STUDIES ON AN ORGANOCATALYTIC SYNTHESIS OF FUNCTIONALIZED NITROCYCLOHEXANONES AND (+)-LYCOPERDIC ACID

SHUBHANGI V. ADSOOL

Studies on an Organocatalytic Synthesis of Functionalized Nitrocyclohexanones and (+)-Lycoperdic Acid.

by
© **Shubhangi V. Adsool**

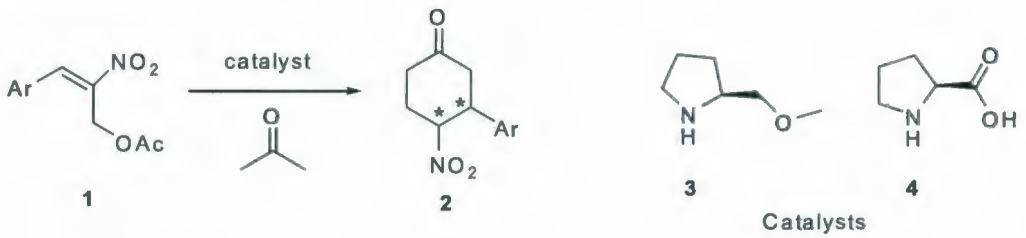
A thesis submitted to the School of Graduate Studies
in partial fulfillment of the requirements for the degree of
Master of Science

Department of Chemistry
Memorial University
March 2010

St. John's Newfoundland

Abstract

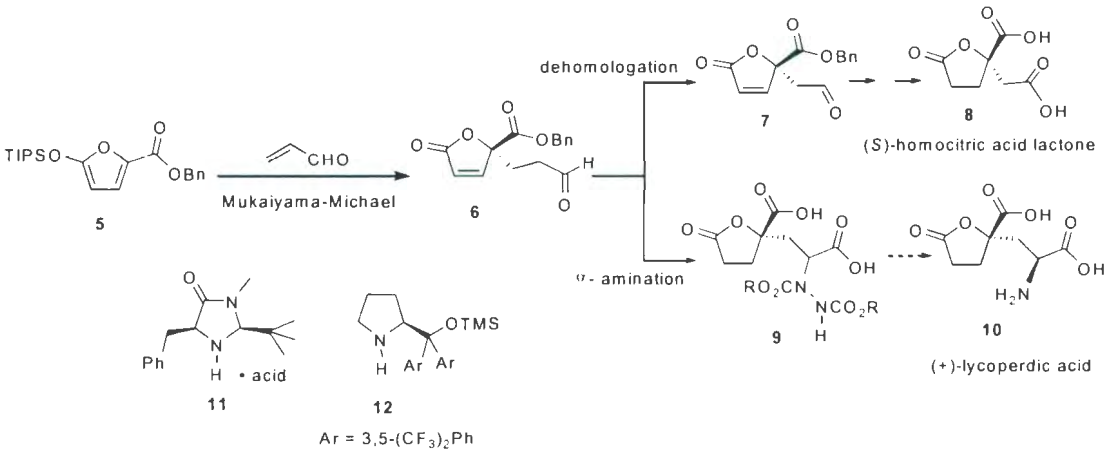
A strategy for enantioselective double Michael addition reactions of acetone to nitroalkene **1** has been investigated. The feasibility of employing an enamine-mediated, organocatalytic route to functionalized cyclohexanones **2** was examined in this study (Scheme 1).



Scheme 1: Synthesis of functionalized nitrocyclohexanones.

Simultaneously, in continuation with the Pansare group's interest in organocatalytic conjugate addition reactions, an organocatalytic, conjugate addition based synthesis of (+)-lycoperdic acid (**10**) was examined. Lycoperdic acid is an unusual amino acid isolated from a mushroom (*lycoperdon perlatum*). Its unique structure and potential glutamate receptor activity, makes it a challenging synthetic target. Our approach to lycoperdic acid is based on the enantioselective organocatalytic Mukaiyama-Michael addition of furan **5** to acrolein, mediated by catalysts **11** and **12** to provide the key butyrolactone **6** (Scheme 2). It is noteworthy that only a few examples of enantioselective organocatalytic Mukaiyama-Michael conjugate additions of furans related to **5** and β-substituted α,β-unsaturated aldehydes are known, and the use of acrolein as a Michael acceptor in these reactions has not previously been reported. Conversion of **6** to (*S*)-

homocitric acid lactone (**8**) not only provided a new synthesis of this natural product enantiomer, and also established the stereochemistry of the Michael addition of **5** to **6**. An organocatalytic α-amination of **6** using catalyst **12** provided **9** which is an advanced intermediate to lycoperdic acid.



Scheme 2: Organocatalytic synthesis of (+) lycoperdic acid.

Acknowledgements

First and the foremost I would like to thank my supervisor Professor Sunil Pansare for his guidance and encouragement throughout the program. The training that I received by working in his lab, I believe, has equipped me with the expertise necessary of a good synthetic chemist. Indeed, if I had decided to embark on my doctoral studies, the Pansare group would have certainly been my first choice.

Besides Professor Pansare, Professor Yuming Zhao and Professor Christina Bottaro deserve special thanks as my committee members for providing me their comments and suggestions during the program and for their valuable evaluations of this document. I am deeply grateful to Professor Graham Bodwell and Professor Paris Georghiou for helpful discussions and encouragement during the program and graduate courses.

I would like to thank Ms. Julie Collins and Dr. Celine Schneider for the training and support with IR and NMR spectroscopy and Ms. Linda Winsor for the training and support with mass spectroscopy.

I would like to thank Mr. Dave Murphy for the computer-related support throughout my program. I thank Ms. Viola Martin, Ms. Mary Flinn, Ms. Rosalind Collins, Ms. Colleen Baker and Ms. Gina Jackson for the administrative support during the program. I thank Mr. Steve Ballard, Ms. Bonita Smith, and Mr. John Power for providing storeroom support.

I thank Mr. Patrick Hannon and Dr. Karen Hattenhauer and Mr. Tiber Reardon for being wonderful colleagues in the teaching labs.

Furthermore, I am also thankful to have supporting colleagues working with me in the lab. I thank Ms. Raie Lene Kirby, Mr. Rajinikanth Lingampally, Mr. Dave Murphy, Mr. Tim Morgan and Mr. Adam Hefferman for their constant help, support and encouragement throughout the program in the lab. Support from my colleagues from other research groups at the chemistry department at MUN is greatly appreciated. I also, thank to all of those who supported me in any respect during the program.

Special thanks go to my beloved husband Vikrant, who gave me the confidence and support to begin my Master's program. He has played the dual role of my colleague and that of my husband with incredible perfection. I am forever grateful to my parents and my in-laws for their support.

Last, but not the least, I also wish to thank the Department of Chemistry, Memorial University of Newfoundland, and Natural Sciences and Engineering Research Council of Canada for Financial support.

Table of contents

List of tables

Chapter 1

Chapter 2

List of figures

Chapter 1:

Chapter 2

List of Abbreviations

Ar	aromatic
atm	atmosphere
Bn	benzyl
S_N2	bimolecular nucleophilic substitution
dr	diastereomeric ratio
ds	diastereoselectivity
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	dichloromethane
DMAP	4-(dimethylamino)pyridine
DDQ	dichlorodicyanoquinone
DIBAL-H	diisobutylaluminium hydride
DIPEA	N,N-diisopropylethylamine
DNBA	dinitrobenzoic acid
Dt-BAD	ditertiarybutyl azodicarboxilate
equiv	equivalent
ee	enantiomeric excess
Et	ethyl
h	hours
HMPA	hexamethylphosphoramide
HPLC	high pressure liquid chromatography

i-Pr	isopropyl
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
min	minute
Me	methyl
MOM	methoxymethyl
MBH	Morita-Baylis-Hillman
MPM	(4-methoxyphenyl)methanol
NOE	nuclear Overhauser enhancement
NMR	nuclear magnetic resonance
NBS	*N*-Bromosuccinimide
nd	not determined
Ph	phenyl
p-TsOH	para toluenesulfonic acid
PPTS	pyridinium p-toluenesulfonate
PDC	pyridinium dichromate
rac	racemic
rt	room temperature
TMS	trimethylsilyl
TBDPS	tertiary-butyl diphenylsilyl
TS	transition state
THF	tetrahydrofuran
t-Bu	tertiary-butyl

TMG	1,1,3,3-tetramethylguanidine
TIPS	tri-isopropylsilyl
Et_3N	triethyl amine
TFA	trifluoroacetic acid
Boc	tertiary-butyl carbamate
THP	tetrahydropyran
TBS	tributyl dimethylsilyl
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TBAF	tetrabutylammonium fluoride
TIPSOTf	tri-isopropylsilyl trifluoromethanesulfonate

Appendix

Chapter 1

Organocatalytic Synthesis of Functionalized Nitro-cyclohexanones

Introduction

An organocatalyst is an organic molecule which increases the rate of an organic reaction when used in a substoichiometric amount.[1] The need for enantiomerically-enriched compounds has given a boost to the study of organocatalysis.[2] Asymmetric carbon-carbon bond formation is one of the challenging fields in organic chemistry.[3] In recent years, the formation of two or more bonds in consecutive steps (tandem reactions) has gained interest. Tandem reactions are more economical because these reactions need fewer numbers of chemical steps and hence may produce less waste.[4] Whenever applicable, these reactions can produce more than one stereocenter in a single step. One of the most important reactions for carbon-carbon bond formation is the Michael reaction.[5] The asymmetric oganocatalytic Michael reaction has been utilized for the addition of various aldehydes and ketones to nitroalkenes.[6] The use of a nitroalkene in this reaction is useful because the nitro functional group can be easily converted into other functional groups such as an amine, amide or ketone, etc. For these reasons, new synthesis of functionalized nitrocyclohexanones by using a double Michael addition reaction of a ketone to a nitroalkene is a topic worthy of extensive and systematic investigations.

Discussion

Several methods have been reported in the literature for the organocatalytic Michael addition of aldehydes or ketones to nitroalkenes. For most of these reactions chiral amines are used as catalysts. Some of these catalysts are shown in Figure 1. The majority of the catalysts are secondary amines which catalyze the Michael reaction by forming an enamine with the aldehyde or ketone. A brief discussion of the application of some of these catalysts follows.

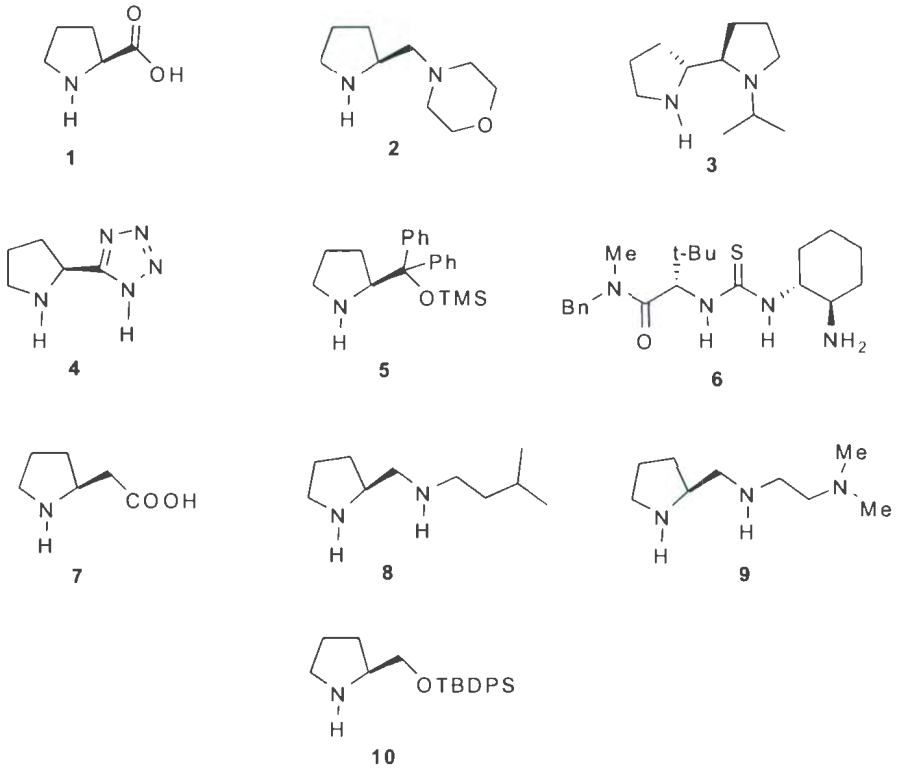
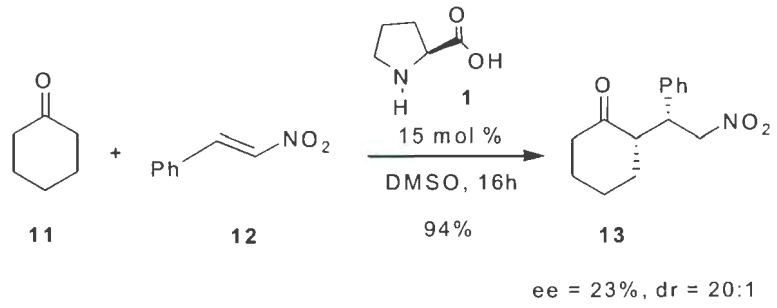


Figure 1: Selected catalysts for the Michael addition of aldehydes or ketones to nitroalkenes.

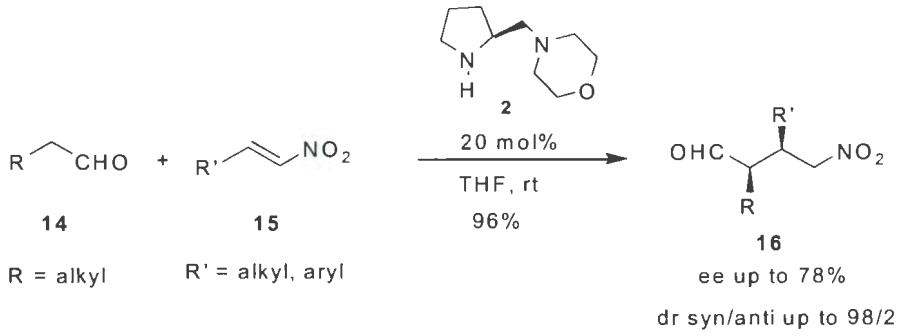
In 2001, List reported the catalytic Michael reaction[7] of cyclohexanone (**11**) and nitroalkenes e.g. **12** using proline (**1**) as catalyst. In this study, an excellent yield of the adduct **13** was achieved, but with low enantioselectivity. A similar study reported by



Scheme 1: Proline catalysed Michael adiition of ketone to nitroalkene.

Salunke et al. used L-proline (**1**) as a catalyst in an ionic liquid[2] and gave good yield and diastereoselectivity (90% of the single diastereomer).

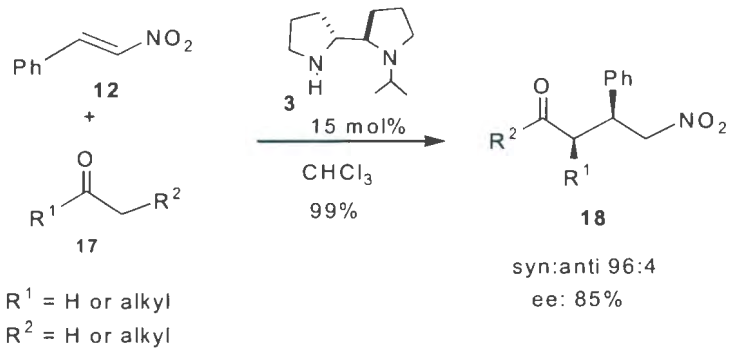
A study reported by Barbas on Michael addition of aldehydes to nitroalkenes using (*S*)-2-(morpholinomethyl)-pyrrolidine (**2**, scheme 2) as a catalyst provided the *syn* product **16** as a major diastereomer (up to 98%), in excellent yield and good



Scheme 2: Organocatalytic Michael adiition of aldehyde to nitroalkene.

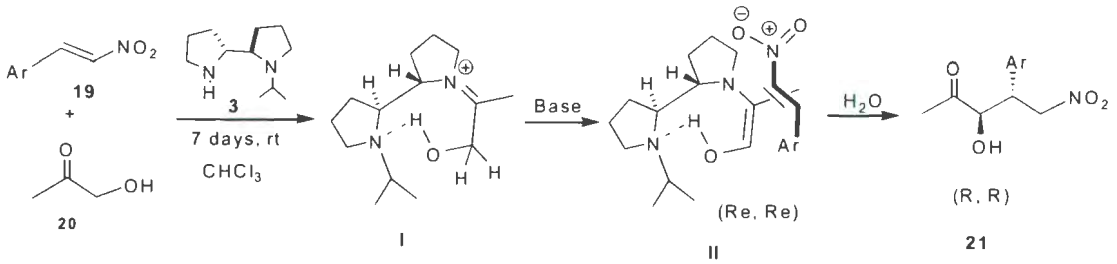
enantioselectivity (up to 78%).[8]

Later, in 2002 Alexakis and Andrey reported a similar study of Michael addition of aldehydes and ketones to nitrostyrenes using *N*-*i*-Pr-2,2'bipyrrolidine[5] (**3**, Figure 1) as a catalyst (Scheme 3). The reaction of an aldehyde with a nitroalkene (with or without HCl as an additive) gave γ-nitroaldehyde **18** with moderate-to-good enantioselectivity and excellent yield. However, a similar reaction with a ketone



Scheme 3: Organocatalytic Michael addition of aldehyde or ketone to nitroalkene.

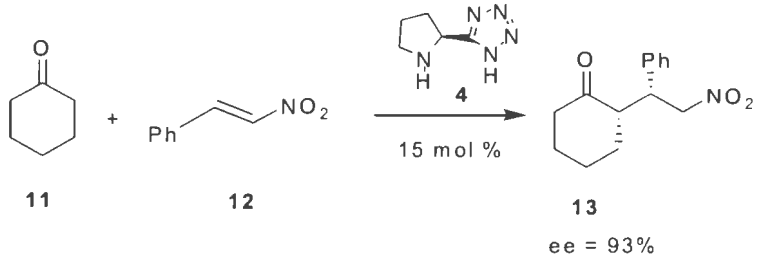
proceeded in low yield and low enantioselectivity. In 2003 Alexakis used the same catalyst **3** for Michael addition of α-hydroxyketones to β-arylnitroolefins.[9] In this case, the product was obtained with excellent enentioselectivity (up to 98%) and good yield. The proposed mechanism is shown in Scheme 4.



Scheme 4: Proposed mechanism for organocatalytic Michael addition.

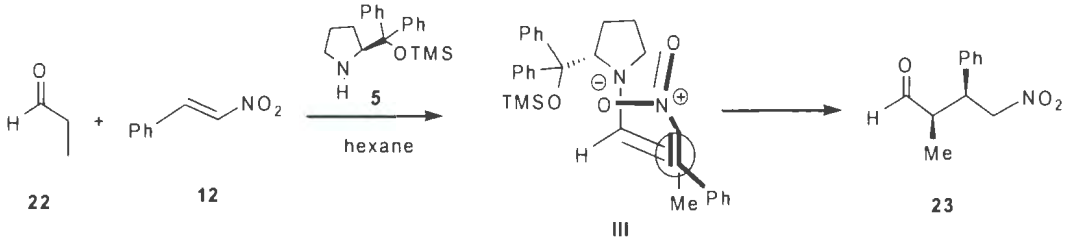
The tertiary nitrogen in catalyst **3** is presumed to form a hydrogen bond with the α-hydroxy group in the ketone (**I**) (Scheme 4) which selectively generates the *Z* enamine (**II**) instead of the *E* enamine. The *Z* enamine undergoes a stereoselective Michael reaction to provide **21**.

In 2005, Ley and co-workers used tetrazolyl pyrrolidine[10] (**4**) as catalyst for the Michael reaction of cyclohexanone (**11**) with β-nitrostyrene (**12**) as the Michael acceptor in a 1:1 mixture of isopropyl alcohol and ethanol as solvent (Scheme 5). The enantioselectivity obtained by using this catalyst was up to 93%.



Scheme 5: Organocatalytic Michael addition with cyclohexanone and tetrazolyl pyrrolidine (**4**).

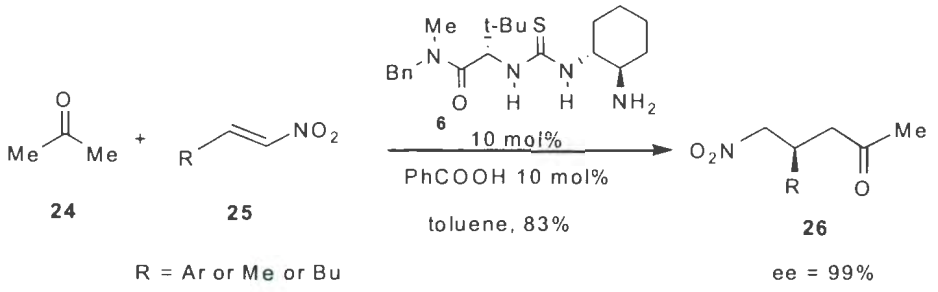
Hayashi and co-workers reported the use of catalyst **5** (Figure 1) in the Michael addition of an aldehyde to a nitroalkene (Scheme 6).[11] In their study, they obtained a nearly optically pure (99%) Michael adduct in good yield and high distereoselectivity (*syn* selectivity up to 96%). The high selectivity was explained on the basis of transition state **III** in which the bulky diphenylsiloxymethyl group on the catalyst ensures the selective formation of the *E* enamine and selectively shields the *re*-face of the enamine.



Scheme 6: Transition state for formation of **23** proposed by Hayashi.

Later on, Hayashi used catalyst **5** for the enantioselective Michael addition of nitroalkenes to α,β-unsaturated aldehydes,[6] in which he obtained up to 98% ee.

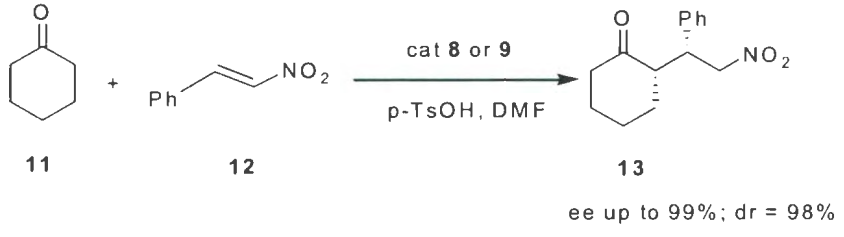
In 2006, Jacobsen reported the Michael addition of acetone to a variety of nitroalkenes in the presence of catalyst **6** (a thiourea derivative) and a catalytic amount of benzoic acid. The adduct **26** was obtained in 99% ee and 83% yield (Scheme 7) [12].



Scheme 7: Michael addition of acetone with nitroalkene in the presence catalyst **6**.

A similar reaction of acetone catalyzed by (*S*)-homoproline (**7**) hydrochloride[13] in the presence of triethylamine gave low yield and enantioselectivity. However, the reaction of ethyl methyl ketone in *t*-butanol proceeds with high enantioselectivity (up to 90% and *syn* selectivity up to 98%) with this homoproline as catalyst.

In 2006, Pansare and co-workers studied the Michael addition of cyclic ketones to nitroalkenes by using the secondary amine substituted pyrrolidine **8** and *N,N*-dimethyl containing analogue **9** as catalysts in the presence of acid additives[14] (scheme 8). In these studies, the *syn* distereomer **13** was obtained as the major product in good yield and high enantioselectivity (up to 99%).

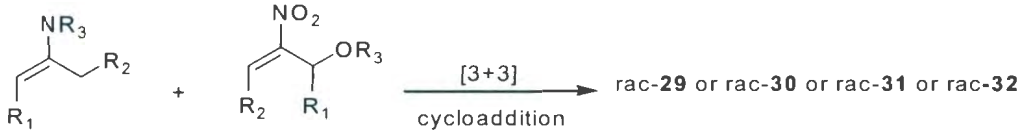


Scheme 8: Organocatalytic Michael addition of cyclohexanone to nitroalkene.

A similar study was reported by Liu et al. employing prolinol *tert*-butyldiphenylsilyl ether (**10**) as catalyst. Good yields of the Michael adduct were obtained in up to 95% ee and 98% de (*syn*).[15] However, reactions with acetone and propanal gave only moderate selectivity.

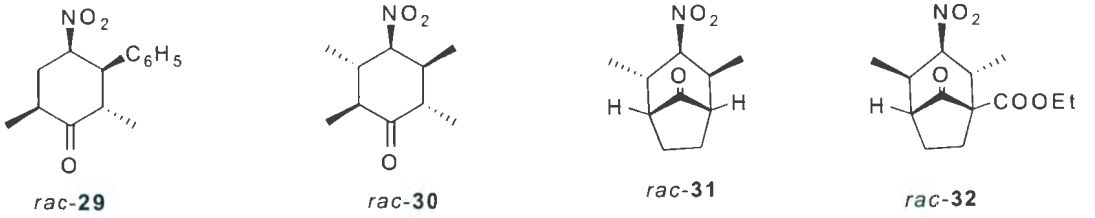
Synthesis of nitrocyclohexanones

Previous studies by Seebach had shown that nitrocyclohexanones could be obtained from a [3+3] cycloaddition reaction of enamine **27** and nitroallylic esters[16] *E* or *Z*, **28** (Scheme 9). This methodology can produce up to five-to-six adjacent stereocenters in the cycloadduct. The enamines were prepared from corresponding ketones and secondary amines in the presence of molecular sieves.



27 **28**

Enamine 27	**R_1**	**R_2**	**R_3**	***E* or *Z* nitroallylic esters 28**	**R_1**	**R_2**	**R_3**
27a	CH_3	CH_3	$-(CH_2)_2-O-(CH_2)2-$	*E*-**28a**	H	C_6H_5	$CO^tC_4H_9$
27b	H	H	$-(CH_2)_4-$	rac-**28b**	CH_3	CH_3	$COCH_3$
27c	COOEt	H	$-(CH_2)_4-$	-	-	-	-



rac-**29** from **27a** and **28a**

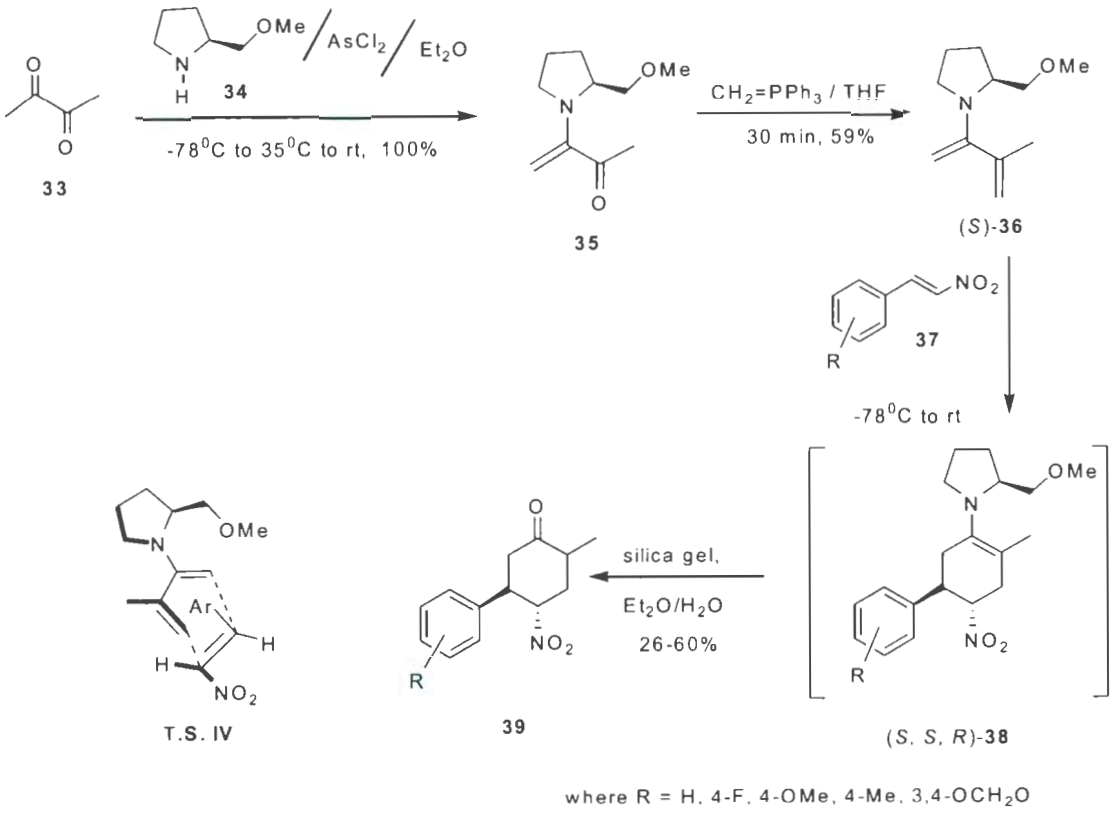
rac-**30** from **27a** and *rac*-**28b**

rac-**31** from **27b** and *rac*-**28b**

rac-**32** from **27c** and *rac*-**28b**

Scheme 9: Products of [3+3]-cycloaddition with racemic or achiral components.

In 1992, Enders and co-workers reported the enantioselective synthesis of nitro-cyclohexanones based on a [4+2] cycloaddition of 3-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-1,3-butadiene (**36**) with *E*-2-aryl-1-nitroethene (**37**).[17] For the preparation of butadiene **36**, 2,3-butanedione (**33**) was treated with (*S*)-2-(methoxymethyl)pyrrolidine (**32**) to obtain a quantitative yield of α-oxoenamine[18] in the presence of arsenic(III) chloride[19] (modified Weingarten method[20]). A Wittig reaction of compound **35** provided the pyrrolidinyl butadiene **36** (59%, scheme 10).

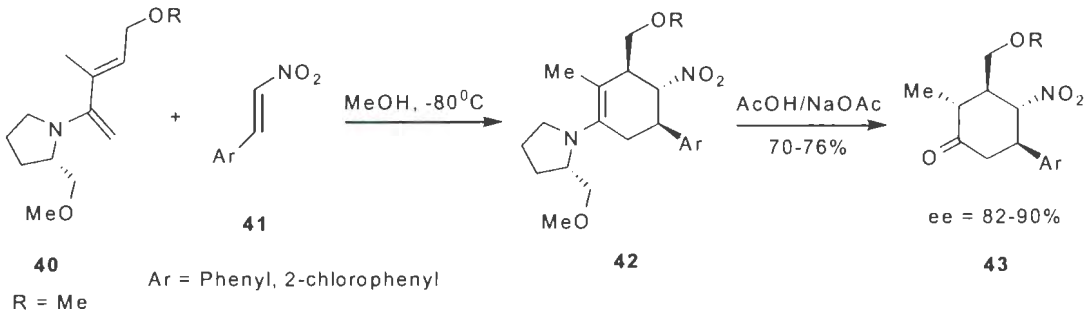


Scheme 10: [4+2] Cycloaddition of chiral 2-aminobutadiene and nitroalkene.

Butadiene **36** was subjected to [4+2] cycloaddition with nitroalkene **37** to obtain intermediate **38** which was hydrolyzed to 3-aryl-4-nitrocyclohexanone **39** in excellent enantiomeric excess (ee = 95-99%) and high diastereoselectivity (ds = 75-95%).

Barluenga et al. reported a similar study using chiral butadiene **40** (Scheme 11) and nitroalkenes **41** to obtain highly-substituted nitrocyclohexanones,[21] such as **43**, (four adjacent stereocenters) in good yield and up to 90% enantioselectivity. Later on, in 1997 he investigated the reactions between a variety of nitroalkenes (aromatic, heteroaromatic

and substituted aliphatic nitroalkenes and the same diene **40** (*E* or *Z*) in the [4+2] cycloaddition.[22] They used different R groups such as TBDMS, Me and MOM in diene

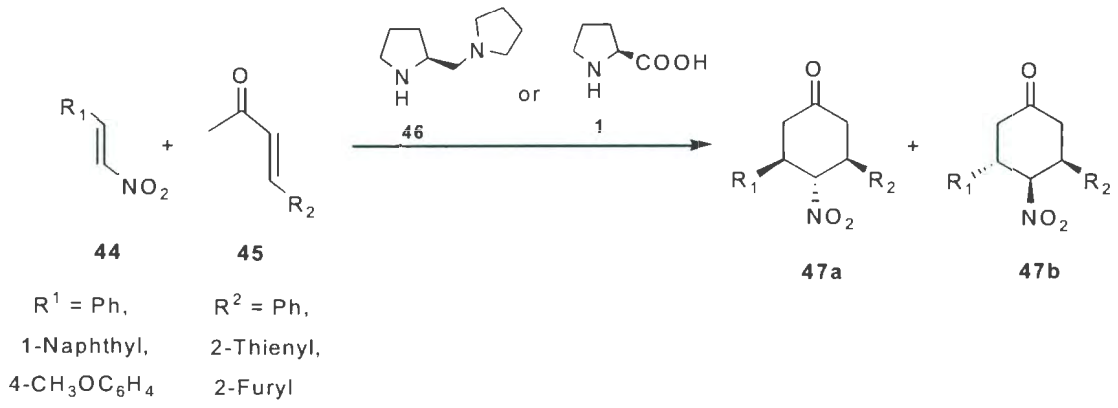


Scheme 11: [4+2] Cycloaddition of butadiene with nitroalkene.

40. *E* diene **40** was first reacted with aromatic and aliphatic nitroalkenes under the same reaction conditions as shown in Scheme 11. Functionalized 4-nitrocyclohexanones were obtained in good yield and in excellent distereoselectivity (83-99% de).

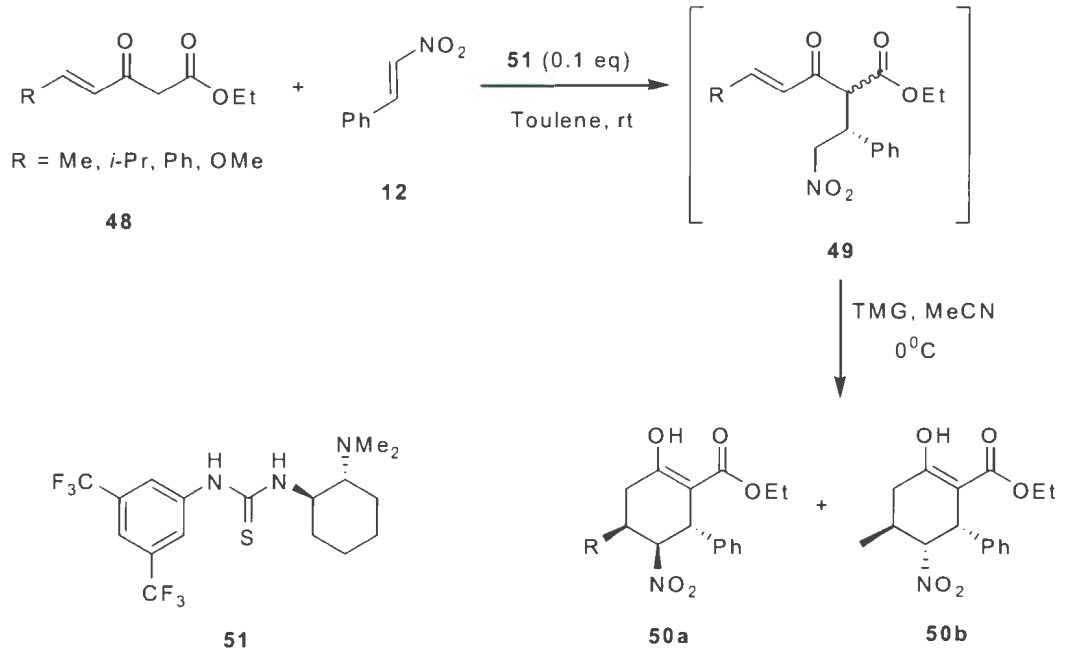
Organocatalytic synthesis of nitrocyclohexanone

Barbas and co-workers have developed the first amine-catalyzed direct Diels-Alder reaction (which may also be considered to be a double Michael reaction) for the synthesis of nitro-cyclohexanones.[23] The catalysts used in this study are (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine (**46**) and L-proline (**1,** Scheme 12). The Diels-Alder reaction of chalcones **45** with nitroalkene (**44**) in the presence of catalyst **46** or **1** gave a mixture of nitrocyclohexanones (**47a** and **47b**) in moderate-to-good yield (32-75%) and moderate enantioselectivity (up to 38%).



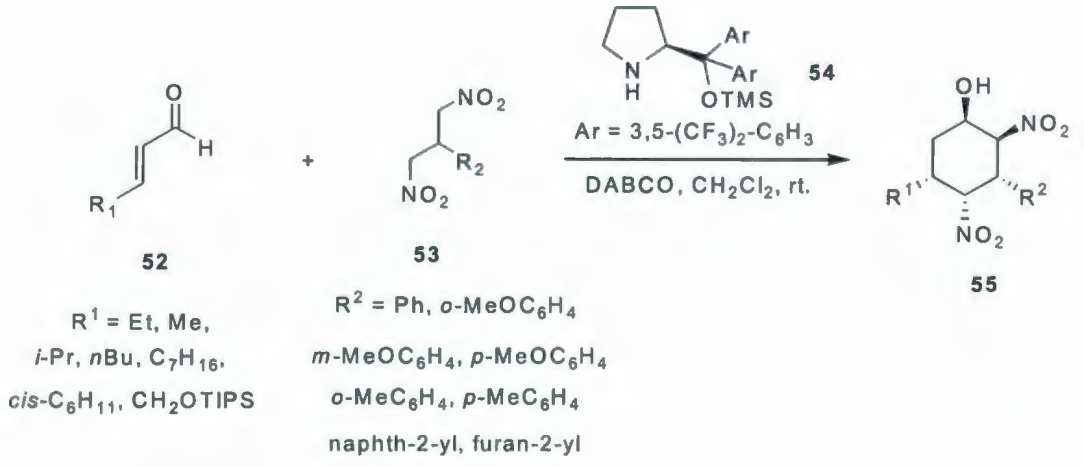
Scheme 12: Organocatalytic Diels-Alder reaction.

In 2004, Takemoto et al. reported a catalytic enantioselective double Michael addition.[3] They synthesised 4-nitrocyclohexanones using γ,δ-unsaturated β-ketoester (**48**) and nitrostyrene (**12**), a bifunctional thiourea catalyst (**51**, Scheme 13) and 1,1,3,3-tetramethylguanidine (TMG). Three contiguous stereocenters were constructed in a single reaction, for example, product **50a** was obtained in good yield along with excellent diastreoselectivity (up to 99%) and good enantioselectivity (up to 62%).



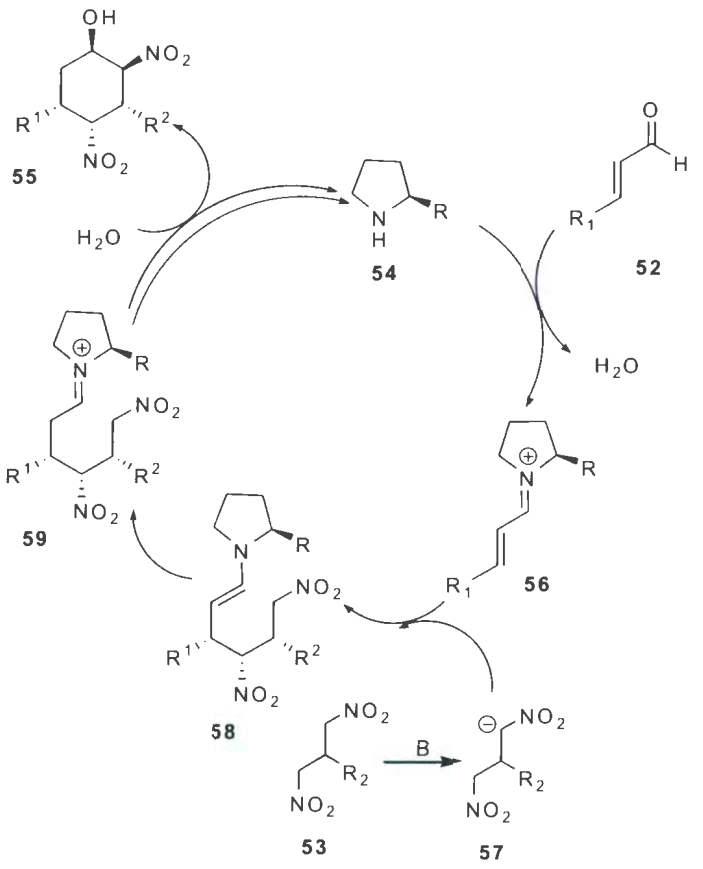
Scheme 13: Thiourea **51**-catalyzed double Michael addition reaction.

Jørgensen et al. reported the first one-pot reaction for the formation of five contiguous stereocenters by an intermolecular two-component reaction.[4] The nitro-cyclohexanol **55** was prepared from α,β-unsaturated aldehyde **52** and 1,3-dinitroalkane **53** in the presence of DABCO and (*S*)-2-[bis(3,5-bistrifluoromethylphenyl)(trimethylsilyloxymethyl)pyrrolidine][24] (**54**, Scheme 14) as catalyst. Compound **55** was obtained as the major isomer in good yield and enantioselectivity (up to 92 %). A bulky β-substituent in aldehyde **52** favors higher enantioselectivity and variation of the substituents in dinitroalkane **53** such as aromatic, heteroaromatic, electron-donating aromatic or electron-withdrawing aromatic groups gave comparable diastereoselectivity and enantioselectivity (88-90% ee).



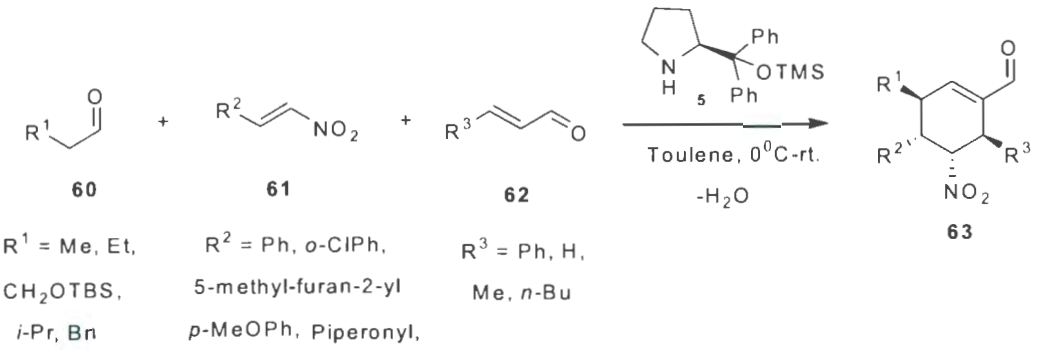
Scheme 14: Organocatalytic nitro-Michael/Henry reaction.

This organocatalytic Michael/Henry reaction proceeds by the proposed mechanism shown in Scheme 15. The first step is the formation of iminium ion **56** between catalyst **54** and aldehyde **52**. Nucleophile **57** (generated from dinitroalkane **53)** then attacks the iminium ion **56** from the less-hindered face to obtain Michael adduct **59**. Enamine **58** provides iminium ion **59** which is hydrolyzed to the corresponding aldehyde. The resulting aldehyde then undergoes an intramolecular Henry reaction to provide product **55** which contains five contiguous stereocenters. Hayashi and co-workers have also reported a two-component Michael/Henry reaction using pentane-1,5-diol and 2-substituted nitroalkenes[25] for the synthesis of nitrocyclohexanones.



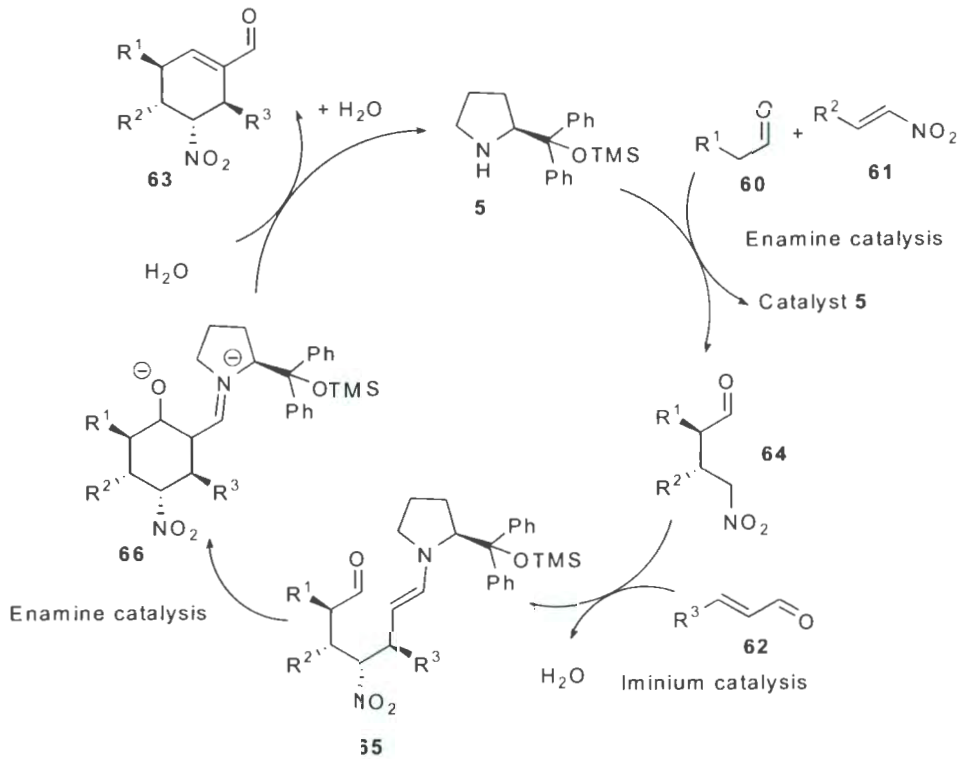
Scheme 15: Proposed mechanism for organocatalytic nitro-Michael/Henry reaction.

Enders and co-workers developed a chemo-, diastereo- and enantioselective organocatalytic triple-cascade reaction for the synthesis of nitrocyclohexenals.[26] This organocatalytic three-component reaction proceeds through a Michael/Michael/aldol condensation sequence which results in the formation of a product with four contiguous stereocenters. In this domino reaction Enders used aldehyde **60**, nitroalkene **61**, α,β-unsaturated aldehyde **62** and the chiral amine catalyst **5** (Scheme 16) to afford product **63** in high diastereoselectivity and complete enantioselectivity (99%).



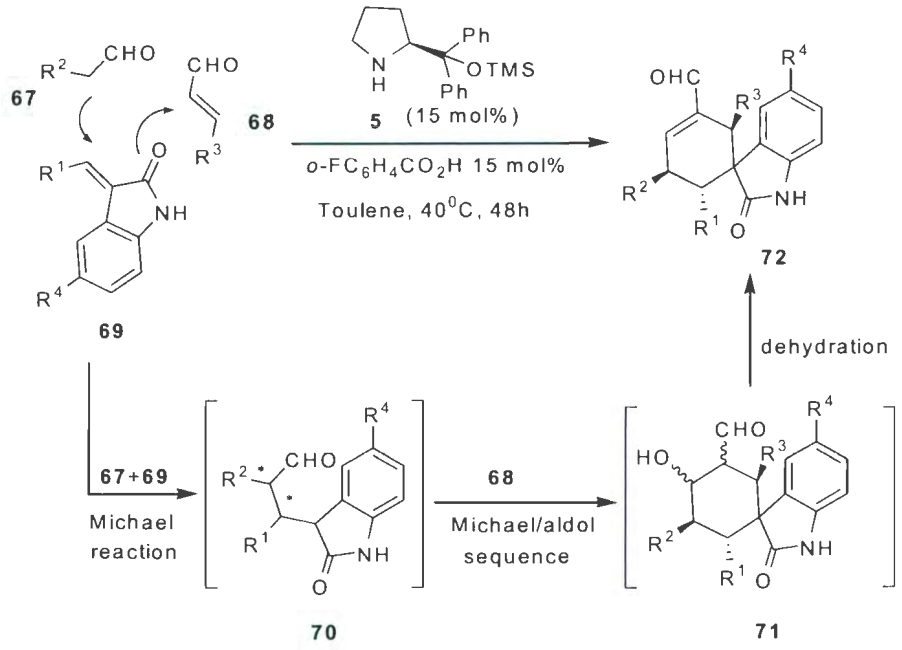
Scheme 16: Organocatalytic triple-cascade reaction.

The proposed mechanism for this reaction involves a sequence of Michael/Michael/aldol reactions as shown in Scheme 17.



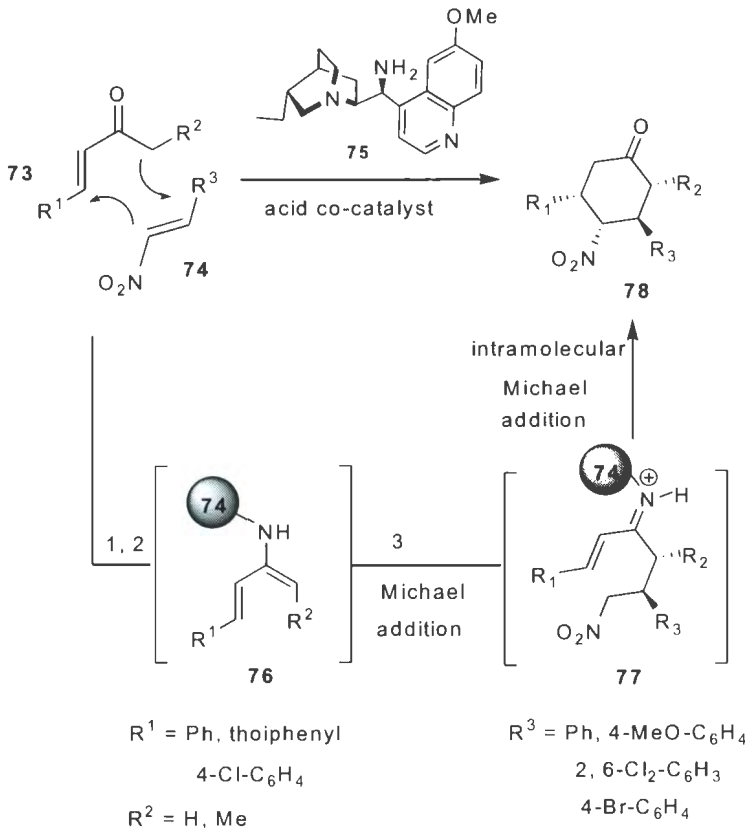
Scheme 17: Proposed mechanism of the triple-cascade reaction.

The catalyst **5** first forms an enamine with aldehyde **60** which then selectively reacts with nitroalkene **61** to obtain the new (intermediate) nitroalkane **64.** The catalyst then forms an iminium ion with α,β-unsaturated aldehyde **62.** This step is followed by conjugate addition with the nitroalkane **64** to afford intermediate **65,**[27] which undergoes an intramolecular aldol condensation to provide iminium ion **66.** Hydrolysis of **66** leads to the formation of product **63** and regeneration of catalyst **5**. Melchiorre et al. have also reported a triple-cascade (Michael/Michael/aldol) using the catalyst **5.** However, their synthesis began with a different starting material. As such, a more complex product **72** (Scheme 18) was obtained in excellent diastereoselectivity and enantioselectivity (99% de and ee).[28]



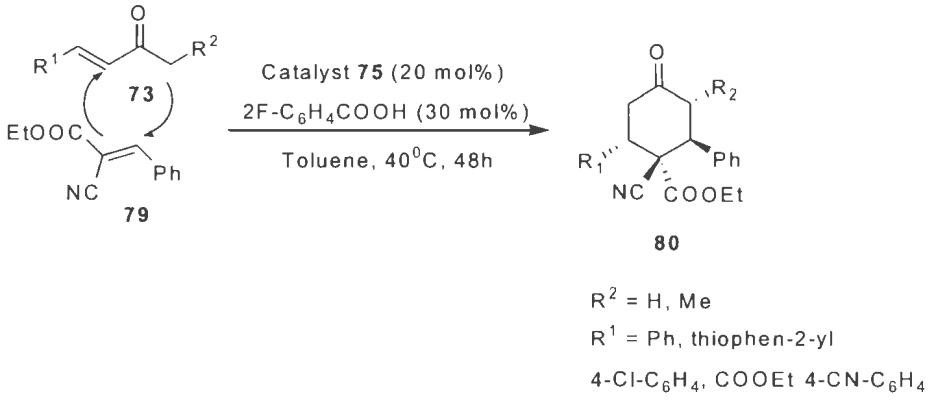
Scheme 18: Organocatalytic triple-cascade reaction.

Later on, Melchiorre and co-workers[29] reported a double Michael addition reaction using a primary amine, 9-amino(9-deoxy)-*epi*-hydroquinine (**75**), which is derived from a natural cinchona alkaloid (Scheme 19).



Scheme 19: Primary amine catalyzed double Michael addition reaction.

A similar reaction reported by Barbas and co-workers[30] used a secondary amine catalyst to produce the isomeric product in only 38% ee. Melchiorre and co-workers[30] also applied this methodology to construct quaternary stereocenters[31] (Scheme 20).

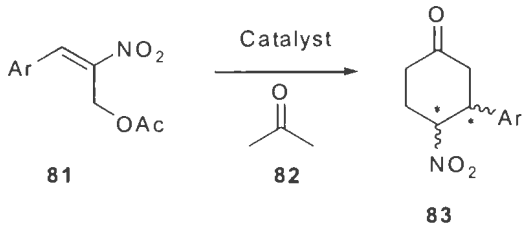


Scheme 20: Formation of all carbon quaternary stereocenters in a molecule.

Reaction of α,β-unsaturated ketones **73** and *trans* α-cyanocinnamate (**79**) in the presence of primary amine catalyst **75** afforded compound **80** in good yield, excellent diastereoselectivity and enantioselectivity (up to 98%). A similar reaction of α,β-unsaturated ketones **73** with *N*-phenyl- or *N*-benzyl maleimides gave bicyclic products containing three contiguous stereocenters in good yield and excellent diastereoselectivity and enantioselectivity (up to 99%).

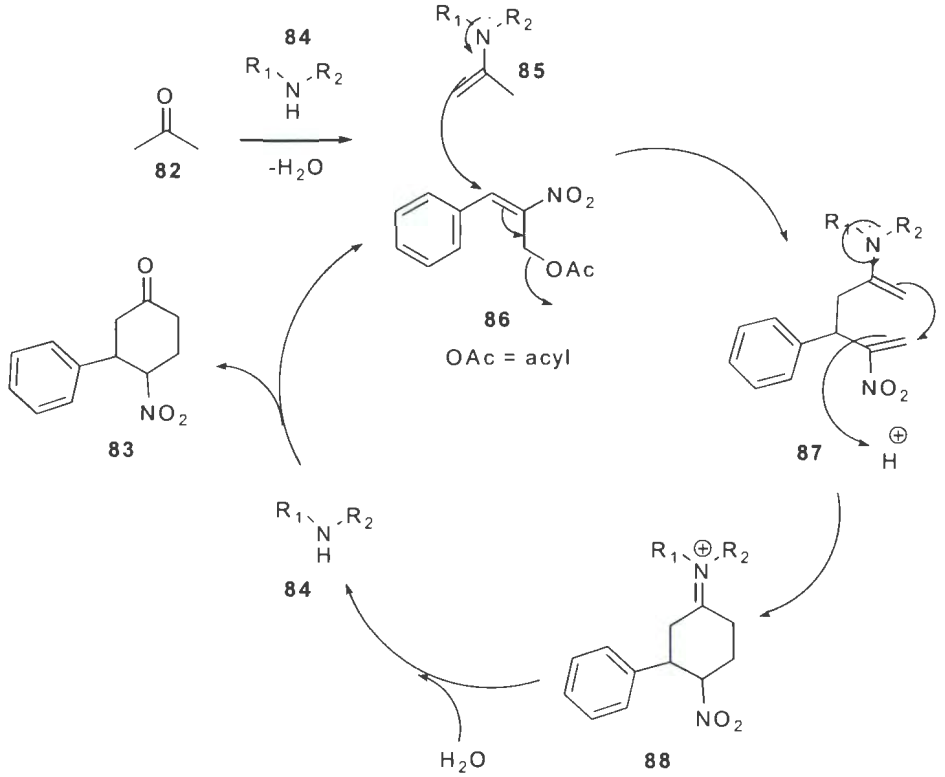
Present work

Given the success of the organocatalytic tandem-Michael reactions outlined above, the possibility of conducting an organocatalytic nitrocyclohexanone synthesis using appropriately functionalized nitroalkenes as the Michael acceptors (Scheme 21) was targeted in this thesis work.



Scheme 21: Proposed organocatalytic reaction.

The proposed mechanism for this reaction is as illustrated in Scheme 22. A chiral amine **84** is expected to form an enamine **85** with acetone. The first Michael addition of **85** at the β-position to the nitro group in nitroalkene **86** with concomitant elimination of the acyl group provides intermediate **87**. A second intramolecular Michael



Scheme 22: Proposed mechanism for double Michael reaction.

addition should give iminium ion **88**. Hydrolysis of iminium ion **88** will give a functionalized nitrocyclohexanone **83** and free chiral amine catalyst **84** for further reaction.

A variety of chiral amines were chosen as potential catalysts in this study (Figure 2). Of these, proline (**1**), **90** and **92** are commercially available and the remaining amines were prepared through known methods. The secondary-secondary diamine catalyst 3-methyl-*N*-(((*S*)-pyrrolidine-2-yl)methyl)butan-1-amine (**89**) has been used

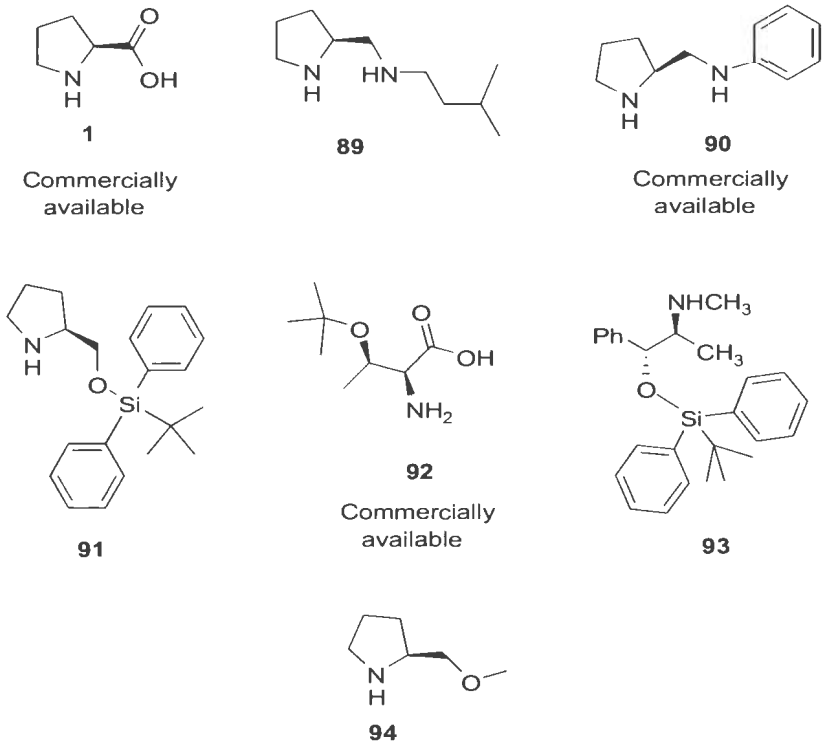
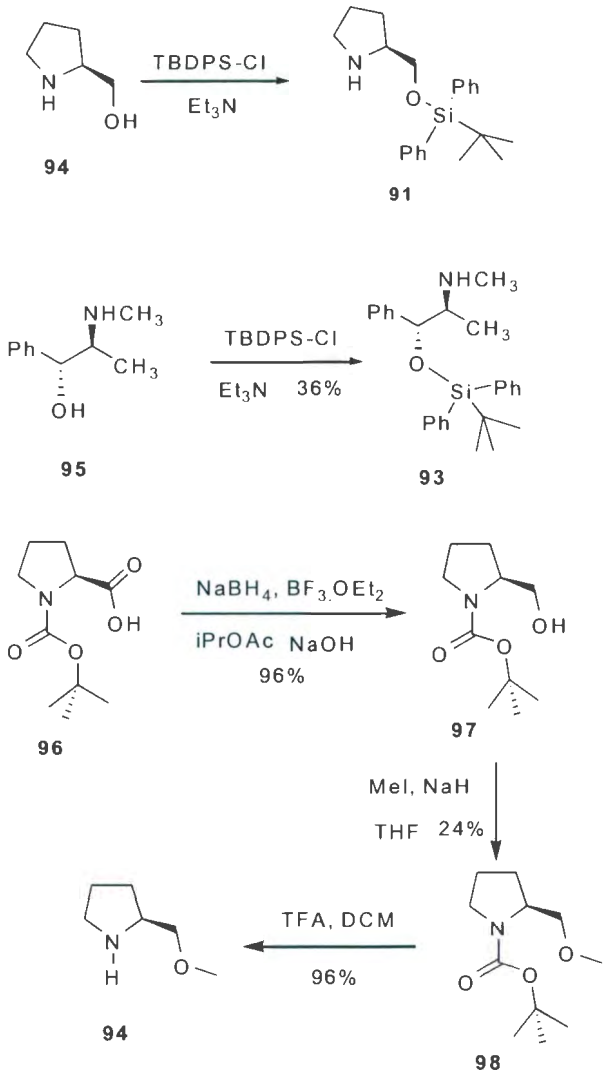


Figure 2: Catalyst used in preparation of nitrocyclohexanone.

previously in the Pansare group for ketone-nitroalkene Michael additions.[14] The amines

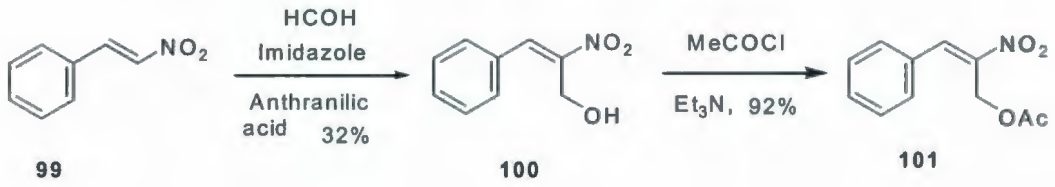
91, **93** and **94** were prepared as follows. For the synthesis of amine **91** (Scheme 23) the primary alcohol group in prolinol (**94**) was protected as *t*-butyldiphenylsilyl ether by treating prolinol with triethylamine and TBDPS-Cl. Amine **93** was obtained in 36% yield from ephedrine by using the same method. (*S*)-2-(Methoxymethyl)pyrrolidine (**94**) was prepared from inexpensive and commercially available *N*-Boc-L-proline (**96**) by adapting



Scheme 23: Preparation of proline and ephedrine based catalysts.

the literature method. [32] Boc-proline **96** was reduced to Boc-prolinol **97** (96%). Treatment of **97** with sodium hydride and methyl iodide provided **98** in 24% yield.[33] Boc deprotection in compound **98** (TFA) followed by basification provided amine **94** (96%).

The functionalized nitroalkene starting material required for the study was prepared from 1-((*E*)-2-nitrovinyl)benzene and formaldehyde using the reported procedure[34] (Scheme 24). Nitrostyrene (**99**) was subjected to a Morita-Baylis-Hillman



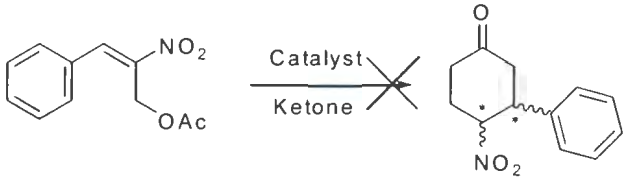
Scheme 24: Preparation of compound **101**.

(MBH) type reaction[34] with formaldehyde in the presence of imidazole (stoichiometric amount) and anthranilic acid (catalytic amount) to obtain (*E*)-2-nitro-3-phenylprop-2-en-1-ol (**100**) in 32% yield. The primary alcohol in compound **100** was acylated to provide compound **101**which is the required nitroalkene substrate for our studies in 92% yield.

Initial studies were conducted with **101** and acetone in the presence of diamines **89**, **90** and **94** (Table 1). All experiments were conducted at room temperature with 1 equivalent of nitroalkene, 5 equivalents of acetone and 20 mol% of the diamine. None of the reactions provided the anticipated nitrocyclohexanone **102.** Instead, diamine **90** reacted with the nitroalkene substrate to give a 1:1 adduct which is likely to be either **103**

or **104.** A detailed structural analysis of this unwanted product however, was not carried out in this study (Scheme 25).

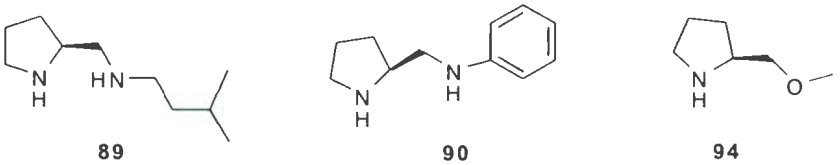
Table 1: Organocatalyic double Michael reaction of acetone to compound **101**.



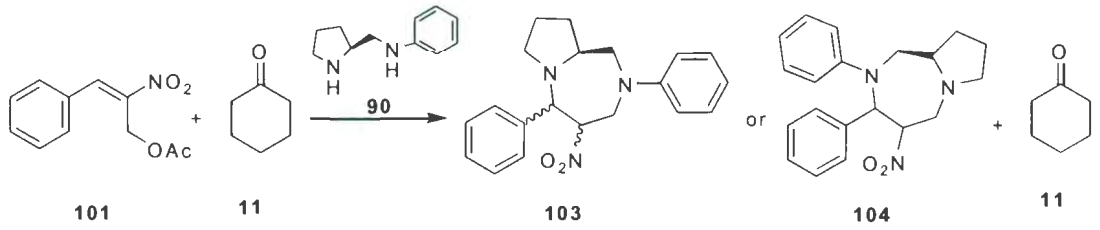
101 **102**

Entry	Ketone	Catalyst	Solvent	Time	Observation
1	Acetone	**89**	THF	2 days	Starting material recovered
2	Acetone	**89**	DMF	2 hours	Decomposition
3	Acetone	**94**	THF	9 days	Starting material recovered
4	Cyclohexanone	**89**	THF	3 days	Starting material recovered
5	Cyclohexanone	**90**	THF	12 hours	**103** or **104** (12%)

Nitroalkene 1 equiv; ketone 5 equiv, catalyst 20 mol% all reactions were stirred at room temperature for the time mentioned in table 1.

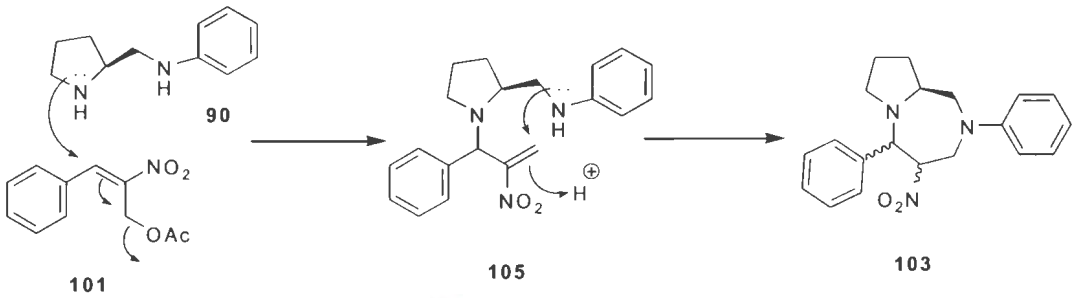


89 **90** **94**



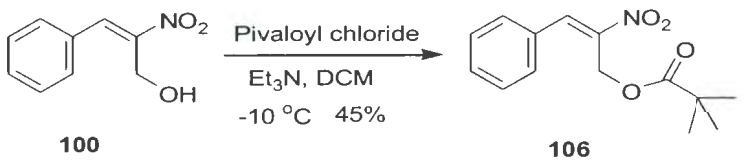
Scheme 25: Reaction of catalyst **90** and starting material **101**.

A probable mechanism for the formation of **103** is shown in Scheme 26. Alternatively **104** can also be formed in a similar manner.



Scheme 26: Proposed mechanism for the formation of compound **103**.

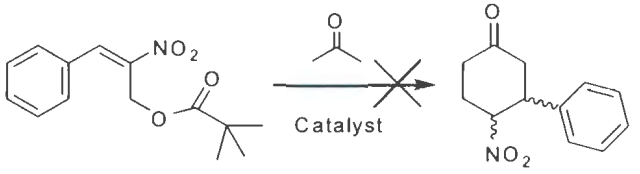
Considering the reactivity of compound **101**, it was decided to use a different alcohol protecting group (instead of acetyl). The pivaloyl group was chosen to favor nucleophilic addition at the β-position of the nitroalkene derivative, due to its steric hindrance. Thus, treatment of compound **100** with pivaloyl chloride in the presence of triethylamine in DCM at -10 °C provided compound **106** in 45% yield (Scheme 27).



Scheme 27: Protection of the primary hydroxyl in **100** with pivaloyl group.

Reaction of **106** and acetone were attempted with amine **92** and **94** (Table 2). However, as with nitroalkene **101**, these reactions did not provide any of the cyclohexanone **102**.

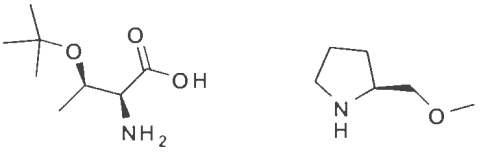
Table 2: Organocatalytic double Michael reaction of acetone to compound **106**.



106 102

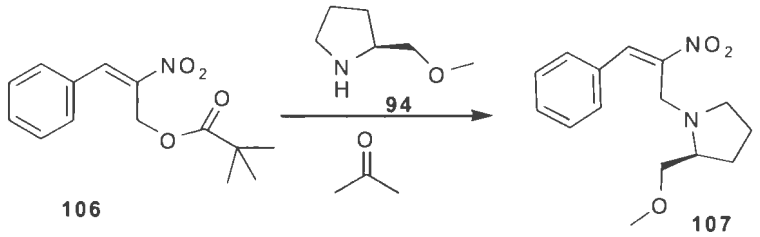
Entry	Catalyst	Solvent	Time	Observations
1	**92**	DMF	4 days	Starting material recovered
2	**94**	DCM	2 days	Starting material recovered
3	**94**	Acetone	9 days	Starting material recovered
4	**94**	THF	15 days	Starting material recovered
5	**94**	DCM	25 hours	**107** (42%)[a]

Nitroalkene 1 equiv; acetone 5 equiv, catalyst 20 mol% all reactions were stirred at room temperature for the time mentioned in table 2. a yield based on catalyst used.



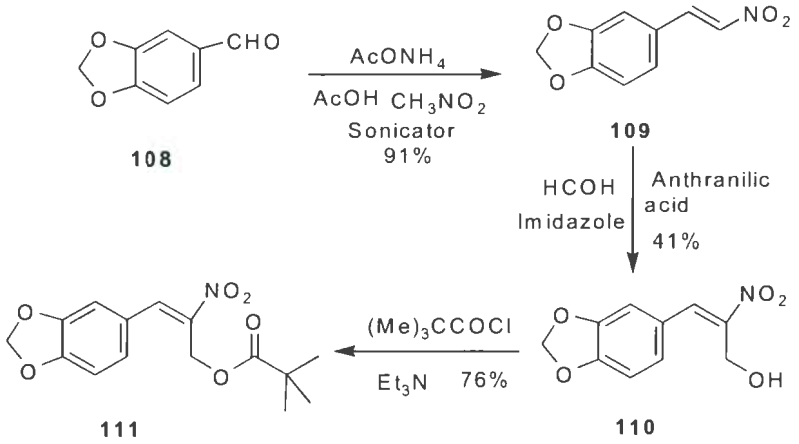
92 94

A reaction in which nitroalkene derivative **106** was treated with acetone in the presence of catalyst **94** (Entry 5) gave adduct **107** as product (Scheme 28). This compound was probably obtained from the direct reaction between catalyst **94** and nitroalkene derivative **106** involving a displacement of the pivaloyl group.



Scheme 28: Reaction of catalyst **94** with nitroalkene derivative **106**.

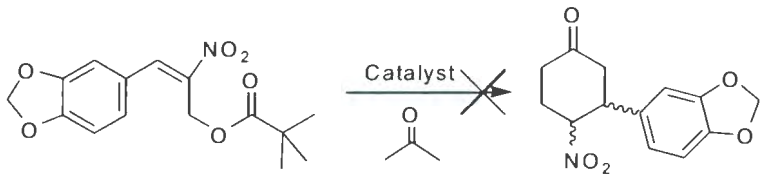
Similar studies were conducted with a nitroalkene substrate derived from piperonal. This choice was based on a possible route to the lycorane family of alkaloids which were a target of these studies. The required nitroalkene was prepared by adaptation of known procedures[34, 35] and the synthesis is summarized in Scheme 29.



Scheme 29: Synthesis of compound **111**.

The results of reactions of **111** with acetone in the presence of amines **91** and **93** are summarized in Table 3. Unfortunately, in this study, the only isolable products were

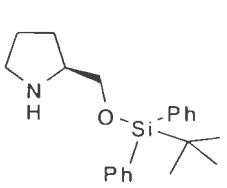
Table 3: Organocatalytic double Michael reaction of acetone to compound **111.**



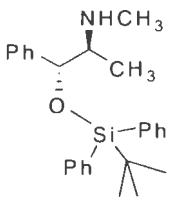
111 **112**

Entry	Catalyst	Solvent	Time	Observation
1	**91**	DMF	4 days	Starting material recovered
2	**91**	DCM	28 hours	**113** (13%)
3	**91**	THF	4 days	Starting material recovered
4	**91**	Acetone	5 days	Starting material recovered
5	**93**	Acetone	3 days	**114** (10%)

Nitroalkene 1 equiv; acetone 5 equiv, catalyst 20 mol% all reactions were stirred at room temperature for the time mentioned in table 3.

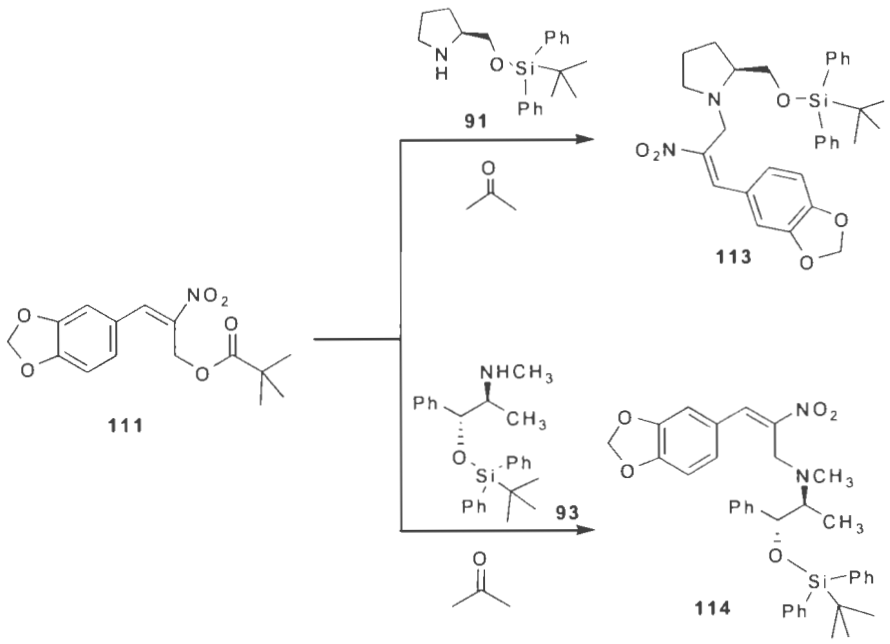


91



93

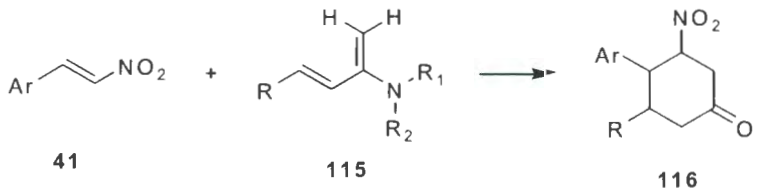
also those obtained from the reaction of the amine and the nitroalkene (Scheme 30).



Scheme 30: Reaction of nitroalkene derivative **111** with amines **91** and **93**.

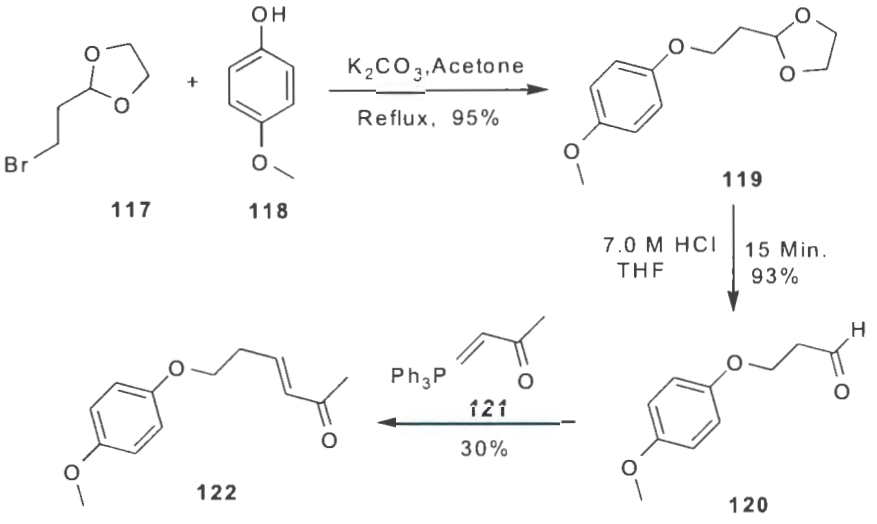
An attempted nitroalkene/ enone cyclization

As part of the studies discussed earlier in this chapter, we also examined the possibility of conducting an organocatalytic, formal [4+2] cycloaddition of a nitroalkene and an amino diene derived from an enone (Scheme 31).



Scheme 31: Organocatalytic [4+2] cycloaddition of nitroalkene with enone.

The synthesis of the required enone precursor to the eminodienes **115** is shown in Scheme 32. 2-2-(Bromomethyl)-1,3-dioxolane (**117**) was refluxed with *p*-methoxy phenol in acetone in the presence of anhydrous potassium carbonate[36] to afford **119** (95%). Deprotection of **119** with HCl (7.0 M) provided aldehyde **120** (93%). The crude aldehyde **120** was treated with Wittig reagent **121** to obtain the required α,β-unsaturted

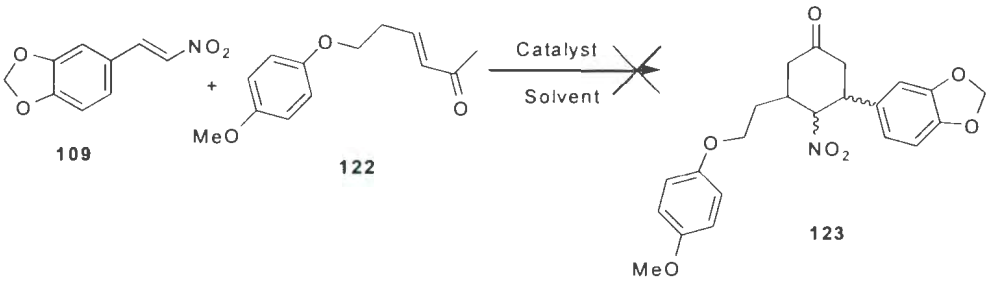


Scheme 32: Synthesis of α,β-unsaturted ketone **132.**

ketone **122**. Wittig reagent **121** (1-triphenylphosphoranylidene-2-propanone) was prepared by known methods from monochloroacetone and triphenylphosphine.[37] The resulting phosphonium salt was then treated with aqueous 10% Na_2CO_3 to obtain the desired Wittig reagent.

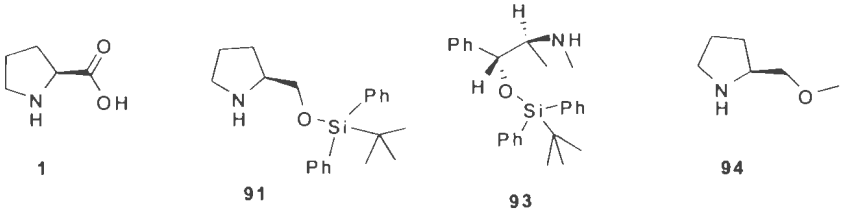
Attempted cycloaddition of **122** with nitroalkene **109** in the presence of catalysts **1**, **91**, **93** and **94** however was unsuccessful, and only unreacted starting material was recovered from these reactions (Table 4).

Table 4: Organocatalytic cycloaddition of nitroalkene and α,β-unsaturted ketone **122.**



Entry	Catalyst	Solvent	Time	Observation
1	**95**	THF	4 days	Starting material recovered
2	**97**	THF	9 days	Starting material recovered
3	**92**	MeOH	3 days	Starting material recovered
4	**98**	THF	7 days	Starting material recovered
5	**95**	Hexane	2 days	Starting material recovered

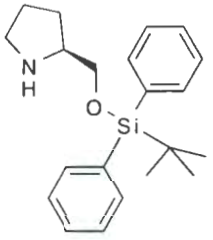
Nitroalkene 1 equiv; acetone 5 equiv, catalyst 20 mol% all reactions were stirred at room temperature for the time mentioned in table 4.



Conclusion

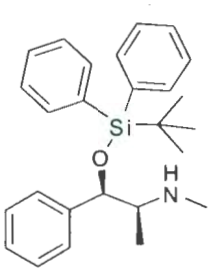
A series of functionalized nitroalkenes were prepared and their reactions with simple ketones were examined in the presence of some selected enamine-forming chiral amines. It was observed that in some cases unwanted side reactions between the chiral amines and the nitroalkenes led to deactivation of the amines by *N*-alkylation. Consequently, no enamine formation occurred and the anticipated nitrocyclohexanone products were not obtained. The exact reasons for the lack of reactivity of the nitroalkenes with the enones examined are unclear.

Experimental



(*S*)-2-(*t*-Butyldiphenylsilyloxy methyl) pyrrolidine (91): Triethylamine (1.1 mL, 7.5 mmol) was added to a solution of (*S*)-prolinol (29 mg, 2.9 mmol) in dry THF (8.0 mL) at room temperature, under an atmosphere of nitrogen. To this was added *tert*-butyldiphenylsilyl chloride (0.84 mL, 3.3 mmol. The mixture was stirred overnight and filtered (filter paper). The filtrate was concentrated and the residue was purified by flash chromatography on silica gel (96:2:2 ethyl acetate: methanol: NH_4OH) to provide 870 mg (86%) of **91**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68-7.65 (m, 4H, Ar*H*), 7.44-7.36 (m, 6H, Ar*H*), 3.66-3.63 (dd, 1H, *J* = 10, 5, C*H*$_2$OSi), 3.60-3.57 (dd, 1H, *J* = 10, 5, C*H*$_2$OSi), 3.25-3.20 (m, 1H, NC*H*CH$_2$), 3.00-2.95 (m, 1H, NC*H*$_2$CH$_2$), 2.87-2.82 (m, 1H, NC*H*$_2$CH$_2$), 2.13 (bs, 1H, N*H*), 1.81-1.69 (m, 3H, C*H*$_2$CH$_2$), 1.50-1.44 (m, 1H, CH$_2$C*H*$_2$), 1.06 (s, 9H, C(C*H*$_3$)$_3$).



(1R,2S)-1-(*tert*-butyldiphenylsilyloxy)-*N*-methyl-1-phenylpropan-2-amine (93). To a solution of (1*R*,2*S*)-(-)-ephedrine (26 mg, 1.6 mmol) in THF (7.0 mL) at room temperature was added triethylamine (0.55 mL (3.1 mmol) and *t*-butyldiphenylsilyl chloride (0.44 mL, 1.7 mmol). The solution was stirred for 2 d and then concentrated. The residue was diluted with ethyl acetate, washed with cold aqueous HCl (1.0M, 15 mL) followed by NH_4OH and water. The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (2:1 hexane: ethyl acetate) to provide 220 mg (35 %) of **93** as a colourless gum.

IR (neat): 3071, 2931, 2857, 2789, 1960, 1890, 1825, 1472, 1427, 1391, 1105, 1028, 821 cm^{-1}.

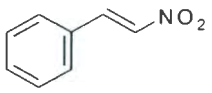
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.7-7.68 (m, 2H, Ar*H*), 7.43-7.41 (m, 3H, Ar*H*), 7.37-7.31 (m, 3H, Ar*H*), 7.26-7.19 (m, 7H, Ar*H*), 4.66 (d, 1H, *J* = 4.6, PhC*H*OSi), 2.68-2.63 (m, 1H, C*H*NH), 2.14 (s, 3H, NHCH_3), 1.03 (s, 9H, C(CH_3)$_3$), 0.93 (d, 3H, J = 6.5, CHCH_3).

^{13}C NMR (125.77 MHz, $CDCl_3$): δ 142.0 (Ar*C*ipso), 136.1 (Ar*C*ipso), 136.0 (Ar*C*ipso), 134.2 (Ar*C*), 133.5 (Ar*C*), 129.8 (Ar*C*), 129.6 (Ar*C*), 127.9 (Ar*C*), 127.7 (Ar*C*), 127.5

(Ar*C*), 127.3 (Ar*C*), 127.2 (Ar*C*), 78.3 (Ar*C*OH), 61.6 (*C*HNH), 60.4 (NH*C*H$_3$), 34.2 (NH*C*H$_3$), 27.2 (C(*C*H$_3$)$_3$), 19.6 (*C*(CH$_3$)$_3$), 15.51 (CH*C*H$_3$).

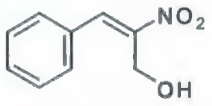
MS (APCI pos.): *m/z* 404.2 (M+H).

HRMS (CI pos.): *m/z* 404.2404 (403.2410 calc. for $C_{26}H_{34}NOSi$, M+H).



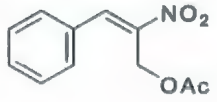
1-((*E*)-2-Nitrovinyl)benzene (99):[34] A solution of benzaldehyde (10 mL, 98 mmol) and nitromethane (5.3 mL, 98 mmol) in methanol (10 mL) was cooled to -10 °C (ice salt mixture), and an aqueous solution of NaOH (4.0 g, 100 mmol) in ice-cold H_2O (5.0 mL) was added dropwise, with constant stirring to ensure that the temperature did not exceed 15 °C (ice was added to the mixture if necessary). A bulky white precipitate was formed. A few mL of methanol were added to facilitate stirring which was continued for a few minutes. The mixture was then allowed to stand for 15 min. and a mixture of ice and water (30 mL) was added to provide a solution. This was acidified with aqueous HCl (4.0 M, 20 mL) with cooling (<5 °C). The nitrostyrene precipitated as a pale yellow solid that was isolated by filtration and air dried. Yield: 9.9 g (68%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, 1H, *J* = 12.5, ArC*H*), 7.59 (d, 1H, *J* = 12.5, C*H*NO$_2$), 7.59-7.44 (m, 5H, Ar*H*).



(*E*)-2-Nitro-3-phenylprop-2-en-1-ol (100):[34] To a solution of 1-((*E*)-2-nitrovinyl)benzene (**99,** 5.0 g, 34 mmol) in THF (68 mL) were added imidazole (2.3 g, 34 mmol), anthranilic acid (0.46 g, 3.3 mmol) and aqueous formaldehyde (38% soln., 66.9 mL) was added. The mixture was stirred for 18 h at ambient temperature. The mixture was then acidified with aqueous HCl (5.0 M, 168 mL) and extracted with ethyl acetate. The combined extracts were washed with aqueous $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (2:1 hexane: ethyl acetate) on silica gel to provide 1.5 g (64 %) of **100** as a yellow oil.

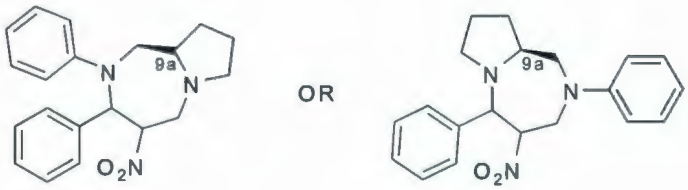
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (s, 1H, PhC*H*), 5.57-7.55 (m, 2H, Ar*H*), 7.50-7.47 (m, 3H, Ar*H*), 4.71 (d, 2H, $J = 7.2$, CH_2OH), 2.59 (t, 1H, $J = 7.2$, CH_2OH).



(*E*)-2-Nitro-3-phenylallyl-2-en-1-acetate (101):[34] To a solution of compound **100** (1.4 g, 8.0 mmol) in dry dichloromethane (19 mL) was added triethylamine (1.4 mL, 10.0 mmol) followed by acetyl chloride (0.70 mL, 10.0 mmol). The mixture was stirred for 3 h, diluted with dichloromethane and the resulting solution was washed with aqueous HCl (2.0 M, 2 x 20 mL). The organic layer was separated, dried (Na_2SO_4) and concentrated.

The residue was purified by flash chromatography on silica gel (2:1 hexane: ethyl acetate) to provide 1.5 g (82 %) of compound **101** as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.36 (s, 1H, PhC*H*), 7.51-7.45 (m, 5H, Ar*H*), 5.22 (s, 2H, CH_2OCO), 2.15 (s, 3H, $OCOCH_3$).



(9a*S*)-Octahydro-4-nitro-2,3-diphenyl-1H-pyrrolo-(1,2-a)(1,4)diazepine) or (9a*S*)-Octahydro-4-nitro-2,5-diphenyl-1H-pyrrolo-(1,2-a)(1,4)diazepine) (103): To a solution of (*S*)-(+)-2-(anilinomethyl)pyrrolidine (**90**, $1.2x10^{-3}$ g, $6.6x10^{-3}$ mmol) in THF (0.8 mL) was added cyclohexanone (0.09 mL, 0.83 mmol) and nitroalkene **101** (0.07 g, 0.33 mmol). The mixture was stirred for 12 h and concentrated. The residue was purified by flash chromatography on silica gel (6:1 hexane: ethyl acetate) to provide 19 mg (83%) of **103**.

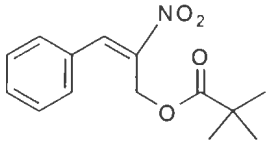
Note: The exact identity of **103** (one of two possible structural isomers) has not been determined.

IR (neat): 1600, 1542, 1506, 1457, 1369, 1341, 1287, 1183 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30-7.25 (m, 5H, Ar*H*), 6.81-6.79 (m, 3H, Ar*H*), 4.86-4.82 (dt, 1H, *J* = 9.5, 2.0, C*H*NO_2), 4.18-4.13 (dd, 1H, *J* = 15.4, 9.5, NCH_2), 4.03-3.99 (m, 2H, NCH_2), 3.55-3.52 (dd, 1H, J = 3.2, 11.2, NC*H*), 3.34-3.28 (m, 1H, CH_2), 3.18-

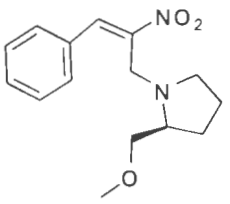
3.14 (t, 1H, J = 11.3, CH_2), 2.64-2.61 (m, 1H, CH_2), 2.35-2.30 (t, 1H, J = 6.6, CH_2), 2.23-2.14 (m, 2H, CH_2), 1.89-1.84 (m, 1H, CH_2), 1.73-1.62 (m, 3H, CH_2CH_2), 0.90-0.80 (m, 1H, CH_2CH_2).

LCMS (CI positive): *m/z* 338.1 (M+1).



(*E*)-2-Nitro-3-phenylallyl pivalate (106): To a solution of compound **100** (180 mg , 1.0 mmol) in dry dichloromethane (19 mL) was solution of pivaloyl chloride (0.18 mL, 1.5 mmol) in dry dichloromethane (2.0 mL) dropwise, at 0 °C. The mixture was stirred at 0 °C for 4 h, acidified with aqueous HCl (1.0 M, 5.0 mL) and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel column (4:1 hexane: ethyl acetate) to provide 116 mg (44%) of compound **106** and 50 mg (28%) of unreacted starting material.

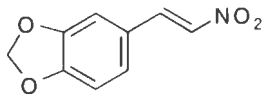
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.35 (s, 1H, PhC*H*), 7.51-7.45 (m, 5H, Ph*H*), 5.19 (s, 2H, CH_2OCO), 1.25 (s, 9H, C(CH_3)$_3$).



(*S*)-2-(Methoxymethyl)-1-((*E*)-2-nitro-3-phenylallyl)pyrrolidine (107): The catalyst **94** (4.0 mg, 0.38 mmol) was dissolved in dichloromethane (1.0 mL) and acetone ($6.9x10^{-2}$ mL, 0.95 mmol), and the nitroalkene **106** (50 mg, 0.19 mmol) were added. The solution was stirred at ambient temperature for 25 h. The reaction mixture was diluted with dichloromethane and the solution was washed with aqueous HCl (1.0 M, 1.0 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated, and the residue was purified by flash chromatography on silica gel (4:1 hexane: ethyl acetate) to provide 5.0 mg (42%) of **107**.

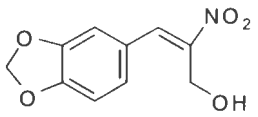
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (s, 1H, ArC*H*=CNO_2), 7.66-7.65 (m, 2H, Ar*H*), 7.45-7.43 (m, 3H, Ar*H*), 4.22 (d, 1H, *J* = 13.7, CH=CCH_2), 3.80 (d, 1H, *J* = 13.7, CH=CCH_2), 3.47-3.44 (dd, 1H, *J* = 9.5, 5.7, CH_2OCH_3), 3.35-3.32 (dd, 1H, *J* = 9.5, 5.7, CH_2OCH_3), 3.34 (s, 3H, OCH_3), 2.96-2.92 (m, 1H, NC*H*), 2.76-2.70 (m, 1H, NCH_2), 2.30-2.27 (m, 1H, NCH_2), 1.91-1.86 (m, 1H, CH_2CH_2), 1.71-1.67 (m, 2H, NCH_2CH_2), 1.6-1.5 (m, 1H, CH_2CH_2).

LCMS (Cl positive): *m/z* 277.1 (M+1).



5-((*E*)-2-Nitrovinyl)benzo(*d*)(1,3)-dioxole (109):[35] A mixture of piperonal (2.0 g, 13 mmol), nitromethane, (8.7 mL, 1.6 mol), NH_4OAc (2.2 g, 29 mmol) and acetic acid (2.2 mL) was sonicated for 8 h at room temperature (reaction was monitored by NMR). The mixture was diluted with dichloromethane and the solution was washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was recrystalised from aqueous methanol to provide 2.4 g (91%) of **109** as a solid.

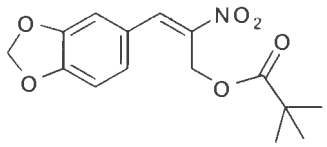
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, 1H, J = 13.5, PhC*H*), 7.48 (d, 1H, J = 13.5, C*H*NO_2), 7.09 (dd, 1H, J = 8.0, 1.6, Ar*H*), 7.0 (d, 1H, J = 1.6, Ar*H*), 6.88 (d, 1H, J = 8.0, Ar*H*), 6.06 (s, 2H, OCH_2O).



(*E*)-3-(Benzo(*d*)(1,3)dioxol-6-yl)-2-nitroprop-2-en-ol (110):[34] To a solution of compound **109** (1.0 g, 5.2 mmol) THF (12 mL) was added imidazole (0.31 g, 5.2 mmol), anthranilic acid (70 mg, 0.52 mmol) and aqueous formaldehyde (38% soln., 10.0 mL, 1.3 mol) was added. The reaction mixture was stirred for 6 d, acidified with aqueous HCl (5.0 M, 34 mL) and the mixture was extracted with ethyl acetate. The combined organic layers were washed with aqueous $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated. The residue was

purified by flash chromatography on silica gel (2:1 hexane: ethyl acetate) to provide 560 mg (49%) of **110** as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (s, 1H, PhC*H*), 7.26 (d, 1H, *J* = 1.5, Ar*H*), 7.13 (d, 1H, *J* = 6.8, Ar*H*), 7.12 (s, 1H, ArH), 6.91 (d, 1H, *J* = 6.8, Ar*H*), 6.06 (m, 2H, OCH_2O), 4.72-4.71 (dd, 2H, *J* = 1.2, 7, CH_2OH), 2.59 (dt, 1H, *J* = 7, 1.4, CH_2O*H*).



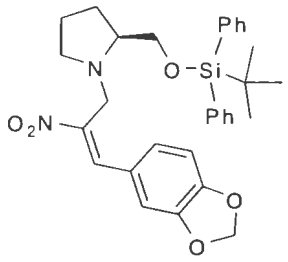
(*E*)-3-(Benzo(*d*)(1,3)dioxol-6-yl)-2-nitroallyl pivalate (111): To a solution of compound **110** (47 mg, 2.1 mmol) in dry dichloromethane (10 mL) at 0 °C was added dropwise, a solution of pivaloyl chloride (0.38 mL, 3.1 mmol) in dry dichloromethane (4 mL). The mixture was stirred at 0 °C for 8 h, acidified with aqueous HCl (1.0 M, 16 mL) and the solution was extracted with ethyl acetate. The combined organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (4:1 hexane: ethyl acetate) to provide 490 mg (76%) of compound **111** and 96 mg (21%) of unreacted starting material.

IR (neat): 2974, 1728, 1490, 1261, 1148, 1032 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (s, 1H, ArC*H*), 7.4 (dd, 1H, *J* = 8, 1.2 Ar*H*), 6.97 (d, 1H, *J* = 1.2, Ar*H*), 6.90 (d, 1H, *J* = 8.0, Ar*H*), 6.06 (s, 2H, OCH_2O), 5.20 (s, 2H, CH_2OCO), 1.24 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (125.77 MHz, $CDCl_3$): δ 178.1 (O*C*O), 150.9 (Ar*C*), 148.9 (Ar*C*)), 144.0 (*C*NO_2), 140.1 (Ar*C*), 126.9 (*C*H=CNO_2), 125.1 (Ar*C*), 109.6 (Ar*C*), 109.3 (Ar*C*), 102.2 (O*C*H_2O), 58.3 (*C*H_2OCO), 39.2 (*C*$(CH_3)_3$), 27.3 (C(*C*$H_3)_3$).

MS (CI): *m/z* 206.0 (M-(($CH_3)_3CO_2$H)+H).



(*E*)-3-(Benzo(*d*)(1,3)dioxol-6-yl)-2-nitroprop-2-en-1-(*S*)-2-(*t*-butyldiphenylsilyloxy methyl) pyrrolidine (113): To a solution of the catalyst **91** (20 mg, $6.00x10^{-2}$ mmol) in dichloromethane (1.0 mL) were added acetone (0.21 mL, 2.9 mmol) and the nitroalkene **111** (85 mg, 0.29 mmol). The mixture was stirred for 28 h at ambient temperature and concentrated. The residue was purified by flash chromatography on silica gel (6:1 hexane: ethyl acetate) to provide 15 mg (12%) of **113**.

IR (neat): 2932, 2857, 1554, 1503, 1487, 1444, 1427, 1248, 1113, 1039 cm^{-1}.

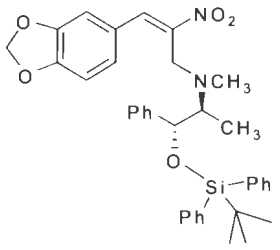
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (s, 1H, C*H*=CNO_2), 7.65-7.62 (m, 4H, Ar*H*), 7.49 (d, 1H, *J* = 1.5, Ar*H*), 7.42-7.33 (m, 6H, Ar*H*), 7.17-7.15 (dd, 1H, *J* = 8.1, 1.5, Ar*H*), 6.75 (d, 1H, *J* = 8.1, Ar*H*), 5.98 (d, 1H, *J* = 1.3, OCH_2O), 5.88 (d, 1H, *J* = 1.3, OCH_2O), 4.14 (d, 1H, *J* = 13.5, NCH_2C=C), 3.85-3.82 (dd, 2H, *J* = 10.3, 6.2, CH_2O), 3.83 (d, 1H, J = 13.5, 1H, NCH_2C=C), 3.59-3.55 (dd, 2H, *J* = 10.3, 6.2, CH_2O), 2.91-2.88 (m, 1H,

NC*H*), 2.81-2.76 (m, 1H, NCH_2), 2.42-2.37 (q, 1H, J = 8.5, m, 1H, NCH_2), 1.92-1.87 (m, 1H, CH_2CH_2), 1.69-1.57 (m, 3H, CH_2CH_2), 1.00 (s, 9H, $C(CH_3)_3$).

LCMS (APCI neg.): *m/z* 544.3 (M+);

(APCI pos.): *m/z* 545.2 (M+H).

HRMS (EI pos.): *m/z* 544.2394 (544.2393 cal. for $C_{31}H_{36}N_2O_5Si$, M+).



(*E*)-3-(Benzo(*d*)(1,3)dioxol-6-yl)-2-nitroprop-2-en-1-(1*R*,2*S*)-2-(methylamino-1-phenylpropan-1-diphenyl trimethylsilanol (114): To a solution of the catalyst **93** (16.0 mg, $4.0x10^{-2}$ mmol) and acetone (1.0 mL) was added the nitroalkene **111** (0.07 g, 0.22 mmol). The solution was stirred at ambient temperature for 3 d and concentrated. The residue was purified by flash chromatography on silica gel (6:1 hexane: ethyl acetate) to provide 16 mg (66%) of **114**.

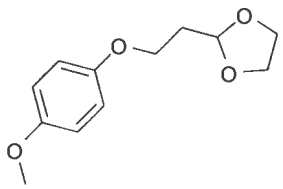
IR (neat): 2932, 2857, 1503, 1488, 1447, 1245, 111, 1039, 934 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (s, 1H, ArC*H*=C), 7.61 (m, 2H, Ar*H*), 7.41 (m, 1H, Ar*H*), 7.39-7.27 (m, 5H, Ar*H*), 7.15 (t, 2H, J = 7.5, Ar*H*), 6.99 (m, 2H, Ar*H*), 6.94 (t, 2H, J = 7.3, Ar*H*), 6.86 (m, 1H, Ar*H*), 6.76 (dd, 1H, J = 6.6, 1.5, Ar*H*), 6.72 (br s, 1H, Ar*H*), 6.65 (d, 1H, J = 8.1, Ar*H*), 5.98 (dd, 2H, J = 7.3, 1.2, OCH_2O), 4.43 (d, 1H, J = 8.5,

C*H*OSi), 3.79 (d, 1H, *J* = 13.8, NCH_2), 3.16 (d, 1H, *J* = 13.8, NCH_2), 2.92-2.87 (m, 1H, C*H*CH_3) 1.96 (s, 3H, NCH_3), 1.1 (d, 3H, *J* = 6.5, CHCH_3), 0.93 (s, 9H, C(CH_3)$_3$).

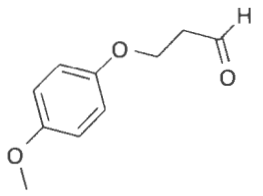
MS (APCI pos.): *m/z* 609.3 (M+1).

HRMS (CI positive): *m/z* 609.2777 (609.2785 cal. for $C_{36}H_{41}N_2O_5Si$, M+H).



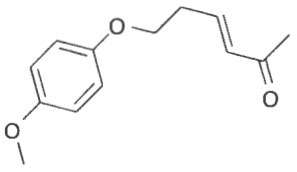
2-(2-(4-Methoxyphenoxy)ethyl)-1,3-dioxolane (119):[36] To a solution of *p*-methoxy phenol (120 mg, 1.0 mmol) acetone (7.0 mL) was added K_2CO_3 (270 mg, 2.0 mmol) and the mixture was stirred for 10 min 2-(2-Bromoethyl)-1,3-dioxalane (**117**, 0.12 mL, 1.0 mmol) was added and the mixture was heated to reflux for 62 h. The mixture was cooled to ambient temperature, concentrated and the residue was dissolved in ethyl acetate. The solution was washed with aqueous NaOH solution (2.0 M, 2.0 mL). The organic layer was dried (Na_2SO_4) and concentrated to provide 220 mg (98%) of **119** as pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.84-6.77 (m, 4H, Ar*H*), 5.09 (t, 1H, *J* = 4.9, C*H*(OCH_2)$_2$), 4.07 (t, 2H, *J* = 6.5, $ArOCH_2$), 4.01-3.98 (m, 2H, OCH_2CH_2O), 3.90-3.86 (m, 2H, OCH_2CH_2O), 3.75 (s, 3H, ArOCH_3), 2.14 (q, 2H, *J* = 6.5, $ArOCH_2CH_2$).



3-(4-Methoxyphenoxy)propanal (120): Compound **119** (2.2 g, 9.6 mmol) was dissolved in THF (20 mL) and aqueous HCl (7.0 M, 20 mL) was added over a period of 15 min. with cooling. The mixture was stirred at room temperature for 20-30 min (monitored by NMR) and concentrated. The residue was dissolved in ethyl acetate and the solution was washed with brine. The organic layer was dried (Na_2SO_4) and concentrated to provide 160 mg (91%) of **120** as a yellow-brown liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.84 (t, 1H, *J* = 1.6, C*H*O), 6.83 (d, 2H, *J* = 1.0, Ar*H*), 6.76 (d, 2H, *J* = 1.0, Ar*H*), 4.25 (t, 2H, *J* = 6.0, ArOCH_2), 3.76 (s, 3H, ArOCH_3), 3.91-3.85 (dt, 2H, J = 1.6, 6.0, ArOCH$_2$CH_2).



(*E*)-6-(4-Methoxyphenoxy)hex-3-en-2-one (122): 3-(4-Methoxyphenoxy)propanal (**120**) (340 mg, 1.9 mmol) was dissolved in THF (10.0 mL) and the Wittig reagent (**121**) 600 mg, 1.9 mmol) was added. The mixture was heated to reflux for 34 h, cooled to ambient temperature and concentrated. The residue was purified by flash chromatography on silica gel (4:1 hexane: ethyl acetate) to provide 220 mg (29%) of **122**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.91-6.85 (m, 1H, C*H*=CHCO), 6.83 (s, 4H, Ar*H*), 6.19 (d, 1H, *J* = 20, CH=C*H*CO), 4.05 (t, 2H, *J* = 6.3, ArOCH_2), 3.77 (s, 3H, ArOCH_3), 2.70-2.66 (dq, 2H, J = 6.5, 1.3, CH_2CH_2CH=CH), 2.26 (s, 3H, COCH_3).

References

1. Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138.

2. Rasalkar, M. S.; Potdar, M. K.; Mohile, S. S.; Salunkhe, M. M. *J. Mol. Cat. A: Chemical* **2005**, *235*, 267.

3. Hoashi, Y.; Yabuta, T.; Takemoto, Y. *Tetrahedron Lett.* **2004**, *45*, 9185.

4. Reyes, E.; Jiang, H.; Milelli, a.; Elsner, P.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 9202.

5. Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611.

6. Hayashi, Y.; Gotoh, H.; Hayato, I. *Org. Lett.* **2007**, *9*, 5307.

7. List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423.

8. Betancort, J. M.; Barbas III, C. F. *Org. Lett.* **2001**, *3*, 3737.

9. Alexakis, A.; Andrey, O.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559.

10. Mitchell, C. E. T.; Alexander, J. A.; Cobb, A. J. A.; Ley, S. V. *Synlett* **2005**, 611.

11. Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212.

12. Huang, H.; Jacobsen, E. R. *J. Am. Chem. Soc.* **2006**, *128*, 7170.

13. Terakado, D.; Takano, M.; Oriyama, T. *Chem. Lett.* **2005**, *34*, 962.

14. Pansare, S. V.; Pandya, K. *J. Am. Chem. Soc.* **2006**, *128*, 9624.

15. Liu, F.; Wang, S.; Wang, N.; Peng, Y. *Synlett* **2007**, 2415.

16. Seebach, D.; Missbach M.; Calderari, G.; Eberle, M. *J. Am. Chem. Soc.* **1990**, *112*, 7625.

17. Enders, D.; Meyer, O.; Raabe, G. *Synthesis* **1992**, 1242.

18. Felluga, F.; Nitti, P.; Pitacco, G.; Valentine, E. *Tetrahedron Lett.* **1988**, *29*, 4165.

19. Arnold, Z. *Synthesis* **1990**, 39.

20. White, W. A.; Weingarten, H. *J. Org. Chem.* **1967**, *32*, 213.

21. Barluenga, J.; Aznar, F.; Valdes, C.; Martin, A.; Granda, S. G.; Martin, E. *J. Am. Chem. Soc.* **1993**, *115*, 4403.

22. Barluenga, J.; Aznar, F.; Ribas, C.; Valdes, C. *J. Org. Chem.* **1997**, *62*, 6746.

23. Thayumanavan, R.; Dhevalapally, B.; Sakthivel, K.; Tanaka, F.; Barbas III, C. F. *Tetrahedron Lett.* **2002**, *43*, 3817.

24. Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 795.

25. Hayashi, Y.; Okano, T.; Aratake, S.; Hazelard, D.; *Angew. Chem. Int. Ed.* **2007**, *46*, 4922.

26. Enders, D.; Huttl, M. R. M.; Grondal, C.; Raabe, G. *Nature*, **2006**, *44*, 861.

27. Prieto, A.; Halland, N.; Jørgensen K. A. *Org. Lett.* **2005**, *7*, 3897.

28. Bencivenni, G.; Wu, L. Y.; Mazzanti, A.; Giannichi, B.; Pesciaioli, F.; Song, M. P.; Bartoli, G.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 1.

29. Wu, L. Y. Bencivenni, G.; Mancinelli, M.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 1.

30. Thayumanavan, R.; Dhevalapally, B.; Sakthivel, K.; Tanaka, F.; Barbas III, C. F. *Tetrahedron Lett.* **2002**, *43*, 3817.

31. Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583.

32. Zhao, D.; Kuethe, J. F.; Journet, M.; Peng, Z.; Humphery, G. R. *J. Org. Chem.* **2006**,

71, 4336.

33. Kurokawa, M.; Shindo, T.; Suzuki, M.; Nakajima, N.; Ishihara, K.; Sugai, T. *Tetrahedron: Asymmetry*, **2003**, *14*, 1323.

34. Moha, R.; Rastogi, N.; Namboothiri, I. N. N.; Mobin, S. M.; Panda, D. *Bioorg. Med. Chem.* **2006**, *14*, 8073.

35. McNulty, J.; Steere, J. A.; Wolf, S. *Tetrahedron Lett.* **1998**, *39*, 8013.

36. a) El-Qisairi, A. K.; Qaseer, H. A.; Henry, P. M. *J. Organomet. Chem.* **2002**, *656*, 168. b) *Vogel's Text Book of Practical Organic Chemistry*, Addison Wesley Longman Ltd:Essex, England, **1996**, p 986.

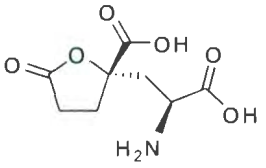
37. Ramirez, F.; Dershowitz, S. *Synthesis* **1957**, 41.

Chapter 2

Organocatalytic Synthesis of (+)-Lycoperdic Acid

Introduction

In 1978, Rhugenda-Banga et al. isolated lycoperdic acid (**1**) as a non-proteinogenic α-amino acid, from the mushroom *Lycoperdon perlactum*.[1] Later on, in 1979 these authors explored the structural details of lycoperdic acid based on spectroscopic and X-ray crystallographic studies.[2,3]



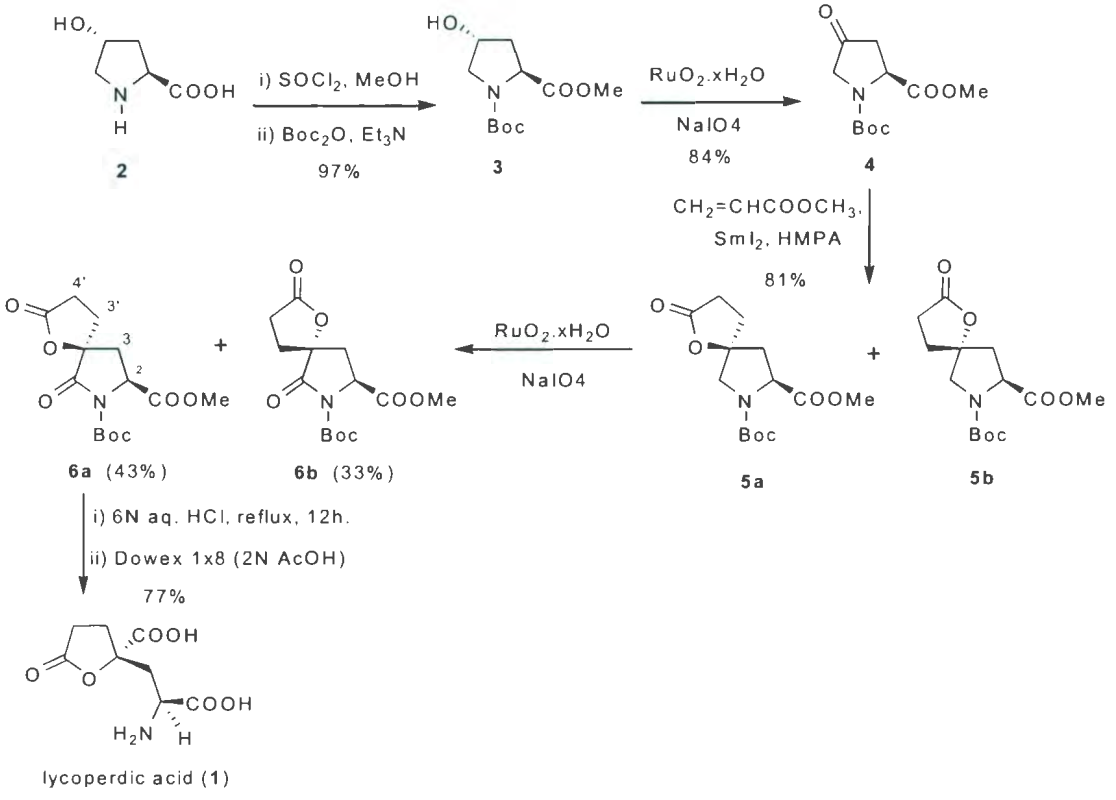
1

This unusual α-amino acid is structurally similar to (*S*)-glutamic acid and it was therefore expected to have antagonistic (a ligand or drug, which binds the receptor but does not induce biological responses, but blocks the agonist mediated responses) or agonistic (a guest or drug, that binds and alters the receptor activity) activity for the glutamate receptor in the mammalian central nervous system.[4] The total synthesis of **1** has been reported in the literature by Yoshifuji,[3,5] Hatakeyama,[6] Hamada,[4] Ishibashi[7] and Chamberlin, respectively.[8] In most of these total syntheses, chiral starting materials were used.

The interesting biological activity, unique structure and its low natural abundance attracted our attention to the total synthesis of lycoperdic acid, using an organocatalytic reaction as the key step involving homocitric acid.

Discussion

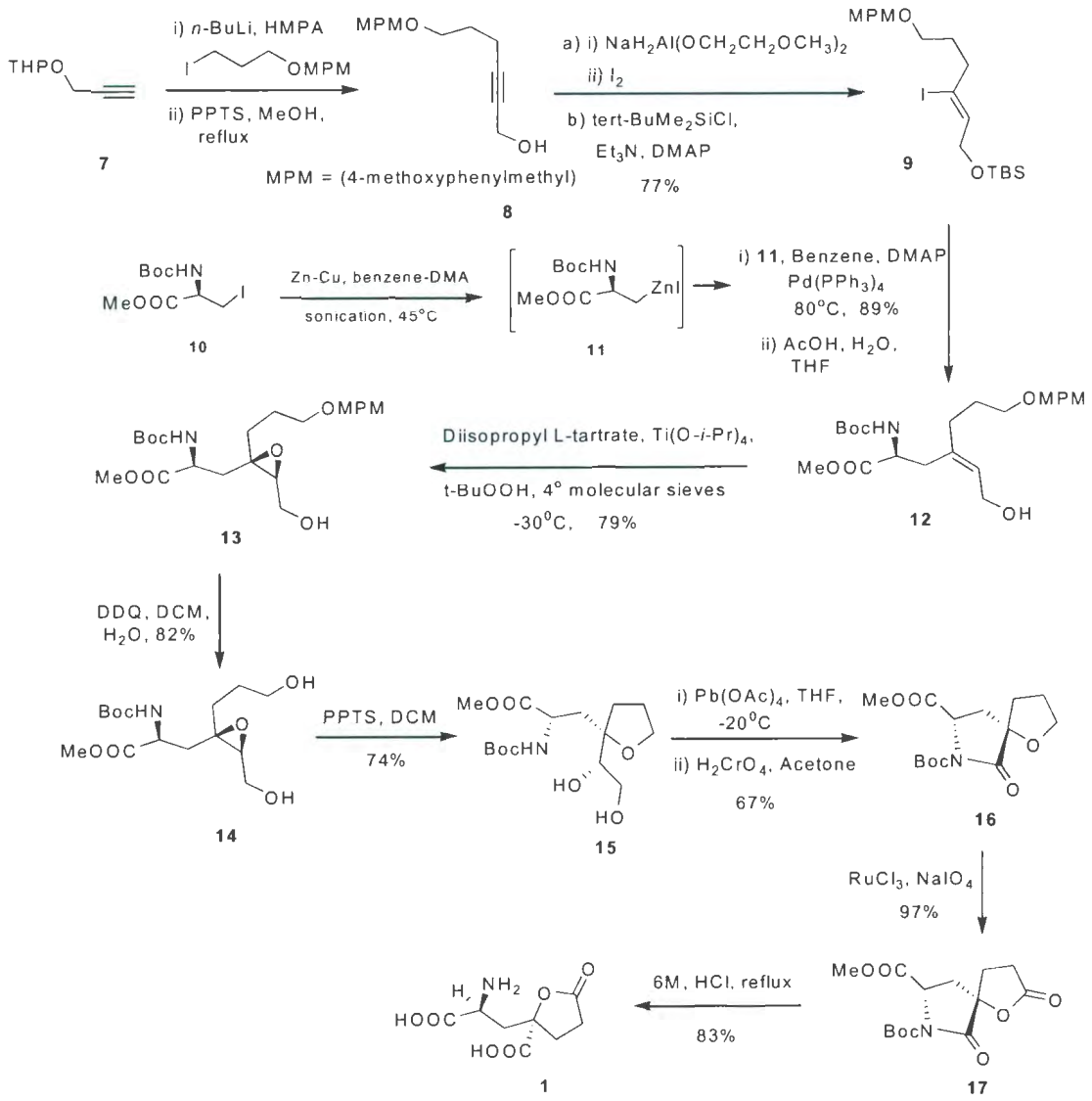
The first total synthesis of lycoperdic acid was reported by Yoshifuji et al. in 1992.[3] Their approach is based on a SmI_2-mediated formation of a spirolactone at the C4 position of commercially available *trans*-4-hydroxy-L-proline (**2** Scheme 1) and oxidation of the pyrrolidine ring using RuO_4 to a pyroglutamic acid derivative.



Scheme 1: Yoshifuji's synthesis of lycoperdic acid.

Trans-4-hydroxy-L-proline (**2**) was converted to the methyl ester and protection of the secondary amine with a Boc group gave compound **3**. Oxidation of **3** with RuO_4 gave compound **4** in 84% yield.[9] The key step in this synthesis is the reductive cross coupling[10] of methyl acrylate and compound **4** with SmI_2. The reaction resulted in a mixture of two inseparable, diastereomeric spirolactones **5a** and **5b** in 81% yield. RuO_4-mediated oxidation of this mixture was done by using Yoshifuji's protocol[11] to obtain pyroglutamic acid derivatives **6a** and **6b**, which were separated by column chromatography. The stereochemistry in **6a** and **6b** was determined by NOE experiments, which proved that **6a** is the proper diastereomer for lycoperdic acid. Removal of the Boc protecting group, ester hydrolysis and amide hydrolysis in compound **6a** were achieved with refluxing aqueous 6.0 M HCl to provide lycoperdic acid. The crude acid was purified by ion exchange chromatography (Dowex 1x8, eluted with aqueous 2.0 M AcOH) followed by recrystalisation from water (77% yield). A similar hydrolysis of **6b** gave *epi*-lycoperdic acid.

In 2002, Hatakeyama et al. reported a new stereo-controlled approach for the synthesis of lycoperdic acid. This approach was based on a palladium-catalyzed cross-coupling reaction (Scheme 2).[6]

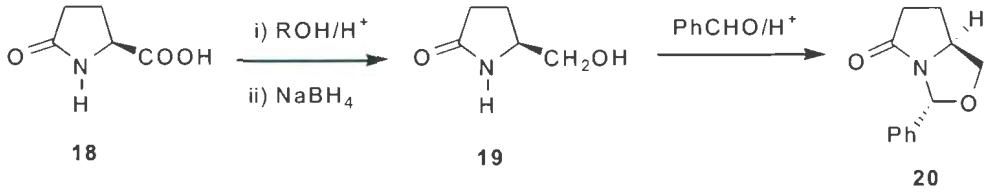


Scheme 2: Hatakeyama's synthesis of lycoperdic acid.

In the synthesis of lycoperdic acid, Hatakeyama used tetrahydro-2-(2-propynyloxy)-2*H*-pyran (**7**) as a starting material (Scheme 2). Lithiation of **7** followed by alkylation with 1-iodo-3-(4-methoxyphenylmethyl)-propane and subsequent removal of

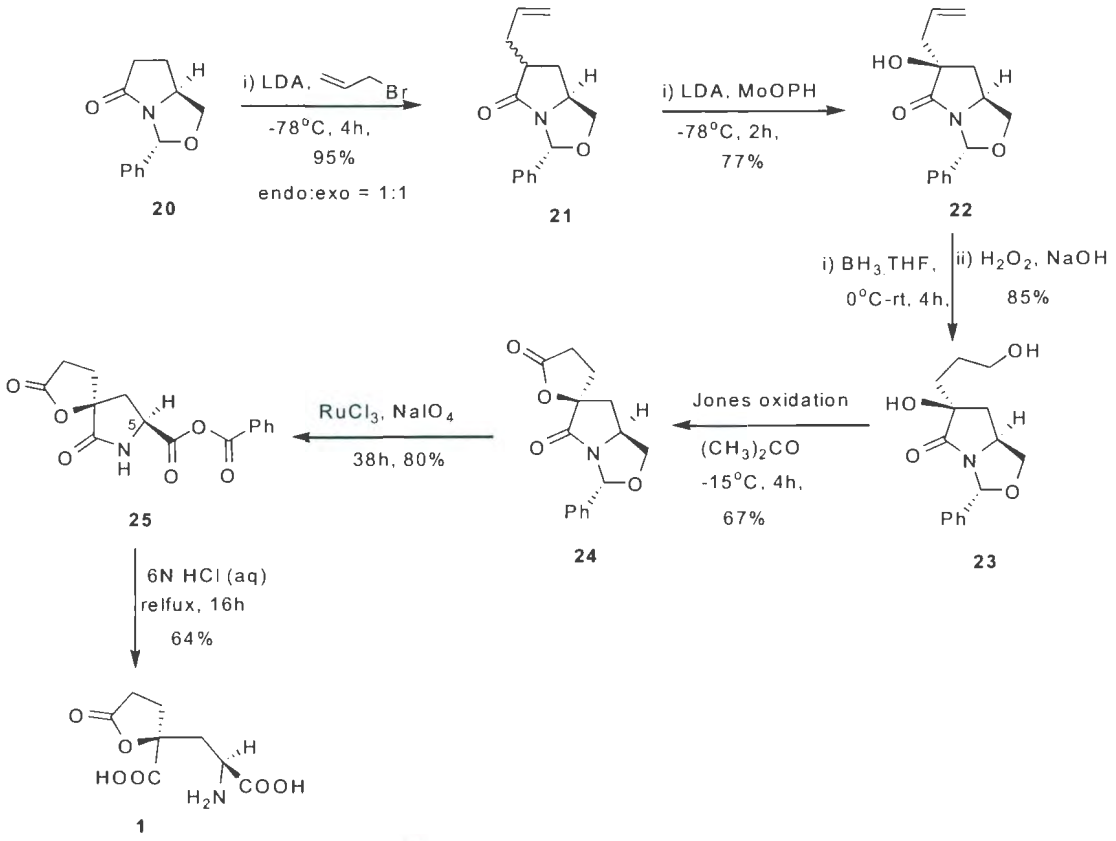
the THP ether with PPTS gave propargyl alcohol **8**. Alcohol **8** was treated with Red-Al[12] and the resulting alkenyaluminum complex was reacted with iodine followed by protection of the primary alcohol as its TBS ether to provide **9**. Thus a stereo- and regioselective synthesis of (*Z*)-iodoalkene **9** was obtained. Palladium-catalyzed coupling of **9** with organozinc reagent **11** (Scheme 3) prepared *in situ* from **11** using Jackson's protocol,[13] followed by desilylation with AcOH, gave alcohol **12**. Catalytic asymmetric epoxidation of **12** using the Katsuki-Sharpless protocol[14] provided epoxide **13**. Diol **14** was then obtained by treating epoxide **13** with DDQ to remove the MPM protecting group. Cyclization of diol **14** with PPTS gave tetrahydrofuran **15** with complete inversion of stereochemistry at one of the epoxide stereocenters. Tetrahydrofuran **15** was directly subjected to $Pb(OAc)_4$ oxidation and Jones oxidation to obtain lactam **16** in 67% yield. RuO_4 oxidation[15] of lactam **16** thus provided compound **17** in excellent yield. The total synthesis of lycoperdic acid was completed by subjecting compound **17** to acid hydrolysis (83% yield).[3]

In 2002, Hamada and co-workers[4] reported the synthesis of lycoperdic acid by using the known chiral bicyclic lactam[16] **20** (Scheme 4), which was prepared through Thottathil's protocol.[16] Pyroglutamic acid (**18**) was converted to an ester which was then reduced to alcohol **19**.[17] Bicyclic lactam **20** was obtained from **19** as a single diastereomer by reaction with benzaldehyde in acidic medium.



Scheme 4: Synthesis of bicyclic lactam **20**.

The bicyclic lactam **20** was treated with lithium diisopropylamide (LDA) followed by addition of allyl bromide at -78°C for 4 h to gave a 1:1 mixture of diastereomers **21** (Scheme 5).

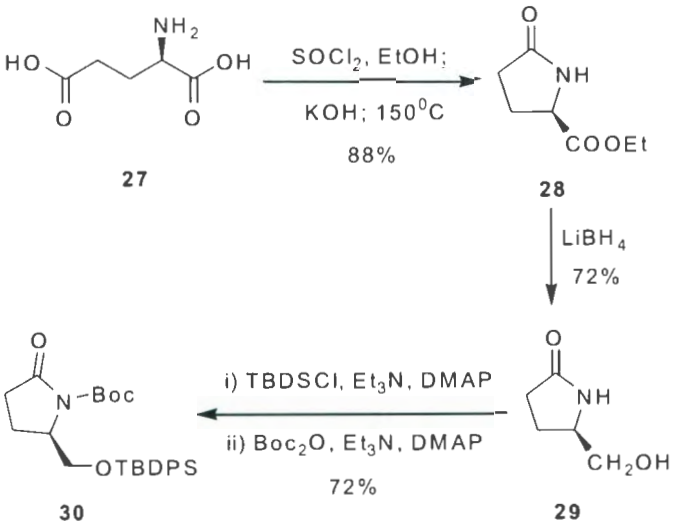


Scheme 5: Hamada's synthesis of lycoperdic acid.

In the key step, reaction of diastereomers **21** with LDA and freshly-prepared

MoOPH (MoO_5·Py·HMPA)[18] gave single diastereomer of α-hydroxy lactam **22.** The *endo* stereochemistry of the allyl group in **22** was confirmed by NOE experiments. α-Hydroxylactam **22** was treated with borane tetrahydrofuran complex followed by alkaline hydrogen peroxide work-up to give alcohol **23**, which was oxidized using Jones reagent to afford crystalline tricyclic γ-lactone **24** in 67% yield. The X-ray structure of compound **24** shows that the oxygen in the lactone ring is at the *endo* position which supports the assigned stereostructure of compound **22** based on the NOE experiment. For the conversion of **24** to **1** a novel two-step conversion was developed, in which compound **24** was oxidized with $RuCl_3$[19] and sodium periodate to provide anhydride **25** (oxidation of **24** at C1 and the N,O-acetal benzylic position), which then was heated to reflux in aqueous 6.0 M HCl for 16 hours to afford lycoperdic acid in 64% yield.

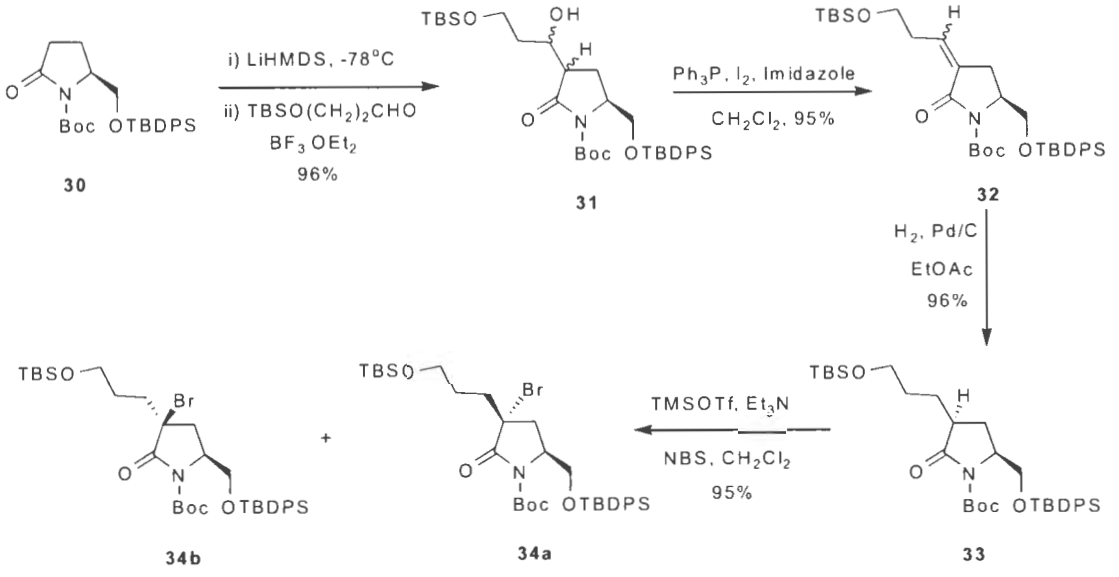
In 2007, Chamberlin and Cohen reported the synthesis of lycoperdic acid, which is based on the intramolecular S_N2 displacement of a bromide by an alkoxide nucleophile in a diastereoselective annulation of an oxolane ring onto a pyroglutamate scaffold to construct a γ-lactone.[8] The starting material for this synthesis was prepared from commercially available D-glutamic acid (**27**) in four steps[20] (Scheme 6). Treatment of D-glutamic acid (**27**) with thionyl chloride in ethanol was followed by addition of potassium hydroxide, and the mixture was then refluxed at 150 °C to give (*R*)-ethyl-5-oxopyrrolidine-2-carboxylate (**28**) in 88% yield. The ester in compound **28** was reduced with lithium aluminum hydride to yield (*R*)-5-(hydroxymethyl)pyrrolidin-2-one (**29**) in 72% yield. The primary hydroxy group in **29** was first protected with TBDSCl followed



Scheme 6: Preparation of compound **30**.

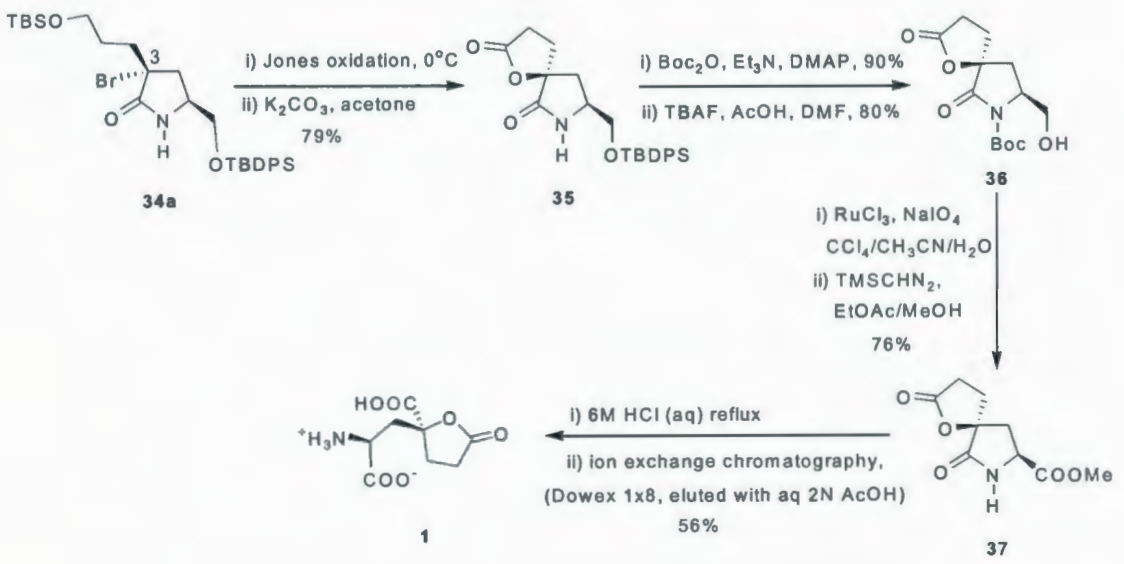
by protection of the secondary amine with Boc anhydride to provide compound **30** in 72% yield.

Deprotonation of compound **30** (Scheme 7) followed by a reaction with 3-(*tert*-butyldimethylsilyloxy)propanal in the presence of $BF_3.OEt_2$ provided an inseparable mixture of diastereomeric aldol adducts **31** in 96% yield. Dehydration of compound **31** with triphenyl phosphonium iodide in the presence of imidazole provided **32** as a 5:1 mixture of *E*/*Z* isomers based on NMR analysis.[21] The 3,5-substituted pyrrolidine **33** was obtained as a single diastereomer after hydrogenation of compound **32**. Bromination of **33** gave a separable mixture of diastereomers **34a** and **34b** (6:1 based on NMR of crude reaction mixture) in 95% yield.



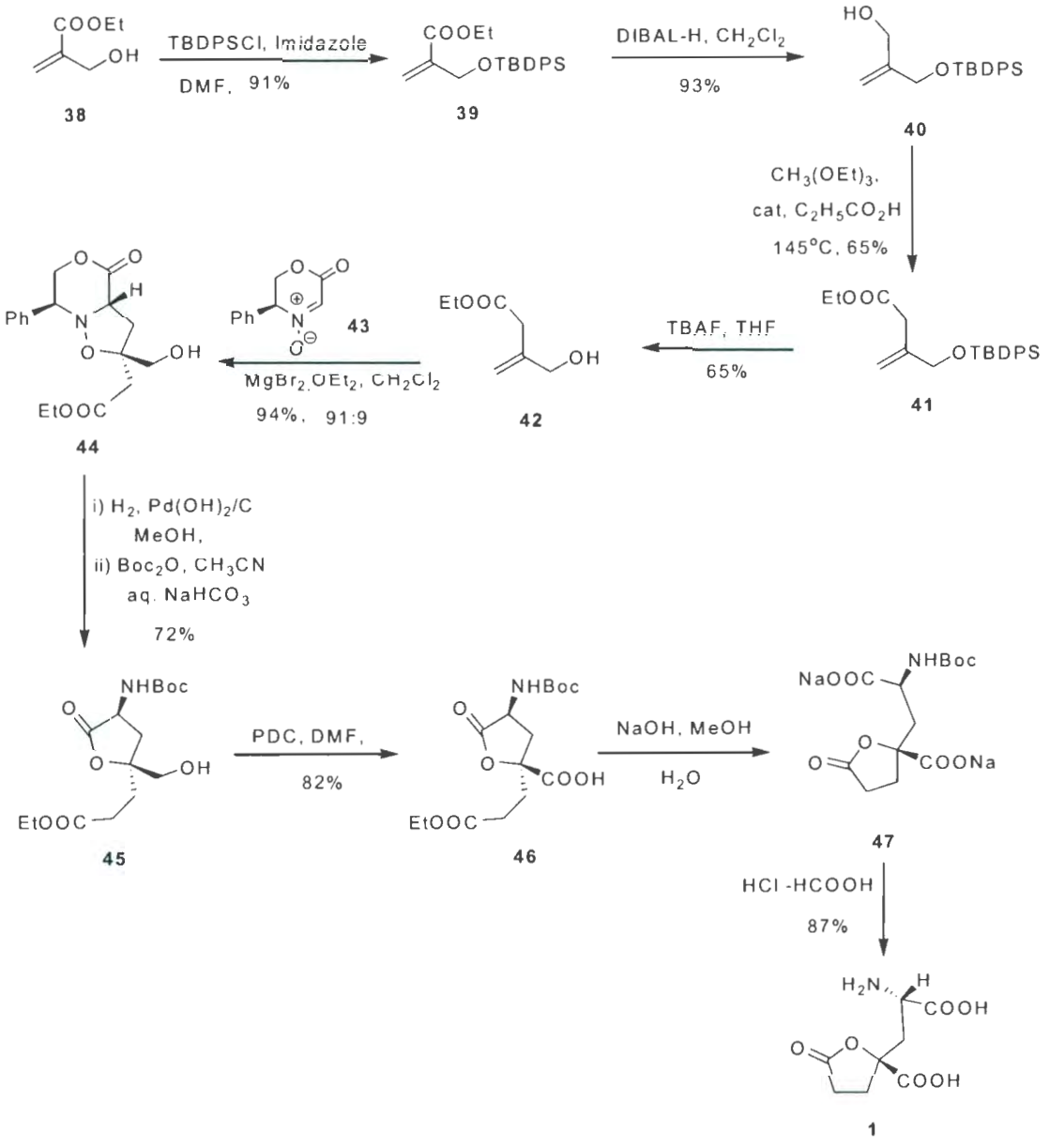
Scheme 7: Synthesis and bromination of 3,5-disubstituted pyrrolidine **31**.

The stereochemistry at C3 in compound **34a** was helpful for the stereospecific generation of the oxolane ring in compound **35** (Scheme 8). The major *anti* isomer **34a** was assigned on the basis of earlier studies on similar γ-lactones or γ-lactams.[22] Oxidative annulation of lactam **34a** was achieved using Jones reagent followed by basic work-up to provide spirolactone **35** in 79% yield. Boc protection of **36** followed by desilylation with TBAF gave pyroglutaminol **36**. Ruthenium tetroxide-mediated oxidation of alcohol **36** followed by esterification of the resulting acid with $TMSCHN_2$ afford methyl ester **37** in 76% yield. Acid hydrolysis of methyl ester **37** followed by ion-exchange chromatographic separation and recrystalisation[3,5] gave pure (*S*)-(+)-lycoperdic acid in 56% yield.



Scheme 8: Synthesis of lycoperdic acid **1** from **34a**.

Ishibashi et al. reported a new methodology for the synthesis of lycoperdic acid[7] (Scheme 9). The synthesis begins with the protection of the alcohol in ethyl-2-(hydroxymethyl)acrylate **38** (Scheme 9) as the tert-butyl diphenyl silyl ether **39**. Reduction of **39** with DIBAL-H gave **40**[23] in 93% yield. Compound **40** was subjected to the Johnson-Claisen rearrangement conditions to provide the γ,δ-unsaturated ester **41**, which was then treated with TBAF to provide the allylic alcohol **42**. Cycloaddition of **42** with nitrone[24] **43** in the presence of $MgBr_2.OEt_2$[25] gave a separable mixture (91:9) of diastereomers of cycloadduct **44** in 94% yield. Cycloadduct **44** was hydrogenated over Pearlman's catalyst and the primary amine was protected as a Boc carbamate to provide lactone **45** in 72% yield. The primary hydroxy group in compound **45** was oxidized with



Scheme 9: Ishibashi's synthesis of lycoperdic acid (**1**).

PDC to the corresponding acid **46** in 82% yield. Hydrolysis of the lactone ring and translactonization in **46** was achieved by treatment with aqueous methanolic NaOH to

afford the sodium salt **47**. Acidification of **47** with formic acid and aqueous 1.0 M HCl provided crude lycoperdic acid which was purified by ion exchange chromatography.

The stereochemistry in cycloadduct **44** can be explained on the basis of the proposed transition states (TS) shown in Figure 1. The structure of TS **I** shows that the *re*-face of nitrone **43** is greatly shielded by the phenyl ring as compared to the *si*-face.[27d]

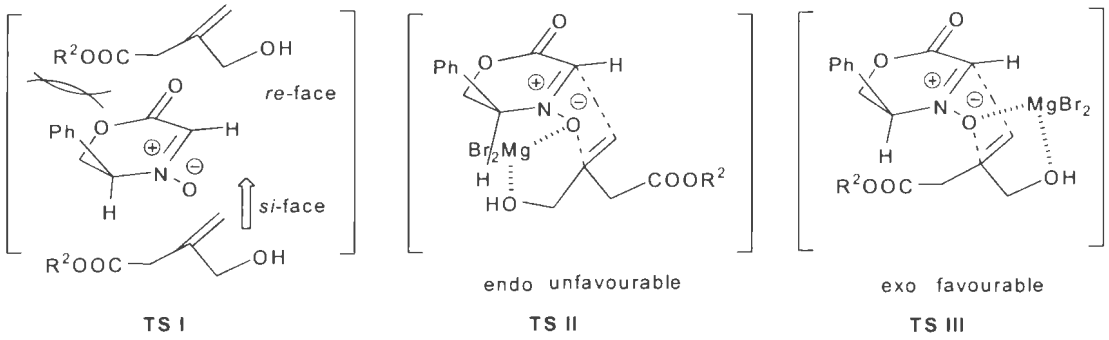
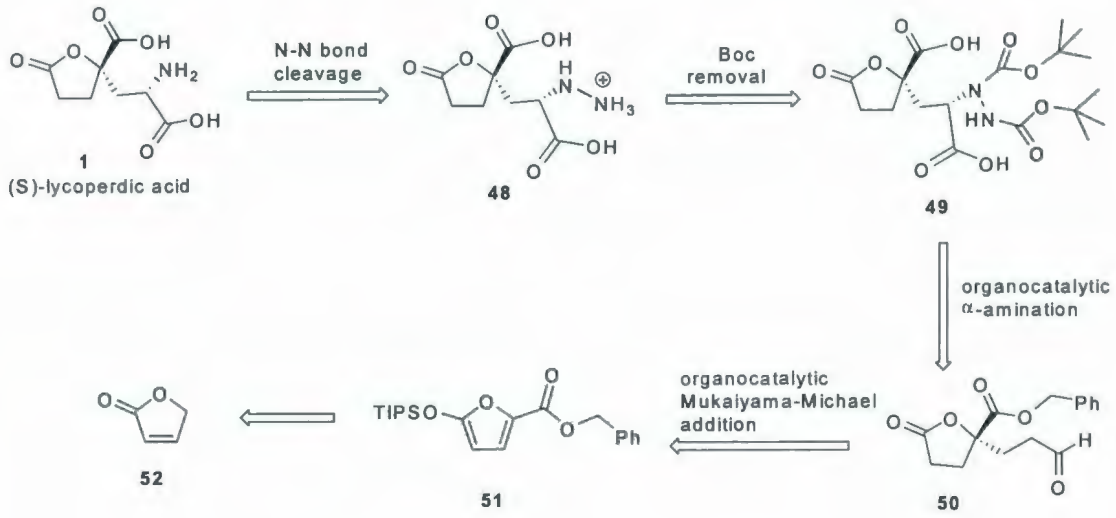


Figure 1: Transition states for cycloaddition of Nitrone **44** with allyl alcohol.

The addition of $MgBr_2.OEt_2$ increases the rate of cycloaddition reaction by chelating with nitrone and allyl alcohol as shown in TS **II** and **III**.[26] TS **II** is more crowded than T. S. **III** (*exo*), hence the latter leads to the obtained product.

Proposed retrosynthesis of lycoperdic acid

The strategy employed for the synthesis of lycoperdic acid by this author is based on an organocatalytic Mukaiyama-Michael addition to acrolein and an organocatalytic α-amination reaction. The retrosynthesis is summarized in Scheme 10.

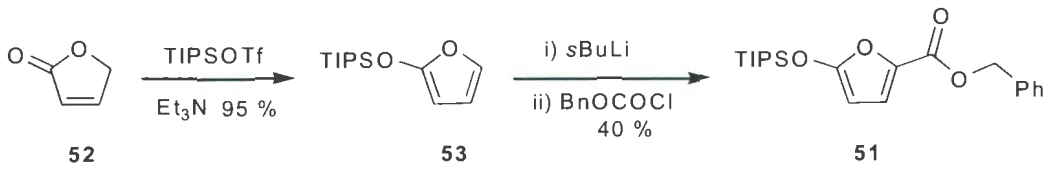


Scheme 10: Proposed retrosynthesis of lycoperdic acid (**1**).

It was reasoned that lycoperdic acid (**1**) (Scheme 10) could be obtained from the hydrazino analogue **48** by *N-N* bond cleavage. Compound **48** can be obtained from acid **49** by Boc deprotection. Acid **49**, in turn, can be obtained from aldehyde **50** by an organocatalytic α-amination reaction followed by oxidation. Aldehyde **50**, the key intermediate in the synthesis, can be obtained from furan **51** by using an organocatalytic Mukaiyama-Michael addition to acrolein. Compound **51** can be obtained from commercially available γ-crotonolactone (**52**) by adaptation of literature procedures.[27,28]

Studies on the synthesis of (+)-lycoperdic acid

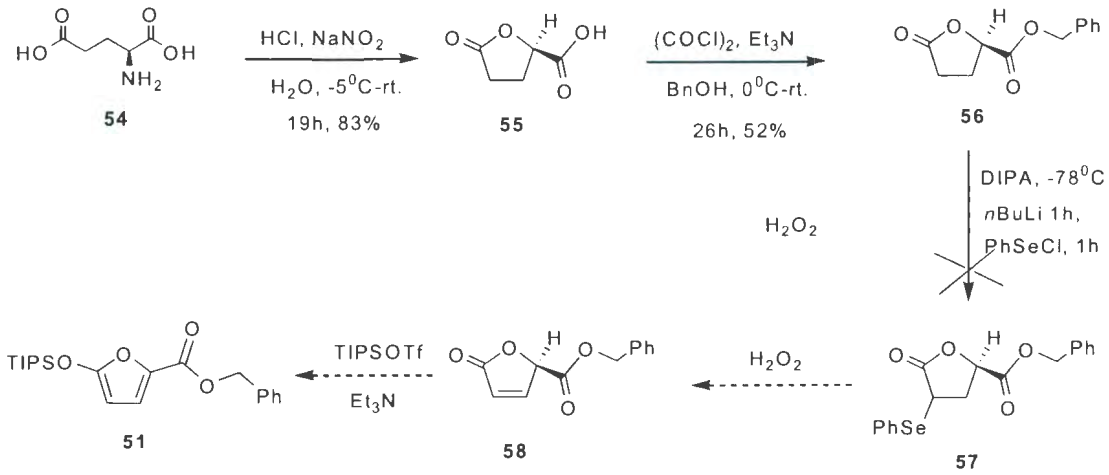
Our studies started with commercially available γ-crotonolactone (**52**, Scheme 11), which was treated with TIPSOTf in the presence of triethylamine to obtain triisopropyl silyloxy furan (**53**) in 95% yield.[27] Furan **53** was then lithiated with *sec*-butyl lithium



Scheme 11: Preparation of furan nucleophile **51**.

followed by acylation with benzyl chloroformate to provide **51** in 40% yield. The purification of compound **51** was achieved by column chromatography followed by distillation. Impurities present in the chromatographed product were distilled over at 120 °C (0.2 mm of Hg), whereas pure **51** remained in the pot.

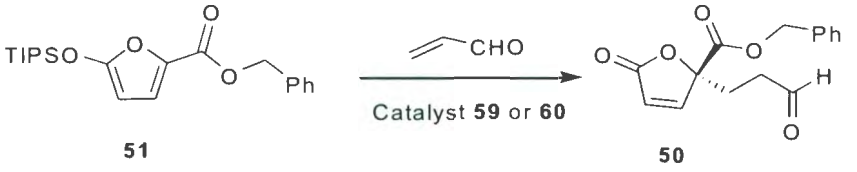
As the purification of **51** is time-consuming we attempted to prepare it by using a different method. L-(+)-glutamic acid (**54**, Scheme 12) was treated with HCl and



Scheme 12: Preparation of compound **52**.

$NaNO_2$ in the presence of water to obtained (*R*)-tetrahydro-5-oxofuran-2-carboxylic acid (**55**) in 83% yield following the reported procedure.[29] The carboxylic acid group in compound **55** was protected as a benzyl ester (**56**). Attempted phenylselenation of **56** (LDA/PhSeCl) to provide **57** was unsuccessful. Consequently this synthetic route, which would have provided **58** via selenoxide elimination from **57**, was abandoned.

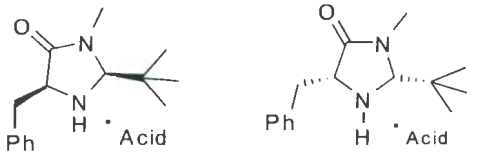
Nevertheless, with furan nucleophile **51** in hand, we planned to react it with acrolein in an organocatalytic Mukaiyama-Michael addition reaction employing iminium ion catalysis (Scheme 13).



51 **50**

Scheme 13: Proposed organocatalytic Mukaiyama-Michael addition to acrolein.

For this purpose, the use of MacMillan's second generation catalyst[30] **59** and its enantiomer **60** (Figure 2) was planned.



59 **60**

Figure 2: MacMillan's catalysts.

The proposed mechanism for the organocatalytic Mukaiyama-Michael addition to acrolein is as shown in Figure 3. According to MacMillan, the imidazoline salt **59** forms an iminium ion such as **62.**[31] Two factors for stereocontrol can be identified in the reaction.

1) Selective formation of *E* iminium ion **61** (Figure 3)[31]

2) The benzyl group on the catalyst shields the *si*-face of the iminium ion but the *re*-face is less hindered for nucleophilic attack.[31]

Taking into consideration these aspects, the furan nucleophile should approach from the less hindered *re*-face of the iminium ion as shown in **62**, which will form enamine **63**. Hydrolysis of enamine **63** will give aldehyde **50** and regenerate the catalyst for further catalytic cycles.

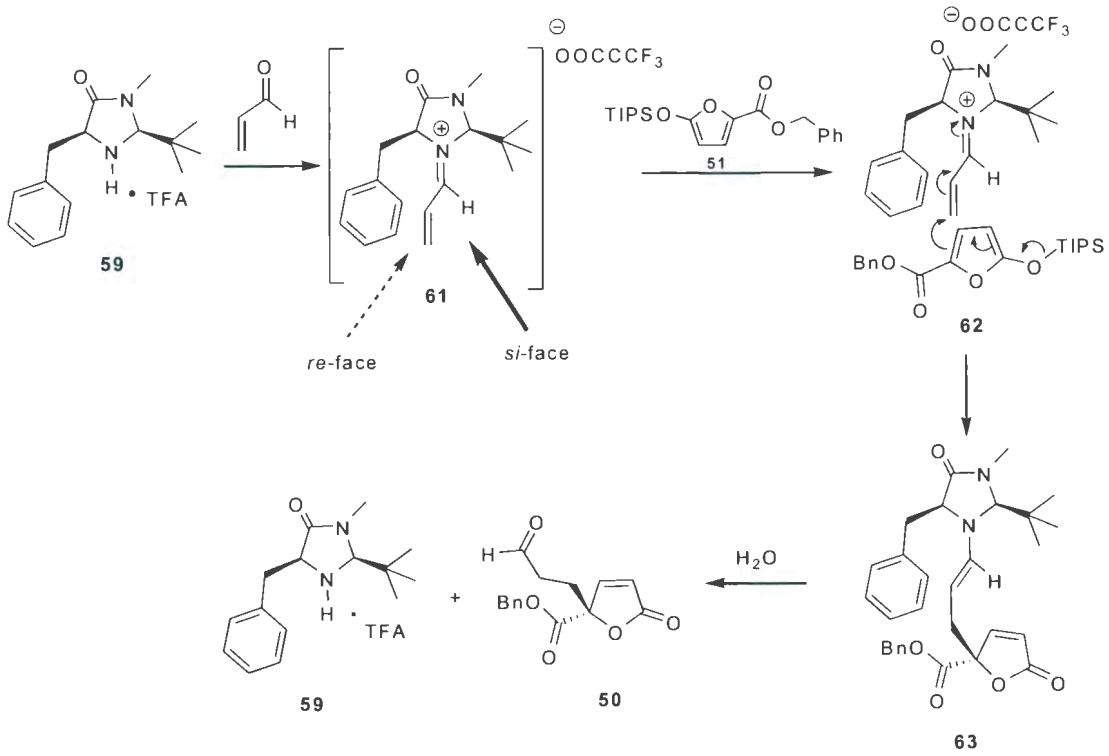
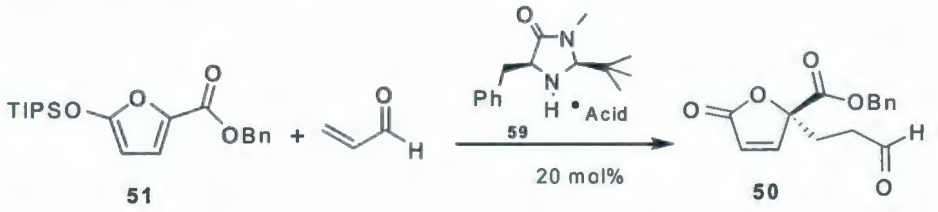


Figure 3: Proposed reaction mechanism for the organocatalytic Mukaiyama-Michael addition to acrolein.

To optimize the enantioselectivity in the conjugate addition reaction, a solvent-effect study was performed using MacMillan's second generation catalyst **59**. In all the reactions, 1 equivalent of benzyl ester and 3 equivalents of acrolein were used. All reactions were done with 20 mol% catalyst and 20 mol% acid additive at different temperatures and in different solvents. The experimental results are summarized in Table 1.

Table 1: Organocatalytic Mukaiyama-Michael addition of furan **51** to acrolein, in the presence of catalyst **59**.



All reactions are performed using 1 equiv. benzyl ester **51** and 3 equiv. acrolein and 20 mol% catalyst. Except noted as a footnote.

Entry	Acid additive[a]	Solvent	Temp. °C	Time (h)	Yield[b] (%)	ee[c] (%)
1	DNBA[d]	DCM	-15	120	58	56
2	TFA[e]	DCM	0	48	41	41
3	TFA[f]	$CHCl_3$	0	72	47	78-66
4	TFA[f]	dioxane	0 - rt.	188	46	75
5	TFA[g]	ether	0	168	34	25
6	-	THF	0	139	35	13
7	TFA	dioxane	rt.	72	50	14

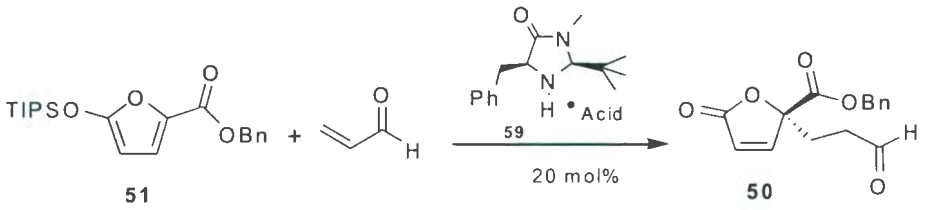
[a] 20 mol% acid additive. [b]Isolated yield. [c]Determined by chiral HPLC (AS-H column). [d]0.16 mmol of ester in 3 ml DCM. [e]0.096 mmol ester in 1.5 ml DCM. [f]0.266 mmol of ester in 1 ml solvent. [g]0.266 mmol ester in 1 ml ether.

The use of 2,4-dinitrobenzoic acid as a co-catalyst led to 58% yield of aldehyde in dichloromethane with moderate (56%) ee (Table 1, Entry 1) at -15 °C. Changing the acid from 2,4-dinitrobenzoic acid to trifluoroacetic acid in dichloromethane (Entry 2), at

0 °C gave 41% yield in 48 h, however, the ee was only 41%. The use of chloroform as a solvent in the presence of TFA provided **50** with moderate-to-good ee (78-66) (Entry 3). Also, TFA in dioxane gave 75% ee and 46% yield after a longer period of time (Entry 4). However, the use of solvents like ether (Entry 5) resulted in low yield as well as low ee at 0 °C. A reaction without any acid additive in THF proceeded with very low enantioselectivity (13%) thereby emphasizing the importance of the acid additive.

To continue this study, the effect of TFA or other acids as additives was investigated by controlled experiments performed in THF (Table 2).

Table 2: Organocatalytic Mukaiyama-Michael addition of furan **51** to acrolein, in the presence of catalyst **59**.



All reactions were performed using 1 equiv. benzyl ester **51** and 3 equiv. acrolein and 20 mol% catalyst. Except noted as a footnote.

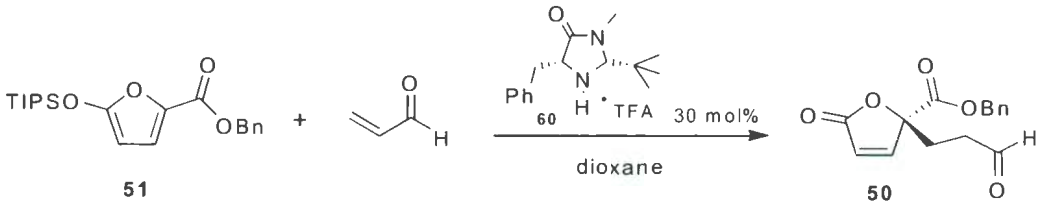
Entry	Acid additive[a]	Solvent	Temp. °C	Time (h)	Yield[b] (%)	ee[c] (%)
1	TFA[d]	THF	0	48	29	69
2	TFA[d]	THF	0-rt	50	50	59
3	TFA[e]	THF	4	72	24	61
4	TFA[f]	THF	-7	72	27	48
5	$Cl_2CHCOOH$[g]	THF	0	80	43	2
6	TFA[h]	DME	0	68	41	58
7	TFA[f]	THF	0	46	29	55[i]
8	TFA[g]	THF	0	115	43	59[j]

[a]20 mol% acid additive. [b]Isolated yield. [c]Determined by chiral HPLC (AS-H column). [d]1.79 mmol of ester in 14 ml THF. [e]0.74 mmol ester in 7 ml THF. [f]0.16 mmol of ester in 3 ml THF. [g]0.5 mmol ester in 4 ml .THF. [h]0.226 mmol ester in 1 ml DME. [i]30 mol% catalyst and 30 mol% acid. [j]1 equiv. acrolein.

The reaction at 0 °C gave low yield (29%) and moderate ee (69%) (Entry 1). Increasing the reaction temperature to 4 °C gave 61% ee and only 24% yield (Entry 3). However, cooling the reaction to -7 °C gave only 48% ee and low yield (Entry 4). The use of dichloroacetic acid instead of TFA was not beneficial, and nearly racemic product (Entry 5) was obtained. TFA in DME as the solvent gave 41% yield and 58% ee (Entry 6). However, use of 30 mol% catalyst in the presence of TFA gave 55% ee (Entry 7). Changing the ratio of ester to acrolein from 1:3 to 1:1 gave better yield (43%) and moderate ee (59%) (Entry 8). Table 2 indicates that there is no specific trend in the yield as well as in the enantiomeric excess in the THF/TFA system. However, the importance of TFA is highlighted by the low ee with dichloroacetic acid.

Table 1 (Entry 4) shows that the use of TFA in dioxane provides 51% yield with 75% ee. This relatively good result suggested that further optimization of the reaction should be based on these conditions. The studies were conducted with the enantiomeric catalyst **60**, in dioxane as solvent and in the presence of TFA as an additive using 1:3 ratio of ester: acrolein (Table 3).

Table 3: Organocatalytic Mukaiyama-Michael addition of furan **51** to acrolein, in the presence of catalyst **60**.



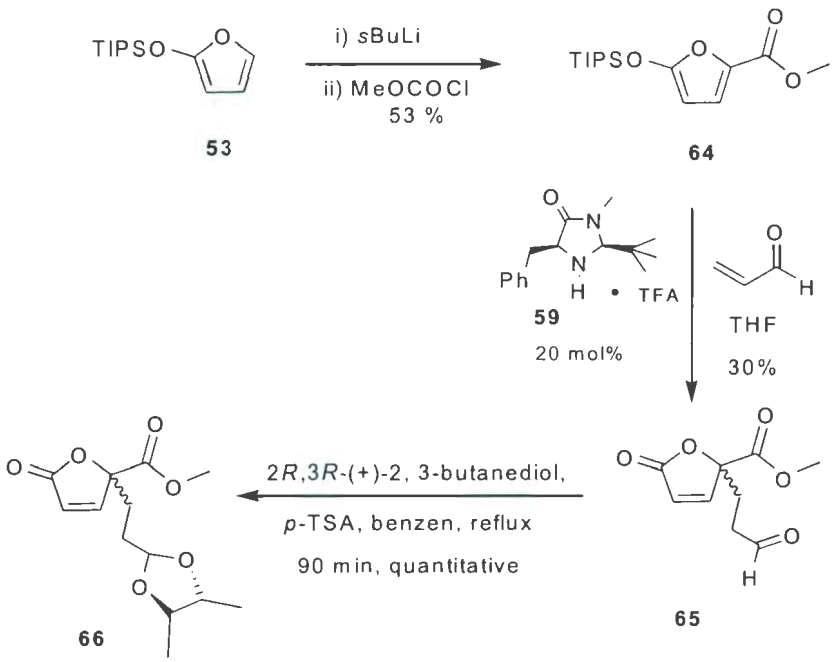
All reactions are performed using 1 equiv. benzyl ester **52** and 3 equiv. acrolein and 30 mol% catalyst. Except noted as a footnote.

Entry	Temp. (^{o}C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	rt.[d]	144	45 %	68 %
2	0[f]	120	23 %	10 %
3	0[d]	96	30 %	25 %
4	rt[d]	240	Nd[g]	-

[a]all reactions were done using 30 mol% acid additive. [b]Isolated yield. [c]Determined by chiral HPLC (AS-H column). [d]0.4 mmol ester in 1 ml dioxane. [e]0.266 ester in 1 ml dioxane. [f]0.82 mmol ester in 2 ml dioxane. [g]Reaction at double dilution.

The reaction in dioxane at room temperature gave 44% yield and good ee (68%) (Entry 1). However, decreasing the temperature to 0 ^{o}C gave low yield and nearly racemic aldehyde (Entry 2, 3). Since dioxane freezes at 0 ^{o}C, these reactions were not homogenous and the reaction medium was a slurry.

The substituent effect of a change in the ester moiety was examined with furan **64** (methyl ester instead of benzyl ester). For the preparation of furan **64** (Scheme 14), triisopropyl silyloxy furan (**53**) was treated with *sec*-butyl lithium and to the resulting reaction mixture methyl chloroformate was added, producing compound **64** in 53% yield.

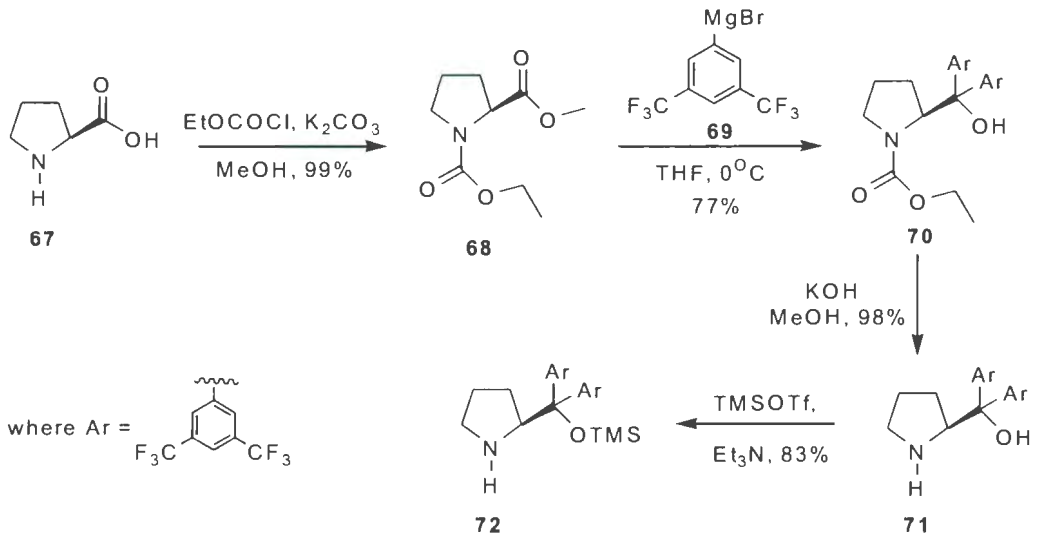


Scheme 14: Preparation of chiral acetal **67**.

Compound **64** was treated with catalyst **59** and acrolein (ester: acrolein 1:3) in the presence of TFA to yield aldehyde **65** in low yield (30%). The enantiomers of aldehyde **65** were inseparable on chiral AS-H and AD columns. It was therefore converted to a chiral acetal. Thus aldehyde **65** was refluxed with 2*R*,3*R*-(+)-2,3-butanediol in the presence of a catalytic amount of *p*-toluenesulfonic acid in benzene, to provide the acetal **66** in quantitative yield.[32] Chiral HPLC analysis of **66** (chiral AS-H) indicated an ee of

59%. This observation indicates that the benzyl ester is a better option which provides up to 69% ee.

The results obtained so far with MacMillan's catalyst were promising, but the enantiomeric excess of aldehyde **50** was not very high. It was therefore decided to examine the prolinol ether **72** (Scheme 15) as catalyst. Previous studies have demonstrated the applicability of **72** in iminium ion catalysis.[33] Catalyst **72** was prepared by using the known method from proline (**67**) (Scheme 15).



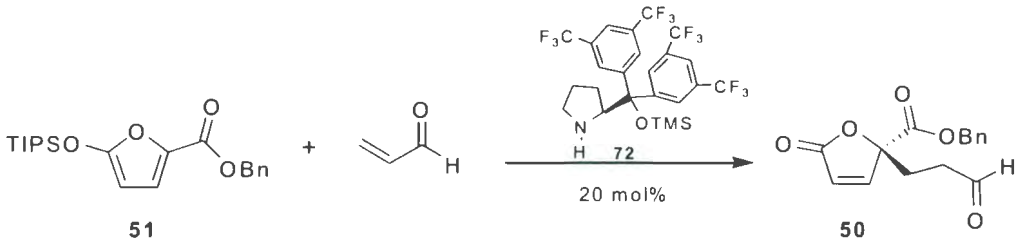
Scheme 15: Preparation of the catalyst **73**.

The secondary amine and carboxylic acid in proline were protected as the ethyl carbamate and methyl ester, respectively. [34] The resulting compound **68** was reacted with Gignard reagent **69** to provide **70** (77%). Hydrolysis of the carbamate in **70** was achieved with KOH in methanol to produce compound **71** in 98% yield.[34] The tertiary alcohol in

71 was selectively protected as its TMS ether to provide catalyst **72** in 83% yield.[35]

With catalyst **72** in hand its efficiency in the Michael-Michael conjugate addition of **51** to acrolein was examined in a variety of solvents. Initial studies with TFA and dioxane provided aldehyde **50** with low ee (Entries 1 and 2, Table 4).

Table 4: Organocatalytic Mukaiyama-Michael addition of furan **51** to acrolein, in the presence of catalyst **72**.



All reactions were performed using 1 equiv. of benzyl ester **51** and 3 equiv. of acrolein and 20 mol% catalyst. Except noted as a footnote.

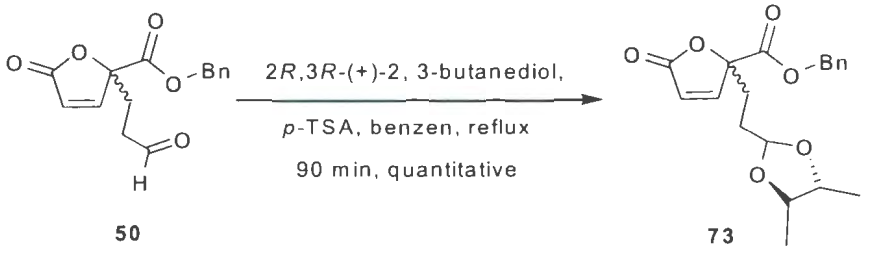
Entry	Solvent[a]	Temp.	Time (h)	Yield[b] (%)	ee[c] (%)
1	THF	rt.	91	74	35
2	Dioxane	rt.	163	47	33
3	DCM	rt.	120	33	44
4	DMF	rt.	48	22	30
5	Toluene	rt.	168	19	78
6	$CHCl_3$	rt.	120	36	89
7	$CHCl_3$	rt.	168	42	90
8	$CHCl_3$	rt.	180	50	64[d]

[a]0.133 mmol ester in 0.5 ml solvent. [b]Isolated yield. [c]Determined by chiral HPLC (AS-H column).

[d]30 mol% catalyst and 30 mol%.

Reactions in dichloromethane and DMF gave low yield of the target product as well as low ee. Surprisingly, the reaction in toluene gave high ee (78%) but in less yield (19%) (Entry 19). Interestingly, changing the solvent to chloroform (Entries 6 and 7)

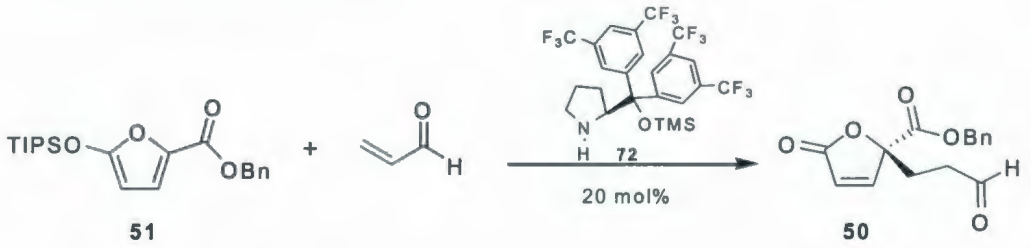
gave a moderate yield of **50,** but also the highest ee so far (89 % and 90%). Unfortunately, this enantioselective reaction could not be reproduced and, despite numerous attempts, provided **50** only as a racemate. The enantiomeric excess of **50** was confirmed by conversion to the chiral acetal **73** and analysis by chiral HPLC (Scheme 16).



Scheme 16: Preparation of chiral acetal **73**.

The inexplicable irreproducibility of the reaction in chloroform prompted a study of the effect of additives on this reaction. Table 5 summarizes this study from which methanol emerged as a good additive for ee (78%), but not for the yield of **50** was found to be only 15%.

Table 5: Effect of additives on the organocatalytic Mukaiyama-Michael addition reaction of **51** and acrolein.



All reactions were performed using 1 equiv. benzyl ester **51** and 3 equiv. acrolein and 20 mol% catalyst in chloroform solvent. Except noted as a footnote

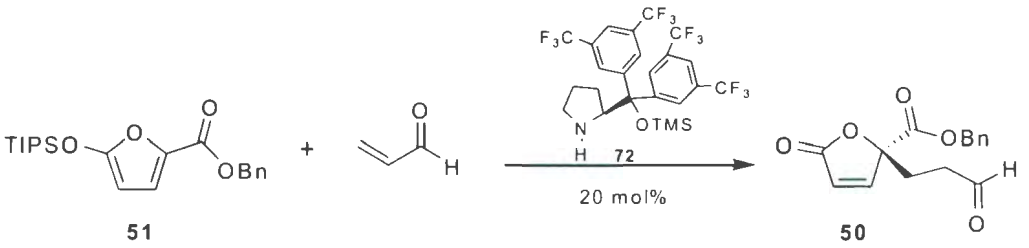
Entry	Additive[a]	Temp. (^{0}C)	Time	Yield[b] (%)	ee[c] (%)
1	MeOH[d,]	rt	6 days	15	78
2	IPA[d]	rt	5 days	53	34
3	BnOH[d]	rt	7 days	10	5
4	TFA[e]	4	12 h	67	16
5	$HClO_4$[e]	-17	4 days	28	9
6	TFA[e]	-17	2 days	20	8
7	MeOH[d]	rt	8 days	ND	ND

[a]0.266 mmol ester in 1 ml solvent. [b]Isolated yield. [c]Determined by chiral HPLC (AS-H column).

[d]2 equivalent with respect to ester. [e]20 Mol% acid additive.

A detailed study of the effect of aqueous conditions was also undertaken (Table 6).

Table 6: Effect of water on organocatalytic Mukaiyama-Michael addition reaction.



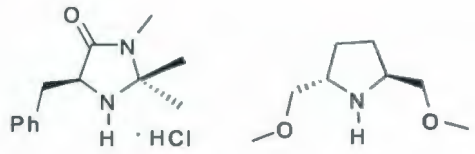
All reactions were performed using 1 equiv. benzyl ester **51** and 3 equiv. acrolein and 20 mol% catalyst. Except noted as a footnote

Entry	Solvent	% H_2O	Time	Yield[a] (%)	ee[b] (%)
1	-	100	17 h	80	2
2	97.5[c]	2.5	144	40	2
3	95[c]	5	108	45	84[d]-1[e]
4	90[c]	10	144	47	2
5	80[c]	20	144	50	3
6	50[c]	50	144	55	0
7	-	-	144	nd	-
8	$CHCl_3$[f]	-	144	10	1
9	ACS $CHCl_3$[g]	-	144	5	3
10	IPA[g]	-	24	20	9
11	DCE[g]	5	144	40	1

[a]Isolated yield. [b]Determined by chiral HPLC (AS-H column). [c]Chloroform. [d] % ee after 16 hours. [e]% ee after 4.5 days. [f]0.133 mmol ester in 0.5 ml moist chloroform. [g]0.133 mmol ester in 0.5 ml solvent.

The reaction in 100% water (Entry 1) gave the aldehyde in 80% yield which is the highest so far, but virtually no enantiomeric excess (2% ee). Other reactions in which the amount of water was gradually reduced (Entries 2-6) also gave nearly racemic aldehyde in moderate yield. Table 6 also shows that as the amount of water in the reaction is increased the yield of the product increases (Entries 2-6) but the enantiomeric excess is unchanged. In one particular reaction, in 5% water and 95% chloroform (Entry 3), the product ee was 84% after 16 hours. However, after the same reaction had been stirred for 108 h the ee dropped to 1% (Entry 3). This indicates that the enantiomeric excess of the product decreases with time. The reaction (Entry 7) without solvent provided a complex mixture. Reactions in ACS chloroform (Entry 8) and moist chloroform (Entry 9) were inefficient. However the reactions in isopropyl alcohol (Entry 11) and DCE (Entry 11) gave better yields, but low ee.

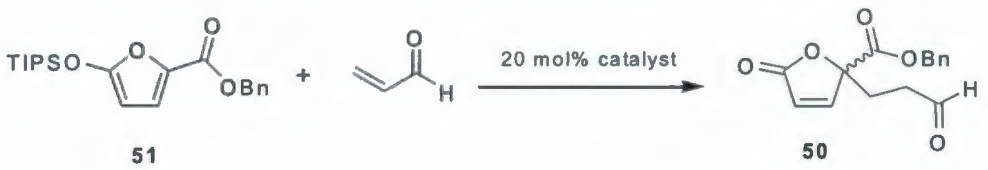
A few reactions were tried with MacMillan's first generation catalyst **74** and the C_2-symmetric amine catalyst **75.** These results are summarized in Table 7.



74 **75**

Figure 4: MacMillan's first-generation catalyst and a C_2-symmetric pyrrolidine catalyst.

Table 7: Organocatalytic Mukaiyama-Michael addition reaction.



51 50

All reactions were performed using 1 equiv. of benzyl ester **51** and 3 equiv. of acrolein and 20 mol% catalyst. Except noted as a footnote.

Entry	Catalyst	Solvent[a]	Additive[b]	Time	Yield[c] (%)	ee[d] (%)
1	**74**	$CHCl_3$	H_2O	3 days	19	84
2	**74**	dioxane	H_2O	5 days	28	ND
3	**75**	$CHCl_3$	H_2O	7 days	27	1
4	**75**	$CHCl_3$	MeOH	8 days	35	3
5	**75**	dioxane	H_2O	12 h	ND	26
6	-	10 M glucose solution (aq)	-	1.5 days	50	3

[a]0.133 mmol ester in 0.5 ml solvent. [b]Additive 2 equivalent with respect to ester. [d]Isolated yield. [d]Determined by chiral HPLC (AS-H column). [e]20 mol% TFA additive.

Reaction with (2*S*,5*S*)-tetrahydro-2,5-bis(methoxymethyl)furan (catalyst **74**) in chloroform and water (Entry1, Table 8) gave high ee (84%) but the yield was only 19%. However the same catalyst in dioxane (Entry 2) did not work as expected. The remaining reactions with these catalysts gave nearly racemic aldehyde in moderate yield. Out of

curiosity one reaction was conducted in 10 M aqueous glucose solution (Entry 6) to examine the effect of a chiral environment on the reaction in the absence of a catalyst. However, this reaction gave 50% yield of almost racemic aldehyde.

Considering that acrolein tends to undergo polymerization at room temperature, we examined acrolein dimethyl acetal as an alternative to acrolein in a reaction catalyzed by **72**. However, there was no significant change in the enantiomeric excess of **50** obtained (64% ee after 48 h).

The moderate-to-low enantiomeric excess obtained in these reactions may be explained as illustrated in Figure 5. Presumably, the lack of a β-substituent on the acrolein accounts for the low enantioselectivity.

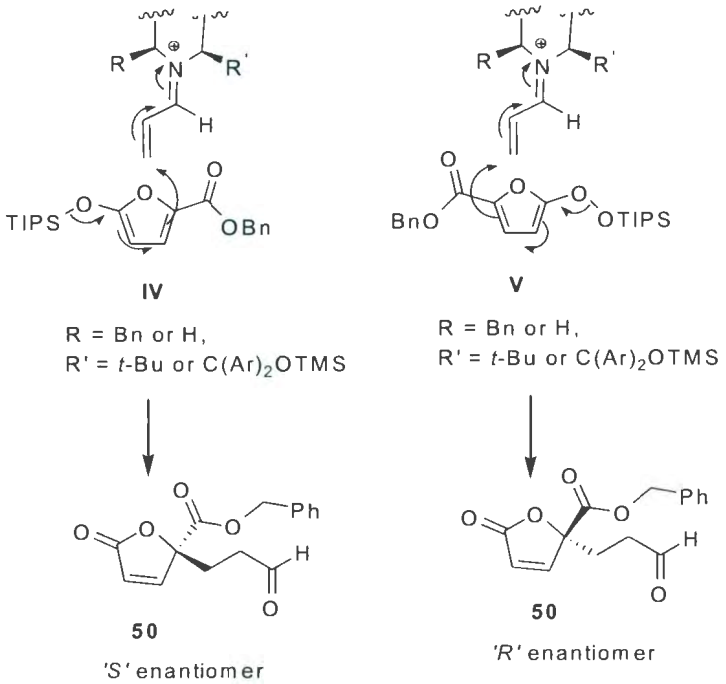
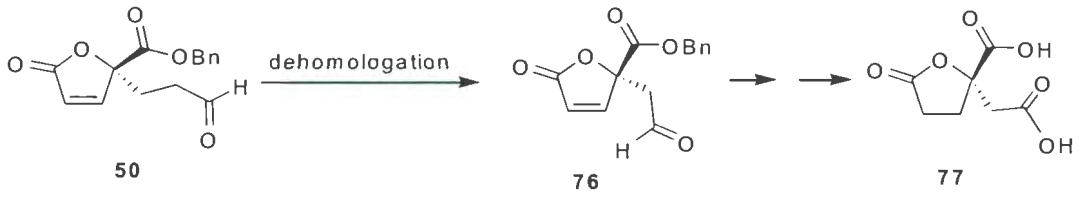


Figure 5: Possible transition states leading to '*R*' and '*S*' **50**.

Synthesis of (*S*)-(+)-homocitric acid

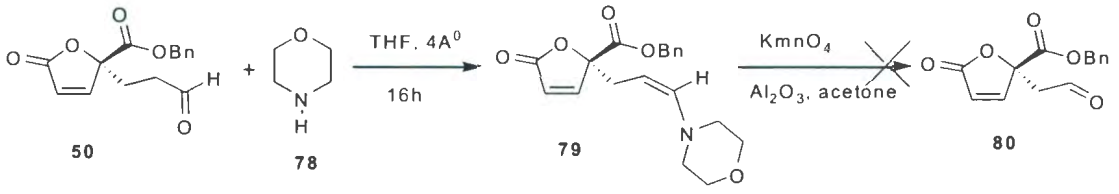
Naturally occurring (-)-(*R*)-homocitric acid is an intermediate in the biosynthesis of lysine in yeast and in some fungi. In nature, homocitric acid is produced by enzymatic condensation of *R*-ketoglutarate and acetyl CoA.[36] Shah and Bill in 1977 first discovered that homocitrate is an essential component in nitrogen fixation (Fe-Mo cofactor).[37] Because of these interesting biological properties, homocitric acid is of interest in the development of antifungal therapies.[38] Biellmann et al. reported the first enantioselective total synthesis of natural and unnatural homocitric acid from (-)-L-lactic acid and (-)-L-serine respectively.[36] The synthesis was based on a Diels-Alder reaction. In 2005, Tatsumi and co-workers reported a three-step synthesis of homocitric acid from D-malic acid.[39] In 2007, Pansare and Adsool reported the enantioselective synthesis of homocitric acid from an ephedrine-derived morpholinedione.[40] To date, several total syntheses of homocitric acid have been reported in the literature, but none of these syntheses employ organocatalysis.

Given the interest in homocitric acid, it was decided to attempt to convert the aldehyde **50** to homocitric acid via a dehomologation sequence as shown in Scheme 17.



Scheme 17: Homocitric acid **77** from aldehyde **50**.

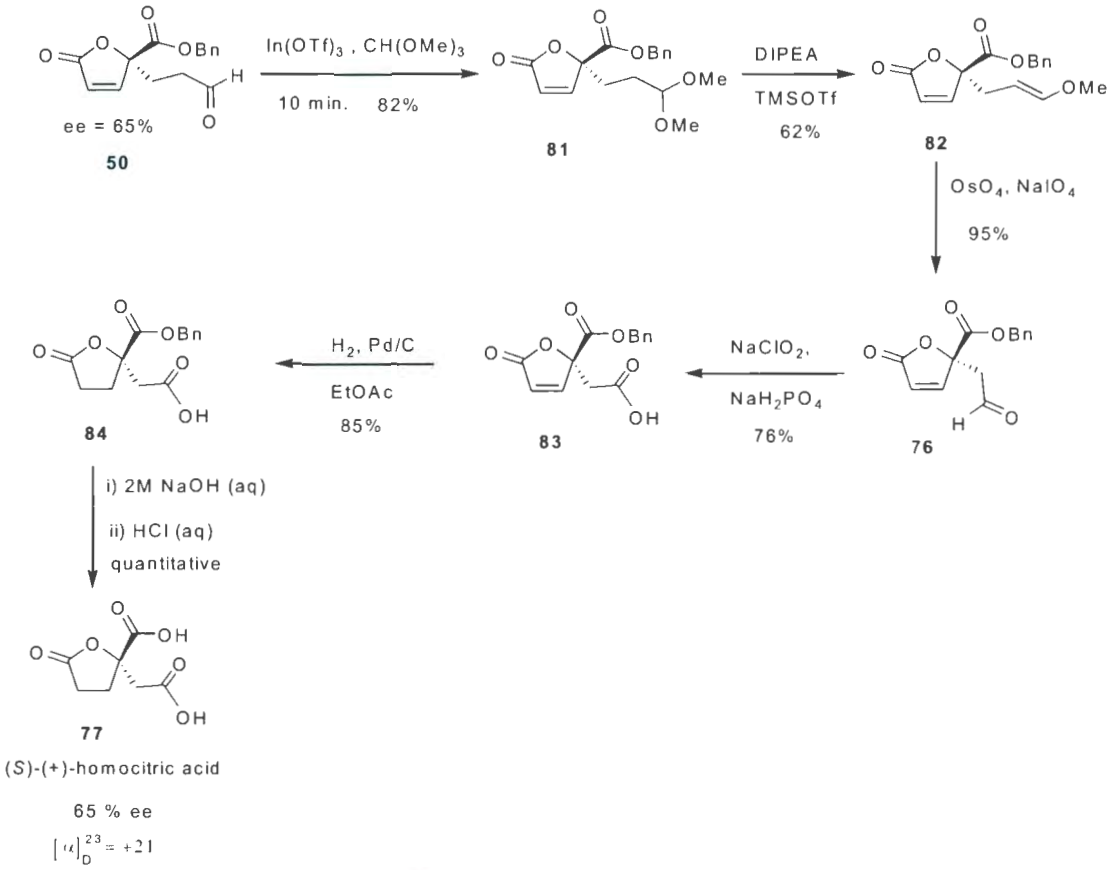
In the present study, aldehyde **50** in 65% ee, obtained from the organocatalytic reaction (Entry 8, Table 4), was employed as the starting material. The first attempt at the dehomologation **50** is shown in Scheme 18.



Scheme 18: Dehomologation of aldehyde **50**.

Singaram's method[41] which relies on enamine oxidation as the key step was chosen. Unfortunately, although the enamine **79** could be obtained, further oxidation with $KMnO_4$ adsorbed on alumina was unsuccessful.

As an alternative, it was decided to convert **50** to its enol ether and to oxidize the enol ether for the dehomologation. To this effect, aldehyde **50** was treated with methyl orthoformate in the presence of a catalytic amount on indium triflate for 10 min at room temperature[42] to obtained dimethyl acetal **81** in 82% yield (Scheme 19). Dimethyl acetal **81** was converted in to the enol ether **82** by using Gassman's methodology.[43]



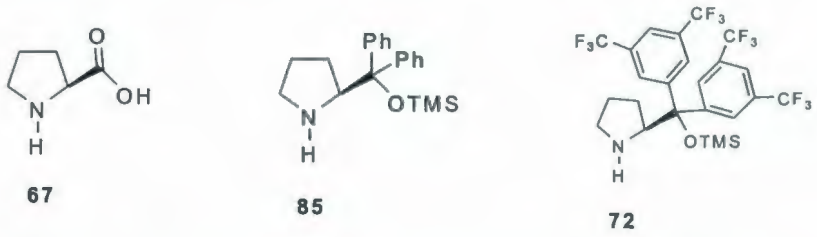
Scheme 19: Synthesis of (*S*)-(+)-homocitric acid (**77**).

Acetal **81** was converted to the enol ether **82** by treatment with diisopropyl ethylamine and TMSOTf. Compound **82** was obtained as a 2:1 mixture of isomers (^{1}H NMR) in 62% yield. Chemoselective oxidation of enol ether **82** with osmium tetroxide/$NaIO_4$ in water gave 95% yield of the dehomologated aldehyde **76**, which was oxidized to carboxylic acid **83** using Pinnic oxidation[44] conditions. Compound **83** was hydrogenated to reduce the double bond in the lactone ring and to effect debenzylation. However, hydrogenation at atmospheric pressure reduced only the double bond and the benzyl ester remained

intact. Changing the solvent from ethyl acetate to methanol had no apparent beneficial effect. Therefore, the benzyl ester in compound **84** was hydrolyzed with aqueous 2.0 M NaOH. Acidic work-up gave homocitric acid in quantitative yield. The naturally-occurring homocitric acid, (*R*)-homocitric acid, has a negative specific rotation.[45] The specific rotation obtained for the synthesized homocitric acid is +21, (c=1), which indicates that it is (*S*)-(+)-homocitric acid. Therefore, aldehyde **50** also has the '*S*' configuration, which is required for the synthesis of the natural isomer of (+)-lycoperdic acid.

Organocatalytic α-amination of aldehyde 50

As discussed in the proposed retrosynthesis of lycoperdic acid (Scheme 10), α-amination of aldehyde **50** would provide a potential intermediate to lycoperdic acid. In this context we examined the organocatalytic α-amination of **50** with selected enamine forming catalysts (Figure 6) and dialkyl azodicarboxylates as the amination reagents. Of these catalysts, L-proline (**67**) is commercially available, catalysts **85** and **72**, were prepared as discussed earlier.



67 **85** **72**

Figure 6: Catalysts used for α-amination of aldehyde **50**.

An alternative approach to the required α-amino aldehyde derivative could involve an iminium ion-catalyzed addition of triisopropyl silyloxy furan to an α-amino acrolein derivative. Both of these approaches are shown in Figure 7.

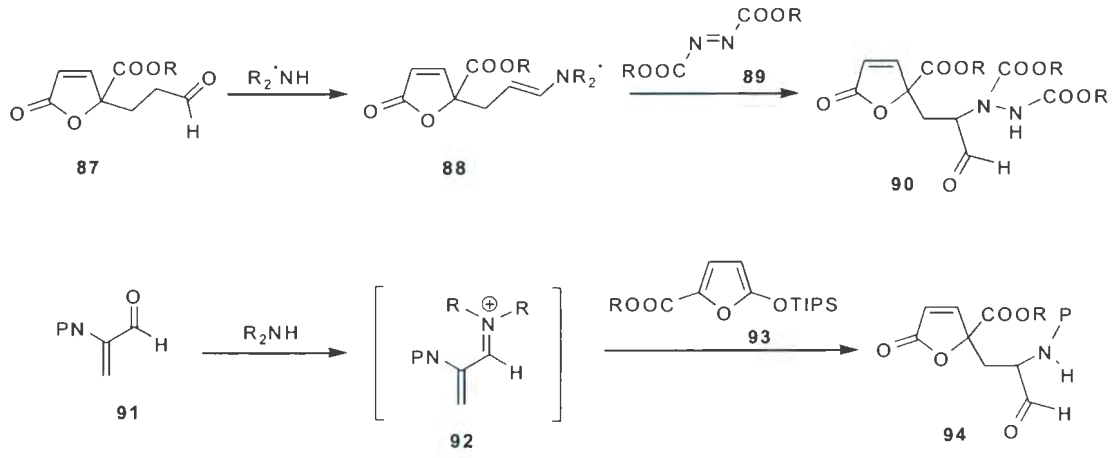
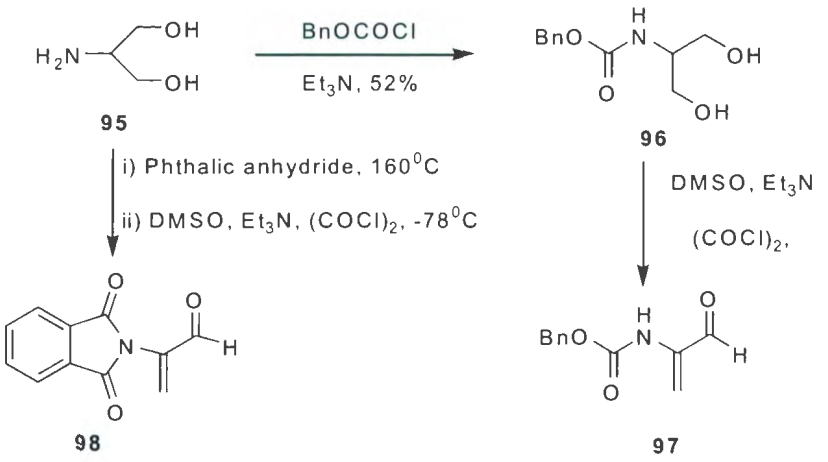


Figure 7: Organocatalytic approaches to potential intermediate to lycoperdic acid.

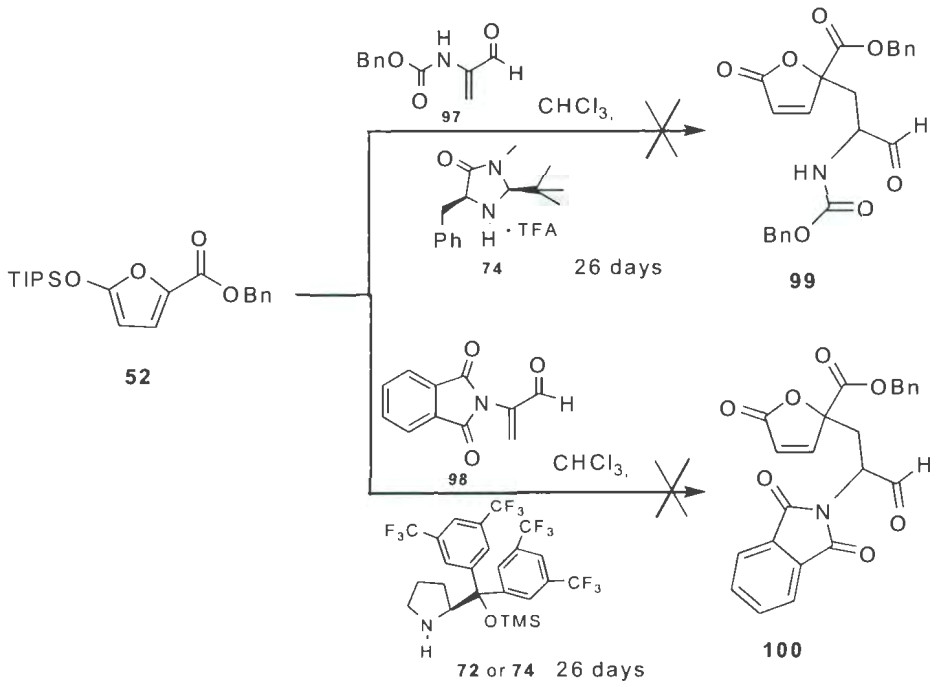
Initially, we examined the iminium ion-catalyzed approach with the α-amino acrolein derivative **97** and **98** which were prepared from serinol (**95**) as shown in Scheme 20.



Scheme 20: Preparation of compound **97** and **98**.

The primary amine in serinol (**95**) was protected with benzyl chloroformate in the presence of triethylamine to form 52% of compound **96**, which was oxidized with oxalyl chloride and DMSO in the presence of triethylamine to provide benzyl-1-formylvinyl carbamate (**97**) in (Scheme 20).[46] Compound **98** was prepared in a similar manner by treating serinol (**95**) with phthalic anhydride followed by oxidation.[47]

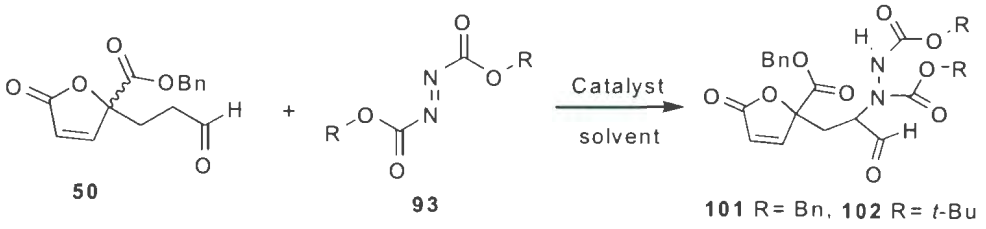
Unfortunately, both **97** and **98** were completely unreactive in attempted iminium ion-catalyzed conjugate addition reactions with **51** (Scheme 21). Presumably, the electron-donating α-amino substituent reduces the electrophilicity of the α,β-unsaturated aldehyde. Consequently, the anticipated products **99** and **100** could not be obtained.



Scheme 21: Organocatalytic α-amination.

We therefore examined the alternative approach of an organocatalytic α-amination of aldehyde **50** with azodicarboxylates. The results from these studies are summarized in Table 9.

Table 9: Organocatalytic α-amination:



All the reactions were performed using 1 equiv. of aldehyde **50**, 1.1 equiv. of dialkyl azodicarboxylate and 20 mol% catalyst. Except noted as a footnote.

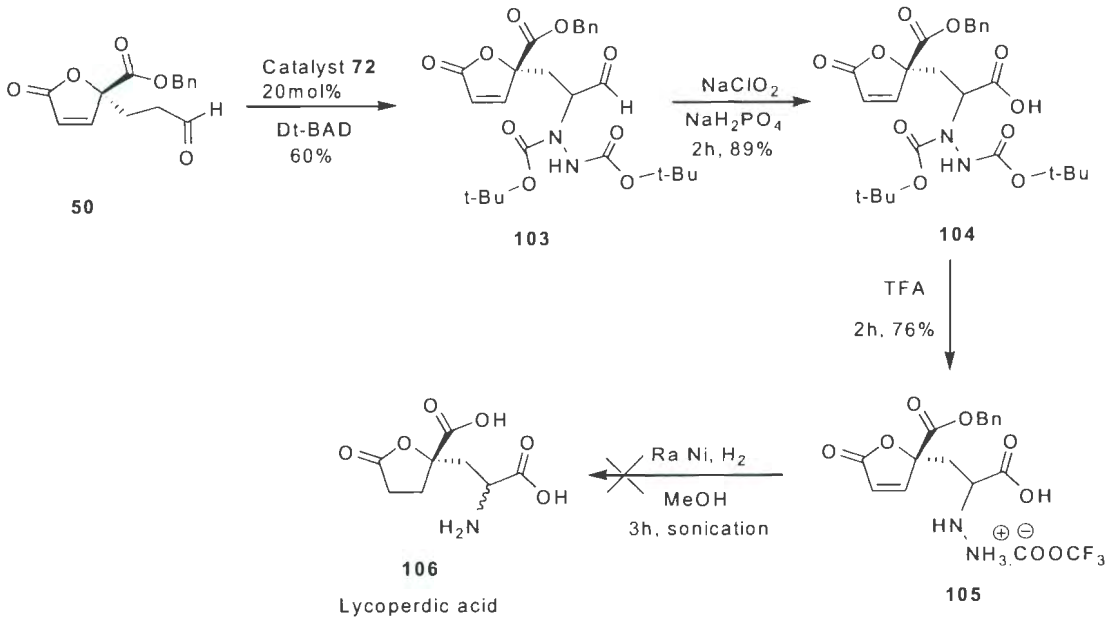
Entry	Catalyst[a]	R	Solvent	Time	% yield[b]
1	**85**	Bn	DCM	72 h	13
2	**85**	Bn	$CHCl_3$	48 h	0
3	**85**	Bn	CH_3CN	48 h	decomposition
4	**85**	Bn	MeOH	8 h	5
5	**72**	Bn	DCM	72 h	0
6	**72**	Et	DCM	17 h	50
7	**72**	t-Bu	DCM	48 h	53
8	**72**	t-Bu	$CHCl_3$	6 h	67

[a]20mol% catalyst. [b]isolated yields.

Reaction of aldehyde **50** with dibenzyl azodicarboxylate **87** (Table 10) in dichloromethane and methanol solvents (Entry 1 and Entry 4) gave very low yield of α-amino aldehyde **101** which could not be isolated pure. The reaction with catalyst **85** did

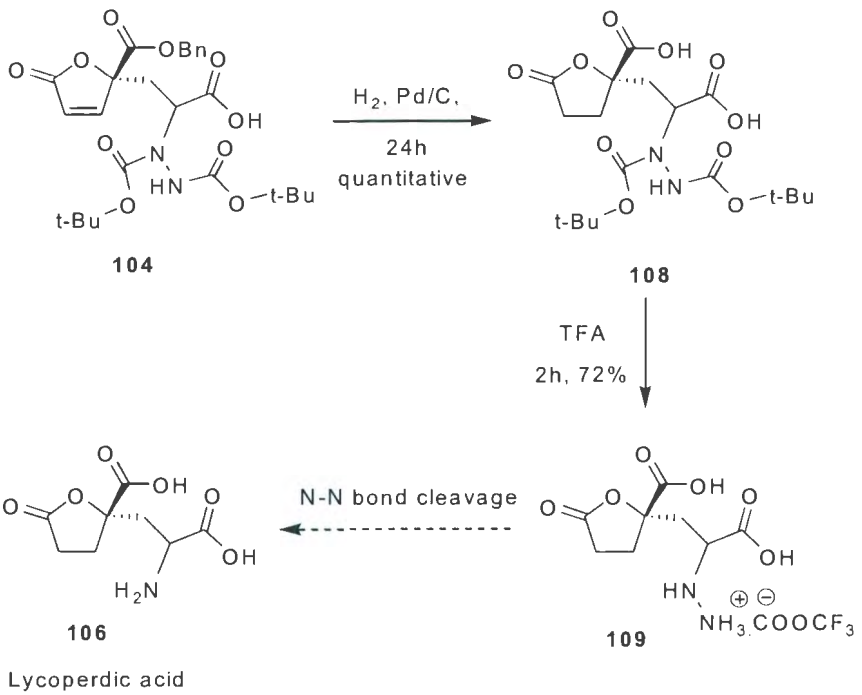
not work in chloroform (Entry 2) and in acetonitrile (Entry 3) decomposition of the aldehyde was observed. Reaction using catalyst **72** with dibenzyl azodicarboxylate in dichloromethane (Entry 5) was not successful. Using diethyl azodicarboxylate instead of dibenzyl azodicarboxylate in dichloromethane (Entry 6) gave a good yield (50%) of the required product. However, the purity of the product was not satisfactory (despite chromatography). The use of di-*tert*-butyl azodicarboxylate in dichloromethane (Entry 7) provided the required product in 53% yield and good purity. The use of chloroform as solvent was beneficial (Entry 8) in the presence of catalyst **72** and the required product **102** was obtained in 67% yield in only 6 h. The stereochemistry of the amination reaction was not determined during this study.

The aldehyde **103** (Scheme 24) was oxidized to the corresponding acid **104** by Pinnic oxidation.[48] Thus, **103** was treated with sodium chlorite in a solution of 2-methyl-2-butene and *t*-butanol in the presence of aqueous sodium dihydrogen phosphate to provide 67% yield of acid **104** in 5 h. Compound **104** was treated with TFA for Boc removal to provide compound **105** in 76% yield. Unfortunately, attempted hydrogenation of **105** (Ra-Ni/H_2 with sonication) led to unidentifiable products and **106** was not obtained.



Scheme 20: Towards the synthesis of lycoperdic acid **106**.

It was therefore decided to change the sequence of reactions. First, the double bond was hydrogenated and the benzyl ester in compound **104** was hydrogenolyzed (H_2, 1 atm, Pd/C) to form diacid **108** (Scheme 21) in quantitative yield, in 24 h. Compound **108** was treated with TFA in dichloromethane for 2 h to obtain the deprotected compound **109** as a hydrazine salt in 72% yield.

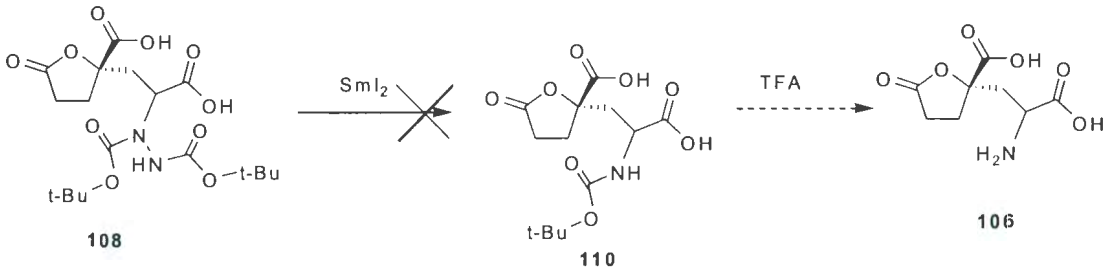


Scheme 21: Towards the synthesis of lycoperdic acid **106**.

With the hydrazine salt **109** in hand; lycoperdic acid was just one step away. Several methods for N-N bond cleavage in hydrazines have been reported in the literature. For example, reductive cleavage has been achieved with hydrogen in the presence of Raney-Ni,[49] or with Pd/C, at high pressure;[50] with Zn/AcOH,[51] with samarium diiodide;[52] with hydrogen and PtO_2,[53] with hydrogen and $Pd(OH)_2$,[54] and with dissolving metal reduction (Li/NH_3,).[55]

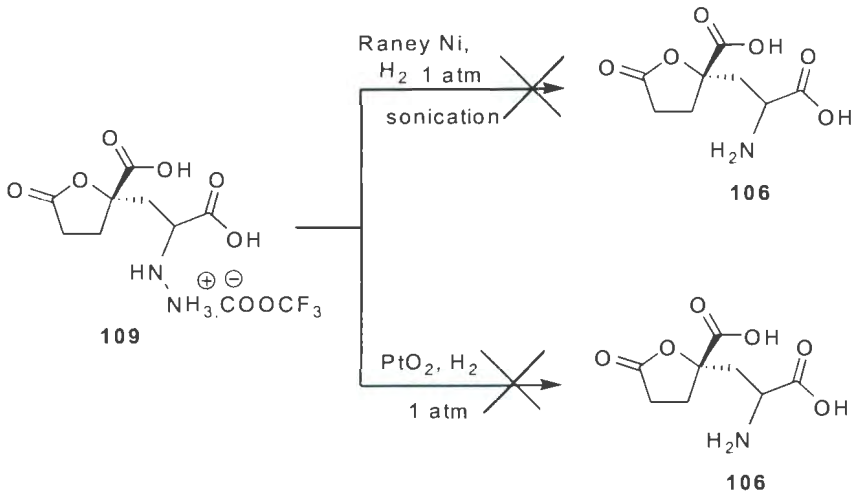
Samarium diiodide was first chosen to react with diacid **108** to obtain compound **110** (Scheme 22), which on Boc deprotection, would provide lycoperdic acid.

Unfortunately, compound **108** was inert to samarium diiodide, and no N-N bond cleavage was observed (Scheme 22).



Scheme 22: Samarium diiodide-mediated N-N bond cleavage.

Attempted reductive cleavage of **109** with Ra-Ni or PtO_2 as catalysts was unsuccessful (Scheme 24). No further studies with **109** were conducted.

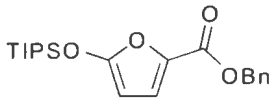


Scheme 24: Attempted reductive cleavage of the N-N bond in **109**.

Conclusion

Extensive studies were conducted on the organocatalytic conjugate addition of silyloxy furan nucleophiles to acrolein. The highest enantiomeric excess that was obtained (90%) is the best obtained to date, using acrolein as an electrophile. Organocatalytic α-amination of the conjugate addition product was also achieved and an advanced intermediate to (*S*)-lycoperdic acid has been prepared. A short synthesis of (+)-homocitric acid lactone involving organocatalysis was also achieved.

Experimental



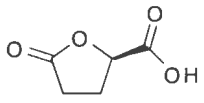
Benzyl-5-triisopropylsiloxy-2-furoate (51): A solution of *sec*-BuLi (12 ml, 11 mmol, 0.9 M solution in cyclohexane) was added dropwise to a stirred solution of (furan-2-yloxy) triisopropylsilane (2.4 g, 10.1 mmol) in 12 ml THF at -78 °C under nitrogen and the reaction was stirred at the same temperature for 1 h. A solution of benzyl chloroformate (1.5 ml, 10.5 mmol) in 13 ml THF (cooled at -78 °C) was added and the mixture was stirred for 90 min and then warmed to room temperature. The mixture was concentrated and the residue was dissolved in ethyl acetate (20 ml). The solution was washed with aqueous saturated $NaHCO_3$ (2 x 10 ml) followed by brine (20 ml). The organic layer was separated, dried over Na_2SO_4 and concentrated. The residue was subjected to flash column chromatography (97:3 hexane:ether). Fractions containing the required product were pooled and concentrated. This material had a volatile impurity which was removed at 120 °C (0.2 mm) to provide 1.5 g (40%) of pure **51** as an orange coloured oil.

IR (neat): 2947, 2869, 1720, 1604, 1531, 1303, 1123 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42-7.31 (m, 5H, Ar*H*), 7.13 (d, 1H, *J* = 3.5, C*H*=CC=O), 5.30 (d, 1H, *J* = 3.5, C*H*=CO), 5.28 (s, 2H, PhCH_2), 1.33-1.26 (sept, 3H, SiC*H*), 1.11 (d, 18H, *J* = 7.5, CH_3CH).

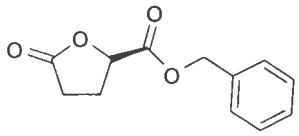
^{13}C NMR (125.77 MHz, $CDCl_3$): δ 159.9 (*C*OSi), 158.4 (*C*=O), 136.43 (*C*C=O), 133.9 (ArC_{ipso}), 128.7 (Ar*C*), 128.3 (Ar*C*), 128.3 (Ar*C*), 122.2 (*C*=CC=O), 87.7 (*C*=CO), 66.0 (Ph*C*), 17.7 (CH_3CH), 12.4 (CH_3*C*H).

HRMS (CI): *m/z* 375.1999 (375.1992 Calc. for $C_{21}H_{31}O_4Si$, M+H).



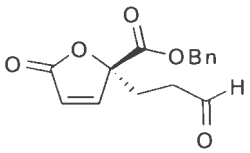
Tetrahydro-5-oxofuran-2-carboxylic acid (55):[29] L-(+)-Glutamic acid (10.0 g, 68 mmol) was dissolved in concentrated HCl (20 ml) and water (40 ml) and the solution was cooled to -10 °C. To this mixture, a solution of $NaNO_2$ (7.0 g, 0.10 mol) in water (20 ml) was added dropwise over a period of 30 min. The mixture was stirred at -10 °C for 1 h and then at room temperature for 18 h. The mixture was then concentrated (below 50 °C) and the residue was dissolved in ethyl acetate (30 mL). The ethyl acetate solution was filtered and the residue was washed with ethyl acetate (20 mL). The organic filtrate was dried (Na_2SO_4) and concentrated to provide 7.4 g (83%) of **55** as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 11.60 (bs, 1H, COO*H*), 5.05-5.02 (dd, 1H, *J* = 8.6, 4.8, C*H*COOH), 2.70-2.63 (m, 1H, COCH_2CH_2), 2.58-2.54 (m, 2H, COCH_2CH_2), 2.36-2.31 (m, 1H, COCH_2CH_2).



Benzyl-tetrahydro-5-oxofuran-2-carboxylate (56): Oxalyl chloride (0.20 ml, 2.2 mmol) was added to a solution of **55** in dichloromethane (3.0 mL) at 0 °C under nitrogen. The reaction mixture was allowed to warm to room temperature, stirred for 2 h and then cooled to 0 °C. Triethylamine (0.31 ml, 2.2 mmol) and benzyl alcohol (0.23 ml, 2.2 mmol) were added and the solution was stirred at room temperature for 24 hours. The mixture was was diluted with dichloromethane (6.0 ml) and the solution was washed with water (2 x 2 ml) followed by aqueous saturated $NaHCO_3$ (2 x 1 ml). The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (3:1 hexane: ethyl acetate) to provide 0.23 g (52%) of **56** as a pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40-7.34 (m, 5H, Ar*H*), 5.26-5.21 (AB system, 2H, *J* = 12.1, PhCH_2O), 4.98-4.96 (dd, 1H, J = 8.3, 4.3 OC*H*), 2.57-2.45 (m, 3H, COCH_2CH_2), 2.34-2.25 (m, 1H, $COCH_2CH_2$).



(*R*)-Benzyl-2-(formylethyl)-2,5-dihydro-5-oxofuran-2-carboxylate (50): To a solution of the imidazolidinone or pyrrolidine catalyst (20 mol%) in chloroform was added acrolein (0.54 ml, 0.80 mmol) at room temperature. The reaction mixture was cooled to

0 °C and compound **51** (0.10 g, 0.27 mmol) and water (21.0 µl, 0.53 mmol) were added. The mixture was warmed room temperature and stirred for 7 d. The mixture was concentrated and the residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate, 7:3) to provide 32 mg (45%) of aldehyde **50** as a gum.

Other reactions of **51** with acrolein (employing different solvents and/or catalysts at selected temperatures) followed the same general procedure described above.

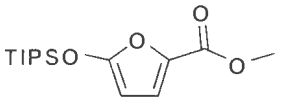
IR (neat): 3092, 2929, 2735, 1768, 1102 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.71 (s, 1H, C*H*O), 7.41 (d, 1H, C*H*=CHC=O, *J* = 5), 7.39-7.32 (m, 6H, Ar*H*), 6.17 (d, 1H, *J* = 5), 5.21 (s, 2H, CH_2Ph), 2.59-2.47 (m, 3H, CH_2CHO, CH_2CH$_2$CHO), 2.30-2.22 (m, 1H, CH_2CH2CHO).

^{13}C NMR (125.77 MHz, $CDCl_3$): δ 199.6 (*C*HO), 171.1 (O*C*=O), 167.1 (*C*O_2Bn), 154.4 (*C*=CC=O), 134.7(ArC_{ipso}), 129.0 (Ar*C*), 129.0 (Ar*C*), 128.6 (Ar*C*), 122.7 (C=*C*C=O), 88.9 (O*C*C=O), 68.5 (*C*H_2Ar), 37.8 (*C*H_2CHO), 27.7 (*C*H_2CH$_2$).

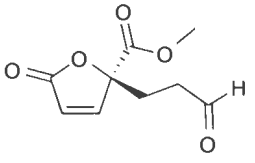
HRMS (CI): *m/z* 275.0917 (275.0919 Calc. for $C_{15}H_{15}O_5$, M+H).

Ee: 90 % (t_R: 51.7 min; t_S: 69.6 min (Chiralpak AS-H, 210 nm, hexanes: iPrOH, 85:15, 1 mL/min).



Methyl-5-triisopropylsilyloxy-2-furoate (64):[30] A solution of *sec*-BuLi (2.8 ml, 1.9 mmol, 0.70 M solution in cyclohexane) was added dropwise to a stirred solution of (furan-2-yloxy) triisopropylsilane (450 mg, 1.9 mmol) in THF (2.0 mL) at -78 °C under nitrogen and the reaction was stirred at the same temperature for an hour. A solution of methyl chloroformate (0.15 mL, 1.9 mmol) was added and the mixture was stirred for 90 min and then warmed to room temperature. The mixture was concentrated and the residue was dissolved in ethyl acetate (20 mL). The solution was washed with aqueous saturated $NaHCO_3$ (2 x 10 mL) followed by brine (10 mL). The organic layer was separated, dried (Na_2SO_4) and concentrated. The residue was purified by distillation to provide 290 mg (53%) of **64** (b.p. 220 °C (0.2 mm of Hg)).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (d, 1H, J = 3.5, C=CHC*H*=CCO), 5.30 (d, 1H, J = 3.5, C=C*H*CH=CCO), 3.82 (s, 3H, OCH_3), 1.34-1.28 (sept, 3H, J = 7.4, C*H*$(CH_3)_2$), 1.11 (d, 18H, J = 7.4, CH$(CH_3)_2$).

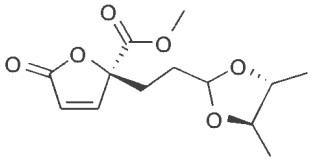


(*S*)-Methyl-2-(2-formylethyl)-2,5-dihydro-5-oxofuran-2-carboxylate (65): This was prepared from **7** (150 mg, 0.50 mmol), acrolein (0.10 ml, 1.5 mmol) and catalyst **59** (24 mg, 0.10 mmol) and TFA (76 µl, 0.10 mmol) in THF (2.0 mL) and water (18 µl, 1.0

mmol). The reaction was stirred for 4 days and 17 hours to provide after purification by flash chromatography on silica gel (hexanes:ethyl acetate 40:60) 30 mg (30%) of the aldehyde **65**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.77 (s, 1H, C*H*O), 7.44 (d, 1H, *J* = 5.6, COCH=C*H*), 6.20 (d, 1H, J = 5.59, COC*H*=CH), 3.82 (s, 3H, $COOCH_3$), 2.63-2.52 (m, 3H, CH_2CH_2CHO), 2.33-2.27 (m, 1H, CH_2CH_2CHO).

An accurate enantiomeric excess determination was not possible for this aldehyde due to a lack of resolution of the enantiomers on chiral columns. Hence, it was converted to the acetal with (2*R*,3*R*)-2,3-butanediol and this acetal was analyzed for enantiomeric excess.



(*S*)-Methyl-2,5-dihydro-2-(2-((4*R*,5*R*)-4,5-dimethyl-1,3-dioxolan-2-yl)ethyl)-5-oxofuran-2-carboxylate (66): A solution of the aldehyde **65** (0.01 g, 0.05 mmol), (2*R*,3*R*)-2,3-butanediol (5.8 µl, 0.07 mmol) and *p*-toluene sulphonic acid (1.9 mg, 0.01 mmol) in benzene (1.0 mL) was heated to reflux for 1 h under nitrogen. The mixture was cooled to ambient temperature and diluted with ethyl acetate. The resulting solution was washed with aqueous $NaHCO_3$, dried (Na_2SO_4) and concentrated to provide 15 mg (quantitative) of acetal **66**.

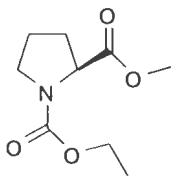
Enantiomeric excess: 59% (Chiralcel AS-H column, hexanes/isopropyl alcohol 96/4; 210nm; 1ml/min.; t_{minor} = 27.28 min.; t_{major} = 29.32 min.).

IR (neat): 2974, 1773 (br), 1446, 1385, 1235, 1111, 1001, 907 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, 1H, *J* = 7.8, COCH=C*H*), 6.16 (d, 1H, *J* = 7.8, COC*H*=CH), 5.06 (t, 1H, J = 4.3, C*H*CH_2), 3.79 (s, 3H, OCH_3), 3.64-3.54 (m, 2H, C*H*CH_3), 2.36-2.29 (m, 1H, CH_2CH_2CH), 2.09-2.03 (m, 1H, CH_2CH_2CH), 1.72-1.61 (m, 2H, CH_2CH_2CH), 1.27 (d, 3H, *J* = 5.7, CHCH_3), 1.22 (d, 3H, *J* = 5.7, CHCH_3).

^{13}C NMR (125.77 MHz, $CDCl_3$): δ 171.4 (O*C*C=C), 168.2 (*C*O_2CH_3), 154.7 (OCC=*C*), 122.52 (OC*C*=C), 102.1 (CH_2CH_2CH), 89.7 (C_{quat}), 80.1 (*C*HCH_3), 78.6 (*C*HCH_3), 53.5 (OCH_3), 29.8 (CH_2), 28.5 (CH_2), 17.4 (CH_3), 17.0 (CH_3).

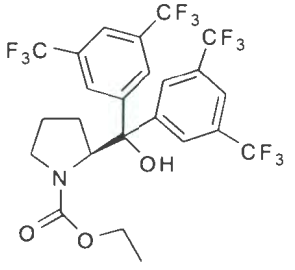
HRMS (CI pos.): m/z 271.1176 (271.1182 calc for $C_{13}H_{19}O_6$ (M+H)).



(*S*)-Ethyl methyl pyrrolidine-1,2-dicarboxylate (68):[34] L-proline (1.0 g, 8.7 mmol) was dissolved in anhydrous methanol (ACS grade, 14 ml) under nitrogen. Anhydrous K_2CO_3 (1.2 g, 8.7 mmol) was added, followed by dropwise addition ethyl chloroformate (1.8 ml, 19 mmol) over a period of 6 min. at room temperature. The reaction mixture was stirred for 17 h. at ambient temperature. The methanol was removed under reduced pressure and

water (20 ml) was added and the aqueous solution was extracted with chloroform. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to provide 1.8 g (99%) of **68** as a colourless liquid.

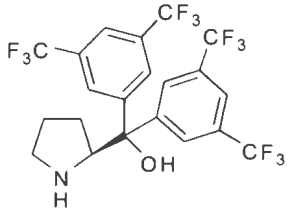
^{1}H NMR (500 MHz, $CDCl_3$): Approximately 1:1 mixture of rotamers: δ 4.38-4.37 (dd, 1H, J = 8.7, 3.5, NC*H*), 4.30 (dd, 1H, J = 8.6, 3.9, NC*H*), 4.25-4.20 (m, 3H, OCH_2CH$_3$), 4.11-4.04 (m, 1H, OCH_2CH$_3$), 3.74 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.59-3.42 (m, 4H, NCH_2), 2.28-2.15 (m, 2H, CH_2CH$_2$), 2.03-1.84 (m, 6H, CH_2CH_2), 1.27 (t, 3H, J = 7.1, CH$_2$CH_3), 1.20 (t, 3H, J = 7.1, OCH$_2$CH_3).



(*S*)-Ethyl 2-(bis(3,5-bis(trifluoromethyl)phenyl)(hydroxy)methyl)pyrrolidine-1-carboxylate (70):[34] A solution of **68** (0.20 g, 1.0 mmol) anhydrous THF (2.0 mL) under nitrogen was cooled to 0 °C and 3,5-bis-(trifluoromethyl)phenyl magnesium bromide (**69**, 8.0 mL of 0.50 M soln. in THF, 4.0 mmol) was added. The mixture was stirred at 0 °C for 2.5 h and aqueous saturated NH_4Cl (2.0 mL) was added. The mixture was warmed to ambient temperature, the organic layer was separated and the aqueous layer was extracted with chloroform. The combined organic layers were washed with brine, dried (Na_2SO_4)

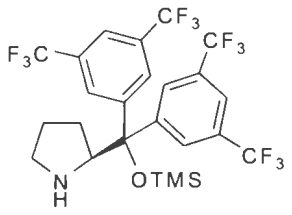
and concentrated. The residue was purified by flash chromatography on silica gel (initial elution with 3 column volumes of hexanes to remove non-polar impurities, followed by elution with 9:1 hexanes:ethyl acetate) to provide 460 mg (77%) of **70** as a brown solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (s, 1H, Ar*H*), 7.86 (s, 3H, Ar*H*), 7.82 (s, 2H, Ar*H*), 4.88-4.85 (m, 1H, NC*H*), 4.20-4.15 (m, 1H, OCH_2CH_3), 4.14-4.08 (m, 1H, OCH_2CH_3), 3.56-3.54 (m, 1H, NCH_2), 2.97-2.92 (m, 1H, NCH_2), 2.15-2.05 (m, 1H, CH_2CH_2), 1.85-1.75 (m, 1H, CH_2CH_2), 1.67-1.57 (m, 1H, CH_2CH_2), 1.22 (t, 3H, J = 7.1, OCH_2CH_3), 1.05-0.98 (m, 1H, NCH_2CH_2).



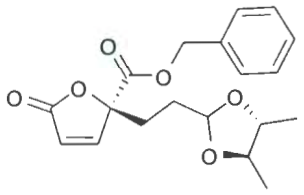
Bis(3,5 bis(trilfuoromethyl)phenyl)((S)-pyrrolidin-2-yl)methanol (71):[34] To a solution of **70** (0.24 g, 0.39 mmol) in methanol (3.0 mL, ACS grade) was added KOH (0.56 g, 10 mmol).The mixture was heated at reflux for 4.5 h, then the methanol was removed under reduced pressure and water (2.0 mL) was added. The aqueous solution was extracted with chloroform, the combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (5:1 hexane:ethyl acetate) to obtain 200 mg (98%) of **71** as a brown solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (s, 2H, Ar*H*), 7.96 (s, 2H, Ar*H*), 7.77 (d, 2H, *J* = 5, Ar*H*), 4.34 (t, 1H, J = 7.6, NC*H*), 3.10-3.02 (m, 2H, NCH_2), 1.83-1.75 (m, 2H, CH_2CH_2), 1.62-1.49 (m, 2H, NCH_2CH_2).



(*S*)-2-(Bis-(3,5-bis(trilfuoromethyl)phenyl)-trimethylsilanyloxy-methyl)-pyrrolidine (72):[35] To a solution of **71** (0.200 g, 0.39 mmol) in anhydrous dichloromethane (6.0 mL) under nitrogen was added triethylamine (0.07 ml, 0.50 mmol). The solution was cooled to 0 °C and trimethylsilyltriflouromethanesulfonate (91.0 µl, 0.50 mmol) was added. The mixture was stirred for 5 min. at 0 °C, warmed to room temperature, and stirred for 1.5 hours. Water (8.0 mL) was added, the phases were separated, and the aqueous phase was extracted with dichloromethane. The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (90:10 ethyl acetate:hexane) to provide 0.190 g (83%) of **71** as a colourless gum.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (s, 2H, Ar*H*), 7.84 (d, 2H, *J* = 5 Ar*H*), 7.76 (s, 2H, Ar*H*), 4.21 (t, 1H, *J* = 7.3, NC*H*), 2.95-2.90 (m, 1H, NCH_2), 2.59-2.54 (m, 1H, NCH_2), 1.73-1.66 (m, 1H, CH_2CH_2), 1.57-1.46 (br m, 2H, CH_2CH_2, N*H*), 1.48-1.38 (m, 1H, CH_2CH_2), 1.15-1.07 (m, 1H, CH_2CH_2), -0.08 (s, 9H, OSi(CH_3)$_3$).



(*S*)-Benzyl-2,5-dihydro-2(2-((4*R*,5*R*)-4,5-dimethyl-1,5-dioxolane-2-yl)ethyl)-5-oxofuran-2-carboxylate (73): A solution of the aldehyde (**50**) (30 mg, 0.09 mmol), (2*R*,3*R*)-2,3-butanediol (0.01 ml, 0.14 mmol) and *p*-toluenesulfonic acid (5.0 mg, 0.03 mmol) in dry benzene (3.0 mL) was heated to reflux under nitrogen for 1 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and the solution was washed with aqueous saturated $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated to provide 36 mg (97%) of **73** as a colourless oil.

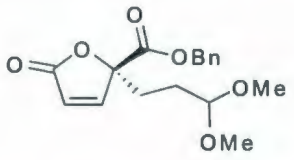
IR (neat): 3523, 2931, 1773, 1499, 1456, 1177, 1098, 906.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, 1H, *J* = 5, C*H*=CHC=O), 7.38-7.31 (m, 5H, Ar*H*), 6.15 (d, 1H, *J* = 5, CH=C*H*C=O), 5.2 (s, 2H, CH_2Ph), 5.04 (t, 1H, *J* = 5, C*H*$(OCH_3)_2$), 3.61-3.52 (m, 2H, OC*H*CH_3) 2.37-2.30 (m, 1H, CH_2), 2.09-2.02 (m, 1H, CH_2), 1.69-1.60 (m, 2H, CH_2), 1.25 (d, 3H, *J* = 5, CH_3) 1.25 (d, 3H, *J* = 5, CH_3).

^{13}C NMR (125.77 MHz, $CDCl_3$): δ 171.4 (O*C*OC=C), 167.6 (OC*C*=O), 154.6 (*C*=CC=O), 134.9 (Ar*C*ipso), 128.9 (Ar*C*), 128.5 (Ar*C*), 122.6 (C=*C*C=O), 102.0 (O*C*C=O) 89.7 (CH_2*C*H), 80.1 (*C*HCH_3), 78.6 (*C*HCH_3), 68.3 (*C*H_2Ph), 29.7 (*C*H_2), 28.6 (*C*H_2), 17.4 (*C*H_3), 17.0 (*C*$H_3)_2$.

LCMS (CI positive): *m/z* 347.1 (M+H).

HPLC: t_S: 37.4 min; t_R: 42.3 min (Chiralpak AS-H, 210 nm, hexanes/iPrOH, 96/4, 1 mL/min).



(*R*)-Benzyl-2,5-dihydro-2-(3,3-dimethoxypropyl)-5-oxofuran-2-carboxylate (81): Indium triflate (1.7 mg, $3.0x10^{-3}$ mmol) was added in two portions to a solution of the aldehyde **50** (0.17 g, 0.60 mmol) and trimethyl orthoformate (0.13 ml, 1.2 mmol) in dichloromethane (8.0 ml) at room temperature. The reaction mixture was stirred for 4 min., a second portion of indium triflate (1.7 mg, $3.0x10^{-3}$ mmol) was added and stirring was continued further for 6 min. The reaction mixture was then filtered through a plug of neutral alumina and the plug was washed with dichloromethane. The filtrate was concentrated to provide 160 mg (83%) of **81** as a colourless oil. This was pure by ^{1}H NMR and was used further without purification.

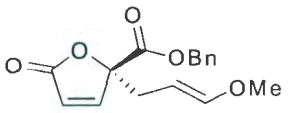
IR (neat): 2932, 1773, 1456, 1128, 1057 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.4 (d, 3H, J = 3.1, C*H*=CHC=O), 7.4-7.3 (m, 6H, Ar*H*), 6.16 (d, 1H, J = 3.1, CH=C*H*C=O), 5.21 (s, 2H, CH_2Ar), 4.32 (t, 1H, J = 5, C*H*$(OCH_3)_2$), 3.28 (s, 3H, OCH_3), 3.27 (s, 3H, OCH_3), 2.30-2.24 (m, 1H, $CH_2C(OCH_3)_2$), 2.0-1.9 (m, 1H,$CH_2C(OCH_3)_2$), 1.7-1.5 (m, 2H, CH_2CH_2).

^{13}C NMR (125.77 MHz, $CDCl_3$): δ 171.4 (C=C*C*O), 167.57 (*C*O_2CH2Ph), 154.6 (*C*H=CHCO), 134.8 (PhCipso), 129.0 (Ph*C*), 128.9 (Ph*C*), 124.5 (Ph*C*), 122.6

(CH=*C*HCO), 103.7 (*C*H(OCH$_3$)$_2$), 89.7 (O*C*CO$_2$CH$_2$Ph), 68.3 (*C*H$_2$Ph), 53.5 (O*C*H$_3$), 53.1 (O*C*H$_3$), 30.7 (CH$_2$*C*H(OCH$_3$)$_2$), 26.8 (*C*H$_2$CH(OCH$_3$)$_2$).

HRMS (CI): *m/z* 320.1255 (320.1260 Calc. for $C_{17}H_{20}O_6$, M+).



(*R*)-Benzyl 2,5-dihydro-2-((*E*)-3-methoxyallyl)-5-oxofuran-2-carboxylate (82):

Dimethyl acetal **81** (150 g, 0.47 mmol) was dissolved in dichloromethane (0.80 ml) and *N*,*N*-diisopropyl ethylamine ($9.7x10^{-2}$ ml, 0.56 mmol) was added at room temperature. The reaction mixture was cooled to -20 °C and TMSOTf ($9.3x10^{-2}$ ml, 0.52 mmol) was added dropwise. The reaction was warmed to room temperature and stirred for 2.5 h after which it was concentrated and filtered through a short silica gel column (hexanes:ethyl acetate, 7:3). The filtrate was concentrated to provide 84 mg (62%) of **82** as a 2:1 mixture of isomers.

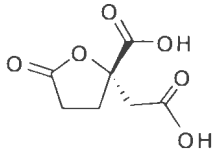
IR (neat): 2936, 1768, 1655, 1456, 1213, 1107, 1027, 922 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): Major isomer: δ 7.40 (d, 1H, *J* = 5, C*H*=CHC=O), 7.36-7.32 (m, 5H, Ar*H*), 6.33 (d, 1H, *J* = 12.7, CH=C*H*OMe), 6.16 (d, 1H, *J* = 5.6, CH=C*H*C=O), 5.2 (m, 2H, OC*H*$_2$Ph), 4.54-4.49 (m, 1H, C*H*=CHOMe), 3.43 (s, 3H, OC*H*$_3$), 2.78-2.73 (dd, 1H, *J* = 14, 8, C*H*$_2$C=CHOMe), 2.58-2.54 (dd, 1H, *J* = 14, 7, C*H*$_2$C=CHOMe). Visible peaks of minor isomer: δ 6.12 (d, 1H, *J* = 5.6, CH=C*H*C=O),

5.99 (d, 1H, J = 7.3, CH=C*H*OMe), 4.24-4.2 (q, 1H, J = 7.3, C*H*=CHOMe), 3.55 (s, 3H, OCH_3), 2.91-2.86 (dd, 1H, J = 7.3, 14.5, CH_2), 2.83-2.80 (dd, 1H, J = 7.3, 14.5, CH_2C=CHOMe).

^{13}C NMR (125.77 MHz, $CDCl_3$): δ 171.4 (C=C*C*O), 167.3 (*C*O_2CH2Ph), 154.4 (*C*=CCO), 151.7 (C=*C*OMe), 150.2 (Ph*C*ipso), 134.9 (Ph*C*), 128.9 (Ph*C*), 128.6 (Ph*C*), 122.8 (C=*C*CO), 93.1 (*C*=COMe), 90.2 (O*C*CO_2Bn), 68.1 (*C*H_2Ph), 56.1 (C=CO*C*H_3), 35.0 (*C*H_2C=CHOMe). Visible peaks of the minor isomer: δ 171.7 (C=C*C*O), 167.5 (*C*O_2CH2Ph), 154.6 (*C*=CCO), 121.9 (Ph*C*), 128.8 (Ph*C*), 128.8 (Ph*C*), 128.4 (*C*Ph), 122.2 (C=*C*CO), 96.5 (*C*=COMe), 89.9 (O*C*CO_2Bn), 68.1 (*C*H_2Ph), 59.9 (C=CO*C*H_3), 30.5 (*C*H_2C=CHOMe).

HRMS: (CI): m/z 288.1000 (288.0998 Calc. for $C_{16}H_{16}O_5$, M+).



(*S*)-Homocitric acid (77): A solution of osmium tetroxide (4% in water, 0.09 ml, $1.4x10^{-2}$ mmol) was added to a stirred solution of the enol ether **82** (0.08 g, 0.28 mmol) in acetone (4.3 ml) and water (0.50 ml). The mixture was stirred for 10 min. and sodium periodate (0.12 g, 0.55 mmol) was added. The mixture was stirred for 20 min. and filtered through a pad of celite. The celite was washed with acetone and the filtrate was concentrated to provide an aqueous solution which was extracted with ethyl acetate (3 x 5 ml). The combined organic layers were dried (Na_2SO_4) and concentrated to provide 64

mg (95%) of **(*R*)-benzyl-2-(formylmethyl)-2,5-dihydro-5-oxofuran-2-carboxylate (76)** as a gum. This was used further without purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.71 (s, 1H, C*H*O), 7.56 (d, 1H, *J* = 5.6, C*H*=CHCO), 7.38-7.30 (m, 5H, Ar*H*), 6.24 (d, 1H, *J* = 5.6, CH=C*H*CO), 5.24-5.18 (AB, 2H, *J* = 15.0, OCH_2Ph), 3.23-3.13 (AB, 2H, *J* = 20.0, CH_2CHO).

The aldehyde **76** (0.06 g, 0.26 mmol) was dissolved in *t*-butanol (5.2 ml) and 2-methyl-2-butene (0.55 ml of a 2.0 M solution in THF, 1.1 mmol). To this was added a solution of $NaClO_2$ (0.07 g, 0.79 mmol) and NaH_2PO_4 (0.03 g, 0.28 mmol) in water (1.3 ml). The mixture was stirred at room temperature for 3 hours and concentrated. The aqueous solution obtained was extracted with ether (3 x 5 ml). The ether layer was separated and the aqueous layer was cooled (<5 °C) and acidified (0.50 M aqueous HCl, 3.0 ml) and the acidic solution was extracted with ether (3 x 5 mL). The combined extracts were dried (Na_2SO_4) and concentrated to provide 64 mg (95%) of the acid **2-((*R*)-2-((benzyloxy)carbonyl)-2,5-dihydro-5-oxofuran-2-yl)acetic acid (83)**. This was used further without purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.0-8.0 (br. 1H, CO_2H), 7.56 (d, 1H, *J* = 5.6, COCH=C*H*), 7.37-7.29 (m, 5H, Ph*H*), 6.24 (d, 1H, *J* = 5.6, COC*H*=CH), 5.22 (s, 2H, PhCH_2O), 3.20-3.05 (AB, 2H, *J* = 16.9, CH_2COOH).

The acid **83** (0.05 g, 0.17 mmol) was dissolved in ethyl acetate (3.0 ml), Pd/C (10 %, 10 mg) was added and the mixture was stirred under hydrogen at atmospheric pressure for

48 h. The reaction mixture was filtered through celite, the celite was washed with ethyl acetate (10 mL) and the combined filtrates were concentrated to provide 40 mg (85%) of **2-((*S*)-2-((benzyloxy)carbonyl)-tetrahydro-5-oxofuran-2-yl)acetic acid (84)**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39-7.33 (m, 5H, Ar*H*), 5.24 (AB, 2H, *J* = 12, OCH_2Ph), 3.19 (d, 1H, *J* = 17.1, CH_2COOH), 3.04 (d, 1H, *J* = 17.1, CH_2COOH), 2.65-2.50, (m, 3H, CH_2CH_2), 2.36-2.29 (m, 1H, COCH_2CH_2).

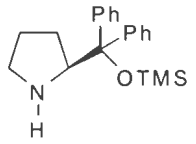
The acid **84** (38 mg, 0.14 mmol) was dissolved in THF (0.50 mL), aqueous NaOH (2.0 M, 0.50 mL) was added and the mixture was stirred at rt for 15 h. The THF was removed under reduced pressure and the resulting aqueous solution was extracted once with dichloromethane. The aqueous solution was cooled, acidified with aqueous HCl (0.50 M) to pH 1 and extracted with dichloromethane (3 x 5 ml). The combined extracts were dried (Na_2SO_4) and concentrated to provide 25 mg (97%) of (*S*)-homocitric acid (**77**).

IR (solid): 3500-2800 (br), 1717, 1416, 1170, 1064, 942, 870 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.39 (d, 1H, J = 17.5, CH_2COOH), 3.05 (d, 1H, J = 17.5, CH_2COOH), 2.75-2.69 (m, 2H, CH_2C=O), 2.60-2.54 (m, 1H, CH_2CH_2), 2.47-2.4 (m, 1H, CH_2CH_2).

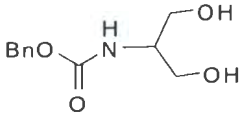
MS (APCI negative): *m/z* 187 (M-H); (APCI positive): *m/z* 189 (M+H).

$[\alpha]_D^{20}$: + 21.0 (c 1, H_2O).



(S)-2-(Diphenyl-trimethylsilanyloxymethyl)-pyrrolidine (85):[35] To a solution of diphenyl ((*S*)-pyrrolidin-2-yl)methanol (0.22 g, 0.84 mmol) in dichloromethane (7.0 ml) under nitrogen was added triethylamine (0.15 ml, 1.0 mmol). The mixture was cooled to 0 °C, TMSOTf (0.20 ml, 1.1 mmol) was added and the mixture was allowed to warm to room temperature and stirred for 1.5 h. Water (5.0 mL) was added, the mixture was extracted with dichloromethane, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (5:1 hexane:ethyl acetate) to provide 220 mg (82%) of **85** as a yellow oil.

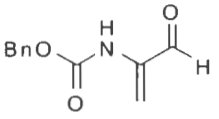
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, 2H, *J* = 7.2, Ar*H*), 7.36 (d, 2H, *J* = 7.3, Ar*H*), 7.29-7.19 (m, 6H, Ph*H*), 4.03 (t, 1H, *J* = 7.3, NC*H*), 2.88-2.83 (m, 1H, NCH_2), 2.81-2.76 (m, 1H, NCH_2), 1.75 (bs, 1H, N*H*), 1.60-1.52 (m, 3H, CH_2CH_2),1.40-1.33 (m, 1H, CH_2CH_2), -0.10 (s, 9H, Si(CH_3)$_3$).



Benzyl-1,3-dihydroxypropane-2-ylcarbamate (96):[46] To a solution of serinol (1.8 g, 20.0 mmol) in ethanol (60 ml) at 0 °C was added triethyl amine (3.1 ml, 22 mmol) and benzyl chloformate (2.9 ml, 21 mmol) and the mixture was stirred for 30 min after which

it was allowed to warm to room temperature, stirred for 2 h and concentrated. The residue was suspended in acetone (30 ml) and the mixture was filtered. The solid residue remaining was washed with acetone and the combined filtrates were concentrated to provide crude **96**. This was purified by flash chromatography on silica gel (2:1 dichloromethane:methanol) to provide 3.2 g (70%) of **96** as a colourless powder.

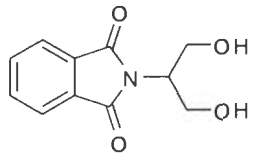
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.4-7.3 (m, 5H, Ar*H*), 5.45 (bs, 1H, N*H*), 5.12 (s, 2H, PhCH_2O), 3.90-3.75 (m, 5H, C*H*(CH_2)$_2$), 2.20 (bs, 2H, O*H*).



Benzyl-1-formylvinylcarbamate (97):[46] To a solution of oxalyl chloride (0.16 ml, 2.0 mmol) in dichloromethane (1.6 ml) at -78 °C, under nitrogen, was added a solution of DMSO (0.89 ml, 13 mmol) in dichloromethane (1.0 ml) and the mixture was stirred for 10 min. A solution of **96** (0.30 g, 1.3 mmol) in dichloromethane (0.80 ml) and DMSO (1.5 mL, 22 mmol) was added dropwise to the above mixture and stirring was continued for 20 min at the same temperature. Triethyl amine (0.88 ml, 6.3 mmol) was added dropwise and the mixture was stirred for 20 min. after which it was gradually warmed to -10 °C (ethylene glycol-dry ice bath) and water (4.0 mL) was added. The mixture was extracted with chloroform; the combined organic layers were washed with aqueous citric acid (10%, 5.0 mL) and brine, dried over (Na_2SO_4) and concentrated. The residue was

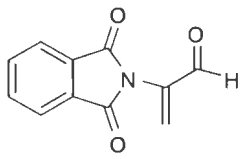
purified by flash chromatography on silica gel (2:1 dichlomethane:methanol) to provide 130 mg (48%) of **97** as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.16 (s, 1H, C*H*O), 7.38 (s, 5H, Ar*H*), 7.21 (bs, 1H, N*H*), 6.79 (s, 1H, CH_2=C), 5.47 (s, 1H, CH_2=C), 5.18 (s, 1H, PhCH_2O).



2-(1,3-Dihydroxypropane-2-yl)isoindoline-1,3-dione (98):[46] A mixture of serinol (1.5 g, 17 mmol) and phthalic anhydride (2.4 g, 17 mmol) was heated (without solvent) at 160 °C under constant stirring for 2 h 15 min. The mixture was cooled to room temperature and the solid obtained (3.5 g) was used further without purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89-7.85 (m, 2H, Ar*H*), 7.77-7.74 (m, 2H, Ar*H*), 4.48 (m, 1H, NC*H*), 4.13-4.04 (m, 4H, CH_2OH), 2.99-2.96 (m, 2H, O*H*).

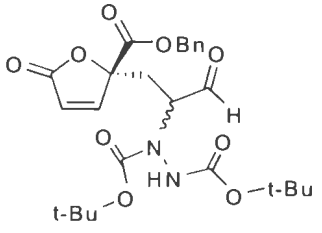


2-(1,3-Dioxoisoindolin-2-yl)acrylaldehyde (99):[47] Prepared by adapting the procedure for making aldehyde **97**. Thus reaction of the diol **98** (3.5 g, 17 mmol) in DMSO (8.2 mL) and dichloromethane (25 mL) by oxidation (oxalyl chloride (2.2 mL, 25 mmol),

DMSO (8.2 mL) in dichloromethane (25 mL) and triethylamine (11 mL, 78 mmoL) followed by a quench with water (50 mL)) provided 1.65 g (50%) of **99**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.59 (s, 1H, C*H*O), 7.93-7.92 (m, 2H, Ar*H*), 7.80-7.78 (m, 2H, Ar*H*), 6.58-6.56 (dd, 2H, *J* = 1.16, 1.15, CH_2=C).

General procedure for α-amination of aldehyde: The aldehyde **50** was dissolved in solvent at room temperature and the pyrrolidine catalyst was added. The mixture was stirred for 5-10 min and the dialkyl azo-dicarboxylate was added in one portion. Upon completion of the reaction, the mixture was concentrated and the product was isolated by flash chromatography on silica gel. The reaction time is mentioned under each product.



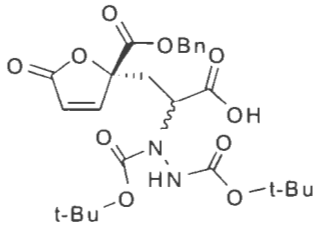
(*R*)-Benzyl-2-(2-(di-*t*-butoxycarbonylhydrazino)-2-formylethyl)-2,5-dihydro-5-oxofuran-2-carboxylate (103): Prepared from aldehyde **50** (0.10 g, 0.36 mmol), catalyst (43 mg, $7.2x10^{-2}$ mmol) and di-*tert*-butyl azodicarboxylate ($9.2x10^{-2}$ g, 0.40 mmol) in chloroform (0.20 mL) according to the general procedure. The mixture was stirred for 5 h to provide 130 mg (67 %) of **103** after purification by flash chromatography on silica gel (2:8 ethyl acetate:hexane).

IR (neat): 3310, 2970, 1734, 1718, 1700, 1684, 1369, 1278, 1246, 1134 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): Mixture of rotamers and diastereomers: δ 9.90 (s, 1H, C*H*O), 9.85 (s, 1H, C*H*O), 9.64 (s, 1H, C*H*O), 9.58 (s, 1H, C*H*O), 7.92 (br s, 1H, N*H*), 7.70 (bs, 1H, N*H*), 7.47-7.44 (m, 1H, COCH=C*H*), 7.38-7.31 (m, 5H, Ar*H*), 6.50 (br m, 1H, COC*H*=CH), 6.18-6.13 (br m, 1H, COC*H*=CH), 5.27-5.00 (m, 2H, PhCH_2), 4.38-4.25 (br m, 1H, NC*H*), 2.77-2.72 (m, 1H, CH_2CHCHO), 2.39-2.28 (m, 1H, CH_2CHCHO), 1.47 (s, 9H, C(CH_3)$_3$), 1.45 (s, 9H, C(CH_3)$_3$).

LCMS (APCI neg.): m/z 503.3 (M-H)

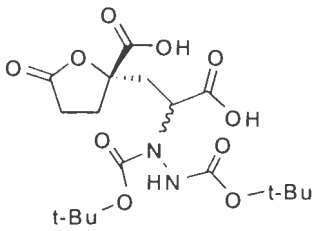
HRMS (CI neg.): *m/z* 504.2130 (504.2108 Calc. for $C_{25}H_{32}N_2O_9$, M+).



3-((*R*)-2-((benzyloxy)carbonyl)-2,5-dihydro-5-oxofuran-2-yl)-2-(di-*t*-butoxycarbonylhydrazino)-propanoic acid (104): To a solution of the amination product **103** (190 mg, 0.37 mmol), in *t*-butyl alcohol (7.3 ml) was added 2-methyl-2-butene (0.78 ml of 2.0 M solution in THF, 1.6 mmol). A solution of $NaClO_2$ (0.10 g, 1.1 mmol) and NaH_2PO_4 (0.05 g, 0.39 mmol), in water (1.8 ml) was added dropwise to this mixture. The resulting mixture was stirred at room temperature for 2 h and concentrated. The residue was diluted with ether and the solution was acidified with aqueous HCl (0.50 M) to pH 6. The organic layer was separated, dried over Na_2SO_4 and concentrated to provide 170 mg (89%) of the acid **104**.

^{1}H NMR (500 MHz, $CDCl_3$): Mixture of rotamers and diastereomers: δ 7.52-7.47 (m, 1H, COCH=C*H*), 7.39-7.32 (m, 5H, Ar*H*), 6.82 (bs, 1H, CHN*H*), 6.20-6.16 (m, 1H, CO*CH*=CH), 5.28-5.25 (m, 1H, PhC*H*2), 5.20-5.15 (m, 1H, PhCH_2), 3.12-3.08 (m, 1H, NC*H*), 2.60-2.38 (m, 2H, CH_2CHCOOH), 1.53-1.42 (m, 18H, C(CH_3)$_3$).

LCMS: (APCI negative): *m/z* 519.2 (M-H).



(S)-2-(2-(Di-*t*-butoxycarbonylhydrazino)-2-carboxyethyl)-tetrahydro-5-oxofuran-2-carboxylic acid (108): The hydrazino acid **104** (35 mg, 0.07 mmol), was dissolved in ethyl acetate (2.0 mL). To this solution Pd/C (10 mg) was added and the mixture was stirred under H_2 at 1 atm. for 24 h (monitored by NMR). The mixture was filtered through a pad of celite and the residue was washed with washed with ethyl acetate. The combined filtrates were concentrated to provide 29 mg (quant) of diacid **108**.

IR (neat): 3400-3100 (br), 2979, 1717, 1480, 1369, 1252, 1147 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.66 (bs, 1H, NC*H*), 2.63-2.53 (m, 4H, COCH_2CH_2, CH_2CHCOOH), 2.42-2.31 (COCH_2CH_2), 1.52 (s, 9H, C(CH_3)$_3$), 1.48 (s, 9H, C(CH_3)$_3$).

HRMS: (CI negative): *m/z* 431.1 (M-1).

References

1. Rhugenda-Banga, N.; Welter, A.; Jadot, J.; Casimir, J. *Phytochemistry* **1979**, *18*, 482.

2. Lamotte, J.; Oleksyn, B.; Dupont, L.; Dideberg, O.; Campsteyn, H.; Vermeire, M.; Rhugenda-Banga, N. *Acta Cryst.* **1978**, *B34*, 3635.

3. Kaname, M.; Yoshifuji, S. *Tetrahedron Lett.* **1992**, *33*, 8103.

4. Makino, K.; Shintani, K.; Yamatake, T.; Hara, O.; Hatano, K.; Hamada, Y. *Tetrahedron* **2002**, *58*, 9737.

5. Kaname, M.; Yoshifuji, S. *Chem. Pharm. Bull.* **1995**, *43*, 1617.

6. Hatakeyama, S.; Masaki, H.; Mizozoe, T.; Esumi, T.; Iwabuchi, Y. *Tetrahedron Lett.* **2000**, *41*, 4801.

7. Ishibashi, H.; Tamura, O.; Shiro, T.; Ogasawara, M.; Toyao, A. *J. Org. Chem.* **2005**, *70*, 4569.

8. Chamberlin, A. R.; Cohen, J. L. *J. Org. Chem.* **2007**, *72*, 9240.

9. Dormoy, J-R.; Castro, B. *Synthesis* **1987**, 81.

10. a) Yamaguchi, M.; Otsubo, K.; Inanaga, J. *Tetrahedron Lett.* **1986**, *27*, 5763. b) Fukuzawa, S.; Nakanishi,A.; Fujinami, T.; Sakai, S. *J. Chem. Soc. Chem. Commun.* **1986**, 624.

11. Yoshifuji, S.; Tanaka, K.; Kawai, T.; Nitta, Y. *Chem. Pharm. Bull.* **1986**, *34*, 3873.

12. Denmark, S.E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595.

13. a) Jackson, R. F. W.; James, K.; Wythes, M. J.; Wood, A. *J. Chem. Soc. Chem. Commun.* **1989**, 644. b) Jackson, R. F. W.; Wishart, N.; Wood, A.; James, K.; Wythe, M. J. *J. Org. Chem.* **1992**, *57*, 3397. c) Dunn, M. J.; Jackson, R. F. W.; Pietruszka, J.; Turner, D. *J. Org. Chem.* **1995**, *60*, 2210.

14. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Org. Chem.* **1987**, *109*, 5765.

15. Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O.; *Tetrahedron* **1986**, *42*, 3021.

16. a) Thottathil, J. K.; Moniot, J. L.; Mueller, R. H.; Wong, M. K. Y.; Kissick, T. P. *J. Org. Chem.* **1986**, *51*, 3140. b) Thottathil, J. K.; Przybyla, C.; Malley, M.; Gougoutas, J. Z. *Tetrahedron Lett.* **1986**, *27*, 1533.

17. a) Silverman, R. B.; Levy, M. A.; *J. Org. Chem.* **1980**, *45*, 815. b) Bruim, J. W.; De-Koning, H.; Huisman, H. O. *Tetrahedron Lett.* **1975**, *15*, 4599.

18. a) Vedejs, E. *J. Am. Chem. Soc.* **1974**, *96*, 5944. b) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1974**, *43*, 188.

19. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

20. Otsuka, M.; Masuda, T.; Haupt, A.; Ohno, M.; Shiaki, T.; Sugiura, Y.; Maeda, K. *J. Am. Chem. Soc.* **1990**, *112*, 838. b) Evans, D.; Lundy, K. *J. Am. Chem. Soc.* **1992**,

114, 1495. c) Barrett, A.; Head, J.; Smith, M.; Stock, N.; White, A.; Williams, D. *J. Org. Chem.* **1999**, *64*. 6005.

21. Ezquerra, J.; Pedregal, C.; Yryretagoyena, B.; Rubio, A. *J. Org. Chem.* **1995**, *60*, 2925.

22. a) Gu, Z.-Q.; Lin, X.-F.; Hesson, D. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1973. b) Ezquerra, J.; Pedregal, C.; Rubio, A. *J. Org. Chem.* **1994**, *59*, 4327.

23. Villieras, J.; Rambaud, M. *Synthesis* **1982**, 924

24. a) Tamura, O.; Gotanda, K.; Terashima, R.; Kikuchi, M.; Miyawaki, T.; Sakamoto, M. *Chem. Commun.* **1996**, 1861. b) Tamura, O.; Kuroki, T.; Sakai, Y.; Takizawa, J.; Yoshino, J.; Morita, Y.; Mita, N.; Gotanda, K.; Sakamoto, M. *Tetrahedron Lett.* **1999**, *40*, 895. c) Tamura, O.; Yoshida, S.; Sugita, H.; Mita, N.; Uyama, Y.; Morita, N.; Ishiguro, M.; Kawasaki, T.; Ishibashi, H.; Sakamoto, M. *Synlett* **2000**, 1553. d) Tamura, O.; Gotanda, K.; Yoshino, J.; Morita, Y.; Terashima, R.; Kikuchi, M.; Miyawaki, T.; Mita, N.; Yamashita, M.; Ishibashi, H.; Sakamoto, M. *J. Org. Chem.* **2000**, *65*, 8544. e) Baldwin, S. W.; Young, B. G.; McPhail, A. T. *Tetrahedron Lett.* **1998**, *39*, 6819.

25. Tamura, O.; Shiro, T.; Toyao, A.; Ishibashi, H. *Chem. Commun.* **2003**, 2678.

26. Kanemasa, S.; Tsuruoka, T.; Wada, E. *Tetrahedron Lett.* **1993**, *34*, 87. b) Kanemasa, S.; Tsuruoka, T. *Chem. Lett.* **1995**, 49. c) Hanselmann, R.; Zhou, J.; Ma, P.; Confalone, P. N. *J. Org. Chem.* **2003**, *68*, 8739.

27. Martin, S. F.; Barr, K. J.; Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc.* **1999**, *121*, 6990.

28. Naito, S.; Escobar, M.; Kym, P. R.; Liras, S.; Martin, S. F. *J. Org. Chem.* **2002**, *67*, 4201.

29. a) Taniguchi, M.; Koga, K.; Yamada, S. *Tetrahedron* **1974**, *30*, 3547. b) Shiro, Y.; Kato, K.; Fuji, M.; Ida, Y.; Akito, H. *Tetrahedron* **2006**, *62*, 8687.

30. Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192.

31. Ahrendt, K. A.; Borth, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

32. Hanessian, S.; Gomtsyan, A.; Malek, N. *J. Org. Chem.* **2000**, *65*, 5623.

33. a) Rueping, M.; Sugiono, E.; Merino, E. *Angew. Chem. Int. Ed.* **2008**, *47*, 3046. b) Palomo, C.; Mielgo, A.; *Angew. Chem. Int. Ed.* **2006**, *45*, 7876.

34. Bhaskar Kanth, J. V.; Periasamy, M. *Tetrahedron* **1993**, *49*, 5127.

35. Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A.; *Angew. Chem. Int. Ed.* **2005**, *44*, 794

36. Gasto'n, H.; Rodri'guez, R.; Biellmann, J. F. *J. Org. Chem.* **1996**, *61*, 1822.

37. Shah, V. K.; Brill, W. J. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 3249.

38. Tanzer, M.; Shuster, J.; Harner, L.; Adachi, K.; Dezwaan, T.; Lo, S.-C.; Montenegro-

Chamorro, M. V.; Frank, S.; Deveraux, B.; Mahanty, S.; Heiniger, R.; Skalchunes, A.;Pan, H.; Tarpey, R. PCT Int. Appl. **2003**, WO 2003046130.

39. Xu, P. F.; Matsumoto, T.; Ohkia, Y.; Tatsumi, K. *Tetrahedron Lett.* **2005**, *46*, 315.

40. Pansare, S. V.; Adsool, V. A. *Tetrahedron Lett.* **2007**, *48*, 7099.

41. Harris, C. E.; Chrisman W.; Bickford, S. A.; Lee, L. Y.; Torreblanca, A. E.; Singaram, B. *Tetrahedon Lett.* **1997**, *38*, 981.

42. Smith, B. M.; Graham, A. E. *Tetrahedon Lett.* **2006**, *47*, 9317.

43. Gassman, P. G.; Burns, S, J.; Pfister, K. B. *J. Org. Chem.* **1988**, *53*, 5576.

44. Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

45. Pansare, S. V.; Adsool, V. A. *Tetrahedron Lett.* **2007**, *48*, 7099.

46. Harada, H.; Morie, T.; Hirokawa, Y.; Kato, S. *Chem. Pharm. Bull.* **1996**, *44*, 220.

47. Ishihara, K.; Nakano, K.; Akakura, M. *Org. Lett.* **2008**, *10*, 2893.

48. Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

49. For examples of N-N bond cleavage using Raney-Ni see: a) Enders, D.; Schubert, H. *Angew. Chem.* **1984**, *96*, 368; *Angew. Chem. Int. Ed. Engl.***1984**, *23*, 365. b) Trimble, L. A.; Vederas, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 6397. Denmark, S. E.; Weber, T.; Piotrowski *J. Am. Chem. Soc.* **1987**, *109*, 2224. d) Alexakis, A.; Lensen, N.; Mangeney, P. *Synlett* **1991**, 625. c) Einhorn, J.; Einhorn, C.; Luche, J.-L. Synlett **1991**, 37.

50. For examples of N-N bond cleavage with H_2, Pd/C see: a) Mellor, J. M.; Smith, N. M. J. *Chem. Soci., Perkin Trans.I* **1984**, 2927. b) Dolle, R. M. Branden, M. C.; Brennan, P. E.; Ahmed, G.; Tran, V.; Ho, D. M. *Tetrahedron Lett.* **1999**, *40*, 2907.

51. For examples of N-N bond cleavage with Zn, AcOH see: a) Beatrice, S-P.; Anne-Marie, H.-F.; Leon, G. *Tetrahedron Lett.* **1982**, *23*, 3261. b) Enders, D.; Demir, A. S.; *Tetrahedron Lett.* **1987**, *28*, 3795. c) Zaltsgendler, I.; Leblanc, Y.; Bernstein, M. A. *Tetrahedron Lett.* **1993**, *34*, 2441. d) Beaudegnies, R.; Ghosez, L. *Tetrahedron: Asymmetry*, **1994**, *5*, 557. e) Leblanc, Y.; Boudreault, N. *J. Org. Chem.* **1995**, *60*, 4268.

52. For examples of N-N bond cleavage with SmI_2 see: a) Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266. b) Ding, H.; Friestad, G. K. *Org. Lett.* **2004**, *6*, 637.

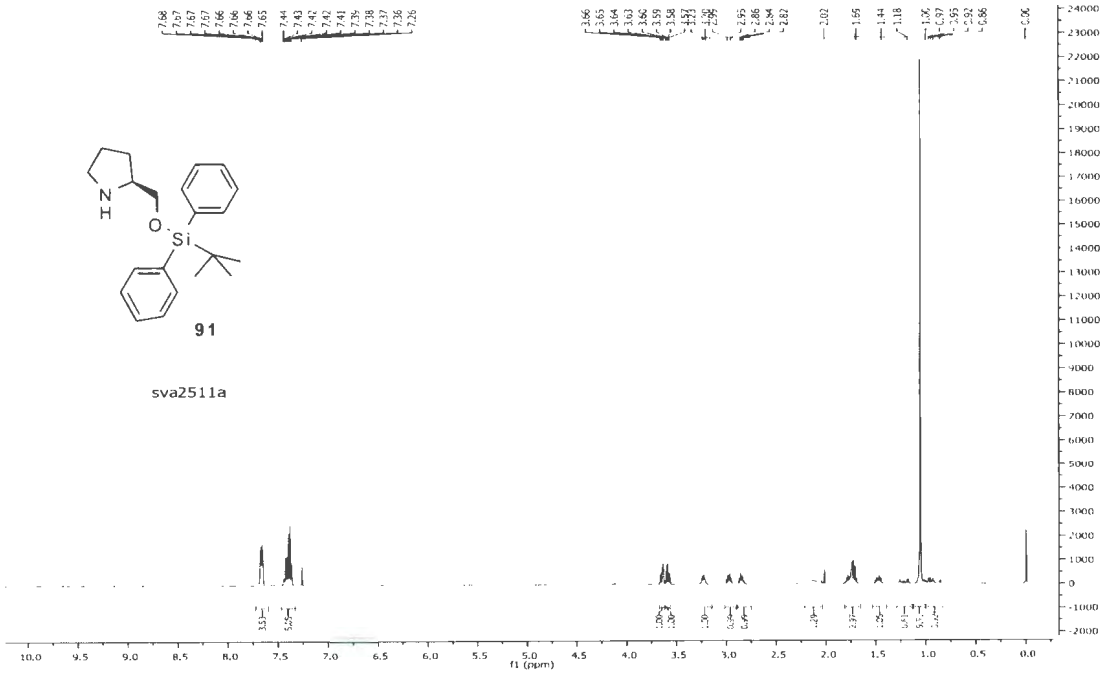
53. For examples of N-N bond cleavage with H_2 and PtO_2 see: a) Banfi, L.; Cascio, G.; Guanti, G.; Manghisi, E.; Narisano, E.; Riva, R. *Tetrahedron* **1994**, *50*, 11983. b) Gennari, C.; Colombo, L.; Bertolini, G. *J. Am. Chem. Soc.* **1986**, *108*, 6394.

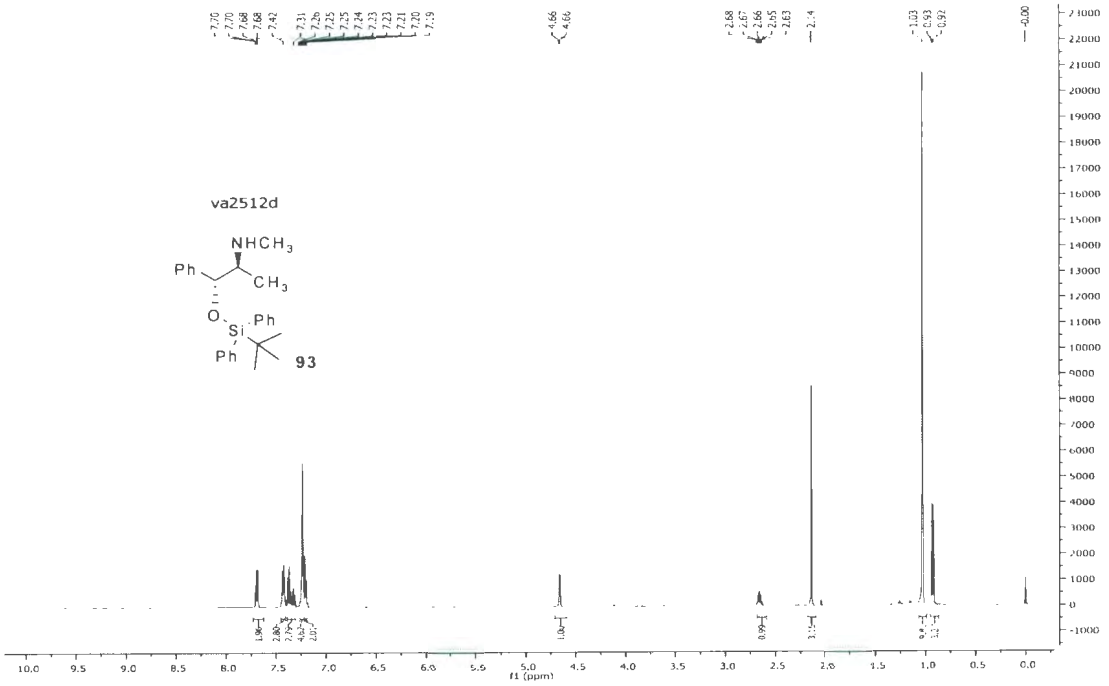
54. For examples of N-N bond cleavage with hydrogen and $Pd(OH)_2$ see: Kim, Y. H.; Choi, J. Y. *Tetrahedron Lett.* **1996**, *37*, 5543.

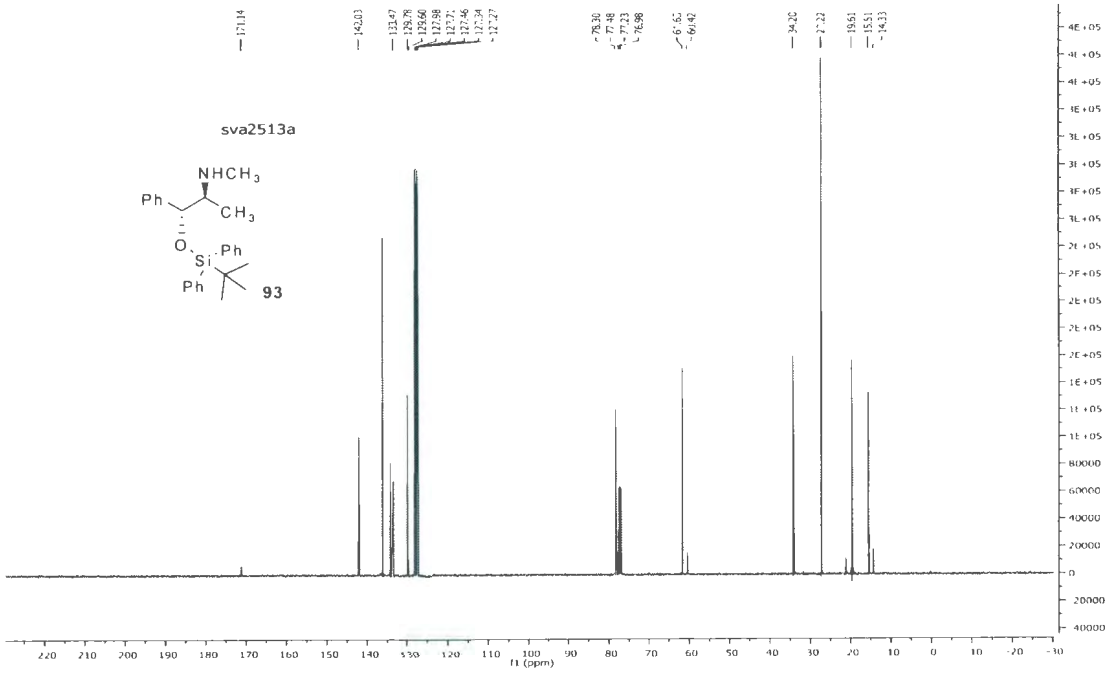
55. For examples of N-N bond cleavage with dissolving metal reduction see: Denmark, S. E.; Nicaise, O.; Edwards, J. P. *J. Org. Chem.* **1990**, *55*, 6219.

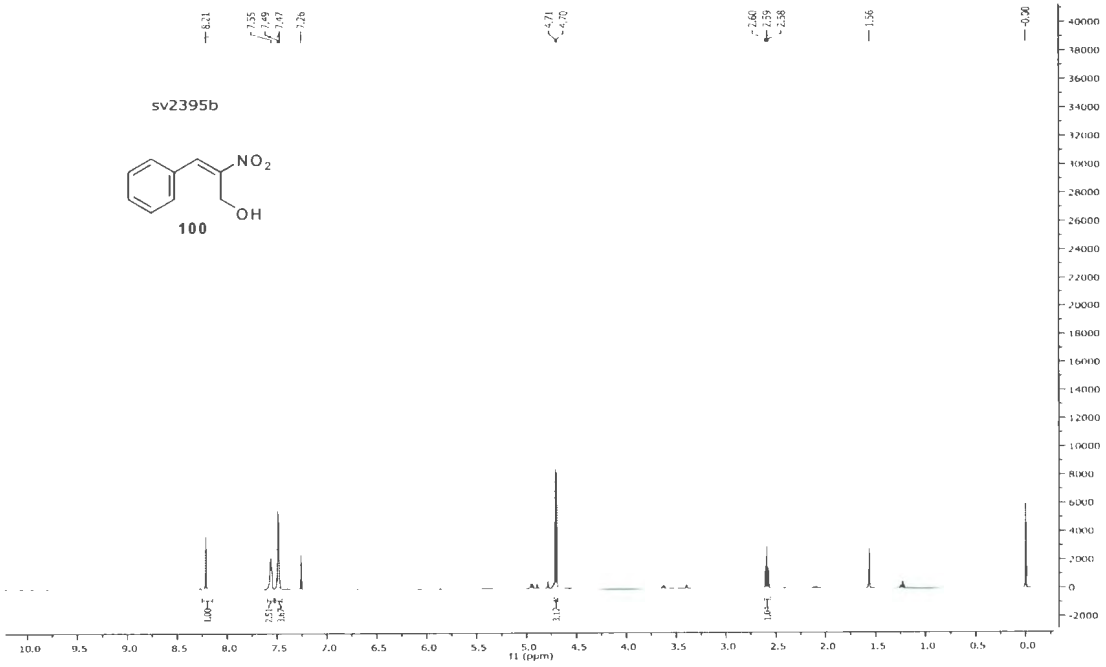
Appendix

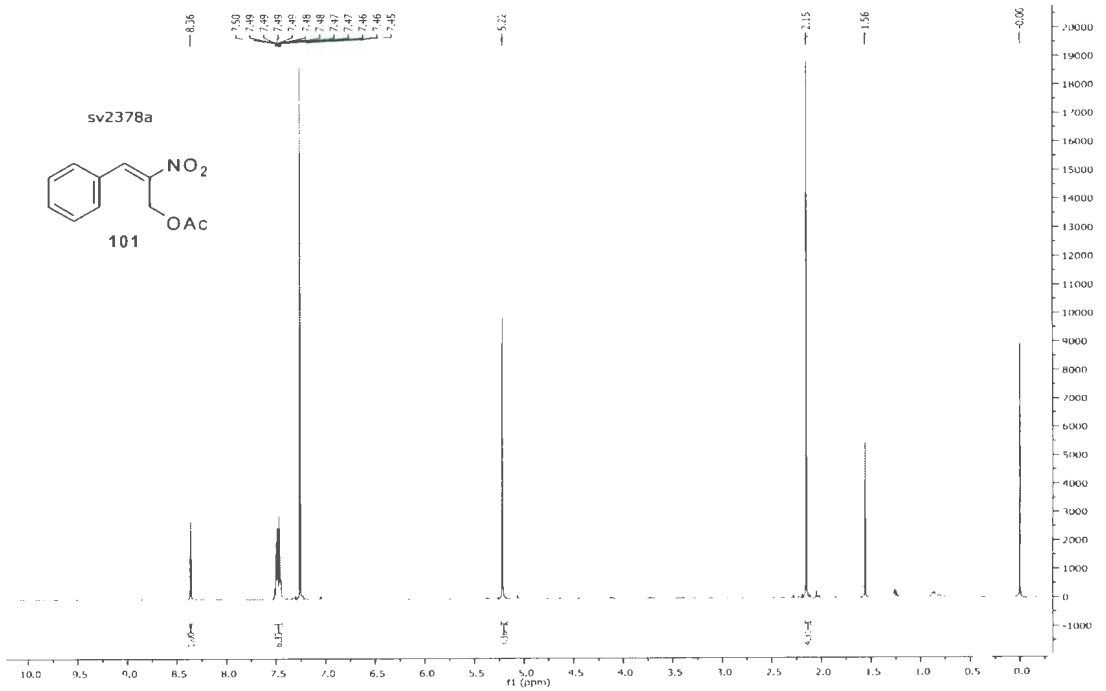
Chapter 1

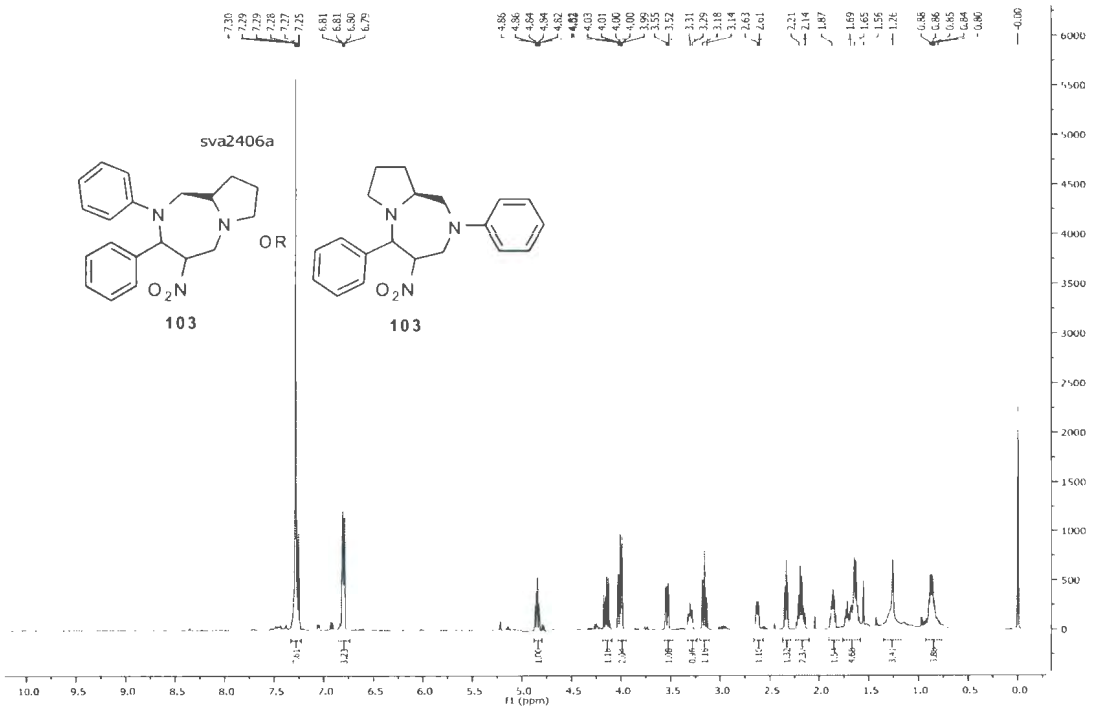


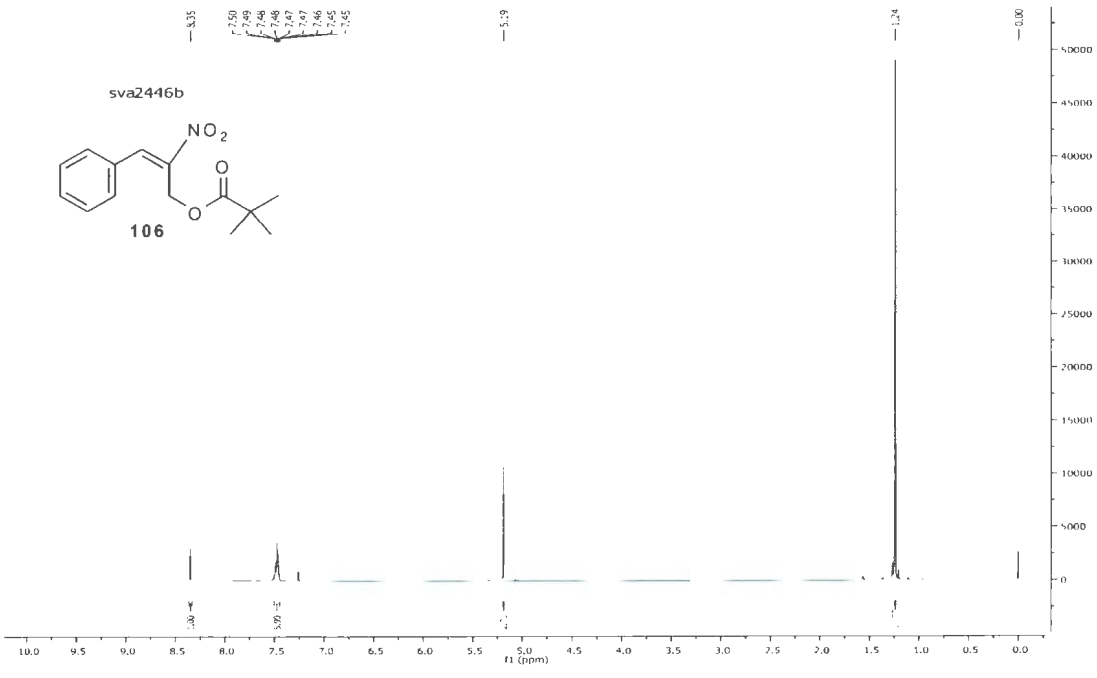

va2512d
NHCH3
Ph
CH3
O
Si
Ph
Ph
93
f1 (ppm)

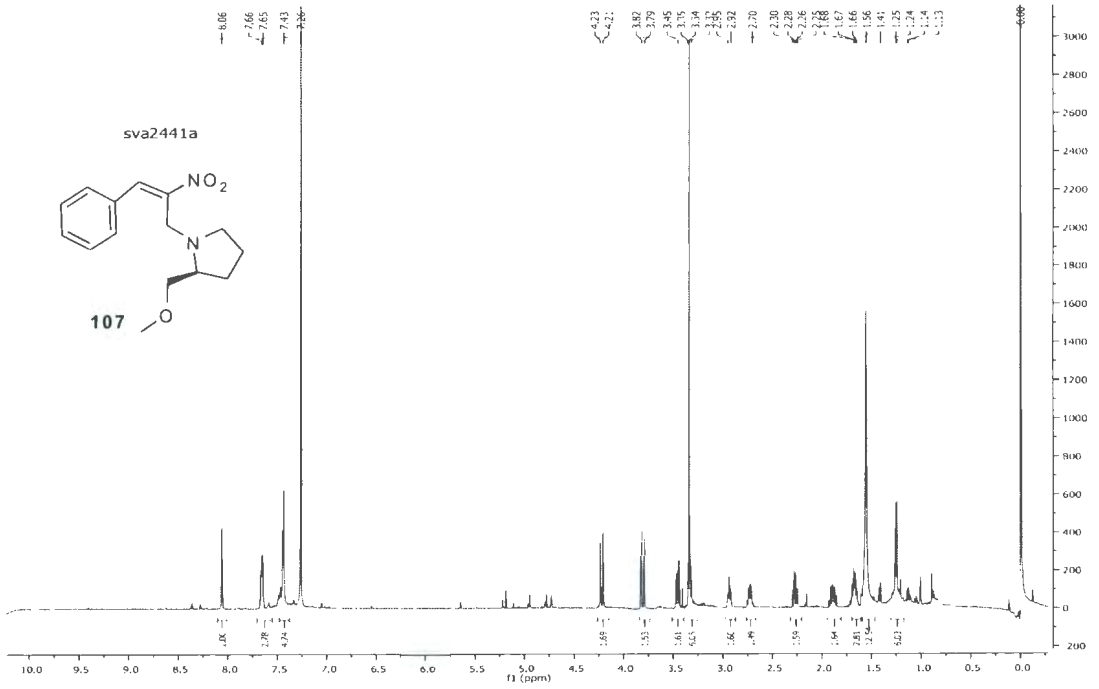

sva2513a
NHCH3
Ph
CH3
O
Si
Ph
Ph
93
f1 (ppm)

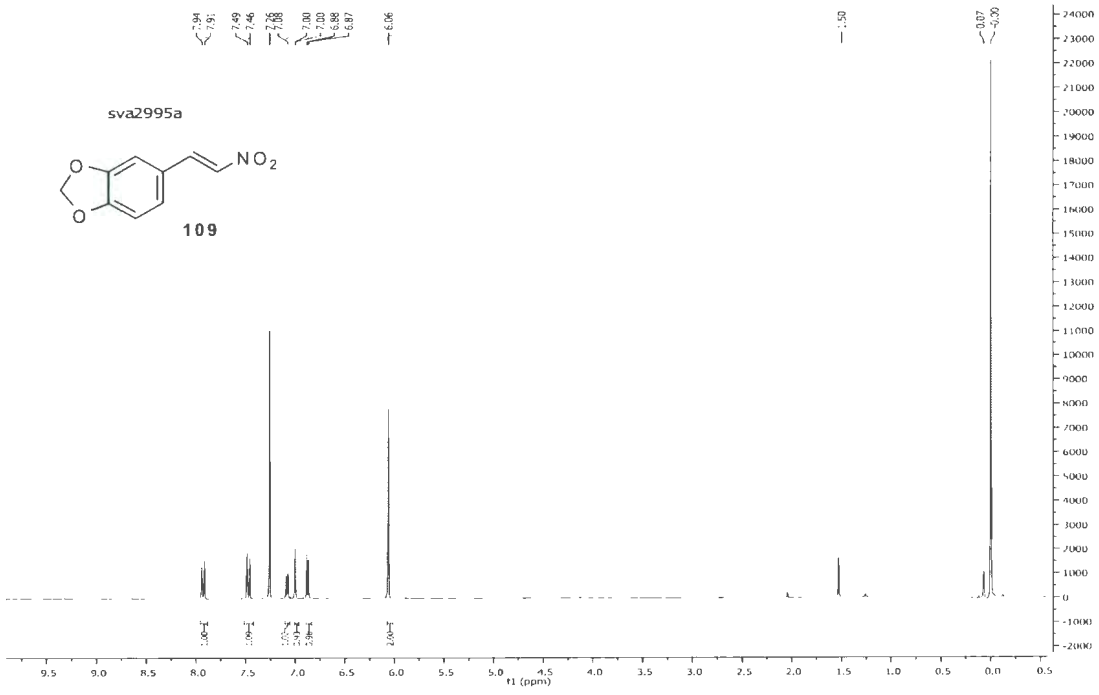

sv2395b
NO2
OH
100
f1 (ppm)

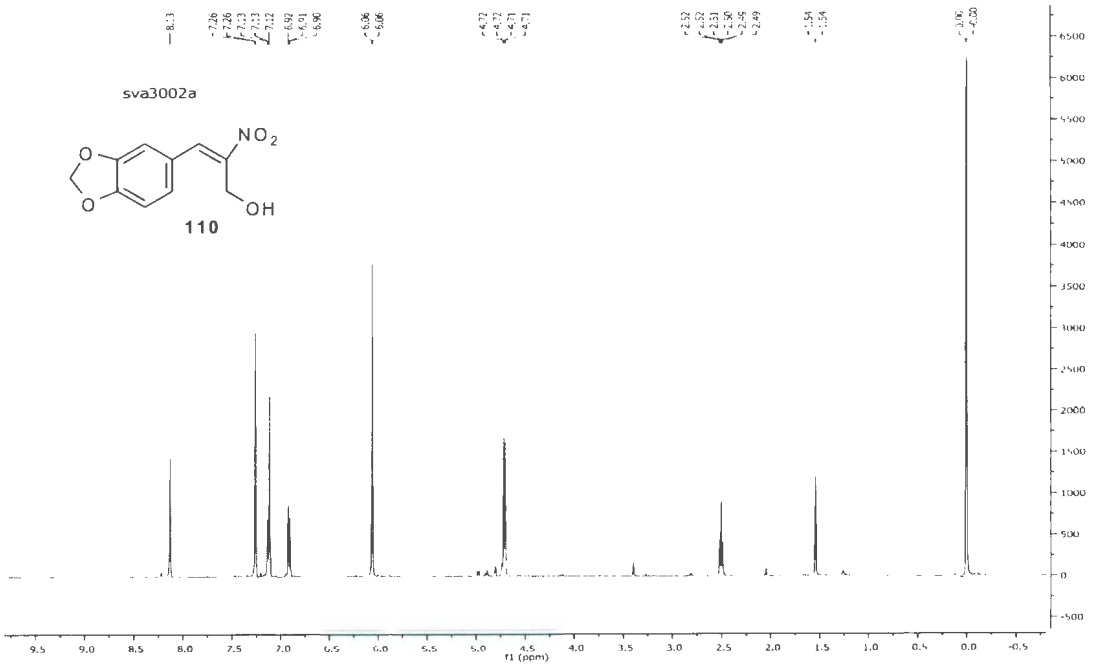

sv2378a
NO2
OAc
101
f1 (ppm)

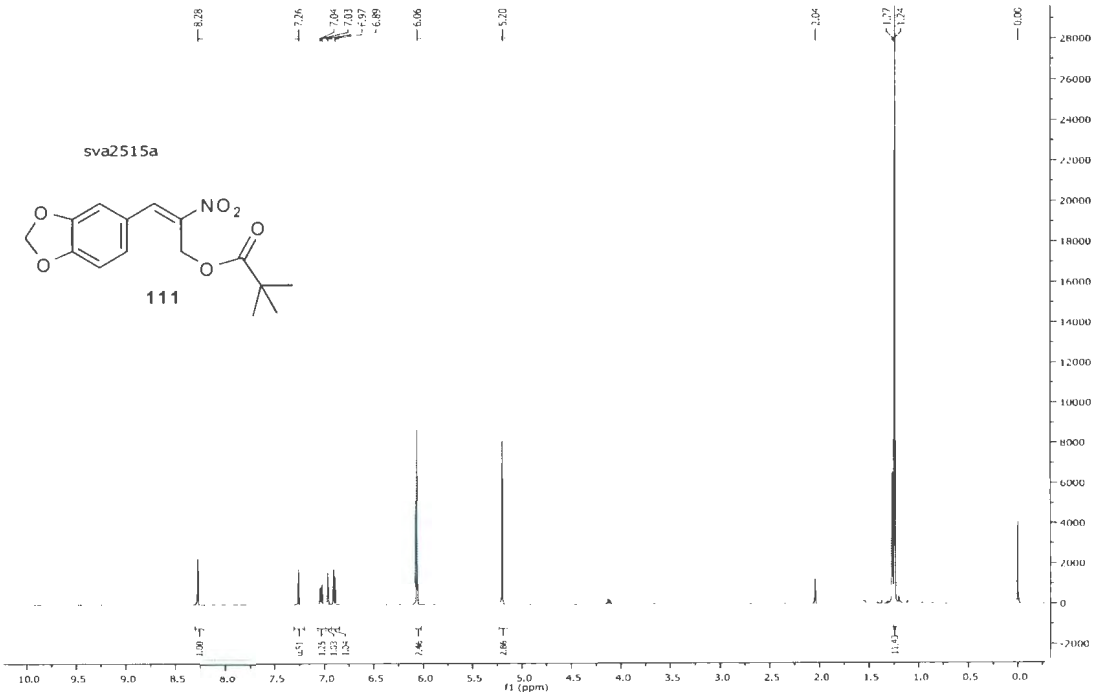

sva2406a
OR
103
103
f1 (ppm)

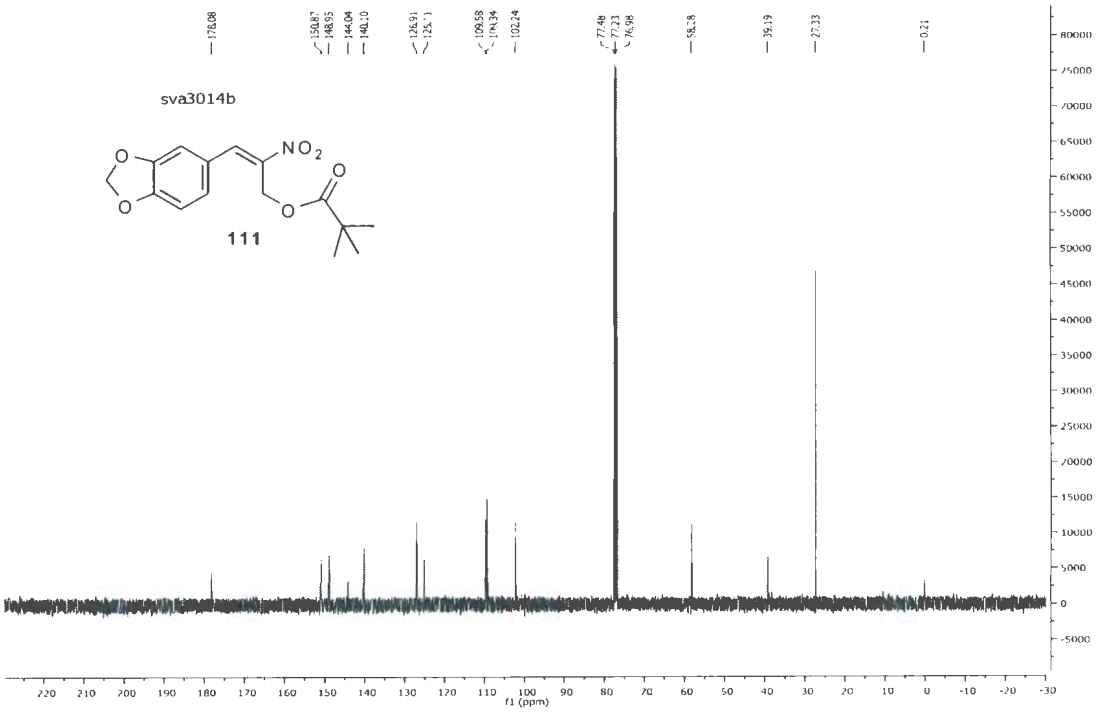

sva2446b
106
f1 (ppm)

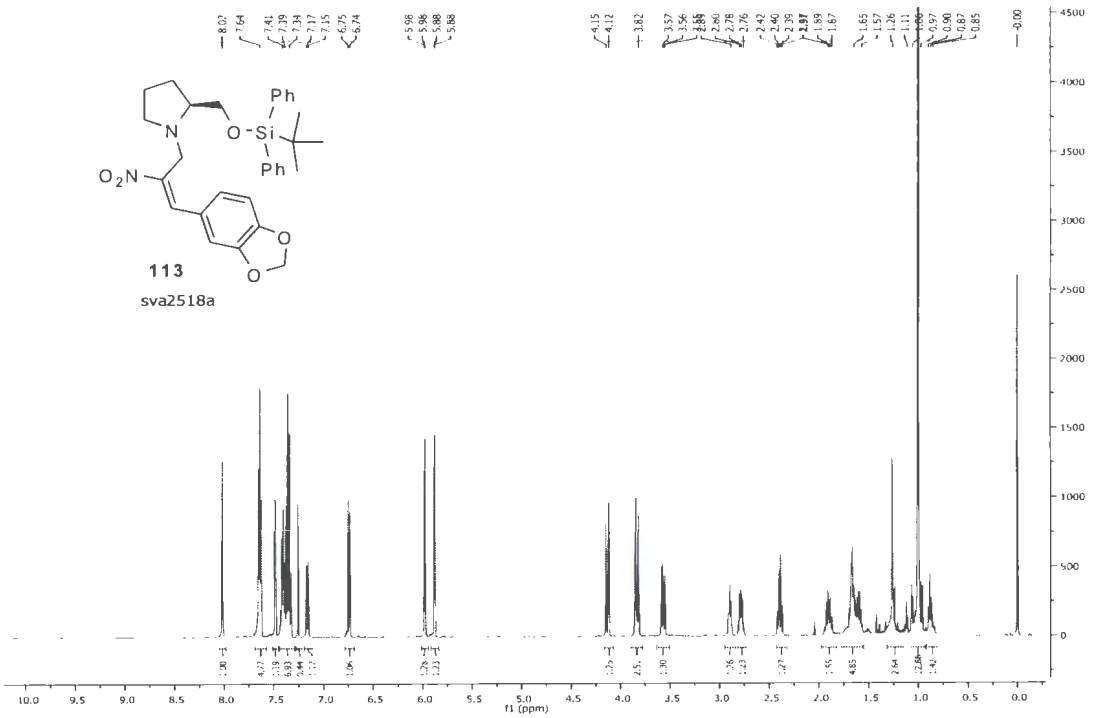

sva2441a
NO2
N
O
107
f1 (ppm)

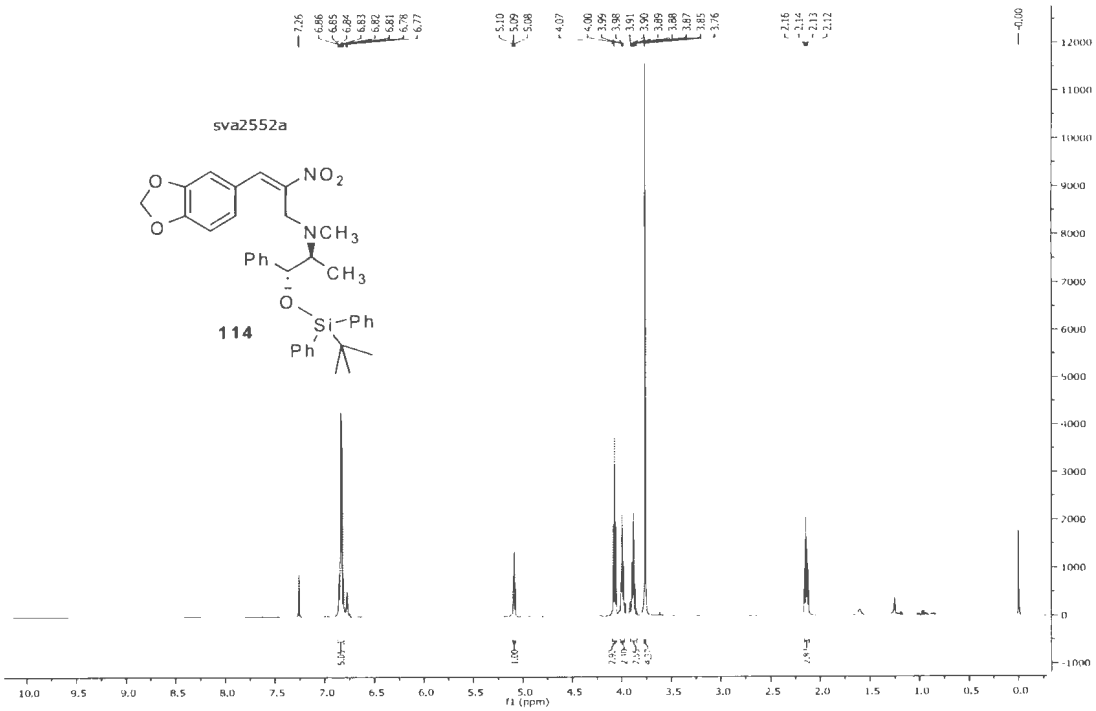

sva2995a
NO2
O
O
109
f1 (ppm)

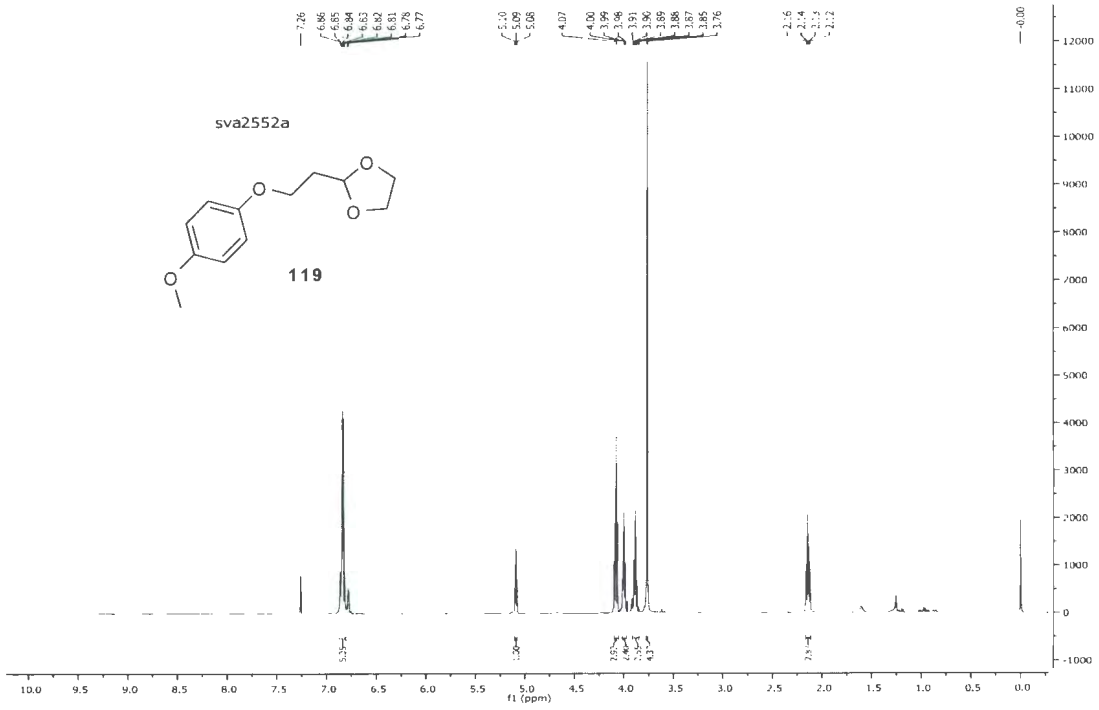

sva3002a
NO2
O
O
OH
110
f1 (ppm)

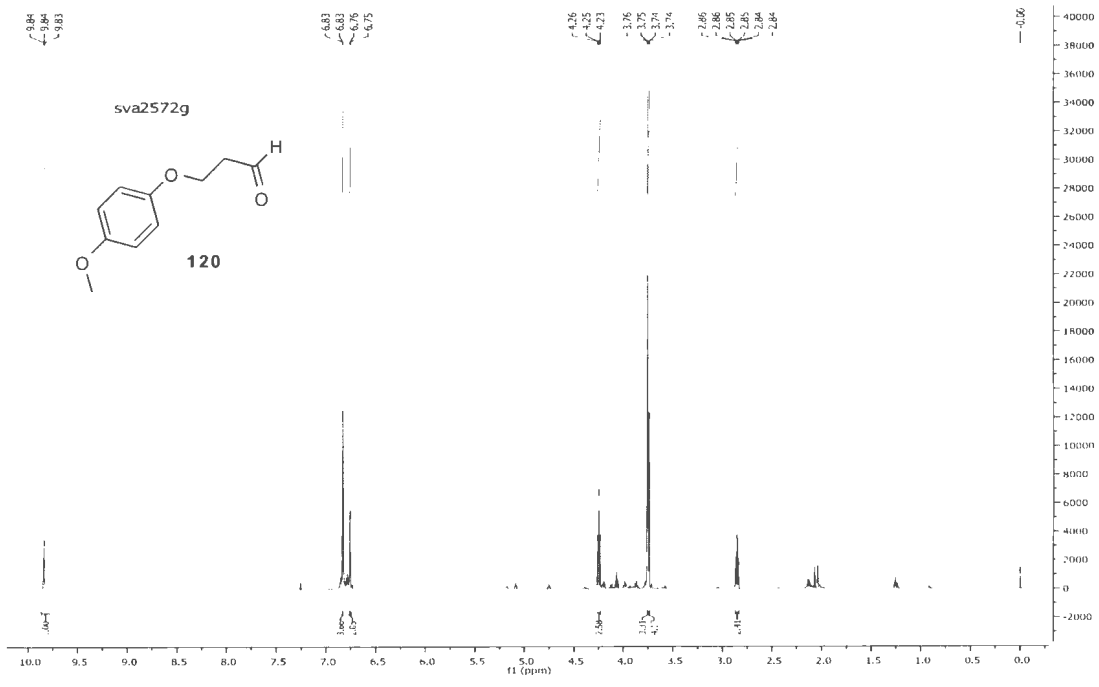

sva2515a
NO2
O
O
O
O
111
8.28
7.26
7.04
7.03
6.97
6.89
6.06
5.20
2.04
1.77
1.24
0.00
f1 (ppm)

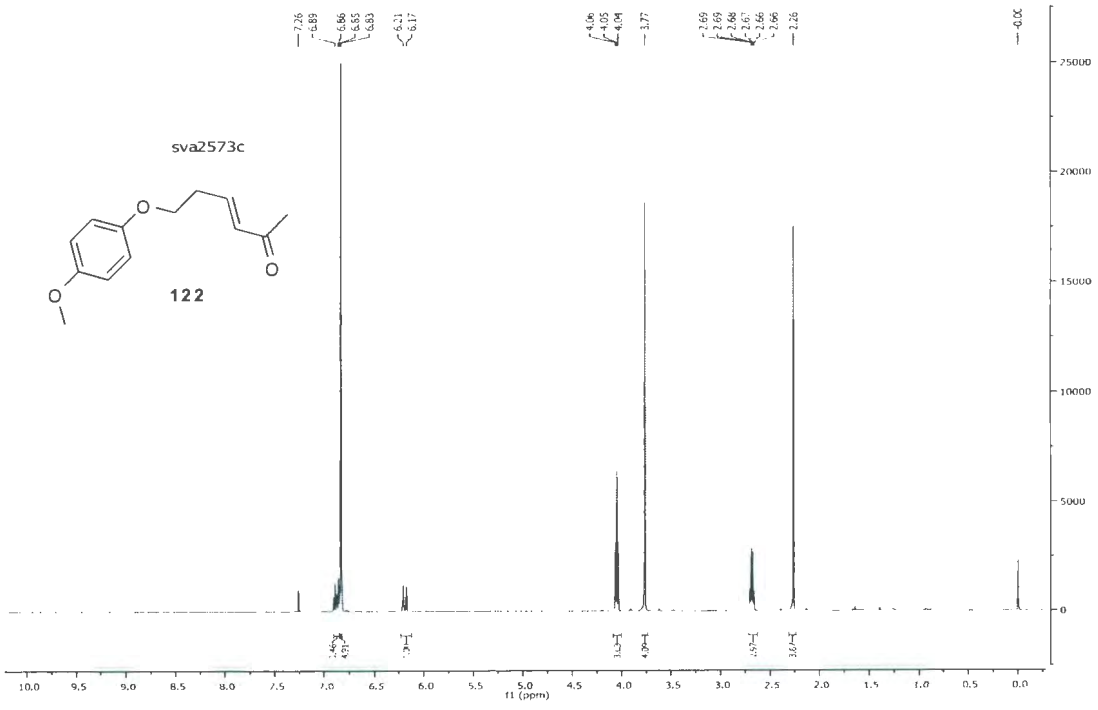

sva3014b
NO2
O
O
O
O
111
178.08
150.87
148.95
144.04
140.10
126.91
125.11
109.58
104.34
102.24
77.48
77.23
76.98
58.28
35.19
27.33
0.21
f1 (ppm)


Ph
N
O-Si
Ph
O2N
O
O
113
sva2518a
f1 (ppm)


sva2552a
NO2
O
O
NCH3
Ph
CH3
O
Si-Ph
Ph
114
f1 (ppm)

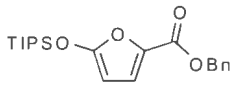

sva2552a
119
f1 (ppm)


sva2572g
120
f1 (ppm)


sva2573c
122
7.26
6.89
6.86
6.85
6.83
6.11
6.17
4.06
4.05
4.04
3.77
2.69
2.69
2.68
2.67
2.66
2.66
2.26
0.00
75000
20000
15000
10000
5000
0
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

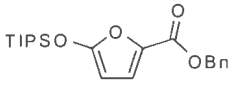
Chapter 2

sva2907c

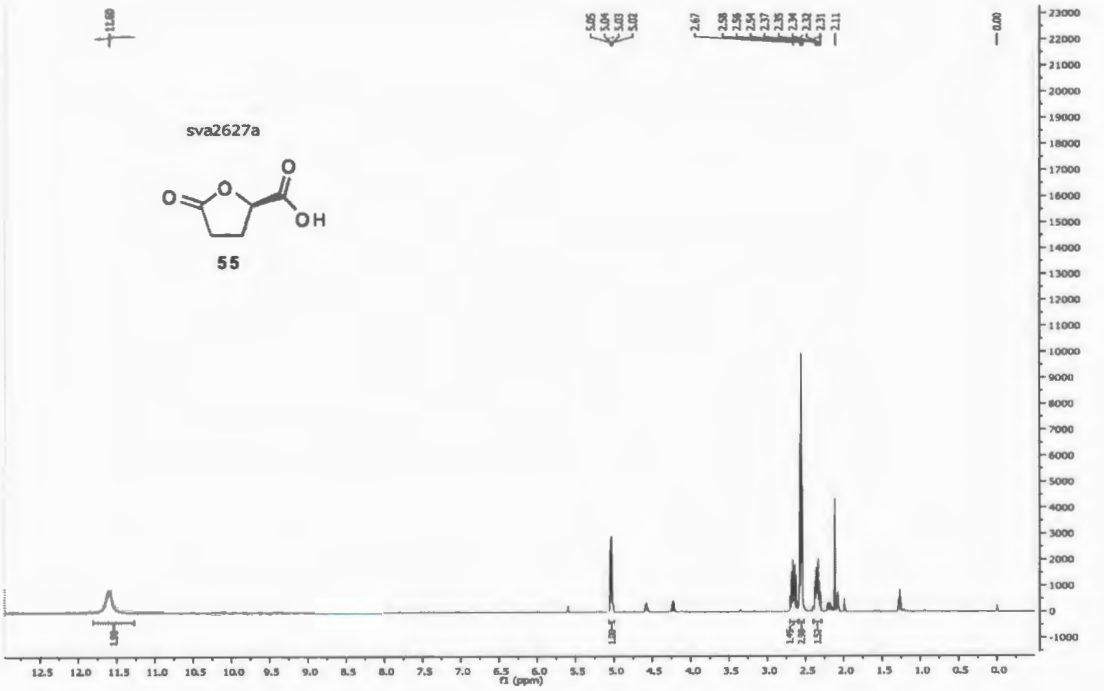


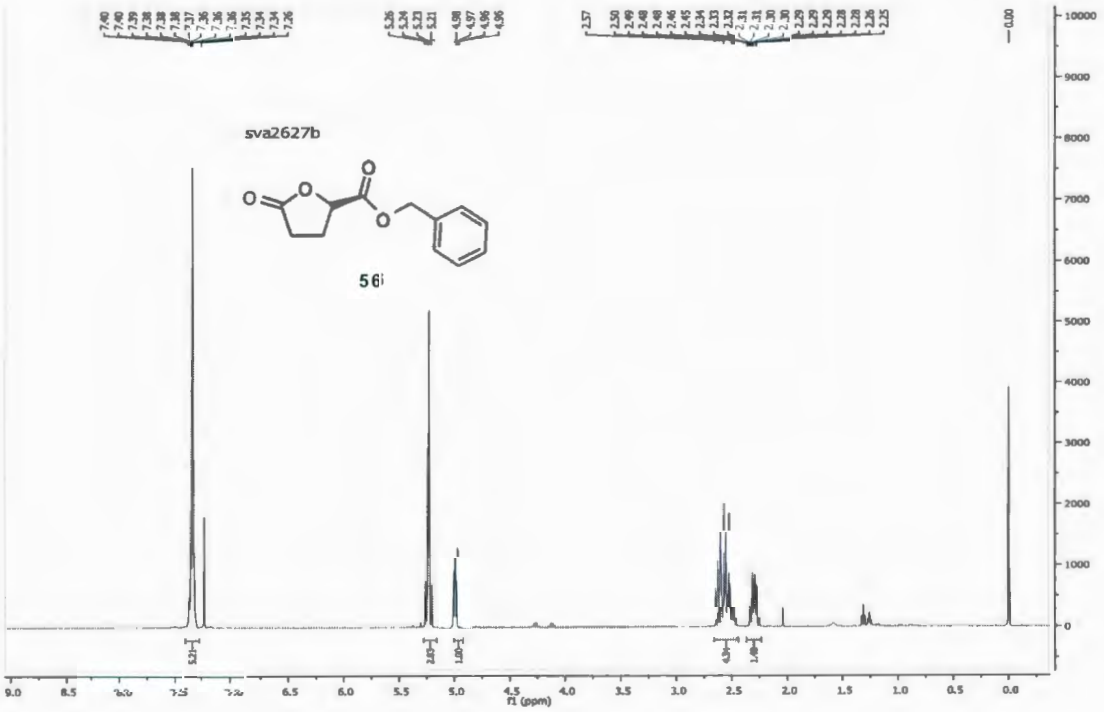
51

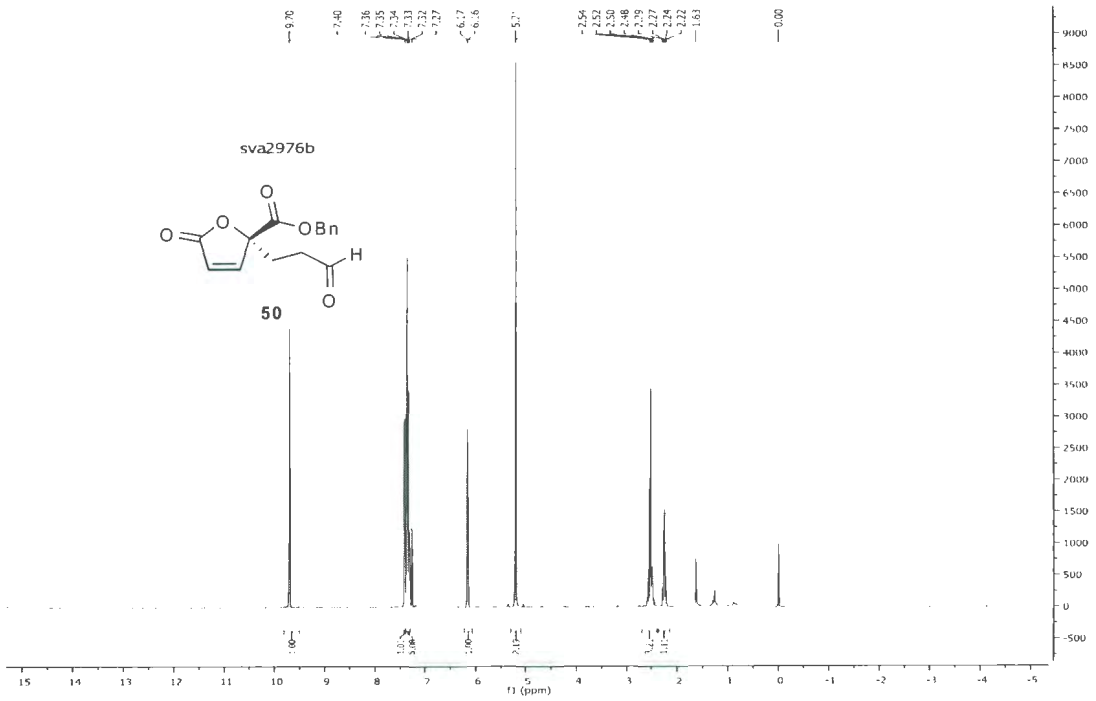
sva2724c

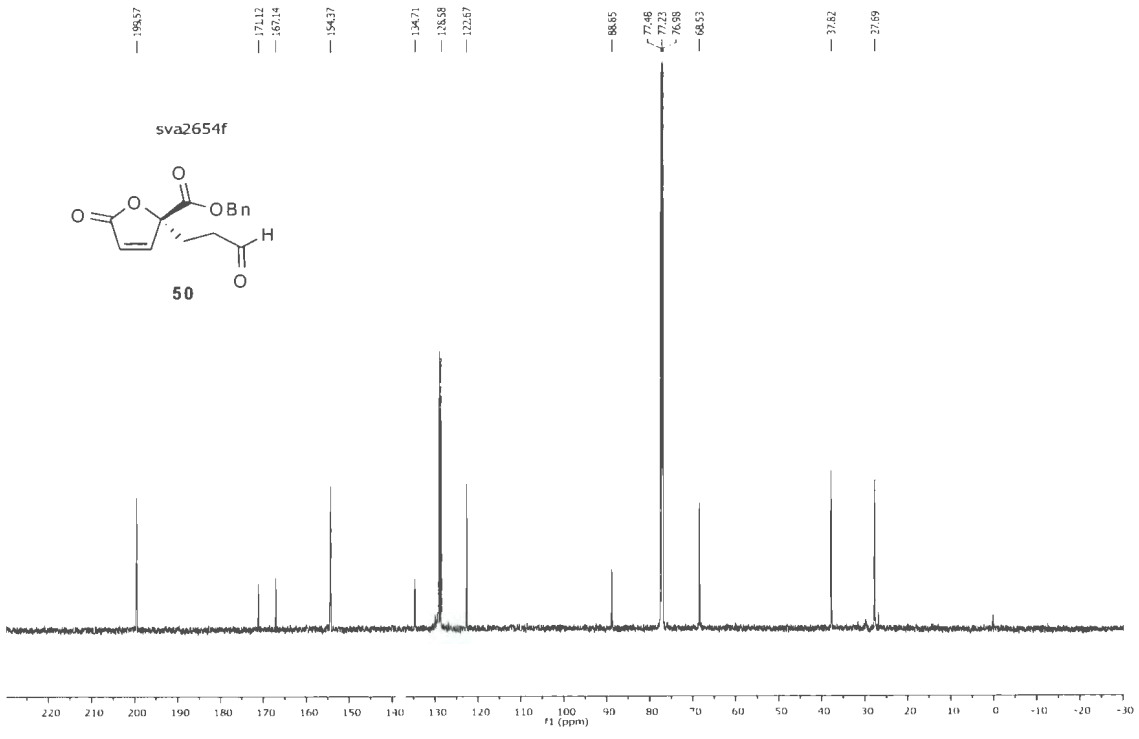


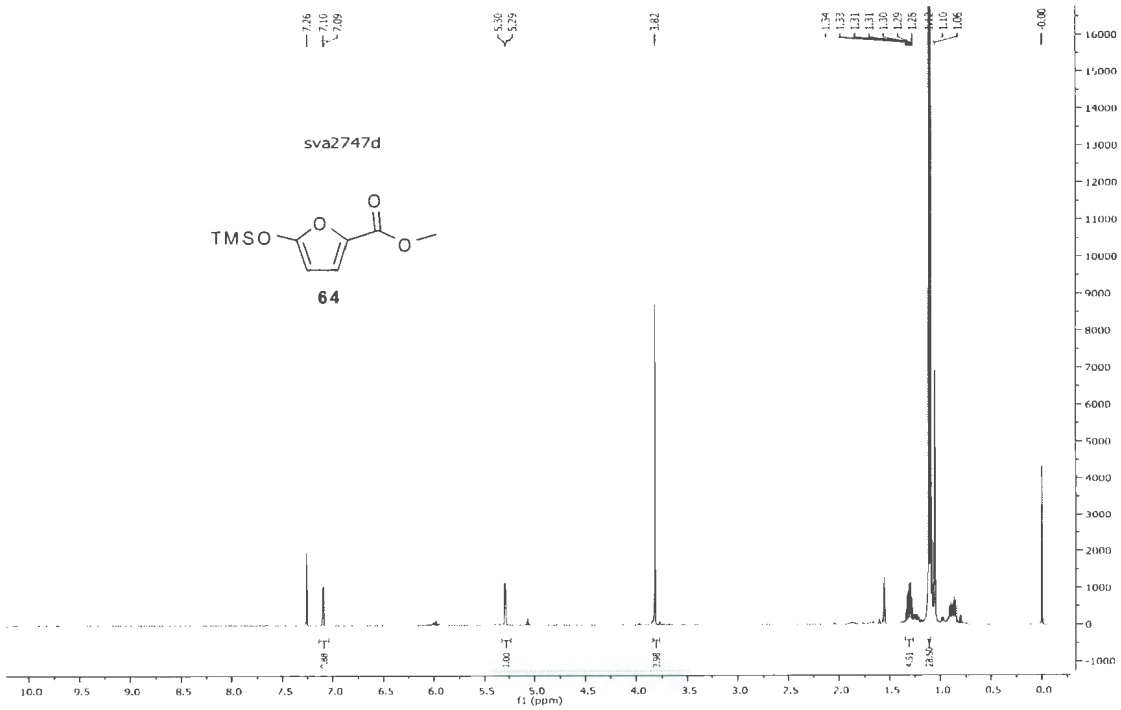
51

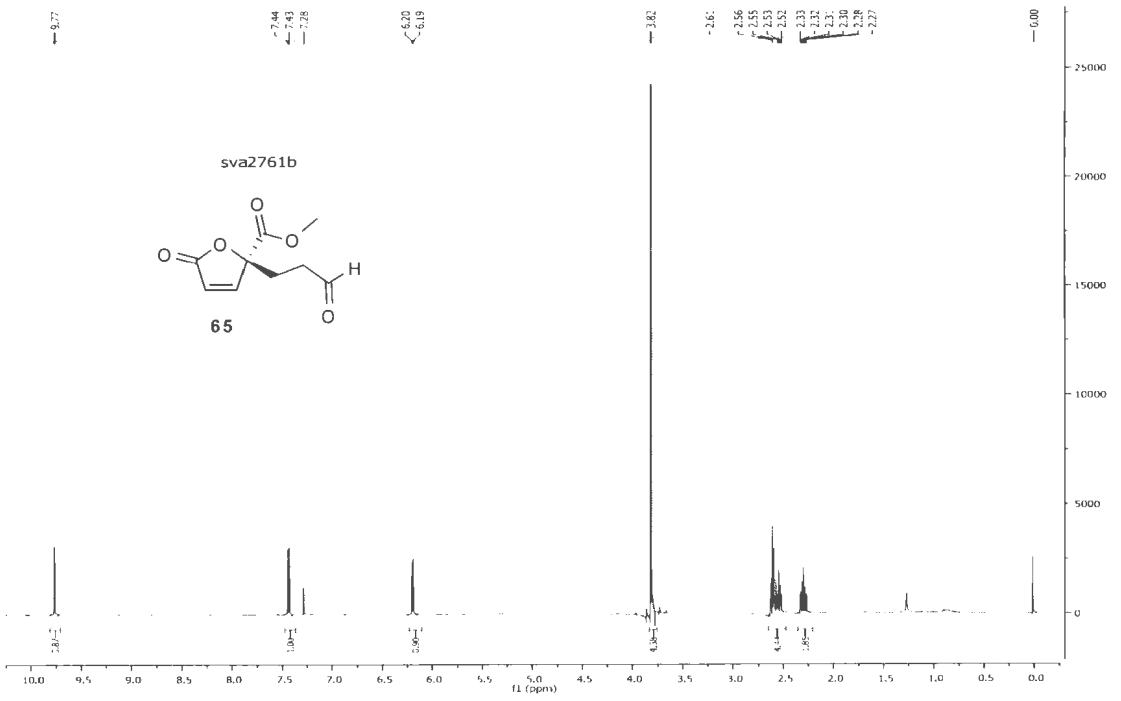

sva2627a
OH
55
f1 (ppm)


sva2627b
56
f1 (ppm)

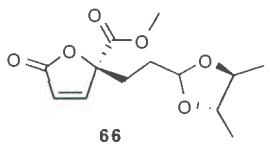

sva2976b
OBn
H
O
50
f1 (ppm)


sva2654f
OBn
H
O
50
f1 (ppm)


sva2747d
TMSO
O
O
O
64
7.26
7.10
7.09
5.30
5.29
3.82
1.34
1.33
1.31
1.31
1.30
1.29
1.25
1.16
1.06
0.00
f1 (ppm)

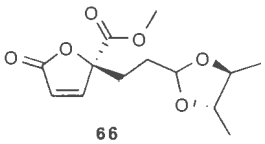

sva2761b
O
O
O
O
H
O
65
9.77
7.44
7.43
7.28
6.20
6.19
3.82
2.61
2.56
2.55
2.53
2.52
2.33
2.32
2.31
2.30
2.28
2.27
0.00
f1 (ppm)

sva2784a

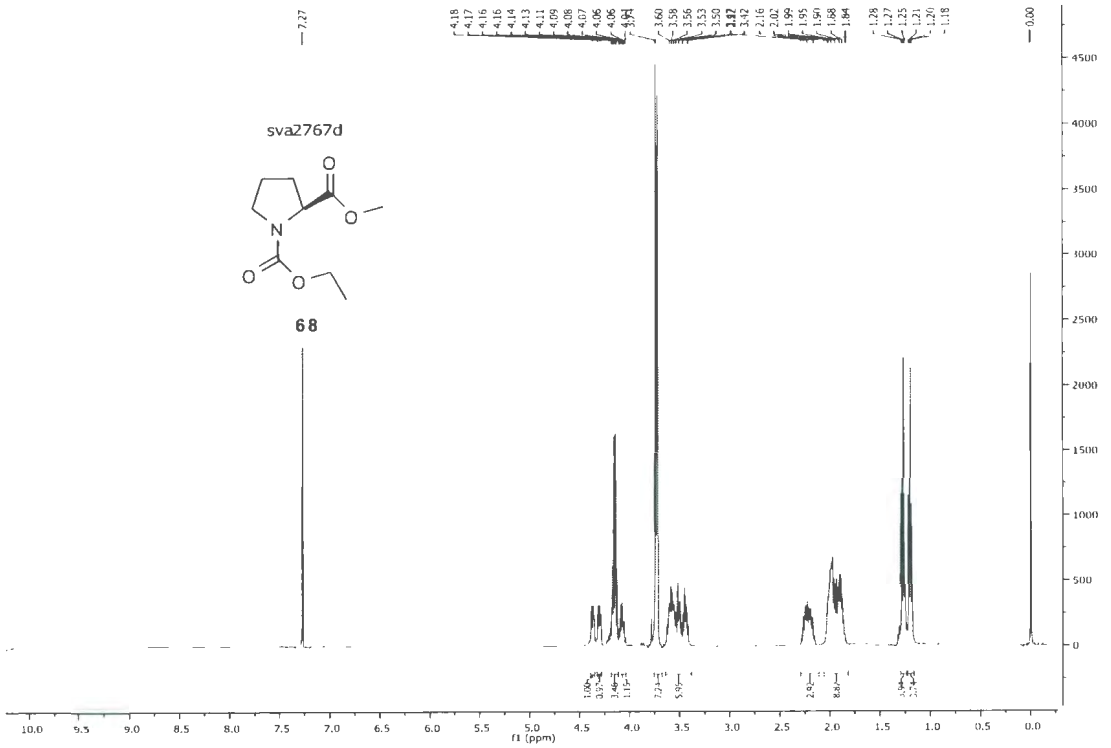


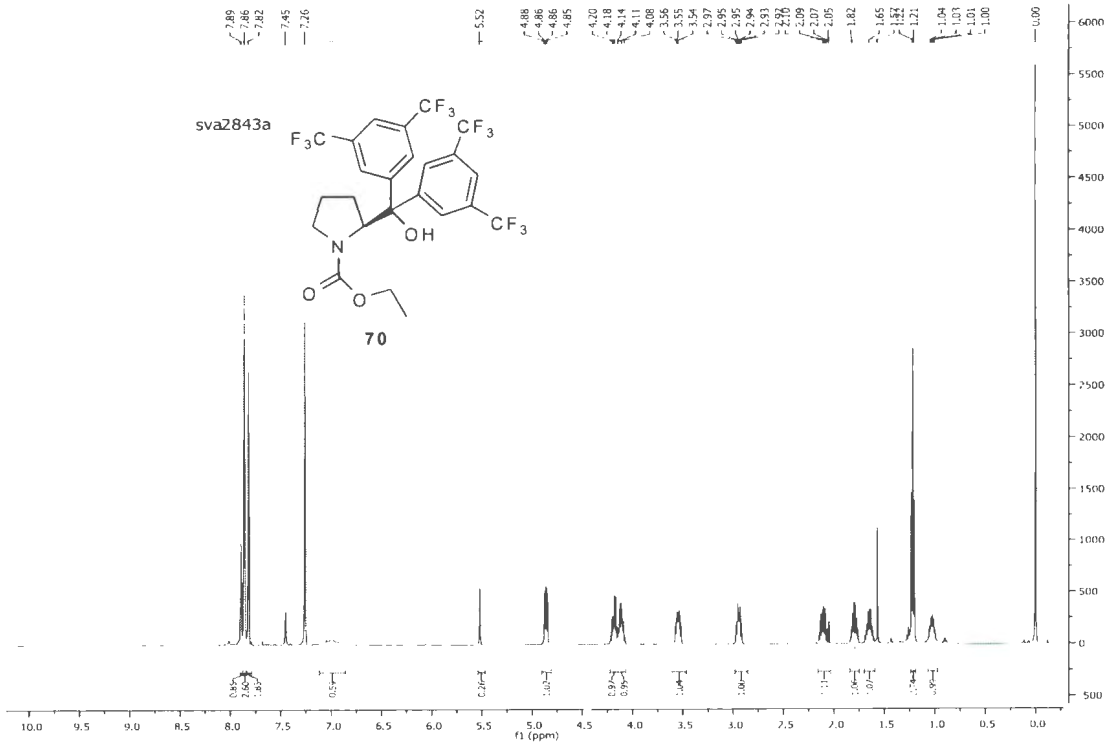
66

sva2786f

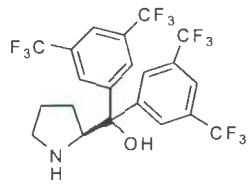


66


sva2767d
68
f1 (ppm)

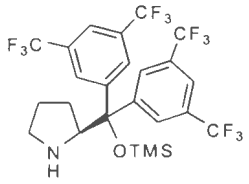

sva2843a
70
f1 (ppm)

sva2951a

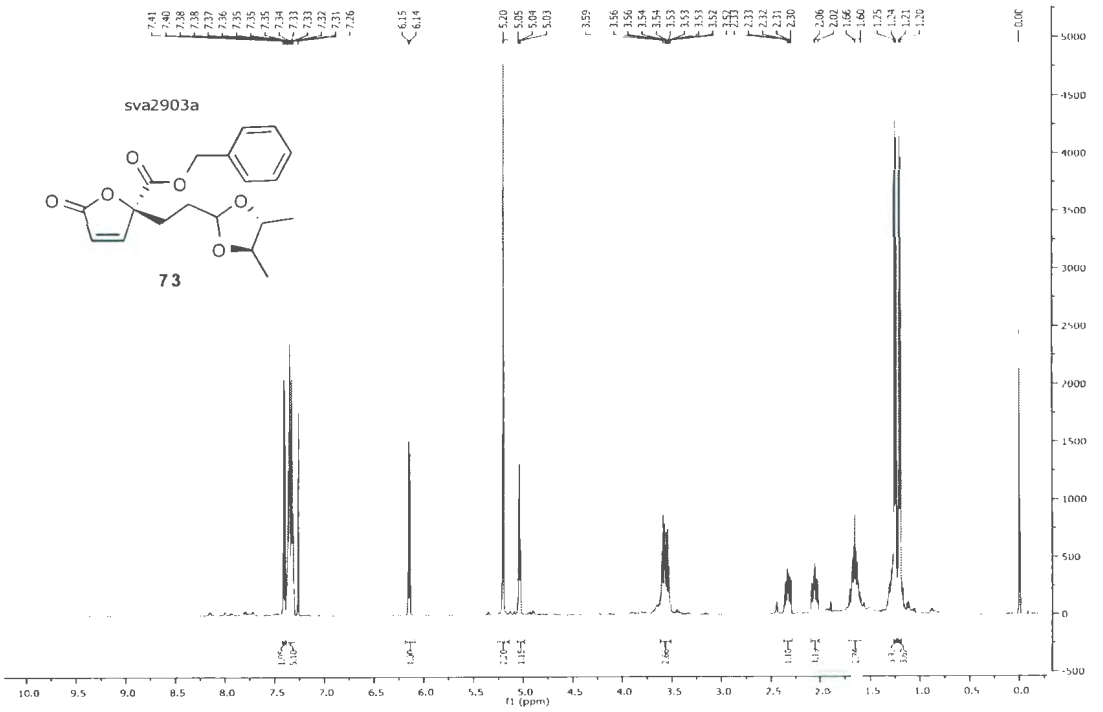


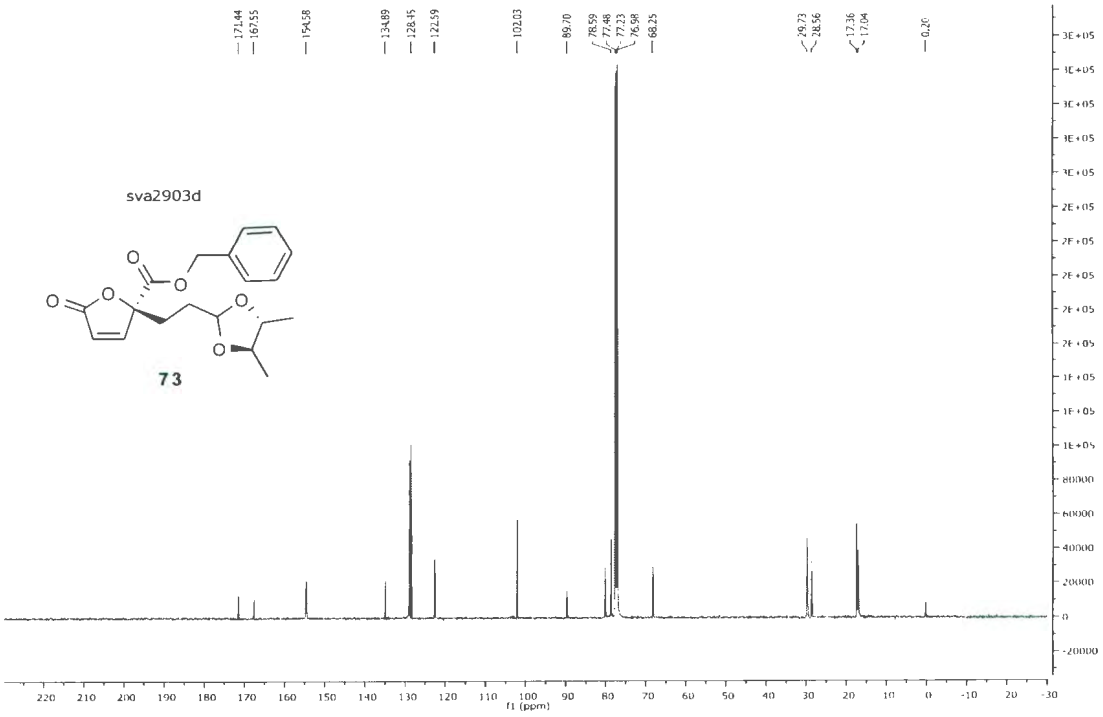
71

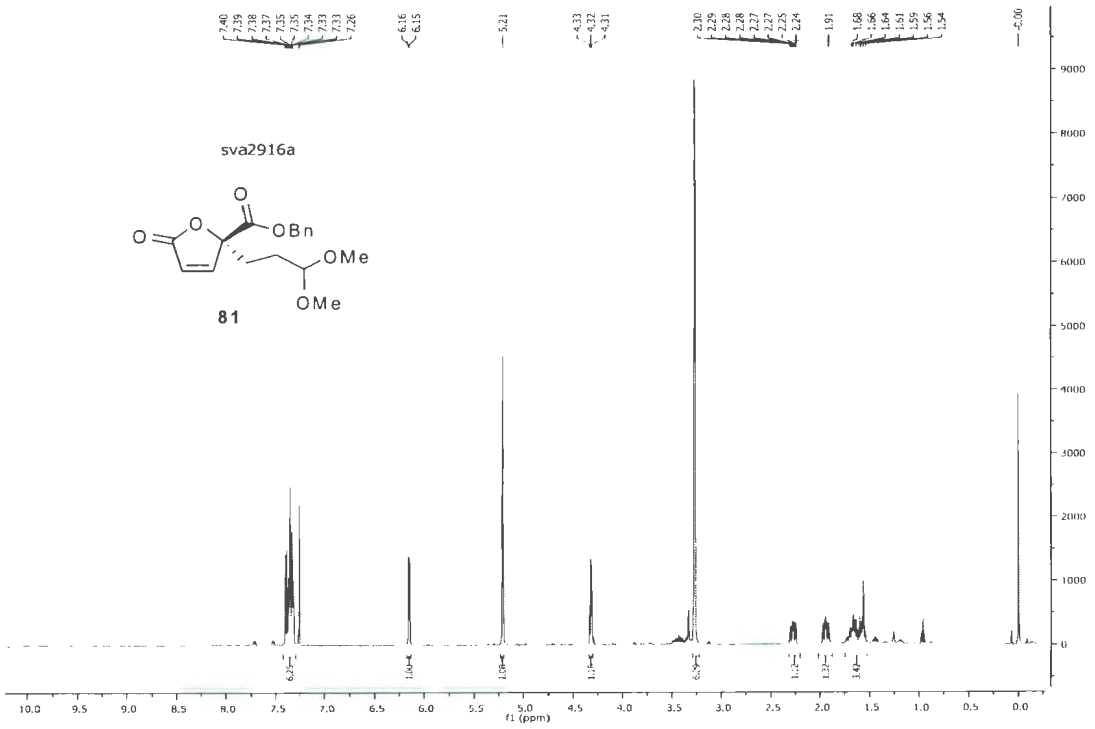
sva2980a

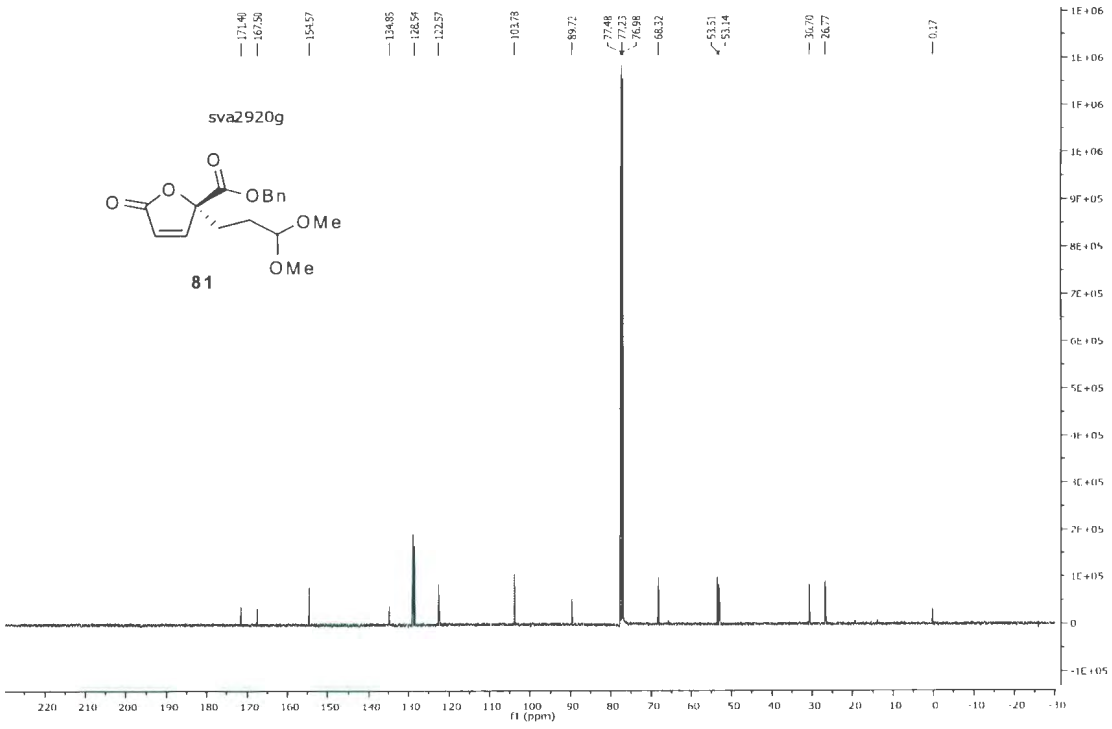


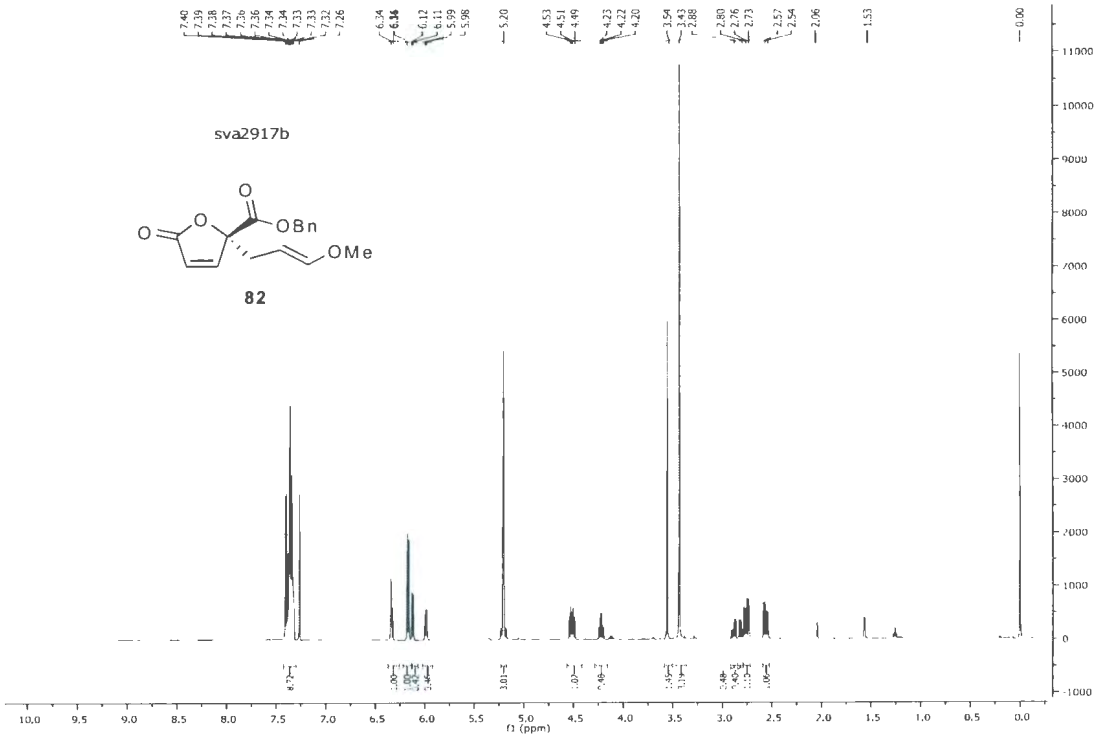
72

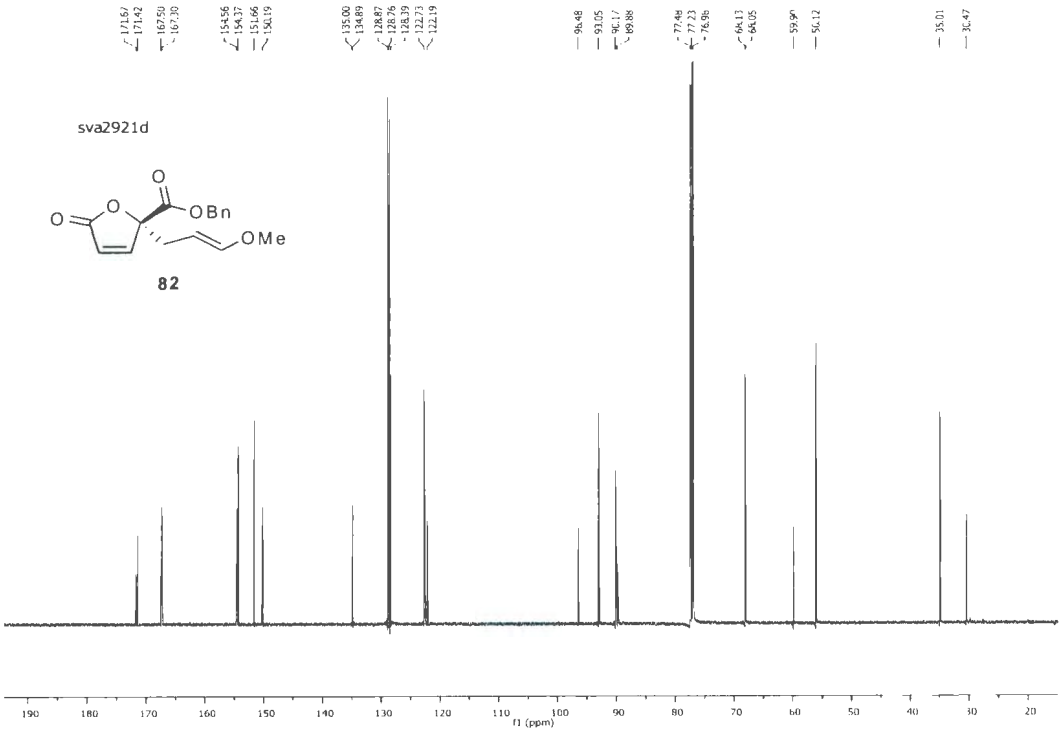

sva2903a
73
f1 (ppm)

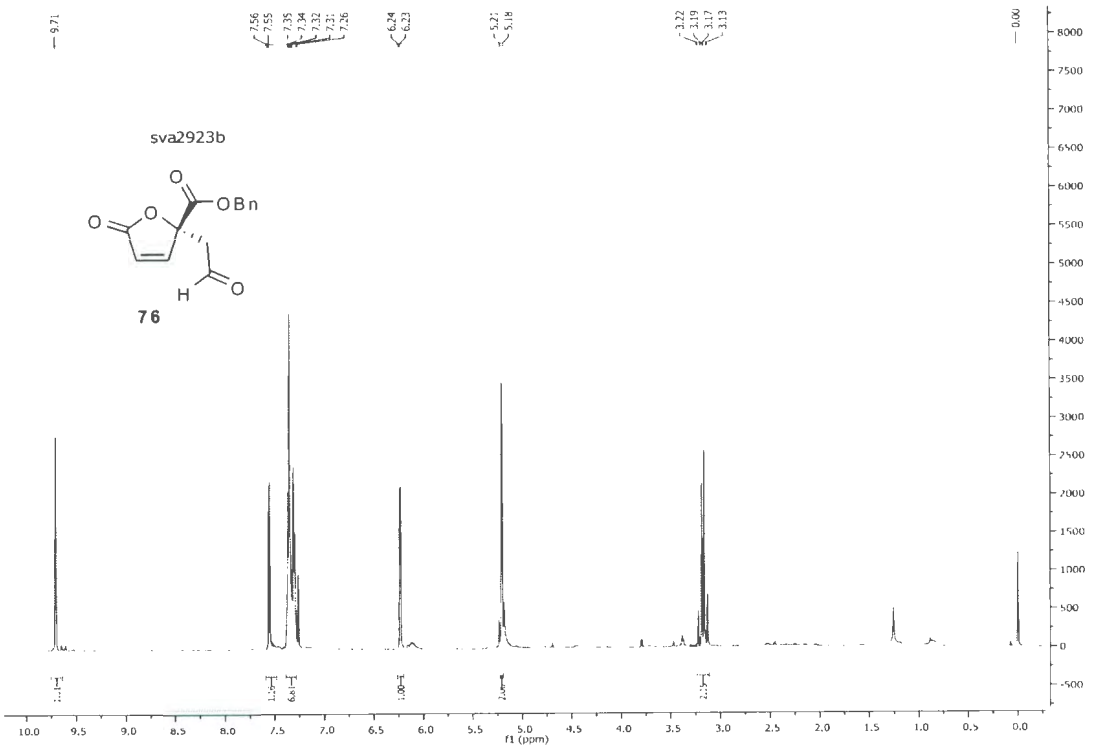

sva2903d
73
f1 (ppm)

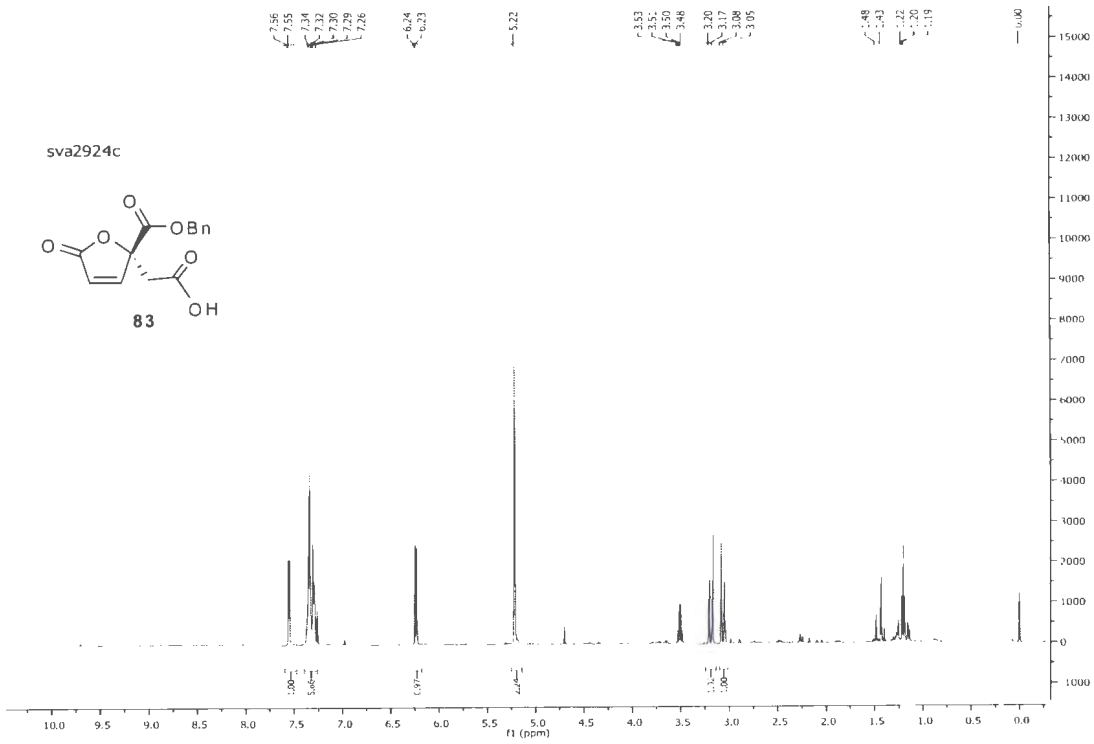

sva2916a
OBn
OMe
OMe
81
f1 (ppm)

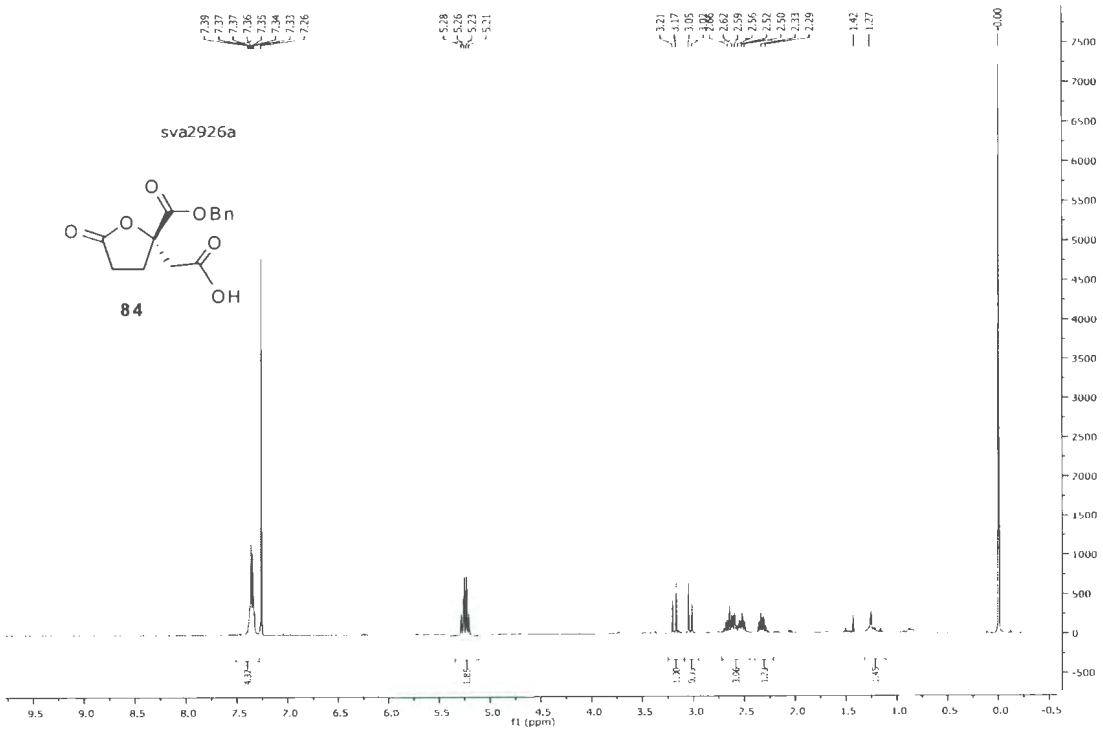

sva2920g
OBn
OMe
OMe
81
f1 (ppm)

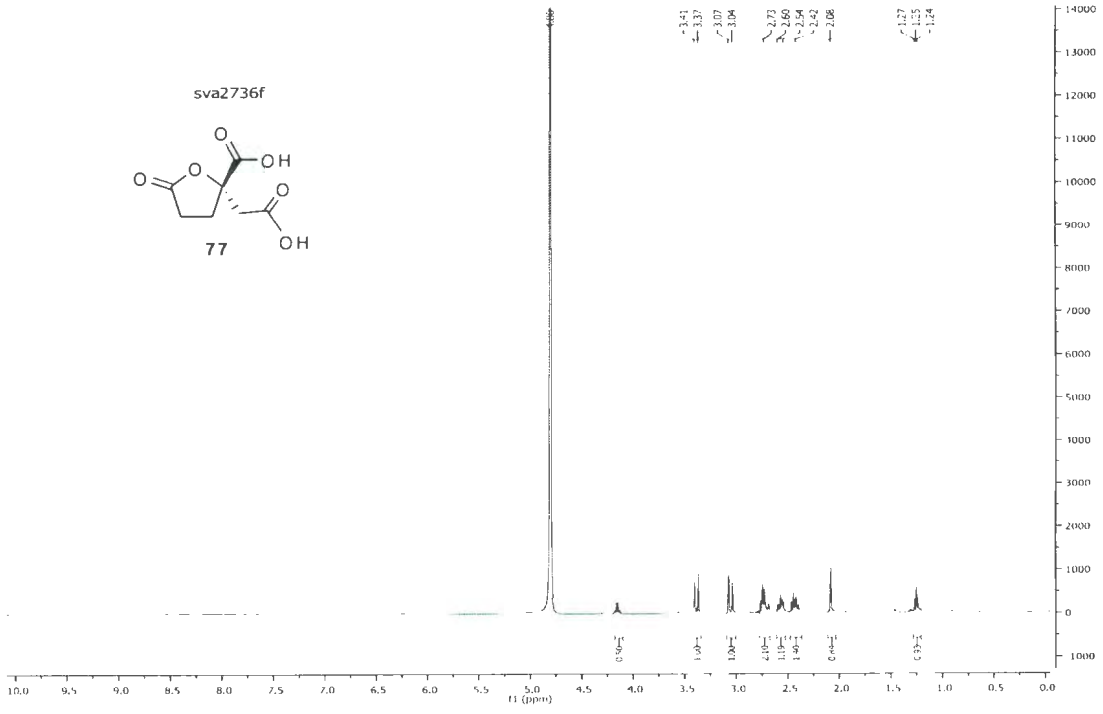

sva2917b
OBn
OMe
82
f1 (ppm)


sva2921d
OBn
OMe
82
f1 (ppm)

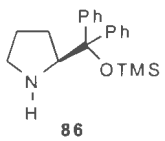

sva2923b
OBn
O
O
O
H
O
76
9.71
7.56
7.55
7.35
7.34
7.32
7.31
7.26
6.24
6.23
5.22
5.18
3.22
3.19
3.17
3.13
0.00
f1 (ppm)


sva2924c
OBn
O
O
O
OH
83
7.56
7.55
7.34
7.32
7.30
7.29
7.26
6.24
6.23
5.22
3.53
3.51
3.50
3.48
3.20
3.17
3.08
3.05
1.48
1.43
1.22
1.20
1.19
0.00
f1 (ppm)


sva2926a
OBn
OH
84
f1 (ppm)

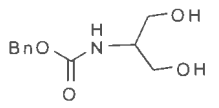

sva2736f
OH
OH
77
f1 (ppm)

sva2620a

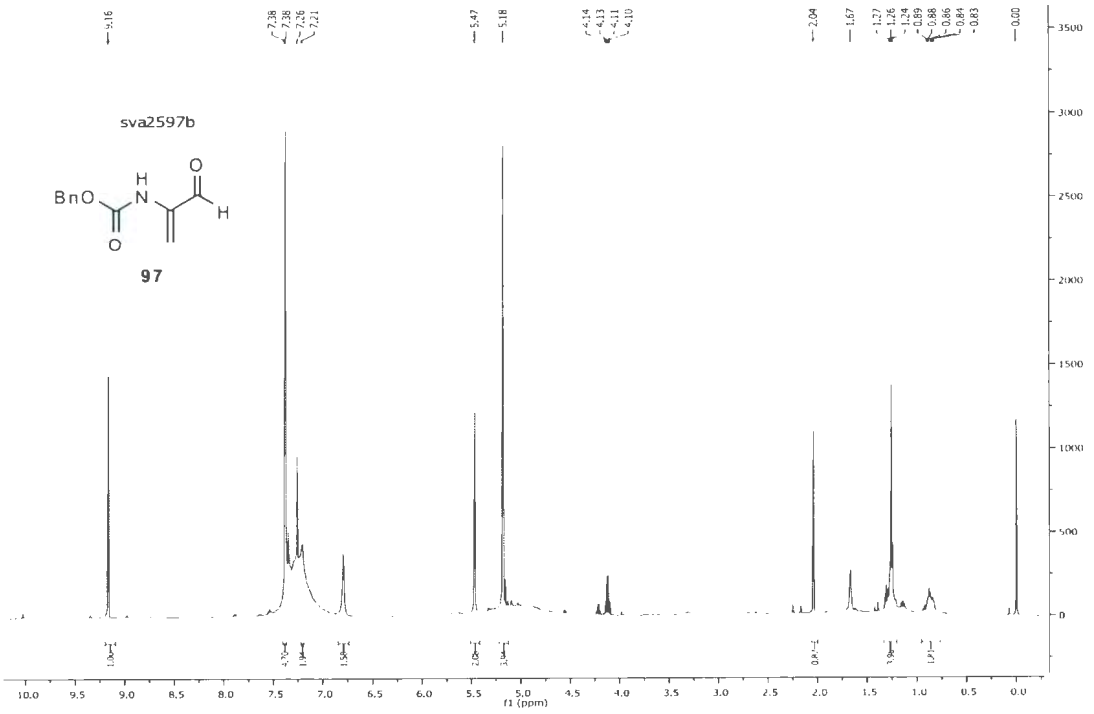


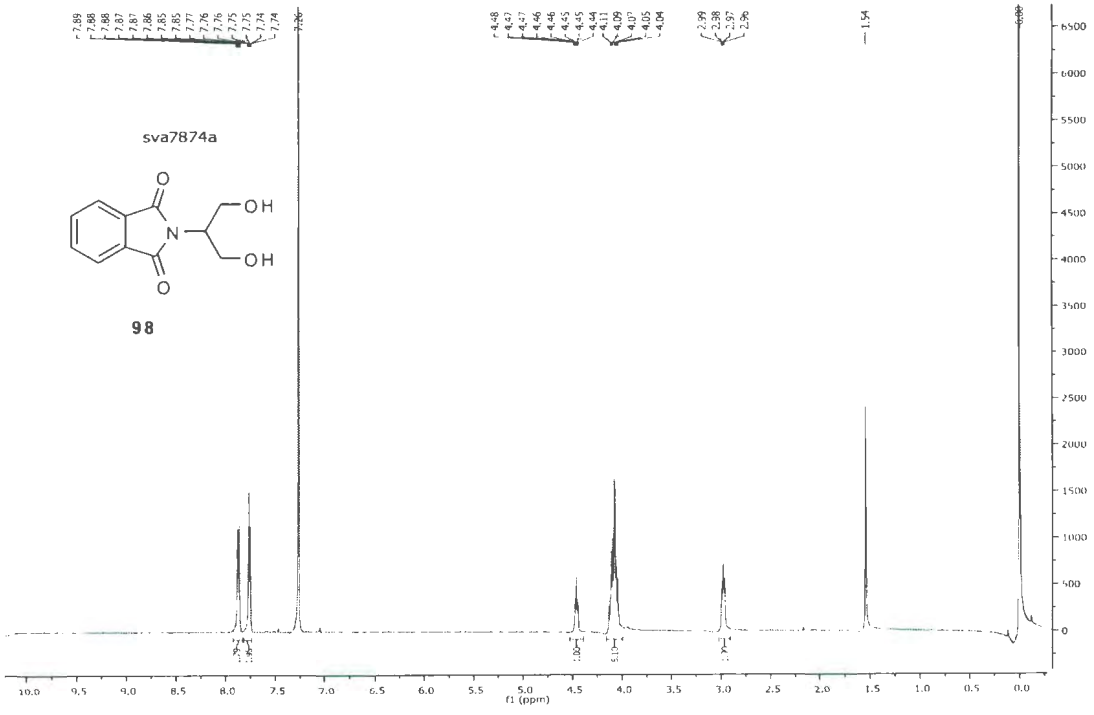
86

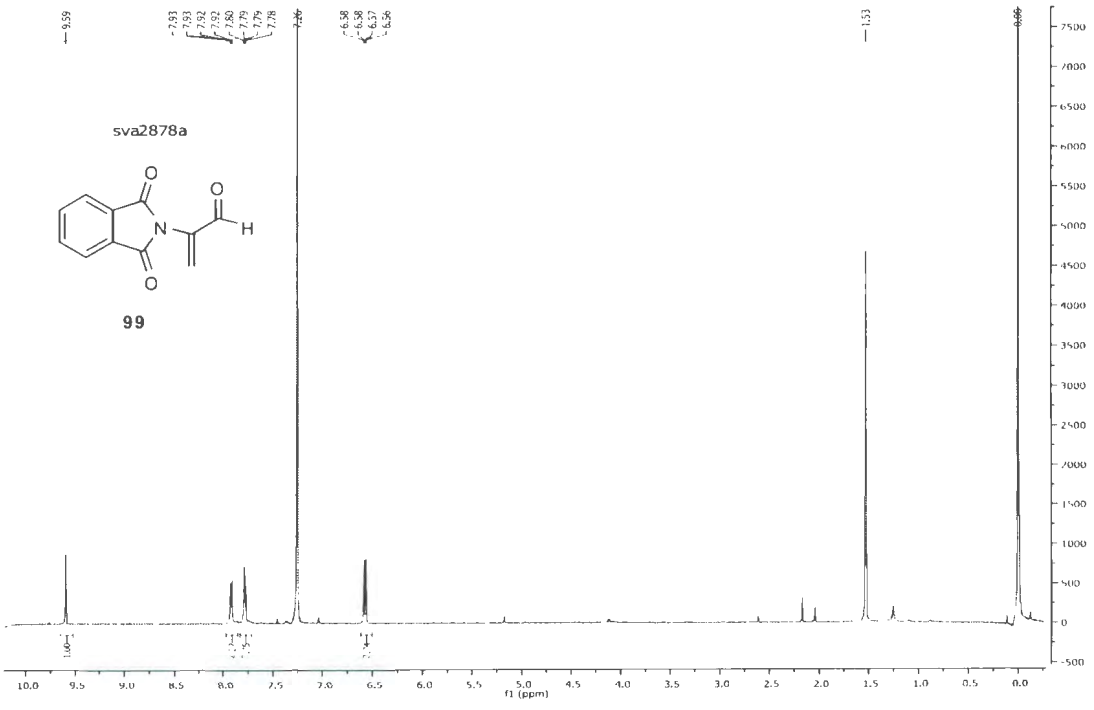
sva2593b

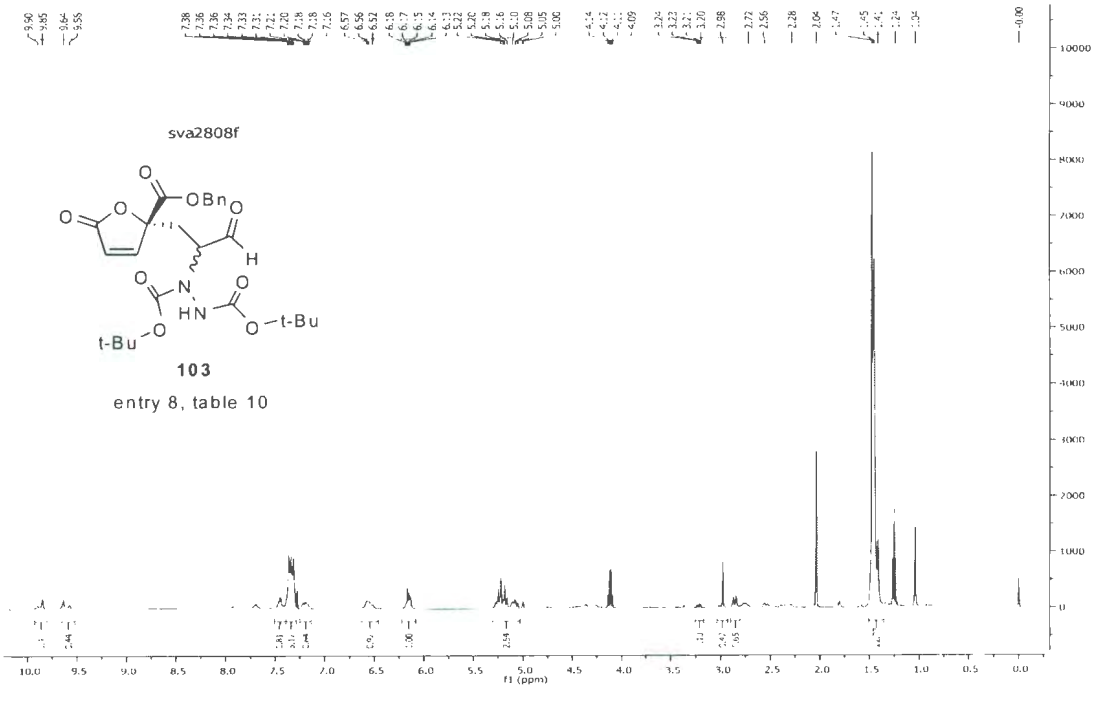


96

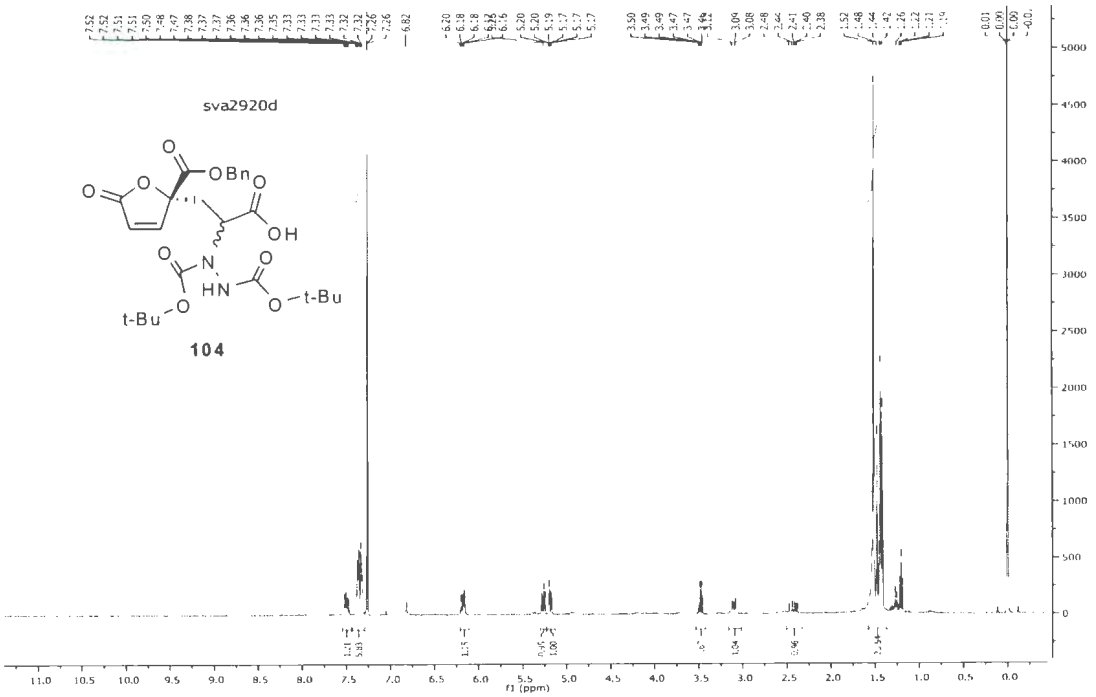

sva2597b
BnO
H
N
O
O
H
O
97
f1 (ppm)

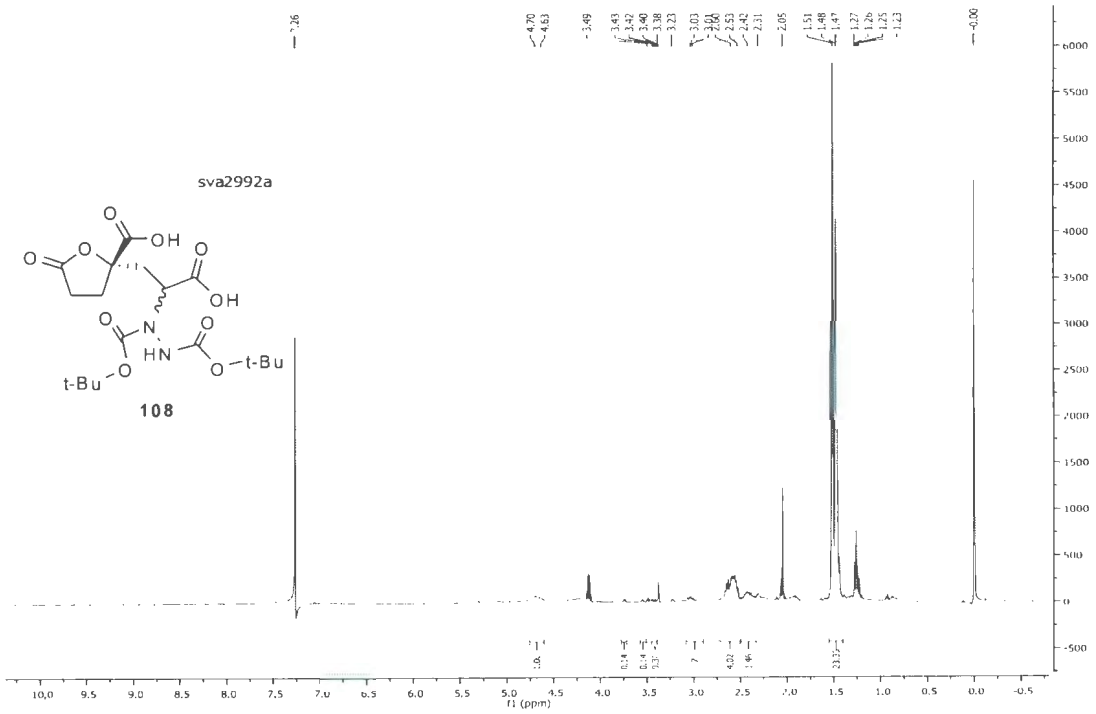

sva7874a
O
N
OH
OH
O
98
f1 (ppm)





entry 8, table 10


sva2920d
OBn
OH
t-Bu
t-Bu
104
f1 (ppm)


sva2992a
OH
OH
t-Bu
t-Bu
108
f1 (ppm)