STEREOSELECTIVE SYNTHESIS OF α-HYDROXY ACID DERIVATIVES AND STUDIES ON THE SYNTHESIS OF ETHOPHENPROX

A THESIS

SUBMITTED TO THE

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IN

CHEMISTRY

BY

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NATIONAL CHEMICAL LABORATORY

PUNE 411 008

DEDICATED TO MY PARENTS

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "**Stereoselective Synthesis of α-Hydroxy Acid Derivatives and Studies on the Synthesis of Ethophenprox"** submitted by Mr. Annyt Bhattacharyya was carried out by him under my supervision at the National Chemical Laboratory, Pune. Material that has been obtained from other sources is duly acknowledged in the thesis

Dr. S. V. Pansare

Date: Research Guide

DECLARATION

I hereby declare that the thesis entitled "**Stereoselective Synthesis of α-Hydroxy Acid Derivatives and Studies on the Synthesis of Ethophenprox"**, submitted for the Degree of Doctor of Philosophy to the University of Pune, has been carried out by me at the National Chemical Laboratory, Pune under the supervision of Dr. S. V. Pansare. The work is original and has not been submitted in part or full by me for any other degree or diploma to this or any other University.

Date: Annyt Bhattacharyya

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Annyt Bhattacharyya

CONTENTS

List of Abbreviations:

aq.	aqueous
cat.	catalytic
Cbz	benzyloxycarbonyl
de	diastereomeric excess
DMAP	4-(dimethylamino)pyridine
dr	diastereomeric ratio
ds	diastereoselectivity
ee	enantiomeric excess
equiv.	equivalent
ESMS	electrospray mass spectrometry
Et	Ethyl
gm	gram
h	hour
HRMS	high resolution mass spectrum
IR	Infrared
i-Pr	isopropyl
M	molar
M^+	molecular ion
Me	methyl
min	minute
ml	milliliter
mmol	millimole
mp	melting point
MS	mass spectrum
NMR	nuclear magnetic resonance
Ph	phenyl
Pr	propyl
rt	room temperature
s	second
t-Bu	Tertiary butyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane

ABSTRACT

CHAPTER I

Asymmetric synthesis of α-hydroxy acid derivatives

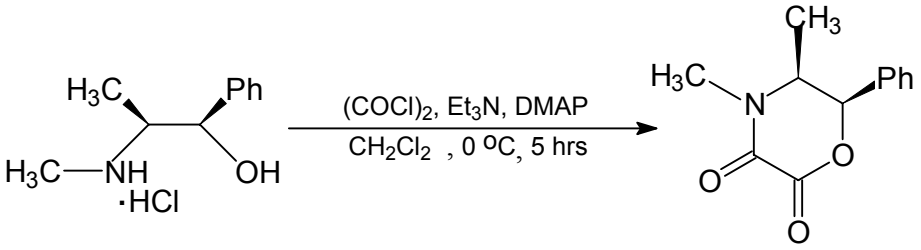
Section A

Asymmetric alkylation and allylation of a 1*R*,2*S* ephedrine derived morpholine dione by a one-pot protocol: Enantioselective synthesis of α-hydroxy acids and their derivatives.

Enantiomerically pure α-hydroxy acids and their derivatives are an important class of organic compounds because of their use as building blocks for asymmetric synthesis of natural products and biologically active molecules. The 2-alkyl-2-allyl morpholinones are valuable intermediates for α-allyl-α-alkyl hydroxy acids, α-alkyl-α-hydroxy acids and α–alkyl-α–hydroxy-γ–butyrolactones. The objective of the investigation was to develop a one-pot protocol for the synthesis of 2-alkyl-2-allyl morpholine-diones.

1*R*,2*S* Ephedrine was chosen as the chiral controller in the present study. The dione **1** was readily prepared from 1*R*,2*S* ephedrine hydrochloride and oxalyl chloride.

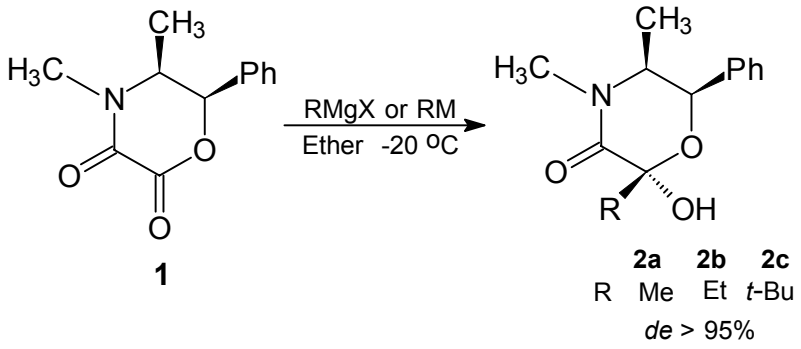
Scheme 1



1

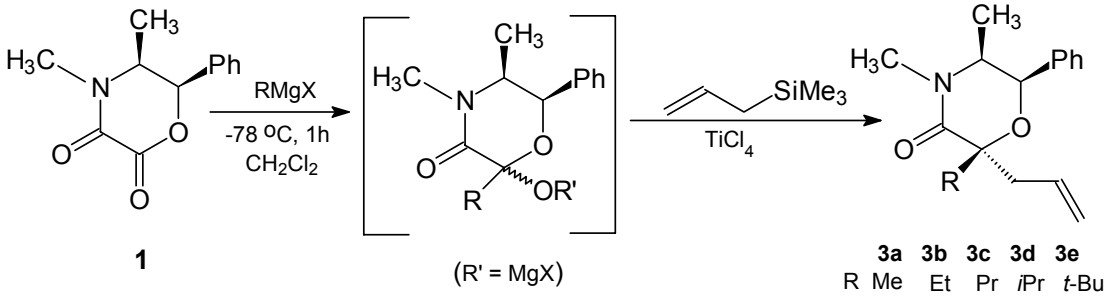
Dione **1** reacts chemoselectively with various alkyl metal reagents to generate hemiacetals in excellent yields (Scheme 2) and high diastereoselectivity (ds ≥ 10/1 by ^{1}H NMR) when conducted in ether at –20 ^{o}C. The stereoselective allylation of the hemiacetals is an ensuing step that generates the 2-alkyl-2-allyl morpholinones from the hemiacetals. The one-pot protocol combines the hemiacetal synthesis and the subsequent allylation.

Scheme 2



The procedure involves addition of alkyl metal reagent to the dione followed by allylation of the resulting salt of the hemiacetal (R′=OMgX) with allyltrimethylsilane and titanium tetrachloride (Scheme 3).

Scheme 3



Reactions of **1** with RMgX or RM at -78°C followed by allylation at –78°C to –20°C over 6-8 hours or gradual warming to ambient temperature overnight gave 2-alkyl-2-allyl morpholinones **3** as single diastereomer in moderate to good yields (50-60%). The diastereoselectivity of the alkyl/allyl morpholinones suggest a S_N1 type allylation process. The morpholinones **3** are valuable synthons for α-alkyl-α-hydroxy acids and α-hydroxy-α-alkyl-γ-butyrolactones. The present one-pot process for **3** is superior to the earlier sequence which relies on the use of ephedrine and α-ketoacids to generate the hemiacetals which are then allylated in a separate step. The one-pot protocol provides access to a wide variety of 2-

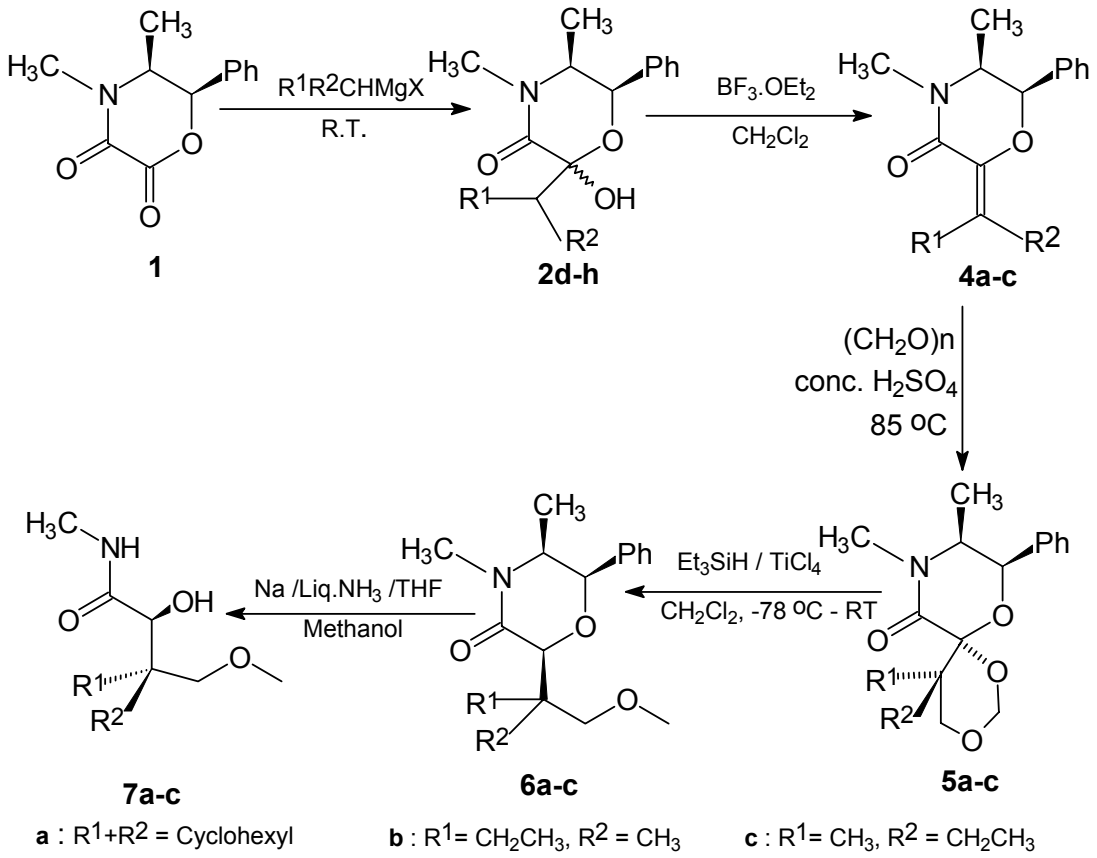
alkyl-2-allyl morpholinones from corresponding organometallic reagents. Also the isolation and purification of the hemiacetals is not necessary.

Section B

Enantioselective synthesis of β,β–dialkyl –α-hydroxy-γ–butyrolactones

The objective of this study was to develop enantioselective synthesis of β,β-dialkyl-α-hydroxy-γ-butyrolactones from morpholine-dione **1**. A number of these lactones are natural products. These lactones have recently been employed as components of interleukin inhibitors. This particular class of butyrolactones and the parent hydroxy acids are also of interest due to their structural similarity to pantolactone and the potential for application as pantothenic acid analogues in biologically relevant molecules. Dione **1** was employed in the synthesis of chiral alkylidene morpholinones **4** by dehydration of hemiacetals **2d-h.** The alky-

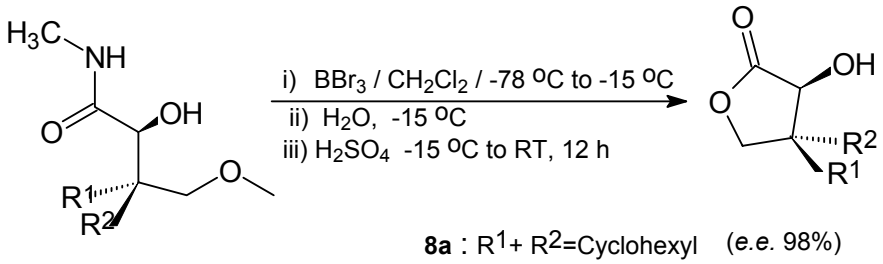
Scheme 4:



lidene morpholinones undergo a highly stereoselective Prins reaction with paraformaldehyde in presence of conc. H_2SO_4 to generate the spiro bis-acetals **5**. Reductive cleavage of acetals **5** in presence of triethylsilane and $TiCl_4$ is also highly stereoselective and generates the masked α,γ-dihydroxy butyramide **6** (Scheme 4).

Dissolving metal reduction of **6** generates the α-hydroxy γ-methoxy butyramides **7**, which are efficiently converted to corresponding butyrolactones **8** with high enantioselectivity. (Scheme 5)

Scheme 5



The first asymmetric synthesis of spiro lactone **8a** (98% *e.e.*) is achieved by this protocol. Lactone **8b** (*e.e.* 97%) is a natural product isolated from *Marshallia tenuifolia* and has absolute configuration 3*S*, 4*S*. Lactone **8c** (*e.e.* 97%) is a diastereomer of the natural product (3*S*, 4*R*).

The above procedure should provide access to a variety of enantiomerically enriched β,β-disubstituted α-hydroxy γ-butyrolactones in either enantiomeric form, since both enantiomers of ephedrine are commercially available.

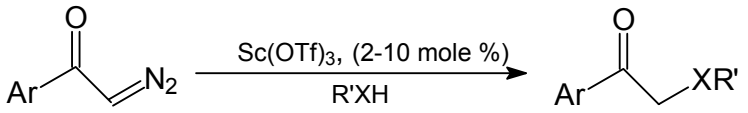
CHAPTER II

Scandium Triflate catalyzed diazocarbonyl insertion into hetero-atom hydrogen bonds

Synthetic applications of metal catalyzed decomposition of diazo compounds, especially diazo carbonyl compounds, has been extensively investigated in recent years. A

large number of methods that employ rhodium-based catalysts are known. We have developed scandium triflate as an alternative catalyst for some of these reactions. Scandium triflate was demonstrated to be an efficient catalyst for diazocarbonyl insertion reactions into O-H, S-H and carbamate N-H bonds (Scheme 6).

Scheme 6:



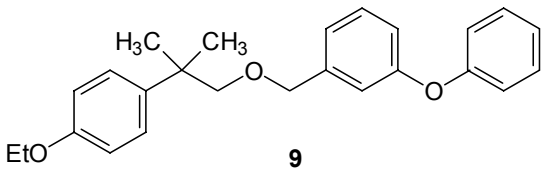
X = O, S R' = alkyl, substituted alkyl, aryl group

Treatment of aryldiazoketones with a variety of alcohols and thiols in the presence of scandiun triflate at ambient temperature generates the corresponding α-alkoxy ketones as products of O-H and S-H insertion. It was also observed that selective O-H insertion is possible in presence of carbamate N-H bond.

CHAPTER-III

Studies on the synthesis of Ethophenprox

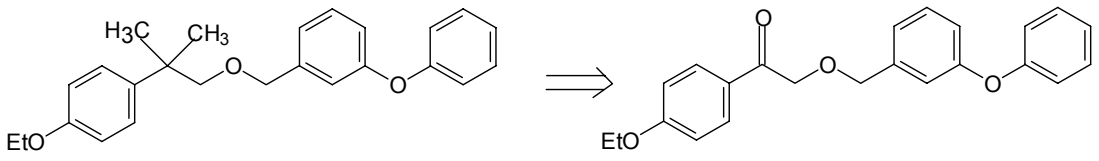
The objective of this study was to develop a concise synthetic route for the potent pesticide ethophenprox (**9**) which is a non-halogen containing pyrethroid-like insecticide, which is particularly non-toxic to fish.



9

We envisaged a ketone as the precursor for the gem-dimethyl group in **9**, since gem-dimethylation on ketones has been successfully employed in the literature. Our primary target was therefore the ketone **10** (Figure 1).

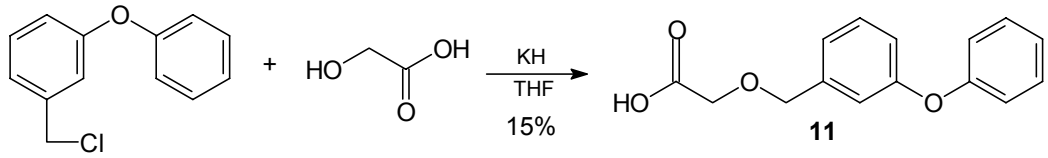
Figure 1.



9 **10**

It seemed plausible that *m*-phenoxybenzyl glycolic acid **11** could be converted to the ketone **10** by reaction with an aryl lithium reagent. Reaction of glycolic acid and *m*-phenoxybenzyl chloride generated the desired acid **11,** but the yield was unsatisfactory (15%, Scheme 7)

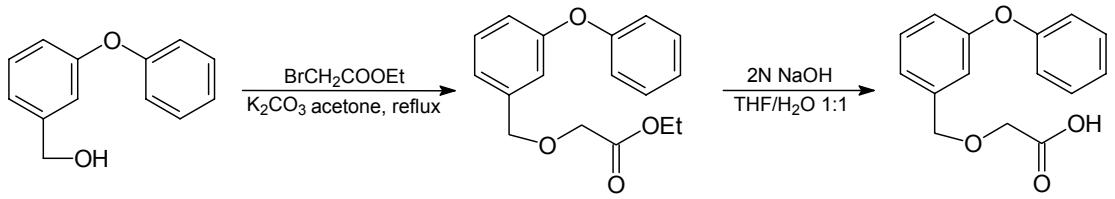
Scheme 7.



11

Alternatively, the ester **12** was obtained in moderate yield (55%) from the reaction of *m*-phenoxybenzyl alcohol and ethyl bromoacetate. The ester was hydrolyzed to the acid **11** in quantitative yield. (Scheme 8)

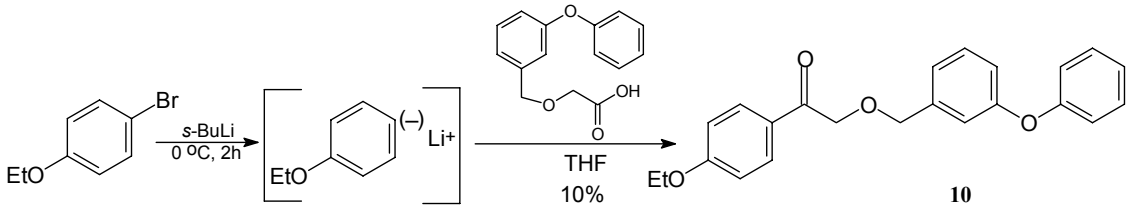
Scheme 8.



12 **11**

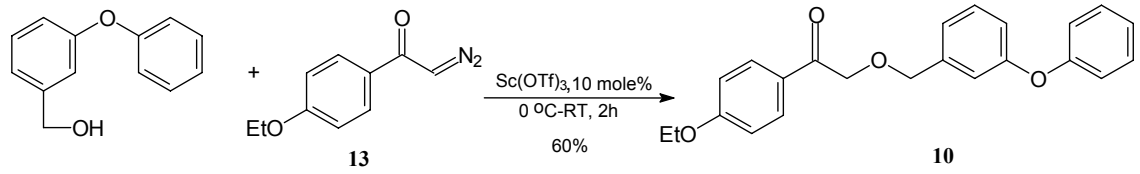
Unfortunately, the reaction of the acid **11** and the aryl lithium derived from 4-bromo phenetole could not be effected successfully. Though **10** was obtained, the reaction was accompanied with side products which made purification complex and substantially diminished the yield (maximum 10%, Scheme 9).

Scheme 9.



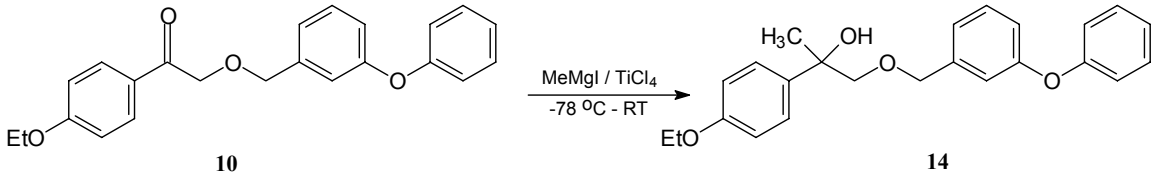
Alternatively, ketone **10** was successfully obtained in good yield (60%) through diazocarbonyl insertion of *m*-phenoxybenzyl alcohol with *p*-ethoxydiazoacetophenone **13** with scandium triflate as the insertion catalyst as described in Chapter II (Scheme 10).

Scheme 10.



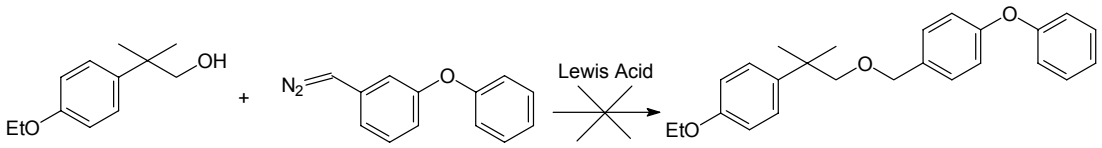
Gem-dimethylation of ketone **10** with Me_2TiCl_2 (generated from MeMgI and $TiCl_4$) was unsuccessful under various conditions. Most of the reactions gave complex mixtures of products, from which the tertiary alcohol **14** could be isolated in low yield (15%) Scheme 11.

Scheme 11.



An alternative synthesis involving the O-H insertion reaction of the alcohol **15** with *m*-phenoxyphenyldiazomethane **16** was also examined by employing a variety of Lewis acid catalysts (Scheme 12). These reactions were also quite complex and the required product was not observed.

Scheme 12.



15 **16** **9**

The reasons for the lack of ether formation from **15** as well as the difficulties in dimethylation of ketone **10** are not clear at present.

Chapter I

Asymmetric Synthesis of α-hydroxy acid derivatives

Section A

Asymmetric alkylation and allylation of a 1R,2S ephedrine derived morpholine dione by a one-pot protocol: Enantioselective synthesis of α-hydroxy acids and their derivatives.

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

Tetrahedron 2002, *58*, 8985

Section B

Enantioselective synthesis of

β,β-dialkyl α-hydroxy γ-butyrolactones

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

Tetrahedron Letters 2001, *42*, 9265

&

Tetrahedron Accepted for publication 2003

Section C

Attempted Synthesis of Citramalic Acid

1. INTRODUCTION

The reaction of carbonyl compounds with allylmetals and silyl enol ethers has been subject of intense investigation in the recent years.[1–4] The stereoselective and chemoselective allylation reaction has been extensively investigated due to it's potential for application in the synthesis of complex molecules. The stereoselective allylation of aldehydes to generate homoallylic alcohols by the addition of allylboranes,[5-7] allylsilanes,[8,9] allylstannes,[10,11] allyldialkylaluminium[12] derivatives and especially the asymmetric allylations of chiral acetals[13-16] has been thoroughly examined. In contrast, stereoselective allylation of ketones has not been very successful[17,18] and an efficient method to achieve this has been described only recently.[19]

The synthesis of α-allyl-α-hydroxy acids and their derivatives has received less attention although these molecules are attractive synthetic intermediates. Their utility has been demonstrated by further elaboration of the carbon-carbon double bond into several attractive synthetic intermediates.[20-22]

A brief summary of the existing methods for the stereoselective allylation of chiral α-keto acid derivatives follows. It may be noted that not all the methods have been applied to the synthesis of α-allyl-α-alkyl-α-hydroxy acids or their derivatives. These have been included since the potential exists for converting key intermediates to the carboxylic acids. In the interest of completeness, methods for synthesis of secondary (α-allyl-α-H) allyl hydroxy acids have also been included.

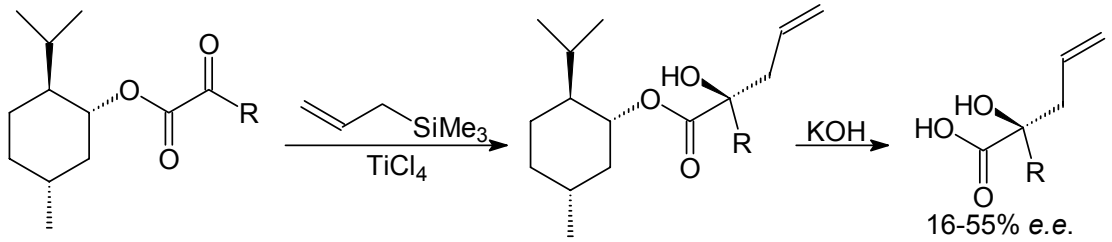
Allylation of α-keto carboxylic acid derivatives

Stereoselective allylation of α-ketoacid menthyl esters

In the first report[23] of an asymmetric allylation of α-ketoesters, Ojima reported the reaction of (-) menthyl pyruvate and menthyl phenylglyoxalate with allyltrimethylsilane in the presence of titanium tetrachloride. The diastereoselectivity of the process is not very high

(16-55% e.e. of the acid after hydrolysis) and the α-hydroxy acids were liberated by basic hydrolysis of the ester (Scheme 1).

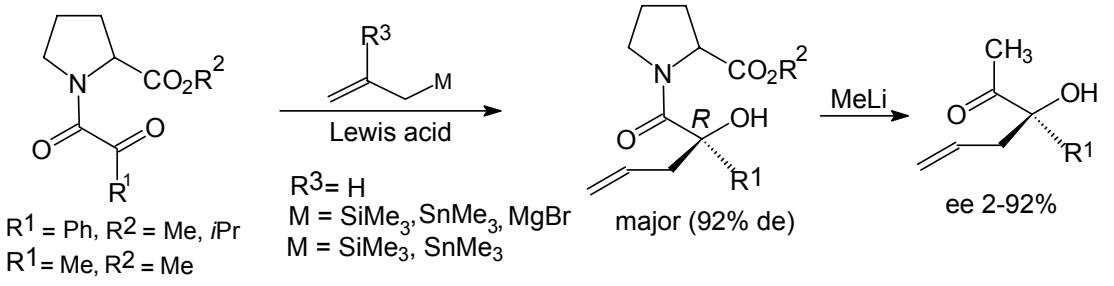
Scheme 1.



Stereoselective allylation of α-ketoamides derived from proline esters

As a corollary of his studies on stereoselective reductions of prolyl α-keto amides[24,25] Soai also examined the allylation of these substrates.[26] Diastereoselective addition of allylsilanes and allylstannanes to α-keto amides derived from several proline esters were examined. The diastereoselectivity of the process ranges from 2-92% and is highly dependent on Lewis acid and solvent. For good diastereoselectivity, tin tetrachloride was found to be a better Lewis acid than titanium tetrachloride and the predominant product had the *'R'* configuration at the newly generated stereocenter. However, in this study, the α-hydroxy amides were not converted to the corresponding acids. The auxiliary was removed by reaction with methyl lithium to generate α-hydroxy methyl ketones.(Scheme 2)

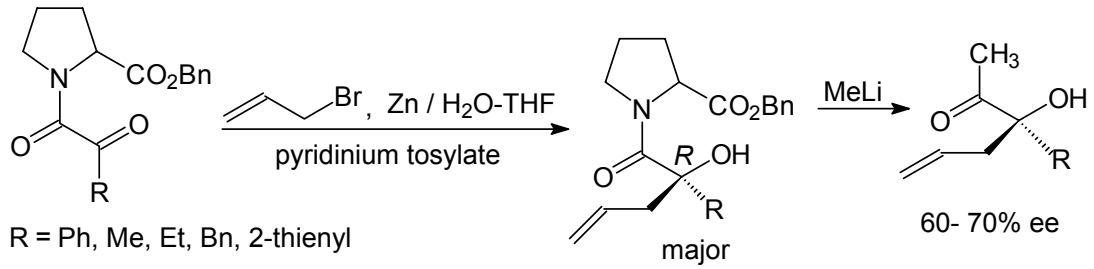
Scheme 2.



In a related study, Waldmann has reported[27] allylation reactions of α-keto amides derived from proline benzyl ester with a variety of allyl halides in an aqueous medium. These

allylations proceed with modest diastereoselectivity (60-72% d.e.) and as in the earlier study, the amides have been converted to methyl ketones by reaction with methyl lithium (Scheme 3).

Scheme 3.

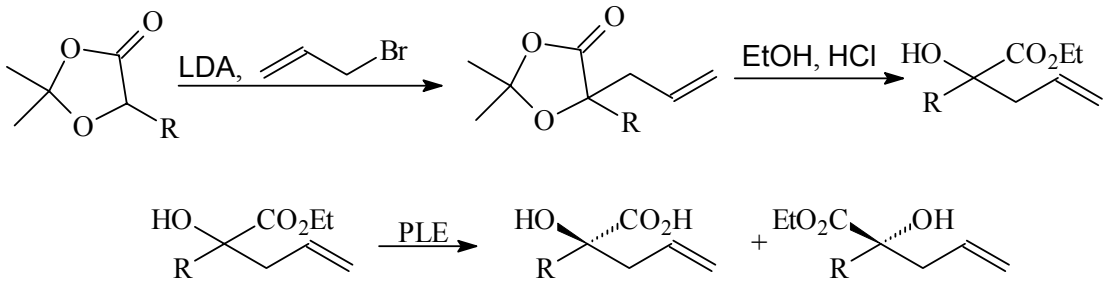


Other than the above studies not much has been reported on the asymmetric allylation of α-keto acid derivatives.

Enzymatic resolution of α-allyl-α-hydroxy esters

Although not an asymmetric synthesis of the target molecules, enzymatic resolution of α-allyl-α-hydroxy acids has been reported as an alternative approach.[28] The requisite α-hydroxy acids were prepared by allylation of the acetonides of lactic and mandelic acids. Pig liver esterase (PLE) catalyzed hydrolysis of these esters provided enantiomerically enriched acids (22-94% e.e., Scheme 4). However, the scope of this reaction remains to be established since only a few substrates have been examined. Also a phenyl group in the allyl portion is not tolerated by the enzyme and the substrate remains unhydrolyzed

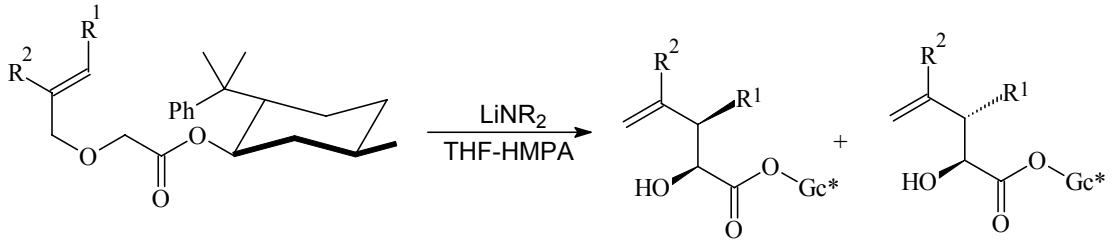
Scheme 4



Stereoselective (2,3) - Wittig rearrangement approach to α-allyl-α-hydroxy acids

A highly efficient method for the enantioselective synthesis of α-allyl-α-hydroxy acids has been reported[29,30] by Nakai. In this study, the asymmetric (2,3)-Wittig rearrangement of (*E*-2-alkenyloxy) acetates derived from (-)–8-phenylmenthol proceeds with high erythro selectivity (> 90%). The level of asymmetric induction in this rearrangement is dictated by the alkyl substituent on the allylic moiety (Scheme 5). This rearrangement provides important α-allyl α-H-α-hydroxy acids which are intermediates for the synthesis of natural products such as (-)-verrucarinolactone.[31]

Scheme 5



a) $R^1 = CH_3$, $R^2 = H$
b) $R^1 = n$Bu, $R^2 = H$
c) $(CH_3)CCHCH_2OCH_2COOGc^*$
d) $R^1 = H$, $R^2 = H$
e) $R^1 = H$, $R^2 = CH_3$

2*S*, 3*R* Erythro
+
2*R*, 3*S* Erythro

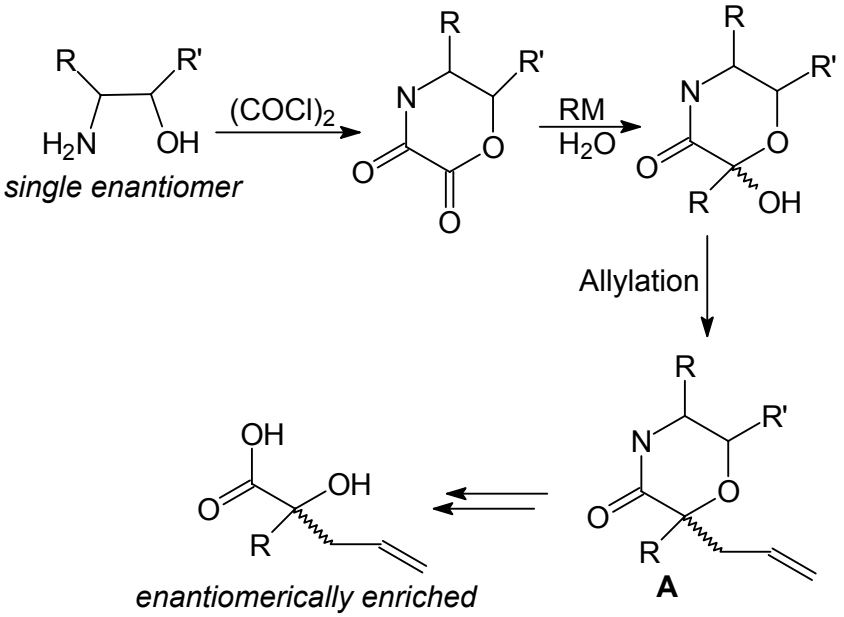
Gc* = 8- phenylmenthyl

2*S*, 3*S* Threo
+
2*R*, 3*R* Threo

2. OBJECTIVES

The objective of this undertaking was to develop a stereoselective synthesis of α-alkyl α-hydroxy acids employing a morpholine-dione derived from an amino alcohol. It was envisioned that reaction of the dione with an organometallic reagent would yield a hemiacetal. Allylation of the hemiacetal would generate the functionalized morpholinone **A** which would provide the target molecules after removal of the amino alcohol portion. The concept is summarized in Figure 1

Figure 1:

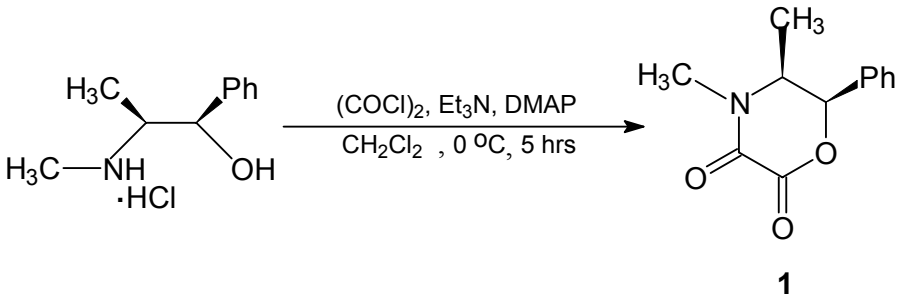


In principal, it should be possible to perform a one-pot alkylation/allylation of the dione and the entire process may be rendered asymmetric by employing an enantiomerically enriched amino alcohol. We decided to examine ephedrine as the chiral amino alcohol since it is readily available in either enantiomeric form.

3. RESULTS AND DISCUSSION

The reaction of ephedrine hydrochloride with oxalyl chloride in the presence of triethylamine, and catalytic DMAP in anhydrous dichloromethane generates morpholine dione **1** in 65% yield (Scheme 6). Initial experiments resulted in low yields of **1**. The yield was elevated upon dilution and control of reaction temperature. Adding a dilute solution of oxalyl chloride over a prolonged period (4 hours) and further stirring at 0 ^{o}C for an hour had a beneficial effect. It should be noted that the dione **1** has been prepared earlier as a proof for the reactivity of an activated oxalic acid derivative[32] but synthetic applications of **1** had not been reported prior to this study.

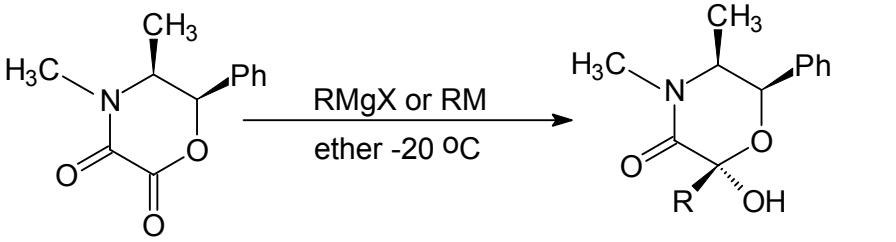
Scheme 6



1

The lactone carbonyl in **1** is akin to an isolated ketone as evidenced through addition of organometallic reagents and Wittig olefination reactions.[33] **1** reacts chemoselectively with various alkyl metal reagents to generate hemiacetals in excellent yields. In particular, the reaction of **1** with Grignard reagents in ether at -20 ^{o}C provides hemiacetals in excellent yields and good diastereoselectivity[34] (ds ≥ 10/1 by ^{1}H NMR) (Scheme 7).

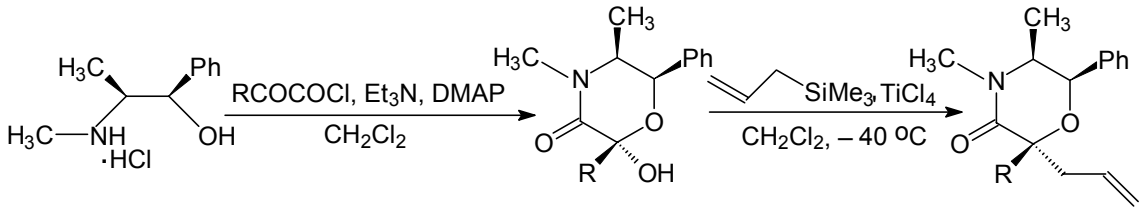
Scheme 7.



1	**2**	**3**	**4**	**5**	**6**	**7**
R	Me	Et	*i*-Pr	*t*-Bu	$CH(CH_2)_2$	$CH(CH_2)_4$
de	82%	88%	> 95%	> 95%	> 95%	> 95%

Some of these hemiacetals were earlier generated stereoselectively by us by the acylation of ephedrine with α–keto acid chlorides. Allylation of the hemiacetals in presence

Scheme 8

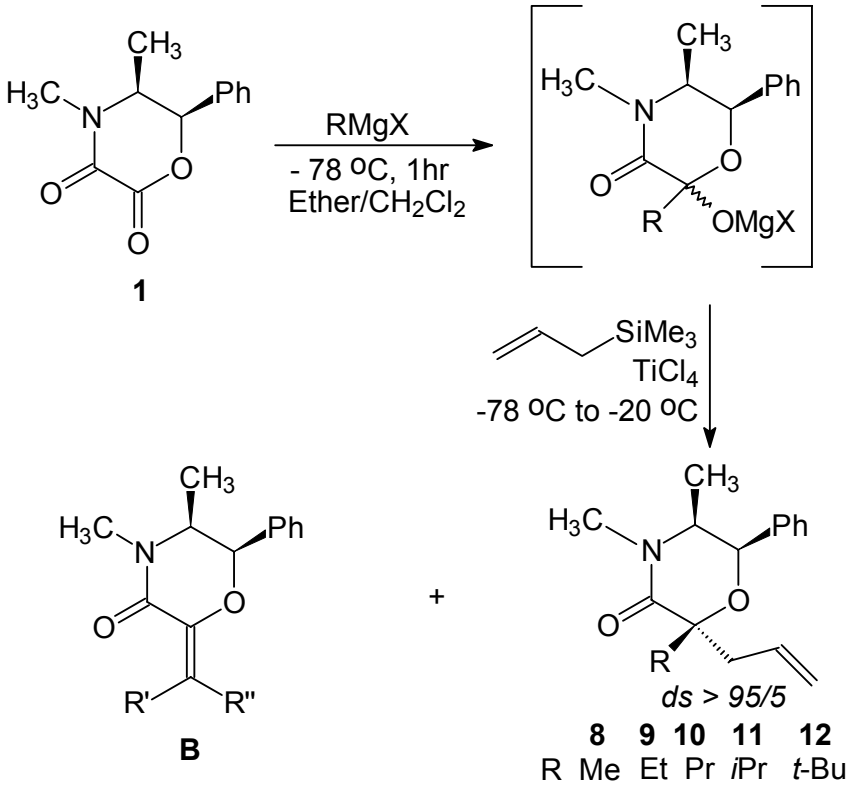


single diastereomer

of allyl trimethylsilane / $TiCl_4$ was the ensuing reaction in the sequence which generated the alkyl / allyl morpholinones as single diastereomers[34] (Scheme 8).

In the present study, a one-pot reaction protocol that combines the hemiacetal synthesis and the allylation step has been developed. The procedure involves addition of the alkyl metal reagent to the dione **1** followed by allylation of the resulting salt of the hemiacetal (R'= MgX) with allyl trimethylsilane/$TiCl_4$ (Scheme 9).

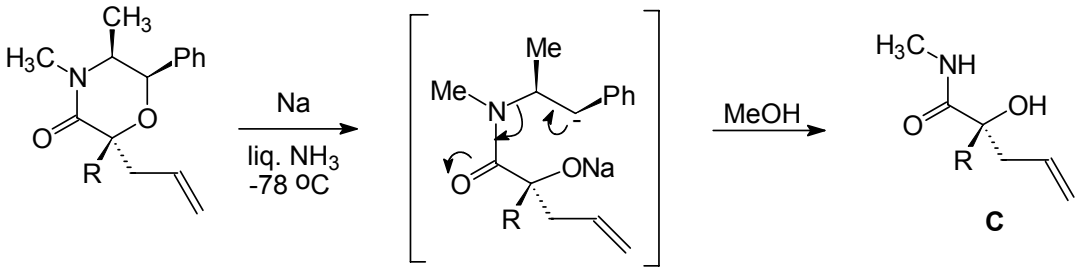
Scheme 9



Thus, reaction of **1** with RMgX at –78 °C followed by allylation at –78 °C to –20 °C for 6-8 hours or gradual warming to ambient temperature overnight furnished morpholinones **8-12** as single diastereomers (^{1}H NMR) in 55-62-% yield. It is noteworthy that the allylation products are obtained as single diastereomers. A small amount of elimination product **B** (< 5%) accompanied the allylated morpholinones as evidenced by ^{1}H NMR spectroscopy of the crude products.

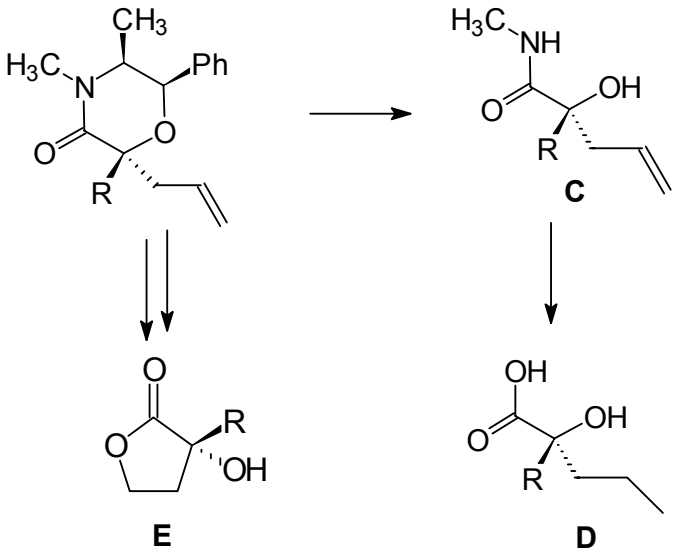
Sodium in liquid ammonia cleanly generates the hydroxy amides **C** in fair yields. Presumably the intermediate benzylic anion derived from the alkyl / allyl-morpholinones undergo facile β-elimination of the *N*-acyl moiety at low temperature (Figure 2).

Figure 2.



Allyl morpholinones are important intermediates in the synthesis of α-hydroxy acids[35] **D** (e.e > 95%) (Figure 3) and are obtained with *R* configuration. More notably they are readily converted to α-hydroxy α-alkyl γ-butyrolactones[35] **E** with high enantioselectivity (e.e.> 95%) (Figure 3)

Figure 3.



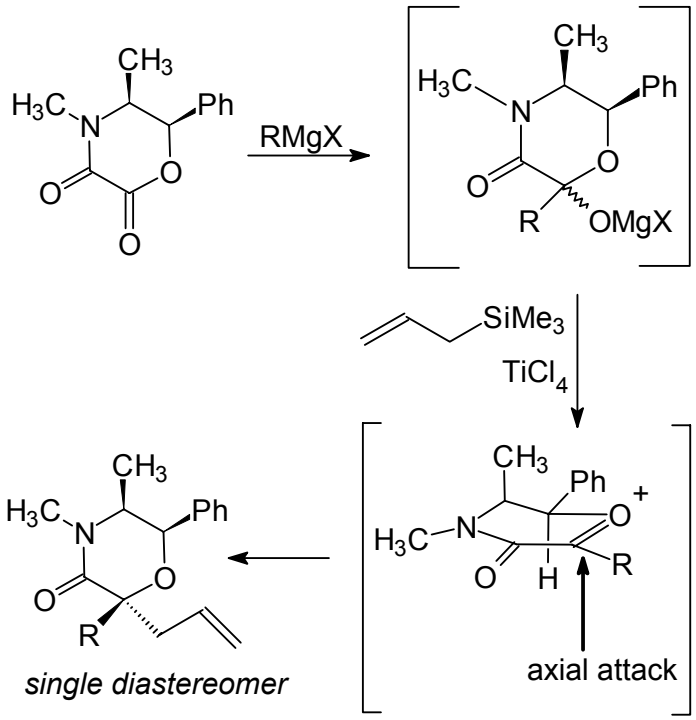
The above one-pot procedure has a significant advantage over the earlier, α-keto acid based method for synthesis of the hemiacetals from ephedrine. The present method does not require α-keto acids and it should now be possible to prepare any hemiacetal by reaction of **1**

and the appropriate organometallic reagent. In addition, isolation and purification of the hemiacetal is not required in this approach. The hemiacetals could be further utilized for enantioselective synthesis of pantolactone and also it's analogues, the later has been described in Section B of this chapter.

Origin of stereoselectivity in the allylation reaction

The mechanism of allylation with allyl trimethylsilane in the presence of Lewis acids has been intensely investigated. Detailed mechanistic studies by Denmark[13] and others[14] have revealed that depending on acetal structure and Lewis acid employed, the reaction proceeds via either an S_N1 like or S_N2 like mechanism. In the present study, the observed stereochemical outcome can be explained only by a S_N1 like substitution reaction that ensues

Figure 4.

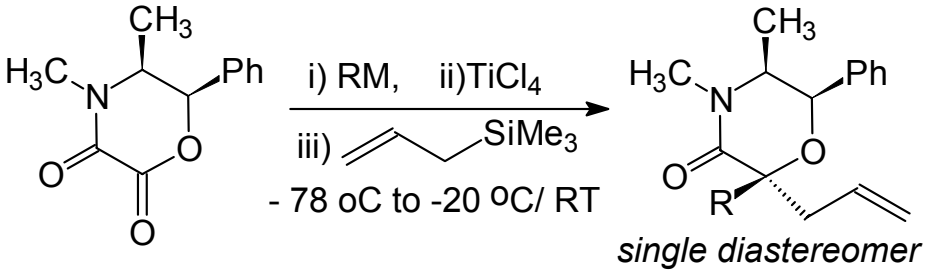


with an overall 'retention' of stereochemistry in that bond cleavage and bond formation take place from the same face of the hemiacetal like intermediate (generated from addition of organometallic reagent to the lactone carbonyl function in **1**) to an oxocarbenium ion which undergoes a highly diastereoselective attack by allylsilane, probably due to a stereoelectronic

effect.[36] Considering a *pseudo* equatorial orientation of the phenyl group in the oxocarbenium ion transition state assembly, an axial attack of the allylsilane would generate the product with observed stereochemistry which is '*R'* (Figure 4).

The high diastereoselectivity is indeed remarkable when one considers that the intermediate oxocarbenium ion must probably exist as a solvent separated ion pair[37] to allow approach of the allylsilane from the side of the original carbon-OMgX bond. It is thus a rare example of an allylation reaction proceeding *via* the S_N1 route with complete selectivity, since it is generally accepted that an oxocarbenium ion mechanism displays lower selectivity than a S_N2 like mechanism.[13,38] The results of allylation are summarized in Table 1.

Table 1: Allylation of morpholine dione **1.**



Organometallic Reagent	Allyl morpholinone	Yield %	diastereomeric excess %
MeMgI	**8**	58	>95
MeLi	**8**	59	>95
EtMgI	**9**	62	>95
PrMgCl	**10**	55	>95
*i*PrMgBr	**11**	53	>95
*t*ButylMgCl	**12**	50	>95

4. CONCLUSIONS

The one-pot addition/allylation protocol with morpholine-dione **1** greatly improves the scope of the hemiacetal approach to α-hydroxy γ-butyrolactones and other α-hydroxy

acid derivatives since it provides access to a wide variety of alkyl/allyl morpholinones. More importantly, it completely avoids the use of α-keto acids, thus overcoming the limitation of α-keto acid based synthesis of hemiacetals, which is of limited commercial availability. Synthesis of hemiacetals from **1** are economically more viable as α-keto acids are expensive substrates. The isolation and purification of the hemiacetals is also avoided thereby greatly improving the practical utility of the ephedrine based approach to α-hydroxy acids.

5. EXPERIMENTAL

General

All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware (120 ^{o}C). All organic layers obtained from extractions were dried over anhydrous sodium sulfate. THF was distilled from sodium benzophenone ketyl and dichloromethane, triethylamine were distilled from CaH_2. Commercially available titanium tetrachloride ($TiCl_4$) was distilled before use. Petroleum ether refers to the fraction boiling in the range 60-80 °C. Reactions were monitored by TLC on commercial precoated silica (Merck 60F-254) by staining in phosphomolybdic acid (10% solution in ethanol) followed by charring at 200^{o}C. Silica gel for column chromatography was 60-120 mesh or 230-400 mesh. All melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker MSL-300 or Bruker AC-200 instruments. Optical rotations were measured at the sodium D line on JASCO P-1020 polarimeter at ambient temperature. Mass spectra (EI) were recorded on a Finnigan-Mat 1020C mass spectrometer at ionization potential of 70 eV. High resolution mass spectra (HRMS) and Electrospray mass spectrometry (ESMS) were recorded on a Jeol JMS-SX-102 spectrometer. All melting points are uncorrected. Elemental analyses were performed by the Microanalysis facility at NCL, Pune.

5*S*,6*R*-4,5-Dimethyl-6-phenyl-morpholin-2,3-dione (1):

To a stirred suspension of ephedrine hydrochloride (2 g, 9.9 mmol) and DMAP (60 mg, 0.49 mmol) in dichloromethane (200 mL) at 0 ^{o}C, was added triethyl amine (5.5 mL, 39.6 mmol). The mixture was stirred for 10 minutes and a solution of oxalyl chloride (1.3 mL, 14.9 mmol) in dichloromethane (100 mL) was added dropwise over a period of 4 hrs at 0 ^{o}C. The mixture was further stirred at 0 ^{o}C for 1 hr and ice was added. The mixture was warmed to ambient temperature and the biphase was separated. The dichloromethane layer was washed with water (70 mL), dried (Na_2SO_4) and concentrated under reduced pressure.

The residue was purified by column chromatography with silica gel (7/3 ethyl acetate/pet.ether) to furnish 1.42 g (65%) of **1** as a white solid.

M.P. = 182 ^{o}C

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.50-7.28 (m, 5H, Ar*H*), 5.90 (d, 1H, *J* = 2.9, C*H*Ph), 3.77-3.66 (dq, 1H, *J* = 2.9, 6.8, C*H*CH_3), 3.19 (s, 3H, NCH_3), 1.12 (d, 3H, *J* = 6.8, CH_3)

^{13}C NMR (50 MHz, $CDCl_3$)

δ 156.4 (N*C*=*O*), 153.0 (O*C*=O), 133.8 (Ar*Cipso*), 128.6 (Ar*C*), 125.3 (Ar*C*), 79.3 (Ph*C*H), 58.1 (CH_3*C*H), 33.2 (N*C*H_3), 11.8 (*C*H_3).

IR ($CHCl_3$)

3018, 1771, 1693, 1406, 1292, 1215, 1186, 1009 cm^{-1}

MS (70ev)

m/z 57 (90), 77 (45), 91 (35), 105 (25), 117 (100), 147 (3), 176 (3), 219 (M^+, 12)

Analysis for $C_{12}H_{13}NO_3$

Calcd: C, 65.74; H, 5.97; N, 6.38,

Found: C, 65.35; H, 6.09, N, 6.36.

$[\alpha]_D^{25}$ = – 184.3 (*c* = 0.82, $CHCl_3$)

General procedure for the preparation of hemiacetals from dione 1:

To a suspention of dione **1** (1 equiv.) in anhydrous ether at –20 ^{o}C was added the Grignard Reagent (5 equiv.) and the mixture was stirred at –20 ^{o}C for one h. Saturated aqueous NH_4Cl was added and the reaction mixture was warmed upto ambient temperature. The precipitated solids were dissolved in water and the solution was extracted in ether. The combined ether extracts were dried (Na_2SO_4) and concentrated to give crude **2-7** which can be used further without purification. An analytical sample is obtained by column chromatography.

2*S*,5*S*,6*R*-2,4,5-Trimethyl-2-hydroxy-6-phenyl morpholin-3-one(2):

The reaction of **1** (219 mg, 1 mmol) with MeMgI (5 mL of ~1 M solution in ether, 5 mmol) in anhydrous ether (3 mL) gave crude product (dr = 10/1) which after purification by column chromatography (3/7 petroleum ether/ethyl acetate) 228 mg (97%) of **2** as a solid.

M.P. 79-80 ^{o}C

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.36-7.23 (m, 5H, Ar*H*), 5.47 (d, 1H, *J* = 2.9, PhC*H*), 4.58 (br s, 1H, O*H*), 3.43 (dq, 1H, *J* = 2.9, 6.5 C*H*CH_3), 2.99 (s, 3H, NCH_3), 1.71 (s, 3H, CH_3COH), 0.93 (d, 3H, *J* = 6.5, CHCH_3).

Visible peak of minor diastereomer:

δ 5.16 (d, *J* = 2.9, PhC*H*).

^{13}C NMR (50 MHz, $CDCl_3$)

δ 168.7 (*C*=O), 137.4 (Ar*Cipso*), 128.1 (Ar*C*), 127.4 (Ar*C*), 125.6 (Ar*C*), 95.9 (Ar*C*), 71.2 (Ph*C*H), 59.2 (N*C*H), 33.5 (N*C*H_3), 26.3 (*C*H_3O), 11.9 (*C*H_3CH)

IR ($CHCl_3$)

3340, 2940, 1635, 1490, 1450, 1381, 1220, 1130, 1010, 940, 890, 750 cm^{-1}

MS (70 eV)

m/z 58 (100), 77 (12), 91 (8), 100 (28), 105 (71), 118 (32), 146 (2), 235 (M^+, <1).

Analysis for $C_{13}H_{17}NO_3$

Calcd: C, 66.36; H, 7.28; N, 5.05,

Found: C, 66.38; H, 7.43, N, 5.97.

$[\alpha]_D^{25}$ = – 107.4 (*c* = 1.1, $CHCl_3$).

2*S*,5*S*,6*R*-2-Ethyl-4,5-dimethyl-2-hydroxy-6-phenyl morpholin-3-one (3):

The reaction of **1** (110 mg, 0.5 mmol) with EtMgI (2.5 mL of ~1 M solution in ether, 2.5 mmol) in anhydrous ether (2 mL) gave crude product (dr = 16/1) after purification by column chromatography (petroleum ether/ethyl acetate, 2/3) 114 mg (92%) of **3** as a solid.

M.P. : 88-89 ^{o}C

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.45-7.20 (m, 5H, Ar*H*), 5.52 (d, 1H, *J* = 3.0, PhC*H*), 3.70 (br s, 1H, O*H*), 3.46 (dq, 1H, *J* = 6.5, CH_3CH), 3.03 (s, 3H, NCH_3), 2.26-2.08 (m, 1H, CH_3CH_2), 2.02-1.84 (m, 1H, CH_3CH_2), 1.06 (t, 3H, *J* = 7.0, CH_3CH_2), 0.97 (d, 3H, *J* = 6.5, $CHCH_3$).

Visible peaks of minor diastereomer:

δ 5.17 (d, *J* = 2.9, PhC*H*), 4.05 (br s, 1H, O*H*).

^{13}C NMR (50 MHz, $CDCl_3$)

δ 168.2 (*C*=O), 137.5 (Ar*Cipso*), 127.9 (Ar*C*), 127.1 (Ar*C*), 125.3 (Ar*C*), 97.9 (*C*OH), 70.4 (Ph*C*H), 58.8 (CH_3CH), 33.2 (NCH_3), 32.0 (CH_2), 12.2 ($CHCH_3$), 7.9 (CH_2CH_3)

IR ($CHCl_3$)

3340, 3120, 1640, 1450, 1452, 1220, 1214, 1140, 1021, 749 cm^{-1}

MS (70 eV)

m/z 57 (43), 77 (15), 86 (35), 91 (15), 105 (8), 118 (100), 143 (7), 174 (2), 232 (2).

Analysis for $C_{14}H_{19}NO_3$

Calcd: C, 67.45; H, 7.68; N, 5.62,

Found: C, 67.21; H, 7.75, N, 5.54.

$[\alpha]_D^{25}$ = –110.0 (*c* = 2.3, $CHCl_3$)

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

The reaction of **1** (300 mg, 1.36 mmol) with *i*-propMgCl (7 mL of ~1 M solution in ether, 5 mmol) in anhydrous ether (5 mL) gave crude product (dr = 19/1) which after purification by column chromatography (3/7, petroleum ether/ethyl acetate) 330 mg (91%) of **4** as a solid.

M.P. 100-102 ^{o}C

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.45-7.20 (m, 5H, Ar*H*), 5.5 (d, 1H, *J* = 3.0, PhC*H*), 3.70 (br s, 1H, O*H*), 3.48 (dq, 1H, *J* = 6.7, 3.0, CH_3CH), 3.03 (s, 3H, NCH_3), 2.55-2.35 (m, 1H, $CH(CH_3)_2$), 1.14 (d, 6H, *J* = 6.9, $CH(CH_3)_2$), 0.99 (d, 3H, *J* = 6.9, $CH(CH_3)_2$), 0.96 (d, 3H, *J* = 6.7, $CH(CH_3)_2$).

^{13}C NMR (50 MHz, $CDCl_3$)

δ 168.9 (N*C*O), 137.6 (Ar*Cipso*), 127.9 (Ar*C*), 127.1 (Ar*C*), 125.3 (Ar*C*), 98.7 (*C*OH), 70.2 (Ph*C*H), 58.7 (CH_3CH), 35.3 ($CH(CH_3)_2$), 33.2 (NCH_3), 17.7 (CH_3), 14.2 (CH_3), 12.2 (CH_3)

IR ($CHCl_3$)

3400, 3018, 1651, 1561, 1451, 1381, 1098 1028, 701 cm^{-1}

MS (70 eV)

m/z 58 (76), 77 (12), 91 (23), 118 (100), 220 (4), 246 (2)

Analysis for $C_{14}H_{19}NO_3$

Calcd: C, 68.42; H, 8.04; N, 5.32,

Found: C, 68.42; H, 7.74; N, 5.28.

$[\alpha]_D^{25}$ = –146.5 (*c* = 2.0, $CHCl_3$).

(2*S*,5*S*,6*R*)-2-*tert*-Butyl-2-hydroxy-4,5-dimethyl-6-phenylmorpholin-3-one (5):

The reaction of **1** (226 mg, 1.04 mmol) with *t*-BuMgCl (5.2 mL of ~1 M solution in ether, 5 mmol) in anhydrous ether (3 mL) gave crude product (dr = 19/1) which after purification by column chromatography (1/1, petroleum ether/ethyl acetate) 257 mg (90%) of **4** as a solid.

M.P. 85-86 °C

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.42-7.24 (m, 5H, Ar*H*), 5.41 (d, 1H, *J* = 2.9, PhC*H*), 3.54-3.41 (m, 2H, O*H*, CH_3CH), 3.00 (s, 3H, NCH_3), 1.18 (s, 9H, $C(CH_3)_3$), 0.99 (d, 3H, *J* = 6.4, CH_3CH)

^{13}C NMR (50 MHz, $CDCl_3$)

δ 168.9 (*C*=O), 137.7 (Ar*Cipso*), 128.1 (Ar*C*), 127.4 (Ar*C*), 125.5 (Ar*C*), 100.3 (*C*OH), 71.0 (Ph*C*H), 59.3 (*C*HCH$_3$), 39.7 (*Cquat*(CH$_3$)$_3$), 33.5 (NCH$_3$), 25.2 (C(*C*H$_3$)$_3$), 12.2 (CH$_3$)

IR ($CHCl_3$)

3382, 2979, 2960, 2933, 1643, 1379, 1078, 757 cm^{-1}

MS (70 eV)

m/z 57 (20), 71 (7), 91 (14), 105 (7), 118 (100), 262 (M-CH$_3$, 22)

Analysis for $C_{16}H_{23}NO_3$

Calcd: C, 69.27; H, 8.36; N, 5.05,

Found: C, 69.42; H, 8.12, N, 5.28.

$[\alpha]_D^{25}$ = – 139.0 (*c* = 1.63, $CHCl_3$).

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

The reaction of **1** (50 mg, 0.23 mmol) with cyclopropylMgBr at –78 °C (freshly prepared in THF, 2 mL) in anhydrous ether (1 mL) gave crude product (dr = 19/1) after purification by column chromatography (petroleum ether/ethyl acetate, 2/3) 13 mg (22%) of **6** as gum. (The experimental conditions are unoptimized.)

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.44-7.20 (m, 5H, Ar*H*), 5.51 (d, 1H, *J* = 3.0, PhC*H*), 3.45 (dq, 1H, *J* = 6.3, 3.5, CH$_3$C*H*), 3.41 (br s, O*H*), 3.04 (s, 3H, NC*H*$_3$), 1.77 (m, 1H, C*H* cyclopropyl), 0.94 (d, 3H, *J* = 6.8, CHC*H*$_3$) 0.89-0.51 (m, 4H, (C*H*$_2$)$_2$, cyclopropyl)

IR ($CHCl_3$)

3340, 2874, 1498, 1342, 1257, 1214, 1120, 1064, 1024, 893 cm^{-1}

$[\alpha]_D^{25}$ = – 102.0 (*c* = 1.0, $CHCl_3$).

(2*S*,5*S*,6*R*)-2-Cyclopentyl-2-hydroxy-4,5-dimethyl-6-phenylmorpholin-3-one (7):

The reaction of **1** (25 mg, 0.11 mmol) with cyclopentylMgI (freshly prepared in THF, 1mL) in anhydrous ether (1 mL) gave after purification by column chromatography (petroleum ether/ethyl acetate, 2/3) 12 mg (40%) of **7** as gum. (The experimental conditions are unoptimized)

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.42- 7.24 (m, 5H, Ar*H*), 5.53 (d, 1H, J = 3.0, PhC*H*), 3.49 (dq, 1H, *J* = 2.9, 6.3, CH_3CH), 3.40 (br s, O*H*), 3.02 (s, 3H, NCH_3), 2.77 (pentet, 1H, *J* = 7.8, C*H* cyclopentyl), 1.93-1.47 (m, 8H, $(CH_2)_4$, cyclopentyl), 0.97 (d, 1H, *J* = 6.3, $CHCH_3$)

IR ($CHCl_3$)

3357, 2954, 1645, 1215, 1049, 756 cm^{-1}

MS (70 eV)

m/z 58 (49), 69 (30), 118 (100), 148 (15), 192 (15)

General procedure for the one-pot alkylation/allylation of dione 1

To a suspension of the dione (1equiv.) in dichloromethane at -78 ^oC was added the Grignard reagent (1-1.5 equiv.) and the mixture was stirred for 1 h. at -78 ^oC. $TiCl_4$ (5 equiv.) was added followed by allyltrimethylsilane (5-10 equiv.) and the mixture was stirred at -20 ^oC or allowed to warm up to ambient temperature. Saturated aq. NH_4Cl was added and the precipitated solids were dissolved in water, the solution was extracted with dichloromethane and the combined extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography on silica gel.

2*R*,5*S*,6*R*-2,4,5-Trimethyl-2-(1- propenyl)-6-phenyl morpholin-3-one (8):

The reaction of **1** (219 mg, 1 mmol) in anhydrous dichloromethane (2 mL) and MeMgI (1.3 mL, ~1M solution in ether, 1.3 mmol) at –78 ^0C for 1 h. followed by $TiCl_4$ (0.60 mL, 5.35 mmol) and allyltrimethysilane (1.7 mL, 10.7 mmol), gradual warming to –20 ^oC for

8 h gave crude product (dr = 19/1) which after purification by flash chromatography on silica gel (7/3 petroleum ether/ethyl acetate) 145 mg (56%) of **8** as colourless gum.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.45-7.20 (m, 5H, Ar*H*), 5.98-5.75 (m, 1H, CH_2=C*H*), 5.20 (d, 1H, *J* = 2.7, PhC*H*), 5.18-5.03 (m, 2H, CH_2=CH), 3.50 (dq, 1H, *J* = 6.5, 2.7, CH_3C*H*), 3.04 (s, 3H, NCH_3), 2.83 (dd, 1H, *J* = 14.4, 5.9, CHCH_2), 2.53 (dd, 1H, J = 14.4, 8.7, CHCH_2), 1.50 (s, 3H, CCH_3), 0.98 (d, 3H, *J* = 6.5, CH_3CH)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 171.4 (*C*=O), 137.7 (ArC*ipso*), 132.6 (Ar*C*), 127.8 (Ar*C*), 127.0 (Ar*C*), 125.1 (*C*H=CH_2), 117.6 (CH=*C*H_2), 78.8 (C*C*H_3), 71.7 (Ph*C*H), 58.7 (CH_3*C*H), 40.2 (*C*H_2), 33.2 (N*C*H_3), 24.8 (C*C*H_3), 12.1 (CH*C*H_3)

IR ($CHCl_3$)

3000, 1630, 1430, 1210, 750 cm^{-1}

MS (70 ev)

m/z 58 (53), 67 (22), 77 (19), 91 (27), 105 (18), 117 (40), 148 (100), 174 (6), 190 (27), 218 (69), 259 (M^+, 8)

HRMS (FAB+) for $C_{16}H_{22}NO_2$

Calcd: 260.1651

Found: 260.1645

$[\alpha]_D^{25}$ = – 67.1 (*c* = 2.1, $CHCl_3$)

2*R*,5*S*,6*R*-2-Ethyl-4,5-dimethyl-2-(1-propenyl)-4,5-dimethyl-6-phenylmorpholin-3-one (9):

The reaction of **1** (219 mg, 1 mmol) in anhydrous dichloromethane (2 mL) and EtMgI (1.3 mL, ~1.3 mmol, 1M solution in ether) at –78 ^{0}C for 1 h. followed by $TiCl_4$ (0.55 mL, 5 mmol) and allyltrimethysilane (1.27 mL, 8 mmol), gradual warming to – 20 ^{o}C and stirring

for 6 h, gave crude product (dr = 19/1). Purification by flash chromatography on silica gel (7/3 petroleum ether/ethyl acetate) gave 170 mg (62%) of **9** as a colourless gum.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.45-7.20 (m, 5H, Ar*H*), 5.95- 5.74 (m, 1H, C*H*=CH_2), 5.25 (d, 1H, *J* = 3.0, PhC*H*), 5.15- 5.02 (m, 2H, CH_2=CH), 3.54 (dq, 1H, *J* = 6.5, 3.0, CH_3C*H*), 3.05 (s, 3H, NCH_3), 2.85 (tdd, 1H, *J* = 16.1, 5.8, 1.3, CHCH_2), 2.55 (dd, 1H, *J* = 14.6, 8.5, CHCH_2), 2.08-1.75 (m, 1H, CH_3CH_2), 1.35-1.10 (m, 1H, CH_3CH_2), 1.02 (t, 3H, *J* = 6.6, CH_3CH_2), 0.98 (d, 3H, *J* = 7.8, CH_3CH)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 171.2 (*C*=O), 138.1 (Ar*Cipso*), 133.0 (Ar*C*), 128.1 (Ar*C*), 127.3 (Ar*C*), 125.5 (*C*H=CH_2), 117.9 (CH=*C*H_2), 82.3 (C*C*H_3), 71.4 (Ph*C*H), 59.1 (CH_3*C*H), 40.1 (CH_2=CH*C*H_2), 33.5 (N*C*H_3), 30.9 (CH_3*C*H_2), 12.9 (*C*H_3), 8.7 (*C*H_3)

IR ($CHCl_3$)

3010, 1625, 1440, 1215, 1140, 1030, 750 cm^{-1}

MS (70 eV)

m/z 58 (100), 67 (23), 77 (21), 91 (31), 105 (12), 117 (39), 148 (90), 204 (35), 232 (78), 245 (1), 273 (M^+, 6)

HRMS for $C_{17}H_{24}NO_2$

Calcd: 274.1808

Found: 274.1812

2*R*,5*S*,6*R*-4,5-Dimethyl-6-phenyl-2-(1-propenyl)-2-propyl morpholin-3-one (10):

The reaction of **1** (110 mg, 0.5 mmole) in anhydrous dichloromethane (1 mL) and PrMgI (0.63 mL, 1.25 mmol, 1M solution in ether) at –78 ^{0}C for 1 hr. followed by $TiCl_4$ (0.27 ml, 2.5 mmol) and allyltrimethysilane (0.63 mL, 4 mmol), gradual warming to –20 ^{o}C and stirring for 6 h gave crude product (dr = 19/1). Purification by flash chromatography on silica gel (7/3 petroleum ether/ethyl acetate) gave 79 mg (55%) of **10** as a colourless gum.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.4-7.2 (m, 5H, Ar*H*), 5.95-5.74 (m, 1H, C*H*=CH_2), 5.24 (d, 1H, *J* = 3.0, PhC*H*), 5.13-4.98 (m, 2H, CH_2=CH), 3.50 (dq, 1H, *J* = 6.5, 3.0, CH_3CH), 3.00 (s, 3H, NCH_3), 2.82 (tdd, 1H, *J* = 15, 5.8, 1.3, CHCH_2), 2.53 (dd, 1H, J = 14.6, 8.5, CHCH_2), 1.98-1.55 (m, 3H, $CH_3CH_2CH_2$), 1.4-1.1 ($CH_3CH_2CH_2$), 0.96 (d, 3H, *J* = 6.5, CH_3CH), 0.94 (t, 3H, *J* = 7.6, $CH_3CH_2CH_2$)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 171.3 (*C*=O), 138.1 (Ar*Cipso*), 133.0 (Ar*C*), 128.1 (Ar*C*), 127.3 (Ar*C*), 125.4 (*C*H=CH_2), 117.9 (CH=*C*H_2), 81.9 (*C*CH_3), 71.3 (Ph*C*H), 59.1 (CH_3*C*H), 40.2 (CH=CH_2*C*H_2, *C*$H_2CH_2CH_3$), 33.6 (N*C*H_3), 17.5 (CH_2*C*H_2CH_3), 14.3 (*C*H_3), 12.9 (*C*H_3)

IR ($CHCl_3$)

3010, 1620, 1215, 1145, 1050, 755 cm^{-1}

MS (70 ev)

m/z 58 (40), 71 (50), 77 (32), 84 (49), 91 (19), 105 (52), 118 (49), 148 (100), 218 (20), 246 (57), 281 (2), 287 (M^+, 2)

$[\alpha]_D^{25}$ = –56.4 (*c* =1.8, $CHCl_3$)

2*S*,5*S*,6*R*-4,5-Dimethyl-6-phenyl-2-(1-propenyl)-2-(2-Propyl) morpholin-3-one (11):

The reaction of **1** (219 mg, 1 mmol) in anhydrous dichloromethane (2 mL) and *i*PrMgI (1.5 mL, 1.50 mmol, ~1M solution in ether) at –78 ^{0}C for 1 hr. followed by $TiCl_4$ (0.55 ml, 5 mmol) and allyltrimethysilane (1.27 mL, 8 mmol), gradual warming to –20 ^{o}C and stirring for 6 hours gave crude product (dr = 19/1). Purification by flash chromatography on silica gel (7/3 petroleum ether/ethyl acetate) gave 144 mg (50%) of **11** as a colourless gum.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.50- 7.20 (m, 5H, ArH), 6.10-5.89 (d, 1H, C*H*=CH_2), 5.34 (d, 1H, *J* = 3, PhC*H*), 5.15-4.95 (m, 2H, CH_2=CH), 3.5 (dq, 1H, J = 6.5, 3.0, CH_3C*H*), 3.03 (s, 3H, NCH_3),

2.85-2.58 (m, 2H, CHCH_2), 2.4-2.15 (m, 1H, CH(CH_3)$_2$), 1.09 (d, 3H, J = 6.9, CH_3CHCH_3), 1.04 (d, 3H, J = 6.9, CH_3CHCH_3), 0.95 (d, 3H, J = 6.5, CH_3CH)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 171.2 (*C*=O), 138.3 (Ar*Cipso*), 134.3 (Ar*C*), 128.1 (Ar*C*), 127.2 (Ar*C*), 125.4 (*C*H=CH_2), 117.1 (CH=*C*H_2), 83.2 (*C*CH_3), 71.2 (Ph*C*H), 58.9 (CH_3*C*H), 40.1 (CH_2=CH*C*H_2), 35.3 (CH_3*C*HCH_3), 33.5 (N*C*H_3), 18.7 (*C*H_3), 16.0 (*C*H_3), 12.9 (*C*H_3)

IR ($CHCl_3$)

2970, 2940, 1625, 1440, 1375, 1281, 1140, 1030, 915, 750, 710 cm^{-1}

MS (70 ev)

m/z 57 (39), 71 (76), 77 (37), 91 (40), 105 (34), 118 (100), 148 (93), 218 (41), 246 (97), 287 (M^+, 12)

HRMS for $C_{18}H_{26}NO_2$

Calcd: 288.1965

Found: 288.1969

$[\alpha]_D^{25}$ = –90.9 (*c* =1.6, $CHCl_3$)

(2*S*,5*S*,6*R*)-2-allyl-2-*tert*-butyl-4,5-dimethyl-6-phenylmorpholin-3-one (12):

The reaction of **1** (110 mg, 0.5 mmol) in anhydrous dichloromethane (1mL) and *t*-butylmagnesium chloride (1.5 mL, ~1M solution in THF) at –78 ^{0}C for 1 h followed by $TiCl_4$ (0.55ml, 5 mmol) and allyltrimethysilane (0.8 mL, 5 mmol), gradual warming to ambient temperature and stirring overnight, gave crude product (dr = 19/1). Purification by flash chromatography on silica gel (5/1 petroleum ether/ethyl acetate) gave 76 mg (50%) of **12.**

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.43-7.23 (m, 5H, Ar*H*), 6.09-5.81 (m, 1H, CH_2=C*H*), 5.40 (d, 1H, J = 3.4, PhC*H*), 5.16-4.88 (m, 2H, CH_2=CH), 3.50 (dq, 1H, J = 3.4, 6.8, CH_3C*H*), 3.01 (s, 3H, NCH_3), 2.95-2.90 (m, 1H, CHCH_2), 2.71 (dd, 1H, J = 8.8, 14.6, CHCH_2), 1.18 (s, 9H, C(CH_3)$_3$), 0.98 (d, 3H, J = 6.8, CH_3CH).

^{13}C NMR (75 MHz, $CDCl_3$)

δ 171.2 (*C*=O), 138.6, (Ar*Cipso*), 135.5 (*C*H=CH_2), 128.2 (Ar*C*), 127.3 (Ar*C*), 125.6 (Ar*C*), 116.7 (CH=*C*H_2), 85.5 (O*Cquat*), 72.0 (Ph*C*H), 59.2 (CH_3*C*H), 39.7 (*C*(CH_3)$_3$), 38.1 (*C*H_2CH=CH_2), 33.7 (N*C*H_3), 26.9 (C(*C*H_3)$_3$), 12.8 (CH*C*H_3).

IR ($CHCl_3$)

3269, 2959, 1643, 1452, 1392, 1379, 1363, 1284, 1217, 1145, 1097, 1033, 914 cm^{-1}

MS (70 ev)

m/z 57 (100), 77 (87), 91 (12), 105 (6), 118 (24), 148 (9), 260 (17), 301 (M^+, 3).

HRMS for $C_{19}H_{27}NO_2$

Calcd: 301.2042

Found: 301.2036

$[\alpha]_D^{25}$ = - 110.2 (*c* = 3.4, $CHCl_3$).

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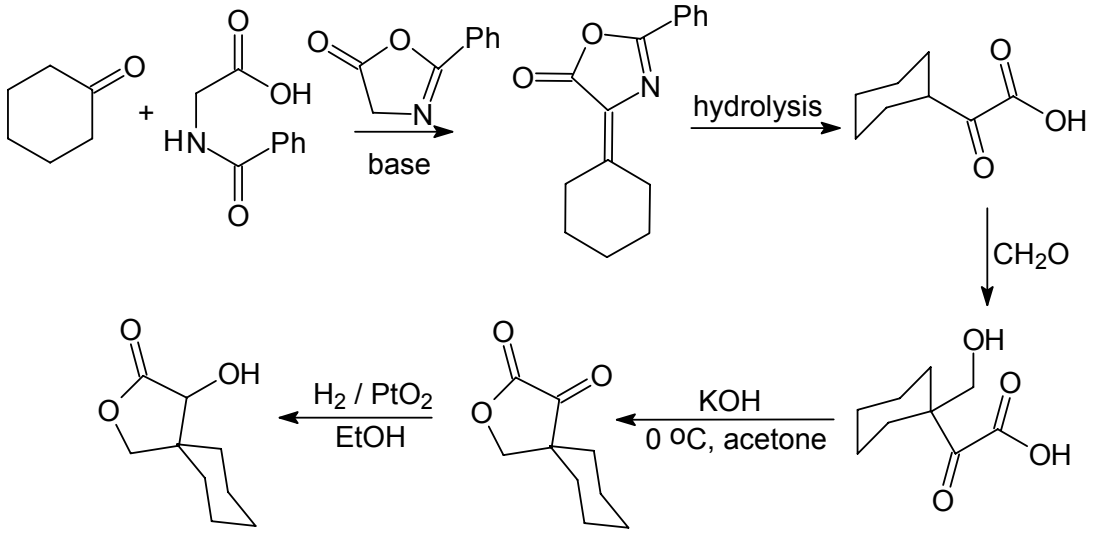
1. INTRODUCTION

The enantioselective synthesis of α-hydroxy γ-butyrolactones[1] has been the subject of several recent investigations. The synthesis of these lactones has attracted considerable interest importance as they comprise vital segments in several naturally occurring chiral molecules.[2] α-Hydroxy γ-butyrolactones with an alkyl chain at the γ-position are useful hunger modulators[3] and serve as key intermediates in the preparation of liquid crystalline compounds.[4] A number of these lactones are natural products and this has spurred interest in their total synthesis.[2] β,β-dialkyl- α-hydroxy γ-butyrolactones have recently been employed as components of interleukin inhibitors.[5] This particular class of butyrolactones and the parent hydroxy acids are also of interest due to their structural similarity to pantolactone[6] and the potential for application as pantothenic acid analogs in biologically relevant molecules[7]. A summary of some of the reported methods for the synthesis of β,β-dialkyl- α-hydroxy γ-butyrolactones is given below.

Fissekis[7a] and co-workers have demonstrated a synthesis of a racemic β-cyclohexyl α-hydroxy γ-butyrolactone starting with the condensation of cyclohexanone and the azlactone derived from hippuric acid. The resulting cyclohexylglyoxalic acid was condensed with

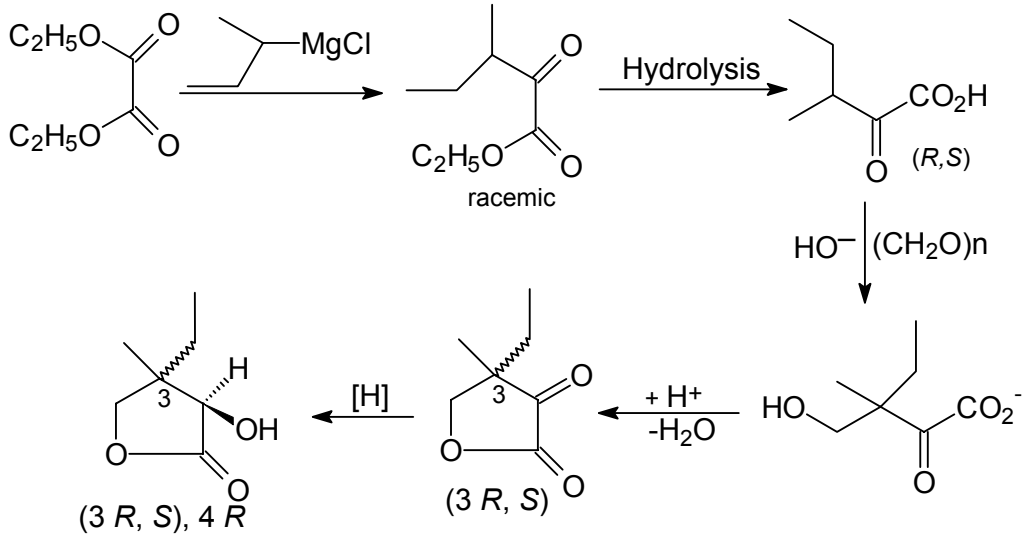
Scheme 1.



formaldehyde and the product was converted to the α-keto lactone. Hydrogenation furnished the required cyclohexyl analogue of pantolactone. This protocol has also been employed for the synthesis of the cyclopentyl derivative (Scheme 1).

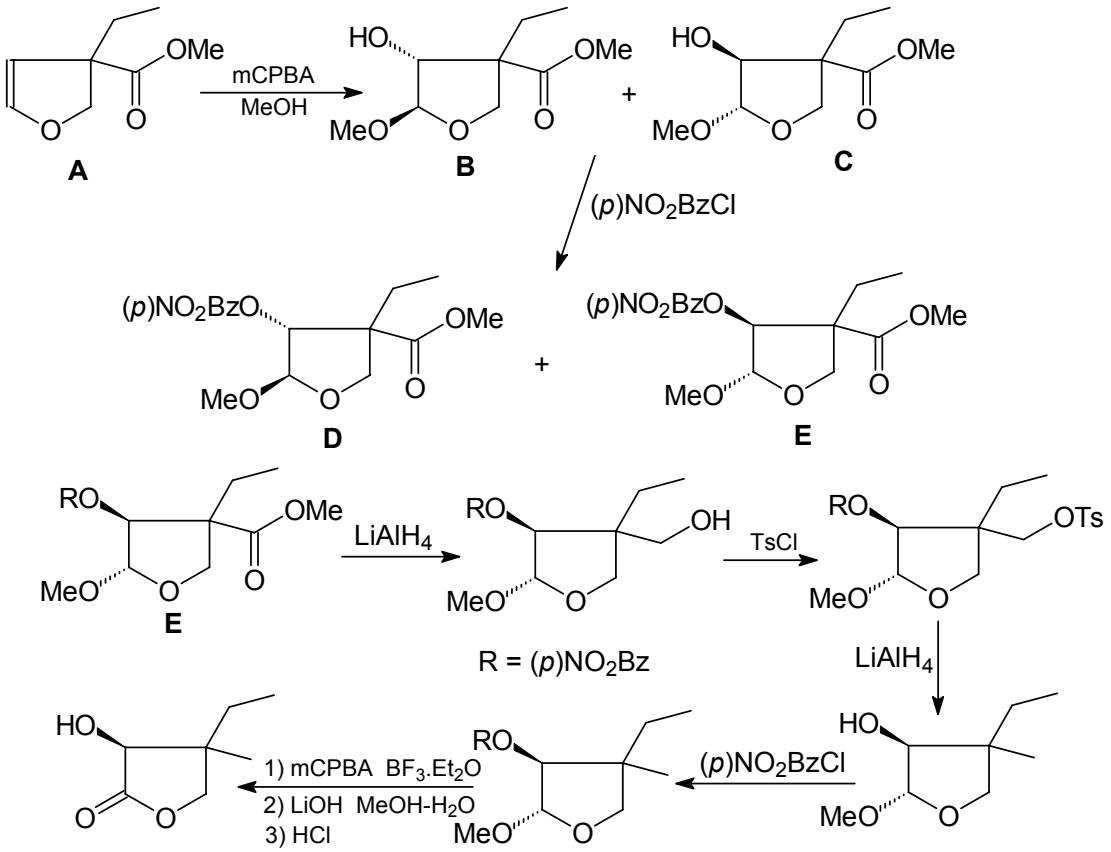
The synthesis of pantolactone homologues as racemates was demonstrated by Wieland and coworkers[8]. The approach involved the reaction of *sec*-butylmagnesium chloride with diethyl oxalate to generate an α-oxo-ester which was hydrolyzed to the corresponding α-keto acid substrate for the key hydroxymethylation reaction with paraformaldehyde. Lactonization of the product α-keto γ-hydroxy butyric acid and subsequent reduction of ketone generated the target α-hydroxy γ-butyrolactones (Scheme 2).

Scheme 2.



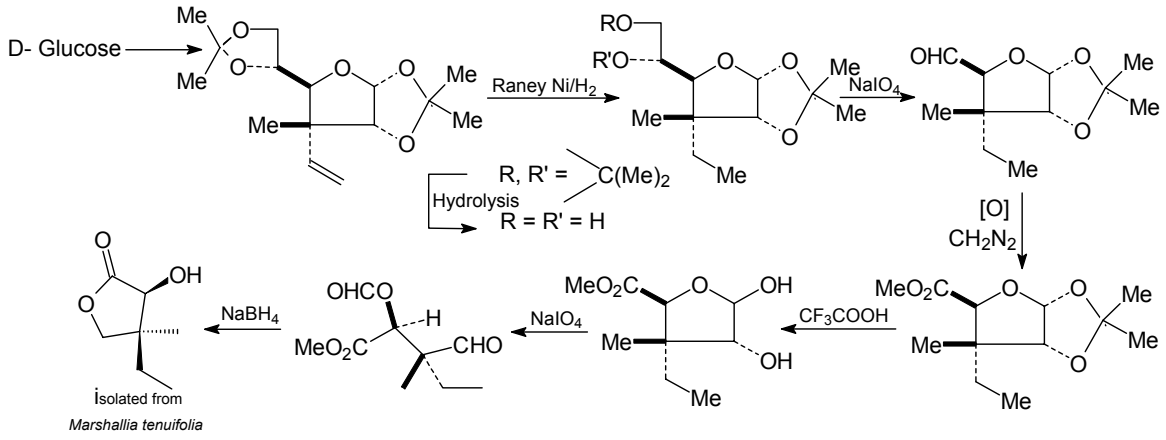
Kinoshita *et al*[9] have also reported a synthesis of pantolactone and its homologues in racemic form. Diastereomers (**B**/**C**= 2/1) generated from **A** were converted to *p*-nitrobenzoate derivatives **D** and **E**, which were separable by silica-gel column chromatography. Further synthetic transformations on **E** resulted in the pantolactone homologue that has been isolated from *Marshallia tenuifolia* (Scheme 3).

Scheme 3



The first asymmetric synthesis of the pantolactone analogue isolated from *Marshallia tenuifolia* (absolute configuration 3*S*,4*S*) was accomplished by Tadano and coworkers in 1988, with an enantiomerically pure tetrahydrofuran derivative from D-glucose by employing

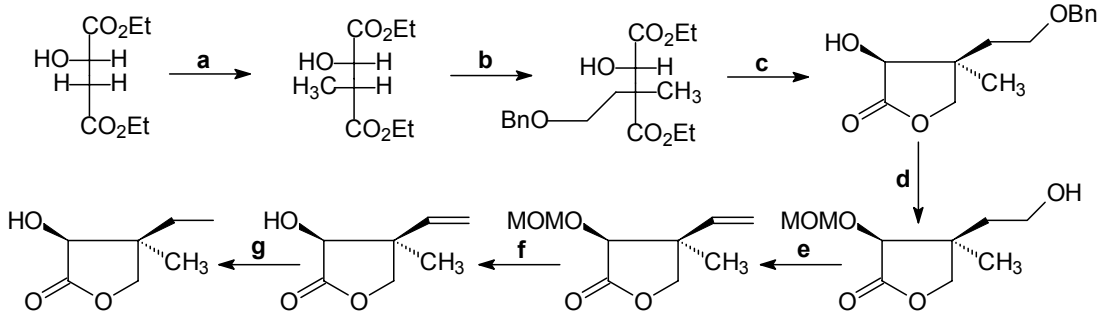
Scheme 4.



the ortho-ester Claisen rearrangement for the introduction of the quartenary stereocenter[10]. Hydrogenation, followed by hydrolysis and subsequent $NaIO_4$ oxidation gave the key aldehyde intermediate which was converted to the natural product in an overall yield of 23% (Scheme 4).

Ueki *et al* have developed an asymmetric synthesis[11] of a pantolactone homologue that has been isolated from the extracts of *Marshallia tenuifolia*. The synthesis employs *S*-malic acid as the starting material. Thus diethyl malate was successfully methylated α to the ester, followed by selective alkaline hydrolysis and ensuing reduction gave α-hydroxy γ-lactone derivative which was converted to the natural product through a series of operations in an overall yield of 15% (Scheme 5).

Scheme 5.



a) Org. Syn. Coll. Vol. VII 1990,153-159 **b**) 2 eqv. LDA, $BnO(CH_2)_2I$, THF -78 ºC **c**) i. KOH,MeOH-H_2O ii.Super hydride **d**) i) MOMCl, $(i\text{-}Pr)_2EtN$, CH_2Cl_2 ii) Pd C, H_2, MeOH **e**) i) o $NO_2C_6H_4SeCN$, Bu_3P, THF ii. 30% H_2O_2, THF **f**) TMSBr, CH_2Cl_2 **g**) Pd-C, H_2

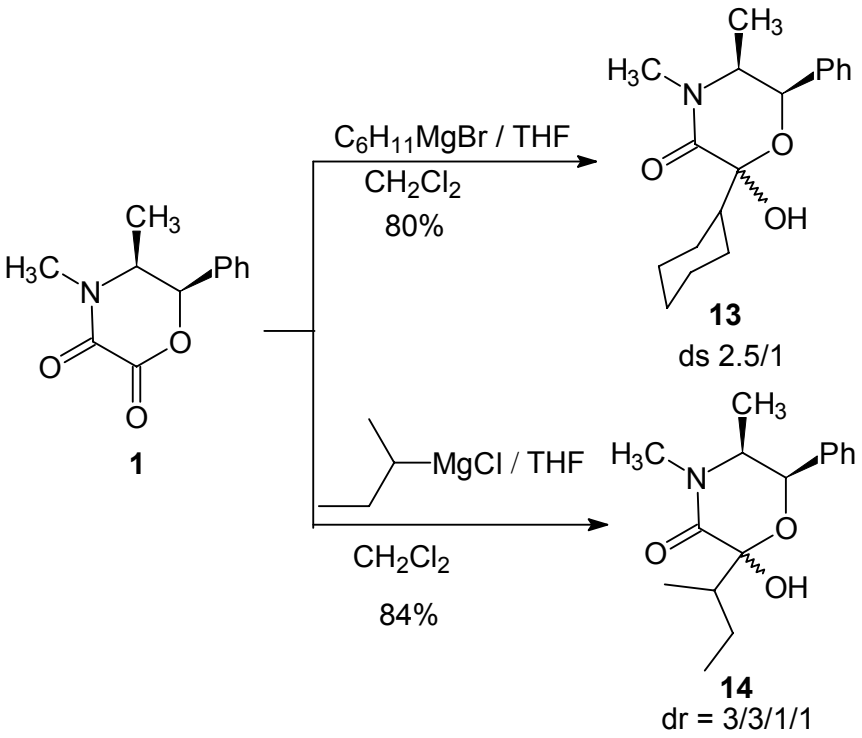
2. OBJECTIVES

The objective of this undertaking was to develop an enantioselective synthesis of β,β-dialkyl α-hydroxy γ-butyrolactones and β-alkyl β-H α-hydroxy γ-butyrolactones from an ephedrine-derived morpholine dione.

3. RESULTS AND DISCUSSION

The observation that organometallic reagents add chemoselectively to the lactone carbonyl of the dione **1** to generate hemiacetals (described in section A) forms the basis of the present investigation. Treatment of dione **1** with cyclohexyl magnesium bromide and *sec*-butyl magnesium chloride for thirty minutes to one hour at ambient temperature generates the respective hemiacetals (Scheme 6).

Scheme 6.

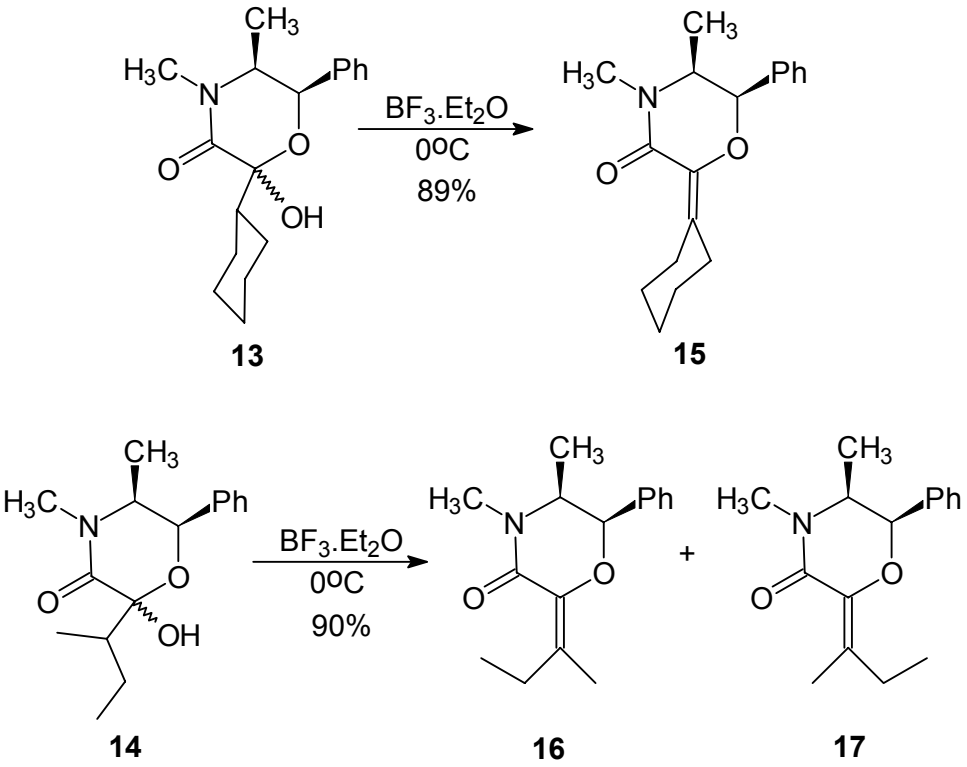


The cyclohexyl hemiacetal **13** was obtained as a mixture of diastereomers in 80% yield and 2.5/1 diastereoselectivity as determined by ^{1}H NMR spectroscopy of the crude product. Complete separation of the diastereomers was difficult. A small quantity of the pure major diastereomer was obtained by repeated flash column chromatography and was characterized. The *sec*-butyl hemiacetal **14** was generated as a mixture of diastereomers (84% yield, dr = 3/3/1/1). The stereochemistry at the hemiacetal carbon for both the hemiacetals

has not been established as the ensuing reaction is dehydration of the hemiacetals to the corresponding olefins.

Dehydration of the hemiacetals **13** and **14** was best achieved with $BF_3.Et_2O$. Dehydration with trifloroacetic acid in refluxing dichloromethane is prohibitively slow, while $TiCl_4$ gave erratic yields. The cyclohexylidene morpholinone **15** was obtained in 89% yield by dehydration of **13**. Dehydration of **14** generated the alkylidene morpholinones **16** (*E*-isomer) and **17** (*Z*-isomer) as 1/1 mixture (Scheme 7).

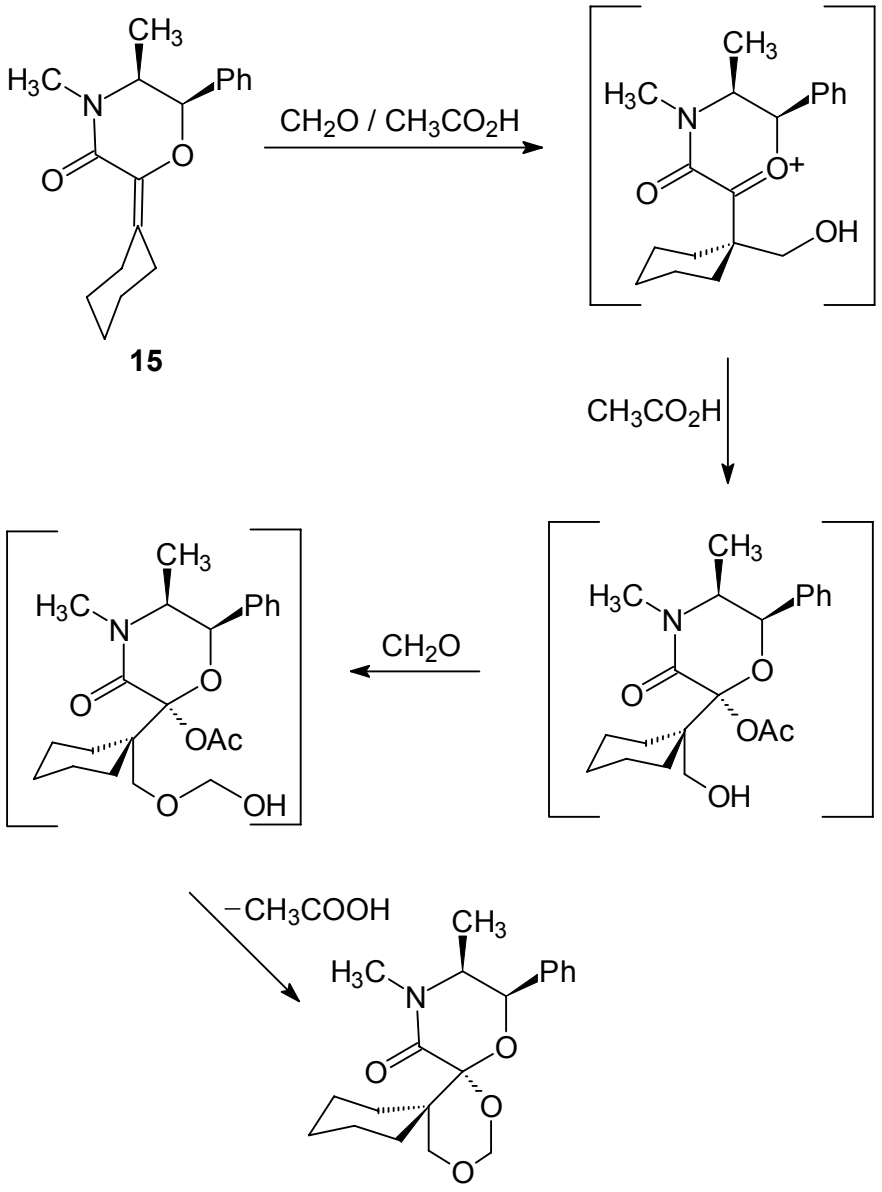
Scheme 7.



The isomers are separable by flash column chromatography. The stereochemistry of **16** and **17** is based on the downfield shift of the methylene hydrogens in **16** (δ 2.6-2.8) as compared to **17** (δ 2.2-2.4). The *E*-isomer (**16**) is white solid while the *Z*-isomer (**17**) is a gum. The overall yield of the reaction is 90% (45% yield of each olefin). Further reactions were conducted on isomerically homogenous **16** and **17**.

We next investigated the Prins reaction[12] of the alkylidene morpholinones **15**, **16** and **17**. Initial investigations of the Prins reaction were conducted with **15** and aqueous formaldehyde as the electrophile.

Scheme 8.

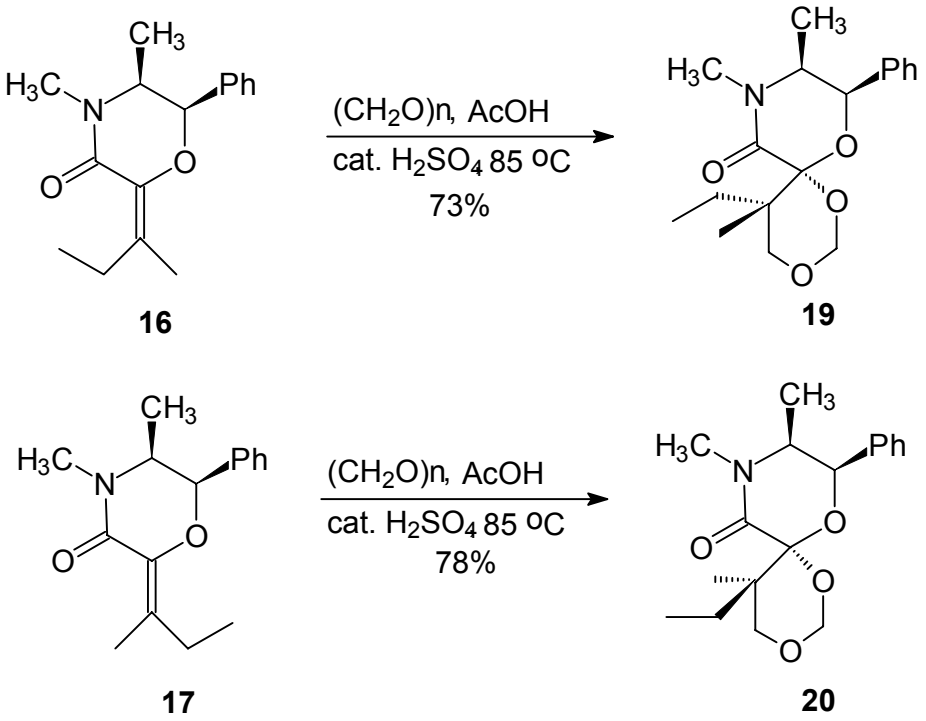


The reaction of **15** and aqueous formaldehyde in dioxane or glacial acetic acid at 85 ^{0}C in presence of concentrated sulphuric acid (catalytic) generated the spiro bis-acetal **18** as a single diastereomer, albeit in very low yields (<10%). Extensive experimentation indicated

that essentially all of **15** is consumed within 90 seconds at 85 ^{o}C, to generate **18** and longer reaction times lead to the complete decomposition of **18**. Thus, the spiro bis-acetal **18** could be efficiently (93% yield) and reproducibly synthesized by strict control of the reaction time and temperature. This is an unusual example of an extremely rapid Prins reaction. The stereochemistry at the spiroacetal stereocentre in **18** is assigned by analogy to other reactions of the oxocarbenium ion intermediate in the ephedrine derived template[13] (Scheme 8).

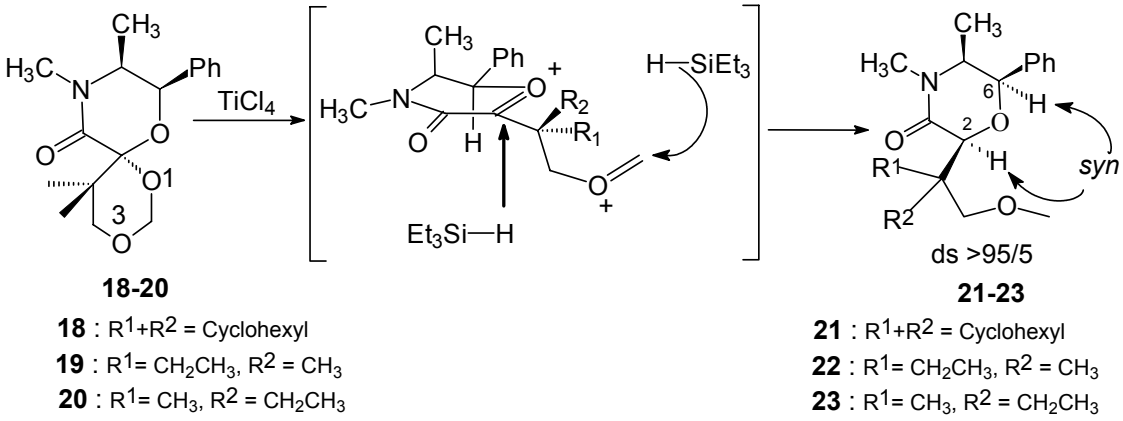
Alkylidene morpholinones **16** and **17** analogously generated spiro bis-acetals **19** (73% yield) and **20** (78% yield**)** stereoselectively. At this stage, the stereochemistry at the quarternary carbon (bearing methyl and ethyl groups) in **19** and **20** was tentatively assigned as delineated in the Scheme 9.

Scheme 9.



Morpholinones **18**-**20** incorporate all the required carbons for the target α-hydroxy butyrates and possess a spiro acetal stereocentre that is subject to stereoselective reduction with silanes. Accordingly, treatment of **18**-**20** with excess $TiCl_4$/triethylsilane efficiently generates the morpholinones **21**-**23** in 90-95% yield as single diastereomers.

Scheme 10.



18-20

18 : R^1+R^2 = Cyclohexyl

19 : R^1= CH_2CH_3, R^2 = CH_3

20 : R^1= CH_3, R^2 = CH_2CH_3

21-23

21 : R^1+R^2 = Cyclohexyl

22 : R^1= CH_2CH_3, R^2 = CH_3

23 : R^1= CH_3, R^2 = CH_2CH_3

The stereochemistry of acetal reduction, presumably, is the result of axial reduction of an intermediate oxocarbenium ion generated by regioselective ring opening of the spiro bis-acetals as shown in Scheme 10.

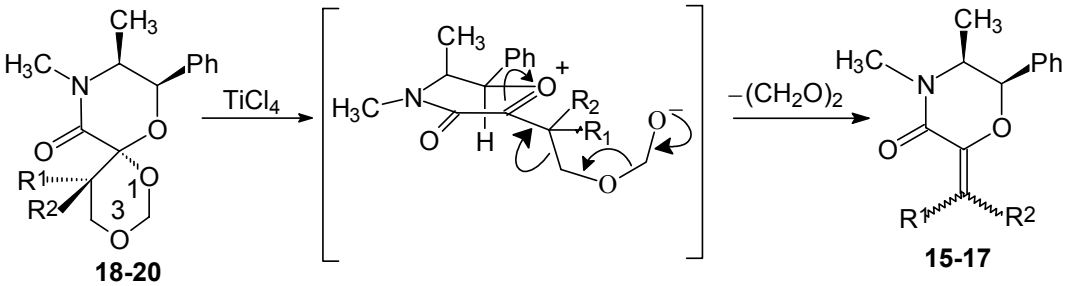
Reasons for the regioselective Lewis acid coordination and acetal cleavage in **18-20** are unclear. Presumably, $TiCl_4$ coordinates with the exocyclic oxygen (O1 Scheme 10) in the spiroacetals **18-20** to generate an endocyclic oxocarbenium ion which is accessible for facile reduction by triethylsilane. Reduction of the resulting methylenedioxy functionality followed by reaction with water generated **21-23**.

It is plausible that the reaction is governed by the stability of the more substituted endocyclic oxocarbenium ion. The opposing dipole of the amide carbonyl may also be a stabilizing factor. The stereochemistry of the newly generated stereocentre was assigned as *S* from a NOESY experiment that indicated a *syn* orientation of the hydrogens on C2 and C6 in morpholinones **21-23**.[14]

It is essential to have an excess triethylsilane (20 equivalents) for successful reductive cleavage of the spiro bis-acetal. Use of lesser equivalents of triethylsilane results in the formation of the olefin which is generated by a competing retro-Prins reaction of the

intermediate oxocarbenium ion. (10% of **15-17** was obtained with 10 equivalents of triethylsilane, Scheme 11).

Scheme 11.



18-20

18 : R^1+R^2 = Cyclohexyl

19 : R^1= CH_2CH_3, R^2 = CH_3

20 : R^1= CH_3, R^2 = CH_2CH_3

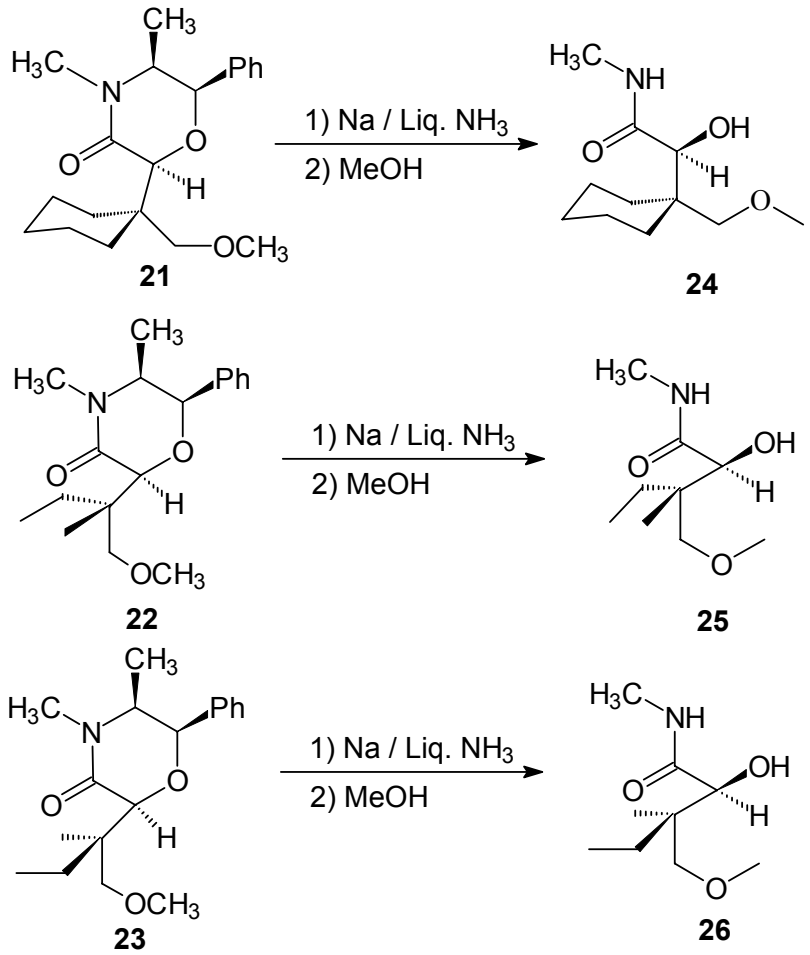
15-17

15 : R^1+R^2 = Cyclohexyl

16 : R^1= CH_2CH_3, R^2 = CH_3

17 : R^1= CH_3, R^2 = CH_2CH_3

Scheme 12



21 **24**

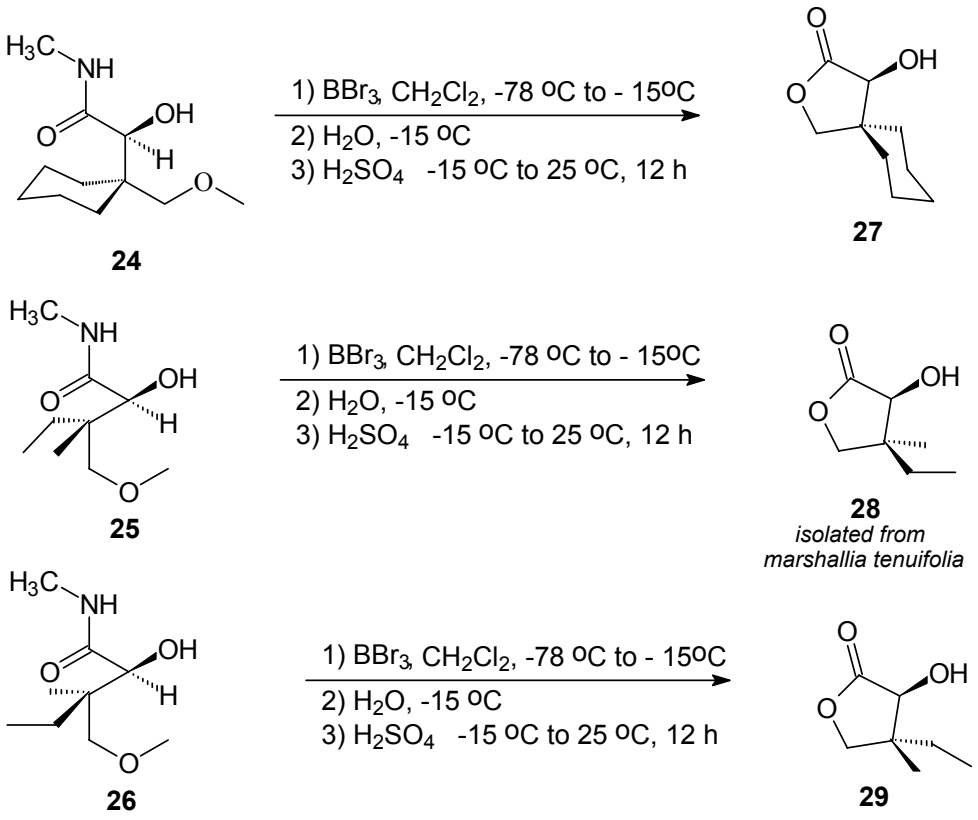
22 **25**

23 **26**

Morpholinones **21-23** are protected versions of the requisite α,γ-dihydroxy butyric acid precursors of the target lactones. Dissolving metal reduction of **21-23** generates the α-hydroxy γ-methoxy butyramides **24-26** in 50-52% yield (Scheme 12).

Conversion of **24-26** to the lactones **27-29** was readily achieved by a one-pot sequence. Liberation of the primary hydroxyl group in **24-26** by demethylation with BBr_3 at –78 ^oC in dichloromethane and subsequent acid catalyzed lactonization (H_2SO_4/H_2O, -15 ^oC to rt) generates the lactones **27-29** in good yields (70-86%). The acid catalyzed lactonization presumably involves a very facile intramolecular acyl transfer from nitrogen to oxygen[15] (Scheme 13).

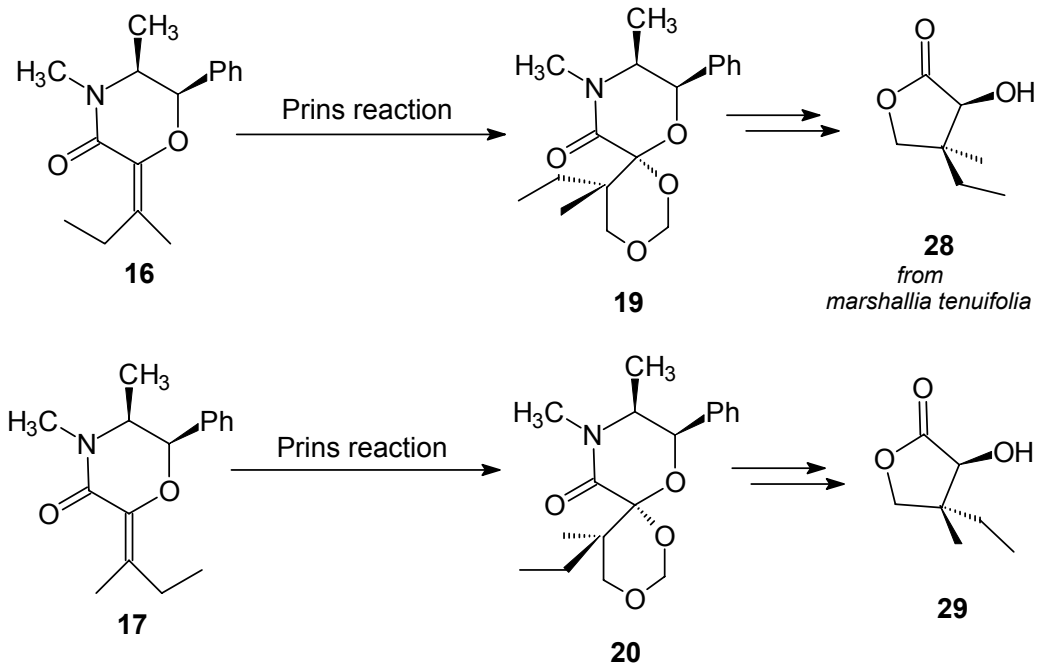
Scheme 13.



The synthesis of **27** constitutes the first asymmetric synthesis of the spiro lactone (*S*) (98% e.e. by chiral GC analysis).[16] Lactones **28** and **29** are diastereomers. One of them is a natural product isolated from *Marshallia tenuifolia*, commonly known as the grassleaf

Barbara's buttons, the absolute configuration of which has been unambiguously established as 3*S*,4*S* by synthesis from D-glucose.[10] A synthesis from (*S*)-malic acid has also been reported recently.[11] The specific rotation and spectroscopic data of **28** (97% e.e.) obtained from our study are in agreement with those of the natural product and **28** therefore has the 3*S*,4*S* configuration. Since the stereochemistry of the α-hydroxy bearing carbon has been established as *S* in the present as well as other related systems, and **28** and **29** are diastereomers, it follows that **29** has 3*S*,4*R* configuration. The Prins reaction of the alkylidene morpholinones **15-17,** is therefore stereospecific and proceeds with retention of olefin geometry. Thus, the *E* isomer **16** generates **19** and *Z*-isomer **17** generates **20**. (Figure 1)

Figure 1



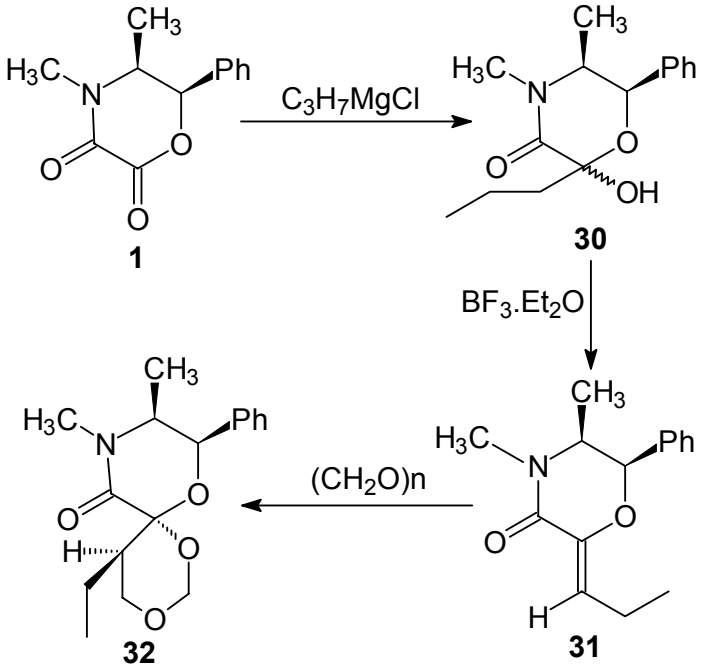
The stereochemistry and the enantiomeric excess of the lactones are summarized in Table 1

Table 1.

Lactone	Absolute Configuration	Enantiomeric Excess%
27	3*S*	98
28	3*S*, 4*S*	97
29	3*S*, 4*R*	97

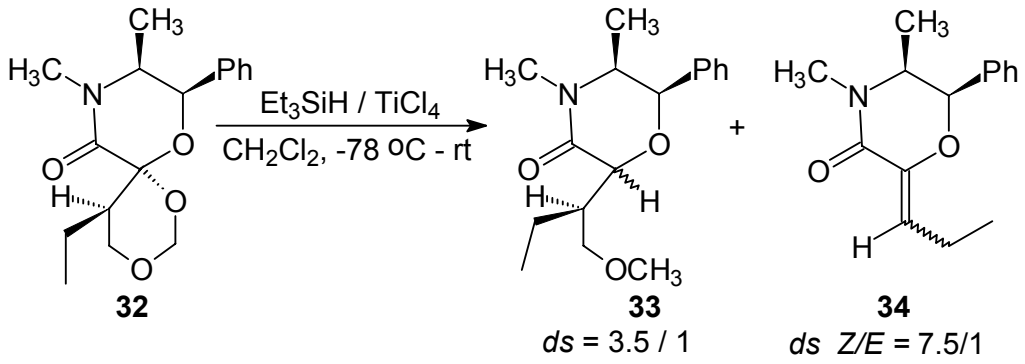
We next explored the above strategy for the synthesis of β-alkyl β-H α-hydroxy γ-butyrolactones. The propyl hemiacetal **30**, prepared from **1** was dehydrated to alkylidene morpholinone **31,** (*Z*-isomer, predominantly)[13] which when subjected to the Prins reaction conditions generated the spiro acetal **32** in a stereoselective manner (ds ≥ 10/1) (Scheme 14).

Scheme 14.



However reductive cleavage of spiro bis-acetal **32** to morpholinone **33** was not stereoselective and generated a mixture of diastereomers (52%, *ds* = 3.5/1) along with the elimination product **34** as a mixture of *E* and *Z* isomers (22%, *ds* = 7.5/1, *Z/E*, Scheme 15).

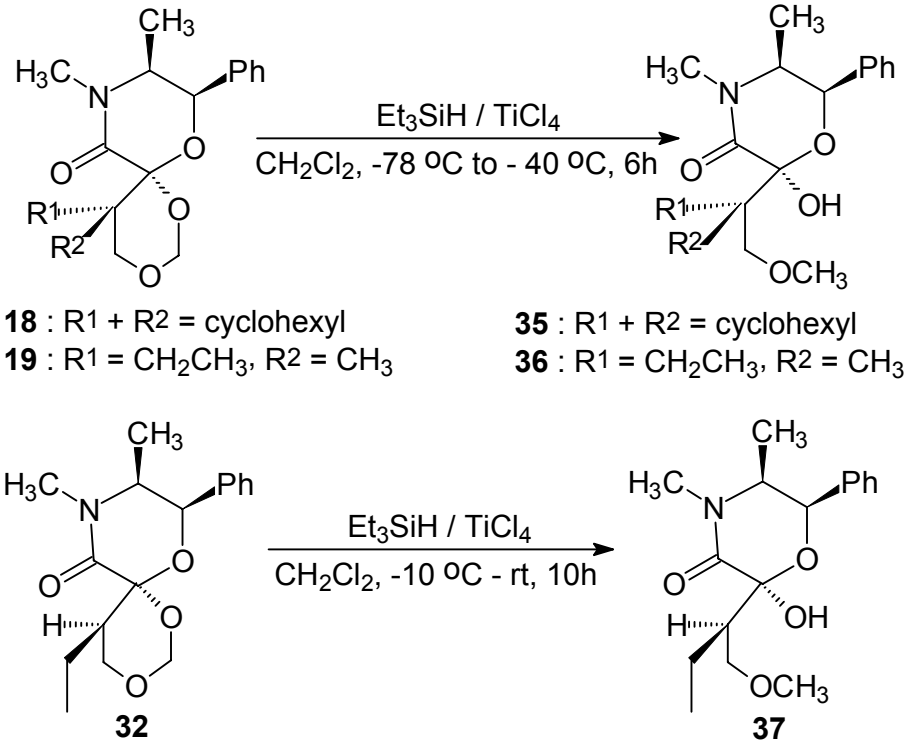
Scheme 15



It is to be noted that there is a marked contrast in the reactions exhibited by the dialkyl spiro bis-acetal (**18**) and monoalkyl spiro bis-acetal (**32**). The reductive cleavage ($TiCl_4/Et_3SiH$) for the former is highly stereoselective while it is not for the latter.

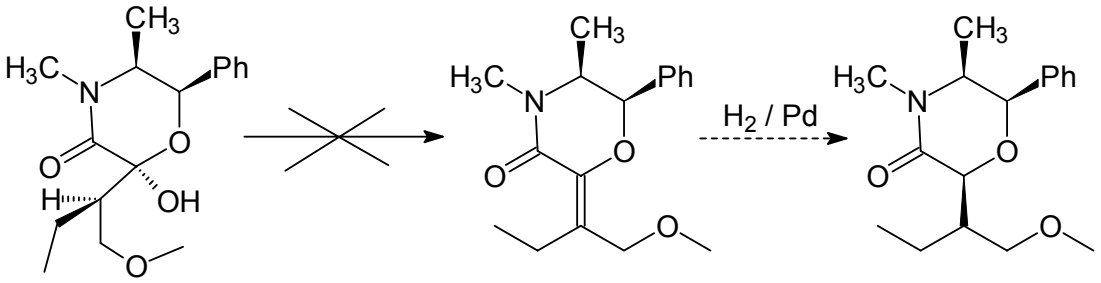
In the course of a detailed investigation on the reduction of these spiro bis-hemiacetals, the hemiacetals **35** and **36** are generated from **18** and **19** respectively by gradual warming from –78 ^oC to –40 ^oC over a period of six hours and quenching the reaction at -40 ^oC with water. In the case of **18** as well as **19**, further warming of the reaction mixture to room temperature (in the presence triethylsilane and without the aqueous quench) leads to the formation of **21** and **22** respectively. In the case of **32**, there is no reaction at -40 ^oC as evidenced by recovery of unreacted **32** after an aqueous quench at -40 ^oC. However, aging the reaction mixture for 10 hours at 0 ^oC, followed by an aqueous quench, generates the hemiacetal **37** *as a single diastereomer* It is not clear why triethyl silane reduction of the oxocarbenium derived from **32** is not as stereoselective as the addition of water (Scheme 16).

Scheme 16



Due to the low diastereoselectivity for reduction of **32**, we attempted to dehydrate **37** to generate the corresponding olefin **F** which could have been utilized to generate **G** by a stereoselective hydrogenation which we have demonstrated to work efficiently for related substrates[13] (Scheme 17).

Scheme 17.



Somewhat surprisingly, the dehydration of **37** could not be affected with several dehydrating agents (conc. H_2SO_4, $BF_3.Et_2O$, CF_3COOH, $POCl_3$, $(CF_3CO)_2O$, $TiCl_4$) under a variety of experimental conditions. The reasons for the resistance of **37** to dehydration are unclear at present.

4. CONCLUSIONS

The ephedrine derived morpholine dione **1** is a convenient precursor for chiral alkylidene morpholinones that are key substrates in a highly stereoselective Prins reaction/acetal reduction protocol. A general, enantioselective route to β,β-disubstituted α-hydroxy butyrolactones has been established. The above procedure should provide access to a variety of enantiomerically enriched β,β-disubstituted α-hydroxy γ-butyrolactones in either enantiomeric form, since both enantiomers of ephedrine are commercially available.

EXPERIMENTAL

General experimental techniques that have been described in the experimental section of Section A were followed.

General procedure for the reaction of 1 with Grignard reagents

To a solution of **1** at an ambient temperature in anhydrous THF was added Grignard reagent over a period of 30 minutes and the reaction mixture was stirred for one hour. Saturated aqueous NH_4Cl solution was added and the precipitated solids were dissolved by adding sufficient water. The mixture was extracted with dichloromethane and the combined extracts were dried over anhydrous Na_2SO_4 and concentrated to furnish the crude product. This was used further without purification.

5*S*,6*R*-2-Cyclohexyl-2-hydroxy-4,5-dimethyl-6-phenyl-morpholin-3-one (13):

Reaction of **1** (1 mmol, 219 mg) and cyclohexyl magnesium bromide (1.5 mL, 1.5 mmol, 1M solution in THF) in anhydrous THF (5 mL) afforded **13** as a mixture of diastereomers (242 mg, 80%). This was used without purification. An analytical sample was obtained by flash column chromatography (2/3 ethyl acetate/ pet. ether)

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.53 -7.24 (m, 5H, Ar*H*), 5.49 (d, 1H, *J* = 3.0, PhC*H*), 3.46 (dq, 1H, *J* = 3.0, 6.3, CH_3CH), 3.03 (s, 3H, NCH_3), 2.23-1.11 (m, 11H, cyclohexyl CH_2, C*H*), 0.95 (d, 3H, *J* = 6.3, $CHCH_3$)

Visible peaks of the minor diastereomer:

δ 5.49 (d, 1H, *J* = 3.0, PhC*H*), 3.55 (dq, 1H, *J* = 3.0, 6.3, CH_3CH), 0.98 (d, 3H, *J* = 6.3, $CHCH_3$).

^{13}C NMR (50 MHz, $CDCl_3$)

δ 169.0 (*C*=O), 137.6 (Ar*Cipso*), 128.1 (Ar*C*), 127.3 (Ar*C*), 125.5 (Ar*C*), 98.8 (O*C*O*quat*), 70.8 (PhCH), 59.0 (NCH), 45.4 (*C*H cyclohexyl), 33.4 (NCH_3), 28.2

(*C*H_2 cyclohexyl), 26.4 (*C*H_2 cyclohexyl), 26.0 (*C*H_2 cyclohexyl), 24.4 (*C*H_2 cyclohexyl), 12.5 (*C*H_3CH)

IR ($CHCl_3$)

3353, 2931, 2854, 1643, 1452, 1380, 1215, 1145, 1020, 756, 700 cm^{-1}

MS (70ev)

m/z 58 (14), 91 (11), 118 (100), 146 (20), 197 (10), 220 (26), 275 (3)

Analysis for $C_{18}H_{25}NO_3$

Calcd: C, 71.25; H, 8.23; N, 4.61,

Found: C, 71.28; H, 8.34; N, 4.38.

(5*S*,6*R*)-2-*sec*-Butyl-2-hydroxy-4,5-dimethyl-6-phenylmorpholin-3-one (14):

Reaction of **1** (1.014 g, 4.63 mmol) and sec-butylmagnesium chloride (6.95 mL, 1M solution in ether) in anhydrous THF (10 mL) furnished a 3:3:1:1 mixture of diastereomers, **14** as a gum (1.08 g, 84%) which was used further without purification. An analytical sample was obtained by flash column chromatography (1/1 ethyl acetate/pet. ether)

^{1}H NMR (200 MHz, $CDCl_3$)

Major diastereomers:

δ 7.49-7.24 (m, 5H, Ar*H*), 5.50 (br, 1H, PhC*H*), 3.62-3.41 (m, 2H, C*H*CH_3, C*H*OH), 3.03 (s, 3H, NCH_3), 2.26-2.07 (m, 1H, C*H*CH_2), 2.02-1.80 (m, 1H, CH_2), 1.50-1.19 (m, 1H, CH_2), 1.14-0.91 (m, 9H, 2 xC*H*CH_3, CH_2CH_3)

Visible peaks for the minor diastereomers:

δ 5.72 (d, 1H, *J* = 2.5, PhC*H*), 5.61 (d, 1H, *J* = 3.0, PhC*H*), 3.12 (s, 3H, NCH_3), 3.05 (s, 3H, NCH_3), 1.15 (d, 3H, CHCH_3)

^{13}C NMR (50 MHz, $CDCl_3$)

δ 169.3 (*C*=O), 137.9 (Ar*Cipso*), 128.4 (Ar*C*), 127.6 (Ar*C*), 125.8 (Ar*C*), 99.8 (*C*OH), 99.5 (*C*OH, diastereomer), 71.0 (Ph*C*H), 59.3 (N*C*H), 42.8 (*C*HCH_2), 42.5 (*C*HCH_2,

diastereomer), 33.7 (N*C*H_3), 25.2 (*C*H_2CH_3), 21.4 (*C*H_2CH_3, diastereomer), 14.8 (CH*C*H_3), 12.7 (CH_2*C*HCH_3), 12.4 (CH_2*C*HCH_3, diastereomer), 10.8 (CH_2*C*H_3).

IR ($CHCl_3$)

3332, 2969, 1738, 1632, 1452, 1147, 700 cm^{-1}

MS (70 ev)

m/z 58 (53), 91 (14), 118 (100), 160 (14), 220 (13), 277 (M^+, 1)

HRMS for $C_{36}H_{33}NO_3$

Calcd: 277.1678

Found: 277.1673

General procedure for dehydration of hemiacetals 13 and 14

To a solution of hemiacetal in anhydrous dichloromethane, at 0 ^oC, was added $BF_3.Et_2O$ at 0 ^oC and the mixture was warmed to ambient temperature. After stirring for six hours cold water was added and the organic layer was separated. The aq. layer was extracted with dichloromethane and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product which was purified by flash chromatography on silica gel to furnish olefins **15-17**.

5*S*,6*R*-2-Cyclohexylidene-4,5-dimethyl-6-phenyl-morpholin-3-one (15):

Reaction of **13** (1.108 g, 3.65 mmol) with $BF_3.Et_2O$ (4.62 mL, 36.5 mmol) in anhydrous dichloromethane (20 mL), gave after purification by flash column chromatography (1/4 ethyl acetate/pet. ether) 1.04g (89%)of **15** as colourless liquid which solidified upon refrigeration.

M.P = 184 - 185 ^oC

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.42-7.32 (m, 5H, Ar*H*), 5.12 (d, 1H, *J* = 2.2, PhC*H*), 3.55 (dq, 1H, *J* = 2.2, 6.7 CH_3CH), 3.22-2.84 (m, 1H, CH_2, cyclohexyl) 3.06 (s, 3H, NCH_3), 2.53-2.34 (m, 2H, CH_2, cyclohexyl), 1.73-1.51 (m, 6H, CH_2, cyclohexyl) 0.98 (d, 3H, *J* = 6.6, $CHCH_3$)

^{13}C NMR (50 MHz, $CDCl_3$)

δ 160.7 (*C*=O), 137.3 (Ar*Cipso*), 135.7 (OC=*C*), 134.0 (OC=*C*), 128.0 (Ar*C*), 127.3 (Ar*C*), 125.1 (Ar*C*), 76.7 (Ph*C*H), 58.4 (N*C*H), 33.1 (NCH_3), 28.3 (CH_2C=C), 28.0 (CH_2C=C), 27.7 (CH_2 cyclohexyl), 27.4 (CH_2 cyclohexyl), 26.1 (CH_2 cyclohexyl), 11.5 (CH_3CH)

IR ($CHCl_3$)

2948, 2850, 1649, 1622, 1448, 1292, 1016, 756, 707 cm^{-1}

MS (70 ev)

m/z 67 (11), 77 (16), 91 (20), 118 (100), 168 (4), 205 (14) , 285 (M^+, 8).

Analysis for $C_{18}H_{23}NO_2$

Calcd : C, 75.75; H, 8.05, N, 4.90,

Found : C, 76.08; H, 8.03; N, 4.77.

$[\alpha]_D^{25}$ = -148.3 (*c* = 2.1, $CHCl_3$)

Olefins 16 and 17

Reaction of **14** (1.08 g, 3.9 mmol) with $BF_3.Et_2O$ (4.95 mL, 39 mmol) in anhydrous dichloromethane (30 ml) gave crude **16** and **17** as mixture of diastereomers. Careful chromatography (crude mixture loaded on 1/19 ethyl acetate/pet.ether and eluted with 3/17 ethy acetate/pet.ether) gave 450 mg (45%) of **16** as a white solid and 450 mg (45%) of **17** as a gum.

(2,1')*E*,5*S*,6*R*-4,5-Dimethyl-2-(1-methylpropylidene)-6-phenylmorpholin-3-one (16):

M.P. = 80-81 ^{0}C

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.41-7.35 (m, 5H, Ar*H*), 5.14 (d, 1H, *J* = 2.9, ArC*H*), 3.56 (dq, 1H, *J* = 2.9, 6.8, CH_3CH), 3.07 (s, 3H, NCH_3), 2.81-2.65 (m, 2H, CH_2CH_3), 1.90 (s, 3H, CCH_3), 1.14 (t, 3H, *J* = 7.3, CH_2CH_3), 0.98 (d, 3H, *J* = 6.8, $CHCH_3$)

^{13}C NMR (50MHz, $CDCl_3$)

δ 160.3 (*C*=O), 138.0 (Ar*C*), 137.6 (O*C*O), 132.5 (CCH_2CH_3), 128.2 (Ar*C*), 127.6 (Ar*C*), 125.3 (Ar*C*), 76.7 (Ar*Cipso*), 58.6 (N*C*H), 33.2 (NCH_3), 26.3 (CH_2CH_3), 17.4 (CH_2CH_3), 12.9 (CCH_3), 11.7 ($CHCH_3$)

IR ($CHCl_3$)

3031, 2957, 2872, 1657, 1498, 1378, 1286, 1172, 1069, 1018, 706 cm^{-1}

MS (70 ev)

m/z 69 (22), 98 (31), 118 (100), 126 (8), 142 (4), 186 (5), 259 (M^+,12).

Analysis for $C_{16}H_{21}NO_2$

Calcd: C, 74.08; H, 8.16; N, 5.40,

Found: C, 73.71; H, 8.48; N, 5.62

$[\alpha]_D^{25}$ = -180.0 (*c* = 0.5, $CHCl_3$)

(2,1')*Z*,5*S*,6*R*-4,5-Dimethyl-2-(1-methylpropylidene)-6-phenylmorpholin-3-one (17):

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.40-7.30 (m, 5H, Ar*H*), 5.13 (d, 1H, *J* = 3.0, ArC*H*), 3.60 (dq, 1H, *J* = 2.9, 6.9, CH_3CH), 3.07 (s, 3H, NCH_3), 2.41-2.28 (m, 2H, CH_2CH_3), 2.25 (s, 3H, CCH_3), 1.09 (t, 3H, *J* = 7.4, CH_2CH_3), 0.97 (d, 3H, *J* = 6.8, $CHCH_3$)

^{13}C NMR (50MHz, $CDCl_3$)

δ 160.4 (*C=O*), 137.6 (Ar*C*), 137.2 (O*C*O), 131.7 (CCH_2CH_3), 127.9 (Ar*C*), 127.2 (Ar*C*), 124.9 (Ar*C*), 76.3 (Ph*C*H), 58.3 (N*C*H), 32.9 (NCH_3), 26.4 (CH_2CH_3), 17.4 (CH_2CH_3), 11.5 (CCH_3), 11.3 ($CHCH_3$)

IR ($CHCl_3$)

2972, 2874, 1657, 1498, 1378, 1260, 1171, 1067, 1020, 707 cm^{-1}

MS (70 ev)

69 (15), 91 (19), 118 (100), 142 (5), 205 (1), 259 (M^+, 19)

Analysis for $C_{16}H_{21}NO_2$

Calcd: C, 74.08; H, 8.16; N, 5.40,

Found: C, 73.70; H, 7.85; N, 5.10

General procedure for the Prins reaction of olefins 15-17:

To a solution of olefins **15-17** and paraformaldehyde in glacial acetic acid was added concentrated H_2SO_4 (2 drops) and the mixture was heated rapidly for 90 seconds in a preheated oil-bath set at 85 ^oC. After cooling reaction mixture it was neutralized with saturated aqueous sodium bicarbonate solution. The mixture was extracted with ether and the combined extracts were washed with water and brine, dried (Na_2SO_4) and concentrated. Removal of ether under reduced pressure gave crude product which was purified by flash chromatography.

2*R*,3*S*,6*R* 3,4-Dimethyl-2-phenyl-1,14,16-trioxa-4-aza-dispiro[5.0.5.4]hexadecane-5-one (18):

Reaction of **15** (830 mg, 2.9 mmol) with paraformaldehyde (437 mg, 14.6 mmol) in glacial acetic acid (10 mL) gave after purification by flash column chromatography (1/4 ethyl acetate / pet.ether) on silica gel 939 mg (93%) **18** as white solid.

M.P. = 74 ^oC

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.45-7.29 (m, 5H, Ar*H*), 5.42 (d, 1H, *J* = 3.0, PhC*H*), 5.12 (d, 1H, *J* = 5.4, OCH_2O), 5.09 (d, 1H, *J* = 5.4, OCH_2O), 4.39 (d, 1H, *J* = 11.0, OCH_2C), 4.13 (d, 1H, *J* = 11.0, OCH_2C), 3.47 (dq, 1H, *J* = 3.0, 6.4, CH_3C*H*), 3.02 (s, 3H, NCH_3), 2.09-1.19 (m, 10H, cyclohexyl), 1.00 (d, 3H, *J* = 6.4, CH_3CH)

^{13}C NMR (50 MHz, $CDCl_3$)

δ 164.7 (*C*=O), 137.1 (Ar*C*), 128.2 (Ar*C*), 127.4 (Ar*C*), 125.2 (Ar*C*), 99.5 (O*C*O*quat*), 88.0 (O*C*H_2O), 70.4 (Ph*C*H), 66.7 (C*C*H_2O), 58.6 (N*C*H), 40.6 (C*quat*), 33.4 (N*C*H_3), 27.7 (*C*H_2 cyclohexyl), 27.3 (*C*H_2 cyclohexyl), 25.7 (*C*H_2 cyclohexyl), 20.9 (*C*H_2 cyclohexyl), 12.2 (*C*H_3CH)

IR ($CHCl_3$)

4214, 3631, 3450, 3018, 2931, 2866, 2401, 1654, 1454, 1215, 985, 765, 669, cm^{-1}.

MS (70 ev)

81 (17), 91 (23), 118 (100), 130 (4), 146 (5), 192 (5), 220 (21), 345 (M^+, 4)

HRMS for $C_{20}H_{27}NO_4$

Calcd: 345.1941

Found: 345.1940

$[\alpha]_D^{25}$ = - 81.1 (*c* = 1.4, $CHCl_3$)

(5*S*,8*R*,9*S*)-5-Ethyl-5,9,10-trimethyl-8-phenyl-1,3,7-trioxa-10-azaspiro[5.5]undecan-11-one (19):

Reaction of **16** (382 mg, 1.47 mmol) with paraformaldehyde (221 mg, 7.4 mmol) in glacial acetic acid (9 mL) gave after purification by flash column chromatography ((3/17 ethyl acetate / pet.ether) 352 mg (75%) of **19** as white solid.

M.P. = 110 ^oC

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.45-7.31 (m, 5H, Ar*H*), 5.48 (d, 1H, *J* = 3.0, PhC*H*), 5.24 (d, 1H, *J* = 5.4, OCH_2O), 5.03 (d, 1H, *J* = 5.4, OCH_2O), 4.26 (d, 1H, *J* = 11.0, OCH_2C), 3.83 (d, 1H, *J* = 11.0, OCH_2C), 3.50 (dq, 1H, *J* = 3.0, 6.4, CH_3C*H*), 3.01 (s, 3H, NCH_3), 1.79 (m, 2H, CC$H_2$$CH_3$), 1.16 (s, 3H, CC$H_3$), 0.99 (d, 3H, *J* = 6.4 CCH_2CH_3), 0.89 (t, 3H, *J* = 7.4, CHCH_3)

^{13}C NMR (50MHz,$CDCl_3$)

δ 164.8 (*C*=O), 137.0 (Ar*Cipso*), 128.1 (Ar*C*), 127.4 (Ar*C*), 125.1 (Ar*C*), 99.1 (O*C*O*quat*), 88.5 (O*C*H_2O), 70.6 (O*C*H_2C), 70.2 (Ph*C*H), 58.5 (N*C*H), 40.6 (*C*CH_2CH_3), 33.2 (N*C*H_3), 25.3 (C*C*H_2CH_3), 17.2 (C*C*H_3), 12.2 (*C*H_3CH), 7.5 (CH_2*C*H_3)

IR ($CHCl_3$)

3018, 2979, 2885, 1650, 1497, 1215, 1095, 975, 757 cm^{-1}

MS (70ev)

m/z 69 (23), 103 (19), 118 (100), 146 (4), 220 (6), 319 (M^+,1).

Analysis for $C_{18}H_{25}NO_4$

Calcd: C, 67.67; H, 7.89; N, 4.38

Found: C, 67.29; H, 8.22; N, 4.13

$[\alpha]_D^{25}$ = -136.0 (*c* = 0.5, $CHCl_3$)

(5*R*,8*R*,9*S*)-5-Ethyl-5,9,10-trimethyl-8-phenyl-1,3,7-trioxa-10-azaspiro[5.5]undecan-11-one (20):

Reaction of **17** (342 mg, 1.3 mmol) with paraformaldehyde (198 mg, 6.6 mmol) in glacial acetic acid (8 mL) gave after purification by flash column chromatography (3/17 ethyl acetate / pet.ether) 328 mg (78%) of **20** as a colourless solid.

M.P. = 85 ^oC

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.40-7.31 (m, 5H, Ar*H*), 5.42 (d, 1H, *J* = 2.9, PhC*H*), 4.99 (AB system, *J* =7.0, 2H, OCH_2O), 4.05 (d, 1H, *J* = 11.0, OCH_2C), 3.76 (d, 1H, *J* = 11.0, OCH_2C), 3.53 (dq, 1H, *J* = 2.9, 6.3, CH_3C*H*), 3.00 (s, 3H, NCH_3), 1.63-1.48 (m, 2H, CH_2CH_3), 1.41 (s, 3H, CH_3), 0.99 (d, 3H, *J* = 6.3, CH_3CH), 0.90 (t, 3H, *J* = 7.3, CH_2CH_3)

^{13}C NMR (50 MHz, $CDCl_3$)

δ 164.6 (*C*=O), 136.9 (Ar*Cipso*), 128.3 (Ar*C*), 127.6 (Ar*C*), 125.2 (Ar*C*), 99.5 (O*C*O *quat*), 87.3 (O*C*H_2O), 72.1 (O*C*H_2C), 70.3 (Ph*C*H), 58.8 (N*C*H), 40.7 (*C*CH_2CH_3), 33.6 (N*C*H_3), 25.7 (C*C*H_2CH_3), 18.4 (C*C*H_3), 12.2 (*C*H_3CH), 7.4 (CH_2*C*H_3)

IR ($CHCl_3$)

3018, 2883, 1658, 1461, 1400, 1215, 1095, 977, 756 cm^{-1}

MS (70 ev)

m/z 73 (81), 103 (100), 118 (73), 133 (10), 220 (3), 319 (M^+, 3).

Analysis for $C_{18}H_{25}NO_4$

Calcd: C, 67.67; H, 7.89; N, 4.38

Found: C, 67.77; H, 8.05; N, 4.49

General procedure for reductive cleavage of spirobisacetal 18-20

To a solution of the Prins product **18-20** in anhydrous dichloromethane was added at –78 ^oC titanium tetrachloride followed by triethylsilane. The reaction mixture was warmed to ambient temperature and stirred for 24 hours. It was then cooled to –5 ^oC and saturated aqueous ammonium chloride was added and warmed to ambient temperature. Water was added to dissolve the precipitated solids and the solution was extracted with dichloromethane. The dichloromethane layer was dried (Na_2SO_4), and concentrated to obtain crude product which on purification by flash column chromatography rendered **21-23** as colourless oils.

2*S*,5*S*,6*R*-2-((1-Methoxymethyl) cyclohexyl)-4,5-dimethyl-6-phenyl-morpholin-3-one (21):

Reduction of **18** (840 mg 2.4 mmol) with titanium tetrachloride (4.6 mL, 42 mmol) and triethylsilane (7.8 mL, 48.6 mmol) in anhydrous dichloromethane (28 mL) gave after purification by flash column chromatography (1/4 ethyl acetate/pet. ether) 747 mg (93%) of **21** as a colourless oil.

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

δ 7.38-7.39 (m, 5H, Ar*H*), 4.92 (d, 1H, *J* = 3.0, PhC*H*), 4.32 (s, 1H, C*H*O), 3.73 (d, 1H, *J* = 9.1, CH_2), 3.52 (d, 1H, *J* = 9.1, CH_2), 3.51 (dq, 1H, *J* = 3.0, 6.3, CH_3C*H*), 3.30 (s, 3H, OCH_3), 2.99 (s, 3H, NCH_3), 2.00-1.35 (m, 10H, cyclohexyl), 0.96 (d, 3H, *J* = 6.3, CH_3CH)

^{13}C NMR (50MHz, $CDCl_3$)

δ 169.0 (*C*=O), 138.1 (Ar*C*), 127.9 (Ar*C*), 127.1 (Ar*C*), 125.1 (Ar*C*), 79.5 (*C*HO), 76.1 (Ph*C*H), 74.2 (*C*H_2O), 58.6 (O*C*H_3), 58.4 (CH_3*C*H), 42.6 (*Cquat* cyclohexyl), 33.2 (N*C*H_3), 29.6 (*C*H_2 cyclohexyl), 29.4 (*C*H_2 cyclohexyl), 25.8 (*C*H_2 cyclohexyl), 21.4 (*C*H_2 cyclohexyl), 21.3 (*C*H_2 cyclohexyl), 12.4 (*C*H_3CH)

IR ($CHCl_3$)

3452, 3005, 2929, 2865, 1642, 1453, 1379, 1249, 1188, 1105, 1061, 702, 666 cm^{-1}

MS (70 ev)

m/z 58 (26), 67 (15), 91 (20), 105 (17), 148 (10), 205 (99), 267 (7), 331 (M^+, 2).

HRMS for $C_{20}H_{29}NO_2$

Calcd : 331.2147

Found : 331.2128

$[\alpha]_D^{25}$ = -123.2 (*c* = 3.4, $CHCl_3$)

(2*S*,5*S*,6*R*)-2-[(1*S*)-1-(Methoxymethyl)-1-methylpropyl]-4,5-dimethyl-6-phenylmorpholin-3-one (22):

Reduction of **19** (334 mg, 1 mmol) with titanium tetrachloride (3.3 mL, 30 mmol) and triethylsilane (3.3 mL, 21 mmol) in anhydrous dichloromethane (15 mL) gave after purification by flash column chromatography (1/4 ethyl acetate/pet. ether) 284 mg (93%) of **22** as a colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.45-7.24 (m, 5H, Ar*H*), 4.93 (d, 1H, *J* = 3.0, PhC*H*), 4.26 (s, 1H, C*H*O), 3.64 (d, 1H, *J* = 8.8, CH_2), 3.51 (dq, 1H, *J* = 3.0, 6.4, CH_3CH), 3.43 (d, 1H, *J* = 8.8, OCH_2), 3.33 (s, 3H, OCH_3), 3.00 (s, 3H, NCH_3), 1.95-1.47 (m, 2H, CCH_2CH_3), 1.13 (s, 3H, CCH_3), 0.97 (d, 3H, *J* = 6.4, CHCH_3), 0.89 (t, 3H, *J* = 7.4, CH_2CH_3)

^{13}C NMR (50MHz, $CDCl_3$)

δ 168.9 (*C*=O), 138.2 (Ar*Cipso*), 128.1 (Ar*C*), 127.2 (Ar*C*), 125.2 (Ar*C*), 80.7 (*C*HO), 76.8 (O*C*H_2), 76.3 (Ph*C*H), 58.8 (O*C*H_3), 58.6 (CH_3*C*H), 42.6 (*Cquat*), 33.3 (N*C*H_3), 26.9 (*C*H_2CH_3), 19.1 (C*C*H_3), 12.8 (CH*C*H_3), 7.9 (CH_2*C*H_3)

IR ($CHCl_3$)

4214, 3016, 2935, 2881, 1641, 1461, 1380, 1215, 756 cm^{-1}

MS (70ev)

m/z 58 (9), 97 (21), 105 (7), 118 (100), 148 (6), 205 (37), 260 (2), 290 (4), 305 (M^+, 7).

HRMS for $C_{20}H_{29}NO_2$

Calcd : 305.1991

Found : 305.1978

$[\alpha]_D^{25}$ = -166.8 (*c* = 1.7, $CHCl_3$)

(2*S*,5*S*,6*R*)-2-[(1*R*)-1-(methoxymethyl)-1-methylpropyl]-4,5-dimethyl-6-phenylmorpholin-3-one (23):

Reduction of **20** (238 mg, 0.75 mmol) with titanium tetrachloride (1.40 mL, 12.8 mmol) and triethylsilane (3.0 mL, 18.75 mmol) in anhydrous dichloromethane (13 mL) for 12 hours gave after purification by flash column chromatography (1/5 ethyl acetate/pet.ether) 212 mg (93%) of **23** as a colourless liquid.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.45-7.20 (m, 5H, Ar*H*), 4.93 (d, 1H, *J* = 2.4, PhC*H*), 4.25 (s, 1H, C*H*O), 3.65-3.41 (m, 3H, CH_2, CH_3C*H*), 3.34 (s, 3H, OCH_3), 3.00 (s, 3H, NCH_3), 1.74 (q, 2H, *J* = 7.3, CC$H_2$$CH_3$), 1.07 (s, 3H, C$H_3$), 0.99-0.85 (m, 6H, CHC$H_3$, CH_2CH_3)

^{13}C NMR (50MHz, $CDCl_3$)

δ 168.7 (*C*=O), 137.9 (Ar*C*), 127.9 (Ar*Cipso*), 127.0 (Ar*C*), 124.9 (Ar*C*), 80.0 (*C*HO), 76.0 (O*C*H_2), 75.9 (Ph*C*H), 58.6 (O*C*H_3), 58.2 (CH_3*C*H), 42.3 (*Cquat*), 33.1 (N*C*H_3), 26.6 (*C*$H_2$$CH_3$), 18.6 (C*C*$H_3$), 12.6 (CH*C*$H_3$), 7.7 ($CH_2$*C*$H_3$).

IR ($CHCl_3$)

3475, 2972, 2877, 1649, 1452, 1251, 1108, 1064, 702 cm^{-1}

MS (70 ev)

58 (9), 97 (13), 117 (27), 148 (7), 205 (50), 290 (10), 305 (M^+, 6)

HRMS for $C_{20}H_{29}NO_2$

Calcd : 305.1991

Found : 305.1983

$[\alpha]_D^{25}$= -177.6 (*c* = 1.2, $CHCl_3$)

General procedure for dissolving metal reduction on morpholinones 21-23

To anhydrous liquid ammonia (distilled over sodium), was added sodium metal at –78 ^{o}C and the mixture was stirred for fifteen minutes. To the resulting blue solution was added a solution of **21-23** dissolved in anhydrous THF. The mixture was stirred at -78 ^{o}C for three and half minutes, methanol was added and the mixture was stirred at room temperature till the ammonia was completely removed. The methanol was removed under reduced pressure and the residue was partitoned with ethyl acetate and water. The ethyl acetate layer was separated and the aqueous layer was extracted several times with ethyl acetate. The

combined extracts were dried (Na_2SO_4) and concentrated to obtain crude product which was purified by flash column chromatography.

2*S*-2-Hydroxy-2-((1-methoxymethyl) cyclohexyl)-*N*-methyl acetamide (24):

Prepared from **21** (293 mg. 0.9 mmol) in THF (2 mL) and Na (116 mg, 4.83 mmol) in ammonia (10 mL). Purification by flash column chromatography (3/2 ethyl acetate / pet ether) furnished 95 mg (50%) **24** as a colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 6.79 (br s, 1H, N*H*), 4.25 (d, 1H, *J* = 6.0, O*H*), 4.04 (d, 1H, *J* = 6.0, C*H*), 3.61 (d, 1H, *J* = 9.3, CH_2), 3.35 (s, 3H, OCH_3) 3.33 (d, 1H, *J* = 9.3, OCH_3,), 2.86 (d, 3H, *J* = 5.3, NCH_3), 2.09 -1.37 (m, 10H, cyclohexyl)

^{13}C NMR (50 MHz, $CDCl_3$)

δ 173.1 (*C*=*O*), 78.2 (*C*HOH), 77.4 (O*C*H_2), 59.4 (O*C*H_3), 40.8 (*Cquat*), 30.0 (*C*H_2 cyclohexyl), 28.9 (*C*H_2, cyclohexyl), 26.0 (*C*H_2 cyclohexyl), 25.7 (N*C*H_3), 21.5 (*C*H_2 cyclohexyl), 21.4 (*C*H_2 cyclohexyl)

IR ($CHCl_3$)

3306, 2920, 1650, 1531, 1409, 1203, 1094, 799 cm^{-1}

MS (70 ev)

58 (8), 81 (15), 89 (100), 95 (23), 139 (14), 183 (5), 215 (M^+, 3)

HRMS for $C_{10}H_{20}NO_3$

Calcd: 215.1521

Found: 215.1525

$[\alpha]_D^{25}$ = - 41.6 (*c* = 3.2, $CHCl_3$)

(2*S*,3*S*)-2-Hydroxy-3-(methoxymethyl)-*N*,3-dimethylpentanamide (25):

Prepared from **22** (86 mg, 0.28 mmol) in THF (0.5 mL) and Na (34 mg, 1.4 mmol) in ammonia (4 mL). Purification by flash chromatography (3/2 ethyl acetate/pet.ether) gave 27 mg (50%) of **25** as a gum.

^{1}H NMR (200MHz, $CDCl_3$)

δ 6.84 (br s, 1H, N*H*), 4.39 (br s, 1H, O*H*), 4.05 (s, 1H, C*H*), 3.35 (s, 5H, CH_2OCH_3), 2.85 (d, 3H, *J* = 4.9, NCH_3), 1.74-1.39 (m, 2H, CCH_2CH_3), 0.97 (s, 3H, CCH_3), 0.92 (t, 3H, *J* = 7.4, CH_2CH_3)

^{13}C NMR (50MHz, $CDCl_3$)

δ 173.3 (*C*=O), 79.6 (OCH_2), 77.6 (*C*HOH), 59.2 (O*C*H_3), 40.9 (*Cquat*), 27.6 (*C*H_2CH$_3$), 25.6 (N*C*H_3), 17.8 (C*C*H_3), 7.6 (CH_2*C*H_3)

IR($CHCl_3$)

3380, 2968, 2881, 2812, 1658, 1411, 1286, 1108, 732 cm^{-1}

MS (70ev)

58 (60), 71 (37), 89 (100), 113 (13), 189 (M^+, 4)

ESMS for $C_9H_{19}NO_3Na$

Calcd : 212.1263

Found : 212.1264

. **$[\alpha]_D^{25}$** = -34.75 (*c* = 0.28, $CHCl_3$)

(2*S*,3*R*)-2-Hydroxy-3-(methoxymethyl)-*N*,3-dimethylpentanamide (26):

Prepared from **23** (199 mg, 0.65 mmol) in THF (1 mL) and Na (78 mg, 3.2 mmol) in ammonia (7 mL). Purification by flash chromatography (3/2 ethyl acetate/ pet.ether) gave 62 mg (50%) of **26** as a gum.

^{1}H NMR (200MHz,$CDCl_3$)

δ 6.81 (br, s, 1H, N*H*), 4.46 (br s, 1H, O*H*), 3.99 (s, 1H, C*H*), 3.43-3.19 (m, 5H, CH_2OCH_3), 2.79 (d, 3H, *J* = 4.9, NCH_3), 1.70-1.50 (m, 1H, CCH_2CH$_3$), 1.38-1.17 (m, 1H, CCH_2CH$_3$) 0.90 (s, 3H, CCH_3), 0.84 (t, 3H, *J* = 7.4, CH_2CH_3)

^{13}C NMR (50MHz, $CDCl_3$)

δ 172.8 (*C*=O), 79.1 (OCH_2), 78.3 (*C*HOH), 59.0 (O*C*H_3), 40.9 (*Cquat*), 25.3 (N*C*H_3), 24.9 (*C*H_2CH$_3$), 18.0 (C*C*H_3), 7.6 (CH_2*C*H_3)

IR ($CHCl_3$)

3382, 2968, 1650, 1537, 1107, 1031 cm^{-1}

MS (70 ev)

58 (43), 71 (28), 81 (7), 89 (100), 113 (13), 131 (10), 189 ((M^+, 2)

ESMS for $C_9H_{19}NO_3Na$

Calcd : 212.1263

Found : 212.1263

$[\alpha]_D^{25}$ = -33.86 (*c* = 0.9, $CHCl_3$)

General procedure for lactonization of 24-26 to 27-29

To a stirred solution of **24-26** in anhydrous dichloromethane was added at –78 ^oC boron tribomide in anhydrous dichloromethane and the resulting reaction mixture was gradually warmed to –15 ^oC with continuous stirring for 4 hours. Water was then added over a period a five minutes, the mixture was stirred for fifteen minutes and 6M H_2SO_4 was added. The mixture was then stirred overnight (approximately 12 hours) during which time it warmed to ambient temerature. The mixture was then cooled in an ice bath and neutralized with saturated sodium bicarbonate solution. It was then extracted with dichloromethane and the combined dichloromethane extracts were dried (Na_2SO_4) and concentrated to obtain the crude lactone which was purified by flash column chromatography.

4*S*-4-Hydroxy-2-oxa-spiro[4,5] decan-3-one (27):

Demethylation of **24** (70 mg 0.32 mmol) in anhydrous dichloromethane (4mL) with boron tribomide (0.26mL, 2.8 mmol diluted in 1ml anhydrous dichloromethane) followed by addition of water (1 mL) and 6M H_2SO_4 (1.5 mL), gave after purification by flash column chromatography (1/4 ethyl acetate/pet. ether) 53 mg (86 %) of **27** as a white crystalline solid.

M.P. 92-93 ^oC

^{1}HNMR (200 MHz, $CDCl_3$)

δ 4.38 (d, 1H, *J* = 9.3, C*H*$_2$), 4.12 (s, 1H, C*H*OH), 3.91 (d, *J* = 9.3, C*H*$_2$), 3.46 (br, s, 1H, O*H*), 1.84-1.10 (m, 10H, cyclohexyl)

^{13}C NMR (50 MHz, CDCl$_3$)

δ 177.9 (*C*=O), 75.6 (*C*HOH), 73.6 (O*C*H$_2$), 44.0 (*Cquat*), 33.7 (*C*H$_2$ cyclohexyl), 25.8 (*C*H$_2$ cyclohexyl), 25.3 (*C*H$_2$ cyclohexyl), 22.9 (*C*H$_2$ cyclohexyl), 21.7 (*C*H$_2$ cyclohexyl)

IR (CHCl$_3$)

3425, 2931, 2857, 1778, 1455, 1166, 1005, 731 cm^{-1}

MS (70 ev)

m/z 55 (97), 67 (100), 79 (51), 83 (59), 95 (77), 108 (14), 170 (M$^+$, 7)

HRMS for C$_9$H$_{14}$O$_2$

Calcd: 170.0943

Found: 170.0942.

[α]$_D^{25}$ = +13.9 (*c* = 0.55, CHCl$_3$)

(3*S*,4*S*)-4-Ethyl-3-hydroxy-4-methyldihydrofuran-2(3*H*)-one (28):

(natural product isolated from Marshallia Tenuifolia)[17]

Demethylation of **25** (17 mg, 0.09 mmol) in anhydrous dichloromethane (4 mL) with boron tribromide (0.08 mL, 0.79 mmol) diluted in anhydrous dichloromethane (0.5 mL), followed by addition of water (0.4 mL) and 6M H_2SO_4 (0.3 mL) gave after purification by flash column chromatography (3/7 ethyl acetate/pet. ether) 9 mg (70%) of **28** as a syrup.

^{1}H NMR (200MHz, CDCl$_3$)

δ 4.23 (d, 1H, *J* = 9.3, C*H*$_2$), 4.16 (s, 1H, C*H*OH), 3.89 (d, 1H, *J* = 9.3, C*H*$_2$), 3.0 (br s, 1H, O*H*), 1.61-1.39 (m, centered at 1.50, 2H, C*H*$_2$CH$_3$), 1.19 (s, 3H, C*H*$_3$), 0.96 (t, 3H, *J* = 7.3, CH$_2$C*H*$_3$)

^{13}C NMR (50MHz, CDCl$_3$)

δ 177.5 (*C*=O), 75.9 (*C*HOH), 73.7 (*C*H_2), 43.5 (C*quat*), 24.2 (*C*H_2CH_3), 20.9 (*C*H_3), 8.2 (CH_2*C*H_3)

$[\alpha]_D^{25}$ = + 4.45 (*c* = 0.25, $CHCl_3$**)**

(3*S*,4*R*)-4-Ethyl-3-hydroxy-4-methyldihydrofuran-2(3*H*)-one (29):

Demethylation of **26** (45 mg, 0.24 mmol) in anhydrous dichloromethane (5 mL), with boron tribromide (0.20 mL, 2.1 mmol) diluted in anhydrous dichloromethane (1 mL) followed by addition of water (1mL) and 6M H_2SO_4 (0.6 mL) gave after purification by flash column chromatography (3/7 ethyl acetate / pet. ether) 26 mg (76 %) of **29** as a colourless oil.

^{1}H NMR (200MHz,$CDCl_3$)

δ 4.21 (s, 1H, C*H*$_2$), 4.05-3.95 (AB system, *J* = 10.8, 2H, C*H*$_2$), 3.45 (br s, 1H, O*H*), 1.60-1.46 (m, centered at 1.60, 2H, C*H*$_2$$CH_3$), 1.08 (s, 3H, C*H*$_3$), 1.01 (t, 3H, *J* = 7.4, CH_2C*H*$_3$)

^{13}C NMR (50MHz, $CDCl_3$)

δ 177.8 (*C*=O), 75.6 (*C*HOH), 75.0 (*C*H_2), 44.0 (C*quat*), 30.1 (*C*H_2CH_3), 15.9 (*C*H_3), 8.5 (CH_2*C*H_3)

IR ($CHCl_3$)

3444, 2968, 1776, 1460, 1112, 999, 715 cm^{-1}

ESMS for $C_7H_{12}O_3Na$

Calcd: 167.0684

Found: 167.0687

$[\alpha]_D^{25}$= +25.65 (*c* = 0.35, $CHCl_3$**)**

(5*R*,6*R*,8*R*,9*S*)-5-Ethyl-9,10-dimethyl-8-phenyl-1,3,7-trioxa-10-azaspiro[5.5]undecan-11-one (32): (obtained from the Prins reaction of 31)

Reaction of **31** (320 mg, 1.3 mmol) with paraformaldehyde (196 mg, 6.5 mmol) in glacial acetic acid (10 mL) gave the crude product which on purification by flash column chromatography (3/7 ethyl acetate/pet. ether) furnished 245 mg (62%) of **32** as a white solid.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.44-7.30 (m, 5H, Ar*H*), 5.50 (d, 1H, *J* = 3.0, PhC*H*), 5.02 (d, 1H, *J* = 5.9, OCH_2O), 4.80 (d, 1H, *J* = 5.9, OCH_2O), 4.09 (dd, 1H, *J* = 4.9, 11.0, OCH_2CH), 3.82 (t, 1H, *J* = 11.0, OCH_2CH), 3.54 (dq, 1H, *J* =3.0, 6.4, NC*H*), 3.05 (s, 3H, NCH_3), 2.90-2.76 (m, 1H, OCH_2CH), 1.43-1.24 (m, 2H, CH_3CH_2), 0.98 (d, 3H, *J* = 6.4, $CHCH_3$), 0.91 (t, 3H, *J* = 7.4, CH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$)

δ 164.6 (*C*=O), 137.2 (Ar*C*), 128.5 (Ar*C*H), 127.8 (Ar*C*H), 125.4 (Ar*C*H), 98.7 (O*C*O (quat)), 86.6 (O-CH_2-O), 70.2 (Ph*C*H), 66.3 (OCH_2CH) 58.9 (N*C*H), 40.9 (OCH_2CH), 33.8 (NCH_3), 20.0 (CH_3CH_2), 12.6 (CH_3), 11.2 (CH_3)

IR ($CHCl_3$)

3040, 1670, 1421, 1399, 1293, 1230 1180, 1050, 990, 950 cm^{-1}

MS (70 eV)

m/z 56 (21), 77 (5), 91 (10), 106 (4), 118 (100), 131 (3), 148 (7), 174 (1), 247 (1), 258 (1), 305 (M^+, 2).

2*S*,2(1*R*),5*S*,6*R*-4,5-Dimethyl-6-phenyl-2-(1-methoxymethylpropyl)-morpholin-3-one (33):

Reductive cleavage of spiro acetal 32 with $TiCl_4$/Et_3SiH:

To a solution of **32** (337 mg, 1.1 mmol) in dichloromethane (10 ml) at -78^{o}C was added Et_3SiH (2.1 mL, 13.1 mmol) followed by $TiCl_4$ (1.2 mL, 10.9 mmol) and the reaction mixture was slowly warmed to and stirred at ambient temperature for 12 h. It was then cooled to 0 ^{o}C, saturated aqueous NH_4Cl was added and the mixture was warmed up to ambient temperature. Water was added to dissolve precipitated solids and the solution was extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were dried (Na_2SO_4) and concentrated to give 0.4 g of the crude product that was a mixture of **33** (*ds* = 3.5/1 by ^{1}H NMR) and **34** (*ds* = 7.5/1 by ^{1}H NMR). Purification by flash chromatography on silica gel (3/2 petroleum ether/ethyl

acetate) furnished 168 mg (52%) of **33** as a colourless gum and 640 mg (22%) of **34** as a colourless gum.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.50-7.20 (m, 5H, Ar*H*), 5.00 (d, 1H, *J* = 3.0, PhC*H*), 4.50 (d, 1H, *J* = 2.5, C*H*-O), 3.65-3.40 (m, 3H, OCH_2, NC*H*), 3.35 (s, 3H, OCH_3), 3.05 (s, 3H, NCH_3), 2.65-2.40 (m, 1H, CH_2C*H*), 1.65-1.35 (m, 2H, CH_3CH_2), 1.10-0.80 (apparent m, 6H, CH_2CH_3, $CHCH_3$)

Visible peaks for the other diastereomer:

δ 5.15 (d, 1H, *J* = 3.0, PhC*H*), 4.40 (d, 1H, *J* = 2.5, C*H*-O), 3.25 (s, 3H, OCH_3)

MS (70 eV)

58 (74), 71 (6), 83 (47), 91 (17), 98 (11), 105 (10), 118 (100), 128 (14), 140 (33), 148 (8), 159 (5), 174 (1), 186 (2), 205 (83), 246 (7), 260 (1), 276 (1), 291 (M^+, 16)

(2*Z*,5*S*,6*R*)-4,5-dimethyl-6-phenyl-2-propylidenemorpholin-3-one (34):

Formed as a mixture of *E*- and *Z*-isomers (*ds* = 7.5/1) during the reductive cleavage of spiro-acetal **32** with $TiCl_4/Et_3SiH$.

^{1}H NMR (200 MHz, $CDCl_3$)

Major diastereomer:

δ 7.50-7.20 (m, 5H, Ar*H*), 5.10 (d, 1H, *J* = 2.9, PhC*H*), 3.55 (dq, 1H, *J* = 2.9, 6.4, NC*H*), 3.05 (s, 3H, NCH_3), 2.40-2.20 (m, 2H, CH_2), 2.25 (s, 3H, olefinic CH_3), 1.05 (t, 3H, *J* = 7.4, CH_2CH_3), 0.95 (d, 3H, *J* = 6.4, $CHCH_3$)

Visible peaks for the other diastereomer:

δ 5.00 (d, 1H, *J* = 2.9, PhC*H*)

(2*S*,5*S*,6*R*)-2-Hydroxy-2-[1-(methoxymethyl)cyclohexyl]-4,5-dimethyl-6-phenylmorpholin-3-one (35):

To a solution of **18** (600 mg, 1.74 mmol) in anhydrous dichloromethane (20 mL) was added at –78 ^oC $TiCl_4$ (3.34 mL, 30.4 mmoles) followed by triethylsilane (5.56 mL, 34.8

mmole). The reaction mixture was allowed to warm to –40 ^{o}C over a period of 1 hour and stirred at the same temperature for further five hours. Quenched with saturated aqueous ammonium chloride. Separated organic layer, dried (Na_2SO_4), concentrated to obtain crude product which on purification by flash chromatography (1/5 ethyl acetate/pet. ether) furnished **35** (520 mg, 89% yield) as clean colourless oil which solidified upon refrigeration.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.22-7.42 (m, 5H, Ar*H*), 5.67 (s, 1H, OCO*H*), 5.58 (d, 1H, *J* = 3.4, PhC*H*), 4.09 (AB system, 2H, *J* = 9.8, CH_2), 3.48 (dq, 1H, *J* = 2.9, 6.3, CH_3C*H*), 3.37 (s, 3H, OCH_3), 3.00 (s, 3H, NCH_3), 2.42 (m, 1H, cyclohexyl), 1.58 (m, 9H, cyclohexyl), 0.96 (d, 3H, *J* = 6.3, CH_3CH).

^{13}C NMR (75 MHz, $CDCl_3$)

δ 167.1 (*C*=O), 138.3 (Ar*C*), 128.0 (Ar*C*H), 127.1 (Ar*C*H), 125.3 (Ar*C*H), 101.0 (*C*OH), 73.1 (*C*H_2O) 70.0 (Ph*C*H), 58.9 (O*C*H_3), 58.7 (CH_3*C*H), 44.6 (*Cquat* cyclohexyl), 33.4 (N*C*H_3), 27.7 (*C*H_2 cyclohexyl), 26.1 (*C*H_2 cyclohexyl), 25.4 (*C*H_2 cyclohexyl), 21.4 (*C*H_2 cyclohexyl), 21.2 (*C*H_2 cyclohexyl), 12.4 (*C*H_3CH)

IR ($CHCl_3$)

3400, 2931, 2244, 1645, 1454, 1105, 906, 753 cm^{-1}

MS (70 eV)

92 (13), 118 (95), 221 (29), 240 (100), 329 (53), 347 (M^+, 2)

HRMS for $C_{20}H_{29}NO_4$

Calcd: 347.2097

Found: 347.2094

(2*S*,5*S*,6*R*)-2-Hydroxy-2-[(1*R*)-1-(methoxymethyl)-1-methylpropyl]-4,5-dimethyl-6-phenylmorpholin-3-one (36):

To a solution of **19** (319 mg, 1.04 mmol) in anhydrous dichloromethane (10 mL) was added at –78 ^{o}C $TiCl_4$ (3.28 mL, 30 mmol) followed by triethylsilane (4.79 mL, 30 mmol).

The reaction mixture was allowed to warm to –40 ^{o}C over a period of 1 hour and stirred at the same temperature for five hours. Saturated aqueous ammonium chloride was added and the organic layer was separated. The aqueous layer was extracted twice with ethyl acetate and the combined organic layers wer dried (Na_2SO_4) and concentrated to obtain the crude product which on purification by flash chromatography (1/3 ethyl acetate/pet. ether) furnished **36** (223 mg, 70% yield) as colourless oil which solidified upon refrigeration.

^{1}H NMR (200 MHz, $CDCl_3$)

δ-7.43-7.29 (m, 5H, Ar*H*), 5.65 (s, 1H, CO*H*), 5.61 (d, 1H, *J* = 3.0, PhC*H*), 3.74 (s, 2H, OCH_2), 3.51 (dq, 1H, *J* = 3.0, 6.9 CH_3C*H*), 3.36 (s, 3H, OCH_3), 3.00 (s, 3H, NCH_3), 2.21-1.75 (m, 2H, CC$H_2$$CH_3$), 1.01 (s, 3H, CC$H_3$), 0.96 (d, 3H, *J* = 6.3, CHCH_3), 0.84 (t, 3H, *J* = 7.3, CH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$)

δ 167.1 (*C*=O), 138.0 (Ar*C*), 127.9 (Ar*C*), 127.0 (Ar*C*), 125.2 (Ar*C*), 100.6 (*C*OH), 76.2 (O*C*H_2), 69.9 (Ph*C*H), 58.8 (*C*HCH_3, O*C*H_3), 44.5 (*Cquat*CH_2CH_3), 33.3 (N*C*H_3), 24.4 (*C*H_2CH_3), 16.5 (C*quatC*H_3), 12.3 (CH*C*H_3), 7.7 (CH_2*C*H_3)

IR ($CHCl_3$)

3360, 2980, 1620, 1410, 1070 cm^{-1}

MS (70 eV)

58 (12), 91 (13), 118 (100), 147 (11), 304 (10), 322 (M+1, <1)

(2*S*,5*S*,6*R*)-2-Hydroxy-2-[1-(methoxymethyl)propyl]-4,5-dimethyl-6-phenylmorpholin-3-one (37):

To a solution of **32** (75 mg, 0.25 mmol) in anhydrous dichloromethane (1 mL) was added at 0 ^{o}C $TiCl_4$ (0.55 mL, 5 mmol) followed by triethylsilane (2 mL, 12.3 mmol). The reaction mixture was allowed to stir at the same temperature for ten hours. Saturated aqueous ammonium chloride was added and the organic layer was separated. The aqueous layer was extracted twice with ethyl acetate and the combined organic layers wer dried (Na_2SO_4) and

concentrated to obtain the crude product which on purification by flash chromatography (3/7 ethyl acetate / pet. ether) furnished **37** (65 mg, 82% yield) as a white solid.

^{1}H NMR (200 MHz, $CDCl_3$)

δ-7.29-7.46 (m, 5H, Ar*H*), 6.09 (s, 1H, CO*H*), 5.68 (d, 1H, *J* = 3.0, PhC*H*), 3.99-3.85 (dd, 1H, *J* = 9.3, 10.7, OCH_2), 3.69-3.62 (dd, 1H, *J* = 3.9, 9.3, OCH_2), 3.50 (dq, 1H, *J* = 3.0, 6.3, CH_3C*H*), 3.38 (s, 3H, OCH_3), 3.03 (s, 3H, NCH_3), 2.65 (m, 1H, C*H*CH_2) 1.45-1.47 (m, 2H, CH_2CH_3) 1.00 (d, 3H, *J* = 7.3, CHCH_3), 0.90 (t, 3H, *J* = 6.3, CH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$)

δ 166.9 (*C*=O), 138.4 (Ar*C*), 128.3 (Ar*C*), 127.4 (Ar*C*), 125.6 (Ar*C*), 100.1 (*C*OH), 72.8 (O*C*H_2), 69.9 (Ph*C*H), 58.9 (O*C*H_3, 58.9 (*C*HCH_3)), 44.8 (*Cquat*CH_2CH_3), 33.5 (N*C*H_3), 20.7 (*C*H_2CH_3), 12.6 (CH*C*H_3), 12.2 (CH_2*C*H_3)

IR ($CHCl_3$)

3382, 3018, 1650, 1215, 1092, 1029, 759 cm^{-1}

MS (70 eV)

58 (100), 71 (10), 91 (10), 118 (100), 146 (8)

Analysis for $C_{17}H_{25}NO_4$

Calcd: C, 66.41; H, 8.20; N, 4.55,

Found: C, 66.44; H, 7.88; N, 4.18.

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16. The enantiomeric excess of the lactones was determined by GC analysis with a HP Chiral (20% permethylated β-cyclodextrin) column (30 m x 0.320 mm x 0.25 μm).

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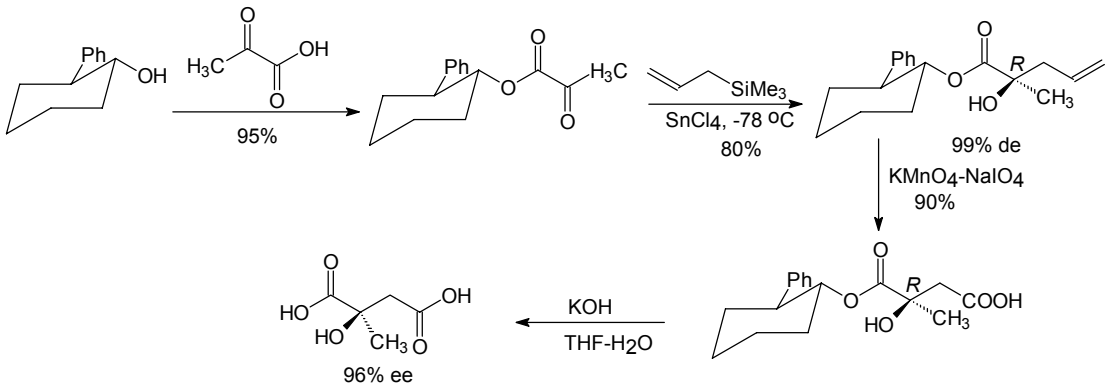
1. INTRODUCTION

Asymmetric synthesis of citramalic acid is an area of active inerest. Both enantiomers of citramalic acid are valuable chiral synthons and a C_4-building block to an extensive realm of natural products and biologically active substances. It has been employed *inter alia* for the synthesis of pheromones[1], prostaglandins[2], Vitamin D_3 derivatives[3] and metabolites,[4] pigments of fungi[5] and chiral aliphatic sulphones[6]. In addition it's utilty as a chiral agent has also been realized in the asymmetric modification of hydrogenation catalysts[7].

Enantiomerically pure citramalic acid is available as a microbial metabolite[8] and has been synthesized with good to excellent control of stereochemistry. Some of the synthetic approaches to citramalic acid are described below.

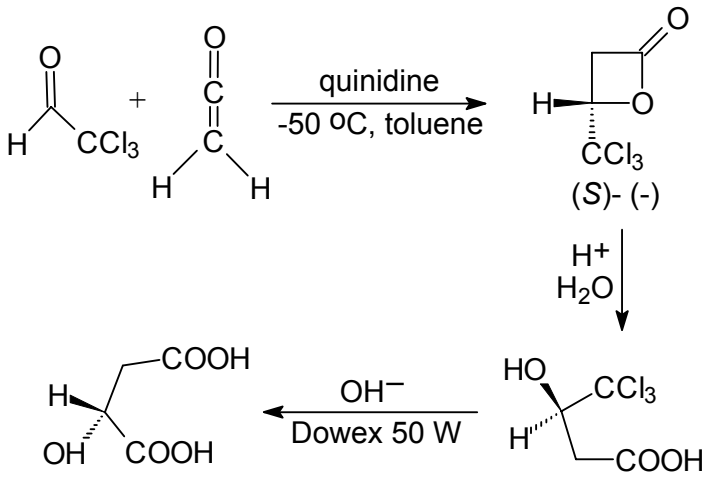
Whiteshell and coworkers[9] have demonstrated the synthesis of both enantiomers of citramalic acid. They key step involved is a diastereoselective allylation reaction. (-) *trans*-2-phenylcyclohexanol and (+) *trans*-2-phenylcyclohexanol generated the *R* and *S* isomers respectively (Scheme 1).

Scheme 1



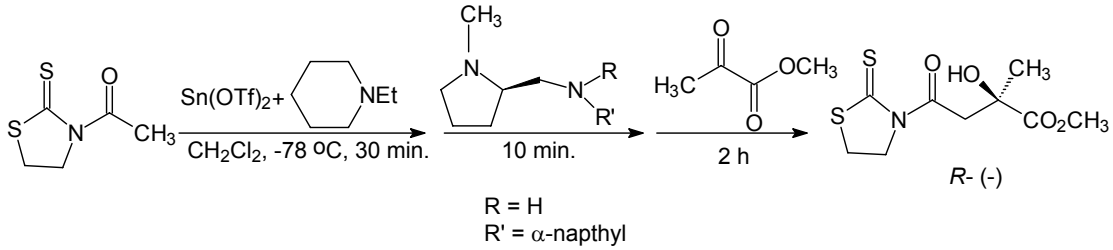
Weinberg et al[10] have shown a very efficient asymmetric synthesis of both enantiomers of malic acid from ketene and chloral by employing diastereomeric cinchona alkaloids (Scheme 2). The protocol could be employed for the synthesis of citramalic acid.

Scheme 2.



Stevens et al[11] obtained a maximum of 85% ee for the aldol condensation of a thioacetimide. The procedure involves generation of the tin enolate of the imide and condensation with methyl glyoxalate. A prolinol derived chiral diamine was employed as the chiral modifier. The high enantiomeric excess of the product was believed to be a consequence of efficient coordination of the bidentate diamine to the metal (tin) center possessing vacant d-orbitals (Scheme 3).

Scheme 3



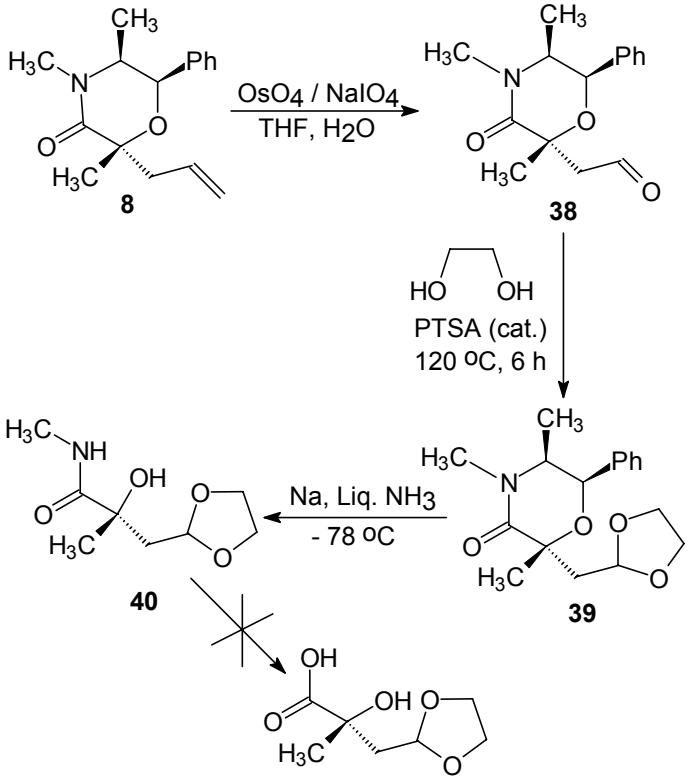
2. OBJECTIVES

The objective of this undertaking was to develop a concise route to stereoselective synthesis of citramalic acid employing the ephedrine-derived morpholine-dione **1**.

3. RESULTS AND DISCUSSION

The starting material for our synthetic scheme is the allyl morpholinone **8**, the synthesis of which was achieved by the one-pot alkylation/allylation protocol described in section A of this Chapter. Oxidative cleavage of allylic double bond in **8** with $OsO_4/NaIO_4$[12] in THF/water at ambient temperature generates aldehyde **38** which was masked as the acetonide **39** by reaction with ethylene glycol in the presence of a catalytic amount of *p*-toluenesulfonic acid at 120 ^oC. Removal of the ephedrine portion by dissolving metal reduction (Na, liq. NH_3 –78 ^oC) rendered the hydroxy amide **40**. Unfortunately, the hydrolysis of the amide could not be affected under a variety of basic conditions and significant decomposition of **40** was observed. Acid hydrolysis of **40** is equally problematic. This, however, is not surprising, given to the acid lability of the acetal protecting group as well as the aldehyde **38**. The exact reasons for the difficulties in hydrolyzing the amide are unclear at present. (Scheme 4)

Scheme 4



4. CONCLUSIONS

While the target citramalic acid was not synthesized in this study due to time restriction, it is possible that a direct oxidation of the double bond to the carboxylic acid and further transformations of the acid may be more fruitful. This alternative will be examined in future studies. The reasons for the difficulties with the amide hydrolysis and decomposition are not clear at present.

5. EXPERIMENTAL

General experimental techniques that have been described in the experimental section of Section A were followed.

***2R,5S,6R*-2-(2-Oxoethyl)-2,4,5-trimethyl-6-phenylmorpholin-3-one (38):**

To a stirred solution of **8** (0.8 g, 3.08 mmol) in THF (12 mL) and water (4 mL), was added OsO_4 (0.5 M in toluene, 0.06 ml, 0.03 mmole) and solid $NaIO_4$ (1.58 g, 7.38 mmol) in portions over a period of 25 min and the reaction mixture was stirred for 4 h. Brine was added and the solution was extracted with ethyl acetate. The organic layers were combined, dried (Na_2SO_4) and concentrated under reduced pressure to furnish 930 mg of the crude aldehyde. Purification by flash chromatography on silica gel (3/2 pet. ether/ ethyl acetate) under argon pressure furnished 768 g (95%) of **38** as a colourless gum.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 9.85 (t, 1H, *J* = 3.0, C*H*O), 7.50-7.20 (m, 5H, Ar*H*), 5.20 (d, 1H, *J* = 2.5, PhC*H*), 3.50 (dq, 1H, *J* = 2.5, 6.8, CH_3CH), 3.05 (s, 3H, NCH_3), 2.9 (m, 2H,CH_2), 1.70 (s, 3H, CCH_3), 1.00 (d, 3H, *J* = 6.8, $CHCH_3$)

^{13}C NMR (50 MHz, $CDCl_3$)

δ 199.2 (*C*HO), 170.3 (N-C=O), 137.4 (ArC*ipso*), 128.3 (Ar*C*H), 127.6 (Ar*C*H), 125.5 (Ar*C*H), 77.7 (*C*-O), 72.9 (Ph*C*H), 59.2 (CH_3CH), 50.2 (CH_2), 33.7 (NCH_3), 26.4 (CCH_3), 12.4 ($CHCH_3$)

IR ($CHCl_3$)

2980, 2934, 1716, 1646, 1496, 1450, 1402, 1378, 1142, 1098, 1018 cm^{-1}

MS (70 eV)

m/z 69 (62), 77 (31), 91 (22), 98 (12), 105 (18), 117 (40), 126 (15), 133 (6), 148 (7), 156 (30), 190 (2), 232 (8), 261 (M^+, 13)

$[\alpha]_D^{25}$ = – 92.3 (*c* = 1.00, $CHCl_3$).

(2*R*,5*S*,6*R*)-2-(1,3-dioxolan-2-ylmethyl)-2,4,5-trimethyl-6-phenylmorpholin-3-one (39):

To a solution of **37** (1.35 g, 5.17 mmol) in anhydrous benzene (30 mL) was added ethylene glycol (60 mL, 6.72 mmol) and *p*TsOH (catalytic). The reaction mixture was heated at 120 ^{o}C for six hours and the water generated was removed with a Dean-Stark apparatus. The mixture was cooled reaction mixture to room temperature and ethyl acetate (50 ml) and water (20 ml) were added. The phases were separated and the aqueous phase as extracted with ethyl acetate. The combined organic layers were washed with sat. aq sodium bicarbonate, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (2/3 ethyl acetate / pet. ether) furnished 900 mg (78%) of **39** as a colourless gum.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.52-7.31 (m, 5H, Ar*H*), 5.41 (d, 1H, *J* = 2.9, PhC*H*), 5.23-5.09 (m, 1H, CH_2CHO), 4.05-3.81 (m, 4H, $(CH_2)_2$), 3.50 (dq, 1H, *J* = 2.9, 6.3, $CHCH_3$), 3.03 (s, 3H, NCH_3) 2.45-2.38 (m, 1H, CH_2), 2.21-2.10 (m, 1H, CH_2), 1.62 (s, 3H, CH_3CO), 1.10 (d, 3H, *J* = 6.3, $CHCH_3$)

IR ($CHCl_3$)

3000, 2866, 1267, 1033, 700 cm^{-1}

MS (70 eV)

m/z 58 (35), 73 (100), 87 (37), 118 (83), 142 (31), 219 (30), 305 (M^+, 21)

$[\alpha]_D^{25}$ = – 60.7 (*c* = 1.10, $CHCl_3$).

(2*R*)-3-(1,3-dioxolan-2-yl)-2-hydroxy-*N*,2-dimethylpropanamide (40):

To anhydrous liquid ammonia (50 mL, distilled over sodium) was added sodium metal (630 mg, 26.9 mmol) at –78 ^{o}C and the mixture was stirred for fifteen minutes. To the resulting blue solution was added a solution of **39** (820 mg, 2.69 mmol) dissolved in anhydrous THF (12 mL). The reaction mixture was stirred at –78 ^{o}C for three minutes, methanol (20 mL) was added and the mixture was warmed to room temperature to remove

excess ammonia. The methanol was then removed under reduced pressure and ethyl acetate (50 mL) and water (50 mL) were added to the residue. The biphase was separated and the aqueous layer was extracted with ethyl acetate. The combined ethyl acetate layers were dried (Na_2SO_4) and concentrated to obtain the crude product (550 mg) which on purification by flash column chromatography (19/1 ethyl acetate / pet. ether) gave 400 mg (80%) of **40** as a colourless liquid.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.10 (br s, 1H, N*H*), 4.95 (AB system, 1H, *J* = 6.9, CH_2CHO), 4.38 (br s, 1H, O*H*), 4.07- 3.78 (m, 4H, $(CH_2)_2$), 2.85 (d, 3H, *J* = 4.9, $NHCH_3$), 2.58-2.41 (m, 1H, CH_2), 1.78-1.91 (m, 1H, CH_2), 1.41 (s, 3H, CH_3)

IR ($CHCl_3$)

3369, 2804, 2663, 1544, 1226, 945 cm^{-1}

MS (70 eV)

73 (100), 87 (25), 131 (49), 190 (M^{+1}, <1)

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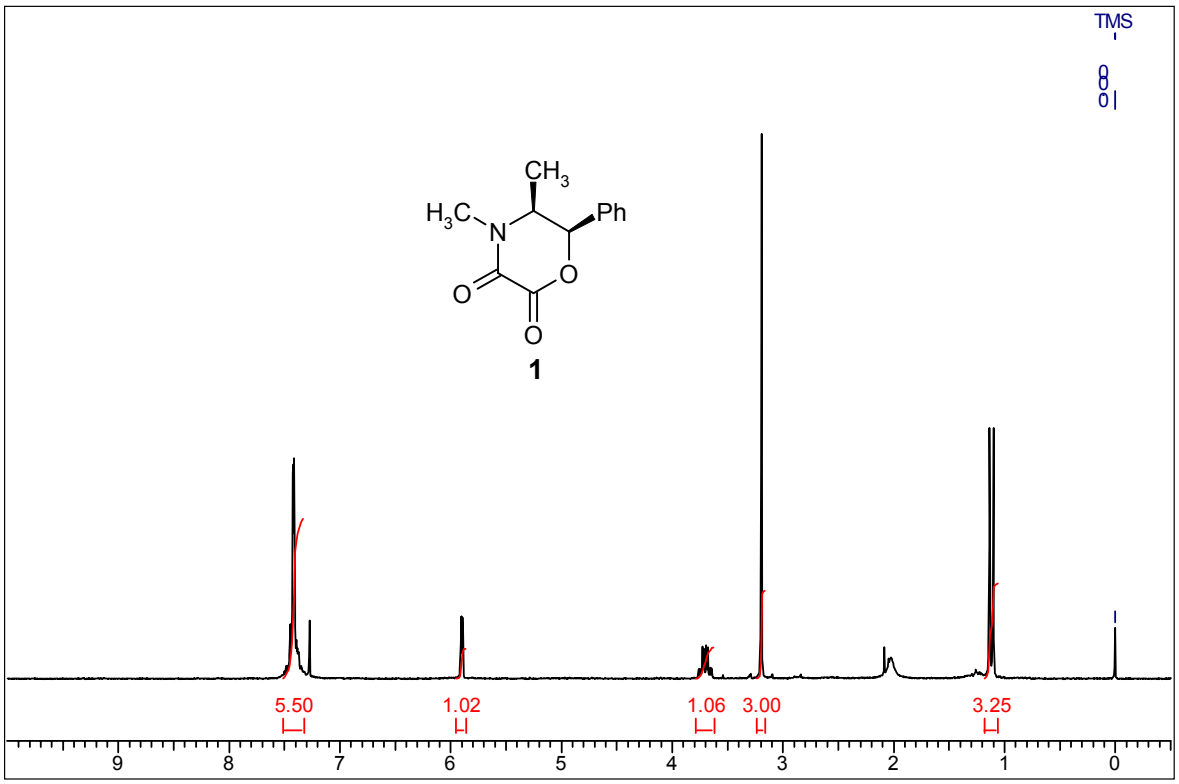
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3.00
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3
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1
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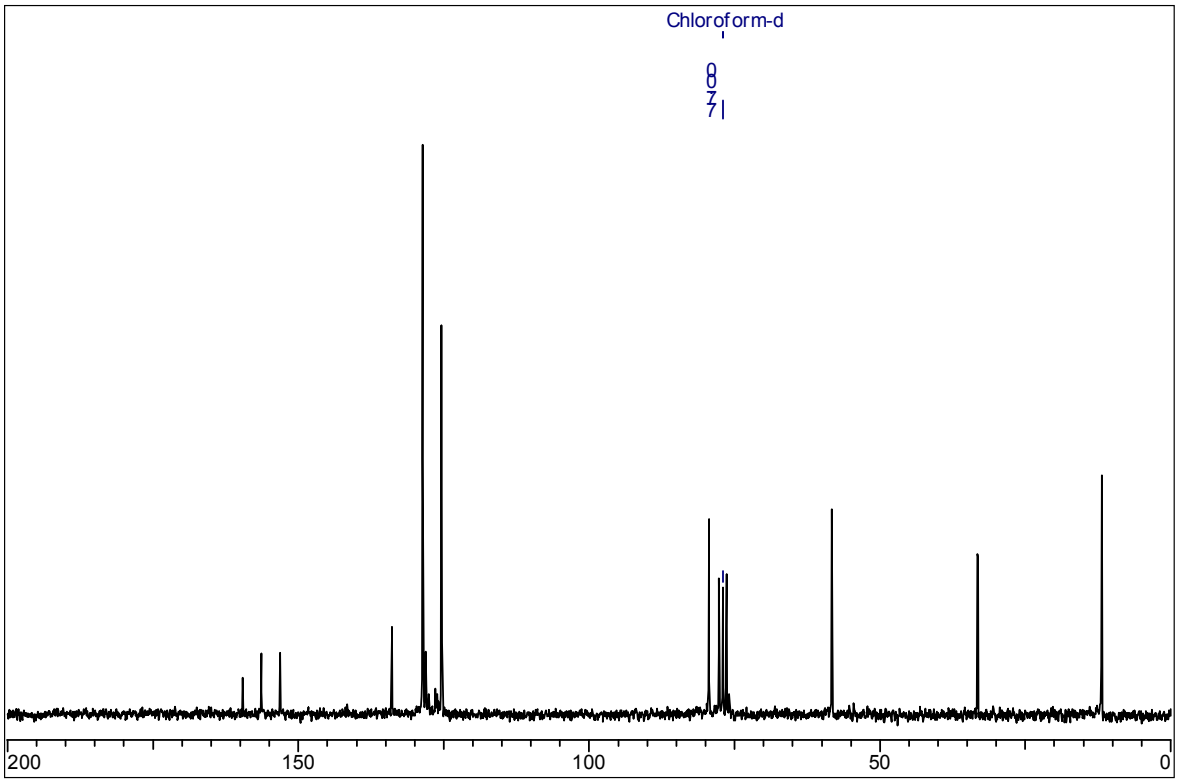
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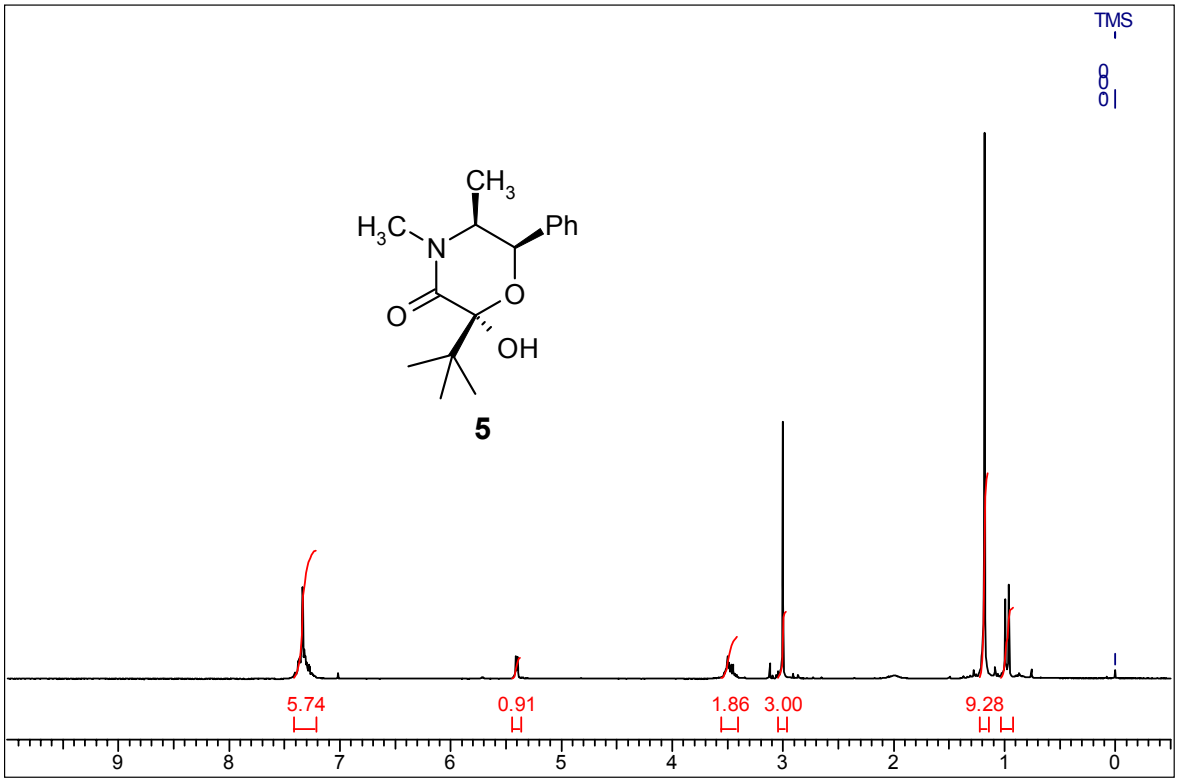
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3.00
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7
6
5
4
3
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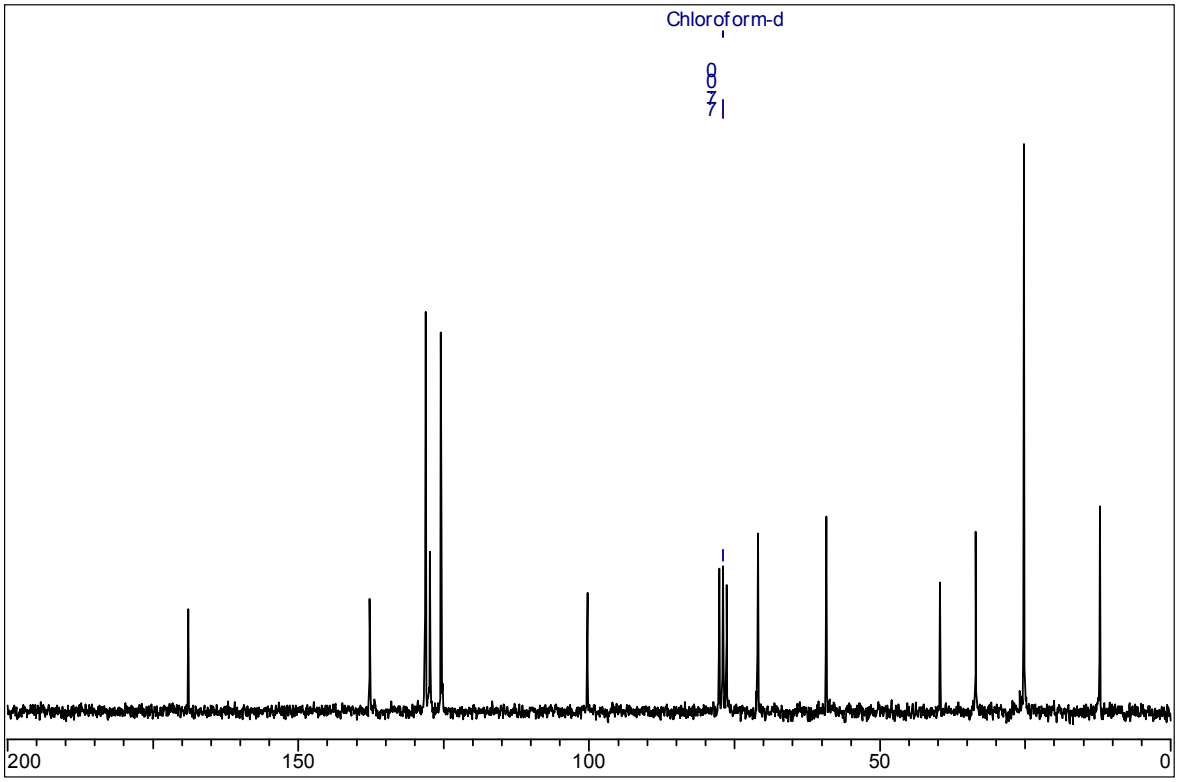
Chloroform-d
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100
50
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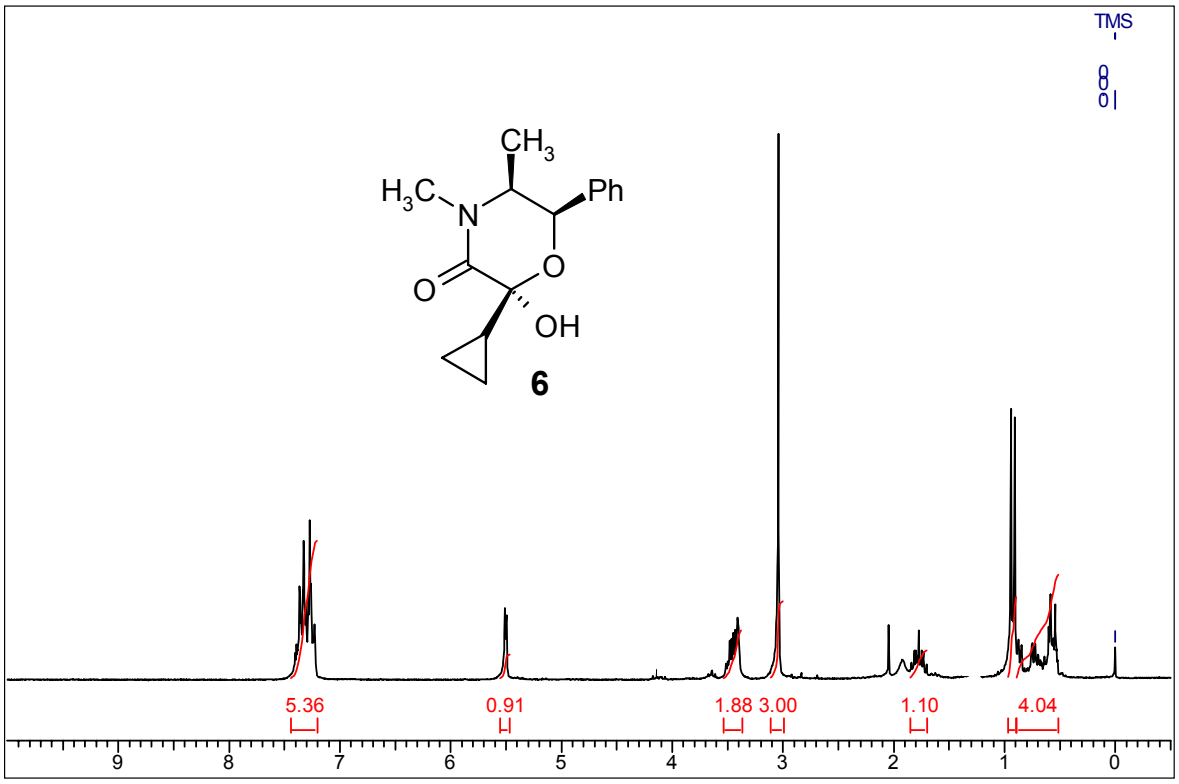
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0.91
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3.00
1.10
4.04
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7
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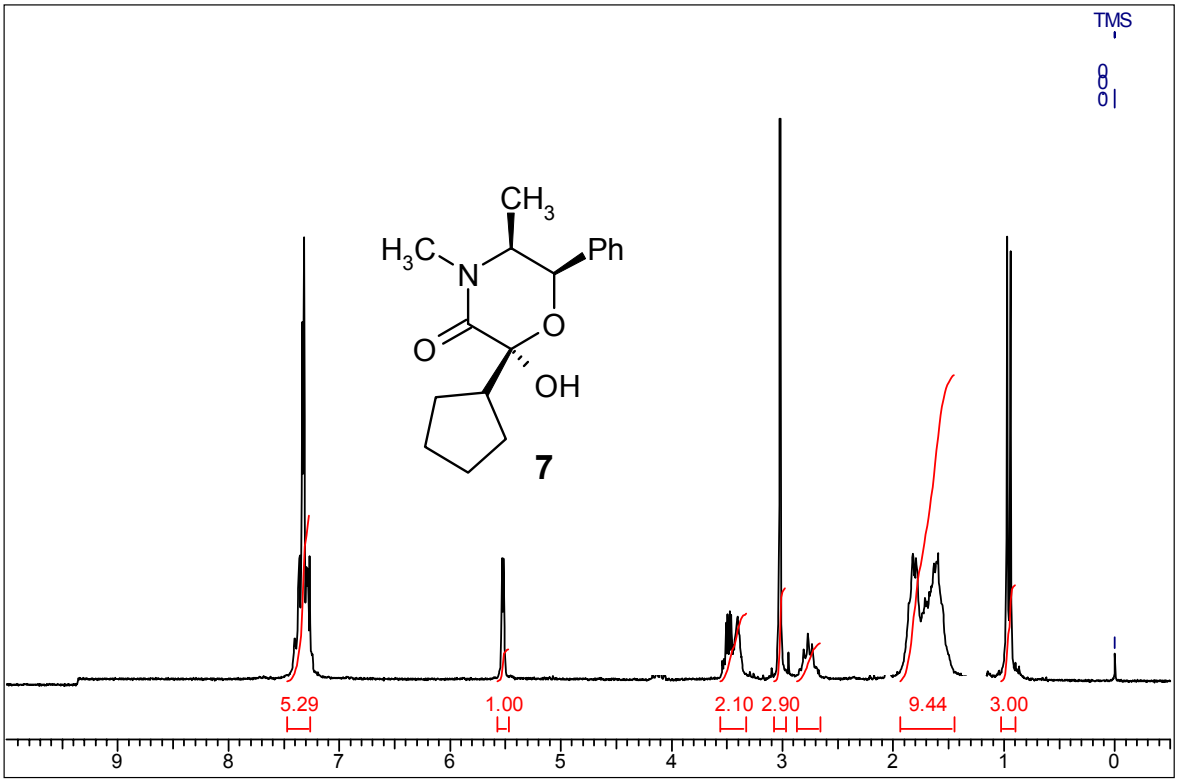
TMS
CH3
H3C
N
Ph
O
O
OH
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2.90
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3.00
9
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7
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3
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1
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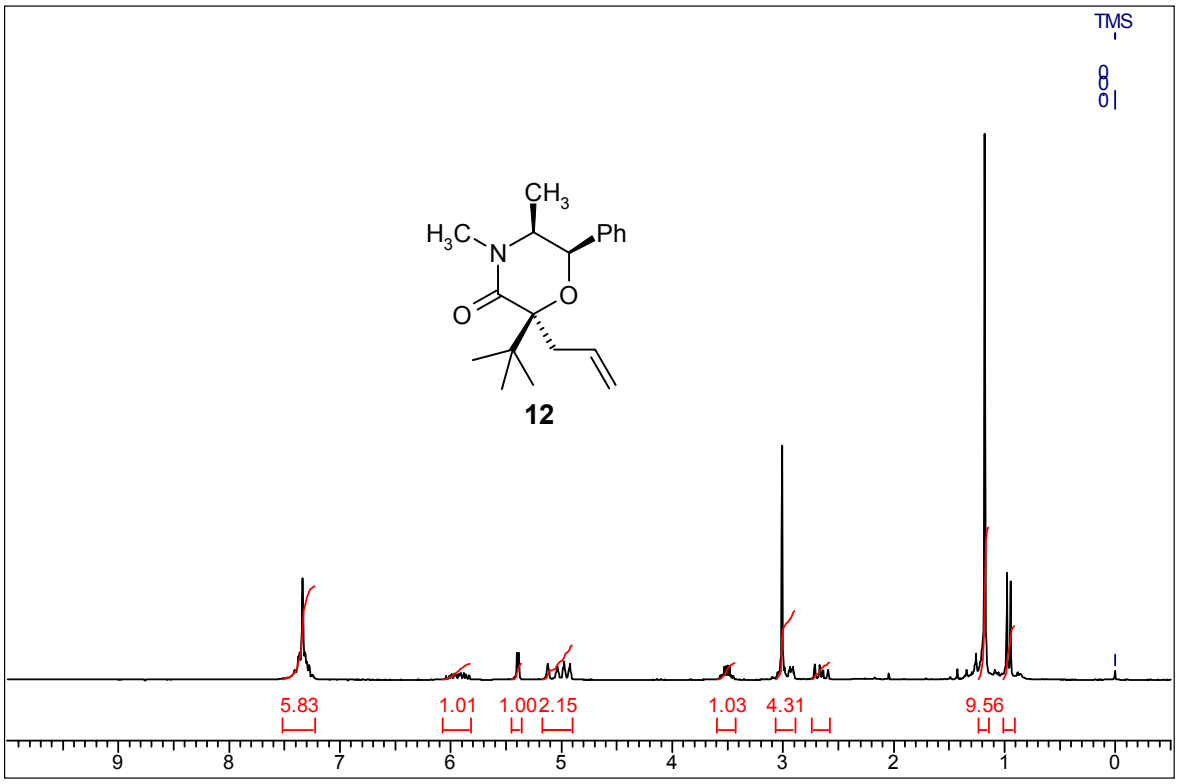
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CH3
H3C
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Ph
O
O
12
5.83
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1.03
4.31
9.56
9
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7
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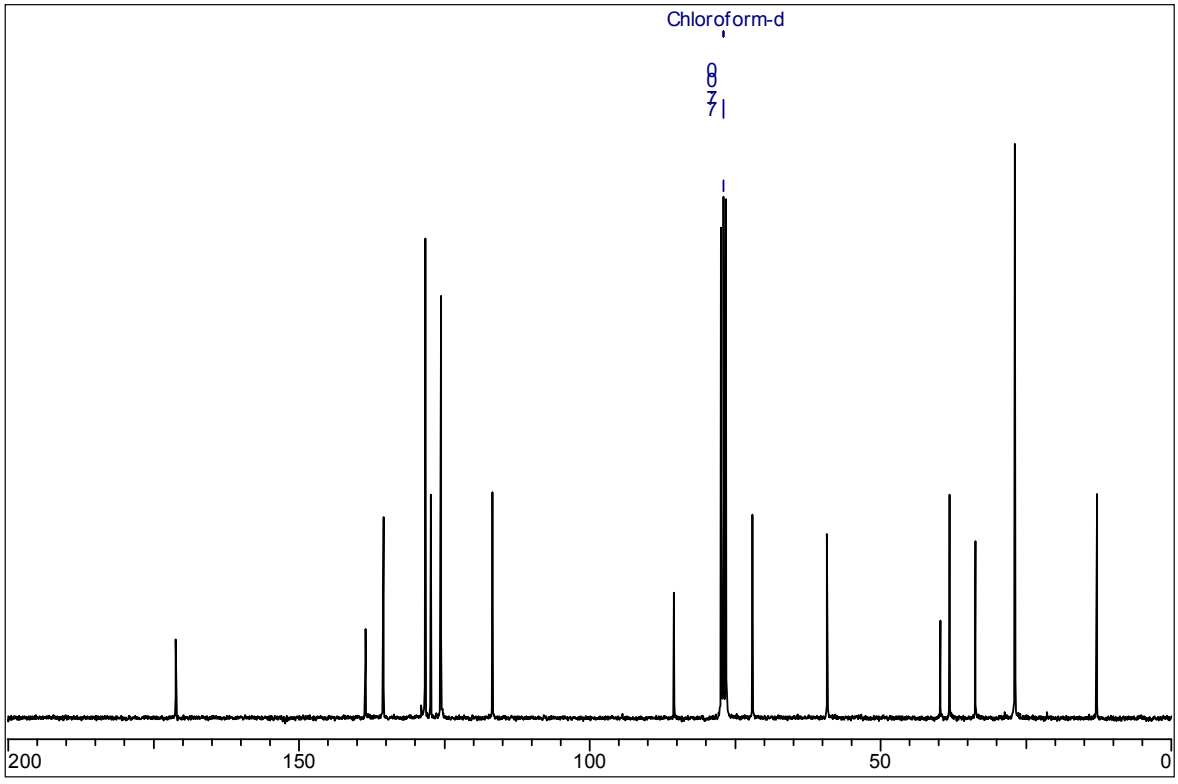
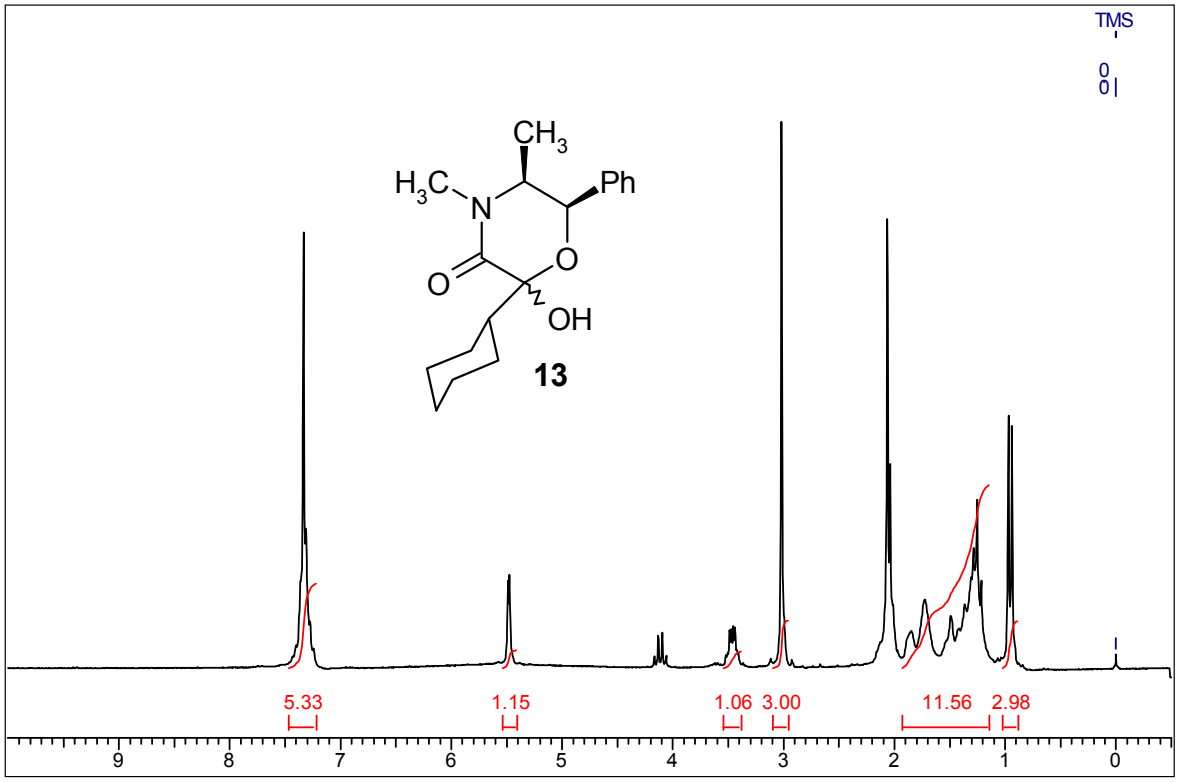

Chloroform-d
200
150
100
50
0


TMS
CH3
H3C
N
Ph
O
O
OH
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1.06
3.00
11.56
2.98
9
8
7
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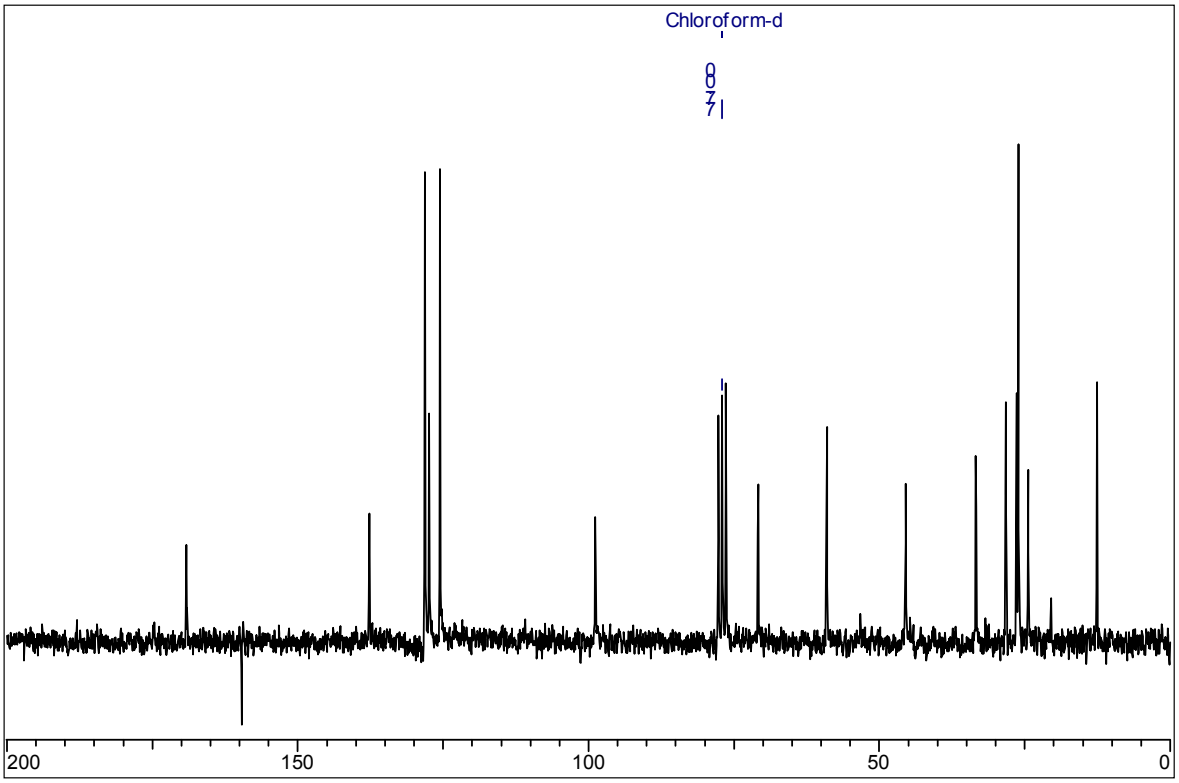
5
4
3
2
1
0


Chloroform-d
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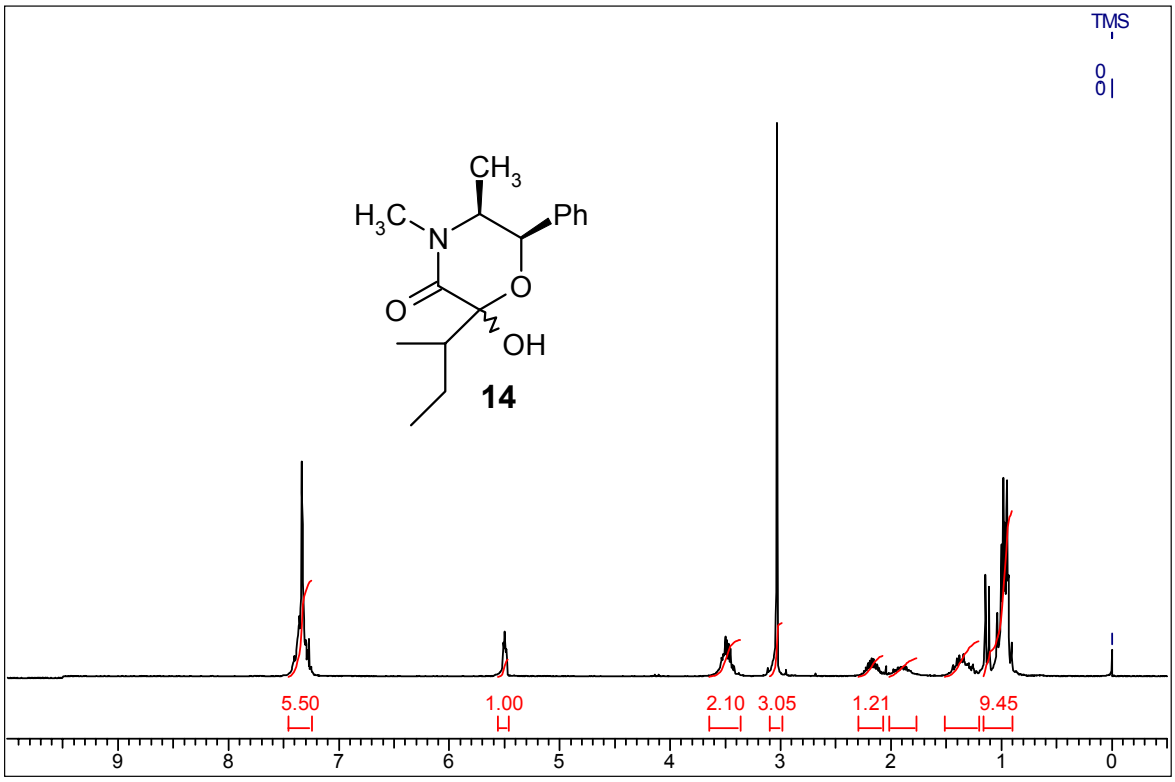
TMS
CH3
H3C
N
Ph
O
O
OH
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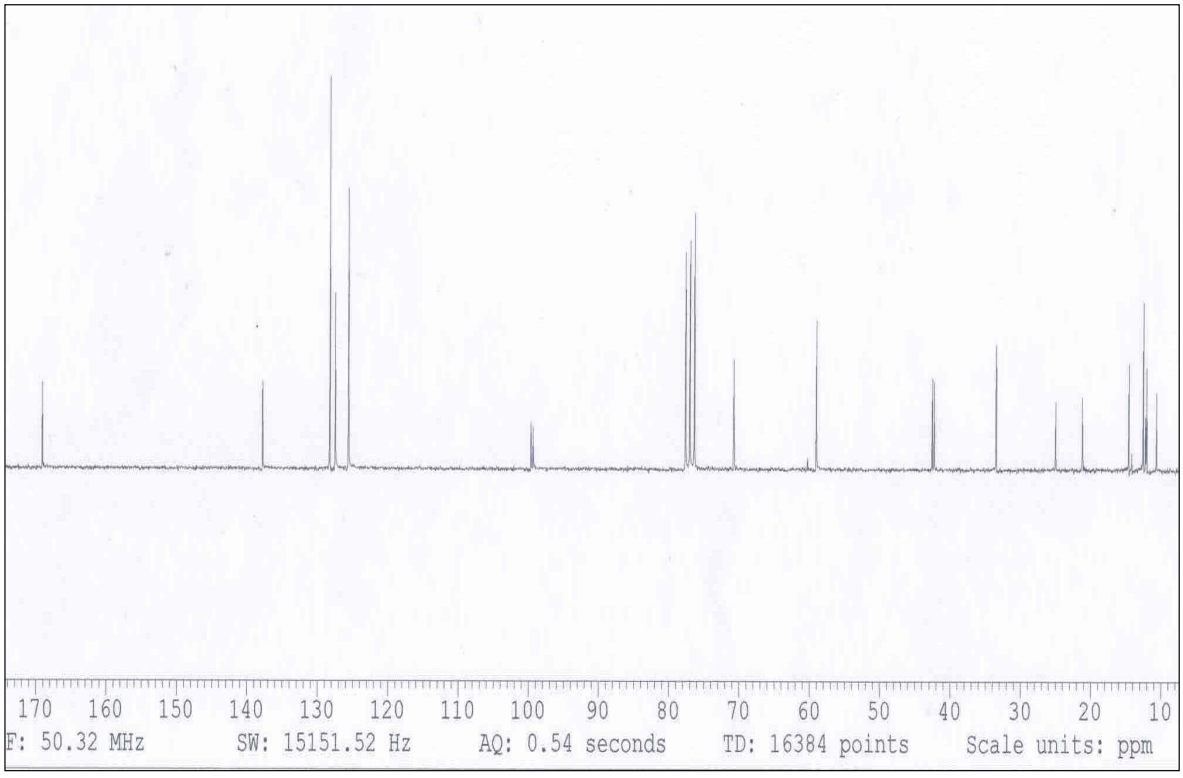
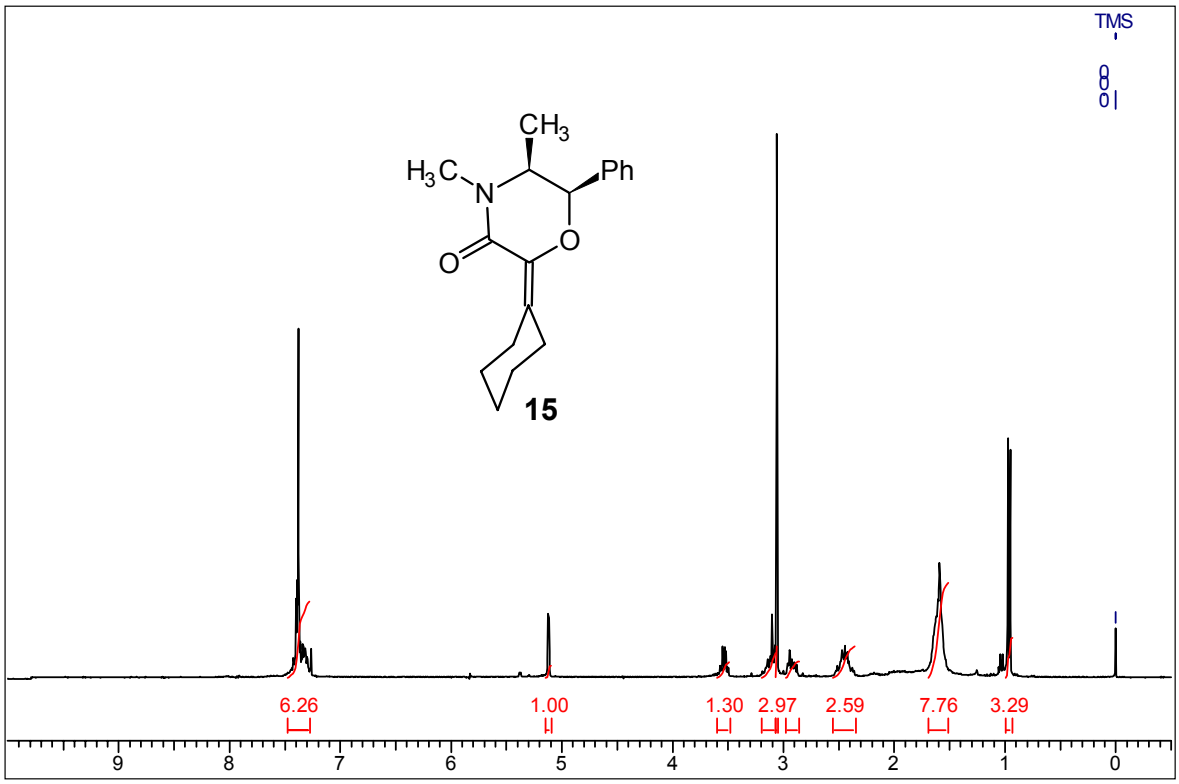
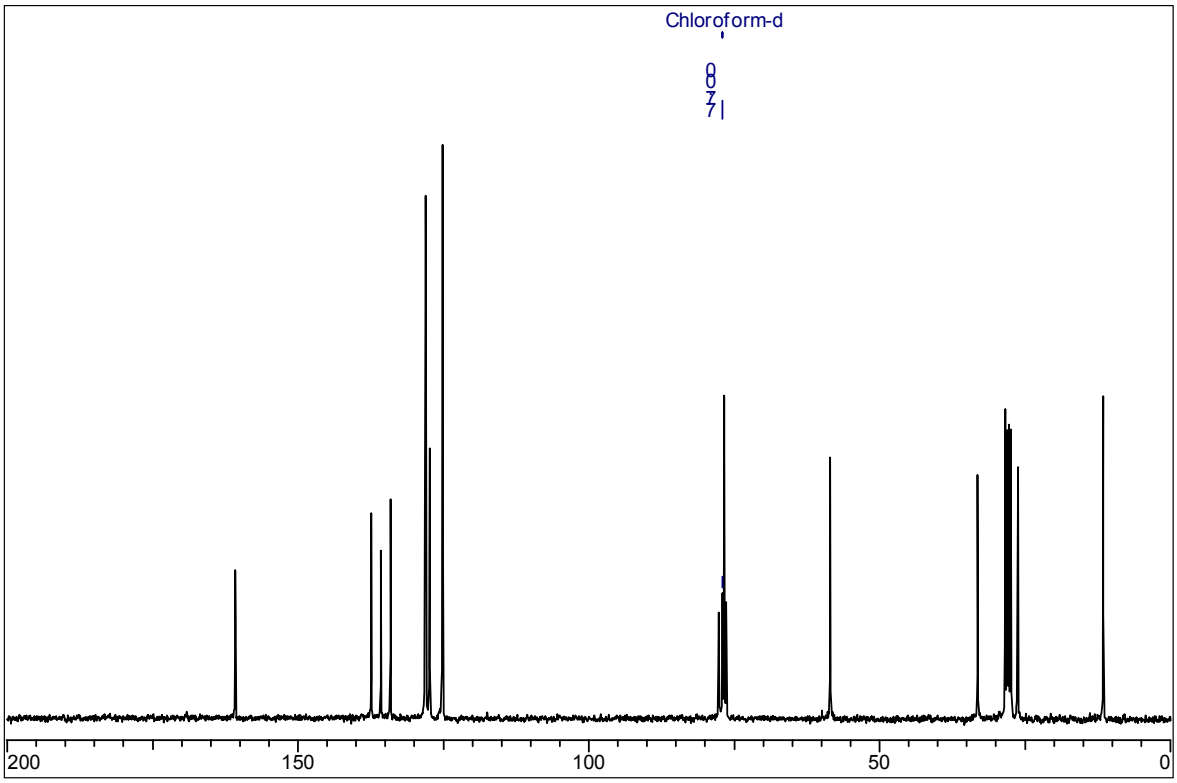
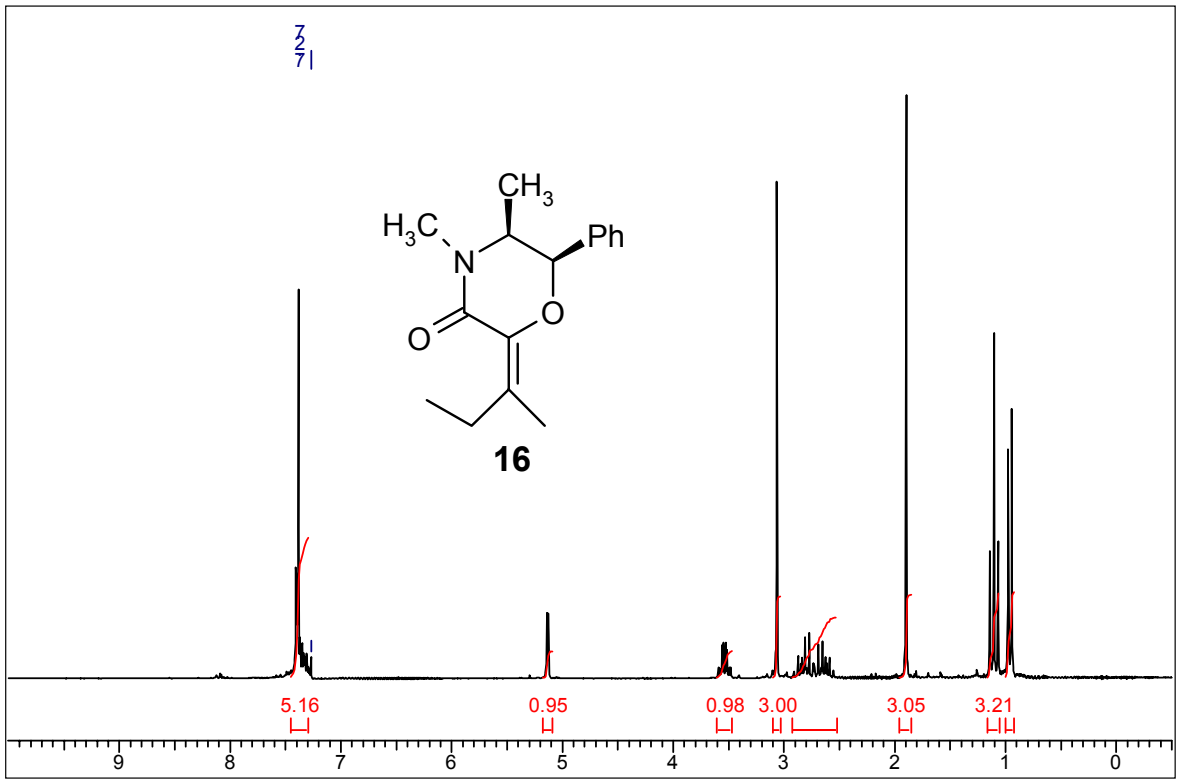
2.10
3.05
1.21
9.45
9
8
7
6
5
4
3
2
1
0


170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
F: 50.32 MHz
SW: 15151.52 Hz
AQ: 0.54 seconds
TD: 16384 points
Scale units: ppm


TMS
CH3
H3C
N
Ph
O
O
15
6.26
1.00
1.30
2.97
2.59
7.76
3.29
9
8
7
6
5
4
3
2
1
0


Chloroform-d
200
150
100
50
0


CH3
H3C
N
Ph
O
O
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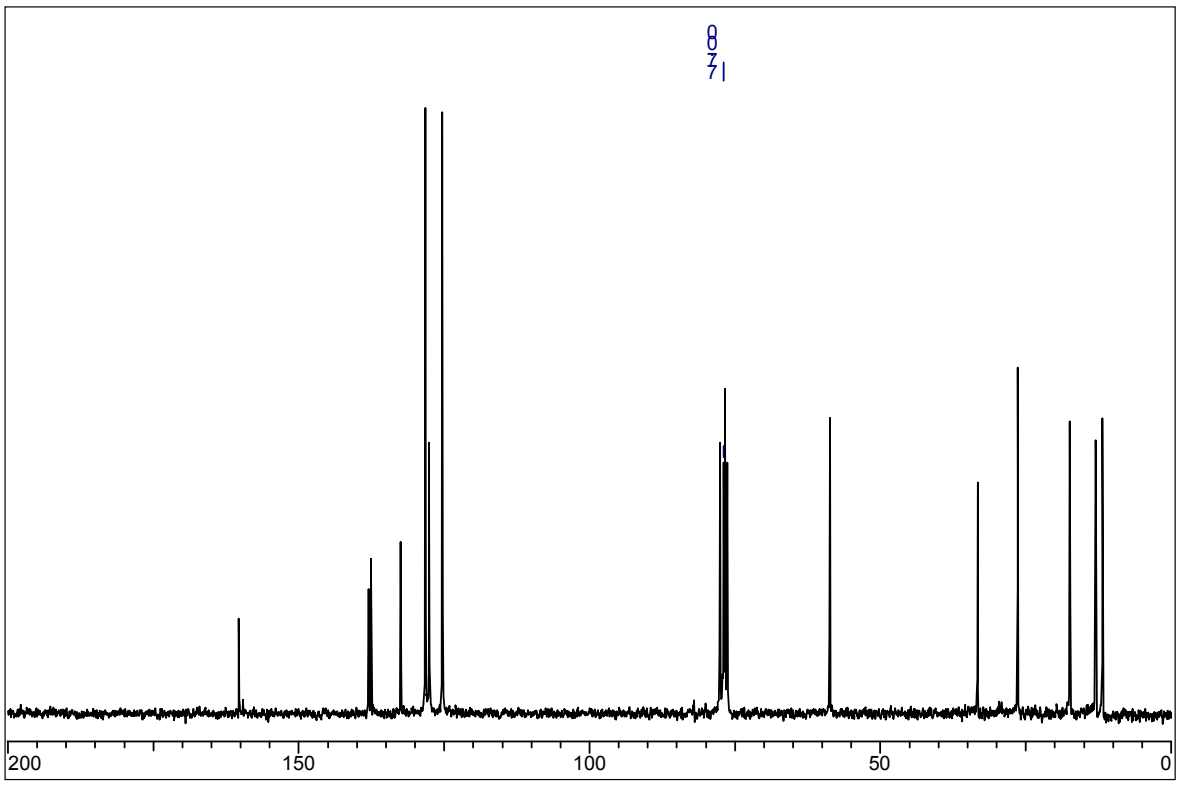
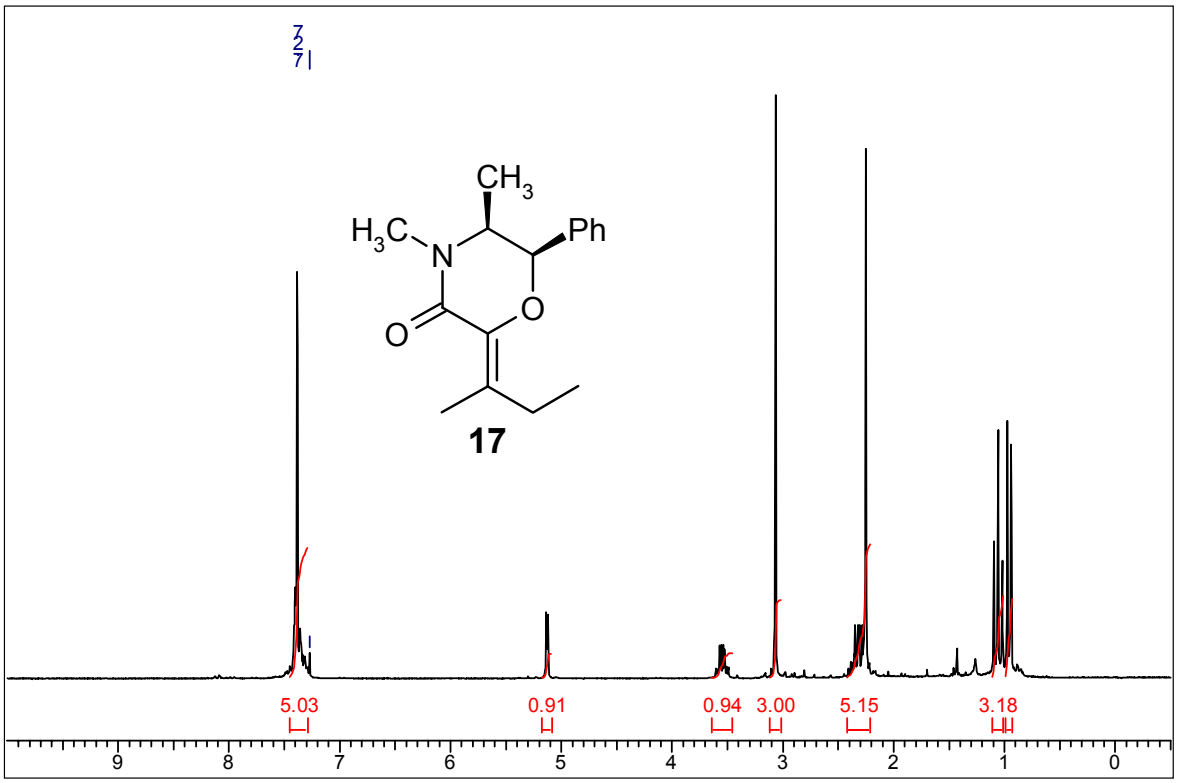
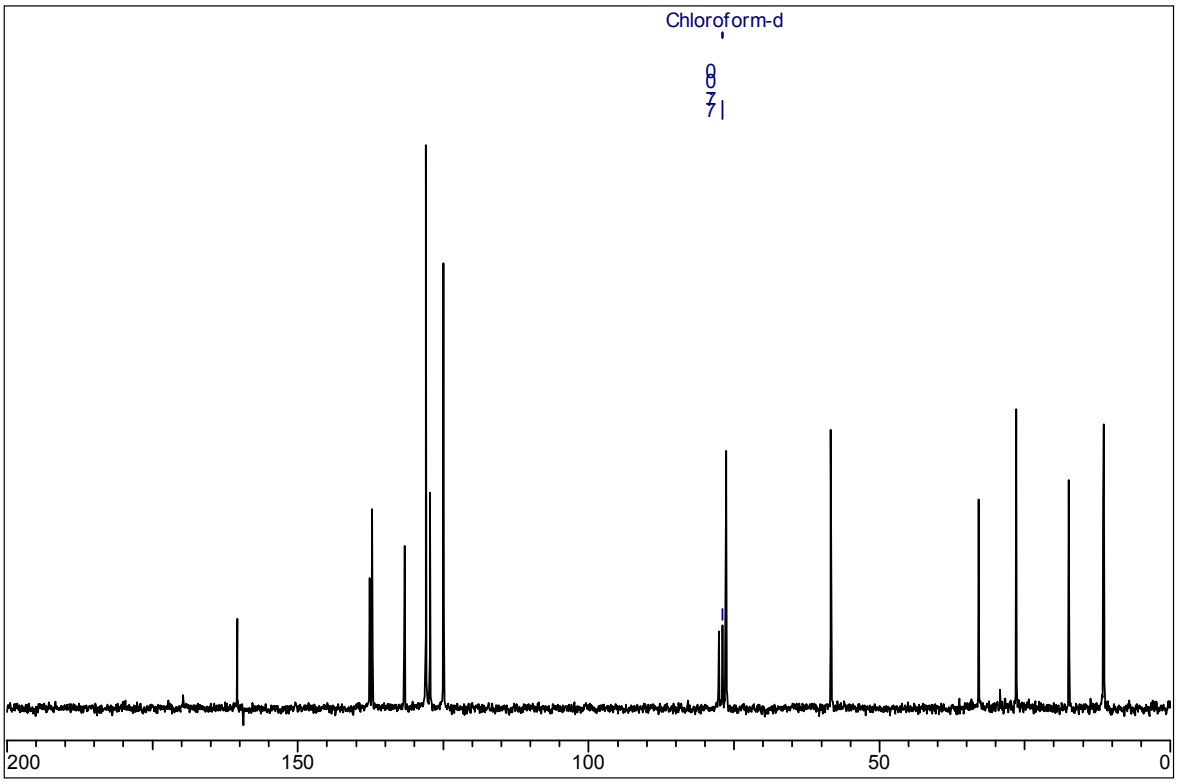
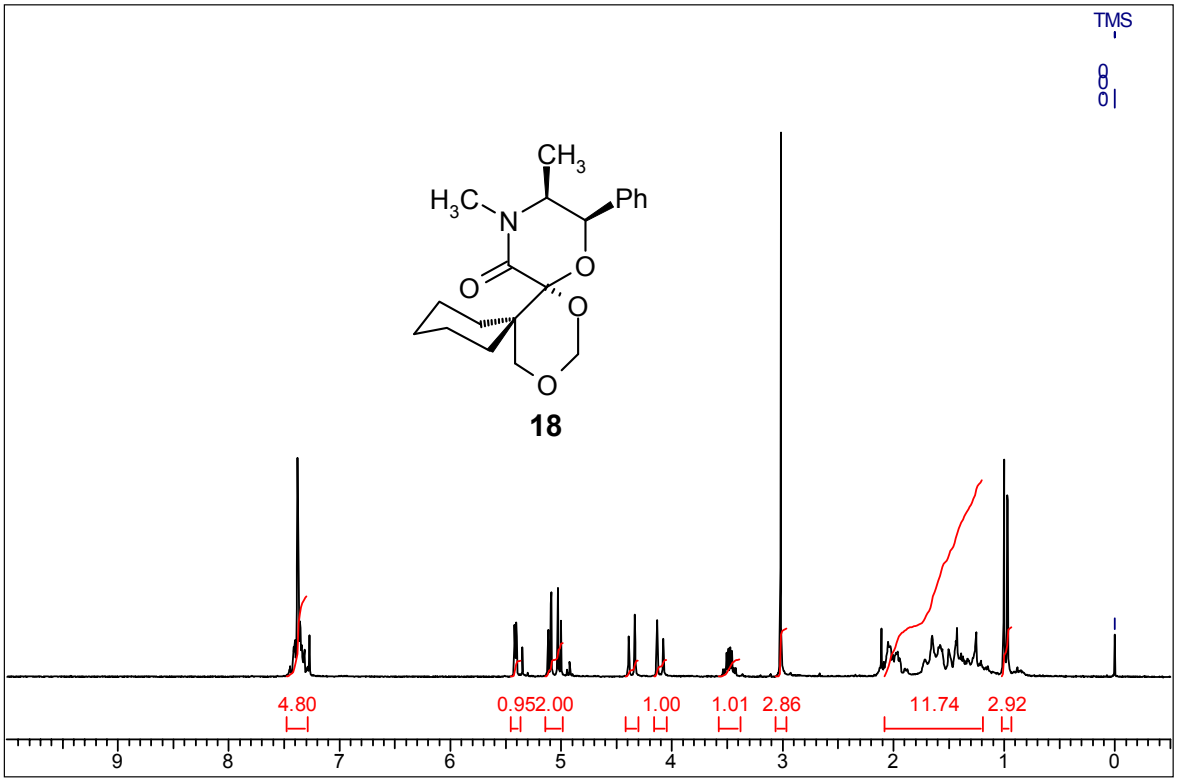
5.16
0.95
0.98
3.00
3.05
3.21
9
8
7
6
5
4
3
2
1
0


200
150
100
50
0


CH3
H3C
N
Ph
O
O
17
5.03
0.91
0.94
3.00
5.15
3.18
9
8
7
6
5
4
3
2
1
0


Chloroform-d
200
150
100
50
0


TMS
CH3
H3C
N
Ph
O
O
O
O
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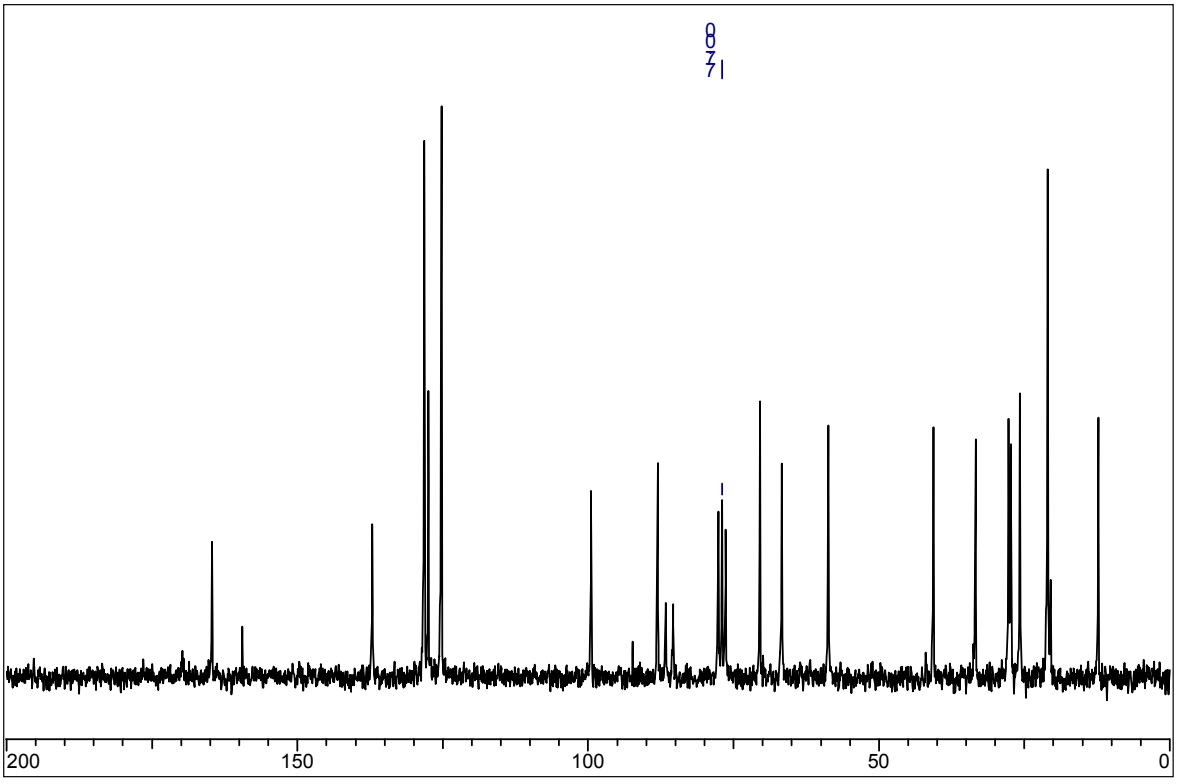
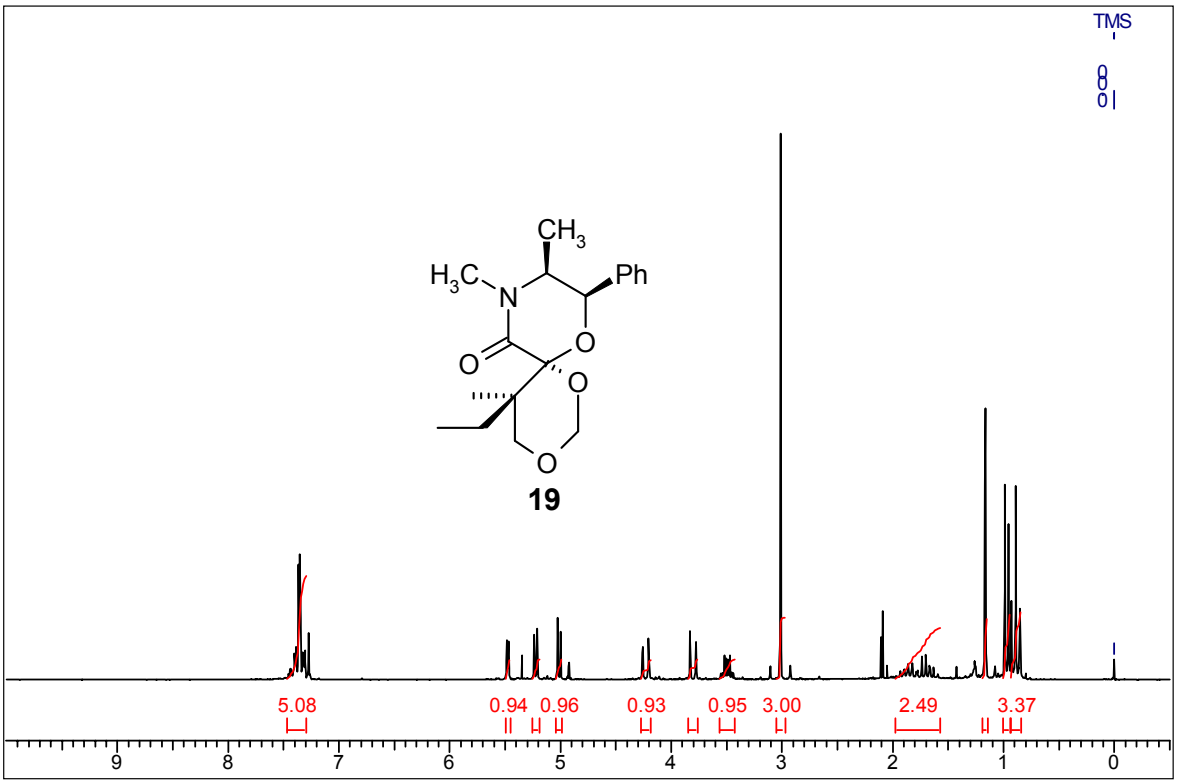
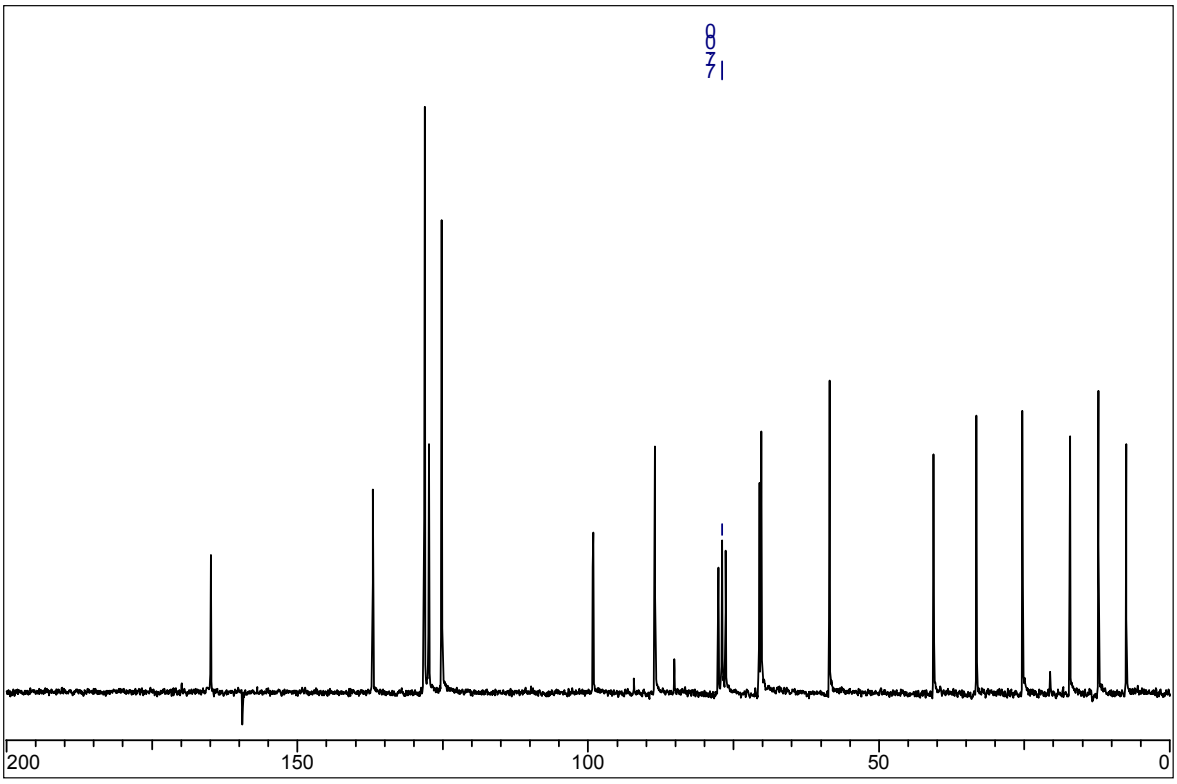
0.95
2.00
1.00
1.01
2.86
11.74
2.92
9
8
7
6
5
4
3
2
1
0

18


200
150
100
50
0


TMS
CH3
H3C
N
Ph
O
O
O
O
19
5.08
0.94
0.96
0.93
0.95
3.00
2.49
3.37
9
8
7
6
5
4
3
2
1
0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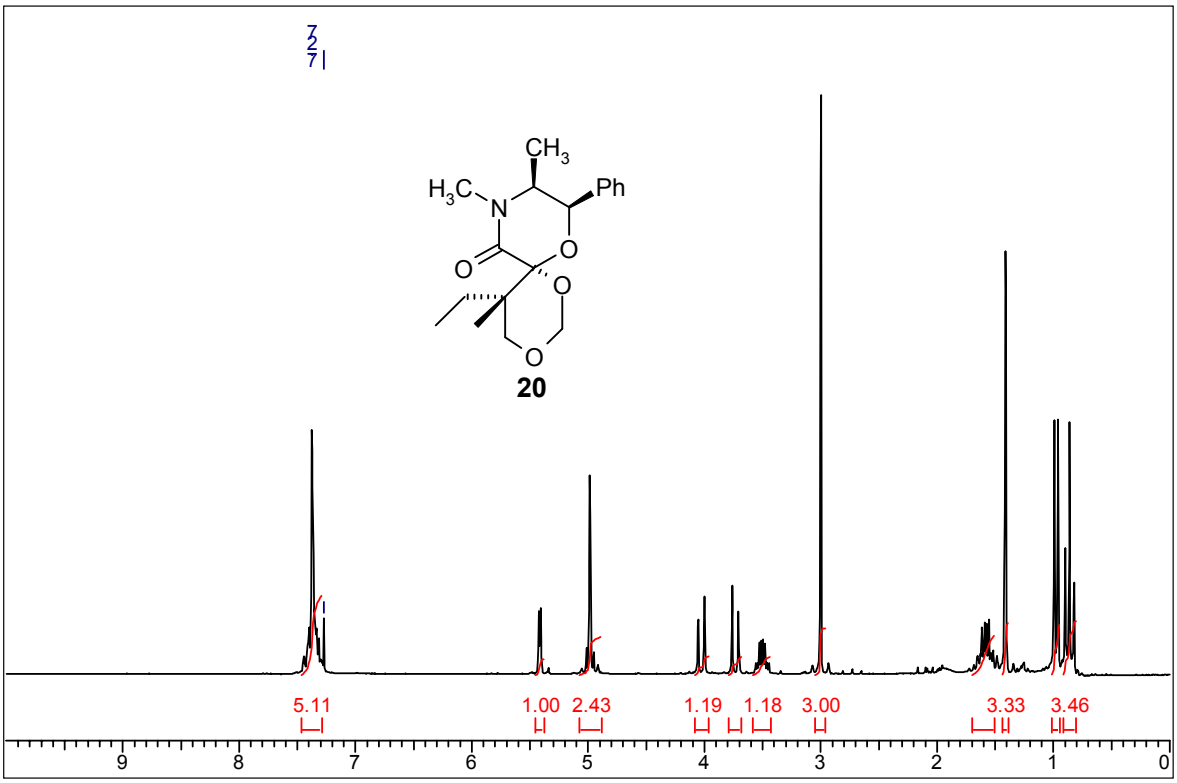
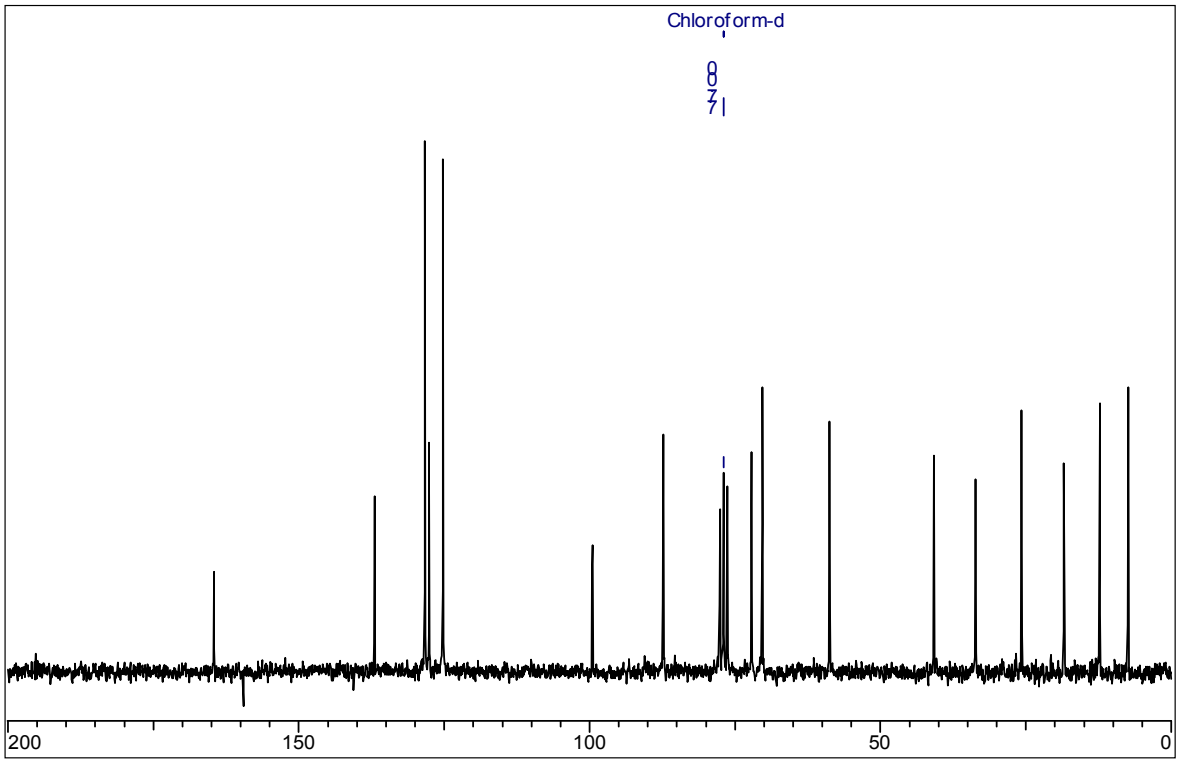
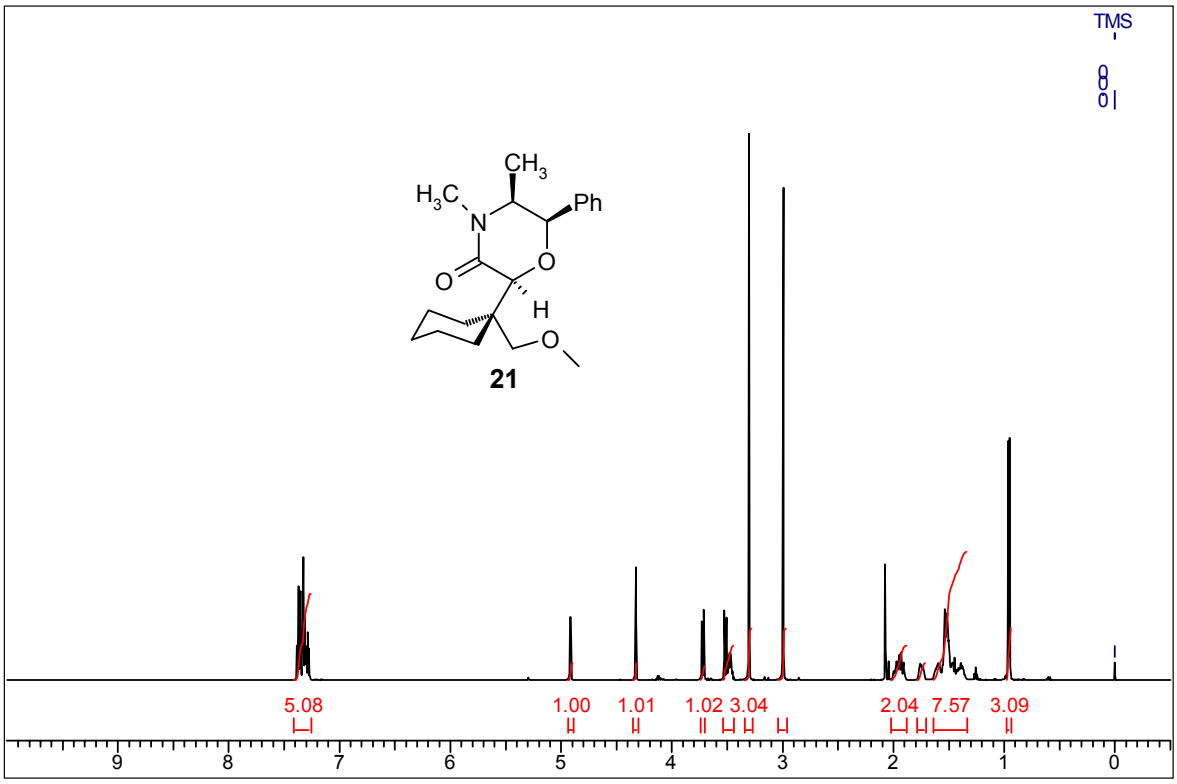
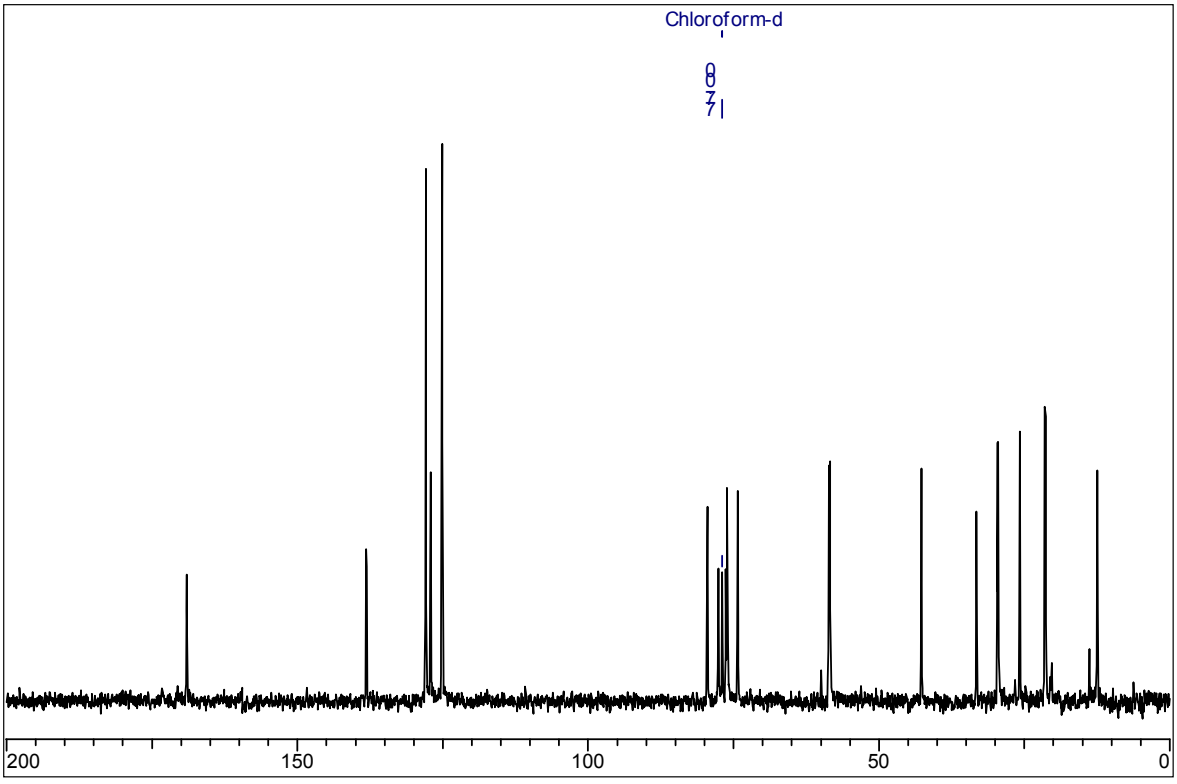
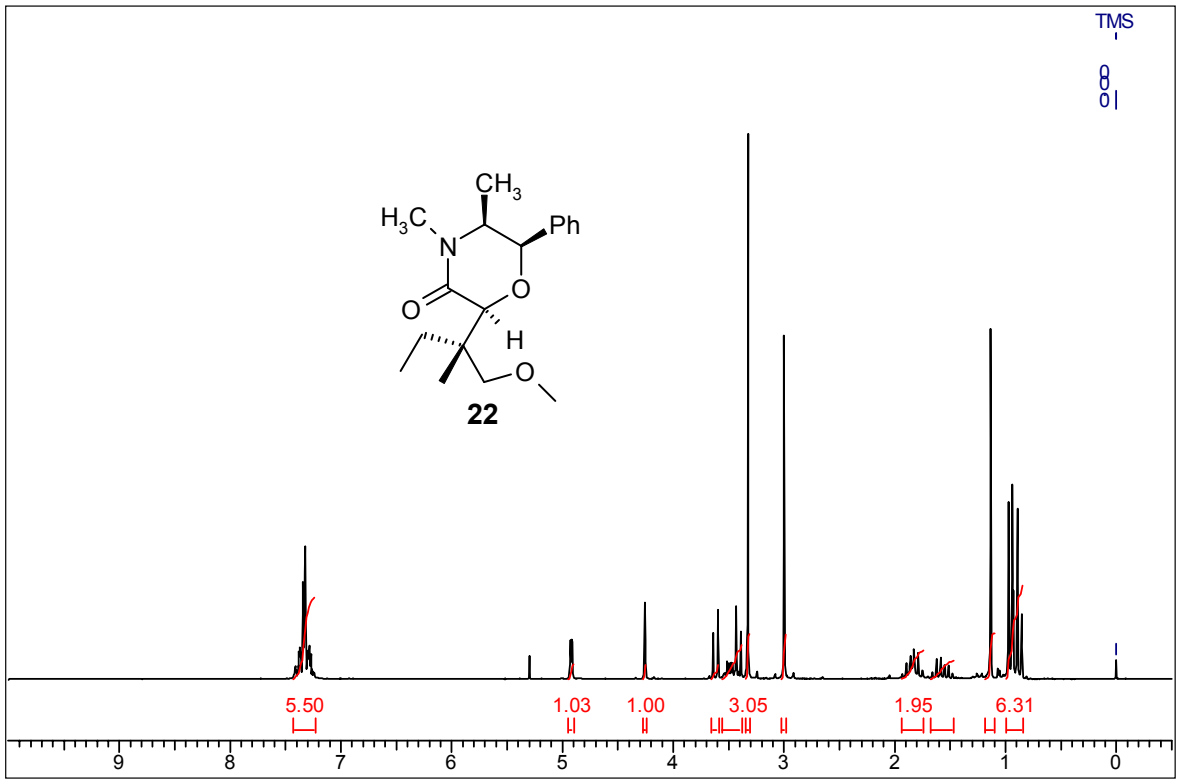
150
100
50
0

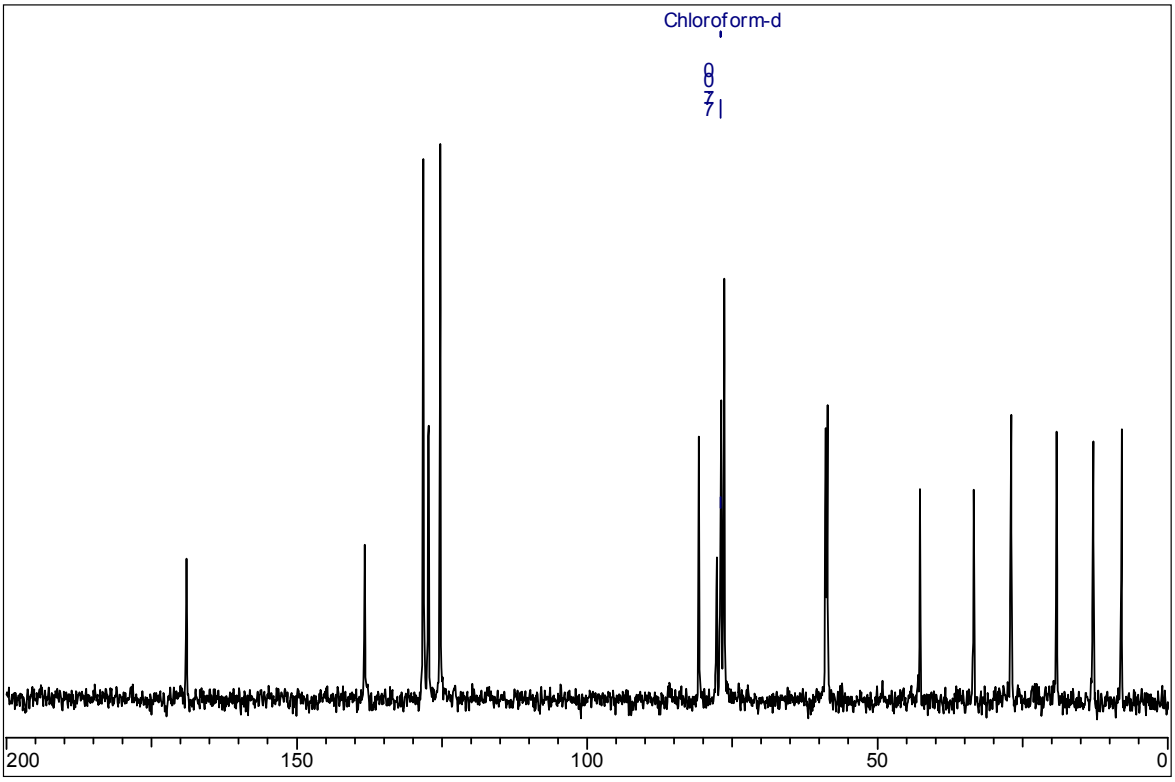

CH3
H3C
N
Ph
O
O
O
O
20
5.11
1.00
2.43
1.19
1.18
3.00
3.33
3.46
9
8
7
6
5
4
3
2
1
0

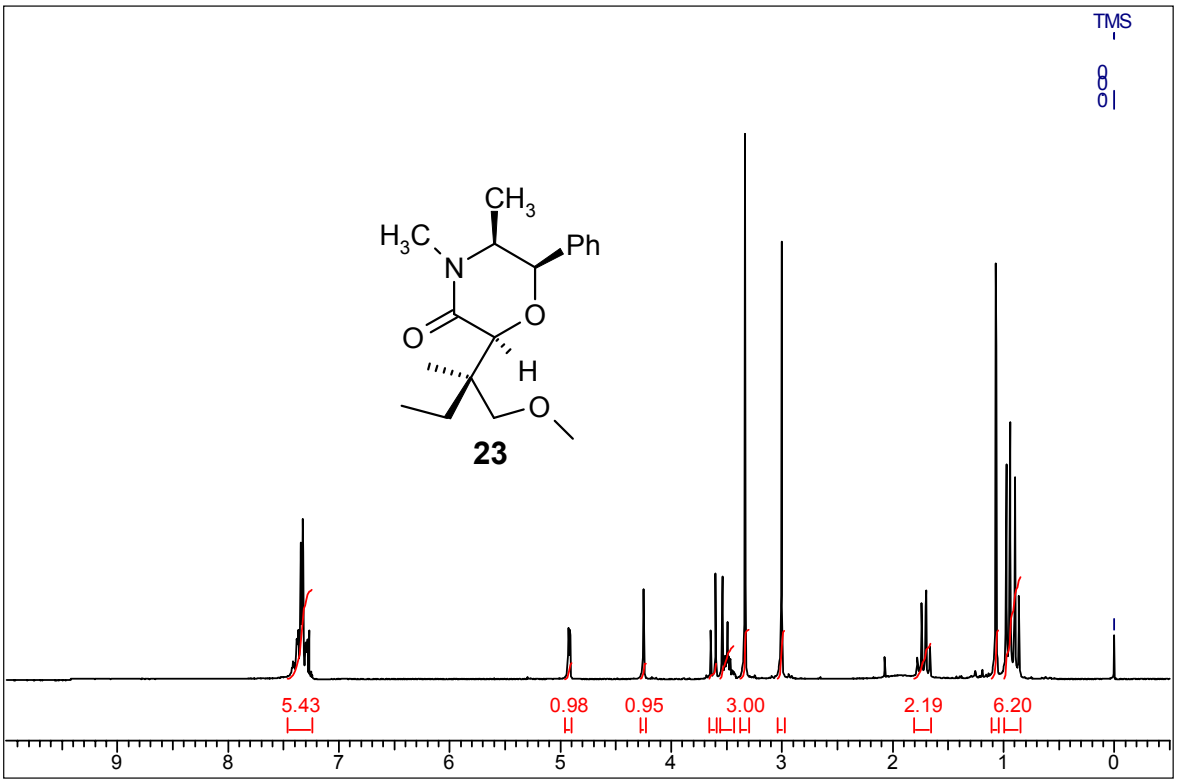

Chloroform-d
200
150
100
50
0

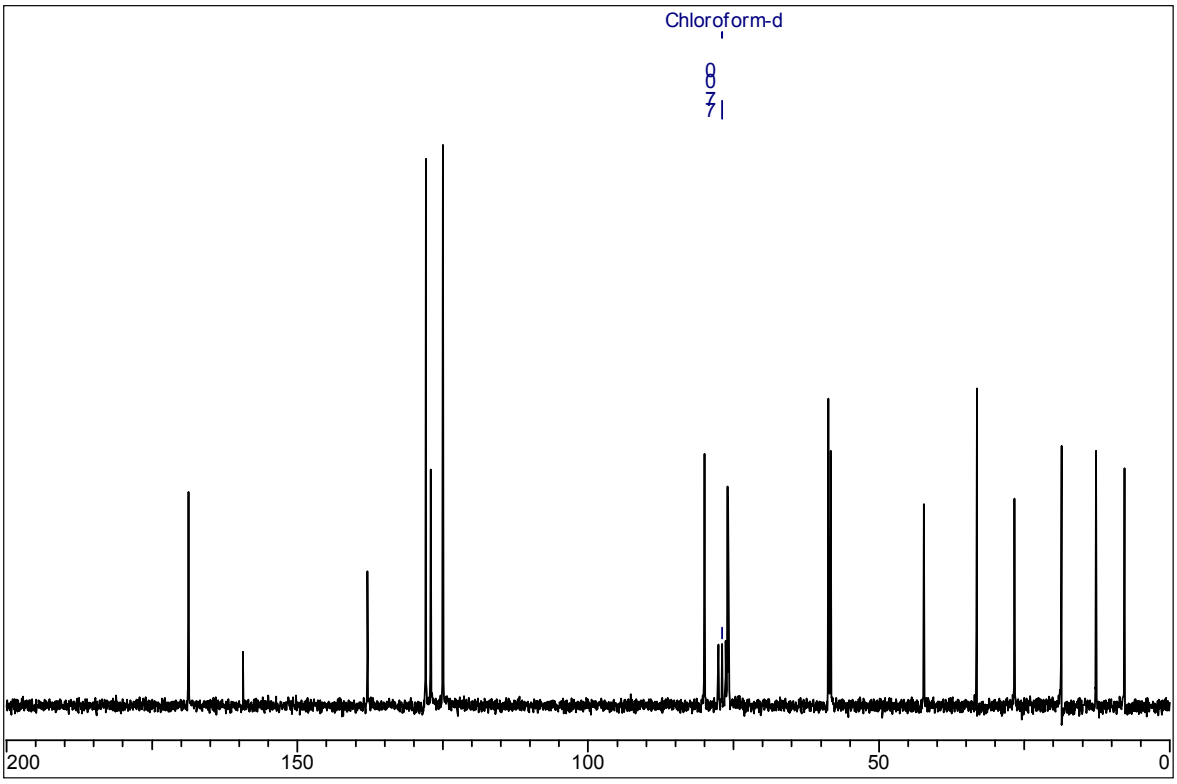

TMS
CH3
H3C
N
Ph
O
O
H
O
21
5.08
1.00
1.01
1.02
3.04
2.04
7.57
3.09
9
8
7
6
5
4
3
2
1
0

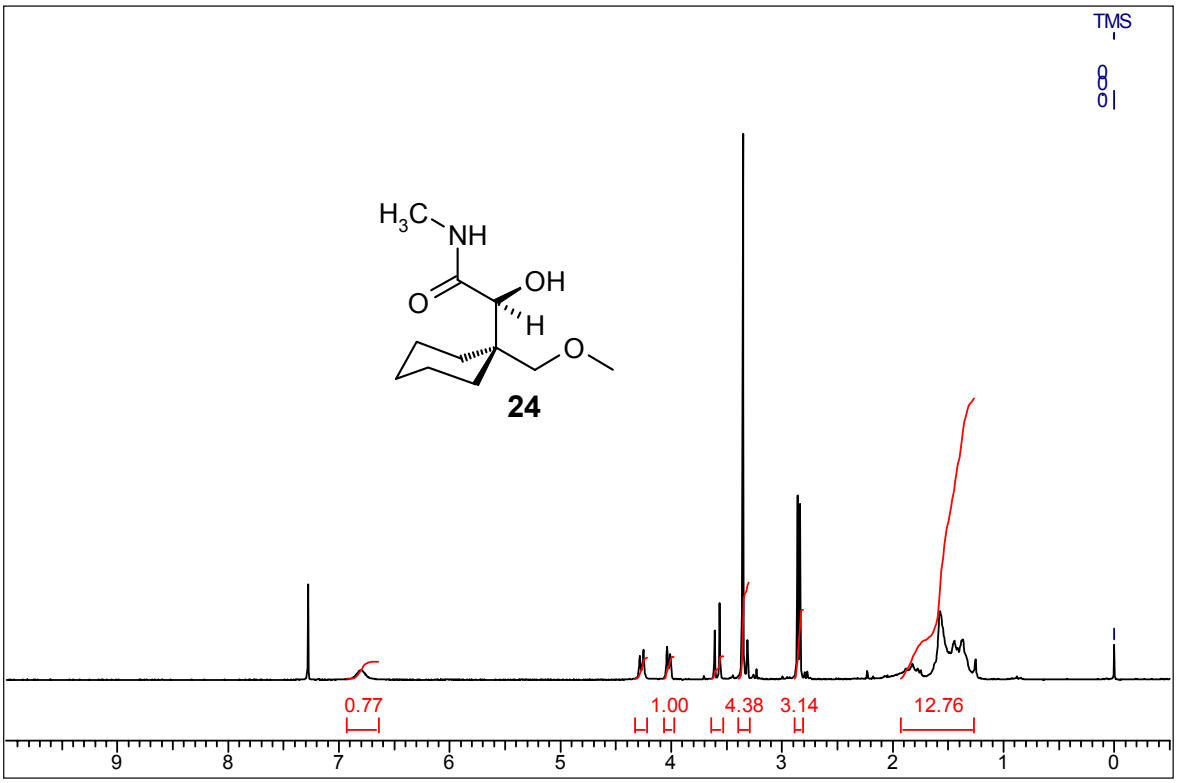

Chloroform-d
200
150
100
50
0


TMS
CH3
H3C
N
Ph
O
O
H
O
22
5.50
1.03
1.00
3.05
1.95
6.31
9
8
7
6
5
4
3
2
1
0


Chloroform-d
200
150
100
50
0


TMS
CH3
H3C
N
Ph
O
O
H
O
23
5.43
0.98
0.95
3.00
2.19
6.20
9
8
7
6
5
4
3
2
1
0


Chloroform-d
200
150
100
50
0


TMS
H3C
NH
O
OH
H
O
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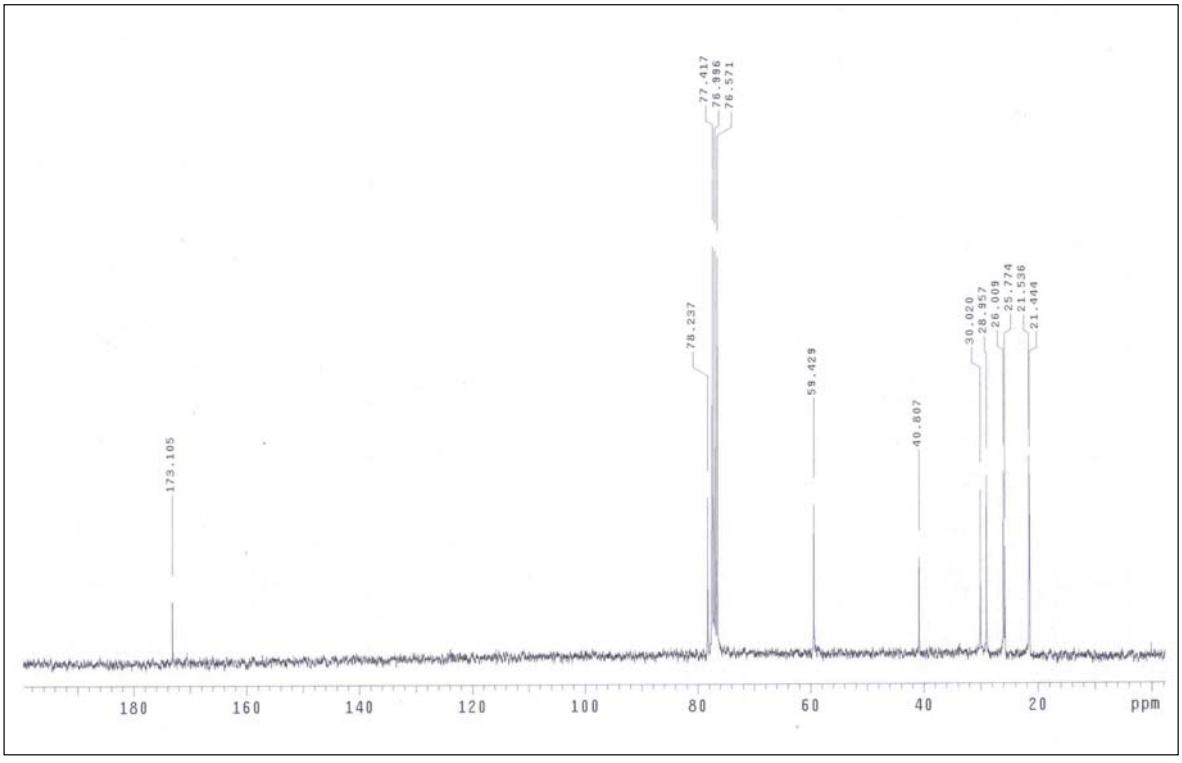
4.38
3.14
12.76
9
8
7
6
5
4
3
2
1
0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76.996
76.571
78.237
59.429
40.807
30.020
28.957
26.009
25.774
21.536
21.444
173.105
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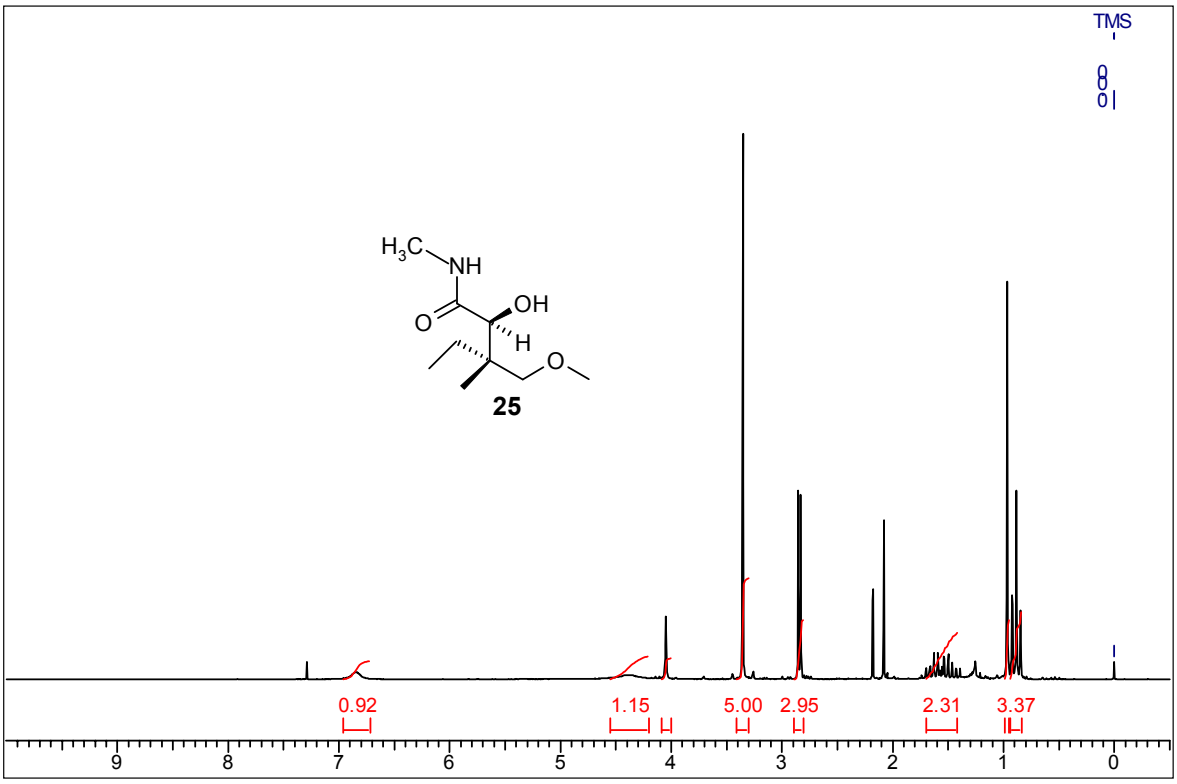
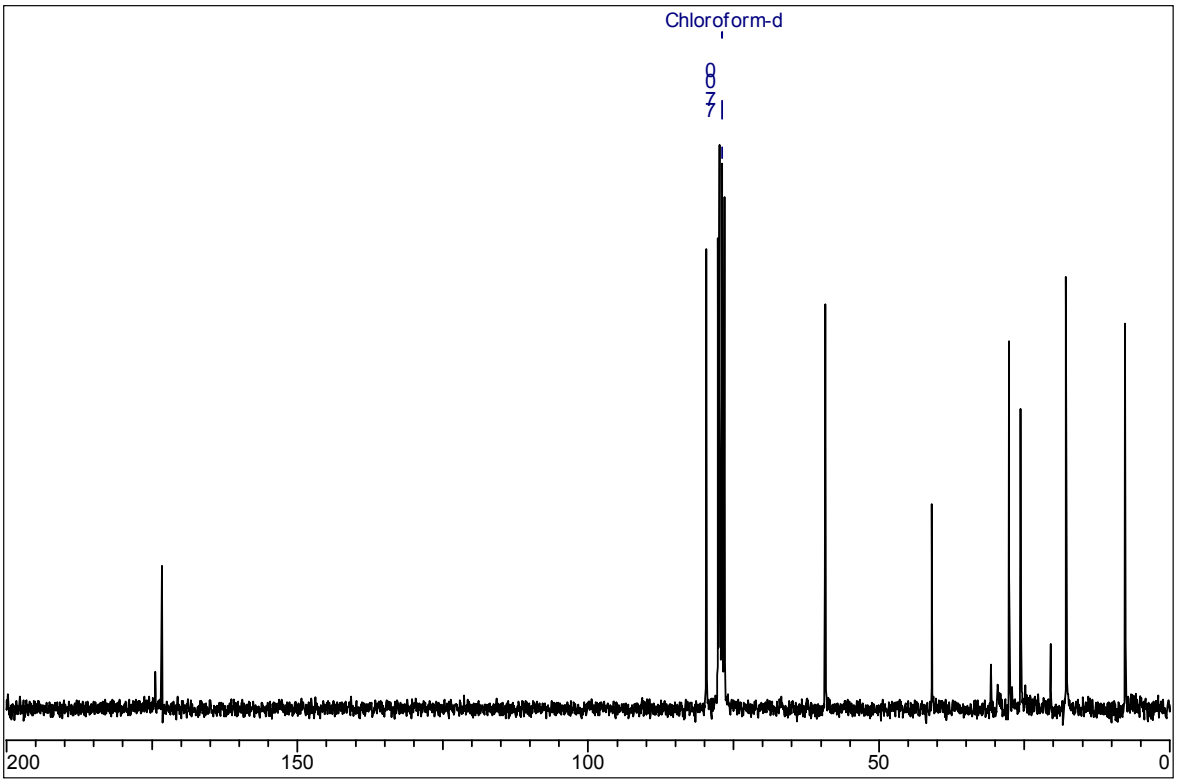
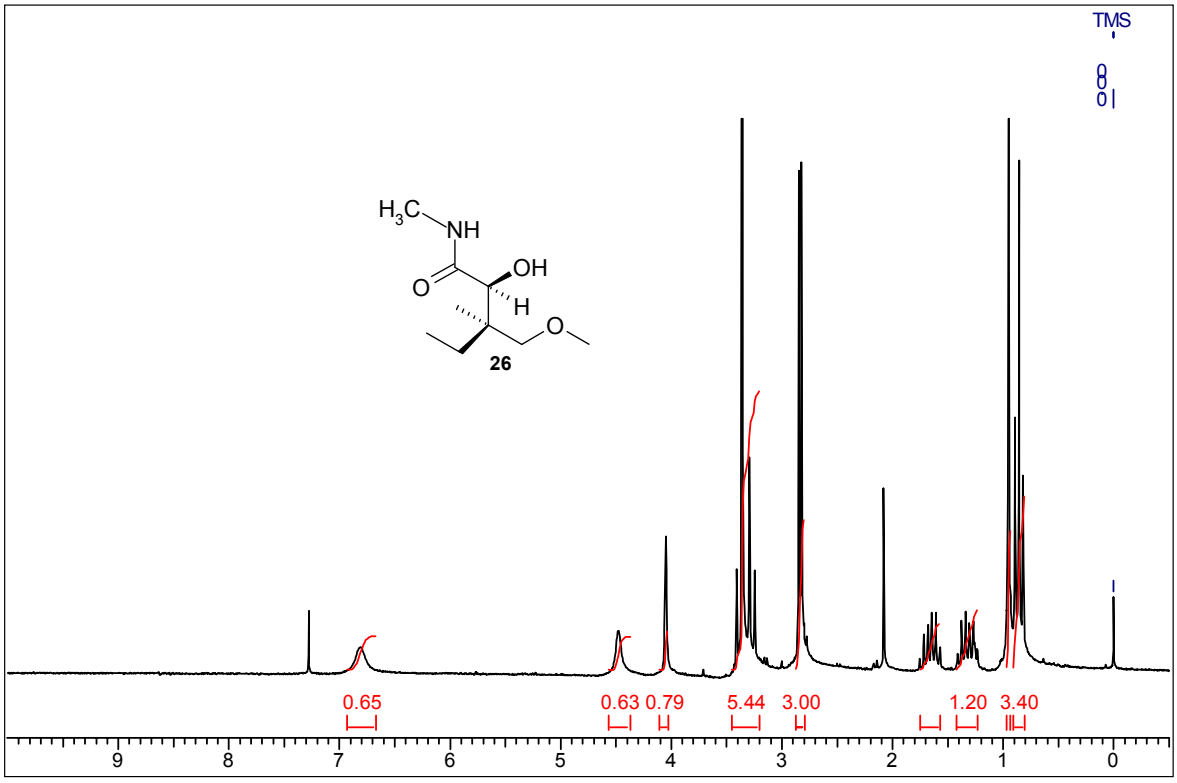
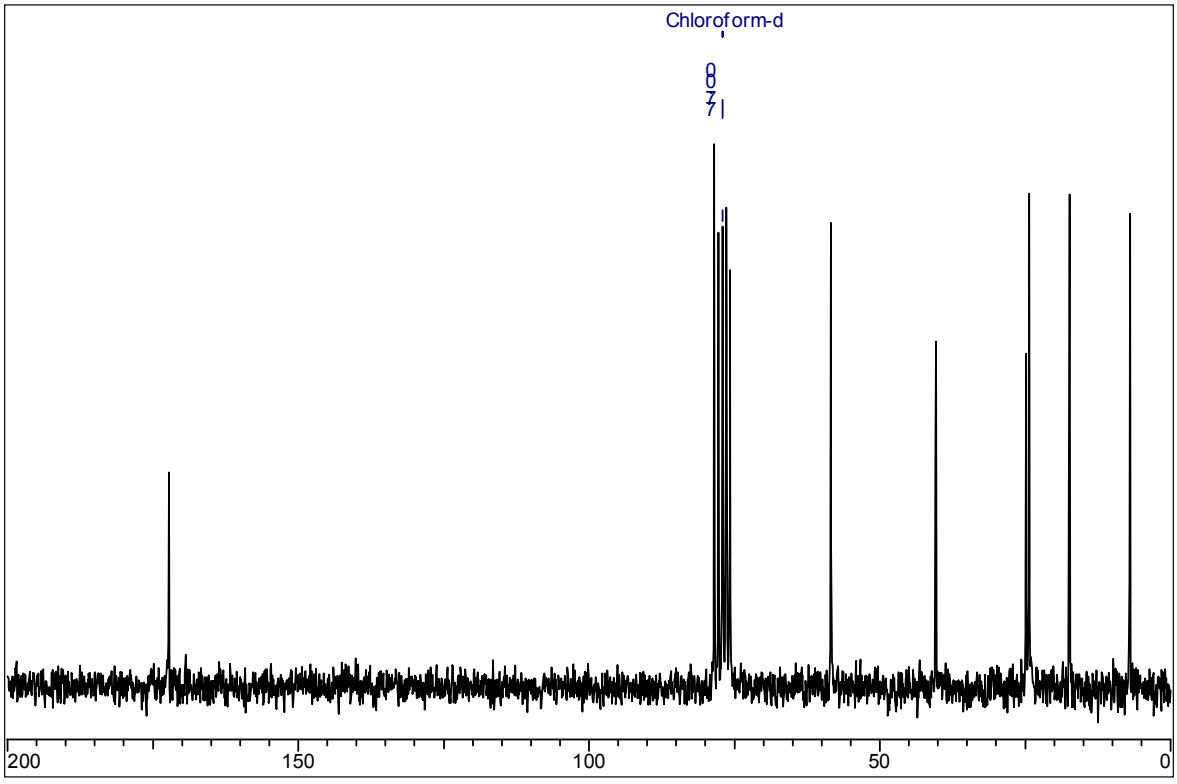
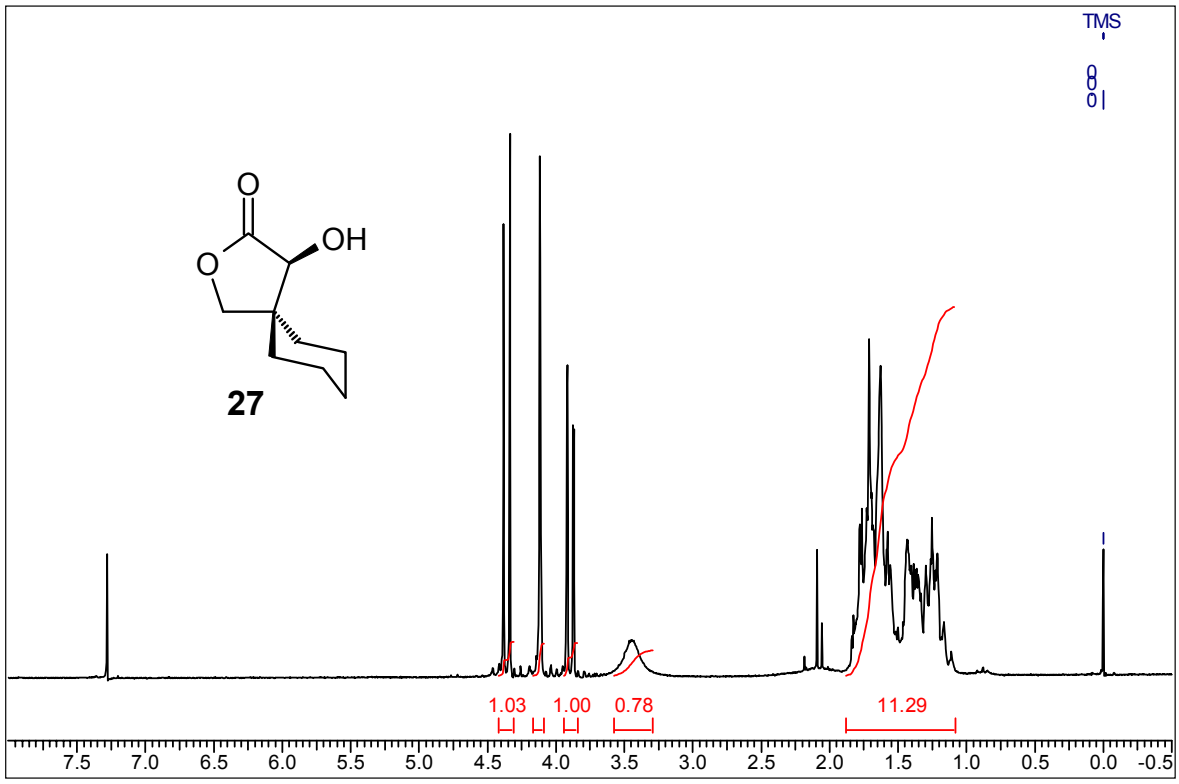
160
140
120
100
80
60
40
20
ppm

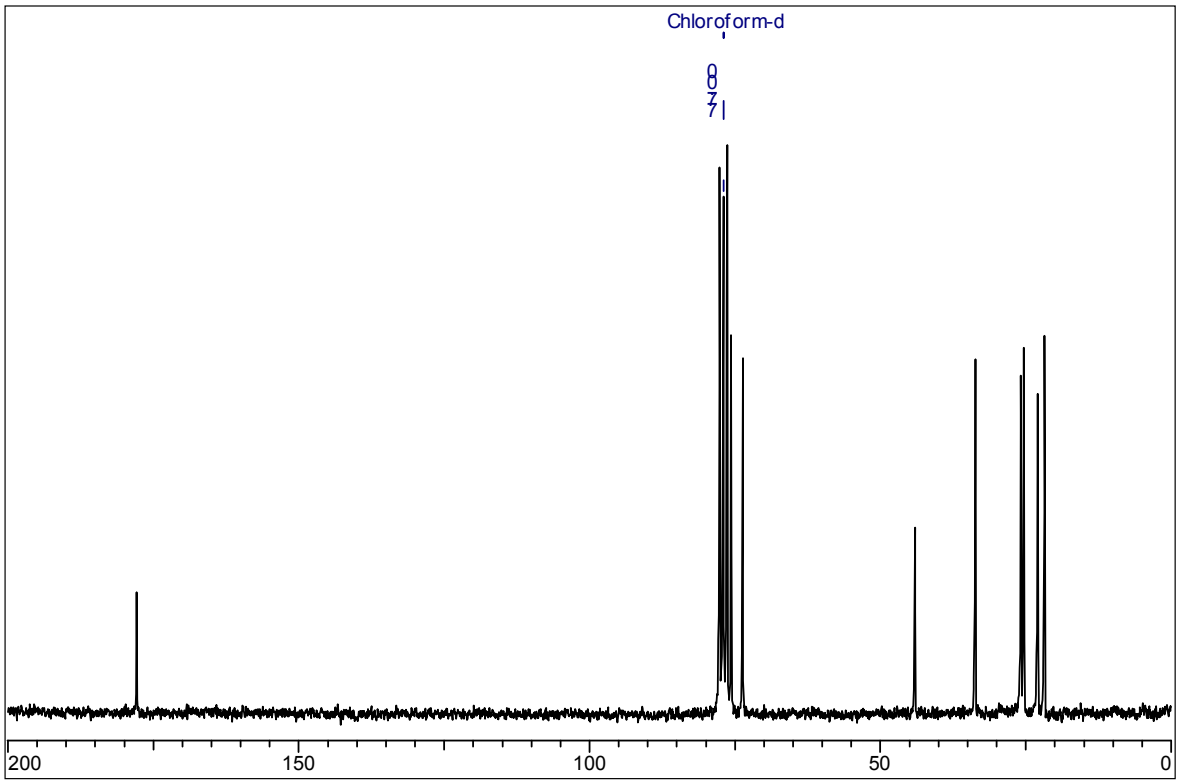

TMS
H3C
NH
O
OH
H
O
25
0.92
1.15
5.00
2.95
2.31
3.37
9
8
7
6
5
4
3
2
1
0

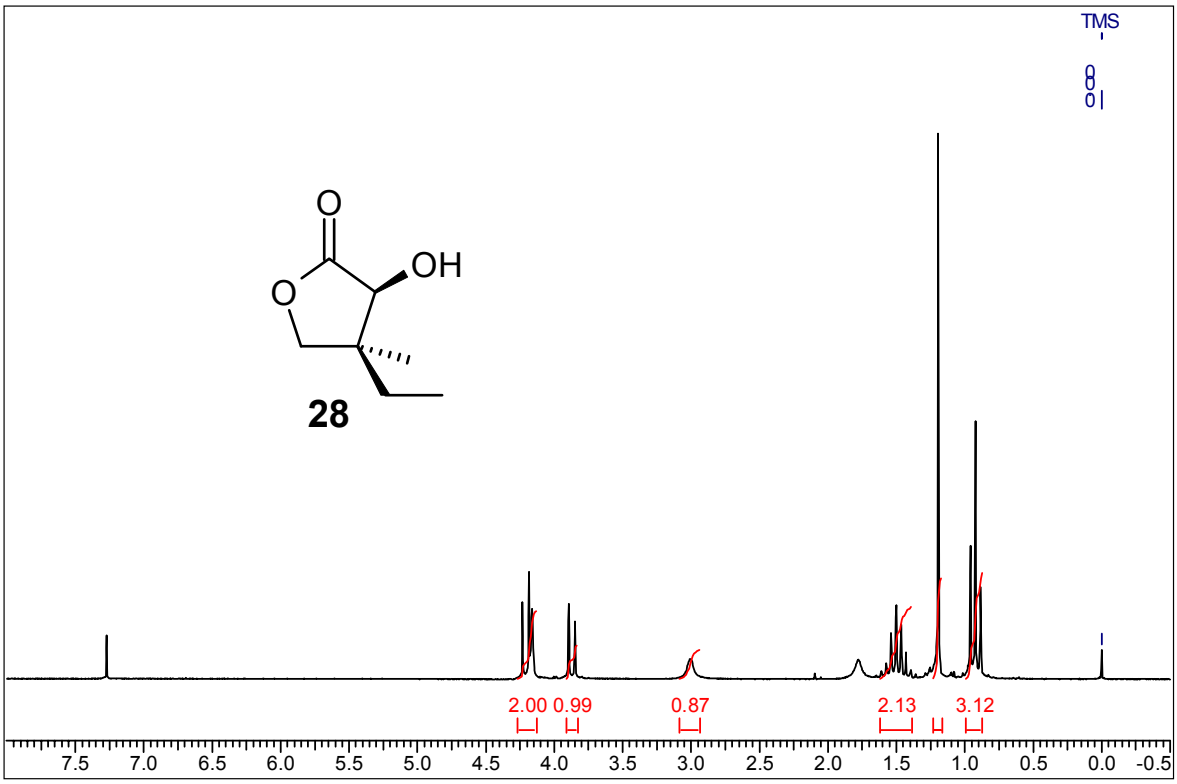

Chloroform-d
200
150
100
50
0

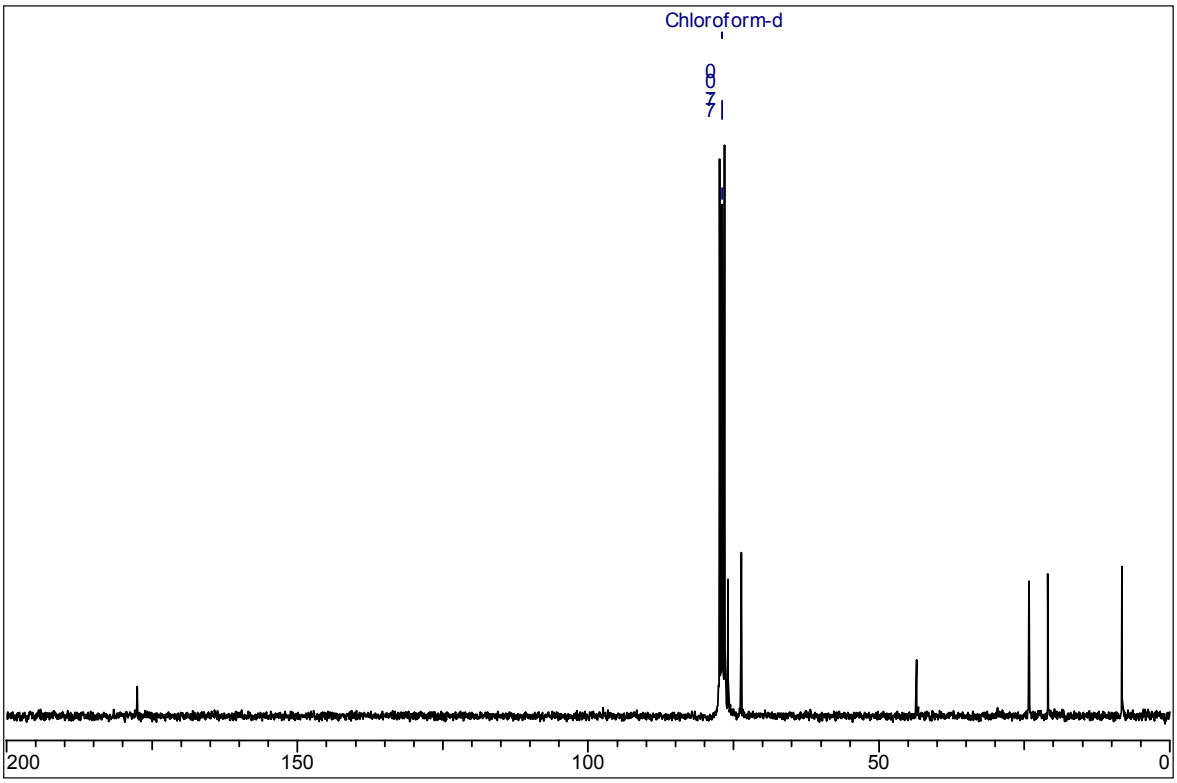

TMS
H3C
NH
O
OH
H
O
26
0.65
0.63
0.79
5.44
3.00
1.20
3.40
9
8
7
6
5
4
3
2
1
0

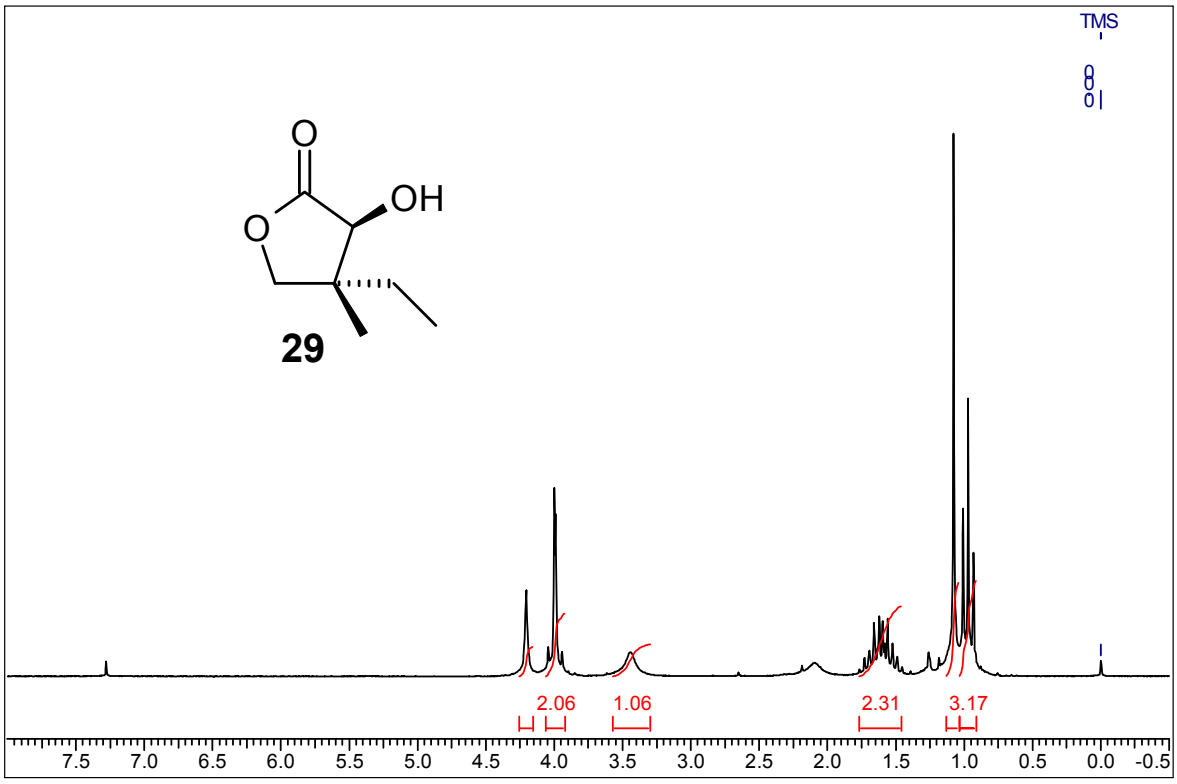

Chloroform-d
200
150
100
50
0

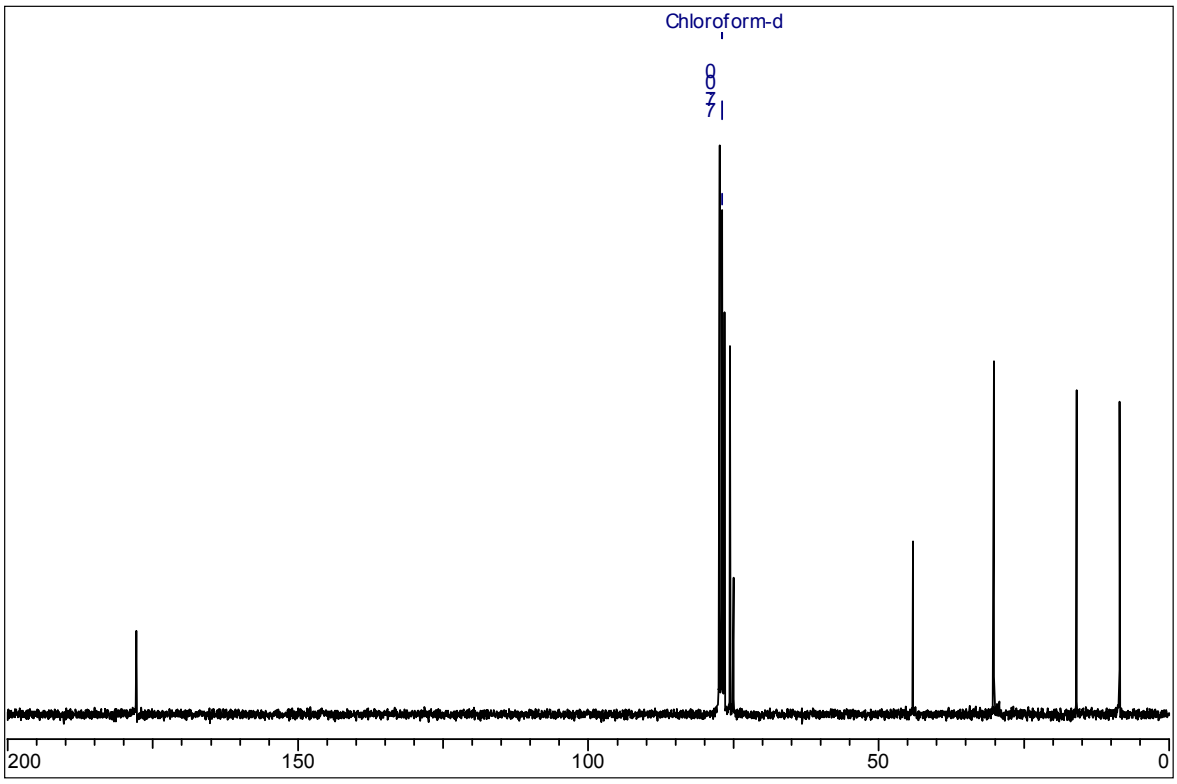

TMS
O
O
OH
27
1.03
1.00
0.78
11.29
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

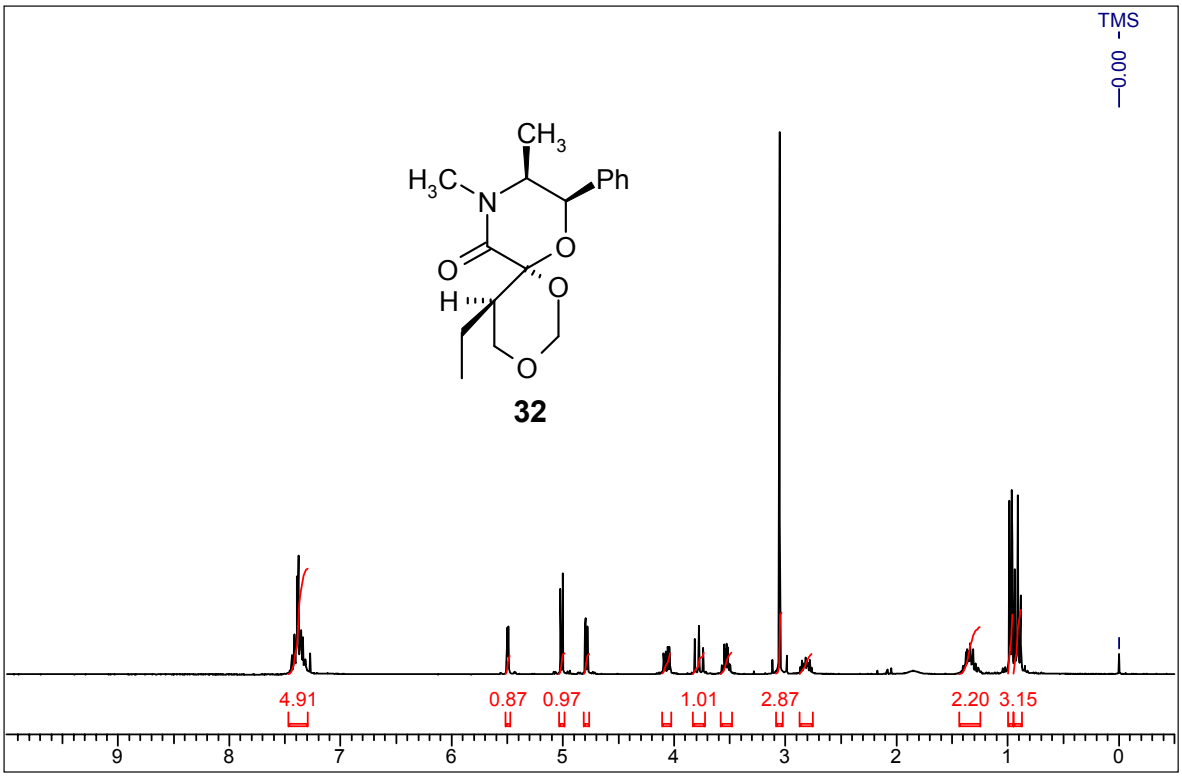

Chloroform-d
200
150
100
50
0


TMS
O
OH
O
28
2.00
0.99
0.87
2.13
3.12
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

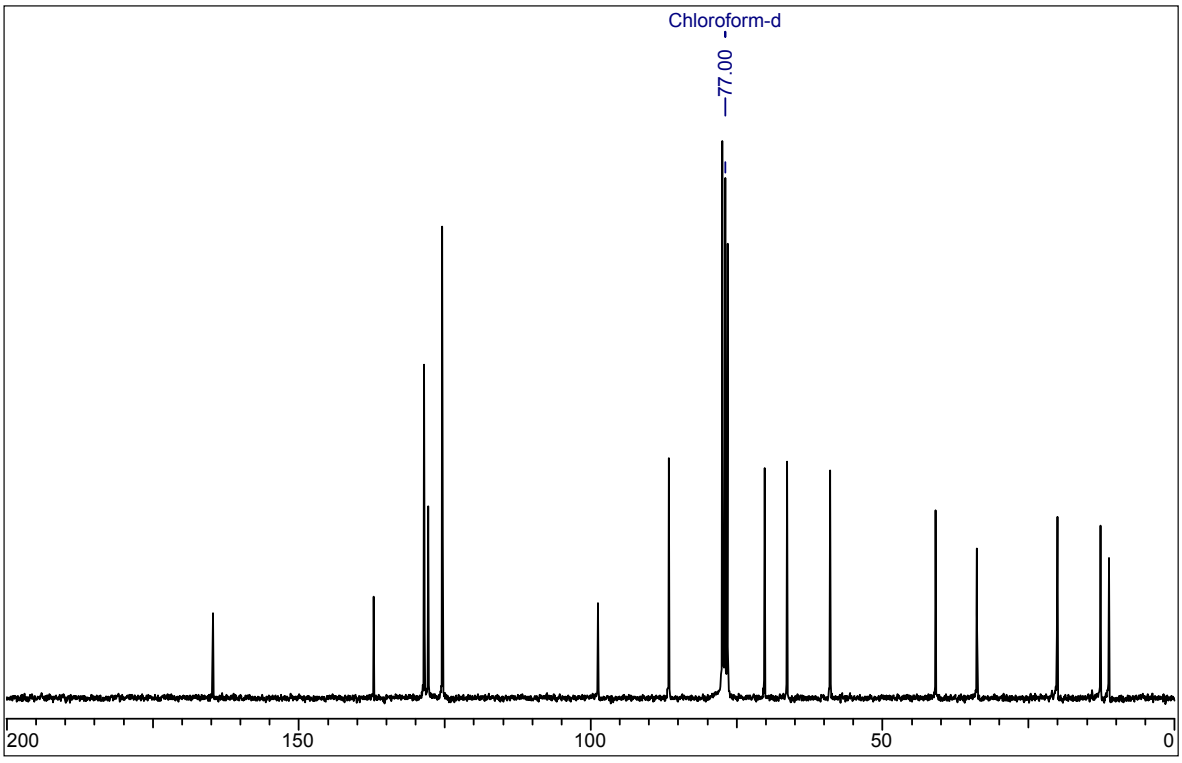

Chloroform-d
200
150
100
50
0

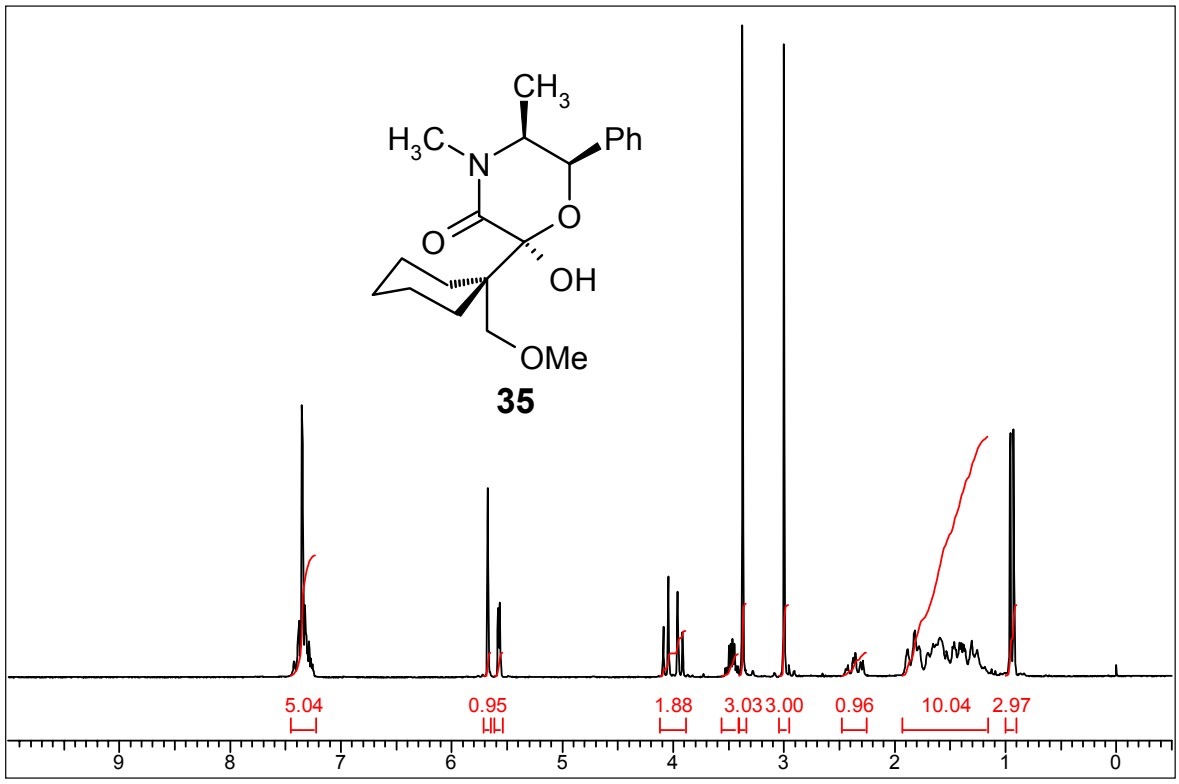

TMS
O
OH
O
29
2.06
1.06
2.31
3.17
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

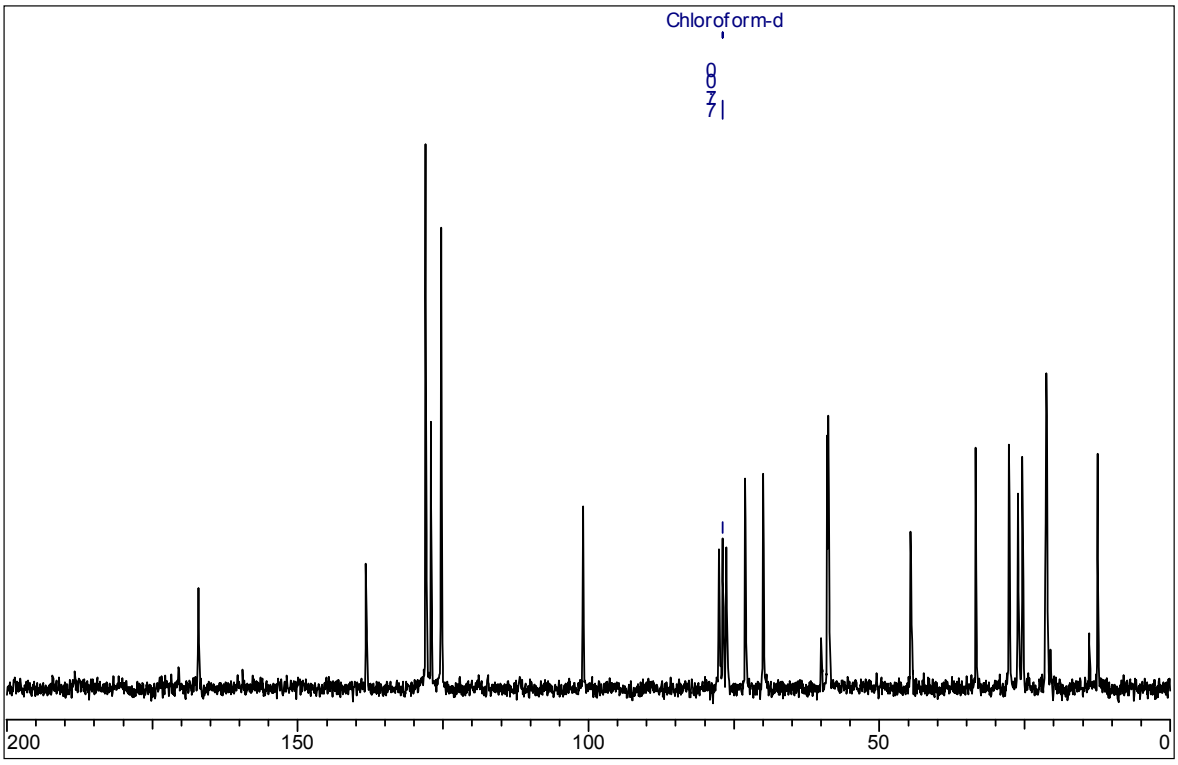

Chloroform-d
200
150
100
50
0


TMS
0.00
CH3
H3C
N
Ph
O
O
O
H
O
4.91
0.87
0.97
1.01
2.87
2.20
3.15
9
8
7
6
5
4
3
2
1
0

32


Chloroform-d
77.00
200
150
100
50
0


CH3
H3C
N
Ph
O
O
OH
OMe
35
5.04
0.95
1.88
3.03
3.00
0.96
10.04
2.97
9
8
7
6
5
4
3
2
1
0


Chloroform-d
77.00
76.68
76.37
200
150
100
50
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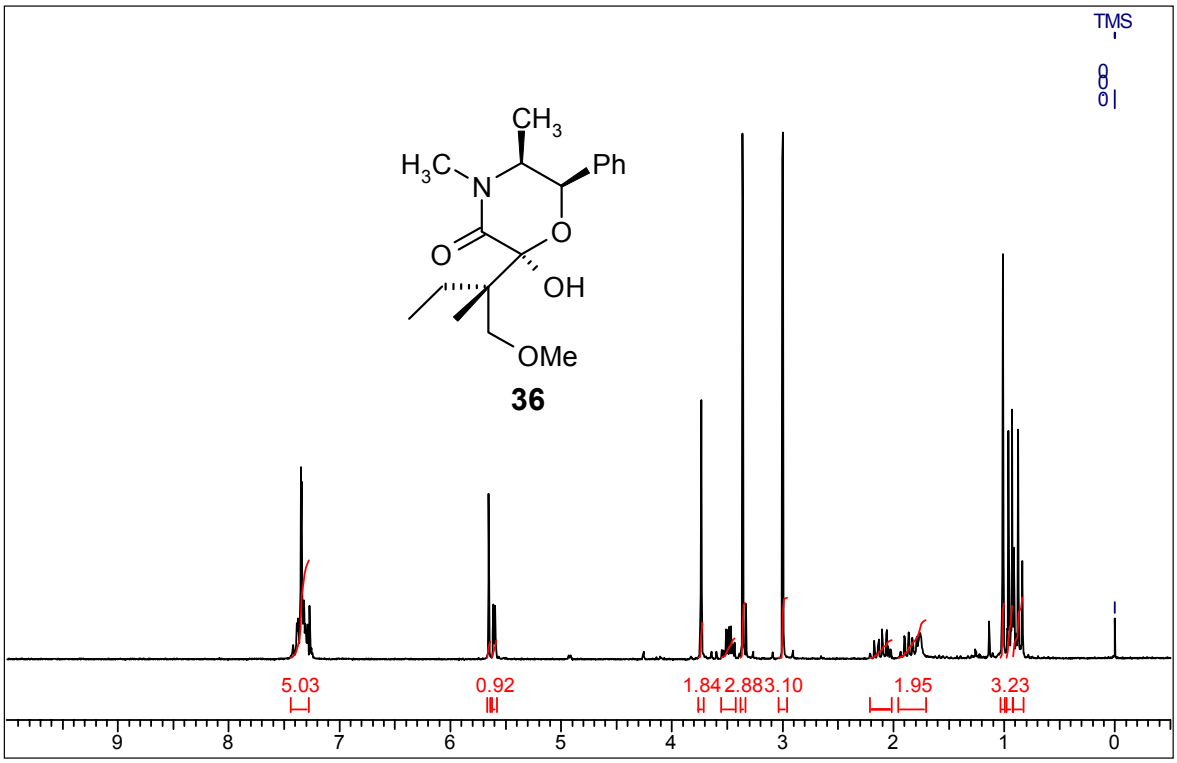
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OH
OMe
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3.23
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8
7
6
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4
3
2
1
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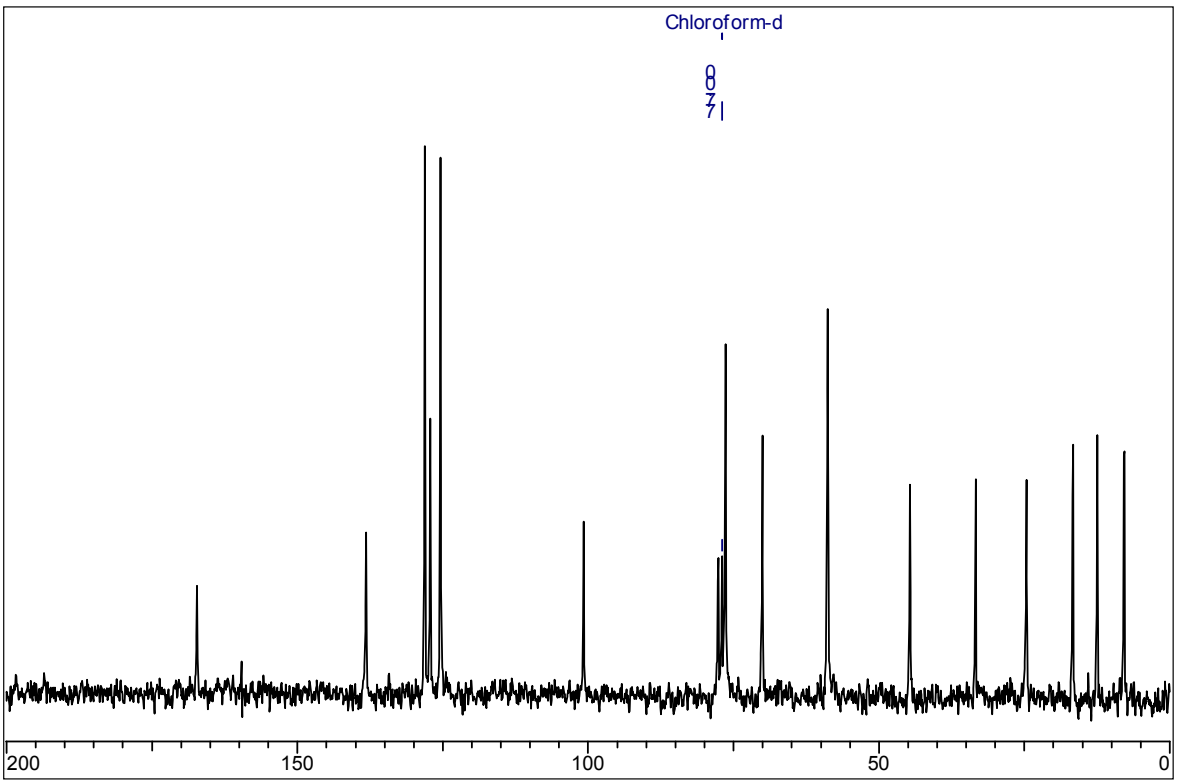
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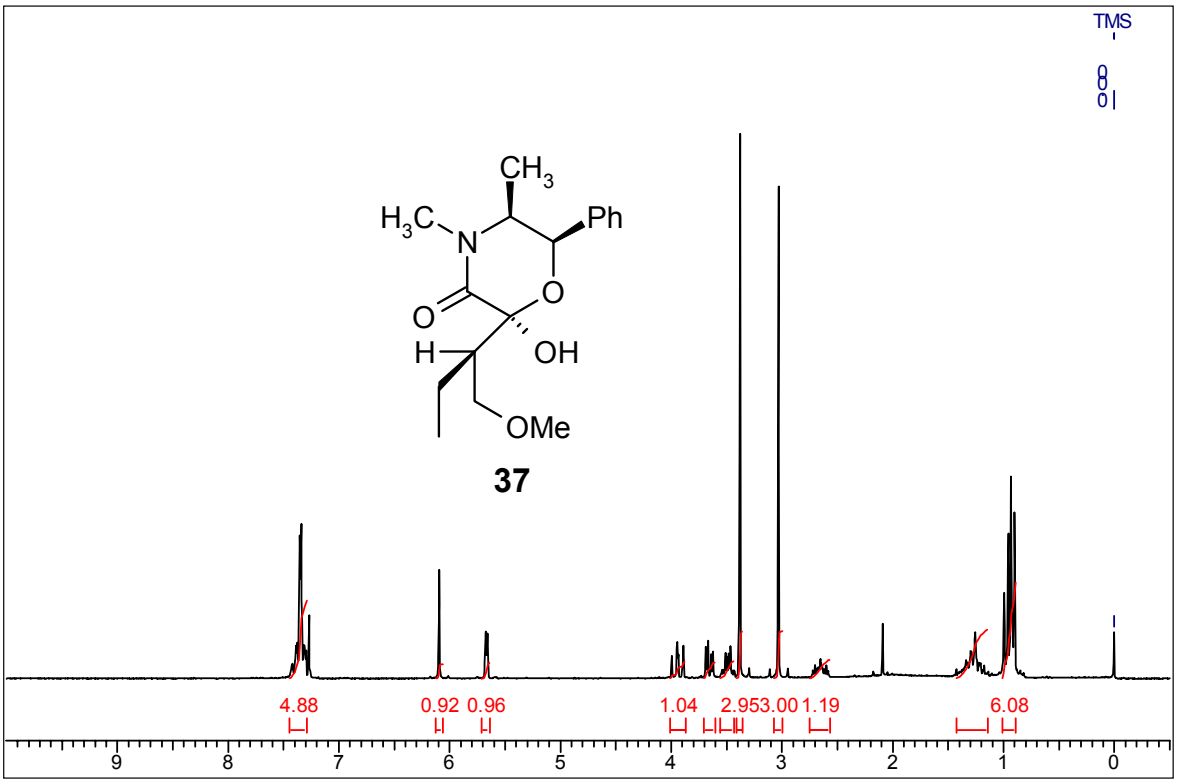
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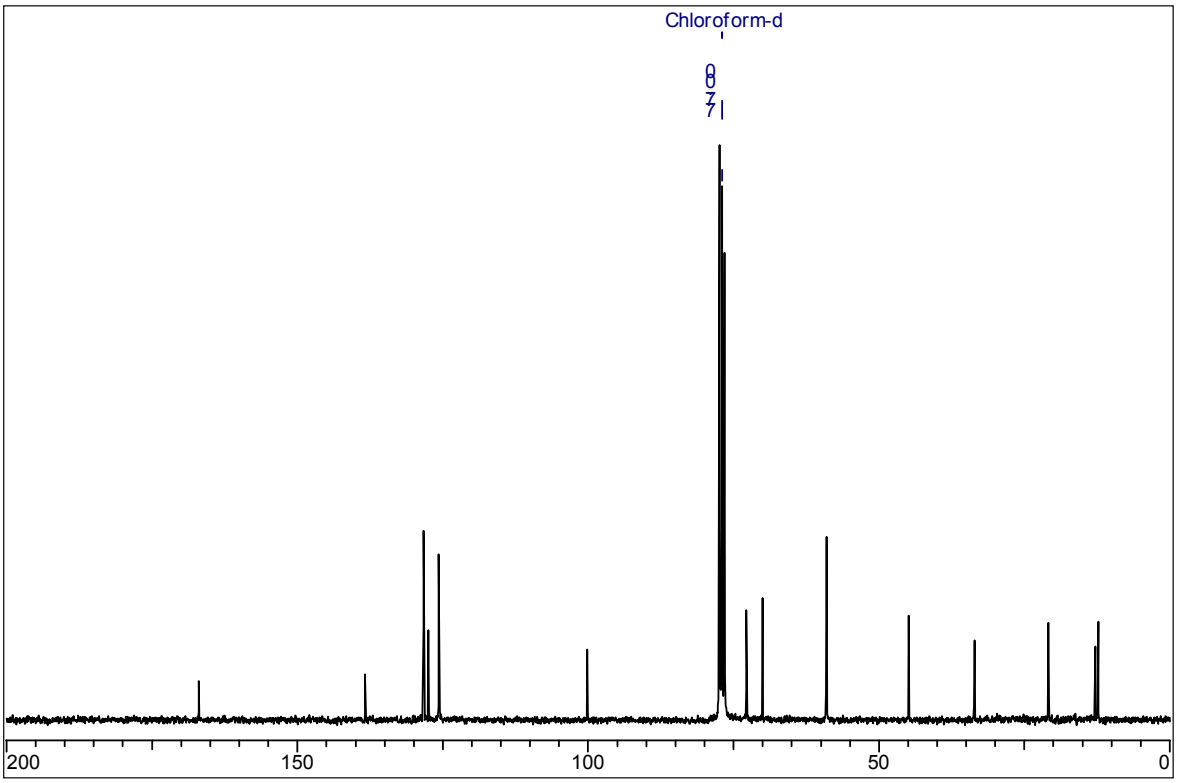
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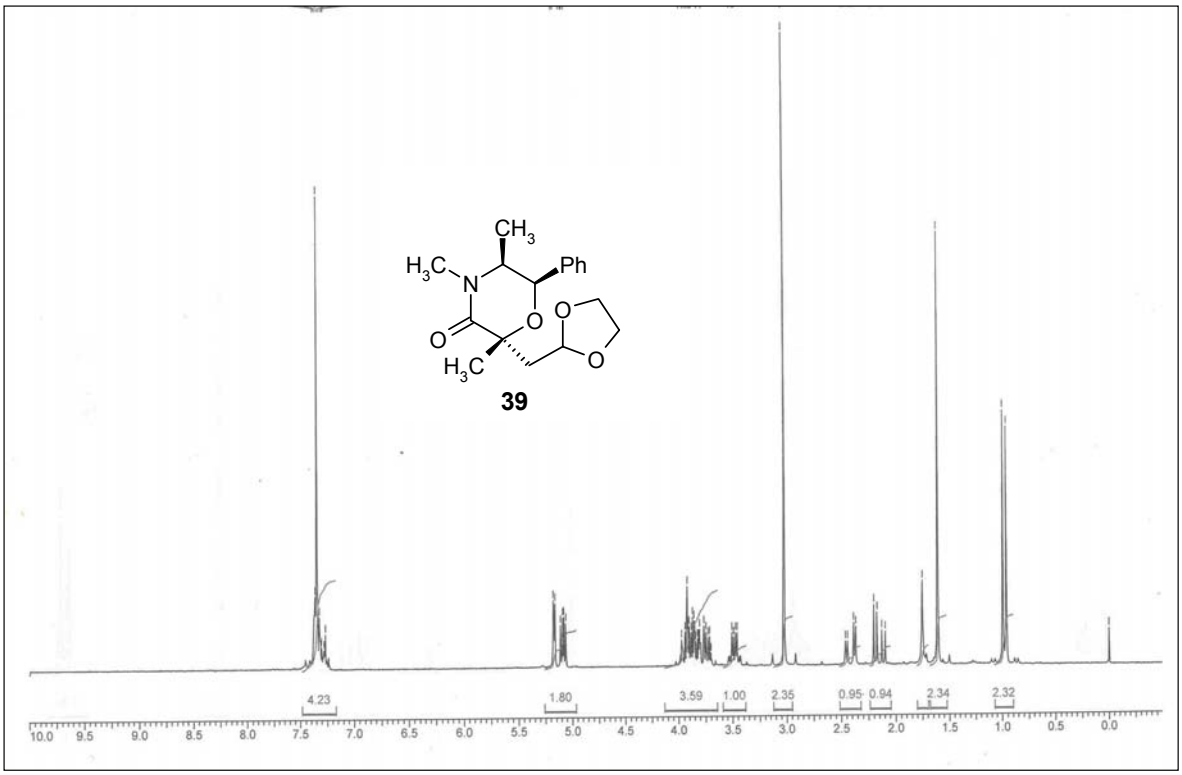
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2.34
2.32
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9.5
9.0
8.5
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7.0
6.5
6.0
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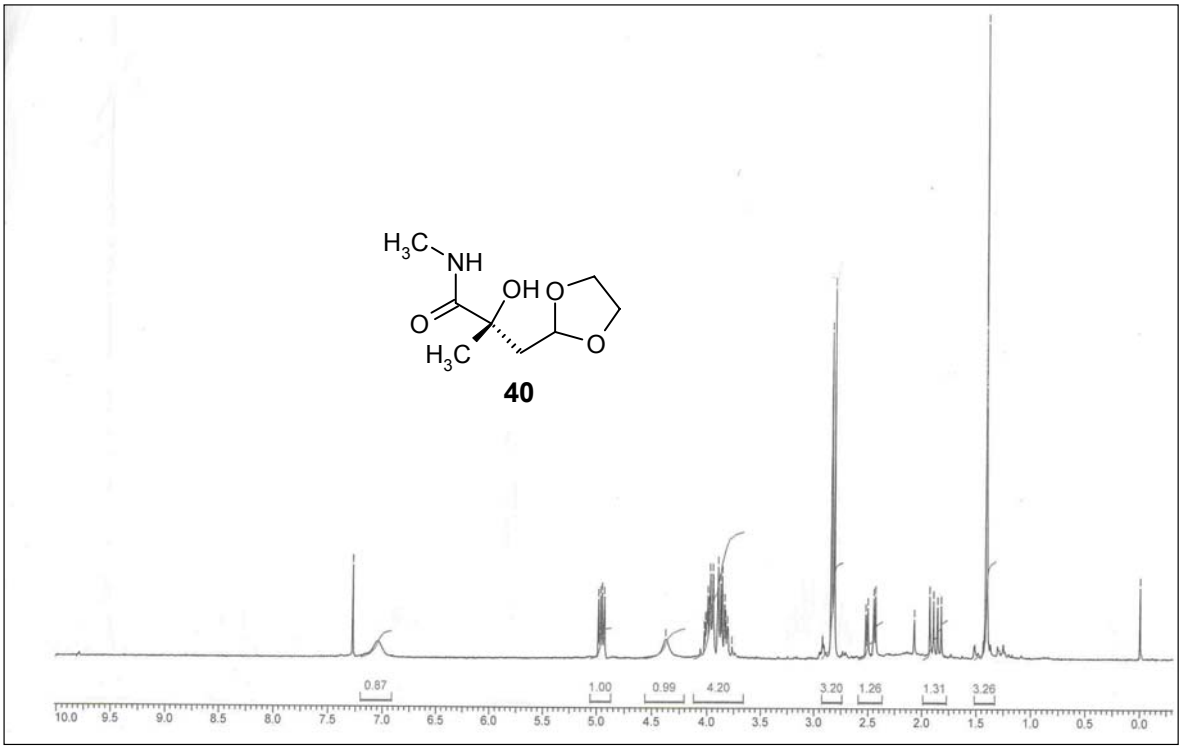
1.5
1.0
0.5
0.0

39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OH
O
O
O
H3C
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1.00
0.99
4.20
3.20
1.26
1.31
3.26
10.0
9.5
9.0
8.5
8.0
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5.5
5.0
4.5
4.0
3.5
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2.5
2.0
1.5
1.0
0.5
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40

Chapter II

Scandium triflate catalyzed diazocarbonyl insertions into hetero-atom hydrogen bonds

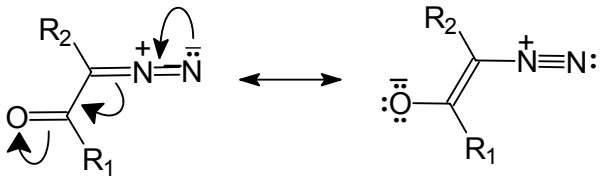
Part of the work described in this chapter has been published in

Tetrahedron Letters 1999, *40*, 5255

1. INTRODUCTION

α-Diazocarbonyl compounds constitute a class of molecules that have exceptional flexibility in organic synthesis. These molecules are exceptionally stable because of the electron withdrawing carbonyl group which stabilizes the diazo dipole (Figure 1) and are excellent sources of carbenes with an α-carbonyl substituent.

Figure 1



The most significant reactions of diazocarbonyl compounds are those that proceed with loss of nitrogen which can be brought about thermally,[1] photochemically[2] or in the presence of metal catalysts.[3] These compounds also react stoichiometrically with many Brönsted acids and electrophiles, and catalytically with numerous transition metals and their salts. Depending on the catalyst and mode of decomposition, the reactive intermediates involved are free carbenes, carbenoids (complexed carbenes) carbonyl ylids or diazonium cations.

The reactions of diazo compounds that are catalysed by transition metal complexes primarily fall into two catagories: a) cyclopropanation and b) insertion into carbon-hydrogen and heteroatom-hydrogen bonds.

The transition metal catalyzed insertions of α-diazocarbonyl compounds into hetero-atom hydrogen bonds is of cardinal importance in synthetic organic chemistry. A wide range of chemical transformations of these compounds can be affected under mild conditions. Useful applications in heterocyclic and carbocyclic ring formation are well precedented.

Curtius et al first synthesized α-diazocarbonyl by diazotization of naturally occurring amino acids[4]. Meerwein and coworkers had pioneered the work on reactions of carbene and 2-

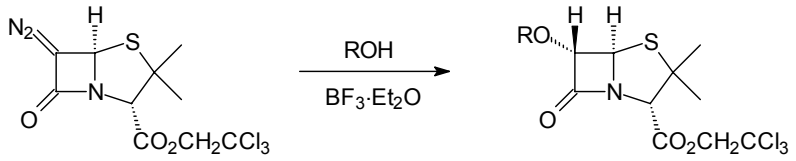
propanol.[5] Further work in this area was done by Yates who examined the copper catalyzed decomposition of diazoketones in alcohols, phenols and thiophenols[6]. The use of insoluble copper catalysts reduced significantly with the advent of homogenous catalysts. The discovery of rhodium (II) carboxylates has escalated the utility of rhodium as a superior catalyst for the generation of transient electrophilic metal-carbenoids from diazocarbonyl compounds. Among the other transition metal complexes that have also been used are Mn(II), Fe(II)[7], Ni(0)[8,9], Ni(II)[10,11], Zn(II)[12,13], Mo(II)[14,15,16], Ru(II)and Ru(III)[14,16] and Pd(II)[17,18]. A brief discussion on the diazocarbonyl/OH insertion reaction follows.

Diazocarbonyl insertion reactions into O-H bonds:

There have been several imaginative uses of diazocarbonyl/OH insertion reactions involving alcohols and water as the heteroatom donors.

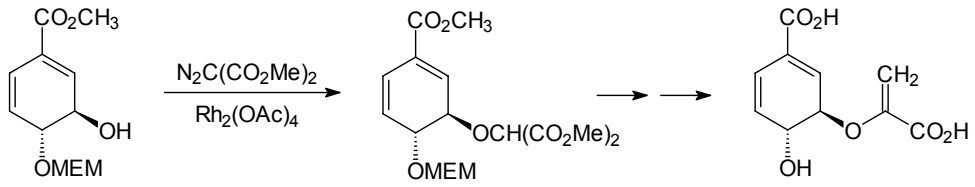
Thomas and coworkers[19] have reported the boron trifluoride catalyzed addition of alcohols to 6-diazopenicillanate as a direct route to 6-oxypenicillanate derivatives (Scheme 1).

Scheme 1.



In a synthesis of chorismic acid, Ganem and coworkers[20] have introduced the enol pyruvate side chain by employing a rhodium (II) acetate catalysed O-H insertion reaction with diazomalonate as the key step (Scheme 2).

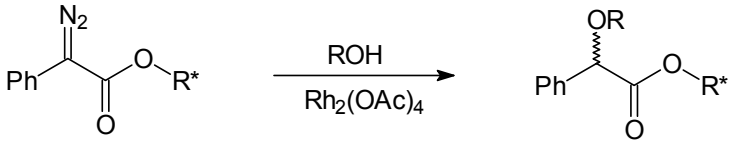
Scheme 2.



Berchtold[21] and Bartlett[22] have also used this approach for the introduction of the enol pyruvate side chain in shikimate-derived metabolites.

An asymmetric version of the intermolecular diazocarbonyl/OH insertion reaction has been studied by Moody[23] by employing phenyldiazoacetate esters of (-)-borneol, (+)-menthol, (-)-menthol, (-)-8-phenylmenthol, (-)-*trans*-2-phenylcyclohexanol, (+)-*trans*-2-phenylcyclohexanol, and (-)-10-(dicyclohexylsulfamoyl)-D-isoborneol. The diastereoselectivity of the insertion was very dependent on the size of the donor alcohol as well as the nature of the chiral auxiliary. The combination of *tert*-butyl alcohol as the donor and an 8-phenylmenthol as the auxiliary gives the highest diastereomeric excess (53%, Scheme 3).

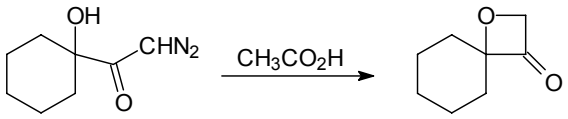
Scheme 3.



1-53% d.e.

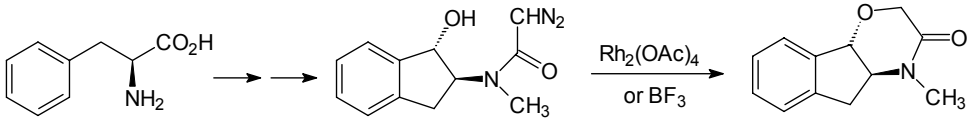
Several aspects of the intramolecular version of the O-H insertion of alcohols into diazocarbonyl substrates have been studied, the earliest example being that of Marshall who observed the cyclisation of an α-hydroxy diazoketone in glacial acetic acid to form an oxetanone derivative[24] (Scheme 4).

Scheme 4.



McClure[25] and coworkers have developed a stereoselective synthesis of a 1,4-oxazinone by employing an intramolecular O-H insertion reaction as the key step. Treatment of the phenylalanine derived β-hydroxy diazoacetamide derivative with rhodium acetate ($Rh_2(OAc)_4$) or borontrifluoride etherate furnishes the required product (Scheme 5).

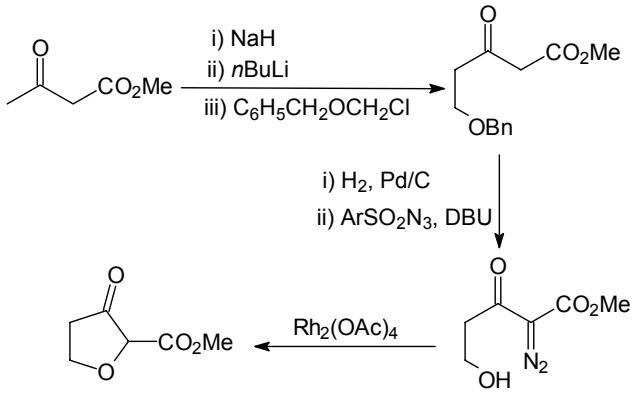
Scheme 5.



There are several reports on the use of Rh(II) catalyzed intramolecular diazocarbonyl/OH insertion reactions for the construction of five, six, seven, and eight membered cyclic ethers.

Rapoport[26] has reported the synthesis of a 3-oxo-tetrahydrofuran derivative in quantit-

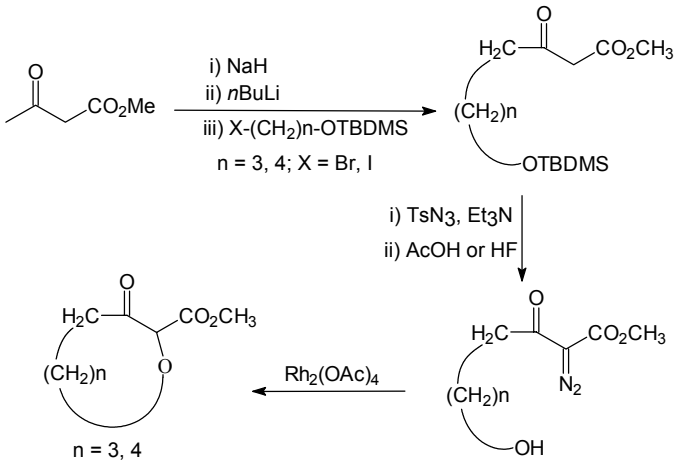
Scheme 6.



ative yield by the Rh(II) acetate catalysed intramolecular O-H insertion reaction of the corresponding α-diazoester which was prepared as shown in Scheme 6.

A similar approach has been used by Moody[27] for the preparation of seven-and eight-

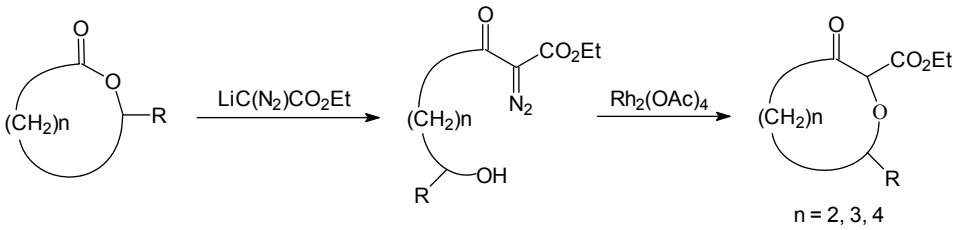
Scheme 7.



membered cyclic ethers (Scheme 7).

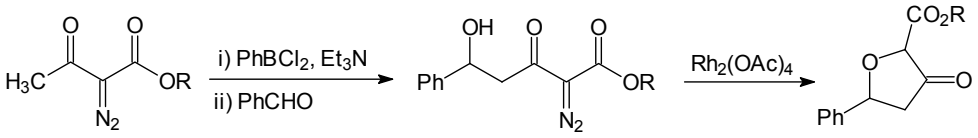
In another intramolecular O-H insertion approach to the synthesis cyclic ethers, Moody has synthesized the requisite acyclic diazocarbonyl precursors by a ring opening reaction of the appropriate lactone with lithio diazoacetate (Scheme 8).[28]

Scheme 8.



In yet another approach, Calter[29] has demonstrated a two step reaction sequence for the synthesis of substituted tetrahydrofurans. In this case, the starting material is prepared by an aldol reaction of an α-diazo-β-ketoester. Subsequent Rh(II) catalysed intramolecular O-H insertion furnishes the required product (Scheme 9).

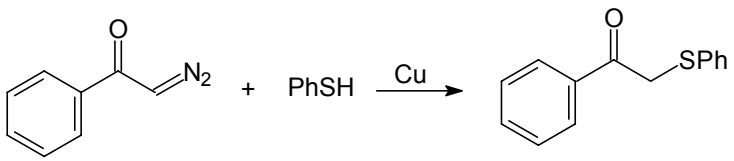
Scheme 9.



Diazocarbonyl insertion reactions into S-H bonds:

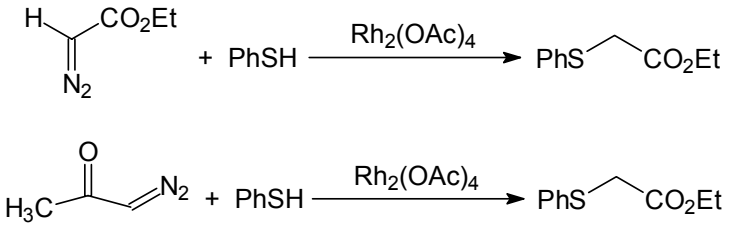
Metal-catalyzed addition of thiols to diazocarbonyl was first investigated by Yates[7] who used copper to catalyze the addition of thiophenol to diazoacetophenone (Scheme 10).

Scheme 10.



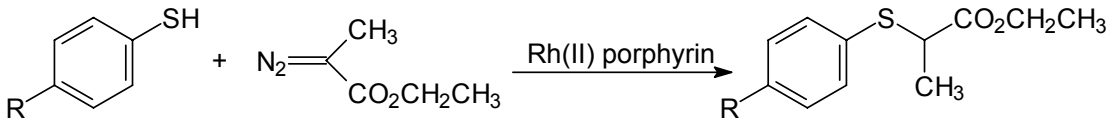
Paulissen *et al*[30] have used rhodium(II) acetate for the insertion reaction of thiophenol and ethyl diazoacetate and diazoacetone in nonpolar solvents (Scheme 11).

Scheme 11.



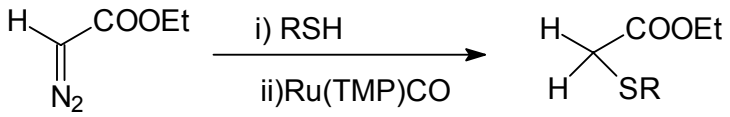
Simonneaux and coworkers[31] have used a homochiral porphyrin ruthenium complex catalyst for intermolecular S-H insertion although with low enantioselectivity (maximum of 8% e.e.) (Scheme 12)

Scheme 12.



Simonneaux and coworkers[32] have also developed a ruthenium porphyrin complex as an effective catalyst for S-H insertion. This catalyst functions under very mild conditions and reasonable to good yields of the product are obtained. The selectivity of this catalyst towards the S-H bond makes it superior over the rhodium catalyst. (Scheme 13)

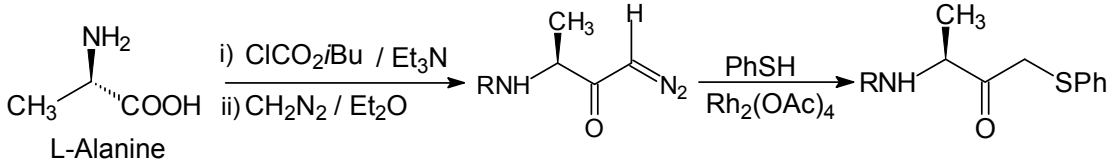
Scheme 13.



R= alkyl,aryl

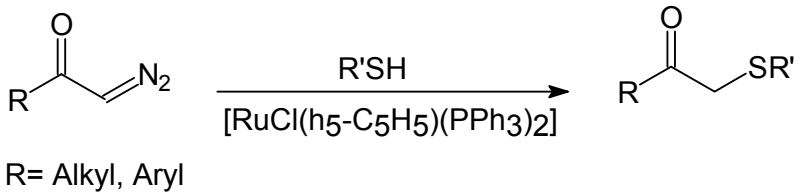
Diazocarbonyl insertion into the S-H bond under Rh(II) catalysis provides access to α-sulfenyl ketones. This has been shown by McKervey and coworkers[33] (Scheme 14).

Scheme 14.



Del Zotto et. al.[34] have used a ruthenium complex in chloroform for chemoselective diazocarbonyl insertion into S-H bonds. This catalyst is also effective for N-H insertion reactions (Scheme 15).

Scheme 15.



2. OBJECTIVES

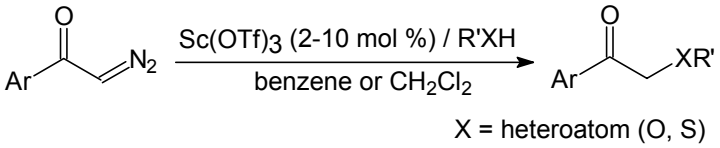
The objective of this undertaking was to examine the possibility of using scandium triflate as a catalyst for diazocarbonyl insertion reactions into hetero-atom hydrogen bonds.

3. RESULTS AND DISCUSSION

The catalytic ability of scandium triflate as a Lewis acid is well established mainly due to the seminal contributions of Kobayashi.[35] Scandium triflate is stable in aqueous solution and can be easily recovered from an organic mixture and reused if necessary. Prior to this study, there was a sole report on the use of scandium triflate for C-H insertion reactions.[36] Although several transition metal based complexes have been developed for the synthetic applications diazocarbonyl compounds, rhodium acetate has been the catalyst of choice. The use of $RuCl_2(PPh_3)_3$ as an alternative to the traditional rhodium acetate in diazoketone insertion has also been reported[37]. Practically all previous studies on Bronsted and Lewis acid mediated diazoketone insertion reactions involving hetero-atom participation are restricted to the intramolecular mode.[25,38] The present intermolecular version renders an attractive alternative to most of the methods for the synthesis of α-alkoxyarylketones. We decided to investigate the intermolecular heteroatom-H bond insertion reactions of α-diazocarbonyl

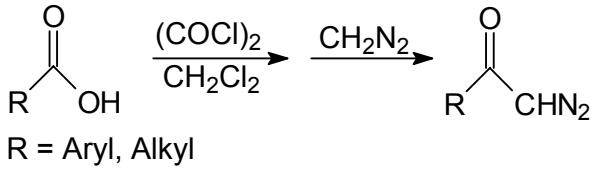
compounds in the presence of scandium triflate. A general representation of the reactions undertaken is shown in Scheme 16.

Scheme 16.



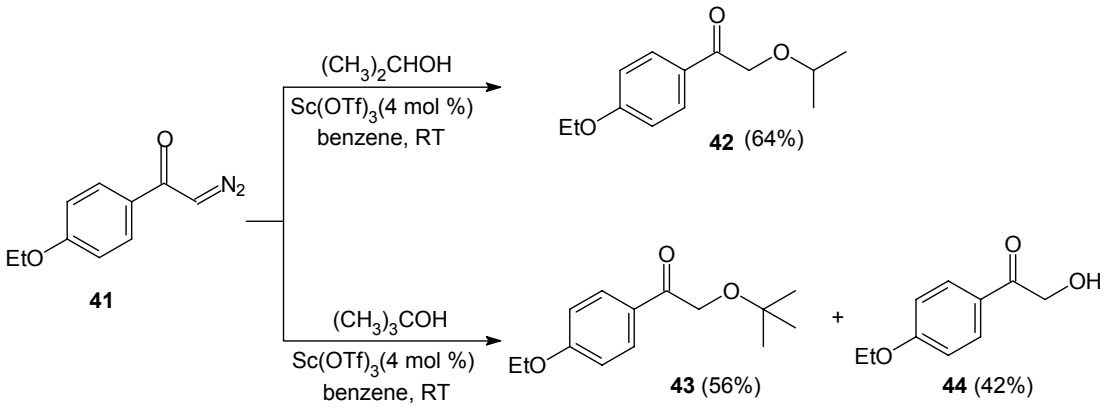
We began our study with simple aliphatic alcohols and aryldiazoketones which were prepared by adaption of the literature procedure which involves reaction of the acid chloride with diazomethane (Scheme 17).

Scheme 17



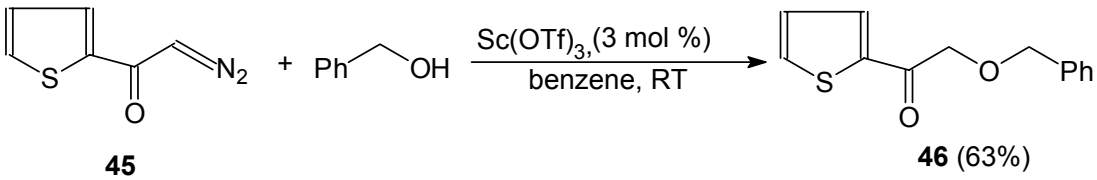
Reaction of 4-ethoxy diazoacetophenone **41** with isopropyl alcohol and tertiary butyl alcohol in the presence of a catalytic amount of scandium triflate (4 mol%) gave the insertion products **42** (64%) and **43** (56%, Scheme 18). Compound **44** (42%) could have formed by loss of the *t*-butyl group in **43** under the reaction conditions due to the high lewis acidity of scandium triflate.

Scheme 18.



The O-H insertion reactions of other diazoketones also worked effectively. Thus, the reaction of thiophene-2-carboxylic acid derived diazoketone **45** with benzyl alcohol in the presence of 3 mol% $Sc(OTf)_3$ generated **46** in (63%, Scheme 19).

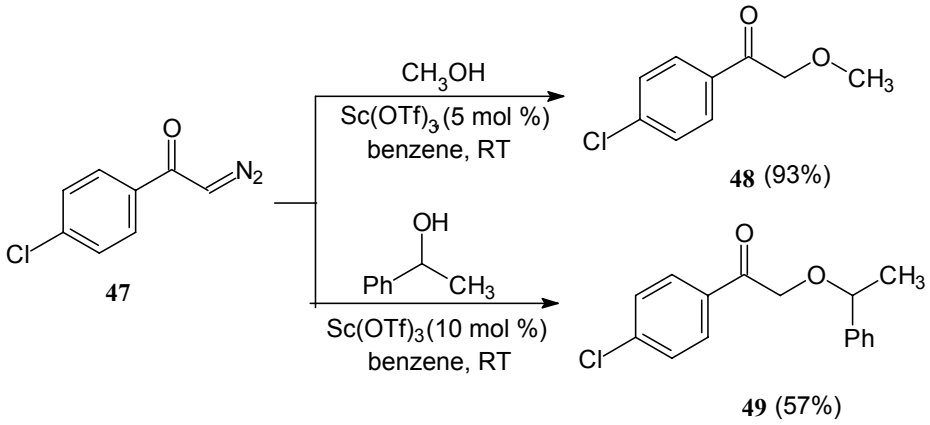
Scheme 19.



45 **46** (63%)

Similar reactions of 4-chlorodiazoacetophenone **47** with anhydrous methanol produced **48** in 93% yield and with phenethyl alcohol under similar conditions gave the O-H insertion product **49** in 57% yield (Scheme 20).

Scheme 20.



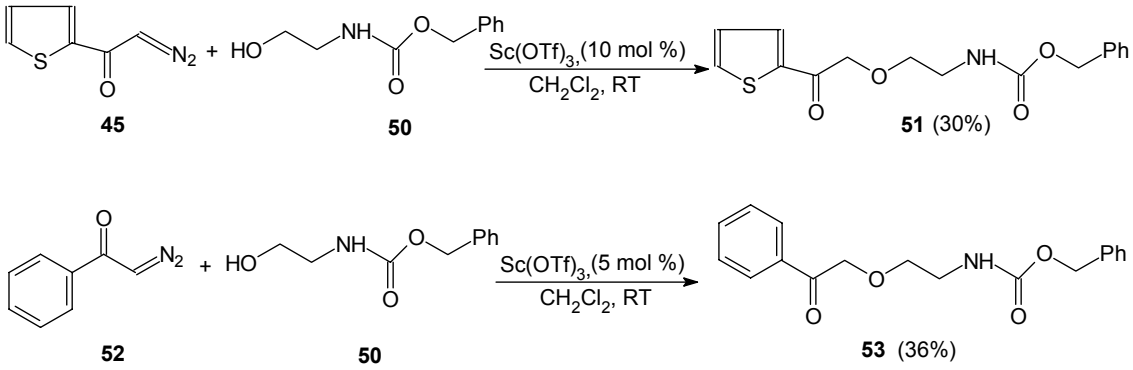
47 **48** (93%) **49** (57%)

In all the above cases the reaction proceeds at ambient temperature and a maximum of 10 mol% scandium triflate is required in some cases.

We next investigated the possibility of selective O-H insertion in the presence of a carbamate N-H bond. *N*-Benzyloxycarbonyl ethanolamine **(50)**[39] was employed as the hetero-atom component. Reactions of **45** and diazoacetophenone **52** and with *N*-Cbz-ethanolamine at ambient temperature did generate the corresponding O-H insertion products **51** and **53** respectively but in low yields. The former gave **51** in 30% yield while the later produced **53** in 36% yield. Conducting the reactions at elevated temperatures did not have a beneficial effect.

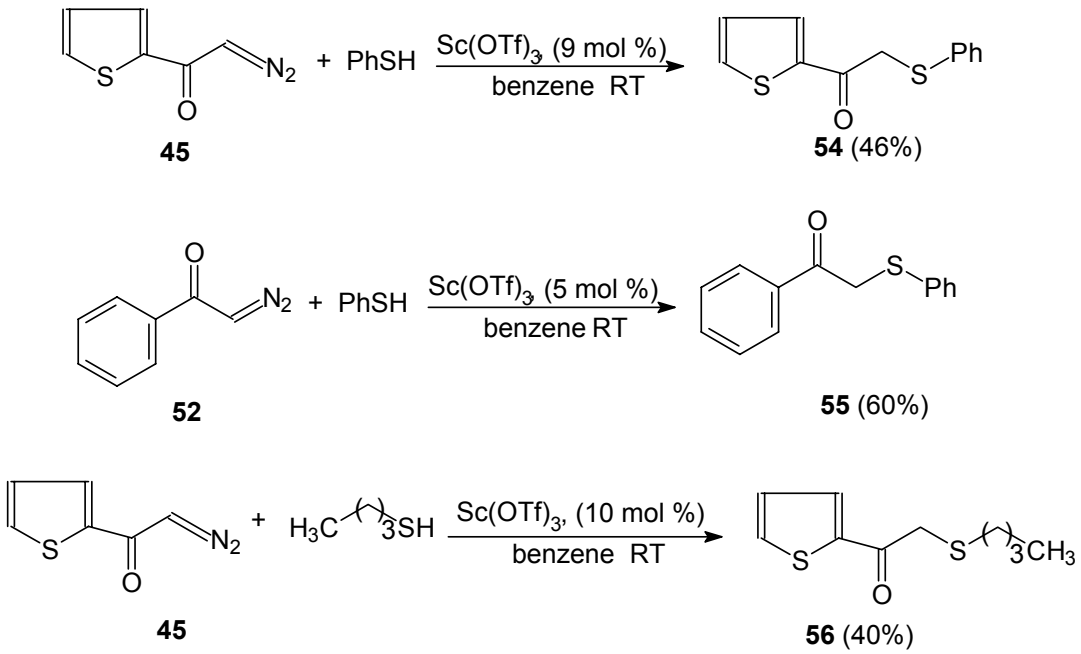
Probably, the presence of carbamate functionality could be detrimental to the intermolecular insertion process. However, the N-H insertion product was not observed in the reaction mixture (Scheme 21).

Scheme 21.



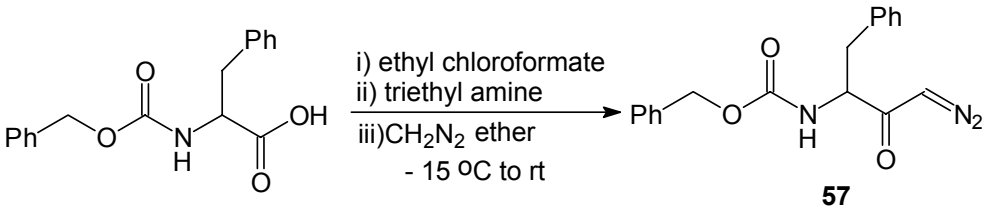
Scandium triflate also catalyzes the carbene/S-H insertion reaction to generate phenylthio ketones by the reaction of diazoketones with thiophenol. Thus **54** and **55** are obtained in 46% and 60% yield respectively. Reaction of **45** with butanethiol generates **56** in moderate yield (40%) (Scheme 22).

Scheme 22.



We next examined amino acid and hydroxy acid derived diazocarbonyl substrates in the O-H insertion reaction. To this effect, diazoketone **57** was prepared from N-Cbz-phenylalanine as described in Scheme 23.

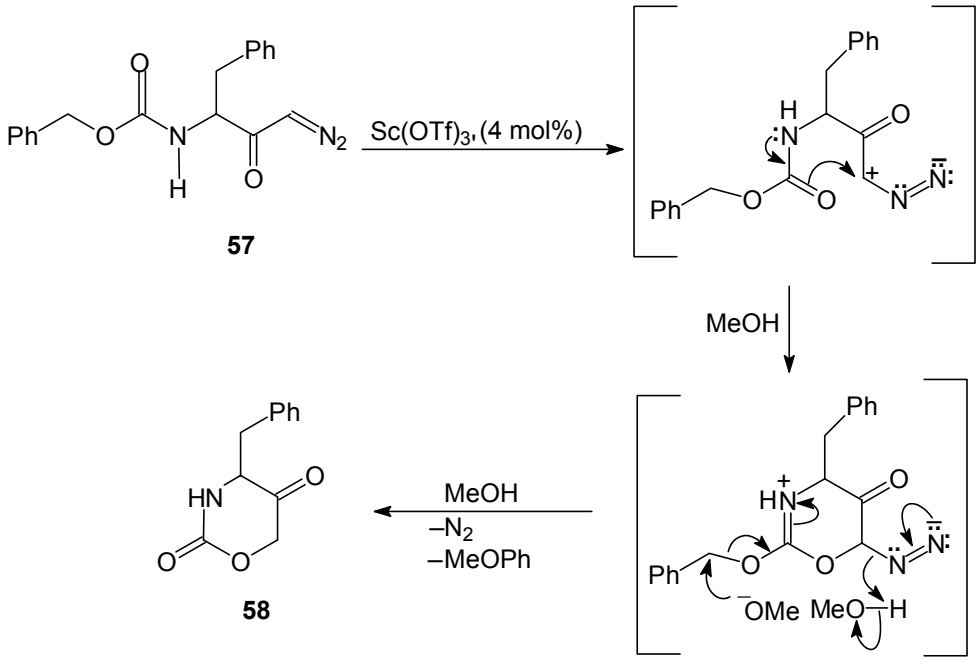
Scheme 23.



57

Treatment of the diazoketone **57** derived from *N*-Cbz-phenylalanine with scandium triflate in the presence of methanol did not generate the expected O-H insertion product. The major product isolated is **58** (61%) arising from an intramolecular reaction of the diazocarbonyl functionality with the *N*-protecting group followed by debenzylation. (Scheme 22). Similar carbonyl group participation has been observed in the rhodium acetate catalyzed decomposition of an oxazolidinone based diazoketone.[40] A possible mechanism for the formation of **58** is included in Scheme 24.

Scheme 24.

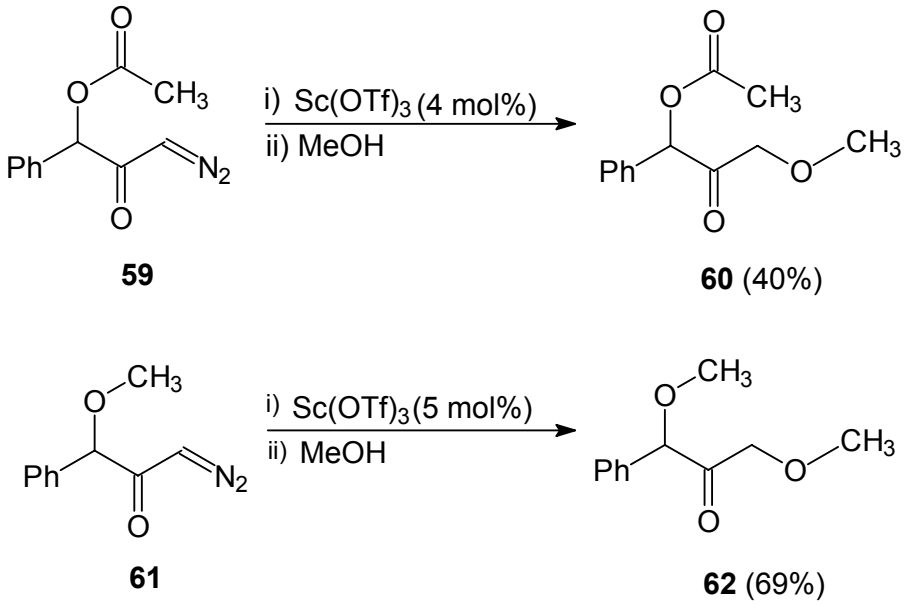


57

58

We then used diazoketones generated from racemic mandelic acid derivatives. Thus, racemic O-acetyl mandelic acid and O-methyl mandelic acid were converted to the corresponding diazoketones **59** and **61**. The insertion products **60** and **62** were obtained in 40% and 69% yields respectively when methanol was used as the donor (Scheme 25).

Scheme 25.



59 **60** (40%)

61 **62** (69%)

Further investigations of insertion reactions with other heteroatom donors for example phenol, morpholine, diethylphosphite and triethylsilane were unsuccessful. Acid or amide donors such as acetamide, pthalimide and benzoic acid did not prove to be fruitful in the insertion reactions. It is likely that in these cases, either the nucleophilicity of the heteroatom bearing functionality is not appropriate for the insertion reaction or the heteroatom binds $Sc(OTf)_3$ irreversibly, rendering it less Lewis acidic and hence unable to catalyze diazo-decomposition. Dimerization of the diazoketone to an olefin or decomposition of the diazoketone was observed in these reactions.

4. CONCLUSIONS

Scandium triflate is an efficient catalyst for diazocarbonyl insertion reactions into aliphatic O-H, S-H and carbamate N-H bonds. The O-H and S-H insertion reactions proceed efficiently at an ambient temperature. Selective O-H insertion is possible in the presence of a carbamate N-H bond and also other heteroatom-hydrogen bonds like N-H, P-H and Si-H bonds.

EXPERIMENTAL

General experimental techniques described in the experimental section of Section A in Chapter 1 have been followed.

Procedure for the preparation of diazoketones:

Preparation of aryldiazoketones

To a suspension of acid (n mmol) in anhydrous dichloromethane (2 n mL) was added oxalyl chloride (0.5 n mL) and stirred for 2 h. Excess oxalyl chloride and dichloromethane was removed under reduced pressure. The resulting acid chloride was diluted in ether (2n mL) and added dropwise to an ice-cooled solution of diazomethane in ether (10 n mmol, generated from *N*-nitroso *N*-methyl urea[41]). The mixture was stirred for 2 h at 0 ^{o}C. Ether was removed under reduced pressure and the crude product was purified by flash column chromatography to obtain the pure diazoketonea as shining, crystalline solids in 60-65% yield.

2-Diazo-1-(4-ethoxy-phenyl)-ethanone (41):

The crude diazoketone obtained from 500 mg of *p*-ethoxybenzoic acid according to the general procedure was purified by flash column chromatography (1/9 ethyl acetate/pet. ether) to give 372 mg (65%) of **41**.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.71 (d, 2H, *J* = 9.1, Ar*H*), 6.90 (d, 2H, *J* = 9.1, Ar*H*), 5.85 (s, 1H, C*H*N_2), 4.06 (q, 2H, *J* = 6.5, CH_2), 1.50 (t, 3H, *J* = 6.5, CH_3)

IR ($CHCl_3$)

2985, 2106, 1772, 1508, 1220, 921, 840 cm^{-1}

2-Diazo-1- thiophen-2-yl-ethanone (45):

The crude diazoketone obtained from 500 mg of thiophene-2-carboxylic acid according to the general procedure was purified by flash column chromatography (3/17 ethyl acetate/pet. ether) to give 362 mg (61%) of **45**.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.61-7.58 (dd, 1H, *J* = 1.0, 4.9 Ar*H*), 7.53-7.50 (dd, 1H, J = 1.0, 4.9, Ar*H*), 7.13-7.09 (dd, 1H, J = 3.9,4.9, Ar*H*), 5.83 (s, 1H, C*H*)

IR ($CHCl_3$)

3020, 2113, 1619, 1420, 1230, 835 cm^{-1}

MS (70ev)

57 (27), 70 (100), 96 (96), 111 (45), 152 (M^+, 31)

2-Diazo-1-(4-Chloro-phenyl)-ethanone (47):

The crude diazoketone obtained from 458 mg of *p*-chlorobenzoic acid according to the general procedure was purified by flash column chromatography (1/9 ethyl acetate/pet. ether) to give 314 mg (62%) of **47**.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.86 (d, 2H, *J* = 8.5, Ar*H*), 7.47 (d, 2H, *J* = 8.5, Ar*H*), 5.81 (s, 1H, C*H*)

IR ($CHCl_3$)

2991, 2110, 1768, 1497, 1231, 910 cm^{-1}

2-Diazo-1-phenyl-ethanone (52):

The crude diazoketone obtained from 400 mg benzoic acid according to the general procedure was purified by flash column chromatography (1/4 ethyl acetate/pet. ether) to give 292 mg (61%) of **52**.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.40-7.25 (m, 5H, Ar*H*), 5.83 (s, 1H, C*H*N_2)

IR ($CHCl_3$)

2998, 2105, 1619, 1392, 1230, 842 cm^{-1}

(1-Benzyl-3-diazo-2-oxo-propyl)-carbamic acid benzyl ester (57):[42]

To a solution of *N*-Cbz-phenylalanine (500 mg, 1.67 mmol) in anhydrous ether (10mL) at –15 ^oC was added ethyl chloroformate (0.2 mL, 2.05 mmol) and a solution of triethylamine (0.3 mL, 2.05 mmol) in ether (3 mL). The resulting mixture was stirred for

thirty min. and then warmed up to 0 ^{o}C. Diazomethane (generated from 16.7 mmol of NMU) was added and the mixture was stirred for 2 h. The reaction mixture was warmed up to ambient temperaure and water was added. The biphase was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with saturated sodium bicarbonate and brine, dried (Na_2SO_4) and concentrated. Purification of the residue by flash column chromatography (1/4 ethyl acetate/pet.ether) gave 296 mg (55%) of **56** as a pale yellow solid.

M.P. = 81-82.5 ^{o}C

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.48-7.10 (m, 10H, Ar*H*), 5.36 (d, 1H, *J* = 8.3, N*H*), 5.14 (s, 1H, C*H*N_2), 5.08 (s, 2H, PhCH_2), 4.50 (m, 1H, C*H*CH_2), 3.05 (d, 2H, *J* = 6.3, CHCH_2).

IR ($CHCl_3$)

3290, 2103**,** 1680, 1625, 1020, 730 cm^{-1}

MS (70ev)

65 (22), 77 (9), 91 (100), 132 (5), 210 (4), 295 (M-N_2, 3)

Analysis for $C_{18}H_{17}N_3O_3$

Calcd: C, 66.80; H, 5.30; N, 12.99.

Found: C, 67.09; H, 5.40; N. 12.50.

1-(4-Ethoxyphenyl)-2-isopropoxyethanone (42):

To a solution of **41** (100 mg, 0.53 mmol) in anhydrous benzene (2mL) was added anhydrous isopropyl alcohol (excess, 4mL) followed by scandium triflate (5mg, 2 mol%). The mixture was stirred at ambient temperature for 10 h. After evaporation of excess alcohol and solvent under reduced pressure, the residue (120 mg) was purified by flash chromatography (1/9 ethyl acetate/pet.ether) to obtain 75 mg (65%) of **42** as a colourless gum which solidified under refrigeration.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.99 (d, *J* = 9.0, 2H, Ar*H*), 6.97 (d, *J* = 9.0, 2H, Ar*H*), 4.70 (s, 2H, COCH_2), 4.14 (q, *J* = 7.0, 2H, OCH_2) 3.74 (septet, *J* = 6.5, 1H, CH(CH_3)$_2$), 1.5 (t, *J* = 7.0, 3H, CH_3), 1.28 (d, *J* = 6.5, 6H, CH(CH_3)$_2$).

IR ($CHCl_3$)

3020**,** 1705, 1620, 1230, 1190, 1130, 1050, 770, 690 cm^{-1}

MS (70ev)

m/z 65 (17), 107 (5), 121 (65), 149 (100), 223 (M^{+1}, 1)

Analysis for $C_{13}H_{18}O_3$

Calcd: C, 70.29; H, 8.16.

Found: C, 70.33; H, 8.26.

2-*tert*-Butoxy-1-(4-ethoxyphenyl)ethanone (43):

To a solution of **41** (100 mg, 0.52 mmol) in anhydrous benzene (2mL) was added anhydrous tertiary butyl alcohol (excess, 4 mL) followed by scandium triflate (8mg, 3 mol%). The mixture was stirred at ambient temperature for 6 h. After evaporation of excess alcohol and solvent under reduced pressure, the residue (130 mg) was purified by flash chromatography (1/9 ethyl acetate/pet.ether) to obtain 70 mg of **43** as colourless viscous mass (56%) which solidified under refrigeration. **44** (45 mg, 42%) was obtained as the other product

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.98 (d, 2H, *J* = 8.8, Ar*H*), 6.94 (d, 2H, *J* = 8.8, Ar*H*), 4.60 (s, 2H, COCH_2), 4.11 (q, 2H, *J* = 6.8, OC$H_2$$CH_3$), 1.44 (t, 3H, *J* = 6.8, OCH_2CH_3), 1.28 (s, 9H, C(CH_3)$_3$)

IR ($CHCl_3$)

3040, 3000, 1710, 1620, `1521, 1490, 1228, 780 cm^{-1}

MS (70ev)

m/z 57 (5), 107 (4), 121 (26), 149 (100), 236 (M^+, 1)

Analysis for $C_{14}H_{20}O_3$:

Calcd: C, 71.14; H, 8.53.

Found: C, 71.33; H, 8.17.

1-(4-Ethoxyphenyl)-2-hydroxyethanone (44):

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.92 (d, 2H, *J* = 8.8, Ar*H*), 6.98 (d, 2H, *J* = 9.3, Ar*H*), 4.84 (d, 2H, *J* = 4.9, CH_2), 4.13 (q, 2H, *J* = 6.8, CH_2CH$_3$), 3.61 (t, 1H, *J* = 4.9, O*H*), 1.49 (t, 3H, *J* = 7.0, CH$_2$CH_3)

IR ($CHCl_3$)

3020, 1690, 1620, 1230, 780 cm^{-1}

MS (70ev)

m/z 65 (69), 93 (77), 121 (51), 149 (100), 180 (M^+, 8)

2-(Benzyloxy)-1-thien-2-ylethanone (46):

To a solution of **45** (100 mg, 0.60 mmol) in anhydrous benzene (3 mL) was added freshly distilled benzyl alcohol (0.07 ml, 0.68 mmol) followed by scandium triflate (10 mg, 3 mol %). The mixture was stirred at ambient temperature for 10 h and concentrated under reduced pressure. The residue was purified by flash column chromatography (1/9 ethyl acetate/pet.ether) to furnish 96 mg (63%) of **46** as pale yellow liquid.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.86-7.10 (m, 8H, Ar*H*), 4.69 (s, 2H, CH_2), 4.62 (s, 2H, CH_2)

^{13}C NMR (50 MHz, $CDCl_3$)

δ 189.7 (*C*=O), 141.1 (Ar*C*), 137.1 (Ar*C*), 133.9 (Ar*C*), 132.6 (Ar*C*), 128.4 (Ar*C*), 73.5 (*C*H$_2$), 73.3 (*C*H$_2$)

IR ($CHCl_3$)

3078, 2864, 2358, 1677, 1413, 1238, 1128, 732 cm^{-1}

MS (70ev)

57 (41), 65 (70), 77 (34), 91 (93), 111 (100), 126 (21), 233 (M+1, <1)

1-(4-Chlorophenyl)-2-methoxyethanone (48):

To a suspension of Scandium triflate (6 mg, 5 mol %) in anhydrous benzene (1 mL), is added a solution of **47** (63 mg, 0.35 mmol) in methanol (4 mL). The mixture was stirred at ambient temperature for 8 h and the solvent was evaporated under reduced pressure to obtain 78 mg of crude product, which on purification by flash chromatography (1/9 ethylacetate/pet. ether) gave 60 mg (93 %) of **48** as a colourless solid.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.87 (d, 2H, *J* = 8.5, Ar*H*), 7.47 (d, 2H, *J* = 8.5, Ar*H*), 4.67 (s, 2H, CH_2O), 3.50 (s, 3H, OCH_3)

^{13}C NMR (50 MHz, $CDCl_3$)

δ 195.0 (*C*=O), 139.7 (Ar*C*H), 133.3 (Ar*C*H), 129.3 (Ar*C*H), 128.8 (Ar*C*H), 75.3 (*C*H_2), 59.1 (O*C*H_3)

IR ($CHCl_3$)

3380, 2931, 2823, 1703, 1402, 1091, 756 cm^{-1}

MS (70ev)

63 (14), 75 (80), 111 (64), 139 (100), 154 (22)

1-(4-Chlorophenyl)-2-(1-phenylethoxy) ethanone (49):

To a suspension of scandium triflate (12 mg, 10 mol%) in benzene (1 mL) was added a solution of **47** (63 mg, 0.35 mmol) and phenethylalcohol (0.03 ml, 0.3 mmol) in anhydrous benzene (3 mL) dropwise over a period of five minutes. The mixture was stirred at ambient temperature for 8 h and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (1/9 ethyl acetate/pet.ether) to furnish 55 mg (64%) of **49** as pale green liquid.

M.P. = 253-255 ^{o}C

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.87-7.79 (m, 2H, Ar*H*), 7.47- 7.23 (m, 7H, Ar*H*), 4.67-4.45 (m, 3H, OCH_2CO, C*H*(CH_3)), 1.58 (d, 3H, *J* = 6.3, CHCH_3).

^{13}C NMR (50 MHz, $CDCl_3$)

δ 195.4 (*C*=O), 142.4 (Ar*C*), 139.8 (Ar*C*), 129.5 (Ar*C*), 128.9 (Ar*C*), 128.6 (Ar*C*), 128.5 (Ar*C*), 127.9 (Ar*C*), 126.4 (Ar*C*), 78.9 (*C*H_2), 71.5 (Ph*C*H), 23.7 (*C*H_3)

IR ($CHCl_3$)

3030, 2927, 1590, 1490, 1401, 1225, 915 cm^{-1}

MS (70ev)

63 (9), 77 (47), 105 (93), 139 (100), 154 (32), 274 (M^+, <1)

Benzyl 2-(2-oxo-2-thien-2-ylethoxy) ethylcarbamate (51):

To a solution of **45** (76 mg, 0.5 mmole) in anhydrous CH_2Cl_2 (3 mL) was added *N*-Cbz-ethanolamine **50** (98 mg, 0.5 mmole) dissolved in anhydrous dichloromethane (1 mL) followed by scandium triflate (25 mg, 10 mole%) and the mixture was stirred for 8 h. The solvent was removed under reduced pressure and the residue (205 mg) was purified by flash chromatography (2/3 ethyl acetate/pet.ether) to obtain 57 mg of **51** (36%) as a colourless gum.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.86-7.12 (m, 8H, thiophenyl-*H*, Ar*H*), 5.52 (br s 1H, N*H*CO), 5.13 (s, 2H, PhCH_2), 4.57 (s, 2H, OCCH_2O), 3.69 (t, 2H, *J* = 5.0, OCH_2CH_2), 3.48 (dd, 2H, *J* = 5.0, 10.8, CH_2NH)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 189.5 (*C*=O), 156.0 (NH*C*O), 140.7 (Ar*C*), 136.6 (Ar*C*), 134.0 (Ar*C*), 132.3 (Ar*C*), 128.4 (Ar*C*), 128.1(Ar*C*), 128.0 (Ar*C*), 73.9 (CO*C*H_2O), 70.8 (Ar*C*H_2O), 66.6 (O*C*H_2), 41.0 (N*C*H_2)

IR ($CHCl_3$)

3350, 2941, 1720, 1517, 1413, 1147, 752 cm^{-1}

MS (70ev)

57 (36), 71 (26), 91 (100), 97 (33), 111 (74), 126 (49), 149 (6), 319 (M^+, 2)

Benzyl 2-(2-oxo-2-phenylethoxy) ethylcarbamate (53):

To a solution of **52** (73 mg, 0.5 mmol) in anhydrous dichloromethane (3 mL) was added Cbz-ethanolamine **50** (98 mg, 0.5 mmol) dissolved in anhydrous dichloromethane (1 mL) followed by scandium triflate (13 mg, 5 mol%) and the mixture was stirred for 8 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (2/3 ethyl acetate/pet.ether) to obtain 47 mg of **53** (30%) as a colourless gum.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.94-7.25 (m, 10H, Ar*H*), 5.63 (br s, 1H, N*H*CO), 5.11 (s, 2H, ArCH_2), 4.79 (s, 2H, OCCH_2O), 3.68 (m, 2H, OCH_2), 3.44 (dd, 2H, J = 5.4, 10.3, CH_2NH)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 196.2 (Ar*C*O), 156.5 (*C*O), 136.6 (Ar*C*), 134.7 (Ar*C*), 133.5 (Ar*C*), 128.7 (Ar*C*), 128.3 (Ar*C*), 127.9 (Ar*C*), 127.7 (Ar*C*), 73.4 (CO*C*H_2O), 70.5 (Ar*C*H_2O), 66.5 (O*C*H_2), 41.0 (N*C*H_2)

IR ($CHCl_3$)

3430, 2982, 1711, 1532, 1242, 1142, 1149, 709 cm^{-1}

MS (70ev)

65 (15), 77 (52), 91 (100), 105 (92), 120 (48), 178 (6), 206 (4), 313 (M^+, 1)

Analysis for $C_{18}H_{19}NO_4$:

Calcd: C, 68.98; H, 6.07; N, 4.47.

Found: C, 69.02; H, 5.83; N, 4.81.

2-(Phenylthio)-1-thien-2-ylethanone (54):[43]

To a suspension of scandium triflate (19 mg, 9 mol %) in anhydrous benzene (2 mL) was added a solution of **45** (76 mg, 0.5 mmol) and thiophenol (0.05 mL, 0.5 mol) in anhydrous benzene (3 ml). The mixture was stirred for 8 h. at ambient temperature and then

diluted with benzene (10 mL). The solution was washed with water (5 mL) and 1N NaOH (5 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure to 103 mg of crude compound which on purification by flash chromatography (1/9 ethyl acetate/pet.ether) furnished 47 mg (46%) of **54** as a pale yellow liquid.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.74-7.12 (m, 8H, ArH), 4.32 (s, 2H, C*H*$_2$SPh)

IR ($CHCl_3$)

3018, 1658, 1579, 1477, 1215, 1021, 759, 853 cm^{-1}

Analysis for $C_{12}H_{10}OS_2$:

Calcd: C, 61.53; H, 4.31; S, 27.32.

Found: C, 61.64; H, 4.08, S, 27.71.

1-Phenyl-2-(phenylthio)ethanone (55):[44]

To a solution of **52** (73 mg, 0.5 mmol) in anhydrous benzene (3 mL) was added thiophenol (0.05 mL, 0.5 mmol) followed by Scandium triflate (13 mg, 5 mol %). The reaction mixture was stirred at ambient temperature for 8 h. Ethyl acetate (15 ml) and water (5 mL) were added and the biphase was separated. The organic layer was washed with 2N KOH (2 x 5 mL), brine, dried over Na_2SO_4 and concentrated to give the crude product. Purification by flash chromatography (1/9 ethyl acetate/pet.ether) furnished 68 mg (62 %) of **55** as a pale yellow gum, which solidified upon refrigeration.

M.P. = 48-49 ^{o}C

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.99-7.89 (m, 2H, *ortho*H ArCO), 7.64-7.14 (m, 8H, Ar*H*), 4.27 (s, 2H, C*H*$_2$)

^{13}C NMR (50 MHz, $CDCl_3$)

δ 194.1 (*C*=O), 133.4 (Ar*C*), 132.8 (Ar*C*), 130.4 (Ar*C*), 129.2 (Ar*C*), 129.1 (Ar*C*), 129.0 (Ar*C*), 128.6 (Ar*C*), 127.0 (Ar*C*), 41.1 (*C*H$_2$)

IR ($CHCl_3$)

3023, 1671, 1571, 1483, 1225, 1021, 761, 864 cm^{-1}

MS (70ev)

57 (8), 65 (69), 77 (21), 109 (100), 154 (17), 185 (11), 228 (M^+, 52)

2-(Butylthio)-1-thien-2-ylethanone (56):

To a solution of **45** (76 mg, 0.5 mmole) in anhydrous benzene (3mL) was added butanethiol (0.05 mL, 0.5 mmol) followed by Scandium triflate (25 mg, 10 mol%) and the mixture was stirred overnight at ambient temperature. It was then concentrated under reduced pressure and the residue (100 mg) was purified by column chromatography (1/19 ethyl acetate/pet.ether) to obtain 43 mg (40%) of **56** as pale yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.78-7.64 (m, 2H, thiophenyl), 7.16-7.12 (m, 1H, thiophenyl), 3.70 (s, 2H, $COCH_2S$), 2.65 (t, 2H, J = 6.8, SCH_2), 1.66-1.25 (m, 4H, $(CH_2)_2CH_3$) 0.93 (t, 3H, J = 6.8, CH_3)

IR ($CHCl_3$)

3365, 2958, 2871, 2362, 1731, 1417, 1232, 1029 cm^{-1}

MS (70ev)

61 (19), 83 (13), 97 (12), 111 (100), 126 (42), 214 (M^+, 3)

4-Benzyl-1,3-oxazinane-2,5-dione (58):

To a solution of **57** (118 mg, 0.37 mmol) in anhydrous benzene (1 mL) was added anhydrous methanol (5 mL, excess) followed by scandium triflate (7 mg, 4 mol%) and the mixture was heated to reflux for 6 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (2/3 ethyl acetate/pet.ether) to obtain 46 mg (61%) of **58** as a white solid.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.66-7.12 (m, 5H, Ar*H*), 6.10 (s, 1H, N*H*), 4.50 (AB system, 2H, *J* = 17.1, OCH_2), 4.10 (dd, 1H, *J* = 4.2, 7.1, PhCH_2C*H*), 3.21 (dd, 1H, *J* = 4.4, 14.0, PhCH_2CH), 2.94 (dd, 1H, *J* = 8.3, 14.0, PhCH_2CH)

^{13}C NMR (50 MHz, $CDCl_3$)

δ 201.7 (*C*O), 154.4 (NH*C*O), 134.5 (Ar*C*), 129.3 (Ar*C*), 129.1 (Ar*C*), 127.7 (Ar*C*), 71.6 (Ar*C*H_2), 60.4 (ArCH_2*C*), 38.2 (CO*C*H_2O)

IR ($CHCl_3$)

3018, 1215, 757, 669 cm^{-1}

MS (70ev)

57 (4), 65 (10), 77 (11), 91 (100), 105 (4), 118 (4), 205 (M^+, 3)

Analysis for $C_{11}H_{11}NO_3$

Calcd: C, 64.36; H, 5.40; N, 6.82.

Found: C, 64.45; H, 5.18; N, 7.19.

3-Methoxy-2-oxo-1-phenylpropyl ethanoate (60): [45]

To a solution of **59** (95 mg, 0.44 mmol) in benzene (1 mL) was added anhydrous methanol (5 mL) followed by Scandium triflate (9 mg, 4 mol%) and the mixture was warmed at 55 ^{0}C for 2 h. The solvent was removed under reduced pressure and the residue (102 mg) was purified by flash chromatography (3/17 ethyl acetate/pet.ether) to obtain 40 mg (41%) of **60** as a colourless liquid.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.55-7.40 (m, 5H, Ar*H*), 6.21 (s, 1H, PhC*H*), 4.08 (s, 2H, CH_2OCH_3), 3.35 (s, 3H, COCH_3), 2.19 (s, 3H, CH_2OCH_3)

IR ($CHCl_3$)

3018, 1718, 1215, 1080, 1027, 756, 700 cm^{-1}

MS (70ev)

m/z 79 (42), 91 (49), 107 (100), 122 (6), 134 (6), 162 (9), 222 (M^+, 4).

1,3-Dimethoxy-1-phenylpropan-2-one (62):

To a solution of **61** (78 mg, 0.36 mmol) in benzene (2 mL) was added anhydrous methanol (3 mL) followed by scandium triflate (5 mol%). The mixture was stirred at ambient temperature for 3 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (3/17 ethyl acetate / pet.ether) to furnish 55 mg of **62** (69 %) as colourless liquid.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.40-7.25 (m, 5H, Ar*H*), 4.84 (s, 1H, PhC*H*), 4.25 (AB system, 2H, *J* = 18.0 CH_2), 3.35 (s, 3H, OCH_3), 3.30 (s, 3H, OCH_3)

IR ($CHCl_3$)

2950, 1743, 1448, 1250, 725 cm^{-1}

MS (70ev):

m/z 60 (6), 77 (65), 91 (23), 105 (43), 121 (100), 194 (M^+,1).

Analysis for $C_{11}H_{14}O_3$:

Calcd: C, 68.00; H, 7.26.

Found: C, 68.02; H, 7.23.

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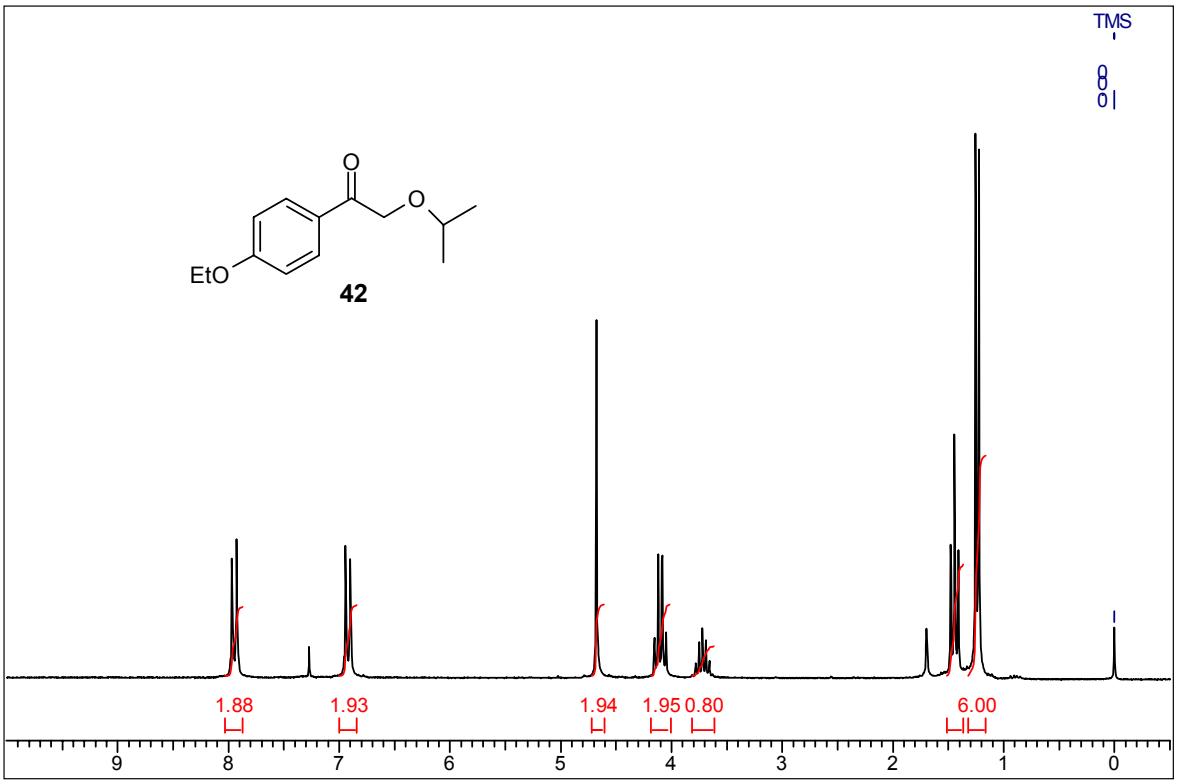
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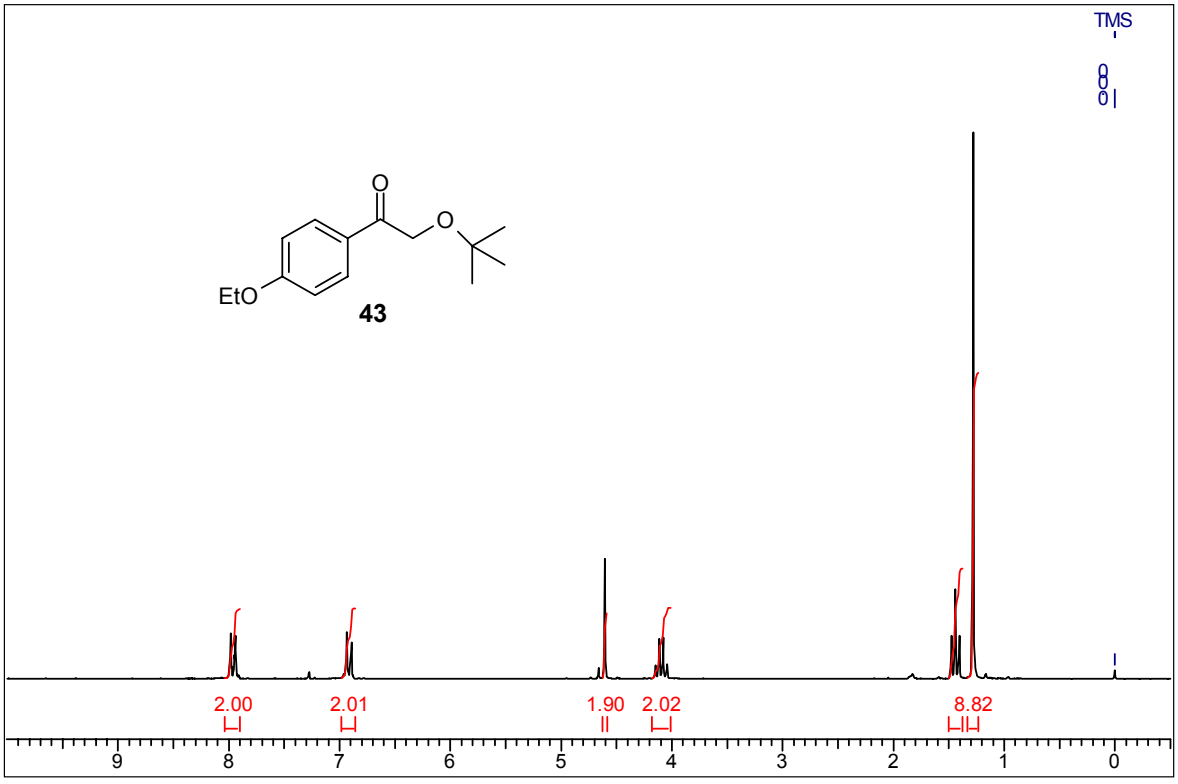
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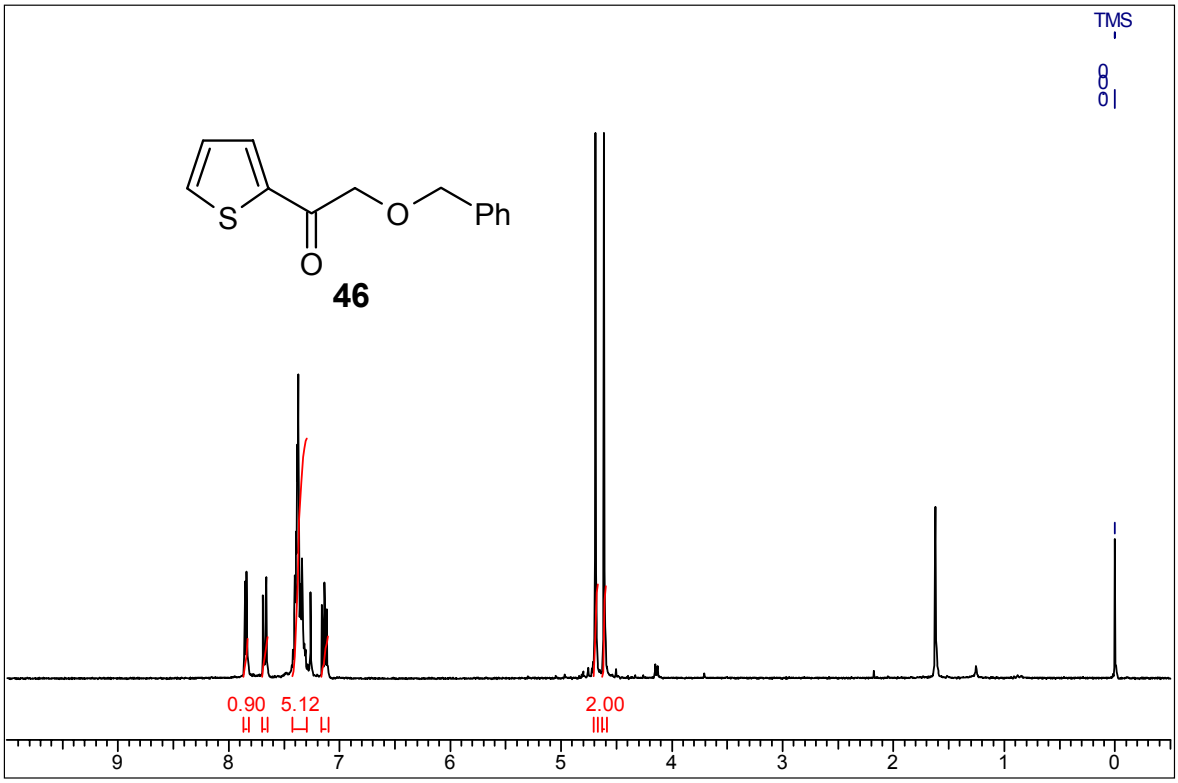
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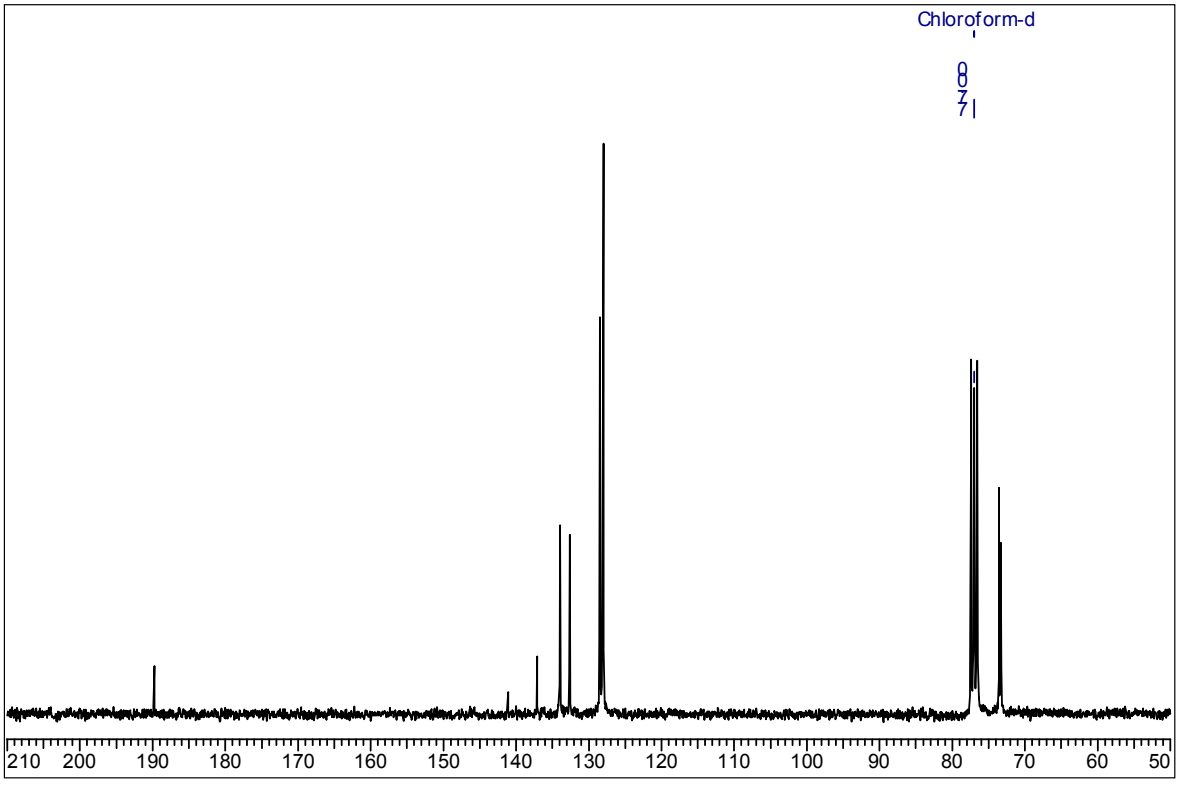
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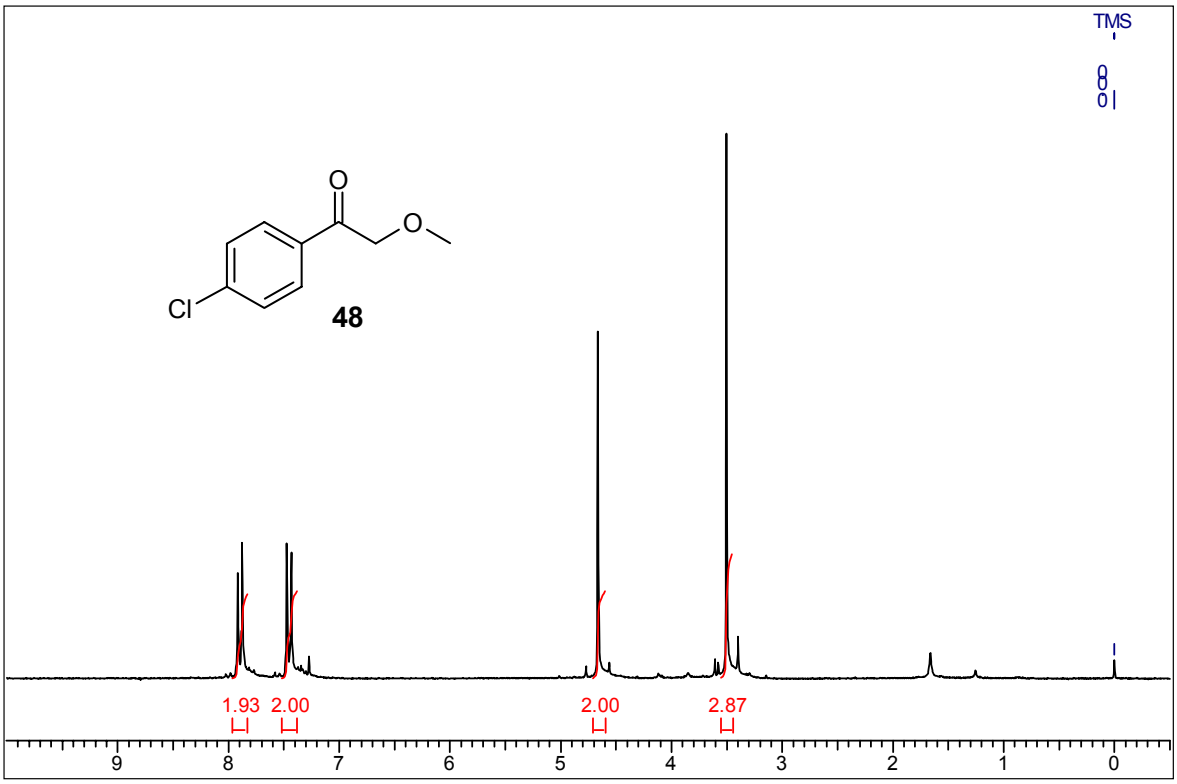
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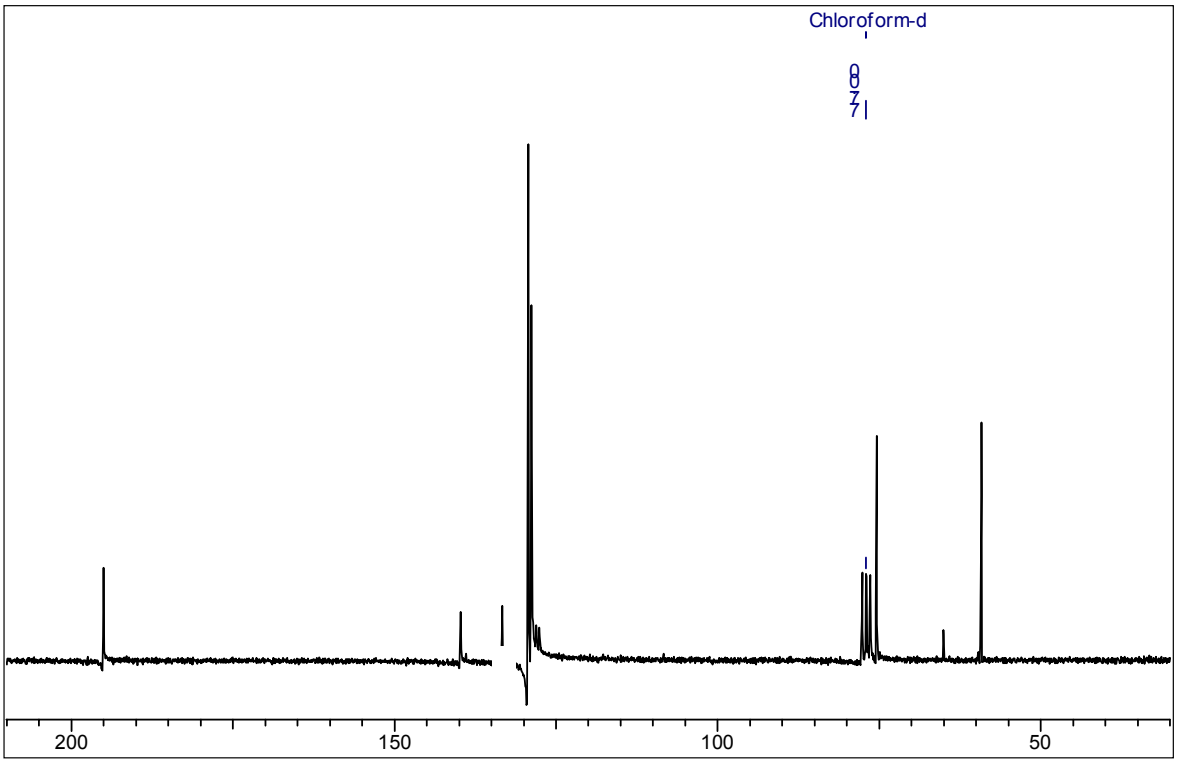
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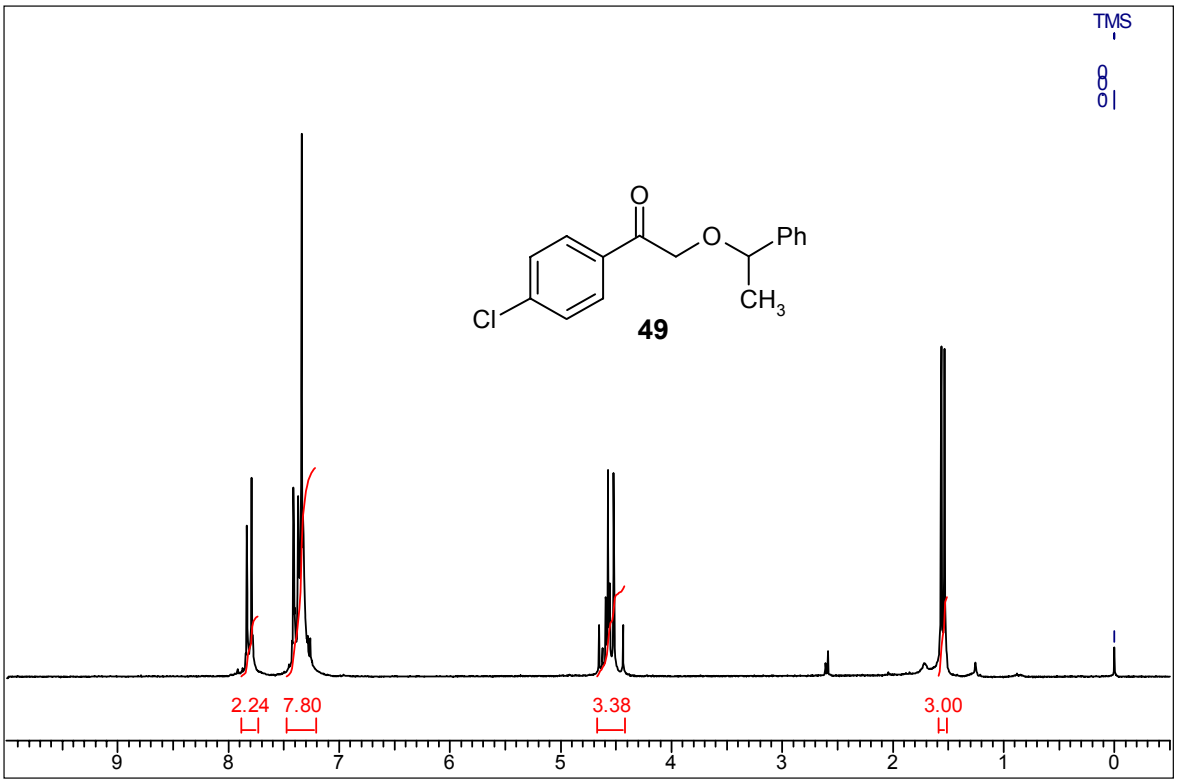
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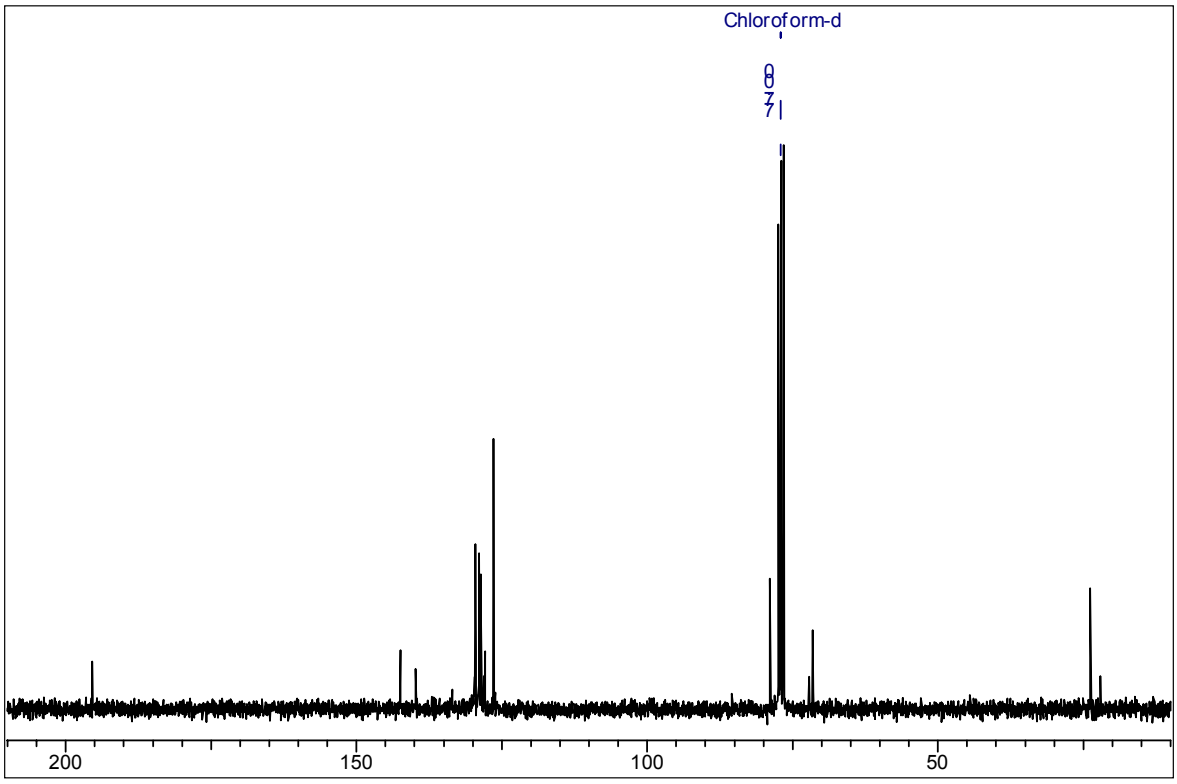
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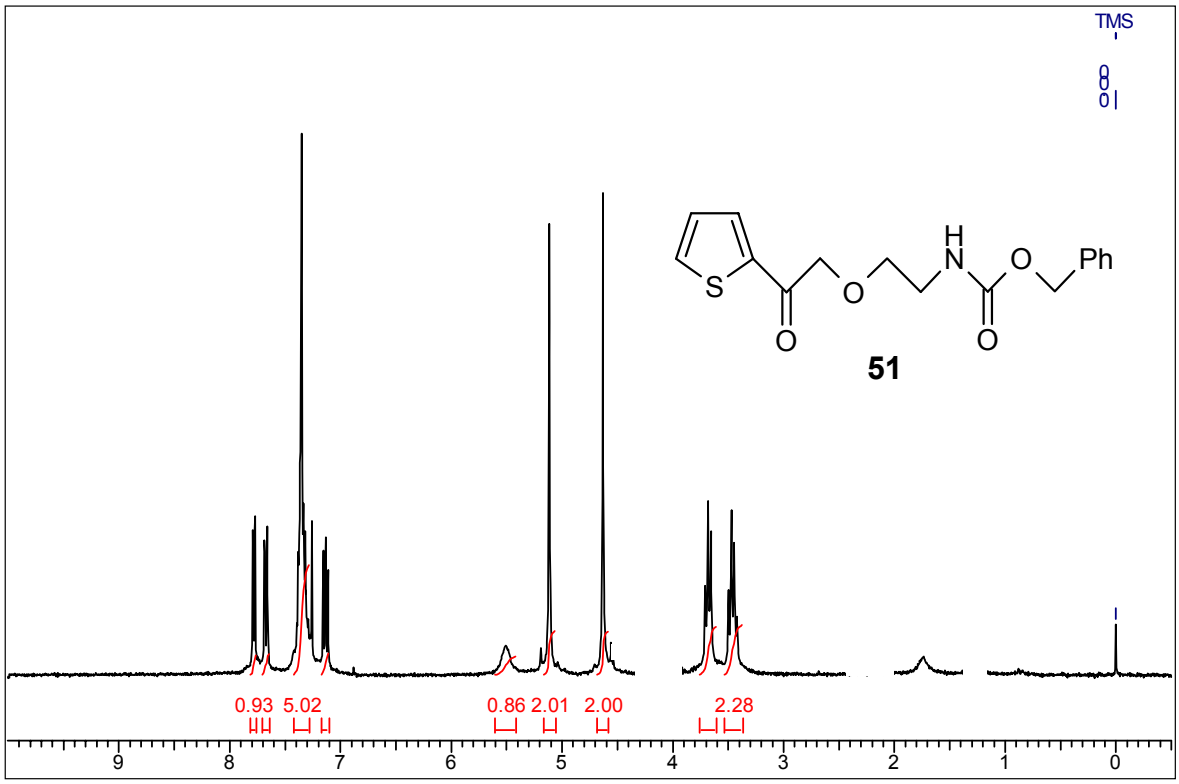
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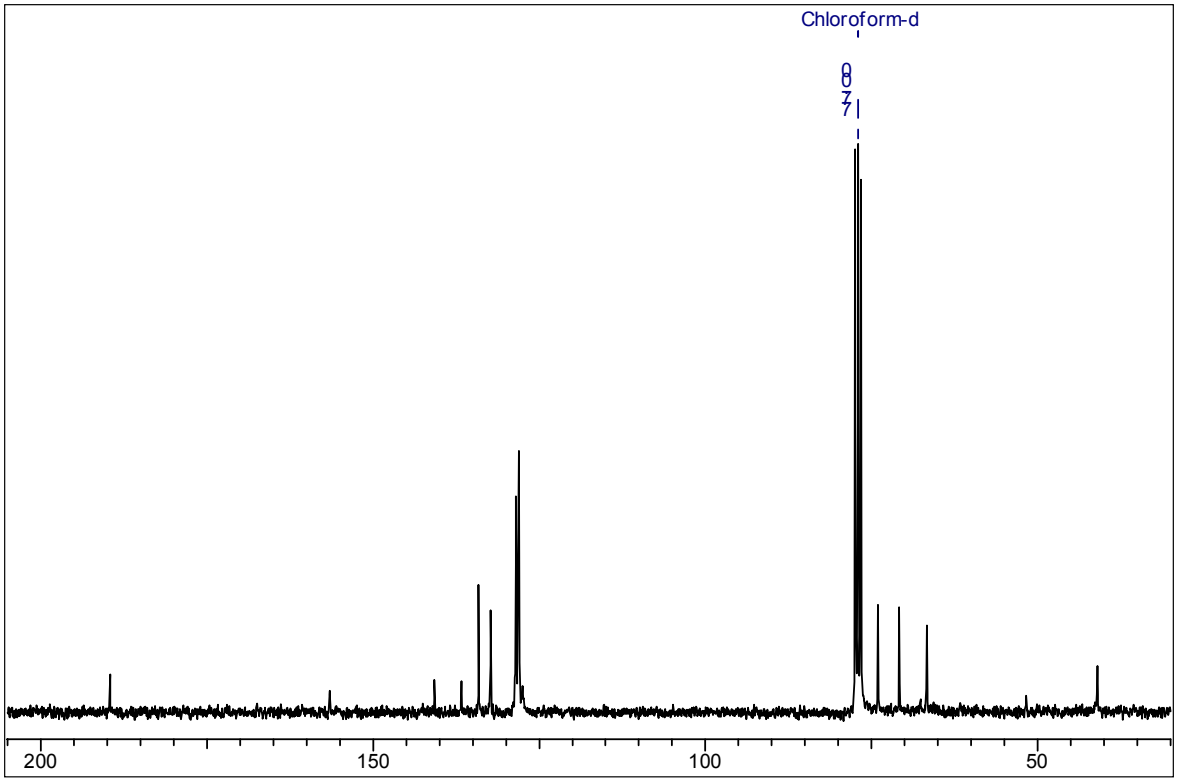
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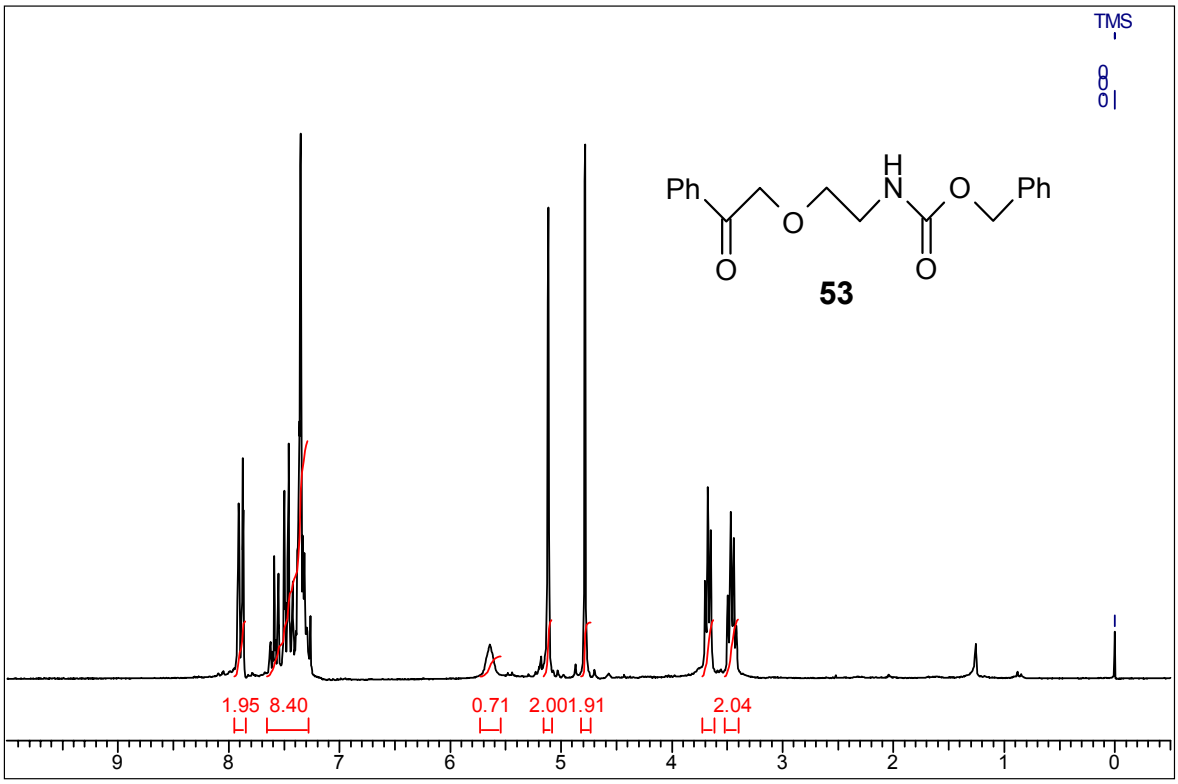
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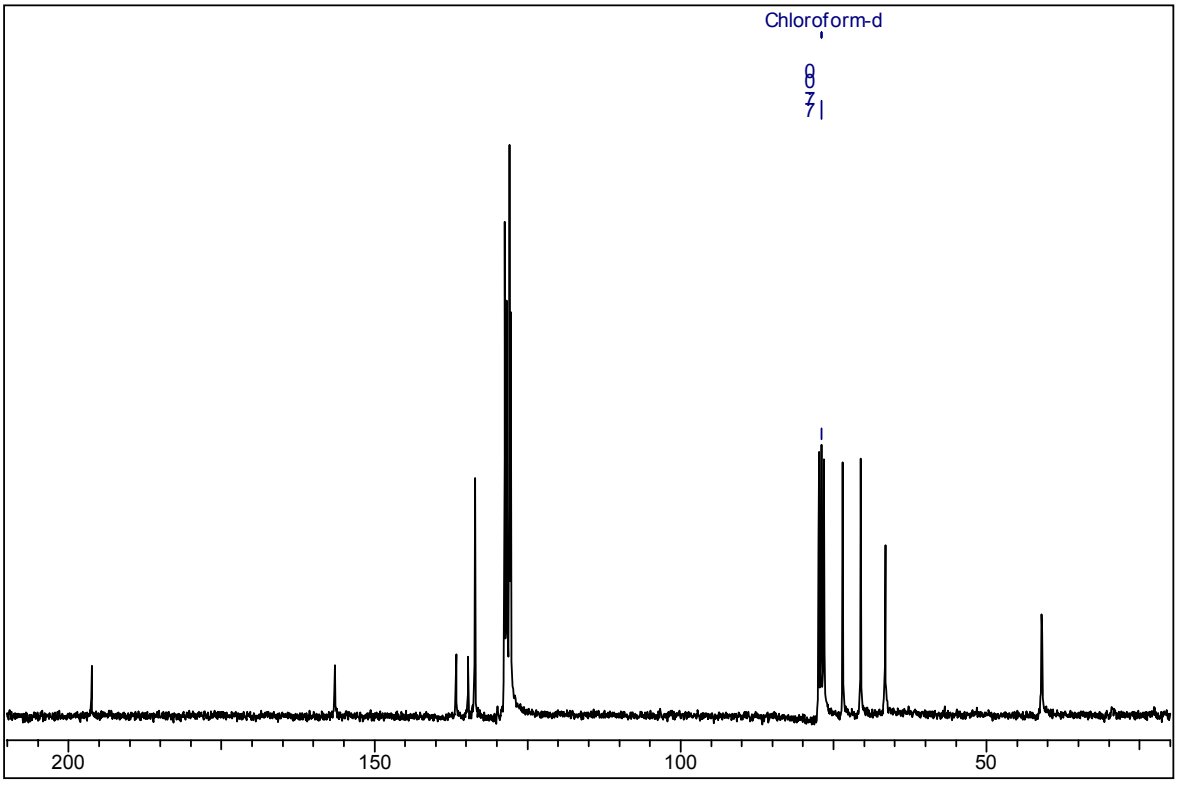
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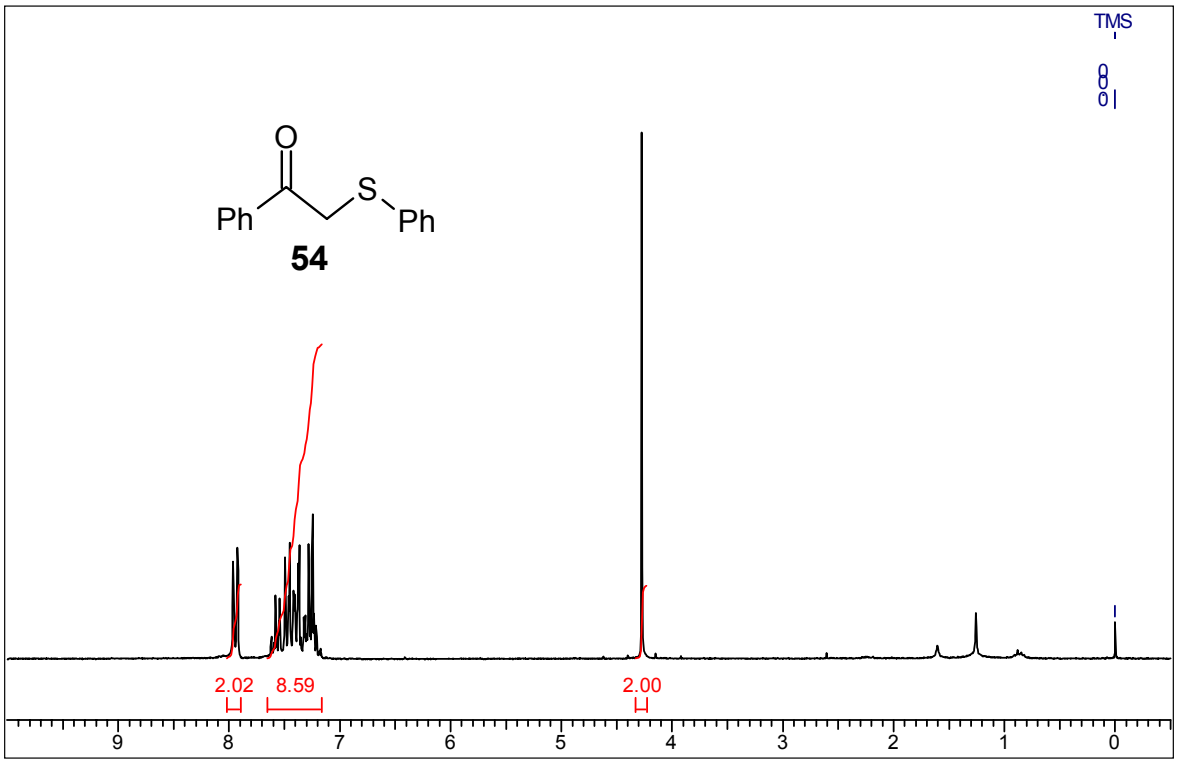
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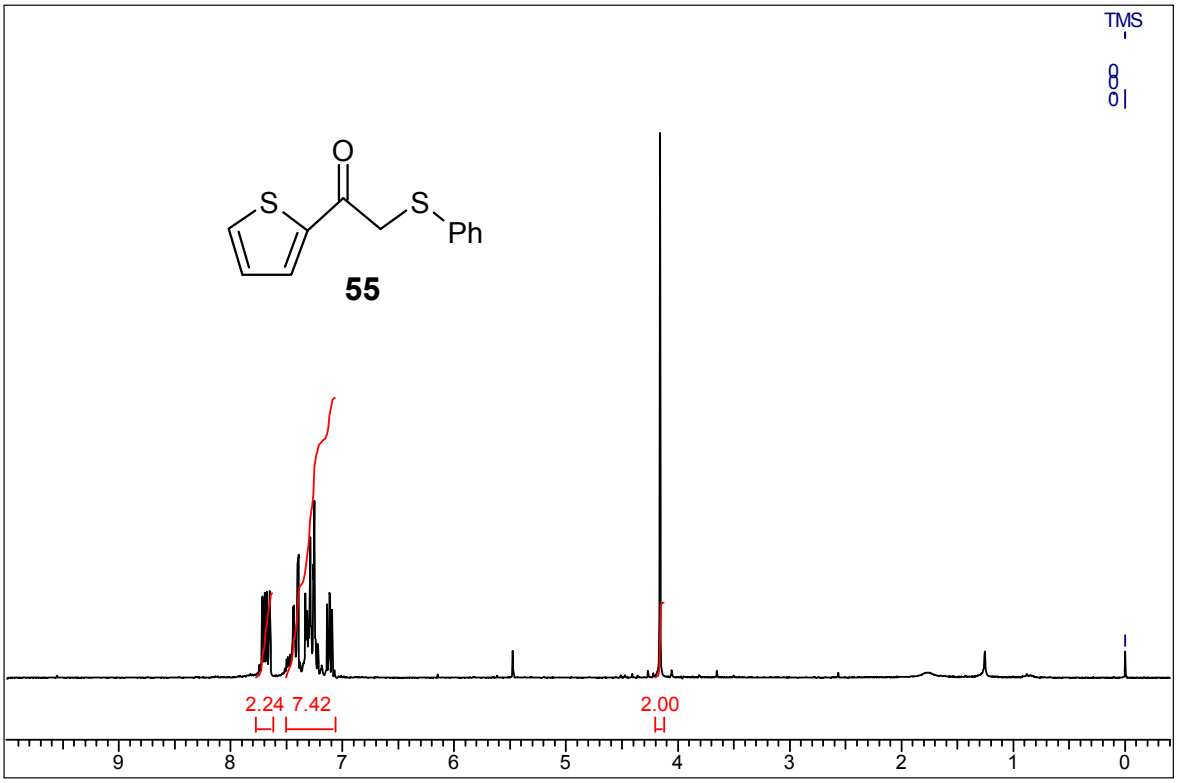
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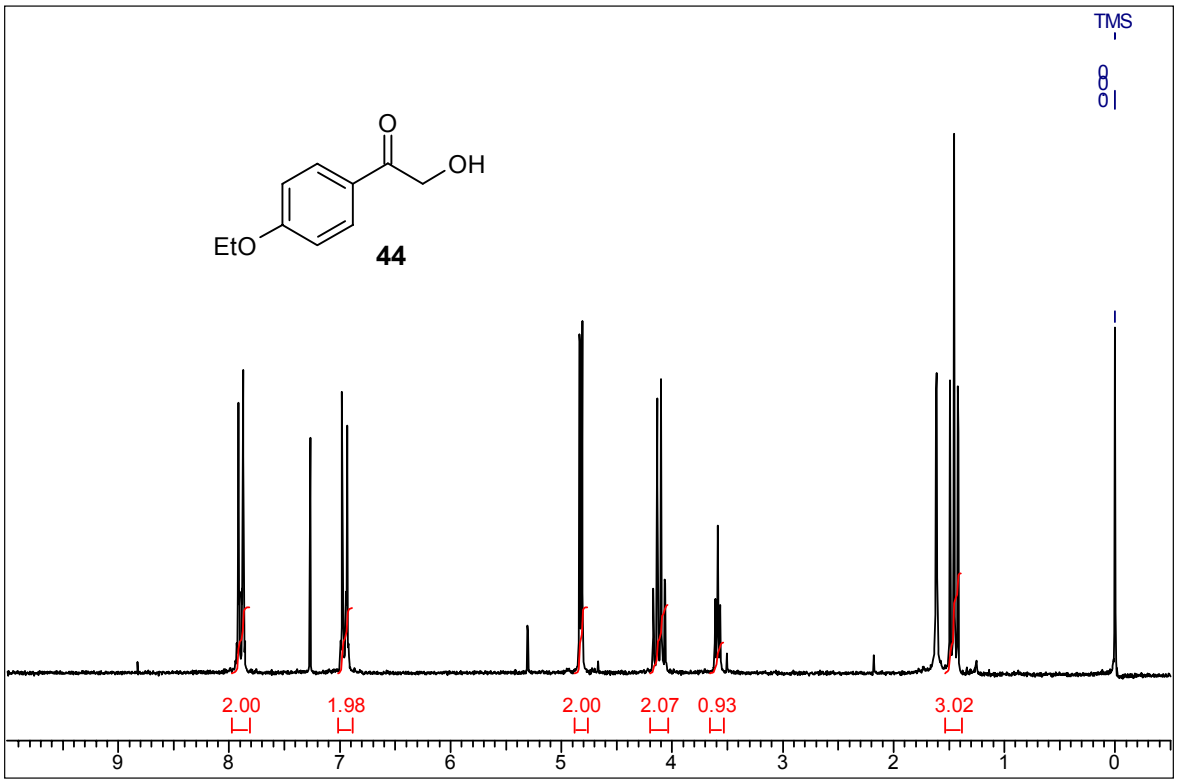
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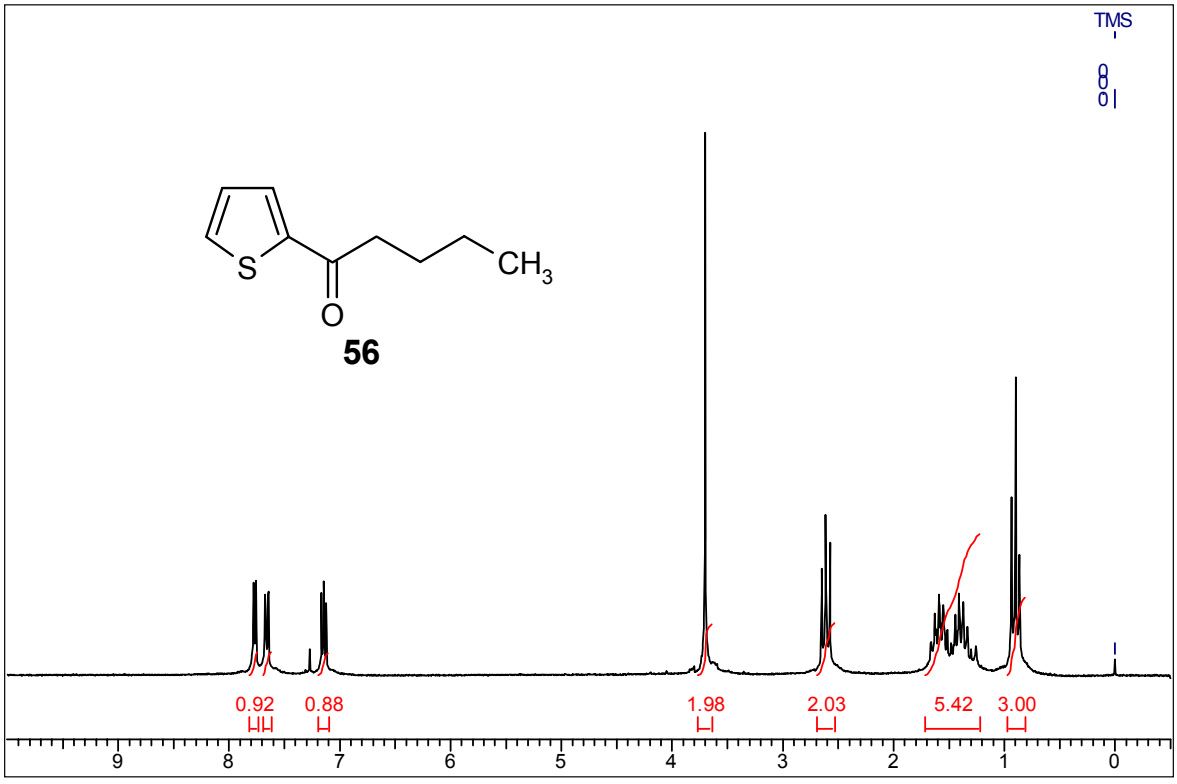
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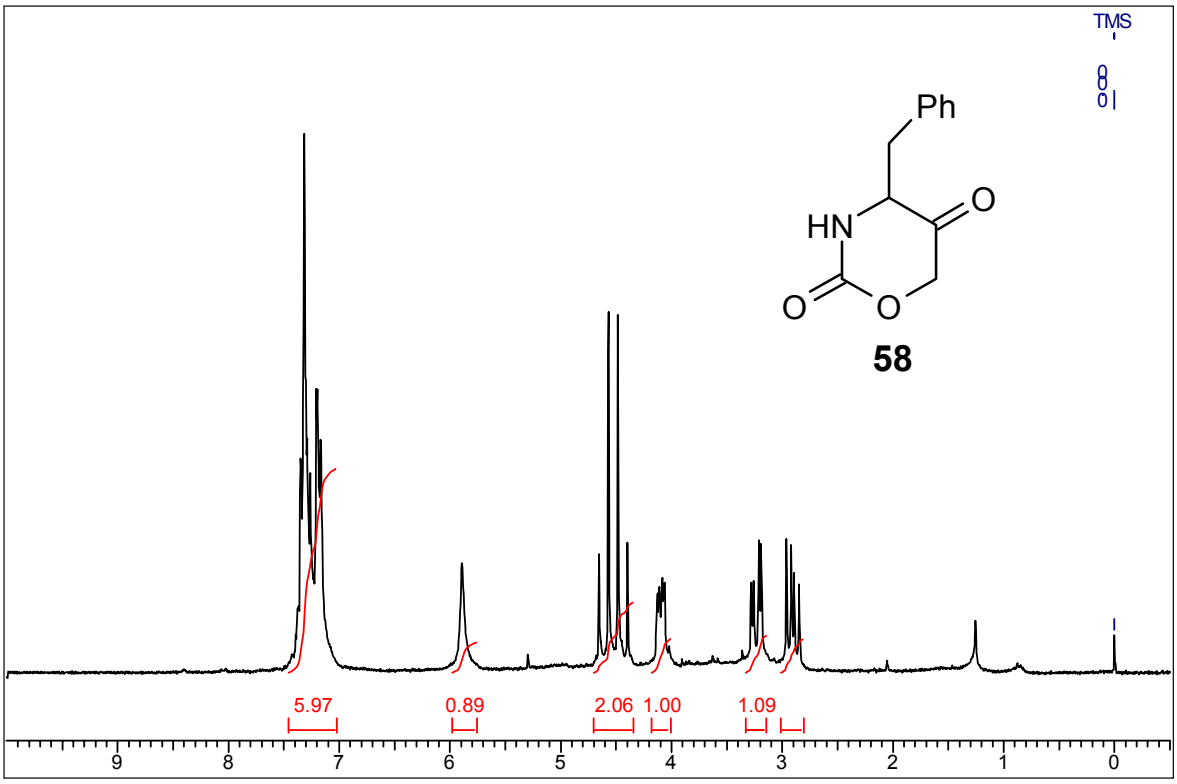
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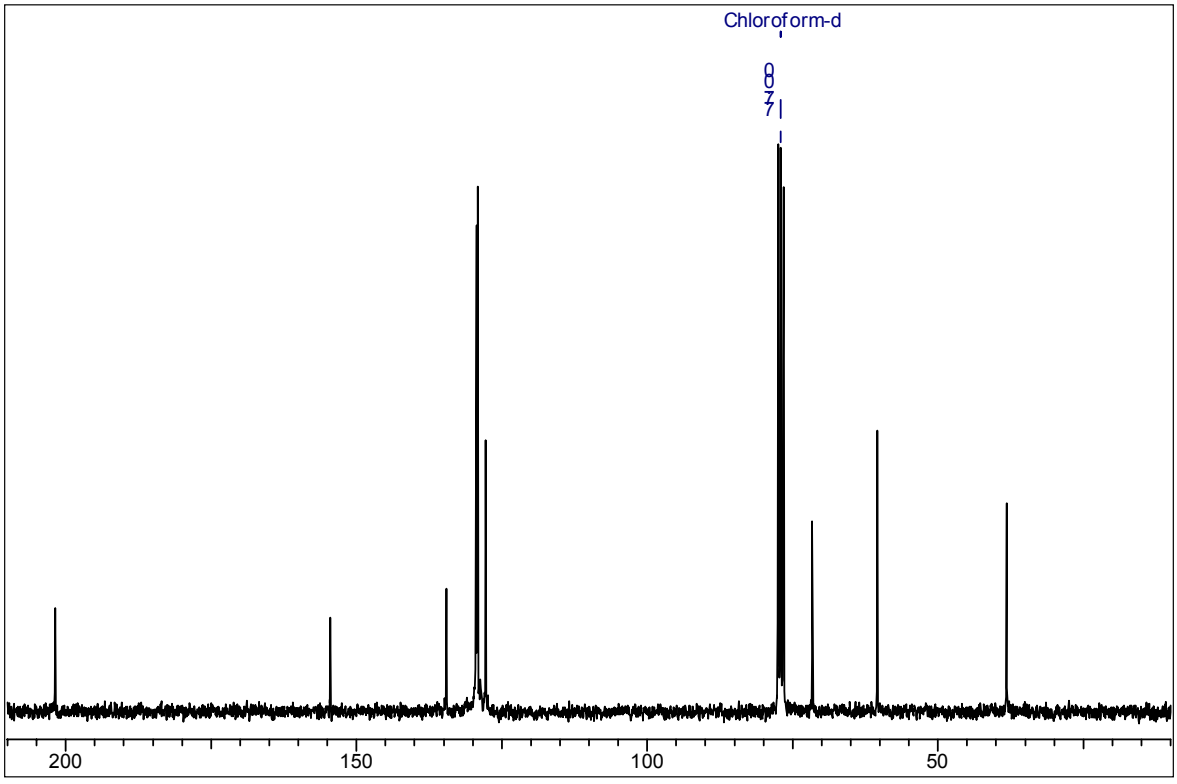
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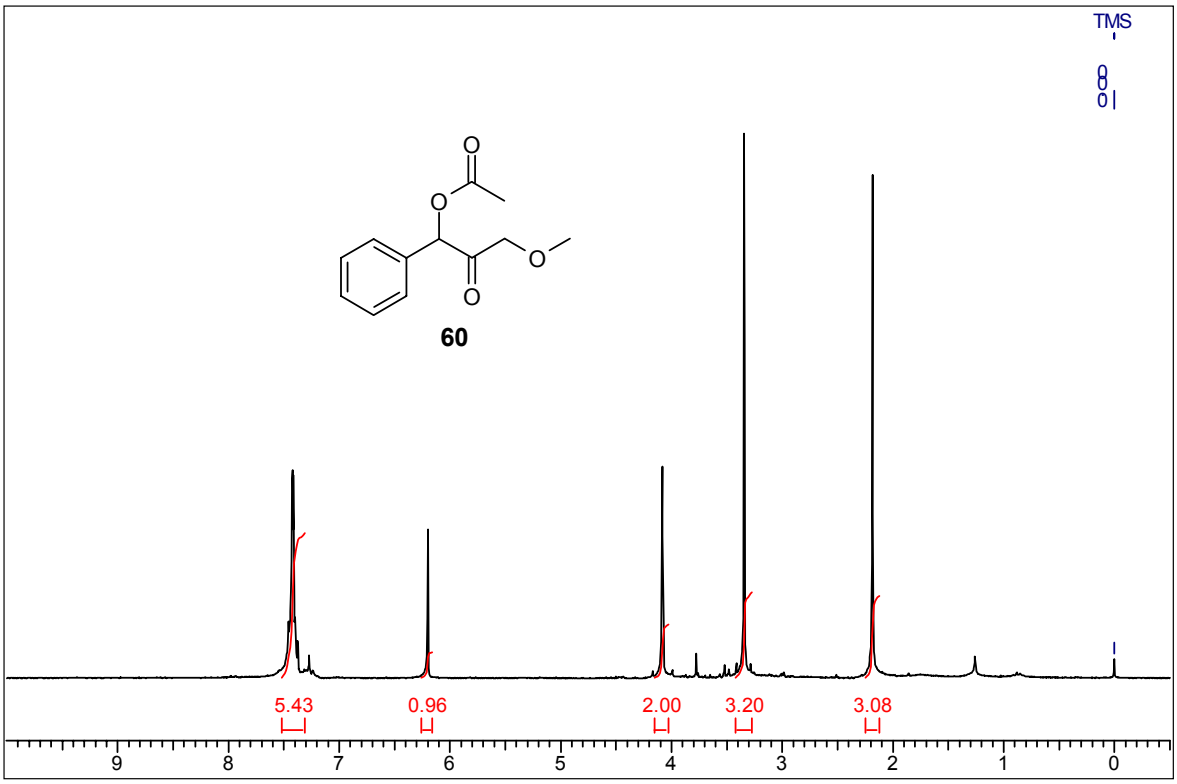
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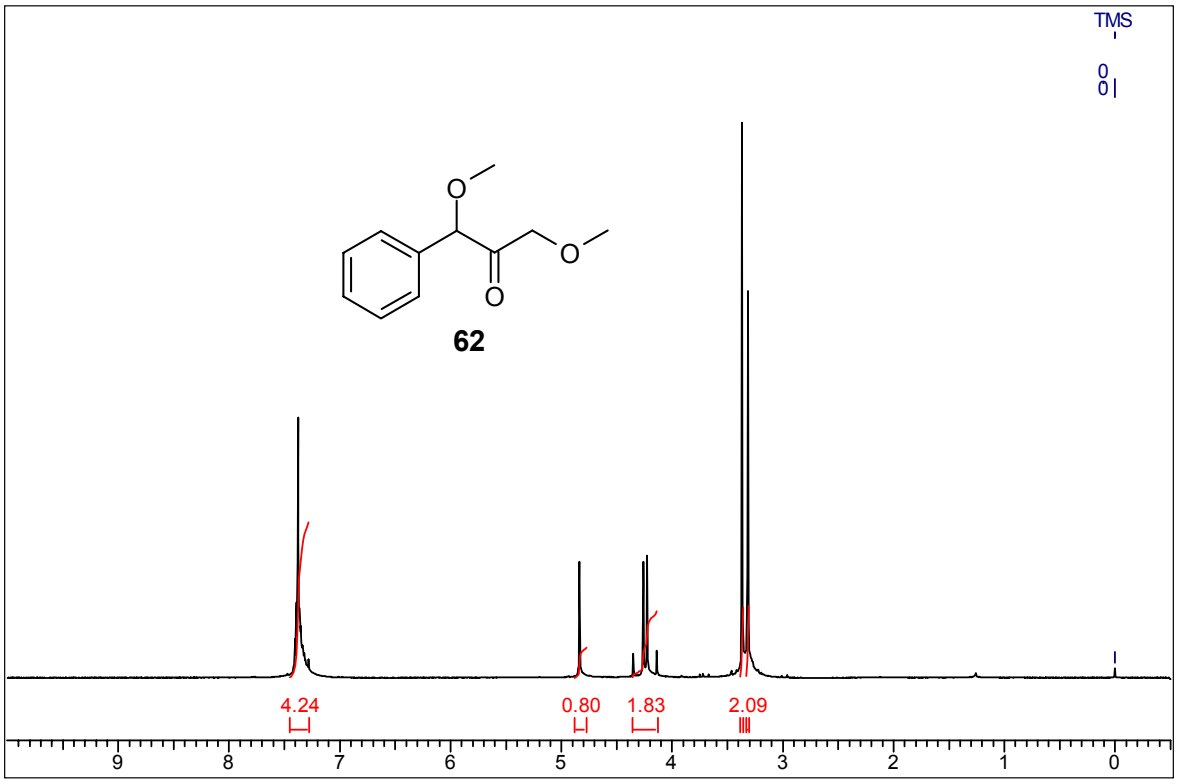
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Chapter III

Studies on the synthesis of Ethophenprox

1. INTRODUCTION

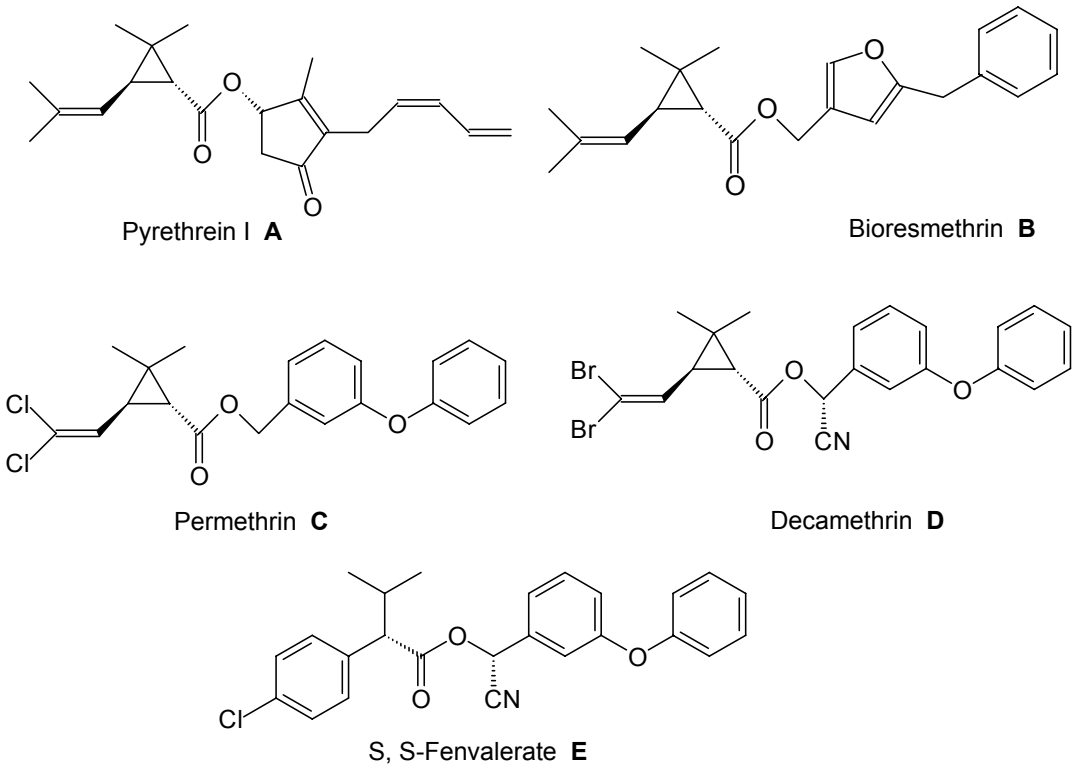
Most insecticidal products belong to four major types, the organophosphates[1], the carbamates[2], the organochlorines[3] and the pyrethroids[4]. Among the others, the organotin compounds such as fenbutatin oxide, the acylureas and the formamides also find suitable applications. The pyrethroids are of cardinal importance as they share about 20% of the insecticide market. Natural pyrethroids are present in *Chrysanthemum cinerarefolium*, a plant that is found in Kenya, Tanzania and Japan. The synthesis of pyrethroids has attracted the attention of organic chemists since the determination of their structures. Photostable pyrethroids were first introduced in 1976. The pyrethroids have posed synthetic challenges due to the presence of i) a cyclopropane ring to which are attached an ester, a vinyl and gem-dimethyl groups which interact with it and ii) stereochemical problems involving relative as well as absolute stereochemistry.

These compounds not only exhibit strong insectiside activity on various species of insects but also possess a powerful effect which almost instantenously paralyses them and prevents the females to introduce their eggs in the fruits. Initially introduced for use in cotton, they have been well received in this outlet because their residual activity results in small number of applications per season compared to other insecticides. Pyrethroids are now used over a wide range of crops including fruits, vegetables, cereals and tobacco. Pyrethroids have been found to be environmentally benign. They are potent at low dose rates and are biodegradable. In insects their toxicity appears just after ingestion or simply by contact since they are absorbed through the cuticulum. Pyrethroids rapidly penetrate into the nerve fibres probably through a pre-interaction with a specific receptor which has not yet been identified and open up presynaptic sodium channels interfering with the transport between sodium and potassium cation and thereby disrupt the entire nervous system. Insecticidal activity of the pyrethroids is believed to be linked to the ester functionality. The biological activities of pyrethroids could also depend on the structure and stereochemical characteristics of both

acidic and alcoholic components. Pyrethroids are innocuous to homeothermic species. In mammals the ester group is easily hydrolyzed to metabolic matter which is eliminated through the excretory system. However they could be harmful to some marine organisms[5].

Pyrethrin I **A** was isolated from *Chrysanthemum cinerarefolium*[3]. Besides **A** five different esters were also isolated[3]. The structures of the bioactive compounds have been established by Staudinger and Rucizka[6-8]. Systematic structure activity studies have led to more potent and stable molecules such as Bioresmethrin **B**[4], Permethrin **C**[9], Decamethrin **D**[10] in which unstable cyano-ester group has been replaced by stable benzyl esters. 2-Substituted isovaleric acid esters not containing cyclopropyl ring such as S, S-fenvalerate **E** are also important pyrethroids. For Pyrethrin I **A** and Decamethrin **D**, each has three chiral centers which gives eight different optical isomers. The isomers differ in biological activity. Bioresmethrin **B,** Permethrin **C** and Fenvalerate **E** with two chiral centers show four optical isomers. The most active isomer for each pyrethroid has been determined (Figure 1).

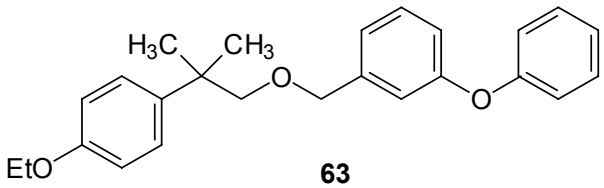
Figure 1.



The structure of these five esters, which are representative of an increasing range of active compounds, have certain features in common, for example, methyl groups near the ester link[11-12] and alcohols in which planar unsaturated rings are connected by methylene or ether bridges. Thus **D** is over ten times[13] more active than the *S*-form of the non-cyclopropane acid (*S*, *S*-fenvalerate) **E**. The activity of the later compound is however remarkable compared to most potent pyrethroids. The dimethyl groups in the β-position of the ester appear to have definite function in the action of these compounds. Ether linkage enhanced the activity. Activity can also be attributed to the presence of the 3-phenoxybenzyl system.

The first non-ester pyrethroids with promising potentiality were oxime ethers but they are vulnerable to natural conditions, hence limiting their applicative exploration. Ethophenprox (Figure 2) is a broad spectrum pyrethroid-like insectiside and exerts pyrethroid like activity but differs from natural and synthetic pyrethroids[14] as it is devoid of the conventional cyclopropane and carboxylic ester function. It is commercially known by several other names like Trebon, MTI-500, Zoecon and RF-316.

Figure 2. Ethophenprox, a pyrethroid-like insecticide



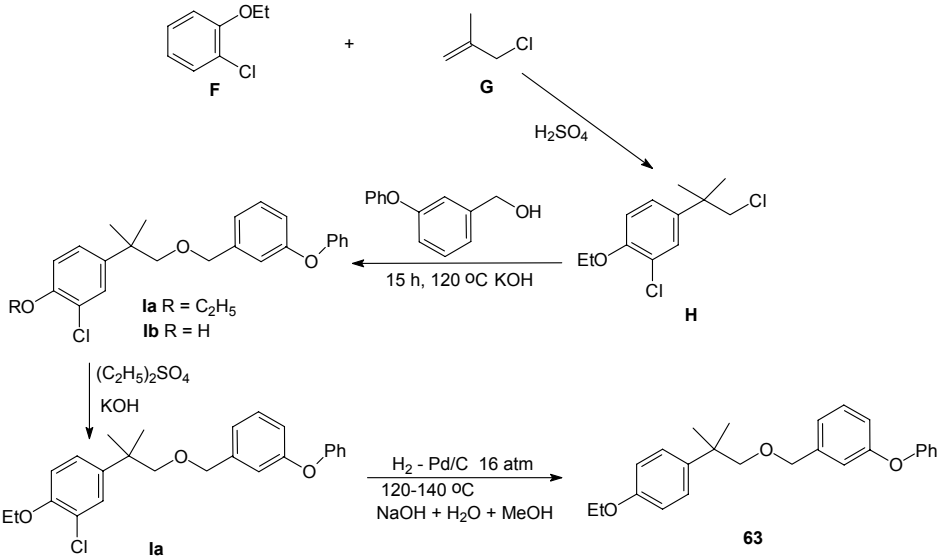
63

Ethophenprox is effective against a number of pests, for example the common cutworm (*Spodoptera litura*), the green rice leafhopper (*Nephotettix cincticeps*) and the rice grasshopper (*Oxya yezoensis*). It also exhibits high insecticidal activity against other various insect species like *Lepidoptera*[15], *Hemiptera*, *Coleoptera*, *Diptera* and *Orthoptera*. Ethophenprox does not show phytotoxicity on most of the crops. It has a very swift killing action but has a moderate residual activity against insect pests. It is effective for both susceptible and resistant strains on green rice leafhoppers, and a resistant strain of the brown

planthopper. Ethophenprox is also mixed with other insecticides to enhance its activity. A significant advantage of ethophenprox is that its toxicity towards mammals and especially fish is minimum. It is stable in alkaline and acidic conditions, and consequently it is advantageously used in combination with other alkaline agricultural chemicals.[16] Ethophenprox is presently one of the most important pesticides in Japan particularly for vegetables, rice and fruits.

The synthetic process for ethophenprox has been patented[17] and consists of the following steps. In the first step a Friedel-Crafts alkylation is affected on 2-chlorophenetole **(F)**, with 3-chloro-2-methyl-1-propene **(G)** in the presence of concentrated sulphuric acid, to afford mainly 2-methyl-2-(3-chloro-4-ethoxyphenyl)-1-chloropropane **(H)**. A small amount of the *ortho*-regioisomer is also formed. The required *p*-disubstituted product **(H)** is converted into a mixture of 3-phenoxybenzyl ether **Ia** by reaction with 3-phenoxybenzyl alcohol in presence of KOH and 1,3 dimethyl–2-imidazolidinone (DMI). The harsh reaction conditions also result in delakylation of the ethoxy group in **H** and the phenol **Ib** is also formed in this reaction. The mixture of **Ia** and **Ib** is alkylated with diethyl sulfate to give pure **Ia**. High pressure hydrogenolysis of **Ia** under alkaline conditions using Pd/C at 120 ^{0}C afforded ethophenprox.

Figure 3.



The above synthesis has several limitations. The main drawbacks are the formation of regioisomeric products in the Friedel-Crafts alkylation step and the drastic conditions required for the hydrogenolytic dehalogenation in the last step. It is evident that there is scope for improving the above synthesis by avoiding these limitations.

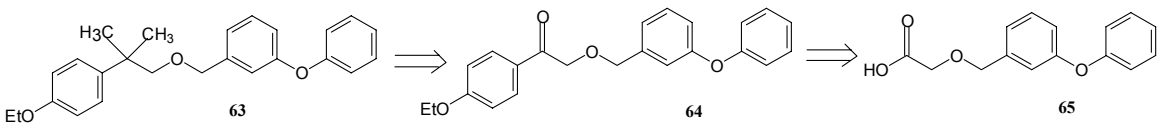
2.OBJECTIVE

The objective of this investigation was to develop a concise synthesis of ethophenprox that would avoid the formation of regioisomers and also utilize mild reaction conditions.

3. RESULTS AND DISCUSSION

We envisaged a ketone as the precursor for the *gem*-dimethyl group in ethophenprox, since *gem*-dimethylation of ketones has been successfully employed in the literature. Our primary target was therefore the ketone **64** which in turn should be readily available from the acid **65**. (Figure 4)

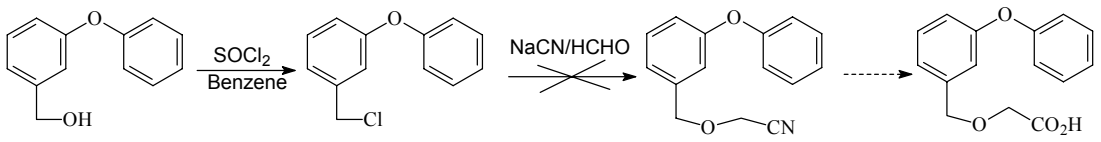
Figure 4.



Studies on the synthesis of acid 65

In the first approach, 3-phenoxy benzyl alcohol **(66)** was converted to 3-phenoxy benzyl chloride **(67)** in presence of thionyl chloride in refluxing benzene. Unfortunately, further conversion of the chloride to the nitrile **J** could not be achieved under a variety of conditions. If the nitrile could be prepared, hydrolysis could have generated the requisite acid **65**. (Scheme 1)

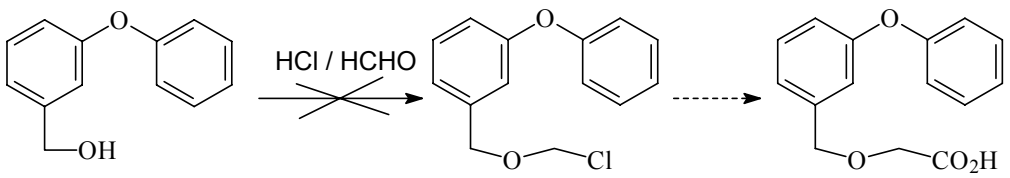
Scheme 1.



66 **67** **J** **65**

Alternatively, we attempted to preparation the chloromethyl ether **(K)** from 3-phenoxy benzyl alcohol by adaptation of the literature procedure for similar substartes[14](Scheme 2). Several possible approaches from **66** to the target acid **65** therefore had to be abandoned.

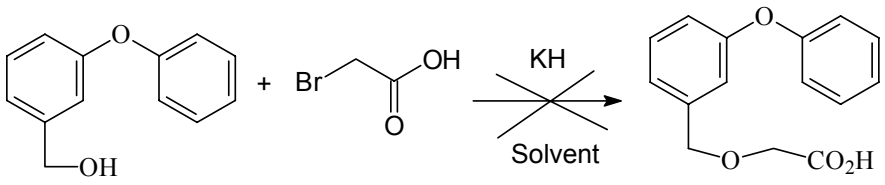
Scheme 2.



66 **K** **65**

In yet another approach, nucleophilic displacement of bromide from potassium bromoacetate by the potassium salt of **66** was examined. This route appeared especially attractive, since both starting materials are easily available and derivatization and/or functionalization is not necessary. However, not surprisingly, the acid **65** could not be prepared, presumably due to the reduced electrophilicity of the bromoacetate salt.

Scheme 3.

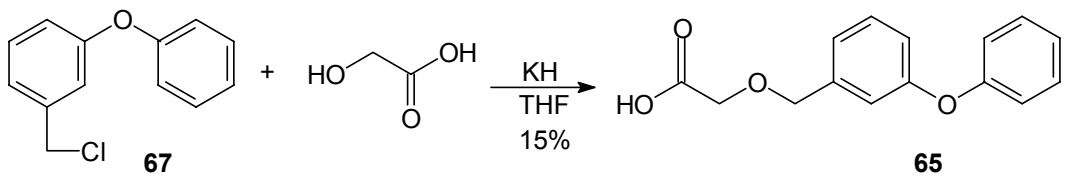


66 **65**

A switch in the role of the reactants proved to be more successful and the reaction of glycolic acid with the chloride **67** in presence of potassium hydride at ambient temperature generated the desired acid **65** but the yield was not satisfactory (maximum 15%, Scheme 4).

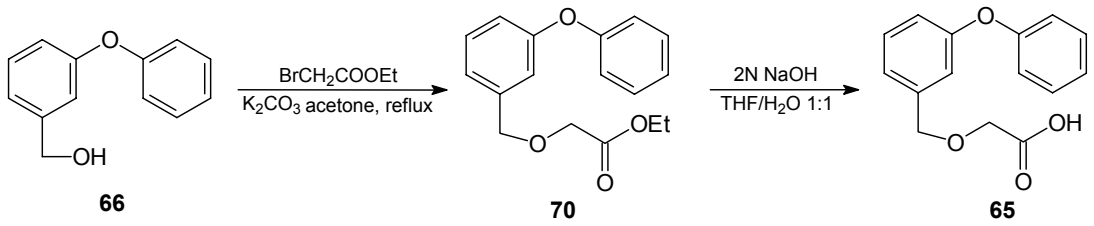
Conducting the reaction at higher temperatures gave rise to side products which hampered the purification of **65**. Altering the base had no significant effect on the yield of **65**.

Scheme 4.



Since it was necessary to have the acid **65** in substantial quantity we prepared it *via* the ester **70** which was obtained in fair yield (55%) from a reaction of 3-phenoxy benzyl alcohol and ethyl bromoacetate in refluxing acetone in the presence of potassium carbonate. Hydrolysis of **70** generated **65** in quantative yield (Scheme 5).

Scheme 5.

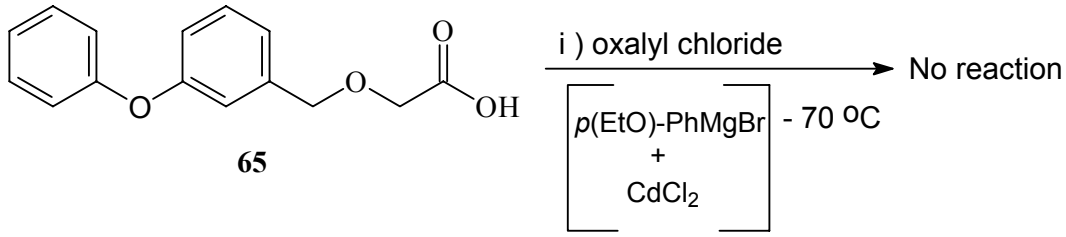


Unsuccessful efforts for the synthesis of 64

We next attempted to prepare the ketone **64**. Dialkyl and diaryl cadmium reagents are easily prepared from corresponding Grignard reagents and $CdCl_2$ and are known to couple with acid chlorides to produce ketones.[15] The acid chloride of **65** was readily prepared by treatment with oxalyl chloride. The diaryl cadmium reagent of 4-bromophenetole **(71)** was prepared by adapting the literature procedure[16] which involves addition of anhydrous $CdCl_2$ to the Grignard reagent derived from, in this case, 4-bromophenetole (Scheme 6). Unfortunately, the reaction did not proceed as expected and the acid **65** was recovered. Although the exact reasons for this are unclear, it is likely that enolization of the acid chloride is a side reaction which consumes the organocadmium reagent. Higher reaction temperatures led to

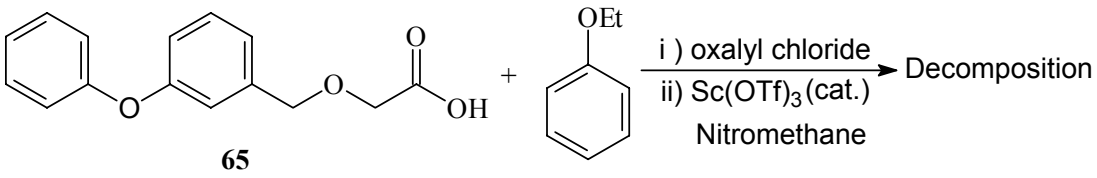
decomposition of the substrate. A direct reaction of the acid chloride of **65** with 4-EtO-PhMgBr at -78 ^{o}C, conditions known to generate ketones from acid chlorides[17] was also not effective.

Scheme 6.



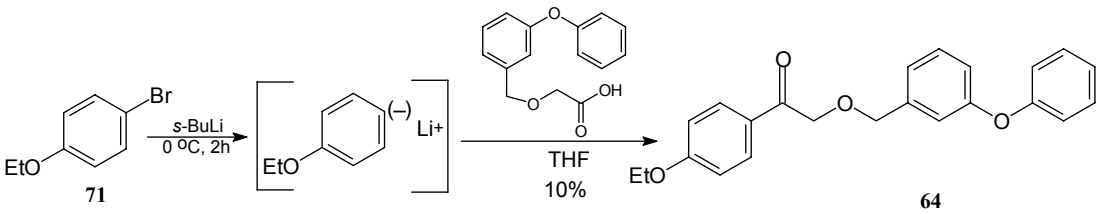
The Friedel-Crafts acylation of phenetole with the acid chloride of **65** in the presence of scandium triflate as Lewis acid in anhydrous nitromethane[18] was also examined. Quite unexpectedly, the reaction also proved to be quite complex and none of the required ketone could be detected in the crude product (Scheme 7). Since one of the objectives was to develop a mild and eco-friendly procedure, aluminum chloride was not examined as the Lewis acid in this reaction.

Scheme 7.



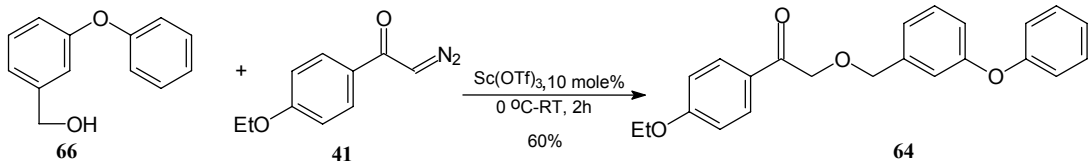
Although **64** could be obtained by coupling the two fragments (Scheme 8) by the metal-halogen exchange protocol (addition of *s*-BuLi to *p*-bromophenetole at 0 ^{o}C), the reaction was highly capricious. Several unidentifiable by-products made purification of the ketone very difficult and substantially reduced its yield (maximum 10%). Conducting the reaction at a lower temperature was not beneficial.

Scheme 8.



Our success with the diazocarbonyl-OH insertion reaction (described in Chapter II) suggested that it could be used favourably for a simple synthesis of **64**. Thus, the synthesis of **64** was ultimately accomplished in a straightforward manner and fair yield (60%) through an O-H insertion reaction of **66** and *p*-ethoxy diazoacetophenone **41** in the presence of scandium triflate as the catalyst (Scheme 9). Rhodium acetate could also generate **64** but the yield was comparably lower (32%).

Scheme 9.



We next investigated the *gem*-dimethylation on **64**. The *gem*-dialkylation of carbonyl substrates has been extensively explored Reetz and coworkers.[19] It is believed that species like Me_2TiCl_2 and $MeTiCl_3$ generated *in situ* from a combination of methyl magnesium halide and $TiCl_4$ is instrumental for the *gem*-dimethylation process.[20] The formation of such species is marked with the development of an intense red or reddish-brown colour after which the carbonyl substrate is added to the reaction mixture.

The attempted *gem*-dimethylation on ketone **64** with Me_2TiCl_2 (generated from MeMgI and $TiCl_4$) was unsuccessful under various conditions. These reactions invariably gave complex mixtures of products, from which the tertiary alcohol **72** could be isolated in low yield (15%, Scheme 11). Small amounts (< 5%) of 3-phenoxy benzyl alcohol were also

isolated from these attempts. The effect of the reaction of organometallic reagent to the ketone was also examined and the results are summarized in Table 2.

Scheme 11

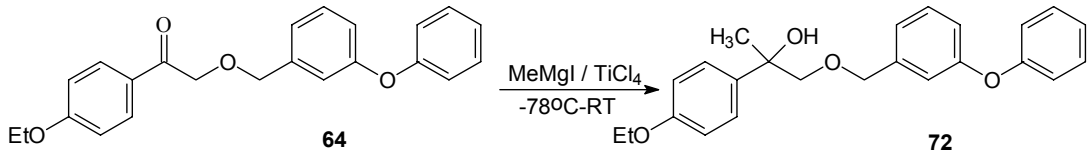


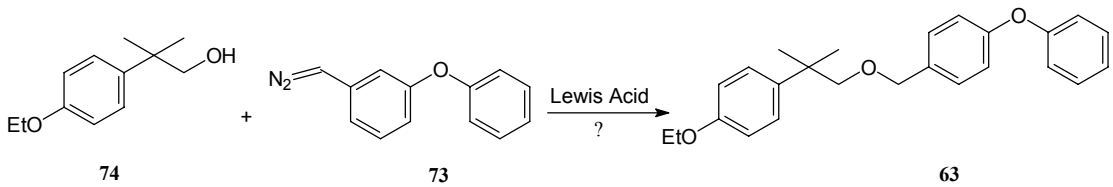
Table 2. Effect of reagent/ketone ratio on the conversion of **64** to **72**.

Reagent / Ketone	Solvent	Condition	Observation
1 /1	dichloromethane	-90 ^{o}C, 2h	unreacted **64**
2 / 1	Ether	-78 ^{o}C to -20^{o}C, 2h	**72**, 15%
4 / 1	dichloromethane	-78 ^{o}C to rt, 2h	**72**, 10%
8 /1	dichloromethane	- 78 ^{o}C to rt, 8h	decomposition

Another reagent known to be useful for the conversion of a ketone to a geminal dimethyl group, namely trimethyl alumunium in presence of $Ni(acac)_2$ did not affect the desired reaction.[21] An attempt to convert **72** to the required *gem*-dimethyl compound **63** with dimethyl zinc in presence of $TiCl_4$[22] was not successful. The alcohol was left partially unconsumed and several decomposition products were observed.

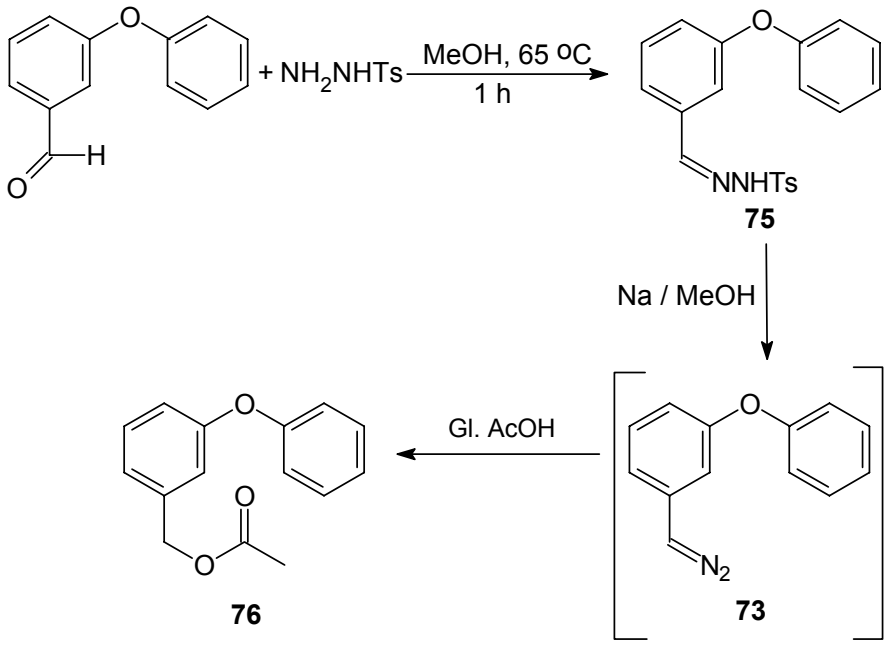
A change in strategy was sought at this point. Acid catalysed insertion reactions of alcohols and diazo alkanes are well known.[23,24] We chose to explore the possibility of conducting this insertion with 3-phenoxy phenyl diazomethane **73** and the alcohol **74**[25] that would give ethophenprox as the product of an O-H insertion reaction (Figure 5).

Figure 5.



3-Phenoxy phenyl diazomethane **73** was prepared from the tosyl hydrazone of 3-phenoxy benzaldehyde **75** by treatment with sodium methoxide in methanol.[26] The insertion reaction of the alcohol **74** was examined under a variety of conditions in the presence of various Lewis acids such as HBF_4,[23] $SnCl_2.2H_2O$,[24] $Rh_2(OAc)_4$ and $Sc(OTf)_3$. Unfortunately, none of these reactions generated ethophenprox. It is possible that 3-phenoxy phenyl diazomethane decomposes in the presence of Lewis acids. In addition, a control experiment in which the *in-situ* generated **73** (from **75**) was quenched with acetic acid, generated the acetate **76** in only 30% yield (Scheme 12). This suggests that the generation of **73** from the tosyl hydrazone is inefficient and this may also have contributed to the overall inefficiency of the OH insertion reactions with **73**.

Scheme 12.



Current efforts are directed towards the generation of 3-phenoxy phenyl diazomethane **(73)** by alternative procedures[27] and also the investigation of other Lewis acids for the insertion reaction.

4. CONCLUSIONS

Although the reasons for the difficulties in converting the ketone **64** to ethophenprox are unclear at present the synthesis of ethophenprox could not be achieved, several key intermediates have been prepared and these will be utilized in ongoing studies.

5. EXPERIMENTAL

General experimental techniques that have been described in the experimental section of Section A in Chapter 1 were followed.

1-(Chloromethyl)-3-phenoxybenzene (67):

To a solution of thionyl chloride (0.74 mL, 10 mmol) in anhydrous benzene (3 mL) was added a drop of pyridine followed by dropwise addition of 3-phenoxy benzyl alcohol (0.9 ml, 5 mmol) dissolved in 7 ml of benzene over a period of 30 minutes. The mixture was heated to reflux for 2 h. and then cooled to ambient temperature. Water and ethyl acetate were added and the biphase was eparated. The aqueous phase was extracted with ethyl acetate and the combined extracts were dried (Na_2SO_4) and concentrated to obtain the crude product. This was filtered through a short silica gel column (1/19 ethyl acetate / pet. ether) to obtain 890 mg (82%) of **67** a colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$)

δ-7.52-6.80 (m, 9H, Ar*H*), 4.55 (s, 2H, CH_2)

IR ($CHCl_3$)

1570, 1468, 1239, 765 cm^{-1}

(3-Phenoxybenzyloxy)acetic acid (65):

A solution of glycolic acid (76 mg, 1 mmol) dissolved in anhydrous THF (2mL) was added dropwise over a period of ten minutes to potassium hydride (251 mg (35% wt%), 2.2 mmol, washed with pet. ether). After fifteen minutes **67** (diluted in 1 mL THF) was added. The mixture was heated to reflux for 6 h. After cooling to room temperature ice and ethyl acetate (20 mL) were added. The organic layer was separated, dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography (1/9 ethyl acetate/pet.ether) to furnished 39 mg (15%) of **65** colourless liquid.

^{1}H NMR (200 MHz, $CDCl_3$)

δ-6.91-7.93 (m, 9H, Ar*H*), 4.68 (s, 2H, CH_2O), 4.18 (s, 2H, CH_2CO)

IR ($CHCl_3$)

1760, 1570, 1450, 1050, 723 cm^{-1}

Ethyl (3-phenoxybenzyloxy) acetate (70):

To anhydrous potassium carbonate (207 mg, 1.5 mmol) suspended in anhydrous acetone (10 ml) was added 3-phenoxy benzyl alcohol (0.135 ml, 1 mmole) followed by ethyl bromoacetate (0.13 mL, 1 mmol). The reaction mixture was heated to reflux for 12 h. Acetone was removed under reduced pressure and ethyl acetate and water were added to the residue. The ethyl acetate layer was washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (1/9 ethyl acetate/pet.ether) to furnish 157 mg (55%) of **70** as a colourless gum.

^{1}H NMR (200 MHz, $CDCl_3$)

δ-6.78-7.55 (m, 9H, Ar*H*), 4.65 (s, 2H, CH_2O), 4.30 (q, 2H, J = 8.1 OCH_2CH$_3$), 4.15 (s, 2H, CH_2O), 3.2 (t, 3H, *J* = 8.1, OCH$_2$CH_3)

IR ($CHCl_3$)

1750, 1585, 1487, 1389, 1256, 1163, 1144, 1023, 756 cm^{-1}

MS (70 ev)

60 (18), 77 (29), 94 (55), 105 (22), 115 (10), 153 (20), 171 (34), 199 (73), 286 (M^+, 54).

Hydrolysis of ester 70 to acid 65:

To a solution of **70** (562 mg, 2 mmol) in THF (2 ml) was added 2N NaOH (1.5 mL). The mixture was stirred at ambient temperature for 2 h., cooled to 0 ^oC and acidified with 2N HCl. Ethyl acetate (15 mL) was added and the biphase was stirred and then separated. The ethyl acetate layer was extracted with saturated aqueous sodium bicarbonate solution (3x10 mL). The combined bicarbonate extracts were acidified and extracted with ethyl acetate. The ethyl acetate extracts were dried (Na_2SO_4) and concentrated to obtain 540 mg (>99%) of **65** as a gum.

1-Bromo-4-ethoxybenzene (71):

p-Bromophenol (1g, 5.78 mmol) was dissolved under ice-cooling in 5N NaOH (20 mL) diethyl sulfate (1.5 mL, 11.56 mmol) was added. The mixture was heated to reflux for 2 h. Ethyl acetate (30 mL) was added and the biphase was separated The organic layer was washed with 0.1N H_2SO_4 (2x5mL), brine and concentrated to obtain 813 mg (76%) of **71** as a liquid.

^{1}H NMR (200 MHz, $CDCl_3$)

δ-7.38 (d, 2H, *J* = 9.8, Ar*H*), 6.80 (d, 2H, *J* = 9.8, Ar*H*), 3.8 (q, 2H, *J* = 6.8, CH_2), 1.4 (t, 3H, *J* = 4.9, CH_3)

1-(4-Ethoxyphenyl)-2-(3-phenoxybenzyloxy) ethanone (64):

Synthesis by the metal-halogen exchange procedure:

To a stirred solution of 4-bromophenetole (880 mg, 2.94 mmol) in anhydrous ether (10 ml) was added at 0 ^oC *sec*- BuLi (3ml, 3mmoles, 1M solution in ether). The solution was stirred for two h. The resulting mixture was added dropwise to an ice-cooled solution of **65** (379 mg, 1.47 mmol) over a period of ten minutes. The reaction mixture was stirred at the same temperature for 3 h. ice-cold 1N HCl (10 mL) was added. After addition of ether (20 mL), the organic layer was separated, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography (1/9 ethyl acetate/pet.ether) to give 53 mg (10%) of **64** as white solid.

Synthesis by the rhodium acetate catalyzed insertion procedure:

To a solution of 3-phenoxy benzyl alcohol (0.13 ml, 1 mmol) and 4-ethoxy diazo acetophenone **(41)** (190 mg, 1 mmol) in anhydrous dichloromethane (4 mL) was added rhodium acetate (18 mg, 4 mol%) and the mixture was stirred at room temperature for 6 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (1/9 ethyl acetate/pet.ether) to furnish 116 mg (32%) of **64** as a white crystalline solid.

Synthesis by the scandium triflate catalyzed insertion procedure:

To a solution of 3-phenoxy benzyl alcohol (0.27 mL, 2 mmol) and **41** (380 mg, 2 mmol) in anhydrous benzene (10 mL) was added scandium triflate (40 mg, 4 mol %) and the mixture was stirred for 2 h at ambient temperature. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (1/9 ethyl acetate/pet. ether) to obtain 434 mg (60%) of **64** as white solid.

^{1}H NMR (200 MHz, $CDCl_3$)

δ-8.88 (d, 2H, *J* = 8.5, Ar*H*), 7.42-7.81 (m, 11H, Ar*H*), 4.65 (s, 2H, OCH_2), 4.60 (s, 2H, COCH_2), 4.2 (q, 2H, *J* = 9.5, CH_2CH_3) 1.44 (t, 3H, *J* = 9.5, CH_2CH_3)

^{13}C NMR (75 MHz, $CDCl_3$)

194.4 (*C*=O), 163.0 (Ar*C*), 157.3 (Ar*C*), 156.9 (Ar*C*), 139.4 (Ar*C*), 130.0 (Ar*C*), 129.5 (Ar*C*), 127.6 (Ar*C*), 123.1 (Ar*C*), 122.4 (Ar*C*), 118.7 (Ar*C*), 117.9 (Ar*C*), 114.3 (Ar*C*), 114.1 (Ar*C*), 72.7 (Ph*C*H_2), 72.5 (CO*C*H_2), 63.5 (O*C*H_2), 14.4 (*C*H_3).

IR ($CHCl_3$)

2979, 1693, 1487, 1215, 1043, 921, 837 cm^{-1}

MS (70 ev)

65 (5), 77 (9), 107 (20), 121 (41), 135 (21), 149 (100), 164 (20), 183 (31), 340 (5), 362 (M^+, 4).

Analysis for $C_{23}H_{22}O_4$:

Calcd: C, 76.42; H, 5.86.

Found: C, 76.22; H, 6.26.

2-(4-Ethoxyphenyl)-1-(3-phenoxybenzyloxy) propan-2-ol (72):

To a solution of $TiCl_4$ (0.22 mL, 2mmol) in anhydrous ether (10 mL) at –78 ^{o}C was added MeMgI (4mL, 4 mmol, ~1M solution in ether) and the mixture was stirred for fifteen min. To the resulting red solution was added a solution of **64** (362 mg, 1mmol) in anhydrous ether (3 mL) and the mixture was warmed to –20 ^{o}C over a period of 2h. Saturated

aq. ammonium chloride was added and the mixture warmed to ambient temperature. Water was added to dissolve the precipitated solids and the mixture was extracted with ether. The combined ether extracts were dried (Na_2SO_4) and concentrated. Purification of the residue by column chromatography (1/19 ethyl acetate pet. ether) gave 57 mg (15%) of **72** as a colourless liquid.

^{1}H NMR (200 MHz, $CDCl_3$)

δ-7.38- 6.80 (m, 13H, *J* = 8.5, Ar*H*), 4.51 (s, 2H, ArCH_2O), 4.03 (*AB* system, 2H, *J* = 6.8, CH_2), 3.56 (q, 2H, *J* = 8.8, CH_2CH$_3$), 2.79 (s, 1H, O*H*), 1.50 (s, 3H, CH_3) 1.44 (t, 3H, *J* = 12.2, CH$_2$CH_3)

^{13}C NMR (50 MHz, $CDCl_3$)

δ-157.8 (Ar*C*), 157.4 (Ar*C*), 156.9 (Ar*C*), 140.0 (Ar*C*), 137.2 (Ar*C*), 129.7 (Ar*C*), 126.1 (Ar*C*), 123.3 (Ar*C*), 122.1 (Ar*C*), 118.9 (Ar*C*), 117.9 (Ar*C*), 113.9 (Ar*C*), 78.2 (Ar*C*H$_2$O), 73.5 (C*quat*), 72.8 (*C*H$_2$CH$_3$), 63.3 (*C*H$_2$), 26.6 (C*C*H$_3$), 14.8 (CH$_2$*C*H$_3$).

IR ($CHCl_3$)

3331, 2985, 1253, 1119, 840 cm^{-1}

Synthesis of 3-phenoxy phenyl diazomethane (73):[28]

This was prepare from the tosyl hydrazone of 3-phenoxy benzaldehyde, which was prepared as follows:

***N*'-[(1*E*)-(3-Phenoxyphenyl)methylene]-4-methyl benzenesulfinohydrazide (75):**

To a solution of 3-phenoxybenzaldehyde (0.38 mL, 2.19 mmol) in methanol (10 mL) was added tosylhydrazone (407 mg, 2.19 mmol) and the mixture was heated at 65 ^{o}C for one hour with continous stirring. The mixture was then concentrated to obtain a solid. Recrystallization of the solid from ethanol gave 795 mg (>99%) of **75** as a white crystalline solid.

^{1}H NMR (200 MHz, $CDCl_3$)

δ-8.25 (s, 1H, C*H*=N), 7.85-6.97 (m, 13H, Ar*H*), 2.40 (s, 3H, CH_3), 1.85 (br, s, N*H*)

Conversion of 75 to 3-phenoxy phenyl diazomethane (73):

To a freshly prepared solution of sodium methoxide (prepared from sodium (20 mg, 0.88 mmol) in anhydrous methanol, 2mL) was added **75** (183 mg, 0.50 mmol) and the mixture was heated to reflux for 10 min. to give a red solution. To this was added dichloromethane and water and the biphase was extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4) and the solution of 3-phenoxy phenyl diazomethane thus obtained was decanted and used immediately.

3-Phenoxybenzyl acetate (76):

To the solution of **73** was added glacial acetic acid (0.5 mL) with continous stirring and the mixture was stirred till the red colour was discharged. The mixture was then diluted with dichloromethane and washed once with saturated aq. sodium bicarbonate. The aqueous layer was extracted once with dichloromethane and the combined dichloromethane layers were dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography (1/9 ethyl acetate/pet.ether) to obtain 34 mg (30% with respect to **75**) of **76** as a colourless gum.

^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.38-6.97 (m, 9H, Ar*H*), 5.07 (s, 2H, C*H*$_2$O), 2.10 (s, 3H, C*H*$_3$)

IR ($CHCl_3$)

1743, 1585, 1180, 1488, 1215, 1024, 692 cm^{-1}

MS (70 ev)

77 (41), 89 (27), 200 (100), 242 (M^+, 12)

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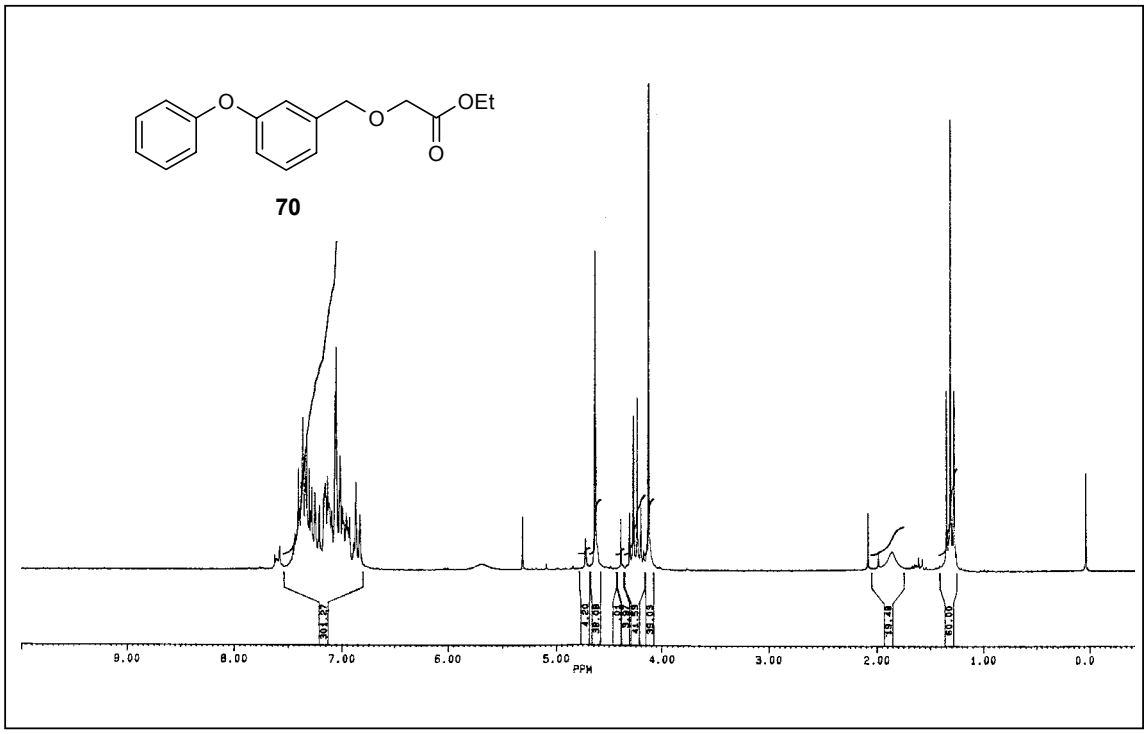
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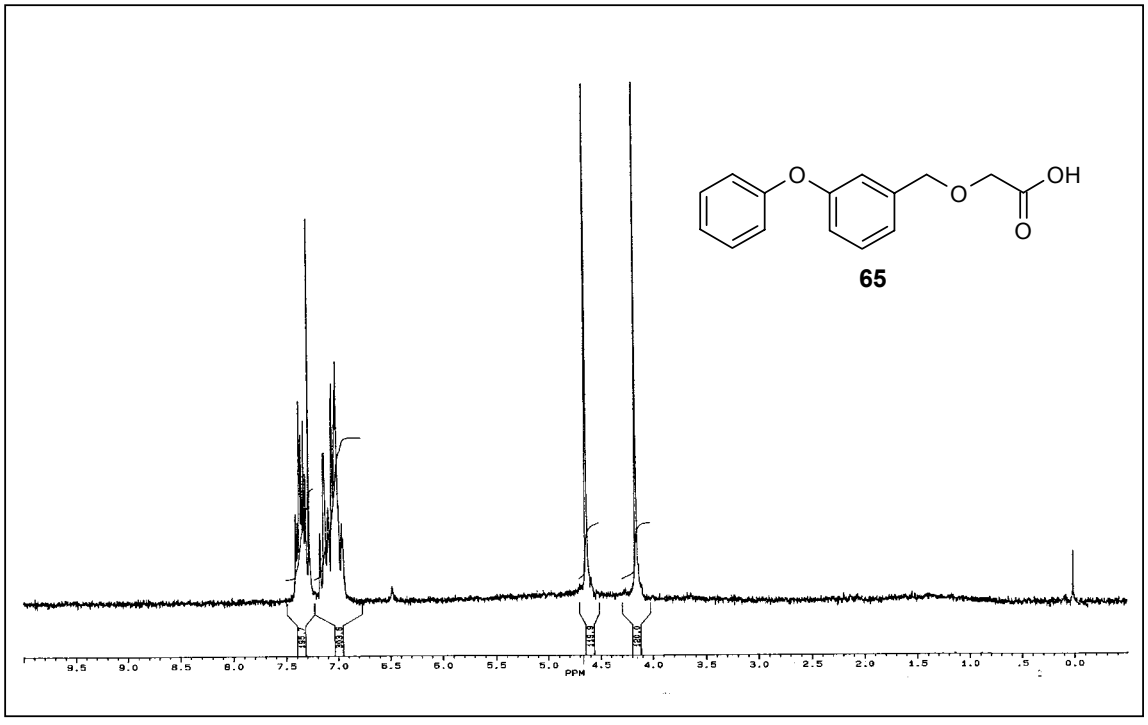
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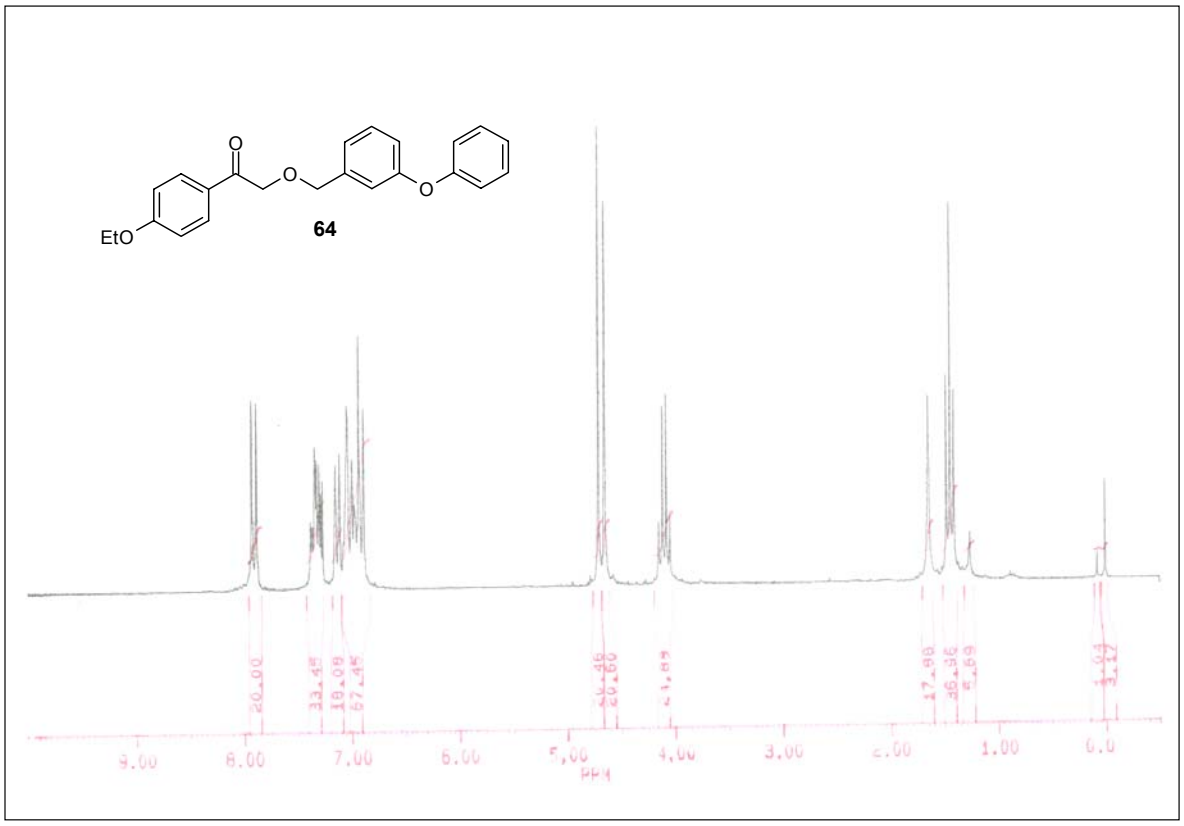
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8.00
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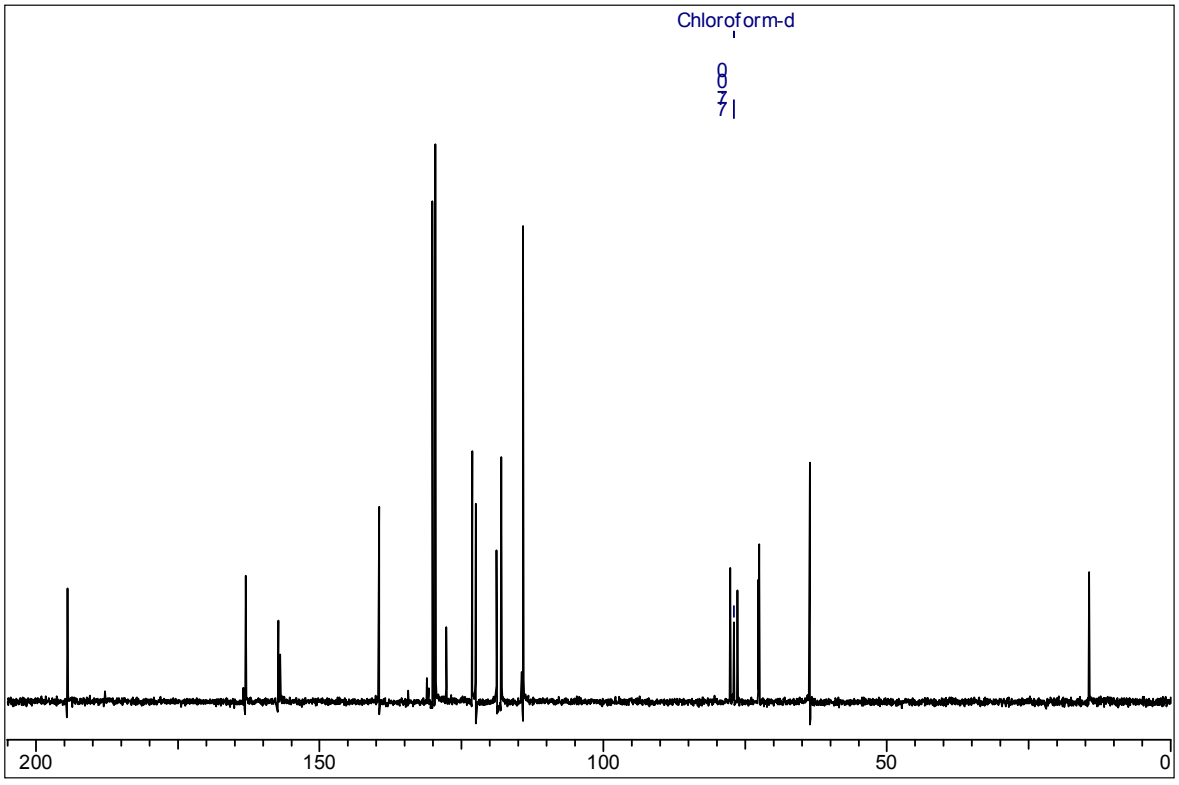
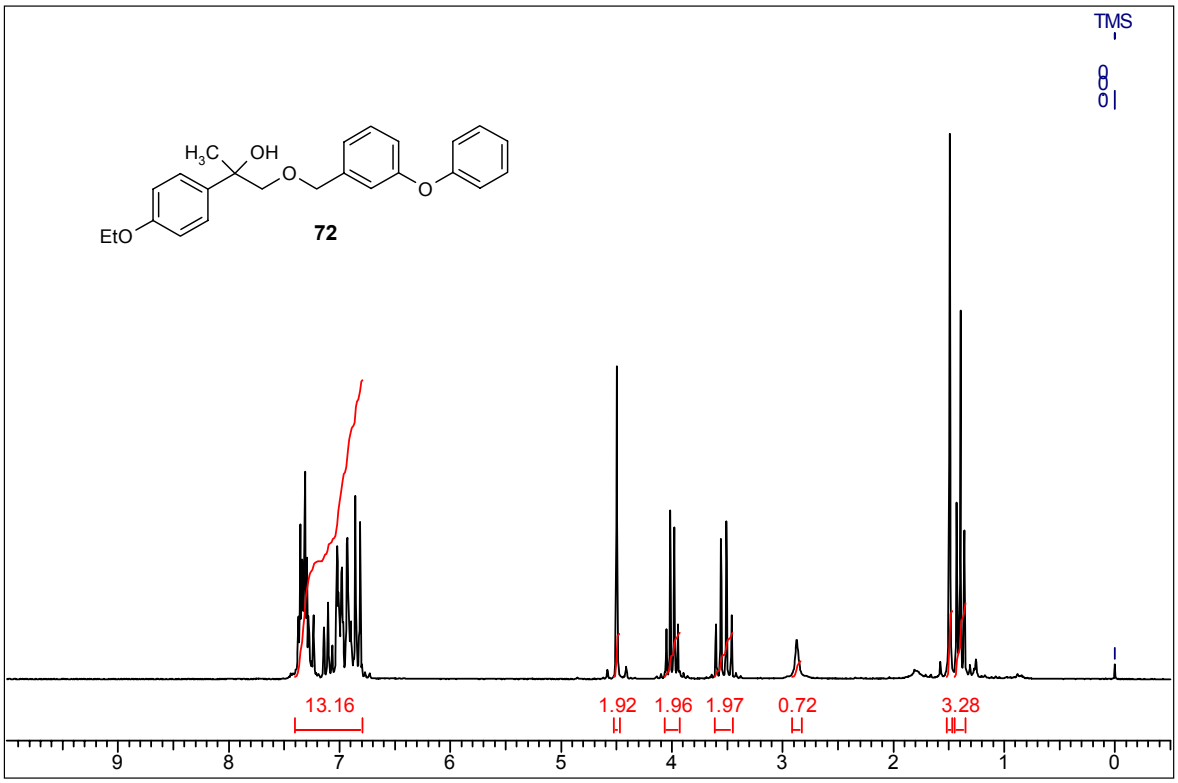
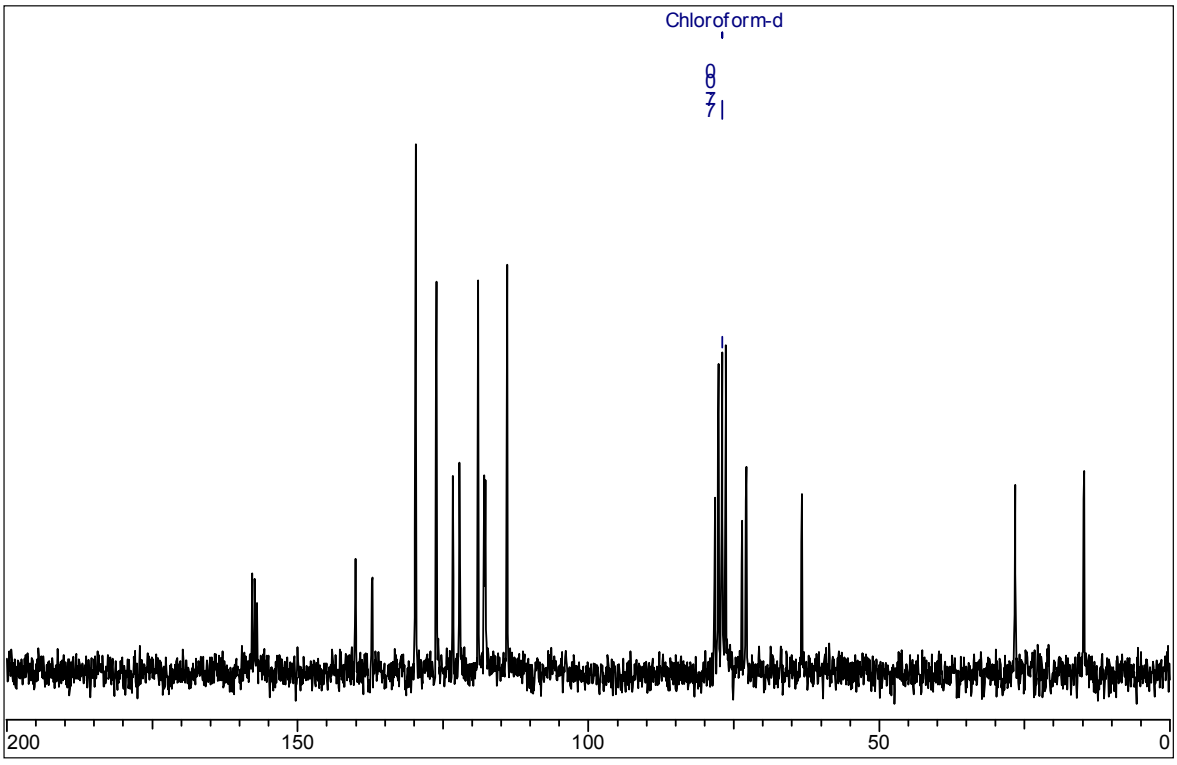
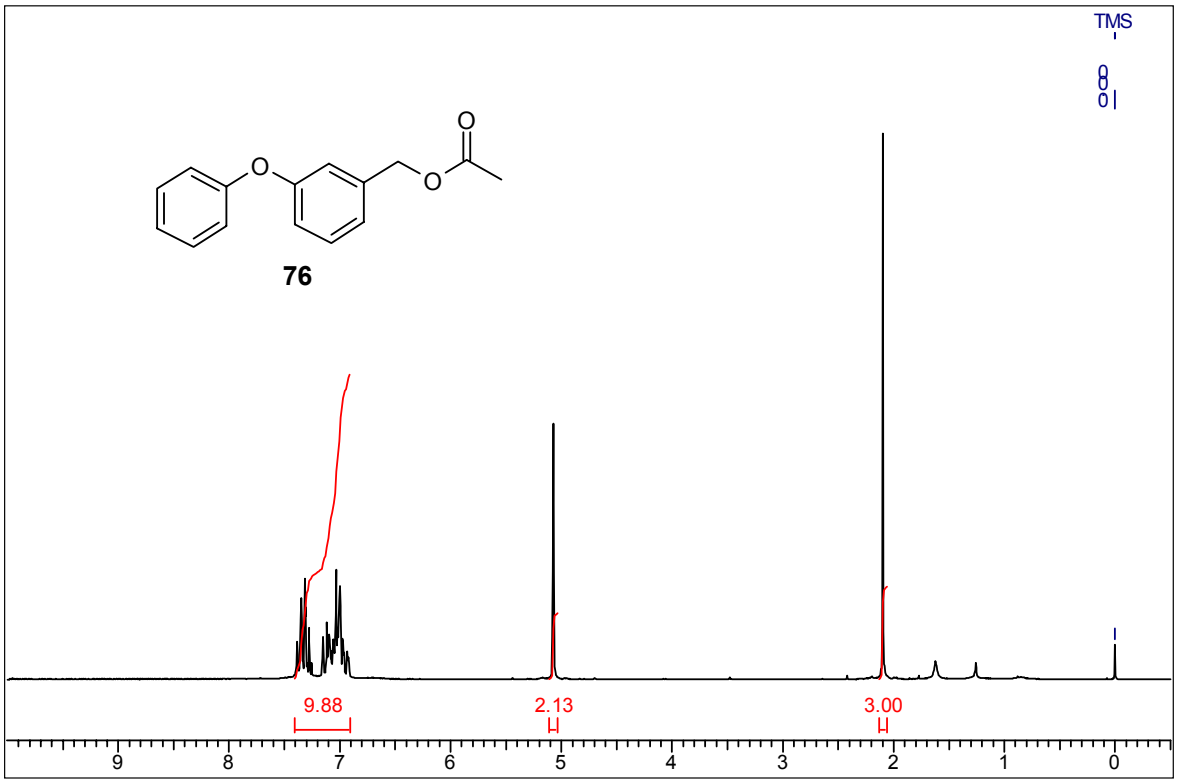
0.0
PPM


Chloroform-d
200
150
100
50
0


TMS
H3C
OH
O
O
EtO
72
13.16
1.92
1.96
1.97
0.72
3.28
9
8
7
6
5
4
3
2
1
0


Chloroform-d
200
150
100
50
0


TMS
O
O
O
O
76
9.88
2.13
3.00
9
8
7
6
5
4
3
2
1
0