Expanding the Organocatalyzed α-Chlorination-Aldol Reaction

by

Gaelen M. Fehr

B.Sc., University of Manitoba, 2016

Thesis Submitted in Partial Fulfillment of the
Requirements for the Degree of
Master of Science

in the
Department of Chemistry
Faculty of Science

SIMON FRASER UNIVERSITY
Fall 2018

Approval

Name:	**Gaelen M. Fehr**
Degree:	**Master of Science**
Title:	**Expanding the Organocatalyzed α-Chlorination-Aldol Reaction**
Examining Committee:	**Chair:** **David Vocadlo** Professor
	Robert A. Britton Senior Supervisor Professor
	Andrew J. Bennet Supervisor Professor
	Peter D. Wilson Supervisor Associate Professor
	Roger Linington Internal Examiner Associate Professor
Date Defended:	December 14th, 2018

Abstract

Organocatalysis, while still a relatively new field in organic chemistry, now plays an indispensable role in organic synthesis. Transformations not accessible by classical synthetic methods are now not only routine, but mild, high yielding and increasingly sophisticated in what they can achieve. One such reaction is the α-chlorination-aldol reaction developed by the Britton group in 2013. This reaction has been demonstrated to provide access to stereochemically rich chlorohydrins from readily available and achiral starting materials. The reaction has found extensive utility in the concise synthesis of imino-cyclitols and carbohydrate analogues.

In this thesis a more general approach to the tandem α-chlorination-aldol with different electrophiles or ketones is investigated. Within, we show that azodicarboxylates can be used as electrophiles to functionalize aldehydes prior to submission to an aldol reaction. These aminated aldol adducts are further investigated for their utility in synthesizing imino-cyclitols, and their ability to form cyclic, polyhydroxylated hydrazones.

As well, new substrates are investigated for their propensity to engage in an α-chlorination-aldol reaction. Four new substrates are demonstrated to form the corresponding chlorinated aldol adducts in moderate yields and high enantioselectivity. Furthermore, we demonstrate that these new aldol adducts can provide access to novel, natural product-like scaffolds.

Keywords: organocatalysis; methodology; proline; amination; aldol

Acknowledgements

Firstly, I would like to thank Dr. Robert Britton for allowing me the opportunity to pursue graduate studies in organic chemistry. His constant optimism and wealth of synthetic knowledge have made for a fantastic learning environment. He has provided me not only an opportunity to learn about organic synthesis but has taught me skills beyond that of organic chemistry, and lessons I will carry with me for many years to come. I am a better chemist and person for having worked in his lab.

I would also like to thank members of the committee, Drs Andrew Bennet and Peter Wilson for serving on the committee for the last two years. Their insight into my project and suggestions were appreciated.

I would be remiss without thanking all current and many of the former members of the Britton group. In particular, I would like to thank Mike Meanwell, Dimitri Panagopolous, Dr. Johannes Lehman and Dr. Bharanishashank Adluri for their extensive help. I would also like to thank undergraduates Lexi Gower-Fry and Terry Rai for their enthusiasm and help in assembling some of the compounds presented in this thesis. Be it practical or otherwise, I was the recipient of a great deal of support throughout my two plus years at SFU. I am forever grateful to all of you who helped me achieve what I have.

I would also like to thank Dr. Rebecca Davis, without whom I would never have pursued graduate school. Her enthusiasm and aptitude at solving organic chemistry problems is unmatched, something I respect greatly, and hope has rubbed off on myself. The opportunity to work in her lab for two years as an undergraduate was invaluable, and ultimately set me on this path.

Finally I would like to thank my family and friends outside the lab. For their support, their encouragement, and patience throughout my pursuit of this degree.

Table of Contents

List of Tables

List of Figures

List of Schemes

List of Abbreviations

$[\alpha]_D^{20}$	Specific rotation at the sodium D line (589 nm) at 20°C
°C	Degrees Celsius
Ac	Acetyl
AcOH	Acetic Acid
Ar	Aryl
Bn	benzyl
Boc	*tert*-Butyloxycarbonyl
c	Concentration
Cbz	Carboxybenzyl
DBnAD	Dibenzyl azodicarboxylate
DtBAD	Ditertbutyl azodicarboxylate
DFT	Density functional theory
DIC	*N,N'*-Diisopropylcarbodiimide
DKR	Dynamic kinetic resolution
DMAP	Dimethylaminopyridine
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
DMP	Dess-Martin periodane
ee	Enantiomeric excess
eq	Equivalents
EtOAc	Ethyl acetate
HPLC	High-performance liquid chromatography
KIE	Kinetic isotope effect
KR	Kinetic resolution
MeOH	Methanol
NCS	*N*-chlorosuccinimide
NEt_3	Triethylamine
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
Ph	Phenyl
Ra-Ni	Raney Nickel
TBAF	Tetrabutylammonium fluoride

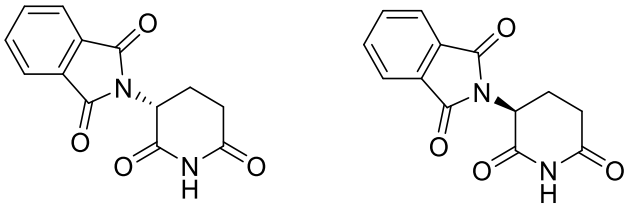
TBS	*tert*-butyl dimethyl silyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
TsOH	*p*-Toluenesulfonic acid monohydrate
VWD	Variable wavelength detector

Chapter 1.

Introduction

1.1. Asymmetric Catalysis

In chemistry, chirality refers to a geometric property of molecules relating to their symmetry.[1] Chirality often originates through unique structural features in a molecule, and can manifest in point chirality, plane chirality or axial chirality, none of which permit an improper axis of rotation. The physical and chemical properties of chiral molecules cannot be distinguished in an achiral environment, but enantiomeric molecules often have unique interactions in a chiral environment, such as enzymatic active sites. For example, thalidomide (**1**+**2**) was a drug marketed as a sedative to pregnant women to aid with morning sickness (Figure 1.1).[2] Tragically, it was discovered that the racemic drug caused teratogenic effects. Thus, while one enantiomer was indeed effective against morning sickness, the other caused birth defects. Further complicating the use of thalidomide, the drug undergoes racemization *in vivo*, precluding the use of enantiomerically pure material. Considering the importance of chirality in drug leads and natural products, significant effort has been expended in the development of new means to selectively and intentionally introduce chirality in organic synthesis.[3,4]



1 **2**

Figure 1.1 ***(R)*** **and** ***(S)*** **Enantiomers of thalidomide respectively.**

Catalysis is defined as a process by which chemical reactions are accelerated using a catalyst.[5] Catalysts facilitate reactions by opening new mechanistic pathways via formation of distinct intermediates between the catalyst and its substrate. A central tenet of catalysis is that the catalyst itself is regenerated in the reaction and can therefore be cycled through a reaction multiple times, allowing for its use in sub-stoichiometric

amounts. In this way, catalysis is both an atom and resource efficient means to perform chemical reactions and is a common tool for organic synthesis.

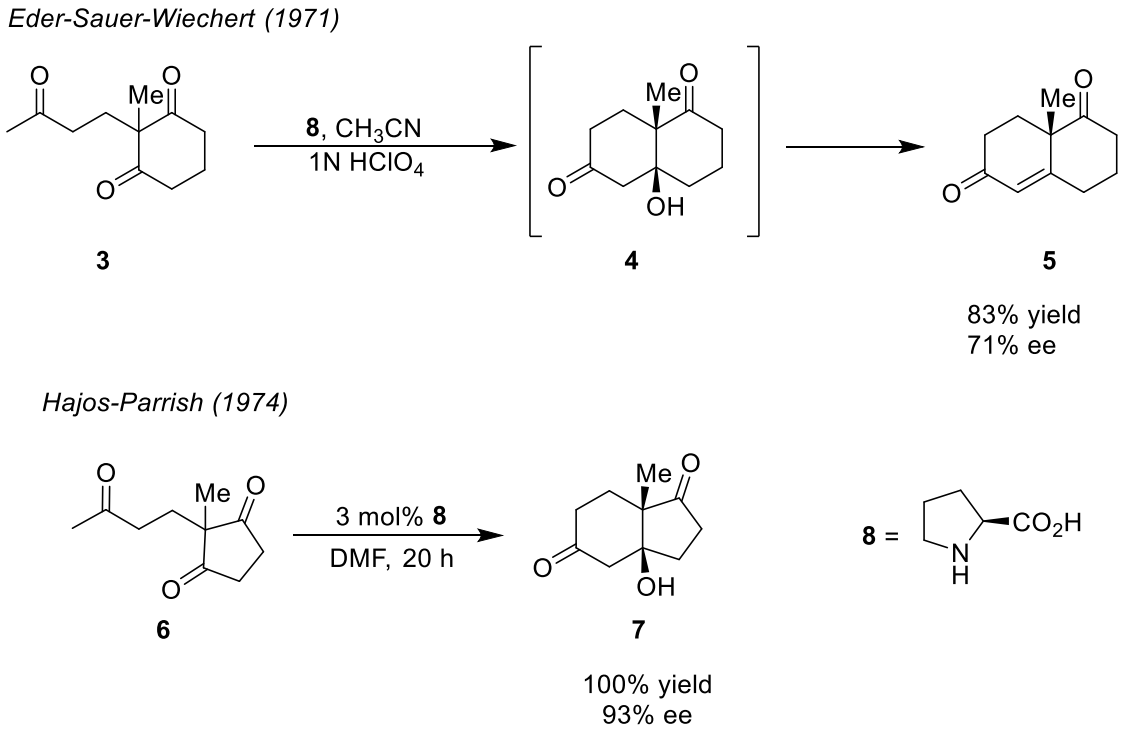
One of the first examples of asymmetric catalysis is the asymmetric hydrogenation of alkenes using rhodium complexes demonstrated by Knowles and coworkers at Monsanto in 1977.[6] Here, they showed that rhodium complexes adorned with appropriate chiral ligands could induce high levels of enantioselectivity in a hydrogenation reaction of several different prochiral olefins. The process was later commercialized and used in the industrial synthesis of L-DOPA, an important drug for treating Parkinson's disease symptoms.[7] For his work, Knowles, along with Noyori (asymmetric hydrogenation) and Sharpless (asymmetric oxidations) shared the 2001 Nobel Prize in Chemistry.[8–11]

Currently, three main categories of asymmetric catalysis include organometallic catalysis, which employs metal complexes with chiral ligands to induce asymmetry, enzyme catalysis, and organocatalysis, which uses small organic molecules as catalysts.

1.2. Asymmetric Organocatalysis

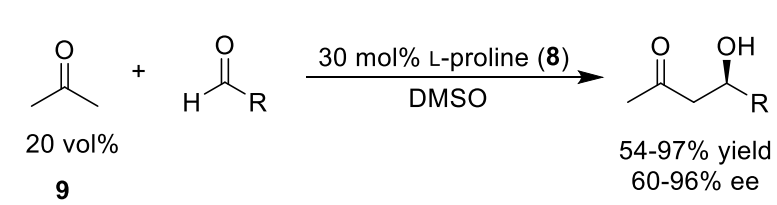
1.2.1. Introduction to Organocatalysis

Organocatalysis can often provide distinct advantages over organometallic catalysis or enzyme catalysis that include reduced sensitivity to moisture, absence of toxic metals, and broad applicability. The often cited first examples of organocatalysis are the Hajos-Parrish and Eder-Sauer-Wiechert reactions described in 1974 and 1971 respectively (Scheme 1.1).[12,13] Each of these reactions employs proline as a catalyst, which promotes an intramolecular aldol reaction. In the case of the Eder-Sauer-Wiechert reaction, the aldol reaction is followed by dehydration to give enone **5**, while the Hajos-Parish reaction provides hydroxyl-dione **7** in high optical purity.



Scheme 1.1 Eder-Sauer-Wiechert (1971) and Hajos-Parrish (1974) Reactions respectively.

After the initial discovery of the proline-catalyzed intramolecular aldol reaction, little else was done in this field until the turn of the century. In 2000, the intermolecular aldol reaction was described by List, Lerner and Barbas (Scheme 1.2).[14] Using acetone **9** and various α-branched aldehydes, the authors were able to promote an intermolecular aldol reaction using proline **8**. This seminal publication also explored different amino acid-based catalysts, showing proline to be the best catalyst for both yield and enantioselectivity.

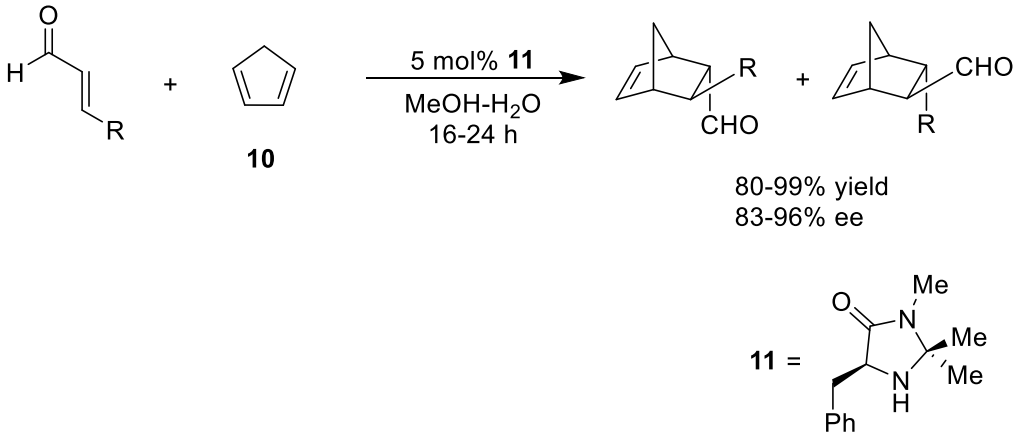


Scheme 1.2 First Organocatalyzed Intermolecular Aldol by List (2000).

Shortly after, MacMillan demonstrated the first organocatalyzed Diels-Alder reaction (Scheme 1.3).[15] While proline was not employed in this reaction, several proline-like molecules were examined as catalysts, including proline methyl ester and a C_2 symmetric proline derivative. The optimal catalyst for this reaction was determined to be

an imidazolidinone derived catalyst **11**, which promoted Diels Alder reactions between various α,β-unsaturated aldehydes and cyclopentadiene **10** in excellent yield and enantioselectivity. This type of imidazolidinone catalyst has since been utilized in a wide variety of asymmetric organocatalytic reactions.[16–19] Notably, this report by MacMillan also marked the first appearance of the word organocatalysis in the literature. Together, the publications by List and MacMillan marked the beginning of an organocatalysis "gold rush", [20,21] as countless additional processes have since been developed.

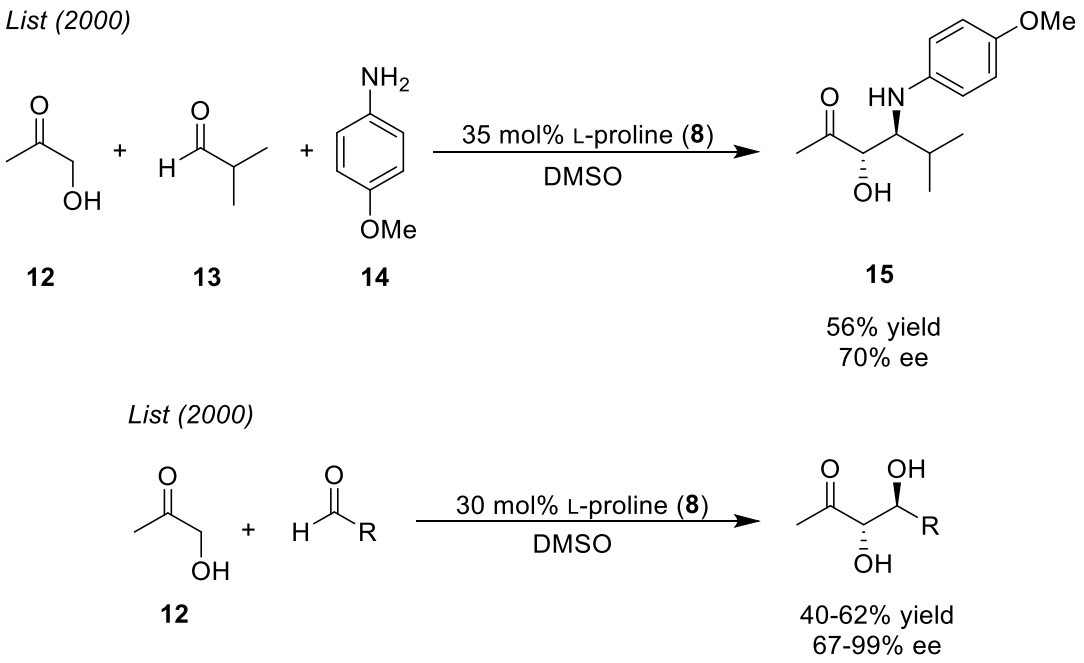
MacMillan (2000)



Scheme 1.3 MacMillan's Organocatalyzed Diels-Alder Reaction (2000).

1.2.2. Organocatalyzed Aldol Reactions

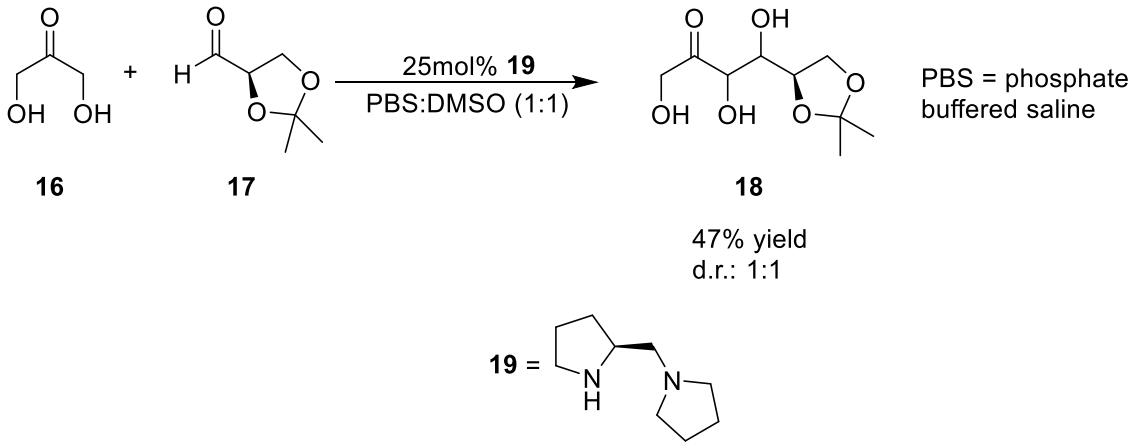
The next significant development in proline organocatalysis was List's variation of the Mannich reaction (Scheme 1.4).[22] This was the first example of an organocatalyzed reaction using an imine as an electrophile, rather than an aldehyde or ketone. This iteration of the Mannich reaction also demonstrated that preformation of the imine acceptor was not necessary, and the reaction could be carried out in one pot with remarkable efficiency. As well, this was the first demonstration that ketones other than acetone could participate as nucleophiles in an organocatalytic aldol reaction. List was able to further demonstrate the utility of hydroxyacetone as a suitable substrate for an aldol reaction in his publication detailing the synthesis of 1,2-diols (Scheme 1.4).[23]



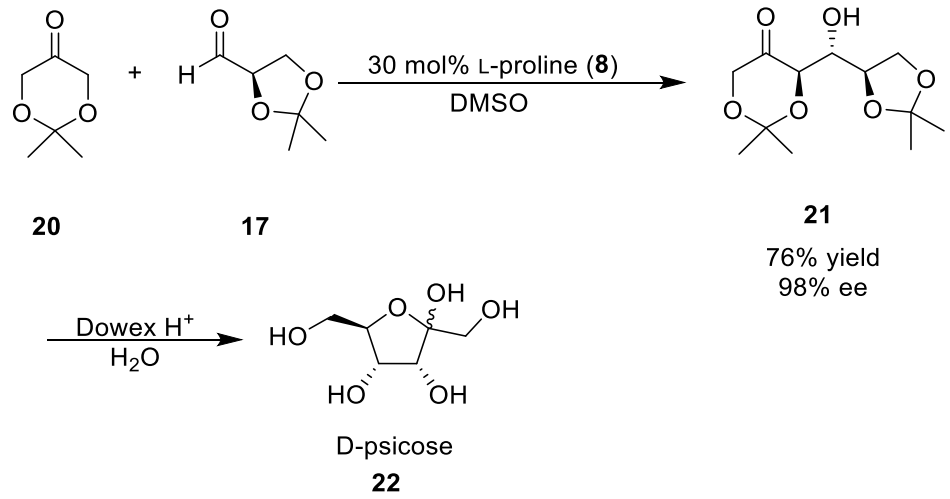
Scheme 1.4 List's Mannich and Aldol Reactions using Hydroxyacetone.

Cordova and coworkers investigated dihydroxyacetone **16** as a substrate in the proline-catalyzed aldol for its potential utility in synthesizing carbohydrates and carbohydrate analogues (Scheme 1.5).[24] While conversions were generally high, poor diastereoselectivity was observed for many substrates. These limitations were overcome three years later when Enders successfully demonstrated the aldol reaction between aldehyde **17** and 2,2-dimethyl-1,3,dioxan-5-one (dioxanone) **20** in excellent yield and enantioselectivity.[25,26] Enders applied this methodology in the synthesis of polyols such as D-psicose **22**.

Cordova et al. (2002)



Enders (2005)



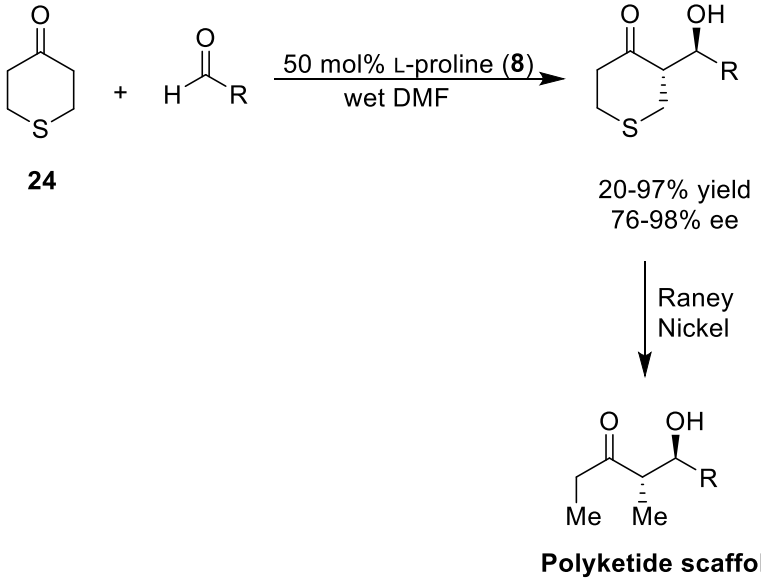
Scheme 1.5 Cordova's and Ender's Reactions of Dihydroxylated Ketones in Aldol Reactions.

In their initial investigations, List and Barbas each independently reported that alkyl ketones made suitable substrates for proline aldol reactions (Scheme 1.6).[22,24] Each showed that cyclohexanone **23** could engage in aldol reactions with moderate yields and excellent enantioselectivity. Additionally, both List and Barbas noted the poor reactivity of 3-pentanone.

Scheme 1.6 Cyclohexanone (23) in an Aldol Reaction.

Recognizing the potential of an organocatalytic 3-pentanone aldol and its applications in polyketide synthesis, Ward and coworkers adapted the lithium promoted tetrahydro-4H-thiopyran-4-one (thiopyranone) **24** aldol reaction to be compatible with organocatalysis in 2004 (Scheme 1.7).[27–31] After considerable optimization, the aldol adducts of thiopyranone could be isolated in up to 97% yield with excellent enantioselectivity and diastereoselectivity. This aldol reaction could also be performed iteratively to build up larger molecules that were subsequently reduced with Raney Nickel to provide access to polyketide-like scaffolds. This strategy has been used in the synthesis of several polyketide-derived natural products.[32]

Ward (2004)

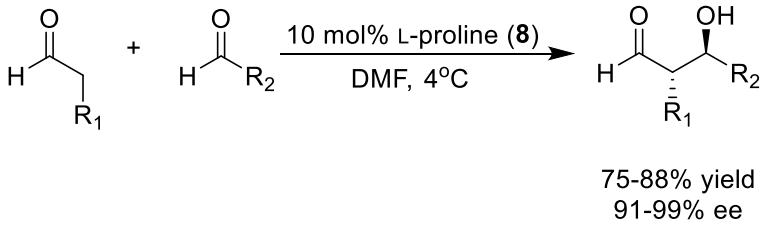


Scheme 1.7 Ward's Thiopyranone (24) Aldol reaction and Application to Polyketide synthesis.

As noted by MacMillan, an aldol between two aldehydes is a challenging synthetic problem due to the tendency of aldehydes to polymerize uncontrollably, and the difficulty

in distinguishing the donor and acceptor aldehydes.[33] Using organocatalysis, MacMillan was able to demonstrate a controlled dimerization of aldehydes employing proline as the organocatalyst (Scheme 1.8).[33] Specifically, MacMillan was able to take advantage of the mild reaction conditions inherent to organocatalysis to avoid polymerization of the aldehydes, while the issue of selectivity was addressed by adding the desired electrophilic partner via syringe pump to the reaction mixture. This iteration provided access to β-hydroxy-aldehydes, which are valuable synthetic intermediates as was demonstrated in MacMillan's application of these adducts in the synthesis of differentially protected hexoses.[34,35] This newfound control of aldehydes as nucleophiles inspired a new subset of organocatalysis.

MacMillan (2002)

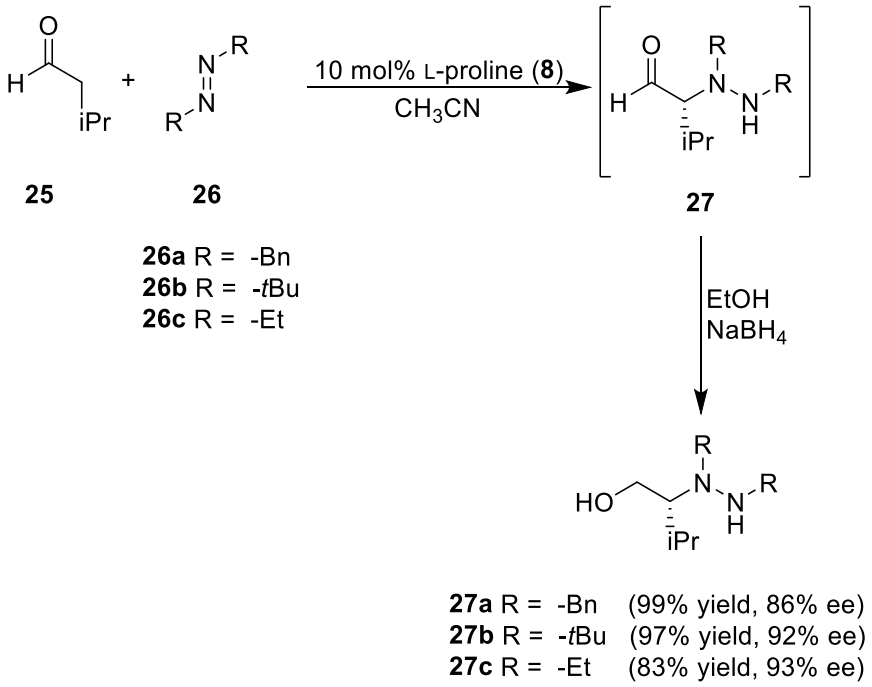


Scheme 1.8 MacMillan Demonstrating Aldehydes as Aldol Reaction Donors.

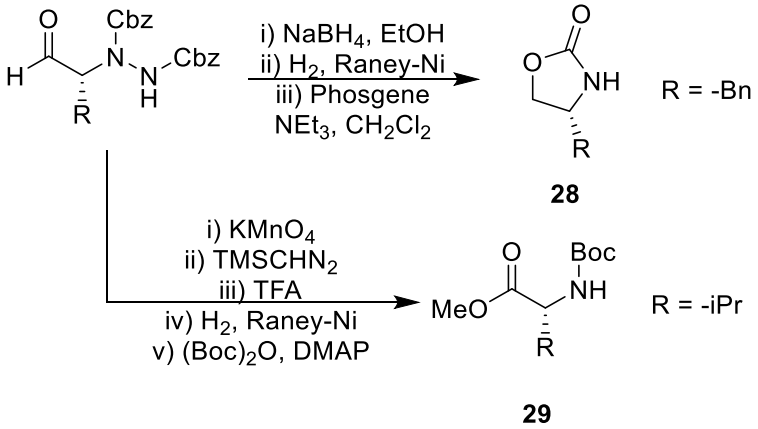
1.2.3. Organocatalyzed α-Functionalization of Aldehydes

α-Functionalized aldehydes are versatile building blocks for the synthesis of biologically relevant scaffolds. To this end, organocatalysis has enabled the α-halogenation[18,36–38], -amination[39–41], -hydroxylation[19,42–44], and -sulfenylation[45] of aldehydes. The first demonstrations of this were by List and Jørgensen, in their adaptations of the amination reaction to organocatalytic conditions (Scheme 1.9).[39–41] Each independently reported the proline-catalyzed α-amination of several alkyl aldehydes utilizing azodicarboxylates **26a-c** as electrophiles to yield α-aminated aldehydes in excellent yields and enantioselectivity. α-Aminated aldehydes are useful building blocks in the synthesis of natural products containing chiral C-N stereocentres including amino acids, alkaloids and carbohydrate scaffolds. This was demonstrated in Jørgensen's short synthesis of an enantioenriched amino acid **29** (Scheme 1.10). Furthermore, the amination reaction has been demonstrated with ketones by Jørgensen and applied to the synthesis

of enantioenriched oxazolidinones (e.g., compound **28**), which are valuable as chiral auxiliaries (Scheme 1.10).



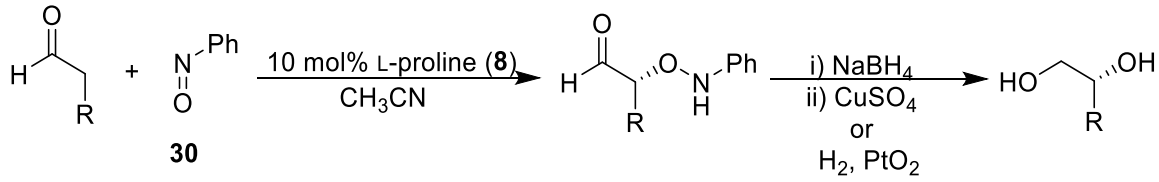
Scheme 1.9 Amination of Aldehydes by List and Jørgensen (2002).



Scheme 1.10 Amination of Aldehydes and Applications to the Synthesis of Evan's Auxilary and a Protected Amino-acid.

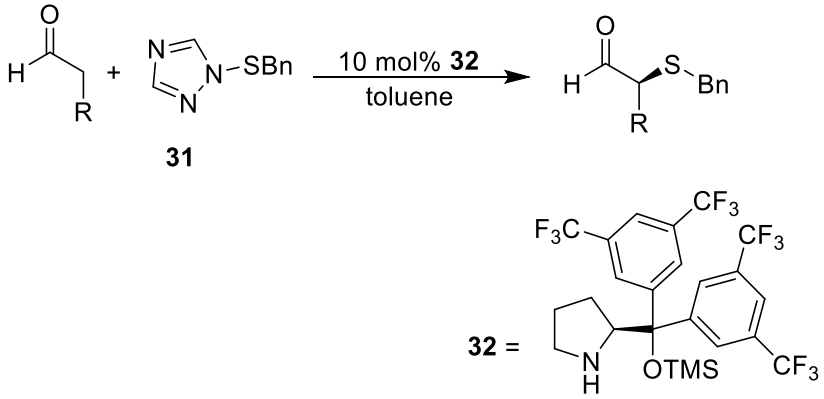
Several organocatalytic methods for α-hydroxylation and -sulfenylation of aldehydes have been developed. Notable examples by MacMillan[19], Cordova[43], Hayashi[44], and others[42,46] have led to useful methods for the synthesis of α-hydroxy

aldehydes which are useful synthetic building blocks for the preparation of carbohydrates.[35] In each case, nitrosobenzene **30** is employed as the electrophilic oxygen source to enable aminoxylation of both ketones and aldehydes in excellent yield and enantioselectivity (Scheme 1.11). The N-O bond can be subsequently cleaved using hydrogenation conditions[42], or $CuSO_4$[43] to give 1,2-diols.



Scheme 1.11 Hayashi and Coworkers Aminooxylation Reaction.

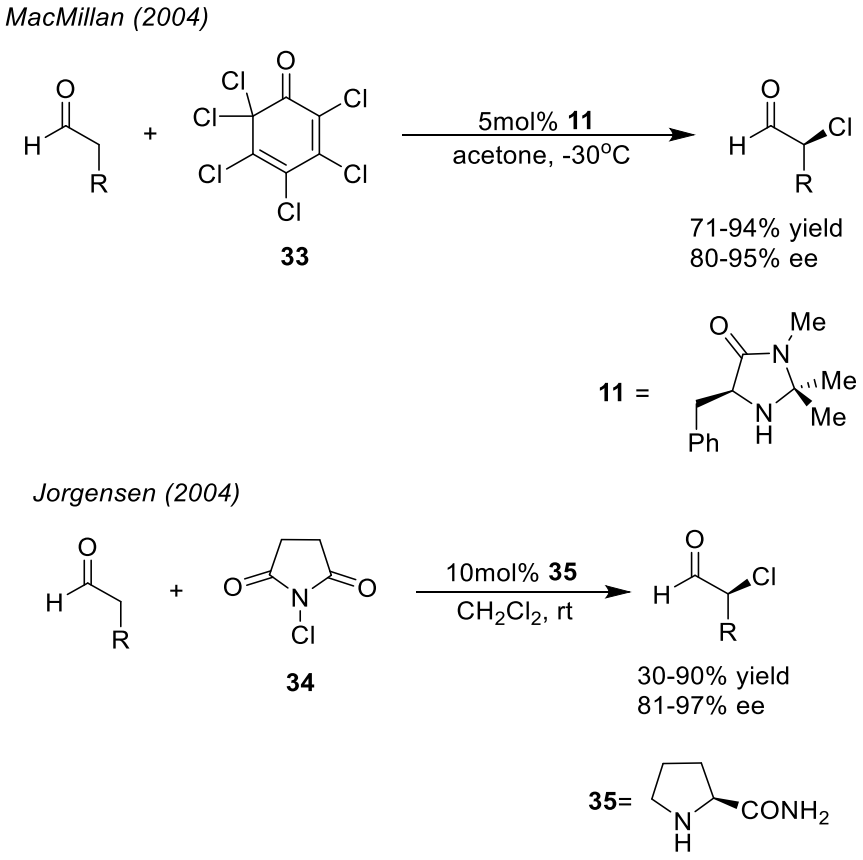
In 2005, Jørgensen and coworkers reported the analogous asymmetric α-sulfenylation of simple aldehydes (Scheme 1.12).[45] For this purpose, Jørgensen designed a novel proline-derived organocatalyst **32** (now known as Jørgensen's catalyst) to overcome the poor yields and enantioselectivity observed when using proline or other proline derivatives. The increased steric bulk of the catalyst imparted greater bias for the addition of incoming nucleophiles. Additionally, the silyl protecting group increased the efficiency of the catalyst by preventing undesired reactivity of the exposed alcohol. Since this first disclosure, Jørgensen's catalyst has found utility in many other organocatalyzed reactions.[47]



Scheme 1.12 Jørgensen's Sulfenylation of Aldehydes.

MacMillan's seminal work on the synthesis of enantioenriched α-chloroaldehydes relied on use of imidazolidinone catalyst **11** and a quinone-derived electrophilic chlorinating reagent **33**.[37] Shortly after, Jørgensen reported using prolinamide **35** and N-chlorosuccinimide (NCS) **34** to effect the same transformation.[38] Interestingly, proline was

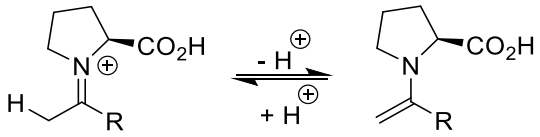
reported to give moderate to excellent conversions of the α-chloroaldehydes, but with poor enantiostereoselectivity (<10%). Jørgensen demonstrated the utility of the α-chloroaldehyde building block in a short synthesis of protected amino acids.[38]



Scheme 1.13 α-Chlorination of Aldehydes by MacMillan and Jørgsensen.

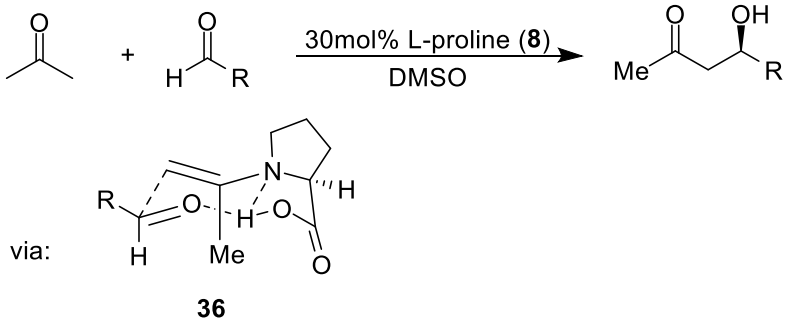
1.2.4. Mechanism of Enamine Catalysis

It is generally agreed that the first step in proline-catalyzed reactions is the condensation of proline with the carbonyl of the donor molecule whether it is an aldehyde or ketone. Upon condensation, proline can form an iminium ion as well as the tautomer enamine, each of which can facilitate different types of reactivity (Scheme 1.14).[20,48] The initially formed iminium ion has a LUMO which is lower in energy than the original carbonyl, thus making it more susceptible to direct nucleophilic addition. Tautomerization to the enamine allows for HOMO-raising activation of the substrate. Experimental confirmation of the existence of these intermediate enamines has been achieved via crystallization of enamines between proline and different ketones.[49]



Scheme 1.14 Iminium and Enamine activation modes facilitated by Proline.

There are different models for how secondary amine organocatalysis directs the facial selectivity of reactions depending on the catalyst employed. In the cases of Jørgensen and MacMillan's catalysts, steric shielding by the bulky substituents on the catalyst favours addition of the incoming electrophile to the less hindered face. Proline on the other hand, does not sterically shield one face over another but instead directs selectivity via hydrogen bonding to the incoming electrophile. The initial proposal by List suggested that the reaction proceeds through an enzyme like transition state, invoking a Zimmerman-Traxler structure **36**, with the carboxylic acid of proline hydrogen bonding to the aldehyde carbonyl.[14]



36

Figure 1.2 Zimmerman-Traxler Transition State (36) Proposed by List for Proline Catalyzed Aldol Reactions.

This transition state was modeled using DFT by Houk and coworkers who suggested that this mode of hydrogen bonding seemed a likely model to explain the high enantioselectivity of proline catalyzed reactions (Figure 1.3).[50] Furthermore, DFT modelling confirmed that proline encourages HOMO-raising reactivity of the donor, and facilitates LUMO lowering of the incoming electrophiles with the Lewis acidic nature of the hydrogen bonding.

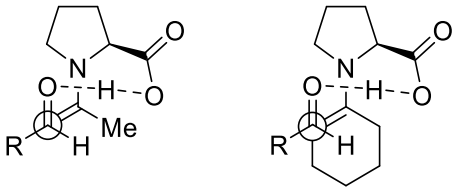


Figure 1.3 Modelled Houk-List Transition States for Acetone and Cyclohexanone.

There is further debate as to whether this model fully encapsulates all the intermediate species in the catalytic cycle. A low energy intermediate oxazolidinone **37a** was modelled by Houk, and its role in the catalytic cycle is still the subject of debate. Some suggest that the oxazolidinone is a "dead end" intermediate, playing no role in the reaction.[51,52] Others, including Seebach, suggest that the oxazolidinone plays a key role in the formation of the enamine species.[53] Seebach has even suggested the oxazolidinone **37b** is involved in the stereodetermining step, as demonstrated in the Seebach-Eschenmoser mechanism (Figure 1.4).[53,54]

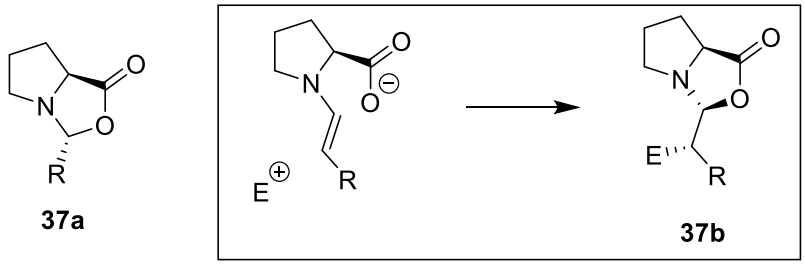
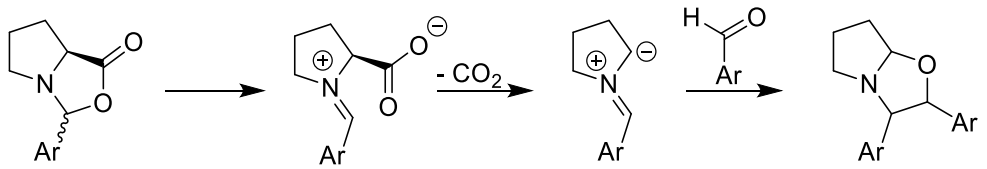


Figure 1.4 Seebach-Eschenmoser Mechanism and Oxazolidinone (37a,b).

DFT and NMR studies by Gschwind indicate that both the enamine and oxazolidinone species exist in solution during the reaction, though the concentrations of these intermediates depend heavily on the identities of the solvent, catalyst, and aldehydes.[55–58] As well, kinetics studies by Blackmond of proline catalyzed aldol reactions corroborate previous studies, and further reveal that the intermediate oxazolidinones can decompose to form irreversibly deactivated species of proline and aldehyde (Scheme 1.15).[59–62] Recent mechanistic studies by Blackmond and Christmann of the α-chlorination reaction, using MacMillan's and Jorgensen's catalysts, have revealed the presence of a reversibly forming succinimide-catalyst-aldehyde adduct which could play a similar role in the mechanism to the oxazolidinone.[60,63]

Both Gschwind and Blackmond report a dependence on water for the concentrations of these types of intermediates in solution. Attempts have been made to

elucidate the role of water in the catalytic cycle of organocatalysis, but no agreed upon universal mechanism has been identified. For example, it has been suggested that water suppresses the formation of the intermediate oxazolidinone,[59] that water increases the rate of hydrolysis of the catalyst, or that water is explicitly involved in the transition state for addition.



Scheme 1.15 Blackmond's Proposed Mechanism for the Decomposition of Oxazolidinone.

The currently accepted mechanism invokes the Houk-List transition state as the stereodetermining step (Figure 1.5). As well, it is the consensus of recent literature that the Seebach-Eschenmoser oxazolidinone **38** should be included in the mechanistic pathway for proline catalyzed reactions, though its exact role in the mechanism is not definitively known.

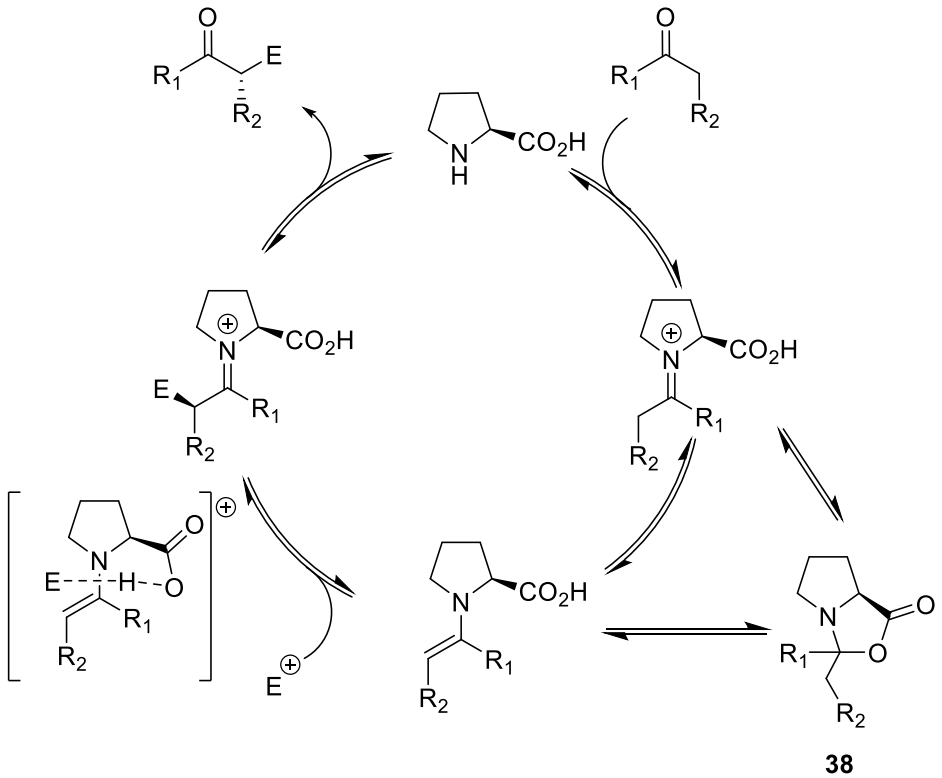


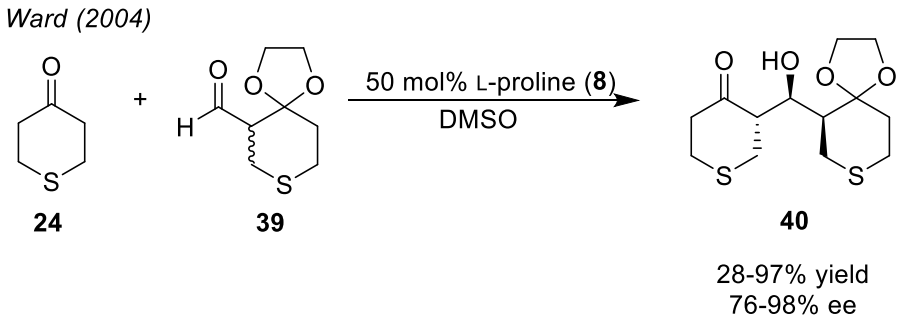
Figure 1.5 Generally Accepted Mechanism for Proline Catalysis.

1.2.5. Kinetic and Dynamic Kinetic Resolutions Facilitated by Secondary Amines

Kinetic resolutions take advantage of differing reaction rates for each enantiomer of a starting material with a chiral reagent and derive from the differences in energy of resulting diastereomeric transition states.[64,65] The differing reaction rates allow for the introduction of enantioenrichment in a product from a racemic starting material. A major limitation of this process is that the theoretical maximum yield is 50% if the starting material is a racemate. A dynamic kinetic resolution (DKR) introduces an interconversion between each of the starting enantiomers. In this way, the theoretical conversion is 100% (Figure 1.6).

Figure 1.6 Kinetic Resolution and Dynamic Kinetic Resolution, where $k_1 \neq k_2$.

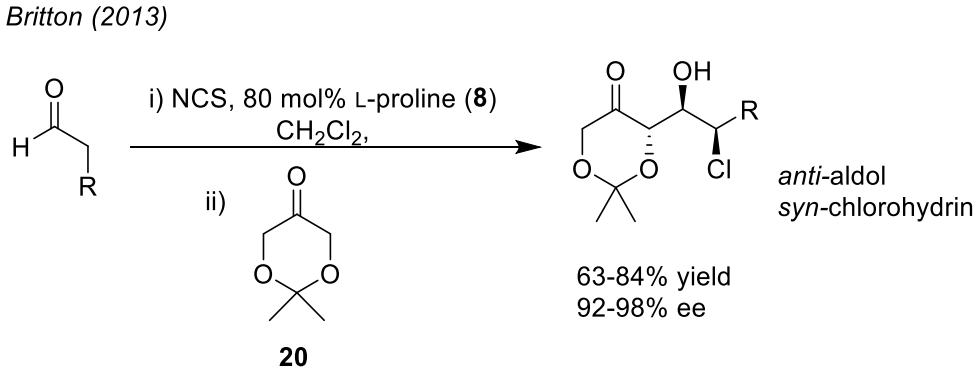
There have been few examples of DKR reactions in synthetic chemistry utilizing secondary amine catalysts.[64,65] In Ward's organocatalyzed aldol reaction using thiopyran aldehydes, a DKR process is facilitated by proline (Scheme 1.16).[29–31,66] Ward initially aimed to effect a kinetic resolution of racemic thiopyran aldehydes **39** by taking advantage of the ability of the proline catalyzed aldol to discriminately react with each enantiomer of the aldehyde. Surprisingly, they were able to isolate a single diastereomer of the aldol adduct in excellent yield, enantioselectivity and diastereoselectivity. Ward rationalized the high diastereoselectivity of the reaction using Evan's model for double stereodifferentiating partners in aldol reactions.[67] The reaction of the matched aldehyde would occur much faster, leading to the kinetic resolution. Crucially, proline was also able to facilitate the racemization of the aldehyde, leading to a DKR.



Scheme 1.16 Ward's DKR Aldol Reaction using Thiopyran Aldehydes.

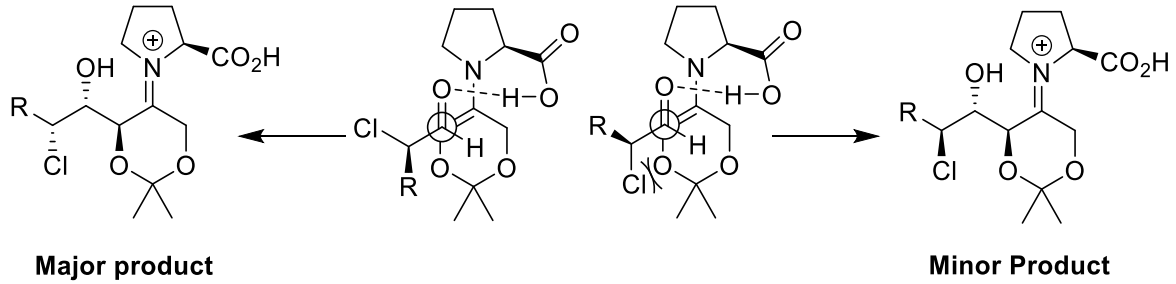
1.3. Britton DKR α-Chlorination-Aldol Reaction

The Britton DKR α-chlorination-aldol reaction facilitates the one-pot chlorination of an aldehyde followed by a proline catalyzed DKR aldol reaction with dioxanone **20** (Scheme 1.17).[68] It has been shown that this reaction takes advantage of a DKR, such that the poorly stereoselective chlorination reaction with proline is inconsequential, and leads to excellent diastereoselectivity for the reaction.



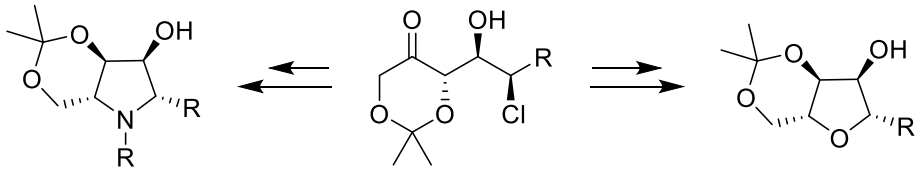
Scheme 1.17 Britton DKR α-Chlorination-Aldol Reaction.

The currently understood mechanism and rationalization for the stereoselectivity of this reaction invokes the Houk-List transition state for aldol reactions to explain the exclusive *anti*-aldol selectivity that is observed for these aldol reactions. To rationalize the typically moderate-excellent selectivity for the *syn*-chlorohydrin, a transition state is proposed whereby steric repulsion between the R-group of the aldehyde and the enamine, and electrostatic repulsion between the oxygen of dioxanone and the chloro-substituent of the aldehydes are minimized (Scheme 1.18).



Scheme 1.18 Currently Understood Mechanism for α-Chlorination-Aldol Reaction.

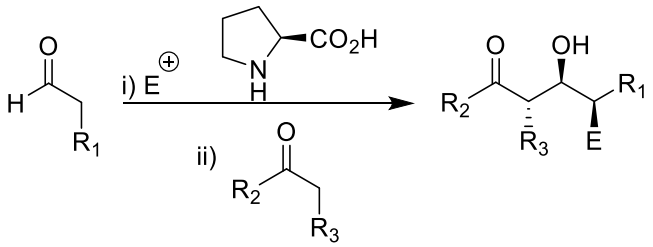
In further studies, the utility of this method was demonstrated in the concise synthesis of both THF's and iminocyclitols (Scheme 1.19).[69–71] By reduction of the ketone and subsequent cyclization of the diol, carbohydrates and analogues can be readily formed after the closure of the THF ring. Similarly, after a reductive amination-cyclization sequence the corresponding pyrrolidines can also be formed.



Scheme 1.19 Current applications of α-Chlorination-Aldol.

1.4. Thesis Overview

While the α-chlorination-aldol reaction has extensive utility in the synthesis of the discussed systems, it is limited in utility to production of compounds that occupy a narrow region of chemical space, namely carbohydrates and carbohydrate analogues. The topic of this thesis is the exploration and expansion of the α-chlorination-aldol reaction in each of the ketone and electrophile dimensions (Scheme 1.20). In *Chapter 2*, the compatibility of the α-amination of aldehydes with the dioxanone aldol is investigated as well as the potential applications towards pyrrolidine synthesis. The proposed synthesis would access similar pyrrolidines as the α-chlorination-aldol, but with altered stereochemistry in a concise manner. The focus of the research presented in *Chapter 3* is the exploration of the ketone dimension of the α-chlorination-aldol reaction and optimization of the reaction conditions such that four different ketones can engage in the reaction.



Scheme 1.20 Goal of this thesis- a more general tandem methodology.

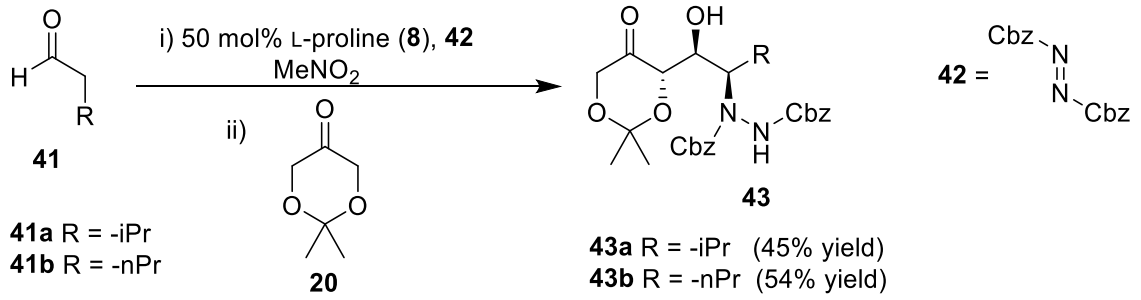
Chapter 2.

Azodicarboxylates in a Tandem Aldol Reaction and Potential Applications

2.1. α-Amination-Aldol Exploration

2.1.1. Discovery and Optimization

In the interest of expanding the concept of the tandem α-chlorination-aldol methodology to other electrophiles, the compatibility of the α-amination of aldehydes developed by List and Jørgensen was explored with a dioxanone aldol by Chris Adamson (MSc: 2016) (Scheme 2.1). Adamson noted simple alkyl aldehydes (**41a**, **41b**) worked well as monitored by thin-layer chromatography (TLC). However, the crude ^{1}H NMR spectra of **43a** and **43b** were difficult to interpret – this did not improve upon purification. We suspected that rotamers of each carbamate broaden the peaks as shown in Figure 2.1.



Scheme 2.1 Amination Aldol Reaction Developed by Adamson.

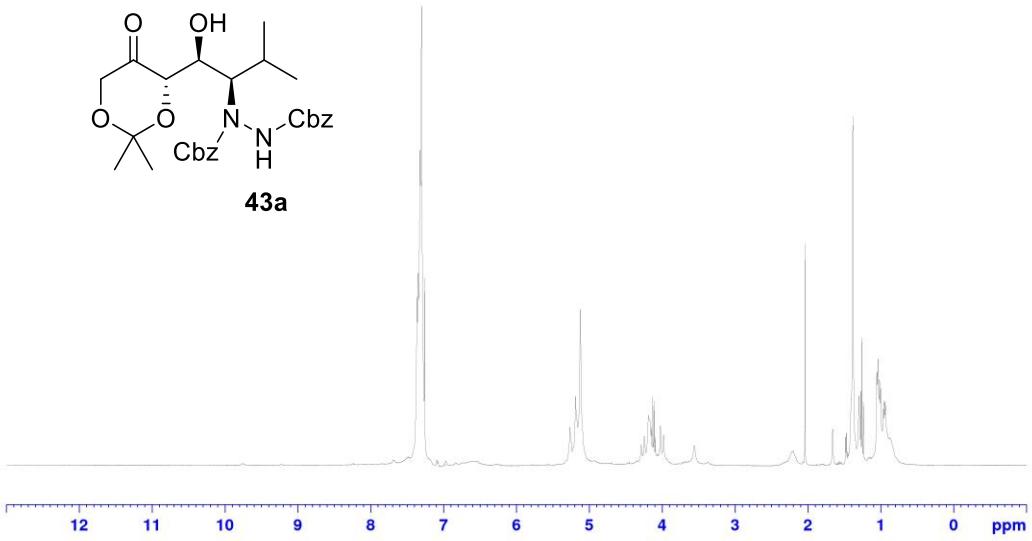


Figure 2.1 **^{1}H NMR (400 MHz) of the Purified Aldol adduct (43a) by Adamson.**

The scope of the amination-aldol reaction was examined with respect to the aldehyde component by Adamson. Unfortunately, other substrates were isolated in poor yields. The known scope of the amination is quite narrow and limited primarily to alkyl aldehydes. Consequently, this limited the scope of the corresponding α-amination-aldol process. Optimization of the reaction revealed that changing the reaction solvent to $MeNO_2$ (entry 4) led to a significant increase in the conversion to aldol product (Table 2.1).

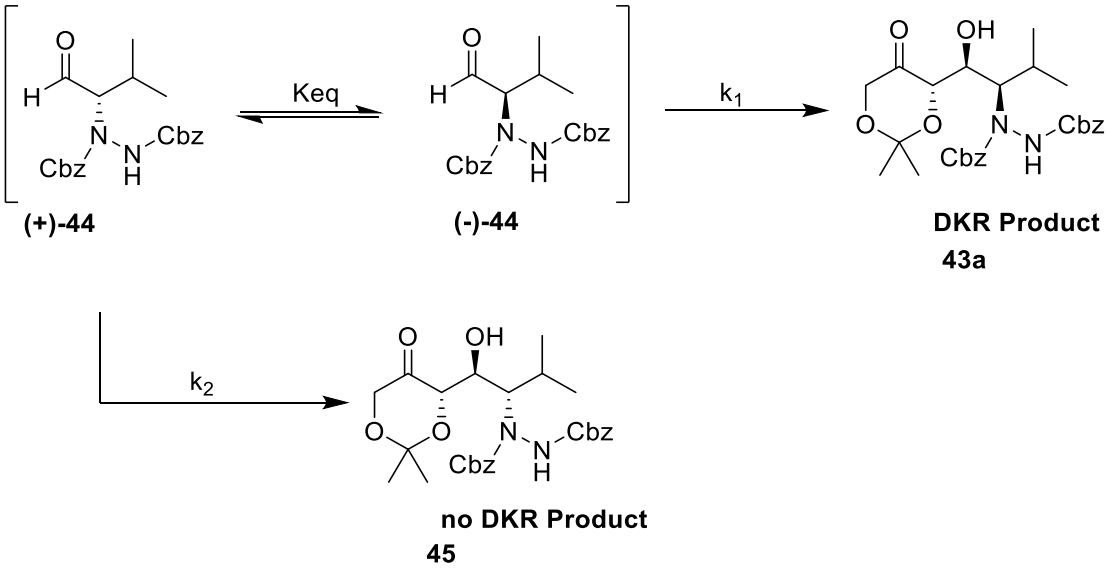
Entry	Solvent	Catalyst Loading	Concentration	Conversion
1	CH_2Cl_2	80mol%	0.1 M	20%
2	CH_2Cl_2	80mol%	0.5 M	92%
3	DMSO	80mol%	0.5 M	0%
4	$MeNO_2$	50mol%	0.5 M	100%

Table 2.1 **Abbreviated Optimization Table of α-Amination-Aldol reaction**

2.1.2. Determination of DKR

Considering the Britton group's previously developed α-chlorination-aldol proceeded via a DKR, it was important to identify if a DKR was operative in the α-amination-aldol reaction. Literature precedent indicated that α-aminoaldehydes do not racemize in the presence of a proline catalyst.[72] However, we sought to demonstrate this under our reaction conditions.

To assess the potential role of a DKR in this process, both enantiomers of the α-aminoaldehyde were synthesized and isolated according to the procedure published by Jørgensen.[41] Subsequently, in separate experiments, the D- and L- α-aminoaldehydes were submitted to aldol conditions using L-proline as the catalyst. If these reactions involved a DKR, then the same product **43a** should be isolated from reaction of both ***+/-*** **44** regardless of initial aldehyde configuration (Scheme 2.2). That is, proline should effect racemization of the aldehydes **(+)-44** and **(-)-44**, and the proline-catalyzed aldol reaction should allow for discrimination via diastereomeric transition states. If a DKR does not operate under these conditions, then we should observe **45** when **(+)-44** is submitted to the aldol reaction and **43a** when **(-)-44** is submitted to the reaction.



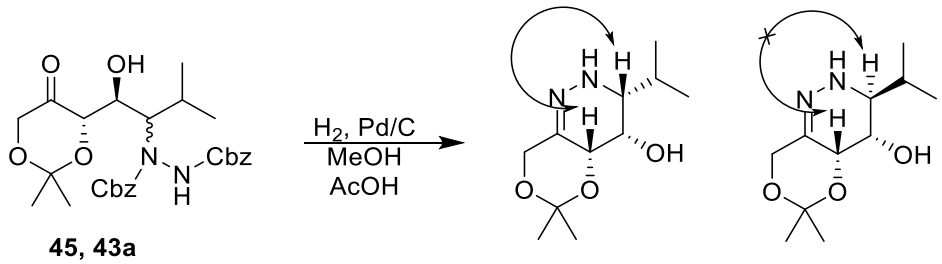
Scheme 2.2 Possible Outcomes of Aldol Reaction with Aldehyde Adducts Formed by D-proline.

Starting Material	Outcome
(+)-44	3% yield, d.r. 1:1 of **43a:45**
(-)-44	45% yield **43a**

Table 2.2 Outcome of DKR Determination Experiments.

When **(+)-44** was submitted to the aldol reaction with L-proline, we observed very little product formation (<10%). Furthermore, the aldol adduct was formed as a 1:1 mixture of diastereomers at the N-stereocentre. This observation suggests that a very slow racemization of the α-aminoaldehyde occurs and is consistent with Jørgensen's observation that the enantiomeric excess of α-aminoaldehydes decreases after prolonged exposure to proline.[41] In our case, while racemization of the α-aminoaldehyde by proline occurs, this process is too slow to be compatible with a DKR. That is, K_{eq} is slow to equilibrize, and $k_1 >> k_2$ (Scheme 2.2). To validate our experimental method, **(-)-44** was submitted to identical reaction conditions, and **43a** was indeed isolated in yields comparable to the normal reaction conditions.

The stereochemistry of the aldol adducts was confirmed by nOe experiments on the corresponding hydrazones **46** and **47**. After hydrogenation to remove the -Cbz protecting groups, the aldol adducts cyclize rapidly to the hydrazones **46** and **47** (Scheme 2.3). This bicyclic system is rigid and allows for assignment of stereochemistry by observation of key transannular nOe correlations. Stereochemical assignment of compound **47** was assigned through analogy, that is, it was a diastereomer of **46**. As the *anti*-aldol stereochemistry is set, the only possible diastereomer is that shown on **47**.

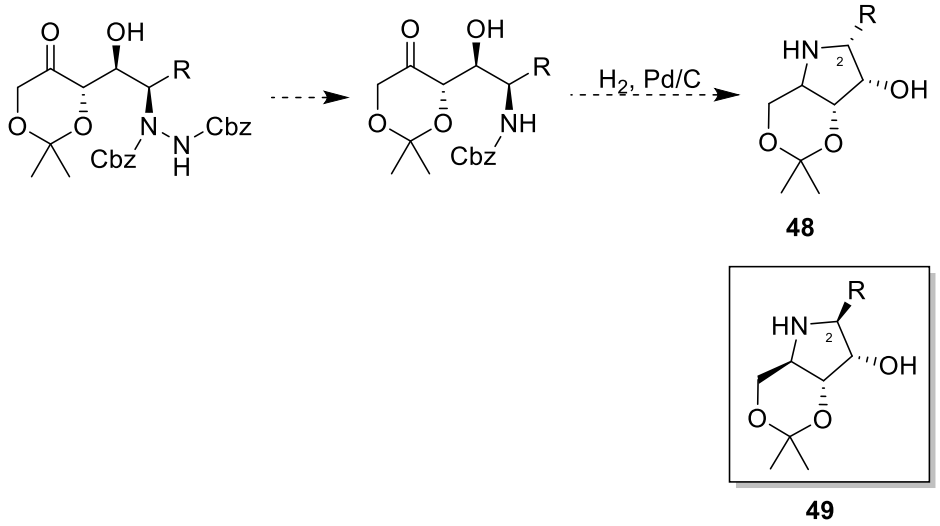


Scheme 2.3 Determination of Configuration by nOe coorelations.

2.2. Elaboration of Amination-Aldol Adducts

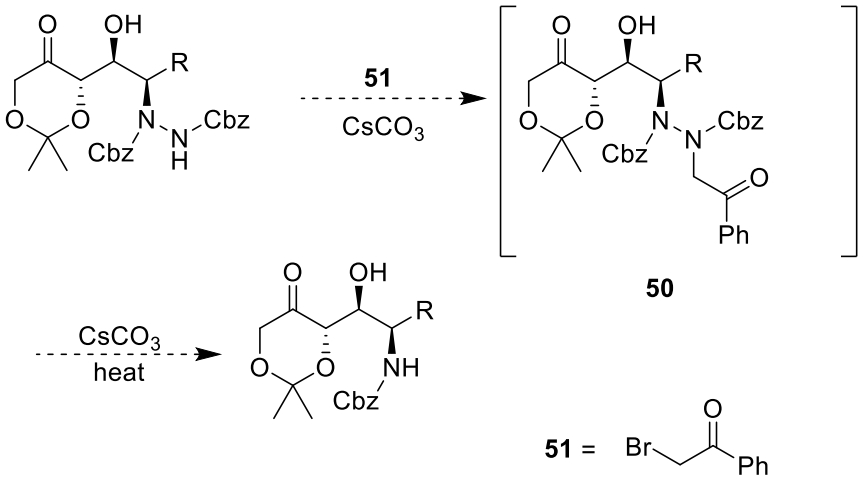
2.2.1. Strategies to Prepare Pyrrolidines

The Britton group has ongoing projects concerning the synthesis of libraries of pyrrolidine structures and envisioned using this methodology in a concise synthesis of new pyrrolidine scaffolds. Presumably, after N-N bond cleavage followed by intramolecular reductive amination, pyrrolidines could be synthesized in a 3-step total sequence from cheap and achiral starting materials (Scheme 2.4). Importantly, these pyrrolidines **48** would differ in configuration at the 2-position when compared to the pyrrolidines synthesized by Bergeron-Brlek and coworkers (e.g., **49**).[70]



Scheme 2.4 Initial Strategy for Pyrrolidine Synthesis.

First, we attempted the cleavage of the N-N bond via an alkylation-elimination sequence using an α-bromo ketone **51** (Scheme 2.5).[73–76] We envisioned alkylation of the free amide in the presence of base would give ketone **50**. The subsequent addition of base is reported to facilitate an elimination reaction upon heating to give the N-N bond cleavage product. Unfortunately, we did not observe any alkylated product under the established reaction conditions.



Scheme 2.5 Elimination Strategy for Cleaving N-N bond.

Other reducing agents are known to cleave N-N bonds, including SmI_2 [73,77], Raney-Nickel[76,78] and Birch reduction with sodium metal.[79] Furthermore, other hydrogenation conditions with Pd/C were attempted in efforts to optimize the conditions for N-N bond cleavage as shown in Table 2.2.

Entry	Reduction	Result
1	SmI_2	decomposition
2	Ra-Ni	hydrazone
3	Na, NH_3	hydrazone
4	H_2, Pd/C (0.01M-0.1M AcOH)	hydrazone
5	Zn dust, conc. AcOH	decomposition

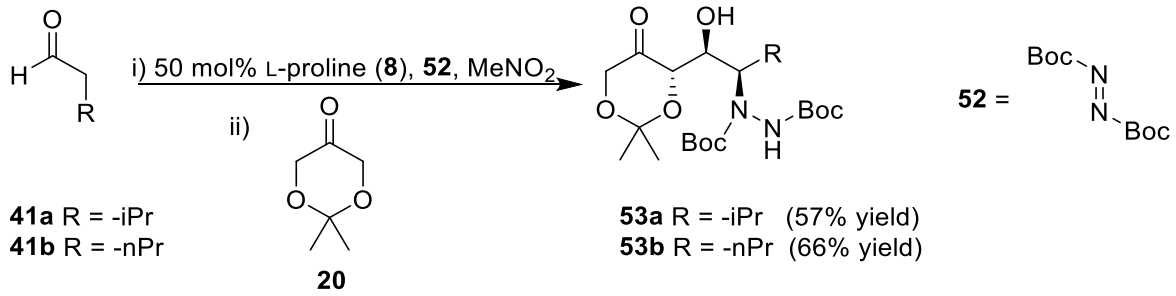
Table 2.3 Reduction Conditions for N-N Bond Cleavage.

As indicated in table 2.2 (entry 1), when SmI_2 was employed for cleavage of the N-N bond, we did not observe any identifiable organic material after reaction work up. The combination of Zn dust and concentrated acetic acid (entry 5)[80] was too also found to remove the acetonide protecting group and we observed formation of the triol followed by further decomposition (entry 5).

In entries 2-4, the hydrazone was the only isolable product. This indicated that the -Cbz protecting group was too labile under most reduction conditions for the direct cleavage of the N-N bond to be possible. Ideally, the N-protecting group would be retained upon cleaving the N-N bond for the subsequent intramolecular reductive amination step.

The amination-aldol reaction sequence was subsequently attempted using a different electrophile, the *bis*-Boc azodicarboxylate **52**, which proceeded in a similar

manner to the corresponding aldol reaction using Cbz-protected reagent **42** (Scheme 2.6). Interestingly, the NMR spectra of the product were well resolved for **53a**, but indicated a mixture of compounds, even after repeated purification.



Scheme 2.6 New Protecting group Strategy using *bis*-Boc Azodicarboxylate (52).

We hypothesized that in the case of a 1,6 relationship between an amine and carbonyl, that there could be an intramolecular cyclization occurring, as depicted in Figure 2.2, resulting in formation of a hemi-aminal. Both diastereomers at the aminal cente would be present, leading to two structures observable by ^{1}H NMR spectroscopy.

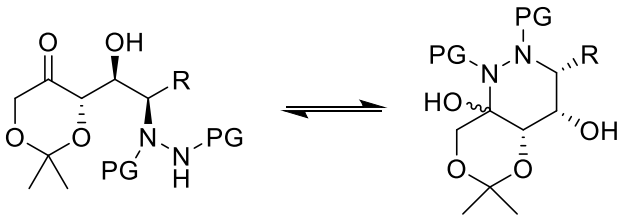
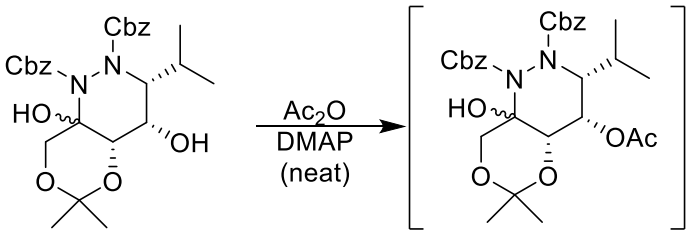


Figure 2.2 Equilibrium between Cyclized Aminal and Aldol Adduct.

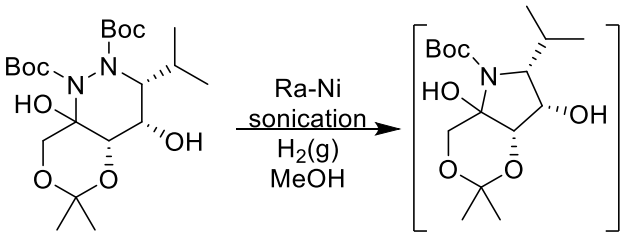
This also explained the failure of our initial N-N bond cleaving strategies, as these reactions require accessibility of the proton on the nitrogen. Further, the presence of diastereomeric hemiaminals also explains the complicated ^{1}H NMR spectrum of **53** (Figure 2.1), which included both rotamers and hemiaminals. Unfortunately, we were unable to trap the aminal **53** in the ketone or open form. For example, attempts to acylate the nitrogen with acetic anhydride resulted in a mono-acylated product **54**, observed by mass spectrometry (Scheme 2.7).



53 **54**

Scheme 2.7 Acylation of Amination-Aldol Adducts.

Based on this insight, we shifted focus to reducing agents capable of cleaving the N-N bond in hemi-aminal **55**. Initial attempts at hydrogenation using Raney Nickel failed. Upon sonication of the reaction mixture, a new spot appeared by TLC, and after 8 hours showed ~90% conversion to the new spot.[78] Column chromatography of this spot yielded a product with a complex and difficult to interpret ^{1}H NMR spectrum. Based on both the R_f (0.4 in 50:50 Hexanes:EtOAc) and m/z of the compound we hypothesized that this product was again a diastereomeric mixture of hemiaminals **56** formed after cleavage of the N-N bond (Scheme 2.8).

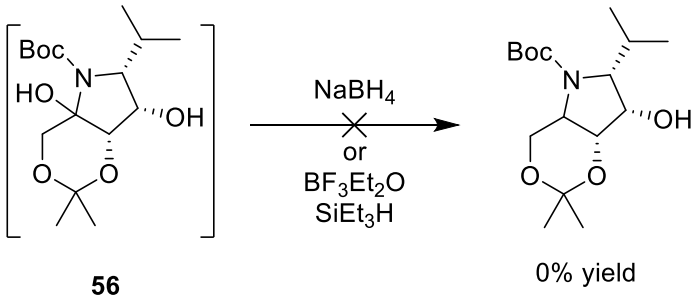


55 **56**

~90% conv.

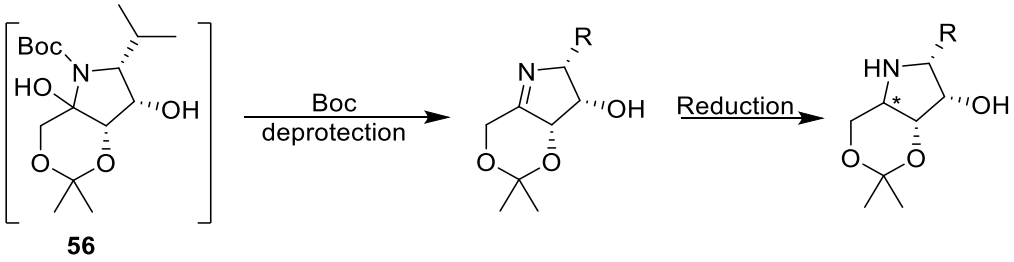
Scheme 2.8 Reduction to Compound (56) using Raney Nickel.

Unfortunately, reduction of **56** using known procedures for reducing hemi-aminals were unsuccessful. For example, reaction with sodium borohydride returned starting materials.[81] We also investigated a reduction involving triethylsilane accompanied by a strong Lewis acid (BF_3) and unfortunately observed none of the desired pyrrolidine.[82,83]



Scheme 2.9 Reducing Presumed Aminal (56).

As typical reduction conditions failed to provide further insight into the structure of compound **56** or afford the pyrrolidine product, we reasoned that deprotection of the -Boc group first should give the imine, which when followed by hydride reduction should afford the desired product (Scheme 2.10).



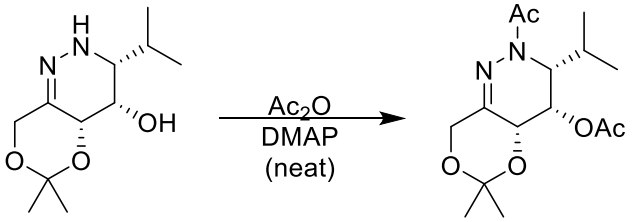
Scheme 2.10 Boc Deprotection of Presumed Hemiaminal (56).

Entry	Conditions	Result
1	TFA	Acetonide deprotection
2	I_2	Starting material recovered
3	$FeCl_3$	Starting material recovered
4	Heat	Starting material recovered- decomposition

Table 2.4 Boc-Deprotection Conditions of Hemiaminal (56).

As indicated in Table 2.3, (entry 1) we found that the acetonide was more labile than the Boc protecting group under TFA conditions. Diluting the TFA did not improve this result. Mild Lewis acids were investigated (entries 2 and 3) to promote Boc deprotection, but only returned starting materials. It has been reported that Boc groups can be removed thermally[84], unfortunately in our case the temperature was increased until the compound decomposed without any observable loss of the Boc protecting group prior to decomposition.

Investigation of strategies to cleave the N-N bond from the hydrazones represented an alternative approach to pyrrolidine structures. This strategy relies on activation of the N-N bond by introducing an electron-withdrawing group on the free secondary-amine followed by an intramolecular reductive amination. In this event, acylation of the hydrazone **45** proceeded smoothly to give **57** (Scheme 2.11).

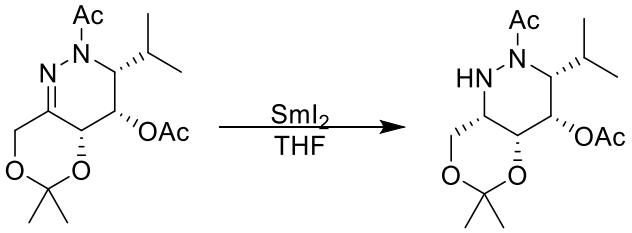


45 **57**

86% yield

Scheme 2.11 Acylation of Hydrazone (45).

When the acetylated-hydrazone **57** was exposed to SmI_2 in THF, the only isolable product was the acetylated hydrazine **58** (Scheme 2.12). This experiment demonstrated that C=N bond was also readily reduced, and more susceptible to reduction than the N-N bond. Since our goal was to synthesize pyrrolidines via a reductive amination sequence, maintaining the oxidation state of the hydrazone carbon was crucial. At this point we determined there was no reasonable synthetic sequence that could give us access to the desired pyrrolidine structures. It is notable that hydrazines such as **58** are known to be inhibitors of α-L-fucosidases and this three-step synthesis represents an efficient means to prepare such scaffolds.[85]



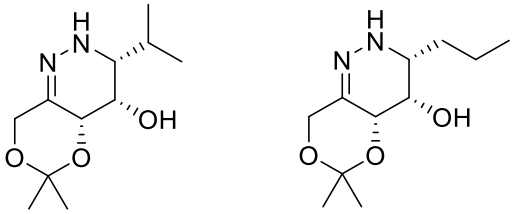
57 **58**

12% yield

Scheme 2.12 Samarium (II) Diiodide Reduction Leading to Hydrazine (58).

2.2.2. Synthesis of Hydrazones and Characterization

The amination-aldol procedure was adapted into a three-step process to synthesize hydrazones for ease of purification and characterization. To evaluate scope, this three-step process was applied to two different aldehydes, and two resulting hydrazone products **45** and **59** were isolated in moderate yields and high enantiomeric excess (Figure 2.3).



45

64% yield
3:1 d.r.
85% ee

59

45% yield
3:1 d.r.
98% ee

Figure 2.3 Synthesis of Hydrazones (45) and (59).

2.3. Conclusion

A novel synthetic method has been developed that combines a proline-catalyzed aldehyde amination reaction developed by List and Jørgensen, with an organocatalytic aldol reaction. These aldol adducts were investigated for their potential applications in the synthesis of pyrrolidines. Unfortunately, incompatible protecting groups and formation of stable hemi-aminals prevented N-N bond cleavage. The amination-aldol was shown to be useful in the synthesis of cyclic hydrazones **45** and **59** and the concise synthesis of hydrazine **58**.

2.4. Experimental Information

2.4.1. General Considerations

L- and D- proline (99% purity) were purchased from Sigma-Aldrich. All other reagents were purchased from Sigma-Aldrich or TCI and used without purification unless indicated. All reactions described were performed at ambient temperature and open to atmosphere unless otherwise indicated.

NMR spectra were recorded using $CDCl_3$ as the solvent. Signal positions are given in ppm relative to tetramethylsilane and were calibrated using the residual solvent signal (^{1}H NMR: $CDCl_3$ 7.26 ppm ^{13}C NMR: $CDCl_3$ 77.0 ppm). ^{1}H NMR multiplicities are given as (*s*, singlet; *d*, doublet; *t*, triplet; *q*, quartet; *dd*, doublet of doublets; *ddd*, doublet of doublet of doublet *m*, multiplet; *bs*, broad singlet). ^{1}H and ^{13}C NMR are recorded on a Bruker 600, Bruker 500 or Bruker 400. Diastereomeric ratios are based on analysis of crude ^{1}H NMR spectra.

Infrared spectra were recorded neat on a Perkin-Elmer Spectrum Two FTIR spectrometer. Only selected wavenumbers are provided for each compound. Optical rotations were measured on a Perkin-Elmer Polarimeter 341 at 589nm at 20°C. HPLC analysis was performed on an Agilent 1100 HPLC equipped with a variable UV-Vis wavelength detector. Enantiomeric excess was determined as indicated for each compound. High resolution mass spectra were measured on an Agilent 6210 TOF LC/MS using ESI-MS.

2.4.2. General Procedures

General Procedure A (One-Pot Organocatalytic Amination-Aldol)

L-proline (0.8 eq) was stirred in nitromethane (0.5 M). To the suspension was added aldehyde (1.1 eq). To this suspension was added azodicarboxylate (1.0 eq). The resulting suspension was stirred until consumption of starting material was observed visually (yellow solution turns colourless) and confirmed by TLC. Once consumption of starting material was observed, 2,2-dimethyl-1,3-dioxan-5-one (2.0 eq) was added. The reaction was monitored by TLC until consumption of intermediate aminated aldehyde was noted. The reaction mixture was diluted with CH_2Cl_2, washed with water, brine and then dried with $MgSO_4$. The resulting organic layer was concentrated using a rotary evaporator. The crude product was either purified as indicated or subjected to hydrogenation.

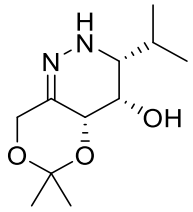
General Procedure B (Hydrogenation of Amination-Aldol Adducts)

Crude product from procedure **A** was dissolved in MeOH (with 1% AcOH, 0.1 M). To this solution is added 25% w/w Pd/C. The resulting suspension was put under H_2

atmosphere by evacuating the reaction vessel and backfilling with H_2 balloon three times. The reaction was stirred until consumption of crude product is observed by TLC. The reaction mixture was filtered through Celite to remove Pd/C, and the Celite was rinsed with more MeOH. The mixture was concentrated on a rotary evaporator, then purified as indicated.

2.4.3. Preparation and Characterization Data

Preparation of Hydrazone (45)



According to General Procedure **A**, L-proline (46 mg, 0.4 mmol) was stirred in nitromethane (1.2 mL). To the suspension was added isovaleraldehyde (54 µL, 0.55 mmol), and dibenzyl azodicarboxylate (DBnAD) (149 mg, 0.5 mmol). Once consumption of DBnAD was observed, dioxanone (130 mg, 1.0 mmol) was added. The reaction was monitored by TLC until consumption of intermediate aminated aldehyde was noted (2 days). The reaction mixture was diluted with 2 mL of CH_2Cl_2, washed with sequentially with 5 mL water, then 5 mL brine and then dried with $MgSO_4$. The resulting organic layer is concentrated using a rotary evaporator.

Following General Procedure **B**, the crude product was dissolved in 4 mL of MeOH containing 1% v/v AcOH. To this solution is added 25% w/w Pd/C (100 mg). The resulting suspension is put under H_2 atmosphere and stirred until consumption of crude product is noted. The reaction mixture was filtered through Celite, rinsed with more MeOH, and concentrated on a rotary evaporator. Purification of crude by flash chromatography on silica (60:40 hexanes:EtOAc and 1% NEt_3) afforded hydrazone **45** as a white solid (146 mg, 64% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ=5.33 (*bs*, 1H), 4.41 (*m*, 1H), 4.39 (*d*, *J* = 15.6 Hz, 1H), 4.22 (*d*, *J* = 15.6 Hz, 1H), 4.03 (*m*, 1H), 2.71 (*d*, *J* = 9.4 Hz, 1H), 2.47 (*bs*, 1H), 1.99 (*m*, 1H), 1.52 (*s*, 3H), 1.43 (*s*, 3H), 1.00 (*d*, *J* = 6.8 Hz, 6H)

^{13}C NMR (100 MHz, $CDCl_3$): δ= 139.4, 99.78, 66.4, 62.77, 62.14, 61.8, 27.4, 27.2, 21.6, 19.5, 19.0

HRMS (ESI) *m/z* calcd for $C_{11}H_{21}N_2O_3$ $[M+H]^+$ 229.1547, found 229.1534

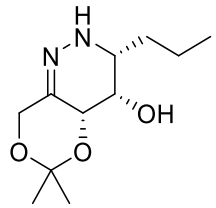
IR: 3359, 2961, 2872, 1643, 1380, 1372, 1165, 1074, 862 cm^{-1}

$[\alpha]_D^{20}$: -22.9 (c = 31.9 mg/mL in $CHCl_3$)

Determination of Enantiomeric Excess of Hydrazone (45)

A racemic sample of hydrazone **45** was prepared using racemic proline. The racemic hydrazone was separated by chiral HPLC using Phenomex Lux (3μm) Cellulose-3 column; flow rate 0.4 mL/min; eluent: hexanes-*i*PrOH 80:20; detection at 254 nm; retention time = 10.6 min and 20.1 min. The enantiomeric excess of the optically-enriched hydrazone was determined using the same method (85% ee).

Preparation of Hydrazone (59)



According to General Procedure **A**, L-proline (46 mg, 0.4 mmol) was stirred in nitromethane (1.2 mL). To the suspension was added valeraldehyde (54 μL, 0.55 mmol), and dibenzyl azodicarboxylate (DBnAD) (149 mg, 0.5 mmol). Once consumption of DBnAD was observed, dioxanone (130 mg, 1.0 mmol) was added. The reaction was monitored by TLC until consumption of intermediate aminated aldehyde is noted (2 days). The reaction mixture was diluted with 2 mL of CH_2Cl_2, washed with sequentially with 5 mL water, then 5 mL brine and then dried with $MgSO_4$. The resulting organic layer was concentrated using a rotary evaporator.

Following General Procedure **B**, the crude product was dissolved in 4 mL of MeOH containing 1% v/v AcOH. To this solution was added 25% w/w Pd/C (100 mg). The

resulting suspension was put under H_2 atmosphere and stirred until consumption of crude product is noted. The reaction mixture was filtered through Celite, rinsed with more MeOH, and concentrated on a rotary evaporator. Purification of crude by flash chromatography on silica (60:40 hexanes:EtOAc and 1%NEt_3) afforded hydrazone **59** as a white solid (103 mg, 45% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ= 5.13 (*bs*, 1H), 4.43 (*m*, 1H), 4.40 (*d*, *J* = 14.6 Hz, 1H), 4.22 (*d*, *J* = 14.6 Hz ,1H), 3.87 (*m*, 1H), 3.14 (*dd*, *J* = 7.1, 6.8 Hz, 1H), 2.46 (*bs*, 1H), 1.69 (*m*, 1H), 1.53 (*s*, 3H), 1.44 (*s*, 3H) 1.69-1.39 (*m*, 3H), 0.96 (*t*, *J* = 7.6 Hz 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ= 139.6, 99.9, 66.1, 63.1, 62.9, 55.9, 31.7, 27.2, 21.6, 18.8, 14.1

HRMS (ESI) *m/z* calcd for $C_{11}H_{21}N_2O_3$ $[M+H]^+$ 229.1547, found 229.1529

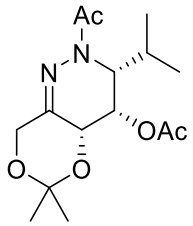
IR: 3348, 2989, 2871, 1648, 14555, 1373, 1167, 1074, 862 cm^{-1}

$[\alpha]_D^{20}$: -24.5 (c = 17.5 mg/mL in $CHCl_3$)

Determination of Enantiomeric Excess of Hydrazone (59)

A racemic sample of hydrazone **59** was prepared using racemic proline. The enantiomeric hydrazone was separated by chiral HPLC using Phenomex Lux (3μm) Cellulose-3 column; flow rate 0.4 mL/min; eluent: hexanes-*i*PrOH 80:20; detection at 254 nm; retention time = 11.5 min and 16.5 min. The enantiomeric excess of the optically enriched hydrazone was determined using the same method (98% ee).

Preparation of Acylated-Hydrazone (57)



Hydrazone **45** (20 mg, 0.09 mmol) was submitted to neat Ac_2O (0.1 M, 1 mL) with 1.0 eq of DMAP (11 mg, 0.09 mmol) and stirred overnight. The reaction was diluted with 5 mL of EtOAc and quenched using aqueous $NaHCO_3$. The organic layer was washed several times with aqueous $NaHCO_3$. The organic layer was then dried with brine and $NaSO_4$ and concentrated using a rotary evaporator. Purification by column chromatography on silica (60:40 hexanes:EtOAc) afforded 37mg (86% yield) of a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 5.24 (*m*, *J* = 5.6 Hz, 1H), 4.57 (*dd*, *J* = 8.0, 5.6 Hz, 1H), 4.50 (*d*, *J* = 14.6 Hz, 1H), 4.29 (*d*, *J* = 14.6 Hz, 1H), 2.55 (*m*, 1H), 2.25 (*s*, 3H), 2.10 (*s*, 3H), 1.49 (*s*, 3H), 1.40 (*s*, 3H), 1.04 (*d*, *J* = 6.8 Hz, 3H), 0.82 (*d*, *J* = 6.8 Hz, 3H)

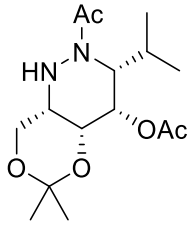
^{13}C NMR (100 MHz, $CDCl_3$): δ= 171.5, 169.8, 153.4, 101.1, 69.5, 62.5, 62.3, 55.7, 26.5, 26.1, 21.5, 21.4, 20.7, 20.1, 19.8

HRMS (ESI) *m/z* calcd for $C_{15}H_{28}N_3O_5$ $[M+NH_4]^+$ 330.2023, found 330.2050

IR: 3476, 2965, 2936, 1744, 1681, 1402, 1373, 1231, 1166, 1072, 1044 cm^{-1}

$[\alpha]_D^{20}$: -69.6 (c = 47 mg/mL in $CHCl_3$)

Reduction of Acylated Hydrazine (58)



SmI_2 was prepared according to a literature procedure.[86] A 250 mL round bottom flask was flame-dried and put under N_2 atmosphere. To the flask was added solid Sm metal chunks (1.65 g, 11.0 mmol) and 1,2-diiodoethane (1.55 g, 5.5 mmol). 55 mL of

anhydrous THF was added to the flask via syringe and the suspension was stirred. The flask was evacuated and backfilled with N_2 several times over the course of 1 h to remove liberated ethylene gas. After 1 h the gas line was removed, the flask sealed, and the solution stirred overnight. The yellow solution slowly turns blue. The next morning the solution was dark blue and can be used as a saturated solution of SmI_2 (~0.06 M).

Acylated hydrazone **57** (10 mg, 0.03 mmol) was dissolved in 0.5 mL MeOH (0.1 M) and added to a flame-dried flask. The flask was put under N_2 atmosphere. 4mL of prepared SmI_2 solution was added to the flask. As blue colour disappears, another 4mL of SmI_2 was added and the blue colour remained. The reaction was monitored by TLC until consumption of starting material is complete. The crude reaction was washed with water and the aqueous layer extracted three times with CH_2Cl_2. Purification by flash chromatography on silica (60:40 hexanes:EtOAc) yielded a clear oil (1.2 mg, 12% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ= 4.86 (*dd*, *J* = 5.8, 2.9 Hz, 1H), 4.45 (*dd*, *J* = 10.2, 5.8 Hz, 1H), 4.38 (*d*, *J* = 12.2 Hz, 1H), 4.25 (*m*, *J* = 2.9, 1.7 Hz, 1H), 4.11 (*dd*, *J* = 12.6, 2.9 Hz 1H), 3.85 (*dd*, *J* = 12.6, 1.4 Hz 1H), 2.64 (*m*, 2H), 2.19 (*s*, 3H), 2.10 (*s*, 3H), 1.44 (*s*, 3H), 1.43 (*s*, 3H), 1.13 (*d*, *J* = 6.6 Hz, 3H), 0.84 (*d*, *J* = 6.6 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ= 172.9, 170.1, 98.9, 71.2, 66.1, 61.9, 54.0, 52.7, 29.7, 29.5, 27.9, 25.6, 21.1, 20.9, 18.0

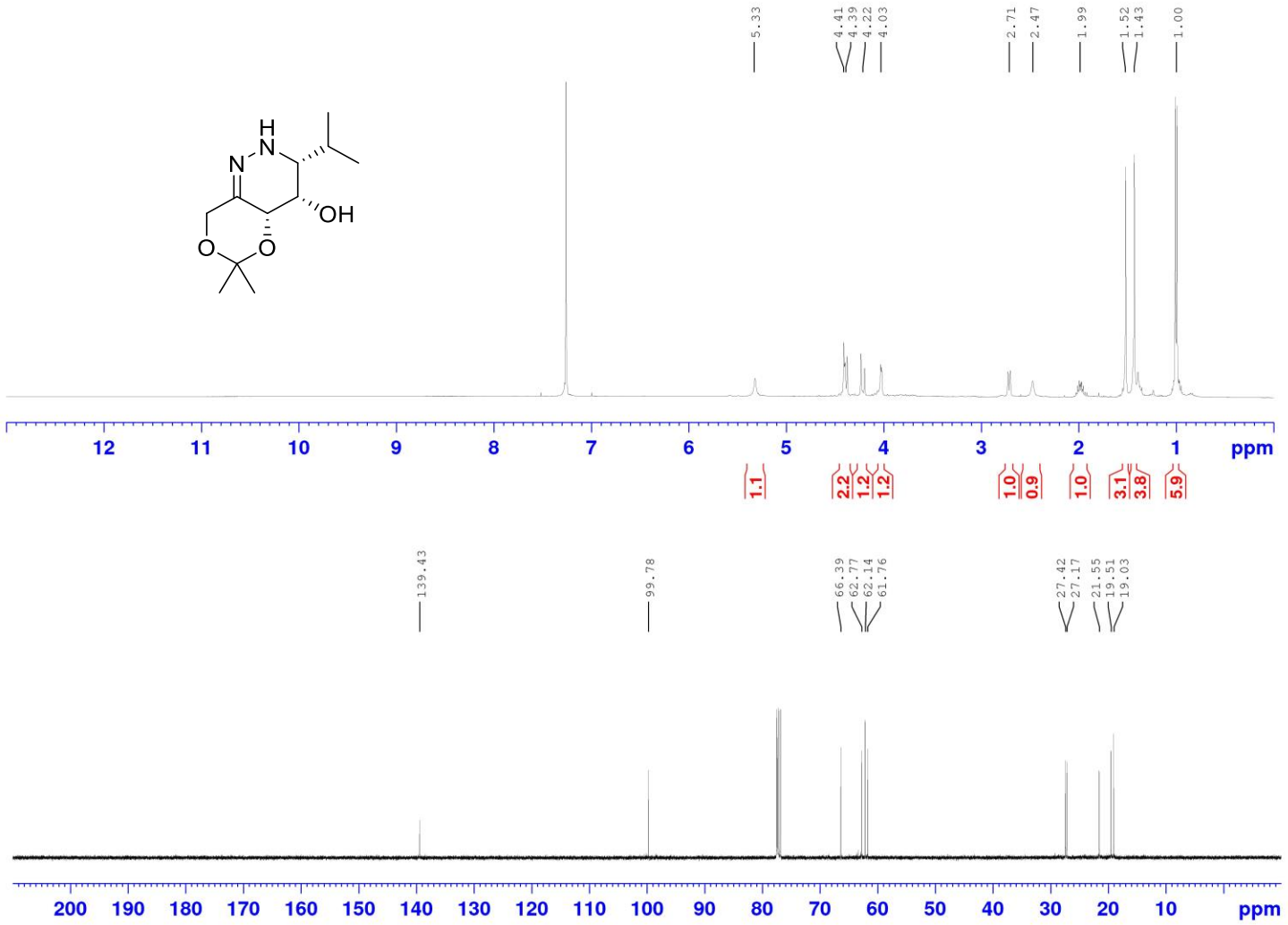
HRMS (ESI) *m/z* calcd for $C_{15}H_{26}N_2O_5$ $[M+H]^+$ 315.1914, found 315.1923

IR: 2926, 1743, 1660, 1496, 1376, 1234, 1199, 1090, 1044 cm^{-1}

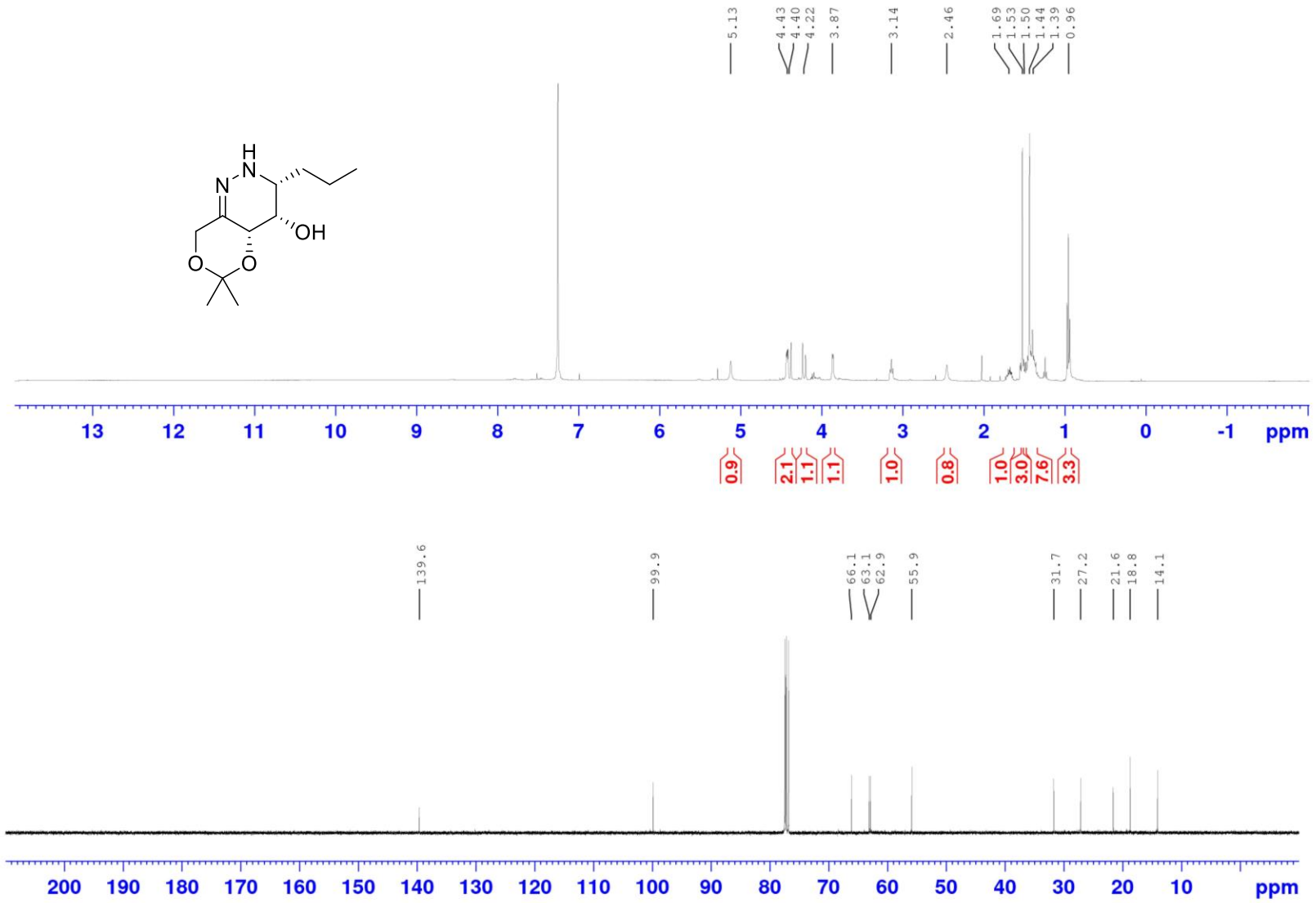
$[\alpha]_D^{20}$: -32.1 (c =1.2 mg/mL in $CHCl_3$)

2.4.4. NMR Spectra

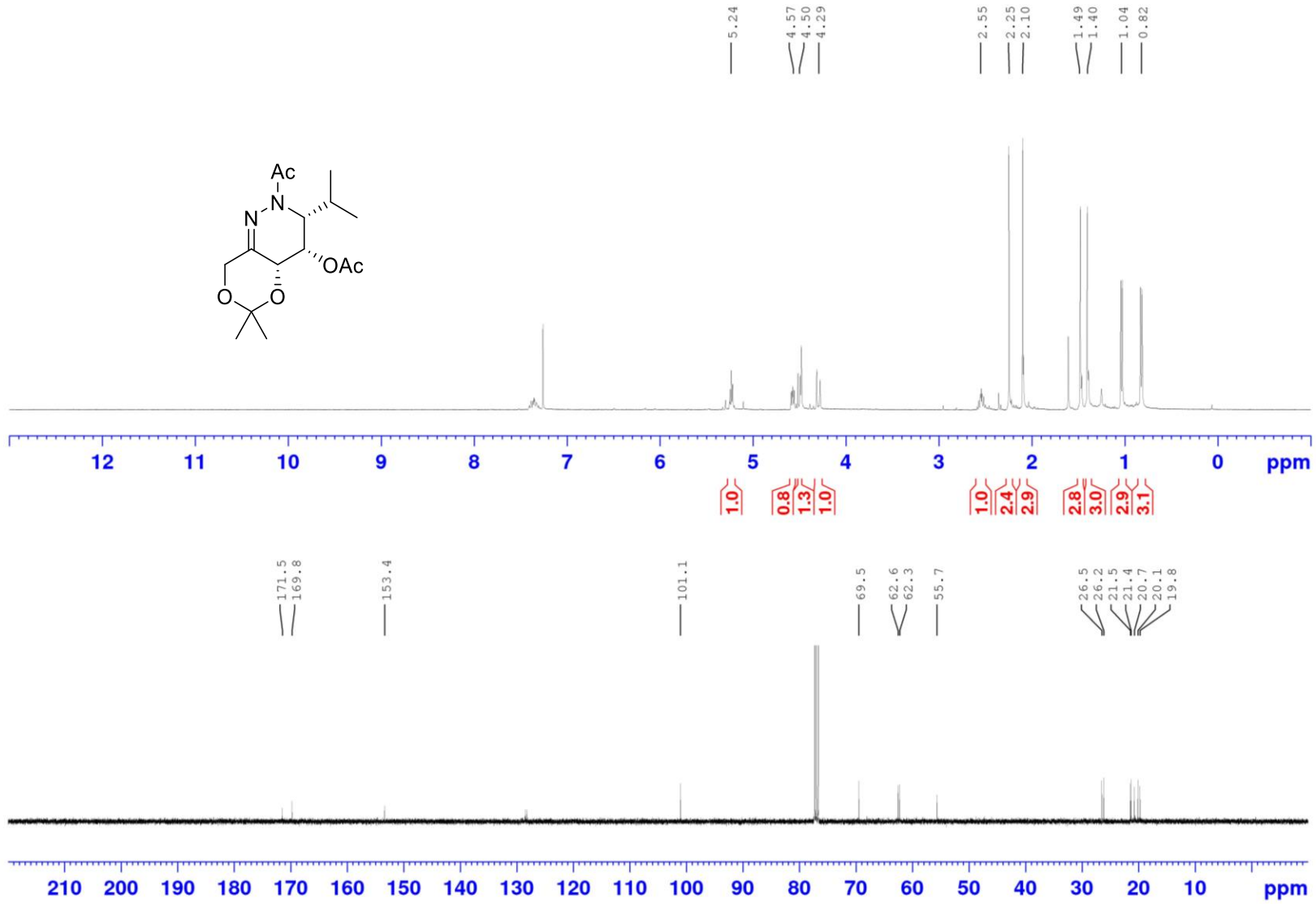
NMR of Hydrazone (45)



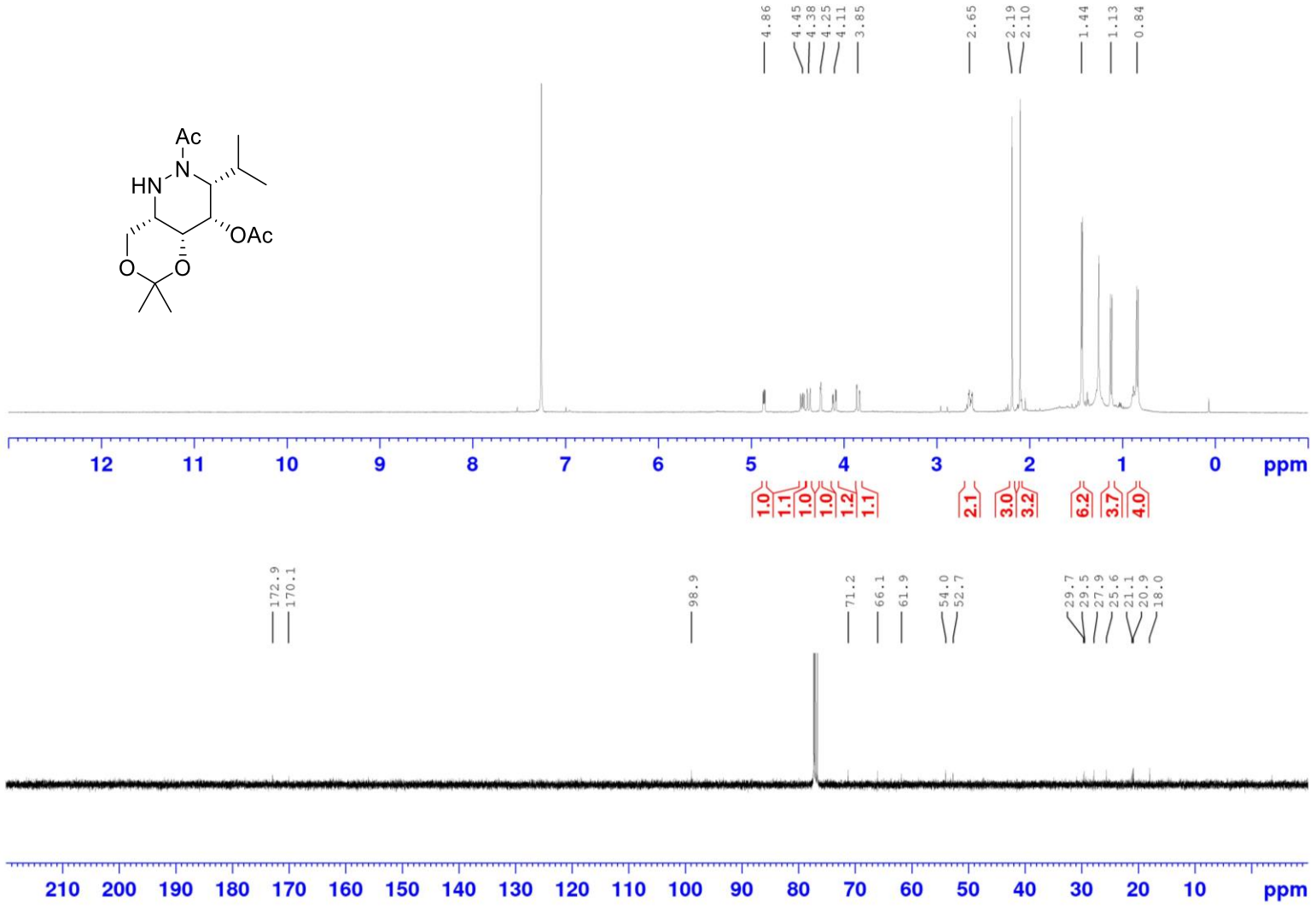
NMR of Hydrazone (59)



NMR of Hydrazone (57)

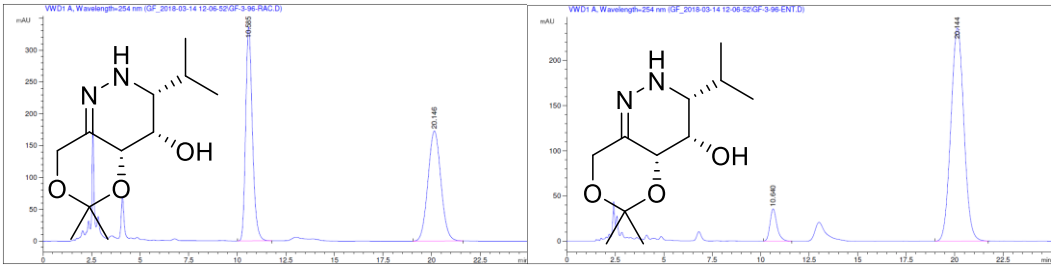


NMR of Hydrazine (58)



2.4.5. HPLC Traces

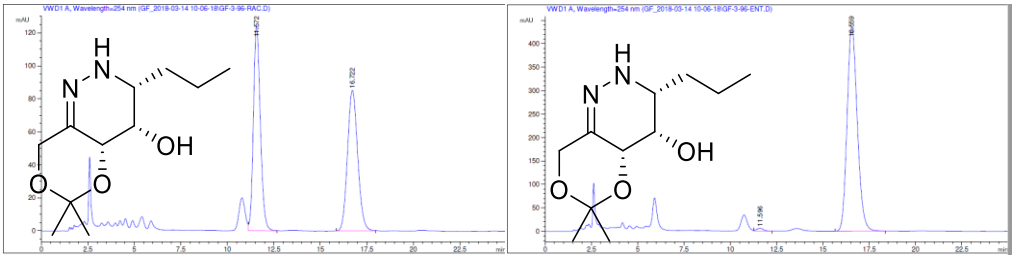
HPLC Traces for Racemic (Left) and Enantioenriched (Right) (45)



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.585	BB	0.3739	8127.26758	336.03912	50.3763
2	20.146	BB	0.7194	8005.85010	172.87167	49.6237

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.640	BB	0.3770	888.06750	35.76637	7.4649
2	20.144	BB	0.7259	1.10085e4	235.51138	92.5351

HPLC Traces for Racemic (Left) and Enantioenriched (Right) (59)



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	11.572	VB	0.3993	3222.68481	123.99079	49.7858
2	16.722	BB	0.6037	3250.41846	85.20957	50.2142

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	11.596	VB	0.4016	154.58374	5.84761	0.9159
2	16.559	BB	0.5943	1.67232e4	436.26291	99.0841

Chapter 3.

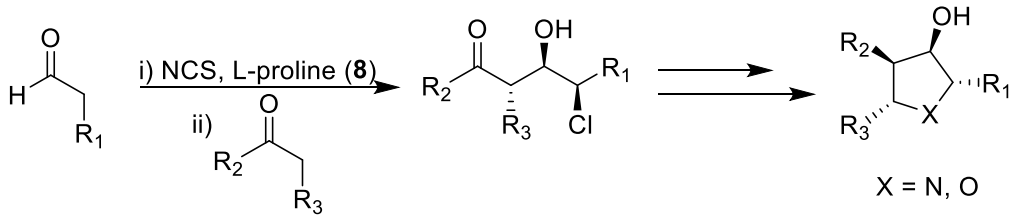
Expanding the Ketone Scope of the α-Chlorination-Aldol Reaction

3.1. Exploration of Potential Aldol Donors

3.1.1. Background

α-Chloroaldehydes are valuable synthetic building blocks and have found extensive application in natural product synthesis. One useful reaction of α-chloroaldehydes involves nucleophilic addition of organometallic reagents to give 1,2-*anti*-chlorohydrins that can be used in the synthesis of various natural products containing epoxides, tetrahydrofurans and pyrrolidines.[87] In particular, it has been found that lithium enolates engage in aldol reactions with α-chloroaldehydes with good to excellent diastereoselectivity favouring formation of 1,2-*anti*-chlorohydrins.[88–92]

As discussed in Chapter 1, a significant development in the reactions of α-chloroaldehydes was the report of a one-pot organocatalyzed α-chlorination-aldol reaction.[68] The conditions for these reactions are mild, and effect both chlorination and C-C bond formation with excellent yields and control of stereochemistry.[68] The organocatalyzed α-chlorination-aldol reaction has found application in the synthesis of small molecules and other natural products.[69,70,93] Considering the limitations to the organocatalyzed α-chlorination-aldol reaction that include only using dioxanone **20** as the ketone partner and "Cl^+" as the electrophile, we sought to expand the scope of this reaction and enable production of more diverse families of tetrahydrofurans and pyrrolidines (Scheme 3.1).

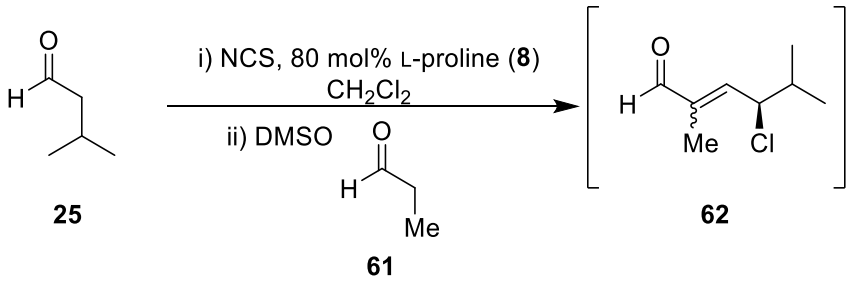


Scheme 3.1 The Goal of the Research Presented in this Chapter.

Based on the established utility of DMSO as a solvent for proline-catalyzed aldol reactions and CH_2Cl_2 as a solvent for organocatalyzed α-chlorination-aldol reactions, we initiated our studies with a solvent mixture of DMSO:CH_2Cl_2 (1:1). Additionally, we began by exploring reactions in a one pot but stepwise manner, unlike the previous α-chlorination-aldol methodology. In the α-chlorination-aldol with dioxanone, the rate of chlorination of the aldehyde was sufficiently fast to ensure that chlorination of dioxanone would not occur. In the present study it was not clear that the additional ketones would not undergo chlorination. We also chose isovaleraldehyde as the model aldehyde, as it demonstrated high levels of diastereoselectivity in previous α-chlorination-aldol and other proline catalyzed aldol reactions.[94,95,68] This choice also made analysis of crude reaction products by ^{1}H NMR spectroscopy more straightforward.

3.1.2. Alkyl ketones and aldehydes

Initially, aldehydes were explored as aldol donors, following work reported by MacMillan involving the use of two aldehydes in an aldol reaction.[33] We first submitted isovaleraldehyde **25** to α-chlorination, followed by the addition of propanal **61** (Scheme 3.2). The reaction yielded a single product was identified as enal **62**. Presumably, an aldol reaction occurred, but underwent elimination to form the enal product. Unfortunately, further attempts to optimize this reaction failed to give the desired aldol adduct.

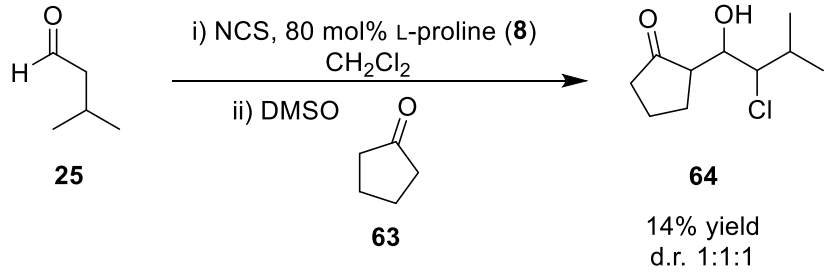


25 **61** **62**

Scheme 3.2 Investigating Aldehydes as Donors in α-Chlorination-Aldol.

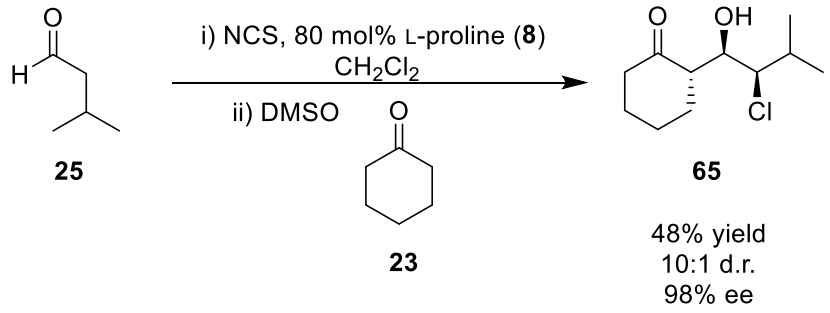
Moving forward, and given our previous success with dioxanone, we examined other cyclic ketones in attempt to develop a more general α-chlorination-aldol reaction. As depicted in Scheme 3.3, we found that cyclopentanone **63** reacted with 2-chloro-isovaleraldhyde to provide a 1:1:1 mixture of diastereomers of the aldol adduct **64** in 14% yield (Scheme 3.3). Column chromatography allowed removal of one diastereomer, while the other two diastereomers remained inseparable. This prevented assignment of

stereochemistry, or any further optimization of the reaction. Poor diastereoselectivity is a noted problem with cyclopentanone in aldol reactions.[96] This is likely due in part to the increased reactivity of a 5-membered ring under organocatalytic conditions. The increased angle strain imparted by the smaller ring angles could lead to less discrimination between diastereomeric transitions states leading to product chlorohydrins. This would be observed as poor diastereoselectivity.



Scheme 3.3 α-Chlorination-Aldol with Cyclopentanone gave poor Diastereoselectivity.

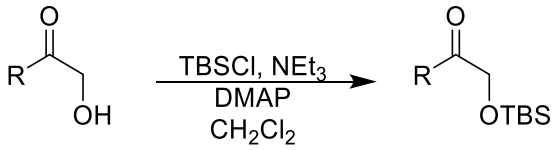
Gratifyingly, cyclohexanone **23** reacted well with aldehyde **25** under the identical reaction conditions to give chlorohydrin **65** (Scheme 3.4). Good conversions and diastereoselectivity were observed by ^{1}H NMR spectroscopic analysis of crude reaction mixtures, all while employing a modest excess of the ketone. This is unlike many previous reports of organocatalytic aldol reactions that typically employ alkyl ketones in large excess, or as a solvent as in List's first intermolecular aldol reaction.[14] The relative stereochemical assignment of compound **65** was based on literature precedent for the observed configuration,[68] and was confirmed by nOe experiments on the reduced and cyclized adducts (compound **97,** p. 55).



Scheme 3.4 α-Chlorination-Aldol Reaction with Cyclohexanone.

3.1.3. Synthesis and Investigation of α-substituted Ketones in α-Chlorination-Aldol Reactions

Building on the previous successes with dioxanone **20**, other protected α-hydroxy ketones were prepared (Scheme 3.5). We determined that the α-hydroxy ketones should be protected to maximize solubility and avoid side reactions of the free alcohol function. The choice of a TBS protecting group was based on literature precedent for organocatalytic aldol reactions of silyl-protected hydroxy-ketones, which typically demonstrate the highest reactivity among protected hydroxy-ketone derivatives.[94]

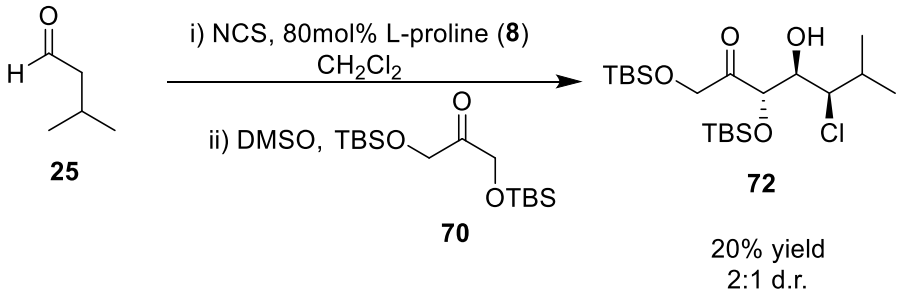


66 R = -Me
67 R = -Ph
68 R = -CH_2OH

69 R = -Me
70 R = -Ph
71 R = -CH_2OTBS

Scheme 3.5 Preparation of TBS protected ketones (69-71).

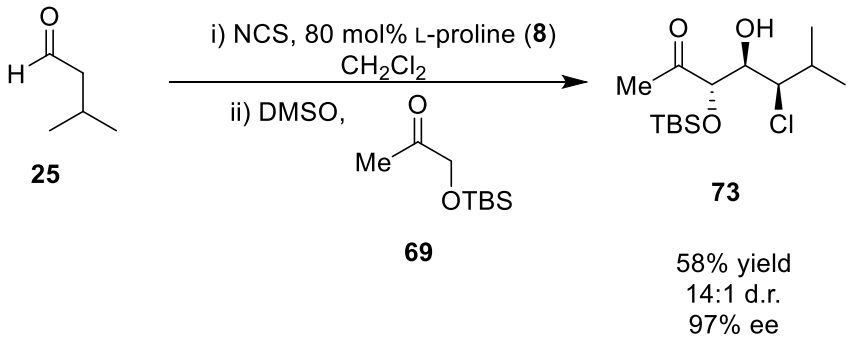
Firstly, *bis*-TBS-protected dihydroxyacetone **71** was prepared, and submitted to the aldol reaction conditions (Scheme 3.6). In this case, the conversion to **72**, and diastereoselectivity were quite low, which is line with observations reported by Barbas in proline catalyzed aldol reactions of this substrate. However, this reaction demonstrates the possibility to access differently protected dihydroxyacetone derivatives such as **72** using the α-chlorination-aldol methodology.



Scheme 3.6 *bis*-TBS protected Dihydroxyacetone (70) in an Aldol Reaction.

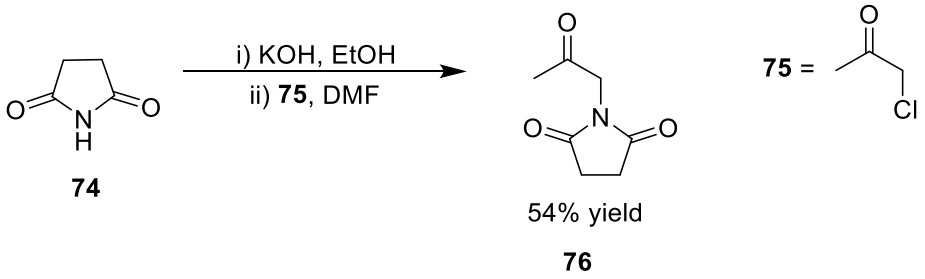
Analysis of the crude product derived from the reaction of methyl ketone **69** and 2-chloroisovaleraldehyde by ^{1}H NMR spectroscopy revealed both good conversion and diastereoselectivity (14:1) to compound **73** (Scheme 3.7). Here, the regioselectivity of the

aldol reaction favors aldol reaction on the silyloxy-substituted side of the ketone. TBS-protected hydroxyacetophenone **70** was also prepared but unfortunately, did not engage in aldol reactions with 2-chloro-isovaleraldehyde.



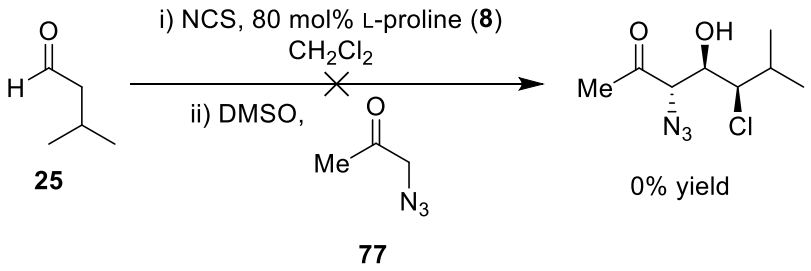
Scheme 3.7 TBS-protected Hydroxyacetone (69) Aldol Reaction.

A protected α-amino ketone were also prepared via displacement of chloride from chloroacetone (**75**) with the potassium salt of succinimide **74** (Scheme 3.8). Unfortunately, we observed no aldol reaction between this ketone **76** and 2-chloro-isovaleraldehyde. We suspect that in this case the succinimide protecting group is too bulky, and thus prevents condensation of proline or the subsequent approach of the electrophile.



Scheme 3.8 Preparation of α-nitrogen Ketones.

In search of a smaller nitrogen protecting group, azidoacetone **77** was prepared by the reaction of chloroacetone with sodium azide. Unfortunately, this substrate reacted with itself too quickly when exposed to proline and there was no indication of reaction with 2-chloro-isovaleraldehyde. The product of two or more molecules of azidoacetone reacting with each other would be quite dangerous and unstable, and so this compound was not isolated nor characterized.

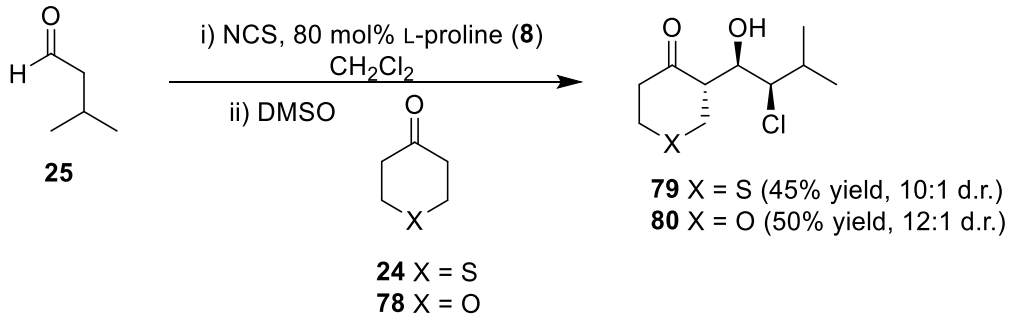


Scheme 3.9 Azidoacetone (76) in an α-Chlorination-Aldol reaction.

At this point, we had identified three compatible ketones for the α-chlorination aldol reaction. Each of these ketones would enable the synthesis of new classes of natural products that either lack a primary alcohol function (i.e., 1-silyloxyacetone) or include other ring systems (e.g., cyclohexanone). Notably, we found that ketones reacted best when constrained in a six-membered ring and anticipated that other 6-membered rings would be suitable substrates for this reaction.

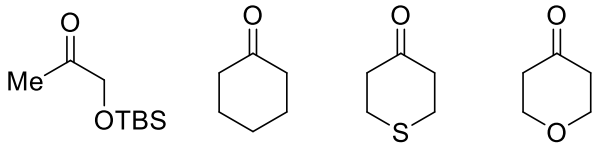
3.1.4. Six-membered rings in the α-Chlorination Aldol Reaction

Inspired by Ward's thiopyranone aldol, we explored the use of thiopyranone **24** in the α-chlorination aldol reaction (Scheme 3.10). Here, thiopyranone reacted with isovaleraldehyde **25** in 45% yield and excellent diastereoselectvity (10:1) (**79**). Similarly, pyranone **78** also engaged in the α-chlorination aldol reaction providing the unusual adduct **80** in 50% yield and excellent diastereoselectivity (12:1).



Scheme 3.10 Thiopyranone in α-Chlorination-Aldol Reaction.

At this point it was determined we had identified a satisfactory scope of new ketones that could be used for this process and we moved forward to further optimize these reactions (Scheme 3.11).



69 **23** **24** **78**

Scheme 3.11 Newly Identified Ketones for α-Chlorination-Aldol Reaction.

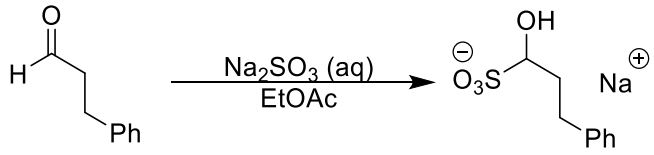
3.2. Optimization of α-Chlorination-Aldol Reaction

3.2.1. Purity of Starting Materials

Purification of Aldehydes

At the outset of this project, we had concerns regarding the quality of commercially available aldehydes. As the α-chlorination-aldol reaction is extremely sensitive to quality of starting materials, this warranted further investigation.

Firstly, upon investigation of the aldehydes, we found that many had undergone oxidation (~30-40%) by reaction with atmospheric oxygen, providing the corresponding carboxylic acids. To purify these aldehydes, we attempted to form sulfite salts of the aldehydes using sodium sulfite (Scheme 3.12).[97] Exposure of the contaminated aldehyde, such as hydrocinnamaldehyde **81** to aqueous sodium sulfite in ethyl acetate resulted in the precipitation of the corresponding sodium sulfite salt (e.g., **82**). Filtration of the salt allowed for easy removal of other organic soluble contaminants.



81 **82**

Scheme 3.12 Formation of Sulfite Salts with Aldehydes.

Reforming the aldehyde proved to be more challenging than expected. Polar aldehydes proved to have significant water solubility and were difficult to isolate following aqueous extraction. Additionally, recovery of volatile aldehydes was made difficult by the necessary concentration (rotary evaporation) after extraction. However, in general, this purification procedure proved useful for non-volatile, less polar aldehydes such as **81**. Alternatively, we found that washing organic solutions of crude aldehydes with saturated

aqueous sodium carbonate was sufficient to remove the corresponding carboxylic acid impurities. Once the aldehydes were determined to be of sufficient purity, we began to investigate the purity of the commercially available ketones.

Purification of Thiopyranone

Thiopyranone did not match the literature description of its physical form. According to SDS, thiopyranone is a white powder while the commercially available material was purchased as a brown/orange solid. While the ^{1}H NMR spectrum of this material was consistent with literature reported spectra, we decided to investigate the effect of purifying the ketone on the subsequent aldol reaction. The colour was removed by dissolving thiopyranone in ethyl acetate and mixing with decolourizing charcoal, which afforded a yellow powder after filtration and concentration. Additional filtration of the ethyl acetate solution through a short plug of silica gel followed by concentration provided a mostly white powder (Figure 3.1)

Figure 3.1 Visual Purity of Thipyranone: (L-R) Commercially available, Purified with just Charcoal, Purified with Charcoal and Silica Plug.

The first and third samples of ketone were submitted to an α-chlorination-aldol reaction to determine the effect of purity on the aldol reaction. In fact, the conversions increased significantly as shown in table 3.1 from entry 1 to entry 2.

Entry	Purity	Yield
1	Commercially pure	24%
2	Charcoal + SiO_2 plug	35%

Table 3.1 Increasing Conversion with Increasing Purity of Thiopyranone.

3.2.2. Optimization of reaction conditions

The thiopyranone aldol reaction was further optimized using internal standard (1,3,5-trimethoxybenzene) for reaction monitoring by ^{1}H NMR spectroscopy. First, the equivalents of ketone and aldehyde were varied, to determine which reagent should be employed in excess, and by how much. As summarized in Table 3.2 (entry 2), using the aldehyde in excess gave very little desired product while (entry 3) increasing the equivalents of ketone had a modest effect on conversion. Further increases in equivalents of ketone (entries 4 and 5) led to modest increases in conversions. In the end, 3 equivalents of ketone (entry 4) was chosen as optimal, as purification of the final product was complicated by excess ketone present in the crude reaction mixture.

Entry	Ratio (aldehyde: ketone)	Conversion
1	1:1	17%
2	2:1	Trace
3	1:2	21%
4	**1:3**	**28%**
5	1:5	34%

Table 3.2 Optimizing Equivalents of Ketone and Aldehyde.

Different solvent systems were examined for the aldol reaction (Table 3.3) and it was found that a chlorinated solvent is necessary for the α-chlorination reaction as no chlorination was observed in DMSO or DMF (entry 2). This observation was also made by Jørgensen's in their initial disclosure of the aldehyde α-chlorination reaction.[38] Using only CH_2Cl_2 as a reaction solvent provided less final aldol product than the 1:1 CH_2Cl_2:DMSO. We also investigated different ratios of CH_2Cl_2: DMSO and CH_2Cl_2: DMF and found small variances in product yield. In the end, for ease of workup and handling of crude reaction mixtures, a 9:1 mixture of CH_2Cl_2: DMSO was chosen as the optimal solvent system (entry 5).

Entry	Solvent	Conversion
1	CH_2Cl_2	trace
2	DMSO	No α-chlorination
3	CH_2Cl_2: DMSO (1:1)	21%
4	CH_2Cl_2: DMSO (1:9)	trace
5	**CH_2Cl_2: DMSO (9:1)**	**25%**
6	CH_2Cl_2: DMF (1:1)	6%

Table 3.3 Solvent Optimization for α-Chlorination-Aldol Reaction.

Catalyst loading was also examined, and larger equivalents of proline led to higher conversions to aldol product. Beyond 80 mol%, additional proline was found to be insoluble in the optimal solvent system and therefore 80 mol% of proline was chosen as optimal.

3.2.3. Purification of New Aldol Adducts

The workup and purifications for the new aldol adducts was intended to be minimal to avoid product loss and thus our goal was to apply each crude reaction mixture (after evaporation of volatiles) directly to a silica gel column and purify the products by flash chromatography. This procedure worked well for the *mono*-OTBS ketone **69**, *bis*-OTBS ketone **70** and thiopyranone **24**.

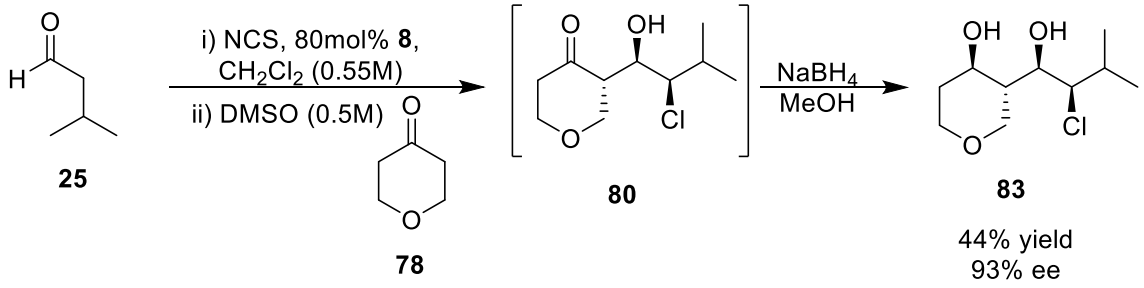
Conversely, aldol products from cyclohexanone **23** and pyranone **78** gave mixtures of diastereomers after flash chromatography. Critically, diastereomeric mixtures isolated following chromatography were not observed in ^{1}H NMR spectra recorded on crude reaction products indicating that these aldol adducts underwent extensive decomposition and epimerization during column chromatography (Table 3.4 entries 3 and 4). Washing the reaction mixture with saturated aqueous NH_4Cl or NaCl to remove DMSO prior to column chromatography prevented decomposition, but not epimerization in these cases (entries 1 and 2). Ultimately, we found that washing the crude reaction mixture with saturated aqueous NH_4Cl (to remove the DMSO), followed by a wash with saturated aqueous $NaHCO_3$, concentration and column chromatography on silica gel allowed facile purification (entry 5). Acidification of the $NaHCO_3$ aqueous layer and re-extraction with CH_2Cl_2 allowed examination of organic components that were removed from the crude reaction product. Analysis of these extracted materials by ^{1}H NMR spectroscopy indicated predominantly succinimide and suggested that succinimide played a role in degradation

or epimerization of these particularly sensitive aldol adducts during purification by flash column chromatography on both silica and alumina.

Entry	Workup/Purification	Result
1	Wash with NH_4Cl, SiO_2 column	Epimerization
2	Wash with NaCl, SiO_2 column	Epimerization
3	Direct application to SiO_2 column	Decomposition
4	Direct application to basic alumina column	Decomposition
5	Wash with NH_4Cl, then $NaHCO_3$, then apply to SiO_2 column	No epimerization

Table 3.4 Workups and Purifications for Crude Cyclohexanone Aldol Adduct.

After applying these optimized purification and workup procedures to pyranone, we found the aldol adduct **80** remained unstable to column chromatography on both silica and alumina stationary phases. Frustratingly, the ^{1}H NMR spectrum recorded on crude pyranone aldol **80** indicated excellent purity and conversion. Thus, the pyranone aldol adduct was isolated as diol **83** after reduction of the intermediate ketone **80**. The latter material proved stable and was readily isolated in good yield over the two steps by flash column chromatography (Scheme 3.13).



Scheme 3.13 Procedure for Isolating Pyranone Aldol Adducts.

3.3. Byproduct Formation and Effect of H_2O on the Reaction

3.3.1. Observation of Proline-Aldehyde Byproducts

While optimizing the aldol reaction, a consistent pattern in the chlorination reaction was observed. A white precipitate would form during chlorination, only to disappear after 1 hour leaving behind a homogenous solution. Filtering off the white solid before it disappeared and analysis by ^{1}H NMR spectroscopy allowed us to determine that there was in fact an adduct forming between the α-chloroaldehyde and proline (Figure 3.2).

Different adducts between proline and aldehydes have been reported, including oxazolidinones (**85**) [58], and adducts involving succinimide (**84**).[63]

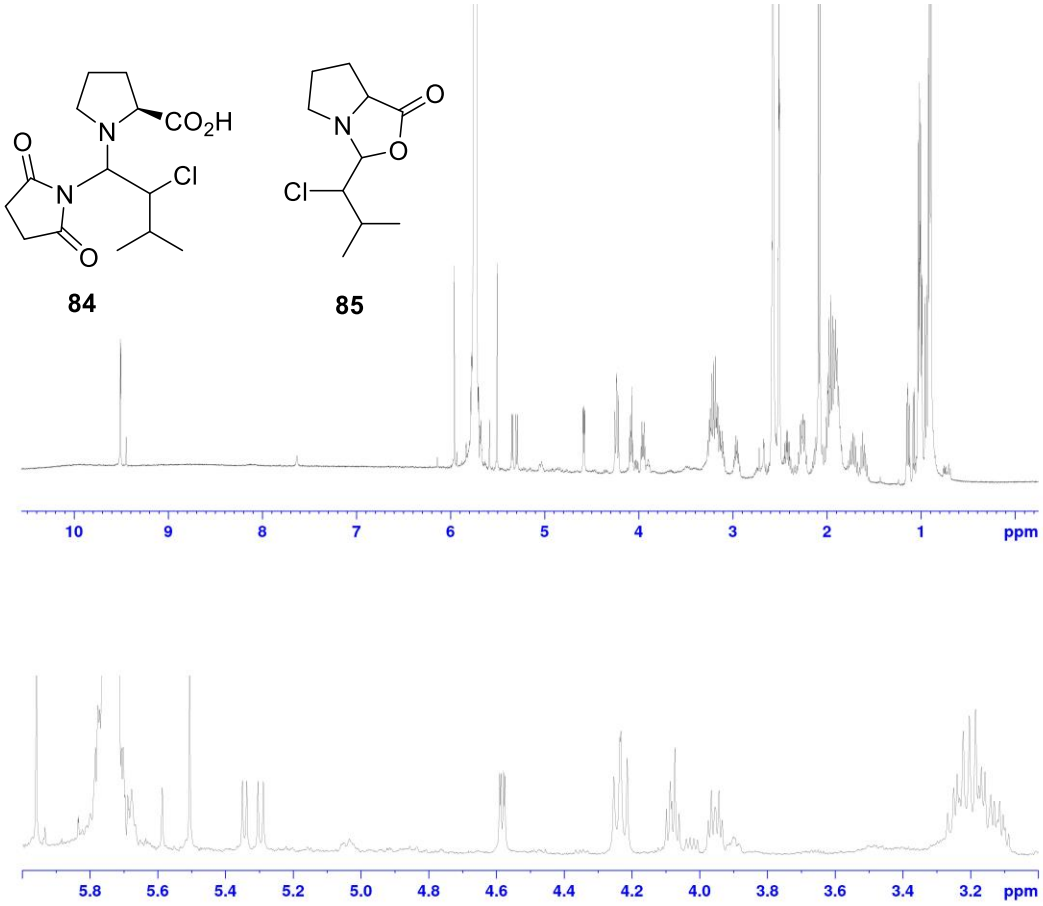


Figure 3.2 Crude ^{1}H NMR of Proposed Intermediate (Compound (84) or (85)) with zoom.

This observation further supports our previous finding that proline reacts readily with α-chloroaldehydes and effects racemization critical to the DKR process. Further, this suggests that the catalyst prefers to exist covalently bound to the α-chloroaldehyde rather than free in solution and prompted us to examine the effect of water on the reaction, which would presumably assist in solubilizing free proline and unveiling α-chloroaldehydes for reaction. It is a known phenomenon that water concentration can affect the concentration of these intermediates in solution[58], and thus the addition of water can perturb this equilibrium and perhaps enhance the reaction rate.

3.3.2. Effect of H_2O on α-Chlorination-Aldol Reaction

Although water was investigated in the original chloro-aldol methodology, it was not used at high concentrations (0.5 eq of water). The effect of water is known to show effects continuing from sub-stoichiometric amounts, until water is used as a reaction solvent. Ward's DKR aldol of thiopyranone employs "wet DMSO" or "wet DMF" which is reported as 0.8 ml water per 6 ml dry DMSO (~12 vol%). Others have reported optimizing the water content for each substrate, in a range of 15-30 eq of water (~9 vol%).

With this in mind, we investigated increasing water concentration from 0% (dry) up to 10 vol%. Here we found significant differences in reaction profiles or "cleanliness" as well as colour changes. The source of colour was not identified, though it should be noted that the products of this aldol reaction are colourless oils or white solids. As expected, the solubility of proline increased with increasing water concentration.

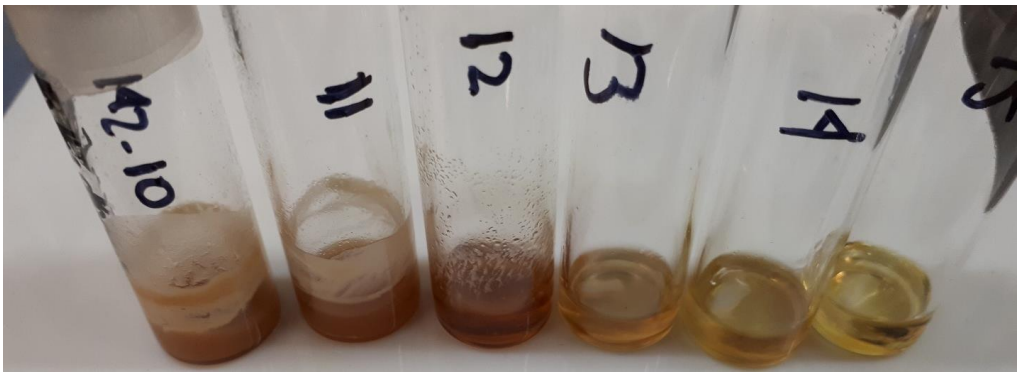


Figure 3.3 Visual Differences in Water Concentration (L-R: 0 vol%, 0.5 vol%, 1.0 vol%, 3.0 vol%, 5.0 vol% and 10 vol%).

Entry	vol%H_2O	Conversion
1	0.0%	21%
2	0.5%	17%
3	1.0%	31%
4	3.0%+	0% (biphasic)

Table 3.5 Effect of Water Concentration on Conversion.

As summarized in Table 3.5, the difference in reaction yield (determined by analysis of ^1H NMR spectra with internal standard recorded on crude reaction products) was significant up to 3 vol% of water (entry 3). At higher concentrations of water, we found reaction conversion decreased and the reactions became biphasic (entry 4). Based on

these results, we repeated several other aldol reactions with 1.0 vol% water and noted increased conversions, cleaner crude reactions and easier purification.

3.4. Demonstrating the Scope of the New Ketones

With the optimized reaction conditions in hand, we set out to demonstrate the applicability of the methodology. With the assistance of Terry Rai (undergraduate student 2018) and Bharanishashank Adluri (PDF) (**86**, **89**), we were able to demonstrate the generality of the methodology by applying the optimized reaction conditions to the compounds shown in figure 3.4.

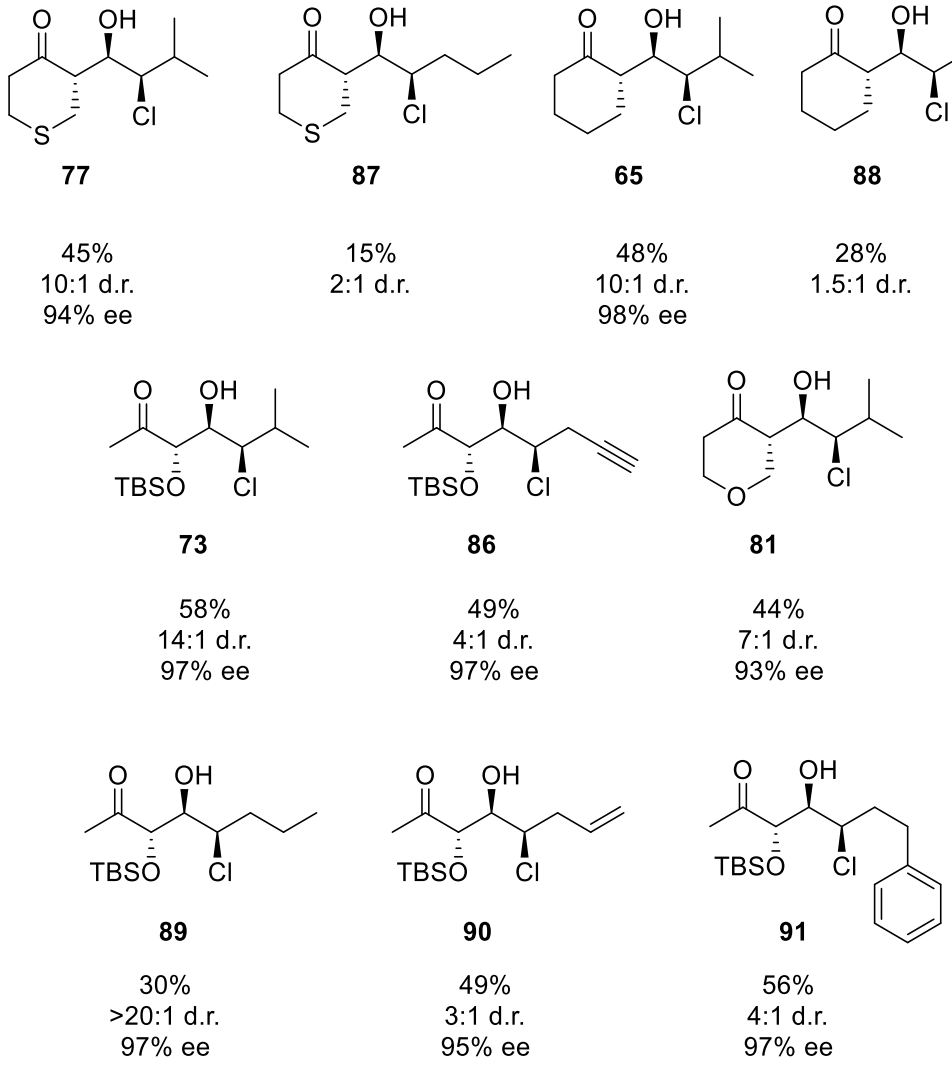
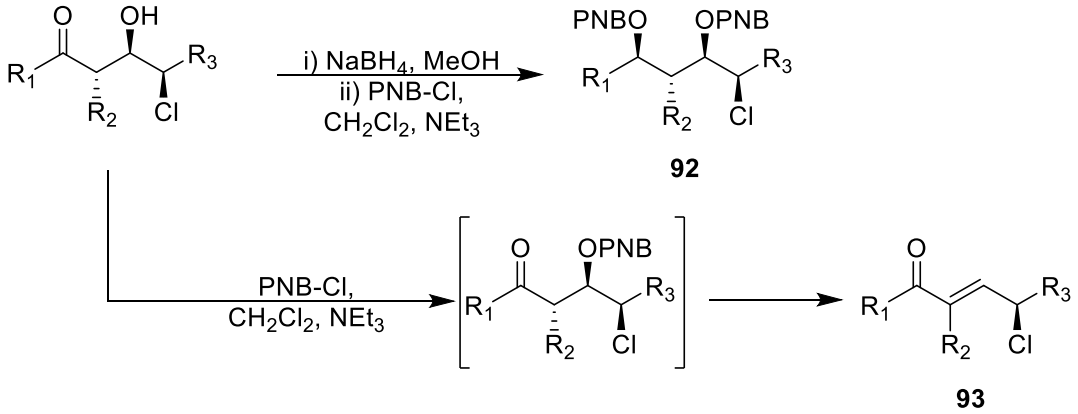


Figure 3.4 Scope of α-Chlorination-Aldol Reaction (Compound (81) isolated as diol after reduction).

3.4.1. Determination of Enantiomeric Excess

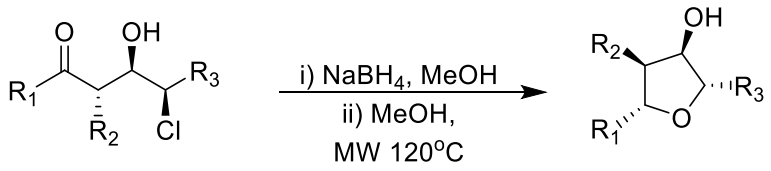
The enantiomeric excess of the aldol adducts was determined in most cases by reducing the ketone function and isolating the corresponding diol (Scheme 3.14). Formation of the bis-*p*-nitrobenzoate (PNB) esters **92** was then effected under standard conditions.[98] Reduction of the ketone was necessary, as elimination products **93** were observed when PNB protection was attempted on the aldol adducts themselves. Once the PNB esters **92** were formed, the UV-absorbing products compounds were amenable to separation by HPLC and detection by a variable wavelength detector (VWD).



Scheme 3.14 Determination of Enantiomeric Excess by Formation of PNB-esters (92).

3.4.2. Synthesis of Novel Small Molecules

To demonstrate the utility of the new aldol adducts, we synthesized a panel of small molecules with the assistance of Lexi Gower-Fry (**93**) (an undergraduate student). THF scaffolds are prevalent throughout nature and found within carbohydrates and polyketides.[96,99] These new aldol reactions provide access to an increased diversity of THFs. Additionally, this exercise provided a means to determine the relative stereochemistry of the chlorohydrins, as nOe correlations could be observed in many of the bicyclic systems (see Experimental). After reduction of aldol adducts to the corresponding diols, cyclization under microwave conditions[68] yielded a range of THFs. Using this synthetic sequence, we were able to generate a small library of THF molecules (Scheme 3.15).



Scheme 3.15 Synthesis of THF Rings from Chlorohydrins.

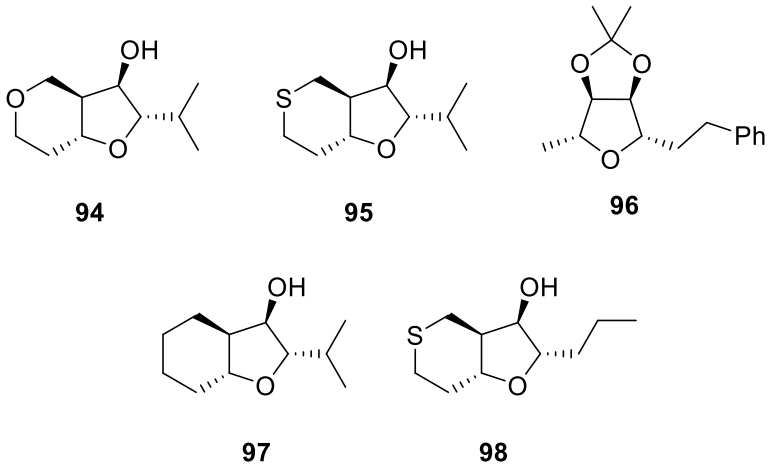
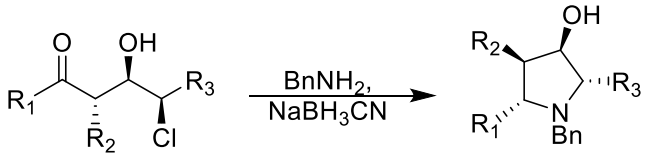
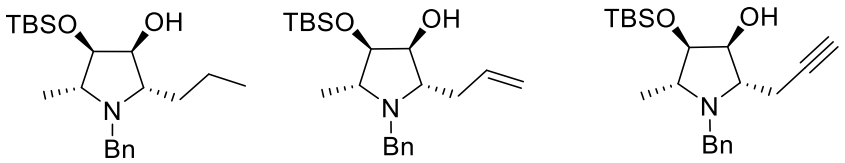


Figure 3.5 Synthesis of THFs (94), (95), (96), (97), and (98).

Additionally, following the procedure established by Bergeron-Brlek[71], reductive amination with benzylamine followed by cyclization under thermal conditions was employed to generate a small library of pyrrolidines with Bharanhishashank Adluri (PDF) and Terry Rai (undergraduate student) (**96**, **97**, **98**). A small library of pyrrolidines was generated and characterized.



Scheme 3.16 Reductive Amination-Cyclization to form Pyrrolidines from Chlorohydrins.



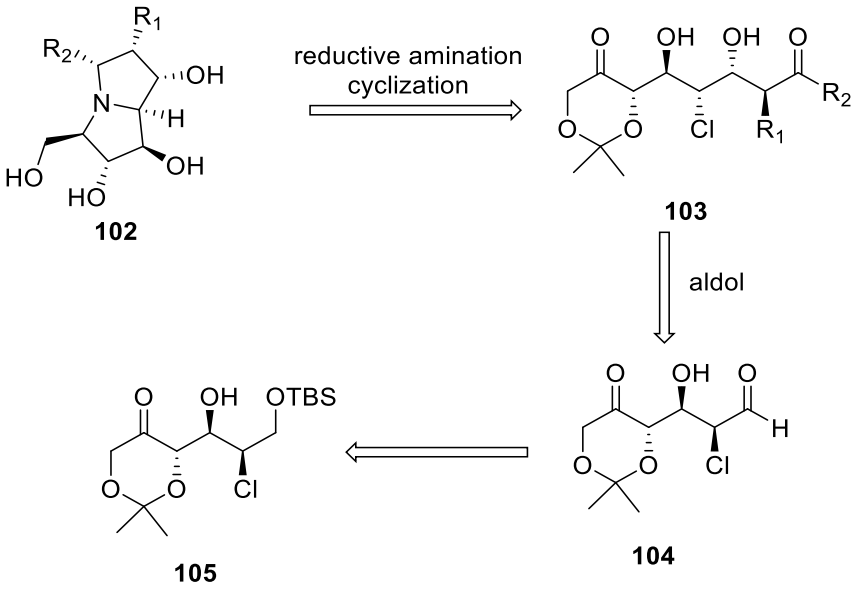
99 **100** **101**

Figure 3.6 Synthesis of Pyrrolidines (99), (100) , and (101).

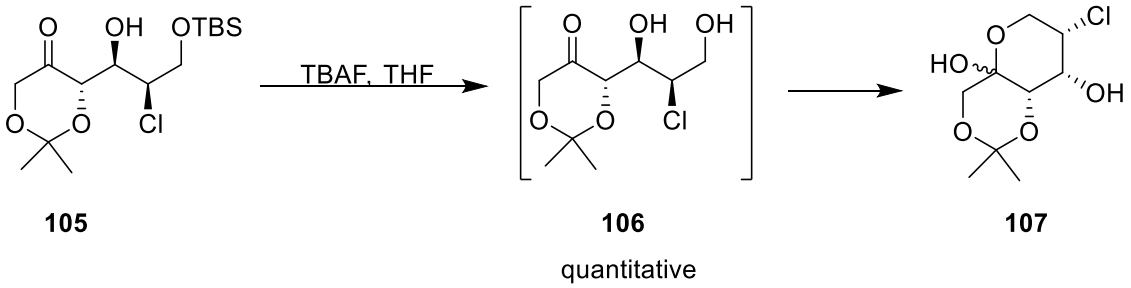
3.5. Studies Towards a Short Synthesis of Hyacinthacine C Derivatives

3.5.1. Initial Strategy to Synthesize Hyacinthacine C Derivative

To further demonstrate the utility of these new aldol adducts, we designed a short synthesis of a member of the hyacinthacine C family **102** (Scheme 3.17).[100] Our initial strategy involved using the previously established dioxanone methodology to provide chlorohydrin **105**. Following deprotection and oxidation to aldehyde **104**, we could then carry out a second aldol to afford **103**. After deprotection, reductive amination and cyclization this sequence should afford **102**. While we were excited to find that deprotection of the known aldol adduct **105** proceeded smoothly, we were unfortunately not able to oxidize the primary alcohol function to aldehyde **104**. We suspected that here, the free alcohol cyclizes to form the corresponding hemiacetal **107** and, consequently, a revised strategy was designed to prevent such processes.



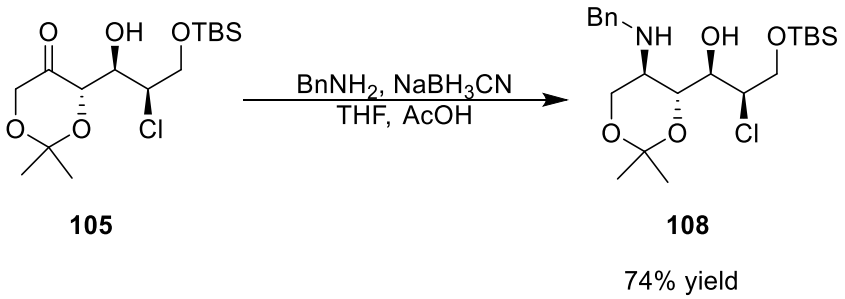
Scheme 3.17 Retrosynthetic Analysis of Hyacynthacine Derivative (102).



Scheme 3.18 Cyclization of the Free Primary Alcohol (106) after Deprotection.

3.5.2. Revised strategy

Based on the observations detailed above, a revised synthetic route was designed to avoid hemiacetal formation. By switching the order of steps, we anticipated that we could avoid hemi-acetal formation. Following the procedures established by Bergeron-Brlek[71], we effected reductive amination of the aldol adduct **105** to give **108** as shown in scheme 3.19.

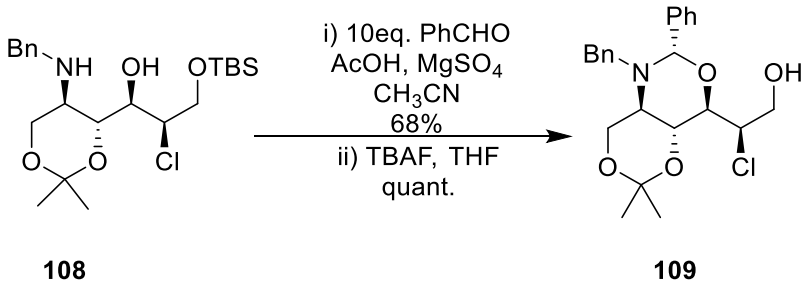


105 **108**

74% yield

Scheme 3.19 Reductive Amination of Aldol Adduct (105).

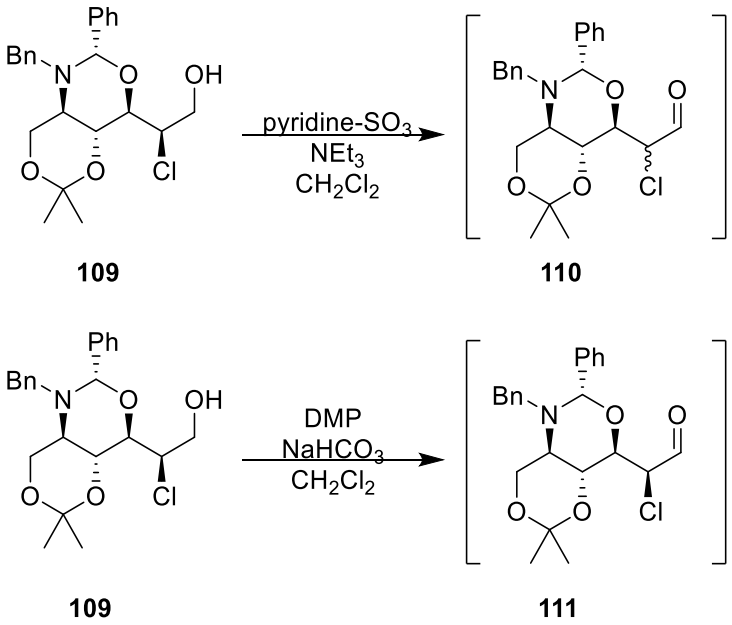
A simple benzylidene protecting group strategy was designed to protect the amine and the secondary alcohol. By mixing **108** in acetonitrile with a large excess of benzaldehyde, $MgSO_4$ and catalytic acetic acid, we were able to isolate a mixture of two diastereomers at the benzylidene position (Scheme 3.20) in good yield. Deprotection of the TBS-alcohol with TBAF proceeded smoothly to give **109**.



108 **109**

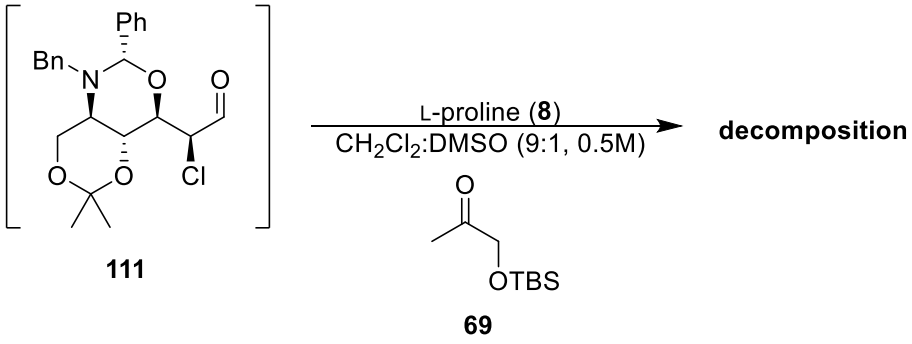
Scheme 3.20 Protection-deprotection sequence to Access Primary Alcohol (109).

Oxidation of the primary alcohol **109** under Parikh-Doering conditions gave a mixture of four aldehydes (Scheme 3.21). We expected two diastereomers at the benzylidene centre and two diastereomers at the α-chloro stereocentre. Fortunately, this was easily remedied following the work of Kang[101] where a Dess-Martin periodane (DMP) oxidation was employed to prevent racemization of the chloromethine-stereocentre. In this case, two diastereomers of the α-chloroaldehyde were isolated, one for each epimer at the benzylidene position.



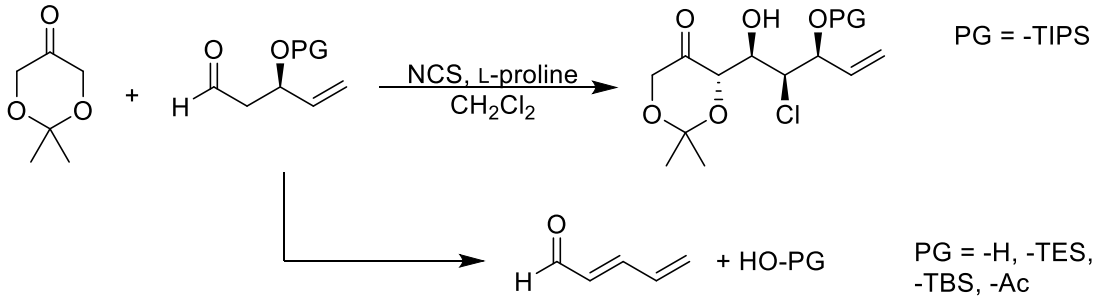
Scheme 3.21 Oxidation of Primary Alcohol (109) with Parikh-Doering and Dess-Martin conditions.

With the α-chloroaldehyde **111** in hand, we attempted the key step, an aldol reaction with one of the new ketones described in this thesis. Unfortunately, upon submission of the aldehyde to the optimized aldol reaction conditions with ketone **69**, we observed rapid decomposition of the aldehyde (Scheme 3.22).



Scheme 3.22 Attempted Aldol Reaction of (111).

Given the lability of the protected hydroxy group under organocatalytic conditions and propensity for this material to undergo elimination this process would require an alternative protecting group strategy. Notably, in the work of Adamson, considerable optimization of the hydroxyl protecting groups was necessary to find a compatible substrate for an organocatalyzed aldol reaction involving a β-hydroxyaldehyde,[102] which ultimately led to the use of a TIPS protecting group (Scheme 3.23).



Scheme 3.23 Adamson's work on Aldehydes Containing Protected β-hydroxy group.

3.6. Conclusion

The scope of the α-chlorination-aldol reaction was expanded to include four new ketones (TBS-protected hydroxyacetone **69**, thiopyranone **24**, pyranone **78**, and cyclohexanone **23**). After identification of these new ketones, a general set of reaction conditions were optimized for this set of substrates. The effect of water on the reaction was investigated and found to have a substantial impact on both the conversions and cleanliness of the reaction. After optimization, ten aldol adducts were synthesized in moderate yields, poor to high diastereoselectivity and high enantioselectivity. The aldol adducts were then used to synthesize a library of eight small molecules (**94-101**). Furthermore, studies towards the concise synthesis of hyacinthacine C natural products using this methodology were examined. Unfortunately, the key reaction utilizing this methodology failed due to an elimination reaction of a protected β-hydroxy group on the intermediate aldehyde.

3.7. Experimental Information

3.7.1. General Considerations

L- and D- proline (99% purity) were purchased from Sigma-Aldrich. All other reagents were purchased from Sigma-Aldrich or TCI and used without purification unless indicated. All reactions described were performed at ambient temperature and open to atmosphere unless otherwise indicated.

Aldehydes were purified by crystallization of bisulfite adducts and regeneration with aqueous K_2CO_3 (1.0 M) or by washing with saturated aqueous Na_2CO_3 prior to

reaction. TBS-protected hydroxyacetone (mono and bis) were synthesized according to literature procedures.[103] 4H-tetrahydrothiopyranone was purchased from TCI America and purified before use by swirling with decolourizing charcoal and filtering with silica plug. All other ketones were purchased from Sigma-Aldrich and used without purification.

NMR spectra were recorded using $CDCl_3$ as the solvent. Signal positions are given in ppm relative to tetramethylsilane and were calibrated using the residual solvent signal (^{1}H NMR: $CDCl_3$ 7.26 ppm ^{13}C NMR: $CDCl_3$ 77.0 ppm). ^{1}H NMR multiplicities are given as (*s*, singlet; *d*, doublet; *t*, triplet; *q*, quartet; *dd*, doublet of doublets; *m*, multiplet; *bs*, broad singlet). ^{1}H and ^{13}C NMR are recorded on a Bruker 600, Bruker 500 or Bruker 400. Diastereomeric ratios are based on analysis of crude ^{1}H NMR spectra.

Infrared spectra were recorded neat on a Perkin-Elmer Spectrum Two FTIR spectrometer. Only selected wavenumbers are provided for each compound. Optical rotations were measured on a Perkin-Elmer Polarimeter 341 at 589nm. HPLC analysis was performed on an Agilent 1100 HPLC equipped with a variable UV-Vis wavelength detector. Enantiomeric excess was determined as indicated for each compound. High resolution mass spectra were performed on an Agilent 6210 TOF LC/MS using ESI-MS.

3.7.2. General Procedures

General Procedure C (Organocatalyzed One-pot α-Chlorination-Aldol)

NCS (1.05 eq) and proline (0.8 eq) were suspended in CH_2Cl_2 (0.56 M) at 0°C. To this suspension was added aldehyde (1 eq). The suspension was allowed to stir at 0°C for 1h. After 1h, ketone (3 eq.), DMSO (final concentration of aldehyde 0.5M, DMSO:CH_2Cl_2 (1:9)) and 1% v/v H_2O were all added to the reaction mixture. The reaction was allowed to warm to room temperature. The reaction was monitored by ^{1}H NMR until disappearance of α-chloro-aldehyde is noted. The reaction was worked up and purified as indicated.

General Procedure D (Reduction of Aldol Adduct)

Dissolve aldol adduct in MeOH (0.5 M) and cool to 0°C. Add 2 eq $NaBH_4$. The reaction was stirred at 0°C until consumption of starting material was observed by TLC (~1 h). The reaction was quenched at 0°C by slow addition of saturated NH_4Cl until bubbling ceased. The reaction mixture was diluted with H_2O to ensure all solids were dissolved. The crude mixture was extracted 3x with CH_2Cl_2. The organic layer was dried with brine, and Na_2SO_4. The organic layer was concentrated under reduced pressure and purified as indicated.

General Procedure E (Cyclization of Diol)

Chlorodiol was dissolved in MeOH (0.5 M) and placed in a microwave vial. The vial was sealed in a CEM Discover LabMate microwave reactor and subjected to microwave radiation. The vial was heated for 5 minutes at 90°C, then for 5 minutes at 110°C, before heating for 1.8 h at 120°C (pressure was kept below 300 psi). The vial was cooled and analyzed by TLC to ensure complete consumption of starting material. The crude mixture was concentrated under reduced pressure and then purified by column chromatography on silica as indicated.

General Procedure F (Synthesis of PNB-esters for Determination of Enantiomeric Excess)

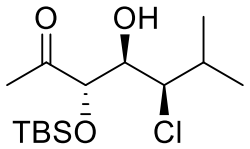
Either the chlorodiol or aldol adduct (depending on stability) was dissolved in 1:1 CH_2Cl_2:NEt_3 (0.4M). To this was added 2 eq of PNB-Cl per alcohol on substrate (2 or 4eq). A spatula tip of DMAP was added to the solution, which was allowed to stir overnight. The reaction mixture was washed with each of H_2O, 1.0M aqueous HCl and brine, dried with Na_2SO_4 and concentrated under reduced pressure. The adducts were purified by column chromatography on silica as indicated

General Procedure G (Reductive Amination)

Chlorohydrin was dissolved in dry THF (0.1 M) with 1 eq of AcOH. Amine (2 eq) was added and allowed to stir for ~1hour or until most of the chlorohydrin has been consumed by TLC. $NaBH_3CN$ (2eq.) was added and the reaction was stirred for another 1h, or until intermediate imine is consumed by TLC. The reaction was quenched with water and the organic layers were separated. Extract the aqueous layer 3x with CH_2Cl_2 and dry with brine, then $NaSO_4$. Concentrate and purify as indicated.

3.7.3. Preparation and Characterization Data of Aldol Adducts

Preparation of Chlorohydrin (73)



According to general procedure **C**, NCS (0.53 mmol, 71 mg) and L-proline (0.40 mmol, 46 mg) were stirred in CH_2Cl_2 (0.9 mL) at 0°C, before adding isovaleraldehyde (0.5 mmol, 54 uL). After 1h, add ketone (1.5 mmol, 282 mg), DMSO (0.1 mL) and H_2O (10 µL). Reaction was stirred for 24h allowing to warm to room temperature. Volatiles were evaporated under reduced pressure and then crude reaction was applied to SiO_2 column. Purification by flash chromatography (hexanes-EtOAc-NEt_3 95%:4%:1%) afforded (180mg, 58%) of a pale-yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ=3.96 (*dd*, *J* = 7.3, 2.0 Hz, 1H), 3.94 (*d*, *J* = 8.2 Hz, 1H), 3.82 (*d*, *J* = 8.2 Hz ,1H), 2.26 (*bs*, 1H), 2.20 (s, 3H), 2.12 (*m*, *J* =6.8 Hz, 1H), 1.07 (*d*, *J* =6.6 Hz, 3H), 1.03(*d*, *J* =6.7 Hz, 3H), 0.89 (*s*, 9H), 0.08 (*s*, 3H), 0.02 (*s*, 3H)

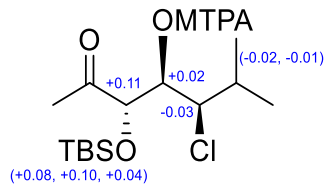
^{13}C NMR (125 MHz, $CDCl_3$) δ= 209.7, 79.0, 73.0, 70.8, 32.5, 25.6, 25.5, 20.3, 20.0, 18.0, -4.9, -5.2 ppm

HRMS (ESI) *m/z* calcd for $C_{14}H_{30}ClO_3Si$ $[M+H]^+$ 309.1647, found 309.1666

IR: 3453, 2956, 2930, 1718, 1254, 1102, 835, 777 cm^{-1}

α_D^{20}= -18.9 (c = 64 mg/mL in $CHCl_3$)

Determination of Absolute Stereochemistry for Chlorohydrin (73)

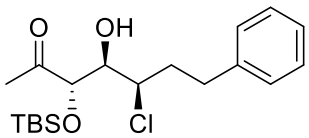


Chlorohydrin **73** (10 mg, 0.03 mmol) was converted to the corresponding (S) and (R) MTPA-esters by exposing the chlorohydrin to 50 eq DMAP, 20 eq DIC, and 5 eq of either (S) or (R) Mosher's acid in 0.1 M dry CH_2Cl_2. The reaction was stirred for 2 days. After 2 days the CH_2Cl_2 was evaporated, and the resulting solid was suspended in EtOAc and filtered through a SiO_2 plug. The crude mixture was concentrated again, dry loaded onto SiO_2 and purified using by flash chromatography (90:10 Hexanes:EtOAc). The absolute stereochemistry was assigned using Mosher's method[104], and matches with previous trends in chlorohydrin stereochemistry.[68]

Determination of Enantiomeric Excess of Chlorohydrin (73)

According to general procedure **F**, the corresponding PNB esters of chlorohydrin **73** were prepared of each a racemic and enantioenriched sample. The enantiomeric PNB esters were separated by chiral HPLC using Phenomex Lux (3 µm) i-Cellulose-5 column; flow rate 0.15 mL/min; eluent: hexanes-*i*PrOH 95:5; detection at 254 nm; retention time = 2.89 min and 3.61 min. The enantiomeric excess of the optically enriched PNB ester was determined using the same method (97% ee).

Preparation of Chlorohydrin (91)



According to general procedure **C**, NCS (0.53 mmol, 71 mg) and L-proline (0.40 mmol, 46 mg) were stirred in CH_2Cl_2 (0.9 mL) at 0°C, before adding in 4-phenylbutanal (0.5 mmol, 74 mg). After 1h, ketone (1.5 mmol, 282 mg), DMSO (0.1 mL) and H_2O (10 µL) were added. The reaction was stirred for 24h allowing to warm to room temperature.

Volatiles were evaporated under reduced pressure and then crude reaction was applied to SiO_2 column and purified using (90:10 hexanes:EtOAc) to give white solid (108 mg, 56% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ= 7.28 (*m*, 2H), 7.21 (*m*, 3H), 4.15 (*ddd*, *J* = 1.6, 4.0, 10.2 Hz, 1H), 3.94 (*d*, *J* = 8.6 Hz , 1H), 3.63 (*m*, *J* =1.6, 8.5, 10.4 Hz, 1H), 2.91 (*m*, *J* = 5.0, 7.5, 12.9 Hz, 1H), 2.78 (*m*, *J* = 7.3, 8.6, 13.9 Hz, 1H), 2.29 (*m*, *J* = 5.0, 7.4, 10.3, 14.3 Hz, 1H), 2.20 (*s*, 3H), 2.13 (*d*, *J* = 11.0 Hz, 1H), 2.07 (*m*, 1H), 0.80 (*s*, 9H), 0.00 (*s*, 6H)

^{13}C NMR (125 MHz, $CDCl_3$) δ= 209.4, 140.3, 128.6, 128.6, 126.3, 79.0, 75.0, 63.1, 36.5, 32.5, 25.6, 25.3, 17.9, -4.9, -5.3

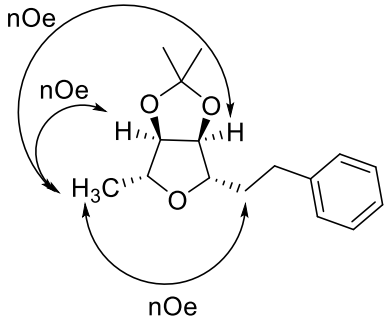
HRMS (ESI) *m/z* calcd for $C_{19}H_{25}ClO_3NSi$ $[M+NH_4]^+$ 388.2069, found 388.2041

IR: 3362, 2958, 2927, 2856, 1708, 1104, 1074, 834, 698 cm^{-1}

m.p.: 70-73°C

α_D^{20}= -9.7 (c=20 mg/mL in $CHCl_3$)

Determination of Relative Stereochemistry for Chlorohydrin (91), preparation of (96)



According to general procedure **D**, chlorohydrin **91** (0.5 mmol, 194 mg) was reduced to the corresponding chlorodiol with $NaBH_4$ (1.0 mmol, 37 mg) in MeOH (1 mL). After consumption of starting material was noted by TLC, the reaction was quenched with aqueous NH_4Cl (5 mL) and extracted 3x with 10 mL of CH_2Cl_2. The crude mixture was concentrated by rotary evaporation. Subsequently, according to general procedure **E**, without purification, the crude reduction product was subjected to microwave irradiation.

After microwave irradiation, the reaction mixture was concentrated by rotary evaporation and dry loaded on to SiO_2. Purification by column chromatography (60:40 Hexanes:EtOAc) to give a white solid in 18% yield (20 mg, 0.09 mmol).

The cyclic diol was stirred in acetone (0.1 M) with TsOH (0.1 eq, 30 mg) and two heaping spatula tips of $MgSO_4$ to form the acetonide protected THF. The crude product was purified by column chromatography (60:40 hexanes:EtOAc) to yield (18 mg, 0.08 mmol) a clear oil in 17% overall yield from aldol adduct. Relative stereochemistry was determined by 2D NOE analysis. Key NOE correlations are shown above.

^{1}H NMR (600 MHz, $CDCl_3$) δ= 7.29 (*m*, 2H), 7.21 (*m*, 3H), 4.37 (*dd*, *J* = 4.9, 7.2 Hz, 1H), 4.27 (*dd*, *J* = 5.0, 7.2 Hz, 1H), 3.92 (*m*, 1H), 3.83 (*td*, *J* = 4.9, 6.7 Hz, 1H), 2.78 (*m*, 1H), 2.72 (*m*, 1H), 1.93 (*m*, 2H), 2.53 (*s*, 3H), 1.34 (*s*, 3H), 1.33 (*d*, *J* = 7.7 Hz, 3H)

^{13}C NMR (150 MHz, $CDCl_3$) δ= 141.6, 128.4, 128.3, 125.8, 114.9, 86.2, 85.3, 83.3, 79.9, 35.4, 31.8, 29.7, 27.3, 25.4, 19.0

HRMS: (ESI) *m/z* calcd for $C_{16}H_{23}O_3[M+H]^+$ 263.1642, found 263.1635

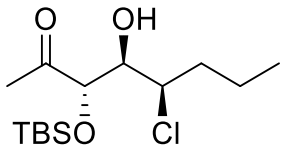
IR: 3027, 2957, 2929, 2871, 1708, 1381, 1210, 1074, 865, 699, 512 cm^{-1}

α_D^{20}= -14.7 (c = 22 mg/mL in $CHCl_3$)

Determination of Enantiomeric Excess of Chlorohydrin (91)

According to general procedure **F**, the corresponding PNB esters of chlorohydrin **85** were prepared of each a racemic and enantioenriched sample. The enantiomeric PNB esters were separated by chiral HPLC using Phenomex Lux (3 µm) Amylose-5 column; flow rate 0.4 mL/min; eluent: hexanes-*i*PrOH 95:5; detection at 254 nm; retention time = 3.24 min and 3.71 min. The enantiomeric excess of the optically enriched PNB ester was determined using the same method (97% ee).

Preparation of Chlorohydrin (89)



According to general procedure **C** NCS (0.53 mmol, 71 mg) and L-proline (0.40 mmol, 46 mg) were stirred in CH_2Cl_2 (0.9 mL) at 0°C, before adding in valeraldehyde (0.5 mmol, 54 µL). After 1h, ketone (1.5 mmol, 282 mg), DMSO (0.1 mL) and H_2O (10 µL) were added. The reaction was stirred for 24h allowing to warm to room temperature. Volatiles were evaporated under reduced pressure and then the crude reaction was applied to SiO_2 column (5-10-15% EtOAc in hexanes gradient) to give pale yellow oil (44 mg, 27% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ= 4.28 (*ddd*, *J* = 1.8, 5.2, 9.2 Hz, 1H), 3.97 (*d*, *J* = 8.5 Hz, 1H), 3.67 (*ddd*, *J* = 1.7, 8.5, 10.3 Hz, 1H), 2.23 (*s*, 3H), 2.08 (*d*, *J* = 10.5 Hz, 1H), 1.92 (*m*, *J* = 4.6, 9.3, 14.3 Hz, 1H), 1.78 (*m*, *J* = 5.3, 6.7, 8.9, 14.0 Hz, 1H), 1.54 (*m*, 2H), 0.96 (*t*, *J* = 7.4 Hz, 3H), 0.91 (*s*, 9H), 0.12 (*s*, 3H), 0.05 (*s*, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ= 209.5, 79.1, 74.4, 63.8, 37.0, 25.6, 25.4, 19.9, 18.0, 13.2, -4.8, -5.1

HRMS: (ESI) *m/z* calcd for $C_{14}H_{33}ClO_3NSi$ $[M+NH_4]^+$ 326.1913, found 326.1889

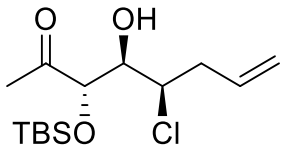
IR: 3446, 2958, 2931, 1716, 1254, 1099, 837, 778, 672 cm^{-1}

α_D^{20}= -0.8 (c = 13 mg/mL in $CHCl_3$)

Determination of Enantiomeric Excess of Chlorohydrin (89)

According to general procedure **F**, the corresponding PNB esters of chlorohydrin **83** were prepared of each a racemic and enantioenriched sample. The enantiomeric PNB esters were separated by chiral HPLC using Phenomex Lux (3 µm) i-Cellulose-5 column; flow rate 0.2 mL/min; eluent: hexanes-*i*PrOH 97:3; detection at 254 nm; retention time = 2.61 min and 3.30 min. The enantiomeric excess of the optically enriched PNB ester was determined using the same method (97% ee).

Preparation of Chlorohydrin (90)



According to general procedure **C**, NCS (0.53 mmol, 71 mg) and L-proline (0.40 mmol, 46 mg) were stirred in CH_2Cl_2 (0.9 mL) at 0°C, before adding in 4-pentenal (0.5 mmol, 42 mg). After 1h, ketone (1.5 mmol, 282 mg), DMSO (0.1 mL) and H_2O (10 µL) were added. The reaction was stirred for 24h allowing to warm to room temperature. Volatiles were evaporated under reduced pressure and then crude reaction was applied to SiO_2 column and purified by flash chromatography (80:20 hexanes:EtOAc) to give a clear oil (51 mg, 49% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ= 5.83 (*m*, *J* = 6.9, 10.2 Hz, 1H), 5.20 (*m*, 2H), 4.26 (*m*, *J* = 1.9, 7.2 Hz, 1H), 3.97 (*d*, *J* = 8.5 Hz, 1H), 3.73 (*m*, *J* = 1.9, 8.5, 10.3 Hz, 1H), 2.65 (*m*, 2H), 2.23 (*s*, 3H), 2.09 (*d*, *J* = 10.3 Hz, 1H), 0.92 (*s*, 9H), 0.12 (*s*, 3H), 0.05 (*s*, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ= 209.4, 133.6, 118.5, 78.9, 73.8, 62.8, 39.3, 25.6, 25.4, 18.0, -4.9, -5.1

HRMS: (ESI) *m/z* calcd for $C_{14}H_{28}ClO_3Si$ $[M+H]^+$ 307.1491, found 307.1504

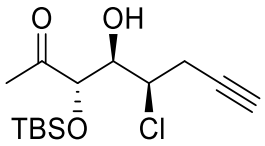
IR: 3443, 2955, 2929, 2858, 1716, 1641, 1255, 1097, 837, 778 cm^{-1}

α_D^{20}= -27.7 (c=18.4 mg/mL in $CHCl_3$)

Determination of Enantiomeric Excess of Chlorohydrin (90)

According to general procedure **F**, the corresponding PNB esters of chlorohydrin **84** were prepared of each a racemic and enantioenriched sample. The enantiomeric PNB esters were separated by chiral HPLC using Phenomex Lux (3 µm) i-Cellulose-5 column; flow rate 0.4 mL/min; eluent: hexanes-*i*PrOH 95:5; detection at 254 nm; retention time = 1.18 min and 1.50 min. The enantiomeric excess of the optically enriched PNB ester was determined using the same method (95% ee).

Preparation of Chlorohydrin (86)



According to general procedure **C**, NCS (0.53 mmol, 71 mg) and L-proline (0.40 mmol, 46 mg) were stirred in CH_2Cl_2 (0.9 mL) at 0°C, before adding in 4-pentynal (0.5 mmol, 41 mg). After 1h, ketone (1.5 mmol, 282 mg), DMSO (0.1 mL) and H_2O (10 µL) were added. The reaction was stirred for 24h allowing to warm to room temperature. Volatiles were evaporated under reduced pressure and then crude reaction was applied to SiO_2 column and the product purified by flash chromatography (70:30 hexanes:EtOAc) to give a clear oil (75 mg, 49% yield)

^{1}H NMR (500 MHz, $CDCl_3$) δ= 4.30 (*m*, 1H), 3.97 (*bs*, 2H), 2.83 (*m*, *J* = 1.3, 2.7, 6.8 Hz, 2H), 2.25 (*s*, 3H), 2.18 (*s*, 1H), 2.14 (*m*, *J* = 2.7 Hz, 1H), 0.93 (*s*, 9H), 0.13 (*s*, 3H), 0.06 (*s*, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ= 209.7, 79.4, 78.7, 73.1, 71.5, 60.4, 25.6, 25.5, 25.1, 18.0, -4.8, -5.1

HRMS: (ESI) *m/z* calcd for $C_{14}H_{29}ClO_3NSi$ $[M+NH_4]^+$ 322.1600, found 322.1604

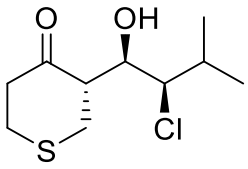
IR: 3450, 3311, 2954, 2929, 1716, 1255, 1101, 837, 778, 635, 505 cm^{-1}

α_D^{20}= -34.3 (c = 8 mg/mL in $CHCl_3$)

Determination of Enantiomeric Excess of Chlorohydrin (86)

According to general procedure **F**, the corresponding PNB esters of chlorohydrin **86** were prepared of each a racemic and enantioenriched sample. The enantiomeric PNB esters were separated by chiral HPLC using Phenomex Lux (3 µm) i-Cellulose-5 column; flow rate 0.4 mL/min; eluent: hexanes-*i*PrOH 99:1; detection at 254 nm; retention time = 3.06 min and 3.79 min. The enantiomeric excess of the optically enriched PNB ester was determined using the same method (97% ee).

Preparation of Chlorohydrin (79)



According to general procedure **C**, NCS (0.53 mmol, 71 mg) and L-proline (0.40 mmol, 46 mg) were stirred in CH_2Cl_2 (0.9 mL) at 0°C, before adding isovaleraldehyde (0.5 mmol, 54 µL). After 1h, thiopyranone (1.5 mmol, 174 mg), DMSO (0.1 mL) and H_2O (10 µL) were added. The reaction was stirred for 48h allowing to warm to room temperature. Volatiles were evaporated under reduced pressure and then the crude reaction was applied to SiO_2 column and product purified by flash chromatography (80:20 hexanes:EtOAc) to give a white solid (53 mg, 45% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ= 4.31 (*m*, *J* = 3.7, 7.4 Hz, 1H), 3.68 (*dd*, *J* = 2.5, 8.0 Hz, 1H), 3.07 (*m*, 1H) 3.00-2.90 (*m*, 4H), 2.84-2.70 (*m*, 3H), 2.19 (*m*, *J* = 2.0, 6.6 Hz, 1H), 1.10 (*d*, *J* = 6.7 Hz, 3H), 1.05 (*d*, *J* = 6.7 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ= 210.8, 70.7, 70.5, 56.5, 44.1, 32.2, 31.9, 30.5, 20.3, 20.1

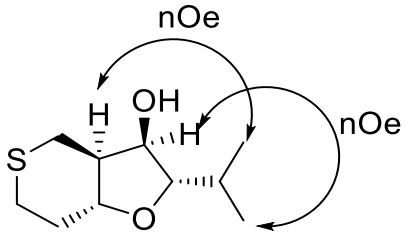
HRMS: (ESI) *m/z* calcd for $C_{10}H_{21}ClO_2NS[M+NH_4]^+$ 254.0976, found 254.0957

IR: 3539, 2970, 2926, 2872, 1684, 1323, 1307, 1248, 1057, 638, 560, 526 cm^{-1}

m.p.: 91-93°C

α_D^{20}= -37.4 (c=32.5 mg/mL in $CHCl_3$)

Determination of Relative Stereochemistry for Chlorohydrin (79), preparation of (98)



According to general procedure **D**, chlorohydrin **79** (1.0 mmol, 250 mg) was reduced to the corresponding chlorodiol with $NaBH_4$ (2.0 mmol, 74 mg) in MeOH (2 mL).

After consumption of starting material was noted by TLC, the reaction was quenched with aqueous NH_4Cl (5 mL) and extracted 3x with 10 mL of CH_2Cl_2. The crude mixture was concentrated by rotary evaporation. Subsequently, according to general procedure **E**, without purification, the crude reduction product was subjected to microwave irradiation. After microwave irradiation, the reaction mixture was concentrated by rotary evaporation and dry loaded on to SiO_2. Purification by column chromatography (80:20 hexanes:EtOAc) gave a white solid (30 mg, 15% yield). Relative stereochemistry was determined by 2D NOE analysis. Key NOE correlations are shown above.

^{1}H NMR (600 MHz, $CDCl_3$) δ= 4.06 (*m*, 1H), 3.43 (*d*, *J* = 6.5 Hz, 1H), 3.38 (*ddd*, *J* = 3.7, 10.95, 10.94 Hz, 1H), 2.84 (*dd*, *J* = 11.6, 13.0 Hz, 1H), 2.73-2.61 (*m*, 3H), 2.46 (*m*, *J* = 3.5, 11.1 Hz, 1H), 1.74 (*m*, 1H), 1.66 (*m*, 1H), 1.60 (*m*, 1H), 0.95 (*d*, *J* = 6.8 Hz, 3H), 0.92 (*d*, *J* = 6.7 Hz, 3H)

^{13}C NMR (150 MHz, $CDCl_3$) δ= 91.9, 78.7, 74.7, 49.9, 33.6, 31.0, 27.3, 18.4, 18.3

HRMS: (ESI) *m/z* calcd for $C_{10}H_{19}O_2S[M+H]^+$ 203.1100, found 203.1098

IR: 3398, 2924, 1437, 1382, 1072, 1015, 945, 880, 634 cm^{-1}

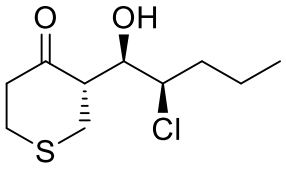
m.p.: 82-86°C

α_D^{20}= +4.7 (c=27 mg/mL in $CHCl_3$)

Determination of Enantiomeric Excess of Chlorohydrin (79)

According to general procedure **F**, the corresponding PNB esters of chlorohydrin **77** were prepared of each a racemic and enantioenriched sample. The enantiomeric PNB esters were separated by chiral HPLC using Phenomex Lux (3 µm) Amylose-3 column; flow rate 0.4 mL/min; eluent: hexanes-*i*PrOH 90:10; detection at 254 nm; retention time = 10.77 min and 16.02 min. The enantiomeric excess of the optically enriched PNB ester was determined using the same method (94% ee).

Preparation of Chlorohydrin (87)



According to general procedure **C**, NCS (0.53 mmol, 71 mg) and L-proline (0.40 mmol, 46 mg) were stirred in CH_2Cl_2 (0.9 mL) at 0°C, before adding valeraldehyde (0.5 mmol, 54 µL). After 1h, thiopyranone (1.5 mmol, 174 mg), DMSO (0.1 mL) and H_2O (10 µL) were added. The reaction was stirred for 48h allowing to warm to room temperature. Volatiles were evaporated under reduced pressure and then the crude reaction was applied to SiO_2 column and the product purified by flash chromatography (80:20 hexanes:EtOAc) to give a clear oil. (17 mg, 15% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ= 4.13 (*m*, *J* = 2.3, 6.3, 8.4 Hz, 1H), 4.00 (*m*, *J* = 2.3, 5.0, 9.0 Hz, 1H), 3.10 (*m*, 1H), 3.03-2.90 (*m*, 4H), 2.86-2.66 (*m*, 4H), 1.95 (*m*, 1H), 1.82 (*m*, 1H), 1.58 (*m*, 1H), 1.45 (*m*, 1H), 0.96 (*t*, *J* = 7.4 Hz, 3H)

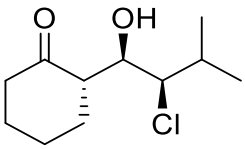
^{13}C NMR (100 MHz, $CDCl_3$) δ= 210.1, 72.3, 63.5, 56.3, 44.2, 37.0, 32.0, 30.6, 20.0, 13.5

HRMS: (ESI) *m/z* calcd for $C_{10}H_{18}ClO_2S[M+H]^+$ 237.0711, found 237.0732

IR: 3442, 2958, 2929, 1705, 1427, 1072, 1052, 752, 618 cm^{-1}

α_D^{20}= -15.0 (c = 17.8 mg/mL in $CHCl_3$)

Preparation of Chlorohydrin (65)



According to general procedure **C**, NCS (1.05 mmol, 142 mg) and L-proline (0.80 mmol, 92 mg) were stirred in CH_2Cl_2 (1.8 mL) at 0°C, before adding in isovaleraldehyde (1.0 mmol, 108 µL). After 1h, ketone (**2.0 eq,** 2.0 mmol, 200 µL) in solution of DMSO (0.2mL) and H_2O (20 µL) was added. The reaction was stirred, and allowed to warm to

room temperature. The reaction was monitored by ^{1}H NMR until consumption of starting material was noted (2d).

Workup: Volatiles were evaporated by rotary evaporation. To the crude reaction mixture was added ~2 mL of saturated aqueous NH_4Cl. The aqueous phase was extracted with Et_2O 2x. The combined organic layers were washed with saturated aqueous $NaHCO_3$, then brine. The organic layer was dried with Na_2SO_4 and concentrated by rotary evaporation. The crude product was purified by flash chromatography on SiO_2 column (90:10 hexanes:EtOAc). The product was isolated as a pale yellow oil (104 mg, 48% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ= 4.09 (*dd*, *J* = 2.0, 8.4 Hz, 1H), 3.58 (*dd*, *J* = 1.8, 8.7 Hz, 1H), 3.51 (*bs*, 1H), 2.76 (*m*, 1H), 2.47-2.27 (*m*, 2H), 2.22 (*m*, 1H), 2.12 (*m*, 2H), 1.91 (*m*, 1H), 1.68 (*m*, 2H), 1.32 (*m*, 1H), 1.11 (*dd*, *J* = 1.7, 6.8 Hz, 3H), 1.02 (*dd*, *J* = 2.0, 6.5 Hz, 3H)

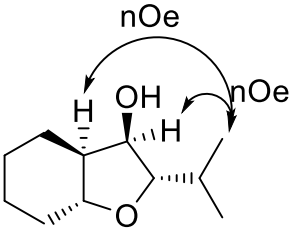
^{13}C NMR (100 MHz, $CDCl_3$) δ= 215.2, 70.9, 70.6, 54.4, 42.6, 32.2, 29.5, 27.5, 24.5, 20.8, 20.1

HRMS: (ESI) *m/z* calcd for $C_{11}H_{20}ClO_2[M+H]^+$ 219.1146, found 219.1135

IR: 3530, 2939, 2870, 1695, 1241, 1131, 1603, 732, 531 cm^{-1}

α_D^{20}= -13.2 (c = 79 mg/mL in $CHCl_3$)

Determination of Relative Stereochemistry of Chlorohydrin (65), preparation of (97)



According to general procedure **D**, chlorohydrin **65** (100 mg, 0.45 mmol) was reduced to the corresponding chlorodiol with $NaBH_4$ (2.0 mmol, 74 mg) in MeOH (2 mL). After consumption of starting material was noted by TLC, the reaction was quenched with aqueous NH_4Cl (5 mL) and extracted 3x with 10 mL of CH_2Cl_2. The crude mixture was

concentrated by rotary evaporation. Subsequently, according to general procedure **E**, After microwave irradiation, the reaction mixture was concentrated by rotary evaporation and dry loaded on to SiO_2. Purification by column chromatography (80:20 Hexanes:EtOAc) to gave a white solid (60 mg, 74% yield). Key NOE correlations are shown above.

^{1}H NMR (600 MHz, $CDCl_3$) δ= 3.97 (*m*, 1H), 3.47 (*m*, *J* = 6.5 Hz, 1H), 3.39 (*m*, *J* = 4.9, 11.0 Hz, 1H), 2.15 (*m*, 1H), 1.84-1.70 (*m*, 5H), 1.37-1.17 (*m*, 4H), 1.13 (*m*, 1H), 0.95 (*d*, *J* = 6.7 Hz, 3H), 0.92 (*d*, *J* = 6.7 Hz, 3H)

^{13}C NMR (150 MHz, $CDCl_3$) δ= 93.1, 79.4, 76.6, 50.2, 31.5, 31.1, 25.5, 23.9, 23.3, 18.49, 18.47

HRMS: (ESI) *m/z* calcd for $C_{11}H_{21}O_2[M+H]^+$ 185.1536, found 185.1541

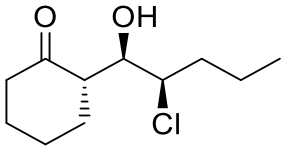
IR: 3368, 2931, 2865, 1446, 1081, 1070, 978, 641 cm^{-1}

α_D^{20}= +4.7 (c = 42.3 mg/mL in $CHCl_3$)

Determination of Enantiomeric Excess of Chlorohydrin (65)

Firstly, according to procedure **D**, the chlorohydrin was reduced to the corresponding diol. Then, according to general procedure **F**, the corresponding PNB esters of chlorohydrin **65** were prepared of each a racemic and enantioenriched sample. The enantiomeric PNB esters were separated by chiral HPLC using Phenomex Lux (3μm) Amylose-5 column; flow rate 0.250 mL/min; eluent: hexanes-*i*PrOH 97:3; detection at 254 nm; retention time = 6.46 min and 7.08 min. The enantiomeric excess of the optically enriched PNB ester was determined using the same method (98% ee).

Preparation of Chlorohydrin (88)



According to general procedure **C**, NCS (0.53 mmol, 71 mg) and L-proline (0.40 mmol, 46 mg) were stirred in CH_2Cl_2 (0.9 mL) at 0°C, and then valeraldehyde (0.5mmol, 54 µL) was added. After 1h, ketone (2 eq, 1.0 mmol, 100 µL) in solution of DMSO (0.1 mL) and H_2O (10 µL) was added. The reaction was stirred and allowed to warm to room temperature. The reaction was monitored by ^{1}H NMR until consumption of starting material was noted (2d).

Workup: Volatiles were removed by rotary evaporation. The crude product was mixed with 2mL of saturated aqueous NH_4Cl and extracted with 5 mL of Et_2O 2x. The combined organic layers were washed with saturated aqueous $NaHCO_3$, then brine. The organic layers were dried with Na_2SO_4 and then concentrated by rotary evaporation. The crude product was purified by flash chromatography on a SiO_2 column (90:10 hexanes:EtOAc) to give a pale yellow oil (30 mg, 28% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ= 3.93 (*m*, 2H), 3.64 (*m*, *J* = 1.4, 3.7 Hz, 1H), 2.76 (*m*, *J* = 1.2, 5.8, 8.3 Hz, 1H), 2.49-2.29 (*m*, 2H), 2.14 (*m*, 2H), 2.03-1.88 (*m*, 2H), 1.85-1.50 (*m*, 4H), 1.48-1.30 (*m*, 3H), 0.94 (*t*, *J* = 7.4 Hz, 3H)

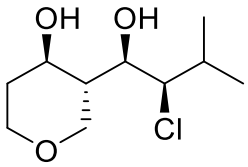
^{13}C NMR (125 MHz, $CDCl_3$) δ= 215.2, 72.7, 63.4, 54.1, 42.6, 37.0, 29.5, 27.5, 24.6, 20.0, 13.5

HRMS: (ESI) *m/z* calcd for $C_{11}H_{20}ClO_2[M+H]^+$ 219.1146, found 219.1126

IR: 3512, 2934, 2865, 1698, 1449, 1309, 1278, 1132, 1063, 612, 541 cm^{-1}

α_D^{20}= +10.0 (c = 100.6 mg/mL in $CHCl_3$)

Preparation of Chlorohydrin (83)



According to general procedure **C**, NCS (1.05 mmol, 142 mg) and L-proline (0.80 mmol, 90 mg) were stirred in CH_2Cl_2 (1.8 mL) at 0°C, and valeraldehyde (1.0 mmol, 108 µL) was added to this suspension. After 1h, tetrahydropyranone (3.0 mmol, 330 µL) in solution of DMSO (0.2 mL) and H_2O (20 µL) was added. The reaction mixture was stirred, and allowed to warm to room temperature. The reaction was monitored by ^{1}H NMR until consumption of starting material (2d).

After complete consumption of α-chloro-aldehyde, the reaction was quenched by addition of saturated aqueous NH_4Cl. The aqueous layer was extracted 3x with CH_2Cl_2. The combined organic layers were dried with brine, then Na_2SO_4 and concentrated by rotary evaporation. Then according to general procedure **D**, the crude aldol product was dissolved in MeOH (2 mL) and cooled to 0°C. To the reaction was added $NaBH_4$ (2.0 mmol, 74 mg). After consumption of aldol adduct is noted by TLC (1 h), the reaction was quenched with 5 mL of saturated aqueous NH_4Cl. The aqueous layer was extracted 3x with 10 mL of CH_2Cl_2. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated by rotary evaporation. The crude product was purified by flash chromatography on SiO_2 (60:40 hexanes:EtOAc) to yield a white solid (98 mg, 44% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ= 3.99-3.86 (*m*, 3H), 3.78 (*m*, *J* = 3.2, 6.4, 7.6 Hz, 1H), 3.65 (*m*, *J* = 3.2, 7.5 Hz, 1H), 3.41-3.33 (*m*, 2H), 3.18 (*d*, *J* = 6.4 Hz, 1H), 3.08 (*dd*, *J* = 11.0 Hz, 1H), 2.17 (*m*, *J* = 6.7 Hz, 1H), 2.01-1.89 (*m*, 2H), 1.65 (*m*, 1H), 1.06 (*d*, *J* = 6.7 Hz, 3H), 1.02 (*d*, *J* = 6.7 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ= 74.0, 72.5, 71.3, 67.4, 66.4, 46.4, 34.6, 31.7, 20.3, 19.6

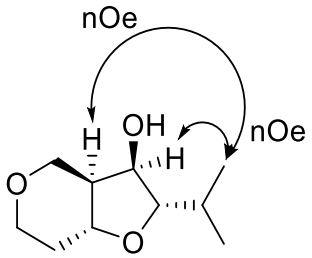
HRMS: (ESI) *m/z* calcd for $C_{10}H_{20}ClO_3[M+H]^+$ 223.1095, found 223.1082

IR: 3380, 2965, 2872, 1217, 1088, 996, 749, 665, 617 cm^{-1}

m.p.: 68-72°C

α_D^{20}= -9.3 (c = 66.3 mg/mL in $CHCl_3$)

Determination of Relative Stereochemistry of Chlorohydrin (83), preparation of (94)



According to general procedure **E**, **81** (20 mg, 0.09 mmol) was submitted to microwave radiation to effect the cyclization. The cyclized product was purified by flash chromatography on SiO_2 (97:3 CH_2Cl_2:MeOH) to yield (11.1 mg, 60% yield) of a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ= 4.17 (*m*, 2H), 4.03 (*m*, *J* = 4.5, 11.7 Hz, 1H), 3.70 (*m*, *J* = 4.2, 11.0 Hz, 1H), 3.52 (*m*, 1H), 3.30 (*m*, *J* = 2.2, 12.0 Hz, 1H), 2.11 (*m*, 1H), 1.76 (*m*, 1H), 1.69 (*m*, 1H), 1.39 (*bs*, 1H), 0.97 (*d*, *J* = 6.0 Hz, 3H), 0.94 (*d*, *J* = 6.0 Hz, 3H)

^{13}C NMR (150 MHz, $CDCl_3$) δ= 93.0, 77.2, 73.6, 67.2, 65.5, 48.9, 33.1, 31.0, 18.6, 18.4

HRMS: (ESI) *m/z* calcd for $C_{10}H_{22}O_3N[M+NH_4]^+$ 204.1594, found 204.1600

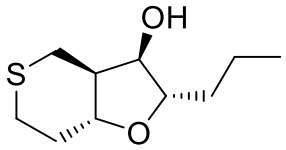
IR: 3349, 2969, 2924, 1084, 1046, 880, 635 cm^{-1}

α_D^{20}= +8.9 (c=11.1 mg/mL)

Determination of Enantiomeric Excess of Chlorohydrin 83

The cyclized product was used to determine the enantiomeric excess. According to general procedure **F**, the corresponding PNB esters of the THF **94** were prepared of each a racemic and enantioenriched sample. Preparation of the bis-PNB ester of the chlorohydrin was necessary to prevent elimination of the β-PNB group of the ketone. The enantiomeric PNB esters were separated by chiral HPLC using Phenomex Lux (3μm) Cellulose-3 column; flow rate 0.4mL/min; eluent: hexanes-*i*PrOH 90:10; detection at 254 nm; retention time = 1.57 min and 2.50 min. The enantiomeric excess of the optically enriched PNB ester was determined using the same method (93% ee).

Preparation of THF (93)



According to general procedure **D**, chlorohydrin **65** (100 mg, 0.45 mmol) was reduced to the corresponding chlorodiol with $NaBH_4$ (2.0 mmol, 74 mg) in MeOH (2 mL). After consumption of starting material was noted by TLC, the reaction was quenched with aqueous NH_4Cl (5 mL) and extracted 3x with 10 mL of CH_2Cl_2. The crude mixture was concentrated by rotary evaporation. Subsequently, according to general procedure **E**, After microwave irradiation, the reaction mixture was concentrated by rotary evaporation and dry loaded on to SiO_2. Purification by column chromatography (80:20 Hexanes:EtOAc) to gave a white solid (60 mg, 74% yield). Key NOE correlations are shown above.

According to general procedure **D**, chlorohydrin **87** (33 mg, 0.14 mmol was reduced to the corresponding chlorodiol with $NaBH_4$ (0.28 mmol, 10 mg) in MeOH (0.5 mL). After consumption of starting material was noted by TLC, the reaction was quenched with aqueous NH_4Cl (2 mL) and extracted 3x with 5 mL of CH_2Cl_2. The crude mixture was concentrated by rotary evaporation. Subsequently, according to general procedure **E**, After microwave irradiation, the reaction mixture was concentrated by rotary evaporation and dry loaded on to SiO_2. Purification by column chromatography (80:20 hexanes:EtOAc) to give a clear oil (8.3 mg, 29% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ= 4.00 (*bs*, 1H), 3.70 (*m*, 1H), 3.42 (*m*, *J* = 3.7, 11.0 Hz, 1H), 2.87 (*dd*, *J* = 11.6, 13.0 Hz, 1H), 2.80-2.53 (*m*, 4H), 2.48 (*m*, *J* = 3.5, 11.0 Hz, 1H), 1.68 (*m*, 3H), 1.63-1.30 (*m*, 7H), 0.95 (*t*, *J* = 7.2 Hz, 3H)

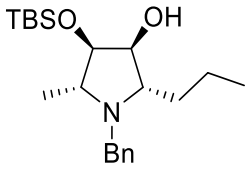
^{13}C NMR (100 MHz, $CDCl_3$) δ= 86.6, 78.9, 49.5, 36.5, 36.2, 33.9, 27.4, 27.3, 19.0, 14.0

HRMS: (ESI) *m/z* calcd for $C_{10}H_{19}O_2S[M+H]^+$ 203.1100, found 203.1099

IR: 3401, 2955, 2974, 2871, 1716, 1429, 1051, 754, 636 cm^{-1}

α_D^{20}= -2.4 (c = 17.6 mg/mL in $CHCl_3$)

Preparation of Pyrrolidine (99)



According to general procedure **G**, chlorohydrin **89** (95 mg, 0.29 mmol) was dissolved in dry THF (3 mL) with AcOH (17 µL, 0.29 mmol). Benzylamine (84 µL, 0.8 mmol) was added and allowed to stir for 1 hour. $NaBH_3CN$ (49 mg, 0.8 mmol) was added and the reaction mixture stirred for another 1h. The reaction was quenched with 5 mL of water and the organic layers separated. The aqueous layer was extracted 3x with CH_2Cl_2 and dried with brine, then $NaSO_4$. The crude product was concentrated and purified by flash chromatography (90:10 hexanes:Et_2O) to give a clear oil (24 mg, 21% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ= 7.29 (*m*, 4H), 7.22 (*m*, 1H), 3.76 (*d*, *J* = 14.2 Hz, 1H), 3.72 (*d*, *J* = 14.2 Hz, 1H), 3.64 (*m*, *J* = 3.3, 5.7 Hz, 1H), 3.60 (*m*, *J* = 5.5, 6.7 Hz, 1H), 2.67 (*m*, 2H), 2.61 (*d*, *J* = 3.3 Hz, 1H), 1.41 (*bs*, 1H), 1.49-1.36 (*m*, 2H), 1.31-1.16 (*m*, 2H), 1.02 (*d*, *J* = 6.2 Hz, 3H), 0.91 (*s*, 9H), 0.85 (*t*, *J* = 7.1 Hz, 3H), 0.10 (*s*, 3H), 0.09 (*s*, 3H)

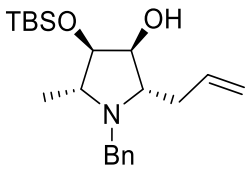
^{13}C NMR (125 MHz, $CDCl_3$) δ= 139.5, 129.0, 127.0, 126.7, 77.8, 74.6, 70.1, 62.9, 56.8, 35.8, 25.7, 18.9, 18.1, 18.0, 14.3, -4.6, -4.8

HRMS: (ESI) *m/z* calcd for $C_{21}H_{38}NO_2Si[M+H]^+$ 364.2666, found 364.2668

IR: 3549, 2956, 2929, 1253, 1123, 835, 776, 732, 698 cm^{-1}

α_D^{20}= +12.3 (c = 23 mg/mL in $CHCl_3$)

Preparation of Pyrrolidine (100)



According to general procedure **G**, chlorohydrin **90** (54 mg, 0.18 mmol) was dissolved in dry THF (0.1M, 2 mL) with (10 µL, 0.18 mmol) AcOH. Benzylamine (49 µL,

0.46 mmol) was added and allowed to stir for 1hour. $NaBH_3CN$ (28 mg, 0.46 mmol) was added and stirred for another 1h. The reaction was quenched with 5 mL of water and the organic layers separated. The aqueous layer was extracted 3x with CH_2Cl_2 and dried with brine, then $NaSO_4$. The crude product was concentrated and purified by flash chromatography (90:10 hexanes:EtOAc) to give a clear oil (16 mg, 25% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ= 7.29 (*m*, 4H), 7.23 (*m*, 1H), 5.85 (*m*, 1H), 5.02 (*m*, *J* = 1.7, 13.8 Hz, 2H), 3.80 (*d*, *J* = 14.1 Hz, 1H), 3.71 (*d*, *J* = 14.1 Hz, 1H), 3.68 (*m*, 1H), 3.60 (*m*, *J* = 5.3, 6.8 Hz, 1H), 2.80 (*m*, *J* = 3.5, 7.4 Hz, 1H), 2.72 (*m*, *J* = 6.3 Hz, 1H), 2.57 (*d*, *J* = 3.6 Hz, 1H), 2.13 (*m*, *J* =1.1, 3.5, 7.3, 13.8 Hz, 1H), 2.00 (*m*, *J* = 1.3, 7.8, 14.3 Hz, 1H), 1.01 (*d*, *J* = 6.2 Hz, 3H), 0.91 (*s*, 9H), 0.11 (*s*, 3H), 0.09 (*s*, 3H)

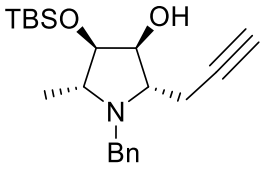
^{13}C NMR (125 MHz, $CDCl_3$) δ= 139.8, 135.6, 128.9, 128.0, 126.8, 116.4, 77.8, 74.1, 69.7, 63.3, 57.4, 37.7, 25.8, 18.3, 18.0, -4.6, -4.8

HRMS: (ESI) *m/z* calcd for $C_{21}H_{36}NO_2Si[M+H]^+$ 362.2510, found 362.2501

IR: 3550, 3028, 2065, 2955, 2928, 1253, 1124, 1092, 835, 776, 698 cm^{-1}

α_D^{20}= +21.4 (c=14 mg/mL in $CHCl_3$)

Preparation of Pyrrolidine (101)



According to general procedure **G**, chlorohydrin **86** (24 mg, 0.07 mmol) was dissolved in dry THF (0.1 M, 1 mL) with AcOH (4.5 µL, 0.07 mmol). Benzylamine (22 µL, 0.21 mmol) was added and allowed to stir for 1hour. $NaBH_3CN$ (12.5 mg, 0.21 mmol) was added and stirred for another 1h. The reaction was quenched with 5 mL of water and the organic layers separated. The aqueous layer was extracted 3x with CH_2Cl_2 and dried with brine, then $NaSO_4$. The crude product was concentrated and purified by flash chromatography (80:20 hexanes:Et_2O) to give (9 mg, 32% yield) a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ= 7.36-7.27 (*m*, 4H), 7.23 (*m*, 1H), 3.89-3.81 (*m*, 2H), 3.75 (*m*, *J* = 4.8, 6.2 Hz, 1H), 3.71 (*d*, *J* = 13.8 Hz, 1H), 2.91 (*m*, *J* = 2.8, 4.2, 6.9 Hz, 1H), 2.80 (*m*, *J* = 6.3 Hz, 1H), 2.62 (*d*, *J* = 3.3 Hz, 1H), 2.19 (*m*, *J* = 2.7, 4.1, 16.9 Hz, 1H), 2.05 (*m*, *J* = 2.6, 6.8, 16.9 Hz, 1H), 1.94 (*t*, *J* = 2.6 Hz, 1H), 1.04 (*d*, *J* = 6.2 Hz, 3H), 0.92 (*s*, 9H), 0.12-0.11 (*s*, 6H)

^{13}C NMR (125 MHz, $CDCl_3$) δ= 139.7, 128.9, 128.1, 126.9, 82.2, 77.8, 74.6, 69.2, 68.7, 63.3, 57.5, 25.8, 23.5, 18.2, 18.0, -4.6, -4.7

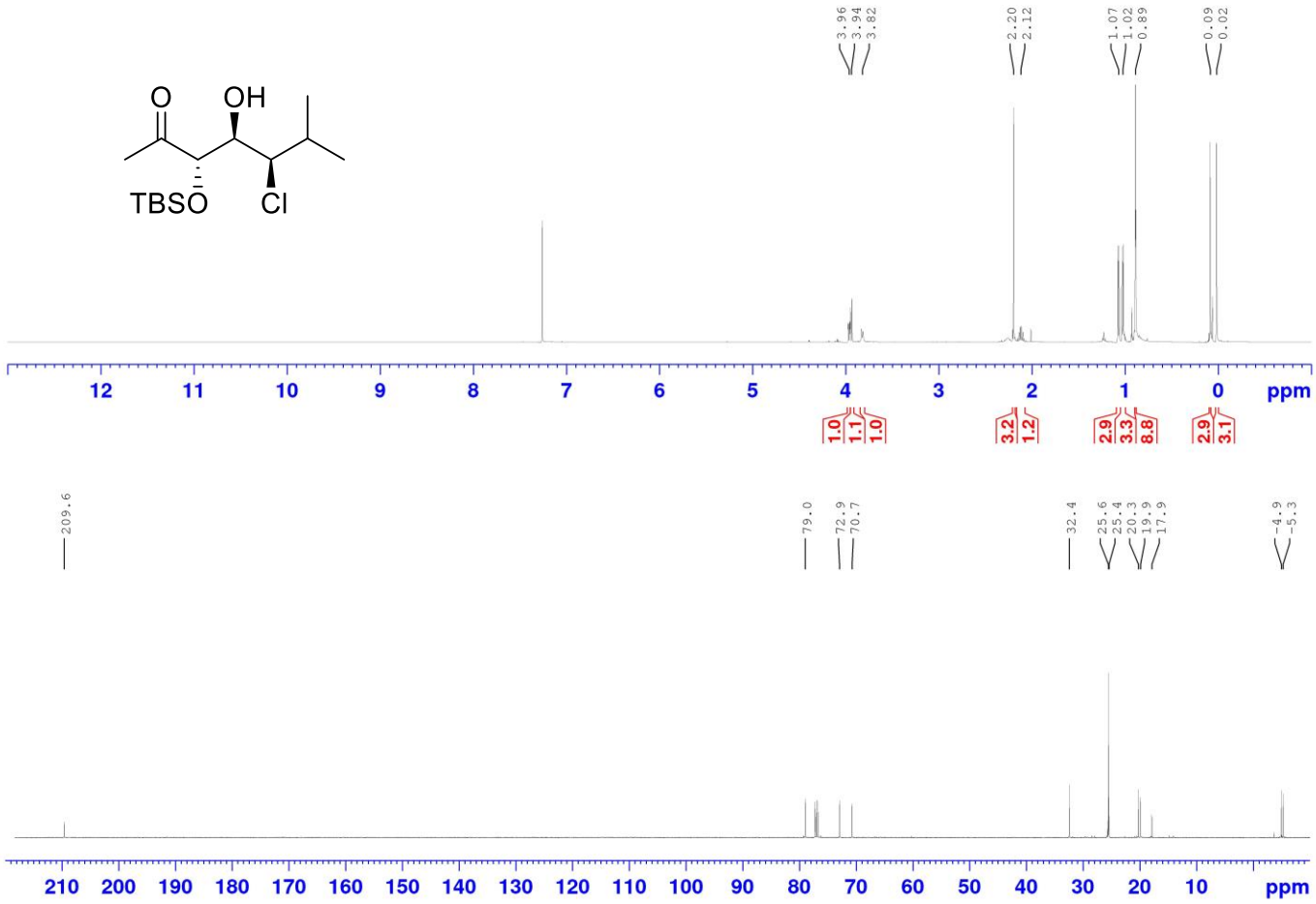
HRMS: (ESI) *m/z* calcd for $C_{21}H_{34}NO_2Si[M+H]^+$ 360.2353, found 360.2348

IR: 3547, 3310, 2955, 2928, 2119, 1253, 1130, 835, 777, 699, 632 cm^{-1}

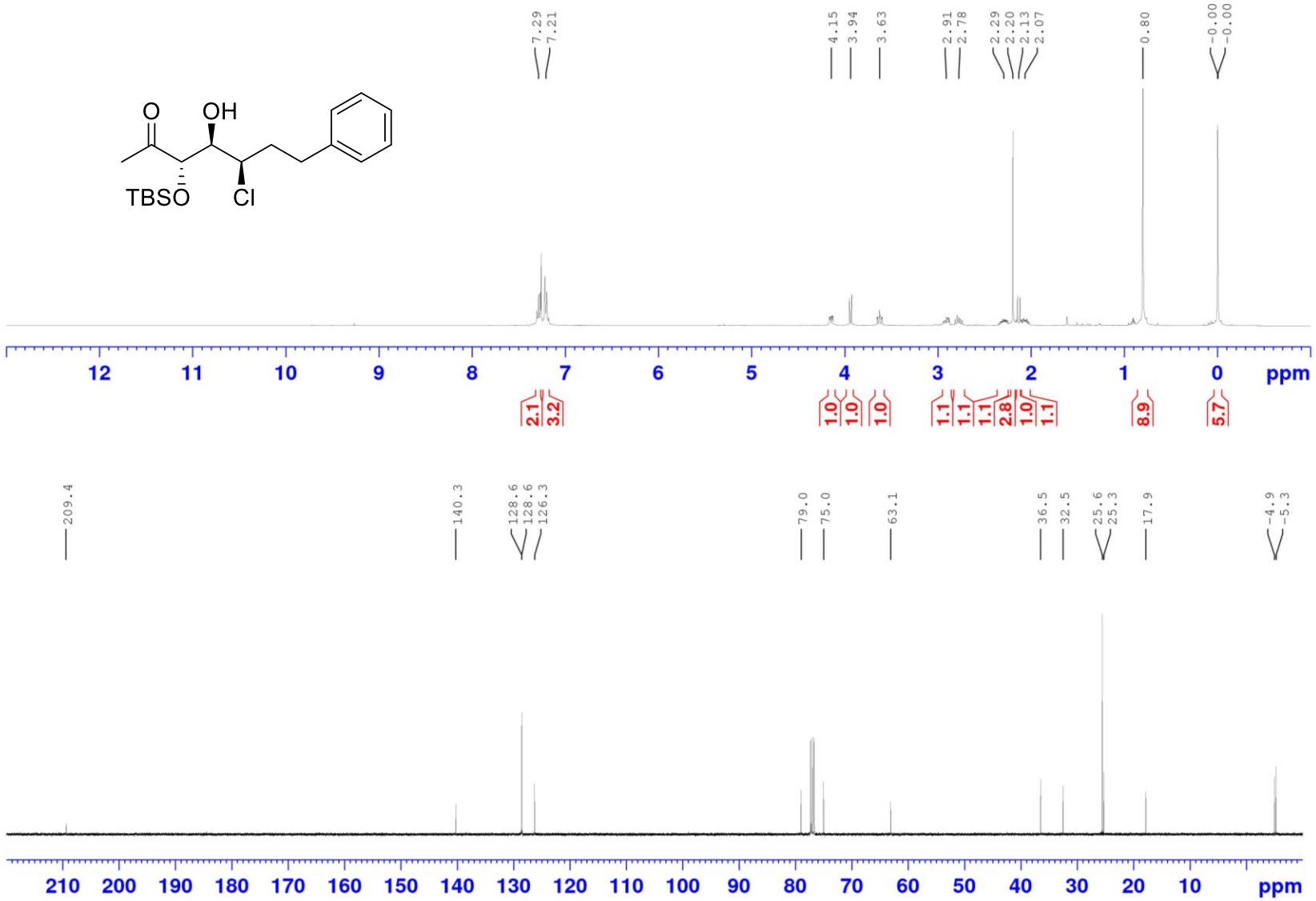
α_D^{20}= +12.6 (c=11 mg/mL in $CHCl_3$)

3.7.4. NMR Spectra

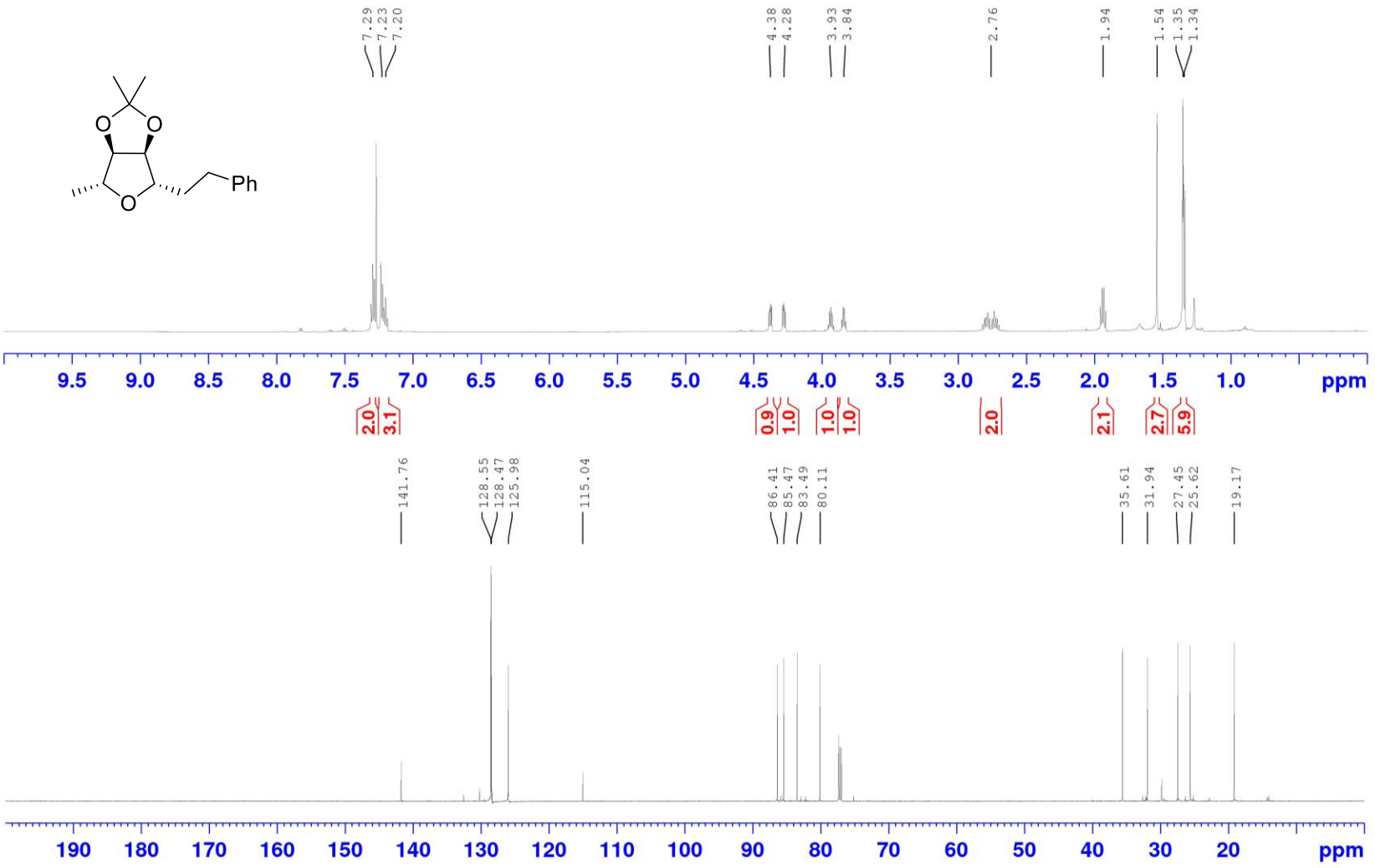
NMR Spectra of Chlorohydrin (73)



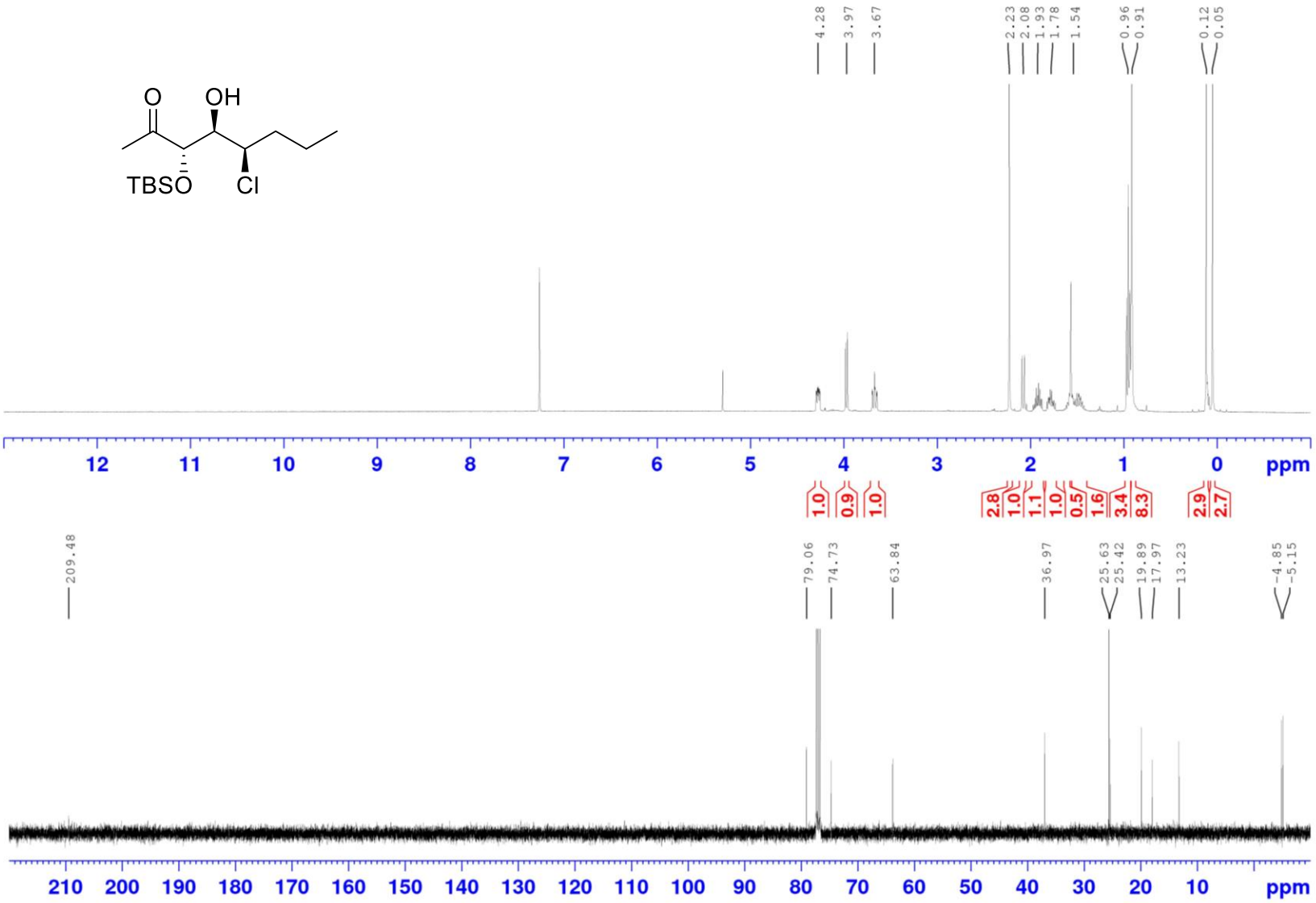
NMR Spectra of Chlorohydrin (91)



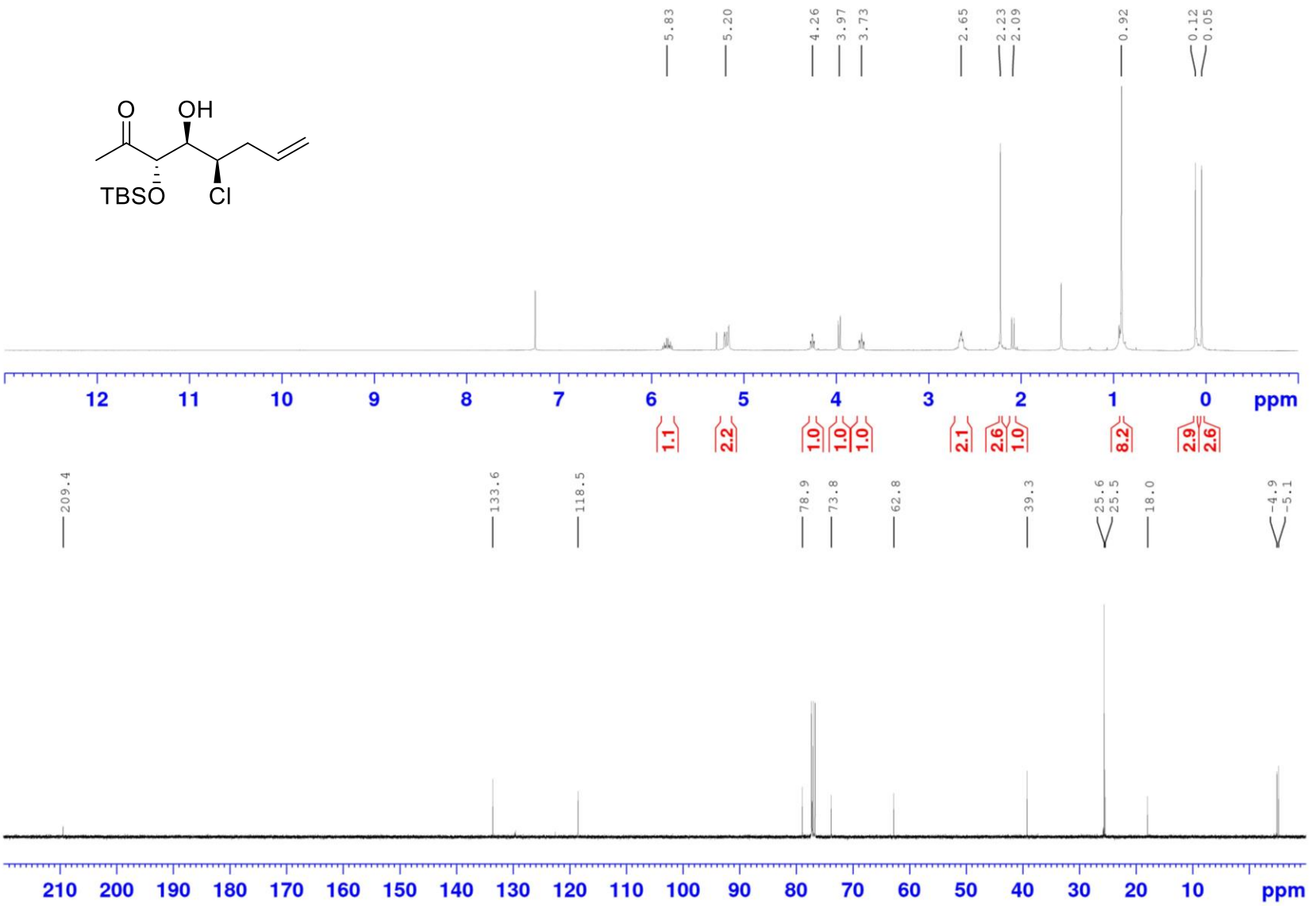
NMR Spectra of THF (96)



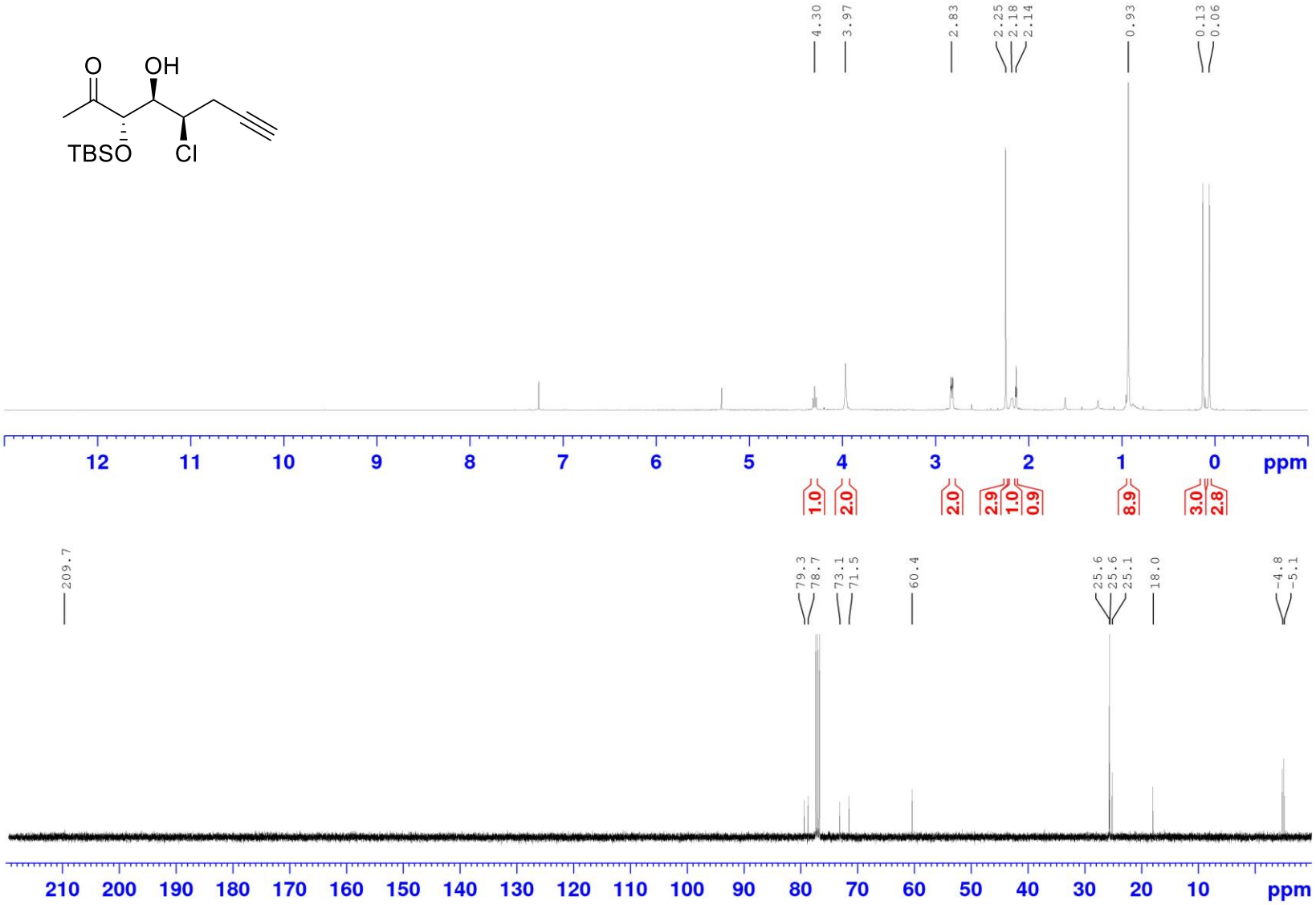
NMR Spectra of Chlorohydrin (89)



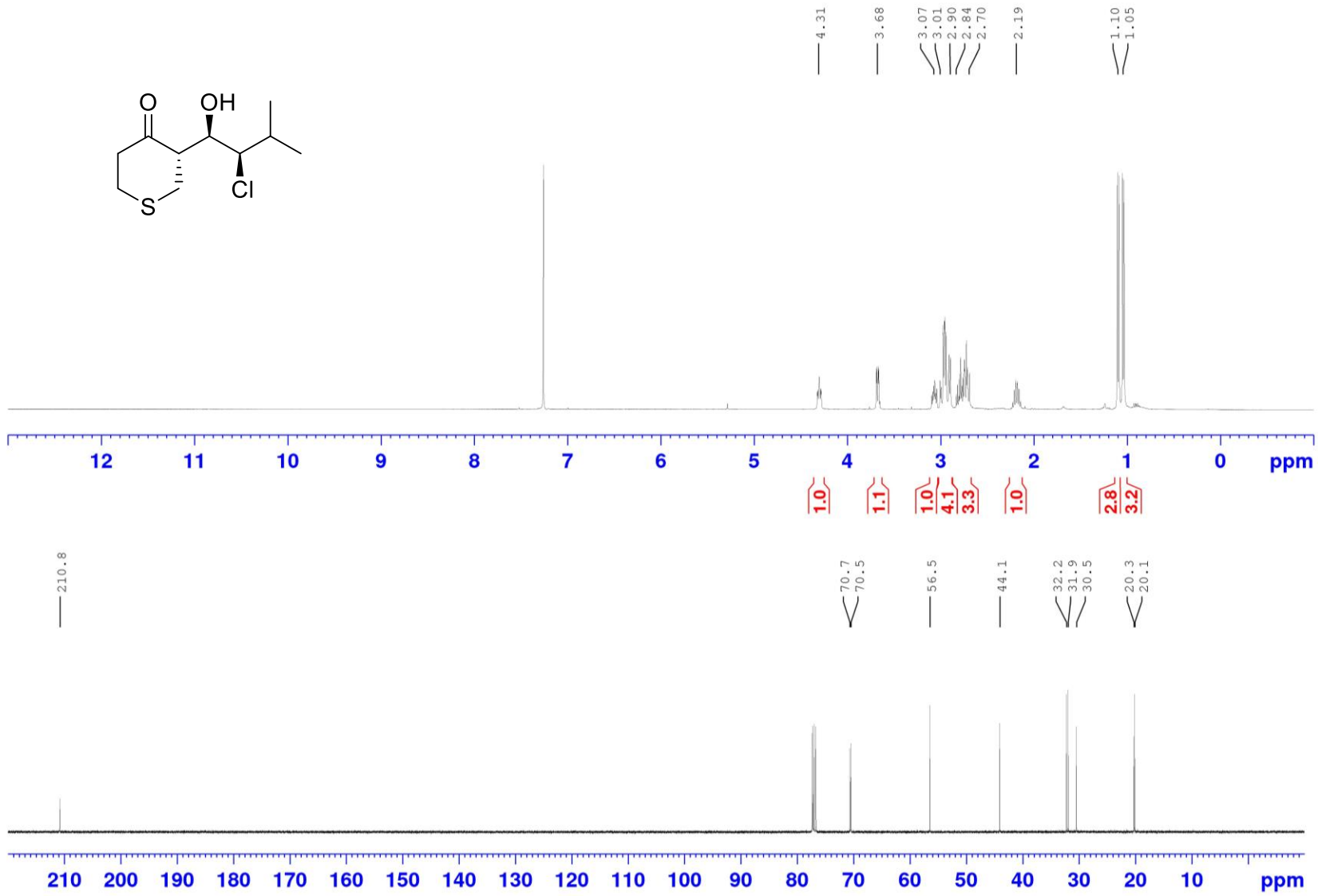
NMR Spectra of Chlorohydrin (90)



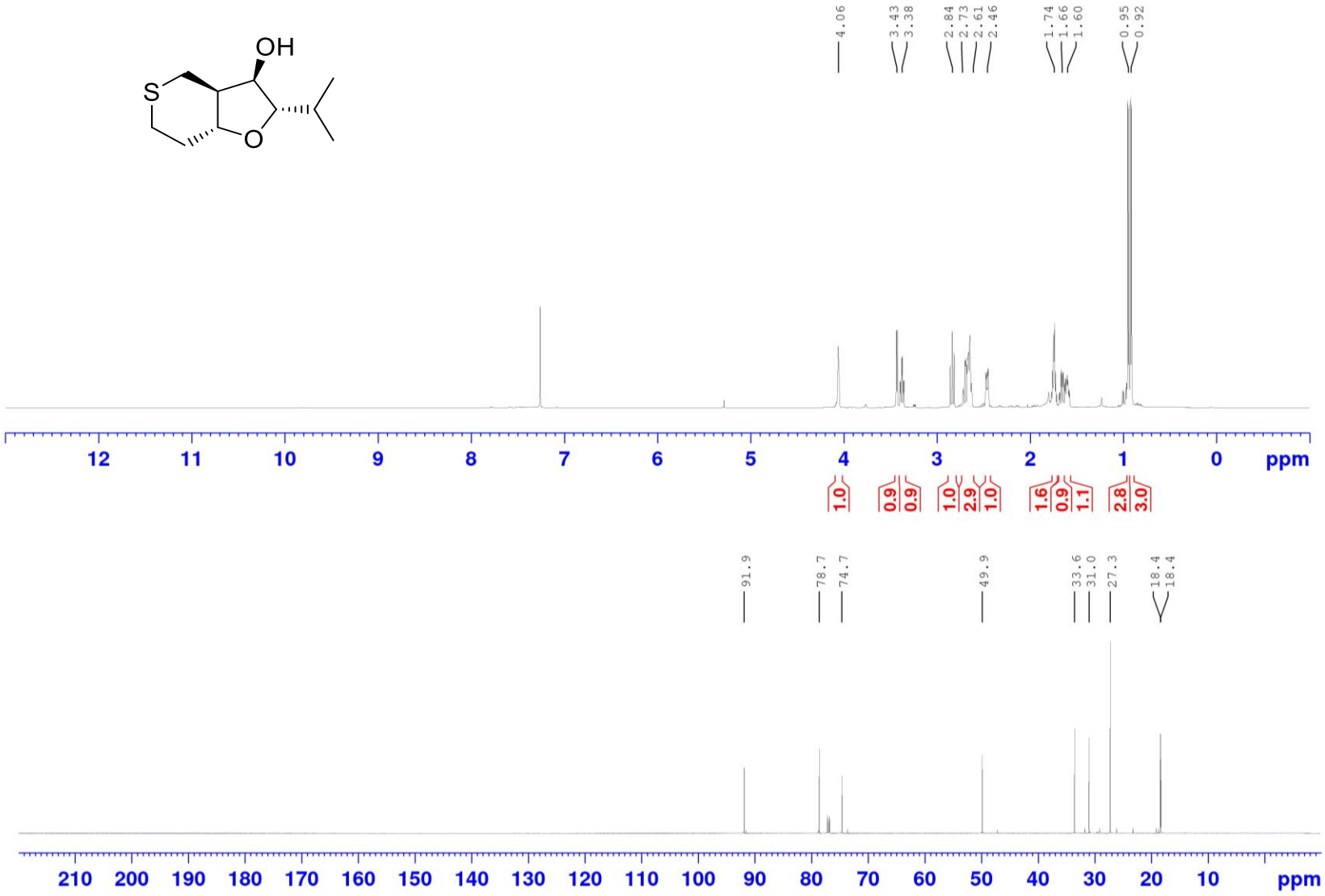
NMR Spectra of Chlorohydrin (86)



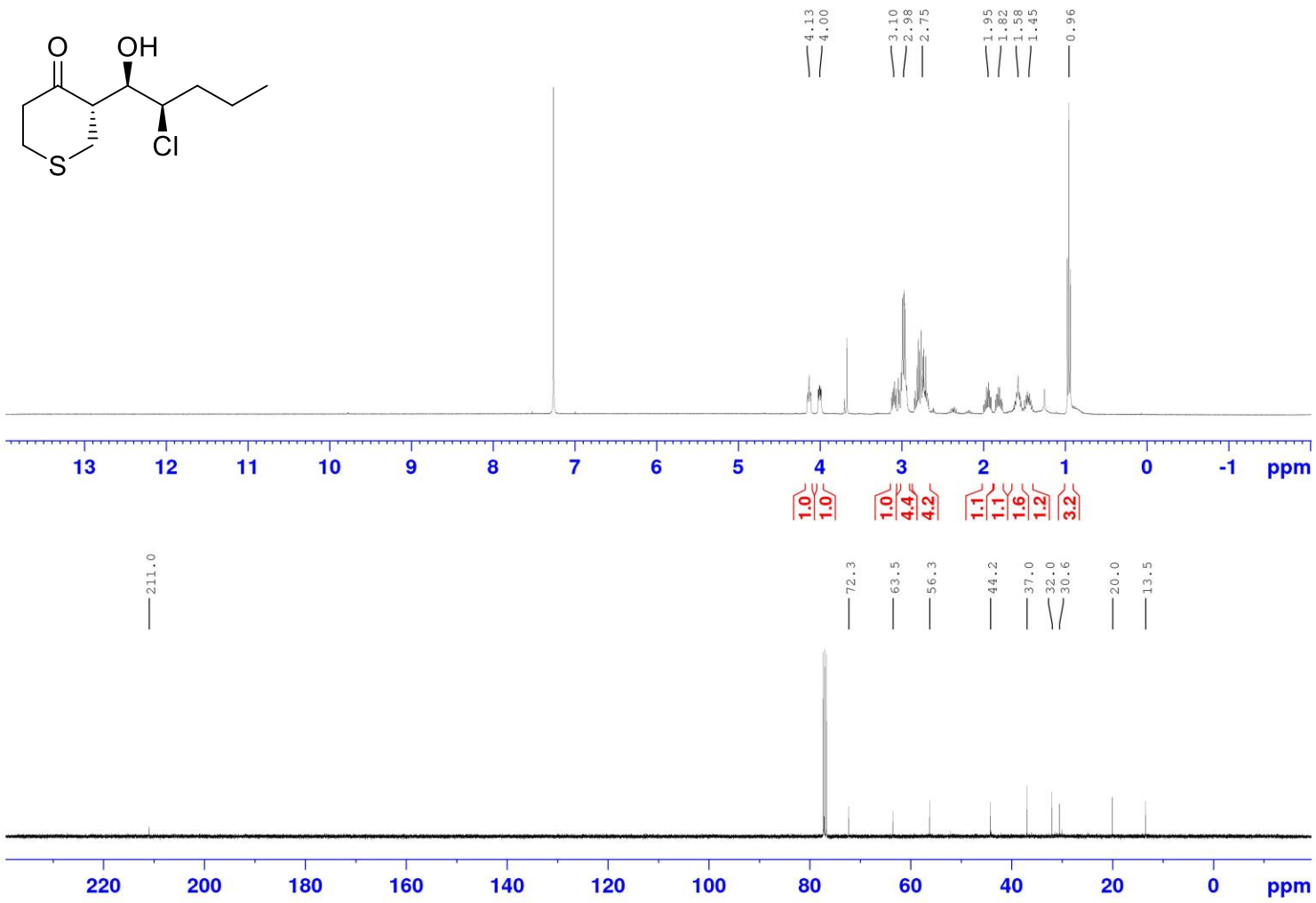
NMR Spectra of Chlorohydrin (79)



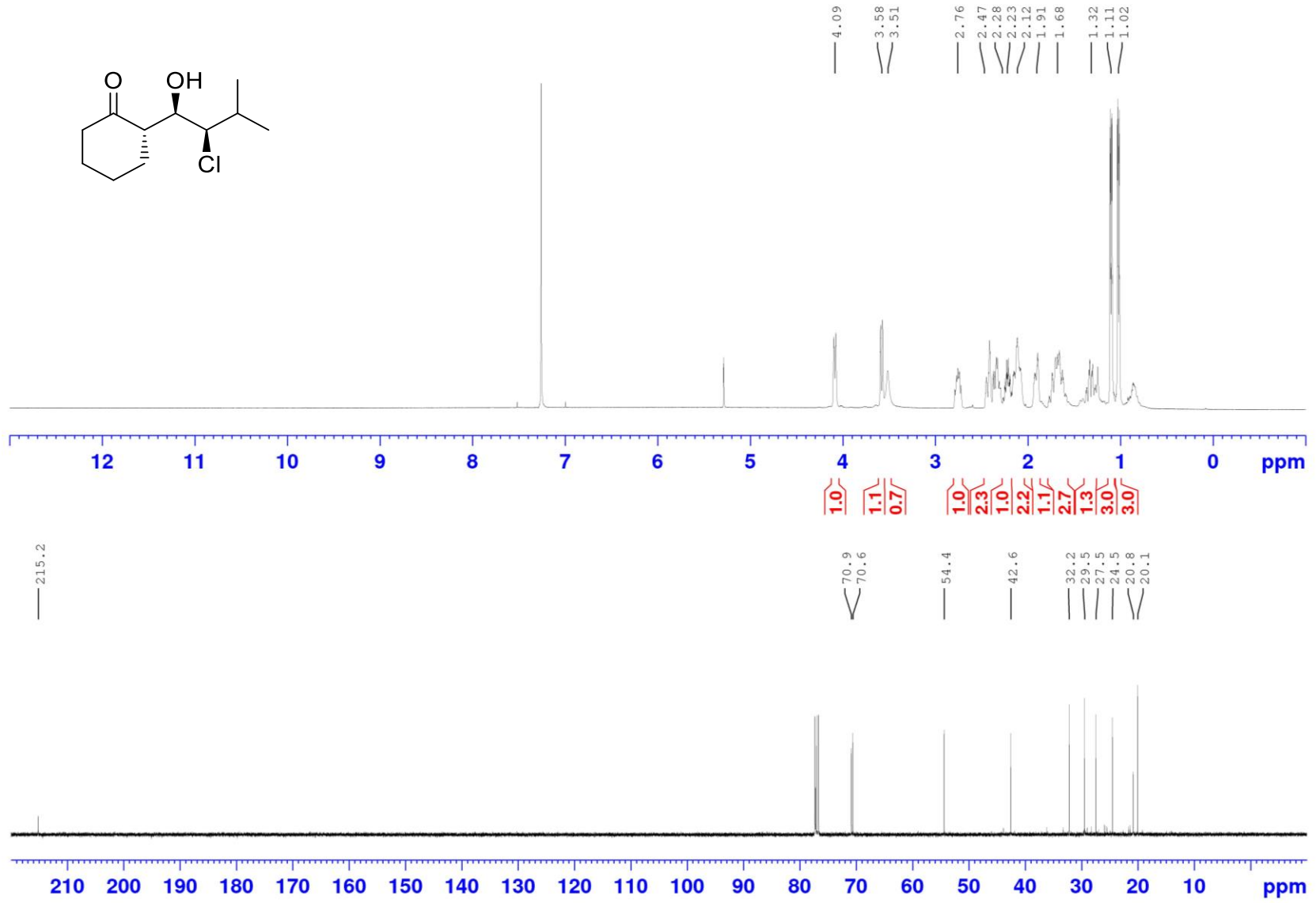
NMR Spectra of THF (98)



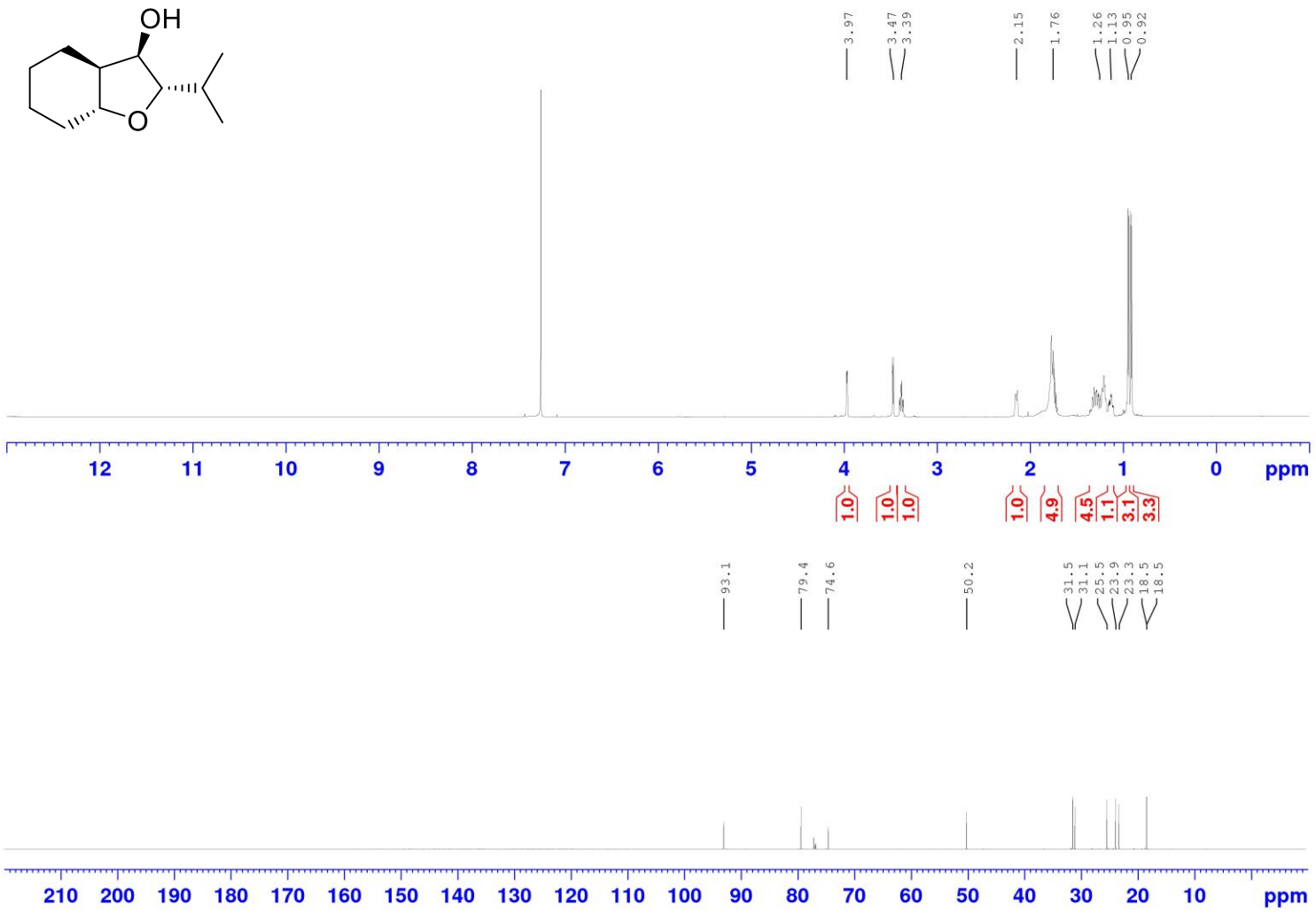
NMR Spectra of Chlorohydrin (87)



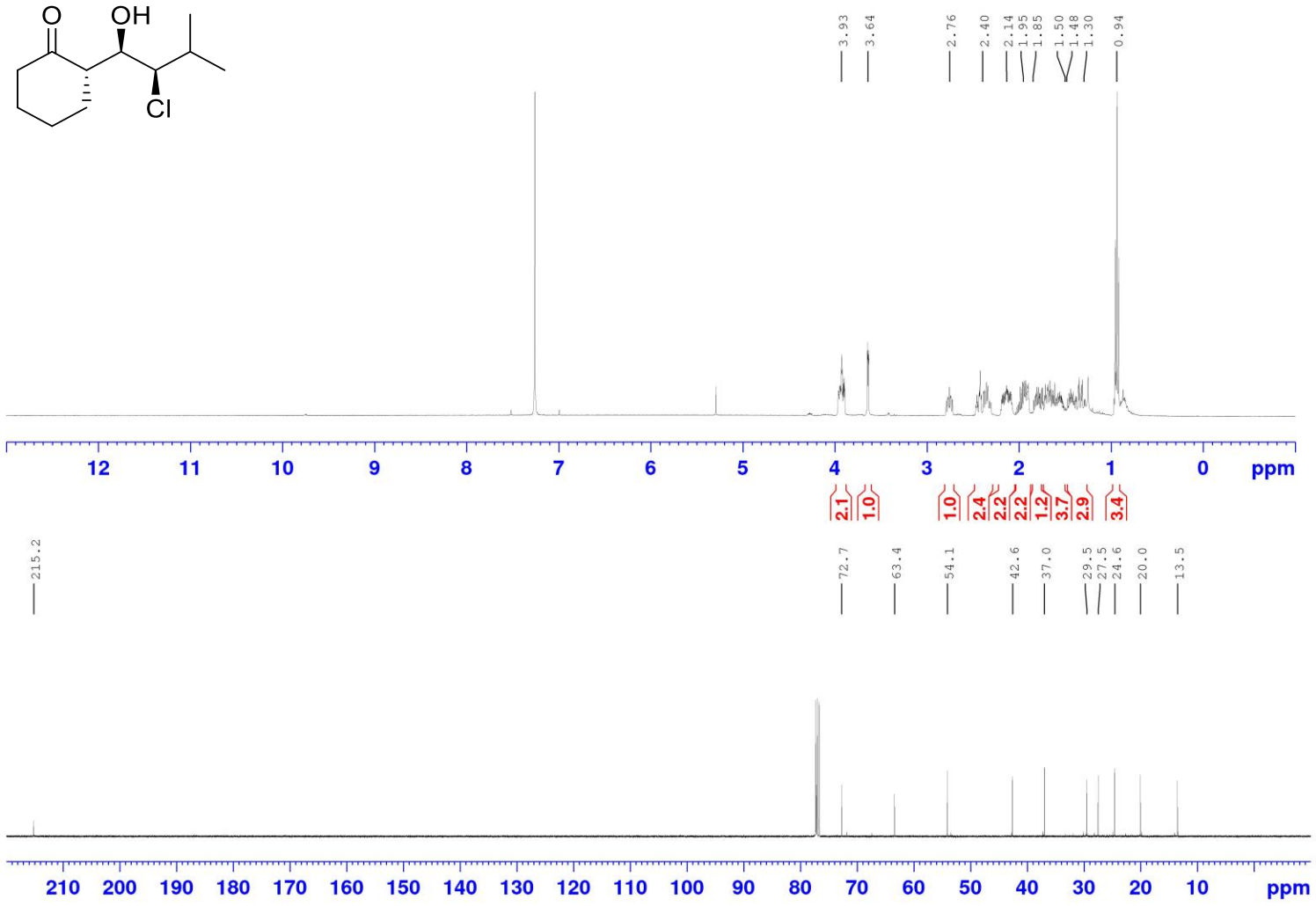
NMR Spectra of Chlorohydrin (65)



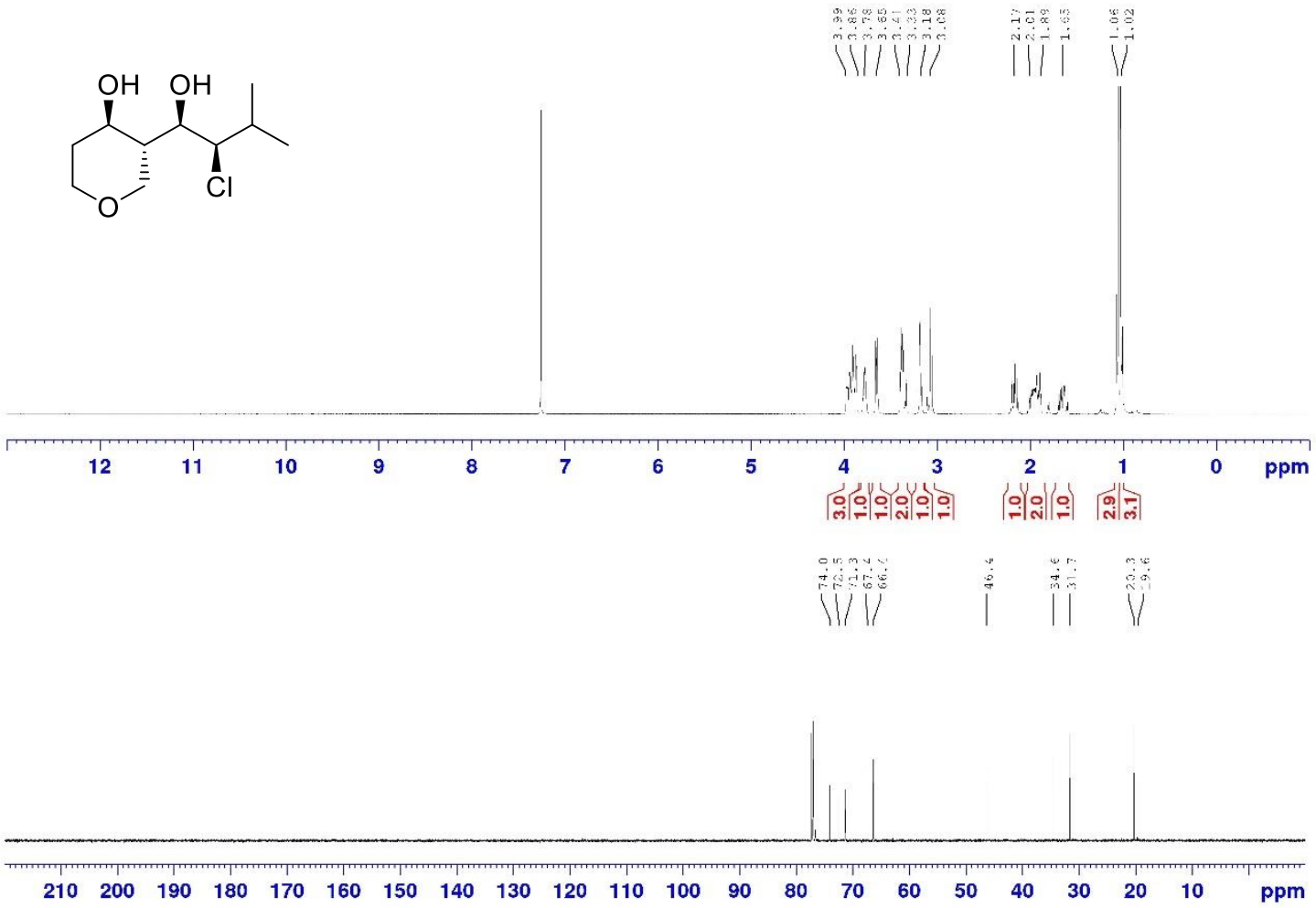
NMR Spectra of THF (97)



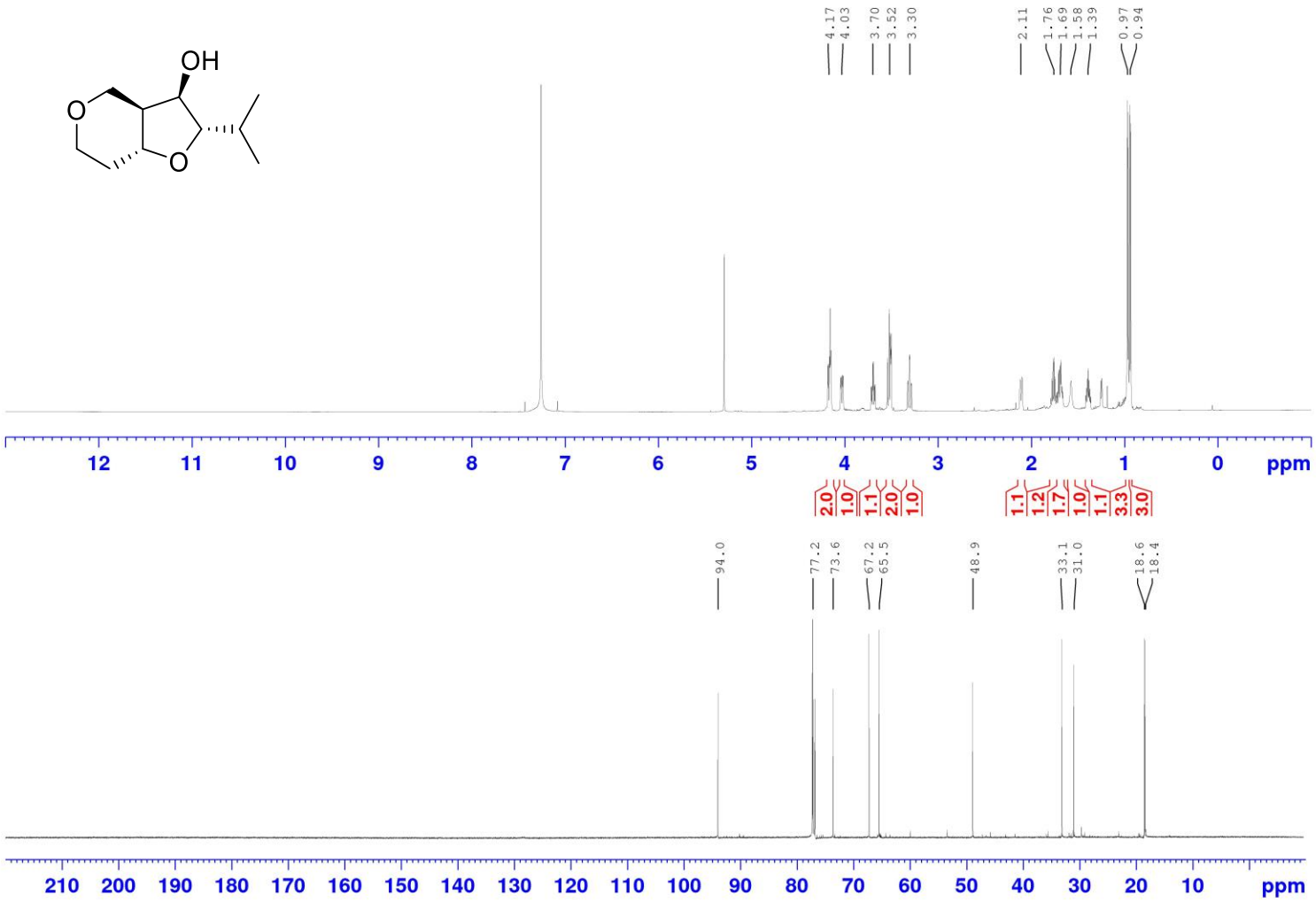
NMR Spectra of Chlorohydrin (88)



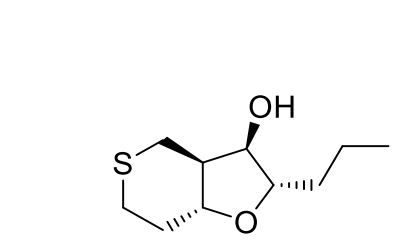
NMR Spectra of Chlorohydrin (83)



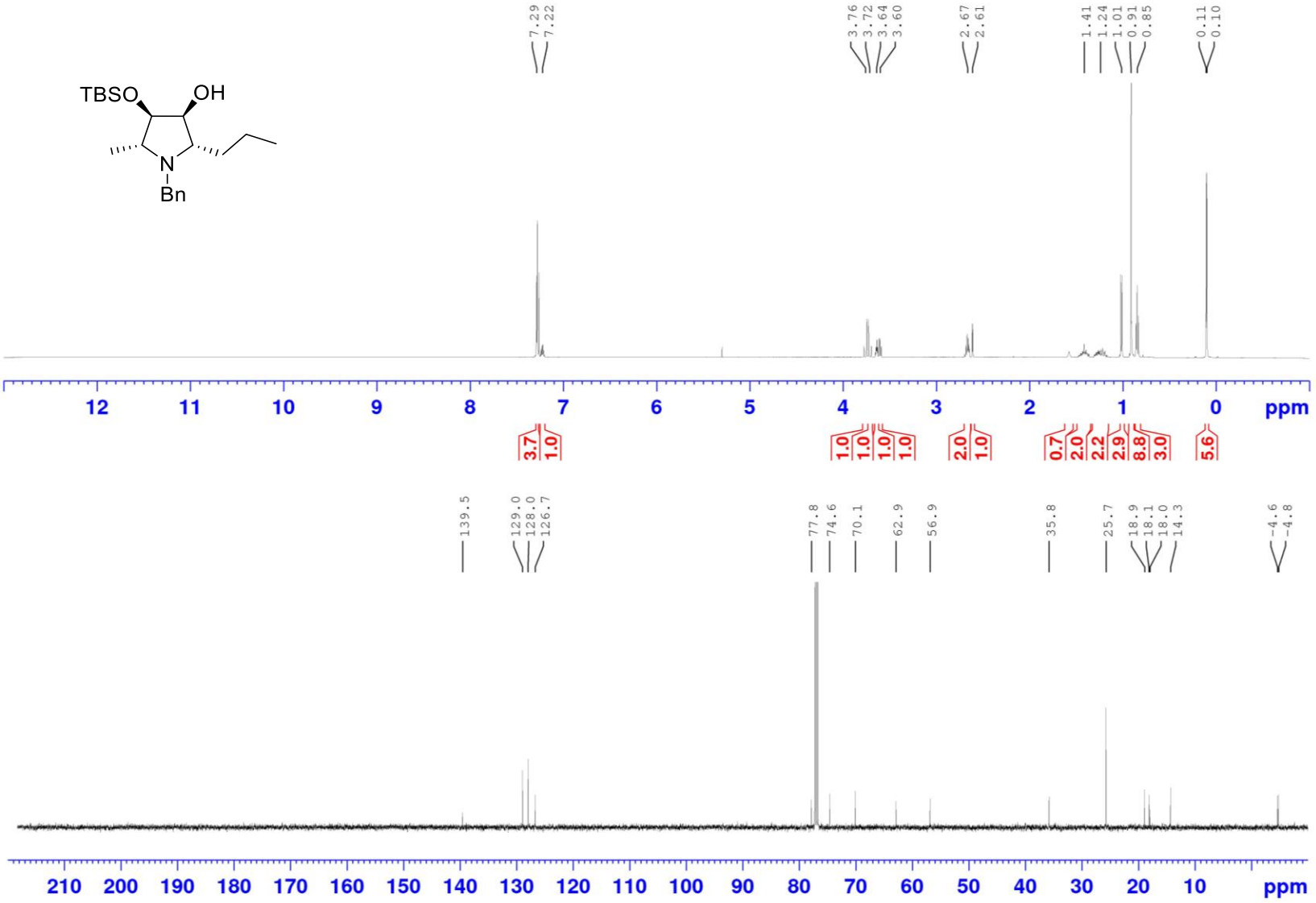
NMR Spectra of THF (94)



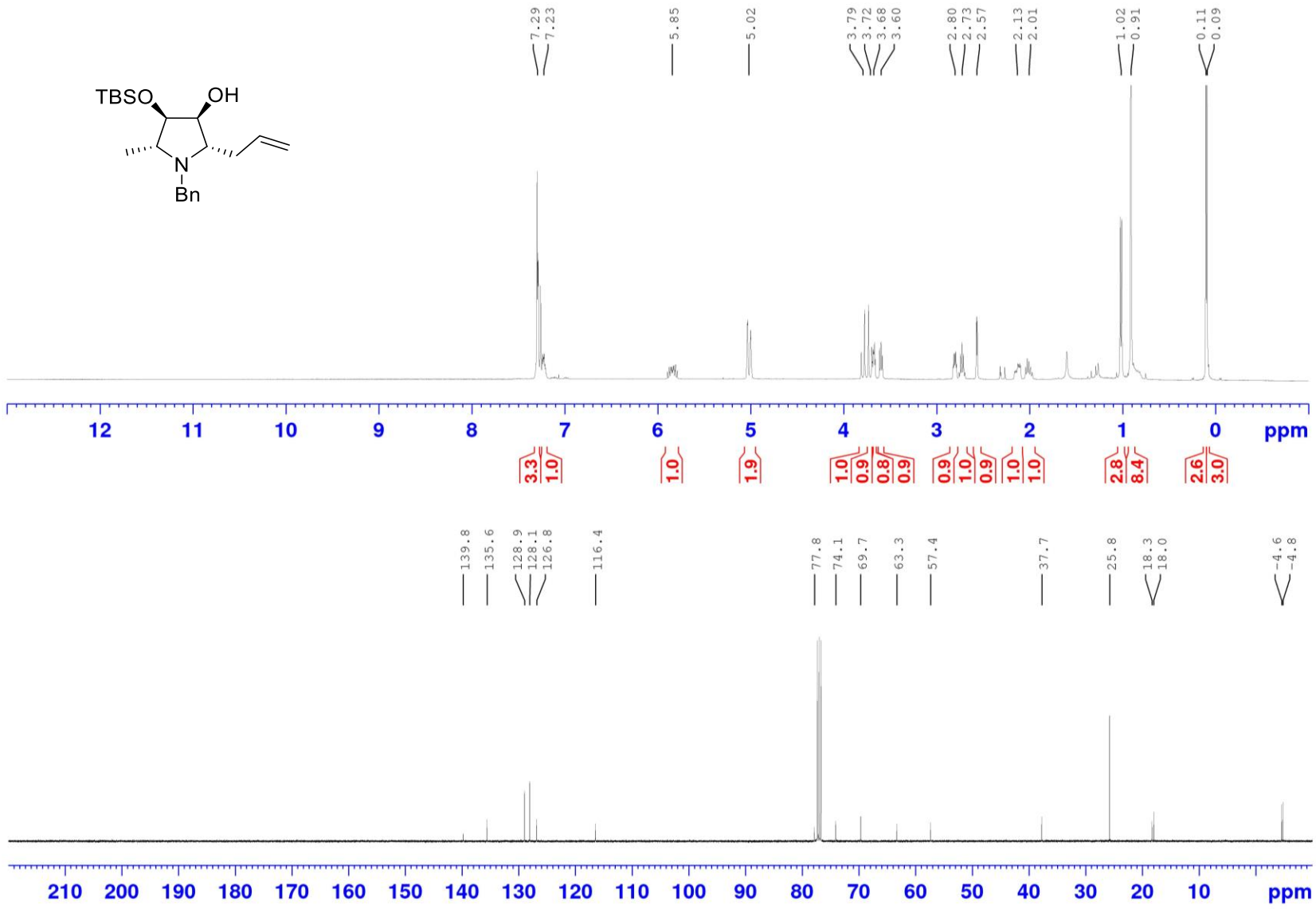
NMR Spectra of THF (93)



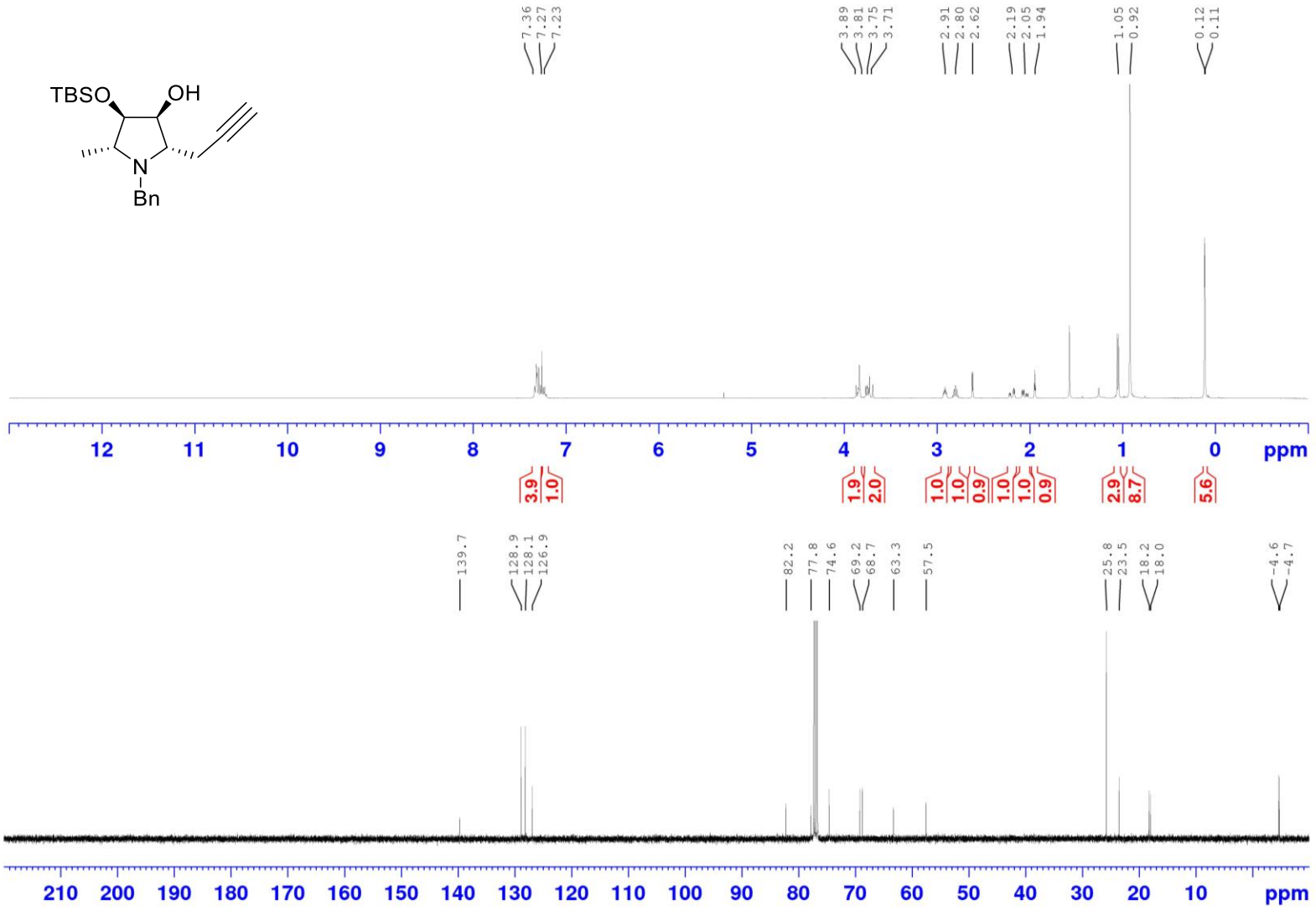
NMR Spectra of Pyrrolidine (100)



NMR Spectra of Pyrrolidine (101)

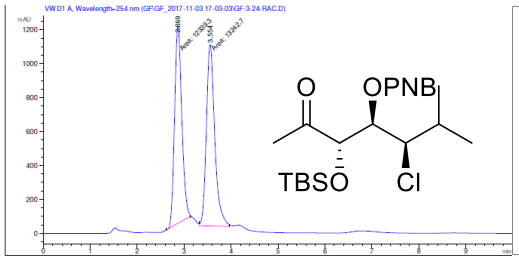


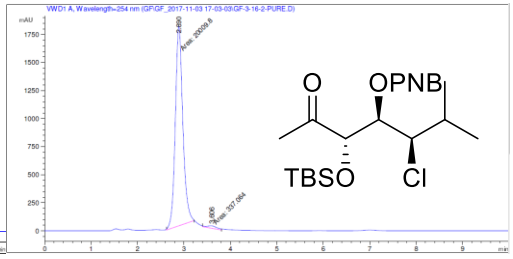
NMR Spectra of Pyrrolidine (102)



3.7.5. HPLC Traces

HPLC Trace of PNB-(73) (Racemic Left, Enantioenriched Right)

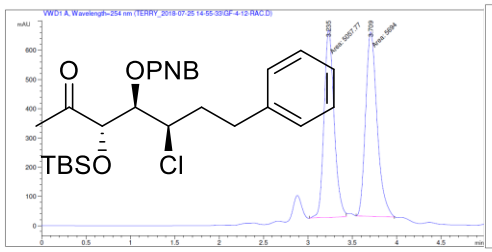


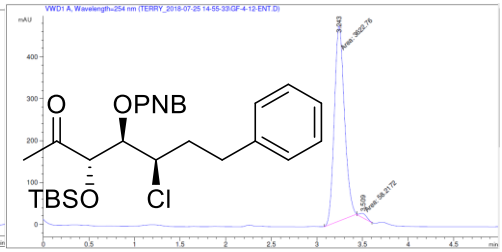


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	2.869	MM	0.1771	1.23393e4	1160.94751	48.2344
2	3.554	MM	0.2064	1.32427e4	1069.40527	51.7656

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	2.890	MM	0.1875	2.00098e4	1778.35852	98.3434
2	3.606	MM	0.2521	337.06369	22.27999	1.6566

HPLC Trace of PNB-(91) (Racemic Left, Enantioenriched Right)

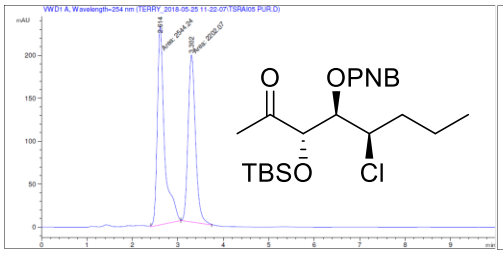


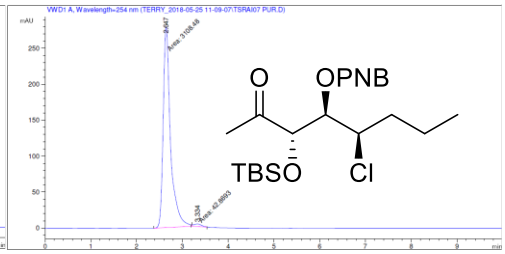


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	3.235	MM	0.1316	5057.76611	640.45544	47.0413
2	3.709	MM	0.1504	5693.99561	631.12048	52.9587

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	3.243	MM	0.1297	3622.75952	465.66965	98.4184
2	3.509	MM	0.0904	58.21724	10.73785	1.5816

HPLC Trace of PNB-(89) (Racemic Left, Enantioenriched Right)

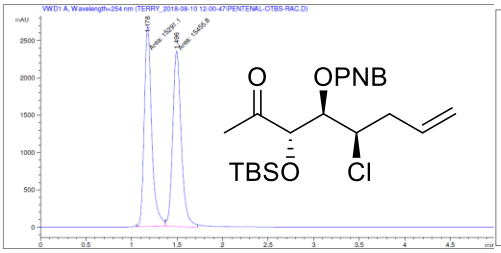


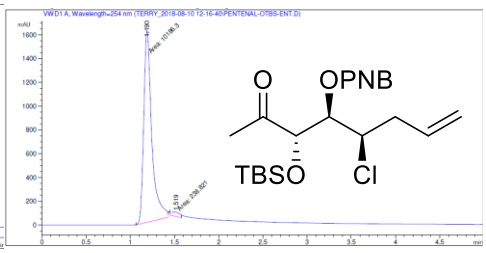


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	2.614	MM	0.1835	2544.23975	231.07678	53.6046
2	3.302	MM	0.1887	2202.07080	194.44383	46.3954

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	2.647	MM	0.1856	3108.48022	279.20975	98.6397
2	3.334	MM	0.1951	42.86931	3.66210	1.3603

HPLC Trace of PNB-(90) (Racemic Left, Enantioenriched Right)

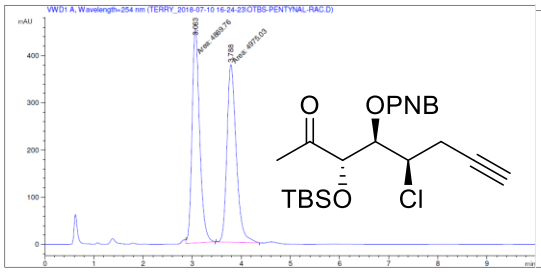


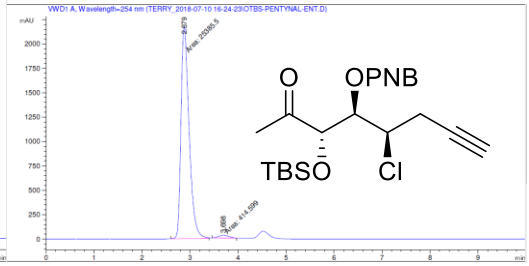


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	1.178	MM	0.0948	1.52911e4	2687.56836	49.7322
2	1.496	MM	0.1094	1.54558e4	2354.75977	50.2678

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	1.190	MM	0.1051	1.01863e4	1615.77222	97.7092
2	1.519	MM	0.1092	238.82076	36.45218	2.2908

HPLC Trace of PNB-(86) (Racemic Left, Enantioenriched Right)

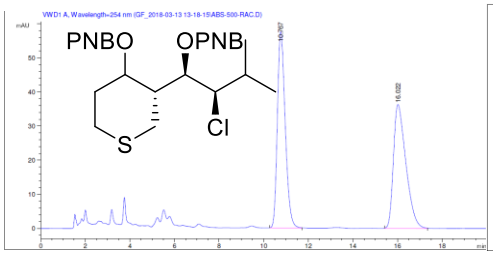


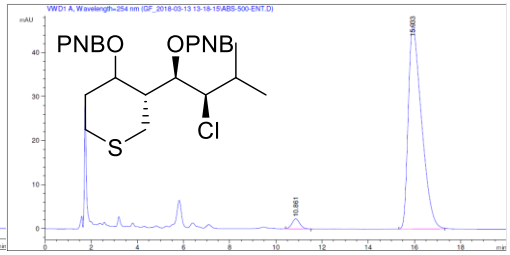


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	3.063	MM	0.1783	4869.75928	455.25430	49.4653
2	3.788	MM	0.2202	4975.03027	376.62704	50.5347

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	2.879	MM	0.1952	2.53855e4	2167.88501	98.3930
2	3.698	MM	0.2541	414.59915	27.19168	1.6070

HPLC Trace of PNB-(79) (Racemic Left, Enantioenriched Right)

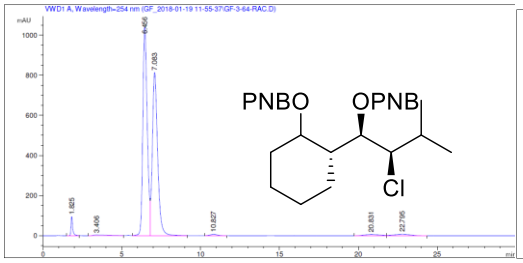


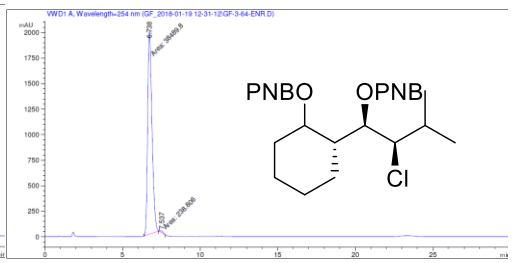


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.767	BB	0.3784	1406.09375	57.52106	50.0987
2	16.022	BB	0.5694	1400.55212	36.31229	49.9013

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.861	BB	0.3750	54.24590	2.26922	2.8605
2	15.933	BB	0.6066	1842.12866	46.03395	97.1395

HPLC Trace of PNB-(65) (Racemic Left, Enantioenriched Right)

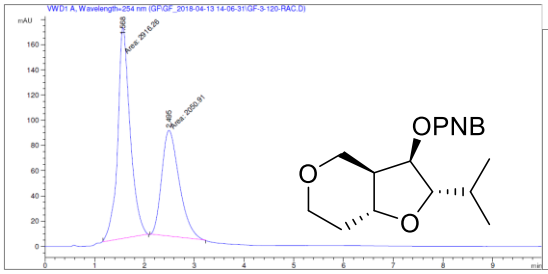


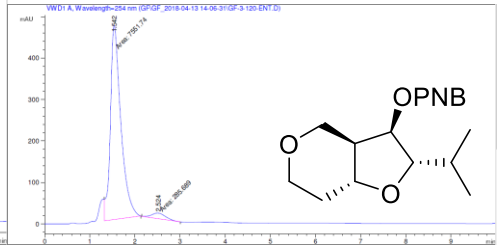


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	1.825	BV	0.1105	715.49103	95.71639	1.7298
2	3.406	BB	0.8502	254.80144	3.87467	0.6160
3	6.456	VV	0.2971	2.02611e4	1040.47473	48.9826
4	7.083	VB	0.3514	1.90217e4	813.52588	45.9864

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.738	MM	0.3231	3.84898e4	1985.21973	99.3834
2	7.537	MM	0.2245	238.80635	17.72810	0.6166

HPLC Trace of PNB-(94) (Racemic Left, Enantioenriched Right)



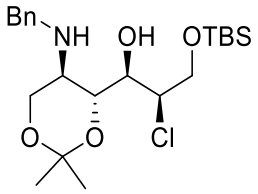


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	1.568	MM	0.2907	2916.25854	167.17921	58.7107
2	2.495	MM	0.4077	2050.90723	83.83390	41.2893

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	1.542	MM	0.2686	7551.74268	468.56067	96.3548
2	2.524	MM	0.3519	285.68860	13.53053	3.6452

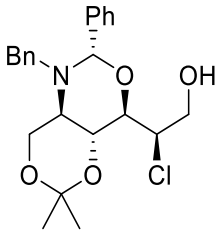
3.7.6. Preparation and Characterization of Hyacinthacine synthesis compounds

Preparation of Amino-Alcohol (108)



Compound **105** was synthesized according to literature procedures.[71] All spectral data matched that reported previously.

Preparation of Primary Alcohol (109)



Compound **108** (0.2mmol, 90mg) was stirred in CH_3CN (0.5M, 4mL) with benzaldehyde (10eq, 2.0mmol, 202µL), AcOH (2eq, 0.4mmol, 23µL) and a spatula tips of $MgSO_4$ for 48h. After TLC indicated reaction progression had stalled, the crude mixture was filtered through cotton and put under vacuum and all volatiles evaporated. The crude was purified by column chromatography (80:20 Hexanes:EtOAc) and taken directly to the next step.

The crude product was dissolved in THF (0.1M, 2mL) and 1.0M TBAF in THF (2eq., 0.6mL) was added at 0°C. The reaction was allowed to warm to room temperature, and stirred for 1 hour. After 1 hour, THF was evaporated by rotary evaporation. The crude was dissolved in EtOAc and filtered through a short SiO_2 plug. The product was purified by flash chromatography (80:20 Hexanes:EtOAc) to afford a clear oil (64% yield). Characterization data is all reported as a mixture of diastereomers (3:1) at the benzylidene position.

^{1}H NMR ($CDCl_3$, 500MHz) δ= 7.6-7.3 (*m*, 7H), 7.2 (*m*, 8H), 5.52 (*bs*, 1H *minor*), 5.26 (*bs*, 1H *major*), 4.40 (*m*, *J* = 2.7, 9.0 Hz, 1H *minor*), 4.4-4.23 (*m*, 2.5H), 4.13 *(m*, 1H), 3.97 (*m*, 1H), 3.89 (*m*, 2.3H), 3.81 (*m*, 1H *minor*), 3.67 (*d*, 1H *major*), 3.59 (*m*, 1.5H), 3.53 (*m*, 2H),

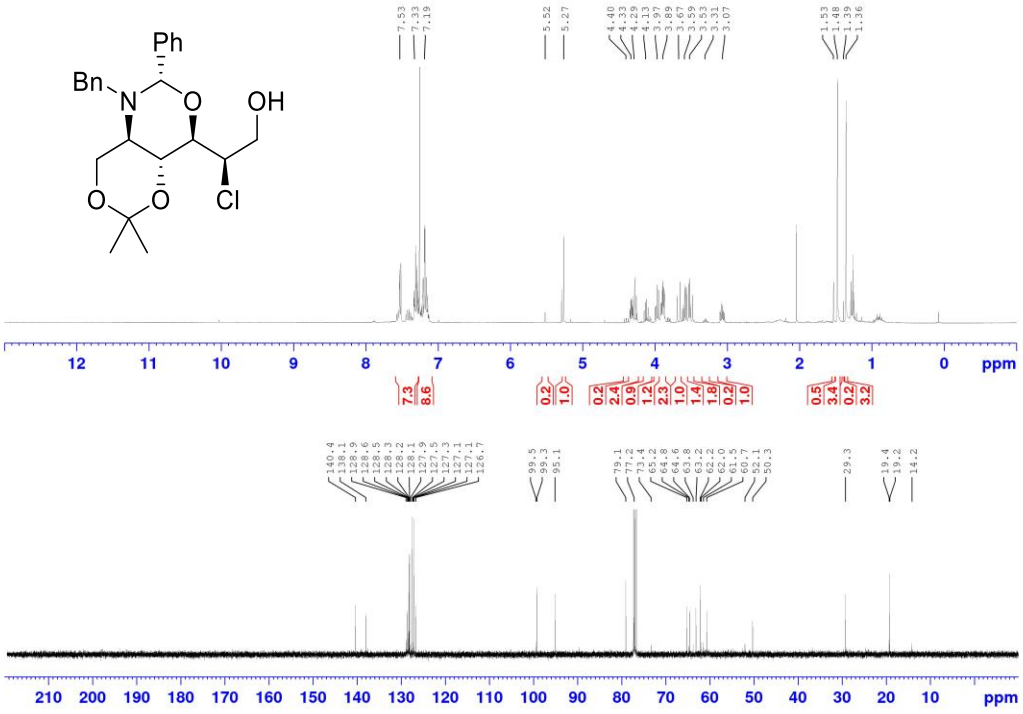
3.31 (*ddd*, *J* = 5.0, 10.8, 10.9 Hz, 1H *minor*), 3.07 (*ddd*, *J* = 5.0, 10.1, 10.2 Hz, 1H *major*), 1.53 (*s*, 3H *minor*), 1.48 (*s*, 3H *major*), 1.39 (*s*, 3H *minor*) 1.36 (*s*, 3H *major*)

^{13}C NMR ($CDCl_3$, 150MHz) δ= 140.4, 138.0, 128.9, 128.6, 128.5, 128.3, 128.2, 128.1, 127.9, 127.5, 127.3, 127.1, 127.1, 126.7, 99.5, 99.3, 95.1, 79.1, 73.4, 65.2, 64.8, 64.6, 63.8, 63.2, 62.1, 62.0, 61.5, 60.7, 52.1, 50.3, 29.3, 19.4, 19.2, 14.1

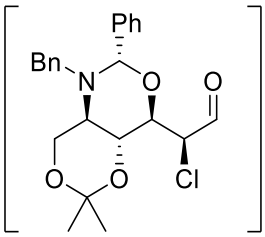
HRMS: (ESI) *m/z* calcd for $C_{23}H_{29}ClNO_4[M+H]^+$ 418.1780, found 418.1767

IR: 3424, 2993, 2939, 1702, 1602, 1495, 1453, 1087, 907, 728, 699, 647 cm^{-1}

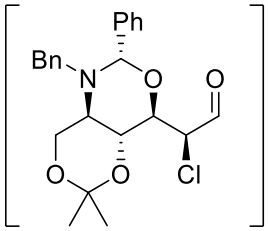
α_D^{20}= -37.6 (c=40 mg/mL in $CHCl_3$)



Preparation of Aldehyde (111)



Primary alcohol **109** (0.05mmol, 20mg) was dissolved in CH_2Cl_2 (0.5mL, 0.1M). Solid $NaHCO_3$ (0.4mmol, 40mg) was added to the vial. To this suspension was added DMP (0.58mmol, 25mg). The suspension was stirred for 1 hour, monitoring conversion by TLC. When starting material no longer appeared by TLC, the reaction was quenched with H_2O and the aqueous layer extracted with CH_2Cl_2 3x. The organic layer was dried with brine and Na_2SO_4. The crude organic product was concentrated by rotary evaporation. Product decomposed by TLC and this crude mixture was used in all further experiments with aldol reactions. Ideally, the next isolable intermediate after the aldol reaction would be characterized, as proper purification of the aldehyde proved difficult. Provided is the crude NMR of aldehyde **111** after oxidation and workup.



References

(1) Carey, F. A. *Organic Chemistry*; McGraw-Hill, 1996.

(2) Teo, S. K.; Colburn, W. A.; Tracewell, W. G.; Kook, K. A.; Stirling, D. I.; Jaworsky, M. S.; Scheffler, M. A.; Thomas, S. D.; Laskin, O. L. *Clin. Pharmacokinet.* **2004**, *43*, 311–327.

(3) Gladiali, S. *C.R. Chim.* **2007**, *10*, 220–231.

(4) Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. *Chem. Rev.* **2006**, *106*, 2734–2793.

(5) Merriam-Webster.com. Catalysis https://www.merriam-webster.com/dictionary/catalysis (accessed Oct 18, 2018).

(6) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946.

(7) Knowles, W. S. *J. Chem. Educ.* **1986**, *63*, 222.

(8) Sharpless, B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768–2771.

(9) Katsuki, T.; Sharpless, B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.

(10) NobelPrize.org. The Nobel Prize in Chemistry 2001 https://www.nobelprize.org/prizes/chemistry/2001/summary/ (accessed Oct 18, 2018).

(11) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97–102.

(12) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed.* **1971**, *10*, 496–497.

(13) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1621.

(14) List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.

(15) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.

(16) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172–1173.

(17) Cecere, G.; König, C. M.; Alleva, J. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 11521–11524.

(18) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826–8828.

(19) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808–10809.

(20) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138–6171.

(21) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178–2189.

(22) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336–9337.

(23) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387.

(24) Córdova, A.; Notz, W.; Barbas, C. F. *Chem. Commun.* **2002**, *8*, 3024–3025.

(25) Grondal, C.; Enders, D. *Tetrahedron* **2006**, *62*, 329–337.

(26) Enders, D.; Grondal, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1210–1212.

(27) Ward, D. E.; Jheengut, V. *Tetrahedron Lett.* **2004**, *45*, 8347–8350.

(28) Ward, D. E.; Guo, C.; Sasmal, P.; Man, C.; Sales, M. *Org. Lett.* **2000**, *2*, 1325–1328.

(29) Ward, D. E.; Jheengut, V.; Akinnusi, O. T. *Org. Lett.* **2005**, *7*, 1181–1184.

(30) Ward, D. E.; Becerril-Jimenez, F.; Zahedi, M. M. *J. Org. Chem.* **2009**, *74*, 4447–4454.

(31) Ward, D. E.; Jheengut, V.; Akinnusi, O. T. *Org. Lett.* **2005**, *7*, 1181–1184.

(32) Ward, D. E.; Zahedi, M. M. *Org. Lett.* **2012**, *14*, 6246–6249.

(33) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799.

(34) Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 2152–2154.

(35) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752–1755.

(36) Steiner, D. D.; Mase, N.; Barbas, C. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 3706–3710.

(37) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108–4109.

(38) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790–4791.

(39) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254–6255.

(40) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656–5657.

(41) Anders, B.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790–1793.

(42) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247–4250.

(43) Córdova, A.; Sundén, H.; Bøgevig, A.; Johansson, M.; Himo, F. *Chem. -- Eur. J.* **2004**, *10*, 3673–3684.

(44) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293–8296.

(45) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794–797.

(46) Garg, Y.; Kaur, R.; Kumar Pandey, S. *Eur. J. Org. Chem.* **2017**, *45*, 6700–6707.

(47) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304.

(48) Jacobsen, E. N.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci.* **2010**, *107*, 20618–20619.

(49) Bock, D. A.; Lehmann, C. W.; List, B. *Proc. Natl. Acad. Sci.* **2010**, *107*, 20636–20641.

(50) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475–2479.

(51) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175.

(52) List, B. *Tetrahedron* **2002**, *58*, 5573–5590.

(53) Seebach, D.; Beck, A. K.; Badine, D. M.; Limbach, M.; Eschenmoser, A.; Treasurywala, A. M.; Hobi, R.; Prikoszovich, W.; Linder, B. *Helv. Chim. Acta* **2007**, *90*, 425–471.

(54) Brown, K. L.; Damm, L.; Dunitz, J. D.; Eschenmoser, A.; Hobi, R.; Kratky, C. *Helv. Chim. Acta* **1978**, *61*, 3108–3135.

(55) Renzi, P.; Hioe, J.; Gschwind, R. M. *Acc. Chem. Res.* **2017**, *50*, 2936–2948.

(56) Lokesh, N.; Seegerer, A.; Hioe, J.; Gschwind, R. M. *J. Am. Chem. Soc.* **2018**, *140*, 1855–1862.

(57) Schmid, M. B.; Zeitler, K.; Gschwind, R. M. *J. Am. Chem. Soc.* **2011**, *133*, 7065–7074.

(58) Schmid, M. B.; Zeitler, K.; Gschwind, R. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4997–5003.

(59) Zotova, N.; Franzke, A.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 15100–15101.

(60) Burés, J.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2012**, *134*, 6741–6750.

(61) Burés, J.; Armstrong, A.; Blackmond, D. G. *Acc. Chem. Res.* **2016**, *49*, 214–222.

(62) Burés, J.; Armstrong, A.; Blackmond, D. G. *Chem. Sci.* **2012**, *3*, 1273–1277.

(63) Ponath, S.; Menger, M.; Ydia Grothues, L.; Anuela Weber, M.; Lentz, D.; Strohmann, C.; Christmann, M. *Angew. Chem., Int. Ed.* **2018**, *57*, 11683–11687.

(64) Pellissier, H. *Tetrahedron* **2016**, *72*, 3133–3150.

(65) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 659–676.

(66) Ward, D. E.; Jheengut, V.; Beye, G. E.; Gillis, H. M.; Karagiannis, A.; Becerril-Jimenez, F. *Synlett* **2011**, *4*, 508–512.

(67) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L. *J. Am. Chem. Soc.* **1995**, *117*, 9073–9074.

(68) Bergeron-Brlek, M.; Teoh, T.; Britton, R. *Org. Lett.* **2013**, *15*, 3554–3557.

(69) Meanwell, M.; Sutherland, M.; Britton, R. *Can. J. Chem.* **2017**, *4*, 144–147.

(70) Bergeron-Brlek, M.; Goodwin-Tindall, J.; Cekic, N.; Roth, C.; Zandberg, W. F.; Shan, X.; Varghese, V.; Chan, S.; Davies, G. J.; Vocadlo, D. J.; Britton, R. *Angew. Chem., Int. Ed.* **2015**, *54*, 15429–15433.

(71) Bergeron-Brlek, M.; Meanwell, M.; Britton, R. *Nat. Commun.* **2015**, *6:6903*.

(72) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L. *J. Am. Chem. Soc.* **1995**, *117*, 9073–9074.

(73) Ferreira, J.; Rees-Jones, S. C. M.; Ramaotsoa, V.; Msutu, A.; Hunter, R. *Org. Biomol. Chem.* **2016**, *14*, 1545–1549.

(74) Magnus, P.; Brozell, A. J. *Org. Lett.* **2012**, *14*, 3952–3954.

(75) Namba, K.; Takeuchi, K.; Kaihara, Y.; Oda, M.; Nakayama, A.; Nakayama, A.; Yoshida, M.; Tanino, K. *Nat. Commun.* **2015**, *6:8731*.

(76) Magnus, P.; Garizi, N.; Seibert, K. A.; Ornholt, A. *Org. Lett.* **2009**, *11*, 5646–5648.

(77) Ding, H.; Friestad, G. K. *Org. Lett.* **2004**, *6*, 637–640.

(78) Alexakis, A.; Lensen, N.; Mangeney, P. *Synlett* **1991**, *9*, 625–626.

(79) Gilchrist, T. L.; Hughes, D.; Wasson, R. *Tetrahedron Lett.* **1987**, *14*, 1573–1575.

(80) Leblanc, Y.; Fitzsimmons, B. J. *Tetrahedron Lett.* **1989**, *30*, 2889–2892.

(81) Barbion, J.; Sorin, G.; Selkti, M.; Kellenberger, E.; Baati, R.; Santoro, S.; Himo, F.; Pancrazi, A.; Lannou, M. I.; Ardisson, J. *Tetrahedron* **2012**, *68*, 6504–6512.

(82) Chung, J. Y. L.; Wasicak, J. T.; Arnold, W. A.; May, C. S.; Nadzan, A. M.; Holladay, M. W. *J. Org. Chem.* **1990**, *55*, 270–275.

(83) Liu, W. J.; Ye, J. L.; Huang, P. Q. *Org. Biomol. Chem.* **2010**, *8*, 2085–2091.

(84) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; John Wiley & Sons, Inc., 2006.

(85) Moreno-Clavijo, E.; Carmona, A. T.; Moreno-Vargas, A. J.; Rodríguez-Carvajal, M. A.; Robina, I. *Bioorganic Med. Chem.* **2010**, *18*, 4648–4660.

(86) Christmann, M.; Ponath, S.; Menger, M.; Grothues, L.; Weber, M.; Lentz, D.; Strohmann, C. *Angew. Chem., Int. Ed.* **2018**, *57*, 11683–11687.

(87) Dhand, V.; Draper, J. A.; Moore, J.; Britton, R. *Org. Lett.* **2013**, *15*, 1914–1917.

(88) Draper, J. A.; Britton, R. *Org. Lett.* **2010**, *12*, 4034–4037.

(89) Halperin, S. D.; Britton, R. *Org. Biomol. Chem.* **2013**, *11*, 1702–1705.

(90) Chang, S.; Desai, S.; Leznoff, D. B.; Merbouh, N.; Britton, R. *Eur. J. Org. Chem.* **2013**, *16*, 3219–3222.

(91) Dhand, V.; Chang, S.; Britton, R. *J. Org. Chem.* **2013**, *78*, 8208–8213.

(92) Holmes, M. T.; Britton, R. *Chem. -- Eur. J.* **2013**, *19*, 12649–12652.

(93) Quintard, A.; Sperandio, C.; Rodriguez, J. *Org. Lett.* **2018**, *20*, 5274–5277.

(94) Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010**, *39*, 1600–1632.

(95) Yang, J. W.; Chandler, C.; Stadler, M.; Kampen, D.; List, B. *Nature* **2008**, *452*, 453–455.

(96) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569.

(97) Kjell, D. P.; Slattery, B. J.; Semo, M. J. *J. Org. Chem.* **1999**, *64*, 5722–5724.

(98) Logue, M. W.; Hee Han, B. *J. Org. Chem.* **1981**, *46*, 1638–1642.

(99) Hertweck, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 4688–4716.

(100) Pecchioli, T.; Cardona, F.; Reissig, H. U.; Zimmer, R.; Goti, A. *J. Org. Chem.* **2017**, *82*, 5835–5844.

(101) Kang, B. Applications of α - Chloroaldehydes toward the Synthesis of Natural Products, SFU, PhD Thesis, 2012.

(102) Adamson, C. W. Synthesis and Evaluation of Novel Carbocyclic Carbohydrate Analogues, SFU, MSc Thesis, 2016.

(103) Martínez, M. M.; Hoppe, D. *Eur. J. Org. Chem.* **2005**, *7*, 1427–1443.

(104) Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nat. Protoc.* **2007**, *2*, 2451–2458.