# A Formal Synthesis of (−)-Aphanorphine and Studies on the Synthesis of (+) Clauslactone S and Enantiomerically Enriched α-Hydroxy Acid Derivatives

by

© **Kaivalya G. Kulkarni**

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*To*

*The late Mr. L. Srikanth*

## Abstract

(−)-Aphanorphine is an alkaloid isolated from the fresh water algae *Aphanizomenon flos-aquae*. The 3-benzazepine scaffold in aphanorphine resembles the benzomorphan analgesics such as pentazocine, eptazocine and morphine. The complex 3-benzazepine scaffold and a quaternary stereocenter has made (−)-aphanorphine an interesting synthetic target. The synthesis of (−)-aphanorphine from an enantiomerically enriched α-hydroxy acid derivative is described in Chapter 1 of this thesis. This hydroxy acid is readily available from an ephedrine-derived morpholinone *via* a highly diastereoselective allylation followed by removal of the ephedrine portion. The methodology developed for the synthesis of (−)-aphanorphine is potentially useful for the synthesis of other *N*-methylpyrrolidine-based natural products and related structural motifs.

Clauslactone S is a terpenoid which was extracted from the leaves and stems of C*lausena excavate* in 2008. There has been no synthesis of clauslactone S reported to date. We envisaged that the substituted δ-lactone in clauslactone S can be synthesized using an enantiomerically enriched α-hydroxy acid derivative. Studies on the development of a modular synthetic strategy for clauslactone S and the details of the synthesis of a potential intermediate to clauslactone S are described in Chapter 2 of the thesis.

The α-hydroxy acid derivative employed as starting material in the aphanorphine and clauslctone S studies is readily obtained by a highly diastereoselective double

alkylation of an ephedrine-derived morpholinedione. However, the limitation of the methodology is that ephedrine is no longer commercially available. Hence, studies were conducted on several morpholinediones, that were derived from enantiomerically enriched amino alcohols, with the objective of finding an alternative to ephedrine. Details of these investigations are presented in Chapter 3 of this thesis.

## Acknowledgments

Foremost, I would like to express my deepest gratitude towards my supervisor Dr. Sunil V. Pansare, who accepted me as a Ph. D. student in his research group and was the main source of innovative ideas and the whole background of this thesis. He always stood with me in all the ups and downs of routine, daily work and shared the happiness of success and the depression of failure when things went wrong. He managed to teach me a great deal; whether it was in the form of laboratory techniques, scientific writing or theoretical knowledge. The particular thing about his style of work I would like to mention is the speed with which he works; whether it is writing manuscripts, preparing posters or correction of this thesis. He has been a guiding light for me over the past five years. Staying away from my home and country, he has not just taken care of my research work but also provided advice on other matters when necessary. I would always look up to him as a mentor and not just a teacher.

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I cannot forget to mention the support provided by all the family members back home; their constant encouragement helped me to pursue my research. I would like to acknowledge my father, who has had biggest contribution in my chemistry education. I had the privilege to learn organic chemistry from him during my B.Sc. and M.Sc. studies. He was the source of inspiration which led me into organic chemistry research.

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## Table of Contents


Page

Abstract..... iii

Acknowledgements..... iv

Table of Contents..... vii

List of Tables..... x

List of Figures..... xi

List of Abbreviations..... xii

Chapter 1 Page

Formal total synthesis of (–)-aphanorphine

1.1 Introduction to (–)-aphanorphine…… 2

1.2 Known synthetic routes to aphanorphine…… 3

1.2.1 Syntheses of aphanorphine using natural amino acids as starting materials……... 3

1.2.2 Synthesis of aphanorphine using substituted aromatic substrates as starting materials…… 10

1.2.3 Synthesis of (+) and (–)-aphanorphine using a chiral sulfonamide starting material…… 16

1.2.4 Synthesis of (+)-aphanorphine employing asymmetric alkene carboamination…… 20

1.3 Present Work……... 22

1.3.1 An enantioselective approach to (–)-aphanorphine employing a chiral α-hydroxyacid as the starting material……. 22

1.3.2 Experimental section…… 36

1.4 References…… 55

1.5 Selected $^{1}$H NMR and $^{13}$C NMR spectral data……. 59

Chapter 2

Studies on the synthesis of clauslactone S

2.1 Introduction to clauslactone S……. 73

2.2 Present work……. 74

2.2.1 Studies on the synthesis of clauslactone S…… 74

2.2.2 Future studies towards the synthesis of clauslactone S…… 81

2.3 Experimental section…… 83

2.4 References……. 92

2.5 Selected $^{1}$H NMR and $^{13}$C NMR spectral data……. 94

Chapter 3

Stereoselective allylation of α-ketoacid derivatives for the synthesis of α-alkyl-α-hydroxy acids


3.1 Introduction……. 103

3.1.1 Methods for the stereoselective allylation of α-ketoacid derivatives…… 103

3.1.1.1 Allylation of chiral *α*-ketoesters…… 104

3.1.1.2 Asymmetric allylation of chiral α-ketoamides…….. 107

3.1.1.3 Asymmetric allylation of 1,3-dioxolanones……... 113

3.1.1.4 Asymmetric allylation of *α*-ketoesters using chiral allylation reagents……. 118

3.1.1.5 Ireland-Claisen rearrangement of *α*-ketoesters in the synthesis of *α*-hydroxyacids…… 121

3.2 Introduction to the present work……. 125

3.2.1 Asymmetric allylation of morpholinones derived from chiral amino alcohols…… 125

3.2.2 Previous investigations of chiral aminoalcohols within the Pansare group…… 127

3.2.2.1 Studies with diphenylprolinol as a potentially recoverable aminoalcohol….. 127

3.2.2.2 Studies with non-recoverable amino alcohols……. 128

3.3 Present work…… 132

3.3.1 Investigation of potentially recoverable amino alcohol substitutes for 1*R*,2*S*-ephedrine……... 132

3.3.2 Investigation of potentially recoverable chiral amino alcohols derived from (*S*)-alanine…… 133

3.3.3 Conclusions…….. 143

3.4 Experimental section……... 142

3.5 References…… 164

3.6 Selected $^{1}$H NMR and $^{13}$C NMR spectral data…… 167

Chapter 4

Conclusions

4.1 Summary of the thesis……... 184

4.2 Future studies…… 190

4.3 References……. 192

**List of Tables**

Table 1.1 Iodolactamization studies with **94**…….. 27

Table 1.2 Amidomecuration conditions for the lactamization of **94**……..... 28

Table 2.1 Optimization of reaction conditions for the synthesis of **7**……. 78

Table 3.1 Survey of pyruvic esters for the asymmetric allylation with **88**……. 119

Table 3.2 Reaction of Grignard reagent and organozinc reagents with **102** and **103**…….. 123

Table 3.3 Attempted hydrolysis of the morpholinones **160** and **162** under acidic conditions…… 137

Table 3.4 Attempted basic hydrolysis and reduction of the amide in the morpholinone **160** and **162**……. 139

Table 3.5 Attempted basic hydrolysis of the morpholinones **161** and **162** under microwave heating…….. 140

## List of Figures

Figure 1.1 Structural similarity of (–)-aphanorphine with benzomorphan alkaloids…… 2

Figure 2.1 Structures of clauslactone S, R, T……. 72

Figure 2.2 Structural details of clauslactone S……... 73

Figure 3.1 Proposed transition state for the allylation of proline based pyruvamide…… 106

Figure 3.2 Transition state models resulting in the opposite stereochemistry……..... 109

Figure 3.3 Transition state models resulting in the opposite stereochemistry 111

Figure 4.1 Chiral aminoalcohols investigated as a substitute for ephedrine… 187

## List of abbreviations

| | |
|---|---|
| aq. | aqueous |
| AIBN | azobisisobutyronitrile |
| BEP | *N*-benzyl-*N*-[(2*S*)-3-isobutoxy-2-pyrrolidin-1-ium-1-yl-propyl]aniline |
| br | broad |
| Bn | benzyl |
| Bz | benzoyl |
| cat. | catalytic |
| Cbz | benzyloxycarbonyl |
| CI | chemical ionization |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCC | 1,3-dicyclohexylcarbodiimide |
| DCE | dichloroethane |
| de | diastereomeric excess |
| DEAD | diethyl azodicarboxylate |
| DET | diethyl tartrate |
| DIBAL | diisobutylaluminium hydride |
| DIPEA | *N*,*N*-diisopropylethylamine |
| DIPT | diisopropyltratrate |
| DMA | dimethyl amine |
| DMAP | 4-(dimethylamino)pyridine |

| | |
|---|---|
| DMF | *N*,*N*-dimethylformamide |
| DMS | dimethyl sulfide |
| DMSO | dimethyl sulfoxide |
| dr | diastereomeric ratio |
| ds | diastereoselectivity |
| EDCI | *N*-[3-(dimethylamino)propyl]-*N*'-ethylcarbodiimide |
| 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 |
| Ms | mesyl |
| NaHMDS | sodium hexamethyldisilazide |
| NBS | *N*-bromosuccinimide |
| NIS | *N*-iodosuccinimide |
| NMR | nuclear magnetic resonance |
| NOE | nuclear Overhauser enhancement |
| PCC | pyridinium chlorochromate |
| Ph | phenyl |
| PLE | pig liver esterase |
| PMB | *para*-methoxybenzyl |
| PMP | *para*-methoxyphenyl |

| | |
|---|---|
| Pr | propyl |
| PTSA | *para*-toluenesulphonic acid |
| Red-Al | Sodium bis(2-methoxyethoxy)aluminium hydride |
| ROESY | rotational Overhauser effect spectroscopy |
| rt | room temperature |
| s | second |
| *t*-Bu | tertiary butyl |
| TBAF | tetra-*N*-butylammonium fluoride |
| TBDMS | *tert*-butyldimethylsilyl |
| TBDPS | *tert*-butyldiphenylsilyl |
| TBHP | *tert*-butyl hydrogenperoxide |
| TEA | triethylamine |
| TEMPO | (2,2,6,6,-tetramethyl-piperidine-1-yl)oxyl |
| TES | triethylsilyl |
| Tf | triflate |
| TFA | trifluoroacetate |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMG | trimethylguanidine |
| TMEDA | tetramethylethylenediamine |
| TMS | tetramethylsilane |
| Ts | *p*-toluenesulphonyl |

# Chapter 1

## Formal Total Synthesis of (−)-Aphanorphine

This chapter is based on the following publication:

Pansare, S. V.; Kulkarni, K. G. *RSC Advances* **2013**, *3*, 19127.

## 1.1 Introduction to (–)-aphanorphine:

Aphanorphine (**1**) is an alkaloid isolated from a fresh water algae *Aphanizomenon flos-aquae* by Shimizu and Clardy.[1] It shares common structural features with the analgesic benzomorphan alkaloids eptazocine (**2**), pentazocine (**3**), and morphine (**4**, Figure 1). The 3-benzazepine ring system and a quaternary stereocenter has made aphanorphine an interesting synthetic target. Over the last two decades, research groups around the globe have reported the synthesis of aphanorphine. The first enantioselective synthesis of (+) and (–)-aphanorphine was reported by Takano and co-workers.[2] Some of the notable syntheses in the last decade are presented in the following discussion.

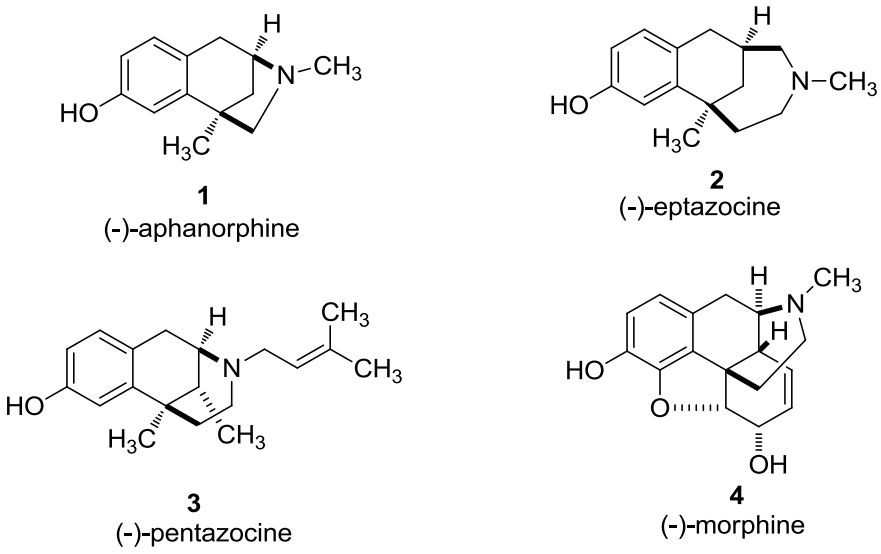
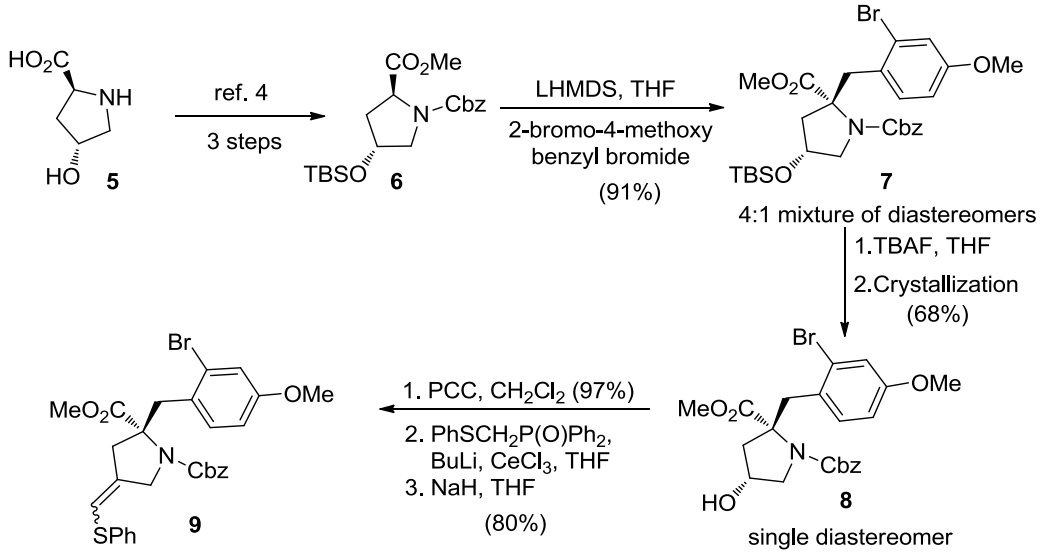



Figure 1.1 Structural similarity of (–)-aphanorphine with benzomorphan alkaloids.

## 1.2 Known synthetic routes to aphanorphine

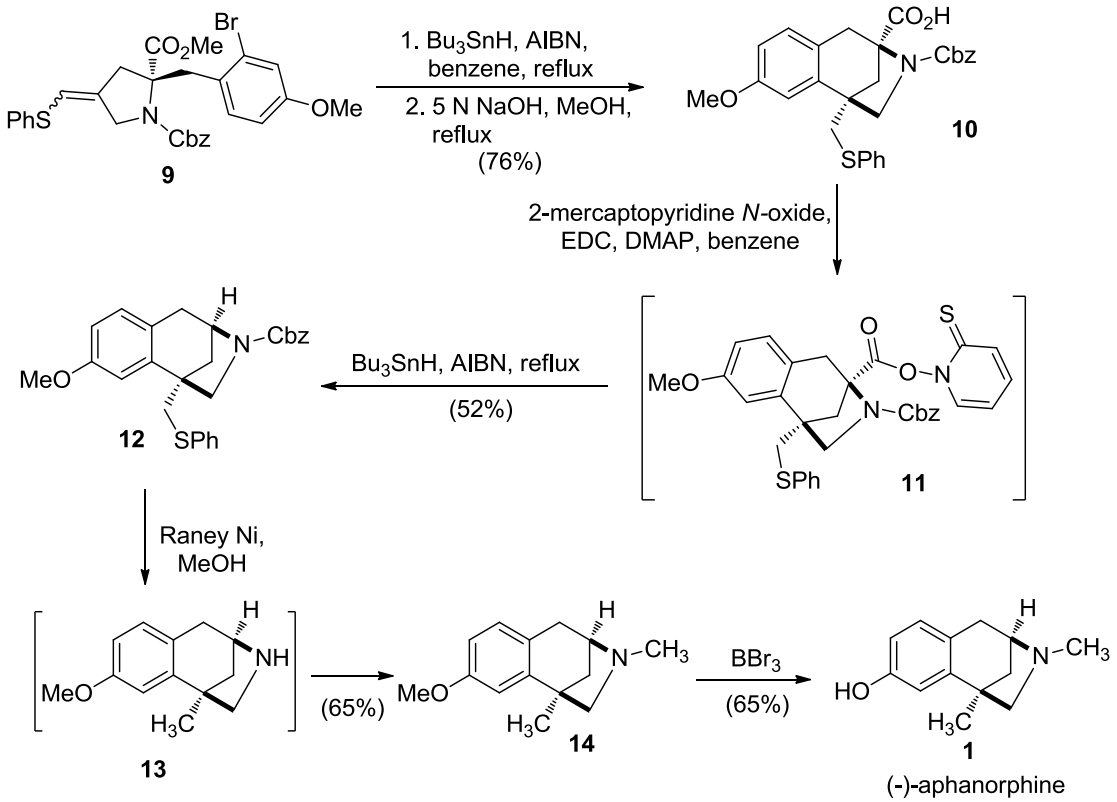
### 1.2.1 Syntheses of aphanorphine using natural amino acids as starting materials:

The Ishibashi group[3] accomplished the synthesis of (–)-aphanorphine using (2*S*,4*R*)-4-hydroxyproline (**5**) as a chiral starting material. An aryl radical cyclization was used as the key step to obtain an important precursor **10**. Acid-catalyzed esterification, amine protection with benzyl chloroformate and silylation of the hydroxyl group in **5** provided **6** as reported earlier.[4] Alkylation of the lithium enolate of **6** afforded **7** as a 4:1 mixture of diastereomers. Removal of the silyl protection in **7** followed by recrystallization of the secondary alcohol provided **8** as a single diastereomer. Oxidation of **8** using pyridinium chlorochromate, followed by a Horner-Wittig reaction of the resulting ketone with the lithium salt of $PhSCH_2P(O)Ph_2$[5] in the presence of $CeCl_3$, followed by treatment of the adduct with NaH afforded the radical precursor **9** (Scheme 1.1).



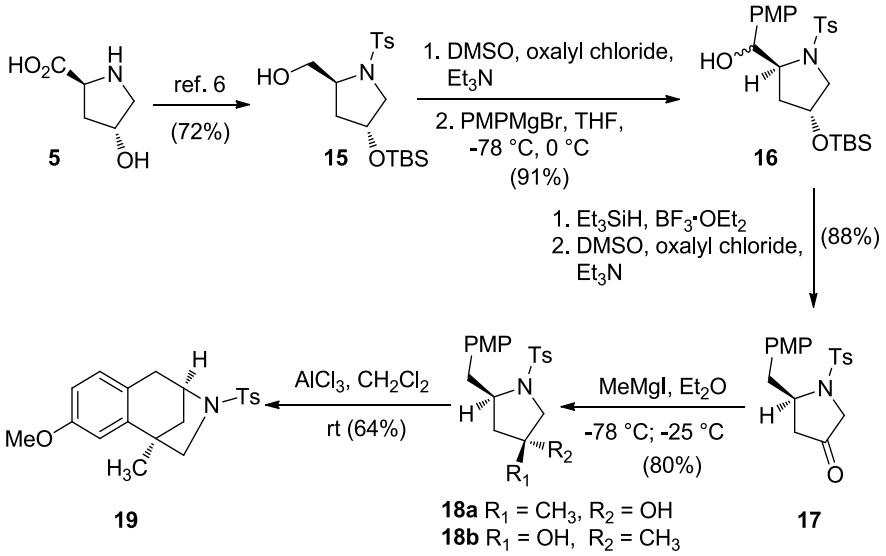

Scheme 1.1

Treatment of **9** with $Bu_3SnH$ and AIBN in refluxing benzene accomplished a 6-*exo* cyclization of the aryl radical onto the vinyl sulfide to provide a tricyclic intermediate. An alkaline hydrolysis of the ester group produced the acid **10** in quantitative yield. Condensation of **10** with 2-mercaptopyridine *N*-oxide and treatment with $Bu_3SnH$ and AIBN provided the decarboxylation product **12**. Treatment of **12** with Raney nickel in hot methanol accomplished the following three steps; desulfurization, removal of the benzyloxycarbonyl group and reductive amination to furnish the amine **14**. *O*-Demethylation in **14** (65%), using $BBr_3$, accomplished the total synthesis of (−)-aphanorphine **1** (Scheme 1.2) with 7.6% overall yield from **6**.



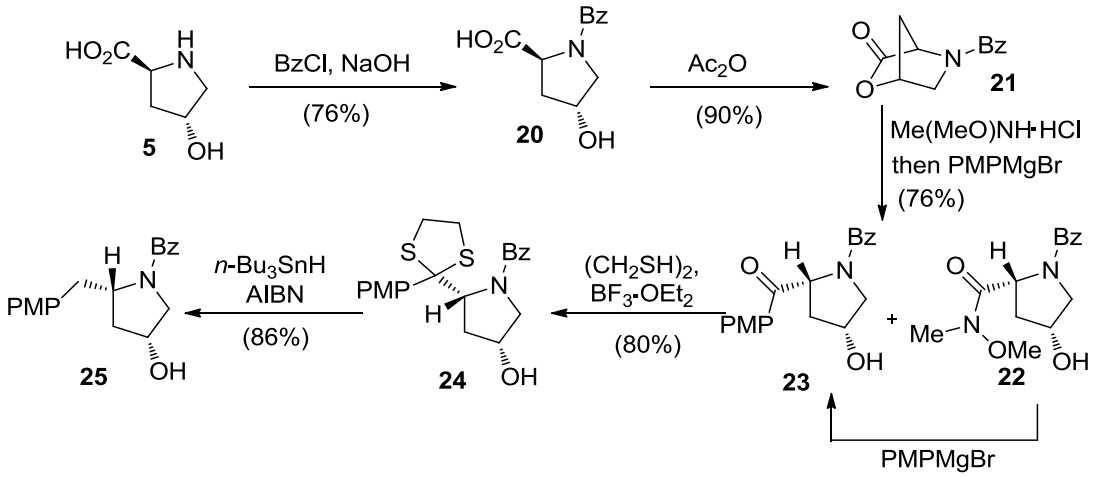

Scheme 1.2

The Zhai group reported a formal total synthesis of (−)-aphanorphine starting from (2*S*,4*R*)-4-hydroxyproline (**5**).[6] A four-step reaction sequence reported earlier by Westwood and Walker[7] was employed to afford **15** from 4-hydroxyproline (**5**) in 72% yield.[7] Swern oxidation of **15** afforded the corresponding aldehyde, which upon treatment with 4-methoxyphenylmagnesium bromide furnished **16** as a 3:2 mixture of diastereomers. Reductive dehydroxylation of **16** using triethylsilane and $BF_3{\cdot}OEt_2$ and concomitant desilylation afforded the corresponding pyrrolidinol, which was oxidized to the pyrrolidinone **17** under Swern oxidation conditions. Methymagnesium iodide was added to ketone **17** to obtain tertiary alcohol **18** as a mixture of diastereomers (**18a**:**18b** = 4:1). Friedel-Crafts cyclization of **18** in the presence of $AlCl_3$ afforded the desired intermediate **19**. This concluded the formal synthesis of (−)-aphanorphine **1** (Scheme 1.3). An important feature of this synthesis is the simultaneous construction of the central six-membered ring and the quaternary stereocenter.



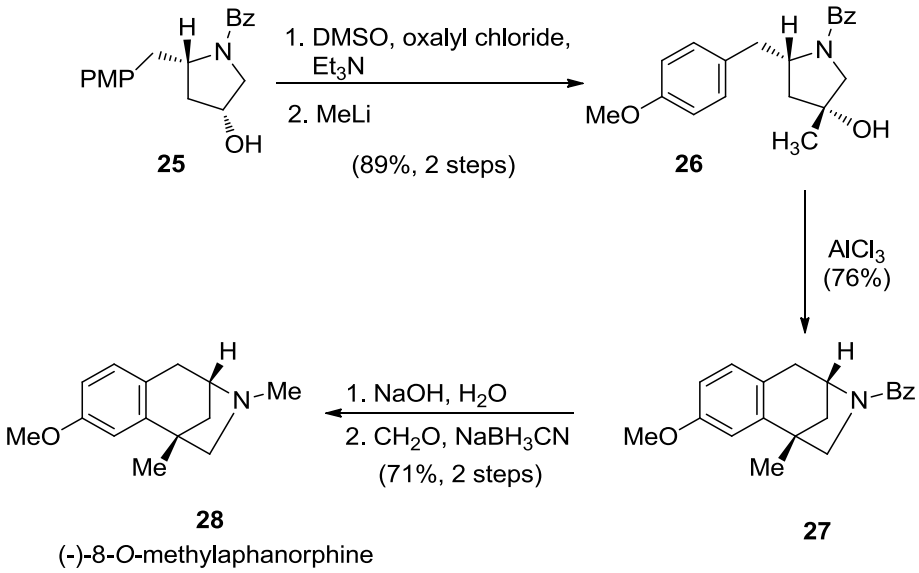

Scheme 1.3

The Zhai group also reported the synthesis of unnatural (+)-aphanorphine using (2*S*,4*R*)-4-hydroxyproline (**5**)[6b,8] as the starting material. In order to use the earlier approach[6b] discussed in Scheme 1.3 for the synthesis of (+)-aphanorphine, inversion of configuration at *C*-2 in **5** was required (Scheme 1.4). This was achieved over three steps. *N*-Benzoylation[9] of **5**, followed by heating in acetic anhydride furnished the lactonization product **21** with inversion of configuration at the *C*-2 stereocenter.[10] Treatment of a mixture of **21** and Me(OMe)NH·HCl with *p*-methoxyphenylmagnesium bromide afforded the pyrrolidinone **23**. This conversion also resulted in the formation of the corresponding Weinreb amide **22**, which can be converted to **23** by further treatment with *p*-methoxyphenylmagnesium bromide. The ketone in **23** was reduced to provide **25** (Scheme 1.4) by 1,3-dithiolane formation and desulfurization with $Bu_3SnH$, AIBN. The inversion of stereochemistry at *C*-2 in **25** was confirmed using NOESY.




Scheme 1.4.

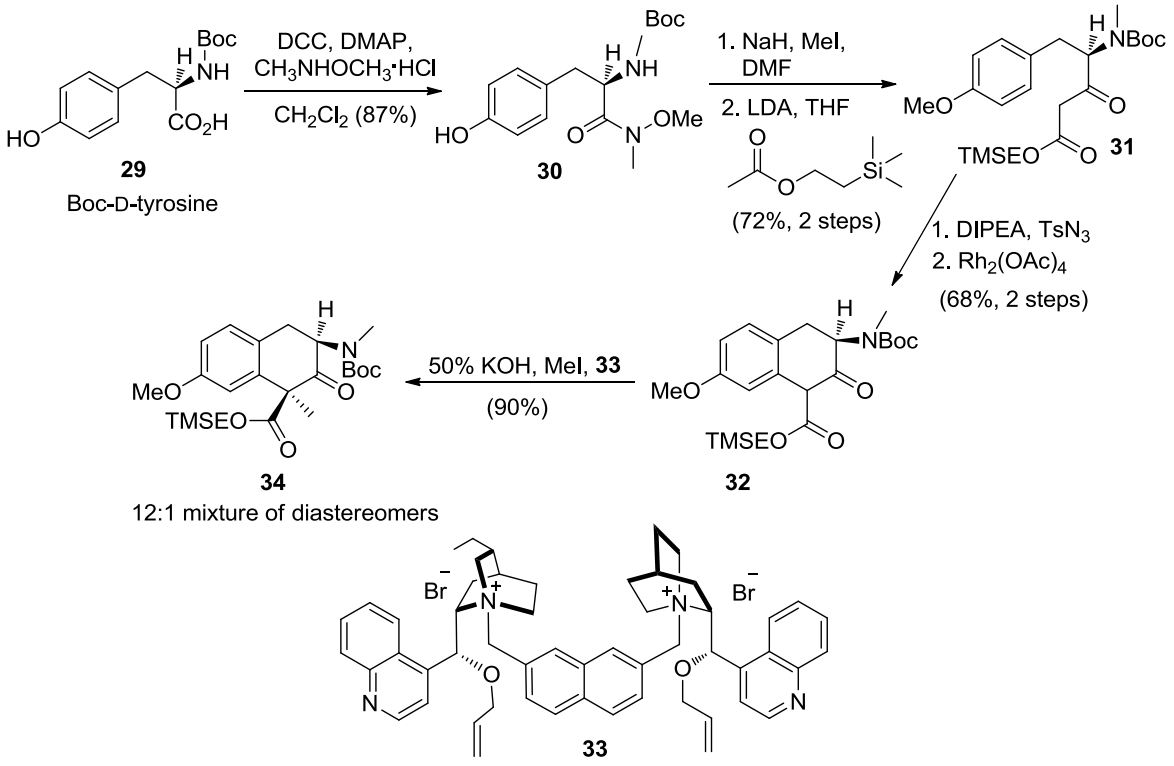
Swern oxidation of **25** furnished a pyrrolidinone, which on addition of methyllithium afforded the tertiary alcohol **26**. Friedel-Crafts cyclization of **26** furnished the tricyclic intermediate **27** as a single diastereomer. Basic hydrolysis of **27**, followed by treatment with formalin and sodium cyanoborohydride furnished (–)-8-*O*-methylaphanorphine **28** (71% over two steps and 17% overall yield Scheme 1.5).




Scheme 1.5

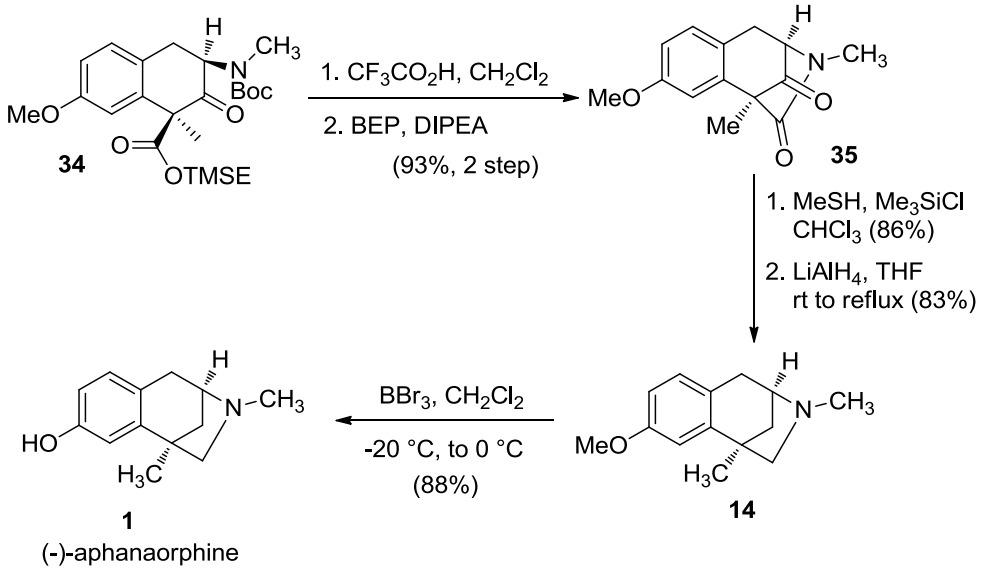
Li and co-workers utilized Boc-D-tyrosine **29** as the chiral starting material for the synthesis of (–)-aphanorphine.[11] Unlike the syntheses discussed earlier, the central 6-membered ring in aphanorphine was constructed first, followed by formation of the pyrrolidine ring. Weinreb amide **30** was obtained from the coupling of Boc-D-tyrosine and *N*,*O*-dimethylhydroxylamine. *N*-Methylation of **30** followed by treatment with the enolate of 2-(trimethylsilyl)ethyl acetate furnished the chain-extended product **31**.

Azidation of **31** with Hunig's base and tosylazide and subsequent cyclization using rhodium acetate provided **32** (78%). Diastereoselective methylation of **32** using 50% KOH and MeI, in the presence of cinchona-derived ammonium salt **33**, furnished **34** as a mixture of diastereomers (**34a**:**34b** = 12:1, Scheme 1.6).



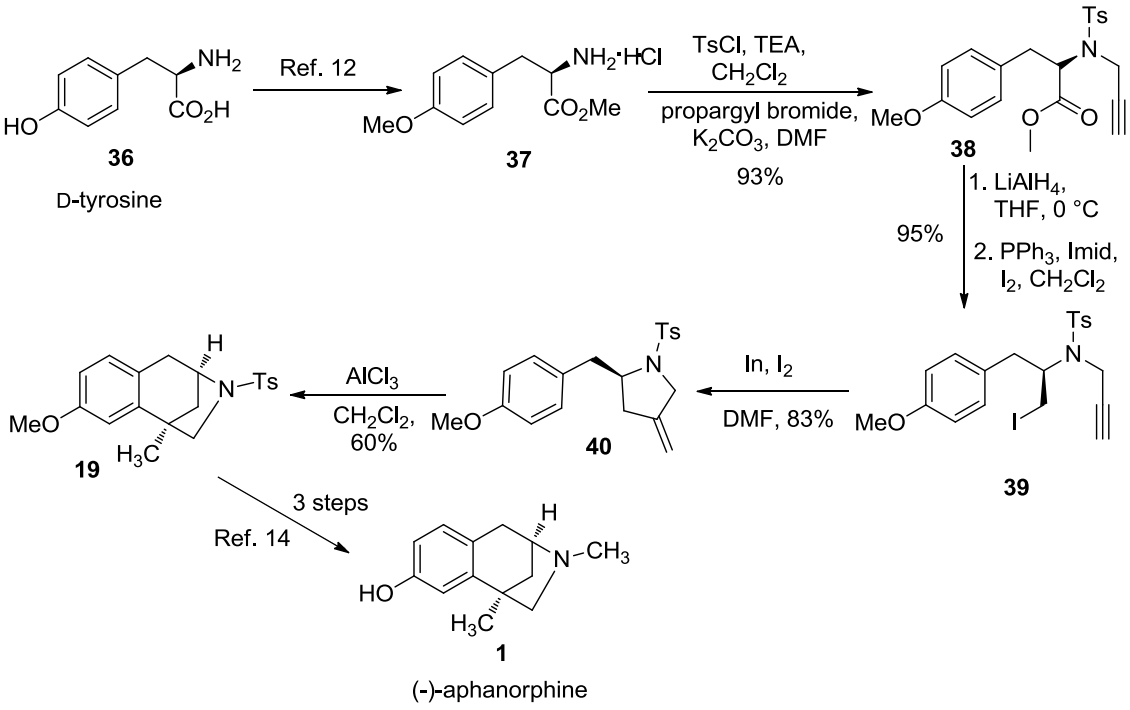

Scheme 1.6

Acid catalyzed deprotection of the major diastereomer of **34** provided the corresponding amino acid which was cyclized to provide the lactam **35** (Scheme 1.7). Conversion of the ketone to a thioketal, followed by $LiAlH_4$ reduction gave (+)-8-*O*-aphanorphine **14**. Boron tribromide mediated *O*-demethylation in **14** furnished (–)-aphanorphine **1** with 22% overall yield (Scheme 1.7).




Scheme 1.7

The Zhai group reported[12] a synthesis of (–)-aphanorphine using *O*-methyl-D-tyrosine methyl ester hydrochloride salt (**37**), prepared from D-tyrosine (**36**) as the starting material (Scheme 1.8) according to the previously reported procedure[13]. Unlike the synthesis shown in Schemes 1.6 and 1.7,[11] the pyrrolidine ring was constructed first followed by the synthesis of the central six membered ring. *N*-Tosylation and *N*-propargylation of **37** furnished **38** in 93% yield over two steps. The ester group in **38** was reduced to an alcohol which, upon treatment with $I_2$, $PPh_3$, and imidazole, afforded **39**. The treatment of **39** with In and $I_2$ in DMF furnished the alkene **40**. $AlCl_3$ mediated cyclization of **40** formed the tricyclic structure of (–)-aphanorphine as a single diastereomer **19** (Scheme 1.8). This concluded the formal synthesis of (–)-aphanorphine **1**. Conversion of **19** into (–)-aphanorphine **1** was previously accomplished over three steps.[14]

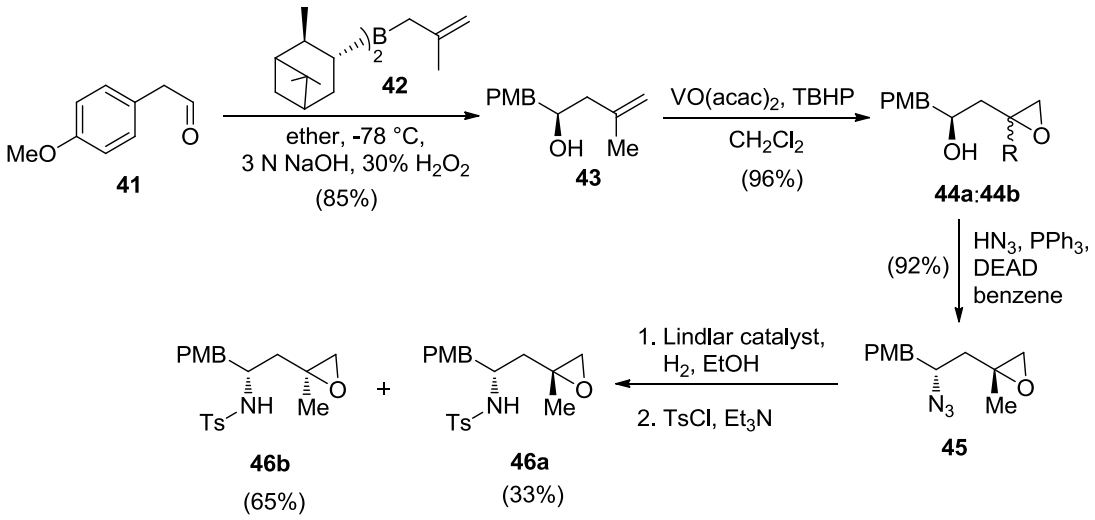



Scheme 1.8

### 1.2.2 Synthesis of aphanorphine using substituted aromatic substrates as starting materials:

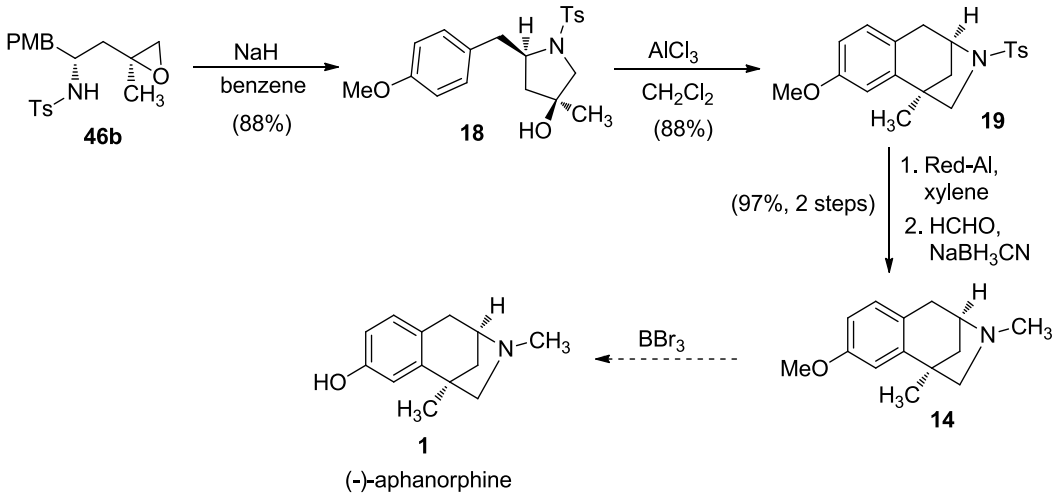
The Zhai group has also reported [14] a second approach for the synthesis of (−)-aphanorphine **1** using 4-methoxyphenylacetaldehyde **41** as the starting material. In this approach as well, the pyrrolidine ring was constructed first, followed by the six-membered ring. The homoallylic alcohol **43** (95% ee) was prepared by treatment of **41** with the diisopinocampheyl(methallyl)borane reagent **42** in ether (prepared from methallylmagnesium chloride and (+)-DIP-chloride).[15] The alcohol **43** was further treated with TBHP in the presence of 2 mol% $VO(acac)_2$ to give epoxy alcohol **44** as a mixture of diastereomers (**44a**:**44b** = 2:1). Conversion of **44** to epoxy azide **45** was done by the treatment of **44** with $HN_3$, $PPh_3$, and DEAD in benzene. Chemoselective

azide reduction (without affecting the epoxide group), was done using hydrogen in the presence of the Lindlar catalyst. The resulting amines were tosylated to obtain **46a** and **46b** (Scheme 1.9) which were separated by chromatography. The sulfonamide **46b** was used further.



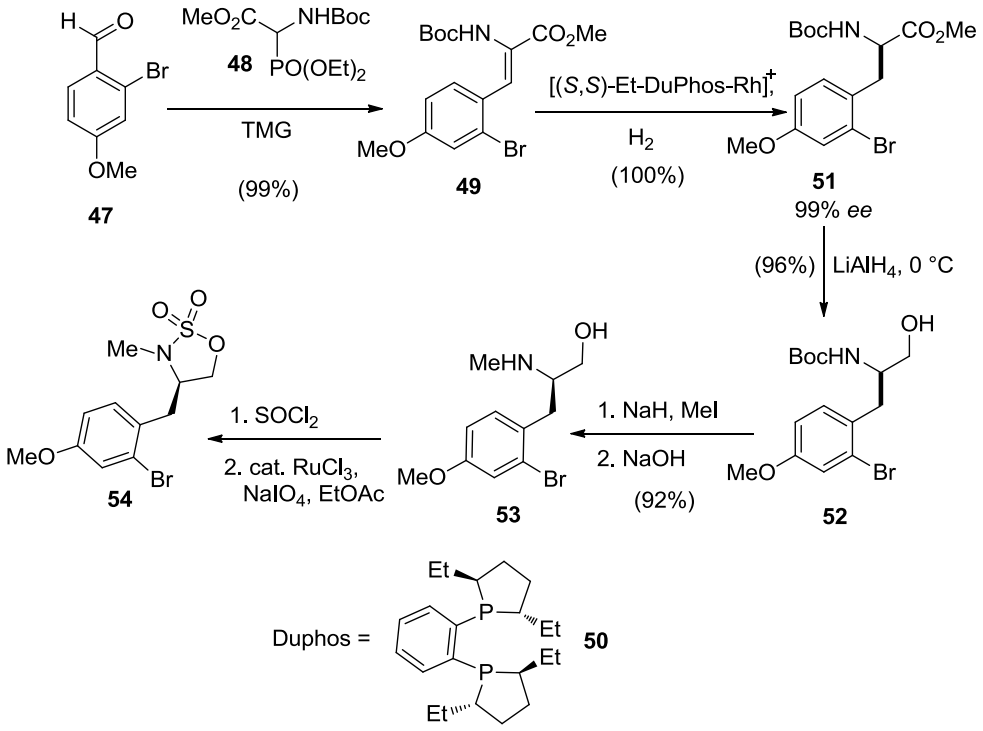

Scheme 1.9

Deprotonation of **46b** and cyclization of the tosyl amide anion onto the epoxide provided **18**. Construction of the aphanorphine framework **19** was accomplished by using $AlCl_3$-mediated Friedel-Crafts cyclization of **18** in good yield (88%). Detosylation of **19** with Red-Al and subsequent *N*-methylation with formaldehyde and $NaBH_3CN$ accomplished the synthesis of (+)-8-*O*-methylaphanorphine **14** (Scheme 1.10). This concluded the formal total synthesis of (−)-aphanorphine **11**.



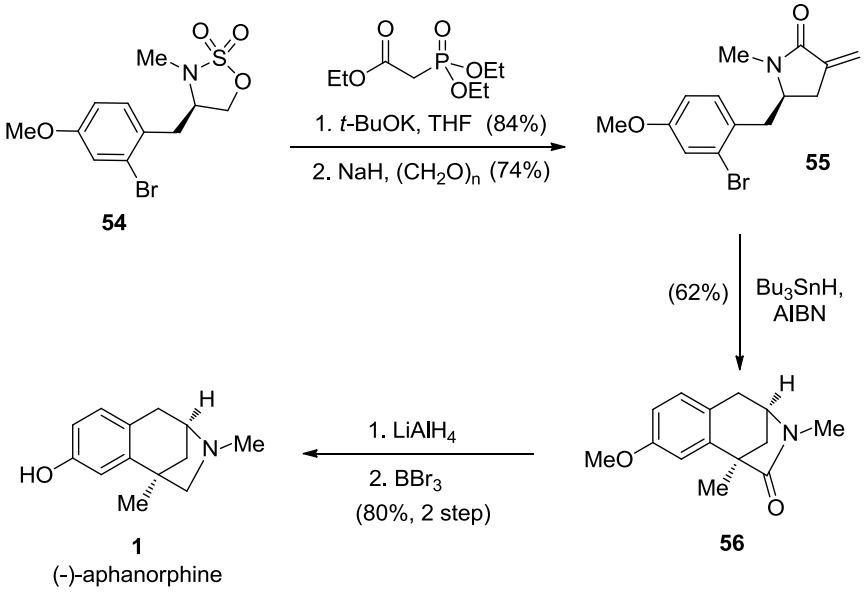

Scheme 1.10

Gallagher and co-workers reported a synthesis of (–)-aphanorphine using 2-bromoanisaldehyde **47** as a starting material.[16] A cyclic sulfimidate **54** was utilized as the key precursor for the pyrrolidine ring in the target (Scheme 1.11). Synthesis of **54** started with reaction of 2-bromoanisaldehyde with phosphonate **48** and tetramethylguanidine (TMG) to provide **49** which was subjected to asymmetric hydrogenation with Rh(DuPHOS)[17] to provide the amino ester **51** with excellent enantioselectivity (99% *ee*). Reduction of **51** with $LiAlH_4$ at 0 °C provided the amino alcohol **52**. The alcohol **52** was subjected to a one pot process of *in situ N*-methylation and hydrolysis of the Boc carbamate to obtain **53** in excellent yield (99%). Amino alcohol **53** was treated with thionyl chloride to obtain a cyclic sulfamidite which was oxidized to the sulfamidate **54** by $RuCl_3/NaIO_4$ mediated oxidation.[18]



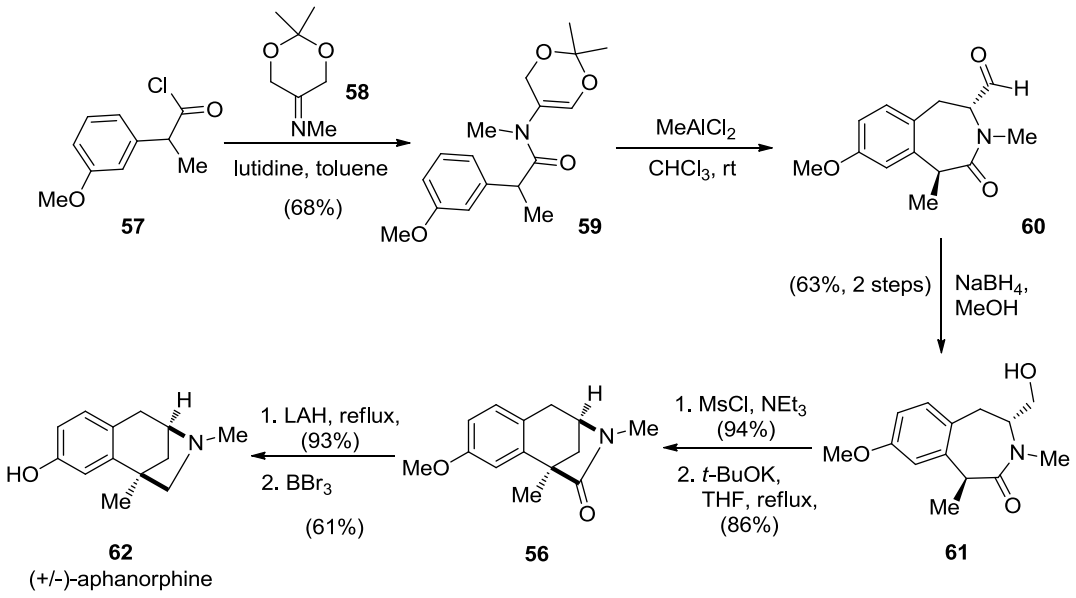

Scheme 1.11

The sulfamidate **54** was then treated with triethyl phosphonoacetate and *t*-BuOK and the resulting cyclic phosphonate was converted to **55** by Wadsworth-Emmons olefination using formaldehyde (Scheme 1.12). $Bu_3SnH$ and AIBN-mediated radical cyclization of **55** furnished **56**. At this point, construction of the cyclic framework for (−)-aphanorphine with desired stereochemistry was achieved. Reduction of the amide in **56** followed by *O*-demethylation afforded (−)-aphanorphine **1** with 20.1% overall yield.




Scheme 1.12

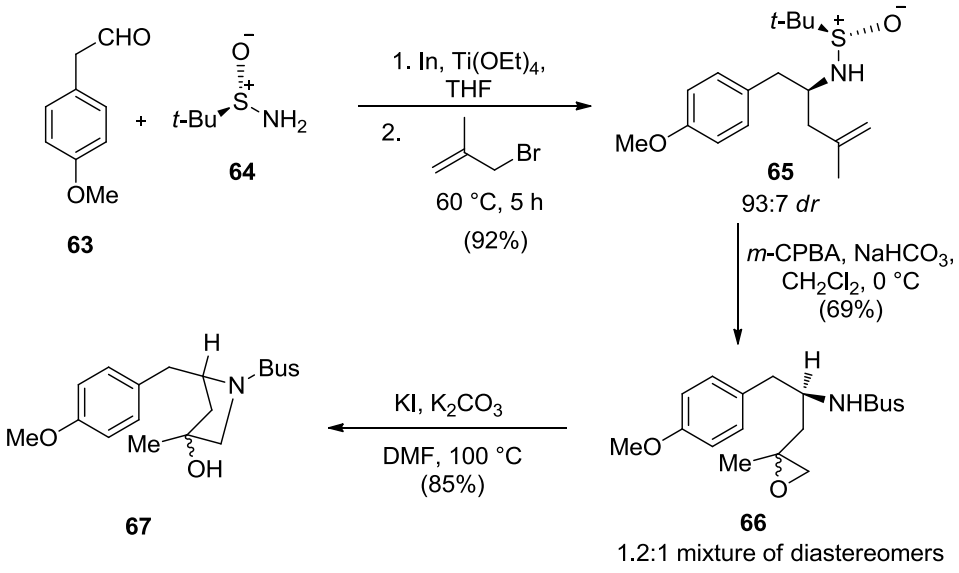
Funk and co-workers reported a concise synthesis of (±)-aphanorphine **62** using the 5-amido-1,3-dioxine **59** as a starting material.[19] Acid chloride **57** was treated with *N*-methylimine **58** to afford **59** (Scheme 1.13). The treatment of **59** with $MeAlCl_2$ resulted in an intramolecular aromatic substitution reaction to furnish aldehyde **60** as a single (*trans*) diastereomer which was reduced to alcohol **61** using $NaBH_4$. Mesylation of **61** followed by cyclization afforded the bridged bicyclic lactam **56**. Lactam reduction with $LiAlH_4$ and *O*-demethylation using $BBr_3$ resulted in the formation of (±)-aphanorphine **62** with 15% overall yield (Scheme 1.13).




Scheme 1.13

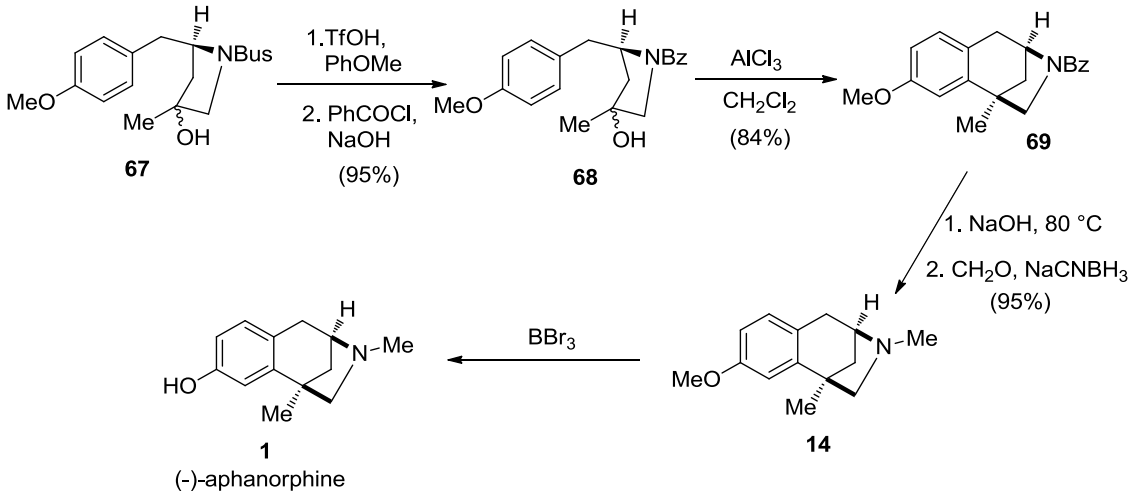
### 1.2.3 Synthesis of (+) and (–)-aphanorphine using a chiral sulfinamide starting material:

Foubelo and co-workers reported a synthesis of (–)-aphanorphine as well as (+)-aphanorphine using 4-methoxyphenylacetaldehyde as the starting material.[20] Indium-mediated one-pot α-amino allylation of **63** using (*R*)-2-methylpropane-2-sulfinamide **64** and methallyl bromide afforded **65** with high diastereoselectivity (dr 93:7). Epoxidation of **65** using *m*-CPBA furnished **66** as a 1.2:1 mixture of diastereomers. Treatment of **66** with KI and $K_2CO_3$ gave **67** by cyclization of an intermediate primary iodide (Scheme 1.14).



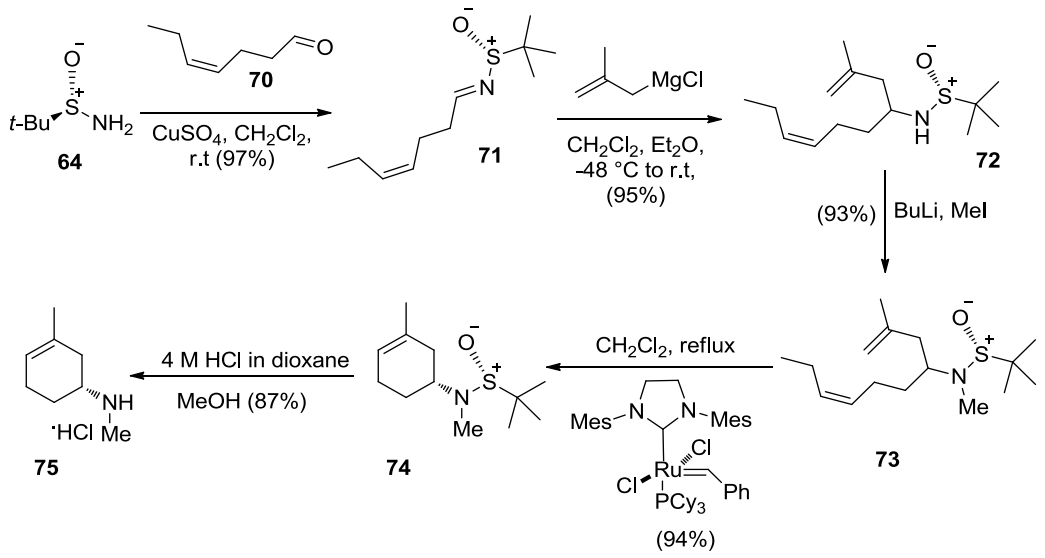

Scheme 1.14

Attempted Friedel-Crafts cyclization of **67** resulted in decomposition under various conditions. Changing the *N*-protection to a benzoyl group was beneficial and the Friedel-Crafts cyclization of **68** furnished **69** as a single diastereomer. Hydrolysis of the benzamide in **69** followed by *N*-methylation provided (+)-8-*O*-methyl aphanorphine **14**. $BBr_3$-mediated *O*-de-methylation furnished (−)-aphanorphine **1** (Scheme 1.15). Similarly, (+)-**1** was prepared using the *S* enantiomer of sulfinamide **64** as the chiral reagent.



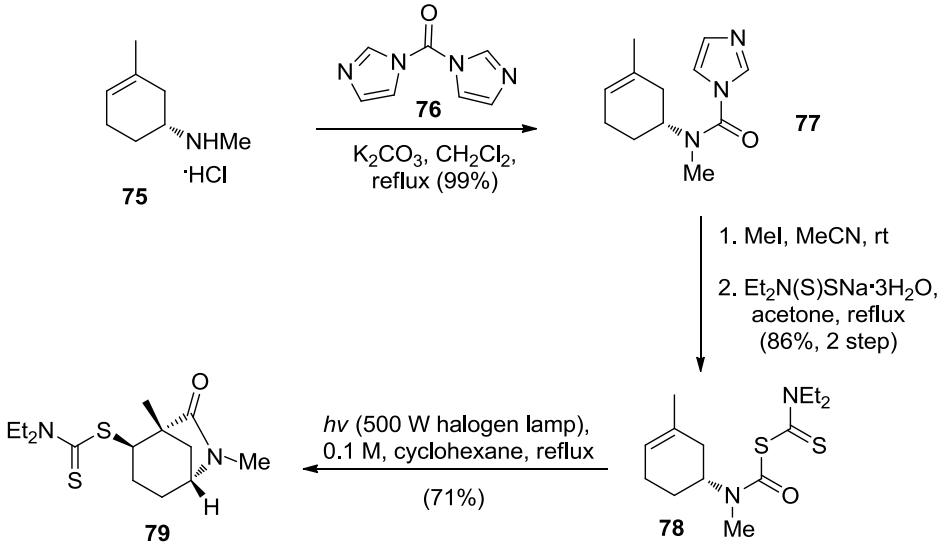

Scheme 1.15

Grainger and co-workers also reported a synthesis of (–)-aphanorphine using (*R*)-*t*-butanesulfinamide **64** as a chiral starting material (Scheme 1.16).[21] A photochemical radical reaction of a dithiocarbamate was used as a key reaction in the synthesis. (*R*)-*t*-butanesulfinamide **64** was condensed with (*E*)-4-heptenal **70** to afford (*E*)-sulfinimine **71**. Methallylmagnesium chloride was added to **71** to provide sulfonamide **72** as a 5:1 mixture of diastereomers. The configuration of the major isomer was assigned as *R* based on the Ellman model for nucleophilic addition to chiral sulfinimines such as **71**.[22] The diastereomeric mixture was carried forward without purification. *N*-methylation of **72** was carried out using *n*-BuLi and MeI and the resulting 1,7-diene **73** was subjected to ring-closing metathesis using the Grubbs second generation catalyst to obtain **74** in excellent yield (94%, Scheme 1.16). The sulfinyl portion was removed using 4 M HCl to provide the salt **75**.



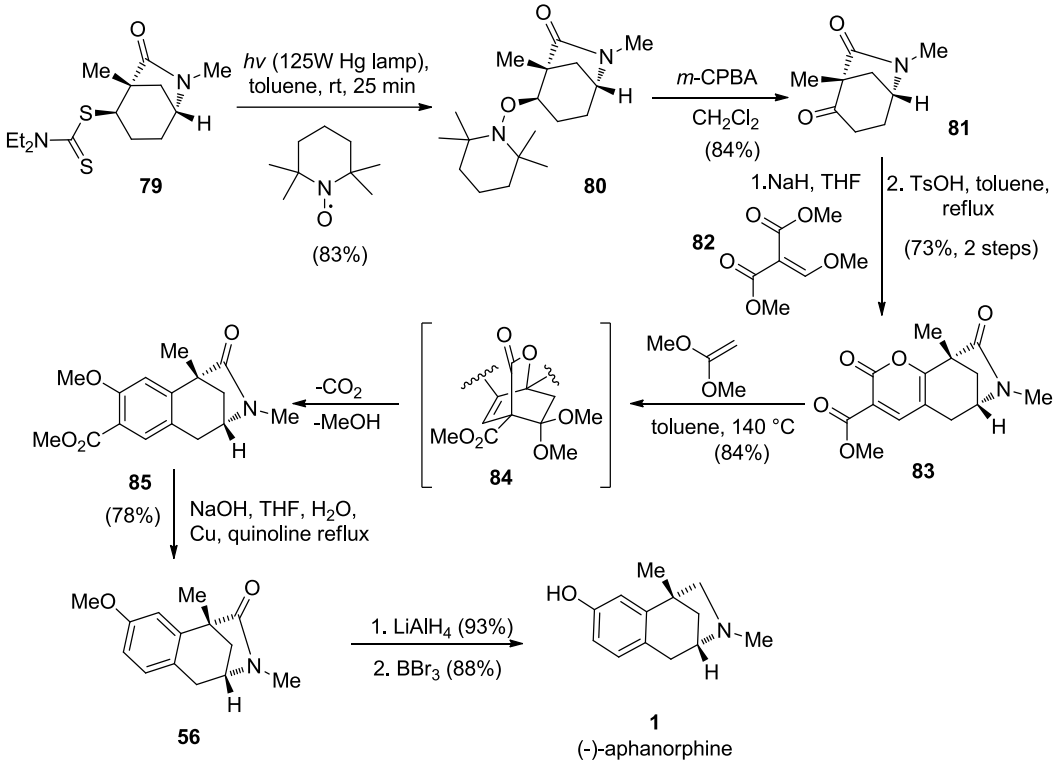

Scheme 1.16

The hydrochloride salt **75** was treated with carbonyldiimidazole **76** and $K_2CO_3$ to obtain carbamoylimidazole **77** in quantitative yield. *N*-methylation of **77** gave the corresponding carbamoyl imidazolium salt,[23] which upon reaction with sodium diethylthiocarbamate provided the radical cyclization precursor **78** (86% yield over two steps). The photochemical radical cyclization of **78** gave **79** in 71% yield (Scheme 1.17). The structure of **79** was confirmed by X-ray crystallography.




Scheme 1.17

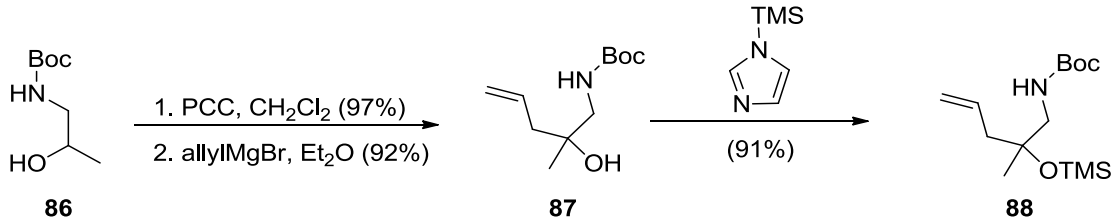
Treatment of **79** with TEMPO under irradiation using a mercury lamp replaced the carbon-sulfur bond with a carbon-oxygen bond to afford **80** with retention of configuration (Scheme 1.18). Oxidation of **80** using *m*-CPBA resulted in formation of ketone **81**. Reaction of **81** with dimethyl 2-(methoxymethylene)malonate **82** under the basic conditions followed by acid-catalyzed cyclization resulted in the formation of the pyrone **83**. An inverse-electron-demand Diels-Alder reaction of **83** with 1,1-dimethoxyethene, followed by loss of $CO_2$ and methanol from the cycloadduct **84**, resulted in the formation of the required tricyclic ring system **85**. Hydrolysis of the ester to an acid, followed by copper-mediated decarboxylation provided **56** (Scheme 1.18). $LiAlH_4$ reduction of **56** and $BBr_3$ mediated *O*-demethylation provided (−)-aphanorphine **1**.




Scheme 1.18

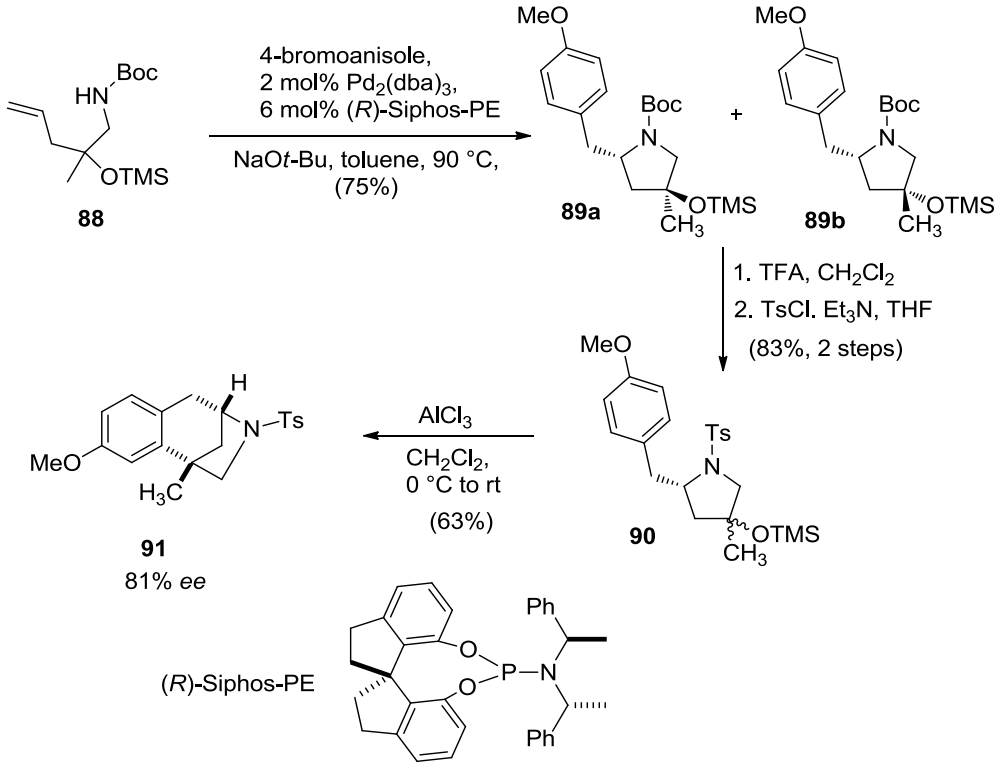
### 1.2.4 Synthesis of (+)-aphanorphine employing asymmetric alkene carboamination:

Wolfe reported the enantioconvergent synthesis of unnatural (+)-aphanorphine using a racemic precursor (±)-**88**.[24] The synthesis of **88** started from *N*-boc-1-amino-2-propanol **86**. Oxidation of **86** to a ketone followed by reaction with allyl magnesium bromide provided **87**. The silyl protection of **87** was done using TMS-imidazole to obtain the precursor (±)-**88** in 91% yield (Scheme 1.19).



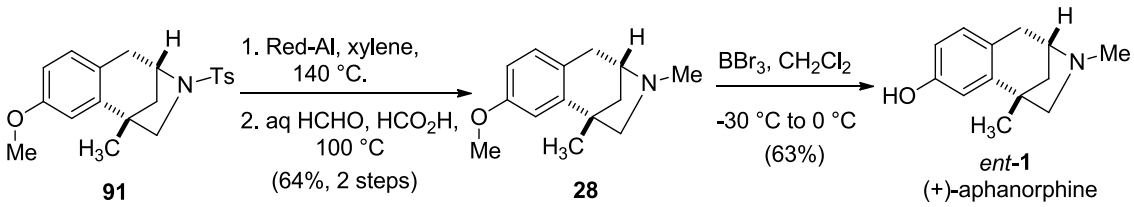

Scheme 1.19

The coupling of **88** with 4-bromoanisole with concomitant ring formation was carried out using a palladium catalyst in the presence of a chiral ligand ((*R*)-Siphos-PE), to provide a 1:1 mixture of pyrrolidines **89a** and **89b**. Removal of the Boc group using TFA and tosylation of the resulting amine provided **90** (1:1 *dr*). $AlCl_3$-mediated Friedel-Crafts cyclization of **90** furnished **91** (81% *ee*, Scheme 1.20).




Scheme 1.20

The tosyl group in **91** was removed using Red-Al and the resulting amine was treated with formalin and formic acid to obtain **28** (Scheme 1.21). $BBr_3$ mediated *O*-demethylation provided (+)-aphanorphine (*ent*-**1**, Scheme 1.21).



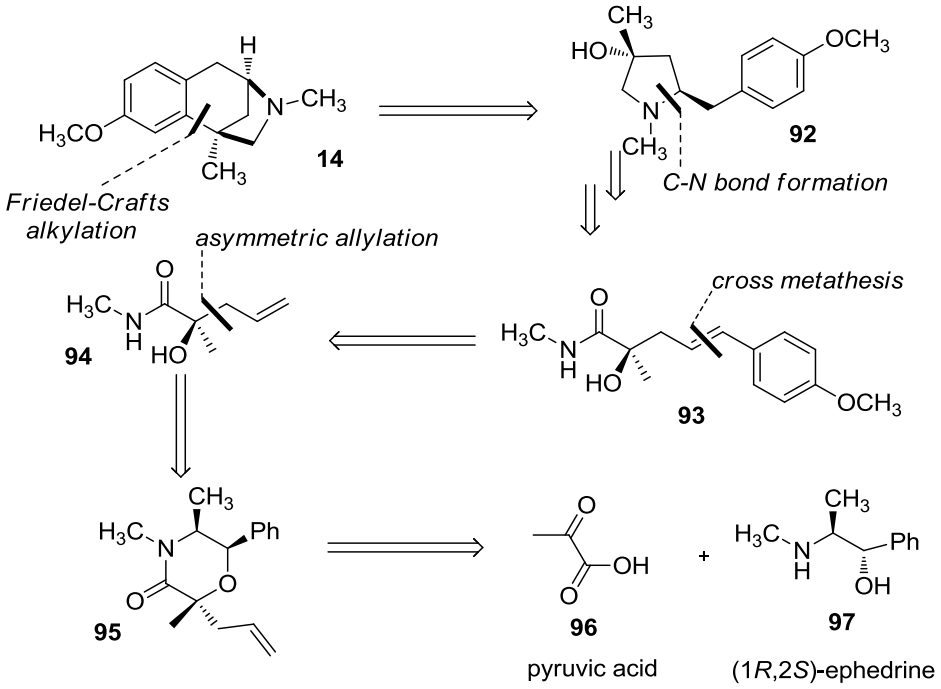

Scheme 1.21

**1.3 Present work:**

**1.3.1 An enantioselective approach to (−)-aphanorphine employing a chiral α-hydroxy acid as the starting material**

The Pansare group has been involved in the synthesis of α-alkyl,α-hydroxy acid derivatives as intermediates in the synthesis of biologically relevant motifs and natural products.[25] In the present study, a synthesis of (−)-aphanorphine was envisioned based on the α-hydroxy acid derivative **94** as a starting material (Scheme 1.22). The synthetic strategy involves Friedel-Crafts cyclization of **92** for the synthesis of a central six membered ring as in previous aphanorphine syntheses.[14,20,24] A stereoselective C-N bond formation is used in the synthesis of the key pyrrolidine intermediate **92**. The precursor to this pyrrolidine is the hydroxy amide **93** which is obtained from an enantiomerically enriched α-hydroxy pentenoic acid derivative **94** by a cross metathesis reaction. The amide **94** can be obtained by the asymmetric

allylation of a chiral pyruvic acid derivative obtained by amidation with (1*R*,2*S*)-ephedrine (**97**).

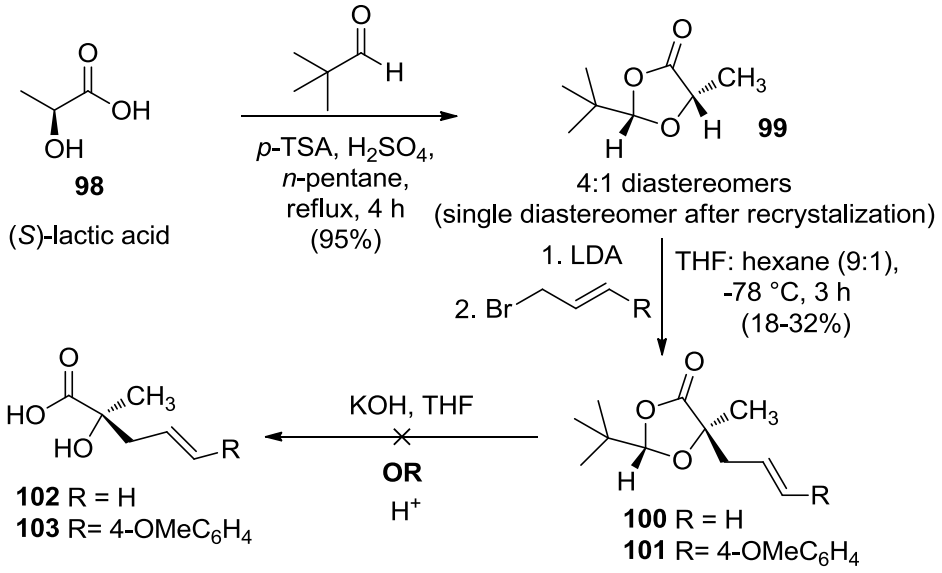



Scheme 1.22 Synthetic strategy for the synthesis of (+)-8-*O*-methylaphanorphine **14.**

The initial approach was aimed at the synthesis of an *N*-methyl pyrrolidinone as a precursor to the pyrrolidine motif in aphanorphine. This approach was attractive for two reasons: 1) several substituted *N*-methylpyrrolidinones are natural products[26] or structural motifs in bioactive molecules[27] and the present study could potentially provide a methodology for their synthesis as well; and 2) the starting material for the pyrrolidinone based approach, the α-hydroxy *N*-methyl amide (*R*)-**94**[28] could be directly obtained by asymmetric allylation of an ephedrine-derived chiral pyruvamide developed in the Pansare group.[28] When the aphanorphine synthesis was first initiated, a gram-scale synthesis of **95** was required. This required a scale-up of the existing

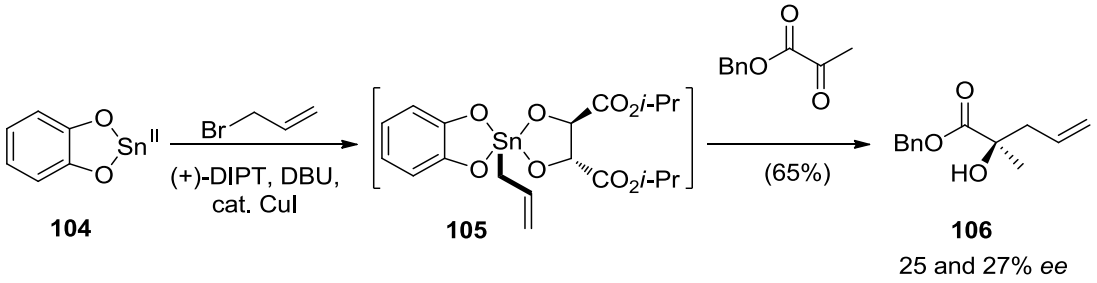
synthesis of **95** developed earlier in the Pansare group.[28] In the interest of time, while the scale-up was being optimized, alternate methods were also examined for the synthesis of **94** via the corresponding acid **102** (Scheme 1.23).

Initially, the asymmetric allylation of a 1,3-dioxolanone, derived from (*S*)-lactic acid and pivalaldehyde, as described by Seebach[29] was investigated. Accordingly, the treatment of (*S*)-lactic acid **98** with pivalaldehyde, *p*-TsOH and catalytic amount of $H_2SO_4$ in refluxing pentane provided **99** as a 4:1 mixture of diastereomers. Pure *cis*-**99** (75%) was obtained by recrystallization from ether/pentane, and then was treated with LDA at –78 °C in THF/hexane (9:1), followed by addition of allyl bromide to obtain **100** in poor yields (27-32%). Similarly, **101** was obtained by alkylation of the anion with the 4-methoxycinnamyl bromide in low yields (18-30%, Scheme 1.23) after several attempts. However, the attempted hydrolysis of **100** and **101** to the acids **102** and **103** respectively, using KOH resulted in complex mixtures. This approach was therefore not pursued further.



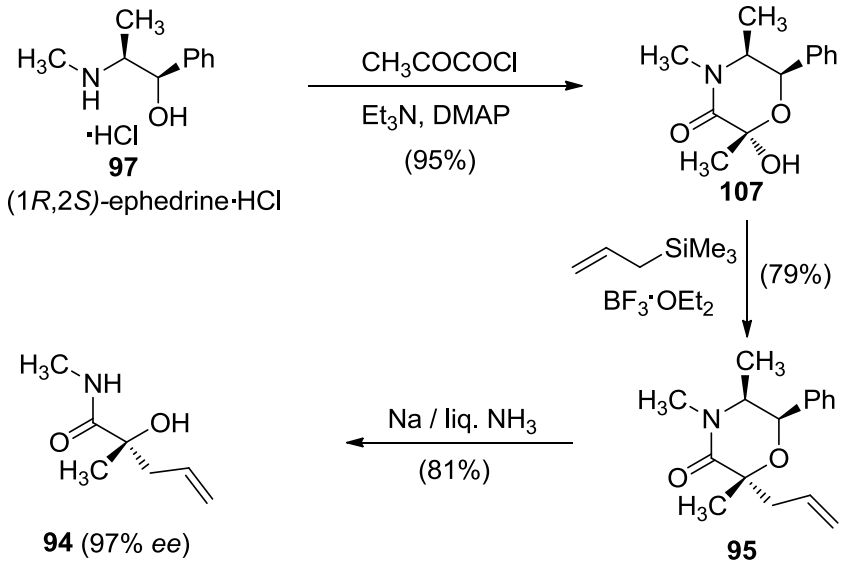

Scheme 1.23

The synthesis of the required $\alpha$-hydroxy acid was next attempted by the asymmetric allylation of benzyl pyruvate, as reported by Mukaiyama.[30] A divalent tin(II) catecholate **104** was treated with allyl bromide in the presence of (+)-diisopropyl tartrate, DBU and a catalytic amount of CuI to obtain the allylating reagent **105**. Treatment of benzyl pyruvate with **105** furnished **106** in 65% yield, but with poor enantioselectivity (25 and 27% *ee*, Scheme 1.24). This approach was therefore also not pursued further.




Scheme 1.24

At this point, it was obvious that the ephedrine-based methodology needed to be optimized[28] to synthesize **94** in gram quantities (Scheme 1.25). During these studies, it was noticed that the use of $TiCl_4$ as the Lewis acid for the allylation step worked well only on a millimolar scale. For gram-scale allylation of **107**, the use of $BF_3{\cdot}OEt_2$ instead of $TiCl_4$, provides **95** with excellent diastereoselectivity. An added advantage is that while the $TiCl_4$ reaction has to be conducted at –78 °C, the $BF_3{\cdot}OEt_2$ -mediated allylation can be conducted at ambient temperature. With the modified procedure, up to 2.0 g of **94** can be routinely prepared from ephedrine and pyruvic acid in two days.[31]

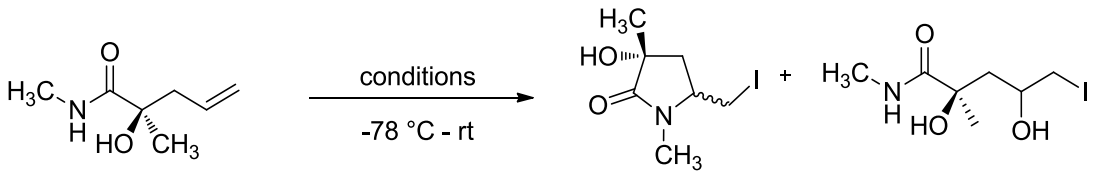



Scheme 1.25

The initial aim of this study was to perform a halolactamization reaction of **94** to provide the functionalized pyrrolidinone **109** as a key intermediate to aphanorphine. A variety of conditions that are reported to promote halolactamization of secondary

amides were screened and the results of these experiments are summarized in Table 1. In some of these reactions, the iodohydrin **109** was also obtained as a byproduct.

Table 1.1 Iodolactamization studies with **94**.



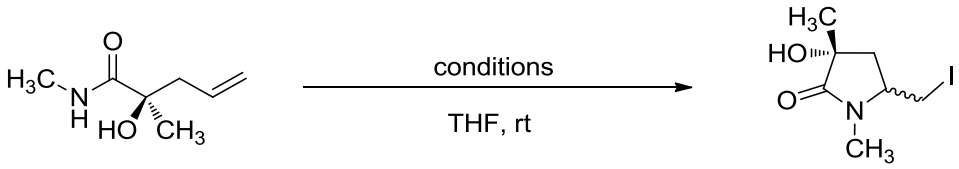

**94** **108** **109**

| No. | Reagents | Solvent | Results |
|---|---|---|---|
| 1 | $NaHCO_3$, $I_2$, | $CH_3CN$ | **109** [a] |
| 2 | NIS, NaOH | MeOH + Dioxane | **109** + lactone + **94** |
| 3 | $DMS(OTf)_2$, $Et_3N$, $I_2$ | $CH_2Cl_2$ | No isolable product |
| 4 | $DMS(OTf)_2$, $Et_3N$, ICl | $CH_2Cl_2$ | No isolable product |
| 5 | *n*-BuLi, TMSOTf, $I_2$ | THF | **94**[b] |
| 6 | $Et_3N$, TMSOTf, Br bis(collidine)$_2$ OTf | $CH_2Cl_2$ | **94** |

*a*: reaction was carried out at 0 °C. *b*: reaction was warmed gradually from -78 °C to room temperature

In addition, intramolecular amidomercuration/halogenation[32] reactions of **94** were also attempted. None of these reactions however provided any of the required lactam. The results of these studies are summarized in Table 2.

Table 1.2 Amidomercuration conditions for the attempted lactamization of **94**

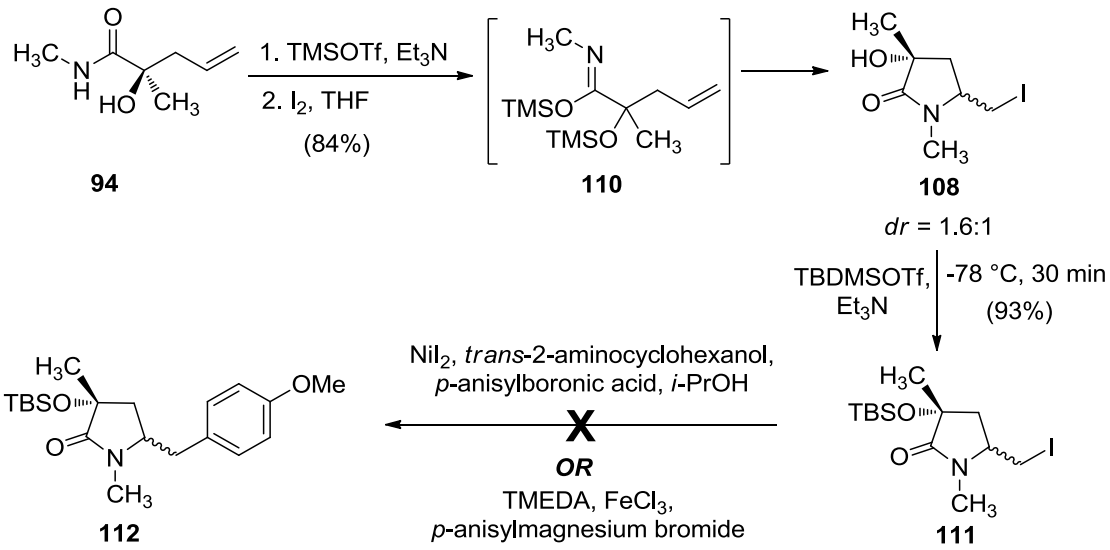



**94** **108**

| Entry | Reagents | T (h) | Result |
|---|---|---|---|
| 1 | $Hg(OAc)_2$, KI, $I_2$ | 20 | Complex reaction mixture |
| 2 | $Hg(CF_3CO_2)_2$, KI | 24 | **94** |
| 3 | $Et_3N$, TMSOTf, $Hg(OAc)_2$ | 24 | Complex reaction mixture |
| 4 | $Et_3N$, TMSOTf, $Hg(CF_3CO_2)_2$, KBr, $NaHCO_3$ | 24 | Silylation |

Finally, under the iodolactamization conditions reported by Knapp,[33] (treatment of **94** with TMSOTf, which presumably forms the *O*-silylimidate **110**, followed by addition of iodine) provided **108** in good yield (84%) but with poor diastereoselectivity (1.6:1 *dr*, Scheme 1.26). The hydroxyl group[34] in **108** was protected as a TBDMS ether using TBDMSOTf and $Et_3N$ to obtain **111**. The next objective was to convert **111** to the pyrrolidine **112**, which is an advanced precursor to aphanorphine. Accordingly, cross coupling reactions of **111** and 4-bromoanisole were investigated (Scheme 1.26). The conditions reported by Fu[35] (treatment with

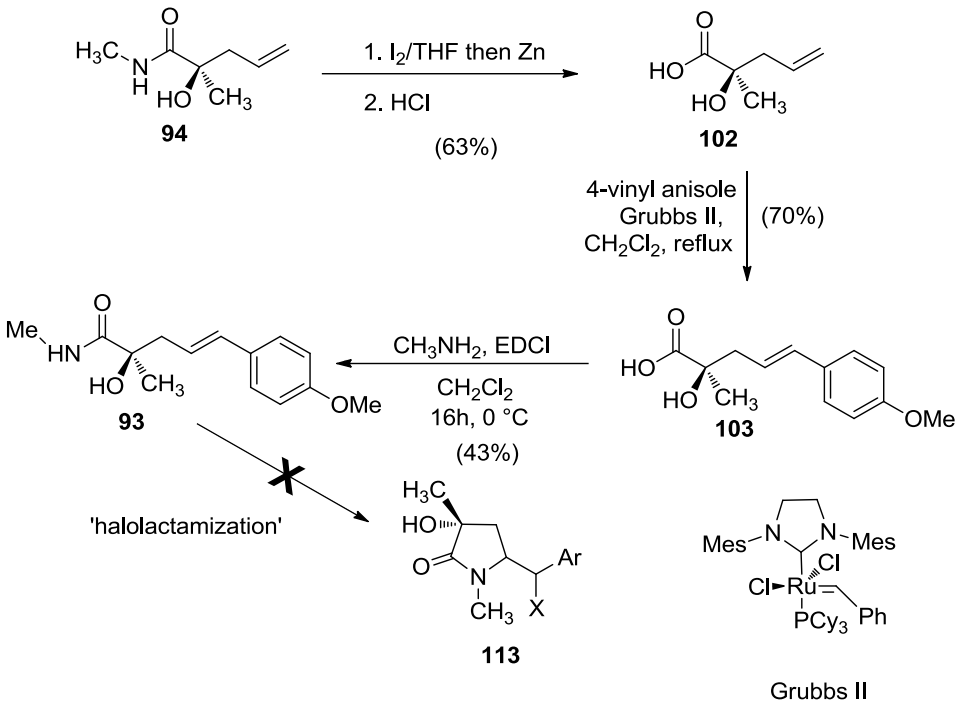
$NiI_2$, *trans*-2-aminocyclohexanol and *p*-anisylboronic acid in *i*-PrOH) resulted in the formation of a complex mixture of products. The treatment of **111** with TMEDA, $FeCl_3$, and *p*-anisylmagnesium bromide, according to the conditions reported by Bedford,[36] resulted only in recovery of unreacted starting material.




Scheme 1.26

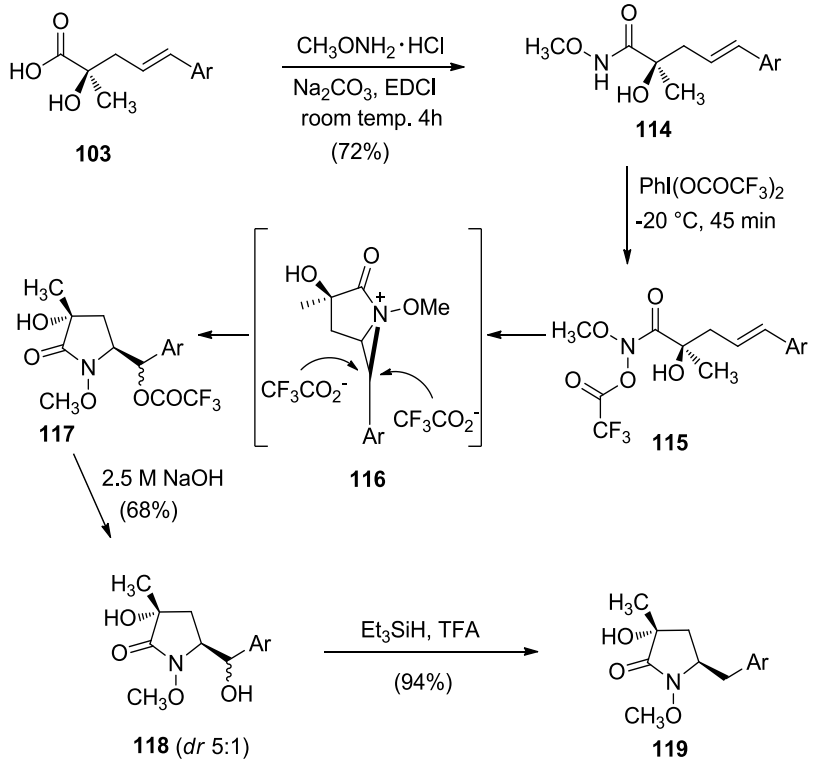
As an alternative, the halolactamization of a suitably substituted pentenamide as a more direct approach to **112** was investigated. It may be noted that the direct halolactamization of 5-aryl-4-pentenamides has not previously been reported. To examine this possibility, amide **94** was subjected to a cross-metathesis[37] reaction with 4-vinyl anisole using the Grubbs II catalyst. Although this reaction appeared to succeed, separation of the desired product from the stilbene byproduct (obtained from the homocoupling of 4-vinyl- anisole) was extremely difficult. Hence, **94** was converted[38] to the acid **102** which was then subjected to a cross-metathesis[37] reaction with 4-vinylanisole using the Grubbs II catalyst to provide the *trans*-pentenoic acid

**103**. The acid **103** could be easily separated from the stilbene by-product by extraction with aqueous sodium bicarbonate. Amidation of **103** with methylamine provided **93**. Unfortunately, reactions of **93** under a variety of halolactamization conditions, including the Knapp procedure, resulted only in complex mixtures (Scheme 1.27).




Scheme 1.27

Clearly, an alternative lactamization strategy was necessary and a nitrenium ion-mediated strategy[39] was explored. To pursue this approach, acid **103** was converted to *N*-methoxy amide **114** under standard conditions (Scheme 1.28). Oxidative ring closure of the crude *N*-methoxy amide, employing bis(trifluoroacetoxy)iodobenzene[40] and *in situ* hydrolysis of the resulting benzylic trifluoroacetate[41] resulted in the formation of hydroxypyrrolidine **119** as 5:1 mixture of diastereomers.

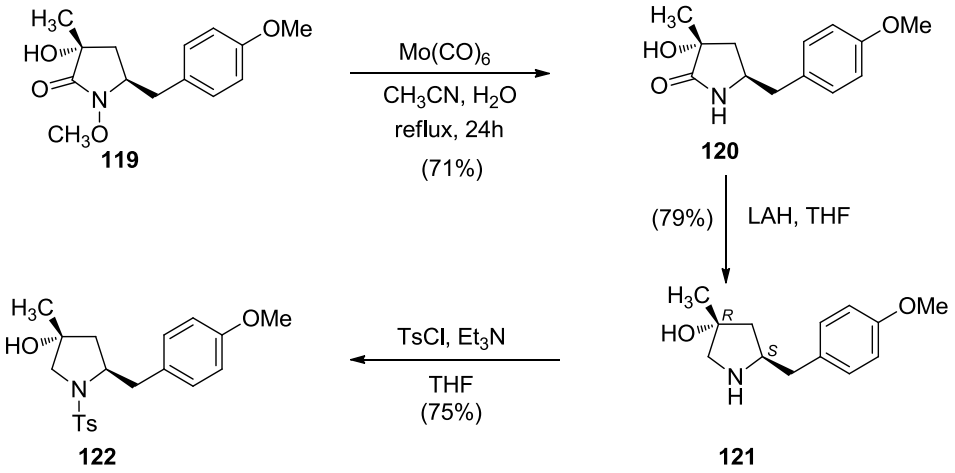



Scheme 1.28

Following the proposed[41] mechanism for such reactions, it is plausible that the cyclization begins with the formation of *N*-methoxy-*N*-trifluoroacetoxy amide **115**, which reacts with the alkene to form the intermediate **116**. Reaction of **116** with trifluoroacetate anion provides the pyrrolidinone **117**. Basic hydrolysis of **117** results in the formation of **118** as a 5:1 mixture of diastereomers. At this stage, it was unclear if this diastereomeric mixture was obtained due to unselective C-N bond formation or due to the unselective capture of an intermediate benzylic cation by trifluoroacetate. Gratifyingly, subsequent reduction of **118** with triethylsilane yielded the pyrrolidinone **119** as a single diastereomer (Scheme 1.29). This indicated that the C-N bond formation step was highly stereoselective. The existing stereocenter in **114** presumably

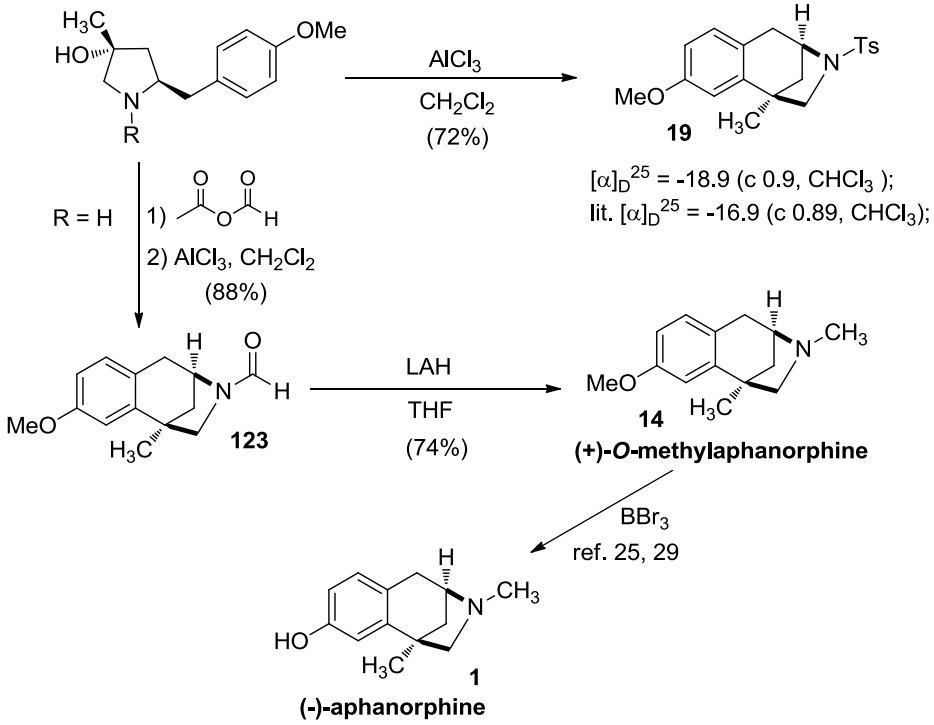
plays an important role in the stereoselective C-N bond formation to provide **119**. The high stereoselectivity for the formation of **119** is contradictory to the moderate diastereoselectivity observed in the iodine (III) mediated cyclization of *N-para*-met5hoxyphenyl-2-benzyl-4-pentenamides.[42] The reasons for the formation of only **119**, and not the corresponding diastereomer, are not clear at present.

Reduction of the N-O bond in **119** was tested under the conditions previously used in the Pansare group such as Zn/AcOH[43] at 50 °C or In/$NH_4Cl$.[44] It was observed that the N-O bond in **119** is inert to these methods. However, treatment of **119** with $Mo(CO)_6$[41] in refluxing $CH_3CN$ effectively reduced the N-O bond to provide **120**. The pyrrolidinone **120** was reduced with $LiAlH_4$ to provide the key pyrrolidine **121** which was tosylated to provide **122** (Scheme 1.29). The *cis* orientation of the $CH_3$ and $CH_2Ar$ groups in **121** (3*R*,5*R*) was confirmed by comparison of the spectroscopic data for the pyrrolidine **121** with data reported for a mixture of (3*S*,5*R*) and (3*S*,5*S*) **121** and that for (3*R*,5*S*) **121**.[20]




Scheme 1.29

Establishment of the stereochemistry of the oxidative amidation step, and hence the absolute configuration of the pyrrolidinone **120**, was done by conversion of tosylamide **122** to the known benzomorphan derivative (–)-**19** (91% *ee*, Scheme 1.30) which has been previously converted to (–)-aphanorphine. Comparison of the optical rotation of **19** ($[\alpha]_D^{25}$ –18.9 (*c* 0.9, $CHCl_3$)) with the reported[12] value for (1*R*,4*S*)-**19** ($[\alpha]_D^{25}$ –16.9 (*c* 0.89, $CHCl_3$)) confirmed the absolute stereochemistry for **19**. This also confirmed the absolute configuration of **120** and hence that of **121**. *N*-formylation of **121** with acetic formic anhydride furnished the corresponding *N*-formyl derivative, and $AlCl_3$-mediated intramolecular Friedel-Crafts cyclization to provide the benzomorphan **123 (**Scheme 1.30). Reduction of the formamide in **123** with $LiAlH_4$ afforded (+)-8-*O*-methylaphanorphine **14** (Scheme 1.30). This completed the formal synthesis of (–)-aphanorphine **1** since the conversion of **14** to (–)-aphanorphine by *O*-demethylation with $BBr_3$ is known.[19,24]




Scheme 1.30

In conclusion, the synthesis of (+)-*O*-methyl aphanorphine **14** (91% *ee*) was achieved from the readily available α-hydroxy acid derivative in 10 steps and 7.1% overall yield. A highly stereoselective intramolecular oxidative amidation was employed to construct the key pyrrolidine precursor to the benzazepine framework of the target. Notably, a *N*-formyl group serves as a *N*-methyl precursor in this synthesis. This avoided the more conventional approach in related aphanorphine syntheses that rely on *N*-deprotection, after the intramolecular Friedel-Crafts cyclization, followed by *N*-methylation. Since the *N*-deprotection step usually requires forcing conditions (detosylation[14,24] using Red-Al in refluxing xylene) or debenzoylation[20] (50% NaOH or KOH in ethanol, reflux, 24 h), the *N*-formylation approach provides a convenient

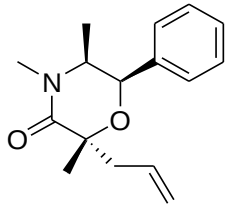
alternative that eliminates a late-stage step in the synthesis of other pyrrolidinone-containing natural products.

## 1.4 Experimental section:

### General experimental methods

All commercially available reagent were used without purification. All reactions requiring anhydrous conditions were performed under an atmosphere of dry nitrogen using oven dried glassware. Dichloromethane and tetrahydrofuran were distilled from $CaH_2$ and sodium/benzophenone respectively. Commercial precoated silica gel plates were used for TLC. Silica gel for column chromatography was 230-400 mesh. All melting points are uncorrected. Optical rotations were measured at the sodium D line on a digital polarimeter at ambient temperature.

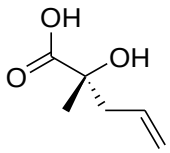
**(2*R*,5*S*,6*R*)-2-Allyl-2,4,5-trimethyl-6-phenylmorpholin-3-one (95):**




To a solution of **107** (0.50 g, 2.1 mmol) in $CH_2Cl_2$ (15 mL) was added allyltrimethylsilane (1.87 mL, 12.7 mmol) at –78 °C followed by $BF_3{\cdot}OEt$ (1.57 mL, 12.7 mmol). The solution was gradually warmed to ambient temperature and stirred for 20 h. The mixture was cooled to 0 °C and water (20 mL) was added. After stirring at ambient temperature for 5 min, the mixture was extracted with $CH_2Cl_2$ (3×30 mL). The combined extracts were dried ($Na_2SO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/ hexanes, 2/3)

to provide **95** (428 mg, 79%) as a colourless gum. The spectroscopic data was in agreement with the previously reported data.

**(*R*)-2-Hydroxy-2-methylpent-4-enoic acid (102):**




To a solution of the amide **94** (405 mg, 2.83 mmol) in THF-water (1:1, 14 mL) at ambient temperature was added iodine (1.69 g, 6.60 mmol) and the solution was stirred in the dark for 12 h. The solution was then extracted with ethyl acetate (3×20 mL), and the combined extracts were washed with saturated aqueous sodium thiosulphate solution, dried ($Na_2SO_4$) and then concentrated under reduced pressure to provide a yellow gum (610 mg). This was dissolved in THF-water (1:1, 12 mL) and zinc (480 mg, 7.40 mmol) was added. The vigorously stirred mixture was heated at 50 °C for 4 h, cooled to room temperature and the THF was removed under reduced pressure. The residue was cooled to 0 °C, aqueous HCl (4 M, 10 mL) was added and the mixture was stirred until all of the solids dissolved. The resulting acidic solution was extracted with EtOAc (3×50 mL) and the combined extracts were dried ($Na_2SO_4$) and concentrated under reduced pressure to provide a brown gum (982 mg). This was dissolved in EtOAc (10 mL) and the solution was extracted with saturated aqueous $NaHCO_3$ (2×10 mL). The combined aqueous extracts were cooled to 0 °C, acidified with concentrated aqueous HCl and the resulting clear solution was extracted with EtOAc (3×30 mL). The combined extracts were dried ($Na_2SO_4$) and concentrated

under reduced pressure to provide a dark yellow gum (800 mg). Purification by flash chromatography on silica gel (EtOAc/hexanes, 1/1) provided the acid **102** (220 mg, 59%) as a pale yellow gum.

**IR** (neat): 3362, 2980, 1719, 1635, 1227, 1163, 919 $cm^{-1}$.

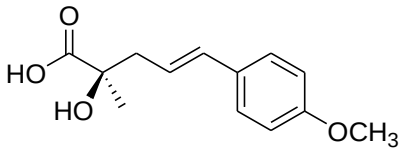
**$^{1}$H NMR** (300 MHz, $CDCl_3$): δ 5.85-5.74 (m, 1H, C*H*), 5.22 (s, 1H, CH=C$H_2$), 5.18 (d, 1H, *J* = 5.0, CH=C$H_2$), 2.61 (dd, 1H, *J* = 7.1, 13.8, C$H_2$CH), 2.44 (dd, 1H, *J* = 7.5, 13.8, C$H_2$CH), 1.50 (s, 3H, $CH_3$).

**$^{13}$C NMR** (75 MHz, $CDCl_3$): δ 180.6 (*C*=O), 131.8 (*C*H=$CH_2$), 120.0 (CH=*C*$H_2$), 74.4 (*C*-$CO_2H$), 44.4 (*C*$H_2$CH), 25.4 (*C*$H_3$).

**MS** (CI Neg.): m/z 128.9 (M-1).

$[\alpha]_D^{25}$ = –11.1 (*c* 1, EtOH); lit.[38] $[\alpha]_D^{25}$ –5.2 (*c* 1, EtOH) for material with 42% *ee*).

**(*R*)-*E*-2-Hydroxy-5-(4-methoxyphenyl)-2-methylpent-4-enoic acid (103):**




To a solution of the acid **102** (300 mg, 2.30 mmol) in $CH_2Cl_2$ (4 mL) under nitrogen was added a solution of Grubbs' II catalyst (390 mg, 0.046 mmol) in $CH_2Cl_2$ (4 mL) followed by the addition of 4-vinylanisole (0.6 mL, 4.6 mmol). The solution was heated at reflux for 7 h, cooled to ambient temperature and the solvent was evaporated under reduced pressure to obtain a brown solid. This was dissolved in EtOAc (5 mL) and the solution was extracted with saturated aqueous $NaHCO_3$ (2×5 mL). The combined bicarbonate extracts were cooled and acidified to pH 2 with

concentrated aqueous HCl. The acidic solution was extracted with EtOAc (3×15 mL) and the combined organic layers were dried ($Na_2SO_4$) and concentrated under reduced pressure to provide **103** (380 mg, 70%) as a white solid. This was pure as determined by $^1$H NMR and was used without further purification. An analytical sample was obtained by flash chromatography on silica gel (EtOAC/hexanes, 1/1).

**Mp**: 169-170 °C.

**IR** (neat): 3434, 2932, 1720, 1509, 1274, 1247, 1202, 1150, 1103, 1027, 961 $cm^{-1}$.

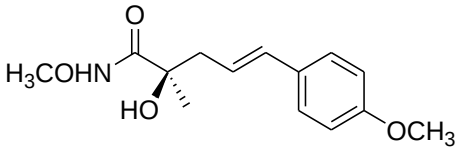
**$^1$H NMR** (300 MHz, $CDCl_3$): δ 7.29 (d, 2H, *J* = 8.7, ArC*H*), 6.83 (d, 2H, *J* = 8.7, ArC*H*), 6.46 (d, 1H, *J* = 15.7, Ar-C*H*=CH), 6.09-5.98 (m, 1H, CH=C*H*$CH_2$), 3.80 (s, 3H, OC*H*$_3$), 2.73 (dd, 1H, *J* = 7.2, 14.0, C*H*$_2$-CH), 2.54 (dd, 1H, *J* = 7.8, 14.0, C*H*$_2$-CH), 1.52 (s, 3H, C*H*$_3$).

**$^{13}$C NMR** (75 MHz, $CDCl_3$): δ 180.7 (*C*O), 159.1 (Ar*C*-$OCH_3$), 134.2 (Ar-*C*H=CH), 129.8 (Ar$C_{ipso}$), 127.5 (Ar*C*), 120.7 (Ar-CH=*C*H), 114.0 (Ar*C*), 74.8 (*C*$CH_3$), 55.3 (Ar-O*C*$H_3$), 43.6 (*C*$H_2$), 25.3 (*C*$H_3$).

**MS** (CI Pos.): *m/z* 236 ($M^+$); HRMS: (EI Pos., TOF) *m/z* 236.1046 (236.1049 calc. for $C_{13}H_{16}O_4$ ($M^+$)).

$[\alpha]_D^{25}$ = –9.5 (*c* 0.5, $CHCl_3$).

**(*R*)-*E*-2-Hydroxy-*N*-methoxy-5-(4-methoxyphenyl)-2-methylpent-4-enamide (114):**




To a solution of the acid **103** (400 mg, 2.54 mmol) in $CH_2Cl_2$ (15 mL) at 0 $^oC$ was added 4-methylmorpholine (0.29 mL, 2.6 mmol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (536 mg, 2.80 mmol), methoxyamine hydrochloride (634 mg, 7.6 mmol) and solid $Na_2CO_3$ (694 mg, 7.6 mmol). The resulting clear, brown solution was warmed to ambient temperature and stirred for 24 h. Aqueous HCl (0.5 M, 5 mL) was added and the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (2×10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, dried ($Na_2SO_4$) and concentrated to provide the amide **114** (480 mg, 72%) as a brown gum. This was pure by $^1H$ NMR and was used without further purification. An analytical sample was obtained by flash chromatography on silica gel (EtOAc/hexanes, 7/3).

**IR** (neat): 3431, 2925, 1704, 1607, 1511, 1363, 1246, 1169 $cm^{-1}$.

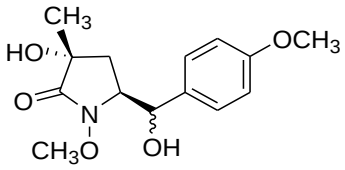
**$^1H$ NMR** (300 MHz, $CDCl_3$): δ 9.14 (bs, 1H, NH), 7.29 (d, 2H, *J* = 8.7, Ar*H*), 6.85 (d, 2H, *J* = 8.7, Ar*H*), 6.48 (d, 1H, *J* = 15.8, Ar-C*H*=CH), 6.07-5.97 (m, 1H, CH=C*H*$CH_2$), 3.81 (s, 3H, N-OC*H*$_3$), 3.77 (s, 3H, Ar-OC*H*$_3$), 2.88 (dd, 1H, *J* = 7.2, 13.8, C*H*$_2$CH), 2.42 (dd, 1H, *J* = 8.4, 13.8, C*H*$_2$CH), 2.25 (bs, 1H, OH), 1.49 (s, 3H, C*H*$_3$).

**$^{13}$C NMR** (75 MHz, $CDCl_3$): δ 172.8 (*C*O), 159.2 (Ar*C*-$OCH_3$), 134.5 (Ar*C*H=CH), 129.0 (Ar$C_{ipso}$), 127.4 (Ar*C*), 121.1 (Ar-CH=*C*H), 114.0 (Ar*C*), 75.5 (*C*$CH_3$), 64.3 (N-O*C*$H_3$), 55.3 (Ar-O*C*$H_3$), 43.7 (*C*$H_2$), 26.0 (*C*$H_3$).

**MS** (CI Pos.): *m/z* 266 $(M+H)^+$; HRMS (EI Pos., TOF): *m/z* 265.1315 (265.1314 calc. for $C_{14}H_{19}NO_4$ ($M^+$)).

$[\alpha]_D^{25}$ = +10.9 (*c* 1, $CHCl_3$).

**(3*R*,5*S*)-3-Hydroxy-5-(hydroxy(4-methoxyphenyl)methyl)-1-methoxy-3-methylpyrrolidin-2-one (118):**




To a stirred solution of amide **114** (130 mg, 0.48 mmol) in $CH_2Cl_2$ (5 mL) at –10 °C (ice-salt bath) was added bis(trifluoroacetoxy)iodobenzene (252 mg, 0.58 mmol). The solution was stirred at –10 °C for 90 min and aqueous NaOH (2.5 M, 1.0 mL) was added. The mixture was stirred vigorously for 5 min at ambient temperature and the resulting biphasic mixture was separated. Aqueous layer was extracted by $CH_2Cl_2$ (2×10 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated under reduced pressure to provide a brown solid which was purified by flash chromatography on silica gel (EtOAc/hexanes, 4/1) to provide the pyrrolidone **118** (88 mg, 68%) as a 5/1 mixture of diastereomers.

**IR** (neat): 3367, 1691, 1511, 1244, 1174, 1024 $cm^{-1}$.

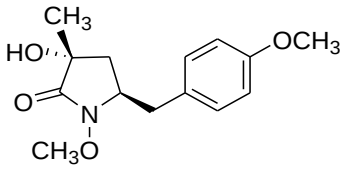
**$^{1}$H NMR** (500 MHz, $CDCl_3$): **Major diastereomer**: δ 7.28 (d, 2H, *J* = 6.5 Hz, Ar*H*), 6.91 (d, 2H, *J* = 8.7 Hz, Ar*H*), 5.14 (br d, 1H, *J* = 2.3, C*H*(OH)Ar), 4.05-4.03 (m, 1H, C*H*$CH_2$), 3.91 (s,3H, N-OC*H*$_3$), 3.81 (s, 3H, Ar-OC*H*$_3$), 2.21 (d, 1H, *J* = 2.9, CHO*H*), 2.10 (dd, 1H, *J* = 6.0, 13.7, C*H*$_2$), 1.82 (dd, 1H, *J* = 8.1, 13.7, C*H*$_2$), 1.44 (s, 3H, C*H*$_3$). **Visible peaks for the minor diastereomer**: δ 7.95 (d, 2H, *J* = 9.0, Ar*H*), 6.99 (d, 2H, *J* = 9.0, Ar*H*), 4.20-4.16 (m, 1H, C*H*$CH_2$), 3.90 (s, 3H, ArO-C*H*$_3$), 3.81 (s, 3H, N-OC*H*$_3$), 2.18 (d, 1H, *J* = 12.3, CHO*H*), 2.02 (dd, 1H, *J* = 5.4, 13.4, C*H*$_2$), 1.92 (dd, 1H, *J* = 8.0, 14.0, C*H*$_2$).

**$^{13}$C NMR** (75MHz, $CDCl_3$): **Major diastereomer**: δ 171.6 (*C*O), 159.3 (Ar*C*-$OCH_3$), 131.2 (Ar$C_{ipso}$), 127.0 (Ar*C*), 113.9 (Ar*C*), 71.6 (C*C*$H_3$), 69.2 (*C*HOH), 62.1 (N-O*C*$H_3$), 59.6 (O*C*$H_3$), 55.3 (*C*HN), 30.8 (*C*$H_2$), 24.9 (*C*$H_3$).

**Visible peaks for minor diastereomer**: δ 130.8 (Ar$C_{ipso}$), 128.1 (Ar*C*), 61.7 (N-O*C*$H_3$), 34.3 (*C*$H_2$).

**MS** (CI Pos.): *m/z* 282 $(M+H)^+$; HRMS (CI Pos., TOF): *m/z* 282.1342 (282.1341 calculated for $C_{14}H_{20}NO_5$ $(M+H)^+$.

**(3*R*,5*S*)-5-(4-Methoxybenzyl)-3-hydroxy-1-methoxy-3-methylpyrrolidin-2-one (119):**




To a mixture of pyrrolidone **118** (180 mg, 0.64 mmol) and triethylsilane (1.02 mL, 6.40 mmol) at 0 °C was added trifluoroacetic acid (0.24 mL, 3.2 mmol) and the

mixture was stirred vigorously at ambient temperature for 7 h (the biphasic reaction mixture turned homogeneous after 7 h). Aqueous NaOH (1.0 M, 2.0 mL) was added and the mixture was extracted with EtOAc (3×10 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated to provide white solid (280 mg) which was purified using flash silica gel (EtOAc/hexanes, 8/2) to obtain **119** (130 mg, 94%) as a white solid.

**Mp**: 95-97 °C.

**IR** (neat): 3391, 1707, 1510, 1249, 1181, 1023 $cm^{-1}$.

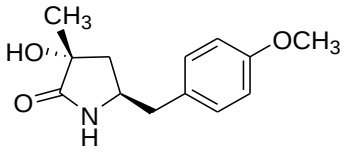
**$^1$H NMR** (500 MHz, $CDCl_3$): δ 7.10 (d, 2H, *J* = 8.4, Ar*H*), 6.85 (d, 2H, *J* = 8.4, Ar*H*), 4.11-4.09 (m, 1H, NC*H*), 3.87 (s, 3H, N-OC*H*$_3$), 3.79 (s, 3H, Ar-OC*H*$_3$), 3.05 (dd, 1H, *J* = 3.7, 13.7, C*H*$_2$Ar), 2.73 (dd, 1H, *J* = 8.0, 13.7, C*H*$_2$Ar), 2.5 (bs, 1H, O*H*), 2.14 (dd, 1H, *J* = 7.7, 13.7, C*H*$_2$CH), 1.73 (dd, 1H, *J* = 5.9, 13.7, C*H*$_2$CH), 1.18 (s, 3H, C*H*$_3$).

**$^{13}$C NMR** (75 MHz, $CDCl_3$): δ 170.9 (*C*O), 158.6 (Ar*C*-OCH$_3$), 130.6 (Ar*C*), 127.7 (Ar*C*$_{ipso}$), 114.1 (Ar*C*), 71.4 (*C*CH$_3$), 62.0 (*C*HN), 55.3 (*C*H$_3$O-N), 54.9 (Ar-O*C*H$_3$), 37.5 (Ar*C*H$_2$), 36.7 (*C*H$_2$CH), 25.2 (*C*H$_3$).

**MS** (CI Pos.): *m/z* 266.1 $(M+H)^+$; HRMS (CI Pos., TOF) *m/z* 265.1312 (265.1314 calculated for $C_{14}H_{19}NO_4$ ($M^+$).

$[\alpha]_D^{25}$ = –4.9 (c 1, $CHCl_3$).

**(3*R*,5*R*)-5-(4-methoxybenzyl)-3-hydroxy-3-methylpyrrolidin-2-one (120):**




To a solution of amide **119** (60 mg, 0.22 mmol) in $CH_3CN$:$H_2O$ (15/1, 6.0 mL) was added $Mo(CO)_6$ (119 mg, 0.45 mmol) and the mixture was heated to reflux under nitrogen for 24 h. The reaction mixture turned yellow after 2 h and gradually turned green and then black. After 24 h the mixture was cooled to room temperature and concentrated. The black residue (180 mg) was purified by flash chromatography on silica gel (EtOAc/hexanes, 7/3 followed by EtOAc/MeOH, 9.5/0.5) to provide the pyrrolidone **120** (37 mg, 71%) as a white solid.

**Mp**: 87- 89 °C.

**IR** (neat): 3301, 2932, 1692, 1604, 1110, 612 $cm^{-1}$.

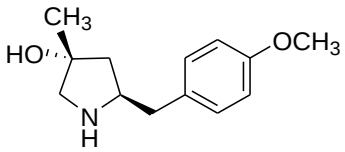
**$^1$H NMR** (300 MHz, $CD_3OD$): δ 7.12 (d, 2H, *J* = 8.6, Ar*H*), 6.86 (d, 2H, *J* = 8.7, Ar*H*), 3.96-3.89 (m, 1H, C*H*NH), 3.76 (s, 3H, OC*H*$_3$), 2.83 (dd, 1H, *J* = 5.7, 13.5 Hz, C*H*$_2$Ar), 2.65 (dd, 1H, *J* = 7.4, 13.6 Hz, C*H*$_2$Ar), 2.13 (dd, 1H, *J* = 6.6, 13.3Hz, C*H*$_2$CH), 1.79 (dd, 1H, *J* = 6.5, 13.7 Hz, C*H*$_2$CH), 1.24 (s, 3H, C*H*$_3$).

**$^{13}$C NMR** (75 MHz, $CD_3OD$): δ180.3 (*C*O), 160.1 (Ar*C*-$OCH_3$), 131.5 (Ar*C*), 130.5 (Ar$C_{ipso}$), 115.0 (Ar*C*), 75.3 (*C*OH), 55.7 (O*C*$H_3$), 53.5 (*C*HNH), 42.9 (*C*$H_2$Ar), 42.0 (*C*$H_2$CH), 24.8 (*C*$H_3$).

**MS** (CI Pos.): *m/z* 235.27 $(M+H)^+$; HRMS (EI Pos., TOF): *m/z* 235.1203 (235.1208 calc. for $C_{13}H_{17}NO_3$ ($M^+$)).

$[\alpha]_D^{25}$ = –5.5 (*c* 1.0, acetone).

**(3*R*,5*R*)-5-(4-Methoxybenzyl)-3-methylpyrrolidin-3-ol (121):**




To a suspension of lithium aluminum hydride (129 mg, 3.40 mmol) in THF (1 mL) at 0 °C was added a solution of the pyrrolidone **120** (100 mg, 0.42 mmol) in THF (3 mL) dropwise. The mixture was warmed to room temperature and then heated to reflux for 12 h. The mixture was cooled to 0 °C and water (0.1 mL), aqueous NaOH (2.5 M, 1.3 mL) and water (0.3 mL) were added sequentially with a 15 min stirring period between each addition and 20 min stirring after the last addition. The resulting mixture was filtered with suction and the white precipitate was washed with THF (2×10 mL). The combined filtrates were dried ($Na_2SO_4$) and concentrated. The residue was dissolved in EtOAc (3 mL) and the solution was extracted with aqueous HCl (1 M, pH 5, 2×3 mL). The combined extracts were cooled (<5 $^oC$) and basified to pH 9 with NaOH pellets. The basic solution was extracted with EtOAc (3×10 mL) and the combined extracts were dried ($Na_2SO_4$) and concentrated to provide the pyrrolidine **121** (74 mg 79%) as a yellow gum. This was pure by $^1H$ NMR and was used without further purification. An analytical sample was obtained by flash chromatography on silica gel ($CH_2Cl_2$/MeOH, 9/1 containing 1% aq. ammonia).

**IR** (neat): 3301, 2924, 1511, 1243, 1034 $cm^{-1}$.

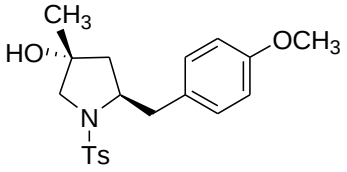
**$^{1}$H NMR** (500 MHz, $CDCl_3$): δ 7.13 (d, 2H, *J* = 8.6, Ar*H*), 6.85 (d, 2H, *J* = 8.6, Ar*H*), 3.80 (s, 3H, OC$H_3$), 3.69-3.64 (m, 1H, C*H*NH), 2.97-2.90 (AB system, 2H, *J* = 11.2, NHC$H_2$), 2.75-2.67 (ABX system, 2H, *J* = 7.0, 13.6, ArC$H_2$), 1.93 (dd, 1H, *J* = 6.3, 13.2, NCHC$H_2$), 1.48 (dd, 1H, J= 9.3, 13.2, NCHC$H_2$), 1.40 (s, 3H, C$H_3$).

**$^{13}$C NMR** (75 MHz, $CDCl_3$): δ 158.1 (Ar*C*-$OCH_3$), 131.5 (Ar$C_{ipso}$), 129.9 (Ar*C*), 113.9 (Ar*C*), 79.0 (*C*$CH_3$), 59.7 (NH*C*$H_2$), 59.4 (NH*C*H), 55.3 (Ar-O*C*$H_3$), 47.3 (*C*$H_2$), 41.5 (Ar*C*$H_2$), 26.4 (*C*$H_3$).

**MS** (CI Pos.): *m/z* 222.1 $(M+H)^+$; HRMS (CI Pos., TOF): *m/z* 222.1489 (222.1494 calc. for $C_{13}H_{20}NO_2(M+1)^+$).

$[\alpha]_D^{25}$ = –70 (*c* 0.5, $CHCl_3$).

**(–)-(2*R*,4*R*)-5-(4-Methoxybenzyl)-3-methyl-1-tosylpyrrolidin-3-ol (122):**




To a stirred solution of *p*-toluenesulfonyl chloride (19.40 mg, 0.10 mmol) in THF (0.5 mL) was added freshly distilled triethylamine (19.0 μL, 0.14 mmol) at 0 °C, followed by a solution of the amine **121** (15 mg, 0.07 mmol) in THF (1.0 mL). The mixture was stirred for 8 h at ambient temperature and then saturated, aqueous $NaHCO_3$ (2 mL) was added. The mixture was extracted with $CH_2Cl_2$ (3 x 10 mL) and the combined extracts were dried ($Na_2SO_4$) and concentrated. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 1/1) to provide **122** (19 mg, 75%) as an off-white foam.

**IR**: 3508, 2929, 1511, 1331, 1245, 1151, 1088, 1033 $cm^{-1}$.

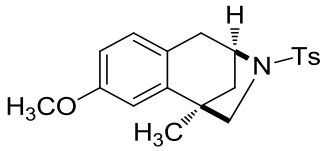
**$^{1}$H NMR** (300 MHz, $CDCl_3$): δ 7.81 (d, 2H, *J* = 8.1, Ar*H*), 7.34 (d, 2H, *J* = 8.1, Ar*H*), 7.15 (d, 2H, *J* = 8.6, Ar*H*), 6.83 (d, 2H, *J* = 8.6, Ar*H*), 4.02-3.94 (m, 1H, C*H*NTs), 3.78 (s, 3H, OC$H_3$), 3.39 (dd, 1H, *J* = 2.3, 12.4, C$H_2$NTs), 3.31 (dd, 1H, *J* = 3.5, 13.5 Hz, C$H_2$Ar), 3.17 (d, 1H, *J* = 12.4, C$H_2$NTs), 2.85 (dd, 1H, *J* = 8.8, 13.5, C$H_2$Ar), 2.42 (s, 3H, ArC$H_3$), 1.80-1.75 (ddd, 1H, *J* = 2.3, 6.9, 13.4, C$H_2$CH), 1.60 (dd, 1H, *J* = 9.7, 13.3 Hz, C$H_2$CH), 1.19 (s, 3H, C$H_3$).

**$^{13}$C NMR** (75 MHz, $CDCl_3$): δ 158.3 (Ar*C*-$OCH_3$), 143.6 (Ar*C*-$CH_3$), 135.0 (Ar*C*Ts), 130.6 (Ar*C*), 129.72 (Ar$C_{ipso}$), 129.65 (Ar*C*), 127.8 (Ar*C*), 113.8 (Ar*C*), 76.0 (*C*$CH_3$), 61.6 (*C*$H_2$N), 61.1 ($OCH_3$), 55.2 (*C*HNTs), 45.6 (*C*$H_2$), 41.0 (Ar*C*$H_2$), 24.2 (*C*$H_3$), 21.6 (Ar*C*$H_3$).

**MS** (CI Pos.): *m/z* 376.1 $(M+H)^+$; HRMS (CI Pos., TOF): *m/z* 376.1589 (376.1583 calc. for $C_{20}H_{26}NO_4S$ $(M+H)^+$).

$[\alpha]_D^{25}$ = –76.8 (*c* 0.5, $CHCl_3$).

**(–)-(1*R*,4*S*)-8-Methoxy-1-methyl-3-tosyl-2,3,4,5-tetrahydro-1*H*-1,4-methanobenzo[*d*]azepine (19)**:




To a suspension of $AlCl_3$ (44 mg, 0.34 mmol) in $CH_2Cl_2$ at 0 °C was added a solution of **121** (12 mg, 0.03 mmol). The mixture was warmed to ambient temperature and stirred for 9 h. The resulting brown solution was poured into saturated aqueous

$NaHCO_3$ (3 mL) and the mixture was extracted with $CH_2Cl_2$ (3×10 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated to provide a yellow solid which was purified by flash chromatography on silica gel (EtOAc/hexanes, 2/3) to provide **19 (**8 mg, 72%) as a pale yellow solid.

**Mp**: 136-138 ºC (lit.[2] Mp: 136-138 °C).

**IR**: 2924, 1336, 1291, 1236, 1154, 1093, 1043, 809 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$): δ 7.69 (d, 2H, *J* = 8.3, Ar*H*), 7.28 (d, 2H, *J*= 8.0, Ar*H*), 6.97 (d, 2H, *J* = 8.3, Ar*H*), 6.77 (d, 1H, *J* = 2.6, Ar*H*), 6.71 (dd, 1H, *J* = 2.7, 8.3, Ar*H*), 4.38 (m, 1H, C*H*-NTs), 3.77(s, 3H, OC$H_3$), 3.39 (dd, 1H, *J* = 1.3, 8.6, ArC$H_2$), 3.11 (d, 1H, *J* = 16.5, C$H_2$-NTs), 3.02 (d, 1H, *J* = 8.6, C$H_2$-NTs), 2.92 (dd, 1H, *J* = 2.9, 16.5, ArC$H_2$), 2.42 (s, 3H, ArC$H_3$), 1.79 (d, 1H, *J* = 11.2, C$H_2$CH), 1.47 (dd, 1H, *J* = 1.3, 6.2, 11.2, C$H_2$CH), 1.40 (s, 3H, C$H_3$).

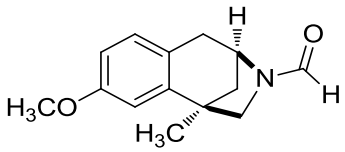
**$^{13}$C NMR** (75 MHz, $CDCl_3$): δ 158.0 (Ar*C*-$OCH_3$), 145.0 (Ar$C_{ipso}$), 143.1 (Ar*C*$CH_3$), 135.8 (Ar$C_{ipso}$), 130.4 (Ar*C*), 129.6 (Ar*C*), 127.1 (Ar*C*), 125.3 (Ar$C_{ipso}$), 111.7 (Ar*C*), 110.1 (Ar*C*), 63.0 (O*C*$H_3$), 57.8 (*C*$H_2$N), 55.3 (*C*HN), 42.4 ($CH_3$-C-*C*$H_2$), 41.7 ($CH_3$-*C*-$CH_2$), 38.4 (*C*$H_2$Ar), 21.6 (Ar*C*$H_3$), 20.8 (*C*$H_3$).

**MS**: (CI Pos.): *m/z* 358.1 $(M+H)^+$; HRMS (EI Pos., TOF): *m/z* 357.1394 (357.1399 calc. for $C_{20}H_{23}NO_3S$ ($M^+$).

$[\alpha]_D^{25}$ = –18.9 (*c* 0.9, $CHCl_3$; lit.[12] $[\alpha]_D^{25}$ –16.9 (*c* 0.89, $CHCl_3$).

HPLC: Chiralpak AD-H, hexanes/2-propanol 72/25, 254 nm, $t_1$ = 7.4 min (minor), $t_2$ = 8.9 min (major), *ee*: 91%; [lit.[24] $t_1$ = 8.04 min, $t_2$ = 9.80 min].

**(−)-(1*R*,4*S*)-8-Methoxy-1-methyl-4,5-dihydro-1*H*-1,4-methanobenzo[*d*]azepine-3(2*H*)-carbaldehyde (123):**




To a solution of **121** (30 mg, 0.13 mmol) in $CH_2Cl_2$ (2.5 mL) was added acetic formic anhydride (14 µL, 0.15 mmol). The mixture was stirred at room temperature for 4 h and then concentrated under reduced pressure to provide the *N*-formyl derivative 29 mg as a yellow gum. This was dissolved in $CH_2Cl_2$ (0.5 mL) and the solution was added dropwise to a cold (0 $^oC$), stirred suspension of $AlCl_3$ (162 mg, 1.21 mmol) in $CH_2Cl_2$ (0.5 mL). The mixture was then stirred at ambient temperature for 24h, cooled to 0 °C and saturated aqueous $NaHCO_3$ (2 mL) was added. The biphasic solution was transferred to a separatory funnel and extracted with $CH_2Cl_2$ (3×5 mL). The combined extracts were dried ($Na_2SO_4$) and concentrated to provide a pale yellow gum. Purification by flash chromatography on silica gel ($CH_2Cl_2$/MeOH 9.5/0.5) provided **123** (23 mg, 88%) as a colourless gum.

**IR**: 2955, 1657, 1612, 1417, 1233, 1036 $cm^{-1}$.

**$^1$H NMR** (300 MHz, $CDCl_3$): M**ajor rotamer** : δ 8.34 (s, 1H, *H*CO), 7.01 (d, 1H, *J* = 8.4, Ar*H*), 6.82 (d, 1H, *J* = 2.6, Ar*H*), 6.73 (dd, 2H, *J* = 2.6, 8.2, Ar*H*), 4.42-4.41 (m, 1H, C*H*), 3.78 (s, 3H, OC$H_3$), 3.53 (d, 1H, *J* = 11.2, C$H_2$Ar ), 3.24 (d, 2H, *J* = 12.1, C$H_2$N), 2.93 (d, 2H, *J* = 16.6, C$H_2$Ar), 2.02 (dd, 1H, *J* =1.4, 5.5, C$H_2$), 1.97 (dd, 1H, *J* = 1.3, 5.0, C$H_2$ ), 1.55 (s, 3H, C$H_3$).

**Minor rotamer**: δ 8.10 (s, 1H, *H*CO), 7.02 (d, 1H, *J* = 8.4, Ar*H*), 6.84 (d, 1H, *J* = 2.6, Ar*H*), 4.65 (m, 1H, C*H*N), 3.79 (s, 3H, OC$H_3$), 3.48 (d, 1H, *J* = 9.2, C$H_2$N), 3.40 (d, 1H, *J* = 9.2,C$H_2$N), 3.13 (dd, 1H, *J* = 2.8, 16.5, C$H_2$Ar), 1.55 (s, 3H, C$H_3$).

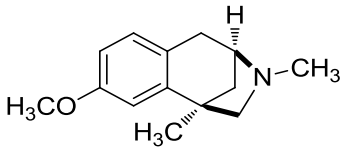
**$^{13}$C NMR** (75 MHz, $CDCl_3$): **Major rotamer**: δ 160.3 (*C*O), 157.9 (Ar*C*-$OCH_3$), 145.4 (Ar*C*-$CCH_3$), 130.2 (Ar*C*), 123.8 (Ar$C_{ipso}$), 111.6 (Ar*C*), 109.7 (Ar*C*), 58.8 (*C*$H_2$N), 55.1 (*C*$H_3$O), 52.5 (*C*HN), 41.4 (*C*$H_2$CH), 38.9 (*C*$CH_3$), 34.9 (*C*$H_2$Ar), 20.7 (*C*$H_3$).

**Minor rotamer**: δ 160.4 (*C*O), 157.8 (Ar*C*-$OCH_3$), 144.6 (Ar*C*-$CCH_3$), 130.4 (Ar*C*), 125.2 (Ar$C_{ipso}$), 111.5 (Ar*C*), 109.8 (Ar*C*), 63.7 (*C*HN), 60.6 (*C*$H_2$N), 54.7 (*C*$H_3$O), 40.4 (*C*$CH_3$), 20.5 (*C*$H_3$).

**MS**: (CI Pos.): *m/z* 232.1 $(M+H)^+$; HRMS (EI Pos., TOF): *m/z* 231.1264 (231.1259 calc. for $C_{14}H_{17}NO_2$ ($M^+$).

$[\alpha]_D^{25}$ = –23.2 (*c* 1, $CHCl_3$).

**(+)-8-*O*-Methylaphanorphine (14):**




A solution of the formamide **123** (10 mg, 0.04 mmol) in ether (0.5 mL) was added to a stirred suspension of lithium aluminium hydride (5 mg, 0.12 mmol) in diethylether (0.5 mL) at 0 °C and the resulting mixture was stirred at ambient temperature for 7 h. The mixture was then cooled to 0 °C and treated sequentially with water (3μL), aqueous NaOH (2.5 M, 50 μL), and water (9 μL) with 5 min of stirring

after each addition. The resulting mixture was filtered with suction and the solid residue was washed several times with ether. The combined filtrates were dried ($Na_2SO_4$) and concentrated to provide (+)-8-*O*-methylaphanorphine **14** (7 mg, 74%) as a yellow liquid.

**IR**: 2923, 1611, 1577, 1290, 1040, 804 $cm^{-1}$.

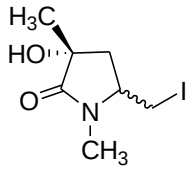
**$^1$H NMR** (500 MHz, $CDCl_3$): δ 7.01 (d, 1H, *J* = 8.3, Ar*H*), 6.78 (d, 1H, *J* = 2.6, Ar*H*), 6.67 (dd, 1H, *J* = 2.6, 8.3, Ar*H*), 3.77 (s, 3H, OC*H*$_3$), 3.40 (m, 1H, NC*H*), 3.02 (d, 1H, *J* =16.7, C*H*$_2$), 2.85 (dd, 1H, *J* = 3.1, 7.9, ArC*H*$_2$), 2.83 (d, 1H, *J* = 9.0, ArC*H*$_2$), 2.74 (d, 1H, *J* = 9.0, NC*H*$_2$), 2.47 (s, 3H, OC*H*$_3$), 2.02 (dd, 1H, *J* = 5.2, 10.8, C*H*$_2$), 1.85 (d, 1H, *J* = 10.9, C*H*$_2$) 1.48 (s, 3H, C*H*$_3$).

**$^{13}$C NMR** (75 MHz, $CDCl_3$): δ 157.4 (Ar*C*-$OCH_3$), 147.9 (Ar*C*-$CCH_3$), 130.0 (Ar*C*), 125.9 (Ar*C*$_{ipso}$), 110.7 (Ar*C*), 109.2 (Ar*C*), 71.2 (*C*H-$NCH_3$), 61.1 (*C*$H_2$-$NCH_3$), 55.0 (O*C*$H_3$), 43.0 (*C*$H_2$), 41.3 (N*C*$H_3$), 35.5 (*C*$CH_3$), 29.5 (*C*$H_2$), 21.3 (*C*$H_3$).

**MS** (CI Pos): *m/z* 218.1$(M+H)^+$; HRMS (CI Pos., TOF): *m/z* 217.1467 (217.1467 calc. for $C_{14}H_{19}NO$ ($M^+$).

$[\alpha]_D^{25}$ = +21.3 (*c* 0.4, ($CHCl_3$), lit.[3] $[\alpha]_D^{23}$= +9.39 (*c* 0.30, $CHCl_3$).

**(3*R*)-3-Hydroxy-5-(iodomethyl)-1,3-dimethylpyrrolidin-2-one (109):**




To a solution of the amide **94** (0.27 g, 1.9 mmol) in $CH_2Cl_2$ (6 mL) at 0 °C, was added freshly distilled triethylamine (0.58 mL, 4.2 mmol) and freshly distilled

trimethylsilyltriflate (0.78 mL, 4.2 mmol). The resulting brown solution was warmed to room temperature and stirred for 45 min. The mixture was cooled to 0 °C and a solution of iodine (1.07g, 4.21 mmol) in $CH_2Cl_2$ (19 mL) was added. The mixture was stirred at room temperature for 20 h and a saturated solution of $NaHCO_3$ (25 mL) was added. The mixture was stirred for 30 min and the phases were separated. The aqueous phase was extracted with $CH_2Cl_2$ (2×30 mL), the combined organic phases were washed with saturated, aqueous sodium thiosulfate (15 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 8/2) to provide the iodolactam **109** (0.43g, 83.8%) as 1.6:1 mixture of diasteroemers.

**IR** (neat): 3316, 2361, 1682, 1254 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$): **Major diastereomer**: δ 3.48-3.35 (m, 2H, C*H*-$NCH_3$, C*H*$_2$I), 3.33-3.27 (m, 1H, C*H*$_2$I), 2.84 (s, 3H, N-C*H*$_3$), 2.34 (dd, 1H, *J* = 7.7, 14.0, $CH_3$-C-C*H*$_2$), 1.81 (dd, 1H, *J* = 5.5, 14.0, $CH_3$-C-C*H*$_2$), 1.51 (s, 3H, C*H*$_3$).

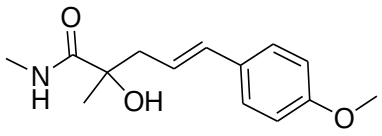
**Minor diastereomer**: δ 3.48-3.35 (m, 2H, C*H*-$NCH_3$, C*H*$_2$I), 3.33-3.27 (m, 1H, C*H*$_2$I), 2.87 (s, 3H, N-C*H*$_3$), 2.27 (dd, 1H, *J* = 7.0, 13.3, $CH_3$-C-C*H*$_2$), 2.00 (dd, 1H, *J* = 6.1, 13.3, $CH_3$-C-C*H*$_2$), 1.40 (s, 3H, C*H*$_3$).

**$^{13}$C NMR** (75 MHz, $CDCl_3$): **Major diastereomer**: δ 177.1 (*C*O), 73.8 (*C*(OH)$CH_3$), 56.6 (*C*H$NCH_3$), 40.9 ($CH_2$), 28.0 (N-*C*H$_3$), 25.2 (*C*H$_3$), 8.6 (*C*H$_2$I).

**Minor diastereomer**: δ 175.1 (*C*O), 73.9 (*C*(OH)$CH_3$), 56.1 (*C*H$NCH_3$), 40.2 ($CH_2$), 27.8 (N-*C*H$_3$), 20.7 (*C*H$_3$), 10.6 (*C*H$_2$I).

**MS** (CI Pos.): m/z 270.0 $(M+H)^+$; HRMS (EI Pos., TOF): m/z 268.9915 (268.9913 calculated for $C_7H_{12}INO_2$ $(M^+)$).

**(*E*)-2-hydroxy-5-(4-methoxyphenyl)-*N*, 2-dimethylpent-4-enamide (93):**



To a stirred solution of acid **103** (0.12 g, 0.50 mmol) in THF at 0 °C, was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride salt (0.145 g, 0.760 mmol), ethyl cyanoglyoxylate-2-oxime (0.10 g, 0.76 mmol), methylamine solution (2.0 M in THF, 0.50 mL,1.01 mmol) and the solution was stirred for a further 24 h. Hydrochloride solution (1 M, 10 mL) was added, stirred for 5 min and warmed to room temperature. THF was removed under reduced pressure, the residue extracted using $CH_2Cl_2$ (2×15 mL) and the combined organic layers were washed with a saturated solution of $NaHCO_3$ (10 mL), dried ($Na_2SO_4$) and concentrated to obtain crude amide as a brown gum. Flash silica gel chromatography (EtOAc/hexane 7/3) gave pure amide **93** as a yellow gum (55 mg, 43.6%).

**IR**: 3380, 2928, 1647, 1510, 1245, 1028, 730 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$): δ 7.28 (d, 2H, *J* = 8.8, Ar*H*), 6.83 (d, 2H, *J* = 8.8, Ar*H*), 6.44 (d, 2H, *J* = 15.8, ArC*H*), 6.01 (ddd, 1H, *J* = 6.8, 8.4, 15.4, C*H*$CH_2$), 3.79 (s, 3H, OC$H_3$), 2.83 (ddd, 1H, *J* = 1.3, 6.9, 8.5, C$H_2$CH), 2.81 (d, 3H, *J* = 4.9, NC$H_3$), 2.44 (ddd, 1H, *J* = 1.0, 8.5, 9.5, C$H_2$CH), 1.45 (s, 3H, C$H_3$).

**$^{13}$C NMR** (75 MHz, $CDCl_3$): δ 176.2 (*C*O), 159.2 (Ar*C*-$OCH_3$), 134.4 (*C*HAr), 129.7 (Ar$C_{ipso}$), 127.4 (Ar*C*), 121.6 (*C*H$CH_2$), 114.0 (Ar*C*), 75.5 (*C*$CH_3$), 55.3 (O-*C*$H_3$), 43.7(*C*$H_2$), 26.1 (N-*C*$H_3$), 26.0 (*C*$H_3$).

**MS** (CI Pos): m/z 250.0 $(M+H)^+$; HRMS (CI Pos., TOF): m/z 250.1445 (250.1443 calculated for $C_{14}H_{20}NO_3$ $(M+H)^+$).

**1.5** References

(1) Gulavita, N.; Hori, A.; Shimizu, Y.; Laszlo, P.; Clardy, J. *Tetrahedron Lett.* **1988**, *29*, 4381.

(2) (a) Takano, S.; Inomata, K.; Sato, T.; Ogasawara, K. *J. Chem. Soc., Chem. Comm.* **1989**, 1591; (b) Takano, S.; Inomata, K.; Sato, T.; Takahashi, M.; Ogasawara, K. *J. Chem. Soc., Chem. Comm.* **1990**, 290.

(3) Tamura, O.; Yanagimachi, T.; Kobayashi, T.; Ishibashi, H. *Org. Lett.* **2001**, *3*, 2427.

(4) Mayer, S. C.; Ramanjulu, J.; Vera, M. D.; Pfizenmayer, A. J.; Joullie, M. M. *J. Org. Chem.* **1994**, *59*, 5192.

(5) Grayson, J. I.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2263.

(6) (a) Hu, H.; Zhai, H. *Synlett* **2003**, 2129; (b) Ma, Z.; Hu, H.; Xiong, W.; Zhai, H. *Tetrahedron* **2007**, *63*, 7523.

(7) Westwood, N. B.; Walker, R. T. *Tetrahedron* **1998**, *54*, 13391.

(8) Ma, Z.; Zhai, H. *Synlett* **2007**, 0161.

(9) Portoghese, P. S.; Turcotte, J. G. *Tetrahedron* **1971**, *27*, 961.

(10) Dalla Croce, P.; La Rosa, C. *Tetrahedron: Asymmetry* **2002**, *13*, 197.

(11) Li, M.; Zhou, P.; Roth, H. F. *Synthesis* **2007**, 55.

(12) Yang, X.; Zhai, H.; Li, Z. *Org. Lett.* **2008**, *10*, 2457.

(13) Hulme, A. N.; Rosser, E. M. *Org. Lett.* **2001**, *4*, 265.

(14) Zhai, H.; Luo, S.; Ye, C.; Ma, Y. *J. Org. Chem.* **2003**, *68*, 8268.

(15) Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 294.

(16) Bower, J. F.; Rujirawanich, J.; Gallagher, T. *Org. Biomol. Chem.* **2010**, *8*, 1505.

(17) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125.

(18) Alker, D.; Doyle, K. J.; Harwood, L. M.; McGregor, A. *Tetrahedron: Asymmetry* **1990**, *1*, 877.

(19) Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3923.

(20) Medjahdi, M.; González-Gómez, J. C.; Foubelo, F.; Yus, M. *Eur. J. Org. Chem.* **2011**, 2230.

(21) Grainger, R. S.; Welsh, E. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 5377.

(22) Cogan, D. A.; Liu, G.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883.

(23) (a) Grzyb, J. A.; Shen, M.; Yoshina-Ishii, C.; Chi, W.; Brown, R. S.; Batey, R. A. *Tetrahedron* **2005**, *61*, 7153; (b) Jencks, W. P.; Oakenfull, D. G.; Salvesen, K. *J. Am. Chem. Soc.* **1971**, *93*, 188.

(24) Mai, D. N.; Rosen, B. R.; Wolfe, J. P. *Org. Lett.* **2011**, *13*, 2932.

(25) (a) Adsool, V. A.; Pansare, S. V. *Org. Biomol. Chem.* **2008**, *6*, 2011; (b) Pansare, S. V.; Adsool, V. A. *Org. Lett.* **2006**, *8*, 5897; (c) Pansare, S. V.; Adsool, V. A. *Org. Lett.* **2006**, *8*, 2035; (d) Pansare, S. V.; Adsool, V. A. *Tetrahedron Lett.* **2007**, *48*, 7099.

(26) (a) Li, J.; Liu, S.; Niu, S.; Zhuang, W.; Che, Y. *J. Nat. Prod.* **2009**, *72*, 2184; (b) Chen, G.-Y.; Huang, H.; Ye, J.-L.; Wang, A.-E.; Huang, H.-Y.; Zhang, H.-K.; Huang, P.-Q. *Chem. Asian J.* **2012**, *7*, 504.

(27) (a) Kato, Y.; Nakano, Y.; Sano, H.; Tanatani, A.; Kobayashi, H.; Shimazawa, R.; Koshino, H.; Hashimoto, Y.; Nagasawa, K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2579; (b) Kato, Y.; Hashimoto, Y.; Nagasawa, K. *Molecules* **2003**, *8*, 488.

(28) Pansare, S. V.; Ravi, R. G.; Jain, R. P. *J. Org. Chem.* **1998**, *63*, 4120.

(29) Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313.

(30) Yamada, K.; Tozawa, T.; Nishida, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2301.

(31) Pansare, S. V.; Kulkarni, K. G. *RSC Advances* **2013**, *3*, 19127.

(32) (a) Harding, K. E.; Burks, S. R. *J. Org. Chem.* **1984**, *49*, 40; (b) Takahata, H.; Banba, Y.; Tajima, M.; Momose, T. *J. Org. Chem.* **1991**, *56*, 240.

(33) Knapp, S.; Levorse, A. T. *J. Org. Chem.* **1988**, *53*, 4006.

(34) Boger, D. L.; Ichikawa, S.; Zhong, W. *J. Am. Chem. Soc.* **2001**, *123*, 4161.

(35) González-Bobes, F.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 5360.

(36) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Hird, M. *Chem. Commun.* **2005**, 4161.

(37) Choi, T.-L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2001**, *40*, 1277.

(38) Moorlag, H.; Kellogg, R. M.; Kloosterman, M.; Kaptein, B.; Kamphuis, J.; Schoemaker, H. E. *J. Org. Chem.* **1990**, *55*, 5878.

(39) Kikugawa, Y. *Heterocycles* **2009**, *78*, 571.

(40) Tellitu, I.; Domnguez, E. *Synlett* **2012**, 2165.

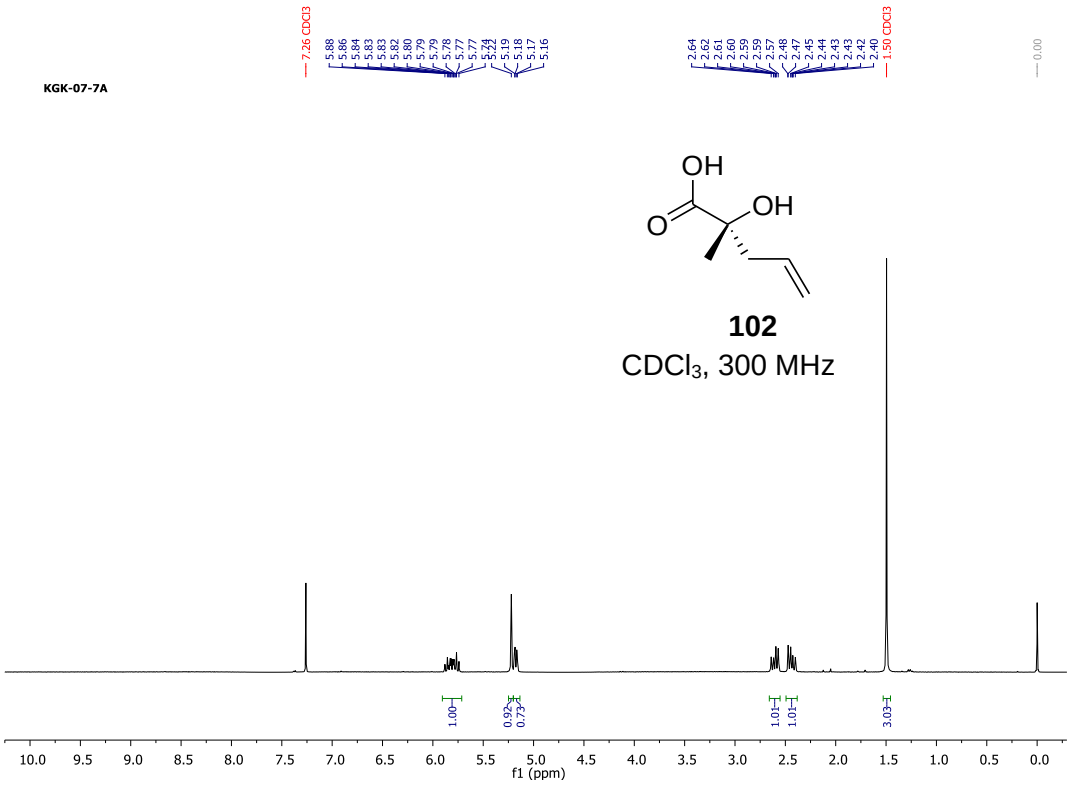
(41) Wardrop, D. J.; Bowen, E. G.; Forslund, R. E.; Sussman, A. D.; Weerasekera, S. L. *J. Am. Chem. Soc.* **2009**, *132*, 1188.

(42) Serna, S.; Tellitu, I.; Domínguez, E.; Moreno, I.; SanMartin, R. *Tetrahedron* **2004**, *60*, 6533.

(43) Revuelta, J.; Cicchi, S.; Brandi, A. *Tetrahedron Lett.* **2004**, *45*, 8375.

(44) Pansare, S. V.; Lingampally, R.; Kirby, R. L. *Org. Lett.* **2010**, *12*, 556.

## 1.6 Selected $^{1}H$ and $^{13}C$ NMR spectra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5.80
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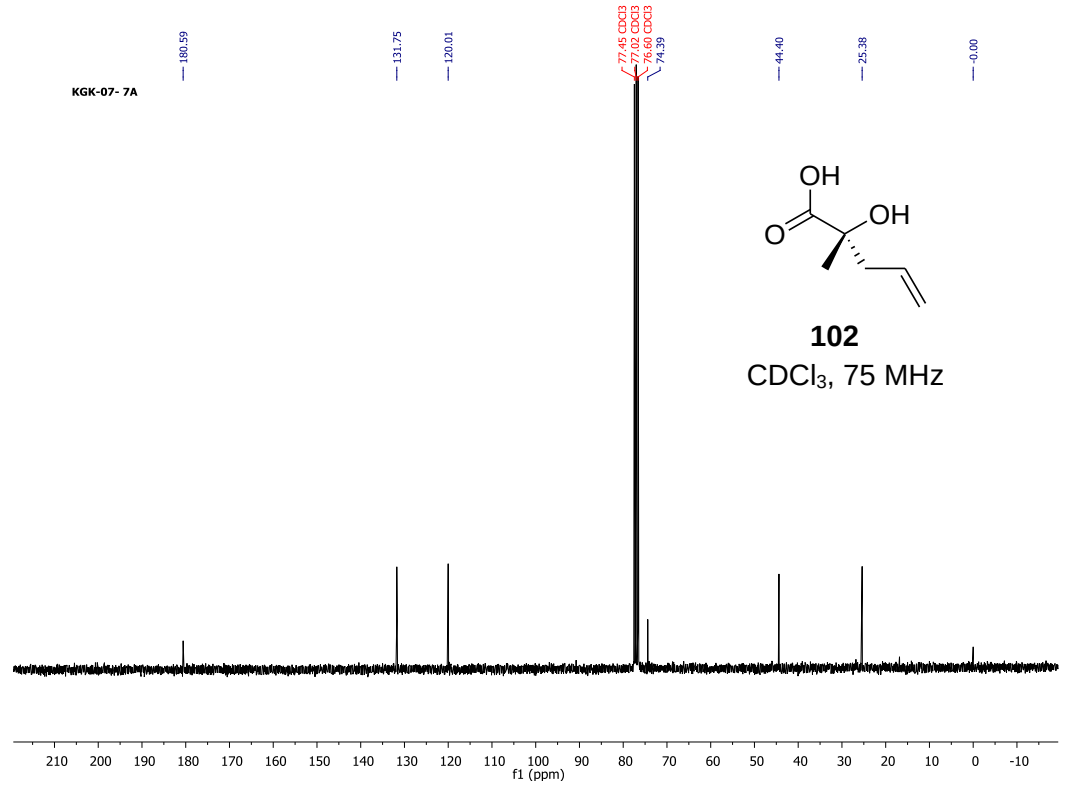
5.77
5.77
5.74
5.22
5.19
5.18
5.17
5.16
2.64
2.62
2.61
2.60
2.59
2.59
2.57
2.48
2.47
2.45
2.44
2.43
2.43
2.42
2.40
1.50 CDCl3
0.00
OH
O
OH
102
CDCl3, 300 MHz
1.00
0.92
0.73
1.01
1.01
3.03
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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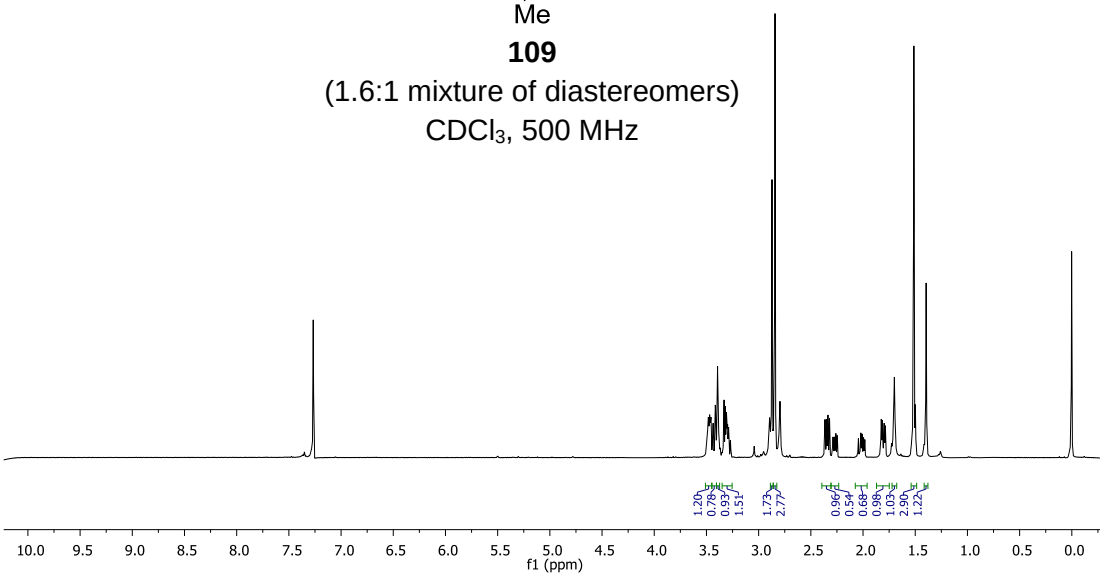
131.75
120.01
77.45 CDCl3
77.02 CDCl3
76.60 CDCl3
74.39
44.40
25.38
-0.00
OH
O
OH
102
CDCl3, 75 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

KGK-03-100A


**109**

(1.6:1 mixture of diastereomers)

$CDCl_3$, 500 MHz

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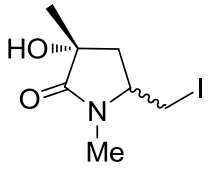


**109**

(1.6:1 mixture of diastereomers)

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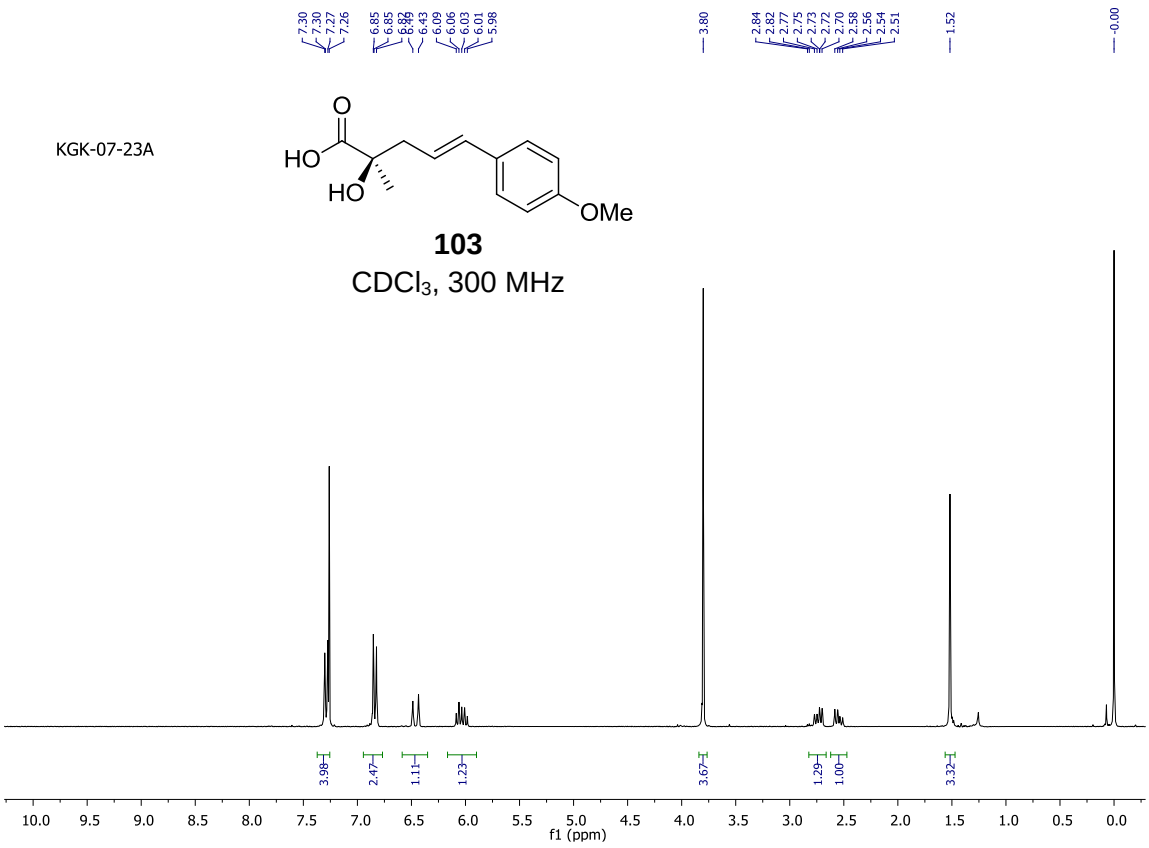
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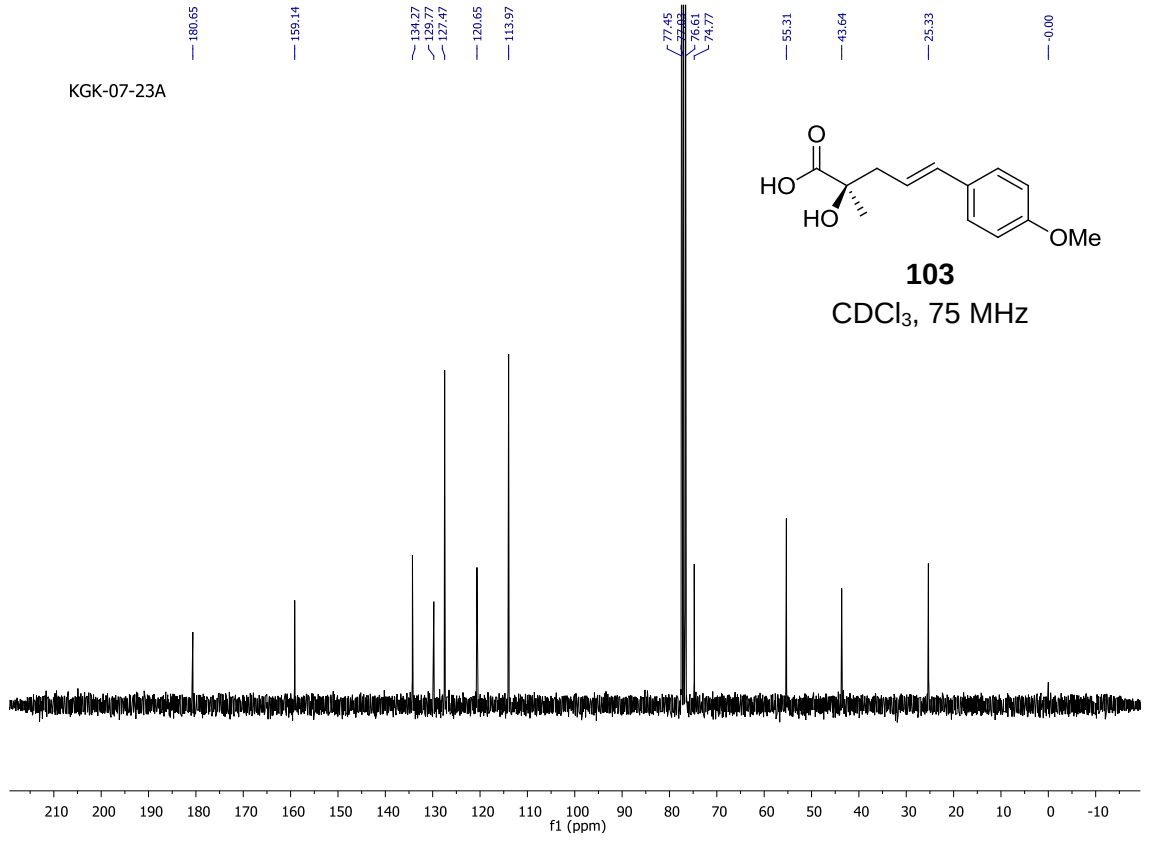
HO
O
OMe
103
CDCl3, 300 MHz
f1 (ppm)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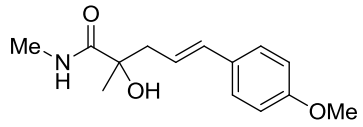
HO
O
OMe
103
CDCl3, 75 MHz
f1 (ppm)

kgk-8-66A



**93**

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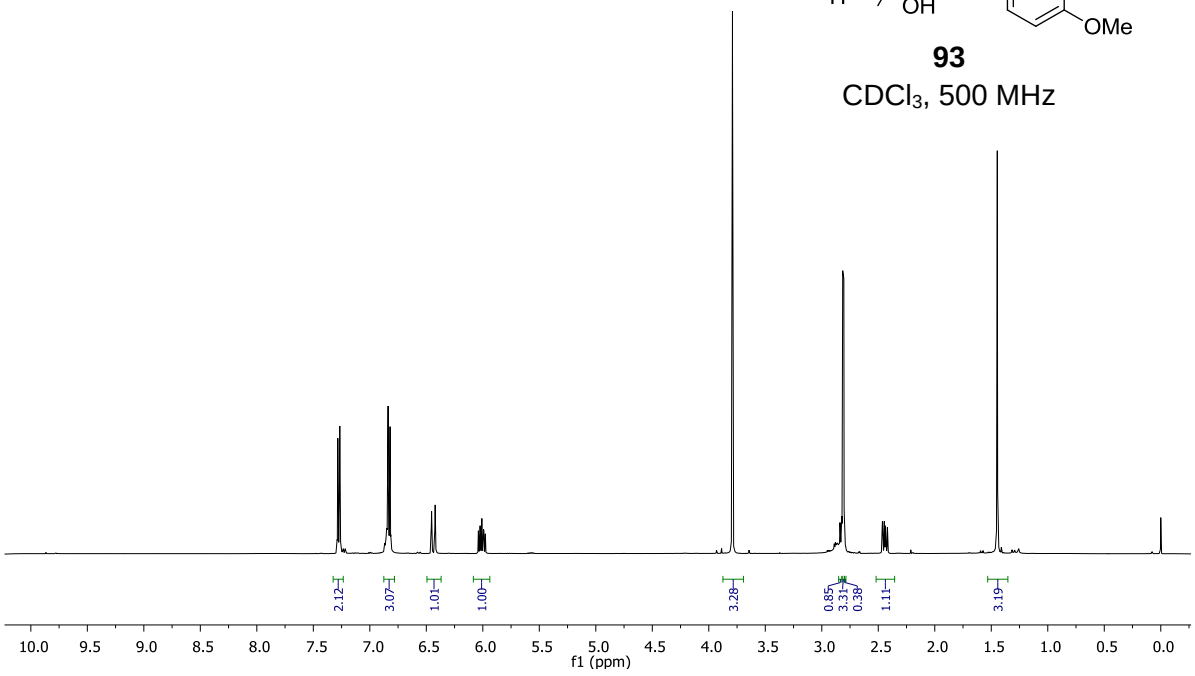


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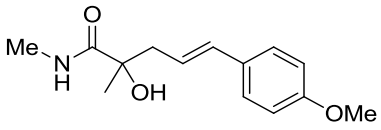
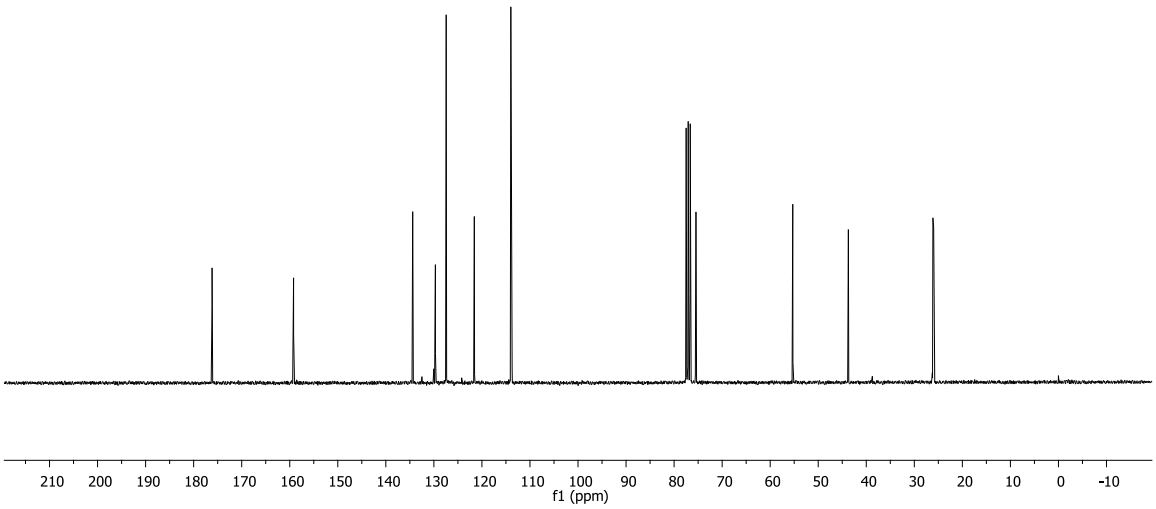
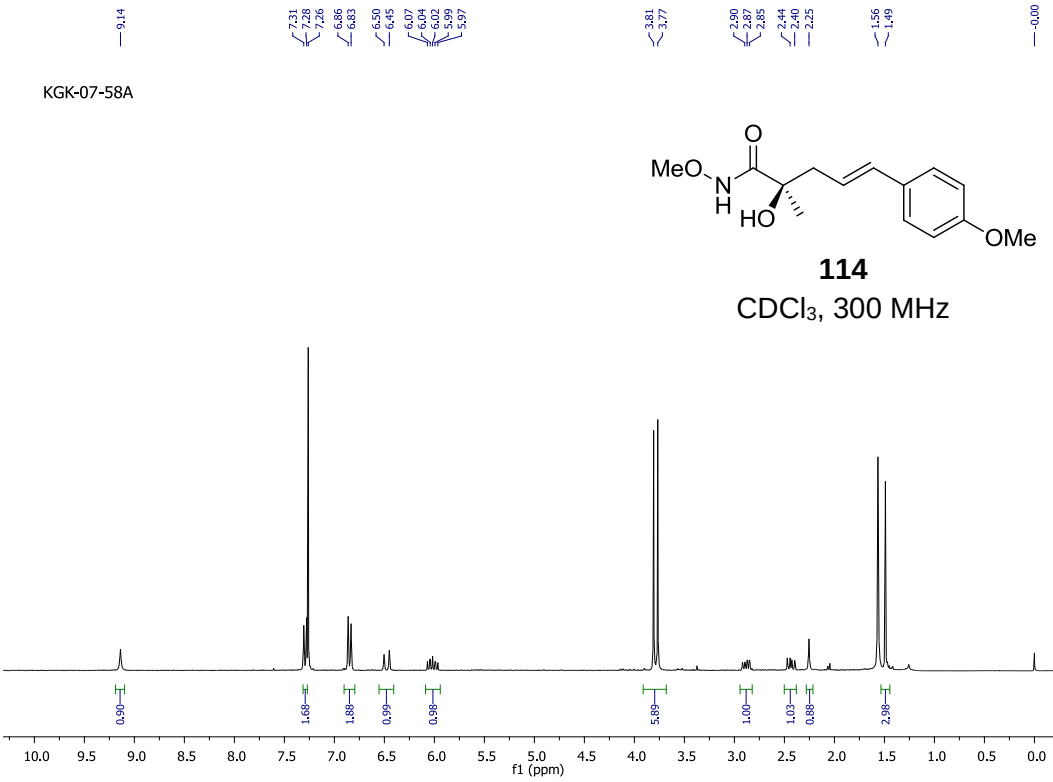


**93**

$CDCl_3$, 75 MHz






**114**

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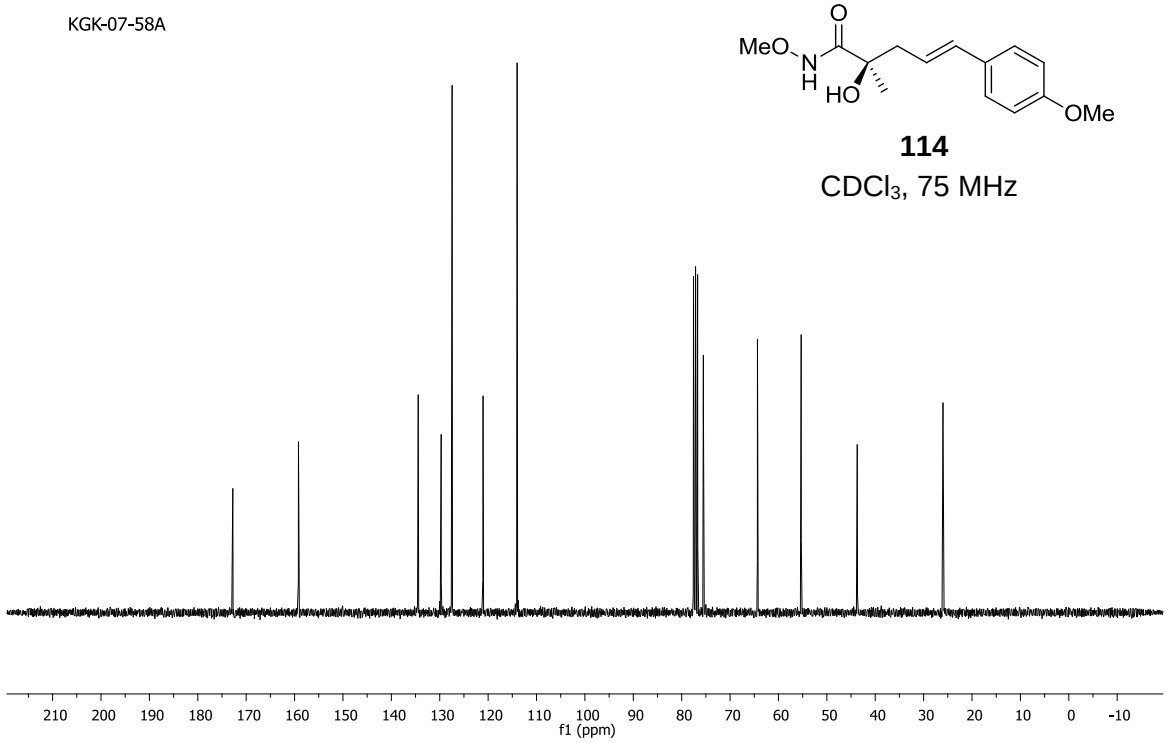


**114**

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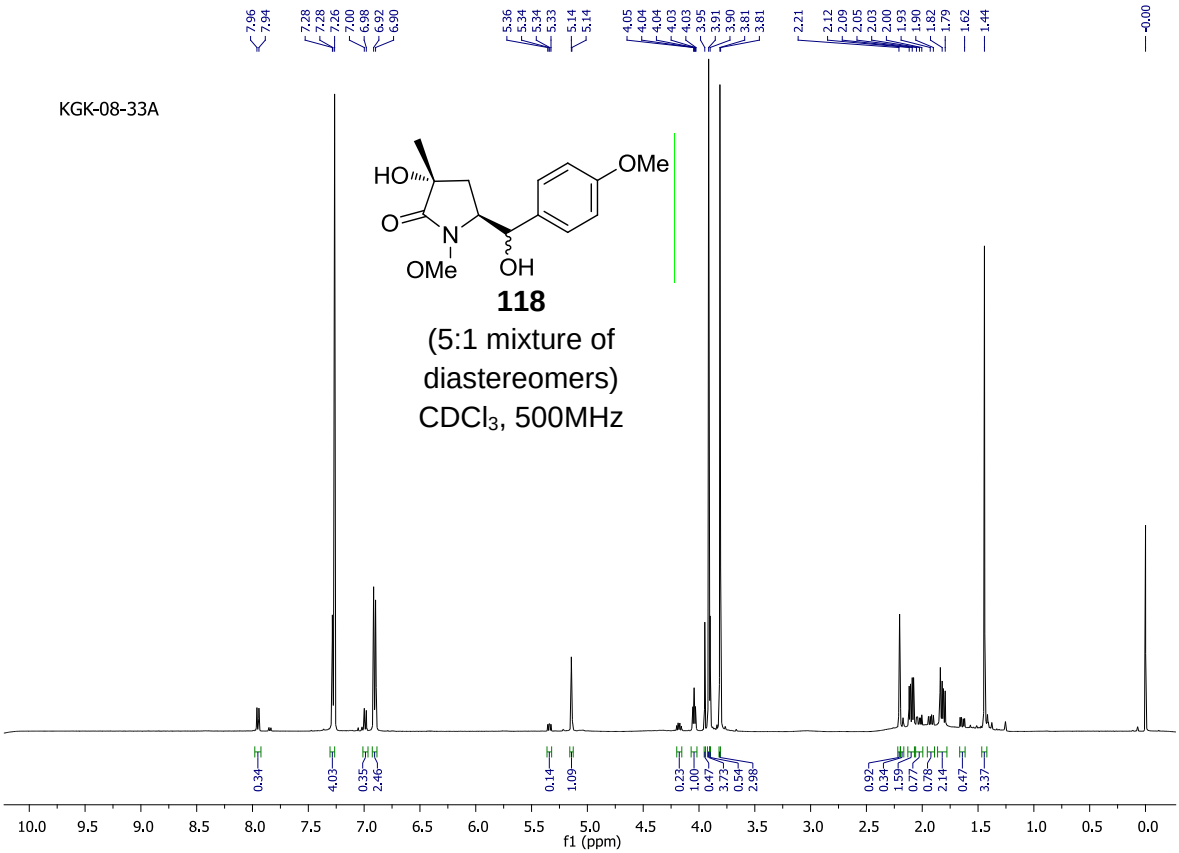


**118**

(5:1 mixture of diastereomers)

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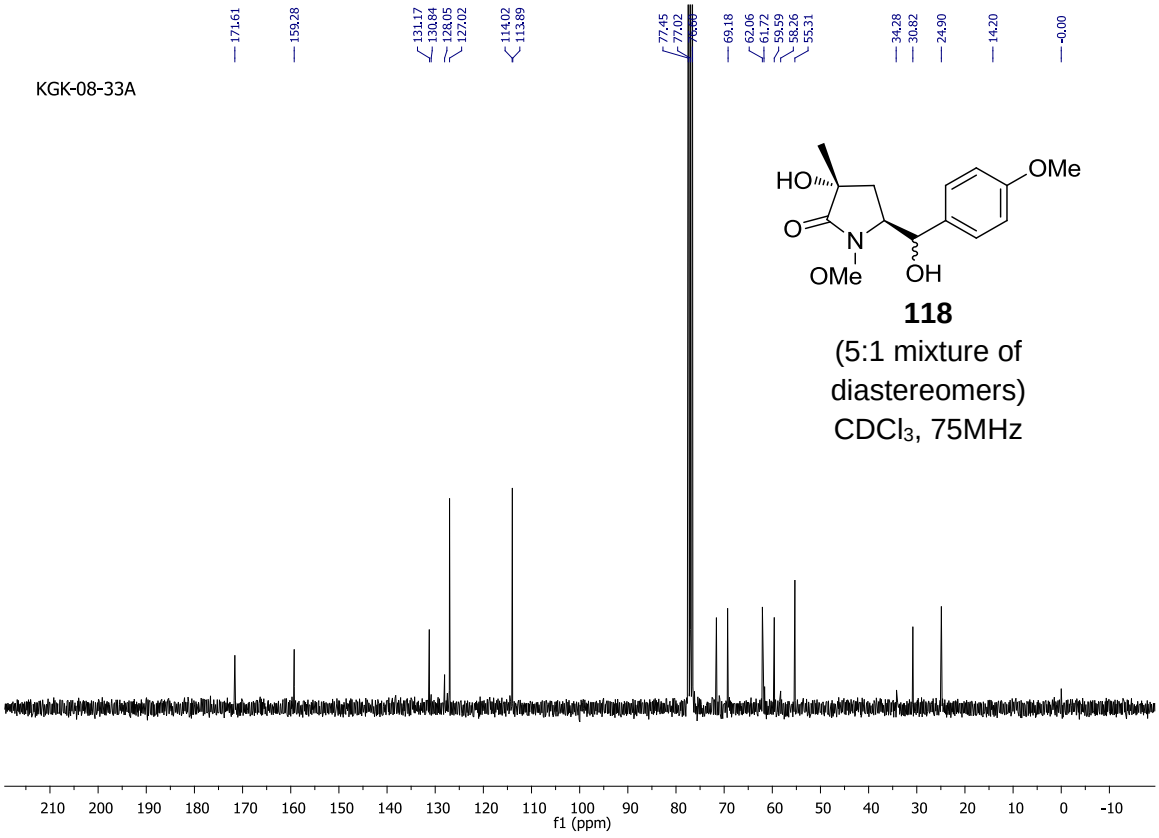
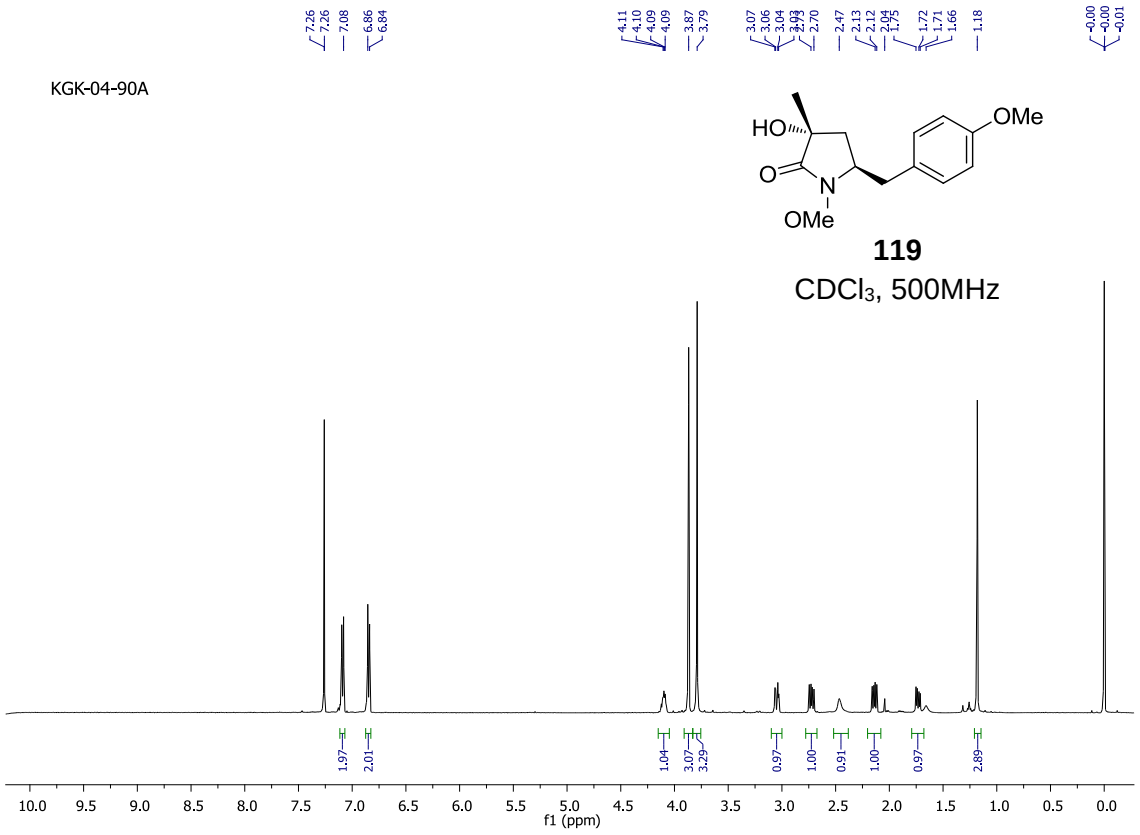



**118**

(5:1 mixture of diastereomers)

$CDCl_3$, 75MHz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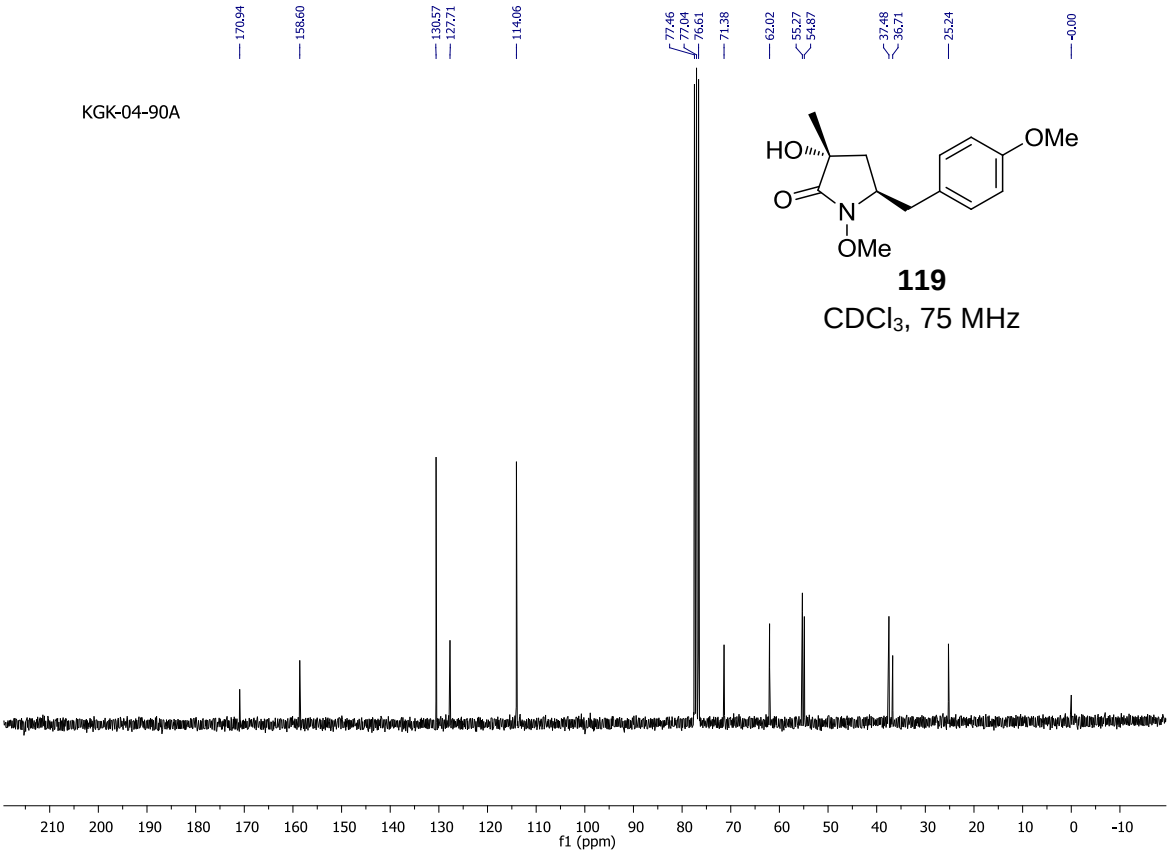
HO
O
N
OMe
OMe
119
CDCl3, 500MHz
f1 (ppm)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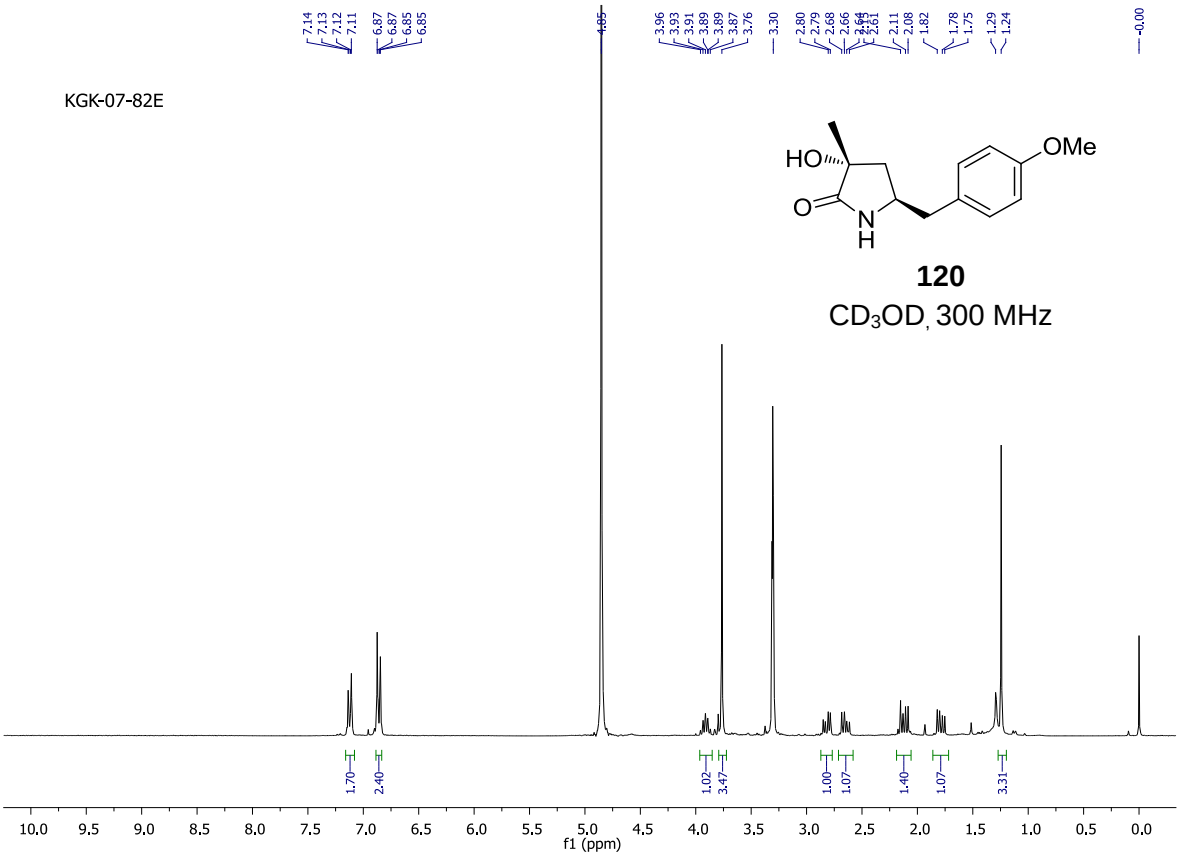
HO
O
N
OMe
OMe
119
CDCl3, 75 MHz
f1 (ppm)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O
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H
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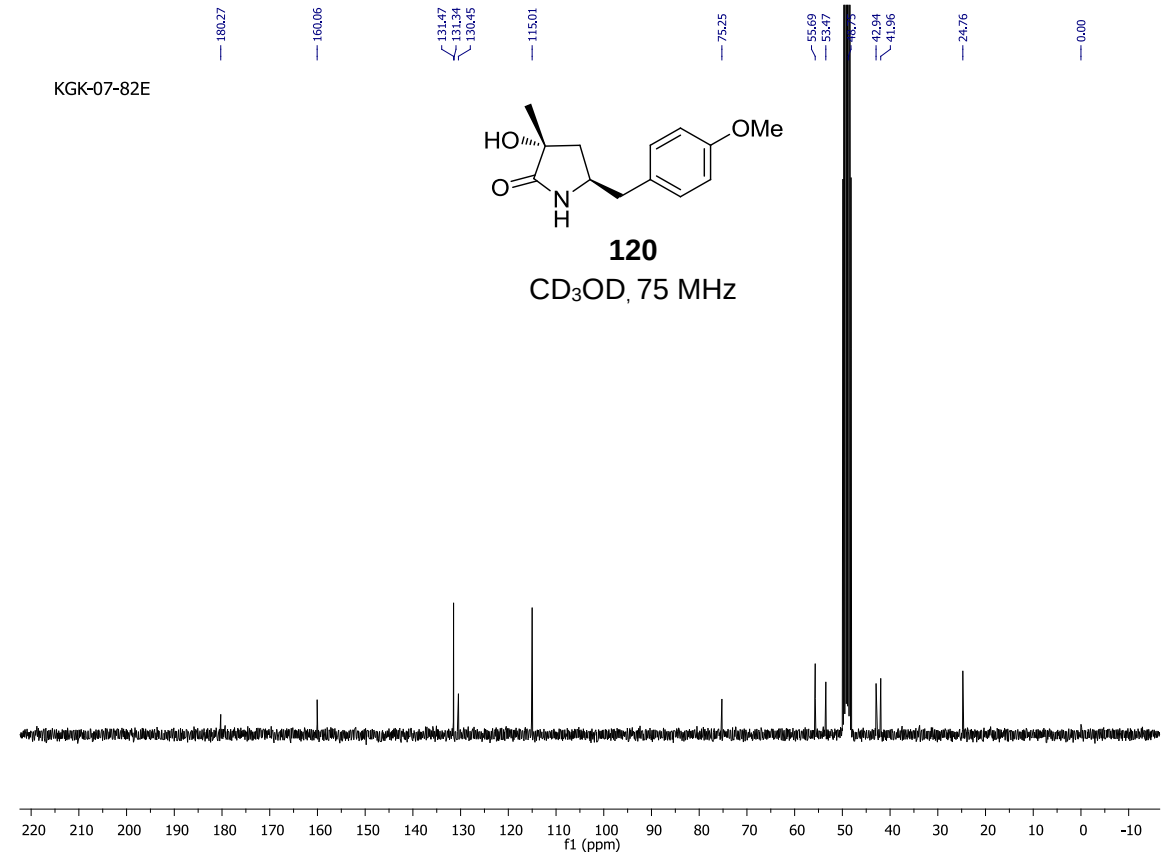
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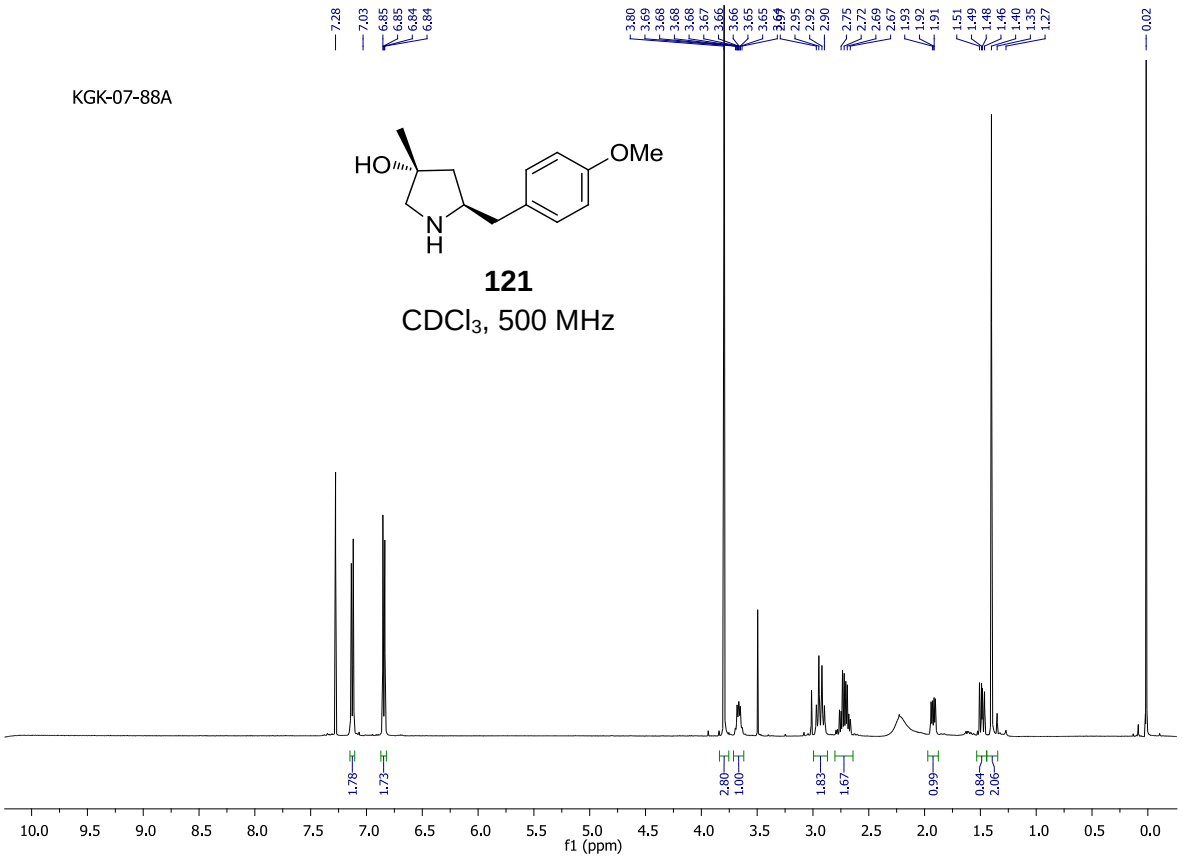
O
N
H
OMe
120
CD3OD, 75 MHz
f1 (ppm)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N
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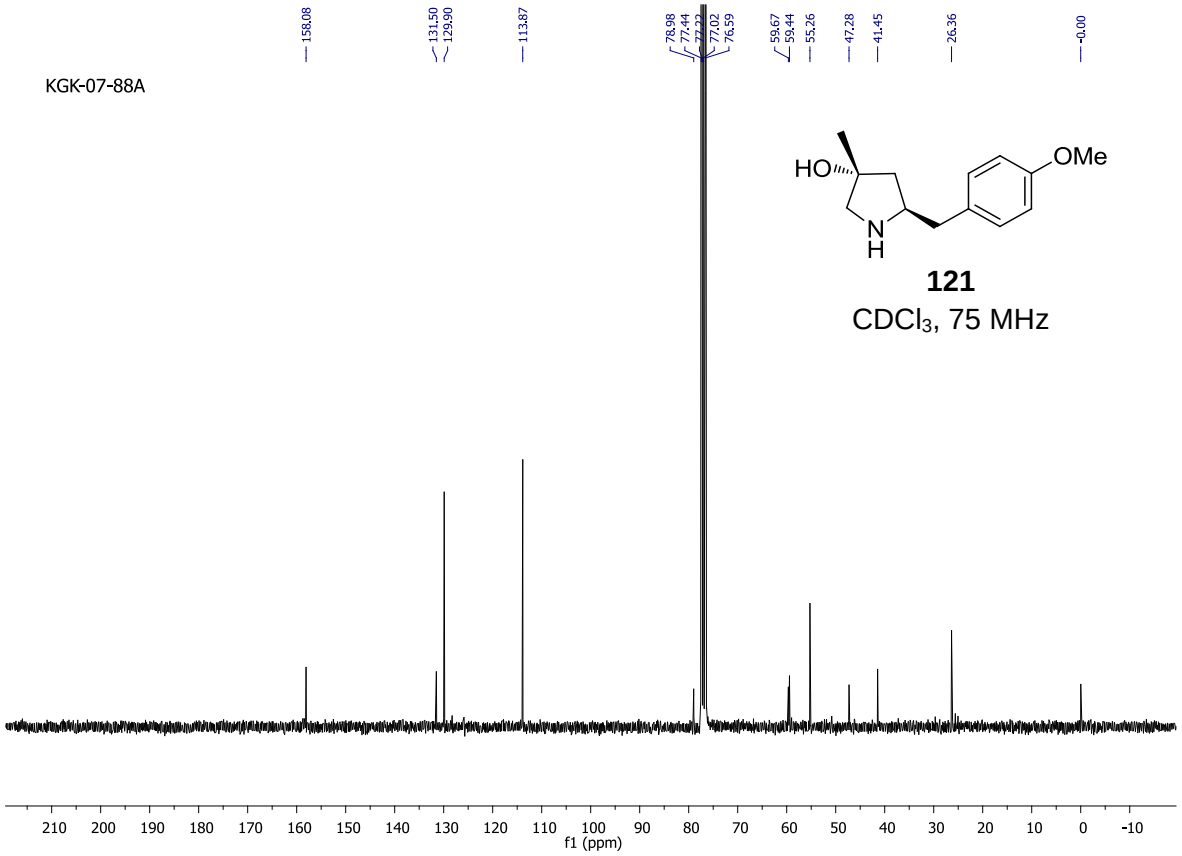
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OMe
N
H
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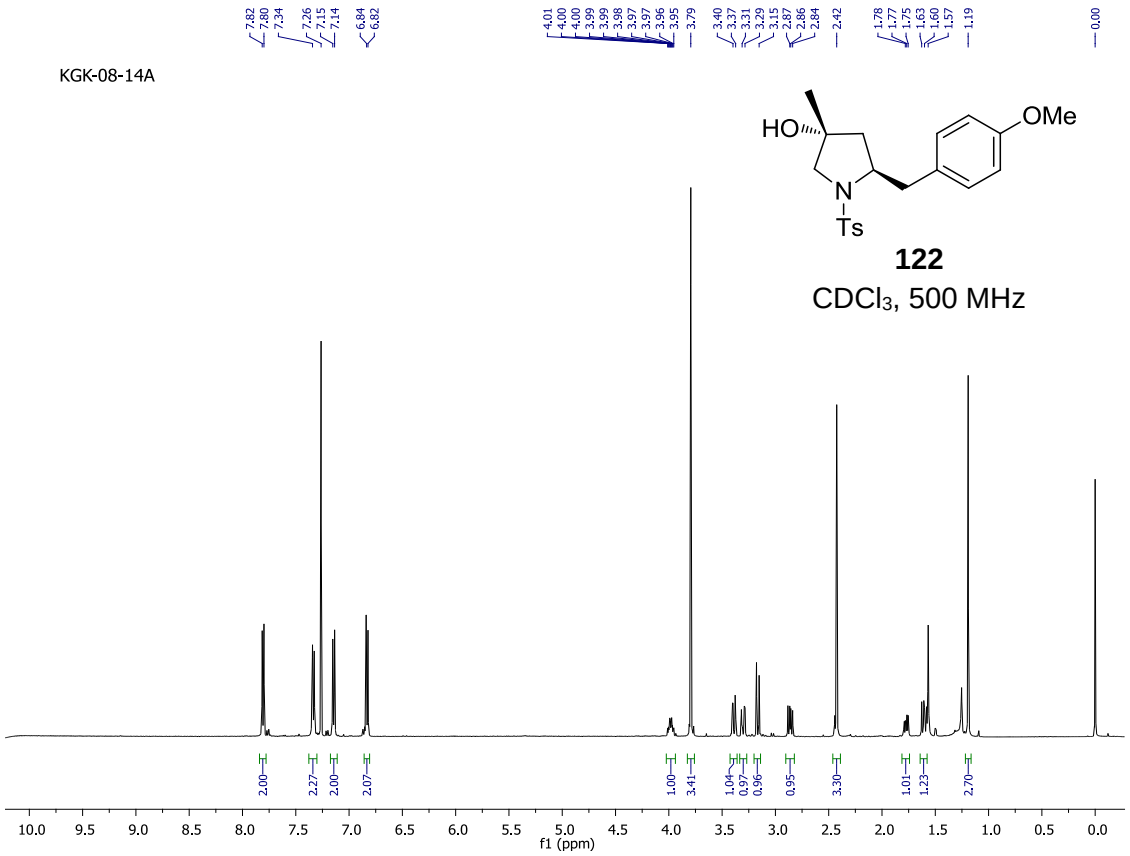
CDCl3, 75 MHz
f1 (ppm)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OMe
N
Ts
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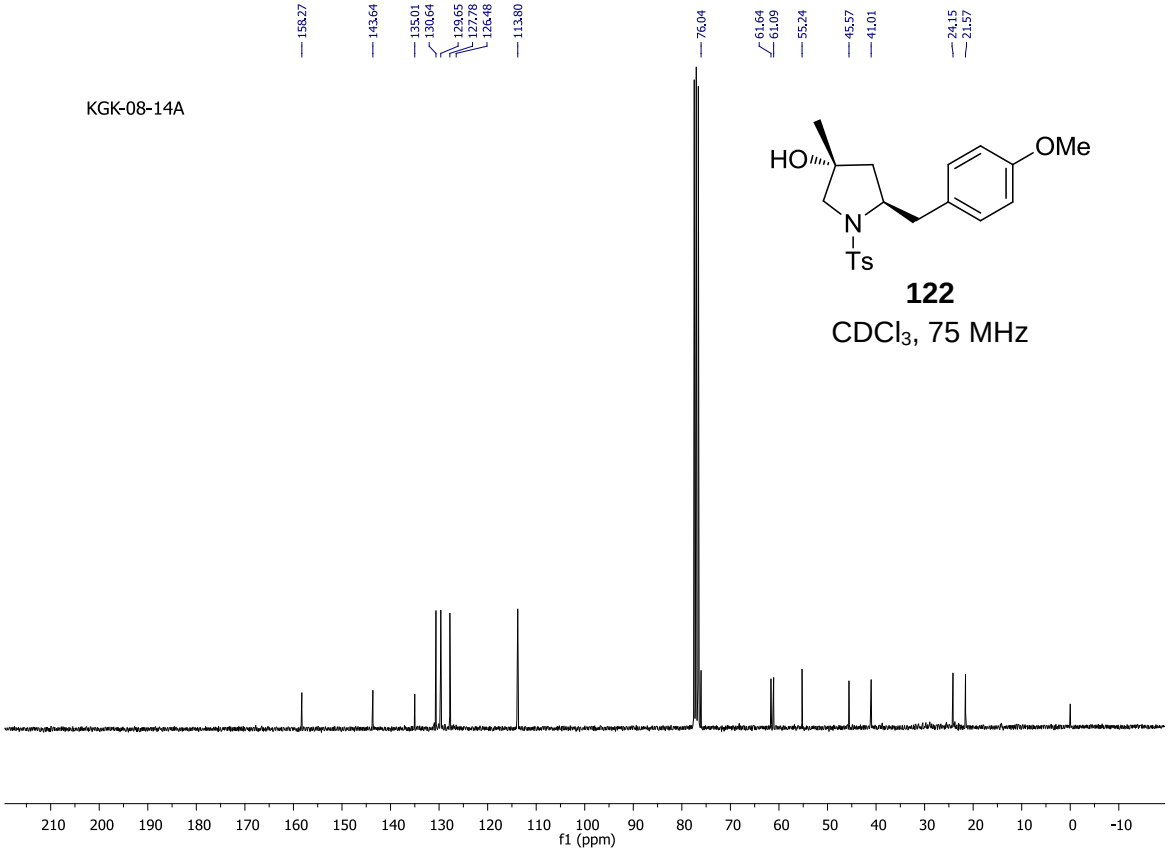
CDCl3, 500 MHz
f1 (ppm)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OMe
N
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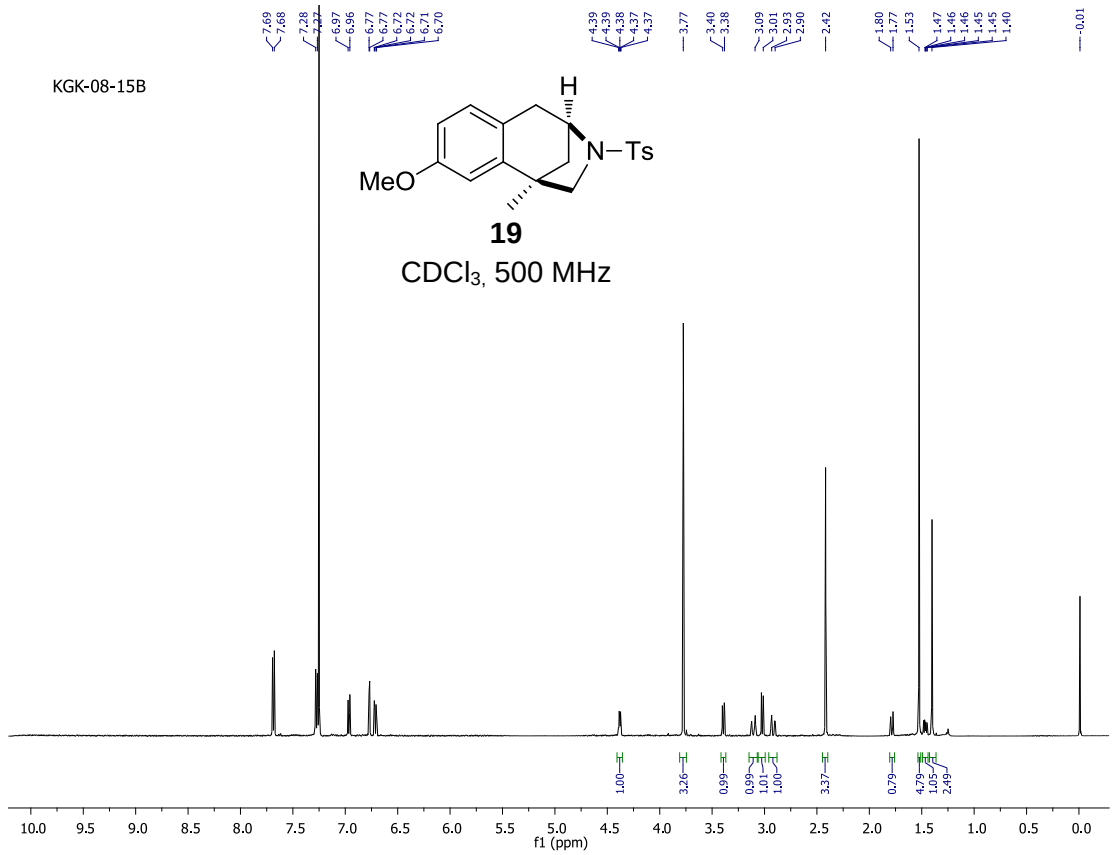
f1 (ppm)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N–Ts
MeO
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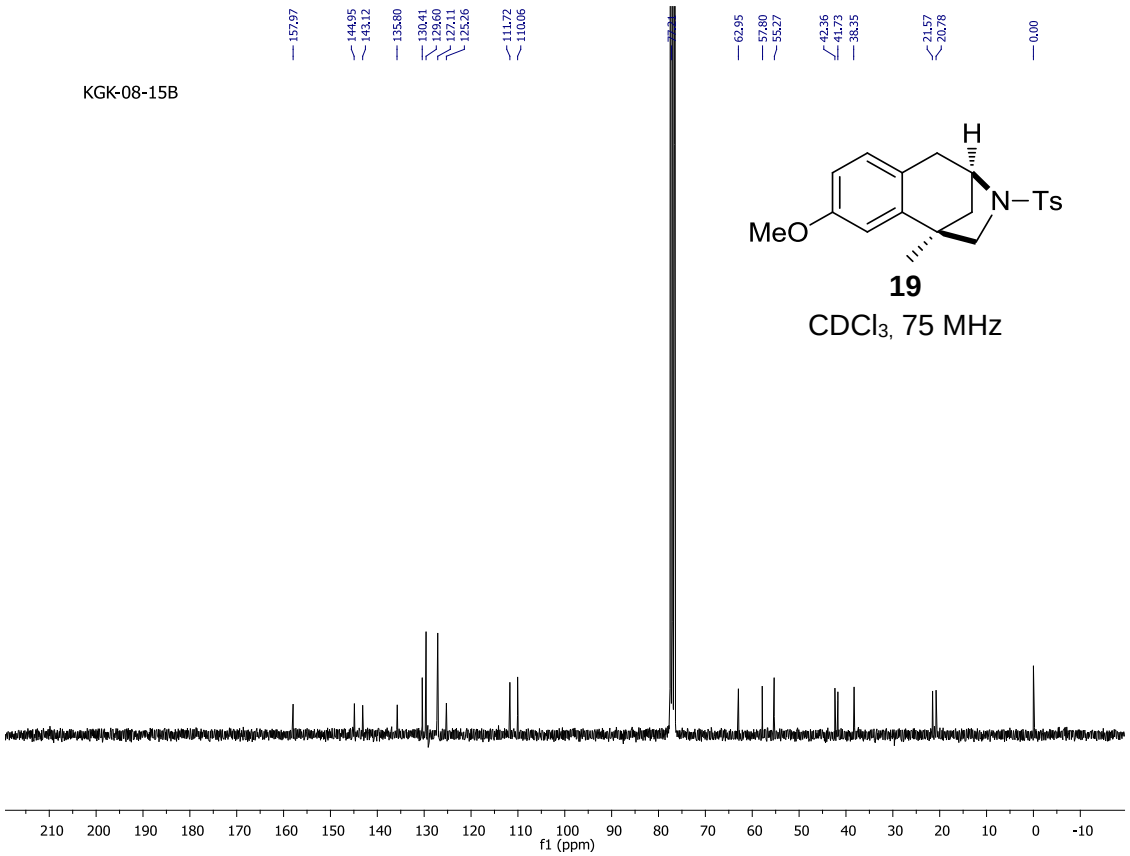
f1 (ppm)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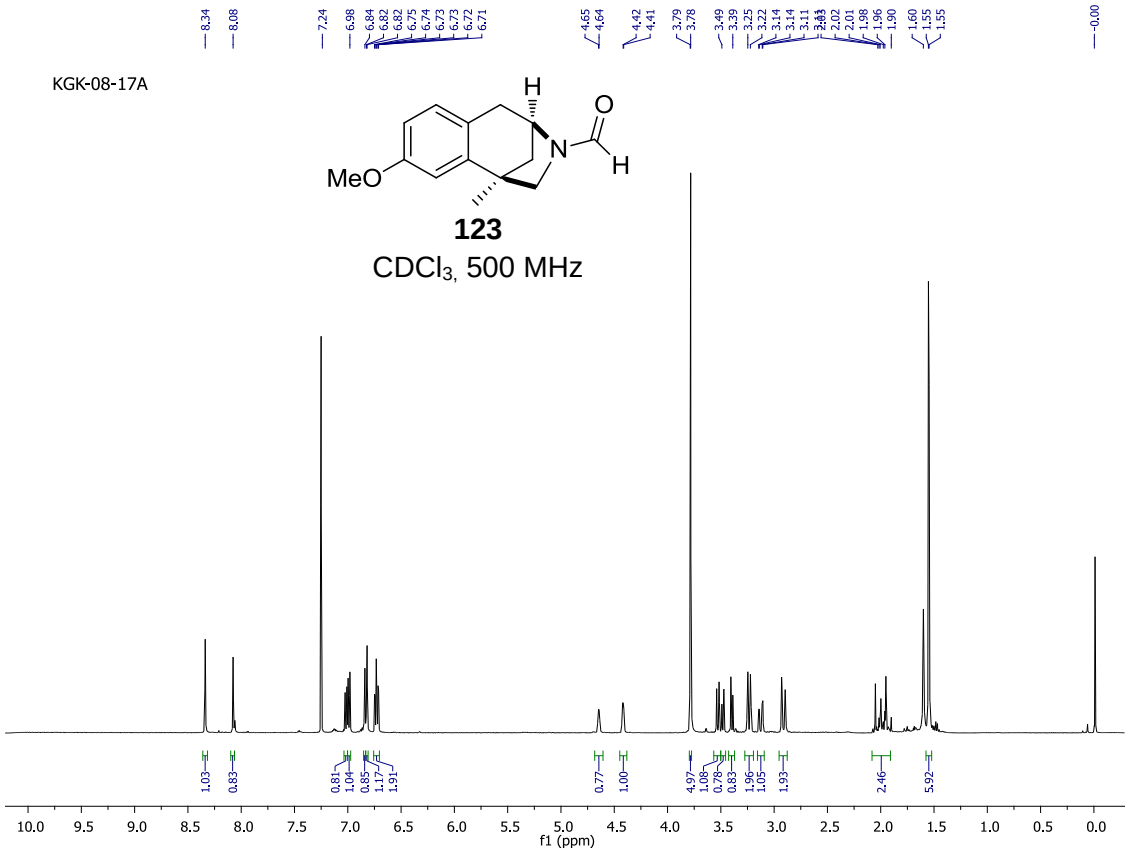
N–Ts
MeO
19
CDCl3, 75 MHz
f1 (ppm)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N
H
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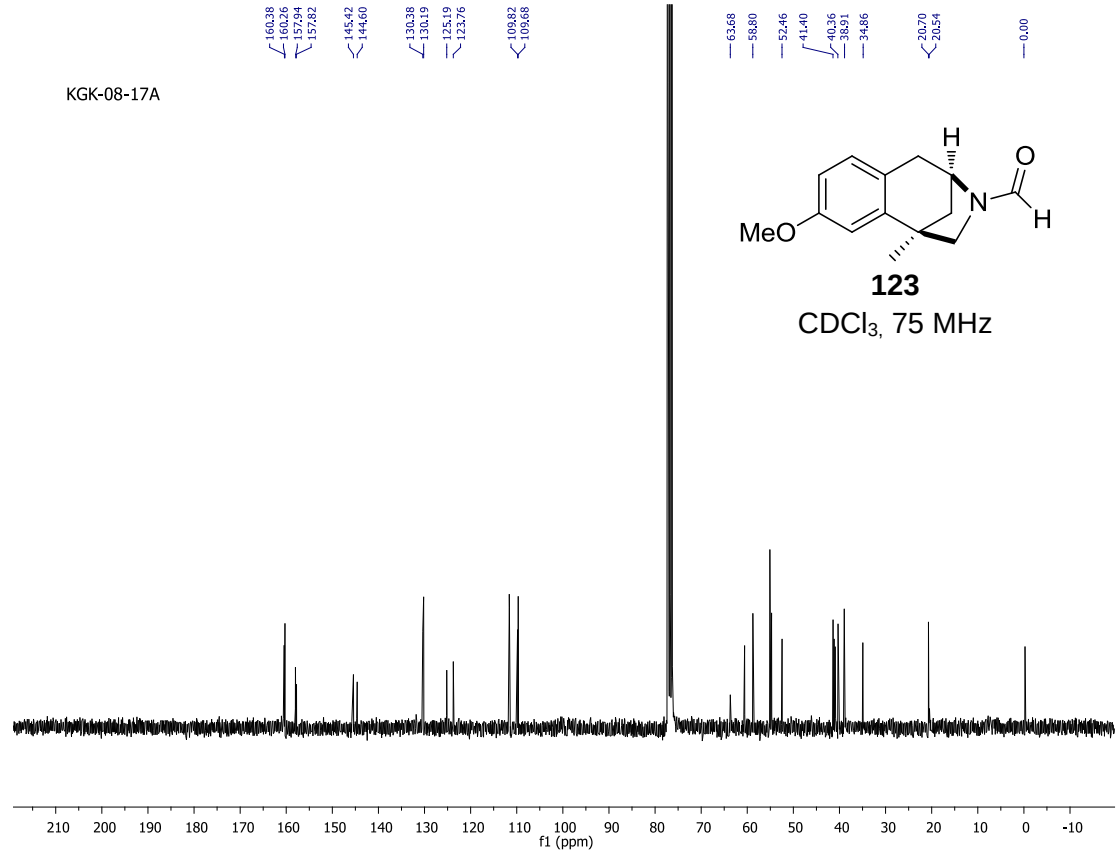
f1 (ppm)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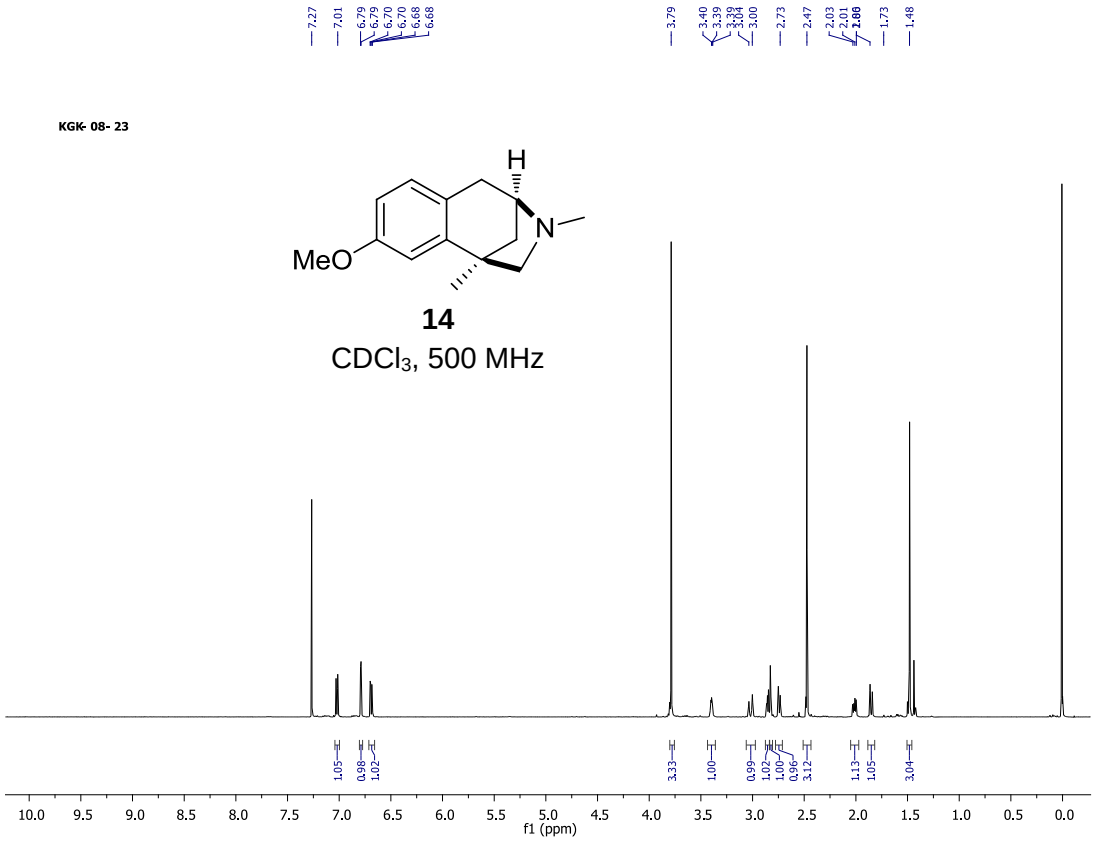
MeO
H
O
N
H
123
CDCl3, 75 MHz
f1 (ppm)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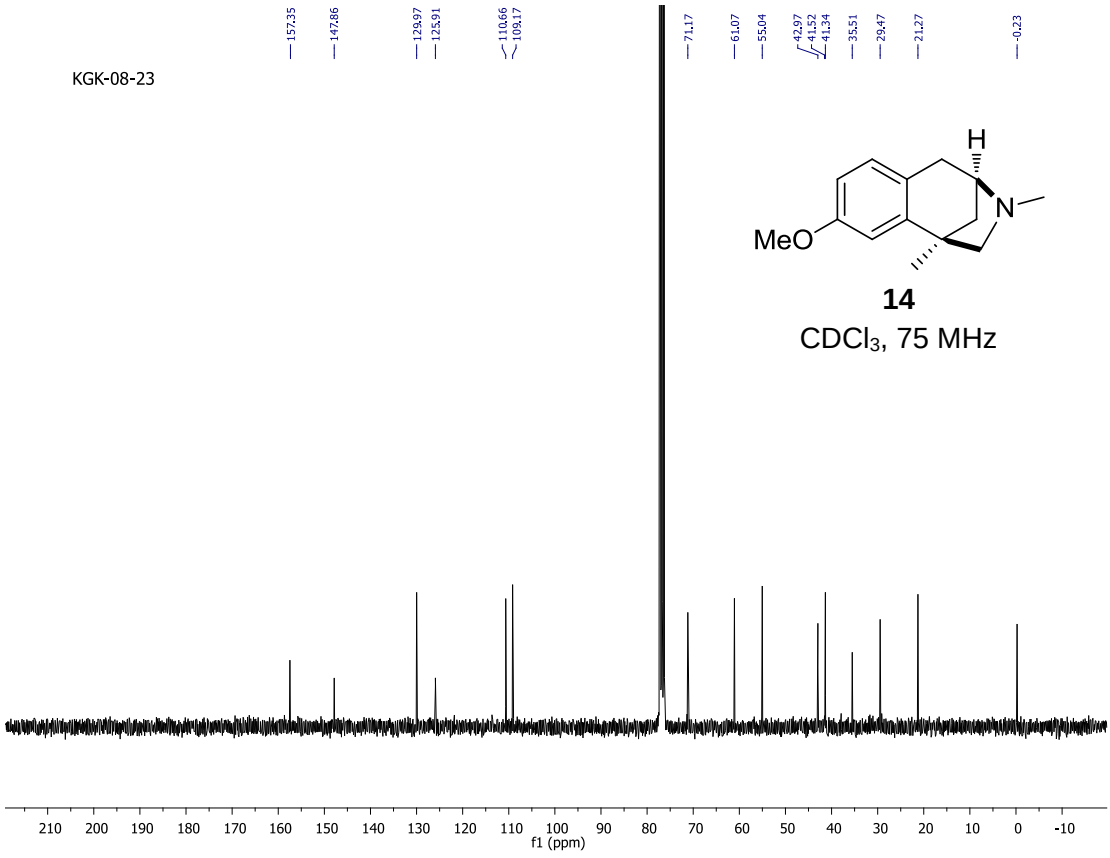
N
MeO
14
CDCl3, 500 MHz
f1 (ppm)


KGK-08-23
H
N
MeO
14
CDCl3, 75 MHz
f1 (ppm)

# Chapter 2

## Studies on the synthesis of Clauslactone S

## 2.1 Introduction to Clauslactone S

Clauslactone S (**1**) is a coumarin containing a $C_{10}$ terpenoid side-chain.[1] It has been extracted from the leaves and stem of *Clausena excavata* (commonly known as Rutaceae). Extracts of the plant stems and leaves have been used in Chinese folk medicine in the treatment of dysentery, enteritis and urethra infection.[2] Chemical constituents of the plant include carbazole alkaloids,[3] coumarins[4] and tetranortriterpenoids.[5] Ye and co-workers isolated a total of fourteen known coumarins and eleven carbazole alkaloids along with the three new coumarins bearing a $C_{10}$ terpenoid side-chain, which were named as Clauslactone S (**1**), Clauslactone R (**2**) and Clauslactone T (**3**, Figure 2.1).[1] Other coumarins featuring a $C_{10}$ terpenoid side chain are also known and these have shown inhibitory effects on the Epstein-Barr virus[4a] and in the inhibition of two-stage mouse-skin carcinogenesis.[4a]

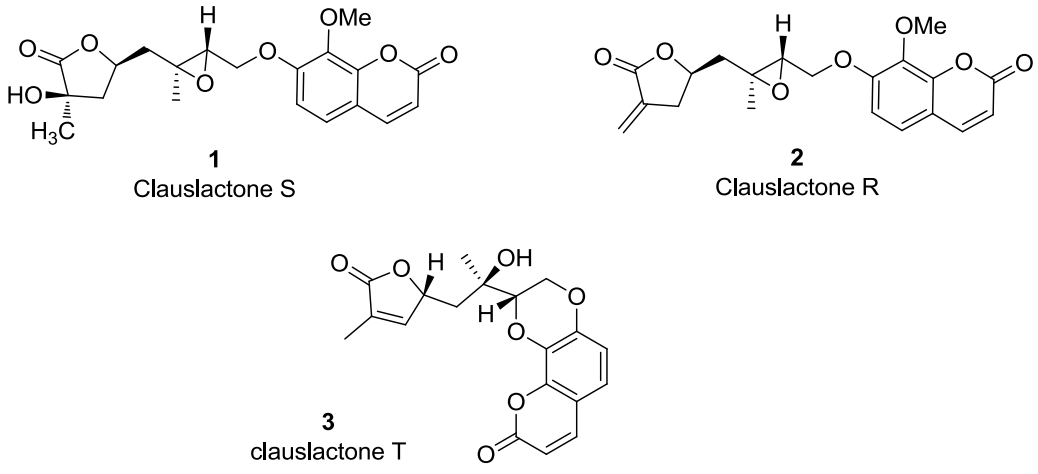
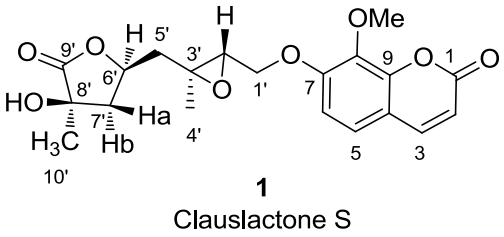



Figure 2.1. Structures of clauslactone S, R and T.

## 2.2 Present work:

### 2.2.1 Studies on the synthesis of clauslactone S

The synthesis of clauslactone S has not previously been reported. The configuration of the *C*-8' quaternary center in the lactone was reported to be *R*, based on the NOE correlations of H-6'/Ha-7' and $CH_3$-10'/Hb-7'. Similarly, the configurations at C-2', C-3' and C-6' were deduced as *R, R,* and *S,* respectively, based on a ROESY experiment. The NOE and ROESY experiment results were confirmed by X-ray crystallography (Figure 2.2).




**1**

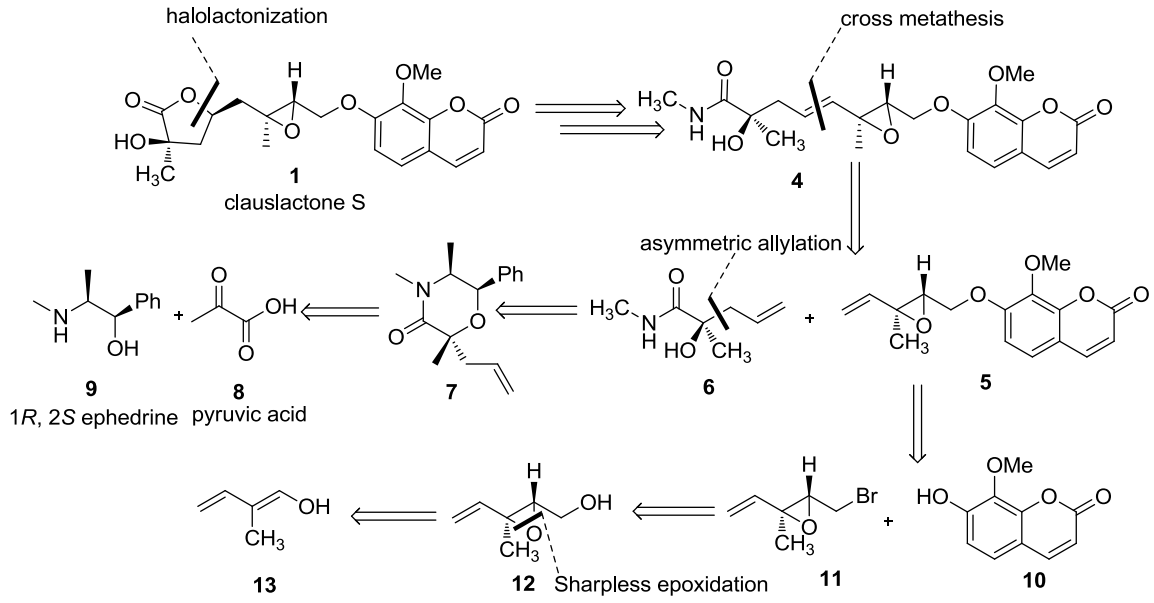
Clauslactone S

Figure 2.2 Structural details of clauslactone S.

Our interest in the synthesis of clauslactone S derives from the α-hydroxy acid motif in the lactone portion of the molecule, and also that its synthesis has not previously been reported, which makes it even more interesting as a synthetic target.

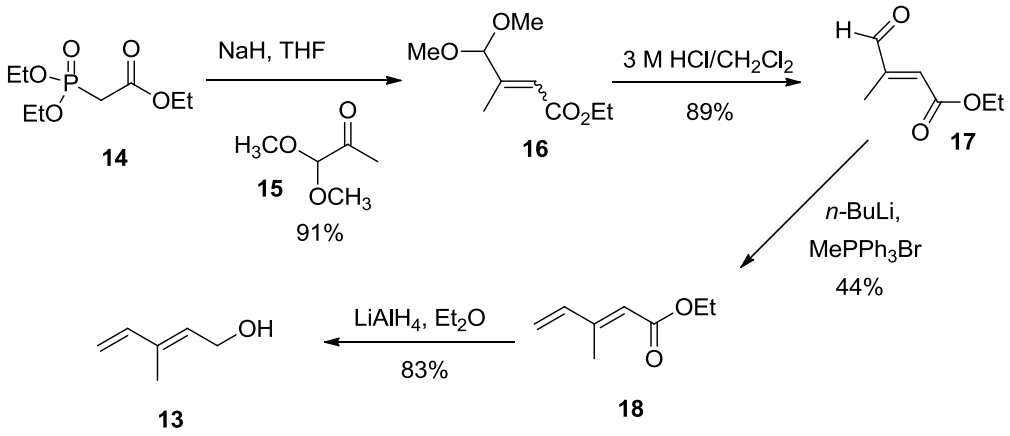
Retrosynthetically, the lactone ring in clauslactone S was envisioned to derive from the α-hydroxy amide **6** as a starting material. The synthetic strategy involves a halolactonization reaction of the intermediate **4** to obtain the lactone in clauslactone S. The intermediate **4** was the expected product of a cross-metathesis reaction of an enantiomerically-enriched α-hydroxy amide **6** with an epoxy alkene **5**. The amide **6** can be

obtained by the asymmetric allylation of a chiral pyruvic acid derivative obtained by amidation with (1*R*,2*S*)-ephedrine (**9**) (Scheme 2.1).




Scheme 2.1 Retrosynthetic analysis of clauslactone S.

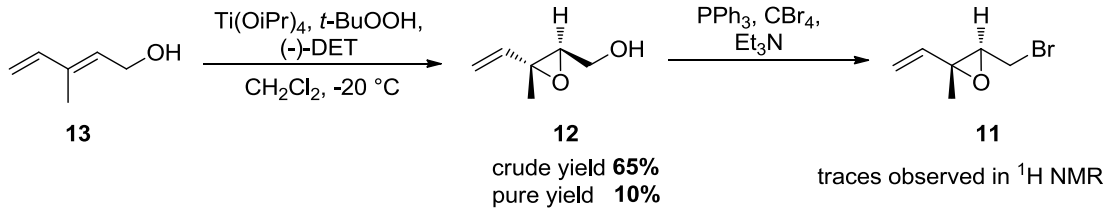
The initial approach was aimed at the synthesis of the intermediate **4** which can be obtained from the coumarin derivative **5** and the amide **6**. The synthesis of amide **6** is explained in Chapter 1 (Scheme 1.25, p 26) of this thesis. The synthesis of **5** started with the synthesis of epoxy alkene **11**. Treatment of triethyl phosphonoacetate **14** with excess NaH followed by addition of pyruvaldehyde dimethylacetal **15** furnished **16** as a mixture of isomers (*E*/*E* = 1:2, Scheme 2.2). Stirring the acetal-ester **16** in $CH_2Cl_2$/3 M aqueous HCl afforded *E*-**17** as a single isomer.[6] Wittig reaction of **17** with the anion generated from methyltriphenylphosphonium bromide, using *n*-BuLi, provided the diene ester **18**. The ester **18** was reduced with $LiAlH_4$ to obtain the alcohol **13** (Scheme 2.2).[7]




Scheme 2.2

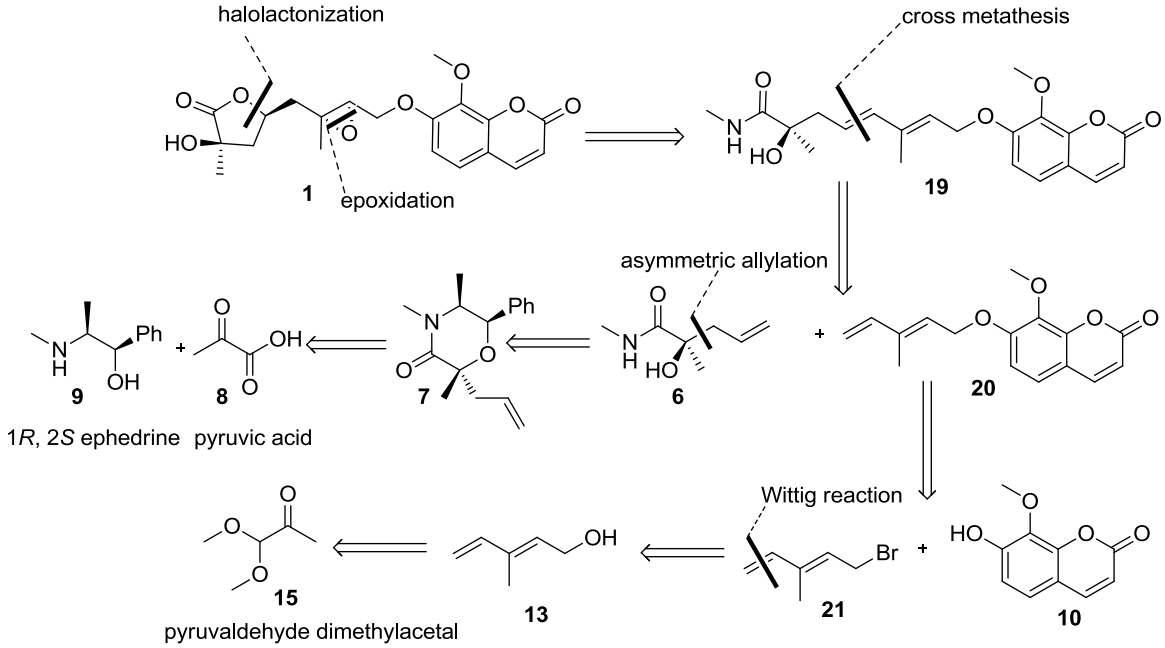
The low yield of the Wittig reaction (conversion of **17** to **18**) is probably due to the volatile nature of **18** which results in evaporative loss during its isolation and purification.

Allylic alcohol **13** was subjected to the Sharpless asymmetric epoxidation with *t*-butyl hydroperoxide (TBHP) in the presence of Ti(O-*i*Pr)$_4$ and (–)-diisopropyl tartrate to provide the epoxy alcohol **12** (65% yield of the crude product, Scheme 2.3). Attempted purification of **12** by chromatography on silica gel resulted in extensive decomposition and provided only a 10% yield of **9**. Therefore, it was decided to employ **12** without purification in further reactions. Attempted conversion of **12** to the bromoepoxide **11** by treatment with $PPh_3$, $CBr_4$, and $Et_3N$ again led to extensive decomposition and only a trace of the desired product **11** was observed in the $^1$H NMR spectrum. This prompted a modification of the planned synthetic strategy.



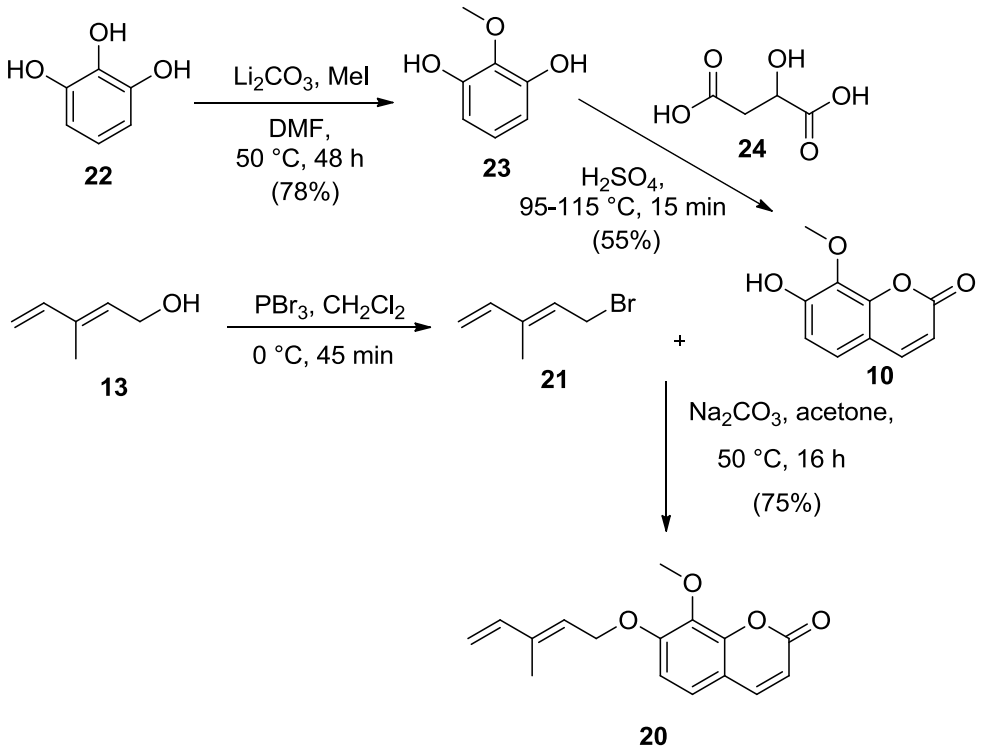

Scheme 2.3

The modified synthetic sequence involved the lactonization and the epoxidation steps as late-stage synthetic transformations to obtain clauslactone S from **19** (Scheme 2.4). The intermediate **19** could in turn be obtained from the cross-metathesis reaction of the enantiomerically-enriched α-hydroxy amide **6** and coumarin derivative **20**. *O*-Alkylation of coumarin **10** with bromodiene **21** could provide **20**. The bromodiene can be obtained from the alcohol **13** which could be prepared from pyruvaldehyde dimethylacetal **15** as shown in Scheme 2.2



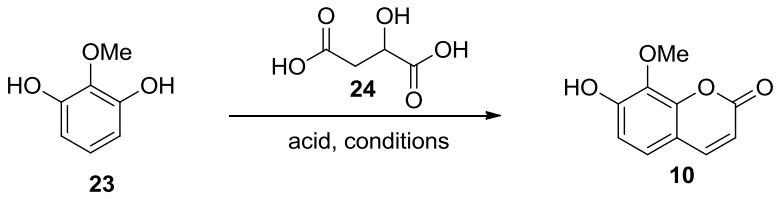

Scheme 2.4 Modified retrosynthesis for clauslactone S.

The synthesis of coumaryl ether **20** started with the selective methylation of pyrogallol **22**. Treatment of **22** with $Li_2CO_3$ and MeI provided **23** in 78% yield.[8] A variety of conditions were screened for the conversion of **23** to coumarin **10**. Details of these experiments are provided in Table 1. The best result was obtained when **23** was treated with malic acid **24** and $H_2SO_4$ for 30 min at 95-115 °C.[9] Alcohol **13** was converted to the corresponding bromide **21** by treatment with $PBr_3$. *O*-Alkylation of **10** with the bromodiene **21** provided coumaryl ether **20** in 75% yield (Scheme 2.5). This reaction did not go to completion and the yield reported is based on the amount of recovered starting material **10**.




Scheme 2.5

Table 2.1 Optimization of reaction conditions for the synthesis of **10**

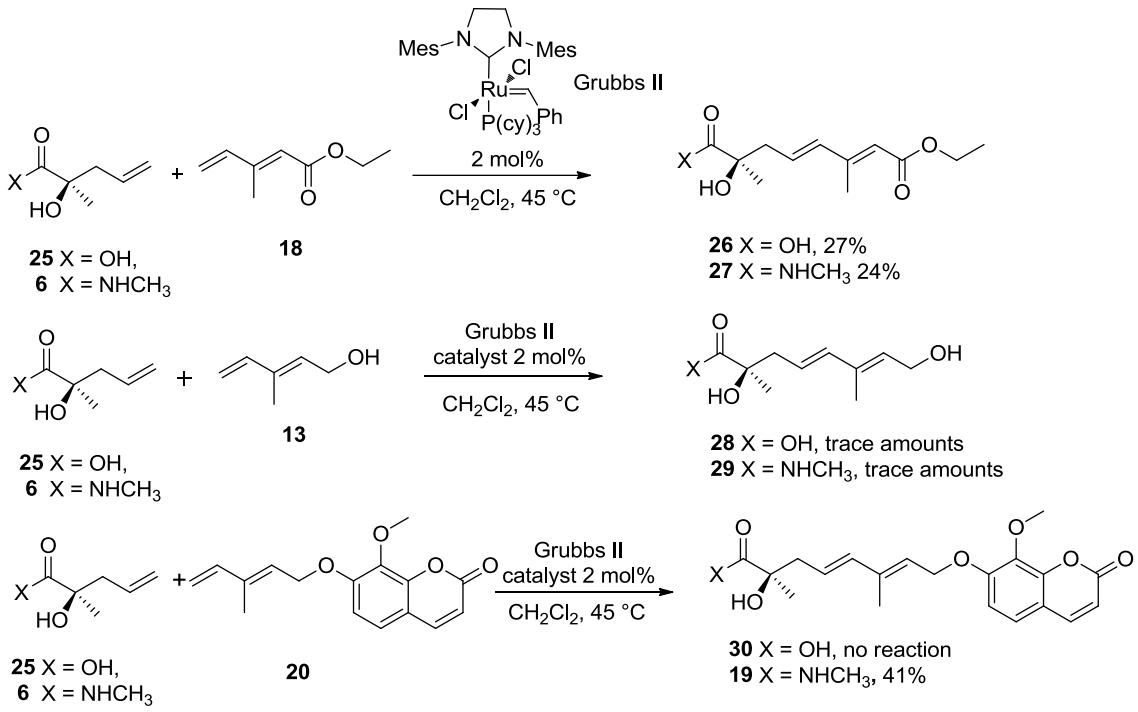



| Entry | Acid | Temperature (°C) | Time | Result | Yield (%) |
|---|---|---|---|---|---|
| 1 | $HClO_4$ | 95 | 4 h | decomposition | - |
| | | 20-25 | 5 h | **23** | - |
| 2 | $H_2SO_4$ | 80 | 1.5 h | **10** | 7[a] |
| | | rt- 80 | 3 h | complex mixture | - |
| | | 80 | 2 h | **10** | 14 |
| | | 120 | 20 min | **10** | 3 |
| | | 95-115 | 30 min | **10** | 55 |
| | | 120[b] | 30+30 sec | decomposition | - |
| | | 145[b] | 15 sec | **10** | trace |
| | | 50[b] | 30 sec | **10** | trace |
| 3 | *p*-TsOH | 20-25 | 20 min | complex mixture | - |

*a*: 75% $H_2SO_4$ was used for the reaction. *b*: microwave heating in a sealed reaction vessel.

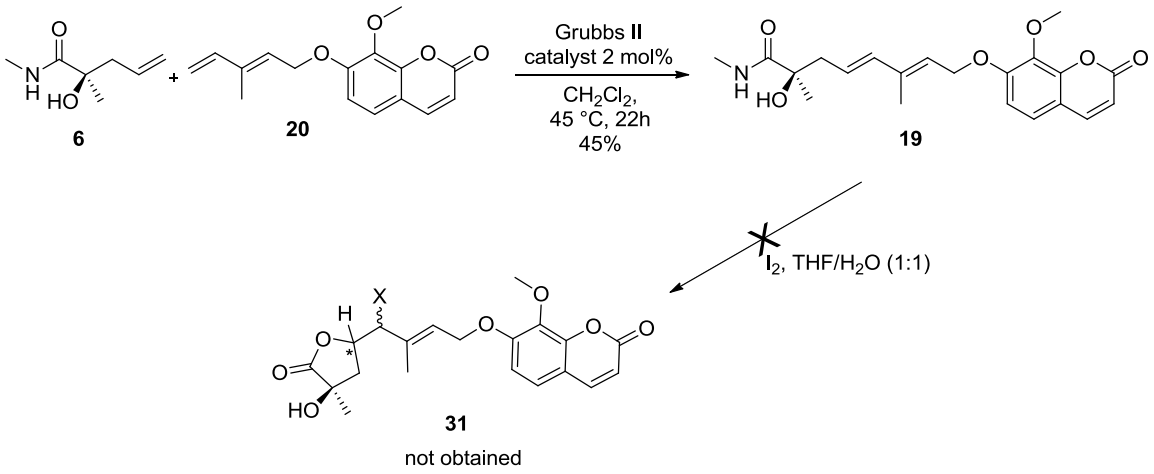
Next, the cross-metathesis reaction of amide **6** and its corresponding acid **25** was attempted with dienes **18**, **13** and **20** using the Grubbs II catalyst. The results of these reactions are summarized in Scheme 2.6. The ester **18** is a better cross-metathesis substrate than alcohol **10** and the cross metathesis of **25** and **6** with **18** provided **26** and **27**,

respectively, in low yield. The best result was obtained with **6** and coumarin derivative **20** which provided the cross-metathesis product **19** in 41% yield.




Scheme 2.6 Screening of the cross-metathesis reaction substrates.

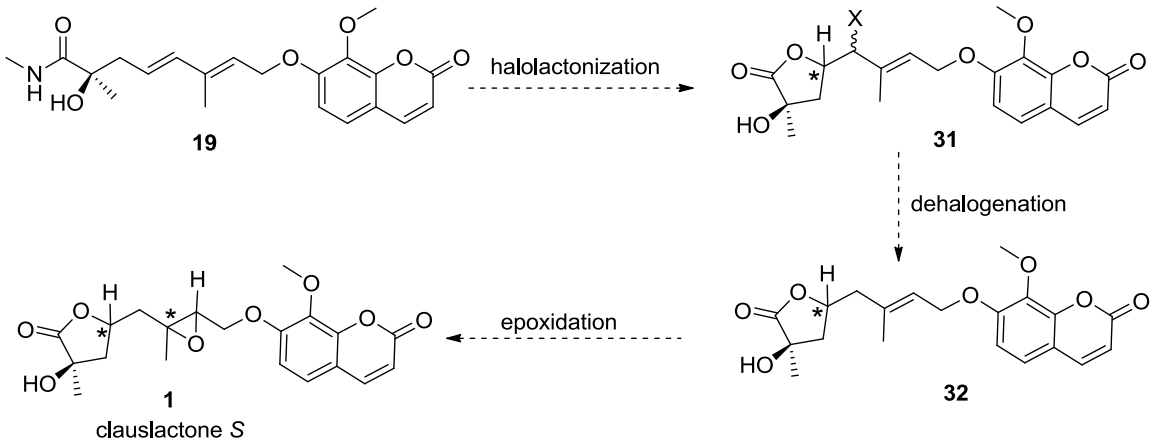
With the amidodiene **19** in hand, its iodolactonization reaction was attempted. Unfortunately, treatment of **19** with iodine in $CH_2Cl_2$ led to a complex mixture of products which did not contain any of the desired lactone **31**. This result was unanticipated since the the iodolactonization of 4,6-dienoic acids that are structurally related to **19** is known, and the lactonization proceeds with iodination at C-5[10] (Scheme 2.7). At this stage, further studies with **19** were discontinued due to the time constraints of the author.




Scheme 2.7

### 2.2.2 Future studies towards the synthesis of clauslactone S

Provided that the halolactonization of the dienamide **19** is successful, and **31** is obtained, the dehalogenation of **31** may provide **32**. Epoxidation of **32** may furnish the basic structure of clauslactone S (**2**, Scheme 2.8). Determination of the stereochemistry of the halolactonization and epoxidation steps will be crucial and optimization of these steps will depend on the stereochemical outcomes.




Scheme 2.8

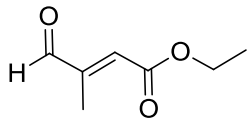
In conclusion, the synthesis of a potential intermediate to clauslactone S was accomplished using the α-hydroxy amide **6** as a key starting material. The synthesis was designed as the assembly of three components **6**, **10** and **13** which can be obtained from readily available starting materials. The Wittig reaction of **17** and the cross metathesis reaction that provides **19** needs to be optimized for better yields.

## 2.3 Experimental section:

### General experimental methods

All commercially available reagent were used without purification. All reactions requiring anhydrous conditions were performed under an atmosphere of dry nitrogen using oven dried glassware. Dichloromethane and tetrahydrofuran were distilled from $CaH_2$ and sodium/benzophenone respectively. Commercial precoated silica gel plates were used for TLC. Silica gel for column chromatography was 230-400 mesh. All melting points are uncorrected.

**(*E*)-Ethyl 3-methyl-4-oxobut-2-enoate (17)[6]:**




To an oven-dried flask equipped with a $N_2$ inlet was added 60% NaH in mineral oil (0.71 g, 17.7 mmol). The mineral oil was removed by washing with hexane. Dry THF (20 mL) was added and the suspension was cooled (0 °C) with stirring. Triethyl phosphonoacetate **14** (3.35 mL, 16.9 mmol) was then added and the mixture was stirred for 1 h. Pyruvaldehyde dimethylacetal **15** (2.05 g, 16.9 mmol) was added and stirring was continued for 24 h at room temperature. The resulting solution was diluted with $H_2O$ and extracted with EtOAc (2×40 mL). The combined organic extracts were washed with brine, dried ($Na_2SO_4$), and concentrated to provide **16 (**2.76 g, 91%) as a pale yellow liquid.

To a solution of **16** in $CH_2Cl_2$ (10 mL) was added aqueous HCl (3 M, 10 mL) and the mixture was stirred at room temperature for 15 h. The organic layer was separated and

washed with saturated aqueous $NaHCO_3$, brine, dried ($Na_2SO_4$) and then concentrated on a rotary evaporator at 15 °C to provide a yellow oil. Purification by flash chromatography on silica gel ($CH_2Cl_2$) provided aldehyde **17** (2.12 g, 89%) as a colourless liquid.

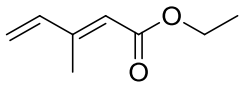
**IR** (neat): 2987, 1699 (br), 1645, 1280, 1214, 1163, 1122, 1036 $cm^{-1}$.

**$^1$H NMR** (300 MHz, $CDCl_3$): δ 9.55 (s, 1H, C*H*O), 6.50 (q, 1H, *J* = 1.5, C*H*CO), 4.28 (q, 1H, *J* = 7.1, C*H*$_2$CH$_3$), 2.16 (d, 2H, *J* = 1.5, C*H*$_3$C=CH), 1.35 (t, 3H, *J* = 7.1, CH$_2$C*H*$_3$).

**$^{13}$C NMR** (75 MHz, $CDCl_3$): δ 194.5 (*C*HO), 165.5 (*C*O$_2$CH$_2$CH$_3$), 150.3 (*C*-CHO), 135.2 (*C*H-CO$_2$CH$_2$CH$_3$), 61.0 (*C*H$_2$CH$_3$), 14.4 (*C*H$_3$), 10.8 (*C*H$_3$).

**MS** (CI Pos): *m*/*z* 143.1 $(M+H)^+$.

**(*E*)-Ethyl 3-methylpenta-2,4-dienoate (18)[7]:**



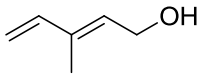

A solution of *n*-butyllithium (1.66 M, 2.10 mL, 3.49 mmoL) was added dropwise to a suspension of methyltriphenylphosphium bromide (1.22 g, 3.40 mmol) in THF (10 mL) at –78 °C. The mixture was brought to 0 °C and stirred for 1 h After cooling to –78 °C, a solution of **17**(0.50 g, 3.20 mmol) in THF (3 mL) was added slowly. The mixture was stirred for 24 h at room temperature, water was added and the mixture was extracted with $Et_2O$ (3×20 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was removed by distillation. The residue was purified by flash chromatography (pentane/$Et_2O$, 40/1). Fractions containing the product were pooled and the solvent was removed by distillation (45 °C) at atmospheric pressure to provide **18** (0.21 g, 44%) as a yellow liquid.

**IR** (neat): 2948, 1711, 1603, 1232, 1156, 1074, 1032 $cm^{-1}$.

**$^{1}$H NMR** (300 MHz, $CDCl_3$): δ 6.40 (apparent dd, 1H, *J* = 17.4, 10.7, C*H*=$CH_2$), 5.79 (br s, 1H, C*H*CO), 5.61 (apparent d, 1H, *J* = 17.4, C*H*$_2$=CH), 5.38 (apparent d, 1H, *J* = 10.7, C*H*$_2$=CH), 4.18 (q, 2H, *J* = 7.1, C*H*$_2$$CH_3$), 2.27 (d, 3H, *J* = 1.4, C*H*$_3$), 1.29 (t, 3H, *J* = 7.1, C*H*$_2$$CH_3$).

**$^{13}$C NMR** (75 MHz, $CDCl_3$): δ 167.0 (*C*$O_2$$CH_2$$CH_3$), 152.0 ($H_3$C-*C*=CH), 140.2 (*C*H=$CH_2$), 120.0 (H*C*-C=O), 119.4 (*C*$H_2$=CH), 59.8 (*C*$H_2$$CH_3$), 14.3 (*C*$H_3$), 13.1 (*C*$H_3$); **MS** (CI Pos): *m*/*z* 141.1 $(M+H)^+$.

**(*E*)-3-Methylpenta-2,4-dien-1-ol (13)[7]**



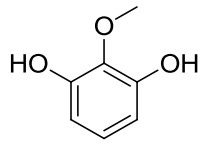

A solution of **18** (1.10 g, 7.14 mmol) in anhydrous $Et_2O$ (4 mL) was added to a suspension of $LiAlH_4$ (0.54 g, 14.2 mmol) in anhydrous $Et_2O$ (10 mL) at 0 °C under a $N_2$ atmosphere. The mixture was stirred at 0 °C for 30 min and cold $H_2O$ was added. The residue formed was dissolved by addition of a 10% aqueous solution of $H_2SO_4$. The resulting biphasic mixture was separated and the aqueous phase was extracted with $Et_2O$ (2×10 mL). The combined extracts were dried ($MgSO_4$) and concentrated to provide **13** (0.58 g, 83%) as a yellow liquid.

**IR** (neat): 3379, 2926, 2859, 1609, 1439, 997, 897 $cm^{-1}$.

**$^{1}$H NMR** (300 MHz, $CDCl_3$): δ 6.39 (apparent dd, 1H, *J* = 17.4, 10.7, C*H*=$CH_2$), 5.68 (br t, 1H, *J* = C*H*$CH_2$OH), 5.25 (apparent d, 1H, *J* = , CH=C*H*$_2$), 5.07 (br d, 1H, *J* = 5.7, CH=C*H*$_2$), 4.30 (t, 2H, *J* = 5.4, C*H*$_2$CH), 2.17 (s, 1H, O*H*), 1.79 (m, 3H, C*H*$_3$).

**$^{13}$C NMR** (75 MHz, $CDCl_3$): δ 140.7 ($CH_2$=*C*H), 136.5 (*C*-$CH_3$), 130.4 (*C*H-$CH_2OH$), 113.2 (*C*$H_2$=CH), 59.4 (*C*$H_2OH$), 11.9 (*C*$H_3$).

**2-Methoxybenzene-1,3-diol (21)[8]:**




Lithium carbonate (0.73 g, 9.9 mmol) was added to a solution of pyrogallol (**22**) (0.50 g, 3.9 mmol) in *N*,*N*-dimethylformamide (15 mL) at room temperature. After 5 min, methyl iodide (0.61 mL, 9.9 mmol) was added and the resulting solution was heated at 50 °C for 48 h. It was then cooled to room temperature, water (50 mL) was added and the solution was extracted with EtOAc (3×60 mL). The combined extracts were dried ($Na_2SO_4$), filtered, and concentrated. The residue was purified by flash silica chromatography on silica gel (EtOAc/hexanes, 1/1) to provide **23** (0.43 g, 78%) as white amorphous solid.

**Mp**: 82-84 °C (lit.[11] Mp 84.5-85 °C).

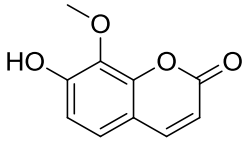
**IR** (neat): 3361 (br), 3323 (br), 2940, 1605, 1485, 1357, 1204, 1156, 1064, 1018, 982 $cm^{-1}$.

**$^{1}$H NMR** (300 MHz, $CDCl_3$): δ 6.87 (t, 1H, *J* = 8.1, Ar*H*), 6.51 (d, 2H *J* = 8.1, Ar*H*), 5.33 (s, 2H, O*H*), 3.88 (s, 3H, OC$H_3$).

**$^{13}$C NMR** (75 MHz, $CDCl_3$): δ 149.0 (2 × Ar*C*-OH), 134.7 (Ar*C*-$OCH_3$), 124.8 (Ar*C*), 108.2 (2 × Ar*C*), 61.2 (O*C*$H_3$).

**MS** (CI Pos.): *m*/*z* 141.1 $(M+H)^+$; HRMS (EI Pos., TOF): *m*/*z* 140.0472 (140.0473 calcd. for $C_7H_8O_3$ ($M^+$)).

**7-Hydroxy-8-methoxy-2*H*-chromen-2-one (10):**




A mixture of **20** (0.20 g, 1.4 mmol), malic acid (**24**) (0.19 g, 1.4 mmol) and conc. sulphuric acid (0.5 mL) was heated for 10 min at 95 °C and then in an oil bath at 100-115 °C for 15 min by which time evolution of carbon monoxide had ceased. A mixture of ice and water (10 mL) was added and the brown solid which precipitated was isolated by filtration. The gummy residue which separated at the bottom of the flask was dissolved in hot methanol (3 mL) and the solution was concentrated to obtain a black solid. The two solids were mixed and purified by flash chromatography on silica gel (EtOAc/hexanes, 1/4) to provide the coumarin **10** (0.14 g, 55%) as a pale yellow solid.

**Mp**: 185-187 °C (lit.[12] Mp 186.5 °C).

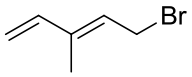
**IR** (neat): 3328, 2934, 1695, 1602, 1570, 1504, 1444, 1331, 1200, 1156, 1126, 1066, 1022 $cm^{-1}$.

**$^1$H NMR** (300 MHz, $CDCl_3$): δ 7.62 (d, 1H, *J* = 9.5, C*H*=CH-C=O), 7.11 (d, 1H, *J* = 8.5, Ar*H*), 6.90 (d, 1H, *J* = 8.5, Ar*H*), 6.24 (d, 1H, *J* = 9.5, C*H*-C=O), 6.18 (s, 1H, O*H*), 4.13 (s, 3H, OC$H_3$).

**$^{13}$C NMR** (75 MHz, $CDCl_3$): δ 160.5 (*C*$O_2$), 152.1 (Ar*C*-OH), 147.1 (Ar$C_{ipso}$), 144.3 (*C*H=CH-C=O), 133.6 (Ar*C*-O$CH_3$), 123.3 (Ar*C*), 113.3 (Ar*C*-CH), 112.6 (Ar*C*), 112.1 (CH=*C*H-C=O), 61.8 (O*C*$H_3$).

**MS** (CI Pos.): *m*/*z* 193.1 $(M+H)^+$; HRMS (EI Pos., TOF): *m*/*z* 192.0425 (192.0423 calcd. for $C_{10}H_8O_4$ ($M^+$)).

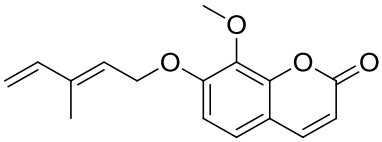
**(*E*)-5-Bromo-3-methylpenta-1,3-diene (21)**[7]




To a solution of the alcohol **13** (0.14 g, 1.4 mmol) in $CH_2Cl_2$ (3 mL) at 0 $^oC$ was added phosphorus tribromide (73 µL, 0.78 mmol) and the mixture was stirred at 0 °C for 30 min. Saturated aqueous $NaHCO_3$ and $CH_2Cl_2$ (5 mL) were added and the biphasic solution was separated. The aqueous layer was extracted with $CH_2Cl_2$ (2×5mL) and the combined extracts were dried ($Na_2SO_4$) and concentrated to provide **21** (0.16 g, 75%) as a brown liquid. This was used in the next step without purification.

**$^1$H NMR** (300 MHz, $CDCl_3$): δ 6.36 (ddd, 1H, *J* = 17.4, 10.7, 0.8, C*H*$CH_2$), 5.79 (apparent t, 1H, *J* = 8.7, C*H*$CH_2$OH), 5.30 (d, 1H, *J* = 17.4, CHC*H*$_2$), 5.12 (d, 1H, *J* = 10.7, CHC*H*$_2$), 4.14 (d, 2H, *J* = 8.7, C*H*$_2$OH), 1.84 (d, 3H, *J* = 1.3, C*H*$_3$).

**(*E*)-8-Methoxy-7-((3-methylpenta-2,4-dien-1-yl)oxy)-2*H*-chromen-2-one (20):**



To a solution of the coumarin **10** (58 mg, 0.3 mmol) and bromodiene **21** (70 mg, 0.4 mmol) in acetone (5 mL), was added $Na_2CO_3$ (54 mg, 0.4 mmol). The suspension was heated at 50 °C for 20 h and then cooled to room temperature. The precipitated solids were removed by suction filtration and the filtrate was concentrated under reduced pressure to obtain a yellow solid. This was purified by flash chromatography on silica gel (EtOAc/hexanes, 3/7) to provide unreacted **10 (**24 mg, 41%) and **20** (44 mg, 79%) as a white solid.

**Mp**: 85-88 °C.

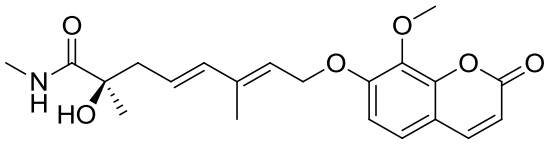
**IR** (neat): 2928, 1707, 1603, 1495, 1454, 1293, 1127, 1086, 1044, 976 $cm^{-1}$.

**$^1$H NMR** (300 MHz, $CDCl_3$): δ 7.62 (d, 1H, *J* = 9.5, *C*H=CH-C=O), 7.15 (d, 1H, *J* = 8.6, Ar*H*), 6.85 (d, 1H, *J* = 8.6, Ar*H*), 6.42 (apparent dd, 1H, *J* = 17.4, 10.7, C*H*=$CH_2$), 6.27 (d, 1H, *J* = 9.5, CH=C*H*-C=O), 5.76 (br t, *J* = 6.4, 1H, C*H*$CH_2$OH), 5.28 (br d, 1H, *J* = 17.4, C*H*$_2$=CH), 5.12 ( br d, 1H, *J* = 10.7, C*H*$_2$=CH), 4.83 (d, 2H, *J* = 6.4, C*H*$_2$-OAr), 3.99 (s, 3H, OC*H*$_3$), 1.55 (s, 3H, C*H*$_3$).

**$^{13}$C NMR** (75 MHz, $CDCl_3$): δ 160.9 (*C*$O_2$), 155.0 (Ar*C*-O-C=O), 148.6 (Ar*C*-$OCH_3$), 143.9 (*C*H=CH-C=O), 140.4 (Ar$C_{ipso}$), 138.4 (*C*H=$CH_2$), 137.0 (*C*-$CH_3$), 126.1 (*C*H$CH_2$O), 123.0 (Ar*C*), 114.3 (Ar*C*-CH), 113.9 (CH=*C*H-C=O), 110.5 (Ar*C*), 66.5 (*C*$H_2$-OAr), 61.8 (O*C*$H_3$), 12.6 (*C*$H_3$).

**MS** (CI Pos.): *m*/*z* 273.4 $(M+H)^+$; HRMS (EI Pos., TOF): *m*/*z* 272.1042 (272.1049 calcd. for $C_{16}H_{16}O_4$ ($M^+$).

**(4*E*,6*E*)-2-Hydroxy-8-((8-methoxy-2-oxo-2*H*-chromen-7-yl)oxy)-*N*-2,6-trimethylocta-4,6-dienamide (19):**



To a solution of **20** (75 mg, 0.27 mmol) and **6** (20 mg, 0.13 mmol) in $CH_2Cl_2$ (3 mL) was added the Grubbs II catalyst (2.3 mg, $2.7 \times 10^{-3}$ mmol, 2 mol%) and the solution was heated to reflux for 22 h. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure. The brown, gummy residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 9/1) to provide **19** (20 mg, 41%) as a brown gum.

**IR** (neat): 3366, 3207, 2925, 1723, 1647, 1601, 1547, 1407, 1262, 1210, 1126, 1047 $cm^{-1}$

**$^1$H NMR** (300 MHz, $CDCl_3$): δ 7.62 (d, 1H, *J* = 9.5, C*H*=CH-C=O), 7.15 (d, 1H, *J* = 8.7, Ar*H*), 6.85 (d, 1H, *J* = 8.7, Ar*H*), 6.73 (br s, 1H, N*H*), 6.27 (d, 1H, *J* = 9.5, CH=C*H*-C=O), 6.22 (d, 1H, *J* = C*H*=C-$CH_3$), 5.78 – 5.68 (m, 1H, C*H*-$CH_2$), 5.68-5.65 (m, 1H, C*H*-$CH_2O$), 4.80 (d, 1H, *J* = 6.5, C*H*$_2$O), 3.98 (s, 1H, $OCH_3$), 2.83 (d, *J* = 4.9, 3H, N-C*H*$_3$), 2.77 (dd, 1H, *J* = 14.1, 6.8, C*H*$_2$-CH), 2.44 – 2.34 (dd, *J* = 14.1, 5.8, 1H, C*H*$_2$-CH), 2.35 (br s, 1H, O*H*), 1.85 (br s, 1H, C*H*$_3$), 1.44 (s, 3H, C*H*$_3$).

**$^{13}$C NMR** (75 MHz, $CDCl_3$): δ 175.8 (*C*ONH), 160.6 (*C*$O_2$), 154.8 (Ar*C*-$OCH_2$), 148.2 (Ar*C*-$OCH_3$), 143.6 (*C*H=CH-C=O), 138.5 (Ar$C_{ipso}$), 137.6 (*C*($CH_3$)CH), 136.8

(*C*HCH$_2$O), 125.1 (*C*HCH$_2$), 124.1 (*C*HCHCH$_2$), 122.7 (Ar*C*), 113.9 (Ar*C*-CH), 113.6 (CH=*C*H-C=O), 110.2 (Ar*C*), 75.5 (*C*-OH), 66.1 (*C*H$_2$-OAr), 61.5 (O*C*H$_3$), 43.6 (*C*H$_2$CH=CH), 26.2 (N-*C*H$_3$), 26.0 (*C*H$_3$COH), 13.1 (*C*H$_3$).

**MS** (CI Pos.): *m*/*z* 388.1 $(M+H)^+$.

## 2.4 References


(1) Xin, Z.-Q.; Lu, J.-J.; Ke, C.-Q.; Hu, C.-X.; Lin, L.-P.; Ye, Y. *Chem. Pharm. Bull.* **2008**, *56*, 827.

(2) Wu, C. Y. *Flora Yunnanica* **1995**, *6*, 975.

(3) (a) Wu, T.-S.; Huang, S.-C.; Wu, P.-L.; Kuoh, C.-S. *Phytochemistry* **1999**, *52*, 523; (b) Tian-Shung, W.; Shiow-Chyn, H.; Pei-Lin, W.; Che-Ming, T. *Phytochemistry* **1996**, *43*, 133.

(4) (a) Ito, C.; Itoigawa, M.; Katsuno, S.; Omura, M.; Tokuda, H.; Nishino, H.; Furukawa, H. *J. Nat. Prod.* **2000**, *63*, 1218; (b) Thuy, T. T.; Ripperger, H.; Porzel, A.; Sung, T. V.; Adam, G. *Phytochemistry* **1999**, *52*, 511; (c) Ito, C.; Katsuno, S.; Furukawa, H. *Chem. Pharm. Bull.* **1998**, *46*, 341.

(5) He, H. P.; Zhang, J. X.; Shen, Y. M.; He, Y. N.; Chen, C. X.; Hao, X. J. *Helv. Chim. Acta* **2002**, *85*, 671.

(6) Curley, R. W.; Ticoras, C. J. *Synth. Commun.* **1986**, *16*, 627.

(7) Yildizhan, S.; Schulz, S. *Synlett* **2011**, *2011*, 2831.

(8) Donnelly, A. C.; Mays, J. R.; Burlison, J. A.; Nelson, J. T.; Vielhauer, G.; Holzbeierlein, J.; Blagg, B. S. J. *J. Org. Chem.* **2008**, *73*, 8901.

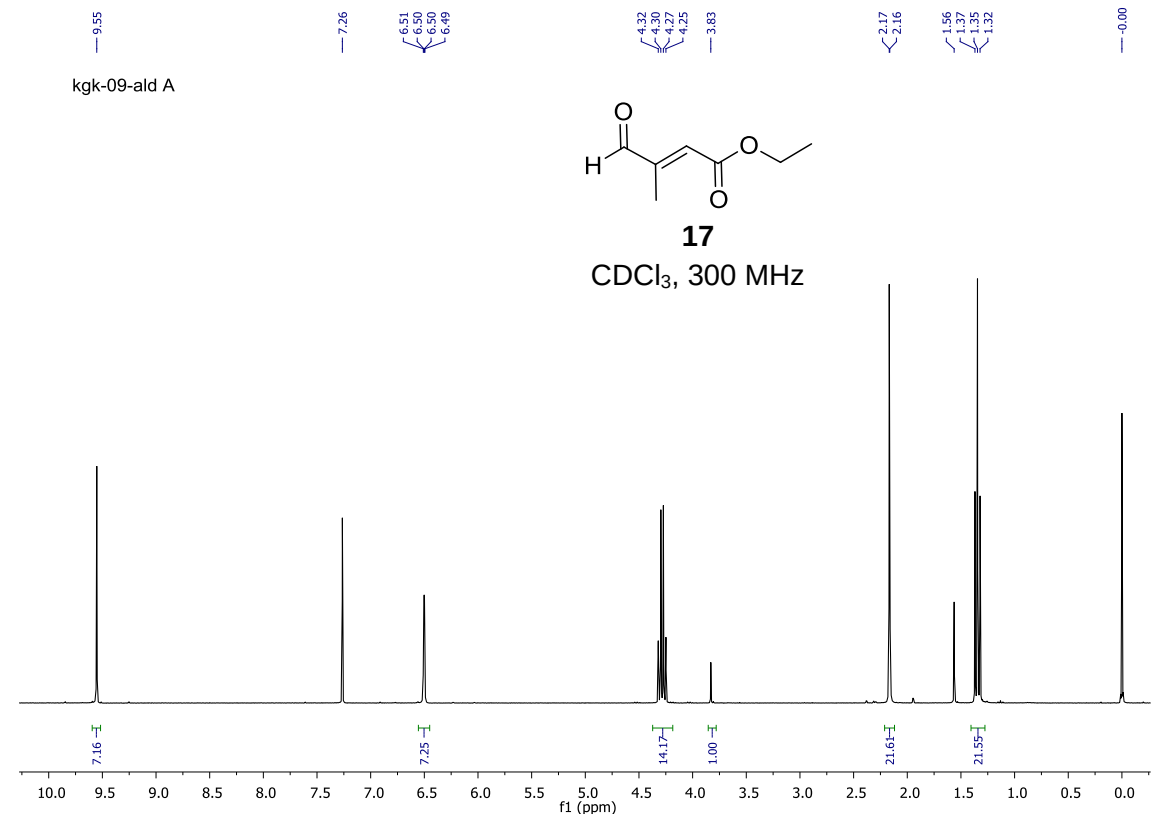
(9) Molyneux, R. J.; Jurd, L. *Aust. J. Chem.* **1974**, *27*, 2697.

(10) (a) Furber, M.; Mander, L. N.; Patrick, G. L. *J. Org. Chem.* **1990**, *55*, 4860; (b) Liu, G.; Wilkerson, P. D.; Toth, C. A.; Xu, H. *Org. Lett.* **2012**, *14*, 858; (c) Stockdill, J. L.; Behenna, D. C.; McClory, A.; Stoltz, B. M. *Tetrahedron* **2009**, *65*, 6571.

(11) Geissman, T. A.; Mojé, W. *J. Am. Chem. Soc.* **1951**, *73*, 5765.

(12) Bohm, B. A.; Ibrahim, R. K.; Towers, G. H. N. *Can. J. Biochem. Physiol.* **1961**, *39*, 1389.

## 2.5 Selected $^{1}H$ and $^{13}C$ NMR spectra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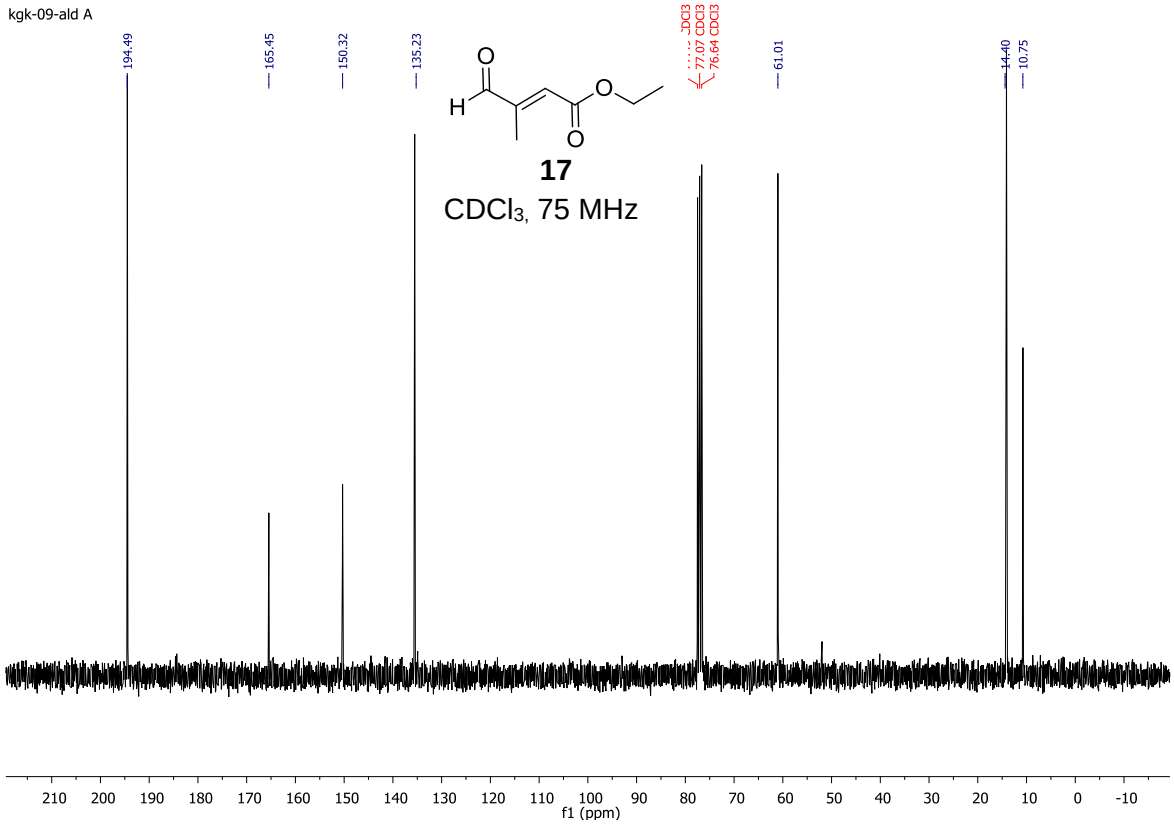
6.51
6.50
6.50
6.49
4.32
4.30
4.27
4.25
3.83
2.17
2.16
1.56
1.37
1.35
1.32
-0.00
kgk-09-ald A
O
H
O
O
17
CDCl3, 300 MHz
7.16
7.25
14.17
1.00
21.61
21.55
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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150.32
135.23
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61.01
14.40
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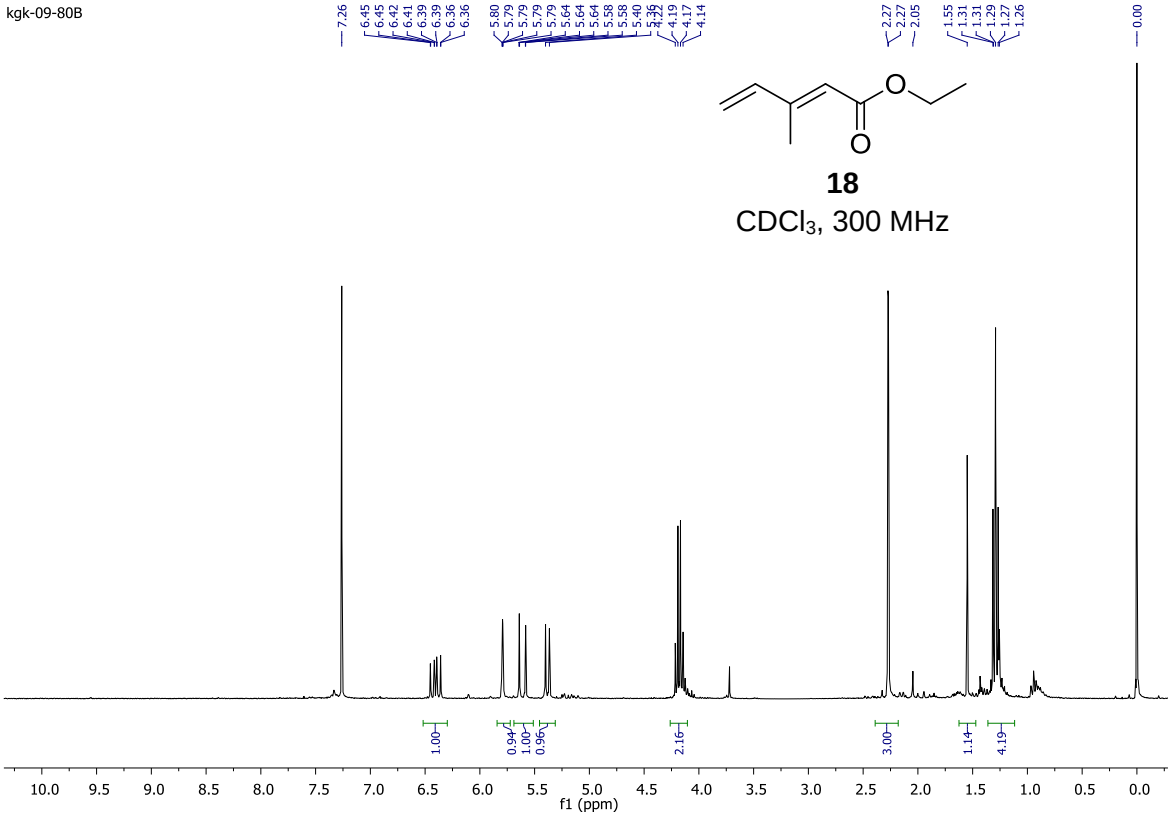
f1 (ppm)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6.42
6.41
6.39
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6.36
6.36
5.80
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5.79
5.79
5.79
5.64
5.64
5.58
5.58
5.40
4.19
4.17
4.14
2.27
2.27
2.05
1.55
1.31
1.31
1.29
1.27
1.26
0.00
O
O
18
CDCl3, 300 MHz
1.00
0.94
1.00
0.96
2.16
3.00
1.14
4.19
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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3.5
3.0
2.5
2.0
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1.0
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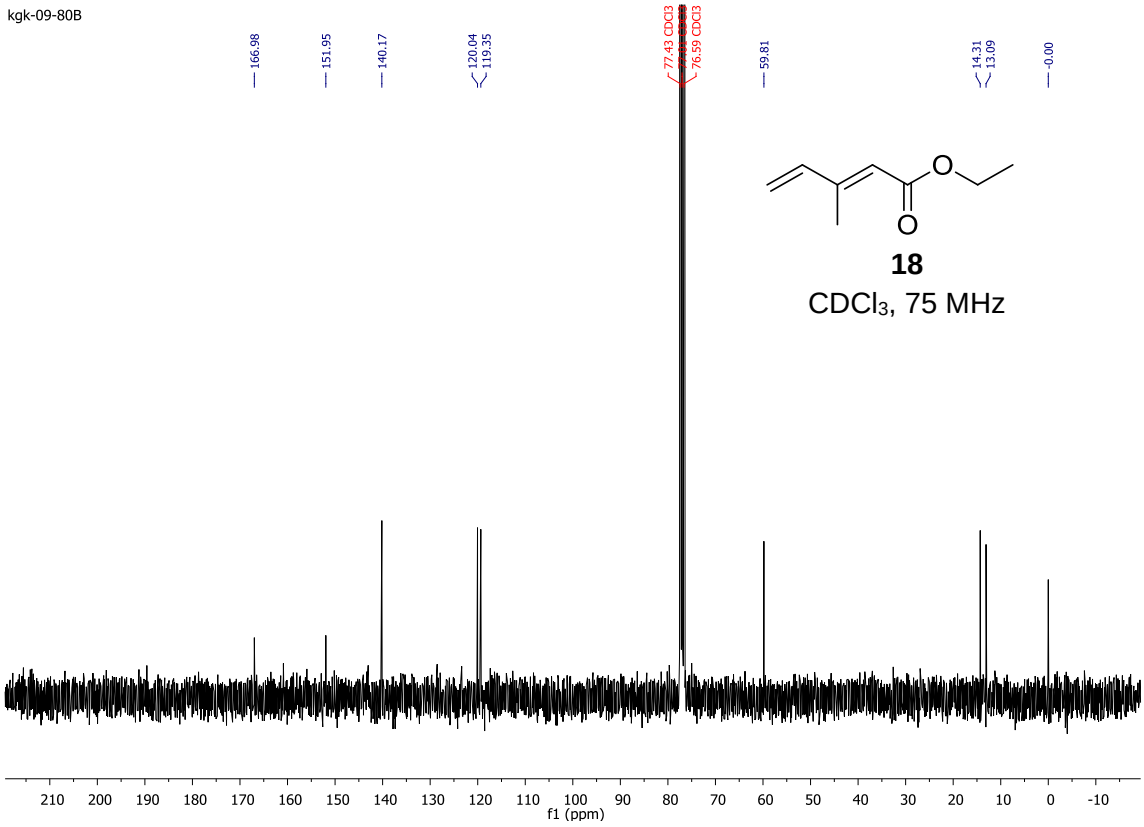
0.0
f1 (ppm)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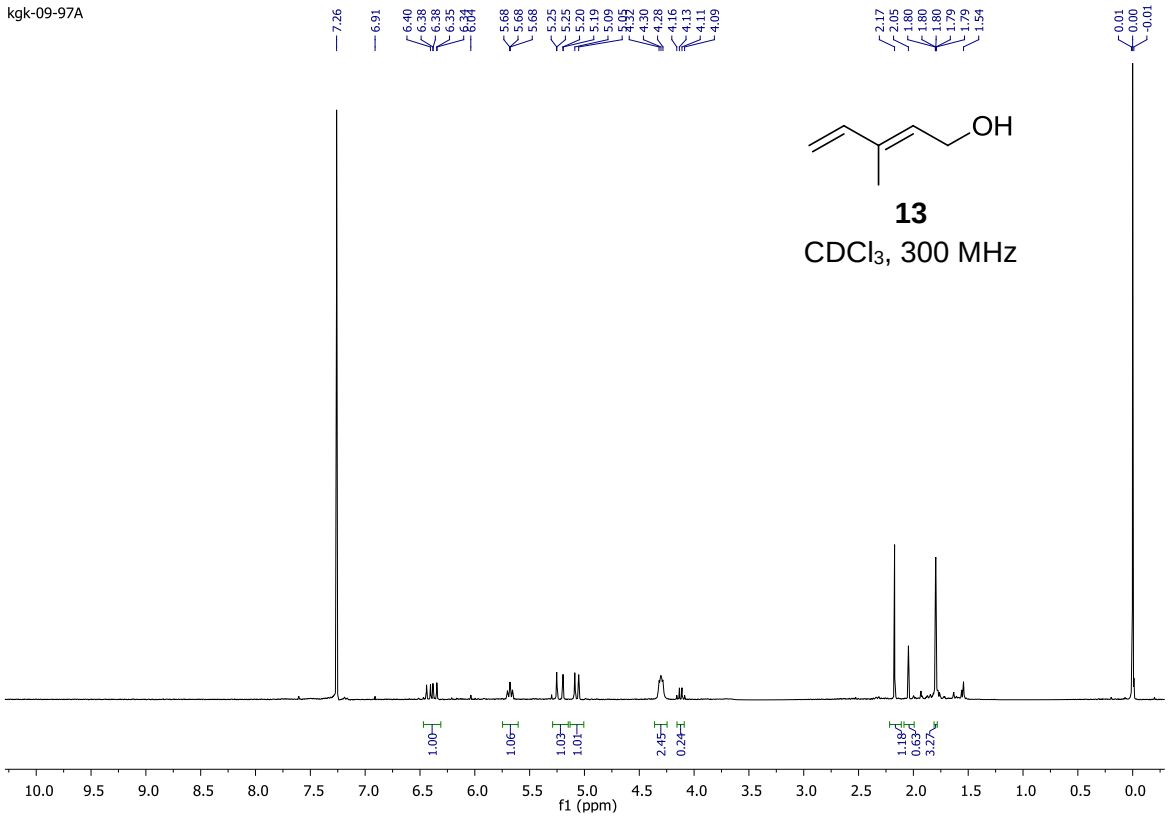
140.17
120.04
119.35
77.43 CDCl3
76.59 CDCl3
59.81
14.31
13.09
-0.00
O
O
18
CDCl3, 75 MHz
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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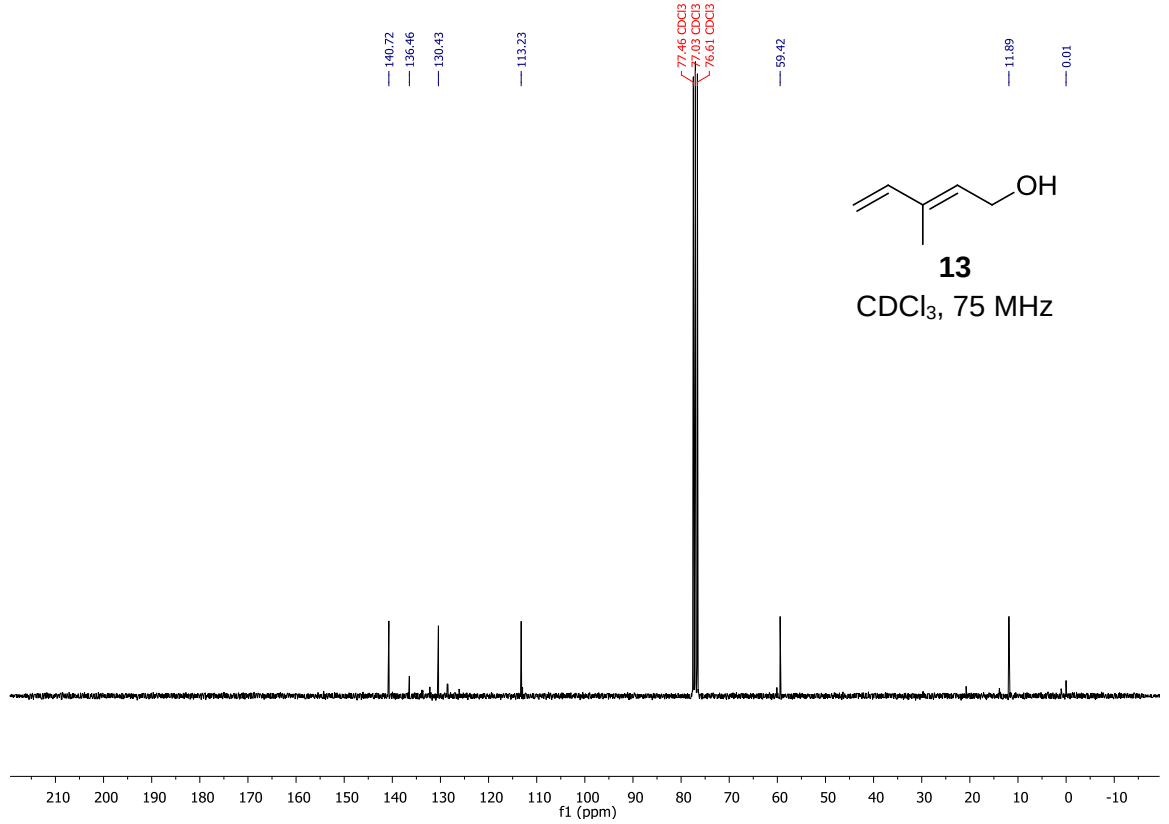
6.91
6.40
6.38
6.38
6.35
6.34
6.34
5.68
5.68
5.68
5.25
5.25
5.20
5.19
5.09
5.09
4.32
4.30
4.28
4.16
4.13
4.11
4.09
2.17
2.05
1.80
1.80
1.80
1.79
1.79
1.54
0.01
0.00
-0.01
OH
13
CDCl3, 300 MHz
1.00
1.06
1.03
1.01
2.45
0.24
1.18
0.63
3.27
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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11.89
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OH
13
CDCl3, 75 MHz
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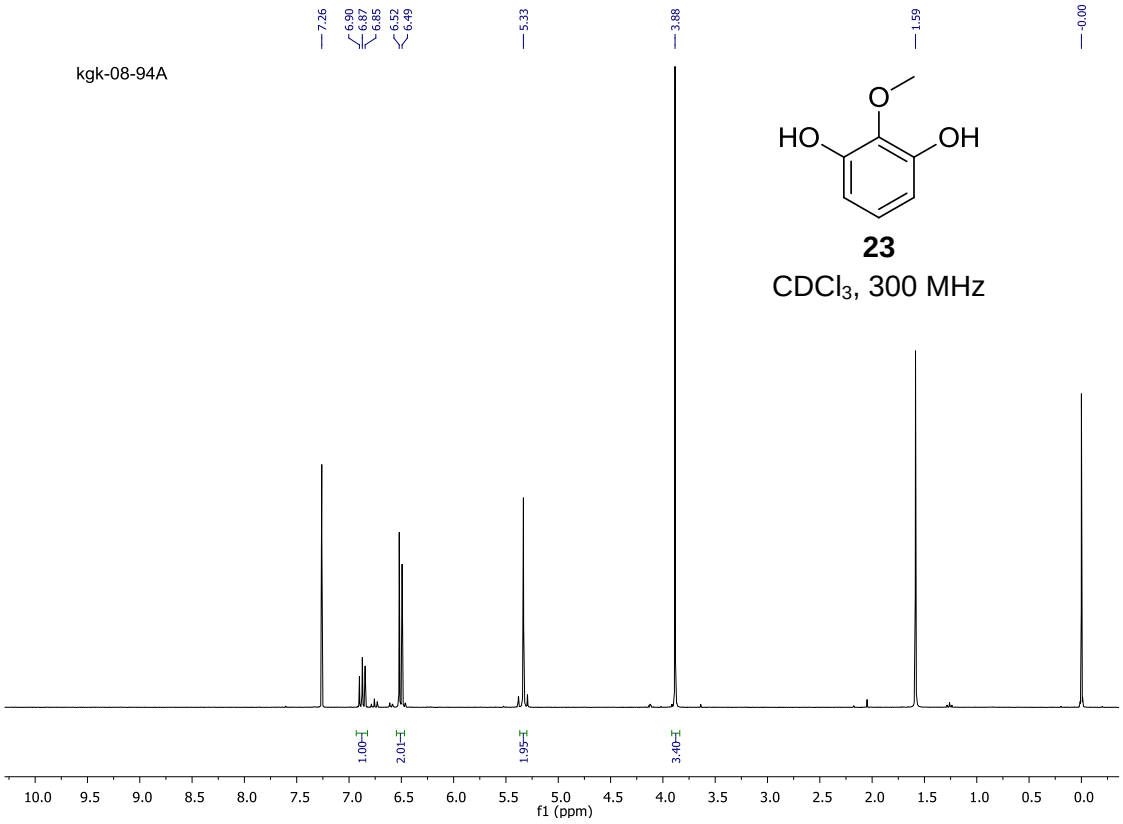
f1 (ppm)


kgk-08-94A
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6.90
6.87
6.85
6.52
6.49
5.33
3.88
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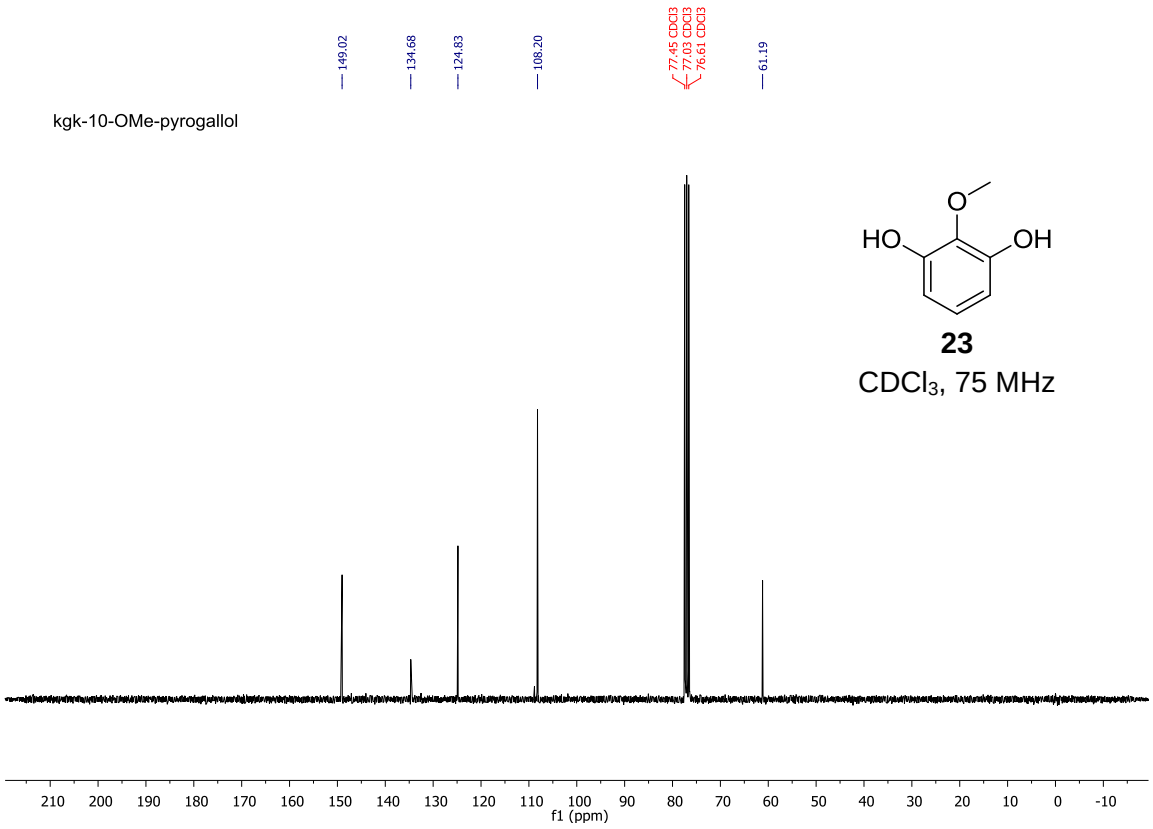
HO
OH
O
23
CDCl3, 300 MHz
1.00
2.01
1.95
3.40
f1 (ppm)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134.68
124.83
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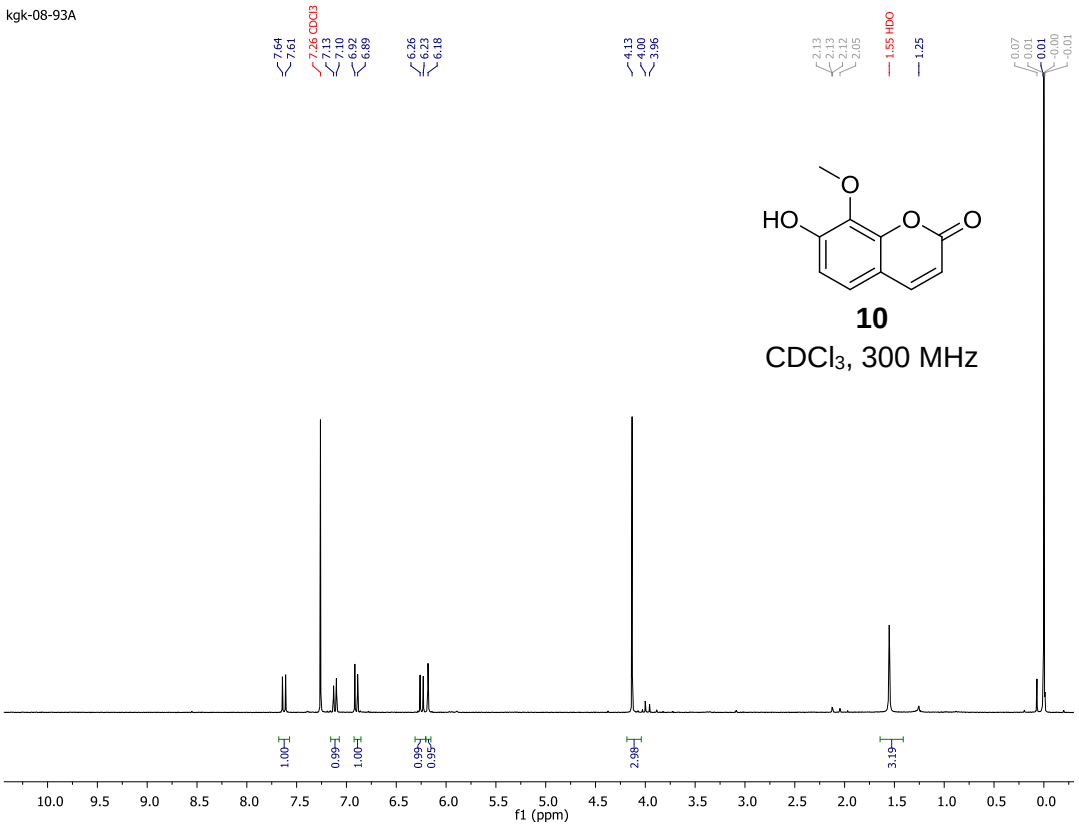
77.03 CDCl3
76.61 CDCl3
61.19
HO
OH
O
23
CDCl3, 75 MHz
f1 (ppm)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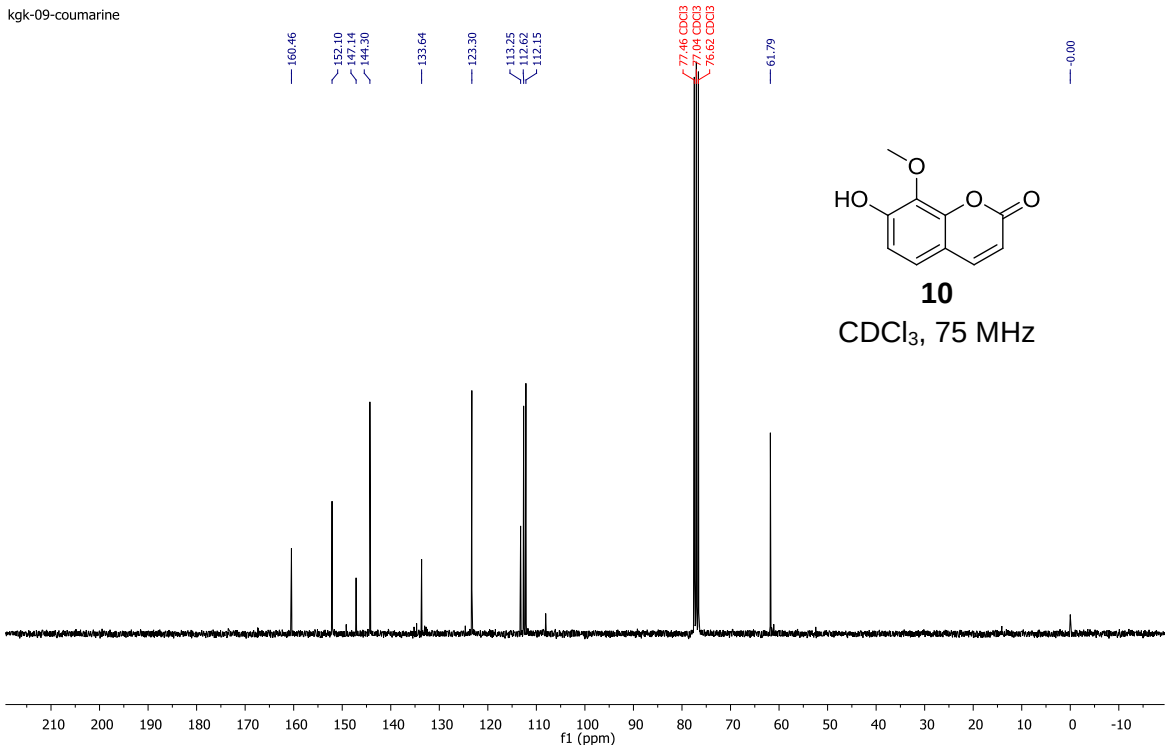
7.64
7.61
7.26 CDCl3
7.13
7.10
6.92
6.89
6.26
6.23
6.18
4.13
4.00
3.96
2.13
2.13
2.12
2.05
1.55 HDO
1.25
0.07
0.01
0.01
-0.00
-0.01
HO
O
O
O
10
CDCl3, 300 MHz
1.00
0.99
1.00
0.99
0.95
2.98
3.19
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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152.10
147.14
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133.64
123.30
113.25
112.62
112.15
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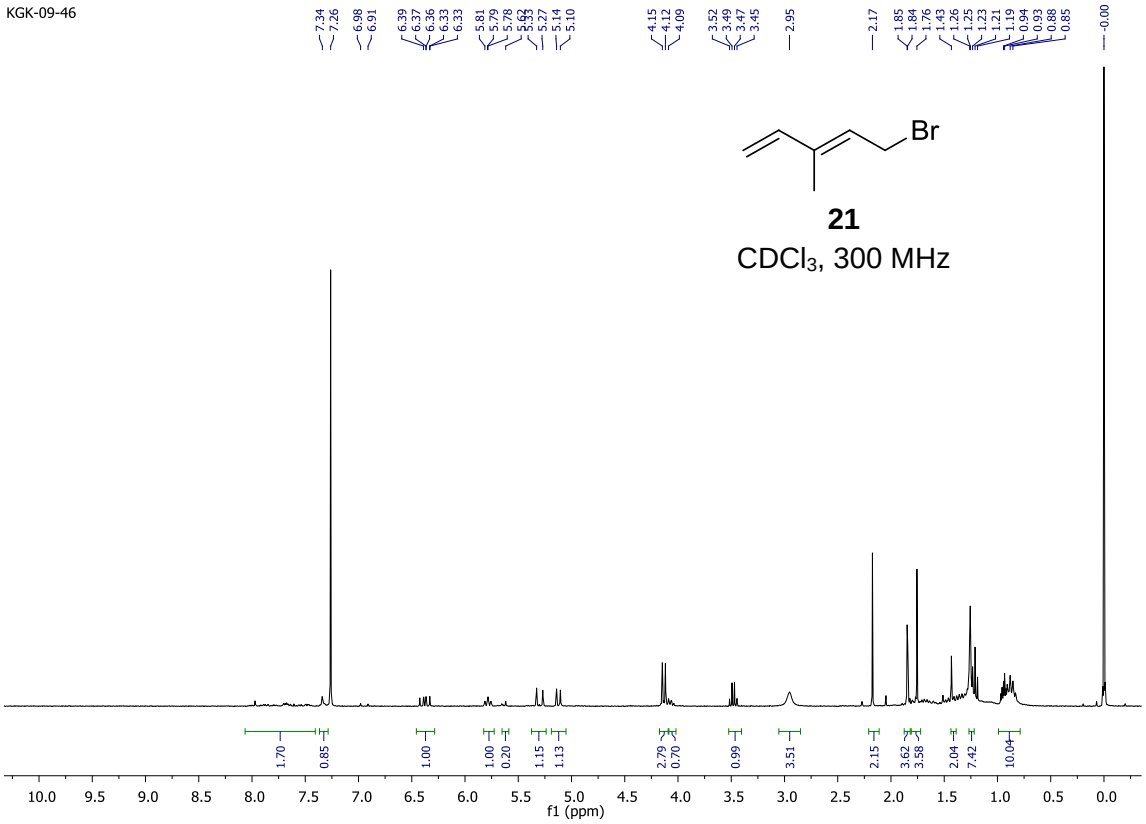
77.04 CDCl3
76.62 CDCl3
61.79
-0.00
HO
O
O
O
10
CDCl3, 75 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

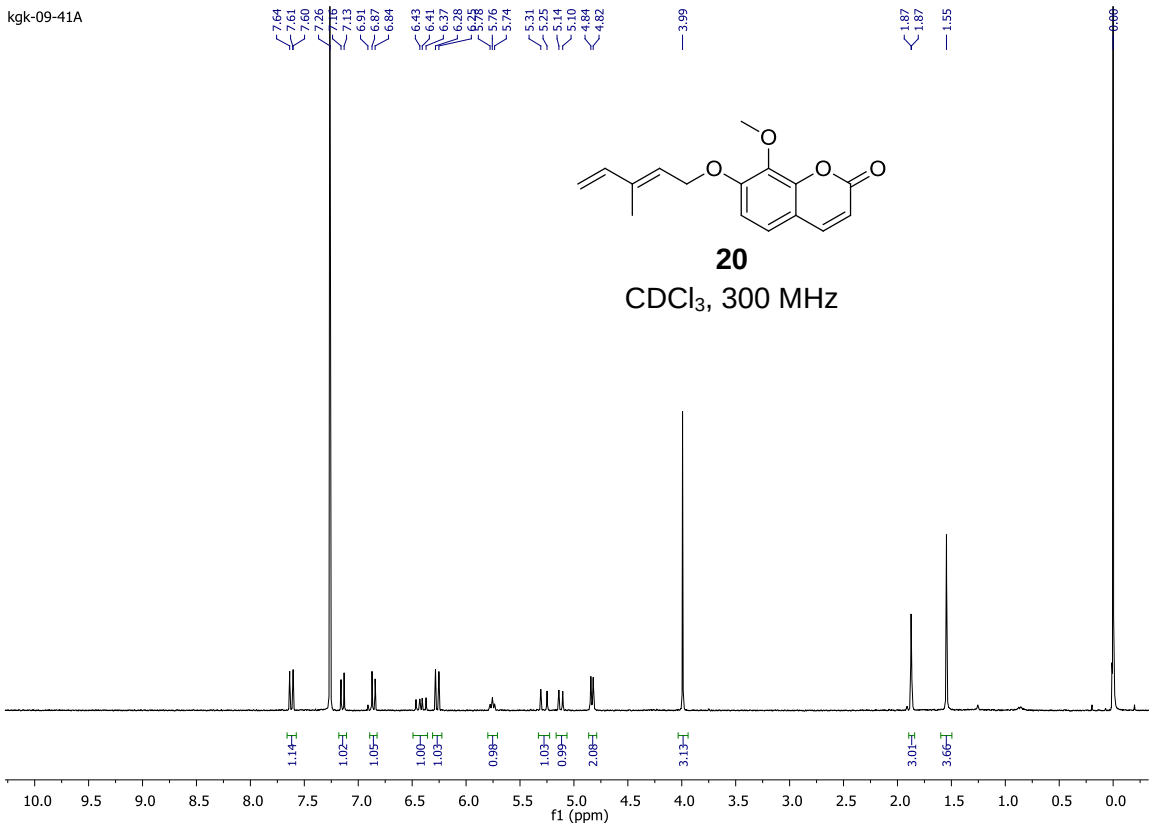
KGK-09-46




**21**

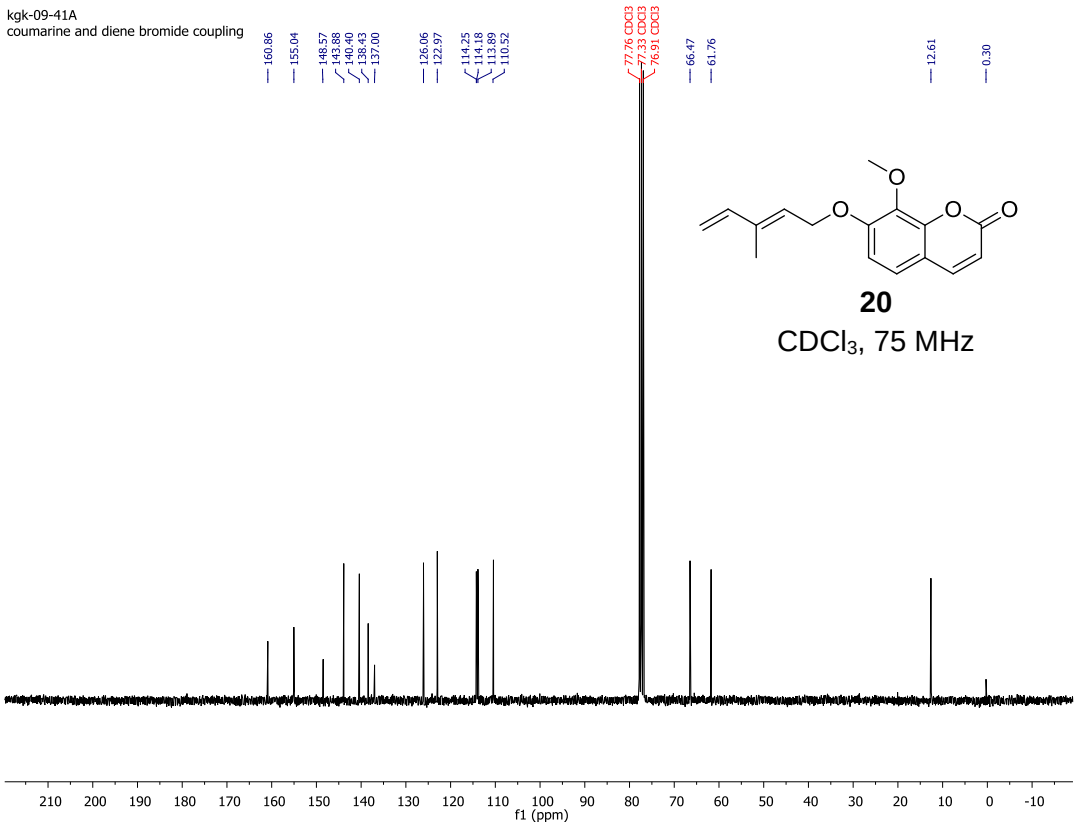
$CDCl_3$, 300 MHz

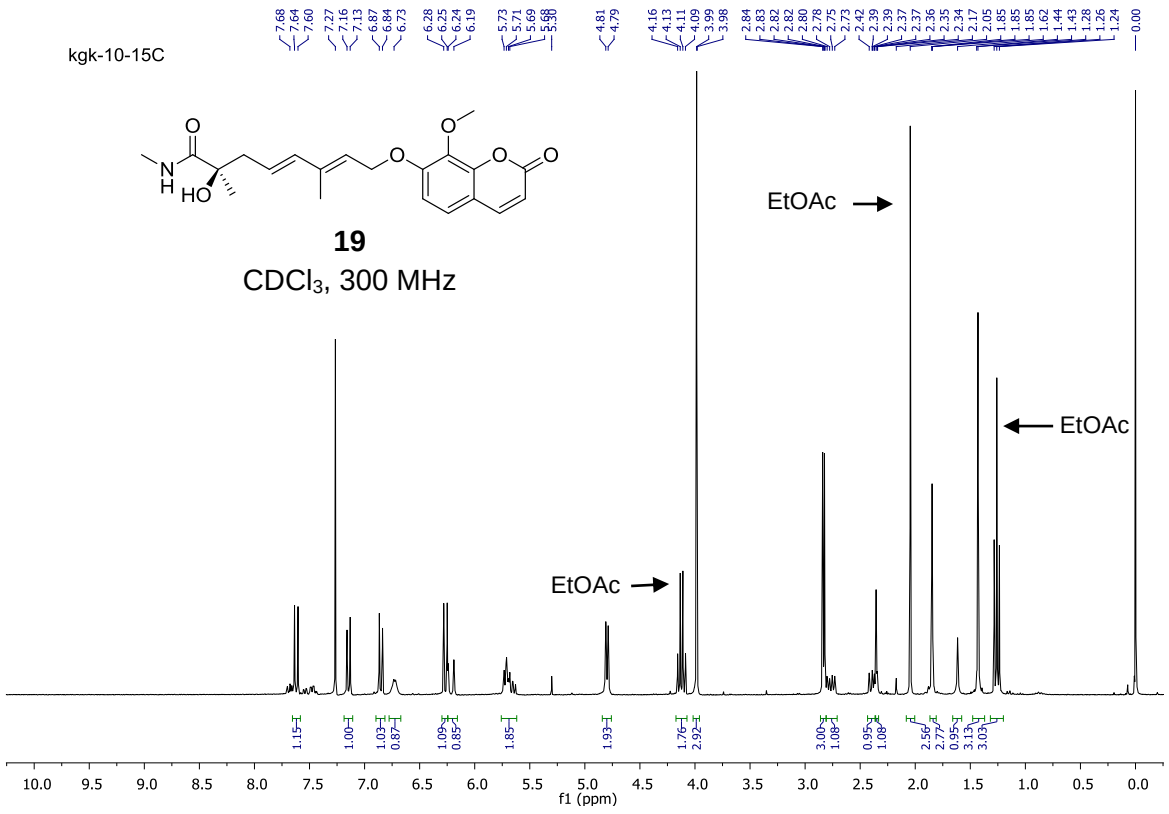
kgk-09-41A




**20**

$CDCl_3$, 300 MHz


kgk-09-41A
coumarine and diene bromide coupling
160.86
155.04
148.57
143.88
140.40
138.43
137.00
126.06
122.97
114.25
114.18
113.89
110.52
77.76 CDCl3
77.33 CDCl3
76.91 CDCl3
66.47
61.76
12.61
0.30
O
O
O
O
20
CDCl3, 75 MHz
f1 (ppm)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7.68
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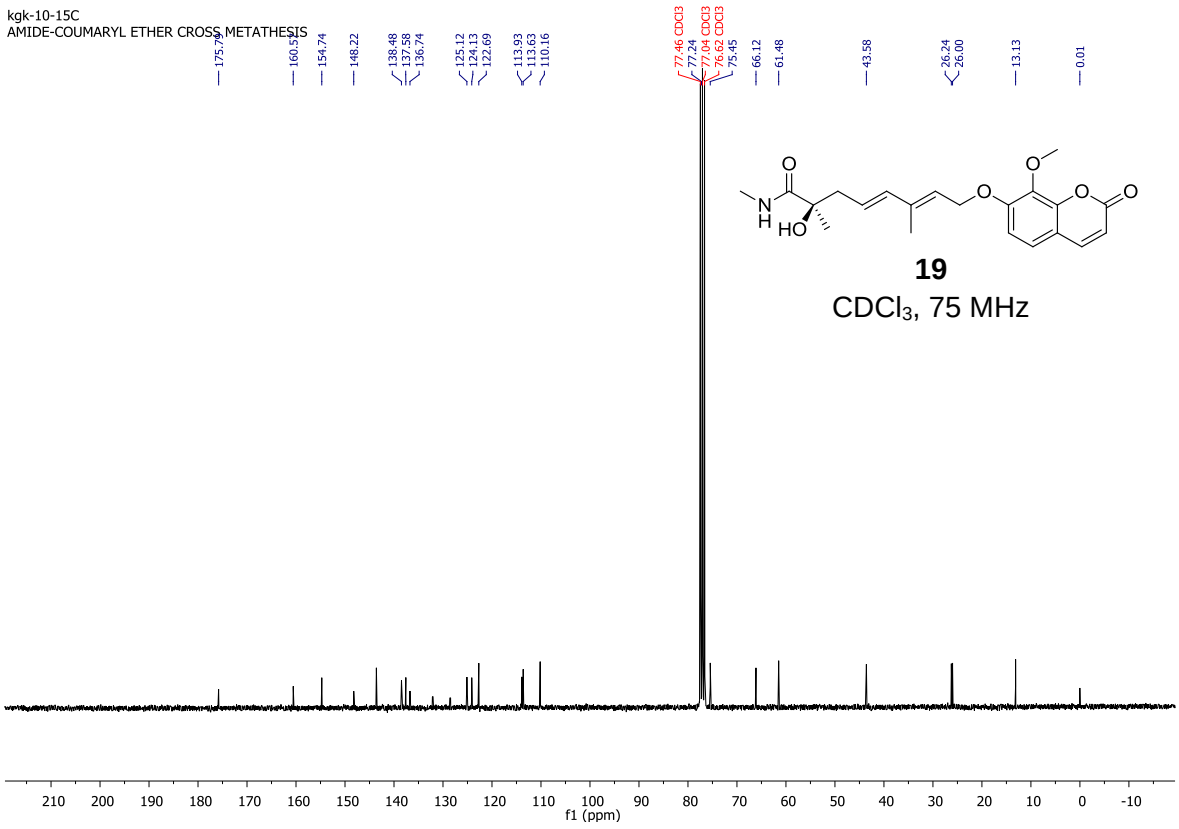
7.60
7.27
7.16
7.13
6.87
6.84
6.73
6.28
6.25
6.24
6.19
5.73
5.71
5.69
5.68
5.50
4.81
4.79
4.16
4.13
4.11
4.09
3.99
3.98
2.84
2.83
2.82
2.82
2.80
2.78
2.75
2.73
2.42
2.39
2.39
2.37
2.37
2.36
2.35
2.34
2.17
2.05
1.85
1.85
1.85
1.62
1.44
1.43
1.28
1.26
1.24
0.00
O
N
H
HO
O
O
O
19
CDCl3, 300 MHz
EtOAc
EtOAc
EtOAc
1.15
1.00
1.03
0.87
1.09
0.85
1.85
1.93
1.76
2.92
3.00
1.08
0.95
1.08
2.56
2.77
0.95
3.13
3.03
f1 (ppm)


kgk-10-15C
AMIDE-COUMARYL ETHER CROSS METATHESIS
175.79
160.51
154.74
148.22
138.48
137.58
136.74
125.12
124.13
122.69
113.93
113.63
110.16
77.46 CDCl3
77.24
77.04 CDCl3
76.62 CDCl3
75.45
66.12
61.48
43.58
26.24
26.00
13.13
0.01
O
N
H
HO
O
O
O
O
19
CDCl3, 75 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

# Chapter 3

## Stereoselective Allylation of α-Ketoacid Derivatives for the Synthesis of α-Alkyl-α-Hydroxy acids

## 3.1 Introduction

In Chapter 1 and Chapter 2 of this thesis, the application of enantiomerically pure α-alkyl,α-hydroxy acid derivatives in the synthesis of selected natural products was presented. The efficient stereoselective synthesis of these acid derivatives has been a challenge for organic chemists for a long time. The asymmetric allylation of aldehydes and ketones is a useful synthetic tool for the preparation of enantiomerically pure α-branched α-hydroxy acids. A number of synthetic methods have been successfully investigated for the asymmetric allylation of aromatic α-ketoacid derivatives for the synthesis of corresponding α-alkyl,α-aryl,α-hydroxy acids.[1] However, relatively few methods are reported for the enantioselective allylation of aliphatic α-ketoacid derivatives. The following discussion will provide a brief review of developments in this field.

### 3.1.1 Methods for the stereoselective allylation of α-ketoacid derivatives:

Procedures for the stereoselective allylation of α-ketoacid derivatives can be broadly classified as follows:

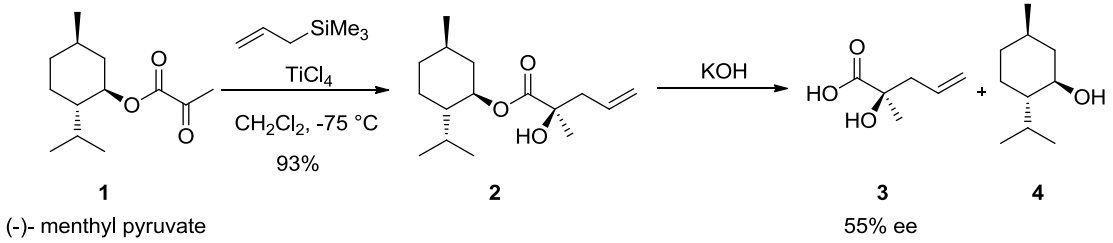
- Allylation of chiral α-ketoesters
- Lewis acid-mediated allylation of chiral α-ketoamides
- Asymmetric allylation of 1,3-dioxolanones
- Asymmetric allylation of α-ketoesters using chiral allylation reagents
- Application of the Ireland-Claisen rearrangement

Initial success in the allylation of α-ketoacid derivatives was obtained by the nucleophilic allylation of chiral auxiliary modified pyruvate esters, and amides.[2] Over the last two decades, the application of chiral allylation reagents has proved to be a promising

method[3] for stereoselective allylation along with the Ireland-Claisen rearrangement.[4] Most of the methods focus on the enantioselective allylation of aromatic α-ketoacid derivatives. Since most of the work described in this thesis is based on the stereoselective allylation of a chiral pyruvic acid derivative, the following sections summarize the reported enantioselective allylations of aliphatic α-ketoacid derivatives.

**3.1.1.1 Allylation of chiral α-ketoesters:**

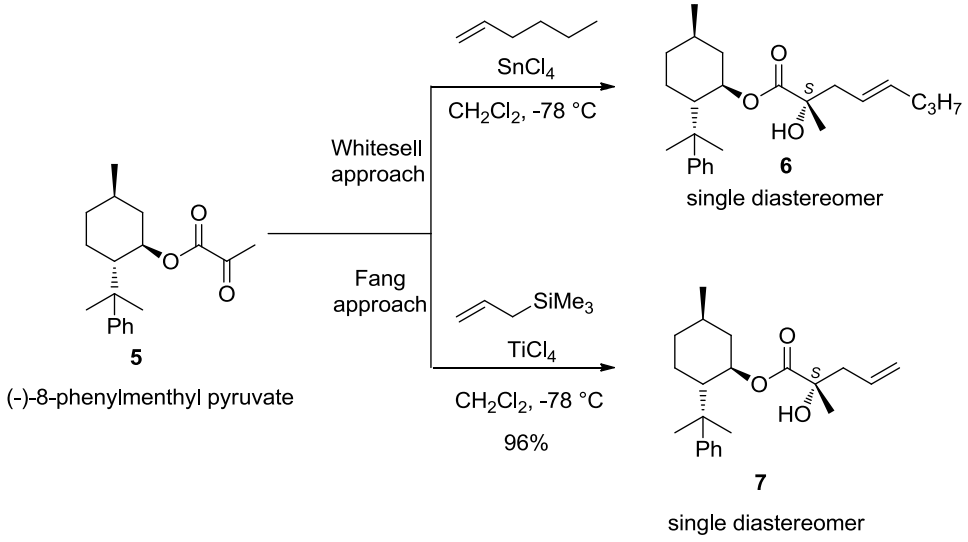
Ojima and co-workers[5] reported the asymmetric allylation of (−)-menthyl pyruvate **1** and phenyl glyoxylate. The treatment of **1** with allyltrimethyl silane and titanium chloride at −75 °C afforded the hydroxy acid derivative **2** in good yield and as a 3.4:1 mixture of diastereomers. An alkaline hydrolysis of **2** provided the *α*-hydroxy acid **3** (55% *ee*) and (−)-menthol **4** was recovered (Scheme 3.1). A similar reaction employing an allyl Grignard reagent did not show any selectivity.




Scheme 3.1

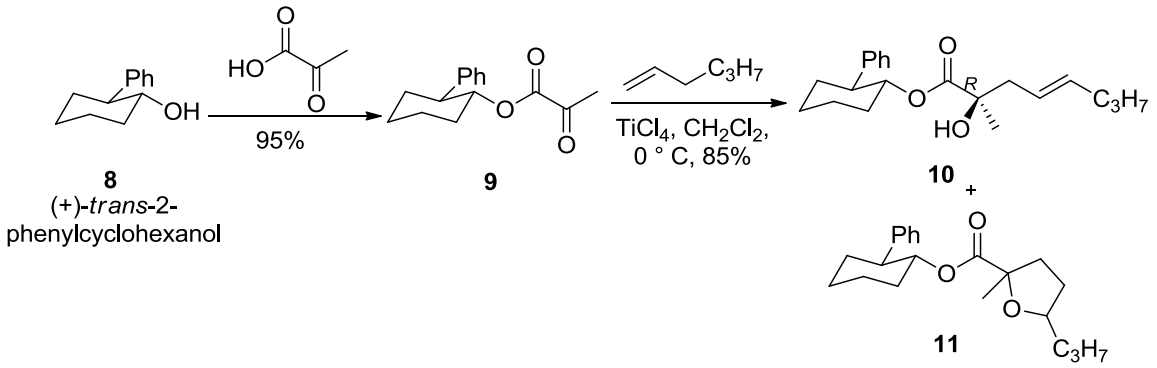
In a later study, Whitesell[2f] and Fang[2g] independently reported a modification of the method reported by Ojima.[5] Instead of (−)-menthyl pyruvate, 8-phenymenthyl pyruvate was subjected to an ene reaction. An earlier study by Whitesell[6] had indicated that (−)-8-phenylmenthol provides good selectivity in the alkylation of pyruvates. Treatment of (−)-8-phenylmenthyl pyruvate **5** with hex-1-ene furnished **6** as a single diastereomer (Scheme 3.2). On the other hand, Fang and co-workers examined the allylation of **5** with

allyltrimethyl silane as the nucleophile and titanium tetrachloride as the Lewis acid to obtain **7** as a single diastereomer (Scheme 3.2). In both reactions, it is assumed that the phenyl group in the auxiliary blocks the *Re* face of the ketone, in the *s*-cis rotamer of the α-ketoester which results in the addition of nucleophiles from the *Si*-face to form (*S*)-α-hydroxy esters selectively. A drawback of the Whitesell protocol is formation of a side product resulting from aldol reaction of **5** with itself. Other limitations of the methodology are the multistep synthesis of 8-phenylmenthol and the high cost of (+)-8-phenylmenthol which is required for preparing the enantiomeric hydroxy acids.




Scheme 3.2

Due to these limitations, the Whitesell group developed a better alternative for (+)-8-phenylmenthol.[7] Thus, the ene reaction of pyruvate ester **9**, made from (+)-*trans*-2-phenylcyclohexanol (**8**), with hex-1-ene in the presence of titanium tetrachloride afforded **10** in good yield (85%) and stereochemical control (up to 91% *de*). However, a significant amount of the cyclic product **11** was formed in this reaction (Scheme 3.3).




**8**
(+)-*trans*-2-phenylcyclohexanol

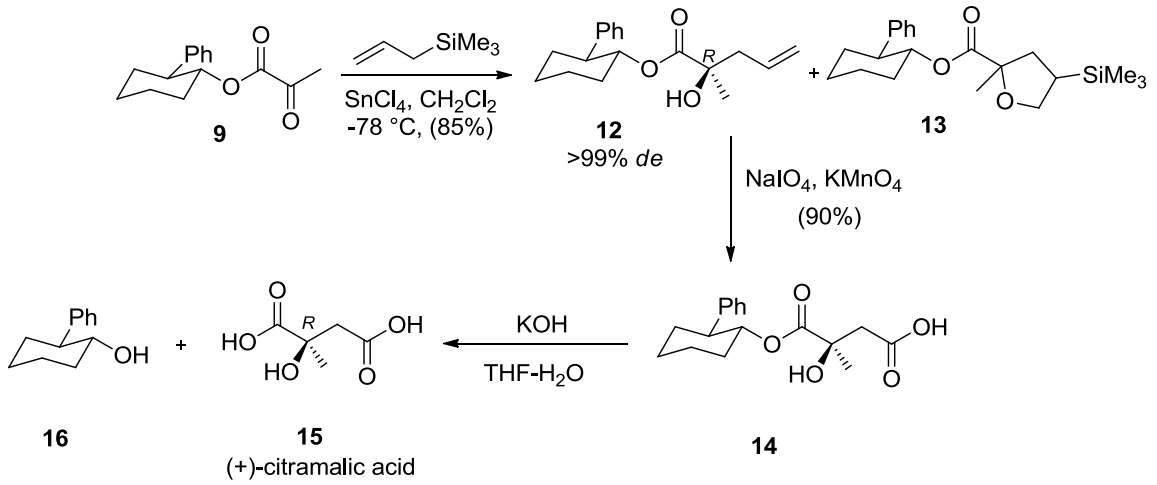
**9**

**10** +

**11**

Scheme 3.3

Allylation of **9** with allyltrimethylsilane provided **12** in excellent diastereomeric excess (>99%) and the corresponding tetrahydrofuran byproduct **13** was formed only in trace amounts (Scheme 3.4). The ester **12** was further converted to (+)-citramalic acid **15** in 96% enantiomeric excess.




**9**

**12**
>99% *de*

**13**

**16**

**15**
(+)-citramalic acid

**14**

Scheme 3.4

Notably, selectivity in the formation of the new stereocenter is reversed in this method compared to the allylation of (–)-8-phenylmenthyl pyruvate. It is suggested that the phenyl ring in the (–)-8-phenylmenthol acts as a π-donor and shields one face of the chelated α-ketoester **5** which results in the selective addition of the nucleophile to the

carbonyl ketone resulting in the formation of **6** (91% *de*, Figure 3.1).[7] The authors suggest that a similar interaction is less likely with *trans*-2-phenylcyclohexanol.[7] However, an explanation for the origin of selectivity in the formation of **10** (99% *de*, Figure 3.1) was not provided.

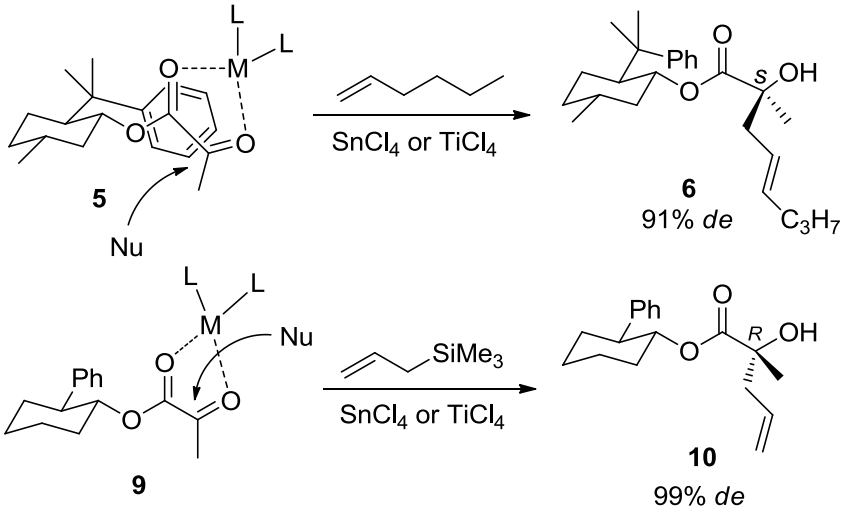
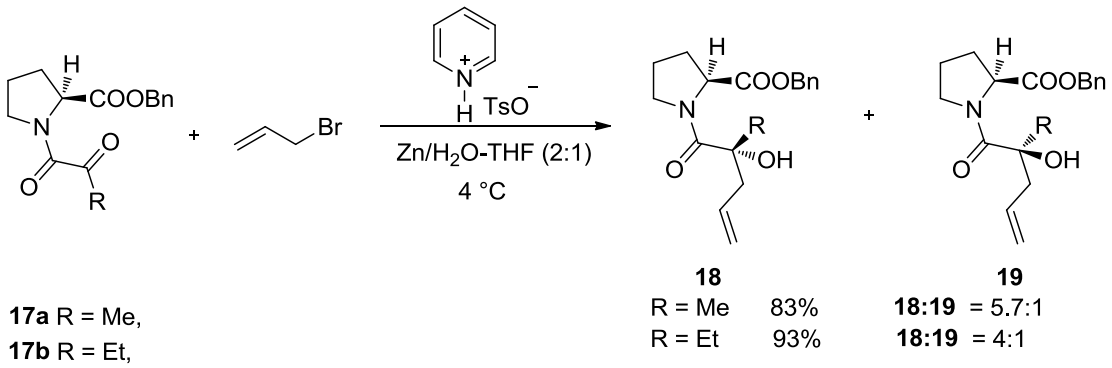



Figure 3.1 Origin of selectivity in allylation of **5** and **9**.

### 3.1.1.2 Asymmetric allylation of chiral α-ketoamides:

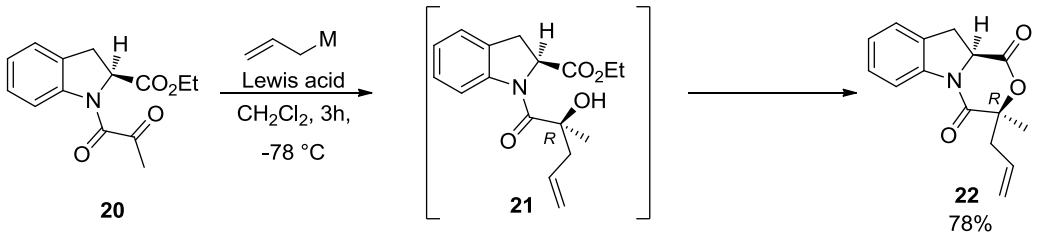
The first asymmetric Barbier-type allylation of α-ketoamides in aqueous medium was reported by Waldmann.[2c] Treatment of **17** with allyl bromide in the presence of zinc and pyridinium *p*-toluenesulfonate in THF-water (2:1) afforded a mixture of diastereomers **18** and **19** in high yields and with moderate stereoselectivities (Scheme 3.5).




Scheme 3.5

Aliphatic α-ketoacids are less reactive compared to aromatic ketoacids and underivatized allyl halides react faster compared to substituted allyl halides. The products were obtained with diastereoselectivity up to 6:1. This level of selectivity was obtained only with proline benzyl ester as the auxiliary and other amino esters were not suitable auxiliaries for this reaction.

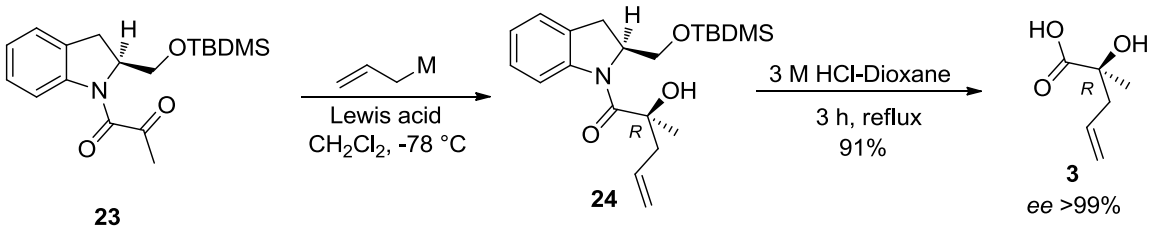
In 1995, Kim and co-workers reported the highly selective asymmetric allylation of α-ketoamides derived from (*S*)-indoline-2-carboxylic acid.[8] Previously, they had demonstrated that (*S*)-indoline derivatives are excellent chiral auxiliaries in the asymmetric alkylation of aldehydes[9] and the asymmetric reduction of ketones.[10] Allylation of pyruvamide **20**, derived from (*S*)-indoline-2-carboxylate, with allyltributyl stannane in the presence of Lewis acids such as $TiCl_4$ and $SnCl_4$ afforded the tertiary homoallylic alcohol **21**, which readily underwent lactonization to form **22.** Depending on the allylation reagent and the Lewis acid, the diastereomeric excess of **22** varied from 80-94% (Scheme 3.6).




| M | Lewis acid (2eq.) | *dr* |
|---|---|---|
| $SiMe_3$ | $TiCl_4$ | 94:6 |
| | $SnCl_4$ | 90:10 |
| $SnBu_3$ | $TiCl_4$ | 90:10 |
| | $SnCl_4$ | 97:3 |

Scheme 3.6

To avoid lactonization, **23** (with a *t*-butyl dimethylsilyloxymethyl moiety in place of the ester in **20**) was prepared, and used in the allylation to obtain **24** with very high diastereoselectivity (Scheme 3.7). The product could be hydrolyzed to obtain (*R*)-2-hydroxy-2-methyl-4-pentenoic acid **3** (>99% *ee*). The proposed transition state suggests that conformer **25** is more favorable compared to **26** due to the repulsion between the methyl group and the phenyl ring. Since the *Re* face of the ketone in **24** is shielded by the *R* group in the auxiliary, addition from the less-hindered *Si*-face of the ketone provides the observed product (Figure 3.2).




| M | Lewis acid (2eq.) | Time (h) | Yield (%) | **24** *dr* |
|---|---|---|---|---|
| $SiMe_3$ | $TiCl_4$ | 3 | 82 | 99:1 |
| | $SnCl_4$ | 4 | 79 | 99:1 |
| $SnBu_3$ | $TiCl_4$ | 2 | 84 | 99:1 |
| | $SnCl_4$ | 2.5 | 81 | 99:1 |

Scheme 3.7

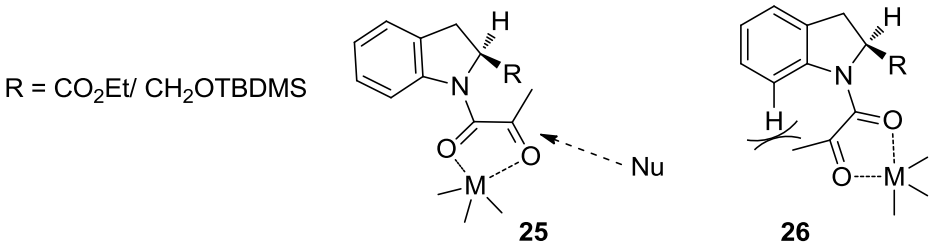
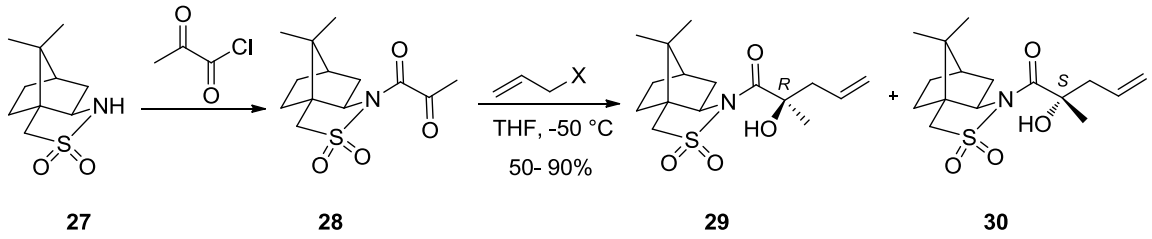



Figure 3.2 Proposed transition state for the allylation of proline-based pyruvamide.

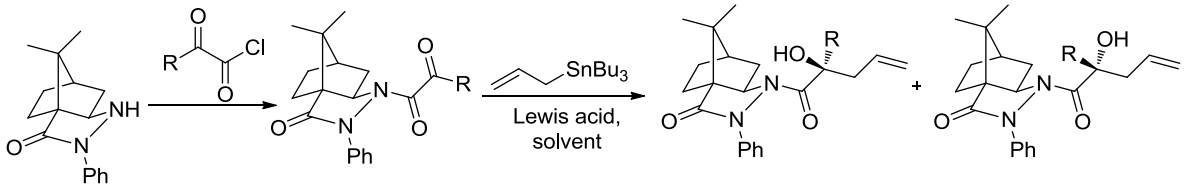
Diastereoselective allylation of α-ketoamides derived from Oppolzer's sultam[11] was reported by Jurczak.[12] *N*-Methyl-(2*R*)-bornane-10,2-sultam **28** was prepared from Oppolzer's sultam **27**, and was treated with a variety of allylation reagents. These included allyl bromide with zinc dust, and allyltrimethyl silane in the presence of Lewis acids (Scheme 3.8). The best results in terms of stereoselectivity (**29**:**30** = 93:7) was obtained with allylmagnesium chloride.




**27** **28** **29** **30**

Scheme 3.8

In 2004, diastereoselective allylation of camphorpyrazolidinone-derived α-ketoamides was reported by Chen and co-workers.[2a] Allylation of **32-34** (Scheme 3.9) was carried out with allyltributyl tin in the presence of a Lewis acid. The chiral auxiliary **31** was treated with the α-ketoacid chloride to obtain chiral α-ketoamides **32-34**. $Sn(OTf)_2$, $Zn(OTf)_2$, $Sc(OTf)_3$, and $Eu(OTf)_3$ were examined as Lewis acids for the allylation of **33** and the best results in terms of stereoselectivity were obtained with $Zn(OTf)_2$ (**37**:**38** = 9:1). For the substrate **34,** $Sn(OTf)_2$ provided **39** and **40** with moderate selectivity (**39**:**40** = 83:17).




**31**

**32** R = Ph
**33** R = Me,
**34** R = Et

R = Ph **35**
R = Me **37**
R = Et **39**

**36**
**38**
**40**

Scheme 3.9

In the initial studies, camphorpyrazolidinone phenylglyoxamide **32** was used as a model compound.[2a] In the absence of Lewis acid, treatment of **32** with allyltributyltin did not provide any of the desired product. The use of 1 eq. $Eu(OTf)_3$ as the Lewis acid afforded 50% conversion in $CH_3CN$ with moderate diastereoselectivity (**35**:**36** = 72:28) and the use of $Zn(OTf)_2$, instead of $Eu(OTf)_3$, afforded a 93% yield of **35** with good diastereoselectivity

(**35**:**36** = 94:6) as indicated by $^1$H NMR spectroscopy. The absolute configuration at the newly-generated stereocenter was assigned as *R* by X-ray crystallography. The scope of the method was examined with camphorpyrazolidinone pyruvamide **33** and ketobutyramide **34.** Pyruvamide **33** afforded the desired product with moderate diastereoselectivity in the presence of $Zn(OTf)_2$ (**37**:**38** = 9:1) and $Sn(OTf)_2$ (**37**:**38** = 79:21). However, the use $Eu(OTf)_3$ resulted in a reversal of selectivity (**37**:**38** = 26:74). The stereochemical outcome of the reaction was reasoned to be due to the different modes of coordination of the metal ion to the $\alpha$-ketoamide moiety (Figure 3.3).

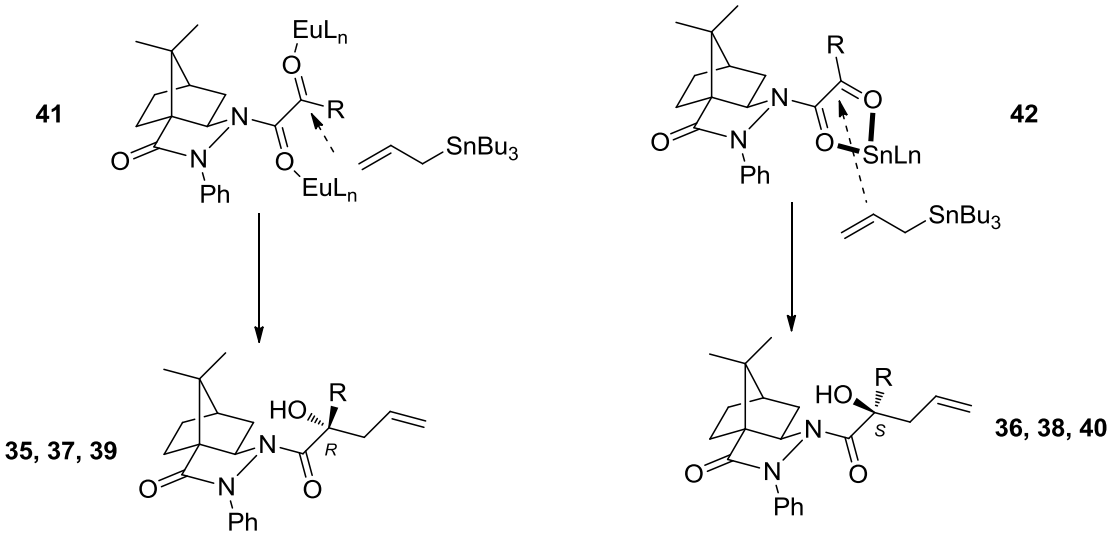



Figure 3.3 Transition state models resulting in the opposite stereochemistry.

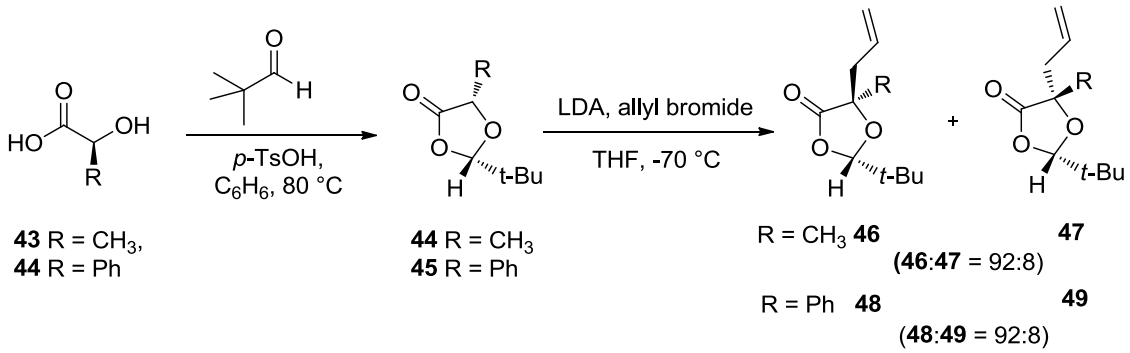
In the case of Lewis acids, such as $Zn(OTf)_2$ and $Sn(OTf)_2$ , dicoordination of the metal with the carbonyl oxygens favors the *s-cis* conformer **42** of the ketoamide, thereby promoting addition to the *Si* face of the ketone under steric control to afford the observed product (Figure 3.2). In the case of $Eu(OTf)_3$, mono-coordination of the metal to the carbonyl oxygen is favored and the *s-trans* conformer in **41** is predominant, resulting in a reversal of the selectivity, with the nucleophile approaching from the less-hindered *Re* face

of the ketone. However, this hypothesis contradicts the results obtained with camphorpyrazolidinone phenylglyoxamide **32**, since the treatment of **32** with $Eu(OTf)_3$ affords **36** as the major product.

### 3.1.1.3 Asymmetric allylation of 1,3-dioxolanones:

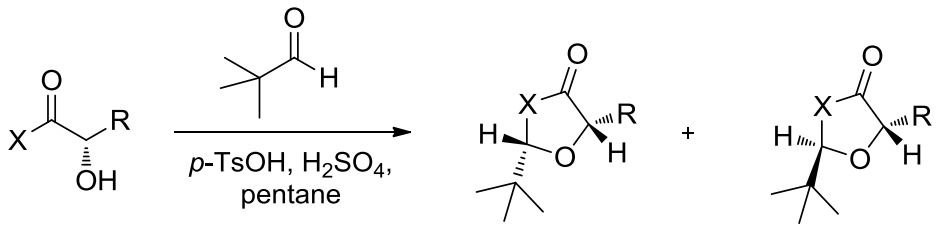
In the previous section, asymmetric allylation of chiral α-ketoesters, where nucleophilic addition of an allyl group occurs at the carbonyl carbon, was presented. The following section describes a complementary strategy in which the alkylation of glycolic acid-derived enolates with allylic electrophiles is examined.

Frater and co-workers,[2d] reported the allylation of 1,3-dioxolan-4-one derived from (–)-*S*-lactic acid (**43**) and (+)-*S*-mandelic acid (**44**) (Scheme 3.10). The 1,3-dioxolanones **44** and **45,** obtained from lactic acid and mandelic acid respectively, by condensation with pivalaldehyde, were treated with LDA and allyl bromide to provide **46** and **47** (**46**:**47** = 98:2) and **48** and **49** (**48**:**49** = 98:2). Hydrolysis of **46**-**49** to the corresponding hydroxy acids was not reported.




Scheme 3.10

In a similar study, Seebach reported the asymmetric allylation of 1,3-dioxolanones derived from (*S*)-lactic acid (**43**), (*S*)-α-isovaleric acid (**50**), (±)-thiolactic acid (**51**), and (±)-thiomalic acid (**52**).[13] In the methods developed by Frater and Seebach, the original stereocenter in the hydroxy acid is destroyed to form an enolate which is still chiral due to the acetal stereocenter. This stereocenter is believed to direct the electrophilic addition.[2d,13] The Seebach group successfully obtained the 1,3-dioxolanones **45** and **56**-**58** as a mixture of diastereomers which were separated by recrystallization from ether/pentane and the *cis* diastereomer was used further (Scheme 3.11).



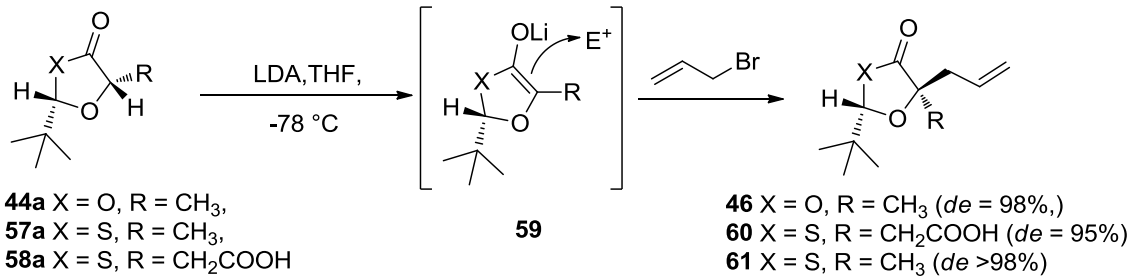

cis-**45a**,**56a- 58a** trans-**45b, 56b- 58b**

**43** X = OH, R = $CH_3$,
**53** X = OH, R = $CH(CH_3)_2$,
**54** X = SH, R = $CH_3$,
**55** X = SH, R = $CH_2COOH$,

**45** (93%, **a:b** = 4:1),
**56** (50%, **a:b** = 5:1),
**57** (92%, **a:b** = 2.5:1),
**58** (72%, **a:b** = 1:1)

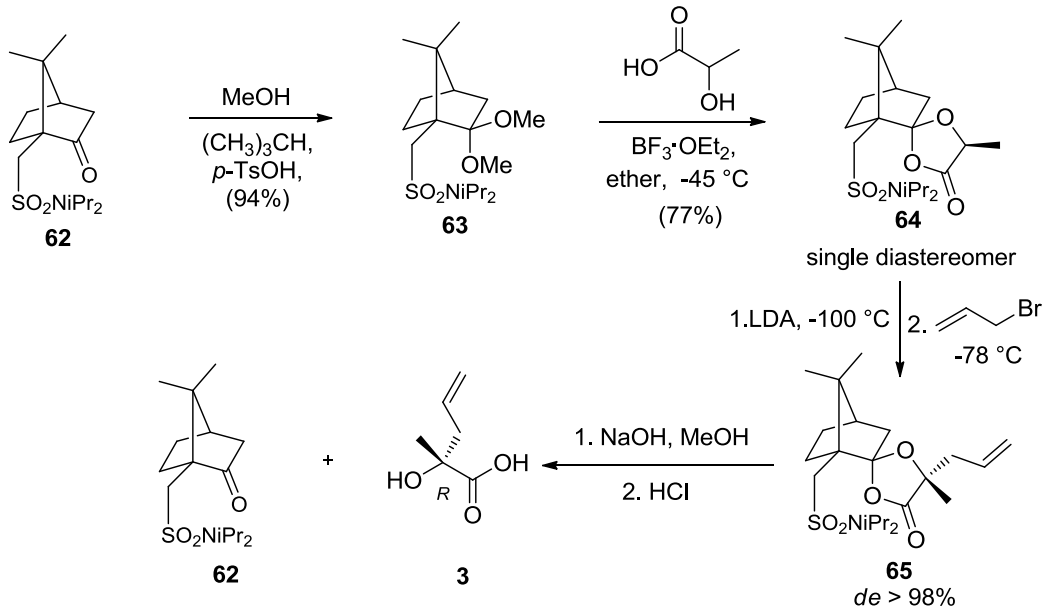
Scheme 3.11

Enolate generation from *cis* dioxolanones using LDA or LHMDS, followed by the addition of allyl bromide resulted in alkylation products with greater than 95% diastereomeric excess (Scheme 3.12). The authors propose that addition of the electrophile to the enolate proceeds from the *Re* face, that is, the face opposite to the *t*-butyl group. Notably, although **46**, **60** and **61** are potential precursors to the corresponding free α-hydroxy acids, upon subsequent hydrolysis, this conversion was not reported in this study.



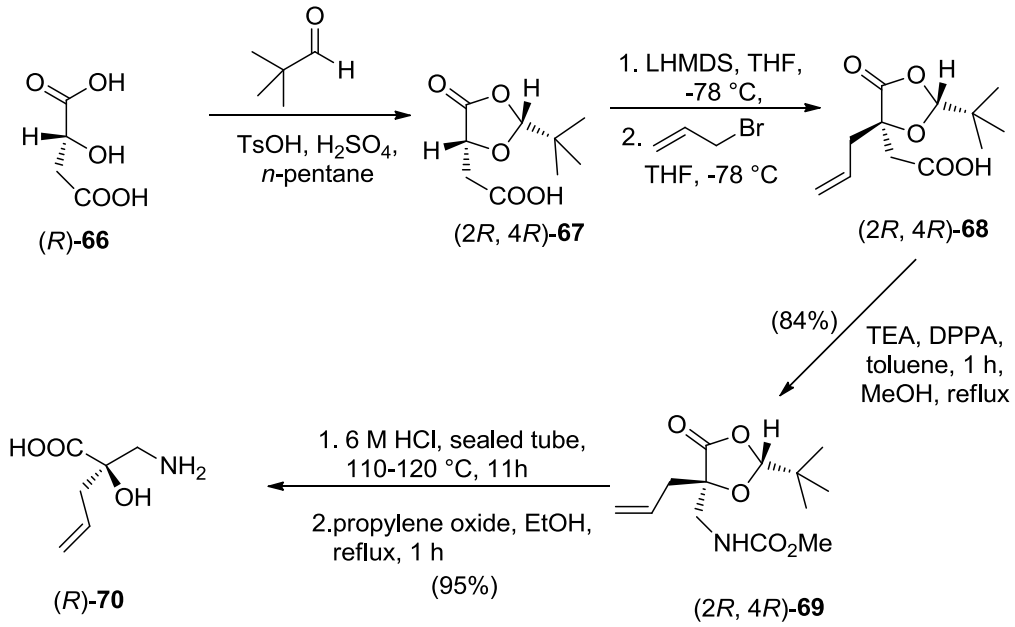

Scheme 3.12

Application of (1*S*)-(+)-*N*,*N*-diisopropyl-10-camphorsulfonamide as an auxiliary was demonstrated in the enantioselective synthesis of α-hydroxy acids by Uang and co-workers.[14] Condensation of **63** with excess *rac*-lactic acid in the presence of $BF_3$•$OEt_2$ resulted in the formation of 1,3-dioxolanone **64** as a single diastereomer (Scheme 3.13). The configuration of the new stereocenter was determined to be *S* using X-ray crystallography. Treatment of **64** with LDA at –100 °C followed by the addition of allyl bromide afforded **65** with excellent diastereoselectivity (98%). The alkylation of the enolate is believed to occur from the less hindered *Si* face. The configuration at the α-carbon was determined to be *R* by X-ray crystallography. The enantiomerically-enriched α,α-dialkyl,α-hydroxycarboxylic acid **3** was obtained by hydrolysis of **65** in methanol and aqueous 2 M NaOH, followed by acidification. The chiral auxiliary **62** was also recovered in high yield (92-96%).



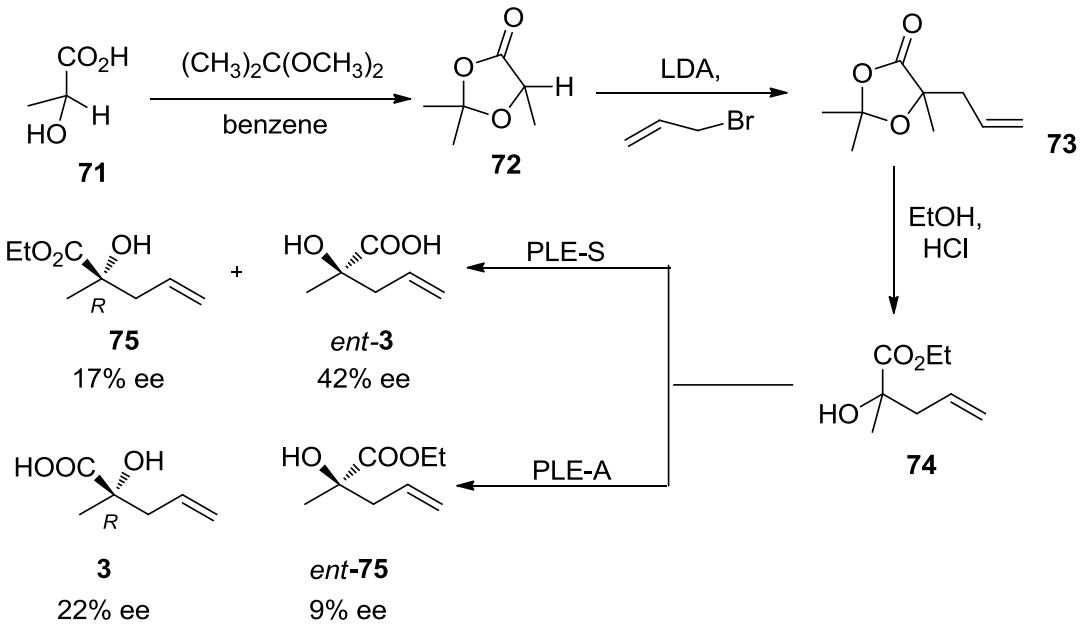

Scheme 3.13

In 2006, Xu and co-workers[2e] demonstrated the application of Frater's[2d] and Seebach's protocols[13,15] (Scheme 3.12) in the synthesis of α-alkyl isoserines by asymmetric allylation of D- and L-malic acids. Isoserine derivatives are β-amino acids which are part of biologically-active natural products such as bestatin,[16] amatatin,[16] norstatin,[17] and taxol.[18] A variety of methods are available for the synthesis of β-substituted isoserines in optically active form.[19] However, only a few studies have been conducted on the synthesis of chiral, α-alkyl isoserines.[20] In a study by Xu,[2e] the dioxolanone **67** was obtained from the condensation of D-malic acid (**66**) and pivalaldehyde. Treatment of **67** with LHMDS, followed by addition of allyl bromide in THF provided (2*R*,4*R*) **68** with >98% *de*. The acid **68** was further converted to the carbamate (2*R*,4*R*) **69.** Hydrolysis of **69** in hydrochloric acid afforded the hydrochloride salt of **70** which was converted into the free β-amino acid (98% *ee*) by reaction with propylene oxide (Scheme 3.14).




Scheme 3.14

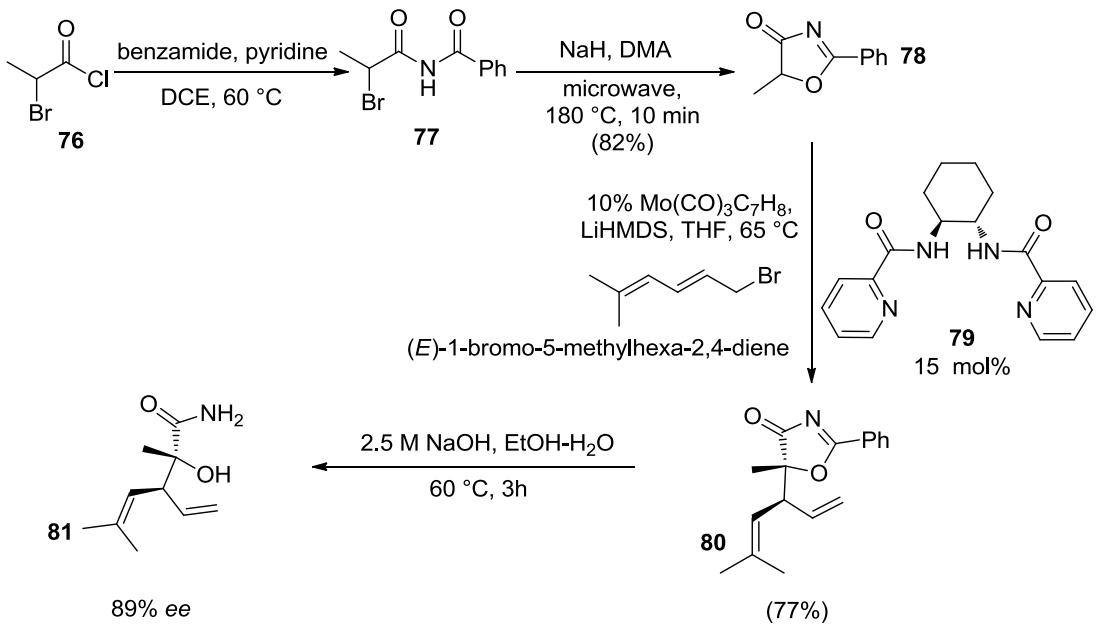
Kellogg[21] reported an enzyme-catalyzed hydrolysis to resolve the mixture of racemic α-substituted α-hydroxy ester **74** using pig lever esterase (PLE). The *α*-substituted α-hydroxy ester **74** was synthesized from the corresponding α-hydroxy acid. Reaction of racemic **71** with acetone provided the dioxolanone **72**. Alkylation of **72** (LDA, allyl bromide) afforded dioxalonone **73**, hydrolysis of which provided the racemic α-hydroxy ester **74**. The ester **74** was treated with PLE-S 3.1.1.1 and PLE-A in 0.05 M phosphate buffer at pH 8. Reactions were terminated when the conversion was 20-50% complete, and optically active acid product **3** and unreacted ester **75** were isolated in good yields (Scheme 3.15). In related studies,[21] moderate to good enantiomeric excess (49 to 86%) was observed for the enzymatic hydrolysis of aromatic esters, but not for aliphatic α-hydroxy,α-allylesters.




Scheme 3.15

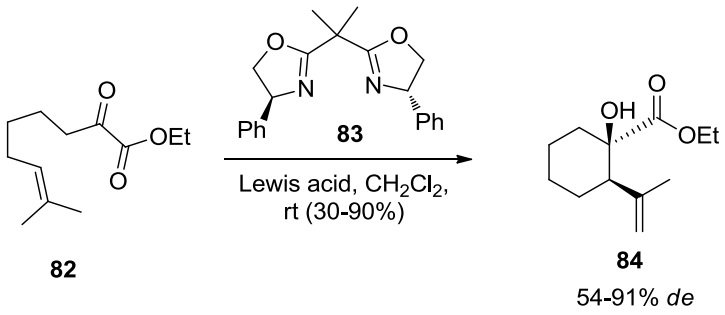
### 3.1.1.4 Asymmetric allylation of *α*-ketoesters using chiral allylation reagents:

Asymmetric allylation of α-ketoacid derivatives using chiral allylation reagents has also been investigated for the synthesis of homoallylic alcohols. For example, Trost and co-workers presented a nucleophilic allylation of oxalactim **78** for the synthesis of homoallylic amides (Scheme 3.16).[22] (*E*)-1-Bromo-5-methylhexa-2,4-diene was the only aliphatic substituent used along with a variety of aromatic substituents. The amide **81** was obtained in 89% *ee*.




Scheme 3.16

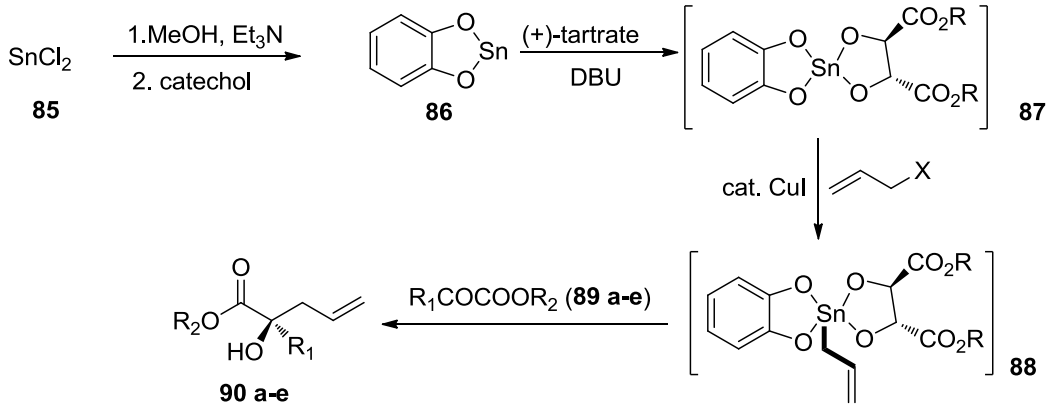
On the other hand, Yang reported an enantioselective intramolecular ene reaction of an unsaturated α-ketoacid.[23] (*R*,*R*)-Ph-pybox (**83**) was employed as a chiral ligand along with the range of Lewis acids to obtain **84** with moderate to very good diastereoselectivity (54-91% *de*, Scheme 3.17).




Scheme 3.17

However, there are very few examples reported for the enantioselective allylation of α-ketoacid derivatives using 1) a Lewis acid with chiral ligands[23] or 2) an allylating metal reagent combined with chiral ligands.[3a,22] A report by Mukaiyama[3a] employs a chiral

tin reagent for the enantioselective allylation of α-ketoesters (Scheme 3.18). A divalent tin(II) catecholate **86** was treated with allyl bromide in the presence of a dialkyl tartrate, DBU and a catalytic amount of CuI to obtain the highly reactive allyl tin reagent **88** *in situ* (Scheme 3.18). Reactions of **88** with a variety of pyruvate esters **89 a-e** proceeded with moderate to high enantioselectivity (60-95% *ee*, Table 3.1). However, allylation of benzyl-3-methyl butyrate proceeded with only 30% *ee* (Table 3.1, entry 5).

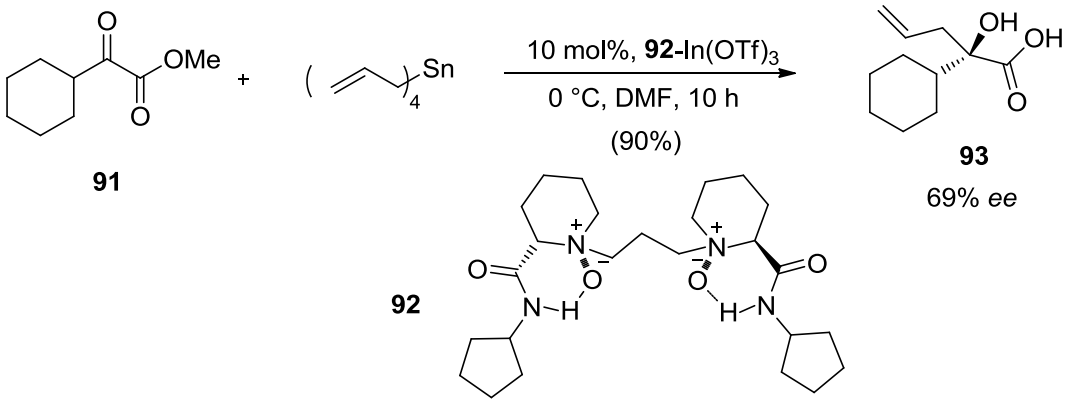



Scheme 3.18

Table 3.1 Survey of pyruvic esters for the asymmetric allylation with **88**

| Entry | **89** | $R_1$ | $R_2$ | **90** | Yield (%) | % *ee* |
|---|---|---|---|---|---|---|
| 1 | a | Me | Ph | a | 81 | 60 |
| 2 | b | Me | Bn | b | 87 | 95 |
| 3 | c | Me | 4-$ClC_6H_4$ | c | 72 | 95 |
| 4 | d | Me | 4-$OMeC_6H_4$ | d | 87 | 95 |
| 5 | e | *i*-Bu | Bn | e | 52 | 30 |

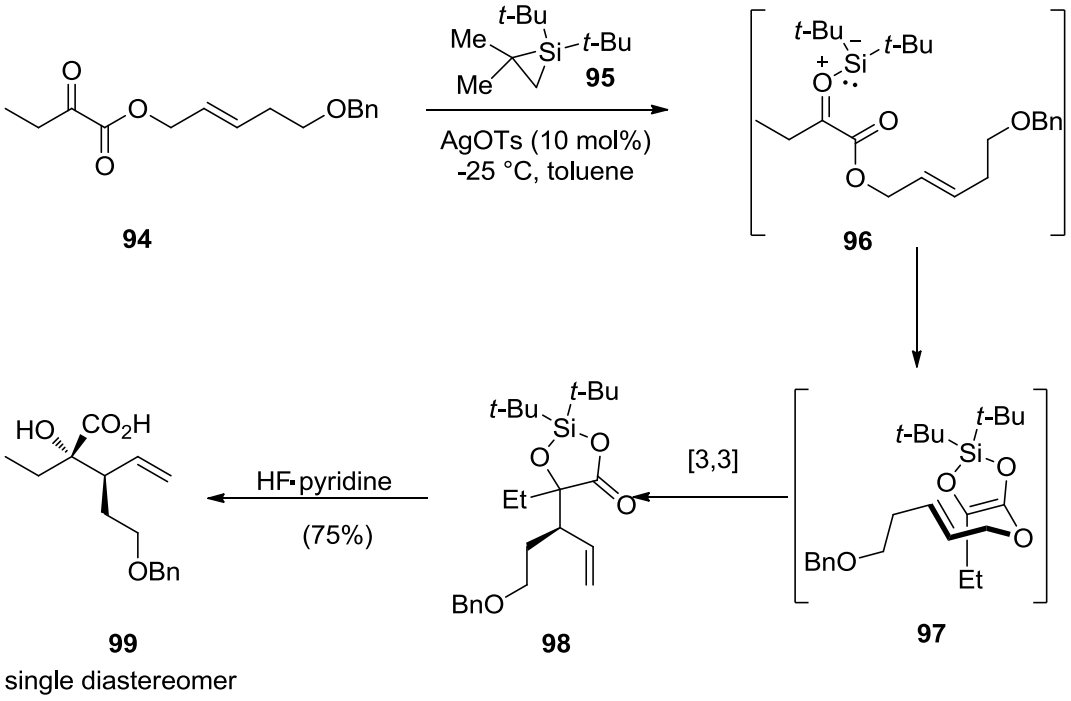
In 2007, Feng reported the application of a $C_2$-symmetric *N*,*N'*-dioxide-In(III) complex **92** in the allylation of α-ketoesters.[3b] Aromatic substrates afforded excellent enantioselectivities. However, the allylation of the aliphatic substrate **91** proceeded with only moderate selectivity (Scheme 3.19).




Scheme 3.19

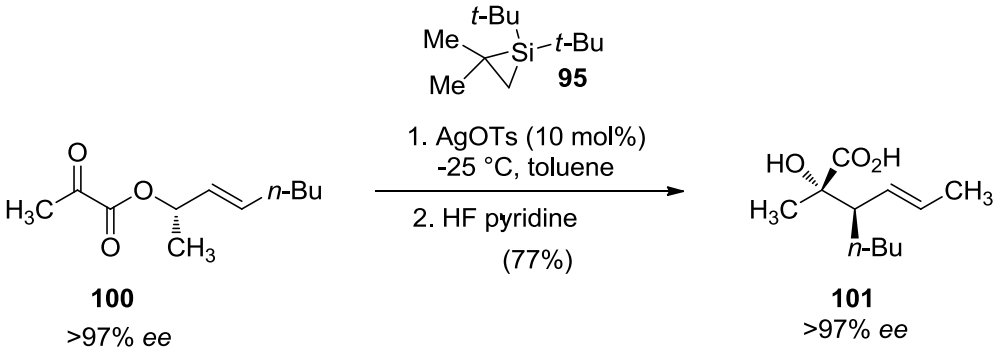
**3.1.1.5 Ireland-Claisen rearrangement of α-ketoesters in the synthesis of α-hydroxy acids:**

Woerpel and co-workers reported the synthesis of α-hydroxy acids by silylene transfer to allylic α-ketoesters.[24] This method has enabled a stereoselective synthesis of α-hydroxy acids possessing two contiguous stereocenters. The treatment of α-ketoester **94** with a silacyclopropane **95** and AgOTs in toluene provided silalactone **98**. Treatment of **98** with HF·pyridine provided the pure α-hydroxy acid **99** exclusively (> 97% dr). The reaction is believed to proceed through a silacarbonyl ylide **96**, which undergoes a 6π-electrocyclization to form a silylketene acetal **97** which then undergoes the Ireland-Claisen rearrangement to provide the silalactone **98** (Scheme 3.20).




Scheme 3.20

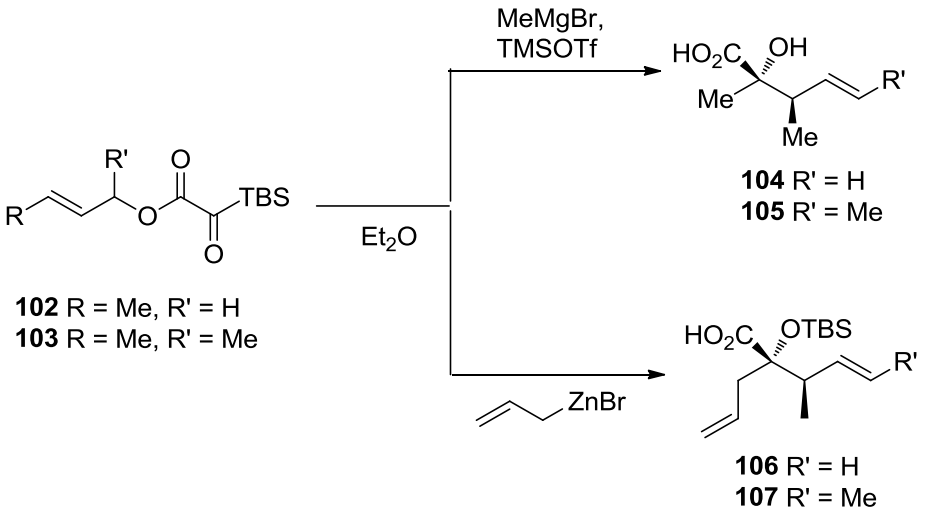
Enantiomerically enriched α-ketoesters showed excellent diastereoselectivity in this protocol. The treatment of **100** with **95** and AgOTs followed by addition of HF·pyridine resulted in the formation of α-hydroxy acid **101** as a single enantiomer (Scheme 3.21).




Scheme 3.21

Johnson and co-workers reported a synthesis of α-hydroxy acids via sequential Brook and Ireland-Claisen rearrangement of silylglyoxylates.[4] Addition of

methylmagnesium bromide to silyl glyoxylates **102** and **103** in the presence of TMSOTf generates the corresponding tetrahedral intermediate which undergoes a [1,2]-Brook rearrangement. The resulting enolate then undergoes an Ireland-Claisen rearrangement and products **104** and **105** are obtained as a mixture of diastereomers (Table 3.2). Similarly, treatment of **102** and **103** with an organozinc nucleophile, such as allylzinc bromide, afforded the α-hydroxy acid TBS ethers **106** and **107** respectively as a mixture of diastereomers (Scheme 3.22, Table 3.2). The use of an organozinc reagent seems to provide products that retain the TBS protection, but this aspect has not been explained in this study.

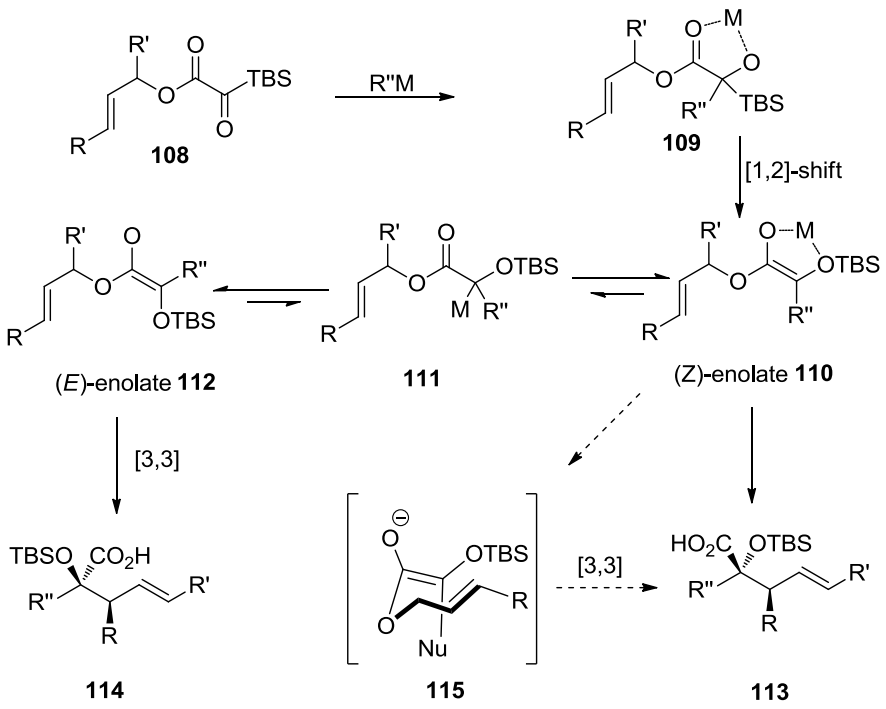



Scheme 3.22

Table 3.2 Reaction of Grignard and organozinc reagents with **102** and **103**

| Entry | Silyl glyoxylate | Nucleophile | Product | Yield (%) | *dr* |
|---|---|---|---|---|---|
| 1 | **102** | MeMgBr/TMSOTf | **104** | 64 | 5.7:1 |
| 2 | **103** | MeMgBr/TMSOTf | **105** | 65 | 4.9:1 |
| 3 | **102** | allylZnBr | **106** | 57 | 8:1 |
| 4 | **103** | allylZnBr | **107** | 67 | 6:1 |

The proposed mechanism of the reaction is described in Scheme 23. The addition of a nucleophile to the ketone in **108** generates the tetrahedral intermediate **109**. A 1,2 shift of the silyl group from the carbon to oxygen (Brook rearrangement) generates the *Z*-enolate **110** which then undergoes a [3,3] Sigmatropic rearrangement leading to the observed product **113**. The diastereoselectivity depends upon the equilibrium between the *Z*-enolate **110** and the *E*-enolate **112** via the intermediate **111**. The major product of the reaction is obtained from the *Z*-enolate.

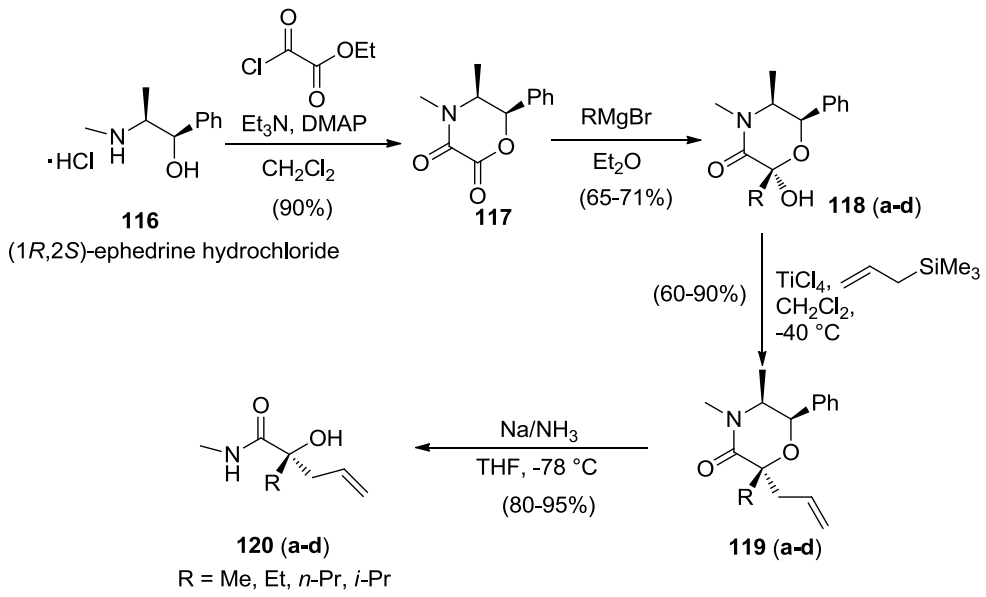



Scheme 3.23

## 3.2 Introduction to the present work

### 3.2.1 Asymmetric allylation of morpholinones derived from chiral amino alcohols.

The Pansare group has developed the synthesis of enantiomerically pure *α*-allyl, *α*-hydroxyamides **120** (Scheme 3.24) by highly diastereoselective allylation of ephedrine derived morpholinones **118**.[25]




Scheme 3.24

This methodology has been utilized as a key component in the synthesis of biologically active natural products and natural product motifs such as (–)-quinic acid,[26] medium sized oxacycles,[27] (*R*)-homocitricacid lactone[28] and (+)-8-*O*-methylaphanorphine.[29] These syntheses use the α-hydroxy amide **120 a** as a chiral starting material.[26-28,30]

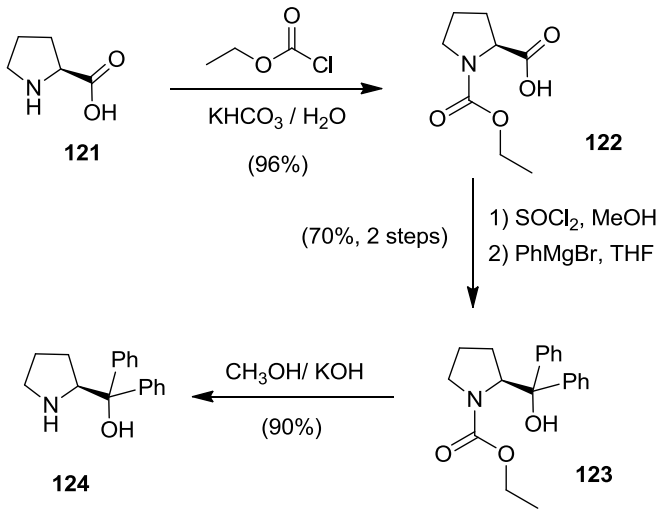
This ephedrine-based method provides two major advantages 1) excellent diastereoselectivity in the allylation step is obtained and 2) α-hydroxy amides were obtained in good overall yield. The drawback of this method is that the removal of the ephedrine portion is achieved by reductive cleavage, which results in the destruction of ephedrine. Also, ephedrine has been declared a controlled substance and it is no longer commercially available. Therefore, efforts were made towards identifying other amino alcohols which can replace ephedrine as the chiral starting material.

The objectives of this study were: 1) to identify and utilize a chiral amino alcohol for the synthesis of morpholinediones which can be used as a replacement for the ephedrine based morpholinedione and 2) to identify an amino alcohol which can be recovered at the end of the synthesis, thus functioning as a chiral auxiliary rather than a chiral starting material.

### 3.2.2 Previous investigations of chiral amino alcohols within the Pansare group

#### 3.2.2.1 Studies with diphenylprolinol as a potentially recoverable amino alcohol:

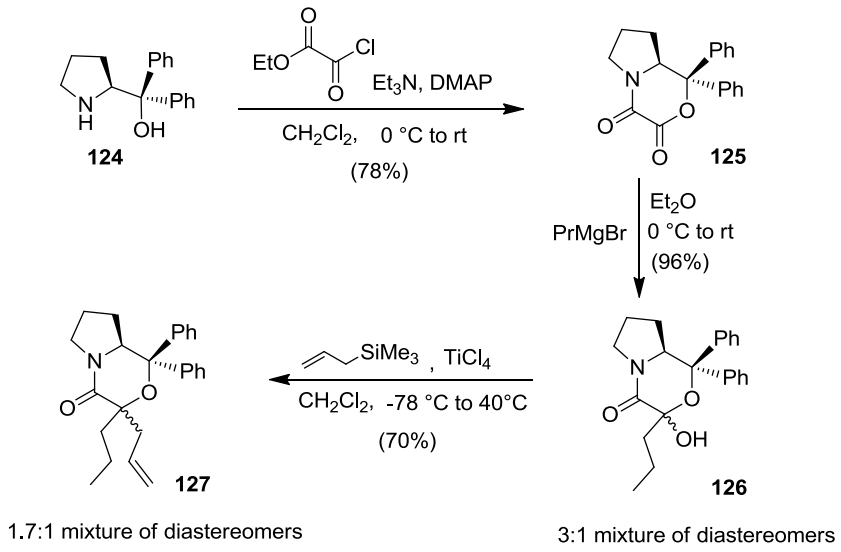
Diphenylprolinol was prepared from (*S*)-proline **121** following the previously reported procedure by Kanth and Periasamy.[31] Protection of the amine in **121** as the ethyl carbamate gave **122** (Scheme 3.25). Conversion of the carboxylic acid to a methyl ester followed by treatment with phenylmagnesium bromide provided the alcohol **123**. Hydrolysis of the carbamate provided the amino alcohol **124**.




Scheme 3.25

Treatment of amino alcohol **124** with ethyl oxalyl chloride gave the morpholine dione **125**. Treatment of dione **125** with propylmagnesium bromide furnished hemiacetal

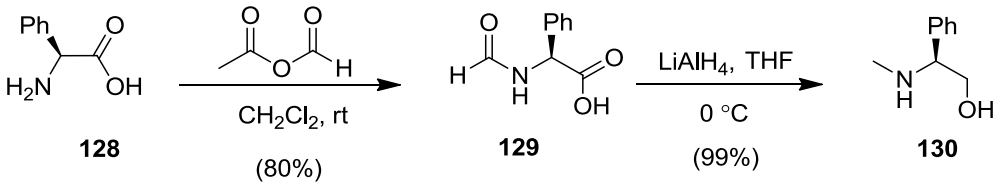
**126** as a mixture 3:1 mixture of diastereomers. Allylation of **126** using $TiCl_4$/allyltrimethylsilane at –40 °C furnished **127** as 1.7:1 mixture of diastereomers (Scheme 3.26). The poor diastereoselectivity for the allylation reaction indicated that diphenylprolinol was not a good auxiliary for the morpholinedione-based synthesis of α-hydroxy acids. Consequently, cleavage of the benzylic C-O bond in **127**, in order to recover **124**, was not examined.




Scheme 3.26

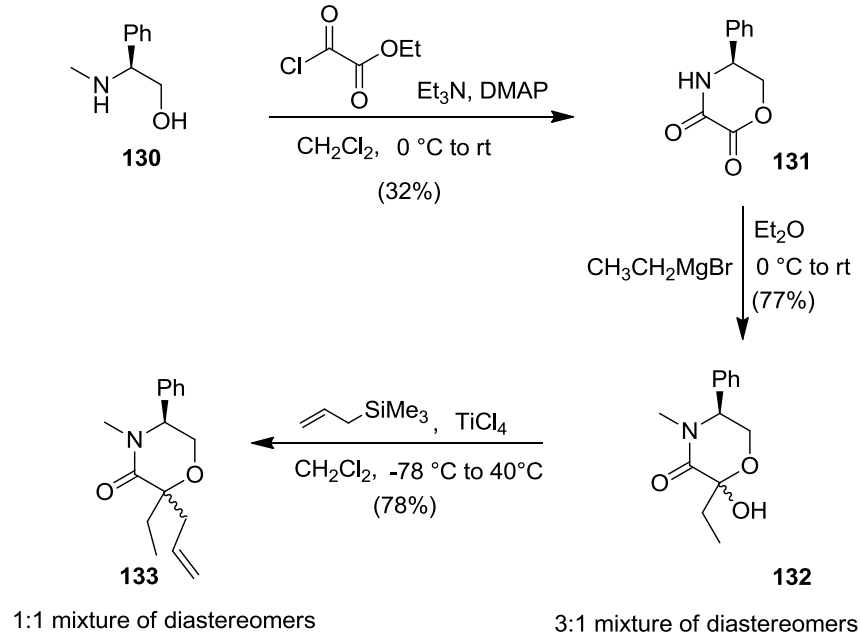
### 3.2.2.2 Studies with non-recoverable amino alcohols:

The amino alcohol **130** was prepared from (*S*)-phenylglycine **128** following a previously reported procedure (Scheme 3.27).[32] Thus, *N*-formylation of (*S*)-phenylalanine (**128**) provided **129**. Reduction of the amide as well as carboxylic acid with $LiAlH_4$ provided the required amino alcohol **130** in excellent yield (99%).[33]



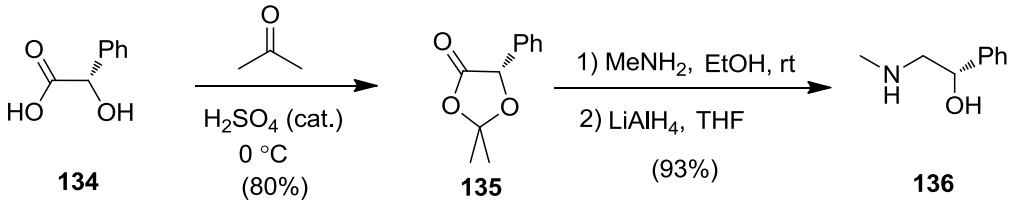

Scheme 3.27

Amino alcohol **130** was treated with ethyl oxalyl chloride to obtain dione **131**. Treatment of **131** with ethylmagnesium bromide provided the hemiacetal **132** as a 3:1 mixture of diastereomers. The allylation of **132** with $TiCl_4$ and allyltrimethylsilane provided **133** as 1:1 mixture of diastereomers (Scheme 3.28). This result suggested that the stereocenter adjacent to the oxygen in the ephedrine-derived morpholine system may be important for good stereoselectivity in the allylation step and the lack of 1,3 stereocontrol in **132** could be responsible for the unselective allylation.[33]



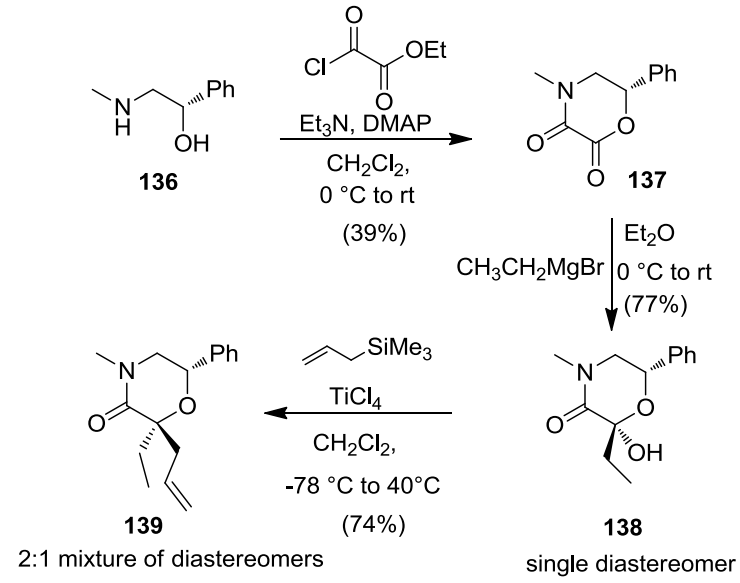

Scheme 3.28

With this reasoning in mind, the amino alcohol **136** was prepared from (*S*)-mandelic acid (**134**) according to the procedure reported by Davis and co-workers.[34] Reaction of (*S*)-mandelic acid (**134**) with acetone generated the derivative **135** (Scheme 3.29). Treatment of **135** with methylamine in ethanol gave *N*-methylmandelamide, which was reduced with $LiAlH_4$ to obtain the amino alcohol **136**.[33]




Scheme 3.29

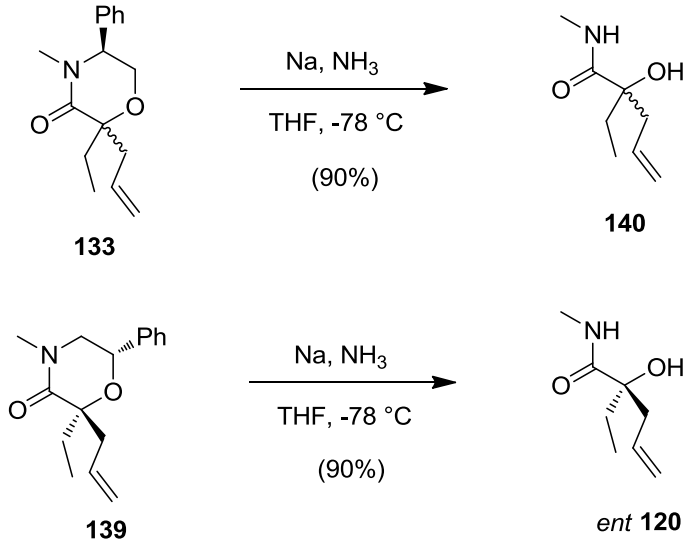
Amino alcohol **136** was converted to the dione **137** by treatment with ethyl oxalyl chloride. Treatment of dione **137** with ethylmagnesium bromide provided the hemiacetal **138** as a 5:1 mixture of diastereomers (Scheme 3.30). Allylation of **138** using $TiCl_4$ and allyltrimethylsilane provided **139** as a 2:1 mixture of diastereomers.[33]




Scheme 3.30

The higher diastereoselectivity in the allylation of **138** (2:1 *dr*) compared to **132** (1:1 *dr*) suggested that 1,3-stereocontrol does play a role in the allylation of amino alcohol-derived morpholinones. However, since the stereoselectivity is still far less than that seen for the ephedrine-derived system, 1,3-stereocontrol is obviously not the only factor controlling the diastereoselectivity. Clearly, the 2,3-disubstituted morpholinone motif obtained by using ephedrine is necessary for high diastereoselectivity in the allylation step.

The dialkyl morpholinones **133** and **139** were subjected to dissolving metal reduction to obtain α-hydroxy amides **140** and *ent*-**120** respectively (Scheme 3.31). The configuration of the newly generated stereocenter in dialkylmorpholinone **139** was assigned as *S* based on the specific rotation of the amide *ent*-**120** ($[\alpha]^{23}_D$ = –6.5 (*c* 1.7, $H_2O$)),[33] which indicated an excess of the '*S*' enantiomer ($[\alpha]^{23}_D$ = +16 (*c* 1.7, $H_2O$) for (*R*)-**120**).[25]

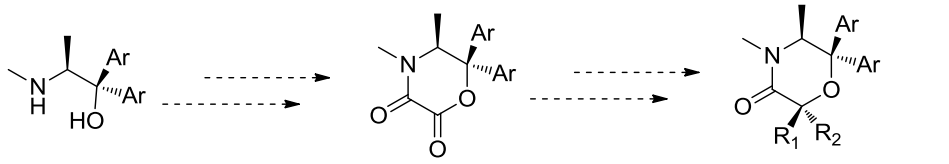



Scheme 3.31

## 3.3 Present work

### 3.3.1 Investigation of potentially recoverable amino alcohol substitutes for 1*R*,2*S*-ephedrine:

The studies described above indicated that a 2,3-disubstituted morpholinone was required and hence we decided to examine the diaryl alaninols **141** and **142** as substitutes for ephedrine. At the outset, we assumed that the synthesis of the dialkylmorpholinones **145** and **146** could be achieved from diones **143** and **144** respectively, hopefully with stereoselectivities similar to those obtained from the ephedrine derived morpholinedione **117**. The morpholinediones in turn, could be obtained from the respective amino alcohols **141** and **142** (Scheme 3.32) using procedures similar to those employed for the ephedrine based morpholinedione.



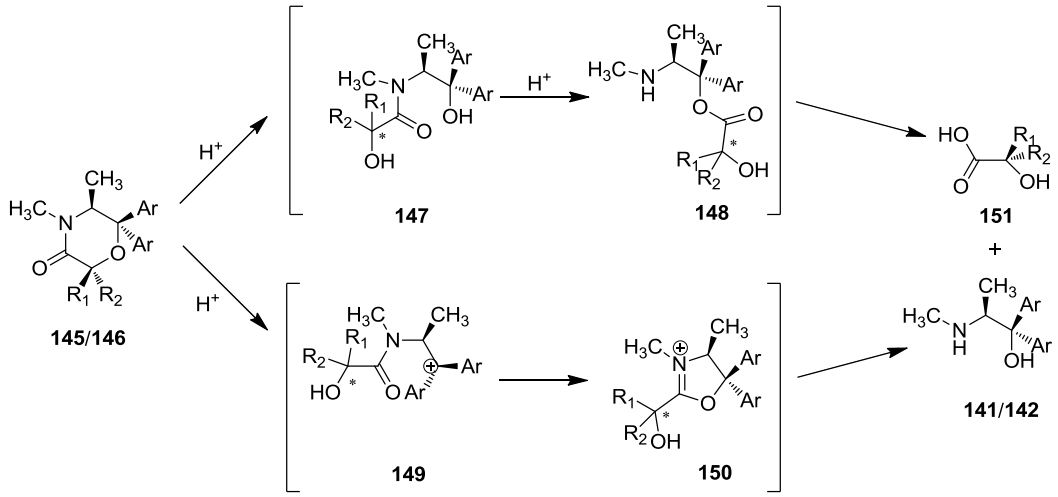

**141** R = Ph
**142** R = 4OMeC$_6$H$_4$

**143** R = Ph
**144** R = 4OMeC$_6$H$_4$

**145** R = Ph
**146** R = 4OMeC$_6$H$_4$

Scheme 3.32

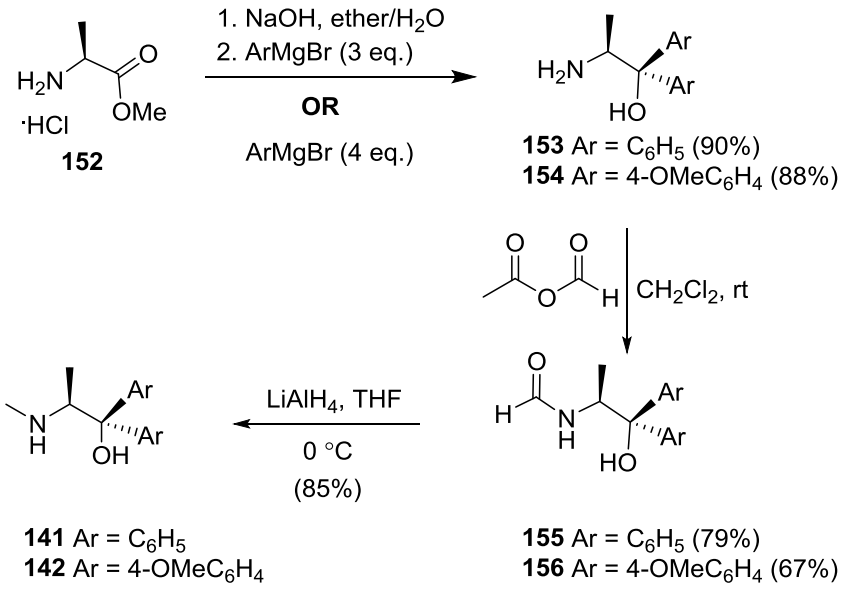
Since diphenylmethyl ethers are known to be cleaved under acidic conditions,[35] it seemed reasonable that, in the presence of an aqueous acid, cleavage of the benzylic C-O bond in **145** and **146** would occur. This could generate either **147** or **149** (Scheme 3.33), which would ultimately provide the required α-hydroxy acid **150** through the intermediates **148** or **150**. The amino alcohols **141** or **142** would therefore be recovered.




Scheme 3.33

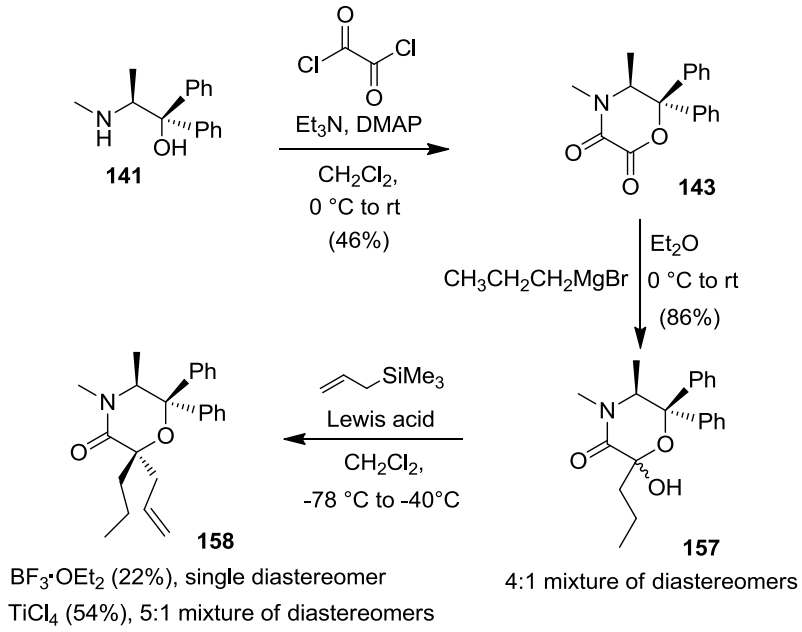
### 3.3.2 Investigation of potentially recoverable chiral amino alcohols derived from (*S*)-alanine:

The diarylalaninols **141** and **142** were prepared from (*S*)-alanine methyl ester hydrochloride (**152**, Scheme 3.34). Reaction of **152** directly with four equivalents of the phenylmagnesium bromide provided the corresponding tertiary alcohol **153**. Alternatively, conversion of **152** to the free base and subsequent reaction with three equivalents of *p*-anisylmagnesium bromide provided **154**. *N*-Formylation of **153** and **154** using acetic formic anyhydride followed by the reduction of the formyl group using $LiAlH_4$ furnished the required amino alcohols **141** and **142** respectively.



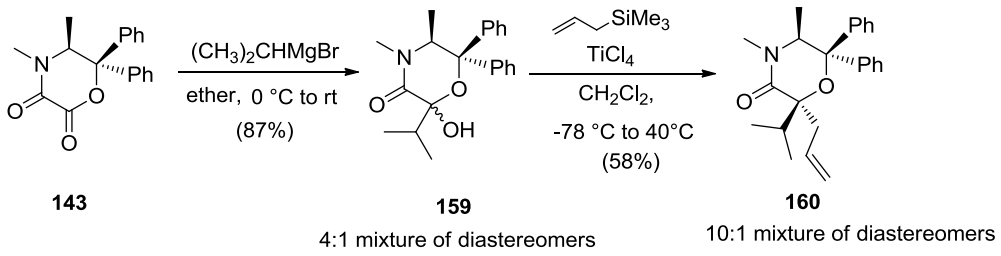

Scheme 3.34

Treatment of **141** with oxalyl chloride provided the dione **143** (46%, Scheme 3.35). Treatment of **143** with propylmagnesium bromide gave **157** as a 4:1 mixture of diastereomers (86%). The hemiacetal **157** was allylated using $BF_3{\cdot}OEt_2$ resulting in the formation of **158** as a single diastereomer in low yield (22%, Scheme 3.35).[33] Allylation of **157** using $TiCl_4$ as the Lewis acid (–78 °C to –40 °C) provided **158** in higher yield (54%) but lower diastereoselectivity (5:1 *dr*).



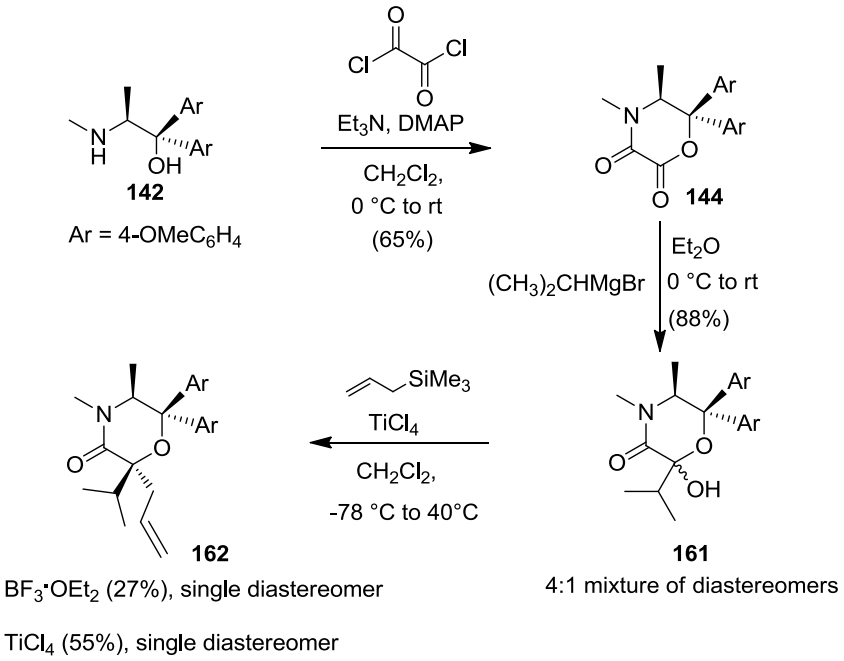

Scheme 3.35

Interestingly, better selectivity in the allylation was observed with the replacement of the propyl group by an isopropyl group. Treatment of **143** with isopropylmagnesium bromide provided the hemiacetal **159** as a 4:1 mixture of diastereomers (87%, Scheme 3.36). Allylation of **159** using $TiCl_4$ and allyltrimethyl silane (–78 °C to –40 °C) provided the dialkyl morpholinone **160** as a 9:1 mixture of diastereomers (58%). Notably, this dependence of the stereoselectivity of allylation on the steric requirements of the alkyl group in the hemiacetal is not observed in the corresponding ephedrine-derived hemiacetals.[25]



Scheme 3.36

In a related set of experiments, the treatment of **142** with oxalyl chloride provided the dione **144** (58%). Treatment of **144** with isopropylmagnesium bromide gave the hemiacetal **161** as a 4:1 mixture of the diastereomers. Allylation of **161** using $BF_3{\cdot}OEt_2$ and allyltrimethylsilane furnished the dialkylmorpholinone **162** (27%, Scheme 3.37) as a single diastereomer. Changing the Lewis acid to $TiCl_4$ furnished **162** in higher yield and diastereoselectivity (55%, single diastereomer).



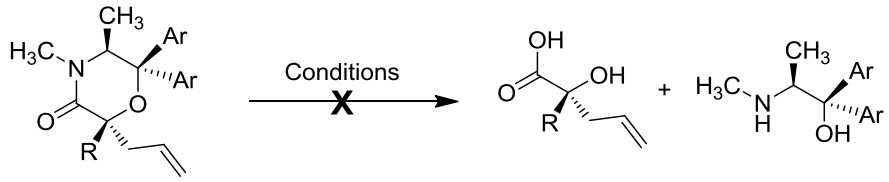

Scheme 3.37

Notably, despite the structural similarity between **161** and **159**, the diastereoselectivity of their allylation reactions is very different (10:1 for **160**, and a single diastereomer for **162**). The reasons for this difference are not known at present.

Since one of the objectives of this study was recovery of the starting amino alcohols **141** and **142**, conversion of the morpholinones **160** and **162** to the α-hydroxy acid **150** and

**141** or **142** was attempted under a variety of conditions that were expected to facilitate cleavage of the benzylic C-O bond.[36] Unfortunately, treatment of morpholinone **160** or **162** with protic acids resulted either in no reaction, even after prolonged exposure, or complete decomposition depending on the acid that was employed. These results are summarized in Table 3.3-3.5.

Table 3.3 Attempted hydrolysis of the morpholinones **160** and **162** under acidic conditions.




**160/162** **150** **141/142**

| No | Reagents | Temperature (°C) | Time (h) | Result |
|---|---|---|---|---|
| 1 | HCl (2 M), dioxane | 100 | 10 | **160**/**162** |
| 2 | $H_2SO_4$ (cat.), $H_2O$ | 100 | 24 | **160**/**162** |
| 3 | $H_2SO_4$ (cat), $HO(CH_2)_2OH$ | 160 | 96 | **160**/**162** |
| 4 | $H_2SO_4$ (3 M), dioxane | rt | 4 | Decomposition |
| 5 | HBr (30%wt in AcOH) | rt | 18 | Decomposition |
| 6 | HBr (48%), dioxane | rt | 20 | Decomposition |
| 7 | $BF_3{\cdot}(OEt)_2$, $CH_2Cl_2$ | rt | 72 | Decomposition |
| 8 | $CF_3COOH$, $CH_2Cl_2$ | rt | 48 | **160**/**162** |
| 9 | $CF_3COOH$, $CH_2Cl_2$ | 55 | 2 | **160**/**162** |
| 10 | CuBr, dioxane:$H_2O$ (1:2) | 60 | 120 | **160**/**162** |
| 11 | HCl (0.1 M)[a] | 150 | 35 | **160**/**162** |
| 12 | HCl (2.5 M), dioxane[a] | 150 | 5 | **160**/**162** |
| 13 | HCl (2.5 M), dioxane[a] | 175 | 10 | decomposition |
| 14 | $H_2SO_4$ (1.0 M), dioxane[a] | 150 | 10 | decomposition |

*a*: reactions carried out under microwave heating

The feasibility of either the reduction or the hydrolysis of the amide linkage in the morpholinones **160** and **162** was next investigated. It was reasoned that the problems encountered in the acidic hydrolysis of **160** and **162** could be overcome by prior ring opening by basic hydrolysis of the amide to provide acyclic diaryl ethers which may be easier to cleave under acidic conditions. However, these attempts at ring-opening were also unsuccesful (entries 1-3, Table 3.4). As an alternative partial reduction of the amide to a hemiaminal was also evaluated. However, treatment of the morpholinones **160** or **162** with $LiAlH(OEt)_3$ at room temperature resulted in decomposition of the starting material. The treatment of morpholinones with $LiAlH_4$ at ambient temperature on the other hand resulted in the recovery of the morpholinones. The outcome of this reaction did not change after prolonged heating, and studies with other reducing reagents also did not show positive results. The results of these studies are summarized in Table 3.4.

Table 3.4 Attempted basic hydrolysis and reduction of the amide in the morpholinone **160** and **162**.

| No | Reagent | Temperature (°C) | Time (h) | Result |
|---|---|---|---|---|
| 1 | *t*-BuOK, $H_2O$, ether | 100 | 12 | **160**/**162** |
| 2 | KOH, ethanol | 85 | 8 | **160**/**162** |
| 3 | KOH, $OH(CH_2)_2OH$ | 200 | 8 | **160**/**162** |
| 4 | $LiAlH(OEt)_3$, ether | rt | 12 | Decomposition |
| 5 | $LiAlH_4$, THF | rt | 24 | **160**/**162** |
| 6 | $LiAlH_4$, THF | 80 | 30 | Decomposition |
| 7 | $Tf_2O$, pyridine, Red Al, THF | rt | 20 | **160**/**162** |
| 8 | $LiH_2NBH_3$, THF | rt | 18 | **160**/**162** |

Basic hydolysis of the amide in **161** and **162** under microwave heating was examined, but these studies were also unsuccessful (Table 3.5).

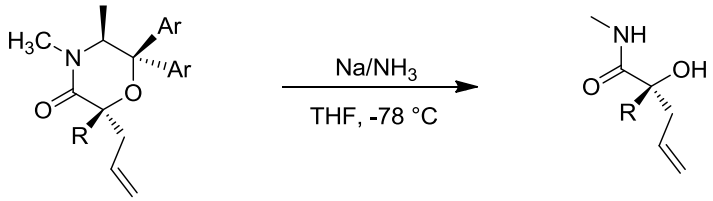
Table 3.5 Attempted basic hydrolysis of the morpholinones **161** and **162** under microwave heating.

| No | Reagent | Temperature (°C) | Time (min) | result |
|---|---|---|---|---|
| 1 | KOH (2.0 M), ethanol | 130 | 10 | **160**/**162** |
| 2 | KOH (2.0 M), ethanol | 150 | 15 | **160**/**162** |
| 3 | KOH (2.0 M), ethanol | 175 | 15 | **160**/**162** |
| 4 | KOH (2.0 M), ethanol | 200 | 15 | decomposition |
| 5 | Powdered KOH, $HO(CH_2)_2OH$ | 200 | 20 | **160**/**162** |

These results suggest that the morpholinone ring in **160** and **162** is very stable and ring-opening under conventional C-O and C-N bond cleavage conditions is challenging. Notably, the ethereal oxygen in these rings is flanked by quaternary carbons which may contribute to the stability of the C-O bonds under acidic conditions. Similarly, the carbonyl group in the amide may also be unreactive toward nucleophilic addition reactions which would involve the approach of nucleophiles over the morpholine ring. This approach may be disfavoured by the quaternary centres.

Fortunately, the morpholinones **158**, **160** and **162** were readily cleaved under dissolving metal reduction conditions ($Na/NH_3$, THF, −78 °C) to provide the corresponding α-hydroxy amides **120c** and **120d** (Scheme 3.38). The configuration of the newly formed stereocenter in **158**, **160** and **162** was designated as *R* on the basis of the specific rotation of the amides (amide **120c:** $[\alpha]_D^{25}$ = +21.7 (*c* 1.9, $CHCl_3$); lit.[25] $[\alpha]_D^{25}$ = +30 (*c* 1.9, $CHCl_3$)

for the *R* enantiomer. Amide **120d** obtained from **160**: $[\alpha]_D^{25}$ = +7.2 (*c* 1.6, $CHCl_3$), and amide **120d** obtained from **162**: $[\alpha]_D^{25}$ = +9.6 (*c* 1.6, $CHCl_3$); lit.[25] $[\alpha]_D^{25}$ = +9.0 (*c* 1.6, $CHCl_3$) for the *R* enantiomer).




**158** Ar = Ph, R = $CH_2CH_2CH_3$
**160** Ar = Ph, R = $(CH_3)_2CH$
**162** Ar = 4-$OMeC_6H_4$, R = $(CH_3)_2CH$

**120c** R = $CH_2CH_2CH_3$, (88%)
**120d** R = $(CH_3)_2CH_2$, (78%)
**120d** (90%)

Scheme 3.38

### 3.3.3 Conclusions

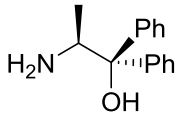
It was determined that the 2,3-disubstituted morpholine motif is essential for good stereoselectivity in the allylation reactions at *C*-6 of these morpholinones. (*S*)-Alanine-derived diarylmorpholinediones **143** and **144** have provided an alternative to the corresponding, ephedrine-derived morpholinedione. Although the attempts to recover the chiral amino alcohol were unsuccessful, the amino alcohols **141** and **142** can certainly be used as substitutes for ephedrine as a chiral starting material in the synthesis of α-hydroxy acid derivatives. However, the reason morpholinone **161** shows better selctivity compared to the morpholinone **159** is still unclear. Studies aimed at understanding the origin of stereocontrol and on the recovery of the amino alcohol at the end of the α-hydroxy acid synthesis are ongoing in the Pansare group.

### 3.4 Experimental section

**General experimental methods:**

All commercially available reagent were used without purification. All reactions requiring anhydrous conditions were performed under an atmosphere of dry nitrogen using oven dried glassware. Dichloromethane and tetrahydrofuran were distilled from $CaH_2$ and sodium/benzophenone respectively. Commercial precoated silica gel plates were used for TLC. Silica gel for column chromatography was 230-400 mesh. All melting points are uncorrected. Optical rotations were measured at the sodium D line on a digital polarimeter at ambient temperature.

**(*S*)-2-Amino-1,1-diphenylpropan-1-ol** (**153**):




A dry, 250 mL, three-necked, round bottom flask, equipped with a reflux condenser, magnetic stirring bar, and nitrogen gas inlet, was charged with magnesium turnings (3.26 g, 0.13 mol). The flask was fitted with a rubber septum and charged sequentially via syringe with THF (40 mL) and bromobenzene (14.2 mL, 0.13 mol) and a crystal of iodine was added. The rubber septum was immediately replaced with a stopper and stirring was initiated. Within 5 min, an exothermic reaction initiated and the mixture began to reflux spontaneously. The mixture was then stirred for an additional 2 h (until all of the magnesium reacted) without external heating or cooling. The resulting solution was added dropwise to an ice-cooled suspension of *s*-alanine methyl ester (**152**) (3.00 g, 38.0 mmol) in THF (20 mL) over a period of 30 min. The mixture was stirred at ambient

temperature for 16 h. Saturated, aqueous ammonium chloride solution (60 mL) was then added, and the mixture was stirred vigorously until the white precipitate disappeared. The resulting solution was extracted with ethyl acetate (3×100 mL). The combined ethyl acetate layers were dried and concentrated under reduced pressure to afford the crude product as a yellow gum. This was dissolved in 1M aqueous HCl solution (20 mL) and the resulting solution was extracted with ethyl acetate (2×50 mL). The aqueous layer was cooled (<5 $^{o}$C), basified with sodium hydroxide pellets (pH = 9) and then extracted with ethyl acetate (3×50 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated under reduced pressure to provide **153** (4.4 g, 90%) as a yellow foam.

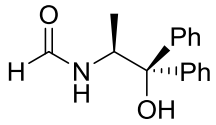
**IR** (neat): 3388, 3064, 2980, 1651, 1445, 1174, 966 $cm^{-1}$.

**$^{1}$H NMR** (300 MHz, $CDCl_3$): δ 7.64-7.63 (m, 1H, Ar*H*), 7.62-7.58 (m, 1H, Ar*H*), 7.49-7.44 (m, 2H, Ar*H*), 7.36-7.23 (m, 4H, Ar*H*), 7.22- 7.12 (m, 2H, Ar*H*), 4.17- 4.11 (q, 1H, *J* = 6.3, C*H*$CH_3$), 0.94 (d, 2H, *J* = 6.3, C*H*$_3$CH).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 146.9 (Ar*C*$_{ipso}$), 144.8 (Ar*C*$_{ipso}$), 128.4 (Ar*C*), 128.0 (Ar*C*), 126.7 (Ar*C*), 126.4 (Ar*C*), 125.9 (Ar*C*), 125.5 (Ar*C*), 78.5 (*C*-OH), 51.9 (*C*H$CH_3$), 17.2 (*C*$H_3$).

**MS** (APCI Pos): *m*/*z* 228.1 $(M+H)^+$, 210.1 $(M+H-H_2O)^+$; HRMS (CI Pos.,TOF): *m*/*z* 228.1400 (228.1388 calcd. for $C_{15}H_{19}NO$ $(M+H)^+$.

**(*S*)-*N*-(1-Hydroxy-1,1-diphenylpropan-2-yl) formamide** (**155**)**:**




To an ice-cooled solution of the amino alcohol **153** (1.8 g, 7.9 mmol) in anhydrous $CH_2Cl_2$ (10 mL), was added aceticformic anhydride (0.76 mL, 8.63 mmol). The resulting clear, brown solution was stirred at ambient temperature for 12 h. The reaction mixture was then diluted with $CH_2Cl_2$ (10 mL) and the solution was washed with aqueous HCl (0.1 M, 10 mL). The organic layer was dried ($Na_2SO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes 3/2) to provide the formamide **155** (1.60 g, 79%) as a white foam.

**IR** (neat): 3362, 3313, 1647, 1500, 1447, 1379 $cm^{-1}$.

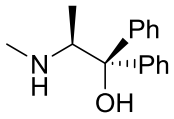
**$^1$H NMR** (300 MHz, $CDCl_3$): **Major rotamer** δ 7.98-7.93 (br d, 1H, *J* = 1.5, C*H*O), 7.52-7.40 (m, 4H, Ar*H*), 7.35-7.26 (m, 4H, Ar*H*), 7.25-7.16 (m, 2H, Ar*H*), 6.15-6.00 (brd, 1H, *J* = 7.7, N*H*), 5.26-5.12 (dq, 1H, *J* = 7.7, C*H*$CH_3$), 3.14-3.04 (s, 1H, O*H*), 1.13-1.11 (d, 3H, *J* = 6.6, C*H*$_3$). **Visible peaks for the minor rotamer**: 2.75 (br s, 1H, O*H*), 1.25 (d, 3H, *J* = 6.6, C*H*$_3$).

**$^{13}$C NMR** (75 MHz, $CDCl_3$): **Major rotamer**: δ 160.8 (*C*HO), 144.9 (Ar*C*$_{ipso}$), 144.6 (Ar*C*$_{ipso}$), 128.43 (Ar*C*), 128.39 (Ar*C*), 127.10 (Ar*C*), 127.06 (Ar*C*), 125.6 (Ar*C*), 125.3 (Ar*C*), 80.2 (*C*OH), 49.6 (*C*H$CH_3$), 15.9 (*C*H$_3$).

**Minor rotamer**: δ 164.1 (*C*HO), 144.2 (Ar*C*$_{ipso}$), 143.8 (Ar*C*$_{ipso}$), 128.6 (Ar*C*), 128.5 (Ar*C*), 127.4 (Ar*C*), 125.9 (Ar*C*), 125.8 (Ar*C*), 80.0 (*C*-OH), 54.7 (*C*H$CH_3$), 17.5 ( *C*H$_3$).

**MS** (APCI Pos): 238.1 $(M–H_2O)^+$; HRMS (CI Pos., TOF): *m*/*z* 256.1328 (256.1338 cal. for $C_{16}H_{18}NO_2$ $(M+H)^+$.

**(*S*)-2-(Methylamino)-1,1-diphenylpropan-1-ol** (**141**):




A 100 mL round bottom flask equipped with a reflux condenser, ice bath, magnetic stir bar, was charged with lithium aluminium hydride (0.44 g, 11.0 mmol), and THF (10 mL). To the stirred suspension was added dropwise a solution of the formamide **155** (1.5 g, 5.8 mmol) in THF (5 mL). The ice bath was removed when the resulting exothermic reaction had diminished and the reaction mixture was heated to reflux for 12 h. The mixture was then cooled (< 5 $^oC$) and water (0.2 mL) was added. The mixture was stirred for 15 min, aqueous sodium hydroxide (2.5 M, 4.6 mL, 11.5 mmol) was added and the stirring was continued for an additional 15 min. Water (0.6 mL) was added and the resulting mixture was suction filtered to remove the thick white precipitate that was formed. The solid residue was washed with THF (2×15 mL) and the combined filtrates were dried ($Na_2SO_4$) and concentrated under reduced pressure to obtain the crude product as a yellow gum. Acid-base purification provided the *N*-methyl amino alcohol **141** (1.21 g, 85%) as a pale yellow gum.

**Mp**: 68-70 °C (lit.[37] 69.8 °C)

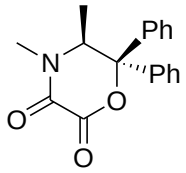
**IR** (neat): 2980, 2851, 2794, 1489, 1446, 1372, 1179, 1156 $cm^{-1}$.

**$^{1}$H NMR** (300 MHz, $CDCl_3$) δ 7.61-7.58 (m, 2H, Ar*H*), 7.48-7.45 (m, 2H, Ar*H*), 7.33-7.23 (m, 4H, Ar*H*), 7.25-7.12 (m, 2H, Ar*H*), 3.65 (q, 1H, *J* = 6.3, C*H*$CH_3$), 2.34 (s, 3H, NC*H*$_3$), 0.96 (d, 3H, *J* = 6.3, C*H*$_3$).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 146.7 (Ar*C*$_{ipso}$), 145.0 (Ar*C*$_{ipso}$), 128.5 (Ar*C*), 128.0 (Ar*C*), 126.9 (Ar*C*), 126.4 (Ar*C*), 126.1 (Ar*C*), 125.8 (Ar*C*), 79.0 (*C*-OH), 60.5 (*C*$HCH_3$), 34.2 (*C*$H_3$N), 13.9 (*C*$H_3$).

**MS** (APCI Pos): *m*/*z* 242.1 $(M + H)^+$; HRMS (CI Pos., TOF): *m*/*z* 242.1549 (242.1545 cal. for $C_{16}H_{20}NO$ $(M+H)^+$.

**(*S*)-4,5-Dimethyl-6,6-diphenylmorpholine-2,3-dione** (**143**)**:**




To a cold (0 ºC), stirred solution of (*S*)-2-(methylamino)-1,1-diphenylpropan-1-ol **141** (1.0 g, 4.1 mmol) in dichloromethane (20 mL) was added DMAP (0.038 g, 0.031 mmol). Triethylamine (0.23 mL, 16.4 mmol) was added followed by dropwise addition of oxalyl chloride (1.05 mL, 12.4 mmol). The mixture was stirred at 0 ºC for 1 h and then at ambient temperature for 4 h. Cold water was added and the mixture was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with aqueous HCl (2 M, 2 × 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 (EtOAc/hexane 7/3) gave **143** (0.52 g, 46%) as a pale yellow foam.

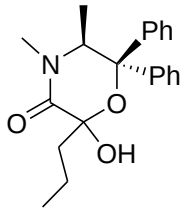
**IR** (neat): 1762, 1680, 1189, 1150 $cm^{-1}$.

**$^{1}$H NMR** (500 MHz, $CDCl_3$) δ 7.42-7.39 (m, 4H, Ar*H*), 7.37-7.33 (m, 4H, Ar*H*), 7.30-7.26 (m, 2H, Ar*H*), 4.46 (q, 1H, *J* = 6.7, C*H*$CH_3$), 3.13 (s, 3H, NC*H*$_3$), 1.21 (d, 3H, *J* = 6.7, $CH_3$).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 156.4 (O*C*O), 153.3 (N*C*O), 141.4 (Ar*C*$_{ipso}$), 139.5 (Ar*C*$_{ipso}$), 129.3 (Ar*C*), 128.9 (Ar*C*), 128.7 (Ar*C*), 128.1 (Ar*C*), 125.4 (Ar*C*), 124.6 (Ar*C*), 87.0 (*C*CH), 59.0 (*C*HCH$_3$), 33.9 (NCH$_3$), 15.00 (*C*H$_3$).

**MS** (APCI Pos): *m*/*z* 296.1 $(M+H)^+$; HRMS (CI Pos., TOF): *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** (**157**):




To a suspension of **143** (495 mg, 1.70 mmol) in anhydrous ether (10 mL) at 0 °C was added propylmagnesium bromide (prepared from Mg (131 mg, 5.40 mmol), and of 1-bromopropane (460 μL, 5.40 mmol) in ether (10 mL) and the mixture was stirred 3 h at ambient temperature. Saturated aqueous $NH_4Cl$ solution was added, the mixture was stirred to dissolve any precipitated solids and was then extracted with ethyl acetate (3×15 mL). The combined extracts were dried ($Na_2SO_4$) and concentrated. The residue was purified by flash chromatography on silica gel (EtOAc/hexane 3/1) to provide **157** (490 mg, 86%) as a pale green oil (5:1 mixture of diastereomers).

**IR** (neat): 2965, 1650, 1493, 1448, 1128, 1071, 1017 $cm^{-1}$.

**$^1$H NMR** (300 MHz, $CDCl_3$): **Major diastereomer**: δ 7.39-7.22 (m, 10H, Ar*H*), 4.30 (q, 1H, *J* = 6.5, C*H*$CH_3$), 3.20 (s, 3H, NC*H*$_3$), 2.53 (s, 1H, O*H*), 1.96-1.90 (m, 2H, C*H*$_2$COH), 1.85-1.75 (m, 1H, C*H*$_2$), 1.75-1.65 (m, 1H, C*H*$_2$), 1.04 (d, 3H, *J* = 6.5, C*H*$_3$CH), 1.03 (t, 3H, *J* = 7.5, $CH_2$C*H*$_3$).

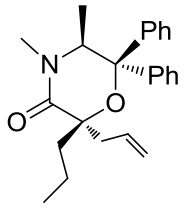
**Visible peaks for the minor diastereomer**: δ 4.25 (q, 1H, *J* = 6.6, C*H*$CH_3$), 3.18 (s, 3H, NC*H*$_3$), 2.88 (s, 1H, O*H*), 1.17 (d, 3H, *J* = 6.6, CHC*H*$_3$), 0.08 (t, 3H, *J* = 7.4, $CH_2$C*H*$_3$).

**$^{13}$C NMR** (75 MHz, $CDCl_3$): **Major diastereomer**: δ 169.4 (*C*O), 143.7 (Ar*C*$_{ipso}$), 142.5 (Ar*C*$_{ipso}$), 128.5 (Ar*C*), 128.3 (Ar*C*), 128.1 (Ar*C*), 128.0 (Ar*C*), 127.0 (Ar*C*), 125.3 (Ar*C*), 96.8 (*C*-OH), 79.9 (N*C*H), 59.3 (*C*H$CH_3$), 43.6 (*C*$H_2CH_2CH_3$), 33.9 (NC$H_3$), 16.5 (*C*$H_3CH_2$), 14.5 (*C*$H_2CH_3$), 14.2 (*C*$H_3$CH).

**Visible peaks for the minor diastereomer**: δ 168.1 (*C*O), 142.9 (Ar*C*$_{ipso}$), 128.3 (Ar*C*), 128.2 (Ar*C*), 127.8 (Ar*C*), 127.4 (Ar*C*), 125.6 (Ar*C*), 97.1 (*C*-OH), 81.5 (N*C*H), 58.5 (*C*H$CH_3$), 39.4 (*C*$H_2CH_2CH_3$), 29.7 (NC$H_3$), 15.3 ($CH_2$*C*$H_3$), 15.0 (*C*$H_2CH_3$), 14.3 (CH*C*$H_3$).

**MS** (APCI Pos): *m*/*z* 322.3 ($(M+H–H_2O)^+$; HRMS (CI Pos.,TOF): *m*/*z* 340.1925 (340.1913 cal. for $C_{21}H_{26}O_3N$ $(M+H)^+$.

**(2*R*,5*S*)-2-Allyl-4,5-dimethyl-6,6-diphenyl-2-propylmorpholin-3-one** (**158**)**:**




To a solution of **157** (0.3 g, 0.8 mmol) in dichloromethane (12 mL) at –78 °C was added $TiCl_4$ (0.58 mL, 5.30 mmol) followed by allyltrimethylsilane (0.84 mL, 5.30 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 $CH_2Cl_2$ (3×10 mL). The combined extracts were dried ($Na_2SO_4$) and concentrated. The residue was purified by flash chromatography on silica gel (EtOAc/hexane 2/1) to provide **158** (0.172 g, 54%) as a colourless gum (3:1 mixture of diastereomers).

**IR** (neat): 2964, 1650, 1448, 1142, 1071, 1016 $cm^{-1}$.

**$^1$H NMR** (300 MHz, $CDCl_3$): **Major diastereomer**: δ 7.26-7.18 (m, 10H, Ar*H*), 5.93-5.79 (m, 1H, C*H*=$CH_2$), 5.02- 4.95 (m, 1H, CH=C*H*$_2$), 4.93- 4.82 (m, 2H, CH=C*H*$_2$), 4.24 (q, 1H, *J* = 6.5, C*H*$CH_3$), 3.17 (s, 3H, NC*H*$_3$), 2.09- 2.01 (dd, 1H, *J* = 15.0, 8.0, C*H*$_2$CH=$CH_2$), 1.85-1.70 (m, 3H, C*H*$_2$CH=$CH_2$, C*H*$_2$$CH_2$$CH_3$), 1.50-1.25 (m, 2H, C*H*$_2$$CH_3$), 0.98 (d, 3H, *J* = 6.5, C*H*$_3$CH), 0.93 (t, 3H, *J* = 7.0, $CH_2$C*H*$_3$).

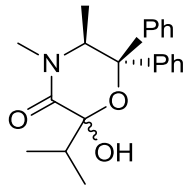
**Visible peaks for the minor diastereomer**: 5.20-5.15 (m, 1H, CH=C*H*$_2$), 5.10-5.05 (m, 1H, CH=C*H*$_2$), 3.15 (s, 3H, NC*H*$_3$).

**$^{13}$C NMR** (75 MHz, $CDCl_3$): **Major diastereomer**: δ 171.4 (*C*O), 145.3 (Ar*C*$_{ipso}$), 143.9 (Ar*C*$_{ipso}$), 134.1 (*C*H=$CH_2$), 128.6 (br, Ar*C*), 128.1 (Ar*C*), 128.08 (Ar*C*), 127.86 (Ar*C*), 126.8 (Ar*C*), 125.8 (br, Ar*C*), 117.2 (CH=*C*$H_2$), 80.6 (N*C*H), 78.9 (C(O)-*C*-O), 58.8 (*C*H$CH_3$), 42.0 (CH=*C*$H_2$), 40.4 (*C*$H_2$$CH_2$), 33.9 (N$CH_3$), 17.8 (*C*$H_2$$CH_3$), 16.1 ($CH_2$*C*$H_3$), 14.5 (CH*C*$H_3$).

**Minor Diastereomer**: δ 144.1 (Ar*C*$_{ipso}$), 134.6 (*C*H$CH_2$), 128.04 (Ar*C*), 127.9 (Ar*C*), 127.6 (Ar*C*), 126.7 (Ar*C*), 118.0 (Ar*C*), 81.2 (N*C*H), 78.8 (C(O)-*C*-O), 43.5 (CH=*C*$H_2$), 37.9 (*C*$H_2$$CH_2$), 33.8 (N*C*$H_3$), 16.3 (*C*$H_2$$CH_3$), 15.3 ($CH_2$*C*$H_3$), 13.7 (CH*C*$H_3$).

**MS** (APCI Pos): *m*/*z* 364.4 $(M+H)^+$ HRMS (CI Pos., TOF): *m*/*z* 364.2295 (364.2277 calc. for $C_{24}H_{30}NO_2$, $(M+H)^+$.

**(2*S*,5*S*)-2-Hydroxy-2-isopropyl-4,5-dimethyl-6,6-diphenylmorpholin-3-one** (**159**):




To a suspension of the dione **143** (600 mg, 2.03 mmol) in anhydrous ether (7 mL) at 0 °C was added isopropylmagnesium chloride (2.00 M solution in THF, 5.10 mL, 10.1 mmol) and the mixture was warmed to ambient temperature. The reaction mixture was stirred for 5 h at ambient temperature and saturated aqueous $NH_4Cl$ solution (4 mL) was added. The resulting mixture was extracted with ethyl acetate (3×10 mL) and the combined extracts were dried ($Na_2SO_4$) and concentrated. Purification of the crude product by flash chromatography on silica gel (EtOAc/hexanes 65:35) gave the hemiacetal **159** (590 mg, 87%) as a white foam (4:1 mixture of diastereomers).

**IR** (neat): 3372, 2978, 1649, 1493, 1448, 1017, 1382, 1311, 1242, 1139, 1076, 1018 $cm^{-1}$.

**$^1$H NMR** (300 MHz, $CDCl_3$): **Major diastereomer**: δ 7.35-7.17 (m, 10H, Ar*H*), 4.29 (q, 1H, *J* = 6.6, C*H*$CH_3$), 3.18 (s, 3H, NC*H*$_3$), 2.31 (s, 1H, O*H*), 2.22 (sep, 1H, *J* = 6.8, C*H*$(CH_3)_2$), 1.17 (d, 3H, *J* = 6.8, CHC*H*$_3$), 1.08 (d, 3H, *J* = 6.8, CHC*H*$_3$), 1.00 (d, 3H, *J* = 6.6, CHC*H*$_3$).

**Minor diastereomer**: δ 4.58- 4.56 (q, 1H, *J* = 6.6, C*H*$CH_3$), 3.41 (s, 3H, NC*H*$_3$), 1.26 (d, 3H, *J* = 6.6, CHC*H*$_3$), 1.22 (d, 3H, *J* = 6.8, CHC*H*$_3$);

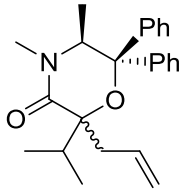
**$^{13}$C NMR** (75 MHz, $CDCl_3$): **Major diastereomer**: δ 169.2 (*C*O), 144.1 (Ar*C*$_{ipso}$), 142.8 (Ar*C*$_{ipso}$), 128.4 (Ar*C*), 128.3 (Ar*C*), 128.2 (Ar*C*), 128.0 (Ar*C*), 127.0 (Ar*C*), 125.4 (Ar*C*),

98.5 (*C*-OH), 79.3 (N*C*H), 59.1 (*C*HCH$_3$), 37.8 (*C*H(CH$_3$)$_2$), 33.91 (N-*C*H$_3$), 18.0 (CH*C*H$_3$), 15.6 (CH(*C*H$_3$)$_2$), 15.4 (CH(*C*H$_3$)$_2$).

**Minor diastereomer**: δ166.3 (*C*O), 143.8 (Ar*C*$_{ipso}$), 128.1 (Ar*C*), 127.9 (Ar*C*), 127.8 (Ar*C*), 127.4 (Ar*C*), 126.8 (Ar*C*), 124.9 (Ar*C*), 95.9 (*C*-OH), 80.4 (N*C*H), 58.6 (*C*HCH$_3$), 33.85 (N-*C*H$_3$), 16.2 (CH(*C*H$_3$)$_2$).

**MS** (APCI Pos): *m*/*z* 322.3 ((M+H–H$_2$O)$^+$; HRMS (CI Pos., TOF): *m*/*z* 339.1842 (339.1834 cal. for C$_{21}$H$_{25}$NO$_3$ (M$^+$), 322.1807 ((M+H– H$_2$O)$^+$.

**(2*S*,5*S*)-2-Allyl-2-isopropyl-4,5-dimethyl-6,6-diphenylmorpholin-3-one** (**160**)**:**




To a solution of **159** (0.6 g, 1.7 mmol) in dichloromethane (6 mL) at –78 °C was added TiCl$_4$ (1.06 mL, 10.6 mmol) followed by allyltrimethylsilane (1.68 mL, 10.6 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$_2$Cl$_2$ (3×10 mL). The combined extracts were dried (Na$_2$SO$_4$) and concentrated. The residue was purified by flash chromatography on silica (EtOAc/hexane 2/1) to give **160** (369 mg, 58%) as a colourless gum.

**IR** (neat): 3068, 2978, 2929, 1641, 1490, 1446, 1382, 1312, 1236, 1143, 1075, 1027, 908 cm$^{-1}$.

**$^1$H NMR** (300 MHz, CDCl$_3$): **Major diastereomer**: δ 7.29-7.18 (s, 10H, Ar*H*), 5.96-5.85 (m, 1H, C*H*=CH$_2$), 4.88-4.83 (m, 1H, CH=C*H*$_2$), 4.82-4.74 (m, 1H, CH=CH$_2$), 4.25 (q,

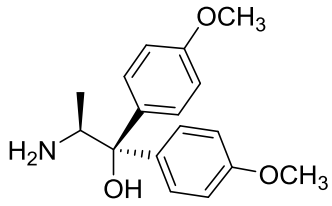
1H, *J* = 6.6, C*H*$CH_3$), 3.18 (s, 3H, NC*H*$_3$), 2.23 (sep, 1H, *J* = 6.8, C*H*$(CH_3)_2$), 1.76-1.58 (m, 2H, C*H*$_2$CH=$CH_2$), 1.13 (d, 3H, *J* = 6.8, CHC*H*$_3$CH), 1.04 (d, 3H, *J* = 6.8, CHC*H*$_3$CH), 0.96 (d, 3H, *J* = 6.6, CHC*H*$_3$).

**Visible peaks for the minor diastereomer**: δ 5.18-5.05 (m, 2H, CH=C*H*$_2$CH), 3.16 (s, 3H, NC*H*$_3$), 0.91 (d, 3H, *J* = 6.8, CHC*H*$_3$), 0.89-0.87 (d, 3H, *J* = 6.6, CH$(CH_3)_2$), 0.61-0.58 (d, 3H, *J* = 6.6, CH$(CH_3)_2$).

**$^{13}$C NMR** (75 MHz, $CDCl_3$): δ 171.4 (*C*O), 145.8 (Ar*C*$_{ipso}$), 144.4 (Ar*C*$_{ipso}$), 135.4 (*C*H=$CH_2$), 128.1 (Ar*C*), 128.0 (Ar*C*), 127.9 (Ar*C*), 126.7 (Ar*C*), 115.9 (CH=*C*$H_2$), 82.4 (*C*$(Ar)_2$), 78.4 (C-*C*=O), 58.6 (*C*H$CH_3$), 41.3 (*C*$H_2$CH=$CH_2$), 35.3 (*C*H$(CH_3)_2$), 33.7 (N*C*$H_3$), 19.2 (CH*C*$H_3$), 16.4 (CH*C*$H_3$), 16.3 (CH*C*$H_3$).

**MS** (APCI Pos): *m*/*z* 364.1 $(M+H)^+$, 345.3 $(M–H_2O)^+$; HRMS (CI Pos., TOF): *m*/*z* 364.2280 (364.2277 cal. for $C_{24}H_{30}NO_2$ $(M+H)^+$.

**(*S*)-2-Amino-1,1-bis(4-methoxyphenyl)propan-1-ol** (**154**)**:**




A dry 250 mL three-necked round bottom flask, equipped with a reflux condenser, magnetic stirring bar and nitrogen gas inlet was charged with magnesium turnings (6.39 g, 0.26 mol), The flask was fitted with a rubber septum and charged sequentially via syringe with diethyl ether (180 mL), 4-bromoanisole (31.60 mL, 251.8 mmol ) and methyl iodide (0.05 mL). The rubber septum was replaced with a stopper. Within 5 min, an exothermic reaction initiated and the mixture began to reflux spontaneously. The mixture was then stirred for an additional 4 h (until all of the magnesium reacted) without external heating

or cooling. The resulting solution was then added drop wise to an ice-cooled suspension of (*S*)-alanine methylester hydrochloride **152** (7.00 g, 50.3 mmol) in THF (30 mL) using a syringe over a period of 30 min and the mixture was stirred at ambient temperature for 16 h. A saturated aqueous solution of ammonium chloride (60 mL) was then added, and the mixture was stirred vigorously until all of the white precipitate dissolved. The resulting solution was extracted with ethyl acetate (3×100 mL). The combined ethyl acetate layers were dried ($Na_2SO_4$) and concentrated under reduced pressure to provide the crude product as a yellow gum. This was dissolved in aqueous HCl (1 M, 10 mL) and the solution was extracted with ethyl acetate (2×50 mL). The aqueous layer was cooled (<5 $^oC$), basified with sodium hydroxide pellets (pH = 9) and then extracted with ethyl acetate (3×50 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated under reduced pressure to provide **154** (11.0 g, 88%) as a sticky, yellow solid.

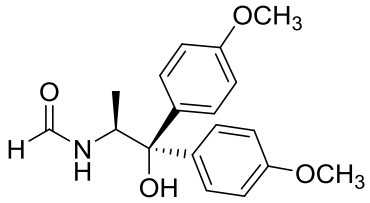
**IR** (neat): 2971, 2903, 2836, 1605, 1506, 1243, 1171, 1030 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$): δ 7.50 (d, 2H, *J* = 8.8, Ar*H*), 7.36 (d, 2H, *J* = 8.8, Ar*H*), 6.85 (d, 2H, *J* = 8.8, Ar*H*), 6.81 (d, 2H, *J* = 8.8, Ar*H*), 4.03 (q, 1H, *J* = 6.3, C*H*$CH_3$), 3.77 (s, 3H, OC*H*$_3$), 3.76 (s, 3H, OC*H*$_3$), 0.94 (d, 3H, *J* = 6.3, CHC*H*$_3$).

**$^{13}$C NMR** (75 MHz, $CDCl_3$): δ 158.2 (Ar*C*-$OCH_3$), 158.0 (Ar*C*-$OCH_3$), 139.3 (Ar*C*$_{ipso}$), 137.4 (Ar*C*$_{ipso}$), 127.1 (Ar*C*), 126.7 (Ar*C*), 113.8 (Ar*C*), 113.3 (Ar*C*), 78.1(*C*-OH), 55.3 (O*C*$H_3$), 55.2 (O*C*$H_3$), 52.1 (*C*H$CH_3$), 17.3 (CH*C*$H_3$).

**MS** (APCI Pos): *m*/*z* 270.1 ($(M+H–H_2O)^+$; HRMS (CI Pos., TOF): *m*/*z* 288.1605 (288.1600 calcd. for $C_{17}H_{22}NO_3$ $(M+H)^+$.

**(*S*)-*N*-(1-Hydroxy-1,1-bis (4-methoxyphenyl)propan-2-yl) formamide** (**156**)**:**




To a cooled (<5 °C) solution of the amino alcohol **154** (2.25 g, 7.84 mmol) in anhydrous $CH_2Cl_2$ (10 mL), was added acetic formic anhydride (0.75 mL, 8.62 mmol). The resulting clear, brown solution was stirred at ambient temperature for 12 h. The reaction mixture was then diluted with $CH_2Cl_2$ (10 mL) and the solution was washed with aqueous HCl (0.1 M, 10 mL). The organic layer was dried ($Na_2SO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 3/2) to provide the formamide **156** (1.64 g, 67%) as a white foam.

**IR** (neat): 3303, 2991, 2941, 1732, 1651, 1606, 1507, 1454, 1376, 1243, 1175, 1034 $cm^{-1}$

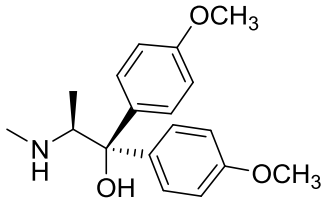
**$^1$H NMR** (500 MHz, $CDCl_3$): **Major rotamer**: δ 7.97 (s, 1H, C*H*O), 7.37 (d, 2H, *J* = 8.9, Ar*H*), 7.32 (d, 2H, *J* = 8.9, Ar*H*), 5.10 (m, 1H, C*H*$CH_3$). 3.77 (s, 3H, OC*H*$_3$), 3.75 (s, 3H, OC*H*$_3$), 1.10 (d, 3H, *J* = 6.6, CHC*H*$_3$).

**Visible peaks for the minor rotamer**: δ 7.29- 7.28 (d, 2H, *J* =8.9, Ar*H*), 6.88 (d, 2H, *J* = 8.9, Ar*H*), 6.70 (d, 2H, *J* = 8.9, Ar*H*), 3.79 (s, 3H, OC*H*$_3$).

**$^{13}$C NMR** (75 MHz, $CDCl_3$): 160.6 (*C*HO), 158.5 (Ar*C*-$OCH_3$), 137.2 (Ar$C_{ipso}$), 137.1 (Ar$C_{ipso}$), 126.8 (Ar*C*), 126.6 (Ar*C*), 113.7 (Ar*C*), 79.8 (N*C*H), 55.23 (O*C*$H_3$), 55.20 (O*C*$H_3$), 49.6 (*C*H$CH_3$), 16.1 (*C*$H_3$).

**MS** (APCI Pos): *m*/*z* 298.1 $((M+H-H_2O)^+$.

**(*S*)-1,1-bis (4-Methoxyphenyl)-2-(methylamino)propan-1-ol** (**142**)**:**




A 100 mL round bottom flask equipped with a reflux condenser, ice bath and magnetic stir bar, was charged with lithium aluminium hydride (0.94 g, 24.7 mmol), and THF (15 mL). To the stirred suspension was added drop wise a solution of the formamide **156** (3.90 g, 12.3 mmol) in THF (20 mL). The ice bath was removed when the resulting exothermic reaction had diminished and the reaction mixture was heated to reflux for 12 h. The mixture was then cooled (<5 $^{o}$C) and water (0.5 mL) was added. The mixture was stirred for 15 min, aqueous sodium hydroxide (2.5 M, 9.8 mL) was added and the stirring was continued for an additional 15 min. Water (1.5 mL) was added and the resulting mixture was suction filtered to remove the thick white precipitate that was formed. The solid residue was washed with THF (2×15 mL) and the combined filtrates were dried ($Na_2SO_4$) and concentrated under reduced pressure to obtain the crude product as a yellow gum. Acid-base purification provided the *N*-methyl amino alcohol **142** (3.08 g, 82%) as a pale yellow gum.

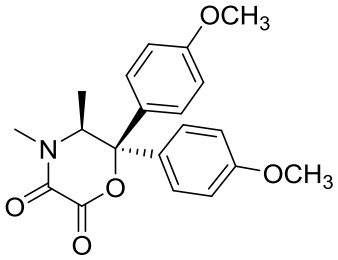
**IR** (neat): 3447, 3381, 2972, 2901, 2835, 1606, 1506, 1451, 1294, 1243, 1169, 1029, 964 $cm^{-1}$.

**$^{1}$H NMR** (500 MHz, $CDCl_3$): δ 7.47 (d, 2H, *J* = 8.8, Ar*H*), 7.35 (d, 2H, *J* = 8.8, Ar*H*), 6.85 (d, 2H, *J* = 8.9, Ar*H*), 6.80 (d, 2H, *J* = 8.9, Ar*H*), 3.77 (s, 3H, OC*H*$_3$), 3.76 (s, 3H, OC*H*$_3$), 3.54 (q, 1H, *J* = 6.3, C*H*CH$_3$), 2.36 (s, 3H, NC*H*$_3$) , 0.96 (d, 3H, *J* = 6.3, CHC*H*$_3$).

**$^{13}$C NMR** (75 MHz, $CDCl_3$): δ 158.3 (Ar*C*-$OCH_3$), 158.0 (Ar*C*-$OCH_3$), 138.8 (Ar$C_{ipso}$), 137.3 (Ar$C_{ipso}$), 127.3 (Ar*C*), 127.0 (Ar*C*), 113.7 (Ar*C*), 113.2 (Ar*C*), 78.5 (*C*-OH), 60.6 (*C*H$CH_3$), 55.22 (O*C*$H_3$), 55.16 (O*C*$H_3$), 34.1 (N*C*$H_3$), 13.9 (*C*$H_3$).

**MS** (APCI Pos): *m*/*z* 284.1 ($(M+H–H_2O)^+$, 302.3 $(M+H)^+$; HRMS (CI Pos., TOF): *m*/*z* 302.1762 (302.1756 calcd. for $C_{18}H_{24}NO_3$ $(M+H)^+$.

**(*S*)-6,6-Bis(4-methoxyphenyl)-4,5-dimethylmorpholine-2,3-dione** (**144**)**:**




To a stirred solution of the amino alcohol **142** (2.0 g, 6.6 mmol) and DMAP (0.85 g, 0.69 mmol) in dichloromethane (25 mL) at 0 °C was added triethylamine (1.65 mL, 19.9 mmol). The mixture was stirred for 10 min and a solution of oxalyl chloride (4.18 mL, 27.9 mmol) in dichloromethane (5 mL) was added drop wise over a period of 30 min. at 0 °C. The mixture was stirred at room temperature for 8 h and water (10 mL) was added. The biphase was separated and the dichloromethane layer was washed with water (10 mL), dried ($Na_2SO_4$) and concentrated. The residue was purified by flash chromatography on silica gel (EtOAc/hexane 7/3) to furnish **144** (1.5 g, 65%) as a white solid.

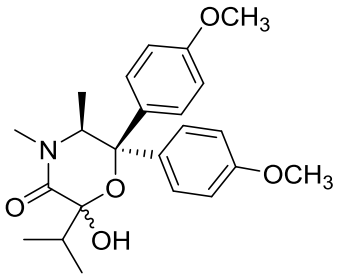
**IR** (neat): 2933, 1760, 1687, 1608, 1511, 1251, 1178, 1031 $cm^{-1}$.

**$^1$H NMR** (300 MHz, $CDCl_3$): δ 7.32-7.26 (m, 4H, Ar*H*), 6.88-6.84 (m, 4H, Ar*H*), 4.35 (q, 1H, *J* = 6.7, C*H*$CH_3$), 3.78 (s, 3H, OC*H*$_3$), 3.77 (s, 3H, OC*H*$_3$), 3.14 (s, 3H, NC*H*$_3$), 1.21 (d, 3H, *J* = 6.7, C*H*$_3$).

**$^{13}$C NMR** (75 MHz, $CDCl_3$): δ 159.5 (Ar*C*-$OCH_3$), 159.2 (Ar*C*-$OCH_3$), 156.7 (*C*(O)N), 153.4 (*C*(O)O), 133.7 (Ar$C_{ipso}$), 132.0 (Ar$C_{ipso}$), 126.9 (Ar*C*), 126.1 (Ar*C*), 114.6 (Ar*C*), 114.1 (Ar*C*), 86.9 (*C*-O), 59.2 (*C*H$CH_3$), 55.3 (O*C*$H_3$), 33.9 (N*C*$H_3$), 15.0 (CH*C*$H_3$).

**MS** (APCI Pos): *m*/*z* 356.1 $(M+H)^+$; HRMS (CI Pos., TOF): *m*/*z* 355.1410 (355.1420 calcd. for $C_{20}H_{21}NO_5$ ($M^+$)).

**(*S*)-2-Hydroxy-2-isopropyl-6,6-bis(4-methoxyphenyl)-4,5-dimethylmorpholin-3-one (161):**




To a suspension of the dione **144** (600 mg, 1.60 mmol) in anhydrous ether (7 mL) at 0 °C was added isopropylmagnesium bromide (4.3 mL, 2.0 M solution in THF, 8.4 mmol) and the mixture was warmed to ambient temperature. The reaction mixture was stirred 5 h at ambient temperature and saturated aqueous $NH_4Cl$ solution was added. The resulting mixture was extracted with ethyl acetate (3×10 mL) and the combined organic layers were dried ($Na_2SO_4$) and concentrated. Purification of the crude product by flash chromatography on silica gel (EtOAc/hexanes 6.5/3.5) provided of the hemiacetal **161** (590 mg, 88%) as a white foam.

**IR** (neat): 2970, 1649, 1605, 1507, 1454, 1301, 1246, 1176, 1020 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$): **Major diastereomer**: δ 7.25-7.15 (br, 2H, Ar*H*), 7.20 (d, 2H, *J* = 8.7, Ar*H*), 7.16 (d, 2H, *J* = 8.7, Ar*H*), 6.82 (d, 2H, *J* = 8.7, Ar*H*), 6.83-6.81 (br, 2H, Ar*H*), 4.19 (q, 1H, *J* = 6.6, C*H*$CH_3$), 3.78 (s, 3H, OC*H*$_3$), 3.76 (s, 3H, OC*H*$_3$), 3.16 (s,

3H, NC*H*$_3$), 2.31 (s, 1H, O*H*), 2.21 (sep, 1H, *J* = 6.8, C*H*(CH$_3$)$_2$), 1.15 (d, 3H, *J* = 6.8, C*H*(CH$_3$)$_2$), 1.04 (d, 3H, *J* = 6.8, C*H*(CH$_3$)$_2$), 0.99 (d, 3H, *J* = 6.6, CHC*H*$_3$).

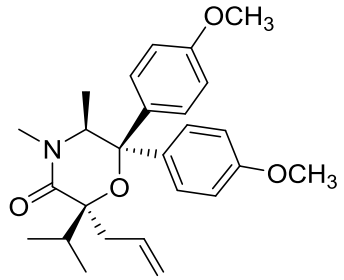
**Visible peaks for the minor diastereomer**: δ 7.44 (d, 2H, *J* = 8.0, Ar*H*), 7.39 (d, 2H, *J* = 8.0, Ar*H*), 4.12 (q, 1H, *J* = 6.9, C*H*CH$_3$), 3.79 (s, 3H, OC*H*$_3$), 3.75 (s, 3H, OC*H*$_3$), 3.19 (s, 3H, NC*H*$_3$).

**$^{13}$C NMR** (75 MHz, CDCl$_3$): **Major diastereomer**: δ 169.4 (*C*=O), 159.1 (Ar*C*-OCH$_3$), 158.4 (Ar*C*-OCH$_3$), 136.7 (Ar*C*$_{ipso}$), 134.8 (Ar*C*$_{ipso}$), 129.5 (Ar*C*), 126.7 (Ar*C*), 113.8 (Ar*C*), 113.5 (Ar*C*), 98.5 (*C*-OH), 78.8 (*C*-O), 59.6 (*C*HCH$_3$), 55.2 (OCH$_3$), 37.7 (*C*HCH$_3$), 33.9 (NCH$_3$), 18.0 (CH*C*H$_3$), 15.6 (CH*C*H$_3$), 15.5 (CH*C*H$_3$).

**Visible peaks for the minor diastereomer**: δ 158.3 (Ar*C*-OCH$_3$), 129.3 (Ar*C*), 113.4 (Ar*C*), 113.3 (Ar*C*), 98.3 (*C*-OH), 60.4 (*C*HCH$_3$), 21.1 (CH*C*H$_3$), 14.2 (CH*C*H$_3$).

**MS** (APCI Pos): *m*/*z* 398.1 (M-1), 399.1 (M)$^+$; HRMS (EI Pos., TOF): *m*/*z* 399.2052 (399.2046 calcd. for $C_{23}H_{29}NO_5$ ($M^+$)); HRMS (CI Pos., TOF): *m*/*z* 400.2120 (400.2124 calcd. for $C_{23}H_{30}NO_5$ $(M+H)^+$).

**(2*S*,5*S*)-2-Allyl-2-isopropyl-6,6-bis(4-methoxyphenyl)-4,5-dimethylmorpholin-3-one (162):**




To a solution of the hemiacetal **161** (600 mg, 1.50 mmol) in dichloromethane (10 mL) at –78 °C was added TiCl$_4$ (0.98 mL, 9.00 mmol) followed by allyltrimethylsilane (1.4 mL, 9.0 mmol). The mixture was gradually warmed to –40 °C and stirred at this

temperature for 4.5 h. Saturated aqueous $NH_4Cl$ (4 mL) was added and the mixture was warmed to ambient temperature. Water (5 mL) was added and the mixture was extracted with $CH_2Cl_2$ (3×15 mL), dried ($Na_2SO_4$) and concentrated. The residue was purified by flash chromatography on silica (hexanes/ethyl acetate, 3:2) to provide **162** (350 mg, 55%) as a white foam.

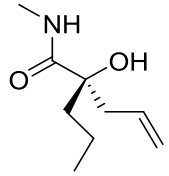
**IR** (neat) 2934, 1641, 1609, 1509, 1442, 1302, 1248, 1174, 1135, 1030 $cm^{-1}$.

**$^1$H NMR** (500 MHz, $CDCl_3$): δ 7.10 (d, 2H, *J* = 8.6, Ar*H*), 6.82 (br s, 2H, Ar*H*), 6.76-6.75 (d, 2H, *J* = 8.8, Ar*H*), 5.97-5.88 (m, 1H, C*H*$CH_2$), 4.87 (d, 1H, *J* = 10.3, CH=C*H*$_2$), 4.80 (d, 1H, *J* = 17.7, CH=C*H*$_2$), 4.17 (q, 1H, *J* = 6.6, C*H*$CH_3$), 3.79 (s, 3H, OC*H*$_3$), 3.77 (s, 3H, OC*H*$_3$), 3.15 (s, 3H, NC*H*$_3$), 2.23– 2.17 (m, 1H, C*H*$(CH_3)_2$), 1.78-1.74 (dd, 1H, *J* = 15.0, 6.5, C*H*$_2$CH=$CH_2$), 1.66-1.62 (dd, 1H, *J* = 15.1, 6.5, C*H*$_2$CH=$CH_2$), 1.11 (d, 1H, *J* = 6.8, CHC*H*$_3$), 1.03 (d, 1H, *J* = 6.8, CHC*H*$_3$), 0.96 (d, 3H, *J* = 6.6, CHC*H*$_3$).

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 172.0 (*C*=O), 159.3 (Ar*C*-$OCH_3$), 158.6 (Ar*C*-$OCH_3$), 138.7 (*C*H=$CH_2$), 137.0 (Ar$C_{ipso}$), 136.0 (Ar*C*), 116.2 (Ar*C*), 113.7 (CH=*C*$H_2$), 82.5 (*C*-$(Ar)_2$), 78.3 (*C*-C=O), 59.5 (*C*H$CH_3$), 55.58 (O*C*$H_3$), 55.56 (O*C*$H_3$), 41.7 (*C*$H_2$CH=$CH_2$), 35.7 (*C*H$(CH_3)_2$ or N*C*$H_3$), 34.1 (N*C*$H_3$ or *C*H$(CH_3)_2$, 19.6 (CH*C*$H_3$), 16.80 (CH*C*$H_3$), 16.73 (CH*C*$H_3$).

**MS** (APCI Pos): *m*/*z* 424.1 $(M+H)^+$; HRMS (EI Pos., TOF): *m*/*z* 423.2410 (423.2410 calcd. for $C_{26}H_{33}NO_4$ ($M^+$)).

**(*R*)-2-Hydroxy-*N*-methyl-2-propylpent-4-enamide** (**120c**)**:**




To anhydrous liquid ammonia (distilled over sodium) was added Na (0.05 g, 1.81 mmol) at –78 °C and the mixture was stirred for 15 min. To the resulting blue solution was added a solution of **155** (0.11 g, 0.30 mmol) in anhydrous THF (2.5 mL) and the mixture was stirred for 1.5 min. A mixture of methanol/water (2:1, 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 chromatography on silica gel (EtOAc/hexanes, 3/2) to yield **120 c** (45 mg, 88%) as a white solid.

**IR**: 2932, 1730, 1551, 1513, 1247, 1149, 1025 $cm^{-1}$.

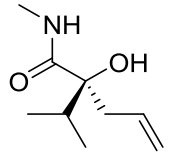
**$^{1}$H NMR** (300 MHz, $CDCl_3$) δ 6.70 (br s, 1H, N*H*), 5.82-5.68 (m, 1H, C*H*=$CH_2$), 5.23-5.14 (m, 2H, CH=C*H*$_2$), 2.82 (d, 3H, *J* = 4.9, NHC*H*$_3$), 2.76- 2.69 (br dd, 1H, *J* = 13.6, 6.2, C*H*$_2$-CH=$CH_2$), 2.33- 2.25 (dd, 1H, *J* = 13.6, 8.6, C*H*$_2$-CH=$CH_2$), 2.30 (s, 1H, O*H*), 1.88-1.78 (m, 1H, C*H*$_2$), 1.57-1.42 (m, 2H, C*H*$_2$), 1.26-1.20 (m, 1H, C*H*$_2$), 0.92- 0.88 (t, 3H, *J* = 7.2, $CH_2$C*H*$_3$).

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 175.2 (*C*O), 132.8 (*C*H=$CH_2$), 120.2 (CH=*C*$H_2$), 77.3 (*C*(OH)$CH_2$), 44.0 (*C*$H_2$-CH=$CH_2$), 41.5 (*C*$H_2CH_2$), 25.9 (NH*C*$H_3$), 16.8 ($CH_2$*C*$H_3$), 14.3 ($CH_2$*C*$H_2$).

**MS** (EI Pos.): *m*/*z* 172.2 $(M+H)^+$.

$[\alpha]_D^{25}$ = +21.7 (*c* 1.9, $CHCl_3$); lit.[25] $[\alpha]_D^{25}$ = +30 (*c* 1.9, $CHCl_3$).

**(*S*)-2-Hydroxy-2-isopropyl-*N*-methylpent-4-enamide** (**120d**):




To anhydrous liquid ammonia (distilled over sodium) was added Na (0.07 g, 3.1 mmol) at –78 °C and the mixture was stirred for 15 min. To the resulting blue solution was added a solution of **162** (167 mg, 0.39 mmol) in anhydrous THF (2.5 mL) and the mixture was stirred for 1.5 min. A mixture of methanol/water (2:1, 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 chromatography on silica gel (EtOAc/ hexanes, 2/3) to provide **120 d** (60 mg, 90%) as a yellow liquid.

**IR**: 3423, 3373, 2968, 1646, 1534, 1409, 1240, 1174, 1004, 915 $cm^{-1}$.

**$^{1}$H NMR** (300 MHz, $CDCl_3$): **Major rotamer**: δ 6.62 (s, 1H, N*H*), 5.74-5.63 (m, 1H, C*H*=$CH_2$), 5.17 (s, 1H, CH=C*H*$_2$), 5.13 (m, IH, CH=C*H*$_2$), 2.80 (d, 3H, *J* = 4.9, NHC*H*$_3$), 2.70 (tdd, 1H, *J* = 13.7, 5.8, 1.2, C*H*$_2$CH), 2.30-2.23 (dd, 1H, *J* = 13.7, 9.0, CH=C*H*$_2$), 2.06 -1.94 (m, 1H, C*H*($CH_3$)$_2$), 0.92 (d, 3H, *J* = 6.9, CH(C*H*$_3$)$_2$), 0.87 (d, 3H, *J* = 6.9, CH(C*H*$_3$)$_2$).

**Visible peaks for minor rotamer**: 2.82 (s, 3H, NHC*H*$_3$), 0.88 (d, 3H, *J* = 5.9, CHC*H*$_3$), 0.82 (d, 3H, *J* = 6.8, C*H*$_3$CH).

**$^{13}$C NMR** (75 MHz, $CDCl_3$): **Major rotamer**: δ 175.2 (*C*O), 133.3 (*C*H=$CH_2$), 119.8 (CH=C*H*$_2$), 79.6 (*C*-OH), 41.7 (*C*$H_2$CH), 35.0 (*C*H($CH_3$)$_2$), 25.8 (NH*C*$H_3$), 17.45 (CH*C*$H_3$), 16.1 (CH*C*$H_3$).

**Visible peaks for minor rotamer**: 175.6 (*C*O), 17.40 (CH*C*$H_3$).

**MS** (APCI Pos): *m*/*z* 172.2 $(M+H)^+$.

$[\alpha]_D^{25}$ = + 9.6 (*c* 1.6, $CHCl_3$); lit.[25] $[\alpha]_D^{25}$ = + 9.0 (*c* 1.6, $CHCl_3$)

**3.5** References

(1) (a) Yus, M.; Gonzalez-Gomez, J. C.; Foubelo, F. *Chem. Rev.* **2013**, *113*, 5595; (b) Yus, M.; Gonzalez-Gomez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774.

(2) (a) Wang, S.-G.; Tsai, H. R.; Chen, K. *Tetrahedron Lett.* **2004**, *45*, 6183; (b) Kulkarni, N. A.; Wang, S.-G.; Lee, L.-C.; Tsai, H. R.; Venkatesham, U.; Chen, K. *Tetrahedron: Asymmetry* **2006**, *17*, 336; (c) Waldmann, H. *Synlett* **1990**, 627; (d) Fráter, G.; Müller, U.; Gunther, W. *Tetrahedron Lett.* **1981**, *22*, 4221; (e) Huang, Y.; Zhang, Y.-B.; Chen, Z.-C.; Xu, P.-F. *Tetrahedron: Asymmetry* **2006**, *17*, 3152; (f) Whitesell, J. K.; Deyo, D.; Bhattacharya, A. *J. Chem. Soc., Chem. Commun.* **1983**, 802; (g) Chen, M.-Y.; Fang, J.-M. *J. Chem. Soc., Perkin Trans 1* **1993**, 1737.

(3) (a) Yamada, K.; Tozawa, T.; Nishida, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2301; (b) Zheng, K.; Qin, B.; Liu, X.; Feng, X. *J. Org. Chem.* **2007**, *72*, 8478.

(4) Schmitt, D. C.; Johnson, J. S. *Org. Lett.* **2010**, *12*, 944.

(5) Ojima, I.; Miyazawa, Y.; Kumagai, M. *J. Chem. Soc., Chem. Commun.* **1976**, 927.

(6) (a) Whitesell, J. K.; Bhattacharya, A.; Aguilar, D. A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982**, 989; (b) Whitesell, J. K.; Bhattacharya, A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982**, 988.

(7) Whitesell, J. K.; Nabona, K.; Deyo, D. *J. Org. Chem.* **1989**, *54*, 2258.

(8) Kim, Y. H.; Kim, S. H. *Tetrahedron Lett.* **1995**, *36*, 6895.

(9) Kim, Y. H.; Park, D. H.; Byun, I. S. *Heteroatom Chem.* **1992**, *3*, 51.

(10) Kim, Y. H.; Park, D. H.; Byun, I. S.; Yoon, I. K.; Park, C. S. *J. Org. Chem.* **1993**, *58*, 4511.

(11) Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Helv. Chim. Acta* **1984**, *67*, 1397.

(12) Kiegiel, K.; Jurczak, J. *Tetrahedron Lett.* **1999**, *40*, 1009.

(13) Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313.

(14) Chang, J.-W.; Jang, D.-P.; Uang, B.-J.; Liao, F.-L.; Wang, S.-L. *Org. Lett.* **1999**, *1*, 2061.

(15) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed.* **1996**, *35*, 2708.

(16) Herranz, R.; Castro-Pichel, J.; Vinuesa, S.; Garcia-Lopez, M. T. *J. Org. Chem.* **1990**, *55*, 2232.

(17) Veeresha, G.; Datta, A. *Tetrahedron Lett.* **1997**, *38*, 5223.

(18) Kingston, D. G. I. *Chem. Commun.* **2001**, 867.

(19) (a) Fringuelli, F.; Pizzo, F.; Rucci, M.; Vaccaro, L. *J. Org. Chem.* **2003**, *68*, 7041; (b) Aoyagi, Y.; Jain, R. P.; Williams, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 3472.

(20) (a) Cativiela, C.; Diaz-de-Villegas, M. D.; Gálvez, J. *Tetrahedron* **1996**, *52*, 687; (b) Pires, R.; Burger, K. *Synthesis* **1996**, *1996*, 1277.

(21) Moorlag, H.; Kellogg, R. M.; Kloosterman, M.; Kaptein, B.; Kamphuis, J.; Schoemaker, H. E. *J. Org. Chem.* **1990**, *55*, 5878.

(22) Trost, B. M.; Dogra, K.; Franzini, M. *J. Am. Chem. Soc.* **2004**, *126*, 1944.

(23) Yang, D.; Yang, M.; Zhu, N.-Y. *Org. Lett.* **2003**, *5*, 3749.

(24) Howard, B. E.; Woerpel, K. A. *Org. Lett.* **2007**, *9*, 4651.

(25) Pansare, S. V.; Ravi, R. G.; Jain, R. P. *J. Org. Chem.* **1998**, *63*, 4120.

(26) Pansare, S. V.; Adsool, V. A. *Org. Lett.* **2006**, *8*, 2035.

(27) Pansare, S. V.; Adsool, V. A. *Org. Lett.* **2006**, *8*, 5897.

(28) Pansare, S. V.; Adsool, V. A. *Tetrahedron Lett.* **2007**, *48*, 7099.

(29) Pansare, S. V.; Kulkarni, K. G. *RSC Advances* **2013**, *3*, 19127.

(30) Adsool, V. A.; Pansare, S. V. *Org. Biomol. Chem.* **2008**, *6*, 2011.

(31) Bhaskar Kanth, J. V.; Periasamy, M. *Tetrahedron* **1993**, *49*, 5127.

(32) Huszthy, P.; Oue, M.; Bradshaw, J. S.; Zhu, C. Y.; Wang, T.; Dalley, N. K.; Curtis, J. C.; Izatt, R. M. *J. Org. Chem.* **1992**, *57*, 5383.

(33) Adsool, V. A. *Ph D Thesis* **2009**, Chapter 5.

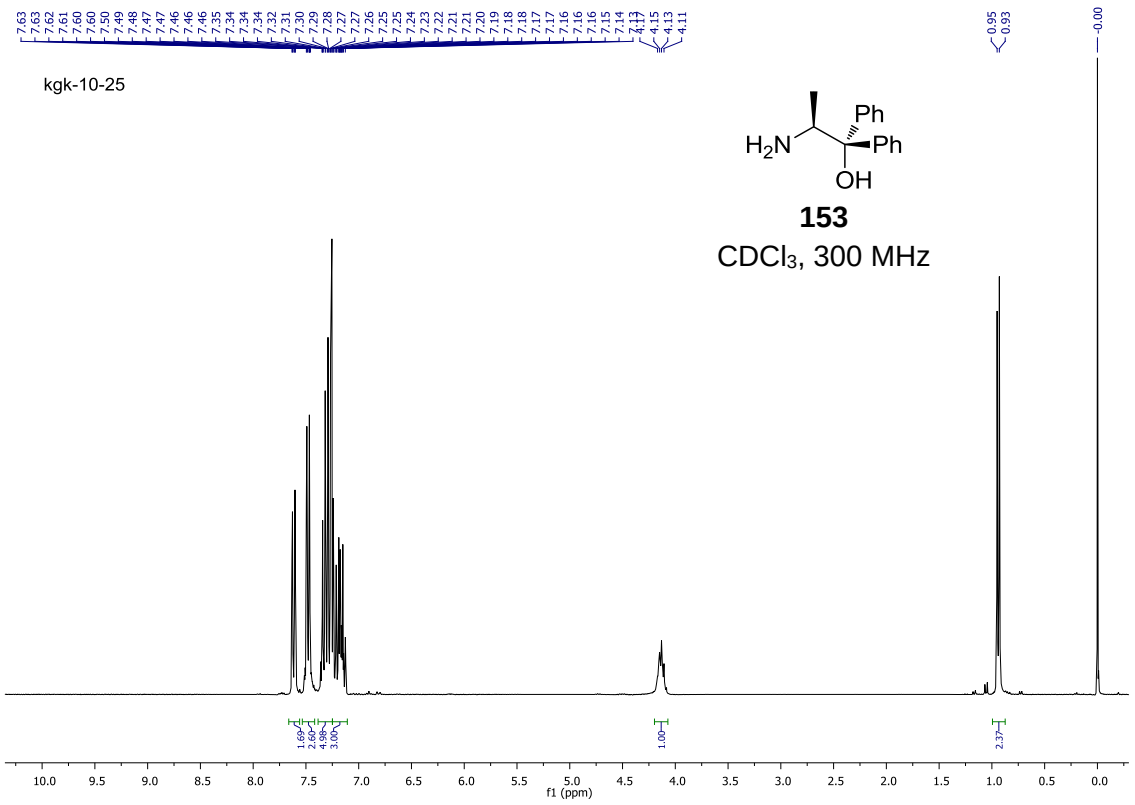
(34) Coote, S. J.; Davies, S. G.; Middlemiss, D.; Naylor, A. *J. Chem. Soc, Perkin Trans. 1* **1989**, 2223.

(35) (a) Froussios, C.; Kolovos, M. *Synthesis* **1987**, *1987*, 1106; (b) Kolovos, M.; Froussios, C. *Tetrahedron Lett.* **1984**, *25*, 3909.

(36) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis. 4th Ed*; John Wiley and Sons, Inc., 2007.

(37) Aratani, T. H., M.; Yoneyoshi, Y.; Suzukamo, G. *Eur. Pat. Appl* **1983**, *EP 75868 A2 19830406.* .

### 3.6 Selected 1H and 13C NMR spectra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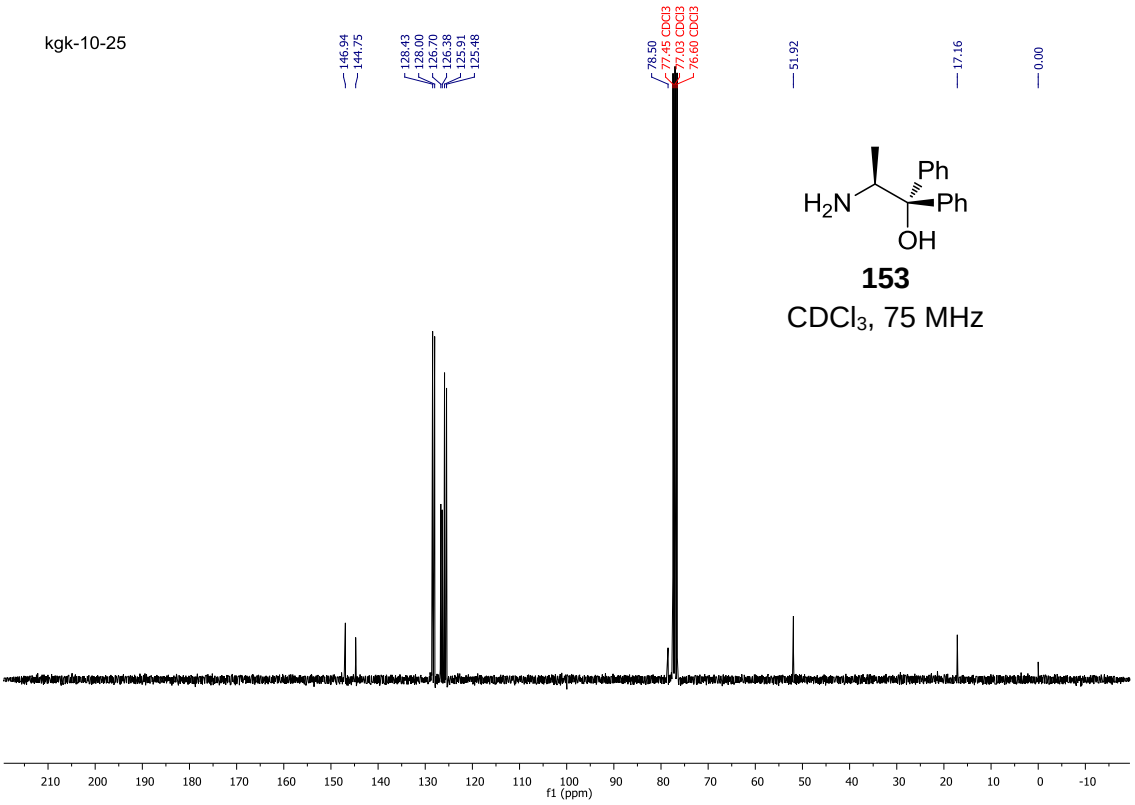
f1 (ppm)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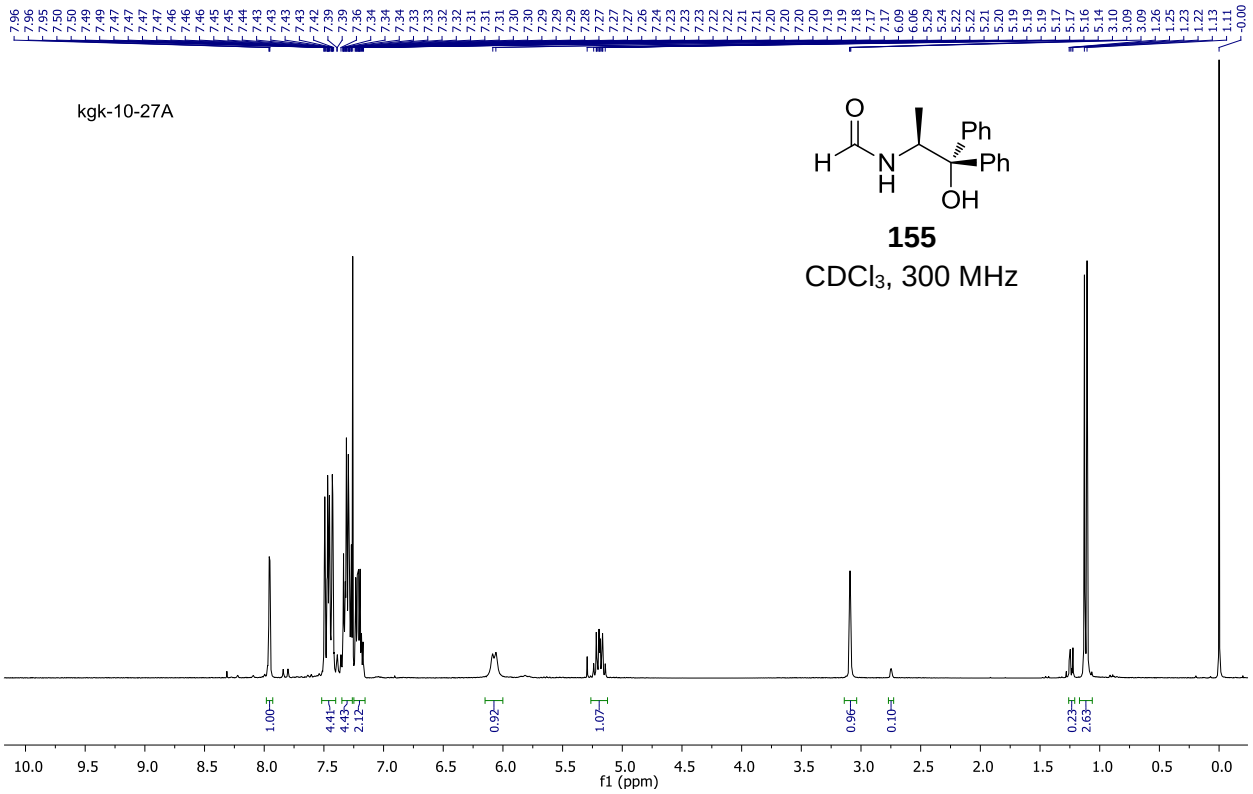
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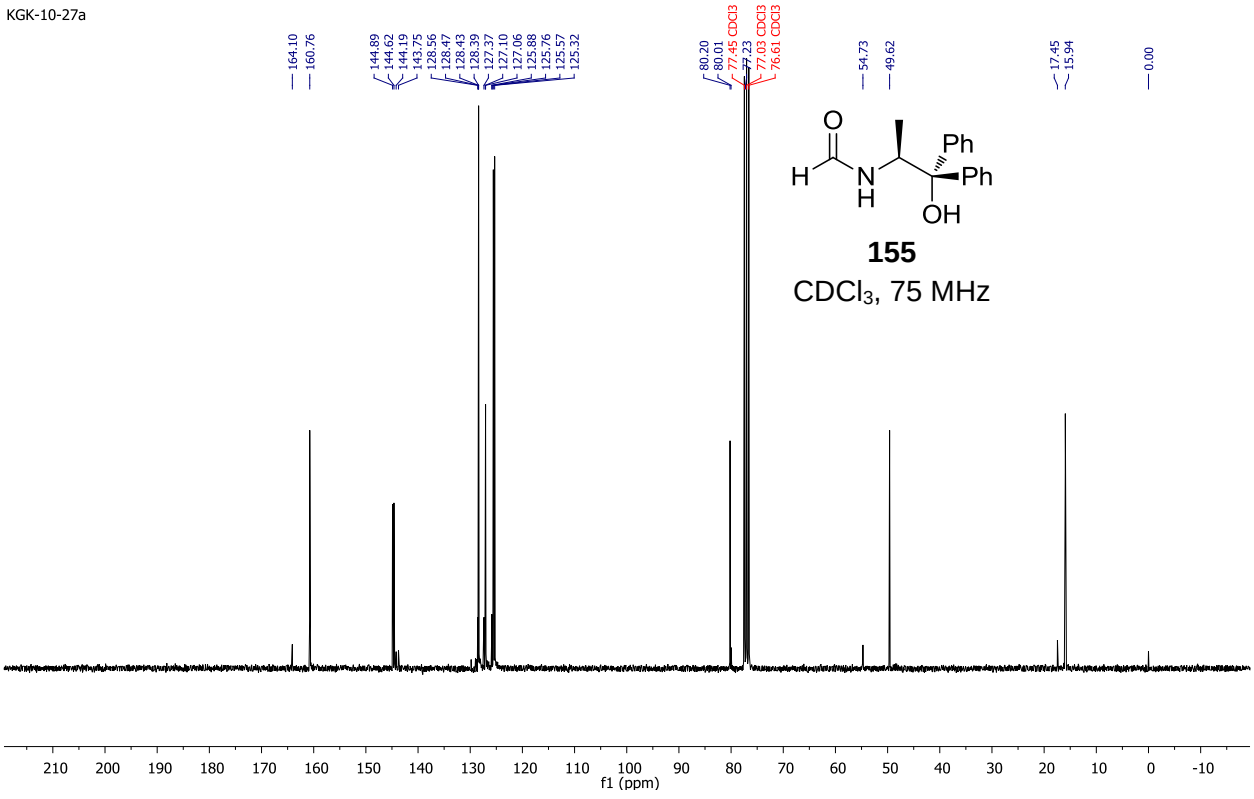
f1 (ppm)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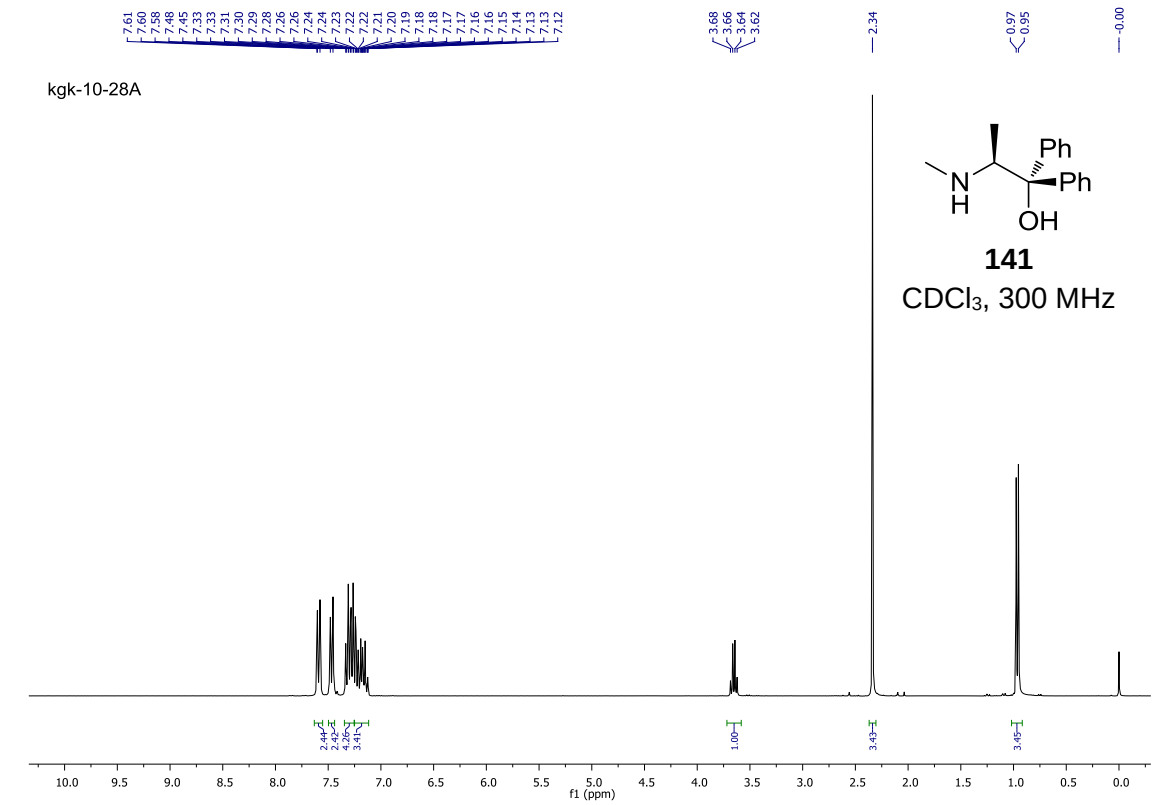
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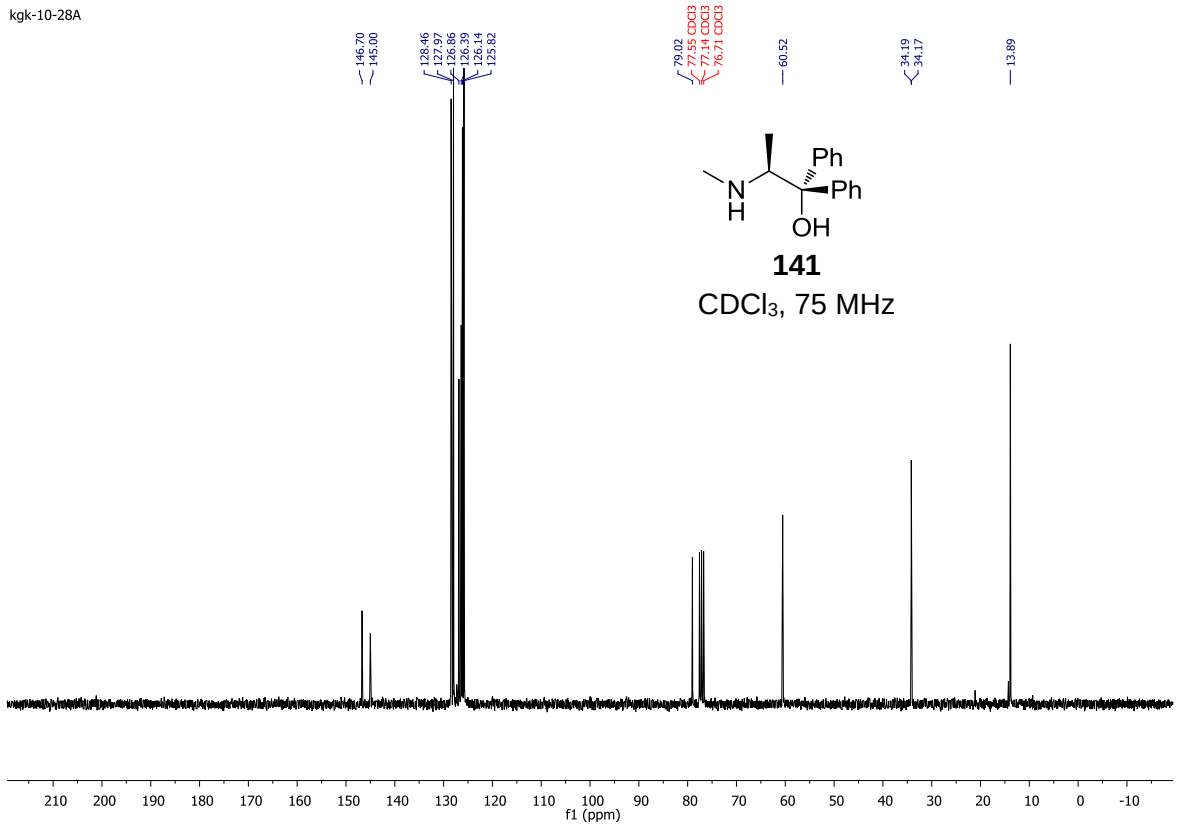
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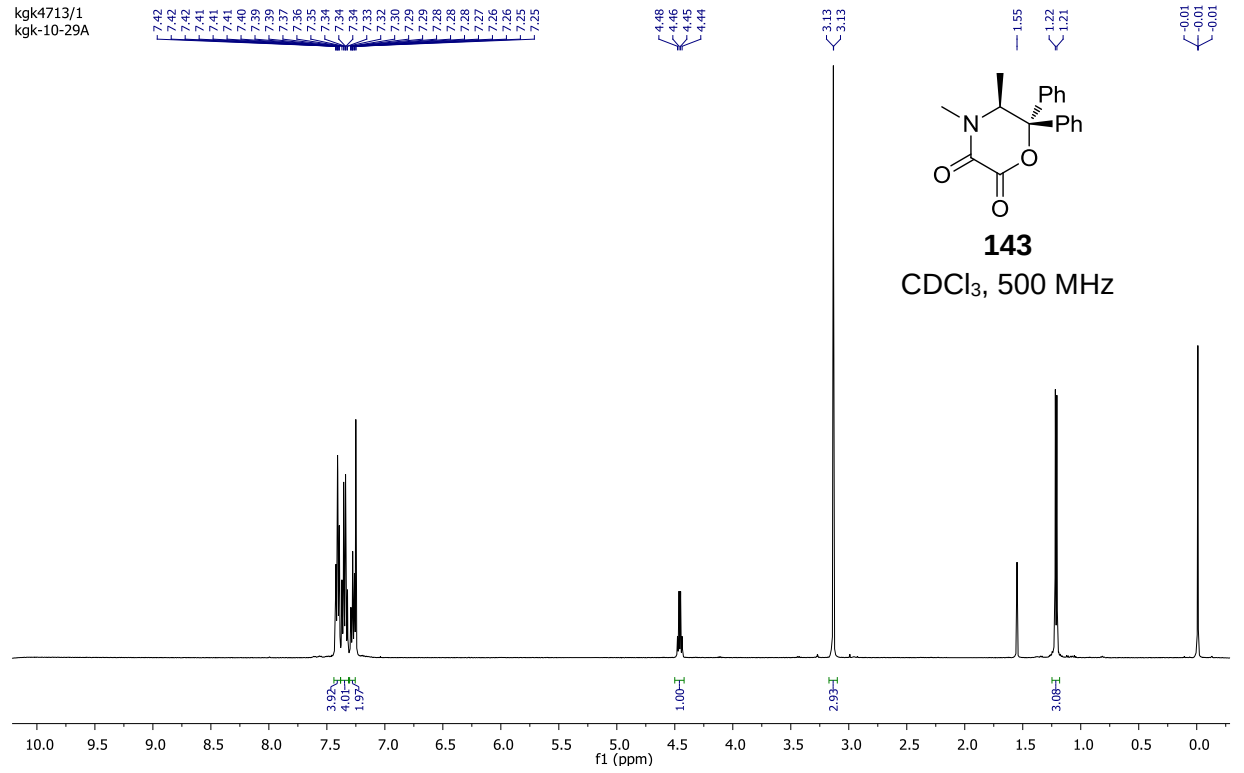
f1 (ppm)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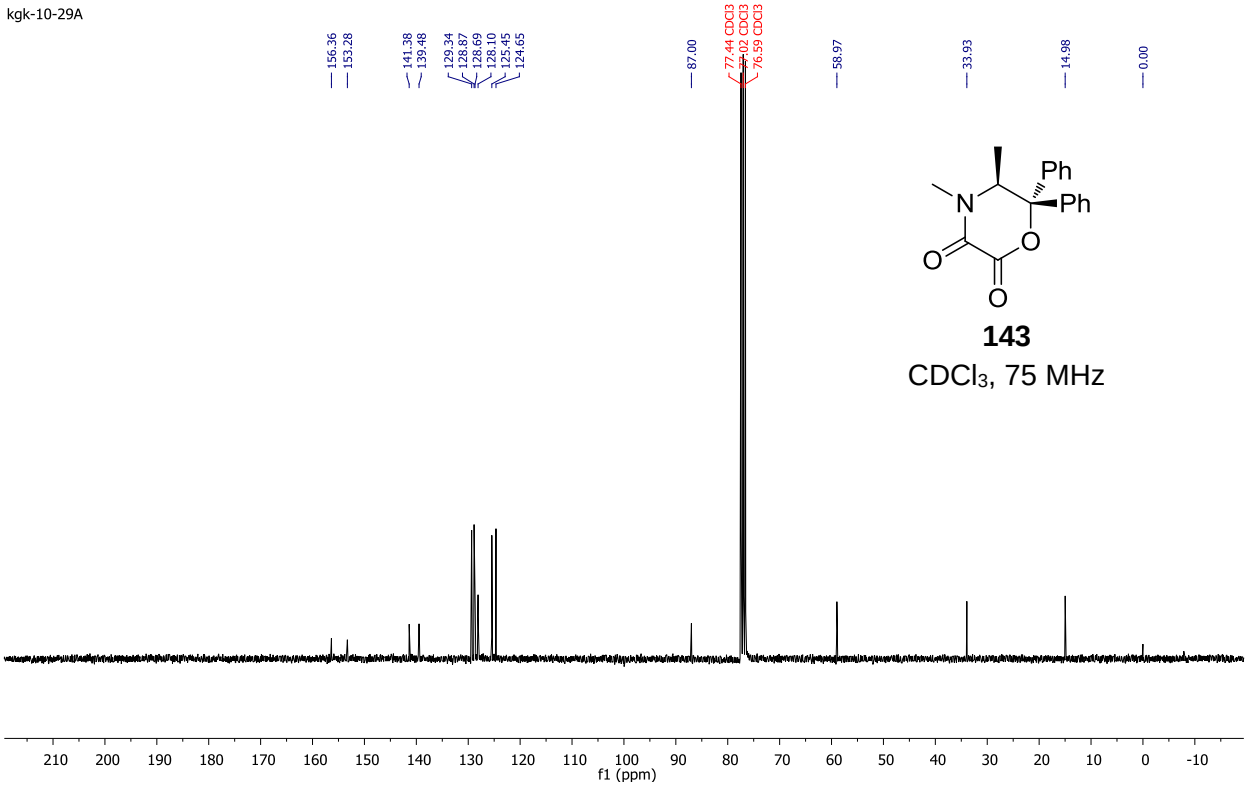
f1 (ppm)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O
O
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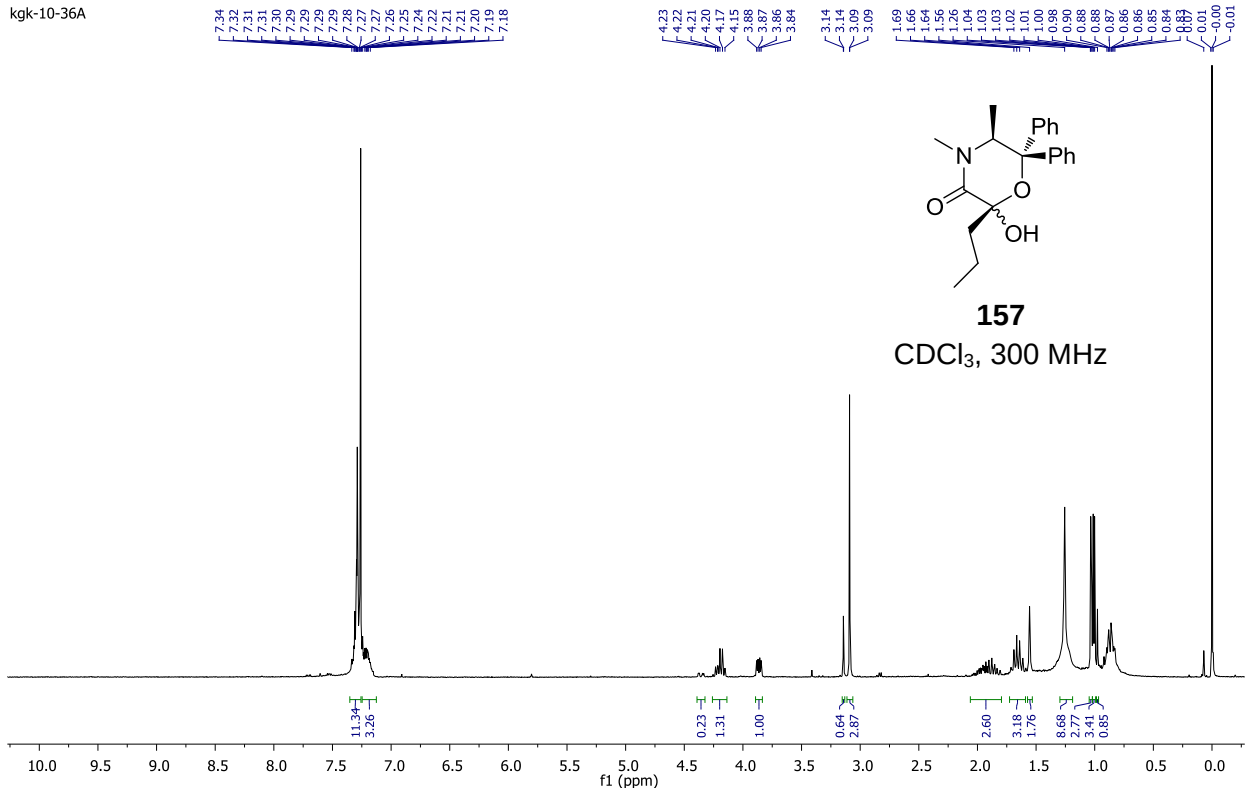
f1 (ppm)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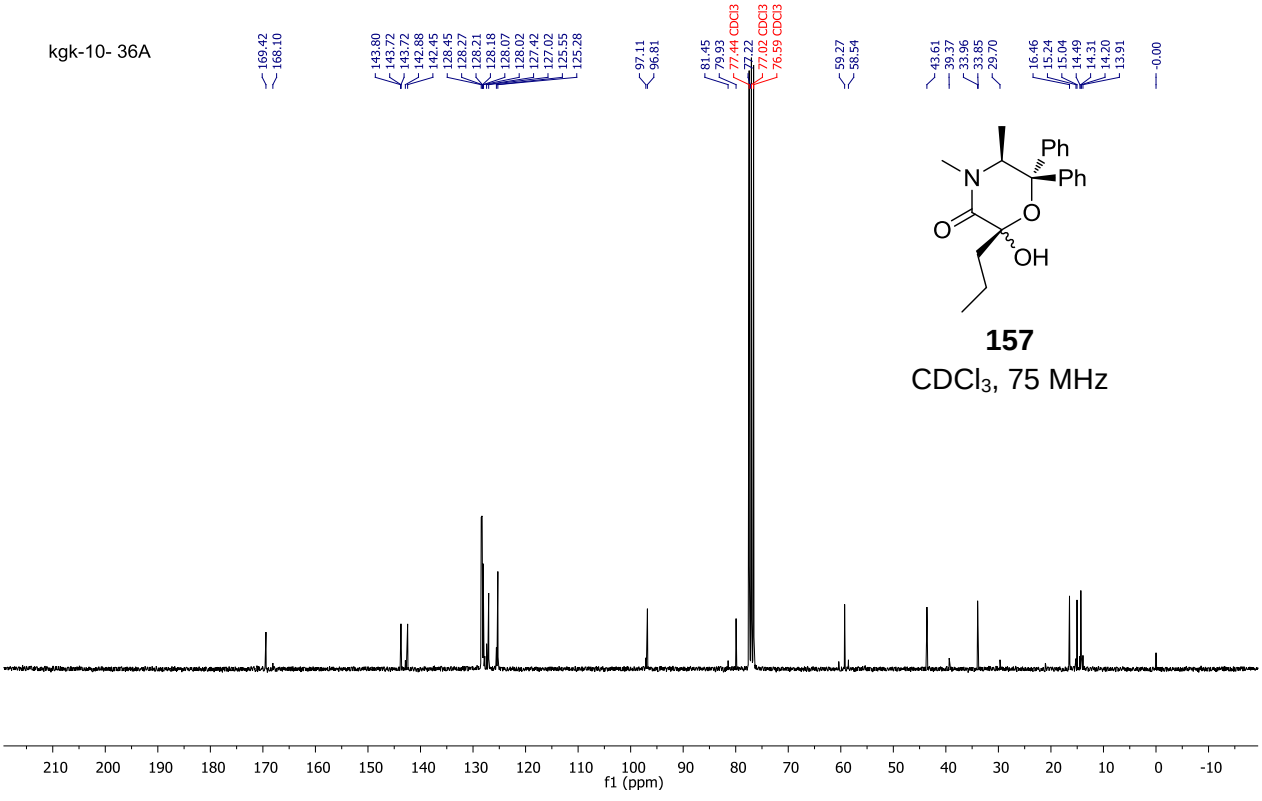
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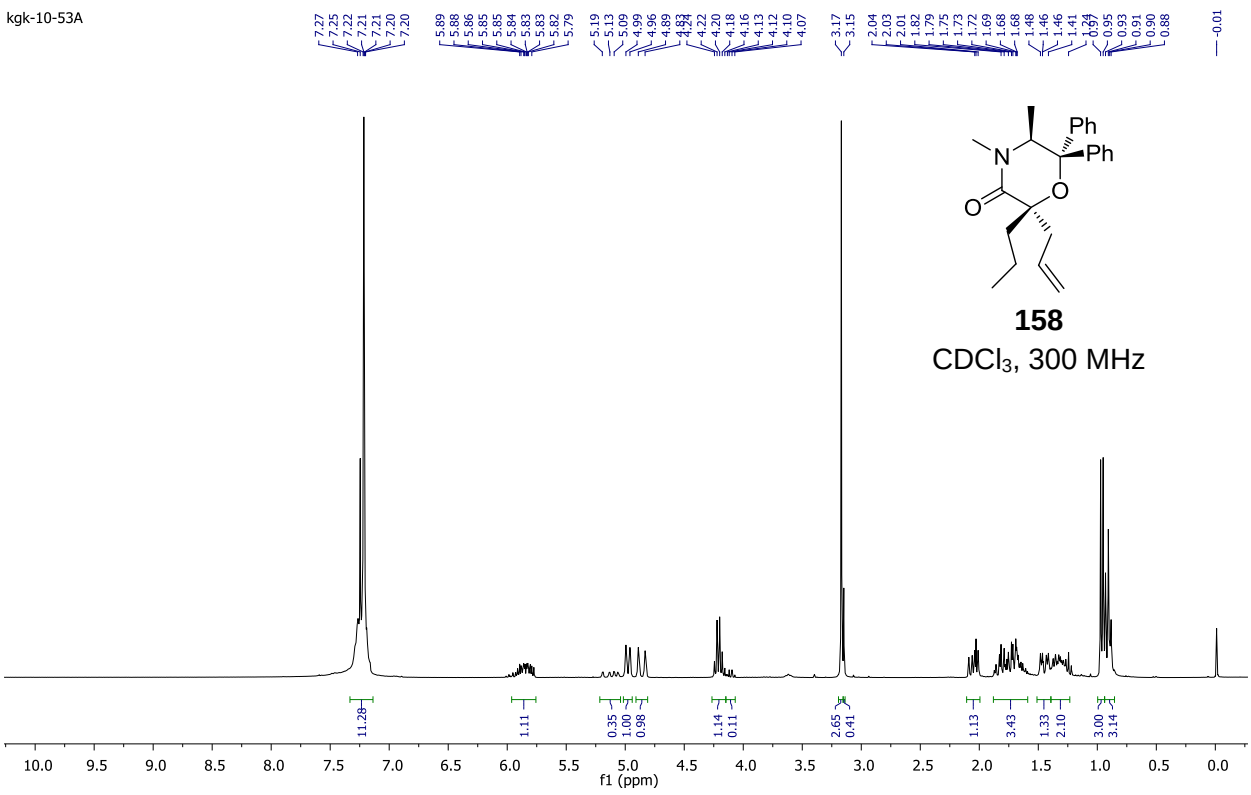
f1 (ppm)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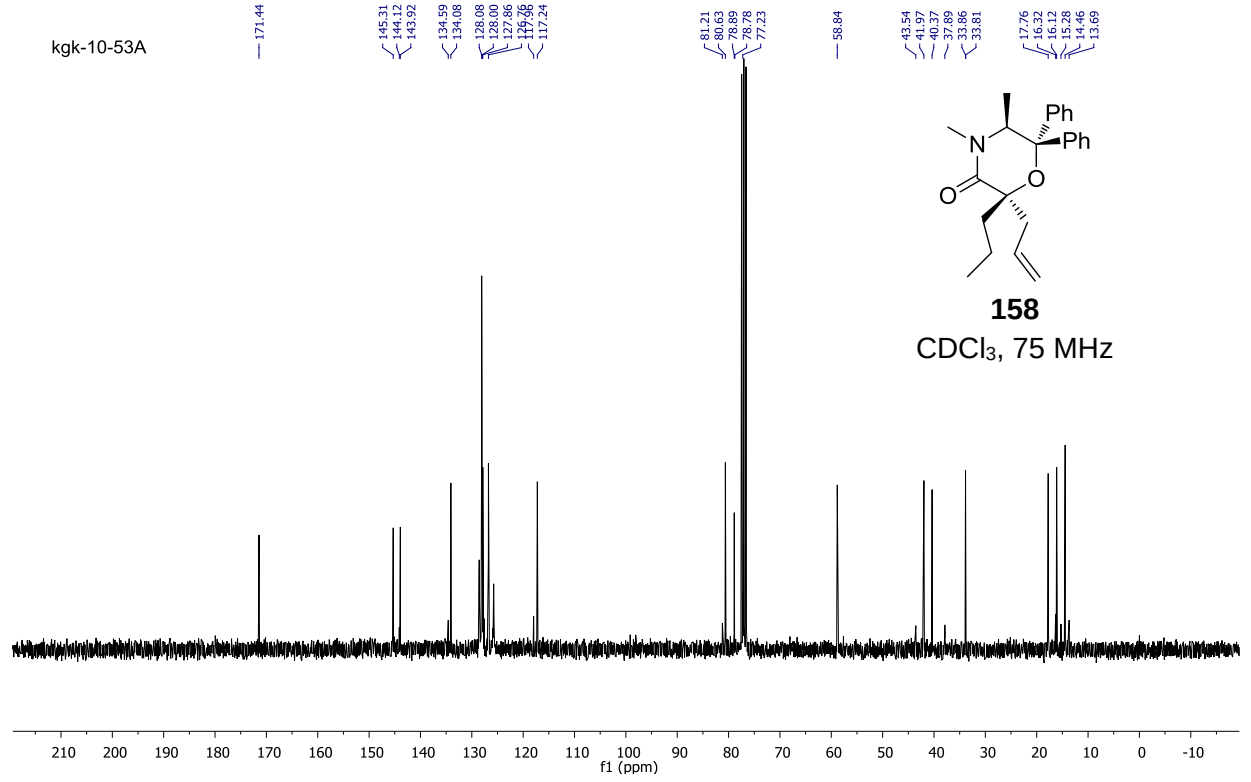
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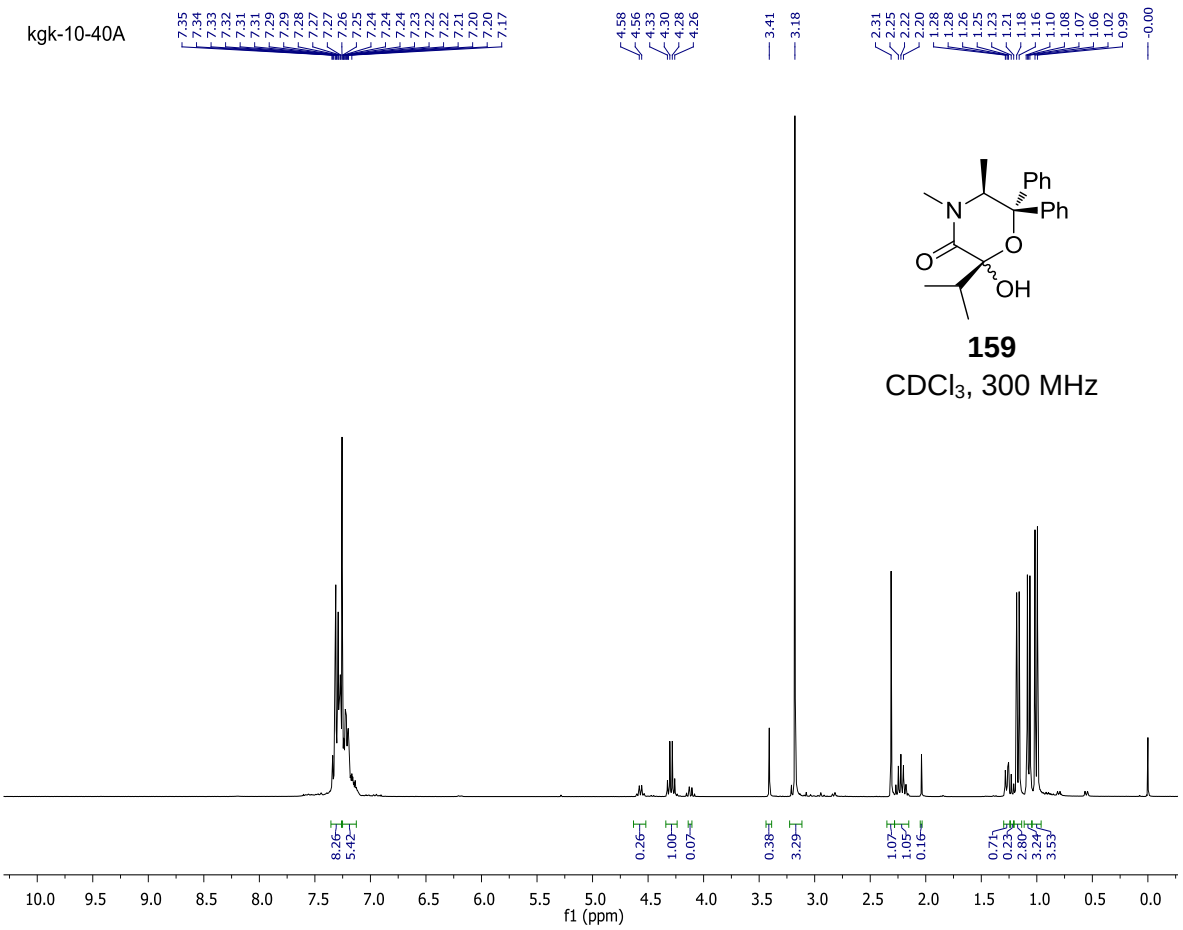
f1 (ppm)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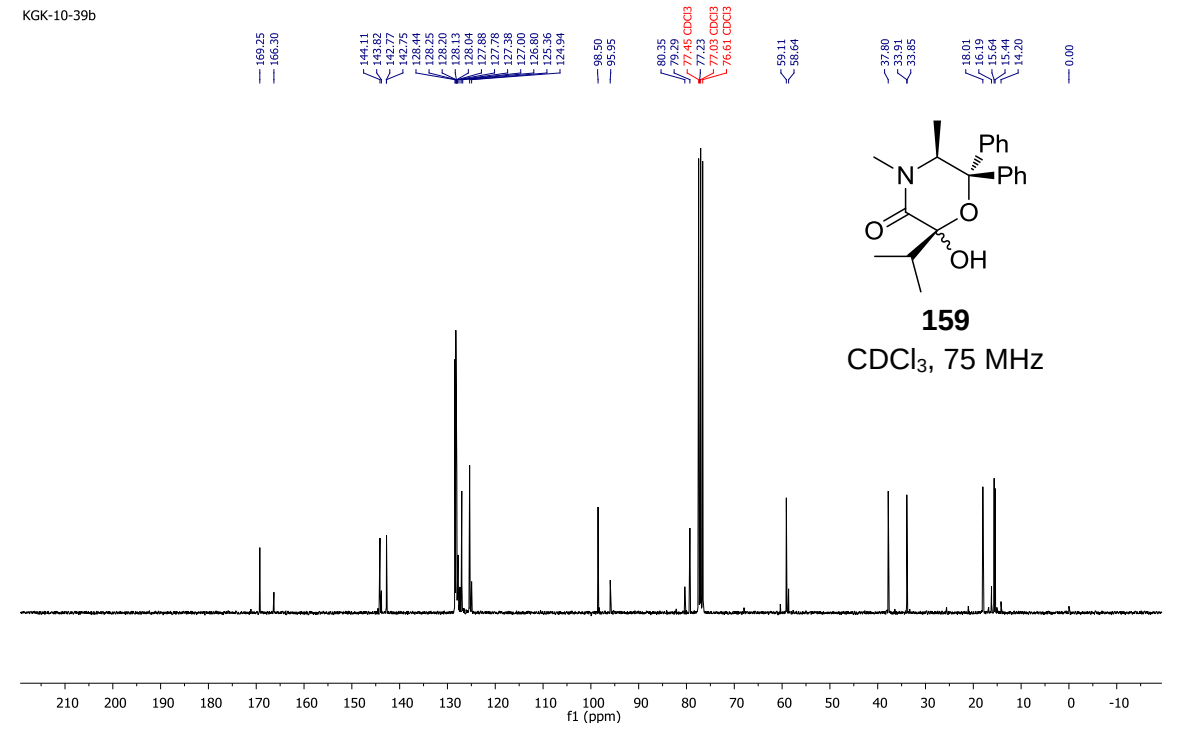
7.35 7.34 7.33 7.32 7.31 7.31 7.29 7.29 7.28 7.27 7.27 7.26 7.25 7.24 7.24 7.23 7.22 7.22 7.21 7.20 7.17
4.58 4.56 4.33 4.30 4.28 4.26
3.41
3.18
2.31 2.25 2.22 2.20 1.28 1.28 1.26 1.25 1.23 1.21 1.18 1.16 1.10 1.08 1.07 1.06 1.02 0.99
-0.00
Ph
Ph
N
O
O
OH
159
CDCl3, 300 MHz
8.26 5.42 0.26 1.00 0.07 0.38 3.29 1.07 1.05 0.16 0.71 0.23 2.80 3.24 3.53
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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169.25 166.30
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98.50 95.95
80.35 79.29 77.45 CDCl3 77.23 77.03 CDCl3 76.61 CDCl3
59.11 58.64
37.80 33.91 33.85
18.01 16.59 15.64 15.44 14.20
0.00
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Ph
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O
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159
CDCl3, 75 MHz
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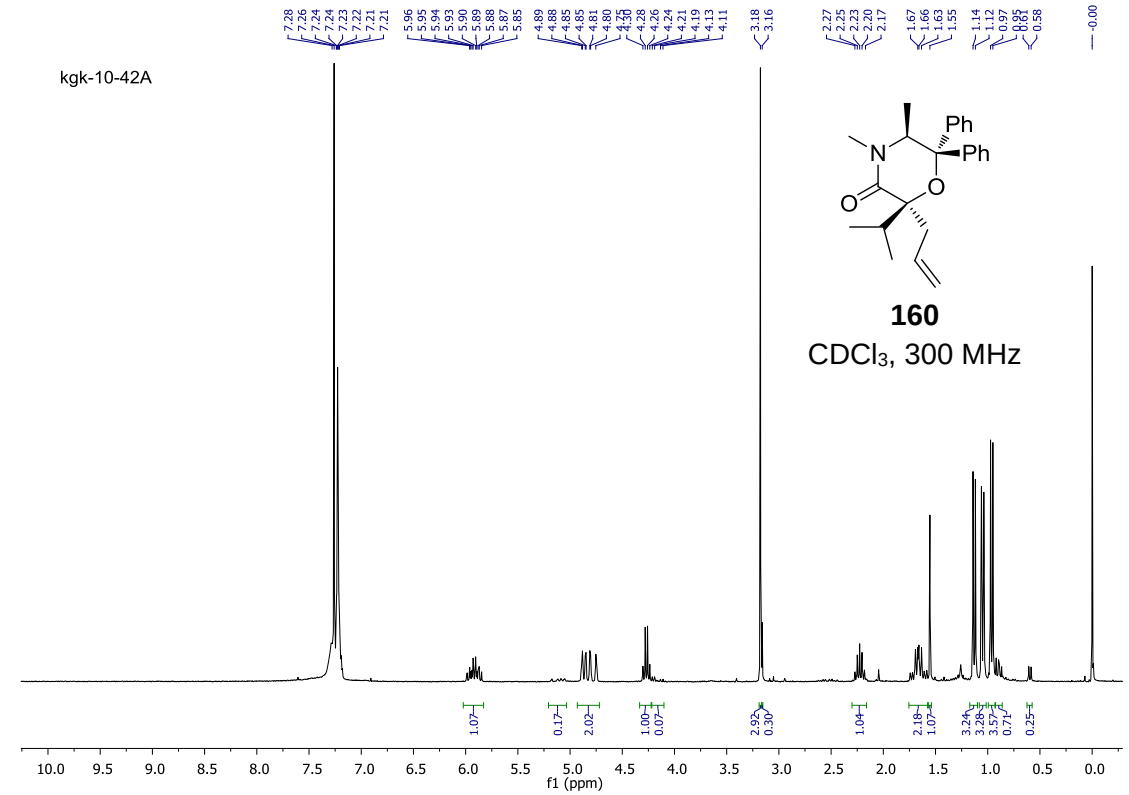
f1 (ppm)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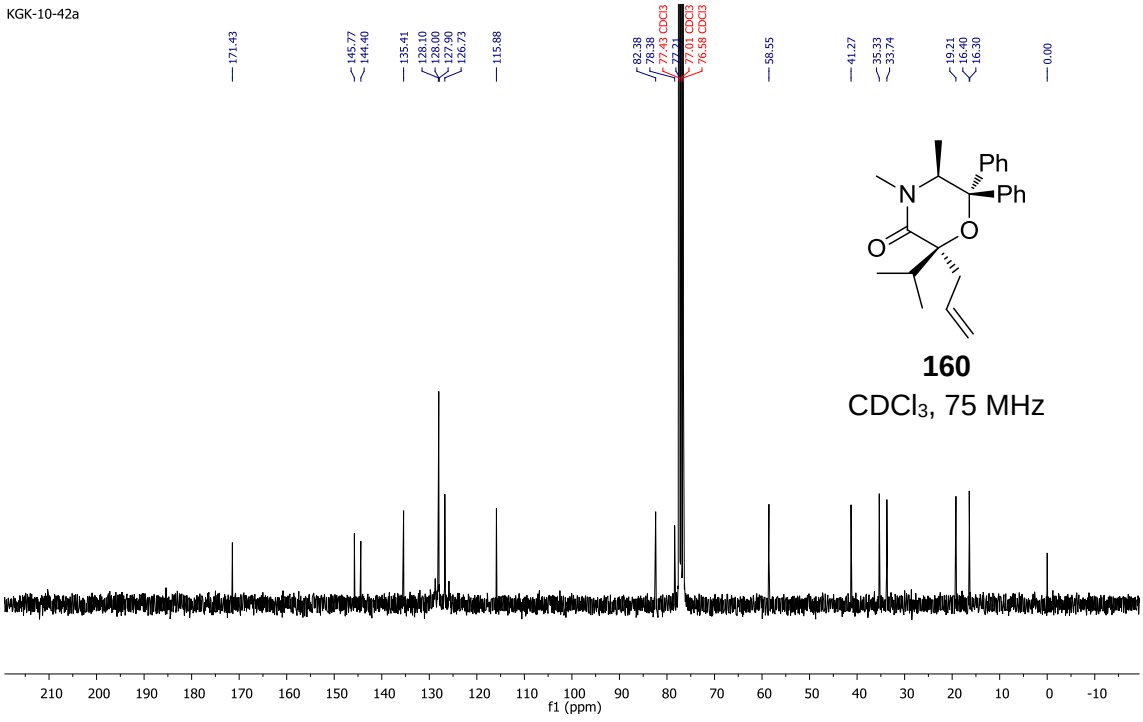
f1 (ppm)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f1 (ppm)

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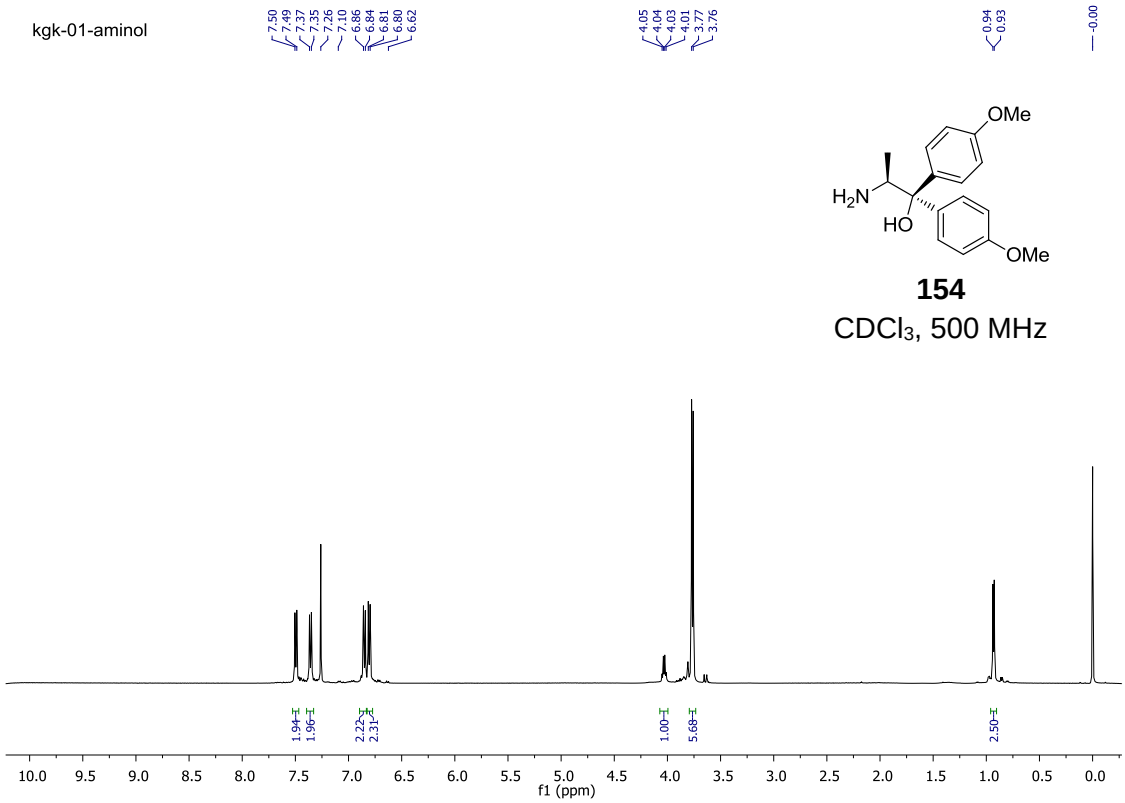


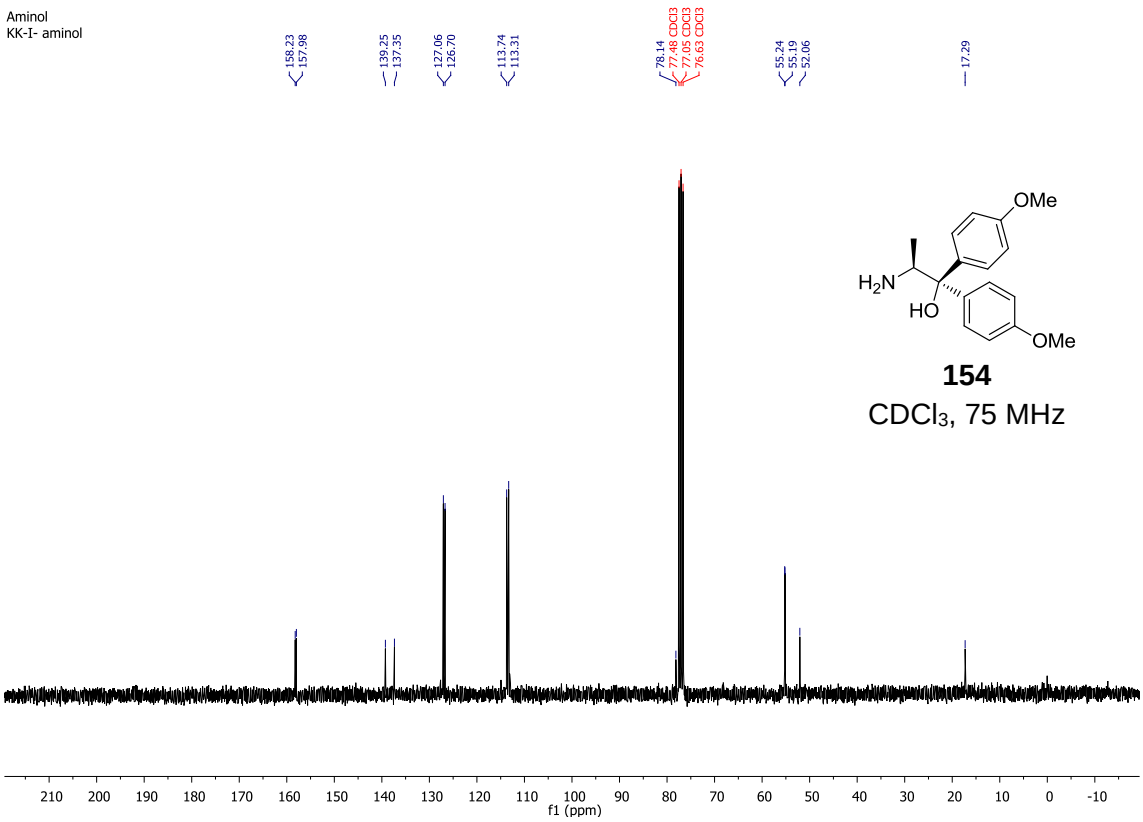




**154**

$CDCl_3$, 500 MHz

Aminol
KK-I- aminol







**154**

$CDCl_3$, 75 MHz

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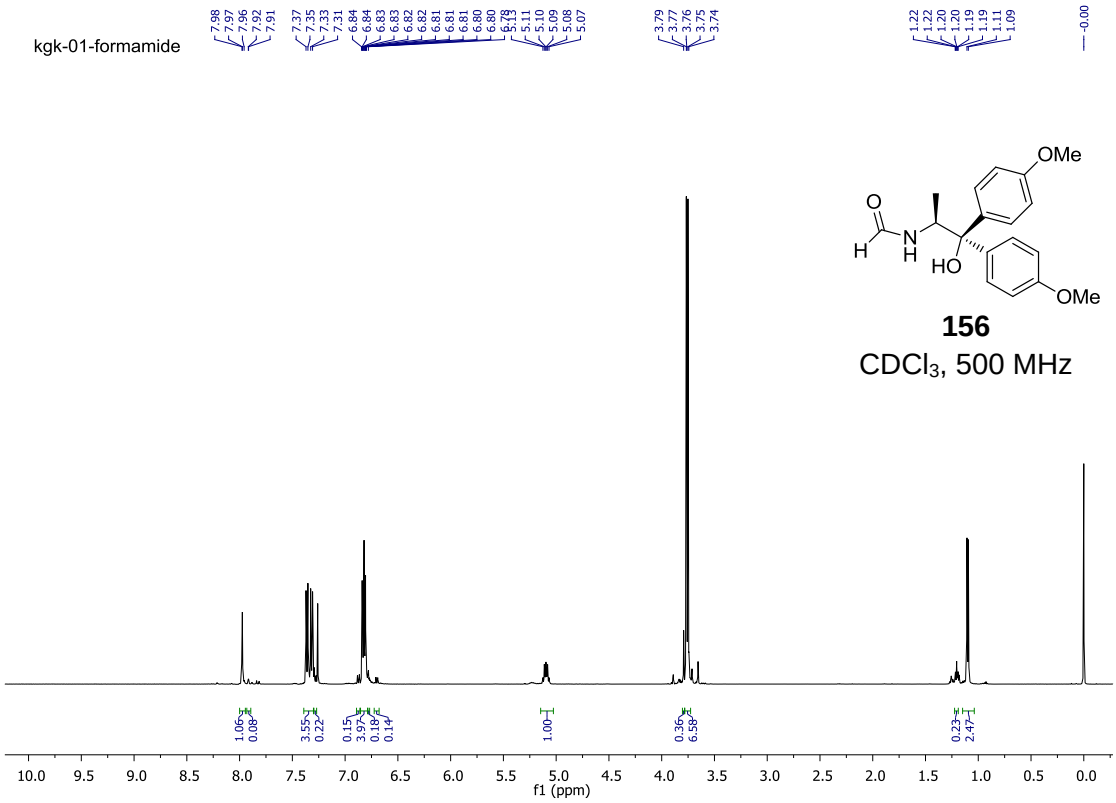





**156**

$CDCl_3$, 500 MHz

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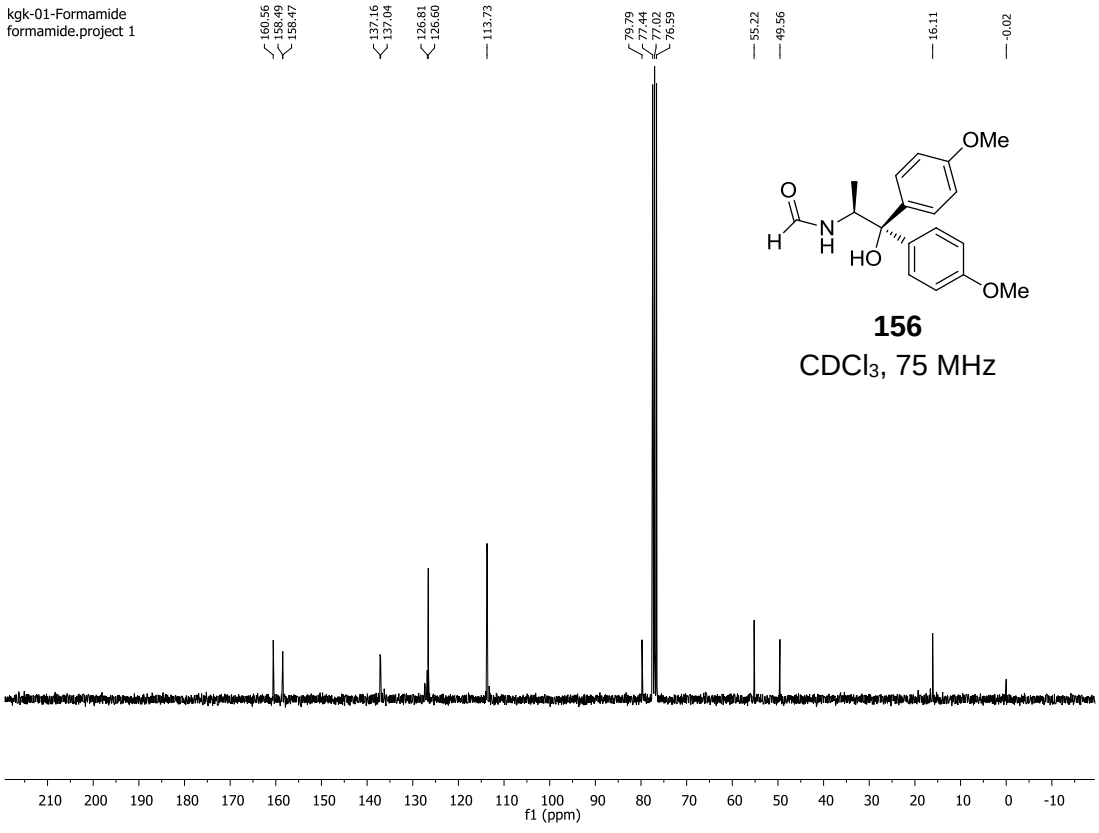
formamide.project 1

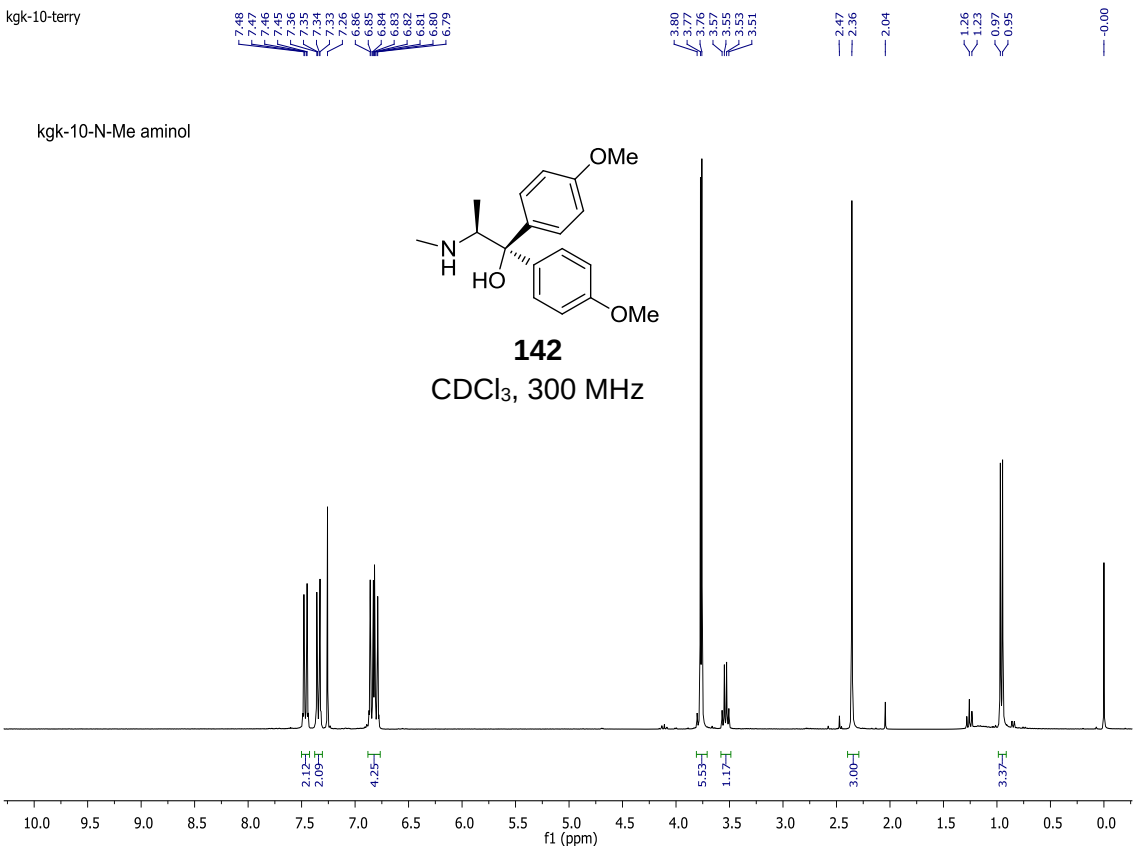






**156**

$CDCl_3$, 75 MHz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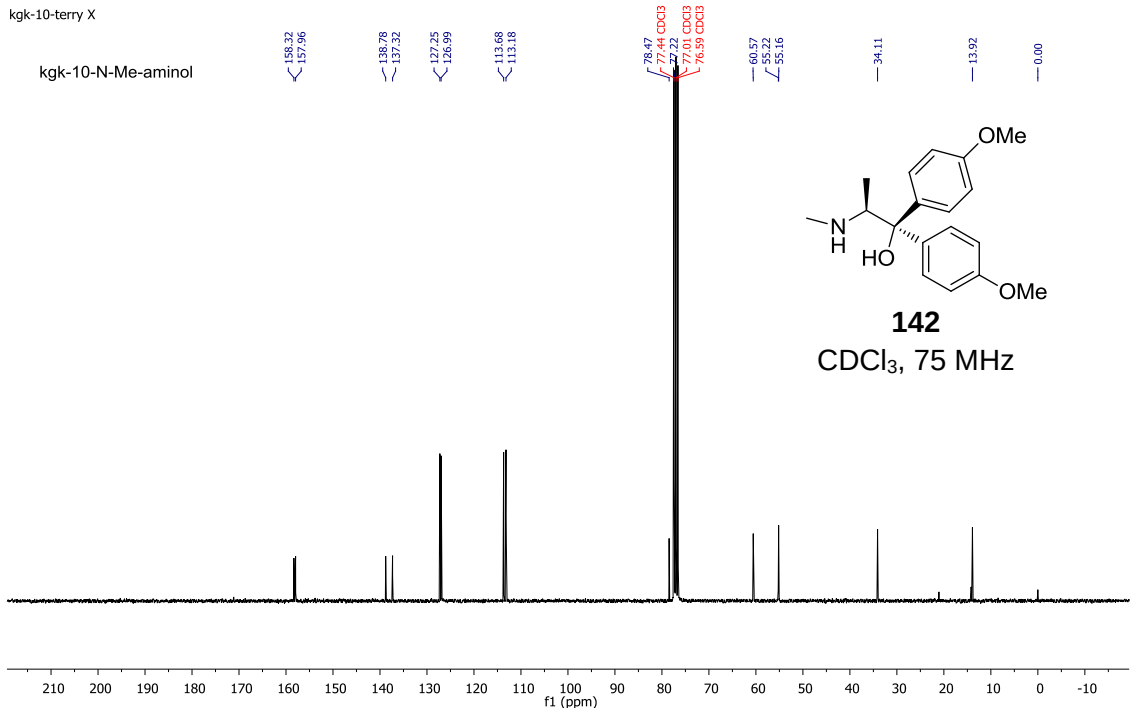
kgk-10-N-Me aminol
OMe
N
H
HO
OMe
142
CDCl3, 300 MHz
f1 (ppm)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OMe
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H
HO
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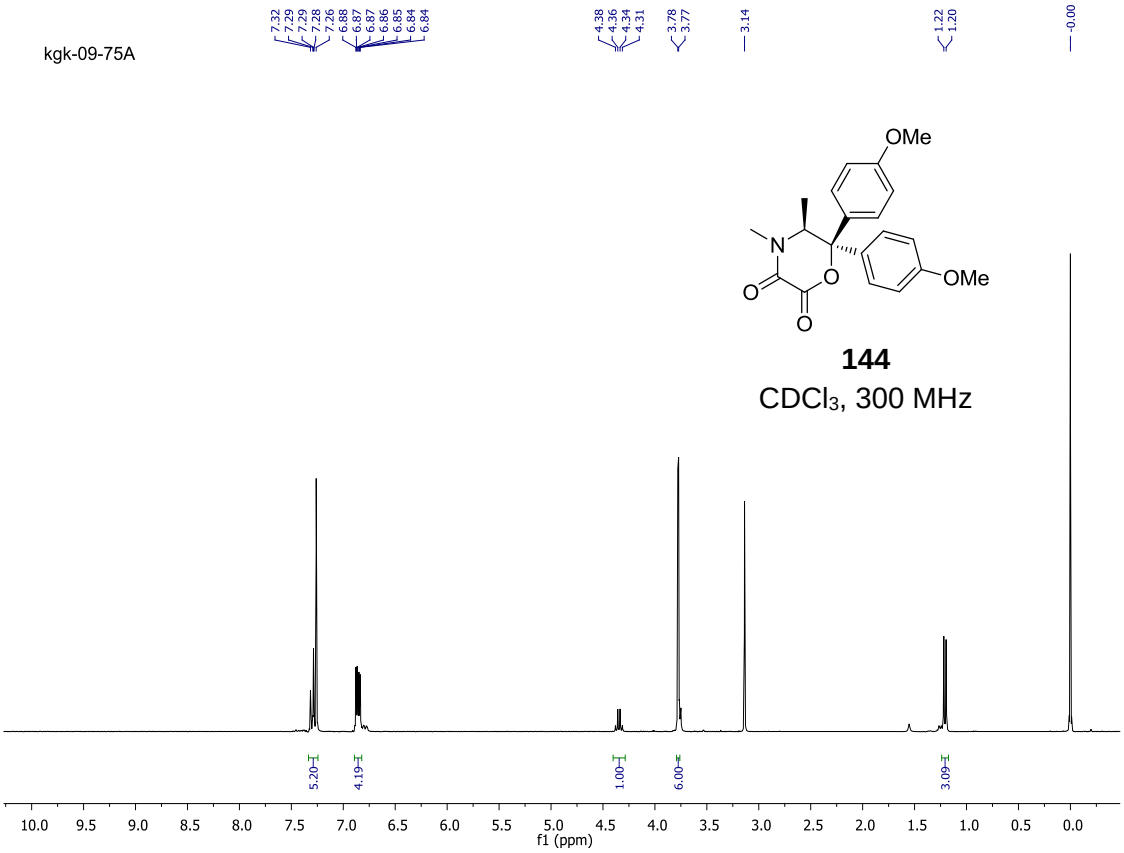
CDCl3, 75 MHz
f1 (ppm)

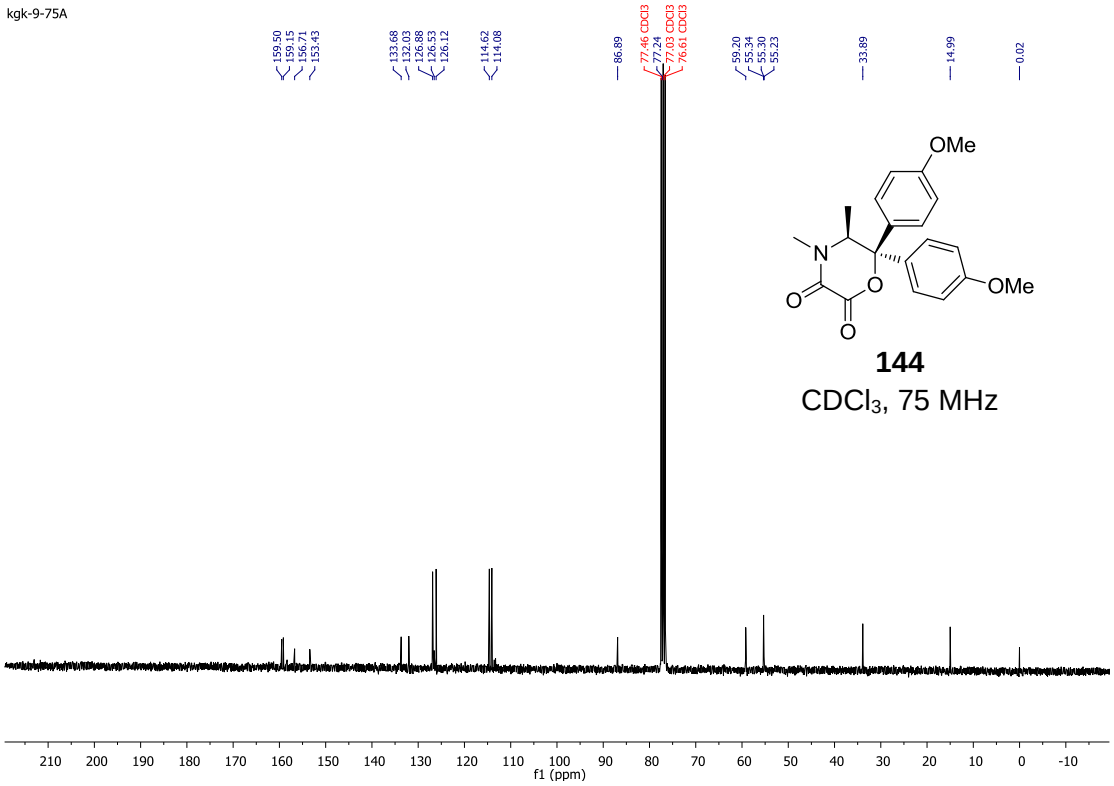
kgk-09-75A




**144**

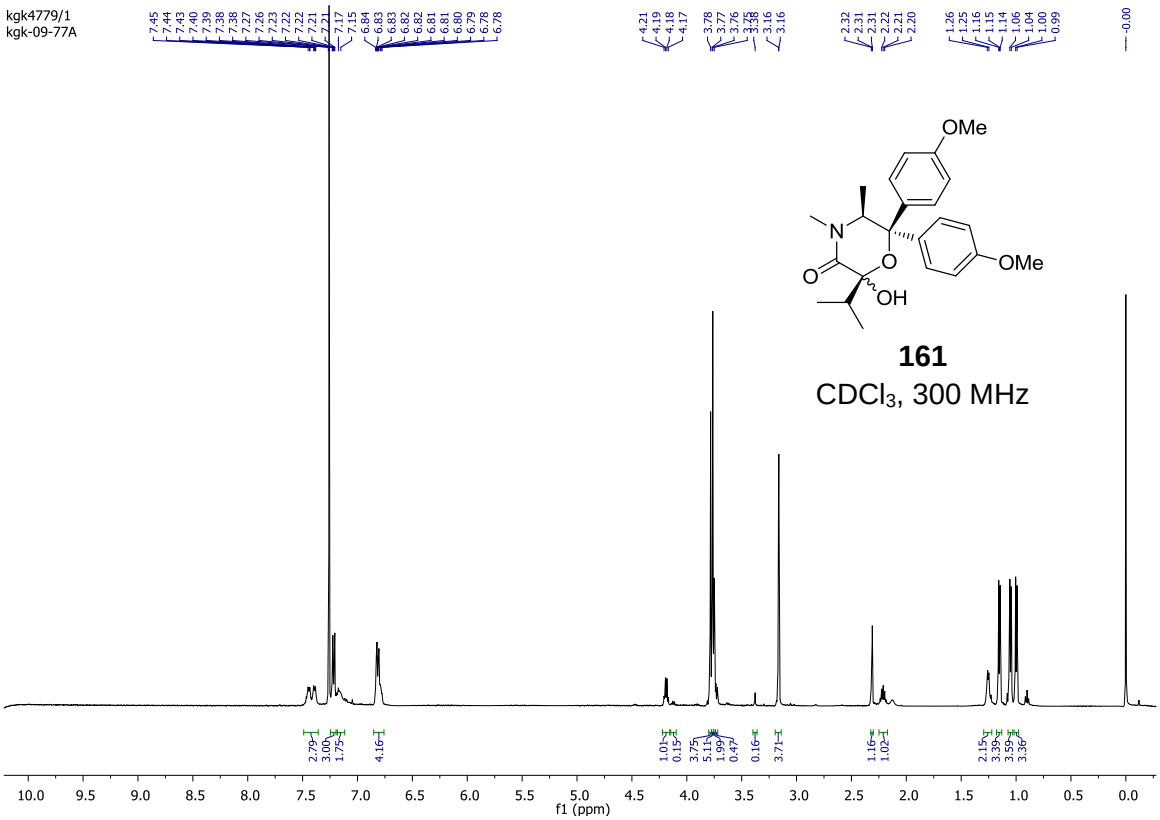
$CDCl_3$, 300 MHz

kgk-9-75A




**144**

$CDCl_3$, 75 MHz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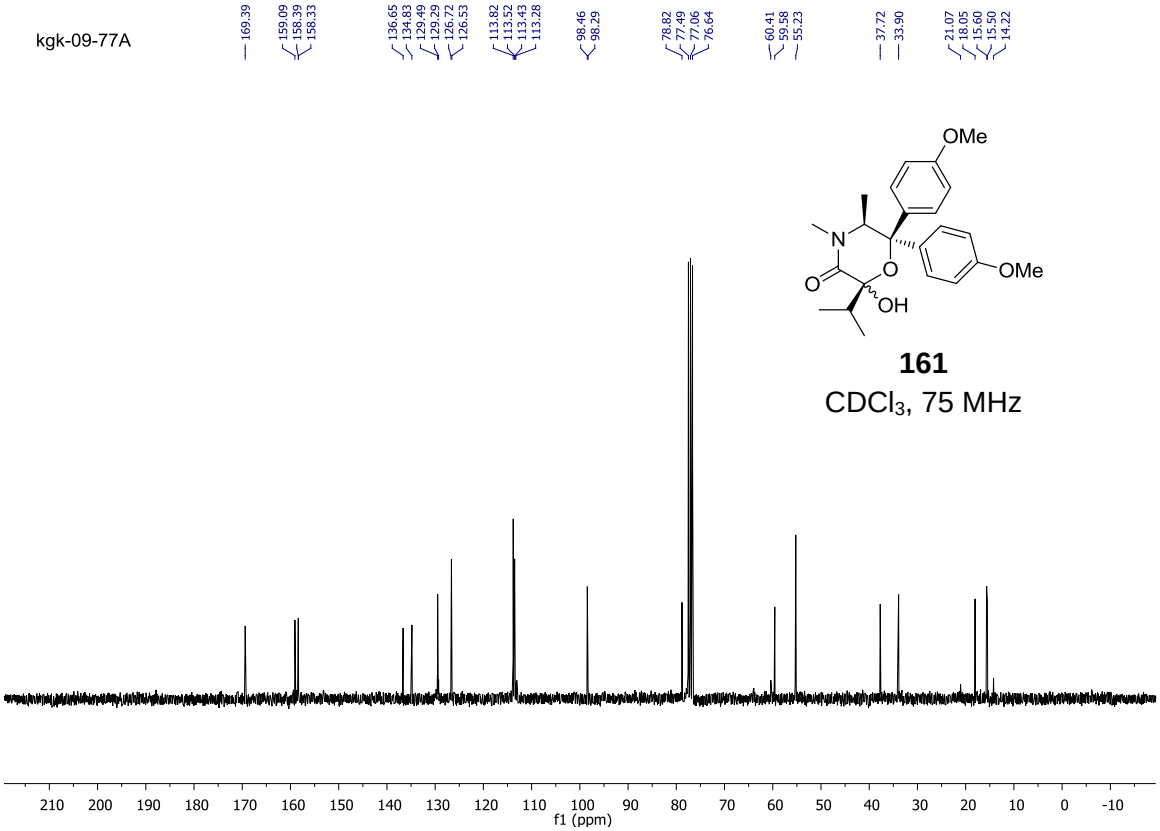
OMe
OH
N
O
O
161
CDCl3, 300 MHz
f1 (ppm)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O
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161
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f1 (ppm)

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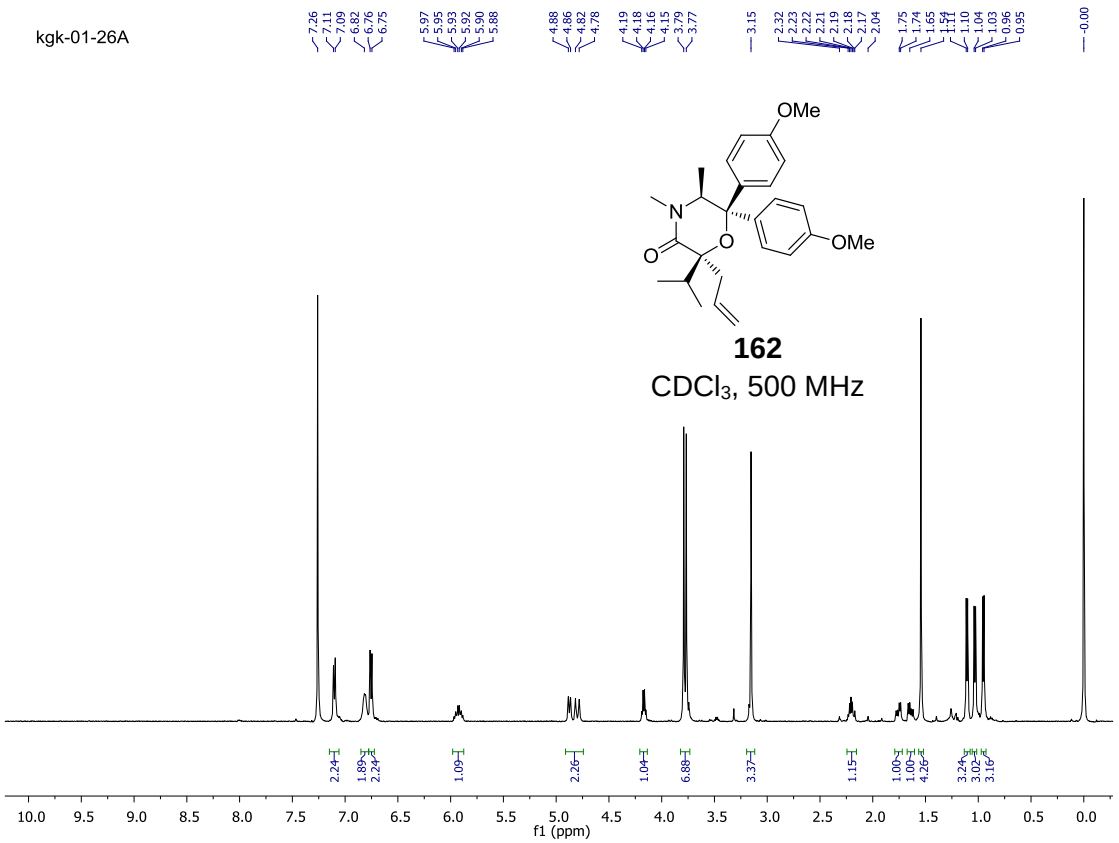


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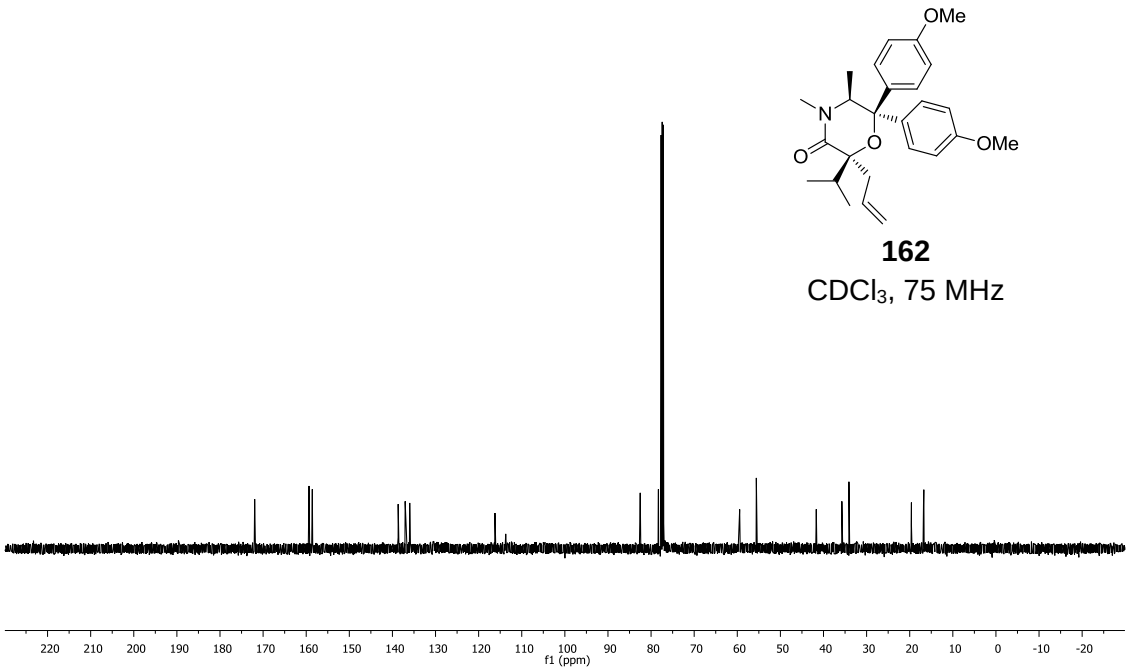

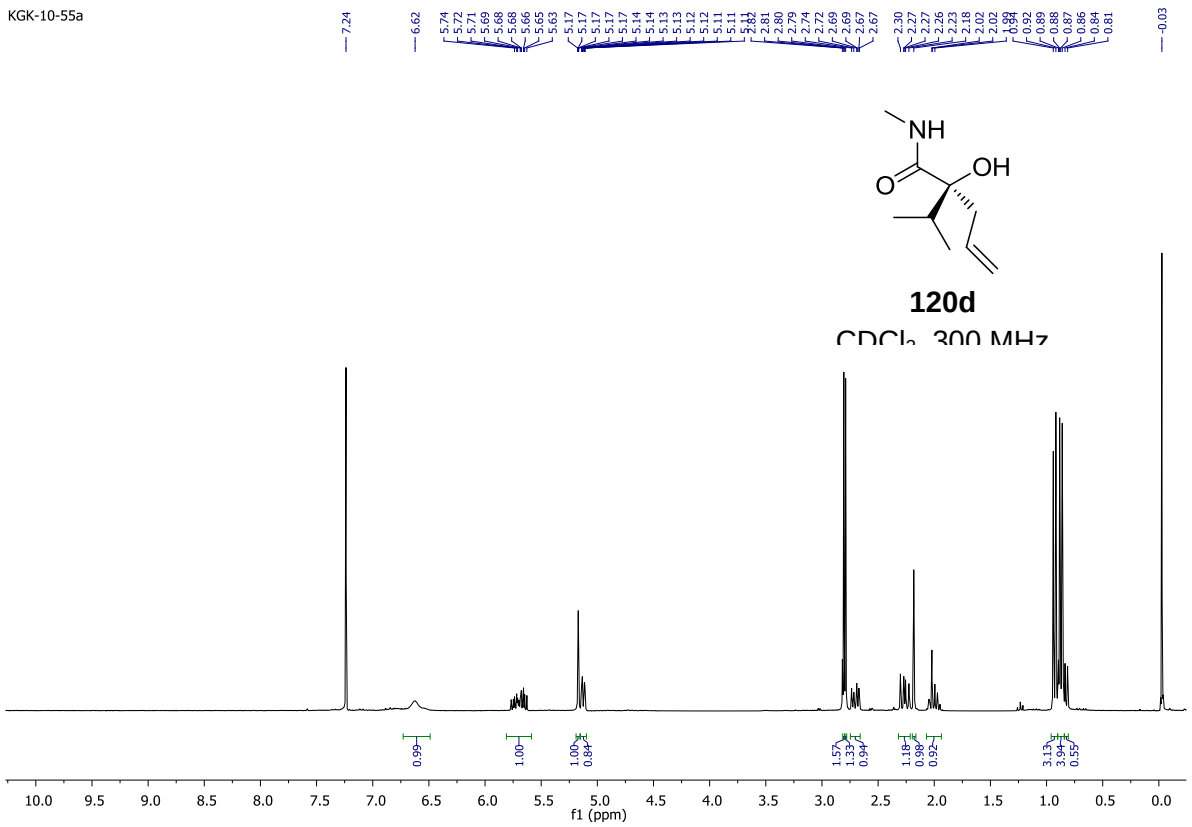
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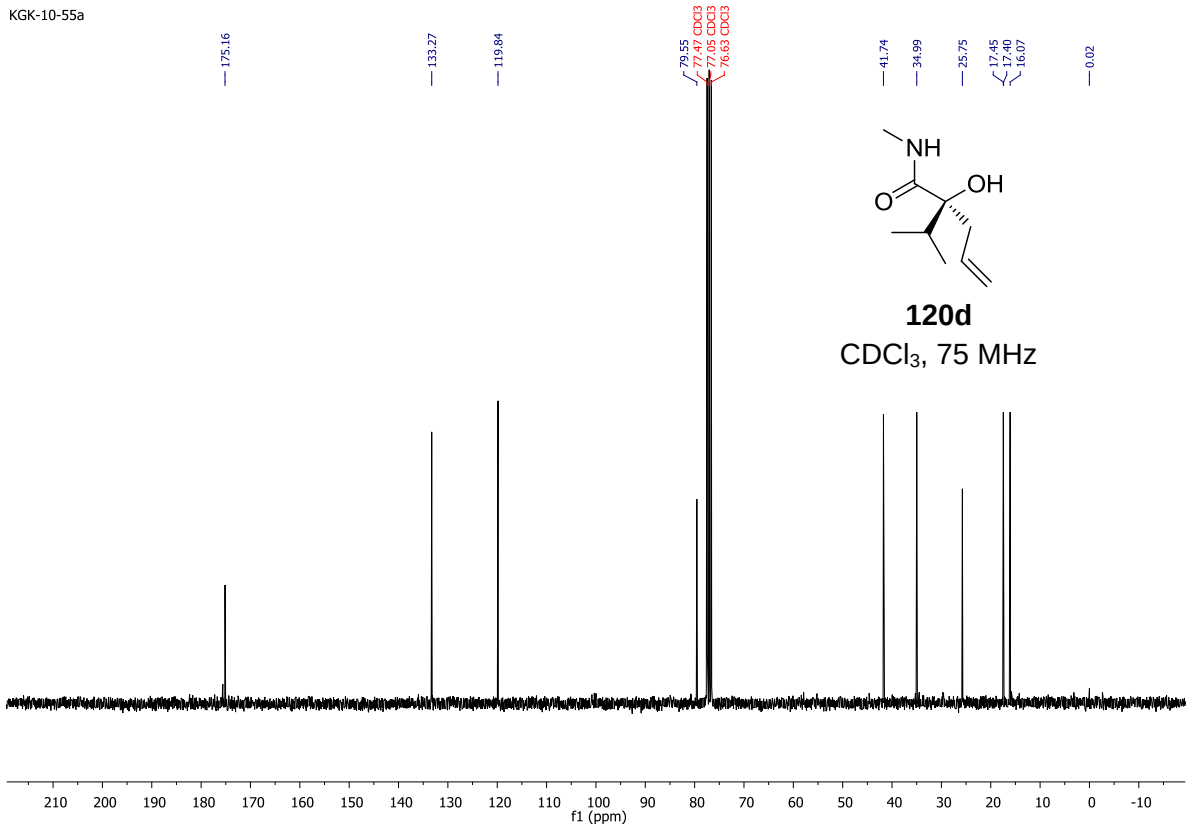
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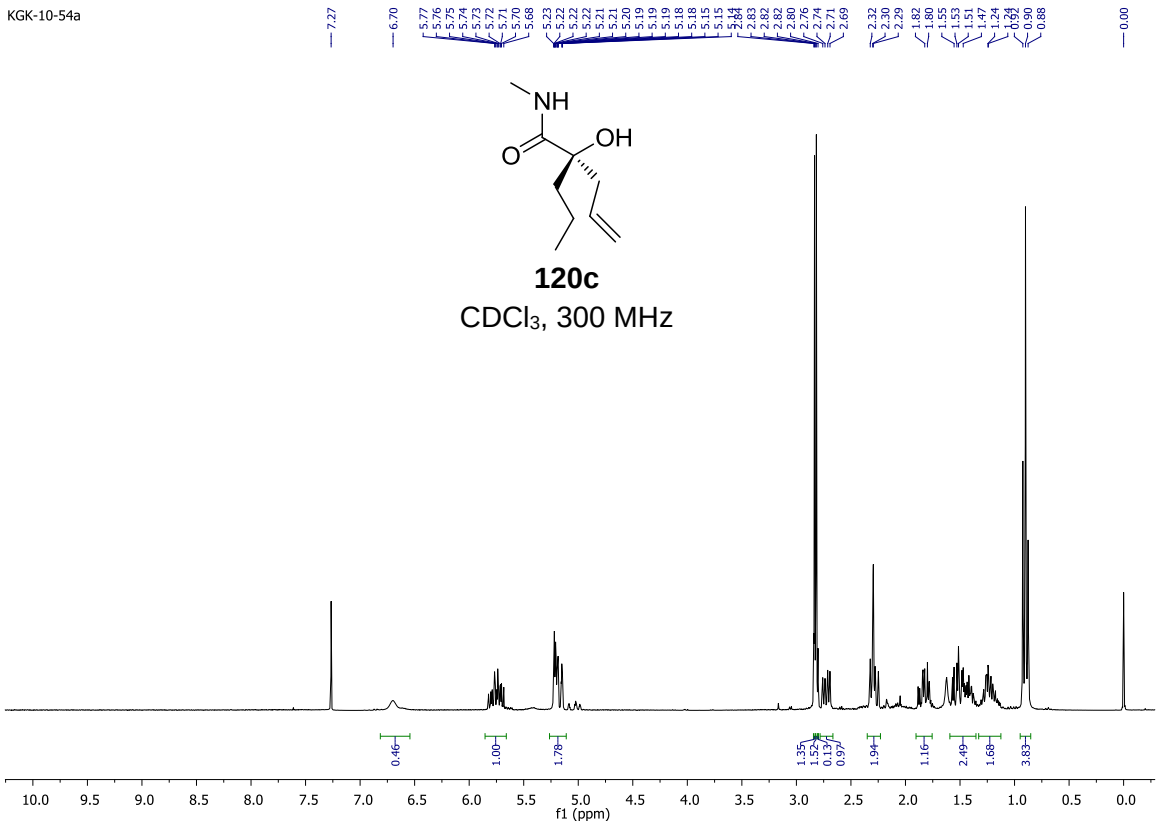
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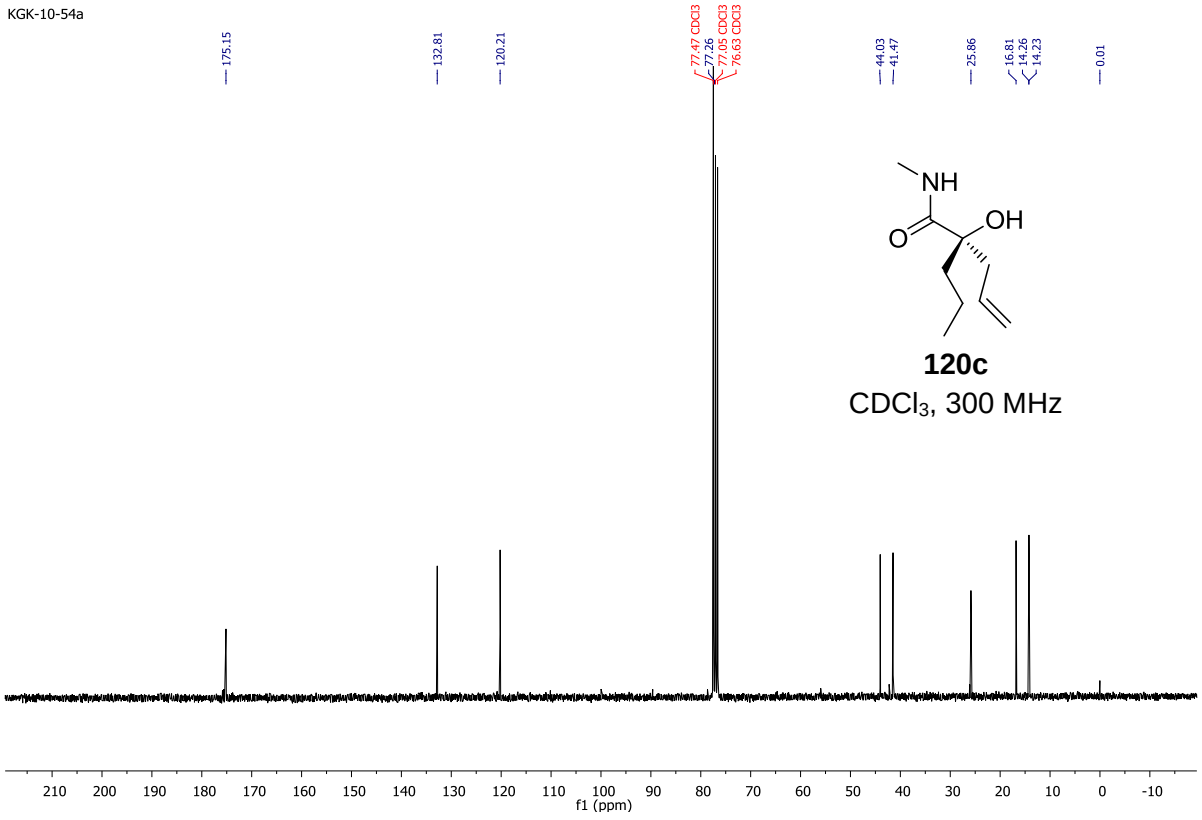
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O
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120c
CDCl3, 300 MHz
f1 (ppm)

# Chapter 4

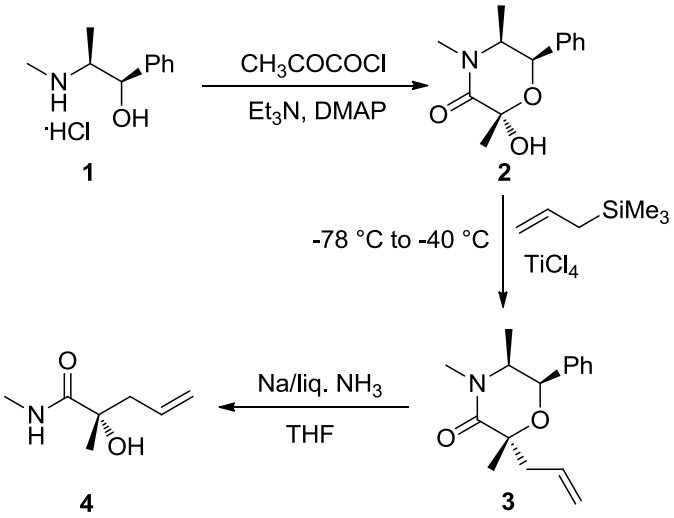
# Conclusions

## 4.1 Summary of the thesis

In Chapters 1 and 2 of this thesis, the application of α-hydroxy acid derivatives toward the synthesis of (−)-aphanorphine and clauslactone S is demonstrated. Chapter 3 focuses on the investigation of asymmetric allylation of morpholinones derived from chiral amino alcohols for the synthesis of α-hydroxy acid derivatives. This methodology, in turn, can be utilized as a substitute for the asymmetric allylation of ephedrine-derived morpholinones.

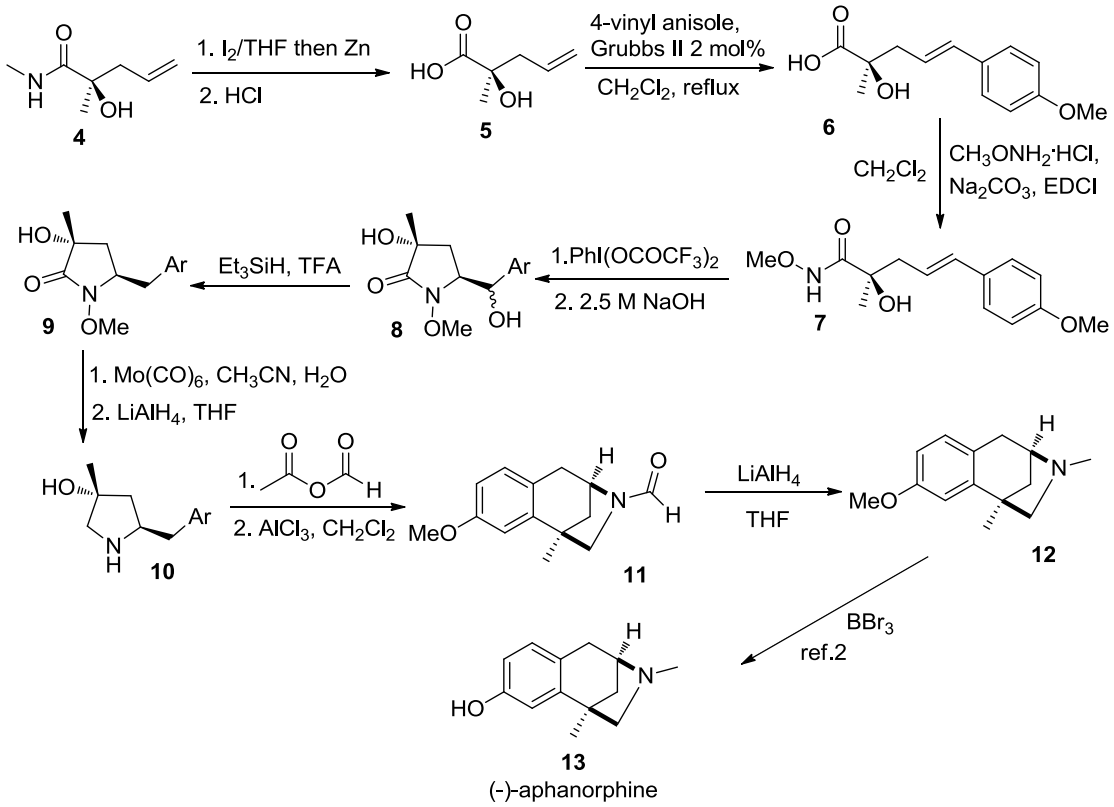
In Chapter 1, the synthesis of (+)-8-*O*-methylaphanorphine (91% *ee*) is described using the readily available α-hydroxy amide **4** (Scheme 4.1) as a chiral starting material. The synthesis was accomplished in 10 steps and 7.1% overall yield. This constituted a formal synthesis of (−)-aphanorphine (91% *ee*).

The α-hydroxy amide **4** (92% *ee*), prepared from an ephedrine-derived morpholinone **2** (Scheme 4.1), was used as a chiral starting material.



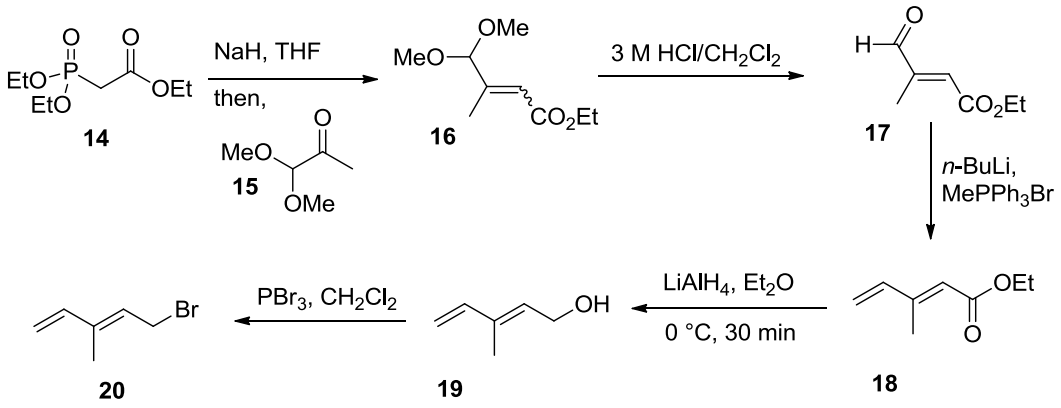

Scheme 4.1

Hydrolysis of amide **4** to the corresponding acid **5** followed by a cross-metathesis reaction provided **6** (Scheme 4.2). Amidation using methoxyamine hydrochloride provided the *N*-methoxyamide **7**. The amide **7** was treated with bis(trifluoracetoxy)iodobenzene[1] and the product was hydrolyzed to provide the hydroxypyrrolidine **8** as a 5:1 mixture of diastereomers. The selectivity for the cyclization step was confirmed by the reductive removal of the hydroxy group in **8**, by the treatment with $Et_3SiH$ in trifluoroacetic acid, which provided the pyrrolidinone **9** as a single diastereomer. This confirmed that the lactamization reaction is highly stereoselective. Cleavage of the *N*-*O* Bond in **9** using $Mo(CO)_6$ followed by reduction of the amide provided the key pyrrolidine intermediate **10**. *N*-Formylation of **10** followed by Friedel-Crafts cyclization provided the tricyclic intermediate **11**, which has all the structural elements of aphanorphine. Reduction of the formyl group in **11** using $LiAlH_4$ provided (+)-8-*O*-methylaphanorphine **12** (Scheme 4.2). Since the conversion of **11** to (−)-aphanorphine (**13**) by *O*-demethylation using $BBr_3$ is known,[2] the formal synthesis of (−)-aphanorphine is achieved.



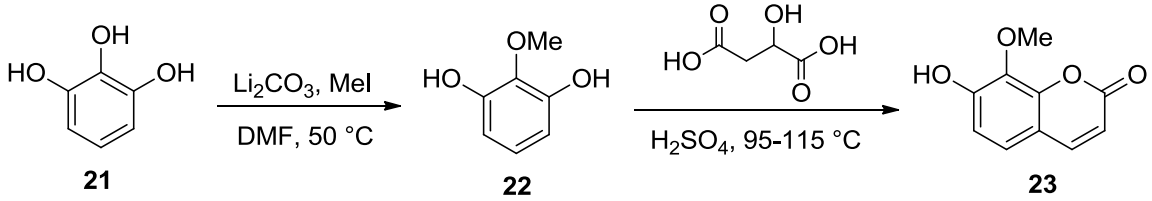

Scheme 4.2

In the second project, the α-hydroxy amide **4** was employed in synthetic studies of clauslactone S. The synthetic strategy was designed as the assembly of three components; the α-hydroxy amide **4**, the bromodiene **20** and the coumarin **23**. The α-hydroxy amide **4** was obtained from the methodology developed in the Pansare lab as explained earlier (Scheme 4.1).[3] The bromodiene **20** was prepared from pyruvaldehyde dimethyl acetal **15** as the starting material.[4] Treatment of **15** with the anion generated from triethylphosphonoacetate **14** provided the ester **16**. Removal of the acetal protection by treatment with 3 M HCl provided **17**. Wittig reaction of **17** provided the diene-ester **18**. The treatment of **18** with $LiAlH_4$ followed by bromination of the allylic alcohol **19** with $PBr_3$ provided the bromodiene **20** (Scheme 4.3).



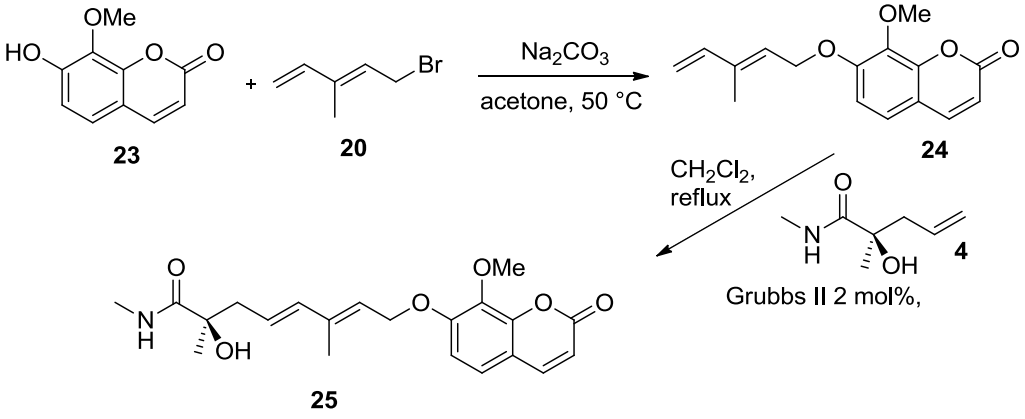

Scheme 4.3

The synthesis of coumarin **23** started with the selective methylation of pyrogallol **21**[5] by treatment with $Li_2CO_3$ and MeI to provide **22**. Treatment of **22** with $H_2SO_4$ and malic acid furnished the coumarin **23** (Scheme 4.4).[6]




Scheme 4.4

Treatment of coumarin **23** with $Na_2CO_3$ and the bromodiene **20** provided the ether **24**. A cross-metathesis reaction between **4** and **24** provided the amide **25** (Scheme 4.5) which is a potential intermediate to clauslactone S.




Scheme 4.5

In the third project, synthesis of α-hydroxy acid derivatives is investigated using morpholinediones obtained from chiral amino alcohols **26**-**30**, Figure 4.1.[7] This approach was aimed at finding a substitute to the ephedrine-derived morpholinedione. Five different chiral amino alcohols **26**-**30** were investigated.

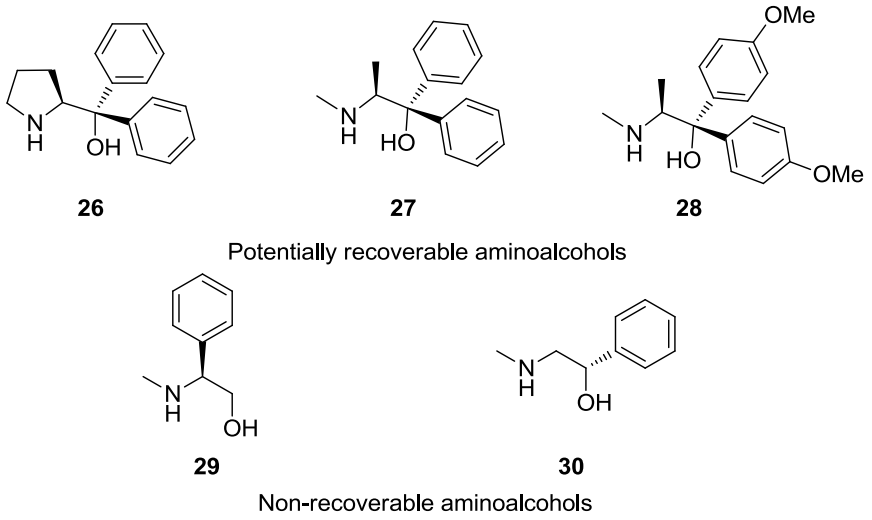
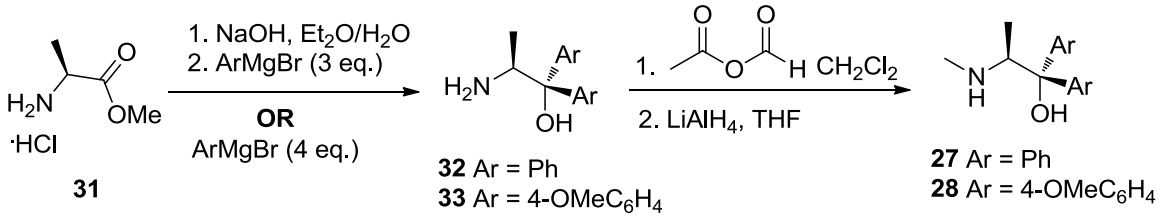



Figure 4.1 Chiral amino alcohols investigated as a substitute for ephedrine.

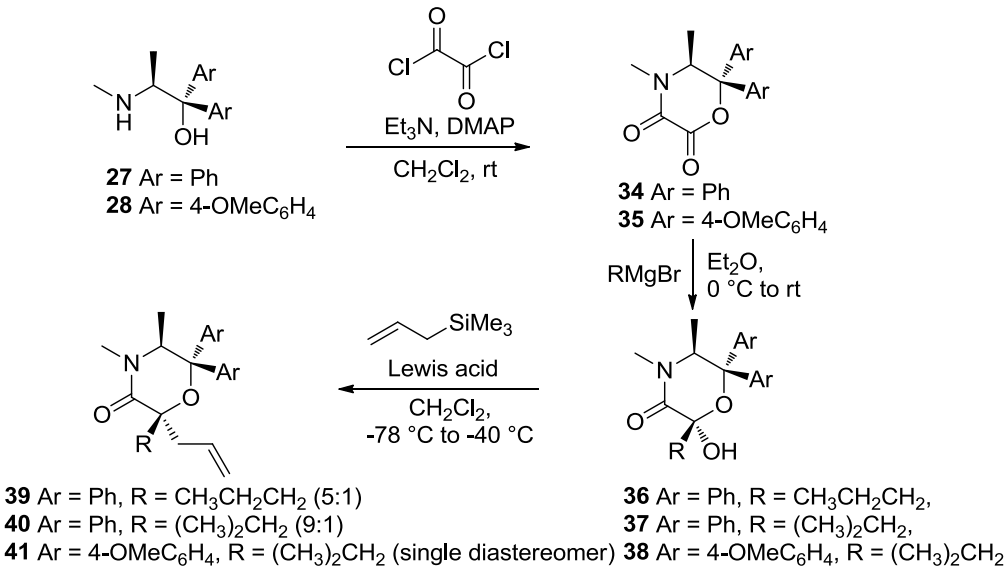
Out of the five amino alcohols, only the morpholinediones derived from amino alcohols **27** and **28** afforded good stereoselectivity in the allylation step. These amino alcohols were prepared from the (*S*)-alanine methyl ester hydrochloride **31**. Treatment of

**31** with an appropriate Grignard reagent provided the amino alcohols **32** and **33** (Scheme 4.6). *N*-Formylation with acetic formic anhydride followed by reduction provided the amino alcohols **27** and **28**.



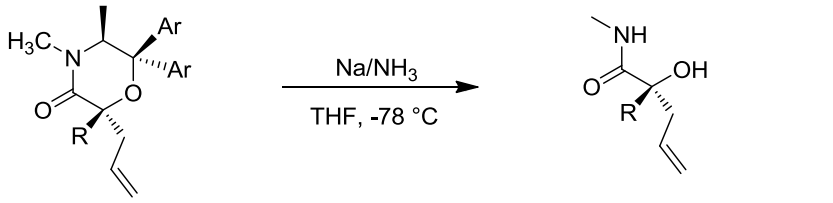

Scheme 4.6

Reaction of **27** and **28** with oxalyl chloride furnished the morpholinediones **34** and **35** (Scheme 4.7), which upon treatment with propylmagnesium bromide and isopropylmagnesium bromide provided the respective hemiacetals (**36**-**38**, Scheme 4.7), all as 4:1 mixtures of diastereomers. Allylation of these hemiacetals provided the dialkyl morpholines **39** (5:1 *dr*), **40** (9:1 *dr*) and **41** (single diastereomer, Scheme 4.7).




Scheme 4.7

After several attempts to hydrolyze either the amide or the ether functionality in the morpholinones **39**, **40** and **41** were unsuccessful, the dissolving metal reduction of these morpholinones was attempted. This cleanly generated the α-hydroxy amides **42** and **43**. The newly generated stereocenter in the morpholinones **39**-**41** was assigned as *R* by comparison of the sign of optical rotation for the amides **42** and **43** (Scheme 4.8) with that previously observed[3a] for these amides obtained from the ephedrine-derived morpholinone **2**, since in the earlier study, these amides have been converted to known α-hydroxy acids.




**39** Ar = Ph, R = $CH_2CH_2CH_3$
**40** Ar = Ph, R = $(CH_3)_2CH$
**41** Ar = 4-$OMeC_6H_4$, R = $(CH_3)_2CH$

**42** R = $CH_2CH_2CH_3$, (88%)
**43** R = $(CH_3)_2CH_2$, (78%)
**43** (90%)

Scheme 4.8

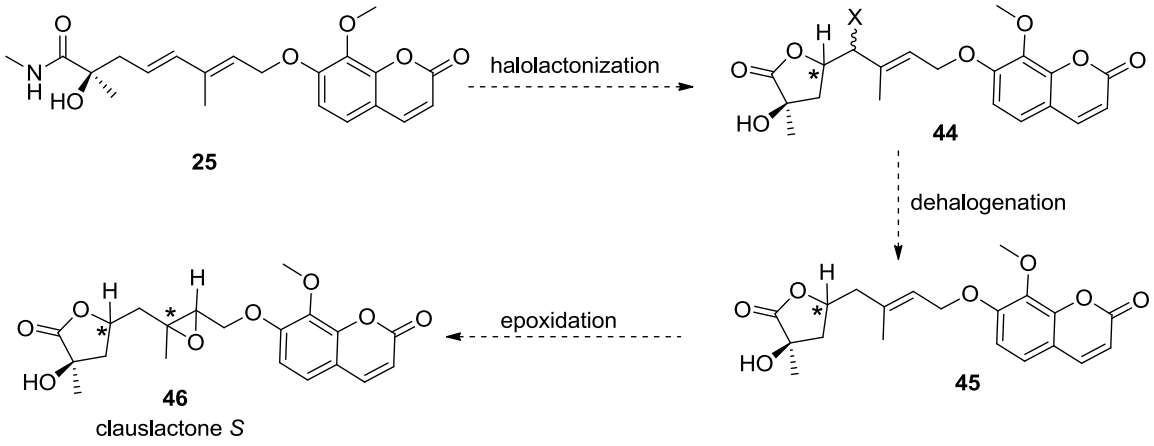
The morpholinediones **34** and **35** have thus provided an alternative to the corresponding ephedrine-derived morpholinedione. Even though the attempts to recover the amino alcohols **27** and **28** were unsuccessful, they can certainly be used as substitutes for 1*R*,2*S*-ephedrine in the synthesis of α-hydroxy acid derivatives.

## 4.2 Future work:

The synthesis of an *N*-methoxypyrrolidinone **9** as a precursor to the functionalized pyrrolidine motif in aphanorphine **13** has provided a promising methodology for the synthesis of several substituted *N*-methylpyrrolidinone natural products[8] and related motifs

in bioactive molecules.[9] The present study could potentially provide methodology for their synthesis.

The clauslactone S (**46**) synthesis can be investigated further from the intermediate **25**. The successful halolactonization of **25** would furnish **44**, which is the core structure of clauslactone S **46**. If successful, the dehalogenation of **44** will provide **45**. Epoxidation of **45** should provide clauslactone S or its stereoisomer (Scheme 4.9). The stereochemical outcomes of the lactonization and the epoxidation reactions are crucial.




Scheme 4.9

## 4.3 References


(1) Wardrop, D. J.; Bowen, E. G.; Forslund, R. E.; Sussman, A. D.; Weerasekera, S. L. *J. Am. Chem. Soc.* **2009**, *132*, 1188.

(2) (a) Mai, D. N.; Rosen, B. R.; Wolfe, J. P. *Org. Lett.* **2011**, *13*, 2932; (b) Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3923.

(3) (a) Pansare, S. V.; Ravi, R. G.; Jain, R. P. *J. Org. Chem.* **1998**, *63*, 4120; (b) Pansare, S. V.; Kulkarni, K. G. *RSC Advances* **2013**, *3*, 19127.

(4) (a) Yildizhan, S.; Schulz, S. *Synlett* **2011**, *2011*, 2831; (b) Curley, R. W.; Ticoras, C. J. *Synth. Commun.* **1986**, *16*, 627.

(5) Molyneux, R. J.; Jurd, L. *Aust. J. Chem.* **1974**, *27*, 2697.

(6) Donnelly, A. C.; Mays, J. R.; Burlison, J. A.; Nelson, J. T.; Vielhauer, G.; Holzbeierlein, J.; Blagg, B. S. J. *J. Org. Chem.* **2008**, *73*, 8901.

(7) Adsool, V. A. *Ph D Thesis* **2009**, Chapter 5.

(8) (a) Li, J.; Liu, S.; Niu, S.; Zhuang, W.; Che, Y. *J. Nat. Prod.* **2009**, *72*, 2184; (b) Chen, G.-Y.; Huang, H.; Ye, J.-L.; Wang, A.-E.; Huang, H.-Y.; Zhang, H.-K.; Huang, P.-Q. *Chem. Asian J.* **2012**, *7*, 504.

(9) (a) Kato, Y.; Nakano, Y.; Sano, H.; Tanatani, A.; Kobayashi, H.; Shimazawa, R.; Koshino, H.; Hashimoto, Y.; Nagasawa, K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2579; (b) Kato, Y.; Hashimoto, Y.; Nagasawa, K. *Molecules* **2003**, *8*, 488.