)	C(5)	N(1)	C(4)	C(3)	-178.21(17)
C(4)	N(1)	C(6)	C(7)	-104.45(19)	C(4)	N(1)	C(6)	C(8)	22.0(2)
C(6)	N(1)	C(4)	O(2)	-176.96(17)	C(6)	N(1)	C(4)	C(3)	4.4(2)
C(5)	N(1)	C(6)	C(7)	78.1(2)	C(5)	N(1)	C(6)	C(8)	-155.46(16)
O(1)	C(2)	C(3)	O(3)	-105.34(16)	O(1)	C(2)	C(3)	C(4)	102.57(17)
C(1)	C(2)	C(3)	O(1)	104.98(19)	C(1)	C(2)	C(3)	O(3)	-0.4(2)
C(1)	C(2)	C(3)	C(4)	-152.44(17)	O(1)	C(3)	C(4)	O(2)	46.3(2)
O(1)	C(3)	C(4)	N(1)	-135.00(16)	O(3)	C(3)	C(4)	O(2)	-174.57(16)
O(3)	C(3)	C(4)	N(1)	4.2(2)	C(2)	C(3)	C(4)	O(2)	-22.6(2)
C(2)	C(3)	C(4)	N(1)	156.12(17)	N(1)	C(6)	C(8)	O(3)	-56.34(17)
N(1)	C(6)	C(8)	C(9)	-176.86(14)	C(7)	C(6)	C(8)	O(3)	68.04(18)
C(7)	C(6)	C(8)	C(9)	-52.5(2)	O(3)	C(8)	C(9)	C(10)	147.44(16)
O(3)	C(8)	C(9)	C(14)	-32.1(2)	C(6)	C(8)	C(9)	C(10)	-92.42(19)
C(6)	C(8)	C(9)	C(14)	88.0(2)	C(8)	C(9)	C(10)	C(11)	-179.52(17)
C(8)	C(9)	C(14)	C(13)	178.67(17)	C(10)	C(9)	C(14)	C(13)	-0.9(2)
C(14)	C(9)	C(10)	C(11)	0.0(2)	C(9)	C(10)	C(11)	C(12)	0.7(3)
C(10)	C(11)	C(12)	C(13)	-0.5(3)	C(11)	C(12)	C(13)	C(14)	-0.4(3)
C(12)	C(13)	C(14)	C(9)	1.0(3)					

The sign is positive if when looking from atom 2 to atom 3 a clock-wise motion of atom 1 would superimpose it on atom 4.

Table 9. Distances beyond the asymmetric unit out to 3.60 Å

atom	atom	distance	atom	atom	distance
O(1)	N(1)[1)]	3.266(2)	O(1)	C(1)[2)]	3.479(2)
O(1)	C(4)[1)]	3.590(2)	O(1)	C(5)[1)]	3.416(2)
O(2)	C(1)[2)]	3.449(2)	O(2)	C(13)[3)]	3.469(2)
O(2)	C(14)[4)]	3.564(2)	N(1)	O(1)[2)]	3.266(2)
C(1)	O(1)[1)]	3.479(2)	C(1)	O(2)[1)]	3.449(2)
C(2)	C(13)[4)]	3.570(2)	C(4)	O(1)[2)]	3.590(2)
C(5)	O(1)[2)]	3.416(2)	C(11)	C(14)[5)]	3.589(2)
C(13)	O(2)[6)]	3.469(2)	C(13)	C(2)[7)]	3.570(2)
C(14)	O(2)[7)]	3.564(2)	C(14)	C(11)[8)]	3.589(2)

Symmetry Operators:

(1) X+1/2-1,-Y+1/2,-Z+1
(2) X+1/2,-Y+1/2,-Z+1
(3) X,Y-1,Z
(4) -X,Y+1/2-1,-Z+1/2
(5) X+1/2,-Y+1/2+1,-Z+1
(6) X,Y+1,Z
(7) -X,Y+1/2,-Z+1/2
(8) X+1/2-1,-Y+1/2+1,-Z+1

Table 10. Distances beyond the asymmetric unit out to 3.60 Å involving hydrogens

atom	atom	distance	atom	atom	distance
O(1)	H(1)[1)]	2.587	O(1)	H(4)[1)]	3.492
O(1)	H(5)[2)]	2.708	O(1)	H(8)[2)]	3.244
O(1)	H(12)[2)]	2.984	O(1)	H(15)[3)]	3.374
O(2)	H(1)[1)]	2.758	O(2)	H(3)[1)]	3.361
O(2)	H(11)[4)]	2.699	O(2)	H(13)[2)]	3.137
O(2)	H(15)[5)]	3.097	O(2)	H(16)[5)]	2.797
O(2)	H(17)[4)]	2.673	O(3)	H(14)[3)]	3.400
O(3)	H(16)[4)]	3.249	N(1)	H(17)[4)]	3.440
C(1)	H(7)[6)]	2.972	C(1)	H(8)[7)]	2.999
C(1)	H(13)[7)]	3.359	C(1)	H(15)[3)]	3.263
C(1)	H(16)[4)]	3.268	C(2)	H(12)[2)]	3.096
C(2)	H(16)[4)]	3.163	C(2)	H(17)[4)]	3.386
C(3)	H(1)[1)]	3.251	C(3)	H(16)[4)]	3.194
C(3)	H(17)[4)]	3.395	C(4)	H(1)[1)]	2.976
C(4)	H(16)[4)]	3.536	C(4)	H(17)[4)]	2.863
C(5)	H(2)[4)]	3.067	C(5)	H(10)[8)]	3.208
C(5)	H(15)[5)]	3.163	C(6)	H(1)[9)]	3.447
C(6)	H(2)[9)]	3.570	C(7)	H(4)[6)]	3.274
C(7)	H(5)[10)]	3.405	C(7)	H(13)[11)]	3.529
C(9)	H(6)[10)]	3.527	C(9)	H(14)[3)]	2.985
C(10)	H(6)[10)]	3.047	C(10)	H(9)[12)]	3.207
C(10)	H(14)[3)]	3.484	C(11)	H(3)[13)]	3.412
C(11)	H(6)[10)]	2.909	C(11)	H(9)[10)]	3.250
C(12)	H(2)[6)]	3.439	C(12)	H(3)[13)]	2.926
C(12)	H(5)[14)]	3.471	C(12)	H(6)[10)]	3.292
C(12)	H(7)[14)]	3.465	C(12)	H(9)[10)]	3.445
C(12)	H(14)[3)]	3.468	C(13)	H(2)[6)]	2.970
C(13)	H(4)[6)]	3.380	C(13)	H(7)[14)]	3.498
C(13)	H(13)[3)]	3.414	C(13)	H(14)[3)]	2.970
C(14)	H(4)[6)]	3.186	C(14)	H(14)[3)]	2.698
H(1)	O(1)[2)]	2.587	H(1)	O(2)[2)]	2.758
H(1)	C(3)[2)]	3.251	H(1)	C(4)[2)]	2.976
H(1)	C(6)[7)]	3.447	H(1)	H(5)[7)]	3.583
H(1)	H(7)[6)]	3.567	H(1)	H(8)[7)]	2.546
H(1)	H(12)[7)]	3.367	H(1)	H(13)[7)]	2.856
H(1)	H(15)[3)]	3.440	H(2)	C(5)[6)]	3.067
H(2)	C(6)[7)]	3.570	H(2)	C(12)[4)]	3.439

Table 10. Distances beyond the asymmetric unit out to 3.60 Å involving hydrogens (continued)

atom	atom	distance	atom	atom	distance
H(2)	C(13)$^{4)}$	2.970	H(2)	H(5)$^{6)}$	3.362
H(2)	H(6)$^{6)}$	3.260	H(2)	H(7)$^{6)}$	2.224
H(2)	H(8)$^{7)}$	2.577	H(2)	H(13)$^{7)}$	3.523
H(2)	H(15)$^{4)}$	3.419	H(2)	H(16)$^{4)}$	2.578
H(3)	O(2)$^{2)}$	3.361	H(3)	C(11)$^{3)}$	3.412
H(3)	C(12)$^{3)}$	2.926	H(3)	H(6)$^{6)}$	3.558
H(3)	H(7)$^{6)}$	2.895	H(3)	H(13)$^{7)}$	3.180
H(3)	H(14)$^{3)}$	3.317	H(3)	H(15)$^{3)}$	2.407
H(4)	O(1)$^{2)}$	3.492	H(4)	C(7)$^{4)}$	3.274
H(4)	C(13)$^{4)}$	3.380	H(4)	C(14)$^{4)}$	3.186
H(4)	H(5)$^{7)}$	3.571	H(4)	H(10)$^{4)}$	2.740
H(4)	H(11)$^{4)}$	2.945	H(4)	H(12)$^{2)}$	2.653
H(4)	H(16)$^{4)}$	3.232	H(4)	H(17)$^{4)}$	2.867
H(5)	O(1)$^{1)}$	2.708	H(5)	C(7)$^{8)}$	3.405
H(5)	C(12)$^{5)}$	3.471	H(5)	H(1)$^{9)}$	3.583
H(5)	H(2)$^{4)}$	3.362	H(5)	H(4)$^{9)}$	3.571
H(5)	H(8)$^{8)}$	3.598	H(5)	H(10)$^{8)}$	2.480
H(5)	H(15)$^{5)}$	2.627	H(6)	C(9)$^{8)}$	3.527
H(6)	C(10)$^{8)}$	3.047	H(6)	C(11)$^{8)}$	2.909
H(6)	C(12)$^{8)}$	3.292	H(6)	H(2)$^{4)}$	3.260
H(6)	H(3)$^{4)}$	3.558	H(6)	H(10)$^{8)}$	3.244
H(6)	H(13)$^{8)}$	3.353	H(6)	H(14)$^{8)}$	3.129
H(7)	C(1)$^{4)}$	2.972	H(7)	C(12)$^{5)}$	3.465
H(7)	C(13)$^{5)}$	3.498	H(7)	H(1)$^{4)}$	3.567
H(7)	H(2)$^{4)}$	2.224	H(7)	H(3)$^{4)}$	2.895
H(7)	H(8)$^{8)}$	3.572	H(7)	H(10)$^{8)}$	3.467
H(7)	H(15)$^{5)}$	2.878	H(7)	H(16)$^{5)}$	2.950
H(7)	H(17)$^{4)}$	3.297	H(8)	O(1)$^{1)}$	3.244
H(8)	C(1)$^{9)}$	2.999	H(8)	H(1)$^{9)}$	2.546
H(8)	H(2)$^{9)}$	2.577	H(8)	H(5)$^{10)}$	3.598
H(8)	H(7)$^{10)}$	3.572	H(9)	C(10)$^{11)}$	3.207
H(9)	C(11)$^{8)}$	3.250	H(9)	C(12)$^{8)}$	3.445
H(9)	H(12)$^{11)}$	3.530	H(9)	H(13)$^{11)}$	3.126
H(9)	H(14)$^{8)}$	2.927	H(9)	H(15)$^{8)}$	3.289
H(10)	C(5)$^{10)}$	3.208	H(10)	H(4)$^{6)}$	2.740
H(10)	H(5)$^{10)}$	2.480	H(10)	H(6)$^{10)}$	3.244
H(10)	H(7)$^{10)}$	3.467	H(10)	H(12)$^{11)}$	3.503

Table 10. Distances beyond the asymmetric unit out to 3.60 Å involving hydrogens (continued)

atom	atom	distance	atom	atom	distance
H(10)	H(15)[8)]	3.282	H(11)	O(2)[6)]	2.699
H(11)	H(4)[6)]	2.945	H(11)	H(13)[11)]	3.095
H(11)	H(16)[4)]	2.809	H(12)	O(1)[1)]	2.984
H(12)	C(2)[1)]	3.096	H(12)	H(1)[9)]	3.367
H(12)	H(4)[1)]	2.653	H(12)	H(9)[12)]	3.530
H(12)	H(10)[12)]	3.503	H(13)	O(2)[1)]	3.137
H(13)	C(1)[9)]	3.359	H(13)	C(7)[12)]	3.529
H(13)	C(13)[13)]	3.414	H(13)	H(1)[9)]	2.856
H(13)	H(2)[9)]	3.523	H(13)	H(3)[9)]	3.180
H(13)	H(6)[10)]	3.353	H(13)	H(9)[12)]	3.126
H(13)	H(11)[12)]	3.095	H(13)	H(16)[13)]	3.273
H(14)	O(3)[13)]	3.400	H(14)	C(9)[13)]	2.985
H(14)	C(10)[13)]	3.484	H(14)	C(12)[13)]	3.468
H(14)	C(13)[13)]	2.970	H(14)	C(14)[13)]	2.698
H(14)	H(3)[13)]	3.317	H(14)	H(6)[10)]	3.129
H(14)	H(9)[10)]	2.927	H(14)	H(16)[13)]	3.344
H(14)	H(17)[13)]	2.945	H(15)	O(1)[13)]	3.374
H(15)	O(2)[14)]	3.097	H(15)	C(1)[13)]	3.263
H(15)	C(5)[14)]	3.163	H(15)	H(1)[13)]	3.440
H(15)	H(2)[6)]	3.419	H(15)	H(3)[13)]	2.407
H(15)	H(5)[14)]	2.627	H(15)	H(7)[14)]	2.878
H(15)	H(9)[10)]	3.289	H(15)	H(10)[10)]	3.282
H(16)	O(2)[14)]	2.797	H(16)	O(3)[6)]	3.249
H(16)	C(1)[6)]	3.268	H(16)	C(2)[6)]	3.163
H(16)	C(3)[6)]	3.194	H(16)	C(4)[6)]	3.536
H(16)	H(2)[6)]	2.578	H(16)	H(4)[6)]	3.232
H(16)	H(7)[14)]	2.950	H(16)	H(11)[6)]	2.809
H(16)	H(13)[3)]	3.273	H(16)	H(14)[3)]	3.344
H(17)	O(2)[6)]	2.673	H(17)	N(1)[6)]	3.440
H(17)	C(2)[6)]	3.386	H(17)	C(3)[6)]	3.395
H(17)	C(4)[6)]	2.863	H(17)	H(4)[6)]	2.867
H(17)	H(7)[6)]	3.297	H(17)	H(14)[3)]	2.945

Symmetry Operators:

(1) X+1/2,-Y+1/2,-Z+1
(2) X+1/2-1,-Y+1/2,-Z+1
(3) X+1/2-1,-Y+1/2+1,-Z+1
(4) -X,Y+1/2-1,-Z+1/2
(5) X,Y-1,Z
(6) -X,Y+1/2,-Z+1/2
(7) X-1,Y,Z
(8) -X+1,Y+1/2-1,-Z+1/2
(9) X+1,Y,Z
(10) -X+1,Y+1/2,-Z+1/2

(11) -X+1/2,-Y+1,Z+1/2-1
(12) -X+1/2,-Y+1,Z+1/2
(13) X+1/2,-Y+1/2+1,-Z+1
(14) X,Y+1,Z